

CAMPBELL-WALSH UROLOGY

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Every 4 years or so, a small group of crazed individuals are privileged to convene and embark on a seemingly near impossible task—to improve upon what, a relatively short time ago, they had created as the gold standard textbook in urology. A week or so later, they emerge with a plan, each with their assignments for what they now are convinced is the best ever repository of total urologic knowledge. This group and this edition are no exceptions to this routine.

The four of us feel very honored and privileged to be a part of this tradition that began in 1954 with the publication of the first Campbell's Urology (then titled simply "Urology"), which consisted of 3 volumes in which 51 individuals contributed 2356 pages and 1148 illustrations. We are grateful to our current colleagues and friends who accepted the responsibility of producing anew the 156 chapters that comprise our text and acknowledge their expertise and the unselfish contribution of their time and effort.

Our gratitude to the chapter authors notwithstanding, we would like ultimately to dedicate this edition to two sets of individuals: One group includes our mentors in urology—those whom each of us separately admired and learned from, and whose educational and clinical achievements in various aspects of our field we have sought to imitate. Hopefully, they would or will be proud of our part in this 11th edition of the gold standard textbook. The greatest debt and thanks, however, are owed to our families, specifically our wives and children who were in the "line of fire" during the preparation of this edition. They deserve more than a medal or a copy of the book. So, to Noele and Nolan; to Julianne, Nick, Rebecca and Dree; to Vicky, Topper, David, Dane and Michael; and to Kathy, Jessica, Lauren, and Ryan, our thanks for your patience, understanding, and continued support. The good news is that you have a few years until the cycle begins again.

For myself and my fellow editors,
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PREFACE

Since it was first published in 1954, Campbell-Walsh Urology (born Urology) has been the gold standard for a comprehensive review of our specialty. We are proud and pleased to present the 11th edition of this text as a worthy successor to the 10 editions that have preceded it. The four volumes remain essentially a series of comprehensive mini-textbooks on every major subject in urology. There are significant changes for this edition in organization, content, and authorship, and these reflect the ever-changing nature of our field, and, for many subjects, the passing of the baton from one generation to the next. Twenty-two totally new chapters have been added, along with 61 new first authors. All other chapters have been revised, new and revised guidelines incorporated, and the well-accepted format of the use of extensive boldface and Key Points boxes and algorithms retained. Ownership of the 11th edition includes the print product, access to the full text online, and a downloadable eBook version through ExpertConsult.com. The online and eBook version of the 11th edition will have updates by key opinion leaders added periodically to reflect important changes and controversies in the field.

Content changes include restructuring of the chapter on basic principles of radiologic imaging in adult urology, a new chapter on pediatric urologic imaging, and separate new chapters on the surgical, radiographic, and endoscopic anatomy of the male reproductive system, the retroperitoneum, the kidney and ureter, the adrenals, and the male and female pelvis. The chapter on androgen deficiency has been expanded to encompass integrated men's health, including cardiovascular risks and metabolic syndrome. There are totally new added chapters on basic energy modalities in urologic surgery, management of urinary tract hemorrhage, strategies for medical management of upper urinary tract calculi, inguinal lymph node dissection, overview of the evaluation and management of urinary incontinence in men, the underactive detrusor, complications related to the use of mesh in the treatment of urinary incontinence and prolapse and their repair, and minimally invasive urinary diversion. Additionally, in the pediatric volume, totally new chapters have been added on the principles of laparoscopic and robotic surgery, functional disorders of the lower urinary tract, management of defecation disorders, and adolescent and transitional urology. Totally new content has been provided for existing chapters on sexually transmitted infections, tuberculosis and other opportunistic infections, the basics of male infertility, disorders of male orgasm and ejaculation, surgery for erectile dysfunction, Peyronie disease, female sexual function and dysfunction, renovascular hypertension and ischemic neuropathy, renal trans-

plantation, and nonmedical management of upper urinary tract calculi. Within the section on urine transport, storage, and emptying, totally new content has been provided for the chapters on physiology and pharmacology of the bladder and urethra, epidemiology and pathophysiology of urinary incontinence and pelvic prolapse, nocturia, conservative management of urinary incontinence, urinary fistulae, geriatric lower urinary tract dysfunction and incontinence, and additional therapies for storage and emptying failure. Reflecting all the latest changes in the field, the chapter on minimally invasive and endoscopic management of benign prostatic hyperplasia has been totally redone. In the area of cancer, many chapters have been totally rewritten to reflect contemporary data and thought: Basic Principles of Immunology and Immunotherapy in Urologic Oncology, Neoplasms of the Testis, Retroperitoneal Tumors, Open Surgery of the Kidney, Nonsurgical Focal Therapy for Renal Tumors, Surgery of the Adrenal Glands, Management of Metastatic and Invasive Bladder Cancer, Transurethral and Open Surgery for Bladder Cancer, Prostate Biopsy: Techniques and Imaging (including fusion techniques), Diagnosis and Staging of Prostate Cancer, Active Surveillance of Prostate Cancer, Focal Therapy for Prostate Cancer, Radiation Therapy for Prostate Cancer, Management of Biochemical Recurrence after Definitive Therapy for Prostate Cancer, and Tumors of the Urethra. In the pediatric volume, a number of existing chapters have been totally rewritten as well: Disorders of Renal Functional Development in Children, Infection and Inflammation of the Pediatric Genitourinary Tract, Surgery of the Ureter in Children, Posterior Urethral Valves, and separate chapters on Management of Abnormalities of the External Genitalia in boys and girls.

We editors are grateful for the support of Elsevier, and special thanks are due to our extraordinary editorial and support staff: Charlotta Kryhl and Stefanie Jewel-Thomas (Senior Content Strategists), Dee Simpson (Senior Content Development Specialist), and Kristine Feeherty (Book Production Specialist). Without their expertise, patience, and gentle pushing, this edition would not have been brought to press on time.

We hope your experience in reading this 11th edition of the gold standard textbook of urology will be as pleasurable as ours has been in watching it develop.

Alan J. Wein, MD, PhD (Hon), FACS

for the editors Louis R. Kavoussi, MD, MBA,
Alan W. Partin, MD, PhD, and Craig A. Peters, MD

CONTENTS

VOLUME 1

PART I Clinical Decision Making

- 1 Evaluation of the Urologic Patient: History, Physical Examination, and Urinalysis, 1**
Glenn S. Gerber, MD, and Charles B. Brendler, MD
- 2 Urinary Tract Imaging: Basic Principles of Computed Tomography, Magnetic Resonance Imaging, and Plain Film, 26**
Jay T. Bishoff, MD, FACS, and Art R. Rastinehad, DO
- 3 Urinary Tract Imaging: Basic Principles of Urologic Ultrasonography, 63**
Bruce R. Gilbert, MD, PhD, and Pat F. Fulgham, MD
- 4 Outcomes Research, 85**
Mark S. Litwin, MD, MPH, and Jonathan Bergman, MD, MPH

PART II Basics of Urologic Surgery

- 5 Core Principles of Perioperative Care, 100**
Manish A. Vira, MD, and Joph Steckel, MD, FACS
- 6 Fundamentals of Urinary Tract Drainage, 119**
Thomas Tailly, MD, MSc, and John D. Denstedt, MD, FRCSC, FACS
- 7 Principles of Urologic Endoscopy, 136**
Brian D. Duty, MD, and Michael J. Conlin, MD, MCR
- 8 Percutaneous Approaches to the Upper Urinary Tract Collecting System, 153**
J. Stuart Wolf, Jr., MD, FACS
- 9 Evaluation and Management of Hematuria, 183**
Stephen A. Boorjian, MD, Jay D. Raman, MD, and Daniel A. Barocas, MD, MPH, FACS
- 10 Fundamentals of Laparoscopic and Robotic Urologic Surgery, 195**
Michael Ordon, MD, MSc, FRCSC, Louis Eichel, MD, and Jaime Landman, MD
- 11 Basic Energy Modalities in Urologic Surgery, 225**
Shubha De, MD, FRCPC, Manoj Monga, MD, FACS, and Bodo E. Knudsen, MD, FRCSC

PART III Infections and Inflammation

- 12 Infections of the Urinary Tract, 237**
Anthony J. Schaeffer, MD, Richard S. Matulewicz, MS, MD, and David James Klumpp, PhD
- 13 Inflammatory and Pain Conditions of the Male Genitourinary Tract: Prostatitis and Related Pain Conditions, Orchitis, and Epididymitis, 304**
J. Curtis Nickel, MD, FRCSC
- 14 Bladder Pain Syndrome (Interstitial Cystitis) and Related Disorders, 334**
Philip M. Hanno, MD, MPH

15 Sexually Transmitted Diseases, 371

Michel Arthur Pontari, MD

16 Cutaneous Diseases of the External Genitalia, 387

Richard Edward Link, MD, PhD, and Theodore Rosen, MD

17 Tuberculosis and Parasitic Infections of the Genitourinary Tract, 421

Alicia H. Chang, MD, MS, Brian G. Blackburn, MD, and Michael H. Hsieh, MD, PhD

PART IV Molecular and Cellular Biology

18 Basic Principles of Immunology and Immunotherapy in Urologic Oncology, 447

Charles G. Drake, MD, PhD

19 Molecular Genetics and Cancer Biology, 459

Mark L. Gonzalgo, MD, PhD, Karen S. Sfanos, PhD, and Alan K. Meeker, PhD

20 Principles of Tissue Engineering, 482

Anthony Atala, MD

PART V Reproductive and Sexual Function

21 Surgical, Radiographic, and Endoscopic Anatomy of the Male Reproductive System, 498

Parviz K. Kavoussi, MD, FACS

22 Male Reproductive Physiology, 516

Paul J. Turek, MD, FACS, FRSM

23 Integrated Men's Health: Androgen Deficiency, Cardiovascular Risk, and Metabolic Syndrome, 538

J. Kellogg Parsons, MD, MHS, FACS, and Tung-Chin Hsieh, MD

24 Male Infertility, 556

Craig Stuart Niederberger, MD, FACS

25 Surgical Management of Male Infertility, 580

Marc Goldstein, MD, DSc (Hon), FACS

26 Physiology of Penile Erection and Pathophysiology of Erectile Dysfunction, 612

Tom F. Lue, MD, ScD (Hon), FACS

27 Evaluation and Management of Erectile Dysfunction, 643

Arthur L. Burnett II, MD, MBA, FACS

28 Priapism, 669

Gregory A. Broderick, MD

29 Disorders of Male Orgasm and Ejaculation, 692

Chris G. McMahon, MBBS, FACHSHM

30 Surgery for Erectile Dysfunction, 709

J. Francois Eid, MD

31 Diagnosis and Management of Peyronie Disease, 722

Laurence A. Levine, MD, FACS, and Stephen Larsen, MD

32 Sexual Function and Dysfunction in the Female, 749*Alan W. Shindell, MD, MAS, and Irwin Goldstein, MD***PART VI Male Genitalia****33 Surgical, Radiographic, and Endoscopic Anatomy of the Retroperitoneum, 765***Drew A. Palmer, MD, and Alireza Moinzadeh, MD***34 Neoplasms of the Testis, 784***Andrew J. Stephenson, MD, MBA, FACS, FRCS(C), and Timothy D. Gilligan, MD, MS***35 Surgery of Testicular Tumors, 815***Kevin R. Rice, MD, Clint K. Cary, MD, MPH, Timothy A. Masterson, MD, and Richard S. Foster, MD***36 Laparoscopic and Robotic-Assisted Retroperitoneal Lymphadenectomy for Testicular Tumors, 838***Mohamad E. Allaf, MD, and Louis R. Kavoussi, MD, MBA***37 Tumors of the Penis, 846***Curtis A. Pettaway, MD, Juanita M. Crook, MD, FRCPC, and Lance C. Pagliaro, MD***38 Tumors of the Urethra, 879***David S. Sharp, MD, and Kenneth W. Angermeier, MD***39 Inguinal Node Dissection, 890***Kenneth W. Angermeier, MD, Rene Sotelo, MD, and David S. Sharp, MD***40 Surgery of the Penis and Urethra, 907***Kurt A. McCammon, MD, FACS, Jack M. Zuckerman, MD, and Gerald H. Jordan, MD, FACS, FAAP (Hon), FRCS (Hon)***41 Surgery of the Scrotum and Seminal Vesicles, 946***Frank A. Celigoj, MD, and Raymond A. Costabile, MD***VOLUME 2****PART VII Renal Physiology and Pathophysiology****42 Surgical, Radiologic, and Endoscopic Anatomy of the Kidney and Ureter, 967***Mohamed Aly Elkoushy, MD, MSc, PhD, and Sero Andonian, MD, MSc, FRCS(C), FACS***43 Physiology and Pharmacology of the Renal Pelvis and Ureter, 978***Robert M. Weiss, MD, and Darryl T. Martin, PhD***44 Renal Physiology and Pathophysiology, 1007***Daniel A. Shoskes, MD, MSc, FRCSC, and Alan W. McMahon, MD***45 Renovascular Hypertension and Ischemic Nephropathy, 1028***Frederick A. Gulmi, MD, Ira W. Reiser, MD, and Samuel Spitalowitz, MD***46 Etiology, Pathogenesis, and Management of Renal Failure, 1041***David A. Goldfarb, MD, Emilio D. Poggio, MD, and Sevag Demirjian, MD***47 Renal Transplantation, 1069***Hans Albin Gritsch, MD, and Jeremy Matthew Blumberg, MD***PART VIII Upper Urinary Tract Obstruction and Trauma****48 Pathophysiology of Urinary Tract Obstruction, 1089***Kirstan K. Meldrum, MD***49 Management of Upper Urinary Tract Obstruction, 1104***Stephen Y. Nakada, MD, FACS, and Sara L. Best, MD***50 Upper Urinary Tract Trauma, 1148***Richard A. Santucci, MD, FACS, and Mang L. Chen, MD***PART IX Urinary Lithiasis and Endourology****51 Urinary Lithiasis: Etiology, Epidemiology, and Pathogenesis, 1170***Margaret S. Pearle, MD, PhD, Jodi A. Antonelli, MD, and Yair Lotan, MD***52 Evaluation and Medical Management of Urinary Lithiasis, 1200***Michael E. Lipkin, MD, Michael N. Ferrandino, MD, and Glenn M. Preminger, MD***53 Strategies for Nonmedical Management of Upper Urinary Tract Calculi, 1235***David A. Leavitt, MD, Jean J. M. C. H. de la Rosette, MD, PhD, and David M. Hoenig, MD***54 Surgical Management of Upper Urinary Tract Calculi, 1260***Brian R. Matlaga, MD, MPH, Amy E. Krambeck, MD, and James E. Lingeman, MD***55 Lower Urinary Tract Calculi, 1291***Brian M. Benway, MD, and Sam B. Bhayani, MD, MS***PART X Neoplasms of the Upper Urinary Tract****56 Benign Renal Tumors, 1300***Vitaly Margulis, MD, Jose A. Karam, MD, Surena F. Matin, MD, and Christopher G. Wood, MD***57 Malignant Renal Tumors, 1314***Steven C. Campbell, MD, PhD, and Brian R. Lane, MD, PhD***58 Urothelial Tumors of the Upper Urinary Tract and Ureter, 1365***Armine K. Smith, MD, Surena F. Matin, MD, and Thomas W. Jarrett, MD***59 Retroperitoneal Tumors, 1403***Philippe E. Spiess, MD, MS, FRCS(C), Dan Leibovici, MD, and Louis L. Pisters, MD***60 Open Surgery of the Kidney, 1414***Aria F. Olumi, MD, Mark A. Preston, MD, MPH, and Michael L. Blute, Sr., MD***61 Laparoscopic and Robotic Surgery of the Kidney, 1446***Michael J. Schwartz, MD, FACS, Soroush Rais-Bahrami, MD, and Louis R. Kavoussi, MD, MBA***62 Nonsurgical Focal Therapy for Renal Tumors, 1484***Chad R. Tracy, MD, and Jeffrey A. Cadeddu, MD***63 Treatment of Advanced Renal Cell Carcinoma, 1500***Ramaprasad Srinivasan, MD, PhD, and W. Marston Linehan, MD*

PART XI The Adrenals

- 64 Surgical and Radiologic Anatomy of the Adrenals, 1519**
Ravi Munver, MD, FACS, Jennifer K. Yates, MD, and Michael C. Degen, MD, MA
- 65 Pathophysiology, Evaluation, and Medical Management of Adrenal Disorders, 1528**
Alexander Kutikov, MD, FACS, Paul L. Crispen, MD, and Robert G. Uzzo, MD, FACS
- 66 Surgery of the Adrenal Glands, 1577**
Sey Kiat Lim, MBBS, MRCS (Edinburgh), MMed (Surgery), FAMS (Urology), and Koon Ho Rha, MD, PhD, FACS

VOLUME 3**PART XII Urine Transport, Storage, and Emptying**

- 67 Surgical, Radiographic, and Endoscopic Anatomy of the Female Pelvis, 1597**
Larissa V. Rodriguez, MD, and Leah Yukie Nakamura, MD
- 68 Surgical, Radiographic, and Endoscopic Anatomy of the Male Pelvis, 1611**
Benjamin I. Chung, MD, Graham Sommer, MD, and James D. Brooks, MD
- 69 Physiology and Pharmacology of the Bladder and Urethra, 1631**
Toby C. Chai, MD, and Lori A. Birder, PhD
- 70 Pathophysiology and Classification of Lower Urinary Tract Dysfunction: Overview, 1685**
Alan J. Wein, MD, PhD (Hon), FACS
- 71 Evaluation and Management of Women with Urinary Incontinence and Pelvic Prolapse, 1697**
Kathleen C. Kobashi, MD, FACS
- 72 Evaluation and Management of Men with Urinary Incontinence, 1710**
Hashim Hashim, MBBS, MRCS (Eng), MD, FEBU, FRCS (Urol), and Paul Abrams, MD, FRCS
- 73 Urodynamic and Video-Urodynamic Evaluation of the Lower Urinary Tract, 1718**
Victor W. Nitti, MD, and Benjamin M. Brucker, MD
- 74 Urinary Incontinence and Pelvic Prolapse: Epidemiology and Pathophysiology, 1743**
Gary E. Lemack, MD, and Jennifer Tash Anger, MD, MPH
- 75 Neuromuscular Dysfunction of the Lower Urinary Tract, 1761**
Alan J. Wein, MD, PhD (Hon), FACS, and Roger R. Dmochowski, MD, MMHC, FACS
- 76 Overactive Bladder, 1796**
Marcus John Drake, DM, MA, FRCS (Urol)
- 77 The Underactive Detrusor, 1807**
Christopher R. Chapple, MD, FRCS (Urol), and Nadir I. Osman, PhD, MRCS
- 78 Nocturia, 1821**
Jeffrey Paul Weiss, MD, and Stephen David Marshall, MD
- 79 Pharmacologic Management of Lower Urinary Tract Storage and Emptying Failure, 1836**
Karl-Erik Andersson, MD, PhD, and Alan J. Wein, MD, PhD (Hon), FACS
- 80 Conservative Management of Urinary Incontinence: Behavioral and Pelvic Floor Therapy and Urethral and Pelvic Devices, 1875**
Diane K. Newman, DNP, ANP-BC, FAAN, and Kathryn L. Burgio, PhD
- 81 Electrical Stimulation and Neuromodulation in Storage and Emptying Failure, 1899**
Sandip P. Vasavada, MD, and Raymond R. Rackley, MD
- 82 Retropubic Suspension Surgery for Incontinence in Women, 1918**
Christopher R. Chapple, MD, FRCS (Urol)
- 83 Vaginal and Abdominal Reconstructive Surgery for Pelvic Organ Prolapse, 1939**
J. Christian Winters, MD, FACS, Ariana L. Smith, MD, and Ryan M. Krlin, MD
- 84 Slings: Autologous, Biologic, Synthetic, and Midurethral, 1987**
Roger R. Dmochowski, MD, MMHC, FACS, David James Osborn, MD, and W. Stuart Reynolds, MD, MPH
- 85 Complications Related to the Use of Mesh and Their Repair, 2039**
Shlomo Raz, MD, and Lisa Rogo-Gupta, MD
- 86 Injection Therapy for Urinary Incontinence, 2049**
Sender Herschorn, MD, FRCS
- 87 Additional Therapies for Storage and Emptying Failure, 2070**
Timothy B. Boone, MD, PhD, and Julie N. Stewart, MD
- 88 Aging and Geriatric Urology, 2083**
Tomas L. Griebing, MD, MPH
- 89 Urinary Tract Fistulae, 2103**
Gopal H Badlani, MD, FACS, Dirk J. M. K. De Ridder, MD, PhD, Jayadev Reddy Mettu, MD, MBBS, and Eric S. Rovner, MD
- 90 Bladder and Female Urethral Diverticula, 2140**
Eric S. Rovner, MD
- 91 Surgical Procedures for Sphincteric Incontinence in the Male: The Artificial Urinary Sphincter and Perineal Sling Procedures, 2169**
Hunter Wessells, MD, FACS, and Andrew Peterson, MD, FACS

PART XIII Benign and Malignant Bladder Disorders

- 92 Tumors of the Bladder, 2184**
David P. Wood, Jr., MD
- 93 Non-Muscle-Invasive Bladder Cancer (Ta, T1, and CIS), 2205**
J. Stephen Jones, MD, MBA, FACS
- 94 Management of Metastatic and Invasive Bladder Cancer, 2223**
Thomas J. Guzzo, MD, MPH, and David J. Vaughn, MD
- 95 Transurethral and Open Surgery for Bladder Cancer, 2242**
Neema Navai, MD, and Colin P. N. Dinney, MD

96 Robotic and Laparoscopic Bladder Surgery, 2254*Lee Richstone, MD, and Douglas S. Scherr, MD***97 Use of Intestinal Segments in Urinary Diversion, 2281***Douglas M. Dahl, MD, FACS***98 Cutaneous Continent Urinary Diversion, 2317***G. Joel DeCastro, MD, MPH, James M. McKiernan, MD, and Mitchell C. Benson, MD***99 Orthotopic Urinary Diversion, 2344***Eila C. Skinner, MD, and Siamak Daneshmand, MD***100 Minimally Invasive Urinary Diversion, 2369***Khurshid A. Guru, MD***101 Genital and Lower Urinary Tract Trauma, 2379***Allen F. Morey, MD, FACS, and Lee C. Zhao, MD, MS***PART XIV The Prostate****102 Development, Molecular Biology, and Physiology of the Prostate, 2393***Ashley Evan Ross, MD, PhD, and Ronald Rodriguez, MD, PhD***103 Benign Prostatic Hyperplasia: Etiology, Pathophysiology, Epidemiology, and Natural History, 2425***Claus G. Roehrborn, MD***104 Evaluation and Nonsurgical Management of Benign Prostatic Hyperplasia, 2463***Thomas A. McNicholas, MB BS, FRCS, FEBU, Mark J. Speakman, MBBS, MS, FRCS, and Roger S. Kirby, MD, FRCS***105 Minimally Invasive and Endoscopic Management of Benign Prostatic Hyperplasia, 2504***Charles Welliver, MD, and Kevin T. McVary, MD, FACS***106 Simple Prostatectomy: Open and Robot-Assisted Laparoscopic Approaches, 2535***Misop Han, MD, MS, and Alan W. Partin, MD, PhD***107 Epidemiology, Etiology, and Prevention of Prostate Cancer, 2543***Andrew J. Stephenson, MD, MBA, FACS, FRCS(C), and Eric A. Klein, MD***108 Prostate Cancer Tumor Markers, 2565***Todd M. Morgan, MD, Ganesh S. Palapattu, MD, Alan W. Partin, MD, PhD, and John T. Wei, MD, MS***109 Prostate Biopsy: Techniques and Imaging, 2579***Leonard G. Gomella, MD, FACS, Ethan J. Halpern, MD, MSCE, and Edouard J. Trabulsi, MD, FACS***110 Pathology of Prostatic Neoplasia, 2593***Jonathan I. Epstein, MD***111 Diagnosis and Staging of Prostate Cancer, 2601***Stacy Loeb, MD, MSc, and James A. Eastham, MD***112 Management of Localized Prostate Cancer, 2609***William J. Catalona, MD, and Misop Han, MD, MS***113 Active Surveillance of Prostate Cancer, 2628***Herbert Ballentine Carter, MD, and Marc Arnaldo Dall'Era, MD***114 Open Radical Prostatectomy, 2641***Edward M. Schaeffer, MD, PhD, Alan W. Partin, MD, PhD, and Herbert Lepor, MD***115 Laparoscopic and Robotic-Assisted Laparoscopic Radical Prostatectomy and Pelvic Lymphadenectomy, 2663***Li-Ming Su, MD, Scott M. Gilbert, MD, and Joseph A. Smith, Jr., MD***116 Radiation Therapy for Prostate Cancer, 2685***Anthony V. D'Amico, MD, PhD, Paul L. Nguyen, MD, Juanita M. Crook, MD, FRCPC, Ronald C. Chen, MD, MPH, Bridget F. Koontz, MD, Neil Martin, MD, MPH, W. Robert Lee, MD, MEd, MS, and Theodore L. DeWeese, MD, MPH***117 Focal Therapy for Prostate Cancer, 2711***Hashim U. Ahmed, PhD, FRCS (Urol), BM, BCh, BA (Hons), and Mark Emberton, MD, MBBS, FRCS (Urol), BSc***118 Treatment of Locally Advanced Prostate Cancer, 2752***Maxwell V. Meng, MD, and Peter R. Carroll, MD, MPH***119 Management of Biochemical Recurrence after Definitive Therapy for Prostate Cancer, 2770***Eugene Kang Lee, MD, and J. Brantley Thrasher, MD***120 Hormonal Therapy for Prostate Cancer, 2786***Joel B. Nelson, MD***121 Treatment of Castration-Resistant Prostate Cancer, 2804***Emmanuel S. Antonarakis, MD, Michael A. Carducci, MD, and Mario A. Eisenberger, MD***VOLUME 4****PART XV Pediatric Urology****SECTION A Development and Prenatal Urology****122 Embryology of the Genitourinary Tract, 2823***John M. Park, MD***123 Disorders of Renal Functional Development in Children, 2849***Victoria F. Norwood, MD, and Craig A. Peters, MD***124 Perinatal Urology, 2873***Richard S. Lee, MD, and Joseph G. Borer, MD***SECTION B Basic Principles****125 Urologic Evaluation of the Child, 2893***Thomas F. Kolon, MD, MS, and Douglas A. Canning, MD***126 Pediatric Urogenital Imaging, 2909***Aaron D. Martin, MD, MPH, and Hans G. Pohl, MD, FAAP***127 Infection and Inflammation of the Pediatric Genitourinary Tract, 2926***Christopher S. Cooper, MD, FAAP, FACS, and Douglas W. Storm, MD, FAAP***128 Core Principles of Perioperative Management in Children, 2949***Carlos R. Estrada, Jr., MD, and Lynne R. Ferrari, MD***129 Principles of Laparoscopic and Robotic Surgery in Children, 2963***Pasquale Casale, MD*

SECTION C Upper Urinary Tract Conditions

- 130 Anomalies of the Upper Urinary Tract, 2975**
Ellen Shapiro, MD, and Shpetim Telegrafi, MD

- 131 Renal Dysgenesis and Cystic Disease of the Kidney, 3006**
John C. Pope IV, MD

- 132 Congenital Urinary Obstruction: Pathophysiology, 3043**
Craig A. Peters, MD

- 133 Surgery of the Ureter in Children, 3057**
L. Henning Olsen, MD, DMSc, FEAPU, FEBU,
and Yazan F. H. Rawashdeh, MD, PhD, FEAPU

- 134 Ectopic Ureter, Ureterocele, and Ureteral Anomalies, 3075**
Craig A. Peters, MD, and Cathy Mendelsohn, PhD

- 135 Surgical Management of Pediatric Stone Disease, 3102**
Francis X. Schneck, MD, and Michael C. Ost, MD

SECTION D Lower Urinary Tract Conditions

- 136 Development and Assessment of Lower Urinary Tract Function in Children, 3121**
Chung Kwong Yeung, MBBS, MD, PhD, FRCS, FRACS, FACS,
Stephen Shei-Dei Yang, MD, PhD, and Piet Hoebeke, MD, PhD

- 137 Vesicoureteral Reflux, 3134**
Antoine E. Khoury, MD, FRCSC, FAAP,
and Darius J. Bägli, MDCM, FRCSC, FAAP, FACS

- 138 Bladder Anomalies in Children, 3173**
Dominic Frimberger, MD, and Bradley P. Kropp, MD, FAAP, FACS

- 139 Exstrophy-Epispadias Complex, 3182**
John P. Gearhart, MD, and Ranjiv Mathews, MD

- 140 Prune-Belly Syndrome, 3234**
Anthony A. Caldamone, MD, MMS, FAAP, FACS,
and Francisco Tibor Dénes, MD, PhD

- 141 Posterior Urethral Valves and Urethral Anomalies, 3252**
Aseem Ravindra Shukla, MD

- 142 Neuromuscular Dysfunction of the Lower Urinary Tract in Children, 3272**
Dawn Lee MacLellan, MD, FRCSC, and Stuart B. Bauer, MD

- 143 Functional Disorders of the Lower Urinary Tract in Children, 3297**
Paul F. Austin, MD, and Gino J. Vricella, MD

- 144 Management of Defecation Disorders, 3317**
Martin Allan Koyle, MD, FAAP, FACS, FRCSC, FRCS (Eng),
and Armando J. Lorenzo, MD, MSc, FRCSC, FAAP, FACS

- 145 Urinary Tract Reconstruction in Children, 3330**

Mark C. Adams, MD, FAAP, David B. Joseph, MD, FACS, FAAP,
and John C. Thomas, MD, FAAP, FACS

SECTION E Genitalia

- 146 Management of Abnormalities of the External Genitalia in Boys, 3368**

Lane S. Palmer, MD, FACS, FAAP,
and Jeffrey S. Palmer, MD, FACS, FAAP

- 147 Hypospadias, 3399**

Warren T. Snodgrass, MD, and Nicol Corbin Bush, MD, MSCS

- 148 Etiology, Diagnosis, and Management of the Undescended Testis, 3430**

Julia Spencer Barthold, MD, and Jennifer A. Hagerty, DO

- 149 Management of Abnormalities of the Genitalia in Girls, 3453**

Martin Kaefer, MD

- 150 Disorders of Sexual Development: Etiology, Evaluation, and Medical Management, 3469**

David Andrew Diamond, MD,
and Richard Nithipaisai Yu, MD, PhD

SECTION F Reconstruction and Trauma

- 151 Surgical Management of Disorders of Sex Development and Cloacal and Anorectal Malformations, 3498**

Richard C. Rink, MD, FAAP, FACS

- 152 Adolescent and Transitional Urology, 3521**

Christopher R. J. Woodhouse, MB, FRCS, FEBU

- 153 Urologic Considerations in Pediatric Renal Transplantation, 3528**

Craig A. Peters, MD

- 154 Pediatric Genitourinary Trauma, 3538**

Douglas A. Husmann, MD

SECTION G Oncology

- 155 Pediatric Urologic Oncology: Renal and Adrenal, 3559**

Michael L. Ritchey, MD, and Robert C. Shamberger, MD

- 156 Pediatric Urologic Oncology: Bladder and Testis, 3582**

Fernando A. Ferrer, MD

Index, I1

VIDEOS

Importance of Survey Scans

Chapter 3, Urinary Tract Imaging: Basic Principles of Urologic Ultrasonography

Bruce R. Gilbert



Ureteroscopy and Retrograde Ureteral Access

Chapter 7, Principles of Urologic Endoscopy

Ben H. Chew
John D. Denstedt



“Eye-of-the-Needle” Fluoroscopically Guided Antegrade Access into the Upper Urinary Tract Collecting System

Chapter 8, Percutaneous Approaches to the Upper Urinary Tract Collecting System

J. Stuart Wolf, Jr.



Glomerulations

Chapter 14, Bladder Pain Syndrome (Interstitial Cystitis) and Related Disorders

Arndt van Ophoven
Tomohiro Ueda



Hunner Ulcer

Chapter 14, Bladder Pain Syndrome (Interstitial Cystitis) and Related Disorders

Arndt van Ophoven
Tomohiro Ueda



General Preparation for Vasovasostomy

Chapter 25, Surgical Management of Male Infertility

Marc Goldstein



Surgical Techniques for Vasovasostomy

Chapter 25, Surgical Management of Male Infertility

Marc Goldstein



Microsurgical Vasovasostomy (Microdot Suture Placements)

Chapter 25, Surgical Management of Male Infertility

Marc Goldstein



General Preparation for Vasoepididymostomy

Chapter 25, Surgical Management of Male Infertility

Marc Goldstein



Preparation for Anastomosis in Vasoepididymostomy

Chapter 25, Surgical Management of Male Infertility

Marc Goldstein



Varicocelelectomy

Chapter 25, Surgical Management of Male Infertility

Marc Goldstein



Vasography

Chapter 25, Surgical Management of Male Infertility

Marc Goldstein



Vasography and Transurethral Resection of the Ejaculatory Ducts

Chapter 25, Surgical Management of Male Infertility

Marc Goldstein



Prosthetic Surgery for Erectile Dysfunction

Chapter 30, Surgery for Erectile Dysfunction

Drogo K. Montague



Implantation of AMS 700 LGX Inflatable Penile Prosthesis

Chapter 30, Surgery for Erectile Dysfunction

Drogo K. Montague



Reconstruction for Peyronie Disease: Incision and Grafting

Chapter 31, Diagnosis and Management of Peyronie Disease

Gerald H. Jordan



Interaortal Caval Region

Chapter 33, Surgical, Radiographic, and Endoscopic Anatomy of the Retroperitoneum

James Kyle Anderson



Right Retroperitoneum

Chapter 33, Surgical, Radiographic, and Endoscopic Anatomy of the Retroperitoneum

James Kyle Anderson



Left Lumbar Vein

Chapter 33, Surgical, Radiographic, and Endoscopic Anatomy of the Retroperitoneum

James Kyle Anderson



Lumbar Artery

Chapter 33, Surgical, Radiographic, and Endoscopic Anatomy of the Retroperitoneum

James Kyle Anderson



Retroperitoneal Lymph Node Dissection: The Split and Roll Technique

Chapter 35, Surgery of Testicular Tumors

Kevin R. Rice

Clint K. Cary

Timothy A. Masterson

Richard S. Foster



Laparoscopic Retroperitoneal Lymph Node Dissection: Patient 1

Chapter 36, Laparoscopic and Robotic-Assisted Retroperitoneal Lymphadenectomy for Testicular Tumors

Frederico R. Romero

Soroush Rais-Bahrami

Louis R. Kavoussi



Laparoscopic Retroperitoneal Lymph Node Dissection: Patient 2

Chapter 36, Laparoscopic and Robotic-Assisted Retroperitoneal Lymphadenectomy for Testicular Tumors

Sylvia Montag

Soroush Rais-Bahrami

Arvin K. George

Michael J. Schwartz

Louis R. Kavoussi



Total Penectomy

Chapter 38, Tumors of the Urethra

Kenneth W. Angermeier



Inguinofemoral Lymphadenectomy

Chapter 38, Tumors of the Urethra

Kenneth W. Angermeier



Male Total Urethrectomy

Chapter 38, Tumors of the Urethra

Hadley M. Wood

Kenneth W. Angermeier



Left Gonadal Vein

Chapter 42, Surgical, Radiologic, and Endoscopic Anatomy of the Kidney and Ureter

James Kyle Anderson



Left Renal Hilum

Chapter 42, Surgical, Radiologic, and Endoscopic Anatomy of the Kidney and Ureter

James Kyle Anderson



Right Kidney before Dissection

Chapter 42, Surgical, Radiologic, and Endoscopic Anatomy of the Kidney and Ureter

James Kyle Anderson



Left Lower Pole Crossing Vessel

Chapter 42, Surgical, Radiologic, and Endoscopic Anatomy of the Kidney and Ureter

James Kyle Anderson



Uteroscopy and Retrograde Ureteral Access

Chapter 46, Etiology, Pathogenesis, and Management of Renal Failure

Ben H. Chew

John D. Denstedt



Technique of Laparoscopic Live Donor Nephrectomy

Chapter 47, Renal Transplantation

Michael Joseph Conlin

John Maynard Barry



Laparoscopic Live Donor Nephrectomy

Chapter 47, Renal Transplantation

Louis R. Kavoussi



Laparoscopic Pyeloplasty

Chapter 49, Management of Upper Urinary Tract Obstruction

Frederico R. Romero

Soroush Rais-Bahrami

Louis R. Kavoussi



Robotic-Assisted Laparoscopic Pyeloplasty

Chapter 49, Management of Upper Urinary Tract Obstruction

Sutchin R. Patel

Sean P. Hedican



Percutaneous Access to the Kidney in the Management of Calculi

Chapter 54, Surgical Management of Upper Urinary Tract Calculi

Samuel C. Kim

William W. Linmouth

Ramsay L. Kuo

Ryan E. Paterson

Larry C. Munch

James E. Lingeman



Open Partial Nephrectomy

Chapter 60, Open Surgery of the Kidney

Andrew C. Novick



Laparoscopic Partial Nephrectomy

Chapter 61, Laparoscopic and Robotic Surgery of the Kidney

Frederico R. Romero

Soroush Rais-Bahrami

Louis R. Kavoussi



Percutaneous Renal Cryoablation

Chapter 62, Nonsurgical Focal Therapy for Renal Tumors

Arvin K. George

Zhamshid Okhunov

Soroush Rais-Bahrami

Sylvia Montag

Igor Lobko

Louis R. Kavoussi



Left Adrenal Vein

Chapter 64, Surgical and Radiologic Anatomy of the Adrenals

James Kyle Anderson



Right Adrenal Vein

Chapter 64, Surgical and Radiologic Anatomy of the Adrenals

James Kyle Anderson

**Laparoscopic Adrenalectomy**

Chapter 66, Surgery of the Adrenal Glands

Frederico R. Romero

Soroush Rais-Bahrami

Louis R. Kavoussi

**Urothelial Cells Responding to Putative Neurotransmitters**

Chapter 69, Physiology and Pharmacology of the Bladder and Urethra

Toby C. Chai

Lori A. Birder

**Actinomyosin Cross-Bridge Cycling**

Chapter 69, Physiology and Pharmacology of the Bladder and Urethra

Toby C. Chai

Lori A. Birder

**Digital Imaging Microscopy of a Muscle Myocyte**

Chapter 69, Physiology and Pharmacology of the Bladder and Urethra

Toby C. Chai

Lori A. Birder

**Calcium Spark Development**

Chapter 69, Physiology and Pharmacology of the Bladder and Urethra

Toby C. Chai

Lori A. Birder

**Discussion of Normal Lower Urinary Tract Function**

Chapter 71, Evaluation and Management of Women with Urinary Incontinence and Pelvic Prolapse

Live Patient Interview

Chapter 71, Evaluation and Management of Women with Urinary Incontinence and Pelvic Prolapse

Case Study of a Patient with Mixed Urinary Incontinence

Chapter 71, Evaluation and Management of Women with Urinary Incontinence and Pelvic Prolapse

Examination of a Patient with Significant Anterior Vaginal Wall Prolapse

Chapter 71, Evaluation and Management of Women with Urinary Incontinence and Pelvic Prolapse

Case Study of a Patient with Symptomatic Prolapse and Incontinence

Chapter 71, Evaluation and Management of Women with Urinary Incontinence and Pelvic Prolapse

Demonstration of “Eyeball” Filling Study in a Patient with Incontinence and Prolapse

Chapter 71, Evaluation and Management of Women with Urinary Incontinence and Pelvic Prolapse

Q-tip Test in a Patient with Minimal Urethral Mobility

Chapter 71, Evaluation and Management of Women with Urinary Incontinence and Pelvic Prolapse

Overview of Specific Urodynamic Studies

Chapter 73, Urodynamic and Video-Urodynamic Evaluation of the Lower Urinary Tract

The Pelvic Organ Prolapse Quantification (POPQ) System

Chapter 74, Urinary Incontinence and Pelvic Prolapse: Epidemiology and Pathophysiology

Jennifer T. Anger

Gary E. Lemack

**Sacral Nerve Stimulation**

Chapter 81, Electrical Stimulation and Neuromodulation in Storage and Emptying Failure

Courtenay Kathryn Moore

Sandip P. Vasavada

Raymond R. Rackley

**Afferent Nerve Stimulation**

Chapter 81, Electrical Stimulation and Neuromodulation in Storage and Emptying Failure

Courtenay Kathryn Moore

Sandip P. Vasavada

Raymond R. Rackley

**Percutaneous Tibial Nerve Stimulation**

Chapter 81, Electrical Stimulation and Neuromodulation in Storage and Emptying Failure

Raymond R. Rackley

Sandip P. Vasavada

**Transvaginal Hysterectomy for Prolapse**

Chapter 83, Vaginal and Abdominal Reconstructive Surgery for Pelvic Organ Prolapse

Shlomo Raz

Larissa Rodriguez

**Transvaginal Enterocele and Vaginal Vault Prolapse Repair**

Chapter 83, Vaginal and Abdominal Reconstructive Surgery for Pelvic Organ Prolapse

Shlomo Raz

Larissa Rodriguez

**Transvaginal Repair of Posterior Vaginal Wall Prolapse**

Chapter 83, Vaginal and Abdominal Reconstructive Surgery for Pelvic Organ Prolapse

Shlomo Raz

Larissa Rodriguez

**Cystocele Repair**

Chapter 83, Vaginal and Abdominal Reconstructive Surgery for Pelvic Organ Prolapse

Shlomo Raz

Larissa Rodriguez

**Sling Repair with Distal Urethral Prolene**

Chapter 84, Slings: Autologous, Biologic, Synthetic, and Midurethral

Shlomo Raz

Larissa Rodriguez

**Rectus Fascia Pubovaginal Sling Procedure**

Chapter 84, Slings: Autologous, Biologic, Synthetic, and Midurethral

SPARC Procedure

Chapter 84, Slings: Autologous, Biologic, Synthetic, and Midurethral

Transobturator Sling: Outside-In Technique (MONARC)

Chapter 84, Slings: Autologous, Biologic, Synthetic, and Midurethral

MiniArc Single-Incision Sling System

Chapter 84, Slings: Autologous, Biologic, Synthetic, and Midurethral

Sling Removal

Chapter 85, Complications Related to the Use of Mesh and Their Repair

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Mesh Removal

Chapter 85, Complications Related to the Use of Mesh and Their Repair

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Cystoscopic Injection of Urethral Bulking Agent (Coaptite)

Chapter 86, Injection Therapy for Urinary Incontinence

Robotic-Assisted Laparoscopic Repair of Complex Vesicovaginal Fistula in a Patient with Failed Open Surgical and Vaginal Repair

Chapter 89, Urinary Tract Fistulae

Ashok K. Hemal

Gopal H. Badlani

Martius Flap

Chapter 89, Urinary Tract Fistulae

Shlomo Raz

Larissa Rodriguez

Transvaginal Repair of a Vesicovaginal Fistula Using a Peritoneal Flap

Chapter 89, Urinary Tract Fistulae

Shlomo Raz

Larissa Rodriguez

Transvaginal Bladder Neck Closure with Posterior Urethral Flap

Chapter 89, Urinary Tract Fistulae

Brett D. Lebed

J. Nathaniel Hamilton

Eric S. Rovner

Bladder Diverticulectomy

Chapter 90, Bladder and Female Urethral Diverticula

Brett D. Lebed

Eric S. Rovner

Urethral Diverticulectomy

Chapter 90, Bladder and Female Urethral Diverticula

Diverticula

Eric S. Rovner

Surgical Treatment of Male Sphincteric Urinary Incontinence: The Male Perineal Sling and Artificial Urinary Sphincter

Chapter 91, Surgical Procedures for Sphincteric Incontinence in the Male: The Artificial Urinary Sphincter and Perineal Sling Procedures

Chapter 91, Surgical Procedures for Sphincteric Incontinence in the Male: The Artificial Urinary Sphincter and Perineal Sling Procedures

David R. Staskin

Craig V. Comitor

Male Sling

Chapter 91, Surgical Procedures for Sphincteric Incontinence in the Male: The Artificial Urinary Sphincter and Perineal Sling Procedures

Chapter 91, Surgical Procedures for Sphincteric Incontinence in the Male: The Artificial Urinary Sphincter and Perineal Sling Procedures

Hunter Wessells

Radical Cystectomy in the Male

Chapter 95, Transurethral and Open Surgery for Bladder Cancer

Peter Nieh

Fray Marshall

Radical Cystectomy in the Female

Chapter 95, Transurethral and Open Surgery for Bladder Cancer

Peter Nieh

Fray Marshall

Robotic Cystectomy

Chapter 96, Robotic and Laparoscopic Bladder Surgery

Lee Richstone

Bladder Reconstruction

Chapter 98, Cutaneous Continent Urinary Diversion

Mitchell C. Benson

T-Pouch Ileal Neobladder

Chapter 99, Orthotopic Urinary Diversion

Eila C. Skinner

Donald G. Skinner

Hugh B. Perkin

The Modified Studer Ileal Neobladder

Chapter 99, Orthotopic Urinary Diversion

Siamak Daneshmand

Penile Replantation

Chapter 101, Genital and Lower Urinary Tract Trauma

Lee C. Zhao

Allen F. Morey

Removal of Metal Ring Constricting Penis and Scrotum

Chapter 101, Genital and Lower Urinary Tract Trauma

Trauma

Daniel D. Dugi III

Allen F. Morey

Holmium Laser Enucleation of the Prostate (HoLEP)

Chapter 105, Minimally Invasive and Endoscopic Management of Benign Prostatic Hyperplasia

Management of Benign Prostatic Hyperplasia

Mitra R. de Cógáin

Amy E. Krambeck

Open Prostatectomy

Chapter 106, Simple Prostatectomy: Open and Robot-Assisted Laparoscopic Approaches

Chapter 106, Simple Prostatectomy: Open and Robot-Assisted Laparoscopic Approaches

Misop Han

Robot-Assisted Laparoscopic Simple Prostatectomy: Technique and Outcomes

Chapter 106, Simple Prostatectomy: Open and Robot-Assisted Laparoscopic Approaches

Chapter 106, Simple Prostatectomy: Open and Robot-Assisted Laparoscopic Approaches

Sung-Wood Park

Gautam Jayram

Mark Ball

Petra Szima-Cotter

Mohamad E. Allaf

Misop Han



Images from a Transrectal Prostate Biopsy

Chapter 109, Prostate Biopsy: Techniques and Imaging

Leonard G. Gomella

Ethan J. Halpern

Edouard J. Trabulsi

**Ultrasonography and Biopsy of the Prostate**

Chapter 109, Prostate Biopsy: Techniques and Imaging

Daniel D. Sackett

Ethan J. Halpern

Steve Dong

Leonard G. Gomella

Edouard J. Trabulsi

**Incision in the Endopelvic Fascia and Division of Puboprostatic Ligaments**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**Control of the Dorsal Vein Complex**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**Division of the Urethra and Placement of the Urethral Sutures**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**Division of the Posterior Striated Sphincter**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**Preservation of the Neurovascular Bundle**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**High Release of the Neurovascular Bundle**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**Use of the Babcock Clamp during Release of the Neurovascular Bundle**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**Wide Excision of the Neurovascular Bundle**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**Reconstruction of the Bladder Neck and Vesicourethral Anastomosis**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**Use of the Babcock Clamp during Vesicourethral Anastomosis**

Chapter 114, Open Radical Prostatectomy

Patrick C. Walsh

**Operating Room Setup**

Chapter 115, Laparoscopic and Robotic-Assisted Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su

Jason P. Joseph

**Vas and Seminal Vesicle Dissection**

Chapter 115, Laparoscopic and Robotic-Assisted Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su

Jason P. Joseph

**Posterior Dissection**

Chapter 115, Laparoscopic and Robotic-Assisted Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su

Jason P. Joseph

**Entering Retropubic Space**

Chapter 115, Laparoscopic and Robotic-Assisted Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su

Jason P. Joseph

**Endopelvic Fascia and Puboprostatics**

Chapter 115, Laparoscopic and Robotic-Assisted Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su

Jason P. Joseph

**Dorsal Venous Complex Ligation**

Chapter 115, Laparoscopic and Robotic-Assisted Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su

Jason P. Joseph

**Anterior Bladder Neck Transection**

Chapter 115, Laparoscopic and Robotic-Assisted Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su

Jason P. Joseph

**Posterior Bladder Neck Transection**

Chapter 115, Laparoscopic and Robotic-Assisted Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su

Jason P. Joseph

**Bladder Neck Dissection: Anterior Approach**

Chapter 115, Laparoscopic and Robotic-Assisted Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su

Jason P. Joseph



Neurovascular Bundle Dissection

Chapter 115, Laparoscopic and Robotic-Assisted
Radical Prostatectomy and Pelvic
Lymphadenectomy
Li-Ming Su
Jason P. Joseph

**Division of Dorsal Venous Complex and Apical Dissection**

Chapter 115, Laparoscopic and Robotic-Assisted
Radical Prostatectomy and Pelvic
Lymphadenectomy
Li-Ming Su
Jason P. Joseph

**Pelvic Lymph Node Dissection**

Chapter 115, Laparoscopic and Robotic-Assisted
Radical Prostatectomy and Pelvic
Lymphadenectomy
Li-Ming Su
Jason P. Joseph

**Entrapment of Prostate and Lymph Nodes**

Chapter 115, Laparoscopic and Robotic-Assisted
Radical Prostatectomy and Pelvic
Lymphadenectomy
Li-Ming Su
Jason P. Joseph

**Posterior Reconstruction**

Chapter 115, Laparoscopic and Robotic-Assisted
Radical Prostatectomy and Pelvic
Lymphadenectomy
Li-Ming Su
Jason P. Joseph

**Vesicourethral Anastomosis**

Chapter 115, Laparoscopic and Robotic-Assisted
Radical Prostatectomy and Pelvic
Lymphadenectomy
Li-Ming Su
Jason P. Joseph

**Extraction of Specimen**

Chapter 115, Laparoscopic and Robotic-Assisted
Radical Prostatectomy and Pelvic
Lymphadenectomy
Li-Ming Su
Jason P. Joseph

**Female Genital Examination**

Chapter 125, Urologic Evaluation of the Child
Douglas A. Canning
Sarah M. Lambert

**Laparoscopic Nephrectomy in Infants and Children**

Chapter 131, Renal Dysgenesis and Cystic
Disease of the Kidney
Steven G. Docimo

**Open Pyeloplasty**

Chapter 133, Surgery of the Ureter in Children
L. Henning Olsen

**Robotic-Assisted Pyeloplasty with the Retroperitoneal Approach**

Chapter 133, Surgery of the Ureter in Children
L. Henning Olsen

**Implanting Catheterizable Channel into Bladder**

Chapter 145, Urinary Tract Reconstruction in
Children
John C. Thomas
Mark C. Adams

**Catheterizable Channel (Monti)**

Chapter 145, Urinary Tract Reconstruction in
Children
John C. Thomas
Mark C. Adams

**Laparoscopic-Assisted MACE in Children**

Chapter 145, Urinary Tract Reconstruction in
Children
Steven G. Docimo

**Hypospadias Distal Tip**

Chapter 147, Hypospadias
Warren T. Snodgrass

**Hypospadias Foreskin Reconstruction**

Chapter 147, Hypospadias
Warren T. Snodgrass

**Hypospadias Proximal Tip**

Chapter 147, Hypospadias
Warren T. Snodgrass

**Hypospadias Staged Buccal Graft**

Chapter 147, Hypospadias
Warren T. Snodgrass

**Right Laparoscopic Orchiopexy in a 6-Month-Old Boy with an Intra-Abdominal Testis**

Chapter 148, Etiology, Diagnosis, and
Management of the Undescended Testis
Jennifer A. Hagerty
Julia Spencer Barthold

**Laparoscopic Fowler-Stephens Orchiopexy**

Chapter 148, Etiology, Diagnosis, and
Management of the Undescended Testis
Mark Chang
Israel Franco

**Laparoscopic Creation of a Sigmoid Neovagina**

Chapter 151, Surgical Management of Disorders
of Sex Development and Cloacal and Anorectal
Malformations
Robert Stein
Steven G. Docimo



1

Evaluation of the Urologic Patient: History, Physical Examination, and Urinalysis

Glenn S. Gerber, MD, and Charles B. Brendler, MD

History

Physical Examination

Urinalysis

Summary

Urologists have a unique position in medicine because their patients encompass all age groups, including prenatal, pediatric, adolescent, adult, and geriatric. Because there is no medical subspecialist with similar interests, **the urologist has the ability to make the initial evaluation and diagnosis and to provide medical and surgical therapy for all diseases of the genitourinary (GU) system.** Historically, the diagnostic armamentarium included urinalysis, endoscopy, and intravenous (IV) pyelography. Recent advances in ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and endourology have expanded our diagnostic capabilities. Despite these advances, however, the basic approach to the patient is still dependent on taking a complete history, executing a thorough physical examination, and performing a urinalysis. These basics dictate and guide the subsequent diagnostic evaluation.

HISTORY

Overview

The medical history is the cornerstone of the evaluation of the urologic patient, and a well-taken history will frequently elucidate the probable diagnosis. However, many pitfalls can inhibit the urologist from obtaining an accurate history. The patient may be unable to describe or communicate symptoms because of anxiety, language barrier, or educational background. Therefore the urologist must be a detective and lead the patient through detailed and appropriate questioning to obtain accurate information. There are practical considerations in the art of history-taking that can help to alleviate some of these difficulties. In the initial meeting, an attempt should be made to help the patient feel comfortable. During this time, the physician should project a calm, caring, and competent image that can help foster two-way communication. Impaired hearing, mental capacity, and facility with English can be assessed promptly. These difficulties are frequently overcome by having a family member present during the interview or, alternatively, by having an interpreter present.

Patients need to have sufficient time to express their problems and the reasons for seeking urologic care; the physician, however, should focus the discussion to make it as productive and informative as possible. Direct questioning can then proceed logically. The physician needs to listen carefully without distractions to obtain and interpret the clinical information provided by the patient. **A complete history can be divided into the chief complaint and history of the present illness, the patient's past medical**

history, and a family history. Each segment can provide significant positive and negative findings that will contribute to the overall evaluation and treatment of the patient.

Chief Complaint and Present Illness

Most urologic patients identify their symptoms as arising from the urinary tract and frequently present to the urologist for the initial evaluation. For this reason, the urologist frequently has the opportunity to act as both the primary physician and the specialist. The chief complaint must be clearly defined because it provides the initial information and clues to begin formulating the differential diagnosis. Most importantly, **the chief complaint is a constant reminder to the urologist as to why the patient initially sought care.** This issue must be addressed even if subsequent evaluation reveals a more serious or significant condition that requires more urgent attention. In our personal experience, a young woman presented with a chief complaint of recurrent urinary tract infections (UTIs). In the course of her evaluation, she was found to have a right adrenal mass. We subsequently focused on this problem and performed a right adrenalectomy for a benign cortical adenoma. We forgot about the woman's original symptoms until she presented for her subsequent postoperative examination. She reminded us of her original symptoms at that time, and subsequent evaluation revealed that she had a nylon suture that had eroded into the anterior wall of her bladder from a previous abdominal vesicourethropepy performed 2 years earlier for stress urinary incontinence. Her UTIs resolved after surgical removal of the suture.

In obtaining the history of the present illness, **the duration, severity, chronicity, periodicity, and degree of disability are important considerations.** The patient's symptoms need to be clarified for details and quantified for severity. Listed next are a variety of typical initial complaints. Specific questions that focus on the differential diagnosis are provided.

Pain

Pain arising from the GU tract may be quite severe and is usually associated with either urinary tract obstruction or inflammation. Urinary calculi cause severe pain when they obstruct the upper urinary tract. Conversely, large, nonobstructing stones may be totally asymptomatic. Thus a 2-mm-diameter stone lodged at the ureterovesical junction may cause excruciating pain, whereas a large staghorn calculus in the renal pelvis or a bladder stone may be totally asymptomatic. Urinary retention from prostatic

obstruction is also quite painful, but the diagnosis is usually obvious to the patient.

Inflammation of the GU tract is most severe when it involves the parenchyma of a GU organ. This is due to edema and distention of the capsule surrounding the organ. Thus pyelonephritis, prostatitis, and epididymitis are typically quite painful. Inflammation of the mucosa of a hollow viscus such as the bladder or urethra usually produces discomfort, but the pain is not nearly as severe.

Tumors in the GU tract usually do not cause pain unless they produce obstruction or extend beyond the primary organ to involve adjacent nerves. Thus pain associated with GU malignancies is usually a late manifestation and a sign of advanced disease.

Renal Pain. Pain of renal origin is usually located in the ipsilateral costovertebral angle just lateral to the sacrospinalis muscle and beneath the 12th rib. Pain is usually caused by acute distention of the renal capsule, generally from inflammation or obstruction. The pain may radiate across the flank anteriorly toward the upper abdomen and umbilicus and may be referred to the testis or labium. A corollary to this observation is that renal or retroperitoneal disease should be considered in the differential diagnosis of any man who complains of testicular discomfort but has a normal scrotal examination. Pain due to inflammation is usually steady, whereas pain due to obstruction fluctuates in intensity. Thus the pain produced by ureteral obstruction is typically colicky in nature and intensifies with ureteral peristalsis, at which time the pressure in the renal pelvis rises as the ureter contracts in an attempt to force urine past the point of obstruction.

Pain of renal origin may be associated with gastrointestinal symptoms because of reflex stimulation of the celiac ganglion and because of the proximity of adjacent organs (liver, pancreas, duodenum, gallbladder, and colon). Thus renal pain may be confused with pain of intraperitoneal origin; it can usually be distinguished, however, by a careful history and physical examination. Pain that is due to a perforated duodenal ulcer or pancreatitis may radiate into the back, but the site of greatest pain and tenderness is in the epigastrium. Pain of intraperitoneal origin is seldom colicky, as with obstructive renal pain. Furthermore, pain of intraperitoneal origin frequently radiates into the shoulder because of irritation of the diaphragm and phrenic nerve; this does not occur with renal pain. Typically, patients with intraperitoneal pathology prefer to lie motionless to minimize pain, whereas patients with renal pain usually are more comfortable moving around and holding the flank.

Renal pain may also be confused with pain resulting from irritation of the costal nerves, most commonly T10-T12. Such pain has a similar distribution from the costovertebral angle across the flank toward the umbilicus. However, the pain is not colicky in nature. Furthermore, the intensity of radicular pain may be altered by changing position; this is not the case with renal pain.

Ureteral Pain. Ureteral pain is usually acute and secondary to obstruction. The pain results from acute distention of the ureter and by hyperperistalsis and spasm of the smooth muscle of the ureter as it attempts to relieve the obstruction, usually produced by a stone or blood clot. The site of ureteral obstruction can often be determined by the location of the referred pain. With obstruction of the midureter, pain on the right side is referred to the right lower quadrant of the abdomen (McBurney point) and thus may simulate appendicitis; pain on the left side is referred over the left lower quadrant and resembles diverticulitis. Also, the pain may be referred to the scrotum in the male or the labium in the female. Lower ureteral obstruction frequently produces symptoms of vesical irritability, including frequency, urgency, and suprapubic discomfort that may radiate along the urethra in men to the tip of the penis. Often, by taking a careful history, the astute clinician can predict the location of the obstruction. Ureteral pathology that arises slowly or produces only mild obstruction rarely causes pain. Therefore ureteral tumors and stones that cause minimal obstruction are seldom painful.

Vesical Pain. Vesical pain is usually produced either by overdistention of the bladder as a result of acute urinary retention or by inflammation. **Constant suprapubic pain that is unrelated to**

urinary retention is seldom of urologic origin. Furthermore, patients with slowly progressive urinary obstruction and bladder distention (e.g., diabetics with a flaccid neurogenic bladder) frequently have no pain at all despite residual urine volumes over 1 L.

Inflammatory conditions of the bladder usually produce intermittent suprapubic discomfort. Thus the pain in conditions such as bacterial cystitis or interstitial cystitis is usually most severe when the bladder is full and is relieved at least partially by voiding. Patients with cystitis sometimes experience sharp, stabbing suprapubic pain at the end of micturition, and this is termed *strangury*. Furthermore, patients with cystitis frequently experience pain referred to the distal urethra that is associated with irritative voiding symptoms such as urinary frequency and dysuria.

Prostatic Pain. Prostatic pain is usually secondary to inflammation with secondary edema and distention of the prostatic capsule. Pain of prostatic origin is poorly localized, and the patient may complain of lower abdominal, inguinal, perineal, lumbosacral, penile, and/or rectal pain. Prostatic pain is frequently associated with irritative urinary symptoms such as frequency and dysuria, and, in severe cases, marked prostatic edema may produce acute urinary retention.

Penile Pain. Pain in the flaccid penis is usually secondary to inflammation in the bladder or urethra, with referred pain that is experienced maximally at the urethral meatus. Alternatively, penile pain may be produced by *paraphimosis*, a condition in which the uncircumcised penile foreskin is trapped behind the glans penis, resulting in venous obstruction and painful engorgement of the glans penis (see later). Pain in the erect penis is usually due to Peyronie disease or priapism (see later).

Testicular Pain. Scrotal pain may be either primary or referred. **Primary pain arises from within the scrotum and is usually secondary to acute epididymitis or torsion of the testis or testicular appendices.** Because of the edema and pain associated with both acute epididymitis and testicular torsion, it is frequently difficult to distinguish these two conditions. Alternatively, scrotal pain may result from inflammation of the scrotal wall itself. This may result from a simple infected hair follicle or sebaceous cyst, but it may also be secondary to Fournier gangrene, a severe, necrotizing infection arising in the scrotum that can rapidly progress and be fatal unless promptly recognized and treated.

Chronic scrotal pain is usually related to noninflammatory conditions such as a hydrocele or a varicocele, and the pain is generally characterized as a dull, heavy sensation that does not radiate. Because the testes arise embryologically in close proximity to the kidneys, pain arising in the kidneys or retroperitoneum may be referred to the testes. Similarly, the dull pain associated with an inguinal hernia may be referred to the scrotum.

Hematuria

Hematuria is the presence of blood in the urine; **greater than three red blood cells (RBCs) per high-power microscopic field (HPF) is significant.** Patients with gross hematuria are usually frightened by the sudden onset of blood in the urine and frequently present to the emergency department for evaluation, fearing that they may be bleeding excessively. Hematuria of any degree should never be ignored and, in adults, should be regarded as a symptom of urologic malignancy until proved otherwise. In evaluating hematuria, several questions should always be asked, and the answers will enable the urologist to target the subsequent diagnostic evaluation efficiently:

Is the hematuria gross or microscopic?

At what time during urination does the hematuria occur (beginning or end of stream or during entire stream)?

Is the hematuria associated with pain?

Is the patient passing clots?

If the patient is passing clots, do the clots have a specific shape?

Gross versus Microscopic Hematuria. The significance of gross versus microscopic hematuria is simply that the chances of

identifying significant pathology increase with the degree of hematuria. Thus patients with gross hematuria usually have identifiable underlying pathology, whereas it is quite common for patients with minimal degrees of microscopic hematuria to have a negative urologic evaluation.

Timing of Hematuria. The timing of hematuria during urination frequently indicates the site of origin. **Initial hematuria usually arises from the urethra;** it occurs least commonly and is usually secondary to inflammation. Total hematuria is most common and indicates that the bleeding is most likely coming from the bladder or upper urinary tracts. Terminal hematuria occurs at the end of micturition and is usually secondary to inflammation in the area of the bladder neck or prostatic urethra. It occurs at the end of micturition as the bladder neck contracts, squeezing out the last amount of urine.

Association with Pain. Hematuria, although frightening, is usually not painful unless it is associated with inflammation or obstruction. Thus patients with cystitis and secondary hematuria may experience painful urinary irritative symptoms, but the pain is usually not worsened with passage of clots. More commonly, **pain in association with hematuria usually results from upper urinary tract hematuria with obstruction of the ureters with clots.** Passage of these clots may be associated with severe, colicky flank pain similar to that produced by a ureteral calculus, and this helps identify the source of the hematuria.

The American Urological Association (AUA) has published guidelines regarding patients with asymptomatic microhematuria (AMH), which is defined as three or more RBCs per HPF in the absence of an obvious benign cause. A determination of AMH should be based on microscopic, not dipstick, examination of the urine. Careful history, physical examination, and laboratory examination should be done to rule out benign causes of AMH, such as infection, medical renal disease, and others. Once these causes are ruled out, urologic evaluation that includes a measurement of renal function is recommended. If factors such as dysmorphic RBCs, proteinuria, casts, or renal insufficiency are present, nephrologic workup should be considered in addition to the urologic evaluation. AMH that occurs in patients who are anticoagulated still warrants urologic evaluation.

The evaluation of patients over 35 years of age with AMH should include cystoscopy, which is optional in younger patients. However, all patients should have cystoscopy if risk factors such as irritative voiding symptoms, tobacco use, or chemical exposures are present. Radiologic evaluation should be performed in the initial evaluation, and the procedure of choice is multiphasic CT urography with and without IV contrast. Magnetic resonance urography, with or without IV contrast, is an acceptable alternative in patients who cannot undergo multiphasic CT scan. In cases where collecting system detail is needed, noncontrast CT, MRI, or renal ultrasonography with retrograde pyelograms is an acceptable alternative if there is a contraindication to the use of IV contrast.

Among the modalities not recommended in the routine evaluation of patients with AMH are urine cytology, urine markers, and blue light cystoscopy. However, cytology may be useful in those patients with persistent AMH following a negative workup or those with other risk factors for carcinoma in situ, such as irritative voiding symptoms, use of tobacco, or chemical exposures. For patients with persistent AMH, yearly urinalysis should be performed. The presence of two consecutive annual negative urinalyses indicates that no further urinalyses are needed for this purpose. For patients with persistent or recurrent AMH, repeat evaluation within 3 to 5 years should be considered.

Presence of Clots. The presence of clots usually indicates a more significant degree of hematuria, and, accordingly, the probability of identifying significant urologic pathology increases.

Shape of Clots. Usually, if the patient is passing clots, they are amorphous and of bladder or prostatic urethral origin. However, **the presence of vermiform (wormlike) clots, particularly if associated with flank pain, identifies the hematuria as coming from the upper urinary tract** with formation of vermiform clots within the ureter.

It cannot be emphasized strongly enough that **hematuria, particularly in the adult, should be regarded as a symptom of malignancy until proved otherwise and demands immediate urologic examination.** In a patient who presents with gross hematuria, cystoscopy should be performed as soon as possible because frequently the source of bleeding can be readily identified. Cystoscopy will determine whether the hematuria is coming from the urethra, bladder, or upper urinary tract. In patients with gross hematuria secondary to an upper tract source, it is easy to see the jet of red urine pulsing from the involved ureteral orifice.

Although inflammatory conditions may result in hematuria, all patients with hematuria, except perhaps young women with acute bacterial hemorrhagic cystitis, should undergo urologic evaluation. Older women and men who present with hematuria and irritative voiding symptoms may have cystitis secondary to infection arising in a necrotic bladder tumor or, more commonly, flat carcinoma in situ of the bladder. **The most common cause of gross hematuria in a patient older than age 50 years is bladder cancer.**

Lower Urinary Tract Symptoms

Irritative Symptoms. *Frequency* is one of the most common urologic symptoms. The normal adult voids five or six times per day, with a volume of approximately 300 mL with each void. **Urinary frequency is due to either increased urinary output (polyuria) or decreased bladder capacity.** If voiding is noted to occur in large amounts frequently, the patient has polyuria and should be evaluated for diabetes mellitus, diabetes insipidus, or excessive fluid ingestion. Causes of decreased bladder capacity include bladder outlet obstruction with decreased compliance, increased residual urine, and/or decreased functional capacity due to irritation, neurogenic bladder with increased sensitivity and decreased compliance, pressure from extrinsic sources, or anxiety. By separating irritative from obstructive symptoms, the astute clinician should be able to arrive at a proper differential diagnosis.

Nocturia is nocturnal frequency. Normally, adults arise no more than twice at night to void. As with frequency, nocturia may be secondary to increased urine output or decreased bladder capacity. **Frequency during the day without nocturia is usually of psychogenic origin and related to anxiety.** Nocturia without frequency may occur in the patient with congestive heart failure and peripheral edema in whom the intravascular volume and urine output increase when the patient is supine. Renal concentrating ability decreases with age; therefore urine production in the geriatric patient is increased at night, when renal blood flow is increased as a result of recumbency. In general, nocturia may be attributed to nocturnal polyuria (nocturnal urine overproduction) and/or diminished nocturnal bladder capacity (Weiss and Blaivas, 2000). Nocturia may also occur in people who drink large amounts of liquid in the evening, particularly caffeinated and alcoholic beverages, which have strong diuretic effects. In the absence of these factors, nocturia signifies a problem with bladder function secondary to urinary outlet obstruction and/or decreased bladder compliance.

Dysuria is painful urination that is usually caused by inflammation. **This pain is usually not felt over the bladder but is commonly referred to the urethral meatus.** Pain occurring at the start of urination may indicate urethral pathology, whereas pain occurring at the end of micturition (strangury) is usually of bladder origin. Dysuria is frequently accompanied by frequency and urgency.

Obstructive Symptoms. *Decreased force of urination* is usually secondary to bladder outlet obstruction and commonly results from benign prostatic hyperplasia (BPH) or a urethral stricture. In fact, except for severe degrees of obstruction, **most patients are unaware of a change in the force and caliber of their urinary stream.** These changes usually occur gradually and go generally unrecognized by most patients. The other obstructive symptoms noted later are more commonly recognized and are usually secondary to bladder outlet obstruction in men due to either BPH or a urethral stricture.

Urinary hesitancy refers to a delay in the start of micturition. Normally, urination begins within a second after relaxing the

urinary sphincter, but it may be delayed in men with bladder outlet obstruction.

Intermittency refers to involuntary start-stopping of the urinary stream. It most commonly results from prostatic obstruction with intermittent occlusion of the urinary stream by the lateral prostatic lobes.

Postvoid dribbling refers to the terminal release of drops of urine at the end of micturition. This is secondary to a small amount of residual urine in either the bulbar or the prostatic urethra that is normally “milked back” into the bladder at the end of micturition (Stephenson and Farrar, 1977). In men with bladder outlet obstruction, this urine escapes into the bulbar urethra and leaks out at the end of micturition. Men will frequently attempt to avoid wetting their clothing by shaking the penis at the end of micturition. In fact, this is ineffective, and the problem is more readily solved by manual compression of the bulbar urethra in the perineum and blotting the urethral meatus with a tissue. Postvoid dribbling is often an early symptom of urethral obstruction related to BPH, but, in itself, seldom necessitates any further treatment.

Straining refers to the use of abdominal musculature to urinate. Normally, it is unnecessary for a man to perform a Valsalva maneuver except at the end of urination. Increased straining during micturition is a symptom of bladder outlet obstruction.

It is important for the urologist to distinguish irritative from obstructive lower urinary tract symptoms. This most frequently occurs in evaluating men with BPH. Although BPH is primarily obstructive, it produces changes in bladder compliance that result in increased irritative symptoms. In fact, men with BPH more commonly present with irritative than obstructive symptoms, and the most common presenting symptom is nocturia. **The urologist must be careful not to attribute irritative symptoms to BPH unless there is documented evidence of obstruction.** In general, lower urinary tract symptoms are nonspecific and may occur secondary to

a wide variety of neurologic conditions, as well as to prostatic enlargement (Lepor and Machi, 1993). In this regard, two important examples are mentioned. Patients with high-grade flat carcinoma in situ of the bladder may present with urinary irritative symptoms. The urologist should be particularly aware of the diagnosis of carcinoma in situ in men who present with irritative symptoms, a history of cigarette smoking, and microscopic hematuria. In our personal experience, we cared for a 54-year-old man who presented with this history and was treated for BPH for 2 years before the diagnosis of bladder cancer was established. Once the correct diagnosis was made, the patient had developed muscle-invasive disease and required a cystectomy for cure.

The second important example is irritative symptoms resulting from neurologic disease such as cerebrovascular accidents, diabetes mellitus, and Parkinson disease. Most neurologic diseases encountered by the urologist are upper motor neuron in etiology and result in a loss of cortical inhibition of voiding with resultant decreased bladder compliance and irritative voiding symptoms. The urologist must be extremely careful to rule out underlying neurologic disease before performing surgery to relieve bladder outlet obstruction. Such surgery not only may fail to relieve the patient's irritative symptoms but also may result in permanent urinary incontinence.

Since its introduction in 1992, the AUA symptom index has been widely used and validated as an important means of assessing men with lower urinary tract symptoms (Barry et al, 1992). The original AUA symptom score is based on the answers to seven questions concerning frequency, nocturia, weak urinary stream, hesitancy, intermittency, incomplete bladder emptying, and urgency. The International Prostate Symptom Score (I-PSS) includes these seven questions, as well as a global quality-of-life question (Table 1-1). The total symptom score ranges from 0 to 35 with scores of 0 to 7, 8 to 19, and 20 to 35 indicating mild, moderate, and severe

TABLE 1-1 International Prostate Symptom Score

SYMPTOM	NOT AT ALL	<1 TIME IN 5	LESS THAN HALF THE TIME	ABOUT HALF THE TIME	MORE THAN HALF THE TIME	ALMOST ALWAYS	YOUR SCORE
1. INCOMPLETE EMPTYING							
Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. FREQUENCY							
Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5	
3. INTERMITTENCY							
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. URGENCY							
Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	

TABLE 1-1 International Prostate Symptom Score—cont'd

SYMPTOM	NOT AT ALL	<1 TIME IN 5	LESS THAN HALF THE TIME	ABOUT HALF THE TIME	MORE THAN HALF THE TIME	ALMOST ALWAYS	YOUR SCORE
5. WEAK STREAM							
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. STRAINING							
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	NONE	1 TIME	2 TIMES	3 TIMES	4 TIMES	≥5 TIMES	
7. NOCTURIA							
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
TOTAL INTERNATIONAL PROSTATE SYMPTOM SCORE							
QUALITY OF LIFE DUE TO URINARY SYMPTOMS	DELIGHTED	PLEASED	MOSTLY SATISFIED	MIXED—ABOUT EQUALLY SATISFIED AND DISSATISFIED	MOSTLY DISSATISFIED	UNHAPPY	TERRIBLE
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

From Cockett A, Aso Y, Denis L. Prostate symptom score and quality of life assessment. In: Cockett ATK, Khoury S, Aso Y, et al, editors. Proceedings of the Second International Consultation on Benign Prostatic Hyperplasia (BPH); 27-30 June 1993; Paris. Channel Island, Jersey: Scientific Communication International; 1994. p. 553-5.

lower urinary tract symptoms, respectively. The I-PSS is a helpful tool both in the clinical management of men with lower urinary tract symptoms and in research studies regarding the medical and surgical treatment of men with voiding dysfunction.

The use of symptom indices has limitations, and it is important for the physician to discuss the patient's responses with him. It has been demonstrated that a grade 6 reading level is necessary to understand the I-PSS, and some patients with neurologic disorders and dementia may also have difficulty completing the symptom score (MacDiarmid et al, 1998). In addition, the symptom score and obstructive and irritative voiding symptoms are nonspecific, and the symptoms may be caused by a variety of conditions other than BPH. Similar symptom scores have been demonstrated to be present in age-matched men and women between 55 and 79 years of age (Lepor and Machi, 1993). Despite these limitations, the I-PSS is a simple adjunct in assessing men with lower urinary tract symptoms and may be used in the initial evaluation of men with lower urinary tract symptoms, as well as in the assessment of treatment response.

Incontinence. Urinary incontinence is the involuntary loss of urine. A careful history of the incontinent patient will often determine the etiology. Urinary incontinence can be subdivided into four categories.

Continuous Incontinence. Continuous incontinence is most commonly due to a urinary tract fistula that bypasses the urethral sphincter. The most common type of fistula that results in urinary incontinence is a vesicovaginal fistula usually secondary to gynecologic surgery, radiation, or obstetric trauma. Less commonly, ureterovaginal fistulae may occur from similar causes.

A second major cause of continuous incontinence is an ectopic ureter that enters either the urethra or the female genital tract. An ectopic ureter usually drains a small, dysplastic upper pole segment of kidney, and the amount of urinary leakage may be quite small. Such patients may void most of their urine normally but have a continuous amount of small urinary leakage that may be misdiagnosed for many years as a chronic vaginal discharge. In our experience, we cared for a 30-year-old woman—who had been misdiagnosed with enuresis in childhood and as having a chronic vaginal discharge in adult life—whose urinary leakage was totally corrected by surgical removal of the dysplastic, upper pole segment of her right kidney. Ectopic ureters never produce urinary incontinence in males because they always enter the bladder neck or prostatic urethra proximal to the external urethral sphincter.

Stress Incontinence. Stress incontinence refers to the sudden leakage of urine with coughing, sneezing, exercise, or other

activities that increase intra-abdominal pressure. During these activities, intra-abdominal pressure rises transiently above urethral resistance, resulting in a sudden, usually small amount of urinary leakage. Stress incontinence is most common in women after childbearing or menopause and is related to a loss of anterior vaginal support and weakening of pelvic tissues. Stress incontinence is also observed in men after prostatic surgery, most commonly radical prostatectomy, in which there may be injury to the external urethral sphincter. Stress urinary incontinence is difficult to manage pharmacologically, and patients with significant stress incontinence are usually best treated surgically.

Urgency Incontinence. Urgency incontinence is the precipitous loss of urine preceded by a strong urge to void. This symptom is commonly observed in patients with cystitis, neurogenic bladder, and advanced bladder outlet obstruction with secondary loss of bladder compliance. It is important to distinguish urgency incontinence from stress incontinence for two reasons. First, **urgency incontinence may result from a secondary underlying pathologic process, which should be identified;** treatment of this primary problem such as infection or bladder outlet obstruction may result in resolution of urgency incontinence. Second, patients with urgency incontinence are usually not amenable to surgical correction but, rather, are more appropriately treated with pharmacologic agents that increase bladder compliance and/or increase urethral resistance.

Overflow Urinary Incontinence. Overflow urinary incontinence, often called *paradoxical incontinence*, is secondary to advanced urinary retention and high residual urine volumes. In these patients, the bladder is chronically distended and never empties completely. Urine may dribble out in small amounts as the bladder overflows. This is particularly likely to occur at night when the patient is less likely to inhibit urinary leakage. **Overflow incontinence has been termed *paradoxical incontinence* because it can often be cured by relief of bladder outlet obstruction.** It is, however, often difficult to make the diagnosis of overflow incontinence by history and physical examination alone, particularly in the obese patient, in whom percussion of the distended bladder may be difficult. Overflow incontinence usually develops over a considerable length of time, and patients may be totally unaware of incomplete bladder emptying. Thus any patient with significant incontinence should undergo measurement of postvoid residual urine.

Enuresis. Enuresis refers to urinary incontinence that occurs during sleep. It occurs normally in children up to 3 years of age but persists in about 15% of children at age 5 and about 1% of children at age 15 (Forsythe and Redmond, 1974). Enuresis must be distinguished from continuous incontinence, which occurs in the day and night and which, in a young girl, usually indicates the presence of an ectopic ureter. All children older than age 6 years with enuresis should undergo a urologic evaluation, although the vast majority will be found to have no significant urologic abnormality.

Sexual Dysfunction

Male sexual dysfunction is frequently used synonymously with *impotence* or erectile dysfunction, although impotence refers specifically to the inability to achieve and maintain an erection adequate for intercourse. Patients presenting with "impotence" should be questioned carefully to rule out other male sexual disorders, including loss of libido, absence of emission, absence of orgasm, and, most commonly, premature ejaculation. It is important to identify the precise problem before proceeding with further evaluation and treatment.

Loss of Libido. Because androgens have a major influence on sexual desire, a decrease in libido may indicate androgen deficiency arising from either pituitary or testicular dysfunction. This can be evaluated directly by measurement of serum testosterone that, if abnormal, should be further evaluated by measurement of serum gonadotropins and prolactin. Because the amount of testosterone required to maintain libido is usually less than that required for full

stimulation of the prostate and seminal vesicles, patients with hypogonadism may also note decreased or absent ejaculation. Conversely, if semen volume is normal, it is unlikely that endocrine factors are responsible for loss of libido. A decrease in libido may also result from depression and a variety of medical illnesses that affect general health and well-being.

Impotence. Impotence refers specifically to the inability to achieve and maintain an erection sufficient for intercourse. A careful history will often determine whether the problem is primarily psychogenic or organic. In men with psychogenic impotence, the condition frequently develops rather quickly secondary to a precipitating event such as marital stress or change or loss of a sexual partner. In men with organic impotence, the condition usually develops more insidiously and frequently can be linked to advancing age or other underlying risk factors.

In evaluating men with impotence, it is important to determine whether the problem exists in all situations. Many men who report impotence may not be able to have intercourse with one partner but will with another. Similarly, it is important to determine whether men are able to achieve normal erections with alternative forms of sexual stimulation (e.g., masturbation, erotic videos). Finally, the patient should be asked whether he ever notes nocturnal or early morning erections. In general, **patients who are able to achieve adequate erections in some situations but not others have primarily psychogenic rather than organic impotence.**

Failure to Ejaculate. A failure to ejaculate may result from several causes: (1) androgen deficiency, (2) sympathetic denervation, (3) pharmacologic agents, and (4) bladder neck and prostatic surgery. Androgen deficiency results in decreased secretions from the prostate and seminal vesicles, causing a reduction or loss of seminal volume. Sympathectomy or extensive retroperitoneal surgery, most notably retroperitoneal lymphadenectomy for testicular cancer, may interfere with autonomic innervation of the prostate and seminal vesicles, resulting in absence of smooth muscle contraction and absence of seminal emission at time of orgasm. Pharmacologic agents, particularly α -adrenergic antagonists, may interfere with bladder neck closure at time of orgasm and result in retrograde ejaculation. Similarly, previous bladder neck or prostatic urethral surgery, most commonly transurethral resection of the prostate, may interfere with bladder neck closure, resulting in retrograde ejaculation. Finally, retrograde ejaculation may develop spontaneously in diabetic men.

Patients who complain of absence of ejaculation should be questioned regarding loss of libido or other symptoms of androgen deficiency, present medications, diabetes, and previous surgery. A careful history will usually determine the cause of this problem.

Absence of Orgasm. Anorgasmia is usually psychogenic or caused by certain medications used to treat psychiatric diseases. Sometimes, however, anorgasmia may be due to decreased penile sensation owing to impaired pudendal nerve function. Most commonly, this occurs in diabetics with peripheral neuropathy. Men who experience anorgasmia in association with decreased penile sensation should undergo vibratory testing of the penis and further neurologic evaluation as indicated.

Premature Ejaculation. Men who complain of premature ejaculation should be questioned carefully because this is obviously a subjective symptom. It is common for men to ejaculate within 2 minutes after initiation of intercourse, and many men who complain of premature ejaculation in actuality have normal sexual function with abnormal sexual expectations. However, there are men with true premature ejaculation who reach orgasm within less than 1 minute after initiation of intercourse. **This problem is almost always psychogenic** and best treated by a clinical psychologist or psychiatrist who specializes in treatment of this problem and other psychological aspects of male sexual dysfunction. With counseling and appropriate modifications in sexual technique, this problem can usually be overcome. Alternatively, treatment with serotonin reuptake inhibitors such as sertraline and fluoxetine has been demonstrated to be helpful in men with premature ejaculation (Murat Basar et al, 1999).

Hemospermia

Hemospermia refers to the presence of blood in the seminal fluid. **It almost always results from nonspecific inflammation of the prostate and/or seminal vesicles and resolves spontaneously, usually within several weeks.** It frequently occurs after a prolonged period of sexual abstinence, and we have observed it several times in men whose wives are in the final weeks of pregnancy. Patients with hemospermia that persists beyond several weeks should undergo further urologic evaluation because, rarely, an underlying etiology will be identified. A genital and rectal examination should be done to exclude the presence of tuberculosis; a prostate-specific antigen (PSA) and a rectal examination done to exclude prostatic carcinoma; and a urinary cytology done to exclude the possibility of transitional cell carcinoma of the prostate. It should be emphasized, however, that hemospermia almost always resolves spontaneously and rarely is associated with any significant urologic pathology.

Pneumaturia

Pneumaturia is the passage of gas in the urine. In patients who have not recently had urinary tract instrumentation or a urethral catheter placed, this is almost always due to a fistula between the intestine and the bladder. **Common causes include diverticulitis, carcinoma of the sigmoid colon, and regional enteritis (Crohn disease).** In rare instances, patients with diabetes mellitus may have gas-forming infections, with carbon dioxide formation from the fermentation of high concentrations of sugar in the urine.

Urethral Discharge

Urethral discharge is the most common symptom of venereal infection. A purulent discharge that is thick, profuse, and yellow to gray is typical of gonococcal urethritis; the discharge in patients with nonspecific urethritis is usually scant and watery. A bloody discharge is suggestive of carcinoma of the urethra.

Fever and Chills

Fever and chills may occur with infection anywhere in the GU tract but are most commonly observed in patients with pyelonephritis, prostatitis, or epididymitis. **When associated with urinary obstruction, fever and chills may portend septicemia and necessitate emergency treatment to relieve obstruction.**

Medical History

The past medical history is extremely important because it frequently provides clues to the patient's current diagnosis. The past medical history should be obtained in an orderly and sequential manner.

Previous Medical Illnesses with Urologic Sequelae

Many diseases may affect the GU system, and it is important to listen to the patient and record previous medical illnesses. **Patients with diabetes mellitus frequently develop autonomic dysfunction that may result in impaired urinary and sexual function.** A previous history of tuberculosis may be important in a patient presenting with impaired renal function, ureteral obstruction, or chronic, unexplained UTIs. Patients with hypertension have an increased risk of sexual dysfunction because they are more likely to have peripheral vascular disease and because many of the medications that are used to treat hypertension frequently cause impotence. Patients with neurologic diseases such as multiple sclerosis are also more likely to develop urinary and sexual dysfunction. In fact, 5% of patients with previously undiagnosed multiple sclerosis present with urinary symptoms as the first manifestation of the disease (Blaivas and Kaplan, 1988). As mentioned earlier, in men with bladder outlet obstruction, it is important to be aware of

preexisting neurologic conditions. Surgical treatment of bladder outlet obstruction in the presence of detrusor hyperreflexia may result in increased urinary incontinence postoperatively. Finally, patients with sickle cell anemia are prone to a number of urologic conditions, including papillary necrosis and erectile dysfunction secondary to recurrent priapism. There are many other diseases with urologic sequelae, and it is important for the urologist to take a careful history in this regard.

Family History

It is similarly important to obtain a detailed family history because many diseases are genetic and/or familial. Examples of genetic diseases include adult polycystic kidney disease, tuberous sclerosis, von Hippel-Lindau disease, renal tubular acidosis, and cystinuria; these are but a few common and well-recognized examples.

In addition to these diseases of known genetic predisposition, there are other conditions in which the precise pattern of inheritance has not been elucidated but that clearly have a familial tendency. It is well known that individuals with a family history of urolithiasis are at increased risk for stone formation. More recently, it has been recognized that **8% to 10% of men with prostate cancer have a familial form of the disease that tends to develop about a decade earlier than the more common type of prostate cancer (Bratt, 2000).** Other familial conditions are mentioned elsewhere in the text, but suffice it to state again that obtaining a careful history of previous illnesses and a family history of urologic disease can be extremely valuable in establishing the correct diagnosis.

Medications

It is similarly important to obtain an accurate and complete list of present medications because many drugs interfere with urinary and sexual function. **For example, most of the antihypertensive medications interfere with erectile function, and changing antihypertensive medications can sometimes improve sexual function.** Similarly, many of the psychotropic agents interfere with emission and orgasm. In our own recent experience, we cared for a man who presented with anorgasmia. He had been to several physicians without improvement in this problem. When we obtained his past medical history, he mentioned that he had been taking a psychotropic agent for transient depression for several years, and his anorgasmia resolved when this no-longer-needed medication was discontinued. The list of medications affecting urinary and sexual function is exhaustive, but, once again, each medication should be recorded and its side effects investigated to be sure that the patient's problem is not drug related. A listing of common medications that may cause urologic side effects is presented in [Table 1-2](#).

Previous Surgical Procedures

It is important to be aware of previous operations, particularly in a patient who may have surgery, because previous operations may make subsequent ones more difficult. If the previous surgery was in a similar anatomic region, it is worthwhile to try to obtain the previous operative report. In our own experience, this small additional effort has been rewarded on numerous occasions by providing a clear explanation of the patient's previous surgery that greatly simplified the subsequent operation. In general, **it is worthwhile to obtain as much information as possible before any intended surgery** because most surprises that occur in the operating room are unhappy ones.

Smoking and Alcohol Use

Cigarette smoking and consumption of alcohol are clearly linked to a number of urologic conditions. **Cigarette smoking is associated with an increased risk of urothelial carcinoma, most notably bladder cancer, and it is also associated with increased peripheral vascular disease and erectile dysfunction.** Chronic alcoholism may result in autonomic and peripheral neuropathy

TABLE 1-2 Drugs Associated with Urologic Side Effects

UROLOGIC SIDE EFFECTS	CLASS OF DRUGS	SPECIFIC EXAMPLES
Decreased libido	Antihypertensives	Hydrochlorothiazide
Erectile dysfunction	Psychotropic drugs	Propranolol Benzodiazepines
Ejaculatory dysfunction	α -Adrenergic antagonists	Prazosin Tamsulosin
	Psychotropic drugs	α -Methyl dopa Phenothiazines Antidepressants
Priapism	Antipsychotics Antidepressants Antihypertensives	Phenothiazines Trazodone Hydralazine Prazosin
Decreased spermatogenesis	Chemotherapeutic agents Drugs with abuse potential	Alkylating agents Marijuana Alcohol Nicotine
	Drugs affecting endocrine function	Antiandrogens Prostaglandins
Incontinence or impaired voiding	Direct smooth muscle stimulants	Histamine Vasopressin
	Others	Furosemide Valproic acid
	Smooth muscle relaxants Striated muscle relaxants	Diazepam Baclofen
Urinary retention or obstructive voiding symptoms	Anticholinergic agents or musculotropic relaxants	Oxybutynin Diazepam Flavoxate
	Calcium channel blockers Antiparkinsonian drugs	Nifedipine Carbidopa Levodopa
	α -Adrenergic agonists	Pseudoephedrine Phenylephrine
	Antihistamines	Loratadine Diphenhydramine
Acute renal failure	Antimicrobials	Aminoglycosides Penicillins Cephalosporins Amphotericin
	Chemotherapeutic drugs Others	Cisplatin Nonsteroidal anti-inflammatory drugs Phenytoin
Gynecomastia	Antihypertensives Cardiac drugs Gastrointestinal drugs	Verapamil Digoxin Cimetidine Metoclopramide
	Psychotropic drugs Tricyclic antidepressants	Phenothiazines Amitriptyline Imipramine

with resultant impaired urinary and sexual function. Chronic alcoholism may also impair hepatic metabolism of estrogens, resulting in decreased serum testosterone, testicular atrophy, and decreased libido.

In addition to the direct urologic effects of cigarette smoking and alcohol consumption, patients who are actively smoking or drinking up to the time of surgery are at increased risk for perioperative complications. Smokers are at increased risk for both pulmonary and cardiac complications. If possible, they should **discontinue smoking at least 8 weeks before surgery to optimize their**

pulmonary function (Warner et al, 1989). If they are unable to do this, they should at least quit smoking for 48 hours before surgery because this will result in a significant improvement in cardiovascular function. Similarly, chronic alcoholics are at increased risk for hepatic toxicity and subsequent coagulation problems postoperatively. Furthermore, alcoholics who continue drinking up to the time of surgery may experience acute alcohol withdrawal during the postoperative period that can be life threatening. Prophylactic administration of lorazepam (Ativan) greatly reduces the potential risk of this significant complication.

Allergies

Finally, medicinal allergies should be questioned because these medications should be avoided in future treatment of the patient. **All medicinal allergies should be marked boldly on the front of the patient's chart** to avoid potential complications from inadvertent exposure to the same medications.

In summary, a careful and thorough medical history including the chief complaint and history of present illness, past medical history, and family history should be obtained for every patient. Unfortunately, time constraints often make it difficult for the physician to spend the necessary time to obtain a full history. A reasonable substitute is to have a trained nurse or other health professional see the patient first. By using a standard history form, much of the information discussed previously can be obtained in a preliminary interview. It then remains for the urologist to only fill in the blanks, have the patient elaborate on potentially relevant aspects of the past medical history, and then perform a complete physical examination.

PHYSICAL EXAMINATION

KEY POINTS

- The urologist can undertake the initial evaluation and establish a diagnosis for almost all patients with diseases of the GU system.
- A complete history and appropriate physical examination is critical in the assessment of urologic patients.
- A complete urinalysis including chemical and microscopic analyses should be performed because this may provide important information critical to the diagnosis and treatment of urologic patients.

A complete and thorough physical examination is an essential component of the evaluation of patients who present with urologic disease. Although it is tempting to become dependent on results of laboratory and radiologic tests, **the physical examination often simplifies the process and allows the urologist to select the most appropriate diagnostic studies.** Along with the history, the physical examination remains a key component of the diagnostic evaluation and should be performed conscientiously.

General Observations

The visual inspection of the patient provides a general overview. The skin should be inspected for evidence of jaundice or pallor. The nutritional status of the patient should be noted. **Cachexia is a frequent sign of malignancy, and obesity may be a sign of underlying endocrinologic abnormalities.** In this instance, one should search for the presence of truncal obesity, a "buffalo hump," and abdominal skin striae, which are stigmata of hyperadrenocorticism. In contrast, debility and hyperpigmentation may be signs of hypoadrenocorticism. Gynecomastia may be a sign of endocrinologic disease and a possible indicator of alcoholism or previous hormonal therapy for prostate cancer. Edema of the genitalia and lower extremities may be associated with cardiac decompensation, renal failure, nephrotic syndrome, or pelvic and/or retroperitoneal lymphatic obstruction. Supraclavicular lymphadenopathy may be seen with any GU neoplasm, most commonly prostate and testis cancer; inguinal lymphadenopathy may occur secondary to carcinoma of the penis or urethra.

Kidneys

The kidneys are fist-sized organs located high in the retroperitoneum bilaterally. In the adult, the kidneys are normally difficult to

palpate because of their position under the diaphragm and ribs with abundant musculature both anteriorly and posteriorly. Because of the position of the liver, the right kidney is somewhat lower than the left. **In children and thin women, it may be possible to palpate the lower pole of the right kidney with deep inspiration.** However, it is usually not possible to palpate either kidney in men, and the left kidney is almost always impalpable unless it is abnormally enlarged.

The best way to palpate the kidneys is with the patient in the supine position. **The kidney is lifted from behind with one hand in the costovertebral angle (Fig. 1-1).** On deep inspiration, the examiner's hand is advanced firmly into the anterior abdomen just below the costal margin. At the point of maximal inspiration, the kidney may be felt as it moves downward with the diaphragm. With each inspiration, the examiner's hand may be advanced deeper into the abdomen. Once again, it is more difficult to palpate kidneys in men because the kidneys tend to move downward less with inspiration and because they are surrounded with thicker muscular layers. In children, it is easier to palpate the kidneys because of decreased body thickness. In neonates, the kidneys can be felt quite easily by palpating the flank between the thumb anteriorly and the fingers over the costovertebral angle posteriorly.

Transillumination of the kidneys may be helpful in children younger than 1 year of age with a palpable flank mass. Such masses are frequently of renal origin. A flashlight or fiberoptic light source is positioned posteriorly against the costovertebral angle. Fluid-filled masses such as cysts or hydronephrosis produce a dull reddish glow in the anterior abdomen. Solid masses such as tumors do not transilluminate. Other diagnostic maneuvers that may be helpful in examining the kidneys are percussion and auscultation. Although renal inflammation may cause pain that is poorly localized, percussion of the costovertebral angle posteriorly more often localizes the pain and tenderness more accurately. Percussion should be done gently because in a patient with significant renal inflammation, this may be quite painful. Auscultation of the upper abdomen during deep inspiration may occasionally reveal a systolic bruit associated with renal artery stenosis or an aneurysm. A bruit may also be detected in association with a large renal arteriovenous fistula.

Every patient with flank pain should also be examined for possible nerve root irritation. The ribs should be palpated carefully to rule out a bone spur or other skeletal abnormality and to determine the point of maximal tenderness. Unlike renal pain, radiculitis usually causes hyperesthesia of the overlying skin innervated by the irritated peripheral nerve. This hypersensitivity can be elicited with a pin or by pinching the skin and fat overlying the involved area. Finally, the pain experienced during the pre-eruptive phase of herpes zoster involving any of the segments between T11 and L2 may also simulate pain of renal origin.

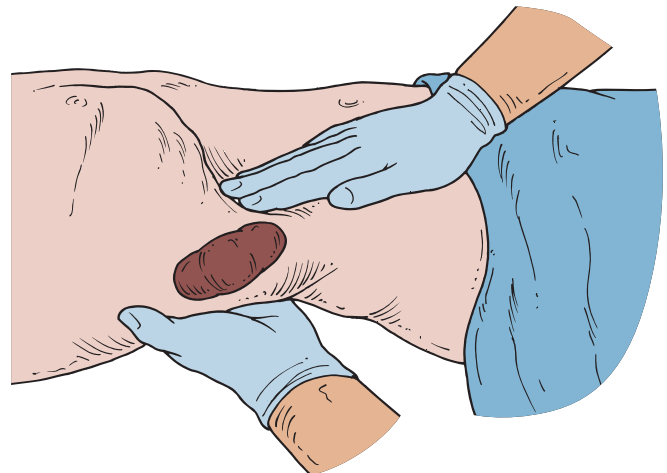


Figure 1-1. Bimanual examination of the kidney.

Bladder

A normal bladder in the adult cannot be palpated or percussed until there is at least 150 mL of urine in it. At a volume of about 500 mL, the distended bladder becomes visible in thin patients as a lower midline abdominal mass.

Percussion is better than palpation for diagnosing a distended bladder. The examiner begins by percussing immediately above the symphysis pubis and continuing cephalad until there is a change in pitch from dull to resonant. Alternatively, it may be possible in thin patients and in children to palpate the bladder by lifting the lumbar spine with one hand and pressing the other hand into the midline of the lower abdomen.

A careful bimanual examination, best done with the patient under anesthesia, is invaluable in assessing the regional extent of a bladder tumor or other pelvic mass. The bladder is palpated between the abdomen and the vagina in the female (Fig. 1-2) or the rectum in the male (Fig. 1-3). In addition to defining areas of induration, the bimanual examination allows the examiner to assess the mobility of the bladder; such information cannot be obtained by radiologic techniques such as CT and MRI, which convey static images.

Penis

If the patient has not been circumcised, the foreskin should be retracted to examine for tumor or balanoposthitis (inflammation of the prepuce and glans penis). **Most penile cancers occur in uncircumcised men and arise on the prepuce or glans penis.** Therefore in a patient with a bloody penile discharge in whom the foreskin cannot be withdrawn, a dorsal slit or circumcision must be performed to adequately evaluate the glans penis and urethra.

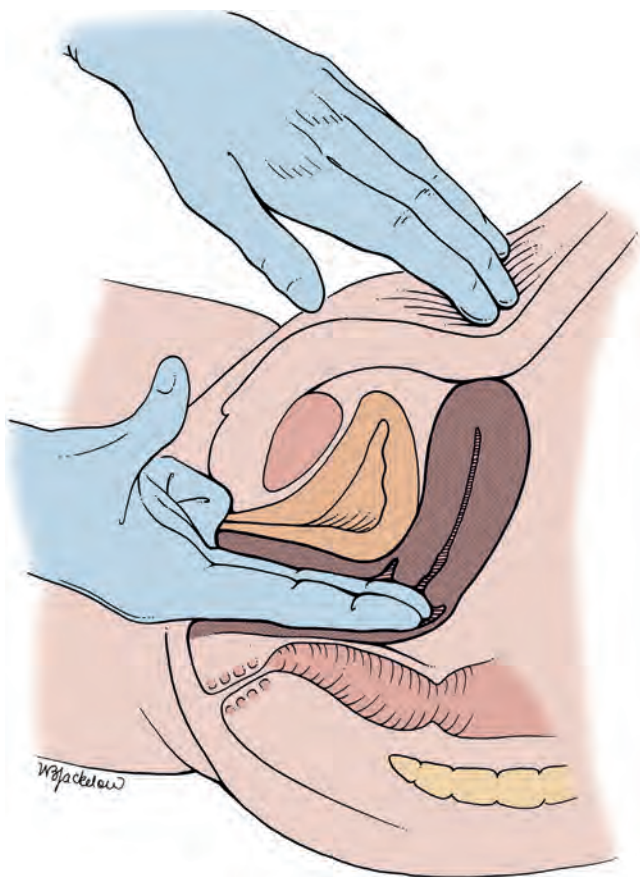


Figure 1-2. Bimanual examination of the bladder in the female. (From Swartz MH. Textbook of physical diagnosis. Philadelphia: Saunders; 1989. p. 405.)

The position of the urethral meatus should be noted. It may be located proximal to the tip of the glans on the ventral surface (hypospadias) or, much less commonly, on the dorsal surface (epispadias). The penile skin should be examined for the presence of superficial vesicles compatible with herpes simplex and for ulcers that may indicate either venereal infection or tumor. The presence of venereal warts (condylomata acuminata), which appear as irregular, papillary, velvety lesions on the male genitalia, should also be noted.

The urethral meatus should be separated between the thumb and the forefinger to inspect for neoplastic or inflammatory lesions within the fossa navicularis. The dorsal shaft of the penis should be palpated for the presence of fibrotic plaques or ridges typical of Peyronie disease. Tenderness along the ventral aspect of the penis is suggestive of periurethritis, often secondary to a urethral stricture.

Scrotum and Contents

The scrotum is a loose sac containing the testes and spermatic cord structures. The scrotal wall is made up of skin and an underlying thin muscular layer. The testes are normally oval, firm, and smooth; in adults, they measure about 6 cm in length and 4 cm in width. They are suspended in the scrotum, with the right testis normally anterior to the left. The epididymis lies posterior to the testis and is palpable as a distinct ridge of tissue. The vas deferens can be palpated above each testis and feels like a piece of heavy twine.

The scrotum should be examined for dermatologic abnormalities. **Because the scrotum, unlike the penis, contains both hair and sweat glands, it is a frequent site of local infection and sebaceous cysts.** Hair follicles can become infected and may present as small pustules on the surface of the scrotum. These usually resolve spontaneously, but they can give rise to more significant infection, particularly in patients with reduced immunity and diabetes. Patients often become concerned about these lesions, mistaking them for testicular tumors.

The testes should be palpated gently between the fingertips of both hands. The testes normally have a firm, rubbery consistency with a smooth surface. Abnormally small testes suggest hypogonadism or an endocrinopathy such as Klinefelter disease. **A firm or hard area within the testis should be considered a malignant tumor until proved otherwise.** The epididymis should be palpable as a ridge posterior to each testis. Masses in the epididymis (spermatocele, cyst, and epididymitis) are almost always benign.

To examine for a hernia, the physician's index finger should be inserted gently into the scrotum and invaginated into the external inguinal ring (Fig. 1-4). The scrotum should be

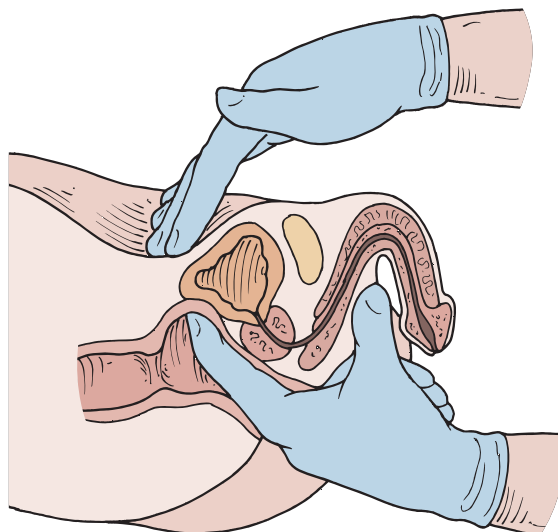


Figure 1-3. Bimanual examination of the bladder in the male.

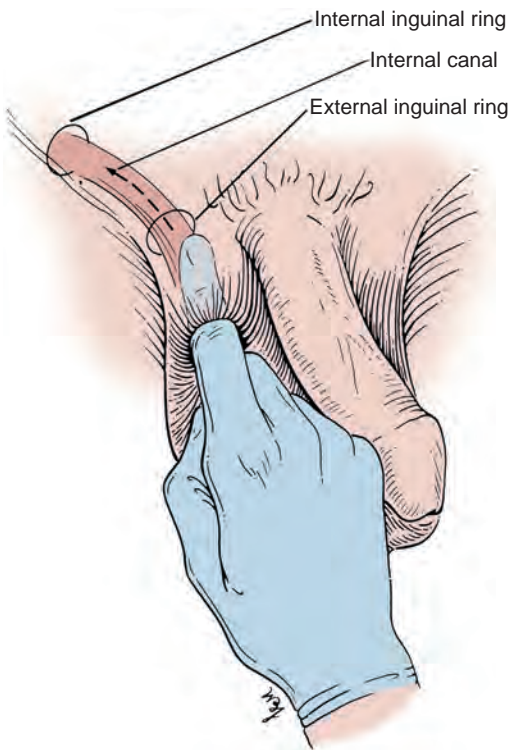


Figure 1-4. Examination of the inguinal canal. (From Swartz MH. *Textbook of physical diagnosis*. Philadelphia: Saunders; 1989. p. 376.)

invaginated in front of the testis, and care should be taken not to elevate the testis itself, which is quite painful. Once the external ring has been located, the physician should place the fingertips of his or her other hand over the internal inguinal ring and ask the patient to bear down (Valsalva maneuver). A hernia will be felt as a distinct bulge that descends against the tip of the index finger in the external inguinal ring as the patient bears down. Although it may be possible to distinguish a direct inguinal hernia arising through the floor of the inguinal canal from an indirect inguinal hernia prolapsing through the internal inguinal ring, this is seldom possible and of little clinical significance because the surgical approach is essentially identical for both conditions.

The spermatic cord is also examined with the patient in the standing position. A varicocele is a dilated, tortuous spermatic vein that becomes more obvious as the patient performs a Valsalva maneuver. The epididymis can again be palpated as a ridge of tissue running longitudinally, posterior to each testis. The testis should be palpated again between the fingers of both hands, once again taking care not to exert any pressure on the testis itself so as to avoid pain.

Transillumination is helpful in determining whether scrotal masses are solid (tumor) or cystic (hydrocele, spermatocele). A small flashlight or fiberoptic light cord is placed behind the mass. A cystic mass transilluminates easily, whereas light is not transmitted through a solid tumor.

Rectal and Prostate Examination in the Male

Digital rectal examination (DRE) should be performed in every male after age 40 years and in men of any age who present for urologic evaluation. Prostate cancer is the second most common cause of male cancer deaths after age 55 years and the most common cause of cancer deaths in men older than 70 years. Many prostate cancers can be detected in an early curable stage by DRE, and about 25% of colorectal cancers can be detected by DRE in combination with a stool guaiac test.

DRE should be performed at the end of the physical examination. It is done best with the patient standing and bent over the examining table or with the patient in the knee-chest position. In

the standing position, the patient should stand with his thighs close to the examining table. The feet should be about 18 inches apart, with the knees flexed slightly. The patient should bend at the waist 90 degrees until his chest is resting on his forearms. The physician should give the patient adequate time to get in the proper position and relax as much as possible. A few reassuring words before the examination are helpful. The physician should place a glove on the examining hand and should lubricate the index finger thoroughly.

Before performing the DRE, the physician should place the palm of his other hand against the patient's lower abdomen. This provides subtle reassurance to the patient by allowing the physician to make gentle contact with the patient before touching the anus. It also allows the physician to steady the patient and provide gentle counterpressure if the patient tries to move away as the DRE is being performed. The DRE itself begins by separating the buttocks and inspecting the anus for pathology, usually hemorrhoids, but, occasionally, an anal carcinoma or melanoma may be detected. The gloved, lubricated index finger is then inserted gently into the anus. Only one phalanx should be inserted initially to give the anus time to relax and to easily accommodate the finger. Estimation of anal sphincter tone is of great importance; a flaccid or spastic anal sphincter suggests similar changes in the urinary sphincter and may be a clue to the diagnosis of neurogenic disease. If the physician waits only a few seconds, the anal sphincter will normally relax to the degree that the finger can be advanced to the knuckle without causing pain. The index finger then sweeps over the prostate; the entire posterior surface of the gland can usually be examined if the patient is in the proper position. **Normally, the prostate is about the size of a chestnut and has a consistency similar to that of the contracted thenar eminence of the thumb (with the thumb opposed to the little finger).**

The index finger is extended as far as possible into the rectum, and the entire circumference is examined to detect an early rectal carcinoma. The index finger is then withdrawn gently, and the stool on the glove is transferred to a guaiac-impregnated (Hemoccult) card for determination of occult blood. Although there may be a significant incidence of false-positive and false-negative results associated with fecal occult blood testing, particularly without dietary and drug restrictions, **the guaiac test is simple and inexpensive and may lead to the detection of significant gastrointestinal abnormalities (Bond, 1999).** Adequate tissues, soap, and towels should be available for the patient to cleanse himself after the examination. The physician should then leave the room and allow the patient adequate time to wash and dress before concluding the consultation.

Pelvic Examination in the Female

Male urologists should always perform the female pelvic examination with a female nurse or other health care professional present. The patient should be allowed to undress in privacy and be fully draped for the procedure before the physician enters the room. The examination itself should be performed in standard lithotomy position with the patient's legs abducted. Initially, the external genitalia and introitus should be examined, with particular attention paid to atrophic changes, erosions, ulcers, discharge, or warts, all of which may cause dysuria and pelvic discomfort. The urethral meatus should be inspected for caruncles, mucosal hyperplasia, cysts, and mucosal prolapse. The patient is then asked to perform a Valsalva maneuver and is carefully examined for a cystocele (prolapse of the bladder) or rectocele (prolapse of the rectum). The patient is then asked to cough, which may precipitate stress urinary incontinence. Palpation of the urethra is done to detect induration, which may be a sign of chronic inflammation or malignancy. Palpation may also disclose a urethral diverticulum, and palpation of a diverticulum may cause a purulent discharge from the urethra. Bimanual examination of the bladder, uterus, and adnexa should then be performed with two fingers in the vagina and the other hand on the lower abdomen. Any abnormality of the pelvic organs should be evaluated further with a pelvic ultrasound or CT scan.

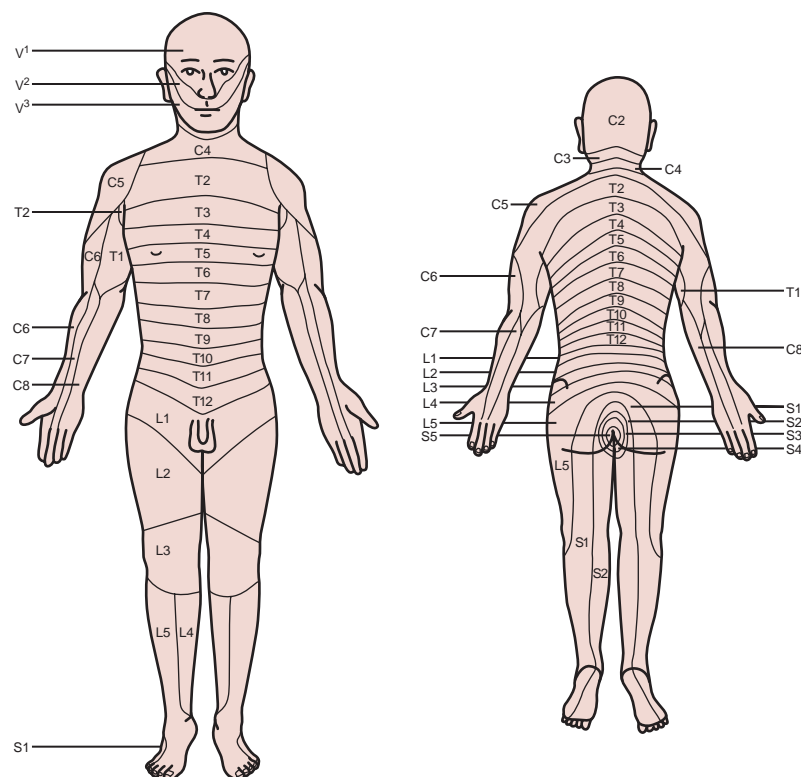


Figure 1-5. Sensory dermatome maps used to help localize the level of neurologic deficit.

Neurologic Examination

There are various clinical situations in which the neurologic examination may be helpful in evaluating urologic patients. In some cases, the level of neurologic abnormalities can be localized by the pattern of sensory deficit noted during physical examination using a dermatome map (Fig. 1-5). Sensory deficits in the penis, labia, scrotum, vagina, and perianal area generally indicate damage or injury to sacral roots or nerves. In addition to sensory examination, testing of reflexes in the genital area may also be performed. The most important of these is the bulbocavernosus reflex (BCR), which is a reflex contraction of the striated muscle of the pelvic floor that occurs in response to various stimuli in the perineum or genitalia. This reflex is most commonly tested by placing a finger in the rectum and then squeezing the glans penis or clitoris. If a Foley catheter is in place, the BCR can also be elicited by gently pulling on the catheter. If the BCR is intact, tightening of the anal sphincter should be felt and/or observed. The BCR tests the integrity of the spinal cord-mediated reflex arc involving S2-S4 and may be absent in the presence of sacral cord or peripheral nerve abnormalities.

The cremasteric reflex can be elicited by lightly stroking the superior and medial thigh in a downward direction. The normal response in males is contraction of the cremasteric muscle that results in immediate elevation of the ipsilateral scrotum and testis. There is limited clinical utility for testing superficial reflexes such as the cremasteric when investigating neurologic dysfunction. However, there may be a role for testing this reflex when assessing patients with suspected testicular torsion or epididymitis. Finally, an overly active cremasteric reflex in children can lead to the mistaken diagnosis of an undescended testis in some cases.

URINALYSIS

The urinalysis is a fundamental test that should be performed in all urologic patients. Although in many instances a simple dipstick

urinalysis will provide the necessary information, a complete urinalysis includes both chemical and microscopic analyses.

Collection of Urinary Specimens

Males

In the male patient, a midstream urine sample is obtained. The uncircumcised male should retract the foreskin, cleanse the glans penis with antiseptic solution, and continue to retract the foreskin during voiding. The male patient begins urinating into the toilet and then places a wide-mouth sterile container under his penis to collect a midstream sample. This avoids contamination of the urine specimen with skin and urethral organisms.

In men with chronic UTIs, four aliquots of urine are obtained. These aliquots have been designated **Voided Bladder 1, Voided Bladder 2, Expressed Prostatic Secretions, and Voided Bladder 3 (VB1, VB2, EPS, and VB3)**. The VB1 is the initial 5 to 10 mL of urine voided, whereas the VB2 is the midstream urine. The EPS is the secretions obtained after gentle prostatic massage, and the VB3 specimen is the initial 2 to 3 mL of urine obtained after prostatic massage. The value of these cultures for localization of UTIs is that the VB1 sample represents urethral flora; the VB2, bladder flora; and the EPS and VB3 samples, prostatic flora. The VB3 sample is particularly helpful when little or no prostatic fluid is obtained by massage. To better obtain prostatic secretions, patients should be instructed to attempt to void during prostatic massage and to avoid tightening the anal sphincter and pelvic floor muscles. The four-part urine sample is particularly useful in evaluating men with suspected bacterial prostatitis (Meares and Stamey, 1968).

Females

In the female, it is more difficult to obtain a clean-catch midstream specimen. The female patient should cleanse the vulva, separate the labia, and collect a midstream specimen as described for the male

patient. If infection is suspected, however, the midstream specimen is unreliable and should never be sent for culture and sensitivity. To evaluate for a possible infection in a female, a catheterized urine sample should always be obtained.

Neonates and Infants

The usual way to obtain a urine sample in a neonate or infant is to place a sterile plastic bag with an adhesive collar over the infant's genitalia. However, these devices may not be able to distinguish contamination from true UTI. Whenever possible, **all urine samples should be examined within 1 hour of collection and plated for culture and sensitivity if indicated.** If urine is allowed to stand at room temperature for longer periods of time, bacterial overgrowth may occur, the pH may change, and red and white blood cell casts may disintegrate. If it is not possible to examine the urine promptly, it should be refrigerated at 5°C.

Physical Examination of Urine

The physical examination of the urine includes an evaluation of color, turbidity, specific gravity and osmolality, and pH.

Color

The normal pale yellow color of urine is due to the presence of the pigment urochrome. **Urine color varies most commonly because of concentration, but many foods, medications, metabolic products, and infection may produce abnormal urine color.** This is important because many patients will seek consultation primarily because of a change in their urine color. Thus it is important for the urologist to be aware of the common causes of abnormal urine color, and these are listed in Table 1-3.

Turbidity

Freshly voided urine is clear. **Cloudy urine is most commonly due to phosphaturia**, a benign process in which excess phosphate crystals precipitate in an alkaline urine. Phosphaturia is intermittent and usually occurs after meals or ingestion of a large quantity of milk. Patients are otherwise asymptomatic. The diagnosis of phosphaturia can be accomplished either by acidifying the urine with acetic acid, which will result in immediate clearing, or by performing a microscopic analysis, which will reveal large amounts of amorphous phosphate crystals.

Pyuria, usually associated with a UTI, is another common cause of cloudy urine. The large numbers of white blood cells cause the urine to become turbid. **Pyuria is readily distinguished from phosphaturia either by smelling the urine (infected urine has a characteristic pungent odor) or by microscopic examination, which readily distinguishes amorphous phosphate crystals from leukocytes.**

Rare causes of cloudy urine include chyluria (in which there is an abnormal communication between the lymphatic system and the urinary tract resulting in lymph fluid being mixed with urine), lipiduria, hyperoxaluria, and hyperuricosuria.

Specific Gravity and Osmolality

Specific gravity of urine is easily determined from a urinary dipstick and usually varies from 1.001 to 1.035. Specific gravity usually reflects the patient's state of hydration but may also be affected by abnormal renal function, the amount of material dissolved in the urine, and a variety of other causes mentioned later. A specific gravity less than 1.008 is regarded as dilute, and a specific gravity greater than 1.020 is considered concentrated. A fixed specific gravity of 1.010 is a sign of renal insufficiency, either acute or chronic.

In general, specific gravity reflects the state of hydration but also affords some idea of renal concentrating ability. Conditions that decrease specific gravity include (1) increased fluid intake,

TABLE 1-3 Common Causes of Abnormal Urine Color

COLOR	CAUSE
Colorless	Very dilute urine Overhydration
Cloudy/milky	Phosphaturia Pyuria Chyluria
Red	Hematuria Hemoglobinuria/myoglobinuria Anthocyanin in beets and blackberries Chronic lead and mercury poisoning Phenolphthalein (in bowel evacuants) Phenothiazines (e.g., Compazine) Rifampin
Orange	Dehydration Phenazopyridine (Pyridium) Sulfasalazine (Azulfidine)
Yellow	Normal Phenacetin Riboflavin
Green-blue	Biliverdin Indicanuria (tryptophan indole metabolites) Amitriptyline (Elavil) Indigo carmine Methylene blue Phenols (e.g., IV cimetidine [Tagamet], IV promethazine [Phenergan]) Resorcinol Triamterene (Dyrenium)
Brown	Urobilinogen Porphyria Aloe, fava beans, and rhubarb Chloroquine and primaquine Furazolidone (Furoxone) Metronidazole (Flagyl) Nitrofurantoin (Furadantin)
Brown-black	Alcaptonuria (homogentisic acid) Hemorrhage Melanin Tyrosinosis (hydroxyphenylpyruvic acid) Cascara, senna (laxatives) Methocarbamol (Robaxin) Methyldopa (Aldomet) Sorbitol

IV, intravenous.

From Hanno PM, Wein AJ. A clinical manual of urology. Norwalk (CT): Appleton-Century-Crofts; 1987. p. 67.

(2) diuretics, (3) decreased renal concentrating ability, and (4) diabetes insipidus. Conditions that increase specific gravity include (1) decreased fluid intake; (2) dehydration owing to fever, sweating, vomiting, and diarrhea; (3) diabetes mellitus (glucosuria); and (4) inappropriate secretion of antidiuretic hormone. Specific gravity will also be increased above 1.035 after IV injection of iodinated contrast and in patients taking dextran.

Osmolality is a measure of the amount of material dissolved in the urine and usually varies between 50 and 1200 mOsm/L. Urine osmolality most commonly varies with hydration, and the same factors that affect specific gravity will also affect osmolality. Urine osmolality is a better indicator of renal function, but it cannot

be measured from a dipstick and must be determined using standard laboratory techniques.

pH

Urinary pH is measured with a dipstick test strip that incorporates two colorimetric indicators, methyl red and bromothymol blue, which yield clearly distinguishable colors over the pH range from 5 to 9. Urinary pH may vary from 4.5 to 8; the average pH varies between 5.5 and 6.5. A urinary pH between 4.5 and 5.5 is considered acidic, whereas a pH between 6.5 and 8 is considered alkaline.

In general, the urinary pH reflects the pH in the serum. In patients with metabolic or respiratory acidosis, the urine is usually acidic; conversely, in patients with metabolic or respiratory alkalosis, the urine is alkaline. Renal tubular acidosis (RTA) presents an exception to this rule. In patients with both type I and II RTA, the serum is acidemic, but the urine is alkalotic because of continued loss of bicarbonate in the urine. In severe metabolic acidosis in type II RTA, the urine may become acidic, but in type I RTA, the urine is always alkaline, even with severe metabolic acidosis (Morris and Ives, 1991). Urinary pH determination is used to establish the diagnosis of RTA; inability to acidify the urine below a pH of 5.5 after administration of an acid load is diagnostic of RTA.

Urine pH determinations are also useful in the diagnosis and treatment of UTIs and urinary calculus disease. **In patients with a presumed UTI, an alkaline urine with a pH greater than 7.5 suggests infection with a urea-splitting organism, most commonly *Proteus*.** Urease-producing bacteria convert ammonia to ammonium ions, markedly elevating the urinary pH and causing precipitation of calcium magnesium ammonium phosphate crystals. The massive amount of crystallization may result in staghorn calculi.

Urinary pH is usually acidic in patients with uric acid and cystine lithiasis. Alkalinization of the urine is an important feature of therapy in both of these conditions, and frequent monitoring of urinary pH is necessary to ascertain adequacy of therapy.

Chemical Examination of Urine

Urine Dipsticks

Urine dipsticks provide a quick and inexpensive method for detecting abnormal substances within the urine. Dipsticks are short, plastic strips with small marker pads that are impregnated with different chemical reagents that react with abnormal substances in the urine to produce a colorimetric change. **The abnormal substances commonly tested for with a dipstick include (1) blood, (2) protein, (3) glucose, (4) ketones, (5) urobilinogen and bilirubin, and (6) white blood cells.**

Substances listed in Table 1-3 that produce an abnormal urine color may interfere with appropriate color development on the dipstick. In our experience, this most commonly occurs in patients taking phenazopyridine (Pyridium) for a UTI. Phenazopyridine turns the urine bright orange and makes dipstick evaluation of the urine unreliable.

Appropriate technique must be used to obtain an accurate dipstick determination. The reagent areas on the dipstick must be completely immersed in a fresh uncentrifuged urine specimen and then must be withdrawn immediately to prevent dissolution of the reagents into the urine. As the dipstick is removed from the urine specimen container, the edge of the dipstick is drawn along the rim of the container to remove excess urine. The dipstick should be held horizontally until the appropriate time for reading and then compared with the color chart. **Excess urine on the dipstick or holding the dipstick in a vertical position will allow mixing of chemicals from adjacent reagent pads on the dipstick, resulting in a faulty diagnosis.** False-negative results for glucose and bilirubin may be seen in the presence of elevated ascorbic acid concentrations in the

urine. However, increased levels of ascorbic acid in the urine do not interfere with dipstick testing for hematuria. Highly buffered alkaline urine may cause falsely low readings for specific gravity and may lead to false-negative results for urinary protein. Other common causes of false results with dipstick testing are outdated test strips and exposure of the sticks, leading to damage to the reagents. In general, when the sticks are damaged, there will be color changes on the pads before their immersion in urine. If such color changes are noted, results with the dipstick may be inaccurate.

Hematuria

Normal urine should contain fewer than three RBCs per HPF. A positive dipstick for blood in the urine indicates either hematuria, hemoglobinuria, or myoglobinuria. **The chemical detection of blood in the urine is based on the peroxidase-like activity of hemoglobin.** When in contact with an organic peroxidase substrate, hemoglobin catalyzes the reaction and causes subsequent oxidation of a chromogen indicator, which changes color according to the degree and amount of oxidation. The degree of color change is directly related to the amount of hemoglobin present in the urine specimen. Dipsticks frequently demonstrate both colored dots and field color change. If present, free hemoglobin and myoglobin in the urine are absorbed into the reagent pad and catalyze the reaction within the test paper, thereby producing a field change effect in color. Intact erythrocytes in the urine undergo hemolysis when they come in contact with the reagent test pad, and the localized free hemoglobin on the pad produces a corresponding dot of color change. The greater the number of intact erythrocytes in the urine specimen, the greater the number of dots that will appear on the test paper, and a coalescence of the dots occurs when there are more than 250 erythrocytes/mL.

Hematuria can be distinguished from hemoglobinuria and myoglobinuria by microscopic examination of the centrifuged urine; the presence of a large number of erythrocytes establishes the diagnosis of hematuria. If erythrocytes are absent, examination of the serum will distinguish hemoglobinuria and myoglobinuria. A sample of blood is obtained and centrifuged. In hemoglobinuria, the supernatant will be pink. This is because free hemoglobin in the serum binds to haptoglobin, which is water insoluble and has a high molecular weight. This complex remains in the serum, causing a pink color. Free hemoglobin will appear in the urine only when all of the haptoglobin-binding sites have been saturated. In myoglobinuria, the myoglobin released from muscle is of low molecular weight and water soluble. It does not bind to haptoglobin and is therefore excreted immediately into the urine. Therefore in myoglobinuria the serum remains clear.

The sensitivity of urinary dipsticks in identifying hematuria, defined as greater than three erythrocytes/HPF of centrifuged sediment examined microscopically, is higher than 90%. Conversely, the specificity of the dipstick for hematuria compared with microscopy is somewhat lower, reflecting a higher false-positive rate with the dipstick (Shaw et al, 1985).

False-positive dipstick readings are most often due to contamination of the urine specimen with menstrual blood. Dehydration with resultant urine of high specific gravity can also yield false-positive results owing to the increased concentration of erythrocytes and hemoglobin. The normal individual excretes about 1000 erythrocytes/mL of urine, with the upper limits of normal varying from 5000 to 8000 erythrocytes/mL (Kincaid-Smith, 1982). Therefore examining urine of high specific gravity such as the first morning voided specimen increases the likelihood of a false-positive result. In addition to dehydration, another cause of false-positive results is exercise, which can increase the number of erythrocytes in the urine.

The efficacy of hematuria screening using the dipstick to identify patients with significant urologic disease is somewhat controversial. Studies in children and young adults have shown a low rate of significant disease (Woolhandler et al, 1989). In older adults, one study from the Mayo Clinic of 2000 patients with asymptomatic hematuria showed that only 0.5% had a urologic

malignancy and only 1.8% developed other serious urologic diseases within 3 years after identification of the hematuria (Mohr et al, 1986). Conversely, investigators at the University of Wisconsin found that 26% of adults who had at least one positive dipstick reading for hematuria were subsequently found to have significant urologic pathology (Messing et al, 1987). The age of the population, the completeness of the subsequent urologic evaluation, and the definition of significant disease all influence the disease rate in the group of patients with asymptomatic hematuria identified by dipstick screening. It is important to remember that, before proceeding to more complicated studies, the dipstick result should be confirmed with a microscopic examination of the centrifuged urinary sediment.

Differential Diagnosis and Evaluation of Hematuria. Hematuria may reflect either significant nephrologic or urologic disease. Hematuria of nephrologic origin is frequently associated with casts in the urine and almost always associated with significant proteinuria. Even significant hematuria of urologic origin will not elevate the protein concentration in the urine into the 100 to 300 mg/dL or 2+ to 3+ range on dipstick, and proteinuria of this magnitude almost always indicates glomerular or tubulointerstitial renal disease.

Morphologic evaluation of erythrocytes in the centrifuged urinary sediment also helps localize their site of origin. Erythrocytes arising from glomerular disease are typically dysmorphic and show a wide range of morphologic alterations. Conversely, erythrocytes arising from tubulointerstitial renal disease and of urologic origin have a uniformly round shape; these erythrocytes may or may not retain their hemoglobin ("ghost cells"), but the individual cell shape is consistently round. In individuals without significant pathology with minimal amounts of hematuria, the erythrocytes are characteristically dysmorphic but the number of cells observed is far fewer than that observed in patients with nephrologic disease. Erythrocyte morphology is more easily determined using phase contrast microscopy, but with practice this can be accomplished using a conventional light microscope (Schramek et al, 1989).

Glomerular Hematuria. Glomerular hematuria is suggested by the presence of dysmorphic erythrocytes, RBC casts, and proteinuria. Of those patients with glomerulonephritis proven by renal biopsy, however, about 20% will have hematuria alone without RBC casts or proteinuria (Fassett et al, 1982).

The glomerular disorders associated with hematuria are listed in Table 1-4. Further evaluation of patients with glomerular hematuria should begin with a thorough history. Hematuria in children and

young adults, usually males, associated with low-grade fever and an erythematous rash suggests a diagnosis of immunoglobulin A (IgA) nephropathy (Berger disease). A family history of renal disease and deafness suggests familial nephritis or Alport syndrome. Hemoptysis and abnormal bleeding associated with microcytic anemia are characteristic of Goodpasture syndrome, and the presence of a rash and arthritis suggest systemic lupus erythematosus. Finally, post-streptococcal glomerulonephritis should be suspected in a child with a recent streptococcal upper respiratory tract or skin infection.

Further laboratory evaluation should include measurement of serum creatinine, creatinine clearance, and, when proteinuria in the urine is 2+ or greater, a 24-hour urine protein determination. Although these tests will quantitate the specific degree of renal dysfunction, further tests are usually required to establish the specific diagnosis and particularly to determine whether the disease is due to an immune or a nonimmune etiology. Frequently, a renal biopsy is necessary to establish the precise diagnosis, and biopsies are particularly important if the result will influence subsequent treatment of the patient. Renal biopsies are extremely informative when examined by an experienced pathologist using light, immunofluorescent, and electron microscopy.

An algorithm for the evaluation of glomerular hematuria is provided in Figure 1-6.

IgA Nephropathy (Berger Disease). IgA nephropathy, or Berger disease, is the most common cause of glomerular hematuria, accounting for about 30% of cases (Fassett et al, 1982). Therefore it is described in greater detail in this section. IgA nephropathy occurs most commonly in children and young adults, with a male predominance (Berger and Hinglais, 1968). Patients typically present with hematuria after an upper respiratory tract infection or exercise. Hematuria may be associated with a low-grade fever or rash, but most patients have no associated systemic symptoms. Gross hematuria occurs intermittently, but microscopic hematuria is a constant finding in some patients. The disease is chronic, but the prognosis in most patients is excellent. Renal function remains normal in the majority, but about 25% will subsequently develop renal insufficiency. An older age at onset, initial abnormal renal function, consistent proteinuria, and hypertension are indicators of a poor prognosis (D'Amico, 1988).

The pathologic findings in Berger disease are limited to either focal glomeruli or lobular segments of a glomerulus. The changes are proliferative and usually confined to mesangial cells (Berger and Hinglais, 1968). Renal biopsy reveals deposits of IgA, IgG, and β_2 -microglobulin, although IgA and IgG mesangial deposits are found in other forms of glomerulonephritis as well. The role of IgA in the disease remains uncertain, although the deposits may trigger an inflammatory reaction within the glomerulus (van den Wall Bake et al, 1989). Because gross hematuria frequently follows an upper respiratory tract infection, a viral etiology has been suspected but not established. The frequent association between hematuria and exercise in this condition remains unexplained.

The clinical presentation of IgA glomerulonephritis is alarming and similar to certain systemic diseases, including Schönlein-Henoch purpura, systemic lupus erythematosus, bacterial endocarditis, and Goodpasture syndrome. Therefore a careful clinical and laboratory evaluation is indicated to establish the correct diagnosis. The presence of RBC casts establishes the glomerular origin of the hematuria. In the absence of casts, a urologic evaluation is indicated to exclude the urinary tract as a source of bleeding and to confirm that the hematuria is arising from both kidneys. The diagnosis of IgA nephropathy is confirmed by renal biopsy demonstrating the classic deposits of immunoglobulins in mesangial cells, as described previously. Once the diagnosis has been established, repeat evaluations for hematuria are generally not indicated. Although there is no effective treatment for this condition, renal function remains stable in most patients and there are no other known long-term complications.

Nonglomerular Hematuria

Medical. Except for renal tumors, nonglomerular hematuria of renal origin is secondary to either tubulointerstitial, renovascular,

TABLE 1-4 Glomerular Disorders in Patients with Glomerular Hematuria

DISORDER	PATIENTS
IgA nephropathy (Berger disease)	30
Mesangioproliferative GN	14
Focal segmental proliferative GN	13
Familial nephritis (e.g., Alport syndrome)	11
Membranous GN	7
Mesangiocapillary GN	6
Focal segmental sclerosis	4
Unclassifiable	4
Systemic lupus erythematosus	3
Postinfectious GN	2
Subacute bacterial endocarditis	2
Others	4
TOTAL	100

GN, glomerulonephritis; IgA, immunoglobulin A.

Modified from Fassett RG, Horgan BA, Mathew TH. Detection of glomerular bleeding by phase-contrast microscopy. *Lancet* 1982;1:1432.

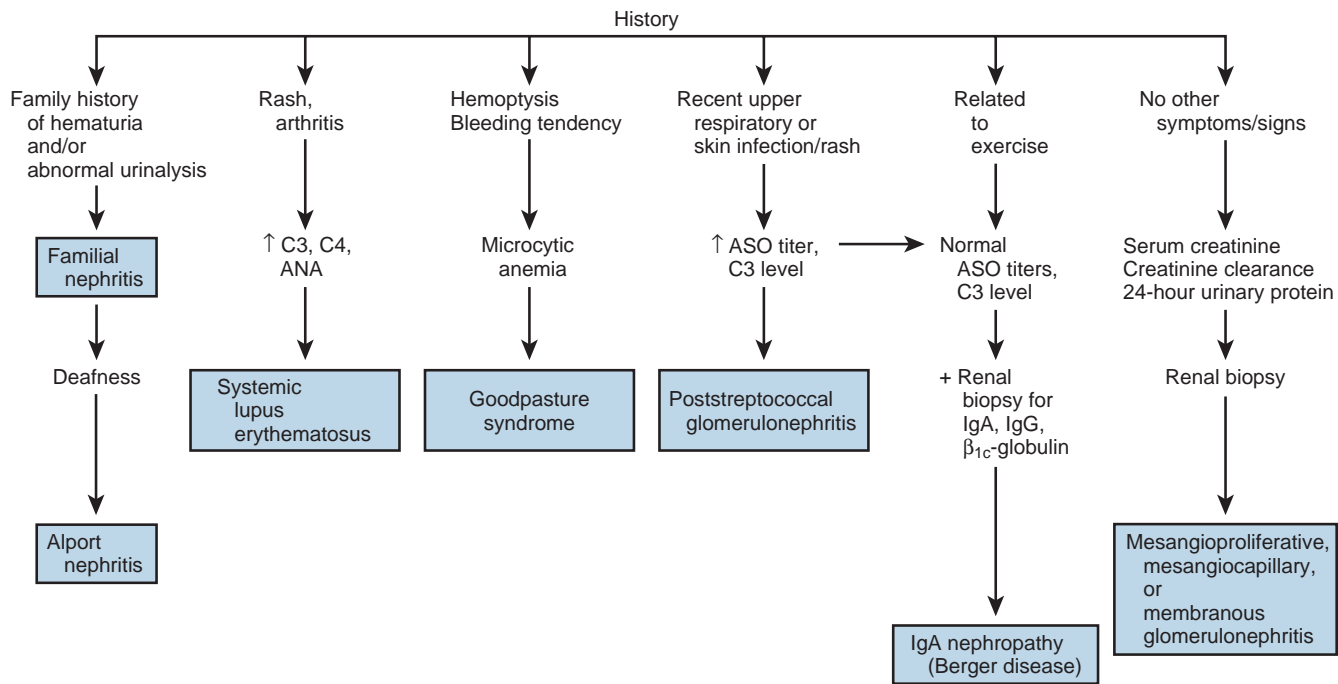


Figure 1-6. Evaluation of glomerular hematuria (dysmorphic erythrocytes, erythrocyte casts, and proteinuria). ANA, antinuclear antibody; ASO, antistreptolysin O; Ig, immunoglobulin.

or systemic disorders. The urinalysis in nonglomerular hematuria is distinguished from that of glomerular hematuria by the presence of circular erythrocytes and the absence of erythrocyte casts. Like glomerular hematuria, nonglomerular hematuria of renal origin is frequently associated with significant proteinuria, which distinguishes these nephrologic diseases from urologic diseases in which the degree of proteinuria is usually minimal, even with heavy bleeding.

As with glomerular hematuria, a careful history frequently helps establish the diagnosis. A family history of hematuria or bleeding tendency suggests the diagnosis of a blood dyscrasia, which should be investigated further. A family history of urolithiasis associated with intermittent hematuria may indicate stone disease, which should be investigated with serum and urine measurements of calcium and uric acid. A family history of renal cystic disease should prompt further radiologic evaluation for medullary sponge kidney and adult polycystic kidney disease. Papillary necrosis as a cause of hematuria should be considered in diabetics, African-Americans (secondary to sickle cell disease or trait), and suspected analgesic abusers.

Medications may induce hematuria, particularly anticoagulants. Anticoagulation at normal therapeutic levels, however, does not predispose patients to hematuria. In one study, the prevalence of hematuria was 3.2% in anticoagulated patients versus 4.8% in a control group. Urologic disease was identified in 81% of patients with more than one episode of microscopic hematuria, and the cause of hematuria did not vary between groups (Culclasure et al, 1994). Thus anticoagulant therapy per se does not appear to increase the risk of hematuria unless the patient is excessively anticoagulated.

Exercise-induced hematuria is being observed with increasing frequency. It typically occurs in long-distance runners (>10 km), is usually noted at the conclusion of the run, and rapidly disappears with rest. The hematuria may be of renal or bladder origin. An increased number of dysmorphic erythrocytes have been noted in some patients, suggesting a glomerular origin. Exercise-induced hematuria may be the first sign of underlying glomerular disease such as IgA nephropathy. Conversely, cystoscopy in patients with

exercise-induced hematuria frequently reveals punctate hemorrhagic lesions in the bladder, suggesting that the hematuria is of bladder origin.

Vascular disease may also result in nonglomerular hematuria. Renal artery embolism and thrombosis, arteriovenous fistulae, and renal vein thrombosis may all result in hematuria. Physical examination may reveal severe hypertension, a flank or abdominal bruit, or atrial fibrillation. In such patients, further evaluation for renal vascular disease should be undertaken.

An algorithm for the evaluation of nonglomerular hematuria is provided in Figure 1-7.

Surgical. Nonglomerular hematuria or essential hematuria includes primarily urologic rather than nephrologic diseases. Common causes of essential hematuria include urologic tumors, stones, and UTIs.

The urinalysis in both nonglomerular medical and surgical hematuria is similar in that both are characterized by circular erythrocytes and the absence of erythrocyte casts. Essential hematuria is suggested, however, by the absence of significant proteinuria usually found in nonglomerular hematuria of renal parenchymal origin. It should be remembered, however, that proteinuria is not always present in glomerular or nonglomerular renal disease.

The AUA Best Practice Policy Panel on Microscopic Hematuria has formulated practice recommendations for the detection and evaluation of asymptomatic microscopic hematuria (Grossfeld et al, 2001a, 2001b). The panel concluded that, due to the lack of specificity of urinary dipstick examination, as well as the risk and expense of evaluation, patients with a positive dipstick test should only undergo complete evaluation for hematuria if this is confirmed by the finding of 3 or more RBCs/HPF on subsequent microscopic evaluation. The mainstays of evaluation, according to the panel, are voided urinary cytology, cystoscopy, and urinary tract imaging using ultrasonography, CT, and/or intravenous urography (IVU). The use of these tests in an individual patient should be based in most cases on the relative risk of significant urinary tract pathology.

An algorithm for the evaluation of essential hematuria is provided in Figure 1-8.

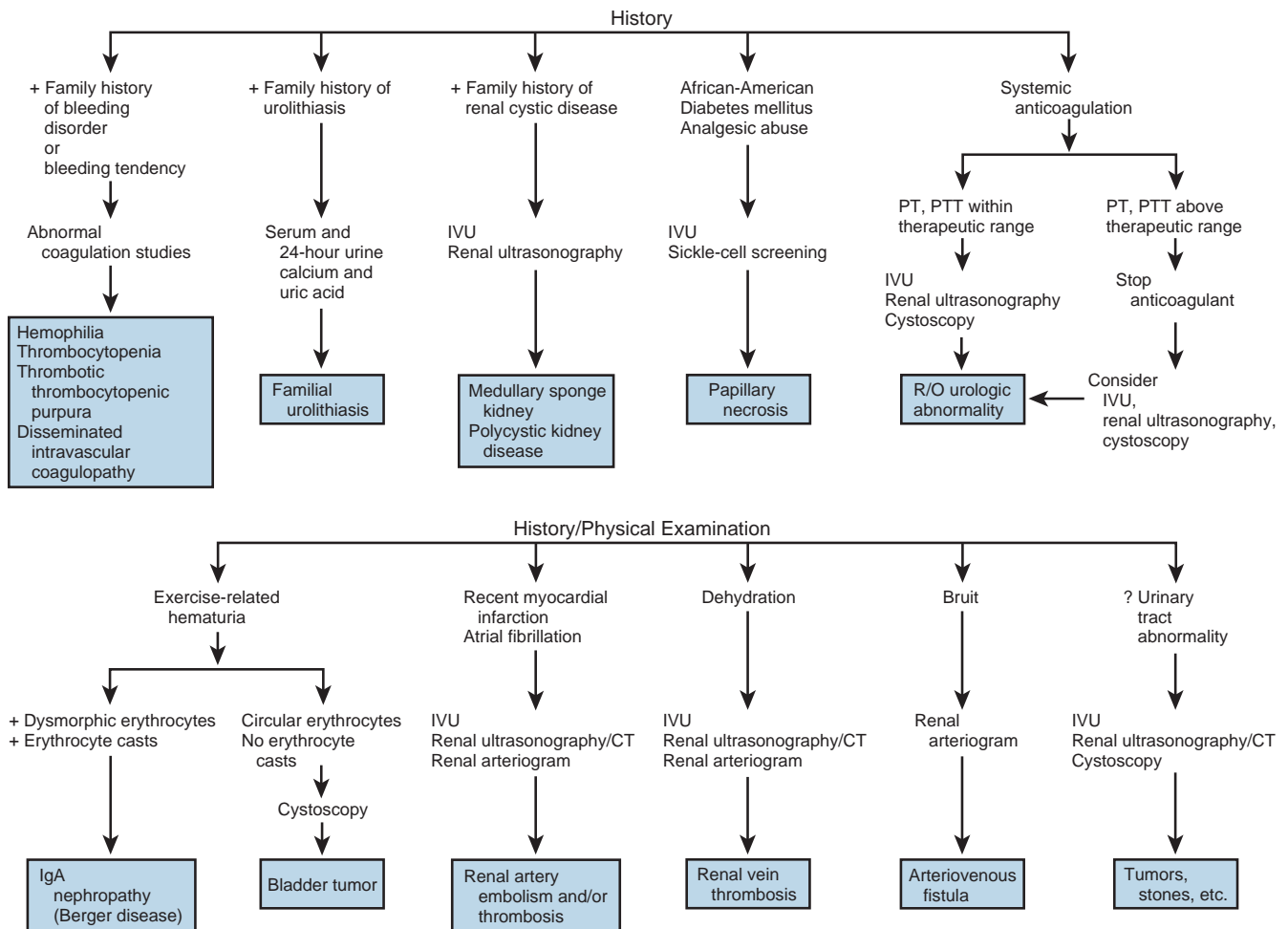


Figure 1-7. Evaluation of nonglomerular renal hematuria (circular erythrocytes, no erythrocyte casts, and proteinuria). CT, computed tomography; IgA, immunoglobulin A; IVU, intravenous urography; PT, prothrombin time; PTT, partial thromboplastin time; R/O, rule out.

Proteinuria

Although healthy adults excrete 80 to 150 mg of protein in the urine daily, the qualitative detection of proteinuria in the urinalysis should raise the suspicion of underlying renal disease. Proteinuria may be the first indication of renovascular, glomerular, or tubulointerstitial renal disease, or it may represent the overflow of abnormal proteins into the urine in conditions such as multiple myeloma. Proteinuria can also occur secondary to nonrenal disorders and in response to various physiologic conditions such as strenuous exercise.

The protein concentration in the urine depends on the state of hydration, but it seldom exceeds 20 mg/dL. In patients with dilute urine, however, significant proteinuria may be present at concentrations less than 20 mg/dL. Normally, urine protein is about 30% albumin, 30% serum globulins, and 40% tissue proteins, of which the major component is Tamm-Horsfall protein. This profile may be altered by conditions that affect glomerular filtration, tubular reabsorption, or excretion of urine protein. Determination of the urine protein profile by such techniques as protein electrophoresis may help determine the etiology of proteinuria.

Pathophysiology. Most causes of proteinuria can be categorized into one of three categories: glomerular, tubular, or overflow. Glomerular proteinuria is the most common type of proteinuria and results from increased glomerular capillary permeability to protein, especially albumin. Glomerular proteinuria occurs in any of the primary glomerular diseases such as IgA nephropathy or in glomerulopathy associated with systemic illness such as diabetes

mellitus. Glomerular disease should be suspected when the 24-hour urine protein excretion exceeds 1 g and is almost certain to exist when the total protein excretion exceeds 3 g.

Tubular proteinuria results from failure to reabsorb normally filtered proteins of low molecular weight such as immunoglobulins. In tubular proteinuria, the 24-hour urine protein loss seldom exceeds 2 to 3 g and the excreted proteins are of low molecular weight rather than albumin. Disorders that lead to tubular proteinuria are commonly associated with other defects of proximal tubular function such as glucosuria, aminoaciduria, phosphaturia, and uricosuria (Fanconi syndrome).

Overflow proteinuria occurs in the absence of any underlying renal disease and is due to an increased plasma concentration of abnormal immunoglobulins and other low-molecular-weight proteins. The increased serum levels of abnormal proteins result in excess glomerular filtration that exceeds tubular reabsorptive capacity. The most common cause of overflow proteinuria is multiple myeloma, in which large amounts of immunoglobulin light chains are produced and appear in the urine (Bence Jones protein).

Detection. Qualitative detection of abnormal proteinuria is most easily accomplished with a dipstick impregnated with tetrabromophenol blue dye. The color of the dye changes in response to a pH shift related to the protein content of the urine, mainly albumin, leading to the development of a blue color. Because the background of the dipstick is yellow, various shades of green will develop, and the darker the green, the greater the concentration of protein in the urine. The minimal detectable protein concentration by this method is 20 to 30 mg/dL. False-negative results can occur in alkaline

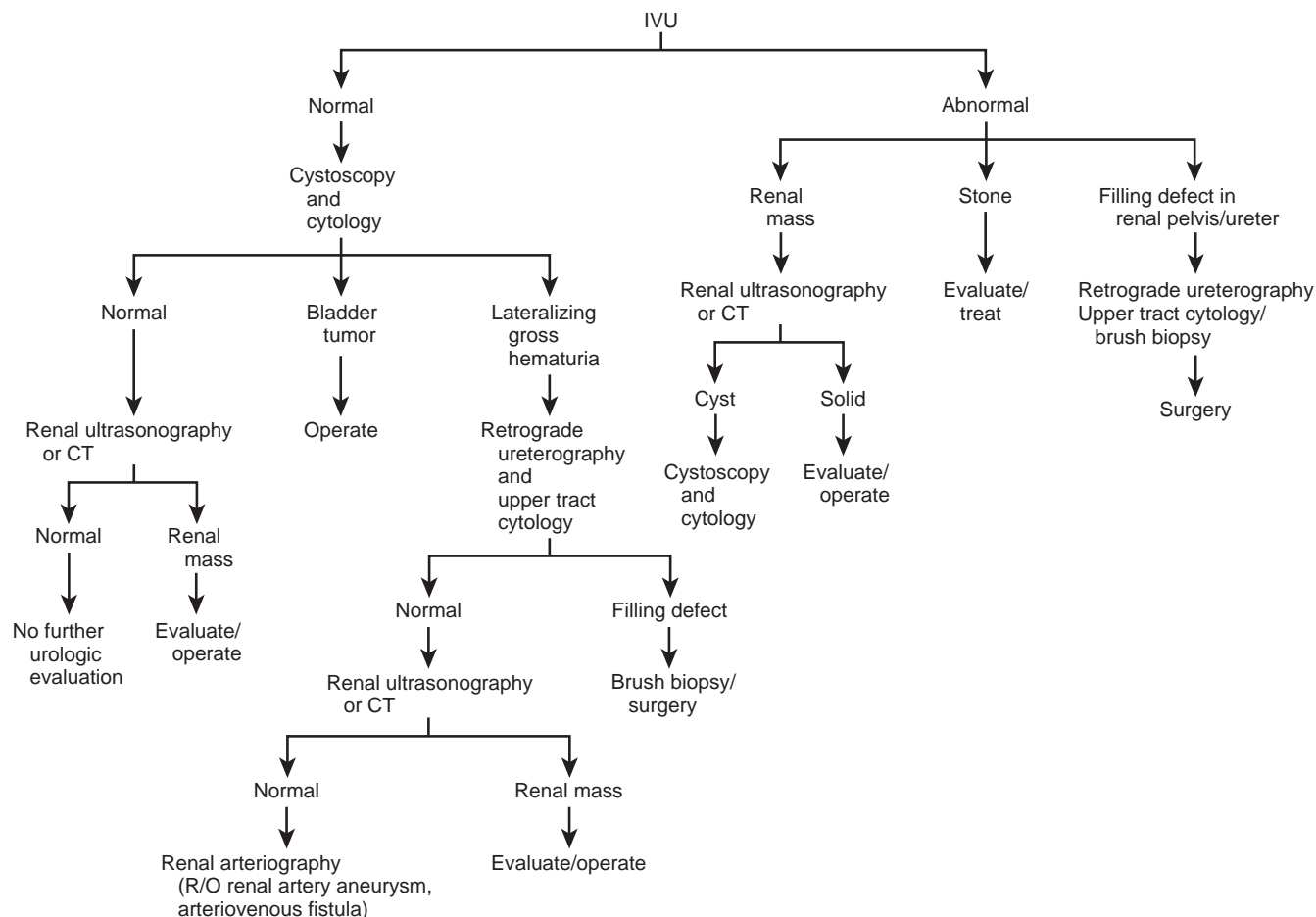


Figure 1-8. Evaluation of essential hematuria (circular erythrocytes, no erythrocyte casts, no significant proteinuria). CT, computed tomography; IVU, intravenous urography; R/O, rule out.

urine, dilute urine, or when the primary protein present is not albumin. Nephrotic range proteinuria in excess of 1 g/24 hr, however, is seldom missed on qualitative screening. Precipitation of urinary proteins with strong acids such as 3% sulfosalicylic acid will detect proteinuria at concentrations as low as 15 mg/dL and is more sensitive at detecting other proteins and albumin. Patients whose urine is negative on dipstick but strongly positive with sulfosalicylic acid should be suspected of having multiple myeloma, and the urine should be tested further for Bence Jones protein.

If qualitative testing reveals proteinuria, this should be titrated with a 24-hour urinary collection. Further qualitative assessment of abnormal urinary proteins can be accomplished by either protein electrophoresis or immunoassay for specific proteins. Protein electrophoresis is particularly helpful in distinguishing glomerular from tubular proteinuria. In glomerular proteinuria, albumin makes up about 70% of the total protein excreted, whereas in tubular proteinuria, the major proteins excreted are immunoglobulins with albumin making up only 10% to 20%. Immunoassay is the method of choice for detecting specific proteins such as Bence Jones protein in multiple myeloma.

Evaluation. Proteinuria should first be classified by its timing into transient, intermittent, or persistent. Transient proteinuria occurs commonly, especially in the pediatric population, and usually resolves spontaneously within a few days (Wagner et al, 1968). It may result from fever, exercise, or emotional stress. In older patients, transient proteinuria may be due to congestive heart failure. If a nonrenal cause is identified and a subsequent urinalysis is negative, no further evaluation is necessary. If proteinuria persists, it should be evaluated further.

Proteinuria may also occur intermittently, and this is frequently related to postural change (Robinson, 1985). Proteinuria

that occurs only in the upright position is a frequent cause of mild, intermittent proteinuria in young males. Total daily protein excretion seldom exceeds 1 g, and urinary protein excretion returns to normal when the patient is recumbent. Orthostatic proteinuria is thought to be secondary to increased pressure on the renal vein while standing. It resolves spontaneously in about 50% of patients and is not associated with any morbidity. Therefore if renal function is normal in patients with orthostatic proteinuria, no further evaluation is indicated.

Persistent proteinuria requires further evaluation, and most cases have a glomerular etiology. A quantitative measurement of urinary protein should be obtained through a 24-hour urine collection, and a qualitative evaluation should be obtained to determine the major proteins excreted. The findings of greater than 2 g of protein excreted per 24 hours, of which the major components are high-molecular-weight proteins such as albumin, establish the diagnosis of glomerular proteinuria. Glomerular proteinuria is the most common cause of abnormal proteinuria, especially in patients presenting with persistent proteinuria. If glomerular proteinuria is associated with hematuria characterized by dysmorphic erythrocytes and erythrocyte casts, the patient should be evaluated as outlined previously for glomerular hematuria (see Fig. 1-6). Patients with glomerular proteinuria who have no or little associated hematuria should be evaluated for other conditions, of which the most common is diabetes mellitus. Other possibilities include amyloidosis and arteriolar nephrosclerosis.

In patients in whom total protein excretion is 300 to 2000 mg/day, of which the major components are low-molecular-weight globulins, further qualitative evaluation with immunoelectrophoresis is indicated. This will determine whether the excess proteins are normal or abnormal. Identification of normal proteins

establishes a diagnosis of tubular proteinuria, and further evaluation for a specific cause of tubular dysfunction is indicated.

If qualitative evaluation reveals abnormal proteins in the urine, this establishes a diagnosis of overflow proteinuria. Further evaluation should be directed to identify the specific protein abnormality. The finding of large quantities of light-chain immunoglobulins or Bence Jones protein establishes a diagnosis of multiple myeloma. Similarly, the finding of large amounts of hemoglobin or myoglobin establishes the diagnosis of hemoglobinuria or myoglobinuria.

An algorithm for the evaluation of proteinuria is provided in Figure 1-9.

Glucose and Ketones

Urine testing for glucose and ketones is useful in screening patients for diabetes mellitus. Normally, almost all the glucose filtered by the glomeruli is reabsorbed in the proximal tubules. Although small amounts of glucose may normally be excreted in the urine, these amounts are not clinically significant and are below the level of detectability with the dipstick. If, however, the amount of glucose filtered exceeds the capacity of tubular reabsorption, glucose will be excreted in the urine and detected on the dipstick. This so-called renal threshold corresponds to serum glucose of about 180 mg/dL; above this level, glucose will be detected in the urine.

Glucose detection with the urinary dipstick is based on a double sequential enzymatic reaction yielding a colorimetric change. In the first reaction, glucose in the urine reacts with glucose oxidase on the dipstick to form gluconic acid and hydrogen peroxide. In the second reaction, hydrogen peroxide reacts with peroxidase, causing oxidation of the chromogen on the dipstick, producing a color change. This double-oxidative reaction is specific for glucose, and there is no cross-reactivity with other sugars. The dipstick test becomes less sensitive as the urine increases in specific gravity and temperature.

Ketones are not normally found in the urine but will appear when the carbohydrate supplies in the body are depleted and body fat breakdown occurs. This happens most commonly in diabetic ketoacidosis but may also occur during pregnancy and after periods of starvation or rapid weight reduction. Ketones excreted include acetoacetic acid, acetone, and β -hydroxybutyric acid. With abnormal fat breakdown, ketones will appear in the urine before the serum.

Dipstick testing for ketones involves a colorimetric reaction: Sodium nitroprusside on the dipstick reacts with acetoacetic acid to produce a purple color. Dipstick testing will identify acetoacetic acid at concentrations of 5 to 10 mg/dL but will not detect acetone or β -hydroxybutyric acid. A dipstick that tests positively for glucose should also be tested for ketones, and diabetes mellitus is suggested. False-positive results, however, can occur in acidic urine of high specific gravity, in abnormally colored urine, and in urine containing levodopa metabolites, 2-mercaptoethane sulfonate sodium, and other sulfhydryl-containing compounds (Csako, 1987).

Bilirubin and Urobilinogen

Normal urine contains no bilirubin and only small amounts of urobilinogen. There are two types of bilirubin: direct (conjugated) and indirect. Direct bilirubin is made in the hepatocyte, where bilirubin is conjugated with glucuronic acid. Conjugated bilirubin has a low molecular weight, is water soluble, and normally passes from the liver into the small intestine through the bile ducts, where it is converted to urobilinogen. Therefore conjugated bilirubin does not appear in the urine except in pathologic conditions in which there is intrinsic hepatic disease or obstruction of the bile ducts.

Indirect bilirubin is of high molecular weight and bound in the serum to albumin. It is water insoluble and therefore does not appear in the urine even in pathologic conditions.

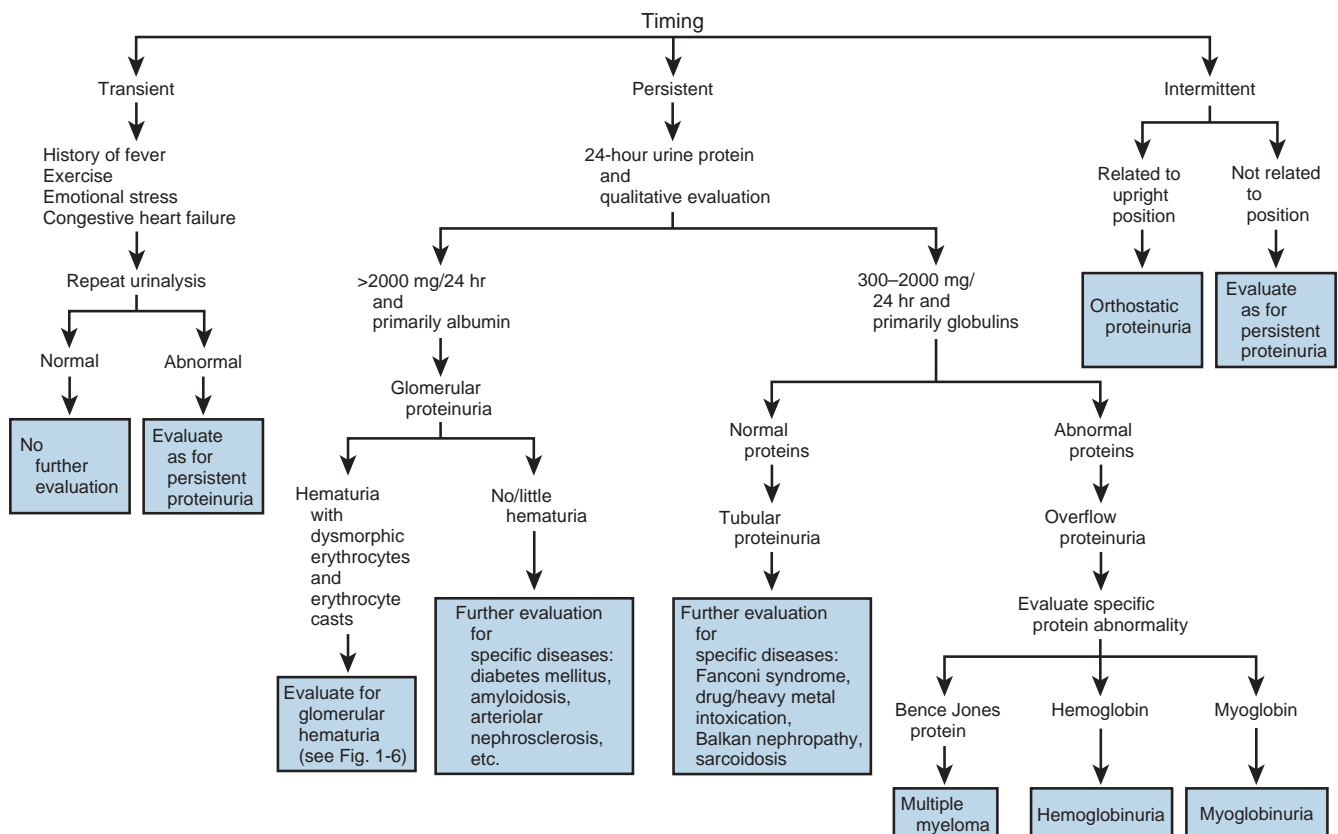


Figure 1-9. Evaluation of proteinuria.

Urobilinogen is the end product of conjugated bilirubin metabolism. Conjugated bilirubin passes through the bile ducts, where it is metabolized by normal intestinal bacteria to urobilinogen. Normally, about 50% of the urobilinogen is excreted in the stool and 50% is reabsorbed into the enterohepatic circulation. A small amount of absorbed urobilinogen, about 1 to 4 mg/day, will escape hepatic uptake and be excreted in the urine. Hemolysis and hepatocellular diseases that lead to increased bile pigments can result in increased urinary urobilinogen. Conversely, obstruction of the bile duct or antibiotic usage that alters intestinal flora, thereby interfering with the conversion of conjugated bilirubin to urobilinogen, will decrease urobilinogen levels in the urine. In these conditions, serum levels of conjugated bilirubin rise.

There are different dipstick reagents and methods to test for both bilirubin and urobilinogen, but the basic physiologic principle involves the binding of bilirubin or urobilinogen to a diazonium salt to produce a colorimetric reaction. False-negative results can occur in the presence of ascorbic acid, which decreases the sensitivity for detection of bilirubin. False-positive results can occur in the presence of phenazopyridine because it colors the urine orange and, similar to the colorimetric reaction for bilirubin, turns red in an acid medium.

Leukocyte Esterase and Nitrite Tests

Leukocyte esterase activity indicates the presence of white blood cells in the urine. The presence of nitrites in the urine is strongly suggestive of bacteriuria. Thus both of these tests have been used to screen patients for UTIs. Although these tests may have application in nonurologic medical practice, the most accurate method to diagnose infection is by microscopic examination of the urinary sediment to identify pyuria and subsequent urine culture. All urologists should be capable of performing and interpreting the microscopic examination of the urinary sediment. Therefore leukocyte esterase and nitrite testing are less important in a urologic practice. For purposes of completion, however, both techniques are described briefly herein.

Leukocyte esterase and nitrite testing are performed using the Chemstrip LN dipstick. Leukocyte esterase is produced by neutrophils and catalyzes the hydrolysis of an indoxyl carbonic acid ester to indoxyl (Gillenwater, 1981). The indoxyl formed oxidizes a diazonium salt chromogen on the dipstick to produce a color change. It is recommended that leukocyte esterase testing be done 5 minutes after the dipstick is immersed in the urine to allow adequate incubation (Shaw et al, 1985). The sensitivity of this test subsequently decreases with time because of lysis of the leukocytes. Leukocyte esterase testing may also be negative in the presence of infection because not all patients with bacteriuria will have significant pyuria. Therefore if one uses leukocyte esterase testing to screen patients for UTI, it should always be done in conjunction with nitrite testing for bacteriuria (Pels et al, 1989).

Other causes of false-negative results with leukocyte esterase testing include increased urinary specific gravity, glycosuria, presence of urobilinogen, medications that alter urine color, and ingestion of large amounts of ascorbic acid. The major cause of false-positive leukocyte esterase tests is specimen contamination.

Nitrites are not normally found in the urine, but many species of gram-negative bacteria can convert nitrates to nitrites. Nitrites can readily be detected in the urine because they react with the reagents on the dipstick and undergo diazotization to form a red azo dye. The specificity of the nitrite dipstick for detecting bacteriuria is higher than 90% (Pels et al, 1989). The sensitivity of the test, however, is considerably less, varying from 35% to 85%. The nitrite test is less accurate in urine specimens containing fewer than 10^5 organisms/mL (Kellogg et al, 1987). As with leukocyte esterase testing, the major cause of false-positive nitrite testing is contamination.

It remains controversial whether dipstick testing for leukocyte esterase and nitrites can replace microscopy in screening for significant UTIs. This issue is less important to urologists, who usually have access to a microscope and who should be trained and

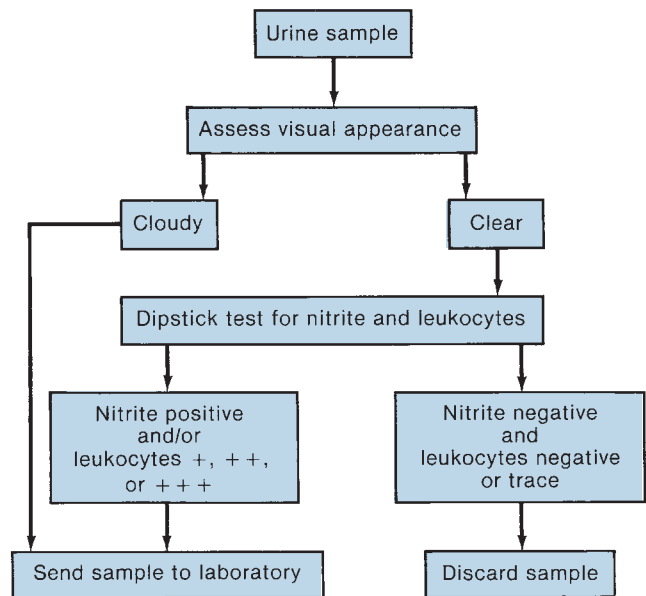


Figure 1-10. Protocol for determining the need for urine sediment microscopy in an asymptomatic population. (From Flanagan PG, Rooney PG, Davies EA, et al. Evaluation of four screening tests for bacteriuria in elderly people. *Lancet* 1989;1:1117. © by The Lancet Ltd., 1989.)

encouraged to examine the urinary sediment. A protocol combining the visual appearance of the urine with leukocyte esterase and nitrite testing has been proposed (Fig. 1-10). It reportedly detects 95% of infected urine specimens and decreases the need for microscopy by as much as 30% (Flanagan et al, 1989). Other studies, however, have shown that dipstick testing is not an adequate replacement for microscopy (Propp et al, 1989). In summary, it has not been demonstrated conclusively that dipstick testing for UTI can replace microscopic examination of the urinary sediment. In our personal experience, we always examine the urinary sediment whenever we suspect a UTI and subsequently culture the urine when pyuria is identified.

Urinary Sediment

Obtaining and Preparing the Specimen

A clean-catch midstream urine specimen should be obtained. As described earlier, uncircumcised men should retract the prepuce and cleanse the glans penis before voiding. It is more difficult to obtain a reliable clean-catch specimen in females because of contamination with introital leukocytes and bacteria. If there is any suspicion of a UTI in a female, a catheterized urine sample should be obtained for culture and sensitivity.

If possible, the first morning urine specimen is the specimen of choice and should be examined within 1 hour. A standard procedure for preparation of the urine for microscopic examination has been described (Cushner and Copley, 1989). Ten to 15 milliliters of urine should be centrifuged for 5 minutes at 3000 rpm. The supernatant is then poured off, and the sediment is resuspended in the centrifuge tube by gently tapping the bottom of the tube. Although the remaining small amount of fluid can be poured onto a microscope slide, this usually results in excess fluid on the slide. It is better to use a small pipette to withdraw the residual fluid from the centrifuge tube and to place it directly on the microscope slide. This usually results in an ideal volume of between 0.01 and 0.02 mL of fluid deposited on the slide. The slide is then covered with a coverslip. The edge of the coverslip should be placed on the slide first to allow the drop of fluid to ascend onto the coverslip by capillary action. The coverslip is then gently placed over the drop of fluid, and this technique allows for most of the air between the drop of

fluid and the coverslip to be expelled. If one simply drops the coverslip over the urine, the urine will disperse over the slide and there will be a considerable number of air bubbles that may distort the subsequent microscopic examination.

Microscopy Technique

Microscopic analysis of the urinary sediment should be performed with both low-power ($\times 100$ magnification) and high-power ($\times 400$ magnification) lenses. The use of an oil immersion lens for higher magnification is seldom, if ever, necessary. Under low power, the entire area under the coverslip should be scanned. **Particular attention should be given to the edges of the coverslip, where casts and other elements tend to be concentrated.** Low-power magnification is sufficient to identify erythrocytes, leukocytes, casts, cystine crystals, oval fat macrophages, and parasites such as *Trichomonas vaginalis* and *Schistosoma hematobium*.

High-power magnification is necessary to distinguish circular from dysmorphic erythrocytes, to identify other types of crystals, and, particularly, to identify bacteria and yeast. In summary, **the urinary sediment should be examined microscopically for (1) cells, (2) casts, (3) crystals, (4) bacteria, (5) yeast, and (6) parasites.**

Cells

Erythrocyte morphology may be determined under high-power magnification. Although phase contrast microscopy has been used for this purpose, circular (nonglomerular) erythrocytes can generally be distinguished from dysmorphic (glomerular) erythrocytes under routine brightfield high-power magnification (Figs. 1-11 to 1-15). This is assisted by adjusting the microscope condenser to

its lowest aperture, thus reducing the intensity of background light. This allows one to see fine detail not evident otherwise and also creates the effect of phase microscopy because cell membranes and other sedimentary components stand out against the darkened background.

Circular erythrocytes generally have an even distribution of hemoglobin with either a round or crenated contour, whereas dysmorphic erythrocytes are irregularly shaped with minimal hemoglobin and irregular distribution of cytoplasm. Automated techniques for performing microscopic analysis to distinguish the two types of erythrocytes have been investigated but have not yet been accepted into general urologic practice and are probably unnecessary. In one study using a standard Coulter counter, microscopic analysis was found to be 97% accurate in differentiating between the two types of erythrocytes (Sayer et al, 1990). **Erythrocytes may be confused with yeast or fat droplets (Fig. 1-16).** Erythrocytes can be distinguished, however, because yeast will show budding and oil droplets are highly refractile.

Leukocytes can generally be identified under low power and definitively diagnosed under high-power magnification (Figs. 1-17 and 1-18; see also Fig. 1-16). It is normal to find 1 or 2 leukocytes/HPF in men and up to 5/HPF in women in whom the urine sample may be contaminated with vaginal secretions. A greater number of leukocytes generally indicates infection or inflammation in the urinary tract. It may be possible to distinguish **old leukocytes, which have a characteristic small and wrinkled appearance** and which are commonly found in the vaginal secretions of normal women, from fresh leukocytes, which are generally indicative of urinary tract pathology. Fresh leukocytes are generally larger and

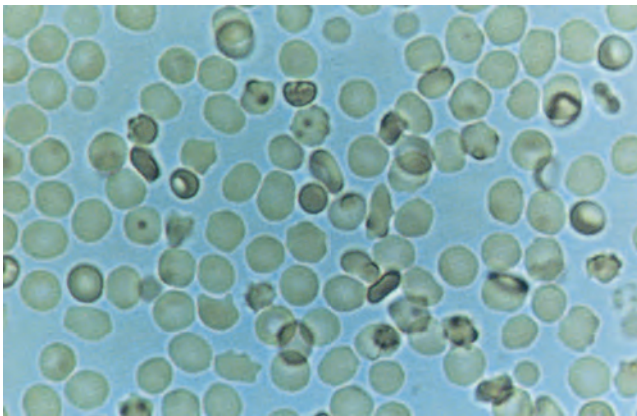


Figure 1-11. Red blood cells, both smoothly rounded and mildly crenated, typical of epithelial erythrocytes.

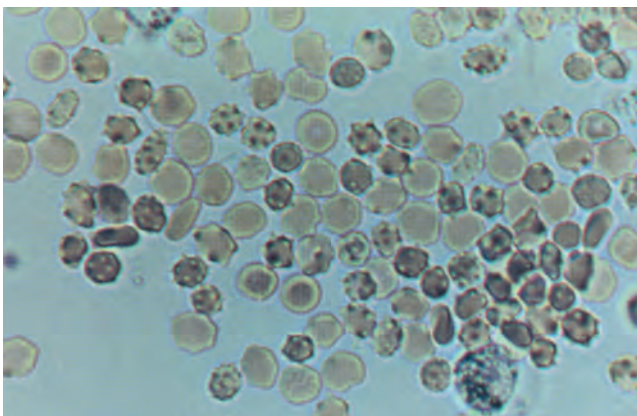


Figure 1-12. Red blood cells from a patient with a bladder tumor.

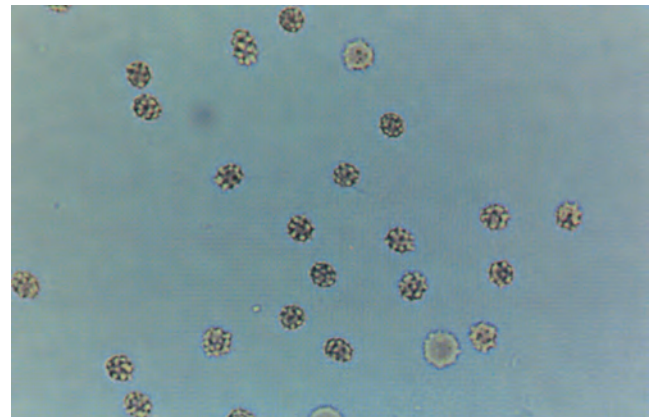


Figure 1-13. Red blood cells from a patient with interstitial cystitis. Cells were collected at cystoscopy.

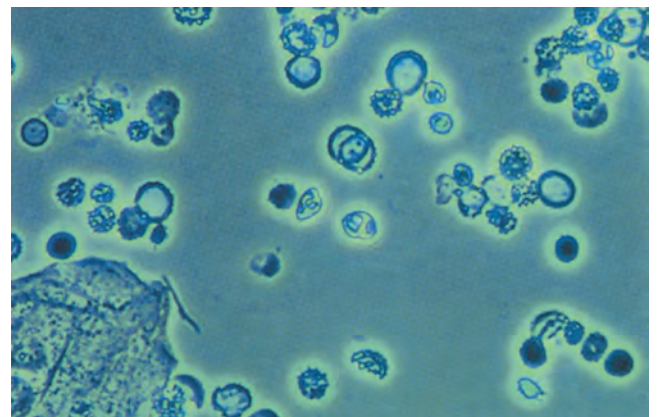


Figure 1-14. Red blood cells from a patient with Berger disease. Note variations in membranes characteristic of dysmorphic red blood cells.

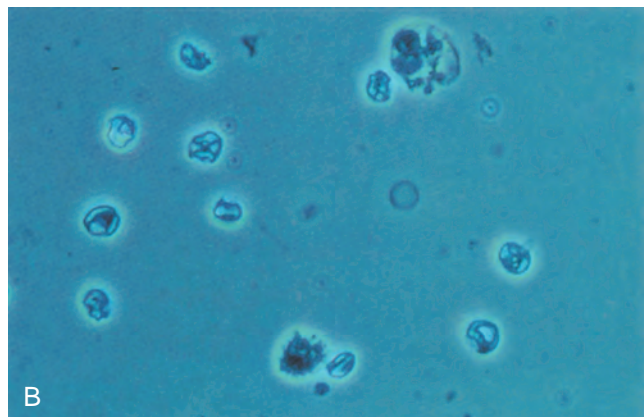
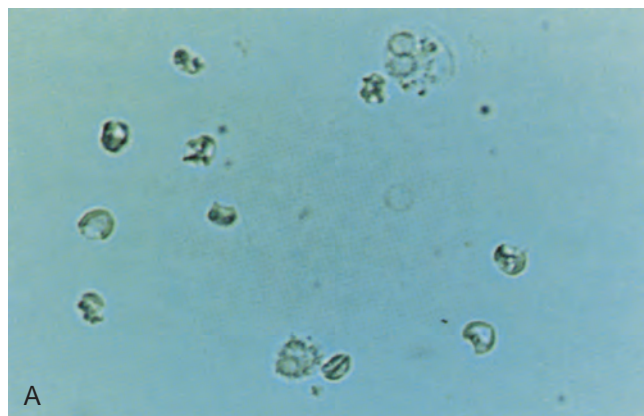


Figure 1-15. Dysmorphic red blood cells from a patient with Wegener granulomatosis. A, Brightfield illumination. B, Phase illumination. Note irregular deposits of dense cytoplasmic material around the cell membrane.

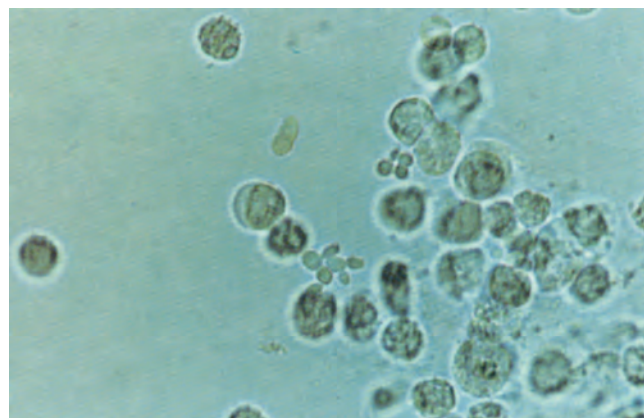


Figure 1-16. *Candida albicans*. Budding forms surrounded by leukocytes.

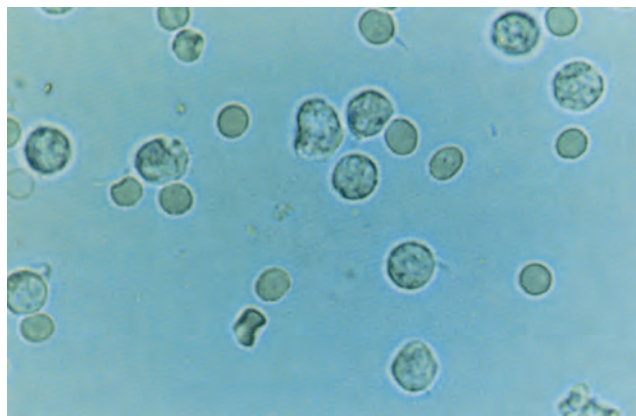


Figure 1-17. Old leukocytes. Staghorn calculi with *Proteus* infection.

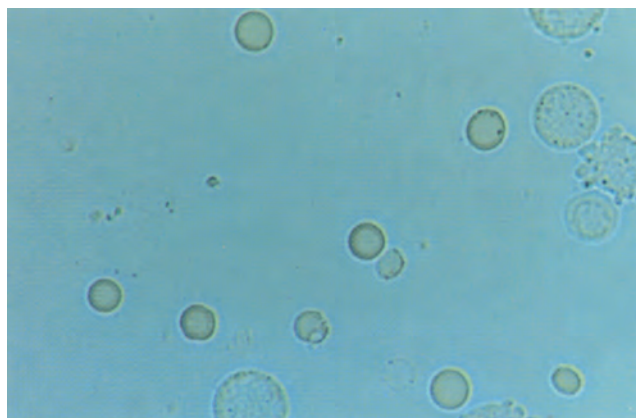


Figure 1-18. Fresh "glitter cells" with erythrocytes in background.

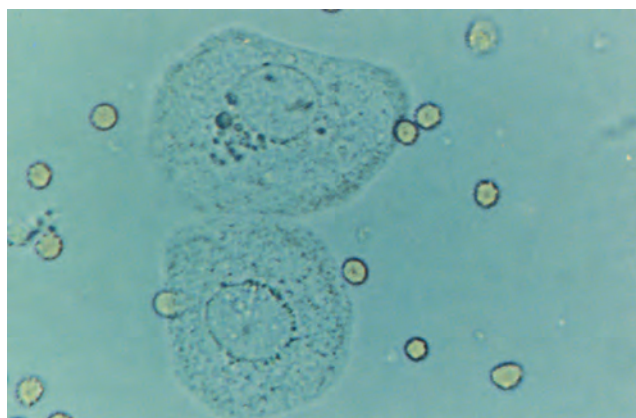


Figure 1-19. Transitional epithelial cells from bladder lavage.

rounder, and, when the specific gravity is less than 1.019, the granules in the cytoplasm demonstrate glitterlike movement, so-called glitter cells.

Epithelial cells are commonly observed in the urinary sediment. Squamous cells are frequently detected in female urine specimens and are derived from the lower portion of the urethra, the trigone of postpubertal females, and the vagina. Squamous epithelial cells are large, have a central small nucleus about the size of an erythrocyte, and have an irregular cytoplasm with fine granularity.

Transitional epithelial cells may arise from the remainder of the urinary tract (Fig. 1-19). Transitional cells are smaller than squamous cells, have a larger nucleus, and demonstrate prominent cytoplasmic granules near the nucleus. Malignant transitional cells have altered nuclear size and morphology and can be identified with either routine Papanicolaou staining or automated flow cytometry.

Renal tubular cells are the least commonly observed epithelial cells in the urine but are most significant because their presence in the urine is always indicative of renal pathology. Renal tubular

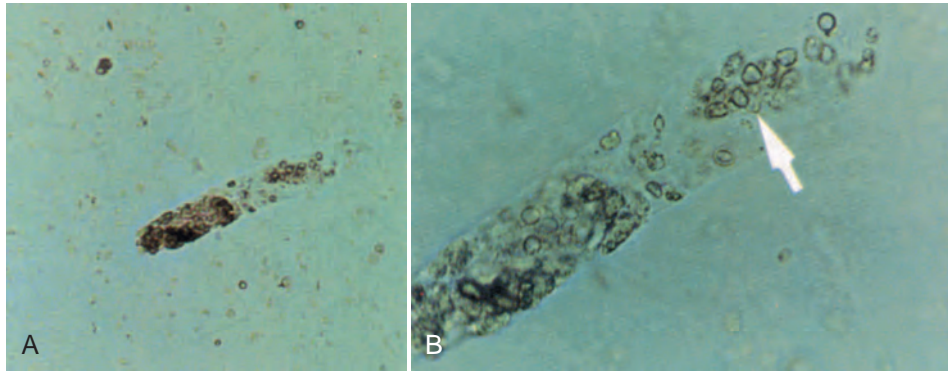


Figure 1-20. Red blood cell cast. A, Low-power view demonstrates distinct border of hyaline matrix. B, High-power view demonstrates the sharply defined red blood cell membranes (arrow). Berger disease.

cells may be difficult to distinguish from leukocytes, but they are slightly larger.

Casts

A cast is a protein coagulum that is formed in the renal tubule and traps any tubular luminal contents within the matrix. **Tamm-Horsfall mucoprotein is the basic matrix of all renal casts; it originates from tubular epithelial cells and is always present in the urine.** When the casts contain only mucoproteins, they are called *hyaline casts* and may not have any pathologic significance. Hyaline casts may be seen in the urine after exercise or heat exposure but may also be observed in pyelonephritis or chronic renal disease.

RBC casts contain entrapped erythrocytes and are diagnostic of glomerular bleeding, most likely secondary to glomerulonephritis (Figs. 1-20 and 1-21). White blood cell casts are observed in acute glomerulonephritis, acute pyelonephritis, and acute tubulointerstitial nephritis. Casts with other cellular elements, usually sloughed renal tubular epithelial cells, are indicative of nonspecific renal damage (Fig. 1-22). Granular and waxy casts result from further degeneration of cellular elements. Fatty casts are seen in nephrotic syndrome, lipiduria, and hypothyroidism.

Crystals

Identification of crystals in the urine is particularly important in patients with stone disease because it may help determine the etiology (Fig. 1-23). Although other types of crystals may be seen in normal patients, **the identification of cystine crystals establishes the diagnosis of cystinuria.** Crystals precipitated in acidic urine include calcium oxalate, uric acid, and cystine. Crystals precipitated in an alkaline urine include calcium phosphate and triple-phosphate (struvite) crystals. Cholesterol crystals are rarely seen in the urine and are not related to urinary pH. They occur in lipiduria and remain in droplet form.

Bacteria

Normal urine should not contain bacteria; in a fresh uncontaminated specimen, the finding of bacteria is indicative of a UTI. Because each HPF views between 1/20,000 and 1/50,000 mL, each bacterium seen per HPF signifies a bacterial count of more than 30,000/mL. Therefore, **5 bacteria/HPF reflects colony counts of about 100,000/mL.** This is the standard concentration used to establish the diagnosis of a UTI in a clean-catch specimen. This level should apply only to women, however, in whom a clean-catch specimen is frequently contaminated. The finding of any bacteria in a properly collected midstream specimen from a male should be further evaluated with a urine culture.

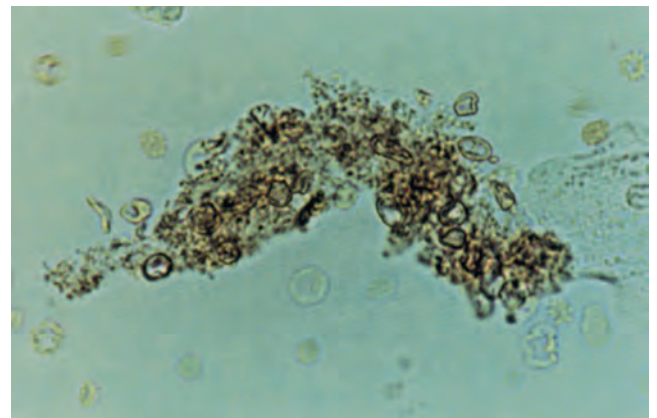


Figure 1-21. Red blood cell cast.

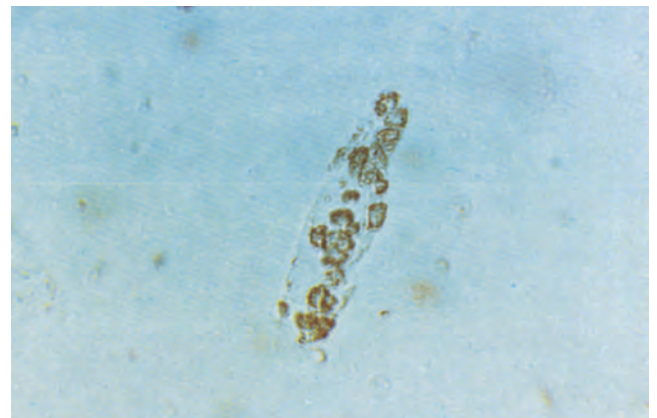


Figure 1-22. Cellular cast. Cells entrapped in a hyaline matrix.

Under high power, it is possible to distinguish various bacteria. Gram-negative rods have a characteristic bacillary shape (Fig. 1-24), whereas streptococci can be identified by their characteristic beaded chains (Figs. 1-25 and 1-26) and staphylococci can be identified when the organisms are found in clumps (Fig. 1-27).

Yeast

The most common yeast cells found in urine are *Candida albicans*. The biconcave oval shape of yeast can be confused with

Crystals

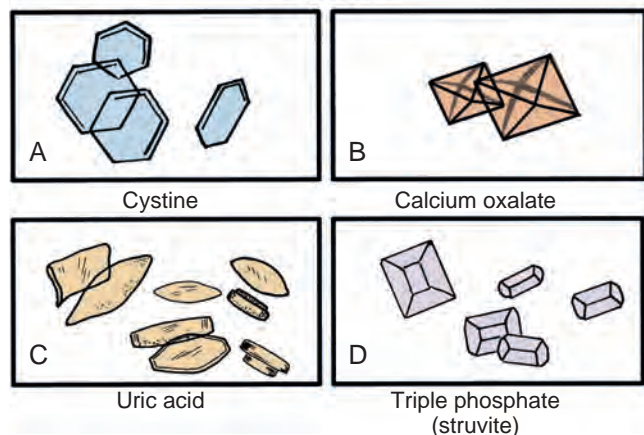


Figure 1-23. Urinary crystals. A, Cystine. B, Calcium oxalate. C, Uric acid. D, Triple phosphate (struvite).

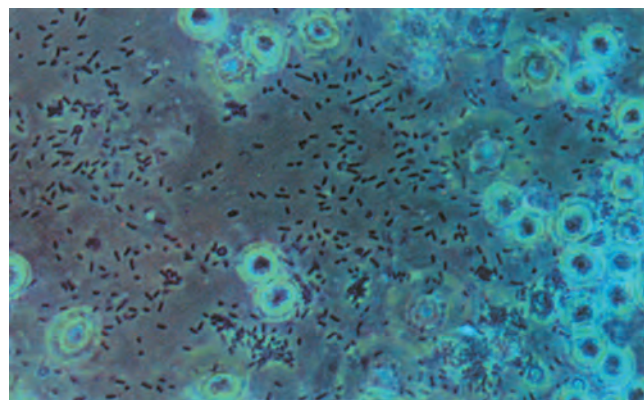


Figure 1-24. Gram-negative bacilli. Phase microscopy of *Escherichia coli*.

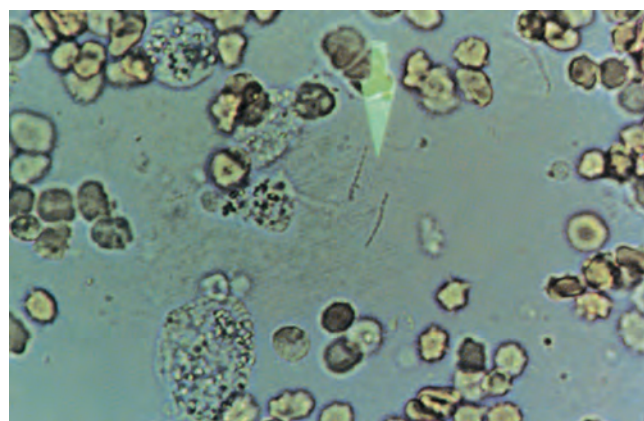


Figure 1-25. Streptococcal urinary tract infection with typical chain formation (arrow).

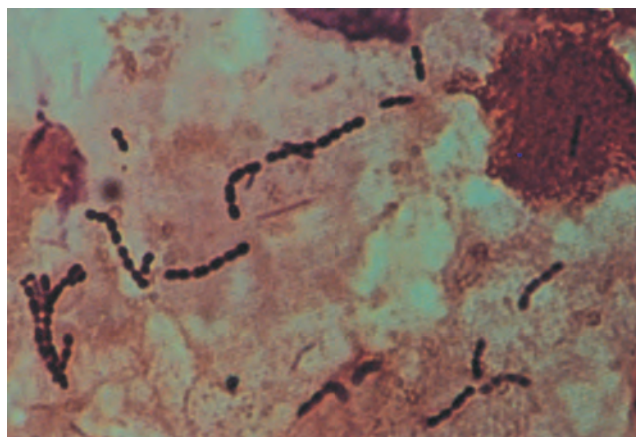


Figure 1-26. Streptococcal urinary tract infection (Gram stain).

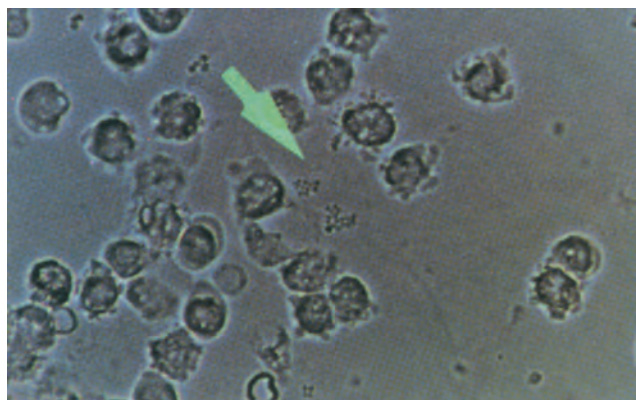


Figure 1-27. *Staphylococcus aureus* in typical clumps (arrow).

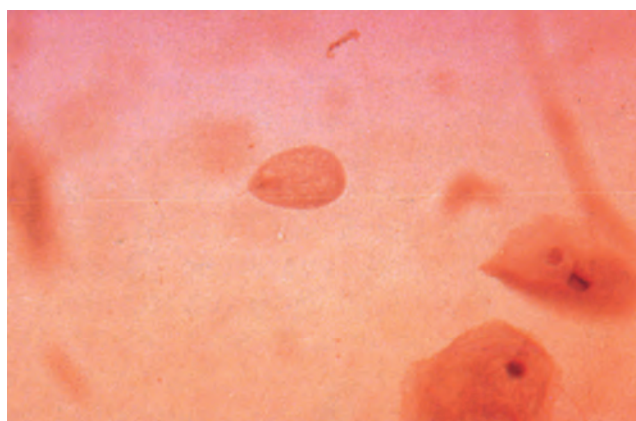


Figure 1-28. Trichomonad with ovoid shape and motile flagella.

erythrocytes and calcium oxalate crystals, but yeasts can be distinguished by their characteristic budding and hyphae (see Fig. 1-16). Yeasts are most commonly seen in the urine of patients with diabetes mellitus or as contaminants in women with vaginal candidiasis.

Parasites

Trichomonas vaginalis is a frequent cause of vaginitis in women and occasionally of urethritis in men. Trichomonads can be readily identified in a clean-catch specimen under low power (Fig. 1-28). Trichomonads are large cells with rapidly moving flagella that quickly propel the organism across the microscopic field.

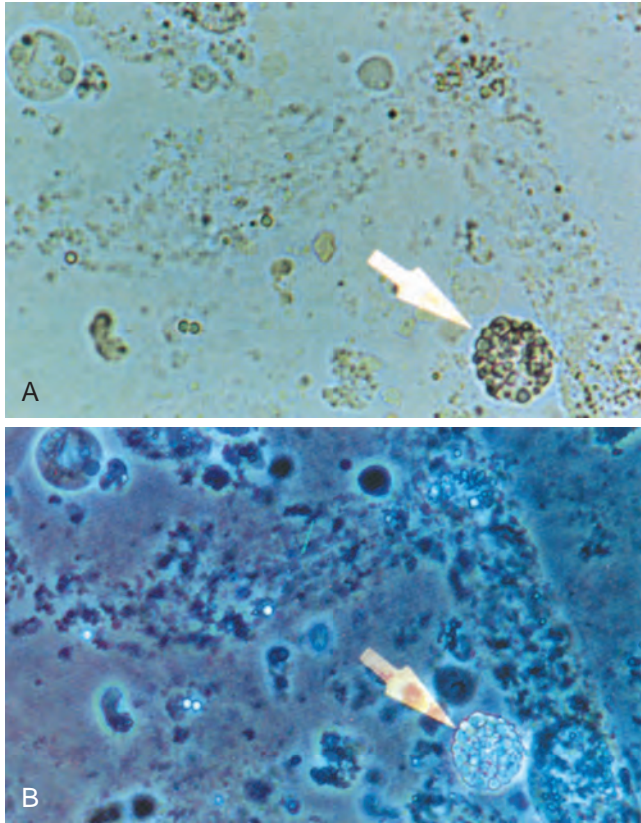


Figure 1-29. Oval fat macrophage. A, High-power view showing doubly refractile fat particles (arrow). B, Phase microscopy of the same specimen (arrow).

Schistosoma hematobium is a urinary tract pathogen that is not found in the United States but is extremely common in countries of the Middle East and North Africa. Examination of the urine shows the characteristic parasitic ova with a terminal spike.

Expressed Prostatic Secretions

Although not strictly a component of the urinary sediment, the expressed prostatic secretions should be examined in any man suspected of having prostatitis. Normal prostatic fluid should contain few, if any, leukocytes, and the presence of a larger number or clumps of leukocytes is indicative of prostatitis. **Oval fat macrophages are found in postinfection prostatic fluid (Figs. 1-29 and 1-30).** Normal prostatic fluid contains numerous secretory granules that resemble but can be distinguished from leukocytes under high power because they do not have nuclei.

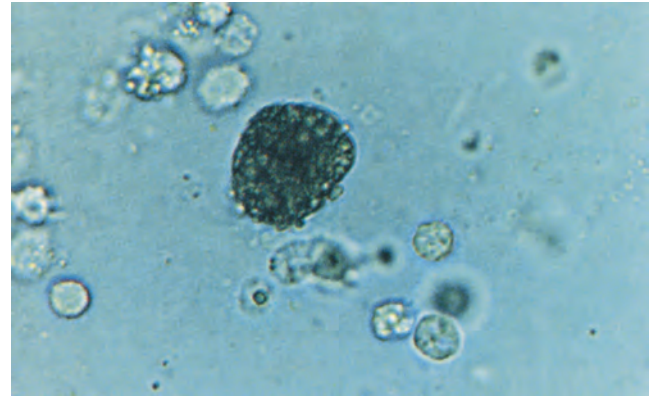


Figure 1-30. Oval fat macrophage, high-power view. Note the fine secretory granules in the prostatic fluid.

SUMMARY

This chapter has detailed the basic evaluation of the urologic patient, which should include a careful history, physical examination, and urinalysis. These three basic components form the cornerstone of the urologic evaluation and should precede any subsequent diagnostic procedures. After completion of the history, physical examination, and urinalysis, the urologist should be able to establish at least a differential, if not specific, diagnosis that will allow the subsequent diagnostic evaluation and treatment to be carried out in a direct and efficient manner.

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2 Urinary Tract Imaging: Basic Principles of Computed Tomography, Magnetic Resonance Imaging, and Plain Film

Jay T. Bishoff, MD, FACS, and Art R. Rastinehad, DO

Conventional Radiography

Radiation Management in Uroradiology

Contrast Media

Intravenous Urography

Plain Abdominal Radiography

Retrograde Pyelography

Loopography

Retrograde Urethrography

Static Cystography

Voiding Cystourethrogram

Nuclear Scintigraphy

Computed Tomography

Magnetic Resonance Imaging

Imaging continues to play an indispensable role in the diagnosis and management of urologic diseases. Because many urologic conditions cannot be assessed by physical examination, conventional radiography has long been critical to the diagnosis of conditions of the adrenals, kidneys, ureters, and bladder. The development of computed tomography (CT) imaging and the use of intravenous contrast agents have provided detailed anatomic, functional, and physiologic information about urologic conditions. In this chapter we will discuss the indications for imaging in urology with an emphasis on the underlying physical principles of the imaging modalities. The strengths and limitations of each modality, as well as the techniques necessary to maximize image quality and minimize the risks and harms to urologic patients, are discussed.

CONVENTIONAL RADIOGRAPHY

Conventional radiography, although eclipsed by CT and magnetic resonance imaging (MRI) for certain indications, remains useful for preoperative diagnosis and postoperative evaluation in a variety of different urologic conditions. Conventional radiography includes abdominal plain radiography, intravenous excretory urography, retrograde pyelography, loopography, retrograde urethrography, and cystography. Urologists frequently perform and interpret conventional radiography examinations, including fluoroscopic examinations, in the office and operating room environments.

Physics

It is important for urologists to understand the physics of conventional radiography and fluoroscopy, as well as the implications and dangers of radiation exposure to the patient and the operator. The underlying physical principles of conventional radiography involve emitting a stream of photons from an x-ray source. These photons travel through the air and strike tissue, imparting energy to that tissue. Some of the photons emerge from the patient with varying amounts of energy attenuation and strike an image recorder such as a film cassette or the input phosphor of an image-intensifier tube, thus producing an image (Fig. 2-1).

RADIATION MANAGEMENT IN URORADIOLOGY

When diagnostic radiation passes through tissue, it creates ion pairs. The resultant charge per unit mass of air is referred to as the **radiation exposure**. The current unit of radiation exposure is coulombs(C)/kg. **Absorbed dose** is the energy absorbed from the radiation exposure and is measured in units called gray (Gy). The older unit of absorbed dose was called the rad (1 rad =100 Gy).

Because different types of radiation have different types of interaction with tissue, a conversion factor is applied to better express the amount of energy absorbed by a given tissue. The application of this conversion factor to the **absorbed dose** yields the **equivalent dose** measured in sieverts (Sv). For diagnostic x-rays the conversion factor is 1, so the absorbed dose is the same as the equivalent dose. When discussing the amount of radiation energy absorbed by patients during therapeutic radiation, the dose is given in gray. When discussing exposure to patients or medical personnel because of diagnostic ionizing radiation procedures, the dose is given in sieverts.

The distribution of energy absorption in the human body will be different based on the body part being imaged and a variety of other factors. The most important risk of radiation exposure from diagnostic imaging is the development of cancer. The **effective dose** is a quantity used to denote the radiation risk (expressed in **sieverts**) to a population of patients from an imaging study. See Table 2-1 for a description of the relationship between these measures of radiation exposure.

The average person living in the United States is exposed to 6.2 mSv of radiation per year from ambient sources, such as radon and cosmic rays, and medical procedures, which account for 36% of the annual radiation exposure (National Council on Radiation Protection and Measurements, 2012). The recommended occupational exposure limit to medical personnel is 50 mSv per year (National Council on Radiation Protection and Measurements, 2012). Exposure to the eyes and gonads has a more significant biologic impact than exposure to the extremities, so recommended exposure limits vary according to the body part. The linear no-threshold model (LNT) used in radiation protection to quantify exposition and to set regulatory limits assumes that the long-term, biologic damage caused by ionizing radiation is directly

proportional to the dose. **Based on the LNT, there is no safe dose of radiation.** An effective radiation dose of as little as 10 mSv may result in the development of a malignancy in 1 of 1000 individuals exposed (National Research Council of the National Academies, 2006).

Relative Radiation Levels

The assessment of biologic risk from radiation exposure is complex. By estimating the range of effective doses for various imaging modalities, they can be assigned a **relative radiation level (RRL)** (Table 2-2). The effective dose from a 3-phase CT of the abdomen and pelvis without and with contrast may be as high as 25 to 40 mSv. Another often overlooked source of significant radiation exposure is fluoroscopy. Fluoroscopy for 1 minute results in a radiation dose to the skin equivalent to 10 times that of a single radiograph of the same anatomic area (Geise and Morin, 2000).

Radiation Protection

The cumulative dose of radiation to patients increases relatively rapidly with repeated CT imaging studies or procedures guided by fluoroscopy. Certain patient populations such as those with recurrent renal calculus disease or those with a urologic malignancy may be at increased risk of developing cancer because of repeated exposures to ionizing radiation. Attempts should be made to limit axial imaging studies to the anatomic area of interest and to substitute imaging studies not requiring ionizing radiation when feasible. The cumulative dose of radiation to medical personnel, including physicians, may increase relatively rapidly when fluoroscopy is used.

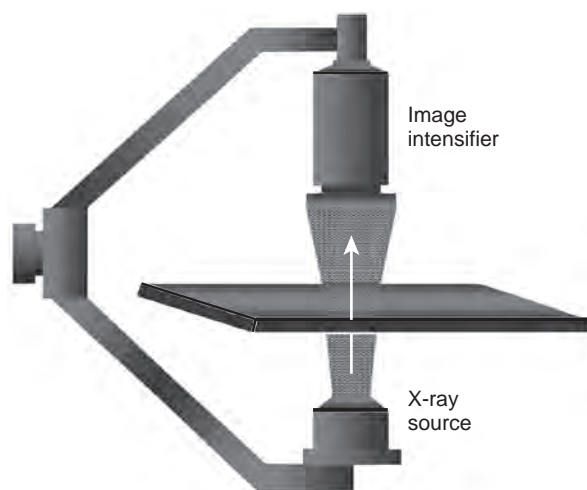


Figure 2-1. Equipment setup for fluoroscopy. The x-ray source located beneath the table reduces the radiation exposure to the surgeon. Locating the image intensifier as close to the patient as feasible reduces scatter radiation. Equipment setup will vary based on application.

Reduction in radiation exposure to medical personnel is achieved by three major mechanisms: (1) limiting the time of exposure; (2) maximizing distance from the radiation source; and (3) shielding. Radiation dose during fluoroscopy is directly proportional to the **time of exposure** and the **number of exposures**. The exposure time during fluoroscopy should be minimized by using short bursts of fluoroscopy and using the “last image hold” feature of the fluoroscopy unit. Radiation beams diverge with distance, and therefore radiation exposure diminishes as the square of the distance from the radiation source. Maintaining the maximum practical distance from an active radiation source significantly decreases exposure to medical personnel. Positioning the image intensifier as close as feasible to the patient substantially reduces scatter radiation. Standard aprons, thyroid shields, proper eye protection, and leaded gloves provide significant shielding for medical personnel and should be worn by all personnel involved in the use of fluoroscopy. **A practice of routinely collimating to the minimum required visual fluoroscopy field results in significant reductions in radiation exposure, compared with a usual approach to collimation. This may have important implications for decreasing the risk of malignancy in patients and operators.**

KEY POINTS: CONVENTIONAL RADIOGRAPHY/ RADIATION MANAGEMENT IN UROLOGY

- The effective radiation dose describes the potential for adverse health effects from ionizing radiation.
- The effective dose is a quantity used to denote the radiation risk (expressed in sieverts) to a population of patients from an imaging study. See Table 2-1 for a description of the relationship between these measures of radiation exposure.
- Based on the LNT model, there is no safe dose of radiation.
- Relative radiation levels (RRL) categorize diagnostic imaging studies by their estimated effective dose of radiation.
- Radiation protection for medical personnel includes (1) limiting time of exposure; (2) maximizing distance from radiation source; and (3) shielding.
- Collimating to the minimum required visual fluoroscopy field reduces exposure to the patient and operator.

CONTRAST MEDIA

The urologist ordering a radiographic evaluation on a patient must consider the risks and benefits associated with a contrast-enhanced imaging study, as well as alternative imaging modalities that could provide the same information without the need for contrast exposure.

Many different types of contrast media have been used to enhance medical imaging and thus improve diagnostic and therapeutic decisions made by urologists. These agents are used on a daily basis throughout the world with great safety and efficacy. However, there are inherent risks associated with the use of contrast

TABLE 2-1 Units of Radiation Exposure and Clinical Relevance of the Measures

RADIATION QUANTITY	TRADITIONAL UNIT	SI UNIT	CONVERSION	CLINICAL RELEVANCE
Exposure	Roentgen (R)	Coulomb (C)/kg	1 C/kg = 3876 R	Charge per unit mass
Absorbed dose	Rad	Gray (Gy)	1 Gy = 100 rad	Energy absorbed by tissue
Equivalent dose	Rem	Sievert (Sv)	1 Sv = 100 rem	Absorbed energy based on tissue type
Effective dose	Rem	Sievert (Sv)		Biologic risk associated with absorbed energy

Modified from Geise RA, Morin RL. Radiation management in urology. In: Pollack HM, McClennan BL, editors. Clinical urography. 2nd ed. Philadelphia: Saunders; 2000. p. 13.

TABLE 2-2 Radiation Exposure from Common Urologic Imaging Procedures

RELATIVE RADIATION LEVEL (RRL)	EFFECTIVE DOSE ESTIMATED RANGE	EXAMPLE EXAMINATIONS
None	0	Ultrasonography, MRI
Minimal	<0.1 mSv	Chest radiographs
Low	0.1-1.0 mSv	Lumbar spine radiographs, pelvic radiographs
Medium	1-10 mSv	Abdomen CT without contrast, nuclear medicine, bone scan, ^{99m} Tc-DMSA renal scan, IVP, retrograde pyelograms, KUB, CT chest with contrast
High	10 mSv-100 mSv	Abdomen CT without and with contrast, whole-body PET

CT, computed tomography; IVP, intravenous pyelogram; KUB, kidneys, ureters, bladder; MRI, magnetic resonance imaging; ^{99m}Tc-DMSA, technetium 99m-dimercaptosuccinic acid; PET, positron emission tomography. Modified from American College of Radiology. ACR appropriateness criteria radiation dose assessment introduction, <http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/RRLInformation.aspx>; 2008.

media, as with other pharmaceuticals. Adverse side effects and adverse drug reactions (ADRs) can directly result from the use of contrast media and vary from minor disturbances to severe, life-threatening situations. Imaging centers must be prepared with trained personnel, readily available medications, equipment, and an ongoing system to educate clinic personnel on the recognition and treatment of ADRs associated with contrast media.

Intravascular Iodinated Contrast Media

Iodine is the most common element in general use as an intravascular radiologic contrast medium (IRCM). With an atomic weight of 127, iodine has radiopacity, whereas other elements included in IRCM have no radiopacity and act only as carriers of the iodine elements, increasing solubility, and reducing toxicity. Four basic types of iodinated IRCM are available for clinical use: ionic monomer, nonionic monomer, ionic dimer, and nonionic dimer. They can be further characterized as being iso-, hyper-, or low-osmolar compared to physiologic osmolality of 300 mOsm/kg water.

All are derived from a 2,4,6 tri-iodinated benzene ring compound with three atoms of iodine in the case of monomers and six atoms of iodine in the case of dimers. The chemical composition of these agents makes them highly hydrophilic, low in lipid solubility, and of low binding affinity for protein receptors or membranes. Because they do not enter red blood cells or tissue cells and are rapidly excreted, they are designed for use in imaging and are not therapeutic. Approximately 90% will be eliminated by the kidneys within 12 hours of administration.

Relative to the body's iodine stores, large quantities of iodine are required for imaging enhancement. The total body iodine content, found mainly in the thyroid gland is 0.01 g and the average daily turnover of iodine is only 0.0001 g. For renal CT imaging a common dose of IRCM will expose the patient to between 25 and 50 g of iodine, which is approximately 400,000 times the daily turnover rate in the human body, but this dose will rarely cause any toxicity or lasting effects (Morris, 1993).

Adverse Reactions to Intravascular Iodinated Contrast Media

ADRs associated with intravenous (IV) contrast media can be divided into two broad categories: idiosyncratic anaphylactoid (IA) and nonidiosyncratic (NI) reactions. The IA reactions are most concerning because they are potentially fatal and can occur without any predictable or predisposing factors. Approximately 85% of IA reactions occur during or immediately after injection of IRCM and are more common in patients who have a prior ADR to contrast media, have impaired renal function or diminished cardiac function, are on β -adrenergic blockers, or have asthma or diabetes (Spring et al, 1997).

The exact mechanism of IA reactions is unknown but thought to be a combination of systemic effects. IA reactions have not been shown to result from a true immunoglobulin E (IgE) antibody immunologic reaction to the contrast media (Dawson et al, 1999). At least four mechanisms may play a role in IA reactions: (1) release of vasoactive substances including histamine, (2) activation of physiologic cascades including complement, kinin, coagulation, and fibrinolytic systems, (3) inhibition of enzymes including cholinesterase, which may cause prolonged vagal stimulation, (4) the patient's own anxiety and fear of the actual procedure. IA reactions are not dose dependent. Severe reactions have been reported after an injection of only 1 mL at the beginning of a procedure and have also occurred after completion of a full dose despite no reaction to the initial test dose (Nelson et al, 1988; Thomsen et al, 1999; American College of Radiology, 2013).

NI reactions are dose dependent and consequently related to the osmolality, concentration, volume, and injection rate of the IRCM. Because the concentration of absorbed or free iodine is very low, only patients with an underlying iodine deficiency are at risk for increased intake of iodine during contrast imaging. Patients with endemic goiter may develop thyrotoxicosis after injection of IRCM agents.

The hyperosmolar contrast media (HOCM) have an osmolality that is five times greater than physiologic osmolality of body cells (300 mOsm/kg water). The hyperosmolar agents are associated with erythrocyte damage, endothelial damage, vasodilation, hypervolemia, interruption of the blood-brain barrier, and cardiac depression. Chemotoxic reactions to IRCM include cardiac, vascular, neurologic, and renal toxicity. The low osmolar contrast media (LOCM) have an osmolality the same as or slightly higher than physiologic osmolality and are associated with fewer ADRs and toxic events (Dawson et al, 1999).

Contrast Complications

The American College of Radiology (ACR) has divided these NI reactions to contrast agents into the following categories (American College of Radiology, 2013):

Mild Nonidiosyncratic Reactions

Fortunately, most NI reactions are classified as mild. Signs and symptoms appear self-limited without evidence of progression. These include the following:

Nausea, vomiting	Flushing
Cough	Chills, shaking
Warmth (heat)	Sweats
Headache	Rash, hives
Dizziness	Nasal stuffiness
Altered taste	Swelling: eyes, face
Itching	Anxiety
Pallor	

Treatment. Treatment consists of observation and reassurance; usually no intervention or medication is required. If needed, an H₁ receptor blocker such as diphenhydramine (Benadryl) orally (PO), intramuscularly (IM), or IV 1 to 2 mg/kg (up to 50 mg) may

be helpful. Be careful because these reactions may progress into a more severe category. If necessary, administer chlorphenamine, 4 to 10 mg PO/IM/IV, or diazepam 5 mg for anxiety.

Moderate Nonidiosyncratic Reactions

The following reactions occur in 0.5% to 2% of patients and require treatment but are not immediately life threatening.

Tachycardia/bradycardia	Dyspnea
Hypertension	Pronounced skin reaction
Pulmonary edema	Bronchospasm, wheezing
Hypotension	Laryngeal edema

Treatment. These reactions are usually transient and will need treatment with close observation. Appropriate treatments are hydrocortisone 100 to 500 mg IM or IV, or β -agonist inhalation for bronchospasm in addition to bronchiolar dilators (metaproterenol [Alupent], terbutaline [Brethaire], or albuterol [Proventil or Ventolin]) 2 to 3 puffs; repeat as necessary.

Severe Nonidiosyncratic Reactions

Life-threatening reactions occur in approximately 1 in 1000 uses for high osmolar agents and are far less frequent for low osmolar contrast media, with both types of agents resulting in mortality rates of 1 in 170,000 uses (Spring et al, 1997). Life-threatening events with more severe signs or symptoms include the following:

Laryngeal edema (severe or progressive)	Hypotension
Unresponsiveness	Convulsions
Cardiopulmonary arrest	Clinically manifest arrhythmias

Treatment. Immediate treatment is required. The patient will usually require emergency care involving particular attention to the respiratory and cardiovascular systems. If bronchospasm is severe and not responsive to inhalers, or if an upper airway edema (including laryngospasm) is present, epinephrine should be used promptly. Rapid administration of epinephrine is the treatment of choice for severe contrast reactions. Epinephrine can be administered in the dose of 0.01 mg/kg of 1:10,000 dilution or 0.1 mL/kg slowly into a running IV infusion of saline and can be repeated every 5 to 15 minutes as needed. If no IV access is available, the recommended IM dose of epinephrine is 0.01 mg/kg of 1:1000 dilution (or 0.01 mL/kg to a maximum of 0.15 mg of 1:1000 if less than 30 kg; 0.3 mg if weight is more than 30 kg) injected in the lateral thigh. Subcutaneous injection is much less effective (Lightfoot et al, 2009; American College of Radiology, 2013). Epinephrine must be administered with care to patients who have cardiac disease or those who are taking β -blockers because the unopposed alpha effects of epinephrine in these patients may cause severe hypertension or angina.

Antihistamines do not have a major role in the treatment of severe reactions. Careful monitoring of patient vital signs is paramount; the presence of both hypotension and tachycardia indicates a higher likelihood of anaphylactic reaction. Bradycardia is a sign of vasovagal reaction, and therefore the use of β -blockers is to be avoided. Hypotension resulting from an anaphylactic reaction can be treated with IV iso-osmolar fluids (e.g., 0.9% normal saline or Ringer lactate solution); several liters of fluid may be needed before obtaining a significant hemodynamic response. If fluid and oxygen are unsuccessful in reversing the patient's hypotension, the use of vasopressors is indicated. The most effective vasopressor is dopamine. Dopamine should be used at infusion rates between 2 and 10 μ g/kg/min.

Premedication Strategies

There is no known premedication strategy that will eliminate the risk of a severe adverse reaction to IRCM. The regimens suggested in the literature include the use of corticosteroids, antihistamines, H_1 and H_2 antagonists, and ephedrine. Patients at high risk should be premedicated with corticosteroids and possibly antihistamines 12 to 24 hours before and after use of IRCM. LOCM should be used in these patients. Several premedication regimens have been proposed to reduce the frequency and/or severity of reactions to contrast media. Two frequently used regimens are outlined in Box 2-1.

It has been demonstrated that the use of nonionic contrast media combined with a premedication strategy including corticosteroids results in a reduction in reaction rates compared to other protocols for patients who have experienced a prior contrast media-induced reaction. However, no controlled studies are available to determine whether pretreatment alters the incidence of serious reactions. Oral administration of steroids seems preferable to intravascular administration, and prednisone and methylprednisolone are equally effective. If the patient is unable to take oral medication, 200 mg of hydrocortisone IV may be substituted for oral prednisone. One consistent finding is that steroids should be given at least 6 hours before the injection of contrast media regardless of the route of steroid administration. It is clear that administration for 3 hours or less before contrast does not decrease adverse reactions (Lasser, 1988).

Supplemental administration of an H_1 antihistamine (e.g., diphenhydramine), PO or IV, may reduce the frequency of urticaria, angioedema, and respiratory symptoms. In emergency situations, IV corticosteroid (e.g., 200 mg hydrocortisone) every 4 hours plus an H_1 antihistamine (e.g., 50 mg diphenhydramine) 1 hour before the procedure has been used. In patients who have a prior, documented contrast reaction, the use of a different contrast agent has been advocated and may be protective. Switching to a different agent should be in combination with a premedication regimen.

Although rare, ADRs are reported after extravascular instillation of IRCM (e.g., retrograde pyelography). In patients with a positive history of previous severe IA or IN reactions to IRCM undergoing a nonvascular study, premedication with corticosteroids should be considered.

Delayed Contrast Reactions

Delayed contrast reactions can occur from 3 hours to 7 days following the administration of contrast. These reactions are identified in as many as 14% to 30% of patients after the injection of ionic monomers and in 8% to 10% of patients after the injection of nonionic monomers. Cutaneous reactions are the most frequent

BOX 2-1 Premedication Strategies to Reduce Severity of Reactions to Contrast Media

1. Prednisone—50 mg PO at 13 hr, 7 hr, and 1 hr before contrast media injection
Plus diphenhydramine (Benadryl)—50 mg IV, IM, or PO 1 hr before contrast medium injection
2. Methylprednisolone (Medrol)—32 mg PO 12 hr and 2 hr before contrast media injection
Plus diphenhydramine (Benadryl)—50 mg IV, IM, or PO 1 hr before contrast medium injection

From ACR Committee on Drugs and Contrast Media. ACR manual on contrast media: version 9, <<http://www.acr.org/quality-safety/resources/-/media/37D84428BF1D4E1B9A3A2918DA9E27A3.pdf>>; 2013 [accessed 06.10.14].

form of delayed contrast reaction with a reported incidence of 0.5% to 9%. The most common reactions include a cutaneous exanthem or pruritus without urticaria. Nausea, vomiting, drowsiness, headache and flulike symptoms can also occur. These signs and symptoms almost always resolve spontaneously.

Specific Contrast Consideration

Cardiac Abnormalities. Patients with underlying cardiac disease, including chest pain and cardiac arrest, have an increased incidence and/or severity of cardiovascular side effects. Pulmonary angiography and intracardiac and coronary artery injections carry the highest degree of risk. Possible reactions include hypotension, tachycardia, and arrhythmias. More severe but uncommon reactions include congestive heart failure, pulmonary edema, and cardiac arrest.

Extravasation of Contrast Material. Large-volume extravasation can be seen with power injections not monitored with electrical skin impedance devices that detect extravasation and arrest the injection process. When large-volume extravasation of IRCM occurs, the result can be swelling, edema, erythema, pain, and cellulitis. The most severe consequences may not be manifest immediately, and the inflammatory reaction usually reaches a maximum in 24 to 48 hours. The primary underlying mechanism is believed to be the hyperosmolality of the contrast agent. Mechanical compression caused by a compartment syndrome may also occur, leading to tissue necrosis. Management steps are immediate cessation of injection, notification of responsible and referring physicians, and elevation of the affected extremity above the level of the heart. If a large volume of extravasate occurs, manual massage is recommended to promote drainage. If the patient becomes symptomatic, plastic surgery consultation may also be needed. Admission to the hospital for observation or frequent follow-up in clinic may be necessary in some cases of large-volume extravasation.

Metformin. Metformin, an oral antihyperglycemic drug used to treat diabetes, is eliminated unchanged through the kidneys, most likely by glomerular filtration and tubular excretion. As a biguanide, it stimulates intestinal production of lactic acid. Some conditions can reduce metformin excretion or increase serum lactate, such as renal disease (decreases metformin excretion), liver disease (decreases lactic acid metabolism), and cardiac disease (increases anaerobic metabolism). Patients with type 2 diabetes mellitus receiving metformin may have an accumulation of the drug after administering IRCM, resulting in biguanide lactic acidosis with symptoms of vomiting, diarrhea, and somnolence. This condition is fatal in approximately 50% of cases (Wiholm and Myrhed, 1993). Biguanide lactic acidosis is rare in patients with normal renal function. Consequently in patients with normal renal function and no known comorbidities there is no need to discontinue metformin before IRCM use, nor is there a need to check creatinine following the imaging study. However, in patients with renal insufficiency metformin should be discontinued the day of the study and withheld for 48 hours. Postprocedure creatinine should be measured at 48 hours and metformin started once kidney function is normal (Bailey and Turner, 1996). It is not necessary to discontinue metformin before gadolinium-enhanced MRI studies when the amount of gadolinium administered is in the usual dosage range of 0.1 to 0.3 mmol per kilogram of body weight.

Contrast-Induced Nephropathy. While there are no standard criteria for contrast-induced nephropathy (CIN), the diagnosis can be made if one of the following occurs within 48 hours after administration of iodinated contrast medium: increase in serum creatinine of greater than 0.3 mg/dL, more than a 50% increase in serum creatinine from baseline, or urine output reduced to less than 0.5 mL/kg/hr for at least 6 hours (Mehta et al, 2007). The precise cause of CIN is still unknown but is believed to be a combination of tubular toxicity, tubular obstruction, and renal ischemia by vasoconstriction (Katholi et al, 1998; Heinrich et al, 2005). High doses of IRCM can impair renal function in some patients for 3 to 5 days, and the creatinine level usually returns to baseline in 10 to 14 days.

The incidence of contrast agent-related nephropathy is estimated to be 2% to 5%, and up to 25% of those with CIN will have persistent renal dysfunction. Clinical manifestations are highly variable and may be absent or proceed to oliguria. CIN in patients with normal kidney function is rare (Pannu et al, 2006; Kelly et al, 2008). CIN is the third most common cause of acute kidney failure in hospitalized patients (Nash et al, 2002).

The most common patient-related risk factors for CIN are chronic kidney disease (creatinine clearance <60 mL/min), diabetes mellitus, dehydration, diuretic use, advanced age, congestive heart failure, hypertension, low hematocrit, and ventricular ejection fraction less than 40%. The patients at highest risk for developing CIN are those with both diabetes and pre-existing renal insufficiency. Other risk factors are concomitant exposure to chemotherapy, aminoglycoside or nonsteroidal anti-inflammatory agents, hyperuricemia, and diseases that affect renal hemodynamics, such as end-stage liver disease and nephrotic syndrome. Patients with a diagnosis of a paraproteinemia syndrome/disease (e.g., multiple myeloma), history of a kidney transplant, renal tumor, renal surgery, or single kidney may also be at higher risk of CIN.

The most common nonpatient-related causes are high osmolar contrast agents, ionic contrast, increased contrast viscosity, multiple contrast-enhanced studies performed within a short period, and large contrast volume infused (Pannu et al, 2006).

Despite significant discussion among radiologists and urologists, the literature does not support an absolute serum creatinine level that prohibits the use of contrast media. Prevention of CIN has been the subject of many research studies, and the results have been summarized by several different meta-analyses. In these meta-analyses the baseline serum creatinine of study participants ranged from 0.9 to 2.5 mg/dL. In one survey the policies regarding the cutoff value for serum creatinine varied widely among radiology practices. Thirty-five percent of respondents used 1.5 mg/dL, 27% used 1.7 mg/dL, and 31% used 2.0 mg/dL (mean, 1.78 mg/dL) as a cutoff value in patients with no risk factors other than elevated creatinine; threshold values were slightly lower in diabetic patients (mean, 1.68 mg/dL). Patients in end-stage renal disease who have no remaining natural renal function are no longer at risk for CIN and may receive LOCM or iso-osmolar contrast media (Elicker et al, 2006).

Prevention of CIN is of great concern and has been a subject of many different studies. Hydration is the major preventative action against CIN. Periprocedural IV hydration with 0.9% saline at 100 mL/hr 12 hours before to 12 hours after has been shown to decrease the incidence of CIN after IV contrast use (Solomon et al, 2007). The use of sodium bicarbonate has not been definitively shown to prevent CIN in patients receiving IV iodinated contrast material. (The use of N-acetylcysteine for the prevention of CIN is controversial) (Safirstein et al, 2000). Currently there is insufficient evidence to make a definitive recommendation for its use, and therefore it should not be considered a substitute for appropriate screening and hydration (Zoungas et al, 2009; Newhouse and RoyChoudhury, 2013). Furosemide was found to increase the risk of developing CIN (Pannu et al, 2006; Kelly et al, 2008).

Magnetic Resonance Imaging Contrast Agents

Because MRI offers previously unseen detailed soft tissue imaging compared with CT, it was initially believed that MRI would not require contrast enhancement. However, by 2005, almost 50% of MRI studies were being performed with contrast media. Extracellular MRI contrast agents contain paramagnetic metal ions. Copper, manganese, and gadolinium (Gd) were the potential paramagnetic ions for use with MRI. Gadolinium, however, is the most powerful with 7 unpaired electrons, but its toxicity required encapsulation by a chelate. Paramagnetic agents such as Gd are positive enhancers reducing the T1 and T2 relaxation times and increasing tissue signal intensity (SI) on T1-weighted images, while having little effect on T2-weighted images.

Gadolinium

Acute adverse reactions are encountered less frequently with Gd-based contrast media (GBCM) than after administration of iodinated contrast media. The frequency, of all acute adverse events after an injection of 0.1 or 0.2 mmol/kg of gadolinium chelate, ranges from 0.07% to 2.4%. The vast majority of these reactions are mild, including coldness at the injection site, nausea, emesis, headache, warmth or pain at the injection site, paresthesias, dizziness, and itching. Reactions resembling an “allergic” response occur with a frequency of 0.004% to 0.7%. Reactions consisting of rash, hives, or urticaria are most frequent; the patient rarely develops bronchospasm. Severe, life-threatening anaphylactoid or nonallergic anaphylactic reactions are exceedingly rare (0.0001% to 0.001%). In a meta-analysis of 687,000 Gd doses for MRI, only five reactions were severe. In another survey based on 20 million administered doses, 55 patients (0.0003%) had severe reactions. Fatal reactions to gadolinium chelate agents have been reported, but they are extremely rare (Murphy et al, 1999). There have been no documented vaso-occlusive or hemolytic complications when administering GBCM to patients with sickle cell disease (Elicker et al, 2006; Dillman et al, 2011). Gd agents are considered to have no nephrotoxicity at approved doses for MRI. However, because of the risk of nephrogenic systemic fibrosis (NSF) in patients with severe renal dysfunction, the use of Gd agents in this patient population requires some precaution and a review of the current recommendations.

Extracellular MRI agents are known to interfere with some serum chemistry assays. For example, serum calcium tests will often be measured as a false reading of hypocalcemia for 24 hours after MRI with Gd enhancement, even though serum calcium is actually in the normal range. Other tests including iron, magnesium, iron-binding capacity, and zinc may also have spurious results. Biochemical assessment is more reliable when performed 24 hours after exposure to Gd contrast media.

Nephrogenic Systemic Fibrosis

NSF is a fibrosing disease of the skin, subcutaneous tissues, lungs, esophagus, heart, and skeletal muscles. Initial symptoms typically include skin thickening and/or pruritus. Symptoms and signs may develop and progress rapidly, with some affected patients developing contractures and joint immobility within days of exposure. Death may result in some patients, presumably as a result of visceral organ involvement.

In 1997 NSF was described in dialysis patients who had not been exposed to GBCM. The condition was previously known as *nephrogenic fibrosing dermatopathy*. In 2006 independent reports surfaced defining a strong association with GBCM in patients with advanced renal disease (Cowper et al, 2000; Grobner, 2006; Marckmann et al, 2006). It is now currently accepted that GBCM exposure is a necessary factor in the development of NSF. Onset of NSF varies between 2 days and 3 months, with rare cases appearing years after exposure (Shabana et al, 2008). Early manifestations include subacute swelling of distal extremities, followed by severe skin induration and later even organ involvement. In a 2007 survey performed by the ACR, 156 cases of NSF were reported by 27 responding institutions; 140 of these 156 patients were known to have received GBCM. In 78 patients, the specific GBCM was known. Forty-five of them received gadodiamide, 17 gadopentetate dimeglumine, 13 gadoversetamide, and three gadobenate dimeglumine. NSF following gadoteridol administration has also been reported. Many of the cases in which agents other than gadodiamide and gadopentetate dimeglumine were used are confounded by the fact that affected patients were injected with other agents as well (American College of Radiology, 2013). Between 12% and 20% of confirmed cases of NSF occurred in patients with acute kidney injury. Patients with chronic kidney disease have a 1% to 7% chance of developing NSF after MRI with Gd agents (Todd et al, 2007).

Patients with a glomerular filtration rate (GFR) less than 30 mL/min/1.73 m² not on chronic dialysis are the most difficult patient population in terms of choosing imaging modality. They are at risk for CIN if exposed to iodinated contrast media for CT imaging and are also at significant risk of developing NSF if exposed to GBCM during MRI. Recent data suggest that the risk of NSF may be greatest in patients with a GFR of less than 15 mL/min/1.73 m². These patients have a 1% to 7% chance of developing NSF after exposure to GBCM during MRI, with the incidence being much less in patients with GFRs that are higher (Kanal et al, 2008). In patients with chronic kidney disease, it is recommended that contrast media be avoided if possible. If MRI contrast media is absolutely essential, use of the lowest possible doses (needed to obtain a diagnostic study) of selected GBCM is recommended. In this setting, patients should be informed of the risks of GBCM administration and must give their consent to proceed. There is no proof that any GBCM is completely safe in this patient group; however, some have suggested avoiding gadodiamide and considering use of macrocyclic agents (Kanal et al, 2008). Patients with chronic kidney disease but GFR more than 30 mL/min/1.73 m² are considered to be at extremely low or no risk for developing NSF if a dose of GBCM of 0.1 mmol/kg or less is used. Patients with GFR more than 60 mL/min/1.73 m² do not appear to be at increased risk of developing NSF, and the current consensus is that all GBCM can be administered safely to these patients. In their publications, the ACR stresses that the current information on NSF and its relationship to GBCM administration is very preliminary and further research is needed to better understand this potentially devastating complication.

KEY POINTS: CONTRAST MEDIA

- Type 2 diabetic patients with renal insufficiency who are receiving oral metformin biguanide hyperglycemic therapy are at risk for developing biguanide lactic acidosis after exposure to intravascular radiologic contrast media; they should stop metformin the day before the procedure and restart 48 hours after if they have a normal or baseline serum creatinine.
- Patients at risk for adverse reaction to contrast include those with previous adverse reactions, history of asthma, severe cardiac disease, renal insufficiency, dehydration, sickle cell anemia, anxiety, apprehension, hyperthyroidism, and presence of adrenal pheochromocytoma.
- Epinephrine can be administered IV in the dose of 0.01 mg/kg of 1:10,000 dilution or 0.1 mL/kg slowly into a running infusion of saline and can be repeated every 5 to 15 minutes as needed. If no IV access is available, the recommended IM dose of epinephrine is 0.01 mg/kg of 1:1000 dilution (or 0.01 mL/kg to a maximum of 0.15 mg of 1:1000 if less than 30 kg; 0.3 mg if weight is greater than 30 kg) injected in the lateral thigh.
- Patients at greatest risk for contrast-induced nephropathy are those with diabetes mellitus and dehydration.
- Steroids given to prevent adverse contrast agents should be given at least 6 hours before injection.

INTRAVENOUS UROGRAPHY

Once the mainstay of urologic imaging, the intravenous excretory urographic (IVU) study has essentially been replaced by CT and MRI. With the ability of new scanners to perform axial, sagittal, and coronal reconstruction of the upper tract urinary system, essentially all of the data and information obtained by traditional IVU can be realized with CT imaging. In addition, some parenchymal defects, cysts, and tumors can be better delineated with CT than with IVU.

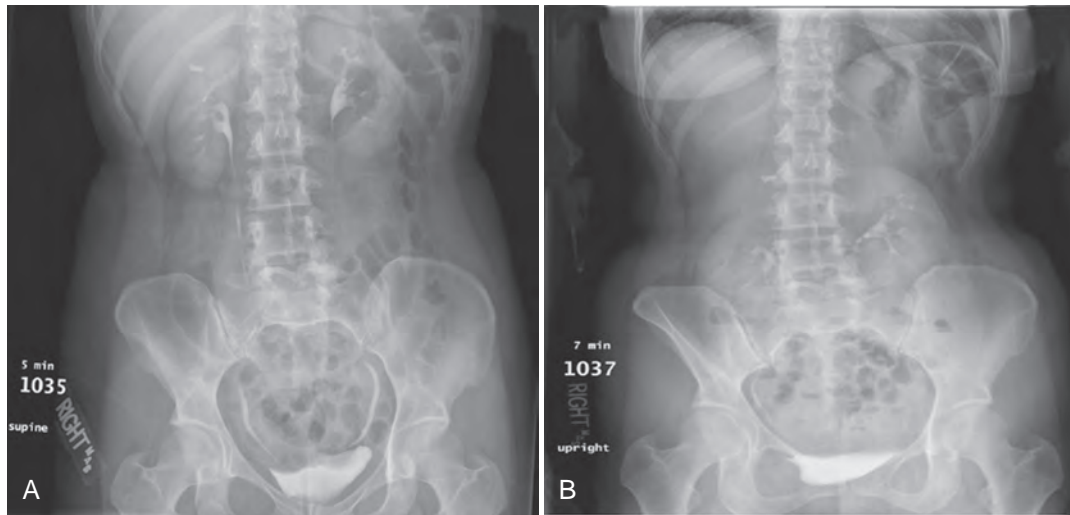


Figure 2-2. Intravenous excretory urogram (IVU) in a 40-year-old woman with the complaint of a mobile mass in the right lower quadrant with standing associated with bilateral flank and back pain that resolved in the supine position. A, Supine IVU shows kidneys in the normal position with normal ureters and proximal collecting systems. B, Standing film shows significant displacement of both kidneys, with the right kidney moving onto the pelvis as described by the patient.

Technique

Bowel prep may help to visualize the entire ureters and upper collecting systems. Patients with chronic constipation may benefit most from complete bowel prep with clear liquids for 12 to 24 hours and an enema 2 hours before the procedure.

Before injection of contrast, a scout radiograph or KUB (kidney-ureter-bladder) film is taken demonstrating the top of the kidneys and the entire pelvis to the pubic symphysis. This allows determination of adequate bowel prep, confirms correct positioning, and exposes kidney stones or bladder stones.

Contrast is injected as a bolus of 50 to 100 mL of contrast. The nephrogenic phase is captured with a radiograph immediately after injection. In the past, tomograms were used to look for parenchymal defects, but now CT or MRI is preferred. A film is taken at 5 minutes and then additional films at 5-minute intervals until the question that prompted the IVU is answered. Abdominal compression may be used to better visualize the ureters. Occasionally, oblique films will be used to better define the course of the ureter in the bony pelvis and to precisely differentiate ureteral stones from pelvic calcifications.

Upright films may be helpful in certain situations. In the rare case of suspected symptomatic renal ptosis, IVU can be particularly helpful (Fig. 2-2). Supine films are compared with upright films to measure the degree of ptosis. Such a comparison cannot be made with MRI or CT imaging. In the case of calyceal stones or milk of calcium stones, layering of the contrast can be helpful to evaluate the anatomy of the calyx harboring the stones.

Postvoid films are obtained to evaluate the presence of outlet obstruction, prostate enlargement, and bladder filling defects, including stones and urothelial cancers.

Indications

1. Demonstration of renal collecting systems and ureters
2. Investigation of level of ureteral obstruction
3. Demonstration of intraoperative opacification of collecting system during extracorporeal shock wave lithotripsy or percutaneous access to the collecting system
4. Demonstration of renal function during emergent evaluation of unstable patients

5. Demonstrate renal and ureteral anatomy in special circumstances (e.g., ptosis, after transureteroureterostomy, and after urinary diversion)

PLAIN ABDOMINAL RADIOGRAPHY

The plain abdominal radiograph is a conventional radiography study, which is intended to display the kidneys, ureters, and bladder. The plain abdominal radiograph may be employed as a primary study or a scout film in anticipation of contrast media. Plain films are widely used in the management of renal calculus disease. Plain radiography is also useful in evaluation of the trauma patient because it can be performed as a portable study in the trauma unit. Secondary findings on plain radiography, such as rib fractures, fractures of the transverse processes of the vertebral bodies, and pelvic fractures, may indicate serious associated urologic injuries.

Technique

An abdominal plain radiograph is obtained with the patient in the supine position, using an anterior to posterior exposure. The study typically includes that portion of the anatomy from the level of the diaphragm to the inferior pubic symphysis. It may occasionally be necessary to make two exposures to cover the desired anatomic field. Depending on the indication for the study, oblique films are obtained to clarify the position of structures in relation to the urinary tract. If small bowel obstruction or free peritoneal air is suspected, upright films will be obtained.

Indications

1. Used as a preliminary film in anticipation of contrast administration
2. Assessment of presence of residual contrast from a previous imaging procedure
3. Assessment of renal calculus disease before and after treatment
4. Assessment of the position of drains and stents
5. Used as an adjunct to the investigation of blunt or penetrating trauma to the urinary tract



Figure 2-3. A, Right ureteral calculus (arrow) overlying the sacrum is difficult to visualize on the plain film. B, The right posterior oblique study fails to confirm the location of the ureteral calculus. C, Computed tomography confirms this 6-mm calculus in the right ureter at the level of the third sacral segment (arrow).

Limitations

Although plain film radiography is often used in the evaluation of renal colic, it is unreliable in the demonstration of calculus disease for a variety of reasons: (1) overlying stool and bowel gas may obscure small calculi; (2) stones may be obscured by other structures such as bones or ribs (Fig. 2-3); (3) calcifications in pelvic veins or vascular structures may be confused with ureteral calculi; and (4) stones that are poorly calcified or composed of uric acid may be radiolucent. Nevertheless, plain film radiography is very valuable in assessing the suitability of a patient for extracorporeal shock wave lithotripsy because the ability to identify the stone on fluoroscopy is critical to targeting. Furthermore, a KUB is very cost-effective for monitoring residual stone burden after treatment (Fig. 2-4). For complex pathology of the urinary tract, plain abdominal radiography has been supplanted by axial imaging. Plain radiography has a very limited role in evaluating soft tissue abnormalities of the urinary tract.

RETROGRADE PYELOGRAPHY

Retrograde pyelograms are performed to opacify the ureters and intrarenal collecting system by the retrograde injection of contrast media. Any contrast media that can be used for excretory urography is also acceptable for retrograde pyelography. Attempts should be made to sterilize the urine before retrograde pyelography because there is a risk of introducing bacteria into the upper urinary tracts or into the bloodstream. Although many studies are able to document the presence or absence of dilation of the ureter, retrograde pyelography has the unique ability to document the normalcy of the ureter distal to the level of obstruction and to better define the extent of the ureteral abnormality.

Technique

Retrograde pyelography is usually performed with the patient in the dorsal lithotomy position. An abdominal plain radiograph (scout film) is obtained to ensure that the patient is in the appropriate position to evaluate the entire ureter and intrarenal collecting system. Cystoscopy is performed and the ureteral orifice is identified.

Contrast may be injected through either a nonobstructing catheter or an obstructing catheter. Nonobstructing catheters include whistle tip, spiral tip, or open-ended catheters. Use of nonobstructing catheters allows passage of the catheter into the ureter and up to the collecting system, over a guidewire if necessary. Contrast can then be introduced directly into the upper collecting system and the

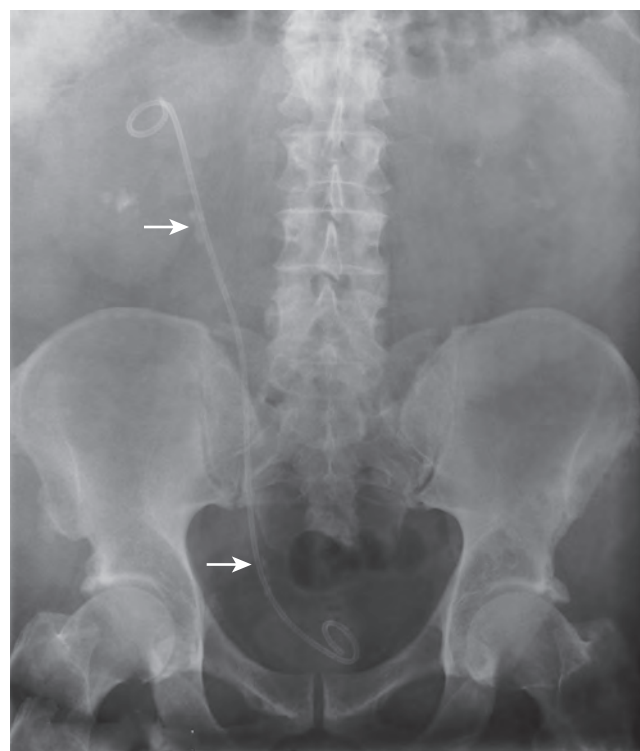


Figure 2-4. KUB (kidney-ureter-bladder) film demonstrating residual stone fragments (arrows) adjacent to a right ureteral stent 1 week following right extracorporeal shock wave lithotripsy.

ureters visualized by injection of contrast as the catheter is withdrawn.

The other commonly employed method is the use of an obstructing ureteral catheter such as a bulb-tip, cone-tip, or wedge-tip catheter. These catheters are inserted into the ureteral orifice and then pulled back against the orifice to effectively obstruct the ureter. Contrast is then injected to opacify the ureter and intrarenal collecting system. Depending on the indication for the study, it is useful to dilute the contrast material (to 50% or less) with sterile fluid. This prevents subtle filling defects in the collecting system or ureter from being obscured. Care should be taken to evacuate air bubbles from the syringe and catheter before injection. Such air bubble artifacts could be mistaken for stones or tumors.

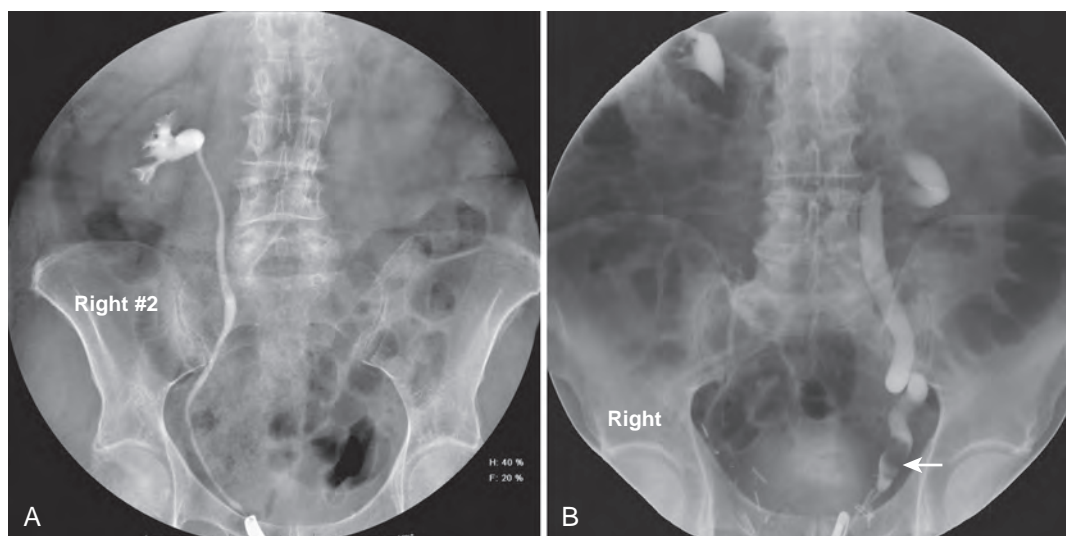


Figure 2-5. A, Right retrograde pyelogram performed using an 8-Fr cone-tipped ureteral catheter and dilute contrast material. The ureter and intrarenal collecting system are normal. B, Left retrograde pyelogram using an 8-Fr cone-tipped ureteral catheter. A filling defect in the left distal ureter (arrow) is a low-grade transitional cell carcinoma. The ureter demonstrates dilation, elongation, and tortuosity, the hallmarks of chronic obstruction.

After air is expelled from the catheter into the bladder, the ureteral orifice is intubated. Contrast is injected slowly, usually requiring 5 to 8 mL to completely opacify the ureter and intrarenal collecting system in adults (Fig. 2-5). More or less contrast may be required, depending on the size of the patient and the capaciousness of the collecting system. Limited use of fluoroscopy while injecting will help prevent overdistention of the collecting system and reduce the risk of extravasation of contrast.

Historically, when a retrograde pyelogram consisted of a series of radiographs taken at intervals, it was important to document various stages of filling and emptying of the ureter and collecting systems. Because of peristalsis the entire ureter will often not be seen on any given static exposure or view. With current equipment, including tables which incorporate fluoroscopy, it is possible to evaluate the ureter during peristalsis in real time, thus reducing the need for static image documentation. Documentary still images or “spot films” may be saved for future comparison. Urologists interpret retrograde pyelograms in real time as they are performed.

Indications

1. Evaluation of congenital ureteral obstruction
2. Evaluation of acquired ureteral obstruction
3. Elucidation of filling defects and deformities of the ureters or intrarenal collecting systems
4. Opacification or distention of collecting system to facilitate percutaneous access
5. In conjunction with ureteroscopy or stent placement
6. Evaluation of hematuria
7. Surveillance of transitional cell carcinoma
8. Evaluation of traumatic or iatrogenic injury to the ureter or collecting system

Limitations

Retrograde pyelography may be difficult in cases where the bladder is involved with diffuse inflammation or neoplastic changes, especially when bleeding is present. Identification of the ureteral orifices may be facilitated in such cases by the IV injection of indigotindisulfonate sodium or methylene blue. Changes associated with bladder outlet obstruction may result in angulation of the

intramural ureters. This may make cannulation with an obstructing catheter quite difficult. Attempts to cannulate the ureteral orifice may result in trauma to the ureteral orifice and extravasation of contrast material into the bladder wall. The potential for damage to the intramural ureter must be weighed against the potential information to be obtained by the retrograde pyelogram.

Complications

Backflow occurs during retrograde pyelography when contrast is injected under pressure and escapes the collecting system. Contrast may escape the collecting system by one of four routes: **Pyelotubular** backflow occurs when contrast fills the distal collecting ducts producing opacification of the medullary pyramids (Fig. 2-6A). **Pyelosinus** backflow occurs when a tear in the calyces at the fornix allows contrast to leak into the renal sinus (Fig. 2-6B). **Pyelolymphatic** backflow is characterized by opacification of the renal lymphatic channels (Fig. 2-6C). **Pyelovenous** backflow is seen when contrast enters the venous system, resulting in visualization of the renal vein.

Although backflow does not usually cause measurable clinical harm, the potential implications of backflow include (1) introduction of bacteria from infected urine into the vascular system and (2) the absorption of contrast media, which could result in adverse reactions in susceptible patients. It has been demonstrated that the risk of significant urinary tract infection is only about 10% and the risk of sepsis is low when antibiotic prophylaxis therapy is administered before endoscopic procedures (including retrograde pyelography) (Christiano et al, 2000). Although contrast reactions are rare with retrograde pyelography, they have been reported (Johanning, 1980; Weese et al, 1993). In patients with documented severe contrast allergy, prophylactic pretreatment may be appropriate. In those patients considered at risk, care should be taken to inject under low pressures to minimize the probability of backflow and absorption of the contrast into the vasculature system.

LOOPOGRAPHY

Loopography is a diagnostic procedure performed in patients who have undergone urinary diversion. Historically the term

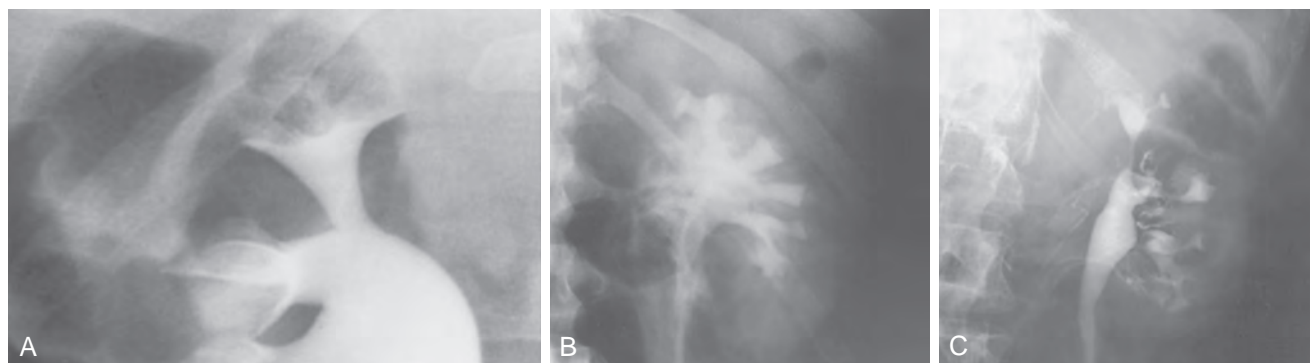


Figure 2-6. Patterns of backflow during retrograde pyelography. A, Pyelotubular backflow. B, Pyelosinus backflow. C, Pyelolymphatic backflow.

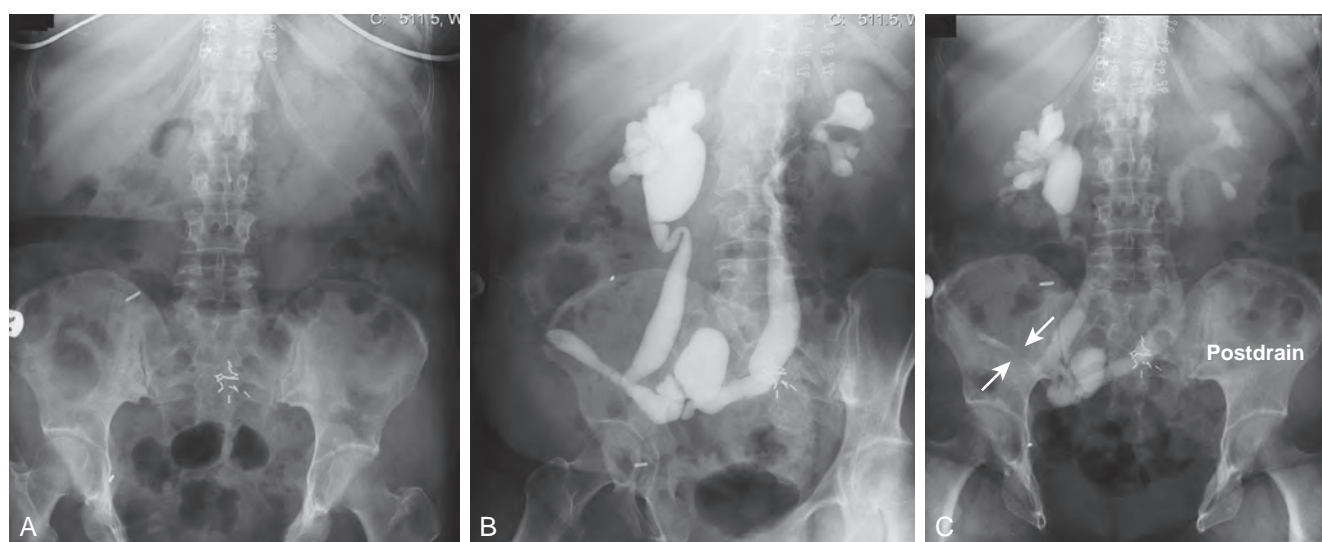


Figure 2-7. Loopogram in a patient with epispadias/exstrophy and ileal conduit urinary diversion. The plain film (A) shows wide diastasis of the pubic symphysis. After contrast administration via a catheter placed in the ileal conduit, free reflux of both ureterointestinal anastomoses is demonstrated (B). A postdrain radiograph (C) demonstrates persistent dilation of the proximal loop, indicating mechanical obstruction of the conduit (arrows).

“loopogram” has been associated with ileal conduit diversion but may be used in reference to any bowel segment serving as a urinary conduit. When imaging patients with a continent diversion involving a reservoir or neobladder, “pouch-o-gram” would be more accurately descriptive. Because an ileal conduit urinary diversion usually has freely refluxing ureterointestinal anastomoses, the ureters and upper collecting systems may be visualized. In other forms of diversion, the ureterointestinal anastomoses may be purposely nonrefluxing. In such circumstances, when opacification of the upper urinary tract is desirable, antegrade ureteral imaging such as IVU, CT or MRI urography, or antegrade nephrostography may be required. When the patient has compromised renal function or is allergic to iodinated contrast material, loopogram can be performed with a low risk of systemic absorption (Hudson et al, 1981).

Technique

The patient is positioned supine. An abdominal plain radiograph is obtained before the introduction of contrast material (Fig. 2-7A). A commonly employed technique is to insert a small-gauge catheter

into the ostomy of the loop, advancing it just proximal to the abdominal wall fascia. The balloon on such a catheter can then be inflated to 5 to 10 mL with sterile water. By gently introducing contrast through the catheter, the loop can be distended, usually producing bilateral reflux into the upper tracts. Oblique films should be obtained in order to evaluate the entire length of the loop (Fig. 2-7B). Because of the angle at which many loops are constructed, a traditional anteroposterior (AP) view will often show a foreshortened loop and could miss a substantial pathology. A drain film should be obtained (Fig. 2-7C). This may demonstrate whether there is obstruction of the conduit.

Indications

1. Evaluation of infection, hematuria, renal insufficiency, or pain after urinary diversion
2. Surveillance of upper urinary tract for obstruction
3. Surveillance of upper urinary tract for urothelial neoplasia
4. Evaluation of the integrity of the intestinal segment or reservoir

RETROGRADE URETHROGRAPHY

A retrograde urethrogram is a study to evaluate the anterior and posterior urethra. Retrograde urethrography may be particularly beneficial in demonstrating the total length of a urethral stricture that cannot be negotiated by cystoscopy. Retrograde urethrography also demonstrates the anatomy of the urethra distal to a stricture that may not be assessable by voiding cystourethrography. Retrograde urethrography may be performed in the office or in the operating room before performing visual internal urethrotomy or formal urethroplasty.

Technique

A plain film radiograph is obtained before injection of contrast. The patient is usually positioned slightly obliquely to allow evaluation of the full length of urethra. The penis is placed on slight tension. A small catheter may be inserted into the fossa navicularis with the balloon inflated to 2 mL with sterile water. Contrast is then introduced via a catheter-tipped syringe. Alternatively, a penile clamp (e.g., Brodney clamp) may be used to occlude the urethra around the catheter (Fig. 2-8).

Indications

1. Evaluation of urethral stricture disease
 - a. Location of stricture
 - b. Length of stricture

2. Assessment for foreign bodies
3. Evaluation of penile or urethral penetrating trauma
4. Evaluation of traumatic gross hematuria

STATIC CYSTOGRAPHY

Static cystography is used primarily to evaluate the structural integrity of the bladder. The shape and contour of the bladder may give information about neurogenic dysfunction or bladder outlet obstruction. Filling defects such as tumors and stones may be appreciated.

Technique

The patient is positioned supine. A plain radiograph is performed to evaluate for stones and residual contrast and to confirm position and technique. The bladder is filled with 200 to 400 mL of contrast, depending on bladder size and patient comfort. Adequate filling is important to demonstrate intravesical pathology or bladder rupture. Oblique films should be obtained because posterior diverticula or fistulae may be obscured by the full bladder. A postdrainage film completes the study (Fig. 2-9).

Indications

1. Evaluation of intravesical pathology
2. Evaluation of bladder diverticula

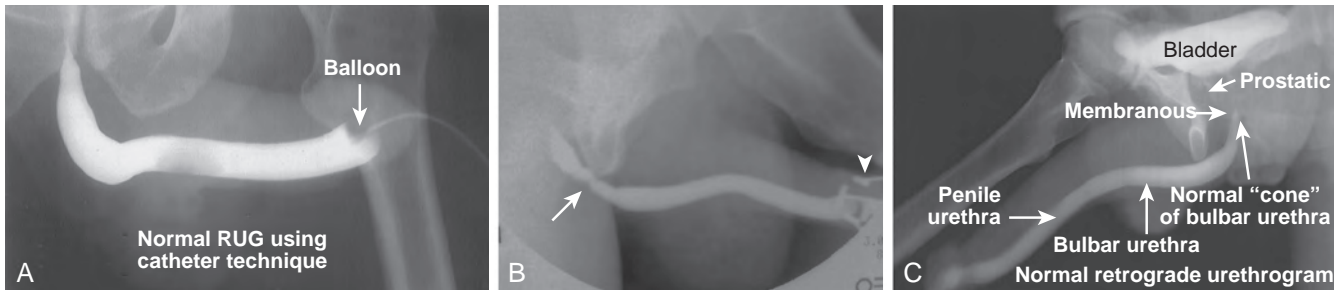


Figure 2-8. Normal retrograde urethrogram demonstrating (A) the balloon technique for retrograde urethrography and (B) Brodney clamp (arrowhead) technique; note the bulbar urethral stricture (arrow). C, Normal structures of the male urethra as seen on retrograde urethrogram.

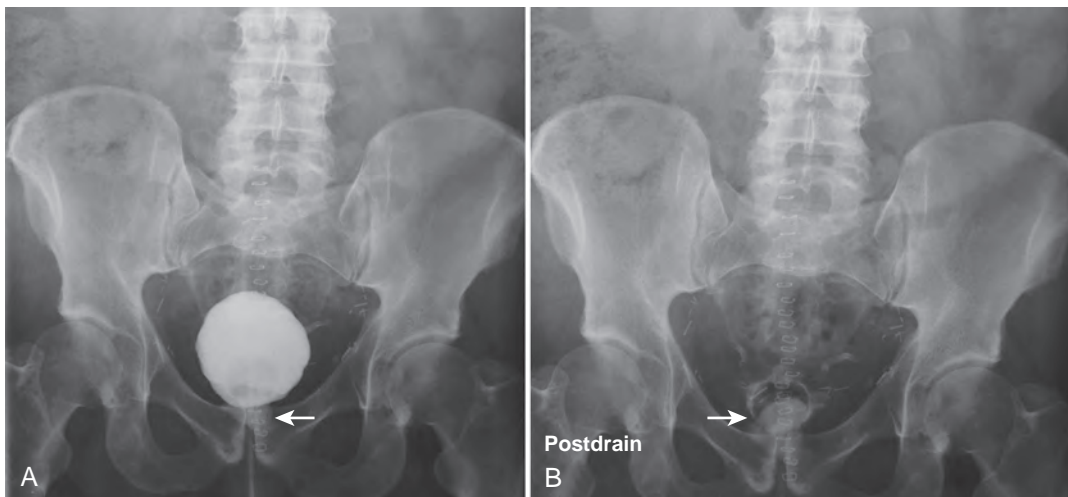


Figure 2-9. The patient has undergone radical retropubic prostatectomy. A, During bladder filling, contrast is seen adjacent to the vesicoureteral anastomoses (arrow). B, The postdrain film clearly demonstrates a collection of extravasated contrast (arrow).

3. Evaluation of inguinal hernia involving the bladder
4. Evaluation of colovesical or vesicovaginal fistulae
5. Evaluation of bladder or anastomotic integrity after surgical procedure
6. Evaluation of blunt or penetrating trauma to the bladder

Limitations

Abdominal and pelvic CT is so commonly used in the evaluation of blunt or penetrating trauma to the abdomen that CT cystography is often performed in conjunction with the trauma evaluation. However, studies have shown that conventional static cystography is as sensitive as CT cystography in detecting bladder rupture (Quagliano et al, 2006; Broghammer and Wesells, 2008).

VOIDING CYSTOURETHROGRAM

A voiding cystourethrogram (VCUG) is performed to evaluate the anatomy and physiology of the bladder and urethra. The study provides valuable information regarding the posterior urethra in pediatric patients. VCUG has long been used to demonstrate vesicoureteral reflux.

Technique

The study may be performed with the patient supine or in a semiupright position using a table capable of bringing the patient into the full upright position. A preliminary pelvic plain radiograph is obtained. In children, a 5- to 8-Fr feeding tube is used to fill the bladder to the appropriate volume. Patient comfort should be taken into account when determining the appropriate volume. In the adult population a standard catheter may be placed and the bladder filled to 200 to 400 mL. The catheter is removed and a film is obtained. During voiding, AP and oblique films are obtained. The bladder neck and urethra may be evaluated by fluoroscopy during voiding. Bilateral oblique views may demonstrate low-grade reflux, which is not able to be appreciated on the AP film. In addition, oblique films will demonstrate bladder or urethral diverticula, which are not always visible in the straight AP projection. Postvoiding films should be performed (Fig. 2-10).

Indications

1. Evaluation of structural and functional bladder outlet obstruction
2. Evaluation of reflux
3. Evaluation of the urethra in males and females

Limitations

This study requires bladder filling using a catheter. This may be traumatic in children and difficult in some patients with anatomic abnormalities of the urethra or bladder neck. Filling of the bladder may stimulate bladder spasms at low volumes and some patients are unable to hold adequate volumes for investigation. **Bladder filling in patients with spinal cord injuries higher than T6 may precipitate autonomic dysreflexia (Barbaric, 1976; Fleischman and Shah, 1977; Linsenmeyer et al, 1996).**

NUCLEAR SCINTIGRAPHY

Radionuclide imaging is the procedure of choice to evaluate renal obstruction and function. It is very sensitive to changes that induce focal or global changes in kidney function. Because neither Gd nor iodinated IV contrast agents are used, scintigraphy does not damage the kidney, has no lingering toxicity, results in minimal absorbed radiation, and is free from allergic reactions. Compared to other diagnostic imaging studies such as retrograde pyelogram, renal scintigraphy is noninvasive, has minimal risk and minimal discomfort, and allows determination of the function of the kidney.

Once the agent is injected IV, gamma scintillation cameras measure radiation emitted from the radioisotope, and digital work stations gather, process, and display the information. There is an extensive list of radiopharmaceuticals used for renal scintigraphy. This section will be limited to those agents most commonly used in urologic practice.

Technetium 99m-diethylenetriamine pentaacetic acid (^{99m}Tc -DTPA) is primarily a glomerular filtration agent (Peters, 1998; Gates, 2004). It is most useful for evaluation of obstruction and renal function. Because it is excreted through the kidney and dependent on GFR, it is less useful in patients with renal failure because impaired GFR may limit adequate evaluation of the collecting

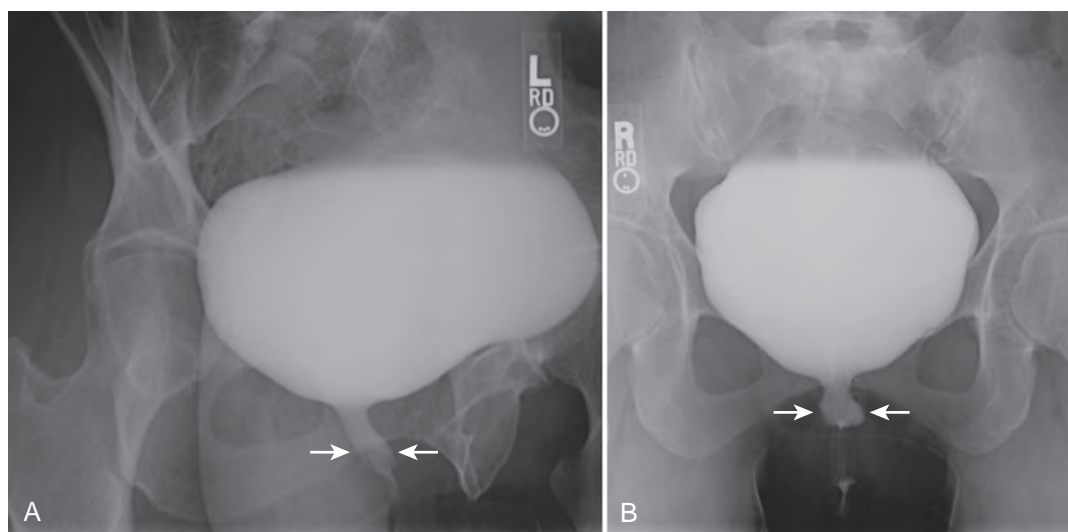


Figure 2-10. A voiding cystourethrogram performed for the evaluation of recurrent urinary tract infection in this female patient. A, An oblique film during voiding demonstrates thickening of the midureteral profile (arrows). B, After interruption of voiding, a ureteral diverticulum is clearly visible extending posteriorly and to the left of the midline (arrows).

system and ureters. It is readily available and relatively inexpensive (Klopper et al, 1972).

Technetium 99m-dimercaptosuccinic acid (^{99m}Tc -DMSA) is cleared by both filtration and secretion. It localizes to the renal cortex with very little accumulation in the renal papilla and medulla (Lin et al, 1974). Therefore it is most useful for identifying cortical defects and ectopic or aberrant kidneys. With these properties, ^{99m}Tc -DMSA can distinguish a benign functioning abnormality in the kidney from a space-occupying malignant lesion, which would not have normal renal function. No valuable information on the ureter or collecting system can be obtained with ^{99m}Tc -DMSA, but it remains a standard for renal cortical imaging.

Technetium 99m-mercaptoacetyl triglycine (^{99m}Tc -MAG3) is an excellent agent for imaging because of its photon emission, 6-hour half-life, and ease of preparation. It is cleared mainly by tubular secretion (Fritzberg et al, 1986). A small amount, approximately 10%, of ^{99m}Tc -MAG3, is excreted by extrarenal means, and most of this is hepatobiliary excretion (Eshima et al, 1990; Itoh, 2001). Because it is extensively bound to protein in plasma, it is limited in its ability to measure GFR, but it is an excellent choice for patients with renal insufficiency and urinary obstruction. The tracer is well suited for evaluation of renal function and diuretic scintigraphy. Also, it is an excellent tracer to evaluate renal plasma flow.

Diuretic Scintigraphy

Nuclear medicine imaging plays a crucial role unmet by CT, MRI, or ultrasonography in the diagnosis of upper tract obstruction, and its unique characteristics provide noninvasive information regarding dynamic renal function. The diuretic renal scan using ^{99m}Tc -MAG3 is able to provide differential renal function and clearance time comparing right and left kidneys, which is pivotal in patient management. The initial phase is the flow phase where 2-second images are gathered for 2 minutes and then 1-second images for 60 seconds. The flow phase shows renal uptake, background clearance, and abnormal vascular lesions, which may indicate arteriovenous

malformations, tumors, or active bleeding. In the second phase, the renal phase, time-to-peak uptake is typically between 2 and 4 minutes. The renal phase is the most sensitive indicator of renal dysfunction. One-minute images are taken for 30 minutes. In the final phase, the excretory phase, 1-minute images are taken for 30 minutes. A diuretic (usually furosemide 0.5 mg/kg) is administered when maximum collecting system activity is visualized. The $T_{1/2}$ is the time it takes for collecting system activity to decrease by 50% from that at the time of diuretic administration. This is highly technician dependent because the diuretic must be given when the collecting system is displaying maximum activity. Transit time through the collecting system in less than 10 minutes is consistent with a normal, nonobstructed collecting system. $T_{1/2}$ of 10 to 20 minutes shows mild to moderate delay and may be a mechanical obstruction. The patient's perception of pain after diuretic administration can be helpful for the treating urologist to consider when planning surgery in the patient with mild to moderate obstruction. A $T_{1/2}$ of greater than 20 minutes is consistent with a high-grade obstruction. The level of obstruction can usually be determined, as can abnormalities such as ureteral duplication (Ell and Gambhir, 2004). A normal renal scan is shown in Figure 2-11.

Hepatobiliary excretion can cause false-positive readings if the area of intestinal activity or gallbladder activity is included in the area of interrogations during the study (Fig. 2-12).

The diuretic renal scan is another imaging study where communication with the interpreting physician is vital for correct performance of the test, as well as appropriate interpretation. For example, there are times when patients with unilateral or bilateral ureteral stents are sent for diuretic scintigraphy to determine differential renal function. If a bladder catheter is not placed and open to drainage during the diuretic renal scan, the radiopharmaceutical excreted from the healthy kidney may wash up into or back flow via the ureteral stent into the stented kidney, giving the false-positive appearance to have more function than is physiologically present. This false-positive test may lead to inappropriately reconstructing a kidney that in reality has little or insufficient function.

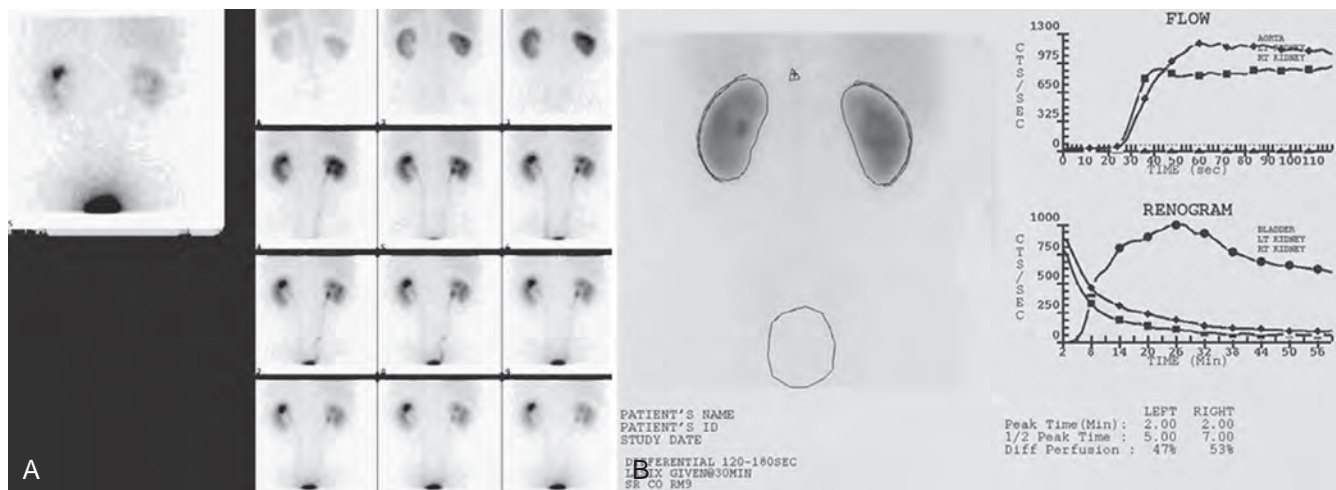


Figure 2-11. A, Technetium 99m-mercaptoacetyl triglycine (^{99m}Tc -MAG3) perfusion images demonstrate normal, prompt, symmetrical blood flow to both kidneys. B, Perfusion time-activity curves demonstrate essentially symmetrical flow to both kidneys. Note the rising curve typical of ^{99m}Tc -MAG3 flow studies. Dynamic function images demonstrate good uptake of tracer by both kidneys and prompt visualization of the collecting systems. This renogram demonstrates prompt peaking of activity in both kidneys. The downslope represents prompt drainage of activity from the kidneys. The printout of quantitative data shows the differential renal function to be 47% on the left, 53% on the right. The normal half-life for drainage is less than 20 minutes when ^{99m}Tc -MAG3 is used. The $T_{1/2}$ is 5 minutes on the left and 7 minutes on the right consistent with both kidneys being unobstructed.

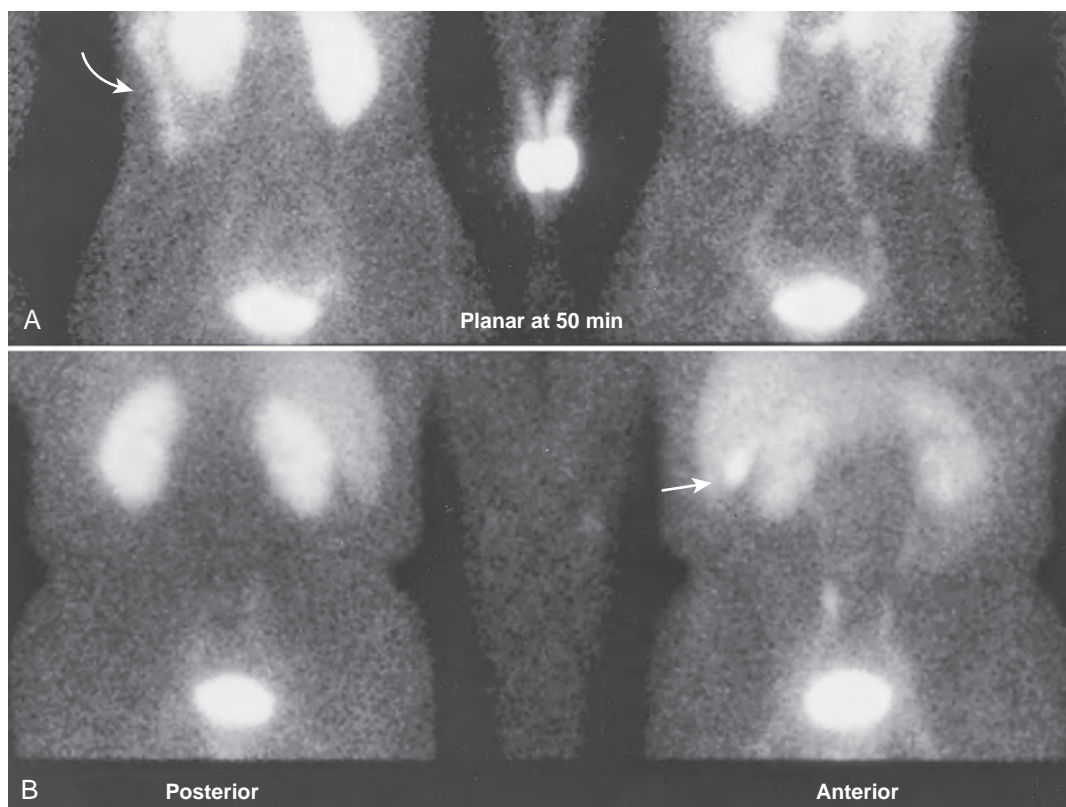


Figure 2-12. Delayed static images in the posterior and anterior projections demonstrate intestinal activity (arrow in A) and gallbladder activity (arrow in B), reflecting a normal mode of excretion of technetium 99m-mercaptoacetyl triglycine (^{99m}Tc -MAG3). Gallbladder activity, in particular, can cause false-positive interpretation when it overlies activity in the renal collecting system or is inappropriately included in the area of interrogation. Liver activity is variable and tends to be more pronounced in children and patients with renal insufficiency.

Nuclear Medicine in Urologic Oncology

Whole-Body Bone Scan

Conventional radionuclide imaging in urologic malignancy has long been the standard for detecting bone metastasis. The whole-body bone scan or skeletal scintigraphy is the most sensitive method for detecting bone metastasis (Narayan et al, 1988). A “positive” bone scan is not specific for cancer and may require plain film radiography, CT, or MRI to confirm, as well as correlation with prior history of bone fractures, trauma, surgery, or arthritis. In patients with diffuse metastatic bone involvement, the bone scan can be mistaken for normal because there is uniformly increased uptake in the bony structures (Kim et al, 1991).

Positron Emission Tomography

The most recent advance in nuclear scintigraphy is in the detection of primary and metastatic cancer using positron emission tomography (PET). Depending on the radiotracer used, PET offers diagnostic information based on glucose, choline, or amino acid metabolism and has also been applied to imaging tumor cell proliferation and tissue hypoxia in urologic malignancies. The diagnostic performance of fluorodeoxyglucose (FDG)-PET is hampered by the renal excretion of FDG and by the low metabolic activity often seen in tumors such as prostate cancer. However, new PET tracers including radiolabeled choline and acetate may offer an alternative approach. There is consistent evidence that FDG-PET provides important diagnostic information in detecting metastatic and recurrent germ cell tumors, and it might offer additional information in the staging and restaging of bladder and renal cancer (Powles et al, 2007; Rioja et al, 2010).

Molecular imaging with PET may help individualize the surgical and medical care of urologic oncology patients. PET is certainly having an impact in general oncology and is being actively investigated for use in urologic malignancies. PET provides unique insights into molecular pathways of diseases. PET using ^{18}F -FDG has gained increasing acceptance for the diagnosis, staging, and treatment monitoring of various tumor types.

There are data on the use of PET/CT in testis cancer, where PET/CT was found to have a higher diagnostic accuracy than CT for staging and restaging in the assessment of a CT-visualized residual mass following chemotherapy for seminoma and non-seminomatous germ cell tumors (Albers et al, 1999; Hain et al, 2000). There may be a role for detection of recurrent nonteratoma disease and the assessment of residual masses after chemotherapy. In a series of seminoma patients who were evaluated after chemotherapy for residual retroperitoneal masses, PET was accurate in 14 of 14 patients with tumors greater than 3 cm and in 22 of 23 patients with lesions less than 3 cm. Overall the sensitivity and specificity was 89% and 100%, respectively (De Santis et al, 2004). The accuracy of PET seems to be compromised if performed within 2 weeks of completion of chemotherapy, likely because of decreased metabolism and increased macrophage activity (Eary, 1999). It is recommended that PET/CT be delayed for 4 to 12 weeks following completion of chemotherapy (Shvarts et al, 2002).

PET/CT may have a promising role in clear cell renal cell carcinoma. An antibody (cG250) recognizing carbonic anhydrase IX has been developed. Carbonic anhydrase IX is a protein related to the unrestrained growth of clear cell renal cancers. A positron-emitting radionuclide (iodine 124) has been attached to the cG250 antibody and injected into renal cell cancer patients. The radionuclide antibody complex attaches to the carbonic anhydrase IX protein from

clear cell renal cancer cells and can be detected on PET/CT imaging. Using this scheme in 26 patients with renal tumors, there was 94% sensitivity and 100% specificity in renal cell carcinoma before surgery (Larson and Schöder, 2008).

There are at least seven tracers being investigated for detection of metastatic prostate cancer. Each tracer is directed at a different part of cell function such as glycolysis, amino acid transport, choline kinase activity, fatty acid synthesis, androgen receptor, and bone mineralization. FDG as a PET tracer was investigated in 91 patients with prostate-specific antigen (PSA) recurrence after radical prostatectomy. FDG-PET was able to detect local or systemic recurrence in only 34% of patients (Schöder et al, 2005).

Very few studies have addressed the use of PET in bladder cancer. FDG is renal excreted and not useful in bladder cancer. Only 78% of bladder cancer could be visualized using ^{11}C -methionine tracer and PET did not improve local staging of the disease. ^{11}C -choline was also found to be a poor predictor of primary or metastatic urothelial carcinoma (Ahlstrom et al, 1996; de Jong et al, 2002).

PET is still in the early stages of investigation for urologic tumors. The exact role in the practice of urology has yet to be determined but will certainly have a great role in the future as more tracers specific to urologic cancers are discovered. Using the combination of nuclear imaging and ever-increasing knowledge about cancer cell biology, radiotracers have been developed to be incorporated into dividing cells or cellular mechanisms involved in the increased metabolic activity of malignancies, which can then be detected using PET imaging. Combining PET with high-resolution CT has the ability to increase our detection of recurrent or metastatic urologic cancers. Many different isotopes are being investigated for the detection of metastatic disease.

KEY POINTS: NUCLEAR SCINTIGRAPHY

- During diuretic renal scan, the diuretic must be given when maximum activity is seen in the kidney.
- An elimination $T_{1/2}$ less than 10 minutes is an unobstructed system, and a $T_{1/2}$ greater than 20 minutes is consistent with high-grade obstruction.
- If ureteral stents are in place, patients undergoing diuretic renal scan should have an unclamped bladder catheter in place during the study.
- ^{99m}Tc -MAG3 is the agent of choice for diuretic renal scan to determine differential renal function and obstruction.

COMPUTED TOMOGRAPHY

The 1979 Nobel Prize in Medicine and Physiology was awarded to Allan M. Cormack and Sir Godfrey N. Hounsfield for the development of computer-assisted tomography. While basic principles remain the same, significant advances over the past 35 years have resulted in the development of multidetector CT devices, improving soft tissue detail and allow the possibility of rapid three-dimensional (3D) reconstruction of the entire genitourinary system.

CT has become one of the most integral parts of urologic practice, and the CT urogram (CTU) has replaced IVU as the imaging modality of choice in modern urology for the workup of hematuria, urologic malignancies, detection of kidney stones, and preoperative planning. As in the case of conventional radiographic imaging, the basis for CT imaging is the attenuation of x-ray photons as they pass through the patient. Tomography is an imaging method that produces 3D images of internal structures by recording the passage of x-rays as they pass through different body tissues. In the case of CT, a computer reconstructs cross-sectional images of the body based on measurements of x-ray transmission through thin slices of the body tissue (Brant, 1999). A collimated x-ray beam is generated on one side of the patient, and the amount of transmitted radiation is measured by a detector placed on the opposite side of the x-ray

beam. These measurements are then repeated systematically, while a series of exposures from different projections is made as the x-ray beam rotates around the patient. The result is production of a 3D image of internal structures in the human body by recording the passage of different energy waves through various internal structures. Data collected by the detectors are reconstructed by computerized algorithms to result in a viewable tomographic display.

There are several different imaging variables that are adjusted to allow adequate, detailed image resolution while minimizing the time on the scanner and limiting exposure to radiation. The variable application of pitch, beam collimation, detector size, and tube voltage are used by the radiologist and imaging technologist for ideal image requisition. A detailed description of each of these variables is beyond the scope of this chapter (see [Suggested Readings](#)).

Perhaps the greatest recent advancement in CT is the use of helical image acquisition techniques with multichannel or multidetectors (MDCT). In a helical CT the patient moves through a continuously rotating gantry. The helical raw images are processed using interpolation algorithms in order to visualize the internal structures as sagittal, coronal, or axial reconstructed images. The "single slice spiral CT," introduced in 1988, had a single row of detectors and required multiple passes to visualize a small area of interrogation. The standard scanners in use today have between 64 and 320 rows of detectors, which allow the patient's entire body to be imaged during a single breath hold, with few or no motion artifacts, more precise diagnostic accuracy, increased concentration of contrast material, shorter scanning time, less radiation exposure, and significant increase in anatomic coverage with a single scan. CT scanners with 750 rows of detectors are currently being developed. For example, in one second, a 320-slice CT scanner can image slices as large as 16 cm (6.3 inches), capturing all of the body's organs in a single rotation of the central x-ray-emitting gantry (Wang et al, 1994; Mahesh, 2002) (Fig. 2-13).

Readily available software is capable of 3D processing of CT images to recreate the urinary system. These 3D images offer improved preoperative planning, appreciation of proximity to adjacent organs, the ability to define vasculature, and improved communication with patients, who can now easily see their particular pathology and better appreciate the challenges faced by their surgeon (Fig. 2-14).

Dual-source CT (DSCT) is a relatively new technique used for diagnostic imaging, using two rotating tubes to acquire both high- and low-voltage images allowing tissue differentiation, visualization of tendons and ligaments, improved CT angiography, and differentiation of kidney stones based on stone composition (Coursey et al, 2010). Using DSCT, a reliable distinction can be made between uric acid and calcium oxalate and between brushite and uric acid stones (Ferrandino et al, 2010; Botsikas et al, 2013).

Real-time CT fluoroscopy is now available as an option on new CT imaging equipment. CT fluoroscopy gives a 3D CT image that is much more detailed and offers greater soft tissue contrast and resolution than conventional CT. The most common use in urology is for biopsy of the kidney. CT fluoroscopy helps to overcome movement of the kidney during respiratory variation. It also has been used for fluid aspiration, drain placement, catheter placement, percutaneous cryoablation, and radiofrequency (RF) ablation of renal tumors. **One significant disadvantage of CT fluoroscopy is the increased radiation exposure to the patient and radiologist or surgeon performing the procedure** (Daly et al, 1999; Keat, 2001; Gupta et al, 2006).

The CTU is an excretory urography in which the MDCT is used for imaging of the urinary tract. It is indicated in the workup of hematuria, kidney stones, renal masses, renal colic, and urothelial tumors. The CT scan examination starts with the physician's request for imaging. Radiologists around the world appreciate a brief description from the urologist of the question to be answered by the CT scan. Equipped with a better understanding of why the CT was ordered, the radiologist and the CT technician can adjust different CT variables and choose the appropriate contrast media needed to deliver a valuable report back to the ordering urologist.

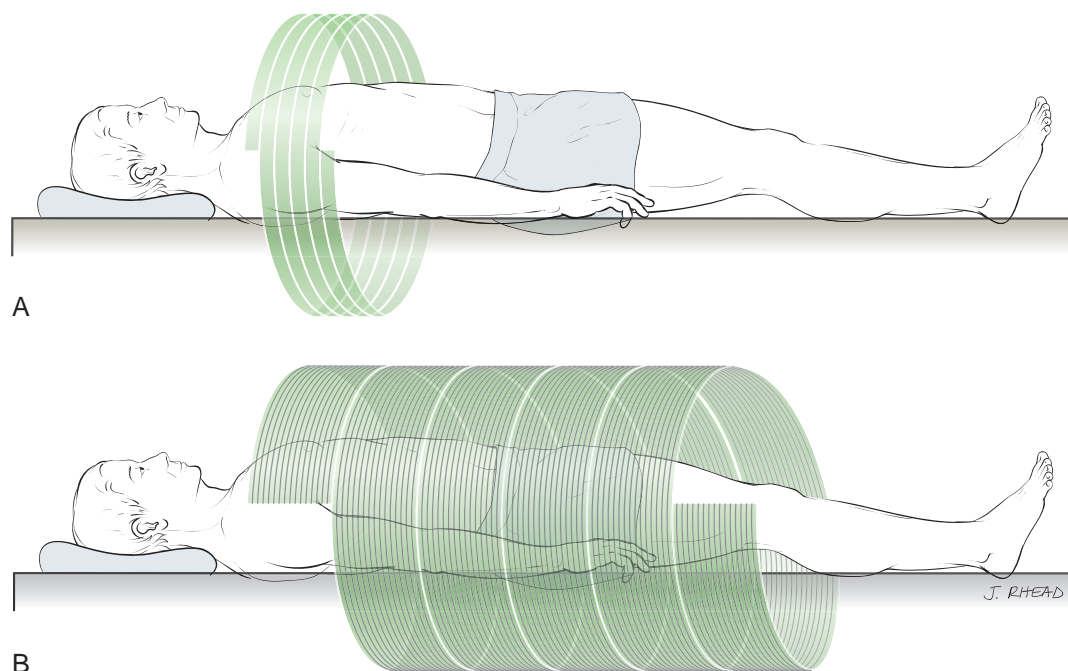


Figure 2-13. A, A computed tomography scanner with a single-row detector requires five circular passes around the patient to image a small area of the patient's body. B, With a 16-slice, multirow detector, the chest, abdomen, and pelvis can be imaged with five circular passes, easily obtained during a single breath hold. The thin slices offered by the 16-slice detector offer much greater detail of internal structures.

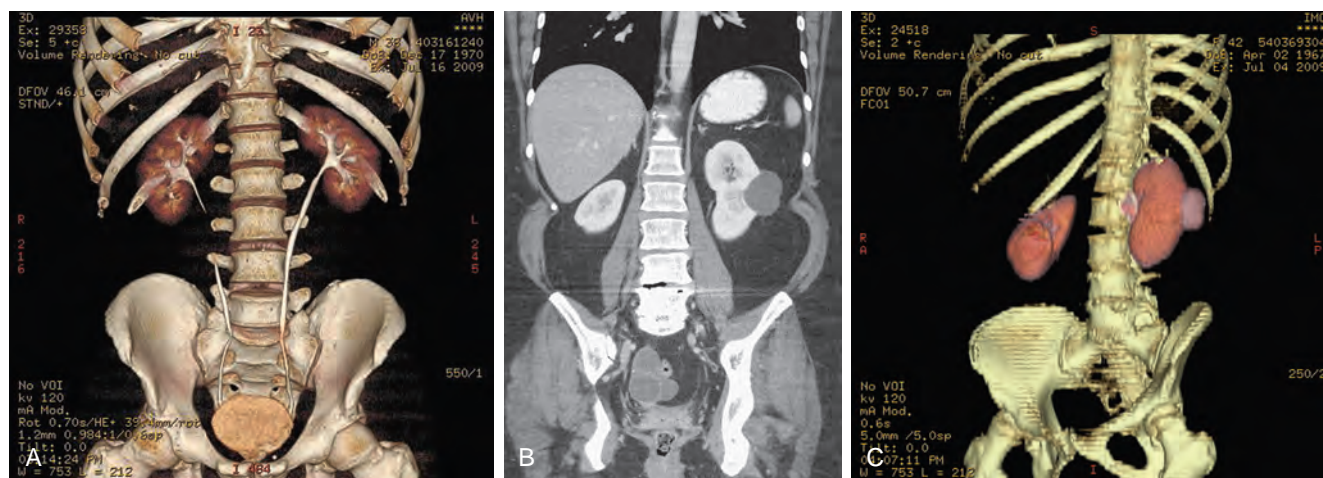


Figure 2-14. A, Three-dimensional (3D) colored reconstruction of the kidneys, ureters, and bladder from computed tomography urogram. B, Coronal reconstruction in a patient with a clear cell renal cell carcinoma in a complex renal cystic mass and enhancing mural nodule. C, 3D reconstruction of the same patient with slight posterior rotation.

Urologists often request a CT evaluation of the abdomen and pelvis. An abdominal CT starts at the diaphragm and ends at the iliac crest. If the pelvis is to be imaged, a separate request is usually required. The pelvic CT begins at the iliac crest and terminates at the pubis symphysis. Intravenous contrast may be required for better delineation of soft tissue. Oral contrast is not commonly used in urology but may be helpful in certain patients to differentiate bowel from lymph nodes, scar, or tumor (Fig. 2-15).

Hounsfield Units

A single CT image generated by the scanner is divided into many tiny blocks of different shades of black and white called pixels. The

actual gray scale of each pixel on a CT depends on the amount of radiation absorbed at that point, which is termed an attenuation value. Attenuation values are expressed in Hounsfield units (HU). The HU scale, or attenuation value, is based on a reference scale in which air is assigned a value of -1000 HU and dense bone is assigned the value of $+1000$ HU. Water is assigned 0 HU.

Urolithiasis

Patients coming to the emergency department with abdominal pain or renal colic are frequently evaluated with CT imaging. The use of unenhanced CT imaging to identify urolithiasis was first reported in 1995 (Smith et al, 1995) and has now become the standard

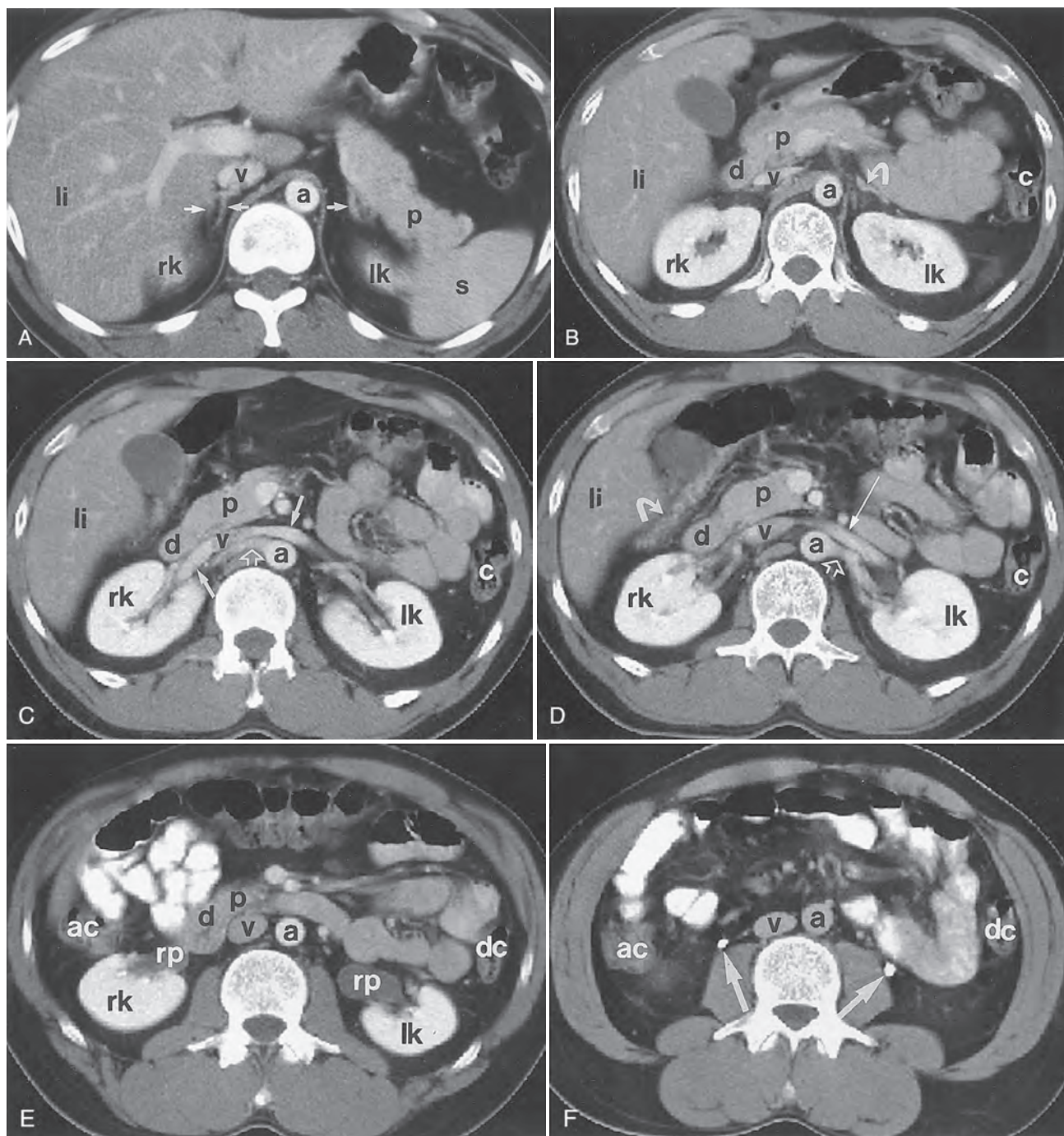


Figure 2-15. Computed tomography of the abdomen and pelvis demonstrating normal genitourinary anatomy. A, The adrenal glands are indicated with *arrows*. The upper poles of the right and left kidneys are indicated with rk and lk, respectively. a, aorta; li, liver; p, pancreas; s, spleen; v, inferior vena cava. B, Scan through the upper pole of the kidneys. The left adrenal gland is indicated with an *arrow*. a, aorta; c, colon; d, duodenum; li, liver; lk, left kidney; p, pancreas; rk, right kidney; v, inferior vena cava. C, Scan through the hilum of the kidneys. The main renal veins are indicated with *solid arrows*, and the right main renal artery is indicated with an *open arrow*. a, aorta; c, colon; d, duodenum; li, liver; lk, left kidney; p, pancreas; rk, right kidney; v, inferior vena cava. D, Scan through the hilum of the kidneys slightly caudal to C. The left main renal vein is indicated with a *solid straight arrow*, and the left main renal artery is indicated with an *open arrow*. The hepatic flexure of the colon is indicated with a *curved arrow*. a, aorta; c, colon; d, duodenum; li, liver; lk, left kidney; p, pancreas; rk, right kidney; v, inferior vena cava. E, Scan through the mid to lower polar region of the kidneys. a, aorta; ac, ascending colon; d, duodenum; dc, descending colon; lk, left kidney; p, pancreas; rk, right kidney; rp, renal pelvis; v, inferior vena cava. F, CT scan obtained below the kidneys reveals filling of the upper ureters (*arrows*). The wall of the normal ureter is usually paper thin or not visible on CT. a, aorta; ac, ascending colon; dc, descending colon; v, inferior vena cava.

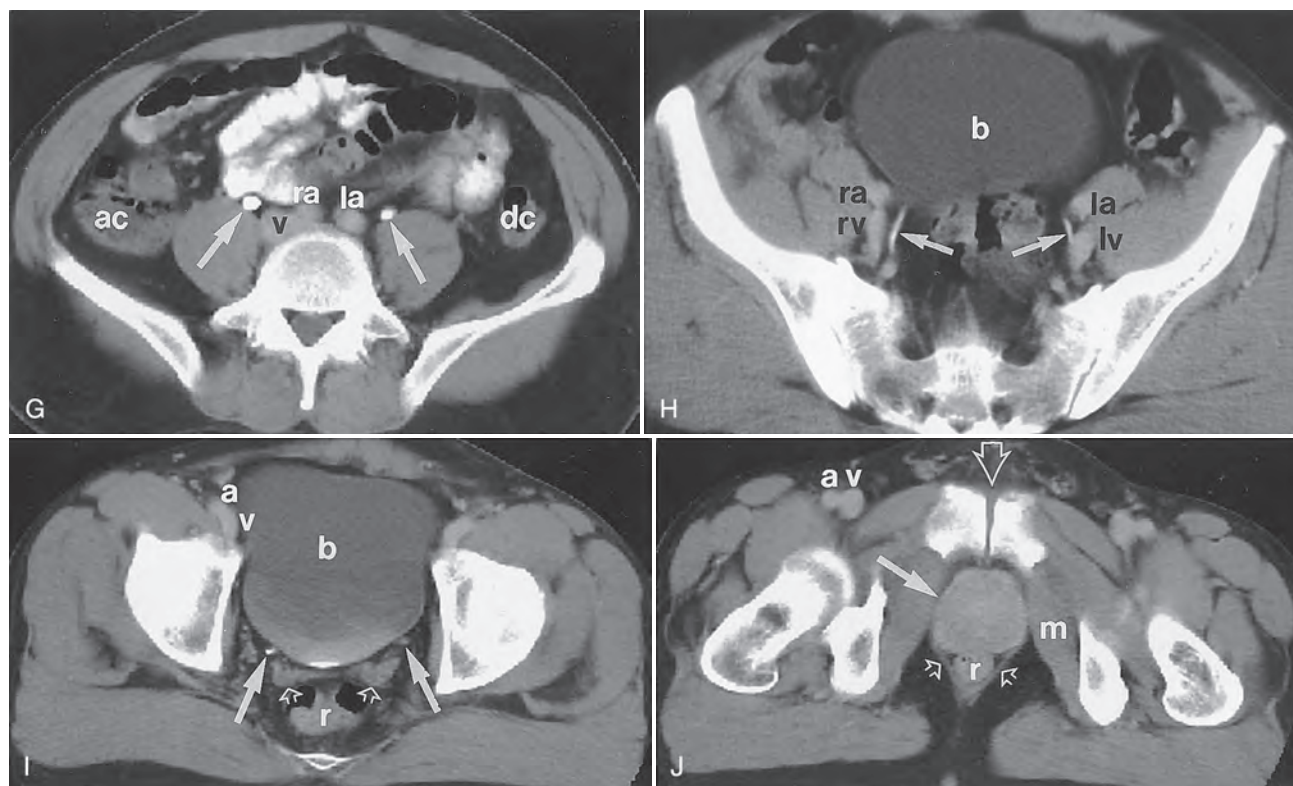


Figure 2-15, cont'd G, Contrast filling of the midureters (arrows) on a scan obtained at the level of the iliac crest and below the aortic bifurcation. ac, ascending colon; dc, descending colon; la, left common iliac artery; ra, right common iliac artery; v, inferior vena cava. H, The distal ureters (arrows) course medial to the iliac vessels on a scan obtained below the promontory of the sacrum. b, urinary bladder; la, left external iliac artery; lv, left external iliac vein; ra, right external iliac artery; rv, right external iliac vein. I, Scan through the roof of the acetabulum reveals distal ureters (solid arrows) near the ureterovesical junction. The bladder (b) is filled with urine and partially opacified with contrast material. The normal seminal vesicle (open arrows) usually has a paired bow-tie structure with slightly lobulated contour. a, right external iliac artery; r, rectum; v, right external iliac vein. J, Scan at the level of the pubic symphysis (large open arrow) reveals the prostate gland (solid arrow). a, right external iliac artery; m, obturator internus muscle; r, rectum; v, right external iliac vein; small open arrows, seminal vesicle.

diagnostic tool to evaluate renal colic. It offers the advantage over IVU of avoiding contrast and being able to diagnose other abdominal abnormalities that can also cause abdominal pain. MDCT can readily diagnose radiolucent stones which may not have been seen on IVU, as well as small stones even in the distal ureter (Federle et al, 1981). With the exception of some indinavir stones, all renal and ureteral stones can be detected on helical CT scan (Schwartz et al, 1999). In the workup of urolithiasis, the unenhanced CT has a sensitivity ranging between 96% and 100% and specificity ranging between 92% and 100% (Memarsadeghi et al, 2005). Stones in the distal ureter can be difficult to differentiate from pelvic calcifications. In these cases, the urologist needs to look for other signs of obstruction which indicate the presence of a stone, including ureteral dilation, inflammatory changes in the perinephric fat, hydronephrosis, and a soft tissue rim surrounding the calcification within the ureter. The soft tissue rim around a stone represents irritation and edema in the ureteral wall (Heneghan et al, 1997; Dalrymple et al, 2000) (Fig. 2-16).

Stone patients are frequently subjected to radiation exposure as part of diagnosis, treatment, and follow-up. Increasing awareness of the potential long-term adverse effects of radiation exposure has encouraged urologists and radiologists to discover means to decrease the amount of radiation exposure. The low-dose, unenhanced helical CT scan is gaining increasing popularity for initial diagnosis of renal colic suspected to be due to urolithiasis and for follow-up

in stone patients. Using low-dose CT protocols, the specificity and sensitivity of unenhanced low-dose helical CT scan is approximately 96% and 97%, respectively. Low-dose techniques offer a 99% positive predictive value and a 90% negative predictive value for urolithiasis. The end result is a 50% to 75% decrease in the patient's total radiation exposure for each CT obtained (Liu et al, 2000; Hamm et al, 2002; Kalra et al, 2005).

Cystic and Solid Renal Masses

The frequent CT imaging of patients in the emergency department has resulted in an increase in the detection of incidental renal masses. Using CT imaging the mass can be characterized as a simple or complex cyst, or a solid mass. Based on the HU attenuation scale, we would expect simple cysts to have HU near zero (Fig. 2-17).

When the unenhanced CT images of a renal mass are compared to the enhanced images obtained in the cortical medullary or nephrogenic phase, an increase in HU (measured in the area of the renal mass) by 15 to 20 HU confirms the presence of a solid enhancing mass, which is usually renal cancer. Pseudoenhancement is maximal when small (≤ 1.5 cm) intrarenal cysts are scanned during maximal levels of renal parenchymal enhancement. The magnitude of this effect varies with scanner type but may be large enough to prevent accurate lesion characterization, despite use of a thin-section helical CT data acquisition technique (Birnbau

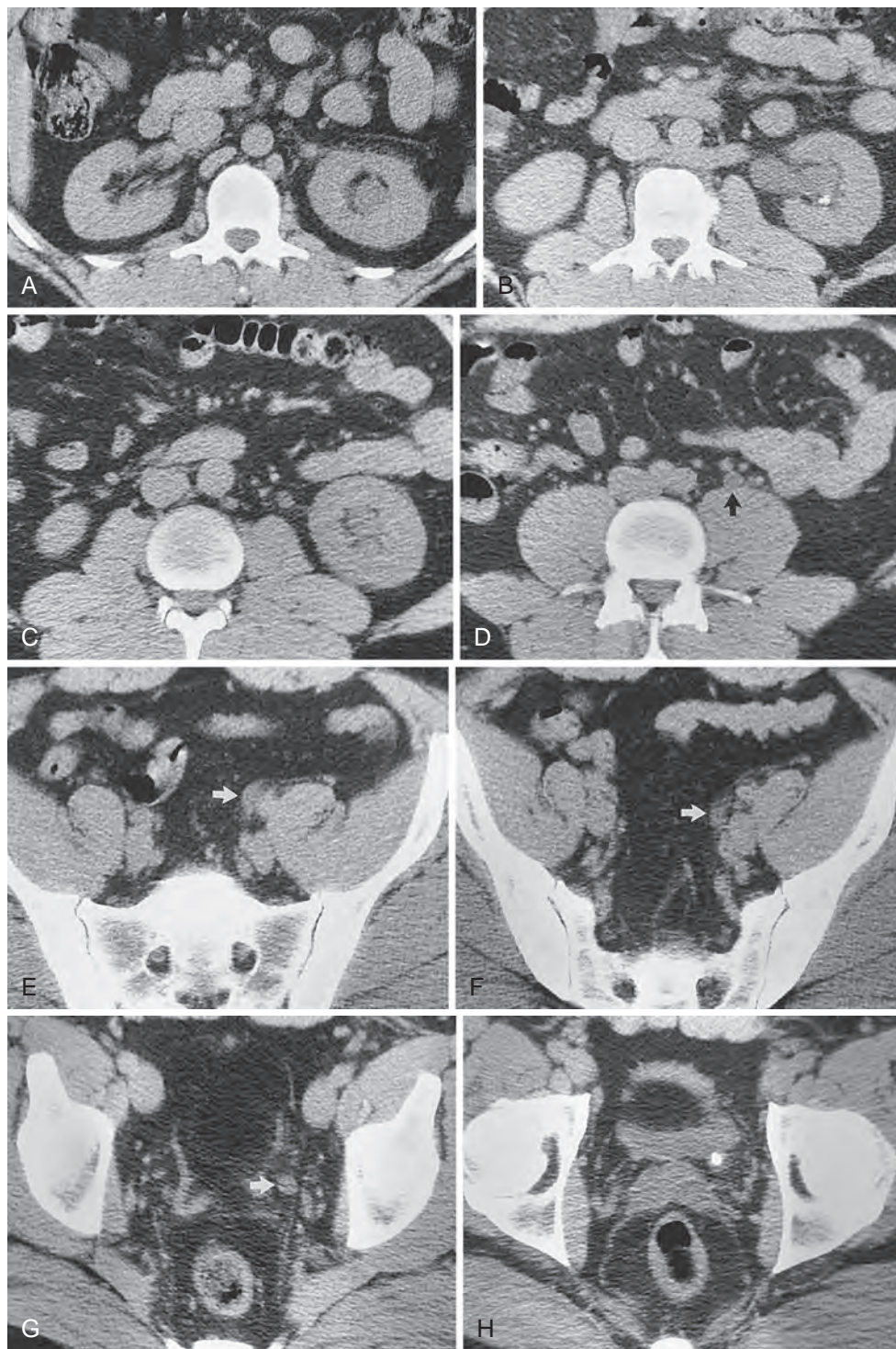


Figure 2-16. Computed tomography of the abdomen and pelvis in patient with an obstructing ureteral stone at the level of the ureterovesical junction (UVJ). A, Level of the left upper pole. Mild renal enlargement, caliectasis, and perinephric stranding are apparent. B, Level of the left renal hilum. Left pyelectasis with a dependent stone, mild peripelvic and perinephric stranding, and a retroaortic left renal vein are shown. C, Level of the left lower pole. Left caliectasis, proximal ureterectasis, and mild periureteral stranding are present. D, Level of the aortic bifurcation. The dilated left ureter (*arrow*) has lower attenuation than do nearby vessels. E, Level of the upper portion of the sacrum. A dilated left ureter (*arrow*) crosses anteromedial to the common iliac artery. F, Level of the midsacrum. A dilated left ureter (*arrow*) is accompanied by periureteral stranding. G, Level of the top of the acetabulum showing a dilated pelvic portion of the left ureter (*arrow*). H, Level of the UVJ. The impacted stone with a “cuff” or “tissue rim” sign that represents the edematous wall of the ureter. (From Talner LB, O’Reilly PH, Wasserman NF. Specific causes of obstruction. In: Pollack HM, McClennan BL, Dyer R, et al, editors. Clinical urography. 2nd ed. Philadelphia: Saunders; 2000.)

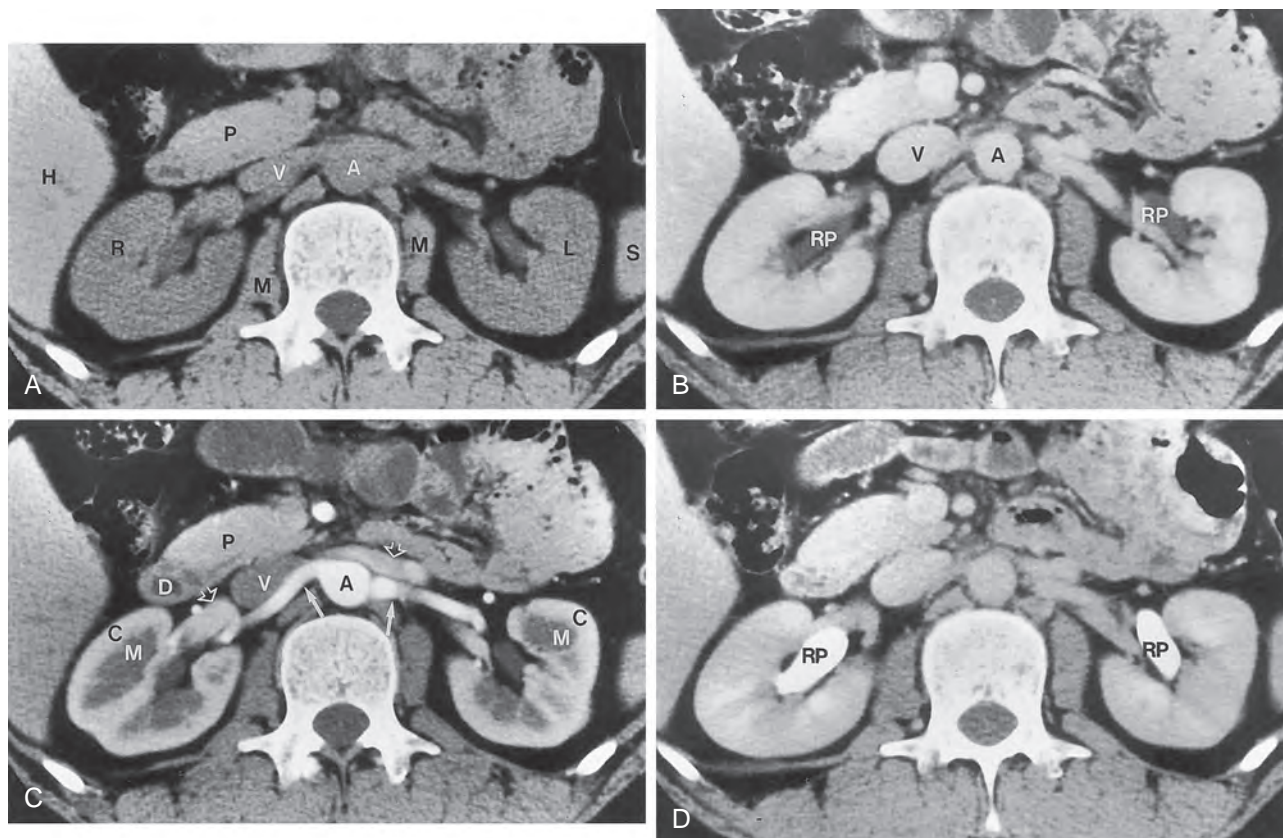


Figure 2-17. Renal computed tomography (CT) demonstrating normal nephrogenic progression. A, Unenhanced CT scan obtained at the level of the renal hilum shows right (R) and left (L) kidneys of CT attenuation values slightly less than those of the liver (H) and pancreas (P). A, abdominal aorta; M, psoas muscle; S, spleen; V, inferior vena cava. B, Enhanced CT scan obtained during a cortical nephrographic phase, generally 25 to 80 seconds after contrast medium injection, reveals increased enhancement of the renal cortex (C) relative to the medulla (M). The main renal artery is indicated with *solid arrows* bilaterally. Main renal veins (*open arrows*) are less opacified with respect to the aorta (A) and arteries. D, duodenum; P, pancreas; V, inferior vena cava. C, CT scan obtained during the homogeneous nephrographic phase, generally between 85 and 120 seconds after contrast medium administration, reveals a homogeneous, uniform, increased attenuation of the renal parenchyma. The wall of the normal renal pelvis (RP) is paper thin or not visible on the CT scan. A, abdominal aorta; V, inferior vena cava. D, CT scan obtained during the excretory phase shows contrast medium in the renal pelvis (RP) bilaterally; this starts to appear approximately 3 minutes after contrast medium administration.

et al, 2002). The presence of fat, which should enhance less than 10 HU, is diagnostic for angiomyolipoma. A hyperdense cyst shows no change in density between the postcontrast and delayed phase images (Fig. 2-18).

Complex cystic masses are usually characterized based on the Bosniak classification system. The most important criteria used to differentiate a lesion that should be considered for surgery versus a nonsurgical lesion is the presence or absence of tissue vascularity or enhancement. Bosniak category I, II, and IIF lesions do not enhance to any measurable degree. Category I lesions are simple cysts and considered to be benign. Category II lesions are more complicated and may have calcifications, high attenuation fluid, and several thin septae. Category III lesions are more complex, have small areas of calcification, and may also have irregular walls or septate where there is measurable enhancement. Cystic lesions discovered on CT scan that are difficult to categorize as either II or III are categorized as IIF. Bosniak III lesions have been reported to be malignant renal cell carcinoma in 60% of cases and require close follow-up or surgical extirpation. Bosniak category IV lesions are cystic masses that meet all the criteria of category

III, but also have enhancing soft tissue components adjacent to or independent of the wall or septum of the cyst; they have been reported to be malignant renal cell carcinoma in 100% of cases (Bosniak, 1997; Curry et al, 2000; Israel and Bosniak, 2005).

Hematuria

The CTU is one of the most common studies ordered for the workup of gross or microscopic hematuria. With MDCT it is possible to perform a comprehensive evaluation of the patient with one single examination (Chai et al, 2001). The study images the abdomen and pelvis and typically includes four different phases. The first scan is an unenhanced CT to distinguish between different masses that can be present in the kidney and uncover kidney stones that would later be obscured by the excretion of contrast into the renal collecting system. At 30 to 70 seconds after contrast injection, the corticomedullary phase is captured with another pass through the MDCT, helping to define vasculature and perfusion. The nephrogenic phase occurs between 90 to 180 seconds after injection of contrast

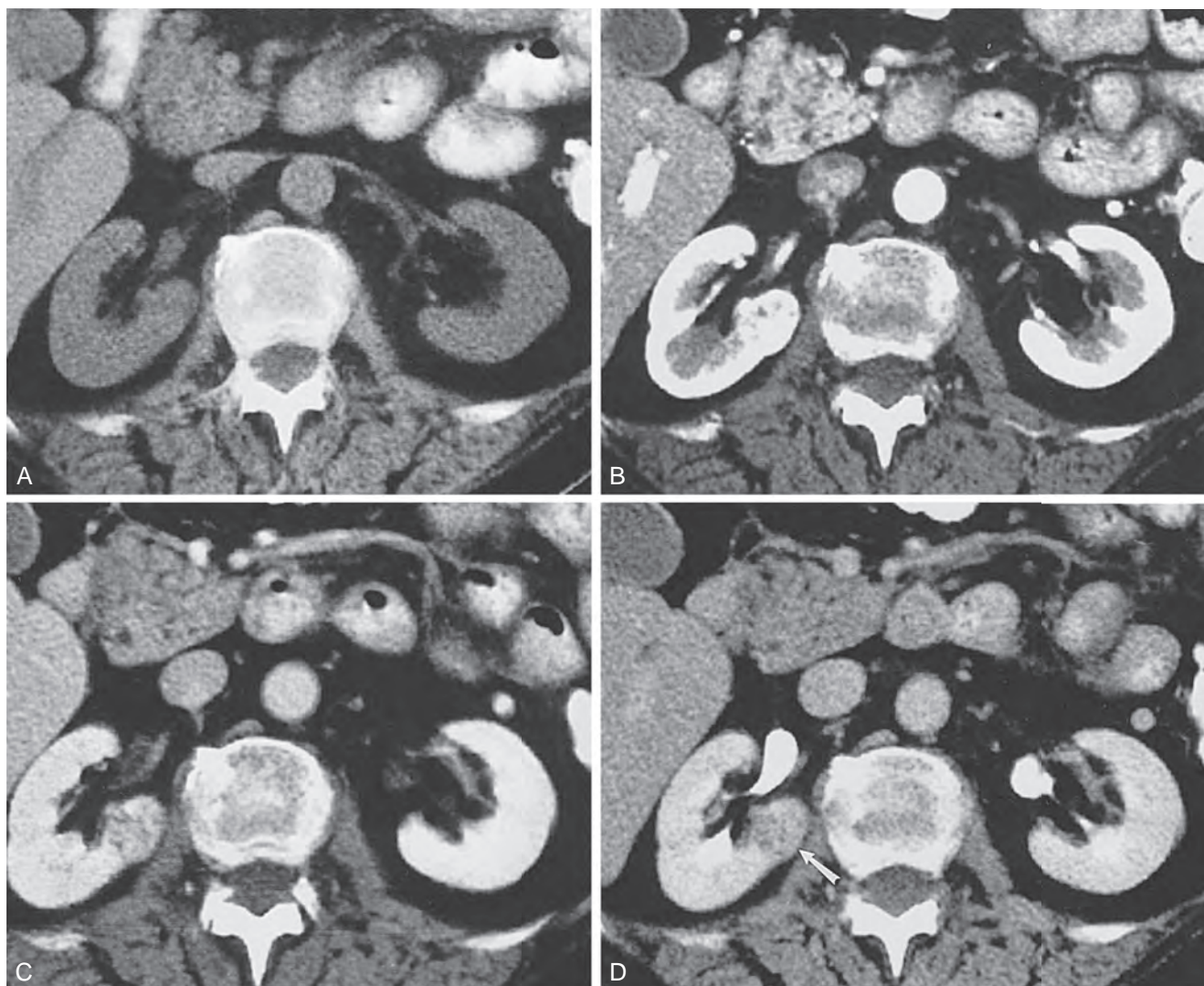


Figure 2-18. Small renal cell carcinoma in the infrahilar lip of the right kidney is not easily seen on unenhanced image (A). On corticomedullary phase image (B), the lesion is subtly visible as a hyperenhancing focus within the renal medulla. On nephrographic (C) and pyelographic phase (D) images, the full extent of the lesion (arrow) within the medulla and cortex is depicted. (From Brink JA, Siegel CL. *Computed tomography of the upper urinary tract*. In: Pollack HM, McClenan BL, Dyer R, et al, editors. *Clinical urography*. 2nd ed. Philadelphia: Saunders; 2000.)

and, when compared to the unenhanced images, allows sensitive detection and characterization of renal masses. The final phase is the excretory phase, imaged approximately 3 to 5 minutes after injection of contrast. This phase allows complete filling of the collecting system and usually allows visualization of the ureter (Joudi et al, 2006) (see Fig. 2-18).

CTU has been shown to be sensitive in detecting upper tract urothelial cancers. In one series of 57 patients with hematuria, 38 were found to have urothelial carcinoma. CT urography detected 37 of 38 urothelial cancers for a sensitivity of 97%, compared to retrograde pyelogram which detected 31 of 38 lesions and had a sensitivity of 82%. Approximately 90% of malignant upper tract lesions can be detected with CT urography (McCarthy and Cowan, 2002; Lang et al, 2003; Caoili et al, 2005). CT urography is not as sensitive as cystoscopy for the detection of urothelial tumors in the bladder. Only large bladder tumors are visualized with CT imaging studies as filling defects in the lumen of the bladder. Carcinoma in situ cannot be visualized on CT scanning, and therefore cystoscopy is still an important part of a comprehensive hematuria workup.

KEY POINTS: CT IMAGING

- The CTU is an excellent imaging choice to evaluate the kidney, upper tract collecting system, and ureter.
- The CTU is highly sensitive and specific for upper tract urothelial carcinoma.
- A renal mass in the kidney seen on CTU that enhances more than 15 to 20 HU is most likely a renal cancer.
- With the exception of indinavir stones, all urinary stones are visible on unenhanced CT of the abdomen and pelvis.

MAGNETIC RESONANCE IMAGING

CT imaging remains the mainstay of urologic cross-sectional body imaging; however, MRI is increasingly being applied to the genitourinary system. With constant improvements in technology, MRI is gradually narrowing the overall resolution quality gap between the two techniques. A significant advantage of MRI is the excellent

signal contrast resolution of soft tissue, without the need for IV contrast in many situations.

To obtain MR images, the patient is placed on a gantry that passes through the bore of the magnet. When exposed to a magnet field of sufficient strength, the free water protons in the patient orient themselves along the magnetic field's z-axis. This is the head-to-toe axis, straight through the bore of the magnet. An RF antenna or "coil" is placed over the body part to be imaged. It is the coil that transmits the RF pulses through the patient. When the RF pulse stops, protons release their energy, which is detected and processed to obtain the MR image. Currently, some coils can transmit and receive a signal, which is referred to as dual channel RF. An MR sequence exploits the body's different tissue characteristics and the particular manner that each type of tissue absorbs and then releases this energy.

Weighting of the image depends on how the energy is imparted through the physics of the pulse sequence and whether the energy is released quickly or slowly. Images are described as being T1 or T2 weighted. The T1-weighted images are generated by the time required to return to equilibrium in the z-axis. The T2-weighted images are generated by the time to return to equilibrium in the xy-axis. On T1-weighted MR images, fluid has a low SI and appears dark. T2-weighted MR images have a high SI and appear bright. In the kidney this translates into the cortex having a higher SI or being brighter than the medulla, which gives off a lower signal and is darker.

MRI has significant advantages over other imaging modalities. First, and most importantly, no risks are associated with secondary malignancies from radiation exposure (Berrington de González and Darby, 2004). It is the modality of choice in patients who are pregnant, suffer from renal insufficiency, and/or have an iodine contrast allergy.

The contrast agents in MRI are noniodinated compounds. Iodinated compounds as used in CT imaging function by absorbing x-rays. Gd-based contrast agents function on MRI secondary to shortening the relaxation times of water. This results in an increase in SI (enhancement), most commonly assessed in a T1 sequence. Gd is a toxic heavy metal that is chelated to prevent cellular absorption and any associated toxicities (Lin and Brown, 2007). The dose of Gd is nontoxic for almost all patients except ones with severe renal insufficiency. NSF occurs in patients with acute or chronic renal insufficiency with a GFR less than 30 mL/min/1.73 m² (see Contrast Media). Gd is deposited in skin and muscle as an insoluble precipitate that leads to the systemic fibrosis (Grobner, 2006). In response, the FDA has issued warnings regarding the association between NSF and Gd-based contrast agents because no effective treatment is available (U.S. Food and Drug Administration, 2006). The current guidelines are available at the FDA.gov official website (U.S. Food and Drug Administration, 2010).

Adrenal Magnetic Resonance Imaging

One of the key differences between MRI and other imaging modalities is its ability to characterize soft tissues without the use of IV contrast. In the adrenal gland, minute quantities of lipids can help differentiate between malignancies or benign adenomas. Most adrenal masses are identified incidentally and are nonfunctioning.

Adrenal adenomas are usually less than 3 cm in size and nonfunctional (Boland et al, 2008). Adrenal adenomas have a high lipid content (74%), which makes them more readily differentiated from malignant processes (Dunnick and Korobkin, 2002).

Inversion-recovery imaging, chemical shift imaging (CSI), and fat saturation imaging are three approaches to assess lipid content on masses. These approaches use the differences in the behavior of fat protons and water protons within the magnetic field. CSI is the most commonly used technique for urologic patients.

Adrenal Adenoma

Adrenal adenomas are characterized by assessing the lipid content within cells. CSI uses the difference in the behavior of water protons

(H₂O) versus fat protons (-CH₂-). The oxygen atom in water pulls on the electron cloud surrounding the hydrogen atom, whereas the carbon atom in fat is less electronegative and has a decreased effect on the hydrogen electron cloud (Pokharel et al, 2013). This difference in the magnetic field (shielding) for these two types of protons is the precessional frequencies or the chemical shift (Pokharel et al, 2013).

CSI obtains images "in-phase" (IP) and "out-of-phase" (OP) with regard to the water and fat protons. The signals detected for a given voxel can be additive or cancelled out. The IP imaging refers to the contribution of both fat and water, or additive to the signal at a given voxel. This occurs when the echo time (TE) is set to align the fat and water protons.

In the OP imaging, the TE is set to cancel the signals obtained, thus the subtraction of the protons results in a decrease, or cancelling, in signal at that given voxel and produces a lower SI if both fat and water are present.

The next step is to compare the two data sets (IP and OP) obtained to determine if there is a loss of signal (decrease) on the OP images, which is indicative of intracytoplasmic fat (Fig. 2-19). If there is no change between the two data sets, then there is a lower probability that fat is present within the mass. This was initially determined on a qualitative basis by visually comparing signal intensities between the two sequences (Korobkin et al, 1996). The loss of signal on CSI is 92% sensitive and has a limited specificity of 17% for adrenal adenoma (Boland et al, 2008).

Other investigators have attempted to determine SI index by quantitatively comparing the IP and OP images. Nakamura reported that using a 5% SI yielded an accuracy of 100% (3 tesla) in determining if intracytoplasmic lipid was present and thus a diagnosis of an adenoma (Nakamura et al, 2012). Although there are currently no set thresholds, cutoff ranges are reported to be between 1.7% and 20% (Nakamura et al, 2012). The limited specificity reported by the qualitative approach (17%) was increased to 100% specificity using quantitative SI index (Boland et al, 2008).

$$\text{SI index (\%)} = (\text{SI in phase} - \text{SI out of phase}) / \text{SI in phase} \times 100$$

In some clinical situations, lipid poor adenomas (10% to 30% incidence) can result in an indeterminate study (Elsayes et al, 2004). The typical washout of an adrenal cortical carcinoma is slow. Therefore an enhanced CT with washout may be a better study to differentiate lipid-poor adrenal adenomas from other adrenal masses (Park et al, 2007).

Adrenal Cortical Carcinoma

An adrenal cortical carcinoma (ACC) diagnosis is usually made using a combination of clinical factors and imaging characteristics (Fig. 2-20). In a review by Ng and Libertino (2003), ACC is hormonally active in 62% of cases. The incidence of ACC is related to size, and adrenal lesions equal to or less than 4 cm represented 2% of all ACC diagnosed. The incidence of ACC increased to 6% for lesions 4 to 6 cm and to 25% for lesions greater than 6 cm (Mansmann et al, 2004). T2- and T1-weighted images with Gd usually are heterogeneous with a high SI and a heterogeneous enhancement, respectively. CSI exhibits a low signal (Bharwani et al, 2011). ACC is also associated with local vascular thrombosis, which can be detected on MRI (Mezhir et al, 2008). ACC has an increased metabolic activity and can be visualized on FDG-PET imaging, and this can differentiate ACC from adenomas with 100% sensitivity and 88% specificity (Groussin et al, 2009).

Myelolipoma

Myelolipoma is a benign adrenal mass that consists of mature fatty tissues and bone marrow elements. Myelolipoma occurs in approximately 6.5% of patients with incidentally detected adrenal masses (Song et al, 2008). The complicating issue with myelolipomas is that the size of the mass can be greater than 4 cm, and this carries significant overlap with malignant adrenal lesions (Meyer

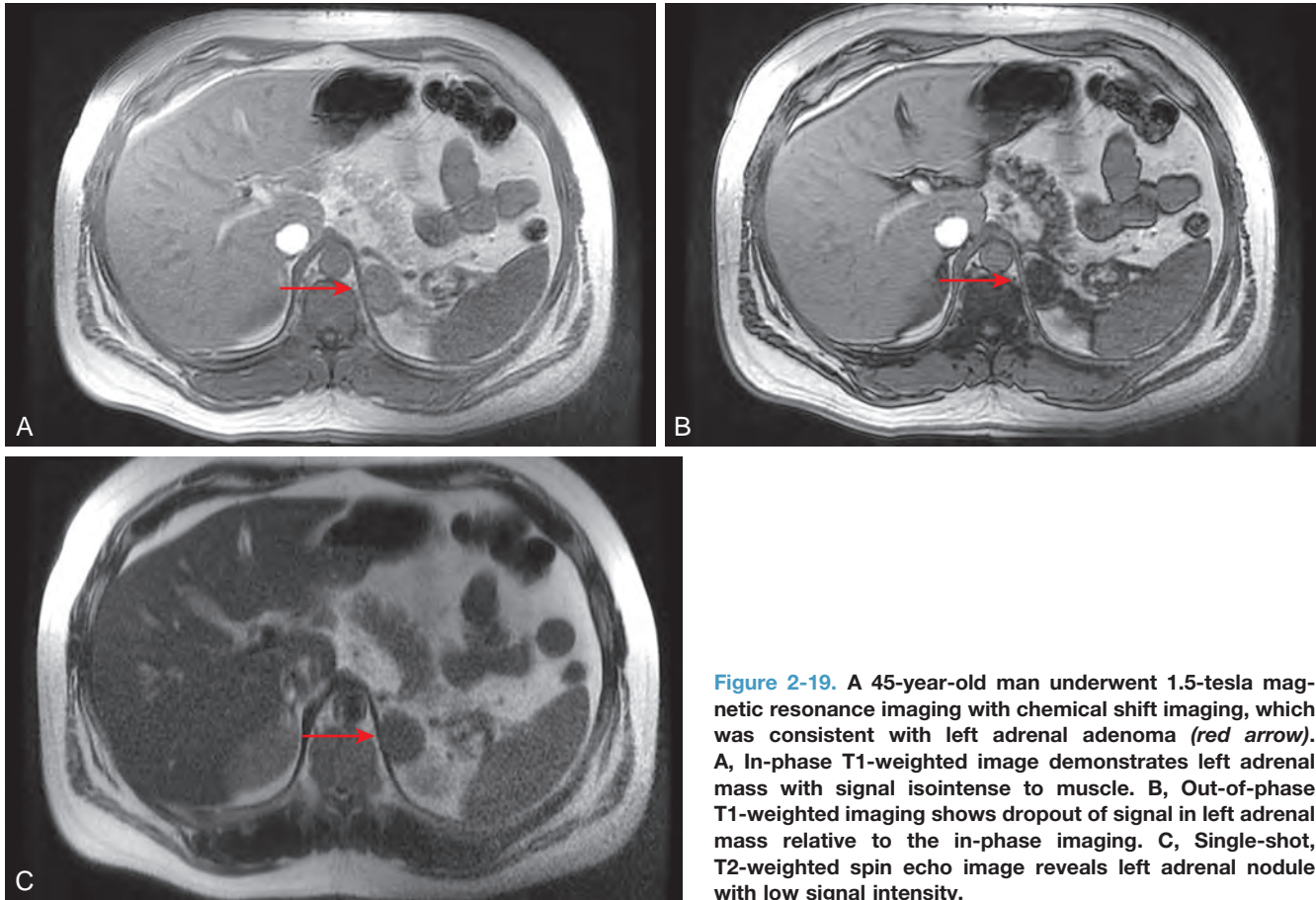


Figure 2-19. A 45-year-old man underwent 1.5-tesla magnetic resonance imaging with chemical shift imaging, which was consistent with left adrenal adenoma (red arrow). A, In-phase T1-weighted image demonstrates left adrenal mass with signal isointense to muscle. B, Out-of-phase T1-weighted imaging shows dropout of signal in left adrenal mass relative to the in-phase imaging. C, Single-shot, T2-weighted spin echo image reveals left adrenal nodule with low signal intensity.

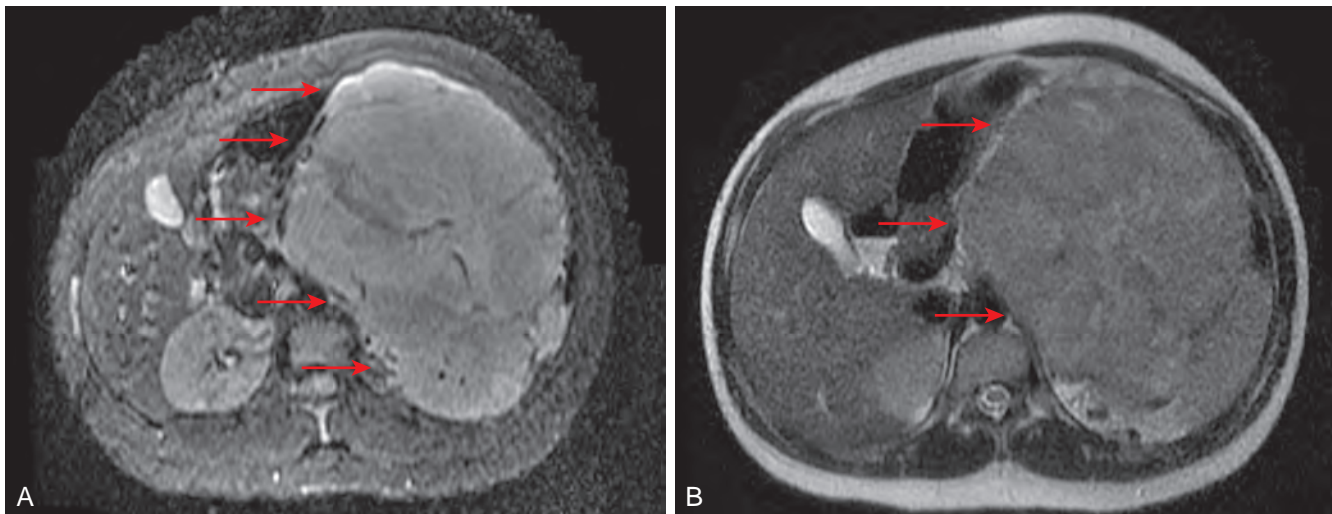


Figure 2-20. A 65-year-old woman with left side heterogeneous enhancing suprarenal lesion (adrenal cortical carcinoma) with select images from a 1.5-tesla abdominal magnetic resonance image. A, Moderately weighted T2 STIR (short-tau inversion recovery) images with a hyperintense signal (red arrows). B, Heavily weighted T2 single-shot, fast spin echo isointense signal. These findings are all dependent on the degree of T2 weighting.

and Behrend, 2005). On MRI a myelolipoma has a high SI on T1-weighted imaging, suppressed signal on frequency selective fat suppression, and an India ink artifact (Taffel et al, 2012) (Fig. 2-21). India ink artifact appears as a dark line around the lesion and/or organs and is the result of a voxel containing both fat and water on chemical shift OP images.

Metastasis

An adrenal mass is considered to be metastatic in the setting of a known primary malignancy. The MRI findings are consistent with a large, irregular, heterogeneous mass with occasional necrosis present on imaging. Metastases have a high signal on T2-weighted

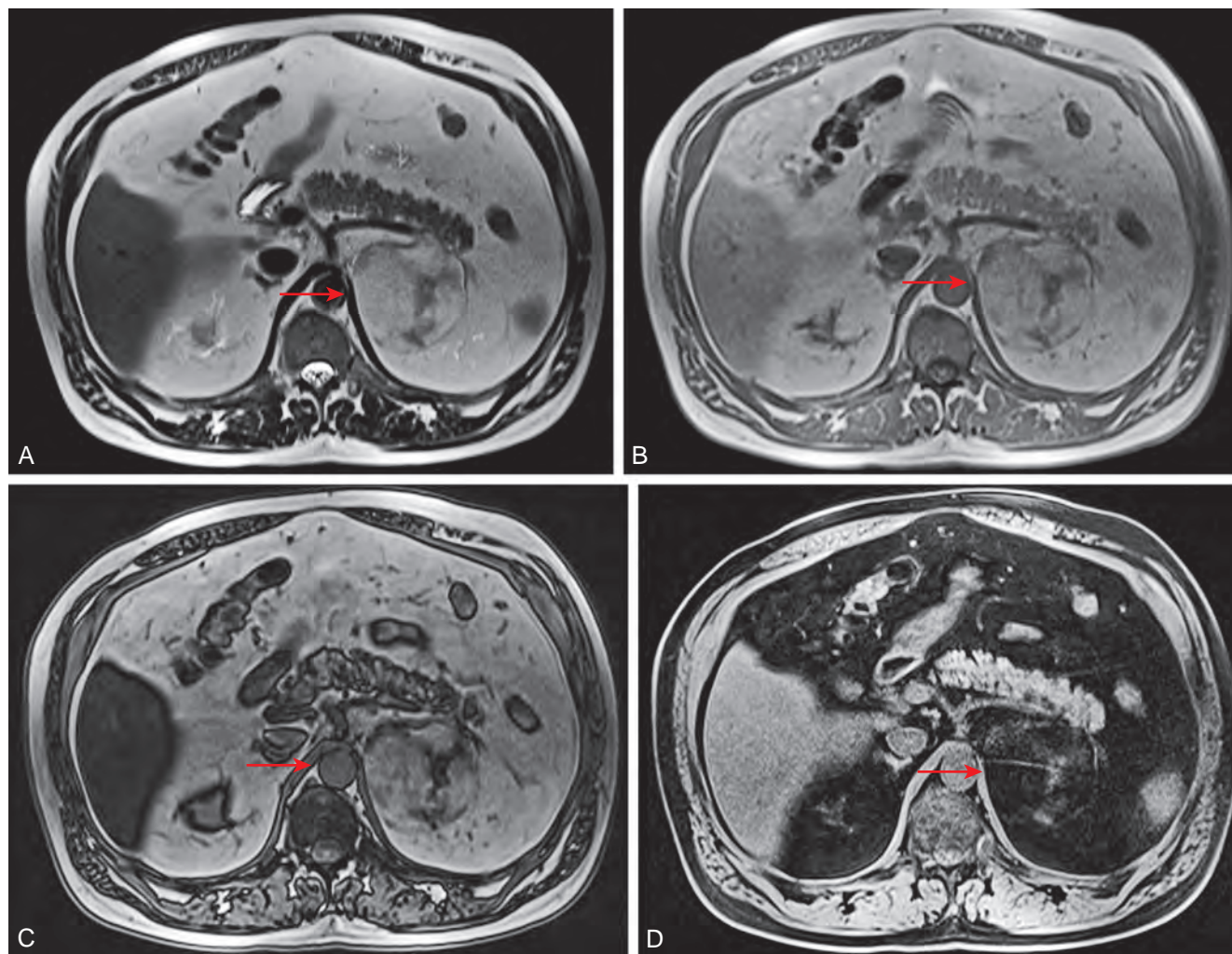


Figure 2-21. A 44-year-old man, with prior abdominal ultrasonography detecting an indeterminate renal mass, underwent 1.5-tesla magnetic resonance imaging with chemical shift imaging, which was consistent with left adrenal myelolipoma (red arrow). A, T2 single-shot spin echo demonstrates a large left adrenal mass with signal isointense to abdominal fat. B, T1 in-phase imaging demonstrates a left adrenal mass with signal similar to the abdominal fat. C, T1 out-of-phase imaging shows no drop of signal compared with in-phase imaging. D, T1 fat-suppressed precontrast imaging shows loss of signal within the mass consistent with gross fat.

images secondary to higher fluid content, compared with adrenal adenoma (Sahdev et al, 2010). Gd enhancement on T1-weighted images demonstrates heterogeneous enhancement with a delayed peak enhancement (65 seconds) when compared with adrenal adenomas (40 seconds). Using a time to peak enhancement cutoff of 53 seconds or greater resulted in 87.5% sensitivity and 80% specificity in characterizing metastatic adrenal lesions (Inan et al, 2008).

Patients with primary lesions that are known to contain intracytoplasmic fat may require additional imaging to better differentiate an adrenal gland lesion. The metastatic sites often carry the same histologic features as the primary tumor. This can result in a false-positive for adrenal adenomas if the primary contains intracytoplasmic lipid content (CSI positive) (Krebs and Wagner, 1998) (Fig. 2-22). This has been reported in liposarcoma, renal cell carcinoma, and hepatocellular carcinoma (Krebs and Wagner, 1998; Sydow et al, 2006).

Pheochromocytoma was traditionally considered to be diagnostic if on T2-weighted images the lesion demonstrated an increased SI (Fig. 2-23). However, Varghese and colleagues (1997) reported that 35% of pheochromocytomas demonstrated low T2 signal,

contrary to conventional teaching. Pheochromocytoma, ACC, and metastatic lesions to the adrenal gland can exhibit a hyperintense SI or appear bright on T2-weighted images. It is important to understand that the SI can vary because of degree of weighting of the T2 signal and not have the traditional findings of being bright on T2-weighted images (see Figs. 2-20, 2-22, and 2-23). The pheochromocytoma can be characterized on MRI without the need for contrast enhancement, avoiding a potential hypertensive crisis that has been associated with iodine contrast media in these patients (Raisanen et al, 1984).

Lymphoma, neuroblastoma, ganglioneuroma, hemangioma, and granulomatous diseases of the adrenal gland have an intermediate SI index on CSI and other imaging findings (Table 2-3).

Adrenal hematomas have variable imaging characteristics on MRI because of changes in the hematoma from initial acute bleeding to breakdown products of red blood cells with deposition of hemosiderin within the hematoma. This progresses from an isointense to hypointense signal on T1 and low signal on T2 to hyperintense on T1 fat-suppressed sequences and T2 sequences at 1 to 7 weeks. A low signal rim is present on both T1 and T2 sequences because of hemosiderin deposits (Taffel et al, 2012).

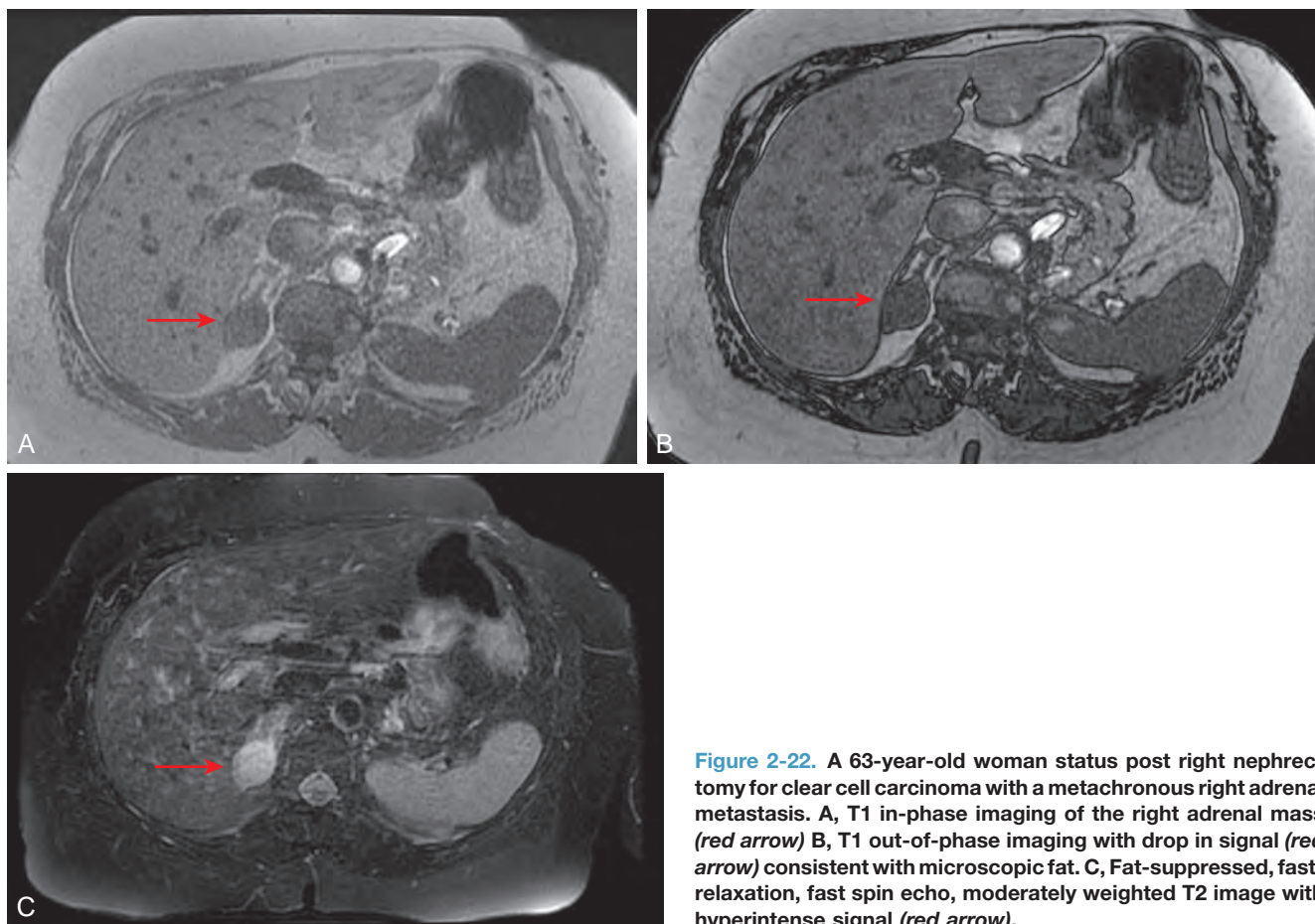


Figure 2-22. A 63-year-old woman status post right nephrectomy for clear cell carcinoma with a metachronous right adrenal metastasis. A, T1 in-phase imaging of the right adrenal mass (red arrow) B, T1 out-of-phase imaging with drop in signal (red arrow) consistent with microscopic fat. C, Fat-suppressed, fast-relaxation, fast spin echo, moderately weighted T2 image with hyperintense signal (red arrow).

Renal Magnetic Resonance Imaging

Simple cysts have similar characteristics on ultrasonography, CT, and MRI. Complex cysts can also be differentiated or characterized using MRI. Hemorrhage within the cyst results in a high signal on T1-weighted images because of the paramagnetic effects of blood breakdown products (hemosiderin) (Roubidoux, 1994) (Fig. 2-24).

Proteinaceous contents within a cyst can also demonstrate high signal on T1-weighted images. Chronic hemorrhage results in a black ring along the cyst wall on T2-weighted images. For benign, complex cysts there should be no enhancement of any component of the cysts (Israel et al, 2004).

Because MRI is insensitive to calcifications, any calcifications present on the lining of a complex cyst are not well visualized. When evaluating independent risk factors for renal cell carcinoma, enhancement of the cyst wall had higher sensitivity and specificity than calcifications on the cyst wall. Calcifications can cause artifacts that may decrease the ability to appreciate enhancement of small nodules within the wall of a complex cyst on CT imaging. MRI has the advantage of not being influenced by calcifications within the wall of a complex cyst. Therefore MRI is more likely to detect enhancement of a renal cell carcinoma in the wall of a complex cyst, compared with CT imaging when mural calcifications are present (Israel and Bosniak, 2003).

MRI offers a distinct advantage over CT imaging with regard to detection and evaluation of the pseudocapsule that appears on T1- and T2-weighted images as a low signal surrounding the lesion. The lack of pseudocapsule surrounding a renal mass had an accuracy of 91% in predicting pT3a disease (Roy et al, 2005).

MRI allows differentiation of different subtypes of renal cell carcinoma by using a multiparametric approach. These sequences can include: T1-weighted images; multiplanar T2-weighted sequences with and without fat suppression; dynamic contrast enhanced

(DCE) sequences with arterial, corticomedullary, and nephrogenic and excretory phases; diffusion-weighted images (DWI) with corresponding apparent diffusion coefficient (ADC) maps; and CSI. Using these unique features we are better able to differentiate the subtypes of renal masses compared with CT imaging.

Renal cell carcinoma clear cell type (cRCC) is the most common type of renal cell carcinoma. It is characterized by a heterogeneous high signal on T2-weighted sequences because of the presence of hemorrhage, necrosis, and/or cysts (see Fig. 2-24). Papillary renal cell carcinoma (pRCC), when compared to cRCC, exhibits a homogeneous lower SI on T2-weighted images, which is secondary to hemosiderin deposition (histiocytes) within the tumor (Fig. 2-25). Hemorrhagic cysts with an enhancing peripheral wall growth and/or a solid hypoenhancing mass with low SI on T2-weighted images resulted in 80% sensitivity and 94% specificity in differentiating pRCC from other types of RCCs (Fig. 2-26) (Pedrosa et al, 2008).

Like adrenal MR imaging, CSI can detect intracytoplasmic lipids and aid in the differentiation of cRCC from other RCC subtypes (see Fig. 2-24). Microscopic intracytoplasmic lipids have been found in 59% of clear cell carcinomas (Outwater et al, 1997). Karlo and colleagues (2013) reported that once angiomyolipoma (AML) has been ruled out using standard MRI techniques (Fig. 2-27) in which macroscopic fat has been detected, CSI sequences with a 25% decrease in SI can be considered diagnostic for cRCC from other renal tumors. Pedrosa and colleagues (2008) reported the sensitivity and specificity of CSI for cRCC was 42% and 100%, respectively. There are rare cases of RCC with macroscopic fat; however, if calcifications are also present, this would favor the diagnosis of RCC over AML (Wasser et al, 2013).

Gd-enhanced T1-weighted images with a relative SI increase of 15% is considered to be positive enhancement, which results in a 100% sensitivity in differentiation of cysts from renal cell carcinoma

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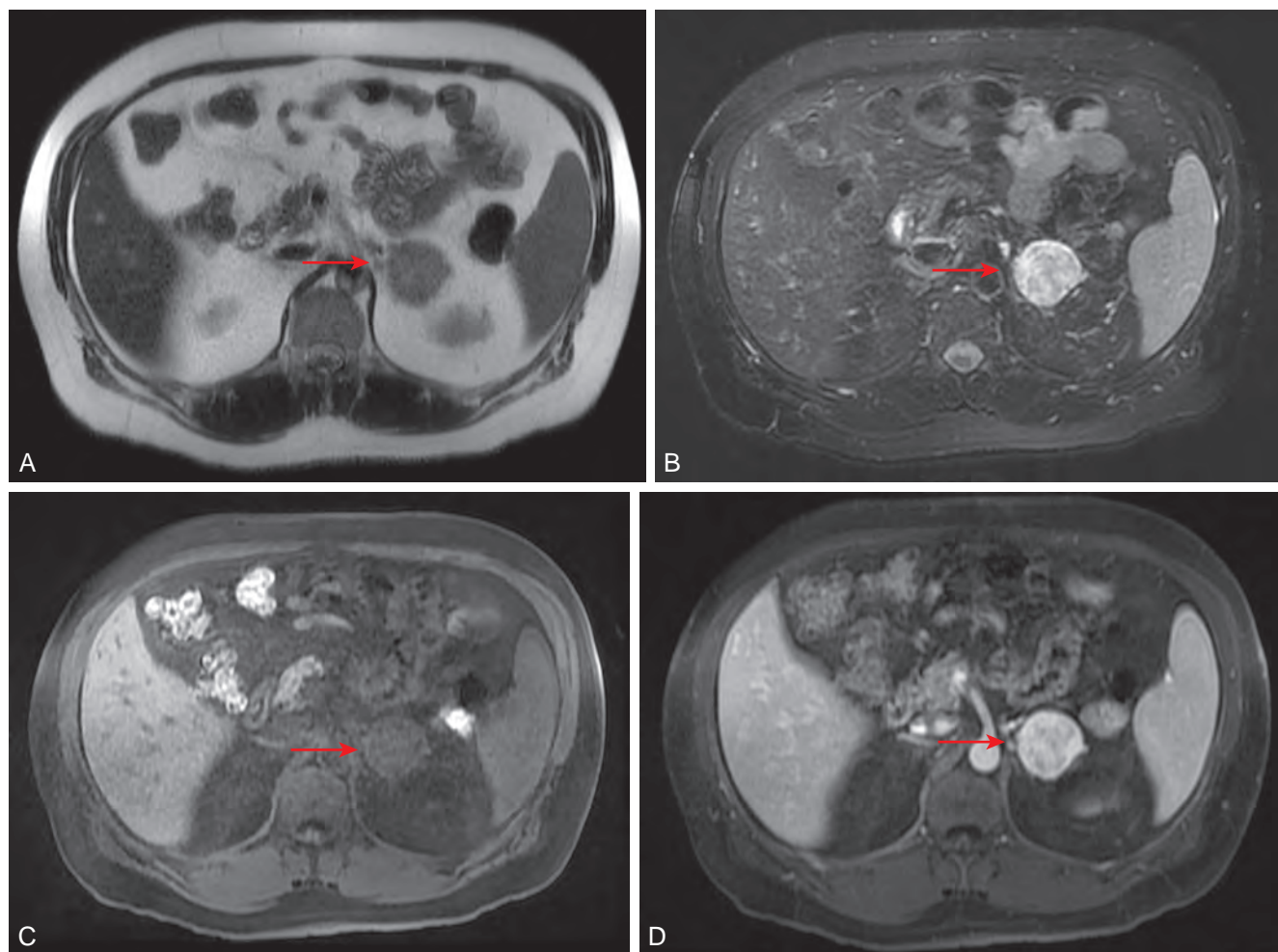


Figure 2-23. A 50-year-old man with a left side pheochromocytoma (as shown by arrows) and select images from 1.5-tesla magnetic resonance imaging. A, Heavily weighted T2 single-shot fast spin echo with an isointense signal (not bright). B, Moderately weighted T2 fat-suppressed, fast-recovery, fast spin echo with hyperintense signal (bright). C, T1-weighted precontrast image. D, T1-weighted postcontrast image with marked early enhancement.

TABLE 2-3 Morphologic and Imaging Characteristics of Incidental Adrenal Lesions

IAL	SIZE (cm)	SHAPE	TEXTURE	UNENHANCED CT ATTENUATION (HU)	15-MINUTE CT WASHOUT (%)	MRI SIGNAL CHARACTERISTICS	NUCLEAR MEDICINE CHARACTERISTICS
Adrenal metastasis	Variable	Variable	Heterogeneous when larger	>10	RPW <40	High T2 signal	Positive on PET images
Adrenal cortical carcinoma	>4	Variable	Variable	>10	RPW <40	Intermediate to high T2 signal	Positive on PET images
Pheochromocytoma	Variable	Variable	Variable	>10, rarely <10	RPW <40	High T2 signal	Positive on MIBG
Cyst	Variable	Smooth, round	Smooth	<10	Does not enhance	High T2 signal	Negative
Adenoma	1-4	Smooth, round	Homogeneous	<10 in 70%	RPW >40; APW >60	SI dropoff on OP images	Variable on PET images
Myelolipoma	1-5	Smooth, round	Variable with macroscopic fat	<0, often ≤50	No data	High T1 signal, India ink, variable SI dropoff on OP images	Negative on PET images
Lymphoma	Variable	Variable	Variable	>10	RPW <40	Intermediate SI	Variable positivity on PET images
Hematoma	Variable	Smooth	Variable	>10, sometimes >50	No data	Variable signal	Negative
Neuroblastoma	Variable	Variable	Smooth, round	>10	RPW <40	Variable if necrotic	Positive
Ganglioneuroma	Variable	Variable	Variable	>10	No data	Usually intermediate SI	Usually negative
Hemangioma	Variable	Variable	Variable	>10	No data	Usually intermediate SI	Usually negative
Granulomatous	1-5	Smooth	Usually homogeneous	>10	No data	Usually intermediate SI	Positive on PET images if active

APW, absolute percentage washout; CT, computed tomography; HU, Hounsfield unit; IAL, incidental adrenal lesion; MIBG, m-iodobenzylguanidine; MRI, magnetic resonance imaging; OP, out-of-phase; PET, positron emission tomography; RPW, relative percentage washout; SI, signal intensity.
From Boland GW, Blake MA, Hahn PF, et al. Incidental adrenal lesions: principles, techniques, and algorithms for imaging characterization. Radiology 2008;249:756-75; and Taffel M, Haji-Momenian S, Nikolaidis P, et al. Adrenal imaging: a comprehensive review. Radiol Clin North Am 2012;50:219-43.

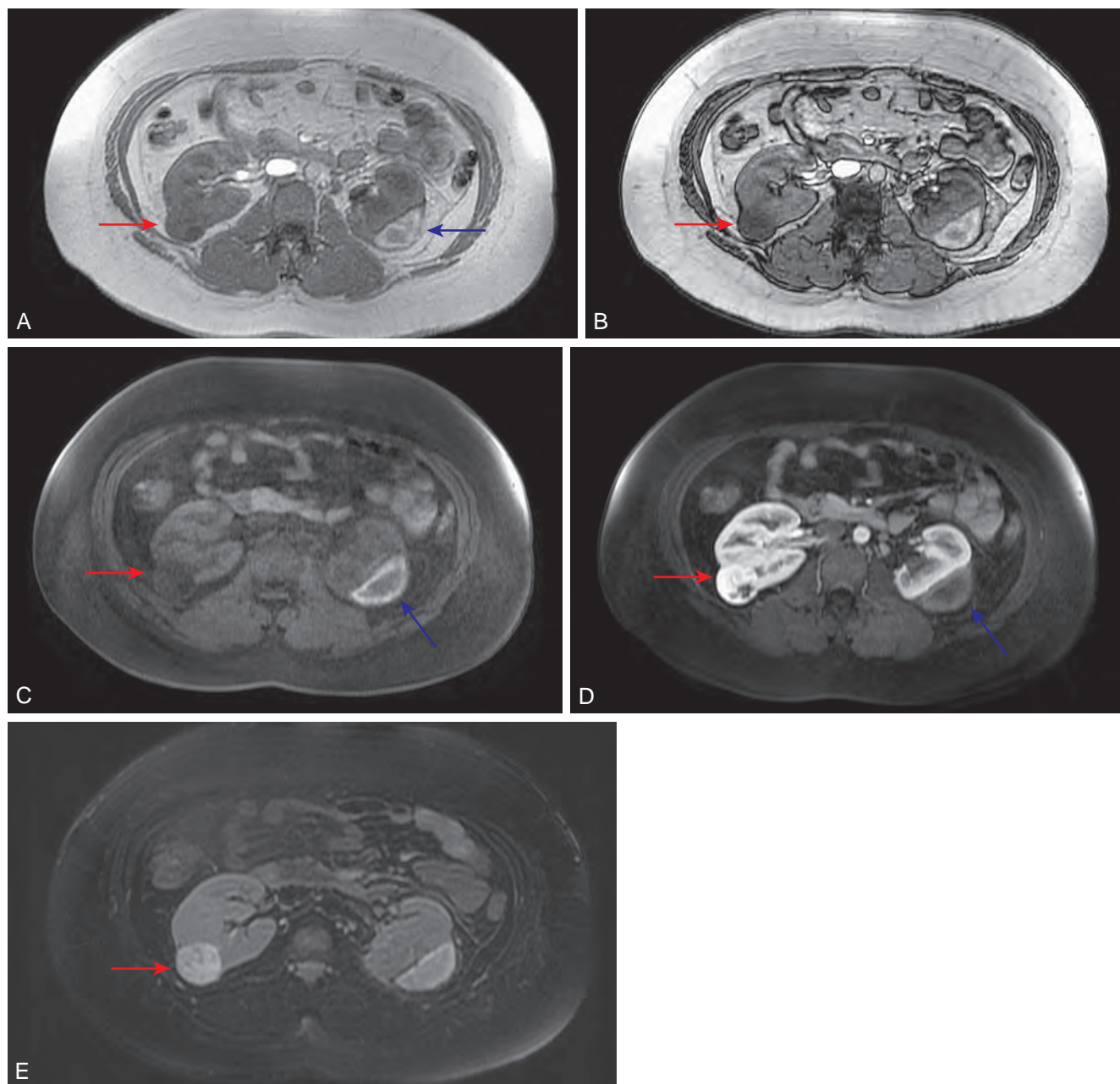


Figure 2-24. A 31-year-old woman, after left extracorporeal shock wave lithotripsy with a subcapsular hematoma and right side pathology confirmed 3.5-cm clear cell carcinoma, underwent 1.5-tesla magnetic resonance imaging of the abdomen. A, T1-weighted in-phase imaging of a right renal nodule with mild heterogeneity (*red arrow*) but primarily isointense signal intensity (SI). Left kidney subcapsular hematoma with a rim of high SI (*blue arrow*). B, T1-weighted out-of-phase image shows diffuse signal dropout within the renal nodule consistent with microscopic fat. C, T1-weighted fat-suppressed precontrast image with a low SI of the right renal nodule (*red arrow*) and high SI of the left subcapsular hematoma (*blue arrow*). Blood is high SI on precontrast T1-weighted images. D, T1 fat-suppressed postcontrast images of the right renal nodule with avid heterogeneous enhancement. Unenhancing left subcapsular hematoma (*blue arrow*). E, Diffusion-weighted imaging b-1000 shows high SI throughout the right renal nodule.

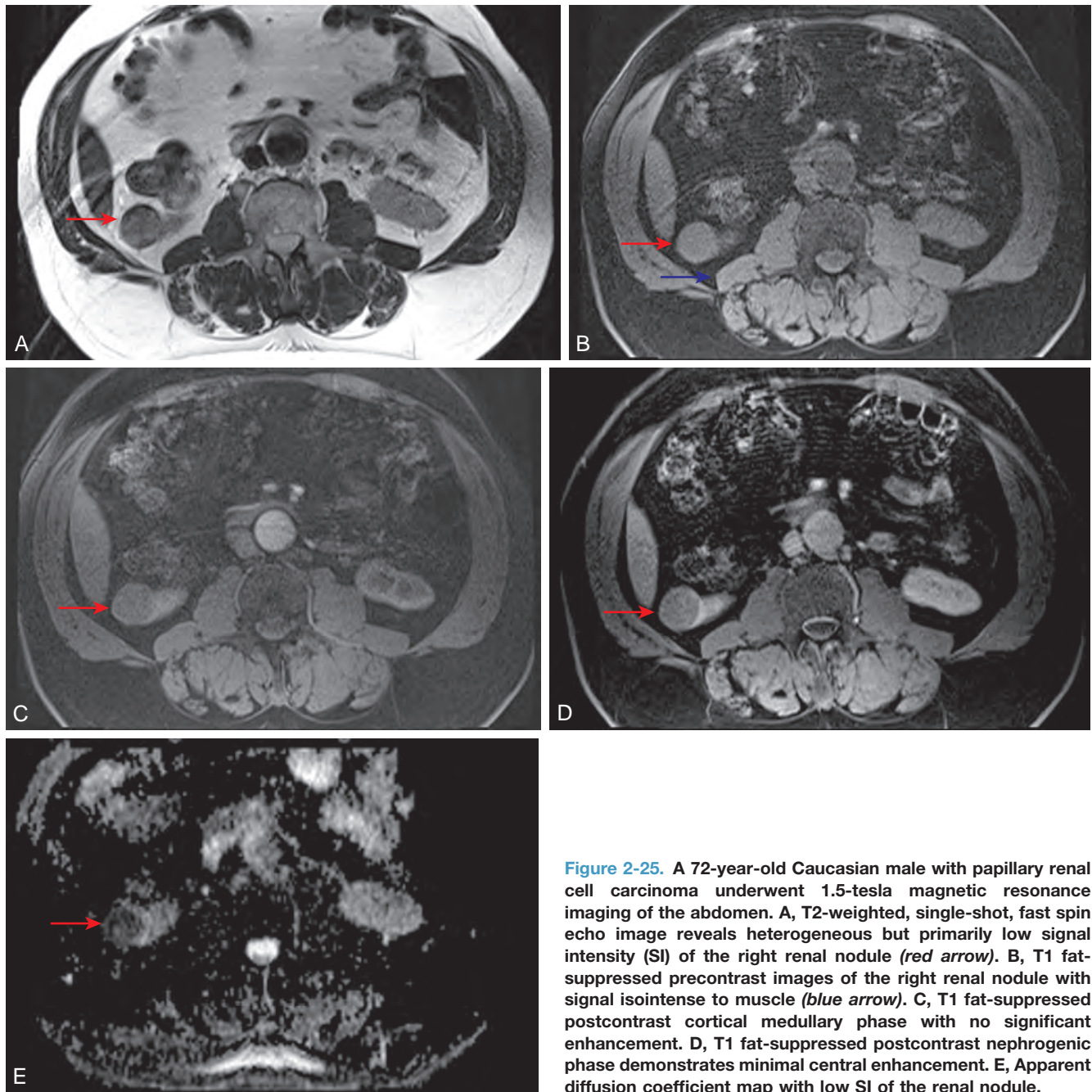


Figure 2-25. A 72-year-old Caucasian male with papillary renal cell carcinoma underwent 1.5-tesla magnetic resonance imaging of the abdomen. A, T2-weighted, single-shot, fast spin echo image reveals heterogeneous but primarily low signal intensity (SI) of the right renal nodule (*red arrow*). B, T1 fat-suppressed precontrast images of the right renal nodule with signal isointense to muscle (*blue arrow*). C, T1 fat-suppressed postcontrast cortical medullary phase with no significant enhancement. D, T1 fat-suppressed postcontrast nephrogenic phase demonstrates minimal central enhancement. E, Apparent diffusion coefficient map with low SI of the renal nodule.

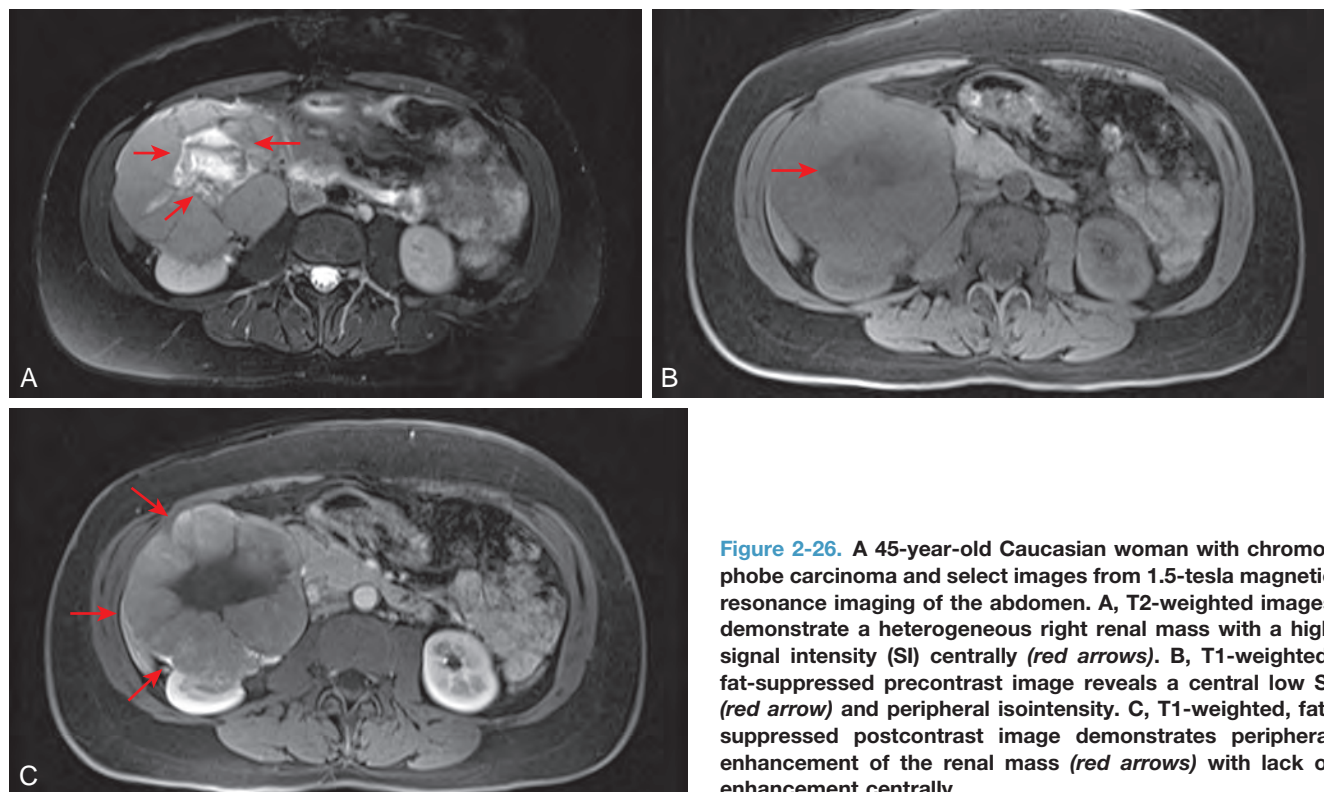


Figure 2-26. A 45-year-old Caucasian woman with chromophobe carcinoma and select images from 1.5-tesla magnetic resonance imaging of the abdomen. A, T2-weighted images demonstrate a heterogeneous right renal mass with a high signal intensity (SI) centrally (red arrows). B, T1-weighted, fat-suppressed precontrast image reveals a central low SI (red arrow) and peripheral isointensity. C, T1-weighted, fat-suppressed postcontrast image demonstrates peripheral enhancement of the renal mass (red arrows) with lack of enhancement centrally.

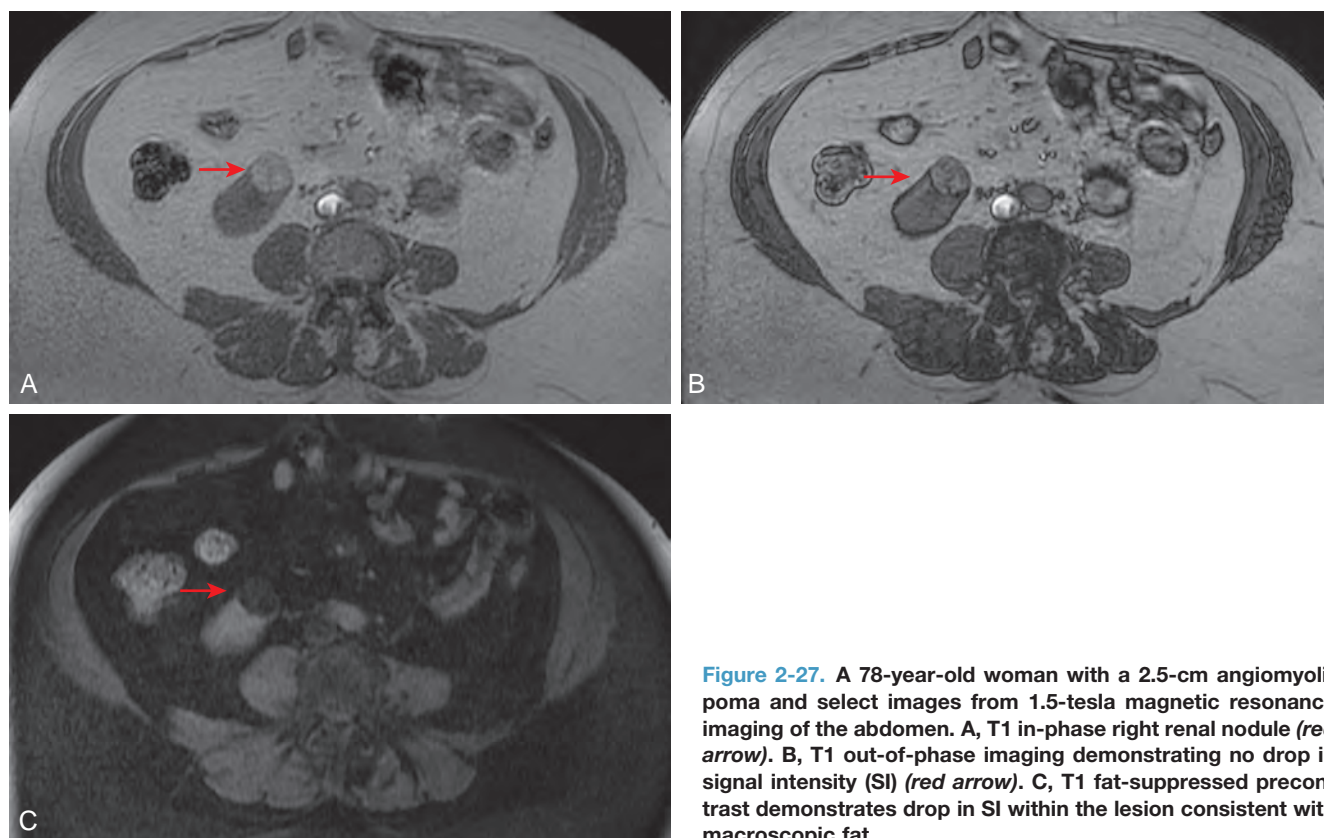


Figure 2-27. A 78-year-old woman with a 2.5-cm angiomyolipoma and select images from 1.5-tesla magnetic resonance imaging of the abdomen. A, T1 in-phase right renal nodule (red arrow). B, T1 out-of-phase imaging demonstrating no drop in signal intensity (SI) (red arrow). C, T1 fat-suppressed precontrast demonstrates drop in SI within the lesion consistent with macroscopic fat.

TABLE 2-4 Magnetic Resonance Imaging Characteristics of Renal Masses

	SIGNAL INTENSITY (SI) % CHANGE			ADC AT B VALUES 0 AND 800 sec/mm ² ($\times 10^{-6}$ mm ² /sec)	T2-WEIGHTED IMAGES SI
	CORTICOMEDULLARY PHASE	NEPHROGENIC PHASE	EXCRETORY PHASE		
Clear cell	230%	250%	227%	1698	High SI heterogeneous
Papillary carcinoma	49%	92%	88%	884	Low SI homogeneous
Chromophobe carcinoma	98%	183%	159%	1135	High T2-weighted SI for central scar
Oncocytoma	208%	265%	237%		High T2-weighted SI for central scar
Angiomyolipoma	353%	285%	222%		Variable
Renal parenchyma				2303	
Transitional cell carcinoma				<450	High signal

ADC, apparent diffusion coefficient.

From Vargas HA, Chaim J, Lefkowitz RA, et al. Renal cortical tumors: use of multiphasic contrast-enhanced MR imaging to differentiate benign and malignant histologic subtypes. *Radiology* 2012;264:779–88; and Wang H, Cheng L, Zhang X, et al. Renal cell carcinoma: diffusion-weighted MR imaging for subtype differentiation at 3.0 T. *Radiology* 2010;257:135–43.

with peak enhancement occurring at 2 to 4 minutes (Ho et al, 2002). Using the specific characteristics of DCE MR sequences, Vargas and colleagues (2012) assessed the enhancement characteristics of cRCC, pRCC, AML, and chromophobe carcinoma in the corticomedullary, nephrogenic, and excretory phases. Clear cell demonstrated greater than 200% SI increase in all three contrast phases, which was significantly higher than chromophobe and papillary carcinoma (Table 2-4). AML was the only renal mass to demonstrate a decrease in SI from the corticomedullary phase to the nephrogenic phase (see Fig. 2-27). Because of a high degree of overlap, it is difficult to assign cutoff points. It was not possible to find characteristics to differentiate oncocytoma from cRCC (Israel and Bosniak, 2003).

Oncocytoma is typically described with a central scar that is observed as a high SI on T2-weighted images. However, this is present only in 54% to 80% of cases (Cornelis et al, 2013). Unfortunately, a central scar has also been reported in 37% of chromophobe carcinomas (Rosenkrantz et al, 2010) (see Fig. 2-26). Both oncocytoma and chromophobe carcinomas are usually peripheral and are hypovascular compared with the renal cortex (Ho et al, 2002). Necrosis has a high SI on T2-weighted images and low SI on T1-weighted images, which is the same for the central scar associated with oncocytoma (Harmon et al, 1996).

DWI is able to detect the restricted movement of water protons within the intracellular and extracellular spaces. Wang and Cheng (2010) reported on using a threshold of 1281×10^{-6} mm²/sec and above for differentiating cRCC from non-clear cell carcinomas with a 95.9% sensitivity and 94.4% specificity (see Table 2-4). Central RCC can be differentiated from transitional cell carcinoma (TCC) of the renal pelvis by setting a threshold of 451×10^{-6} mm²/sec and below on normalized ADC values, resulting in a 83% sensitivity and 71% specificity for detecting TCC (Wehrli et al, 2013).

Historically, MRI has been reported to be superior to earlier CT imaging techniques when attempting to assess if tumor thrombus is present within the renal vein or inferior vena cava. Currently, MRI and CT have the same performance when evaluating for tumor thrombus (Hallscheidt et al, 2005). Gd-contrast agent is used to differentiate tumor thrombus, which exhibits enhancement, compared with a bland thrombus (clot), which exhibits no enhancement.

The size of the lymph nodes observed via MRI and CT is used to detect lymphadenopathy. Several investigators have been evaluating the use of nanoparticles that are composed of superparamagnetic iron oxide in the evaluation of lymphadenopathy (Eisner and

Feldman, 2009). Normal lymph nodes take up the iron oxide particles via phagocytosis, which results in a signal loss on T2-weighted sequences.

Upper Tract and Lower Tract Imaging for Urothelial Carcinoma

Urothelial carcinoma of the upper tract can be assessed by an MR urogram (MRU) in addition to the standard renal mass MRI techniques. MRU can be used in patients for whom other imaging modalities are contraindicated. MRU is accomplished by using heavily weighted T2 sequences in which fluid/urine have a high SI on T1-weighted images with Gd (Chahal et al, 2005). MRU and CTU have the same accuracy in assessing renal obstruction (Silverman et al, 2009). Nephrolithiasis/calcification on MRI has no signal characteristics; therefore it appears as a void on imaging. Urothelial tumors, blood clots, gas, or sloughed renal papilla may exhibit a low signal or signal voids on T2-weighted images secondary to the high signal of urine (Kawashima et al, 2003).

MRI is advantageous over CT imaging of the bladder because of the increased signal contrast between the layers of the bladder. This allows for differentiation between invasive and superficial bladder cancer with an accuracy of 85% (Tekes et al, 2005) (Fig. 2-28).

Prostate

Prostate cancer is one of the few solid organ malignancies that have not had reliable imaging. Over the past 10 years several developments have led to the increased use of MRI for the detection of prostate cancer. The increase in the field strength of magnets from 1 to 3 tesla improved techniques and surface coils have increased the signal contrast (differentiation of normal prostate versus cancer) leading to improved visualization within the gland.

Several authors have reported on varying standards that should be used for prostate imaging. The currency in MRI is signal. Signal detection is optimized by using external surface coils and/or an endorectal coil (ERC) and therefore leads to improved image quality. The National Institutes of Health (NIH) recently completed a study comparing the diagnostic accuracy at 3 tesla with and without ERC in the same patients and compared findings to whole mount histopathology. Results indicated a 36% decrease in sensitivity in detecting prostate cancer when the ERC was not used (Turkbey et al, 2014).

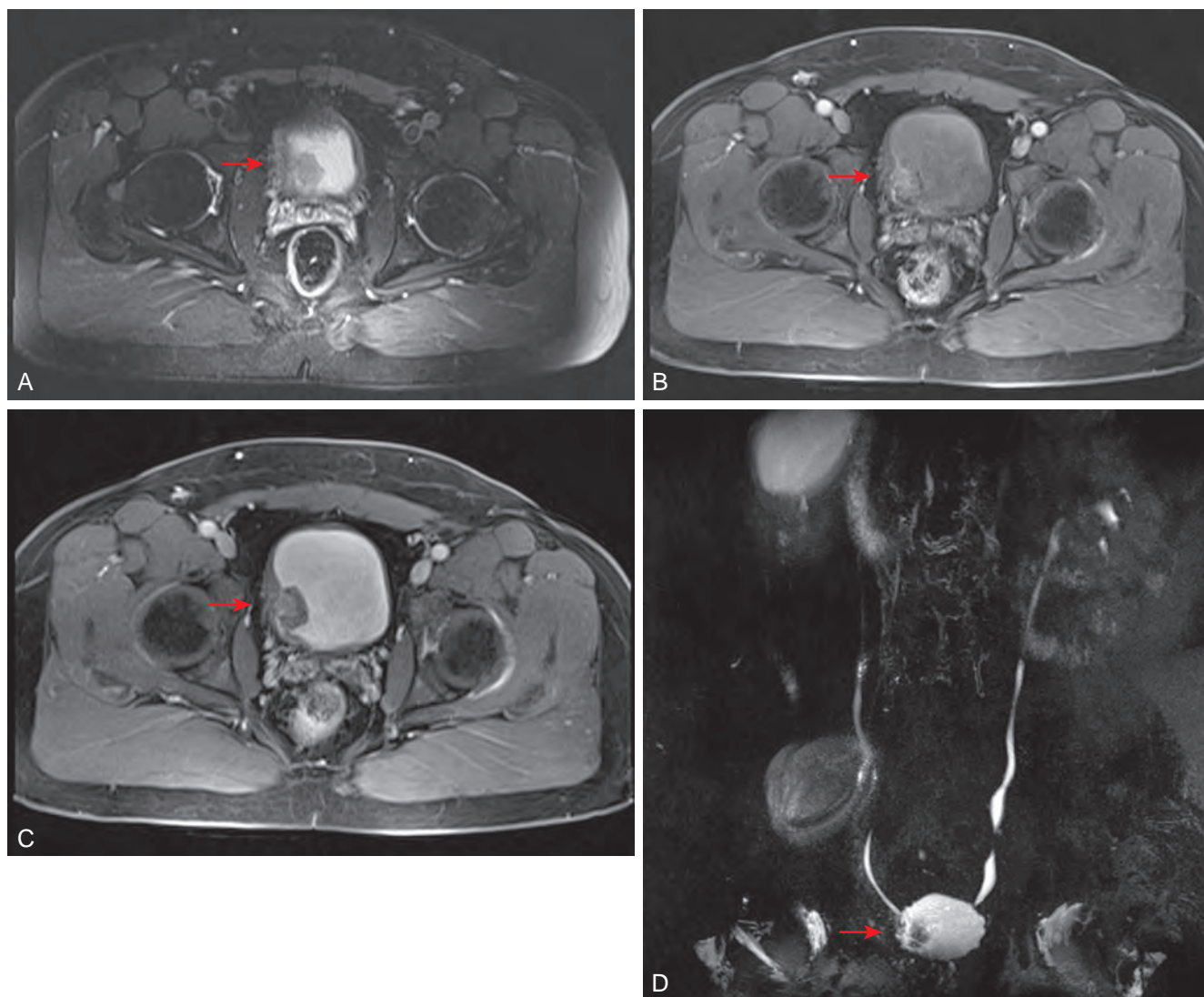


Figure 2-28. A 51-year-old man with a history of gross hematuria underwent a 1.5-tesla magnetic resonance urogram. A, T2 fat-saturated sequence with high T2 signal in bladder (urine). Right bladder wall low signal intensity filling defect (red arrow). B, Fat-suppressed T1 postcontrast arterial phase shows enhancing right bladder wall polypoid mass and is without bladder wall invasion. C, Fat-suppressed T1 delayed contrast imaging shows high signal in bladder consistent with intravenous contrast excretion. Mild persistent signal in right bladder wall mass. D, Heavily weighted T2 urogram selectively demonstrates high signal of fluid within the ureters and bladder. Right wall bladder filling defect (red arrow) is evident. Transurethral resection of bladder tumor confirmed no bladder wall invasion of a high-grade papillary urothelial carcinoma.

Prostate MRI is usually referred to as a multiparametric (MP) MRI. This consists of anatomic and functional imaging techniques. Anatomic imaging should include T1- and T2-weighted images. Functional imaging includes DWI with ADC maps, DCE sequences, and possibly spectroscopy. MR spectroscopy is not always included in the standard MP-MRI. MR spectroscopy takes approximately 15 minutes to perform, is labor intensive, and may not add additional information to affect the clinical interpretation of the study.

Initial T1-weighted sequences are obtained to determine if hemorrhage is present within the prostate; this may limit the diagnostic interpretation of the study. If there is hemorrhage, it can lead to false positives on T2 sequences, DWI/ADC, and DCE images, although some authors report no difference in diagnostic accuracy with or without hemorrhage present (Rosenkrantz et al, 2010). There is debate regarding the time between biopsy and the MP-MRI, which can be performed 3 to 8 weeks after a biopsy to optimize

intraprostatic anatomy (Ikonen et al, 2001; Qayyum et al, 2004; Muller et al, 2014). The wait period is not required for presurgical staging to determine if there is extraprostatic extension (EPE) and/or seminal vesicle invasion (SVI).

The most recent consensus meeting reported that the minimum examination should be a 1.5-tesla MRI with an ERC or a 3 tesla with or without an ERC and a multiparametric approach (Muller et al, 2014). Use of external phased array coils increases signal detection and therefore improves image quality. A 3-tesla MP-MRI with a minimum of 16-channel phased array coil with an ERC detects the highest signal and therefore provides the highest quality images. However, it is unclear if a radiologist needs this level of quality to make a diagnostic impression. It is important that an ERC should never be filled with air or water (Rosen et al, 2007). The result is a decrease in the performance of the T2, DWI, and MR spectroscopy. The most optimal fluids are diamagnetic and proton neutral (Rosen et al, 2007).

T2-Weighted Imaging

T2-weighted sequences of the prostate provide anatomic information and should include triplanar (axial, coronal, and sagittal) sequences. These images provide a detailed anatomic assessment of the gland. The normal peripheral zone appears as an area of high SI. The central gland with benign prostatic hyperplasia (BPH) appears as areas of well-demarcated nodules with heterogeneous SIs. Areas of low SI on T2-weighted sequences can represent prostate cancer or prostatitis, atrophy, scars, hemorrhage after prostate biopsy, and/or BPH nodules (Barentsz et al, 2012). Rarely, BPH nodules can be observed within the peripheral zone and can lead to a false-positive MRI for cancer (Fig. 2-29).

T2-weighted imaging alone results in 58% sensitivity and 93% specificity for detecting prostate cancer within the gland at 3 tesla with an ERC (Turkbey et al, 2011). These limitations reinforce the need to perform a multiparametric assessment that incorporates functional imaging and increases the positive predictive value (PPV) and negative predictive value (NPV) of the examination to greater than 90% (Turkbey et al, 2011). T2-weighted sequences are used to assess EPE and SVI. These areas are represented by low SI. MP-MRI at 3 tesla with an ERC has an approximate 90% accuracy when assessing EPE on a per lesion analysis. At the patient level, comparing the accuracy of staging, including microscopic EPE, overall accuracy decreased to 78.5%. The use of ERC improves the accuracy of detecting EPE and SVI (Heijmink et al, 2007).

Diffusion-Weighted Imaging/Apparent Diffusion Coefficient

DWI assesses the diffusion of water (Brownian motion) within the magnetic field. The MR magnet is able to detect the phase shift changes in the motion of the water protons. The more cellular a

tissue is, the closer the cells are together, resulting in a limited motion of water, which is reflected as a high signal on DWI (Manenti et al, 2006).

As with all MR sequences, there are several details that one should observe. Most important is the b-values associated with DWI. B-values represent a threshold for detecting restriction. As a b-value is increased, less restricted tissues do not exhibit a high signal on DWI. DWI can include multiple b-values, and it is recommended to include at least one b-value greater than 1000 (Rosenkrantz et al, 2010). The ADC is a quantitative assessment of the DWI. This is represented by an area of low signal on the images (dark spot) (Fig. 2-30D). Some authors recommend including a b-2000 sequence on DWI; it has been shown that prostate cancer exhibits a high SI compared with the rest of the gland (Ueno et al, 2013) (Fig. 2-30F).

The ADC value computed from DWI has been shown to directly correlate with Gleason score (Turkbey et al, 2011). Intuitively this makes sense because an increase in cellularity results in an increase in Gleason score. The extracellular/intracellular spaces between the cells are decreased and therefore are reflected as areas of increased restriction.

Dynamic Contrast Enhanced Magnetic Resonance Imaging

DCE-MRI refers to T1-weighted imaging with Gd-based contrast agents. DCE-MRI is not a simple assessment of enhancement versus no enhancement. It assesses vascular permeability and perfusion of the prostate by obtaining multiple image acquisitions over 5 to 10 minutes at a temporal resolution of less than or equal to 5 seconds (Verma et al, 2012). The 5-second temporal resolution requires a decrease in the size of the imaging matrix, therefore resulting in a lower resolution image. DCE-MRI is not meant to obtain clear

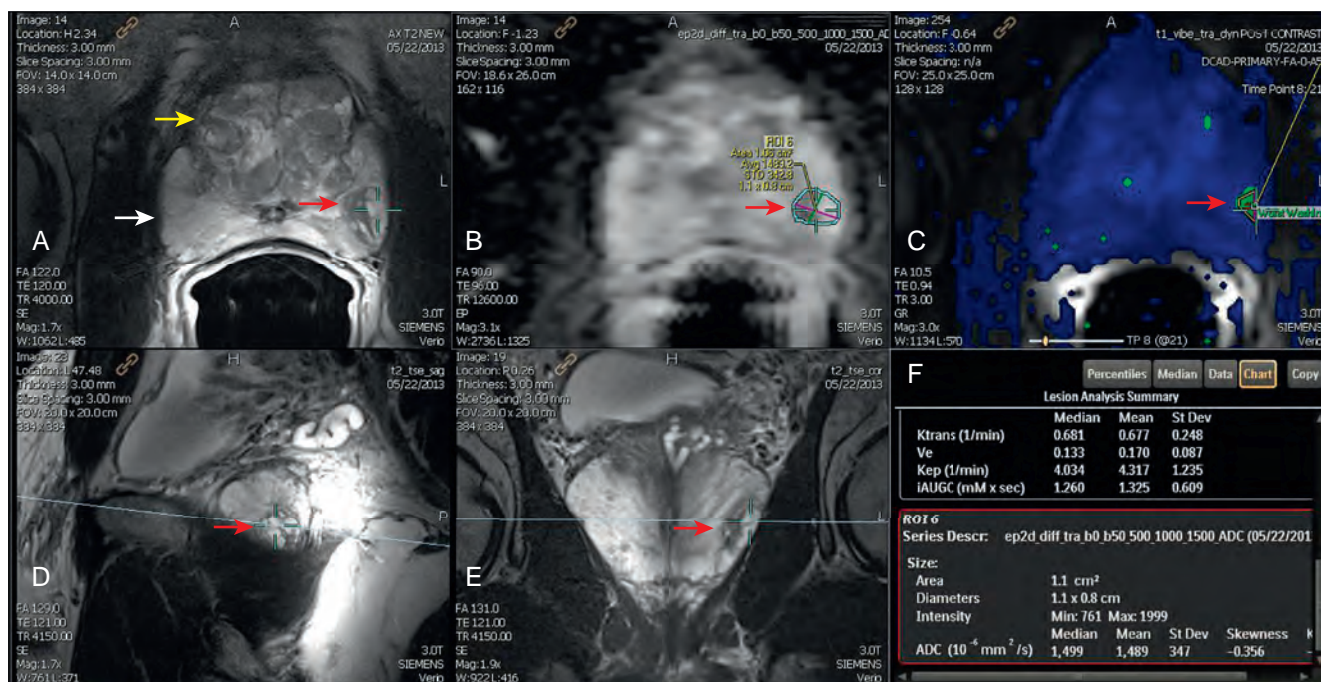


Figure 2-29. A 66-year-old man with a prostate-specific antigen of 7.0 and two prior negative biopsies. A 3-tesla multiparametric magnetic resonance imaging (MP-MRI) with an endorectal coil of the prostate was obtained. There were two suspicious areas. A, D, and E, Triplanar images in axial, sagittal, and coronal planes. The peripheral zone (white arrow) and the central gland (yellow arrow) are well visualized. The red arrow represents a well-circumscribed heterogeneous benign prostatic hypertrophy nodule (11 mm × 11 mm × 14 mm) within the peripheral zone with no communication to the central gland. The corresponding apparent diffusion coefficient map (B) demonstrates areas of heterogeneous restriction (761 × 10⁻⁶ mm²/sec). The lesion on the dynamic contrast enhanced MRI (DCE-MRI) (C) exhibits focal type 2 and 3 enhancement curves. The DCE-MRI quantitative analysis is listed (F). The patient underwent a fusion biopsy. The lesion was also appreciated on ultrasonography, and no cancer was detected.

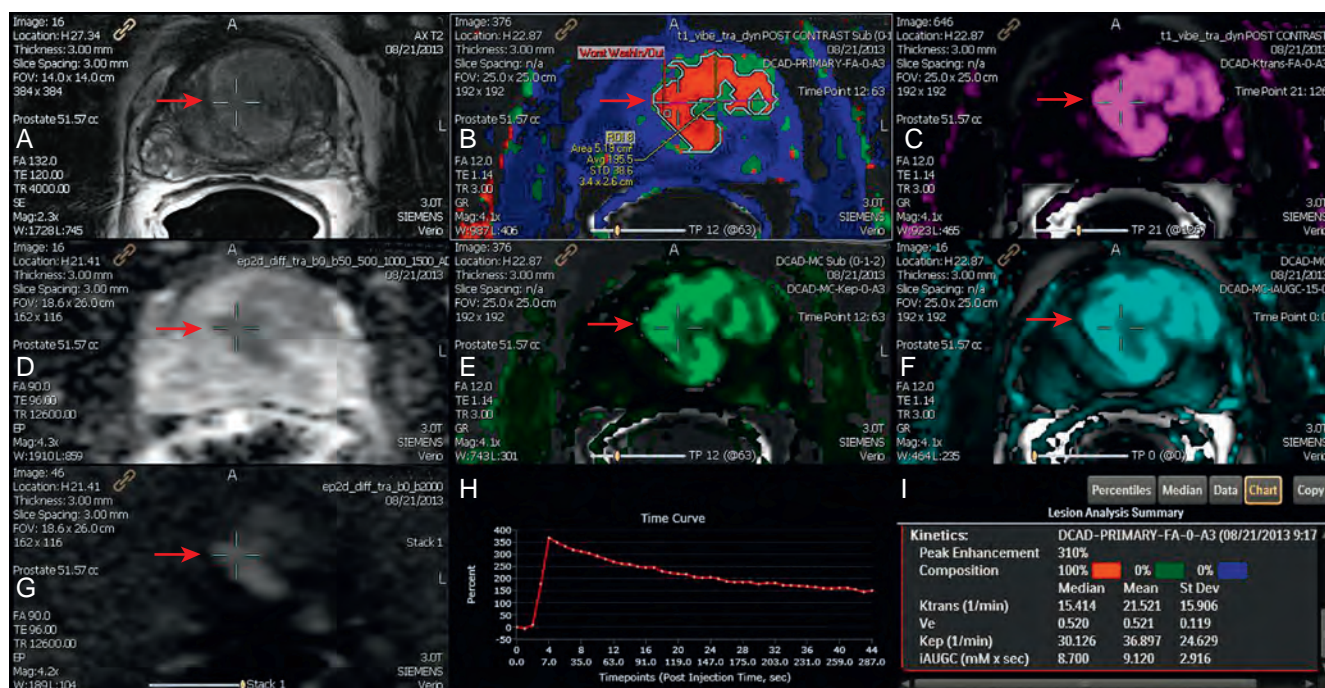


Figure 2-30. A 65-year-old man with a prostate-specific antigen of 38.9 and 16 prior negative biopsies with magnetic resonance (MR) ultrasound fusion biopsy proven Gleason 4 + 4 prostate cancer. **A**, T2-weighted image with an anterior lesion within the central gland, 3.5 cm × 2.7 cm × 3.5 cm (red arrow). **B** and **H**, Dynamic contrast enhanced MRI (DCE-MRI) with color mapping exhibiting a focal type 3 enhancement curve. **C**, Elevated K^{trans} (transfer constant). **D**, Apparent diffusion coefficient map with low signal. **E**, Elevated K^{ep} (rate constant). **F**, Area under the curve. **G**, B-2000 diffusion-weighted sequence with an area of high signal intensity. **I**, Quantitative summary of the large anterior central gland lesion.

anatomic images; it is used to assess the blood flow and vascular permeability throughout the gland over time.

DCE-MRI provides qualitative, semiquantitative, and quantitative information regarding enhancement within the prostate. A qualitative approach consists of visually assessing early enhancement and early washout within the prostate. The use of computer-aided diagnostic systems allows one to obtain specific information with regard to enhancement characteristics. A semiquantitative approach assesses enhancement over time (Tofts et al, 1991). There are three distinct curves associated with prostate imaging (Fig. 2-31). Because of the overlap of all three curve types with benign conditions, it is useful to combine these approaches in a MP-MRI. A quantitative assessment for cancer was first proposed by Tofts and colleagues (1991), observing the pharmacokinetics of the contrast within the gland. K^{trans} (transfer constant) represents the transfer rate (permeability) of contrast between the intravascular space and the extracellular space (or blood flow) to the tissues depending on the hemodynamics at the time of the study. K^{ep} (rate constant) is the rate of efflux of contrast back into the vascular space (Tofts et al, 1999). These quantitative metrics have not been incorporated in the daily work flow of most radiologists; however, they are currently being evaluated for possible decision analysis software (see Fig. 2-30C, D, E, H).

DCE-MRI has a reported 46% to 96% sensitivity and a 74% to 96% specificity for detecting prostate cancer. These large ranges can be the result of the high variability related to patient selection, MRI technique, pathology correlation, and reader experience (Tofts et al, 1991).

Magnetic Resonance Spectroscopy

Proton MR spectroscopic imaging (MRSI) is able to detect the concentration of citrate, choline, and creatine within the prostate. As

cells go through malignant transformation, citrate decreases and creatine and choline levels increase secondary to increased cellular turnover (Choi et al, 2007). An increase of two standard deviations of choline-to-citrate ratio is indicative of cancer (Kurhanewicz et al, 1996). This process is time consuming (15 minutes and has fallen out of favor when used in a nonresearch setting. Turkbey and colleagues (2011) reported only a 7% increase in PPV and NPV using MRSI. Therefore the additional time may not clinically impact cancer detection rates. There is still a significant research potential associated with MRSI. Some authors are using MRSI assessment of cellular metabolism (choline, creatine, and citrate) to evaluate recurrence after radiation therapy (Zhang et al, 2014).

Multiparametric Magnetic Resonance Imaging

The combination of T2, DCE, and DWI has yielded both NPV and PPV greater than 90% (Turkbey et al, 2011; Abd-Alazeez et al, 2014). It is important to understand that high-quality MRI requires tuning of the MR magnets, a dedicated staff to perform the studies, and pathology correlation for the radiologists. There are thousands of settings one can adjust to obtain high-quality images. It is important to start with the basics, which are outlined in European Society of Urogenital Urology (ESUR) 2012 guidelines (Barentsz et al, 2012). If an ERC is used during the study, an antispasmodic agent should be used to decrease the artifact created by rectal spasms. Also, to get the highest quality images, the MR technologist should actively review images during the study and make adjustments or repeat sequences as needed. The goal is to have a prostate MRI scanning time of 30 minutes or less to maintain economical feasibility. Using new magnets with higher field strength, external coils, and an ERC can decrease image acquisition time and may also improve image quality (Heijmink et al, 2007) (Fig. 2-32).

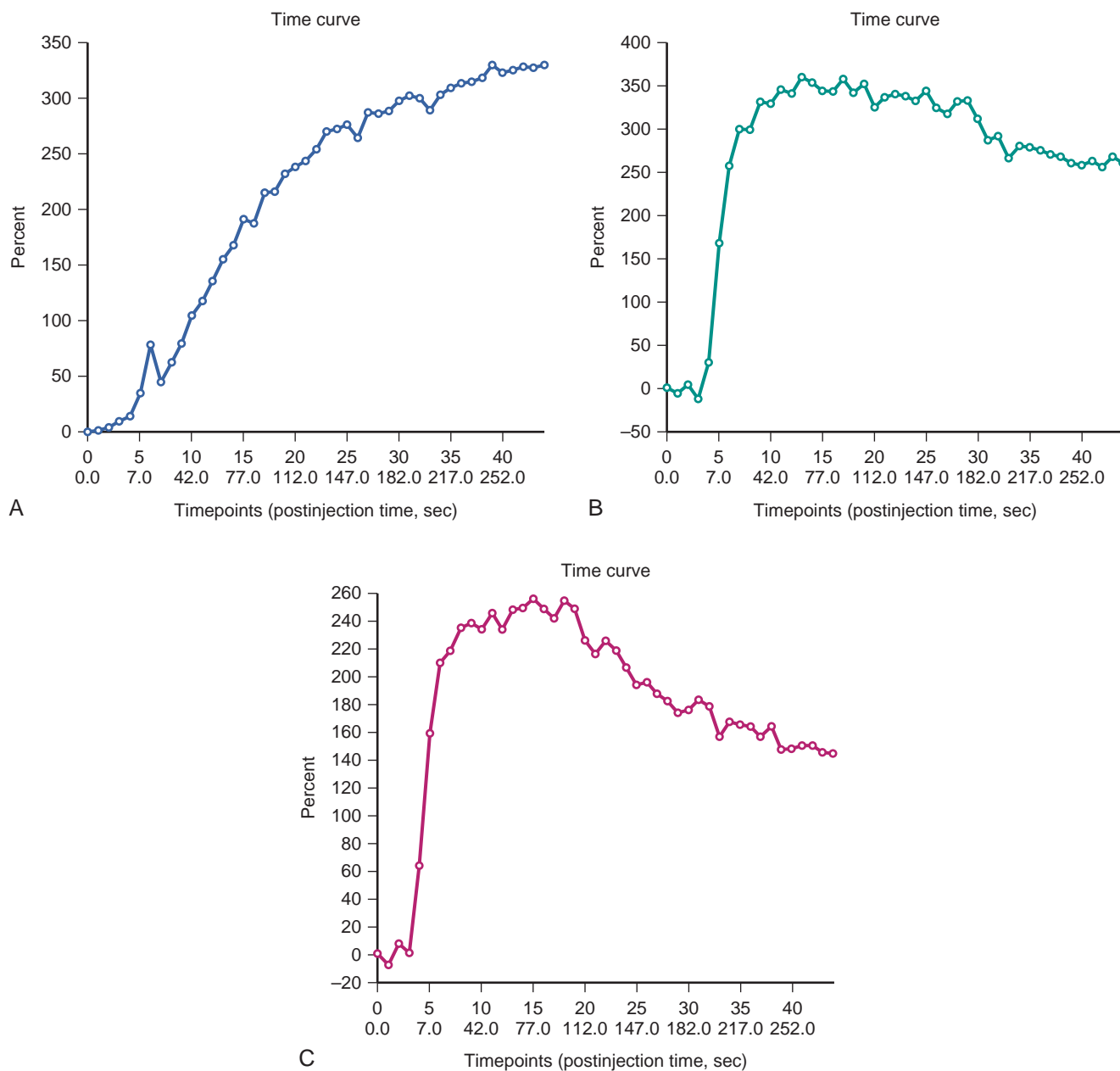


Figure 2-31. A, Type 1 curve is normal enhancement with persistent increase in enhancement over time. B, Type 2 curve is early enhancement with a plateau (no washout). C, Type 3 curve, which is the most indicative of prostate cancer, can overlap with inflammation; this is characterized by early enhancement with an early washout of contrast.

As more physicians begin to use MP-MRI of the prostate, maintaining quality and improving interpretation is extremely important. Each center should have designated readers. Prostate MRI is like no other study in radiology; it benefits from consensus reading and pathology correlation (Muller et al, 2014). Currently, there is no consensus on how a prostate MRI report should be completed. An international working group attempted to standardize reporting for MR targeted biopsies (Moore et al, 2013). The group used predefined prostate zones dividing the prostate into apex, mid, and base (Fig. 2-33A). Unfortunately, these zones do not always correlate well with end-fire images in the United States. However, if slices are used instead of the predefined zones, urologists can use the information regarding sequence, slice number, and primary zones to find the suspicious area within the prostate to aid in targeting during biopsy and possible surgical planning (Fig. 2-33B). In addition to location and 3D size, the radiologist's report should include a score for clinical

suspicion of disease. Multiple scoring systems exist; objective criteria for each sequence can be reported using the Prostate Imaging Reporting and Data System (PI-RADS) and the NIH scoring systems, as well as a subjective assessment using a five-point Likert scale for each lesion and the overall clinical suspicion for the patient (Barentsz et al, 2012; Moore et al, 2013; Turkbey et al, 2014) (Box 2-2).

In summary, MP-MRI of the prostate is a potential new tool that is able to detect, quantify, stage, and influence treatment planning for patients with prostate cancer. MP-MRI has also been shown to correctly select patients with low-grade/low-volume disease for active surveillance with an accuracy of 92% (Turkbey et al, 2014). MP-MRI of the prostate also provides information on possible bone involvement or lymphadenopathy at the time of diagnosis. The accuracy of MRI detecting lymphadenopathy has a sensitivity up to 86% and specificity of 78% to 90% (Talab et al, 2012).

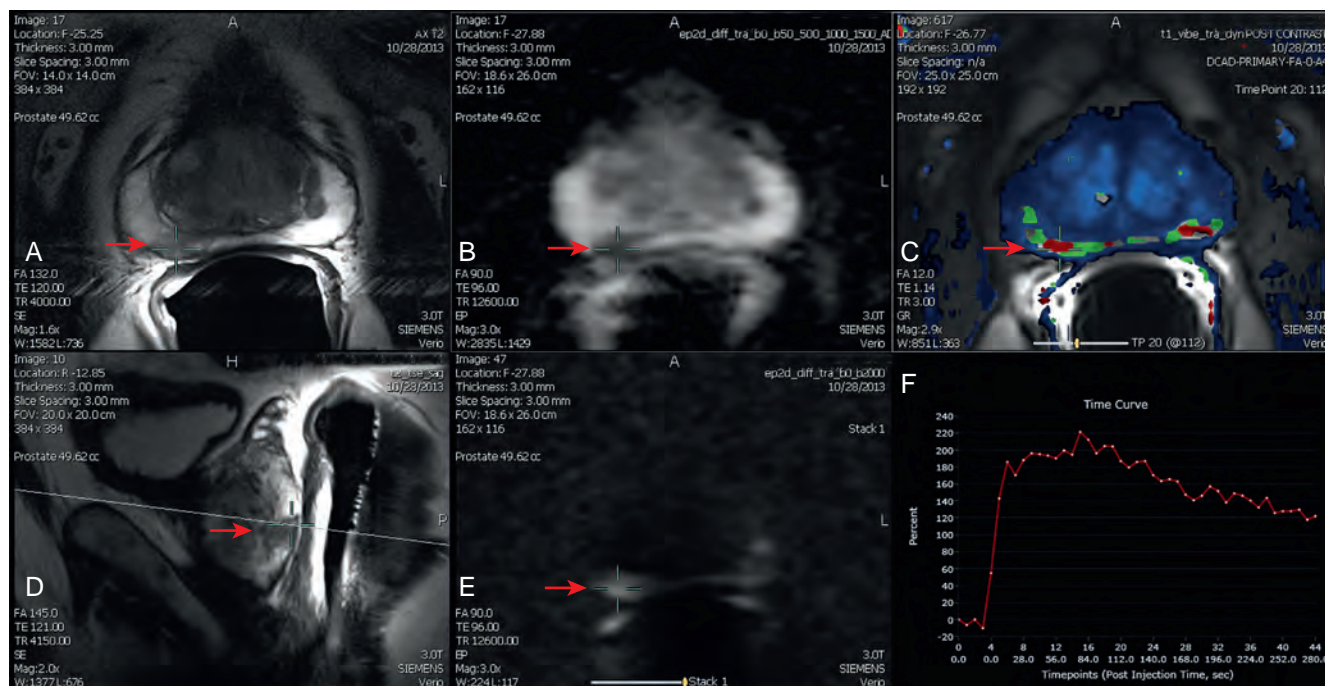


Figure 2-32. A 61-year-old Caucasian man with an increasing prostate-specific antigen (4.65 ng/mL) after a prior negative biopsy 1 year ago. Three-tesla multiparametric magnetic resonance imaging (MP-MRI) of the prostate with an endorectal coil was obtained. **A**, T2-weighted image with a homogeneous low signal intensity (SI) lesion within the right posterior peripheral zone (red arrow). **B**, Apparent diffusion coefficient (ADC) map with a corresponding low SI to the T2 sequence. **C**, Dynamic contrast enhanced MRI (DCE-MRI) with color mapping exhibiting a focal type 3 enhancement curve. **D**, Sagittal T2 sequence with a low-signal lesion within the peripheral zone. **E**, B-2000 diffusion-weighted imaging with high signal corresponding to T2, ADC, DCE abnormalities. **F**, Type 3 enhancement curve. The pathology was Gleason 3+4 prostate cancer, zone 3L, volume 0.3 mL (9 mm × 8 mm × 9 mm).

Magnetic Resonance Ultrasound Fusion-Guided Prostate Biopsy

MR ultrasound fusion-guided prostate biopsy is the next step in the integration of high-quality intraprostatic imaging for screening and diagnosing prostate cancer. There are multiple fusion biopsy systems on the market. The performance of these systems differs slightly from one vendor to the other. However, the most important factor is the quality of the MP-MRI and abilities of the imaging team. These two factors have been shown to result in increased cancer detection rates in patients undergoing targeted biopsies (Pinto et al, 2011; Sonn et al, 2013).

Currently, a targeted biopsy or MP-MRI alone is not an alternative to the standard of care in screening men for prostate cancer. MP-MRI offers a distinct advantage when selecting men to undergo a biopsy with an elevated PSA. PSA is not prostate cancer specific and can be elevated for numerous reasons, including inflammation/infection, BPH, and physical manipulation. The MRI is able to assess BPH and inflammation before biopsy, and this may allow men who have persistently elevated PSA and an initial negative 12-core biopsy to avoid undergoing a second biopsy. Additionally, MP-MRI of the prostate can detect intermediate- and high-risk disease, but it has difficulty detecting low-grade/low-volume cancers, which may decrease overdiagnosis and overtreatment of clinically insignificant disease. Moore and colleagues (2013) reported that 38% of men with an elevated PSA did not have any visible lesions on MP-MRI. In this study, a 12-core biopsy detected only clinically significant cancer for 2.3% of the patients (Gleason score ≥ 7 or a core length of >5 mm).

The MR ultrasound fusion-guided biopsy has the advantage of using the MRI to target specific areas (i.e., anterior or central gland lesions) within the prostate that may be missed on a standard systematic 12-core biopsy. In addition, the 12-core biopsy may miss many lesions within the peripheral zone.

The cancer detection rates for targeted biopsies are superior to using the information from the MRI and then attempting to cognitively find the same area on ultrasonography to perform the biopsy (Wysock et al, 2014). The cancer detection rates for these types of targeted biopsies in patients with moderate to high suspicion on MRI are approximately 50% to 72% (Pinto et al, 2011; Sonn et al, 2013; Rastinehad et al, 2014).

All these new technologies do come at a cost. However, if one is able to select specific areas of the prostate to be targeted, instead of performing a 12-core biopsy, the savings from the decrease in number of pathology specimens collected could offset the cost of the MRI (Rastinehad et al, 2014). There is mounting evidence that a negative MP-MRI may effectively rule out a patient having clinically significant disease. The group from the University College London reported that a MP-MRI has an 89% to 100% NPV for ruling out clinically significant prostate cancer in patients with a negative MP-MR (Abd-Alazeez et al, 2014). This may result in patients foregoing a prostate biopsy and avoiding associated side effects.

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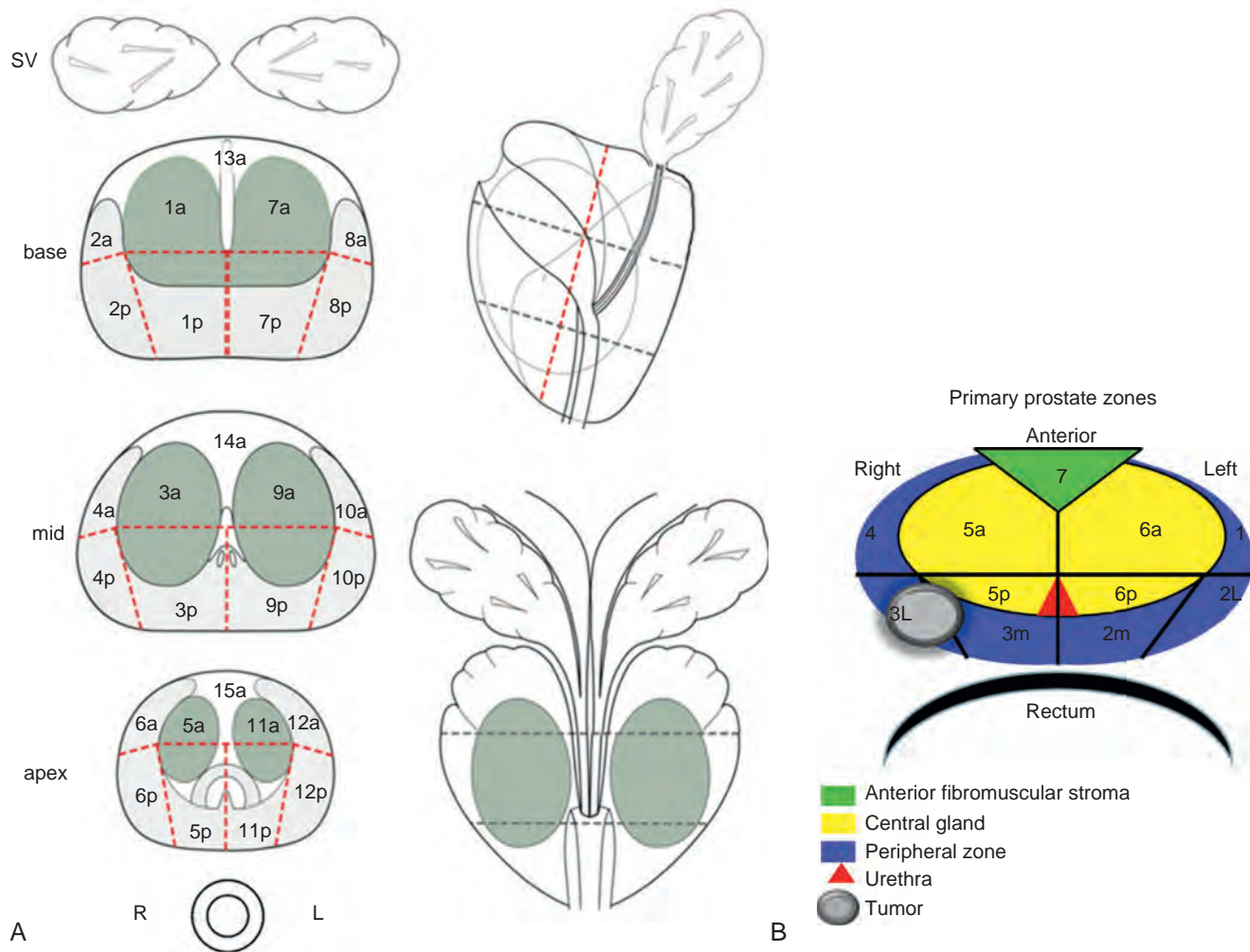


Figure 2-33. A, Standards of reporting for MRI-targeted biopsy studies (START) reporting zones. SV, seminal vesicle. B, Primary prostate zones for reporting. The lesion is marked in the T2-weighted sequence because this is typically the sequence used for fusion-guided biopsies. This would be a Zone 3L (lateral) lesion on slice 17 (see Fig. 2-32). The slice levels for base and apex of the prostate are also reported. This allows one to convert the information to the START criteria zones for publication; however, this approach allows the urologist to locate the lesion on the multiparametric magnetic resonance image with ease (sequence, slice number, and zone number).

BOX 2-2 Five-Point Likert Scale for Prostate Imaging

1. Clinically significant disease is highly unlikely to be present.
2. Clinically significant disease is unlikely to be present.
3. Clinically significant disease is equivocal.
4. Clinically significant disease is likely to be present.
5. Clinically significant disease is highly likely to be present.

From Moore CM, Kasivisvanathan V, Eggener S, et al; START Consortium. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. *Eur Urol* 2013;64:544–52.

KEY POINTS: MRI

- When a renal mass is seen on MRI, the most important characteristic indicating the presence of a malignancy is enhancement of the mass.
- NSF is seen in patients with severe renal insufficiency who are exposed to Gd contrast media.
- Pheochromocytoma, metastatic lesion to the adrenal gland, and primary ACC are all bright on T2-weighted images.

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The complete reference list is available online at www.expertconsult.com.

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3

Urinary Tract Imaging: Basic Principles of Urologic Ultrasonography

Bruce R. Gilbert, MD, PhD, and Pat F. Fulgham, MD

Brief History of Ultrasonography in Urology

Physical Principles

Modes of Ultrasonography

Contrast Agents in Ultrasonography

Documentation and Image Storage

Patient Safety

Clinical Urologic Ultrasonography

Practice Accreditation

Ultrasonography has often been referred to as the “urologist’s stethoscope” because much of the genitourinary system is not easily evaluated by physical examination and requires imaging for diagnosis. Therein lies one of the unique aspects of ultrasound studies performed and interpreted by urologists. The mandate to examine the patient coupled with the urologist’s experience in both surgical and medical treatment engenders an unparalleled ability to meld the healer’s art with advanced imaging technology. In addition, ultrasonography is a versatile and relatively inexpensive imaging modality that has the unique feature of being the only imaging modality to provide real-time evaluation of urologic organs and structures without the need for ionizing radiation. To use this technology best on behalf of their patients, urologists must have a mature understanding of the underlying physical principles of ultrasonography. They must also understand how the manipulation of ultrasound equipment can affect the quality of ultrasound images. The technical skills required to perform and interpret urologic ultrasonography represent a combination of practical scanning ability and knowledge of the underlying disease process in organs being imaged. To communicate the findings appropriately, urologists should understand the nomenclature of ultrasonography and have a specific plan for documentation of each type of study. Understanding how ultrasonography interacts with human tissues allows urologists to use this modality effectively, appropriately, and safely. The aim of this chapter is to encourage urologists to embrace the art and science of ultrasonography in their mission to provide excellence in patient care.

BRIEF HISTORY OF ULTRASONOGRAPHY IN UROLOGY

In 1963, Japanese urologists Takahashi and Ouchi became the first to attempt ultrasonic examination of the prostate. However, the image quality that resulted was not interpretable and carried little medical utility (Takahashi and Ouchi, 1963). Wild and Reid (1952) also attempted transrectal ultrasonography (TRUS) but were met with the same result. Progress was not made until Watanabe and colleagues (1974) demonstrated radial scanning that could adequately identify prostate and bladder pathology. Using a purpose-built device modeled after a museum sculpture entitled “Magician’s Chair,” Watanabe seated his patients on a chair with a hole cut in the center such that the transducer tube could be passed through the hole and into the rectum of the seated patient (Watanabe et al, 1974). Images from Watanabe’s seated probe are shown in Figure 3-1. As is evident in Figures 3-1B (demonstrating an area of circumscribed symmetric echogenicity, representing benign prostatic

hyperplasia), and 3-1C (demonstrating an asymmetric area of hyperechogenicity, representing prostate cancer), resolution was poor, and images displayed extreme contrast. Subsequent development of biplanar, high-frequency probes created increased resolution and allowed for TRUS to become the standard for diagnosis of prostatic disease.

In 1971 Goldberg and Pollack, frustrated with the inability of intravenous pyelography to differentiate benign from malignant lesions, employed A-mode ultrasonography to evaluate the kidney. In their report on “nephrosoundography,” they demonstrated in a series of 150 patients the capability of ultrasonography to discern solid, cystic, and complex masses with an accuracy of 96%. Diagrammatic representations of the three ultrasound patterns they found are depicted in Figure 3-2 (Goldberg and Pollack, 2002). In cystic lesions, the first spike represents the striking of the front wall of the cyst and the second spike represents the striking of the back wall. More complex lesions have return of more spikes.

In 1974 Holm and Northeved introduced a transurethral ultrasonic device that would be interchangeable with conventional optics during cystoscopy for the purpose of imaging the prostate and bladder. Their other goals for this device included the ability to determine depth of bladder tumor penetration, to determine prostatic volume, to evaluate prostatic tumor progression, and to assist with transurethral resection of the prostate (Holm and Northeved, 1974).

Perri and colleagues were the first to use Doppler as a sonic “stethoscope” in their work-up of patients with an acute scrotum in 1976. Although they were able to identify patients with epididymitis and torsion of the appendix testis as having increased flow and patients with spermatic cord torsion as having no blood flow, they also reported that false-negative images in cases of torsion could result from increased flow secondary to reactive hyperemia (Perri et al, 1976).

Watanabe and colleagues (1976), pioneers in the use of ultrasonography in urology, demonstrated that Doppler could be used to identify the renal arteries in a noninvasive way in 1976, and Greene and colleagues (1981) documented 5 years later that Doppler could adequately differentiate stenotic from normal renal arteries. In 1982 Arima and associates used Doppler to differentiate acute from chronic rejection in patients with renal transplants, noting that acute rejection is characterized by the disappearance of diastolic phase, with reappearance being indicative of recovery from rejection. These authors concluded that Doppler could guide the management of rejection as an index for steroid therapy (Arima et al, 1982).



Figure 3-1. A, Watanabe's chair. B, Display of patient with benign prostatic hyperplasia. C, Display of prostate cancer. (From Watanabe H, Igari D, Tanahasi Y, et al. Development and application of new equipment for transrectal ultrasonography. *J Clin Ultrasound* 1974;2:91–8.)

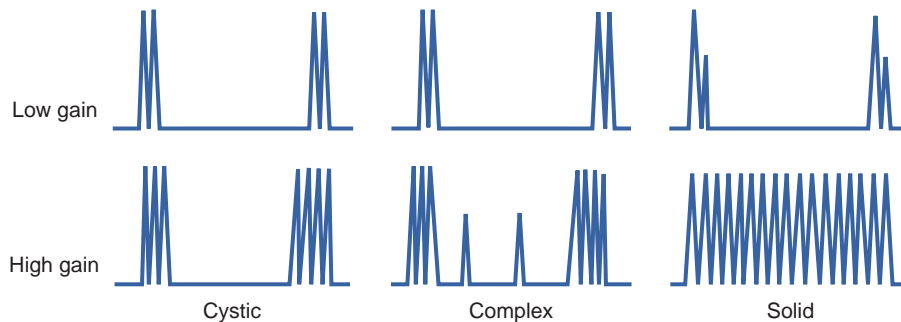
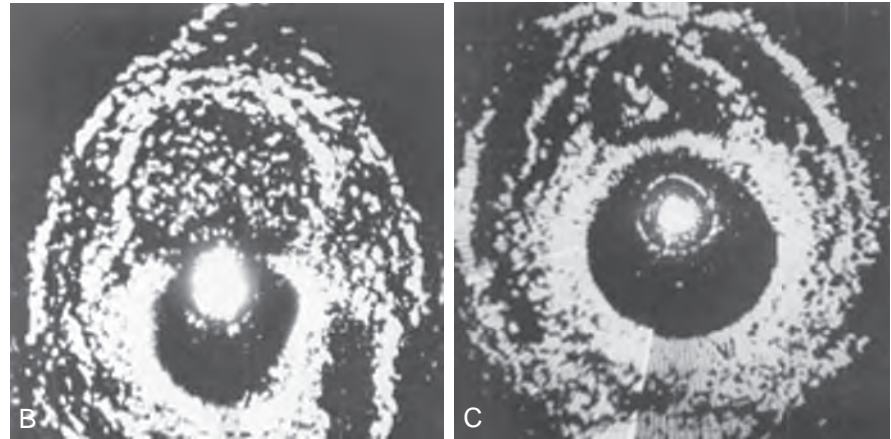


Figure 3-2. Goldberg and Pollack were the first to differentiate between solid, complex, and cystic masses by ultrasonography. In cystic lesions, the first spike represents the striking of the front wall of the cyst, and the second spike represents the striking of the back wall. More complex lesions have return of more spikes. (From Goldberg B, Pollack H. Differentiation of renal masses using A-mode ultrasound. *J Urol* 2002;167:1022–6.)

In the early 1990s numerous authors investigated the therapeutic uses of high-intensity focused ultrasonography (HIFU). Following prior reports of histologic changes after HIFU (Burgess et al, 1987), Madersbacher and colleagues (1993) were the first to report the safety and efficacy of HIFU in patients with symptomatic benign prostatic hyperplasia. The utility of HIFU in the treatment of testicular cancer (Madersbacher et al, 1998), early prostate cancer (Chapelon et al, 1999), recurrent prostate cancer (Berge et al, 2010), and renal cell cancer transcutaneously (Köhrmann et al, 2002) and laparoscopically (Margreiter and Marberger, 2010) was soon explored as well.

The field of urology continues to demand and discover novel uses for ultrasound technology. Chen and coworkers (2010) used TRUS guidance to inject botulinum toxin into the external urethral sphincters of a series of patients with detrusor external sphincter dyssynergia. Ozawa and colleagues (2010) used perineal ultrasound video-urodynamics to diagnose bladder outlet obstruction accurately in a noninvasive manner. The possibilities for application of ultrasonography in diagnosing or treating urologic conditions are endless.

Urologic ultrasonography continues to evolve with the use of contrast agents and new modalities such as sonoelastography that include groundbreaking discoveries and new applications of basic

physical principles. This homage to the innovators of the past serves both to recognize prior achievements and to acknowledge that future work in the development of new applications for ultrasonography will always be needed.

PHYSICAL PRINCIPLES

All ultrasound imaging is the result of the interaction of sound waves with tissues and structures within the human body. Ultrasound waves are produced by applying short bursts of alternating electrical current to a series of crystals housed in the transducer. Alternating expansion and contraction of the crystals via the piezoelectric effect creates a mechanical wave that is transmitted through a coupling medium to the skin and then into the body. The waves that are produced are longitudinal waves. In a longitudinal wave, the particle motion is in the same direction as the propagation of the wave (Fig. 3-3). This motion produces areas of rarefaction and compression of tissue in the direction of travel of the ultrasound wave (Fig. 3-4). A portion of the wave is reflected toward the transducer. The transducer serves as a receiver and “listens” for the returning sound wave reconverts the mechanical wave to electrical energy. The transducer must be in direct,

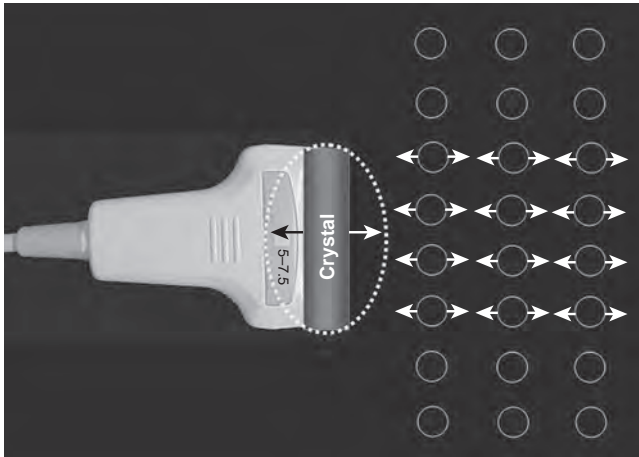


Figure 3-3. The alternating expansion and contraction of the crystal produces longitudinal mechanical waves. In this simplified schematic drawing, the individual molecules (depicted as circles) are displaced in the direction of the propagated wave.

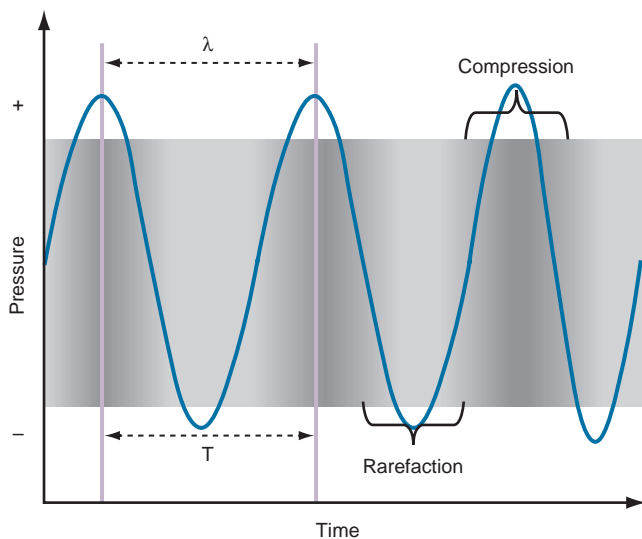


Figure 3-4. Areas of compression alternating with areas of rarefaction are depicted as a sine wave. The wavelength (λ) is the length from peak compression to peak compression in this drawing. This graphic depiction is critical to understanding the behavior of sound waves in the human body and how ultrasound images are generated. (From Merritt CRB. *Physics of ultrasound*. In: Rumack CM, Wilson SR, Charboneau JW, Johnson J, editors. *Diagnostic ultrasound*. 3rd ed. St. Louis: Mosby; 2005. p. 3–34.)

secure contact with the subject to transmit and receive the reflected sound waves.

The appearance of the image produced by ultrasonography is the result of the interaction of mechanical ultrasound waves with biologic tissues and materials. Because ultrasound waves are transmitted and received at frequent intervals, the images can be rapidly reconstructed and refreshed, providing a real-time image. The frequencies of the sound waves used for urologic ultrasound imaging are in the range of 3.5 to 12 MHz.

Mechanical waves are represented graphically as a sine wave alternating between a positive and negative direction from the baseline. In the case of ultrasonography, the amplitude of the sine wave describes differences in pressure. Ultrasound waves are described using the standard nomenclature for sine waves. A wavelength (λ) is described as the distance between one peak of the wave and the

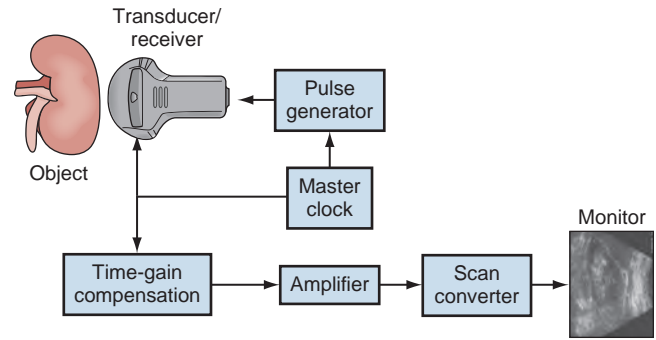


Figure 3-5. In this simplified schematic diagram of ultrasound imaging, the ultrasound wave is produced by means of a pulse generator controlled by a master clock. The reflected waves received by the transducer are analyzed for amplitude and transit time within the body. The scan converter produces the familiar picture seen on the monitor. The actual image is a series of vertical lines that are continuously refreshed to produce the familiar real-time, gray-scale image.

next peak. The complete path traveled by the wave from one peak to the next is called a *cycle*. One cycle per second is known as 1 hertz (Hz). The “period” is the time it takes for one complete cycle of the wave.

The “amplitude” of a wave is the maximal excursion in the positive or negative direction from the baseline. Amplitude corresponds to the mechanical energy associated with the sound wave and is a key property in assigning pixel brightness to a gray-scale ultrasound image. The greater the amplitude, the brighter is the corresponding pixel.

Ultrasound Image Generation

The image produced by an ultrasound machine begins with the transducer. In ultrasound imaging, the transducer has a dual function as a sender and a receiver. Sound waves are created in short pulses and transmitted into the body and are then at least partially reflected. Reflected mechanical sound waves are received by the transducer and converted back into electrical energy. The transducer acts as a receiver more than 99% of the time. The electrical energy is converted by the ultrasound machine to an image displayed on a monitor (Fig. 3-5).

Resolution

The resolution of an ultrasound image refers to the ability to discriminate two objects in close proximity to one another. **Axial resolution** refers to the ability to identify as separate two objects in the direction of the traveling sound wave. Axial resolution is directly dependent on the frequency of sound waves. The higher the frequency of the sound wave, the better the axial resolution. **Lateral resolution** refers to the ability to identify separately objects that are equidistant from the transducer. Lateral resolution is a function of the focused width of the ultrasound beam and is a characteristic of the transducer. The location of the narrowest beam width can be adjusted by the user. The more focused the beam, the better the lateral resolution at that location. Image quality can be enhanced by locating the narrowest beam width (focus or focal zone) at the depth of the object or tissue of interest (Fig. 3-6).

The velocity with which a sound wave travels through tissue is a product of its frequency and wavelength (Fig. 3-7). The **average velocity of sound in human tissues is 1540 m/sec**. Because the average velocity of sound in tissue is a constant, changes in frequency result in changes in wavelength.

The optimal ultrasound image requires tradeoffs between resolution and depth of penetration. High-frequency transducers of 6 to 10 MHz may be used to image structures near the surface of the

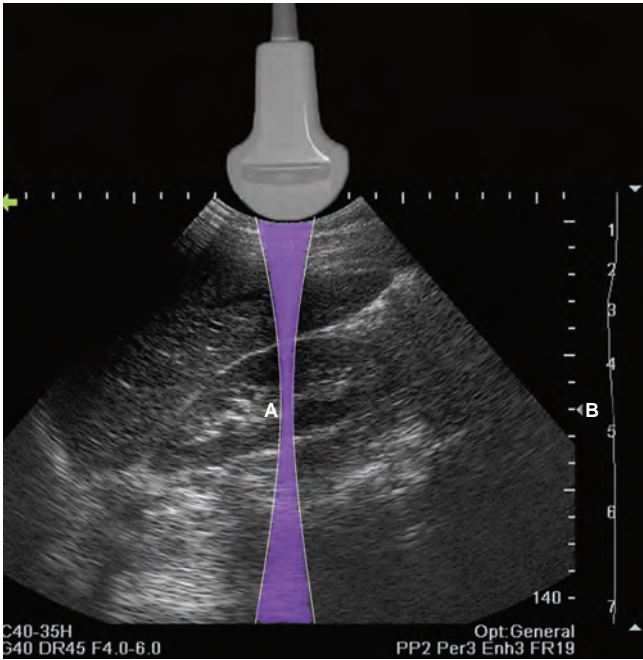


Figure 3-6. The shape of the ultrasound beam is simulated in this drawing (purple). The focal zone (A) is located to produce the best lateral resolution of the medial renal cortex. The location of the focal zone is designated by the caret (B). The location of the focal zone can be adjusted by the operator.

$$v = f \times \lambda$$

velocity = frequency × wavelength

Figure 3-7. The relationship between velocity, frequency, and wavelength of sound waves in tissue. Wavelength and frequency vary in an inverse relationship.

body (e.g., testis, pediatric kidney) with excellent resolution. However, deeper structures (e.g., right kidney, bladder) require lower frequencies of 3.5 to 5 MHz to penetrate. Such images have poorer axial resolution.

Mechanisms of Attenuation

As sound waves transit tissues, energy is lost or attenuated. Mechanisms of attenuation include **reflection, scattering, interference, and absorption**. Reflection is the key physical phenomenon that allows for information to return to the transducer as mechanical energy. Reflection occurs when ultrasound waves strike an object, a surface, or a boundary (called an **interface**) between unlike tissues. The shape and size of the object and the angle at which the advancing wave strikes the object are critical determinants of the amount of energy reflected. The amount of energy reflected from an interface is also influenced by the **impedance** of the two tissues at the interface. Impedance is a property that is influenced by tissue stiffness and density. The difference in impedance allows an appreciation of interfaces between different types of tissue (Table 3-1).

The impedance difference between perinephric fat and the kidney allows a sharp visual distinction at the interface. If the impedance difference between tissues is small (e.g., between liver and kidney), the interface between the tissues is more difficult to see (Fig. 3-8A). If impedance differences are large, there is

TABLE 3-1 Density and Impedance of Tissues Encountered During Urologic Ultrasonography

	DENSITY	IMPEDANCE
Air and other gases	1.2	0.0004
Fat tissue	952	1.38
Water and other clear liquids	1000	1.48
Kidney (average of soft tissue)	1060	1.63
Liver	1060	1.64
Muscle	1080	1.70
Bone and other calcified objects	1912	7.8

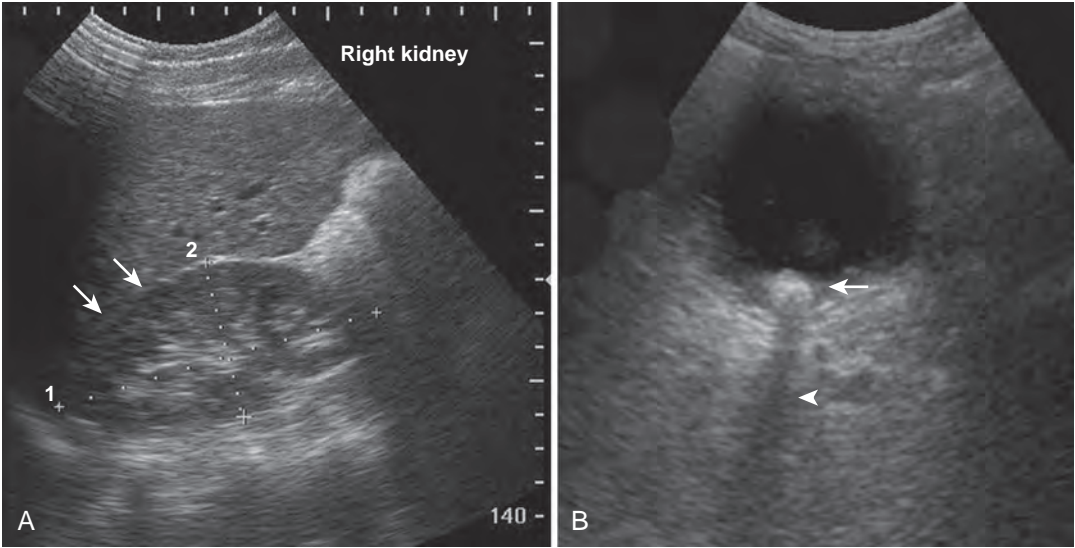


Figure 3-8. A, In this sagittal view of the right kidney, the paucity of perinephric fat and the small impedance difference make it difficult to distinguish the interface between the kidney and the liver (arrows). B, The large impedance difference at the interface between urine and a bladder stone (arrow) results in significant reflection and attenuation of the sound wave. An acoustic shadow is seen distal to the stone (arrowhead).

significant reflection of the sound wave producing an acoustical shadow distal to the interface (Fig. 3-8B).

Scattering occurs when sound waves strike a small or irregular object. The resulting spherical wave overlaps waves of surrounding scattering objects (Fig. 3-9).

When interacting sound waves are in phase or out of phase, their amplitude is enhanced or diminished. This **pattern of interference** is partially responsible for the echo architecture or texture of organs. One pattern of interference, commonly called “**speckling**” (Fig. 3-10), is seen in organs with fine, internal histology (i.e., reflectors such as the testis).

Absorption occurs when the mechanical energy of the ultrasound waves is converted to heat. Absorption is directly proportional to frequency. The higher the frequency of the incident wave,

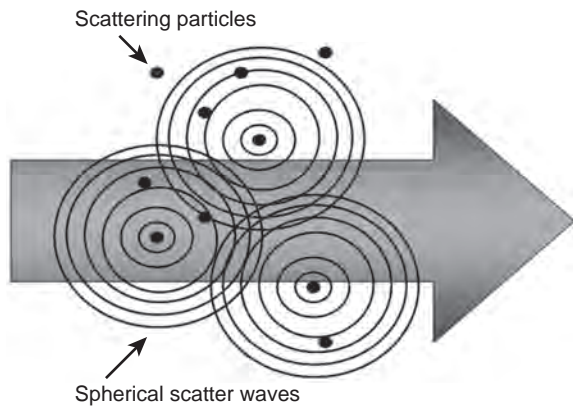


Figure 3-9. Scattering is a phenomenon that occurs when sound waves strike small objects. The resulting pattern of energy dispersal often results in interference.

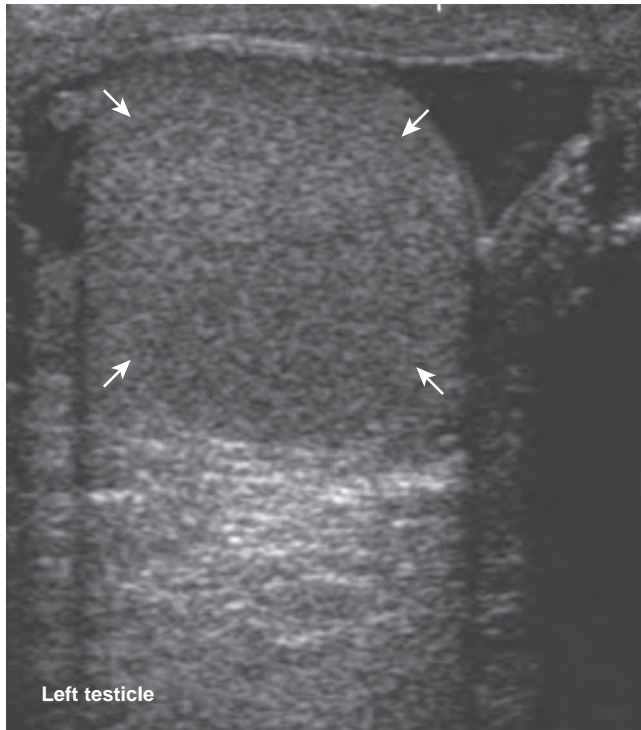


Figure 3-10. Fine internal echogenicity called “speckle” is caused by scattering of sound waves, resulting in a pattern of interference. Note the resulting finely granular, homogeneous echogenicity (arrows) of the testicular parenchyma.

the greater the absorption of energy, and more tissue heating results. It follows that higher frequency waves are more rapidly attenuated and have a limited depth of penetration (Fig. 3-11).

Artifacts

The interaction of ultrasound waves with tissues may produce images that do not reflect the true underlying anatomy. These misrepresentations are called “**artifacts**.” Artifacts may be misleading but, if recognized, may also assist diagnosis. **Acoustical shadowing** occurs when there is significant attenuation or reflection of sound waves at a tissue interface. Echo information posterior to the interface may be obscured or lost. An anechoic or hypoechoic “shadow” is produced. Under these conditions, three-dimensional (3D) objects such as stones may appear as crescentic objects, making it difficult to obtain accurate measurements (Fig. 3-12). Important pathology posterior to such an interface may be missed. This problem may often be overcome or mitigated by changing the angle of insonation, changing the frequency of the transducer, or changing the focal zone of the transducer.

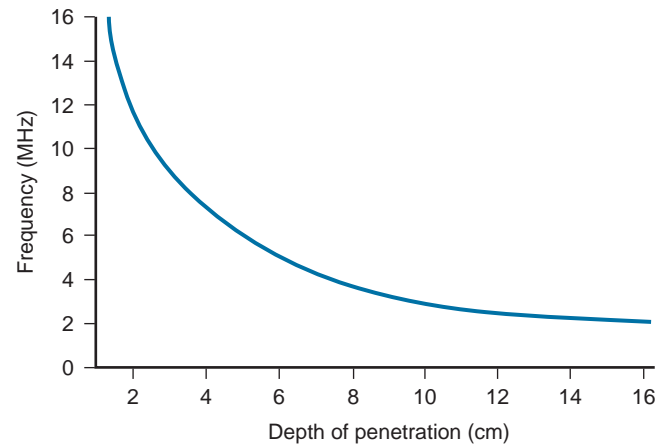


Figure 3-11. Relationship between frequency and tissue penetration. High-frequency sound waves are rapidly attenuated and are unable to penetrate deeply. Conversely, low-frequency waves are less attenuated and able to penetrate deeply to internal structures.

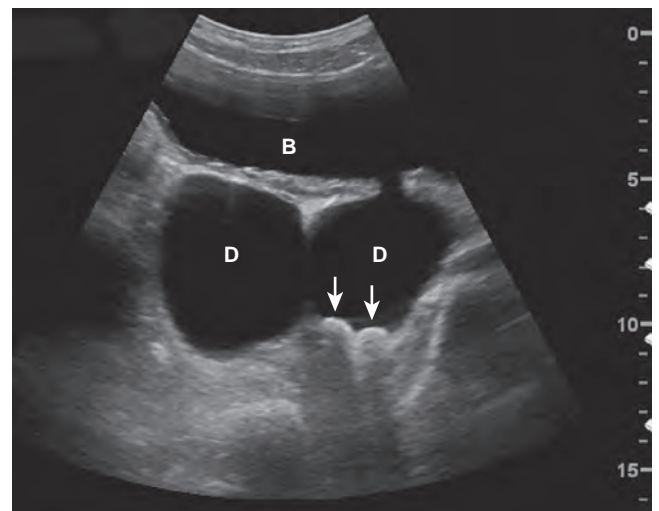


Figure 3-12. In this transverse view of the urinary bladder (B), there are two large bladder diverticula (D). Two stones (arrows) strongly reflect and attenuate the incident sound wave, producing an acoustical shadow. The stones appear crescentic even though they are ovoid in shape.

Increased through-transmission is observed when sound waves are less attenuated while passing through a given structure or tissue than by the surrounding tissues. For example, when imaging a simple cyst of the kidney, sound waves passing through the cyst are less attenuated than sound waves passing through the surrounding renal cortex and renal sinus. When the waves transiting the cyst strike the back wall of the cyst and posterior renal tissue, the waves are more energetic on arrival to these tissues. The reflected sound waves are also more energetic and less attenuated as they return to the transducer. The result is that tissue posterior to the cyst appears hyperechoic compared with the surrounding renal tissue, even though the tissues are histologically identical (Fig. 3-13). The effect of this artifact can be mitigated by changing the angle of insonation or adjusting the time-gain compensation settings.

An **edging artifact** occurs when sound waves strike a curved surface or interface at an incident angle, resulting in refraction of the wave along the plane of the interface (Fig. 3-14). An incident wave at this angle (the critical angle) is not directly reflected to the

transducer, resulting in a hypoechoic “shadow.” This artifact is commonly seen in testicular ultrasonography and TRUS (Fig. 3-15). It can be overcome by changing the angle of insonation.

A **reverberation artifact** results when there are large differences in impedance between two adjacent tissues or surfaces with a strong reflection of the incident wave. The ultrasound wave bounces back and forth (reverberates) between the reflective interfaces. With the second transit of the sound wave, the ultrasound equipment interprets a second object that is twice as far away as the first. There is ongoing attenuation of the sound wave with each successive reverberation, resulting in a slightly less intense image displayed on the screen. Echoes are produced, spaced at equal intervals from the transducer but progressively less intense (Fig. 3-16).

The reverberation artifact can also be seen in cases where the incident sound wave strikes a series of smaller reflective objects (e.g., the gas-fluid mixture in the small bowel), which results in multiple reflected sound waves of various angles and intensity (Fig. 3-17). The resultant echo pattern is a collection of hyperechoic artifactual reflections distal to the structure with progressive attenuation of the sound wave.

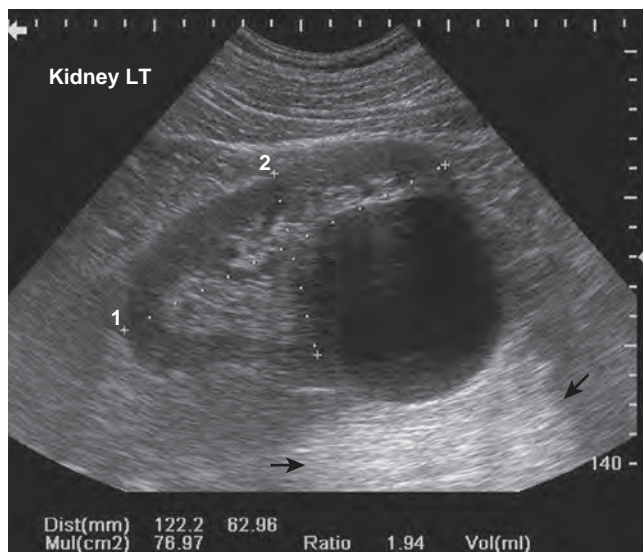


Figure 3-13. Increased through-transmission (also called “distal enhancement”) is demonstrated in this longitudinal view of the left kidney. The tissue distal to the cyst appears hyperechoic (arrows) compared with adjacent tissue.

MODES OF ULTRASONOGRAPHY

Gray-Scale Ultrasonography

Gray-scale B-mode ultrasonography is the most commonly employed mode of ultrasonography. This pulsed-wave technique produces real-time two-dimensional images consisting of shades of gray. The generation of this image involves assigning a pixel brightness to the amplitude of the returning sound waves received by the transducer. The position of the pixel is determined by the duration of the round trip of the sound wave. Individual lines of data are displayed sequentially on the monitor to produce a continuous or real-time image. Evaluation of gray-scale imaging requires the ability to recognize normal patterns of echogenicity from anatomic

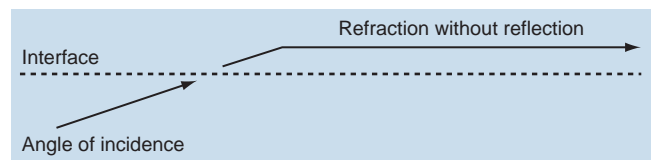


Figure 3-14. When sound waves strike a surface or interface at a “critical angle,” the wave is refracted without significant reflection.

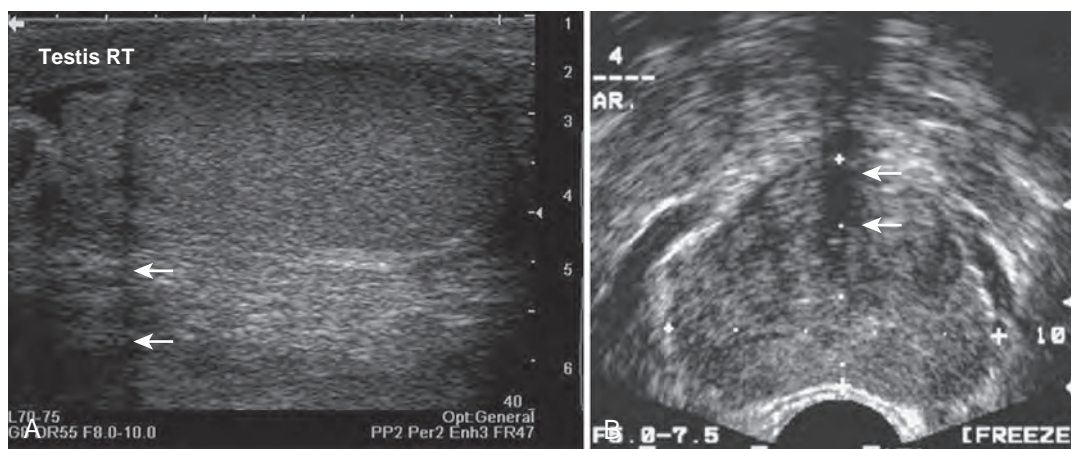


Figure 3-15. A, The curved surface of the tunica albuginea of the upper pole of the testis creates a critical angle edging artifact (arrows). B, The rounded surfaces of the lateral lobes of the prostate as they meet in the prostatic urethra create an edging artifact (arrows) in this transverse image of the prostate.

structures. Variations from these expected patterns of echogenicity indicate disorders of anatomy or physiology.

Doppler Ultrasonography

Doppler ultrasonography depends on the physical principle of frequency shift when sound waves strike a moving object. The basic principle of Doppler ultrasonography is that sound waves of a certain frequency are shifted or changed on the basis of the direction and velocity of the moving object as well as the angle of insonation. This phenomenon allows for the characterization of motion, most commonly the motion of blood through vessels, but it may also be useful for detecting the flow of urine.

Color Doppler ultrasonography allows for evaluation of the velocity and direction of motion. A color map may be applied to direction with the most common assignment of the color blue to

motion away from the transducer and red to motion toward the transducer. The velocity of motion is designated by the intensity of the color: The brighter the color, the greater the velocity. Color Doppler may be used to evaluate the presence or absence of blood flow in the kidney, testes, penis, and prostate. It also may be useful in the detection of ureteral “jets” of urine emerging from the ureteral orifices.

Color flow with spectral display allows the interrogation of particular areas within an ultrasound field for flow and displays the flow as a continuous waveform. This mode is commonly used to evaluate the pattern and velocity of blood flow in the intrarenal or penile vasculature. The waveform provides information about peripheral vascular resistance in the tissues. The most commonly used index of these velocities is the resistive index. The **resistive index** is peak systolic velocity (PSV) minus the end-diastolic velocity over the PSV. This index is helpful in characterizing many clinical conditions including renal artery stenosis, ureteral obstruction, and penile arterial insufficiency.

Power Doppler ultrasonography assigns the amplitude of frequency change to a color map. This mode does not permit evaluation of velocity or direction of flow but is less affected by backscatter waves and is a more sensitive mode for detecting blood flow. Power Doppler is less angle dependent than color Doppler and is three to five times as sensitive as color Doppler ultrasonography for detecting flow. It may be useful for evaluating testicular torsion.

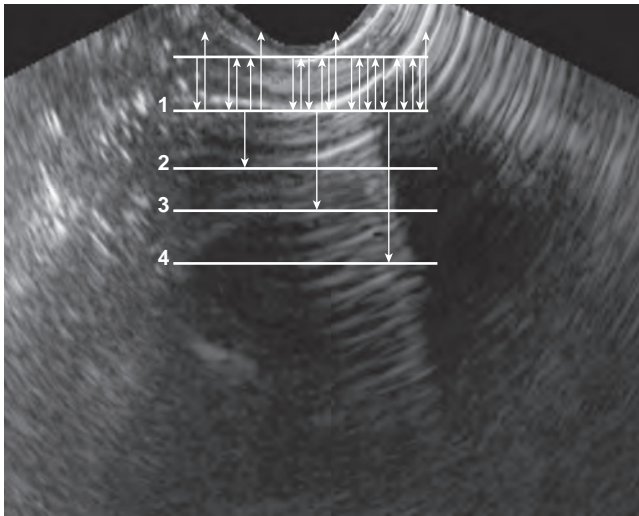


Figure 3-16. Reverberation artifact. A virtual representation of the strongly reflective interface is projected with decreasing amplitude as the incident sound wave makes multiple round trips.

Harmonic Scanning

Harmonic scanning uses aberrations related to the nonlinear propagation of sound waves within tissue. These asymmetrically propagated waves generate fewer harmonics, but those that are generated have greater amplitudes. Because these harmonics are not subject to scattering at the frequency associated with the incident wave, there is less noise associated with the signal. By concentrating on the harmonic frequencies produced within the body and reflected to the transducer, it is possible to produce an image with less artifact and greater resolution (Fig. 3-18).

Spatial Compounding

Spatial compounding is a scanning mode whereby the direction of insonation is electronically altered, and a composite image is

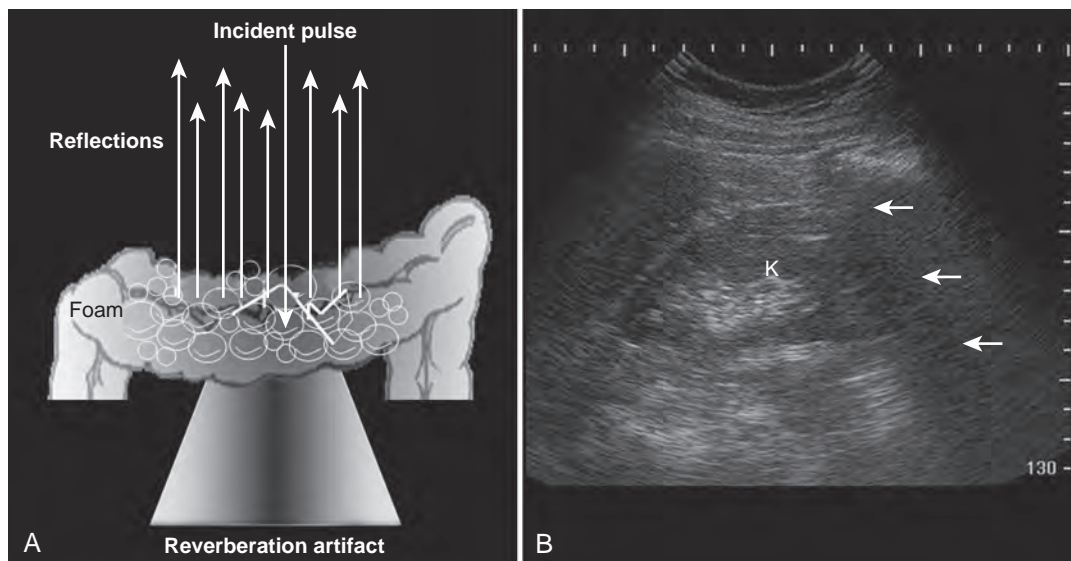


Figure 3-17. When an ultrasound wave strikes a structure such as bowel, which contains gas bubbles (A), the resultant reverberation artifact has a characteristic appearance sometimes called a “comet tail.” B, A comet tail artifact produced by bowel gas (arrows) obscures the lower pole of the kidney (K).

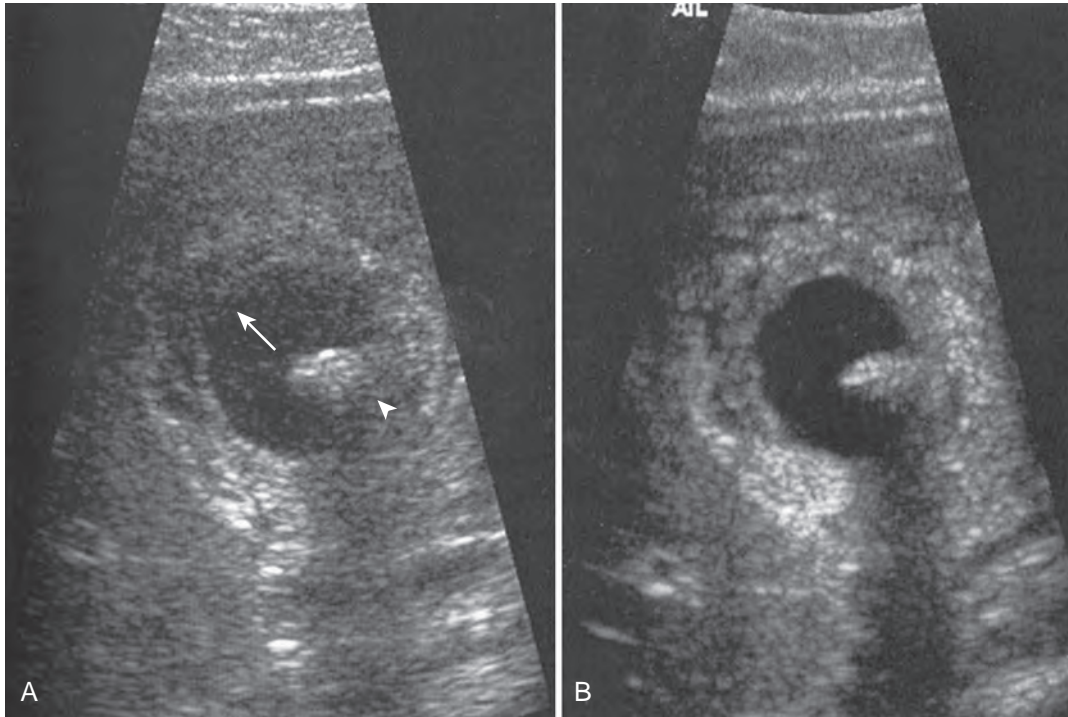


Figure 3-18. A, Standard gray-scale image of a cyst containing a mural nodule (*arrowhead*). Note the artifactual echogenicity within the cyst (*arrow*). B, The same structure on harmonic scanning is seen more clearly. There is less artifact within and distal to the cyst. (From Merritt CRB. *Physics of ultrasound*. In: Rumack CM, Wilson SR, Charboneau JW, Johnson J, editors. *Diagnostic ultrasound*. 3rd ed. St. Louis: Mosby; 2005. p. 3–34.)

generated. This technique reduces the amount of artifact and noise, producing a scan of better clarity.

Sonoelastography

The ability to access pathology by palpation has long been a key part of a physician's physical examination. Hard lesions are often a sign of pathology. Sonoelastography (tissue elasticity imaging) is an evolving ultrasound modality that adds the ability to evaluate the elasticity (compressibility and displacement) of biologic tissues. Essentially, it gives a representation, using color, of the softness or hardness of the tissue of interest. To use ultrasonography to "palpate" an organ requires a compressing mechanical wave to be produced in the tissue of interest. Presently, there are two ways to produce this mechanical wave: real-time elastography (RTE) and shear wave elastography (SWE).

In RTE, as in standard diagnostic ultrasonography, an external, nonquantifiable mechanically produced compression wave travels in tissue (1540 m/sec). These waves successively compress tissue layers producing backscatter reflected waves that are received and processed by the ultrasound equipment producing an image. Because the stress producing the mechanical compression wave cannot be directly measured, only a relative elasticity can be determined.

With RTE (*Fig. 3-19*), deformation is induced by manually pressing on the anatomy with the transducer and is measured using ultrasonography. RTE is a qualitative technique and highly user-dependent. Because of the requirement of manual displacement, RTE is unable to measure absolute tissue stiffness as currently employed. Its major benefits are that it has a high spatial resolution, it is a real-time measurement, and it does not require any modifications to conventional ultrasound hardware. Spatial resolution is the ability to distinguish two separate objects that are close together and encompasses both axial resolution and lateral resolution as defined previously.

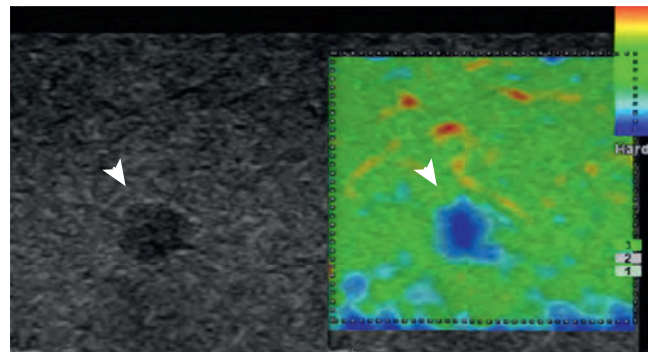


Figure 3-19. Real-time elastography. A 4-mm hypoechoic nodule (*arrow, left panel*) was found with Doppler ultrasonography with vascular flow internally. Real-time sonoelastography suggested a hard nodule (with this equipment blue is hard, not soft). Close follow-up with ultrasound examinations every 3 months found no increase in size of the nodule, and it was considered "probably" benign. (From Goddi A, Sacchi A, Magistretti G, Almolla J. Real-time tissue elastography for testicular lesion assessment. *Eur Radiol* 2012;22:721–30.)

In SWE, the shear wave produced can be precisely measured and travels more slowly (1 to 10 m/sec). The shear wave is propagated by a tangential "sliding" force between tissue layers. The elasticity (E), density of the tissue (ρ , kg/m²), and shear wave propagation speed (c) are directly related through the equation $E = 3\rho c^2$. By measuring the shear wave propagation speed, the elasticity of the tissue can be directly determined.

With SWE (*Fig. 3-20*), low-frequency (approximately 100 Hz) pulses are rapidly transmitted into the tissue to induce a vibration in the tissue. Depending on the manufacturer's implementation, the

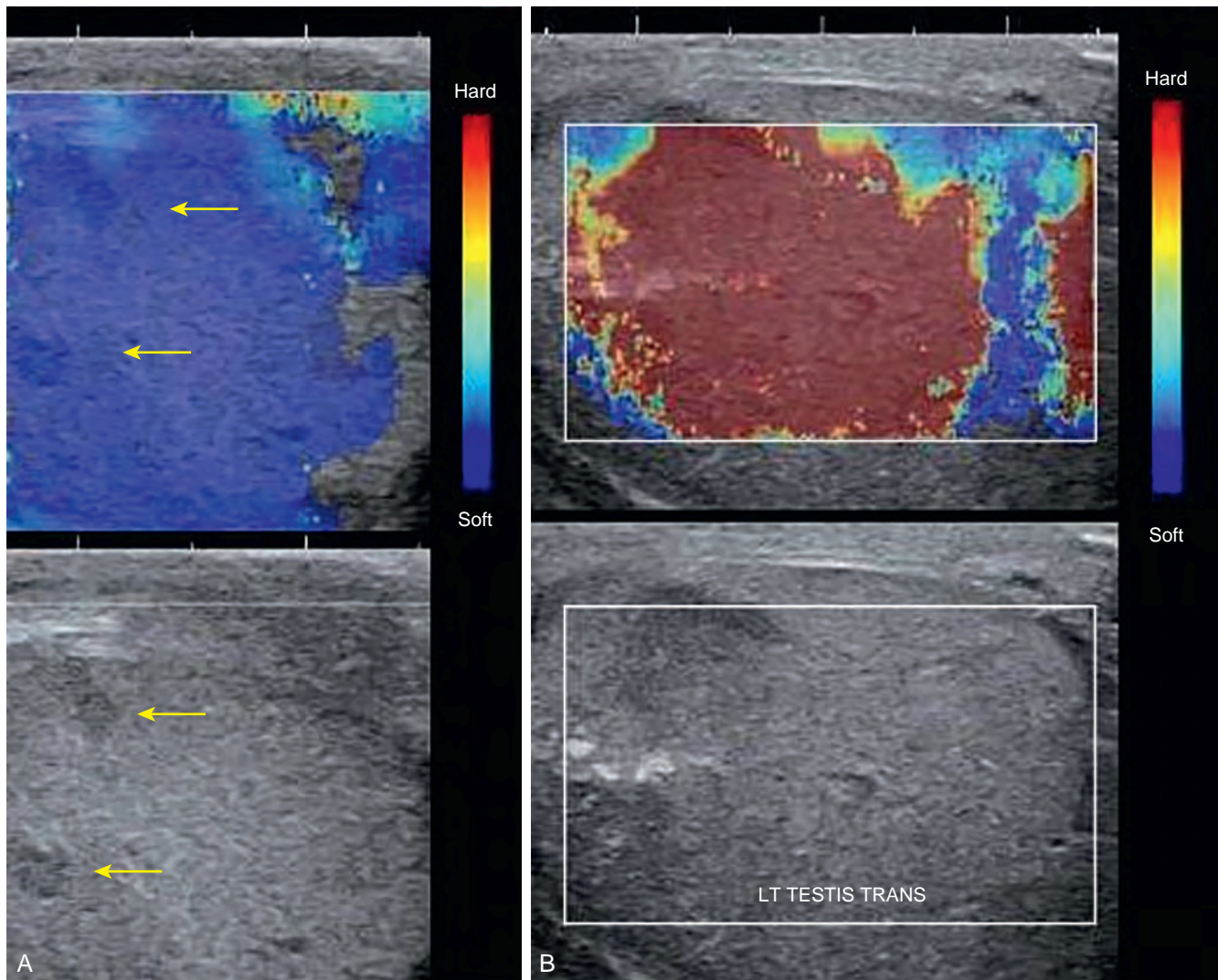


Figure 3-20. Shear wave elastography (SWE). A, Two small hypoechoic vascular lesions (arrows, lower panel) found with B-mode ultrasonography are shown in the upper panel to be soft (blue) lesions with SWE ultrasonography. Biopsy confirmed a Sertoli cell nodule. B, A larger lesion with heterogeneous echogenicity on B-mode ultrasonography (lower panel) demonstrates diffuse “hardness” on SWE (upper panel). Pathology demonstrated a nonseminomatous germ cell tumor.

vibrations can be induced in a single area or in a vertical plane by rapidly altering focal depth. Subsequently, the observation of the propagation velocity of the resultant transient shear waves determines the viscoelastic properties of the tissues. Two typical limitations of generated shear waves are as follows: (1) They are very weak resulting in only a few millimeters of propagation, and (2) detection of shear wave propagation requires very rapid acquisition speeds (pulse repetition frequency is >5000 Hz), which may limit the area of detection. However, some new-generation ultrasound systems have overcome these obstacles and allow large areas of interest to be displayed at near real-time imaging frame rates.

Several approaches for elastography have been introduced. All of them have three common steps, as follows:

1. The sonographer manually compresses (RTE) or the machine automatically generates (SWE) a low-frequency vibration in tissue to induce stress.
2. The tissue is imaged with the goal of analyzing the resulting strain.
3. Parameters are defined related to tissue stiffness.

The principle of elastography is based on the concept that a given force applied to softer tissue results in a larger displacement than

the same force applied to harder tissue. By measuring the tissue displacement induced by compression, it is possible to estimate the tissue hardness and to differentiate benign (soft) from malignant (hard) lesions. This relationship between stress (s) and strain (e) is given by Young's modulus or elasticity (E):

$$E = s/e$$

E is larger in hard tissues and lower in soft tissues.

Visually, the elasticity of a tissue is represented by color spectrum. The color given to hard lesions is determined by the manufacturer of the equipment and can be set by the user. Just as in using color Doppler, the user needs to look at the color bar (see Figs. 3-19 and 3-20) to know what colors represent “hard” and “soft” lesions.

Three-Dimensional Scanning

3D scanning has been used extensively in obstetrics and gynecology but so far has limited application in urology. 3D scanning produces a composite of images (data set), which can be manipulated to generate additional views of the anatomy in question (Fig. 3-21).

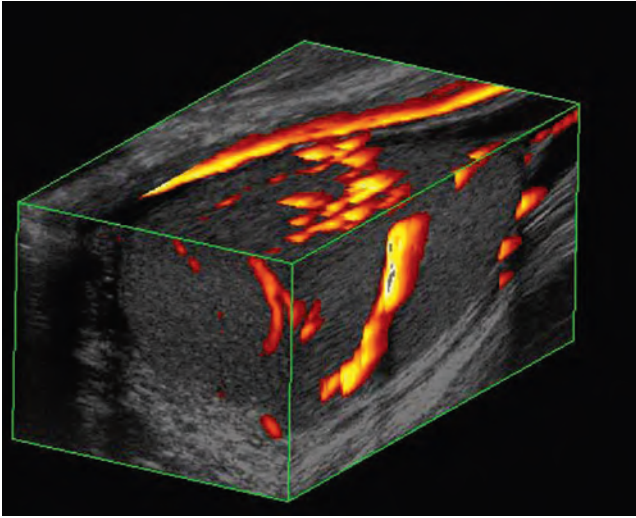


Figure 3-21. Three-dimensional image of the testis demonstrating intratesticular blood flow on power Doppler. The image can be virtually rotated and manipulated to produce unique anatomic perspectives. (Used with permission by BK Medical, Peabody, MA.)

3D rendering may be important in procedural planning and precise volumetric assessments (Chani et al, 2008a, 2008b). 3D scanning may allow the recognition of some tissue patterns that would otherwise be unapparent on two-dimensional scanning (Mitterberger et al, 2007b; Onik and Barzell, 2008).

CONTRAST AGENTS IN ULTRASONOGRAPHY

Intravenous compounds that contain microbubbles have been used for enhancing the echogenicity of blood and tissue. Microbubbles are distributed in the vascular system and create strong echoes with harmonics when struck by sound waves. The bubbles themselves are rapidly degraded by their interaction with the sound waves. Contrast agents may be useful in ultrasonography of the prostate by enhancing the ability to recognize areas of increased vasculature. The use of intravenous ultrasound contrast agents is considered investigational but has shown promise in numerous urologic scanning situations (Mitterberger et al, 2007a; Wink et al, 2008).

DOCUMENTATION AND IMAGE STORAGE

Documentation is essential for insuring high-quality patient care. Proper documentation includes the production of a permanent record of the ultrasound examination and interpretation of the examination. This documentation is inclusive of the report and acquired images (American Institute of Ultrasound in Medicine, 2009). All documentation must be retrievable and comply with local, state, and federal requirements.

Report

The report should include specific information, including patient identification details, the date of the examination, and the measurement parameters and a description of findings of the examination. Ideally, the report should also include specifics on how the evaluation was performed, including the transducer used, machine used, and settings employed. Most of these details should be on the recorded image that is also stored with the report. The report must be signed by the physician who performed the ultrasound examination, and the indications for performing the examination should be prominently displayed at the top of the report.

Description of ultrasound images

The liver is used as a benchmark for echogenicity:

- Hypoechoic = darker
- Hyperechoic = brighter and white
- Isoechoic = similar to reference point of liver
- Anechoic = black, without echoes

Figure 3-22. Nomenclature for describing the appearance of ultrasound images.

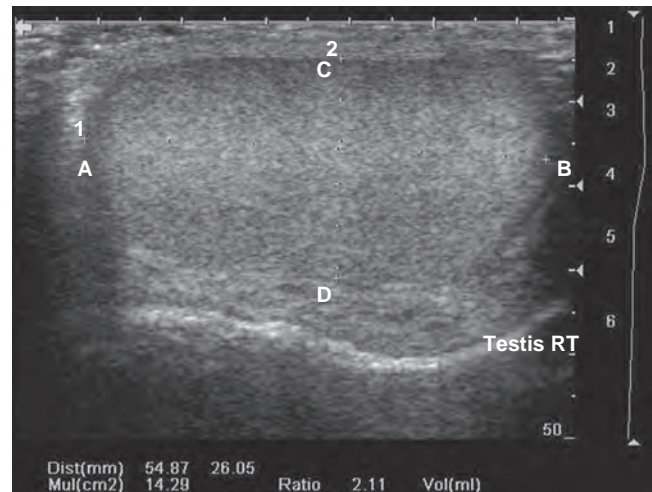


Figure 3-23. In this sagittal image of the right testis, the superior pole of the testis (A) is to the left, the inferior pole of the testis (B) is to the right. The anterior aspect of the testis (C) is at the top of the image, and the posterior aspect (D) is at the bottom. Without the label, there would be no way to distinguish the right from the left testis.

When urologists perform and interpret ultrasound studies, it is important that appropriate nomenclature be used to describe the objects imaged (Fig. 3-22). By convention, the liver is used as a benchmark for echogenicity. If a structure is hypoechoic, it means it is darker than the surrounding tissues. If it is hyperechoic, it means it is brighter than the surrounding tissues. If a structure is isoechoic, it is similar to the surrounding tissues. Structures that do not generate echoes are called *anechoic*. A simple cyst is an example of a structure with an anechoic interior. In general, a high fat content causes tissue to appear hyperechoic, and a high water content causes tissue to appear hypoechoic.

Images

Images should include patient identification details, the date and time of each image, and clear image orientation. Measurements should also be clearly identified with labeling of anatomy and any abnormalities. The image should be able to be interpreted by any appropriately trained sonographer and demonstrate a clear, unimpeded ultrasound image of the anatomy of interest. Images should always be attached to the report or be easily accessible from the report.

By convention, structures imaged by ultrasonography should be oriented so that the superior aspect of the structure is to the left as the image is viewed and the inferior aspect of the structure to the right. With paired structures, it is critical to document right or left. It is useful to use equipment-generated icons to illustrate patient position and the orientation of insonation (Fig. 3-23).

The appropriate number of images to be captured for documentation is the number necessary to document a systematic and complete examination and to document relevant pathology.

Report and Image Storage

The use of electronic medical records has made the documentation of ultrasound examinations easier. However, it has also created challenges in the archiving of images for easy reviewing. These images can occupy large portions of digital storage, and because they are part of the medical record and contain protected health information, they must comply with local, state, and federal regulations. Many validated systems are available for both small and large practices that meet current regulatory requirements.

PATIENT SAFETY

Diagnostic ultrasonography transmits energy into the patient that has the potential to produce biologic effects. The two main categories of biologic effects are **mechanical effects** and **thermal effects**.

The mechanical effects of ultrasonography are torque and streaming. The mechanical effects of an acoustic field may produce a phenomenon called *cavitation*. **Cavitation** occurs when small gas-filled bubbles form and then collapse. These collapsing bubbles liberate a large amount of energy, which may cause damage to tissue in certain circumstances. Mechanical effects are most likely to be observed around gas-containing structures such as lung and bowel.

The thermal effects of ultrasonography are primarily the result of tissue heating resulting from the absorption of energy. The amount of tissue heating is influenced by several factors, including beam focusing, transducer frequency, exposure time, scanning mode, and tissue density.

To assist the sonographer in monitoring the biologic effects of ultrasonography, the **output display standard (ODS)** has been adopted. Two values are typically displayed: the **mechanical index (MI)** and the **thermal index (TI)**. These indices are calculated estimates of the potential for biologic effects of ultrasonography based on the mode of ultrasonography being used, frequency, power output, and time of insonation. The MI indicates the probability that cavitation will occur. For tissues not containing stabilized gas bodies (lung and intestine), the risk of cavitation is low as long as the MI is less than or equal to 0.7. For structures adjacent to lung or intestine, scanning time should be limited if the MI exceeds 0.4. The TI indicates the probability that tissue temperature within the sonographic field will be increased by 1°C. Although the precise consequences of tissue heating are not completely understood, tissue temperature elevations of up to 6°C are not likely to be dangerous unless exposure time exceeds 60 seconds. TI values should be less than 2 for most urologic ultrasound studies (Nelson et al, 2009). The MI and TI are typically displayed on the monitor during ultrasound examinations, and all practitioners should be familiar with the location. **These indices are not safety limits.**

Ultrasonography performed by urologists generally has a low risk for patient harm as long as standard protocols are followed (Rumack et al, 2005). Although tissue heating may occur, there are no confirmed biologic effects of tissue heating in nonfetal scanning except when heating is sustained for extended periods. Users should be aware that for soft tissues not known to contain gas bodies, there is no basis in present knowledge to suggest an adverse nonthermal biologic effect from current diagnostic instruments not exceeding the U.S. Food and Drug Administration output limits (Rumack et al, 2005). Nevertheless, all urologists should endeavor to follow the principles of **ALARA**, which stands for “**As Low As Reasonably Achievable**.” The ALARA principle is intended to limit the total energy imparted to the patient during an examination. This limitation can be accomplished by (1) keeping power outputs low, (2) using appropriate scanning modes, (3) limiting examination times, (4) adjusting focus and frequency, and (5) using the sine function during documentation.

Ultrasound scanning offers an excellent, cost-effective modality for diagnosing and treating urologic conditions. **The most important factor in ultrasound safety is an informed operator.**

Urologists should endeavor to perform limited examinations using consistent technique for specific indications. Patient safety and equipment maintenance should be emphasized in all environments where ultrasound technology is used.

CLINICAL UROLOGIC ULTRASONOGRAPHY

The use of ultrasonography in urology has expanded dramatically because of its profound utility in the clinic and operating room. Long the mainstay of the diagnosis of prostatic disease, ultrasonography is increasingly being used by urologists in the clinical environment for initial diagnosis, interventional management, and longitudinal follow-up of urologic diseases.

Renal Ultrasonography

Urologists, by virtue of their intimate knowledge of surgical anatomy of the kidneys and retroperitoneum, are uniquely qualified to perform and interpret selected ultrasound examinations of the abdomen. These skills are relevant in both the office and the operating room environment. Urologists generally perform abdominal ultrasonography for a specific clinical indication and less often for general screening of the abdominal contents. In most clinical situations, a limited retroperitoneal examination is used in urologic practice.

Technique

The transducer normally used for renal ultrasonography is a curved array transducer of 3.5 to 5.0 MHz. Transducers of a higher frequency may be used for pediatric patients. For intraoperative and laparoscopic renal ultrasonography, a linear array transducer of 6 to 10 MHz is typically employed.

Scanning of the right kidney is performed with the patient supine. The kidney is located by beginning in the midclavicular line in the right upper quadrant. In the sagittal plane, the transducer is moved laterally until the midsagittal plane of the kidney is imaged. After the kidney has been imaged anteriorly and posteriorly in the sagittal plane, the probe is rotated 90 degrees counterclockwise. The midtransverse plane demonstrates the renal hilum containing the renal vein. The kidney is scanned from upper pole to lower pole.

The technique and documentation for left renal ultrasonography are identical to right renal ultrasonography. However, the left kidney is slightly more cephalad than the right kidney. Bowel gas is more problematic on the left because of the position of the splenic flexure of the colon. Visualization of the left kidney often requires the patient to be turned into a lateral position. Ultrasound imaging of the left kidney lacks the liver as an acoustic window, and it is sometimes more difficult to image the left kidney in a true sagittal plane.

Indications

1. Assessment of renal and perirenal masses
2. Assessment of the dilated upper urinary tract
3. Assessment of flank pain during pregnancy
4. Evaluation of hematuria in patients who are not candidates for intravenous pyelography, computed tomography, or magnetic resonance imaging because of renal insufficiency, allergy to contrast media, or physical impediment
5. Assessment of the effects of voiding on the upper urinary tract
6. Evaluation for and monitoring of urolithiasis
7. Intraoperative renal parenchyma and vascular imaging for ablation of renal masses
8. Percutaneous access to the renal collecting system
9. Guidance for transcutaneous renal biopsies, cyst aspiration, or ablation of renal masses
10. Postoperative evaluation of patients after renal and ureteral surgery
11. Postoperative evaluation of patients with renal transplants

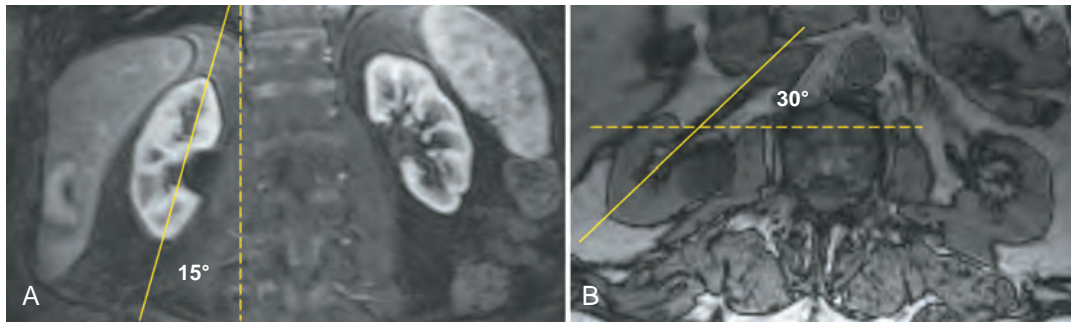


Figure 3-24. A, The lower pole of the kidney is displaced 15 degrees laterally compared with the upper pole. B, The kidney is rotated 30 degrees posterior to the true coronal plane. The lower pole of the kidney is slightly anterior compared with the upper pole.

Normal Findings

It is helpful during scanning of the kidney to understand its anatomic position within the retroperitoneum. This understanding assists identifying the midsagittal plane, which serves as a reference point for a complete examination (Fig. 3-24).

The adult right kidney in the sagittal view demonstrates a cortex that is usually hypoechoic with respect to the liver. The central band of echoes in the kidney is a hyperechoic area that contains the renal hilar adipose tissue, blood vessels, and collecting system. Acoustic shadowing from ribs overlying the inferior pole can be eliminated by moving the probe to a more lateral position or into the intercostal space. By having the patient take a deep breath, the kidney can be moved inferiorly to assist complete imaging (Fig. 3-25).

The echogenicity of the kidney varies with age. The renal cortex of an infant is relatively hyperechoic compared with that of an adult. In addition, there is a smaller and less apparent central band of echoes in the infant. In the adult, the echogenicity of the renal cortex is usually hypoechoic with respect to the liver (Emamian et al, 1993). In patients with chronic renal diseases, the renal cortex is often thinned and isoechoic or hyperechoic with respect to the liver (O'Neill, 2001).

Renal size changes over the lifetime of an individual. Nomograms for pediatric renal size should be consulted; these are based on age, height, and weight of the patient. The average adult kidney measures 10 to 12 cm in length and 4 to 5 cm in width. Measurements of renal volume may be appropriate in cases of severe renal impairment. Renal measurements should be obtained in the midsagittal plane and midtransverse plane. Measurements taken in other than the midsagittal plane and midtransverse plane may be spuriously low. The thickness of the parenchyma is the average distance between the renal capsule and the central band of echoes. The precise location for making this measurement is subjective. The midlateral renal parenchyma in the sagittal view is a common choice for obtaining this measurement (Fig. 3-26). Although there is no universal standard, the renal cortical thickness should be greater than 7 mm (Roger et al, 1994), and the renal parenchymal thickness should be greater than 15 mm in adults (Emamian et al, 1993).

Doppler ultrasound may be helpful in evaluating the renal artery and renal vein and assessing the vascular resistance in the kidney. Doppler modes may also be useful in evaluating neovascularity associated with renal tumors and in correctly characterizing hypoechoic structures in the renal pelvis, such as a parapelvic cyst, the renal vein, or the dilated collecting system.

Procedural Applications

Percutaneous renal biopsy has been performed as an office procedure by several groups for the past 2 decades and found to be a safe and effective procedure (Christensen et al, 1995; Fraser and Fairley, 1995; Hergesell, 1998). In a series of 131 ultrasound-guided

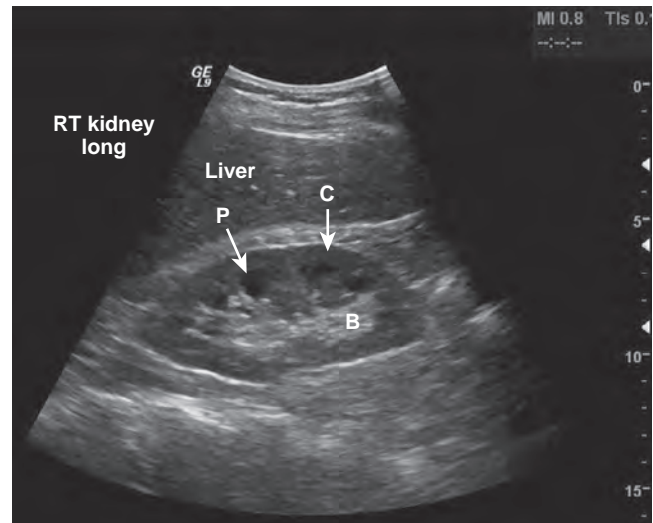


Figure 3-25. Midsagittal plane of the kidney. Note the relative hypoechoic nature of the renal pyramids (P) compared with the cortex (C). The central band of echoes (B) is hyperechoic compared with the cortex. The midsagittal plane has the greatest length measurement pole to pole. A perfectly sagittal plane results in a horizontal long axis of the kidney.

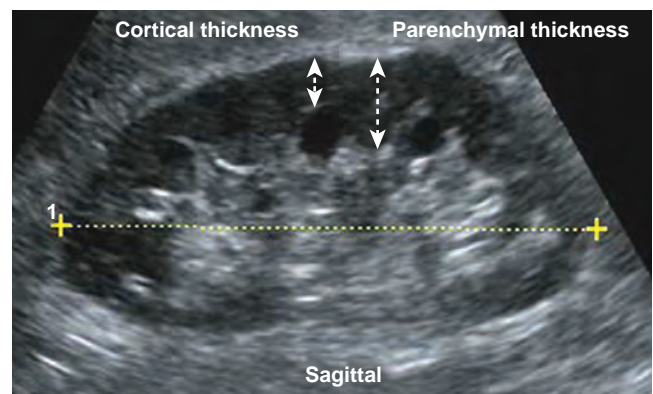


Figure 3-26. The distinction between renal cortical thickness and renal parenchymal thickness is that the renal parenchyma is measured from the central band of echoes to the renal capsule. The renal cortex is measured from the outer margin of the medullary pyramid to the renal capsule.

biopsies by Christensen and colleagues (1995), complications occurred in 21% of patients (18% minor complications and 3% major complications). In their series, increasing the number of biopsy passes did not increase the complication rate, whereas the presence of severe hypertension did. Fraser and Fairley (1995) compared 118 outpatient ultrasound-guided biopsies with 232 inpatient procedures and found no difference in complication rate. Hergesell (1998) reviewed a series of 1090 percutaneous biopsies performed with local anesthesia and ultrasound guidance. Only one case required interventional radiology for persistent blood loss, 2.2% (25 of 1090) of cases had minor hematoma that was conservatively treated, and self-limited macrohematuria was found in 0.8% (9 of 1090) of cases. In a subset of the population evaluated by Doppler ultrasonography, hemodynamically irrelevant arteriovenous fistula was found in 9% (48 of 533) of cases. Sufficient tissue was obtained in 98.8% of cases.

Al-Hweish and Abdul-Rehman (2007) followed two groups. Patients in group I ($n = 22$) had a 24-hour hospital admission after the biopsy, and patients in group II ($n = 22$) were observed for 6 hours after the biopsy and then discharged. A small perinephric hematoma that resolved spontaneously was observed in a single patient in group II. Gross hematuria (13.6% in group I and 9.1% in group II) was the only significant complication observed and occurred in all cases within 6 hours.

The safety and efficacy of outpatient percutaneous renal biopsy have also been reported for pediatric patients (Davis et al, 1998; Kamitsuji et al, 1999; Hussain et al, 2003) and elderly patients (Kohli et al, 2006; Stratta et al, 2007; Moutzouris et al, 2009).

Limitations

Some patients are not favorable candidates for renal ultrasonography. Obesity, intestinal gas, and physical deformity may be impediments to complete renal evaluation. Renal ultrasonography has poor sensitivity for renal masses less than 2 cm (Warshauer et al, 1988). There is a lack of specificity for renal tumor type except for angiomyolipoma. Angiomyolipoma has characteristics that are distinctive on ultrasonography (highly echoic), but some small renal cell carcinomas have been shown to be indistinguishable from angiomyolipoma by ultrasound criteria (Yamashita et al, 1992; Forman et al, 1993).

Transabdominal Pelvic Ultrasonography

Transabdominal pelvic ultrasonography is a tremendously versatile tool for the urologist. It is a noninvasive method for evaluating the lower urinary tract and prostate in men and the bladder in women. A curved array transducer of 3.5 to 5 MHz is most commonly employed to perform transabdominal ultrasonography. In pediatric

patients, a higher frequency transducer may be used. In cases in which only a residual urine or bladder volume is to be determined, an automated bladder scanner is often employed.

Technique

Bladder ultrasonography is most commonly performed with the patient supine and the sonographer on the patient's right side. The scan should be performed in a warm room, and the patient should be draped to provide for comfort and privacy. If necessary, a roll may be placed beneath the patient's hips. The scanning technique depends on the circumstances and the reason for the examination, but in general the scan should be performed with a moderately filled bladder. The bladder should be scanned in a sagittal and transverse manner angling the probe into the pelvis so that the bladder can be visualized beneath the pubic bone. Although the prostate cannot be imaged with the same resolution achieved during transrectal scanning, the size and morphology of the prostate can be demonstrated. Although transabdominal scanning is the most common means of evaluating the bladder, the bladder may also be assessed using transvaginal and transrectal approaches. These approaches are useful in patients who are obese or who are not suitable candidates for transabdominal scanning.

Indications

1. Measurement of bladder volume or postvoid residual urine
2. Assessment of prostate size and morphology
3. Demonstration of secondary signs of bladder outlet obstruction
4. Evaluation of bladder wall configuration and thickness
5. Evaluation of hematuria of lower urinary tract origin
6. Detection of ureterocele
7. Assessment for ureteral obstruction
8. Detection of perivesical fluid collections
9. Evaluation of clot retention
10. Confirmation of catheter position
11. Removal of retained catheter
12. Guidance of suprapubic tube placement
13. Establishment of bladder volume before and after flow rate determination

Normal Findings

Transabdominal pelvic ultrasonography should include evaluation of the lumen of the bladder and bladder wall configuration and thickness. The presence of specific lesions such as stones or tumors should be documented. The structures immediately surrounding the bladder may also be evaluated, including the distal ureters, the prostate in men, and the uterus and ovaries in women (Fig. 3-27).

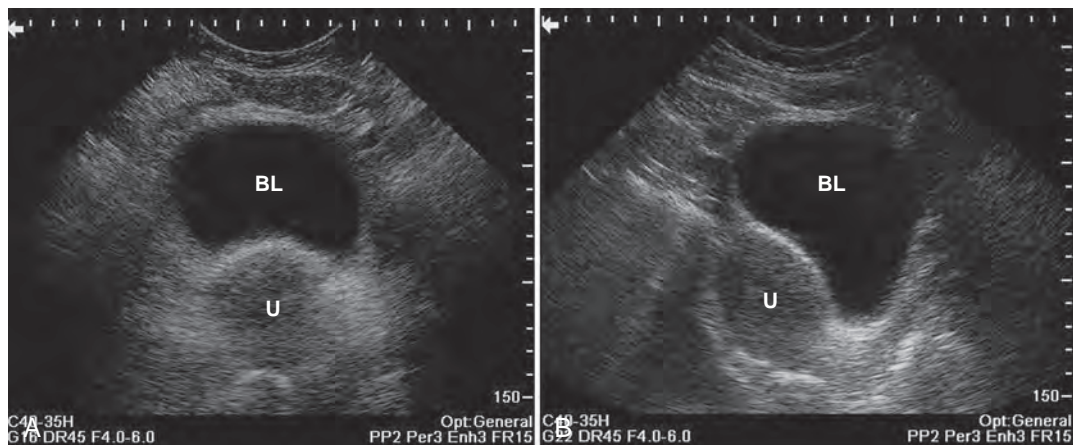


Figure 3-27. A, Transverse view of the bladder (BL) in a female patient demonstrates the uterus (U). B, Sagittal view of the bladder shows the uterus posterior to the bladder.

The emergence of urine from the ureteral orifices (ureteral jets) can be demonstrated. The clinical value of demonstrating ureteral jets has been questioned. To verify the absence of a ureteral jet, 10 minutes of continuous observation may be required (Fig. 3-28) (Delair and Kurzrock, 2006).

Bladder volume can be calculated manually by obtaining measurements in the midtransverse plane and midsagittal plane (Fig. 3-29). Numerous studies have shown that for bladder volumes of 100 to 500 mL, such calculated volumes are within 10% to 20% of the actual bladder volume (Simforoosh et al, 1997; Ghani et al, 2008b; Park et al, 2011). Measuring bladder wall thickness may assist the clinician in understanding the degree of bladder outlet obstruction (Fig. 3-30). Bladder wall thickness varies depending on the volume of urine in the bladder and on which part of the bladder wall is measured. It has been shown that measuring bladder wall thickness may predict bladder outlet obstruction with greater accuracy than free uroflowmetry, postvoid residual urine, and prostate volume (Oelke et al, 2007).

Transabdominal ultrasonography of the prostate requires angling the probe beneath the pubic bone. In the transverse plane, the transducer is fanned inferiorly until the largest transverse diameter of the prostate is identified. Measurements of the transverse width and height are obtained (Fig. 3-31A). The transducer is then rotated 90 degrees clockwise to produce a true sagittal image of the

prostate. The transducer is fanned until the midline is identified; this is recognized by a V-shaped indentation at the bladder neck (Fig. 3-31B). Depending on the degree of prostatic hypertrophy and the presence or absence of a middle lobe, this V may be more or less apparent and more or less anterior or posterior in its position. A sagittal measurement is made from the bladder neck to the apex of the prostate. The apex of the prostate may be identified by using the hypoechoic urethra as a guide.

The degree of protrusion of the prostate into the bladder may have some predictive value for bladder outlet obstruction. It has been shown that intravesical prostatic protrusion correlates well with formal urodynamic evaluation of bladder outlet obstruction (Chia et al, 2003; Keqin et al, 2007). The measurement is obtained by drawing a line corresponding to the bladder base on a sagittal scan and measuring the perpendicular distance from bladder base to greatest protrusion of the prostate into the bladder (Fig. 3-32).

Transabdominal ultrasonography of the prostate is useful in characterizing prostatic urethral length, the size and configuration of the middle lobe of the prostate, and some secondary information about the physiology of bladder outlet obstruction. This information is valuable in treatment planning for bladder outlet obstruction.

Procedural Applications

Transabdominal ultrasound-guided percutaneous bladder aspiration with or without catheter placement has been successfully used in neonates, children, and adults (Gochman et al, 1991; Wilson and Johnson, 2003). It has also been employed for treatment of bladder stones (Ikari et al, 1993; Sofer et al, 2004). Ultrasound-guided aspiration has also been used for peritoneal drainage after bladder perforation (Manikandan et al, 2003).

Limitations

Transabdominal pelvic ultrasonography yields limited information in patients with an empty bladder. The ability to identify distal

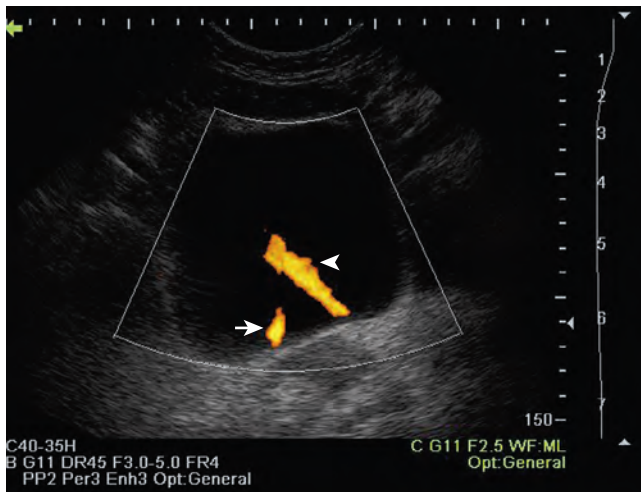


Figure 3-28. In this transverse view of the bladder, urine “jets” emerging from the left (arrow) and right (arrowhead) ureteral orifices are demonstrated by power Doppler.

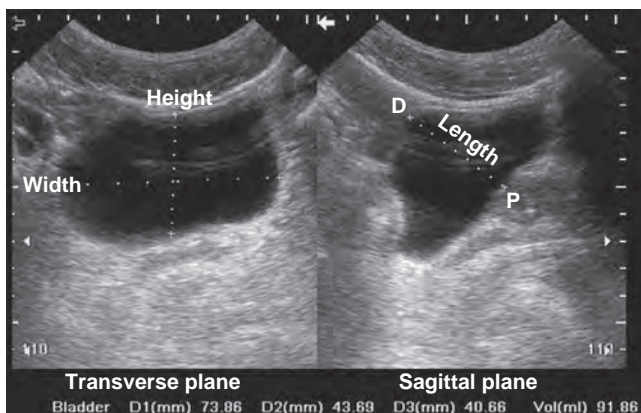


Figure 3-29. Measurement of bladder volume using the formula: bladder volume = width (transverse plane) × height (transverse plane) × length (midsagittal plane) × 0.625. In the sagittal plane, the dome (D) of the bladder is to the left, and the prostate (P) is to the right.

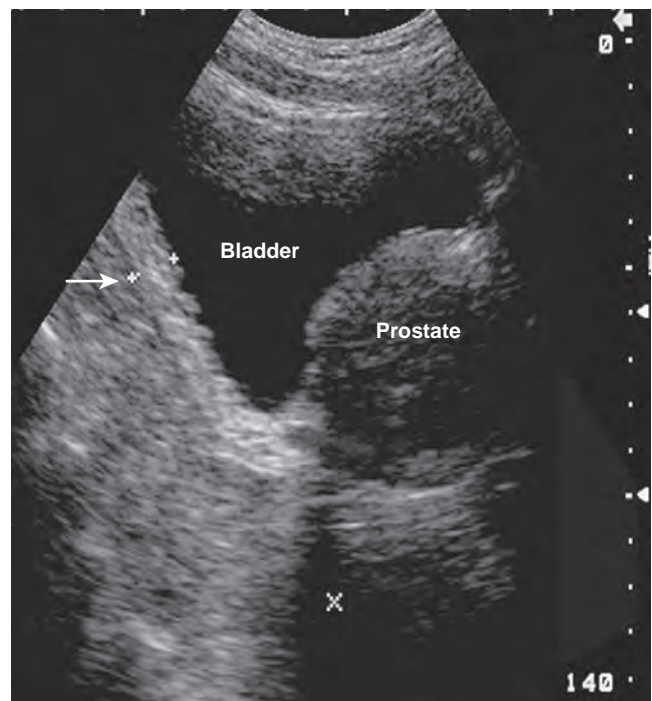


Figure 3-30. Bladder wall thickness may provide information about bladder outlet obstruction. In this sagittal view, bladder wall thickness is measured posteriorly (arrow) near the midline. Note the trabeculation of the relatively hyperechoic bladder wall.

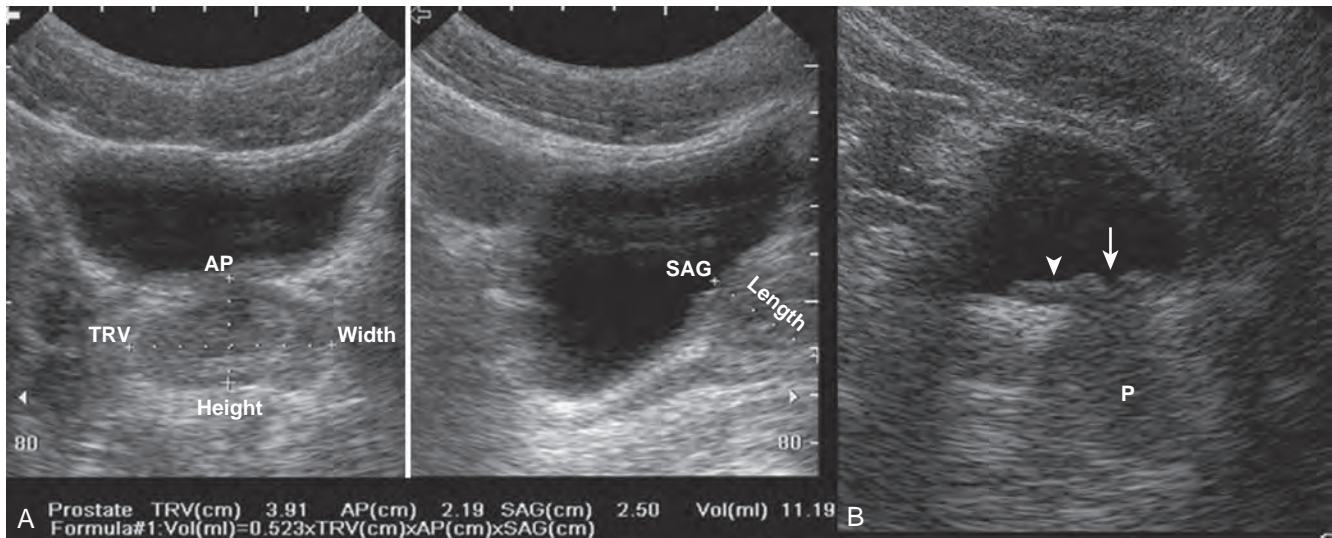


Figure 3-31. A, Transabdominal ultrasonography is extremely useful for measuring prostatic volume and evaluating prostatic morphology. The volume of the prostate can be calculated using the formula: prostate volume (mL) = width (cm) × height (cm) × length (cm) × 0.523. B, In this midsagittal view of the prostate (P), the bladder neck is identified as a V-shaped indentation (arrow). Note the characteristically hyperechoic trigone (arrowhead).

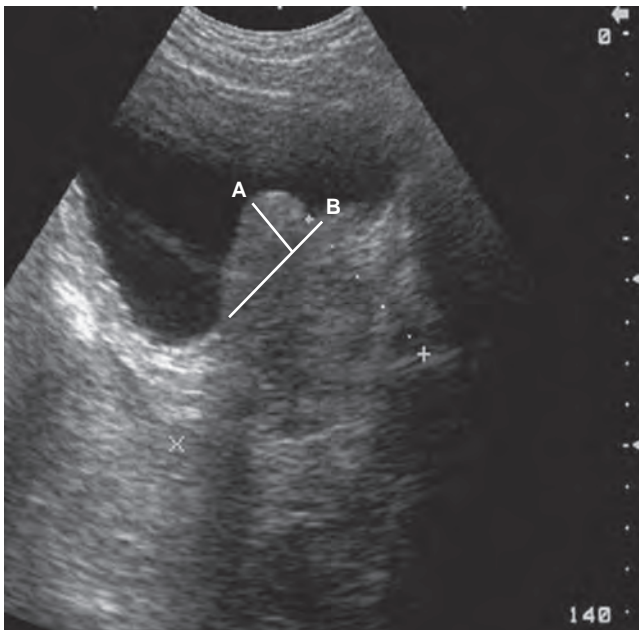


Figure 3-32. In this sagittal view of the prostate, the middle lobe extends into the bladder (A). The bladder base is defined by the line B. The length of line A is the intravesical prostatic protrusion.

ureteral obstruction, bladder stones, and bladder tumors requires a full bladder. Although prostatic morphology and volume can be assessed with an empty bladder, it is much easier when the bladder is full. Pelvic structures may be difficult to evaluate in patients with a protuberant abdomen or panniculus. **Although ultrasonography is used, automated measurement of bladder volume or residual urine is not an imaging study.** Lack of imaging confirmation can lead to inaccurate residual urine determinations in patients with obesity, clot retention, ascites, bladder diverticulum, or perivesical fluid collection (e.g., urinoma, lymphocele).

Ultrasonography of the Scrotum

No aspect of urologic care is better suited to the use of ultrasonography than evaluation of the scrotum. Urologists have a surgical understanding of the anatomy and extensive experience with the diagnosis and treatment of disorders that affect the scrotum. Because the scrotum and its contents are superficial, high-frequency transducers may be employed to yield excellent and detailed anatomic and physiologic information. Imaging information can be correlated with findings on direct physical examination.

Technique

Sound technique is critical to performing adequate ultrasonography of the scrotum. In general, the examination should be carried out in a quiet room that is adequately warm for patient comfort. The patient should be supine with the scrotum supported on a towel or on the anterior thighs. The patient should be draped in such a way as to hold the penis out of the way and to ensure patient privacy. Copious amounts of conducting gel should be used to provide a good interface between the transducer and the scrotal skin because air trapping by scrotal hair results in unwanted artifacts. Complete but gentle contact between skin and transducer is essential because excessive pressure results in movement of testis or compression of the testis. Compression may change echogenicity and obscure fine anatomic detail. In addition, compression may significantly alter volume measurements.

Scrotal ultrasonography is performed with a high-frequency linear array transducer, generally in the range of 7 to 18 MHz. Transducers may be 4 to 7.5 cm in width. Some sonographers prefer the maneuverability of a 4-cm transducer, whereas others prefer the longer 7.5-cm transducer for its ability to image the entire testis simultaneously in the sagittal plane. Imaging should be done in a systematic fashion and should include sagittal and transverse views of the testis. The sagittal view should proceed from the midline medially and then laterally and from the midtransverse section of the testis to the upper pole and the lower pole of the testis. In addition to the testis, the epididymis and entire scrotal contents should be imaged.

Indications

1. Assessment of scrotal and testicular mass
2. Assessment of scrotal and testicular pain
3. Evaluation of scrotal trauma
4. Evaluation of infertility
5. Follow-up of scrotal surgery
6. Evaluation of empty or abnormal scrotum

Normal Findings

It is important to document the size and, if appropriate, the volume of the testes. The echo architecture of the testis should be described (Fig. 3-33). It is important to compare the testes for echogenicity because some infiltrative processes may result in diffuse changes in a testis that would be noticed only when that testis is compared with its contralateral mate (Fig. 3-34). For example, lymphomatous or leukemic involvement of the testis may result in a diffusely hypoechoic and homogeneous appearance, which may be unilateral (Mazzu et al, 1995). If paratesticular fluid is present, the

epididymis and the testicular and epididymal appendages are more easily identified (Fig. 3-35).

Normal testicular blood flow may be demonstrated with color or power Doppler (Fig. 3-36) (Barth and Shortliffe, 1997). Intratesticular blood flow is low velocity with the average PSV of less than 10 cm/sec (Middleton et al, 1989). Intratesticular blood flow is primarily supplied by the testicular artery, which ultimately divides to supply the individual testicular septa. The fibrous septa coalesce to form the mediastinum testis, which is a hyperechoic linear structure seen in the sagittal plane (Fig. 3-37).

Spectral Doppler is useful in evaluating the intratesticular blood flow with elevated resistive index greater than 0.6 suggestive of impaired spermatogenesis (Fig. 3-38) (Biagiotti et al, 2002; Pinggera et al, 2008; Hillelsohn et al, 2013).

Procedural Applications

The testis lends itself to easy access for ultrasound localization of internal structures and for percutaneous access. In particular, small nonpalpable lesions can be localized by ultrasonography, guiding

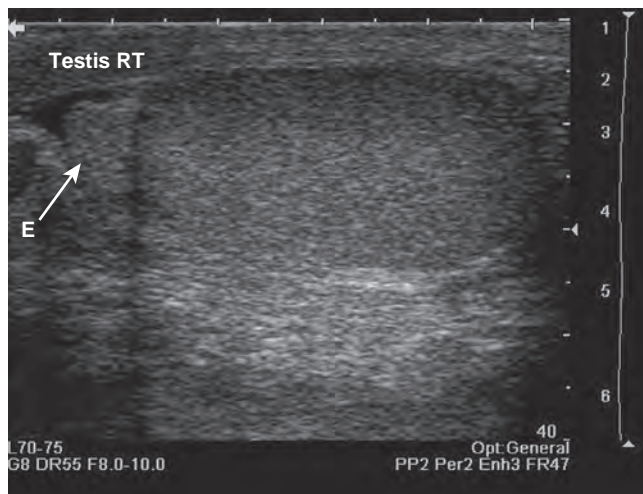


Figure 3-33. In this longitudinal view, the head of the epididymis (E) is seen to the left, and the lower pole of the testis is to the right. Normal testicular sonographic anatomy is characterized by a homogeneous, finely granular appearance of the testis.

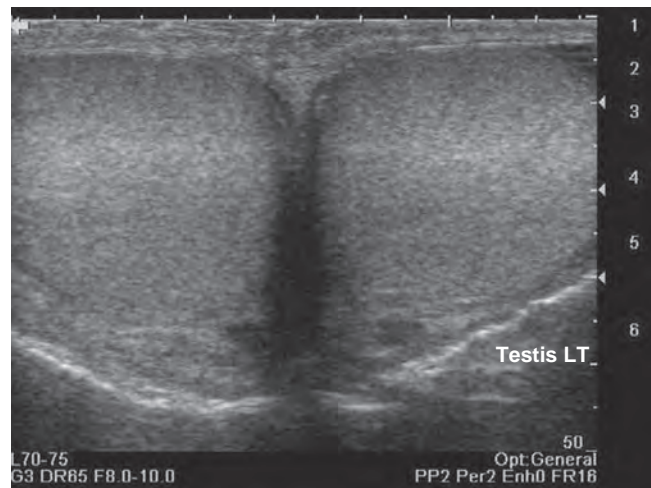


Figure 3-34. Simultaneous bilateral views are important to rule out a diffuse infiltrative process such as lymphoma. A diffuse and homogeneous change in echogenicity in one testis could otherwise be unappreciated. In this example, the testes are symmetric and normal. This view is also required to document the presence of two testes.

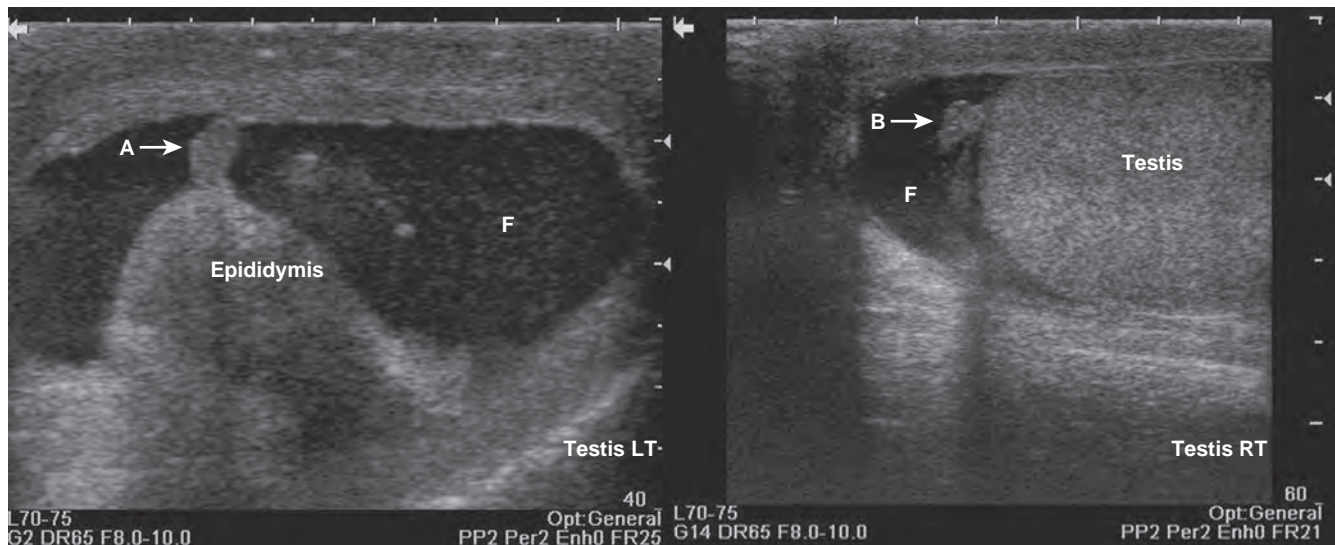


Figure 3-35. The presence of paratesticular fluid (F) permits the identification of the appendix epididymis (A) and the appendix testis (B).

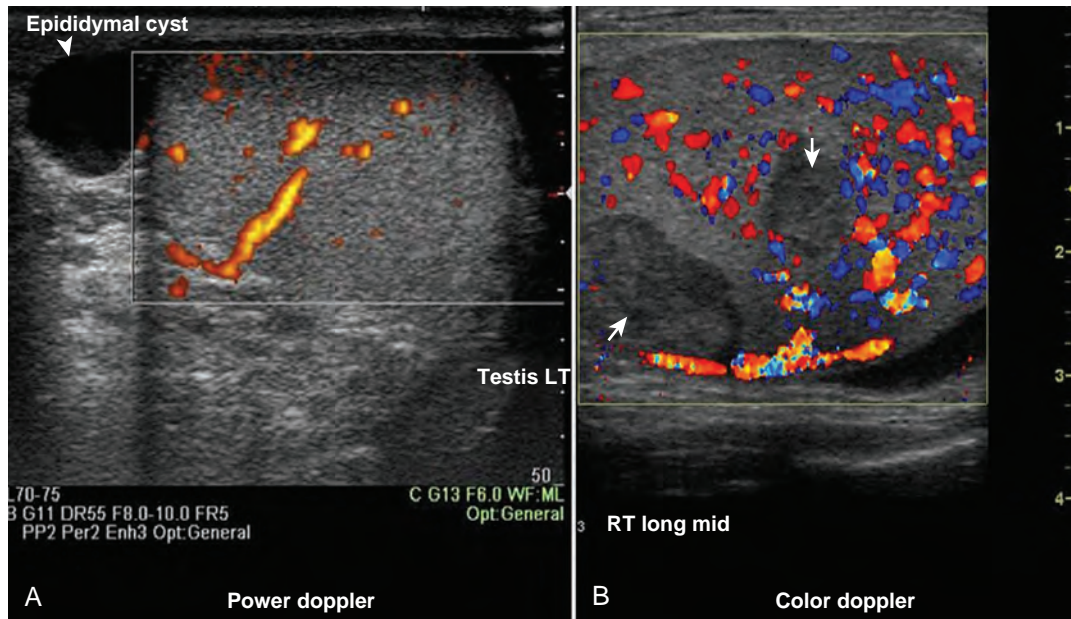


Figure 3-36. A, Normal intratesticular blood flow by power Doppler; note the epididymal cyst (arrowhead). B, Increased blood flow in an irregular pattern demonstrated by color Doppler was associated with necrotizing vasculitis; note the relatively hypoechoic areas of decreased vascularity (arrows).

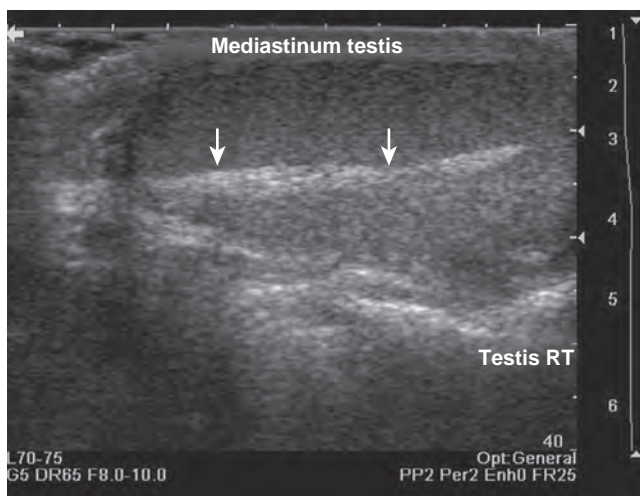


Figure 3-37. Sagittal image of this testis demonstrates a common anatomic finding, the hyperechoic mediastinum testis (arrows). The mediastinum testis is a normal structure resulting from the coalescence of the fibrous septa of the testis.

placement of a needle for percutaneous biopsy or injection of a dye for localization during open biopsy (Buckspan et al, 1989).

Current therapeutic applications using ultrasound guidance include percutaneous testicular sperm aspiration (Friedler et al, 1997; Belker et al, 1998; Khadra et al, 2003) and percutaneous epididymal sperm aspiration (Craft et al, 1995; Belker et al, 1998; Levine and Lisek, 1998; Meniru et al, 1998; Rosenlund et al, 1998; Lin et al, 2000; Pasqualotto et al, 2003). Future ultrasound-guided applications might include spermatogonia stem cell transfer to testes devoid of germ cells after gonadotoxic therapies.

Sonoelastography

Two more recent studies used real-time elastography to differentiate benign from malignant testicular lesions because it is postulated

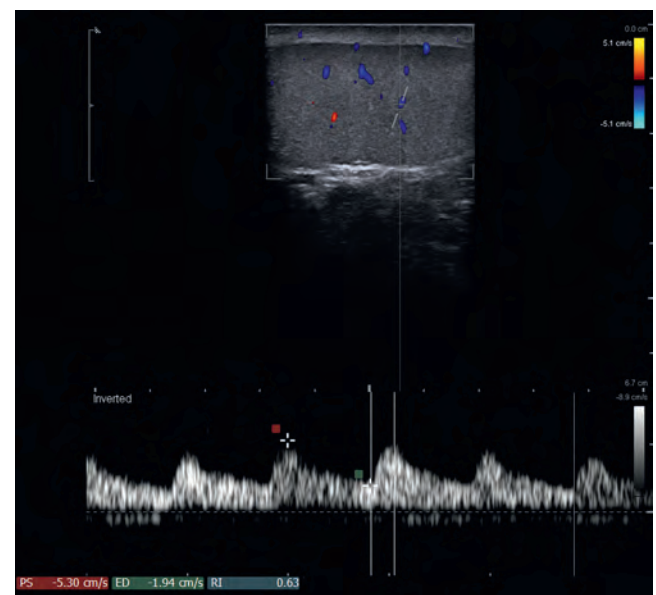


Figure 3-38. Spectral Doppler analysis of an intratesticular artery demonstrating a peak systolic velocity of 5.3 cm/sec, an end-diastolic velocity of 1.94 cm/sec, and a calculated resistive index of 0.63 in a patient with dyspermia.

that malignant lesions have an increased stiffness secondary to a higher concentration of vessels and cells compared with surrounding tissues. Goddi and colleagues (2012) assessed 88 testes with 144 lesions and found a 93% positive predictive value, 96% negative predictive value, and 96% accuracy (see Fig. 3-19). Aigner and associates (2012) assessed 50 lesions and found a 92% positive predictive value, 100% negative predictive value, and 94% accuracy in differentiating malignant from benign lesions. Additionally, Li and coworkers (2012) found that men with non-obstructive azoospermia had significantly different testicular elasticity compared with patients with obstructive azoospermia and healthy controls with a normal semen analysis. Real-time tissue

elastography (see Fig. 3-20) is an exciting new innovation in assessing abnormalities on scrotal examination; however, more data are necessary before surgical intervention can be safely avoided based on the findings.

Limitations

Caution should be used when interpreting Doppler flow studies in the evaluation of suspected testicular torsion. The hallmark of testicular torsion is the absence of **intratesticular** blood flow (Fig. 3-39). Paratesticular flow in epididymal collaterals may appear within hours of torsion. Comparison with the contralateral testis should be performed to ensure that the technical attributes of the study are adequate to demonstrate intratesticular blood flow.

Ultrasonography of the Penis and Male Urethra

Ultrasonography of the penis and male urethra provides exquisite anatomic detail and may be used in many cases in lieu of studies requiring ionizing radiation.

Technique

Penile and urethral ultrasonography is best performed with a 12- to 18-MHz linear array transducer for optimal resolution. The technique for penile and urethral ultrasonography includes imaging the phallus in the longitudinal and transverse planes. Both ventral and dorsal surfaces of the phallus can be interrogated. Similar to scrotal ultrasonography, the examination is best carried out in a quiet room that is adequately warm for patient comfort. Draping is done to ensure patient privacy. The examination is performed in a systematic fashion beginning at the base of the penis and proceeding distally to the glans. It is possible to obtain an image of the proximal urethra and corporeal bodies by scanning through the scrotum or the perineum.

It may be helpful when evaluating the penile urethra, especially for stricture disease, to inject a sterile gel into the urethra in a retrograde fashion. The gel distends the urethra and allows better identification of urethral anatomy and the anatomy of the corpus spongiosum.

Indications

1. Evaluation of penile vascular dysfunction
2. Documentation of fibrosis of the corpora cavernosa
3. Localization of foreign body
4. Evaluation of urethral stricture
5. Evaluation of urethral diverticulum
6. Assessment of penile trauma or pain

Normal Findings

Scanning of the external portion of the phallus can be performed either from the dorsal or from the ventral surface (Fig. 3-40). Transverse scanning of the phallus reveals the two corpora cavernosa dorsally and the urethra ventrally. The sagittal view of the phallus demonstrates the corpora cavernosa with a hyperechoic, double linear structure representing the cavernosal artery (Fig. 3-41). The corpus spongiosum is isoechoic to slightly hypoechoic and contains the coapted urethra. The urethra is collapsed except during voiding.

Perineal Ultrasonography

The more proximal aspects of the urethra and corpora cavernosa are best assessed through a perineal approach by placement of the transducer on the perineum. The bulbar urethra with the bulbar branch of the pudendal artery and the proximal cavernosal bodies and the cavernosal branch of the pudendal artery can be visualized (Fig. 3-42).

Transperineal and translabial ultrasonography has also been used for evaluation of the pelvic floor for both diagnostic purposes and postprocedural follow-up. The anterior, central, and posterior compartments are well visualized. In contrast to a transvaginal approach, this approach is noninvasive and does not distort the pelvic anatomy (Baxter and Firoozi, 2013).

Procedural Applications

The most common application of penile ultrasonography is in the evaluation of erectile dysfunction and penile curvature. Pharmacostimulation provides quantification of cavernosal artery blood flow velocity (Fig. 3-43). Primary criteria for arteriogenic erectile

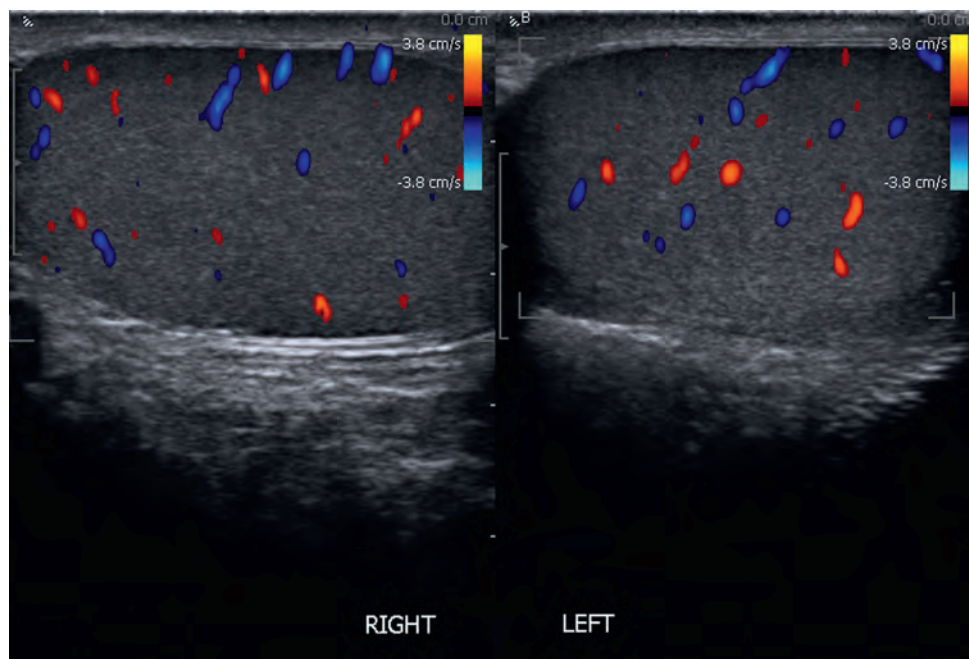


Figure 3-39. Demonstration of normal bilateral intratesticular blood flow by color Doppler.

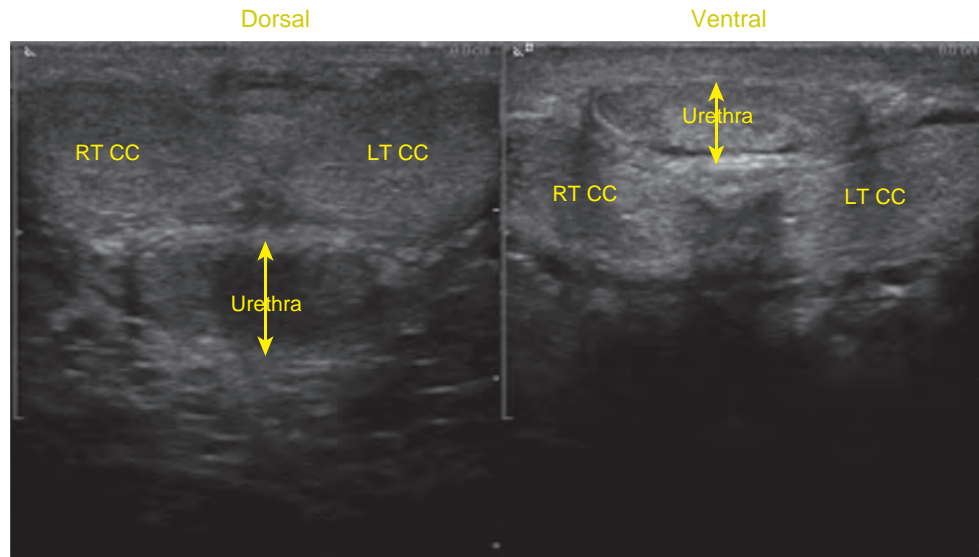


Figure 3-40. Transverse view of the phallus with the transducer placed either on the dorsal or the ventral surface. Note the compression of the urethra and corporal spongiosum compression in the ventral projection with minimal pressure applied to the phallus. CC, corpora cavernosa.

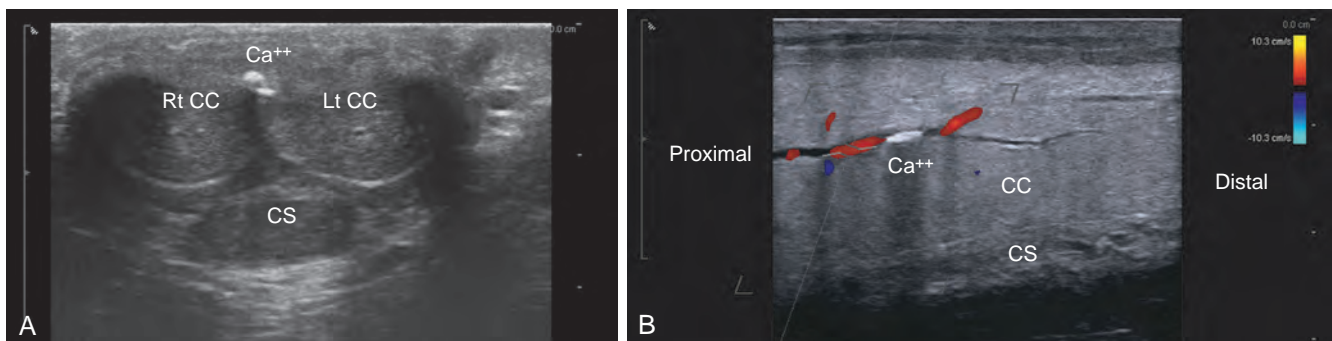


Figure 3-41. A, In the transverse plane scanning from the dorsal surface of the midshaft of the penis, the corpora cavernosa (CC) are paired structures seen dorsally, whereas the corpus spongiosum (CS) is seen ventrally in the midline. A calcification (Ca^{++}) is seen between the two CC with posterior shadowing. B, In the parasagittal plane, the corpus cavernosum (CC) is dorsal with the relatively hypoechoic CS seen ventrally. Within the CC, the cavernosal artery is shown with a calcification (Ca^{++}) in the wall of the artery and posterior shadowing.

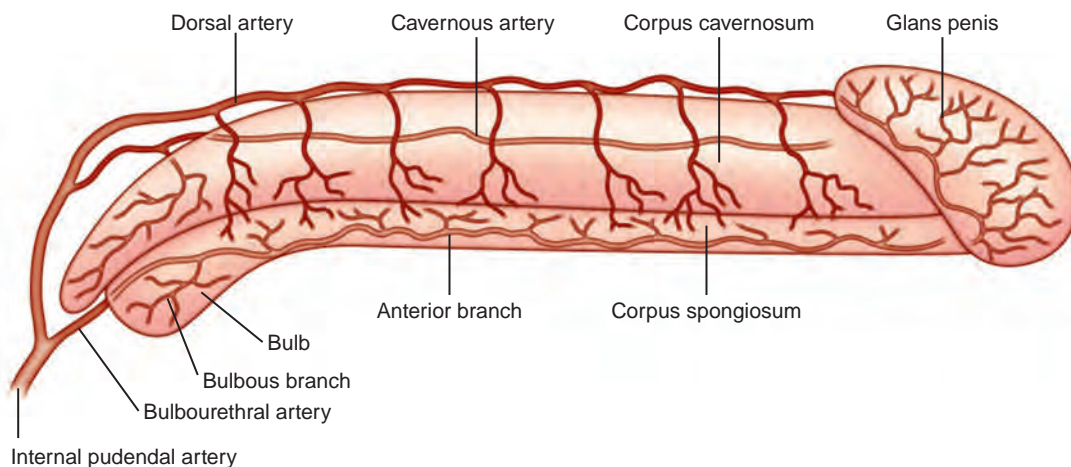


Figure 3-42. The internal pudendal artery gives rise to the bulbourethral artery, dorsal artery, and cavernous artery. The most proximal aspect of the cavernous artery is best imaged through the perineum. (From Gilbert BR. *Ultrasound of the male genitalia*. New York: Springer. In press.)

dysfunction include a PSV less than 25 cm/sec, cavernosal artery dilation less than 75%, and acceleration time greater than 110 msec. In cases of equivocal PSV measurements, particularly when PSV is between 25 cm/sec and 35 cm/sec, additional criteria are asymmetry of greater than 10 cm/sec in PSV comparing the two cavernosal arteries, focal stenosis of the cavernosal artery, and cavernosal-spongiosal flow reversal (Benson et al, 1993).

In addition, arteriogenic erectile dysfunction has been found to correlate directly with other systemic cardiovascular diseases,

including coronary artery disease and peripheral vascular disease, in many population studies. PSV is the most accurate measure of arterial disease as the cause of erectile dysfunction. The average PSV after intracavernosal injection of vasoactive agents in healthy volunteers without erectile dysfunction ranges from 35 to 47 cm/sec, with a PSV of 35 cm/sec or greater signifying arterial sufficiency after pharmacostimulation (Lue et al, 1985; Mueller and Lue, 1988; Benson and Vickers, 1989; Shabsigh et al, 1990; Broderick and Lue, 1991; Pescatori et al, 1994; Schaeffer et al, 2006). The first indication of vascular disease often can be the penile cavernosal artery being less than 1 mm. The finding of arteriogenic dysfunction can often provide a window of opportunity (Miner, 2011) to identify and potentially to alter the progressive nature of systemic vascular disease (Montorsi et al, 2006; Gazzaruso et al, 2008; Seftel, 2011).

Assessment of penile curvature most often involves palpation and ultrasound interrogation of the phallus after pharmacostimulation. However, a palpable plaque is not easily identified (Prando, 2009; Kalokairinou et al, 2012). In many cases, standard B-mode and color Doppler ultrasound modalities often do not localize pathology. Sonoelastography (tissue elasticity imaging) evaluates the stiffness of biologic tissues and localizes these nonpalpable lesions not visualized on ultrasonography for potential treatment (Fig. 3-44) (Richards et al, 2014).

Limitations

The complete evaluation of the penile urethra, corpora cavernosa, and corpus spongiosum requires a dorsal or ventral interrogation of the exposed phallus and a perineal approach to the nonexposed portions of the phallus; this is particularly important in evaluation of the bulbourethra and proximal corpora. In addition, the evaluation of erectile dysfunction requires qualitative and quantitative measurements of blood flow in the penile arteries. Such evaluation requires blood flow measurements before and after intracavernosal injection of vasoactive substances.

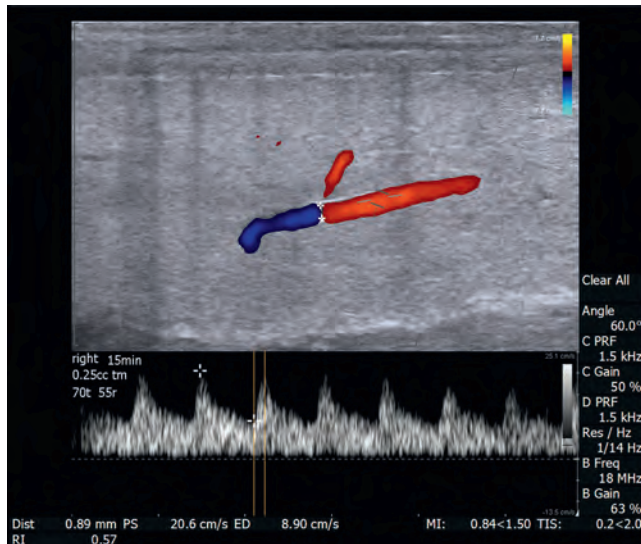


Figure 3-43. Longitudinal view of the right corpora cavernosa demonstrating peak systolic and end-diastolic flow velocity in the right cavernosal artery, which measures 0.89 mm in diameter.

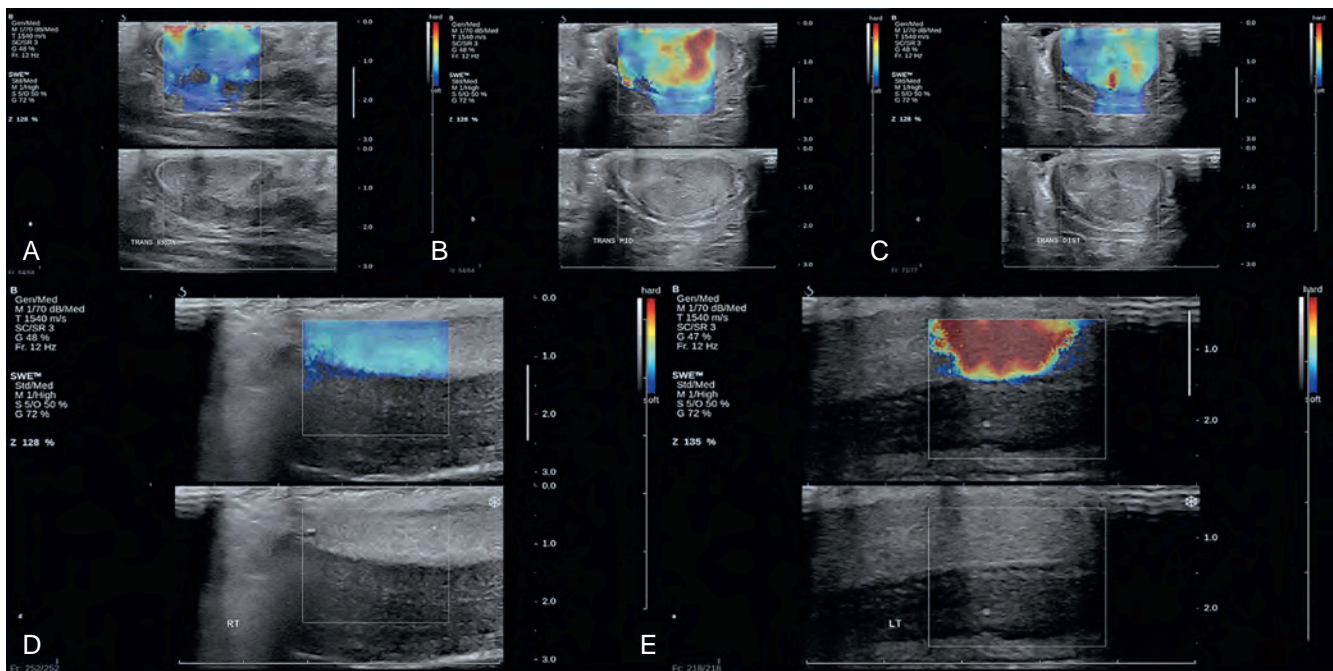


Figure 3-44. Sonoelastograms (scaled with red more firm and blue less firm) superimposed over transverse B-mode ultrasound images of the (A) proximal, (B) mid and (C) distal phallus. Sonoelastograms superimposed over parasagittal views of the (D) right and (E) left cavernosal bodies. (From Richards G, Goldenberg E, Pek H, Gilbert BR. Penile sonoelastography for the localization of a non-palpable, non-sonographically visualized lesion in a patient with penile curvature from Peyronie's disease. *J Sex Med* 2014;11:516–20.)

Transrectal Ultrasonography of the Prostate

TRUS of the prostate is the sonographic imaging procedure most commonly performed by urologists (Trabulsi et al, 2013). It is minimally invasive and provides exquisite anatomic detail of the prostate and periprostatic tissues. An overview is presented here of transrectal prostate imaging. A comprehensive discussion is provided in Chapter 109. TRUS performed by the urologist enhances patient care by providing a minimally invasive procedure that gives real-time information for a rapid and accurate diagnosis.

Technique

A systematic scan insures that a comprehensive examination is performed and appropriately documented. A high-frequency 7.5- to 10-MHz transducer is usually used. This can be a biplanar or single-plane transducer (i.e., “end fire” or “side fire”).

It is essential to perform a digital rectal examination **before** inserting the ultrasound probe. Pain or tenderness, rectal stricture, mass, lesion, or bleeding that is encountered when performing the rectal examination or when inserting the probe might preclude TRUS.

After probe insertion, a “survey” scan is performed of the prostate from base to apex including the seminal vesicles and rectal wall. The seminal vesicles are then examined in the transverse plane for comparative evaluation of echogenicity and measurements of seminal vesicle height and ampulla (vas deferens) diameter. Next, the midsagittal transverse and longitudinal image of the prostate is examined, and anteroposterior, height, and length measurements are taken. Prostate volume, predicted prostate-specific antigen (PSA), and PSA density can be calculated usually by formulas already programmed in the ultrasound machine. As in many urologic applications of sonography, color Doppler can add valuable information.

The rectal wall thickness must be evaluated and documented as well as any other notable findings (Trabulsi et al, 2013). Rectal cancer, polyps, and inflammatory processes require further evaluation. The appearance of rectal abnormalities should be documented, and a referral may need to be made.

Indications

1. Measurement of prostate volume for determination of PSA density
2. Abnormal digital rectal examination
3. Prostatic assessment with sonographic controlled biopsy
4. Cysts
5. Evaluation for and aspiration of prostate abscess
6. Assessment for suspected congenital abnormality
7. Lower urinary tract symptoms
8. Pelvic pain
9. Prostatitis or prostatic dysplasia
10. Hematospermia
11. Infertility (e.g., azoospermia)
 - a. Low volume or poorly motile specimen
 - b. Cysts
 - c. Hypoplastic or dilated seminal vesicle
 - d. Impaired motility
 - e. Antisperm antibodies

Normal Findings

Echogenicity is best evaluated by comparing the left and right sides of the prostate (Fig. 3-45). In a young man, TRUS is often indicated in the evaluation of subfertility. The young male prostate is homogeneous with zones often difficult to visualize. The “sonographic capsule” can be identified because of the impedance difference between the prostate and surrounding fat. The prominence of the urethra (“u” in Fig. 3-45) is related to the surrounding low reflectivity of urethral muscles. In the young male prostate,

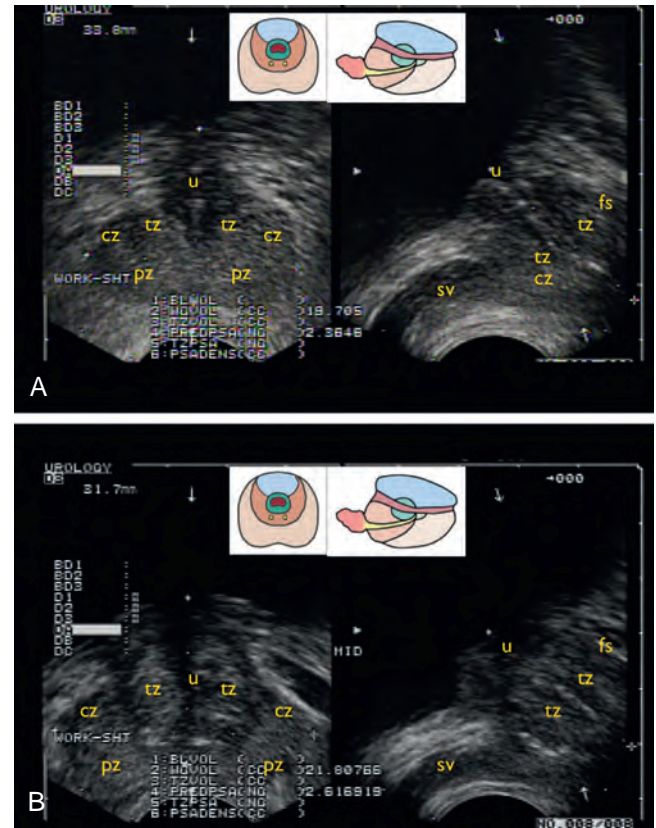


Figure 3-45. A, Young male prostate. The peripheral zone (pz) is often hyperreflective to the central (cz) and transition (tz) zones. The cz and tz are difficult to differentiate from each other, and the fibromuscular stroma (fs) is positioned anterior to the urethra. B, Older male prostate. The glandular and stromal elements enlarge increasing the size of the tz and occasionally pz. The tz is seen independent of other zones, and the cz is difficult to visualize.

the peripheral zone (“pz” in Fig. 3-45) is often hyperreflective to the central and transition zones (“cz” and “tz” in Fig. 3-45). The central and transition zones are difficult to differentiate from each other, and the fibromuscular stroma (“fs” in Fig. 3-45) is positioned anterior to the urethra. In an older man, the glandular and stromal elements enlarge increasing the size of the transition zone and occasionally the peripheral zone. The transition zone is seen independent of other zones, and the central zone is difficult to visualize.

The base of the prostate is located at the superior aspect of the prostate contiguous with the base of the bladder. The apex of the prostate is located at the inferior aspect of the prostate continuous with the striated muscles of the urethral sphincter.

Procedural Applications

Biopsy of the prostate guided by TRUS is most often initially performed for a specific clinical indication, such as an elevation or change in the PSA or an abnormal digital rectal examination (Porter, 2013). High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation on an initial biopsy specimen are considered by some clinicians to be indications for immediate or planned repeat biopsy. TRUS biopsy may be performed for an increasing PSA after initial therapy. In the case of a patient with an increasing PSA after radical retropubic prostatectomy, ultrasonography and biopsy of the prostatic fossa and vesicourethral anastomosis may be performed to aid in diagnosis of local recurrence. TRUS biopsy is performed after radiation therapy or cryotherapy to aid in diagnosis of local treatment failure.

Prostatic cyst aspiration is a therapeutic procedure easily performed in the office with minimal patient discomfort. It is often indicated when a large midline cyst obstructs the ejaculatory ducts resulting in dilation of the ejaculatory ducts or seminal vesicles or both. Refilling of the cyst is common.

Limitations

Bowel preparation is sometimes necessary for imaging. In addition, the patient's body habitus might make it difficult to image the base of the prostate, seminal vesicles, and bladder adequately. Current technology limits the diagnostic capabilities of TRUS to anatomic anomalies.

PRACTICE ACCREDITATION

When performing office ultrasonography, urologists must be committed to ensure that equipment, sonographers, and protocols are able to provide high-quality diagnostic information. Likewise, patients rightfully expect that the ultrasound examination performed uses equipment that is safe and can effectively image the organ of interest. In addition, third-party payers have instituted requirements for practices, including urology practices, to follow to be compensated for their work in providing ultrasound imaging services. One way the urologist sonographer ensures that his or her ultrasound examination is compliant with current standards and protocols is through practice accreditation. There are presently two acknowledged accrediting agencies: the American College of Radiology (ACR) and the American Institute for Ultrasound in Medicine (AIUM). The AUA and the AIUM have partnered to develop a pathway whereby urology practices can obtain accreditation that is recognized by regulatory authorities and third-party payers.

There are few laws regulating the performance and interpretation of ultrasound examinations. Any licensed physician may purchase an ultrasound machine and begin performing and interpreting sonograms. To ensure quality of an ultrasound examination, the ACR and the AIUM began to develop programs in 1995 to accredit ultrasound practices, and the two organizations accredited the first ultrasound practices in 1996. As of this writing, there are 4401 practices (each site applies as a single practice) with ACR ultrasound accreditation and 1210 (a total of 2039 sites) with AIUM ultrasound accreditation.

The ACR offers ultrasound practice accreditation in breast, general, gynecologic, obstetric, and vascular ultrasonography. The AIUM offers ultrasound practice accreditation in abdominal/general, breast, dedicated musculoskeletal, dedicated thyroid/parathyroid, gynecologic, fetal echocardiography, obstetric, and more recently urologic ultrasonography.


How does ultrasound practice accreditation differ from AUA board certification? Certification is granted to an individual who has demonstrated a level of knowledge and who continues to meet the requirements necessary to maintain the certification. The individual remains certified regardless of where he or she works. Accreditation is granted to a practice (which may be the practice of a solo practitioner) that demonstrates that all of the individuals in the practice, all the relevant policies and procedures, and equipment and maintenance meet certain requirements. Practices must continue to demonstrate compliance at regular intervals, regardless of whether there are changes in personnel, policies, or equipment. An individual who works in an accredited practice cannot go to another practice and claim that the services provided at the second facility are accredited.

The process of practice accreditation is not without challenges to both the urologists and the urology practice. Urologists have traditionally viewed imaging as a tool, similar to a stethoscope, that assists them in providing care for their patients. The process of accreditation changes this traditional view by requiring both the urologist and the urology practice to expend resources to meet the requirements of accreditation. However, the accreditation process


helps organize the approach to the ultrasound examination and markedly improves quality. This translates into improved diagnostic ultrasound examinations and improved patient care ([Abuhamad and Benacerraf, 2004](#)).

KEY POINTS

- An ultrasound wave is a mechanical wave that creates alternating areas of compression and rarefaction in tissue.
- Axial resolution improves with increasing frequency of the ultrasound wave.
- Depth of ultrasound penetration decreases with increasing frequency.
- Optimal ultrasound imaging requires tradeoffs between resolution and depth of penetration.
- Artifacts may be helpful in the diagnosis of certain conditions.
- The appropriate number of images to be captured for documentation is the number necessary to document a systematic and complete examination and to document relevant pathology.
- The mechanical index and the thermal index are not safety limits.
- The ALARA principle is intended to limit the total energy imparted to the patient during an examination.
- The most important factor in ultrasound safety is the informed operator.
- Angiomyolipoma has a characteristic hyperechoic appearance, but some renal cell carcinomas are also hyperechoic.
- Although ultrasonography is used in automated measurement of bladder volume or residual urine, this is not an imaging study.
- Sonoelastography extends the ability of ultrasonography to detect "hardness" of a lesion.
- The hallmark of testicular torsion is the absence of intratesticular blood flow. However, ultrasonography cannot diagnose torsion—only the surgeon or the pathologist can.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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4

Outcomes Research

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Access to Care

Costs of Care

Quality of Care

Health-Related Quality of Life

Health Services Research Methodologies

Future Implications

Health services research, often loosely described as *outcomes research*, is the study of the end results of health services, taking into account patient preferences, values, and experiences (Ware, 1984; Clancy and Eisenberg, 1998). It focuses on access to care, cost of care, quality of care, health systems, and population health (Epstein and Sherwood, 1996; Israel et al, 1998; Kane, 2006; Minkler and Wallerstein, 2008).

ACCESS TO CARE

Access to care includes the “actual use of personal health services and everything that facilitates or impedes their use. It is the link between health services systems and the populations they serve” (Aday and Andersen, 1974; Andersen et al, 2002; Andersen and Davidson, 2007). Improving access can reduce mortality, increase self-reported health, and decrease delays in care (Zweifel et al, 2011; Sabik, 2012; Sommers et al, 2012). Variations in access correlate with variable quality, including receipt of preventive care (Radley and Schoen, 2012). As certain aspects of urologic care become centralized, access to care is an increasingly important issue in urology (Stitzenberg et al, 2012).

Andersen presented a behavioral model for considering health care access in which three categories of factors determine how and whether individuals use medical services (Andersen and Davidson, 2007). These include predisposing factors (e.g., health beliefs, attitudes); enabling factors (e.g., health insurance, geographic proximity); and need factors (e.g., the presence of symptoms or diseases) (Northam, 1996; Shaw, 2012). Barriers to health care access often result from financial determinants such as the lack of health insurance or adequate income; logistic challenges in coordinating child care, public transportation, and work schedules; clinic waiting times; and difficulties with the geographic proximity of clinics and hospitals (DeVoe et al, 2007; Carrillo et al, 2011; Parikh et al, 2012). Adequate access requires more than a guarantee of payment for services; even with generous benefits, individuals must navigate nonfinancial barriers. Among these are minority status (Mandelblatt et al, 1999; Rosenbaum et al, 2000; Lurie and Dubowitz, 2007; Barocas et al, 2013a; Dickson et al, 2013; Flores and Lin, 2013); gender (Li et al, 2007; Kullgren et al, 2012; Ghani et al, 2013; Kates et al, 2013); sexual orientation (Buchmueller and Carpenter, 2010; Ponce et al, 2010; Mattocks et al, 2014; McKimman et al, 2013); environmental factors (Davidson et al, 2004; Capezuti et al, 2012); health behaviors (Andersen, 1995; Lasser et al, 2006; Stringhini et al, 2010); acculturation, language, and citizenship (Derose et al, 2009; Kinsler et al, 2009; Zambrana and Carter-Pokras, 2010; Wright et al, 2013); provider proximity (Cordasco et al, 2011; Paquette et al, 2011); available safety-net services (Katz, 2010; Cordasco et al, 2011; Katz and Brigham, 2011; Ku et al, 2011; Chatterjee et al, 2012; Spatz et al, 2012); and the absence of a usual source of care (Phillips et al, 2009; Bodenheimer and Pham, 2010). Even in health care

systems that are considered to provide “equal access,” such as the U.S. Department of Veterans Affairs hospitals, different patient groups use outpatient and inpatient care at markedly different rates, leading to variations in outcomes (Jha et al, 2001; Kizer and Dudley, 2009; Frayne et al, 2013).

In this context, differential access to care has been proposed as an important determinant of racial and ethnic disparities in prostate cancer screening, treatment, morbidity, and mortality (Moul et al, 1995; Optenberg et al, 1995; Klabunde et al, 1998; Stitzenberg et al, 2012; Barocas et al, 2013a). Discrepancies in accessibility and continuity of medical care may explain the lower use and awareness of prostate-specific antigen (PSA) testing among Hispanic men in the United States (McFall, 2006; Spencer et al, 2006; McFall, 2007); it remains unknown whether access or continuity issues mediate the greater dissatisfaction with prostate cancer treatment decisions among Hispanic men (Hoffman et al, 2003; Resnick et al, 2013a). Access to health care reflects not only the potential for entry into the health care system, but also the actual consumption of services. In one public-assistance program for low-income, uninsured men with prostate cancer, special attention to overcoming the financial and nonfinancial barriers has eliminated racial and ethnic disparities in health services use (Miller et al, 2008a). Nonetheless, because men from historically disadvantaged groups often do not access adequate and timely care, they continue to suffer a disproportionate burden (Miller et al, 2009a).

COSTS OF CARE

The cost of medical care may be measured in many ways. Although it is difficult to put a price tag on the toll of human suffering, physicians today are asked to reduce costs, improve quality, and provide services for greater numbers of patients in an increasingly austere environment. This often requires rationing of resources, though it is seldom explicitly labeled as such. In the present era of sweeping change in health care financing and health services delivery, increasing emphasis has been placed on efficiency in the allocation of scarce medical resources. The field of medical economics is well beyond its nascence, and broad public interest has emerged in studying the costs of medical and surgical therapies. As we spend more administrative dollars on cost containment, scrutiny is reaching all potential areas for conservation, including oncology—a province once considered sacred and off limits to cost-cutting efforts.

Health policy decisions today must be based not only on biomedical research but also on sound evaluations of health care costs. The use of oral erectogenic medications, beginning in the late 1990s, provides a perfect illustration of the tension between therapeutic advances and economic forces. The scientific discoveries that led to the advent of sildenafil and similar agents (Rajfer et al, 1992) were rewarded with a Nobel Prize, yet insurers initially fervently

resisted paying for them (McGarvey, 2000; Smith and Roberts, 2000). This led to widespread controversy, generated numerous studies, and even raised questions of constitutional law (Finley, 1999; Julka, 1999; Connolly, 2001; Haff, 2006; Ki and Kim, 2008). As a surgical subspecialty whose practitioners have discovered and use several exciting but expensive new drugs (Kantoff et al, 2010; de Bono et al, 2011; Fizazi et al, 2011; Cabot et al, 2012; Parker et al, 2013), urology is at the forefront of helping patients make rational health care choices and balance competing priorities. Urologists must be especially conscientious and evidence based in advocating for new and expensive therapies, given the human toll (Gore et al, 2009a; Huang et al, 2010; Johansson et al, 2011; Song et al, 2011; Holmberg et al, 2012; Harden et al, 2013) and economic ramifications (Bolenz et al, 2010; Krahn et al, 2010; Andersson et al, 2011; Nguyen et al, 2011; Lowrance et al, 2012b) of overtreatment of indolent prostate cancer (Daskivich et al, 2010a, 2010b, 2011a, 2011c; Chamie et al, 2012a) over the past two decades.

Terms and Methods of Analysis

In its purest form, research on health care costs involves counting the amount of money that is spent on facilities, equipment, supplies, and personnel during the provision of medical care. But many costs are hidden. A more extensive approach would also include the opportunity cost of the time patients spend receiving care. For example, when estimating the cost of an interval cystoscopy after resection of a bladder tumor, a thorough assessment would include not only the cost of overhead, supplies, lidocaine jelly, urine cytology, and professional fees, but also the cost to the patient in lost wages—or to his or her employer in lost productivity—during the time away from work for the procedure, travel, or any complications. This component is not insignificant. Employee absence from work has been estimated to cost U.S. businesses tens of millions of dollars annually (Loeppke et al, 2009; Volpp et al, 2011; Zhang et al, 2011).

Because true costs are difficult to quantify at the individual, institutional, or population level, researchers instead often report data on charges. *Charges* represent the amount that is billed for a service, whereas *costs* reflect what the provider spent to supply that service. Most of the available administrative databases in health care are based on either financial discharge abstracts from hospitals or claims data from large payers, insurance companies, or government agencies such as the Centers for Medicare and Medicaid Services. These data sets primarily include information on charges and payments, but not costs. The major advantage of using charge data is that they are much easier to obtain. The primary disadvantage is that they may not accurately reflect the true underlying costs of individual medical services. For example, a hospital that is losing money on magnetic resonance imaging may make up the deficit by increasing its charges for urine cytology procedures. This practice may help balance the annual budget, but it corrupts the quality of the charge data. An economic analysis using charges for bladder cancer follow-up in such a hospital will err by incorporating the inflated amounts charged for interval urine cytology procedures. Some analysts attempt to circumvent this problem by calculating a ratio of costs to charges for entire facilities, individual medical services, or diagnosis-based categories of care. Charges are frequently used to estimate the amount of money spent on health care, although such calculations are imperfect. To avoid the inherent problems in calculating costs and charges, some researchers instead measure *resource utilization* in terms of duration, frequency, and intensity of services (Washburn et al, 2006; Unroe et al, 2010).

One of the most commonly reported units of comparative analysis is length of stay (LOS). After 1983, when the prospective payment system was instituted to reimburse hospitals a predetermined amount of money on the basis of the diagnosis-related group (DRG) into which each Medicare inpatient is classified (Vladeck, 1984; Hsia et al, 1988; Goldfield, 2010), attention to LOS as an outcome variable in cost analyses greatly increased. In the United States, inpatient LOSs are now believed to have reached their floor, and effort has shifted from this measure. Costs of care may be

measured as intensity or numbers of services provided. For example, rather than calculating the costs or charges for a 3-day hospitalization for radical nephrectomy, analysis may be based on the total number of complete blood counts, chest radiographs, bags of intravenous fluid, doses of antibiotic, and doses of narcotic and antibiotic ordered on any given day of the hospital stay or during the entire stay. By examining duration or frequency of medical services when studying costs, researchers can avoid the biases involved in using financial data. Although the overall costs of diseases such as bladder cancer are high (James and Gore, 2013), opportunities for quality improvement often go hand in hand with cost reduction when pharmacoeconomics are considered (Gore and Gilbert, 2013).

Cost-effectiveness analysis is another popular technique used to evaluate new or established medical therapies. Ideally, preventive care can obviate the need to treat a disease by preventing its onset, and the cost of prevention can be compared with the cost of disease treatment (Maciosek et al, 2010). Alternatively, a cost-effectiveness analysis is performed by developing a probability model of the possible medical outcomes of one intervention compared with another, such as sacral neuromodulation versus medication for storage symptoms (Anger et al, 2014), or with a nonintervention such as watchful waiting for benign prostatic hyperplasia (Saigal and Joyce, 2005; Bellinger et al, 2012; Strope et al, 2012), identifying the expenses associated with each outcome, and comparing the results, typically reported as cost per year of life saved (Lee et al, 2009; Binagwaho et al, 2010; MacKenzie et al, 2010; Wheeler et al, 2010; Ciaranello et al, 2013). Years of life saved, or *life years (LYs)*, are calculated for a population, not for individuals. Ten LYs might represent two patients, each of whom survives for 5 additional years, or 120 patients, each of whom survives for 1 additional month (Baker et al, 2010; Jia and Lubetkin, 2010; Soerjomataram et al, 2012). LYs are usually adjusted to account for different health states that may result from various treatments. These are called *quality-adjusted life years (QALYs)*. For example, when comparing two treatments for localized prostate cancer, if both options are determined to cost \$10,000 per year of life saved, then the two may seem equivalent. However, if one treatment yields years that are compromised by bothersome sexual dysfunction (Le et al, 2010), whereas the other yields years that are free of such problems, then the difference in quality of the years saved must be factored into the equation. Analyses that rely on QALYs are facilitated by the estimation of patient utilities, or preferences, for various health states (Albertsen et al, 1998; Saigal et al, 2001, 2002; Owens and Shekelle, 2013). If patients appraise an impotent year as being worth less than a potent year, then quality adjustments may make the first treatment more expensive per QALY saved. Couples approached 1 year after treatment for prostate cancer were found to be willing to pay approximately \$800 per month for a hypothetical new treatment that cures prostate cancer without side effects (Zeliadt et al, 2010, 2011; Ramsey et al, 2011; Li et al, 2012).

Cost-benefit analysis differs by including not only the costs but also the equivalent monetary value of any benefits garnered during the extra years of life. Often, this refers to wages earned or income accrued during that time. In more sophisticated analyses, future income and expenses related to a particular health state are discounted to present value by incorporating projected interest and inflation rates over time. Reducing cost in the treatment of one disease liberates resources to invest in exciting new projects (Beheshtian and Yel, 2005; Chu et al, 2012). Cost studies may be undertaken as descriptive analyses that chronicle the economic burden of one disease in a group of patients, such as the cost of care for interstitial cystitis in a managed care plan (Clemens et al, 2009; Anger et al, 2011; Beckett et al, 2014). They may examine the financial impact on the general population such as national annual expenditures for urolithiasis (Raman et al, 2010; Lotan and Pearle, 2011; Lotan et al, 2012; Sutherland et al, 2013). They may also track cumulative costs over time, such as for different prostate cancer treatments (Krahn et al, 2010; Snyder et al, 2010; Krahn et al, 2014). Alternatively, they may present economic models comparing different approaches to managing an illness, such as whether it is more

costly to correct cryptorchidism in infants or in older boys (Hsieh et al, 2009), or to manage small renal tumors with laparoscopic or percutaneous cryoablation (Bensalah et al, 2008; Hui et al, 2008; Pandharipande et al, 2008; Panumatrassamee et al, 2013).

Value of Care

The cost of health care should be considered in the context of the outcomes it produces. The “value” of a health care service or intervention is defined as quality divided by cost (Porter, 2010; Weinberger, 2011). Outcomes are more relevant than services rendered, or health care inputs, because significant health inputs without good outcomes do not produce value (Kaplan and Porter, 2011; Berwick and Hackbarth, 2012). Considering cost in the context of value can help policy makers decide which interventions should be amplified and which may be reduced (Orszag and Emanuel, 2010). The ultimate reflection of value is life expectancy divided by cost. The Organisation for Economic Co-operation and Development (www.oecd.org) reports these outcomes. Among 34 participating countries, the United States ranks first in total health expenditures per capita and 26th in life expectancy (Auerbach and Kellermann, 2011; Fuchs, 2013; van Baal et al, 2013). Among 28 participating countries reporting public expenditure on education and 24 describing tertiary education rates, the United States ranks 16th and 15th, respectively (Hudson and Kühner, 2009; Mahon, 2013).

Patterns of Care

Variations in patterns of care are vast, and incompletely understood. The Dartmouth Atlas Project has studied practice patterns most broadly, and for over 20 years has documented glaring variations in distribution and use of medical resources in the United States (Hudson, 1996; Wennberg, 1998). The project uses Medicare data to provide information and analysis about national, regional, and local markets, as well as hospitals and their affiliated physicians. Data from the project demonstrate significant variation among different regions of the country (Weinstein et al, 2006; Wennberg et al, 2008; Wennberg, 2011), especially at the end of life (Morden et al, 2012; Prigerson and Maciejewski, 2012) and often incongruously with patient preferences (Keating et al, 2010; Mitchell, 2010; Patel and Schulman, 2012). That variation in health care spending does not correlate with outcomes suggests that good outcomes can be achieved with lowered cost, and that current spending can be targeted more thoughtfully. In urology, significant hospital-level variation exists in outcomes and readmission after surgery (Gore et al, 2012).

Performance of appropriate and inappropriate procedures often varies concomitantly, as is the case with imaging of men with prostate cancer. Regions with higher rates of indicated imaging also have higher rates of extraneous imaging, and those with lower rates of unnecessary scans have lower rates of appropriate utilization (Lavery et al, 2011; Makarov et al, 2012a, 2012b). National efforts to decrease inappropriate imaging by disseminating utilization data and imaging guidelines to urologists can lead to meaningful decreases in unsupported imaging, but may also reduce appropriate use among high-risk patients (Makarov et al, 2013). Meaningfully improving practice patterns requires fastidious collaboration (Miller et al, 2010, 2011).

Regional variation in bladder cancer cost and outcomes has been noted, with higher-spending regions using more services and interventions, but lower-spending regions demonstrating superior cancer-specific survival (Skolarus et al, 2010). Significant regional variation also exists in the cost of radical prostatectomy (Makarov et al, 2010). Clearly, practice patterns are not always driven by data. For instance, acquisition of a surgical robot increases the number of both robotic and open prostatectomies performed in a hospital referral region (Makarov et al, 2011; Stitzenberg et al, 2012), and increases in surgical treatment of prostate cancer are both geographically and temporally related to acquisition of robotic surgical systems (Makarov et al, 2011; Lowrance et al, 2012a; Stitzenberg

et al, 2012). The increase in the overall number of surgical prostatectomies performed raises concern of overtreatment of men who would otherwise die with, rather than of, their disease (Burgess et al, 2006; Tewari et al, 2006; Steinberg et al, 2008; Andriole et al, 2009; Hu et al, 2009; Hugosson et al, 2010; Andriole et al, 2012; Carter et al, 2012a, 2013b; Huang et al, 2013; Laviana and Hu, 2013; Bolenz et al, 2014). Concerning patterns abound beyond cancer care. Opening of ambulatory surgery centers is associated with increased use of discretionary surgery (Strope et al, 2009; Hollingsworth et al, 2010, 2011; Schroek et al, 2012), and introduction of physician ownership of lithotripter units influences treatment selection (Tan et al, 2011).

Conversely, some evidence-based advances have diffused much more slowly. Adoption of laparoscopic approaches to radical nephrectomy is variable, as is quality of kidney cancer care (Harper et al, 2012). Diffusion of evidence-based technologies and practices is limited by physician preferences, as is the case with partial or laparoscopic nephrectomy for small renal masses (Miller et al, 2006; Morris et al, 2007; Miller et al, 2008b) or continent reconstruction after cystectomy (Gore et al, 2006). Patient age and physician variables do affect practice patterns (Quinn et al, 2009; Cooperberg et al, 2010; Dulabon et al, 2010; Bleich et al, 2011; Klabunde et al, 2013).

The National Institute of Diabetes and Digestive and Kidney Diseases funds the Urologic Diseases in America project (www.udaonline.net), which seeks to define the burden of urologic disease on the American public by quantifying trends in resource usage, practice patterns, costs, outcomes, and epidemiology across the spectrum of urologic conditions (Litwin et al, 2005a, 2005b; Miller et al, 2009b). Documenting these trends has broad implications for quality of health care, access to care, and the equitable allocation of scarce resources, in terms of both medical services and research budgets. Among the most financially burdensome urologic conditions are urolithiasis (Scales et al, 2011), urinary tract infection (Griebing, 2005a, 2005b; Carter et al, 2012b), urinary incontinence (Anger et al, 2006a, 2006b, 2006c; Rogo-Gupta et al, 2013), and benign prostatic hyperplasia (Nickel, 2006; Roehrborn et al, 2011b; Stewart et al, 2012). Urologic diseases exert a substantial impact on resource usage within the U.S. Veterans Affairs health system (Anger et al, 2008).

Analyses from the Urologic Diseases in America project have revealed not only disturbing trends and variations in care, but also avenues for potential improvements for both benign and malignant disease. Surgical quality among Medicare beneficiaries undergoing outpatient urologic surgery varies by location of care delivery (Hollingsworth et al, 2012a). The prevalence of kidney stones has increased sharply, particularly in black, non-Hispanic and Hispanic individuals, and now affects 1 in 11 people in the United States (Scales et al, 2012). Once an individual has been diagnosed with a kidney stone, treatment varies significantly, often driven by nonclinical factors associated with provider and/or patient preferences or experience (Scales et al, 2011). In bladder cancer, delays before radical cystectomy can increase mortality (Gore et al, 2009b), and use of radical cystectomy varies by clinical and sociodemographic factors (Gore et al, 2010b). Adherence to guideline-recommended bladder cancer care is poor (Chamie and Litwin, 2011; Chamie et al, 2011; Chamie et al, 2012b). One exciting positive avenue for expansion is smoking cessation: smokers newly diagnosed with bladder cancer are five times as likely as the general population to quit smoking, especially if counseled appropriately by their urologist (Bassett et al, 2012). For men with prostate cancer, patterns of care after failure of primary prostate cancer treatment depended on use of standardized clinical algorithms, initial therapy, and geographic region (Krupski et al, 2006). Patients with kidney cancer who are treated with partial rather than radical nephrectomy have fewer adverse renal outcomes, including less frequent receipt of dialysis services, dialysis access surgery, or renal transplantation (Miller et al, 2008c). These findings are consistent with a subsequent population-based study using instrumental variable analysis to assess outcomes after partial versus radical nephrectomy, which showed that for individuals with early-stage kidney

cancer, treatment with partial nephrectomy was associated with improved survival (Tan et al, 2012).

Case Mix

In studying patterns of care or medical costs, it is critical to adjust for case mix. *Case mix* refers to the severity of illness and degree of comorbidity in a group of patients (Iezzoni, 1989; Covinsky et al, 1997b; Birkmeyer et al, 2012; Maas et al, 2013). These characteristics may influence treatment outcomes. For example, because they typically have a greater burden of comorbidity, older patients are more likely to experience complications after surgery. This comorbidity must be accounted for in evaluations of clinical outcomes (Hong et al, 2010; Zelefsky et al, 2010; Epstein et al, 2011). Kidneys from donors older than 50 years may provide fewer years of service to their recipient (Ng et al, 2012). If these facts are not considered when comparing surgical complication rates across hospitals, evaluators may erroneously conclude that a hospital with an older patient population is providing poorer care. To use outcomes to measure quality of care, we need to adjust for these other factors including baseline patient characteristics and intervening treatments. This adjustment (referred to as *case-mix adjustment* or *risk adjustment*) can be extremely complex, and the selection of factors must be carried out carefully so that outcomes can be interpreted accurately. For a variety of reasons, sicker patients cost more, and it is important to control for this difference in comparative analyses. In examining the factors that lead to higher hospital charges for more ill patients, two forces must be considered: duration and intensity of care. Duration is usually quantified as inpatient LOS, whereas intensity of care may be assessed as numbers of services or charges per day. Patients with greater comorbidity may remain hospitalized longer even if they do not receive more intense care during their stays. Duration and not intensity appears to be the primary force driving up hospital charges for sicker urology patients (Litwin et al, 1993). Various comorbidity measures (Kaplan and Feinstein, 1974; Charlson et al, 1987; Stier et al, 1999; Crabtree et al, 2000; Di Gangi Herms et al, 2003; Daskivich et al, 2011b, 2011c, 2013a) have been used by researchers to adjust for case mix and predict mortality from competing causes in clinical studies.

The impact of case mix on urologic disease outcomes has been studied most broadly in men treated for prostate cancer. Comorbidity is more important than age in predicting perioperative mortality after radical prostatectomy (Alibhai et al, 2004, 2005; Chamie et al, 2012a; Daskivich et al, 2013b). Among men with high comorbidity, low- and intermediate-risk prostate cancer is overtreated (Daskivich et al, 2010a, 2011a, 2011b, 2011c, 2013a; Chamie et al, 2012a), and often with advanced treatment technologies that have not been shown to be superior to prior standards (Jacobs et al, 2013). Conversely, men with high-risk prostate cancer are undertreated across all levels of comorbidity (Chamie et al, 2012a; Daskivich et al, 2011a, 2013a, 2013b). A revised index that reweighs Charlson comorbidities can more accurately identify men at highest risk for non-prostate cancer mortality, and aid in medical decision making (Daskivich et al, 2011b, 2011c, 2013a).

Comorbidities such as obesity also affect the incidence and severity of benign urologic conditions, including urinary incontinence (Richter et al, 2010), chronic prostatitis and chronic pelvic pain syndrome (Anothaisintawee et al, 2011), benign prostatic hyperplasia and lower urinary tract symptoms (Schenk et al, 2010; Parsons et al, 2013), and erectile dysfunction (Chitale et al, 2009; Tsai and Sarwer, 2009). Weight loss meaningfully reduces incontinence in overweight and obese women (Subak et al, 2009; Smith et al, 2010), and lengthens life expectancy as well (Keating et al, 2009; Stewart et al, 2009; Majer et al, 2011).

Cost Savings in Urology

As the cost of health care expands (Sutherland et al, 2009; Kellermann and Weinick, 2012) and crowds out other societal priorities (Auerbach and Kellermann, 2011), urologists have continued their central role in the ongoing struggle to balance the

sometimes-competing priorities of minimizing costs and maximizing quality (Botteman et al, 2003; Lotan, 2009; Lotan and Pearle, 2011; Staskin et al, 2012). For common procedures, such as transurethral resection of the prostate, urologists standardized care and cut costs long before it was mandated by the government (Sage et al, 1988). They made similar improvements for radical prostatectomy (Kramolowsky et al, 1995a, 1995b; Konety et al, 1996) and nephrectomy (Wilson et al, 1995; Uzzo et al, 1999). Unfortunately, such initiatives were insufficiently broad and sustained (in urology and beyond) to achieve high-quality care at sustainable cost throughout health systems, and the government intervened to buttress efforts to minimize cost and maximize quality. Medicare's pay-for-performance program differentially reimburses hospitals, medical groups, and clinicians based on adherence to quality metrics and elimination of medical errors (Rosenthal et al, 2004; Kindig, 2006). The need to realign incentives was reinforced by the Institute of Medicine's report, *Rewarding Provider Performance: Aligning Incentives in Medicare*, which stated, "The existing systems do not reflect the relative value of health care services in important aspects of quality, such as clinical quality, patient-centeredness, and efficiency" (Fisher, 2006). It recommended pay-for-performance as an immediate opportunity to better align incentives for improved performance. Methods of standardizing care and improving quality include clinical pathways, which have maximized value for hematuria (Vasdev et al, 2012), incontinence (Romeyke and Stummer, 2012; Rotter et al, 2012), and prostatitis (Shoskes, 2008), among others.

As an extension of this concept, under the Patient Protection and Affordable Care Act of 2010 (which was almost fully implemented in 2014), Medicare fee-for-service is being restructured into "bundled payments." A bundled payment is a single payment for an episode of care, such as a radical prostatectomy, rather than reimbursement to individual entities or providers based on services rendered. An interesting historical footnote is that the first self-imposed bundled payment was taken on by the father of American urology, Hugh Hampton Young. In his autobiography, Dr. Young described a patient on whom he agreed to perform a prostatectomy in the 1920s for a fixed fee of \$500 with a promise of only 3 weeks in the hospital. Because the patient developed complications and remained hospitalized for much longer than planned, Young had to spend his entire professional fee plus an additional \$350 to pay off the hospital bill (Young and Didusch, 1940).

The Affordable Care Act also includes several incentive programs that should affect individuals with urologic diseases. For instance, the act supports participatory wellness programs, which would reimburse for the cost of membership in a fitness center, potentially mitigating the noxious effect of obesity on prostate cancer (Freedland et al, 2008a, 2008b; Jayachandran et al, 2008, 2009; De Nunzio et al, 2012; Gollapudi et al, 2012; Keto et al, 2012; Byrd et al, 2013; Wu et al, 2013). Likewise, it supports employees attending no-cost health education seminars, including smoking cessation classes, which has significant consequences for individuals with bladder cancer (Bassett et al, 2012).

QUALITY OF CARE

Quality of care research evaluates "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" (Brook and Lohr, 1981, 1985; Lohr, 1988; Lohr et al, 1988; Donabedian et al, 1989). The Institute of Medicine's landmark report *Crossing the Quality Chasm* outlined six principles that define high-quality health care: care that is safe, effective, efficient, patient-centered, timely, and equitable (Institute of Medicine, 2001). More recently, greater emphasis has been placed on efficiency, or value-based care, with value defined as patient-centered health outcomes divided by cost (Porter, 2010; Swensen et al, 2010; James and Savitz, 2011).

To reach a desired patient-centered health outcome, provided services must satisfy both content quality and delivery quality.

Content quality involves the technical component of health care and includes quality processes and metrics (James, 1989; Washington and Lipstein, 2011). It is defined and evaluated by health care providers. Delivery quality addresses interpersonal relationships on which delivery of health services are based, and is evaluated by patients and caregivers. Continuous quality improvement is the guiding principle for establishing a high-quality health care delivery system, and relies on an electronic health record system as well as on quality improvement oversight (Pham et al, 2007; Gabow et al, 2012; Cosgrove et al, 2013). An electronic health record system can improve quality on the front end with electronic order entry, built-in order sets, and standardized clinical care pathways, and on the back end with facile data abstraction and reports built around broad sets of quality outcomes (Gabow and Mehler, 2011; Cosgrove et al, 2012). Electronic systems are easily modifiable for changing metrics over time, and cloud-based systems allow sharing of information between inpatient and outpatient facilities, as well as with other institutions (Schweitzer, 2012). Compared with other industries, information technology has been less aggressively adopted in health care (Menachemi et al, 2006; Simon et al, 2007). As of 2008, fewer than 20% of physicians used an electronic health record (DesRoches et al, 2008; Jha et al, 2009). The Health Information Technology for Economic and Clinical Health Act of 2009, part of the government's stimulus package, provided funding for adoption and meaningful use of electronic health records, to achieve improvements in care (Blumenthal, 2009; Jha et al, 2009). Hospitals and physicians not using electronic health records by 2015 are subject to financial penalties under Medicare. Quality improvement oversight is typically undertaken by a quality improvement department, and involves data collection and monitoring systems, confidential reporting, and dashboards (Gabow et al, 2012). Such quality improvement projects have been piloted in urology but have not yet been implemented broadly (Gambone and Broder, 2007; Lee et al, 2011).

Descriptive quality measures abound, but for quality metrics to affect outcomes, they must be based on solid evidence, be feasible, and have resources devoted to tracking and improvement. In 2005, the U.S. Congress passed the Patient Safety and Quality Improvement Act, which helped reinforce ongoing quality improvement initiatives and also launched several new initiatives to collect and disseminate performance information about medical care (Patient Safety and Quality Improvement Act, 2005). For example, the ECRI Institute (www.ecri.org) collects and analyzes data about adverse events as well as near misses. The National Committee for Quality Assurance (www.ncqa.org) provides information to health care purchasers about the comparative performance of health plans in the United States. The Joint Commission (TJC, www.jointcommission.org) applies outcomes-based quality measures to accredited hospitals, and TJC accreditation is mandatory for participation in Medicare. Hundreds of performance indicators have been collected in its National Library of Healthcare Indicators, and a root cause analysis system was developed to understand the causes of sentinel events. The National Quality Forum (www.qualityforum.org/home.aspx) has focused on patient safety and endorsed six sets of "never events." The Leapfrog Group (www.leapfroggroup.org) includes almost 200 large private and public health care purchasers that attempt to leverage their purchasing power to influence quality and affordability. The Leapfrog Safe Practices Score assesses computer physician order entry, evidence-based hospital referral, and appropriate intensive care unit staffing. Leapfrog volume thresholds suggest that individuals undergoing radical prostatectomy at high-volume institutions have shorter LOSs and receive fewer blood transfusions compared with those treated at low-volume institutions (Penson, 2013). The Institute for Healthcare Improvement (www.ihl.org) is a nonprofit organization seeking to optimize health care performance by improving quality and patient satisfaction, improving the health of populations, and reducing the per capita cost of health care. The National Patient Safety Foundation (www.npsf.org) was formed in partnership between the American Medical Association and private industry to provide research support, education, and leadership training in

patient safety. It holds an annual Patient Safety Congress and publishes the *Journal of Patient Safety*. The Institute for Safe Medication Practices (www.ismp.org) aims to reduce medication error and operates an anonymous practitioner reporting program to understand the causes of medication errors and to eliminate them.

One of the most widely used performance measures, maintained by the National Committee for Quality Assurance, is the Healthcare Effectiveness Data and Information Set (HEDIS, www.ncqa.org/hedisqualitymeasurement). HEDIS's 75 measures are divided into eight domains: effectiveness, access/availability, experience, health plan stability, utilization and relative resource use, cost, informed health care choices, and health plan descriptive information. Consumers can use these data to compare the performance of health plans; the Centers for Medicare and Medicaid Services uses HEDIS to determine reimbursement for enrollees in Medicare Advantage. The broadest set of measures specific to surgery is the American College of Surgeon's National Surgical Quality Improvement Program (NSQIP) (Birkmeyer et al, 2008). The measures quantify risk-adjusted 30-day surgical outcomes, including mortality and morbidity in 21 categories. Collection and reporting of NSQIP measures have been shown to improve outcomes (Hall et al, 2009). Another often-used set of indicators is the Patient Safety Indicators (www.qualityindicators.ahrq.gov) published by the U.S. Department of Health and Human Services' Agency for Healthcare Research and Quality (AHRQ). The indicators focus on hospital and postoperative complications. On the basis of extensive reviews of available evidence, AHRQ developed four categories of quality indicators (prevention, patient safety, inpatient, and pediatric), which are now being used to modulate hospital and physician reimbursement.

Several consumer groups also publish health care performance metrics. The Foundation for Accountability (www.facct.org), a consumer organization, creates tools that help people understand and use quality information, develops consumer-focused quality measures, supports efforts to gather and provide quality information, and encourages health policy to empower and inform consumers. Consumer Reports uses Medicare billing data to rate surgical performance (www.consumerreportshealth.org); such approaches have been criticized for lacking critical clinical data (Conaboy, 2013). Families USA (www.familiesusa.org) is a nonprofit organization that produces health policy reports outlining problems from a consumer perspective and describing steps to solve them.

Quality Conceptual Framework

The conceptual framework for the measurement of quality of care in medicine was established almost 50 years ago by Donabedian (Donabedian, 1966). In this model, quality-of-care measures are categorized into three domains—structure, process, and outcome.

Structure of Care

Structure encompasses the fixed aspect of health care delivery and includes the space, equipment, human resources, and provider experience necessary to provide care. Examples include clinician characteristics (e.g., percentage of physicians who have board certification, average years of experience, distribution of specialties); organizational characteristics (e.g., staffing patterns, reimbursement method); patient characteristics (e.g., insurance type, illness profile); and community characteristics (e.g., per capita hospital beds, transportation system, environmental risks). Structural measures specific to prostate cancer quality could include the presence of a multidisciplinary cancer center or psychological support services (Spencer et al, 2003).

Although certain structural characteristics may be necessary to provide good care, they are usually insufficient to ensure high-quality care. Therefore the best structural measures are those that can be shown to have a positive influence on the process of care and on patient outcomes (Brook and McGlynn, 1996). One structural measure that is positively associated with outcomes is the number of patients treated by a particular physician or institution, especially for major procedures such as radical cystectomy

(Hollenbeck et al, 2007a, 2007b; Porter et al, 2011; Morgan et al, 2012) or radical prostatectomy (Siu et al, 2008; Trinh et al, 2013). Surgeon volume is also associated with structural covariates such as lymph node count at the time of robotic cystectomy (Marshall et al, 2013). Hospitals with higher lymph node counts have been shown to have higher survival rates after radical cystectomy (Hollenbeck et al, 2008). Patients with renal trauma are more likely to be offered conservative management and have a lower chance of requiring multiple procedures if they are treated at a level 1 trauma center (Hotaling et al, 2012).

Process of Care

Process of care is the set of activities that goes on between patients and practitioners and is often divided into interpersonal process and technical process. Examples include antibiotic prophylaxis and discussion of treatment options (Wolf et al, 2008). Process measures are often considered to be the best measure of quality (Brook and McGlynn, 1996; Brook et al, 2000), and the most fertile area for improvement in value (Schneider et al, 2004; Malin et al, 2006). *Interpersonal process* refers to how the clinician relates to the patient and includes issues such as whether the clinician supplies sufficient information in a clear enough manner for the patient to make an informed treatment choice. Patient survey data are generally used to assess quality of interpersonal process. *Technical process* refers to whether medically appropriate decisions are made when diagnosing and treating the patient and whether care is provided in an effective and skillful manner—for instance, selecting the correct operative repair for female urethral stricture disease (Ackerman et al, 2010). One way to evaluate the appropriateness of medical treatment is to determine if the care provided is consistent with current medical knowledge and adheres to the professional standard. This assessment can be done by developing *quality indicators*, such as those delineated earlier, that describe a process of care that should occur for a particular type of patient in a specific clinical circumstance. To be valid, these quality indicators should be based on the evidence in the medical literature and on current professional standards of care. Determining the latter often requires an expert panel to achieve consensus. The performance of physicians and health plans is then assessed by calculating rates of adherence to the indicators for a sample of patients. Using quality indicators to evaluate appropriateness of care is relatively straightforward. However, assessing the effectiveness or skill of technical process of care is much more difficult. Indeed, direct observation may be necessary to assess the quality of technical process of care. Alternatively, it may be necessary to rely on measuring outcomes to evaluate whether care was provided in a skillful manner. For example, measurement of surgical blood loss or number of specimens with positive margins, both surgical outcomes, may be indicators of the quality of surgical technical process. Conversely, operative time may represent the surgeon's manual dexterity or the technical complexity of a case. Hence celerity is not generally considered an accurate indicator of operative quality.

Outcomes of Care

Outcomes include changes in patients' current and future health status including health-related quality of life (HRQOL) and satisfaction. Cancer researchers generally use survival or progression-free survival as the main outcome measure in clinical studies. Sometimes proxy measures (also called *surrogate end points* or *intermediate outcomes*) that do not measure the outcome directly but are thought to be correlated with it are used. When a proxy measure is used as a quality indicator, there must be evidence that the proxy measure is truly a substitute for the outcome of interest. For example, the presence of unfavorable PSA kinetics after treatment for localized prostate cancer appears to be associated with cause-specific mortality (Freedland et al, 2005; Roach et al, 2006; Stephenson et al, 2009; Eggener et al, 2011), so this may be a reasonable proxy outcome. Although the ultimate outcome may be mortality, many conditions in urology such as prostate cancer

take an indolent course, making mortality impractical (and often irrelevant). In such conditions, more proximal outcomes such as LOS, complications, and the need for salvage therapy provide a useful proxy (Bastide et al, 2010; Eggener et al, 2011). For proxy measures to be useful as quality measures, intervention should affect both the measure and the underlying disease (Guyatt et al, 1993; Girling et al, 2012).

The most important patient-reported outcome is HRQOL, a multi-dimensional construct that includes somatic symptoms, functional ability, emotional well-being, social functioning, and body image, as well as overall well-being (Guyatt et al, 1993; Wilson and Cleary, 1995). Quality-of-life assessment, typically by patient survey, provides a comprehensive evaluation of how the illness and its treatment affect patients.

Quality Metrics Applied to Urology

General quality metrics applied to urology have shown that patients undergoing cystectomy, nephrectomy, and prostatectomy are at significant risk of developing deep venous thromboses or pulmonary emboli (Gore et al, 2012). Readmission and mortality are highest after cystectomy, with readmission rates of over 35% and mortality over 6% after 90 days. Measurable variation in surgical quality exists by location of surgery for a range of outpatient urologic procedures (Hollingsworth et al, 2012a).

Urology-specific quality indicators and covariates have been developed, validated, and applied for localized prostate cancer (Spencer et al, 2003; Miller et al, 2007; Spencer et al, 2008; Ritchey et al, 2012). The 48 quality-of-care indicators include 5 structure, 23 process, and 20 outcome variables, plus 15 covariates (such as patient age). Quality metrics specific to bladder cancer have been proposed but have yet to be developed and validated (Montgomery et al, 2013). Candidate structure indicators include use of multidisciplinary teams, operating room facilities, and surgical volume (Cooperberg et al, 2009); process measures include adequate staging, complication rates, chemotherapy at transurethral resection, neoadjuvant or adjuvant chemotherapy use, time to cystectomy, adequate lymphadenectomy, and discussion of continent diversion if appropriate (Cooperberg et al, 2009; Gore et al, 2009b; Chamie et al, 2012b); and outcome measures include morbidity, mortality (overall and disease specific), and HRQOL, which would be best evaluated with bladder cancer-specific instruments (Gore et al, 2012).

Quality metrics for kidney cancer also have not been formalized, but use of partial versus radical nephrectomy in individuals with early-stage cancer may be a good candidate. All-cause and kidney cancer-specific mortality are lower when partial nephrectomy is employed when feasible (Tan et al, 2012). Clinical pathways for patients undergoing radical nephrectomy hold promise in shortening hospital stay and reducing cost (Chang et al, 2000). Disease-specific metrics have been developed and validated for urinary incontinence (Anger et al, 2013a) and prolapse (Anger et al, 2013b), but they still need to be tested for feasibility.

Advanced cancer and benign diseases have been left behind in urologic quality monitoring. Disease-specific metrics are needed for nephrolithiasis (Donnelly et al, 2011), benign prostatic hyperplasia (McVary et al, 2011), stricture disease (Jackson et al, 2012), and erectile dysfunction (Avasthi et al, 2011), among others (Clavijo et al, 2010; Kaplan and Hu, 2013). For end-of-life care, the National Quality Forum has endorsed the need to improve quality (Lorenz et al, 2006, 2007; Seow et al, 2009a, 2009b). Although knowledge about interventions to improve supportive care is abundant (McNiff et al, 2008; Wright et al, 2008; Zhang et al, 2009; Engelberg et al, 2010; Temel et al, 2010; Walling et al, 2010; Curtis et al, 2011; Malin et al, 2011; Meyer, 2011; Teno et al, 2013), tools to evaluate whether patients receive effective supportive care are lacking, limiting provider ability to improve over time. The Cancer Quality-ASSIST Project used the VA Health Services Research and Development appropriateness method to identify quality indicators in six categories: pain, depression, dyspnea, nausea and vomiting, fatigue and anorexia, and other treatment-related toxicities (Lorenz et al, 2009;

Dy et al, 2010). These metrics are specific neither to urology nor to life's final days. Moving forward, quality-of-care indicators need to be defined, validated, and used for individuals with kidney cancer, bladder cancer, locally invasive and metastatic prostate cancer, benign disease, and advanced urologic malignancies.

Quality Improvement Frameworks

Several health systems have committed to institution-wide quality improvement frameworks. The Lean model of continuous quality improvement was used by most of these systems, although each adapted Lean principles to suit the specific needs of its organization (Mazzocato et al, 2010; Blackmore et al, 2013). The method was originally used by the Toyota Production System, which sought to eliminate waste in production and maximize value for the customer. The process empowers all stakeholders in an institution to identify waste (defined as anything that does not add value or serve the patient's needs), suggest improvement, measure results, and pursue continuous improvement. Several health care systems, including Virginia Mason, ThedaCare, Intermountain, and Denver Health, have employed Toyota's Lean methodology to improve value (Mazzocato et al, 2010; Gabow and Mehler, 2011; James and Savitz, 2011; Gabow et al, 2012; Blackmore et al, 2013; Cosgrove et al, 2013). Nursing always plays a critical role in quality improvement initiatives. Return on investment is high, with savings of up to \$160 million over a 5-year period (Cosgrove et al, 2013; Gabow and Mehler, 2011).

Quality improvement frameworks have been created specifically for and implemented in urology. The Urological Surgery Quality Collaborative and the Michigan Urologic Surgery Improvement Collaborative connect urologists from different practices and feed back data for individual and group quality improvement (Miller et al, 2010, 2011; Burks et al, 2012; Barocas et al, 2013b). The collaboration has succeeded in improving the appropriate use of bone scan and computed tomography imaging for men with localized prostate cancer by lowering overuse when imaging is not indicated and increasing use when it is needed (Miller et al, 2010). It has also improved use of intravesical chemotherapy after transurethral resection of bladder tumors (Barocas et al, 2013b) and reduced variations in practice patterns and improved adherence to recommended staging practices (Miller et al, 2010). Another paradigm shift led by urology involves graphic representation of quality-of-life outcomes, to make measures more actionable for individuals with urologic malignancies. This user-centered design improves patient comprehension and enhances the clinical experiences of men with prostate cancer (Izard et al, 2012).

Integrated patient-centered medical homes also hold promise in improving value and quality in urology (Fisher, 2008). Such a model, with each patient empanelled to a unique primary care physician overseeing his or her medical care, improves care integration and quality (Coleman et al, 2010; Marx et al, 2011; Driscoll et al, 2013; Sarfaty et al, 2013). Nearly three quarters of urology practices currently meet the National Committee for Quality Assurance's standard for a medical home (Sakshaug et al, 2013), and primary care providers devote significant time to care for survivors of urologic malignancies. In contrast, only 54% of all physician practices have sufficient medical home infrastructure (Hollingsworth et al, 2012b). However, in safety-net and other systems, specialty resources are scarce, and successful strategies have placed the face-to-face onus on primary care providers, buttressed by specialist support (Chen et al, 2010; Neuhausen et al, 2012; Chen et al, 2013). Whether the optimal medical neighborhood will be built by employing urologists at the center of a medical home (Sakshaug et al, 2013) or in a supportive role (Chen et al, 2010, 2013) remains an open question (Hollingsworth et al, 2012b; Sakshaug et al, 2013).

Challenges to Using Outcomes to Evaluate Quality of Care

Adverse outcomes may be uncommon events, so large samples of patients may be necessary when using outcome measures to detect

differences in quality among health systems or hospitals. For example, to detect a 2% difference in the rate of postoperative wound infections between two hospitals (e.g., 5% for 1 and 7% for the other), each hospital would need to have at least 1900 patients who had undergone the surgery. In addition, a single outcome may be affected by many different factors, making it difficult to establish accountability. When comparing differences in surgical outcomes across hospitals, one does not know if the differences in outcomes are related to the skill of the surgeon, the competence of the surgical team, the postoperative care, the case mix, or some unmeasured factor. And the more time that elapses between the intervention and the outcome, the more difficult this problem becomes. For example, in comparing 10-year outcomes in women treated for incontinence at different facilities, what is more important, the quality of the initial treatment or the quality of care for recurrent symptoms?

Using patient satisfaction as an outcome is also fraught with limitations (Neuhausen and Katz, 2012). Although higher patient satisfaction is associated with increased overall health care expenditures and drug prescription (Fenton et al, 2012), a relationship between patient experience and quality of care does not necessarily exist (Chang et al, 2006; Rao et al, 2006). In one study, high satisfaction correlated with increased mortality (Fenton et al, 2012). Factors other than quality appear to affect patient satisfaction, and incentives based on satisfaction scores may unintentionally lead to worse outcomes and higher cost. Medicare's Value-Based Purchasing program will penalize hospitals that score poorly on patient satisfaction surveys (Chatterjee et al, 2012; Shoemaker, 2012; VanLare and Conway, 2012; Weston et al, 2013).

Levels of Evidence

Ranking systems to classify levels of evidence were first described by the Canadian Task Force on the Periodic Health Examination in the late 1970s (Delbanco and Taylor, 1980). These have since been adapted to reflect the strength of a study or clinical trial. Evidence levels range from I to IV, as follows:

- Level Ia: Meta-analysis of randomized controlled trials
- Level Ib: At least one randomized controlled trial
- Level IIa: At least one well designed, controlled trial, not randomized
- Level IIb: At least one well designed experimental trial
- Level III: Case, correlation, or comparative study
- Level IV: Expert opinion

Level I evidence is considered most strongly when policy recommendations are being constructed (Moyer, 2012).

HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life encompasses a wide range of human experience including the daily necessities of life such as food and shelter, intrapersonal and interpersonal responses to illness, and activities associated with professional fulfillment and personal happiness (Barofsky, 2012). Contemporary interpretations of HRQOL are based on the World Health Organization's long-standing definition of health as a "state of complete physical, mental, and social well-being and not merely the absence of disease" (Sharp, 1947; World Health Organization, 1948). HRQOL involves patients' own perceptions of their health and ability to function in life. In light of evidence that survival and clinical outcomes may be similar across treatments for many conditions, quality-of-life considerations may be the critical factor in medical decision making in some instances. Data are collected with HRQOL surveys, called *instruments*. Instruments typically contain questions, or items, that are organized into scales. Each scale measures a different aspect, or domain, of HRQOL. Instruments are best when they are self-administered by the patient, but if interviewer assistance is required, it must be from a neutral third party in a standardized fashion (Chang et al, 2011).

Health-Related Quality-of-Life Instruments

HRQOL instruments may be general or disease specific. General HRQOL domains address the components of overall well-being, whereas disease-specific domains focus on the impact of particular organic dysfunctions that may affect HRQOL. Numerous HRQOL instruments have been validated for use in urologic and other conditions. In urology, HRQOL research has been broad, but much has focused on individuals with prostate cancer (Litwin et al, 1995; Litwin et al, 1998; Huang et al, 2010; Mehnert et al, 2010; Ramsey et al, 2010; Szymanski et al, 2010; Resnick and Penson, 2012; Resnick et al, 2013a, 2013b; Resnick and Penson, 2013), urinary incontinence (Richter et al, 2010; Smith et al, 2010; Chong et al,

2011; Coyne et al, 2012; Liebergall-Wischnitzer et al, 2012), benign prostatic hyperplasia (McConnell et al, 2003; Coyne et al, 2009; Montorsi et al, 2010; Roehrborn et al, 2011a; Chokkalingam et al, 2012; Roehrborn et al, 2013), end-stage renal disease (Abdel-Kader et al, 2009; Goldstein et al, 2009; Griva et al, 2009), and bladder cancer (Nagele et al, 2006; Gilbert et al, 2010; Hedgepeth et al, 2010; Large et al, 2010; Nagele et al, 2012). A comprehensive resource for validated HRQOL instruments is available at www.proqolid.org. The National Cancer Institute has been particularly active in establishing interest in outcomes measurement for patients with malignant disease (www.outcomes.cancer.gov). Table 4-1 presents many of the validated HRQOL instruments available for the assessment of patients with urologic conditions. For each

TABLE 4-1 Characteristics of Health-Related Quality-of-Life (HRQOL) Instruments in Urologic Diseases

INSTRUMENT NAME	ITEMS	TIME RECALL, WEEKS	READING GRADE LEVEL OF ITEMS, MEDIAN (RANGE)	REFERENCE
GENERAL HRQOL				
Medical Outcomes Study 36-Item Health Survey (SF-36)	36	4	5.9 (2.2-12.0)	Ware and Sherbourne, 1992
Medical Outcomes Study 12-Item Health Survey (SF-12)	12	4	5.2 (2.2-12.0)	Ware et al, 1996
Quality of Well-Being Scale (QWB)	24	1	6.3 (0.9-12.0)	Kaplan et al, 1976
Sickness Impact Profile (SIP)	136	1 and 7	7.4 (0.5-12.0)	Bergner et al, 1981
Nottingham Health Profile (NHP)	38	At present	4.5 (2.1-12.0)	Hunt et al, 1985
Profile of Mood States (POMS)	65	1	7.2 (0.6-12.0)	Norcross et al, 1984
Mental Health Inventory (MHI)	38	4	5.8 (0.6-12.0)	Berwick et al, 1991
McGill-Melzack Pain Questionnaire	20	At present	N/A	Melzack, 1975
GENERAL HRQOL IN CANCER				
Functional Assessment of Cancer Therapy–General (FACT-G)	28	1	3.4 (1.1-12.0)	Cella et al, 1993
Cancer Rehabilitation Evaluation System Short Form (CARES-SF)	59	4	8.2 (1.0-12.0)	Schag et al, 1991
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30)	30	1	2.6 (1.8-12.0)	Aaronson et al, 1993
Rotterdam Symptom Checklist	27	1	4.6 (0.7-12.0)	de Haes et al, 1990
Prostate Cancer Treatment Outcome Questionnaire (PCTO-Q)	41	1	6.2 (2.1-12.0)	Shrader-Bogen et al, 1997
PROSTATE CANCER				
University of California, Los Angeles Prostate Cancer Index (UCLA-PCI)	20	4	5.2 (1.2-12.0)	Litwin et al, 1998
UCLA-PCI Short Form (UCLA-PCI-SF)	15	4	4.9 (1.2-12.0)	Litwin and McGuigan, 1999
Expanded Prostate Cancer Index-50 (EPIC-50)	50	4	5.8 (2.5-11.9)	Wei et al, 2000
Functional Assessment of Cancer Therapy–Prostate (FACT-P)	47	1	2.8 (0.5-12.0)	Esper et al, 1997
Prostate Cancer Specific Quality of Life Instrument (PROS-QOLI)	10	1 and 7	6.4 (2.8-10.4)	Stockler et al, 1998
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Module (EORTC-QLQ-PR25)	25	1	6.7 (0.5-12.0)	Borghede and Sullivan, 1996
Total Illness Burden Index–Prostate Cancer (TIBI-CaP)	25	26	7.6 (2.4-11.3)	Litwin et al, 2007
The Prostate Cancer Radiation Late Toxicity Questionnaire (PCRT)	29	4	9.2 (3.6-12.0)	Rodrigues et al, 2007
Quality of Life Module–Prostate 14 (QOLM-P14)	14	1	3.2 (0.6-9.0)	Osoba et al, 1999
Memorial Anxiety Index–Prostate Cancer (MAX-PC)	18	1	6.2 (3.7-12.0)	Roth et al, 2003
Clark and Talcott	20	1	5.8 (2.4-10.4)	Clark and Talcott, 2001

TABLE 4-1 Characteristics of Health-Related Quality-of-Life (HRQOL) Instruments in Urologic Diseases—cont'd

INSTRUMENT NAME	ITEMS	TIME RECALL, WEEKS	READING GRADE LEVEL OF ITEMS, MEDIAN (RANGE)	REFERENCE
Clark et al	35	4	5.2 (1.0-10.7)	Clark et al, 2003
Dale et al	35	1	7.1 (2.8-11.8)	Dale et al, 1999
Borghede et al	19	1	6.7 (2.3-12.0)	Borghede et al, 1997
Giesler et al	52	4	8.8 (3.6-12.0)	Giesler et al, 2000
BLADDER CANCER				
Functional Assessment of Cancer Therapy–Bladder (FACT-BL)	40	1	3.6 (0.7-12.0)	Mansson et al, 2002
Functional Assessment of Cancer Therapy Vanderbilt Cystectomy Index (FACT-VCI)	19	1	3.7 (0.6-10.2)	Cookson et al, 2003
European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Bladder Module (EORTC-QLQ-BLS24)	24	1	5.5 (0.5-12.0)	Pavone-Macaluso et al, 1997
BENIGN PROSTATIC HYPERPLASIA AND LOWER URINARY TRACT SYMPTOMS				
American Urological Association Symptom Index (AUASI) (i.e., IPSS)	7	4	9.3 (2.2-12.0)	Barry et al, 1992a, 1992b
Benign Prostatic Hyperplasia Health-Related Quality of Life Survey (BPH-HRQOL)	49	4	7.3 (1.8-12.0)	Lukacs et al, 1997
Benign Prostatic Hyperplasia Impact Index (BPHII)	4	4	9.8 (5.9-11.8)	Barry et al, 1995b
Danish Prostatic Symptom Score-1 (DAN-PSS-1)	15	4	8.1 (2.2-12.0)	Meyhoff et al, 1993
International Continence Society–Male Questionnaire (ICSmale)	34	4	5.4 (1.2-12.0)	Donovan et al, 2000
International Continence Society–Quality of Life questionnaire (ICSQoL)	8	4	6.9 (3.6-9.0)	Donovan et al, 1997
Nocturia Quality of Life Questionnaire (NQOL)	13	2	5.3 (2.3-9.3)	Mock et al, 2008
Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire (OAB-q)	33	4	4.7 (0.6-12.0)	Coyne et al, 2005
Urgency Questionnaire (UQ)	19	1	4.2 (1.0-12.0)	Coyne et al, 2004
Primary Overactive Bladder Symptom Questionnaire (POSQ)	5	2	6.2 (2.4-12.0)	Matza et al, 2005
Patient Perception of Bladder Condition (PPBC)	1	At present	8.8 (8.1-9.4)	Matza et al, 2005
PROSTATITIS				
National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)	9	1	7.7 (3.8-11.7)	Litwin et al, 1999
Giessen Prostatitis Symptom Score (GPSS)	12	Not specified	8.8 (1.2-12.0)	Brahler et al, 1997
Nickel and Sorensen	20	1	8.7 (5.0-12.0)	Nickel and Sorensen, 1996
Neal and Moon	4	Not specified	12.0 (12.0-12.0)	Neal and Moon, 1994
ERECTILE DYSFUNCTION				
International Index of Erectile Function (IIEF)	15	4	7.7 (4.7-12.0)	Rosen et al, 1997
Self-Esteem and Relationship Questionnaire (SEAR)	14	4	4.8 (2.1-12.0)	Cappelleri et al, 2004
Male Sexual Health Questionnaire (MSHQ)	25	4	9.0 (5.2-12.0)	Rosen et al, 2004
Brief Sexual Function Inventory (BSFI)	11	4	6.9 (5.0-12.0)	Mykletun et al, 2006
Erectile Dysfunction Inventory of Treatment Satisfaction Questionnaire (EDITS)	11	4	6.7 (4.4-12.0)	Althof et al, 1999
Erection Distress Scale (EDS)	5	Not specified	6.7 (3.6-9.0)	Seftel et al, 2007
URINARY INCONTINENCE				
Incontinence Impact Questionnaire (IIQ)	30	Not specified	7.0 (2.3-12.0)	Shumaker et al, 1994
Incontinence Impact Questionnaire Short Form (IIQ-7)	7	Not specified	12.0 (4.4-12.0)	Uebersax et al, 1995
Urological Distress Inventory (UDI)	19	Not specified	5.8 (0.8-12.0)	Shumaker et al, 1994

Continued

TABLE 4-1 Characteristics of Health-Related Quality-of-Life (HRQOL) Instruments in Urologic Diseases—cont'd

INSTRUMENT NAME	ITEMS	TIME RECALL, WEEKS	READING GRADE LEVEL OF ITEMS, MEDIAN (RANGE)	REFERENCE
Urogenital Distress Inventory Short Form (UDI-6)	6	Not specified	8.4 (4.8-12.0)	Uebersax et al, 1995
International Consultation on Incontinence Questionnaire—Female Lower Urinary Tract Symptoms (ICIQ-FLUTS)	12	4	1.0 (0.5-9.3)	Brookes et al, 2004
International Consultation on Incontinence Questionnaire (ICIQ)	4	4	4.6 (0.7-8.7)	Avery et al, 2004
Symptoms of Incontinence Questionnaire (i.e., PRAFAB-Q)	20	Not specified	6.7 (2.2-11.9)	Hendriks et al, 2008
Urinary Incontinence Quality of Life Questionnaire (I-QOL)	22	Not specified	8.9 (4.3-12.0)	Wagner et al, 1996
Stress-Related Leak, Emptying Ability, Anatomy, Protection, Inhibition, Quality of Life, Mobility and Mental Status (SEAPI-QMM)	15	Not specified	9.4 (3.6-12.0)	Raz and Erickson, 1992
King's Health Questionnaire (KHQ)	21	At present	4.5 (0.7-12.0)	Kelleher et al, 1997
Bristol Female Lower Urinary Tract Symptoms Questionnaire (BFLUTS)	33	Not specified	7.1 (2.2-12.0)	Jackson et al, 1996
Bristol Female Lower Urinary Tract Symptoms Questionnaire Short Form (BFLUTS-SF)	19	Not specified	6.3 (3.2-12.0)	Brookes et al, 2004
Urge-Incontinence Impact Questionnaire (U-IIQ)	32	4	4.1 (0.5-12.0)	Lubeck et al, 1999
Urge-Urinary Distress Inventory (U-UDI)	10	4	4.9 (1.8-12.0)	Lubeck et al, 1999
Symptom Severity Index (SSI)	13	1 and 52	3.6 (2.2-6.2)	Black et al, 1996
Symptom Impact Index (SII)	3	Not specified	7.3 (4.9-10.8)	Black et al, 1996
Stress and Urge Incontinence and Quality of Life Questionnaire	9	1 and 26	5.8 (0.8-12.0)	Kulseng-Hanssen and Borstad, 2003
Urinary Incontinence Severity Score (UISS)	10	Not specified	9.2 (2.8-12.0)	Stach-Lempinen et al, 2001
CONTILIFE	28	2 and 4	5.6 (0.8-12.0)	Amarenco et al, 2003
Female Incontinence Severity Index (ISI)	2	Not specified	5.8 (0.8-10.7)	Sandvik et al, 1993
INTERSTITIAL CYSTITIS				
O'Leary-Sant Interstitial Cystitis Symptom Index and Problem Index (OSICSI-PI)	23	4	7.1 (2.3-11.0)	O'Leary et al, 1997
Pelvic Pain and Urgency/Frequency Questionnaire (PUF)	8	Not specified	4.9 (0.5-12.0)	Parsons et al, 2002
Female Genitourinary Pain Index (FGUPI)	9	1	7.7 (3.8-11.7)	Parsons et al, 2002
KIDNEY CANCER				
Functional Assessment of Cancer Therapy—Kidney Symptom Index (FKSI-15)	15	1	1.3 (0.3-8.2)	Cella et al, 2006
RENAL TRANSPLANT				
End-Stage Renal Disease Symptom Checklist—Transplantation Module (ESRD-SCL)	43	4	6.2 (1.8-12.0)	Franke et al, 1999
Kidney Disease and Quality of Life Questionnaire (KDQOL-36)	36	4	4.9 (0.8-12.0)	Hays et al, 1997
URINARY TRACT INFECTION				
Activity Impairment Assessment (AIA)	5	1 and 7	9.7 (3.6-12.0)	Wild et al, 2005
SEXUALITY				
Index of Premature Ejaculation (IPE)	10	4	9.1 (1.3-12.0)	Althof et al, 2006
Sexual Quality of Life (Male) Instrument (SQOL-M)	11	Not specified	8.6 (2.6-12.0)	Abraham et al, 2008
Profile of Female Sexual Function (PFSF)	38	Not specified	4.3 (0.5-12.0)	Derogatis et al, 2004
Brief Profile of Female Sexual Function (B-PFSF)	7	Not specified	3.9 (0.9-9.2)	Rust et al, 2007
Male Sexual Quotient Questionnaire (MSQ)	10	6	7.0 (1.4-12.0)	Abdo, 2007

instrument, the table includes the number of items, recall time, and Flesch-Kinkaid reading grade level (Flesch, 1948; Kincaid et al, 1975).

General Health-Related Quality-of-Life Instruments

General quality-of-life instruments have been extensively studied and validated in many types of patients, sick and well. Examples include the RAND Medical Outcomes Study 36-Item Health Survey, also known as the SF-36 (Ware and Sherbourne, 1992; Hays et al, 1993; McHorney et al, 1994), the Quality of Well-Being scale (Kaplan et al, 1979; Bush et al, 1982; Anderson et al, 1989), the Sickness Impact Profile (Bergner et al, 1976a, 1976b; Carter et al, 1976; Martin et al, 1976; Pollard et al, 1976; Gilson et al, 1980; Bergner et al, 1981), and the Nottingham Health Profile (Martini and McDowell, 1976; Hunt et al, 1981). Each assesses various components of HRQOL including physical and emotional functioning, social functioning, and symptoms. Each has been thoroughly validated and tested for reliability, validity, and responsiveness. Another approach to quantifying general HRQOL is to blend a self-assessment of physical, emotional, and social functioning and well-being with a self-report of preferences, or utilities, for those health states. Developed by the Euroqol Group, a measurement collaborative, the EQ-5D is such an instrument (Brooks et al, 1991; Johnson et al, 1998; Johnson and Coons, 1998; Johnson et al, 2005; Shaw et al, 2005; Nan et al, 2007; Pickard et al, 2012).

Benign Disease–Targeted Health-Related Quality-of-Life Instruments

The best-known outcomes instrument in urology is no doubt the American Urological Association Symptom Index (AUASI) (Barry et al, 1992a, 1992b; O’Leary et al, 1992; Barry et al, 1995a). Its simplicity belies its elegance and utility. It includes seven items, each self-rated on a scale of 0 to 5, yielding a summary score that ranges from 0 to 35. Symptom scores are considered mild (0 to 7), moderate (8 to 19), or severe (20 to 35). It has been used to longitudinally assess symptoms in men treated for prostate cancer (Gore et al, 2010a). With the addition of a separate quality-of-life item, the worldwide urology community embraced the AUASI as the International Prostate Symptom Score (IPSS) (Plante et al, 1996; Badia et al, 1997, 1998; Garcia-Losa et al, 2001).

Modeled after the AUASI, and in an attempt to standardize assessment of urinary incontinence and allow cross-cultural comparisons, the Scientific Committee of the International Consultation on Incontinence (ICIQ) supported the development and validation of a universally applicable questionnaire for research as well as clinical practice (Abrams et al, 2010). The ICIQ–Urinary Incontinence Short Form has now been translated into 30 languages (Abrams et al, 2006; Hashim et al, 2006; Klovning et al, 2009; Timmermans et al, 2013). Other high-quality questionnaires were included under the ICIQ umbrella and are available at www.iciq.net. Table 4-2 details some of the validated and published ICIQ modules endorsed by the Fourth International Consultation on Incontinence (Abrams et al, 2010).

Cancer-Specific Health-Related Quality-of-Life Instruments

Because of the well-documented impact of malignancies and their treatment on HRQOL, cancer-specific domains have also been investigated extensively. Numerous instruments have been developed and tested that measure the special impact of cancer (regardless of primary site) on patients’ routine activities. Readers are directed to the Quality of Life Instruments Database (www.proqolid.org) for guidance when selecting an instrument for quality-of-life measurement in studies of prostate or other cancers.

Selecting a Health-Related Quality-of-Life Instrument

Investigators or clinicians considering measuring HRQOL in a clinical study or in clinical practice should base their choice of instrument(s) on the particular population being studied and the clinical questions being asked. Using previously validated instruments, to the extent to which they are applicable and appropriate, obviates the need for an arduous process of instrument development and validation. Use of a general and a disease-specific module in combination is suitable for most studies. However, if a particular domain (e.g., pain) is the focus of the study, specific, expanded questionnaires focusing on the area of interest should be sought. Respondent burden needs to be considered, particularly for longitudinal studies in which subjects will complete the same instruments multiple times. Pretesting of instruments that will be used in clinical studies is advisable.

TABLE 4-2 International Consultation on Incontinence Questionnaire (ICIQ) Modules

MODULE	QUESTIONNAIRE FROM WHICH DERIVED	SYMPTOMS ASSESSED	REFERENCE
ICIQ-FLUTS	BFLUTS Short Form (Brookes et al, 2004)	Female urinary	Brookes et al, 2004
ICIQ-FLUTS Long Form	BFLUTS (Jackson et al, 1996)	Female urinary	Jackson et al, 1996
ICIQ-MLUTS	ICSmale Short Form (Donovan et al, 2000)	Male urinary	Donovan et al, 2000
ICIQ-MLUTS Long Form	ICSmale (Donovan et al, 1996)	Male urinary	Donovan et al, 1996
ICIQ-LUTSqol	KHQ (Kelleher et al, 1997)	Urinary quality of life	Kelleher et al, 1997
ICIQ-N	ICSmale (Donovan et al, 1996)	Nocturia	Donovan et al, 1996
ICIQ-Nqol	BFLUTS (Jackson et al, 1996)	Nocturia quality of life	Jackson et al, 1996
ICIQ-VS	N-QOL (Abraham et al, 2004)	Nocturia quality of life	Abraham et al, 2004
ICIQ-B		Vaginal	Abrams et al, 2006
ICIQ-FLUTSsex		Bowel	Abrams et al, 2006
ICIQ-MLUTSsex	BFLUTS (Jackson et al, 1996)	Female sexual related to urinary symptoms	Jackson et al, 1996
ICIQ-OAB	ICSmale (Donovan et al, 1996)	Male sexual related to urinary symptoms	Donovan et al, 1996
	ICSmale (Donovan et al, 1996)	Overactive bladder	Donovan et al, 1996
	BFLUTS (Jackson et al, 1996)		Jackson et al, 1996
ICIQ-OABqol	OABq (Coyne et al, 2002)	Overactive bladder quality of life	Coyne et al, 2002
ICIQ-UI Short Form		Urinary incontinence	Abrams et al, 2006

Psychometric Validation of New Health-Related Quality-of-Life Instruments

The development and validation of new instruments and scales is a long and arduous process. When scales and instruments are developed, they are first pilot tested to ensure that the target population can understand and complete them with ease. Pilot testing is usually preceded by work with focus groups, and includes formal cognitive testing. Pilot testing can reveal problems that might otherwise go unrecognized by researchers. For example, many terms that are commonly used by medical professionals are poorly understood by patients. In fact, because the average adult reads at the fifth- to eighth-grade level, items should be drafted at no higher than an eighth-grade reading level (Paasche-Orlow et al, 2003; Osborn et al, 2007; Paasche-Orlow and Wolf, 2007, 2010; Osborn et al, 2011; Waite et al, 2013). In addition, the digital divide between those of low and high socioeconomic status should be considered (Levy et al, 2013).

Scales and instruments are also evaluated for three fundamental statistical properties—reliability, validity, and responsiveness (Litwin, 1995; Ware et al, 1996; Resnick and Nahm, 2001; DeVellis, 2011).

Reliability

Reliability (Table 4-3) refers to how free the scale is of measurement error—that is, what proportion of a patient's test score is true and what proportion is the result of chance variation. Two of the most commonly used metrics are test-retest and internal consistency reliability. *Test-retest reliability* is the most commonly used indicator of survey instrument reliability. It is measured by having the same respondents complete a survey at two different points in time to see how stable their responses are. It is a measure of how reproducible a set of results is. When measuring test-retest reliability, one must be careful not to select items or scales that measure variables likely to change over short periods of time. Variables that are likely to change over a given period of time will produce low test-retest reliability in measurement instruments. This does not mean that the survey instrument is performing poorly but simply that the attribute itself has changed.

When measuring test-retest reliability, one must also consider that individuals may become familiar with the items and answer partly on the basis of their memory of what they answered the last time. Called the *practice effect*, this presents a challenging problem to address in measures of test-retest reliability over short periods of time. As a result of the practice effect, test-retest reliability figures

can be falsely inflated. *Alternate-form reliability* provides one way to escape the problem of the practice effect. It involves using differently worded items to measure the same attribute. Questions and responses are reworded or their order is changed to produce two items that are similar but not identical. One way to test alternate-form reliability is to change the wording of the response sets without changing the meaning. Another common method to test alternate-form reliability is to change the actual wording of the items themselves.

The correlation between two data sets from the same individual is commonly known as *intraobserver reliability*. It measures the stability of responses from the same respondent and is a form of test-retest reliability. *Interobserver (inter-rater) reliability* provides a measure of how well two or more evaluators agree in their assessment of a variable. When survey instruments are self-administered and designed to measure the respondent's own behaviors or attitudes, interobserver reliability is not used. *Internal consistency reliability* is a measure of the similarity of an individual's responses across several items, indicating the homogeneity of a scale (Henson, 2001). It is applied not to single items but to groups of items that are thought to measure different aspects of the same concept.

Validity

Validity (Table 4-4) refers to how well the item, scale, or instrument measures the attribute it is intended to measure. Validity has three general forms: content, criterion, and construct. *Content validity*, sometimes referred to as *face validity*, involves a subjective assessment of the scope and completeness of a scale and is usually measured in the early stages of an instrument's development by experts and through use of patient focus groups. The assessment of content validity typically involves an organized review of an instrument's contents to ensure that it includes everything it should and does not include anything it should not. *Criterion validity* is a more quantitative approach to assessing the performance of scales and instruments. It requires the correlation of scale scores with results from other established tests (concurrent validity) or with future measurable outcomes (predictive validity). *Concurrent validity* requires that the survey instrument in question be judged against some other method that is acknowledged as a gold standard for assessing the same variable. It may be a published psychometric index, a scientific measurement of some factor, or another generally accepted test. *Predictive validity* is the ability of a survey instrument to forecast future events, behaviors, attitudes, or outcomes. It may be used during the course of a study to predict response to a stimulus, success of an intervention, or time to a medical end point. *Construct*

TABLE 4-3 Reliability Assessments for Health-Related Quality-of-Life Instruments

TYPE OF RELIABILITY	CHARACTERISTICS	COMMENTS
Test-retest	Measures the stability of responses over time, typically in the same group of respondents	Requires administration of survey to a sample at two different and appropriate points in time. Time points that are too far apart may produce diminished reliability estimates that reflect actual change over time in the variable of interest.
Intraobserver	Measures the stability of responses over time, in the same individual respondent	Requires completion of a survey by an individual at two different and appropriate points in time. Time points that are too far apart may produce diminished reliability estimates that reflect actual change over time in the variable of interest.
Alternate-form	Uses differently worded stems or response sets to obtain the same information about a specific topic	Requires two items in which the wording is different but aimed at the same specific variable and at the same vocabulary level.
Internal consistency	Measures how well several items in a scale vary together in a sample	Usually requires a computer and statistician to carry out calculations.
Interobserver	Measures how well two or more different respondents rate the same phenomenon	May be used to demonstrate reliability of a survey or may itself be the variable of interest in a study.

TABLE 4-4 Validity Assessments for Health-Related Quality-of-Life Instruments

TYPE OF VALIDITY	CHARACTERISTICS	COMMENTS
Content	Formal expert review of how good an item or series of items appear	Usually assessed by individuals with expertise in some aspect of the subject under study
Criterion: Concurrent	Measures how well the item or scale correlates with gold-standard measures of the same variable	Requires the identification of an established, generally accepted gold standard
Criterion: Predictive	Measures how well the item or scale predicts expected future observations	Used to predict outcomes or events of significance that the item or scale might subsequently be used to predict
Construct	A theoretic measure of how meaningful a survey instrument is, usually after years of experience by numerous investigators	Not easily quantifiable

validity is the most valuable yet most difficult way of assessing a survey instrument. It is a measure of how meaningful the scale or survey instrument is when in practical use.

Responsiveness

Responsiveness of an HRQOL instrument refers to how sensitive the scales are to change over time (Murawski and Miederhoff, 1997; Terwee et al, 2003). That is, a survey may be reliable and valid when used at a single point in time, but in some circumstances it must also be able to detect meaningful improvements or decrements in quality of life during longitudinal studies. The instrument must “react” in a time frame that is relevant for patients over time. Because HRQOL may change over time, longitudinal measurement of these outcomes is important. In urology, widely used instruments such as the University of California–Los Angeles Prostate Cancer Index and the National Institutes of Health Chronic Prostatitis Symptom Index are highly responsive to clinical changes.

Comparison Groups

Prospective, longitudinal data collection beginning at baseline before treatment is always best because this approach may reveal time-dependent evolution of HRQOL domains (Litwin et al, 2001; Malcolm et al, 2010; Reeve et al, 2012). Patients may then serve as their own controls. Assessing HRQOL at baseline before treatment allows for the inclusion of baseline age- or comorbidity-related changes that should not be attributed to treatment. This approach facilitates the stratification of discriminants from determinants of HRQOL.

Caveats on the Collection of Health-Related Quality-of-Life Data

The overarching goals of HRQOL research are summarized in Box 4-1. Although there are some single instruments that are multidimensional, many quality-of-life researchers have endorsed a “battery approach,” in which the various components of HRQOL are measured with different scales to ensure that each domain receives adequate attention. Longer instruments can provide greater precision, but they also increase the chance that patients will tire of the exercise and not provide reliable or valid answers. Hence, shorter instruments are usually preferable when one is performing HRQOL measurements in such circumstances. In general, it is easier and more efficient to use established instruments that have already undergone psychometric validation. Use of HRQOL data collected using published instruments allows the researcher to compare the study results with data from other samples or diverse populations with various chronic diseases. Nevertheless, sometimes it is necessary to develop new questionnaire items to ensure that a particular concept is adequately evaluated. Under such circumstances new

BOX 4-1 Quality-of-Life Objectives in Research and Practice

- To assess overall treatment efficacy including subjective morbidity
- To help determine whether the goals of treatment have been met
- To educate patients and clinicians about the full spectrum of treatment outcomes
- To facilitate medical decision making
- To provide the defining issue if treatments are otherwise equivalent

scales can be tested for reliability and validity during the course of data collection.

HEALTH SERVICES RESEARCH METHODOLOGIES

Retrospective Review of the Medical Record

The image of an “outcomes” researcher retrospectively reviewing charts to understand variations in an outcome of interest originated in the Crimean War, when Florence Nightingale documented high death rates among injured soldiers treated at overcrowded facilities with poor hygiene (Cook, 1914; Kopf, 1916). Although retrospective chart review is only one arrow in a health services researcher’s quiver, it can unearth important health systems failings, such as poor follow-up of positive fecal occult blood testing results at the time of hospital admission (Scales et al, 2006). Such failings can then be targeted for quality improvement interventions.

Secondary Data Analysis

Secondary data involve an analysis of information collected by someone other than the researcher. Examples include hospital and outpatient claims, censuses, and pharmaceutical records, as well as qualitative data obtained by a third party. One of the main benefits of secondary data analyses is that the data have already been collected; a corollary downfall is that the researcher is limited to those data. In selecting an optimal data set, criteria to consider include availability of information regarding the data collection process, issues related to study design, the need for adjustment for sample design characteristics, the relative robustness of the data set, and the time required to procure and analyze the data (Litwin et al, 2005b). If several different data sets are chosen for a common venture, selecting complementary rather than overlapping data sets affords a view through the broadest

possible lens. One limitation of secondary data analysis is the reliance of accurate coding, without which overestimation or underestimation is possible.

Community-Partnered Participatory Research

Community-partnered participatory research involves a collaborative process among researchers, communities, and others; all partners collaborate and are valued equally (Humphreys et al, 2008; Chung et al, 2009; Khodyakov et al, 2009; Wells and Jones, 2009; Chung et al, 2010, 2011; Lizaola et al, 2011; Hunt et al, 2012; Wells et al, 2013a, 2013b). Its goal is to develop, implement, and disseminate work that will benefit a community. Community strengths can then be celebrated, and community needs not only identified, but also addressed from within. For example, interventions in which urologists partner with barbershops help promote prostate cancer knowledge and, when appropriate, screening (Relford et al, 2010). Results are then shared with the community to promote ongoing partnerships and build trust and capacity. Interventions do not need to focus on disadvantaged communities; when researchers collaborate with physician practices and feed findings back to those groups, substantial improvement can be made in clinical care, including use of immediate intravesical therapy after resection for non-muscle invasive bladder cancer and appropriate metastatic workup for men with prostate cancer (Miller et al, 2010; Barocas et al, 2013b).

Implementation Science

In medicine, translating good evidence into broadly implemented practice takes, on average, 17 years (Pfeffer and Sutton, 2006). Delays in uptake exist in medical treatment to facilitate passage of urinary stones (Hollingsworth et al, 2006; Scales et al, 2007), chemoprevention of prostate cancer (Hamilton et al, 2010), and weight loss for urinary incontinence (Bland et al, 2003; Subak et al, 2009; Wing et al, 2010; Holroyd-Leduc et al, 2011; St Sauver et al, 2011; Phelan et al, 2012). Implementation science seeks to compress the timeline. Implementation research studies methods for systematically adopting evidence-based practices into routine care, to improve quality and effectiveness (Stetler et al, 2008; Proctor et al, 2009; Eccles et al, 2012; Methodology Committee of the Patient-Centered Outcomes Research Institute, 2012; Yano et al, 2012; Meissner et al, 2013). It encompasses field research, clinical work, communities, and health policy. In surgery, implementation of evidence-based infection control processes using comprehensive unit-based safety programs reduces rates of surgical site infections (Wick et al, 2012). For urologists, evidence-based guidelines abound (Davis et al, 2012; Sharlip et al, 2012; Carter et al, 2013a; Cookson et al, 2013; Donat et al, 2013), but broad implementation remains an unmet challenge (Chamie et al, 2011; Chamie and Litwin, 2011; Chamie et al, 2012b; Strobe et al, 2011, 2012). Implementation strategies may focus on small-group continuing education with urologists and primary care providers, lectures, patient education materials, and public endorsement by national figures (Puech et al, 1998). Engagement of all stakeholders during guideline development and dissemination is key (Smith and Hillner, 2001).

Qualitative Research

Qualitative research involves interviews, group discussions, field notes, and observations. It allows exploration of aspects of care that may not be accessible from other data sources, and issues may be unearthed that were not readily apparent at the beginning of data collection. Qualitative methods can also be used to explore options for overcoming obstacles, such as renegotiating masculine identity after treatment for prostate cancer (Maliski et al, 2008). Methodologic rigor must be applied to data collection and analysis, and data analysis options include coding, recursive abstraction, interpretive techniques, and mechanical techniques (Erickson, 2012).

FUTURE IMPLICATIONS

Balancing Analysis of Current Shortcomings with Interventions for Change

That current urologic care leaves significant space for improvement has now been well documented. Likewise, disparities in quality of care often overshadow the more salient understanding that care is often mediocre, even in the best circumstances, and must be improved for all individuals. Although further analyses of shortcomings and disparities are important, the most pressing need is development and broad implementation of interventions that can improve care. For example, a novel method of patient preference elicitation using conjoint analysis improves decision-making quality in men with prostate cancer (Saigal et al, 2012). Developing similar interventions and identifying strategies to broadly implement them will allow urology to remain at the forefront of health care innovation and value.

Patient-Centeredness and Comparative Effectiveness

Comparative effectiveness research uses outcomes data to guide health care policy. The American Recovery and Reinvestment Act of 2009 invested \$1.1 billion to fund comparative effectiveness research (American Recovery and Reinvestment Act, 2009), and the recently enacted Patient Protection and Affordable Care Act formalized a private, nonprofit Patient-Centered Outcomes Research Institute (www.pcori.org) to equitably distribute funding (Selby et al, 2012). The allocated funds target not only reviews of existing evidence, but also new prospective, randomized trials.

Evidence-Based Health Care Policy

To maintain control over treatment decisions, urologists must work fastidiously to improve value and ensure broad implementation of evidence-based practices. For instance, if PSA screening is to continue, more nuanced strategies must be implemented to minimize overdiagnosis and overtreatment (Gulati et al, 2013). Policy makers can use several levers to encourage evidence-based care. For example, when reimbursement levels were high, androgen deprivation therapy was overused in treatment of localized prostate cancer (Cooperberg et al, 2003; Shahinian et al, 2005a; Sharifi et al, 2005; Badiozamani et al, 2009), despite well documented noxious effects (Potosky et al, 2002; Shahinian et al, 2005b; Saigal et al, 2007). Inappropriate use of androgen deprivation fell significantly after the Medicare Modernization Act lowered reimbursement (Elliott et al, 2010; Shahinian et al, 2010; Gilbert et al, 2011).

Maximizing Value

Ultimately, a urologist cares for an individual, not merely that individual's urologic needs. Whereas organizations such as the U.S. Food and Drug Administration (FDA) may approve a medication or device if it is "safe and effective" (Meadows, 2002; Institute of Medicine, 2011), physicians are held to a higher standard. We must consider not only whether a drug extends life by 3 to 5 months (Kantoff et al, 2010; de Bono et al, 2011; Fizazi et al, 2011; Cabot et al, 2012; Parker et al, 2013), but whether use of the drug is sensible in the context of competing priorities. Examples of alternative investments include early childhood and depression: each dollar invested in a child yields \$7 in return (Campbell and Ramey, 1994; Clarke and Campbell, 1998; Campbell et al, 2012), and of all socioeconomic and clinical variables, depression is singly linked with health (Covinsky et al, 1997a; Jackson-Triche et al, 2000) and wealth (Wells et al, 2000; Beddington et al, 2008). As our population ages (Vincent and Velkoff, 2010), urologists are uniquely empowered to continue to lead the effort to maximize value and shape rational policies that will make each person as healthy and happy as possible.



KEY POINTS

- Health services research focuses on access to care, cost of care, quality of care, health systems, and population health.
- The “value” of a health care service or intervention is defined as patient-centered health outcomes divided by cost. Considering cost in the context of value can help policy makers decide which interventions should be amplified and which may be reduced.
- That variation in health care spending does not correlate with outcomes suggests that good outcomes can be achieved with lowered cost, and that current spending can be targeted more thoughtfully. In urology, significant hospital-level variation exists in outcomes and readmission after surgery.
- Quality of care research evaluates “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.” Descriptive quality measures abound, but for quality metrics to affect outcomes, they must be based on solid evidence, be measurable, and have resources devoted to tracking and improving them.
- Health-related quality of life (HRQOL) encompasses a wide range of human experience including the daily necessities of life such as food and shelter, intrapersonal and interpersonal responses to illness, and activities associated with professional fulfillment and personal happiness.
- To maintain control over treatment decisions, urologists must work fastidiously to improve value and ensure broad implementation of evidence-based practices.

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The complete reference list is available online at www.expertconsult.com.

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5

Core Principles of Perioperative Care

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Preoperative Evaluation

Presurgical Testing

Surgical Risk Evaluation

Optimization of Comorbid Illness

Special Populations

Preparation for Surgery

Anesthetic Considerations

Blood Products

Patient Environment

Abdominal Incisions and Wound Closure

While the practice of urology continues to move toward office-based and nonsurgical treatments, the diversity of genitourinary disease requires that the practicing urologist be familiar with perioperative surgical principles to improve clinical care. This chapter provides the reader with basic tools to understand the preoperative assessment, intraoperative techniques, and postoperative management necessary to promote a culture of patient safety and optimal surgical outcomes.

PREOPERATIVE EVALUATION

The perioperative management of patients undergoing urologic surgery continues to evolve. Over the past two decades, the economics of health care has added increasing pressure for more outpatient surgery, decreased hospital stays, and decreased complication rates. Furthermore, the acuity of surgical patients is increasing in that patients are older with more significant comorbidities. It has become standard for patients undergoing even the most sophisticated and complex urologic procedures in the hospital to be admitted on the same day as the surgery. **Therefore the urologic surgeon is responsible for ensuring that the patient has been thoroughly evaluated by the other physicians on the health care team and arrives in the operating room in the most optimized medical condition.** The preoperative use of appropriate medical specialist consultations will result in improved patient safety and obviate the need for unnecessary cancelled surgeries resulting from the inadequacy of medical optimization.

PRESURGICAL TESTING

The goal of presurgical testing is to identify an undiagnosed comorbidity, an undertreated medical problem, or a significant exacerbation of existing comorbid illness that may affect the operative outcome (Townsend et al, 2008). Ideally, the preoperative evaluation should be individualized on the basis of age, history, physical examination findings, and the surgical procedure to be performed. Although most hospitals or ambulatory surgery centers have requirements for baseline evaluation, routine testing has never been shown to be cost-effective. In fact, the results of routine testing are less predictive of perioperative morbidity than the American Society of

Anesthesiologists (ASA) status or the American Heart Association (AHA) and American College of Cardiology (ACC) guidelines for surgical risk. A recent systematic review found no evidence to support routine preoperative testing in patients undergoing noncardiac elective surgery (Johansson et al, 2013). Most commonly, presurgical testing includes complete blood count (CBC); basic metabolic panel (BMP); prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) (controversial); electrocardiogram (ECG); and chest radiograph. The routine ordering of a PT/PTT in a patient not currently on warfarin or in a patient without a prior history of increased bleeding with other surgical procedures is controversial, and these tests can be omitted in the majority of patients. **Any woman of childbearing age, unless the ovaries or uterus have been previously surgically removed, must undergo a urine pregnancy test on the morning of surgery** (Halaszynski et al, 2004). The value of a preoperative ECG in identification of underlying acute cardiac disease and prediction of perioperative cardiac morbidity is also controversial. Some studies have shown that ECG abnormalities have no significant predictive value (Goldman et al, 1978), whereas others found that an abnormal ECG was the best diagnostic predictor of an adverse cardiac event (Carliner et al, 1985). Nonetheless, current recommendations, in general, suggest that a preoperative ECG be obtained from patients older than 40 years or those with a history of any cardiac disease. Similarly, the routine preoperative use of a chest radiograph, in the absence of preexisting cardiopulmonary disease, is not indicated. Overall, even an ASA Task Force on Preanesthesia Evaluation could not make firm recommendations other than “preoperative tests may be ordered, required, or performed on a selective basis for purposes of guiding or optimizing perioperative management” (Practice advisory for preanesthesia evaluation, 2002).

SURGICAL RISK EVALUATION

American Society of Anesthesiologists Classification and Risk Stratification

Approximately 27 million patients undergo surgery each year in the United States, and 8 million (30%) have significant coronary artery disease or other cardiac comorbidities. Appropriately,

the cardiovascular system is targeted during the preoperative assessment of patients. The ASA classification was first developed in 1961 and has been revised to categorize risk into six stratifications (Box 5-1).

The goal of the classification system is to assess the overall physical status of the patient before surgery (not to assess surgical risk), and although quite subjective, it remains a significant independent predictor of mortality (Davenport et al, 2006). Other tools to assess the preoperative risks were developed by multivariate statistical analysis of patient-related factors correlated with surgical outcomes. One such scoring system, Goldman's criteria (Table 5-1), assigns points to easily reproducible characteristics. The points are then added to compute the perioperative risk of cardiac-related complications. Another system, the Cardiac Risk Index, simplified this concept; it uses only six predictors to estimate cardiac complication risk in noncardiac surgical patients (Table 5-2) (Akhtar and Silverman, 2004).

Cardiac Evaluation

The preoperative cardiac evaluation, which consists of an initial history and physical examination and ECG, attempts to identify potential serious cardiac disorders such as coronary artery disease, heart failure, symptomatic arrhythmias, the presence of a pacemaker or implantable defibrillator, or a history of orthostatic hypotension (Eagle et al, 1996). Furthermore, it is essential

BOX 5-1 American Society of Anesthesiologists (ASA) Classification

- ASA Class I—Normal healthy patient
- ASA Class II—Patient with mild systemic disease
- ASA Class III—Patient with severe systemic disease that limits activity but is not incapacitating
- ASA Class IV—Patient who has incapacitating disease that is a constant threat to life
- ASA Class V—Moribund patient not expected to survive 24 hours with or without an operation
- ASA Class VI—A declared brain-dead patient whose organs are being removed for donor purposes
- ASA Class E—In the event of emergency surgery, an E is added after the Roman numeral (in I through V classes)

TABLE 5-1 Goldman's Cardiac Risk Index

PATIENT RISK FACTORS	POINTS
Third heart sound or jugular venous distention	11
Recent myocardial infarction	10
Nonsinus rhythm or premature atrial contraction on electrocardiogram	7
More than five premature ventricular contractions	7
Age older than 70 yr	5
Emergency operations	4
Poor general medical condition	3
Intrathoracic, intraperitoneal, or aortic surgery	3
Significant valvular aortic stenosis	3
For noncardiac surgery, the risk of cardiac complications is:	
• 6-12 points = 7% risk	
• 13-25 points = 14% risk	
• >26 points = 78% risk	

Modified from Akhtar S, Silverman DG. Assessment and management of patients with ischemic heart disease. Crit Care Med 2004;32:S126-36.

to define the severity and stability of existing cardiac disease before surgery. Cardiac-specific risk is also altered by the patient's functional capacity, age, and other comorbid conditions such as diabetes, peripheral vascular disease, renal dysfunction, and chronic obstructive pulmonary disease (COPD). The ACC and AHA recently collaborated to develop guidelines regarding perioperative cardiac evaluation before surgery (Fleisher et al, 2007a). In general, the guidelines use three categories of clinical risk predictors: clinical markers, functional capacity, and type of surgical procedure (Eagle et al, 2002).

Clinical Markers

The major clinical predictors of increased perioperative cardiovascular risk are a documented acute myocardial infarction less than 7 days previously, a recent myocardial infarction (defined as at least 7 days but less than 1 month before surgery), unstable angina, evidence of any ischemic burden by clinical symptoms or noninvasive testing, decompensated heart failure, significant arrhythmias, and severe valvular disease. Intermediate predictors include mild angina, previous myocardial infarction by history or pathologic Q waves, compensated heart failure, diabetes, or renal insufficiency (creatinine >2 mg/dL). Minor predictors of risk are advanced age, abnormal ECG, rhythms other than sinus (i.e., atrial fibrillation), history of stroke, or uncontrolled systemic hypertension. The historical dictum suggesting that elective surgery after a myocardial infarction be performed after a 3- to 6-month interval is now currently avoided (Tarhan et al, 1972). The ACC cardiovascular database committee stratifies risk on the basis of the severity of the myocardial infarction and the likelihood of reinfarction based on a recent exercise stress test. However, in the absence of adequate clinical trials on which to base firm recommendations, it is reasonable to wait 4 to 6 weeks after myocardial infarction to perform elective surgery.

Functional Capacity

Functional capacity, or one's ability to meet aerobic demands for a specific activity, is quantified as metabolic equivalents (METs). For example, a 4-MET demand is comparable with a patient's ability to climb two flights of stairs. This simple measurement continues to be an easy and inexpensive method to determine a patient's cardiopulmonary functional capacity (Biccard, 2005). The Duke Activity Status Index (Table 5-3) allows the physician to easily determine a patient's functional capacity (Hlatky et al, 1989). In general, a capacity of 4 METs indicates no further need for invasive cardiac evaluation.

Surgery-Specific Cardiac Risk

Two important factors determine the surgery-specific cardiac risk: the type of surgery and the degree of hemodynamic stress.

TABLE 5-2 Modified Cardiac Risk Index

PATIENT RISK FACTORS	POINTS
Ischemic heart disease	1
Congestive heart failure	1
Cerebral vascular disease	1
High-risk surgery	1
Preoperative insulin treatment for diabetes	1
Preoperative creatinine ≥ 2 mg/dL	1
Each increment in point increases risk of perioperative cardiovascular morbidity.	

Modified from Akhtar S, Silverman DG. Assessment and management of patients with ischemic heart disease. Crit Care Med 2004;32:S126-36.

TABLE 5-3 Duke Activity Status Index*

ACTIVITY	YES	NO
Can you take care of yourself (eating, dressing, bathing, or using the toilet)?	2.75	0
Can you walk indoors such as around your house?	1.75	0
Can you walk a block or two on level ground?	2.75	0
Can you climb a flight of stairs or walk up a hill?	5.50	0
Can you run a short distance?	8.00	0
Can you do light work around the house such as dusting or washing dishes?	2.70	0
Can you do moderate work around the house such as vacuuming, sweeping floors, or carrying in groceries?	3.50	0
Can you do heavy work around the house such as scrubbing floors or lifting and moving heavy furniture?	8.00	0
Can you do yardwork such as raking leaves, weeding, or pushing a power mower?	4.50	0
Can you have sexual relations?	5.25	0
Can you participate in moderate recreational activities such as golf, bowling, dancing, doubles tennis, or throwing a baseball or football?	6.00	0
Can you participate in strenuous sports such as swimming, singles tennis, football, basketball, or skiing?	7.50	0
Duke activity status index (DASI) = SUM (values for all 12 questions).		
Estimated peak oxygen uptake ($\dot{V}O_{2peak}$) in mL/min = $0.43 \times$ (DASI) + 9.6.		
$\dot{V}O_{2peak}$ mL/kg/min – 0.286 (mL/kg/min) ⁻¹ = METs		

*The most widely recognized measure of cardiorespiratory fitness is maximal oxygen consumption ($\dot{V}O_{2peak}$) measured in mL/kg/min. The Index score correlates directly with $\dot{V}O_{2peak}$ and therefore is an indirect measure of maximal METs.

Modified from Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;64:651–4.

Surgery-specific risk is stratified into high-, intermediate-, and low-risk procedures. High-risk procedures include both major emergent surgery, particularly in the elderly, and surgery associated with increased operative time resulting in large fluid shifts or blood loss. Intermediate risk procedures include intraperitoneal surgery, laparoscopic procedures, and robotic-assisted laparoscopic surgeries. Low-risk procedures include endoscopic procedures or superficial surgeries (i.e., not involving entrance into a body cavity) (Eagle et al, 2002).

Pulmonary Evaluation

Preoperative pulmonary evaluation is important in all urologic procedures but critical in those surgeries involving the thoracic or abdominal cavities. These procedures, which include intra-abdominal, laparoscopic, or robotic surgeries, can decrease pulmonary function and predispose to pulmonary complications. Accordingly, it is wise to consider pulmonary functional assessment in patients who have significant underlying medical disease, significant smoking history, or overt pulmonary symptoms. Pulmonary function tests that include a forced expiratory volume in 1 second (FEV₁), forced vital capacity, and the diffusing capacity of carbon monoxide are quite easily performed and provide a preoperative baseline. Patients with an FEV₁ of less than 0.8 L/sec or 30% of predicted are at high risk for complications

(Arozullah et al, 2003). Specific pulmonary risk factors include COPD, smoking, preoperative sputum production, pneumonia, dyspnea, and obstructive sleep apnea. It has been shown that smokers have a fourfold increased risk for postoperative pulmonary morbidity and as high as a 10-fold higher mortality rate (Fowkes et al, 1982). In general, it is interesting to note that patients with restrictive pulmonary disease fare better than those with obstructive pulmonary disease because the former group maintains an adequate maximal expiratory flow rate, which allows for a more effective cough with less sputum production (Pearce and Jones, 1984). In addition to the specific pulmonary risk factors, general factors contribute to increased pulmonary complications such as increased age, lower serum albumin levels, obesity, impaired sensorium, previous stroke, immobility, acute renal failure, and chronic steroid use.

Hepatobiliary Evaluation

Because the survival of patients with advanced liver disease has improved over the past decade, surgery is being performed more frequently in these patients. Furthermore, patients with mild to moderate hepatic disease are often asymptomatic. These patients need to be identified and evaluated before surgery. Patients are usually aware of a prior diagnosis of hepatitis, and they should be questioned regarding the timing of diagnosis and the precipitating factors. This history is particularly important if a member of the health care team is inadvertently stuck with a needle or scalpel during the surgical procedure. A review of systems should include questions regarding pruritus, excessive bleeding, abnormal abdominal distention, and weight gain. On physical examination, jaundice and scleral icterus may be evident with serum bilirubin levels higher than 3 mg/dL. Skin changes such as caput medusae, palmar erythema, spider angiomas, and clubbing all indicate hepatic dysfunction. Severe manifestations include abdominal distention, encephalopathy, asterixis, or cachexia. Again, identification of underlying hepatic illness is important in the preoperative risk assessment of the patient. Although the estimation of perioperative mortality is limited by the lack of high-quality clinical studies, the use of the Child classification and Model for End-Stage Liver Disease (MELD) score offers a reasonable estimation.

The Child classification assesses perioperative morbidity and mortality in patients with cirrhosis and is based on the patient's serum markers (bilirubin, albumin, PT) and severity of clinical manifestations (i.e., encephalopathy and ascites). Mortality risk for patients undergoing surgery stratified by Child class is as follows: Child Class A—10%, Child Class B—30%, and Child Class C—76% to 82%. The Child classification also correlates with the frequency of complications such as liver failure, encephalopathy, bleeding, infection, renal failure, hypoxia, and intractable ascites. Independent risk factors other than the Child class that can increase the mortality rate in patients with liver disease include emergency surgery and COPD (Pearce and Jones, 1984; O'Leary et al, 2009).

The MELD score is perhaps a more accurate assessment of perioperative mortality in patients with hepatic dysfunction. The score is derived from a linear regression model based on serum bilirubin, creatinine levels, and the INR. It is more accurate than the Child classification in that it is objective, gives weights to each variable, and does not rely on arbitrary cutoff values (Teh et al, 2007). Clinicians can use a website (<http://mayoclinic.org/meld/mayomodel9.html>) to calculate the 7-day, 30-day, 90-day, 1-year, and 5-year surgical mortality risk on the basis of the patient's age, ASA class, INR, serum bilirubin, and creatinine levels. A recent study also found that MELD score was tightly correlated with 30-day mortality risk in all patients undergoing colorectal surgery regardless of the presence of liver disease (Hedrick et al, 2013). Taken together, the Child classification and the MELD score complement each other and provide an important assessment of the risk of surgery in cirrhotic patients (O'Leary and Friedman, 2007; O'Leary et al, 2009).

OPTIMIZATION OF COMORBID ILLNESS

Just as adequate preoperative evaluation is important, optimization of comorbid illness is critical in reducing perioperative morbidity and mortality. With regard to cardiac disease, many studies have evaluated the prophylactic use of nitrates, calcium-channel blockers, and β -blockers for patients who are at risk for perioperative myocardial ischemia. Only β -blockade has been shown to improve outcomes (Pearse et al, 2004). In a landmark study, Mangano and colleagues reported in the *New England Journal of Medicine* that there was an improvement in outcomes with the prophylactic use of atenolol in patients undergoing vascular surgery (Mangano et al, 1996). Similarly, a retrospective, cooperative group study of more than half a million patients showed that perioperative β -blockade is associated with a reduced risk of death among high-risk patients undergoing major noncardiac surgery (Lindenauer et al, 2005). In addition to β -blockade, the concept of goal-directed therapy, employing the judicious use of fluids, inotropes, and oxygen therapy to achieve therapeutic goals, may further reduce perioperative risk (Pearse et al, 2004). This concept was validated by Shoemaker, who reported an impressive reduction in mortality from 28% to 4% ($P < .02$) when goal-directed therapy was used (Shoemaker et al, 1988).

Specific preoperative interventions can decrease pulmonary complications. Smoking must be discontinued at least 8 weeks before surgery to achieve a risk reduction. Patients who discontinue smoking less than 8 weeks before surgery may actually have a higher risk of complication because the acute absence of the noxious effect of cigarette smoke decreases postoperative coughing and pulmonary toilet. **However, patients who stop smoking at least 8 weeks preoperatively will significantly lower their complication rate, and patients who have ceased smoking for more than 6 months have a pulmonary morbidity comparable with that of nonsmokers (Warner et al, 1989).** The use of preoperative bronchodilators in COPD patients can dramatically reduce postoperative pulmonary complications. Aggressive treatment of preexisting pulmonary infections with antibiotics, as well as the pretreatment of asthmatic patients with steroids, is essential in optimizing pulmonary performance. Likewise, the use of epidural and regional anesthetics, vigorous pulmonary toilet, rehabilitation, and continued bronchodilation therapy are all beneficial (Arozullah et al, 2003).

As with cardiopulmonary comorbidities, the preoperative management and optimization of diabetic patients are quite important. Perioperative hyperglycemia can lead to impaired wound healing and a higher incidence of infection (Golden et al, 1999). Hypoglycemia in an anesthetized or sedated diabetic patient may be unrecognized and carries its own significant risks. **Non-insulin-dependent diabetic patients may need to discontinue long-acting hypoglycemics because of this risk of intraoperative hypoglycemia. Shorter-acting agents or sliding scale insulin regimens are preferable, in general.** It is recommended that blood glucose levels be controlled between 80 and 250 mg/dL. Frequent fingerstick glucose checks and a sliding scale short-acting insulin regimen are used in the postoperative period. Once the patient is eating, the usual insulin regimen can be resumed. Patients who monitor their diabetes with the use of insulin pumps should continue their basal insulin infusions on the day of surgery. The pump is then used to correct the glucose level as it is measured. It is important to know the sensitivity factor that corrects the glucose so that the patient's sugars can be managed in the operating room (Townsend et al, 2008).

Patients with either hyperthyroidism or hypothyroidism should be evaluated by an endocrinologist, and surgery should be deferred until a euthyroid state has been achieved. **The greatest risk in the hypothyroid patient is thyrotoxicosis or thyroid storm, which can manifest with fevers, tachycardia, confusion, and cardiovascular collapse.** Atrial fibrillation may also be present in 20% of hyperthyroid patients (Klein and Ojamaa, 2001). With regard to hyperthyroidism, careful attention should be given to the airway because the trachea can be compressed or deviated by a large goiter. In general, antithyroid medications such as propylthiouracil or

methimazole, as well as β -blockers, are continued on the day of surgery. In the event of thyroid storm, iodine and steroids may be necessary (Schiff and Welsh, 2003). Hypothyroidism is usually associated with an increased sensitivity to medications such as anesthetic agents and narcotics. Severe hypothyroidism can be associated with myocardial dysfunction, coagulopathy, electrolyte imbalance, and a decreased gastrointestinal (GI) motility. Symptoms include lethargy, cold intolerance, hoarseness, constipation, dry skin, and apathy. The decrease in metabolic rate produces periorbital edema, thinning of the eyebrows, brittle hair, dry skin, hyperthermia, bradycardia, and a prolonged relaxation of the deep tendon reflexes (Murkin, 1982). Once the diagnosis has been confirmed by a low thyroxine level and an elevated thyroid stimulating hormone level, thyroid replacement with levothyroxine can be initiated (Schiff and Welsh, 2003).

The evaluation of the patient either taking corticosteroids or suspected of having an abnormal response of the hypothalamic-pituitary-adrenal (HPA) axis is also important. There is a wide variability in HPA suppression in patients receiving exogenous steroids. Nonetheless, it seems clear that the administration of oral steroids equivalent to less than 5 mg of prednisone for any duration of time does not cause clinically significant suppression of the HPA axis. **By contrast, any patient taking more than 20 mg of prednisone or its equivalent per day for more than 3 weeks or who is clinically cushingoid has probable HPA axis suppression (LaRoche et al, 1993).** HPA suppression can occur even in patients using potent topical steroids at doses of 2 g/day, as well as in patients using inhaled corticosteroids at doses of 0.8 mg/day. Although the duration of functional HPA axis suppression after glucocorticoids have been stopped is debatable, perioperative supplemental steroids are recommended for patients who have received HPA axis-suppressive doses within 1 year of surgery. A low-dose adrenocorticotrophic hormone (ACTH) stimulation test can be used to assess the HPA axis and the need for stress steroids. For patients who take 5 mg of prednisone or the equivalent each day, no supplemental steroids are necessary and the usual daily glucocorticoid dose may be given in the perioperative period. **For those in whom the HPA axis is presumed to be suppressed or is documented to be suppressed, then 50 to 100 mg of intravenous hydrocortisone is given before the induction of anesthesia and 25 to 50 mg of hydrocortisone is given every 8 hours thereafter for 24 to 48 hours until the usual steroid dose can be resumed.** Minor procedures under local anesthesia do not require stress-dose steroids (Schiff and Welsh, 2003).

SPECIAL POPULATIONS

Elderly

It is estimated that by 2050 the number of Americans over the age of 65 will more than double to 89 million individuals, with more than 20% over the age of 85 (Jacobsen et al, 2011). Accordingly, octogenarians and nonagenarians are undergoing an increasing number of surgeries annually. Because of elderly patients' special physiologic, pharmacologic, and psychological needs, a unique set of health care challenges is encountered. It is still unclear whether advanced age independently predicts surgical risk or whether it is coexisting medical conditions that adversely affect surgical outcomes. However, in a large study published by Turrentine, it was shown that increased age independently predicted morbidity and mortality (Turrentine et al, 2006). This confirmed the study by Vemuri, who also found increased age to be an independent risk factor for morbidity and mortality in patients undergoing aneurysm surgery (Vemuri et al, 2004). Within the urologic literature, Liberman and colleagues reported 90-day mortality rates after radical cystectomy in patients younger than 70 years, 70 to 80 years, and older than 80 years of 2%, 5.4%, and 9.2%, respectively (Liberman et al, 2011). The studies suggest that independent of comorbidities, perhaps the elderly patient cannot meet the increased functional demand required during the perioperative and postoperative periods. Hypertension and dyspnea were the most frequently seen comorbid risk factors in patients older than 80 years, and

preoperative transfusion history, emergency operation, and weight loss best predicted postoperative morbidity. Each 30-minute increase of operative time increased the odds of mortality by 17% in octogenarians (Turrentine et al, 2006). A unique and important factor in the perioperative care of the elderly is in the identification and prevention of delirium. Often overlooked as “sundowning,” delirium can be the first clinical sign of metabolic and infectious complications (Townsend et al, 2008).

Morbid Obesity

With the rising incidence of obesity, as well as the vast experience gathered from bariatric surgery, the care of the morbidly obese patient has been extensively studied. One must carefully weigh the risk of any surgical procedure with the natural history of the disease when deciding the optimal time of the surgery in the morbidly obese. **It is estimated that patients with a body mass index (BMI) of 45 kg/m² or higher may lose anywhere from 8 to 13 years of life expectancy** (Fontaine et al, 2003). The careful selection of the morbidly obese patient for elective surgery is of paramount importance. Cardiac symptoms such as exertional dyspnea and lower extremity edema are nonspecific in morbidly obese patients, and many of these patients have poor functional capacity. The physical examination often underestimates cardiac dysfunction in the severely obese patient. Severely obese patients with more than three coronary heart disease risk factors may require noninvasive cardiac evaluation (Poirier et al, 2009). Obesity is associated with a vast array of comorbidities. Morbidly obese patients often have atherosclerotic cardiovascular disease, heart failure, systemic hypertension, pulmonary hypertension related to sleep apnea and obesity, hypoventilation, cardiac arrhythmias, deep vein thrombosis, history of pulmonary embolism, and poor exercise capacity. There are also numerous pulmonary abnormalities that result in a ventilation-perfusion mismatch and alveolar hypoventilation. Obesity is a risk factor for postoperative wound infections, and, when appropriate, laparoscopic surgery should be considered.

Pregnancy

Urologic surgery in the pregnant woman is most commonly related to the management of renal colic and urinary tract stones. In the asymptomatic woman, the stones can be discovered during the sonographic evaluation of the fetus or during the evaluation of the pregnant woman who is experiencing renal colic. **The fetus is at the highest risk from radiation exposure from the preimplantation period to approximately 15 weeks' gestation.** Because the radiation dose that is associated with congenital malformations is 10 cGy, the evaluation of renal colic in a pregnant patient is performed usually with sonography (radiation dose with abdominal computed tomography [CT]—1 cGy; intravenous pyelogram—0.3 cGy). The indications for operative intervention in the pregnant patient are discussed elsewhere in this book. Anesthetic risks during pregnancy concern both the mother and the fetus. During the first trimester the fetus may be directly exposed to the teratogenic effects of certain anesthetic agents. Later in pregnancy, anesthesia places the mother at risk for preterm labor and the fetus at risk for hypoxemia secondary to changes in uterine blood flow and maternal acid base balance. These risks seem to be greatest during the first and third trimesters. **For semielective procedures, an attempt should be made to delay surgery until after the first trimester.** However, one must consider the continued exposure of the underlying condition in relation to the operative risks to both the mother and the fetus. **The second trimester is the safest time to perform surgery because organ system differentiation has occurred and there is almost no risk for anesthetic-induced malformation or spontaneous abortion.** When one is contemplating surgery on a pregnant patient, consultation with the obstetrician, perinatologist, and anesthesiologist is essential. These specialists will help determine the optimum technique to monitor the status of the fetus. Fetal heart rate monitors and tocometer monitoring for

uterine activity are used before and after the procedure. Postoperative pain is best managed with narcotic analgesics because they have not been shown to cause birth defects in humans when used in normal dosages. Nonsteroidal anti-inflammatory medication should be avoided because of the risk for premature closure of the ductus arteriosus. Chronic use of narcotics during pregnancy may cause fetal dependency, and it is recommended that the pregnant postsurgical patient be weaned off narcotic use as soon as possible (Mikami et al, 2008).

Nutritional Status

Malnutrition compromises host defenses and increases the risk of perioperative morbidity and mortality. Adequate nutritional status is essential for proper wound healing, management of infections, return of GI activity, and maintenance of vital organ status (McDougal, 1983). The preoperative evaluation and classification of the patient's nutritional status typically consist of the assessment of any recent weight loss and the measurement of laboratory values, such as lymphocyte count and serum albumin. A 20-pound weight loss in the preceding 3 months before surgery is considered to be a reflection of severe malnutrition. The lymphocyte count and serum albumin level reflect visceral protein status, with lower levels indicating malnutrition (Reinhardt et al, 1980). Several assessment tools have been validated to quantitate nutritional status, including the Subjective Global Assessment (<http://subjectiveglobalassessment.com>).

There are two methods for nutritional support. Total parenteral nutrition (TPN) is used for patients who are severely malnourished and who have a nonfunctioning GI tract. Several studies have shown that 7 to 10 days of preoperative parenteral nutrition improves postoperative outcome in undernourished patients (Von Meyenfeldt et al, 1992). However, its use in well-nourished or mildly undernourished patients either is of no benefit or increases risk of sepsis (**Perioperative total parenteral nutrition in surgical patients, 1991**). On the other hand, enteral nutrition has fewer complications than TPN and can provide a more balanced physiologic diet. Elemental nutrition is accomplished via a feeding tube, gastrostomy, or feeding jejunostomy. Enteral nutrition maintains the gut-associated lymphoid tissue, enhances mucosal blood flow, and maintains the mucosal barrier. There are hundreds of enteral products on the market, and most have a caloric density of 1 to 2 kcal/mL. These formulas are also lactose free and provide the recommended daily allowances of vitamins and minerals in less than 2 L/day. The patients receiving enteral feedings must be monitored for improvement in nutritional status, GI intolerance, and fluid and electrolyte imbalance. **Preoperative enteral feedings can decrease postoperative complication rates by 10% to 15% when used for 5 to 20 days before surgery** (**Guidelines for the use of parenteral and enteral nutrition, 2002**). **The guidelines recommend postoperative parenteral nutrition in patients who are unable to meet their caloric requirements within 7 to 10 days.** Just as in the perioperative state, enteral feedings are preferred over parenteral nutrition when feasible. Moreover, the routine use of postoperative TPN has not proven useful in well-nourished patients or in those with adequate oral intake within 1 week after surgery (Byers and Hameed, 2008). Complications can occur with either enteral nutrition or parenteral nutrition. Dislodgement of nasoenteral tubes and percutaneous enteral catheters can result in pulmonary and peritoneal complications. Adynamic ileus may also occur because of decreased splanchnic perfusion, sympathetic tone, or opiate use. With regard to TPN, establishing central access is associated with a significant risk of complications. These include pneumothorax or hemothorax secondary to poor line placement and chylothorax secondary to thoracic duct injury. Line sepsis is the most common complication of indwelling central catheters and necessitates catheter removal. Venous thrombosis with associated thrombophlebitis and extremity edema has been reported. Catheter thrombosis has also been reported and can be treated with thrombolytic agents (**Guidelines for the use of parenteral and enteral nutrition, 2002**).

PREPARATION FOR SURGERY

Antibiotic Prophylaxis

In 1999 the Centers for Disease Control and Prevention (CDC) issued its third report on the prevention of surgical site infections (SSIs), highlighting the importance of standardization of prophylactic treatment to prevent this universal surgical complication (Mangram et al, 1999). The report indicated that SSIs account for approximately 40% of nosocomial infections in surgical patients and potentially prolong hospital stay by 7 to 10 days. A study of national SSIs from the 2005 Healthcare Cost and Utilization Project National Inpatient Sample (HCUP NIS) calculated an increase in hospital stay of 9.7 days and in per-patient cost of \$20,892 (de Lissoy et al, 2009). This translated nationally into an additional 1 million inpatient hospital days and additional health care cost of \$1.6 billion. Bowater and colleagues published a systematic review of meta-analyses (level 1 evidence) and concluded that there was substantial evidence that antibiotic prophylaxis was an effective prevention for SSI over a wide variety of surgical procedures (Bowater et al, 2009). Given both the ethical responsibility of the surgeon to decrease surgical morbidity and the recent policy shift by the Centers for Medicare and Medicaid Services to withhold reimbursement for hospital admissions secondary to specific SSI, it is mandatory for urologists to understand the principles behind and to practice SSI prevention.

Along with antibiotic prophylaxis, proper hand washing and scrubbing and sterile preparation of the operative field have always been central to the prevention of SSI. For procedures involving the GI tract, mechanical and oral antibiotic bowel preparation had been standard practice until more recent literature, calling into question its usefulness (discussed later). Preoperative hair removal has not been associated with a decrease in SSI, but if performed, use of mechanical clippers or depilatory creams as opposed to razors is associated with a decreased risk of SSI (Wolf et al, 2008).

The risk of SSI and therefore the recommendation for antibiotic prophylaxis is composed of three risk factors: the patient's susceptibility to and ability to respond to localized and systemic infection, the procedural risk of infection, and the potential morbidity of infection. Patient-related factors, listed in Box 5-2, increase risk by decreasing natural defenses, increasing the local bacterial concentration, and/or altering the spectrum of bacterial flora. Second, surgical procedure-specific factors can affect the route of entry, site of infection, and pathogen involved. This idea was first described in the landmark study from the National Research Council and later formalized by the CDC; specifically, surgical wounds are now classified by degree of contamination (i.e., the inoculum of potential

BOX 5-2 Patient Factors That Increase the Risk of Infection

Advanced age
Anatomic anomalies
Poor nutritional status
Smoking
Chronic corticosteroid use
Immunodeficiency
Chronic indwelling hardware
Infected endogenous or exogenous material
Distant coexistent infection
Prolonged hospitalization

Data from Cruse PJ. Surgical wound infection. In: Wonsiewicz MJ, editor. Infectious disease. Philadelphia: Saunders; 1992. p. 758–64; and Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250–78; quiz 279–80.

pathogen) (Box 5-3; Hart et al, 1968). To predict the risk of SSI, several scoring systems have been developed incorporating patient-related factors with wound classification. Finally, the risk to the patient from SSI is an important consideration in determining the need for prophylaxis. For example, routine cystoscopy in the evaluation of microhematuria in an otherwise young, healthy patient may not warrant prophylaxis; however, the same procedure in an elderly, insulin-dependent diabetic (immunocompromised) does warrant prophylaxis given the high likelihood that a postprocedural urinary tract infection would result in a significant deterioration in the patient's overall health. Understanding the three factors together then allows the urologist to make a rational decision regarding the risks and benefits of antibiotic prophylaxis.

Once the decision for antibiotic prophylaxis has been made, the keys to successful prevention are proper timing and administration of the antibiotic and the proper choice of antibiotic for the particular procedure. Since the pivotal study by Classen and colleagues, particular emphasis has been placed on the timing of prophylaxis to be given within 2 hours of incision (Classen et al, 1992). This emphasis was exemplified by the Joint Commission's Surgical Care Improvement Project (SCIP) guideline for administration of antibiotic prophylaxis 60 minutes before incision in a broader effort to decrease overall surgical complications by 25% by 2010. A multi-institutional trial involving more than 4400 patients at 29 institutions reported results of their analysis on the optimal timing of antibiotic prophylaxis (Steinberg et al, 2009). The results suggested an improvement in prevention of SSI when antibiotics were administered within 30 minutes of incision as compared with 31 to 60 minutes (adjusted odds ratio [OR] 1.48, $P = .06$). More important, this larger study confirmed the significantly increased risk of SSI when antibiotics were administered at the time of or following incision, with an adjusted OR of 2.20, $P = .02$. The duration of antibiotic prophylaxis is more controversial; however, most recommendations advocate no more than 24 hours in a patient without an established infection. Routine antibiotic use beyond 24 hours increases the risk of *Clostridium difficile* colitis, increases the development of antibiotic resistance, and increases costs. Along with timing and duration, proper administration of

BOX 5-3 Surgical Wound Classification

CLEAN

- Uninfected wound without inflammation or entry into the genital, urinary, or alimentary tract
- Primary wound closure, closed drainage

CLEAN CONTAMINATED

- Uninfected wound with controlled entry into the genital, urinary, or alimentary tract
- Primary wound closure, closed drainage

CONTAMINATED

- Uninfected wound with major break in sterile technique (gross spillage from gastrointestinal tract or nonpurulent inflammation)
- Open fresh accidental wounds

DIRTY INFECTED

- Wound with preexisting clinical infection or perforated viscera
- Old traumatic wounds with devitalized tissue

Data from Garner JS. CDC guideline for prevention of surgical wound infections, 1985. Supersedes guideline for prevention of surgical wound infections published in 1982. (Originally published in 1995.) Revised. Infect Control 1986;7(3):193–200; and Simmons BP. Guideline for prevention of surgical wound infections. Infect Control 1982;2:185–96.

antibiotics implies proper dosage. Antibiotic dose is dependent on the patient's body weight, renal function and hepatic function, and duration of procedure (readministration is required if longer than 4 hours). The second key to successful prevention is the proper choice of antibiotic for the procedure in question. As mentioned earlier, surgery-specific factors affect the type of pathogen, route of entry, and likelihood of systemic infection. For example, the choice of antibiotic is different for transurethral resection of the prostate (TURP; need coverage for common urinary tract pathogens) than for a cystectomy with planned sigmoid colon urinary diversion (need coverage for anaerobic bacteria). Another important consideration is the rate of antibiotic resistance in the community. **Although there is level 1 evidence for the use of fluoroquinolones as prophylaxis for urologic endoscopic procedures, the emerging *Escherichia coli* resistance in the community is changing practice patterns in many practices and high-resistance hospitals.** One resource that is particularly useful is the hospital antibiogram. These reports are published monthly at most major hospitals and quantify the susceptibility and resistance of common organisms to a wide variety of antibiotics. A summary of the recent American Urological Association (AUA) best practice statement on antibiotic prophylaxis

is shown in Table 5-4. In 2012 the AUA issued an amendment to the best practice statement with regard to prostate biopsy, acknowledging the emerging resistance to fluoroquinolones and recommending cephalosporins and/or aminoglycosides in certain communities.

Bowel Preparation

Since antibiotics were first shown to reduce infectious complications in GI surgery, mechanical and antibiotic bowel preparation has been a mainstay of urologic surgery employing intestinal segments. The rationale for bowel preparation before intestinal surgery is to decrease intraluminal feces and decrease bacterial colony counts to decrease the rate of anastomotic leak, intra-abdominal abscesses, and wound infections. The bacterial flora in the bowel consists of aerobic organisms, the most common of which are *E. coli* and *Enterococcus faecalis*, and anaerobic organisms, the most common of which are *Bacteroides* species and *Clostridium* species. **The bacterial concentration ranges from 10 to 10⁵ organisms per gram of fecal content in the jejunum, 10⁵ to 10⁷ in the distal ileum, 10⁶ to 10⁸ in the ascending colon, and 10¹⁰ to 10¹² in the**

TABLE 5-4 American Urological Association Best Practice Statement on Recommended Antimicrobial Prophylaxis for Urologic Procedures

PROCEDURE	ORGANISMS*	PROPHYLAXIS INDICATED?	ANTIMICROBIALS OF CHOICE	ALTERNATIVE ANTIMICROBIALS	DURATION
LOWER TRACT INSTRUMENTATION					
Removal of external urinary catheter	GU tract	If risk factors	Fluoroquinolone TMP-SMX	Aminoglycoside ± ampicillin First- or second-generation cephalosporin Amoxicillin/clavulanate	≤24 hr
Cystography, urodynamic study, or simple cystoscopy	GU tract	If risk factors	Fluoroquinolone TMP-SMX	Aminoglycoside ± ampicillin First- or second-generation cephalosporin Amoxicillin/clavulanate	≤24 hr
Cystoscopy with manipulation	GU tract	All	Fluoroquinolone TMP-SMX	Aminoglycoside ± ampicillin First- or second-generation cephalosporin Amoxicillin/clavulanate	≤24 hr
Prostate brachytherapy or cryotherapy	Skin	Uncertain	First-generation cephalosporin	Clindamycin	≤24 hr
Transrectal prostate needle biopsy	Intestine	All	Fluoroquinolone Second- or third-generation cephalosporin	Aminoglycoside + metronidazole or clindamycin	≤24 hr
UPPER TRACT INSTRUMENTATION					
Shock-wave lithotripsy	GU tract	All	Fluoroquinolone TMP-SMX	Aminoglycoside ± ampicillin First- or second-generation cephalosporin Amoxicillin/clavulanate	≤24 hr
Percutaneous renal surgery	GU tract Skin	All	First- or second-generation cephalosporin Aminoglycoside + metronidazole or clindamycin	Ampicillin/sulbactam Fluoroquinolone	≤24 hr
Ureteroscopy	GU tract	All	Fluoroquinolone TMP-SMX	Aminoglycoside ± ampicillin First- or second-generation cephalosporin Amoxicillin/clavulanate	≤24 hr

TABLE 5-4 American Urological Association Best Practice Statement on Recommended Antimicrobial Prophylaxis for Urologic Procedures—cont'd

PROCEDURE	ORGANISMS*	PROPHYLAXIS INDICATED?	ANTIMICROBIALS OF CHOICE	ALTERNATIVE ANTIMICROBIALS	DURATION
OPEN OR LAPAROSCOPIC SURGERY					
Vaginal surgery (including urethral sling procedures)	GU tract Skin Group B <i>Streptococcus</i>	All	First- or second-generation cephalosporin Aminoglycoside + metronidazole or clindamycin	Ampicillin/sulbactam Fluoroquinolone	≤24 hr
Open or laparoscopic surgery without entering GU tract	Skin	If risk factors	First-generation cephalosporin	Clindamycin	Single dose
Surgery involving entry into GU tract	GU tract Skin	All	First- or second-generation cephalosporin Aminoglycoside + metronidazole or clindamycin	Ampicillin/sulbactam Fluoroquinolone	≤24 hr
Intestinal surgery	GU tract Skin Intestinal flora	All	Second- or third-generation cephalosporin Aminoglycoside + metronidazole or clindamycin	Ampicillin/sulbactam Ticarcillin/clavulanate Piperacillin/tazobactam Fluoroquinolone	≤24 hr
Implanted prosthesis	GU tract Skin	All	Aminoglycoside + first- or second-generation cephalosporin or vancomycin	Ampicillin/sulbactam Ticarcillin/clavulanate Piperacillin/tazobactam	≤24 hr

*Common pathogens include the following: GU tract—*Escherichia coli*, *Proteus*, *Klebsiella*, *Enterococcus*; skin—*Staphylococcus aureus*, coagulase-negative *Staphylococcus* species, group A *Streptococcus*; and intestine—*E. coli*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus*, *Enterococcus*, and anaerobes.

GU, genitourinary; TMP-SMX, trimethoprim-sulfamethoxazole.

Modified from Wolf JS Jr, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol* 2008;179:1379–90.

descending colon. The preparation itself consists of two components: antibiotic preparation and mechanical preparation. Because there are only a few small series in the urologic literature, the rationale for each must be inferred from the general surgery literature—specifically, from colorectal surgery literature.

Although preoperative parenteral antibiotic prophylaxis before intestinal surgery is well established and widely used, oral antibiotic preparation is still somewhat controversial. Several oral antibiotic regimens are used today. The most commonly used regimen, oral neomycin and erythromycin, first became established with the landmark study by Nichols and Condon in 1977 (Clarke et al, 1977). In a double-blind, placebo-controlled study, 167 patients undergoing elective colonic surgery were randomized to receive mechanical bowel preparation with or without oral neomycin and erythromycin. The overall rates of septic complications were 43% with mechanical-only preparation and 9% with antibiotic plus mechanical preparation ($P = .001$). However, with current standards of the use of preoperative parenteral antibiotics, the benefit of oral antibiotic preparation was debated. Several older studies reported decreased infectious complications; however, these studies were small and there have been no randomized controlled trials (RCTs) to document the benefit. The disadvantage of oral antibiotic preparation is primarily related to increased incidence of pseudomembranous colitis secondary to *C. difficile* infection. In a retrospective analysis of 304 patients, Wren and colleagues reported a significantly decreased incidence of *C. difficile* colitis in patients who did not receive oral antibiotics before elective colorectal surgery (2.6% vs. 7.2%, $P = .03$) (Wren et al, 2005). Inferring from the

colorectal literature, most current guidelines and a 2009 Cochrane review recommend both intravenous and oral antibiotic prophylaxis before elective colorectal surgery (Nelson et al, 2009). Despite the lack of level 1 evidence in the literature, a recent survey of colorectal surgeons revealed that up to 87% of surgeons continue to administer oral antibiotic bowel preparation before elective surgery (Zmora et al, 2003).

Mechanical bowel preparation predates the use of antibiotics in intestinal surgery and was thought to decrease the rate of anastomotic complications. Before the development of nonabsorbable liquids, patients underwent several days of oral laxatives, bowel irrigations via nasogastric tubes, and repeat enemas. These regimens were associated with significant patient discomfort and clinical morbidity caused by electrolyte imbalances. The development of polyethylene glycol solution (GoLYTELY) and sodium phosphate solution (Fleet Phospho-soda) reduced much of the electrolyte disturbance and allowed for mechanical bowel preparation to be done in the outpatient setting. Both regimens are suitable for most patients; however, polyethylene glycol is preferred in the elderly and in patients with renal insufficiency, congestive heart failure, existing electrolyte disturbances, and cirrhosis because it is completely nonabsorbable.

The benefit of mechanical bowel preparation has been assumed for decades as evidenced by 99% positive response by colorectal surgeons when asked if mechanical preparation is routinely used (Zmora et al, 2003). However, RCTs have called into doubt the true benefit. Slim and colleagues published a meta-analysis of RCTs including a total of 4859 patients (Slim et al, 2009). The analysis

included 14 trials including two large trials from the Netherlands and Sweden (Contant et al, 2007; Jung et al, 2007). Overall, the analysis revealed that mechanical bowel preparation provided no benefit for anastomotic leak (OR 1.12, 95% confidence interval [CI] 0.82 to 1.53, $P = .46$); abdominal or pelvic abscess (OR 0.90, 95% CI 0.47 to 1.72, $P = .75$); or mortality (OR 0.91, 95% CI 0.57 to 1.45, $P = .70$). In fact, when overall SSI was considered, mechanical bowel preparation was associated with a significantly increased risk (OR 1.40, 95% CI 1.05 to 1.87, $P = .02$). These results were reiterated in an updated Cochrane review, which found no significant differences in anastomotic leak rate or wound infection, need for reoperation, and mortality rates (Guenaga et al, 2011). The authors concluded that there was no evidence that mechanical bowel preparation improves patient outcome after elective colorectal surgery. Although similar studies have not been done in patients undergoing elective urologic surgery, urologists can make inferences from the colorectal literature and should reevaluate the common practice of mechanical bowel preparation before urologic intestinal surgery. To date there have been multiple single institution reports suggesting equivalent SSI outcomes with or without bowel preparation before radical cystectomy and urinary diversion (Zaid et al, 2013). Two specific exceptions are transrectal ultrasound-guided prostate needle biopsy and laparoscopic urologic surgery. Given the portal of entry and subsequent risk of bacteremia, most urologists have advocated for mechanical rectal cleansing with an enema before transrectal ultrasound-guided prostate needle biopsy. With regard to laparoscopy, surgeons who perform minimally invasive procedures have long believed that preoperative bowel preparation improves operative exposure because of bowel decompression and decreases the incidence of postoperative ileus. However, to date there have been no trials to support this assertion.

In the early postoperative period, most patients experience some degree of primary ileus and delayed GI activity. Any patient with ileus lasting more than 72 to 96 hours after surgery should be evaluated for a mechanical bowel obstruction secondary to adhesions, an intra-abdominal pathologic process, or retroperitoneal hemorrhage. Given that return of GI function is often the rate-limiting factor for hospital discharge, efforts to reduce ileus including minimization of parenteral or oral opioid use, selective use of nasogastric tubes, and correction of electrolyte imbalances should be employed. More recently, methods to accelerate GI recovery have been investigated. Gum chewing—that is, sham feeding—was evaluated and reported to be associated with improvements in GI recovery and reduction in length of stay in patients undergoing colorectal surgery (Ho et al, 2014). Alvimopan (Entereg) is a peripherally acting opioid antagonist that was approved by the U.S. Food and Drug Administration (FDA) in 2008 to help restore bowel function after surgery. With the validation of alvimopan established in the colorectal literature, there have been several studies performed in

patients undergoing cystectomy including a phase 4 trial whose findings were recently published. Use of alvimopan compared with placebo resulted in decreased length of stay of 2.6 days in patients undergoing radical cystectomy (Kauf et al, 2014). Many high-volume centers are now incorporating both strategies into enhanced recovery after surgery (ERAS) clinical pathways to reduce postoperative ileus and reduce hospital stays.

Venous Thromboembolic Prophylaxis

Venous thromboembolic complications are a major cause of potentially preventable morbidity and mortality among surgical patients in the United States. A recent study from the Center for Quality Improvement and Patient Safety and the Agency for Healthcare Research and Quality found postoperative venous thromboembolism (VTE) to be the second most common cause of excess length of stay, charges, and mortality among surgical patients discharged from acute care hospitals (Zhan and Miller, 2003). Urology patients in particular have an increased incidence, estimated to be 10% to 40% in patients without any prophylaxis (Geerts et al, 2008). Although these estimates are based on historical studies conducted before the routine use of mechanical prophylaxis and the recognition of the benefits of early ambulation, the increased risk persists, with more recent studies reporting incidences of 1% to 5%. Urologic patients followed prospectively in the European @RISTOS study developed VTE in 1.9% undergoing open surgery despite a high rate of prophylaxis (Scarpa et al, 2007). For patients in the United Kingdom undergoing urologic procedures, Dyer and colleagues reported an overall incidence of 0.66% including a 2.8% incidence among patients undergoing radical cystectomy (Dyer et al, 2013). Overall, VTE is the most important cause of nonsurgical mortality among urology patients (Forrest et al, 2009).

Although the use of perioperative mechanical prophylaxis (pneumatic compression stockings) is fairly universal, pharmacologic prophylaxis is administered only after weighing the risk of VTE versus risk of perioperative bleeding complications (Table 5-5). Leonardi and colleagues reviewed and analyzed 33 RCTs to assess the incidence of bleeding complications in general surgery patients receiving pharmacologic prophylaxis (Leonardi et al, 2006). Although there was a significantly higher rate of minor complications (injection site bruising and wound hematoma), there was no significant difference in major complications (i.e., GI tract bleeding [0.2%] or retroperitoneal bleeding [$<0.1\%$]). Although these results are applicable in general to urology patients, certain urologic procedures, such as TURP and partial nephrectomy, have a specifically higher rate of bleeding complications. Regarding an individual's risk of VTE, both surgery-related risk factors and patient-related risk factors must be considered. Surgical factors specific to urologic surgery to be weighed include general versus

TABLE 5-5 Mechanical and Pharmacologic Venous Thromboembolism Prophylaxis

PROPHYLAXIS	DOSE	ADVANTAGES	DISADVANTAGES
Pneumatic compression stockings	—	Can be used in patients with high bleeding risk Easily standardized for all patients Studied in multiple patient groups	No standards for size, pressure Individual models not specifically studied Less effective than pharmacologic prophylaxis in high-risk groups
Low-molecular-weight heparin	40 mg SC once daily	Once-daily administration Less risk of heparin-induced thrombocytopenia No blood monitoring necessary	Not reversible High cost Relative contraindication in patients with renal insufficiency
Low-dose unfractionated heparin	5000 U SC q8h	Reversible Can be used safely in patients with renal insufficiency Relatively inexpensive	Needs readministration q8-12h Heparin-induced thrombocytopenia

BOX 5-4 Patient-Related Factors Increasing Risk for Venous Thromboembolism

Surgery
 Trauma (major trauma or lower extremity injury)
 Immobility, lower extremity paresis
 Cancer (active or occult)
 Cancer therapy (hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy)
 Venous compression (tumor, hematoma, arterial abnormality)
 Previous venous thromboembolism
 Increasing age
 Pregnancy and the postpartum period
 Estrogen-containing oral contraceptives or hormone replacement therapy
 Selective estrogen receptor modulators
 Erythropoiesis-stimulating agents
 Acute medical illness
 Inflammatory bowel disease
 Nephrotic syndrome
 Myeloproliferative disorders
 Paroxysmal nocturnal hemoglobinuria
 Obesity
 Central venous catheterization
 Inherited or acquired thrombophilia

Modified from Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:381S–453S.

neuraxial anesthesia, supine versus dorsal lithotomy position, abdominal versus pelvic surgery with or without lymphadenectomy, and open versus laparoscopic approach. Patient-related risk factors are listed in [Box 5-4](#), with increasing age, malignancy, history of cancer therapy, and others being fairly common among urology patients. In fact, both the *@RISTOS* study and a recent report on minimally invasive radical prostatectomy confirmed several of these factors as being associated with increased risk of VTE in urologic patients ([Scarpa et al, 2007](#); [Secin et al, 2008](#)). In 2008 the American College of Chest Physicians (ACCP) issued guidelines on the prevention of VTE with a strong recommendation that hospitals develop a formal, active strategy to address VTE prevention. **Although prior recommendations from the ACCP advocated individualized risk assessment models to guide therapy, the current recommendations advocate implementation of group-specific thromboprophylaxis routinely for all patients who belong to each of the major surgical groups (e.g., urologic surgery) ([Geerts et al, 2008](#)).** The AUA has published a best practice statement on the use of VTE prophylaxis in urologic patients ([Forrest et al, 2009](#)). These recommendations combine an individualized risk assessment model with each type of urologic surgery. For example, a high-risk patient (multiple patient risk factors) undergoing low-risk surgery may require pharmacologic prophylaxis, as might a low-risk patient undergoing high-risk surgery. The recommendations are summarized in [Table 5-6](#).

Antithrombotic Therapy

Most urologic patients have medical comorbidities; urologists frequently encounter patients on chronic vitamin K antagonist therapy (e.g., warfarin) or antiplatelet therapy for the management of atrial fibrillation, mechanical heart valves, or coronary artery disease. Perioperative management including interruption of this antithrombotic therapy can be a challenging problem. Unlike VTE pharmacologic prophylaxis, warfarin and antiplatelet

TABLE 5-6 Patient Risk Assessment Model and American Urological Association Best Practice Recommendations

PATIENT RISK STRATIFICATION	
Low risk	Minor surgery in patients younger than 40 yr with no additional risk factors
Moderate risk	Minor surgery in patients with additional risk factors Surgery in patients aged 40–60 yr with no additional risk factors
High risk	Surgery in patients older than 60 yr Surgery in patients aged 40–60 yr with additional risk factors (see Box 5-4)
Highest risk	Surgery in patients with multiple risk factors (e.g., age older than 40 yr, cancer, prior venous thromboembolism)
LEVEL OF RISK	RECOMMENDATIONS
Low risk	No prophylaxis other than early ambulation
Moderate risk	Heparin 5000 units q12h SC starting after surgery or Enoxaparin 40 mg (for CrCl <30 mL/min, use 30 mg) SC daily or Pneumatic compression device if risk of bleeding is high
High risk	Heparin 5000 units q12h SC starting after surgery or Enoxaparin 40 mg (for CrCl <30 mL/min, use 30 mg) SC daily or Pneumatic compression device if risk of bleeding is high
Highest risk	Enoxaparin 40 mg (for CrCl <30 mL/min, use 30 mg) SC daily and adjuvant pneumatic compression device or Heparin 5000 units q8h SC starting after surgery and adjuvant pneumatic compression device

CrCl, creatinine clearance.

Modified from Forrest JB, Clemens JQ, Finamore P, et al. AUA best practice statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery. *J Urol* 2009;181:1170–7.

therapies have been shown to be associated with significant bleeding complications after surgery. Therefore urologists must carefully consider the risk of interruption of chronic anticoagulation to determine the best course of perioperative management of these medications.

Chronic anticoagulation with warfarin is most frequently encountered in patients with atrial fibrillation, mechanical heart valves, or prior VTE. **The pharmacologic half-life of warfarin is 36 to 42 hours, and therefore most guidelines recommend cessation of therapy 5 days before surgery to ensure an INR less than 1.5.** Recently, several new oral anticoagulants (e.g., apixaban, dabigatran, and rivaroxaban), have been introduced to improve efficacy, decrease patient variability, and improve patient convenience. Each of the new medications has different pharmacologic properties, and therefore it is imperative for the surgeon to be familiar with these medications to properly advise the patient ([Douketis, 2010](#)). The larger issue is whether patients require a bridge with short-term anticoagulation between the time of subtherapeutic INR and

TABLE 5-7 Risk Stratification for Arterial or Venous Thromboembolism Events during Perioperative Period in Patients on Chronic Anticoagulant Therapy

INDICATIONS FOR ANTICOAGULANT THERAPY			
	MECHANICAL HEART VALVE	ATRIAL FIBRILLATION	RECENT VTE
Low	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	CHADS ₂ score of 0-2 (and no prior stroke or transient ischemic attack)	Single VTE occurred >12 mo ago and no other risk factors
Moderate*	Bileaflet aortic valve prosthesis plus one of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age above 75 yr	CHADS ₂ score of 3-4	VTE within the past 3-12 mo Nonsevere thrombophilic conditions (e.g., heterozygous factor V Leiden mutation, heterozygous factor II mutation) Recurrent VTE Active cancer (treated within 6 mo or palliative)
High*	Any mitral valve prosthesis Recent (within 6 mo) stroke or transient ischemic attack	CHADS ₂ score of 5 or 6 Recent (within 3 mo) stroke or transient ischemic attack Rheumatic valvular heart disease	Recent (within 3 mo) VTE Severe thrombophilia (e.g., deficiency of protein C, protein S, or antithrombin; presence of antiphospholipid antibodies; multiple abnormalities)

*Patients at moderate or high risk are recommended to undergo bridging anticoagulation with therapeutic-dose subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin.

CHADS₂, congestive heart failure–hypertension–age–diabetes–stroke; VTE, venous thromboembolism.

Modified from Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:299S–339S.

surgery. The decision is based on risk of a thrombotic event. Regarding atrial fibrillation, clinical scoring systems such as congestive heart failure–hypertension–age–diabetes–stroke (CHADS₂), stratify patients into risk groups that predict risk of stroke while patients are not undergoing anticoagulation therapy. Patients with mechanical heart valves can also be stratified into risk groups according to the location (mitral versus aortic) and type of valve used. Similarly, patients with a prior history of VTE are stratified according to duration since last VTE and the patient's risk of recurrent VTE (Table 5-7). In general, the ACCP, which released its guidelines in 2008, recommends that patients in the moderate- and high-risk groups undergo bridging anticoagulation with therapeutic-dose subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin (Douketis et al, 2008).

An increasing number of patients are receiving chronic antiplatelet therapy in the prevention of cardiovascular events and, more important, in the prevention of coronary stent thrombosis. Although the former indication poses little controversy for the urologist, the latter indication presents a significant and complex clinical question in which the urologist must weigh the risk of bleeding with the potentially devastating risk of perioperative stent thrombosis. Aspirin and clopidogrel are the two most commonly used antiplatelet drugs and are frequently used together. Both are irreversible inhibitors of platelet function and therefore need to be stopped 7 to 10 days before surgery to minimize bleeding risk. Current recommendations require dual antiplatelet therapy for 6 weeks after bare metal coronary stents and 12 months for drug-eluting stents. Premature interruption of antiplatelet therapy has been associated with a 25% to 50% risk of significant myocardial infarction with resultant increased perioperative mortality (O'Riordan et al, 2009). In most patients, urologists should defer elective surgery until after antiplatelet therapy can be safely interrupted. In a review of the literature, Gupta and colleagues recommend delay of elective urologic surgery for at least 30 days for bare metal stents and, if possible, longer than 1 year for drug-eluting stents (Gupta et al, 2012). Even then, because acute stent thrombosis has been described with drug-eluting stents after 12 months, urologists should strongly consider at least single-agent antiplatelet therapy in these patients. Given the current lack of

clinically useful alternatives to antiplatelet therapy, when surgery cannot be delayed (e.g., because of malignancy), the ACCP strongly recommends continuing aspirin and clopidogrel during the perioperative period in patients with drug-eluting stents (Douketis et al, 2012). Obviously, communication between the urologist and the cardiologist throughout the perioperative period is essential to minimize complications.

ANESTHETIC CONSIDERATIONS

The basic tenet of anesthesia is to deliver hypnosis, amnesia, and analgesia while maintaining satisfactory operating conditions. An understanding of the basic pharmacologic principles, anesthetic equipment and monitoring, and patient analgesia is important to any surgeon including the urologist for successful operative outcomes and avoidance of surgical complications. Although urologists are performing increasingly more procedures in the office, the bulk of urologic surgery occurs in the operating room under monitored anesthesia care, regional anesthesia, or general anesthesia. Current practice in operative anesthesia employs a combination of inhalational agents and intravenous medications along with analgesics (for pain control) and benzodiazepines (for anxiolysis and amnesia). Of course, improved presurgical evaluation, pharmacologic drugs, and perioperative monitoring have dramatically decreased the risks of anesthesia. A recent study of New York hospital-based and freestanding ambulatory surgical centers reported the risk of all-cause mortality to be 1 in 49,012 and the rate of immediate admission to an inpatient facility to be 0.6% (Fleisher et al, 2007b).

Selection of Mode of Anesthesia

An important role of the urologist in the anesthetic evaluation is to determine what mode of anesthesia is best for the particular patient and surgical procedure. The choice depends on patient-related factors including comorbidities, airway, and patient preference and procedural factors including complexity, duration, anatomic location, and expected fluid and blood loss. A basic

understanding of each method of anesthesia and the pharmacologic principles will aid the urologist in making recommendations to the anesthesiologist.

Monitored Anesthesia Care

Although *monitored anesthesia care* is defined as conscious sedation under the care of an anesthesiologist in a monitored situation, it encompasses a wide range of levels of anesthesia from minimal sedation to brief intervals of unconscious general anesthesia. Most commonly, anesthesiologists combine intravenous opioid analgesics and benzodiazepines to maintain a sufficient level of patient comfort and anxiolysis. Monitored anesthesia care is widely used in urology in the ambulatory setting and is suitable for short-duration endoscopic procedures, transrectal ultrasound-based procedures, and, when combined with a local anesthetic, superficial procedures of the external genitalia. Conscious sedation can be administered in the office setting but only with proper monitoring of the patient during and after the procedure. **The Joint Commission has strict guidelines to ensure that the patients receive the same level of monitoring as if under the care of an anesthesiologist including a requirement for a trained monitoring assistant, immediate access to airway and resuscitation equipment, and specific preprocedure and postprocedure evaluations.**

Regional Anesthesia

Regional anesthesia incorporates different levels of anesthesia directed toward the surgical site, including local anesthesia, spinal anesthesia, and epidural anesthesia. The use of local anesthetics is typically combined with monitored anesthesia care for superficial procedures in an isolated anatomic location. The keys to proper local anesthetic administration are avoidance of intravascular injection and knowledge of pharmacology. The two most commonly used drugs are lidocaine and bupivacaine, with the primary differences being the onset and duration of action. Infiltration of local anesthetics before surgical incision decreases nociceptor sensitization and conduction and results in decreased postoperative pain and analgesic requirements.

Spinal and epidural anesthesia involves injection of anesthetic (most commonly lidocaine or bupivacaine) into the subarachnoid space or epidural space with direct effect on the spinal cord, resulting in sensory, motor, and sympathetic blockade. In urologic procedures, epidural anesthesia is most useful for postoperative pain management for major abdominal procedures, thereby avoiding the adverse effects of high doses of intravenous opioids (i.e., respiratory depression, GI dysfunction). Spinal anesthesia is suitable for most urologic endoscopic procedures and lower abdominal surgical procedures and is limited only by the duration of anesthesia required. Spinal anesthesia avoids the cardiopulmonary effects and complications of general anesthesia. Several factors affect the spinal level and efficacy of administration. In general, larger volume and increased doses result in longer duration and increased cephalad migration. The addition of low-dose opioids and/or vasoconstrictors prolongs the duration of analgesia while reducing the dose of anesthetic. The anesthetic-related adverse effect is hypotension as a result of sympathetic blockade and occurs in 10% to 40% of patients (Di Cianni et al, 2008). **The primary technique-related complication is post-dural puncture headache (results from cerebrospinal fluid leak) with an incidence of less than 2% with currently used 29-gauge pencil-tipped needles (Turnbull and Shepherd, 2003).** Overall, spinal anesthesia has become safe, with the incidence of serious neurologic deficits being 0.05%.

General Anesthesia

Inhalational General Anesthesia. Inhalational drug development has emphasized inhalational agents that facilitate rapid induction and emergence and are nontoxic. Two of the most important characteristics of inhalational anesthetics are the blood/gas solubility coefficient (B/G) and the minimum alveolar

concentration (MAC). The B/G refers to the serum uptake of the inhaled agent, and the MAC is a measure of the potency of a volatile anesthetic (i.e., the serum level required to prevent movement in response to a skin incision in 50% of patients). The various inhalational agents differ not only in the B/G and MAC but also in their cardiopulmonary effects. Obviously, a basic understanding of these properties is important for the urologic surgeon, especially during instances of surgical complication.

Nitrous oxide (NO) is one of the most commonly used agents because of its propensity for rapid induction and emergence; however, because of its low potency, it is often combined with other agents. Because of NO's high B/G and tendency to increase the volume and pressure of closed spaces, its use is contraindicated in certain clinical situations such as small bowel obstruction and pneumothorax. During laparoscopic abdominal procedures, surgeons often prefer to avoid the use of NO because of resultant bowel distention and subsequent interference in the operative field. Although this effect is debated in the surgical literature, El-Galley and colleagues reported significantly increased bowel distention and surgical interference with NO use in patients undergoing laparoscopic donor nephrectomy (El-Galley et al, 2007).

Once introduced in the 1950s, halothane rapidly became one of the most commonly used anesthetic agents because of its high potency. However, halothane has several important risks that have since limited its use. It has significant cardiac effects and can precipitate failure in patients with left ventricular dysfunction. Furthermore, it sensitizes the myocardium to the effects of catecholamines (relevant for local anesthetics injected into the surgical site). Finally, there is a 1 in 35,000 incidence of fulminant hepatitis, which can be lethal as a result of overaccumulation of toxic metabolites. More recent advancements in inhalational agents have focused on reduction in toxicity while maintaining the potency and rapidity of halothane. Three of the most commonly used current agents are isoflurane, sevoflurane, and desflurane. Isoflurane, less expensive than the other agents because of the availability of generic equivalents, is widely used as a result of its low cardiac depression, lower myocardial sensitization to catecholamines, and minimal metabolism. The primary unique toxicity is variable response tachycardia, which can lead to significantly increased myocardial oxygen consumption. Unlike isoflurane, which has a putrid odor, sevoflurane is often used for inhalation induction (odorless) because of its rapid induction and emergence, decreased incidence of postoperative nausea (important in outpatient surgery), and minimal cardiac toxicity. It is, in general, the preferred agent for difficult airways requiring mask induction and in patients with severe bronchospastic disease. Desflurane, like isoflurane, has a pungent odor and is not used for inhalational induction. Its primary advantage over isoflurane is a more rapid recovery in patients requiring anesthesia over 3 hours.

Intravenous General Anesthesia. Intravenous anesthesia consists of a combination of induction agent, opioid, and neuromuscular relaxant. Anesthesiologists often prefer intravenous induction with a combination of inhalational and intravenous agents for maintenance of anesthesia. Intravenous induction offers several advantages in that it is rapid, minimizes patient discomfort, and is preferred by children and most adults. Thiopental, the oldest and least expensive agent, is a suitable choice for uncomplicated situations but is limited in more complex cases because of its significant vasodilation, cardiac depression, and risk of bronchospasm, especially in patients with reactive airway disease. Ketamine is a preferred choice for procedures that are brief and superficial because of its profound amnesia and somatic analgesia. It is associated with increased arteriolar and bronchomotor tone and is advantageous during induction for hypovolemic and asthmatic patients. Propofol is among the most commonly used anesthetic agents, especially in outpatient surgery. It has a rapid onset, produces excellent bronchodilation in patients with reactive airway disease, and, perhaps most important, is associated with smooth, nausea-free emergence from anesthesia. Its primary adverse effect is significant blood pressure reduction. Midazolam, never used as a single agent, produces profound amnesia and anxiolysis while

having a rapid onset and short duration and producing minimal cardiac side effects.

Although these agents induce unconsciousness and amnesia, opioids have become an integral component to all forms of anesthesia. Opioids result in significant analgesia without an increase in cardiac side effects. Several studies have documented the decreased requirements of other agents when used in combination with opioids, thus reducing the overall cardiopulmonary side effects of anesthesia (Fukuda, 2009). Opioids themselves are differentiated in their potency, onset of action, duration of action, and metabolism and excretion. **Fentanyl (synthetic opioid) is probably the most widely used because of its potency (100 to 150 times that of morphine), rapid onset, and short duration of action.** Newer synthetics are geared toward shorter duration and more rapid metabolism.

For major operative cases, complete neuromuscular relaxation is required for sufficient exposure and successful outcome. Although full relaxation can be achieved with intravenous and inhalational agents, the dose required is extremely high. The use of intravenous neuromuscular blockers allows for neuromuscular relaxation and minimization of inhalational and intravenous drugs. **There are two types of neuromuscular blockers: depolarizing drugs, which depolarize the plasma membrane of skeletal muscle fibers, making the fibers resistant to further stimulation by acetylcholine; and nondepolarizing drugs, which block the binding of acetylcholine to cholinergic receptors on the presynaptic and postsynaptic membrane.** Succinylcholine, the only depolarizing drug on the market, is chosen for its rapid onset (used in rapid induction sequences), relatively short duration (around 5 minutes), and rapid metabolism. Its use is limited because of the risk of malignant hyperthermia (when used in combination with volatile inhalational agents), hyperkalemia, and bradycardia in children. When succinylcholine is contraindicated, nondepolarizing agents are used. Several nondepolarizing drugs are available and differ in routes of metabolism and adverse effects. Furthermore, multiple medications including desflurane can alter the metabolism of these drugs and potentiate their actions. The most important consideration in the use of neuromuscular blockers is the assessment of adequate return of neuromuscular function after withdrawal of the drug. The most common complication of neuromuscular-blocking drugs is inadequate reversal resulting in respiratory failure and reintubation. Numerous reports in the literature correlate residual neuromuscular blockade with increased postoperative pulmonary complications in the postanesthesia care unit (PACU) and in the postoperative period. **The concept of train-of-four fade ratio (TOF) was developed to devise an objective measure of adequate neuromuscular function.** This concept refers to the magnitude of the fourth of four twitches in response to maximal stimuli to the ulnar nerve delivered at 0.5-second intervals. Historically, a TOF of 0.7 (meaning that the fourth twitch was 70% the magnitude of the first twitch) correlated with adequate return of neuromuscular function; however, more recent standards have raised the threshold to 0.9 as an indicator of complete return of neuromuscular function (Kopman et al, 1997). Currently, anesthesiologists use several clinical assessments including head lift, tongue depressor test, and hand grip to estimate a TOF of 0.9. A recent study revealed that with use of clinical assessments alone, 16% and 45% of patients 2 hours after a single intubating dose of neuromuscular blocker had a TOF of less than 0.7 and less than 0.9, respectively, in the PACU (Debaene et al, 2003). As such, current recommendations are that quantitative TOF measurement (acceleromyography) be combined with clinical assessments before extubation in the operating room (Viby-Mogensen, 2009).

Pain Management

Equally important to intraoperative anesthetic considerations, proper pain management after surgery is crucial to minimizing postoperative complications and delayed recovery. **Untreated acute pain not only is unacceptable for the patient, but also may increase the risk of complications by causing increased**

physiologic stress in the recovery period. The neural process, referred to as *nociception*, involves signal transduction from noxious stimuli via sensory afferent nerves to the spinal cord and cerebral cortex, resulting in the perception of pain. Analgesia aims to block the pain sensation along various points of this signal transduction pathway.

Opioids are perhaps the most commonly used analgesic medications in the immediate postoperative period. These drugs primarily act in the CNS at both the dorsal root ganglion and the cerebral cortex to modulate the perception of pain. Administration can be oral, intravenous, neuraxial, or transdermal. In general, the choice of route of administration is dependent on patient's severity of pain and ability to take oral medications. Although typically very effective for providing analgesia, opioids can cause decreased GI activity, respiratory suppression, sedation, and mental confusion. Weaker (less potent) opioids, such as hydrocodone and codeine, may minimize these adverse effects but are often combined with acetaminophen and should be used with caution in patients with hepatic insufficiency.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are being employed in the postoperative setting more frequently now to avoid the unwanted effects of opioids. These medications act by inhibition of cyclooxygenase enzyme activity, resulting in decreased prostaglandin production. Prostaglandins are the primary mediators of nociceptor activation at the tissue level. **Multiple studies have demonstrated that the appropriate use of NSAIDs can result in decreased use of opioid analgesics and decreased nausea and vomiting after anesthesia** (Rawlinson et al, 2012). In a randomized study of patients undergoing laparoscopic colon surgery, the use of intravenous ketorolac was associated with improved pain scores and reduced postoperative ileus (Schlachta et al, 2007). NSAIDs are usually very well tolerated but should be avoided in patients with renal insufficiency and used with caution in patients with a history of esophageal reflux or peptic ulcer disease.

For major abdominal surgery in which prolonged opioid use is expected, neuraxial analgesia (i.e., epidural) can provide significant patient benefits. Epidural analgesia is administered and monitored by the anesthesia or pain management team. Both opioids and local anesthetic medications are infused in the epidural space via catheter and are given as a continuous infusion and/or patient-controlled infusion. Epidural analgesia has the advantage of improved pain control while minimizing the central nervous and GI adverse effects of intravenous opioid medications. Block and colleagues performed a meta-analysis of randomized trials to review the efficacy and concluded that epidural analgesia, regardless of agent or location of catheter placement, provided better pain control than parenteral opioids (Block et al, 2003). In fact, a recent review of RCTs found that in patients undergoing general anesthesia, the use of concomitant epidural analgesia resulted in decreased perioperative mortality and improved comorbidity end points across multiple organ systems (Pöpping et al, 2014).

BLOOD PRODUCTS

Given the vascular nature of urologic organs, the urologist often confronts the issue of indication and necessity of transfusion in the perioperative period. Therefore it is important that the urologist understand the indications, implications, and risks associated with blood product transfusion. Before the acquired immunodeficiency syndrome (AIDS) epidemic, blood transfusion was liberally administered, often for any patient with a hematocrit less than 30%. However, fear and concern about the infectious risk led to the convening of a National Institutes of Health (NIH) panel to develop consensus recommendations for the indication of blood product transfusion (NIH Consensus Statement, 1988). The principles in these guidelines largely hold true today as reflected by the ASA practice guidelines issued in 2006 (*Practice guidelines for perioperative blood transfusion and adjuvant therapies*, 2006). To summarize, the guidelines indicate that transfusion is rarely indicated with hematocrit greater than 30% and often indicated

for hematocrit less than 21%. For levels between 21% and 30%, clinical factors such as risk of complications from inadequate oxygenation should guide the need for transfusion, balancing the risks and benefits. In general, patients with relatively minor comorbidities can tolerate hematocrit of greater than 21% before transfusion is indicated. Patients with moderate to severe comorbidity (e.g., significant pulmonary compromise, coronary artery disease, or vascular insufficiency, or with signs or symptoms of hypovolemic, hemorrhagic shock) warrant transfusion to achieve hematocrit greater than 30%. Ultimately, until technology is available to directly measure inadequate oxygen-carrying capacity, the urologist should individualize the decision to transfuse for each patient and clinical situation.

A major advance in blood banking and product transfusion has been the development of component therapy allowing for administration for specific fractions of whole blood. Packed red blood cells (PRBCs) are equivalent to whole blood minus the plasma component. Whereas the hematocrit in whole blood is 40%, it is 70% in PRBC units. These units are reconstituted and administered with crystalloid. Given the lack of the remaining components, in instances of massive PRBC transfusions and associated bleeding, platelets and occasionally fresh frozen plasma (FFP) should be given to avoid dilutional coagulopathy. Platelet transfusion is rarely indicated empirically except in patients with significant thrombocytopenia ($<50,000/\text{mm}^3$) and a planned surgical procedure or with moderate thrombocytopenia (50,000 to $100,000/\text{mm}^3$) and either a high-risk procedure or evidence of platelet dysfunction. Similarly, empirical transfusion with FFP for massive transfusion is not indicated. With the development of component therapy, the use of FFP increased dramatically, leading to consensus statements from the NIH and the ASA to guide practitioners ([Consensus conference, 1985](#); [Practice guidelines for perioperative blood transfusion and adjuvant therapies, 2006](#)). The current indications for FFP transfusion are immediate reversal of warfarin-induced coagulopathy, replacement in patients with specific clotting factor deficiencies, and evidence of bleeding and INR greater than 1.5. According to the ASA guidelines, in patients with massive transfusion and no INR readily available, FFP should be given after replacement of 1 blood volume.

There are well-documented risks of transfusion, and these risks should always be discussed with the patient before administration. Hemolytic transfusion reactions occur as a result of incompatibility between donor and recipient (either ABO or non-ABO incompatibility). According to the 2007 FDA Annual Summary, from 2005 to 2007 transfusion reactions accounted for 22% of transfusion-related fatalities in the United States ([U.S. Food and Drug Administration, 2007](#)). Transfusion reactions occur relatively frequently and, if identified early, can be treated with rare catastrophic events. The early signs and symptoms include fever, chills, chest pain, hypotension, and bleeding diathesis occurring during or immediately after transfusion. Reactions may also occur in a delayed fashion, which is characterized by significant intravascular hemolysis secondary to recipient antibodies. The treatment of transfusion reaction is centered on fluid resuscitation, cessation of the transfusion, and alkalization of the urine to prevent renal failure. **The most common cause of transfusion-related fatality is transfusion-related acute lung injury (TRALI). This entity accounted for 55% of transfusion mortality from 2005-2007. The injury is characterized by noncardiogenic pulmonary edema injury and manifests 1 to 2 hours after transfusion. Although no specific treatment other than supportive measures is indicated, most patients recover without significant sequelae. Finally, one of the most feared complications (at least in the public eye) is the transmission of bacterial or viral infection. Although the risk of hepatitis virus and human immunodeficiency virus (HIV) transmission was unacceptably high in the 1970s and 1980s, the initiation of more stringent screening procedures for high-risk populations and the development of nucleic acid amplification technology (polymerase chain reaction [PCR] and transcription-mediated amplification) have resulted in dramatically reduced risk and incidence of viral transmission. Currently, the risk of HIV and hepatitis C transmission is approximately 1 in 2**

million cases, whereas the risk of hepatitis B transmission is 1 in 200,000. The highest risk of infectivity occurs with platelet transfusion, in which bacterial contamination develops at a rate of 1 in 5000 units ([Eder et al, 2007](#)).

Although very high-blood loss procedures in urology are uncommon, given the proximity of major vascular structures to several genitourinary organs, occasionally the urologist is faced with a clinical situation in which a large-volume blood transfusion is necessary. Traditionally, component transfusion would not begin until more than 6 units of PRBCs had been given to the patient. More recently, evidence from the trauma literature supports the use of an increased ratio of platelets to fresh frozen plasma to red blood cells (RBCs)—that is, massive transfusion protocol. The protocol is triggered in the anticipation of greater than 10 units of PRBCs per 24 hours and mobilizes blood bank and hospital resources to provide an adequate supply of RBC and component transfusion. There are multiple reports of improved survival of trauma patients managed with massive transfusion protocols. A study from Ball and colleagues demonstrated improved abdominal wall closure rates among patients with high-grade liver injuries when a massive transfusion protocol was used ([Ball et al, 2013](#)).

PATIENT ENVIRONMENT

Patient Temperature

Although hypothermia can be therapeutic in certain situations of trauma and brain injury, for elective surgical procedures, hypothermia is associated with significantly increased morbidity to the patient. There are two primary reasons for hypothermia to develop in the operating room. Anesthetic agents induce peripheral vasodilation, redistributing heat from the core (trunk, head) with a resultant drop in immediate core temperature after induction. Throughout the rest of the surgical procedure, radiation and conductive heat loss account for most of the heat loss. Normothermia is defined as a core temperature between 36°C and 38°C , and hypothermia of even 1°C to 2°C results in adverse effects. Rajagopalan and colleagues performed a meta-analysis of RCTs and reported that mild hypothermia (decrease of 1°C) resulted in a 16% increase in estimated blood loss and 22% increase in transfusion requirements ([Rajagopalan et al, 2008](#)). The increased bleeding risk is thought to result from a hypothermia-associated decrease in clotting cascade enzymatic function and platelet aggregation. Even more significant is the increase in the risk of SSIs associated with mild hypothermia (34°C to 36°C). Hypothermia increases the risk of SSI by impairing immune mechanisms and vasoconstriction, resulting in regional tissue hypoxia. In a landmark study, Kurz and colleagues with the Study of Wound Infection and Temperature Group tested in 200 patients undergoing elective colorectal surgery the hypothesis that hypothermia increases the rate of wound infection and hospital stay ([Kurz et al, 1996](#)). **Hypothermia was associated with a three times increased risk of wound infection and a 2.6-day increase in hospitalization.** More recent studies have confirmed these findings in general in other series of surgical patients ([Mauermann and Nemergut, 2006](#)). In its overall goal of reducing SSI, the SCIP has also included perioperative normothermia as one of its guidelines. Strategies to improve maintenance of normothermia include regular use of warming blankets, warmed intravenous fluids, warmed irrigation fluids (especially during TURP and other prolonged endoscopic procedures), warmed humidified CO_2 gas during laparoscopy, and increase in ambient operating room temperature. Although there have been few studies in the urologic literature, the findings can be generalized to all surgical patients.

Skin Preparation

Sterile skin preparation is fundamental in the prevention of SSI for any procedure. Currently the most commonly used skin antiseptics are alcohol, povidone-iodine, or chlorhexidine based. Whichever antiseptic is chosen, the solution should be applied in concentric

circles from the center of the surgical site and allowed to dry before incision. The Cochrane Wound Study group recently published their updated second analysis on various preoperative skin preparations. The authors again were unable to report conclusive evidence of superior efficacy of one particular skin preparation (Dumville et al, 2013). Furthermore, although the CDC clearly recommends preoperative showering or bathing to reduce SSI, there is no evidence that bathing with an antiseptic solution reduces the rate of infection (Webster and Osborne, 2007). Regarding hair removal, the CDC recommends that if hair removal is performed, it should be performed immediately before the surgical procedure and performed with clippers (rather than shaving) (Mangram et al, 1999).

Patient Safety

In 1991 Brennan and colleagues published their seminal work describing adverse events, defined as injuries caused by medical management in hospitalized patients, revealing that 48% of the events accompanied a surgical operation (Brennan et al, 1991; Leape et al, 1991). This important study inspired the publication of "To Err Is Human: Building a Safer Health System," a comprehensive study by the Institute of Medicine on medical errors. Regarding surgical patients, the most frequent venue of preventable injuries is the operating room. **Although the surgeon is the "captain of the ship" and ultimately responsible, it takes cognizance and attention to detail from each member of the operating room team to prevent iatrogenic injuries to the patient.** Three causes of immediately preventable injuries are retractor-associated injuries, thermal injuries, and patient position-related injuries. There are several reports in the literature documenting an increased rate of neuropathy (especially femoral nerve) after laparotomy with self-retaining retractors versus without self-retaining retractors (Irvin et al, 2004). Careful attention to be certain that the lateral blades do not directly

compress the psoas muscle and only cradle the rectus abdominal muscles will ensure avoidance of femoral neuropathy. Furthermore, periodic reinspection of the retractor blades is also warranted. Many devices used in urologic surgery employ thermal energy for desired effect and therefore can result in thermal injury to the patient. These include Bovie cautery, the argon beam coagulator, bipolar devices, and lasers. In both endoscopic and laparoscopic surgery, high-wattage light sources are used to illuminate the operative field. While it is illuminated, the ends of the light cords can result in burns when in direct contact with the patient (even through draping). These light sources should be turned off at all times when not in use. Special mention is deserved for the morbidly obese patient. The operating room should be equipped with a hydraulic table, extra-long instruments, additional padding, wide venous compression devices, and side extensions to ensure a safe operating room environment for the patient.

Patient Positioning

Although often given only a cursory evaluation, proper patient positioning in the operating room can prevent potentially devastating complications. Ultimately, proper positioning is the shared responsibility of each member of the operating room team. Much of the knowledge and guidelines for avoidance of position-related injury are drawn from the anesthesia literature. In fact, in response to a 1999 study of the ASA Closed Claims Database, which found neuropathy as second-leading cause of liability, the ASA published a practice advisory for the prevention of perioperative peripheral neuropathies (Practice advisory for the prevention of perioperative peripheral neuropathies, 2000). The recommendations are listed in Box 5-5. **Although the exact mechanisms of peripheral neuropathy are not always known, the cause of position-related neuropathy is usually secondary to excessive stretch, prolonged compression, or ischemia.** Given the variety of different patient

BOX 5-5 American Society of Anesthesiologists Task Force Recommendations on the Prevention of Perioperative Peripheral Neuropathies

PREOPERATIVE ASSESSMENT

- When judged appropriate, it is helpful to ascertain that patients can comfortably tolerate the anticipated operative position.

UPPER EXTREMITY POSITIONING

- Arm abduction should be limited to 90 degrees in supine patients; patients who are positioned prone may comfortably tolerate arm abduction greater than 90 degrees.
- Arms should be positioned to decrease pressure on the post-condylar groove of the humerus (ulnar groove). When arms are tucked at the side, a neutral forearm position is recommended. When arms are abducted on armboards, either supination or a neutral forearm position is acceptable.
- Prolonged pressure on the radial nerve in the spiral groove of the humerus should be avoided.
- Extension of the elbow beyond a comfortable range may stretch the median nerve.

LOWER EXTREMITY POSITIONING

- Lithotomy positions that stretch the hamstring muscle group beyond a comfortable range may stretch the sciatic nerve.
- Prolonged pressure on the peroneal nerve at the fibular head should be avoided.
- Neither extension nor flexion of the hip increases the risk of femoral neuropathy.

PROTECTIVE PADDING

- Padded armboards may decrease the risk of upper extremity neuropathy.
- The use of chest rolls in laterally positioned patients may decrease the risk of upper extremity neuropathies.
- Padding at the elbow and at the fibular head may decrease the risk of upper and lower extremity neuropathies, respectively.

EQUIPMENT

- Properly functioning automated blood pressure cuffs on the upper arms do not affect the risk of upper extremity neuropathies.
- Shoulder braces in steep head-down positions may increase the risk of brachial plexus neuropathies.

POSTOPERATIVE ASSESSMENT

- A simple postoperative assessment of extremity nerve function may lead to early recognition of peripheral neuropathies.

DOCUMENTATION

- Charting specific positioning actions during the care of patients may result in improvements of care by (1) helping practitioners focus attention on relevant aspects of patient positioning and (2) providing information that continuous improvement processes can use to effect refinements in patient care.

positions used in urologic surgery, it is critical for the urologist to be an active participant in the positioning of the patient and to understand the potential patient compromise that accompanies each position.

The supine position, used in abdominal, pelvic, and penile procedures, is in general considered the safest patient position. However, several specific issues should be considered. **Excessive upper extremity abduction (>90 degrees) can lead to tension on the brachial plexus, leading to upper extremity neuropathy.** The armboard should be padded to avoid excessive pressure on the ulnar groove and spiral groove of the humerus (radial nerve injury). In cases in which the arms are tucked at the patient's side, care must be taken to avoid excessive pressure on the hand and forearm. Moreover, peripheral intravenous catheter infiltration must be identified quickly because forearm compartment syndrome may develop.

One of the most frequent positions used in urology is the lithotomy position. Improper positioning can lead to transient and occasionally prolonged lower extremity neuropathy. In a retrospective evaluation of more than 190,000 cases from 1957 to 1991 involving the lithotomy position, persistent neuropathy was found in 0.03%; however, the same group in a prospective study of 991 patients reported an incidence of 1.5% (15 patients) with resolution of symptoms by 6 months in all but one patient (Warner et al, 1994, 2000). **The basic principle of position involves manipulation of both lower extremities simultaneously with flexion of the hips at 80 to 100 degrees with 30- to 45-degree abduction.** The legs should be padded to avoid excessive compression against the stirrup. Particular caution should be given to the patient's hands to avoid entrapment within the moving parts of the stirrups.

For most open and laparoscopic upper urothelial tract and renal procedures, the patient is placed in some degree of lateral decubitus position. Proper padding of the patient is important, with appropriate anterior and posterior support to maintain the decubitus position. The most frequent focus of compromise involves positioning of the arms and the potential for brachial plexus injury. The ipsilateral arm should be placed on an elevated arm rest or gel pad, avoiding abduction of more than 90 degrees and excessive stretch on the shoulder. The contralateral arm should be placed on an armboard with ulnar padding. Furthermore, in patients in full flank position, an axillary roll should be placed just caudal to the axilla (not in the axilla) to avoid compression of the contralateral brachial plexus. Finally, after the patient has been positioned and before sterile draping, the operating table should be fully rotated to ensure that the patient is adequately secured in all positions.

Two patient positions used in specific urologic cases deserve attention: the prone position for percutaneous nephroscopy and the full Trendelenburg position for robotic-assisted laparoscopic procedures in the pelvis. In the prone position, special care should be taken to pad the torso, elbows, hips, and legs. The anesthesiologist should ensure that the endotracheal tube and all vascular accesses are properly secured. Coordination of the entire team is required during transfer from the supine position on the stretcher to the prone position on the operating room table. A stretcher should always be available immediately in case of airway compromise and the need for rapid transfer to the supine position. Regarding the full Trendelenburg position for minimally invasive pelvic procedures, the primary issues involve the physiologic changes in respiratory function, cardiovascular function, and increases in central venous and intracranial pressures. Patient positioning should focus on properly padding and securing the patient to the operating table to prevent cephalad sliding. Although fixed shoulder braces will undoubtedly prevent patient movement, these braces should be avoided because of the risk of brachial plexus compression and resultant neuropathy.

ABDOMINAL INCISIONS AND WOUND CLOSURE

Abdominal Incisions

Urologic surgery can encompass a large area of the trunk, and therefore the urologist should be familiar with all type of incisions

of the abdomen. The most commonly used incision in surgery including urology is the midline abdominal incision. This incision can provide access to the entire peritoneum and retroperitoneum. For procedures focused on particular areas of the abdomen, alternative incisions provide more focused exposure with certain benefits. A Pfannenstiel incision (transverse lower abdominal incision) can be used for virtually all pelvic procedures and results in improved cosmesis and possibly decreased pain. For access to the lower third of the ureter, a Gibson incision (i.e., an oblique incision in the lower quadrant) can be used. With a Gibson incision, entry into the retroperitoneum is gained by splitting the external and internal oblique muscles in the direction of its fibers. Access to the upper abdomen and retroperitoneum for renal and adrenal surgery can be gained using various kinds of incisions. An extraperitoneal approach is best performed via a flank incision over the 11th or 12th rib, with or without partial rib removal. An extraperitoneal approach avoids the complications of transperitoneal surgery such as bowel injury, postoperative ileus, and adhesion formation. Transperitoneal access can be obtained via an anterior subcostal incision (two fingerbreadths below the costal margin). This incision provides better access to the midline vascular structures by allowing for complete medial mobilization of the posterior peritoneum. For large or locally advanced (vena cava thrombus) tumors, a thoracoabdominal or chevron incision provides the best exposure in general. A thoracoabdominal approach is preferred for large upper retroperitoneal tumors or tumors with extension into the thoracic cavity (supradiaphragmatic vena cava tumor thrombus). On the other hand, a chevron incision is preferred for access to both the right and left abdomen (e.g., bilateral renal tumors). In summary, proper choice of incision is often critical to successful surgical outcome, especially for complex operative cases.

Wound Healing

Knowledge of the basic principles of wound healing is important to properly assess incision closure and its associated complications. All cutaneous wounds progress stepwise through a series of events toward complete wound repair; in a particular wound, different phases of events may occur simultaneously. **The series of steps can be divided broadly into three stages: reactive phase, proliferative phase, and maturational phase.** The reactive phase occurs immediately with the two primary responses of hemostasis and inflammation. Disruption of vascular membranes results in platelet activation and aggregation, which in turn initiate the inflammatory response. During this stage of wound healing, inflammatory cells including polymorphonuclear cells, macrophages, and lymphocytes migrate into the wound and become activated, leading to cytokine activation and secretion of various growth factors. The second stage, proliferative, results in the formation of granulation tissue. The stage is characterized by proliferation of endothelial cells and fibroblasts leading to angiogenesis and epithelialization, which eventually results in growth of immature blood vessels and deposition of extracellular matrix and early collagen scaffolding. Finally, the maturation stage occurs with further deposition of collagen and wound contraction. **The maturational phase begins approximately 1 week after injury and progresses rapidly over 6 weeks, with increasing wound strength over the next 12 months. The scar regains approximately 3% strength after 1 week, 20% after 3 weeks, and 80% after 3 months (Witte and Barbul, 1997).**

Wound Closure

Along with choice of incision, proper closure is necessary to avoid certain surgical complications including wound infection and fascial dehiscence. In general there are three types of wound closure: primary, secondary, and tertiary (or delayed primary closure). In the vast majority of elective procedures, the urologist should attempt a permanent closure after the operation (primary closure). Secondary closure is reserved for heavily contaminated wounds for which the fascia is closed primarily but the skin and subcutaneous tissues are

allowed to heal via re-epithelialization and contraction. Tertiary closures are reserved for patients with abdominal compartment syndrome or patients requiring re-explorations, in whom temporary closure is initially performed with intention of future permanent closure. Unless the procedure involves heavy contamination, incision closure involves reapproximation of the fascia (in one or multiple layers) and the skin. Choice of suture type by the surgeon depends on preferences of braided versus nonbraided, monofilament versus multifilament, and absorbable versus nonabsorbable. A full description of different suture types and their properties is listed in Table 5-8 (Hochberg et al, 2009). Although the method of fascial closure has been studied extensively, a definitive, superior method is not universally agreed upon. van 't Riet and colleagues performed a meta-analysis of available RCTs (van 't Riet et al, 2002). In all, 6566 patients from 15 studies were included; the primary outcome measure was incidence of incisional hernia. The analysis indicated that between slowly absorbable and nonabsorbable sutures there was no difference in risk of incisional hernia in continuous versus interrupted fascial closures, although nonabsorbable closure was associated with increased wound pain and sinus formation. For rapidly absorbable suture types, continuous fascial closure was significantly associated with increased rate of incisional hernias. Because of the limited number of patients, a definitive conclusion could not be made for interrupted rapidly absorbable suture closure versus continuous slowly nonabsorbable suture closure. The authors, however, concluded that mass closure with slowly absorbable suture in a continuous fashion is the optimal method. To address the limitation found in previous meta-analyses, Seiler and colleagues completed an RCT of 625 patients (Seiler et al, 2009). Patients were randomized to one of three arms: interrupted closure with rapidly absorbable suture or continuous closure with one of two different slowly absorbable sutures. They found no significant difference in incisional hernia (15.9% vs. 8.4% vs.

12.2%, $P = .09$), fascial dehiscence, wound infection, or serious adverse events. In conclusion, although incisions may be closed either with interrupted, rapidly absorbable suture closure or with continuous slowly absorbable suture closure, careful attention should be paid to the technique, given the relatively high incidence of incisional hernia. A subsequent meta-analysis of existing literature again could not find a significant difference between continuous closure with slowly absorbable suture versus interrupted closure with rapidly absorbable suture (Diener et al, 2010).

Perhaps the most frequently encountered complication of abdominal wounds is the SSI. Because of different reporting methods and descriptions in the literature, the National Health Care Safety Network of the CDC published definitions of SSIs with clearly defined, objective criteria (Kirby and Mazuski, 2009). The infections are classified as follows:

- Superficial incisional infection: involves only skin and subcutaneous tissue and occurs within 30 days of surgery
- Deep incisional infection: involves deep soft tissues (muscle or fascial planes) and occurs within 30 days of surgery (or within 1 year if implant is in place)
- Organ or space infection: involves any part of the body that is opened or manipulated during the operative procedure and has purulent drainage from a drain placed in the wound or evidence of infection on radiographic imaging

Specific risk factors predisposing to SSIs were previously listed in Box 5-2. The mainstay of treatment centers on adequate drainage of the infected area. Superficial infections and some deep incisional infections can usually be managed with opening of the skin incision and packing of the wound. Care should be taken to open the incision widely to ensure complete drainage of underlying purulent fluid. The use of oral or intravenous antibiotics is not necessary unless the infection is associated with significant skin cellulitis (erythema extending >2 cm from

TABLE 5-8 Properties of Suture Materials

SUTURE	ORIGIN	TISSUE ABSORPTION	PHYSICAL CONFIGURATION	TENSILE STRENGTH	COMMENTS
Vicryl	Synthetic	Absorbable	Braided	65% 2 wk 40% 4 wk	Slower loss of function and higher knot-breaking strength compared with polyglycolic acid (Dexon).
Dexon	Synthetic	Absorbable	Braided	63% 2 wk 17% 3 wk	Lubricant coating decreases coefficient of friction.
Monocryl	Synthetic	Absorbable	Monofilament	30%–40% 2 wk (dyed) 25% 2 wk (undyed)	Excellent tensile strength allows use of smaller sutures for skin closure.
PDS	Synthetic	Delayed absorbable	Monofilament	74% 2 wk 50% 4 wk 25% 6 wk	No absorption until after 90 days; low reactivity, tends to maintain strength in presence of infection; newer barbed version is knotless.
Maxon	Synthetic	Delayed absorbable	Monofilament	81% 2 wk 59% 4 wk 30% 6 wk	
Chromic gut	Natural	Absorbable	Monofilament	0% 3 wk	Can also be found as plain gut (untreated) for faster absorption.
Nylon	Synthetic	Nonabsorbable	Monofilament	50% 1-2 yr	Very low tissue reactivity.
Prolene	Synthetic	Nonabsorbable	Monofilament	No significant loss over time	High plasticity, extremely smooth surface (requires extra knot throws).
Silk	Natural	Nonabsorbable	Braided	Degraded over time	Braided for easier handling; can be prone to infection.
Mersilene	Synthetic	Nonabsorbable	Braided or monofilament	No significant loss over time	Braided should not be used in infection.

incision edge or systemic signs of toxicity, e.g., fever, sepsis) (Barie and Eachempati, 2005). Once opened, the wound should be allowed to heal by secondary intention. Many deeper incisional infections are too extensive for bedside incision and require operative debridement under anesthesia. It is critical to carefully examine any infected wound for signs of necrotizing infection, most commonly secondary to *Clostridium perfringens*. Signs include drainage of grayish, dishwater-colored fluid, frank necrosis of the fascial layer, and wound crepitus. A necrotizing infection requires immediate return to the operating room for wide debridement and washout. In contrast to incisional infections, deeper organ and space infections may cause no superficial signs at the level of the incision. Rather, patients often show systemic signs of infection, pain, or sepsis; cross-sectional imaging is used to reveal the putative source. Again, the principle of adequate drainage applies, and management involves percutaneous or operative drainage of the abscess fluid. A controversial issue in the prevention of organ and space infections is the routine placement of drainage systems at the time of the initial operative procedure. A wide variety of surgical drains is available. Drains are broadly categorized as open nonsuction, closed nonsuction, and closed suction drains. Open nonsuction drains are employed when accurate quantification of drainage amount is not necessary. These drains are associated with less patient discomfort and are the easiest to remove. Closed drains are chosen if quantification of drainage amounts or characterization of drainage fluid is necessary. The use of suction in closed drain systems is in general preferred if immediate recognition of small amounts of drainage is important (e.g., a drain around a ureterointestinal anastomosis). Although drains continue to be widely used in various urologic procedures, several prospective studies in the general surgical literature have failed to show significant benefit; therefore most experts caution against their routine use (unless strong indication exists) (Barie, 2002).

Perhaps the most dreaded complication of surgical incisions is acute wound failure (or fascial dehiscence). Overall the incidence of fascial dehiscence is 1% to 2%, and the complication usually occurs 1 week after surgery, although it may occur up to 30 days postoperatively. Risk factors for dehiscence include patient-related factors (advanced age, malnutrition, corticosteroid use, obesity, and prior history of radiotherapy); SSI; and technical errors at the time of wound closure. The most common technical errors associated with wound failure are placing the suture too close to the fascial edge, knot slippage, and excessive suture tension. **Multiple studies have investigated the type of closure, and there is no difference in dehiscence risk between interrupted and continuous closures as long as rapidly absorbable sutures are not used with the latter.** Historically, in high-risk patients retention sutures were strongly advocated and widely used as a preventive measure for wound dehiscence. Literature evidence, however, was primarily retrospective, and subsequent prospective trials have failed to show evidence of benefit (Carlson, 1997). One recent trial by Rink and colleagues randomized 95 high-risk patients to retention sutures versus standard closure; the researchers reported that although no difference in wound failure rates was seen, retention sutures were associated with a significantly increased rate of patient morbidity, primarily pain (Rink et al, 2000). Accordingly, recent surgical trends suggest a movement away from the use of retention sutures and, alternatively, toward the increased use of grafts and synthetic mesh in wounds thought to be at increased risk of fascial dehiscence. **When acute wound failure does occur, it is usually immediately preceded by a sudden gush of serosanguineous fluid from the wound.** Some small fascial disruptions can be managed conservatively with wound packing and close observation, but the majority of disruptions, particularly in the setting of bowel evisceration, mandate urgent return to the operating room. At the bedside, a sterile, saline-moistened towel should be placed over the eviscerated components while the patient is being prepared for the operating room. At the time of reoperation, the fascial edges are inspected for the cause of the disruption. In cases of technical errors or fascial tearing in which the fascial edges are healthy and can be brought together without tension, a primary closure is

appropriate. In all other cases, the fascial edges are debrided and the wound is closed with absorbable mesh or biologic prosthetic grafts. A full discussion of the different materials is beyond the scope of this chapter, but strong consideration should be given to an intraoperative general surgical consultation.

Whether because of a deep abdominal infection or an acute wound failure, the urologist is often faced with decisions regarding temporary versus permanent closure and primary versus secondary permanent abdominal wall closure. In general, a temporary abdominal closure is considered in situations of significant deep abdominal infection (e.g., bacterial peritonitis secondary to bowel anastomosis breakdown, ischemic bowel) or significant abdominal wall failure (e.g., necrotizing fasciitis). **Perhaps the biggest recent advance in temporary abdominal wall closure was the development of the negative-pressure vacuum pack.** This technique allows safe, inexpensive temporary closure, facilitates wound healing by reducing chronic bowel edema and improving local blood flow, and can result in relatively high delayed primary abdominal wall closure rates. To determine the effectiveness of temporary closure, Bhangu and colleagues performed a meta-analysis of the existing literature on whether temporary closure of contaminated abdominal wounds reduces the rate of deep SSI (Bhangu et al, 2013). **Although the currently available literature is not substantial, they concluded that delayed primary closure of the abdomen was a reliable and potentially cost-saving method to prevent SSI in contaminated wounds.** When delayed primary fascial closure is not feasible, newer biologic prosthetic mesh can be used to close the abdomen and the remaining wound can close secondarily (in conjunction with use of a negative-pressure vacuum-assisted device). These mesh prosthetics are derived from human, porcine, or bovine sources and in general are synthesized at acellular collagen matrices. Although the long-term durability of these materials is not known, they are usually safer in contaminated wounds.

KEY POINTS

- Proper preoperative evaluation of the patient will prevent unanticipated cancellations and decrease the risk of postoperative complications.
- The indications for preoperative cardiac testing depend on three groups of factors: the functional capacity of the patient, cardiac risk factors, and surgery-specific risk factors.
- SSIs are one of the leading causes of perioperative complications and increased hospital stay. Antibiotic prophylaxis is indicated in virtually all surgical procedures.
- VTE is a common complication of urologic procedures, and the AUA recommends either mechanical or pharmacologic prophylaxis (or both for patients at highest risk) for all urologic procedures.
- Proper understanding of the pharmacologic principles of anesthesia will allow the urologist to actively participate in the decision process of choosing which mode of anesthesia will be appropriate for a particular patient and procedure.
- Current guidelines advocate blood product transfusion for hematocrit less than 21% in most patients unless there are specific cardiopulmonary risk factors.
- Perioperative hypothermia of even 1° C to 2° C is associated with increased estimated blood loss and increased risk of SSI.
- Proper choice of surgical incision results in optimal surgical exposure and therefore improved outcomes.
- Current literature suggests that closure with continuous, slowly absorbing suture results in the lowest risk of incision-related complications.

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The complete reference list is available online at www.expertconsult.com.



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6

Fundamentals of Urinary Tract Drainage

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Lower Urinary Tract: Historic Note

Anatomic Considerations

Indications for Lower Urinary Tract Drainage

Catheter Selection

Catheter Design

Technique of Urethral Catheterization

Complications

Lower Urinary Tract: Suprapubic Catheter Drainage

Upper Urinary Tract: Ureteral Stents and Catheters

Upper Urinary Tract: Nephrostomy Tube

Understanding the fundamentals of urinary tract drainage is essential to every practicing urologist and urology trainee. This chapter covers basic aspects of the indications, devices, and descriptions of the various techniques of urinary tract drainage.

LOWER URINARY TRACT: HISTORIC NOTE

Descriptions of draining bladder urinary retention predate the ancient Egyptian civilization and have surfaced from Asian, Chinese, Egyptian, Roman, Byzantine, and Greek civilizations, emphasizing the long-standing importance of this clinical problem. Reports from ancient times describe catheterization with straws, reeds, polished or waxed rolled-up leaves, and hollow twigs (Mattelaer and Billiet, 1995).

In the Hippocratic writings *On Diseases* (around 400 BCE), the use of a bladder catheter for urinary drainage was considered a basic skill of any physician (Moog et al, 2005a). In the 7th century AD, Paulus Aegineta described bladder drainage with use of a slender silver catheter, a technique that became very popular in medieval times. Remarkably, even in that scientifically naive era, the concept of silver having an antiseptic function was postulated (Mattelaer and Billiet, 1995). The use of silver catheters remained popular until the introduction of natural rubber for the manufacture of urinary catheters. Galen (2nd century AD), Paulus Aegineta (7th century AD), and Avicenna (11th century AD) also describe the use of a catheter to deliver a substance into the bladder to treat several ailments including pyocystis, hematuria, and inflammation (Moog et al, 2005a, 2005b; Madineh, 2009).

The 19th century was pivotal in the evolution of the catheter to the devices we use to this day. Joseph F. B. Charrière introduced the Charrière unit to measure the size of a catheter, a scale which has been adopted worldwide. One French unit equals 0.33 mm in the external diameter (Mattelaer and Billiet, 1995). Mercier invented the coudé-tipped catheter in 1836 (*coudé* means “elbow” in French) (Mattelaer and Billiet, 1995). In 1860 Auguste Nelaton created the Nelaton catheter, a soft tubular rubber bladder catheter with a solid straight tip and one side hole, made of vulcanized rubber (Mattelaer and Billiet, 1995). In the 1930s, Frederick E. B. Foley invented a catheter with an inflatable balloon attached to the catheter tip as a retainment mechanism (Tatem et al, 2013). This represented a foundational development that forms the basis for most lower urinary tract catheters used today.

ANATOMIC CONSIDERATIONS

Thorough knowledge of the relevant anatomy is a prerequisite to performing urinary tract drainage.

Male Urethra

The average length of the male urethra is 17.5 to 20 cm from bladder neck to external urethral meatus from postmortem studies as reported in *Gray's Anatomy* (Standring, 2008). More recent literature, measuring the urethra in vivo with a bladder catheter, confirms these lengths to be quite accurate (Kohler et al, 2008; Krishnamoorthy and Joshi, 2012).

In general, the male urethra is divided into segments: bladder neck or preprostatic urethra, prostatic urethra, membranous urethra, and penile or spongy urethra, which in turn can be subdivided into the bulbous urethra, pendulous urethra, and fossa navicularis. An alternative classification for urethral segments is anterior and posterior urethra; the posterior segment consists of the prostatic and membranous urethra, and the anterior segment equates to the penile urethra.

The caliber of the urethra varies throughout its course. The normal healthy external meatus should allow a 24-F catheter to pass. More proximal portions of the adult urethra have a larger caliber, the largest being the prostatic urethra with a caliber of approximately 32 F. The normal bladder neck is usually of a caliber to allow passage of a 28-F instrument (Davis, 1913).

Female Urethra

In nulliparous, continent women, the urethra and bladder neck reside in the connective tissue of the anterior vaginal wall. The urethra measures approximately 4 cm and can be divided into three segments: the distal segment, mid-urethra, and proximal segment (Wieczorek et al, 2012). In a supine position, the urethra has a downward inclination with a slight angle more horizontally approximately midway, and the mean caliber is approximately 22 F (Uehling, 1978).

INDICATIONS FOR LOWER URINARY TRACT DRAINAGE

The indications for inserting a bladder catheter can conveniently be divided into two categories: therapeutic or diagnostic catheterization.



Figure 6-1. A, Urethral dilators with tapered tip (12 and 18 Fr). B, Close-up. C, Filiform and followers.

The most common indication for transurethral bladder catheterization is for drainage of an acute or chronic urinary retention or postvoid residual volume. Drainage can be accomplished by an indwelling catheter or by intermittent catheterization, depending on the pathology, the recurring need for drainage, and the dexterity of the patient or caregivers. Although ultrasound-based bladder scanners are widely used to estimate postvoid residual urine volume, the most accurate method of measurement is by emptying the bladder with transurethral catheterization. The second most common indication for bladder catheterization is to monitor urinary output. Patients with gross hematuria, regardless of its cause, will often require a catheter for bladder irrigation and drainage of bloody urine and blood clots.

Dilation with urethral catheters is the most commonly used primary treatment in the management of urethral strictures (Bullock and Brandes, 2007). Simple urethral dilation can be performed by blind insertion of a filiform leader followed by coaxial followers of increasing diameter or by passing Council catheters of increasing diameter over a cystoscopically placed guidewire (Fig. 6-1). A recent Cochrane meta-analysis comparing simple dilation with endoscopic urethrotomy and open urethroplasty for urethral stricture was not definitive in providing recommendations surrounding preferred treatment of urethral stricture (Wong et al, 2012). The only randomized trial comparing dilation with urethrotomy reported no significant difference in efficacy and stricture-free rates (Steenkamp et al, 1997; Heyns et al, 1998).

In patients unable to provide a clean urine sample with repeated contamination of a midstream urine sample, single catheterization may be used to obtain an uncontaminated urine sample.

Manometer-tipped catheters are used in urodynamic studies to measure the intravesical and urethral pressure. Thermometer-tipped catheters are occasionally used during prolonged surgeries providing both continuous thermometry and adequate drainage for urinary output measurement.

Intravesical therapy with, for instance, dimethyl sulfoxide for interstitial cystitis (Colaco and Evans, 2013), alum for intractable hematuria (Abt et al, 2013), or Mitomycin C or bacille

TABLE 6-1 Catheter Size Based on Age

AGE IN YEARS	CATHETER SIZE (Fr)
<5	5-8
5-10	8-10
10-14	10
>14	10-14

Calmette-Guérin (BCG) solution for nonmuscle invasive bladder cancer (van Lingen and Witjes, 2013) is also administered through a transurethral catheter.

In performing retrograde cystography, radiographic contrast material is administered by bladder catheterization to opacify the urinary tract for diagnostic purposes.

In urogenital trauma, which is covered elsewhere in this text, insertion of a bladder catheter is, depending on the extent of the trauma, often the first choice of treatment. This should be considered only after diagnostic workup of the possible urethral trauma has been completed so that the feasibility and appropriateness of transurethral catheter placement can be defined.

CATHETER SELECTION

A wide variety of catheters are available for transurethral catheterization. Differences in materials used in manufacture; variations in length, circumference, shape of the catheter tip, and number of channels; and varieties of coatings contribute to this vast array of such devices.

The choice of catheter design and size depends on the indication for use, expected fluid requiring drainage, anticipated indwelling time, age, gender, previous history, and patient anatomy. One should choose the smallest size available based on these variables (Table 6-1). The use of feeding tubes as urethral catheters should

be discouraged because their stiffness and length can be a source of complications (ischemic ulcers, urethral strictures, and knotting in the bladder) (Smith, 2003; Sarin, 2011).

The optimal catheter for an initial attempt at transurethral bladder catheterization in adult patients with no past urologic history, no risk of urinary tract abnormality, and no known allergies, is a 16-Fr latex straight-tipped catheter.

CATHETER DESIGN

The most basic catheter design is constructed with a single lumen to allow for drainage or instillation. The most frequently used retention mechanism is the retention balloon, which is inflated through a dedicated channel. The three-way catheter allows for simultaneous instillation and drainage of fluids and is especially useful in patients with hematuria, clot retention, and pyuria. Continuous bladder irrigation is most commonly used postoperatively after urologic surgery, when hematuria and possible clot formation are to be expected. The three-way catheter is designed with a larger-than-average balloon to allow for instillation of 30 mL or more, which can be helpful in achieving hemostasis after transurethral resection of the prostate by applying traction on the catheter, thus compressing vessels at the bladder neck (Fig. 6-2).

The addition of channels to the initial single catheter design comes with potentially negative design requirements. The extra lumens occupy space in the internal lumen of the catheter, reducing the internal diameter. The inner diameter of a 24-Fr single-lumen catheter is larger than the inner lumen of a 24-Fr two-way catheter, which in its turn is larger than the inner lumen of a 24-Fr three-way catheter.

There are basically two available tip shapes, the Nelaton blind-ending straight tip and the coude tip, or elbowed or Tiemann tip. Both versions exist in a Councill catheter version, which can be passed into the bladder over a guidewire if necessary. Multiple variations such as tapered tips or multiple side holes exist throughout the wide array of available catheters.

Materials and Coatings

Most catheters for everyday use are composed of latex, rubber, silicone, or polyvinylchloride (PVC). For short-term catheterization, latex or rubber catheters are preferred because of their availability and low cost. Silicone is relatively inert, and randomized controlled trials (RCTs) have demonstrated silicone to induce significantly less tissue inflammation than latex catheters (Nacey et al, 1985; Talja et al, 1990; Schumm and Lam, 2008). Silicone is preferred over latex catheters for long-term catheterization. Silicone catheters are

stiffer and less prone to buckling when encountering resistance (Villanueva et al, 2011).

Several coatings have been studied in an attempt to reduce trauma, urethritis, and catheter-associated urinary tract infection (CAUTI). The use of hydrophilic-coated catheters is of interest for intermittent catheterization. Such catheters have been associated with less discomfort, fewer traumatic catheterizations, and decreased incidence of symptomatic urinary tract infections (UTIs) and urethral strictures (Wyndaele, 2002; De Ridder et al, 2005; Cardenas et al, 2011). A recent meta-analysis by Bermingham was unable to identify a significant difference in the incidence of symptomatic UTIs when comparing different catheter types used for clean intermittent catheterization (CIC). Li and colleagues, on the other hand, in a meta-analysis focusing on the spinal cord injury population, demonstrated that the use of hydrophilic-coated catheters in CIC significantly reduced the UTI and hematuria rates (Bermingham et al, 2013; Li et al, 2013). Because the use of clean uncoated catheters for CIC was most cost-effective and the use of gel-reservoir was second most cost-effective in the Bermingham analysis (Bermingham et al, 2013), **the routine use of hydrophilic catheters for CIC in non-spinal cord injury patients is not recommended.**

Antibiotic-impregnated catheters may delay bacteriuria in short-term catheterization (<1 week). Such benefit has not been substantiated in patients requiring longer-term catheterization (Schumm and Lam, 2008; Hooton et al, 2010).

Bacterial-coated catheters have the theoretic benefit of colonizing the urine with a nonvirulent strain of *Escherichia coli* and have shown promising results in small pilot trials. Studies on the feasibility and efficacy of clinical use of such catheters are ongoing (Trautner et al, 2007; Prasad et al, 2009; Darouiche and Hull, 2012).

A 2008 Cochrane meta-analysis demonstrated that the use of silver-alloy-coated catheters significantly reduced the incidence of asymptomatic bacteriuria in short- and long-term (>1 week) use of such catheters (Schumm and Lam, 2008). In a more recent multicenter RCT including more than 6000 patients, antimicrobial-coated catheters demonstrated a statistically significant benefit in reducing CAUTI compared with polytetrafluoroethylene (PTFE)-coated catheters, whereas silver-alloy catheters demonstrated no beneficial effect. **Because no clinically significant benefit was noted for short-term catheterization with either catheter, the routine use of these catheters cannot be recommended (Pickard et al, 2012).**

New coatings to enhance biocompatibility are still being developed and investigated, with the desired outcome being coatings that prevent encrustation and UTIs (Siddiq and Darouiche, 2012).

TECHNIQUE OF URETHRAL CATHETERIZATION

After establishing the indication for catheterization, a medical and surgical history, including allergies, focusing on previous urologic history, surgeries, and catheterization attempts should be obtained. This information is necessary for optimal catheter choice and complication risk assessment.

When performing urethral catheterization, the physician assumes a position at the side of the patient corresponding to the physician's dominant hand (if the physician is right handed, the position is on the right-hand side of the patient). All materials expected to be required should be readily available on the sterile drape. The patient should be in supine position at a comfortable height for the individual performing the catheterization. A frog-leg position is preferred for female patients. Catheterization should be carried out in a sterile fashion and should start with sterile draping of the patient. When an indwelling catheter is being placed, the balloon should be checked for integrity before catheterization.

The most recent American Heart Association guidelines no longer recommend routine use of infective endocarditis prophylaxis for any genitourinary procedure, even in patients with the highest-risk cardiac conditions (Wilson et al, 2007).

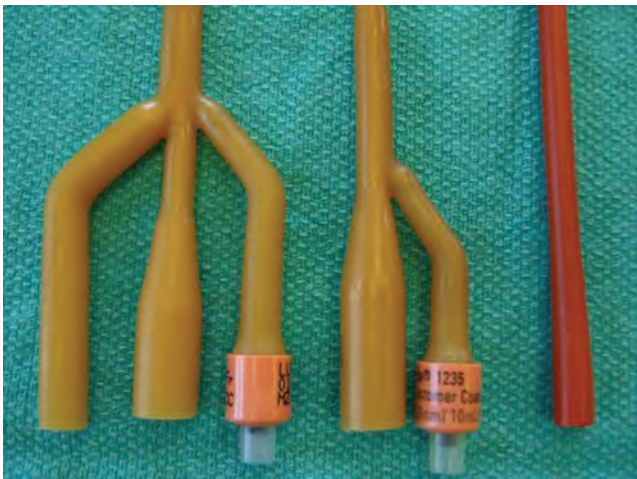


Figure 6-2. Three-way, two-way, and single-lumen catheters.

Lubrication of the catheter is advised for smooth catheterization and minimization of risk of urethral trauma. Four categories of lubricants exist: plain lubricant, lubricant-anesthetic, lubricant-disinfectant, and lubricant-anesthetic-disinfectant.

The use of 2% lidocaine urethral instillation before instrumentation was first reported safe and efficacious in the mid-20th century (Haines and Grabstald, 1949; Persky and Davis, 1953) and is still widely practiced; however, evidence of benefit has been a topic of conflicting literature.

The safety of urethral lidocaine use has been well established in situations in which the urethra is intact. The systemic uptake of lidocaine through intact mucosa after instillation of doses of up to 550 mg (approximately 27 mL of 2% lidocaine lubricant) reaches a very low peak concentration that never reaches a toxic level (Ouellette et al, 1985; Eardley et al, 1989; Birch and Miller, 1994). However, toxicity has been reported in patients in whom lidocaine gel was used in the presence of a disrupted mucosal barrier, leading to a high peak serum concentration within minutes. Reported symptoms are confusion, lethargy, seizures, disorientation, and anaphylactic shock (Sundaram, 1987; Clapp et al, 1999; Priya et al, 2005; Sinha and Sinha, 2008).

Chitale and McFarlane showed no difference in pain experience during flexible cystoscopy after plain or anesthetic lubricant (McFarlane et al, 2001; Chitale et al, 2008). Ho and coworkers concluded that insertion of an anesthetic lubricant is paradoxically more painful than plain lubricant (Ho et al, 2003). Cooling the lubricant to 4° C has been shown to significantly decrease pain perception compared with lubricant at room or body temperature, possibly because of a cryoanalgesic effect (Thompson et al, 1999; Goel and Aron, 2003).

The anesthetic lubricant should be indwelling in the urethra longer than 15 minutes to provide a beneficial effect (Choong et al, 1997; Siderias, 2004). A short delay (<15 minutes) does not seem to have any benefit compared with no delay (Birch et al, 1994; Garbutt et al, 2008; Losco et al, 2011). In female catheterization, the use of an anesthetic lubricant has been shown to be effective even after only several minutes of indwelling time (Chan et al, 2013; Chung et al, 2007).

Two available meta-analyses on the use of anesthetic versus non-anesthetic lubricant report conflicting results and recommendations, possibly because of different inclusion criteria and a high grade of heterogeneity in included studies. Patel and colleagues demonstrated no difference in use of anesthetic versus plain lubricant; in contradistinction, Aaronson and colleagues reported a statistical beneficial effect (Patel et al, 2008; Aaronson et al, 2009).

Considering the conflicting data available, the routine use of anesthetic lubricant cannot be recommended. If anesthetic lubricant is to be used, the limited evidence available suggests slowly instilling (3 to 10 seconds) a minimum amount of 20 mL of cooled lubricant and allowing a minimum of 15 minutes of exposure to maximize benefit to the patient (Schede and Thüroff, 2006; Tzortzis et al, 2009).

Catheterization in Male Patients

The true external urethral meatus is exposed by retracting the foreskin if present. In the presence of phimosis, catheterization can be attempted blindly with a smaller-gauge flexible catheter. Hypospadias is not uncommon, and some hypospadiac patients have a blind-ending navicular fossa, which should not be catheterized.

If a meatal stricture or stenosis is apparent, passing a catheter of a smaller size should be attempted first. Gentle dilation of the stenosis with sounds can be attempted if catheterization is unsuccessful.

After skin and meatus preparation and sterile draping, the initial maneuver is to grasp the penis with the nondominant hand, which is from then on regarded as no longer sterile. The pendulous curvature of the penis is eliminated by pulling the shaft upward. The catheter is inserted into the meatus after lubrication and advanced approximately 7 to 12 cm. The penis should be brought into a horizontal position, parallel to the patient. Some slight resistance can be appreciated at the membranous urethra, the most fragile

segment. The entire catheter is introduced into the penis, up to the bifurcation of the catheter and balloon valve. Spontaneous drainage of urine should occur if the bladder is not empty. If no spontaneous urine drainage appears, gently pushing down on the suprapubic region or instilling a small amount of clear sterile fluid and aspirating the catheter with a syringe should result in drainage. The lumen of the catheter can be obstructed with lubricant jelly, pus, or blood. If after such maneuvers no drainage occurs, the bladder is empty or the catheter is malpositioned.

After verifying the correct position of the catheter in the bladder, inflate the balloon with sterile water, which has been demonstrated to be the optimal filling solution, especially if the catheter is to be in place for several days or longer (Sharpe et al, 2011). Although not conclusively proven, saline or glucose-based solutions can theoretically occlude the tubing by precipitation (Hui et al, 2004; Huang et al, 2009). In uncircumcised patients, the foreskin is reduced to its normal position to avoid paraphimosis.

The penis and catheter should be taped in an upright position to prevent pressure ulceration from occurring at the curve in the pendulous urethra and iatrogenic hypospadias at the urethral meatus. Iatrogenic hypospadias, when missed or untreated, can evolve into severe deformations (Andrews et al, 1998; Gokhan et al, 2006; Cipa-Tatum et al, 2011).

Ideally, a closed circuit should be maintained with the catheter connected to a sterile closed bag system, positioned lower than the bladder to allow gravity to assist in bladder emptying.

Although it is believed that rapid complete emptying of a urinary retention results more frequently in possible complications such as hematuria, hypotension, or pain, **efficient complete emptying has been demonstrated to be safe and is recommended** (Nyman et al, 1997; Muhammed and Abubakar, 2012).

Catheterization in Female Patients

With the patient in a frog-leg position and adequately draped, the nondominant hand is used to spread the inner labia to reveal the external urethral meatus. This hand is now considered contaminated. The urethral meatus should be found 1 to 2.5 cm inferior to the clitoris. After the meatus has been cleaned and lubricated, the catheter is inserted into the meatus and gently advanced until approximately half the catheter has been inserted. It is not necessary to advance the catheter up to the valve bifurcation. The balloon is inflated after confirming the correct position of the catheter in the bladder.

Catheterization in Children

Catheter use in children is predominantly for diagnostic purposes or postoperative drainage. In infants, suprapubic puncture for obtaining a urine sample is often preferred over a bag sample because it is more likely to be sterile. Bladder catheterization, however, is preferred over suprapubic aspiration because it is less painful and has a higher success rate in obtaining a satisfactory urine sample (Pollack et al, 1994; Kozar et al, 2006; El-Naggar et al, 2010). Portable bedside bladder ultrasound is useful to identify a sufficient amount of urine in the bladder before attempted catheterization (Chen et al, 2005; Robson et al, 2006; Baumann et al, 2008).

Children are presented with a phimosis more frequently than men. As in adults, it is useful to align the preputial opening with the meatus to facilitate catheterization. Compared with women, the urethral orifice in young girls may be partly obscured behind the hymen. To reveal the meatus, it is useful to apply some downward pressure on the hymen. If the meatus cannot be visualized, the same maneuver as in women should be applied: the tip of the catheter is slid down from the clitoris toward the introitus, above the hymen.

Difficult Catheterization

The most commonly encountered cause of difficult catheterization in men without previous relevant history is inability to pass the

catheter beyond the prostate. This is commonly the result of an enlarged prostate or a closed striated sphincter. The attempted catheter is retracted, and the catheter tip evaluated for the presence of blood. If the catheter tip is clean, the next option is a 14-Fr or 16-Fr silicone catheter because it is somewhat stiffer and may pass the slight resistance more effectively. If blood is present at the catheter tip, there is a possibility of a false passage and a coudé-tipped catheter should be used for the next attempt. A false passage is most commonly created in the membranous urethra, the most fragile segment of the urethra, which can be palpated transrectally at the apex of the prostate. One can try guiding the catheter past the false passage transrectally with the index finger. If transrectal guidance does not facilitate passage and if the caliber of the urethra allows, placement of a small-caliber catheter (10 or 12 Fr) in the false passage may be attempted. This may close off the false passage and allow for passage of a second transurethral catheter into the bladder. If passage of a catheter is still not possible, a flexible cystoscope is used to assess the urethra for size, strictures, false passage, or bladder neck stenosis. If the bladder is successfully accessed, a guidewire can be passed and used to pass a Councill catheter. If a stricture is apparent and cannot be catheterized with a smaller catheter, a guidewire is cystoscopically passed through the stricture into the bladder, and the urethra dilated to allow for a catheter of adequate size to be placed. If the urethral stricture is a new diagnosis, this should be documented with a view toward follow-up and treatment if necessary. The use of stylets is recommended only in experienced hands and only if cystoscopic guidance is unavailable. If all attempts at urethral catheterization including with flexible cystoscopy guidance are unsuccessful and there are no absolute contraindications, one should consider placing a suprapubic catheter (Fig. 6-3).

Although the female urethra is short, catheterization can be challenging because of inability to find the urethral meatus. In obese patients or in patients unable to assume the frog-leg position, the use of stirrups and assistance for retraction to optimize visualization is advised and may be useful.

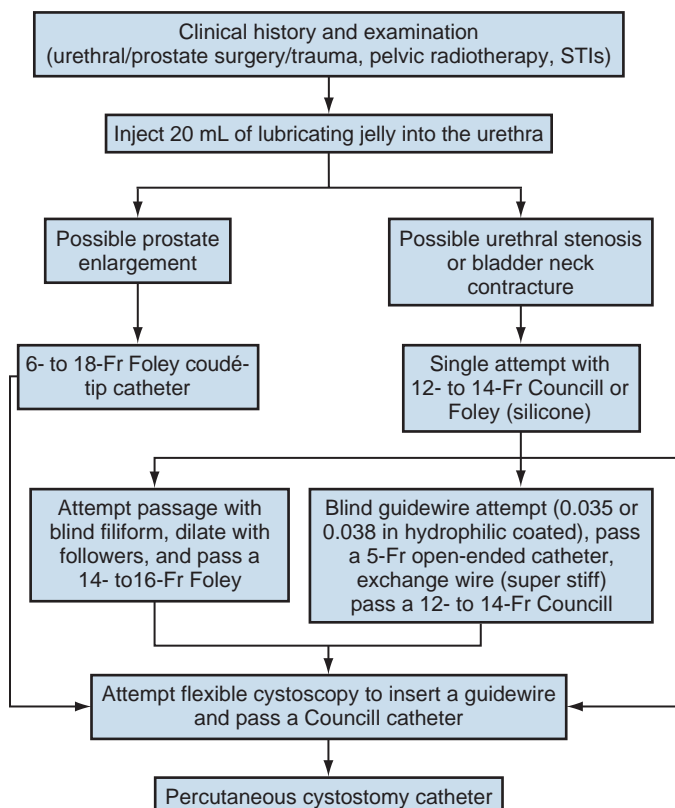


Figure 6-3. Flowchart for managing difficult catheterization. STIs, sexually transmitted infections.

In rare instances such as extreme labial adhesions, introital stenosis, or stricture or stenosis of the female urethra, urethral catheter placement is sometimes not feasible. The same approach as described for male urethral stricture should be applied.

COMPLICATIONS

Catheterization of the urethra is an everyday practice on almost every hospital ward. It is an intervention of significance, however, that may be associated with short- and long-term complications.

From 15% to 25% of hospitalized patients undergo a urethral catheter placement at some point during their stay (Glynn et al, 1997). UTIs account for approximately 35% of hospital-acquired infections, with almost 95% of UTIs in the intensive care unit setting resulting from bladder catheters (Richards et al, 2000; Klevens et al, 2007). Overuse of bladder catheterization has been reported to range from 15% to 40% of cases and is correlated with prolonged hospital stay (Apisarnthanarak et al, 2007; Tiwari et al, 2012). In the United States, the economic impact associated with CAUTI accumulates to an annual cost of about \$300 million (Zimlichman et al, 2013). Implementation of quality improvement and awareness projects has contributed to significantly reducing the incidence and duration of catheterization, and ultimately CAUTI rates (Janzen et al, 2013; Parry et al, 2013; Saint et al, 2013).

As of 2009, the definition for CAUTI was modified to exclude asymptomatic bacteriuria (Dudeck et al, 2011). In current guidelines, a CAUTI is defined as significant bacteriuria in a patient with symptoms or signs indicating a UTI, whereas asymptomatic bacteriuria refers to significant bacteriuria in asymptomatic patients. Asymptomatic bacteriuria does not require antibiotic treatment. Because there is no evidence supporting that treatment of asymptomatic bacteriuria provides any benefit in reducing morbidity or mortality, the European Association of Urology (EAU) and Infectious Diseases Society of America (IDSA) guidelines specifically recommend against screening and treatment of asymptomatic bacteriuria (Tenke et al, 2008; Hooton et al, 2010). The most important risk factor for developing CAUTI is prolonged catheterization (longer than 6 days). Other risk factors include catheterization outside of the operating room, female sex, body mass index (BMI) greater than 30, diabetes, and other active site of infection (Maki and Tambyah, 2001; Stenzelius et al, 2011).

Universal recommendations in guidelines for preventing CAUTI are avoidance of catheter use, maintenance of a closed drainage system, and removal of a catheter as soon as deemed possible. Catheters should be placed under antiseptic conditions, placing the smallest possible catheter with adequate lubrication. Routine irrigation should be avoided (Gould et al, 2010; Hooton et al, 2010; Tambyah and Oon, 2012).

A recent Cochrane meta-analysis showed no difference in urinary infection rates in long-term catheterized patients when different catheter types were compared (Jahn et al, 2012). There is insufficient evidence to reliably recommend the use of one catheter type over another.

Short-term antibiotic treatment (5 days) with catheter exchange has been proven to be equally as effective as long-term treatment (10 days) without catheter exchange in treating CAUTI (Darouiche et al, 2014).

Long-term antibiotic prophylaxis has not been demonstrated to significantly reduce symptomatic CAUTI in patients performing CIC. Interrupting long-term prophylaxis in spina bifida patients results in a nonsignificant increase in UTIs, without clinical significance (Wolf et al, 2008; Hooton et al, 2010; Zegers et al, 2011). Use of prophylactic antibiotics on removal of a bladder catheter, even after short-term catheterization, has been both recommended and discouraged (Wolf et al, 2008; Hooton et al, 2010). American Urological Association (AUA) guidelines published in 2008 recommended the use of antibiotic prophylaxis after catheter removal if bacteriuria is present, particularly in patients with risk factors such as advanced age, immunodeficiency, or corticosteroid use (Wolf et al, 2008). In 2010 the IDSA discouraged the use of prophylactic

antibiotics before catheter removal or catheter change (Hooton et al, 2010). The most recent meta-analysis attempting to answer this question reports a reduction in UTI incidence when antibiotic prophylaxis is administered on removal of a bladder catheter in surgical patients (Marshall et al, 2013). Taking into consideration that up to 25% of hospitalized patients are catheterized at some point during their stay, recommending the **routine use of antibiotics after catheter removal** would entail an enormous usage of antibiotics with the associated risks of bacterial resistance and other drug-related side effects. Therefore, prophylaxis **should be considered a recommendation only in patients with risk factors**, as previously stated by the AUA guidelines panel.

A comprehensive overview and meta-analysis of all possible complications of urethral catheterization reports that noninfectious complications are at least as frequent as CAUTI in short-term catheterizations and up to four times more prevalent in long-term catheterizations. Complications include pericatheter urine leakage, accidental removal, catheter blockage, hematuria, bladder stones, and bladder cancer. The subgroup of patients with spinal cord injuries is at greater risk of complications (Hollingsworth et al, 2013).

Inability to remove a transurethral bladder catheter can be a challenging complication. Entrapment of the catheter by anastomotic sutures after urethroplasty or radical prostatectomy poses a unique postoperative complication. When sutures are known to be degradable, one can retry catheter removal 1 or 2 weeks after the initial attempt. If the sutures are nondegradable, the urethra can be accessed with a semirigid ureteroscope to visualize and divide the suture with laser energy (Nagarajan et al, 2005; Nagele et al, 2006). Cuffing of the balloon after deflation can cause the catheter to bind at the bladder neck. This phenomenon is dependent on the catheter used (material and manufacturer), indwelling time, urinary infection, and deflation method, with indwelling time being the most significant predictor. Slow deflation of the balloon and the use of hydrogel-coated or PTFE catheters reduce the chance of balloon cuffing (Chung and So, 2012). Gonzalgo proposed a technique of instillation of 0.5 to 1 mL of fluid in the balloon to smooth out the cuff for easier catheter removal (Gonzalgo and Walsh, 2003).

Inability to deflate the Foley balloon is not uncommon. Resolution of this problem may be achieved by instilling an extra 1 or 2 mL of fluid in the balloon and trying to repeat aspiration. Overinflation of the balloon with the intention of having it burst should be avoided because this may be painful and possibly result in retained fragments of the catheter balloon in the bladder. Cutting off the inflation valve may assist if the valve is not functioning correctly. If the balloon still does not deflate, one can pass a guidewire through the inflation channel to try and perforate the balloon. If all else fails, ultrasound-guided needle puncture of the balloon is typically the final approach. Inability to remove a catheter with a fully deflated balloon can also be caused by catheter encrustation, especially if the catheter has been indwelling for an extended time. There is strong evidence that the main causal factor of catheter encrustation is infection with *Proteus mirabilis*. Especially in patients with long-term bladder catheterization, this circumstance can cause recurrent blockage of the catheter (Stickler and Feneley, 2010). Applying gentle traction to the catheter can cause the encrustation to dislodge, facilitating catheter removal. If this does not solve the problem and encrustation is suspected, ultrasound or x-ray imaging can be used for confirmation. For more significant encrustations, one can consider using a semirigid ureteroscope and the holmium:YAG laser to remove the encrustation material. Increasing patient fluid intake and ingestion of citrate could delay or control this problem in known stone formers and chronic catheter blockers (Stickler and Feneley, 2010).

Urethral stricture is not an uncommon complication after catheterization. Lumen and colleagues reported that 11.2% of urethral stricture disease requiring urethroplasty is causally related to urethral catheterization. When site of stricture was taken into account, history of urethral catheterization was the most important causal factor of multifocal or panurethral strictures (Lumen et al, 2009).

Fenton and associates reported 32% of urethral strictures as being caused by iatrogenic trauma; 36.5% of these were the result of prolonged catheterization. The authors proposed that prolonged catheterization leads to urethral inflammation and ischemia, and ultimately to urethral stricture (Fenton et al, 2005).

Inflation of the balloon in the prostatic urethra or in a false passage can cause severe hematuria, urethral rupture, and subsequent stricture (Lang et al, 2012).

Prevention of Iatrogenic Trauma

The pressure in the catheter balloon when an incorrectly placed catheter is being inflated is much higher than when the catheter is in a correct position. Forces of extraction of a catheter are much lower with 5 mL in the balloon than with 10 mL in the balloon (Wu et al, 2012). When high pressure is perceived when inflating the balloon, one should reassess and ensure that the catheter is in the bladder. In patients at risk of inadvertent traumatic catheter extraction, the balloon is filled with 5 mL instead of 10 mL to decrease the chance of significant urethral trauma.

When prolonged catheterization is required, a smaller catheter, such as 16 Fr, should be used. There should be a lower threshold for placing a suprapubic catheter when prolonged catheterization is anticipated (Fenton et al, 2005). With training and education, trauma from urethral catheterization can be reduced fivefold (Kashefi et al, 2008; Thomas et al, 2009).

LOWER URINARY TRACT: SUPRAPUBIC CATHETER DRAINAGE

Indications

If bladder drainage is necessary but access to the bladder cannot or should not be obtained transurethrally, the placement of a suprapubic catheter should be considered.

During transurethral resection of the prostate, suprapubic catheter placement is preferred by some urologists because a continuous flow can be maintained at all times without influencing bladder pressure (Sánchez Zalabardo et al, 2003).

Short-term suprapubic catheter placement is often useful in postoperative situations after urogenital surgery to allow for bladder or urethral tissue healing. Although a suprapubic catheter is more invasive than a transurethral catheter, evidence suggests that the former is more acceptable than a transurethral catheter to surgical patients (McPhail et al, 2006). There is **insufficient evidence supporting superiority of a suprapubic catheter over a transurethral catheter in short-term postoperative catheterization** (Phipps et al, 2006). However, when considering the population of hospitalized patients in need of short-term catheterization (up to 14 days), a significant benefit has been found in favor of the suprapubic catheter in terms of bacteriuria incidence and patient comfort (Niël-Weise and van den Broek, 2005).

In patients requiring a long-term indwelling catheter in whom CIC is not feasible, a suprapubic catheter is often a better option than a transurethral catheter. A recent Cochrane meta-analysis did not identify any eligible trials for analysis to determine whether a transurethral or suprapubic catheter is better in terms of effectiveness, complications, cost-effectiveness, and quality of life in long-term catheterized patients (Jamison et al, 2011; Niël-Weise et al, 2012). This reflects the lack of evidence-based data and limits the recommendation of a suprapubic catheter over a transurethral catheter for long-term catheterization.

Long-term suprapubic catheter placement in infants or children is rarely necessary. Whenever suprapubic catheter placement in children is required, the use of ultrasound guidance during the catheter placement is advised.

Contraindications to suprapubic catheter placement include previous lower abdominal surgery resulting in unsafe percutaneous passage to the bladder, bladder cancer, uncorrected coagulopathies or anticoagulation, abdominal wall infection at the desired

puncture site, and the presence of vascular grafts near the preferred tract (Harrison et al, 2011).

In patients in whom one may suspect the presence of ascites, ultrasound is always used to confirm a large postvoid residual urine volume because ascites can sometimes be mistaken for a large post-micturitional volume on ultrasound bladder scan.

Advantages of a suprapubic catheter include elimination of risk of urethral stricture and penile erosion. A trial to void can be attempted without the need for recatheterization if unsuccessful. Wound care for a suprapubic catheter is often easier, especially in chair-bound patients.

In patients requiring long-term catheter drainage, the placement of a suprapubic catheter as an alternative to a transurethral catheter can be considered, and advantages and disadvantages should be discussed with the patient.

Technique of Suprapubic Catheter

Placement: Percutaneous

For suprapubic catheter placement, the patient should be placed in supine position at a comfortable height for the physician.

In most patients the distended bladder displaces the intraperitoneal bowel loops out of the pelvis and away from the pubic symphysis. A minimum bladder volume of 300 mL on bladder scan is advised before suprapubic catheter placement is attempted (Albrecht et al, 2004).

The patient's infraumbilical abdomen should be prepared and draped in a sterile fashion. In performing blind puncture, the symphysis should be palpated and the access site should be chosen approximately one to two fingerbreadths above the symphysis. In obese patients with an abdominal pannus, placement of the tract in a skin fold is avoided to prevent dermatitis (Harrison et al, 2011). Local anesthetic is injected into the skin and along the preferred trajectory using a 10- to 20-mL syringe and an 18-gauge needle. The tract should be almost perpendicular to the skin. Aspirating urine will confirm access to the bladder. A midline 5- to 10-mm transverse incision is made at the injection site.

The safest technique for catheterization is the **Seldinger technique**. A floppy-tip guidewire is advanced into the bladder through an 18-Fr access needle. The percutaneous tract is dilated with coaxial dilators. A Cope loop or Councill catheter can be placed over the guidewire into the bladder after the tract is dilated (Fig. 6-4).

The **trocár technique** employs a peel-away trocar that envelops the catheter. The trocar should be advanced firmly but under steady control of the trocar. Once entry into the bladder has been confirmed by urine flashback or aspiration, the catheter is advanced completely into the bladder, and the trocar is retracted and peeled away. If the suprapubic catheter does not have a retention mechanism, the catheter is sutured to the skin.

Obesity, previous lower abdominal or pelvic surgery or radiation therapy, and a nondistended bladder that cannot be palpated should prompt the physician to use ultrasound guidance. It is preferable to have an assistant operate the ultrasound probe, thus allowing both hands to be available for catheter placement. When the bladder is being punctured, the needle tip will appear as a hyperechoic structure on the ultrasound image (Jacob et al, 2012). The use of ultrasound-guided suprapubic catheter placement has a high success ratio, and the procedure is safe and has a low complication rate (Cronin et al, 2011). Cystoscopic visual guidance can be of additional help in performing percutaneous suprapubic catheter placement.

Technique of Suprapubic Catheter Placement: Open

Open suprapubic catheter placement should be undertaken when a percutaneous technique cannot be performed safely. After the infraumbilical abdomen is prepared and draped, a small incision is made about one to two fingerbreadths above the pubic symphysis, providing access to the retroperitoneal space of Retzius. Two stay sutures are placed to stabilize the bladder, and a small incision is

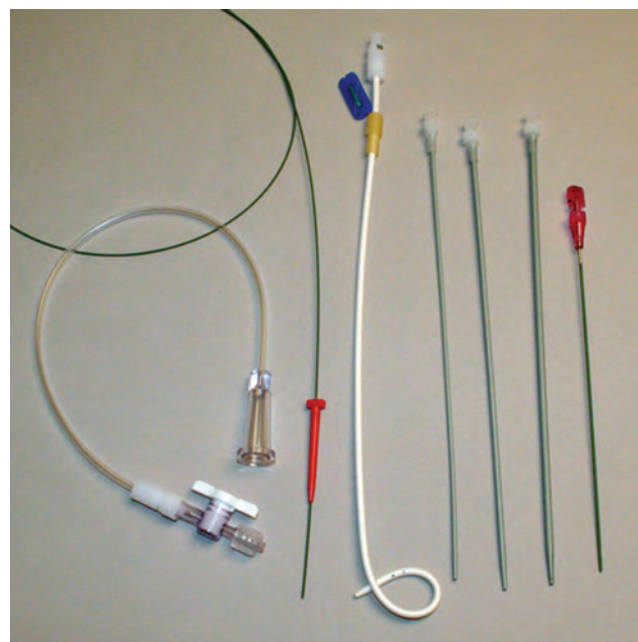


Figure 6-4. Percutaneous suprapubic catheter kit. *Left to right, Guidewire, drainage bag connection tubing, Cope loop catheter, Amplatz dilators, and cystostomy needle.* (Courtesy Cook Medical, Bloomington, IN.)

made through the bladder wall between the sutures, allowing for easy passage of a 16- to 18-Fr catheter. The catheter should be introduced through the skin in line with the bladder incision to prevent kinking and should be secured in the bladder with a purse suture to prevent urine extravasation.

Because of the invasiveness of suprapubic catheter placement and its transcutaneous character, it is subject to complications such as wound infection, hematoma, and perivesical fluid collection. **Surrounding organ injury is the most severe complication and has been reported to occur in less than 1% to 2.7% of procedures** (Sheriff et al, 1998; Ahluwalia et al, 2006; Cronin et al, 2011).

Catheter Exchange

Before exchanging a suprapubic catheter, it should be left in place for at least 2 to 4 weeks to allow for tract maturation. After the patient has been prepared and all required materials are readily available, the physician deflates the balloon and extracts the catheter. Some lubricant gel is instilled in the tract, and the new catheter is placed into the bladder. A small amount of fluid in the bladder adds safety by providing the possibility of aspirating the catheter to ensure correct placement. Catheter exchange over a guidewire can be performed in patients with difficult tracts.

Complications

Complications from the presence of the suprapubic catheter are similar to those of a transurethral catheter. A meta-analysis comparing suprapubic to transurethral drainage after gynecologic surgery concluded that suprapubic catheterization significantly reduces the rate of UTI but, on the other hand, was significantly correlated with a higher rate of minor complications such as hematuria, leakage, blockage, or accidental catheter loss. Superiority of one over the other could not be determined (Healy et al, 2012, 2013).

Frequent blockage of a suprapubic catheter can be caused by encrustation or bladder stones. Frequent catheter blockage should prompt consideration of cystoscopy to evaluate for the presence of bladder stones. Excessive granulation tissue at the suprapubic tract can be treated by silver nitrate application.

Catheter placement technique with a trocar or Seldinger technique, catheter type, and catheter size do not seem to influence the complication rate of ultrasound-guided suprapubic catheterization (Cronin et al, 2011).

Bowel perforation during catheter exchange has been reported and has been associated with difficult exchange and use of stiffer catheters (Mongiu et al, 2009; Kass-Iliyya et al, 2012).

An accidentally removed suprapubic catheter is a unique, sometimes challenging complication. Pigtail or Cope loop catheters are more prone to dislodgement than balloon retained catheters (Cronin et al, 2011). The tract of the suprapubic catheter can close in a short period of time, encouraging prompt tube replacement. Smaller catheters, guidewire placement, and dilation of the tract can be of assistance for catheter replacement.

Although there is no available literature on learning curve in suprapubic catheter placement, practice and experience are expected to translate to a lower complication rate. Hossack recently proposed the first design of a simple, useful, and cheap training model for percutaneous suprapubic catheter placement for practitioners to gain experience before placing suprapubic catheters in patients (Hossack et al, 2013).

UPPER URINARY TRACT: URETERAL STENTS AND CATHETERS

Historic Note

The use of ureteral stents in surgery was described as early as the 19th century (Shoemaker, 1895). The first urologist to access the ureter endoscopically was Dr. James Brown at Johns Hopkins Hospital in 1893 (Arcadi, 1999). Zimskind, however, in 1967 was the first to describe the cystoscopic placement of indwelling ureteral stents for obstructed ureters (Zimskind et al, 1967). At that time, stents were very prone to migration and device expulsion, which deterred widespread adoption. Gibbons was the first to patent a barbed stent as a self-retaining mechanism (Gibbons et al, 1976). The first “double-J” (DJ) or double pigtail stent was developed

almost simultaneously by Finney and Hepperlen (Finney, 1978; Hepperlen et al, 1978). After this novel advance, the use of DJ stents increased dramatically in urology departments worldwide, which had a tremendous positive impact on endourologic surgery and patient care. Today, ureteral stents are of fundamental importance to any urologic practice.

Stent Technology

The ideal stent is easy to insert, has the ability to relieve intraluminal and extraluminal obstruction, has excellent flow characteristics, is resistant to encrustation and infection, is chemically stable after implantation in a urinary environment, and does not induce patient symptoms. Stents should therefore have high tensile strength, a low friction coefficient, memory, and a self-retainment mechanism and should be both biocompatible and affordable. The number of new patents filed annually related to ureteral stents is shown in Figure 6-5 and demonstrates that development of new designs, biomaterials, and coatings for ureteral stents has increased dramatically over the past decade. This effort reflects the many initiatives in stent design aligned to achieve the ideal characteristics.

Biomaterials

Early ureteral stents were manufactured from silicone (Zimskind et al, 1967). Although silicone is the most biocompatible material tested to date (Beiko et al, 2003; Watterson et al, 2003b), the high friction coefficient and flexibility that are characteristic of silicone make silicone stents more difficult to navigate through a tortuous or obstructed ureter. Polyethylene was introduced as the first plastic polymer in the commonly used DJ stents (Mardis et al, 1979). Polyethylene stents become brittle after prolonged exposure to the urinary environment and are prone to encrustation, blockage, and fragmentation, leading to the discontinuation of use of this material in stent manufacture and the development of newer polymers. Currently used stents are commonly composed of polyurethane, silicone, or proprietary copolymers such as Silitek (Surgitek, Medical Engineering Company, Racine, WI), C-Flex (Cook Medical,

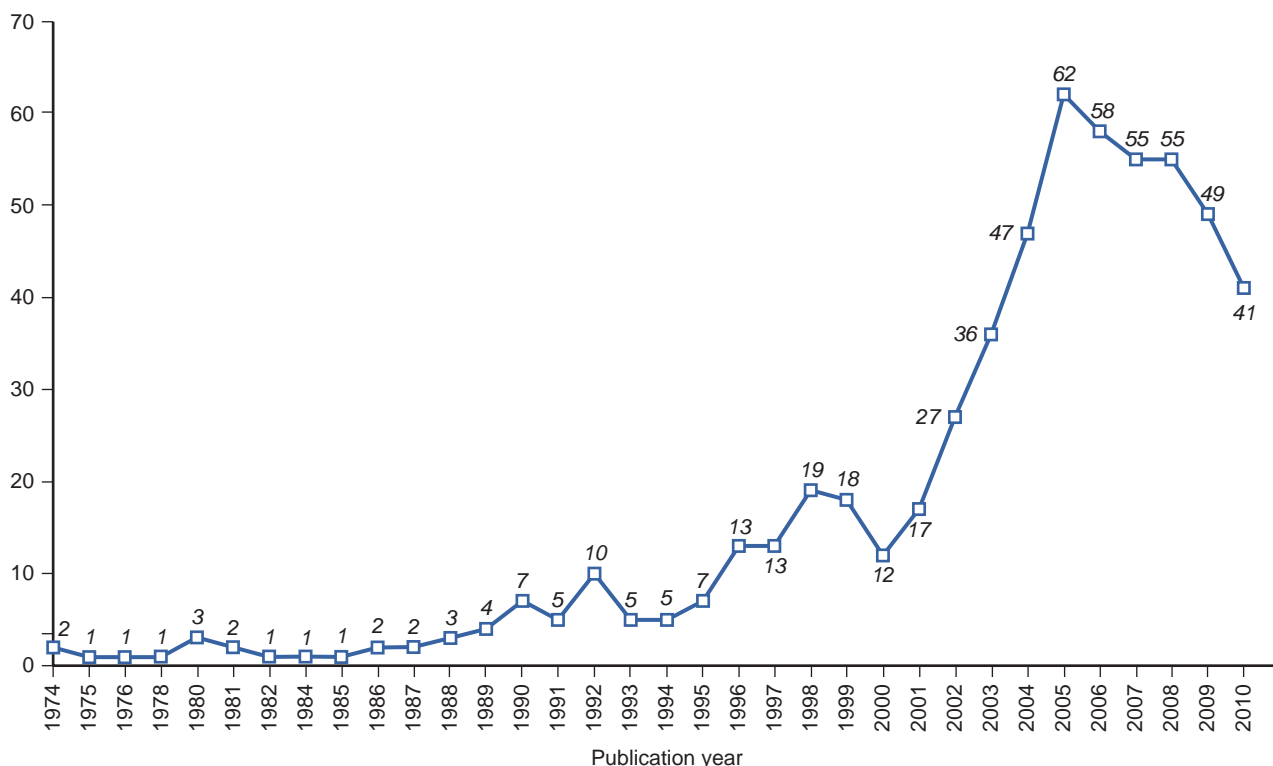


Figure 6-5. Graph showing annual number of patents filed related to ureteral stents. (Courtesy Dolcera Patent and Market Research Services.)

Bloomington, IN), Percuflex (Boston Scientific, Marlborough, MA), or Tecoflex (PNN Medical, Kvistgaard, Denmark).

Ureteric obstruction caused by extrinsic, usually malignant, compression requires stents that can withstand these radial compressive forces. Mechanical tests on nonmetal stents evaluating resistance to radial compression demonstrated the C-Flex (Cook Medical, Bloomington, IN) stent to resist extrinsic compressive forces best (Hendlin et al, 2006). Although it is common practice to use a larger-lumen stent to achieve adequate drainage, stents with a smaller lumen have been shown to be more resistant to radial compressive forces in experimental studies (Hendlin et al, 2006).

The self-expanding metallic Wallstent has been used to treat ureteric obstruction since 1992 (Pauer and Lugmayr, 1992). Although the stent is reported to be safe and effective, its primary patency rates are low, ranging from 29% to 54% at 3 to 12 months, mainly because of hyperplastic tissue ingrowth. With additional endoscopic interventions, secondary patency can be maintained in up to 100% of stents in short- and long-term follow-up (Flueckiger et al, 1993; Lugmayr and Pauer, 1996; Lang et al, 1998, 2013).

The Resonance metallic ureteral stent (Cook Medical, Bloomington, IN) is constructed from tightly coiled spirals of a corrosion-resistant nickel-cobalt-chromium-molybdenum alloy wire and is designed to resist encrustation and tissue overgrowth. Although the overall flow was inferior compared with conventional stents in an in vivo porcine study, the Resonance stent can easily withstand compression forces that completely obstruct conventional stents (Blaschko et al, 2007; Pedro et al, 2007). Long-term results and follow-up in larger cohorts demonstrate a failure rate of 28% to 35%, which is comparable to conventional stents (Liatsikos et al, 2010; Goldsmith et al, 2012; Kadlec et al, 2013). Because the Resonance stent can be safely retained in the ureter for extended periods, the reduced hospital and procedure costs may mitigate the higher cost of the stent itself (López-Huertas et al, 2010; Polcari et al, 2010; Taylor et al, 2012).

Newer metal stents have been designed and tested in vitro and are awaiting clinical trials. The Silhouette stent (Applied Medical Resources Corporation, Rancho Santa Margarita, CA) is a soft, coil-reinforced stent with a hydrophilic coating. It is less prone to kinking than other stents and can resist higher compressional forces than the Resonance stent, theoretically resulting in a lower chance of stent failure (Pedro et al, 2007; Christman et al, 2010; Miyaoka et al, 2010). The Passage and Snake stents (ProSurg, San Jose, CA) are open-ended and less tightly coiled than the Resonance and Silhouette stents, allowing for more flexibility. Both stents sustain higher extrinsic radial compression forces than the Silhouette stent and have lower tensile strength (Hendlin et al, 2012).

The Memokath 051 ureteral stent (PNN Medical, Kvistgaard, Denmark) is a nickel-titanium alloy (nitinol) stent with a

thermo-expandable anchoring mechanism. The initial report on the use of the Memokath stent in obstructed ureters demonstrated a high patency rate of the lumen after 10.6 months of follow-up (Kulkarni and Bellamy, 1999). In addition to having long-term patency in ureteral obstruction, the Memokath 051 is better tolerated than conventional ureteral stents in terms of urinary symptoms, pain, and general health (Maan et al, 2010). Late complications include stent migration in 15% to 18% and encrustation in 3% to 5%. Stent manipulation or reinsertion has been reported to be necessary in 20% to 25% of patients (Agrawal et al, 2009; Papatsoris and Buchholz, 2010).

The Uventa stent (Taewoong Medical, Gimpo, South Korea) is also a nickel-titanium alloy, segmental, thermally expandable stent. A PTFE coating is positioned between the outer and inner mesh. The outer mesh provides extra friction to prevent stent migration, and the PTFE coating prevents hyperplastic stent ingrowth (Chung et al, 2008). Kim reported a 100% primary patency in 20 stents with an average follow-up of 7.3 months (Kim et al, 2012). After a 10-month follow-up period, primary patency rates decrease to 64.8% and secondary patency rates to 81.7%. Stent failure is predominantly a result of tumor progression at an adjacent ureteral segment. Migration has not been reported (Chung et al, 2013).

The Allium stent (Allium Medical Solutions, Israel) is a large-caliber (24 Fr or 30 Fr) nickel-titanium alloy, expandable mesh stent coated with a biocompatible polymer to prevent stent ingrowth. The Allium stent was specifically developed for use in the distal ureter and has an intravesical anchor to facilitate removal. Limited data are available in the published literature, reporting patency rates of greater than 95% and migration in 14% of stents, necessitating removal. No encrustation was documented at an average of 17-months' follow-up (Moskovitz et al, 2012; Leonardo et al, 2013) (Fig. 6-6).

A common problem among metal mesh stents is reduced patency in long-term follow-up and late complications such as migration, encrustation, and erosion. Coatings to prevent hyperplasia and stent ingrowth in metal mesh stents have been adopted from the endovascular stent realm. In comparison to uncoated metal mesh stents, a paclitaxel drug-eluting metal mesh stent was shown to generate less inflammation and hyperplasia of the surrounding tissue in a porcine model (Liatsikos et al, 2007). The zotarolimus-eluting metal stent induced a significantly lower hyperplastic reaction without influencing inflammation rates in a porcine and rabbit model (Kallidonis et al, 2011). These coatings have the potential to improve patency and reduce complication rates.

The development of a biodegradable stent could theoretically eliminate the need for cystoscopic stent removal and could help prevent the occurrence of forgotten stents. Biodegradable materials are composed of high-molecular-weight polymers such as

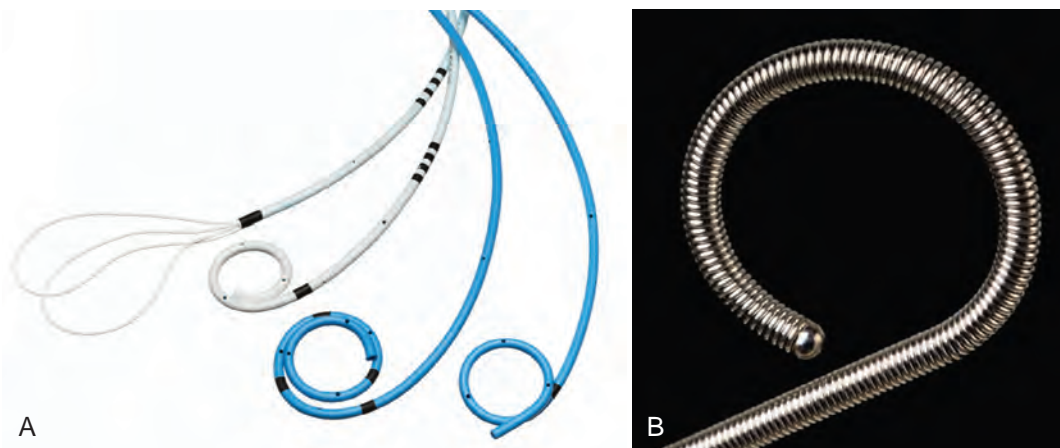


Figure 6-6. Different stent designs. A, Polaris Loop stent, Polaris Ultra stent, Percuflex Plus stent, and Contour VL stent. B, Resonance metal stent. (A, Courtesy Boston Scientific, Marlborough, MA; B, courtesy Cook Medical, Bloomington, IN.)

polylactide or polyglycolide. Surface modification of bioresorbable polymers with, for instance, hydroxyethylmethacrylate (HEMA), oligo(ethyleneoxide)-monomethacrylate (OEOMA), or acrylic acid (AAc) results in improved biocompatibility without toxicity of these polymers and thus allows use in a urinary environment (Brauers et al, 1998). The main challenge of biodegradable materials is controlling the rate of degradation. In vivo tests with a poly-L,D-lactide polymer in a canine model demonstrated promising results with complete degradation of all stents within 24 weeks without induction of ureteral histologic changes (Lumiaho et al, 1999, 2000).

In vivo tests in a porcine model with Uripren, a biodegradable copolymer composed of L-glycolic acid, polyethylene glycol, and barium sulfate, show promising preliminary results. With the current chemical formulation, Uripren stents reliably achieve degradation after 4 weeks. The Uripren stents induced a lower degree of ureteral inflammatory change when compared with conventional stents in a porcine model (Hadaschik et al, 2008; Chew et al, 2010, 2013). Olweny and colleagues established that use of a degradable poly-L-lactide-co-glycolide polymer stent in a porcine ureter after endopyelotomy was feasible but induced more tissue inflammation than a conventional stent (Olweny et al, 2002).

Newer polymer components are currently under investigation for future stent development. Magnesium-yttrium alloy potentially offers many benefits over currently existing stents because the alloy is biodegradable and seems to inhibit bacterial viability in vitro. The rate and mode of degradation can be controlled through alloy design and surface modification (Lock et al, 2012, 2014). Degradable polyfilament, fibrous stents composed of polyglycolic acid (PGA) and polylactic acid (PLA) demonstrated complete degradation after 8 weeks. The resistance to compression of the stent was comparable to that of conventional stents during the first 2 weeks after insertion (Shang et al, 2011).

The feasibility of a natural, tissue-engineered ureteral stent has been investigated in vitro with the goal of achieving optimal biocompatibility. Amiel demonstrated that seeding chondrocytes on a polylactic-co-glycolic acid enforced PGA polymer scaffold was feasible in vitro and that the tissue-engineered stents were readily elastic and could withstand compression (Amiel et al, 2001). No in vivo trials have yet been reported.

The first and to date only trial studying the use of biodegradable stents in human subjects demonstrated adequate drainage while maintaining a high patient tolerance. After 90 days, 96.6% of patients were stent free. Three patients, however, required shock-wave lithotripsy (SWL) and one patient subsequently required ureteroscopy (URS) to clear retained stent fragments (Lingeman et al, 2003).

Coatings

Drug-eluting and antiadhesive stent coatings are under investigation with the goal of improving stent handling, reducing biofilm formation, preventing encrustation, and improving patient comfort.

Hydrogel is a commonly applied stent coating composed of hydrophilic polymers that absorb water. This added surface water reduces friction and increases elasticity, rendering the stent easier to insert and theoretically more biocompatible. In vitro tests, however, have demonstrated hydrogel-coated stents to both reduce and increase encrustation and biofilm formation (Tunney et al, 1996; Desgrandchamps et al, 1997; Gorman et al, 1998).

Pentosan polysulfate (PPS), phosphorylcholine (PC) copolymer, and polyvinylpyrrolidone (PVP) are newer coatings that have been demonstrated to reduce inflammatory response, encrustation, and biofilm formation. Polyvinylpyrrolidone-iodine (PVP-I) complex modified polyurethane Tecoflex stents (Lubrizol, Wickliffe, OH) appear to be highly hydrophilic and to reduce encrustation deposits and adherence of *Pseudomonas aeruginosa* and *Staphylococcus aureus* by 80% to 86% in vitro tests (Khandekar and Doble, 2011). A diamond-like carbon (DLC) coating has been noted to render the stent surface ultrasMOOTH, thereby decreasing friction and improving biocompatibility. DLC-coated

polyurethane demonstrated significant resistance to biofilm formation and microbial adherence in in vitro and in vivo studies (Jones et al, 2006; Laube et al, 2007). Silicone coated with *Oxalobacter formigenes*-derived oxalate degrading enzymes demonstrated a modest reduction in encrustation in vivo compared with uncoated controls (Watterson et al, 2003a). Triclosan-eluting stents (Triumph [Boston Scientific, Marlborough, MA]) initially demonstrated a significant decrease in growth and survival of *P. mirabilis* in a rabbit study (Cadieux et al, 2006). The Triumph stent significantly reduced stent-related pain and urinary symptoms in short-term stented patients and reduced symptomatic UTI rate in long-term stented patients without, however, influencing biofilm formation, encrustation, or urine cultures (Cadieux et al, 2009; Mendez-Probst et al, 2012). A ketorolac-eluting stent (Lexington [Boston Scientific, Marlborough, MA]) was developed with the goal of reducing stent-induced pain symptoms. A prospective multicenter double-blind RCT evaluating the effect of Lexington stents reported no statistical difference in unplanned postoperative medical visits or pain perception. The authors did, however, demonstrate a significant reduction in the need for analgesia in the ketorolac-eluting stent group on post-URS day 2. Benefits of the stent were most evident in a subgroup of men and patients younger than 45 years (Krambeck et al, 2010). Although in vitro tests with heparin-coated stents did not show a significant benefit, in vivo tests demonstrated a significantly reduced encrustation rate. Tenke and Cauda noted that heparin-coated stents may remain indwelling for longer than 6 months and potentially up to 12 months, translating into an economic benefit (Riedl et al, 2002; Tenke et al, 2004; Cauda et al, 2008; Lange et al, 2009). Polyethylene glycol conjugated with 3,4-dihydroxyphenylalanine polymer, mPEG-DOPA₃, is a novel antifouling coating that demonstrated in vitro and in vivo resistance to bacterial attachment and biofilm formation. A cross-linked DOPA-anchored antifouling polymer was identified as the most resistant to *E. coli* adherence (Ko et al, 2008; Pechey et al, 2009). Sustained-release varnish containing chlorhexidine (CHX-SRV)-coated stents significantly reduce bacterial growth in vitro and in vivo with the initial 1% chlorhexidine concentration. The newly tested 2% concentration prolonged the inhibitory effect on bacterial growth up to 2 weeks (Shapur et al, 2012; Segev et al, 2013; Zelichenko et al, 2013).

Development of antibiotic coatings is still in a preliminary phase. Tests on rat models show promising results for rifampin-coated stents in combination with tigecycline and clarithromycin-coated stents in combination with systemic amikacin (Cirioni et al, 2011; Minardi et al, 2012).

Applying silver coatings on ureteral stents appears to be an effective strategy in reducing biofilm adherence without the risk of inducing resistance (Schierholz et al, 2002).

Stent Design

Simple variations to the initial DJ stent developed by Finney (Finney, 1978) include different biomaterials as discussed previously, different diameters and lengths, more or fewer side holes, and an open or closed tip.

The newly developed 3F Microstent (Percutaneous Systems, Palo Alto, CA) uses a film anchor as a proximal retaining mechanism. Once above the obstruction, the film anchor is deployed by retracting the integrated guidewire. Flow characteristics of the 3F Microstent are equivalent to those of a 4.7-Fr DJ stent and significantly better than those of a 3-Fr DJ stent (Lange et al, 2011). Because a smaller-caliber stent occupies less space in the ureter, stone passage may theoretically improve.

The grooved stent, initially invented by Finney in 1980 (U.S. patent 4,307,723), was demonstrated to have better extraluminal and total flow compared with a regular stent of equal size (Koleski et al, 2000). The Towers stent (Cook Medical, Bloomington, IN) and the LithoStent (Boston Scientific, Marlborough, MA) are two grooved stents still manufactured today.

The dual-lumen stent, developed with the goal of optimizing urinary drainage, significantly improved the flow in an ex vivo

obstructed ureter model compared with a single 7-Fr stent and had similar flow rates compared with two ipsilateral 7-Fr stents (Hafron et al, 2006). Insertion of a dual-lumen stent has a practical advantage over insertion of two ipsilateral stents because it can be inserted in one pass.

The Spirastent (Urosurge Medical, Coralville, IA), a DJ stent with helical metal ridges, was designed to obtain better flow and easier stone fragment passage by theoretically increasing the distance between ureter wall and stent. Although an in vitro study showed promising results, the stent appeared to allow less flow than the conventional DJ stent in an in vivo porcine model and was not successful in promoting enhanced stone clearance (Olweny et al, 2000; Stoller et al, 2000; Gerber et al, 2004).

The Open-Pass ureteral stent (Fossa Medical, Sandy Hook, CT) has 15 to 17 radially expanding baskets along its length and was developed for dilation of the ureter up to 20 Fr and stone fragment entrapment after SWL. Entrapped stone fragments are subsequently removed with the removal of the stent (L'Esperance et al, 2007).

Animal studies with a novel helical-cut Percuflex stent demonstrate the device to have flow characteristics and biocompatibility comparable to those of a conventional Percuflex stent. The touted advantage of the stent and its possible benefit in reducing stent-related symptoms depends on improved conformity to the ureter (Mucksavage et al, 2012).

Stents equipped with an antireflux valve mechanism at the intravesical portion of the stent demonstrate a significant decrease in reflux rate compared with a conventional DJ stent, resulting in less flank and bladder pain and thus improved patient comfort (Ecke et al, 2010; Ritter et al, 2012). Lumiaho reported that a 4-cm-long double-helix spiral stent made from biodegradable material allowed for adequate or improved flow compared with a conventional DJ stent in an in vivo porcine study. The absence of an intravesical coil prevented vesicoureteral reflux (Lumiaho et al, 2011).

The hypothesis that less or softer material in the bladder would result in fewer symptoms has influenced stent design toward variable diameter, dual durometer, and softer stents. Stents developed for use after endopyelotomy have a conventional 7-Fr proximal and distal coil and a broader body of 10 Fr or more. Tail stents or buoy stents were developed to prevent stent-related lower urinary tract symptoms and are composed of a 7-Fr or 10-Fr upper body that tapers down to a 3-Fr distal tail rather than a coil. Tail stents and buoy stents (10 Fr to 3 Fr) are reported to have significantly better drainage, reduced bladder inflammation, and reduced irritative bladder symptoms (Dunn et al, 2000; Krebs et al, 2009).

Reports on dual durometer stents, composed of a conventional upper body and a softer biomaterial at the distal segment, have not been proven to be consistently beneficial. Whereas Lingeman and colleagues reported significant reduction of stent-related symptoms with dual durometer stents, Davenport and Joshi could not identify significant differences between dual durometer and conventional DJ stents (Lennon et al, 1995; Joshi et al, 2005; Davenport et al, 2011; Kawahara et al, 2012a).

The Magnetip stent (Surgitek, Medical Engineering Company, Racine, WI) has been developed to avoid cystoscopic removal of the stent. It has a metallic bead at the distal tip and can be removed with a magnetic-tipped urethral catheter. Studies have demonstrated up to 100% successful retrieval in women and 75% to 97% in men (Macaluso et al, 1989; Taylor and McDougall, 2002).

Indications

Ureteral stent placement is most commonly performed to relieve ureteral obstruction. Intrinsic obstruction is typically caused by stones, tumors, or strictures, whereas extrinsic obstruction is often caused by compression by tumor, overlying vessels, retroperitoneal fibrosis, or lymphadenopathies. This relief of obstruction by stent placement can be temporary until more definitive treatment is performed or permanent if further definitive treatment is not feasible or desired.

Absolute and usually emergent indications for drainage of the kidney(s) are bilateral obstruction, unilateral obstruction

in the absence of a functional contralateral kidney, and ureteral obstruction with hydronephrosis and urinary infection or sepsis. Intractable renal colic that cannot be controlled by analgesia also requires urinary drainage by either a ureteral stent or nephrostomy placement.

Stent placement before or after treatment of urolithiasis has been a subject of controversy. A meta-analysis of the available literature demonstrated that stenting before SWL of upper urinary tract calculi may have a beneficial effect on the incidence of Steinstrasse after SWL. This result was, however, heavily influenced by one RCT with 400 participants with stones between 1.5 and 3.5 cm (Al-Awadi et al, 1999). There was no difference in need for auxiliary treatments between the two groups in the meta-analysis. Stenting has not conclusively demonstrated a beneficial effect on stone-free rates, and patients with a stent had more lower urinary tract symptoms (Ather et al, 2009; Shen et al, 2011a).

Current stone treatment guidelines from both the EAU and the AUA indicate that routine use of DJ stenting before SWL for kidney or ureteral stones does not improve stone-free rates. Although the guidelines advise against stent placement before an SWL-treatment regardless of stone size, it is still common practice and considered by many safer to place a ureteral stent in combination with SWL for a stone larger than 1.5 to 2 cm.

The requirement for routine stent placement after ureteroscopic lithotripsy (URSL) for stone treatment has also been widely debated. Findings from RCTs illustrating that stenting after uncomplicated URSL is not routinely required were published as early as 2001 (Denstedt et al, 2001). Three meta-analyses over the following decade all confirmed that routine stenting has no beneficial effect on stone-free rate or ureteral stricture formation. The procedure takes longer and costs more, especially combined with the cost of subsequent cystoscopic stent extraction. Quality of life appears to be better in the non-stented group (Shen et al, 2011b; Tang et al, 2011; Song et al, 2012a). The 2013 EAU stone guidelines advise that stenting is not routinely required after uncomplicated URSL (Türk et al, 2013). Stenting a ureter post-URSL is, on the other hand, still advised if there are sizeable residual fragments, in the presence of an anatomically or functionally solitary kidney, if the ureter has been balloon dilated, if the patient has a UTI, or if a complication such as bleeding or perforation has occurred. Even these commonly accepted indications for stent placement have been challenged in recent studies. A multicenter RCT demonstrated no benefit from stent placement after ureteric balloon-dilatation in an otherwise uncomplicated URSL. Stented patients had more discomfort, and there was no beneficial effect on postoperative pain, stone-free rate, or short- or long-term complication rates (Başeskioğlu et al, 2011).

A single retrospective study has evaluated the recommended indwelling time of ureteral stents post-URSL. The authors suggest that indwelling time shorter than 14 days was associated with fewer adverse effects compared with having the stent in for 15 days or longer (Shigemura et al, 2012). Because there are no RCTs in the current literature, there is not sufficient evidence to make conclusive recommendations on the indwelling time of a ureteral stent post-URSL. Common clinical practice is to remove a stent 1 to 2 weeks post-URSL if the patient is stone free or has small passable fragments on postoperative follow-up imaging.

Stenting as a preemptive maneuver before URS was first described and found beneficial as early as 1990 (Jones et al, 1990). Cetti and colleagues reported prestenenting to be useful in 8% of patients in a tertiary referral center (Cetti et al, 2011). Although no prospective RCTs have been performed to date, current literature suggests that placing a ureteral stent for 1 to 2 weeks after initial unsuccessful URSL leads to a higher success rate of secondary URSL (Rubenstein et al, 2007; Shields et al, 2009; Ji et al, 2012; Netsch et al, 2012). This passive dilative effect of an indwelling stent has also been demonstrated in the pediatric population (Hubert and Palmer, 2005; Corcoran et al, 2008). In addition, placement of a ureteral access sheath is easier in prestenented patients (Kawahara et al, 2012b).

Chu and coworkers demonstrated that stenting before a first attempt at URSL did not significantly improve stone-free rates; the authors reported, however, that preoperative stenting for stones larger than 1 cm was associated with decreased operative time, lower reoperative rates, and lower cost (Chu et al, 2011a, 2011b). **Whether or not a priori stenting before initial URSL should be routinely recommended for large impacted stones remains unclear because of a lack of qualitative trials.**

Routine placement of an internal stent after uncomplicated percutaneous nephrolithotomy (PCNL) with a low tract is not necessarily required. Stenting is, however, advised in the presence of residual stone burden in the kidney, migration of residual fragments to the ureter, extensive edema, perforation of the collecting system, or high tract placement with risk of hydrothorax; for performance of tubeless PCNL; or in the presence of persistent urinary leakage after nephrostomy tube removal.

The first RCT comparing **drainage modalities for pyonephrosis** was reported by Pearle and colleagues in 1998 and did not demonstrate superiority of stenting versus nephrostomy tube placement (Pearle et al, 1998). Mokhmalji concluded nephrostomy tube placement to be superior compared with internal stents, based mainly on more discomfort and pain in the stented group (Mokhmalji et al, 2001). Although Joshi reported significantly more irritative symptoms in stented patients compared with those with nephrostomy tubes, a patient preference for either could not be demonstrated (Joshi et al, 2001). The proportion of patients treated with percutaneous nephrostomy (PCN) for pyonephrosis in the United States decreased from 16% in 1999 to 11% in 2009. Recent literature suggests a preference for PCN tube for patients who have larger stones and are more acutely ill. These patients are also more likely to be admitted to an intensive care unit (Goldsmith et al, 2013; Sammon et al, 2013). **When considering the training and skill sets of most urologists, a “stent first where possible” policy has been suggested by Ramsey and associates (Ramsey et al, 2010).**

Stents are widely used in urologic reconstructive surgery for splinting the ureter. Stents have a dual role in this setting, the first being scaffolding the tissue to improve organized healing, and the second being to allow urine to flow unhindered past the operated field. Stents have shown usefulness in ureteral trauma treatment, ureteral realignment, pyeloplasty, ureteral reimplantation, uretero-ureterostomy, and other reconstructive procedures. A particularly important and well-studied postoperative use of ureteral stents is **after renal transplantation.** A recent meta-analysis in the renal transplant population demonstrated that **routine prophylactic stenting significantly reduces the incidence of major urologic complications (Wilson et al, 2013).** Removing the stent after 8 days as opposed to after 15 days reduces UTI rate (40% vs. 73%) and is more cost-effective (Parapiboon et al, 2012).

Stents are often placed **prophylactically before gynecologic, urologic, or abdominal surgery.** This facilitates identification of the ureter during surgery and theoretically may reduce iatrogenic ureteral trauma. Although such benefit has been suggested in gynecologic surgery, especially in patients with risk factors such as previous pelvic radiation or surgery, endometriosis, or pelvic inflammatory disease, a single-center RCT in a cohort of over 3000 patients showed **no significant difference in ureteral injury rate with or without prophylactic stenting (1.09% vs. 1.2%, $P = .774$).** It is, however, **easier to identify ureteric trauma with a stent in situ (Chou et al, 2009; Park et al, 2012).**

Several authors have reported on the use of stents in the **treatment of malignant pathology of the upper urinary tract** with, for instance, BCG or Mitomycin C. After intravesical instillation of the agent, vesicoureteral reflux may permit the substance to reach the upper urinary tract (Nonomura et al, 2000; Irie et al, 2002; Hayashida et al, 2004). Audenet suggests that BCG instillation in the upper urinary tract by single-J ureteral catheter, via reflux through DJ stent, or antegrade via a nephrostomy tube should be considered a first-line treatment for upper tract carcinoma in situ in patients who are not candidates for surgery (Audenet et al, 2013).

When a single ureteric stent is insufficient in relieving benign or malignant extrinsic ureteral compression, placing an additional ipsilateral stent has been reported to be successful in achieving adequate kidney drainage (Liu and Hrebinko, 1998; Rotariu et al, 2001; Elsamra et al, 2013). This technique has also been successfully applied in ureteral anastomotic strictures in renal transplant patients (Miyaoka et al, 2011).

Persistent urinary extravasation after blunt renal trauma can be treated by ureteral stent placement with high success rates (Matthews et al, 1997; Haas et al, 1998; Alsikafi et al, 2006; Long et al, 2013). Simultaneous bladder drainage is advised to maintain low intrarenal pressure and optimal drainage.

Technique

Stents can be placed using various techniques including endoscopic retrograde or antegrade placement or during open or laparoscopic surgery of the urinary tract. The following procedure describes a commonly used technique for retrograde endoscopic placement of a simple 7-Fr DJ stent of appropriate length without special design or coating and with a regular pusher, under cystoscopic and fluoroscopic guidance.

Antibiotic prophylaxis before endoscopic stent placement by means of oral fluoroquinolones is deemed appropriate and is recommended in AUA guidelines with level 1B evidence (Wolf et al, 2008).

Stent placement in males can be performed with the patient in a supine position with flexible cystoscopy or in lithotomy position when a rigid cystoscope is used. In females one can attempt flexible cystoscopy with the patient in a frog-leg position or perform rigid cystoscopy using the lithotomy position. Fluoroscopic guidance during the procedure to confirm the correct position of the guidewire and subsequently placed stent is advised. Ultrasound guidance can be used instead of fluoroscopy when placing a stent in a pregnant woman.

Ureteral stents are most commonly placed over a guidewire, and there is a vast array of available guidewires for this purpose. Hydrophilic nitinol guidewires have the optimal characteristics to easily overcome obstruction or follow the course of a tortuous ureter with a minimal risk of perforation. Stiffer wires such as Teflon-containing Benson wires provide higher resistance against bending when placing ureteral stents (Clayman et al, 2004; Liguori et al, 2008; Sarkissian et al, 2012; Torricelli et al, 2013).

Because stent diameter does not seem to influence stent symptoms, one should choose the largest fitting stent available for optimal drainage (Candela and Bellman, 1997; Erturk et al, 2003). In general, a 6-Fr or 7-Fr diameter stent is preferred.

After fluoroscopically confirming the position of the guidewire in the renal pelvis, the stent is advanced over the guidewire with a pusher under cystoscopic guidance. When the tip of the pusher is visualized at the bladder neck, the guidewire is retracted while the stent coils are fluoroscopically confirmed in the renal pelvis and the distal stent coil is cystoscopically confirmed in the bladder.

Alternatively, one can place a stent by primarily relying on fluoroscopic guidance. After placement of the guidewire in the renal pelvis, the cystoscope is removed and an 8-Fr to 10-Fr coaxial Amplatz dilator is advanced over the guidewire under fluoroscopic guidance until the 10-Fr component is at the urethral meatus. After removal of the 8-Fr component, the 10-Fr sheath will allow a 7-Fr stent to be passed through it over the guidewire while the stent is prevented from coiling in the bladder. Under fluoroscopic guidance, the stent is advanced with a pusher that has a radiopaque marker at the tip. The distal end of the stent is positioned by advancing the radiopaque marker under fluoroscopic guidance at the middle of the pubic symphysis in male patients and the lower border of the pubic symphysis in female patients. The 10-Fr sheath is removed and subsequently the guidewire, with fluoroscopic confirmation of the proximal stent coils in the renal pelvis and the distal loop coils in the bladder (Fig. 6-7).

Although usually performed with the patient under general anesthesia, stent placement with local anesthesia using lidocaine

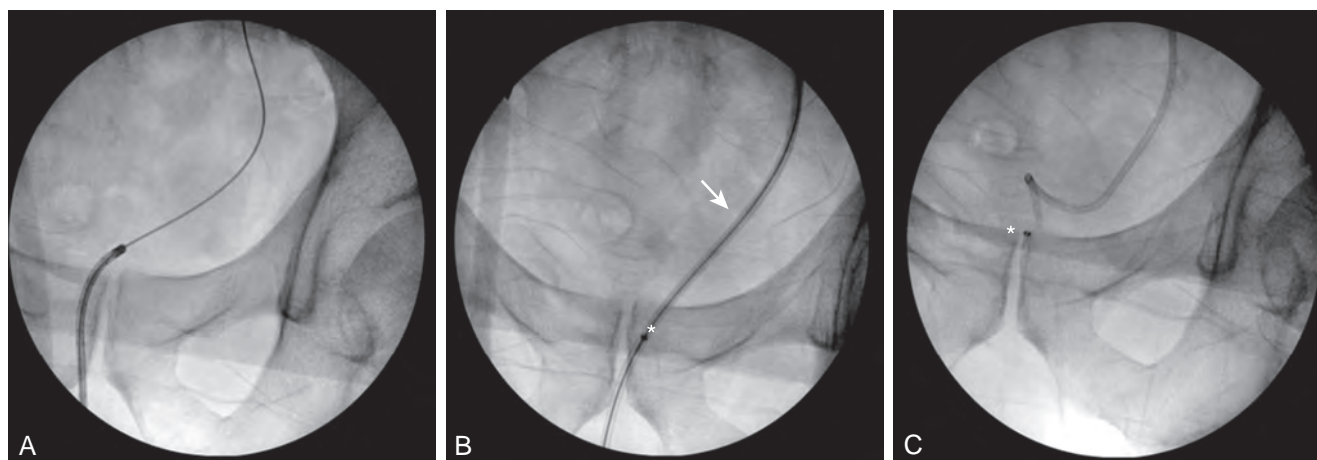


Figure 6-7. A, Cystoscope in bladder plus guidewire in ureter. B, Stent placed in ureter through 10-Fr sheath (asterisk indicates radiopaque marker of pusher; arrow indicates 10-Fr sheath). C, Guidewire and 10-Fr sheath removed, distal stent section coiled in bladder.

jelly is feasible (Mark and Montgomery, 1996). Sivalingam describes that in compliant patients in whom difficult stent placement is not expected, in-office stent placement is feasible, is less costly, and has a low failure rate of approximately 9% (Sivalingam et al, 2013).

Complications

Stent Symptoms

Stent-associated symptoms can have a significant impact on patient quality of life. Hematuria, urgency, frequency, dysuria, and both bladder and flank pain are the most prevalent symptoms related to indwelling ureteral stents. Joshi and colleagues developed the ureteral stent symptom questionnaire (USSQ) to evaluate symptoms and impact on quality of life of ureteral stents. The authors reported quality of life to be influenced in 80% of stented patients. From an economic perspective, 58% of patients had reduced work capacity because of stent discomfort, and approximately half of the patients had sought medical professional help for stent-related symptoms (Joshi et al, 2003a, 2003b). Leibovici reported that 45% of patients had been unable to work for at least 2 days for a total of 435 work-days lost in 135 stented patients (Leibovici et al, 2005). A prospective cohort study reported that approximately one third of patients required early removal of ureteral stents because of stent discomfort (Ringel et al, 2000). Sexual dysfunction has been reported in 42% to 82% of male patients and 30% to 86% of female patients with an indwelling ureteral stent (Joshi et al, 2003b; Leibovici et al, 2005; Sighinolfi et al, 2007).

The pathophysiologic explanation for such stent-related symptoms is not yet fully understood. Irritation of the bladder mucosa and especially the trigone by the distal portion of the stent, reflux of urine, and smooth muscle spasm are thought to contribute to stent-related symptoms (Miyaoka and Monga, 2009; Regan et al, 2009). Vesicoureteral reflux as measured on cystoureterogram has been reported in 56% to 62% of stented patients (Mosli et al, 1991; Yossepowitch et al, 2005). Fluoroscopic imaging in patients with an indwelling stent revealed positional changes of the stent in relation to standing, sitting, and bending, which may explain why physical activity can influence stent discomfort (Chew et al, 2007).

Positioning the proximal coil in the upper pole of the kidney in contrast to in the renal pelvis appears to be better tolerated by stented patients (Liatsikos et al, 2001). Several authors have reported that stents crossing the midline of the bladder have a significant and deleterious influence on associated discomfort. Choosing the

appropriate stent length may therefore aid in ameliorating stent symptoms (Rane et al, 2001; Al-Kandari et al, 2007; Ho et al, 2009, 2010; Giannarini et al, 2011a). Predictive parameters for ideal stent length have been studied extensively. The in vivo measurement of the ureter with a 5-Fr ureteric catheter is often assumed as the true ureteral length. Pilcher and Patel suggested a predictive model for ideal stent length based on patient height: shorter than 5 feet 10 inches, 22-cm stent; 5 feet 10 inches to 6 feet 4 inches, 24-cm stent; and taller than 6 feet 4 inches, 26-cm stent (Pilcher and Patel, 2002). This model has been adopted widely and has been both confirmed by many (Hruby et al, 2007; Ho et al, 2009) and also contested (Paick et al, 2005; Kawahara et al, 2012d; Novaes et al, 2013; Shrewsbury et al, 2013). Paick and colleagues suggested that straight linear measurement from ureteropelvic junction to vesico-ureteric junction on preoperative intravenous pyelography correlated better with the actual ureteric length than the patient's height (Paick et al, 2005). Postmortem measurement of ureteric length could not identify a significant correlation with any anthropomorphic measurement (Novaes et al, 2013). Recent reports demonstrate actual ureteric length to correlate better with computed tomography (CT)-measured length than with any other imaging-based or anthropomorphic measurement (Kawahara et al, 2012d; Shrewsbury et al, 2013). Ideal stent length for children has been formulated as "child's age + 10" cm (Resnick et al, 2007).

Pharmacologic agent and altered stent design have been extensively studied in attempts to reduce stent-related symptoms. Meta-analysis of four RCTs with a total of 341 patients that assessed the efficacy of α -blockers with the USSQ has demonstrated that the use of α -blockers significantly reduces urinary symptoms and pain and significantly improves general health (Yakoubi et al, 2011). The use of α -blocker medications to mitigate stent discomfort has been recommended by EAU guidelines (Türk et al, 2013). Solifenacin and tolterodine can significantly reduce irritative urinary tract symptoms and pain symptoms with a very low complication rate (Park et al, 2009; Lee et al, 2013). The combination of tamsulosin and solifenacin appears to significantly improve stent-related irritative and obstructive symptoms compared with monotherapy with either agent alone (Lim et al, 2011). Intravesical instillation with ketorolac seems to have a short-lived but significant beneficial effect on postoperative stent-related pain (Beiko et al, 2004). Periureteral injection of botulinum toxin A has been demonstrated to safely reduce stent-related pain and need for narcotic pain medication up to 1 week after stent placement (Gupta et al, 2010). Injection of ropivacaine in proximity to the ureteric orifice and at the bladder neck demonstrated a trend toward decreased postoperative pain and voiding symptoms when

assessed in a small RCT (Sur et al, 2008). Appropriate stent position with the distal coil not crossing over the midline of the bladder appeared to have more effect on stent-related symptoms than α -blockers or anticholinergics in a prospective RCT (Lee et al, 2010).

Stent Migration

Despite the self-retaining design of DJ ureteral stents, distal migration into the bladder or proximal into the ureter is possible. Proximal stent migration into the ureter has been reported to occur in 1% to 8% of patients. This can largely be prevented by choosing a sufficiently long stent and having an adequate loop both in the renal pelvis and in the bladder (Slaton and Kropp, 1996; Richter et al, 2000; Breau and Norman, 2001). A proximally migrated stent can be retrieved ureteroscopically (Bagley and Huffman, 1991). The use of toothed graspers, grasping or coaxial cannulation of the stent with a basket, and a dilation balloon have been reported to aid in the retrieval of proximally migrated stents (Chin and Denstedt, 1992; Livadas et al, 2007; Meeks et al, 2008). Migration of the stent into the bladder can be treated by stent exchange.

Urinary Tract Infection

Ureteral stents are inherently subject to bacterial colonization and therefore represent a source of UTI. Short-term ureteral stent placement (3 weeks) in a cohort of 209 children after ureteral reimplantation eventuated in UTI in only 4.8% of patients. Asymptomatic bacteriuria was reported in an additional 6.5% of patients, whereas almost half of the stents were colonized with bacteria (Uvin et al, 2011). **In chronically stented patients, bacterial colonization reaches 100% (Riedl et al, 1999).** Indwelling time, female sex, diabetes, and chronic kidney disease are factors influencing colonization of ureteral stents (Kehinde et al, 2002). A negative urine culture has low predictive value for stent bacterial colonization (Kehinde et al, 2004; Rahman et al, 2012). Routine screening for bacteriuria and treatment of asymptomatic bacteriuria is not recommended. **Antibiotics are recommended only in instances of symptomatic UTI and appear not to have a role in long-term prophylaxis.** A small RCT with 95 patients demonstrated that continuous low-dose antibiotic treatment during the indwelling time of ureteral stents does not influence the incidence or severity of stent-related symptoms or UTIs (Moltzahn et al, 2013).

Encrustation

Minor encrustation on stent surfaces is often present and usually does not result in stent blockage or resistance at stent removal. More extensive and clinically significant encrustation can be a very challenging complication and often arises from a forgotten or retained stent. Removal of encrusted stents requires endourologic experience and, depending on the extent of encrustations, may include multiple interventions. Failure to acknowledge the presence of and render treatment for an encrusted stent can lead to significant renal functional impairment including renal unit loss and in rare instances mortality (Singh et al, 2005; Aron et al, 2006).

The duration of indwelling time of ureteral stents is the most important risk factor for development of encrustation. Encrustation has been reported to occur in 9.2% to 26.8% of stents indwelling for less than 6 weeks, in 47.5% to 56.9% of stents indwelling 6 to 12 weeks, and in approximately 75% of stents indwelling longer than 12 weeks (el-Faqih et al, 1991; Kawahara et al, 2012c). Kawahara and coworkers observed that **stents smaller than 6 Fr were significantly more likely to encrust than stents 7 Fr or larger.** The authors reported complete obstruction in 8.6% of stents after more than 12 weeks, and 1% of stents required additional treatments to facilitate stent removal (Kawahara et al, 2012c). Additional risk factors for stent encrustation include pregnancy, UTI or uropes- sis, history of stone disease, metabolic or congenital abnormalities,

urinary diversions, and chronic renal failure (Robert et al, 1997; Vanderbrink et al, 2008; Ahallal et al, 2010). Calcium oxalate appears to be the major component of stent encrustation in the absence of UTI, pH values below 5.5, and hyperuricosuria (Robert et al, 1997; Grases et al, 2001).

Because indwelling time is the most important risk factor for encrustation, **timely stent removal or exchange is the most important preventive measure.** Most stent manufacturers recommend stent removal or exchange within 4 months of placement. In patients with additional risk factors for encrustation, a 6- to 8-week interval is recommended (Aravantinos et al, 2006). Pregnant patients are especially prone to stent encrustation, and stent exchange is suggested every 4 to 6 weeks in this population (Denstedt and Razvi, 1992).

Encrustation and inability to extract a stent are usually diagnosed in an office setting at a trial of stent removal. Applying excessive force to achieve stent extraction is not recommended, to avoid the risk of inflicting ureteral damage, avulsion, or stent fragmentation. Adequate cross-sectional imaging to assess the extent of encrustation is assistive in developing a treatment strategy because conventional x-ray examination may underestimate the extent of encrustation. Mistry and coworkers reported on the placement of an additional stent for 1 to 2 weeks adjacent to mildly encrusted stents, facilitating a second extraction attempt. The authors hypothesize that friction between the two stents might disrupt the encrustation in addition to the beneficial effect of ureteral dilation (Mistry et al, 2013).

Several authors have created an algorithm for the treatment of encrusted stents involving SWL, URS, cystolitholapaxy, and PCNL. One to six multiple sequential procedures are often necessary to successfully remove the encrusted stent (Borboroglu and Kane, 2000; Singh et al, 2001; Lam and Gupta, 2002; Bultitude et al, 2003; Aravantinos et al, 2006; Weedon et al, 2011). The multitude of different algorithms reflects the lack of consensus on optimal treatment. In general, the site and level of encrustation burden guide the specific approach.

Forgotten or Neglected Stents

The forgotten or neglected stent is a multifactorial problem that originates from both poor patient compliance and health system issues related to patient follow-up. The surgeon responsible for stent insertion is also accountable for its timely removal.

The cost of forgetting a stent, including radiologic investigations, medical treatment, invasive and noninvasive interventions, and hospital stay is on average sevenfold higher than the cost of cystoscopic timely removal (Sancaktutar et al, 2012).

Divakaruni and colleagues identified male patients and uninsured patients to be at higher risk of noncompliance with planned stent removal. When relying only on patient information and education, the authors reported a 16% forgotten stent rate (Divakaruni et al, 2013). In addition to patient education, several reminder mechanisms incorporated into patient follow-up protocols such as log books, card- or Web-based registries, computerized logs, and software that arranges stent change or removal and sends reminder e-mails to patient and physician have been proposed to prevent the forgotten stent scenario from occurring, with variable effectiveness. None of these preventive mechanisms can completely eliminate the retained stent issue (Monga et al, 1995; McCahy and Ramsden, 1996; Ather et al, 2000; Lynch et al, 2007; Thomas et al, 2007; Tang et al, 2008; Withington et al, 2013).

Forgotten stents can develop severe encrustation, as previously described. In the presence of a large encrustation burden, nuclear imaging to quantify the renal function of the affected kidney is advised for planning stent removal. If split renal function shows insufficient contribution of the stented kidney, nephrectomy may be the most appropriate course of action.

Forgotten ureteral stents account for the highest number of postoperative-related claims pertaining to urology that are closed with indemnity payment in the United Kingdom (Osman and Collins, 2011).

UPPER URINARY TRACT: NEPHROSTOMY TUBE

Historic Note

Thomas Hillier reported on the first PCN for the drainage of a hydronephrotic kidney in a 4-year old boy in 1865 (Hillier, 1865). Goodwin described PCN to drain an obstructed kidney in 16 patients almost a century later (Goodwin et al, 1955). Fernström's report on the first percutaneous stone extraction in 1976 initiated the PCNL era, enhancing popularity of the percutaneous access and drainage of the kidney (Fernström and Johansson, 1976). The early literature review, pooling data of 516 PCN insertions, reported a success rate of 90%, major complication rate of 4%, and minor complication rate of 15% (Stables et al, 1978).

Available Materials and Nephrostomy Tube Design

Similar to ureteral stents, an ideal nephrostomy tube is biocompatible; has excellent flow characteristics; is easy to insert; resists infection, encrustation, and dislodgement; and does not induce symptoms.

The pigtail and balloon catheter are probably the most commonly used tube designs. In general, pigtail catheters are smaller than other nephrostomy tubes and are very useful for drainage of clear fluids but are often insufficient in the presence of gross hematuria or thick pus. Councill catheters are particularly useful because they can be inserted or exchanged over a guidewire without losing access to the kidney. Malecot and Pezzar nephrostomies have the advantage of a larger lumen because of their lack of retention balloon tubing. Re-entry catheters are designed to permit nephrostomy drainage while ensuring access to the ureter, should this be necessary. A tamponade (Kaye) catheter can be of specific use in instances of postoperative bleeding (Paul et al, 2003). Although small-bore catheters (smaller than 18 Fr) are less painful and better tolerated than large-bore catheters (larger than 18 Fr) (Maheshwari et al, 2000; Pietrow et al, 2003; Desai et al, 2004), overall complication rate and bleeding incidence after PCNL may be lower with a large-bore catheter (Cormio et al, 2013). Currently the placement of a 16-Fr to 18-Fr nephrostomy tube is common practice in non-tubeless PCNL.

Canales and colleagues compared a pigtail stent, a Malecot catheter, a catheter with a symmetrical balloon, and a catheter with an eccentric balloon in an artificial kidney model in an effort to identify the best tube design for nephrostomy placement after PCNL. The catheter with a symmetrical balloon had significantly better flow with water and higher-viscosity fluid and better retention strength compared with the other catheters (Canales et al, 2005) (Fig. 6-8).

Indications

When upper urinary tract drainage is desired and retrograde ureteral stent placement is not successful or feasible, PCN tube placement

is considered the procedure of choice. Advantages of PCN drainage include the placement and exchange of the tube under local anesthesia and the belief that a nephrostomy tube offers better flow characteristics. Anesthesia may not be an option in ill patients with acute renal failure or sepsis with hemodynamic instability. Because stent placement under local anesthesia appears to be feasible even in an office setting, this relative advantage may decline in the future (Sivalingam et al, 2013). In contrast to a DJ stent, the external drainage nephrostomy tube can be easily unblocked by gentle irrigation in the event of blockage.

Whereas patients with a stent have more discomfort from stent-related symptoms, the presence of a PCN tube has a negative influence on quality of life because of the external drainage characteristics. Overall quality of life, however, has not been demonstrated to be statistically different between the two groups (Joshi et al, 2001; Monsky et al, 2013). Although Monsky reported more minor complications and dislodgement in the PCN group resulting in more frequent exchanges, Song and colleagues reported a shorter interval of exchanges in the DJ stent group than in the PCN group (respectively, every 2.7 vs. 4.2 months). DJ stent placement was, however, less costly, and the procedure time was shorter (Song et al, 2012b; Monsky et al, 2013). Exchange frequency may have an economic and quality-of-life impact.

Acute decompression of obstructed pyonephrosis is a urologic emergency, and failure to achieve prompt drainage is related to a higher mortality risk (Borofsky et al, 2013). As previously discussed, there is not enough evidence from the current literature to demonstrate superiority of either nephrostomy or stent drainage in centers where both are readily available (Pearle et al, 1998; Mokhmali et al, 2001).

Multiple meta-analyses have consistently reported that tubeless PCNL is feasible and considered safe after an uncomplicated procedure without residual fragments, infection, bleeding, or collecting system perforation. In addition, a tubeless procedure reduces hospital stay, analgesia requirement, and time to return to normal activity (Yuan et al, 2011; Shen et al, 2012; Wang et al, 2012; Zhong et al, 2013).

Nephrostomy tubes may also be used to administer therapeutic drugs to the upper urinary tract. BCG or Mitomycin C for the treatment of upper urinary tract urothelial cancer as well as chemolytic agents to achieve stone dissolution are examples. Giannarini identified patients with carcinoma in situ of the upper urinary tract to benefit the most from upper tract BCG instillations (Giannarini et al, 2011b). If a nephrostomy tube is in place, it can be used to obtain a nephrostogram for diagnostic imaging.

In the treatment of malignant ureteric obstruction, drainage failure is significantly more prevalent in patients with ureteral stents compared with patients with a nephrostomy tube (Ku et al, 2004). Song suggested that patients with an obstruction larger than 3 cm are more likely to benefit from PCN than from DJ stent placement (Song et al, 2012b).



Figure 6-8. Nephrostomy tubes: types of nephrostomy catheters. A to C, Malecot, Pezzar, and Hulbert re-entry catheter. (Permission for use granted by Cook Medical, Bloomington, IN.)

How to obtain percutaneous access to the kidney is described in Chapter 8.

Complications

Hemorrhage, hematuria, clot colic, and UTIs are frequently reported minor complications of nephrostomy tube insertion. Sepsis occurs in 1.3% to 7% of patients, and trauma to adjacent organs caused by the procedure is uncommon. Transfusion rates of 2% to 4% have been reported as a result of venous or arterial bleeding. Venous bleeding is usually self-limiting. Persistent arterial bleeding or arteriovenous fistula is an uncommon but more severe complication that requires adequate imaging assessment and, if necessary, treatment with angioembolization. Thoracic complications (pneumothorax, hemothorax, hydrothorax, empyema) occur in 0.1% to 0.2% of nephrostomy tube placements. Late complications include tube dislodgement and blockage. Nephrostomy tube dislodgement is reported to occur in 2.5% of patients; this requires urgent assessment and, if necessary, tube replacement. A self-retaining catheter or retention suture fixation to the skin can aid in preventing tube dislodgement (Lewis and Patel, 2004; Wah et al, 2004; Hausegger and Portugaller, 2006; Rana et al, 2007; Ali et al, 2013).

Major complications are more common when procedures are performed during on-call hours, with lack of experienced staff implicated as a contributing factor (Lewis and Patel, 2004). Performing 10 to 20 PCNs per year improves success rate of the procedure (Lee et al, 1994).

Biofilm Formation on Urinary Tract Biomaterials

A *biofilm* is defined as a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface.

Bacteria attempt to control their immediate environment by limiting exposure to harmful factors (waste products, antimicrobial agents, the host's immune response) while enhancing the exposure to trophic factors.

Despite continuing developmental efforts to achieve more biocompatible materials and surface coatings, indwelling catheters, stents, and nephrostomy tubes completely resistant to biofilm formation are as yet unavailable.

Biofilm-producing bacteria are the most important factor in inducing catheter- or stent-associated UTI and encrustation and the most common cause of stent failure (Ando et al, 2004; Chew et al, 2006; Ferrières et al, 2007).

Biofilm structures consist of three layers: (1) the **innermost layer**, attached to the surface of the biomaterial, which **functions as a linking film** for subsequent layers; (2) the **base film**, composed of microorganisms attached to the linking film; and (3) an **outer layer or surface film**, where microorganisms can be released (Tenke et al, 2012). The thickness of a biofilm can range from 3 to 490 μm and is composed of a few cell layers ranging from up to 400 cells deep (Ganderton et al, 1992).

The initial step in biofilm formation is the creation of a conditioning film on the surface of the biomaterial within minutes of insertion (Reid et al, 1995). This conditioning film is composed of **urinary components such as polysaccharides, Tamm-Horsfall proteins, electrolytes, and glycoproteins that adhere to the biomaterial surface**. The conditioning film alters the surface characteristics of the biomaterial, facilitating bacterial adhesions (Reid and Busscher, 1992). The initial bacterial adhesion is influenced by hydrophobic and electrostatic interactions, ionic forces, osmolality, and urinary pH and is **still reversible** (Gristina, 1987). The bacteria produce a matrix of exopolysaccharides and glycocalyx, rendering their adhesion irreversible. Eradication of the biofilm at this point is deemed impossible. Approximately 5% to 35% of the biofilm consists of bacterial microcolonies. The remainder is composed of interstitial spaces filled with fluid and water channels that allow transportation of nutrients and oxygen to the colonies (Tenke et al, 2012).

Resistance to antimicrobial treatment of bacterial biofilm infections is multifactorial:

1. **Quorum sensing** is a bacterial communication process depending on population density. Diffusible signaling molecules allow bacterial colonies to react to their environment in a synchronized manner, regulating biofilm formation, virulence, and antibiotic resistance (Li and Nair, 2012; Bhardwaj et al, 2013).
2. **The polymicrobial nature of biofilm** increases antibacterial resistance. Bacteria contained in biofilm actively recruit other bacterial strains, resulting in biofilm consisting of up to six different strains. *E. coli*, *P. aeruginosa*, and *Enterococcus faecalis* are most frequently found in biofilm in the urinary tract. *P. mirabilis*, *E. faecalis*, and *S. aureus* have a stronger biofilm forming capacity (Holá et al, 2010).
3. **Persister cells**, contributing up to 1% to the entire biofilm, reside in a dormant state and do not grow, which enhances resistance to the usual antibiotic mechanism of action. They are often the cause of chronic infections (Wood et al, 2013).
4. Although antimicrobial agents may have the ability to penetrate into a biofilm, antimicrobial action is compromised by **waste accumulation and an altered microenvironment** (low pH, low PO_2 , high PCO_2 , low divalent cation and pyrimidine concentration, low hydration level) (del Pozo and Patel, 2007).

Urease-producing bacteria in biofilm, such as *P. mirabilis*, *Proteus vulgaris*, and *Providencia rettgeri*, are able to raise the urinary pH to an alkaline level at which calcium and magnesium phosphates (hydroxyapatite and struvite) crystallize, deposit onto catheter or stent surfaces, and are incorporated into the organic matrix, creating encrustation (Broomfield et al, 2009). Canales and colleagues demonstrated that components of the conditioning film, α_1 -antitrypsin, Ig kappa, IgH G₁, and histone H2B and H3A, were highly associated with stent encrustation (Canales et al, 2009).

The difficulty in preventing and treating biofilm and biofilm-induced infections is the consequence of the complexity of biofilm

KEY POINTS

- The routine use of coated catheters for short-term catheterization is not recommended.
- Screening for asymptomatic bacteriuria in patients with an indwelling catheter or ureteral stent should not be performed.
- Surrounding organ injury is the most significant complication of suprapubic catheter placement and has been reported to occur in less than 1% to 2.7% of procedures.
- Stent symptoms influence the quality of life in 80% of stented patients and reduce work capacity in 58%.
- α -Blockers and anticholinergic medications may be useful for modifying irritative and obstructive symptoms related to indwelling double-J stents.
- The indwelling time of a ureteral stent is the most important risk factor for encrustation.
- Metal and segmental stents such as Resonance, Memokath 051, Uventa, and Allium stents are useful in relieving extrinsic ureteric compression.
- Innovations in stent design and coatings are undergoing investigation with the desired goal of reducing stent-associated complications and symptoms.
- Tubeless PCNL is feasible and considered safe after an uncomplicated procedure without residual fragments, bleeding, infection, or collecting system perforation.
- Biofilm-producing bacteria are the most important factor in inducing catheter- or stent-associated urinary tract infection and encrustation and the most common cause of stent failure.
- Bacterial biofilm resistance to antimicrobial treatment is a result of multiple factors including quorum sensing, polymicrobial nature of biofilm, the presence of persister cells, and an altered microenvironment in the biofilm.

structure and the different mechanisms that compromise antibacterial mechanisms of action. Better understanding of basic processes and insights into biofilm formation and resistance mechanisms will guide the next generation of catheter and stent development and design in search of the ideal biomaterial and coating.

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The complete reference list is available online at www.expertconsult.com.

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History of Endoscopy

Basic Equipment and Video-Endoscopic Systems

Cystourethroscopy

The development of rigid and flexible endoscopes in combination with their myriad ancillary equipment transformed many of the surgical specialties including urology. Management of bladder outlet obstruction, urothelial tumors, ureteral obstruction, and nephrolithiasis have all been revolutionized by endoscopic procedures. This chapter highlights major events in the development of modern endoscopes and indications for cystourethrography and ureteropyeloscopy along with patient preparation; techniques are then described in detail. Many of these principles are greatly expanded on in other sections of this book.

HISTORY OF ENDOSCOPY

The term *endoscope* is credited to the French urologist Antonin Jean Desormeaux in 1853; however, attempts to look inside the human body date back to antiquity (Natalin and Landman, 2009). Major progress occurred in 1806 when Philipp Bozzini developed the first “modern” endoscope (Engel, 2003). The Lichtleiter or “Light Conductor” used angled mirrors to conduct candlelight from a sharkskin-covered box into the body through aluminum tubing. The instrument was too large to be used on the genitourinary system. In 1853 Desormeaux introduced a similarly designed but smaller-profile endoscope with improved mirrors that used a kerosene lamp for illumination (Shah, 2002). Through this instrument he excised a urethral papilloma, becoming the first individual to perform a therapeutic endoscopic procedure.

Both Bozzini’s and Desormeaux’s endoscopes were severely hampered by their poor illumination and limited field of view. In 1877 Max Nitze designed a cystoscope that helped overcome both obstacles (Herr, 2006). He moved the source of illumination (water-cooled electric platinum filament) to the end of the instrument and used a series of optical lenses placed at precise distances along the length of a hollow, air-filled scope to conduct and magnify the image. In 1887 Nitze abandoned the platinum filament for Edison’s light bulb.

The development of the Amici prism in 1906 allowed cystoscopic images to be offset 90 degrees while maintaining correct image orientation, (Gow, 1998). No major developments occurred in cystoscope design until 1966, when Harold Hopkins introduced glass rods with only short gaps of air between. Hopkins was able to greatly improve light transmission while decreasing scope size, paving the way for contemporary rigid cystoscopes and the first rigid ureteroscope in 1979 (Lyon et al, 1979).

The development of flexible endoscopes was made possible by the advent of fiberoptics. In 1854 John Tyndall demonstrated that light could travel through a curved stream of water by internal reflection (Whewell et al, 1854). This finding led to molten glass being drawn into flexible, small-diameter fibers for light transmission. Further refinements in this process eventually led to the development of fiberoptics for medical use.

Upper Tract Endoscopy

Conclusions

Although still widely used, fiberoptics are fragile and have limited optical resolution. In 1970 Boyle and Smith developed the charge-coupled device (CCD), a sensor with the ability to convert photons to an electrical charge and ultimately a digital image (Samplaski and Jones, 2009). Traditionally these chips were housed within cameras attached to existing scopes. Over the last three decades, advancements in endoscope design led to the incorporation of the CCD chip within the distal tip. Introduced in 2005, the ACMI DCN-2010 flexible cystoscope was the first commercially available digital endoscope (Natalin et al, 2009). Compared with rod-lens and fiberoptic bundle systems, digital sensor technology offers improved image resolution and durability without the need for a separate light cable and camera (Quayle et al, 2005).

BASIC EQUIPMENT AND VIDEO-ENDOSCOPIC SYSTEMS

At minimum, cystourethroscopy requires irrigation fluid, a light source, and an endoscope. Typical irrigation fluids include sterile water, glycine, and normal saline. If electrocautery is needed, a solution free of electrolytes should be used.

A high-intensity xenon or halogen external light source is used to deliver white light to the endoscope through a fiberoptic cable. Some units include an automatic light-sensing feature that provides constant illumination by adjusting light output.

First introduced into urologic practice in 2007, narrow band imaging uses only blue (415 nm) and green (540 nm) wavelengths to image the urothelium (Bryan et al, 2008). These two wavelengths are strongly absorbed by hemoglobin, improving visibility of urothelial capillaries, small papillary lesions, and carcinoma in situ. A meta-analysis of eight studies including 1022 patients found that narrow band imaging improves accuracy of detection of noninvasive lesions, including carcinoma in situ (Zheng et al, 2012). The impact of narrow band imaging on tumor recurrence has not been prospectively evaluated.

In the absence of an endoscope camera the practitioner views the image directly through the optical eyepiece at the proximal end of the instrument. However, in most instances the image will be viewed on a monitor that is part of a dedicated video-endoscopic unit arranged in a fixed or mobile tower (Fig. 7-1). Video-endoscopic units have several advantages, including better visualization, enhanced patient safety and surgical training, decreased risk of bodily fluid exposure to the urologist, and improved operative ergonomics.

Traditional video-endoscopic systems consist of a light source, endoscope camera, image processor and recorder, and monitor. Newer digital units have eliminated the need for an external camera, allowing the light source and video cable to be incorporated into a single, built-in housing (Fig. 7-2). In the traditional system the endoscopic image is conveyed to the camera via a series of glass



Figure 7-1. Video-endoscopic unit consisting of a fixed tower, monitor, light source, image processor, video-recording device, and printer.

rods or fiberoptic bundles. The optical image is then converted to an electrical charge (voltage waveform) by the camera's CCD chip. The unit's video processor then converts the analog voltage waveform into a digital video signal that is sent to the monitor. In contrast, digital video-endoscopic systems have the CCD chip located at the distal end of the endoscope. The image is immediately converted into an electrical signal that is once again managed by the video processor without the need for internal optics and a CCD camera.

CYSTOURETHROSCOPY

Indications

Cystourethroscopy is one of the most common procedures in urology. Routinely performed in both the office and operating room setting, cystourethroscopy provides direct visualization of the urethra and bladder. The upper urinary tract may be evaluated fluoroscopically by ureteral catheterization with retrograde instillation of contrast material.

Indications for office-based cystourethroscopy are summarized in [Box 7-1](#). Most are for diagnostic purposes, but a limited number of therapeutic procedures may also be performed. One of the most frequent reasons to perform cystourethroscopy is for microscopic and gross hematuria. In addition to directly visualizing the lower urinary tract, cystourethroscopy permits collection of cytologic specimens and retrograde pyelography in patients who are not candidates for intravenous contrast.

Urothelial carcinoma surveillance is another routine indication for cystourethroscopy. Small urothelial lesions may be biopsied and fulgurated in the clinic. Upper tract surveillance may be accomplished by selective ureteral catheterization with retrograde

pyelography, upper tract washes for cytology, and brush biopsies for histologic evaluation.

Lower urinary tract complaints such as recurrent infections, obstructive and irritative voiding symptoms, and chronic pelvic pain may be worked up cystoscopically. In select patients, urethral strictures, bladder stones, and foreign bodies may be treated in the office. Ureteral stents can also be placed or exchanged in clinic with fluoroscopic assistance.

Equipment

Cystourethroscopes are manufactured in a variety of sizes expressed in French (Fr) gauge. **In the system devised by French instrument designer Joseph-Frédéric-Benoît Charrière (1803-1876), a 1-Fr instrument has a circumference of $\frac{1}{3}$ mm (Osborn and Baron, 2006).**

Cystourethroscopes are available in rigid and flexible models. Each has its own advantages and disadvantages. Rigid cystoscopes use the Hopkins rod-lens optical system, which provides improved optical clarity compared with the fiberoptic bundles used in flexible endoscopes. This is becoming less noticeable because of the increasing adoption of digital flexible cystourethroscopes. Visualization is also enhanced by the greater irrigant flow rate of rigid endoscopes. Rigid cystourethroscopes have larger working channels, allowing a wider array of instruments to be used. Their rigid design also makes them easier to control with one hand, freeing the surgeon's second hand to manipulate ancillary instruments.

In contrast, the smaller size of flexible cystourethroscopes improves patient comfort, making them ideal for office-based procedures. Endoscope passage does not require the patient to be in the frog-leg or lithotomy position. Their active tip deflection makes it easier to completely inspect the bladder and negotiate an elevated bladder neck or median lobe of the prostate.

Rigid Cystourethroscopes

Rigid cystourethroscopes are manufactured in sets consisting of an optical lens, bridge, sheath, and obturator ([Fig. 7-3](#)). Configurations differ by vendor ([Table 7-1](#)). Optical lenses come with tip angles ranging from 0 to 120 degrees. Visualization of the urethra is best performed with a 0- or 12-degree lens. A 25- or 30-degree lens is commonly used for therapeutic purposes. A 70- or 120-degree lens may be required to completely inspect the anterior and inferolateral walls, dome, and neck of the bladder.

The bridge connects the optical lens to the sheath. Diagnostic bridges do not have a working channel. Therapeutic bridges have one or two working channels. Patients with an elevated bladder neck, large median lobe of the prostate, or ureteroneocystostomy may require use of an Albarran bridge. This specialized bridge contains a lever that deflects wires and catheters passed through the working channel to facilitate ureteral orifice canalization ([Fig. 7-4](#)).

Cystourethroscope sheaths come in a variety of sizes. Most have markings indicating the size of the sheath and associated working channels ([Fig. 7-5](#)). Smaller sheaths (15 and 17 Fr) are ideal for diagnostic cystoscopy; the larger models are used for therapeutic procedures requiring improved irrigant flow and larger working channels. Each sheath has an associated obturator that blunts the distal end of the sheath for passage into the bladder without visual assistance. In most instances blind endoscope passage should be performed only in women.

Flexible Cystourethroscopes

Flexible cystourethroscopes range between 16 and 17 Fr. Models differ with regard to tip deflection, direction of view, field of view, working channel size, illumination, and optics ([Table 7-2](#)). Most models do not have an offset lens and provide a field of view of approximately 120 degrees. Tip deflection ranges from 120 to 210 degrees and is either intuitive (same direction as lever deflection) or counterintuitive (opposite direction of lever deflection). Irrigation and instrument passage occur through the same working

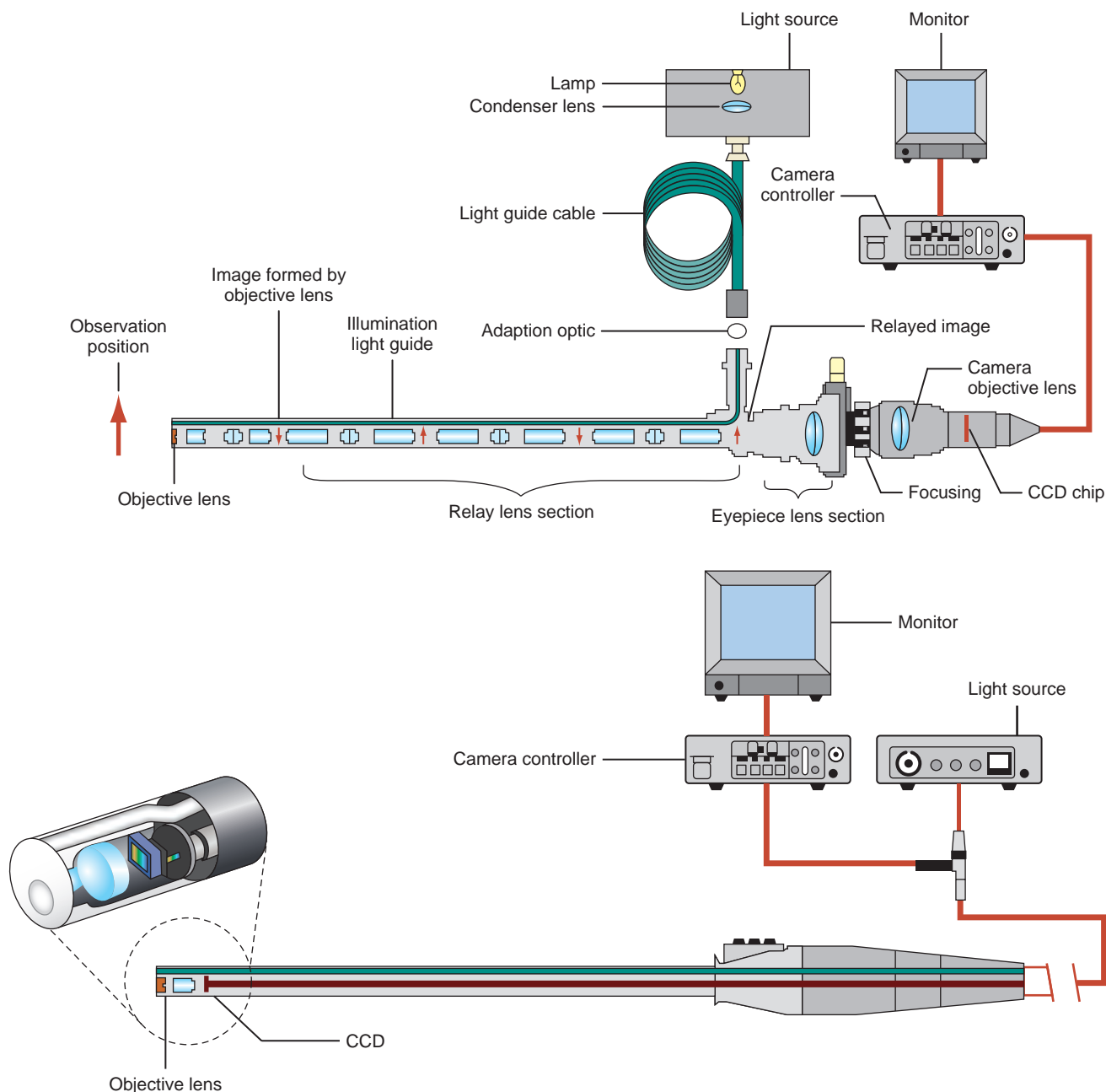


Figure 7-2. Traditional rod-lens optical system compared with digital sensor video-endoscopes. CCD, charge-coupled device. (Courtesy Olympus, Center Valley, PA.)

channel. Photodynamic and narrow band imaging capabilities are available in some models.

Flexible cystourethroscopes are available in fiberoptic and digital models. Digital scopes do not require focusing or white balancing. They are now available in high-definition (1920×1080 pixels) and standard-definition (720×480 pixels) models. An in vitro study compared the resolution, contrast evaluation, depth of field, color representation, and illumination of fiberoptic, standard-definition, and high-definition flexible cystoscopes (Lusch et al, 2013). All three scopes were manufactured by Olympus (Olympus, Center Valley, PA). Compared with the fiberoptic and standard-definition models, the high-definition scope had a significantly higher resolution and depth of field. The high-definition scope's resolution was five times greater and it had a 37% larger image than the standard-definition model. Color representation was only slightly better, and there was no difference in contrast evaluation among the three

models. Illumination was significantly better in the fiberoptic model compared with both digital cystoscopes.

A randomized study of 1022 flexible cystoscopy cases compared optics, performance, and durability of fiberoptic and standard-definition digital scopes (Okhunov et al, 2009). There was a trend toward improved mean surgeon optical ranking in favor of the digital scopes ($P = .076$). There was no difference in durability between the models. Only two cystoscopes required repair (0.2% incidence rate), and both were damaged when the endoscope was placed in a storage case rather than during use.

Data from an independent endoscope repair company found that flexible cystoscopes require less than one repair every 2 years (Canales et al, 2007). The most common repair was to the rubber overlying the distal flexible segment. Unlike flexible ureteroscopes, flexible cystourethroscopes are robust, likely making the optical mechanism a lesser determinant of scope durability.

BOX 7-1 Indications for Office-Based Cystourethroscopy**HEMATURIA**

Gross
Microscopic

MALIGNANCY

Urethral cancer
Bladder cancer
Atypical cytology
Upper tract transitional cell carcinoma surveillance

LOWER URINARY TRACT SYMPTOMS

Recurrent urinary tract infections
Obstructive voiding symptoms
Irritative voiding symptoms
Urinary incontinence
Chronic pelvic pain syndrome
Urethral stricture disease

MISCELLANEOUS

Trauma
Bladder abnormalities seen on imaging
Removal of foreign bodies and small bladder stones
Hematospermia
Obstructive azoospermia

Patient Preparation

Informed consent must be obtained before any cystoscopic procedure is performed. A urinalysis and urine culture, if indicated, should be completed before cystoscopy. All urinary tract infections must be treated, given the risk of bacteremia and sepsis after lower urinary tract manipulation.

The American Urological Association (AUA) Best Practice Policy Statement on antimicrobial prophylaxis does not recommend antibiotic administration for routine diagnostic

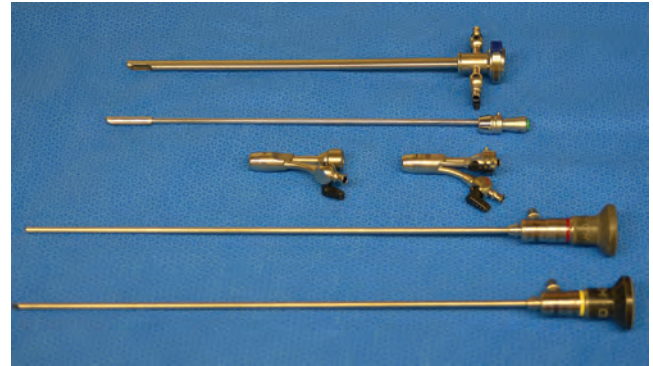


Figure 7-3. Rigid cystourethroscope set consisting of sheath, obturator, bridges, and lenses (from top to bottom).

TABLE 7-1 Rigid Cystoscopes (Information Supplied by Manufacturers)

	KARL STORZ	OLYMPUS	GYRUS/ACMI	WOLF
Lenses	0, 12, 30, 70, 120 Diameter: 4 mm Length: 30 cm	0, 12, 30, 70, 110 Diameter: 4 mm Length: 28 cm	0, 12, 30, 70, 110 Diameter: 4 mm Length: 28 cm	0, 12, 30, 70 Diameter: 4 mm Length: 29.5 cm
Bridges	Telescopic • Diagnostic • Single and dual channel Deflecting (Albarran lever) • Single and dual channel	Telescopic • Diagnostic • Single and dual channel Deflecting (Albarran lever) • Single and dual channel	Telescopic • Diagnostic • Single and dual channel Deflecting (Albarran lever) • Single and dual channel	Telescopic • Diagnostic • Single and dual channel Deflecting (Albarran lever) • Single and dual channel
Sheaths and working channels	17 Fr SB: 5 Fr DB: 5 Fr × 1 19 Fr SB: 6 Fr DB: 5 Fr × 2 20 Fr SB: 7 Fr DB: 6 Fr × 2 22 Fr SB: 10 Fr DB: 7 Fr × 2 25 Fr SB: 12 Fr DB: 8 Fr × 2	15 Fr SB: none DB: none 17 Fr SB: none DB: none 19.8 Fr SB: 6 Fr DB: 5 Fr, 6 Fr 21 Fr SB: 8 Fr DB: 6 Fr, 7 Fr 22.5 Fr SB: 10 Fr DB: 8 Fr × 2 25 Fr SB: 12 Fr DB: 8 Fr × 2	17 Fr SB: 5 Fr DB: 4 Fr × 2 21 Fr SB: 9 Fr DB: 6 Fr × 2 23 Fr SB: 10 Fr DB: 8 Fr × 2 25 Fr SB: 12 Fr DB: 8 Fr × 2	16 Fr SB: 5 Fr DB: none 17.5 Fr SB: 5 Fr DB: 4 Fr × 2 19.5 Fr SB: 7 Fr DB: 5 Fr × 2 21 Fr SB: 10 Fr DB: 6 Fr × 2 23 Fr SB: 12 Fr DB: 7 Fr × 2 25 Fr SB: 15 Fr DB: none

DB, dual bridge; Fr, French; SB, single bridge.

cystoscopy in the absence of patient-related risk factors (Box 7-2) (Wolf et al, 2008). Prophylaxis lasting less than 24 hours with either a fluoroquinolone or trimethoprim-sulfamethoxazole is recommended for therapeutic procedures. Second-line alternatives include an aminoglycoside with or without ampicillin, a first- or second-generation cephalosporin, or amoxicillin/clavulanate. This recommendation is largely based on a meta-analysis of 32 randomized controlled trials evaluating antimicrobial prophylaxis before transurethral resection of the prostate (TURP), which showed a decrease in bacteriuria, bacteremia, symptomatic urinary tract infection, and high-grade fever (Berry and Barratt, 2002). Similar trials have not been performed for minor cystoscopic procedures.

Before cystourethroscopy the skin is prepared with an antiseptic agent. Most commercially available agents contain iodophors or chlorhexidine gluconate in either an aqueous or alcohol-based solution. Both chlorhexidine gluconate and alcohol-based solutions can damage mucous membranes and therefore are not recommended for use on the genitalia. Aqueous-based iodophor-containing products such as Betadine are safe on all skin surfaces regardless of patient age.

After application of an antiseptic agent a lubricating gel is injected into the urethra of patients undergoing flexible cystourethroscopy. Either a plain or lidocaine gel may be used. A meta-analysis of four randomized trials involving 411 patients found that patients who received lidocaine gel were 1.7 times less likely

to experience moderate to severe pain during the procedure (Aaronson et al, 2009). However, only one of the four trials showed a statistical benefit to lidocaine gel, which is consistent with a larger meta-analysis involving 817 patients from nine randomized trials that showed no difference in procedure tolerance (Patel et al, 2008b).



Figure 7-4. Albarran bridge, which is used to deflect wires and catheters passed through the rigid cystoscope working channel.

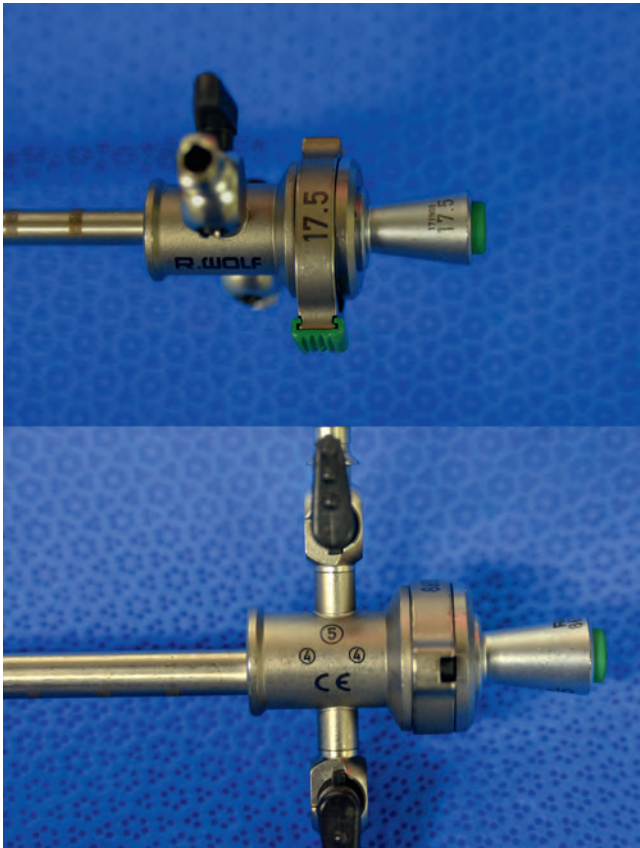


Figure 7-5. Markings on rigid cystoscope sheath. The largest number on the base of the scope indicates the outer diameter (17.5 Fr). The numbers on the side of the sheath indicate the maximum working channel size when a dual bridge is used (4 Fr for both lumens) or when a single bridge is employed (5 Fr).

TABLE 7-2 Flexible Cystoscopes (information Supplied by Manufacturers)

MANUFACTURER	OPTICS	DEFLECTION (DEGREES)	DIRECTION OF VIEW (DEGREES)	ANGLE OF VIEW (DEGREES)	WORKING LENGTH	WORKING CHANNEL	SHEATH SIZE
Karl Storz	Fiberoptic	Up: 210 Down: 140	0	110	37 cm	7.0 Fr	15.5 Fr
	Digital (standard definition)	Up: 210 Down: 140		120	37 cm	6.5 Fr	16.0 Fr
Olympus	Fiberoptic	Up: 210 Down: 120	0	120	38 cm	7.2 Fr	16.5 Fr
	Digital (standard definition)	Up: 210 Down: 120		120	38 cm	6.6 Fr	16.2 Fr
	Digital (high definition)	Up: 210 Down: 120		120	38 cm	6.6 Fr	16.5 Fr
	Model CYF-VH	Up: 210 Down: 120		120	38 cm	6.6 Fr	16.5 Fr
Wolf	Fiberoptic	Up: 180 Down: 170	0	105	37 cm	6.4 Fr	15.9 Fr
	Model CAN-2	Up: 180 Down: 170		105	37 cm	6.4 Fr	15.9 Fr

BOX 7-2 Patient Risk Factors Requiring Antimicrobial Prophylaxis

Advanced age
Anatomic anomalies of the urinary tract
Chronic corticosteroid use
Colonized endogenous or exogenous material
Distant coexistent infection
Immunodeficiency
Poor nutritional status
Prolonged coexistent infection
Smoking

Other techniques have been employed to improve patient comfort during flexible cystourethroscopy. For the majority of men, the most uncomfortable part of the procedure is when the scope passes through the membranous urethra (Taghizadeh et al, 2006). A randomized trial was performed on 151 men undergoing flexible cystourethroscopy (Gunendran et al, 2008). Half of the subjects had the hydrostatic pressure of the irrigation solution increased by manual compression of the irrigation bag during passage of the scope through the membranous urethra. Gravity irrigation alone was used for the remaining patient. A significant improvement on an analog pain scale score was noted (1.38 vs. 3.00, $P < .001$) in the manual compression group.

The impact of being allowed to observe the procedure has also been evaluated. One hundred male patients undergoing flexible cystourethroscopy were randomized; half the subjects were allowed to observe the procedure on a video monitor whereas the remaining patients were not (Patel et al, 2007). Men who watched the procedure had significantly less pain on a 100-mm visual analog pain scale (14 vs. 23, $P = .02$). These findings were confirmed by another randomized study of 76 male patients (Soomro et al, 2011). Men in the observation group had less pain and lower postprocedure pulse rates. In contrast, a randomized study of 100 women undergoing office-based cystoscopy with a 17-Fr rigid scope found no difference in procedural pain (Patel et al, 2008a).

The potentially calming effect of music has also been examined. Seventy men undergoing flexible cystoscopy were randomized to either no music or classical music played during the procedure (Yeo et al, 2013). Patients listening to classical music had significantly less pain, greater satisfaction, lower postprocedure pulse rates, and lower systolic blood pressures.

Technique

Before insertion of the cystourethroscope, the external genitalia is inspected for cutaneous lesions and anatomic abnormalities. Mild meatal stenosis may be addressed with sequential metal dilators. Dilation should be performed to at least 2 Fr wider than the intended endoscope.

In women, rigid cystourethroscope insertion is safest using the sheath obturator. The scope will often need to be directed anteriorly as it is advanced into the bladder. Flexible cystourethroscopes can often be inserted into the bladder like a Foley catheter, with active deflection being used as needed.

In men, the penis is placed on maximal stretch to straighten the urethra. When a rigid cystourethroscope is being passed, the penis is typically grasped with all five digits of the surgeon's nondominant hand. With flexible cystourethroscopy the penis is pinched between the fourth and fifth digits of the nondominant hand at the corona while the thumb and index finger help advance and direct the scope into the urethra (Fig. 7-6). In morbidly obese



Figure 7-6. During flexible cystoscopy the distal penis is grasped between the surgeon's third and fourth fingers and placed on stretch while the thumb and index finger advance the cystoscope into the urethral meatus.

patients it is often easier to lay the scope down, retract the pannus with the nondominant hand, and direct the tip of the flexible scope into urethra like a Foley catheter. Once in the mid-penile urethra the scope is placed in the dominant hand and advanced as usual.

The penis should be angled 45 to 90 degrees relative to the abdominal wall while the scope is passed through the anterior urethra. Once beyond the membranous urethra the cystoscope is directed anteriorly to enter the bladder. With flexible cystoscopes this is accomplished by active upward deflection and with rigid cystoscopes by dropping the distal end of the scope toward the operative table.

The lower urinary tract is systematically evaluated under maximal irrigation as the scope is advanced. The penile and bulbar urethra are inspected for strictures. The periurethral glands of Littre should be noted as they drain into the urethra dorsally. Patients, in particular young men, should be encouraged to relax as much as possible as the scope is advanced through the membranous urethra. Once the scope is in the prostatic urethra, the verumontanum and utricle are identified posteriorly. The length of the posterior urethra is measured and the size of the prostatic lobes is evaluated.

Once the scope is in the bladder, the mucosa is carefully inspected. Rigid cystoscopy is usually begun with a 25- or 30-degree lens. The floor of the bladder and trigone are surveyed. The number, location, and configuration of the ureteral orifices are noted. Efflux from each ureter should be observed for the presence of gross blood. The remainder of the bladder is inspected for stones, trabeculation, cellulules, diverticula, erythematous patches, and papillary and sessile lesions. Visualization of the lateral walls is accomplished by rotating the cystoscope while keeping the camera orientation fixed. The dome and anterior and posterolateral walls are inspected with a 70- or 120-degree lens. After completion of the procedure, the bladder is emptied and the endoscope withdrawn. If a Foley catheter is to be placed after the procedure, it is best to leave the bladder at least partially full before removing the cystoscope.

Special Circumstances

Suprapubic Cystostomy

The indications for cystoscopy in patients with suprapubic cystostomy tubes are the same as for those without chronic indwelling

catheters. Nevertheless, these individuals are at increased risk of infection, bladder calculi, and bladder cancer (Subramonian et al, 2004; Welk et al, 2013; El Masri et al, 2014). At present there are no level 1 data showing improved survival in patients with long-term indwelling catheters undergoing surveillance cystoscopy. However, in patients with catheters for more than 5 to 10 years, surveillance cystoscopy is a common practice.

Cystoscopic evaluation may be performed transurethrally or via the patient's suprapubic tract. However, many patients with long-term suprapubic tubes have urethral stricture disease, making the suprapubic tract the only feasible route to the bladder. Every effort should be made to avoid endoscopy through a suprapubic tract until it has had time to mature, which usually takes several weeks from the time of creation. If endoscopy of an immature tract is required, it is advisable to place a wire through the tract into the bladder to guide the endoscope. This technique is also helpful in morbidly obese patients with long, often tortuous tracts.

Ureteral access is often challenging during rigid cystoscopy because of the acute angle required to cannulate the ureteral orifice via the cystostomy tract. Use of angled catheters such as the Kumpe Catheter (Cook Medical, Bloomington, IN) or an Albarran deflector may facilitate ureteral access. Use of a flexible cystoscope will often overcome these problems. Alternatively, patients with low-grade urethral strictures may be able to accommodate transurethral passage of a semirigid ureteroscope facilitating standard ureteral access. Lastly, the ureteral orifices may be difficult to identify because of edema caused by the chronic suprapubic tube. Administering intravenous indigo carmine or methylene blue early in the procedure may help visualize the ureteral orifices.

Continent Urinary Diversions

There are two general classes of continent urinary diversions after cystectomy. Orthotopic urinary diversions are anastomosed to the urethra and rely on the striated urinary sphincter to maintain continence. Continent cutaneous reservoirs use a catheterizable channel anastomosed to the diversion and anterior abdominal wall. The catheterizable channel may be composed of the appendix (Mitrofanoff), tapered or imbricated terminal ileum and ileocecal valve, or an intussuscepted nipple valve.

Before any endoscopic procedure involving a continent urinary diversion, it is imperative to obtain the operative note. It is important to know the bowel segment used, type and location of the ureteroenteric anastomoses, continence mechanism employed, and whether an afferent limb was created.

Transurethral access to orthotopic diversions is often straightforward and can be accomplished using a rigid cystoscope. If a contracture is noted at the urethral anastomosis and the patient does not have outlet obstruction, then it is advisable to use the smallest scope possible rather than dilate or incise the stricture because of the risk of worsening urinary incontinence.

Diagnostic procedures on continent cutaneous reservoirs are best accomplished with a flexible cystoscope through the catheterizable channel. Therapeutic procedures should be performed percutaneously, given that continence mechanisms are often fragile and excess manipulation may result in either stomal stenosis or urinary incontinence (L'Esperance et al, 2004). Preoperative computed tomography (CT) or intraoperative ultrasound should be used to minimize the risk of bowel injury during percutaneous access.

Once within the diversion, visualization is often challenging because of mucus, mucosal folds, bowel peristalsis, and, if present, tortuous afferent limb. Begin by irrigating out all of the mucus. Irrigation should then be used judiciously. Too little irrigation will make mucosal folds more prominent and impair visualization, but overdistending the diversion will prevent access to the afferent limb. Once again, ancillary techniques such as use of angled catheters and indigo carmine or methylene blue may be required.

KEY POINTS: CYSTOURETHROSCOPY

- Rigid cystourethrosopes are manufactured in sets consisting of an optical lens, a bridge, a sheath, and an obturator.
- Flexible cystourethrosopes are available in fiberoptic, standard-definition, and high-definition digital models.
- Cystourethroscope sizes are expressed using the French gauge system; 1 Fr is equal to $\frac{1}{3}$ mm in circumference.
- The smallest-diameter cystourethroscope that can be used to perform the procedure should be selected to decrease the risk of genitourinary tract trauma.
- Antimicrobial prophylaxis is not recommended for diagnostic cystourethrosopy unless patient risk factors are present.
- Increasing the hydrostatic pressure during scope passage and allowing men to observe the procedure have been prospectively shown to improve comfort during flexible cystourethrosopy.

UPPER TRACT ENDOSCOPY

Indications

Urolithiasis

The treatment of stones is the most common indication for ureteroscopy. Rigid ureteroscopy has long been the preferred treatment for distal ureteral stones. Shock wave lithotripsy (SWL) was favored for stones above the iliac vessels, because early results using rigid ureteroscopy for mid-ureteral and proximal ureteral calculi were discouraging. However, improvements in ureteroscopes and working instruments, the use of the holmium laser, and greater use of the flexible ureteroscope have significantly improved stone-free rates after ureteroscopic treatment of stones above the iliac vessels.

Although SWL remains a valuable treatment option for renal and ureteral stones, there are certain clinical situations in which, because of SWL limitations, ureteroscopy is preferred. Frequent causes of shock wave lithotripsy failure include radiolucent or difficult-to-visualize calculi, concomitant obstruction distal to the calculus, poor passage of lower pole fragments, and failure to fragment dense calculi. In addition, morbidly obese patients who exceed the weight limit or focal length of many shock wave lithotripters can be successfully treated ureteroscopically.

Percutaneous nephrostolithotomy is the treatment of choice for large (>2 cm) intrarenal calculi. However, in patients with significant comorbidities that would make percutaneous nephrostolithotomy dangerous, flexible ureteroscopy has been successfully used. Two studies have reported stone-free rates of 91% and 93% for ureteroscopic treatment of patients with stones larger than 2 cm (Grasso et al, 1997; Breda et al, 2008).

Upper Urinary Tract Transitional Cell Carcinoma

The standard treatment for upper urinary tract transitional cell carcinoma is nephroureterectomy. However, with improvements in flexible ureteroscopic instrumentation and technique, there is increased use of endoscopic treatment of well-selected patients with upper urinary tract transitional cell carcinoma. Accordingly, the principles of endoscopic management of transitional cell carcinoma have been extended from the bladder to the upper urinary tract. With expansion of ureteroscopy for the diagnosis, ablation, and subsequent surveillance phases of upper tract transitional cell carcinoma management, this is becoming a frequent indication for ureteroscopy.

Many patients treated ureteroscopically for upper urinary tract transitional cell carcinoma are those in whom nephroureterectomy would be dangerous: patients with a solitary kidney, renal insufficiency, bilateral upper tract transitional cell carcinoma, or significant medical comorbidities. There is also increasing use of ureteroscopic treatment for patients with low-grade, low-volume

disease. Endoscopic management of these patients has proven to be a reasonable option, without compromise of patient survival (Cutress et al, 2012b; Grasso et al, 2012). Larger tumors can be difficult to fully ablate in one session. Percutaneous nephroscopy and electroresection have been used and permit resection of large amounts of tumor (Irwin et al, 2010; Cutress et al, 2012a). However, the ureteroscopic approach may be preferred because it avoids the risk of seeding the percutaneous tract and retroperitoneum with tumor. The risk of tract seeding is small, but it has been reported (Sharma et al, 1994; Sengupta and Harewood, 1998).

Ureteropelvic Junction Obstruction and Ureteral Stricture

Despite the growing and successful use of laparoscopic ureteropyeloplasty, endopyelotomy is still a reasonable choice for the management of select patients with ureteropelvic junction (UPJ) obstruction. This can be performed percutaneously, ureteroscopically, or with the Acucise (Applied Medical Resources, Laguna Hills, CA) cutting balloon catheter device. The advantages of the ureteroscopic approach include the ability to control the length and depth of the incision under direct vision, the avoidance of percutaneous renal access, and the ability to perform the procedure in an outpatient setting.

There are two situations in which ureteroscopic endopyelotomy may not be the preferred approach. Patients with concomitant renal calculi should be treated via a percutaneous approach to allow simultaneous removal of the calculi and endopyelotomy. Also, several studies have demonstrated a decreased success rate with endopyelotomy in patients who have vessels crossing at the UPJ (Van Cangh et al, 1994; Bagley et al, 1995; Conlin et al, 1998; Tawfik et al, 1999). **It may be best to limit ureteroscopic endopyelotomy to those patients without known crossing vessels, and treat those with crossing vessels with laparoscopic ureteropyeloplasty.**

Patients with ureteral strictures can also be managed from a ureteroscopic approach. The technique is nearly identical to the ureteroscopic endopyelotomy technique. Endoureterotomy will be less successful in patients with ureteral strictures longer than 1.5 cm, allograft ureters, previously irradiated ureters, ureters draining poorly functioning kidneys, and ureteral-enteral anastomotic strictures (Wolf et al, 1997). Ureteroscopic incision of short ureteral strictures in otherwise healthy ureters is a reasonably successful treatment option.

Other Indications for Ureteroscopy

Diagnostic flexible ureteroscopy can be performed in patients with persistent positive cytology, filling defects, hematuria, and recurrent urinary tract infections localized to a single renal unit. With the miniaturization of flexible ureteroscopes, the safety of flexible ureteroscopy has increased significantly. Rather than relying on ureteropyelography alone, we can now safely and easily perform diagnostic ureteroscopy.

Ureteroscopy has also been used for removal of foreign bodies including suture, proximally migrated ureteral stents, balloon catheters, and other fractured working instruments. The three-pronged grasping forceps are ideally suited for grasping and removing these foreign bodies.

Benign essential hematuria can be diagnosed and treated with flexible ureteroscopy. This condition is defined as unilateral gross hematuria for which there is no radiographically defined cause (Lano et al, 1979; Bagley et al, 1987). These patients frequently have had studies including excretory urography, renal sonography, and/or arteriography. Flexible ureteroscopic inspection of the kidney involved usually results in diagnosis and successful treatment. The most common finding in patients with benign essential hematuria is a small hemangioma, which can often be fulgurated. Other endoscopic findings in patients with benign essential hematuria include small venous ruptures, papillary tumors, varices, and calculi (Dooley and Pietrow, 2004).

Equipment

Semirigid Ureteroscopes

Performance of successful ureteroscopy requires a variety of instrumentation—most important, appropriate and modern ureteroscopes. Although larger rod-lens rigid ureteroscopes are still available in some operating rooms, the smaller-diameter fiberoptic ureteroscopes are less traumatic, less often require ureteral dilation, and are equally effective.

Semirigid ureteroscopes are smaller in diameter because of the incorporation of fiberoptics into their construction. Fiber optic bundles are created from molten glass that has been pulled into small-diameter fibers. Each individual glass fiber is “cladded” with a second layer of glass of a different refractive index. This cladding improves the internal reflection, light transmission, and durability of the fiberoptic bundle. The meshlike appearance of the image from fiberoptic image bundles is caused by the lack of light transmission through this cladding. These fibers uniformly transmit light from one end of the fiber to the other proportional to the light input. The glass fibers of a fiberoptic bundle can be arranged randomly or in a precise orientation with identical location at each end of the fiber (i.e., coherent). When the fibers are grouped randomly, such as those within the light bundle, they provide excellent light transmission for illumination, but no image. When the fibers are arranged in a coherent fashion, the light from each fiber within the bundle will coalesce to transmit images.

Small lenses are attached to the proximal and distal ends of the image bundle to create a telescope. By controlling the number of fibers in the bundle, and the type and orientation of the lenses, the manufacturers can determine the degree of image magnification, field of view, and focusing ability for different fiberoptic endoscopes. For example, by changing the axis of the lens at the distal tip of the image bundle, the angle of view of the ureteroscope can be changed to improve visibility of any working instruments passed out the working channel (Higashihara et al, 1990).

Improvements in image bundle construction have allowed closer packing of more fibers, resulting in improved images, smaller outer diameters, and larger working channels in both rigid and flexible ureteroscopes. Another design modification is the splitting of the light bundle distally into two points of light transmission (Conlin et al, 1997). This makes possible a more centrally placed working channel as well as better distribution of the light within the working field of view.

Current semirigid ureteroscopes typically have tip diameters of 7 Fr or smaller and working channels larger than 3 Fr. Semirigid ureteroscopes have either large single or two smaller individual working channels. **An advantage of the separate working channels is the ability to irrigate through one unrestricted channel while a working instrument occupies the other. Separate working channels also permit passage of a lithotripsy device through the separate channel to fracture a stone that cannot be disengaged from a basket in the other channel.** With a single channel, this can be difficult because of entanglement between the two working instruments.

Eyepieces are commonly “in line” with the ureteroscope, which allows easy introduction of the scope (Fig. 7-7). Offset eyepiece design makes possible a straight working channel for the use of more rigid working instruments such as rigid biopsy forceps or a pneumatic lithotripsy probe (Fig. 7-8). Increased availability and use of the holmium laser for ureteroscopic lithotripsy has decreased the need for ureteroscopes with offset eyepieces.



Figure 7-7. Semirigid ureteroscope with “in-line” eyepiece.



Figure 7-8. Semirigid ureteroscope with an offset eyepiece, which has a straight working channel permitting passage of rigid instruments.

Larger ureteroresectoscopes (11.5 Fr) can be useful for large distal ureteral tumor resection. Some surgeons also preferred using this instrument for ureteroscopic endopyelotomies (Thomas et al, 1996). Preoperative ureteral stenting will be necessary in this setting to allow passage of the larger-diameter ureteroresectoscope, especially to the UPJ.

Currently available semirigid ureteroscopes and their characteristics are listed in Table 7-3.

Flexible Ureteroscopes

The fundamental components of flexible ureteroscopes include the optical system, deflection mechanism, and working channel. The nondigital optical system consists of flexible fiberoptic image and light bundles. Improvements in the fiberoptic image bundles are discussed in the preceding section and are similar to those used in semirigid ureteroscopes.

The deflection mechanism is an integral part of every flexible ureteroscope. It permits complete maneuverability within the intrarenal collecting system (Bagley, 1989). The deflecting mechanism consists of control wires running down the length of the ureteroscope that are attached proximally to a manually operated lever mechanism. The control wires pass through movable metal rings to the distal end of the scope where they are fixed. Moving the lever up or down pulls the control wire through these rings and deflects the tip. When the tip moves in the same direction as the lever, the deflection is said to be “intuitive” (i.e., down is down and up is up). Most modern flexible ureteroscopes allow both up and down deflection in a single plane (Grasso and Bagley, 1994). The plane of deflection is designated by the reticle, seen as a notch within the field of view of the ureteroscope (Fig. 7-9). When the flexible ureteroscope is maneuvered, it must be rotated to align the plane of deflection with the intended target. The active deflection mechanism eventually wears out with repeated use, necessitating repair or replacement of the ureteroscope. Improvements in the construction of the deflecting mechanism with each new generation of flexible ureteroscopes continue to improve durability.

Most current flexible ureteroscopes permit deflection of 180 degrees or more. The amount of deflection necessary to reach the lower pole of the kidney varies among patients. One group of investigators measured ureteroinfundibular angle (between the major axis of the ureter and the lower pole infundibulum) in 30 patients. They determined an average angle of 140 degrees with a maximum of 175 degrees (Bagley and Rittenberg, 1987). Active deflection of the ureteroscope of 180 degrees should allow visualization of the lower pole in most patients. However, reaching into the lower pole calyx with the tip of the ureteroscope in a fashion that allows endoscopic work to be done can still be challenging.

Active deflection occurs only at the distal tip of the ureteroscope, and the deflected segment may not be long enough to reach the lower pole calyx. Most flexible ureteroscopes have a more flexible segment of the ureteroscope because of a weakness in the durometer of the sheath, located just proximal to the point of active deflection. This secondary, passive deflection mechanism addresses the difficulty of reaching the lower pole in some patients. By passive bending of the tip of the ureteroscope off the superior margin of

the renal pelvis, the point of deflection is effectively moved more proximally on the ureteroscope, thereby extending the tip of the ureteroscope. When passive deflection is used, the lower pole calyx can be reached in the majority of patients. Many of the failures to reach the lower pole will occur in patients with significant hydronephrosis, which can limit the ability to engage passive secondary deflection.

To address the difficulties with ureteroscopic access to the lower pole, two innovations in ureteroscope deflection have been developed. These are active secondary deflection and exaggerated deflection. The first ureteroscope incorporating active secondary deflection, the DUR-8 Elite, was developed by Circon-ACMI, now part of Olympus (Center Valley, PA). In addition to active primary deflection of 185 degrees down and 175 degrees up, there is a second control lever for active secondary deflection of 165 degrees, which can be locked in place. Combining both primary and secondary deflection resulted in a maximum deflected angle of 234 degrees (Shvarts et al, 2004). This ureteroscope can assist the urologist to reach the lower pole even under conditions in which access with passive secondary deflection is not possible (Fig. 7-10). Locking the secondary deflection in place simplifies manipulation of the primary deflection within the lower pole calyx. The usefulness of active secondary deflection has been evaluated by Ankem and coworkers (Ankem et al, 2004). In a series of 54 patients, they found the dual deflecting DUR-8 Elite ureteroscope helpful in cases in which the single-deflection flexible instruments failed in accessing and treating upper urinary tract pathology. Despite these advantages, the DUR-8 Elite is no longer manufactured by Olympus, and there is currently no available flexible ureteroscope with active secondary deflection.

Karl Storz Endoscopy (Tuttlingen, Germany) introduced exaggerated deflection with their Flex-X model flexible ureteroscope (Johnson and Grasso, 2004). This modification of the deflection mechanism permits active primary deflection of greater than 300 degrees (Fig. 7-11). When approaching the lower pole calyx, the deflected segment of the ureteroscope will effectively lengthen as it is deflected against the lower pole infundibulum. This improvement of the deflection mechanism results in easier lower pole access and improved deflection when working instruments are used.

All currently available flexible ureteroscopes have working channels of 3.6 Fr diameter. This allows use of instruments up to 3 Fr while still permitting adequate irrigation. When working instruments are used, higher pressure irrigation will be necessary to compensate for the effectively smaller irrigation channel (Bach et al, 2011). This higher pressure irrigation can be delivered using a pressurized irrigation bag, roller pump, or hand-held devices. The development of a dual channel flexible ureteroscope, the Cobra from Richard Wolf (Vernon Hills, IL), is an innovation that can improve irrigation through the ureteroscope. The dual 3.3 Fr channels will permit unimpeded irrigation through one channel while the working instrument occupies the other (Haberman et al, 2011). One may also use both channels for working instruments, such as a laser and a basket, but this is rarely necessary.

Digital Ureteroscopes

Digital flexible ureteroscopes have been developed and released by each of the three primary endoscope manufacturers. Like digital flexible cystoscopes described earlier in this chapter, these ureteroscopes integrate the endoscope, the digital camera, and the light source. A separate camera head is not needed because the scope has a digital camera chip (CCD or complementary metal-oxide semiconductor [CMOS]) mounted on its tip. Because these devices do not require a separate light cord or camera head, they are potentially less prone to damage and may have a prolonged life span.

Currently the digital flexible ureteroscopes available are larger diameter. One group of investigators performed a prospective comparison between digital and fiberoptic ureteroscopes to determine the influence of these larger-diameter digital scopes on patient outcomes. They found a higher use of ureteral access sheaths and related complications in those patients who underwent

TABLE 7-3 Semirigid Ureterscopes (Information Supplied by Manufacturers)

MODEL	EYEPiece	DIAMETER (Fr)	WORKING LENGTH (cm)	NO. OF CHANNELS	SIZE OF CHANNELS (Fr)	FIELD OF VIEW (DEGREES)	ANGLE OF VIEW (DEGREES)	AUTOCLAVABLE
OLYMPUS (WHITE PLAINS, NY)								
MR-6A	Straight	6.9/8.2/10.2	33	2	2.3; 3.4	61	5	Yes
MR-6AL	Straight	6.9/8.2/10.2	43	2	2.3; 3.4	61	5	Yes
MRO-733A	Angled offset	7.7/9.2/10.8	33	1	5.4	65	5	Yes
MRO-742A	Angled offset	7.7/9.2/10.8	42	1	5.4	65	5	Yes
WA29040A	Angled	6.4/7.8/12	43 (WA29040A); 33 (WA29041A)	1	4.2	90	7	Yes
WA29042A	Angled	8.6/9.8/13.5	43	1	6.4	95.1	7	Yes
WA29048A; WA29049A	Straight	6.4/7.8/12	43 (WA29048A) 33 (WA29049A)	1	4.2	90	7	Yes
WA02943A	Angled	7.5	43	2	2.5; 3.6	90	7	Yes
WA02944A	Straight	7.5	43	2	2.5; 3.6	90	7	Yes
WA02946A	Straight	7.5	33	2	2.5; 3.6	90	7	Yes
KARL STORZ ENDOSCOPY (CULVER CITY, CA)								
27001KA/LA	Angled	7/8/12	34 (KA)/43(LA)	1	5		6	Yes
27002KA/LA	Angled	8/9.5/12	34 (KA)/43(LA)	1	6		6	Yes
27003KA/LA	Angled	9/9.5/12	34 (KA)/43(LA)	2	3.8; 5		6	Yes
27000KA/LA	Angled	6/7/9.9	34 (KA)/43(LA)	1	4.8		6	Yes
27010KA/LA	Straight	7/8.4/9.9	34 (KA)/43(LA)	2	2.4; 3.4		6	Yes
RICHARD WOLF MEDICAL INSTRUMENTS (VERNON HILLS, IL)								
8701.517	Straight	4.5/6	33 (517)	2	2.5; 3	75	5	Yes
8701.518			43 (518)					
8701.533	Angled	4.5/6	31.5 (533)	2	2.5;3	75	5	Yes
8701.534			43 (534)					
8702.517	Straight	6/7.5	33 (517)	1	4.2 × 4.6 (oval)	75	5	Yes
8702.518			43(518)					
8702.523	Offset	6/7.5	31.5 (523)	1	4.2 × 4.6 (oval)	75	5	Yes
8702.524			43 (524)					
8702.533	Angled	6/7.5	31.5 (533)	1	4.2 × 4.6 (oval)	75	5	Yes
8702.534			43 (534)					
8703.517 8703.518	Straight	8/9.8	33 (517)	1	5.2 × 6.2 (oval)	75	12	Yes
			43 (518)					
8704.523	Offset	8.5/11.5	31.5 (523)	1	Accepts 6.0	75	12	Yes
8704.524			43 (524)					
8708.517	Straight	6.5/8.5	33 (517)	2	2.55; 4.2	75	5	Yes
8708.518			43 (518)					
8708.533	Angled	6.5/8.5	31.5 (517)	2	2.55; 4.2	75	5	Yes
8708.534			43 (518)					

ureteroscopy performed with a digital ureteroscope (Bach et al, 2012). In another analysis of the efficacy of digital and flexible ureteroscopes, investigators determined a statistically equivalent stone-free rate but a significantly shorter operative time in the digital group (Somani et al, 2013). This is presumed to be a result of the improved visibility of the digital ureteroscopes (Fig. 7-12). These digital ureteroscopes may advance future miniaturization, optimize digital resolution, and improve durability.

The specifications of currently available flexible ureteroscopes are detailed in Table 7-4.

Care and Sterilization

Rigid and especially flexible ureteroscopes are very delicate instruments and need to be handled accordingly. Any damage to the working channel, deflecting mechanism, or fibers within the image bundle can render the ureteroscope useless. One series reported that repairs of flexible ureteroscopes were necessary after only 3 to 13 hours of use (Afane et al, 2000). The repairs were usually caused by deterioration of the deflecting mechanism.

The working channels of flexible ureteroscopes are also easily damaged. This primarily occurs during passage of the small (200 μ) holmium laser fiber. When the fiber is introduced into a flexible ureteroscope that is even minimally deflected, the tip of the fiber may scrape the inner working channel. This can raise a small irregular area of the channel that will be more prone to damage.

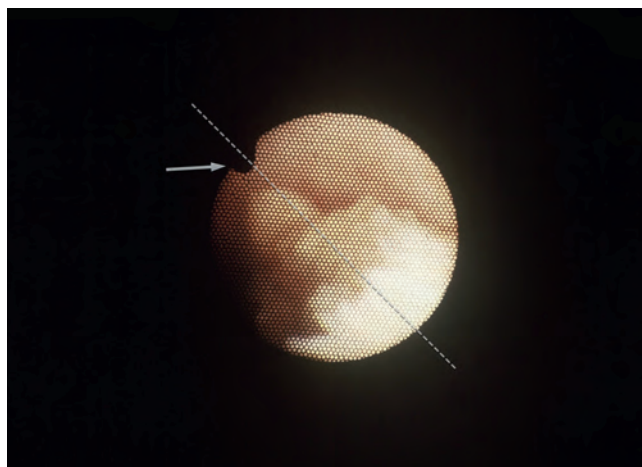


Figure 7-9. Flexible ureteroscopic image showing the reticle (arrow), which designates the plane of deflection (dotted line).

With each future pass of a laser fiber, the working channel can be increasingly damaged and ultimately perforated by the fiber. Once perforated, sterilization of the flexible ureteroscope will result in fluid damage to the imaging system of the scope, making the scope unusable. **Firing the fiber within the working channel will also result in damage. The holmium laser may damage the working channel when the tip is very near the end of the working channel (Fig. 7-13).** To prevent this, the tip of the fiber must be seen in the central portion of the field of view. **The golden rule of safe holmium laser lithotripsy is “Do not step on the pedal if you cannot see the tip of the fiber in contact with the stone.”** This will prevent injury to the ureter, as well as damage to the ureteroscope.

A recent development in flexible ureteroscope design is the ability of the video system to prevent laser activation when the laser fiber is too close to the tip of the endoscope (Xavier et al, 2009). This “endoscope protection system” is activated in response to the video imaging system not “seeing” the blue color of the outer cladding of the laser fiber. When this “proximity alert” is activated, the laser will automatically pause firing to prevent damage to the scope.

Ureteroscopes, including the working channel, should be cleansed with warm water and a nonabrasive detergent after each use. Sterilization of ureteroscopes can be performed by gas (ethylene oxide), by soaking in a glutaraldehyde solution, or by use of the STERIS system (STERIS, Mentor, OH) (Gregory et al, 1988). The STERIS system provides automated washing and rinsing of the endoscopes in a peracetic acid solution.

Guidewires

Guidewires are essential to endourologic procedures. They are used for many portions of these procedures including establishment of percutaneous and ureteroscopic access, for straightening of the ureter, as a guide for dilation of the ureter or percutaneous tract, and for stent placement. There are many guidewires available differing in diameter, rigidity, tip design, materials, and coating. The choice of the most appropriate wire depends on the task involved and the patient’s anatomy and upper urinary tract problem being confronted.

The most common design is a solid stainless steel core around which an outer wire is wrapped. Nitinol (nickel-titanium) can be used for inner core construction, and this gives guidewires a kink-resistant, slightly stiffer character. Many newer wires (Zebra wire, Boston Scientific, Natick, MA; Roadrunner wire, Cook Medical, Bloomington, IN) have a nitinol core wire and polyurethane outer layer. These wires are well suited for passage of the ureteroscope because there is less friction of the ureteroscope over the polyurethane, and the stiffer core allows more reliable transmission of the “push” from the urologist to the tip of the ureteroscope. Angling of the tip is also possible because of the “memory” quality of the

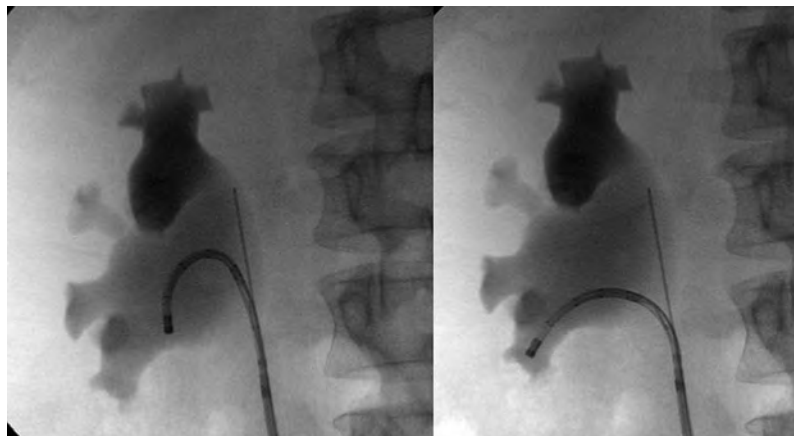


Figure 7-10. Inability to access the lower pole calyx with typical primary deflection (left). Successful access of the lower pole using active secondary deflection (right).

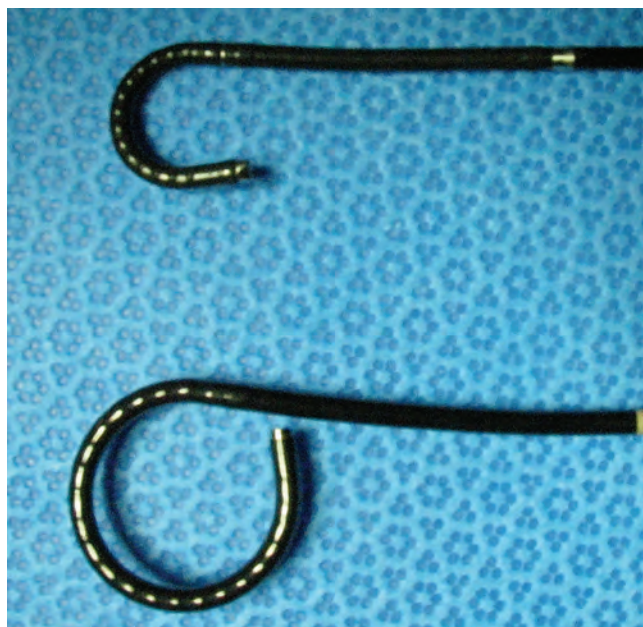


Figure 7-11. Flexible ureteroscopes with standard primary deflection (*top*) and exaggerated primary deflection (*bottom*).

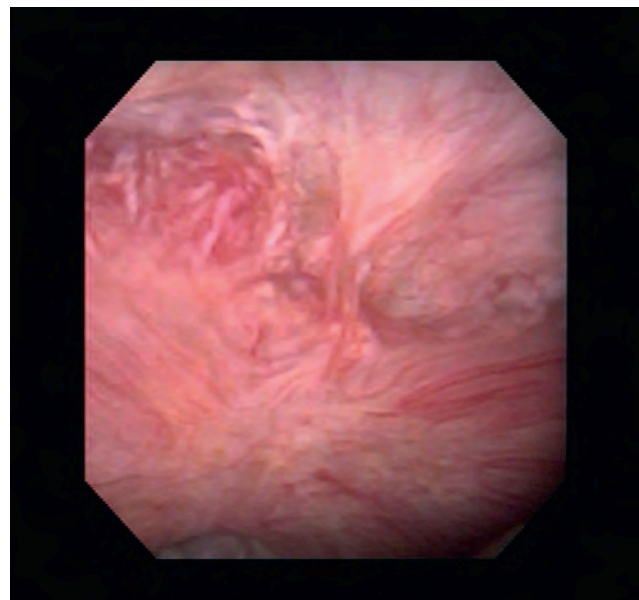


Figure 7-12. Excellent optical clarity of a digital ureteroscope image of a compound calyx.

TABLE 7-4 Flexible Ureteroscopes (Information Supplied by Manufacturers)

CHARACTERISTIC	OLYMPUS				KARL STORZ		RICHARD WOLF	
	URF-V	DUR-D	URF-P5	URF-P6	FLEX-XC	FLEX-X2	VIPER	COBRA
Digital or fiberoptic?	Digital	Digital	Fiberoptic	Fiberoptic	Digital	Fiberoptic	Fiberoptic	Fiberoptic
Tip diameter (Fr)	8.5	8.7	5.3	4.9	8.5	7.5	6.0	6.0
Shaft diameter (Fr)	9.9	9.3	8.4	7.9	8.5	8.4	8.8	9.9
Working length (cm)	67	65	70	67	67.5	70	68	68
Channel size (Fr)	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.3 (x2)
Up deflection (degrees)	180	250	180	275	270	270	270	270
Down deflection (degrees)	275	250	275	275	270	270	270	270
Angle of view (degrees)	0	9	0	0	0	0	0	0
Field of view (degrees)	90	80	90	90	90	85	85	85
Depth of field (mm)	2-50	2-40	2-50	2-50	Focal length = 15 mm	2-40	2-40	2-40
Magnification (x)	Digital zoom	Digital zoom	52	52	Digital zoom	50	50	50
Comments							Digital model soon	Dual channels; digital model soon

nitinol material. When the outer polyurethane layer is coated with a hydrophilic polymer, these wires become exceptionally slippery. These “glide wires” are useful for negotiating around impacted ureteral calculi, tortuous ureters, and ureteral strictures. **Hydrophilic-coated wires are too slippery to be reliable safety wires, because of their tendency to slide out of the patient. When these wires are used for initial access, they are exchanged for a standard safety wire through an open-ended catheter.** A new hybrid designed wire (Sensor, Boston Scientific, Natick, MA) incorporating

a hydrophilic tip with a standard polytetrafluoroethylene (PTFE)-coated shaft may serve as both an access and safety wire for procedures in which access is difficult.

Guidewires for urology range in diameter from 0.018 to 0.038 inch, the most commonly used being 0.038 inch. Lengths vary from 80 to 260 cm. The most useful length for endourology is 145 cm. The tips of these wires are typically “floppy” for 1 to 3 cm. Benton and Newton wire designs have flexible tips of up to 15 cm and are seldom used today. Some wires have a movable core that can be



Figure 7-13. Image of the tip of a flexible ureteroscope that has been damaged by firing of the holmium laser within the working channel (arrow).

partially withdrawn to increase the length of the flexible tip. Other variable characteristics in guidewire construction include the distal tip design and the wire stiffness. The distal tip can be straight, angled, or J tipped. The rigidity of the wires can be varied by changing the diameter and design of the inner core wire. Stiffer wires can be useful for straightening out tortuous ureters or displacing a large prostatic lobe.

The choice of the most appropriate guidewire for the endourologic task at hand can mean the difference between success and failure. Despite all of these advances in wire design and construction, a 0.038-inch diameter, straight, flexible-tip, Teflon-coated, stainless steel wire is still a good choice for most cases.

Dilation Devices

Ureteral dilation is less necessary for ureteroscopy with the advent of newer, smaller-diameter ureteroscopes. Hudson and colleagues determined that the need for dilation was directly related to the diameter of the ureteroscope and was as low as 0.9% for 7.4-Fr diameter scopes (Hudson et al, 2005). When needed, ureteral dilation can be accomplished passively with indwelling stent placement or actively with dilating catheters or balloons. Ureteral dilating catheters are hydrophilic-coated polyurethane catheters tapered from a 6-Fr tip to a 12-Fr shaft and are passed over a wire to dilate the ureter (Gaylis et al, 2000). Ureteral balloon dilators are also passed over a wire, have a low profile of 3 to 8 Fr, and have dilation diameters of 12 to 30 Fr. **Dilation of the ureter beyond 15 Fr is rarely necessary for routine ureteroscopy.** Balloons can have maximum inflation pressures of 8 to 20 atmospheres depending on the design and the balloon material. Zero-tipped design ureteral balloon dilators are useful for dilating immediately adjacent to an impacted ureteral calculus. Ureteroscopic balloon dilators are 3 Fr in size, can be inflated to 12 Fr, and are passed directly through the ureteroscope. They are used to dilate under direct vision such as dilation of stenotic infundibula or calyceal diverticular necks. Once inflated, these ureteroscopic balloons cannot be removed through the ureteroscope but must be removed together with the ureteroscope.

Intraluminal Lithotripsy Devices

Intraluminal lithotripsy can be performed with several different modalities. Electrohydraulic lithotripsy (EHL) is widely available worldwide and is cost effective. Fragmentation of calculi is produced by shock waves generated from an electric spark produced on the tip of the electrode (Denstedt and Clayman, 1990). Fragmentation of most calculi is good but can be less effective for more dense calculus compositions such as cystine or calcium oxalate monohydrate. The small flexible EHL probes can be used with both rigid and flexible ureteroscopes. EHL can cause ureteral trauma because the energy is poorly focused. Although this rarely results in stricture formation, it can hinder visibility.

Pneumatic lithotripsy devices fragment calculi using mechanical ("jackhammer") energy (Schulze et al, 1993). Fragmentation is very good, and the potential for ureteral injury is low. Unfortunately, the mechanical energy can produce significant stone retropulsion. In general, the rigid probes are limited to use with rigid scopes. There are flexible probes available that can be used with flexible ureteroscopes, but they significantly limit scope deflection (Zhu et al, 2000).

The first laser successfully used for intraluminal lithotripsy was the pulsed dye laser. This laser energy is essentially no longer used because of the inability to fragment certain compositions of calculi, and the high cost of purchase and maintenance. The holmium:YAG laser has become the intraluminal lithotripsy energy of choice. It has a wavelength of 2100 nm, which is absorbed in 3 mm of water, making it very safe for use in urology (Blomley et al, 1995). Fragmentation is produced by a photothermal reaction with the crystalline matrix of calculi and produces stone dust rather than fragments, effectively removing a moderate volume of the stone (Zagone et al, 2002). The flexible quartz fibers can be used with both rigid and flexible ureteroscopes and are reusable. The holmium laser is effective for any composition of calculi (Bagley and Erhard, 1995; Denstedt et al, 1995; Erhard and Bagley, 1995; Grasso, 1996).

The thulium fiber laser (TFL) has been investigated as a potential alternative to the holmium laser for endoscopic lithotripsy. The TFL has a higher absorption coefficient and shorter optical penetration in water, which results in a 4-times lower ablation threshold for the TFL compared with the holmium laser. It is also a diode-pumped laser (holmium is flashlamp pumped), allowing greater control over the pulse length and duration (Hutchens et al, 2013). Most important, the TFL has been shown in vitro to have 5- to 10-times higher rates of stone vaporization than the holmium laser (Blackmon et al, 2010). There are still some practical fiber issues that need to improve before this laser can become commercially available, but it is a promising new development in endoscopic lithotripsy.

Stone Retrieval Devices

The components of stone retrieval devices include the control handle, the control wire, the sheath, and the device itself. Stone retrieval devices have shaft diameters that vary in size from 1.9 to 7.0 Fr. Devices for ureteroscopy are 3.0 Fr, and larger sizes can be used for cystoscopic or percutaneous procedures.

Three-pronged stone-grasping forceps are the safest instruments for removing calculi with the flexible ureteroscope. They permit disengagement of calculi that have been found to be too large to be safely removed from the ureter. In addition, the weak grasp will release the stone if too much force is applied, preventing damage to the ureter. This is critical when performing flexible ureteroscopy because there is no second channel to permit fragmentation of an unyielding stone trapped within a basket. Rigid ureteroscopes with two working channels have this additional degree of safety, permitting more routine use of baskets for removal of ureteral calculi. Although three-pronged graspers are the safest devices for ureteroscopic stone removal, they are seldom used because of improvements in the design and safety of stone baskets.

Stone baskets are available in helical, flat-wire, and other shapes. Baskets can also vary in the number and type of wires used. Two sheathing materials, PTFE and polyimide, are commonly used for

working instruments including stone baskets. A sheath made of polyimide is very durable but stiff and limits deflection of the flexible ureterscope. PTFE does not limit deflection as much as polyimide but is less durable and prone to stretching. Hybrid sheath designs incorporate Teflon at the tip and polyimide in the shaft, maximizing the advantages of each material. Helical baskets can be made with three-, four-, or double-wire designs with six or more wires. The double-wire designs have improved opening strength, which may facilitate removal of impacted calculi. Other basket designs such as the Parachute and LithoCatch from Boston Scientific (Natick, MA), the NCompass and NTrap from Cook Medical (Bloomington, IN), and the Sur-Catch basket from Olympus (Center Valley, PA) have more wires exposed on the distal end of the basket, making them effective for removing multiple small fragments. Helical baskets have round wires and, unlike flat-wire baskets, are safe to rotate within the ureter. They are opened above the stone and pulled down while rotating the basket to engage the stone.

Flat-wire baskets are nonhelical and are designed to have larger spaces among the four wires to allow engagement of larger stones. They were originally designed for percutaneous use, where, by filling the calyx when opened, they could more easily engage calyceal stones. They are also useful for biopsy of papillary ureteral tumors (Bagley, 1998).

There are two basket designs that attempt to combine the safety of three-prong graspers with the reliable grasp of baskets, the Graspit from Boston Scientific (Natick, MA) and NGage from Cook Medical (Bloomington, IN). These tipless devices open like three-pronged graspers and are advanced onto the stone, permitting easier disengagement of a calculus that is too large to be safely withdrawn from the ureter.

The latest material innovation is the use of nitinol for the basket wires. The soft nitinol wires have memory, maintain their shape, resist kinking, and therefore open more safely and allow disengagement of stones more reliably than stainless steel baskets. The unique qualities of nitinol also allow basket construction in a tipless fashion. These tipless baskets are soft and safe for use in the ureter and can be more fully deployed in a calyx without the interference from the tip, unlike stainless steel baskets.

Retropulsion Prevention Devices

Any type of intraluminal lithotripsy within the ureter will risk propelling the stone upward ("retropulsion"). The amount of retropulsion depends on the size and location of the stone, the degree of ureteral dilation, and the lithotripsy energy being used. If the stone is pushed back into the kidney, passing the flexible ureterscope into the kidney and treating the stone there is usually not a problem. However, prevention of retropulsion may be more time efficient and is particularly important when no flexible ureterscope is available.

Several devices are designed to prevent retropulsion of ureteral stones (Fig. 7-14). The Stone Cone and BackStop (Boston Scientific, Natick, MA), the NTrap (Cook Medical, Bloomington, IN), and the Accordion and CoAx (Accordion Medical, Indianapolis, IN) (Eisner et al, 2009; Wang et al, 2011; Wu et al, 2013). The Stone Cone is a 3-Fr device with a distal coil that can be deployed above the stone before fragmentation to help prevent stone migration. After fragmentation of the stone, it can be withdrawn to remove fragments. Any fragments too large to safely remove will be left behind because the coil simply unravels around the stone. The NTrap device is similar, 3 Fr, and is deployed above the ureteral stone. It is a meshlike wire basket that deploys perpendicular to the shaft, preventing migration of all but the smallest stone fragments. A recent development in the prevention of stone retropulsion is the BackStop device (Rane et al, 2010). This is a reverse-thermosensitive gel that is injected above the stone, conforming to and completely occluding the ureter. The deployment catheter can then be removed from the ureter, preventing hindrance of the ureteroscopic procedure. The gel is then dissolved by irrigating with cold saline solution.

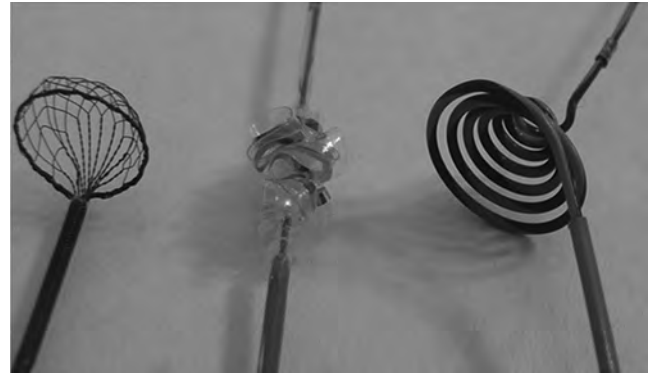


Figure 7-14. Stone migration devices designed to prevent stone retropulsion during lithotripsy. *Left to right*, NTrap (Cook Medical, Bloomington, IN), Accordion (PercSys, Palo Alto, CA), and Stone Cone (Boston Scientific, Natick, MA).



Figure 7-15. The distal (*top*) and proximal (*bottom*) portions of a typical ureteral access sheath. The distal portion of the internal obturator (*blue*) is tapered. The access sheath is placed over a super-stiff guidewire, and the internal obturator is removed before ureterscope insertion. The proximal end of the obturator accepts a Luer-Lock syringe, facilitating retrograde pyelography.

Miscellaneous Devices

Other devices are available for ureterscope use. Small 3-Fr cup biopsy forceps can be used to perform biopsy of sessile tumors. A larger biopsy forceps, the BIGopsy (Cook Medical, Bloomington, IN) provides a much larger biopsy specimen, which may improve diagnostic yield (Wason et al, 2012). The large forceps requires backloading of the device into the ureterscope, and after the biopsy it must be removed together with the ureterscope. Electrodes are available in various shape including pencil point, ball point, and angled and straight tips. These can be used for fulguration and incision procedures such as endoureterotomy and endopyelotomy.

Ureteral Access Sheaths

Ureteral access sheaths allow repeated access to the intrarenal collecting system without having to replace the working guidewire with each passage of the endoscope (Fig. 7-15). They are available in 11- to 16-Fr sheath outer diameters. Currently available ureteral access sheaths are listed in Table 7-5.

In addition to facilitating stone fragment retrieval, access sheaths have been shown to decrease the intrapelvic pressure during ureteroscopy, which may decrease the risk of infectious complications from pyelovenous backflow (Auge et al, 2004). Their primary disadvantage is related to their size and their (small) potential for ureteral injury (Delvecchio et al, 2003; Traxer et al, 2013). Furthermore, the majority of intrarenal stones require only a single passage of the ureterscope to access and fully fragment the calculi. For these patients, an access sheath is usually unnecessary.

TABLE 7-5 Access Sheaths (Information Supplied by Manufacturers)

MANUFACTURER	SHEATH NAME	DILATOR/SHEATH (Fr)	LENGTHS (cm)	UNIQUE FEATURES
Boston Scientific	Navigator	11/13	28, 36, 46	
		13/15		
	Navigator HD	11/13	28, 36, 46	
		12/14 13/15		
Applied	Forte (AxP and HD)	10/12-16; 12/14-18; 14/16-18	20, 28, 35, 45, 55	
	Forte Plus	10/14	35, 55	
Bard Cook	AquaGuide	10/12-14; 11/13-15	25, 35, 45, 55	Dual-lumen design
	Flexor	9.5/11; 12/13.7; 14/16	13, 20, 28, 35, 45, 55	Dual-lumen design Rapid release design for single wire external to sheath
	Flexor DL	9.5/14; 12/16.7	13, 20, 28, 35, 45, 55	
	Flexor Parallel	9.5/11; 12/13.7; 14/16	13, 20, 28, 35, 45, 55	
Olympus	UroPass	12/14	24, 28, 54	

Fluoroscopy Equipment

Fluoroscopy is critical for ureteroscopic procedures and is needed for initial ureteral access, monitoring during endoscopy, and stent placement. Although tables designed for urologic endoscopy with fixed fluoroscopy units are available, mobile C-arm fluoroscopy units are preferable. **C-arm fluoroscopy units allow greater mobility, improved image quality, and less scatter radiation exposure to the surgeon because the x-ray source is below the patient.** Modern C-arm fluoroscopy units incorporate digital enhancement of the image and “last image hold” technology to minimize radiation exposure. Exposure can also be decreased by using image collimation and pulsed fluoroscopy. The urologist should control the fluoroscopy unit with foot pedal control, which will facilitate the speed of the procedure and minimize excessive fluoroscopy time. When possible, collimation and pulsed fluoroscopy should be employed to further limit exposure.

Ureteroscopy Technique

Preparation for Ureteroscopy

Upper tract imaging is performed to fully delineate the pathologic process being treated and to define the collecting system anatomy. This can be accomplished via intravenous pyelography or, more commonly, helical CT scan. Urinary tract infections are treated preoperatively, and infections above an obstruction are drained. **According to the AUA Best Practice Policy Statement, a routine preoperative antibiotic (first line, a fluoroquinolone) is given to all patients unless a culture provides antibiotic sensitivities for more targeted therapy (Wolf et al, 2008).** Anesthesia can be general (endotracheal or laryngeal mask), regional, or local with sedation (Vögeli et al, 1993; Hosking et al, 1996). It is important to communicate to the anesthesiologist the need for the patient to remain still throughout the procedure. Significant patient movement during rigid ureteroscopy can result in ureteral injury or perforation.

Endourologic procedures should be performed in a fully equipped operating room. The urologist should be prepared for any unanticipated problem encountered. In addition to routine Teflon-coated stainless steel guidewires, angled hydrophilic, nitinol core, and extra-stiff guidewires should be readily available. Dilation devices including dilating catheters, high-pressure balloon catheters, and zero-tipped balloon catheters are standard. Angled catheters that can be reliably rotated or “torqued” are very useful for gaining access around impacted calculi, strictures, or tortuous ureters. These include the Imager II catheter (Boston Scientific, Natick, MA) and the Kumpe catheter (Cook Medical, Bloomington, IN). The urologist should be very familiar with the endoscopes

available and the size of their working channels to choose appropriately sized working instruments when needed (see Tables 7-3 and 7-4). The largest working channels of most of the fiberoptic rigid ureteroscopes are just over 3 Fr, so instruments 3 Fr or smaller are appropriate. Backup flexible and semirigid ureteroscopes should also be available to ensure availability of appropriately functioning endoscopic equipment to treat pathology regardless of location in the upper urinary tract. A list of common items needed for successful ureteroscopy is provided in Box 7-3.

Accessing the Ureter

The patient is placed in the cystolithotomy position. If a longer rigid ureteroscope is being used, the contralateral leg is elevated to allow for easier introduction of the ureteroscope. With the advent of improved flexible ureteroscopes, most rigid ureteroscopy is confined to below the iliac vessels, and shorter rigid ureteroscopes can be routinely used, decreasing interference from the contralateral leg.

Cystoscopy is performed, primarily to place a safety guidewire but also to fully inspect the bladder. Usually a simple 0.038-inch diameter flexible-tip Teflon-coated guidewire is sufficient. A safety guide is critical during rigid ureteroscopy to maintain access and allow placement of a ureteral stent if any problems are encountered. Care must be taken when trying to gain access around an impacted stone because the ureter can easily be perforated. Manipulation of the guidewire around the stone may require use of an angled hydrophilic-coated wire, an angled torqueable catheter, or both. If a guidewire cannot be safely passed beyond the stone, direct inspection of the ureter up to the stone with the rigid ureteroscope will permit passage of the wire under direct vision. Once access above the stone has been achieved, the hydrophilic wire is exchanged for a more secure standard 0.038-inch diameter Teflon-coated guidewire. If there is any suspicion about possible infection above the stone, an open-ended catheter should be passed over the wire to aspirate the renal pelvis. The hydronephrosis can be decompressed to permit irrigation; if the fluid appears very cloudy, a stent is placed and the ureteroscopy is canceled until the infection has been treated. Before the ureteroscopy proceeds, the bladder is drained to permit accumulation of irrigation fluid during ureteroscopy and minimize buckling of the flexible ureteroscope into the bladder (Fig. 7-16).

Semirigid Ureteroscopy Technique

Because flexible ureteroscopes better accommodate the natural tortuosity of the ureter and with deflection provide better access to the intrarenal collecting system, semirigid ureteroscopy is usually limited to the ureter distal to the iliac vessels. The rigid ureteroscope is passed through the urethra and into the bladder

BOX 7-3 Common Supplies for Ureteroscopy**URETEROSCOPES****Rigid**

7-Fr or smaller semirigid ureteroscope

Larger ureteroscope with straight working channel (optional)

Flexible

7.5 Fr

8.6 Fr or larger

Secondary deflection or exaggerated deflection capable ureteroscope

DISPOSABLE SUPPLIES**Guidewires**

0.038 Angled hydrophilic

0.038 Straight Teflon coated

0.038 Nitinol core, polyurethane coated

0.038 Extra stiff

Irrigation

Power irrigation device

High-pressure working port seal

Stone Retrieval Devices (3.0 Fr or smaller)

Helical basket

Tipless basket

Three-pronged grasping forceps or equivalent

Catheters

Dual-lumen catheter

6- to 12-Fr dilating catheter

5-Fr open-ended catheter

5-Fr angled-tip torqueable catheter

Dilation Devices

High-pressure ureteral dilating balloons (5 to 7 mm)

Zero-tipped ureteral dilating balloon

Biopsy Devices

3-Fr cup biopsy device

Flat-wire basket

BiGopsy (optional)

Ureteral Stents

5- to 7-Fr, 20- to 28-cm double pigtail

INTRALUMINAL LITHOTRIPSY DEVICES

Holmium laser

Pneumatic (optional)

Electrohydraulic (optional)

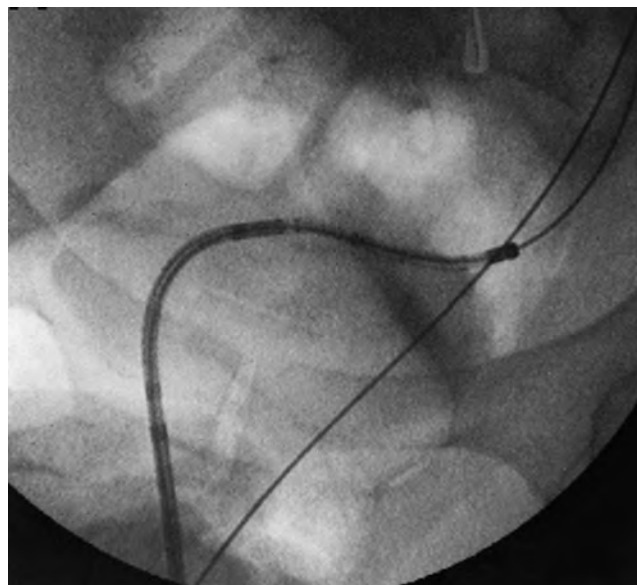


Figure 7-16. The bladder should be emptied before flexible ureteroscope passage to prevent buckling of the instrument within the bladder if resistance is met at the ureteral orifice.

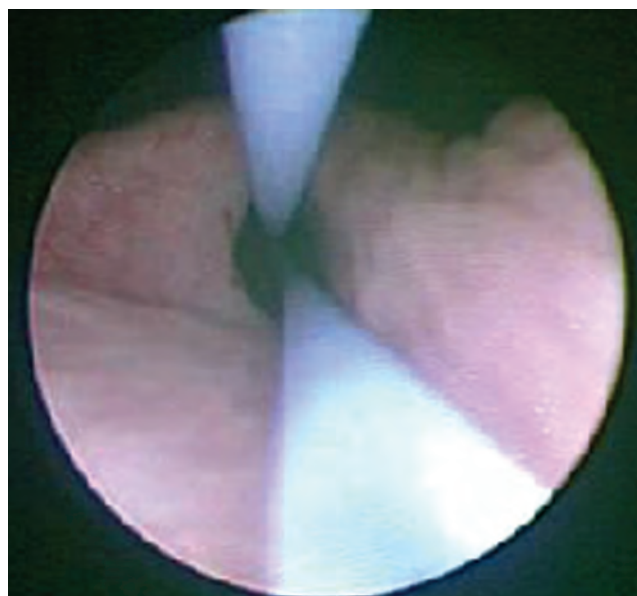


Figure 7-17. Semirigid ureteroscope passage between two wires ("railroad" technique). After safety wire placement (*bottom wire*), a second wire (*top wire*) is passed through the working channel and up the ureter under fluoroscopic guidance and used to "tent open" the ureteral orifice. The ureteroscope is then gently advanced between the wires until ureteral access has been achieved.

under direct vision, usually with the aid of the video camera. Following the guidewire permits easy identification of the ureteral orifice.

By maneuvering the tip of the ureteroscope next to the guidewire posterolaterally, the physician can elevate the wire, thereby propping the ureteral orifice open to allow scope passage. If necessary, an additional guidewire can be passed through the ureteroscope just proximal to the intramural ureter. The ureteroscope is then rotated until it is directly between the two wires, which will hold the orifice wide open for entry of the scope (Fig. 7-17). Once the ureteroscope is through the intramural ureter, the additional guidewire can be

removed. This technique can also be useful for negotiating through tortuous segments of ureter and above the iliac vessels.

If the intramural ureter is too tight to allow safe passage of the ureteroscope, a dilating balloon catheter can be used to expand the orifice. In general, a 4-mm diameter balloon is sufficient. If there is a stricture beneath the stone that prevents safe visualization and lithotripsy, dilation beneath the stone is performed with a zero-tipped dilating balloon catheter. This balloon catheter can be passed over the safety wire immediately below the stone so dilation of the stenotic segment can be performed. The ureteroscope can then be safely introduced and the stone visualized. If the stone is impacted,

it can be helpful to gently manipulate it with the tip of the ureteroscope proximally out of the traumatized area of ureter for improved visibility and safer lithotripsy. If this is not possible, the holmium laser energy can be used in a “drill and core” technique. This will ablate the central portion of the stone, and the outer shell of the stone will protect the ureteral wall. The outer shell can then be safely fragmented. The stone can be fragmented until no fragments are greater than 2 mm, or alternatively it can be cleaved until the fragments are small enough to be easily removed with a helical basket. A stent is placed and in general is left for 3 to 7 days.

Flexible Ureteroscopy Technique

The cystoscope is removed and a dual-lumen catheter is passed over the initial guidewire. This dual lumen catheter is 10 Fr, which will gently dilate the ureteral orifice and allow placement of a second, working wire. The flexible ureteroscope is then passed in a monorail fashion over the taut working wire to the point of the pathology being treated. Dilation of the ureteral orifice with the dual-lumen catheter is usually sufficient to permit passage of the flexible ureteroscope. The working channel of flexible ureteroscopes is not centrally located, so the tip of the ureteroscope will be eccentrically positioned in relation to the guidewire. If the flexible ureteroscope does not pass the ureteral orifice, the scope should be rotated 90 to 180 degrees on the guidewire to better position the tip of the ureteroscope relative to the ureteral orifice. If difficulty passing the flexible ureteroscope through the ureteral orifice is still encountered, a dilating catheter (Nottingham) or a dilating balloon catheter can be used to dilate the ureteral orifice. **Formal ureteral dilation is reported in most ureteroscopy series to be needed in 8% to 25% of patients; this incidence has obviously decreased with the advent of smaller-diameter flexible ureteroscopes (Elashry et al, 1997; Grasso and Bagley, 1998; Tawfik and Bagley, 1999).**

If passing the flexible ureteroscope up the ureter is difficult in the absence of any significant ureteral stricture or other source of obstruction, the use of a nitinol core polyurethane-coated guidewire may be helpful. As previously discussed, these stiffer, smoother wires enable more efficient transmission of the push from the urologist to the tip of the ureteroscope.

The basic movements of the flexible ureteroscope include deflecting, rotating, and advancing and retreating the ureteroscope. The reticle of the flexible ureteroscope marks the plane of deflection, and rotation of the ureteroscope is often necessary to align this plane of deflection in the direction desired. **Failure to adequately rotate the ureteroscope is the most common mistake of the novice ureteroscopist.** Irrigation through the ureteroscope should be provided with a pressurized irrigation bag, roller pump, or hand-held syringe. **Normal saline should be used to prevent accumulation and absorption of hypotonic solution and resultant transurethral resection (TUR) syndrome.**

When the holmium laser is used, it is important to pass the laser fiber through a straightened flexible ureteroscope (confirmed fluoroscopically) to prevent damage to the working channel. Once the fiber has been passed beyond the tip, the ureteroscope can be deflected appropriately. The most commonly used sizes of holmium laser fibers include the 365-micron fiber and the 200-micron fiber. When significant deflection of the ureteroscope is needed, the 200-micron fiber is preferred because it does not limit the deflection of the ureteroscope as much as the larger fibers. The tip of the fiber must be in contact with the stone during treatment because the holmium laser energy is absorbed in 3 mm of water. **The holmium laser can damage the ureteroscope, the guidewire, and the ureteral wall. These problems can be avoided by not activating the laser unless the tip of the fiber is seen to be in contact with the stone (Beaghtler et al, 1998).** In addition, if the helium-neon aiming beam is not seen, the laser should not be activated because this may be an indication of fiber damage. Firing the holmium laser through a broken fiber can cause significant damage to the ureteroscope.

Once the pathology has been adequately addressed, a ureteral stent is typically placed and left indwelling for 3 to 5 days.


Postoperative pain management can be facilitated with the use of a cyclooxygenase-2 (COX-2) inhibitor and/or an α -adrenergic blocker (Nazim and Ather, 2012).

KEY POINTS: URETEROSCOPY

- Semirigid ureteroscopy is used below the iliac vessels and flexible ureteroscopy above.
- Semirigid ureteroscopes with two working channels permit better irrigation and offer the added safety of being able to pass a lithotripsy device through one channel when needing to fragment a stone engaged in a basket in the other channel.
- Flexible ureteroscopes must be straight during passage of a laser fiber or the working channel will be damaged.
- The golden rule of safe laser lithotripsy is “Do not step on the pedal if you cannot see the tip of the fiber in contact with the stone.”
- Stone baskets made of nitinol maintain their shape, resist kinking, and allow disengagement of stones more reliably than stainless steel baskets.
- Ureteral access sheaths facilitate repeated passage of flexible ureteroscopes and decrease the intrapelvic pressure during ureteroscopy.
- Mobile C-arm fluoroscopy is preferred because of greater mobility, improved image quality, and less scatter radiation exposure to the surgeon compared with urology tables with fixed fluoroscopy units.
- A routine preoperative antibiotic should be given to all patients undergoing ureteroscopy.
- Normal saline should be used for irrigation during ureteroscopy to prevent absorption of a hypotonic solution.

CONCLUSIONS

Over the past 150 years tremendous advances have been made in endoscope design, revolutionizing urologic surgery. Visualization of both the upper and lower urinary tracts is now routinely performed with rigid and flexible endoscopes. A variety of urologic conditions can be evaluated efficiently with minimal discomfort in the office by flexible cystoscopy. A wide array of benign and malignant conditions affecting the bladder and urethra can be managed transurethrally with rigid cystourethrosopes in the operating room with limited morbidity. Improvements in flexible ureteroscopes, working instruments, and endoscopic techniques have significantly improved our ability to effectively treat upper urinary tract problems as well. With continued innovation and refinement, the role of ureteroscopy in the treatment of complex intrarenal calculi, ureteral obstruction, and upper tract tumors should continue to expand.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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8

Percutaneous Approaches to the Upper Urinary Tract Collecting System

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History and Introduction

Indications for Percutaneous Access

Anatomic Considerations

Obtaining Percutaneous Access

Postprocedural Nephrostomy Drainage

Training in Percutaneous Access and Procedures

Complications

HISTORY AND INTRODUCTION

Commonly ascribed to [Goodwin and colleagues \(1955\)](#), the first therapeutic percutaneous nephrostomy was actually performed by Thomas Hillier in 1865 ([Bloom et al, 1989](#)). Hillier, at the Hospital for Sick Children at Great Ormond Street, repeatedly aspirated the hydronephrotic kidney of a young boy for symptom relief throughout a 4-year period until his death at 8 years of age. Subsequently there were a few reports of diagnostic percutaneous renal aspirations, but it was not until Goodwin and colleagues published their landmark report in 1955 that therapeutic percutaneous nephrostomy was rediscovered. Even then, the use of percutaneous access to the upper urinary tract collecting system was limited to drainage of obstructed kidneys until [Fernström and Johansson \(1976\)](#) described the percutaneous removal of renal calculi, termed “percutaneous pyelolithotomy.”

In the years since that report appeared, a number of procedures have been performed using the convenient and safe percutaneous route to access the upper urinary tract collecting system, including drainage of an obstructed kidney, nephrolithotomy, endopyelotomy, and resection of urothelial tumors. More recently, percutaneous access to portions of the kidney other than the collecting system has expanded the diagnostic and therapeutic choices for patients with renal diseases. Other chapters in this book address these indications, including Chapters 57 and 62. This chapter addresses only percutaneous access to the upper urinary tract collecting system, focusing on the creation, maintenance, and postprocedure management of the percutaneous tract. The final section of the chapter reviews the general complications of percutaneous access to the upper urinary tract collecting system. Specific aspects of the procedures performed through the percutaneous access are covered in Chapters 6, 49, 54, and 58.

INDICATIONS FOR PERCUTANEOUS ACCESS

Simple Drainage or Access

Percutaneous drainage of the upper urinary tract collecting system can be for diagnostic or therapeutic indications. **The only remaining popular indication for diagnostic percutaneous nephrostomy is to perform a Whitaker test**, which requires placement of a small-caliber nephrostomy tube through which contrast material is instilled at specific flow rates while pressures are measured to assess for ureteral obstruction (see a more detailed description in Chapter 49). In other cases, diagnostic nephrostography is performed as an adjunct to therapeutic percutaneous nephrostomy.

Therapeutic percutaneous nephrostomy tubes can be placed to drain the kidney (see Chapter 6) to access the upper urinary tract for direct instillation of therapeutic agents (see Chapter 58) or to perform a surgical procedure. **Percutaneous nephrostomy is indicated to drain the upper urinary tract collecting system in cases of obstruction at an intrarenal location, at the ureteropelvic junction, or anywhere in the ureter.** Obstruction of the lower urinary tract is best treated by drainage of the bladder rather than the kidney, unless secondary obstruction of the upper tract has developed that is refractory to vesicle drainage. An alternative to percutaneous drainage is drainage through a ureteral catheter or stent placed in a retrograde fashion (cephalad from the bladder to the kidney, as opposed to antegrade, which is placement from the kidney toward the bladder). **The choice of antegrade or retrograde drainage of the upper urinary tract collecting system depends on the indication for the procedure, patient’s medical condition, particular anatomy of the patient, and preferences of both the patient and the physician.**

All things being equal, a retrograde route to drainage is preferred instead of the antegrade route. This includes most cases of acute and chronic ureteral obstruction without infection ([Rosevear et al, 2007](#); [Wenzler et al, 2008](#)). **In the setting of upper urinary tract collecting system obstruction complicated by infection, however, drainage is an emergency and in many such cases percutaneous rather than retrograde drainage may be best** ([Ng et al, 2002](#)), unless retrograde drainage can be obtained expeditiously and assuredly. Percutaneous nephrostomy tubes and retrograde ureteral stents are generally equivalent in their capacity to resolve fever in patients with upper urinary tract obstruction and fever ([Pearle et al, 1998](#); [Goldsmith et al, 2013](#)), but in a given patient, circumstances may dictate a preference for one access instead of the other. Retrograde placement of a ureteral stent generally requires regional or general anesthesia, whereas a percutaneous nephrostomy tube can be inserted under local anesthesia; this is an important consideration for an ill patient. Because the percutaneous route includes a greater initial success rate than the retrograde route in cases in which the collecting system is dilated, it might be preferred in a patient who needs rapid intervention. This is especially true when the ureteral obstruction is long, severe, or involving the ureteral orifice—all of which can make retrograde stent placement more difficult. Conversely, untreated coagulopathy is a contraindication to percutaneous access, but internal ureteral stents can be placed safely in an anticoagulated patient. A final consideration is patient preference. Although the health-related quality of life for patients with percutaneous nephrostomy tubes and for those with internal ureteral stents is similar, a given patient may prefer one

route instead of the other (Joshi et al, 2001). For additional discussion of percutaneous nephrostomy versus internal ureteral stent for drainage of the upper urinary tract, see Chapter 6.

Percutaneous Surgery

Access into the upper urinary tract collecting system may be indicated to instill therapeutic agents directly. This includes chemolysis of urinary calculi and intracavitary topical therapy for urothelial carcinoma. In most cases, the access elected for the instillation will already be present after the preceding surgical procedure.

An important indication for percutaneous access into the upper urinary tract collecting system is the need for intrarenal or intraureteral surgery. This includes percutaneous endopyelotomy and endoureterotomy (see Chapter 49), nephrolithotomy, treatment of calyceal diverticula and hydrocalyces, and antegrade ureteroscopic treatment of large ureteral stones (see Chapter 54); it also includes percutaneous resection of urothelial tumors (see Chapter 58) and less-common procedures such as management of fungal bezoars. For all of these procedures, skillfully attaining access, properly managing postoperative drainage, and preventing and treating complications related to the percutaneous access are major procedural components. The remainder of this chapter centers on these topics.

ANATOMIC CONSIDERATIONS

Given that the visualization of the kidney and surrounding structures during standard percutaneous entry guided by fluoroscopy or ultrasonography is limited, understanding of the renal and perirenal anatomy is critical for obtaining access that is both effective and safe. Even armed with this knowledge, variations in anatomy can make access challenging for the experienced surgeon and prohibitive for the inexperienced one.

Perirenal Anatomy

The kidneys are well-protected organs, situated retroperitoneally and surrounded by adipose tissue. The short renal hilar vessels limit the mobility of the kidneys, although nephroptosis ("falling kidney") can occur, especially in thin women with a paucity of perirenal fat. In such cases the kidney not only descends but also rotates anteriorly. This can be troublesome during percutaneous punctures with the patient in a prone position.

The kidneys lie adjacent to the vertebral bodies, usually extending from the 11th or 12th thoracic to the 2nd or 3rd lumbar vertebrae (Fig. 8-1). The right kidney is displaced a few centimeters inferior to the left kidney. The longitudinal axis of the kidneys parallels the lateral edges of the psoas muscles, about 30 degrees from vertical, with the lower poles lateral to the upper poles. The kidneys are also tilted 30 degrees off the frontal plane, with the lower poles

anterior to the upper poles. Finally, the kidneys are rotated out of the frontal plane as well, with the lateral aspect of the kidney posterior to the medial aspect, such that each kidney is rotated 30 degrees posteriorly from the renal hilum.

Immediately posterior to the kidneys are the quadratus lumborum and psoas muscles, except at the upper poles where the diaphragm is posterior (Fig. 8-2). The pleura can be violated during percutaneous entry into the upper pole of the kidney. This risk is greater as the access to the kidney is moved cephalad. The lung itself lies above the 11th rib, so direct lung injury is unlikely unless the 10th intercostal space (superior to the 11th rib) is used as the entry site. The ribs curve inferiorly from medial to lateral, such that more portions of the kidney can be approached subcostally with a medial as opposed to a lateral access site.

The lateral, anterior, and medial perirenal relationships are more varied than the posterior ones (Fig. 8-3). On the right side, the liver is anterior to the upper pole of the kidney and can extend in some individuals to cover the entire anterior surface. On the left, the spleen covers less of the kidney anteriorly. Both the liver and spleen can extend lateral to the kidneys and are therefore at risk of injury with a lateral puncture into the kidney. The ascending and descending colon can be lateral or even posterior to the right and left kidneys, respectively. The apposition of the colon to the kidney varies with location; it is greatest on the left side and at the lower pole. In one study of computed tomograms, the left colon was posterior in 16.1% of cases, and the right colon was posterior in 9% of cases at the level of the lower pole. At the midaspect of the kidney the colon was posterior in 5.2% and 2.8%, respectively, and at the upper pole 1.1% and 0.4%, respectively (Boon et al, 2001).

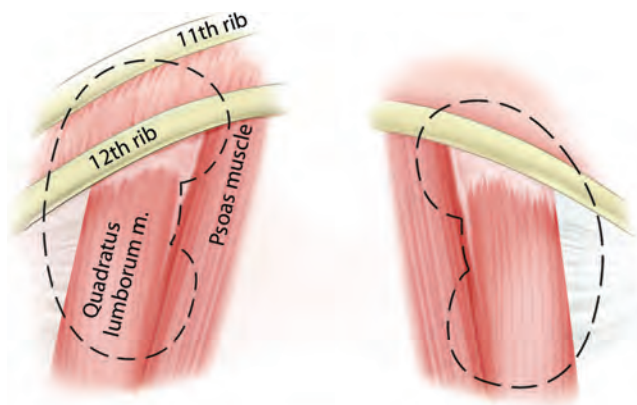


Figure 8-2. Muscles and ribs posterior to the kidneys.

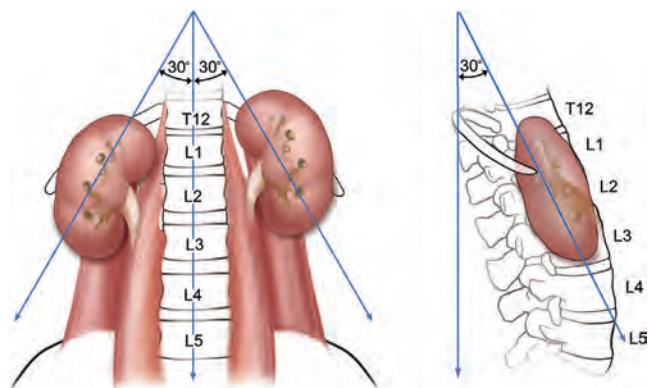


Figure 8-1. Location of kidneys in the retroperitoneum.

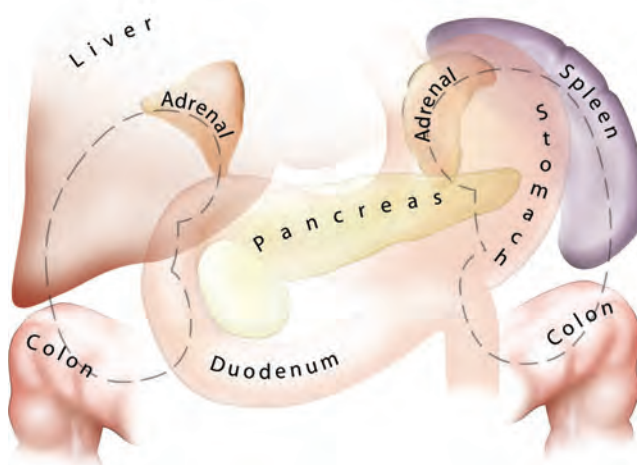


Figure 8-3. Viscera lateral, anterior, and medial to the kidneys.

Additional visceral relations to the kidney include the adrenal glands (medial to the upper pole of both kidneys), the duodenum and gallbladder (anterior and medial to the right kidney), and the tail of the pancreas (anterior and medial to the left kidney). These structures can be injured with a misdirected or excessively deep puncture.

Renal Parenchyma and Collecting System

The renal parenchyma is composed of cortical and medullary tissue. The renal cortex is the outermost layer. It contains the glomeruli and proximal and distal convoluted tubules. The more interior medulla contains the renal pyramids. These are inverted cones (the base of which is superficial and the apex of which is deep) that comprise the loops of Henle and the collecting ducts, which coalesce at the apex of the pyramid into papillary ducts that open on the surface of the renal papillae. There are approximately 20 papillary ducts draining into each papilla. The columns of Bertin are invaginations of cortical tissue that surround the renal pyramids except at their apices.

The renal papillae drain into the minor calyces, which are the most peripheral portions of the intrarenal collecting system. If only one papilla drains into a minor calyx, it is described as a simple calyx. When there are two or more papillae entering the calyx, it is termed a *compound calyx*. The outermost wall of the calyx, into which the papilla is set, is the calyceal fornix. There are 5 to 14 minor calyces in each kidney (mean of 8, with 70% of kidneys having 7 to 9 minor calyces) (Sampaio and Mandarim-de-Lacerda, 1988). There are three calyceal groups: the upper, middle, and lower. Compound calyces are the rule in the upper calyceal group, are common in the lower calyceal group, and are rare in the middle calyceal group. The minor calyces, either directly or after coalescing into major calyces, drain by infundibula into the renal pelvis (Fig. 8-4). Occasionally a minor calyx will open directly

into the renal pelvis without an intervening infundibulum. Some infundibula are unusually narrow, even if they drain adequately, and they can present an obstacle to endoscopy, especially with the relatively large rigid nephroscope.

The compound calyces of the poles of the kidney are oriented facing their respective poles. The simple calyces usually come in pairs, with one facing anteriorly and one facing posteriorly (Fig. 8-5). The upper pole calyceal system almost always contains at least one compound calyx, and in some cases this is the only calyx in the system. Drainage of the upper pole into the renal pelvis is by a single midline infundibulum in the majority of kidneys. The lower pole system often contains a compound calyx as well. The calyceal drainage from the lower pole is via a single infundibulum in about half of human kidneys and through a series of paired anterior and posterior calyces in approximately half of kidneys. With compound calyces rare in the middle calyceal system, the middle calyces are typically arranged in a series of paired anterior and posterior calyces. In about two thirds of kidneys, there are two major calyceal systems—an upper one and lower one—and the middle calyces drain into either or both systems. In the other third of kidneys, the middle calyceal system is distinct from the upper and lower systems, either coalescing into a middle major calyx before emptying into the renal pelvis or with drainage of the middle minor calyces directly into the renal pelvis through short infundibula.

An important consideration for percutaneous renal surgery is the determination of the anteroposterior orientation of the calyces, because access (from the typical posterior or posterolateral approach) into a posterior calyx allows relatively straight entry into the rest of the kidney, whereas percutaneous puncture of an anterior calyx requires an acute angulation to enter the renal pelvis, which may not be possible with rigid instrumentation (Fig. 8-6). Efforts have been made to determine which calyces are likely to be anterior and which are likely to be posterior, solely on the basis of their mediolateral position on anteroposterior radiography. The distinction pertains to the middle and lower calyceal system, which contains (in almost all middle systems and approximately half of the lower system) paired anterior and posterior minor calyces. The upper pole system, with its almost uniformly compound calyceal system, is less problematic in this regard. Paired anterior and posterior calyces usually enter at about 90 degrees from each other. As such, the relative mediolateral orientation (on anteroposterior radiography) is determined by the relationship of this 90-degree unit to the frontal plane of the kidney. In a Brödel-type kidney, this unit is rotated anteriorly, such that the posterior calyces are about 20 degrees behind the frontal plane and the anterior calyces are 70 degrees in front of the frontal plane. The posterior calyces are lateral, and the anterior calyces are medial in this case. The Hodson-type kidney is the opposite; the calyceal pairs are

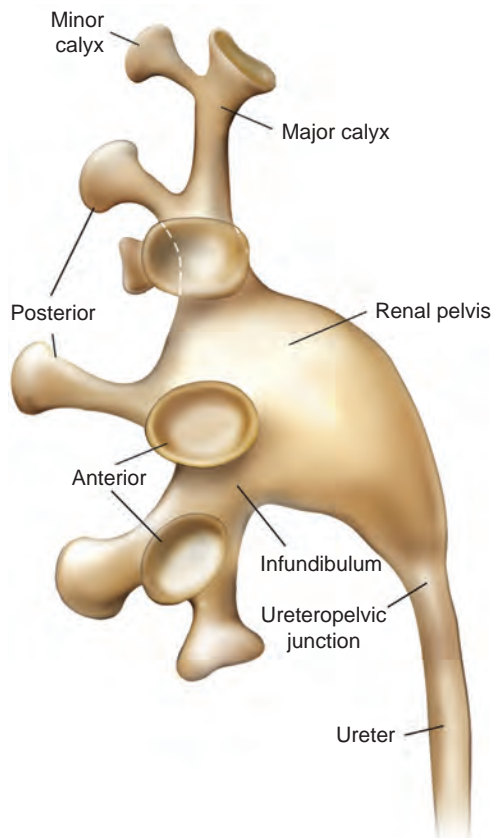


Figure 8-4. Upper urinary tract collecting system.

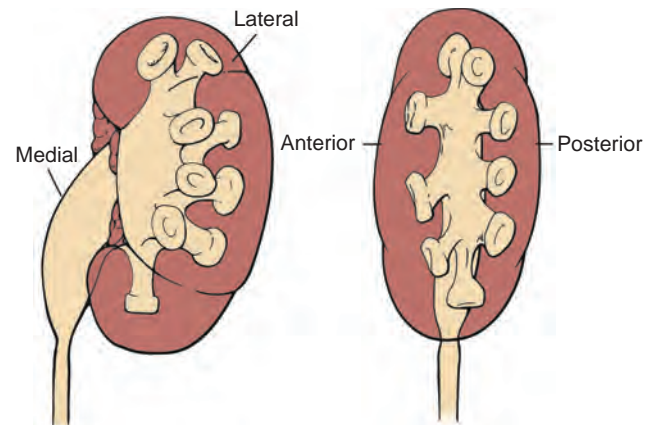


Figure 8-5. Calyceal orientation of polar and middle calyces. (From Smith AD. Controversies in endourology. Philadelphia: Saunders; 1995.)

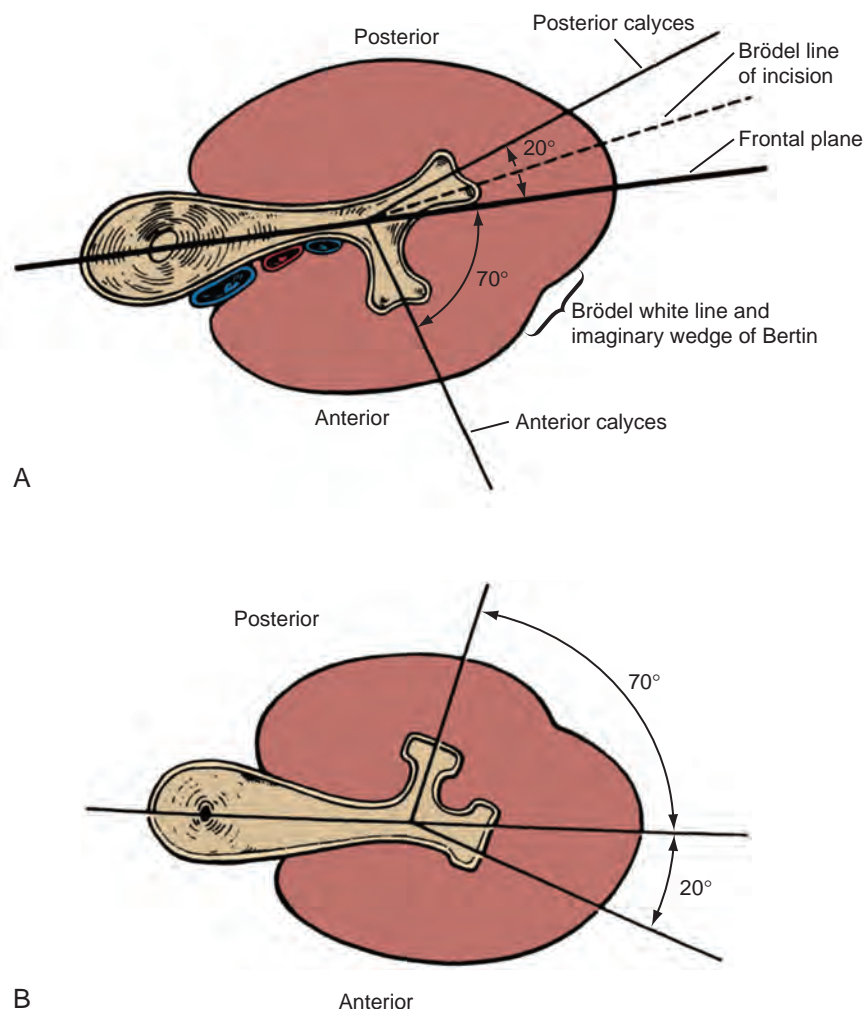


Figure 8-6. Relation of anterior and posterior calyces to renal parenchyma in Brödel-type kidney (A) and Hodson-type kidney (B). The optimal site of percutaneous entry from the posterior aspect of the kidney is into a posterior calyx because the path into the renal pelvis is fairly straight. If entry is into an anterior calyx (from the posterior aspect of the kidney) then an acute angulation must be made to enter the renal pelvis, which may not be possible with rigid instrumentation. (From Smith AD. *Controversies in endourology*. Philadelphia: Saunders; 1995.)

rotated posteriorly, with the posterior calyces 70 degrees behind the frontal plane and appearing medial and with the anterior calyces 20 degrees in front of the frontal plane and appearing lateral (see Fig. 8-6). Most right kidneys have a Brödel-type orientation (posterior calyces are lateral), and most left kidneys have a Hodson-type orientation (posterior calyces are medial). The results of one study showed that in the lower calyceal system, the medial calyces are anterior and the lateral ones are posterior most of the time (Eisner et al, 2009). Because variation is considerable, the mediolateral orientation of the calyces on anteroposterior radiography cannot be used to determine reliably the optimal calyx for entry, and additional maneuvers are required to determine the exact calyceal anatomy. One reliable anatomic distinction is that the upper calyceal group is situated in a mediolateral orientation in 95% of kidneys, in contrast to the anteroposterior orientation of the middle and lower calyceal groups in 100% and 95%, respectively (Miller et al, 2013.) This means that most calyces of the upper pole are suitable for percutaneous access from the posterior approach, whereas care must be taken to select a posterior minor calyx in the middle and lower groups. Within the lower calyceal group, the most inferior calyx is usually anterior, but the next most cephalad calyx is usually posterior (Miller et al, 2013).

Intrarenal Vasculature

Although the renal arterial anatomy is variable, in general the main renal artery divides into an anterior and a posterior branch. The former then divides within or before the renal sinus into four anterior segmental arteries: the apical and lower segmental arteries (which supply the tip of the upper pole and the entire lower pole, respectively), and the upper and middle segmental arteries (which supply the remainder of the anterior half of the kidney). The posterior branch of the renal artery supplies the remainder of the posterior half of the kidney (Fig. 8-7). After the anterior segmental arteries and the posterior branch of the renal artery enter the renal parenchyma, they divide into interlobar arteries, which are also called infundibular arteries owing to their course adjacent to the calyceal infundibula of the renal collecting system. At the cortico-medullary junction, near the base of the renal pyramids, each interlobar artery usually divides into two arcuate arteries that run along the renal pyramid. The next division is into the interlobular arteries, which run along the outer surface of the renal pyramids and are derived at right angles from the arcuate arteries. The final divisions, the afferent arterioles of the glomeruli, come off the interlobular arteries in the peripheral renal cortex. Each renal

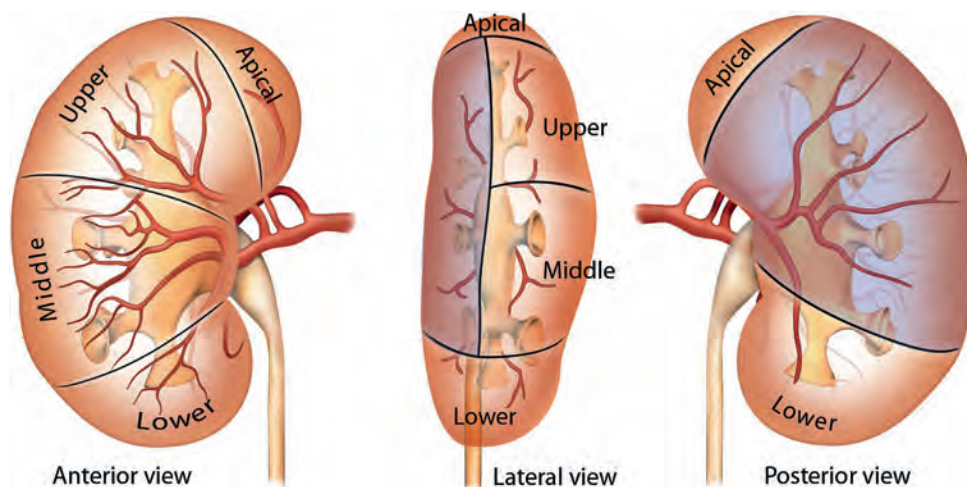


Figure 8-7. Arterial supply to the kidney. The kidney is supplied by the anterior and posterior branches of the main renal artery. The anterior branch supplies both the anterior half of the kidney and the polar regions via four segmental branches. The posterior branch of the renal artery supplies the posterior aspect of the kidney (represented by the shaded region). An avascular plane, known as Brödel line, separates the anterior and posterior circulations.

arteriole is an “end-artery,” meaning that each cell in the kidney derives its blood supply from one arteriole. For this reason renal arterial vascular injury must be avoided to prevent loss of renal function. The potential for arterial injury is least in the Brödel line, which is an avascular plane approximately at the lateral margin of the kidney, extending from the superior apex of the kidney (limited by the circulation of the apical anterior segmental artery) to the lower pole of the kidney (limited by the circulation of the lower anterior segmental artery). **Additionally, the safest place to access percutaneously the collecting system is directly into the calyceal fornix, because this will avoid the interlobar (infundibular) arteries adjacent to the calyceal infundibula and the arcuate arteries that skirt the renal pyramid (Sampaio et al, 1992).**

The venous anatomy of the kidney does not have the same defined structure as the arteries. Moreover, there is free cross-circulation among the intrarenal veins via arcades. This enhances vascular outflow from the kidneys, reduces the risk of venous congestion, and makes renal venous injury less damaging to renal function than arterial injury.

KEY POINTS: ANATOMIC CONSIDERATIONS

- Both the diaphragm and pleura can be violated during percutaneous entry into the upper pole of the kidney.
- The ascending and descending colon can be lateral or even posterior to the right and left kidneys, respectively. The apposition of the colon to the kidney varies with location; it is greatest on the left side and at the lower pole.
- An important consideration for percutaneous renal surgery is the determination of the anteroposterior orientation of the calyces.
- The mediolateral orientation of the calyces on anteroposterior radiography cannot be reliably used to determine the optimal calyx for entry.
- Most calyces of the upper pole are suitable for percutaneous access from the posterior approach, whereas care must be taken to select a posterior minor calyx in the middle and lower groups
- The safest place to access percutaneously the collecting system is directly into the calyceal fornix.

OBTAINING PERCUTANEOUS ACCESS

Adequate percutaneous access to the upper urinary tract collecting system is a critical part of the percutaneous procedure. As time passes, more urologists are being trained to attain percutaneous access (Spann et al, 2011), but only a minority of urologists in the United States maintains this skill in practice (Bird et al, 2003; Lee et al, 2004a). Survey data from the United Kingdom suggest that the attainment of access for percutaneous surgery is almost equal between urologists and radiologists, with a combined urologist-radiologist team used in the most complex cases (Aslam et al, 2011). Although there is some controversy regarding the success and complications associated with access for percutaneous renal surgery attained by urologists versus radiologists (Watterson et al, 2006; El-Assmy et al, 2007; Tomaszewski et al, 2010a), the critical distinction in ensuring effective access for a subsequent percutaneous procedure is not who obtains access but rather that the access for urologic surgery is directed by a urologist. **The optimal situation is for the urologist to be present at the time access is attained, either performing the access procedure or actively directing the radiologist.** When access is gained without input of the urologist (whether present in person or directed beforehand), the access site is not acceptable for the subsequent percutaneous procedure in a large portion of cases (Tomaszewski et al, 2010a).

Periprocedural Antimicrobials

Prevention of infectious complications is a major consideration when considering percutaneous access into the upper urinary tract collecting system. **In an elective setting, confirmation that urine is sterile is optimal.** In cases of anatomic abnormality, recent hospitalization, distant coexistent infection, recent catheterization, or other situations that suggest increased likelihood of bacteriuria, a urine culture is recommended. **In the setting of an externalized catheter or staghorn renal calculus, bacteriuria is likely and a preoperative urine culture should be considered standard practice.** In other cases, a screening urinalysis may be adequate, with subsequent culture if the urinalysis is suspicious for infection. When there is bacteriuria, a therapeutic course of culture-directed antimicrobials should be administered to sterilize the urine. Optimally, a repeat urine culture should be obtained to confirm urine sterility, although this might not be practical. In cases with colonized exogenous material such as an externalized urinary

catheter or an infected calculus, it may not be possible to eradicate the infection before the percutaneous procedure. The goal then is to suppress the bacterial count before intervention.

The American Urological Association (AUA) recommends periprocedural antimicrobial prophylaxis for all cases of percutaneous renal surgery (Wolf et al, 2008). Although there are no randomized, controlled trials to support this recommendation, nonrandomized data suggest a postprocedure urinary infection rate of 35% to 40% if antimicrobial prophylaxis is not used compared with 0% to 17% if prophylaxis is used (Charton et al, 1986; Darenkov et al, 1994). In a large retrospective but matched case-control study, comparing 162 patients with and 162 patients without antimicrobial prophylaxis undergoing percutaneous nephrolithotomy, the rate of fever and other postoperative complications was threefold to tenfold greater in the group without antimicrobial prophylaxis (Gravas et al, 2012). The need for antimicrobial coverage for simple percutaneous drainage of the upper urinary tract collecting system is not certain.

Antimicrobial coverage should include organisms common to the urinary tract (*Escherichia coli*, *Proteus* sp., *Klebsiella* sp., *Enterococcus* sp.) and the skin (*Staphylococcus aureus*, coagulase-negative *Staphylococcus* sp., group A *Streptococcus* sp.). Recommended agents include first- and second-generation cephalosporins; aminoglycosides (or aztreonam in patients with renal insufficiency) plus either metronidazole or clindamycin; ampicillin/sulbactam; or a fluoroquinolone. Although there are some series that suggest that the administration of antimicrobials for the week before percutaneous nephrolithotomy reduces the risk of infectious complications (Mariappan et al, 2006; Bag et al, 2011), the preponderance of evidence suggests that when the antimicrobial is being administered only for prophylaxis (i.e., not treatment of known or presumed infection), immediate perioperative treatment for percutaneous nephrolithotomy (≤ 24 hours) is just as effective as a longer course and is therefore preferred (Dogan et al, 2002; Demirtas et al, 2012; Seyrek et al, 2012; Tuzel et al, 2013). A short (≤ 24 hours) course of antimicrobials at the time of nephrostomy tube removal also can be considered (Wolf et al, 2008).

Management of Anticoagulation

With the increasing use of antiplatelet and anticoagulant medications in the general population, the urologist is faced more frequently with planning percutaneous renal surgery for patients taking such medications (Riley and Averch, 2012). In addition, other medications—such as nonsteroidal anti-inflammatory agents and some nutritional supplements—include anticoagulant or antiplatelet activity. Except as outlined in the following, these medications should generally be discontinued before percutaneous renal surgery. The preoperative cessation periods vary: herbal medicines, 1 week; aspirin, 1 week; warfarin, 5 days; clopidogrel, 5 days; nonsteroidal anti-inflammatory agents, 3 to 7 days. In their consensus document, the International Consultation on Urological Diseases and AUA (Culkin et al, 2014) recommend the following as related to percutaneous renal surgery:

1. Oral anticoagulant or antiplatelet activity medications should be discontinued before percutaneous renal surgery (except as noted in the following). Bridging with heparin derivatives may be required with resumption of oral anticoagulant or antiplatelet agents as soon as the risk of periprocedural hemorrhage has lessened. Expert multidisciplinary management may be required for those at high thromboembolic risk.
2. Because withdrawal of dual antiplatelet therapy (i.e., aspirin plus clopidogrel) should never occur within 12 months of drug-eluting stent placement or within 3 months of bare metal stent placement, elective percutaneous renal surgery should not be performed within these time periods.
3. For patients on clopidogrel or aspirin for secondary stroke prevention, especially after a recent stroke, cessation of the agent may be ill advised, and neurologic consultation is recommended if percutaneous renal surgery is being considered.

4. Low-dose aspirin can be continued in the perioperative period, although in patients without specific medical indications the surgical team may elect to hold the agent perioperatively.
5. For patients taking warfarin who are at high risk of thrombosis (any mechanical mitral valve replacement or a mechanical aortic valve with any risk factor), warfarin should be stopped 5 days before the surgical procedure and appropriate bridging therapy (heparin or heparin-derivative) should be instituted. For patients taking warfarin for other indications (atrial fibrillation, history of deep venous thrombosis, etc.), bridging may not be required.

In some patients who must continue anticoagulant or antiplatelet therapy, ureteroscopy might be a satisfactory alternative to percutaneous renal surgery because it can be performed with ongoing anticoagulant or antiplatelet therapy.

Local and Regional Anesthesia

Regardless of the type of primary anesthesia that is used for percutaneous renal surgery, the addition of local and regional anesthesia may be beneficial. Of eight randomized controlled trials assessing the impact of tract infiltration with various local anesthetics versus placebo on early postoperative pain and narcotic use, all but one demonstrated a benefit (Haleblian et al, 2007; Ugras et al, 2007; Jonnavithula et al, 2009; Gokten et al, 2011; Akbay et al, 2012; Shah et al, 2012; Kirac et al, 2013; Parikh et al, 2013). Additionally, intercostal nerve blocks and thoracic paravertebral block with long-acting local anesthetics have provided a similar benefit in randomized controlled trials (Ak et al, 2013; Honey et al, 2013; Ozkan et al, 2013).

Patient Positioning

Goodwin and colleagues (1955) described the prone position for percutaneous access to the upper urinary tract collecting system, and with time this position became standard. A “prone-flexed” position has also been described (Ray et al, 2009). The prone position has the advantage of presenting a large surface area (the patient’s back) that provides many choices of access sites and a stable horizontal working surface. The posterior or posterolateral approach is the most direct one to the desirable posterior calyces and comes closest to approaching the kidney through the Brödel avascular line. Prone positioning does have some disadvantages, however. It is associated with a decrease in cardiac index (Hatada et al, 1991), and in cases where inadequate padding is provided it is associated with decreased pulmonary capacity, although if enough padded support ensures free abdominal and chest wall movement, then pulmonary capacity is greater in the prone compared with the supine position (Edgcombe et al, 2008). The anesthesiologist has poor access to the airway with the patient in the prone position. Prone positioning might not be possible in patients with morbid obesity and/or spinal concavity, and the prone position can be associated with neuromusculoskeletal complications such as nerve compression or stretch injury, ocular or facial injury, and rhabdomyolysis. Finally, the prone position requires that the surgeon stand, often holding instruments at a distance using outstretched arms, which leads to surgeon fatigue. To address these deficiencies, urologists have introduced supine and lateral decubitus positioning for percutaneous renal surgery.

Valdivia Uribe and colleagues (1987) first reported the supine approach to percutaneous nephrolithotomy, culminating in their 1998 review of 557 patients with percutaneous nephrolithotomy performed in this position (Valdivia Uribe et al, 1998). They reported few complications; there were no hydrothoraces or pneumothoraces, no colon injuries, and only a 0.5% rate of major hemorrhage (see later for further discussion of complications). Variations of this position include completely supine, supine with the ipsilateral flank elevated, and supine combined with varying degrees of ipsilateral flank elevation (in some with 90-degree rotation) and asymmetric lithotomy position (Falahatkar et al, 2008; Papatsoris et al, 2008; Scoffone et al, 2008; Zhou et al, 2008; Moraitis et al, 2012). In the

prone position, with a posterior or posterolateral skin entry, the posterior calyces are the best to enter because they allow access to the renal pelvis and the rest of the kidney. In the supine position, the skin entry site is lateral or anterolateral, so the best calyces to enter are often the anterior ones. For a procedure such as percutaneous nephrolithotomy with the patient in the supine position, the access sheath is angled toward horizontal (compared with vertical during percutaneous nephrolithotomy in the prone position), which reduces the pressure in the collecting system and facilitates stone fragments to wash out through the sheath. Supine positioning does not require repositioning after induction of anesthesia, and the urethra is more easily accessed than in the prone position. The supine position is a safer position with regard to neuromusculoskeletal complications, and the anesthesia team may prefer this position (Atkinson et al, 2011). Finally, because the percutaneous entry is more lateral than during a prone procedure, the instruments are closer to the surgeon, which results in less physical strain on the surgeon and the opportunity for the surgeon to sit during the procedure.

There are some disadvantages to the supine position for percutaneous renal surgery, however. First, it is not familiar to most urologists because the prone position is used in most training programs. Second, the reduced pressure in the collecting system results in a lower volume and thus less room for visualization and manipulation. Third, upper pole calyceal access is more difficult in the supine compared with prone position, and percutaneous tract length is longer than in the prone position (Azhar et al, 2011; Duty et al, 2012). Finally, with optimal placement of pads and bolsters, the prone position may provide better ventilation than the supine position (Edgcombe et al, 2008, Atkinson et al, 2011).

In a large, multi-institutional and retrospective study of percutaneous nephrolithotomy, including 4637 patients and 1138 patients with prone and supine positioning, respectively, operative time and stone-free rates favored the prone position, but some patient safety parameters favored the supine position (Valdivia et al, 2011). Two meta-analyses of supine versus prone positioning for percutaneous nephrolithotomy, 1 incorporating two randomized controlled trials and 2 case-control studies (Liu et al, 2010) and 1 including the same 4 studies plus 27 case series (Wu et al, 2011), both documented conclusions that operative time is shorter in the supine position but that there are no differences in other parameters.

The flank (lateral decubitus) position, which first was described by Kerbl and colleagues (1994), is less commonly used for percutaneous renal surgery. This position allows simultaneous access to the anterior and posterior aspects of the kidney and appears to be particularly useful for morbidly obese patients or those with spinal deformities in whom both supine and prone positioning are difficult (Gofrit et al, 2002; Basiri et al, 2008b; El-Husseiny et al, 2009). Randomized trials comparing flank to prone position (Karami et al, 2010) and flank to supine to prone positions (Karami et al, 2013) showed no difference in outcomes.

Although both the supine and flank positions offer some potential benefits over prone positioning in certain settings, particularly morbid obesity and spinal deformities, the evidence suggests no overwhelming differences, so surgeon preference can determine the choice of position for percutaneous renal surgery. As such, the remainder of this chapter concerns access into a posterior calyx from a posterior or posterolateral direction with the patient in the prone position, which remains the standard.

The initial step in a percutaneous procedure is often cystoscopic retrograde placement of a ureteral catheter. This can be performed with the patient in prone position (using a flexible cystoscope) or in lithotomy with subsequent prone repositioning. In the “upside-down” bladder, the bubble of air from initial introduction of the cystoscope often approximates the location of the ureteral orifices. Prone cystoscopy can be performed on a standard operating or fluoroscopy table but is simplified by the use of “spreader bars” on the foot of the table (also called a “split-leg table”). Abducting the legs with the knees straight spreads the legs. This provides better access to the external urethral meatus.

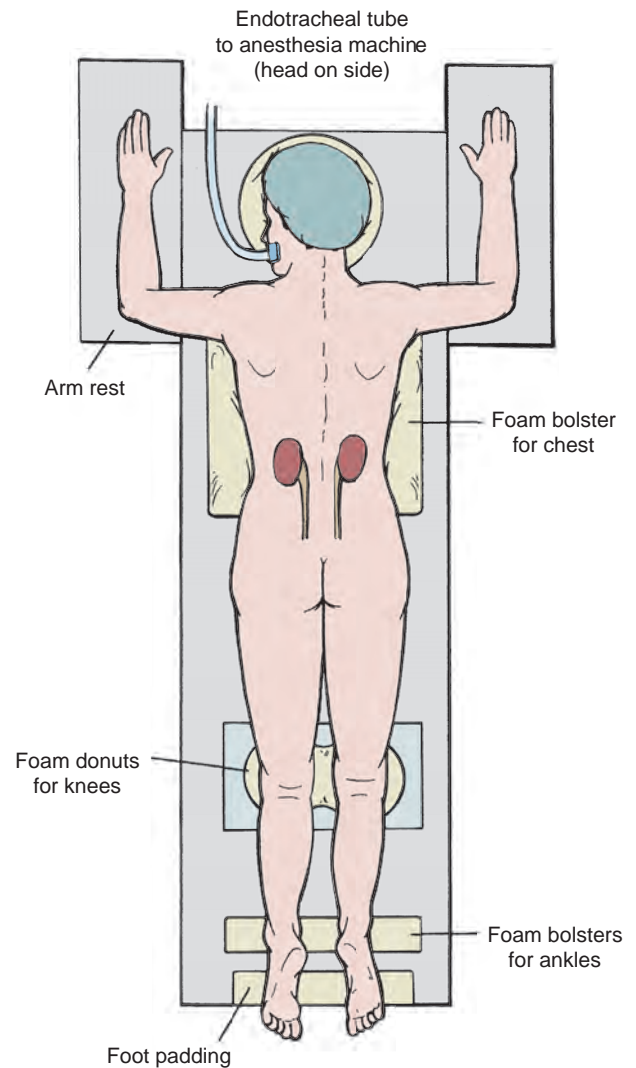


Figure 8-8. Padding for prone positioning.

Careful placement of padding is important in the prone position (Fig. 8-8). Support of the head with padding in a neutral position allows access to the mouth. Make sure there is not undue pressure on the facial bones, nose, and ears. Place the ipsilateral arm above the head to move it from the operative field, with the shoulder and elbow at right angles, and pad generously. Position the contralateral arm in the same way, or leave it straight and tucked at the side. Rest the lateral aspects of the chest on rolled blankets or other bulky foam or gel bolsters to allow for chest and abdominal wall expansion. Alternatively, purpose-made pads and supports provide more assured patient positioning (Papatsoris et al, 2009). Provide support under the ankles to take pressure off the feet, and pad the knees and feet. Prepare the perineum and ipsilateral flank sterilely, and cover unsterile areas with drapes. Cover the flank with an adherent drape that incorporates a fluid collection pouch.

Choice of Access Site to the Collecting System

The access site into the upper urinary tract collecting system is a critical determinant of the success of the subsequent procedure. In the prone position, the preferred calyces are the posterior ones (or the posterior aspect of compound calyces), which allow better access to the remainder of the collecting system. The anterior calyces can usually be approached through a posterior calyx. In cases that involve a calyceal diverticulum, narrow infundibulum, or pathology in an eccentric anterior calyx, direct puncture into an anterior location might be required. The ability to access the rest of

the collecting system is limited with such access. **Percutaneous access should never be directly into an infundibulum or the renal pelvis, which greatly increases the risk of vascular injury (Sampaio et al, 1992).** The state of the renal parenchyma overlying the intended calyx of entry also must be considered because if it is thin, the tract into the collecting system may not close well after nephrostomy tube removal.

An upper pole calyx is generally the most versatile site through which to enter the upper urinary tract collecting system. The renal pelvis, lower pole calyces, and ureter usually can be entered with a rigid nephroscope from a well-placed upper pole access. Because of the posterior tilt of the upper pole of the kidney, the lower pole does not offer assured access to the upper pole. Access to the middle calyces will usually require a separate access or use of flexible instrumentation. Often a middle calyx will offer adequate access to the ureteropelvic junction, as needed in cases such as endopyelotomy. In other cases, the calyx of entry should be selected based on the distribution of the pathology to be treated. Efforts should be made to select a calyx that will allow treatment through a single site with rigid instrumentation. If this is impossible, then one should select the site that will allow the largest portion of the pathology to be treated. The remaining pathology can be addressed with a second (and rarely a third or more) access or with flexible instrumentation through the initial access site.

Subcostal access is the safest route to the kidney because pleural injuries are rare with entry below the 12th rib. Nonetheless, if entry directly above the 12th rib (11th intercostal space) provides the best access to the optimal calyx, then the benefit generally exceeds the risk (Fig. 8-9). Entry above the 11th rib, however, has a greater potential for pleural and even lung injury, so when the best access calls for a direct puncture above the 11th rib, additional maneuvers should be considered to displace the kidney inferiorly. These include: cephalad tilt of a subcostal access sheath or access needle placed into a lower calyx (Karlin and Smith, 1989; Lezrek et al, 2011); gentle traction on a through-and-through guidewire placed through a lower pole access (Goyal et al, 2012); and attaining access during full inspiration (Falahatkar et al, 2010). Another alternative is to angle the access tract cephalad from a subcostal entry site (Liatsikos et al, 2005; Rehman et al, 2008). This approach provides limited access to the rest of the kidney. All of these alternatives can result in damage if the kidney is moved caudally with excessive force. A multicenter retrospective study of patients undergoing percutaneous nephrolithotomy via upper pole access showed that patients with an intercostal approach experienced greater stone-free rates, fewer complications, and reduced

operating times compared to patients with a subcostal approach (Lang et al, 2009). Access above the 10th rib is associated with a high incidence of pleural violation and lung injury and should be avoided unless absolutely necessary. Thoroscopically guided access superior to the 10th rib can be performed to reduce the risk of lung injury (Finelli and Honey, 2001).

Although standard preoperative ultrasonography or intravenous urography is sufficient in many cases for treatment planning, in complex cases cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) might be helpful. CT is a standard at many centers. For a more accurate representation of the renal collecting system, three-dimensional imaging reconstructions using CT or MRI are useful (Hubert et al, 1997; Buchholz, 2000; Ng et al, 2005; Thiruchelvam et al, 2005; Ghani et al, 2009; Kalogeropoulos et al, 2009; Patel et al, 2009). With specific timing of contrast injections and CT imaging, the vascular and collecting systems can be visualized simultaneously (Dalela et al, 2009).

Retrograde Assistance for Access into the Collecting System

One of the advantages of urologist participation in obtaining the initial percutaneous access is the opportunity to provide retrograde transurethral assistance. This assistance can take many forms, from placing a ureteral catheter, to inserting a flexible ureteroscope, to obtaining the percutaneous access using a retrograde-inserted device.

The simplest form of retrograde transurethral assistance is to place a 5- or 6-Fr straight ureteral catheter up into the renal pelvis (Fig. 8-10 on the Expert Consult website). Air and/or contrast material can be injected to delineate and dilate the intrarenal collecting system anatomy (Fig. 8-11 on the Expert Consult website), and a guidewire can be passed from below and grasped by the nephroscope to establish through-and-through access from the external urethral meatus to the percutaneous entry site. A dual-lumen catheter can be placed as well. The small caliber of either catheter, however, does not provide much outflow from the kidney and may not prevent stone or tumor fragments from passing into the ureter along the catheter. A ureteral occlusion balloon catheter, which incorporates an approximately 15-Fr spherical balloon on the distal tip, more consistently prevents material from migrating down the ureter. The balloon should be carefully inflated in the renal pelvis, making sure the balloon is not in the ureter—which could lead to ureteral rupture—and then gently pulled down to occlude the ureteropelvic junction (Fig. 8-12). Another alternative is to place a ureteral access sheath (usually 11 to 15 Fr) over a retrograde-inserted guidewire (Landman et al, 2003). The large outer diameter of the sheath effectively prevents particles from passing around the sheath into the ureter, and the large inner diameter affords excellent outflow of small stone particles. The disadvantages of using a ureteral access sheath include the potential ureteral trauma from passing such a large device into the ureter and the clogging of the catheter lumen by oversized stone fragments.

A ureteroscope passed retrograde can greatly facilitate percutaneous entry into the intrarenal collecting system (Grasso et al, 1995; Kidd and Conlin, 2003; Patel et al, 2008) by allowing the surgeon to observe and correct the percutaneous placement of a needle. A basket can then be passed through the ureteroscope to grasp the end of the percutaneous guidewire; pulling this out through the urethra provides through-and-through access (Fig. 8-13). Even if the pathology being addressed is so large that direct visualization of the percutaneous needle is obscured (e.g., complete staghorn calculus), one can still use the ureteroscope to rapidly attain through-and-through access. Moreover, the ureteroscope may have better access to some sites in the kidney than the nephroscope and can be used to assist in the procedure (e.g., fragment or relocate stones, fulgurate small tumors). Retrospective nonrandomized comparisons of ureteroscopic-assistance versus solely fluoroscopic guidance for access during percutaneous nephrolithotomy suggest

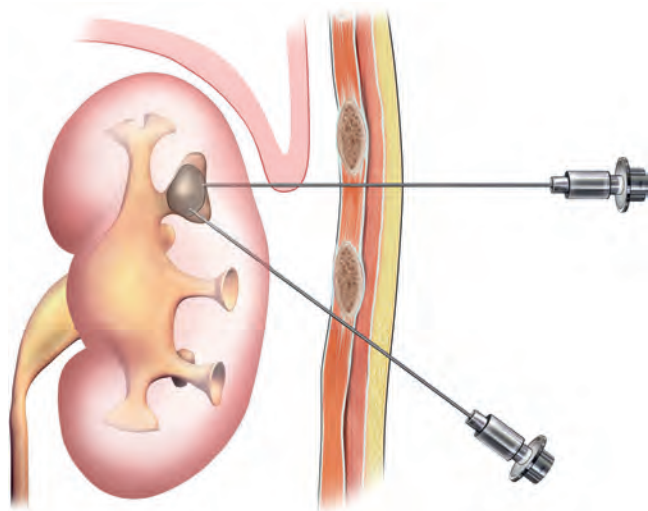


Figure 8-9. Subcostal and supracostal percutaneous access to an upper pole calyx. The supracostal approach provides more direct access and provides a better angle for endoscopy of the rest of the kidney.

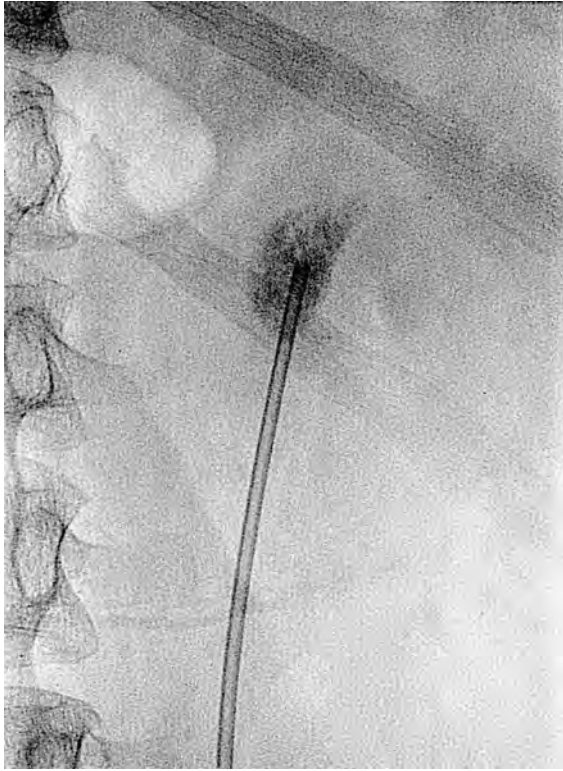


Figure 8-10. Straight ureteral catheter has been passed up into stone-containing renal pelvis.

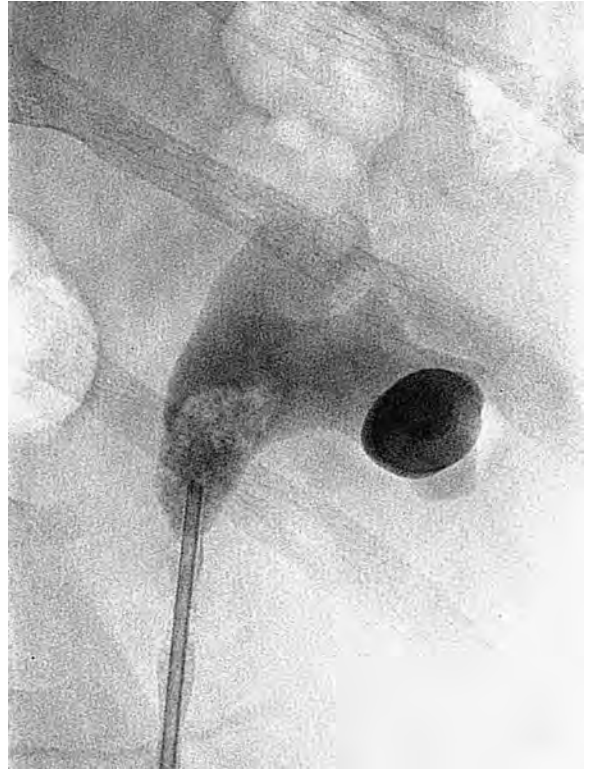


Figure 8-11. Retrograde pyelogram with air and contrast shows air in upper pole compound calyx and posterior lower pole calyx.

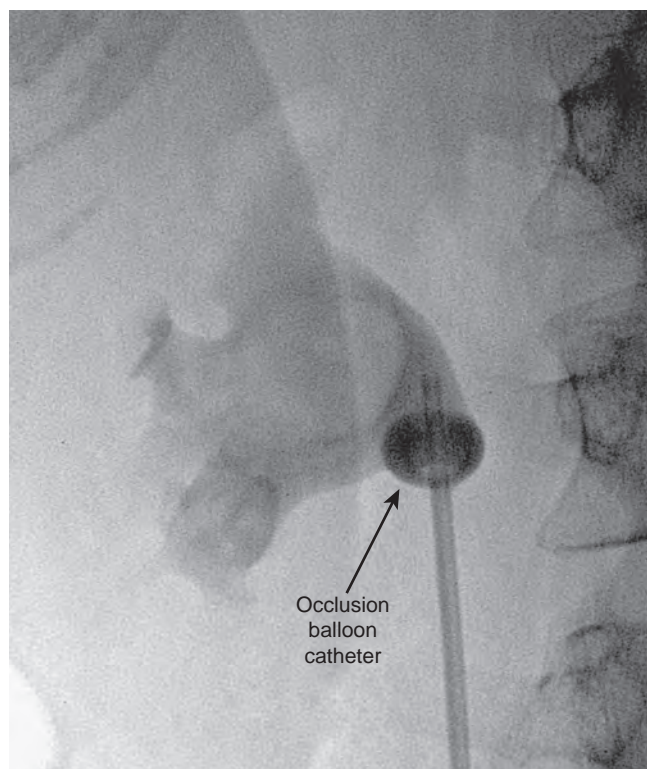


Figure 8-12. Occlusion balloon inflated and snugged down at ureteropelvic junction of contrast-filled upper tract collecting system.

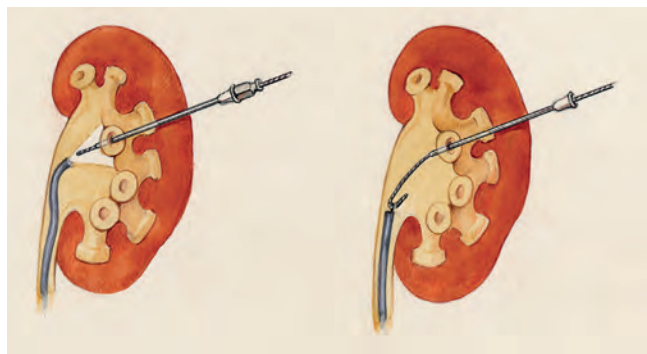


Figure 8-13. Ureteroscope retrograde assistance. The needle can be directly visualized entering the calyx, and a wire can be grasped and pulled down the ureter and out the urethra.

that the former may be associated with a lower transfusion rate (Sountoulides et al, 2009), decreased fluoroscopy time, reduced need for multiple accesses, and a reduction in the early termination of the procedure as a result of hemorrhage (Isac et al, 2013).

The “ultimate” retrograde assistance to percutaneous access into the upper urinary tract collecting system is the retrograde approach to percutaneous access. Although the antegrade approach is much more commonly performed, a retrograde approach may be selected when the surgeon has limited experience with antegrade percutaneous renal puncture or in situations where there might be a technical advantage to the retrograde approach, such as morbid obesity or a hypermobile or abnormally situated kidney (Mokulis and Peretsman, 1997). The Lawson Retrograde Nephrostomy Wire Puncture Set (Cook Urological, Spencer, IN) is the device commercially available for this approach. The fundamental maneuver of this procedure is to pass a stiff wire from inside the kidney toward and through the external body wall. This can be directed

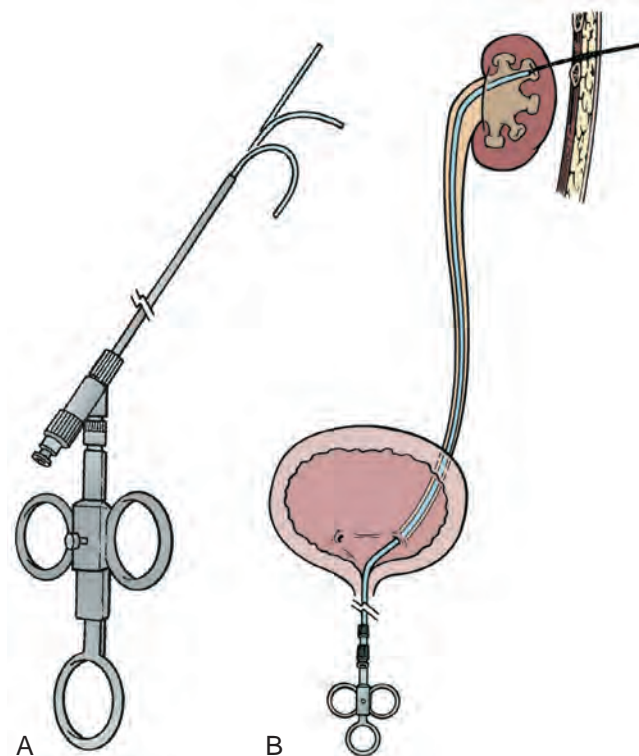


Figure 8-14. Retrograde percutaneous access. A, Torcon deflectable catheter. B, Assembled unit passing puncture needle out through the abdominal wall and skin.

fluoroscopically or under direct vision with ureteroscopy. For the former, pass a 7-Fr Torcon catheter (actively deflectable from 0 to 140 degrees; Fig. 8-14A) over a guidewire and direct it fluoroscopically into the targeted calyx. Insert the 3-Fr polytetrafluoroethylene (PTFE) sheath containing the 0.017-inch stainless steel puncture wire through the Torcon catheter. Advance the puncture wire through the kidney and body wall under fluoroscopic control, withdrawing and repositioning it if any obstacles such as a rib are encountered (Fig. 8-14B). Make a small skin incision and grasp the wire externally. Use the fascial dilators in an antegrade fashion until the Torcon catheter can be advanced through the tract. When the end of the catheter exits the skin, exchange the puncture wire for a standard 0.035-inch guidewire, thus attaining through-and-through access. This fluoroscopic technique is reported to be safe and effective (Sivalingam et al, 2013).

For the ureteroscopic approach to retrograde percutaneous access, direct the ureterscope into the desired calyx and pass the 0.017-inch stainless steel puncture within the 3-Fr PTFE sheath through the working channel. First described in 1989 (Munch, 1989), in more recent reports it has been suggested that urologists without training in percutaneous antegrade access may be able to adopt this technique more readily (Wynberg et al, 2012) and that this approach may be associated with shorter operation time and fewer complications compared to antegrade access (Kawahara et al, 2012). Further experience is required before the role of retrograde percutaneous access (whether fluoroscopically or ureteroscopically directed) can be ascertained.

Antegrade Approach to Access into the Collecting System: Needles and Guidewires

The antegrade approach to percutaneous access into the upper urinary tract collecting system is the standard. It affords the most control of the skin entry site and can be guided by ureteroscopy or a variety of imaging modalities.

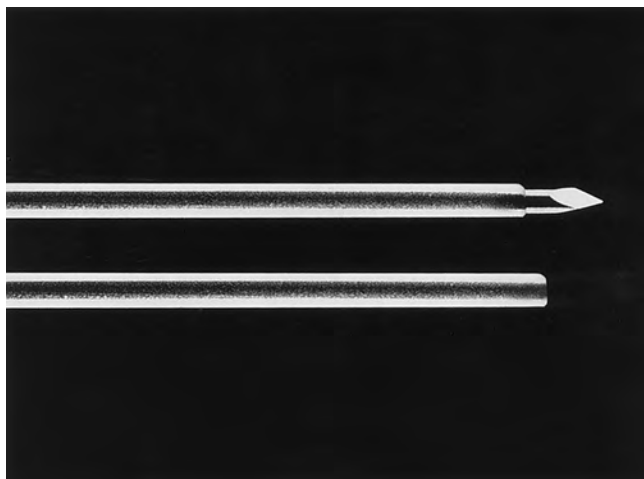


Figure 8-15. Percutaneous access needle, with a blunt sheath and a sharp obturator.

The general scheme of antegrade access is to place a needle through the skin into the upper urinary tract collecting system. A guidewire is placed through the needle and then catheters and other devices are placed over the guidewire, eventually enlarging the tract until the desired lumen is reached for the purpose of the procedure. This is the Seldinger technique, described (for vascular access) by [Sven-Ivar Seldinger \(1953\)](#). The standard choices for the needle are a 21-gauge needle through which is passed a 0.018-inch guidewire or an 18-gauge needle through which is passed a standard 0.035-inch guidewire. Both needles have a blunt sheath and a sharp obturator ([Fig. 8-15](#)). The 21-gauge needle has the advantage of causing relatively minor injury as it is passed through tissue. Multiple passes can generally be made with little risk of hemorrhage from the needle itself; the option to place and replace the needle multiple times is advantageous because getting the tip of the needle into the right spot in the kidney is the most difficult aspect of percutaneous access into the upper urinary tract collecting system. The 18-gauge needle is more traumatic, and multiple passes should be avoided. The advantage of the 18-gauge needle is that it is stiffer. In a number of circumstances the 21-gauge needle does not adequately maintain trajectory (e.g., scarred kidney, obese patient) and the 18-gauge needle is more effective. In addition, the 0.018-inch guidewire that passes through the 21-gauge needle ([Fig. 8-16](#)) must be exchanged for a standard 0.035-inch guidewire for subsequent tract dilation or catheter placement. This requires an extra step, which adds to the complexity of the procedure and increases the risk of a loss of access. Balancing the reduced efficacy of the 21-gauge needle and its increased potential for loss of access, versus the increased risk of trauma with the 18-gauge needle, it is recommended that the 21-gauge needle be used when the operator is less experienced or if minimizing trauma is paramount. The 18-gauge needle should be used when an experienced operator is confident that the tip of the needle can be placed within the desired calyx with just a few attempts.

Two methods can be used to exchange the 0.018-inch for a 0.035-inch guidewire. A coaxial introducer incorporates a small catheter within a slightly larger catheter. After inserting the 0.018-inch guidewire and removing the needle, the coaxial introducer is advanced over the guidewire until the end is within the renal collecting system. The surgeon should remove the inner catheter and 0.018-inch guidewire and then should advance a 0.035-inch guidewire through the outer catheter into the collecting system. The second method uses a graduated introducer that fits over the 0.018-inch guidewire at its tip but then enlarges to a lumen that will accept the 0.035-inch guidewire. A few centimeters back from the tip is a hole through which the 0.035-inch guidewire can pass. After inserting the 0.018-inch guidewire and removing the needle, pass the graduated introducer over the guidewire until it is a few centimeters

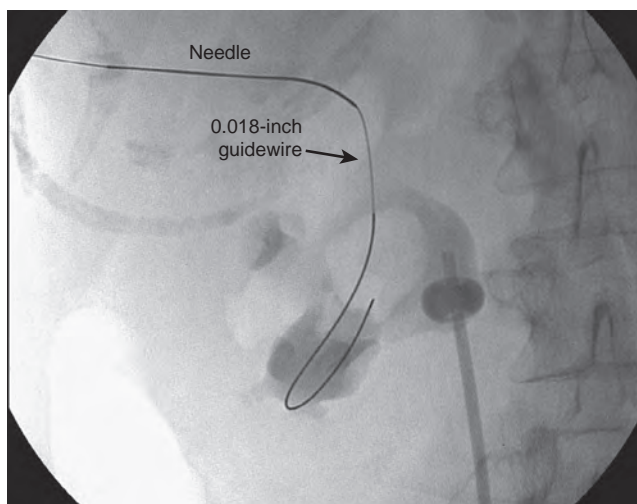


Figure 8-16. A 0.018-inch guidewire passed through percutaneous needle. This wire is exchanged for a 0.035-inch guidewire for subsequent manipulation.

inside the kidney, such that the side hole is within the renal collecting system. Remove the 0.018-inch guidewire and then insert an angled or J-tipped 0.035-inch guidewire through the introducer until the end of the wire exits the catheter within the collecting system. With either the coaxial or graduated introducer, a stiffener can be used to assist in passing the device over the relatively insecure 0.018-inch guidewire.

The safest initial 0.035-inch guidewire to use for upper urinary tract percutaneous access is a PTFE-coated J-wire. The “J” tip makes the guidewire unlikely to perforate out of the collecting system. This guidewire will not easily pass down the ureter, however, which is more easily handled with a floppy-tip PTFE-coated guidewire or a hydrophilic guidewire with a straight or angled tip.

Antegrade Approach to Access into the Collecting System: Technique of Initial Access

The initial percutaneous access to the upper urinary tract collecting system described by [Goodwin and colleagues \(1955\)](#) was “blind.” In 1974 Pedersen first reported ultrasonographic guidance ([Pedersen, 1974](#)). Although “blind” access is still occasionally reported and in expert hands can be successful, in most cases the initial antegrade percutaneous access into the upper urinary tract collecting system is obtained with real-time imaging guidance. Ultrasonography and fluoroscopy are most commonly used, with the choice based on patient characteristics and physician preference ([Basiri et al, 2008a](#)). A large multi-institutional matched-case analysis did not show any differences between ultrasonographic and fluoroscopic guidance of percutaneous access for nephrolithotomy in terms of hemorrhage and treatment success ([Andonian et al, 2013](#)).

Ultrasonographic Guidance

Ultrasonography has the advantages of portability (the mobile ultrasound machine is easier to maneuver than a C-arm fluoroscopy unit and does not require a radiolucent operating table), the ability to assess intervening structures, and no delivery of ionizing radiation. In addition, retrograde injection of contrast material or air is not necessary because the collecting system can readily be distinguished within the kidney based on ultrasonographic appearance alone. The disadvantages of ultrasonography include less clear visualization of the percutaneous needle (although etched needles created for enhanced sonographic appearance are available), a limited field of view compared with fluoroscopy, and difficulty monitoring the subsequent steps of

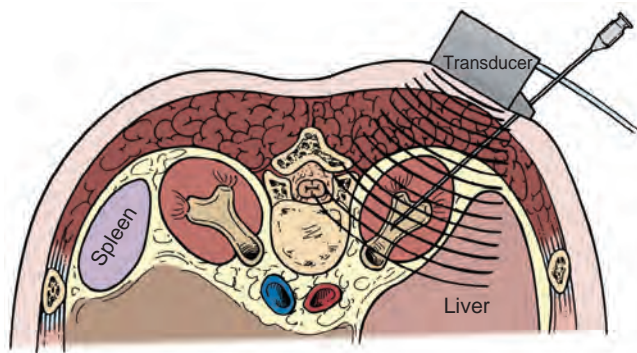


Figure 8-17. Ultrasonographic guidance of puncture needle.

the procedure. Ultrasonography is the first choice in imaging when retrograde access cannot be attained or is difficult to attain, such as in kidneys above urinary diversions, transplanted kidneys, kidneys above a completely obstructed ureter, or when radiation exposure is a concern. Ultrasonography also may be useful in the setting of skeletal abnormalities or anomalous kidneys, when intervening anatomy may differ from the norm (Chen et al, 2013; Penbegul et al, 2013). When percutaneous access is necessary for simple drainage of the kidney, such that the exact site of access is not critical as long as puncture into the renal pelvis or an infundibulum is avoided, ultrasonography is more expedient and more convenient than fluoroscopy.

Using a handheld 3.5- or 5-MHz ultrasound transducer, inspect the kidney and select a calyx for percutaneous entry. Needle guides can be placed on the transducer to direct the needle in the plane of visualization of the probe. Some prefer to place the needle freehand instead, moving the transducer around to gain different views of the kidney and needle. Observe the needle as it is advanced until it appears that the tip is within the collecting system (Fig. 8-17). Removing the obturator and aspirating urine confirms entry. Saline infusion and furosemide administration may improve ultrasonographic visualization of a nondilated intrarenal collecting system (Yagci et al, 2013). In one nonrandomized comparison (Lu et al, 2010) and one randomized controlled trial (Tzeng et al, 2011), the addition of Doppler to ultrasound imaging (which facilitates visualization of blood vessels) was associated with less blood loss and/or lower transfusion rate than ultrasound alone.

Fluoroscopic Guidance

Fluoroscopic guidance is more commonly used for gaining antegrade access to the upper urinary tract collecting system for percutaneous renal surgery. Although retrograde instillation of air and/or contrast material is not absolutely essential (Tabibi et al, 2007), most urologists find that it enhances fluoroscopically guided percutaneous access (Fig. 8-18). Fluoroscopy provides excellent delineation of the intrarenal collecting system anatomy and pathology (when contrast-enhanced), a wide field of view (that can be collimated down to reduce radiation exposure), and the ability to monitor all steps of the procedure. In some cases combining the techniques is an excellent approach, using ultrasonography to guide the initial needle placement and then using fluoroscopy (after injection of air and contrast through the sonographically guided needle) to confirm that the desired calyx has been accessed and to monitor the subsequent steps of the procedure (Osman et al, 2005). If the entry site is incorrect, then fluoroscopy of the air-and-contrast-filled collecting system can be used to guide another needle into the desired calyx. With this combination, retrograde assistance is not necessary. A randomized controlled trial between percutaneous nephrolithotomy access directed only by fluoroscopy versus ultrasonography plus fluoroscopy showed fewer puncture attempts, shorter access time and reduced

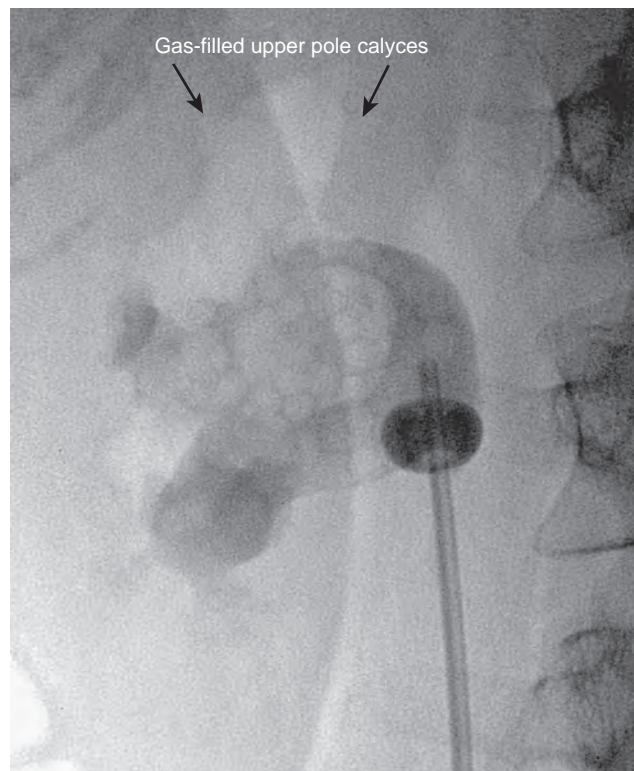


Figure 8-18. Injection of air into contrast-filled upper tract collecting system shows posterior calyces, in this case most clearly the upper pole calyces. Compare with Figure 8-12, before injection of air.

fluoroscopy time in the ultrasonography-plus-fluoroscopy group, without differences in success rate or hemorrhage (Agarwal et al, 2011). This technique is especially useful in accessing nondilated systems without retrograde assistance (Patel and Hussain, 2004).

There are two well-described methods of fluoroscopic guidance for antegrade percutaneous access into the upper urinary tract collecting system: the “eye-of-the-needle” technique and the “triangulation” technique (Miller et al, 2007). Both have their proponents, and there is no clear advantage of one rather than the other, as confirmed by one randomized controlled trial (Tepeler et al, 2012). Through the retrograde device, inject contrast material to delineate the collecting system after first taking note of any radiopaque pathology for later reference. Comparing a spot film of the unopacified collecting system with the opacified view is useful in this regard. After the options for the calyces of entry are identified, inject air to define the calyces that are posterior. In the prone position, air rises up the posterior calyces. The “double-contrast” pyelogram (both contrast material and air) provides the best determination of the pertinent intrarenal anatomy.

To perform the “eye-of-the-needle” technique, first inspect the kidney with the fluoroscopy unit directly above the patient (directed vertically) and select the desired calyx. Next, rotate the top of the fluoroscopic unit 30 degrees toward the operator, which brings the fluoroscopic view more or less end-on with the posterior calyces. The unit can be additionally rotated slightly cephalad or caudad to line it up more exactly with the axis of the calyx. Place the tip of a hemostat on the skin and move it until it is directly over the desired calyx. Mark this site and make an incision large enough to accept the needle and initial dilators. Place the tip of the access needle into this incision, and then move the shaft of the needle while keeping the tip in place until the needle is directly in line with the axis of the fluoroscopy unit; doing so gives the appearance of a “bull’s eye” with the hub of the needle (appearing as a circle) around the shaft (which appears as a dot). The fluoroscopic view is as if the operator is looking down the shaft of the needle at the targeted calyx—thus

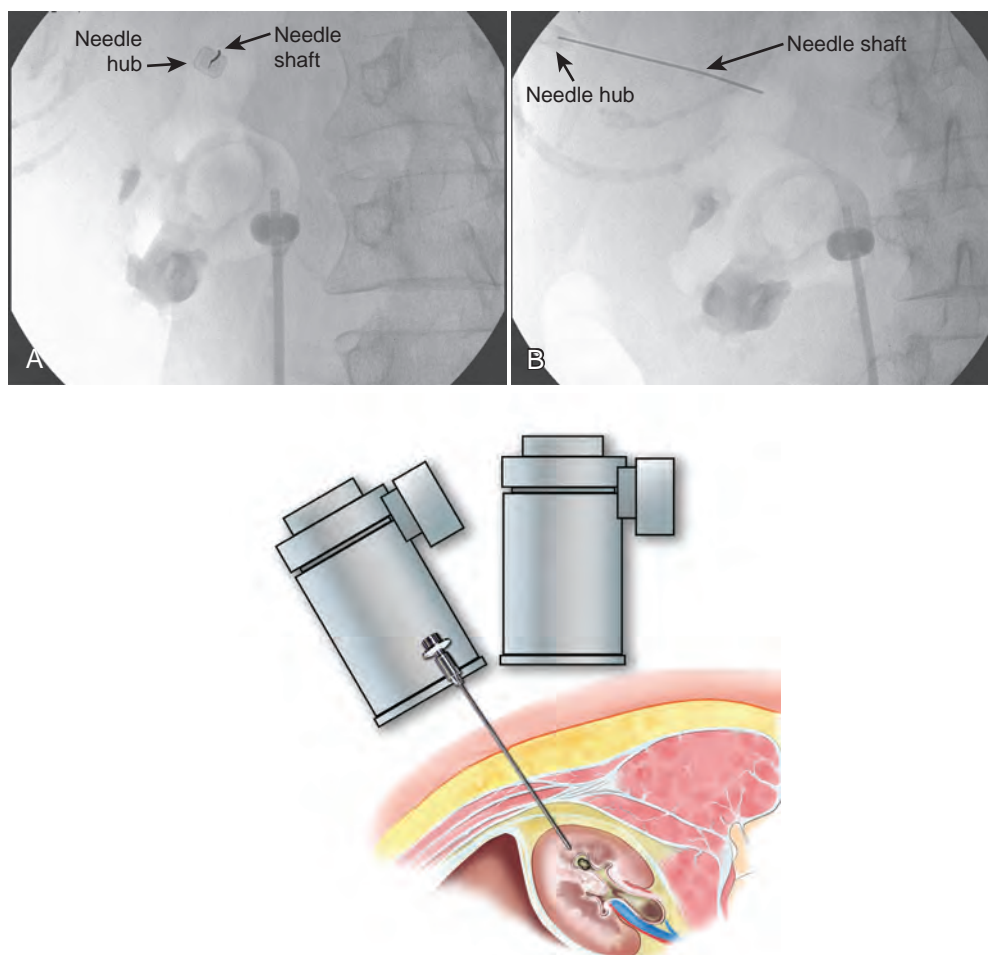


Figure 8-19. “Eye-of-the-needle” fluoroscopic guidance. **A,** With the top of the fluoroscopic unit rotated 30 degrees toward the operator, the needle is lined up directly over the intended calyx of entry. **B,** With the fluoroscopy unit rotated away from the operator, the needle is now seen in profile, and in the figure has already been advanced under fluoroscopic control to achieve collecting system entry.

the term “eye of the needle” (Fig. 8-19A). Advance the needle straight in, while checking with fluoroscopy and adjusting the angle of the needle as needed to maintain the “bull’s-eye” appearance. If the needle is more than a few centimeters deep and readjustment is necessary, the needle may have to be withdrawn before a new trajectory can be followed. The 21-gauge needle can be difficult to control during this step. If difficulty occurs, substitute the more easily passed 18-gauge needle. After the needle’s axis is fixed and it is thought that the needle is approaching or is in the kidney (typically a “pop” can be felt when the renal capsule is punctured), then rotate the fluoroscopy unit away from the operator, back to vertical or even 10 to 15 degrees beyond vertical. Now the needle appears “in profile” as a straight line. With the cephalo-caudad and mediolateral axes of the needle now fixed, advance or withdraw the needle to change its anteroposterior position (depth) to move the tip of the needle into the desired calyx (Fig. 8-19B). Aspiration of urine or air after removing the obturator confirms entry. Instillation of contrast material can be used to confirm entry as well, but if the needle is misplaced, the extravasated contrast material can obscure subsequent fluoroscopic visualization. If a gently passed guidewire stays within the contours of the collecting system, then this confirms proper entry without risking the troublesome extravasation of contrast material.

To use the “triangulation” technique, inspect the kidney with the fluoroscopy unit directly above the patient to select the desired calyx, and hold the needle in the approximate position of the

desired angle of entry. Rotate the top of the fluoroscopy unit cephalad and lateral, and widen the field of view with the collimator such that mediolateral (left-right) movements of the needle are apparent. Move the shaft of the needle while keeping its tip in place until the needle is aimed toward the desired calyx (Fig. 8-20A). Then rotate the top of the fluoroscopy unit medially 45 degrees. While keeping the mediolateral orientation of the needle constant, move the needle in the cephalo-caudad (up-down) plane until the needle is again aimed toward the desired calyx (Fig. 8-20B). Resting the forearm on the patient’s back will help stabilize the needle in one plane while moving in the other. Move the fluoroscopy unit back and forth between these two positions until the needle remains aimed at the desired calyx on both views. Advance the needle under fluoroscopic guidance while monitoring the anteroposterior direction (depth) of the needle tip. If the needle position in the mediolateral and cephalo-caudad planes is maintained, the needle should enter the targeted calyx.

With the “eye-of-the-needle” technique, the proper cephalo-caudad and mediolateral axes of the needle are verified and maintained on a single fluoroscopic view, and the confirmatory view is necessary only to assure the depth of the needle tip. For the “triangulation” technique, one fluoroscopic view is used to assess the mediolateral axis and another is used to assess the cephalo-caudad axis, with the depth of the needle tip being assessed on both views (Miller et al, 2007). The advantage of the triangulation technique instead of the “eye-of-the-needle” technique is that the needle

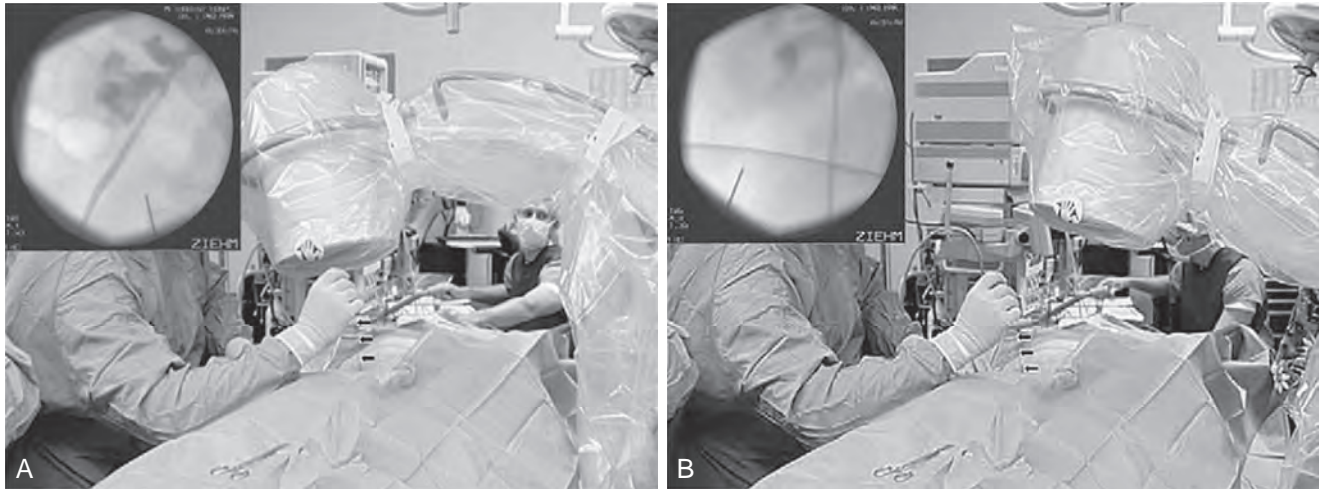


Figure 8-20. Triangulation fluoroscopic guidance. **A**, With the top of the fluoroscopy unit rotated laterally and cephalad, adjust the access needle (arrows) to a mediolateral orientation of the needle. **B**, After rotating the top of the fluoroscopy unit medially, and while keeping mediolateral orientation of the needle constant, move the needle in the cephalo-caudad plane until the needle is again aimed toward the desired calyx. (From Miller NL, Matlaga BR, Lingeman JE. Techniques for fluoroscopic percutaneous renal access. *J Urol* 2007;178:15–23.)

cannot be passed too deeply because the depth of advancement is monitored continuously. The disadvantage of the “triangulation” technique is that maintaining both the mediolateral and cephalo-caudad planes is difficult because both are not being monitored at the same time, as in the “eye-of-the-needle” technique. Use of the 18-gauge rather than a 21-gauge needle is recommended with the “triangulation” technique to help maintain the angle of entry. Mechanical devices that stabilize the needle during insertion might be helpful as well (Lazarus and Williams, 2011).

It should be remembered that the ionizing radiation presents a small but real risk. When the operator must grasp the access needle within the fluoroscopy field, it is best to hold the needle with a hemostat, sponge forceps, or purpose-built needle holder to reduce radiation exposure to the operator’s hand. Collimating the field down as much as possible while still maintaining an adequate field of view reduces radiation exposure to the patient and all personnel in the room. Moving a collimated field around to maintain the object of interest in the field is preferable to maintaining a wide field that includes the operator’s hands and unnecessary body parts of the patient. Increased body mass index, greater stone burden, nonbranched stones, a greater number of access sites, and the use of air rather than contrast during initial retrograde pyelography are associated with an increased radiation dose (Mancini et al, 2010; Lipkin et al, 2011). For additional information about radiation safety, see Chapter 2.

Advanced Guidance

In some complex cases, one might consider percutaneous access into the kidney guided by CT or MRI. The initial access is obtained into the desired calyx with the patient on the CT or MRI table, similar to the techniques used for needle biopsy (Barbaric et al, 1997; Hagspiel et al, 1998; Thanos et al, 2006). Bowel and other viscera can be imaged to protect against their injury, and this approach is especially useful in cases of anatomic abnormalities (LeMaitre et al, 2000; Matlaga et al, 2003; Srivastava et al, 2010) and for nondilated collecting systems (Merkle et al, 1999; Egilmez et al, 2007; Sommer et al, 2011).

A stereotactic fluoroscopy technique using three-dimensional coordinates for localization was reported as associated with greater accuracy and lower blood loss compared to standard fluoroscopy (Li et al, 2012a). The same principle can be computerized, as demonstrated in an experimental ex vivo model (Zarrabi et al, 2010).

An even more advanced modification of fluoroscopy is three-dimensional fluoroscopy, which provides images with a level of quality equivalent to CT. Application to percutaneous access of porcine kidneys appeared to be effective (Soria et al, 2009), and a clinical series has suggested potential benefits (Roy et al, 2012).

Three-dimensional ultrasonography accurately represents the renal collecting system (Ghani et al, 2008) and appears useful for renal imaging (Kim et al, 2008) and for teaching percutaneous access into an in vitro renal model (John et al, 2009). Given that three-dimensional ultrasonography has been applied to other therapeutic urologic applications (such as percutaneous drainage of prostatic abscesses) (Varkarakis et al, 2004), investigation of its use for clinical percutaneous access of the collecting system is anticipated.

Imaging modalities can also be combined. There has been one report of a novel image localization system that projects the ultrasonographic puncture tract onto the fluoroscopy screen (Mozer et al, 2007). Preoperative MRI data can be merged with intraoperative ultrasonography to improve puncture accuracy (Li et al, 2012b). More frequently reported is the integration of preoperative CT images with intraoperative ultrasonography (Leroy et al, 2004; Mozer et al, 2005; Wein et al, 2008).

In addition to advanced image guidance of percutaneous access to the intrarenal collecting system, technologic enhancements have been applied to the initial needle puncture. The URrobotics Laboratory at Johns Hopkins University has developed the robotic percutaneous access to the kidney with remote center of motion device (PAKY-RCM) (Cadeddu et al, 1997b). This is a robotic arm with 7 degrees of freedom that places a needle into the intrarenal collecting system as directed by the control device that pivots the tip of the needle about a fixed point on the skin. In a nonrandomized clinical trial, the PAKY-RCM system was equivalent to an expert physician in gaining access to the collecting system in terms of time and accuracy (Su et al, 2002). In a randomized trial in an in vitro kidney model, the PAKY-RCM took slightly more time but was more accurate than manual needle insertion (Challacombe et al, 2005b). This device can also be controlled at distance with telepresence technology (Bove et al, 2003; Netto et al, 2003). The same group subsequently developed a robot for percutaneous access that is MRI-compatible (Mozer et al, 2009). Percutaneous access needles incorporating advanced characteristics such as piezoelectric crystals that allow the needle to be adjusted for particular orientations (Yan et al, 2007), electromagnetic sensors that provide real-time

information of position and orientation (Yaniv et al, 2009; Huber et al, 2011; Rodrigues et al, 2013), and impedance-based sensing systems to detect entry into the collecting system have also been developed (Hernandez et al, 2001; Roberts et al, 2002), but clinical use for percutaneous intrarenal surgery has not been reported. The “all-seeing needle” consists of a modified percutaneous access needle with 1.6-mm (4.85-Fr) outer diameter through which is inserted micro-optics (0.9-mm diameter) coupled to a zoom ocular that allows visualization of the needle access tract during initial entry (Bader et al, 2011). Clinical application has been reported and appears to be favorable. Finally, Rassweiler and associates (2012) have described an “augmented reality” application of an iPad combined with CT images obtained with markers, integrating radiographic and visual information, to direct percutaneous renal access.

“Blind” Access

The upper urinary tract collecting system can also be accessed “blindly,” without any imaging guidance (Chien and Bellman, 2002). The only situation in which this should be considered is when sonography is not available and there is complete ureteral obstruction (precluding retrograde instillation of contrast material or opacification of the collecting system with intravenous contrast). The lumbar notch, also known as the *superior lumbar triangle* or *Grynfeltt lumbar triangle*, has been reported as a reliable landmark for blind percutaneous renal access (Fig. 8-21). The lumbar notch is an area of muscular insufficiency through which hernias can occur. It is located posteriorly below the 12th rib. The superior border is the 12th rib and the latissimus dorsi muscle, the lateral border is the transversus abdominis and external oblique muscles, the medial border is the quadratus lumborum and sacrospinalis muscles, and the inferior border is the internal oblique muscle. Insert a needle 3 to 4 cm deep into the notch at a 30-degree cephalad angle to enter the collecting system. Another blind approach to the collecting system is to insert a needle directly perpendicular to the body surface 1 to 1.5 cm lateral to the L1 vertebral body, which

will lead directly to the renal pelvis if anatomy is normal. If fluoroscopy is available, then air and contrast material can be injected through a blindly placed needle to assess fluoroscopically its position and to guide another needle if needed. In the only randomized clinical trial comparing “blind” access to image-guided access, entry into the collecting system was successful in 50% and 90% of cases, respectively (Basiri et al, 2007). Use of the technique is not recommended in most settings.

Working Access

After good access to the collecting system is attained, exchange the initial guidewire through a catheter for a different one as needed. Dilate the tract over the guidewire with stiff plastic dilators or a metal fascial cutter to enlarge the tract to 8 to 12 Fr. If the goal of the procedure is simple drainage, then a small-caliber nephrostomy tube can be placed over the single guidewire to complete the procedure.

Safety Wire

If ureteroscopic assistance is used, the first guidewire inserted into the kidney can be grasped with the ureteroscope and pulled down the ureter and out the external urethral meatus. With this through-and-through access, the guidewire cannot be lost. **In all other situations, the goal for a therapeutic percutaneous procedure is to move two guidewires down the ureter into the bladder, generally a super-stiff (working) guidewire and a floppy-tip or J-tipped PTFE-coated (safety) guidewire.** One important exception is in cases where a dependent lower pole has been accessed percutaneously. If there is extreme angulation to get from the lower pole calyx to the ureteropelvic junction and down the ureter, placing a super-stiff guidewire down the ureter may put undue force on the kidney and risk tearing the parenchyma. In such cases, the flexible safety guidewire should still be directed down the ureter if possible, but the stiff working wire over which the dilation is performed can

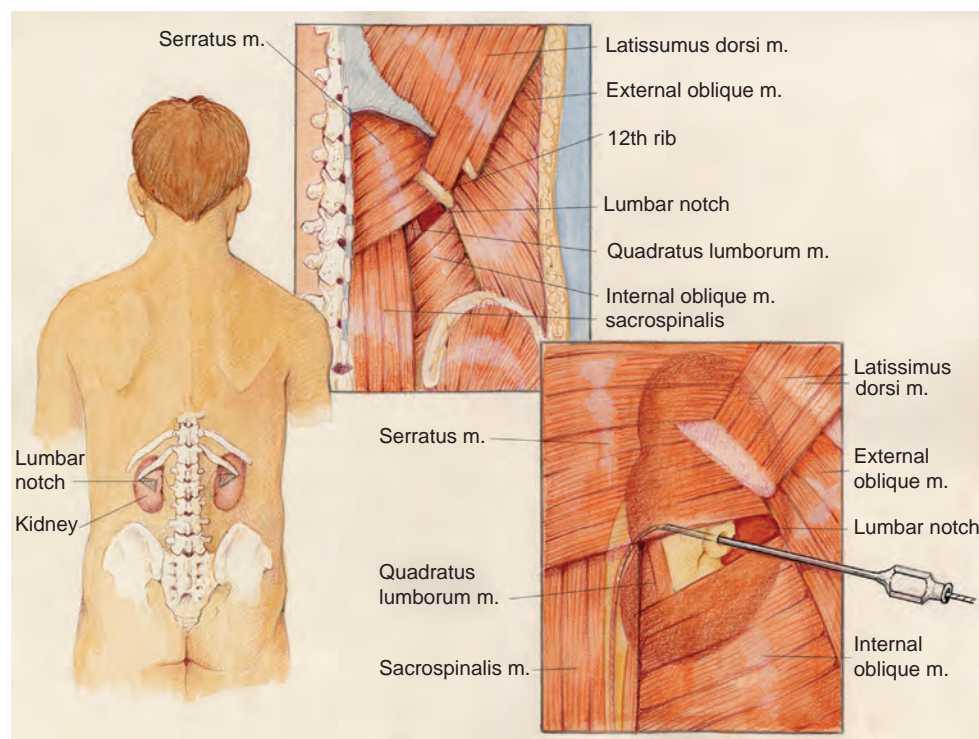


Figure 8-21. The lumbar notch is a useful anatomic landmark for blind percutaneous access to the renal collecting system. It is bounded superiorly by the latissimus dorsi muscle and the 12th rib, medially by the sacrospinalis and quadratus lumborum muscles, laterally by the transversus abdominis and external oblique muscles, and inferiorly by the internal oblique muscle.

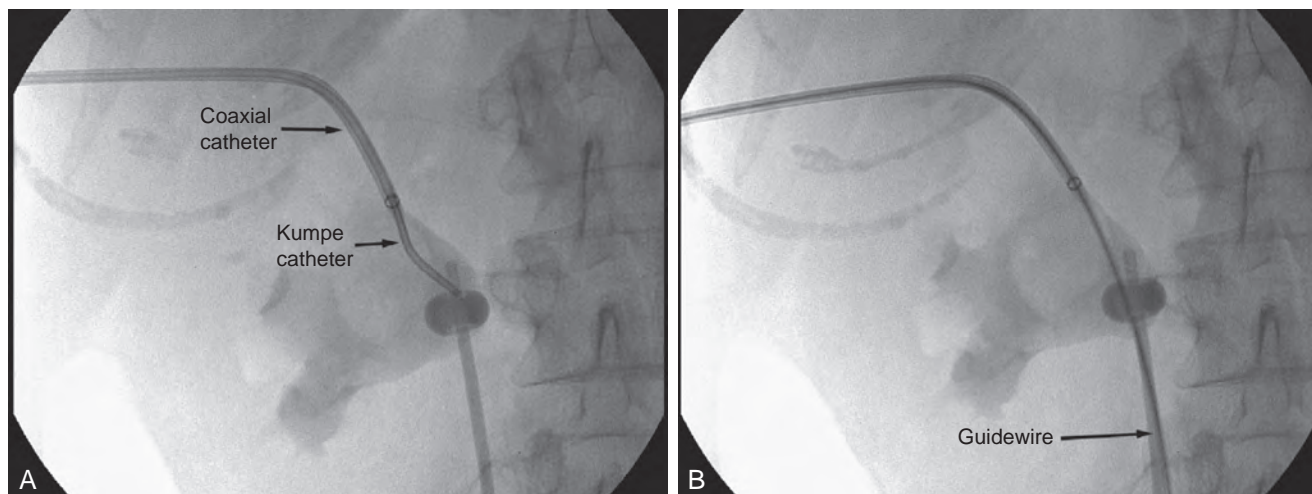


Figure 8-22. A, Kumpé catheter placed through the outer sheath of a coaxial catheter and manipulated toward the ureteropelvic junction helps direct a guidewire (B) down the ureter.

simply be directed toward the upper pole. Additionally, in some cases the pathology (e.g., calyceal obstruction, impacted ureteral stone, large staghorn stone) prevents the surgeon from getting a guidewire down the ureter or even into the remainder of the intrarenal collecting system. In such cases attempts should be made to move as much guidewire as possible into the upper urinary tract collecting system. A guidewire with a moveable core is useful in this setting because it can be coiled more tightly.

There are several techniques for inserting a guidewire down the ureter. The safest maneuver is to place a stiff angled-tip hydrophilic guidewire adjacent to the initial stiff angled-tip hydrophilic guidewire using a coaxial or dual-lumen catheter. Remove the coaxial or dual-lumen catheter and place an angled-tip catheter (Kumpé, Cobra, or coudé tip) over the angled-tip hydrophilic guidewire to help direct it down the ureter. After the stiff angled-tip hydrophilic guidewire is down the ureter, optimally all the way into the bladder, use the coaxial or dual-lumen catheter to place a second guidewire down the ureter. In cases of secure access, the initial wire can be exchanged for a stiff angled-tip hydrophilic guidewire through an angled-tip catheter to pass down through the ureter quickly (Fig. 8-22); alternatively, the surgeon can use a stiff angled-tip hydrophilic guidewire as the initial wire.

Dilation of Tract

After there is adequate wire access into the upper urinary tract collecting system, dilate the tract to allow insertion of working instruments. In most cases the goal of dilation for percutaneous renal surgery is to place a 30-Fr inner-diameter/34-Fr outer-diameter plastic access sheath. In some cases a smaller sheath, with an inner diameter measuring 12- to 24-Fr, is adequate. Renal access sheaths generally have a beveled tip, such that one side of the sheath extends farther than the other part. This bevel is used to maintain access into part of the collecting system on one side of the sheath while allowing extra mobility on the other side. Sheath repositioning is facilitated by the bevel. In cases of pathology at the edge of the collecting system, however, the bevel presents a disadvantage because the entire tip of the sheath cannot be placed into the collecting system. Both opaque and clear sheaths are available; some prefer the clear sheaths because structures next to the sheath can be visualized.

In the early years of therapeutic percutaneous renal procedures, the tract was dilated gradually through the course of many days by placing sequentially larger tubes. Castañeda-Zúñiga and associates (1982) first reported acute dilation of the tract. There are several dilator systems available. Regardless of the method used, it is imperative that the dilator does not pass too far into the

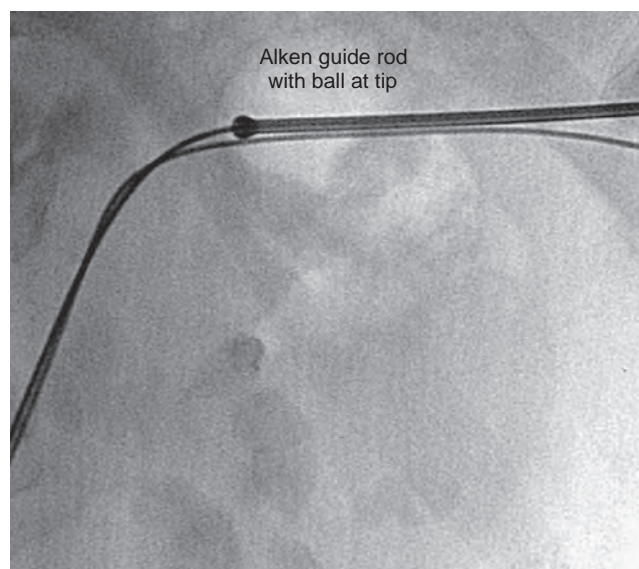


Figure 8-23. Alken guide rod is positioned with the ball at the tip of the rod positioned at the intended depth of the dilation.

collecting system. If this occurs, an infundibulum, the renal pelvis, or the ureteropelvic junction can be torn or perforated, either directly by the dilator or indirectly by a stone pushed aside by the dilator. The dilator should be passed just into the calyx. It is better to dilate a bit “short” of the targeted calyx than to dilate too far, which would create trauma. The initial inspection with the nephroscope confirms entry of the sheath into the calyx. If the sheath is not deep enough, then simply replace the dilating device and redilate after advancing the device. The dilators should not be used to dilate the skin; the skin should be incised to allow entry of the final sheath without pressure on the skin edges.

Sequential rigid metal dilators, introduced by Alken (1985), are a series of progressively enlarging coaxial stainless steel rods that pass over an 8-Fr guide rod. The first step in tract dilation is to pass the 8-Fr guide rod over a 0.035-inch guidewire. The end of the guide rod has a ball that prevents advancement of the first dilating rod beyond the tip. The ball is positioned at the intended depth of the dilation (Fig. 8-23). After passing the first rod, each successive metal rod is passed sequentially over the former until the desired tract is achieved, up to a 30-Fr rod over which is passed a 30/34-Fr plastic



Figure 8-24. Amplatz dilators with sheaths.

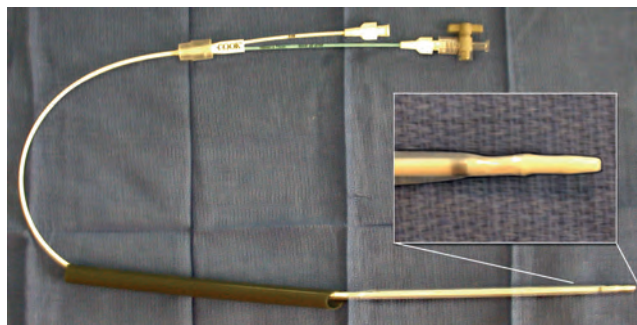


Figure 8-25. Balloon dilation catheter with preloaded sheath.

sheath. The advantages of the rigid metal dilator system are that it is the most effective dilator, able to dilate even when there is dense perirenal scarring from previous procedures, and that it is inexpensive on a per-case basis because it is reusable. The disadvantage is that, for the same reason they are so effective, the rigid metal dilators can do considerable damage. The depth of the dilation can be difficult to maintain accurately, especially when pushing against tough scar tissue. One group has modified the rigid metal rods, tapering the ends and adding centimeter markings (Shen et al, 2007).

Progressive semirigid plastic dilation sets (often referred to as “Amplatz” dilators after Kurt Amplatz, the senior author in the initial publication [Rusnak et al, 1982]) consist of progressively larger firm plastic (polyurethane) dilators that are passed over an 8-Fr PTFE guiding catheter that fits over a 0.035-inch guidewire (Fig. 8-24). The dilators are passed one after the other, not coaxially like the rigid metal dilators but progressively, advancing one dilator, removing it, advancing the next largest dilator, and so on until the final tract diameter is achieved. The working sheath is passed over the final dilator and then the dilator and 8-Fr catheter are removed, leaving the working wire and sheath in place. The dilators are made in increments of 2 Fr, but if the tissue being dilated is soft, then not every dilator needs to be used. The advantage of the semirigid plastic dilation system is that trauma to the collecting system is theoretically less likely than with the rigid metal dilators (although experienced urologists have found no difference between the two systems in terms of safety), but the disadvantage is that hemorrhage can occur each time a dilator is withdrawn. Current semirigid plastic dilators are sold as disposable devices, so they are more expensive on a per-case basis than rigid metal dilators. One retrospective comparison of the two techniques showed no other differences (Ozok et al, 2012).

Balloon dilators (Fig. 8-25) were developed to obviate the repetitive dilations of the rigid metal and semirigid plastic dilation systems, which are both time consuming and potentially dangerous. This is the most common dilation method for percutaneous renal surgery today (Benway and Nakada, 2008). The appropriate working sheath is back-loaded onto the balloon dilation catheter, which is passed over the working wire until the radiopaque marker is at the intended depth of dilation (Fig. 8-26A). The dilating balloon is inflated with a pressure syringe. A “waist” appears at the site(s) of greatest resistance, usually the abdominal wall fascia and the renal capsule (Fig. 8-26B). After the balloon is fully expanded (Fig. 8-26C), the working sheath is passed over the balloon (Fig. 8-26D) (Fig. 8-27 on the Expert Consult website). The balloon catheter has a “shoulder,” which is the portion between the end of the balloon and the point at which the maximal diameter is achieved. The sheath should not be passed beyond the maximal diameter of the balloon because this can cause significant injury.

Balloon dilators, which are expensive one-time-use devices, are less effective than rigid metal and semirigid plastic dilation systems in densely scarred tissue but are more effective when the kidney is hypermobile (Kumar and Keeley, 2008). Most (Heggagi et al, 1991; Davidoff and Bellman, 1997; Safak et al, 2003; Kukreja et al, 2004), but not all (Gonen et al, 2008a; Wezel et al, 2009), single-series reports have suggested that hemorrhage and transfusion rates are less with the balloon dilators compared with rigid metal and semirigid plastic dilators. In a large multi-institutional study, however, balloon dilation was associated with longer operative time and greater bleeding and transfusion rates compared to rigid metal and semirigid plastic dilators (Lopes et al, 2011). Baseline differences between the groups, including more stones per kidney and more frequent treatment of staghorn calculi in the balloon dilation, may have created bias against balloon dilation.

In an effort to simplify dilation of the renal access tract further, a number of single-step techniques have been described. The simplest is passage of the final semirigid plastic dilator without previous dilation by the smaller dilators (Frattini et al, 2001). A meta-analysis of 4 randomized controlled trials comparing a single plastic dilator with sequential rigid metal dilators suggested that the former was associated with reduced access and fluoroscopy times without increased complications (Li et al, 2013b). Devices designed specifically for single-step dilation include a balloon dilator with an expandable sheath (Pathak and Bellman, 2005; Baldwin et al, 2006; Maynes et al, 2008; Kalpee et al, 2012) and a rigid dilator with an expandable sheath (Goharderakhshan et al, 2001). Preliminary results with these devices appear favorable.

The most common cause of difficult tract dilation is previous renal surgery (Joel et al, 2005). Densely scarred kidneys present a challenge. Even if semirigid plastic or rigid metal dilators fail, novel uses of devices such as Collings knives and atherotome cutting balloons can be used (Davis et al, 1991; Williams et al, 2008). One group has reportedly used a bipolar resectoscope with a plasma vaporization electrode to enlarge the percutaneous tract, and in their randomized controlled trial there were some advantages over balloon dilation (Chiang et al, 2013).

Modifications in Special Situations

In cases of anomalous kidneys (malrotated, ptotic, ectopic, horseshoe, and other fused kidneys), alteration of the percutaneous approach to the upper urinary tract collecting system may be necessary. As noted earlier, in some situations real-time guidance of the needle puncture with CT or MRI might be considered, and ultrasonographic guidance may be useful, but in most cases preoperative CT or magnetic resonance suffices. Because the orientation of some organs might change with patient position, imaging in the intended position of surgery might be useful. Preoperative cross-sectional imaging of anomalous kidneys helps plan patient position, choice of calyx, and orientation of the tract, taking into account distance of the kidney from the skin, calyceal orientation, vascularity, and the relative orientation of adjacent organs.

Horseshoe kidneys frequently require percutaneous intervention. Although antegrade access into horseshoe kidneys is

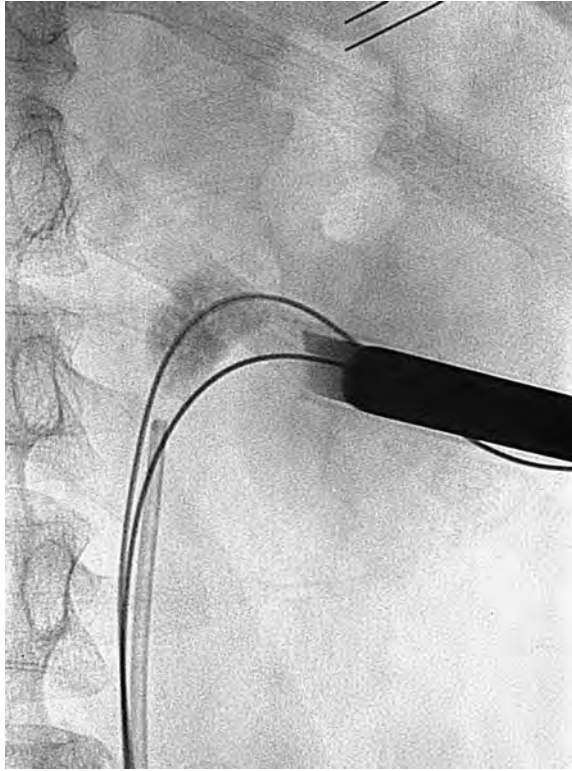


Figure 8-27. Working sheath is passed over dilating balloon in lower pole access site. The working and safety guidewires both go down the ureter.

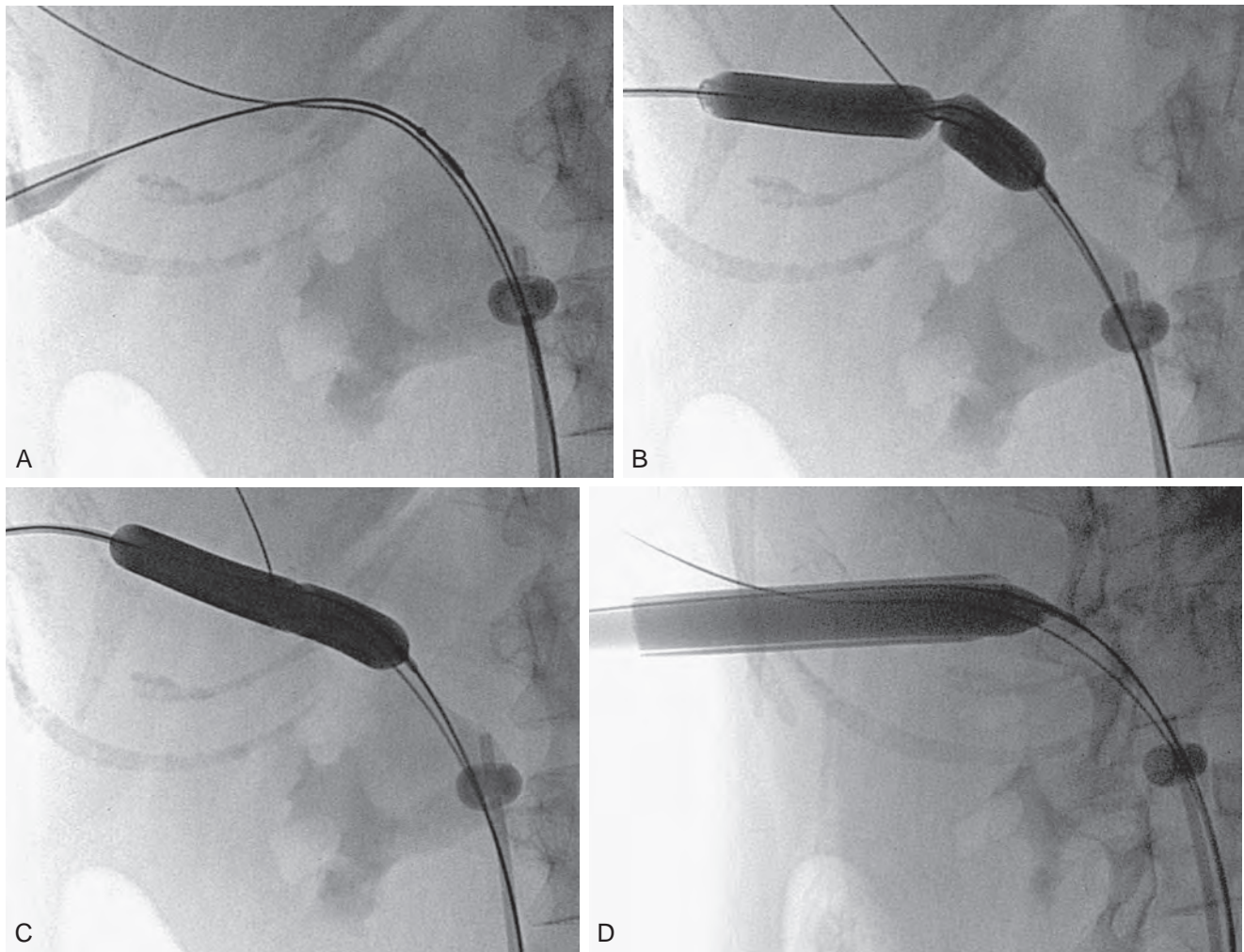


Figure 8-26. Balloon dilation of tract and placement of working sheath. **A,** Balloon catheter is inserted over wire, with distal radiopaque marker at the intended depth of dilation. **B,** “Waist” appears as balloon is inflated. **C,** Balloon is fully expanded. **D,** Sheath is passed over balloon, taking care not to advance it beyond the point of maximal diameter of the balloon.

somewhat different than into normal kidneys, standard techniques can generally still be used. CT or MRI should be considered for preoperative assessment of horseshoe kidneys, both to assess for the possibility of retrorenal colon ([Skoog et al, 1985](#)) and to assess the vasculature and relationship of the calyces to the anticipated puncture site. In a series of 12 patients undergoing percutaneous nephrolithotomy in horseshoe kidneys, 5 had bowel posterior to the kidney on CT ([Al-Otaibi and Hosking, 1999](#)). Horseshoe kidneys often have extra and eccentric calyces that can be difficult to access. In other ways, however, percutaneous access to a horseshoe kidney is more favorable than in normal kidneys. The anteroposterior tilt of the kidney is prominent, which makes the upper pole the most superficial and posterior aspect of the horseshoe kidney. In addition, the upper pole is usually inferior to the ribs. Upper pole access is useful in horseshoe kidneys because this is the easiest calyx to enter, the puncture rarely needs to be supracostal, and it provides excellent access to most of the kidney and the ureter owing to the alignment of the long axis of the moiety ([Fig. 8-28](#)). The initial entry into a horseshoe kidney is more medial than in normal kidneys and can pass through the paraspinous musculature. The distance to the lower pole and ureter can be great in an obese or muscular patient, such that extra-long rigid nephroscopes or flexible nephroscopy may be necessary. In some cases, middle calyceal access is preferred because the upper pole is so far away from the pathology, but lower pole calyces are usually not safely accessible with direct percutaneous puncture. The vasculature of

horseshoe kidneys is aberrant, but vessels enter and exit the kidney in an anteromedial location (except for some at the isthmus), so direct vessel injury is rare with well-planned access ([Janetschek and Kunzel, 1988](#)). Overall, among a total of 256 percutaneous procedures (primarily nephrolithotomy) recently reported in horseshoe kidneys, there were 11 (4.3%) major hemorrhagic complications and only 1 (<0.4%) colon injury ([Al-Otaibi and Hosking, 1999](#); [Shokeir et al, 2004](#); [Lojanapiwat, 2005](#); [Darabi Mahboub et al, 2007](#); [Mosavi-Bahar et al, 2007](#); [Viola et al, 2007](#); [Majidpour and Yousefinejad, 2008](#); [Miller et al, 2008](#); [Symons et al, 2008](#); [Gupta et al, 2009](#)).

Another way to access anomalous kidneys is with an anterior approach using laparoscopic assistance. This is most applicable to pelvic ectopic kidneys because a posterior approach is often blocked by the bony pelvis, although laparoscopic assistance has been used for percutaneous nephrolithotomy of a large calculus in an anteriorly directed calyx in the isthmus of a horseshoe kidney ([Maheshwari et al, 2004b](#)) and a large calculus in an anterior diverticulum of a horseshoe kidney ([Wong and Zimmerman, 2005](#)). The bowels can be mobilized off the surface of the kidney laparoscopically, and the access needle is passed through the anterior abdominal wall into the kidney under vision from the laparoscope. Retrograde assistance is still desirable because opacifying the collecting system assists in simultaneous fluoroscopic confirmation of calyceal entry and wire passage. Dilation and sheath insertion can be assessed both laparoscopically and fluoroscopically. In a

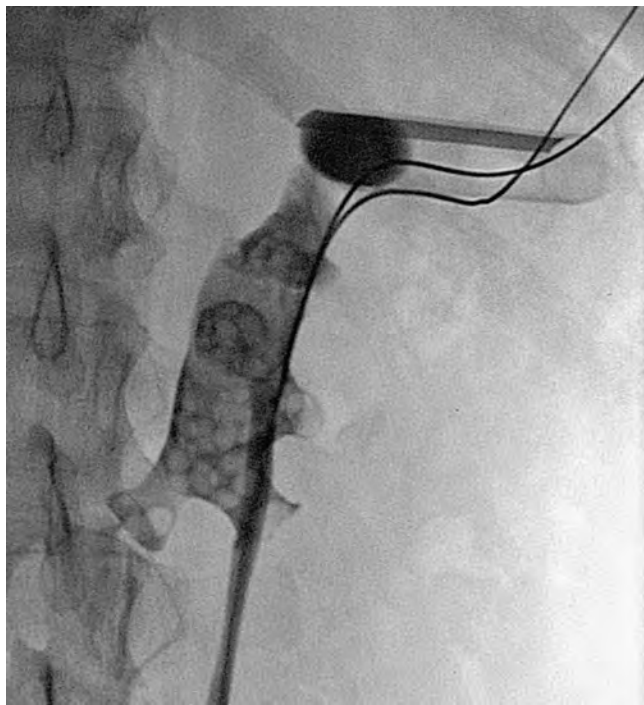


Figure 8-28. Percutaneous access sheath (radiolucent except for a radiopaque stripe) in upper pole of horseshoe kidney. Note medially directed lower pole calyx. Although not apparent from this radiograph, the access site is subcostal.

series of 12 laparoscopically directed antegrade percutaneous nephrolithotomies into pelvic kidneys published since 2001 that described a total of 35 patients, all procedures were reported to be successful and without complications (Troxel et al, 2002; Maheshwari et al, 2004a; Santos et al, 2004; Aron et al, 2005b; Aquil et al, 2006; Goel et al, 2006; Matlaga et al, 2006; El-Kappany et al, 2007; Mousavi-Bahar et al, 2008; Gupta et al, 2009; Tahmaz et al, 2009; Tepeler et al, 2013). As a simpler alternative to laparoscopic assistance, anterior percutaneous access into pelvic kidneys using a supine oblique position with a pad under the ipsilateral hemipelvis, as well as using ultrasonography to assess for intervening bowel, has been reported to be a safe technique in selected patients (Desai and Jasani, 2000; Mosavi-Bahar et al, 2007). If bone does not intervene between the appropriate calyx and the skin, then a posterior approach can be used just above the iliac bone (Atmaca et al, 2007) or through the greater sciatic foramen (Watterson et al, 2001).

Transplanted kidneys also mandate changes in the approach to percutaneous access of the upper urinary tract. The transplanted kidney, typically positioned extraperitoneally in the iliac fossa, has variable angles of the calyces depending on the placement of the kidney by the transplant surgeon. The usual approach is from the anterolateral direction, with the patient in the supine position. Percutaneous nephrostomy is the preferred approach to obstruction and for endoscopy of the collecting system in the transplant kidney (Mostafa et al, 2008). Ultrasonography is most convenient for initial access to the collecting system because retrograde assistance for fluoroscopy is difficult owing to the site and angle of the reimplanted ureter. Fluoroscopy can then be used as needed to facilitate subsequent steps. The dense fibrosis that often surrounds a transplant kidney can make dilation of the tract difficult, and semirigid plastic or rigid metal dilators may be necessary if balloon dilation fails. Of 75 percutaneous procedures in transplant kidneys reported in 10 recent series that used ultrasonographically and/or fluoroscopically directed percutaneous access, all but six were technically successful and there were no major complications (Francesca et al, 2002; Klingler et al, 2002; Challacombe et al, 2005a; He et al,

2007; Krambeck et al, 2008b; Rifaoglu et al, 2008; Wyatt et al, 2009; Oliveira et al, 2011; Stravodimos et al, 2012; Verrier et al, 2012).

KEY POINTS: OBTAINING PERCUTANEOUS ACCESS

- Optimally, the urologist is present at the time percutaneous access is attained, either performing the procedure or actively directing the radiologist.
- If there is increased likelihood of bacteriuria, preprocedure urine culture is recommended. Perioperative antimicrobial prophylaxis is recommended in all cases.
- Except for aspirin in some cases, oral anticoagulant or antiplatelet activity medications should be discontinued before percutaneous renal surgery.
- Preoperative cross-sectional imaging of complex cases, especially anomalous kidneys, helps plan patient position, choice of calyx, and orientation of the tract.
- Supine and flank positions offer some potential benefits over prone positioning in certain settings, but surgeon preference generally can determine the choice of position for percutaneous renal surgery.
- In the prone position, the preferred calyces are the posterior ones. Percutaneous access should never be directly into an infundibulum or the renal pelvis.
- An upper pole calyx is generally the most versatile site through which to enter the upper urinary tract collecting system.
- Subcostal access is the safest route to the kidney, but if entry directly above the 12th rib provides the best access to the optimal calyx, then the benefit generally exceeds the risk.
- Retrograde assistance facilitates antegrade access to the upper urinary tract collecting system.
- Ultrasonography and fluoroscopy are both commonly used to guide percutaneous access to the intrarenal collecting system. A useful combination is ultrasonography to guide the initial needle placement, which is followed by fluoroscopy to confirm that the desired calyx has been accessed and to direct and monitor the subsequent steps of the procedure.

POSTPROCEDURAL NEPHROSTOMY DRAINAGE

The final surgical consideration after percutaneous renal surgery is deciding which drain(s), if any, to insert into the upper urinary tract collecting system. Options include an externalized nephrostomy tube or nephroureteral stent, an internal or externalized ureteral stent, or no drainage tube at all. Additional discussion of these options can be found in Chapter 6.

Nephrostomy Tube

For years, the standard drainage after percutaneous surgery of the upper urinary tract collecting system has been an externalized nephrostomy tube. There are a variety of choices for postoperative nephrostomy tubes.

Balloon Catheters

The Foley and Councill catheters used for transurethral drainage can be used as nephrostomy tubes as well (Fig. 8-29). These tubes come in a range of diameters; typically 16- to 24-Fr catheters are used for postoperative nephrostomy drainage. The 5-mL retention balloon might be too large for some collecting systems and does not need to be completely inflated. The balloon can cause calyceal obstruction if it is pulled into an infundibulum. Saline or water should be used to inflate the balloon because viscous contrast material

might hinder emptying of the balloon when removal is attempted. An advantage of the Councill catheter is the ability to pass a small-caliber catheter through the end hole and down the ureter, providing more secure access to the upper urinary tract collecting system and maintaining ureteral patency. All nephrostomy tubes, even ones with robust internal retention devices, should be fixed to the skin externally with a suture or other mechanism. External fixation of a tube, however, does not necessarily prevent internal dislodgement of the tube. Especially in a large patient, the distance from the skin to the upper urinary tract collecting system can change with patient movement, and the tube (fixed at the skin) can pull out of the kidney. The potential for tube dislodgement is one of the best arguments in favor of nephrostomy tubes that have some extension down the ureter to maintain a conduit to the upper urinary tract collecting system, even if the renal pelvic portion of the tube is pulled out of the kidney.

Malecot Catheter

The wings of the Malecot catheter expand when the catheter is at rest, providing a modest but atraumatic and nonobstructive

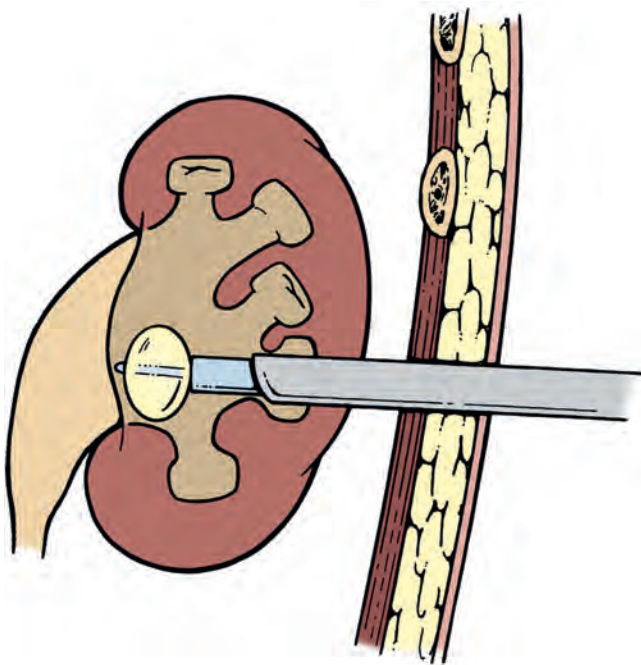


Figure 8-29. Councill catheter.

retention mechanism (Fig. 8-30A). When the catheter is being placed or removed, a stiffener is inserted through it to push on the distal end of the Malecot tip and straighten the wings. During removal this stiffener can misalign with the Malecot tip if the tube is not straight; pulling the catheter back until the tube is straight helps the stiffener line up properly. The Malecot catheter is also available with an extension that is directed down the ureter. This modification is called a “re-entry” catheter, because it simplifies placing a guidewire through the Malecot catheter and down the ureter into the bladder (Fig. 8-30B). The extension is long enough (18 cm) so that in most patients the Malecot tube can be withdrawn until the wings are externalized and a guidewire can be placed into the ureter. Malecot catheters for renal use are large-bore catheters, ranging from 16 to 30 Fr, although Malecot catheters as small as 8 Fr are available.

Cope Catheter

Cope nephrostomy tubes provide a more secure retention mechanism. A string exits the catheter a few centimeters from the distal tip and then re-enters the catheter near the tip (Fig. 8-31). Pulling on the string forms a secure coil that is not easily dislodged from the renal pelvis. The string is fixed at the external end of the tube with a locking mechanism or by wrapping it around the tube and fixing it in place with a rubber cuff. Cope catheters use the same coil shape used in pigtail ureteral stents. The active reinforcement of the coil strength by the string is thought to provide more secure retention than the passive coil of a pigtail, although one comparative study did not confirm this (Chuang et al, 2011), and as such Cope catheters have replaced pigtail catheters for most percutaneous uses. Cope nephrostomy tubes, ranging from 6 to 14 Fr in diameter, can be used for simple upper urinary tract drainage and instillation procedures, as well as after percutaneous surgery.

Nephroureteral Stent

The Cope retention mechanism is also used in nephroureteral stents. A nephroureteral stent has a renal coil like that of a Cope nephrostomy tube, but the tube continues on to a ureteral extension that travels down the ureter to end in a passive pigtail that rests in the bladder (Fig. 8-32). The ureteral portion can be the same diameter as the nephrostomy portion, or it can be narrower. A nephroureteral stent is passed percutaneously over a wire that ends in the bladder. After the end is coiled generously in the bladder, careful inspection of the fluoroscopy image shows the location of the side holes in the renal coil. By moving the catheter in and out while pulling on the string and rotating the external portion of the tube clockwise, the Cope retention coil is formed in the renal pelvis (Figs. 8-33 and 8-34 on the Expert Consult website) A nephroureteral

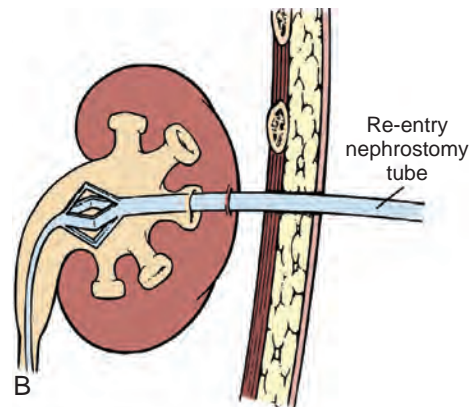


Figure 8-30. A, Malecot catheter. B, Malecot catheter with ureteral extension (“re-entry” catheter).

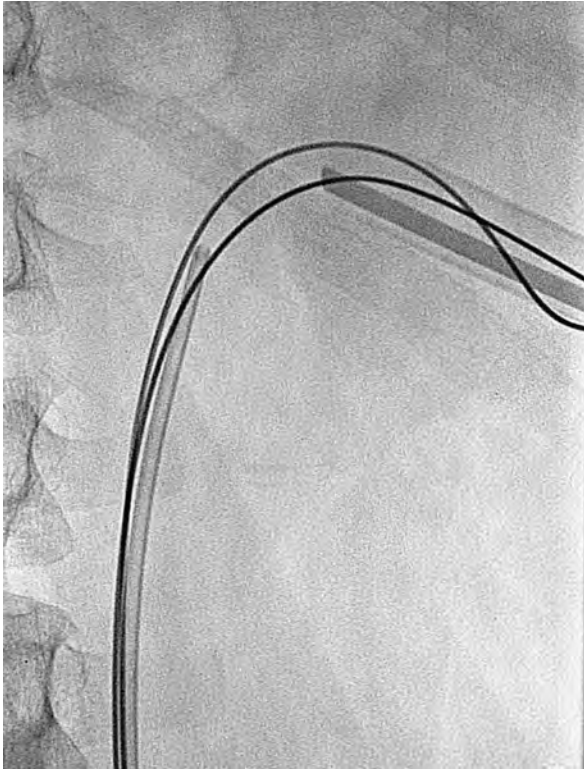


Figure 8-33. Stone removal is complete.

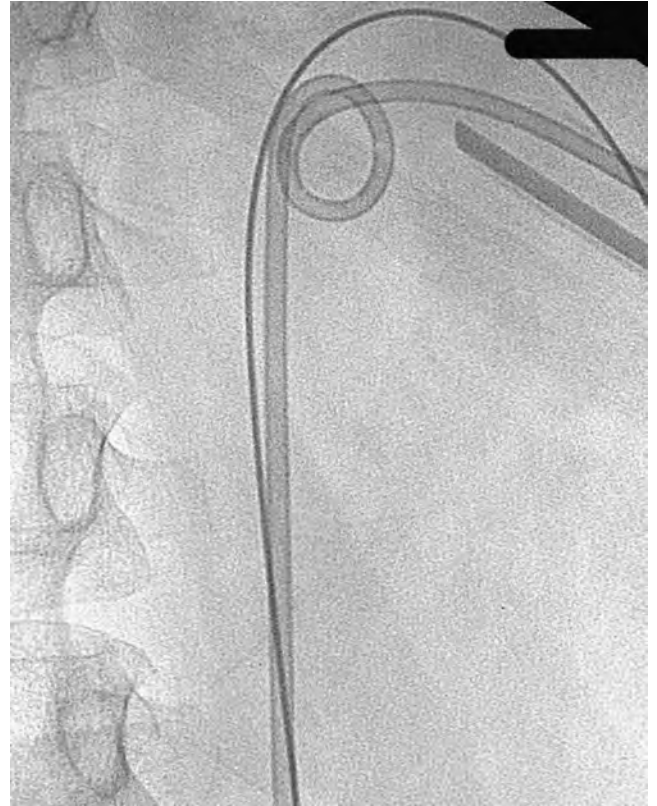


Figure 8-34. Nephroureteral stent has been placed over working wire. Removing the sheath and safety guidewire will complete the procedure.

stent offers excellent control of the entire upper urinary tract, from renal pelvis to bladder, and is unlikely to become dislodged. Nephroureteral stents are available in diameters of 8.5 or 10.2 Fr, and the standard lengths (from renal to bladder coil) are 20 to 28 cm.

Circle Catheter

A final type of nephrostomy tube is the circle nephrostomy tube (Fig. 8-35), which is secure, easily exchanged, causes little trauma, rarely occludes, and provides excellent drainage and avenue for irrigation of the renal pelvis. The circle nephrostomy tube requires two percutaneous access sites to the kidney, and this tube is most useful when maintenance of two tracts is desired, such as for irrigation of the renal pelvis or if more than one access is necessary for second-look nephroscopy (Kim et al, 2005). After obtaining access at two distant calyces, a flexible nephroscope or flexible ureteroscope passed over one wire is used to grasp the wire coming from the other site. When the endoscope is withdrawn, the wire is now in position to guide placement of the circle nephrostomy tube. Radiopaque markers on the tube delineate the location of the

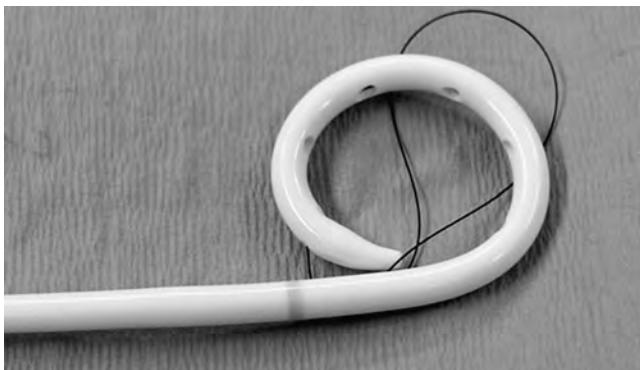


Figure 8-31. Cope catheter, with the retention string loosened for demonstration.

drainage holes, which should be maintained within the intrarenal collecting system. External drainage of the circle nephrostomy tube requires a Y-connector.

General Considerations

The advantages of a postoperative nephrostomy tube include good drainage and control of the upper urinary tract, and maintenance of percutaneous access for additional procedures. It was initially thought that a postoperative nephrostomy served to tamponade the nephrostomy tract and reduce hemorrhage, but subsequent studies have suggested that this is not the case. When hemorrhage does occur, however, the larger caliber of a nephrostomy tube provides better drainage of the upper urinary tract collecting system than does an internal ureteral stent. In addition, if a large perforation has occurred during the procedure, the additional diversion of urine away from the site might be advantageous. When a nephrostomy tube is left in place following percutaneous renal surgery, it is usually in the dilated access site. At least one group has attempted to reduce the discomfort associated with supracostal percutaneous renal surgery by placing a small-caliber postoperative nephrostomy tube in a new subcostal site and leaving the dilated supracostal access site without a nephrostomy tube (although there was no control cohort for comparison) (Kim et al, 2006).

Along with the nephrostomy, including a tube that goes down the ureter provides the greatest control and assurance of drainage. Because entry of a tube into the bladder is associated with additional symptoms, however, such a tube should only be used when needed. Considerations include the size of the patient (which determines to a large extent the risk of tube dislodgement), the importance of maintaining drainage, and the desire for ureteral intubation (e.g., ureteral obstruction that might resolve if intubated, ureteral injury that should be bypassed). Aside from the choice of retention mechanism, the main remaining consideration is the diameter of the nephrostomy tube.

A number of studies have compared the impact of nephrostomy tube diameter after percutaneous renal surgery, including two nonrandomized prospective trials (Maheshwari et al, 2000; De Sio et al, 2011) and four randomized controlled trials comparing

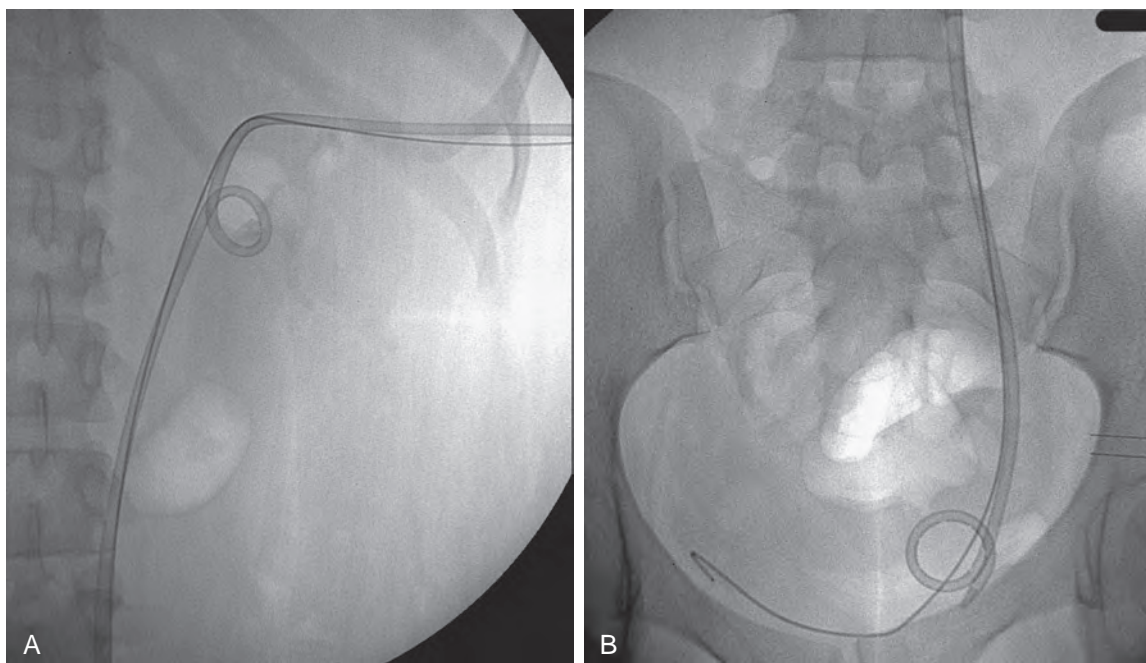


Figure 8-32. Nephroureteral stent. A, Renal coil. B, Bladder coil.

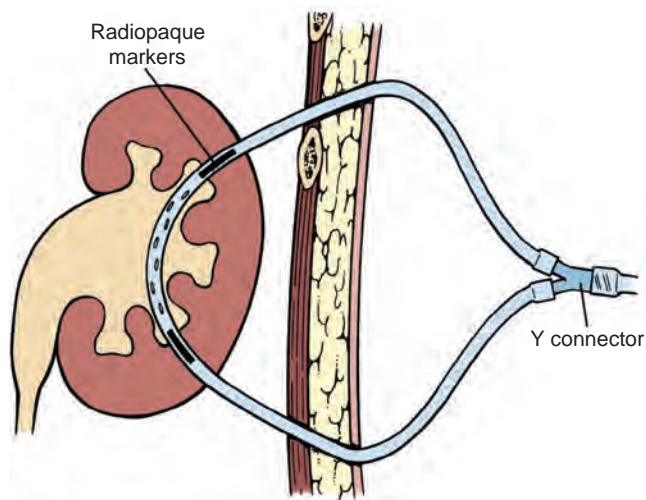


Figure 8-35. Circle nephrostomy tube.

large-caliber tubes (20 to 24 Fr) to small-caliber tubes (8 to 18 Fr) (Liatsikos et al, 2002; Pietrow et al, 2003; Desai et al, 2004; Marcovich et al, 2004). Among the six studies, comprising a total of 215 patients with nephrostomy tubes, five showed less pain and two reported less urinary leakage in the patients with smaller tubes. Bleeding did not increase in any of the studies for the groups with smaller tubes. Only one study showed no benefit to the smaller tube (Marcovich et al, 2004). Although tube diameter is not related to bleeding overall, the removal of larger tubes occasionally can be followed by immediate hemorrhage; this is rare with smaller tubes. As such, large-caliber nephrostomy tubes should be removed in a radiology suite where there is the opportunity for immediate replacement of the tube. Small-caliber tubes can be removed safely at the bedside after a period of clamping to assess clinically for distal ureteral obstruction.

“Tubeless” with Ureteral Stent

Wickham and colleagues (1984) initially proposed a “tubeless” percutaneous procedure—one that omits the postoperative nephrostomy tube. This practice never met with widespread acceptance, especially after Winfield and colleagues (1986) reported disastrous outcomes with this technique. The concept was revived in 1997 by Bellman and colleagues (1997), with the addition of an internal ureteral stent left in place for a week or two. Since then, many studies have evaluated the practice of omitting the nephrostomy tube after percutaneous renal surgery. Although this technique is called “tubeless,” most series employ a ureteral stent for a short period postoperatively.

Options for ureteral stenting without a nephrostomy tube after percutaneous renal surgery include an internal ureteral stent that is removed cystoscopically, an internal ureteral stent with an attached string that exits out the flank to allow removal of the ureteral stent without cystoscopy, and an externalized (out the urethra) ureteral stent that is removed along with the urethral catheter to which it is attached. The potential advantages of omitting the nephrostomy tube after percutaneous renal surgery include decreased pain and analgesic use, avoidance of an external drainage device, abbreviated hospital stay, and decreased health care costs (secondary to shortening the duration of hospitalization). Since the report of Bellman and colleagues (1997), many studies including several randomized controlled trials have evaluated the omission of a nephrostomy tube postoperatively with the placement of an internal ureteral stent. It is important to note that most of these studies excluded patients with significant bleeding or perforation or those for whom a second percutaneous procedure was anticipated.

A meta-analysis of tubeless percutaneous nephrolithotomies published in 2012 included 9 randomized controlled trials involving 547 patients (Shen et al, 2012). The results were stratified into 4 groups relative to the postprocedure drainage: tubeless with internal ureteral stent, small nephrostomy tube (8 to 9 Fr), medium nephrostomy tube (16 to 18 Fr), and large nephrostomy tube (20 to 24 Fr). The meta-analysis demonstrated that hospital stay and postoperative pain were reduced in the tubeless group compared to the medium and large tube groups, but were similar in the tubeless and small tube groups. There were no significant differences between the tubeless group and any of the nephrostomy tube groups with regard to fever/infection, transfusion, or operative time. In two earlier meta-analyses that combined the nephrostomy groups into two instead of three groups, 4 to 10 Fr versus 14 to 24 Fr (Yuan et al, 2011) and 8 to 9 Fr versus 14 to 26 Fr (Ni et al, 2011), shorter hospital stay and reduced postoperative pain were noted in the tubeless groups even in comparison to the small nephrostomy group. Thus the preponderance of evidence suggests that **tubeless percutaneous nephrolithotomy leads to shorter hospital stay and reduced postoperative pain in comparison to use of large post-procedure nephrostomy tubes, but that these benefits are less certain in comparison to small nephrostomy tubes.** Subsequent randomized controlled trials (Kara et al, 2010; Etemadian et al, 2011; Marchant et al, 2011; Shoma and Elshal, 2012; Lu et al, 2013) and one large multi-institutional matched case-control study involving 488 patients (Cormio et al, 2013) have yielded similar results with the exception of one study that indicated no benefit to the tubeless approach when the nephrostomy tube in the comparison group was removed the morning after the procedure (Mishra et al, 2010). This latter study was underpowered, however, with only 22 patients; all trends favored the tubeless group, but the differences did not reach statistical significance. In one randomized controlled trial, omission of the nephrostomy tube was associated with decreased cost (Feng et al, 2001). The tubeless approach appears to be safe even when supracostal access is used (Shah et al, 2006b; Jun-Ou and Lojanapiwat, 2010; Duty et al, 2013) and in the setting of bilateral simultaneous procedures (Gupta et al, 2003; Shah et al, 2005).

There are some disadvantages to using an internal ureteral stent as an alternative to a nephrostomy tube, however, including loss of the percutaneous tract for a secondary procedure and the cost, inconvenience, and discomfort associated with an internal ureteral stent that requires cystoscopic removal at a later date. To obviate the problems associated with the ureteral stent, several groups have offered alternatives including insertion of an externalized ureteral stent or insertion of an internal stent with an attached string that exits out the flank. In both cases the stent can then be removed before hospital discharge without an additional procedure. Goh and Wolf (1999) first reported the use of an externalized ureteral stent (single pigtail) as an alternative to a postoperative nephrostomy tube. Since then there have been a number of reports of this option (Lojanapiwat et al, 2001; Abou-Elela et al, 2007; Karami et al, 2007; Rana and Mithani, 2007; Al-Ba’adani et al, 2008) including three randomized controlled trials, one comparing an externalized ureteral stent to a large-caliber nephrostomy tube, which suggested a benefit in terms of reduced narcotic use and length of hospital stay (Tefekli et al, 2007), and two comparing internal and external ureteral stents, which showed no difference between the two techniques except for the association of the external stent with a lack of outpatient stent-related symptoms in one study (Gonen et al, 2009) and shorter hospital stay and less hematocrit drop in another study (Mercado et al, 2013). Shpall and colleagues (2007) described the modification of leaving the attached string on the stent and placing the stent “upside down” so that the string can exit the flank. They described removing the stent as an outpatient 3 and 12 days postoperatively, but since then others have reported removing the stent at the bedside on the first postoperative day (Berkman et al, 2008). Use of a Polaris Loop stent (Boston Scientific, Natick, MA) placed “upside down” offers less resistance at the time of removal (Fig. 8-36).

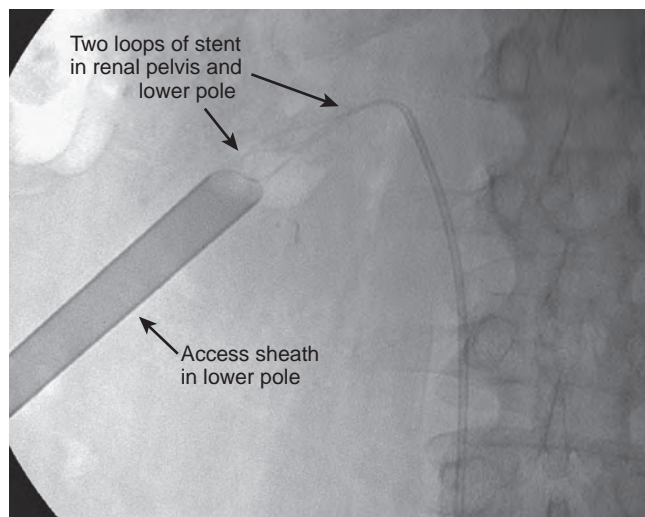


Figure 8-36. Use of a Polaris Loop stent (Boston Scientific, Natick, MA) placed “upside down.” An attached string is left exiting the flank, which allows removal of the stent without an additional procedure.

These modifications of nephrostomy tube omission avoid many of the disadvantages of an internal ureteral stent but still leave the problem of loss of access in case a secondary procedure is required. With improved endoscopes, better ancillary tools, and growing experience with percutaneous surgery, the need for secondary procedures is declining. In properly selected patients including those who do not for some other reason need external drainage (e.g., pyonephrosis, significant bleeding, significant collecting system injury) and those who are unlikely to need a secondary procedure, omission of the postoperative nephrostomy tube appears to be safe and effective.

No Drainage Tube

More recently, the idea of a “totally tubeless” percutaneous renal surgery, omitting both the nephrostomy tube and ureteral catheter, has been reintroduced. This can be considered in selected patients with low-volume stones, atraumatic single access, and no hemorrhage, perforation, or obstruction. A meta-analysis of five randomized controlled trials and four nonrandomized comparative studies comparing “totally tubeless” percutaneous nephrolithotomy to percutaneous nephrolithotomy with a postprocedure nephrostomy tube suggests that the “totally tubeless” approach reduces hospital stay, analgesic requirement, and time to return to normal activity without increasing complications (Zhong et al, 2013). A more pertinent comparison is “totally tubeless” versus internal stent without nephrostomy tube (“tubeless”); one retrospective nonrandomized comparison showed that the “totally tubeless” approach was associated with a longer hospital stay than the “tubeless” approach (Istanbulluoglu et al, 2010).

Adjuncts to Drainage without Nephrostomy Tubes

One of the concerns with any approach that omits the nephrostomy tube after percutaneous renal surgery is that of hemorrhage from the tract. Although the evidence from randomized controlled trials suggests that the size or presence of the nephrostomy tube does not affect the degree of postoperative bleeding, there is still a potential for dramatic bleeding after any percutaneous procedure—and such bleeding would be more problematic without a nephrostomy tube in place. Several groups have described adjuncts intended to enhance hemostasis of the percutaneous tract including placing a fascial suture (Li et al, 2011), direct monopolar cauterization of the tract (Mouracade et al, 2008; Chang et al, 2011), cryotreatment of the tract (Okeke et al, 2009), and

insertion/instillation of hemostatic agents into the tract including oxidized cellulose (Aghamir et al, 2006), gelatin sponge (Singh et al, 2008), gelatin granules plus thrombin (Lee et al, 2004b; Nagele et al, 2006; Li et al, 2011), fibrin glue (Noller et al, 2004; Gudeman et al, 2012), and collagen matrix coated with fibrin glue (Cormio et al, 2012). One nonrandomized comparison of percutaneous nephrolithotomy with and without electrode cauterization of the tract reported a lower blood transfusion rate in the first group (1.2% vs. 6.5%, respectively) (Jou et al, 2004). A nonrandomized comparison of tract cryotherapy without a nephrostomy tube in 30 patients versus a 24-Fr nephrostomy tube without tract cryotherapy in 30 patients suggested that there was shorter hospitalization and less hemorrhage and urine leakage in the patients treated with cryotherapy. The high rate of postoperative hemorrhage requiring angioembolization in the control group (13%) confounds the analysis (Okeke et al, 2009). There have been four randomized controlled trials of hemostatic adjuncts for percutaneous renal surgery without nephrostomy tubes, which compared patients managed without hemostatic adjuncts with those managed with gelatin sponge (Singh et al, 2008), oxidized cellulose (Aghamir et al, 2006), fibrin glue (Shah et al, 2006a), and collagen matrix coated with fibrin glue (Cormio et al, 2012). None of the three studies showed an impact of the adjunct on measures of hemostasis (postoperative hematocrit, hemorrhage, and/or blood transfusions). Narcotic use was less in the adjunct group in two of the three studies in which it was evaluated. Hospital stay and urinary leakage were each assessed in three studies, and each was improved in two studies. Some nonrandomized studies also have suggested a shortened hospitalization and/or reduced narcotic use after tract hemostatic maneuvers, but because improvements in hemostasis and urinary leakage are not consistently found, the mechanism for improvement in these secondary outcomes is not clear (Mikhail et al, 2003; Aron et al, 2004; Borin et al, 2005). Alternatives to local treatment of the tract include systemic enhancements to hemostasis. In one randomized trial, oral administration of the antifibrinolytic agent tranexamic acid was associated with less reduction in hematocrit and lower blood transfusion rate (Kumar et al, 2013). Overall, the usefulness of any of the adjuncts for tract hemostasis is not certain and further study is necessary.

KEY POINTS: POSTPROCEDURAL NEPHROSTOMY DRAINAGE

- The advantages of a postoperative nephrostomy tube include good drainage and control of the upper urinary tract, as well as maintenance of percutaneous access for additional procedures. Inclusion of an extension down the ureter provides the greatest control and assurance of drainage.
- Small-caliber nephrostomy tubes are associated with less pain than large-caliber nephrostomy tubes and are not associated with any increased hemorrhage.
- The use of a ureteral stent instead of a large-caliber nephrostomy tube is associated with reduced narcotic use and decreased length of hospitalization. The benefit of nephrostomy omission is less apparent when compared with a small-caliber nephrostomy. In properly selected patients, the use of a ureteral stent instead of a nephrostomy tube does not affect stone-free or complication rates.
- Options for ureteral stenting without using a nephrostomy tube afterward include an internal ureteral stent that is removed cystoscopically, an internal ureteral stent removed by a string exiting out of the flank, and an externalized ureteral stent that is removed along with the urethral catheter to which it is taped.
- Following straightforward procedures with atraumatic single access and no hemorrhage, perforation, or obstruction, some patients can be managed without a nephrostomy tube or a ureteral stent.
- The usefulness of adjuncts for tract hemostasis is uncertain.

TRAINING IN PERCUTANEOUS ACCESS AND PROCEDURES

Efforts to enhance training for percutaneous surgery of the upper urinary tract have focused on obtaining percutaneous access. Summarizing their own experience and other reports (Allen et al, 2005; Tanriverdi et al, 2007), de la Rosette and colleagues (2008) estimated that a trainee must perform approximately 24 percutaneous nephrolithotomies to attain proficiency, whereas competence is not achieved until the experience includes 60 cases, and excellence is not obtained until more than 100 cases have been performed. The American College of Radiology's "Practice Guideline for the Performance of Percutaneous Nephrostomy" recommends that a physician must have performed at least 15 percutaneous nephrostomies as primary operator, with acceptable outcomes, to be considered qualified as a supervising physician (ACR, 2007). Training during residency is the most effective process for developing the skills, but maintenance of skills requires ongoing experience. In a survey of urologists who completed a single residency program, those trained in percutaneous access were more likely to perform percutaneous surgical procedures than those not trained in percutaneous access (92% vs. 33%). Of those who performed percutaneous surgery, urologists with training performed more procedures than those without training (14.0 vs. 3.3 procedures annually). However, only about one third of respondents in both groups continued to attain their own percutaneous access (27% vs. 11%) (Lee et al, 2004a).

Nonhuman models can also assist in training (Laguna et al, 2002). Inanimate trainers can be homemade using gelatin and a vinyl glove (Rock et al, 2010) and Limbs and Things (Savannah, GA) market a commercial model. Several biologic models using ex vivo porcine kidneys incorporate a body wall simulator composed of a chicken carcass (Hammond et al, 2004; Hacker et al, 2007) or full-thickness porcine skin including subcutaneous tissue and muscle, with or without ribs (Strohmaier and Giese, 2009; Imkamp et al, 2011; Qiu et al, 2011). The most advanced trainer is the PERC Mentor (Simbionix, Lod, Israel), a computer-assisted simulator for percutaneous access procedures guided by fluoroscopy (Fig. 8-37).



Figure 8-37. PERC Mentor (Simbionix, Lod, Israel).

Some of the biologic models can be used to teach steps in the subsequent procedure (e.g., nephrolithotomy, endopyelotomy), but the main focus is on attaining percutaneous access. The PERC Mentor has undergone preclinical validation, confirming that training on the PERC Mentor improves performance on the PERC Mentor (Knudsen et al, 2006; Zhang et al, 2013), and that trained individuals more proficiently attain percutaneous renal access in a porcine in vivo model (Margulis et al, 2005), but validation of the impact on performance in the human operating room is lacking (Stern et al, 2007). At the least, these trainers can serve as an introduction for the trainee by orienting them to the necessary anatomic considerations and familiarizing them with the physical movements of the procedure. Whether these or other devices can be used to validate the skills of trainees and practitioners is unknown. Moreover, the most effective training will incorporate cognitive tasks as well as psychomotor ones (Tjiam et al, 2012; Mishra et al, 2013).

Taking simulation even farther, Bruyère and colleagues (2008) used computer-assisted design and rapid prototyping based on CT images to create a silicon model of a patient's kidney, complete with artificial flank and respiratory motion. After practicing percutaneous nephrolithotomy on the model several times, the percutaneous nephrolithotomy on the patient went smoothly using the practiced technique. Creating a specific renal model for each patient is too expensive and laborious for routine application currently, but with anticipated technical improvements, this iteration of "personalized medicine" might play a role in training and treatment planning.

COMPLICATIONS

Given enough time and access sites to the upper urinary tract collecting system, in most cases the primary goal of the percutaneous procedure can be achieved. The challenge with percutaneous surgery, then, is to do so while also avoiding complications. If complications do occur, then prompt recognition and management will usually prevent major morbidity. CT appears to be the most sensitive tool for determining postoperative complications (Semins et al, 2011; Gnassin et al, 2012). Some complications of percutaneous renal surgery are specific to the procedure, including migration of stone outside the kidney, retained foreign bodies such as tips of wires and probes, and tumor seeding of the percutaneous tract. In this section the general complications of percutaneous renal surgery are discussed.

Using the Dindo-modified Clavien system to categorize complications following percutaneous nephrolithotomy, 77% of patients in a systematic review of reports including a total of 11,929 patients experienced no complications (Clavien 0) (Seitz et al, 2012). An additional 11% of patients exhibited only minor deviations from the normal postoperative course (only minimal pharmacologic treatment, Clavien 1), and 7.0% showed Clavien 2 complications (includes additional pharmacologic treatment, blood transfusion, and parenteral nutrition). "Major" complications occurred in <5% of patients (4.1% Clavien 3, requiring surgical, endoscopic, or radiologic intervention; 0.6% Clavien 4, including life-threatening complications; 0.04% Clavien 5, mortality). Similar results were reported in a large multi-institutional study (including 5724 patients), which also used the Dindo-modified Clavien system (Labate et al, 2011). Of the patients, 79% had no complications, 16% had Clavien category 1 or 2 complications, and 4.2% had complications categorized as Clavien category 3 or greater.

Acute Hemorrhage

Acute hemorrhage is the most common significant complication of percutaneous access into the upper urinary tract collecting system. Percutaneous nephrostomy alone results in hemorrhage requiring transfusion in 0.5% to 4% of procedures (Radecka and Magnusson, 2004; Wah et al, 2004; ACR, 2007; Rana et al, 2007). With the addition of percutaneous nephrolithotomy, likely owing to the larger caliber of the percutaneous tract and increased intrarenal manipulation, the incidence of hemorrhage requiring

blood transfusion rises to between 0.8% and 20% (Kukreja et al, 2004; Netto et al, 2005; Preminger et al, 2005; Muslumanoğlu et al, 2006; Duvdevani et al, 2007; Chew et al, 2009; Tomaszewski et al, 2010b; Akman et al, 2011; Labate et al, 2011; Keoghane et al, 2012). This wide variation in transfusion rate, which likely is more variable than the rate of significant hemorrhage, reflects differences in the complexity of the procedure, patient factors, and physician triggers for the use of blood products. In a systematic review of reports including a total of 11,929 patients, a 7% blood transfusion rate was reported (Seitz et al, 2012). Factors associated with hemorrhage during percutaneous renal surgery include patient characteristics, multiple access sites, supracostal access, increasing tract size, tract dilation with methods other than balloon dilation, prolonged operative time, and renal pelvic perforation (Stoller et al, 1994; Martin et al, 1999; Kukreja et al, 2004; Netto et al, 2005; Hegarty and Desai, 2006; Chew et al, 2009; Rastinehad et al, 2009; Akman et al, 2011; Keoghane et al, 2012). In a large multi-institutional study including 5537 patients, the only factors associated with hemorrhage during percutaneous renal surgery were larger sheath size, prolonged operative time, and greater stone burden (Yamaguchi et al, 2011).

Technical errors predispose to hemorrhage as well. Infundibular entry risks injury to interlobar (infundibular) arteries. Access into an anterior calyx or any calyx that does not afford direct access to the pathology invites overly aggressive torquing of the sheath and rigid endoscope, which also can lead to hemorrhage. If direct access cannot be obtained, then flexible instrumentation should be considered. Additionally, misuse of any tool—lithotrites, resectoscopes, wires, sheaths, graspers, baskets, and so on—can cause hemorrhage.

Most hemorrhage occurs from the renal parenchyma, and in most cases this hemorrhage is not significant. Small arteries and veins are always injured to some degree by percutaneous entry into the kidney. Parenchymal bleeding is minimized by proper entry and dilation and by careful manipulation of the sheath, but it still can occur. The access sheath provides intraoperative tamponade of parenchymal bleeding. Postoperatively, hemostasis is achieved by collapse of the parenchyma onto itself. Unless the postoperative nephrostomy tube is as large as or larger than the sheath used during the procedure, it likely does not contribute to hemostasis. There is no difference in measures of postoperative bleeding between small (8- to 18-Fr) and large (20- to 28-Fr) tubes (Maheshwari et al, 2000; Liatsikos et al, 2002; Pietrow et al, 2003; Desai et al, 2004; Marcovich et al, 2004; De Sio et al, 2011), and randomized controlled trials suggest that hemorrhage is no greater when the nephrostomy tube is omitted altogether (Shen et al, 2012). If there is noticeable bleeding from the tract after sheath removal following an otherwise unremarkable procedure, this suggests bleeding from intraparenchymal vessels. Hemostatic maneuvers such as cauterization or placement of hemostatic material can be considered, but in general the best management is to insert and occlude a nephrostomy tube, apply pressure to the incision, and allow the collecting system to clot off. A tubeless approach is not advised in such cases because maintenance of percutaneous access to the upper tract might facilitate management. Nephrostomy tubes should not be irrigated on the day or evening of the procedure if they are not draining; it is best to allow the collecting system to remain occluded to tamponade bleeding. By the next morning, it is safe to irrigate the tube gently because hemostasis is more certain.

If the procedure was not complicated by bleeding, but severe hemorrhage occurs following sheath removal and is refractory to the hemostatic measures described earlier, then use of a Kaye Nephrostomy Tamponade Balloon (Cook Urological, Spencer, IN) should be considered. This is a nephrostomy tube surrounded by a balloon (Fig. 8-38) (Kaye and Clayman, 1986), which is inflated up to 36 Fr to tamponade the parenchymal bleeding just as the sheath did intraoperatively. This device should be removed under fluoroscopic guidance with guidewire access down the ureter in case tube reinsertion is required for recurrent bleeding.

Intraoperative hemorrhage from an injured vein or artery within the collecting system mandates cessation of the procedure

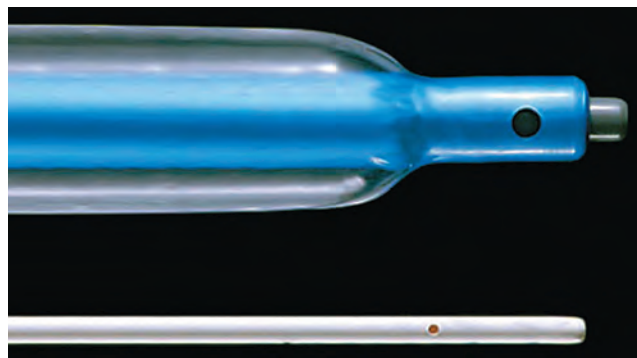


Figure 8-38. Kaye Nephrostomy Tamponade Balloon.

if vision is lost. In most cases, especially if the injury appears to be venous, then placing a nephrostomy tube and letting the collecting system clot off is effective. If this is not effective, however, Gupta and colleagues (1997) have described the insertion of a Councill catheter as a nephrostomy tube, with the balloon inflated slowly at the site where contrast material enters into the venous system until repeated nephrostography shows no more extravasation of contrast material (Fig. 8-39). A hole should be cut into the tube proximal to the balloon to provide drainage of calyces obstructed by the balloon (Fig. 8-40). Millard and associates (2010) have reported an addition to this technique, in which gelatin matrix hemostatic sealant is injected into the tract peripheral to the balloon occluding the renal injury and then a second catheter is inserted with the balloon placed just underneath the skin surface, such that the tract is occluded and the gelatin matrix hemostatic sealant contributes to hemostasis. Another alternative, described in one case of a large venous injury, is to place a large-bore catheter through the injury site into the main renal vein and then back it out several days later (Shaw et al, 2005). A small arterial injury can sometimes be addressed with fulguration under direct vision, but if this is not successful and bleeding does not cease with pressure, or in cases of significant arterial hemorrhage, then selective angioembolization will likely be required (see later).

Delayed Hemorrhage

Postoperative hemorrhage can occur with the nephrostomy tube in place, at time of tube removal, or after discharge from the hospital. Approximately 1% of major percutaneous procedures are complicated by delayed hemorrhage requiring treatment (Kessaris et al, 1995; Martin et al, 2000; Richstone et al, 2008; Tomaszewski et al, 2010b; Keoghane et al, 2012). In one large series, the incidence was greatest following percutaneous resection of upper tract urothelial carcinoma (3.2%) and least following percutaneous endopyelotomy (0.8%) (Richstone et al, 2008). In a systematic review of reports including a total of 11,929 patients, a 0.4% rate of delayed hemorrhage requiring treatment was reported (Seitz et al, 2012). Delayed hemorrhage is usually a result of arteriovenous fistulas or arterial pseudoaneurysms, with the latter being more common. Arteriovenous fistulas occur when a paired set of artery and vein is injured, and arterial blood enters directly into the vein (Fig. 8-41). The weak vein wall cannot sustain the high arterial pressure and ruptures. Bleeding into the collecting system is most commonly noted, but it can be outside the kidney as well. The latter should be suspected if the hematocrit falls but the urine remains relatively clear. It can be confirmed with CT or ultrasonography. An arterial pseudoaneurysm occurs when an artery is injured, clots off, and then intermittently ruptures, often clotting off again at variable intervals (Fig. 8-42A). Continuous bleeding suggests an arteriovenous fistula, and intermittent bleeding suggests arterial pseudoaneurysm, but the distinction is not critical because treatment is the same. In a large series conducted by Kessaris and colleagues (1995), of the 0.8% of 2200 patients requiring treatment for

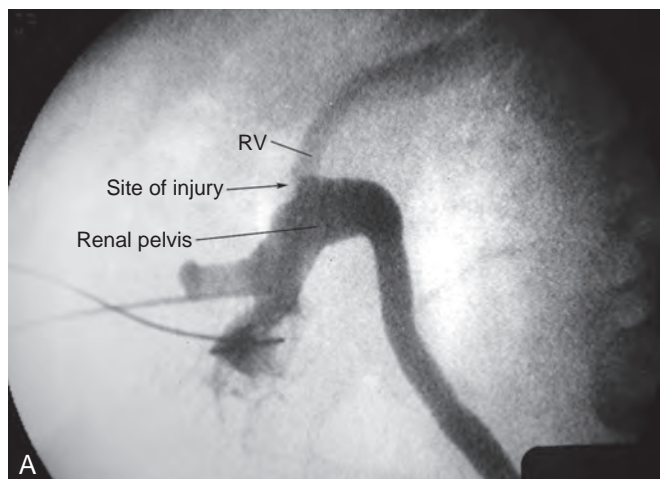


Figure 8-39. A, Nephrostogram shows contrast material entering the renal vein (RV), indicating a large venous injury. B, The balloon of a Council catheter nephrostomy tube is inflated at the site of injury (C) until contrast material no longer enters the RV.

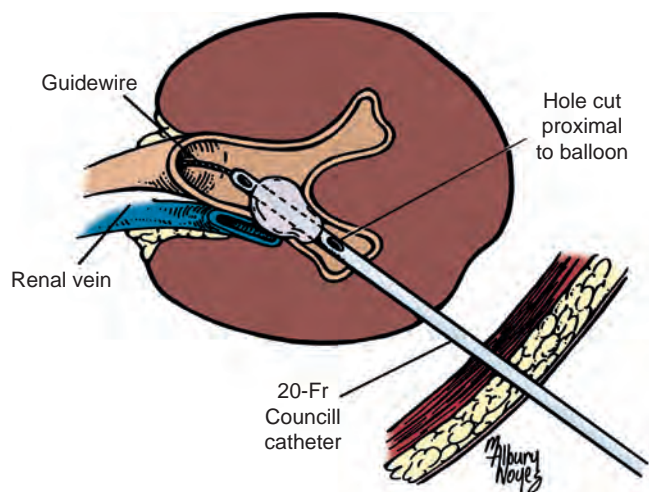
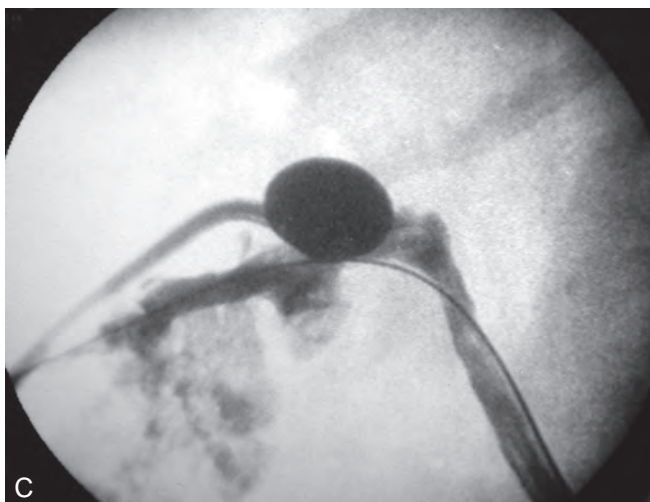
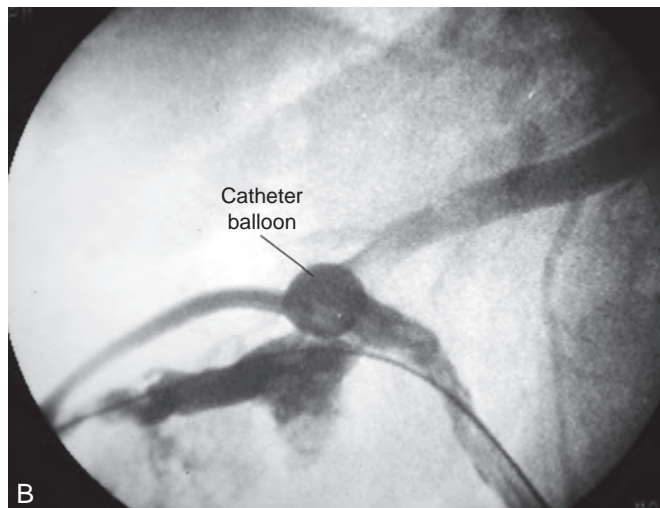


Figure 8-40. An extra hole created proximal to the balloon of the Council catheter allows for drainage of calyces obstructed by the balloon.

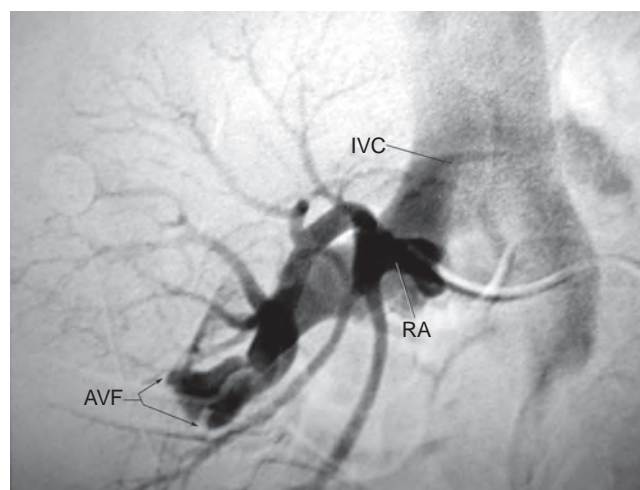


Figure 8-41. Angiography of the renal artery (RA) is followed promptly by contrast material appearing in the inferior vena cava (IVC), suggesting the presence of an arteriovenous fistula (AVF).

delayed hemorrhage after percutaneous renal surgery, 24% of the hemorrhages occurred within 24 hours of surgery, 41% between 2 and 7 days after surgery, and 35% more than 7 days later. Any report of bright red blood in the urine after percutaneous renal surgery should prompt hospital admission and consideration of angiography, which is diagnostic in more than 90% of

cases (Richstone et al, 2008). The standard treatment of renal arteriovenous fistulae and arterial pseudoaneurysms is selective angioembolization, which is highly effective. Among five series reporting a total of 109 patients undergoing selective angioembolization after percutaneous renal surgery, there was success after a single treatment in 98 patients (90%) (Patterson et al, 1985; Martin

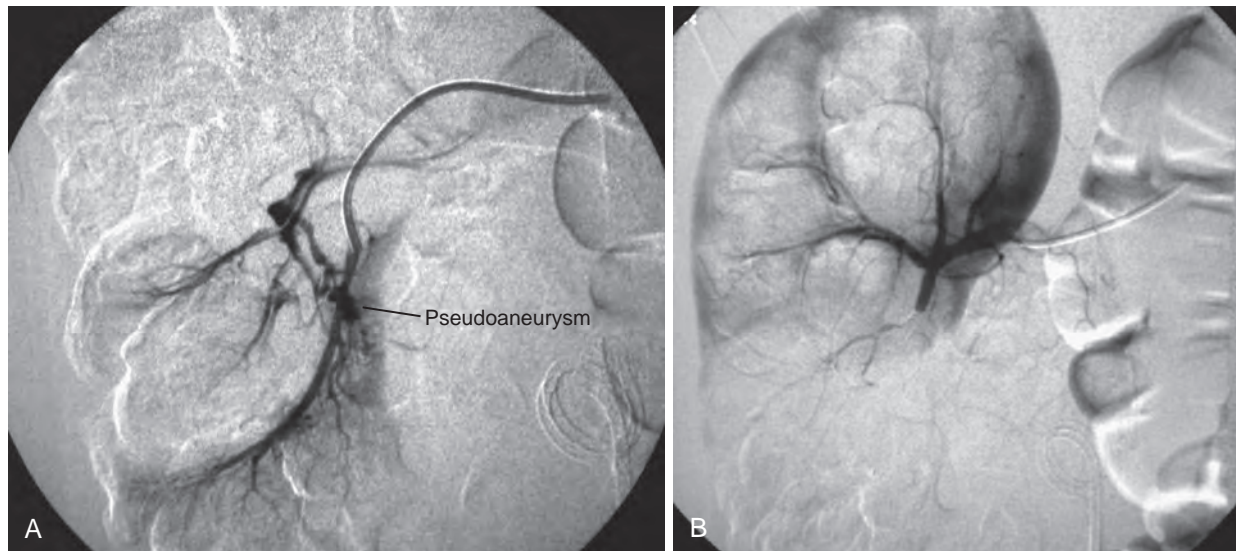


Figure 8-42. A, Angiography demonstrates a pseudoaneurysm in the lower pole of the right kidney. B, Angioembolization was successful at occluding the pseudoaneurysm, but it also devascularized a large portion of the lower pole.

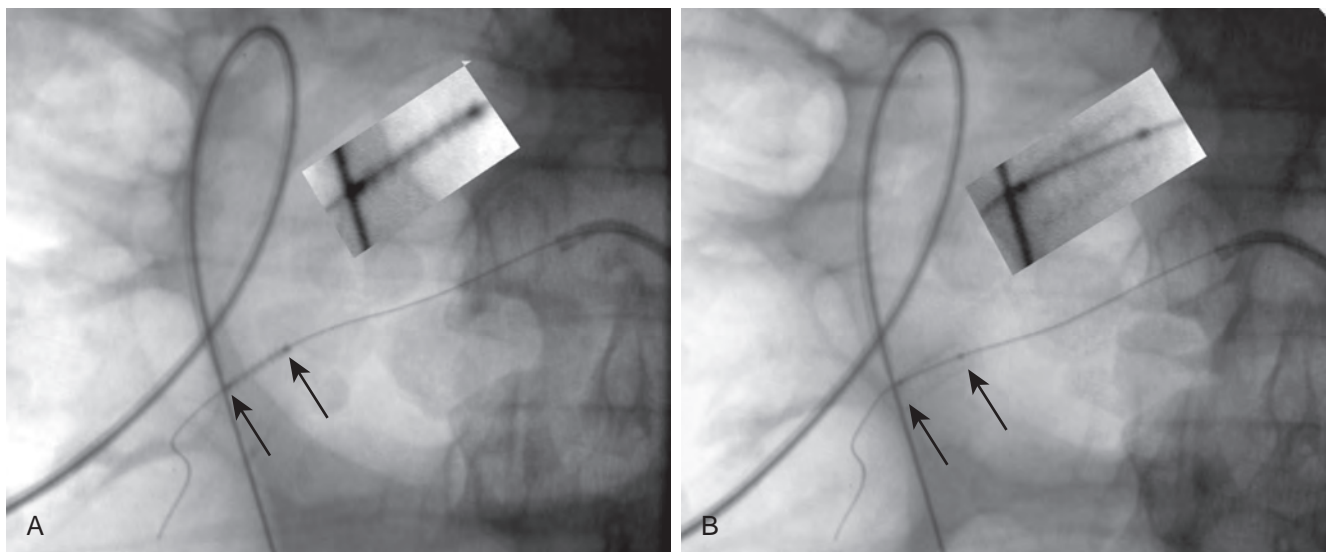


Figure 8-43. Covered arterial stent placed in branch of renal artery injured during endopyelotomy. A, Stent before balloon expansion. B, Stent after balloon expansion. Inset in each image is a 2× enlargement of stent (arrows).

et al, 2000; Richstone et al, 2008; Jain et al, 2009; Ji et al, 2012). Nephrectomy may be required if selective angioembolization fails, and partial or total renal loss may occur if angioembolization is not selective enough (Fig. 8-42B). Additionally, the embolization coils can migrate to unwanted locations immediately or this migration might be delayed.

A recently introduced alternative to angioembolization is endovascular placement of a covered stent to occlude the site of arterial injury (Sprouse and Hamilton, 2002; Areste et al, 2005). This treatment maintains patency of the feeding artery, thereby preserving renal parenchyma, and obviates the risk of migration of embolization coils (Fig. 8-43). Another alternative is ultrasonographically guided percutaneous puncture of an arterial pseudoaneurysm, with injection of thrombin or fibrin tissue adhesive into the pseudoaneurysm (Benjaminov and Atri, 2002; Lagana et al, 2006; Sakr et al, 2009).

Untreated coagulopathy is an absolute contraindication to percutaneous renal surgery. Percutaneous access can be obtained safely if coagulopathy is reversed or anticoagulant medications are stopped. Anticoagulants can be restarted after the urine clears, preferably after nephrostomy tube removal, but the patient should be closely monitored.

Collecting System Injury

Tears in the infundibulum are not uncommon during percutaneous surgery of the upper urinary tract collecting system. They generally do not cause problems intraoperatively as long as there is no hemorrhage. Ureteral injuries are rare but can occur as a result of inflating the ureteral balloon occlusion catheter in the ureter or during other ureteral manipulation. These injuries generally will heal over a ureteral stent. Renal pelvic perforation can occur during initial



Figure 8-44. Renal pelvic perforation confirmed with injection of contrast material through flexible nephroscope.

access or during dilation. Pushing too hard on a renal pelvic stone during lithotripsy, or misusing a lithotripter or resectoscope, can also perforate the renal pelvis. Renal pelvic perforation is usually recognized intraoperatively (Fig. 8-44). Collapse of a previously distended renal pelvis is a usual sign if the perforation is not visualized directly at first. A perforation that has not been recognized intraoperatively might be heralded by postoperative abdominal distention, ileus, and/or fever. If noted intraoperatively, abort the procedure unless it is near completion, in which case the task can be completed at lower irrigation pressure if the patient is doing well clinically. At the completion of a case in which renal pelvic perforation has been noted, insert a nephroureteral stent or a nephrostomy tube plus an internal ureteral stent to optimize drainage, and then wait 2 to 7 days before nephrostography and tube removal, depending on the severity of the injury. If renal pelvic perforation is detected postprocedure, despite adequate drainage of the collecting system, then placement of a percutaneous drain into the urinoma might be required. There have been reports of massive intra-abdominal collection of extravasated fluid after percutaneous renal surgery (Peterson et al, 1985; Pugach et al, 1999; Ghai et al, 2003; Etemadian et al, 2012).

Visceral Injury

Any abdominal organ close to the kidney can be injured during percutaneous renal surgery including the colon, duodenum, jejunum, spleen, liver, and biliary system.

Colon injury occurs during percutaneous renal surgery in the prone position at a rate of less than 1% (Segura et al, 1985; Lee et al, 1987; Gerspach et al, 1997; El-Nahas et al, 2006; Duvdevani et al, 2007; Michel et al, 2007; Kachrilas et al, 2012). As one would expect based on the anatomy, with the apposition of the colon to the kidney being greatest on the left side and at the lower pole, the left colon is injured twice as often as the right colon, and the majority of colon injuries involve access to the lower pole (El-Nahas et al, 2006). Additional risk factors include advanced patient age, dilated colon, previous colon surgery or disease, thin body habitus, and the presence of a horseshoe kidney (Goswami et al, 2001; El-Nahas et al, 2006; Michel et al, 2007; Korkes et al, 2009). Injury might be less likely with the patient in the supine position; one study reported a retrorenal colon on CT in 1.9% of

patients in the supine position versus 10% in prone patients (Hopper et al, 1987). The clinical incidence of colon injury, however, is much lower than this figure suggests.

Intraoperative detection of colonic injury confers easier management. If not determined intraoperatively, colon injury should be considered postoperatively if a patient develops unexplained fever, prolonged ileus, unexplained leukocytosis, rectal bleeding, evidence of peritoneal inflammation, or fecaluria or pneumaturia. Clinically apparent nephrocolonic fistula may be the presenting sign, or the injury may not be noted until the time of postoperative nephrostogram. **Most colon injuries are extraperitoneal and can be managed conservatively** (Gerspach et al, 1997; El-Nahas et al, 2006; Korkes et al, 2009; Traxer, 2009; Goger et al, 2012; Kachrilas et al, 2012). The main principle of care is prompt and separate drainage of the colon and urinary collecting system. The surgeon should back out the offending nephrostomy tube into the colon to serve as a colostomy tube, consider exchanging it for a larger tube to enhance colonic drainage, and obtain separate access to the upper urinary tract with either a new percutaneous access that does not traverse the colon or a retrograde-placed ureteral stent. Administer broad-spectrum antibiotics. Give nothing by mouth for a few days, and then start clear liquids. If there is no increase of colostomy output, then administer high-calorie protein supplementation and eventually a regular diet. Parenteral feeding is usually not required. Confirm lack of communication between the colon and collecting system with contrast injection of the tubes before removing them. If the injury is intraperitoneal, or if the patient develops peritonitis or sepsis, then open surgical repair may be required.

Small bowel injuries are even less common than colonic injury, described in only a few case reports (Culkin et al, 1985; Morris et al, 1991; Kumar et al, 1994; Ahmed and Reeve, 1995; Santiago et al, 1998; Lopes-Neto et al, 2000; Al-Assiri et al, 2005; Ricciardi et al, 2007; Traxer, 2009; Winer et al, 2009). Detection is by clinical signs and symptoms of peritonitis or by noting a nephroenteric fistula during postoperative nephrostography. Although open surgery may be required, conservative management using percutaneous intraduodenal catheterization or simple nasogastric or nasoduodenal drainage, combined with drainage of the upper urinary tract, fasting, and parenteral feeding, has been successful.

Studies based on CT and MRI have suggested that splenic and hepatic injuries should be unlikely unless the kidney is accessed above the 10th rib, although access above the 11th or 12th rib might traverse these organs in rare cases (Hopper and Yakes, 1990; Robert et al, 1999). If splenomegaly or hepatomegaly is present, these relationships change and access guided by CT is recommended. Splenic or hepatic injuries to orthotopic and normal-sized organs occur almost exclusively with supracostal upper pole renal access. Splenic injury might require laparotomy and potentially splenectomy owing to hemorrhage (Kondas et al, 1994; Shah et al, 2007), but conservative management has been successful as well (Goldberg et al, 1989; Santiago et al, 1998; Carey et al, 2006; Schaeffer et al, 2008; Thomas et al, 2009; Desai et al, 2010). Liver injury is less likely to be associated with significant hemorrhage—indeed the liver can be traversed percutaneously to obtain biliary access (Nadler et al, 2002), and purposeful transhepatic percutaneous renal surgery has been reported (Matlaga et al, 2006). As such, liver injuries during percutaneous renal surgery can be managed conservatively (El-Nahas et al, 2008).

There have been a few reported cases of biliary peritonitis resulting from injury of the gallbladder or biliary tree, which require exploratory laparotomy/laparoscopy and cholecystectomy owing to the high mortality rate of bile peritonitis (Martin et al, 1996; Saxby, 1996; Kontothanassis and Bissas, 1997; Fisher et al, 2004; Ricciardi et al, 2007; Patel and Nakada, 2010). Postoperative pancreatitis, without evidence of direct pancreatic injury, has been described as well (Chitale et al, 2005).

Pleural Injury

Hydrothorax, and occasionally pneumothorax, is a risk of percutaneous access to the upper urinary tract collecting system.

Supracostal access is the main risk factor; access below the 12th rib rarely results in hydrothorax or pneumothorax (<0.5%) (Munver et al, 2001; Radecka et al, 2003; Lojanapiwat and Prasopsuk, 2006; Maheshwari et al, 2009). The incidence of pleural complications with punctures above the 12th rib (the 11th intercostal space) is generally considered an acceptable risk if that approach provides optimal access to the upper urinary tract. Access above the 11th rib or higher carries a much greater risk of pleural injury. Among 16 reports that distinguished between access above the 12th rib and access above the 11th rib, reporting a total of 1384 supracostal percutaneous accesses, the incidence of hydro/pneumothorax that required intervention varied from 0% to 18% for access superior to the 12th rib (weighted mean of 4.6%) and from 0% to 100% for access superior to the 11th rib (weighted mean of 24.6%) (Young et al, 1985; Picus et al, 1986; Narasimham et al, 1991; Golijanin et al, 1998; Kekre et al, 2001; Munver et al, 2001; Gupta et al, 2002; Wong and Leveille, 2002; Muzrakchi et al, 2003; Radecka et al, 2003; Aron et al, 2005; Lojanapiwat and Prasopsuk, 2006; Yadav et al, 2006; Shaban et al, 2008; Sukumar et al, 2008; Yadav et al, 2008).

Nephropleural fistula (urinothorax) is a direct and persistent communication between the intrarenal collecting system and the intrathoracic cavity (Ray et al, 2003; Shleyfer et al, 2006; Handa et al, 2007). It can follow percutaneous renal access of the upper urinary tract in the setting of pleural transgression. Some degree of distal ureteral obstruction usually contributes to the problem. Most commonly, nephropleural fistula is diagnosed after the percutaneous tube is removed, but it can occur in the setting of a recognized hydrothorax when the persistent communication is documented on nephrostography at the time of intended tube removal. Lallas and colleagues (2004) reported that nephropleural fistula never occurred in association with subcostal access but did complicate 2.3% of punctures superior to the 12th rib and 6.3% of punctures superior to the 11th rib.

Pleural complications of supracostal percutaneous access can often be detected with chest fluoroscopy during or at the conclusion of the procedure. Fluid can be seen tracking along the lateral borders of the chest cavity and compressing the ipsilateral lung. Although postoperative chest radiography is more sensitive than intraoperative fluoroscopy, some authors report that thoracostomy was never required on the basis of postoperative chest radiography when intraoperative chest fluoroscopy was negative (Ogan et al, 2003; Bjurlin et al, 2012). Nonetheless, formal chest radiography is recommended following all cases of supracostal percutaneous renal access.

Thoracostomy is not necessary for all patients with hydrothorax. If hydrothorax is noted intraoperatively, then insert a small-caliber (8-Fr to 12-Fr) Cope nephrostomy tube as the thoracostomy (Fig. 8-45), using fluoroscopic guidance and the same general techniques as for antegrade percutaneous renal access (Ogan and Pearle, 2002). A Heimlich valve, rather than water seal drainage, is all that is necessary in the absence of lung injury. If a hydrothorax is noted on the postoperative chest radiograph, then place a small-caliber tube only if the effusion is large or if there is evidence of respiratory compromise or hemodynamic instability. A large-bore thoracostomy tube for lung injury is rarely required.

Metabolic and Physiologic Complications

Normal saline should be the irrigant for percutaneous renal surgery, with the exception of glycine or similar nonelectrolytic isotonic fluids when monopolar electrocautery is used. Irrigation with water during percutaneous renal surgery risks intravascular hemolysis, which can be fatal. At least one death associated with water irrigation during percutaneous nephrolithotomy has been described (Bennett et al, 1984), and the author is aware of an unreported case. Intravascular or extravascular extravasation of nonelectrolytic isotonic fluid from continued irrigation in the setting of a large venous injury or collecting system perforation, respectively, can result in hyponatremia and other electrolyte abnormalities, renal or hepatic dysfunction, and mental status changes. When



Figure 8-45. A 12-Fr Cope catheter placed into the chest when a large hydrothorax was noted intraoperatively on fluoroscopy.

normal saline is used in uncomplicated cases, the amount of fluid absorption is generally clinically insignificant (Kukreja et al, 2002; Koroglu et al, 2003), although in one study 28% of patients absorbed more than a liter (Malhotra et al, 2001). A large amount of saline extravasation can lead to clinically significant respiratory distress or cardiac failure resulting from volume overload.

Venous gas embolism is a rare but potentially fatal complication of percutaneous renal surgery. The gas (in this case, air) enters the venous system and passes through the right heart into the pulmonary circulation, blocking the output of the right heart, which results in hypoxemia, hypercapnia, and depressed cardiac output. Gas can also pass through a patent foramen ovale to enter the arterial system, which can result in neurologic deficits. Among six reported cases of venous gas embolism in association with percutaneous renal surgery, three were associated with air pyelography in combination with percutaneous access of the kidney (Miller et al, 1984; Cadeddu et al, 1997a; Droghetti et al, 2002), one involved percutaneous surgery without air pyelography (Turillaz et al, 2009), and two occurred after retrograde injection of air into the renal pelvis but before percutaneous puncture (Varkarakis et al, 2003; Song et al, 2007). Venous gas embolism is indicated by hypoxemia, evidence of pulmonary edema, increased airway pressure, hypotension, jugular venous distention, facial plethora, dysrhythmias, and auscultation of a mill-wheel cardiac murmur and/or the appearance of a widened QRS complex with right heart strain patterns on electrocardiography. The most sensitive measure is a sudden decrease in capnometry reading of the P(end-tidal)CO₂. Swift response is required and includes rapid ventilation with 100% oxygen, positioning the patient head down with the right side up, and general resuscitative maneuvers.

Postoperative Fever and Sepsis

After percutaneous nephrolithotomy, 15% to 30% of patients develop a fever. Risk factors for fever/infectious complications following percutaneous nephrolithotomy include diabetes mellitus, paraplegia, indwelling ureteral stent or nephrostomy tube, previous percutaneous nephrolithotomy, multiple access tracts, infection stone, positive preoperative urine culture, larger stones, and hydro-nephrosis (Charton et al, 1986; Troxel and Low, 2002; Aghdas et al,

2006; Draga et al, 2009; Korets et al, 2011; Lojanapiwat and Kitirattrakarn, 2011; Kumar et al, 2012; Gutierrez et al, 2013). Most patients with fever after percutaneous nephrolithotomy, assuming appropriate antimicrobial prophylaxis, do not have infection (Cadeddu et al, 1998). Sepsis occurs in 0.5% to 2.5% of patients after percutaneous nephrolithotomy (Dogan et al, 2007; Duvdevani et al, 2007; Gonen et al, 2008b; Labate et al, 2011; Lojanapiwat and Kitirattrakarn, 2011; Seitz et al, 2012; Li et al, 2013a). Sepsis implies an infection, which is not always present; “systemic inflammatory response syndrome” is a more accurate description. Positive preoperative urine cultures should be treated. Even if bacteriologic cure is not possible (e.g., infectious stone, indwelling nephrostomy tube), bacterial counts should be suppressed as much as possible to reduce the risk of infectious complications. Nonetheless, a negative urine culture does not guarantee against sepsis because the voided urine culture may not reflect the intrarenal urine (Rao et al, 1991; Mariappan et al, 2005; Lojanapiwat and Kitirattrakarn, 2011; Korets et al, 2011). Because the febrile patient who will progress to sepsis cannot be predicted, careful observation, appropriate diagnostic evaluation, and initiation of antimicrobial therapy and other supportive care are indicated if a postoperative fever does not resolve promptly.

If pus is aspirated upon initial percutaneous entry to the upper urinary tract, the safest measure is to abort the procedure and leave a nephrostomy tube for drainage. Aron and associates (2005a), based on their experience in 19 patients with purulent fluid from the kidney at initial puncture for percutaneous nephrolithotomy, suggested that aborting the procedure might not always be necessary. They continued the procedure in 12 patients and delayed it in 7. Of the 12 patients in whom the procedure was continued, two (17%) experienced postprocedure sepsis. Among the seven patients in whom the procedure was delayed (for 3 to 7 days), two (29%) developed sepsis after the second procedure (both of whom had additional portions of the kidney containing undrained pus, which were discovered at the time of the delayed percutaneous nephrolithotomy). An important difference was in the quality of the aspirated material. One patient in whom percutaneous nephrolithotomy was continued and two in whom the procedure was delayed had “frank pus” as opposed to “purulent fluid” in the other cases. All three of these patients with frank pus were among the four who developed sepsis. The authors recommend that if frank pus is aspirated, then the procedure should be aborted. If the aspirate is a cloudy nonviscous liquid, it might be safe to proceed. This approach has not yet been validated in additional studies. This report also suggests that not all patients with “purulent fluid” are infected. Of the 19 patients, the culture of the aspirate showed bacteria in only 6. This suggests that infection may have been sterilized by previous antibiotic use. The turbid fluid may indicate a sterile inflammatory response to the stone, or the fluid may consist of debris related to the renal calculus. Another important point is that a single nephrostomy tube may not drain all areas of infection in the kidney, especially if there is intrarenal obstruction.

Neuromusculoskeletal Complications

Prone positioning for percutaneous renal surgery has the potential for a number of neuromusculoskeletal injuries (Shermak et al, 2006; Edgcombe et al, 2008). Excessive pressure on neural and vascular structures, whether directly from the operative table or indirectly through the positioning of limbs, may lead to short- or long-term disability. Most reported injuries associated with prone positioning are related to the head and neck region including ocular injury resulting in visual loss, facial nerve injury or necrosis over facial bones or the tip of the nose, and cerebrovascular accident resulting from carotid or vertebralbasilar artery dissection. Careful padding of the head, in a neutral and nonextended position, is important. Malpositioning of the extremities can lead to peripheral nerve injury (Winfree and Kline, 2005). The shoulder and elbow should not be abducted more than 90 degrees, so as to prevent brachial plexopathy, and generous padding at the elbow and forearm reduces the risk of nerve compression. Knees need to be

padded. Ankles should be elevated to reduce pressure on the dorsum of the foot.

Venous Thromboembolism

The incidence of venous thromboembolism with percutaneous renal surgery is low (<3% in older series of percutaneous nephrolithotomy) (Segura et al, 1985; Lee et al, 1987), but there are no recent data. The AUA's Best Practice Statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery does not include percutaneous renal surgery among procedures for which prophylaxis against venous thromboembolism is recommended (Forrest et al, 2009). Early ambulation is the best measure to reduce the already low risk of venous thromboembolism.

Tube Dislodgement

Whether the percutaneous nephrostomy tube is intended to be short term or long term, inadvertent tube dislodgement risks poor patient outcomes. The tube does not need to fall out of the patient completely; especially in a patient with a large subcutaneous layer, the tube can remain attached at the skin but pull out from within the kidney when the distance between the skin and kidney increases with patient movement. Nonetheless, all tubes should be secured at the skin to reduce the risk of at least one mechanism of tube removal. Tubes vary in their inherent ability to resist removal. Malecot tubes are the easiest to pull out, and circle nephrostomy tubes are the most difficult. The Cope retention mechanism is more secure than Malecot wings but does not retain as well as a balloon (Canales et al, 2005). For long-term indwelling, circle nephrostomy tubes and Cope nephrostomy tubes are most commonly used. Ironically, the Malecot tube is also the one most likely to become entrapped; tissue can grow over the wings, making removal difficult and traumatic (Sardina et al, 1995; Tasca and Cacciola, 2004).

If a nephrostomy tube has been in for only a short time, then complete dislodgement often leads to complete loss of percutaneous access. Using a nephrostomy tube with a ureteral extension, whether it is only partially down the ureter as in the Malecot re-entry tube or all the way into the bladder as in a nephroureteral stent, will increase the chance of having some access back into the kidney even if the renal retention device pulls out of the kidney. For tubes that have been in place for more than a few weeks, the tract is usually mature enough that carefully probing with an angled hydrophilic wire and judicious use of contrast material to outline the tract can allow restoration of the percutaneous access. Tube malposition can usually be corrected under fluoroscopic control, but guidance by CT might be helpful as well (Jones and McGahan, 1999).

Collecting System Obstruction

Transient ureteral obstruction owing to ureteral edema or blood clot occurs commonly. To assess for this, nephrostomy tubes should be removed after nephrostography or after a period of clamping to assess clinically for distal ureteral obstruction. Much more uncommon is stricture formation, which can occur in the ureter, at the ureteropelvic junction, or in an infundibulum. If the stricture occurs early in the postprocedure course, then a nephrocuteaneous fistula will develop. If it develops late, then hydronephrosis or hydrocalyx will occur. In one large series there was a 2% rate of infundibular stenosis after percutaneous nephrolithotomy (Parsons et al, 2002). The obstructions developed in the areas that had been accessed percutaneously. Predisposing factors in this and other smaller reports (Ballanger et al, 1987; Weir and Honey, 1999; Buchholz, 2001) include large stone burden requiring multiple or long procedures and prolonged nephrostomy tube drainage, previous open stone surgery, diabetes mellitus, and obesity. The ureter (Culkin et al, 1987; Lopes-Neto et al, 2008) and the ureteropelvic junction (Green et al, 1987; Ben Slama et al, 2005) are smaller in

caliber than the intrarenal collecting system and are therefore also susceptible to trauma.

Obstruction after percutaneous renal surgery should respond to endoscopic treatment in most cases, but open surgical reconstruction or excision with partial nephrectomy or total nephrectomy might be required.

Loss of Renal Function


Despite the direct puncture of renal parenchyma and enlargement of sometimes multiple tracts to as much as 34 Fr, the kidney suffers little permanent damage after uncomplicated percutaneous renal surgery. Renal function does decrease slightly immediately after percutaneous renal surgery, reaching a nadir 48 hours postprocedure (Nouralizadeh et al, 2011), but there is negligible long-term loss of function (Ekelund et al, 1986; Chen et al, 1992; Saxby, 1997; Kilic et al, 2006), and in one study there appeared to be less damage to the kidney after percutaneous nephrolithotomy than after shock wave lithotripsy (LeChevallier et al, 1993). In the setting of impaired function, especially because of obstructing calculi, percutaneous surgery will often improve renal function (Chandhoke et al, 1992; Chatham et al, 2002; Bilen et al, 2008). Percutaneous renal surgery also causes no significant change in function of solitary kidneys (Jones et al, 1991; Liou and Streem,

2001; Canes et al, 2009). In one study of patients who were surveyed a mean of 19 years after treatment, there was no difference between shock wave lithotripsy and percutaneous nephrolithotomy in the development of renal insufficiency or hypertension (Krambeck et al, 2008a).

When there is renal loss following percutaneous renal surgery, it usually is a result of disastrous vascular injury or the angioembolization used to treat hemorrhage. In the original AUA guideline on staghorn calculi (Segura et al, 1994), renal loss after percutaneous nephrolithotomy was estimated at 1.6%; data were insufficient to calculate a new figure in the 2005 update of the guidelines (Preminger et al, 2005).

Death


Death after percutaneous renal surgery is extremely rare, and when it occurs it is usually a result of underlying cardiovascular conditions (Labate et al, 2011; Seitz et al, 2012). In the current AUA guideline on the management of staghorn calculi, the median death estimate for percutaneous nephrolithotomy was zero, which reflects the paucity of data on the subject (Preminger et al, 2005).

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

KEY POINTS: COMPLICATIONS

- Hemorrhage during percutaneous surgery is associated with inappropriate access site, multiple access sites, supracostal access, increasing tract size, tract dilation with methods other than balloon dilation, prolonged operative time, and renal pelvic perforation or other intraoperative technical errors.
- In most cases of hemorrhage during percutaneous surgery or at the time of sheath removal, placing a nephrostomy tube and letting the collecting system clot off is effective. If bleeding is more severe, additional measures may be required.
- Delayed hemorrhage is usually caused by arteriovenous fistulas or arterial pseudoaneurysms. Bright red blood in the urine after percutaneous renal surgery should prompt hospital admission and the consideration of angiography. Selective angioembolization is highly successful in treating this condition.
- If renal pelvic perforation is noted intraoperatively, abort the procedure unless it is near completion. Insert a nephroureteral stent or a nephrostomy tube plus a ureteral stent to optimize drainage.
- Most colon injuries from percutaneous renal surgery are extraperitoneal and can be managed conservatively by draining the colon and urinary collecting system separately.
- Hydrothorax or pneumothorax requiring intervention is related to the level of percutaneous access. Incidence estimates are less than 0.5% below the 12th rib, 4.6% above the 12th rib, and 24.6% above the 11th rib. Pleural complications can often be detected with chest fluoroscopy during the procedure, but a chest radiograph should also be obtained following all cases of supracostal percutaneous renal access.
- Normal saline should be the fluid used for irrigation during percutaneous renal surgery, with the exception of glycine or a similar nonconductive solution when monopolar electrocautery is used.
- If pus is aspirated on initial percutaneous entry to the upper urinary tract, the safest measure is to abort the procedure and leave a nephrostomy tube for drainage.

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9

Evaluation and Management of Hematuria

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Classification and Timing of Hematuria

Microscopic Hematuria

Evaluation of Patients with Microhematuria

Symptomatic Microscopic Hematuria

Gross Hematuria

Hemorrhagic Cystitis

Hematuria from Prostatic Origin

Urethral Bleeding

Hematuria Originating from the Upper Urinary Tract

Hematuria has been recognized as a sign of medical illness since antiquity (Ellis, 1979; Shokeir and Hussein, 1999; Armstrong, 2006). Yet it is only in the modern era that we have developed the technology to detect microscopic blood, the means to identify the source of hematuria, and the understanding of anatomy, physiology, and disease processes underlying this important sign. Today, hematuria is one of the most common indications for urologic evaluation (Mariani et al, 1989) and is recognized as a sign of potentially important illness. Therefore knowledge of the differential diagnosis, principles of evaluation, and strategies for management of hematuria is critical.

CLASSIFICATION AND TIMING OF HEMATURIA

Hematuria may be classified according to its visibility and timing during the urinary stream. That is, gross hematuria (GH), sometimes referred to as *frank hematuria*, *macrohematuria*, or *visible hematuria*, is hematuria that can be seen with the naked eye. GH may be further characterized as initial, terminal, or total, depending on the phase of the urinary stream in which it is visible. This characterization may give some indication of the source of hematuria, with initial hematuria most commonly emanating from a urethral source; terminal hematuria from the bladder trigone, bladder neck, or prostate; and total hematuria from the bladder or above (Sokolosky, 2001).

GH must be distinguished from pigmenturia, which may be due to endogenous sources (e.g., bilirubin, myoglobin, porphyrins), foods ingested (e.g., beets and rhubarb), drugs (e.g., phenazopyridine), and simple dehydration. This distinction can be made easily by urinalysis with microscopy. Notably, myoglobinuria and other factors can cause false-positive chemical tests for hemoglobin, so urine microscopy is required to confirm the diagnosis of hematuria. GH also must be distinguished from vaginal bleeding in women, which usually can be achieved by obtaining a careful menstrual history, collecting the specimen when the patient is not having menstrual or gynecologic bleeding, or, if necessary, obtaining a catheterized specimen. GH may also be detected by the presence of blood spotting on the undergarments of incontinent patients. After ruling out vaginal bleeding and mimics of hematuria, a urologic source must be suspected.

MICROSCOPIC HEMATURIA

In contrast to GH, microscopic hematuria, or microhematuria (MH), is a sign rather than a symptom; a laboratory diagnosis defined as the presence of red blood cells (RBCs) on microscopic

examination of the urine not evident on visual inspection of the urine. The prevalence of MH among healthy participants in screening studies is 6.5% (95% confidence interval [CI] 3.4 to 12.2), with higher rates in studies with a predominance of males, older patients, and smokers (Davis et al, 2012). MH may be categorized by the presence or absence of associated symptoms and may be quantified according to number of RBCs per high-power field (HPF). The proper collection of a urine specimen and the details of urine dipstick testing and urinalysis are covered in Chapter 1.

Criteria for the Diagnosis of Microhematuria

A small number of RBCs may pass into the urine even under normal conditions, and normal processes (e.g., sexual activity, exercise) can result in minor amounts of MH (Kohanpour et al, 2012). The American Urologic Association (AUA) guideline panel defined MH as three or more RBCs/HPF, concluding that higher thresholds would lead to missed opportunities to diagnose treatable urologic conditions (Davis et al, 2012). Additionally, it has been shown that MH caused by significant medical conditions, such as urinary tract malignancy, can be intermittent (Davis et al, 2012). In fact, a meta-analysis reported that the rate of malignancy detected among patients evaluated for a single positive urinalysis was 3.6% (Davis et al, 2012). Thus the most recent AUA guideline panel has determined that a single positive urinalysis is sufficient to prompt evaluation (Davis et al, 2012).

Requirement for Microscopic Evaluation

The results of urine dipstick tests must be confirmed on urinalysis with microscopy and alone are considered insufficient to prompt an evaluation. Indeed, chemical tests for hematuria detect the peroxidase activity of hemoglobin using benzidine, and therefore conditions such as myoglobinuria can falsely activate the test (Mariani et al, 1984). Thus a positive dipstick test merits microscopic examination of the urinary sediment, but does not warrant full evaluation unless microscopy confirms the presence of three or more RBCs/HPF. If the urinalysis with microscopy is not confirmatory, but the clinician remains suspicious, repeat microscopic testing is reasonable with the frequency individualized based on provider judgment.

Specimens collected immediately after prolonged recumbency (first void in morning) or after vigorous physical or sexual activity may be falsely positive for hematuria (Addis, 1926; Kincaid-Smith, 1982). Additionally, dilute urine (osmolality <308 mOsm) may result in false-negative microscopic examination as a result of RBC lysis (Vaughan and Wyker, 1971).

Evaluation of Patients with Microhematuria

In most studies, one third to two thirds of patients evaluated for MH have been found to have a demonstrable cause (Mohr et al, 1986; Murakami et al, 1990), including calculus (6.0%), benign prostatic enlargement (12.9%), urethral stricture (1.4%), and various other conditions (Table 9-1) (Davis et al, 2012). Notably, the evaluation of patients with MH yields a diagnosis of malignancy in 1.8% to 4.3% of cases, depending on the characteristics of the population evaluated, the threshold for evaluation, and the completeness of the evaluation (Davis et al, 2012). The likelihood of

identifying a malignancy is higher among patients with higher levels of microscopic hematuria (>25 RBCs/HPH), GH, or risk factors for malignancy (Sultana et al, 1996; Shephard et al, 2012; Loo et al, 2013). Risk factors for malignancy among patients with hematuria include male gender, older age, and tobacco use (Box 9-1).

Selecting Patients for Evaluation of Microhematuria

Recognizing that one third to two thirds of patients with MH will have a negative hematuria evaluation, interest is growing in an evidence-based selection of patients for hematuria evaluation to

TABLE 9-1 Differential Diagnosis of Asymptomatic Microhematuria*

CATEGORY	EXAMPLES	COMMON CLINICAL PRESENTATION AND RISK FACTORS
Neoplasm	Any Bladder cancer Ureteral or renal pelvis cancer Renal cortical tumor Prostate cancer Urethral cancer	See Box 9-1 Older age, male predominance, tobacco, occupational exposures, irritative voiding symptoms Family history of early colon cancers or upper tract tumors, flank pain Family history of early kidney tumors, flank pain, flank mass Older age, family history, African-American Obstructive symptoms, pain, bloody discharge
Infection/inflammation	Any Cystitis Pyelonephritis Urethritis Tuberculosis Schistosomiasis Hemorrhagic cystitis	History of infection Female predominance, dysuria Fever, flank pain, diabetes, female predominance Exposure to sexually transmitted infections, urethral discharge, dysuria Travel to endemic areas Travel to endemic areas See Box 9-2
Calculus	Any Nephroureterolithiasis Bladder stones	Flank pain, family history, prior stone Bladder outlet obstruction
Benign prostatic enlargement		Male, older age, obstructive symptoms
Medical renal disease†	Any Nephritis IgA nephropathy	Hypertension, azotemia, dysmorphic erythrocytes, cellular casts, proteinuria
Congenital or acquired anatomic abnormality	Polycystic kidney disease Ureteropelvic junction obstruction Ureteral stricture Urethral diverticulum Fistula	Family history of renal cystic disease History of UTI, stone, flank pain History of surgery or radiation, flank pain, hydronephrosis; stranguria, spraying urine Discharge, dribbling, dyspareunia, history of UTI, female predominance Pneumaturia, fecaluria, abdominal pain, recurrent UTI, history of diverticulitis or colon cancer
Other	Exercise-induced hematuria‡ Endometriosis Hematologic or thrombotic disease Papillary necrosis Arteriovenous malformation Renal vein thrombosis Interstitial cystitis Trauma Recent genitourinary surgery or instrumentation	Recent vigorous exercise Cyclic hematuria in a menstruating woman Family history of personal history of bleeding or thrombosis African-American, sickle cell disease, diabetes, analgesic abuse Voiding symptoms History History

*Differential diagnosis, having ruled out obvious benign causes, such as menstruation, recent instrumentation, uncomplicated cystitis, etc.

†Presence of hematologic illness, medical renal illness or use of anticoagulants or antiplatelet agents does not preclude the need for a hematuria evaluation.

‡Exercise-induced hematuria is a diagnosis of exclusion. Absence of hematuria after abstinence from exercise must be confirmed.

IgA, immunoglobulin A; UTI, urinary tract infection.

BOX 9-1 Common Risk Factors for Urinary Tract Malignancy in Patients with Microscopic Hematuria

Male gender
 Age older than 35 years
 Past or current smoking history
 Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines)
 Analgesic abuse
 History of gross hematuria
 History of urologic disorder or disease
 History of irritative voiding symptoms
 History of pelvic irradiation
 History of chronic urinary tract infection
 Exposure to known carcinogenic agents or chemotherapy such as alkylating agents
 History of chronic indwelling foreign body

Modified from American Urological Association guidelines.

minimize the financial burden and risks in evaluating all patients (Mohr et al, 1986; van der Molen and Hovius, 2012; Loo et al, 2013). For example, the Kaiser Permanente group demonstrated that, among patients undergoing a complete evaluation for hematuria, those at high risk for malignancy (age >50 years, history of GH, tobacco use, male gender, or >25 RBCs/HPF) had higher rates of malignancy (10.7% to 11.6%) than patients at intermediate (1.1% to 2.5%) or low (0 to 0.3%) risk (Loo et al, 2013). However, although the Kaiser study shows that we may be able to decide which patients referred to urologists can safely avoid complete evaluation, the reality is that fewer than 25% of patients found to have hematuria are referred for evaluation and fewer than 10% undergo a complete evaluation with cystoscopy and imaging, even among patients at high risk for malignancy (Elias et al, 2010; Buteau et al, 2012). Taken together, these studies suggest that ample room exists for improvement in developing evidence-based algorithms to guide the use of hematuria evaluation and in reducing nonclinical sources of variability in adherence to evidence-based practices.

The AUA guidelines recommend evaluating patients with MH “in the absence of an obvious benign cause” such as infection and menstruation. Therefore it is imperative that patients who are found to have MH in the setting of a suspected benign cause have that benign cause substantiated by clinical evidence and be further evaluated once the suspected benign cause is resolved. Unfortunately, uniform agreement does not exist on how to identify benign causes of hematuria. Perhaps, as a result, substantial delays in diagnosis and inferior bladder cancer outcomes have occurred related to repeated empirical treatment of urinary tract infection (UTI) and voiding symptoms, particularly among women (Henning et al, 2013; Lyratzopoulos et al, 2013; Tracey et al, 2014). Our recommendation is that the presence of infection should be confirmed with a urine culture and the urinalysis should be repeated after treatment of the UTI to document resolution of the hematuria. If hematuria persists, further evaluation is warranted.

In addition, recent vigorous exercise may be associated with MH, but this entity should be considered a diagnosis of exclusion (Kincaid-Smith, 1982; McInnis et al, 1998; Kohanpour et al, 2012). Thus it is necessary to confirm the absence of MH after a period of abstinence from exercise. In addition, patients who develop hematuria (microscopic or gross) who are taking anticoagulation or antiplatelet medications (e.g., warfarin, enoxaparin, heparin, aspirin, clopidogrel, nonsteroidal anti-inflammatory agents) should undergo a complete evaluation in the same manner as patients not taking such medications, because the prevalence of hematuria, as well as the likelihood of finding genitourinary

cancers, among patients with hematuria on anticoagulation has been reported to be no different from patients not taking such medications (Culclasure et al, 1994; Khadra et al, 2000; Davis et al, 2012; Jeong et al, 2013). In fact, it has been noted that these medications may unmask genitourinary lesions at an earlier stage (Antolak and Mellinger, 1969; Kraus et al, 1984; Schuster and Lewis, 1987; Mariani, 1989). In one series, 82% of anticoagulated male patients evaluated for GH were found to have significant urologic lesions (Antolak and Mellinger, 1969), and 13.9% of such lesions in another series were found to be malignant (Schuster and Lewis, 1987). Meanwhile, MH in the setting of trauma is detailed elsewhere (see Chapters 50 and 101) and will not be covered here.

The Question of Screening for Hematuria and Bladder Cancer

Bladder cancer is the sixth most commonly diagnosed cancer in the United States, and although no large-scale screening trials have been performed, most believe that the harms and costs of mass screening for bladder cancer would prove to outweigh the potential benefits (<http://seer.cancer.gov/statfacts/html/urinb.html>; Chou and Dana, 2010). Nonetheless, many primary care providers perform urinalysis as part of routine health examinations, creating numerous opportunistic screening events (Prochazka et al, 2005).

KEY POINTS: MICROSCOPIC HEMATURIA

- MH is defined as three or more RBCs/HPF, identified on one or more occasions on urine microscopy. Urine dipstick testing is insufficient for the diagnosis of MH.
- MH is quite common, with a prevalence of approximately 6.5% of adults, varying according to the characteristics of the population.
- Malignancy has been detected in approximately 4% of patients evaluated for asymptomatic MH. The proportion of malignancies detected is higher in patients with higher degrees of hematuria and/or risk factors for malignancy.

EVALUATION OF PATIENTS WITH MICROHEMATURIA

See Figure 9-1 for the evaluation algorithm of MH from the most recent AUA guidelines (Davis et al, 2012). Importantly, it is recommended that patients meeting criteria for evaluation undergo a complete evaluation, even if one phase of the evaluation shows a suspected cause for the MH. For example, a patient found to have a kidney tumor or stone disease during initial workup of MH should still undergo cystoscopy for clearance of bladder and urethral pathologic processes.

The evaluation of an appropriately selected patient with MH begins with a thorough history and physical examination. Specifically, one should aim to identify causes that would warrant variation from the standard evaluation, such as infection, menstruation, recent vigorous exercise, known medical renal disease, acute viral illness, trauma, and the presence of foreign bodies in the urinary tract or recent urologic instrumentation. The history also should include an assessment of associated symptoms, such as GH, voiding symptoms, or flank pain. Patients' risk factors for known causes of hematuria also should be queried. It is important to know the patient's urologic history, particularly any surgeries or febrile UTIs. It is also critical to ask about the patient's general medical history, to identify potentially contributory diagnoses, such as hypertension, renal insufficiency, bleeding disorders, or sickle cell disease. Current medication use, including anticoagulants and antiplatelet therapies, should be elicited, along with recent coagulation values and any concomitant medications that would potentiate the effects of blood thinners. Family history of nephritis, polycystic kidneys, and rare familial tumor syndromes of the kidney (e.g., von Hippel-Lindau) or urothelium (e.g., Lynch syndrome) also may

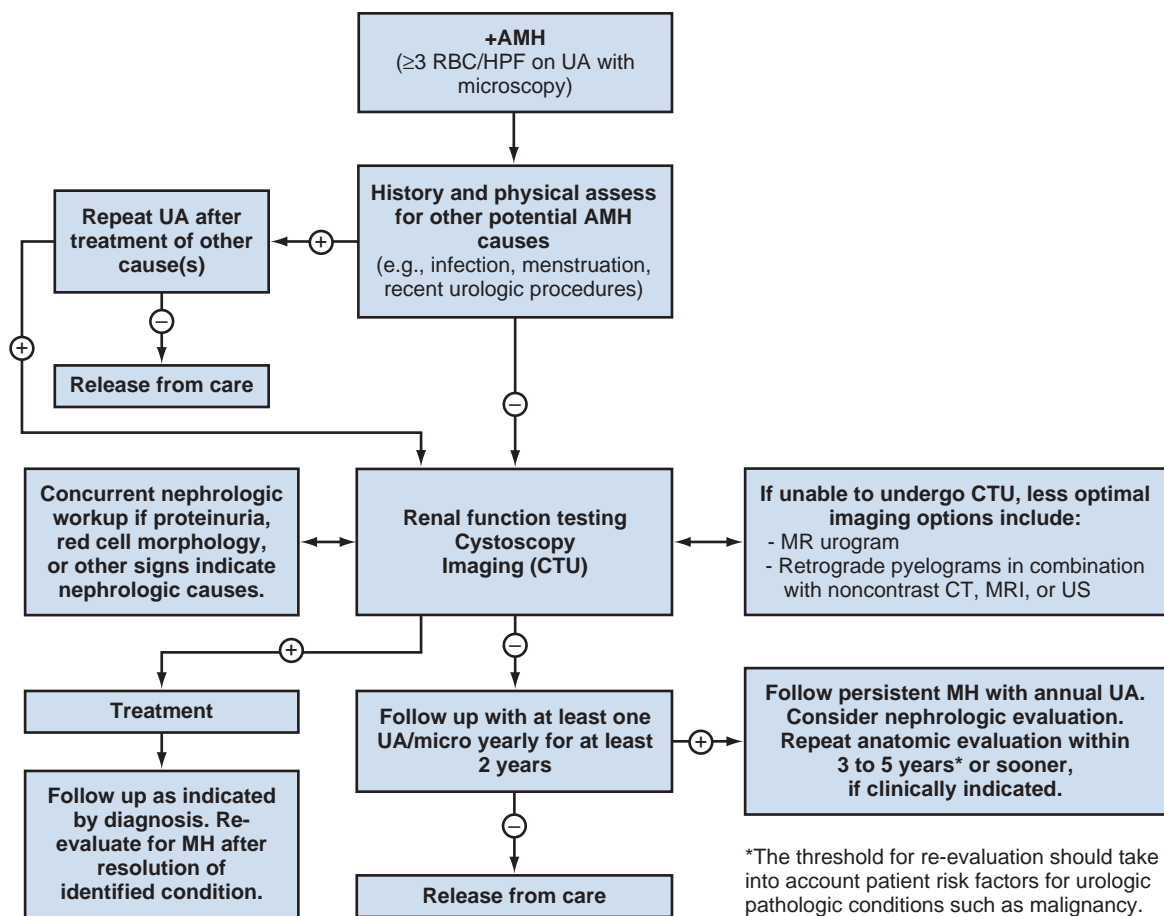


Figure 9-1. American Urological Association guideline algorithm for evaluation of adult patients with asymptomatic microhematuria. AMH, asymptomatic microhematuria; CT, computed tomography; CTU, computed tomography urogram; HPF, high-power field; MH, microhematuria; MR, magnetic resonance; MRI, magnetic resonance imaging; RBC, red blood cell; UA, urinalysis; US, ultrasound. (From the American Urological Association.)

be informative. In addition, the possibility of finding a tobacco-related illness, such as bladder cancer, makes this a potential “teachable moment” for tobacco users (Bassett et al, 2012; Fiore and Baker, 2013). Thus smoking cessation counseling should be a standard component of the hematuria evaluation discussion.

Physical examination should focus on the genitourinary system (e.g., flank tenderness; masses in the flank, abdomen, suprapubic area, or urethra; and enlarged, nodular, tender, or fluctuant prostate.) Physical examination also may identify signs of coagulopathy (bruising), infection (fever), or renal disease (hypertension, edema). If urethral stricture or benign prostatic hyperplasia (BPH) is suspected, a urine flow rate and postvoid residual measurement may be helpful as well.

Laboratory testing includes urinalysis (if not performed previously) to confirm the presence of hematuria and check for dysmorphic red cells, cellular casts, or proteinuria; a urine culture if the urinalysis or clinical presentation suggests infection; renal function testing (serum creatinine) to determine whether concomitant nephrologic evaluation is indicated and to guide the selection of appropriate upper tract imaging; and prostate-specific antigen in the appropriate setting.

If a benign cause of hematuria is discovered during the initial history and physical (e.g., UTI), that cause should be verified and treated and then the urine should be retested to ensure that the hematuria has resolved in the absence of the presumed benign cause. Moreover, if a medical renal cause of hematuria is suspected based on the presence of renal insufficiency, hypertension, or abnormalities on urinalysis, nephrology evaluation is

recommended, but the patient should still undergo urologic evaluation.

Cystoscopy in the Diagnostic Evaluation of Hematuria

Cystoscopy is a key component of the hematuria evaluation because it is the most reliable way to evaluate the bladder for the presence of bladder cancer and provides the opportunity to evaluate the urethra. Cystoscopy should be performed in all adults who meet criteria for hematuria evaluation who are 35 years of age or older and/or have risk factors for malignancy. The potential risks include discomfort, injury to the urethra, infection, and the need for additional procedures, such as biopsy. At the population level, bladder cancer is quite rare (<1 per 100,000) among persons 35 years old or younger (van der Molen and Hovius, 2012; <http://seer.cancer.gov/statfacts/html/urinb.html>). That is, among 3762 individuals with asymptomatic MH from 17 screening studies, 98 (2.6%) were diagnosed with a urinary tract malignancy, of whom 95 (97%) were older than 35 years of age. For these reasons, cystoscopy may be omitted in persons younger than age 35 years without risk factors or clinical suspicion for bladder cancer or urethral pathology (see Box 9-1).

Of note, blue-light cystoscopy using 5-aminolevulinic acid (ALA) or hexyl-aminolevulinic acid (HAL) instillation is approved by the U.S. Food and Drug Administration (FDA) for evaluation of patients with suspicion of papillary bladder cancer, but the studies supporting its use have been conducted in patients with known bladder cancer, thereby limiting generalizability to MH patients

(Davis et al, 2012; Malmstrom et al, 2012). In light of the small incremental risk associated with ALA or HAL and blue-light cystoscopy (rare anaphylactoid shock, hypersensitivity, pain, cystitis, dysuria, hematuria) and the risk for unnecessary biopsies compared to conventional white light cystoscopy, the AUA guideline recommends against using blue-light cystoscopy for evaluation of MH (Davis et al, 2012).

Upper Tract Imaging in the Diagnostic Evaluation of Hematuria

Multiphasic computed tomography (CT) urogram (i.e., CT with precontrast, nephrographic, and excretory series) is the imaging study of choice for the evaluation of asymptomatic MH (Vikram et al, 2009), because CT urography offers complete imaging of the urinary tract and has the highest sensitivity and specificity for detecting lesions of the renal parenchyma and the upper tracts. Nonetheless, CT urography does carry risks and may not be appropriate for all patients (e.g., pregnancy, iodinated contrast allergy, renal insufficiency). Indeed, in the setting of a contraindication to CT urogram, magnetic resonance urogram may be used as the upper tract study. Moreover, for patients with a contraindication to magnetic resonance imaging (e.g., pacemaker), as well as in the setting of significant renal function compromise (i.e., estimated glomerular filtration rate <30) when the administration of gadolinium risks nephrogenic systemic fibrosis, renal parenchymal imaging with noncontrast CT or ultrasound, in conjunction with retrograde pyelography to evaluate the calyces, renal pelvis, and ureters, may be most appropriate.

Urine Cytology and Urinary Biomarkers in the Diagnostic Evaluation of Hematuria

Urine cytologic examination is highly sensitive and specific for the detection of high-grade urothelial carcinoma, but sensitivity decreases significantly for low-grade urothelial carcinoma, resulting in an overall sensitivity of 15.8% to 54.5%, and specificity of 95.0% to 100% for bladder cancer detection (Miyanaga et al, 1999; Zippe et al, 1999; Chahal et al, 2001; Grossman et al, 2005; Steiner et al, 2008). Indeed, in a large study of patients with hematuria, the sensitivity and specificity of positive/suspicious/atypical cytology were 45.4% and 89.5%, respectively (Mishriki et al, 2013).

Meanwhile, although several urine biomarkers have been approved or cleared by the FDA for detection and surveillance of bladder cancer, few studies have been conducted to evaluate these markers in patients with MH who do not have a history of bladder cancer. Available assays include nuclear matrix protein-22 (NMP-22), bladder tumor antigen, fluorescence in situ hybridization (FISH) for abnormalities of chromosomes 3, 7, 17, and 9p21 (UroVysion [Abbott Molecular, Abbott Park, IL]) and immunocytology for carcinoembryonic antigen and mucin glycoproteins (ImmunoCyt [Scimedx, Denville, NJ] and CertNDx [PCLS, Rock Hill, SC]).

NMP-22 offers a potential advantage in management of patients with MH in that it is available as a point-of-care test. However, only two studies to date have focused on the asymptomatic patient with MH, with one finding a high sensitivity (90.9%), and the other, in a screening population, demonstrating very low sensitivity (6.0%). Specificity was moderate or high in both studies (76.3% and 82.5%, respectively) (Miyanaga et al, 1999; Steiner et al, 2008). Meanwhile, one study assessed FISH testing in patients with asymptomatic MH with a negative cytology and found that sensitivity and specificity may be high for upper tract tumors in this setting (Huang et al, 2012). A separate FISH study in asymptomatic MH patients (albeit without prior negative cytologic findings) showed sensitivity and specificity of 61% and 93%, respectively, for bladder tumors (Steiner et al, 2008). Immunocytology has been tested in the asymptomatic MH setting in one study of 189 patients (Schmitz-Drager et al, 2007). Here, eight bladder tumors were identified, of which seven were identified by

the ImmunoCyt test, for a sensitivity of 87%. However, studies in the urothelial carcinoma follow-up setting have found a far more modest sensitivity (68.1%) (Comploj et al, 2013). Finally, the multianalyte urine test CertNDx assesses several markers (mutant *FGFR3*, quantified matrix metalloproteinase-2 [MMP2], and hypermethylation of *TWIST1* and *NID2*). In a population of patients with hematuria (gross and microscopic) 50 years of age or older without diagnosis of bladder cancer, the sensitivity and specificity of this test were noted to be 87.9% and 56.3%, respectively (Karnes et al, 2012).

Together, because current evidence indicates that none of the available urinary biomarkers, including cytology, appear to be sufficiently sensitive or sufficiently validated to replace cystoscopy or imaging, these studies are not recommended in the initial evaluation of patients with asymptomatic MH (Davis et al, 2012). However, cytologic examination may be considered in patients with a negative initial workup in whom urothelial carcinoma is still suspected, as well as in patients with symptomatic MH.

Natural History of Microhematuria in Patients with a Negative Initial Evaluation

One of the most vexing questions in the management of MH is how to proceed in patients for whom the initial evaluation is negative. MH has been reported to resolve in approximately one third of these patients over a period of 3 months to several years (Yamagata et al, 1996; McGregor et al, 1998; Jaffe et al, 2001). Nevertheless, it is worth noting that these studies contained large proportions of younger patients, many of whom did not undergo a complete workup at any time, raising the possibility of persistent occult urologic disease. In a set of studies in which patients underwent further evaluation for MH after an initial negative evaluation, 41 malignancies were identified among 1475 patients (2.8%). However, the initial evaluations in these series were often incomplete, the follow-up evaluations were variable, and most of the malignancies were found in a study using CT urography in patients who were not evaluated by CT in the first evaluation (Davis et al, 2012).

In the absence of high-quality evidence, the AUA has issued three guidelines statements, based on expert opinion, pertaining to the follow-up of patients with an initial negative workup (Davis et al, 2012). The first two can be summarized as recommending following up annual urinalysis for 2 years after a complete negative hematuria workup and releasing the patient from care if the urinalyses confirm resolution of hematuria. The third statement recommends repeating the hematuria evaluation within 3 to 5 years in cases of persistent or recurrent asymptomatic MH or for development of symptoms or GH. We would add that patients with persistent or recurrent MH in the setting of an incomplete initial evaluation should have the evaluation completed or repeated.

KEY POINTS: EVALUATION OF PATIENTS WITH MICROHEMATURIA

- Evaluation of adults with microscopic hematuria includes a history and physical examination, renal function testing, and upper tract imaging for all patients.
- White light cystoscopy is recommended in the evaluation of asymptomatic MH for patients 35 years of age or older and/or those with risk factors for malignancy.
- CT urogram is the preferred imaging modality for the evaluation of hematuria.
- Urine cytologic examination and biomarkers are not indicated in the initial evaluation of asymptomatic MH.
- Patients with a negative complete evaluation can be released from care if subsequent urinalyses confirm resolution of MH. Re-evaluation should be considered in patients with persistent/recurrent MH and those with an incomplete initial evaluation.

SYMPTOMATIC MICROSCOPIC HEMATURIA

The differential diagnosis for symptomatic MH is equivalent to that for patients with asymptomatic MH. However, the risk for malignancy may be significantly higher than in asymptomatic MH (10.5% vs. 5.0% or less) (Sultana et al, 1996; Shephard et al, 2012). To the extent that symptoms help identify an obvious benign cause of hematuria (e.g., infection), and the hematuria resolves after management of this (culture-documented) benign cause, a complete workup can be avoided. Nevertheless, in situations in which an obvious benign cause is not definitively identified, the hematuria does not resolve after treatment of the benign cause, or the symptoms or other risk factors could be consistent with malignancy, full evaluation is recommended. Moreover, because the presence of symptomatic hematuria has been linked to an increased risk for malignancy, current AUA guidelines include several slight modifications to the recommendations for evaluation. Specifically, **cystoscopy is recommended in such patients, regardless of age** (Davis et al, 2012). Moreover, although routine cytology is not recommended as part of the routine evaluation for the asymptomatic patient with microscopic hematuria, **cytologic examination is considered an option in the setting of irritative voiding symptoms**, although cystoscopy should not be omitted even if the cytologic findings are negative (Davis et al, 2012).

GROSS HEMATURIA

The differential diagnosis for GH remains the same as outlined earlier for MH. Of note, however, **as the degree of hematuria increases, so does the likelihood of finding clinically significant lesions during evaluation**. That is, the difference between the yield of life-threatening lesions in patients with gross versus microscopic hematuria has been found to be highly significant (Mariani, 1989). Specifically, among patients with GH, 50% have been found to have a demonstrable cause, with 20% to 25% found to have a urologic malignancy, most commonly bladder cancer and kidney cancer (Lee and Davis, 1953; Khadra et al, 2000; Alishahi et al, 2002; Edwards et al, 2006).

Given the increased frequency with which clinically significant findings are associated with GH, the recommended evaluation in this setting is relatively uniform. That is, **patients presenting with GH in the absence of antecedent trauma or culture-documented UTI should be evaluated with a urine cytologic examination, cystoscopy, and upper tract imaging, preferably CT urogram**. Meanwhile, patients with GH in the setting of a culture-documented UTI should have the infection treated and then a follow-up urinalysis obtained to ensure clearance of the hematuria. The initial assessment for patients presenting with GH should include the history, physical examination, and laboratory studies recommended for patients with MH. Further, patients with GH must be assessed for hemodynamic stability with careful attention to vital signs, anemia with a complete blood count, and, for patients on anticoagulation, coagulation parameters to ensure that levels are within the therapeutic range. After initial stabilization, diagnostic evaluation should then proceed, with cause-specific management as outlined below.

Although clear recommendations are lacking for the follow-up of patients with GH who are found to have a nondiagnostic initial evaluation, the follow-up schedule as outlined for patients with asymptomatic MH may be used as a reference, with consideration given for a full repeat evaluation if episodes of GH recur.

HEMORRHAGIC CYSTITIS

Intractable hematuria localizing to the bladder, or hemorrhagic cystitis, may range in severity from a transient condition that quickly resolves after conservative management to a life-threatening condition requiring urgent intervention. Unfortunately, patients in this situation are often elderly and infirm, with medical comorbidities that complicate plans for care.

Hemorrhagic cystitis is characterized by diffuse inflammation and bleeding from the bladder mucosa (Rastinehad et al, 2007). Numerous causes for this condition have been described (Box 9-2), a few of which merit particular mention here. Bacterial infections, for example, are a common cause of GH, with symptomatic resolution typically noted after appropriate treatment. Meanwhile, viral-induced hemorrhagic cystitis may affect children and immunosuppressed adults particularly, as following renal or bone marrow transplantation. **BK virus, a member of the polyomavirus family, is the most common virus associated with hemorrhagic cystitis** (Gorczynska et al, 2005), and adenovirus, particularly types 11 and 35, has been correlated with hemorrhagic cystitis in children and renal transplant patients (Lee et al, 1996; Hofland et al, 2004). Treatment for viral hemorrhagic cystitis is primarily supportive, with hydration, diuresis, and bladder irrigation, although case reports of antiviral therapy exist (Rastinehad et al, 2007).

Hemorrhagic cystitis also may result from exposure to the oxazaphosphorine class of chemotherapeutic agents, specifically cyclophosphamide and ifosfamide. Indeed, hemorrhagic cystitis has been reported to occur in 2% to 40% of patients treated with cyclophosphamide (Rastinehad et al, 2007) and is dose dependent.

BOX 9-2 Differential Diagnosis for Hemorrhagic Cystitis*

Infectious
Bacterial
Viral (especially BK virus, adenovirus)
Fungal
Parasitic
Trauma
External
Postsurgical (e.g., transurethral resection of the bladder)
Malignancy
Bladder primary
Bladder invasion from local/distant primary
Vascular malformation
Chemical exposure
Cyclophosphamide
Ifosfamide
Busulfan
Thiotepa
Temozolomide
Aniline dye
Ether
Nonoxynol-9 (accidental urethral insertion of vaginal contraceptive)
Radiation therapy history (e.g., prostate cancer, cervical cancer)
Medication induced
Penicillin and derivatives (via immune reaction)
Bleomycin
Danazol
Tiaprofenic
Allopurinol
Phensuximide
Methenamine mandelate
Acetic acid
Manifestation of systemic disease
Amyloidosis
Rheumatoid arthritis
Crohn disease

*Bleeding localized to bladder after diagnostic workup for gross hematuria with cystoscopy, urine cytology, and upper tract imaging is without clear cause of alternative bleeding source

Bladder toxicity results from renal excretion of the metabolite acrolein, which is produced by the liver and which stimulates bladder mucosal sloughing and subsequent tissue edema/fibrosis (O'Reilly et al, 2002). The onset of hematuria is typically within 48 hours of treatment (Cox, 1979; Stillwell and Benson, 1988). 2-Mercaptoethane sulfonate (mesna), which binds to acrolein and renders it inert, has been suggested for prophylaxis against cyclophosphamide-induced hemorrhagic cystitis (O'Reilly et al, 2002). Nevertheless, 10% to 40% of patients will develop the condition despite preventive treatment (Shepherd et al, 1991), and debate continues as to whether mesna is more effective at preventing hemorrhagic cystitis than hyperhydration with forced diuresis and/or continuous bladder irrigation (Shepherd et al, 1991; Vose et al, 1993).

Meanwhile, radiation therapy for pelvic malignancy represents another predisposing factor to hemorrhagic cystitis. Indeed, moderate-to-severe hematuria has been reported in approximately 5% of patients after pelvic radiotherapy, with onset between 6 months and 10 years after treatment (Corman et al, 2003). Mechanistically, radiation damages the vascular endothelium, thereby inducing subsequent inflammation, fibrosis, and ischemia, with tissue necrosis and mucosal sloughing occurring through progressive obliterative endarteritis (Hader et al, 1993; Bevers et al, 1995;

Chong et al, 2005). In the setting of such local vascular compromise, moreover, secondary infection frequently ensues, further compromising tissue healing (Del Pizzo et al, 1998).

Management of Hemorrhagic Cystitis

The management of hemorrhagic cystitis may occasionally be guided by the particular cause for the condition (e.g., treatment of infection), although in most cases no cause-directed therapy can be offered and instead a sequential approach, depending on the severity of the condition, should be undertaken (Fig. 9-2). Supportive management in the form of increasing urine output via hydration/diuresis, catheter placement with continuous bladder irrigation, and transfusion as needed represent the mainstay of first-line therapy and typically suffice for mild cases. If hematuria continues and/or clotting of the urine cannot be controlled with bladder irrigation, cystoscopy under anesthesia with clot evacuation and fulguration of discrete bleeding sites is then recommended.

For hematuria that persists despite such conservative measures, various agents have been investigated for bleeding control. Importantly, there is a lack of large, prospective trials reporting comparative treatment efficacy and safety. Nevertheless, an overview of these measures is warranted to facilitate a systematic approach to

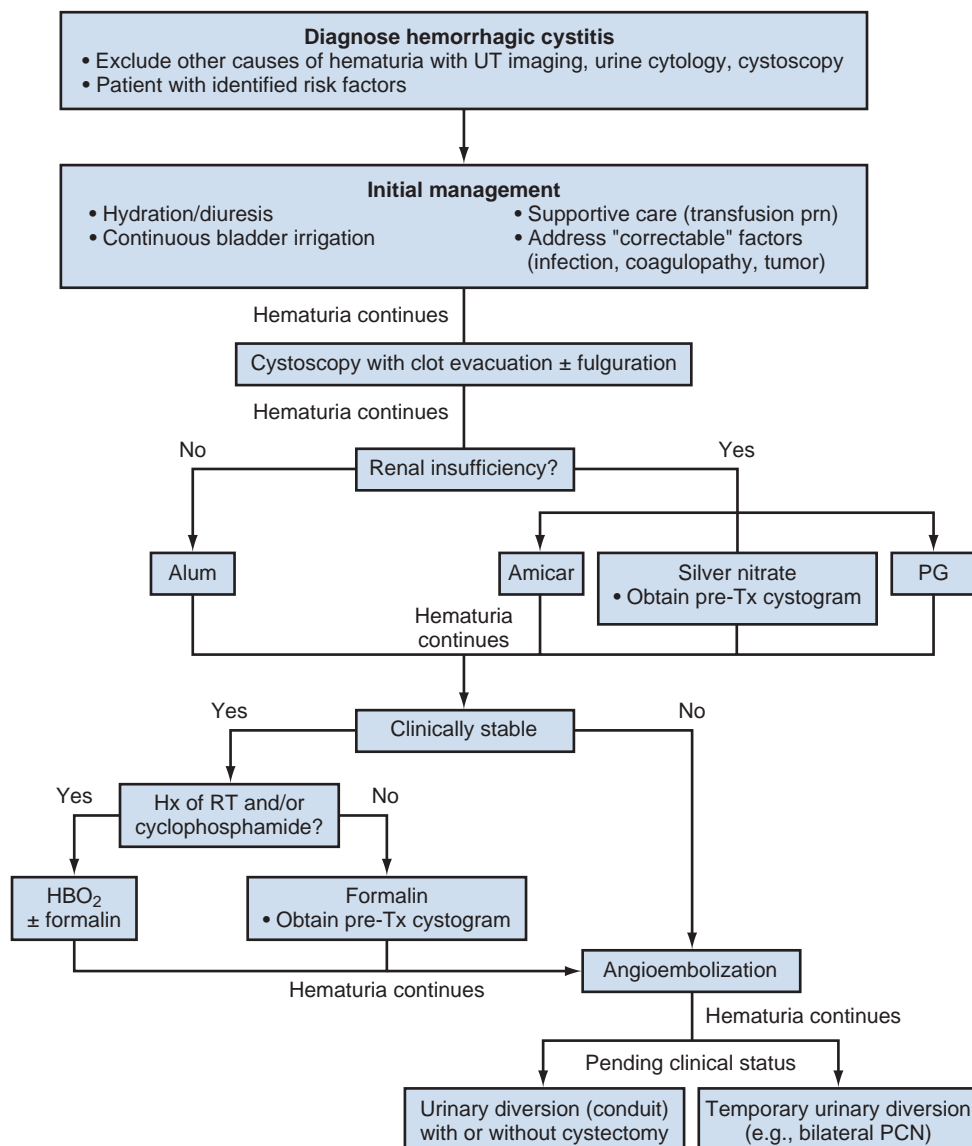


Figure 9-2. Management algorithm for patients with hemorrhagic cystitis. HBO₂, hyperbaric oxygen; Hx, history; PCN, percutaneous nephrostomy; PG, prostaglandin; Tx, treatment; UT, upper tract.

management. For one, alum (aluminum ammonium sulfate or aluminum potassium sulfate) may be dissolved in sterile water (50 g alum in a 5-L bag of sterile water [1% alum solution]) and then used to irrigate the bladder at a rate of 200 to 300 mL/hr. Through its action as an astringent at sites of bleeding, **alum may cause protein precipitation on the urothelial lining (Ostroff and Chenault, 1982) and thereby stimulate vasoconstriction and a decrease in capillary permeability (Choong et al, 2000).** In albeit small series to date, success rates of 66% to 100% have been reported after alum instillation (Choong et al, 2000; Abt et al, 2013). Although cell penetration and therefore overall toxicity of this agent are low (consisting mainly of suprapubic discomfort and bladder spasms), **systemic absorption may nevertheless occur and may result in aluminum toxicity, with consequent mental status changes, particularly among patients with renal insufficiency.** However, alum may be instilled without anesthesia and has an overall relatively favorable efficacy and safety profiles. Thus this agent may be considered for first-line intravesical therapy among patients with hemorrhagic cystitis failing initial supportive measures, particularly among those who are without renal insufficiency.

In addition, several alternative agents exist for intravesical instillation therapy. Prostaglandins (e.g., carboprost tromethamine [PGF₂-α]) (Abt et al, 2013) have been used intravesically for hemorrhagic cystitis, and although the precise mechanism of activity remains unclear, these agents are thought to cause vasoconstriction, platelet aggregation, and cytoprotection via mucous barrier regulation (Choong et al, 2000; Abt et al, 2013). Response rates of 50% to 60% have been noted (Choong et al, 2000; Abt et al, 2013), and in fact in a small (19 patients) prospective randomized study, no significant difference in efficacy was noted between PGF₂ and alum (Praveen et al, 1992). Notably, however, difficulties with PGF₂ access, storage, and high costs have limited generalized utility (Abt et al, 2013). Alternatively, silver nitrate may be instilled into the bladder, resulting in chemical coagulation at bleeding sites. A 0.5% to 1% solution is instilled for 10 to 20 minutes (Rastinehad et al, 2007). The potential for precipitation and upper tract obstruction with this agent led to the recommendation for a cystogram to rule out reflux before administration (Rastinehad et al, 2007).

Aminocaproic acid represents another intravesical treatment alternative. A lysine analogue, aminocaproic acid is a competitive inhibitor of activators of plasminogen, including urokinase, and thus interrupts fibrinolysis and the cascade that perpetuates hemorrhage (Garber and Wein, 1989; Stefanini et al, 1990; Abt et al, 2013). Continuous bladder irrigation with 200 mg aminocaproic acid/L of 0.9% normal saline has been described, with irrigation continued for 24 hours after hematuria resolves. Symptom resolution has been reported in up to 92% of patients (Singh and Laungani, 1992). The risk for thromboembolic events may be increased with this treatment, and, importantly, aminocaproic acid must be given only after the bladder has been rendered clot-free, because the agent will otherwise lead to the formation of hard clots difficult to eradicate from the bladder (Rastinehad et al, 2007).

Management for patients in whom hematuria remains refractory to the aforementioned measures is particularly challenging and is often guided by the patients' clinical status. That is, for clinically stable patients, intravesical formalin, a solution of formaldehyde that induces cellular protein precipitation and capillary occlusion (Choong et al, 2000), may be used. Control of bleeding has been reported in 80% to 90% of cases with formalin (Choong et al, 2000), which are relatively higher rates than what has been noted with other intravesical treatments. However, because formalin instillation may induce significant pain, administration under general or spinal anesthesia is recommended. Moreover, intravesical formalin therapy is associated with significant complications, including bladder fibrosis with associated decreased bladder capacity and ureteral stricturing with proximal hydronephrosis/renal injury (Choong et al, 2000; Abt et al, 2013). Thus pretreatment cystogram is recommended to exclude the presence of vesicoureteral reflux and/or bladder perforation (Donahue and Frank, 1989). If reflux is documented, placement of occlusive ureteral

catheters is recommended to limit upper tract exposure to the medication. Regardless, moreover, low concentrations of formalin (1% to 2%) should be used initially, because complication rates (albeit efficacy rates as well) have been linked to dosage (Donahue and Frank, 1989). Irrigation (with volumes up to 300 mL or to bladder capacity) (Choong et al, 2000) should be done under gravity, with the catheter no more than 15 cm above the pubic symphysis. Irrigation should be limited to 10 to 15 minutes and should be performed with the catheter on light traction to prevent urethral exposure, with care taken to protect all external areas of skin from exposure. Given the potential toxicities of formalin, together with the requirement for administration under anesthesia, this agent should be reserved for second-line therapy.

Another treatment option for patients with refractory hemorrhagic cystitis, particularly resulting from radiation therapy or cyclophosphamide-induced cystitis (Brastas et al, 2004), is hyperbaric oxygen (HBO₂) therapy. Treatment is carried out in a specially designed chamber and involves administration of 100% oxygen at a pressure of 2 to 3 atmospheres for approximately 90 minutes in 30 to 40 sessions (Bevers et al, 1995; Del Pizzo et al, 1998; O'Reilly et al, 2002). With this, local tissue oxygen tension increases and thus oxygen extraction by tissues increases, thereby diminishing edema and promoting neovascularization, critical steps in the wound healing process (Hader et al, 1993). Response rates to HBO₂ of 80% to 90% have been reported (Bevers et al, 1995; O'Reilly et al, 2002; Corman et al, 2003; Chong et al, 2005) and have been maintained up to 2.5 years after treatment (Weiss et al, 1994). However, with longer follow-up, most patients become symptomatic again, such that the 5-year complete response rate has been noted to be only 27% (Del Pizzo et al, 1998). Reported complications include claustrophobia (20%), otalgia (17%), and, rarely, seizures (O'Reilly et al, 2002).

For clinically unstable patients, as well as for patients with continued intractable bleeding, **internal iliac artery angioembolization represents a potential next step** in management. As reported in 1974 (Hald and Mygind, 1974), angioembolization may be performed unilaterally or bilaterally, even in debilitated patients, with relatively limited risk (Ward et al, 2003). Selective embolization of the anterior branch of the internal iliac artery bilaterally is typically required to achieve hemostasis. Care should be taken to avoid embolization of the posterior branch of the internal iliac artery, which, because of subsequent occlusion of the superior gluteal artery, may result in significant gluteal pain.

In the setting of failed angioembolization and other conservative approaches, **cystectomy with urinary diversion may be necessary to control bleeding.** Of note, pending the patients' clinical/comorbidity profile, consideration may be given to suprapubic urinary diversion alone, including bilateral nephrostomy tube insertion with occlusion of the ureters (Gonzalez et al, 2001), or ileal conduit diversion without cystectomy. The intention of such efforts is to decrease exposure of the hemorrhagic bladder to urokinase and thereby theoretically facilitate hemostasis (Rastinehad et al, 2007) while minimizing procedure-related morbidity. However, complications have been reported in up to 80% of patients with a retained bladder, including rehospitalization in 43% (Eigner and Freiha, 1990), suggesting that cystectomy should be performed at the time of urinary diversion if feasible. Unfortunately, such patients are typically ill and therefore in poor condition for surgery. As a result, complication rates may be even higher than what has been reported after cystectomy for bladder cancer.

HEMATURIA FROM PROSTATIC ORIGIN

As with hemorrhagic cystitis, hematuria from prostatic origin is a diagnosis made after a complete GH evaluation (including cytology, upper tract imaging, and cystoscopy) to confirm that no other source of hematuria exists. Varied causes exist for prostate-related hematuria, and the severity of such bleeding likewise may range from transient self-limiting episodes to continuous bleeding

KEY POINTS: HEMORRHAGIC CYSTITIS

- Oxazaphosphorine chemotherapeutic agents have been linked to the development of hemorrhagic cystitis through exposure of the metabolite acrolein to the urothelium.
- Alum may be used as a first-line intravesical therapy for hemorrhagic cystitis in patients without renal dysfunction.
- Formalin is a highly effective form of intravesical therapy for hemorrhagic cystitis. A cystogram should be obtained before therapy to ensure no vesicoureteral reflux.
- HBO₂ has been associated with response rates of 80% to 100% for patients with hemorrhagic cystitis.

resulting in the obstruction of urinary flow and in transfusion dependence. Most commonly, prostate-related bleeding is due to BPH, prostate-related infection (prostatitis), or prostate cancer (Fig. 9-3).

BPH represents the most common cause of prostate-related bleeding and has been cited as the most common cause of GH in men older than 60 (Borth and Nickel, 2006). In fact, BPH has been reported to be the only pathologic condition identified in approximately 20% of cases from hematuria studies (Hasan et al, 1994; Lynch et al, 1994). The cause for BPH-related hematuria has been thought to be increased prostatic vascularity resulting

from higher microvessel density in hyperplastic prostate tissue (Deering et al, 1995; Foley et al, 2000; Pareek et al, 2003; Borth and Nickel, 2006). This noted increase in microvessel density has in turn been linked to higher levels of vascular endothelial growth factor (VEGF) (Walsh et al, 2002; Pareek et al, 2003; Borth and Nickel, 2006).

Frequently, BPH-related hematuria episodes are mild and self-limiting, such that once the diagnosis has been established, expectant management with encouraged hydration can be undertaken. Interestingly, although GH has historically been considered an indication for surgery in the setting of BPH, increased understanding of the molecular pathway contributing to the pathophysiologic process (i.e., increased VEGF) has translated into the incorporation of what may be considered targeted medical therapy in the management of patients with BPH-related hematuria.

Specifically, because the pathophysiology of BPH-related bleeding has been postulated as increased cell proliferation stimulating increased vascularity, efforts to suppress prostate growth via androgen ablation have been explored (Marshall and Narayan, 1993; Foley et al, 2000). Both estrogens and antiandrogens have, in small case reports, been associated with decreased prostate bleeding, presumably through the repression of androgen-stimulated angiogenesis and the induction of programmed cell death within the prostate (Marshall and Narayan, 1993; Rittmaster et al, 1996). In particular, finasteride, a 5 α -reductase inhibitor that blocks conversion of testosterone to dihydrotestosterone and is a treatment for

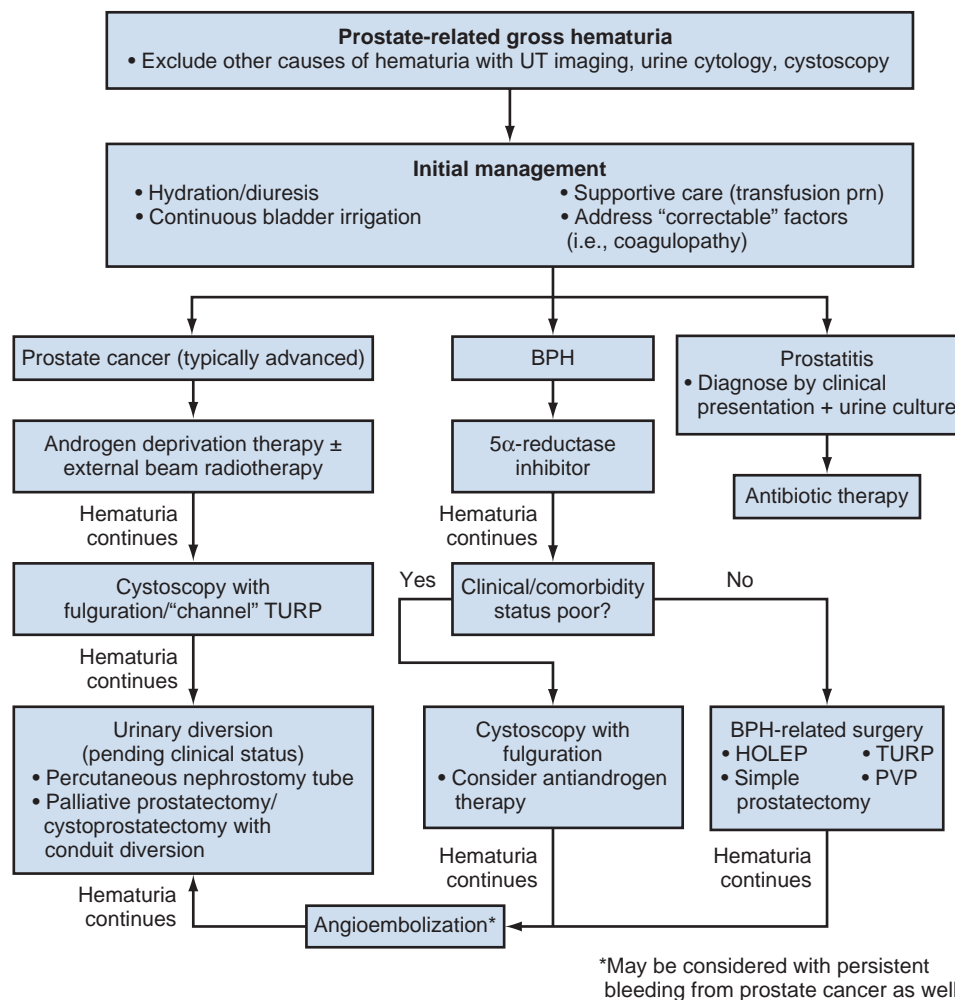


Figure 9-3. Management algorithm for patients with persistent hematuria of prostate origin. BPH, benign prostatic hyperplasia; HOLEP, holmium laser enucleation of the prostate; PVP, photovaporization of the prostate; TURP, transurethral resection of the prostate; UT, upper tract.

prostate-related outlet obstructive symptoms, has been investigated extensively for BPH-related bleeding. **Treatment with finasteride is associated with decreased VEGF expression (Pareek et al, 2003), prostate microvessel density (Pareek et al, 2003), and prostatic blood flow (Frauscher et al, 2003).**

Clinically, multiple series have demonstrated efficacy of finasteride for BPH-related hematuria, including in patients being treated with anticoagulation. Symptom improvement or resolution has been consistently noted in approximately 90% of patients (Puchner and Miller, 1995; Carlin et al, 1997; Miller and Puchner, 1998; Sieber et al, 1998; Kearney et al, 2002). A prospective randomized trial of finasteride versus expectant management in 57 patients with BPH-induced hematuria found that the rate of recurrent hematuria was significantly higher among patients in the control arm (63%) versus finasteride (14%) ($P < 0.05$), with 26% of patients in the control arm requiring surgery for bleeding versus none of the finasteride-treated patients (Foley et al, 2000). The onset of action for finasteride is variable, with improvement in bleeding noted from as short as 2 weeks to up to 9 months after initiating therapy. In addition, a randomized trial of finasteride versus cyproterone acetate versus watchful waiting demonstrated a significant decrease in recurrent hematuria in both the finasteride and in the cyproterone acetate cohorts, with no noted difference in efficacy between finasteride and cyproterone acetate in patients treated with this agent (Perimenis et al, 2002). Thus, although various forms of hormonal therapy remain options for BPH-related bleeding, the best data to date exist for 5 α -reductase inhibition, which likely entails the least side-effect profile as well.

In cases of BPH-bleeding in which patients have difficulty with bladder emptying and/or presence of clot, large-bore catheter placement with irrigation to evacuate all clot material from the bladder should ensue, followed by continuous bladder irrigation until the urine has cleared. If such measures are not sufficient to control bleeding, patients should be taken for endoscopic management under anesthesia, with clot evacuation and electric or laser cauterization. Although the variety of nonspecific intravesical therapies as are used in hemorrhagic cystitis (e.g., aminocaproic acid) have been suggested for use in this setting as well (Borth and Nickel, 2006), limited evidence exists to support the efficacy of these agents for BPH-related bleeding. Thus patients with persistent bleeding from BPH despite conservative therapies and/or endoscopic fulguration have traditionally been managed with transurethral resection of the prostate (TURP), particularly when additional indications for BPH surgery coexist. Although alternative forms of such endoscopic prostate tissue removal/destruction are available (e.g., photoselective vaporization of the prostate, holmium laser enucleation of the prostate) and even suprapubic/retropubic prostatectomy may be undertaken, the principle with all such interventions is to remove the hyperplastic and friable transition-zone prostate tissue. In cases with persistent bleeding despite TURP, selective angioembolization (Michel et al, 2002) and even radical prostatectomy or cystoprostatectomy should be considered, although, as with hemorrhagic cystitis, often such patients are poor surgical candidates because of comorbidity status.

Prostatitis, traditionally secondary to bacterial infection, also may result in GH. Indeed, a prior study reported hematuria as the manifesting symptom in 2.5% of men with prostatitis (Rizzo et al, 2003). The mechanism of hematuria in prostatitis is unclear and may be related to inflammation (Borth and Nickel, 2006). Management in this setting should consist of antibiotics when culture-documented bacterial prostatitis is present. Significant recurrent hematuria in the setting of nonbacterial prostatitis is relatively uncommon, and it has been suggested that such cases should be treated with antibiotics in addition to standard supportive measures (Borth and Nickel, 2006).

Meanwhile, hematuria from prostate cancer typically results in cases of significantly locally advanced tumors, often with bladder base/trigonal invasion. Indeed, hematuria has been noted to be the most common local symptom among patients with advanced symptomatic prostate cancers (Din et al, 2009). Importantly, the hematuria in these patients, particularly in those who

have previously received radiation therapy in the management of their prostate cancer, should be confirmed with endoscopic evaluation to be from a prostate source and not, for example, as a result of hemorrhagic cystitis or secondary bladder malignancy. Unfortunately, these tumors are typically invasive of the bladder and/or pelvic sidewall (T4) and the patients are often elderly and unwell. Thus treatment is primarily with palliative intent. Initial conservative measures, including catheter drainage with or without continuous bladder irrigation, suffice for most cases of mild prostatic bleeding. For patients in whom hematuria is not acutely life-threatening, palliative external beam radiotherapy with or without androgen deprivation therapy may be administered. Indeed, one series reported that hematuria from advanced prostate cancer responded to palliative radiation in 81% of patients at 6 weeks after treatment; however, durable symptom control was limited, such that the response rate 7 months after treatment in these patients was only 29% (Din et al, 2009). Among patients who are not candidates for local therapy, as well as among patients in whom disease has recurred after previous local therapy, androgen deprivation therapy may resolve the hematuria (Marshall and Narayan, 1993) by decreasing prostate vascularity (Kaya et al, 2005).

In the situation of persistent hematuria with prostate cancer, and in particular in the setting of bladder outlet obstruction, cystoscopy under anesthesia with fulguration and/or limited, or channel, transurethral resection of prostatic tissue should be undertaken. Moreover, selective internal iliac artery embolization, as has been reported for severe post-TURP bleeding (Barbieri et al, 2002; Michel et al, 2002), may be considered, although data on this approach in the setting of prostatic malignancy are scant. Ultimately, if bleeding persists or escalates, consideration should be given to urinary diversion, which initially may be attempted with percutaneous nephrostomy tube insertion. With continued prostate hemorrhage, palliative extirpative surgery, which may be in the form of radical prostatectomy, but more typically requires cystoprostatectomy and conduit diversion, should be considered pending patients' clinical and comorbidity status.

KEY POINTS: HEMATURIA FROM PROSTATIC ORIGIN

- BPH represents the most common cause of GH in men older than 60 years.
- 5 α -Reductase inhibitors may be used for BPH-related GH.
- Androgen deprivation may be effective for patients with locally advanced prostate cancer with GH.
- Angioembolization and/or urinary diversion represent salvage options for management for patients with refractory hematuria, pending clinical status.

URETHRAL BLEEDING

Urethral bleeding (urethrorrhagia) is defined as bleeding emanating from the urethra at a point distal to the bladder neck, occurring separate from micturition (Gontero, 2013). A careful history and physical examination may help elucidate whether the source of bleeding is truly from the urethra as opposed to other sites within the lower urinary tract. For example, blood at the urethral meatus in the absence of volitional micturition, initial hematuria, or blood at the start of urination frequently implies pathologic processes distal to the external urinary sphincter. Of note, in women, differentiating urethral bleeding from that of gynecologic origin based on history alone may be challenging and pelvic examination is typically necessary to clarify the site of origin (Sandhu et al, 2009). Importantly, retrograde urethrogram and cystourethroscopy remain the mainstays for diagnosis in patients with suspected urethral bleeding, because direct visualization permits identification of pathologic processes in the urethra and biopsy and fulguration allow for histologic characterization and cessation of bleeding.

Causes of urethral bleeding are best classified by gender (**Box 9-3**). In men, trauma to the urethral epithelium represents the most common cause of urethral bleeding. For example, blunt trauma via straddle injury, kick to the perineum, or pelvic fracture often manifests with bleeding and concurrent urinary retention (**Mundy and Andrich, 2011**). Perineal or penile bruising, accompanied by a hematoma, often is a clear indication of injury related to trauma. Retrograde urethrography is essential in instances of trauma when a urethral injury is suspected (**Avery and Scheinfeld, 2012**). Meanwhile, a history of foreign body insertion in patients with hematuria may necessitate imaging to ensure no residual foreign elements remain that could perpetuate bleeding or result in subsequent calculus formation (**Rahman et al, 2004**). Particular mention should be made to the evaluation of bloody urethral discharge and/or hematuria occurring in patients with a penile fracture. In this setting, prompt evaluation via retrograde urethrography or cystoscopy should be undertaken to evaluate for a urethral injury and to identify the nature and location of the injury before surgical exploration (**Avery and Scheinfeld, 2012**).

Urethritis refers to infection or inflammation of the epithelial lining of the urethra and has been reported secondary to bacterial or viral infection, chemical irritants (i.e., spermicidal jelly), and, rarely, autoimmune systemic conditions (human leukocyte antigen B27 [HLA-B27] Reiter syndrome). Urethral discharge on palpation may be noted with urethritis in men. Urine microscopy and cultures, as well as urethral swabs for causative organisms, represent essential components of the evaluation.

Urethral tumors are rare, although blood per meatus may be a manifesting sign in patients with urothelial carcinoma, specifically in men who have undergone a radical cystectomy with urethra still in situ (**White and Malkowicz, 2010**). At the same time, urethral caruncles are benign urethral lesions typically originating from the posterior lip of the urethra, most commonly found in postmenopausal women (**Conces et al, 2012**). These lesions are thought to arise from prolapse of distal urethra as a consequence of estrogen deficiency. In addition to the classic presentation

of dysuria, dyspareunia, and dribbling, women with a urethral diverticulum also may report intermittent episodes of bleeding, and urethral discharge may be noted on examination.

HEMATURIA ORIGINATING FROM THE UPPER URINARY TRACT

Hematuria emanating from the upper urinary tract is frequently asymptomatic, although macroscopic bleeding with clots can result in subsequent ureteral obstruction, with patients experiencing “clot colic,” as well as anemia, and even rarely hemodynamic instability (**Lano et al, 1979**). Most often, hematuria from the upper tract manifests as total hematuria, or bleeding throughout the duration of the urinary stream (**Mazhari and Kimmel, 2002**), and may be characterized by wormlike clots passed per urethra. A variety of causes can result in bleeding from the upper tract (**Box 9-4**), with

BOX 9-3 Differential Diagnosis for Urethral Bleeding

MALE

Trauma

- Blunt (straddle injury, kick to perineum)
- Penetrating (foreign body insertion, failed urethral catheterization)
- Intercourse related (penile fracture, masturbation)

Urethritis

- Bacterial (gonococcal, nongonococcal)
- Viral
- Chemical
- Autoimmune (Reiter syndrome)

Malignancy

- Urothelial carcinoma
- Squamous cell carcinoma (meatus/glans)

Condyloma

Calculus disease

FEMALE

Trauma

- Blunt (pelvic fracture)
- Penetrating (foreign body)

Urethral diverticulum

Urethral caruncle

Urethritis

Malignancy

Calculus disease

BOX 9-4 Differential Diagnosis for Upper Urinary Tract Bleeding

Renal glomerular diseases

- IgA nephropathy (Berger disease)
- Thin basement membrane disease
- Acute glomerulonephritis (e.g., poststreptococcal)
- Lupus nephritis
- Hereditary nephritis (e.g., Alport syndrome)

Renal tubulointerstitial diseases

- Papillary necrosis
- Sickle cell nephropathy
- Analgesic nephropathy
- Polycystic kidney disease
- Medullary sponge kidney

Vasculitis

- Henoch-Schönlein purpura
- Wegener granulomatosis

Infection

- Pyelonephritis
- Xanthogranulomatous pyelonephritis
- Renal tuberculosis
- Fungal infection

Obstruction

- Ureteropelvic junction obstruction
- Ureteral stricture

Nephrolithiasis

Malignancy

- Renal cortical tumors (renal cell carcinoma, benign tumors)
- Upper tract urothelial carcinoma

Fibroepithelial polyp

Vascular diseases

- Renal arteriovenous malformations (congenital, acquired)
- Iliac arterio-ureteral fistula
- Renal artery aneurysm (especially ruptured)
- Renal artery pseudoaneurysm
- Renal artery and/or vein thrombosis
- Hemangioma
- Atheroembolic disease
- Nutcracker syndrome
- Loin-pain hematuria syndrome

Trauma

- Blunt
- Penetrating
- Lateralizing essential hematuria

the most common causes of hematuria from the upper urinary tract including stones, trauma, and malignancy. The evaluation and management of these entities is described elsewhere. Herein, we highlight several particularly salient, albeit less frequent, causes of upper tract hematuria.

Medical Renal Disease

Glomerular diseases are a constellation of acquired or inherited conditions in which the glomeruli are damaged. Consequences include loss of RBCs and protein in the urine, with the clinical sequelae of hematuria, hypoproteinemia with associated edema, and reduced glomerular filtration rate. **Urinary findings suggestive of a glomerular cause include the presence of RBC casts in the urinary sediment, dysmorphic RBCs, and proteinuria (Yun et al, 2004).** Common acquired causes of glomerular diseases are covered in Chapter 46.

Meanwhile, tubulointerstitial diseases broadly refer to kidney diseases affecting structures in the kidney outside the glomerulus. For example, sickle cell nephropathy is associated with sickle cell disease, whereby sickled erythrocytes decrease medullary blood flow, causing local ischemia, microinfarction, and papillary necrosis (Pham et al, 2000). Analgesic nephropathy can likewise cause renal papillary necrosis and subsequently chronic interstitial nephritis. Percutaneous renal biopsy may be a valuable diagnostic modality when a suspicion exists for glomerular or tubulointerstitial causes of hematuria.

Vascular Conditions Affecting the Urinary Tract

A variety of vascular conditions can cause hematuria. For example, ureteroiliac artery fistula is an uncommon but potentially life-threatening cause of hematuria. **Predisposing factors include pelvic or vascular surgery, pelvic irradiation, extensive ureteral mobilization, and chronic ureteral stenting (Muraoka et al, 2008).** With regard to management, high mortality rates have been reported with surgical repair of ureteroiliac fistulas, and as such angiographic localization with vascular stenting has become the current preferred management approach (Keller et al, 1990). Renal arteriovenous malformations (AVMs), meanwhile, are abnormal communications between intrarenal arterial and venous systems, with congenital and acquired (iatrogenic) causes. **Acquired AVMs account for 75% of such cases and have been associated with renal biopsy, renal surgery (partial nephrectomy, nephrolithotomy), and trauma (Muraoka et al, 2008).** Arteriography with selective angioembolization is considered the primary diagnostic and therapeutic option for suspected renal AVMs, affording symptom resolution with maximal preservation of functional renal parenchyma. Thus **expeditious angiography should be considered for patients with a recent history of a renal procedure presenting with GH.** The goal of AVM embolization is eradication of the site where abnormal arterial and venous communication exists. Renal artery aneurysms, moreover, may be related to connective tissue disorders and are generally asymptomatic. Hypertension may be present in up to 90% of affected persons, and dissecting aneurysms may cause flank pain with GH. Renal artery aneurysms and pseudoaneurysms are generally managed via endovascular approaches in the hemodynamically stable patient, whereas surgical intervention is typically necessary in the unstable patient (Mohan and Stephens, 2013).

Additionally, **"nutcracker syndrome" (i.e., renal vein entrapment syndrome)** is defined as the compression of the left renal vein between the abdominal aorta posteriorly and the superior mesenteric artery anteriorly. Hematuria has been postulated to occur as a result of increase in left renal vein pressure causing small-volume rupture of thin-walled capillaries into the collecting system (Wolfish et al, 1986). Left renal vein transposition, superior mesenteric artery transposition, and nephrectomy have been described as surgical approaches for management of this condition (Hohenfellner et al, 2002). More recently, endovascular stenting to maintain a patent renal vein has been reported as well.

Lateralizing Essential Hematuria and the Evaluation of Upper Urinary Tract Bleeding

Lateralizing essential hematuria, also termed *benign essential hematuria* or *chronic unilateral essential hematuria*, is defined as macroscopic hematuria cystoscopically localized to one side of the urinary system (Nakada, 2003). Patients have typically had normal prior radiographic studies. Although rare, manifestations of lateralizing essential hematuria may range from minimally symptomatic GH to clot retention and anemia (Nakada, 2003). The differential diagnosis for this entity is as noted earlier for upper tract bleeding (see Box 9-4), although in many such cases no identifiable cause can be determined.

Cystoscopy at the time of bleeding may allow lateralization of the source of hematuria. Subsequently, in the absence of a clear cause for bleeding localized to the upper tract in a patient with lateralizing essential hematuria, direct endoscopic inspection with ureteropyeloscopy is recommended as a diagnostic and potentially therapeutic modality (Nakada, 2003). **Critical components of diagnostic ureteropyeloscopy include the judicious use of guidewires (to avoid inadvertent urothelial injury), low-pressure irrigation, and systematic evaluation of all calices from a superior-to-inferior approach (Ankem and Nakada, 2006).** Biopsy samples can be obtained for lesions suspicious for malignancy, and fulguration of such tumors or other noted sources of bleeding (i.e., hemangioma) can be accomplished as well.

KEY POINTS: URETHRAL BLEEDING AND HEMATURIA ORIGINATING FROM THE UPPER URINARY TRACT

- Urethral bleeding should be suspected with blood at the meatus and/or initial hematuria.
- A concern for traumatic urethral injury should prompt retrograde urethrogram.
- Urinary findings suggestive of a glomerular cause include the presence of RBC casts in the urinary sediment, dysmorphic RBCs, and proteinuria.
- In patients with GH after a recent renal procedure, expeditious angiography should be considered to allow for the diagnosis and management of renal AVM.

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10

Fundamentals of Laparoscopic and Robotic Urologic Surgery

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Preoperative Preparation

In the Operating Room

Strategic Placement of Operative Team and Equipment

Performing the Procedure

Physiologic Considerations in the Adult

Complications and Troubleshooting in Laparoscopic and Robotic Surgery

Training and Practicing Laparoscopic and Robotic Surgery

Conclusion

More than 100 years ago the “father of modern medicine,” Sir William Osler, challenged surgeons to perpetually refine their craft, stating, “Diseases that harm require treatments that harm less.” In pursuit of this noble goal, the urologists of the 20th century brought us great achievements in our field, but it has been over the past 25 years, in particular, that the specialty of minimally invasive urology has become predominant. The earliest techniques that laid the foundation for modern laparoscopic and robotic urologic procedures were developed at academic institutions throughout the world and have continuously been validated and improved. Subsequently, an increasing number of multi-institutional studies have emerged comparing laparoscopic and robotic procedures with their open surgical counterparts and showing equivalent efficacy and acceptable efficiency, as well as the distinct advantages of decreased postoperative pain, better cosmesis, faster recovery, a shorter hospital stay, and, in many cases, lower cost. Indeed, it has become increasingly clear that the objectives of many open urologic surgeries, be it of the adrenal gland, kidney, ureter, bladder, prostate, or lymph nodes, can now be achieved with minimally invasive surgery with less patient injury and suffering. Therefore, whereas open surgery has had a steadily diminishing role in the treatment of urologic diseases, laparoscopic and robotic surgery have moved into the mainstream of urologic surgery, and knowledge of the required principles and techniques is essential for the practicing urologist. This chapter is intended to provide a basic foundation of knowledge on which the aspiring minimally invasive urologist can build.

PREOPERATIVE PREPARATION

Patient Selection and Contraindications

Careful patient selection and identification of possible relative and absolute contraindications to laparoscopic and robotic procedures are vital to a successful outcome. To this end, a meticulous past history, focusing on prior surgeries, and physical examination, detailing the location and extent of all abdominal scars, are the initial steps in patient evaluation.

Age- and health-based laboratory studies, an electrocardiogram, and a chest radiograph should be obtained according to the same criteria established for any other significant surgical procedure that is undertaken with general anesthesia.

In patients with severe chronic obstructive pulmonary disease (COPD), further studies (i.e., arterial blood gases and pulmonary function tests) are required because of the physiologic effects of the CO₂ pneumoperitoneum. Cardiac arrhythmias should be evaluated

and treated preoperatively because hypercarbia and the resulting acidosis, from the pneumoperitoneum, may have adverse effects on the myocardium, thereby exacerbating any preexisting myocardial instability.

Contraindications to laparoscopic surgery include uncorrectable coagulopathy, intestinal obstruction unless there is an intention to treat, significant abdominal wall infection, massive hemoperitoneum or hemoretroperitoneum, generalized peritonitis, and suspected malignant ascites. Select circumstances in which laparoscopy is being contemplated necessitate careful risk-benefit analysis and detailed and specific informed consent with the patient. The following conditions may portend potential difficulties with a laparoscopic approach.

Morbid Obesity

Laparoscopic procedures in morbidly obese patients are technically challenging. Difficulties may include inadequate length of instruments, decreased range of motion of trocars and instruments, need for higher pneumoperitoneum pressures to elevate the abdominal wall, and poor anatomic orientation owing to excessive amounts of adipose tissue. Traditionally, these difficulties translated into a higher rate of associated complications (Mendoza et al, 1996; Anast et al, 2004; Parker et al, 2008; Aboumarzouk et al, 2012). However, in comparison to open surgery it has been found that the laparoscopic approach to renal and adrenal procedures actually has several advantages. Studies have shown for laparoscopic adrenalectomy and nephrectomy in obese patients that the laparoscopic group had significantly superior outcomes regarding blood loss, resumption of oral intake and ambulation, narcotic analgesic requirements, median hospital stay, and convalescence compared with the open approach (Fazeli-Matin et al, 1999; Fugita et al, 2004; Kapoor et al, 2004; Shuford et al, 2004). These findings have been confirmed for complicated procedures such as laparoscopic and robotic partial nephrectomy (Colombo et al, 2007; Romero et al, 2008; Isac et al, 2012) and laparoscopic nephroureterectomy (Brown et al, 2008).

With regard to laparoscopic and robotic radical prostatectomy in obese men, it has been found that although the operation can be performed without compromising pathologic outcomes, obese patients have a greater risk of perioperative complications (26% vs. 5%) (Ahlering et al, 2005).

Extensive Prior Abdominal or Pelvic Surgery

When extensive intra-abdominal or pelvic adhesions are suspected, careful consideration must be given to the possible site of Veress

needle insertion as well as to obtaining open access with a Hasson-style cannula. The Palmer point (subcostal in the midclavicular line on the left side) is the preferred site for Veress needle insertion when extensive intra-abdominal adhesions are suspected (Palmer, 1974). Alternatively, in these patients a retroperitoneal approach may be preferable to a transperitoneal approach or the procedure can be initiated retroperitoneally and the peritoneum then entered (Cadeddu et al, 1999).

Pelvic Fibrosis

Pelvic fibrosis caused by previous peritonitis, pelvic surgery, or extensive endometriosis may constitute a severe technical challenge to the laparoscopic surgeon when surgery of the lower urinary tract is indicated. Similar problems may be encountered when trying to perform pelvic lymph node dissection in patients who have a hip prosthesis; leakage of the polymethyl methacrylate cement can create a dense inflammatory reaction and fibrosis in the adjacent pelvis (Cooper et al, 1997).

Organomegaly

Known or preoperatively diagnosed organomegaly (e.g., hepatomegaly or splenomegaly) necessitates a cautious approach when obtaining the pneumoperitoneum. The site of Veress needle insertion must be chosen at a safe distance from any enlarged organs, or, preferably, open access with the Hasson cannula may be considered.

Ascites: Benign Cause

Patients with severe ascites are under increased risk of injury to the bowel owing to closer proximity of bowel loops to the anterior peritoneum. In addition, a watertight wound closure is required and a firm wound dressing should be applied to prevent prolonged postoperative leakage.

Pregnancy

Initial access to the abdomen must be obtained at a safe distance from the fundus of the gravid uterus. Therefore, trocar placement is usually performed more cephalad on the abdominal wall, depending on the fundus of the uterus. The left upper quadrant in the subcostal midclavicular line (i.e., Palmer point) is often the preferred site of access. Prolonged intra-abdominal pressures of 15 mm Hg or greater may result in hypotension owing to significantly reduced venous return because the vena cava is already mechanically compromised by the enlarged uterus. Prolonged CO₂ pneumoperitoneum, which may result in maternal hypercarbia and acidosis with subsequent adverse effects on the fetus, should be avoided. Accordingly, a working pneumoperitoneum of 10 to 12 mm Hg is recommended in the pregnant patient. **The second trimester is a preferred time for necessary surgery, given the completion of fetal organogenesis and reduced chance of inducing labor.**

As pregnancy progresses beyond the 20th week, the possibility of performing laparoscopic procedures decreases significantly, correlating with the increasing size of the gravid uterus. Of note, both laparoscopic nephrectomy and adrenalectomy have been successfully accomplished in pregnant women (Nezhat et al, 1997; O'Connor, et al, 2004; Sainsbury et al, 2004).

Hernia

A diaphragmatic hernia may result in leakage of a significant amount of CO₂ into the mediastinum, which, although rarely noted, may eventually result in clinical problems such as respiratory compromise or cardiac tamponade (e.g., pneumopericardium) (Knos et al, 1991).

Any evidence of uncorrected or surgically corrected umbilical hernia or abdominal wall hernia should rule out these sites for obtaining a pneumoperitoneum.

Iliac or Aortic Aneurysm

Significant aneurysms warrant evaluation by the vascular surgeon. If the aneurysm does not require immediate surgical correction, insertion of the Veress needle should be performed in the left upper quadrant to stay well away from the area of the aneurysm. Of course, open access with the Hasson technique can be used alternatively. Insertion of accessory trocars must be done under strict endoscopic control to avoid the area of the aneurysm.

Bowel Preparation

For extraperitoneoscopy and retroperitoneoscopy, no bowel preparation is necessary. Similarly, for transperitoneal laparoscopic or robotic procedures *not* involving the use of bowel segments for urinary tract reconstruction, a mechanical bowel preparation is not necessary. A recent large-scale propensity score-matched analysis demonstrated no benefit for mechanical bowel preparation in operative time, postoperative stay, or overall complications for patients undergoing laparoscopic nephrectomy (Sugihara et al, 2013a). Likewise, the same group found no benefit to mechanical bowel preparation in patients undergoing laparoscopic radical prostatectomy in terms of complications, operative time, and postoperative length of stay (Sugihara et al, 2013b).

More recently, emphasis has been placed on “fast-tracking” patients in an effort to streamline care and decrease length of hospital stay. Breda and associates (2007) found that a modified bowel preparation and avoidance of narcotic analgesics postoperatively (with routine administration of ketorolac) was instrumental in achieving a hospital stay of 1.1 days for patients undergoing laparoscopic donor nephrectomy. The bowel preparation consists of clear liquids for 2 days before surgery, two bottles of magnesium citrate the day before surgery, an enema the night before surgery, and nothing to eat after midnight (Breda et al, 2007).

The need for a full mechanical and antibiotic bowel preparation is subject to question and becomes an issue only if one anticipates encountering dense intra-abdominal adhesions or if the surgery involves entering the bowel. However, emerging literature suggests no benefit to a full mechanical bowel preparation for patients undergoing radical cystectomy with creation of ileal conduit or orthotopic neobladder (Hashad et al, 2012; Large et al, 2012; Raynor et al, 2013).

Preparation of Blood Products

Serum type and screen are sufficient for laparoscopic and robotic procedures with a low chance of major hemorrhage. Procedures such as laparoscopic radical nephrectomy and nephroureterectomy have a low rate of transfusion (3% to 12%), with an estimated average blood loss in the range of 106 to 255 mL (Ono et al, 1999; Dunn et al, 2000; Jeschke et al, 2000; Shalhav et al, 2000). Similarly, the transfusion rate with laparoscopic or robotic radical prostatectomy is low (2.5% at experienced centers) (Guillonneau and Vallancien 2000; Ahlering et al, 2004).

More extensive laparoscopic robotic procedures (e.g., partial nephrectomy, radical cystectomy, radical nephrectomy with inferior vena cava thrombectomy), especially early in one's experience, should be managed like any other major open surgical procedure, with packed red blood cells available before surgery. With greater experience, a type and screen may suffice for certain more extensive procedures (e.g., partial nephrectomy) because the risk for transfusion is low (6% to 7%) (Ghani et al, 2014).

IN THE OPERATING ROOM

Setup of the Operating Room

The operating room has to provide enough space to accommodate all necessary personnel and the equipment required by both the surgeon and the anesthesiologist. Positioning of equipment, surgeon, assistants, nurses, anesthesiologist, and other support staff

BOX 10-1 Instrumentation Checklist for Making a Skin Incision for Obtaining the Pneumoperitoneum

1. Irrigation-aspiration unit is working.
2. Electrosurgical unit is working.
3. CO₂ tank is full, with extra CO₂ tank in the room.
4. Camera is white balanced, and light source is working.
5. Insufflation is checked for flow and response to kinking of the tubing.
6. Veress needle is checked for flow and proper tip retraction.

KEY POINTS: PREOPERATIVE PREPARATION

- Careful patient selection and identification of possible relative and absolute contraindications are vital to a successful outcome of laparoscopic and robotic procedures. To this end, a meticulous past history, focusing on prior surgeries, and physical examination, detailing the location and extent of all abdominal scars, are the initial steps in patient evaluation for possible minimally invasive surgery.
- Contraindications to laparoscopic surgery include uncorrectable coagulopathy, intestinal obstruction unless treatment is intended, significant abdominal wall infection, massive hemoperitoneum or hemoretroperitoneum, generalized peritonitis, and suspected malignant ascites.

should be clearly defined and established for each laparoscopic or robotic case. All equipment must be fully functional and in operating condition before any laparoscopic procedure is started (Box 10-1). A separate tray with open laparotomy instruments must be ready for immediate use in the event of complications or problems necessitating emergent open surgery.

Patient Positioning

Positioning of the patient depends primarily on the procedure to be performed. In the supine position the arms can be tucked snugly at the sides or rest on specially designed sleds. In the Trendelenburg or lateral position, tape and security belts applied across the chest and thighs provide safe and stable positioning of the patient. In the lateral position, all bony prominences in contact with the table must be carefully padded; likewise, the point of contact between any of the positioning straps and the hip or shoulder should be padded. In the lateral position, the bottom leg is flexed approximately 45 degrees while the upper leg is kept straight; pillows are placed between the legs as a cushion and also to elevate the upper leg so that it lies level with the flank, thereby obviating any undue stretch on the sciatic nerve. Pads should be placed between the table and the knee and ankle of the lower leg because these are high-pressure areas. In the lateral decubitus position an axillary roll should be used. Application of an active warming system may prevent hypothermia, should a lengthy laparoscopic procedure be anticipated.

A host of new advances in padding and table-mounted accessories are now available, but none has been conclusively demonstrated to significantly reduce pressure on the patient's flank in the lateral position. Researchers at the University of California, Irvine, showed that women have significantly lower interface pressures than men (Deane et al, 2008). A body mass index (BMI) greater than or equal to 25, use of a kidney rest, and full-table flexion as opposed to half-table flexion were all associated with increases in interface pressures; of these, **use of the kidney rest was believed to be the most detrimental and its use beyond 20 to 30 minutes was discouraged.** Therefore, male patients with a BMI of 25 or higher

undergoing laparoscopic surgery in the lateral position with the kidney rest elevated and the table completely flexed are at highest risk of developing rhabdomyolysis from flank pressure. In this study the unaugmented operating table mattress was superior to egg crate or gel padding as an augmenting surface material; of note, egg crate padding was equal or superior to the more expensive gel padding.

Table-mounted accessories for all major commercial operating room tables now exist that aid in safely and effectively positioning patients in the lateral decubitus position and in the prone position. For laparoscopic or robotic procedures on the pelvis, the patient can be placed in Trendelenburg position with the legs on split-leg positioners (Fig. 10-1A on the Expert Consult website) or in Allen stirrups (Fig. 10-1B on the Expert Consult website). **Shoulder supports or braces should never be used in this position owing to the risk of brachial nerve injury.**

Prophylaxis and Other Preparations

Pneumatic compression stockings can be applied for antiembolic prophylaxis. In addition, the administration of 5000 units of subcutaneous heparin preoperatively is also an option. In higher-risk patients, such as the morbidly obese, both may be considered (see the discussion of early postoperative complications). Before laparoscopic or retroperitoneoscopic procedures, placement of a Foley catheter should be performed to allow for accurate measurement of urine output, to decompress the bladder to improve visibility and working space, and to reduce the risk of injury with pelvic procedures. Similarly, when needed, a nasogastric or orogastric tube can be inserted to improve the working space available in the upper abdomen.

STRATEGIC PLACEMENT OF OPERATIVE TEAM AND EQUIPMENT**Standard Laparoscopic Carts**

Traditionally, the mandatory hardware for laparoscopic procedures (monitor, light source, insufflator) is located on carts or "towers" that can be rolled around the operating room and adapted to various types of surgical procedures and approaches (Fig. 10-2A on the Expert Consult website). The main laparoscopic cart should contain the insufflator, light source, camera controls, and any recording device. Ideally, the insufflator should be placed at the surgeon's eye level to allow continuous monitoring of the CO₂ pressure.

Integrated Endoscopy Systems

More recently, most major manufacturers of endoscopy equipment offer "integrated" systems that consist of flat panel displays and equipment towers that are mounted on adjustable ceiling booms (see Fig. 10-2B on the Expert Consult website). This allows the display monitors to be suspended over the patient and placed directly in front of the surgeon at any height or angle. This feature may reduce eye and body strain. Furthermore, the tower containing the light source, camera system, and insufflator can be placed in any area around the patient depending on the operation at hand.

Robotic Systems

Currently, the only robotic surgical system in widespread use for laparoscopic surgery is the da Vinci Robotic System (Intuitive Surgical, Sunnyvale, CA). The three major components of the system are the robotic tower (i.e., patient-side cart) to which are attached the instruments that are mechanically manipulated within the patient; a surgeon's console, which is the workstation at which the surgeon sits to manipulate the robotic instruments; and finally the ancillary vision cart, which supports a flat screen monitor, an insufflator, a light source, and components of the camera system (Fig. 10-3 on the Expert Consult website). Additional monitors can be linked



Figure 10-1. A, Split-leg positioners. B, Allen stirrups.



Figure 10-2. A, A standard laparoscopic cart. B, An integrated laparoscopic vision system.

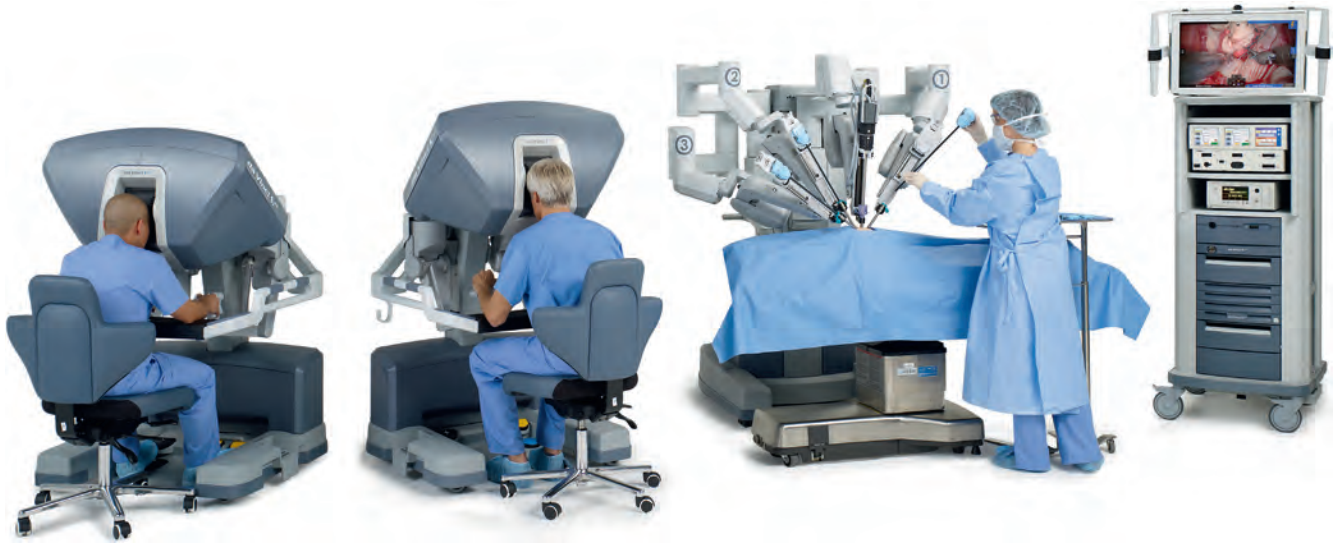


Figure 10-3. The da Vinci Si Robotic System (Intuitive Surgical, Sunnyvale, CA) with dual surgeon console. (© 2015 Intuitive Surgical, Inc. Used with permission.)

with the robotic system and used for the assistant and support staff image viewing. The newest generation of the robotic surgical system (da Vinci Si) has the capacity for a second surgeon's console to support training and collaboration.

Placement of the Operative Team for Laparoscopic Procedures

Transperitoneal Procedures in the Upper Abdomen

Laparoscopic. For transperitoneal laparoscopic renal and adrenal surgical procedures, the patient is positioned in a modified lateral decubitus position. The surgeon and assistant usually stand in front of the abdomen with the patient in the lateral decubitus position (i.e., for a left nephrectomy the surgeon and assistant stand on the right side of the operating table). The instrument table and the scrub nurse are best located on the opposite side of the patient near the foot of the bed, such that instruments can be handed to the surgeon over the table (Fig. 10-4A). Incoming lines from insufflators, suction and irrigation, electrosurgical devices, and so on enter from the contralateral side of the table or from the ipsilateral head of the table. Additional technology (e.g., laparoscopic ultrasound probe) may be moved to the operating table depending on the surgeon's needs, as well as on the availability of space.

To provide more comfortable positioning of the surgeon's arms, a 6- × 4-foot, 6-inch lift can be used when the operating table cannot be lowered sufficiently to allow the surgeon to hold the laparoscopic instruments with his or her elbows held comfortably at the side rather than extended laterally. This is most important during suturing.

Robotic. For transperitoneal robotic-assisted laparoscopic renal and adrenal surgical procedures, the patient is again positioned in a modified lateral decubitus position. The assistant usually stands in front of the abdomen with the patient in the lateral decubitus position (i.e., for a left nephrectomy the assistant stands on the right side of the operating table). The robotic arms (i.e., patient-side cart) are brought in from the opposite side (i.e., facing the back with the patient in the lateral decubitus position), such that the robotic arms stretch over the patient and can then be docked to the preplaced ports. In general, it is best to angle the robot slightly such that the

camera is pointing directly toward the site of interest. Accordingly, depending on the exact port placement, the robotic arms may be brought in at an angle toward the head of the patient, as opposed to perpendicular to the operating table, to minimize clashing of the robotic arms once docked (Fig. 10-5 on the Expert Consult website). The instrument table and the scrub nurse are best located at the foot of the bed on the same side of the patient as the surgical assistant, such that instruments can be easily handed to the surgical assistant (see Fig. 10-4B). The robotic console can be placed anywhere in the room remote from the operating table and instrument table such that it is out of the way, but in view of the patient and anesthetic monitors. All incoming lines from insufflators, suction and irrigation, and electrosurgical devices enter either from the contralateral foot side of the table or the ipsilateral head of the table.

Retroperitoneal Procedures in the Upper Abdomen

Laparoscopic. For retroperitoneal renal and adrenal procedures, the patient is placed in the true, 90-degree lateral decubitus position with the body at a right angle to the table. All of the proper steps for padding in this position should be followed (see earlier). The table is angled at the hip to accentuate and increase the distance between the 12th rib and the iliac crest. Maximizing this distance is paramount with regard to port placement. Both the primary surgeon and the camera assistant stand facing the patient's back (Fig. 10-6A). The scrub nurse or technician stands facing the patient's front, and instruments are handed across the patient accordingly.

Robotic. For retroperitoneal robotic-assisted renal and adrenal procedures, the patient is similarly placed in the true 90-degree lateral decubitus position. The surgical assistant can stand facing either the patient's abdomen or his or her back depending on the surgeon's preference for port placement. The instrument table and scrub nurse are best placed on the same side as the assistant near the foot of the table. The robotic arms are brought in over the head of the patient (Fig. 10-6B). Because the robotic arms are positioned over the patient's head, the anesthesiologist and the anesthetic cart and monitors should be positioned off to the side, in front of the patient, at the head of the bed.

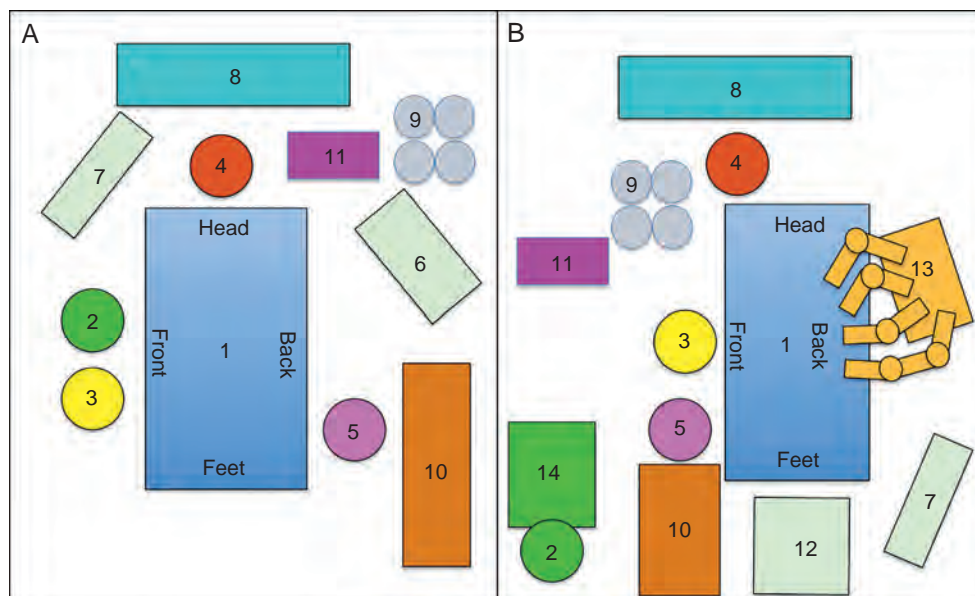


Figure 10-4. Placement of the operative team for transperitoneal procedures in the upper abdomen. A, Laparoscopic procedure. B, Robotic procedure. 1, Operating table; 2, surgeon; 3, assistant; 4, anesthesiologist; 5, scrub assistant; 6, laparoscopic cart or tower; 7, auxiliary video monitor; 8, anesthesia equipment; 9, suction and irrigation unit; 10, scrub assistant's instrument table; 11, electrocautery unit; 12, ancillary vision cart; 13, robotic tower; 14, surgeon's console.

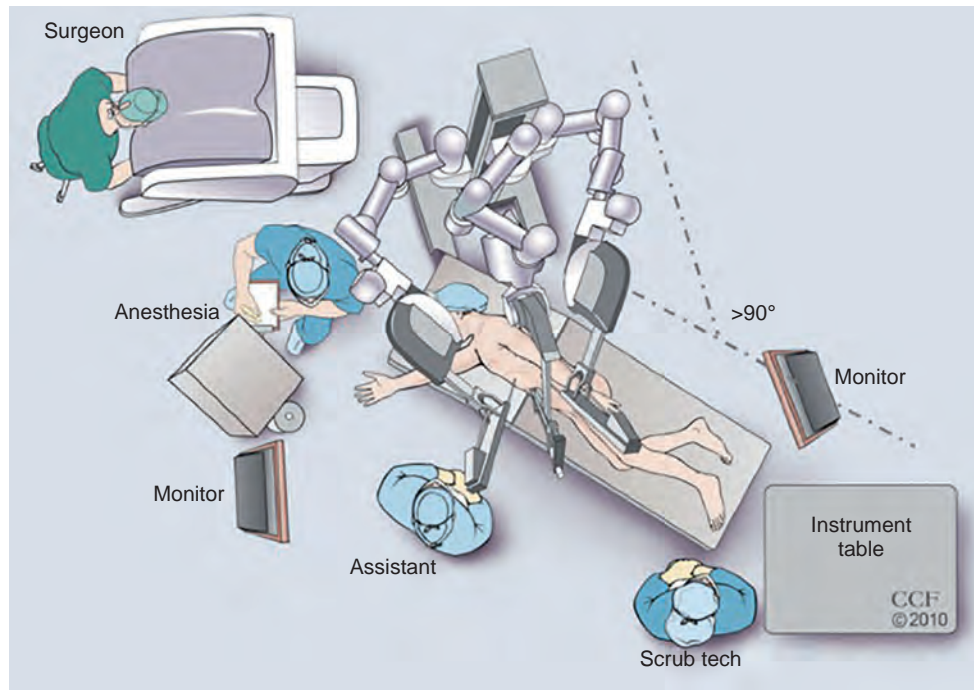


Figure 10-5. Angulated placement of the robotic tower to minimize clashing of the robotic arms during transperitoneal upper abdominal procedures (i.e., renal and adrenal).

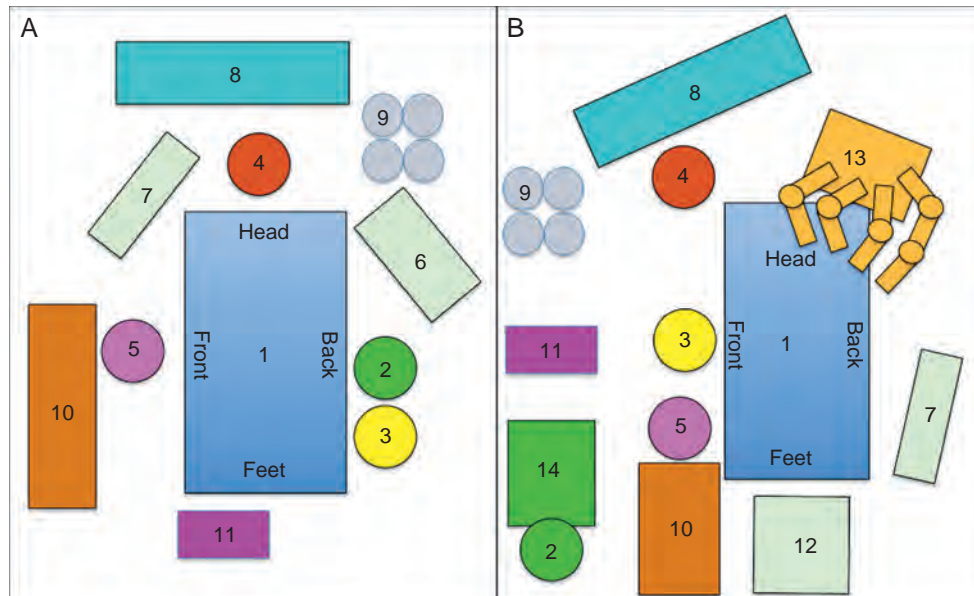


Figure 10-6. Placement of the operative team for retroperitoneal procedures in the upper abdomen. A, Laparoscopic procedure. B, Robotic procedure. 1, Operating table; 2, surgeon; 3, assistant; 4, anesthesiologist; 5, scrub assistant; 6, laparoscopic cart or tower; 7, auxiliary video monitor; 8, anesthesia equipment; 9, suction and irrigation unit; 10, scrub assistant's instrument table; 11, electrocautery unit; 12, ancillary vision cart; 13, robotic tower; 14, surgeon's console.

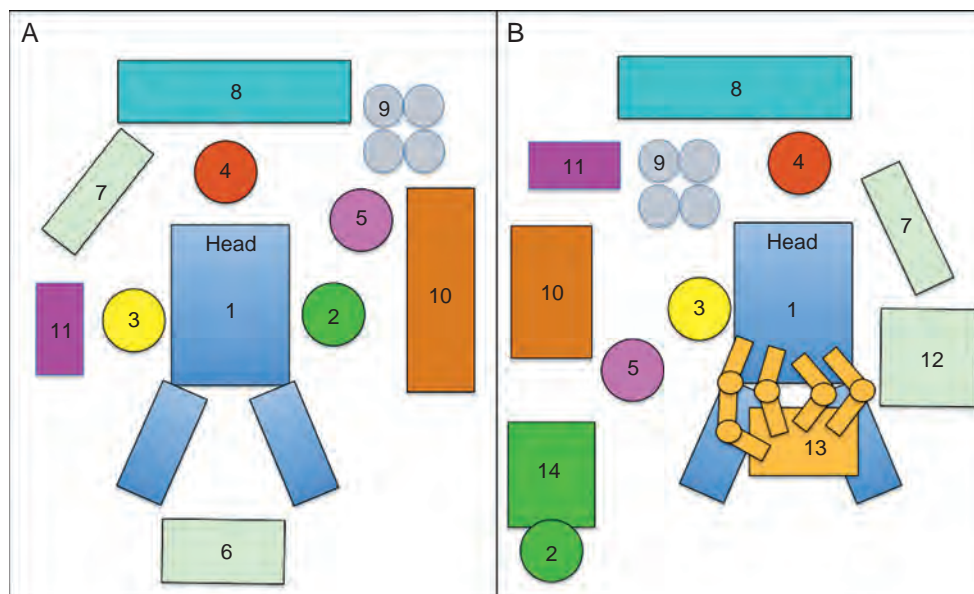


Figure 10-7. Placement of the operative team for pelvic surgery. A, Laparoscopic procedure. B, Robotic procedure. 1, Operating table; 2, surgeon; 3, assistant; 4, anesthesiologist; 5, scrub assistant; 6, laparoscopic cart or tower; 7, auxiliary video monitor; 8, anesthesia equipment; 9, suction and irrigation unit; 10, scrub assistant's instrument table; 11, electrocautery unit; 12, ancillary vision cart; 13, robotic tower; 14, surgeon's console.

Transperitoneal and Extraperitoneal Pelvic Procedures

Laparoscopic. The patient is positioned in the supine position with the legs on split-leg positioners or elevated in stirrups that have knee and leg supports to avoid perineal nerve injury. The table is angled (flexed) slightly at the hip to accentuate the pelvis. The patient's arms are tucked at the sides; plastic sleds can be used to support the arms. A slightly snug chest strap should be placed directly across the patient's chest. The table is placed in the 30-degree Trendelenburg position. The surgeon stands on the side of the table

where he or she is comfortable, and the assistant stands on the opposite side (Fig. 10-7A).

Robotic. For robotic procedures on the pelvis the patient is positioned exactly as described previously for laparoscopic pelvic procedures. After port placement the robotic arms are placed between the patient's legs, and the assistant can remain on either side of the table depending on surgeon preference (Fig. 10-7B). The scrub nurse or technician can be positioned on the same side as the assistant to facilitate passing instruments because passing instruments across the robotic arms can be cumbersome.

PERFORMING THE PROCEDURE

Before the Initial Incision

A checklist ensuring that all essential equipment is present and operational should be completed just before initiation of the pneumoperitoneum (see Box 10-1).

Additional items to check when using the da Vinci Robotic System include ensuring that all plugs for the console, vision cart, and patient-side cart are plugged into different circuits and that all cables connecting these carts are connected properly. The system should be turned on and the self-test and homing routine should be complete. The three-dimensional (3D) camera and endoscopes should be calibrated, the image black and white balanced, and target alignment performed according to the manufacturer's instructions. The patient-side cart should be draped and ready.

Achieving Transperitoneal Access and Establishing the Pneumoperitoneum

Achieving transperitoneal access is the first step before establishing a pneumoperitoneum. This can be done using either a closed (i.e., Veress needle) or open (i.e., Hasson cannula) technique.

Closed Techniques

Veress Needle. A disposable (70- or 120-mm, 14-gauge, and 2-mm outer diameter) or nondisposable Veress needle can be used. Proper needle function should be ensured before the procedure. Specifically, the blunt tip of the needle is tested to make sure it retracts easily and the needle is connected to the CO₂ line to ensure that there is no resistance to gas inflow (i.e., at 2-L/min flow, pressure remains at ≤ 2 mm). Last, saline is flushed through the needle with the tip manually occluded to make sure there is no leakage at the juncture between the shaft and the hub of the needle.

For proper placement the Veress needle is grasped at midshaft and is passed perpendicularly through skin using a gentle, steady pressure. Two points of resistance are traversed: the abdominal wall fascia and the peritoneum.

Sites for Needle Passage. With the patient in the supine position, the head of the bed is lowered 10 to 20 degrees; insertion of the Veress needle is commonly accomplished at the superior border of the umbilicus. There are certain advantages to choosing the umbilical area as the site for initial trocar placement: the abdominal wall is thinnest, and postoperative cosmesis is excellent. However, this point of entry is fraught with the potential for injury to a major vessel, in particular the left common iliac vessels, aorta, or vena cava. As such, it is important to note when considering the abdominal area as the site for Veress needle placement that body habitus influences the relative location of the umbilicus to underlying vascular structures. In obese patients, the umbilicus tends to migrate inferiorly, whereas in nonobese patients the umbilicus lies in its commonly described position, directly above the bifurcation of the aorta and vena cava. Thus, for umbilical access in nonobese patients the Veress needle should be passed through the abdominal wall angled toward the pelvis to avoid injury to the bowel and great vessels that lie directly beneath. In more obese patients, because the umbilicus lies more caudad, less angulation is needed and the Veress needle should be passed perpendicular to the umbilical incision (Loffer and Pent, 1976).

The right or left lower quadrant can also be used with the patient in the supine position, decreasing the likelihood of vascular injury. However, one must be cognizant of risk for colonic injury with this site. If the patient is in a lateral decubitus position, then the Veress needle can be passed two fingerbreadths medial and two fingerbreadths superior to the anterior superior iliac spine.

Other potential insertion sites when the patient is either supine or in a lateral decubitus position are at the Palmer point (i.e., subcostal in the midclavicular line on the left side) and at the corresponding site on the right side. The Palmer point is the preferred

site when extensive intra-abdominal adhesions are suspected (Palmer, 1974). With either of these insertion sites care must be exercised; if the needle is inserted too deeply, there is the potential to hit the liver on either side or, rarely, the spleen on the left side. Alternatively, in the abdomen that has previously been operated on, insertion should be performed in an unscarred quadrant of the abdomen. If there is no scar-free area, then an open technique (see later) should be used.

The safety of the Veress needle technique has been demonstrated in numerous studies including a study by Chung and coworkers (2003) that examined the outcome of 622 consecutive cases with Veress needle insertion. Prior abdominal surgery had been performed in 192 patients (31%), and the BMI was 30 or greater in 98 patients. Blind Veress needle placement was successful in 579 (93%), and outcome was not associated with laterality, type of surgery, or prior surgery. In 34 cases (5%), a minor laceration to the liver was managed conservatively without sequelae; and in 21 cases (3%) the omentum or falciform ligament was traversed without significant injury. No major complications, such as vascular or hollow-organ perforation, were caused by either the Veress needle or trocar. Neither the spleen nor bowel was ever injured.

Assessing Proper Needle Placement. First the aspiration-irrigation-aspiration test is performed. With the use of a 10-mL syringe containing 5 mL of saline, the Veress needle is aspirated to check for blood or bowel contents. If this test result is negative, then the saline is injected into the abdominal cavity; this should occur without any resistance. Next, the plunger of the syringe is again withdrawn; no fluid should return into the barrel of the syringe. An additional injection of 2 to 3 mL of saline will help to expel any omentum that may have been sucked into the needle tip with the original aspiration technique. Last, the syringe is detached from the Veress needle and any fluid left in the hub of the needle should fall swiftly into the peritoneal cavity (i.e., the "drop" test).

Second, the advancement test can be performed. If the needle has truly just entered the peritoneal cavity, then the surgeon ought to be able to advance the needle 1 cm deeper without the tip meeting any resistance. Resistance at this stage usually means the needle is still in the preperitoneal space and needs to be advanced through the remaining peritoneum.

Insufflation should never be initiated unless all the signs for proper peritoneal entry (negative aspiration, easy irrigation of saline, negative aspiration of saline, positive drop test, and normal advancement test) have been confirmed. Once proper needle placement is verified, insufflation is started at 2 L/min with the abdominal pressure set at 10 mm Hg. If free flow of CO₂ is noted (i.e., intra-abdominal pressure remains <10 mm Hg), then after 0.5 L has entered the abdomen the flow can be increased to maximal capacity of 9 L/min (however, no more than 2 L/min flow can be achieved through a 14-gauge needle) and the abdominal pressure set at 15 mm Hg. As soon as the preset limit of 15 mm Hg of intra-abdominal pressure is reached, free flow stops.

Stabilization of the abdominal wall fascia with towel clips or Allis clamps at the time of Veress needle puncture may help in stabilizing the fascia; however, one should not lift up on the fascia because this will only increase the space between the fascia and the peritoneum while not changing the intra-abdominal space.

EndoTIP Entry. See the Expert Consult website for details.



Open Access Techniques

Hasson Technique. The pneumoperitoneum can be more easily, and in one's early experience, more safely established using the open Hasson technique; however, its use involves making a larger incision and increases the chances of port-site gas leakage during the procedure. The open technique is recommended specifically when extensive adhesions are anticipated. Studies in general surgery have shown the open technique to be as efficient as the closed approach and slightly more or equally safe (Bonjer et al, 1997).

In the unscarred abdomen, with the patient in the supine position, a 2-cm semicircular incision is made at the lower edge or

A 5- or 10-mm incision is made in the skin at an appropriate site for a 5- or 10-mm port. The EndoTIP trocar (Karl Storz, Tuttlingen, Germany) is a trocar with a “corkscrew”-type self-advancing and self-retaining entry system and a blunt tip (Fig. 10-8). The trocar can be advanced through the abdominal wall while a 0-degree lens is positioned inside the trocar 1 cm from the advancing tip. Once the abdominal wall muscle is engaged, the EndoTIP can be lifted up slightly while continuing to rotate it through the tissues; this maneuver lifts the peritoneum, and one can watch as the blunt tip works its way through the peritoneum and into the abdominal cavity. Again, this technique should be used only in patients in whom intra-abdominal adhesions are unlikely.



Figure 10-8. The EndoTIP trocar (Karl Storz, Tuttlingen, Germany).



Figure 10-9. Various reusable Hasson type trocars.

slightly below the umbilicus. The fascia and peritoneum are opened individually with a transverse incision, sufficient to accommodate the surgeon's index finger. After visual and digital confirmation of entry into the peritoneal cavity, two 0 silk traction sutures are placed on either edge of the fascia. Next, the Hasson cannula is advanced through the incision with the blunt tip protruding (Fig. 10-9). The funnel-shaped adapter of the Hasson cannula is advanced until it rests firmly in the incision, and it is then tightened onto the cannula with the attached screw; fixation to the abdominal wall is provided with the fascial sutures that are wrapped around the struts on the funnel-shaped adapter of the Hasson cannula, thereby anchoring it in place. After removal of the obturator, free flow of CO₂ into the peritoneal cavity is achieved by attaching the CO₂ tubing to the cannula. The insufflator can be set at maximum inflow, thereby creating the pneumoperitoneum quickly.

A far simpler type of blunt cannula is a balloon retention device (e.g., Blunt Tip Trocar with Balloon Tip, US Surgical, Norwalk, CT or the Kii Balloon Blunt Tip System, Applied Medical Resources, Rancho Santa Margarita, CA) (Fig. 10-10 on the Expert Consult website). Once the cannula is positioned in the abdominal cavity, the balloon is inflated; the cannula is pulled upward until the balloon is snug on the underside of the abdominal wall. Next, the soft foam or rubber collar on the outside surface of the cannula is slid down until it is snug on the skin and locked in place. This process creates an excellent seal, precluding gas leakage and subcutaneous emphysema.

Hand Port Access. The pneumoperitoneum can be obtained before or after making the hand port incision. If the surgeon has little experience with achieving a pneumoperitoneum, the safest maneuver is to use an open technique and place the hand port into a 6.5- to 7.5-cm open incision and then create the pneumoperitoneum through the hand port (i.e., hand port access). For this technique, the procedure begins with making a standard midline or lower quadrant incision at the planned hand-assist site. The peritoneal cavity is entered in the standard open surgical fashion, after

which the hand-assist device is placed according to the manufacturer's instructions. Next, a blunt cannula is passed through the hand-assist device and a pneumoperitoneum is established. Additional 5-mm or 10- to 12-mm ports can be placed rapidly under manual control with the surgeon's intra-abdominal hand being used to guide the additional trocars through the abdominal wall. Alternatively, a laparoscope can be placed through the port placed in the hand-assist device for insufflation, and the rest of the trocars can then be placed under direct vision.

Technique for Laparoendoscopic Single-Site Surgery

See the Expert Consult website for details.

Achieving Retroperitoneal Access and Developing the Retroperitoneal Space

Technique for Balloon or Self-Styled Dilator Placement: Open (Hasson) Technique

The Hasson technique is the most commonly used technique because it affords the greatest precision during development of the retroperitoneal space (Gill, 1998). Initial access is obtained through a 2.0- to 2.5-cm transverse incision in the midaxillary line, just below the tip of 12th rib. The wound is opened with a pair of S-retractors. Under direct vision, the posterior layer of the lumbar fascia is incised and muscle fibers are split or divided. The retroperitoneal space is entered, **under direct vision**, by making a small incision in the anterior thoracolumbar fascia with an electrocautery blade or, less commonly, by bluntly piercing the fascia digitally or with a hemostat. Care should be taken that this fascial opening is snug around the index finger and no larger, so that intraoperative air leak is minimized. Index finger palpation of the belly of the psoas muscle posteriorly and the Gerota fascia-covered inferior pole of the kidney anteriorly confirms proper entry into the retroperitoneal space (Fig. 10-11A). The index finger is used to digitally create a space in this precise location for placement of the balloon dilator; two inflations of the balloon are then done—one directed cephalad and the second directed caudad to fully dilate the retroperitoneal space (Fig. 10-11B). Thus, balloon dilation is performed anterior to the psoas muscle and fascia and outside and posterior to the Gerota fascia. In cases involving definitive ureteric mobilization (e.g., retroperitoneoscopic donor nephrectomy, nephroureterectomy), additional balloon dilation may be performed more caudad to the primary site of dilation (Gill et al, 1995). Similarly, during a retroperitoneoscopic adrenalectomy, it is helpful after the initial balloon dilation to move the balloon up higher in the retroperitoneum and perform a second, even more cephalic balloon dilation along the undersurface of the diaphragm (Sung and Gill, 2000).

Balloon Dilation. Gradual distention of a balloon dilator in the retroperitoneal space atraumatically displaces the mobile fat and moves the peritoneum forward relative to the immobile body musculature. This device thus creates a working space equivalent to the size of the balloon. Either commercially available balloon dilators (Fig. 10-12) or a self-styled dilator can be used.

See the Expert Consult website for details on commercially available balloons and self-styled dilators.

Manual Dilation. See the Expert Consult website for details.

Achieving Extraperitoneal Access and Developing the Extraperitoneal Space

Technique for Balloon or Self-Styled Dilator Placement: Open (Hasson) Technique

A 1.5- to 2-cm curvilinear incision is made along the inferior umbilical crease. The anterior rectus sheath is incised vertically for 1.5 cm, and the rectus muscle is separated in the midline to expose the

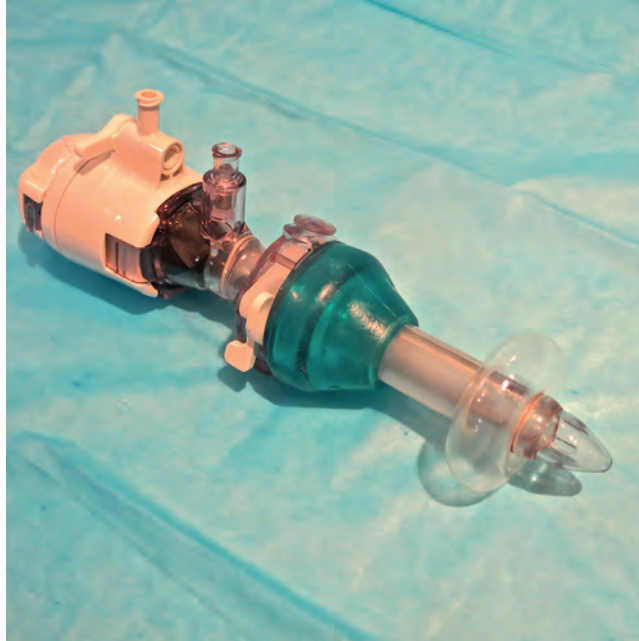


Figure 10-10. Blunt-tipped trocar with balloon tip.

Recent advances in abdominal access technology combined with the development of curved and articulating laparoscopic instrumentation have made it possible to perform selected procedures through a single incision (typically a 2.5-cm transumbilical incision); using three access ports through this incision, the laparoscope and two working instruments can be introduced.

Much the same as for hand port access, the incision can be made before or after obtaining a pneumoperitoneum depending on surgeon preference. Typically, the incision is made periumbilically for cosmetic purposes. The size of the skin incision should correspond to the surgical task at hand. If the procedure does not require removal of a large intact specimen, then the incision should be minimized to as little as 2.5 cm. If the procedure requires large intact specimen removal (as in donor nephrectomy), then the incision should be large enough to extract the specimen.

Once the incision has been made, several ports side by side or a single triport access device (see later) can be placed and a pneumoperitoneum is reestablished at high flow.

Thus far, laparoendoscopic single-site surgery (LESS) has been used for a variety of upper abdominal procedures including adrenalectomy (Hirano et al, 2005; Castellucci et al, 2008); renal biopsy (Kaouk et al, 2008b); renal cyst decortication; renal tumor cryoablation (Goel and Kaouk, 2008); pyeloplasty (Kaouk et al, 2008a); ileal ureter interposition; psoas hitch ureteroneocystostomy; simple,

radical, and donor nephrectomy (Gill et al, 2008; Ponsky et al, 2008b; Raman et al, 2008; Rane and Rao, 2008); and partial nephrectomy (Kaouk et al, 2008b). In addition, pelvic procedures have been performed including varicocelectomy (Kaouk and Palmer, 2008), sacrocolpopexy (Kaouk et al, 2008b), radical prostatectomy, and radical cystectomy with extended lymphadenectomy (Kaouk et al, 2008b).

The theoretic advantages of LESS over standard multi-incision laparoscopy are improved cosmesis, decreased pain, and faster recovery time. At the present time, however, there are insufficient data regarding LESS to either support or refute these potential benefits (Raman et al, 2008; Merseburger et al, 2013). Considering the technically demanding character of the single-site approach, only experienced laparoscopic surgeons should attempt this technique in clinical settings. Research in this area is ongoing, and until well-established methods and results are available, surgeons are urged to approach LESS in a responsible and graduated fashion. One method of transitioning from standard laparoscopy to LESS for selected procedures is to gradually decrease the number of ports one uses until the procedure can be performed through a single incision. Conversely, when one is having difficulty performing a procedure using LESS, the surgeon should not hesitate to place one or more extra trocars at separate incision sites to improve triangulation and thereby ensure safety and a high-quality result.

Commercially Available Balloons. Commercially available trocar-mounted preperitoneal balloon dissectors (PDBs) (e.g., Covidien Ltd., Mansfield, MA) are typically a transparent, high-tensile strength silicone balloon that is inflated with a sphygmomanometer bulb insufflator using room air (see Fig. 10-12). The balloon has a maximum capacity of 800 mL (40 pumps of the inflating bulb). A primary advantage of commercially available balloons is that the balloon is affixed to the end of a stiff, hollow, transparent plastic shaft. This shaft allows precisely directed placement of the balloon dilator. Furthermore, because the laparoscope can actually be inserted into the shaft of the balloon dilator during the inflation process, it provides the capability for endoscopic confirmation of the proper positioning of the transparent balloon and of the adequacy of the controlled radial dilation of the extraperitoneal area. Balloon dilators are commercially available in two different shapes: a round balloon for dilation of the pelvic extraperitoneal space and a horizontally oriented, oblong balloon for dilation of the retroperitoneal space.

Self-Styled Dilators. Gaur's original (1992) version of the balloon dilator was a size 7 surgeon's glove mounted on a No. 8 red rubber catheter. The external end of the catheter was connected to a sphygmomanometer bulb insufflator, and the balloon was insufflated to 110 mm Hg. After this initial description, several other self-styled dilators were described: the middle finger of a size 7 to 8 glove, two fingers of a size 7 to 8 glove tied over each other for additional strength, a sterile condom, and the cot of an O'Connor-style drape mounted on a 16- or 18-Fr red rubber or whistle-tip catheter (Webb

et al, 1993; Chiu et al, 1995). For the balloons made from the middle finger of a surgeon's glove, the finger is affixed to the rubber catheter with two 0 silk sutures. These self-styled dilators were filled with saline rather than air. The device may be back-loaded into a well-lubricated (i.e., K-Y jelly) 30-Fr Amplatz sheath to facilitate introduction through a laparoscopic port. Although it is economically advantageous, drawbacks of the self-styled balloon include the lack of a stiff shaft to manually direct the balloon into a specific location for precise dilation, and the inability to endoscopically monitor the dilation process from within the balloon.

An ex vivo laboratory study demonstrated that increasing volumes of saline induced gradual pressure increments within the middle finger of a surgeon's glove. At a volume of 1000 mL, the average pressure was 15 mm Hg. Pressures remained 15 mm Hg at 1500 mL and increased to 17 mm Hg at 2000 mL (McDougall et al, 1994). In practice there is no need to exceed the 1000-mL limit. Also, latex balloons have less tensile strength than silicone balloons, making them more likely to rupture. Regardless, with either balloon setup, on the few occasions that either type of balloon has ruptured there has been no obvious complication. However, the latex balloon has a tendency to rupture into multiple pieces whereas the Silastic balloon usually leaves only one large fragment, making retrieval an easier task.

Complications associated with balloon dilation stem from improper balloon placement or balloon rupture. Intramuscular dilation may result in hernia formation, or inadvertent peritoneal disruptions may occur (Gaur, 1992; Adams et al, 1996).

Creation of a working space within the retroperitoneum may also be achieved exclusively with a combination of digital and laparoscopic instrument dissection ([Kerbl et al, 1993](#)). After access to the extraperitoneal area is gained, to-and-fro movements of the laparoscope are performed to create a working space ([McKernan, 1995](#)). This technique has been used to perform various simple and advanced procedures in the retroperitoneum ([Rassweiler et al, 1998a](#); [Abbou et al, 1999](#)). Although it is effective, potential disadvantages of this technique include frequent cleaning of the laparoscope and the lack of clear landmarks initially due to the smaller, undeveloped working space.

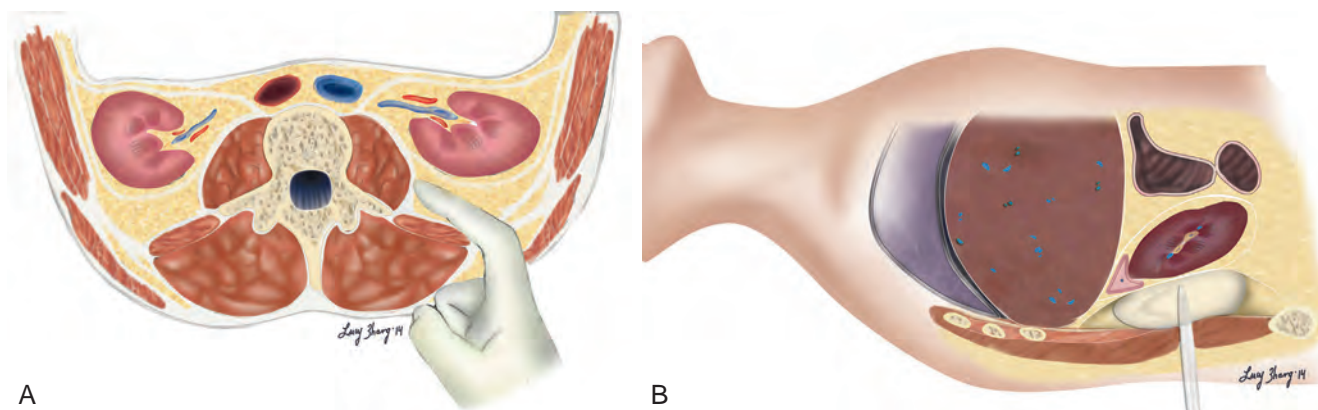


Figure 10-11. A, Access into the right retroperitoneum. Through the primary port incision at the tip of the lowest (12th) rib, open access is gained into the retroperitoneum after piercing the thoracolumbar fascia. Finger dissection is performed anterior to the psoas muscle and fascia to create a space for insertion of the balloon dilator. Confirmation that the finger dissection is indeed being performed in the proper plane is obtained by palpating the psoas and erector spinae muscles between the retroperitoneally located index finger and the fingertips of the opposite hand positioned on the patient's back. The fat-covered lower pole of the kidney can be palpated in a cephalad direction by turning the finger clockwise in the retroperitoneum on the right side. B, Balloon dilation in the posterior pararenal space facilitates the creation of a working space for retroperitoneal laparoscopic nephrectomy (*coronal view*).



Figure 10-12. Example of a commercially available balloon dilator for creating space in the retroperitoneum: preperitoneal balloon dissector. (Courtesy Covidien Ltd., Mansfield, MA.)

posterior rectus sheath. With the surgeon's index finger positioned posterior to the rectus muscle and anterior to the posterior rectus sheath, gentle tunneling motions are made in a caudal direction until the area of the symphysis pubis is reached. At this distal location, the fascia transversalis is punctured with the fingertip, and gentle side-to-side digital dissection is performed in the prevesical space, posterior to the pubic bone. Into this predeveloped space, a balloon dilator or self-styled dilator (see earlier) is inserted and distended to create an adequate working space. Balloon dilation or self-styled dilation effectively displaces the prevesical fat and reflects the peritoneum cephalad. The balloon is initially inflated in the midline and then reinflated on either side to further expand the working area (Meraney and Gill, 2001).

Caveat: In earlier studies of retroperitoneoscopy, excessive subcutaneous emphysema and higher carbon dioxide levels were the norm owing to use of the standard Hasson cannula (Wolf et al, 1995; Ng et al, 1999); this situation was rectified with the introduction of the open access blunt balloon port, which has a balloon to secure it against the underside of the abdominal wall and a soft foam cuff to secure it to the outer abdominal wall, creating an airtight seal (Ng et al, 1999).

Limitations and Advantages of Transperitoneal versus Extraperitoneal Approach to the Flank and Pelvis

See the Expert Consult website for details.



Access Technology: Trocars, Hand Ports, and Single-Port Access

Trocars

Trocars enable the laparoscopist to introduce working instruments into the gas-filled abdomen or retroperitoneum. They also maintain the pneumoperitoneum by conveying the insufflant and may serve as pathways for delivering small amounts of dissected tissue from the surgical area. Typically a trocar consists of an outer hollow sheath (also called a *cannula* or *port*) and an inner obturator, which is removed as soon as the outer sheath has entered the peritoneal cavity.

A variety of nondisposable and disposable trocars are available (Fig. 10-13). Standard models range from 3 to 20 mm in diameter and 5 to 20 cm in length. One-way valves within the trocar allow the surgeon to exchange instruments through the port without the escape of significant amounts of gas. Some older trocar models have trapdoor or flap valves. In such trocars it is necessary to depress the valve lever to open the valve widely during retrieval of tissue or needles. More recently, **multiseal**-type valves have become available for 10- and 12-mm trocars that accommodate the passage of 5-mm and larger instruments without any air leak occurring; if large amounts of tissue are to be withdrawn, removal of the outer seal or of the entire valve is necessary for this procedure. The outer seal and valve can then be replaced before reinsertion of instruments.

Initially, only sharp-tipped or bladed trocars were available. On these trocars the sharp obturator incised the various layers of tissue as it entered the peritoneal cavity. To protect the underlying viscera from the sharp tip of these trocars, a plastic safety shield was later incorporated into the disposable trocars that would spring forward to shield the blade once the trocar entered the gas-filled abdomen. However, bladed trocars should be only of historical interest because they have been superseded by safer noncutting dilating trocars (i.e., blunt), which no longer require a safety shield. These trocars enter the abdomen by spreading the abdominal wall musculature, rather than cutting it. Therefore there is less chance of injuring an abdominal wall vessel, and the resulting entry site is less prone to subsequent herniation. Indeed, studies have shown the

Transperitoneal versus Retroperitoneal Renal and Adrenal Surgery. The transperitoneal and retroperitoneal approaches to the upper abdomen each offer advantages and disadvantages. Retroperitoneoscopy is associated with unique anatomic orientation with limited anatomic landmarks, save the psoas muscle. In comparison, the transperitoneal approach offers a very familiar anatomic approach with a number of landmarks (e.g., liver, spleen, large bowel). Retroperitoneal laparoscopy is also associated with a relatively restricted working space compared with transperitoneal laparoscopy. This results in a steeper learning curve with the retroperitoneal approach. Moreover, the fact that a comparatively limited space is available necessitates precise accuracy regarding the strategic placement of ports.

The degree of technical difficulty of the retroperitoneal approach increases in the presence of large specimens, including entrapment of these larger specimens, which may be very difficult. The latter problem of entrapment can be overcome by laparoscopically creating an intentional peritoneotomy at the end of the procedure to allow entrapment of the specimen within the larger peritoneal cavity.

Laparoscopic reconstruction and intracorporeal suturing are technically demanding procedures regardless of the approach. However, in the retroperitoneal space, reconstruction can be more challenging compared with transperitoneal laparoscopy owing to suboptimal instrument angulation and a smaller working space. One potential way to overcome some of these limitations is to use a robotic approach to the retroperitoneum. [Kaouk and coworkers \(2008c\)](#) reported the Cleveland Clinic experience using a robotic retroperitoneal approach to perform dismembered pyeloplasty in 10 patients. They noted that the enhanced dexterity of the robotic platform did facilitate reconstructive suturing in a smaller working space.

Offsetting the limitations of retroperitoneoscopy are some distinct advantages. First, the risks of inadvertent bowel injury and postoperative ileus are minimized, although not eliminated ([Kavoussi et al, 1993](#)). This results in a slightly more rapid postoperative recovery compared with the transperitoneal approach. During retroperitoneoscopy and extraperitoneoscopy the bowel can be effectively and safely retracted within its peritoneal cover. Although out of sight, the bowel should never be out of mind, because bowel injuries can still occur.

Transperitoneal laparoscopy may be associated with an increased incidence of postoperative shoulder-tip pain, a feature rarely associated with retroperitoneoscopy. In addition, **extraperitoneoscopy and retroperitoneoscopy are associated with a significantly lower incidence of postoperative trocar site hernias.**

Another significant benefit of the retroperitoneal approach is the rapid and direct access to the renal hilum, with the renal artery being the first hilar structure encountered and controlled. Furthermore, if a partial nephrectomy is planned, it may be more effective to approach a posterior tumor from the retroperitoneal approach, whereas anterior tumors are often more easily approached from the transperitoneal approach.

Contrary to common conception, the occurrence of an inadvertent peritoneotomy during retroperitoneoscopy does not usually interfere with the subsequent steps of the procedure, and conversion to a transperitoneal laparoscopic technique is not mandatory ([Gill et al, 2000](#)).

Although a retroperitoneal approach might not be advantageous for every surgery, there are certain instances in which this approach might be more appropriate, as in the case of multiple prior transabdominal surgeries. Conversely, a history of prior retroperitoneal surgery increases the difficulty of re-entering the retroperitoneal space and therefore should be approached with caution. Subsequent attempts at extraperitoneoscopy or retroperitoneoscopy should be ventured only by individuals with considerable experience and comfort with this approach. In our experience, prior percutaneous renal procedures do not necessarily constitute a contraindication to subsequent retroperitoneoscopy, provided that entry is away from the area of the prior nephrostomy tube placement.

Transperitoneal versus Extraperitoneal Pelvic Surgery. As with the upper abdomen, the transperitoneal and extraperitoneal approaches to the pelvis both offer distinct advantages and disadvantages. The transperitoneal approach to the pelvis offers easy access to all areas of the pelvic cavity once the space of Retzius, iliac and obturator fossa, or the rectovesical space has been entered directly through the peritoneum. The working space is maximized because the peritoneum does not limit camera or instrument motion. However, potential limitations associated with this approach as compared with the extraperitoneal approach include the possibility of causing mechanical or thermal injury to the bowel and the necessity to use more extreme Trendelenburg positioning or additional retraction of the bowel to prevent it from impinging on the operative field. The possibility of prolonged ileus has also been suggested; however, in a large prospective study comparing 165 transperitoneal versus 165 extraperitoneal laparoscopic radical prostatectomy patients, [Ruiz and colleagues \(2004\)](#) did not find significant differences between the two groups in terms of hospital stay or medical and surgical complications. Operative time was half an hour shorter in the extraperitoneal group (220.0 vs. 248.5 minutes, $P < .0001$). These findings were reinforced in two other studies comparing the two approaches. In these two studies, patients undergoing radical prostatectomy via the two approaches were matched with regard to important preoperative attributes and the outcomes compared. The authors found no significant differences between the extraperitoneal and transperitoneal approaches regarding all important parameters, except that the operative time for the extraperitoneal approach was in general a little shorter (30 minutes) ([Erdogru et al, 2004](#); [Madi et al, 2007](#)).

One undeniable advantage of the extraperitoneal approach is that it avoids the necessity of lysis of adhesions in patients who have had prior abdominal surgery. In contrast, for patients who have had prior laparoscopic inguinal hernia repair, a transperitoneal approach is more advantageous.

Unlike with retroperitoneoscopy, the occurrence of a peritoneotomy during extraperitoneoscopy may interfere with the performance of subsequent extraperitoneal dissection, and conversion to a transperitoneal technique may be required ([Meraney and Gill, 2001](#)).

In summary, for most cases there does not seem to be a clear advantage to use of a transperitoneal versus extraperitoneal approach for laparoscopic and robotic pelvic surgery. In selected cases described earlier there may be advantages of one approach over the other.



Figure 10-13. Various trocar designs showing (left to right) reusable blunt-tipped, reusable bladed, and two disposable visual obturator fascial dilating designs.

risk of inferior epigastric injury or port site herniation is fivefold less with blunt versus sharp trocars (Hashizume and Sugimachi, 1997; Thomas et al, 2003). In addition, a recent meta-analysis demonstrated a lower relative risk of trocar site bleeding (3% vs. 9%) and overall complications (3% vs. 10%) with blunt compared with bladed trocars (Antoniou et al, 2013).

As with the older sharp trocars, there are both disposable and nondisposable blunt trocar units. One form of blunt disposable trocar unit is the Step needle and sleeve (Covidien). This disposable system uses a needle port with an outer diameter of 2.1 mm (6.5 Fr) that incorporates a Veress needle introducer (Fig. 10-14 on the Expert Consult website). After correct and successful puncture of the abdomen and establishment of the pneumoperitoneum, the Veress needle introducer is removed and the remaining sheath is an expandable port that can then be expanded by passage of a blunt-tipped obturator to expand the collapsed sheath to 5 mm, 10 mm, or 12 mm, depending on the surgeon's needs.

Other blunt-tipped trocars are produced by all of the major trocar manufacturers. These devices have a variety of tips that enable their placement by spreading the tissues; some also have a clear plastic tip (i.e., optical trocar) such that the surgeon can pass an endoscope into the trocar to endoscopically monitor its passage through the abdominal wall and its entry into the gas-filled abdomen.

A unique reusable blunt-tipped port, the EndoTIP system (Karl Storz), is a screwlike device that has no sharp points or cutting edges (see Fig. 10-8). It comes in 5-, 10-, and 12-mm designs; however, the 10- and 12-mm trocars require use of a cumbersome reducer system because they are not a multiseal design (see earlier). Unlike the action of trocars with a sharp tip, the tissue is not cut but is only displaced and bluntly dilated, thereby preserving the closing mechanism of the overlying muscle and fascia. Because of its innovative design, this device reduces injury to the intra-abdominal organs, stays securely in place, and seals the point of entry against any inadvertent loss of gas.

For the da Vinci Robotic System the camera lens fits through a variety of standard 12-mm disposable trocars. The 8- and 5-mm instruments fit through proprietary reusable 8- and 5-mm trocars that couple directly with the robotic arms. These reusable metal trocars have disposable valves that must be changed with each new case and the option of a reusable blunt inner cannula or a bladeless disposable inner cannula for use during placement.

In traditional flap-valve or trap door ports, a reducer is necessary to allow downsizing of working channels in 10-mm or larger trocars to accommodate smaller, 5-mm working instruments without any leakage of CO₂. However, the development of multiseal technology and the even newer AirSeal technology (discussed later), has resulted in valves that can accommodate 5- to 12-mm instruments without the need for a reducer, which can save significant time during a long procedure.

Retention of the cannula at the port site is essential to decrease air leak and subcutaneous emphysema and facilitate the timely completion of a procedure. In the past it was necessary to affix a suture to the insufflation side port and the skin to secure the trocar. At present, myriad retention mechanisms exist to prevent dislocation of cannulae such as threaded sleeves, adjustable threaded sleeves, expandable arms, and inflatable balloons. The Blunt Tip Trocar with Balloon Tip (US Surgical) and the Kii Balloon Blunt Tip System (Applied Medical Resources) (see Fig. 10-10 on the Expert Consult website) have a retention balloon that can be inflated in the peritoneal cavity and then drawn up tightly against the peritoneal side of the abdominal wall; an outer foam or rubber sealing ring can then be advanced down the extra-abdominal shaft of the cannula, thereby sandwiching the abdominal wall between the inflated balloon and the foam or rubber seal, effectively precluding any leakage of gas during the case. Use of this device minimizes CO₂ leakage around the primary port incision, thus reducing the incidence of subcutaneous emphysema and hypercarbia. This is especially effective when doing retroperitoneoscopic procedures. Another self-sealing trocar, the AnchorPort (SurgiQuest, Milford, CT) has an elastic self-sealing trocar shaft that automatically forms to the patient's body wall when the inner cannula is removed, creating a tight seal.

A recent technologic advance in trocar and insufflation technology has addressed some of the limitations of existing trocar systems including air leak, need for reducers, and specimen removal. This new system, the AirSeal System (SurgiQuest), consists of a specialized Intelligent Flow System insufflator (Fig. 10-15A on the Expert Consult website) featuring a circulatory flow design, a valve-free Access Port (Fig. 10-15B and C on the Expert Consult website), and a Tri-Lumen Filtered tube set (Fig. 10-15D on the Expert Consult website). This system has the ability to provide a stable pneumoperitoneum despite continuous high-flow suction, trocar dislodgement, or excessive port-side leakage. The valve-free design of the Access Port allows smudge-free scope insertion, intact specimen removal, and easy insertion and withdrawal of instruments of varying sizes. The AirSeal System also provides continuous smoke evacuation without the fear of venting surgical smoke and plume into the operating room.

Hand-Assist Devices

A number of hand-assist devices exist, including the GelPort (Applied Medical Resources), the Omniport (Advanced Surgical Concepts, Wicklow, Ireland), and the Lap Disc (Ethicon, Cincinnati, OH).

A study of 130 urologists participating in a series of hand-assist courses evaluated these three different hand-assist devices for a variety of features. The GelPort device emerged with the highest overall score, followed by the Lap Disc and then the Omniport (Patel and Stifelman, 2004). Advantages of the GelPort included sturdiness, ease of hand exchange, maintenance of the pneumoperitoneum, and the ability to pass both a hand and a laparoscopic instrument simultaneously.

An important caveat with respect to using hand-assist devices is the impact on the surgeon. Studies have shown that compared with standard laparoscopy, pain and numbness of the surgeon's hand, wrist, and forearm and, to a lesser extent, overall fatigue are much greater with use of a hand-assist device (Monga et al, 2004; Gofrit et al, 2008).

See the Expert Consult website for details of the hand-assist devices.

Laparoendoscopic Single-Site Surgery Access Devices

See the Expert Consult website for details.

Trocar Placement

Placement of Initial Trocar

When the Veress needle technique is used, after establishment of the pneumoperitoneum an incision is made for placement of the



Figure 10-14. Step needle and sleeve disposable trocar system. (Courtesy Covidien Ltd., Mansfield, MA. All rights reserved. Used with permission of Covidien.)

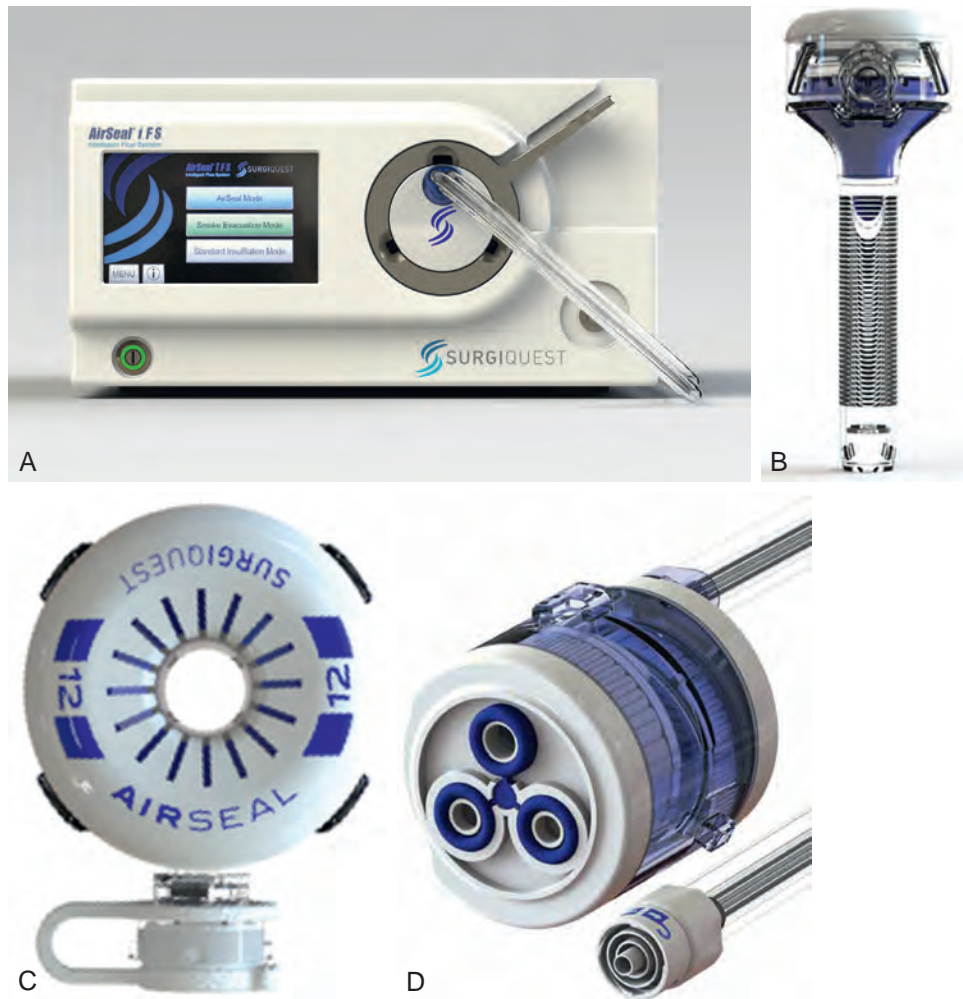


Figure 10-15. AirSeal System. A, Intelligent Flow System insufflator. B, Trocar. C, Valve-free Access Port. D, Tri-Lumen Filtered tube set.

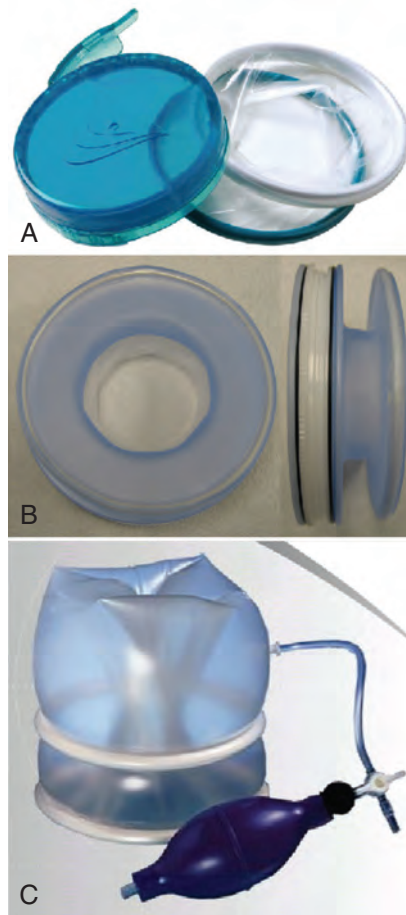


Figure 10-16. Hand port devices. A, GelPort. B, Lap Disc. C, Omniport. (Courtesy SurgiQuest, Milford, CT.)

The GelPort (Fig. 10-16A) consists of a gel-like disc that easily admits the surgeon's hand and then molds around the wrist and arm. The latest GelPort design has a 12-cm footprint. The GelPort offers the advantages of never losing a pneumoperitoneum on hand exchange because it immediately seals after hand removal, and it does not require adjustment to maintain a seal. Additional instruments can be passed alongside the surgeon's hand, through the gel material, also without loss of the pneumoperitoneum.

The Lap Disc (Fig. 10-16B) is a one-piece unit that has an inner diaphragm that is used to anchor it across the abdominal wall and an outer appliance that dials down a thin plastic sheet, like a camera

iris, around the surgeon's wrist. Although this device has a low profile and small footprint (12 cm), it does result in loss of the pneumoperitoneum every time the hand is removed and reinserted, and instruments cannot be passed parallel to the surgeon's hand.

The Omniport (Fig. 10-16C) is a balloon-like device that anchors itself as one piece across the abdominal wall. The inflated device also creates a seal between itself and the surgeon's wrist. The device has a small footprint (12 cm); however, it must be uninflated and reinflated each time a hand is exchanged, which results in loss of the pneumoperitoneum. Furthermore, no additional devices can be passed parallel to the surgeon's hand through the device.



Figure 10-17. Commercially available ports for laparoendoscopic single-site surgery. A, TriPort. B, SILS Port.

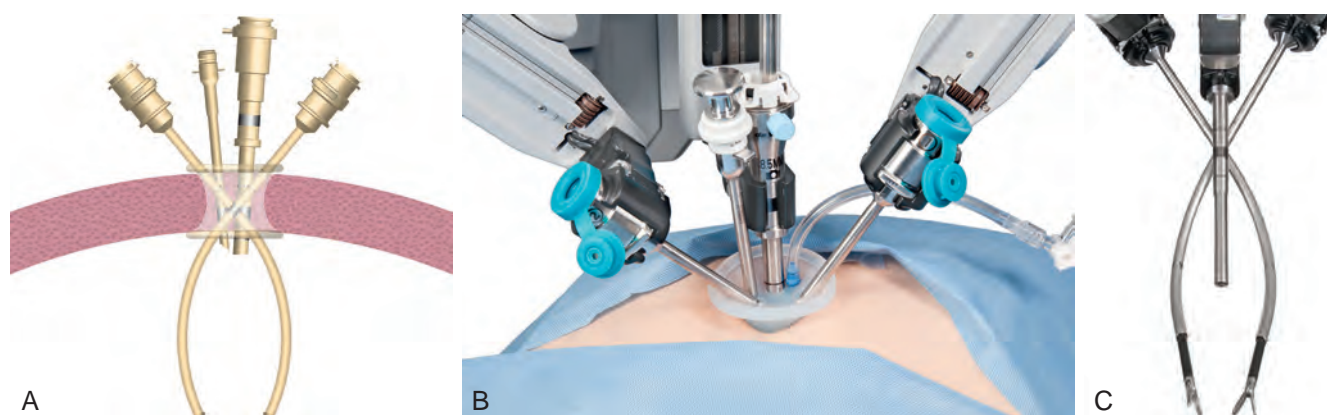


Figure 10-18. Single-site platform for the da Vinci Si System. A, Schematic diagram of access port with curved trocars. B, Robotic arms docked to single-site platform. C, Curved robotic instruments within trocars with camera. (© 2015 Intuitive Surgical, Inc. Used with permission.)

There are two basic methods used to perform LESS. One technique is to make a 2.5-cm incision, typically periumbilical or transumbilical (although an alternate site may be necessary), through which a skin flap can be raised off the abdominal wall fascia. Then, through this single incision, several (two to four) standard 5-mm laparoscopic ports can be placed in close proximity to one another. A laparoscope and working instruments can then be placed through these ports. This is obviously the most cost effective technique.

Alternatively, a commercially available single-site surgery device can be used. These devices currently require a single incision that is typically placed periumbilically or transumbilically unless the procedure dictates an alternate site. Currently there are three devices that are available for commercial use: the TriPort (Advanced Surgical Concepts), the Uni-X (Pnavel Systems, Cleveland, OH), and the SILS Port (Covidien).

The TriPort is a two-piece system consisting of an inner diaphragm that works like a wound protector and an outer piece containing the ports (Fig. 10-17A). The wound protector component is adjustable and cinches down the outer attachment, creating a tight seal on the abdominal wall. The TriPort, which requires a

12- to 25-mm incision, has room for a 5-mm laparoscope and two 5-mm working instruments plus a separate insufflation valve. The same manufacturer also makes a four-port model called the QuadPort that contains two 12-mm and two 5-mm instrument insertion sites; it requires a 2.5- to 6.5-cm incision.

The Uni-X is a similar device that is anchored to the abdominal wall by preplaced facial sutures. It has three 5-mm insertion sites and can be placed through a 1.5-cm incision (Kaouk et al, 2008b).

The third available device is the SILS Port, which can be placed into a 2-cm incision and can house three 5-mm ports or two 5-mm ports and a 5- to 10-mm port (see Fig. 10-17B).

Robotic Considerations. Intuitive Surgical has recently developed a single-site platform for the da Vinci Si System. The da Vinci single-site port is a five-lumen port that provides access for two single-site instruments, the 8.5-mm endoscope, a 5- or 10-mm accessory port, and an insufflation adaptor (Fig. 10-18A and B). The port has a pliable architecture that enables simple and safe entry into a 2.0- to 2.5-cm incision. Curved 5-mm instrument cannulae and trocars have been designed for specific use with the single-site port and are meant to optimize triangulation toward the target anatomy and provide an unobstructed view of the surgical field (Fig. 10-18C).

initial trocar. Alternatively, if an incision was made for placement of the Veress needle, the edges of the wound and subcutaneous tissue are spread with blunt forceps. Next, the trocar is held in the dominant hand with the middle finger extending along the shaft and the trocar is inserted using a twisting downward motion. The nondominant hand can be placed at the level of the skin, gently holding the trocar to stabilize it and prevent a sudden advancement. If the surgical site is in the mid to upper abdomen, then the trocar is passed perpendicular to the umbilical incision; however, for pelvic procedures, the trocar is directed 70 degrees caudad. Proof of entering the gas-filled intraperitoneal cavity is the sound of CO₂ escaping from the open sidearm. After the sidearm is closed, the obturator is removed and the CO₂ insufflation line is connected to the side port of the trocar. Alternatively, if a clear blunt port (i.e., optical trocar) is used, a 0-degree laparoscopic lens is placed within the port so the entire entry of the trocar is endoscopically monitored.

Some advocate for increasing the pneumoperitoneum after achieving access with the Veress needle in preparation for initial trocar placement to decrease the risk of underlying vascular or visceral injury with trocar insertion (Vilos et al, 2007). It is recommended to increase the pressure to 20 mm Hg. However, some data exist that suggest this may not increase the volume of the pneumoperitoneum or ease of trocar insertion (McDougall et al, 1994).

When an **open technique** is performed to obtain the pneumoperitoneum, the Hasson-style cannula used to obtain access to the abdomen also serves as the initial trocar.

Hand-Assist Placement

The hand-assist device can be placed either as an initial “port,” described earlier, or as a secondary port depending on the surgeon’s preference. When placed as a secondary port, a Veress or Hasson pneumoperitoneum is initially established and the hand-assist device is then placed under endoscopic monitoring. Establishing the pneumoperitoneum before hand port placement can help to minimize the size of skin incision for the hand port, as the skin is on stretch. The surgeon should carefully plan out the hand port entry site as well as the additional instrument and camera port sites. Every hand port device has a “footprint” that can be drawn on the abdominal wall; that footprint varies depending on the diameter of the external appliance. Care should be taken to plan out the additional trocar sites carefully to avoid interference between the hand port and the instrument ports; this is most easily done once the pneumoperitoneum has been established. After the footprint has been traced, the hand port incision site is marked; the length of the incision should correspond to the surgeon’s glove size (e.g., 7 glove size = 7-cm incision). The skin is incised, and the fascia is divided. The peritoneum is entered, and the insufflation is temporarily stopped. The hand port device is then placed according to the manufacturer’s instructions.

Before initiating a hand-assist procedure, the surgeon is advised to wrap the arm-glove seam on the hand that is to be used through the hand port either with a 1010 drape or an Ioban (3M, St. Paul, MN) “sticky drape” to waterproof his or her arm. **Lastly, the use of a brown glove on the intra-abdominal hand is recommended because they do not reflect the light from the laparoscope and thus reduce glare (Wolf, 2005).**

Secondary Trocar Placement

After obtaining access, the first step before secondary trocar placement is to inspect the entire abdomen systematically to rule out any injury to the underlying viscera that may have occurred during access or placement of the initial trocar. After this, one can proceed with secondary port placement.

Number, size, and exact location of secondary trocars depend largely on the intended laparoscopic procedure. Their configuration should be planned so that neither the tips nor handles of the cannulas cross or come into close contact with one another (a problem termed *crossing swords* and *rollover*, respectively) such that adequate working space is provided for all instruments to be used during a

particular procedure and allowing for effective triangulation at the surgical site by the endoscope and two working ports. In general, it is reasonable to place the ports in a four-point diamond pattern such that the site of the operation is encircled within the diamond. **This is particularly important when considering reconstructive renal procedures, because the angle between the horizontal plane and the needle drivers should be less than 55 degrees, whereas the angle between the surgeon’s suturing instruments should be in the 25- to 45-degree range (Rassweiler and Frede, 2002).**

It is also important to place each port so that it is pointing toward the surgical field, to avoid continued forceful redirection of the port during the procedure that may result in widening of the tissue tract around the port and development of subcutaneous emphysema.

Standard Approach. Secondary trocars are placed under direct optical control. The 30-degree lens is ideal for this portion of the procedure because turning the lens 180 degrees away from the surgical site provides the surgeon with a panoramic view of the anterior abdominal wall. The operative lights are dimmed, and the tip of the laparoscope is moved upward toward the intended site of port placement, thereby, in the thin patient, transilluminating any superficial blood vessels that need to be avoided while passing the trocar. With a blade, a skin incision is made just wide enough to accept the selected cannula. When placing secondary ports, it is of great importance to direct them toward the intended surgical field to provide tension-free maneuverability of the laparoscopic instruments. This is especially important in obese patients because the errant port will provide resistance to the surgeon throughout the rest of the procedure. Similar to placement of the initial port, all secondary ports are advanced through the abdominal wall using a slow, twisting motion and constant pressure. Each secondary port is passed into the peritoneal cavity under meticulous endoscopic monitoring. To prevent dislocation, ports that do not possess self-retaining mechanisms may be anchored to the skin using No. 2 nonabsorbable sutures. **In this regard, one should never use a metal trocar in conjunction with an outer plastic retaining ring because stray current can no longer be harmlessly dissipated through the metal cannula directly to the surrounding peritrocar abdominal wall, and hence any juxtaposed visceral structure may be damaged in an area remote to the laparoscopist’s vision.**

Hand-Assist Approach. When the hand-assist device is in place, then secondary trocars can be placed with digital guidance. After inspection of the abdomen rules out any potentially interfering adhesions, the surgeon’s index finger is placed on the underside of the abdominal wall at the planned site of trocar placement. A skin incision is made over the surgeon’s index finger and the nonbladed trocar is passed with the other hand and guided by the surgeon’s finger into the abdominal cavity. This is a very rapid and safe way to place all of the secondary nonbladed trocars.

Trocar Configuration

A number of different trocar configurations exist depending on whether one is performing transperitoneal or retroperitoneal upper abdominal laparoscopy or robotics. Details and diagrams of these configurations can be found in Chapter 61. Similarly, a number of trocar configurations exist for transperitoneal and extraperitoneal laparoscopic and robotic pelvic procedures, which are detailed in Chapter 115. Most important, regardless of the configuration chosen, is to ensure meticulous placement of the ports to minimize instrument clashing both intracorporeally and extracorporeally.

Robotic Considerations

If a robotic procedure is planned, then the camera port is a 12-mm trocar site and the two (or three if the fourth arm is used) auxiliary ports are 8 mm. **All the ports need to be placed 8 to 10 cm apart to reduce the possibility of the robotic arms clashing with each other.** In addition, if the patient is in a flank position, then the lowest port placement should not be inferior to the umbilicus or else the arm may be blocked from a full range of motion by the

patient's upside leg. An assistant's port is placed on a line either caudal or inferior to the robotic arms; placement of the assistant's port between the arms of the robot makes it quite awkward for the assistant to work and limits the range of motion of the assistant's instrument owing to clashing with the arms of the robot. Of note, all 8-mm robotic ports need to be advanced to ensure that the thick black marking on the shaft of the trocar is below the abdominal wall.

Laparoscopic Instrumentation

Instruments for Visualization

To create a laparoscopic image, four components are required: the laparoscope, light source, camera, and monitor. To record the image, video recorders, digital video disc, and video printers are available.

Laparoscope and Camera

Standard Systems. The most commonly used laparoscopes have 0- or 30-degree lenses (range, 0 to 45 degrees) and are available in sizes from 2.7 to 10 mm. Typically, the 30-degree lens provides the surgeon with a more complete view of the surgical field than the 0-degree lens, allowing the surgeon to peer around vascular structures by rotating the lens. Recently, newer deflectable laparoscopes have been developed in which the tip of the endoscope can deflect in four directions up to 90 degrees (EndoEYE Deflectable-Tip Video Laparoscope [Olympus, Melville, NY]); which offers many potential angles from which to view a structure, but requires an adept assistant. Another novel endoscope design is the EndoCAMEleon (Karl Storz). This scope maintains the familiar feel of a standard rigid laparoscope but has a variable-view swing prism that enables the surgeon to change viewing angles from 0 to 30, 45, 90, or 120 degrees. An advantage of the EndoCAMEleon is that it has a standard eyepiece, allowing it to be used with most camera systems.

With standard laparoscopes, image transmission uses an objective lens, a rod-lens system with or without an eyepiece, and a fiberoptic cable. From the eyepiece, the optical image is magnified and transferred to the camera and onto the monitor. Light is transmitted from the light source through the fiberoptic cable onto the light post of the laparoscope (Fig. 10-19A on the Expert Consult website). Some newer laparoscopes have a mini charge-coupled device (CCD) camera mounted at the tip (EndoEYE [Olympus]), which improves image quality and avoids the need for an external light chord that can sometimes impede the movement of other instruments (Fig. 10-19B on the Expert Consult website).

The most vexing problem with any laparoscope is fogging of the lens. To prevent fogging of the laparoscope after insertion into the warm intraperitoneal cavity, it is advisable to initially warm the laparoscope in a container holding warm saline before it is passed into the abdomen. The most efficient way to warm the laparoscope is to use a dedicated solution warming basin that is long enough to accommodate the laparoscope; alternatively a warming thermos can be used (Applied Medical Resources). In addition, wiping the tip with a commercial defogging fluid or with povidone-iodine solution is also recommended. Should moisture buildup occur between the eyepiece and the camera, both components must be disconnected and carefully cleansed with a dry gauze pad; this is not a problem with the digital endoscopes because the only connection is from the endoscope directly into the display box.

A final important note is to ensure that the sterile scope is white balanced.

The camera system consists of a camera and a video monitor. All currently made cameras can be gas or liquid sterilized, thereby facilitating their use and limiting possible intraoperative contamination. For standard laparoscopes the camera is attached directly to the end of the laparoscope and transfers the view of the surgical field through a cable to the camera box unit. After reconstruction of the optical information the image is displayed on one or two video monitors.

Three-Dimensional Laparoscopic Systems. Three-dimensional laparoscopic systems offer the surgeon the distinct advantage of depth

perception. Optimal 3D laparoscopy is performed with a two-lens system that duplicates the two-eye perception of 3D. In this way binocular vision is maintained. The most commonly used 3D vision system currently in use is the InSite Vision System (Intuitive Surgical), which provides vision for the da Vinci Robotic System. The laparoscope and high-definition camera are heavy (5.5 pounds for the high-definition scope and camera head) but are controlled by a robotic arm that is under direct control of the surgeon from the ergonomic console. The surgeon maintains a steady, magnified 3D view of the surgical field. Zero- and 30-degree lenses are currently available.

Handheld 3D laparoscopic systems are also available, but currently require the surgeon to wear headgear with miniature video screens to display the 3D image (EndoSite 3Di Digital Vision System [Viking Systems, La Jolla, CA]) or specialized passive polarized glasses while viewing the image on a 3D monitor (Karl Storz) (Fig. 10-20 on the Expert Consult website). A few recent studies (Honeck et al, 2012; Tanagho et al, 2012; Lusch et al, 2014) have demonstrated superior depth perception, spatial location, and precision of surgical performance with 3D systems compared with two-dimensional (2D) systems while completing laparoscopic tasks in an ex vivo setting.

Instrumentation for Grasping and Blunt Dissection

Most graspers and dissectors are used in their 5-mm size, but are available in a range from 3 to 12 mm, in predominantly reusable forms. Grasping instruments have either single-action (only one jaw moves during opening) or double-action (both jaws move) tip design.

Wide variations exist with regard to configuration of tip, surface characteristics of jaws, handle design, and possible electrosurgical properties. Tip designs include blunt-coarse, pointed (dolphin), straight (duck bill), curved (Maryland), and angled. The surface of the jaws may be atraumatic or traumatic. Serrated or smooth surfaces allow gentle tissue manipulation in atraumatic graspers (e.g., bowel forceps with a 3-cm long grasping jaw). Traumatic graspers have toothed or clawed surfaces on their jaws to allow them to grasp and hold tissues firmly. In addition, each of these instruments may be equipped with tip-rotation and/or articulating features. Both reusable and disposable instruments are available.

Depending on the design of the handle, grasping instruments may be locking or nonlocking. Most nonlocking forceps have a scissor-type handle. Different designs allow for locking capabilities; in particular, bar-type and spring-loaded locking handles are convenient when prolonged grasping of tissue is required. Some newer dissectors in addition to grip and rotation actually offer additional degrees of freedom by means of an articulating joint activated through wrist movements of the surgeon (RealHand [Novare Surgical Systems, Cupertino, CA]; Autonomy Lapar-Angle [Cambridge Endoscopic Devices, Framingham, MA]). **These instruments are most helpful if one is to perform a LESS procedure because the angulation of the shaft then provides the triangulation necessary for approaching the surgical field.** In addition, the shafts of these instruments may be of variable length (i.e., 34, 45, or 75 cm), again allowing for less clashing of handles during a LESS procedure.

In addition to standard dissecting instruments, both the laparoscopic suction apparatus and the "heel" of the hook electrode can be used for effective and rapid blunt dissection. Along these same lines, the development of laparoscopic "peanuts" or Kittners (i.e., 5- and 10-mm gauze-tipped disposable dissectors) has been most helpful. These dissectors can be twirled or moved side to side or up and down in an area of adipose tissue to rapidly tease away the fat surrounding vital structures such as the renal hilum or the adrenal gland. In addition, the device can be used to raise an entire "line" of tissue (e.g., pararenal fat), allowing for its rapid and safe division because neither the shaft nor tip of the Kittner will conduct electrosurgical current.

Water jet dissectors, such as the Helix Hydro-Jet (ERBE Elektromedizin, Tübingen, Germany), use an extremely thin, high-pressure laminar liquid jet to develop a cleavage plane in tissues. Pressures



Figure 10-19. A, Standard rod and lens laparoscope and camera. B, Laparoscope with a mini-charge-coupled device camera mounted at the tip.



Figure 10-20. Handheld 3D laparoscopic systems. (Courtesy Karl Storz, Tuttlingen, Germany.)

of 250 to 350 psi are sufficient for dissecting soft tissue while leaving vascular structures and nerves intact (Shekarritz et al, 2004). The device is activated using a foot pedal and the water jet is administered from a 5-mm wand. This device may have particular application in parenchymal transection as in partial nephrectomy or in nerve-sparing procedures such as during retroperitoneal lymph node dissection (Basting et al, 2000; Shekarritz et al, 2004). However, owing to fluid accumulation in the abdomen, changes in tissue turgor and, in particular, splash back from the fluid stream that can foul the laparoscope lens, these devices have not come into widespread use.

Instrumentation for Incising and Hemostasis

Laparoscopic scissors, scalpels, electrocautery, ultrasonic devices, and lasers (CO₂, neodymium:yttrium-aluminum-garnet [Nd:YAG], or potassium titanyl phosphate [KTP]) are used to incise or cut tissue during laparoscopic surgery. Cutting of tissue with electrocautery and lasers is achieved when the cell temperature is elevated until the concomitant gas pressure causes the cells to explode. Conversely, with ultrasonic devices the cutting mechanism is a relatively sharp blade vibrating at 25 kHz to 55 kHz over a distance of up to 100 μ m.

Monopolar and bipolar electrocautery and other technologies exist for achieving hemostasis. The basic mechanism for coagulating bleeding vessels is similar among the various modalities, in that vessels are sealed and occluded with denatured protein; however, the manner in which protein is denatured is different for each modality. Electrosurgery and lasers denature protein by heating the tissues with electric current in the former and light in the latter, at a very high temperature. Conversely, ultrasonic devices denature protein by transferring mechanical energy to ultrasonic high-frequency vibration (25 kHz to 55 kHz).

Sharp Dissectors. Laparoscopic scissors are available in disposable and nondisposable forms. The blades of laparoscopic scissors are shorter than their open surgical counterparts. The configuration of the tip may be useful for selected situations: hooked tips for cutting sutures, microscissors for spatulating the ureter during a pyeloplasty, and curved tips for dissection. The scissors may come with either permanent blades or with replaceable tips; use of the latter ensures “sharp” scissors for each procedure. In addition, the shaft of the scissors may rotate and, in some disposable scissors, even articulate up to 90 degrees. A **laparoscopic scalpel** is also available.

Monopolar Electrosurgical Devices. For electrosurgical incision of tissue, a selection of different electrodes are available: needle electrodes (Corson type) produce fine cuts that are useful in making peritoneal incisions, spatula electrodes are used in blunt dissection and cutting, and hook electrodes (J and L configurations) are of particular value during dissection of vessels because tissue can be pulled away from delicate structures before the cutting current is activated. **The thinner the metal tip of the probe, the higher the density of the electrical current, and the greater the cutting power.**

As with all insulated instruments, certain precautions must be followed during monopolar electrosurgery to avoid local or distant transmitted thermal injury. Consequently, **the electrosurgical probe should not be activated unless the metal part is in complete view. The insulation of the electrosurgical instrument should be carefully checked for any damage. The probe should not be activated unless it is in direct contact with the tissue to be incised.**

To avoid the potential dangers of stray current from use of monopolar electrosurgical equipment, the surgeon can use monopolar current in conjunction with active electrode monitoring (Encision, Boulder, CO). This instrumentation is constructed such that there is ongoing feedback during activation of the electrosurgical current; therefore, any break in the insulation of the shaft results in immediate deactivation of the instrument.

For monopolar electrosurgical coagulation, the floating ball electrode (Salient Surgical Technologies, Dover, NH), which is a saline-cooled radiofrequency surface coagulator-sealer, also exists. Skimming the floating ball over a tissue surface in small circles seals

the tissue, stopping the flow of blood and other fluids by effectively shrinking the natural collagen in the tissue. The wet energy cools tissue and keeps temperatures below 100° C, preventing tissue charring and eschar formation. This device has been proven to be quite useful for coagulating the parenchymal bed after partial nephrectomy before application of a hemostatic agent and/or bolster (Stern et al, 2004; Urena et al, 2004).

Bipolar Electrosurgical Devices. The laparoscopic surgeon can also use bipolar electrosurgical devices that require less energy for performance than their monopolar counterparts. There is also a decreased likelihood of injury to surrounding tissue for a couple of important reasons. First, because the **electrical current is only passing from one jaw of the instrument to the other, it precludes the potential problem of capacitive coupling**, commonplace with monopolar electrosurgical current. Second, **with bipolar current, the extent of coagulative damage is less than with monopolar electrosurgery: 1 to 6 mm versus 5 to 7 mm with monopolar current** (Landman et al, 2003a).

One of the currently available bipolar electrosurgical devices is the LigaSure vessel-sealing system (Covidien) (Fig. 10-21 on the Expert Consult website). It consists of a 5- or 10-mm grasper-dissector connected to a bipolar radiofrequency generator. When the vascular structure is grasped by the instrument, the tissue is evaluated by a feedback-response system that subsequently delivers the optimal energy required to seal the vessel effectively. Because of the high-current and low-voltage output, the vascular structure enclosed by the jaws of the instrument degrades quickly and a protein-based seal is presumably created; this mechanism of electrical current delivery to the tissues results in less charring and less collateral thermal damage (1 to 3 mm) (Landman et al, 2003a). Indeed, use of this instrument during partial nephrectomy does not compromise the ability of the pathologist to read the surgical margin (Phillips et al, 2008). An audible signal alerts the surgeon that the sealing of the vessel is complete; the instrument has a trigger-activated blade that the surgeon can then use to cut the sealed tissue. Vessels up to and including 7 mm in diameter appear to be effectively occluded, to above normal physiologic pressures, with this device (Carbonell et al, 2003; Landman et al, 2003a). However, only one LigaSure application to the structure being sealed is recommended, because multiple applications may weaken the seal (Truong et al, 2008).

Another simultaneous vessel sealing and cutting device is the EnSeal PTC (Ethicon). This is a 5-mm instrument that can also act as a grasper-dissector. The electrode design uses a temperature-sensitive polymer that helps to limit current spread to surrounding tissues. The device has an I-beam-shaped blade that draws the jaws of the instrument together with increasing force as the blade is advanced through the tissue. Hence, the surgeon can control the rate of cutting by how quickly the instrument handle is squeezed. The device can be used to seal vessels up to 7 mm but is reported to require a longer vessel sealing time than the LigaSure V (Covidien) (Lamberton et al, 2008).

Laser Instrumentation. Lasers are most frequently used through the working channel of an operating laparoscope. The CO₂ laser provides excellent cutting and vaporization of surface lesions and requires a rigid hand piece and probe. In contrast, the 400- and 600- μ m KTP fibers are flexible and allow for noncontact cutting and fulguration. Nd:YAG laser fibers are also flexible and allow noncontact fulguration and contact cutting. Holmium laser fibers are also flexible and are used in a contact mode for cutting. Typically, lasers are not used in urologic laparoscopy, where they have largely been supplanted by electrosurgical instruments. Only in gynecology is the CO₂ laser used extensively, in general in the treatment of endometriosis.

Ultrasound Instrumentation. Ultrasonic technology (Harmonic scalpel, Ethicon; and Sonicbeat, Olympus, Center Valley, PA) is another option for cutting and hemostasis in endoscopic surgery. It provides an especially attractive alternative to monopolar electrosurgery when one is working around particularly delicate tissues or operating on patients with an implanted pacemaker or cardioverter defibrillator (Gossot et al, 1999; Strate et al, 1999). In ultrasonic



Figure 10-21. A, Example of a LigaSure vessel-sealing system. B, LigaSure tip. (A, Courtesy Covidien Ltd., Mansfield, MA. All rights reserved. Used with permission of Covidien.)

devices, electrical energy is transformed into mechanical energy by the use of a piezoelectric crystal system. Specifically, electrical energy is produced by a power-supply generator and transformed into mechanical vibration at the tip of the instrument through a piezoelectric crystal interface (Suzuki et al, 1995; Takeda et al, 1997; Gossot et al, 1999). Mechanical vibrations produced by this system in the tip of the instrument are capable of causing cavitation, coaptation and coagulation, and cutting in the targeted tissue (Strate et al, 1999). There are several important benefits to the ultrasonic system. These include the absent risk of local thermal damage and tissue charring because of a working temperature lower than 80° C. Subsequently, reduced tissue charring may result in a reduced rate of postoperative adhesions (Amaral and Chrotstek, 1997). A second benefit is that the depth of penetration is limited to the targeted tissue within a diameter of 1 mm, so there is minimal lateral thermal spread and potential for tissue damage (Landman et al, 2003a). Ultrasonic devices also minimize smoke for improved visibility in the surgical field. In addition, the ultrasonic systems eliminate other problems associated with monopolar electrosurgery, specifically, problems of remote site tissue damage caused by capacitive coupling, insulation defects in the instrumentation, and direct coupling. Lastly, as with bipolar energy, use of ultrasonic energy during partial nephrectomy does not compromise the ability of the pathologist to read the surgical margin (Phillips et al, 2008).

Potential disadvantages of ultrasonic technology include slower vessel sealing (Lamberton et al, 2008) and the fact that the metal portion of the shears becomes quite hot during activation (often over 200° C compared with the bipolar energy-based devices, which stay below 100° C) and must not come into direct contact with any bowel surrounding the area of dissection. In fact, the harmonic shears take roughly twice as long to cool to a “safe” temperature after firing (often up to 45 seconds) compared with the LigaSure device (Covidien) (Kim et al, 2008).

Combined Devices and Other Instrumentation. See the Expert Consult website for details.

Surgical Pharmaceuticals

Recently, a vast array of topical hemostatic agents and sealants that can be used for a variety of surgical tasks have entered the surgical realm and have become valuable additions to the surgeon’s tray. A comparison of popular hemostatic agents is presented in Table 10-1.

See the Expert Consult website for further details.

Instrumentation for Suturing and Tissue Anastomosis

Needle Drivers. Suturing and knot tying are among the most difficult tasks in laparoscopic surgery. A significant amount of practice

is needed to achieve a sufficient level of proficiency. **Laparoscopic needle holders** have one fixed jaw and one jaw that opens by squeezing the spring-loaded handle of the instrument. They all have a locking mechanism to secure the needle in their jaws; this is done with a ratchet, spring-loaded, or Castroviejo-type mechanism. Some needle holders also possess a feature that allows the jaws to rotate around the main axis relative to the handle. The handles may be straight or provide a pistol-type grip (Fig. 10-22 on the Expert Consult website). In addition to standard rigid needle drivers, some companies have recently developed articulating needle drivers that aid in obtaining more optimal suturing angles with the needle. The actuation of the articulation mechanism is controlled by the surgeon’s wrist motion (Laparo-Angle [Cambridge Endoscopic Devices]; RealHand [Novare Surgical Systems]).

Endo Stitch. The Endo Stitch (Covidien) device is an innovative, disposable, 10-mm instrument that facilitates laparoscopic suture placement and knot tying (Adams et al, 1995). With increased experience with standard laparoscopic needle holders and especially with the advent of robotic-assisted procedures, use of the Endo Stitch has become less common.

See the Expert Consult website for further details.

Lapra-Ty clips. Lapra-Ty clips (Ethicon) are a very useful adjunct to suturing and knot tying. The clip acts as a knot, thereby precluding time-consuming intracorporeal laparoscopic knot tying (Fig. 10-23). These 3.5-mm clips are made of absorbable polydioxanone and are designed to provide secure anchoring of sutures for up to 14 days in low-tension to mid-tension environments (Ames et al, 2005). According to the manufacturer, these suture anchors can be secured to the end of a single strand of polyglactin 910 (Vicryl) suture as fine as 4-0. Experimental models from two different laboratories have shown that these clips are least likely to fall off polyglactin 910 sutures from size 1-0 to 3-0 (Ames et al, 2005; Weld et al, 2008). In the laboratory environment Lapra-Ty clips have been shown to be slip resistant with 2-0 Monocryl and polydioxanone suture (PDS) as well. In multiple test trials for each suture type, a percentage of monofilament sutures size 3-0 and smaller as well as 4-0 suture of any type did have slippage of the clip. Hence, it seems logical to avoid Lapra-Ty use with 4-0 suture and to avoid excessive tension when using these clips with 3-0 monofilament suture. Lapra-Ty clips can be used to secure a single suture or a running suture and for anchoring bolsters during renorrhaphy for laparoscopic or robotic partial nephrectomy (Orvieto et al, 2004).

Instrumentation for Stapling and Clipping

Stapling Devices. Various stapling devices are available for tissue occlusion and division. The Endo GIA Universal 12-mm stapler and

TABLE 10-1 Some Commonly Used Topical Tissue Sealants and Hemostatic Agents

AGENT	MANUFACTURER (TIME TO SET UP)	ACTIVE INGREDIENTS	KEY USES AND PROPERTIES
Tisseel	Baxter, Glendale, CA (20 min)	Fibrinogen CaCl Aprotinin Thrombin	Topical hemostasis Tissue glue
Crosseal	Johnson & Johnson, New Brunswick, NJ (Immediate)	Fibrinogen CaCl Aprotinin Thrombin	Topical hemostasis Tissue glue
Floseal	Baxter (2 min)	Cross-linked gelatin granules Thrombin	Topical hemostasis
EndoAvitene	Davol, Cranston, RI (Immediate)	Avitene microfibrillar collagen powder	Topical hemostasis
BioGlue	CryoLife, Kennesaw, GA (Immediate)	Bovine serum albumin and glutaraldehyde	Tissue sealant
Coseal	Baxter (Immediate)	Two polyethylene glycol polymers	Tissue sealant

CaCl, calcium chloride.

A recently developed device called Thunderbeat (Olympus, Center Valley, PA) combines ultrasonic and advanced bipolar energies into a single multifunctional instrument allowing surgeons to seal and cut vessels up to and including 7 mm in size with minimal thermal spread. Initial porcine studies have shown the Thunderbeat to surpass the dissection speed of ultrasonic devices while having the sealing efficacy of bipolar devices ([Milsom et al, 2012](#); [Seehofer et al, 2012](#)).

The **argon beam coagulator** provides a noncontact form of electrocoagulation. Electrical current originating from a monopolar electrosurgical generator is conducted to the tissue through an ionized argon gas stream. The gas stream blows away blood from the tissue, resulting in better exposure of the bleeding site and

hence more effective delivery of the electrosurgical current. Argon is a colorless, odorless, inert gas that clears the body within one respiratory cycle ([Quinlan et al, 1992](#)). Holding the hand piece at an oblique 60-degree angle within 1 cm of the surface of the target tissue provides optimal coagulation effects. During argon beam coagulation, the sidearm on one of the laparoscopic ports must be opened to prevent buildup of excessive intra-abdominal pressures. Because argon beam coagulation has its major advantage when hemostasis must be achieved over a diffusely bleeding surface, its most practical indication in laparoscopic urologic surgery is during partial nephrectomy or for control of small liver or spleen lacerations.

Fibrin-Based Glue. Fibrin glue has been used to promote hemostasis in parenchymal beds, in particular after partial nephrectomy or to seal a liver laceration. The two components of the fibrin glue, fibrinogen and thrombin, are delivered through separate channels and then combine at the tip of the delivery system during application to the tissue. Fibrin glue provides topical hemostasis and has sealant and adhesive qualities once dry; it essentially hardens into a rubbery coagulum. Tisseel VH Fibrin Sealant (Baxter, Glendale, CA) has the maximum concentration of human fibrinogen available (75 to 115 mg/mL). It can be delivered by means of a laparoscopic applicator in liquid form or in an aerosolized form. One disadvantage of Tisseel is that it requires 15 minutes to prepare before the surgeon can apply it. If immediate application is required (e.g., because of bleeding), then fibrin glue is not a viable option unless it has been prepared in anticipation of possible hemorrhage. Once prepared, Tisseel VH is available for use for 4 hours.

Another fibrin-based sealant that can be delivered in a similar manner is Evicel (Johnson & Johnson, New Brunswick, NJ). This agent contains 40 to 60 mg/mL of human fibrinogen and is the only all-human, aprotinin-free fibrin sealant. Because it contains no bovine serum components (e.g., aprotinin) it can be used in individuals with allergies to bovine-derived products. Another advantage of this sealant is it comes frozen and thus requires no reconstitution. It can be thawed in the hand in 5 minutes and available in another minute. Once thawed, Evicel has a shelf life of 1 month under refrigeration (Tredree et al, 2006). This product can also be applied laparoscopically with an available applicator.

Although all types of fibrin glue use pooled human fibrinogen, the preparations are treated to inactivate viruses. As of 2006 there had been no reported cases of viral transmission to a recipient (Tredree et al, 2006).

Non-Fibrin-Based Surgical Hemostats. In contrast to the fibrin-based glues, other hemostatic agents such as thrombin-soaked oxidized cellulose particles (FloSeal [Baxter]; Surgiflo [Johnson & Johnson]) have no adhesive capability but are excellent hemostatic agents in the presence of active bleeding from parenchymal surfaces such as a partial nephrectomy bed, a liver or spleen laceration, or an oozing adrenal bed. These agents are composed of both human-derived thrombin and bovine- or porcine-derived gelatin matrix. The gelatin granules swell 10% to 20% to produce a tamponade effect, whereas the high concentration of thrombin promotes conversion of fibrinogen to fibrin, as well as activating platelets and several coagulation factors. This agent is also prepared by the scrub assistant; it takes 2 minutes to prepare and is usable for 2 hours. It is applied through a tube applicator with a syringe. It is most effective when pressure is applied after its delivery; this can be done either with an instrument (e.g., 10-mm gauze-tipped dissector) or with a bolster.

The Avitene Microfibrillar Collagen Hemostat (Davol, Cranston, RI) is an active collagen hemostat that accelerates clot formation by enhancing platelet aggregation and the release of fibrin. Similar to FloSeal, it has no tissue sealing capability, but is useful for counteracting parenchymal bleeding. EndoAvitene is available for use in endoscopic procedures. EndoAvitene comes prepared in a pre-loaded endoscopic delivery system, developed to easily pass through standard trocars and cannulae. It is available in both 5- and 10-mm diameters.

Chemical-Based Sealants. BioGlue (CryoLife, Kennesaw, GA) is a two-component adhesive composed of purified bovine serum albumin (BSA) and glutaraldehyde. The solutions are mixed during application from a controlled delivery system. The glutaraldehyde then cross-links the BSA molecules to one another and then to the tissue protein at the site of use. Once applied, the agent polymerizes within 20 to 30 seconds and reaches its full bonding strength within 3 minutes. The delivery system comes ready for immediate use. BioGlue is a sealant and must be applied to a dry field and allowed to dry. Thus it cannot be used to counteract active bleeding but can be used to seal a raw, nonbleeding surface.

Coseal (Baxter) and AdvaSeal-S (Genzyme, Cambridge, MA) are completely synthetic products composed of two distinct polyethylene glycol polymers that chemically bond together to form a hydrogel that seals tissue surfaces, suture lines, and synthetic grafts. It does not require thawing, heating, or light activation and hence can be ready in 1 minute. It must be applied to a dry (nonbloody) surface because it does not interact with the clotting cascade and hence is not useful in the setting of active hemorrhage.

Now that the benefits of such substances have come into the spotlight in surgery, it is important for the surgeon to be familiar with the properties of these various agents and thereby able to choose one that is most appropriate for the job at hand.

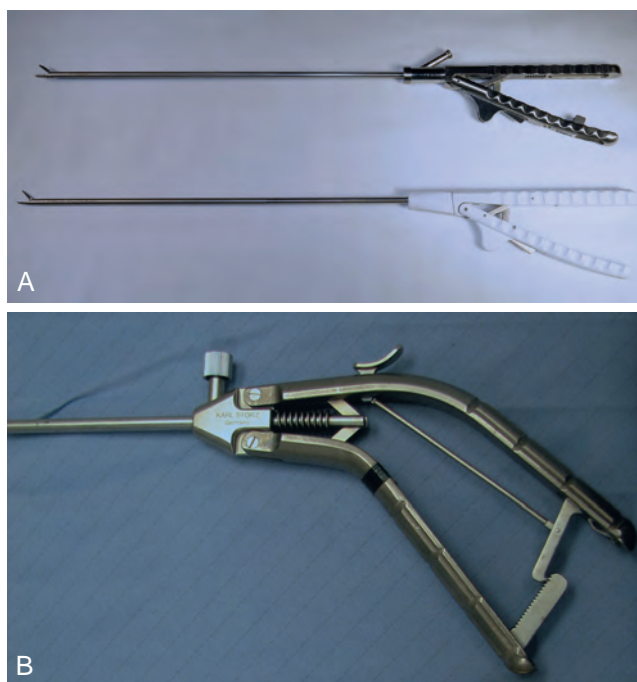


Figure 10-22. Different handle designs for commonly used laparoscopic needle drivers. A, Straight handle reusable (top) and disposable (bottom). B, Pistol-type grip.

The suture is secured to the center of a straight needle with two pointed ends, thereby allowing tissue penetration in either direction. The needle is shuttled back and forth between the jaws of the instrument after each passage through the tissue, applying a long-known principle used in sewing machines. In this way, passing the needle through the tissue and regrasping the needle after it has traversed the tissue become simple tasks because they are done by a one-handed squeeze of the handle and a flip of the needle-securing lever, respectively. Use of this sewing apparatus has had a major impact on decreasing operative times, especially in laparoscopic pyeloplasty ([Chen et al, 1998](#)).

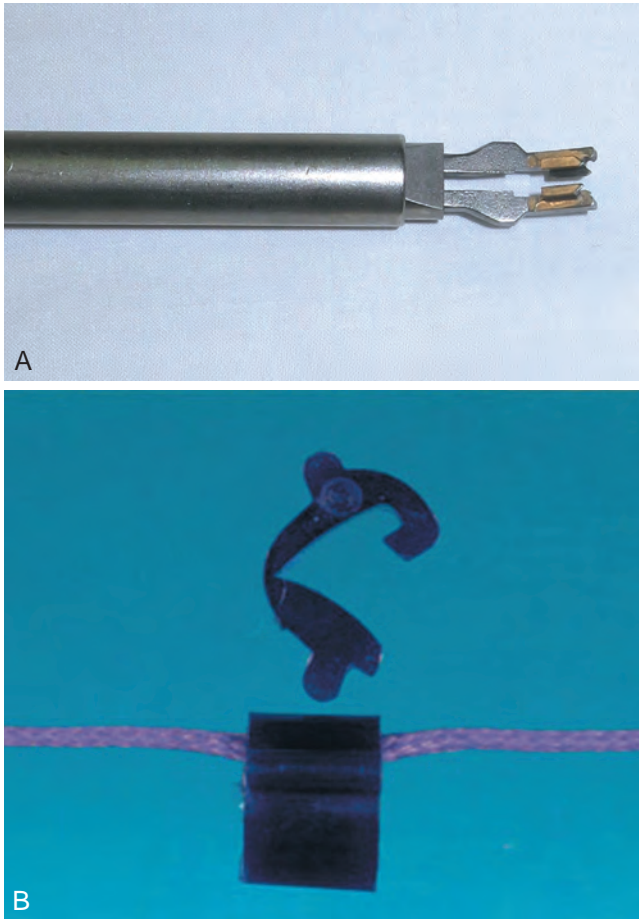


Figure 10-23. A, Tip of laparoscopic device for applying Lapra-Ty clip (Ethicon, Somerville, NJ). B, Lapra-Ty clip affixed to a suture.



Figure 10-24. A, Example of Endo GIA laparoscopic stapling device. B, Stapling device tip. (A, Courtesy Covidien Ltd., Mansfield, MA. All rights reserved. Used with permission of Covidien.)

linear cutting device (Covidien) requires a 12-mm port and delivers two triple-staggered rows of staples and simultaneously cuts between the rows (Fig. 10-24). The Universal stapler can be loaded with a variety of 30-, 45-, or 60-mm loads and fired any number of times. Similarly, the ETS-Flex 45 stapler (Ethicon) also requires a 12-mm port and delivers two triple rows of staples while cutting between

rows 3 and 4. This stapler has a maximum fire limit of eight staple loads. Articulating and roticulating staplers are available from both companies, which enable the surgeon to properly align the instrument with the tissue to be occluded and divided. Each staple load cartridge is color coded depending on the size of the staples: 2.0-mm staples (gray) or 2.5-mm staples (white) are preferred for vascular (renal vein or renal artery) stapling, whereas 3.8-mm (blue) and 4.8-mm (green) staples are used in thicker tissues (ureter, bowel, bladder). In addition, for laparoscopic live donor nephrectomy, a single Endo-TA (linear noncutting) stapler can be used to secure the patient's side of the renal vein, thereby providing a longer donor renal vein, because there is no need to trim staples from the vessels before anastomosis in the recipient (Meng et al, 2003). Linear noncutting staplers deliver either three or four staple rows, 30 or 60 mm long. These staplers can also be used to close an enterotomy after a side-to-side bowel anastomosis. When laparoscopic staplers are used, special attention must be paid to the markers on the cartridge to ensure that all the targeted tissue is properly situated proximal to the markers before the cartridge is fired. The stapler should not be fired across any previously placed clips because this is thought to possibly cause stapler malfunction. Indeed, in a 9-year review of stapler use (1992 to 2001), Brown and Woo (2004) noted U.S. Food and Drug Administration–recorded reports of 112 mortalities and 2180 injuries attributed to use of the stapler; overall, malfunctions were reported 22,804 times.

Clipping Devices. Disposable and nondisposable clip applicators are available from different manufacturers and require 5-, 10-, or 12-mm laparoscopic ports. In general, they contain occlusive clips ranging in size from 6 to 11 mm. Disposable clip applicators possess a rotating shaft and multifire, self-reloading features, whereas nondisposable instruments have to be reloaded for each clip to be deployed at the site of surgery (Fig. 10-25).

Electrocoagulation must be avoided in the vicinity of clips placed for occlusion of vessels to prevent conductive tissue necrosis and subsequent clip dislocation. To ensure reliable function, the closed ends of the occlusive clips must be seen extending slightly beyond the targeted vessel and should be placed perpendicular to the longitudinal axis of the vessel.

In addition to titanium clips, polymer clips that completely encircle and lock down around a vessel are available (Weck Hem-o-lok polymer ligation clip system [Teleflex, Research Triangle Park, NC]) (see Fig. 10-25). They are available in four sizes (M, ML, L, and XL). Up to 10 mm of tissue can be ligated through a 5-mm trocar, and up to 16 mm of tissue can be ligated through a 10-mm trocar. Of note, because of results from a survey put forth by the American Society of Transplant Surgeons, in which use of these clips was associated with hemorrhage from the renal artery stump, the company producing the clips put forth a statement contraindicating their use for securing the renal artery during laparoscopic live donor nephrectomies (Friedman et al, 2006). Subsequently, a multi-institutional study of 1695 patients from nine different institutions undergoing laparoscopic donor nephrectomy with ligation of the renal artery with Hem-o-lok clips concluded that the clips were safe to use because in this review there were no adverse bleeding events (Ponsky et al, 2008a). The authors did acknowledge, however, that proper technique of application must be strictly adhered to, including application of at least two clips on the stump of the artery, and that a 2-mm cuff of artery should be left distal to the clips (Box 10-2). Removal of a Hem-o-lok clip is possible using the specified removal instrument, should a structure be clipped in error.

Instrumentation for Specimen Entrapment

Various organ entrapment and retrieval systems are available. Depending on the size of the tissue and on whether in situ morcellation or intact organ retrieval is planned, the laparoscopic surgeon is able to choose among different-sized sacks, materials, and designs. Studies have been conducted to test organ retrieval bags for permeability to tumor cells and bacteria before and after

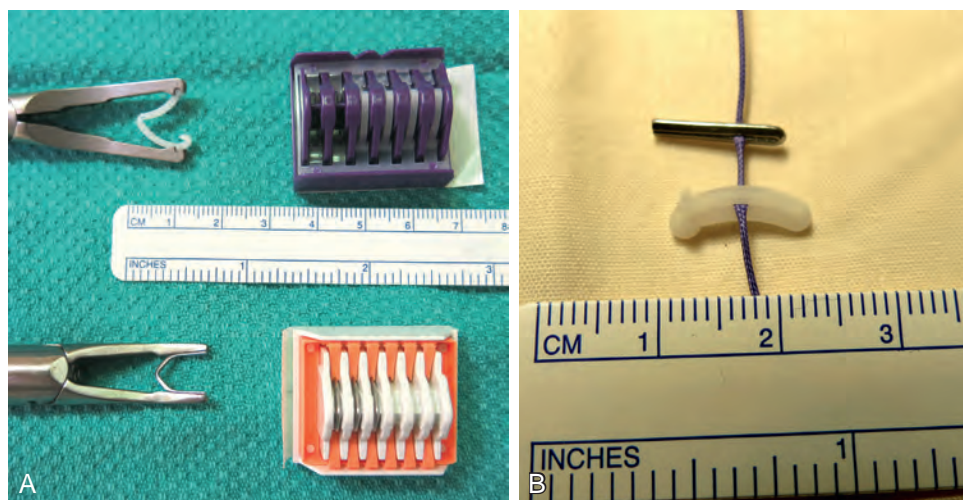


Figure 10-25. A, Weck Hem-o-lok clip and tip of laparoscopic applicator (top) (Teleflex, Research Triangle Park, NC) and metal clip and tip of laparoscopic applicator (bottom). B, Metal clip (top) and Weck Hem-o-lok clip (bottom) affixed to a suture.

BOX 10-2 Basic Principles of Hem-o-lok Clip Placement

- Complete circumferential dissection of the vessel
- Visualization of the curved tip of the clip around and beyond the vessel, often with curved end of the clip placed between artery and vein
- Confirmation of the tactile snap when the clip engages
- No cross-clipping
- Not squeezing clip handles too hard (compared with the application of metal clips)
- Careful removal of the applicator after application given; the tips are sharp and can cause a laceration of nearby vessels (e.g., renal vein)
- During transaction of vessels only a partial division is performed initially to confirm hemostasis before complete transaction
- Minimum of two clips placed on the patient side of the renal hilar vessel

From Ponsky L, Cherullo E, Moynadeh A, et al. The Hem-o-lok clip is safe for laparoscopic nephrectomy: a multi-institutional review. *Urology* 2008;71:593–6.

morcellation, as well as for stability during morcellation and resistance to tearing forces (Urban et al, 1993; Rassweiler et al, 1998b). The originally designed (1990) LapSac (Cook Urological, Spencer, IN), which is made of nylon with a polyurethane inner coating and a polypropylene drawstring, is the least susceptible entrapment sack to tearing (Eichel et al, 2004) or leakage of cells. Up to a 2-kg specimen can be secured within the LapSac; however, deployment of the LapSac and subsequent organ entrapment remain challenging endeavors.

Other entrapment sacks offer marked advantages when the only goal is organ entrapment and intact removal, rather than morcellation. These sacks have spring wires that, when activated by the surgeon, deploy the bag after its introduction into the abdomen; this facilitates tissue entrapment because the broad wire supports stabilize the opened sack, thereby allowing the surgeon to literally scoop the specimen into the sack (Fig. 10-26). The entrapped specimen can easily be withdrawn through a hand-assist site or by enlarging a laparoscopic port site, usually to 5 to 7 cm for most specimens.

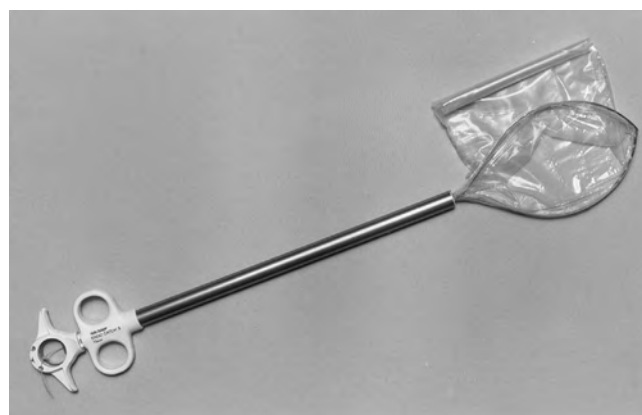


Figure 10-26. Organ retrieval bag.

Instrumentation for Morcellation

Various techniques of tissue morcellation have been used in laparoscopic surgery. The simplest method for fragmentation of tissue within the entrapment sack is use of the index finger, ring forceps, or Kelly clamp. Recently, however, it has been shown that ring forceps are the preferred instrument for manual morcellation because they are less likely to puncture the entrapment sack (Eichel et al, 2004).

See the Expert Consult website for further details.

Instrumentation for Retraction

Many varieties of retractors with different features are available.

See the Expert Consult website for details.

Robotic Instrumentation

For the da Vinci Robotic System (Intuitive Surgical), a wide variety of articulating instruments are available. The proprietary EndoWrist technology offers articulation at the tip of the instruments with 7 degrees of freedom and 90 degrees of articulation, mimicking the wrist movements of the surgeon at the robotic console (Fig. 10-27). A full line of 8-mm EndoWrist instruments are available, but it should be noted that all robotic instruments for the da Vinci Surgical System (except the laparoscopes) have a 10-case limit before they must be replaced. The number of “lives” left on each instrument should be recorded with each case.

If morcellation is performed intracorporeally, the entrapment sack should be a LapSac; however, a variation reported by [Landman and colleagues \(2003b\)](#) for morcellation uses one of the plastic entrapment sacks. In this method, the morcellation is performed above the abdominal wall, by extending the extraction site incision to 3 cm in length. All tissue is fragmented and removed under direct vision above the abdominal surface; at no time is the morcellating instrument out of the direct vision of the surgeon. With this approach, specimens could be morcellated rapidly, with the entire entrapment and morcellation process taking only 13 minutes for clinical specimens as large as 700 g; also fragment size increased from 1.5 to 4.5 g, which might afford better tissue assessment with regard to capsular, vascular, or renal sinus fat invasion ([Landman et al, 2003b](#)).

For morcellation of a renal malignancy, the neck of the sack is triply draped to preclude any contamination: a towel drape, Ioban (3M), and nephrostomy drape can be used. At the end of the morcellation procedure, the surgeon and assistants regown and glove.

The use of an entrapment sac is important, because wound seeding with tumor has been reported with intact specimen extraction without entrapment ([Iwamura et al, 2004](#)). In contrast, there has been only one noted wound seeding with morcellation in a LapSac ([Fentie et al, 2000](#)), and a multi-institutional study comprising 2064 radical nephrectomies, among which 826 were removed by entrapment and morcellation, showed no instance of a wound seeding with tumor ([Micali et al, 2004](#)).

The simplest retractor is a metal bar with an atraumatic tip or a curved saddle shape; the latter is helpful for retracting a vessel during lymph node dissection. Similarly, the disposable laparoscopic “peanut,” in either its 5- or 10-mm rendition, is very helpful because it can both dissect and atraumatically retract tissue.

However, the most useful retractors are the expanding types: fan retractors with three or four atraumatic finger-like extensions, fan retractors with V-hinge joints, balloon retractors, and kite-style instruments (e.g., Padron Endoscopic Exposing Retractor [PEER] retractors) (Jarit, Hawthorne, NY) (Brooks, 1993). The 5-mm kite style retractor provides a 2- × 3-cm retracting area, whereas the 10-mm version provides a 4- × 3-cm retracting area. This type of retractor is very helpful for firm retraction, such as on the kidney to put the renal hilum on stretch.

Another type of retractor is malleable and thus can be shaped to the needs of the surgeon. The Diamond-Flex angled 80-mm triangular retractor (Snowden-Pencer Instrumentation, Carefusion, Waukegan, IL) can be adapted to many different angles, curves, and shapes, and the surgeon can lock in its particular configuration. This feature is of particular value when retraction of a delicate organ such as the liver is required. This instrument forms a broad retracting surface 8 cm in length.

Retraction of tubelike structures (e.g., vessels, ureter) can also be achieved by placing a suture, a vessel loop, or an umbilical tape

around the tissue and applying traction either with a grasper inside the abdomen or by pulling the ends of the retraction loop out of the abdomen through a small stab incision using a Carter-Thomason device (Carter, 1994) or by encircling the structure with a suture affixed to a Keith needle, which can be passed across the abdominal wall, around the structure to be retracted, and then back out the abdominal wall (see later discussion of exiting the abdomen). The retraction loop can then be secured under slight tension on the surface of the abdomen with a small hemostat. Care should be taken during the use of this technique because excessive tension may injure the structure being retracted.

Mechanical Assistants. External mechanical devices such as the EndoHolder (Codman, Raynham, MA) or the Laparostat (Civco, Kalona, IA) can be used to keep grasping forceps or locking retractors in position, thereby taking the place of a tableside assistant. This device is usually mounted on the side of the table opposite the surgeon. The malleable free arm is then affixed to the shaft of a grasping forceps or laparoscopic retractor. When the surgeon has used the retractor for its given purpose, the malleable arm of the external mechanical device is locked in place, thereby providing reliable, continued traction.

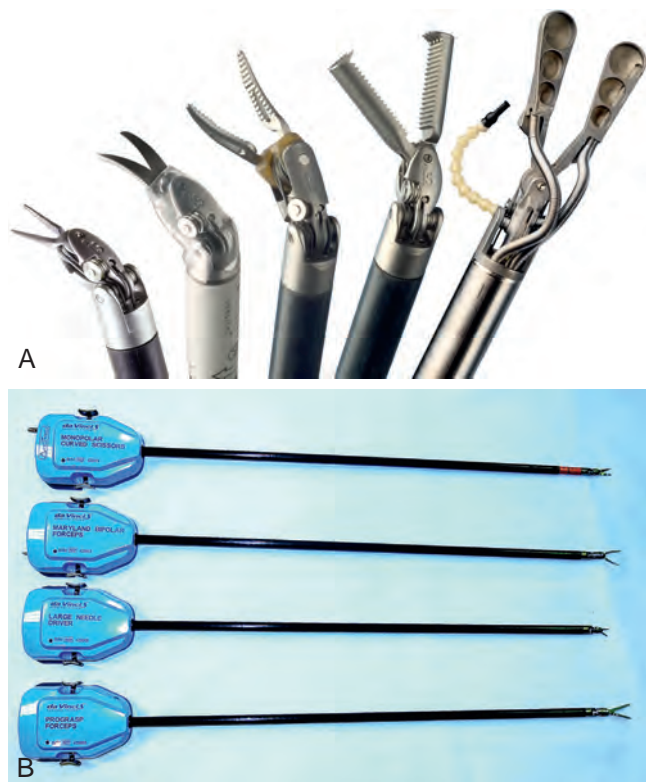


Figure 10-27. A and B, Examples of 8-mm interchangeable instruments for the da Vinci Robotic System. (© 2015 Intuitive Surgical, Inc. Used with permission.)

Instrumentation for Incising and Hemostasis

A variety of EndoWrist scissors and scalpels exist for incising tissue and include the round tip, curved and Potts scissors, and the Snap-fit scalpel instrument. EndoWrist monopolar and bipolar electrocautery instruments are available for incision, dissection, and hemostasis during procedures. Monopolar instruments include the Hot Shears curved scissors and cautery hook and spatula. Bipolar instruments include the Maryland, PK dissecting (Intuitive Surgical), fenestrated, micro, PreCise and curved bipolar forceps. An ultrasonic device (Harmonic ACE curved shears [Ethicon]) is also available for dissection and hemostasis.

Instrumentation for Grasping and Blunt Dissection

A large array of EndoWrist graspers exist that cover the range of blunt to toothed and fine to gross, for use in varying situations. The most commonly used grasper in urologic procedures is the Pro-Grasp blunt forceps.

A safety feature on all robotic grasping devices is a small Allen bolt that can manually open the jaws of the instrument in the case of a robotic arm malfunction or loss of power in which the grasper is locked onto tissue or a needle at the time of failure. Of note, robot failure is quite rare. In the series from the University of Chicago, a robot failure was recorded in less than 1% of cases, and half of these problems (e.g., failure to power up, optical malfunction) were discovered before the patient entered the operating room. In addition, in the few instances in which there was a system malfunction (e.g., loss of 3D vision, robotic arm failure) during the case (0.4%), the procedure could still be completed without converting to an open procedure (Zorn et al, 2007).

Instrumentation for Suturing and Tissue Anastomosis

Four different EndoWrist needle drivers are available for suturing. There are two sizes of needle drivers available in both the standard

and SutureCut design. The SutureCut design allows the surgeon to be able to cut the suture material using the crotch of the instrument.

Other Available 8-mm and 5-mm Instruments

A number of other robotic instruments are also available. Endo-Wrist clip appliers exist for both small titanium clips and medium-large and large Weck Hem-o-lok polymer clips (Teleflex). In addition, an articulating suction device and irrigator, a probe stabilizer, and specialty retractors exist.

A 5-mm line of instruments is also available that is slightly more limited, but still offers a relatively complete line of instruments. It should be noted, however, that the 5-mm robotic laparoscope offers a 2D not 3D image.

Instrumentation for Laparoendoscopic Single-Site Surgery

See the Expert Consult website for details.

Instrumentation for Natural Orifice Transluminal Endoscopic Surgery

See the Expert Consult website for details.

Exiting the Abdomen

Port Removal and Fascial Closure

Port removal and fascial closure are key elements of the procedure that, if not performed in a step-by-step, organized fashion, can result in major, possibly fatal, complications. Herniation, possible bowel incarceration, and postoperative hemorrhage are the results of a poorly performed or haphazard, overly rapid exiting of the abdomen.

Before port removal is initiated, the operative site and the intra-abdominal entry sites of each cannula must be carefully inspected with the intra-abdominal pressure lowered to 5 mm Hg. After achievement of perfect hemostasis, removal of all laparoscopic ports must be undertaken strictly under laparoscopic visual control, to avoid any possible acute herniation of intra-abdominal contents into the previous port sites.

Presently, with the shift away from bladed to nonbladed trocars, the need for fascial closure for even 12-mm ports has come into question. Most will recommend that on removal of any of the blunt-tipped ports, the fascia does not need to be sutured, except for ports larger than 10 mm placed in the midline. However, a report has shown that 12-mm ports, regardless of site (i.e., midline vs. transmuscular), do not require fascial closure, provided that postoperative palpation of the entry site reveals a small defect (Siqueira et al, 2004). In the literature, the switch from bladed to blunt trocars has resulted in a marked decrease in abdominal wall bleeding (from 0.83% to only 0.16%) and in port site hernia formation (1.83% to 0.19%) (Hashizume and Sugimachi, 1997; Thomas et al, 2003).

In the rare case in which bladed trocars are used, the fascia at all 10- to 12-mm port sites should be closed. After inspection at 5 mm Hg, the first 10- or 12-mm port is removed and the fascia at the entry site is secured with 0-0 Vicryl either by direct placement of a fascial suture or use of a suture-passing device (see later). Five-millimeter ports are not closed in the adult, but are closed in the pediatric patient with a single absorbable suture. Ideally, each fascial suture will be placed under direct endoscopic vision prior to definitive port removal. In this manner, each port is visually assessed for any bleeding at 5 mm Hg, thereby precluding the possibility of removing a port and missing an injured vessel. After removal of all ports, the CO₂ is allowed to pass out passively through the 5-mm port sites.

With regard to the hand-assist device, it should be removed before removal of the other port sites. The hand-assist device wound

A detailed description of access devices for LESS such as the TriPort and Uni-X has previously been presented in this chapter. By definition, in LESS, all of the instrumentation for the case including a camera and lens for visualization and the working instruments to perform the procedure must be placed through a single incision. This creates ergonomic challenges with regard to instrument collisions inside and outside the abdominal cavity. Furthermore, the typical trocar arrangement for laparoscopy, which affords one the ability to “triangulate,” is largely lost with LESS. Much of the emphasis on instrumentation for LESS therefore centers on minimizing instrument collisions outside the abdominal cavity and re-creating the “triangulation” necessary to approach the surgical site safely (Fig. 10-28).

With regard to endoscope choice, one issue encountered is that the light cord often attaches to the telescope at a 90-degree angle and can thus hinder the movement of the lens or other instruments. To avoid this problem one can use an endoscope that has the light cord attached end-on from the back directly into the endoscope (Karl Storz) or a one-piece endoscope that already has an end-on integrated light cord (EndoEYE, Olympus, Orangeburg, NY). Alternatively, an extra-long laparoscopic lens can be used to keep the light cord away from the shorter standard working laparoscopic instruments. Similarly, use of laparoscopic instruments of different lengths can help keep the handles from clashing with one another.

With regard to overcoming the parallel nature of the instrument paths and reestablishing a triangular arrangement of instrumentation, several technologic advances have been developed so far with endoscopes and instruments. In terms of endoscopes, a laparoscope with a deflecting tip (EndoEYE Flex [Olympus]) or adjustable angle tip (EndoCAMEleon [Karl Storz]) should be used because these telescope designs offer the greatest adjustability for optimal viewing. At the very least an angled lens (30- or 45-degree fixed angle) should be used. In terms of instruments, the use of articulating or curved instrumentation is essential to avoid instrument collision outside the abdomen and to achieve proper triangulation for tissue retraction, exposure, and dissection. Disposable articulating instruments are available from RealHand (Novare Surgical Systems) and Autonomy Laparo-Angle (Cambridge Endoscopic Devices). Curved reusable laparoscopic instruments are also available (Karl Storz-Endoskope; Sklar Instruments, West Chester, PA) and provide a nondisposable alternative to the articulating instruments, which are one-time-use items. Both single-curved and

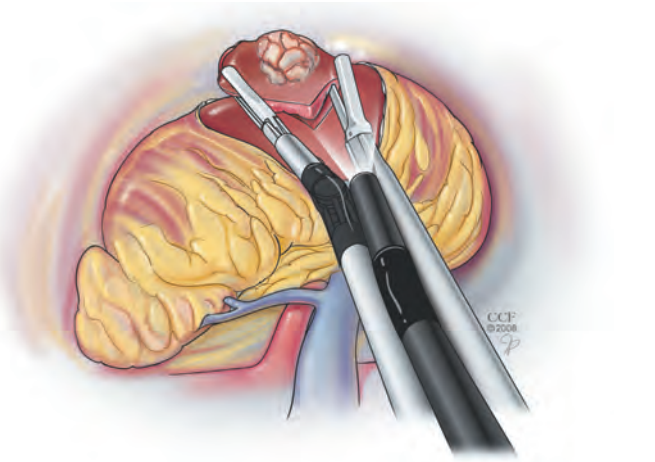


Figure 10-28. Deflecting laparoscopic instrumentation can be used to maintain triangulation during laparoendoscopic single-site surgery. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©1998-2011. All rights reserved.)

double-curved reusable instruments exist. In addition, the recent development of the SPIDER surgical system (TransEnterix, Morrisville, NC) provides a flexible laparoscopic platform for single-site surgery with restoration of triangulation. Disposable flexible, articulating instruments specifically designed for the SPIDER surgical system allow for transmission of force and torque via a flexible, catheter-based instrument with true left and right instrumentation and elimination of crossed arm movements.

Finally, the use of the robot for LESS procedures has been demonstrated. A recent systematic review revealed that a cumulative number of roughly 150 robotic urologic cases have been reported in the literature including pyeloplasties, partial nephrectomies, living donor, simple and radical nephrectomies, adrenalectomies, and radical prostatectomies (Autorino et al, 2013). The ability of the robotic arms to articulate is a major plus, and one can envision that LESS will follow the path of standard laparoscopy into the robotic age.

The concept of natural orifice transluminal endoscopic surgery (NOTES) is not truly new; indeed, the first NOTES procedure would have been Philipp Bozzini's cystoscopy in 1804. What is new is the use of flexible endoscopic technology to perform procedures heretofore unthinkable with a transgastric (e.g., appendectomy in 2004 by Rao and Reddy) or transvaginal approach (e.g., appendectomy in 2004 and cholecystectomy in 2007 independently by Bressler and then Marescaux). Over time these increasingly complex endoscopes have developed from purely diagnostic instruments for visualization of intraluminal surfaces to highly functional endoscopes capable of carrying therapeutic tools that can be used to treat visualized problems. Recently, further advances in this type of technology have led to the development of endoscopes specifically for transluminal surgery. The potential advantages of transluminal endoscopic surgery are better cosmesis, less pain, elimination of the risk for wound infection and hernias, and a reduction in adhesions (Swanstrom et al, 2008a, 2008b).

There are several prototype endoscopes currently under evaluation for NOTES. In general, these endoscopes offer larger working channels than standard endoscopes and allow larger instrumentation. Some endoscopes such as the Transport (USGI Medical, San Juan Capistrano, CA) are designed with a guidable locking overtube through which other instruments can be placed; within the 20-mm overtube there are four ports (7 mm, 6 mm, 4 mm, and 4 mm) to accommodate the endoscope and up to three additional instruments. One of the working channels houses a standard 6-mm endoscope for vision, and the other working channels are for instrumentation. Some endoscopes offer triangulating instrumentation. Major hurdles still exist in terms of developing better and more effective instrumentation and especially devices for suturing and enterotomy closure. The Transport, for instance, can be used to perform enterotomy closure using special suture anchors (g-Cath [USGI Medical]).

is then closed as one would close a typical abdominal wound. After closure, the pneumoperitoneum is reestablished and the other port sites are closed as previously described. Proceeding in this fashion precludes the chance of injuring the bowel or omentum beneath the hand-port site and ensures an airtight closure.

Instrumentation for Port Site Closure

Several possibilities for fascial closure of port sites exist. The **simplest method** is retracting the skin with retractors, grasping the fascia, and suturing it with absorbable 0-0 suture. However, in patients with a BMI above 30, securely accessing the fascia is very difficult to accomplish.

Fortunately, several devices for complete en bloc closure of fascia, muscle, and peritoneum under direct vision have been developed (Carter 1994; Monk et al, 1994; Garzotto et al, 1995; Elashry et al, 1996). These work well in patients of all sizes.

The **Carter-Thomason needle-point suture passer** (CooperSurgical, Pleasanton, CA) consists of a 5-, 10-, or 12-mm cone that has two integrated, hollow, angled, cylindric passages located 180 degrees opposite each other (Fig. 10-29). With the sharp needle-point, single-action grasper, the 0-0 Vicryl suture is inserted through one of the cylinders in the metal or plastic cone, thereby traversing muscle, fascia, and peritoneal layers in an ever-widening angle. The end of the suture is grasped with a 5-mm grasper through one of the other ports. The needle-point grasper is reintroduced through the other cylinder of the cone, and the intraperitoneal end of the suture is grasped by the needle-point grasper and pulled out of the abdomen. The cone is slid off both ends of the suture. Subsequently, closure of the fascia, muscle layer, and peritoneum is accomplished by tying the suture. **The Carter-Thomason needle-point device is not only helpful for wound closure, but also can be used as a fifth port during nephrectomy to help hold the sack open or to encircle the ureter with a vessel loop through a small stab incision.**

The **disposable Endo Close suture carrier** (Covidien) is a device with a spring-loaded suture carrier at its tip. Loaded with a suture, the device traverses fascia, muscle, and peritoneum alongside the port. After reinsertion on the opposite side of port entry, it is reloaded with the suture, aided by a 5-mm grasper, and is pulled out again so that the suture can then be tied.

A far simpler, less expensive, homemade solution is available to all surgeons for closing ports in a large patient. This **angiocatheter technique** applies the previously described principles. A 14-gauge, sheathed needle is passed alongside the port through the abdominal layers. After removal of the needle, a 0-0 Vicryl suture is inserted through the angiocatheter sheath until it is deep inside the peritoneal cavity. After the sheath is removed, the same maneuver is repeated on the opposite side, but this time a 30-inch 0-0 Prolene suture folded in half is passed into the peritoneal cavity through the sheath to act as a retrieving loop. A 5-mm grasper passed through another port is then passed through the loop of 0-0 Prolene suture and used to grasp the end of the 0-0 Vicryl suture. The 0-0

Vicryl suture is pulled through the Prolene loop and released. By pulling the Prolene loop upward through the angiocatheter sheath, the entrapped 0-0 Vicryl suture is then retrieved from the abdomen. After the angiocatheter sheath is removed, the two ends of the suture can be tied.

Closure of the Skin

The skin of all 10-mm port sites is closed with subcuticular 4-0 absorbable suture. Adhesive strips are applied to all port sites to close (for incisions <10 mm) or to further approximate (for incisions ≥10 mm) the skin. As an alternative, the skin can be closed using octylcyanoacrylate glue. This has been found to speed closure time and provide an equivalent cosmetic result compared with suturing (Sebesta and Bishoff, 2004).

KEY POINTS: PERFORMING THE PROCEDURE

- A checklist ensuring that all essential equipment is present and operational should be completed just before initiating the pneumoperitoneum. Additional items to check when using the da Vinci Robotic System include ensuring that all plugs for the console, vision cart, and patient-side cart are plugged into different circuits and that all cables connecting these carts are connected properly.
- After placement of the Veress needle, insufflation should never be initiated unless all of the signs for proper peritoneal entry (negative aspiration, easy irrigation of saline, negative aspiration of saline, positive drop test result, and normal advancement test) have been confirmed.
- The open technique is recommended specifically when extensive adhesions are anticipated.
- Noncutting dilating trocars have superseded bladed trocars because they are safer. These trocars enter the abdomen by spreading the abdominal wall musculature, rather than cutting it, and therefore there is less chance of injuring an abdominal wall vessel and the resulting entry site is less prone to subsequent herniation.

PHYSIOLOGIC CONSIDERATIONS IN THE ADULT

The rapidly expanding number of newly developed laparoscopic and robotic procedures in operative urology has resulted in an increasing need for urologists to familiarize themselves with both the physiology and the potential complications related to the pneumoperitoneum and patient positioning.

Choice of Insufflant

Carbon Dioxide

CO₂ is the most commonly used insufflant for laparoscopic surgery and is favored by most laparoscopists thanks to its properties (colorless, noncombustible, very soluble in blood, and inexpensive). Prolonged postoperative distention of the abdomen does not occur because CO₂ is quickly absorbed (Wolf and Stoller, 1994). It is highly soluble in water and easily diffuses in body tissues. It readily moves out of the peritoneal cavity, as a result of a high diffusion gradient caused by the difference in concentration of CO₂ between the intraperitoneal space and the surrounding components (e.g., blood). However, the characteristic of rapid absorption, which lessens the chance of a CO₂ gas embolus, may also lead to potential problems (e.g., hypercapnia, hypercarbia, associated cardiac arrhythmias). In particular, patients with COPD may not be able to compensate for the absorbed CO₂ by increased ventilation; this may result in dangerously elevated levels of CO₂ in these patients, thereby necessitating the direct testing of arterial blood gases during laparoscopy in the pulmonary compromised



Figure 10-29. Carter-Thomason device. Cone and needle-point single-action grasper in open position.

patient. Carbon dioxide also stimulates the sympathetic nervous system, which results in an increase in heart rate, cardiac contractility, and vascular resistance. Lastly, CO₂ is also stored in various body compartments (e.g., viscera, bones, muscles). After prolonged laparoscopic procedures it may take hours before the patient has eliminated the extra CO₂ that has accumulated in these storage areas; again, this is more often the case and a problem in patients with pulmonary compromise (Lewis et al, 1972; Puri and Singh, 1992; Tolksdorf et al, 1992; Wolf and Stoller, 1994). Therefore, as previously noted, all patients, and in particular those with pulmonary disease, must be closely monitored after a lengthy laparoscopic procedure for possible signs or symptoms of hypercarbia; indeed, their greatest chance of compromise as a result of hypercarbia may occur after extubation in the postanesthesia recovery room.

Alternative Gases

Nitrous oxide is less irritating to the peritoneum and causes fewer acid-base changes and cardiovascular adverse effects (e.g., arrhythmias) than CO₂ (Scott and Julian, 1972; El-Minawi et al, 1981; Minoli et al, 1982; Sharp et al, 1982). However, some studies have shown that nitrous oxide insufflation reduces cardiac output and increases mean arterial pressure, heart rate, and central venous pressure (Marshall et al, 1972; Shulman and Aronson, 1984). Because nitrous oxide supports combustion, it can be used only during laparoscopic procedures that do not involve the use of electro-surgical instruments.

Helium is an inert and noncombustible insufflant. Initial studies performed in various animal models showed favorable effects on arterial partial pressure of CO₂ and pH with **no evidence of hypercarbia** (Fitzgerald et al, 1992; Leighton et al, 1993; Rademaker et al, 1995). These results were corroborated by clinical studies (Bongard et al, 1991; Fitzgerald et al, 1992; Leighton et al, 1993; Neuberger et al, 1994; Rademaker et al, 1995; Jacobi et al, 1997). Therefore, helium is particularly useful for the patient with pulmonary disease in whom hypercarbia would be poorly tolerated. In a relatively recent study from Johns Hopkins University, 10 patients at high risk for hypercarbia underwent laparoscopic renal surgery with helium insufflation. These patients were successfully managed, with only one patient developing an end-tidal CO₂ over 45 mm Hg (Makarov et al, 2007). Likewise, if hypercarbia develops during a laparoscopic procedure with CO₂, rather than aborting the procedure or converting to an open approach the surgeon can change the insufflant to helium and usually salvage the case (Brackman et al, 2003). There is also evidence that the use of helium may cause a decrease in tumor cell growth and inflammatory reactions within the peritoneal cavity (Jacobi et al, 1997, 1999; Dahn et al, 2005). Helium insufflation can be used for laparoscopic procedures (e.g., cholecystectomy, appendectomy, hernia repair) performed with local and regional anesthesia in high-risk patients, not only because of its favorable metabolic features, but also because of its lack of peritoneal irritation and its association with decreased postoperative pain (Crabtree and Fishman, 1999). However, laparoscopists have to bear in mind that helium may be associated with a higher risk of gas embolism because of its **lower blood solubility**. When helium is going to be used, it is advised to initially obtain the pneumoperitoneum with CO₂ and then change to helium, thereby lowering the chances of a helium gas embolus. Also, helium is significantly more expensive than CO₂. Lastly, with use of helium a separate “yoke” (i.e., line from the gas tank to the insufflator) is needed; accordingly, one needs to make sure that a “helium yoke” is available in the operating room or make arrangements to have one provided when performing laparoscopy on patients with severe pulmonary compromise. In practice, the use of helium may be quite difficult; however, argon may also be used in circumstances when hypercarbia occurs. Indeed, the gas from the argon beam coagulator can be used to maintain the pneumoperitoneum. However, with argon being an inert gas, like helium, the same precautions apply (Badger et al, 2008).

Other insufflants (e.g., room air, oxygen) have been used to establish a pneumoperitoneum in the past. However, possible

serious side effects (e.g., air embolus, intra-abdominal explosion, combustion with oxygen and room air) have terminated their clinical use. Other options for insufflants include some of the other noble gases (e.g., xenon, argon, and krypton), which are inert and nonflammable; however, their widespread clinical use has not been adopted because of their high cost and poor solubility in blood.

Choice of Pneumoperitoneum Pressure

Overall, the most commonly selected pressure for performing laparoscopy is 15 mm Hg; however, recent studies support a pressure of 12 mm Hg as more optimal, because this results in no perturbations in cardiac parameters (i.e., no change in stroke volume) versus a pressure of 15 mm Hg (Mertens zur Borg et al, 2004). Working at lower pneumoperitoneum pressures has also been found to reduce postoperative pain (Sarli et al, 2000). Using an even lower working pressure of 10 mm Hg has been shown to result in a marked reduction in oliguria (McDougall et al, 1994), but this is likely at the expense of smaller working space. Conversely, a pressure of 20 mm Hg has been noted to produce a 22% increase in insufflant filling volume and possibly less venous bleeding during the procedure (Adams et al, 1999). However, the absolute benefit of increased insufflant filling is debatable; McDougall and colleagues (1994) noted that, despite the increased volume, there was only a very small increase in abdominal girth at higher pressures.

Various cardiovascular, renal, and respiratory effects seen during different intra-abdominal pressures in the supine state are summarized in Table 10-2. It is of note that these physiologic parameters may be further altered (i.e., overridden or reversed) owing to the health of the individual patient and to changes in the patient's position.

Cardiovascular Effects of the Pneumoperitoneum

Venous Flow

Animal studies have shown that the effects of the pneumoperitoneum on venous return depend on atrial pressures, which, in turn, are a reflection of the hydration state of the subject (Ivankovich et al, 1975; Diamant et al, 1978; Kashtan et al, 1981). If atrial pressures are low (normal or hypovolemic state), then, during a pneumoperitoneum of up to 20 mm Hg, venous return is reduced owing to increased compression of the vena cava from the pneumoperitoneum. If atrial pressures are high (hypervolemic state), the vena cava resists elevated intra-abdominal pressure and venous return is actually enhanced. However, these principles apply only to an intra-abdominal pressure of up to 20 mm Hg. By further increasing pneumoperitoneum pressures, especially to 40 mm Hg and above, capacitance vessels are collapsed, vascular resistance increases, blood flow decreases markedly, and venous return is significantly reduced. Lower extremity venous return is also reduced by elevated intra-abdominal pressures. Reduced venous blood flow in the lower extremities could facilitate deep vein thrombosis; however, this remains a rare clinical complication of laparoscopy (Jorgensen et al, 1993).

These pathophysiologic insights, gained through animal experiments, have been corroborated by clinical studies (Kelman et al, 1972; Motew et al, 1973; Lee, 1975; Jorgensen et al, 1993). As a result of these trials, intra-abdominal pressures during laparoscopy should not be allowed to exceed 20 mm Hg over extended periods (Arthur, 1970; Seed et al, 1970; Lee, 1975), and a working pressure of 10 to 12 mm Hg is recommended.

Cardiac Arrhythmias

Tachycardia and ventricular extrasystoles may be seen as results of hypercapnia (Scott and Julian, 1972). Peritoneal irritation may lead to vagal stimulation and subsequently to bradyarrhythmias (Doyle and Mark, 1989). Also, dysrhythmias can serve as clinical warning signs for the occurrence of pneumothorax, hypoxia, and gas embolism (Wolf and Stoller, 1994).

TABLE 10-2 Pressure Effects: 5, 10, 20, and 40 mm Hg

EFFECTS	5 mm Hg	10 mm Hg	20 mm Hg	40 mm Hg
CARDIOVASCULAR				
Heart rate	↑	↑	↑	↓
Mean arterial pressure	↑	↑	↑	↑
Systemic vascular resistance	↑	↑	↑	↑
Venous return	→/↓	↓ ↑	↓ ↑	↓
Cardiac output	→/↓	→/↑	→/↓	↓
RENAL				
Glomerular filtration rate	→	↓	↓ ↓	↓ ↓
Urine output	→	↓	↓ ↓	↓ ↓
RESPIRATORY				
End-tidal CO ₂	→	→/↑	→/↑	↑
PCO ₂	→	↑	↑	↑
Arterial pH	→	→/↓	↓	↓

CO₂, carbon dioxide; PCO₂, partial pressure of carbon dioxide.

Unreliability of Central Venous Pressure Readings

As previously noted, intravenous pressures may actually rise with low intra-abdominal pressures. In addition, increasing intra-abdominal pressures may artificially elevate central venous pressure readings owing to an increase in intrathoracic pressure. Therefore, it is important for the anesthetist *not* to rely on central venous pressure readings for any clinical decision making.

Respiratory Effects of the Pneumoperitoneum

Pressure-Mediated Effects

Owing to increased intra-abdominal pressure, diaphragmatic motion is limited. Pulmonary dead space remains unchanged, but functional reserve capacity decreases (Wolf and Stoller, 1994). The average peak airway pressure needed to keep up a constant tidal volume increases parallel to the increasing intra-abdominal pressure (Alexander et al, 1969; Motew et al, 1973; Wolf and Stoller, 1994).

Although usually not of great clinical importance in a healthy patient population, it is advisable to use positive end-expiratory pressure techniques when patients with lung disease undergo general anesthesia for a laparoscopic procedure (Ekman et al, 1988; Wolf and Stoller, 1994; Hazebroek et al, 2002).

Non-Pressure-Related Respiratory Effects

The head-down position, commonly used in laparoscopic procedures, has an adverse effect on respiration. It elevates the diaphragm and decreases vital capacity. It can also lead to a dislocation of the endotracheal tube that, in turn, may cause right main bronchus intubation. Although of little clinical significance in healthy patients, the head-down position may cause pulmonary edema in patients with increased left-sided heart pressures (Prentice and Martin, 1987). Also, during lengthy procedures performed with the patient in the head-down position, it is useful to limit fluid administration if possible because it will minimize facial swelling postoperatively.

Renal Effects of the Pneumoperitoneum

Increased intra-abdominal pressure was found to be associated with a significant decrease in urinary output. A number of investigators, with the oldest study dating back to 1923, have observed **oliguria** and anuria associated with an ongoing increase in intra-abdominal pressure (Thorington and Schmidt, 1923; Harmann

et al, 1982; Richards et al, 1983). Decreased renal vein blood flow and direct renal parenchymal compression, rather than marked hormonal changes or ureteral compression, have been shown to be the likely reasons for the oliguric state (Chiu et al, 1994; McDougall et al, 1996). Of interest, renal cortical blood flow decreases with increasing intra-abdominal pressures, whereas renal medullary blood flow increases up to pressures of 20 mm Hg; above this level, medullary blood flow also decreases (Chiu et al, 1994).

In general, if one desires to avoid an oliguric state during a laparoscopic procedure, a pressure of 10 mm Hg or less is recommended. In addition, clinically the use of furosemide (Lasix), mannitol (12.5 to 25 g), and dopamine at 2 µg/kg/min can help to overcome oliguria. With this regimen and judicious fluid administration, the patient can usually be maintained with a urine output in excess of 100 mL/hr. The key is to use these pharmaceutical modalities in lieu of excessive hydration and fluid boluses (Perez et al, 2002), which may lead to significant fluid overload and edema.

Effects of the Pneumoperitoneum on Mesenteric Blood Flow and Intestinal Motility

Decreased blood flow during laparoscopic procedures was found not only in the kidney, but also in mesenteric vessels and other organs (e.g., liver, pancreas, stomach, spleen, small and large intestines) (Caldwell and Ricotta, 1987; Ishizaki et al, 1993; Hashikura et al, 1994). This may rarely lead to mesenteric thrombosis with catastrophic results. This complication may take days to develop (Schorr, 1998).

Open, incisional abdominal surgery usually results in some postoperative impairment of gastric and intestinal emptying owing to intestinal paralysis (physiologic ileus) (Kemen et al, 1991). It is interesting to note that clinical observation and studies undertaken during laparoscopic and open surgical cholecystectomy have shown that laparoscopic surgery causes less significant disturbances of the gastrointestinal motility pattern, therefore resulting in no or less postoperative physiologic ileus than occurs with open surgery (Sezeur et al, 1993; Halevy et al, 1994). The exact mechanisms responsible for this difference have yet to be defined; however, it is postulated that perhaps it is related to the hypercarbia (Aneman et al, 2000). In addition, intestinal perfusion does not change significantly during prolonged pneumoperitoneum at a pressure of 15 mm Hg with CO₂ or helium (Goitein et al, 2005); however, at least in the rat model, there does seem to be an increase in bacterial translocation that is proportional to the pneumoperitoneum pressure (Sukhotnik et al, 2006).

Also, despite the increased intra-abdominal pressures associated with laparoscopy, there has been no increased incidence of gastroesophageal reflux and regurgitation in patients undergoing laparoscopic procedures (Schippers et al, 1992).

Acid-Base Metabolic Effects of Pneumoperitoneum

Animal and human studies have demonstrated that prolonged laparoscopic procedures may result in hypercarbia and respiratory acidosis (Motew et al, 1973). Because there is no increase in ventilatory dead space during laparoscopy, the resulting respiratory acidosis has been attributed to transperitoneal absorption of CO₂ during establishment and maintenance of the pneumoperitoneum (Motew et al, 1973; Leighton et al, 1993). Although the resulting mild respiratory acidosis does not adversely affect otherwise normal patients and can be corrected by increasing the minute ventilation, increased absorption of CO₂ can become dangerous in patients with COPD owing to their impaired ability to release pulmonary CO₂. To ensure proper monitoring of acid-base status, intermittent arterial blood gas sampling should be performed in patients with COPD, during any laparoscopic procedure that requires more than 1 hour of CO₂ insufflation; also in patients with COPD, arterial blood gas sampling should continue in the postanesthesia recovery area because after extubation these patients may be at risk of significant hypercarbia owing to subsequent mobilization of procedurally absorbed CO₂.

The potential for developing hypercarbia exists during both transperitoneal and preperitoneal laparoscopy. Carbon dioxide is absorbed from the peritoneal membrane during transperitoneal laparoscopy and from preperitoneal adipose and connective tissue during retroperitoneoscopy and extraperitoneoscopy (Collins, 1981). Others have also implicated the disrupted microvascular and lymphatic channels for CO₂ absorption during preperitoneal laparoscopy (Glascok et al, 1996). Several studies have demonstrated that CO₂ absorption during either transperitoneal or retroperitoneal laparoscopy increases significantly during the initial 30 to 60 minutes of the procedure and reaches a steady-state plateau thereafter (Wolf et al, 1995; Ng et al, 1999). Which one of the two approaches is associated with greater CO₂ absorption remains a debated issue. Although some studies have demonstrated greater absorption during transperitoneal laparoscopy (Giebler et al, 1997), others have demonstrated greater absorption during retroperitoneal laparoscopy using a standard Hasson cannula (Wolf et al, 1995). However, in another study, no significant clinical difference was seen (Ng et al, 1999), provided a balloon tip-type cannula was used that tightly sealed the site of entry between the balloon and soft cuff carried on the shaft of the cannula.

Although transperitoneal and retroperitoneoscopic approaches are routinely used safely at numerous centers worldwide, vigilant perioperative anesthetic management is essential to prevent the development of potential complications related to CO₂ buildup, particularly in patients with preexisting airway and cardiovascular compromise. End-tidal CO₂ and O₂ saturation should be monitored intraoperatively with a capnometer. Furthermore, arterial blood gases are obtained during prolonged laparoscopic procedures and in patients with increased risk of developing hypercarbia (owing to airway disease, renal failure, congestive heart failure, or advanced age). A rise in end-tidal CO₂ should prompt the anesthesiologist to adjust the respiratory rate and tidal volume to enhance CO₂ elimination. Simultaneously, the surgeon should decrease the insufflation pressure of CO₂ or, if necessary, desufflate the abdomen until the hypercarbia has resolved.

Hemodynamic Effects Related to Patient Position and Type of Approach

Several animal and human studies have examined hemodynamic changes resulting from different surgical positions during laparoscopy (Kelman et al, 1972; Joris et al, 1993; Williams and Murr,

1993). In the supine position, cardiac output remains unchanged or decreases when intra-abdominal pressures are less than 15 mm Hg, whereas mean arterial pressure (MAP) and systemic vascular resistance increase (Pearle, 1996). If pneumoperitoneum pressures are increased beyond 20 mm Hg, cardiac output is reduced because of decreasing venous return and hence MAP decreases. Alternatively, in the head-up position, heart rate increases, MAP decreases, systemic vascular resistance increases, and cardiac output decreases. In the head-down position, heart rate drops, MAP rises, systemic vascular resistance falls, and cardiac output increases (Pearle, 1996). These results have also been shown to hold true in steep Trendelenburg position used for laparoscopic and robotic radical prostatectomy (Falabella et al, 2007). The head-down position seems to be favorable for the laparoscopy patient owing to higher cardiac output caused by increased venous return.

There is some evidence that the extraperitoneal approach may be beneficial with regard to hemodynamic effects compared with transperitoneal laparoscopy. Giebler and coworkers (1997) demonstrated that transperitoneal laparoscopy was associated with more pronounced changes in cardiac output ($P = .001$), pulmonary artery pressure ($P = .007$), central venous pressure ($P = .001$), iliac venous pressure ($P = .001$), and inferior vena caval pressure gradient ($P = .00001$) as compared with retroperitoneal laparoscopy. With regard to pelvic laparoscopy, Meininger and associates (2004) compared the effects of prolonged intraperitoneal and extraperitoneal CO₂ insufflation on hemodynamics and gas exchange. With both insufflation methods, arterial CO₂ pressure increased rapidly, reaching higher levels with extraperitoneal insufflation. Therefore patients managed with extraperitoneal insufflation required significantly higher minute ventilation. Heart rate and central venous pressure increased in both groups, whereas mean arterial blood pressure and pH decreased in both groups.

Hormonal and Metabolic Effects during Laparoscopic Surgery

As in other surgical procedures, several hormones (e.g., β -endorphin, cortisol, prolactin, epinephrine, norepinephrine, dopamine) have been noted to increase during laparoscopic surgery as a response to tissue manipulation, intraoperative trauma, and postoperative pain (Cooper et al, 1982; Lehtinen et al, 1987; Lefebvre et al, 1992). The clinical significance of increased serum arginine vasopressin levels seen in open surgery and in response to intraperitoneal insufflation during laparoscopy remains unexplained (Cochrane et al, 1981; Melville et al, 1985; Solis Herruzo et al, 1989).

Several adverse metabolic changes observed during open cholecystectomy are less pronounced with laparoscopic cholecystectomy: (1) reduced postoperative plasma glucose elevation, (2) less decrease in insulin sensitivity, and (3) reduced hepatic stress response (Thorell et al, 1993; Jakeways et al, 1994; Glerup et al, 1995).

One important feature of the catabolic response is a complex intra-organ shift of nitrogen; this reaction has been best characterized in the liver (Glerup et al, 1995). The conversion of amino acids to urea by the liver is much higher after open cholecystectomy than it is after laparoscopic cholecystectomy. Hence, the catabolic reaction of the body is decreased with a laparoscopic versus an open approach (Fischer, 1995). Indeed, in the laparoscopic patient, the reduced postoperative hepatic catabolic stress associated with reduced tissue loss of amino-nitrogen may, in some way, be responsible for the more rapid convalescence that is the hallmark of laparoscopy in general. Lastly, catabolic responses, in the form of released cytokines and opioids, resulting from augmented neurohumoral stimuli caused by incisional tissue trauma may also be lessened with a laparoscopic approach (Fischer, 1995).

Immunologic Effects of Laparoscopic Surgery

A number of animal and clinical studies measuring a wide spectrum of inflammatory response mediators (e.g., C-reactive protein,

interleukin-6) and other markers of cellular immune functions (pan-T cells [CD3], helper T cells [CD4], suppressor cells [CD8], and natural killer cells [CD16]); delayed-type hypersensitivity skin tests; serial phytohemagglutinin-induced T-cell proliferation) have suggested that laparoscopic procedures in general result in less immunosuppression than do their open counterparts (Kloosterman et al, 1994; Trokel et al, 1994; Cristaldi et al, 1997; Karayiannakis et al, 1997; Nguyen et al, 1999; Bolla and Tuzzato, 2003). This may also play a role in hastening convalescence after laparoscopic procedures. Some data have suggested that the CO₂ pneumoperitoneum in and of itself, as opposed to exposure of tissues to room air, results in a more favorable immunologic state (Watson et al, 1995). Also, experimental evidence shows that less tumor cell growth occurs after laparoscopic procedures than after open procedures (Bouvy et al, 1997). Although these data are intriguing, further well-designed, prospectively randomized clinical studies are needed to compare immunologic responses after laparoscopic versus open surgical procedures for urologic cancer. Indeed, in a study by Landman and colleagues (2004) there was no discernible difference in immunologic parameters between patients undergoing open or transperitoneal laparoscopic radical or total nephrectomy for renal cancer. Ultimately, whether a decrease in inflammatory response mediators and improved postlaparoscopic immune status will translate into a better long-term prognosis for patients with urologic cancers remains to be determined.

KEY POINTS: PHYSIOLOGIC CONSIDERATIONS IN THE ADULT

- Carbon dioxide is the most commonly used insufflant because it is noncombustible and rapidly absorbed in the blood.
- Helium is particularly useful for the patient with pulmonary disease in whom hypercarbia would be poorly tolerated.
- Intra-abdominal pressures during laparoscopy should not be allowed to exceed 20 mm Hg over extended periods, and a working pressure of 10 to 12 mm Hg is recommended.

COMPLICATIONS AND TROUBLESHOOTING IN LAPAROSCOPIC AND ROBOTIC SURGERY

Historically, in large series the overall incidence of laparoscopic complications in urology has been in the range of 4% and mortality has been distinctly unusual, with a rate of 0.03% to 0.08% (Mintz 1977; Winfield et al, 1991; Fahlenkamp et al, 1999). More contemporary series demonstrate a complication rate in the range of 13% to 22% (Table 10-3) (Vallancien et al, 2002; Parsons et al,

2004; Permpongkosol et al, 2007), likely representative of the introduction of new, more sophisticated laparoscopic procedures and more widespread use of laparoscopy. Vascular followed by adjacent organ injuries are the most common complications (Permpongkosol et al, 2007; Breda et al, 2009). The following section covers the myriad complications that can occur with any laparoscopic or robotic procedure. Recognition, resolution, and prevention of these various problems are discussed.

Minimizing the Incidence of Complications during the Learning Curve

Early in one's experience with laparoscopic and robotic surgery, it is wise to first apply this approach to low-risk surgical candidates of normal body habitus. In addition, it is advisable and recommended by many laparoscopic organizations, as well as by hospital credentialing boards, that the neophyte minimally invasive surgeon seek training in three arenas: (1) in-depth instructional courses, including didactic, "live-case" transmissions and "hands-on" laboratory sessions; (2) preceptor training in which the surgeon-in-training views five or more procedures being done by an already skillful laparoscopic or robotic surgeon; and (3) a mentoring experience, during which a trained laparoscopic or robotic surgeon oversees the initial procedures performed by the surgeon-in-training (Society of American Gastrointestinal and Endoscopic Surgeons, 2010). Further training can be obtained through self-teaching using videotapes, a laparoscopic box trainer, and virtual reality (VR) simulators. A laparoscopic box trainer is extremely helpful for developing one's sense of laparoscopic proprioception and for becoming facile with laparoscopic suturing and knot tying. Data have clearly shown benefits for individuals who have taken the time to practice their laparoscopic skills using a box trainer in all areas of laparoscopy (cutting, clipping, and suturing) compared with individuals who had no such training (Derossis et al, 1998). Similarly, participation in a 1-week mini-residency has been found to increase the likelihood that participants would perform more complex laparoscopic procedures (81% of participants) (Corica et al, 2006). In addition, VR simulators have been shown to improve the operative performance of surgical trainees with limited laparoscopic experience when compared with no training or with box-trainer training (Nagendran et al, 2013).

Aside from training in the basic psychomotor skills, neophyte minimally invasive surgeons must be educated with regard to prevention, recognition, and appropriate treatment of complications.

General Procedural Complications

Malfunction of Equipment

A successful outcome of any laparoscopic or robotic procedure depends not only on the psychomotor technical skills of the surgeon, but also on a proper working knowledge of all the equipment involved in performing these procedures. To ensure undisturbed functioning of all technology, the surgeon must be supported by well-trained staff who are capable not only of quickly recognizing any equipment malfunction, but also of providing an immediate, adequate response to correct problems. In this regard, the Society of American Gastrointestinal Endoscopic Surgeons has issued a troubleshooting guide for video and electronic failure. For integrated operating room systems offered by most major equipment manufacturers and the da Vinci Robotic System, the surgeon and operating room staff need to receive in-depth training on the system's operation, capabilities, and limitations. In this way, equipment failure will be minimized. In addition, the contact information for both the equipment vendor's troubleshooting experts and any in-house support should be readily available.

With regard to the da Vinci Robotic System, equipment malfunction is rare. In a review of 11 institutions with a total of 8240 cases reviewed, the overall incidence of malfunction was 0.4%. Of the 34 cases with malfunction, 24 cases were canceled before the

TABLE 10-3 Major Complications of Transperitoneal Abdominal Surgery

TOTAL PROCEDURES	894* (100% ABDOMINAL)	1311† (84% PELVIC)
Overall complications	13.2%	22.6%
Intraoperative/postoperative	5.7%/7.5%	3.6%/19%
Death	0.2%	0%
Vascular injury	2.8%	0.5%
Bowel injury	1.1%	1.2%
Adjacent organ injury	1.1%	0.8%
Conversion rate	1.7%	1.7%

*Data from Parsons JK, Varkarakis I, Rha KH, et al. Complications of abdominal urologic laparoscopy: longitudinal five-year analysis. *Urology* 2004;63:27–32.

†Data from Vallancien G, Cathelineau X, Baumert H, et al. Complications of transperitoneal laparoscopic surgery in urology: review of 1,311 procedures at a single center. *J Urol* 2002;168:23–6.

procedure, 2 cases were converted to laparoscopic procedures, and 8 were converted to open surgery (Lavery et al, 2008).

Complications Related to Obtaining the Pneumoperitoneum

Complications Associated with Closed Access (Veress Needle Placement)

Preperitoneal Placement. Preperitoneal placement of the Veress needle may preclude successful trocar placement. If not recognized early, 1 to 2 L of CO₂ may be instilled, and once this much CO₂ has been insufflated into the preperitoneal space, many signs indicative of correct intraperitoneal insufflation may be present (e.g., distention, tympanic sound on percussion) thereby misleading the surgeon until the first trocar is placed. **The first sign of preperitoneal insufflation is that there may be a steep rise in pressure with only 500 mL of CO₂; plus, if more CO₂ is instilled, unequal distention of the abdomen occurs.** If this early sign is missed, then the laparoscope reveals only fat after trocar placement; the intraperitoneal viscera are not seen.

The next step is to evacuate the CO₂ through the sidearm of the trocar and proceed with an open insertion technique. The initial incision can be widened, and the peritoneal surface can be grasped with a pair of Allis clamps and incised. A Hasson cannula is placed and the peritoneal cavity is insufflated.

Several steps can be taken to avoid this complication. First, if the Veress needle is preperitoneal on initial insufflation, pressures are usually higher than the maximal initial allowable pressure of 10 mm. Second, if the Veress needle is preperitoneal, it cannot be easily advanced 1 cm deeper without resistance. If one has truly entered the peritoneal cavity properly, the Veress needle should be able to be moved 0.5 to 1 cm deeper without meeting any resistance.

Vascular Injuries. During initial placement of the Veress needle at the umbilicus, minor or major intra-abdominal blood vessels may be punctured by the 14-gauge needle. The first sign of intravascular entry is blood appearing in the hub of the needle. Aspiration results in additional blood filling the syringe. As long as the needle has not been manipulated, it can usually be withdrawn without excessive bleeding. An alternative site for Veress needle placement or open cannula insertion should be used at this point. On proper entry into the peritoneal cavity and establishment of a pneumoperitoneum, it is important that the path of the initial Veress needle passage be traced. The prior site of the Veress needle passage should be carefully inspected at a pressure of 5 mm Hg. Any site of bleeding can be expeditiously treated by applying gentle pressure and the application of a surgical hemostatic agent as needed.

To prevent this problem it is important when using an umbilical approach to direct the Veress needle toward the pelvis. One technique to help prevent this problem, when using an umbilical access, is to pass the Veress needle after making a 12-mm incision, bluntly spreading the subcutaneous fat, and grasping and stabilizing the anterior fascia with a pair of Allis clamps. These maneuvers become especially important in children, who have less space between intra-abdominal structures and the abdominal wall.

Surgeons should also be cognizant that any hemodynamic instability associated with loss of "working space" within the abdomen during the procedure might represent an expanding "unseen" retroperitoneal hematoma from unrecognized Veress needle injury.

Prevention of vascular complications can be further achieved by using a nonumbilical site for Veress needle passage (i.e., just superior and medial to the iliac crest or subcostal in the midclavicular line) where no major vessels are placed in danger.

Visceral Injuries. During Veress needle placement, intra-abdominal organs may be punctured. The initial signs of this complication consist of aspiration of blood, urine, or bowel contents through the Veress needle or, in the case of a solid organ, high pressures on initial insufflation.

Management consists of simply removing the Veress needle. The Veress needle may then be reintroduced at a different site, or an open Hasson technique can be used through a separate incision site. On entry into the abdomen, any bleeding site on the liver or spleen

can be treated with gentle pressure, an argon beam coagulator, or the application of a surgical hemostatic agent as needed. General surgical consultation should be sought in those cases in which there is difficulty achieving hemostasis.

Bowel or bladder entry by the Veress needle needs no further treatment other than needle withdrawal. Placing a nasogastric tube and a transurethral indwelling bladder catheter to decompress the stomach and bladder, respectively, before Veress needle passage can help to prevent these problems.

Complications during Open Access (Hasson Technique). Potential problems associated with open access are similar to, albeit less frequent than, problems associated with a closed Veress needle access. The principal risk with the open access is injury to underlying viscera while traversing the peritoneum. In a densely scarred abdomen, the bowel may be adherent to the underside of the abdominal wall and hence may still be injured. If a bowel injury is recognized early, it can often be repaired through the same incision that was made for insertion of the Hasson cannula. Although vascular injury with this approach is distinctly rare, the surgeon must realize that even with open access this devastating complication can occur (Hanney et al, 1999).

Complications Related to Insufflation and Pneumoperitoneum

Bowel Insufflation. If entry into the bowel is not recognized at the time of irrigation and aspiration through the Veress needle, then the surgeon may well insufflate the small or large bowel. **The first sign of this problem is asymmetrical abdominal distention followed by flatus and insufflation of only a small amount of CO₂ (<2 L) before high pressures are reached.**

If this complication is suspected, then the insufflation line should be disconnected; the outflow of gas will immediately confirm bowel entry. The needle can be withdrawn, and open access cannula placement should be done at a different abdominal site. Prevention of this problem is ensured if one properly performs the aspiration, irrigation, and aspiration tests recommended for safe Veress needle placement and if one avoids sites of prior surgery. Alternatively, initial use of open access technique should avoid this complication.

Gas Embolism. Carbon dioxide gas has favorable solubility in blood, as opposed to air, helium, or nitrous oxide; however, use of CO₂ may still result in a gas embolus. The most common cause of CO₂ embolism is puncture of a blood vessel or organ with the Veress needle, followed by insufflation; this can occur only when the surgeon has ignored the previously described tests for proper entry into the peritoneal cavity. The first sign of intravascular insufflation is acute cardiovascular collapse. Other signs include dysrhythmias, tachycardia, cyanosis, and pulmonary edema. **The dysrhythmias is usually made by the anesthesiologist based on an abrupt increase of end-tidal CO₂ accompanied by a sudden decline in oxygen saturation and then a marked decrease in end-tidal CO₂ (Loris, 1994).** Sometimes, a "millwheel" precordial murmur can be auscultated (Keith et al, 1974). In addition, the anesthesiologist may notice foaming of a blood sample, if drawn, as a result of the presence of insufflated CO₂.

The treatment is immediate cessation of insufflation and prompt desufflation of the peritoneal cavity. The patient, if at all possible, is turned to a left lateral decubitus (i.e., right side up), head-down position in hopes of minimizing right ventricular outflow problems and forcing the air embolus to rise into the apex of the right ventricle. The patient is hyperventilated with 100% oxygen. Advancement of a central venous line into the right side of the heart with subsequent attempts to aspirate gas may rarely be helpful. The use of hyperbaric oxygen and cardiopulmonary bypass have also been reported (McGrath et al, 1989; Diakun, 1991; Abdel-Meguid and Gomella, 1996).

This devastating complication can be precluded by meticulous attention to Veress needle and initial trocar placement and performance of each of the recommended tests for intraperitoneal

entry. Insufflation should never be initiated if the surgeon has even the slightest doubt about correct positioning of the Veress needle; instead, the surgeon should withdraw the Veress needle and pass it at an alternate site or should immediately proceed with open access.

Barotrauma. Prolonged elevated pressures (>15 mm Hg) may result in barotrauma (McGrath et al, 1989; Diakun, 1991; Abdel-Meguid and Gomella, 1996). Prolonged high pressures may be caused by insufficient and infrequent monitoring of CO₂ pressure, malfunction of the insufflator, or additional pressures produced by auxiliary devices (e.g., argon beam coagulator, CO₂-cooled laser). Furthermore, barotrauma may be caused by ventilation techniques using positive end-expiratory pressure resulting in rupture of a pulmonary bleb or bulla.

The initial sign of barotrauma may be hypotension caused by decreased cardiac output, secondary to an acute drop in venous return caused by compression of the vena cava. Also, a pneumothorax or pneumomediastinum may develop because of the high ventilation pressures. In addition, increased intra-abdominal pressures may exacerbate a hiatal hernia.

The anesthesiologist, who will notice an increase in ventilation pressures, usually alerts the surgeon to excessive intra-abdominal pressure. The surgeon should desufflate the abdomen and, once the hemodynamic changes have been reversed, reinitiate the pneumoperitoneum at 10 mm Hg. Any malfunctioning insufflator should be replaced. Also, if one is using an argon beam coagulator or a CO₂-cooled laser device, the sidearm on one port should be left open to allow excess high-pressure gas to escape while the device is being activated.

Barotrauma secondary to insufflator malfunction can be avoided by routinely troubleshooting the insufflator before every case.

Subcutaneous Emphysema. Subcutaneous emphysema develops owing to improper placement of the Veress needle or, more commonly, to leakage of CO₂ around ports. The latter situation occurs when a secure seal around the Hasson cannula is not obtained, port site incisions are too large, the procedure is particularly lengthy, or high intra-abdominal pressures are used. The pathognomonic sign is crepitus over the abdomen and thorax; in male patients, a pneumoscrotum may also develop.

If the problem is caused by improper placement of the Veress needle, then withdrawal of the Veress needle and use of the open technique are recommended. If the problem develops intraoperatively, the surgeon should check for gas leakage around a port site, including the Hasson cannula if the open technique was used. If leakage is found, the surgeon can either place a purse-string suture around the port or, preferably, change the trocar to a larger size or switch to a balloon trocar, which creates a tight seal between the intra-abdominal balloon and outer cuff. Also, the surgeon should consider reducing the insufflation pressure. This complication is eminently avoidable if the surgeon adheres to all the diagnostic tests for proper Veress needle placement and ensures all port site incisions are carefully tapered to the size of the port to be placed. In this regard, it is important to place each port so that it is pointing toward the surgical field, to avoid the continued forceful redirection of the port during the procedure that results in widening of the tissue tract around the port and subsequent escape of CO₂ into the surrounding subcutaneous tissues.

Several studies have demonstrated that the incidence of subcutaneous emphysema is higher during retroperitoneal laparoscopy than during transperitoneal laparoscopy, albeit without any clinically significant sequelae (Wolf et al, 1995; Zhao et al, 2008). In any event, the risk of surgical emphysema and other CO₂-related sequelae during retroperitoneoscopic and extraperitoneoscopic surgery can be effectively minimized by working at a lower pressure (i.e., 12 mm Hg vs. 15 mm Hg) (Rassweiler et al, 1998a) and using a balloon trocar to seal the initial entry site (Gill, 1998; Ng et al, 1999).

Pneumomediastinum, Pneumothorax, and Pneumopericardium. Gas leaking along major blood vessels through congenital defects or secondary enlargement of openings in the diaphragm may lead to pneumomediastinum, pneumopericardium, or

pneumothorax (Kalhan et al, 1990; Pascual et al, 1990; See et al, 1993; Abreu et al, 2004; Zhao et al, 2008). Although a pneumomediastinum is usually not associated with specific clinical symptoms, a pneumopericardium may result in impaired cardiac function. The incidence of the pneumopericardium is estimated to be 0.8% (Abreu et al, 2004). The diagnosis is usually made on a chest radiograph taken in the recovery room, except in rare instances when cardiac impairment occurs during the procedure. If there is sudden cardiac decompensation during a procedure, the same maneuvers should be undertaken as described for treatment of a suspected gas embolism, including interruption of the procedure and desufflation of the abdomen. If there is a strong suspicion of pericardial tamponade, pericardiocentesis is indicated.

A pneumothorax may be associated with pneumomediastinum, barotrauma, or direct puncture of the pleural space with a trocar (Doctor and Hussain, 1973; Kalhan et al, 1990; Pascual et al, 1990). The incidence of this complication has been found to be 1.6% to 4.0% (Abreu et al, 2004; Zhao et al, 2008). Like subcutaneous emphysema, the incidence of pneumothorax is more common in retroperitoneal procedures (Zhao et al, 2008). The earliest signs of this problem may be the development of subcutaneous emphysema, especially in the neck and chest area. More ominous signs, such as hypotension and decreased breath sounds with an increase in ventilatory pressure, are indicative of a tension pneumothorax. Although a chest radiograph will confirm the diagnosis, the development of pulmonary collapse with loss of breath sounds on one side mandates immediate decompression of the chest by passage of a 16-gauge needle into the second or third intercostal space in the midclavicular line followed by tube thoracostomy, if a tension pneumothorax is suspected (See et al, 1993).

Prevention of these problems is similar to the means to avoid subcutaneous emphysema: Keep the intra-abdominal pressure preferably at 12 mm Hg, make sure all port site incisions are tight around the laparoscopic cannulae, and make sure all cannulae are well seated in the peritoneal cavity. In addition, all trocars must remain below the 12th rib. While dissecting in the upper quadrants of the abdomen, especially during laparoscopic ablative renal surgery, the surgeon should be aware of the anatomic relationships of the kidneys, adrenal glands, and great vessels to the diaphragm to avoid direct injury.

Complications Related to Initial “Blind” Placement of the First Trocar after Obtaining a Veress Needle Pneumoperitoneum

With the advent of nonbladed trocars (several of which also have clear tips for direct visualization of individual abdominal wall layers during port placement), the likelihood of catastrophic injuries to vital structures has been markedly reduced (Thomas et al, 2003).

Injury to Gastrointestinal Organs. Perforation of the small or large intestine during passage of the primary port is the most common cause of trocar-induced injury of gastrointestinal organs. Other organs (e.g., stomach) are affected much less frequently. Given the lateral positioning of the spleen and liver, injury of these organs with the passage of the primary trocar is distinctly unusual. The first sign that one has entered the bowel depends on whether the injury is through one wall or both walls of the bowel. In the former instance, as soon as the laparoscope is introduced the surgeon sees the mucosal folds of the interior of the bowel. However, with a through-and-through injury the diagnosis is not made until the first secondary trocar is passed; **at that time the surgeon should routinely pass the laparoscope through the secondary port to inspect the puncture site of the initial port.** The trocar will be seen passing completely through both walls of the bowel. If the surgeon fails to perform this maneuver routinely this injury will not be noted until the end of the case when the trocars are being removed, thereby resulting in a broader injury and a prolonged time of intraperitoneal contamination. A missed bowel injury of this nature leads to peritonitis when diagnosed intraoperatively, and possible death when discovered only in the postoperative period.

In the case of a one-wall injury of the bowel, the surgeon can elect to leave the trocar in place and pass a second trocar in another location using an open access technique. On inspection of the abdomen the site of injury to the bowel will be immediately apparent because the initial trocar will still be residing in the bowel. At this time, the surgeon may elect to open and repair the bowel or, if skilled in laparoscopy, may place two more ports and proceed to close the bowel using laparoscopic suturing or stapling techniques. An intraoperative consultation with a general surgeon should be obtained regardless of whether the urologist performs the repair; from a medicolegal and quality of care standpoint, involvement of the general surgeon at the time of the acute event facilitates subsequent care should further complications arise while ensuring the best possible repair of the injury at the time of the acute event.

When the injury to the bowel is a through-and-through injury, it can similarly be repaired with an open or laparoscopic approach. In either case, the abdomen should be irrigated with 4 to 5 L of saline containing an antibiotic solution, and the patient must be placed on broad-spectrum antibiotic coverage.

Perforation of the stomach is distinctly rare; however, to best preclude this problem patients should refrain from oral intake for 12 hours before surgery. The management of this complication is the same as for injury to the bowel, with primary closure and general surgery consultation. In addition, when the stomach is noted to be distended, a nasogastric or orogastric tube should be placed to decompress the stomach and facilitate further trocar insertion.

Injury to Intra-Abdominal Vessels. Major vascular injury is a rare but serious complication, occurring in 0.11% to 2% of cases (Hanney et al, 1995; Geers and Holden, 1996; Usal et al, 1998; Lin and Grow, 1999; Vallancien et al, 2002; Parsons et al, 2004). It is far more common in procedures related to the retroperitoneum, as opposed to pelvic laparoscopy. The aorta and common iliac arteries are most frequently involved. The inferior vena cava is less affected because of its lateral location in relation to the aorta; likewise, the common iliac vein is rarely involved given its posterior position in relation to the common iliac artery. Rarely, in a patient with adhesions or prior surgery, intestinal mesenteric vessels servicing a "fixed" loop of bowel may be injured. In addition, the epigastric vessels are at risk for injury during trocar placement.

The first sign of a major vascular complication is the onset of sudden hypotension and associated tachycardia. If the trocar has not been moved, then, as the obturator is withdrawn, the diagnosis is made immediately based on whether there is a pulsatile (arterial) or nonpulsatile (venous) profuse bleeding from the trocar sheath. If the trocar has been displaced from the injured vessel, then, depending on the vessel injured, when the laparoscope is introduced the surgeon will see blood rapidly accumulating in the abdominal cavity, a mesenteric hematoma, blood dripping from the trocar entry site, or, rarely, blood that preferentially accumulates retroperitoneally, in which case the space within the peritoneal cavity will appear to be markedly reduced and actively decreasing because of the expanding retroperitoneal hematoma.

The response to injury to a major arterial or venous structure must be rapid. A vascular or trauma surgeon should be called to the room. If blood is coming through the trocar, then the trocar should be closed and left in place. An emergency laparotomy is performed, and the trocar is followed to its point of entry into the vessel. The injured vessel should be controlled proximal and distal to the site of trocar injury with vessel loops or bulldog clamps, or alternatively a Satinsky clamp can be placed to isolate the area of injury so that as the trocar is withdrawn the wound can be controlled and repaired quickly. If the injury is discovered at the time of passage of the laparoscope (i.e., the trocar is no longer residing in the vessel), then the sheath and laparoscope can be swung up to the underside of the abdominal wall and an immediate cutdown can be done on top of the laparoscope and sheath, thereby providing for a rapid and safe laparotomy. Alternatively in this situation, the procedure can be converted to a hand-assist approach and the surgeon can then use the intra-abdominal hand to control the bleeding vessel.

BOX 10-3 Contents of Hemorrhage Tray for Laparoscopic Surgery

Laparoscopic Satinsky clamp
Ten-millimeter suction-irrigation tip
Endo Stitch device with 4-0 absorbable suture
Lapra-Ty clip applier and a packet of Lapra-Ty clips
Six-inch length of 4-0 vascular suture on an SH needle with a Lapra-Ty clip preplaced on the end
Two laparoscopic needle drivers
Topical hemostatic agent of choice

The best way to handle this complication is to avoid it completely. In this regard, knowledge of the exact location and possible anatomic variations of major intra-abdominal blood vessels is mandatory. The preoperative computed tomography (CT) scan should be reviewed before operating to look for vena caval or other abnormalities of the great vessels. Because of limited intraperitoneal space, special care must be given to trocar placement in children and very thin adults. It is important to note that several maneuvers can be used to help prevent vascular injury. These include ensuring that all the safety signs of passage of a Veress needle are present before proceeding with trocar passage, obtaining an adequate pneumoperitoneum before trocar passage (intra-abdominal pressure may be raised to 25 mm Hg temporarily for placement of the primary trocar), passing the initial trocar under direct endoscopic control (i.e., optical trocar), using blunt nonbladed trocars, and avoiding initial trocar passage through an abdominal scar.

Furthermore, it is helpful to consider having a "hemorrhage" tray available in the operating room at all times (Box 10-3). This laparoscopic tray should contain a Satinsky clamp, a 10-mm suction tip for large clot evacuation, an Endo Stitch device with 4-0 Vicryl suture, a Lapra-Ty clip applier and a rack of Lapra-Ty clips (six clips per rack), two laparoscopic needle holders, and 4-0 vascular suture. With this tray available, some injuries to major venous structures can be successfully resolved laparoscopically.

Injury to the Urinary Tract. Urinary tract injuries during laparoscopy are most commonly associated with trocar passage, specifically injury to the bladder at the time of initial trocar placement. The incidence varies widely in the gynecologic literature, ranging from 0.02% to 8.3% (Ostrzenski and Ostrzenska, 1998; Lin and Grow, 1999; Soong et al, 2007). Chances of this problem occurring have been greatly reduced by the introduction of blunt trocars.

The initial sign of this problem is pneumaturia or gross hematuria. The diagnosis can be confirmed by retrograde intravesical instillation of indigo carmine diluted with saline; this allows the surgeon to rapidly identify the cystotomy site. The injury can be repaired laparoscopically with laparoscopic suturing techniques; however, extensive defects may require open surgical repair (Ostrzenski and Ostrzenska, 1998). These injuries should always be closed and not left to heal on their own with prolonged Foley catheter drainage.

Prevention of this problem is simple. Preoperative placement of a urethral catheter to drain the bladder is recommended for all major laparoscopic urologic cases. Not only does it largely preclude bladder injury, but it also provides the necessary means for monitoring urine output during major laparoscopic procedures.

Complications Related to Placement of Secondary Trocars

Bleeding at the Sheath Site. Blood dripping from the port entry site and onto the underlying abdominal viscera is the first sign of an injured abdominal wall vessel. The exact site of hemorrhage is determined by cantilevering the trocar into each of the four quadrants and noting which position of the trocar tamponades the bleeding.

Definitive therapy for this problem can be undertaken in one of three ways. The simplest method, albeit the most costly, is the insertion of curved electrosurgical scissors or forceps through another port, which can then be articulated up into the port site to coagulate the bleeding.

The least expensive method is to suture the area of hemorrhage. This can be accomplished by inserting a straight Keith needle with a 0-0 absorbable suture from the outside of the abdomen at one side of the affected quadrant and then grasping the needle with laparoscopic forceps and pushing it back out of the abdomen at the opposite side of the affected quadrant until it can be recovered on the surface of the abdomen (Fig. 10-30). This broad suture is then tied over a gauze 4- × 4-inch bolster on the abdominal surface; the port can be used throughout the procedure. Alternatively, various port closure devices, in particular the Carter-Thomason device, may be used to similarly pass a suture to control the bleeding (Ortega, 1996). Ultimately, at the end of the procedure a device of this nature should be used to definitively close the port site and occlude the injured vessel no matter which of the aforementioned techniques is used.

This problem can often be avoided by routinely transilluminating the abdominal wall, especially in the thin patient, before trocar placement so large surface vessels and overlying peritoneal vessels can be avoided and to help identify the area of the inferior epigastric vessels. In addition, the routine spreading of the subcutaneous tissues at the proposed port site with a blunt clamp (e.g., Kelly clamp) may be helpful, and the use of only blunt trocars has been shown to reduce the chance of vascular wall injury significantly (Bhojru et al, 2000). In particular, a fivefold decrease in epigastric vessel injury has been demonstrated with blunt trocars (reduced incidence from 0.83% to 0.16%) (Hashizume and Sugimachi, 1997; Thomas et al, 2003). The incidence of any abdominal wall bleeding has also been shown to be dramatically reduced (3% vs. 9%) with blunt vs. bladed trocars

(Antoniou et al, 2013). Placing trocars either in the midline or at least 6 cm lateral to the midline has also been shown to reduce the risk of epigastric vessel injury (Hashizume and Sugimachi, 1997).

Trocar Position–Related Problems. Three potential problems may occur when the secondary trocars are not properly positioned: “crossing swords,” “striking handles,” and “rollover.” The problem of crossing swords is caused by the trocars being placed too close to one another; as a result, the intra-abdominal portions of two trocars cross each other so that the two trocars cannot be easily used to deliver instruments to the same surgical site. Similarly, the problem of striking handles is also caused by trocars being placed too close to one another. As a result, the upper portions of the trocars strike one another on the abdominal surface, again precluding delivery of instruments to a specific surgical site. Rollover is a variant of the crossing swords problem, but it occurs between the laparoscope and an instrument. Instead of running parallel to the surgical site, the primary cannula holding the laparoscope and one of the instrument-holding secondary ports are pointed toward each other. Consequently, as the instrument is advanced toward the surgical site, it strikes and is deflected by the larger laparoscope, thereby rolling over the laparoscope and hence suddenly moving out of the field of view.

By definition, these problems are more likely to occur during LESS. Because the ports are purposely placed in close proximity to one another, the surgeon must use advanced techniques or special equipment to overcome these pitfalls. This special equipment may include articulating instrumentation, instruments with different shaft lengths, and a low-profile 5-mm laparoscope.

When the da Vinci Robotic System is used, the ports should be placed at least 8 to 10 cm away from one another to avoid robotic arm collision—the robotic equivalent of striking handles. This can sometimes be challenging in thin patients with limited abdominal wall space.

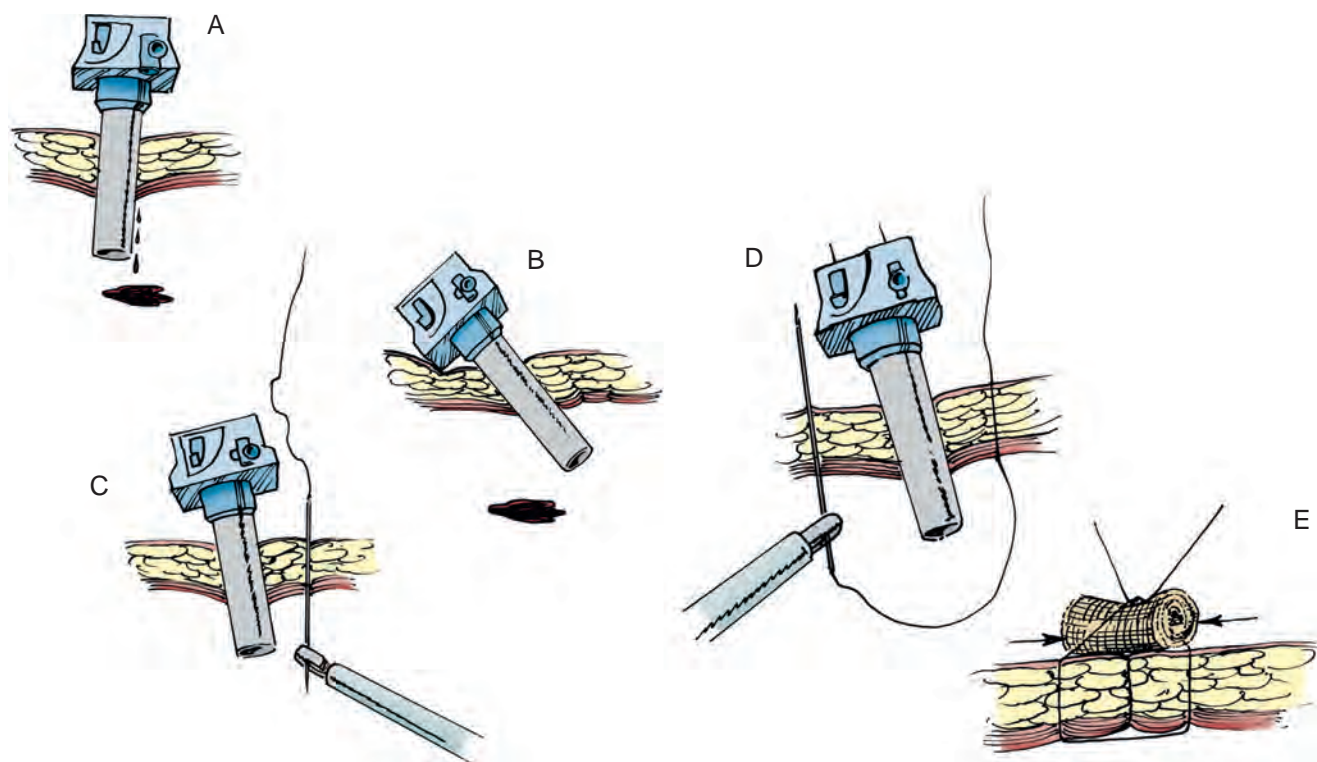


Figure 10-30. A, Bleeding at the cannula site. B, Cannula can be cantilevered into each of the four different quadrants to identify the source of bleeding. C and D, Straight Keith needle may be used to traverse the site of bleeding. E, Suture is tied down over a gauze bolster. (From Clayman RV, McDougall EM, editors. *Laparoscopic urology*. St. Louis: Quality Medical Publishing; 1993.)

Usually these problems are a minor annoyance, and the surgeon and assistant need to experience the problem only once to adjust for it. To compensate for the problem of striking handles, if it should occur, the sheaths can be withdrawn a bit from the abdomen, thereby increasing the space between the handles of the instruments. The problems of crossing swords and rollover can be remedied by moving the handles of the crossing trocars closer to each other, thereby moving the tips of the trocars farther apart. When this is done to correct a rollover, the surgical site may be displaced into one corner of the monitor; however, the desired delivery of the instrument to the surgical site can then be accomplished. A 30-degree laparoscopic lens can usually allow the laparoscope to be placed parallel to the instrument it is rolling over and then rotated to maintain the operative site image and eliminate the rollover.

The best way to handle these situations is to properly place and direct each trocar at the beginning of the case, to avoid encountering these problems. For some procedures, such as pyeloplasty, this may be accomplished by placing all the trocars on the same line (i.e., midline) so they are all working parallel to one another, whereas for procedures such as nephrectomy the goal is to place the trocars so that they surround the surgical site, forming a diamond pattern within which the kidney lies. Regardless, each trocar needs to be inserted such that it points to the pathology; this precludes the problem of having to redirect the trocar throughout the case, adding to surgeon fatigue and unnecessary trauma to the peritoneum and abdominal wall musculature. **Lastly, if trocar interactions become particularly vexing during a procedure, the surgeon should not hesitate to place an additional 5-mm trocar in a more conducive site to eliminate the problem.**

Complications Related to General Anesthesia Unique to Laparoscopy



See the Expert Consult website for details.

Complications Related to the Surgical Procedure

Bowel Injury: Electrosurgical. Electrosurgically induced thermal injury may occur through one of four mechanisms: inappropriate direct activation; coupling to another instrument; capacitive coupling; and insulation failure.

Active electrode trauma by unintended activation causes direct bowel or other organ injury and may occur when the electrosurgical instrument is left unobserved within the peritoneal cavity, when it is out of the camera's view, or when someone other than the primary surgeon carries out electrode activation. Furthermore, active electrode trauma may be seen when coagulation extends beyond the intended site (thermal spread) and reaches other adjacent structures (e.g., bowel, blood vessels, ureter). This is more commonly seen when high electrocoagulation settings (i.e., >30 watts) are used.

Direct coupling may occur when the active electrosurgical instrument touches another instrument that is in direct contact with other tissue (e.g., bowel). If this happens outside the field of view of the laparoscope, it may remain unnoticed by the surgical team.

Injury caused by capacitive coupling occurs when the surrounding charge, which is intrinsic to all activated monopolar electrodes, is not allowed to conduct back to and disperse through the abdominal wall (Zucker et al, 1995; Munro, 1997). This condition may develop when a metal cannula is anchored to the skin with a nonconductive plastic grip, which, as previously noted, should never be done (Fig. 10-31). As a result, the electrical field, which builds up around the activated electrosurgical instrument and is conducted to the metal trocar through which it has been placed, cannot then be conducted to the abdominal wall because the plastic retainer acts as an insulator. This may lead to a high power density along the portion of the metal cannula that is inside the abdomen. The electrical charge built up on the cannula can then travel to other tissues in contact with the cannula. Similarly, capacitive coupling may constitute a risk when electrosurgical probes are used through operating laparoscopes, which are, in turn, inserted through plastic sheaths. The metal shaft of the laparoscope then becomes a repository for electrical current and may discharge this energy to any tissue in contact with the laparoscope. The risk of this complication is also increased when older generators with high-voltage output and/or electrodes with thicker diameters are used, especially in coagulation rather than cutting mode (Munro, 1997).

Lastly, insulation breakdown may allow current to escape along the shaft of the instrument, thereby harming tissues that are otherwise outside the field of view of the laparoscope. Insulation breakdown along the shaft of the instrument may be a result of repeated use, resterilization, or mechanical damage to the instrument during repeated insertion through a trocar. In this situation, the small

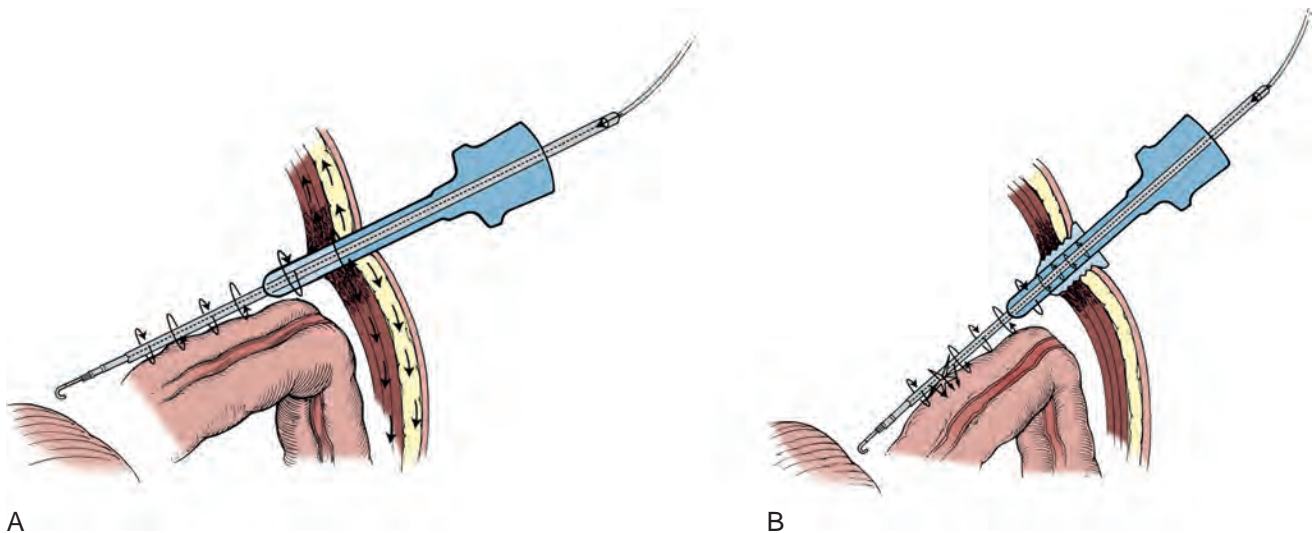


Figure 10-31. Capacitive coupling. **A**, Charge surrounding the activated monopolar electrode is conducted back to the all-metal cannula and dispersed by the abdominal wall. **B**, The electrosurgical instrument is being used through a metal cannula that has been anchored to the skin with a nonconductive plastic grip; accordingly, the electrical field cannot be conducted to the abdominal wall because the plastic retainer acts as an insulator; a stronger electrical charge is thus conducted to any other tissue in contact with the cannula.

Cardiac Arrhythmias and Cardiac Arrest. Cardiac arrhythmias can be frequently seen during anesthesia in laparoscopic procedures; the most common is sinus tachycardia. Bradyarrhythmias (e.g., atrioventricular dissociation, nodal rhythm, sinus bradycardia) may develop independently or in combination with tachycardia during the same procedure (Myles, 1991). Conditions in laparoscopy leading to development of arrhythmias include CO₂ insufflation; hypercapnia; Trendelenburg position; anesthetic drugs (especially halothane in combination with spontaneous ventilation); and gas embolism (Harris et al, 1984; Myles, 1991). In rare cases, asystolic cardiac arrest and cardiovascular collapse may develop (Shifren et al, 1992).

The role of the anesthesiologist throughout the laparoscopic procedure is of paramount importance. Continuous monitoring of cardiovascular parameters (electrocardiogram, arterial blood pressure) and pulmonary parameters (capnometry, in-line oxygen, airway pressures and tidal volume, frequent arterial blood gas analyses when indicated) is essential. Invasive cardiac monitoring should be instituted as appropriate in patients with heart disease or in high-risk patients (i.e., American Society of Anesthesiologists type 3 or 4) when prolonged and complicated laparoscopic procedures are expected.

Because hypercarbia is one of the most common underlying causes of cardiac arrhythmias, it is essential to monitor and control this problem. Overall, hypercapnia can be corrected rapidly by adjustment of ventilatory rate and tidal volume, use of positive end-expiratory pressure as needed, and reduction of intra-abdominal pressure to 10 mm Hg. The surgeon can also desufflate the abdomen for 5 to 10 minutes to allow the anesthesiologist to “catch up” and correct the hypercarbia; pneumoperitoneum can then be reinitiated at a lower pressure.

In rare cases, if the hypercarbia cannot be controlled by these maneuvers, helium should be substituted for CO₂ as the insufflant. For patients with preoperatively known severe pulmonary compromise, it is prudent to have a tank of helium and the proper helium yoke available in the operating room so the insufflant can be easily switched. Alternatively, argon gas can be used in the acute situation because it is readily available in many operating rooms owing to the argon beam coagulator (Badger et al, 2008).

In the event of cardiac arrest, the surgeon should immediately desufflate the abdomen and provide cardiac massage (compressions) while the anesthesiologist administers 100% oxygen and appropriate drug therapy. If a CO₂ embolus is suspected, additional maneuvers, such as immediately turning the patient to a left lateral decubitus, head-down position and possibly attempting to aspirate the embolus, may be performed.

Changes in Blood Pressure. Hypertension may be caused by inadequate general anesthesia, elevated intra-abdominal pressures, or hypercarbia. Hypotension may be the result of hypoxia, pneumothorax, pneumomediastinum, gas embolus, or hemorrhage (Abdel-Meguid and Gomella, 1996).

In the event of a marked change in blood pressure, one of the aforementioned conditions must be ruled out. The initial response of the surgeon, provided that there is neither active bleeding nor

evidence of retroperitoneal hemorrhage, should be to desufflate the abdomen. In addition, therapy specific to an underlying cause should be enacted.

Aspiration of Gastric Contents. Aspiration of gastric contents may occur more frequently in patients with a hiatal hernia, significant obesity, diabetes with a history of gastroparesis, or any form of gastric outlet obstruction (Hanley, 1992). The combination of elevated intra-abdominal pressures from the pneumoperitoneum, morbid obesity, and use of the Trendelenburg position increases the likelihood of this complication (Abdel-Meguid and Gomella, 1996).

To prevent this problem in high-risk patients, oral or intravenous administration of 10 mg of metoclopramide is recommended. This medication may decrease the incidence of aspiration by increasing the tone of the lower esophageal sphincter. In addition, in patients with known gastroesophageal reflux, H₂ blockers reduce gastric acidity and attendant morbidity if aspiration of gastric contents should occur (Hanley, 1992; Abdel-Meguid and Gomella, 1996). Also, in patients with known gastroesophageal reflux or other predisposing factors for gastric aspiration, a cuffed endotracheal tube should always be placed. Lastly, among these high-risk patients, administration of atropine should be avoided because it decreases the tone of the lower esophageal sphincter (Duffey, 1979).

Hypothermia. The patient's core temperature may drop during prolonged laparoscopic procedures, especially if there is leakage of insufflant around the port sites. The CO₂ that is used is typically neither warm nor humidified. The resulting decrease in temperature may be 0.3° C for each 50 L of CO₂ insufflated (Ott, 1991b). The ambient operating room temperature may exacerbate this effect.

The clinical effects of hypothermia are well described. Core body temperatures around 35° C may result in (1) increased bleeding tendency caused by impaired platelet function, reduced activity of coagulation factors, and enhanced fibrinolysis; (2) increased adrenergic response with vasoconstriction and increased arterial blood pressure; (3) prolonged recovery time as a result of increased blood gas solubility; (4) twofold to threefold increase in the incidence of early postoperative myocardial ischemia in high-risk patients; and (5) impaired wound healing and increased susceptibility to wound infections (Rosenberg and Frank, 1999).

In general there are no specific signs that can be appreciated intraoperatively except for cardiac arrhythmias. In particular, atrial fibrillation may occur in extreme cases of hypothermia (body core temperature of approximately 30° C). In almost all cases, hypothermia can be avoided. Adjuncts to support the patient's body temperature include intravenous fluid warming, active warming by forced-air systems, circulating warm-water mattresses, and radiant heaters (Rosenberg and Frank, 1999). In addition, warming and humidifying CO₂ to physiologic levels, especially when a prolonged laparoscopic procedure is anticipated, is helpful (Ott, 1991a). However, warming the insufflant alone should be avoided, because this causes a drying of the intraperitoneal tissues and has been associated with increased postoperative patient discomfort (Slim et al, 1999).

break in insulation results in an area of very high power density that then discharges to the nearest soft tissue.

Intraoperatively, thermal injuries of the bowel may manifest as whitish spots on the serosal lining. In severe cases, the muscularis mucosae or the intestinal lumen may be seen. However, in many patients, thermal injury to the bowel is not recognized at the time of the procedure. **Postoperatively, the patient with unrecognized bowel trauma may not develop fever, nausea, or signs of peritonitis for many days, as the full extent of bowel necrosis may take up to 18 days to fully develop (Abdel-Meguid and Gomella, 1996).** Therefore, the problem may not become evident until the patient has actually been discharged from hospital.

Accordingly, bowel injury must be ruled out for any patient who develops a fever beyond postoperative day 1 or who complains of increasing abdominal discomfort. Although many patients may have the typical signs of fever, abdominal pain, ileus, and nausea and vomiting, this is not always the case. Instead many patients may have low-grade temperature, leukopenia, and persistent and relatively extreme pain at the trocar site closest to the bowel injury (Bishoff et al, 1999). Alternatively, laboratory values may be remarkable for leukocytosis with an associated left shift (i.e., increased percentage of neutrophils). In some patients, this occurs in the face of a normal or even low leukocyte count, making the left shift a more reliable sign than the absolute white cell count. Abdominal radiographs are notoriously inaccurate because the CO₂ from the laparoscopy may remain as free air for up to 9 days after the procedure; however, an ileus pattern is usually present. A more sensitive test is an abdominal CT scan with oral contrast accompanied by delayed films.

Minor postoperative thermal injuries of the bowel discovered late in the postoperative period (i.e., more than 5 to 7 days postoperatively) may be managed conservatively, aided by administration of antibiotics and an elemental diet. Indeed, a closed fistula may develop that will heal with this approach. However, if the patient does not respond rapidly or develops worsening peritonitis, open surgical exploration is mandatory. Thermal injury caused by monopolar cautery often results in tissue damage that extends beyond the visible area of necrosis. With this in mind, the surgeon should perform a bowel resection with a safety margin of 6 cm on either side before completing an end-to-end anastomosis (Abdel-Meguid and Gomella, 1996).

Thermal injury caused by bipolar electrosurgery is more confined to the visible area of damage. These injuries occur only as a result of direct firing of the instrument on the bowel. If the injury is small, it can be managed by simple excision of the defect and closure of the bowel wall. Bipolar injuries that involve more than half the circumference of the bowel should be treated by excision of the affected segment of the bowel followed by end-to-end anastomosis (Abdel-Meguid and Gomella, 1996).

The goal of every laparoscopic surgery is to never experience a thermal complication. To this end there are several actions the surgeon can take to lessen the risks. First, electrosurgical instruments must be carefully inspected before use for any "breaks" in the insulation; if these are found, the instrument must be sent for recoating. Second, electrosurgical instruments should never be left untended within the abdomen; when not in use they must be removed from the abdomen. Third, *only* the primary surgeon should control electrode activation. Fourth, isolation of the area to be cauterized from the surrounding tissues (vessels, nerves, ureter), as well as use of bipolar electrocautery, reduces the risk of thermal spread and injury to other tissues. Fifth, the electrosurgical device should never be activated unless the entire extent of the metal portion of the instrument is in view. This includes not only the active tip of the instrument, but also any exposed, uncoated metal joints that may lie just behind the tip of the instrument. In this manner both inadvertent direct injury to adjacent tissue and direct coupling to another instrument can be avoided. Sixth, problems of capacitive coupling can be precluded by not creating a situation in which a mixture of conducting and nonconducting elements is used by the surgeon (e.g., metal trocars combined with plastic retainers). In addition, use of modern generators and small-diameter

electrodes can significantly decrease the risk of capacitive coupling (Munro, 1997), as can the use of blended or pure cutting current. The high voltages needed for pure coagulation current pose the greatest threat for electrosurgical injury, especially through the mechanism of capacitive coupling and insulation failure. Lastly, an active electrode monitoring system (Encision, Boulder, CO) is extremely helpful. With this system, any sudden break in the insulation of the electrosurgical instrument (e.g., with scissors or hook electrode) results in immediate shutdown of the electrosurgical current, thereby precluding an electrosurgical injury.

Bowel Injury: Mechanical. Inadvertent mechanical damage can be caused by a wide variety of sharp and blunt instruments (e.g., laparoscopic graspers, scissors, retractors). This type of injury is more visible to the surgeon and is usually discovered intraoperatively or at the end of the procedure. Direct visual identification during the procedure allows the surgeon to repair the injury laparoscopically, even though the patient has not had a formal bowel preparation. Given its localized nature, bowel resection is rarely necessary. The abdomen should be irrigated copiously at the end of the procedure with 4 to 5 L of an antibiotic-containing solution.

If mechanical bowel injury is missed during the procedure, then postoperative symptoms typically develop much earlier than with an electrosurgical injury. Fever, nausea, ileus, and peritonitis develop in the very early postoperative period, and the diagnosis is confirmed by an abdominal CT scan with oral contrast. This type of injury should be managed with immediate return to the operating room to correct the problem by local excision or resection of bowel with subsequent end-to-end anastomosis and copious irrigation of the abdomen.

Delicate handling of tissue with laparoscopic instruments by the main surgeon and the assistants is essential to avoiding this complication. Atraumatic graspers should always be used when handling bowel. Likewise, it is important that all instruments be introduced under strict visual guidance into the peritoneal cavity. Instruments should never be left unattended and should be withdrawn from the abdominal cavity when not in use. Attentiveness, economy of motion, and deftness of touch are essential characteristics of both the successful open and laparoscopic surgeon.

Vascular Injury. Fortunately, direct major vascular injury during laparoscopic dissection is a rare event. The use of only blunt trocars, the small nature of the instrumentation, the limitations on surgical speed, and the magnification of the surgical field by the laparoscope all combine to decrease this potential problem.

During right renal dissection, in particular, the chance of a vena cava, renal vein, or gonadal vein injury is heightened. When this occurs the surgeon can undertake several steps to resolve the bleeding. First, the pneumoperitoneum pressure can be raised to 25 mm Hg, thereby slowing or stopping any venous bleeding. With the use of the irrigator-aspirator, the blood can be cleared and the bleeding site identified. Next, through one of the 12-mm ports, a gauze sponge or pledget can be introduced into the abdomen and handled with a grasping forceps, thereby allowing the surgeon to identify and tamponade the area of bleeding. If the injury is small, then it may respond simply to direct pressure. Alternatively, surgical pharmaceuticals such as fibrin glue or gelatin matrix thrombin sealant (e.g., Floseal [Baxter, Deerfield, IL]) may be applied. If the injury is larger, then the surgeon must decide whether to convert to an open or hand-assist procedure or to attempt to secure and repair the injury laparoscopically. Depending on the severity of injury, a vascular surgery consultation may be appropriate. If a laparoscopic repair is attempted, intracorporeal suturing and possibly the use of a laparoscopic Satinsky clamp may be required. Throughout this period, it is essential for the anesthesiologist to administer sufficient fluids or blood replacement to preclude a hypovolemic state because the hypovolemic patient has a higher risk of possible air embolism at these higher intra-abdominal pressures (O'Sullivan et al, 1997).

If the surgeon is able to gain temporary control of the vessel with a grasper, then it is often helpful to place an extra 5-mm port that can be used by the assistant for suction and irrigation or to optimize the plan of approach to the injury, thereby facilitating laparoscopic

suturing. Either way, the additional port allows the surgeon to repair the bleeding site using two hands and with excellent visualization of the surgical field.

Alternatively, the surgeon can convert from standard laparoscopy to a hand-assisted approach. The hand, in this case, is valuable because it can rapidly tamponade the bleeding site. In this regard it is recommended, if at all possible, to pinch the sidewalls of the vein (e.g., inferior vena cava) closed rather than just putting direct pressure on the top of the injury; the latter approach has a tendency to result in a gradual enlargement of the hole in the vein. Also, if the hole is pinched closed, a Satinsky clamp can be more easily passed beneath the surgeon's fingers to provide reliable control of the injury in preparation for a sutured repair.

Minor arterial injuries usually respond to tamponade. Larger aortic or renal artery injuries are much more difficult to resolve laparoscopically. Although the latter, if it occurs during a planned nephrectomy, can be handled by expeditiously taking the renal artery with a vascular stapler, the former may lead to immediate conversion and open repair. As mentioned earlier, addition of an additional 5-mm port can be very useful to help establish a clear field and provide the surgeon with two hands to control the injury. If conversion to an open procedure is necessary, the area of injury should be tamponaded with laparoscopic forceps and the surgeon can proceed to rapidly make a midline or subcostal incision by swinging one of the ports up to the underside of the abdominal wall and cutting down on the shaft of the port. The tamponading laparoscopic forceps are important to directing the surgeon immediately to the site of injury, which can then be properly repaired. Again, a vascular surgeon should be called into the room as necessary.

As mentioned previously in this chapter, because most bleeding episodes are unexpected, it is wise to have in the room a hemorrhage tray equipped with all instruments necessary to control bleeding and for potential open conversion (see Box 10-3).


Nerve Injury. Nerve injury is invariably a result of patient positioning in combination with the duration of the procedure. The exact incidence of this problem is not known. A survey of neuromuscular injuries associated with laparoscopic urologic surgery completed by 18 urologists from 15 institutions in the United States, published in 2000, found that of a total of 1651 procedures there were 46 neuromuscular injuries in 45 patients (2.8%). This included abdominal wall neuralgia (14), extremity sensory deficit (12), extremity motor deficit (8), clinical rhabdomyolysis (6), shoulder contusion (4), and back spasm (2) (Wolf et al, 2000).

If the patient is inadequately positioned and/or padded, nerve damage may result from abnormal nerve stretching or compression. Among position-related nerve injuries, the brachial plexus appears to be most at risk. Injury may be inflicted in several ways: (1) abduction of the arm beyond 90 degrees, (2) extreme outward rotation of the head of the humerus, and (3) compression damage when shoulder braces are used in the Trendelenburg position (Phong and Koh, 2007), which pushes the clavicle into the retroclavicular space. In particular, this has been reported as a problem with robotic radical prostatectomy when a steep Trendelenburg position is required and strapping the patient might be necessary to avoid slippage. Other nerves that can be affected by positioning include the femoral nerve, because of extreme lateral rotation and abduction of the hip joint, specifically in the lithotomy position, and the sciatic nerve, because of stretching along the superior leg when the patient is in the lateral decubitus position (Hershlag et al, 1990; Abdel-Meguid and Gomella, 1996; Liss et al, 2013). In addition, nerves may be injured during the surgery itself because of either direct mechanical injury or monopolar electrosurgical current.

Nerve palsy caused by positioning is recognized only postoperatively, often on the first postoperative day when the patient tries to ambulate. From both a medical and a legal standpoint, a neurology consultation should be obtained as soon as the patient calls the surgeon's attention to a possible nerve injury. Neurologic examination with possible nerve conduction studies to document acute damage is important. Physical therapy may facilitate recovery. However, recovery in these cases, if it does not occur within the first few postoperative days, is often slow, requiring months.

Prevention is paramount. Table-mounted accessories for all major commercial operating room tables now exist that aid in safely and effectively positioning patients in the lateral decubitus position and in the prone position. If the arms are to be at the patient's sides, they should be pronated to protect the brachial plexus. If the patient is to be in a lateral decubitus position, all bony prominences should be padded with additional gel pads (i.e., hip, knee, and ankle on the downside leg), and a pillow is always placed between the legs. Padding should also be placed beneath Velcro straps and tape, which may be used on the upside hip and shoulder. If the patient is in the lithotomy position with steep Trendelenburg, as is often required during laparoscopic or robotic radical prostatectomy, shoulder braces should not be used owing to risk of brachial plexus injury. Instead, use of well-padded wide straps directly across the upper chest and use of the surgical beanbag (Carey and Leveillee 2007) are excellent ways to secure the patient. Extreme abduction of the hip is also to be avoided; meticulous care to position the patient with attention to hip flexion should be taken when the patient is placed in lithotomy for a prolonged period. Padding must be checked each time the table position is changed, and the patient should be rechecked if he or she is suspected of sliding on the table.

Injury to the Urinary Tract, Spleen, or Pancreas. Similar to open surgery, during laparoscopic or robotic surgical procedures the urinary tract, spleen, or pancreas may be injured.

See the Expert Consult website for a discussion of the incidence, presentation, management and prevention. 

Complications Related to Exiting the Abdomen

Bowel Entrapment. During removal of laparoscopic ports and desufflation of the pneumoperitoneum, omentum or bowel may be entrapped at one of the port sites. If missed during the process of cannula removal, then in the early postoperative period, usually on the second or third postoperative day, the patient may develop an ileus and point tenderness at the port site incision.

The treatment is operative. The pneumoperitoneum is reestablished through one of the unaffected port sites, and three ports are replaced: one for the camera and two for grasping forceps. The entrapped bowel is visualized, and an atraumatic bowel clamp is placed on the bowel on either side of the area of herniation. Once this is done, the skin sutures of the affected port site are carefully cut and the wound is opened. The surgeon uses a fingertip to manually reduce the bowel into the abdominal cavity. The bowel can then be carefully inspected; if it appears viable, which is usually the case, it can be left in place and the port site closed. Rarely are formal bowel resection and reanastomosis required.

This particular problem is the result of a technical error. Indeed, most laparoscopic ports have a hole drilled into the side of the port within a few millimeters of the end of the port's shaft. This hole equalizes the pressure in the port and the abdomen as the port is pulled out of the abdomen, thereby precluding any bowel being withdrawn with the port. Furthermore, if each port site is endoscopically inspected at the time of cannula removal, bowel or omentum that may have entered the port site can be readily identified and positioned back into the abdominal cavity. When the last endoscope-bearing port is removed, the assistant should pull up on the closure sutures or on a fascial clamp, and the surgeon should back the cannula out of the wound and up onto the shaft of the endoscope so that the endoscope is the last thing to leave the abdomen.

Bleeding at the Sheath Site. Bleeding at the sheath site was previously discussed under Complications Related to Placement of Secondary Trocars. However, there are times when this problem does not become apparent until the end of the procedure owing to tamponade from the trocar itself. Again, it is essential to inspect each trocar site at 5 mm Hg to rule out this problem.

Early Postoperative Complications

Pain. Pain may be localized or diffuse. Early in the postoperative course, port site discomfort is to be expected. However, if

Injury to the Urinary Tract

Bladder Injury. Electrocautery and blunt, sharp, and laser dissection have been identified as intraoperative causes of bladder injury (Ostrzenski and Ostrzenska, 1998). Concomitant bladder or pelvic anomalies or pathologic conditions (prior pelvic or bladder surgery, endometriosis, malignant infiltration, bladder diverticula, amyloidosis, or previous radiation) are predisposing factors that increase the chances of this bladder injury (Ostrzenski and Ostrzenska, 1998).

When a bladder injury has occurred, the intraoperative signs may be subtle. One of the first signs is the presence of blood or gas in the Foley catheter bag. Also, the surgeon may notice clear fluid welling up in the pelvis, although this sign is often obscured if irrigation has been used during the procedure.

Postoperatively, if the bladder injury was missed, the patient may develop oliguria and urinary ascites; this may be accompanied by hyponatremia and, rarely, hyperkalemia with mild elevation of the serum creatinine concentration caused by the peritoneal absorption of urine. Patients who have been discharged from the hospital because of the minor nature of their laparoscopic procedure may contact their physician complaining of lower abdominal discomfort, abdominal swelling, fever, and, in the case of a gynecologic procedure, vaginal discharge.

The intraoperative suspicion of a bladder injury may first arise as a result of the recognition of an air-expanded urine collection bag; this presumptive diagnosis can be confirmed by the injection of saline mixed with indigo carmine through the Foley catheter. Postoperatively, the diagnosis can be made by conventional cystogram or CT cystogram.

The intraoperative diagnosis of a bladder injury can be followed by laparoscopic repair—either suturing with absorbable suture or, if the injury is quite small, using preformed suture loops to encircle and secure the cystotomy (Poffenberger, 1996; Ostrzenski and Ostrzenska, 1998). More extensive defects may require open repair.

When bladder injury is diagnosed postoperatively, the key factor is whether the drainage is extraperitoneal or intraperitoneal, which is largely dependent on the preceding laparoscopic access. Extraperitoneal extravasation without any complicating additional problems may be treated by simple placement of a transurethral indwelling Foley catheter. Intraperitoneal drainage is an indication for subsequent laparoscopic or open repair.

Prevention of bladder injury begins with preoperative placement of a Foley catheter. Avoidance of excessive coagulation near the bladder and dissection with exact knowledge of bladder anatomy (urachus, medial umbilical, and vesicocervical ligaments) are also key.

Ureteral Injury. Ureteral injury is usually a result of thermal damage caused by dissection using monopolar electrocautery in the immediate vicinity of the ureter. Its incidence in laparoscopic hysterectomy is 1%; it may also occur during laparoscopic endometriosis ablation and tubal ligation and has been reported during pelvic lymphadenectomy and laparoscopic and robotic radical prostatectomy (Baumann et al, 1988; Grainger et al, 1990; Poffenberger, 1996; Liu et al, 1997; Ostrzenski and Ostrzenska, 1998; Guillon-neau et al, 2002; Yuh et al, 2014).

Typically, ureteral injuries remain unnoticed throughout the laparoscopic procedure. As opposed to a bladder injury, macroscopic hematuria or pneumaturia is distinctly unusual with this injury. The astute laparoscopist might make the diagnosis intraoperatively when urine is seen to be welling up in the wound. However, if irrigation has been used during the procedure this sign is invariably obscured. Within 2 to 3 days after surgery, patients may have abdominal and/or flank pain, fever, signs of peritonitis, and leukocytosis (Grainger et al, 1990; Liu and McFadden, 2000).

The diagnosis of ureteral injury is most often made during the postoperative period when a contrast enhanced abdominal or pelvic CT scan with delayed images is ordered because of the patient's complaint of flank pain, abdominal swelling, hematuria, urinary leakage from the wound, and/or the physical signs of urinary ascites. Depending on the function of the contralateral kidney and the amount of urine leakage, serum chemistries may reveal hyponatremia and, rarely, hyperkalemia with a mild elevation in the serum creatinine concentration.

If identified intraoperatively, the injury can be repaired laparoscopically, but conversion to an open procedure may be required. If the problem is detected in the postoperative period, the first step is to place an indwelling ureteral stent and a bladder catheter. If a stent cannot be placed, then a percutaneous nephrostomy should be placed and an antegrade attempt at stent placement can be made. Depending on the severity of injury, either early laparoscopic or open surgical intervention may be indicated versus a conservative approach.

Prevention of this injury again harkens back to the importance of the surgeon's knowledge of laparoscopic anatomy and the course of the ureter with regard to its topographic relation to other anatomic structures (medial umbilical ligament, round ligament or vas deferens, and common iliac artery). During dissection, monopolar electrosurgical coagulation current should be used with great discretion around the ureter. Ideally, fine-tipped electrosurgical instruments should be used and the duration of discharge should be brief (i.e., multiple short bursts of current rather than a continuous multisecond discharge).

Pancreatic Injury. Injury to the pancreas during left-sided laparoscopic adrenalectomy or radical nephrectomy is most commonly associated with mechanical retraction. The tail of the pancreas overlies the adrenal and may be injured during dissection of the medial aspect of the adrenal and division of the splenorenal ligament. The incidence of this complication is 2.1% for radical left nephrectomy and 8.6% for left adrenalectomy (Varkarakis et al, 2004). Of note, the diagnosis is rarely made intraoperatively, with 75% of pancreatic injuries diagnosed postoperatively.

The typical presentation is postoperatively with abdominal discomfort, elevated serum lipase and amylase levels, and leukocytosis. CT reveals a fluid collection that can often be drained percutaneously. A nasogastric tube is placed and oral intake is stopped. When drainage drops below 50 mL/24 hr, the drain can be removed, followed by removal of the nasogastric tube and initiation of a low fat diet.

Prevention of this complication requires the surgeon to widely dissect the line of Toldt and the splenophrenic attachments. The latter are freed to the level of the diaphragm. The colon is broadly reflected from the Gerota fascia, and the splenocolic and splenorenal ligaments are divided. With these maneuvers the spleen and colon rotate medially, carrying with them the tail of the pancreas, well away from the medial surface of the adrenal gland.

Splenic Injury. The advent of laparoscopic surgery has been associated with a significant decrease in incidental splenectomy during left nephrectomy, with a fall from 4.3% to only 1.5% (Cooper et al, 1996; Breda et al, 2009). These injuries are invariably discovered intraoperatively and can effectively be treated with argon beam coagulation or with one of the newer hemostatic agents such as fibrin glue or thrombin-impregnated granules. **Avoidance of this complication is best achieved by wide mobilization of the spleen during left nephrectomy.** To this end the splenophrenic attachments, as well as the splenocolic and splenorenal ligaments, need to be divided. Retraction in the area of the spleen should never be on the spleen itself but beneath the area of the splenocolic ligament such that the retractor is placed on these thicker tissues (Cooper et al, 1996; Simon et al, 2004).

postoperative pain is limited to a port site, it may also be secondary to herniation (immediate or late), bowel injury, or infection (late). Localized pain combined with a subcutaneous bulge may indicate a rectus sheath hematoma, bleeding and hematoma formation at a port site, or a port site hernia. Pain at a port site without swelling may be due to a particularly broad fascial suture or palpation of the knot of a port site fascial suture in a thin patient. Ultimately, if port site pain appears to be increasing on subsequent postoperative days, herniation should be suspected.

Immediate, severe, diffuse abdominal pain may be related to the release of noxious material during the procedure (e.g., cyst fluid in patients with autosomal-dominant polycystic kidney disease) or to a bowel injury. Immediate postoperative scapular discomfort may be a result of the CO₂ pneumoperitoneum itself causing some irritation of the diaphragm. Rarely, this discomfort may be sufficiently severe to mimic the symptoms of a pulmonary embolus. Of note is that this pain is invariably along the area of the right posterior shoulder region. Delayed diffuse abdominal discomfort and development of peritoneal signs or simply ongoing abdominal discomfort accompanied by low-grade fever may be results of an unsuspected bowel injury.

Incisional Hernia. In adults, the occurrence of an incisional hernia is usually confined to port sites larger than 10 mm. However, in the pediatric population, this complication can occur even with 5-mm ports. The patient usually reports localized discomfort accompanied by nausea and signs of ileus. Rarely, diffuse abdominal pain and/or signs of a complete bowel obstruction may be present. Examination reveals tenderness and, at times, swelling overlying the affected port site. A plain film of the abdomen may show an ileus pattern; however, the definitive study is abdominal CT, which can actually reveal the bowel protruding above the fascial level.

Laparoscopic repair with dissection of the hernia and subsequent intra-abdominal closure can be accomplished. The method for performing this procedure has already been described. In complicated cases in which a strangulated hernia is suspected or confirmed laparoscopically, general surgical consultation should be sought.

As discussed previously, **the risk of incisional hernia can be greatly reduced by using nonbladed as opposed to bladed trocars.** When bladed trocars are used, hernias can be avoided by performing a meticulous fascial suture closure of all trocar entry sites 10 mm or larger in all adults. In children, it is advisable to perform fascial closure of any “bladed” port site 5 mm or larger. The fascial layer is usually closed with an absorbable suture as previously described. **For patients in whom only nonbladed trocars have been used, fascial closure is indicated only of midline ports 10 mm or larger (Kang et al, 2012) or any port site that has been unduly stretched.** Indeed, some authors recommend no closure even of midline nonbladed trocar sites (Siqueira et al, 2004). Although there have been a few reports of a hernia developing after use of a nonbladed trocar (Lowry et al, 2003; Kouba et al, 2007; Zemet et al, 2012), this is distinctly rare. Indeed, the incidence of postoperative hernia formation fell from 1.8% with bladed trocars to only 0.19% for nonbladed trocars (Boike et al, 1995; Hashizume and Sugimachi, 1997; Thomas et al, 2003). Of note, with midline hand-assist approaches, a higher incidence of hernia formation has been identified than would otherwise be expected: 4.0% to 7.3% (Troxel and Das, 2005). Therefore some authors have recommended closure of this midline incision with interrupted nonabsorbable suture rather than a running closure (Troxel and Das, 2005).

In addition, transverse midline fascial incision has been shown to be superior to vertical midline fascial incision for reducing hernia risk (Brown and Goodfellow 2005; Halm et al, 2009). Specifically, for robotic radical prostatectomy the change from vertical to horizontal incisions for the camera port and subsequent prostate removal port site has resulted in a reduction in incisional hernias of 5.4% to 0.4% (Liss et al, 2013).

Deep Venous Thrombosis and Pulmonary Embolism. Although it seems reasonable to expect decreased venous return and hence increased stasis with concomitant higher risk of deep venous

thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing laparoscopy, this is remarkably **not** the case. Indeed, there is no evidence that this complication occurs more often during laparoscopic or robotic procedures versus open surgery (Abdel-Meguid and Gomella, 1996; Secin et al, 2008).

Thus far there have been no randomized controlled trials addressing the issue of DVT prophylaxis in patients undergoing laparoscopic and robotic surgery. The American Urological Association has released a Best Practice Policy Statement for the prevention of DVT in patients undergoing urologic surgery. Noting the lack of data available directly pertaining to laparoscopic and robotic surgery, the panel recommended the use of pneumatic compression stockings placed at the time of laparoscopic procedure for all patients. In addition, they acknowledged that certain high-risk groups may require the use of low-dose unfractionated heparin or low-molecular-weight heparin before, during, or after surgery.

Pneumatic compression stockings should be placed preoperatively and continued for 48 to 72 hours postoperatively. In addition, in morbidly obese patients or in individuals at high risk for thrombosis (smoking, past history of DVT), the addition of unfractionated perioperative heparin (5000 units 2 hours preoperatively and then every 12 hours postoperatively) has also been recommended (Clagett et al, 1995; Capan and Miller, 1999; Secin et al, 2008). Of note, with specific respect to upper retroperitoneal (renal, adrenal, ureter) laparoscopic procedures, at least one study (Montgomery and Wolf, 2005) indicated that sequential pneumatic compressive stockings provide equivalent DVT prophylaxis compared with subcutaneous fractionated heparin and that the use of subcutaneous heparin may increase the incidence of hemorrhagic complications. However, it must be stressed that this was a nonrandomized study obtained from a prospective database augmented by retrospective chart review.

Wound Infections. Overall, this is a rare complication with standard laparoscopy. However, with the hand-assist approach a higher incidence of wound infections has been noted. In one report the postoperative wound infection rate at the hand-assist site was 9% (Nelson and Wolf, 2002). Prevention of this complication is similar to open surgery and includes attention to antiseptic preparation and sterile draping of the abdominal wall, irrigation of each port site at the end of the procedure, and meticulous closure of the wound.

Rhabdomyolysis. Rhabdomyolysis is a devastating complication after laparoscopic surgery. The exact incidence of this problem is not known, but one survey of neuromuscular injuries associated with laparoscopic urologic surgery found that of a total of 1651 procedures there were 6 cases (0.4%) of clinical rhabdomyolysis (Wolf et al, 2000). In a more recent study, it was estimated that the occurrence of this problem among patients undergoing retroperitoneal laparoscopic procedures (e.g., renal, ureteral, adrenal) was higher at 1% (Reisiger et al, 2005). Rhabdomyolysis is invariably associated with male patients undergoing longer laparoscopic renal procedures, especially if the kidney rest has been used for the entire case. Although extra padding applied to pressure areas can be useful in avoiding nerve compression and rhabdomyolysis, gel pads and foam egg crate padding have not been conclusively demonstrated to significantly reduce pressure on the patient's flank in the lateral position (Deane et al, 2008). As discussed previously, **male patients with a BMI of 25 or greater undergoing laparoscopic surgery in the lateral position with the kidney rest elevated and the table completely flexed are at highest risk of developing rhabdomyolysis as a result of flank pressure.**

Rhabdomyolysis manifests immediately in the postanesthesia recovery room with the patient complaining of severe pain in the downside hip area. Brown urine may also be noted. The serum creatine kinase value invariably exceeds 5000 units/dL.

Prevention of this problem is essential. This can, to some extent, be done by avoiding use of the kidney rest or using it for only the earliest part of the case (i.e., less than an hour) and avoiding prolonged periods of hypotension during the procedure (Cadeddu et al, 2001; Kuang et al, 2002; Parsons et al, 2004;

Reisiger et al, 2005). Lastly, with increasing skill and experience, few procedures should proceed beyond 5 hours.

Late Postoperative Complications

Complications beyond the 3-week postoperative period are rare. These primarily include lymphatic complications and incisional hernia. The latter is addressed in the prior discussion because it can also appear as an early postoperative complication.



See the Expert Consult website for further details.

KEY POINTS: COMPLICATIONS AND TROUBLESHOOTING IN LAPAROSCOPIC AND ROBOTIC SURGERY

- Early in one's experience with laparoscopic and robotic surgery, it is wise to apply the minimally invasive approach to low-risk surgical candidates of normal body habitus.
- The first sign of gas embolism is an abrupt increase of end-tidal CO₂ accompanied by a sudden decline in oxygen saturation and then a marked decrease in end-tidal CO₂.
- Electrosurgically induced thermal bowel injury may occur through one of four mechanisms: inappropriate direct activation; coupling to another instrument; capacitive coupling; and insulation failure.
- Careful planning of trocar placement is essential to avoid crossing swords, striking handles, rollover, and robotic arm collisions.

TRAINING AND PRACTICING LAPAROSCOPIC AND ROBOTIC SURGERY



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CONCLUSION

Laparoscopic procedures unthinkable in early 1990 are now performed routinely. Furthermore, the use of a robotic surgical platform to perform complex reconstructive procedures is improving the precision and often the outcomes of these operations and, more important, making it possible for a greater number of urologists to perform high-quality laparoscopic procedures. The widespread adoption of laparoscopy and robotic-assisted laparoscopy highlights the importance of having a detailed and robust understanding of the basics of minimally invasive surgery including the physiologic effects of the pneumoperitoneum, obtaining access, and managing complications. As robotics and flexible endoscopically guided technologies advance in the future, we may see adoption of NOTES and our patients may undergo operations that leave no visible scar. The benefit will be both more proficient laparoscopic and robotic surgeons who can handle any procedure and any complication without the massive incisions of years past, and patients treated with a truly minimally invasive technique. Such should be the next step of our surgical path of discovery and evolution. At that point Osler's 20th century admonition, "Diseases that harm require treatments that harm less," will be truly fulfilled. We are as yet still on the bridge to the future.

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The complete reference list is available online at www.expertconsult.com.

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Lymphocele Formation. Lymphocele formation is most commonly associated with pelvic procedures, such as pelvic lymph node dissection during radical prostatectomy (0.4% to 1.3% incidence) (Kavoussi et al, 1993; Liss et al, 2013) or with renal transplantation (0.6% to 18% incidence) (Bailey et al, 2003). The lymphocele may take weeks to develop and may occur despite a transperitoneal approach. Presentation may be by a mass effect, but the astute clinician should realize that it may also occur as a result of local compression causing lower extremity edema, and, in rare cases, venous thrombosis and PE. The lymphocele is diagnosed readily by CT. **Treatment is percutaneous drainage. Sclerosant therapy can be used to treat the lymphocele; however, if unsuccessful or if the lymphocele is not amenable to percutaneous drainage, then a transperitoneal laparoscopic marsupialization procedure is usually successful.** At the time of the procedure, a tag of omentum can be placed into the opening made in the lymphocele to try to prevent closure of the opening and recurrence.

Prevention of lymphocele formation requires meticulous attention to clipping suspected lymphatic structures. Monopolar electrocoagulation does not work well to seal lymphatics. Bipolar or harmonic devices have been shown to effectively seal lymphatic channels; however, the bipolar device created a seal that was 5- to 10-fold stronger than the harmonic device (Box et al, 2009).

Chylous Ascites. After left-sided retroperitoneal surgery (i.e., left radical nephrectomy, donor nephrectomy), the patient may return complaining of a distended abdomen. Although this complaint is

common in the initial few days after a laparoscopic procedure, because of the pneumoperitoneum, irrigation fluid, and/or ileus, it is distinctly rare late in the patient's course. There is no associated fever, pain, or bowel dysfunction, and routine laboratory study findings are within normal limits. Usually the condition is self-limited and resolves without any intervention. If the presentation is not straightforward, then abdominal CT will reveal the underlying problem and allow diagnosis of the presence of ascites. If tapped, the fluid may reveal elevations in the level of lymphocytes, cholesterol, and triglycerides.

Treatment is usually dietary, with a low-fat, medium-chain triglyceride diet. One may also consider giving somatostatin or octreotide (Leibovitch et al, 2002; Negoro et al, 2006). In the rare situation in which the fluid does not resolve with these conservative measures or if the patient is symptomatic, the fluid can be tapped once or twice. If it continues to accumulate, then an open or laparoscopic exploration is undertaken. Once identified, the leaking lymphatic channel is dissected and secured with either suture or clips (Molina et al, 2003).

Prevention of this type of problem is extremely difficult because the lymphatics are not readily visible during the procedure. In particular with laparoscopic procedures, lymphatic leakage might be overlooked as result of tamponade by the pneumoperitoneum. To date, instances of postlaparoscopic chylous ascites have been cited only sparingly in the literature (Leibovitch et al, 2002; Shafizadeh et al, 2002; Molina et al, 2003; Negoro et al, 2006; He et al, 2011).

Surgeons learning how to perform laparoscopic procedures face several hurdles, including an altered 2D view of a 3D space, counterintuitive control of instruments, different ergonomic constraints, and an altered perspective of surgical anatomy (Piechaud and Pansadoro, 2006). Robotic surgical systems such as the da Vinci Robotic System overcome several of these issues by providing binocular, 3D vision and intuitive instrument motion. However, the robotic system does have its own hurdles to overcome, such as complete lack of tactile feedback and a learning curve regarding the syncope of the surgeon's console. In addition, much like life in general, the only thing constant about laparoscopic and robotic surgery is change. It is therefore necessary for minimally invasive surgeons, no matter how experienced, to master new skills and familiarize themselves with new technologies as they develop. With an ever-increasing emphasis on patient safety and operating room efficiency, it is widely accepted that new surgical skills and techniques should be developed and honed outside the operating room and then transferred into the operating room once proficiency has been developed. The tools and systems available for practicing and acquiring laparoscopic and robotic skills are detailed here.

Equipment for Practicing Laparoscopic and Robotic Surgery

A wide variety of practice models exist for both laparoscopic and robotic surgery ranging from inanimate laparoscopic training boxes to live animal and human cadaveric models. There has also been heightened interest in the development of computer-driven VR trainers that can be used to practice standard techniques and whole procedures. As a general premise, nonliving models should be used unless it is absolutely essential to have a live model.

Standard Laparoscopic Training Boxes

The items necessary for a basic laparoscopic training box are a box with an opaque top that is suitable for placement of laparoscopic ports and a vision system consisting of a video monitor, a light source, and a camera or camera-lens combination. Several commercially available training boxes are available that contain all of the necessary components (Fig. 10-32). Alternatively, one can construct a training box from relatively inexpensive materials such as a cardboard box and a web camera with a computer screen or video camera. Tablets, such as the iPad, are also now readily available and can serve as both the camera and monitor for self-constructed trainers (Ruparel et al, 2014). Although the use of trocars gives a hint of reality, it is not mandatory. In general, the instruments and camera should be configured in a triangular fashion such that the camera lies between the right- and left-hand instruments. For optimal ergonomic positioning, the angle formed between the camera and the right- and left-hand instruments should be 25 to 45 degrees. In addition, the angle between the instruments and the horizontal plane should be less than 55 degrees (Frede et al, 1999). Some more formal training boxes will have built-in camera holders such that one person can practice alone without the assistance of a "camera driver." When possible, however, a camera driver can adjust the lens and camera in, out, up, and down to match the motions of the surgeon. This is most helpful during more delicate maneuvers such as suturing in which panning the view from wide to close-up is essential. This gives the assistant the opportunity to practice "driving camera," which is also an essential skill for laparoscopy. Necessary instruments might include laparoscopic graspers, scissors, and dissectors or essentially any instrument necessary to meet the requirements of the training drill. Practice for basic suturing requires a pair of laparoscopic needle drivers and some suture. A 3-0 suture on an SH needle is best for general practice.

Whether simple or complex, inanimate training models can be placed within standard training boxes and act as the basis for general skill acquisition and progression. Training models for basic tasks such as touching areas of the box at different depths and heights within space, passing objects between instruments and



Figure 10-32. A, Example of a standard laparoscopic training box with a monitor, camera-lens combination, and light source. B, LapED EZ Trainer is a portable briefcase-like box that opens to accommodate a laptop computer that is then connected through the USB port to the contained camera, thereby allowing the laparoscopic skill practice platform to be visualized on the laptop screen.

through and around obstacles, and other helpful maneuvers such as cutting and tissue manipulation can be constructed from common materials such as paper, sponges, rubber gloves or tubing, and other commonly found materials. Alternatively, a wide variety of commercially available models exist that are more realistic looking and may mimic actual operative scenarios more closely (Fig. 10-33).

Alternatively, nonliving animal tissue can be placed within the box trainer for skill acquisition exercises. The advantage of using real, but nonliving animal tissue to construct training models is that it creates a more realistic environment providing closer-to-life tissue handling. Generally the tissues used are inexpensive and can be purchased at a butcher shop or market. The disadvantage is that it requires more intense cleanup after practice. Generally the field inside the training box is set up to mimic a specific surgical scenario and develop specific skills. For instance, the stomach and esophagus of a chicken can be divided and then sewn back together laparoscopically to practice the fashioning of a vesicourethral anastomosis or pyeloplasty (Laguna et al, 2006; Ramachandran et al, 2008).

Live Animal Models. The obvious advantage of use of live animal models is the opportunity to train under more realistic conditions, including more accurate anatomic relationships of tissue and the necessity for hemostasis that does not exist with inanimate models. The disadvantages of use of live animal models are that it requires extensive resources such as a veterinary facility, personnel to care for and provide anesthesia for the animals, and, eventually, euthanasia of the animals. Obviously this can be quite costly. For these

reasons, practicing surgical skills on live animals is not appropriate for daily practice. Instead, these opportunities are usually reserved for formal training courses or when the need for a realistic environment warrants the necessary resources. In general, the species of animal used for practice must have a sufficient peritoneal compartment to provide an adequate working space. For fine procedures, animals as small as rabbits can be used. Swine are the most common animals used for laparoscopic and robotic training because they are readily available, they have the appropriate size peritoneal compartment, and their anatomy mimics relatively well that of humans. It must be noted, however, that the amount of bleeding that comes from a pig kidney (e.g., in partial nephrectomy) is not realistic compared with that of a human. In addition, the porcine bladder is almost completely intraperitoneal.

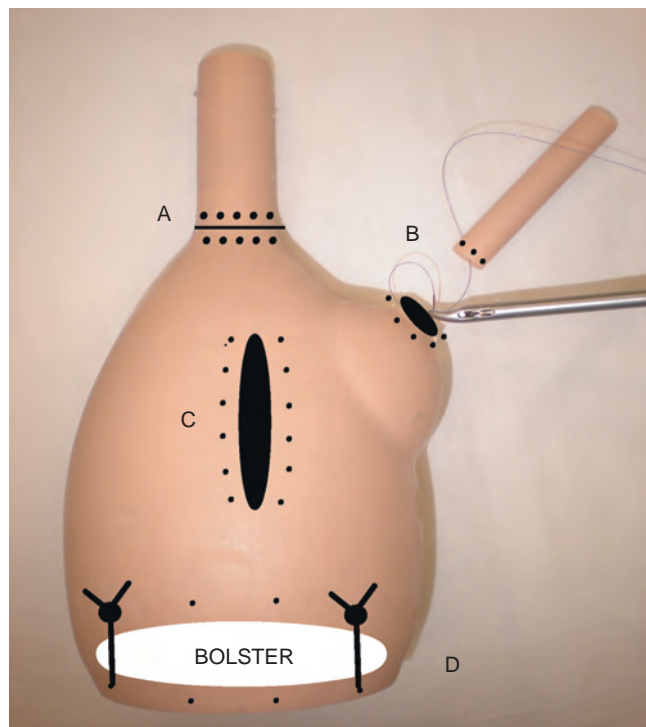


Figure 10-33. Example of a task-specific training model LapED (4-in-1) model. This model can be used to practice four different urology-specific tasks: (A) vesicourethral anastomosis, (B) dismembered pyeloplasty anastomosis, (C) closure of cystotomy, and (D) renorrhaphy. (From Abraham JB, Abdelshehid CS, Lee HJ, et al. LapED 4-in-1 silicone training aid for practicing laparoscopic skills and tasks: a preliminary evaluation. *J Endourol* 2008;22:1351-7.)

Cadaveric Models. One of the first experiences most medical students have in their training is anatomy, and this entails cadaveric dissection. The reason is simple. Short of operating on real patients, there is no better or more realistic way to learn human anatomy. This holds true for surgical practice as well: however, owing to the major resources necessary to have an anatomic gift program and the significantly high cost for a cadaver compared with alternative models, it is often not practical to use cadavers. If, however, facilities and funding are available and there is a need for practicing a procedure in the most realistic environment, there is no substitute for cadaveric models.

Virtual Reality Trainers

VR trainers are computer-based simulators that offer the opportunity to practice laparoscopic and robotic skills through specific tasks, as well as whole procedures. Typically, trainees view the computer-generated operative field or training drill on a computer monitor and perform tasks using laparoscopic manipulators. The instruments are depicted on the viewer and correspond with the trainee's movements. A major advantage of VR trainers is that they can collect information regarding trainee performance and track progress over time in terms of precision, economy of motion, and other parameters of interest. Because the trainers are computer based, it is possible to develop training programs and curricula including didactics, videos, and live practice sessions. The trainee can progress through the curriculum based on performance. VR trainers have been shown to improve the skills of trainees, helping to prepare them for better performance during live surgery (Seymour et al, 2002; Lucas et al, 2008). In addition, a recent systematic review demonstrated that VR training appears to decrease the operating time and improve the operative performance of surgical trainees with limited laparoscopic experience when compared with no training or with box-trainer training (Nagendran et al, 2013). Several commercially produced VR trainers for laparoscopy are available but are quite costly owing to the advanced technology and software development necessary. These include the LapSim (Surgical Science, Minneapolis, MN), the LAP Mentor (Simbionix, Airport City, Israel), the CAE ProMIS (CAE Healthcare USA, Sarasota, FL), and the Reachin Laparoscopic Trainer (Reachin Technologies, Stockholm, Sweden). Several VR trainers for robotic surgery have also been developed. These include the Robotic Surgical Simulator (RoSS) (Simulated Surgical Systems, Williamsville, NY), the MIMIC dV-Trainer (Mimic Technologies, Seattle, WA), the SimSurgery Educational Platform (SEP) Robot (SimSurgery, Boston, MA), and the da Vinci Skills Simulator (Intuitive Surgical), among several others (Fig. 10-34). All of these VR robotic trainers, however, have been shown to have face, content, and construct validity, and all of these simulators except the SEP Robot have shown educational impact (Abboudi et al, 2013). Lastly, a VR simulator has even been designed for single port laparoscopy, the SEP Single Port (SimSurgery).

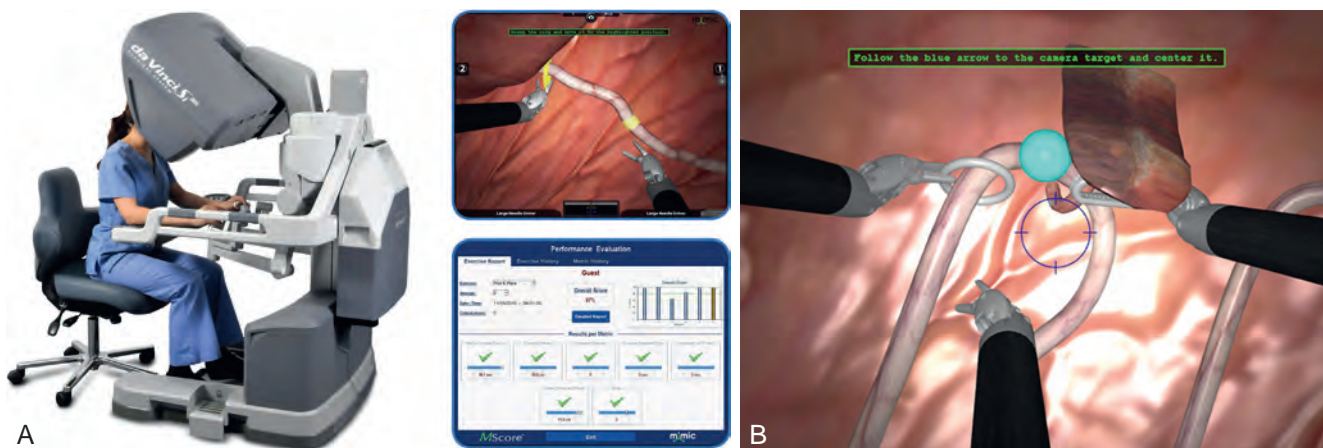


Figure 10-34. A and B, da Vinci Skills Simulator. (© 2015 Intuitive Surgical, Inc. Used with permission.)

Formal Training Programs

Surgical competence is defined by technical and nontechnical skills (Hoznek et al, 2006). Traditionally these skills have been passed down from teacher to apprentice in the process of caring for and operating on real patients during residency training. The technical skills were taught during real operative procedures, and the nontechnical skills such as surgical judgment, problem anticipation and avoidance, economy of motion, and so on were gained by experience of the trainee with supervision from a more senior instructor. In this way, traditional residency programs have been more “learning” programs than “teaching” programs. With ever-increasing emphasis being placed on patient safety, operating room efficiency, and cost containment, there has been a great interest in evaluating the efficacy of formal training programs in laparoscopic and robotic surgery. Such programs offer the opportunity to receive formal instruction in a safe, stress-free environment with the intention of honing both technical and nontechnical skills.

With this concept in mind, one method of concentrated instruction and skill acquisition is the “mini-residency” or “mini-fellowship.” In this training model, surgeons spend a period of several days (typically 5 days) receiving concentrated instruction on a given set of surgical skills or procedures including didactic sessions, clinical case observation, and laboratory training using both

inanimate and animate models. Typically, the attendees also gain access to expert proctors during their initial learning curve for the new procedure. Mini-residency training has been shown to be effective in helping postgraduate urologists incorporate new laparoscopic and robotic procedures into their clinical practices. In one study of laparoscopic renal surgery mini-fellowship trainees at the University of California, Irvine, 73% of attendees were performing laparoscopic renal surgery 3 years later (Kolla et al, 2010). This was also found with robotic surgical training: Of 47 urologists who took a 5-day training course for robotic radical prostatectomy, 90% were performing the procedure in their own practice at 3-year follow-up (Gamboa et al, 2009).

KEY POINTS: TRAINING AND PRACTICING LAPAROSCOPIC AND ROBOTIC SURGERY

- Laparoscopic VR trainers have been shown to improve the skills of trainees, helping to prepare them for better performance during live surgery.
- VR robotic trainers have been shown to have face, content, and construct validity.

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Tissue Dissection and Cauterization

Intracorporeal Lithotripters

TISSUE DISSECTION AND CAUTERIZATION

Electrosurgery

Electrosurgery is the application of electrical current to tissue to achieve the effects of cutting, coagulation, desiccation, or fulguration. Monopolar and bipolar electrosurgery techniques are used in urology in numerous applications. An understanding of the basic scientific principles as well as the tissue effects is necessary for the surgeon to use the technology in a safe and efficient manner. Although the technology can be of great assistance to the surgeon, improper settings or poor application can result in patient injury (Massarweh et al, 2006).

Electrosurgical technology was first developed in the late 1800s. The technology originated from spark gap transmitters that were used to generate radio waves at that time. The waveform produced was of a steady frequency but varied in amplitude. Using a combination of inductors and capacitors, the waveform could be smoothed out, although this resulted in some power loss. French scientists in the 1890s experimented with the technology and determined that the raw output from the spark gap transmitter could coagulate tissue, and the smoothed-out current could cut tissue. Around the turn of the 20th century, the technology began to be used in clinical surgical cases in Europe (Van Way, 2000; Massarweh et al, 2006).

In the 1920s, Bovie, an electrical engineer at the Massachusetts Institute of Technology, studied the work of his predecessors and developed a cutting loop that delivered electrical energy that could be used for cutting, coagulation, and desiccation. On October 1, 1926, at the Peter Bent Brigham Hospital in Boston, Cushing used the device to remove a highly vascular myeloma from the head of a patient that previously had been deemed inoperable because of the vascularity of the mass (Van Way, 2000; Massarweh et al, 2006).

Monopolar Electrosurgery

Basic Physics. Electrosurgery uses radiofrequency current in the range of 400,000 to 600,000 Hz to pass through tissue and create the desired effects. The generators deliver more than 100 W of power to the tissue at voltages ranging from 100 to 5000 volts. As the current is delivered to the tissue, the tissue is heated, and the effect occurs. **In contrast, with electrocautery, the instrument itself is heated and then applied to the tissue.** Ohm's law, $\text{Current (I)} = \text{voltage (V)} / \text{resistance (R)}$, applies and states that the current is determined by the applied voltage and the tissue's resistance. The higher the resistance of the tissue, the greater the voltage needed to drive the current through the tissue. Current is calculated as the flow of electrons during a specific period of time. Voltage is used to drive the current through the resistance, which in surgery is the tissue. When alternating current is used, resistance is termed *impedance*. As the resistance increases, the amount of voltage to drive the same amount of current also increases. As tissues become cauterized, their impedance increases, and a higher voltage is needed for the current to penetrate the tissue beneath (Van Way, 2000; Van Way and Hinrichs, 2000; Jones et al, 2006; Massarweh et al, 2006).

Cutting and coagulation currents can be applied and use similar frequencies. For coagulation to occur, the current is interrupted approximately 30,000 times per second. This interruption results in short bursts of radiofrequency energy. For cutting current, the radiofrequency current is delivered continuously (Fig. 11-1). With continuous energy delivery, the cells heat up rapidly to the point of boiling and then rupture, which results in the cutting effect. With coagulation, because the energy is interrupted, the cells are allowed to cool as the energy is cycled off, and the cells dry out instead of rupturing (Van Way, 2000; Jones et al, 2006; Massarweh et al, 2006).

Most generators also offer blended cutting, which adds some coagulation properties to the cutting current. This blended cutting is produced when the cutting current is interrupted similar to coagulation current. In contrast to coagulation current, where the generator output is concentrated into two or three cycles, blended cutting delivers more cycles to the tissue. The number of cycles delivered determines the degree of cutting versus coagulation. For example, a Blend 1 setting may allow 50% of the current through, whereas a Blend 3 setting might allow only 10% of the energy through, resulting in a greater coagulation effect (Van Way, 2000; Jones et al, 2006; Massarweh et al, 2006; Vilos and Rajakumar, 2013).

Modern electrosurgical generators are capable of high voltage and high wattage. This capability allows for either type of current to cut or coagulate. However, differences remain, and the coagulation current results in much more widespread tissue damage and charring but deeper hemostasis owing to the higher voltages used compared with a lower voltage cutting current. **Cutting current employs voltages 10 to 20 times less than coagulation but is still greater than 100 volts. Alternatively, coagulation current is delivered in short bursts at much higher voltage but with less current flow at the same amount of power.** The desiccation of the tissue results in increased impedance and lower current flow compared with cutting. Desiccation results in drying of the tissue and coagulation of blood vessels. The tissue is typically pale and dry with an eschar developing next to the electrode (Goddard et al, 1972; Van Way, 2000; Van Way and Hinrichs, 2000; Jones et al, 2006; Massarweh et al, 2006; Vilos and Rajakumar, 2013).

Fulguration results when the electrode is placed about 2 to 5 mm from the tissue. Electrical energy in the form of a spark arcs from the electrode to the tissue. A coagulation current setting on the generator usually is used, producing a darker char on the tissue with a superficial eschar. Fulguration can be effective at achieving hemostasis, but care must be taken to ensure the eschar is not too superficial, allowing for bleeding deeper in the tissue below the coagulum (Van Way, 2000; Jones et al, 2006).

Argon Beam Coagulator. Traditional monopolar devices do not work well in a liquid environment, such as when there is significant blood in the targeted field. The fluid results in dispersion of the current rendering it ineffective. To address this shortcoming, the argon beam coagulator was developed. **It works by adding a column of argon gas that passes over the electrode, and then electrosurgical energy ionizes the argon gas and helps to displace the blood in the surgical field.** Because it is a noble gas, the current from the electrode is effectively transmitted to the underlying tissue. The

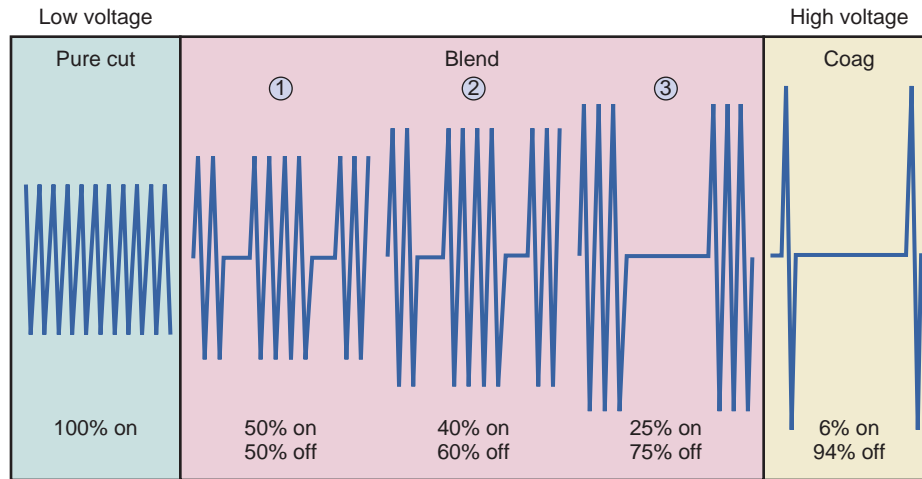


Figure 11-1. Instrument settings relating voltage and current. Pure cut uses continuous delivery, whereas coagulation uses interrupted delivery. Blended modes modify the degree of interruption to desired effect.

current follows the beam of gas and allows for diffuse superficial coagulation; this is ideal for obtaining hemostasis over a broad surface, such as during a partial nephrectomy. Typically, the argon beam coagulator is held slightly farther from the tissue at about 5 to 10 mm. It uses a standard generator and grounding pad but is operated at a higher power setting compared with traditional monopolar cautery in coagulation mode to desiccate the target tissues (Massarweh et al, 2006).

Generator Settings. When adjusting the generator settings, it is important to set the generator at a high enough power setting to achieve effective cutting and coagulation. Setting the generator too low results in an inability of the electrode to cut the tissue and poor or limited effect of the coagulation. For coagulation to occur, approximately 30 to 50 W is needed. For cutting, setting the generator at 60 W is a reasonable starting point subsequently adjusting the power as needed. Typically, fatty tissue is less conductive than muscle and may require higher settings of approximately 80 W. This information is intended as a rough guideline only; experience with individual generators varies (Van Way, 2000; Massarweh et al, 2006; Vilos and Rajakumar, 2013).

Although coagulation current may be used to “cut” tissue using lower power settings, it results in greater collateral damage compared with using a cutting setting. Although it may be reasonable to use coagulation when dividing muscle, it is better practice to use pure cut or cut on a blend setting to produce less charring and less ancillary tissue damage (Massarweh et al, 2006).

Safety

The incidence of electrosurgical injuries is estimated to be 2 to 5 per 1000 (Loffer and Pent, 1975; Nduka et al, 1994; Hulka et al, 1997). Understanding the principles of the electrosurgical devices and operating them within their safety parameters can help to decrease the risk of unintentional injuries.

During monopolar electrosurgery, the patient is part of a complete electrical circuit. Current is initially produced in the generator and is conducted over wires to the electrosurgical electrode. The electrode is used to deliver the current to the surgical site where it is focused. The current is distributed through the patient's body to the dispersive electrode (grounding pad), where it leaves the patient's body and travels over wires back to the generator to complete the circuit. This system is designed to concentrate the energy at the tip of the electrode and then disperse it widely while traveling through the patient's body. If the current is allowed to concentrate in other locations, potential morbidity could ensue.

Most electrosurgical injuries occur at the grounding pad site. Historically, the grounding pad was a metal plate that had contact gel applied to it before placing it in contact with the patient. Modern grounding pads are called dispersive electrodes and function in a similar but safer manner. The old-style metal grounding pads that were used with conductive gel could dry out during a case. Rather than have the current travel through a large contact patch, the dried-out pad could result in a very small contact patch that focused the current and resulted in electrical burns on the skin and underlying structures. Modern dispersive electrodes do not dry out and produce a safer, stable contact patch with the patient. Modern generators have a built-in self-test system that monitors the status of the dispersive electrode. If the generator becomes dislodged or loses contact in some way, the system shuts itself down and the ground fault warning is activated (Nduka et al, 1994; Hutchisson et al, 1998; Alkatout et al, 2012).

Injuries can ensue from inadvertent activation of the electrosurgical electrode. Injury can occur if a foot pedal is accidentally depressed and the electrode burns the drape or burns the patient at a site not intended. Handheld electrodes with a finger actuator are less likely to cause such an injury, although it is still possible. Other injuries can occur if electrosurgical energy is applied to unintended structures during surgery; this can occur when blood vessels and nerves are running close together. For example, the parasympathetic nerves that run near the prostate and are responsible for erections may be inadvertently injured when hemostasis is obtained with coagulation. During laparoscopic nephrectomy, the heel of a monopolar hook electrode may be inadvertently brought into contact with the bowel while activated, resulting in a bowel injury. Keeping the instruments in view, being aware of the surrounding structures, using low but effective power settings, and maintaining a general awareness of the instruments may help reduce such injuries.

The tissues of the body vary in their impedance (ability to conduct electrical energy). Structures such as blood vessels have lower impedance and preferentially conduct and concentrate current, whereas fat has high impedance. Tissue impedance is an important consideration when operating on structures such as the bowel, where current could get concentrated in the thin vascular pedicle that supports the structure. Current concentrated in the pedicle could damage the vascular supply to the tissue.

In patients with pacemakers or implantable cardioversion devices, the manufacturer should be consulted before surgery involving monopolar cautery to ensure that interference with the devices does not occur during surgery. The devices may need to be temporarily deactivated during the procedure.

Prosthetic joints can also affect current conduction but are not an absolute contraindication to use of monopolar cautery. Ideally, the direct path of the electrical circuit should be directed away from the prosthetic joint. For example, if the patient has a right hip prosthesis, the dispersion electrode pad should be placed on the contralateral hip (Massarweh et al, 2006).

Insulation failures can occur if there is a breakdown in the insulating material that surrounds the electrosurgical electrode. Usually only the tip of the electrode is left without surrounding insulation, but if defects occur in other locations, the current may arc out in these spots leading to unintended injuries. Such an occurrence is more likely when higher voltage coagulation modes are used. Reused instruments may be more likely to experience such failures because the defects in the insulation may occur during the reprocessing, although disposable devices could also have defects (Massarweh et al, 2006). Several clinical reports of insulation failures during robotic-assisted laparoscopic surgery have been published (Mues et al, 2011; Cormier et al, 2012). A 33% failure rate of the first-generation robotic monopolar scissors tip cover accessory after one clinical use has been described (Engebretsen et al, 2013).

The surgeon is also at risk for electrosurgical burns. Surgical gloves do not provide much insulation from electrical current. Current can penetrate gloves when they become wet, through capacitance conducting, or when mechanical breakdown of the glove occurs (Tucker and Ferguson, 1991).

Capacitive Coupling. Capacitive coupling is the transfer of energy within an electrical network by means of the capacitance between circuit nodes. Capacitive coupling occurs when two conductive elements are spaced apart by an insulator and energy is stored creating an electrostatic field. When the net charge exceeds the insulator's capacity, current is transmitted from the first conductor to the second. This occurrence is rare but can lead to complications during laparoscopic procedures using electrosurgery. When an active electrode that is surrounded by insulation is passed down a metal trocar, capacitive coupling can occur. However, it can also occur with plastic trocars. The injuries typically occur out of the surgeon's field of vision. An active electrode monitoring system and limiting the amount of time that high-voltage settings are used can decrease the risk of capacitive coupling (Tucker and Voyles, 1995; Vilos et al, 2001; Jones et al, 2006; Wang and Advincula, 2007).

General Safety Tips. Using the lowest possible energy setting that achieves the desired surgical effect is the simplest of the basic principles for the safe use of electrosurgical instruments. Rather than starting at a high setting, the surgeon should slowly ramp up the energy setting until the desired effect is reached. With higher settings, the potential for arcing and capacitive coupling increases. The settings should not exceed settings recommended by the manufacturer.

During surgical use, the electrode tip can become coated with eschar, which causes an increase in impedance and can lead to arcing, spark generation, and ignition of the eschar. A scratch pad can be used to clean the eschar, but this can cause grooves to form on the electrode, which can promote further eschar buildup. Alternatively, a sponge can be used to clean the electrode tip. A sponge effectively clears the eschar and does not cause scratches to the electrode (Massarweh et al, 2006).

A common technique during open surgical procedures is for the surgeon to grasp a bleeding vessel with a forceps or hemostat and then have the assistant touch the instrument with the activated electrode of the Bovie; this delivers current through the instrument to the bleeding vessel. During these maneuvers, the surgeon must be careful not to touch the patient with his or her free hand. Doing so would create an alternative circuit that could allow the current to travel to a different part of the patient's body. Keeping a firm grasp on the forceps can also help to reduce the possibility of current traveling in an alternate path (Hutchisson et al, 1998; Jones et al, 2006; Alkatout et al, 2012).

Basic principles that should be observed include keeping the operating field neatly organized and not tangling cords when multiple corded instruments are used. Care should be taken not to wrap

cords around metal instruments because insulation defects could lead to burns. The handheld electrodes should be secured in an insulated holster when not being used rather than resting them on the patient; this reduces the possibility of burns or injury through inadvertent activation (Massarweh et al, 2006).

Types of Electrosurgical Instruments

Monopolar Devices. Electrosurgical instruments can be divided into two categories of delivery devices—monopolar and bipolar. For monopolar devices, the Bovie is the most widely used example and has broad applications in many surgical specialties including urology. The size and shape of the electrode affect its interaction with the tissue. A smaller contact area results in higher current concentration, whereas a larger contact area results in the current being more dispersed. Greater power settings would be needed with the larger electrode to achieve a similar tissue effect. Many systems allow the surgeon to select the tip appropriate to the given procedure, and the tips can be changed if needed during the procedure to fit the application (Massarweh et al, 2006; Vilos and Rajakumar, 2013).

Bipolar Devices. In contrast to monopolar systems in which a circuit is created by delivering the energy via an electrode and then removed from the patient using a dispersive electrode (grounding pad), bipolar delivery does not require a dispersive electrode. Rather, the active and return electrodes are integrated in the delivery hand piece. The tissue contained between the electrodes is the target tissue.

Bipolar "vessel sealing" devices have been developed that use computing technology built into the electrosurgical generators. These closed-looped feedback systems allow for vascular structures up to 7 mm in diameter to be fused and can help obviate the need for sutures, clips, or surgical staples. Several studies have confirmed the effectiveness of such devices demonstrating clinically equivalent burst pressures when compared with surgical staples, sutures, and titanium clips. Compared with the harmonic scalpel, burst pressures were higher for vessels 4 to 7 mm in diameter (Kennedy et al, 1998; Harold et al, 2003; Landman et al, 2003; Takada et al, 2005). The LigaSure vessel sealing system (Covidien, Dublin, Ireland) has been used successfully for radical prostatectomy and cystectomy with a benefit in operating time and blood loss demonstrated compared with conventional vessel ligation. However, long-term damage to neurovascular structures was not addressed in these studies (Sengupta and Webb, 2001; Daskalopoulos et al, 2004). In a study comparing the use of the LigaSure device with a harmonic scalpel during laparoscopic radical prostatectomy, a benefit in functional outcomes including return to continence and erectile function was demonstrated in favor of the LigaSure device (Pastore et al, 2013).

Ultrasonic Instrumentation (High-Frequency Vibratory Device)

Ultrasonic devices offer an alternative to electrosurgical instruments. These devices have elements that vibrate at ultrasonic frequencies of approximately 55,000 Hz. Mechanical energy and heat are generated, and these cause the denaturation of proteins and the formation of a coagulum that can seal small vessels. Depending on the instrument, vessels 2 to 3 mm in diameter can be sealed, and vessels up to 5 mm in diameter can be sealed with some newer instruments. Newer instruments also produce less heat and charring to the surrounding tissue, limiting thermal injury. The heat generated is usually less than 80° C. The device is best applied to the tissue in a tension-free manner; this allows the instrument to divide the tissue effectively while coagulating at the same time, limiting blood loss. Aerosolized fatty droplets may develop as the tissue is divided, and this can negatively affect visualization through the laparoscope. Examples of such devices are the Ultra Shears (Covidien), Harmonic Scalpel (Ethicon Endo-Surgery, Johnson & Johnson, New Brunswick, NJ), and Thunderbeat (Olympus, Tokyo, Japan). Devices for open and

laparoscopic surgery have been developed. The Harmonic Scalpel has been shown to allow for effective tissue dissection and bleeding control during laparoscopic partial nephrectomy (Harris, 1978; Helal et al, 1997; Tremp et al, 2011).

A study comparing the vessel sealing times and thermal spread of two bipolar vessel sealing systems (LigaSure and PK [Gyrus ACMI, Southborough, MA]) and an ultrasonic device (Harmonic Scalpel) was performed. This study demonstrated that the two bipolar systems had faster vessel-sealing times with higher burst pressures compared with the ultrasonic device. However, the ultrasonic device had less thermal spread and smoke production (Lamberton et al, 2008). The smoke plume produced by ultrasonic devices may also be less toxic compared with electrosurgically generated smoke (Fitzgerald et al, 2012).

Laser Instrumentation: Soft Tissue Applications

A laser is a device that emits light through the process of optical amplification by the stimulated emission of electromagnetic radiation. The word *laser* is derived from an acronym for “light amplification by stimulated emission of electromagnetic radiation.” In the 1980s, lasers first became of interest to researchers and clinicians in urology, and at the present time a wide range of lasers are employed to treat various soft-tissue and stone conditions. Although the holmium:yttrium-aluminum-garnet (Ho:YAG) laser has become the accepted gold standard for the treatment of urinary calculi at this time, various wavelengths of lasers are employed to treat soft-tissue conditions such as stricture disease, benign prostatic hyperplasia (BPH), urothelial cell cancer, and genital skin lesions (Marks and Teichman, 2007; Heinrich et al, 2010; Zarrabi and Gross, 2011).

Lasers are a source of electromagnetic radiation that emit a beam of energy that may include nonoptical wavelengths and visible light. The properties of this light create the therapeutic effects used during surgical procedures. General components exist with all lasers including an energy source, an active medium, and a resonant cavity. Light is generated with the active medium, which can be a solid, liquid, or gas. For the laser action to occur, most of the atoms or molecules within the active medium must be brought simultaneously to a higher energy state by an energy source; this is also referred to as pumping. The energy source energizes the atoms in the active medium and produces a population inversion, which is an excited state in which the atoms or molecules are primed for stimulated emission (Troup, 1963; Siegman, 1986).

Numerous types of energy sources drive lasers. Broadly, either electrical current or a different wavelength of light is used. The pump light can be generated by a flash lamp or a different wavelength laser. The specific energy source used depends on the type of laser; however, all are designed to produce laser light in a collimated beam (Siegman, 1986; Teichmann et al, 2007).

Light exists as electromagnetic waves representing spatial concentrations of energy. Each wave exists as a bundle of energy or as a particle called a photon. Photons are emitted and stimulate surrounding atoms and cause additional photons to be released. These have the same energy and travel in phase with the initial stimulating wave. The result is that the entire light is the same wavelength and travels in the same direction. The highly ordered, in-phase light arrangement is termed *coherence*. A long tube or cylinder is ideal for this process but not practical. A resonant cavity is created using mirrors to reflect light, allowing it to have many passes through the medium. A small portion of the amplified light escapes out of the resonant cavity and forms the beam of laser light (Stein and Kendall, 1984a; Stein, 1986; Welch et al, 1989).

Laser light has specific properties. It is monochromatic and of a single wavelength. The light is coherent with a uniform spatial relationship between all portions of the electromagnetic wave. It has directionality with minimal divergence, which allows it to maintain brightness over long distances. It is the high concentration of the bright laser light when focused on a small spot that gives it the properties to be a useful surgical tool but also a potential hazard (Stein and Kendall, 1984a; Welch et al, 1989).

The wavelength of laser light can vary and may be in the ultraviolet, the visible, or the infrared portions of the optical spectrum. Most lasers emit one or a couple of wavelengths; examples include the argon (488 nm—blue; 514 nm—green), the neodymium:YAG (Nd:YAG; 1064 nm and 1318 nm), and the Ho:YAG (2100 nm) lasers (Stein and Kendall, 1984a; Teichmann et al, 2007).

Pulsed and Continuous Wave Lasers

Depending on how the excitation energy is applied and how the laser cavity is configured, the output beam of laser light is either pulsed wave or continuous wave. The duration and energy of individual pulses can vary and depend on the type of laser. Pulses may be delivered individually, in groups, or continuously over a wide range of frequencies. A laser is considered continuous wave if the output emission is greater than 0.25 second. Clinically, a continuous wave laser delivers output that is continuous and of a constant amplitude; this allows for a stable, easy-to-control instrument. In contrast, a pulsed wave laser delivers bursts of energy, which works well for stone fragmentation but may be more difficult to control during soft-tissue interactions (Teichmann et al, 2007; Zarrabi and Gross, 2011).

The power of the laser is equal to the energy over time ($P = \text{energy/time}$ or $W = J/\text{sec}$), and a high degree of power can be reached with even a small amount of energy if very short pulses are used. Several techniques exist that can compress or shorten the pulse. Examples include Q-switching and mode locking. Q-switching involves interrupting the light beam in a controlled fashion so that the laser action is delayed until maximal population inversion has occurred in the active medium. It generates lower pulse repetition rates, higher pulse energy, and longer pulse duration compared with mode locking, another technique used to shorten the pulse. Mode locking, which can be combined with Q-switching, can create ultrashort pulses by fixing the way photons bounce back and forth in the resonant cavity. It can create very high power pulses because of their ultrashort duration (Stein and Kendall, 1984a; Teichmann et al, 2007; Zarrabi and Gross, 2011).

Delivery Systems

All medical lasers have a delivery system that allows for the laser energy to be directed to the intended target site. Delivery systems may be fixed rigid systems such as articulating arms or flexible systems such as fiberoptic glass fibers. Fiberoptic systems are generally inexpensive and quite versatile; however, fiberoptic materials are unable to transmit all laser wavelengths. For example, the carbon dioxide (CO₂) laser, with a wavelength of 10.6 μm , does not pass through quartz or glass fiber optics, and instead a more rigid system composed of an articulating arm with a series of mirrors is employed. The final tissue interface usually contains a focusing device to optimize the laser energy delivery (Stein and Kendall, 1984a, 1984b; Marks and Teichman, 2007; Teichmann et al, 2007; Zarrabi and Gross, 2011).

Light-Tissue Interaction

Laser light is absorbed by tissue in a wavelength-dependent fashion. However, some of the light, independent of the wavelength, may be reflected by the boundary layer of the tissue. This light is lost for the surgical purpose and may cause heating and collateral damage in the surrounding tissue. The optical properties of the tissue and the surrounding irrigant can affect the degree of reflection. Because this process is not dependent on the wavelength, reflection is often not considered when selecting a wavelength for surgical lasers (Teichmann et al, 2007).

Some scattering of the laser energy may also occur. By scattering, some of the intended laser energy is taken out of the surgical field. The degree of scattering varies with the wavelength of the laser. Typically, lasers with shorter wavelengths have a much greater amount of scatter compared with lasers of longer wavelengths. This

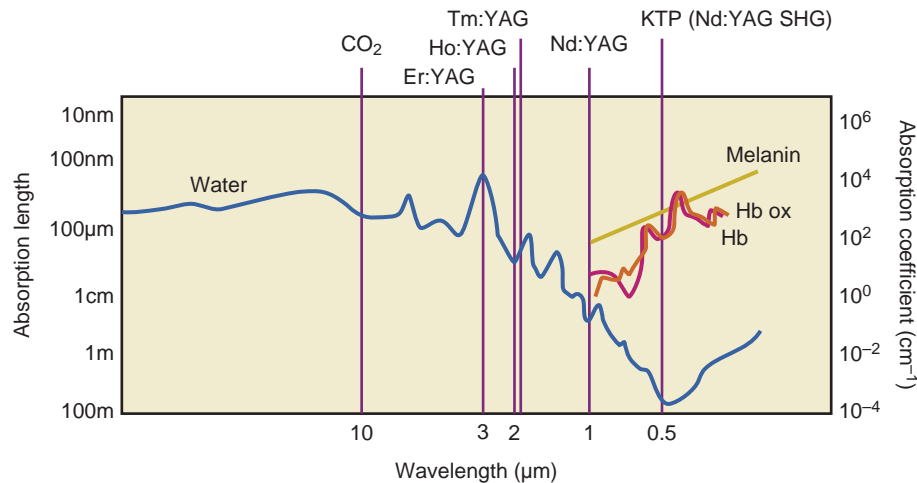


Figure 11-2. Comparison of various laser wavelengths and absorptions in various media. CO₂, carbon dioxide; Er:YAG, erbium:YAG; Hb, hemoglobin; HbO₂, oxyhemoglobin; Ho:YAG, holmium:YAG; KTP, potassium titanyl phosphate; Nd:YAG, neodymium:YAG; SHG, second harmonic generation; Tm:YAG, thulium:YAG.

is an important consideration in selecting an appropriate laser for surgical applications (Teichmann et al, 2007).

The most important light-tissue interaction is absorption. When the laser beam enters into a medium in which it is absorbed, the intensity of the laser energy decreases in an exponential fashion that is consistent with Beer-Lambert law. This law states that a logarithmic dependence exists between the transmission of light through a substance, the product of the absorption coefficient of the substance, and the distance the light travels through the material. Absorbed laser energy is converted to heat and increases the temperature of the target tissue. If enough heat is generated, coagulation and subsequently vaporization can occur. A chromophore is required for absorption to occur. In the body, melanin, hemoglobin, and water are available chromophores with hemoglobin and water being most important for urologic applications (Teichmann et al, 2007; Zarrabi and Gross, 2011) (Fig. 11-2).

Types of Lasers

Neodymium:Yttrium-Aluminum-Garnet. The Nd:YAG laser has a wavelength of 1064 nm and has a tissue depth of penetration of about 1 cm. It has hemostatic and coagulative tissue properties. Historically it has been used in urology for the treatment of BPH with visual laser ablation of the prostate (VLAP) and interstitial laser coagulation of the prostate. During VLAP, a side-firing laser fiber is used to direct the laser beam at 60- to 90-degree angles. The fiber is held off the prostatic tissue, and an area of heat-induced coagulative necrosis is produced as the tissue is targeted. The coagulated tissue is not entirely cleared at the time of surgery, but rather a sloughing process occurs in the weeks after surgery with associated edema. Prolonged postoperative catheterization may be needed in 30% of individuals (Norris et al, 1993; Cowles et al, 1995; Muschter, 2003).

Interstitial laser coagulation of the prostate involves placing laser-diffusing fibers directly into the adenoma of the prostate and can be performed either transurethral or via a perineal approach. Similar to VLAP, the tissue undergoes coagulative necrosis and subsequently atrophies. The procedure can be safely performed in anticoagulated patients, but significant postoperative tissue edema can occur. Prolonged periods of catheterization after surgery—often 7 to 21 days—are required because of the high risk of urinary retention. Published re-treatment rates of up to 20% at 2 years and 50% at 54 months suggest poor long-term durability (Perlmutter and Muschter, 1998; Daehlin and Frugard, 2007). With the advent of newer laser technology and techniques, the use of the Nd:YAG laser for BPH has largely been abandoned.

Potassium Titanyl Phosphate. The potassium titanyl phosphate (KTP) laser, commonly referred to as the “green light” laser, is a frequency-doubled Nd:YAG laser. The Nd:YAG laser beam is passed through a KTP crystal, which results in doubling of the frequency and halves the wavelength to 532 nm resulting in a visibly green laser beam. This wavelength is strongly absorbed by hemoglobin and in well-vascularized tissue has only 1 to 2 mm of tissue penetration compared with 10 mm for the standard Nd:YAG laser. The KTP laser is widely used for photoselective vaporization of the prostate in which the well-vascularized prostate tissue is treated in a noncontact fashion with a side-firing laser fiber. The targeted tissue quickly increases in temperature above the boiling point and is vaporized leaving behind a rim of coagulated tissue that provides a layer of hemostasis. In contrast to VLAP, the limited depth of tissue penetration results in less tissue edema, and prolonged catheterization is usually not required (Barber and Muir, 2004; McAllister and Gilling, 2004; Teichmann et al, 2007; Zarrabi and Gross, 2011).

The early KTP laser systems were low-powered 34-W systems and were used in conjunction with a standard Nd:YAG laser. A hybrid surgical technique evolved in which the surgeon first performed a VLAP with the Nd:YAG laser and then used the KTP laser to perform bladder neck incisions. The goal was to try to reduce the prolonged catheterization and bothersome postoperative lower urinary tract symptoms after standard VLAP (Barber and Muir, 2004). Subsequently, a higher powered 60-W KTP laser was developed. This KTP laser was a pulsed wave system but allowed for rapid delivery of the pulses that simulated the effect of a continuous wave laser. This laser permitted the photoselective vaporization of the prostate procedure to be performed independently of the standard Nd:YAG laser. Further refinement resulted in the development of an 80-W KTP laser, which demonstrated favorable outcomes and complications comparable to traditional transurethral resection of the prostate (TURP) (Kuromatsu et al, 2006; Ruszat et al, 2008).

Lithium Triborate. The 120-W lithium triborate (LBO) laser was developed in an effort to increase the efficiency of the tissue vaporization compared with the 80-W KTP laser, especially for men with large prostates in whom procedures remained time-consuming (Wosnitzer and Rutman, 2009). The LBO remains a 532-nm wavelength laser. The higher power allows the distance between the fiber tip and the target prostate tissue to be increased to 3.0 mm versus 0.5 mm for the KTP laser. The greater distance may help preserve the laser fiber and make it technically easier to use. However, hemostasis with the higher-powered system appears to be less compared with the 80-W system (Heinrich et al, 2010). Most recently, a 180-W LBO laser that works in conjunction with a liquid-cooled fiber

delivery system (GreenLight XPS, AMS, Minnetonka, MN) was developed to increase efficiency further. The European GOLIATH study confirmed efficacy similar to TURP, and a North American multicenter trial demonstrated shorter laser and operating times for the 180-W system compared with 120-W systems (Hueber et al, 2013; Bachmann et al, 2014). However, a steeper learning curve has been reported with the 180-W systems, with up to 120 procedures needed to work through the process and handle the higher power of the system safely and effectively (Misrai et al, 2014).

Diode. Diode lasers with wavelengths of 808 to 980 nm are absorbed well in water and behave similarly to Nd:YAG lasers (Orihuela et al, 1996). However, the laser is much more efficient than the Nd:YAG and requires only a standard wall plug for operation; this allows for a smaller, more portable laser design with fewer cooling requirements. More recently, interest in the diode laser as a tool for the surgical management of BPH increased. The 980-nm diode laser was used when the higher powered LBO lasers were found to be not quite as effective in terms of hemostasis compared with the older 80-W KTP lasers. The diode laser appears to provide better hemostasis compared with the LBO laser but a higher complication rate; postoperative frequency and urgency and epididymitis have been associated with its use (Chiang et al, 2010).

Holmium:YAG. The Ho:YAG laser is a 2140-nm pulsed laser that is used for soft-tissue and lithotripsy applications in urology. The 2140-nm wavelength is strongly absorbed in water, traveling only about 0.5 mm in the fluid medium, making it ideal for the urologic environment. In the prostate, the absorption depth is about 0.4 mm resulting in a high-energy density that leads to the rapid vaporization of tissue. Heat is also generated during this process and allows for coagulation of small blood vessels up to a depth of approximately 2 mm.

It is held that the onset of vaporization occurs in the irrigant that is adjacent to the tip of the laser fiber. With each pulse of the laser, a steam bubble of a few millimeters in diameter is created. The bubble is not visible because it is present for only about 500 μ sec—about the same length of time as the laser pulse duration. During holmium laser enucleation of the prostate (HoLEP), the laser pulses create the steam bubbles, which lead to the separation of the prostatic adenoma from the capsule of the prostate. Tissue vaporization occurs and leads to the white fibrous appearance of the tissue. The heat generated during the process allows for hemostasis to occur in the adjacent tissue. For persistently bleeding vessels, the laser can be “defocused” by increasing the distance between the fiber tip and the target bleeding vessel; this results in only the coagulation effect occurring with limited or no vaporization.

Before the development of the HoLEP technique, the use of the Ho:YAG laser for the treatment of BPH went through a series of steps. Similar to the KTP laser, the Ho:YAG laser was initially combined with the Nd:YAG laser to perform hybrid techniques in which the Nd:YAG was used first to perform VLAP, and then the Ho:YAG was used to make bladder neck incisions that reduced the need for prolonged postoperative catheterization (Gilling and Fraundorfer, 1998). These hybrid techniques subsequently led to holmium laser ablation of the prostate in which the laser energy was used to vaporize the prostatic tissue. This was a relatively easy procedure to learn but did require a high-powered Ho:YAG laser (80 to 100 W) and a side-firing laser fiber. However, the rate of vaporization was slow, and long procedure times were needed to treat men with large prostates adequately. The side-firing fibers would also fail if held too closely to the tissue, likely owing to thermal breakdown (Tan et al, 2003). The development of holmium laser resection of the prostate followed. This technique involved cutting pieces of the prostate off as it was resected, similar to a TURP. The sizes of the pieces could be larger than typical TURP chips but had to be small enough to be able to irrigate them out of the bladder at the completion of the resection. This technique was more challenging than holmium laser ablation of the prostate and remained time-consuming in patients with large prostates (Cresswell et al, 1997).

The next development was HoLEP, in which the median and two lateral lobes are enucleated and pushed into the bladder in a manner mimicking an open prostatectomy. Before the introduction

of an effective tissue morcellator, some surgeons employed a traditional transurethral resection loop to cut up the adenoma in the bladder after the enucleation was completed. However, the tissue morcellator streamlined this process, and although it still carries with it the risk of bladder injury, it would appear to be much safer and less cumbersome than using a transurethral resection loop. HoLEP is performed in an almost bloodless field as a result of the coagulation produced by the Ho:YAG wavelength but also as a result of the extensive blunt dissection from the tip of the endoscope, similar to the use of a surgeon's finger during an open retropubic prostatectomy (Elzayat and Elhilali, 2006). HoLEP has proven to be a highly effective procedure with durable long-term results in men undergoing surgical management of BPH. It is effective for men with a broad range of prostate sizes and can be performed in men on anticoagulation (Elzayat et al, 2005, 2006; Tyson and Lerner, 2009; Krambeck et al, 2010). However, adoption of HoLEP has been slowed by the steep learning curve and the availability of other techniques that are easier to learn (Bae et al, 2010).

Thulium:YAG. The thulium:YAG (Thu:YAG) laser is a continuous wave laser operating at a wavelength of approximately 2000 nm. It differs from the Ho:YAG laser in that the thulium ions are excited by high-power laser diodes as opposed to flashlamp excitation with the Ho:YAG. As a result, there is less heat generation and increased power efficiency by a factor of five with the Thu:YAG laser, and no special electrical installation is needed to operate the laser (Teichmann et al, 2007). The slightly shorter wavelength compared with the Ho:YAG laser results in slightly less depth of tissue penetration. The continuous wave output promotes more of a direct cutting action of the laser versus tissue tearing and splattering with the pulsed output of the Ho:YAG. As the tissue is cut with the Thu:YAG, a seam of coagulated tissue is created and produces hemostasis. The coagulated tissues retain some water for efficient absorption of the laser energy during subsequent tissue passes (Teichmann et al, 2007).

Similar to other lasers, the Thu:YAG has been used in a variety of manners to treat BPH. Early reports described a tangerine technique in which the prostate was cut into slices with the laser (Xia et al, 2005). Hybrid techniques involving both vaporization and resection (vaporesction) were developed and shown to be effective (Bach et al, 2010). Thulium laser enucleation of the prostate followed and was demonstrated to have results similar to HoLEP (Lancono et al, 2012; Zang et al, 2012).

Carbon Dioxide. The CO₂ laser produces a beam of infrared light with a wavelength of 9.4 to 10.6 μ m. It is strongly absorbed by water and used for numerous medical purposes including dermatologic applications. It is a continuous wave laser and highly efficient with a ratio of output power to pump power of 20%. The infrared beam is delivered with a rigid arm containing a series of mirrors (Stein and Kendall, 1984b; Malek, 1992). In urology, it is primarily used to treat skin lesions such as condyloma, but it is also used to treat penile carcinoma when an organ-preserving strategy is employed (Finkelstein, 1984; Bandieramonte et al, 2008; Colechia et al, 2009).

INTRACORPOREAL LITHOTRIPTERS

Table 11-1 summarizes characteristics of commonly used intracorporeal lithotripters.

Electrohydraulic Lithotripsy

Electrohydraulic lithotripsy (EHL) has been implemented in biliary, pancreatic, and renal calculi. Initially employed in 1950 for bladder stones using 9-Fr probes, renal applications through flexible ureteroscopy became possible with technologic advances. First described in 1988, at a time when laser fiber technology was unable to flex in the same way, EHL became an innovative strategy to treat lower pole kidney stones endoscopically. Since then, more contemporary modalities have improved efficiency, while minimizing complication risks.

TABLE 11-1 Characteristics of Commonly Used Intracorporeal Lithotripters

MODALITY	BLADDER	URETER	KIDNEY	FLEXIBLE	CONTACT	MECHANISM OF ACTION	TISSUE EFFECTS	ADVANTAGES	DISADVANTAGES	PROBE SIZES (FR)
EHL	✓	✓	✓	✓	1 mm from stone	Electrical spark produces vapor bubble and subsequent cavitation bubble creates shockwaves that fracture stones	>1 mm distance from mucosa <500 mJ—no injury >1000 mJ—ureteric perforation	Able to reach lower pole Inexpensive	Significant tissue damage at higher energy Durability of probe tip	1.6, 1.9, 3.3, 9
Ultrasonic	✓	✓	✓	✓	Direct contact	Rapidly vibrating probe tip results in fragmentation, while simultaneous aspiration removes debris	Mucosal stripping No muscularis damage	Most efficient single modality In-line suction for simultaneous stone removal	Reduced efficiency in hard stones	2.5, 3, 4.5, 9
Pneumatic	✓	✓	✓		Direct contact	Ballistic tip repeatedly strikes stone similar to jackhammer	Focal areas of hemorrhage and mucosal erosions Least traumatic of all intracorporeal lithotripters	Least traumatic Works well on harder stones Least expensive	Least efficient Significant retropulsion	2.4, 3, 4.8, 6, 10.5
Ho:YAG laser	✓	✓	✓	✓	Direct contact	Photothermal energy transfer rapidly heats and disintegrates stone producing fine fragments	Thermal injury to depth of 0.5-1.0 mm	Flexible enough to reach lower pole Smallest fragments Works on all stone compositions Can be used for nonstone indications	Mucosal injuries with 0.5-1 mm depth of penetration Fiber breakage can damage flexible scope High initial cost	200-μm, 365-μm, 550-μm, 1000-μm
Combination ultrasonic/pneumatic	✓		✓		Direct contact	Simultaneous pneumatic and ultrasonic lithotripsy	Subepithelial denudation, muscularis rupture	More efficient than pneumatic or ultrasonic alone Works on all stone compositions	Only rigid probes available Requires large-diameter working channel	9.9 (Swiss LithoClast Ultra) 11.25 (CyberWand)

EHL, electrohydraulic lithotripsy; Ho:YAG, holmium:YAG.

Physics and Mechanism of Action

Two electrodes are positioned at the tip of the probe, creating a spark when triggered. Immersed in a liquid, the electrical spark creates an immediate transition from fluid to gas, creating a rapidly expanding plasma shockwave radiating from the spark outward 360 degrees. The collapse of this shockwave creates a cavitation bubble, which creates a secondary shockwave and high-pressure microjets (Vorreuther et al, 1995).

By adjusting spark discharge, the electrical and subsequent acoustic fragmentation potential can be optimized. Vorreuther and Engelking (1992b) identified that higher voltage shocks produce linearly increasing peak pressures and steeper shockwave fronts. Lower capacity probes produced shorter currents and shorter sparks with more narrow pulse widths. Because fluid vaporization provides the force required for fragmentation, a small space between the probe and stone is recommended during fragmentation. Typically, 1 mm is required because increasing the probe-to-stone distance leads to exponential decreases in shockwave power.

Probes between 1.9 and 3.3 Fr are available. Thinner probes are considered more versatile because of their application in flexible and semirigid ureteroscopy. Reducing probe diameter does not clearly lessen fragmentation potential; however, durability is decreased (Elashry et al, 1996). Pressure generated by EHL probes is estimated using the formula: Maximum pressure = energy/(pulse duration × fiber cross-sectional diameter).

Tissue Effect

Vorreuther and colleagues (1995) attempted to quantify tissue damage resulting from the use of a 3.3-Fr Wolf EHL probe. Using freshly harvested human ureters, histologic changes were measured after direct contact with the EHL probe. At 100 mJ, only punctate mucosal injuries were noted, whereas increasing to 400 to 600 mJ caused superficial mechanical defects in the muscularis. Increasing the energy to 1000 mJ caused transmural perforations. Microscopically, no thermal injuries were noted, and defects appeared to be due to mechanical disruptions, although limited to the cross-sectional diameter of the probe. When maintaining constant energy levels, altering voltage and/or capacity did not affect the resulting histologic findings. No damage was encountered at a distance of 1 mm between the probe tip and mucosa, even at maximal energy and pulse rates (Vorreuther et al, 1995). In a porcine model, bladder exposure to varying energy and total pulse numbers was performed using a 3-Fr probe. Scanning electron microscopy identified that the depth of mechanical mucosal denudation correlated independently with the energy setting and number of delivered pulses (Wu et al, 1994).

When tested in an intact ureter, the probe tip was centered in the lumen, and no histologic damage was encountered at energy settings less than 500 mJ/pulse. When energy levels reached 1000 mJ, a single pulse could produce a 1-cm longitudinal ureteric perforation. Thought to be secondary to cavitation bubbles, which can reach 1.5 cm in diameter at greater than 1300 mJ, the rapid expansion effectively burst the ureter (Vorreuther et al, 1995). The safe use of this (and any other) lithotripter requires a working knowledge of the physics behind stone fragmentation and the collateral effects on surrounding fluid and tissues (Fig. 11-3).

See the Expert Consult website for further details.

Chemical stone composition has been shown to affect fragmentation efficiency during EHL ureteroscopy. A review of operating room times for 193 patients was compared with the chemical composition of ureteric stones. Uric acid stones required the most time, followed by calcium oxalate monohydrate, and in multivariate analysis, stone size was negatively associated with successful fragmentation (Song et al, 2012). This association may be due to the smooth outer surface and lamination of uric acid stones being more difficult for shockwave-generated fragmentation.

See the Expert Consult website for further details.

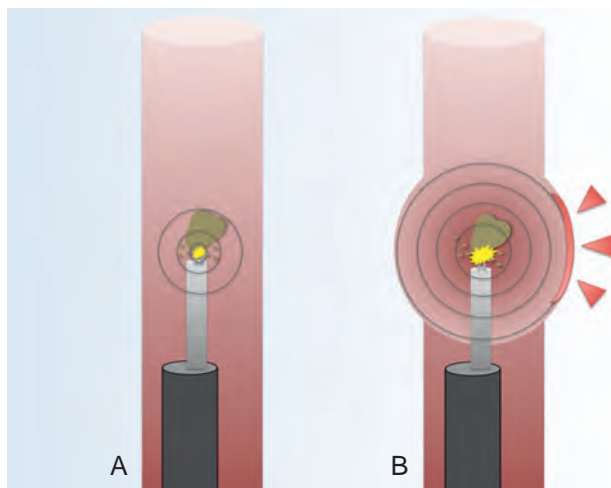


Figure 11-3. A, Electrohydraulic lithotripter probe spark producing a concentric shockwave within the ureter. B, Higher energy settings create cavitation bubbles up to 1.5 cm, increasing the risk of ureteric injury and/or perforation.

KEY POINTS: ELECTROHYDRAULIC LITHOTRIPSY

- EHL probes create a spark, which produces a rapidly expanding plasma shockwave and cavitation bubble with high-pressure microjets.
- Increasing the distance from the target reduces its peak pressure exponentially.
- At less than 500 mJ, mucosal injuries are rare; at greater than 1000 mJ, the risk of tissue damage is increased.
- A 1.9-Fr probe can be used with flexible ureteroscopy and allows active deflection for acceptable rates of stone fragmentation in all calyces.
- Chemical stone composition and surface characteristics affect the efficiency of EHL fragmentation.

Pneumatic Lithotripsy

Pneumatic lithotripsy provides a versatile and dependable approach to urolithiasis throughout the genitourinary tract. Early clinical reports confirmed the efficacy of pneumatic lithotripsy, and success rates of 95% (Teh et al, 1998) have been reported. With good fragmentation effect in hard stone compositions and attractive safety ratings, it continues to be popular globally in upper and lower tract stone disease.

Basic Physics

Pneumatic lithotripsy uses ballistic forces to transfer kinetic energy from a handheld probe to the stone surface (Michel et al, 2008). Either compressed gas (medical air or CO₂ cartridges) or electromagnetic oscillations are used to drive a projectile forcefully against the probe tip, thrusting it forward like a piston. Repetitive strikes (LithoClast [Boston Scientific, Marlborough, MA/Electro Medical Systems, Dallas, TX]), 12 Hz; electrokinetic lithotripter, 15 to 30 Hz) from the probe tip act as a jackhammer, fragmenting stones at the point of contact. When applied to compliant surfaces such as soft tissue, the impact energy is absorbed and dispersed, whereas rigid objects are not compliant resulting in fracture. Pneumatic lithotripters are safe for use in close proximity to the mucosa because soft tissue injuries from probe contact are relatively mild (see later). Other advantages of pneumatic lithotripters are their durability, simplicity of use, and completely reusable components (Hofbauer et al, 1995). Adding to dependability are the successful fragmentation of all chemical stone composition

Ureteroscopy

Initially, ureteral stone fragmentation with EHL was performed before the ability to visualize the upper urinary tract directly was available. When scope technology allowed adequate visualization with a sufficient working channel, EHL became a viable option for stone treatment ([Goodfriend, 1984](#)).

The collateral damage of EHL causing ureteral perforations during lithotripsy was reported in early studies using blind, fluoroscopically guided probe positioning and unreported energy settings ([Goodfriend, 1984](#); [Watson et al, 1987](#)). In contrast, a series of 82 ureteroscopic cases using 2.4-Fr and 3.3-Fr probes through a 6.5-Fr semirigid ureteroscope reported no complications or perforations during lithotripter use and no strictures at 6 months ([Vorreuther and Engelking, 1992a](#)). In 99% of cases, probe-to-stone contact was made, and using adjustable energy settings (265 to 1382 mJ/pulse), the average pulse energy was 450 mJ, resulting in 90% success rates.

[Elashry and coworkers \(1996\)](#) performed a retrospective review of 45 patients failing extracorporeal shockwave lithotripsy (ESWL) who underwent EHL fragmentation. Performing 36 cases using

flexible ureteroscopes (and 1.9-Fr probe), 64% were middle pole and 17% were lower pole stones. Of cases, 98% were considered successful (fragments <2 mm on direct visualization). Lower pole stones were effectively treated in 94% of patients, and at the time, laser fibers were not flexible enough to achieve active deflection into the lower pole. Another study of 114 patients undergoing flexible ureteroscopy confirmed the effective lower pole fragmentation by EHL; no statistical difference was noted between intrarenal stones based on location, and overall stone clearance rate was 80% (which decreased to 50% for stones >2 cm) ([Dasgupta et al, 2004](#)).

Larger stones have been successfully treated with flexible ureteroscopy and EHL when combined with Ho:YAG laser. [Mariani \(2007\)](#) reported on 15 patients with stones 2 to 4 cm ([Kressel et al, 1992](#)) and 17 patients with stones greater than 4 cm. With up to four outpatient treatment sessions, endoscopic management included laser lithotripsy to weaken large stones and EHL to debulk the fragments. The stone-free (fragments <4 mm) rate was 90%, and no reports of perforations or follow-up strictures were noted. Although not the current standard of care for stones of this size, with improvements in flexible scope and probe technology, larger stone burdens are commonly being attempted ureteroscopically.

Bladder Stones

Cystolithotripsy was the initial application for EHL, and the reduced morbidity experienced with intracorporeal lithotripsy under direct vision was a major stepping-stone for endoscopy in urology. Although initial reports showed poor recurrence rates of bladder stones with EHL (50%) compared with vesicolithotomy (7.4%)

([Short et al, 1984](#)), very few complications were encountered. Since 1981, older patients were being treated, and cystolithotripsy was being combined with concurrent TURP ([Bülow and Frohmüller, 1981](#)). Because tip breakage and bladder perforations can still occur, it still must be used with caution ([Pelander and Kaufman, 1980](#); [Bülow and Frohmüller, 1981](#)).

(Teh et al, 1998) and the ability to use interchangeable probes to facilitate stone breakage anywhere in the genitourinary tract.

Probes are available in diameters of 0.8 mm (2.4 Fr), 1 mm (3 Fr), 1.6 mm (4.8 Fr), 2 mm (6 Fr), and 3.5 mm (10.5 Fr). In a head-to-head bench comparison of pneumatic (4.8-Fr probe, 2.5 bar), EHL (3-Fr probe, 80% power), laser (0.32-mm fiber, 100 mJ), and ultrasonic (4.5-Fr probe, power setting 3) lithotripters by Teh and colleagues (1998), fragmentation efficacy index (minutes/gram of fragmented stone) was compared. Pneumatic lithotripsy (5.00 ± 0.94 min/g) was the least efficient, whereas ultrasonic was the most efficient (8.49 ± 1.15 min/g), followed by laser (7.62 ± 0.78 min/g) and EHL lithotripters (6.60 ± 1.58 min/g). When increasing probe sizes at constant pressures (2 bar), incremental improvements in fragmentation were noted (3 Fr = 14 min/g, 6 Fr = 6 min/g). Pneumatic lithotripsy is effective in fragmenting harder stones and is less efficient in very soft stones; this is likely because the jackhammer effect produces numerous tiny fragments or because, in the case of extremely soft stones (i.e., matrix stones), the probe punches holes into stones without fragmentation.

Tissue Effects

A survival porcine model was used to test the short-term and long-term effects of 5- to 7-second bursts of LithoClast mucosal exposure to bladder and ureteric urothelium. A short duration was selected to simulate inadvertent contact experienced during stone fragmentation. Histologic changes in immediately sacrificed animals included focal areas of hemorrhage with mucosal erosions and transmural edema. At 3 and 6 weeks, the treated areas were unidentifiable, and histology failed to identify any significant changes. All animals experienced 24 to 48 hours of hematuria but failed to show any other systemic or diagnostic differences (Denstedt et al, 1995).

In a four-way comparison of intracorporeal lithotripters on iatrogenic urothelial trauma, Piergiovanni and associates (1994) found perpendicular exposure to pneumatic probes to be the least traumatic (compared with laser, ultrasonic lithotripsy, and EHL). Assessing perforation thresholds for each modality, at 250 pulses, the 0.8-mm probe perforated ureteric walls, whereas larger probes (1- and 2-mm probes) were unable to perforate the ureter or bladder, regardless of total number of pulses.

See the Expert Consult website for further details.

KEY POINTS: PNEUMATIC LITHOTRIPSY

- Pneumatic lithotripsy uses compressed air to drive a projectile forcefully against the probe tip, transmitting repetitive ballistic forces to the stone surface similar to a jackhammer.
- Causing limited mucosal erosions and transmural edema, pneumatic lithotrites cause the least amount of trauma compared with other intracorporeal lithotripters.
- The efficiency of stone fragmentation is improved by increasing probe diameter and pulse frequency independently.
- Stone migration is a significant disadvantage when treating ureteric stones with pneumatic lithotripsy.

Ultrasonic Lithotripsy

Ultrasonic lithotripsy affords a straightforward method of stone fragmentation, while simplifying extraction. Instead of manually extracting fragments after treatment, a central channel for suction provides simultaneous stone debris aspiration during lithotripsy. The most common applications at the present time are percutaneous nephrolithotomy and cystolithotripsy, although applications in ureteroscopy exist.

Basic Physics

Ultrasonic lithotrites pass electrical current through piezoceramic crystals, producing directional sound waves of 23,000 to 27,000 Hz.

The hand piece houses the piezoelectric interface, and waves propagate as mechanical vibrational energy longitudinally down a solid or metal probe to where contact is made with the stone (Segura and LeRoy, 1984). As the metal probe vibrates, when contact is made with the stone, this reverberation transmitted to the stone causes fracturing (Teh et al, 1998) along with the mechanical trauma of the oscillating metal tip against the surface (LeRoy and Segura, 1984). Solid metal probes disintegrate stones by transmitting mechanical energy in a transverse plane, rather than longitudinally as with hollow probes. Local fracture can produce fine debris, which is aspirated by the probe; or if the probe is applied to fault lines, regional breakage can be created leading to larger fragments.

Tissue Effects

Using an amplitude of 50 μ m, no perforations could be created in rabbit bladders. Edema and submucosal hemorrhages were caused when only suction was applied, and irrigation (20 mL/min) kept frictional heating to a minimum. Metal splinters were observed embedding into the bladder wall, but after 9 weeks, minimal inflammation was noted on histology (Stackl and Marberger, 1985).

Piergiovanni and coworkers (1994) compared the Olympus ultrasonic lithotripter with EHL, pneumatic, and Ho:YAG laser lithotripters to assess tissue effects on a porcine bladder. Ureteral and bladder perforations were impossible with perpendicular application of the ultrasonic and pneumatic probes. Histologic analysis immediately after application displayed denuded epithelial layers and edema.

When applied to immediately removed human renal pelvis samples (postnephrectomy), perpendicular application of suction alone caused 50% to 80% mucosal denudation, whereas the ultrasonic probe (21,000 Hz) caused 100% mucosal stripping, with no evidence of muscularis injury, regardless of application time (Khemees et al, 2013a). A case report from 1988 described symptomatic hyponatremia during cystolithotripsy using an ultrasonic lithotrite and distilled water with a resulting intraperitoneal perforation. Although this treatment is not common practice today, it highlights that clinical conditions may not always reflect animal or in vitro models, and caution should still be exercised (Batra et al, 1988).

See the Expert Consult website for further details.

KEY POINTS: ULTRASONIC LITHOTRIPSY

- Piezoceramic crystals produce directional sound waves of 23,000 to 27,000 Hz. Vibrational energy is transmitted from the probe tip to the stone surface, and fragment debris are aspirated through the central lumen of the tip.
- In vitro testing shows that direct contact with the urothelium causes mucosal stripping, although deeper perforations are difficult to achieve.
- Ultrasonic lithotripsy is useful in large soft stones; however, for harder stones, ultrasonic lithotripsy is most efficacious when paired with pneumatic lithotripsy in dual modality lithotrites.

Holmium:YAG and Erbium:YAG Laser Lithotripsy

See the Expert Consult website for details.

Basic Physics

Laser physics for tissue-based applications are discussed in detail in Laser Instrumentation: Soft Tissue Applications.

Early on, questions existed surrounding the mechanism of lithotripsy of holmium lasers. Preceding technologies, such as the ruby and Nd:YAG lasers, used photoacoustic or photomechanical processes, where light energy created shockwaves that fragmented

Ureteroscopy

Thin pneumatic probes, ranging from 0.8 to 1 mm, are easily accommodated by ureteroscopes and are commonly used for semirigid ureteroscopy. Because of the high safety threshold, fragmentation efficacy, and cost-effectiveness, it continues to be a popular modality. Comparing the shearing potential of four intracorporeal lithotripters on endoscopic baskets, **pneumatic devices are the only modality not to cut through wire** (Cordes et al, 2011). In ureteroscopy, where safety guidewires, trapped or hung baskets, and antiretropulsion devices may lie in close proximity to targeted stones, pneumatic lithotripters can provide an additional level of safety. Knowing that mucosal injury and wire damage are minimized with this technology may help provide confidence when aggressively treating difficult ureteric stones.

Probe size and pulse frequency settings can alter fracture efficiency. Even with the smallest diameter probes, hard stones can be fragmented through anterograde or retrograde ureteroscopy. An in vitro study using avian gut as a ureteric model examined the differing fragmentation rates of 5-mm phantom stones using different probes and settings. **Increasing probe diameter (0.8 to 1.6 mm) and pulse frequency (6 to 12 Hz) both independently decreased the total number of required pulses to treat the stones completely** (Shadpour et al, 2009).

Stone migration is a significant disadvantage when treating ureteric stones because the ballistic effect of the probe can propel stones in capacious ureters into the kidney. Retropulsion has been reported in 10% of distal and 40% of proximal stones treated with pneumatic lithotripsy (Knispel et al, 1998). If flexible instruments are not readily available, stones washed into the kidney may require secondary procedures (i.e., ESWL). The risk of fragment migration is related to site, degree of impaction, size, lithotripsy modality, irrigation system, and degree of proximal ureteric dilation (Delvecchio et al, 2000; Lee et al, 2003; Hendlin et al, 2008). Antiretropulsion strategies such as stone pinning (between probe and urothelium), reverse Trendelenburg positioning, basket stabilization, and proximal placement of lidocaine gel may be used. Specific antiretropulsion products include the Stone Cone (Boston Scientific, Marlborough, MA), N Trap (Cook Urological, Spencer, IN), Passport Balloon (Boston Scientific), Parachute (Boston Scientific), Accordion (PercSys, Palo Alto, CA), and BackStop (Boston Scientific). Developed for markets where flexible instrumentation is not feasible, these products may help reduce the risk of stone migration (Bastawisy et al, 2011).

A randomized controlled trial of Ho:YAG laser (365 μ m) and pneumatic lithotripsy (2.4-Fr probe) was performed in 79 patients undergoing semirigid ureteroscopy. Mean stone size was 12 mm, and most stones were located distally. Laser lithotripsy resulted in a superior stone-free rate at 1 month on radiographic and ultrasound follow-up (95% vs. 80.5%). Stone retropulsion was more common with pneumatic lithotripsy, and no significant complications were reported in either arm (Maghsoudi et al, 2008). A retrospective review of 500 patients treated during the period 1995-2002 showed that **stone-free rates are dramatically affected by stone position and size**. Stone-free rates for stones 10 mm or less were 97.1% for distal ureteric stones and 91% for proximal stones. For stones greater than 10 mm, distal stone-free rates were 89% for distal stones and 71.4% for proximal stones (Sözen et al, 2003). With a 6.4% overall complication rate, only 1.4% of patients developed mucosal injuries or perforations as a result of probe use.

Two series highlighted the safety of pneumatic lithotripsy in pregnant women with symptomatic ureteral stones (Hoşcan et al, 2012; Abdel-Kader et al, 2013). In both reports, the mean gestational age at presentation was 25 to 26 weeks, and most stones were located in the distal ureter. Using semirigid ureteroscopy, a stone-free rate of 85.3% to 100% was reported with no major anesthetic, surgical, or obstetric complications (Abdel-Kader et al, 2013). One patient developed premature contractions, which did not progress to early labor.

Ideally, a semirigid ureteroscope with a straight end on working channel should be used for pneumatic stone treatment

because bending pneumatic probes reduce the transmitted energy from the generator to the stone (Grocela and Dretler, 1997). Although 2.4-Fr probes are flexible and can be accommodated by flexible ureteroscopes, an analysis by Zhu and coworkers (2000) quantified the energy loss secondary to probe bending. By measuring tip mechanics, impact momentum decreased 50% and energy by 76% when probe tips were deflected 33 degrees. With 48 degrees of deflection, only 30% of full fragmentation efficiency could be achieved.

Bladder Stones

Transurethral (Teh et al, 1998; Khosa et al, 2012; Rabani, 2012) and percutaneous (Agrawal et al, 1999; Wollin et al, 1999) **pneumatic lithotripsy have been found to be useful in large hard stones such as calcium oxalate monohydrate and cystine stones** (Denstedt et al, 1992). A retrospective series comparing ultrasonic, pneumatic, and mechanical lithotripsy for bladder stones showed equal efficacies for stones less than 3 cm (Razvi et al, 1996).

Khosa and colleagues (2012) reported a series of 100 children younger than 15 years old from Pakistan who underwent pneumatic cystolithotripsy using a 4-Fr "mini-scope" or a 7/8.5-Fr ureteroscope for bladder stones less than 3 cm. The average patient was 5 years old, and all surgeries were performed as outpatient procedures. Only 5% of patients developed hematuria, and one experienced postoperative urinary retention.

Cases of calcified foreign bodies such as encrusted ureteric stents (Grocela and Dretler, 1997) and eroded transobturator tapes (Osório et al, 2011) have been treated with pneumatic lithotripsy. An advantage of this modality with retained stents is that pneumatic lithotripters can be applied safely in transurethral or percutaneous cystolithotripsy, ureteroscopy, and percutaneous nephrolithotomy. Also, when stones abutted against the urothelium need to be fragmented, pneumatic lithotripsy is safe to make contact with the urothelium for short periods of time.

Single setting TURP and percutaneous or transurethral pneumatic lithotripsy have been reported as treatments in patients in whom outlet obstruction is the precipitating cause of bladder stones (Sinik et al, 1998; Aron et al, 2007). Stone removal is performed initially, and if a percutaneous approach is used, the working sheath is maintained until after TURP to reduce the risk of extravasation. In a comparative analysis of patients undergoing either percutaneous or transurethral lithotripsy with simultaneous TURP, the percutaneous approach (using a 30-Fr sheath) decreased stone removal time by 45% and the need for secondary procedures (Tugcu et al, 2009). Patients who underwent purely transurethral procedures had their catheters removed earlier (2.2 days vs. 3.2 days) and had shorter admissions (1.2 days vs. 2.3 days); however, three patients (7.9%) developed subsequent urethral strictures.

Percutaneous Nephrolithotomy

Similar to treatment of bladder stones, percutaneous nephrolithotomy allows the use of larger scopes and larger probes. A Canadian trial comparing the StoneBreaker (Cook Urological, Spencer, IN) with the Swiss LithoClast showed improved fragmentation times, reduced setup time, and decreased user fatigue with the StoneBreaker. No differences in stone-free rates or complications were noted. The LithoClast uses medical air and requires a pedal for activation, whereas the lighter weight StoneBreaker uses a CO₂ cartridge, is triggered by hand, and produces 10 times the impact pressure. Because pneumatic lithotripsy is valuable in large and hard stone compositions, it has been combined with ultrasonic lithotripters to improve on the advantageous characteristics of both modalities (see later). The Clinical Research Office of the Endourological Society reviewed 5800 percutaneous nephrolithotomy procedures (from 96 centers) to assess success rates based on mean Hounsfield units and various surgical characteristics. On regression analysis, pneumatic lithotripsy showed the highest probability of stone-free status (90%) even when compared with combination ultrasonic/pneumatic modalities (82%) (Anastasiadis et al, 2013).

Ureteroscopy

The first clinical series reporting the use of ultrasonic lithotripsy comprised 412 patients treated for bladder stones in 1984. Probe diameters range from solid 2.5-Fr probes (for semirigid ureteroscopy) to 6.0-Fr used for cystoscopy and nephroscopy. Several bladder stone series corroborate the low complication rates and high success rates for stones of varying sizes using transurethral and suprapubic approaches (Cetin et al, 1988; El Khader et al, 1995; Razvi et al, 1996). A review of 176 patients undergoing bladder stone surgery during the period 1976-1994 noted an 88% success rate for ultrasonic lithotripsy, failing with “very hard stones” (Razvi et al, 1996).

Ureteroscopic fragmentation using ultrasonic probes was slower to gain popularity because of the required advancement in ureteroscopic technology and reduced probe sizes (2.5 to 4.5 Fr) required. With 2.5-Fr “solid wire” probes, a central lumen for aspiration is impossible. Some flexibility can be achieved for applications requiring active deflection during flexible ureteroscopy. Because EHL, pneumatic lithotripsy, and laser lithotripsy gained popularity around the same time as solid wire probes were developed, ureteroscopic applications of this technology never reached the same popularity as use of the technology in upper and lower tract indications (Gur et al, 2004). Preliminary reports documented flexible ultrasonic probes used through fiberoptic flexible scopes resulting in an 87.5% success rate in 16 patients (Higashihara and Aso, 1989).

Pedro and Netto (2008) compared ESWL with ultrasonic lithotripsy in 235 consecutive patients with proximal ureteric stones with near-equal efficacy (85.6% ultrasonic lithotripsy vs. 90% ESWL success rates) and no differences in complication rates and mean procedure times. A review of all semirigid ureteroscopic ultrasonic series by Gur and coworkers (2004) identified 9 studies from 1983-1999 ranging from 7 to 311 patients. Pooled analyses of 863 patients identified an overall fragmentation rate of 89%, perforation rate of 2.5%, and “other complications” rate of 3.8% (including strictures, avulsions, sepsis, and false passage formation).

Percutaneous Surgery

Applications in percutaneous surgery closely followed cystolithotripsy, and by the mid 1980s, ultrasonic lithotripsy was being applied to percutaneous renal surgery (Segura and LeRoy, 1984). Used in pediatrics, horseshoe kidneys (Holman et al, 1986), and total staghorn calculi (Rodrigues Netto et al, 1988), ultrasonic

lithotripsy has been a versatile tool in percutaneous surgery. In approaches ranging from anatomic nephrolithotomy to percutaneous surgery, ultrasonic fragmentation was found to reduce operating times (from 210 minutes to 120 minutes), admission times (from 7 days to 5 days), and secondary interventions (from 50% to 20%), with a much earlier return to normal physical activity (43 days vs. 9 days) (Rodrigues Netto et al, 1988).

Newer combined technologies have improved on the fragmentation capabilities of ultrasonic lithotripsy by combining it with pneumatic lithotrites (see later). Dual modality fragmentation with combined ultrasonic lithotripsy and pneumatic lithotripsy showed improved stone-free rates (92% vs. 85% ultrasonography alone), fewer secondary procedures, and decreased operative times, without an increase in complication rates (Cho et al, 2010). With regard to harder stones, a prospective randomized trial assessing 30 patients with cystine, calcium oxalate monohydrate, or calcium phosphate stones showed a clear advantage for combined fragmentation, whereas softer stones had more favorable results with the ultrasonic lithotripter alone (Lehman et al, 2008).

Because contact must be made between the probe and stone, drilling or painting motions are used to trap the stone between urothelium and the probe. Smaller stones may be brought to the probe and held in place with suction alone. Continuous irrigation helps improve visualization, decrease heat buildup, and wash stone debris through the probe. When soft stones (e.g., struvite) are encountered, complete fragmentation and suction removal of the stone may be facilitated with ultrasonic lithotripsy. For harder stones, a drilling technique can be used to fracture the stone into manually extractable stones.

Larger pieces can be fragmented further or extracted manually. **Using continuous irrigation and suction keeps the probe tip cool, while continuously removing particles (Hofmann et al, 2002).** As the fluid is evacuated through the hand piece, it cools the piezoceramic crystals, which can rapidly increase in temperature if proper suction is not maintained. Without adequate suction, in addition to a noticeably hot hand piece, visualization and stone clearance are impeded. It is important to tailor suctioning to the irrigation rate during probe activation; otherwise, air can be introduced when aspiration outpaces irrigation inflow, obscuring the field with bubbles. This situation can be avoided by reducing the suction pressure, increasing irrigation height (or pressure), or intermittently clamping the suction tubing to allow enough fluid to remain in the renal pelvis/bladder for distention and visualization.

Holmium:YAG lasers have revolutionized kidney stone management and flexible ureteroscopy. In conjunction with improved optical systems in actively deflecting ureteroscopes, all areas of the genitourinary tract are now safely accessible for endoscopic lithotripsy using these lasers. Preliminary testing of the erbium:YAG

(Er:YAG) laser showed improved fragmentation efficiency of kidney stones compared with the Ho:YAG laser. Producing larger fragments with a smaller soft tissue penetration depth, this technology holds promise for future application in endourology.

stones. In contrast, photothermal stone breakage during holmium laser use was hypothesized based on early observations of “glowing hot stones.” Photothermal processes involve direct light energy absorption (“photo”) by stone surfaces causing rapid temperature (“thermal”) increases, before significant heat diffusion can occur.

Using a combination of techniques, **Chan and colleagues (1999)** identified the predominant mode of Ho:YAG lithotripsy to be photothermal. Mass loss experiments showed less fragmentation when stones -80°C were treated. As expected with a thermal mechanism, more energy was required to increase temperatures to ejection thresholds when starting below physiologic temperatures. After treatment, chemical analysis of all stone types showed thermal breakdown components. Finally, synchronized photography failed to identify fragmentation during bubble expansion or collapse, and measured pressures were too low (2 to 20 bar) to induce fracture.

Ablation crater volumes are associated with the irradiated surface photon density (fluence) and pulse energy. A “Moses effect” occurs by the rapid vaporization of fluid creating a vapor channel between the fiber tip and stone surface, allowing for more direct energy transfer. Although photoacoustic forces are not thought to contribute to fracture, interstitial water vaporization is likely involved with fragment ejection. Tensile and compressive forces, which dictate Nd:YAG lithotripsy, ESWL, and EHL, are not important (**Chan et al, 1999**).

Ho:YAG lasers produce fine fragments in large part owing to photothermal energy absorption by urolithiasis; this results in the breakdown and disintegration of the heated area, causing craters and fragmentation (**Qiu et al, 2010**). As a result of the relatively long pulse rate (250 to 350 μsec), the Ho:YAG laser is considerably less efficient than other shorter pulse lasers. Because Er:YAG lasers have a shorter pulse duration and longer wavelength (2940 μm), they can still produce small fragments, but with improved efficiency over Ho:YAG lithotripsy.

The Er:YAG laser uses optical energy, and similar to Ho:YAG, irradiation of the stone’s surface leads to increasing temperatures. Er:YAG lasers produce a 2940-nm wavelength, which has a fivefold increase in photothermal absorption by urolithiasis. Although shockwave production is insufficient for stone breakage in Ho:YAG lasers, Er:YAG lasers also show improved photoacoustic vapor bubble force transmission. With higher acoustic transients, the Er:YAG laser forms a torpedo-shaped vapor bubble in the interfacing fluid between probe and stone. The vapor bubble of the Ho:YAG laser is pear-shaped, leading to increased energy loss laterally, producing weak shockwaves with minimal effect on stone fracture.

The radiant threshold for Er:YAG to initiate lithotripsy is 0.47 J/ cm^2 at 2940 nm for calcium oxalate monohydrate compared with a Ho:YAG threshold of 7.36 J/ cm^2 . Deeper craters and larger ablation volumes are produced at this wavelength (**Lee et al, 2006**). The combination of effective photothermal and photoacoustic lithotripsy of Er:YAG leads to faster fragmentation, with larger subsequent pieces. In vitro studies showed larger fragments are created by Er:YAG; however, calcium oxalate monohydrate and cystine stone lithotripsy resulted in fragments less than 1 mm for both lasers, which clinically would be considered equivalent. Soft tissue depth of penetration is 0.79 μm , which is a significant improvement in safety compared with Ho:YAG (0.5 to 1 mm).

A problem with Er:YAG laser technology is that the hydroxy silica quartz fibers used in Ho:YAG machines are not compatible. Although sapphire fibers used with Er:YAG are too brittle and thick to be used in routine endourologic procedures, salivary stones were treated in wet-field applications using semirigid instrumentation (**Raif et al, 2006**). ZBLAN fluoride glass fibers have favorable properties in regard to reflection losses and light attenuation. However, because of a much lower melting point, durability is inadequate for clinical use. Before this technology can be applied to kidney stones, improved mechanical, thermal, and chemical fiber reliability is required. Hybrid fibers using fluoride cores with sapphire protection tips and circumferential cladding may help provide the transmission and flexibility required for endourology (**Qiu et al, 2010**).

See the Expert Consult website for further details.

A technique dubbed “popcorning” uses both the photoacoustic and the photothermal mechanisms of laser lithotripsy. **Photoacoustic and photothermal properties of a laser are functions of pulse duration and energy. Longer pulse duration produces greater photothermal functionality.** Although most Ho:YAG lasers have fixed durations of 250 to 350 μm , adjustable units are becoming more common. Shorter pulses yield higher peak power in resulting shockwaves. In a ureteric model, increasing pulse duration from 300 to 700 μm reduced stone retropulsion by 50% (**Finley et al, 2005**). Pulse duration is inversely related to power and can manipulate stone motion depending on the circumstance; this can be helpful in difficult-to-reach anatomy (i.e., lower pole stones) or when numerous fragments exist in a confined area (i.e., minor calyx). The fiber tip is placed several millimeters away from the stones (and mucosa), and shockwaves produced by vapor bubbles collapsing cause stones to bounce like popcorn. As stones are agitated, intermittent contact with the laser fiber causes photothermal disintegration. As time passes, the “popcorning” effect continues to produce smaller and smaller fragments, resulting in a fine stone dust, which is passed without consequence. An in vitro experiment identified settings of 1.0 J and 20 Hz as giving the most efficient fragmentation when using this technique (**Chawla et al, 2008**).

See the Expert Consult website for further details.



KEY POINTS: HOLMIUM:YAG LASER LITHOTRIPSY

- Laser lithotripsy has brought versatility to intracorporeal lithotripsy by allowing safe fragmentation in virtually all areas of the genitourinary tract.
- Ho:YAG laser fragmentation is predominantly due to photothermal decomposition and possibly photoacoustic propulsion of fragments.
- Laser output can be adjusted based on rate (Hz), energy (J), pulse duration (μsec), and fiber size (μm).
- Maximal deflection is achieved with 200- μm fibers during flexible ureteroscopy; however, maximal efficiency is seen with 360- μm fibers.
- Proper laser fiber handling can help reduce scope damage and prolong the life of reusable fibers.
- Techniques used during stone fragmentation include painting and “popcorning,” which create fine stone dust (precluding removal), or crude fragmentation for basket extraction.
- Laser lithotripsy can produce the smallest fragments and is efficacious in all stone compositions.

Dual Modality Lithotripters

Newer modalities have been developed by combining ultrasonic and pneumatic lithotripters into a single hand piece. The Swiss LithoClast Ultra and CyberWand (Olympus, Southborough, MA) use different strategies to capitalize on the advantages of each modality. Pneumatic lithotripsy is effective at fragmenting harder stones, whereas ultrasonic action produces smaller fragments, while simultaneously removing them from the field. These hybrid systems are available only as rigid probes and can be used only in transurethral or percutaneous procedures (**Fig. 11-5**).

LithoClast Ultra

The LithoClast Ultra was the first dual modality lithotripter, combining two independently functioning hand pieces that are fixed together. **The front piece houses the ultrasonic lithotripter, with a central channel allowing throughway for the slender pneumatic probe.** The 1-mm solid pneumatic probe sits within the suction channel of the 3.3-mm hollow ultrasonic probe. Fine-tuning of positioning of the pneumatic probe tip (relative to the ultrasonic tip) can be achieved using the depth wheel built into the hand piece. Pneumatic activity can be triggered as needed or continuously



Ureteroscopy

By reducing the diameter of ureteroscopes, slender intracorporeal lithotripters must pass easily through a working channel smaller than 4 Fr, while allowing room for irrigation. These instruments also must be durable enough to be advanced and retracted repeatedly through a scope without breaking, even when deflected 270 degrees. Ho:YAG laser lithotripsy fulfills these requirements because hydroxy silica fibers are thin, flexible, and durable and possess transmission efficiencies allowing for effective photothermal stone fragmentation.

Flexible ureteroscopy typically uses 200- μ m laser fibers, which have a minimal impact on scope deflection. For semirigid ureteroscopy, 365- μ m fibers are more suitable, although they can be used with flexible nephroscopy if minimal deflection is required (i.e., upper pole stones). These are considered workhorse fibers because they have been shown to display maximal efficiency and durability while being typically cheaper (than 200- μ m fibers) (Kuo et al, 1998).

Laser fiber tips should be advanced until clearly visualized by the operator (several millimeters past the lens). During flexible ureteroscopy, this may become problematic for lower pole stones because fiber advancement can damage the scope liner or optics or fracture the fiber itself. If a fractured fiber is used while in a scope, catastrophic damage and costly repairs can result. Fiber advancement should be performed with the scope tip in neutral

position and then actively deflected to the area of interest. Newer fibers (i.e., Flexiva TracTip [Boston Scientific, Marlborough, MA]) have been created with a carved bulbous tip, theoretically allowing the fiber to pass through an already deflected scope without damage. The cladding helps permit high energy transfer even when bent, and using a 240- μ m core, it is rated to handle settings up to 50 W. In an analysis of 96 clinically used fibers, none were broken. Bench testing revealed only a loss of 5 degrees of ureteroscopic active deflection (U-500 flexible ureteroscope [Stryker Endoscopy, San Jose, CA]; from 275 degrees to 270 degrees) (Khemees et al, 2013b). Alternatively, for stone repositioning from difficult-to-reach areas to the upper pole, using endoscopic baskets may help reduce the need for prolonged extreme deflection.

Ureteroscopic laser fragmentation can be performed by several techniques. Dust-sized fragments are produced by painting the fiber across the surface of a stone. Avoiding the creation of large fragments that are difficult to pass makes basket extraction unnecessary. By using lower energy levels of 0.2 J and higher pulse rates (i.e., 40 Hz), small debris and minimal retropulsion are encountered, while trading off a reduction in total fragmentation. Controlling for total energy, increasing pulse energy levels were found to result in larger fragments, with faster fragmentation times. Alternatively, as laser fragmentation becomes more time-consuming as fragments become smaller, one can create large pieces and remove them using an endoscopic basket.

With improving endoscopic technology, ureteroscopy and intracorporeal lithotripsy have replaced ESWL for treatment of many ureteric stones. A review of 82 patients undergoing either ESWL or ureteroscopy for impacted proximal stones showed no difference in 3-month stone-free rates (80% vs. 68%) or complications, although patients undergoing ESWL required more secondary procedures (Khalil, 2013). Similar results were achieved in a prospective randomized trial comparing 180 patients undergoing ESWL or semirigid ureteroscopy and laser lithotripsy for stones less than 2 cm. No significant differences were found between the two modalities in terms of 3-month stone-free rates, although re-treatment rates were higher for ESWL (6.1% vs. 1.1%, $P < .001$) (Kumar et al, 2013). In contrast, a multicenter randomized trial of distal and mid-ureteric stones ($n = 156$) treated with ESWL or ureteroscopy and laser lithotripsy showed an advantage for ureteroscopy. The 3-month stone-free rate was 91% for ureteroscopy (vs. 51% for ESWL), and re-treatment rates were significantly lower (9% vs. 45% in ESWL) (Hendriks et al, 1999). Several authors found cost savings associated with ureteroscopy and laser use compared with ESWL because of higher success rates and lower re-treatment rates (Parker et al, 2004; Cone et al, 2014). Laser lithotripsy had lower initial (\$7575 vs. \$9507) and total (\$9378 vs. \$15,583) charges.

Comparing other intracorporeal lithotripsy modalities, a retrospective review of 394 patients with proximal ureteral stones treated with laser or pneumatic lithotripsy via semirigid ureteroscopy was performed showing 86% were treated successfully with pneumatic lithotripsy; 14% required secondary ESWL for residual fragments (identified on radiograph). Laser lithotripsy produced a 97% stone-free rate, and only 2% required secondary procedures. Ureteral perforations were uncommon and not significantly different between groups (Bapat et al, 2007). In larger distal and mid-ureteric stones (mean diameter 13 mm), a prospective randomized trial showed a delayed stone-free rate of 95% with laser lithotripsy versus 85% with pneumatic lithotripsy on noncontrast computed tomography. Laser use was associated with less stone migration, although complication rates were for both arms (Kassem et al, 2012).

Stone position plays a large part in the success rates of ureteroscopy and laser lithotripsy. In a retrospective study, 272 patients undergoing flexible ureteroscopy from 2002-2006 and laser lithotripsy for renal stones were found to have an overall stone-free rate of 94% on follow-up noncontrast computed tomography. Stone-free rates were best for upper pole stones (100%), followed by middle pole stones (95%) and lower pole stones (90%), although not significantly different ($P = .338$). Similarly for the ureter, stone-free rates decreased from distal ureteral (96.8%) to proximal ureteral (79.4) stone location. Complication and re-treatment rates were significantly higher with proximal stone location (Seitz et al, 2007).

Effective fragmentation using laser lithotripsy can be accomplished for any chemical stone composition, although efficiency is decreased with harder stones. Maintaining consistent power settings, magnesium ammonium phosphate stones are the most readily fractured, followed by calcium hydrogen phosphate dehydrate, cystine, uric acid, and calcium oxalate monohydrate. Increasing energy improves fragmentation for all stone types (Teichman et al, 1998). The differences are partly related to the melting points of the various stones as well as the vapor-surface interface. However, after reviewing ureteroscopic procedures performed on 86 renal and 101 ureteral stones, Wiener and colleagues (2012) failed to show any differences in operating room time related to stone composition. Perhaps owing to active fragment removal using endoscopic baskets, coarse fragmentation techniques may not be as sensitive to chemical composition. Instead, if disintegrated to stone dust, one could hypothesize that harder stones would require more time.

Because of its relatively high safety profile, laser lithotripsy has been applied to children (Fraser et al, 1999; Yeow et al, 2009), patients with bilateral stones (Huang et al, 2012; Atis et al, 2013), and patients with anatomic abnormalities (i.e., horseshoe kidney, duplicated systems, transplant grafts) (Molimard et al, 2010; Hyams et al, 2012). Ureteroscopy and laser use have been found to be safe in a retrospective review of 25 anticoagulated patients. Semirigid (6.9-Fr probe) and flexible (7.5-Fr probe) ureteroscopy was

performed, and basket extraction was avoided by dusting all stones. Distal ureteral dilation (8/10-Fr coaxial dilator, balloon dilator, 14-Fr ureteric access sheath) was performed in 11 patients, and stents were placed in all patients after the procedure. Stone-free rates were 96% (100% distal ureter and mid-ureter, 89% proximal and intrarenal locations). For lower pole stones, upper pole repositioning was performed. No cases of significant bleeding or early termination secondary to bleeding were reported with laser use. Similar findings were reported in children with von Willebrand disease (Christman et al, 2012) (Fig. 11-4).

Up-front and disposable costs for laser lithotripters may be an issue for some hospitals. Because of the versatility of the Ho:YAG laser, it can be used not only in all parts of the genitourinary tract but also for interventions not involving stones. Reusable laser fibers allow a significant cost savings; one study from two hospitals showed a savings of more than \$64,000 by using 37 fibers (varying manufacturers and sizes) for 540 semirigid and flexible ureteroscopy cases (Knudsen et al, 2011).

Percutaneous Nephrolithotomy

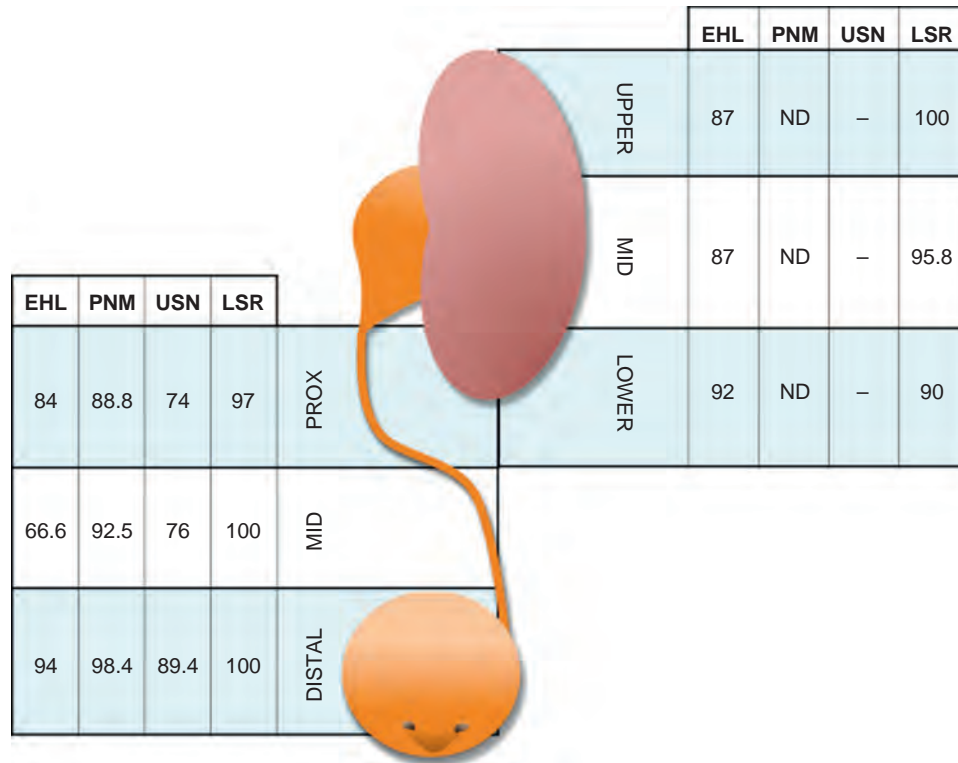
Although laser lithotripsy is not the favored modality for use in large renal stone burdens treated percutaneously, it plays an important role in flexible instrumentation. Anterograde nephroscopy using flexible scopes can access calyces that rigid nephroscopes cannot reach, reducing the need for multiple accesses. For patients with large impacted ureteric stones, reimplanted ureters, and reconstructed bladders, anterograde flexible ureteroscopy and laser lithotripsy can allow straightforward access to the stone. Coarse fragmentation and basket extraction simplify the procedure because the ureteric portion proximal to the obstruction is often dilated, allowing for active retrieval of larger stones.

Laser fragmentation is central to percutaneous nephrolithotomy performed with reduced-diameter sheaths (i.e., minipercutaneous, ultra-minipercutaneous, micro percutaneous). Developed initially for pediatrics, the procedure is now used in adults with sheath diameters ranging from 24 Fr (8 mm) to 16 gauge (1.3 mm). When using extremely narrow sheaths, techniques require special miniaturized imaging technologies and laser lithotripsy. Because stone extraction is impossible with extremely narrow sheaths, 200- μ m laser fibers are used to dust stones, and debris is cleared by pressurized irrigation or passive urine flow. Indications have yet to be clearly defined; however, studies comparing efficacy with flexible ureteroscopy, standard percutaneous nephrolithotomy, and ESWL have been performed. A randomized study comparing flexible ureteroscopy and micro percutaneous nephrolithotomy (16-gauge "all-seeing needle" and 272- μ m laser fiber) was performed in 70 patients for stones less than 1.5 cm. Equivalent stone-free rates, complication rates, and length of stay were identified. Increased pain scores (1.9 vs. 1.6, $P = .046$), analgesic requirements, and hemoglobin loss (0.96 g/dL vs. 0.56 g/dL, $P < .001$) were observed in the minipercutaneous nephrolithotomy arm. All patients had ureteric access sheaths placed, although 40% fewer patients required stent placement in the minipercutaneous nephrolithotomy arm (20% vs. 60%) (Sabnis et al, 2013).

Bladder Stones

In 1978, Fair reported the benefits of using a ruby laser to produce "stress pulses," which were able to fracture stones of any color, shape, size, hardness, and composition (Fair, 1978). Since then, Ho:YAG has become a useful option in transurethral and percutaneous approaches. In larger stone burdens, laser may not be the first choice; however, many still prefer laser cystolithotripsy because of its safety and ease of use.

With larger stones, the degree of fragmentation and stone dust produced by laser lithotripsy can reduce efficiency and visualization and increase operating room time. Combining lithotripter modalities and approaches in patients with stones greater than 4 cm may help reduce operative time and improve visualization and stone clearance (Sofer et al, 2004). The combination of laser



	EHL	PNM	USN	LSR
UPPER	87	ND	–	100
MID	87	ND	–	95.8
LOWER	92	ND	–	90

	EHL	PNM	USN	LSR
PROX	84	88.8	74	97
MID	66.6	92.5	76	100
DISTAL	94	98.4	89.4	100

Figure 11-4. Stone-free rates (percentage) for intracorporeal lithotripters used in ureteroscopy by anatomic region. EHL, electrohydraulic lithotripsy; LSR, laser; ND, no data; PNM, pneumatic; PROX, proximal; USN, ultrasonic.

and ultrasonic lithotripsy allows for fragmentation of hard stones, while suctioning fragments and improving visualization. A combined percutaneous and transurethral approach can also improve flow and allow larger fragment removal and stone manipulation by two surgeons simultaneously without increasing complication rates (Sofer et al, 2004). Use of a 24-Fr scope through a 30-Fr Amplatz sheath (Cook Urological, Spencer, IN) placed through the urethra (with or without urethral dilation) has been reported to improve irrigation drainage, visualization, and stone localization during laser lithotripsy in female (Ramanathan, 1999; Kawahara et al, 2012a) and male (Okeke et al, 2004) patients.

Total stone burden (volume and area on noncontrast computed tomography) was the only variable found to correlate with total procedural time required for laser cystolithotripsy. Using 550- μ m laser fibers (100-W laser, set between 1.5 and 3.5 J, 5 Hz), cystolithotripsy was performed through a 26-Fr resectoscope. Stone hardness (measured by Hounsfield units and chemical stone composition) did not appear to affect operating room time significantly. Male gender added procedural time, although lithotripsy time was not significantly different between sexes (Kawahara et al, 2012b).

An advantage of laser cystolithotripsy is its use in flexible cystoscopy, allowing for treatment in reconstructed bladders and challenging genitourinary anatomy that precludes use of rigid instruments. Flexible laser lithotripsy has been used under local anesthetic in healthy men with stones greater than 3 cm, with minimal pain and improvements in lower urinary tract symptoms, without significant complications (Kara et al, 2009).

In pediatric urolithiasis, instrument diameter plays a key role in management options. Bladder stones have been successfully treated using 8-Fr ureteroscopes with 550- μ m laser fibers for stones less than 4 cm (Ramakrishnan et al, 2005). No laser-related complications were encountered perioperatively, and no children showed recurrences or urethral stricture formation in long-term follow-up (mean 48 months). In children with complicated genitourinary reconstructions, augmentations, and continence procedures, percutaneous laser cystolithotripsy through a previous suprapubic catheter site allowed for maximal stone fragmentation, while minimizing the risk to intraperitoneal structures and/or vascular supply to bowel segments used for augmentation (Cain et al, 2002).

When indicated, concomitant treatment of bladder stones and BPH has been reported using several modalities of prostatic resection, including green light laser (De la Torre et al, 2012), HoLEP (Shah et al, 2007), and TURP (Philippou et al, 2011), without significantly increasing the rate of complications. Bladder calculi are treated first so as to avoid injuring the resection bed after prostatic surgery or risk leaving stones behind should the procedure be terminated early. Rare cases of prostatic stones causing lower urinary tract symptoms and bladder outlet obstruction can also be treated with laser lithotripsy. Using a 550- μ m laser fiber (1 to 1.5 J, 15 to 20 Hz) through a rigid cystoscope, Goyal and colleagues (2013) reported complete stone removal resulting in improved International Prostate Scoring System scores and improved peak flow rates at 3 months. Concurrent laser urethrotomy can be performed if necessary.

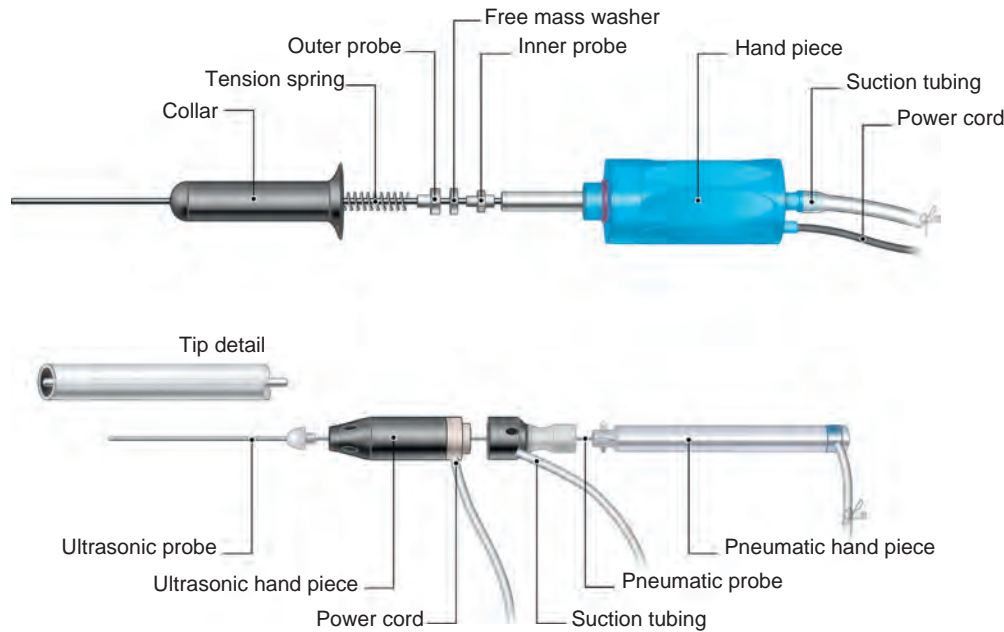


Figure 11-5. Dual modality lithotripter configurations.

from 2 to 12 cycles per second. The ultrasonic probe can be adjusted based on power and duty cycle. A composite pedal allows selective or combined use of each modality. Three cords attach to the hand piece for medical air, ultrasonic power, and suction. In-line suction allows continuous fragment removal and collection (using a stone trap) and hand piece cooling.

For maximal control, the tip of the pneumatic probe should be slightly recessed from the outer ultrasonic probe. In this way, the ultrasonic probe can make maximal contact with the stone surface, and pneumatic retropulsion is limited. When activated, the pneumatic tip advances and strikes the stone beyond the ultrasonic probe tip. If large immobile stones are being treated (i.e., staghorn calculi), better fragmentation can be achieved by adjusting the pneumatic probe 2.5 mm past the ultrasonic sheath; however, simultaneous treatment of smaller fragments may become more challenging (VonDerHaar et al, 2010).

CyberWand

The CyberWand uses an ultrasonic hand piece producing vibrational energy by means of a piezoceramic crystal. Disposable probes are made of an inner 2.77-mm and outer 3.75-mm cylindrical metal tube. The inner probe screws onto the handset extending 1 mm past the tip of the outer sheath. The fixed inner probe vibrates at a frequency of 21,000 Hz. Owing to a free mass washer and dampening spring, the free-floating outer probe vibrates at approximately 1000 Hz, oscillating longitudinally 1 mm. Selecting “large stone” on the foot pedal couples both sheaths. **Ultrasonic energy from the inner sheath is transmitted to the outer, which moves in a ballistic manner, similar to pneumatic lithotripters (Auge et al, 2002).** The “small stone” pedal allows for finer control and activates only the ultrasonic action of the inner probe. The hollow lumen of the inner sheath of the probe incorporates irrigation suction, which simultaneously clears stone debris during fragmentation, while cooling the hand piece.

Noise levels related to CyberWand fragmentation (93 dB) were determined to be the loudest (at ear level) compared with the Storz Ultrasonic lithotrite (Storz, El Segundo, CA; 77 dB), Olympus LUS-2 single modality ultrasonic lithotripter (Olympus, Southborough, MA; 68 dB), and Ho:YAG laser (60 dB). If used for more than 90 minutes per day, only the CyberWand is above the threshold set by the U.S. Department of Labor and Occupational Health and

Safety Administration for risk of noise-related occupational hearing loss (Soucy et al, 2008).

Tissue Effects

Using fresh human urothelium from nephrectomy specimens, perpendicular application of the CyberWand and LithoClast was done for 2 to 8 seconds. Tissue effects were compared with untreated areas and control specimens (suction-only probe contact). Suction alone showed 50% to 80% denudation of urothelium, with no changes identified in the subepithelial or muscular layer. The CyberWand “small stone” setting showed 100% urothelial denudation, with separation of the subepithelial connective tissue layer and no muscular damage. During use with the “large stone” setting, a greater amount of subepithelial edema and muscular rupture was noted with increasing contact time to the mucosa.

For ultrasonography-only settings, the Swiss LithoClast Ultra and CyberWand (“small stone” setting) showed 100% urothelial denudation, with separation of the subepithelial connective tissue layer and no muscular damage. With 2 seconds of exposure, minimal tissue damage was noted. **Increasing contact time led to increased mucosal denudation and submucosal vacuolation. Muscle rupture worsened with increasing exposure times except for the single modality “small stone” setting on the CyberWand, which was unable to cause muscle rupture.** Based on these findings, the authors concluded that both modalities were safe, although contact time when using dual modality settings should be minimized when possible (Khmees et al, 2013a).

Clinical Use

Several studies showed the combination of pneumatic and ultrasonic lithotripters is more efficient compared with pneumatic or ultrasonic lithotripsy alone. Each modality separately cleared phantom stones 3.8 times (pneumatic) and 1.7 times (ultrasonic) slower than combination lithotripsy with the Swiss LithoClast Ultra (Soucy et al, 2008). An in vitro experiment using gypsum stones was performed to compare penetration times of the CyberWand and Swiss LithoClast Ultra. Penetration times were 41% shorter with the CyberWand with no significant differences in overheating, blockages, or malfunctioning (Kim et al, 2007).

See the Expert Consult website for further details.



Clinical use was assessed by randomly assigning 20 patients to either ultrasonic or combined modality lithotripsy during percutaneous nephrolithotomy. Combination lithotripsy reduced fragmentation time from 43.7 minutes to 21.1 minutes ($P = .036$), with slightly improved complication and stone-free rates (Pietrow et al, 2003). To compare the clinical efficacy between dual modality lithotrites, 138 patients with staghorn calculi were randomly assigned to either CyberWand or Swiss LithoClast Master fragmentation. Although shorter operative times were encountered with CyberWand allocation (77.1 minutes vs. 84.3 minutes, $P = .049$), no differences in stone clearance or complication rates were noted (Li et al, 2013).

Surgical technique during treatment can affect efficiency of stone fracture. Applying force to a hand piece against a stone can improve or reduce fragmentation efficacy. The rate of stone mass removal

was measured in an in vitro analysis using 400g, 1000g, and 2000g of in-line force on a CyberWand and Swiss LithoClast Ultra hand piece. For the CyberWand dual modality settings, 400g and 1000g were significantly more efficient than 2000g, whereas with ultrasonography alone (on the Swiss LithoClast), efficiency increased with pressure and rotation of the probe by 90 degrees. This study also corroborates the improved fragmentation of the CyberWand against all settings of the Swiss LithoClast (Goldman et al, 2009). Too much pressure on the CyberWand may impede the movement of the outer low-frequency probe, leaving fragmentation to occur only with the ultrasonic action of the inner probe. However, the LithoClast Ultra functions better at higher pressures and with rotation. Because both the pneumatic and the ultrasonic components are actively driven by separate mechanisms, applying pressure does not prevent movement, as in the CyberWand (Goldman et al, 2009).

KEY POINTS: DUAL MODALITY LITHOTRIPTERS

- Dual modality lithotripters combine ultrasonic and pneumatic lithotripsy to take advantage of the benefits of each.
- Swiss LithoClast uses two independently driven lithotrites combined in one hand piece.
- The CyberWand uses a double-layered probe with a central ultrasonic probe and a passively coupled low-frequency outer probe, which provides ballistic stone fragmentation.
- In vitro and clinical studies showed more efficient stone fragmentation with the CyberWand, although no improvements in stone-free or complication rates have been identified.
- When friable tissues are present or visualization is suboptimal secondary to bleeding or challenging anatomy, single modality lithotripsy should be used. By reducing lithotripsy to ultrasonic only activity and minimizing urothelial contact time, one can reduce the potential for mucosal complications (i.e., bleeding, perforation, future stricture formation).

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The complete reference list is available online at www.expertconsult.com.

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12

Infections of the Urinary Tract

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Definitions

Incidence and Epidemiology

Pathogenesis

Clinical Manifestations

Imaging Techniques

Principles of Antimicrobial Therapy

Antimicrobial Prophylaxis for Common Urologic Procedures

Bladder Infections

Kidney Infections

Bacteremia, Sepsis, and Septic Shock

Bacteriuria in Pregnancy

Bacteriuria in the Elderly

Catheter-Associated Bacteriuria

Management of Urinary Tract Infections in Patients with Spinal Cord Injury

Other Infections

Urinary tract infections (UTIs) are common, affect men and women of all ages, and vary dramatically in their presentation and sequelae. They are a common cause of morbidity and can lead to significant mortality. Although the urinary tract is normally free of bacterial growth, bacteria that generally ascend from the rectal reservoir may cause UTIs. When bacterial virulence increases or host defense mechanisms decrease, bacterial inoculation, colonization, and infection of the urinary tract occur. Careful diagnosis and treatment result in successful resolution of infections in most instances. A better understanding of the pathogenesis of UTIs and the role of host and bacterial factors has improved the ability to identify patients at risk and prevent or minimize sequelae. Clinical manifestations can vary from asymptomatic bacterial colonization of the bladder to irritative symptoms such as frequency and urgency associated with bacterial infection; upper tract infections associated with fever, chills, and flank pain; and bacteremia associated with severe morbidity, including sepsis and death. New antimicrobial agents that achieve high urinary and tissue levels, can be administered orally, and are not nephrotoxic have significantly reduced the need for hospitalization for severe infection. Shorter-course therapy and prophylactic antimicrobial agents have reduced the morbidity and cost associated with recurrent cystitis in women. Although the vast majority of patients respond promptly and are cured by therapy, early identification and treatment of patients with complicated infections that place them at significant risk remains a clinical challenge to urologists.

DEFINITIONS

UTI is an inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria.

Bacteriuria is the presence of bacteria in the urine, which is normally free of bacteria. It has been assumed to be a valid indicator of either bacterial colonization or infection of the

urinary tract. Although this is usually true, studies in animals (Hultgren et al, 1985; Mulvey et al, 1998) and humans (Elliott et al, 1985) have indicated that bacteria may be in the urothelium in the absence of bacteriuria. Alternatively, bacteriuria may represent bacterial contamination of an abacteriuric specimen during collection.

The possibility of contamination increases as the reliability of the collection technique decreases from suprapubic aspiration to catheterization to voided specimens. The term *significant bacteriuria* has a clinical connotation and is used to describe the number of bacteria in a suprapubically aspirated, catheterized, or voided specimen that exceeds the number usually caused by bacterial contamination of the skin, the urethra, or the prepuce or introitus, respectively. Hence it represents a UTI.

Bacteriuria can be *symptomatic* or *asymptomatic*. When it is detected by population studies (screening surveys), *screening bacteriuria* is a more precise and descriptive term than *asymptomatic bacteriuria*, especially because the latter term is clinically useful for describing the presence or absence of symptoms in an individual patient.

Pyuria, the presence of white blood cells (WBCs) in the urine, is generally indicative of infection and/or an inflammatory response of the urothelium to the bacterium, stones, or other indwelling foreign body. Bacteriuria without pyuria is generally indicative of bacterial colonization without infection of the urinary tract. Pyuria without bacteriuria warrants evaluation for tuberculosis, stones, or cancer.

Infections are often defined clinically by their presumed site of origin. *Cystitis* describes a clinical syndrome of dysuria, frequency, urgency, and occasionally suprapubic pain. These symptoms, although generally indicative of bacterial cystitis, may also be associated with infection of the urethra or vagina or noninfectious conditions such as interstitial cystitis, bladder carcinoma, or calculi. Conversely, patients may be asymptomatic and have infection of the bladder and possibly the upper urinary tract.

Acute pyelonephritis is a clinical syndrome of chills, fever, and flank pain that is accompanied by bacteriuria and pyuria, a combination that is reasonably specific for an acute bacterial infection of the kidney. The term should not be used if flank pain is absent. It may have no morphologic or functional components detectable by routine clinical modalities. There may be serious difficulties in diagnosing spinal cord-injured and elderly patients who may be unable to localize the site of their discomfort.

Chronic pyelonephritis describes a shrunken, scarred kidney, diagnosed by morphologic, radiologic, or functional evidence of renal disease that may be postinfectious but is frequently not associated with UTI. Bacterial infection of the kidney may cause a *focal, coarse scar* in the renal cortex overlying a calyx, almost always accompanied by some calyceal distortion (Fig. 12-1), which can be detected radiographically or by gross examination of the kidney. Less commonly, renal scarring from infection can result in atrophic pyelonephritis or generalized thinning of the renal cortex, with a small kidney appearing radiographically similar to one with postobstructive atrophy (Fig. 12-2).

UTIs may also be described in terms of the anatomic or functional status of the urinary tract and the health of the host.



Figure 12-1. Excretory urogram demonstrates focal, coarse scarring in the right kidney of an 18-year-old girl with a history of many recurrent fevers between 2 months and 2 years of age. A cystogram when the patient was 2 years old established an atrophic left kidney with marked reflux up to the left kidney and slight reflux up to the right kidney. Excretory urography at the age of 6 years established severe atrophy of the left kidney. She had no infections between the ages of 6 and 15 years. Several reinfections occurred at the age of 15 years, and they ceased with prophylactic therapy. Her blood pressure has remained normal, and her serum creatinine level was 0.9 mg/dL at the age of 18 years. At 21 years of age she stopped antimicrobial prophylaxis for 18 months without infections or introital colonization with *Enterobacteriaceae*. Note that all calyces are blunted and that one extends to the capsule (arrowhead) because of atrophy of the overlying cortex.

Uncomplicated describes an infection in a healthy patient with a structurally and functionally normal urinary tract. The majority of these patients are women with isolated or recurrent bacterial cystitis or acute pyelonephritis, and the infecting pathogens are usually susceptible to and eradicated by a short course of inexpensive oral antimicrobial therapy.

A **complicated** infection is associated with factors that increase the chance of acquiring bacteria and decrease the efficacy of therapy (Box 12-1). The urinary tract is structurally or functionally abnormal, the host is compromised, and/or the bacteria have increased virulence or antimicrobial resistance. The majority of these patients are men.

Renal diseases that reduce the concentrating ability of the kidney or neurologic conditions that alter bladder-emptying capabilities are commonly encountered functional abnormalities.

Examples of anatomic abnormalities include obstruction associated with calculi or enlargement of the prostate or congenital or acquired sites of residual urine, such as calyceal or bladder diverticula. A complicated infection is frequently caused by bacteria that have exposure to many antimicrobial agents.

Chronic is a poor term that should be avoided in the context of UTIs, except for chronic pyelonephritis or bacterial prostatitis, because the duration of the infection is not defined.

UTIs may also be defined by their relationship to other UTIs:

A **first** or **isolated** infection is one that occurs in an individual who has never had a UTI or has one remote infection from a previous UTI.

An **unresolved** infection is one that has not responded to antimicrobial therapy and is documented to be the same organism with a similar resistance profile.

A **recurrent** infection is one that occurs after documented, successful resolution of an antecedent infection. Consider these two different types of recurrent infection:

1. **Reinfection** describes a new event associated with reintroduction of bacteria into the urinary tract from outside.
2. **Bacterial persistence** refers to a recurrent UTI caused by the same bacteria reemerging from a focus within the urinary tract, such as an infectious stone or the prostate. **Relapse** is frequently used interchangeably. These definitions require careful clinical and bacteriologic assessment and are important because they influence the type and extent of the patient's evaluation and treatment.

Antimicrobial prophylaxis is the prevention of reinfections of the urinary tract by the administration of antimicrobial drugs. If the term is used correctly in reference to the urinary tract, it can be assumed that bacteria have been eliminated before prophylaxis is begun. **Surgical antimicrobial prophylaxis** entails administration of an antimicrobial agent before and for a **limited** time after a procedure to prevent local or systemic postprocedural infections.

Antimicrobial suppression is the prevention of growth of a focus of bacterial persistence that cannot be eradicated. A low, nightly dosage of an antimicrobial agent usually results in the urine showing no growth, as in the case of a stone colonized with bacteria (i.e., infection stone) or in bacterial prostatitis caused by *Escherichia coli*. **Suppressive** is also a useful term when recurrent acute symptoms are prevented in a poor-risk patient, such as one with a large staghorn calculus in whom the antimicrobial agent reduces but does not eliminate the bacteria in the urine.

Domiciliary or **outpatient UTIs** occur in patients who are not hospitalized or institutionalized at the time they become infected. The infections are generally caused by common bowel bacteria (e.g., *Enterobacteriaceae* or *Enterococcus faecalis*) which are susceptible to most antimicrobial agents.

Nosocomial or **health care-associated UTIs** occur in patients who are hospitalized or institutionalized, and these are typically caused by *Pseudomonas* and other more antimicrobial-resistant strains.

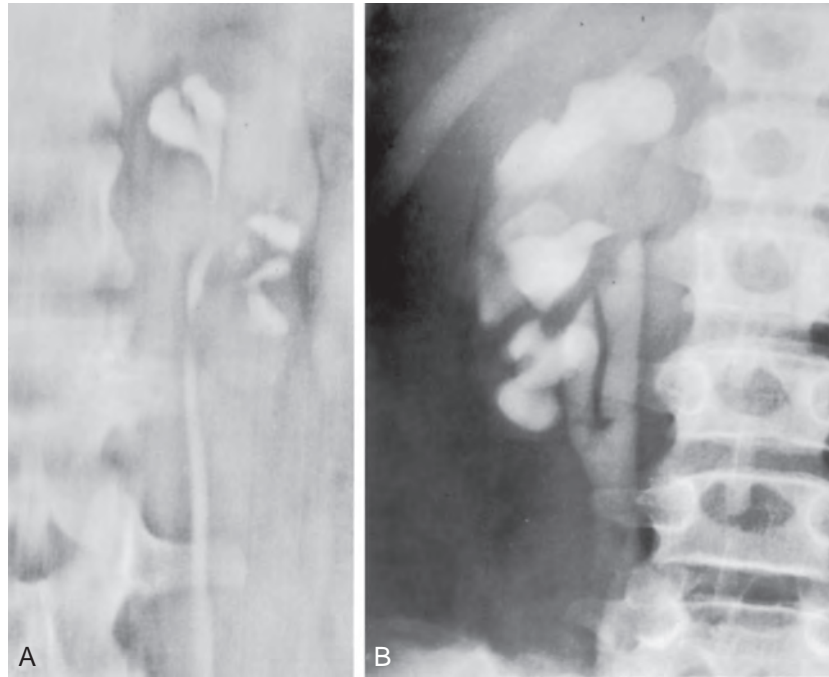


Figure 12-2. A, Excretory urogram of the contralateral left kidney from the same patient as in Figure 12-1. The severe pyelonephritic atrophy, undoubtedly caused by febrile urinary infections during early infancy with reflux into different segments of the kidney, produced irregular cortical scarring. Note how all the calyces extend to the capsule with irregular, intervening areas of cortex. B, Pyelonephritic atrophy, suggestive of postobstructive atrophy, in a 20-year-old woman with spina bifida, neurogenic bladder, and many episodes of fever and bacteriuria in early childhood. Observe the uniform, regular atrophy of the renal cortex that suggests reflux of bacteria simultaneously into virtually all nephrons. This type of pyelonephritic atrophy is uncommon compared with that shown in A and is characteristic of obstruction with superimposed infection.

BOX 12-1 Factors That Suggest a Complicated Urinary Tract Infection

Functional or anatomic abnormality of urinary tract
 Male gender
 Pregnancy
 Elderly patient
 Diabetes
 Immunosuppression
 Childhood urinary tract infection
 Recent antimicrobial agent use
 Indwelling urinary catheter
 Urinary tract instrumentation
 Hospital-acquired infection
 Symptoms for more than 7 days at presentation

From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 212.

KEY POINTS: DEFINITIONS

- Infection of the urinary tract occurs when bacterial virulence increases and/or host defense mechanisms decrease.
- The majority of patients respond promptly to short courses of antimicrobial therapy.
- Early identification and treatment of complicated UTIs is essential to prevent major sequelae or death.

INCIDENCE AND EPIDEMIOLOGY

UTIs are considered to be the most common bacterial infection. They account for more than 7 million visits to physicians' offices and necessitate or complicate over 1 million office visits and 1 million emergency department visits, resulting in 100,000 hospitalizations annually (Patton et al, 1991; Hooton and Stamm, 1997; Foxman 2002). They account for 1.2% of all office visits by women and 0.6% of all office visits by men (Schappert, 1997).

The overall prevalence of bacteriuria in women has been estimated at 3.5%, with prevalence generally increasing with age in a linear trend (Evans et al, 1978). Surveys screening for bacteriuria have shown that about 1% of schoolgirls (aged 5 to 14 years) (Kunin et al, 1962) have bacteriuria and that this figure increases to about 4% by young adulthood and then by an additional 1% to 2% per decade of age (Fig. 12-3). Nearly 30% of women will have had a symptomatic UTI requiring antimicrobial therapy by age 24, and almost half of all women will experience a UTI during their lifetime. The prevalence of bacteriuria in young women is 30 times more than in men. However, with increasing age, the ratio of women to men with bacteriuria progressively decreases. At least 20% of women and 10% of men older than 65 years have bacteriuria (Boscia and Kaye, 1987; Juthani-Mehta, 2007).

The incidence of bacteriuria also increases with institutionalization or hospitalization and concurrent disease (Sourander, 1966). In a study of women and men older than 68 years, Boscia and Kaye (1987) found that 24% of functionally impaired nursing home residents had bacteriuria, compared with 12% of healthy domiciliary subjects (Boscia et al, 1986). UTIs account for approximately 38% of the 2 million nosocomial infections each year (Sedor and Mulholland, 1999; Lo et al, 2008); catheter-associated UTIs (CAUTIs) are the most common nosocomial infection. More than

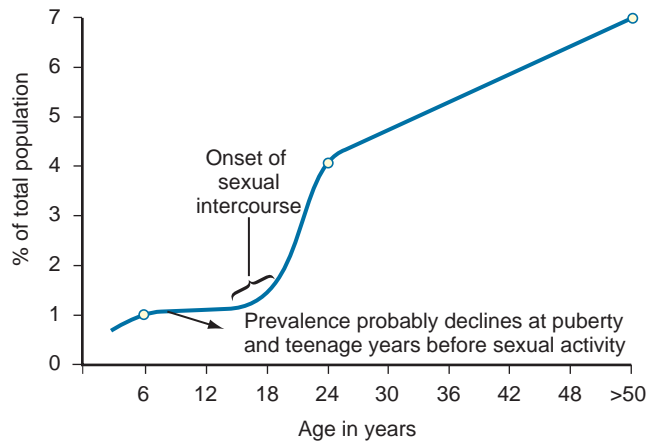


Figure 12-3. Prevalence of bacteriuria in females as a function of age. (From Stamey TA. The prevention of recurrent urinary infections. New York: Science and Medicine; 1973.)

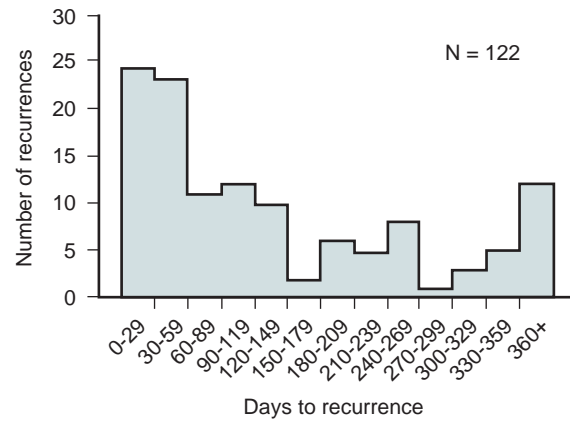


Figure 12-4. Days between recurrent urinary tract infections grouped by 30-day intervals. (From Kraft JK, Stamey TA. The natural history of symptomatic recurrent bacteriuria in women. *Medicine* 1977;56: 55-60.)

80% of nosocomial UTIs are secondary to an indwelling urethral catheter (Sedor and Mulholland, 1999; Foxman, 2002). The incidence of UTIs is also increased during pregnancy and in patients with spinal cord injuries, diabetes, multiple sclerosis, and human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS).

The financial impact of community-acquired UTIs is nearly \$1.6 billion in the United States alone (Foxman, 2002); the annual cost of nosocomial UTIs has been estimated to range from between \$515 million and \$548 million (Jarvis, 1996). Each CAUTI is estimated to cost between \$589 and \$758 (Tambyah et al, 2002; Anderson et al, 2007). In patients requiring intensive care, the cost is roughly \$2,000 per nosocomial UTI (Chen et al, 2009).

Little is known about the natural history of untreated bacteriuria in women because most women are treated when they are diagnosed, but a few studies in which treatment with antimicrobial agents is compared with placebo have been done. These show that 57% to 80% of bacteriuric women who are untreated or treated with placebo clear their infections spontaneously (Mabeck, 1972; Guttman, 1973). Mabeck (1972) found that 8 of 53 bacteriuric women placed on placebo needed treatment with an antimicrobial agent because of symptoms, but 32 of the remaining 45 women cleared without treatment within a month, and 43 of the 45 had spontaneously cleared of bacteriuria within 5 months; only 2 women remained persistently bacteriuric.

Once a patient has an infection, he or she is likely to develop subsequent infections. Many adults had UTIs as children, underscoring the importance of genotypic factors in UTIs (Gillenwater et al, 1979). Of 45 women with untreated UTIs whose infection cleared, 20 (46%) had recurrences within a year (Mabeck, 1972).

When women with recurrent bacteriuria were observed after treatment, about one sixth (37 of 219) had a very high recurrence rate (2.6 infections per year), whereas the remaining women had a recurrence rate of only 0.32 per year (Mabeck, 1972). Similar separation was seen in a prospective study, in which only 28.6% of 60 women who experienced their first symptomatic UTI had recurrent infections over the first 18 months of observation, as opposed to recurrences in 82.5% of 106 women who had had previous UTIs (Harrison et al, 1974). Other investigators also have found that the probability of recurrent UTIs increases with the number of previous infections and decreases in inverse proportion to the elapsed time between the first and the second infections (Mabeck, 1972). Of these recurrent infections, 71% to 73% are caused by reinfection with different organisms, rather than recurrence with the same organism (Mabeck, 1972; Guttman, 1973).

Women with frequent reinfections have a rate of 0.13 to 0.25 UTIs per month (1.6 to 3.1 infections per year) when the infections

are treated with antimicrobial agents (Mabeck, 1972; Guttman, 1973; Kraft and Stamey, 1977; Vosti, 2002).

In a prospective long-term study of 235 women with more than 1000 confirmed infections studied over a period ranging from 1 to nearly 20 years, about half of the patients had clusters of infections, which ranged in frequency from 2 to 12 infections per cluster. Infections were followed by remission-free intervals that averaged approximately 1 year. Most reinfections occurred after 2 weeks (Harrison et al, 1974) and within 5 months (Mabeck, 1972), and most occurred early in this interval (Kraft and Stamey, 1977; Vosti, 2002) (Fig. 12-4). Rates of reinfection were independent of bladder dysfunction, radiologic changes of chronic pyelonephritis, and vesicoureteral reflux (Guttman, 1973). The reinfections did not occur evenly over time. In the Stanford series (Kraft and Stamey, 1977), 23 women with frequent recurrent infections were studied with monthly urine cultures when asymptomatic and with immediate cultures when symptomatic for cystitis, for a mean of 3 years. Thirty-four percent of infections were followed by infection-free intervals of at least 6 months (average, 12.8 months), and 22 of the 23 women had such intervals. However, even these long intervals were followed by further infections (Kraft and Stamey, 1977), thus underscoring the importance of genotypic factors in the pathogenesis of UTIs in women (Schaeffer et al, 1981).

When the Stanford data (Kraft and Stamey, 1977) on recurrent UTIs in highly susceptible females is analyzed by examining sets of infections separated by remissions of at least 6 months, 69% of the sets contain only one infection. After this first set, the remaining sets show a 33% remission rate in infections, which means a patient who has two or more infections within 6 months has only a 33% probability of remaining free of infection for the next 6 months. Therefore, if antimicrobial prophylaxis is started after the second or any succeeding infection within a set, about two thirds of the women will benefit.

Whether a patient receives no treatment at all or short-term, long-term, or prophylactic antimicrobial treatment, the risk of recurrent bacteriuria remains the same; prophylactic antimicrobial therapy reduces reinfections but does not alter the underlying predisposition to recurring infection. Asscher and associates (1973) found that reinfections occurred in 17 patients (34%) treated with a 7-day course of nitrofurantoin and in 13 patients (29%) receiving placebo during a 3- to 5-year follow-up. Mabeck (1972) found that 46% (20 of 43) of untreated patients had recurrent infections by 12 months compared with about 40% of treated patients who had recurrences. Both studies suggest that it makes little difference whether a UTI is cured with an antimicrobial agent or is allowed to clear spontaneously—the susceptibility to recurrent UTI remains the same. Moreover, patients with frequent UTI who take prophylactic antimicrobial agents for extended periods (≥ 6

months) may decrease their infections during the time of prophylaxis, but the rate of infection returns to the pretreatment rate after prophylaxis is stopped (Stamm et al, 1980a; Vosti, 1975). Even long interruptions in the pattern of recurrence, therefore, do not appear to alter the patient's basic susceptibility to infections.

The sequelae of complicated UTIs are substantial. It is well established in the presence of obstruction, infection stones, diabetes mellitus, and other risk factors that UTIs in adults can lead to progressive renal damage (Freedman, 1975). The long-term effects of uncomplicated recurrent UTIs are not completely known, but, so far, no association between recurrent infections and renal scarring, hypertension, or progressive renal azotemia has been established (Asscher et al, 1973; Freedman, 1975). Indeed, one investigator was unable to find a single case of unequivocal nonobstructive chronic pyelonephritis in 22 patients in whom chronic pyelonephritis was the cause of end-stage renal failure (Schechter et al, 1971). Similar data were reported by Huland and Busch (1982).

In pregnant women, the prevalence and rate of recurrent infection are the same, but their bacteriuria progresses to acute clinical pyelonephritis more frequently than in nonpregnant women. This variation in the natural history of recurrent infections in females is discussed in a later section on UTIs in pregnancy.

KEY POINTS: INCIDENCE AND EPIDEMIOLOGY

- UTIs are the most common bacterial infection.
- They cause significant morbidity but do not cause renal damage unless comorbidities are present.
- Prophylactic antimicrobial therapy reduces morbidity and the time to recurrent bacteriuria, but the risk of recurrence remains the same.

PATHOGENESIS

UTIs are a result of interactions between the uropathogen and the host. Successful infection of the urinary tract is determined in part by the virulence factors of the bacteria, the inoculum size, and the inadequacy of host defense mechanisms. These factors also play a role in determining the ultimate level of colonization and damage to the urinary tract. Whereas increased bacterial virulence appears to be necessary to overcome strong host resistance, bacteria with minimal virulence factors are able to infect patients who are significantly compromised.

Routes of Infection

Ascending Route

Most bacteria enter the urinary tract from the bowel reservoir via ascent through the urethra into the bladder. Adherence of pathogens to the introital and urothelial mucosa plays a significant role in ascending infections. This route is further enhanced in individuals with significant soiling of the perineum with feces, women who use spermicidal agents (Hooton et al, 1996; Foxman, 2002; Handley et al, 2002), and patients with intermittent or indwelling catheters.

Although cystitis is often restricted to the bladder, approximately 50% of infections can extend into the upper urinary tract (Busch and Huland, 1984). The weight of clinical and experimental evidence strongly suggests that most episodes of pyelonephritis are caused by retrograde ascent of bacteria from the bladder through the ureter to the renal pelvis and parenchyma. Although reflux of urine is probably not required for ascending infections, edema associated with cystitis may cause sufficient changes in the ureterovesical junction to permit reflux. Once the bacteria are introduced into the ureter, they may ascend to the kidney unaided.

However, this ascent would be greatly increased by any process that interferes with the normal ureteral peristaltic function. Gram-negative bacteria and their endotoxins, as well as pregnancy and ureteral obstruction, have a significant antiperistaltic effect.

Bacteria that reach the renal pelvis can enter the renal parenchyma by means of the collecting ducts at the papillary tips and then ascend upward within the collecting tubules. This process is hastened and exacerbated by increased intrapelvic pressure from ureteral obstruction or vesicoureteral reflux, particularly when it is associated with intrarenal reflux.

Hematogenous Route

Infection of the kidney by the hematogenous route is uncommon in normal individuals. However, the kidney is occasionally secondarily infected in patients with *Staphylococcus aureus* bacteremia originating from oral sites or with *Candida fungemia*. Experimental data indicate that infection is enhanced when the kidney is obstructed (Smellie et al, 1975).

Lymphatic Route

Direct extension of bacteria from the adjacent organs via lymphatics may occur in unusual circumstances, such as a severe bowel infection or retroperitoneal abscesses. There is little evidence that lymphatic routes play a significant role in the vast majority of UTIs.

Urinary Pathogens

Most UTIs are caused by facultative anaerobes usually originating from the bowel flora. Uropathogens such as *Staphylococcus epidermidis* and *Candida albicans* originate from the flora of the vagina or perineal skin.

E. coli is by far the most common cause of UTIs, accounting for 85% of community-acquired and 50% of hospital-acquired infections. Other gram-negative Enterobacteriaceae, including *Proteus* and *Klebsiella*, and gram-positive *E. faecalis* and *Staphylococcus saprophyticus* are responsible for the remainder of most community-acquired infections. Nosocomial infections are caused by *E. coli*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Pseudomonas aeruginosa*, *Providencia*, *E. faecalis*, and *S. epidermidis* (Kennedy et al, 1965). Less common organisms such as *Gardnerella vaginalis*, *Mycoplasma* species, and *Ureaplasma urealyticum* may infect patients with intermittent or indwelling catheters (Josephson et al, 1988; Fairley and Birch, 1989).

E. coli strains mediating extraintestinal infections are typically grouped into broad phylogenetic classes by multiplex polymerase chain reaction (Clermont et al, 2000), where 70% of uropathogenic *E. coli* (UPEC) isolates fall into the B2 group (Johnson et al, 2001). More recent studies have used multilocus sequence typing to further define and characterize *E. coli* strains mediating UTI and other infections at the level of "sequence type." *E. coli* sequence type ST131 (serotype O25b:H4) merits special attention as a rapidly emerging cause of multidrug-resistant infections, including UTI (Johnson et al, 2010; Kuditinha et al, 2013). Although first noted for extended-spectrum β -lactamases, fluoroquinolone resistance is a hallmark phenotype among ST131 isolates. Recent work with geographically diverse ST131 isolates revealed that a single ST131 subclonal lineage, H30, has emerged within approximately a decade as the major cause of multidrug-resistant *E. coli* infections and is highly associated with recurrent UTI and sepsis (Johnson et al, 2013; Tchesnokova et al, 2013). However, because ST131 isolates were not more virulent in a murine sepsis model, it is likely that the epidemiologic success of ST131 is due to enhanced fitness in early infection events or transmission (Johnson et al, 2012).

The prevalence of infecting organisms is influenced by the patient's age. For example, *S. saprophyticus* is now recognized as causing approximately 10% of symptomatic lower UTIs in young, sexually active females (Latham et al, 1983), whereas it rarely causes infection in males and elderly individuals. A seasonal variation with

a late summer to fall peak has been reported (Hovelius and Mardh, 1984).

Fastidious Organisms

Anaerobes in the Urinary Tract

Although symptomatic anaerobic infections of the urinary tract are documented, they are uncommon. However, the distal urethra, perineum, and vagina are normally colonized by anaerobes. Whereas 1% to 10% of voided urine specimens are positive for anaerobic organisms (Finegold, 1977), anaerobic organisms found in suprapubic aspirates are much more unusual (Gorbach and Bartlett, 1974). Clinically symptomatic UTIs in which only anaerobic organisms are cultured are rare, but these organisms must be suspected when a patient with bladder irritative symptoms has cocci or gram-negative rods seen on microscopic examination of the centrifuged urine (catheterized, suprapubic aspirated, or voided midstream urine) and routine quantitative aerobic cultures fail to grow organisms (Ribot et al, 1981).

Anaerobic organisms are frequently found in suppurative infections of the genitourinary tract. In one study of suppurative genitourinary infections in males, 88% of scrotal, prostatic, and perinephric abscesses included anaerobes among the infecting organisms (Bartlett and Gorbach, 1981). The organisms found are usually *Bacteroides* species, including *B. fragilis*, *Fusobacterium* species, anaerobic cocci, and *Clostridium perfringens* (Finegold, 1977). The growth of clostridia may be associated with cystitis emphysematosa (Bromberg et al, 1982).

Mycobacterium tuberculosis and Other Nontuberculous Mycobacteria

Mycobacterium tuberculosis and other nontuberculous mycobacteria may be found when cultures for acid-fast bacteria are requested; they do not grow under routine aerobic conditions and may be found during evaluation for sterile pyuria. It has been emphasized that the mere presence of mycobacteria may not indicate tissue invasion. Therefore factors such as symptoms, endoscopic or radiologic evidence of infection, abnormal urine sediment, the absence of other pathogens, repeated demonstration of the organism, and the presence of granulomas should be considered before therapy is instituted (Brooker and Aufderheide, 1980; Thomas et al, 1980). (*M. tuberculosis* is discussed in Chapter 17.)

Chlamydia

Chlamydiae are not routinely grown in aerobic culture but have been implicated in genitourinary infections. (Their role in the urinary tract is discussed in Chapter 15.)

Bacterial Virulence Factors

Virulence characteristics play a role in determining both if an organism will invade the urinary tract and the subsequent level of infection within the urinary tract. It is generally believed that uropathogenic strains resident in the bowel flora, such as UPEC, can infect the urinary tract not only by chance but also by the expression of virulence factors that enable them to adhere to and colonize the perineum and urethra and migrate to the urinary tract where they establish an inflammatory response in the urothelium (Schaeffer et al, 1981; Yamamoto et al, 1997; Schlager et al, 2002; Moreno et al, 2008). The same virulence factors can be found on bacterial strains that cause recurrent UTI in patients (Foxman et al, 1995). Some of these virulence determinants are located on one of approximately 20 UPEC-specific pathogenicity-associated islands ranging in size from 30 to 170 kb (Hacker et al, 1999; Oelschlaeger et al, 2002). These pathogenicity islands collectively increase the size of the pathogen genome by about 20% over a commensal strain. A recent genomic analysis of a UPEC

strain revealed the presence of genes for putative chaperone-usher systems, as well as autotransporter proteins that may function as adhesins, toxins, proteases, invasins, serum resistance factors, or motility mediators (Henderson and Nataro, 2001). One UPEC-specific autotransporter, Sat, seems toxic to urinary tract cells in vitro (Guyer et al, 2000) and can cause cytoplasmic vacuolation and severe histologic damage in mouse kidneys (Guyer et al, 2002). Another toxin, hemolysin (HlyA), forms pores in a variety of host cell membranes (Uhlen et al, 2000). In addition to proteases and toxins, UPEC produces several iron acquisition systems, including aerobactin (Johnson et al, 1988; Johnson, 2003) and the more recently described *Iron* system (Russo et al, 1999; Sorsa et al, 2003). Lastly, most UPEC strains produce an acid polysaccharide capsule that protects the bacteria from phagocytosis by human polymorphonuclear leukocytes and inhibits activation of complement (Johnson, 2003).

Early Events in UPEC Pathogenesis

Bacterial Adherence

Bacterial adherence to vaginal and urothelial epithelial cells is an essential step in the initiation of UTIs. This interaction is influenced by the adhesive characteristics of the bacteria, the receptive characteristics of the epithelial surface, and the fluid bathing both surfaces. Bacterial adherence is a specific interaction that plays a role in determining the organism, the host, and the site of infection. Portions of this section on bacterial adherence have been published (Schaeffer et al, 1981).

Bacterial Adhesins. UPEC expresses a number of adhesins that allow it to attach to urinary tract tissues (Mulvey, 2002). These adhesins are classified as either fimbrial or afimbrial, depending on whether the adhesin is displayed as part of a rigid fimbria or pilus (Fig. 12-5). Bacteria may produce a number of antigenically and functionally different pili on the same cell; others produce a single type; in some, no pili are seen (Klemm, 1985). A typical piliated cell may contain 100 to 400 pili. The pilus is usually 5 to 10 nm in diameter, is up to 2 μ m long, and appears to be composed primarily of subunits known as *pilin* (Klemm, 1985). Pili are defined functionally by their ability to mediate hemagglutination of specific types of erythrocytes. The most well-described pili are types 1, P, and S.

Type 1 (Mannose-Sensitive) Pili. Type 1 pili are commonly expressed on both nonpathogenic and pathogenic *E. coli*. Type 1 pili consist of a helical rod composed of repeating FimA subunits joined to a 3-nm wide distal tip structure containing the adhesin FimH (Jones et al, 1995). These pili mediate hemagglutination of guinea pig erythrocytes (Duguid et al, 1979). The reaction is inhibited by the addition of mannose; thus type 1 pili are termed *mannose-sensitive hemagglutination* (MSHA) (Svenson et al, 1984; Reid and Sobel, 1987).

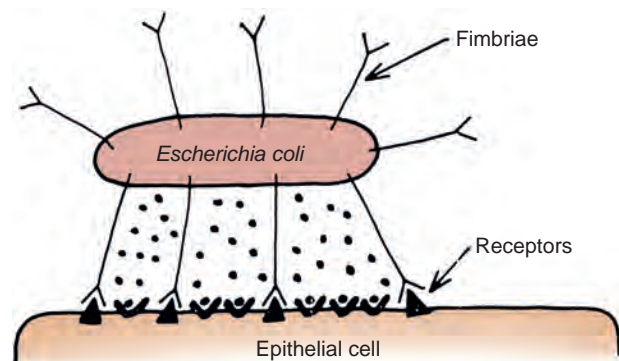


Figure 12-5. Bacterial adherence. Adhesins on pili (fimbriae) mediate attachment to specific epithelial cell receptors.

The role of type 1 pili as a virulence factor in UTIs has been established. This evidence has been obtained (1) from the analysis of bacteria isolated from the urine of patients with UTIs, which were found to express mannose-sensitive (MS) adhesins (Ljungh and Wadstrom, 1983); (2) from studies with animal models (Fader and Davis, 1982; Hagberg et al, 1983a, 1983b; Iwahi et al, 1983; Hultgren et al, 1985) in which inoculation of type 1 pilated organisms into the bladder resulted in significantly more colonization of the urinary tract than inoculation of nonpilated organisms; and (3) from the observation that anti-type 1 pili antibodies and competitive inhibitors such as methyl- α -D-mannopyranoside protected mice from contracting UTIs (Aronson et al, 1979; Hultgren et al, 1985). Recent studies have demonstrated that interactions between FimH and receptors expressed on the luminal surface of the bladder epithelium are critical for the ability of many UPEC strains to colonize the bladder and cause disease (Connell et al, 1996; Langermann et al, 1997; Thankavel et al, 1997; Mulvey et al, 1998).

P (Mannose-Resistant) Pili. P pili confer tropism to the kidney, the designation “P” standing for pyelonephritis (Mulvey, 2002). P pili, which are found in most pyelonephritogenic strains of UPEC, mediate hemagglutination of human erythrocytes that is not altered by mannose and is thus termed *mannose-resistant hemagglutination* (MRHA) (Kallenius et al, 1979). The adhesin PapG, at the tip of the pilus, recognizes the α -D-galactopyranosyl-(1-4)- β -D-galactopyranoside moiety present in the globoseries of glycolipids (Kallenius et al, 1980; Leffler and Svanborg-Eden, 1980), which are found on P blood group antigens and on uroepithelium (Svenson et al, 1983).

The MRHA adhesins of UPEC that do not show the digalactoside-binding specificity have been provisionally named *X adhesins* (Vaisanen et al, 1981). In some strains of UPEC, hemagglutination is mediated by nonpilated adhesins or hemagglutinins (Duguid et al, 1979).

Svanborg-Eden and coworkers (1978) were the first to report a correlation between bacterial adherence and severity of UTIs. They showed that UPEC strains from girls with acute pyelonephritis had high adhesive ability, whereas strains causing asymptomatic bacteriuria or from the feces of healthy girls had low bacterial adherence. Between 70% and 80% of the pyelonephritic strains, but only 10% of the bowel isolates, had adhesive capacity. Furthermore, P pili were present in 91% of urinary strains causing pyelonephritis, 19% of strains causing cystitis, and 14% of strains causing asymptomatic bacteriuria but only 7% of bowel isolates from healthy children, highlighting the correlation between bacterial adherence and UTIs (Kallenius et al, 1981).

Whereas MRHA and P pili are strongly associated with pyelonephritis, these virulence factors are not associated with renal scarring and reflux caused by bacterial infection (Vaisanen et al, 1981). Studies suggest minimal correlation between P-piliated *E. coli* strains and recurrent pyelonephritis with gross reflux in girls (Lomberg et al, 1983). Thus it would appear that P pili in acute pyelonephritis are important mainly in nonrefluxing or minimally refluxing children.

Other Adhesins. S pili, which bind to sialic acid residues via the SfaS adhesin, have been associated with both bladder and kidney infection (Mulvey, 2002). F1C pili bind to glycosphingolipids in renal epithelial cells and induce an interleukin-8 inflammatory response (Backhed et al, 2002).

UPEC also expresses a group of afimbrial adhesins (AFA), which have been clustered with the Dr adhesin family for their recognition of decay-accelerating factor and for their similar genetic structure. Decay-accelerating factor is found on numerous different epithelial sites, and Dr adhesins are known to bind to many locations throughout the urinary tract (Anderson et al, 2004b).

Catch Bonds. Not surprisingly, UPEC adhesins have evolved to meet the physical dynamics of the urinary tract, and this is best understood for FimH. Using hemagglutination assays and flow cell approaches, the affinity of *E. coli* expressing specific FimH alleles for erythrocytes was found to be enhanced by shear stress, and mutations that abolished FimH-erythrocyte interactions in static

conditions did not impact dynamic affinities (Thomas et al, 2002). Conversely, static conditions reduced FimH-erythrocyte interactions. Known as *catch bonds*, this fingertrap-like mechanism is mediated by shear-altered interactions between the FimH pilin and mannose-binding domains that result in force-induced tightening of the mannose-binding pocket (Le Trong et al, 2010). Similar shear-enhanced binding now appears widespread in biology and includes *E. coli* P-fimbriae (reviewed in Sokurenko et al, 2008). The implications of catch bonds for UPEC adherence and UTI pathogenesis are obvious. Enhanced adherence in the presence of shear would promote UPEC retention in the urethra and bladder during voiding and in the ureters against peristalsis. In the absence of shear, reduced FimH affinity would facilitate diffusion and thereby promote ascending infection.

Phase Variation of Bacterial Pili in Vivo

Early evidence for the role of type 1 and P pili in adherence in UTIs in humans was contradictory. Pili were visible by electron microscopy on *E. coli* in the urine of 31 of 37 patients (Ljungh and Wadstrom, 1983). Conversely, no MS adhesins were found in 22 of 24 urine isolates from patients with indwelling catheters (Ofek et al, 1981), and 19 of 20 samples from patients with acute UTIs were devoid of pili and nonadherent until subcultured in broth (Harber et al, 1982). Assessment of pili production by clinical *E. coli* isolates demonstrates that environmental growth conditions can produce rapid changes in pilus expression (Duguid et al, 1966; Goransson and Uhlin, 1984; Hultgren et al, 1986), wherein cells switch back and forth between pilated and nonpilated phases (Eisenstein, 1981). For example, some bacteria grown in a broth medium express pili, whereas the same strain grown on the same medium in a solid state will cease production of pili. This process, called *phase variation*, can also occur in vivo and has obvious biologic and clinical implications. For example, the presence of type 1 pili may be advantageous to the bacteria for adhering to and colonizing the bladder mucosa but disadvantageous because the pili enhance phagocytosis and killing by neutrophils (Silverblatt et al, 1979).

An animal model of ascending UTIs and studies of bacterial isolates from different sites in patients with UTI provide evidence that phase variation can occur during *E. coli* UTI in vivo. Type 1 pilated *E. coli* organisms that were capable of phase variation were introduced into the mouse bladder in the pilated phase, and the bacteria recovered from the bladder and urine 24 or more hours after inoculation were tested for piliation. All of the animals had bladder colonization, and 78% of the bacteria recovered showed type 1 piliation. The bacteriologic state of the urine often differed from that of the bladder. The urine was sterile in 59% of the animals with bladder colonization, and the organisms recovered from the urine were often nonpilated.

When bladder and kidney cultures were examined 1, 3, and 5 days after intravesical inoculation of pilated bacteria, organisms recovered from the bladder remained pilated, whereas organisms recovered from the kidney showed significantly less piliation (Schaeffer et al, 1987) (Fig. 12-6).

Studies in humans using indirect immunofluorescence of fresh urine bacteria have confirmed in vivo expression and phase variation of pili. Analysis of the urine of adults with lower UTI detected type 1 pili in 31 of 41 specimens and P pili in 6 of 18 specimens (Kisielius et al, 1989). The piliation status of the bacterial population in the urine was heterogeneous, varying from predominantly pilated to a mixture of pilated and nonpilated cells (Fig. 12-7). Strains isolated from different sites in the urogenital tract showed variation in the state of piliation. These results demonstrate that type 1 and P pili are expressed and subject to phase variation in vivo during acute UTIs.

This process of phase variation has obvious biologic and clinical implications. For example, the presence of type 1 pili may be advantageous to the bacteria for initially adhering to and colonizing the bladder mucosa. Subsequently, type 1 pili may be unnecessary for strains in suspension in urine and in fact detrimental because they enhance apoptosis, phagocytosis, and killing by neutrophils

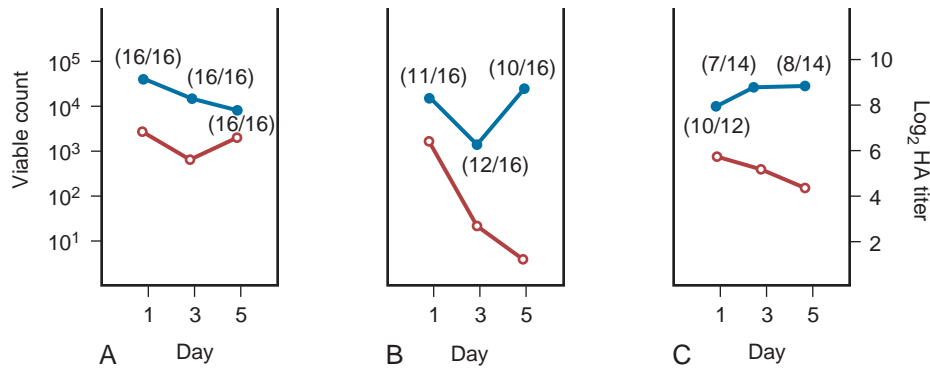


Figure 12-6. Time study after intravesical inoculation with *Escherichia coli* strain I-149 that compared the mean viable bacteria count (solid circles) and hemagglutination (HA) titer (open circles) for bladders (A), kidneys (B), and urine specimens (C) from the same animals. Each point is the mean of all the animals tested. The numbers in parentheses show the proportion of animals inoculated that gave positive cultures. The HA titers were tested after 18 hours of growth on agar. The HA titer of bacteria recovered from the kidney decreased significantly by day 5 ($P < 0.001$). (From Schaeffer AJ, Schwan WR, Hultgren SJ, et al. Relationship of type 1 pilus expression in *Escherichia coli* to ascending urinary tract infections in mice. *Infect Immun* 1987;55:373–80.)

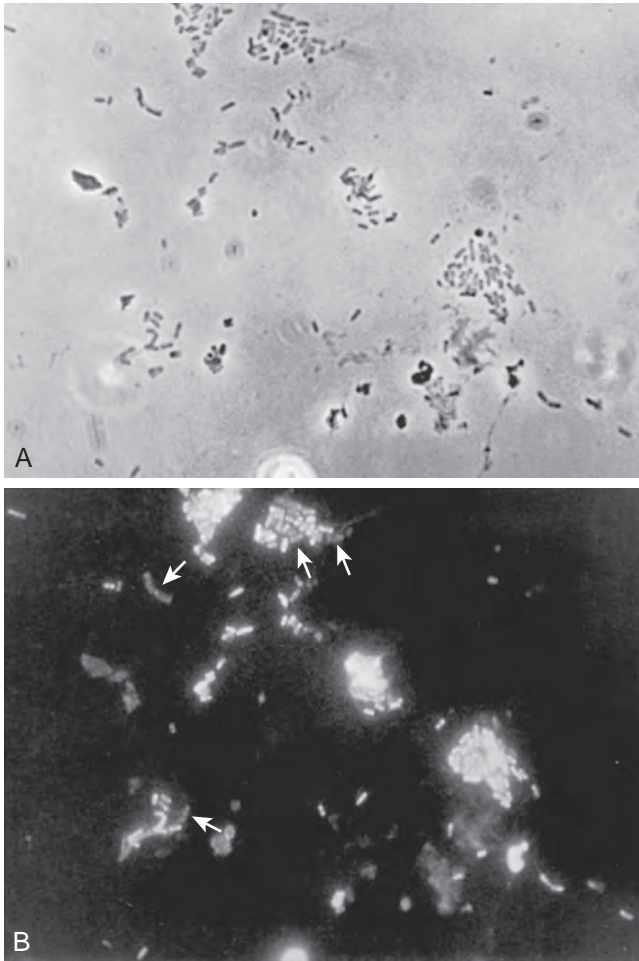


Figure 12-7. Phase-contrast micrograph (A) and immunofluorescence micrograph (B) of a sample stained with antiserum to type 1 pili of strain I-49 and with fluorescein isothiocyanate-conjugated second antibody against nonadherent *Escherichia coli* in the urine of a patient with acute urinary tract infection show a mixture of piliated and nonpiliated (arrows in B) cells. (From Kisieli PV, Schwan WR, Amundsen SK, et al. In vivo expression and variation of *Escherichia coli* type 1 and P pili in the urine of adults with acute urinary tract infections. *Infect Immun* 1989;57:1656–62.)

(Silverblatt et al, 1979; Mulvey et al, 1998). In the kidney, P pili may then take over as the primary mediator of bacterial attachment via their binding to the glycolipid receptors (Stapleton et al, 1995).

Epithelial Cell Receptivity

Vaginal Cells

The significance of epithelial cell receptivity in the pathogenesis of ascending UTI has been studied initially by examining adherence of *E. coli* to vaginal epithelial cells and uroepithelial cells collected from voided urine specimens. Fowler and Stamey (1977) established that certain indigenous microorganisms (e.g., lactobacilli, *S. epidermidis*) avidly attached themselves to washed epithelial cells in large numbers. When vaginal epithelial cells were collected from patients susceptible to reinfection and compared with such cells obtained from controls resistant to UTI, the *E. coli* strains that cause cystitis adhered much more avidly to the epithelial cells from the susceptible women. These studies established increased adherence of pathogenic bacteria to vaginal epithelial cells as the first demonstrable biologic difference that could be shown in women susceptible to UTI.

Subsequently, Schaeffer and colleagues (1981) confirmed these vaginal differences in women, but in addition they observed that the increased bacterial adherence was also characteristic of buccal epithelial cells. As can be seen in Figure 12-8, there is a striking similarity in the ability of both cell types to bind to the same *E. coli* strain. In addition, there was a significant relationship between vaginal cell and buccal cell receptivity. Seventy-seven different *E. coli* strains were tested for their ability to bind to vaginal and buccal epithelial cells. A direct nonlinear relationship between buccal and vaginal adherence in controls and patients was confirmed for urinary, vaginal, and anal isolates. Thus high vaginal cell receptivity was associated with high buccal cell receptivity.

These observations emphasize that the increase in receptor sites for UPEC on epithelial cells from women with recurrent UTIs is not limited to the vagina and thus suggest that a genotypic trait for epithelial cell receptivity may be a major susceptibility factor in UTIs. This concept was extended by examining the human leukocyte antigens (HLAs), which are the major histocompatibility complex in humans and have been associated statistically with many diseases (Schaeffer et al, 1983). The A3 antigen was identified in 12 (34%) of the patients, which is significantly higher than the 8% frequency observed in healthy controls. Thus, HLA-A3 may be associated with increased risk of recurrent UTIs.

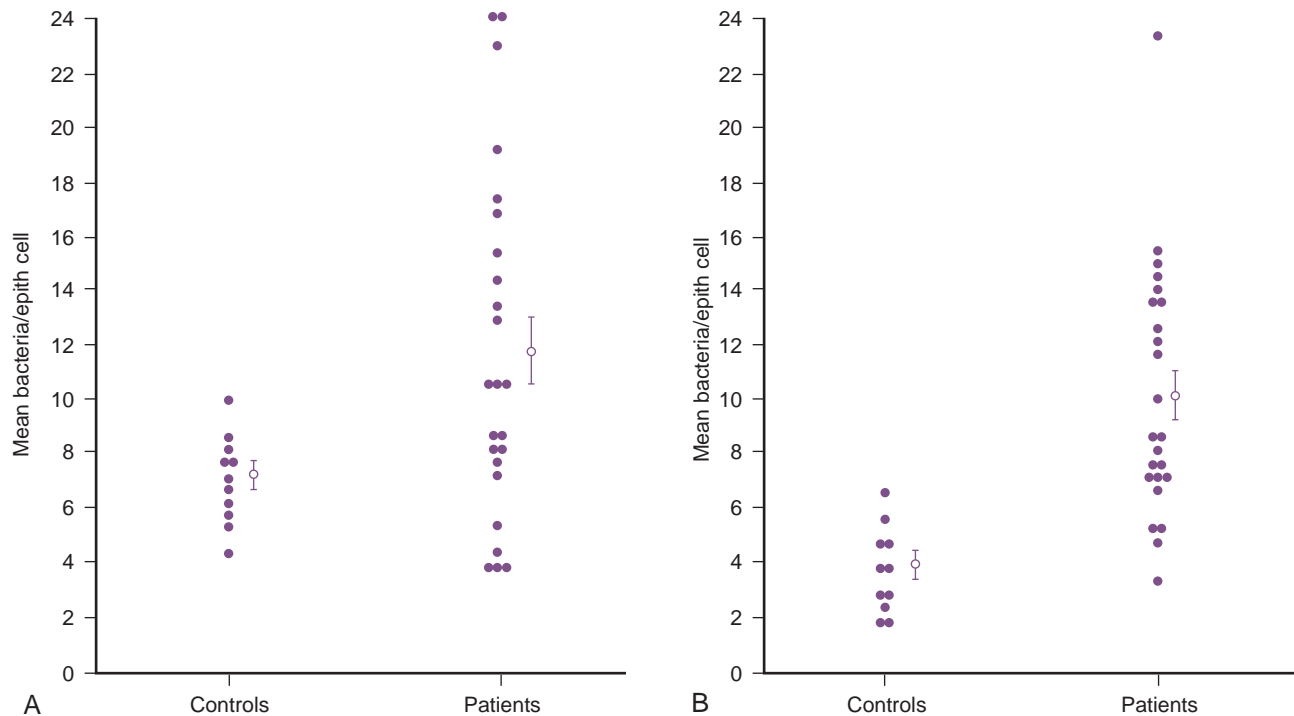


Figure 12-8. In vitro adherence of *Escherichia coli* to vaginal (A) and buccal (B) cells from healthy controls and patients with recurrent urinary tract infections. Values represent an average of 14 (A) and 11 (B) determinations in each individual. The open circles and bars represent the means + standard error of the mean. (From Schaeffer AJ, Jones JM, Dunn JK. Association of in vitro *Escherichia coli* adherence to vaginal and buccal epithelial cells with susceptibility of women to recurrent urinary tract infections. *N Engl J Med* 1981;304:1062–6.)

Variation in Receptivity. A small variation in both vaginal cell and buccal cell receptivity may be observed from day to day in healthy controls. Adherence ranges from 1 to 17 bacteria per cell and appears to be both cyclic and repetitive. When adherence was correlated with the days of a woman's menstrual cycle, higher values were noted in the early phase, diminishing shortly after the time of expected ovulation (day 14). The number of bacteria per epithelial cell often correlated with the value obtained on the same day of the menstrual cycle 1 or 2 months previously. Premenopausal women are particularly susceptible to attachment of uropathogenic *E. coli* and nonpathogenic lactobacilli at certain times during the menstrual cycle and to *E. coli* during the early stages of pregnancy. The importance of such hormones as estrogens in the pathogenesis of UTI is therefore a matter of great interest, especially because the clinical urologist may see women who have recurrent cystitis at regular intervals, possibly in response to these hormonal changes.

Reid and Sobel (1987) found that uropathogens attached in larger numbers to uroepithelial cells from women older than 65 years of age than to cells from premenopausal women 18 to 40 years of age. Raz and Stamm (1993) noted that susceptibility to recurrent UTI was increased by the lowered estrogen levels found in the postmenopausal women and that estrogen replacement decreased uropathogenic bacterial colonization and the incidence of UTI.

Blood group antigens and carbohydrate structures bound to membrane lipids or proteins also constitute an important part of the uroepithelial cell membrane. The presence or absence of blood group determinants on the surface of uroepithelial cells may influence an individual's susceptibility to a UTI. Sheinfeld and associates (1989) determined the blood group phenotypes in women with recurrent UTI and compared them with those of age-matched women controls. There is a higher frequency of Lewis

nonsecretor Le(a+b-) and recessive Le(a-b-) phenotypes among women with recurrent UTIs. There was no significant difference in the distribution of ABO or P blood group phenotypes. The Lewis antigen controls fucosylation. The protective effect in women with the secretor Le(a-b+) phenotype may be due to fucosylated structures at the vaginal cell surface or in the overlying mucus, which decreases availability of putative receptors for *E. coli* (Navas et al, 1993). The nonsecretor status has also been associated with female acute uncomplicated pyelonephritis, especially in premenopausal women (Ishitoya et al, 2002). Stapleton and coworkers (1995) have shown that unique *E. coli*-binding glycerides are found in vaginal epithelial cells from nonsecretors but not from secretors. These studies individually and collectively support the concept that there is an increased epithelial receptivity for *E. coli* on the introital, urethral, and buccal mucosa that is characteristic of women susceptible to recurrent UTIs and may be a genotypic trait.

The possibility that vaginal mucus might influence bacterial receptivity was investigated by Schaeffer and colleagues (1994). Type 1 piliated *E. coli* bound to all of the vaginal fluid specimens (Venegas et al, 1995). The binding capacity of vaginal fluid from women colonized with *E. coli* in vivo was greater than that from noncolonized women (Schaeffer et al, 1999). The importance of vaginal fluid in bacteria/epithelial cell interactions was investigated in an in vitro model that measured the effect of vaginal fluid on the binding of bacteria to an epithelial cell line (Gaffney et al, 1995). Vaginal fluid from colonized women enhanced binding of bacteria to epithelial cells. Conversely, vaginal fluid from noncolonized women inhibited adherence. Thus the vaginal fluid appears to influence adherence to cells and, presumably, vaginal mucosal colonization. Subsequent studies demonstrated that secretory IgA is the primary glycoprotein responsible for vaginal fluid receptivity (Rajan et al, 1999).

Bladder Cells

FimH binds mannosylated residues on the uroplakin molecules covering bladder superficial epithelial cells. The luminal surface of the bladder is lined by umbrella cells. The apical surfaces of umbrella cells appear as a quasi-crystalline array of hexagonal complexes composed of four integral membrane proteins known as *uroplakins* (Sun, 1996). In vitro binding assays have shown that two of the uroplakins, UPIa and UPIb, can specifically bind UPEC expressing type 1 pili (Wu et al, 1996). High-resolution freeze-fracture electron microscopy has shown that the tips of these pili, including the adhesins, are buried in the central cavity of the uroplakin hexameric rings (Mulvey et al, 2000) (Fig. 12-9A). Thus FimH-mediated binding to the bladder epithelium is the initial step in the intricate cascade of events leading to UTIs. Immediate urothelial responses to UPEC may be triggered by uroplakins themselves because FimH binding to UPIb was shown to result in phosphorylation of UPIII and subsequent UPIII-mediated increases in intracellular calcium (Thumbikat et al, 2009b).

UPEC Persistence in the Bladder. Soon after attachment to the epithelium, UPEC is quickly internalized into the bladder superficial cells (Martinez and Hultgren, 2002; Anderson et al, 2004b) (Fig. 12-9B). FimH is essential for UPEC invasion; isogenic FimH-mutants do not invade, and invasion of wild-type bacteria can be inhibited by the addition of mannose. In addition, polystyrene latex beads coated with FimH are quickly internalized in a process identical to bacteria expressing type 1 pili. This process is the result of localized actin rearrangement and engulfment of the

bound bacterium by zippering of the membrane around the microorganism (Martinez and Hultgren, 2002). Invasion into the superficial epithelium of the bladder allows UPEC to establish a new niche in an effort to protect itself from the host innate immune response (Anderson et al, 2004b).

Multiple urothelial receptors have been implicated in UPEC invasion. FimH was shown to bind integrins α_3 and β_1 in vitro, and anti-integrin antibodies blocked UPEC invasion of cultured urothelial cells, a process modulated by Src family kinases and integrin phosphorylation (Eto et al, 2007). FimH binding was also shown to result in phosphorylation of UPIII by casein kinase II (Thumbikat et al, 2009b). UPEC invasion was significantly reduced in cultured cells by targeted mutagenesis of the UPIII phosphorylation site, and perturbing casein kinase II function reduced UPEC invasion in vitro and in vivo. Thus UPEC invade urothelial cells by distinct receptors that, in turn, trigger diverse signaling cascades.

Once intracellular, the UPEC organisms rapidly grow and divide within the cell cytosol, forming small clusters of bacteria termed *early intracellular bacterial communities* (IBCs) (Anderson et al, 2004b; Justice et al, 2004). As they grow, the bacteria maintain their typical rod shape of approximately 3 μm and form a loosely organized cluster, with microorganisms randomly oriented in the cell cytoplasm. Between 6 to 8 hours after inoculation, early IBCs show a drop in bacterial growth rate resulting in doubling times greater than 60 minutes, a significant shortening of the bacterial morphology to an average of 0.7 μm , and a phenotypic switch into a biofilm-like community (Justice et al, 2004) (Fig. 12-9C). Similar bacteria-engorged urothelial cells have been identified in 22% of

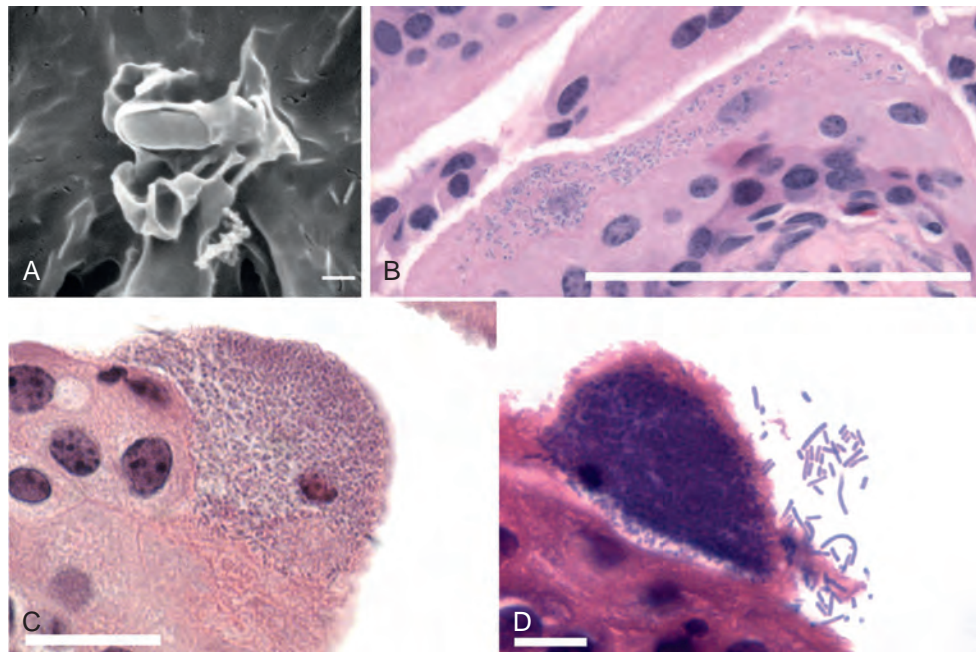


Figure 12-9. Uropathogenic *Escherichia coli* (UPEC) binds, invades, and multiplies inside the superficial cells of the bladder epithelium. A, Scanning electron microscopy shows a single UPEC bound to the surface of a bladder cell. Type 1 pilus-mediated contact between bacterium and host cell initiates signaling cascades in the bladder cell, leading to localized actin rearrangements and membrane protrusions around the bacterium. Scale bar, 0.5 μm . B, Once inside the bladder superficial cells, UPEC rapidly multiplies to form disordered bacterial clusters in the host cell cytoplasm, called an early intracellular bacterial community (IBC). Bacteria are visible as dark-staining rods inside the cell in this hematoxylin and eosin (H&E)-stained thin bladder section. Scale bar, 100 μm . C, H&E-stained thin bladder section reveals a middle IBC, wherein the constituent bacteria have organized themselves into a biofilm-like state within the bladder cell. Scale bar, 20 μm . D, A late IBC, visible by H&E staining, is typified by detachment of peripheral bacteria and fluxing of these organisms into the bladder lumen. Scale bar, 10 μm . (From Anderson GG, Martin SM, Hultgren SJ. Host subversion by formation of intracellular bacterial communities in the urinary tract. *Microbes Infect* 2004;6:1094–101.)

voided urine specimens from patients with UTI with *E. coli* (Rosen et al, 2007). Importantly, UPEC isolated from the human IBC-like cells were capable of infecting mice and recapitulating IBCs (Garofalo et al, 2007).

Biofilms shield bacteria from environmental challenges such as antimicrobial agents and the host immune response (Donlan and Costerton, 2002). Characteristics of the biofilm that increase protection include the slower growth rate of the bacteria with associated physiologic changes, expression of factors that inhibit antimicrobial activity, and the inability of the antimicrobial agent to penetrate the biofilm matrix (Anderson et al, 2004b). The biofilm also protects the bacteria from neutrophils because they are unable to effectively penetrate the IBC and engulf the bacteria. In animal models, bacteria on the edge of IBCs eventually detach, differentiate to typical rod morphology, become motile, and then escape the host cell into the bladder lumen in a process called *fluxing* (Mulvey et al, 2001) (Fig. 12-9D). These bacteria may become highly filamentous, reaching up to 70 μm or greater in length. This process occurs by approximately 24 hours after inoculation (Justice et al, 2004). It is possible that the filaments may help the bacteria evade the immunologic response.

The escaped bacteria re-adhere and reinvade superficial cells to lead to second IBC formation. In subsequent rounds, further IBC formation occurs. After a few days, the invasive bacteria become more quiescent. In animal models, the bacteria can persist in this dormant reservoir state for some time before reemerging to cause recurrent UTIs (Anderson et al, 2004a). Indeed, in murine UTI, individuals with sterile urine nonetheless may contain thousands of viable UPEC within bladder tissue (Mulvey et al, 2001), suggesting that IBCs may be a transient intermediate in the establishment of stable UPEC reservoirs within the bladder. Exfoliation of superficial urothelial cells (see later) exposes underlying transitional cells. In contrast to the cytosolic UPEC aggregates characteristic of IBCs, UPEC invasion of transitional cells results in membrane-bound bacteria limited to two to four bacteria per cell (Justice et al, 2004). These intracellular UPEC remain quiescent, and thus such transitional cells are referred to as *quiescent intracellular reservoirs* (QIR) (Mysorekar and Hultgren, 2006). However, chemically perturbing the urothelium to evoke urothelial differentiation caused reemergence of UPEC from QIR marked by significant bacterial proliferation. Together, these findings suggest that bladder reservoirs of intracellular UPEC may contribute to recurrent UTI in susceptible individuals as the transitional cells undergo differentiation.

Natural Defenses of the Urinary Tract

Periurethral and Urethral Region

The normal flora of the vaginal introitus, the periurethral area, and the urethra usually contain microorganisms such as lactobacilli, coagulase-negative staphylococci, corynebacteria, and streptococci that form a barrier against uropathogenic colonization (Fair et al, 1970; Pfau and Sacks, 1977; Marrie et al, 1978). Changes in the vaginal environment related to estrogen, cervical IgA (Stamey et al, 1978), and low vaginal pH (Stamey and Timothy, 1975) may alter the ability of these bacteria to colonize. More commonly, however, acute changes in colonization have been associated with use of antimicrobial agents and spermicidal agents that alter the normal flora and increase the receptivity of the epithelium for uropathogens.

Little is known about the factors that predispose patients to urethral colonization with uropathogens. The proximity of the urethral meatus to the vulvar and perianal areas suggests that contamination occurs frequently. The nature of urethral defense mechanisms other than flow of urine is largely unknown. Bacterial multiplication in the normal urethra may be inhibited by the indigenous flora (Chan et al, 1984). Although colonization of the periurethral and urethral regions is prerequisite to most infections, the ability of the organisms to overcome the normal defense mechanisms of the urine and the bladder is clearly pivotal.

Urine

In general, fastidious organisms that normally colonize the urethra will not multiply in urine and rarely cause UTIs (Cattell et al, 1974). In contrast, urine will usually support the growth of nonfastidious bacteria (Asscher et al, 1968). Urine from normal individuals may be inhibitory, especially when the inoculum is small (Kaye, 1968). The most inhibitory factors are the osmolality, urea concentration, organic acid concentration, and pH. Bacterial growth is inhibited by either very dilute urine or a high osmolality when associated with a low pH. Much of the antimicrobial activity of urine is related to a high urea and organic acid content (Solomon et al, 1983). From a clinical perspective, however, these conditions do not appear to significantly distinguish between patients who are susceptible or resistant to infection.

Uromodulin (Tamm-Horsfall protein), a kidney-derived mannosylated protein that is present in an extraordinarily high concentration in the urine (>100 mg/mL), may play a defensive role by saturating all the mannose-binding sites of the type 1 pili, thus potentially blocking bacterial binding to the uroplakin receptors of the urothelium (Duncan, 1988; Kumar and Muchmore, 1990).

Recent studies have exploited next-generation DNA-sequencing technology to quantify any bacteria in normal urine and thus characterize the normal female urinary microbiome. Flora were identified in urine obtained by suprapubic aspiration from healthy participants that differed from voided urine and contained species that were uncultivable under either aerobic or anaerobic conditions (Wolfe et al, 2012). Aspirated urine (or urine obtained by catheter) that was culture-negative revealed diverse genera in a majority of participants. And while urine culture remains the gold standard for assessing UTI, this work also suggests a more complex bladder ecology: a single participant whose urine culture was positive for *E. coli* had relative DNA abundance of approximately 45% *Aerococcus*, 21% *Actinobaculum*, and only 2% *E. coli*. The authors then ask whether clinical symptoms reflect the low-abundance uropathogen, the more abundant fastidious bacteria, or both. Because most healthy participants exhibited urinary flora, future studies should define the role of the urinary microbiome in resistance and susceptibility to UTI.

Bladder

Bacteria presumably make their way into the bladder fairly often. Whether small inocula of bacteria persist, multiply, and infect the host depends in part on the ability of the bladder to empty (Cox and Hinman, 1961). Additional factors responsible for defense involve both innate and adaptive immunity and exfoliation of epithelial cells.

Immune Response

Pathogen Recognition. The host recognition of the pathogen is mediated by a series of pathogen-associated molecular pattern receptors (PAMPs), such as Toll-like receptors (TLRs) (Anderson et al, 2004b), which provide the link between recognition of invading organisms and development of the innate immune response. TLRs recognize molecular patterns that are conserved among many species of pathogens, such as lipopolysaccharide (LPS) and peptidoglycan (PG), and activate signaling pathways that initiate immune and inflammatory responses to kill pathogens. Superficial bladder epithelial cells express TLR4 on their membranes, which along with CD14 recognize LPS from the bacteria and activate the innate immune response (Anderson et al, 2004a). The newly identified TLR11, which recognizes UPEC and protects the kidneys from ascending infection, is also expressed on uroepithelial cells, as well as renal cells (Zhang et al, 2004).

The innate system response to an infection in the bladder or kidneys is primarily local inflammation.

The innate immune response occurs more rapidly than the adaptive response and involves a variety of cell types, including

polymorphonuclear leukocytes, neutrophils, macrophages, eosinophils, natural killer cells, mast cells, and dendritic cells. In addition, increased transcription of inducible nitric oxide synthase by polymorphonuclear leukocytes results in high levels of nitric oxide and related breakdown products that also have toxic effects on the bacteria (Poljakovic et al, 2001; Poljakovic and Persson, 2003). The innate response aids in establishing adaptive immunity because of interactions of macrophages, dendritic cells, and natural killer cells with T and B lymphocytes. Adaptive immunity involves the specific recognition of pathogens by T and B lymphocytes and production of high-affinity antibodies, a process that occurs 7 to 10 days after infection.



For additional data regarding the immunologic response to UTI, the idea of immunization, and the roles of lipopolysaccharide, see the Expert Consult website.

Multiple Roles for Lipopolysaccharide. Because TLR signaling triggers innate immune responses and mediates innate-adaptive interactions, diverse pathogens target TLR signaling. Consistent with this, TLR modulation has been identified in UPEC. UPEC was found to modulate urothelial inflammatory responses at the levels of nuclear factor- κ B (NF- κ B) activation and cytokine suppression, and this inflammatory suppression is widespread among clinical *E. coli* strains (Klumpp et al, 2001; Hunstad et al, 2005; Billips et al, 2007). In contrast to bacteria that modulate inflammatory responses through the action of secreted virulence factors, UPEC genetic screens identified genes associated with modification of TLR ligands (Hunstad et al, 2005; Billips et al, 2008). One such screen revealed that UPEC genes inhibiting urothelial cytokine responses were *walA*, *ampG*, and *alr*, genes encoding LPS O-antigen ligase, mureopeptide permease, and alanine racemase, respectively (Billips et al, 2008). *WalA* is involved in LPS biosynthesis, whereas both *ampG* and *alr* contribute to peptidoglycan metabolism, ligands for TLR4 and TLR2, respectively. UPEC strains with targeted deletions of *walA* or *ampG* were attenuated in a murine UTI model (Billips et al, 2008), indicating that modulation of TLR-mediated responses is important to UTI pathogenesis by UPEC. In a similar genetic screen, LPS biosynthesis operons *rfa* and *rfb* and the membrane protein isomerase *surA* were found to mediate cytokine suppression (Hunstad et al, 2005). Some UPEC strains even encode direct inhibitors of TLR signaling (Cirl et al, 2008). Together, these findings suggest that UPEC enhances virulence by modulating inflammatory responses at the level of TLR recognition, thereby extending a “window of opportunity” to establish infection by evading innate surveillance mechanisms.

Studies in murine UTI also suggest that these observations can be exploited for the development of novel vaccines against UPEC because immunizing with the *walA* mutant of UPEC strain NU14 conferred protection against challenge with wild-type NU14 (Billips et al, 2009). Immunization with the *walA* mutant of NU14, a phylogenetic group B2 strain, also conferred protection against other B2 strains, as well as A and D strains, and prevented kidney infection. Consistent with TLR-mediated skewing of immune responses (Schnare et al, 2001), *walA* mutant also promoted bladder sterilization of stable UPEC reservoirs, indicating enhanced cell-mediated immunity. These findings suggest that UPEC mutants represent live-attenuated vaccine candidates for recurrent UTI.

LPS has also emerged as a key determinant of the symptomatic response to *E. coli* in the urinary tract in recent studies using tactile allodynia as a measure of pelvic pain in murine UTI. The cystitis isolate NU14 evoked an acute pelvic pain response, whereas the asymptomatic bacteriuria *E. coli* strain 83972 did not, thus recapitulating the spectrum of human symptomatic response to bladder colonization (Rudick et al, 2010). Surprisingly, purified LPS preparations from NU14 and 83972 yielded the same pain/no pain responses as intact bacteria, yet the level of neutrophil influx and cytokines induced by each LPS was similar. Pain responses were also mediated by the LPS receptor TLR4. The O-antigen moiety that defines *E. coli* serotypes is an important determinant of the bacterial pain phenotype because, depending

upon O-antigen status, it was shown that a single *E. coli* strain could be shifted from an acute pain phenotype to a chronic pain phenotype, to a null pain phenotype (Rudick et al, 2012). Again, although pain responses were dependent upon TLR4, bacteria that elicited distinct pain responses induced similar pathology and neutrophil influx. These findings indicate that LPS defines the pain phenotype of *E. coli* and that bacterial pain is not correlated with inflammation. Moreover, because some strains lacking O antigen caused pain that persisted long after bacterial clearance, these findings demonstrate that *E. coli* can cause post-UTI chronic pain.

Induced Exfoliation. Mulvey and colleagues (1998) demonstrated that exfoliation and excretion of infected and damaged superficial cells is mediated by type 1 piliated bacteria that induce programmed cell death. By utilizing an in vivo mouse model, it has been demonstrated that mice exhibiting a strong exfoliation response to UPEC infiltration are unlikely to form IBCs (Anderson et al, 2004b). However, mice with a much milder exfoliation response tend to form biofilms, which become sequestered in the bladder and presumably could lead to recurrent UTIs. It has also been shown that many uropathogenic bacteria can suppress NF- κ B, increase apoptosis, and decrease the inflammatory responses (Klumpp et al, 2001), a process that could lead to subsequent bacterial invasion into deeper tissues. Thus in some instances apoptosis may be a bacterial offense maneuver rather than a host defense.

The same UPIII-casein kinase II signaling cascade mediating UPEC invasion also drives FimH-induced urothelial apoptosis (Thumbikat et al, 2009b). Consistent with this, increased UPIII expression during urothelial differentiation sensitizes urothelial cells to UPEC and FimH-induced apoptosis (Thumbikat et al, 2009a). However, because FimH-induced urothelial apoptosis and successful establishment of the UPEC intracellular life cycle are mutually exclusive, UPEC and/or host factors must define individual urothelial cell fates and thus the bifurcation between invasion and apoptosis.

Alterations in Host Defense Mechanisms

Obstruction

Obstruction to urine flow at all anatomic levels is a key factor in increasing host susceptibility to UTI. Obstruction inhibits the normal flow of urine, and the resulting stasis compromises bladder and renal defense mechanisms. Stasis also contributes to the growth of bacteria in the urine and their ability to adhere to the urothelial cells. In the animal model of experimental hematogenous pyelonephritis, the kidney is relatively resistant to infection unless a ureter is ligated. Under these circumstances, only the obstructed kidney becomes infected (Beeson and Guze, 1956). Clinical observations support the role of obstruction in pathogenesis of UTI and in increasing severity of infection. Mild episodes of cystitis or pyelonephritis can become life threatening when obstruction to urine flow becomes present. Although obstruction clearly increases the severity of infection, it need not be a predisposing factor. For example, men with large residual urine may remain uninfected for years. However, if they are catheterized, even small inocula may lead to severe infections that are difficult to eradicate.

Vesicoureteral Reflux

Hodson and Edwards (1960) first described the association of vesicoureteral reflux, UTI, and renal clubbing and scarring. Children with gross reflux and UTIs usually develop progressive renal damage manifested by renal scarring, proteinuria, and renal failure. Those with a lesser degree of reflux usually improve or completely recover spontaneously or after treatment of the UTI. In adults, the presence of reflux does not appear to decrease renal function unless there are stasis and concurrent UTIs.

The urinary tract is part of the secretory immune system. In pyelonephritis, IgG and SIgA appear in the urine and may become evident before antibodies are detected in the serum. These antibodies are synthesized locally within the kidney and may enhance bacterial opsonization and ingestion by local phagocytic cells. These antibodies may have further protective function. [Svanborg-Eden and Svennerholm \(1978\)](#) showed that IgG and SIgA derived from the urine of patients with acute pyelonephritis reduced in vitro adherence of the same strain of *E. coli* to uroepithelial cells. Similarly, immunization with *E. coli* P pili resulted in immunoglobulin production in experimental animals that prevented ascending pyelonephritis by reducing the adhesive capacity of the invading

autologous uropathogenic *E. coli* ([Roberts and Phillips, 1979](#); [O'Hanley et al, 1983](#)).

The possibility that immunologic factors may be modified to reduce susceptibility to infection has been explored primarily through immunization in animal and human systems. For example, in a monkey model, vaccination with P fimbria has been shown to reduce adherence of P-fimbriated *E. coli* to uroepithelial cells and prevent acute pyelonephritis ([Roberts and Phillips, 1979](#)). Similarly, vaccination of mice with FimH adhesin prevents cystitis in mice ([Langermann et al, 1997](#)). Vaccination of women may reduce colonization of the vaginal introitus and subsequent ascending bacteria ([Uehling et al, 1994](#)).

Underlying Disease

There is a high incidence of renal scarring in patients with underlying conditions that cause chronic interstitial nephritis, virtually all of which produce primary renal papillary damage. These conditions include diabetes mellitus, sickle cell disorders, adult nephrocalcinosis, hyperphosphatemia, hypokalemia, analgesic abuse, sulfonamide nephropathy, gout, heavy-metal poisoning, and aging (Freedman, 1979).

Diabetes Mellitus

An increased incidence of clinical asymptomatic and symptomatic UTIs appears to occur in women with diabetes mellitus, but there is no substantial increase among diabetic men (Vejlsgaard, 1973; Ooi et al, 1974; Forland et al, 1977; Meiland et al, 2002). Diabetes also results in three times more hospitalizations for acute pyelonephritis among women (10.86/10,000) than for men (3.32/10,000) (Nicolle et al, 1996). Autopsy studies have shown the incidence of pyelonephritis to be fourfold to fivefold higher in diabetic than in nondiabetic individuals (Robbins and Tucker, 1944). However, such studies may be misleading because it is difficult to distinguish renal parenchymal changes resulting from pyelonephritis from the interstitial inflammatory changes of diabetic nephropathy.

Although most UTIs in diabetic patients are asymptomatic, diabetes appears to predispose the patient to more severe infections. There is no evidence that increased frequency of infection is due to glycosuria (Geerlings et al, 2000). One study using antibody-coated bacteria techniques to localize the site of infection showed the upper urinary tract to be involved in nearly 80% of diabetic patients with UTIs (Forland et al, 1977). This evidence of increasing immunologic response in diabetic patients who acquire bacteriuria suggests renal parenchymal involvement and a potential increase in morbidity.

Infections are frequently caused by atypical organisms such as yeast and result in upper tract infections and significant sequelae such as emphysematous pyelonephritis, papillary necrosis, perinephric abscess, or metastatic infection (Wheat, 1980; Stapleton, 2002).

Renal Papillary Necrosis

The role of infection in the development and progression of renal papillary necrosis (RPN) is controversial. Multiple predisposing conditions have been associated with the development of RPN, particularly diabetes, analgesic abuse, sickle cell hemoglobinopathy, and obstruction (Box 12-2).

BOX 12-2 Conditions Associated with Renal Papillary Necrosis

Diabetes mellitus
 Pyelonephritis
 Urinary tract obstruction
 Analgesic abuse
 Sickle cell hemoglobinopathies
 Renal transplant rejection
 Cirrhosis of the liver
 Dehydration, hypoxia, and jaundice of infants
 Miscellaneous: renal vein thrombosis, cryoglobulinemia, renal candidiasis, contrast media injection, amyloidosis, calyceal arteritis, necrotizing angitis, rapidly progressive glomerulonephritis, hypotensive shock, acute pancreatitis

From Eknayan G, Qunibi WY, Grissom RT, et al. Renal papillary necrosis: an update. *Medicine* 1982;61:55.

Clinically, RPN is a spectrum of disease. Patients may have an acute fulminating illness with rapid progression or may have a chronic disease that is incidentally discovered. Some patients may chronically pass necrotic tissue in their urine (Hernandez et al, 1975), and some may never pass papillae (Lindvall, 1978). Retained necrotic papillae may calcify, especially in association with infection. Furthermore, this necrotic tissue may form the nidus for chronic infection. Opportunistic fungal infections have been reported (Madge and Lombardias, 1973; Juhasz et al, 1980; Vordermark et al, 1980; Tomashefski and Abramowsky, 1981). Renal sonography may be useful to diagnose RPN (Buonocore et al, 1980; Hoffman et al, 1982).

The early diagnosis of RPN is important to improve prognosis and reduce morbidity. In addition to chronic infection, patients with analgesic abuse-associated papillary necrosis may have an increased incidence of urothelial tumors; routine urinary cytologic examinations may be helpful to diagnose these tumors early (Jackson et al, 1978). In patients who have analgesic abuse-induced RPN, the disease stabilizes if the analgesic intake is stopped (Gower, 1976). Furthermore, adequate antimicrobial therapy to control infection and early recognition and treatment of ureteral obstruction caused by sloughed necrotic tissue can minimize a decline in renal function. A patient who suffers from an acute ureteral obstruction caused by a sloughed papilla and who has a concomitant UTI has a urologic emergency. In this case, immediate removal of the obstructing papilla by stone basket (Jameson and Heal, 1973) or acute drainage of the kidney by ureteral catheter or percutaneous nephrostomy is necessary.

Other conditions that may increase the susceptibility of the kidney to infection include hypertension and vascular obstruction (Freedman, 1979). The association of renal infection with several other renal diseases, including glomerulonephritis, atherosclerosis, and tubular necrosis, which are not associated with papillary necrosis, does not lead to pyelonephritis and scarring.

Human Immunodeficiency Virus

UTIs are fivefold more prevalent in HIV-positive individuals than in control subjects (Schonwald et al, 1999). Furthermore, the pathologic flora is typically more reminiscent of complicated UTIs. It also appears that HIV-positive patients with UTIs have a tendency for recurrence and require longer treatment.

Pregnancy

The prevalence of bacteriuria in pregnant women varies from 4% to 7%, and the incidence of acute clinical pyelonephritis ranges from 25% to 35% in untreated bacteriuric women (Stamey, 1980). This is probably the result of dilation of the ureters and pelvis of the kidney secondary to pregnancy-related hormonal alterations. In addition, urine obtained from pregnant women exhibits a more suitable pH for growth of *E. coli* in all stages of gestation (Asscher et al, 1973). It is not surprising that untreated bacteriuria in the first trimester is accompanied by a substantial increase in the incidence of acute pyelonephritis because half of these women have upper tract bacteriuria (Fairley et al, 1966).

For further details, see the Expert Consult website.

Spinal Cord Injury with High-Pressure Bladders

Of all patients with bacteriuria, no group compares in severity and morbidity with those who have spinal cord injury. Nearly all these patients require catheterization early after their injuries because of bladder overactivity or flaccidity, and significant numbers develop ureterectasis, hydronephrosis, reflux, and renal calculi. Bacteriologic and urodynamic advances in the management of these patients have vastly reduced their morbidity and mortality. Special problems associated with spinal cord injury are presented in a later section.

Untreated bacteriuria involving these dilated upper tracts could be expected to cause a significant number of abnormalities that should be radiologically apparent. [Kincaid-Smith and Bullen \(1965\)](#) performed a culture on 4000 women at their first antenatal visit. Of 240 bacteriuric women, 148 returned for excretory urography 6 weeks after delivery. Approximately 40% of these patients had radiologic abnormalities consistent with pyelonephritis or analgesic nephritis. [Brumfitt and colleagues \(1967\)](#) showed that the incidence of radiologic abnormalities in bacteriuria of pregnancy was

proportional to the difficulty in clearing the infection. Patients who responded promptly to a single course of therapy had a 23% incidence of radiologic abnormalities, but those who remained bacteriuric despite repeated therapeutic efforts had a 65% incidence of radiologic changes. Thus prolonged bacteriuria and pyelonephritis of pregnancy appear to be **associated** with significant radiologic abnormalities. However, there is little evidence to suggest that bacteriuria of pregnancy or acute pyelonephritis of pregnancy **causes** these renal radiologic abnormalities.

KEY POINTS: PATHOGENESIS

- Most UTIs are caused by bacteria, usually originating from the bowel flora.
- Bacterial virulence factors, including adhesin, play a role in determining which bacteria invade and the extent of infection.
- Increased epithelial cell receptivity predisposes patients to recurrent UTIs and is a genotypic trait.
- Obstruction to urine flow is a key factor in increasing host susceptibility to UTIs.

CLINICAL MANIFESTATIONS**Symptoms and Signs**

Cystitis is usually associated with dysuria, frequency, and/or urgency. Suprapubic pain and hematuria are less common. Lower tract symptoms are commonly present and usually predate the appearance of upper tract symptoms by several days. Pyelonephritis is classically associated with fever, chills, and flank pain. Nausea and vomiting may be present. Renal or perirenal abscess may cause indolent fever and flank mass and tenderness. In the elderly, the symptoms may be much more subtle (e.g., epigastric or abdominal discomfort) or the patient may be asymptomatic (Romano and Kaye, 1981). Patients with indwelling catheters often have asymptomatic bacteriuria, but fever associated with bacteremia may occur rapidly and become life threatening.

Diagnosis

Presumptive diagnosis of UTI is made by direct or indirect analysis of the urine and is confirmed by urine culture. The urine and the urinary tract are normally free of bacteria and inflammation. False-negative urinalysis and culture can occur in the presence of UTI, particularly early in an infection when the numbers of bacteria and WBCs are low or diluted by increased fluid intake and subsequent diuresis. Occasionally, the urine may be free of bacteria and WBCs despite bacterial colonization and inflammation of the uroepithelium (Elliott et al, 1985; Hultgren et al, 1985). False-positive urinalysis and culture are caused by contamination of the urine specimen with bacteria and WBCs during collection. This is most likely to occur in voided specimens but can also occur during urethral catheterization. Suprapubic aspiration of bladder urine is least likely to cause contamination of the specimen; therefore it provides the most accurate assessment of the status of bladder urine.

Urine Collection

Voided and Catheterized Specimens. Diagnostic accuracy can be improved by reducing bacterial contamination when the urine is collected. In circumcised men, voided specimens require no preparation. For men who are not circumcised, the foreskin should be retracted and the glans penis washed with soap and then rinsed with water before specimen collection. The first 10 mL of urine (representative of the urethra) and a midstream specimen (representative of the bladder) should be obtained. Prostatic fluid is obtained by performing digital prostatic massage and collecting the expressed prostatic fluid on a glass slide. In addition, collection of the first 10 mL of voided urine after massage will reflect the prostatic fluid added to the urethral specimen. Catheterization of a male patient for urine culture is not indicated unless the patient cannot urinate.

In women, contamination of a midstream urine specimen with introital bacteria and WBCs is common, particularly when the woman has difficulty spreading and maintaining separation of the labia. Therefore the female should be instructed to spread the labia, wash and cleanse the periurethral area with moist gauze, and then collect a midstream urine specimen. Cleansing with antiseptics is

not recommended because they may contaminate the voided specimen and provide a false-negative urine culture. The voided specimen is contaminated if it shows evidence of vaginal epithelial cells and lactobacilli on urinalysis, and a midcatheterized specimen should be collected.

Catheterization and collection of a midcatheterized specimen is more accurate than a voided specimen, but carries a risk of iatrogenic infection. Although a single dose of an oral antimicrobial agent such as trimethoprim-sulfamethoxazole (TMP-SMX) may be effective for prophylaxis because antimicrobial usage encourages development of bacterial resistance, prophylaxis should be limited to high-risk patients.

Suprapubic Aspiration. Suprapubic aspiration is highly accurate, but because it carries some morbidity there is limited clinical usefulness except for a patient who cannot urinate on command, such as patients with spinal cord injuries. It is highly useful in newborns (Newman et al, 1967) and in patients with paraplegia. A single aspirated specimen reveals the bacteriologic status of the bladder urine without introducing urethral bacteria, which can start a new infection.

Before a suprapubic aspiration is performed, the patient should force fluids until the bladder is full. The site of the needle puncture is in the midline, between the symphysis pubis and the umbilicus and directly over the palpable bladder. The full bladder in the male is usually palpable because of its greater muscle tone; unfortunately, the full bladder in the female is frequently not palpable. In such patients, the physician performing the aspiration must rely on the observation that suprapubic pressure directly over the bladder produces an unmistakable desire to urinate. After determining the approximate site for needle puncture, the local area is shaved and the skin is cleansed with an alcohol sponge; a cutaneous wheal is raised with a 25-gauge needle and any local anesthetic. A 3.5-inch spinal, 22-gauge needle is introduced through the anesthetized skin. The progress of the needle is arrested just below the skin within the anesthetized area, and with a quick plunging action, similar to that of any intramuscular injection, the needle is advanced into the bladder. Most patients experience more discomfort from the initial anesthetization of the skin than during the second stage when the needle is advanced into the bladder. After the needle has been introduced, a 20-mL syringe is used to aspirate 5 mL of urine for culture and 15 mL of urine for centrifugation and urinalysis. The obturator is reintroduced into the needle, and both needle and obturator are withdrawn. A small dressing is placed over the needle site in the skin. If urine is not obtained with complete introduction of the needle, the patient's bladder is not full and is usually deep within the retropubic area. When no urine is obtained on the first attempt, it is probably wise to wait until the bladder is full.

Urinalysis

For patients with urinary symptoms, microscopic urinalysis for bacteriuria, pyuria, and hematuria should be performed. Urinalysis provides rapid identification of bacteria and WBCs and presumptive diagnosis of UTI. Usually, the sediment from an approximately 5- to 10-mL specimen obtained by centrifugation for 5 minutes at 2000 rpm is analyzed. Microscopic bacteriuria is found in more than 90% of infections with counts of 10^5 colony-forming units (cfu) per milliliter of urine or greater and is a highly specific finding (Stamm, 1982; Jenkins et al, 1986). However, bacteria are usually not detectable microscopically with lower colony count infections (10^2 to 10^4 /mL). This important error (i.e., a false-negative result) occurs because of the limitation imposed by the microscope on the volume of urine that can be observed. If the volume of urine that can easily rest beneath a standard 22-mm cover glass is carefully measured (0.01 mL) and the number of high dry fields ($\times 570$ magnification) present beneath the cover glass is estimated, it is disturbing to find that one high dry field represents a volume of approximately 1/30,000 mL. There are excellent studies showing that the bacterial count must be approximately 30,000/mL before bacteria can be found in the sediment, stained or unstained, spun or unspun (Sanford et al, 1956; Kunin, 1961). For these

reasons, a negative urinalysis for bacteria never excludes the presence of bacteria in numbers of 30,000/mL and less.

The second error of urinalysis (i.e., a false-positive result) is the reverse of the first error: bacteria are seen in the microscopic sediment, but the urine culture shows no growth. The voided urine from a female patient can contain many thousands of lactobacilli and corynebacteria. These bacteria are readily seen under the microscope; and although they are gram-positive, they often appear gram-negative (gram-variable) if stained. Strict anaerobes, usually gram-negative bacilli, also make up a significant mass of the normal vaginal flora (Marrie et al, 1978).

In practice, these problems can be minimized by using other information provided by urinalysis that can help the clinician to decide whether a patient has a UTI such as pyuria (Stamm et al, 1982b). The validation of the midstream urine specimen can be questioned if numerous squamous epithelial cells (indicative of preputial, vaginal, or urethral contaminants) are present.

Pyuria and hematuria are good indicators of an inflammatory response. Although the number of WBCs per high-power field in a centrifuged urine sample is useful, it is important to remember that other factors can influence the number of cells seen. These include the state of hydration; the intensity of tissue reaction; the method of urine collection; the volume, speed, and time of centrifugation; and the volume in which the sediment is resuspended.

The presence of bacteriuria has a sensitivity for UTI of 40% to 70%, and a specificity of 85% to 95%, depending on the number of bacteria observed (Fihn, 2003).

Significant pyuria can be determined simply and reliably with a microscope by accurately examining the centrifuged sediment or by using a hemocytometer to count the number of WBCs in the unspun urine. One to 2 WBCs per high-power field (HPF) in sediment from a centrifuged specimen represents about 10 WBCs/mm³ in an unspun specimen. More than 2 WBCs per HPF in a centrifuged specimen or 10 WBCs/mm³ of urine correlates well with the presence of bacteriuria and is rarely seen in nonbacteriuric patients (Stamm et al, 1981). In clinical studies, determination of pyuria in voided urine specimens has a reported sensitivity of 80% to 95% and a specificity of 50% to 76% for UTI (depending on the definition of infection, the patient population, and the method used to evaluate for pyuria) (Stamm, 1982; Schultz et al, 1984; Wong et al, 1984; Wigton et al, 1985).

The absence of pyuria should cause the diagnosis of UTI to be questioned until urine culture data are available. Conversely, many diseases of the urinary tract produce significant pyuria in the absence of bacteriuria. Whereas tuberculosis is the well-recognized example of abacterial pyuria, staghorn calculi and stones of smaller size can produce intense pyuria with clumps of WBCs in the absence of UTI. Almost any injury to the urinary tract, from chlamydial urethritis to glomerulonephritis and interstitial cystitis, can elicit large numbers of fresh polymorphonuclear leukocytes (glitter cells). Depending on the stage of hydration, the intensity of the tissue reaction producing the cells, and the method of urine collection, any number of WBCs can be seen in the microscopic sediment in the presence of an uninfected urinary tract.

Microscopic hematuria is found in 40% to 60% of cases of cystitis and is uncommon in other dysuric syndromes (Stamm et al, 1980b; Wigton et al, 1985).

Rapid Screen Methods. Biochemical and enzymatic tests have been devised to detect bacteriuria and pyuria (Pezzlo, 1988). The Griess test detects the presence of nitrite in urine that is formed when bacteria reduce the nitrate normally present in urine. Tests for detecting pyuria by determining leukocyte esterase activity have also been developed (Chernow et al, 1984). In a study comparing traditional urine culture with these indirect tests, the combination of nitrite and leukocyte esterase tests (either test positive) had a sensitivity of 71% and a specificity of 83% when compared with 10³ cfu/mL or greater of urine cultures (Pfaller and Koontz, 1985). However, several investigators (Pels et al, 1989; Hurlbut and Litenberg, 1991) noted substantial variability in the sensitivity and specificity results, which could be markedly influenced by the types of patients and infections chosen to evaluate the tests. This concept

of spectrum bias was illustrated by a study that reported differences in the sensitivity of reagent strip testing, ranging from 56% to 92%, by changing only the groups of patients included in the analysis. Although false-positive results are relatively uncommon, the borderline sensitivity of these tests, especially among patients with less characteristic symptoms of UTIs, does not allow these inexpensive tests to replace careful microscopic urinalysis in symptomatic patients (Semeniuk and Church, 1999). Their main role is in screening asymptomatic patients (Pezzlo, 1988).

Urine Culture

Two techniques for urine culture are available. Direct surface plating of a known amount of urine on split-agar disposable plates is the traditional quantitative culture technique used by most microbiology laboratories. One half of the plate is blood agar, which grows both gram-positive and gram-negative bacteria, and the other is desoxycholate or eosin-methylene blue (EMB), which grows gram-negative bacteria (some of them, such as *E. coli*, in a very characteristic manner). Simple curved-tip eye droppers are sufficient to deliver about 0.1 mL of urine onto each half of the plate. After overnight incubation, the number of colonies is estimated, often identified (after some experience), and multiplied by 10 to report the number of cfu per milliliter of urine. The technique has been presented elsewhere in detail (Stamey, 1980).

A simpler but somewhat less accurate technique is the use of dip slides (Fig. 12-10). These inexpensive plastic slides are attached to screw-top caps; they have soy agar (a general nutrient agar to grow all bacteria) on one side and EMB or MacConkey agar for gram-negative bacteria on the opposite side. A slide is dipped into urine, the excess is allowed to drain off, and the slide is replaced in its plastic bottle and incubated. The volume of urine that attaches to the slide is between 1/100 mL and 1/200 mL. Hence, the colony count is 100 to 200 times the number of colonies that become visible with incubation. In actual practice, the growth is compared with a visual standard and reported as such. The species of bacteria is more difficult to recognize when this technique is used, but the technique is completely adequate.

The urine must be refrigerated immediately on collection and should be cultured within 24 hours of refrigeration. One advantage to the dip slide is the ease with which the urine can be immediately cultured without the necessity of refrigeration. Patients can culture their own urine at home, keep the slide at room temperature, and bring it to the office within 48 hours.

Although most bacteria allowed to incubate for several hours in bladder urine reach cfu counts of 10⁵/mL, this statistical

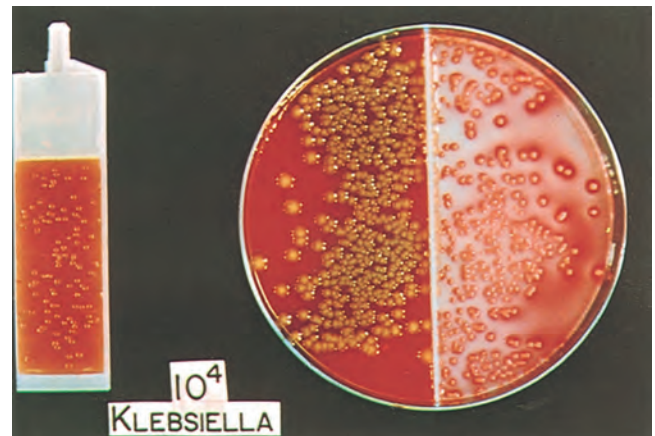


Figure 12-10. The dip slide on the left is compared with a split-agar surface plate on the right. The urine contained 10,000 colonies of *Klebsiella* per milliliter (about 200 times the number of colonies on the dip slide and 10 times the number on either side of the split-agar plate).

number is fraught with two limitations. The first is that 20% to 40% of women with symptomatic UTIs present with bacteria counts of 10^2 to 10^4 cfu/mL of urine (Stamey et al, 1965; Mabeck, 1969; Kunz et al, 1975; Kraft and Stamey, 1977), probably because of the slow doubling time of bacteria in urine (every 30 to 45 minutes) combined with frequent bladder emptying (every 15 to 30 minutes) from irritation. Thus, in dysuric patients, an appropriate threshold value for defining significant bacteriuria is 10^2 cfu/mL of a known pathogen (Stamm and Hooton, 1993). Fortunately, most of these patients have symptoms of UTI and pyuria on urinalysis.

The second limitation of the 10^5 cutoff is overdiagnosis. Women susceptible to infection often carry large numbers of pathogenic bacteria on the perineum that contaminate otherwise sterile bladder urine. Uncircumcised men may harbor uropathogenic bacteria on their foreskins. In the original studies by Kass (1960), a single culture of 10^5 cfu/mL or more had a 20% chance of representing contamination. There is no statistical way to avoid these two major limitations on the interpretation of the midstream voided culture in women and in uncircumcised men without careful preparation.

Localization

Kidney

Fever and Flank Pain. Fever and flank pain are thought to indicate pyelonephritis, but few studies have tested the hypothesis. Aggressive localization studies in children and adults (Huland and Busch, 1982; Busch and Huland, 1984), as well as in patients with end-stage renal disease (Huland et al, 1983), have shown substantial incidences of fever and even flank pain in bacteriuric patients in whom infection was localized to the bladder (see the later section on Acute Pyelonephritis).

Ureteral Catheterization. Ureteral catheterization allows not only separation of bacterial persistence into upper and lower urinary tracts but also separation of the infection between one kidney and the other, and even localization of infection to ectopic ureters or to nonrefluxing ureteral stumps (by using saline solution irrigation) (Stamey, 1980).

Stamey began in 1959 to localize the site of bacteriuria by ureteral catheterization studies; the technique was published in 1963 (Stamey and Pfau, 1963) and the results in 1965 (Stamey et al, 1965). The technique is simple but exacting; the urologist should consult a more detailed description (Stamey, 1980) before actually performing this localization technique. The validity depends on controlling the number of bacteria from the bladder that contaminate the ureteral catheters as they pass through the bladder into the ureteral orifices. The bladder must be thoroughly irrigated before both ureteral catheters are passed into a small volume of residual irrigating fluid. A sample is obtained through both ureteral catheters simultaneously, and then each catheter is passed into the ureter or renal pelvis. Four serial cultures are obtained from each kidney. It is mandatory that the patient be started on the appropriate antimicrobial agent before leaving the cystoscopy room. In addition to quantitative bacterial counts on each specimen, determination of either specific gravity or urine creatinine levels on the renal samples can be very helpful in interpreting a change in diuresis in relation to bacterial counts. Examples of infections localized to the bladder, to one kidney, and to both kidneys have been published (Stamey, 1980). Clinical examples of results from each site are shown in Table 12-1 on the Expert Consult website.

When this technique was applied to large numbers of bacteriuric patients, 45% were found to have bladder infection only; 27%, unilateral renal bacteriuria; and 28%, bilateral renal bacteriuria (Table 12-2 on the Expert Consult website) (Stamey et al, 1965). These figures have been confirmed by at least five investigators in three countries (the United States, England, and Australia) and can be taken as a good approximation for any general bacteriuric adult population. Although renal stones and other kidney abnormalities in the presence of bacteriuria can increase the proportion of

renal infections, the urologist should never assume the kidney is involved if an important decision is to be made.

Tissue and Stone Cultures. It is clinically useful to culture stones removed from the urinary tract to document that bacteria reside within their interstices. Tissue cultures are primarily useful for research information.

Using sterile technique at the operating table, the surgeon places the stone or fragment of tissue into a sterile culture tube containing 5 mL of saline solution; the culture is packed in ice and sent to the bacteriologic laboratory, where, after agitation of the stone or tissue in the 5 mL of saline solution, 0.1 mL is surface-streaked on both blood agar and EMB agar. The saline solution is then poured off the specimen, and, with sterile forceps, the stone or tissue is transferred to a second 5 mL of sterile saline solution. After agitation to ensure a reasonable washing action, the saline solution is again decanted and the specimen is transferred to a third 5 mL of saline solution and finally to a fourth 5 mL of saline solution. This last saline solution wash is cultured quantitatively in the same manner as the first. The remainder of this fourth 5 mL of saline solution is poured with the stone into a sterile mortar and pestle dish.

After the stone is crushed (or the tissue is ground in a tissue blender) in the fourth saline solution wash, 0.1 mL is again cultured on both blood agar and EMB agar. The difference in colony counts between the first and the fourth saline solution washes represents the washing effect of the saline solution transfers on the surface bacteria of the stone or tissue. The difference between the fourth saline wash before and after crushing (or grinding, for tissue) represents the difference between surface bacteria and bacteria within the specimen.

Prostate and Urethral Localization Studies. The technique for localizing infections to the urethra or prostate is covered in detail in Chapter 13.

KEY POINTS: CLINICAL MANIFESTATIONS

- The urine and the urinary tract are normally sterile.
- Bacteriuria and WBCs provide a presumptive diagnosis of UTI.
- In diagnosing patients, 10^2 cfu/mL confirms a symptomatic UTI.

IMAGING TECHNIQUES

Imaging studies are not required in most cases of UTI because clinical and laboratory findings alone are sufficient for correct diagnosis and adequate management of most patients. However, infection in most men or a compromised host, febrile infections, signs or symptoms of urinary tract obstruction, failure to respond to appropriate therapy, and a pattern of recurrent infections suggesting bacterial persistence within the urinary tract warrant imaging for identification of underlying abnormalities that require modification of medical management or percutaneous or surgical intervention.

Indications

Radiologic studies are unnecessary for evaluation of most women with genitourinary infections. Several reports of women patients with recurrent UTIs show that excretory urograms are unnecessary for routine evaluation if women who have special risk factors are excluded (Fair et al, 1979; Engel et al, 1980; Fowler and Pulaski, 1981; Fairchild et al, 1982). In none of these studies did excretory urograms yield information that was useful in the management of these patients. Furthermore, excluding excretory urograms in the routine evaluation of such patients represents a substantial financial saving.

However, in high-risk patients, including women with febrile infections and most men, radiologic studies may determine acute

TABLE 12-1 Clinical Examples of Ureteral Catheterization Studies in Localizing the Site of Bacteriuria

SOURCE OF RENAL INFECTION	BLADDER INFECTION (BACTERIA/mL)	LEFT RENAL INFECTION (BACTERIA/mL)	RIGHT RENAL INFECTION (BACTERIA/mL)	BILATERAL (BACTERIA/mL)
CB	>10 ⁵	5000	>10 ⁵	4000
WB	900	300	1000	20
LK ₁	20	2000	20	400
LK ₂	0	2200	0	350
LK ₃	0	2500	0	500
LK ₄	0	2200	0	400
RK ₁	10	0	10,000	260
RK ₂	0	0	10,000	220
RK ₃	0	0	8000	300
RK ₄	0	0	12,000	250

CB, catheterized patient, cystoscopic specimen; LK₁, LK₂, etc., serial cultures of urine from the left kidney; RK₁, RK₂, etc., serial cultures of urine from the right kidney; WB, controlled, "wash bladder" specimen collected after copious irrigation of the bladder.
 From Stamey T. Pathogenesis and treatment of urinary tract infections. Baltimore: Williams & Wilkins; 1980.

TABLE 12-2 Localization of Urinary Tract Infections in 95 Females and 26 Males with Bacteriuria

NO. PATIENTS	BLADDER ONLY	UNILATERAL RENAL BACTERIURIA	BILATERAL RENAL BACTERIURIA
95 females	38 (40%)	27 (28%)	30 (32%)
26 males	16 (62%)	6 (26%)	4 (15%)
121 combined	54 (45%)	33 (27%)	34 (28%)

From Stamey TA, Govan DE, Palmer JM. The localization and treatment of urinary tract infections: the role of bactericidal urine levels as opposed to serum levels. *Medicine* 1965;44:1.

BOX 12-3 Indications for Radiologic Investigation in Acute Clinical Pyelonephritis

Potential ureteral obstruction (e.g., caused by stone, ureteral stricture, tumor)
 History of calculi, especially infection (struvite) stones
 Potential papillary necrosis (e.g., patients with sickle cell anemia, severe diabetes mellitus, analgesic abuse)
 History of genitourinary surgery that predisposes to obstruction, such as ureteral reimplantation or ureteral diversion
 Poor response to appropriate antimicrobial agents after 5 to 6 days of treatment
 Diabetes mellitus
 Polycystic kidneys in patients in dialysis or with severe renal insufficiency
 Neuropathic bladder
 Unusual infecting organisms, such as tuberculosis, fungus, or urea-splitting organisms (e.g., *Proteus*)

infectious processes that require further intervention or may find the cause of complicated infections.

First, radiologic procedures are needed in patients with risk factors that may require intervention in addition to antimicrobial treatment (Box 12-3).

A UTI associated with possible urinary tract obstruction must be evaluated. These are patients with calculi, especially infection (struvite) stones; ureteral tumors; ureteral strictures; congenital obstructions; or previous genitourinary surgery, such as ureteral reimplantation or urinary diversion procedures that may have caused obstruction. Patients with diabetes mellitus can develop special complications from UTIs; they may acquire emphysematous pyelonephritis or papillary necrosis. Impacted necrotic papillae may cause acute ureteral obstruction. Patients with polycystic kidney disease who are on dialysis are particularly prone to developing perinephric abscesses.

Urologic imaging is indicated in patients whose symptoms of acute clinical pyelonephritis persist after 5 to 6 days of appropriate antimicrobial therapy; they often have perinephric or renal abscesses. In addition, patients with unusual organisms, including urea-splitting organisms (e.g., *Proteus* species), should be examined for abnormalities within the urinary tract, such as obstructing stones, strictures, or fungus balls.

The second reason for radiologic evaluation is to diagnose a focus of bacterial persistence. In patients whose bacteriuria fails to resolve after appropriate antimicrobial therapy or who have rapid recurrence of infection, abnormalities that cause bacterial persistence should be sought. Although these patients are uncommon, it is important to identify them because they may have correctable urologic abnormalities that represent the only surgically curable causes of recurrent UTIs. Acquired or congenital urologic abnormalities that can cause unresolved or recurrent UTIs are listed in Box 12-4.

Ultrasonography

The renal ultrasound study is an important renal imaging technique because it is noninvasive, easy to perform, and rapid and offers no radiation or contrast agent risk to the patient. It is particularly useful in identifying calculi and hydronephrosis, pyonephrosis, and perirenal abscesses. A single radiograph for calculi should accompany ultrasonography. Ultrasonography is also useful for diagnosing postvoid residual urine. A disadvantage is that the study is dependent on the interpretative and performance skills of the examiner. Furthermore, the study may be technically poor in patients who are obese or who have dressings, drainage tubes, or open wounds overlying the area of interest.

BOX 12-4 Correctable Urologic Abnormalities That Cause Bacterial Persistence

Infection stones
 Chronic bacterial prostatitis
 Unilateral infected atrophic kidneys
 Ureteral duplication and ectopic ureters
 Foreign bodies
 Urethral diverticula and infected periurethral glands
 Unilateral medullary sponge kidneys
 Nonrefluxing, normal-appearing, infected ureteral stumps after nephrectomy
 Infected urachal cysts
 Infected communicating cysts of the renal calyces
 Papillary necrosis
 Perivesical abscess with fistula to bladder

Computed Tomography and Magnetic Resonance Imaging

The radiologic modalities that offer the best anatomic detail are CT and MRI. They are more sensitive than excretory urography or ultrasonography in the diagnosis of acute focal bacterial nephritis, renal and perirenal abscesses, and radiolucent calculi (Kuhn and Berger, 1981; Mauro et al, 1982; Wadsworth et al, 1982; Soulen et al, 1989; Soler et al, 1997). When used to localize renal and perirenal abscesses, CT improves the approach to surgical drainage and permits percutaneous approaches. MRI has not superseded CT in the evaluation of renal inflammation, but it has provided some advantages in delineating extrarenal extension of inflammation.

Voiding Cystourethrogram

The voiding cystourethrogram is an important examination in assessing vesicoureteral reflux. It may be used to evaluate patients with neuropathic bladders and the rare female patient who has a urethral diverticulum causing her persistent infections.

Radionuclide Studies

Hippuran I-131 and technetium-99m (^{99m}Tc) glucoheptonate scans are used to detect focal parenchymal damage, renal function impairment, and decreased renal perfusion in acute renal infections (McAfee, 1979). Although gallium-67 scanning has been reported to be useful in the diagnosis of pyelonephritis and renal abscess, it is uncommonly required and may be positive in noninfectious entities. Indium-111-labeled WBC studies have limited efficacy in establishing the presence of an inflammatory focus, particularly when the patient's clinical presentation does not suggest an infectious process.

KEY POINTS: IMAGING TECHNIQUES

- Imaging studies are not required in most women with UTIs.
- Men and compromised patients or those who do not respond to therapy require imaging to identify abnormalities.
- CT and MRI provide the best anatomic data on the site, cause, and extent of infection.

PRINCIPLES OF ANTIMICROBIAL THERAPY

Therapy for UTIs must ultimately eliminate bacterial growth in the urinary tract. This can occur within hours if the proper antimicrobial agent is used (Stamey, 1980). Efficacy of the antimicrobial therapy is critically dependent on the antimicrobial levels in the

TABLE 12-3 Serum and Urinary Antimicrobial Levels in Adults*

ANTIMICROBIAL AGENT	DOSE (mg)	PEAK SERUM LEVEL (mg/L)	PERCENTAGE BOUND TO PROTEIN	HALF-LIFE SERUM PEAK (hr)	MEAN (ACTIVE) URINE LEVELS* (g/mL)	DOSE EXCRETED IN URINE (%)	DOSE ACTIVE IN URINE (IF DIFFERENT) (%)
Ampicillin	250 PO qid	3 at 2 hr	15	1	350	42	—
Carbenicillin	764 PO qid	11-17 at 1.5 hr	60	1.2	1000	40	—
Cephalexin	250 PO qid	9 at 2 hr	12	0.9	800	98	—
Ciprofloxacin	500 PO bid	2.3 at 1.2 hr	35	3.9	200	50	—
Colistin	75 IM bid	1.8 at 4 hr	10	2	34	75	50
Gentamicin	1 mg/kg IM tid (200 mg/day)	4 at 1 hr	Negligible	2	125	80	—
Kanamycin	500 IM bid	18 at 1 hr	Negligible	2	750	94	—
Levofloxacin	500 mg PO qd	6.0 mg/L	30-50	6	N/A	95	95
Nalidixic acid	1000 PO qid	34 at 2-23 hr	85	1.5	75	79	5
Nitrofurantoin	100 PO qid	<2		0.3	150	42	—
Penicillin G	500 PO qid	1 at 1 hr	60	0.5	300	60-85	—
Sulfamethizole	250 PO qid		98	10	700	95	85
Tetracycline hydrochloride	250 PO qid	2-3 at 4 hr	31	6	500	60	—
Trimethoprim-sulfamethoxazole	160/800 PO bid	1.7/32 at 2 hr	45/66	10/9	150/400	55/50	—/37
Trimethoprim	100 PO bid	1.0 at 2-4 hr	45	10	92	55	—

*These average urinary concentrations are based on the amount of biologically active drug excreted by normal kidneys at a urine flow rate of 1200 mL/24 hr.

Modified from Stamey TA. The pathogenesis and treatment of urinary infections. Baltimore: Williams & Wilkins; 1980. p. 59.

urine and the duration that this level remains above the minimal inhibitory concentration of the infecting organism (Hooton and Stamm, 1991). Hence, resolution of infection is closely associated with the susceptibility of the bacteria to the concentration of the antimicrobial agent achieved in the urine (McCabe and Jackson, 1965; Stamey et al, 1965, 1974). The concentration of useful antimicrobial agents in the serum and urine of healthy adults is shown in Table 12-3, which demonstrates that the urinary levels are often several hundred times greater than the serum levels. Inhibitory concentrations in urine are achieved after oral administration of all commonly used antimicrobial agents, except for the macrolides (erythromycin). The question of serum levels versus urinary levels is a practical one because the policy of testing antimicrobial susceptibility agents at concentrations obtainable only in the serum discourages the physician from using drugs that are effective at the urinary level; for example, oral penicillin G for *E. coli* and *Proteus mirabilis* and tetracycline for *P. aeruginosa*.

The concentration of the antimicrobial agent achieved in blood is not important in treatment of uncomplicated UTIs. However, blood levels are critical in patients with bacteremia and febrile urinary infections consistent with parenchymal involvement of the kidney and prostate.

In patients with renal insufficiency, dosage modifications are necessary for agents that are cleared primarily by the kidneys and cannot be cleared by another mechanism. In renal failure, the kidneys may not be able to concentrate an antimicrobial agent in the urine; hence, difficulty in eradicating bacteria may occur. Urinary tract obstruction may also reduce concentration of antimicrobial agents within the urine.

A decision regarding the antimicrobial selection and the duration of therapy must consider the spectrum of activity of the drug against the known pathogen or the most probable pathogen based on the presumed source of acquisition of infection, whether the infection is judged to be uncomplicated or

complicated, potential adverse effects, and cost. An often under-emphasized but important characteristic is the drug's impact on the bowel and vaginal flora and the hospital bacterial environment. Bacterial susceptibility will vary dramatically in patients exposed to antimicrobial agents and in individuals in inpatient and outpatient settings. It is imperative that each clinician keep abreast of changes that affect antimicrobial use and susceptibility patterns.

Bacterial Resistance

In the past several years, the frequency and spectrum of antimicrobial-resistant UTIs have increased in both the hospital and community. The increasing frequency of drug resistance has been attributed to combinations of microbial characteristics, bacterial selection pressure caused by antimicrobial use, and societal and technologic changes that enhance the transmission of drug resistance (Shepherd and Pottinger, 2013). Resistance patterns have been shown to vary by geographical location (Manges et al, 2001).

Bacterial resistance may occur because of inherited chromosomal-mediated resistance or by acquired chromosomal- or extrachromosomal (plasmid)-mediated resistance caused by exposure of an organism to antimicrobial agents.

Inherited chromosomal resistance exists in a bacterial species because of the absence of the proper mechanism on which the antimicrobial agent can act. For example, *Proteus* and *Pseudomonas* species are always resistant to nitrofurantoin.

Acquired chromosomal resistance occurs during therapy for UTIs. Before antimicrobial therapy, relatively resistant bacteria called *mutators* may be present in the urine at very low concentrations. Frequencies in mutations for high-level antimicrobial resistance are 1000-fold higher in mutators than in normal strains, indicating the increased adaptability of these strains (Miller et al, 2004). The remainder of the bacteria, which are susceptible to the administered

antimicrobial agent, will be eradicated by therapy, but within 24 to 48 hours a repeat urine culture will show high bacterial counts of the resistant mutant. In essence, the antimicrobial therapy has selected out the resistant mutant. This phenomenon is most likely to occur when the antimicrobial level in the urine is close to or below the minimal inhibitory concentration of the drug. **Selection of resistant clones in the course of therapy for a previously sensitive bacteriuric population occurs between 5% and 10% of the time, clearly not an insignificant factor and one that must be considered in resolving bacteriuria.** Underdosing and noncompliance, as well as diuresis induced by increased fluid intake, can contribute to this process. Therefore the clinician should select an antimicrobial agent with a urinary concentration that exceeds the minimal inhibitory concentration by the widest margin possible, avoid underdosing, and emphasize patient compliance.

Extrachromosomal-mediated resistance may be acquired and transferable via plasmids, which contain the genetic material for the resistance. This so-called R-factor resistance occurs in the bowel flora and is much more common than selection of preexisting mutants in the urinary tract. All antimicrobial classes are capable of causing plasmid-mediated resistance. However, for the fluoroquinolones, resistance is rarely transmitted by plasmids, and nitrofurantoin plasmid-mediated resistance has not been reported. Therefore patients previously exposed to β -lactams, aminoglycosides, sulfonamides, TMP, and tetracycline will often have R-factor resistance to both the antimicrobial agent to which the bacteria were exposed and also to other antimicrobial agents. In addition, the plasmids carrying the resistant genetic material are transferable both within species and across genera. Thus, for example, a patient receiving tetracycline may harbor several bowel strains that are resistant to tetracycline, ampicillin, sulfonamides, and TMP. **Because the bowel flora is the major reservoir for bacteria that ultimately colonize the urinary tract, infections that occur after antimicrobial therapy and that can cause plasmid-mediated resistance are commonly caused by organisms with multidrug resistance.** However, resistant *E. coli* in the bowel flora that infect the urinary tract almost always show susceptibility to nitrofurantoin or to the quinolones.

Antimicrobial resistance is also influenced by the duration and amount of antimicrobial agent used. For example, documented increased use of fluoroquinolones in the hospital setting has been directly associated with increased resistance of bacteria (particularly *Pseudomonas*) to the fluoroquinolones. Resistance tends to increase the longer the agent is used. Conversely, reduction in duration of therapy and in the amount of the drug used may lead to reemergence of more susceptible strains.

Most studies reporting antimicrobial resistance have been based on surveys of laboratory isolates, generally without correlation with clinical or epidemiologic factors (e.g., the presence and nature of symptoms, age, sex, and whether the infection was complicated). Gupta and colleagues (2011) determined the prevalence of and trends in antimicrobial resistance among uropathogens isolated from a large, well-defined population of women with acute uncomplicated cystitis. The prevalence of resistance to TMP-SMX and ampicillin is greater than 20% in many countries worldwide (Gupta et al, 2011) and resistance to cephalothin has increased significantly, whereas resistance to nitrofurantoin and ciprofloxacin has remained uncommon. **However, fluoroquinolone resistance of *E. coli* is still less than 10% in most parts of North America and Europe (Gupta et al, 2011).** Fluoroquinolone resistance was also associated with more frequent multidrug resistance (Karlowksy et al, 2006). More recent single-center hospital studies have found resistance patterns to be even higher, roughly 26% (Siddiqui, 2008). In a transplant unit, where fluoroquinolones are commonly administered prophylactically, *E. coli* resistance can be 80%. **Previous use of fluoroquinolones and the presence of underlying urologic diseases were the strongest determinants for UTIs caused by resistant strains (Ena et al, 1995).** Fluoroquinolone resistance is an increasing problem in some European countries. A multiple-resistant phenotype involving fluoroquinolone resistance is now present in most countries in Europe, and this phenotype is selected for not only by the use of quinolones but also by the use of ampicillin, sulfamethoxazole, and TMP-MX (Kahlmeter and Menday, 2003). This is a concern because fluoroquinolones, which are associated with chromosomal-mediated but not plasmid-mediated resistance, are the current drug of choice for patients who have been exposed to agents causing plasmid-mediated resistance.

The clinical significance of these in vitro trends in resistance has been addressed in studies that correlated in vitro resistance to TMP-SMX with clinical outcome in uncomplicated cystitis and pyelonephritis (Gupta and Stamm, 2002). Clinical failures occurred in 40% to 50% of women if the bacteria were resistant and the bacteriologic failure approached 60%. (For further information on the role of TMP-SMX in prophylaxis, see [Bladder Infections](#) later in this chapter.)

Antimicrobial Formulary

The mechanism of action, reliable coverage, and common adverse reactions, precautions, and contraindications for antimicrobial agents used in the treatment of UTIs are indicated in [Tables 12-4, 12-5, and 12-6](#), respectively.

TABLE 12-4 Mechanism of Action of Common Antimicrobials Used in the Treatment of Urinary Tract Infections

DRUG OR DRUG CLASS	MECHANISM OF ACTION	MECHANISMS OF DRUG RESISTANCE
β -Lactams (penicillins, cephalosporins, aztreonam)	Inhibition of bacterial cell wall synthesis	Production of β -lactamase Alteration in binding site of penicillin-binding protein Changes in cell wall porin size (decreased penetration)
Aminoglycosides	Inhibition of ribosomal protein synthesis	Downregulation of drug uptake into bacteria Bacterial production of aminoglycoside-modifying enzymes
Quinolones	Inhibition of bacterial DNA gyrase	Mutation in DNA gyrase-binding site Changes in cell wall porin size (decreased penetration) Active efflux
Fosfomycin	Inhibition of bacterial cell wall synthesis	Novel amino acid substitutions or the loss of function of transporters
Nitrofurantoin	Inhibition of several bacterial enzyme systems	Not fully elucidated—develops slowly With prolonged exposure
Trimethoprim-sulfamethoxazole	Antagonism of bacterial folate metabolism	Draws folate from environment (enterococci)
Vancomycin	Inhibition of bacterial cell wall synthesis (at β -lactams)	Enzymatic alteration of peptidoglycan at different point than target

TABLE 12-5 Reliable Coverage of Antimicrobials Used in the Treatment of Urinary Tract Infections of Commonly Encountered Pathogens*

ANTIMICROBIAL AGENT OR CLASS	GRAM-POSITIVE PATHOGENS	GRAM-NEGATIVE PATHOGENS
Amoxicillin or ampicillin	<i>Streptococcus</i> Enterococci	<i>Proteus mirabilis</i>
Amoxicillin with clavulanate	<i>Streptococcus</i> Enterococci	<i>P. mirabilis</i> <i>Klebsiella</i> species
Ampicillin with sulbactam	<i>Staphylococcus</i> (not MRSA) Enterococci	<i>P. mirabilis</i> <i>Haemophilus influenzae</i> , <i>Klebsiella</i> species
Antistaphylococcal penicillins	<i>Streptococcus</i> <i>Staphylococcus</i> (not MRSA)	None
Antipseudomonal penicillins	<i>Streptococcus</i> Enterococci	Most, including <i>Pseudomonas aeruginosa</i>
First-generation cephalosporins	<i>Streptococcus</i> <i>Staphylococcus</i> (not MRSA)	<i>Escherichia coli</i> <i>P. mirabilis</i> <i>Klebsiella</i> species
Second-generation cephalosporins (cefamandole, cefuroxime, cefaclor)	<i>Streptococcus</i> <i>Staphylococcus</i> (not MRSA)	<i>E. coli</i> , <i>P. mirabilis</i> <i>H. influenzae</i> , <i>Klebsiella</i> species
Second-generation cephalosporins (cefoxitin, cefotetan)	<i>Streptococcus</i>	<i>E. coli</i> , <i>Proteus</i> species (including indole-positive) <i>H. influenzae</i> , <i>Klebsiella</i> species
Third-generation cephalosporins (ceftriaxone)	<i>Streptococcus</i> <i>Staphylococcus</i> (not MRSA)	Most, excluding <i>P. aeruginosa</i>
Third-generation cephalosporins (ceftazidime)	<i>Streptococcus</i>	Most, including <i>P. aeruginosa</i>
Aztreonam	None	Most, including <i>P. aeruginosa</i>
Aminoglycosides	<i>Staphylococcus</i> (urine)	Most, including <i>P. aeruginosa</i>
Fluoroquinolones	<i>Streptococcus</i> *	Most, including <i>P. aeruginosa</i>
Nitrofurantoin	<i>Staphylococcus</i> (not MRSA) Enterococci	Many Enterobacteriaceae (not <i>Providencia</i> , <i>Serratia</i> , <i>Acinetobacter</i>) <i>Klebsiella</i> species
Fosfomycin	Enterococci	Most Enterobacteriaceae (not <i>P. aeruginosa</i>)
Pivmecillinam	None	Most, excluding <i>P. aeruginosa</i>
Trimethoprim-sulfamethoxazole	<i>Streptococcus</i> <i>Staphylococcus</i>	Most Enterobacteriaceae (not <i>P. aeruginosa</i>)
Vancomycin	All, including MRSA	None

MRSA, methicillin-resistant *Staphylococcus aureus*.

*Depends on the antimicrobial agent.

TABLE 12-6 Common Adverse Reactions, Precautions, and Contraindications for Antimicrobial Agents Used in Treatment of Urinary Tract Infection

DRUG OR DRUG CLASS	COMMON ADVERSE REACTIONS	PRECAUTIONS AND CONTRAINDICATIONS
Amoxicillin or ampicillin	Hypersensitivity (immediate or delayed) Diarrhea (especially with ampicillin), GI upset AAPMC Maculopapular rash (not hypersensitivity) Decreased platelet aggregation	Increased risk of rash with concomitant viral disease, allopurinol therapy
Amoxicillin with clavulanic acid	Increased diarrhea, GI upset with amoxicillin/clavulanic acid	
Ampicillin with sulbactam	Same as with amoxicillin/ampicillin	
Antistaphylococcal penicillins	Same as with amoxicillin/ampicillin GI upset (with oral agents) Acute interstitial nephritis (especially with methicillin)	

TABLE 12-6 Common Adverse Reactions, Precautions, and Contraindications for Antimicrobial Agents Used in Treatment of Urinary Tract Infection—cont'd

DRUG OR DRUG CLASS	COMMON ADVERSE REACTIONS	PRECAUTIONS AND CONTRAINDICATIONS
Antipseudomonal penicillins	Same as with amoxicillin/ampicillin Hypernatremia (these drugs are given as sodium salt; especially carbenicillin, ticarcillin) Local injection site reactions	Use with caution in patients very sensitive to sodium loading.
Cephalosporins	Hypersensitivity (less than with penicillins) GI upset (with oral agents) Local injection site reactions AAPMC Positive Coombs test Decreased platelet aggregation (especially with cefotetan, cefamandole, cefoperazone)	Should not be used in patients with immediate hypersensitivity to penicillins; may use with caution in patients with delayed hypersensitivity reactions
Aztreonam	Hypersensitivity (less than with penicillins)	Less than 1% incidence of cross-reactivity in penicillin- or cephalosporin-allergic patients; may be used with caution in these patients
Aminoglycosides	Ototoxicity: vestibular and auditory components Nephrotoxicity: nonoliguric azotemia Neuromuscular blockade with high levels	Avoid in pregnant patients, except in pyelonephritis. Avoid if possible in patients with severely impaired renal function, diabetes, or hepatic failure. Use with caution in myasthenia gravis patients (owing to potential for neuromuscular blockade). Use with caution with other potentially ototoxic and nephrotoxic drugs.
Fluoroquinolones	Mild GI effects; dizziness, lightheadedness; photosensitivity Central nervous system effects, including dizziness, tremors, confusion, mood disorder, hallucinations Tendon rupture	Avoid in children or pregnant patients due to arthropathic effects. Concomitant antacid, iron, zinc, or sucralfate use dramatically decreases oral absorption; use another antimicrobial agent or discontinue sucralfate use while on quinolones. Space administration of quinolones from antacids, iron, or zinc products by at least 2 hr to ensure adequate absorption. Ensure adequate patient hydration. These agents can significantly increase theophylline plasma levels (ciprofloxacin and enoxacin seem to have a greater effect than norfloxacin or ofloxacin); avoid quinolones or monitor theophylline levels closely. These agents can lower seizure threshold; avoid in patients with epilepsy and in patients with other risk factors (medications or illness) that may lower the seizure threshold. Monitor glucose levels in patients on antidiabetic agents because hypoglycemia and hyperglycemia have been reported in patients treated concurrently with fluoroquinolones and antidiabetic agents. These agents can enhance warfarin effects; closely monitor coagulation tests.
Fosfomycin	Headache GI upset Vaginitis	Hypersensitivity to fosfomycin or any component of the formulation
Pivmecillinam	Rash GI upset	Use with caution in patients with penicillin hypersensitivity.

Continued

TABLE 12-6 Common Adverse Reactions, Precautions, and Contraindications for Antimicrobial Agents Used in Treatment of Urinary Tract Infection—cont'd

DRUG OR DRUG CLASS	COMMON ADVERSE REACTIONS	PRECAUTIONS AND CONTRAINDICATIONS
Nitrofurantoin	GI upset Peripheral polyneuropathy (especially in patients with impaired renal function, anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitated) Hemolysis in patients with G6PD deficiency Pulmonary hypersensitivity reactions can range from acute to chronic and include cough, dyspnea, fever, and interstitial changes.	Do not use in patients with low creatinine clearance (<50 mL/min) because adequate urine concentrations will not be achieved. Monitor long-term patients closely. Avoid concomitant probenecid use, which blocks renal excretion of nitrofurantoin. Avoid concomitant magnesium or quinolones, which are antagonistic to nitrofurantoin.
Trimethoprim-sulfamethoxazole	Hypersensitivity, rash GI upset Photosensitivity Hematologic toxicity (AIDS patients)	Higher incidence of all adverse reactions occurs in AIDS patients and the elderly. Avoid in pregnant patients. Avoid in patients receiving warfarin; concomitant use can significantly elevate prothrombin time.
Vancomycin	“Red-man syndrome”: flushing, fever, chills, rash, hypotension (histaminic effect) Nephrotoxicity and/or ototoxicity when combined with other nephrotoxic and/or ototoxic drugs Local injection site reactions	Use with caution with other potentially ototoxic and nephrotoxic drugs.

AAPMC, antimicrobial-associated pseudomembranous colitis; AIDS, acquired immunodeficiency syndrome; GI, gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase.

Modified from McEvoy GK, editor. American Hospital Formulary Service drug information. Bethesda (MD): American Society of Health-System Pharmacists; 1995.

Nitrofurantoin

Nitrofurantoin is effective against common uropathogens, but it is not effective against *Pseudomonas* and *Proteus* species (Iravani, 1991). It is rapidly excreted from the urine but does not obtain therapeutic levels in most body tissues, including the gastrointestinal (GI) tract. Therefore it is not useful for upper tract and complicated infections (Wilhelm and Edson, 1987). It has minimal effects on the resident bowel and vaginal flora and has been used effectively in prophylactic regimens for more than 40 years. Acquired bacterial resistance to this drug is exceedingly low. Nitrofurantoin should be used only during the first two trimesters of pregnancy. Nitrofurantoin can cause GI upset and rare pulmonary issues when used chronically. Nitrofurantoin should also be avoided in patients with suspicion of or known glucose-6-phosphate dehydrogenase (G6PD) deficiency because it can lead to hemolytic anemia.

Trimethoprim/Sulfamethoxazole

The combination of TMP-SMX has been the most widely used antimicrobial agent for the treatment of acute UTIs. TMP alone is as effective as the combination for most uncomplicated infections and may be associated with fewer side effects (Johnson and Stamm, 1989); however, the addition of SMX contributes to efficacy in the treatment of upper tract infection via a synergistic bactericidal effect and may diminish the emergence of resistance (Burman, 1986) and attains therapeutic levels in most tissues. TMP alone or in combination with SMX is effective against most common uropathogens, with the notable exception of *Enterococcus* and *Pseudomonas* species. TMP and TMP-SMX are inexpensive and have minimal adverse effects on the bowel flora. Disadvantages are relatively common adverse effects, consisting primarily of rashes and gastrointestinal complaints (Cockerill and Edson, 1991). TMP-SMX should be avoided during pregnancy.

Fosfomycin

Fosfomycin, an oral bactericidal antimicrobial agent similar to phosphonic acid in chemical structure, is active against most uropathogens. Its major benefit is its limited cross-resistance between most other common antibacterial agents, as well as its efficacy against the majority of gram-negative organisms and vancomycin-resistant *Enterococcus* (VRE). Further, it has been shown to be effective as a single-dose agent when used as an empirical treatment for uncomplicated cystitis. It is generally well tolerated with low incidences of GI upset and headache and very rare adverse events seen in multiple trials (Patel et al, 1997).

Fluoroquinolones

Fluoroquinolones share a common predecessor in nalidixic acid and inhibit DNA gyrase, a bacterial enzyme integral to replication. The fluoroquinolones have a broad spectrum of activity that makes them ideal for the empirical treatment of UTIs. They are highly effective against Enterobacteriaceae, as well as *P. aeruginosa*. Activity is also high against *S. aureus* and *S. saprophyticus*, but, in general, antistreptococcal coverage is marginal. Most anaerobic bacteria are resistant to these drugs; therefore the normal vaginal and bowel flora are not altered (Wright et al, 1993). Bacterial resistance initially appeared to be uncommon, but it is being reported at an increasing rate because of indiscriminate use of these agents (Wright et al, 1993; Vromen et al, 1999).

These drugs are not nephrotoxic, but renal insufficiency prolongs the serum half-life, requiring adjusted dosing in patients with creatinine clearances of less than 30 mL/min. Adverse reactions are uncommon; gastrointestinal disturbances are more common. Hypersensitivity, skin reactions, mild central and peripheral nervous system reactions, and even acute renal failure have been reported (Hootkins et al, 1989). Achilles tendon disorders,

including rupture, have been estimated to occur in 20 cases per 100,000 and therefore fluoroquinolone use should be discontinued at the first sign of tendon pain (Greene, 2002). The mechanism of tendon rupture is unclear, but ciprofloxacin stimulates matrix-degrading protease activity from fibroblasts and exerts an inhibitory effect on fibroblast metabolism and synthesis of matrix ground substance, factors that may contribute to tendinopathy (Williams et al, 2000). Administration of the fluoroquinolones to immature animals has caused damage to the developing cartilage; therefore they are currently contraindicated in children, adolescents, and pregnant or nursing women (Christ et al, 1988). There are important drug interactions associated with the fluoroquinolones. The World Health Organization (WHO) warns of rare increases in the anticoagulant effects of Coumadin when taken with fluoroquinolones. Antacids containing magnesium or aluminum interfere with absorption of fluoroquinolones (Davies and Maesen, 1989). Certain fluoroquinolones (enoxacin and ciprofloxacin) elevate plasma levels of theophylline and prolong its half-life (Wright et al, 1993). For most uncomplicated UTIs, the fluoroquinolones have been only slightly more effective than TMP-SMX. However, as resistance to TMP-SMX increases, the fluoroquinolones have distinct advantages in empirical treatment of patients recently exposed to antimicrobial agents and in the outpatient treatment of complicated UTIs (Dalkin and Schaeffer, 1988; Gupta et al, 1999). They may be considered as first-line agents in areas where a significant level of resistance (>20%) exists (in common bacteria) to agents such as ampicillin and TMP-SMX.

Cephalosporins

All three generations of cephalosporins have been used for the treatment of acute UTIs (Wilhelm and Edson, 1987). In general, as a group, activity is high against Enterobacteriaceae and poor against enterococci. First-generation cephalosporins have greater activity against gram-positive organisms, as well as common uropathogens such as *E. coli* and *Klebsiella pneumoniae*, whereas second-generation cephalosporins have activity against anaerobes. Third-generation cephalosporins are more reliably active against community-acquired and nosocomial gram-negative organisms than other β -lactam antimicrobials. Selective pressure engendered by these broad-spectrum agents should limit their use to complicated infections and situations in which parenteral therapy is required and resistance to standard antimicrobial agents is likely. They are also safe for use during pregnancy.

Aminopenicillins

Ampicillin and amoxicillin have been used often in the past for the treatment of UTIs, but the emergence of resistance in 40% to 60% of common urinary isolates has lessened the usefulness of these drugs (Hooton and Stamm, 1991; Gupta et al, 2011). The effects of these agents on the normal bowel and vaginal flora can predispose patients to reinfection with resistant strains and often lead to candidal vaginitis (Irvani, 1991). The addition of the β -lactamase inhibitor clavulanate to amoxicillin greatly improves activity against β -lactamase-producing bacteria resistant to amoxicillin alone. However, its high cost and frequent gastrointestinal side effects limit its usefulness. The extended-spectrum penicillin derivatives (e.g., pivmecillinam, piperacillin, mezlocillin, azlocillin) retain ampicillin's activity against enterococci and offer activity against many ampicillin-resistant gram-negative bacilli. This makes them attractive agents for use in patients with nosocomially acquired UTIs and as the initial parenteral treatment of acute uncomplicated pyelonephritis acquired outside of the hospital, although less expensive agents are equally effective.

Aminoglycosides

When combined with TMP-SMX or ampicillin, aminoglycosides are the first drugs of choice for febrile UTIs. Their nephrotoxicity and ototoxicity are well recognized; hence, careful monitoring of

patients for renal and auditory impairment associated with infection is indicated. Once-daily aminoglycoside regimens have been instituted to maximize bacterial killing by optimizing the peak concentration-to-minimal inhibitory concentration ratio and reduce the potential for toxicity (Fig. 12-11) (Nicolau et al, 1995). Administering an aminoglycoside as a single daily dose can take advantage not only of its concentration-dependent killing ability but also of two other important characteristics: time-dependent toxicity and a more prolonged postantimicrobial effect (Gilbert, 1991; Zhanel et al, 1991). The regimen consists of a fixed 7 mg/kg dose of gentamicin or 5 to 7 mg/kg tobramycin. Subsequent interval adjustments are made by using a single concentration in serum and a nomogram designed for monitoring of once-daily therapy (Fig. 12-12). Antimicrobial doses are given at the interval determined by the drug concentration of a sample obtained after the start of the initial infusion. For example, if the serum concentration was 7 $\mu\text{g/mL}$ 10 hours after the start of the infusion, subsequent 7-mg/kg doses would be given every 36 hours. This regimen is

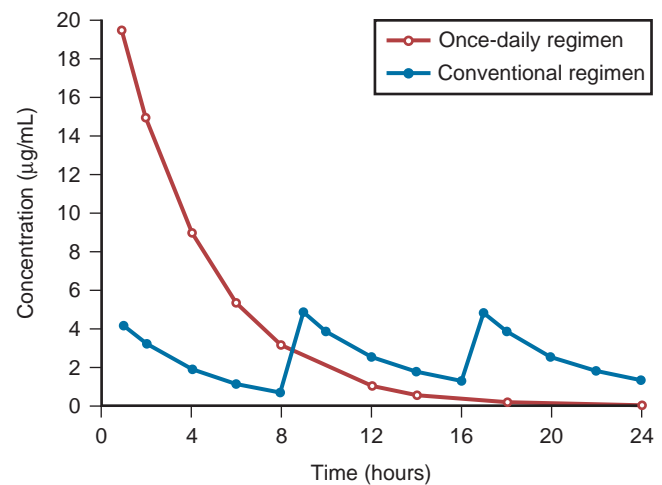


Figure 12-11. Simulated concentration-versus-time profile of once-daily (7 mg/kg/24 hr) and conventional (1.5 mg/kg/8 hr) regimens for patients with normal renal function. (From Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother* 1995;39:650-5.)

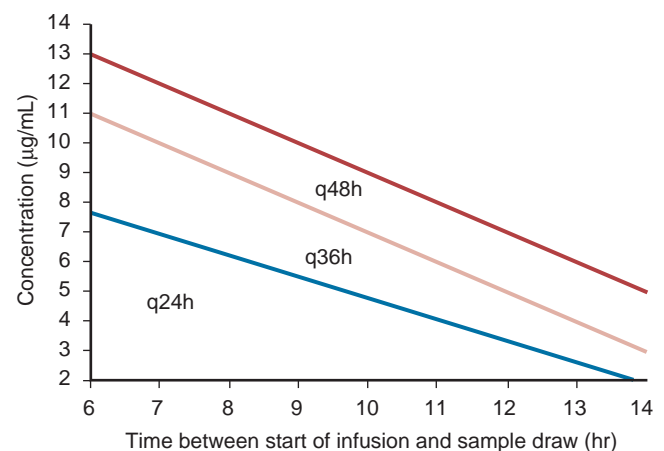


Figure 12-12. Once-daily aminoglycoside nomogram for gentamicin and tobramycin at 7 mg/kg. (From Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother* 1995;39:650-5.)

clinically effective, reduces the incidence of nephrotoxicity, and provides a cost-effective method for administering aminoglycosides by reducing ancillary service times and serum aminoglycoside determinations.

Aztreonam

Aztreonam has a similar spectrum of activity as the aminoglycosides, and as with all β -lactams, it is not nephrotoxic. However, its spectrum of activity is less broad than the third-generation cephalosporins. It should be used primarily in patients who have penicillin allergies.

Pivmecillinam

Pivmecillinam is a penicillin-like β -lactam antibiotic which is the prodrug of mecillinam. It has high activity against gram-negative organisms and is primarily used in Nordic countries for empirical treatment of uncomplicated cystitis. **It is not currently available in the United States**, but it has been shown to have low resistance patterns (roughly 2% of *E. coli*) as well as being safe and effective (Graninger, 2003).

Choice of Antimicrobial Agents

Many antimicrobial agents have been shown to be effective in the treatment of UTIs. **Factors important in aiding selection of empirical therapy include whether the infection is complicated or uncomplicated; the spectrum of activity of the drug against the probable pathogen; a history of hypersensitivity; potential side effects, including renal and hepatic toxicity; and cost.** In addition, favorable or unfavorable effects of the antimicrobial agent on the vaginal and bowel flora are important in women with recurrent UTIs. The bacterial susceptibility and cost of the drug vary dramatically among inpatient and outpatient settings throughout the country. It is imperative, therefore, that each clinician keep abreast of changes in bacterial susceptibility and cost and use current information when choosing antimicrobial agents.

Duration of Therapy

The duration of therapy needed to cure a UTI appears to be related to a number of variables, including the extent and duration of tissue invasion, the bacterial concentration in urine, the achievable urine concentration of the antimicrobial agent, and risk factors (see later) that impair the host and natural defense mechanisms.

KEY POINTS: PRINCIPLES OF ANTIMICROBIAL THERAPY

- Effective antimicrobial therapy must eliminate bacterial growth in the urinary tract.
- Antimicrobial resistance is increasing because of excessive utilization.
- Antimicrobial selection should be influenced by efficacy, safety, cost, and compliance.

ANTIMICROBIAL PROPHYLAXIS FOR COMMON UROLOGIC PROCEDURES

Principles

Surgical antimicrobial prophylaxis entails treatment with an antimicrobial agent before and for a *limited* time after a procedure to prevent local or systemic postprocedural infections. For most procedures, prophylaxis should be initiated between 30

minutes and 120 minutes before the procedure (Bratzler and Houck, 2004). Efficacious levels should be maintained for the duration of the procedure and, in special circumstances, a limited time (24 hours, at most) after the procedure (Bratzler and Houck, 2004). Although prospective studies addressing prophylaxis for urologic procedures exist, most focus on only a narrow spectrum of procedures. However, application of the principles of these studies with additional consideration of both the patient and the type of procedure provides a framework for determining when and what type of antimicrobial prophylaxis may be indicated. An additional, nontraditional type of prophylaxis in urology entails periprocedural treatment of the urinary tract with an antimicrobial agent to prevent local or systemic sequelae from the manipulation of colonized hardware such as a stent or urethral catheter.

A wide array of patients undergo invasive procedures in urology. The ability of a host to respond to bacteriuria or bacteremia and the sequelae of a possible infection are two important considerations when assessing the need for antimicrobial prophylaxis. Factors that affect the host's ability to respond to infection include advanced age, anatomic anomalies, poor nutritional status, smoking, chronic corticosteroid use, other concurrent medication use, and immunodeficiencies such as untreated HIV infection (Box 12-5). Additionally, chronic indwelling hardware, infected endogenous material such as stones, distant infectious sites, and prolonged hospitalizations also increase the risk of infectious complications by increasing the local bacterial concentration and/or altering the spectrum of bacterial flora. The potential seeding of artificial heart valves or prosthetic joints increases the sequelae of a systemic infection in hosts who otherwise may not be at an increased risk of infection. Thus a thorough history and examination of the patient is crucial in directing antimicrobial prophylaxis before a urologic procedure.

The type of procedure will also help direct the timing, duration, and spectrum of antimicrobial prophylaxis needed (see Table 12-7 for a summary of antimicrobial prophylaxis recommendations). Consideration should be given to the extent of the local tissue injury incurred and the anticipated type of flora at the site.

Antimicrobial prophylaxis is not without morbidity because allergic complications, although rare, may result in minor reactions such as rash or gastric disturbances or significant sequelae such as early withdrawal of therapy, allergic nephritis, or anaphylaxis.

Urethral Catheterization and Removal

The indications for the routine use of prophylactic antimicrobial agents before urethral catheterization vary and depend on the health, sex, and specific living circumstances of the individual

BOX 12-5 Host Factors That Increase the Risk of Infection

Advanced age
Anatomic anomalies
Poor nutritional status
Smoking
Chronic corticosteroid use
Immunodeficiency
Chronic indwelling hardware
Infected endogenous/exogenous material
Distant coexistent infection
Prolonged hospitalization

Data from Cruse PJ. Surgical wound infection. In: Wonsiewicz MJ, editor. Infectious disease. Philadelphia: WB Saunders; 1992. p. 758–64; and Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250–78; quiz 279–80.

patient, as well as the indication for catheterization (Schaeffer 2006). The risk of infection after one-time urethral catheterization is 1% to 2% in healthy domiciliary women; however, this risk rises significantly in hospitalized patients (Turck et al, 1962; Thiel and Spuhler, 1965). Thus, for patients with risk factors for infection (see Box 12-5), antimicrobial prophylaxis with an oral agent such as TMP-SMX or a fluoroquinolone should decrease the risk of postprocedural infection (see Table 12-7).

Prolonged use of an indwelling urethral catheter is common in hospitalized patients and is associated with an increased risk of bacterial colonization, with a 3% to 10% incidence of bacteriuria per catheter day in one study and 100% incidence of bacteriuria

with long-term catheterization (>30 days) (Kass, 1956; Nickel et al, 1985; Liedl, 2001). Prophylactic administration of antimicrobial agents during catheterization is not generally recommended because bacterial resistance can develop rapidly and complicate subsequent antimicrobial treatment (Clarke et al, 2005). This is supported by the Cochrane Database of Systematic Reviews that concluded that antimicrobials given postprocedurally until removal or for the first three postoperative days did not reduce rates of bacteriuria or infection (Niël-weise and van den Broek, 2005).

The natural history of bacteriuria after catheter removal has not been comprehensively studied. Harding and associates (1991) reported that in asymptomatic bacteriuric women who had been

TABLE 12-7 Guide for Antimicrobial Prophylaxis for Uncomplicated Urologic Procedures

PROCEDURE	ORGANISMS	PROPHYLAXIS INDICATED	ANTIMICROBIAL(S) OF CHOICE	ALTERNATIVE ANTIMICROBIAL(S)	DURATION OF THERAPY ^a
LOWER TRACT INSTRUMENTATION					
Removal of external urinary catheter	GU tract ^b	If risk factors ^c	Fluoroquinolone TMP-SMX ^d	Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin ^d	≤24 hr ^d
Cystography, urodynamic study, or simple cystourethroscopy	GU tract	If risk factors ^c	Fluoroquinolone TMP-SMX	Amoxicillin/clavulanate Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin	≤24 hr
Cystourethroscopy with manipulation ^e	GU tract	All	Fluoroquinolone TMP-SMX	Amoxicillin/clavulanate	≤24 hr
Prostate brachytherapy or cryotherapy	Skin	Uncertain	1st gen. cephalosporin	Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin Amoxicillin/clavulanate Clindamycin ^f	≤24 hr
Transrectal prostate biopsy	Intestine ^g	All	Fluoroquinolone Targeted prophylaxis ^h	TMP-SMX Aminoglycoside ± metronidazole or clindamycin ^f	≤24 hr
UPPER TRACT INSTRUMENTATION					
Shockwave lithotripsy	GU tract	All	Fluoroquinolone TMP-SMX	Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin	≤24 hr
Percutaneous renal surgery	GU tract and skin ⁱ	All	1st/2nd gen. cephalosporin Aminoglycoside + metronidazole or clindamycin	Amoxicillin/clavulanate Ampicillin/sulbactam Fluoroquinolone	≤24 hr
Ureteroscopy	GU tract	All	Fluoroquinolone TMP-SMX	Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin Amoxicillin/clavulanate	≤24 hr
OPEN OR LAPAROSCOPIC SURGERY					
Vaginal surgery	GU tract, skin, and group B <i>Streptococcus</i>	All	1st/2nd gen. cephalosporin Aminoglycoside + metronidazole or clindamycin	Ampicillin/sulbactam	≤24 hr
Without entering urinary tract	Skin	If risk factors	1st gen. cephalosporin	Fluoroquinolone	Single dose
Involving entry into urinary tract	GU tract and skin	All	1st/2nd gen. cephalosporin Aminoglycoside + metronidazole or clindamycin	Clindamycin	≤24 hr

Continued

TABLE 12-7 Guide for Antimicrobial Prophylaxis for Uncomplicated Urologic Procedures—cont'd

PROCEDURE	ORGANISMS	PROPHYLAXIS INDICATED	ANTIMICROBIAL(S) OF CHOICE	ALTERNATIVE ANTIMICROBIAL(S)	DURATION OF THERAPY ^a
Involving intestine ^d	GU tract, skin, and intestine	All	2nd/3rd gen. cephalosporin Aminoglycoside + metronidazole or clindamycin	Ampicillin/sulbactam Fluoroquinolone	≤24 hr
Involving implanted prosthesis	GU tract and skin	All	Aminoglycoside + 1st/2nd gen. cephalosporin or vancomycin	Ampicillin/sulbactam Ticarcillin/clavulanate Piperacillin/tazobactam Fluoroquinolone Ampicillin/sulbactam Ticarcillin/clavulanate Piperacillin/tazobactam	≤24 hr

Order of agents in each column is not indicative of preference. The absence of an agent does not preclude its appropriate use depending on specific situations.

^aAdditional antimicrobial therapy may be recommended at the time of removal of an externalized urinary catheter.

^bGU tract: common urinary tract organisms are *E. coli*, *Proteus* species, *Klebsiella* species, *Enterococcus*.

^cIf urine culture shows no growth before the procedure, antimicrobial prophylaxis is not necessary.

^dOr full course of culture-directed antimicrobial agents for documented infection (which is treatment, not prophylaxis).

^eIncludes transurethral resection of bladder tumor and prostate, and any biopsy, resection, fulguration, foreign body removal, urethral dilation or urethrotomy, or ureteral instrumentation, including catheterization or stent placement/removal.

^fClindamycin or an aminoglycoside + metronidazole or clindamycin is an alternative to penicillins and cephalosporins in patients with penicillin allergy, even when not specifically listed.

^gIntestine: common intestinal organisms are *E. coli*, *Klebsiella* species, *Enterobacter*, *Serratia* species, *Proteus* species, *Enterococcus*, and anaerobes.

^hPerform prebiopsy rectal swab culture and bacterial susceptibility; select appropriate antimicrobial prophylaxis.

ⁱSkin: common skin organisms are *S. aureus*, coagulase-negative *Staphylococcus* species, group A *Streptococcus* species.

^jFor surgery involving the colon, bowel preparation with oral neomycin + either erythromycin base or metronidazole can be added to or substituted for systemic agents.

gen., generation; GU, genitourinary; TMP-SMX, trimethoprim-sulfamethoxazole.

Drug doses: ampicillin, 25 mg/kg/dose; gentamicin, 1.5 mg/kg/dose; cefazolin, 25 mg/kg/dose.

Modified from Wolf JS Jr, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol* 2008;179:1379–90.

catheterized for 4 to 6 days, 25% developed a UTI within 14 days of catheter removal. In this study, 1-day treatment with TMP-SMX was as effective as a 10-day course at resolving infections. Similar studies on the natural history of postcatheterization bacteriuria have not been performed in male patients. Note that antimicrobial treatment before removal of an indwelling catheter in a patient suspected of having bacteriuria is not considered prophylaxis but rather is treatment for a presumptive UTI; duration of treatment generally should follow previously outlined guidelines for uncomplicated or complicated UTIs.

Data from Polastri and colleagues (1990) suggest that antimicrobial prophylaxis for chronic indwelling catheter changes is not indicated. In their study of 46 catheter changes, bacteremia occurred 4% of the time and, when noted, was associated with very low concentrations of bacteria in the cultures. Systemic sequelae were not noted.

Urodynamics

Urodynamics, like cystoscopy, is a minimally traumatic procedure with limited urothelial injury that poses a small risk of local infection in hosts with normal anatomy and immune response. Several recent studies support this notion. In a series of women with urinary incontinence randomized to receive 1 day of nitrofurantoin or placebo, Cundiff and coworkers (1999) noted no difference in postprocedural UTI (5% vs. 7%) 1 week after evaluation. Similarly, Peschers and associates (2001) reported infections 1 week after multichannel urodynamics in 5% and 6% in nondiabetic women

treated with placebo or co-trimoxazole. Conversely, Kartal and colleagues (2006) demonstrated a reduction in UTIs from 14% to 1% with administration of a single dose of ciprofloxacin in a blinded 192-patient trial. Most series examining the use of antimicrobial prophylaxis exclude patients with altered anatomy such as large prostates or comorbidities, including neurogenic bladder, spinal cord injury, or diabetes, all factors that increase the risk of infection. This is illustrated in work performed by Payne and colleagues in which frequencies of bacteriuria after urodynamics were much higher in men (36%) compared with the women studied (15%) (Payne et al, 1988). In sum, antimicrobial prophylaxis should be considered for patients with a more complex clinical history or anatomy such as men with large postvoid residuals or spinal cord-injured patients.

Transrectal Ultrasound-Guided Prostate Biopsy

The use of prophylactic antimicrobials for transrectal ultrasound-guided prostate (TRUSP) biopsy reduces postprocedural fever and UTI in most studies. The class and duration of antimicrobial treatment are more varied and controversial. Antimicrobial prophylaxis with fluoroquinolones has been shown to significantly reduce the rates of infectious complications compared to placebo (8% vs. 25%) (Sieber et al, 1997; Taylor and Bingham, 1997a, 1997b; Kapoor et al, 1998; Shandera et al, 1998; Tal et al, 2003; Zani et al, 2011).

However, several recent studies have highlighted an increasing trend of infectious complications caused by fluoroquinolone-resistant organisms among men undergoing TRUSP (Binsaleh

et al, 2004; Han et al, 2005; Feliciano et al, 2008; Ng and Chan, 2008; Lange et al, 2009; Young et al, 2009; Zaytoun et al, 2011). Prevalence rates for colonization with fluoroquinolone-resistant organisms in this patient population have been reported to be as high as 22% (Liss et al, 2011). Nevertheless more than 90% of urologists continue to use fluoroquinolones empirically for antimicrobial prophylaxis before TRUSP (Shandera et al, 1998). The increasing prevalence of infectious complications with fluoroquinolone-resistant bacteria in men undergoing TRUSP suggests that this approach may be injudicious for some patients (Taylor et al, 2012). Indeed, of fluoroquinolone-resistant strains obtained by rectal swabs of men prior to prostate biopsy, 70% were ST131 isolates (Liss et al, 2013). See *Urinary Pathogens* earlier in chapter for more in-depth information on ST131 and resistance.

Empiric prophylaxis with a combination of aminoglycosides and fluoroquinolones has been effective in recent studies (Kehinde et al, 2013; Ho et al, 2009), but it is inevitable that this approach will also eventually fail because of antimicrobial resistance. **Rectal swab culture obtained before TRUSP allows for the isolation and identification of fluoroquinolone-resistant organisms from a patient's native intestinal flora.** In a study using targeted prophylaxis based on bacterial sensitivities of rectal swabs prior to TRUSP, 19.6% of men had fluoroquinolone-resistant organisms. There were no infectious complications in the men who received targeted prophylaxis, while there were infectious complications, including sepsis, in 2.6% on empiric prophylaxis (Taylor et al, 2012). Cost-effectiveness analysis revealed that targeted prophylaxis yielded a cost savings of \$4,499 per post TRUSP infectious complication averted. Per estimation, 38 men would need to undergo rectal swab before TRUSP to prevent one infectious complication. Thus a benefit to screening before TRUSP and targeted prophylaxis should be considered as a thoughtful, predictable alternative to empiric prophylaxis.

Recent studies suggest a single-dose/day of fluoroquinolones is as effective as 3 days of treatment (Sabbagh et al, 2004). Together these data suggest that a minimum of 1 day of an antimicrobial agent is indicated for transrectal ultrasound-guided prostate biopsies.

Shockwave Lithotripsy

The incidence of UTIs after shockwave lithotripsy is reported to range from 0% to 28% without antimicrobial prophylaxis. A recent meta-analysis of contemporary randomized controlled trials examined the utility and cost-effectiveness of antimicrobial prophylaxis for shockwave lithotripsy and demonstrated, in individuals with sterile preprocedure urine cultures, a reduction in the rate of UTIs after shockwave lithotripsy from 5.7% to 2.1% (Pearle and Roehrborn, 1997). This analysis also demonstrated cost-effectiveness of prophylaxis when consideration was given for the treatment of the rare but more morbid complications of urosepsis and pyelonephritis. A history of a recent UTI or of infection stones should warrant a full treatment course of antimicrobial agents before shockwave lithotripsy.

Endoscopic Procedures: Lower Urinary Tract

Cystoscopy

Cystoscopy is a minimally traumatic procedure with limited urothelial injury performed on a diverse spectrum of patients, including young healthy women and older men. Several prospective trials (Manson, 1988; Clark and Higgs, 1990; Burke et al, 2002) of patients with preprocedure sterile urine report culture-proven rates of UTI between 2.2% and 7.8% after cystoscopy without antimicrobial prophylaxis. In Clark's report the risk of infection was higher in patients with a previous history of UTI. In a similarly designed study, Rane and colleagues (2001) reported a significantly higher postprocedure culture-proven infection rate of 21% without antimicrobial prophylaxis. More recently, Johnson and colleagues (2007) reported a randomized controlled trial of over 2000 patients that demonstrated reductions in bacteriuria with administration of

single-dose trimethoprim or ciprofloxacin. In all the studies, single doses of antimicrobial agents reduced infections to between 1% and 5%. In none of these studies were significant systemic infections reported after the cystoscopic procedures.

Together these studies illustrate two key concepts: (1) despite appropriate periprocedural preparation, a small inoculum of bacteria is likely introduced into the bladder during cystoscopy, and (2) the significance of the bacteriuria is dependent on host factors, including the ability to mount an appropriate immune response to bacterial inoculation and the ability to clear the bacterial inoculation. For example, in a man with urinary retention, a small inoculum of bacteria could persist and divide in the retained fraction of urine and result in a symptomatic infection. In a host with a reduced ability to respond to infection, this bacteriuria could become significant. In contrast, a middle-aged woman undergoing cystoscopy for microscopic hematuria is more likely to efficiently empty her bladder and clear the inoculum but may be exposed to an increased inoculum of bacteria if inappropriately prepared for the examination. **Thus we recommend prophylaxis when aberrant host factors could increase the probability or significance of an infection** (see Table 12-7). A single dose of a fluoroquinolone is commonly used but other agents such as trimethoprim have also been utilized.

Transurethral Resection of the Prostate and Bladder

Therapeutic transurethral lower urinary tract procedures increase the risk of localized infections compared with simple diagnostic cystoscopy. Although not delineated in any prospective studies, several risk factors likely increase infectious complications, including trauma to the mucosa, increased duration and/or degree of difficulty of the procedure, pressurized irrigants, and manipulation or resection of infected material. The most well-studied lower urinary tract procedure is **transurethral resection of the prostate**. In a meta-analysis of 32 studies (Berry and Barratt, 2002), a risk reduction was noted in bacteriuria from 26% to 9% on postoperative urine cultures obtained 2 to 5 days after the procedure for patients treated with prophylactic antimicrobial agents. Similarly, septicemia (defined as rigors, persistently elevated temperature [$>38.5^{\circ}\text{C}$], and an elevated C-reactive protein level) decreased from 4.4% to 0.9% with antimicrobial prophylaxis. The most effective antimicrobial classes included fluoroquinolones, aminoglycosides, cephalosporins, and TMP-SMX. **Single doses of antimicrobial agents did lower the relative risk of bacteriuria but not as significantly as antimicrobial agents administered for short courses (2 to 5 days) while the urethral catheter remained in place.** Although continuation of antimicrobial therapy while the catheter is in place is not truly prophylaxis, continuation of the initial prophylactic antimicrobial agent for an anticipated short period of time (with catheter in place) does not increase the risk of developing antimicrobial-resistant organisms. No recent trials have investigated prophylaxis for **transurethral resection of bladder tumors**; however, evidence from transurethral resection of the prostate procedures would suggest that prophylaxis would reduce bacteriuria in these procedures.

Patients who are known preoperatively to have UTIs should have the infections eradicated before the procedure is started; hence, in these patients, preoperative antimicrobial agents are therapeutic and not prophylactic. Failure to eradicate bacteriuria results in bacteremia in 50% of patients (Morris et al, 1976).

Diagnostic and therapeutic upper tract studies that are performed with pressurized irrigants may induce urothelial injury. Prophylaxis with antimicrobial agents that cover uropathogens is indicated.

Endoscopic Procedures: Upper Urinary Tract

Ureteroscopy

Diagnostic and therapeutic upper tract endoscopic procedures have an increased risk of localized infections compared with simple diagnostic cystoscopy because of several factors, including increased

trauma to the mucosa, increased duration and/or degree of difficulty of most ureteroscopic procedures, increased pressure of irrigants, and (when applicable) manipulation or resection of infected material. The use of antimicrobial prophylaxis is supported by a randomized trial by Knopf and colleagues (2003) in which prophylactic fluoroquinolone administration significantly reduced post-procedure UTIs in a healthy population of individuals with ureteral stones and uninfected preoperative urine. If an infection or infectious material is suspected, culture and a full treatment course of an appropriate antimicrobial are recommended before the procedure. Some urologists advocate for medical diuresis during the procedure with furosemide.

Percutaneous Procedures

Percutaneous renal surgery is commonly performed for large renal stones, ureteropelvic junction obstruction, and transitional cell carcinoma surveillance. Pyrexia and bacteremia occur frequently and likely stem from a combination of renal parenchymal injury, pressurized irrigation, and, in some cases, manipulation of infectious stones. Several studies demonstrated a relationship between the risk of postoperative infectious complications (including bacteriuria and sepsis) and the duration of the procedure and amount of irrigant used (Dogan et al, 2002). If preoperative urine cultures are positive, treatment of the infection should occur before surgery. Conversely, if preoperative cultures are negative, antimicrobial prophylaxis covering common urinary pathogens should be instituted (Wolf et al, 2008) (see Table 12-7).

Open and Laparoscopic Surgery

Open surgical procedures can be classified as clean, clean contaminated, contaminated, and dirty (Table 12-8). Antimicrobial prophylaxis is indicated for clean contaminated and contaminated wounds, whereas antimicrobial treatment with an appropriate agent should be instituted for dirty-infected wounds. To date, no large studies have evaluated the risk of surgical site infections for different laparoscopic urologic procedures. However, data in the general surgery literature suggest that the laparoscopic approach lowers the risk of surgical site infections (Kluytmans, 1997). Clean surgeries in urology include radical nephrectomy if the urinary tract is not entered. All urologic procedures in which the urinary tract

is opened electively are considered clean contaminated procedures, whereas entry into an infected urinary tract is considered a contaminated procedure and carries a higher rate of surgical site infection (Cruse, 1992). Antimicrobial agents should be active against the most likely infecting organism and should be administered within 1 hour of the procedure and discontinued 24 hours after because several studies have failed to demonstrate beneficial effects of long courses of prophylaxis (Conte et al, 1972; Goldmann et al, 1977). In the United States, first-generation cephalosporins are commonly used for prophylaxis of clean contaminated procedures because they have low incidences of allergic reactions, long half-lives, and low cost. For patients with a β -lactam allergy, the 2004 National Surgical Infection Prevention Project (NSIPP) guidelines recommend either vancomycin or clindamycin. Prophylaxis for urinary reconstruction with intestine requires increased anaerobic coverage, and thus use of second-generation cephalosporins is recommended (Bratzler and Houck, 2004). When use of the colon or appendix is anticipated for urologic reconstruction, the 2004 NSIPP recommendations include orally administered antimicrobial bowel preparation (neomycin plus erythromycin or neomycin plus metronidazole) 18 to 24 hours before surgery and parenteral cefotetan or cefoxitin 30 to 60 minutes before incision (Bratzler and Houck, 2004). Recommendations for patients with a β -lactam allergy include clindamycin plus gentamicin, aztreonam, or ciprofloxacin. Dirty wounds in urology include all abscesses and traumatic perforation of the genitourinary tract. Treatment of a dirty wound should begin with broad coverage of anticipated organisms and intraoperative wound cultures. Subsequent therapy and treatment duration depends on the sensitivities of the cultured organism.

Special Considerations

Patients with Risk of Endocarditis

The risk of infectious endocarditis (IE) after urologic procedures is low. Previous guidelines from the American Heart Association (AHA) had recommended routine prophylaxis, but the current recommendation is that the use of prophylactic antibiotics solely to prevent IE is **not recommended** (Wilson et al, 2007). However, these guidelines do acknowledge that instrumentation of the GU tract may result in transient enterococcal bacteremia. The evidence supporting this claim is anecdotal, and no data exist to demonstrate either a conclusive link between this bacteremia and IE or that administration of antimicrobial prophylaxis prevents IE. Regardless, the guidelines do state that for patients with certain concomitant conditions (prosthetic cardiac valve, previous IE, congenital heart disease, cardiac transplantation) and an active infection or colonization who are to undergo GU tract manipulation, including elective cystoscopy, antibiotic therapy to sterilize the urine may be reasonable (Class IIb evidence). Amoxicillin or ampicillin is suggested as a first-line agent for enterococci, vancomycin for those who cannot tolerate ampicillin, or culture-directed agents as possible (Wilson et al, 2007).

Patients with Indwelling Orthopedic Hardware

Bacterial seeding of implanted orthopedic hardware is a rare but morbid event. A joint commission of the American Urological Association (AUA), the American Academy of Orthopaedic Surgeons (AAOS), and infectious disease specialists convened in 2003 and released an advisory statement on antimicrobial prophylaxis for urologic patients with total joint replacement (American Urological Association and American Academy of Orthopaedic Surgeons, 2003) (Table 12-9). In general, antimicrobial prophylaxis for urologic patients with total joint replacements, pins, plates, or screws is not indicated. Prophylaxis is advised for individuals at higher risk of seeding a prosthetic joint, including those with recently inserted implants (within 2 years) and/or host risk factors as delineated earlier. Prophylaxis on the basis of potential seeding of a prosthetic joint should be instituted for procedures

TABLE 12-8 Surgical Wound Classification

TERM	DESCRIPTION
Clean	Uninfected wound without inflammation or entry into the genital, urinary, or alimentary tract Primary wound closure \pm closed drainage
Clean contaminated	Uninfected wound with controlled entry into the genital, urinary, or alimentary tract Primary wound closure \pm closed drainage
Contaminated	Uninfected wound with major break in sterile technique (gross spillage from gastrointestinal tract or nonpurulent inflammation) Open fresh accidental wounds
Dirty infected	Wound with preexisting clinical infection or perforated viscera Old traumatic wounds with devitalized tissue

Modified from Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250-78; quiz 279-80.

TABLE 12-9 Antimicrobial Regimens for Patients with Indwelling Orthopedic Hardware

PATIENT TYPE	ANTIMICROBIAL RECOMMENDATION
Total joint inserted >2 yr ago, pins, plates, screws + no host risk factors	Not recommended empirically
Total joint inserted <2 yr ago or aberrant host factor(s)	Oral quinolone or ampicillin, 2 g IV + gentamicin, 1.5 mg/kg IV, 30-60 min before procedure Substitute vancomycin, 1 g IV, over 1-2 hr before procedure if ampicillin allergy

From American Urological Association and American Academy of Orthopaedic Surgeons. Antibiotic prophylaxis for urological patients with total joint replacements. *J Urol* 2003;169:1796-7.

including stone manipulation, transmural incision of the urinary tract, upper tract endoscopic procedures, procedures involving bowel segments, and transrectal prostate biopsy. Additionally, patients with recent prosthetic joints or compromised host factors and urinary diversions, indwelling stents or catheters, a recent history of urinary retention, or UTIs should receive antimicrobial prophylaxis before urinary tract procedures. The AUA Advisory Statement recommends for these patients either an oral quinolone or ampicillin, 2 g intravenous (IV) (vancomycin, 1 g IV over 1 to 2 hours for ampicillin-allergic patients), and gentamicin, 1.5 mg/kg IV, 30 to 60 minutes before the procedure.

KEY POINTS: ANTIMICROBIAL PROPHYLAXIS FOR COMMON UROLOGIC PROCEDURES

- Antimicrobial prophylaxis entails treatment with an antimicrobial agent before and for a limited time after a procedure to prevent local or systemic postprocedural infections.
- The type of procedure and competency of the host defenses determine the need for antimicrobial prophylaxis.
- Special considerations for antimicrobial prophylaxis include patients undergoing TRUSP, those with a risk of endocarditis, and patients with indwelling orthopedic hardware.

BLADDER INFECTIONS

Uncomplicated Cystitis

Most cases of uncomplicated cystitis occur in women. Each year, approximately 10% of women report having had a UTI and more than 50% of all women have at least one such infection in their lifetime (Foxman et al, 2000). Uncomplicated cystitis occasionally occurs in prepubertal girls, but it increases greatly in incidence in late adolescence and during the second and fourth decades of life. Twenty-five to 30 percent of women 20 to 40 years of age have a history of UTIs (Kunin, 1987). Although it is much less common, young men may also experience acute cystitis without underlying structural or functional abnormalities of the urinary tract (Krieger et al, 1993). Risk factors (Box 12-6) include sexual intercourse and use of spermicides (Hooton et al, 1996; Foxman, 2002; Handley et al, 2002). Sexual transmission of uropathogens has been suggested by demonstrating identical *E. coli* in the bowel and urinary flora of sex partners (Johnson and Stamm, 1989).

BOX 12-6 Risk Factors for Urinary Tract Infections

REDUCED URINE FLOW

Outflow obstruction, prostatic hyperplasia, prostatic carcinoma, urethral stricture, foreign body (calculus)
Neurogenic bladder
Inadequate fluid uptake (dehydration)

PROMOTE COLONIZATION

Sexual activity—increased inoculation
Spermicide—increased binding
Estrogen depletion—increased binding
Antimicrobial agents—decreased indigenous flora

FACILITATE ASCENT

Catheterization
Urinary incontinence
Fecal incontinence
Residual urine with ischemia of bladder wall

Clinical Presentation

The presenting symptoms of cystitis are variable but usually include dysuria, frequency, and/or urgency (Fig. 12-13). Suprapubic pain, hematuria, or foul-smelling urine may develop. The probability of cystitis in a woman with these symptoms alone or in combination is 50% to 90%, respectively (Bent et al, 2002). When a woman who previously has had cystitis has symptoms suggesting a recurrence, the probability that an infection is present is about 90% (Gupta et al, 2001). By definition, acute cystitis is a superficial infection of the bladder mucosa, so fever, chills, and other signs of dissemination are not present. Some patients may experience suprapubic tenderness, but most have no diagnostic physical findings. In women, physical examination should include the possibility of vaginitis, herpes, and urethral pathology, such as a diverticulum.

A remarkably narrow spectrum of etiologic agents with highly predictable profiles of antimicrobial susceptibility causes infections in young women with acute uncomplicated cystitis. *E. coli* is the causative organism in 75% to 90% of cases of acute cystitis in young women (Latham et al, 1983; Ronald, 2002). *S. saprophyticus*, a commensal organism of the skin, is the second most common cause of acute cystitis in young women, accounting for 10% to 20% of these infections (Jordan et al, 1980). Other organisms less commonly involved include *Klebsiella* and *Proteus* species and *Enterococcus*. In men, *E. coli* and other Enterobacteriaceae are the most commonly identified organisms.

Laboratory Diagnosis

The presumptive laboratory diagnosis of acute cystitis is based on microscopic urinalysis, which indicates microscopic pyuria, bacteriuria, and occasionally hematuria. Indirect dipstick tests for bacteria (nitrite) or pyuria (leukocyte esterase) may also be informative and more convenient but are less sensitive than microscopic examination of the urine. Dipsticks are most accurate when the presence of either nitrite or leukocyte esterase is considered a positive result. Urine culture remains the definitive test; and in symptomatic patients, the presence of 10^2 cfu/mL or more of urine usually indicates infection (Stamm et al, 1982b). However, as previously discussed, different thresholds are needed based on different clinical situations.

However, routine urine cultures are often not necessary. It is generally more cost-effective to manage many patients who have symptoms and urinalysis findings characteristic of uncomplicated cystitis without an initial urine culture because treatment decisions

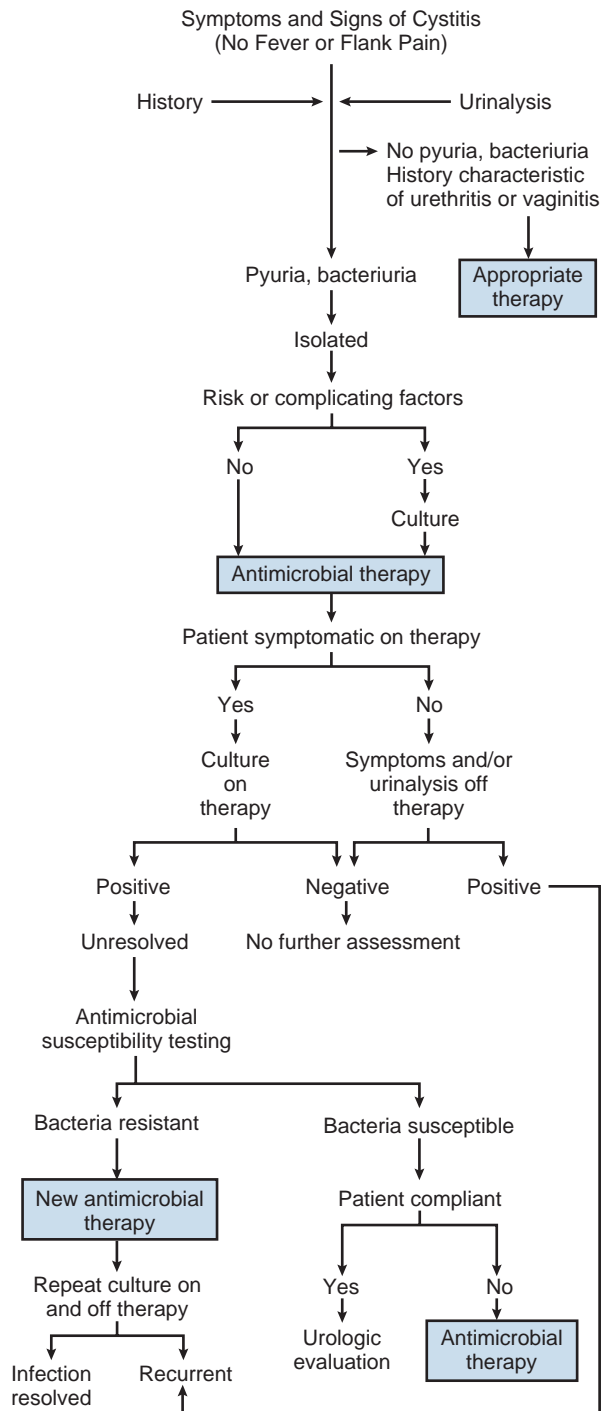


Figure 12-13. Management of acute cystitis.

are usually made and therapy is often completed before culture results are known (Komaroff, 1986). This position was supported by a cost-effectiveness study (Carlson and Mulley, 1985) in which it was estimated that the routine use of pretherapeutic urine cultures for lower UTI increases costs by 40% but decreases the overall duration of symptoms by only 10%.

Thus, in women with recent onset of symptoms and signs suggesting acute cystitis and in whom factors associated with upper tract or complicated infection are absent, a urinalysis that is positive for pyuria, bacteriuria, or hematuria, or a combination should provide sufficient documentation of UTI, and a urine culture may be omitted (McIsaac et al, 2002). A urine culture should be obtained for patients in whom symptoms and urine examination findings leave the diagnosis of cystitis in doubt. Pretherapeutic cultures and susceptibility tests are also essential

in the management of patients with recent antimicrobial therapy or UTI. In these situations, various pathogens may be present and antimicrobial therapy is less predictable and must be tailored to the individual organism (Stamm, 1986).

Differential Diagnosis

Cystitis must be differentiated from other inflammatory infectious conditions in which dysuria may be the most prominent symptom, including vaginitis, urethral infections caused by sexually transmitted pathogens, and miscellaneous noninflammatory causes of urethral discomfort (Komaroff, 1984). Characteristic features of the history, physical examination, and voided urine or other specimens allow patients with dysuria to be assigned to one of these diagnostic categories. **Vaginitis** is characterized by irritative voiding associated with vaginal irritation and is subacute in onset. A history of vaginal discharge or odor and multiple or new sexual partners is common. Frequency, urgency, hematuria, and suprapubic pain are not present. Physical examination reveals a vaginal discharge, and examination of vaginal fluid demonstrates inflammatory cells. Differential diagnosis includes herpes simplex virus, gonorrhea, *Chlamydia*, trichomoniasis, yeast, and bacterial vaginosis. **Urethritis** causes dysuria that is usually subacute in onset and is associated with a history of discharge and new or multiple sexual partners. Frequency and urgency of urination may be present but are less pronounced than in patients with cystitis, and fever and chills are absent. Urethral discharge with inflammatory cells or initial pyuria in the male is characteristic. The common causes of urethritis include *Neisseria gonorrhoeae*, *Chlamydia*, herpes simplex virus, and trichomoniasis. Appropriate cultures and immunologic tests are indicated. **Urethral injury** associated with sexual intercourse, chemical irritants, or allergy may also cause dysuria. A history of trauma or exposure to irritants and a lack of discharge or pyuria are characteristic.

Management

Antimicrobial Selection. Oral antimicrobial agents for treatment of acute uncomplicated cystitis are listed in Table 12-10.

Nitrofurantoin has maintained an excellent level of activity over 4 decades and is well tolerated, but it is more expensive than TMP-SMX and is considerably less active against aerobic gram-negative rods other than *E. coli*. Furthermore, it is usually prescribed for 5 days and may cause gastrointestinal upset. It is not associated with plasmid-mediated resistance, however, so it is an excellent choice for patients with recent exposure to most other antimicrobial agents. The high in vitro resistance to ampicillin and sulfonamide and the high cost of amoxicillin/clavulanate and the cephalosporins limit their usefulness.

TMP and TMP-SMX are effective and inexpensive agents for empirical therapy, resulting in bacteriologic cure (i.e., eradication of the pathogen from the urine) within 7 days after the start of treatment in approximately 94% of women (Warren et al, 1999). They are recommended in areas where the prevalence of resistance to these drugs among *E. coli* strains causing cystitis is less than 20% (Gupta et al, 2011). The probability of resistant strains can be predicted in part from the history of recent antimicrobial usage. Women who have taken TMP-SMX recently are approximately 16 times as likely to be infected with an isolate resistant to this agent compared with women who have not taken the antimicrobial agent recently. In addition, those who have taken any other antimicrobial agent are more than twice as likely to be infected with a resistant isolate (Brown et al, 2002). With a 30% rate of resistance to TMP-SMX, the bacteriologic eradication rate is predicted to be 80% and the clinical cure rate is predicted to be 85% (Gupta et al, 2001). When used alone, TMP is as efficacious as TMP-SMX and is associated with fewer side effects, presumably because of the absence of the sulfa component (Harbord and Gruneberg, 1981). It can be prescribed to patients who are allergic to sulfa. However, TMP can cause hypersensitivity and rashes that may be erroneously attributed to sulfa (Alonso et al, 1992).

TABLE 12-10 Treatment Regimens for Acute Cystitis

CIRCUMSTANCES	ROUTE	DRUG	DOSAGE (mg)	FREQUENCY PER DOSE	DURATION (DAYS)	COST PER DAY
WOMEN						
Healthy	Oral	Nitrofurantoin macrocrystals	100 mg	bid	5	\$3.24
		TMP-SMX	1 double-strength tablet (160-800 mg)	bid	3	\$0.26
		Trimethoprim	100 mg	bid	3	\$1.32
		Fosfomycin trometamol	3 g	Single dose	—	\$47.99
		Pivmecillinam	400 mg	bid	3-7	Not available in the U.S.
		Ciprofloxacin	250 mg†	bid	3	\$0.50
		Levofloxacin	250 mg†	qd	3	\$5.07
Symptoms for >7 days, recent urinary tract infection, age >65 yr, diabetes, diaphragm use		TMP-SMX or fluoroquinolone	As above	As above	7	As above
Pregnancy	Oral	Amoxicillin	As above	As above	3-7	\$0.68
		Cephalexin	As above	As above		\$1.76
		Nitrofurantoin macrocrystals	As above	As above		As above
		TMP-SMX*	As above	As above		As above
MEN						
Healthy and age <50 yr	Oral	TMP-SMX	As above	As above	7	As above
		Ciprofloxacin	500 mg	bid	7	As above
		Levofloxacin	500 mg	qd	7	As above

*Use of TMP-SMX during the first trimester of pregnancy is cautioned because there is early potential for teratogenicity and late potential for kernicterus after delivery.

†Fluoroquinolones should be reserved for important infections other than acute cystitis except in select situations.

Modified from Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211-72; and Gupta K, Hooton TN, Naber KG, et al: International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.

Fosfomycin trometamol (3 g in a single dose) is an appropriate choice for therapy where it is available because of minimal resistance and propensity for collateral damage, but it may have inferior efficacy compared with standard short-course regimens according to data submitted to the U.S. Food and Drug Administration (FDA) and summarized in the Medical Letter (A-I) ([Fosfomycin for urinary tract infections, 1997; Gupta et al, 2011](#)).

Pivmecillinam (400 mg twice daily for 3 to 7 days) is an appropriate choice for therapy in regions where it is available (availability limited to some European countries; not licensed and/or available for use in North America) because of minimal resistance and propensity for collateral damage, but it may have inferior efficacy compared with other available therapies (A-I) ([Gupta et al, 2011](#)).

The fluoroquinolones offer excellent activity, and are well tolerated. Resistance to the fluoroquinolones remains below 5% in most places ([Fihn et al, 1988](#)); however, it is increasing in certain areas. Twice-daily and once-daily extended-release fluoroquinolones are equally effective ([Henry et al, 2002](#)). They have a high propensity for collateral damage (i.e., ecological adverse effects, such as drug resistance) and should be reserved for important infections other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis ([Gupta et al, 2011](#)). Their use for uncomplicated cystitis should be limited to patients who are allergic to TMP-SMX, to patients with previous exposure to antimicrobial agents causing bacterial resistance, and to areas where the prevalence of resistance to TMP or TMP-SMX is 20% or greater ([Warren et al, 1999; Hooton et al, 2004](#)).

The effects of an antimicrobial agent on the vaginal flora are also important in recurrence of bacteriuria ([Fihn et al, 1988](#)). The concentrations of TMP and the fluoroquinolones that have been studied in vaginal secretions are high, eradicating *E. coli* but minimally altering normal anaerobic and microaerophilic vaginal flora ([Hooton and Stamm, 1991](#)). Single-dose regimens using these drugs are less effective than multiple-day regimens in this regard ([Fihn et al, 1988](#)), which probably explains why there are more early recurrent infections after single-dose therapy with these drugs. Nitrofurantoin and β -lactam drugs are generally not effective in eliminating *E. coli* from the vagina.

Duration of Therapy. Three-day therapy is the preferred regimen for uncomplicated cystitis in women ([Norrby, 1990; Warren et al, 1999](#)). In an excellent review of more than 300 separate clinical trials of single-dose, 3-day, or 7-day treatment with TMP, TMP-SMX, fluoroquinolones, and β -lactam antimicrobial therapies, it was concluded that, irrespective of the antimicrobial used, 3-day therapy is more effective than single-dose therapy. Three-day therapy with TMP-SMX, TMP, amoxicillin, or cefaclor has been associated with cure rates similar to longer courses of therapy and an incidence of adverse effects about as low as that seen with single-dose therapy and lower than seen with longer courses of therapy ([Charlton et al, 1976; Kunin, 1985; McCue, 1986; Warren et al, 1999](#)). Because 7-day therapy often causes more adverse effects, it is recommended only for women with symptoms of 1 week or more, men, and individuals with possible complicating factors. Other options include nitrofurantoin, perhaps as 7-day therapy, and fosfomycin single-dose therapy; each of these requires further study. β -Lactams as a

group are less effective in treatment of cystitis than TMP, TMP-SMX, and the fluoroquinolones.

Seven-day therapy is the preferred regimen in uncomplicated cystitis in men.

Cost of Therapy. The cost of treating a UTI involves not only the initial evaluation and cost of the drug but also what occurs subsequently. The most important prediction of high cost-effectiveness is high efficacy against the most common urinary pathogen, *E. coli*. The lower the effectiveness against this bacterium, the greater the number of revisits, cases of progression to pyelonephritis, and follow-up costs. Antimicrobial cost is a poor prediction of cost-effectiveness, as illustrated by the finding that the most expensive and least expensive drugs, the fluoroquinolones and TMP-SMX, are approximately equally cost-effective (Rosenberg, 1999). Both of these drugs are more cost-effective than nitrofurantoin and amoxicillin.

Follow-Up

Approximately 90% of women are asymptomatic within 72 hours after initiating antimicrobial therapy (Fihn et al, 1988). A follow-up visit or culture is not required in young women who are asymptomatic after therapy. A follow-up visit, urinalysis, and urine culture are recommended in older women or those with potential risk factors and in men. Urologic evaluation is unnecessary in women and is usually unnecessary in young men who respond to therapy (Lipsky, 1989; Abarbanel et al, 2003). However, UTIs in most men should be considered complicated until proven otherwise. Andrews and associates (2002) showed that approximately 50% of men with UTIs have a significant abnormality. Furthermore, if a patient does not respond to therapy, appropriate microbiologic urologic evaluations should be undertaken for the causes of unresolved and complicated UTIs.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is a microbiologic diagnosis based on the isolation of a specified quantitative count of bacteria in a properly collected specimen of urine from a patient who is without symptoms or signs referable to UTI. In healthy individuals, the absence of symptoms is clear cut, but, for example, in catheterized or neurologically compromised patients, it may be difficult to discern whether the UTI is truly asymptomatic. Kass (1962) originally proposed that for asymptomatic women two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts of 10^5 cfu/mL is consistent with asymptomatic bacteriuria. In men, a single clean-catch voided specimen with similar counts is adequate. A single catheterized urine specimen with a solitary isolate with a quantitative count of 10^2 cfu/mL identifies bacteriuria in women or men (Nicolle et al, 2005). The prevalence of pyuria with asymptomatic bacteriuria ranges from approximately 30% in young women (Hooton et al, 2000) to 100% in catheterized patients. In addition, many coexisting factors, such as stones, can incite inflammation in these patients, and therefore the presence or absence of pyuria is not sufficient to diagnose bacteriuria nor does it differentiate symptomatic from asymptomatic patients or provide indication for antimicrobial treatment (Nicolle et al, 2005).

The prevalence of asymptomatic bacteriuria varies widely and depends on the age, sex, and the presence of other genitourinary abnormalities (Table 12-11). *E. coli* is the most common isolate among patients with bacteriuria, and it contains fewer virulence characteristics than isolates from patients with symptomatic infections (Svanborg and Godaly, 1997). Other Enterobacteriaceae (e.g., *P. mirabilis*) and gram-positive uropathogens, including group B streptococci and coagulase-negative staphylococci, become more prevalent in concert with increased underlying abnormalities. For patients who are institutionalized and/or with indwelling urologic devices, *P. aeruginosa*, *Proteus*, and other highly resistant organisms are more prevalent.

TABLE 12-11 Prevalence of Asymptomatic Bacteriuria in Selected Populations

POPULATION	PREVALENCE (%)	REFERENCE
Healthy, premenopausal women	1.0-5.0	Nicolle, 2003
Pregnant women	1.9-9.5	Nicolle, 2003
Postmenopausal women aged 50-70 years	2.8-8.6	Nicolle, 2003
Diabetic patients		
Women	9.0-27	Zhanel, 1991
Men	0.7-11	Zhanel, 1991
Elderly persons in the community		
Women	10.8-16	Nicolle, 2003
Men	3.6-19	Nicolle, 2003
Elderly persons in a long-term care facility		
Women	25-50	Nicolle, 1997
Men	14-50	Nicolle, 1997
Patients with spinal cord injuries		
Intermittent catheter use	23-89	Bakke and Digranes, 1991
Sphincterotomy and condom catheter in place	57	Waites et al, 1993b
Patients undergoing hemodialysis	28	Chaudhry, 1993
Patients with indwelling catheter use		
Short-term	9-23	Stamm, 1991
Long-term	100	Warren, 1982

From Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005;40:643-54.

Management of asymptomatic bacteriuria is determined by the population and their risk for adverse outcome, which can be prevented with antimicrobial treatment of asymptomatic bacteriuria (Nicolle et al, 2005) (Table 12-12). These recommendations are based on the observation that in adult populations asymptomatic bacteriuria has not been shown to be harmful. Furthermore, although persons with bacteriuria are at increased risk of symptomatic urinary tract infections, treatment of asymptomatic bacteriuria does not decrease the frequency of symptomatic infections or improve other outcomes. Thus, in populations other than those for whom treatment has been documented to be beneficial (e.g., pregnant women and patients undergoing urologic interventions), screening for or treatment of asymptomatic bacteriuria is not appropriate and should be discouraged (Nicolle et al, 2005).

Complicated Cystitis

Complicated UTIs are those that occur in a patient with a compromised urinary tract or that are caused by a very resistant pathogen (Box 12-7). These complicating factors may be readily apparent

from the severity of the presenting illness or the past medical history. However, they may not be obvious at first and may only become evident from subsequent failure of the patient to respond to appropriate therapy (see later discussion on [unresolved](#) or [recurrent UTIs](#)).

The clinical spectrum ranges from mild cystitis to life-threatening kidney infections and urosepsis (kidney infections and urosepsis are discussed subsequently). These infections can be caused by a broad range of bacteria with resistance to multiple

antimicrobial agents. Therefore urine cultures are mandatory to identify the bacteria and its antimicrobial susceptibility.

Because of the wide range of host conditions and pathogens and a lack of adequate controlled trials, guidelines for empirical therapy are limited. For patients with mild to moderate illness who can be treated as an outpatient with oral therapy, the fluoroquinolones provide a broad spectrum of activity with excellent urine and tissue levels and safety. If the susceptibility pattern of the pathogen is known, TMP-SMX may be effective ([Table 12-13](#)).

For patients requiring hospitalization, IV antimicrobials should be administered based on the susceptibility patterns of the known uropathogens at that institution.

Because therapy will be compromised without addressing complicating factors, every effort should be made to correct any underlying urinary tract abnormalities and treat host factors that exacerbate the infection.

Therapy is usually continued for 10 to 14 days and switched from parenteral to oral therapy when the patient is afebrile and clinically stable. Repeat urine cultures should be performed if the patient fails to respond to therapy.

TABLE 12-12 Screening for and Treatment of Asymptomatic Bacteriuria

Premenopausal nonpregnant women	Not recommended
Pregnant women	Recommended
Diabetic women	Not recommended
Older persons residing in the community	Not recommended
Elderly institutionalized subjects	Not recommended
Subjects with spinal cord injuries	Not recommended
Patients with indwelling urethral catheters	Not recommended
<i>Note:</i> Antimicrobial treatment of asymptomatic women with catheter-associated bacteriuria that persists 48 hours after catheter removal may be considered.	
Urologic interventions	Recommended
Immunocompromised patients and transplant patients	Not recommended

From Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005;40:643–54.

BOX 12-7 Complicating Host Factors

Functional/structural abnormalities of urinary tract
Recent urinary tract instrumentation
Recent antimicrobial agent use
Diabetes mellitus
Immunosuppression
Pregnancy
Hospital-acquired infection

Unresolved UTIs

Clinical Presentation

Unresolved infection indicates that initial therapy has been inadequate in eliminating symptoms and/or bacterial growth in the urinary tract. If the symptoms of UTI do not resolve by the end of treatment or if symptoms recur shortly after therapy, urinalysis and urine culture with susceptibility testing should be obtained. If the patient's symptoms are significant, empirical therapy with a fluoroquinolone is appropriate, pending results of the culture and susceptibility testing.

The causes of unresolved bacteriuria during antimicrobial therapy are shown in [Box 12-8](#). Most commonly, the bacteria are resistant to the antimicrobial agent selected to treat the infection. Typically, the patient has received the antimicrobial therapy in the recent past and developed bowel colonization with resistant bacteria. β -lactams, tetracycline, and sulfonamides are notorious for causing plasmid-mediated R factors that simultaneously carry resistance to multiple antimicrobial agents. The second most common cause is development of resistance in a previously susceptible population of bacteria during the course of treatment of UTIs. This problem occurs in approximately 5% of the patients receiving antimicrobial therapy. It is easy to recognize clinically because the culture on therapy shows that the previous susceptible population has been replaced by resistant bacteria of the same species. It can be shown that resistant organisms were actually present

TABLE 12-13 Treatment of Complicated Urinary Tract Infections

COMMON PATHOGENS	MITIGATING CIRCUMSTANCES	RECOMMENDED EMPIRICAL TREATMENT
<i>E. coli</i> , <i>Proteus</i> species, <i>Klebsiella</i> species, <i>Pseudomonas</i> species,	Mild-to-moderate illness, no nausea or vomiting—outpatient therapy	Oral* ciprofloxacin or ofloxacin for 10–14 days
<i>Serratia</i> species, enterococci, staphylococci	Severe illness or possible urosepsis—hospitalization required	Parenteral† ampicillin and gentamicin, ciprofloxacin, levofloxacin, ceftriaxone, aztreonam, ticarcillin-clavulanate or imipenem-cilastatin until fever gone; then oral* trimethoprim-sulfamethoxazole, norfloxacin, ciprofloxacin, or levofloxacin for 14–21 days

*Oral regimens for pyelonephritis and complicated urinary tract infection: trimethoprim-sulfamethoxazole, 160 and 800 mg q12h; ciprofloxacin, 500 mg q12h; levofloxacin, 500 mg/day.

†Parenteral regimens: ciprofloxacin, 400 mg q12h; levofloxacin, 250 mg/day; gentamicin, 1 mg/kg q8h; ceftriaxone, 1 to 2 g/day; ampicillin, 1 g q6h; imipenem-cilastatin, 250 to 500 mg q6–8h; ticarcillin-clavulanate, 3.1 g q6h; and aztreonam, 1 g q8–12h.

Modified from Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med* 1993;329:1328–34. Copyright 1993, Massachusetts Medical Society. All rights reserved.

BOX 12-8 Causes of Unresolved Bacteriuria, in Descending Order of Importance

Bacterial resistance to the drug selected for treatment
 Development of resistance from initially susceptible bacteria
 Bacteriuria caused by two different bacterial species with mutually exclusive susceptibilities
 Rapid reinfection with a new, resistant species during initial therapy for the original susceptible organism
 Azotemia
 Papillary necrosis from analgesic abuse
 Giant staghorn calculi in which the “critical mass” of susceptible bacteria is too great for antimicrobial inhibition
 Self-inflicted infections or deception in taking antimicrobial drugs (a variant of Munchausen syndrome)

before contact with the initial antimicrobial agent, but they were present in such low numbers that it was impossible to detect by *in vitro* susceptibility studies before therapy. When the antimicrobial concentration in the urine is insufficient to kill all the bacteria present, the more resistant forms will emerge. This characteristically is seen in patients who are underdosed or who are poorly compliant and hence have inadequate dose regimens. The third cause is the presence of an unsuspected, second pathogen that was present initially and is resistant to the antimicrobial therapy chosen. Treatment of the dominant organism unmasks the presence of the second strain. The fourth cause is rapid reintroduction of a new resistant species while the patient is undergoing initial therapy. Rapid reinfection that mimics unresolved bacteriuria should alert the clinician to the possibility of an enterovesical fistula.

If the culture obtained on therapy shows that the initial species is still present and susceptible to the antimicrobial chosen to treat the infection, the unresolved infection must be caused by either inability to deliver an adequate concentration of antimicrobial agents into the urinary tract or an excessive number of bacteria that “override” the antimicrobial activity. In patients with azotemia, a determination of urinary antimicrobial concentrations usually shows that the level of the drug is below the minimal inhibitory concentration of the infecting organism.

In patients with papillary necrosis, severe defects in the medullary concentrating ability dilute the antimicrobial agent. A large mass of bacteria within the urinary tract is most commonly associated with a giant staghorn calculus. Even though adequate urinary levels of bactericidal drugs are present, the concentration is inadequate to sterilize the urine. This occurs because even susceptible bacteria cannot be inhibited once they reach a certain critical density, particularly if attached to a foreign body.

The last cause of unresolved bacteriuria occurs in those patients who have variants of Munchausen syndrome. These patients secretly inoculate their bladders with uropathogens or omit their oral antimicrobial agents while steadfastly asserting that they never miss a dose. The patient with Munchausen syndrome presents with an inconsistent clinical history and invariably a normal urinary tract on urologic imaging. Careful bacteriologic observations usually indicate the implausibility of the clinical picture.

Laboratory Diagnosis

Urinalysis and urine culture are mandatory to determine the cause of unresolved bacteriuria. The first four causes that are associated with resistant bacteria require no further evaluation. However, if reculture shows that the bacteria are sensitive to the antimicrobial agent the patient is taking, renal function and radiologic evaluation should be performed to identify renal or urinary tract abnormalities.

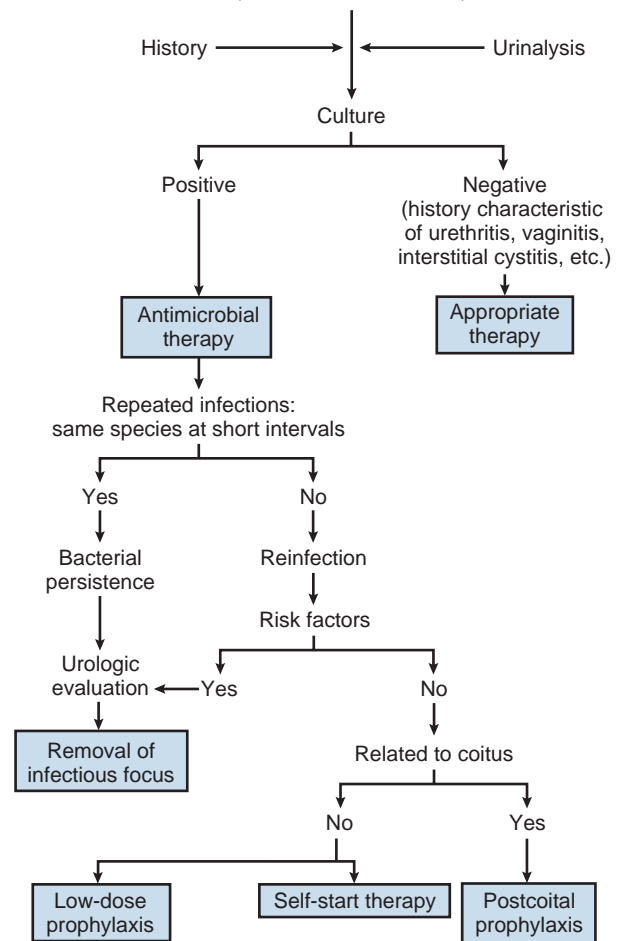
Symptoms and Signs of Recurrent Urinary Tract Infection (No Fever or Flank Pain)

Figure 12-14. Management of recurrent urinary tract infection.

Management

Initial empirical antimicrobial selection should be based on the assumption that the bacteria are resistant. Therefore an antimicrobial agent different from the original agent should be selected. Fluoroquinolones offer excellent coverage in most cases and should be given for 7 days. When the bacterial susceptibilities are available, adjustments can be made if necessary. Urine cultures should be performed during and 7 days after therapy to ensure microbiologic efficacy.

Recurrent UTIs

Recurrent UTIs are caused by either reemergence of bacteria from a site within the urinary tract (bacterial persistence) or new infections from bacteria outside the urinary tract (reinfection). Clinical identification of these two types of recurrence is based on the pattern of recurrent infections (Fig. 12-14). Bacterial persistence must be caused by the same organism in each instance, and infections that occur at close intervals are characteristic. Conversely, reinfections usually occur at varying and sometimes long intervals and often are caused by different species. The distinction between bacterial persistence and reinfection is important in management because patients with bacterial persistence can usually be cured of the recurrent infections by identification and surgical removal or correction of the focus of infection. Conversely, women with reinfection usually do not have an alterable urologic abnormality and require long-term medical management. Reinfections in men are uncommon and may be associated

with an underlying abnormality, such as urethral stricture; therefore, at a minimum, endoscopic evaluation is indicated.

Bacterial Persistence

Once the bacteriuria has resolved (i.e., the urine shows no growth for several days after the antimicrobial agent has been stopped), recurrence with the same organism can arise from a site *within* the urinary tract that was excluded from the high urine concentrations of the antimicrobial agent. The 12 correctable urologic abnormalities that cause bacteria to persist within the urinary tract between episodes of recurrent bacteriuria are listed in **Box 12-4**. The relationship of these abnormalities to bacterial persistence, as well as the documentation that surgical excision removes the infection as a source of recurrent bacteriuria, is presented elsewhere in detail (**Stamey, 1980**). Once the urologist recognizes that the cause of the patient's recurrent bacteriuria is bacterial persistence, **Box 12-4** should serve as a checklist for known, correctable causes. Some of the causes are subtle, and many require cystoscopic localization of the infection with ureteral catheters to accurately define the focus of bacterial persistence.

Although patients with bacterial persistence are relatively uncommon, their identification is important because they represent the only surgically curable cause of recurrent UTIs. A systematic radiologic and endoscopic evaluation of the urinary tract is mandatory. CT and cystoscopy provide the initial screening. Retrograde urography may be required in selected patients to delineate abnormalities, such as diverticulum or nonrefluxing ureteral stump.

Urea-Splitting Bacteria That Cause Struvite Renal Stones. The infection that ultimately leads to an infection stone commonly begins inconspicuously as inadequately treated cystitis. Most patients with *P. mirabilis* cystitis do not form struvite stones. But struvite stones form in those patients who have a protracted infection with *P. mirabilis*, an infection that is often asymptomatic or minimally symptomatic. *P. mirabilis* causes intense alkalization of the urine with precipitation of calcium, magnesium, ammonium, and phosphate salts and the subsequent formation of branched struvite renal stones. Bacteriuria in most of these patients with struvite stones recurs almost immediately on stopping antimicrobial therapy, usually within 5 to 7 days. The bacteriologic consequences are substantial because the bacteria persist inside these struvite stones even when the urine shows no growth. Indeed, struvite infection stones, together with the occasional oxalate or apatite stone that becomes secondarily colonized, constitute the major cause of bacterial persistence in women in the absence of azotemia.

Underlying urinary tract abnormalities are not a prerequisite for this type of infection. However, patients with indwelling catheters, urinary diversions, or other urinary tract abnormalities are particularly susceptible to these infections. Urea-splitting organisms, such as *P. mirabilis*, cause infection stones that are relatively radiolucent. If such a stone is suspected, plain film tomograms or CT scans without contrast medium enhancement should be obtained (**Greenberg et al, 1982**). Medical management with continued suppressive antimicrobial therapy and acidification temporarily relieves symptoms and retards deterioration of renal function in some patients. Complete removal of the calculus is generally required for bacteriologic cure and to prevent renal damage caused by obstruction (**Silverman and Stamey, 1983**). Percutaneous nephrolithotomy and extracorporeal shockwave lithotripsy are now the preferred treatment for most renal and upper ureteral calculi.

When extracorporeal shockwave lithotripsy is used to fragment infection stones, the patient should be maintained on appropriate antimicrobial therapy until the fragments pass. Occasionally, long-term antimicrobial therapy can result in eradication of bacteriuria even if some fragments persist after lithotripsy, presumably because the shockwaves have rendered the entrapped bacteria more susceptible to antimicrobial therapy (**Michaels et al, 1988**). If percutaneous or open surgery is used, all the residual particles of struvite stones must be removed at surgery to prevent recurrent bacteriuria from bacterial persistence in the calculus.

Rocha and Santos (1969) have shown that soaking these stones in iodine and alcohol for 6 hours will not kill the bacteria within the interior of the stone. The importance of recognizing this fact is twofold: (1) The bacteria cannot be killed by antimicrobial therapy, even though the urine may show no growth for months or even years (**Shortliffe et al, 1984**), and (2) any fragments left behind at the time of surgical removal leave residual bacteria within the interstices of the stone; these bacteria ensure recurrence of the staghorn calculus with its attendant morbidity.

If fragments remain after surgery, a small, multihole polyethylene catheter should be left for postoperative irrigation with Renacidin or Suby G solution (**Silverman and Stamey, 1983**). Follow-up radiographs are essential to ensure that all the stone fragments are removed, and cultures must demonstrate that the urease-splitting bacteria are eradicated.

Most of the other congenital or acquired abnormalities listed in **Box 12-4** require surgical removal for eradication of the source of bacterial persistence. Chronic bacterial prostatitis is treated initially with long-term antimicrobial therapy and, in select cases, by radical transurethral resection (**Meares, 1978**).

In patients in whom the focus of infection cannot be eradicated, long-term, low-dose antimicrobial suppression is necessary to prevent symptoms of infection. The antimicrobial drugs used for low-dose prophylaxis will also be effective for bacterial suppression if the persistent strain is susceptible. These include nitrofurantoin, TMP-SMX, cephalexin, and the fluoroquinolones.

Reinfections

Patients with recurrent infections caused by different species or occurring at long intervals almost invariably have reinfections. These reinfections most often occur in women and girls and are associated with ascending colonization from the bowel flora. Reinfections in men are often associated with a urinary tract abnormality. The possibility of a vesicoenteric or vesicovaginal fistula should be considered when the patient has any history of pneumonia, fecaluria, diverticulitis, obstipation, previous pelvic surgery, or radiation therapy. Evaluation of the patient with presumed reinfections must be individualized.

Failure to recognize and correct abnormalities that reduce formation, transmission, and elimination of urine by the urinary tract increases the incidence of reinfection in susceptible patients and reduces the effectiveness of antimicrobial therapy. Abnormalities should be corrected and urinary tract function restored by medical, pharmacologic, or surgical management. A thorough urologic evaluation is essential in all men and in women with evidence of upper tract infections (fevers, chills, flank pain, hemorrhagic cystitis, or other risk factors, such as history of unexplained hematuria, obstructive symptoms, neurogenic bladder dysfunction, renal calculi, fistula, analgesic abuse, or severe disease such as diabetes mellitus). In women, diaphragm-spermicide use has been associated with an increased risk of UTI and vaginal colonization with *E. coli* (**Hooton et al, 1991b**). Spermicides containing the active ingredient nonoxynol-9 may provide a selective advantage in colonizing the vagina, perhaps by a reduction in vaginal lactobacilli and through enhancement of adherence of *E. coli* to epithelial cells (**Hooton et al, 1991a; Gupta et al, 2000**). Thus spermicides should be discontinued in women with recurrent UTI, and other forms of contraception should be used.

Postmenopausal women have frequent reinfections (**Hooton and Stamm, 1991; Raz and Stamm, 1993**). These infections are sometimes attributable to residual urine after voiding, which is often associated with bladder or uterine prolapse. In addition, the lack of estrogen causes marked changes in the vaginal microflora, including a loss of lactobacilli and increased colonization by *E. coli* (**Raz and Stamm, 1993**). Estrogen replacement frequently restores the normal vaginal environment, allows recolonization with lactobacilli, and thus eliminates bacterial uropathogenic colonization. A reduced incidence of UTIs has been documented with this approach (**Raz and Stamm, 1993**).

Urinary tract imaging will demonstrate the anatomy of the urinary tract and provide reasonable assessment of its functional status. In healthy women, upper tract abnormalities associated with reinfections are very rare; therefore routine urologic imaging is not indicated. Cystoscopy should be performed in men or women who have frequent reinfections and symptoms suggestive of obstruction, bladder dysfunction, and fistula. If the patient has residual urine that is judged to be significant (e.g., 100 mL) and due to a narrowing of the urethra, a single dilation of the urethra to improve bladder emptying would appear appropriate. There is little evidence, however, that repeated urethral dilation is indicated in the routine management of most women.

Antimicrobial management in women who have had two or more symptomatic UTIs over a 6-month period or three or more episodes within a 12-month period involves one of three regimens: low-dose continuous prophylaxis, self-start intermittent therapy, or postintercourse prophylaxis.

Low-Dose Continuous Prophylaxis

Biologic Basis of Successful Prophylaxis: Antimicrobial Effect on Bowel and Vaginal Bacterial Flora. The success of prophylaxis depends, in large part, on the effect an antimicrobial agent has on the introital and bowel reservoirs of pathogenic bacteria. Antimicrobial agents that eliminate pathogenic bacteria from

these sites and/or do not cause bacterial resistance at the sites can be effective for antimicrobial prophylaxis of UTIs (Table 12-14).

Winberg and his colleagues were among the first to emphasize that oral antimicrobial therapy causes resistant strains in the bowel flora and subsequent resistant UTIs (Lincoln et al. 1970; Winberg et al. 1973). The increase in resistant strains of *E. coli* is well documented, as is the proliferation of other Enterobacteriaceae species, *Candida albicans*, enterococci, and other pathogenic bacteria in the bowel and vaginal flora that accompanies even short-term, full-dose oral administration of tetracyclines, ampicillin, sulfonamides, amoxicillin, and cephalexin (Sharp, 1954; Daikos et al. 1968; Hinton, 1970; Lincoln et al. 1970; Datta et al. 1971; Gruneberg et al. 1973; Winberg et al. 1973; Toivanen et al. 1976; Ronald et al. 1977; Preiksaitis et al. 1981). These ecologic changes may interfere with antimicrobial prophylaxis in the urinary tract and must be considered in the choice of prophylactic agents.

Effective Drugs. The oral antimicrobial agents with minimal adverse effects on the bowel and vaginal flora are TMP-SMX or TMP alone, nitrofurantoin, cephalexin (in minimal dosage), and the fluoroquinolones.

TMP-SMX eradicates gram-negative aerobic flora from the bowel and vaginal fluid. Vaginal fluid measurements of TMP and

TABLE 12-14 Low-Dose Prophylaxis for Recurrent Urinary Tract Infections in Women

INVESTIGATORS	REGIMEN	INFECTIONS PER PATIENT-YEAR
Bailey et al (1971)	Nitrofurantoin, 50 or 100 mg daily	0.09
	Nitrofurantoin, 50 mg daily	0.19
	Placebo	2.1
Harding and Ronald (1974)	Sulfamethoxazole, 500 mg daily	2.5
	TMP-SMX, 40 and 200 mg daily	0.1
	Methenamine mandelate, 2 g daily, plus ascorbic acid, 2 g	1.6
Kasanen et al (1974)	Nitrofurantoin, 50 mg daily	0.32
	Methenamine hippurate, 1 g daily	0.39
	Trimethoprim, 100 mg daily	0.13
	TMP-SMX, 80 and 400 mg daily	0.19
Gower (1975)	Cephalexin, 125 mg daily	0.10
Stamey et al (1977)	TMP-SMX, 40 and 200 mg daily	0.00
	Nitrofurantoin macrocrystals, 100 mg daily	0.74
Harding et al (1979)	TMP-SMX, 40 and 200 mg three times weekly	0.1
Stamm et al (1980)	TMP-SMX, 40 and 200 mg daily	0.15
	Trimethoprim, 100 mg daily	0.00
	Nitrofurantoin macrocrystals, 100 mg daily	0.14
	Placebo	2.8
Brumfitt et al (1981)	Nitrofurantoin, 50 mg twice daily	0.19
	Methenamine hippurate, 1 g twice daily	0.57
Harding et al (1982)	TMP-SMX, 40 and 200 mg three times weekly	0.14
Brumfitt et al (1983)	Trimethoprim, 100 mg daily	1.53
	Methenamine hippurate, 1 g daily	1.38
	Povidone-iodine wash, twice daily	1.79
Wong et al (1985)	TMP-SMX, 40 and 200 mg daily	0.2
	Self-administered cotrimoxazole, 4 × 80 and 400 mg	2.2
Martinez et al (1985)	Cephalexin, 250 mg daily	0.18
Brumfitt et al (1985)	Trimethoprim, 100 mg daily	1.00
	Nitrofurantoin macrocrystals, 100 mg daily	0.16
Nicolle et al (1989)	Nitrofurantoin, 200 mg daily	0.00

TMP-SMX, trimethoprim-sulfamethoxazole.

Modified from Nicolle LE, Ronald AR. Recurrent urinary tract infection in adult women: diagnosis and treatment. *Infect Dis Clin North Am* 1987;1:793–806.

SMX in patients showed that TMP infused across the noninflamed vaginal wall and produced concentrations that exceeded serum levels (Stamey and Condy, 1975); SMX was undetectable in vaginal fluid. These observations on diffusion and concentration of TMP and vaginal fluid and on the effects of TMP-SMX in clearing Enterobacteriaceae from the rectal and vaginal flora clearly indicate why TMP-SMX is such a powerful prophylactic agent for the prevention of reinfections in the female. These important biologic effects occur in addition to the bactericidal levels of TMP-SMX that are present in the urine during nightly prophylaxis.

Kasanen and his colleagues (1978) in Finland studied the bowel flora in volunteers and patients who took 100 mg of TMP per day for periods of 3 weeks to 36 months; 4 of 20 patients treated for long periods developed coliforms resistant to TMP ($>8 \mu\text{g/mL}$). Svensson and his associates (1982) gave 100 mg of TMP once daily for 6 months to 26 patients with recurrent UTIs. The infection recurrence rate before prophylaxis was 26 per 100 months compared with 3.3 recurrences per 100 months during prophylaxis ($P = .001$). The postprophylactic infection rate returned to 23 recurrences per 100 months. It is important to note that all *E. coli* UTIs after prophylaxis were sensitive to TMP, the number of rectal Enterobacteriaceae was markedly reduced during prophylaxis, and, although a 10% incidence of TMP-resistant organisms from rectal swabs was observed less than 1 month into prophylaxis, there was no significant further accumulation of resistant bacteria.

These studies on TMP alone suggest that it should be as effective as TMP-SMX for prophylactic prevention of recurrent UTIs. Stamm and coworkers (1980a) noted only one resistant strain of *E. coli* in 316 rectal, urethral, and vaginal isolates from 15 patients receiving 100 mg of TMP and 15 others receiving 40 mg of TMP with 200 mg of SMX nightly for 6 months; their unbelievably low recovery of TMP-resistant *E. coli* was due to their method of sampling, which did not include streaking cultures from these colonization sites directly onto media containing TMP.

These studies on TMP-SMX and TMP prophylactic therapy usually have been limited to 6 months to test continuing susceptibility in patients with reinfections. Two studies (Pearson et al, 1979; Harding et al, 1982), however, continued TMP-SMX prophylaxis from 2 to 5 years without showing any increase in "breakthrough" infections or any increase in TMP-resistant recurrent infections. Indeed, in the 15 patients treated for 2 years with one-half tablet of TMP-SMX thrice weekly (Harding et al, 1982), 100 of 116 cultures from the periurethral area (91%) and 60 of 97 cultures from the anal canal (68%) showed no aerobic gram-negative bacilli at these colonization sites.

Nitrofurantoin, which does not alter the bowel flora, is present for brief periods at high concentrations in the urine and leads to repeated elimination of bacteria from the urine, presumably interfering with bacterial initiation of infection. Because of either its complete absorption in the upper intestinal tract or its degradation and inactivation in the intestinal tract, it produces minimal effects on bowel flora (Stamey et al, 1977). Unlike the situation in prophylaxis with TMP-SMX that eliminates colonization, in prophylaxis with nitrofurantoin colonization of the vaginal introitus with Enterobacteriaceae continues throughout therapy. The bacteria colonizing the vagina nearly always remain susceptible because of the lack of bacterial resistance in the bowel flora. Patients on long-term therapy should be monitored for adverse reactions, (e.g., pulmonary fibrosis). The risk of an adverse reaction increases with age, with the greatest number occurring in patients older than 50 years. If a patient develops a chronic cough, the drug should be discontinued and a chest radiograph obtained.

Fairley and his associates (1974) first reported on the prophylactic efficacy of 500 mg of cephalexin per day in preventing recurrent infections during a 6-month period of observation. Of the 22 patients, 17 remained free of infection, an impressive record because several patients had papillary necrosis, chronic pyelonephritis, and even renal calculi. Gower (1975) treated 25 women with 125 mg of cephalexin nightly for 6 to 12 months and found only 1 infection, whereas 13 of 25 women receiving a placebo had infection.

Martinez and coworkers (1985) studied the effect on the vaginal and rectal flora of 250 mg of cephalexin nightly for 6 months in 23 patients with reinfections of the urinary tract. Throughout prophylaxis, 22 of the 23 patients maintained a sterile urine; a single patient developed two enterococcal UTIs, both of which responded to nitrofurantoin. No change was detected in the rectal or vaginal carriage of Enterobacteriaceae. More importantly, not a single resistant strain of *E. coli* was detected in 154 cultures obtained at monthly intervals during cephalexin therapy. These results are in contrast to those of Preiksaitis and colleagues (1981), who found rectal Enterobacteriaceae resistance in 38% of patients when cephalexin was administered at a dose of 500 mg four times daily for 14 days. **Cephalexin at 250 mg or less nightly is an excellent prophylactic agent because bowel flora resistance does not develop at this low dosage.**

With short-course fluoroquinolone therapy (Hooton et al, 1989), eradication of Enterobacteriaceae from the bowel and vaginal (Nord, 1988; Tartaglione et al, 1988) flora has been documented—observations that have been exploited in the use of these agents for prophylaxis. More recently, Nicolle and coworkers (1989) documented the prophylactic efficacy of norfloxacin for the prevention of recurrent UTIs in women. Of 11 women who completed 1 year of prophylaxis (200 mg orally), all remained free of infection. By comparison, the majority of individuals receiving placebos developed UTIs. The drug was well tolerated. In addition to preventing symptomatic UTIs, norfloxacin virtually eradicated periurethral and bowel colonization with aerobic gram-negative organisms. A larger study by Raz and Boger (1991) confirmed these results.

Because the fluoroquinolones are expensive and can be used only in nonpregnant women, we favor their use only when antimicrobial resistance or patient intolerance to TMP-SMX, TMP, nitrofurantoin, or cephalexin occurs. Further studies are required to determine the minimal effective regimen and efficacy of the fluoroquinolones for prophylaxis of recurrent UTIs in women.

Efficacy of Prophylaxis. Low-dose continuous prophylaxis is indicated when the urine culture shows no growth (usually when a patient has completed antimicrobial therapy). Nightly therapy is then begun with one of the following drugs: (1) nitrofurantoin, 50 to 100 mg half-strength (HS) (Stamey et al, 1977); (2) TMP-SMX, 40 to 200 mg (Stamm et al, 1982a); (3) TMP, 50 mg (Stamm et al, 1982a); or (4) cephalexin (Keflex), 250 mg (Martinez et al, 1985). Prophylactic therapy has been repeatedly documented as being effective in the management of women with recurrent UTIs, with recurrences decreased by 95% when compared with placebo or with the patients' prior experiences as controls. These reported results of prophylaxis, together with agents and doses, have been summarized by Nicolle and Ronald (1987) (see Table 12-14). These studies consistently show a remarkable reduction in the reinfection rate from 2.0 to 3.0 per patient-year to 0.1 to 0.4 per patient-year with the use of prophylaxis. Urinary antiseptics, such as methenamine mandelate or hippurate, have resulted in some decrease in recurrences, but they are not as effective as antimicrobial agents.

Every-other-night therapy is also effective and is probably practiced by most patients. When breakthrough infections occur, they are not necessarily accompanied by symptoms; therefore we advocate monitoring for infections every 1 to 3 months, even in asymptomatic patients. Breakthrough infections usually respond to full-dose therapy with the drug used for prophylaxis. However, cultures and susceptibility tests may indicate that another drug is indicated. After the infection is cured, prophylaxis may be reinstituted. Low-dose prophylaxis is usually discontinued after about 6 months, and the patient is monitored for reinfection. Approximately 30% of women will have spontaneous remissions that last up to 6 months (Kraft and Stamey, 1977). Unfortunately, many of the remissions are followed by reinfections, and low-dose prophylaxis must be reinstituted. At this point, many patients prefer an alternative form of management.

Self-Start Intermittent Therapy. With self-start intermittent therapy, the patient is given a dip slide device to culture the urine and is instructed to perform a urine culture when symptoms of UTI occur (Schaeffer and Stuppy, 1999; Blom et al, 2002). The patient is also provided a 3-day course of empirical, full-dose antimicrobial therapy to be started immediately after performing the culture. It is important that the antimicrobial agent selected for self-start therapy have a broad spectrum of activity and achieve high urinary levels to minimize development of resistant mutants. In addition, there should be minimal or no side effects on the bowel flora. Fluoroquinolones are ideal for self-start therapy because they have a spectrum of activity broader than any of the other oral agents and are superior to many parenteral antimicrobials, including aminoglycosides. Nitrofurantoin and TMP-SMX are acceptable alternatives, although they are somewhat less effective. Antimicrobial agents such as tetracycline, ampicillin, SMX, and cephalexin in full doses should be avoided because they can give rise to resistant bacteria (Wong et al, 1985).

The culture is brought to the office as soon as possible. If the culture is positive and the patient is asymptomatic, a culture is performed 7 to 10 days after therapy to determine efficacy. In most cases, the therapy is limited to two inexpensive dip slide cultures and a short course of antimicrobial therapy. If the patient has symptoms that do not respond to initial antimicrobial therapy, a repeat culture and susceptibility testing of the initial culture specimen are performed and therapy adjusted accordingly. If symptoms of infection are not associated with positive cultures, urologic evaluation should be performed to rule out other causes of irritative bladder symptoms, including carcinoma in situ, interstitial cystitis, and neurogenic bladder dysfunction. Our experience with this technique has been very favorable and is particularly attractive to patients who have less frequent infections and are willing to play an active role in their diagnosis and management.

Postintercourse Prophylaxis. Antimicrobial management through postintercourse prophylaxis is based on research establishing that sexual intercourse can be an important risk factor for acute cystitis in women (Nicolle et al, 1982). Diaphragm users have a significantly greater risk of UTI than do women who use other contraceptive methods (Fihn et al, 1985). Postintercourse therapy with antimicrobial agents, such as nitrofurantoin, cephalexin, TMP-SMX, or a fluoroquinolone taken as a single dose, will effectively reduce the incidence of reinfection (Pfau et al, 1983; Melekos et al, 1997).

Other Strategies. Cranberry juice contains proanthocyanidins that block adherence of pathogens to uroepithelial cells in vitro (Foo et al, 2000). Randomized trials in low-risk patients show that 200 to 750 mL daily of cranberry or lingonberry juice or cranberry-concentrate tablets reduce the risk of symptomatic, recurrent infection by 12% to 20% (Avorn et al, 1994; Kontiokari et al, 2001; Stothers, 2002; McMurdo et al, 2009). However, the actual cranberry content of juices and tablets varies substantially; therefore their efficacy is not predictable (Consumer Reports, 2001; Klein, 2002). Furthermore, other trials of cranberry products show no benefit and there is no evidence that they are effective for treatment of UTIs (Jepson et al, 2001; Raz et al, 2004).

Other factors, such as hygiene, frequency and timing of voiding, wiping patterns, use of hot tubs, and type of undergarments, have not been shown to predispose women to recurrent infection, and there is no rationale for giving women specific instructions regarding them.

KEY POINTS: BLADDER INFECTIONS

- Uncomplicated cystitis should be treated for 3 days.
- Asymptomatic bacteriuria should be treated only in pregnant women and prior to urologic intervention.
- Recurrent UTIs caused by bacterial persistence require urologic management; reinfections can be managed medically.

KIDNEY INFECTIONS

Renal Infection (Bacterial Nephritis)

Although renal infection is less prevalent than bladder infection, it often is a more difficult problem for the patient and his or her physician because of its often varied and morbid presentation and course, the difficulty in establishing a firm microbiologic and pathologic diagnosis, and its potential for significantly impairing renal function. Although the classic symptoms of acute onset of fever, chills, and flank pain are usually indicative of renal infection, some patients with these symptoms do not have renal infection. Conversely, significant renal infection may be associated with an insidious onset of nonspecific local or systemic symptoms, or it may be entirely asymptomatic. Therefore a high clinical index of suspicion and appropriate radiologic and laboratory studies are required to establish the diagnosis of renal infection.

Unfortunately, the relationship between laboratory findings and the presence of renal infection often is poor. Bacteriuria and pyuria, the hallmarks of UTI, are not predictive of renal infection. Conversely, patients with significant renal infection may have sterile urine if the ureter draining the kidney is obstructed or the infection is outside of the collecting system.

The pathologic and radiologic criteria for diagnosing renal infection may also be misleading. Interstitial renal inflammation, once thought to be caused predominantly by bacterial infection, is now recognized as a nonspecific histopathologic change associated with a variety of immunologic, congenital, or chemical lesions that usually develop in the absence of bacterial infection. Infectious granulomatous diseases of the kidney often have either radiologic or pathologic characteristics that mimic renal cystic disease, neoplasia, or other renal inflammatory disease.

The effect of renal infection on renal function is varied. Acute or chronic pyelonephritis may transiently or permanently alter renal function, but nonobstructive pyelonephritis is no longer recognized as a major cause of renal failure (Baldassarre and Kaye, 1991; Fraser et al, 1995). However, pyelonephritis, when associated with urinary tract obstruction or granulomatous renal infection, may lead rapidly to significant inflammatory complications, renal failure, or even death.

Pathology

The opportunity for pathologic confirmation of acute bacterial nephritis is rare. The kidney may be edematous. Focal acute suppurative bacterial nephritis caused by hematogenous dissemination of bacteria to the renal cortex is characterized by multiple focal areas of suppuration on the surface of the kidney (Fig. 12-15). Histologic examination of the renal cortex shows focal suppurative destruction of glomeruli and tubules. Adjacent cortical structures and the medulla are not involved in the inflammatory reaction. Acute ascending pyelonephritis is characterized by linear bands of inflammation extending from the medulla to the renal capsule (Fig. 12-16). Histologic examination usually reveals a focal wedge-shaped area of acute interstitial inflammation with the apex of the wedge in the renal medulla. Polymorphonuclear leukocytes or a predominantly lymphocytic and plasma cell response are seen. Bacteria also may be present.

The changes that appear to be most specific for chronic pyelonephritis are evident on careful gross examination of the kidney and consist of a cortical scar associated with retraction of the corresponding renal papilla (Hodson, 1965; Hodson and Wilson, 1965; Heptinstall, 1974; Freedman, 1979). The kidney shows evidence of patchy involvement with numerous chronic inflammatory foci mainly confined to the cortex but also involving the medulla (Fig. 12-17).

The scars may be separated by intervening zones of normal parenchyma, causing a grossly irregular renal outline. The microscopic appearance, as with most chronic interstitial disease, includes the presence of lymphocytes and plasma cells. Although glomeruli within scars may be surrounded by a cuff of fibrosis or be partially

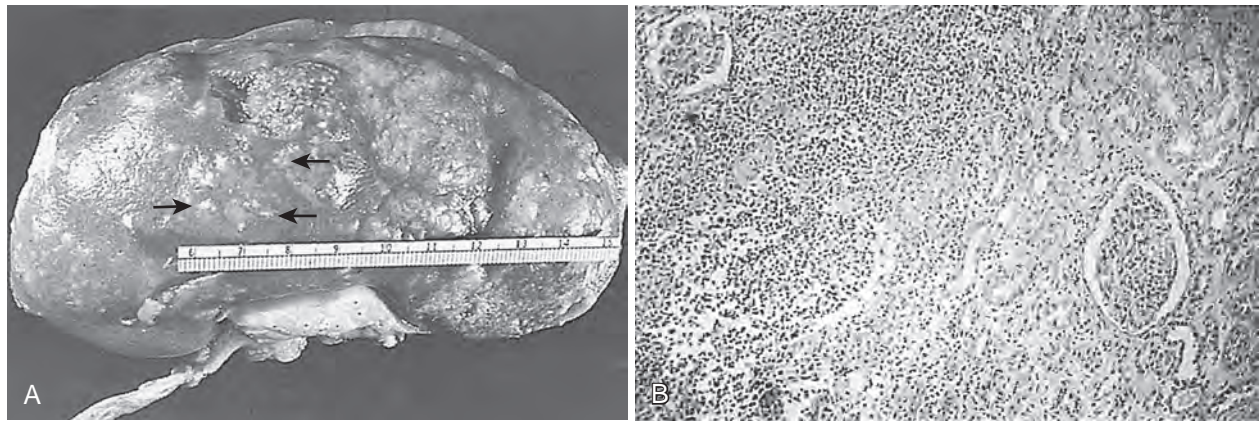


Figure 12-15. Acute focal suppurative bacterial nephritis. A, Surface of kidney. Arrows indicate focal areas of suppuration. B, Renal cortex showing focal suppuration destruction of glomeruli and tubules. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

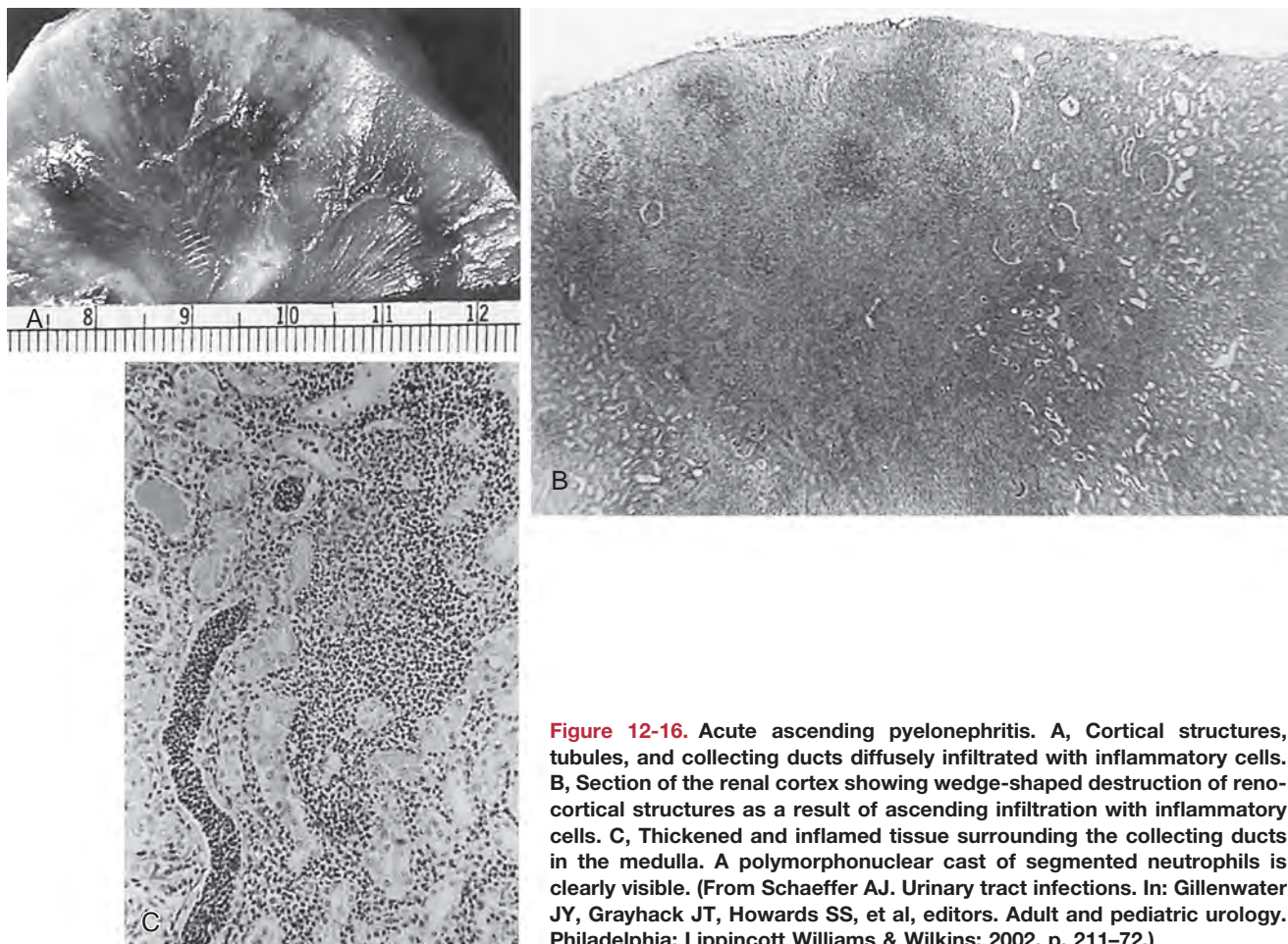


Figure 12-16. Acute ascending pyelonephritis. A, Cortical structures, tubules, and collecting ducts diffusely infiltrated with inflammatory cells. B, Section of the renal cortex showing wedge-shaped destruction of renocortical structures as a result of ascending infiltration with inflammatory cells. C, Thickened and inflamed tissue surrounding the collecting ducts in the medulla. A polymorphonuclear cast of segmented neutrophils is clearly visible. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

or completely hyalinized, glomeruli outside these severely scarred zones are relatively normal. Vascular involvement is variable, but in patients with hypertension, nephrosclerosis may be found. Papillary abnormalities include deformity, sclerosis, and sometimes necrosis. Studies in animals have clearly indicated the critical role of the papilla in the initiation of pyelonephritis (Freedman and Beeson, 1958). However, these changes are not necessarily specific for bacterial infection and may occur in the absence of infection as

a result of other disorders such as analgesic abuse, diabetes, and sickle cell disease.

Acute Pyelonephritis

Although pyelonephritis is defined as inflammation of the kidney and renal pelvis, the diagnosis is clinical. True infection of the “upper urinary tract” can be proved by catheterization tests (ureteral

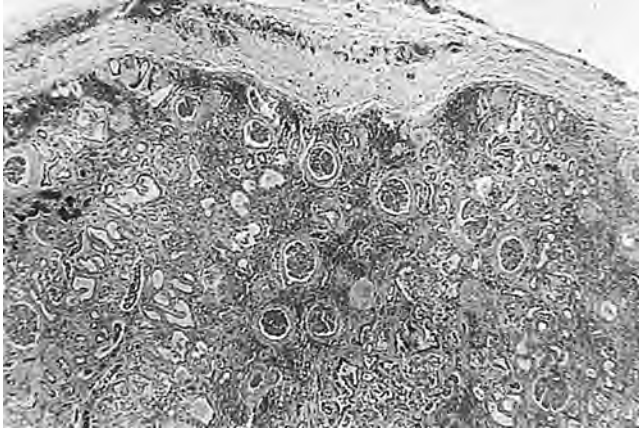


Figure 12-17. Chronic pyelonephritis. The renal cortex shows thickened fibrous capsule and focal retracted scar on surface of kidney. Focal destruction of tubules in center of picture is accompanied by periglomerular fibrosis and scarring. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

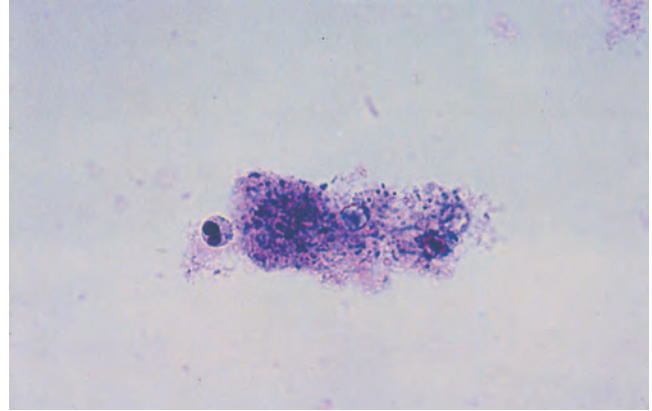


Figure 12-18. Brightfield micrograph of a mixed bacterial leukocyte cast from patient with acute pyelonephritis. Only the bacteria and the nucleus of a leukocyte stain strongly. Many bacteria are clearly demonstrated by through-focusing (toluidine blue O stain, magnification $\times 640$). (From Lindner LE, Jones RN, Haber MH. A specific urinary cast in acute pyelonephritis. *Am J Clin Pathol* 1980;73:809–11.)

catheterization or bladder washout) as described in this chapter, but these are impractical and unnecessary in most patients with acute pyelonephritis. None of the noninvasive tests that have been developed to determine infection in the kidney or bladder are totally reliable.

Clinical Presentation. The clinical spectrum ranges from gram-negative sepsis to cystitis with mild flank pain (Stamm and Hooton, 1993). The classic presentation is an abrupt onset of chills, fever (100.3°F or greater), and unilateral or bilateral flank or costovertebral angle pain and/or tenderness. These so-called upper tract signs are often accompanied by dysuria, increased urinary frequency, and urgency.

Although some authors regard loin pain and fever in combination with significant bacteriuria as diagnostic of acute pyelonephritis, it is clear from localization studies using ureteral catheterization (Stamey and Pfau, 1963) or the bladder washout technique (Fairley et al, 1967) that clinical symptoms correlate poorly with the site of infection (Stamey et al, 1965; Eykyn et al, 1972; Fairley, 1972; Smeets and Gower, 1973).

In a large study of 201 women and 12 men with recurrent UTIs, Busch and Huland (1984) showed that fever and flank pain are no more diagnostic of pyelonephritis than they are of cystitis. Of patients with flank pain and/or fever, over 50% had lower tract bacteriuria. Conversely, patients with bladder symptoms or no symptoms frequently had upper tract bacteriuria. Approximately 75% of patients give a history of previous lower UTIs.

On physical examination, there often is tenderness to deep palpation in the costovertebral angle. Variations of this clinical presentation have been recognized. Acute pyelonephritis may also simulate gastrointestinal tract abnormalities with abdominal pain, nausea, vomiting, and diarrhea. Asymptomatic progression of acute pyelonephritis to chronic pyelonephritis, particularly in compromised hosts, may occur in the absence of overt symptoms. Acute renal failure may be present in the rare case (Richet and Mayaud, 1978; Olsson et al, 1980).

Laboratory Diagnosis. The patient may have leukocytosis with a predominance of neutrophils. Urinalysis usually reveals numerous WBCs, often in clumps, and bacterial rods or chains of cocci. Leukocytes exhibiting brownian motion in the cytoplasm (glitter cells) may be present if the urine is hypotonic, but they are not in themselves diagnostic of pyelonephritis. The presence of large amounts of granular or leukocyte casts in the urinary sediment is suggestive of acute pyelonephritis. A specific type of urinary cast characterized by the presence of bacteria in its matrix has been demonstrated in the urine of patients who have had acute

pyelonephritis (Fig. 12-18) (Lindner et al, 1980). Bacteria in the casts were not easily distinguished by simple brightfield microscopy without special staining of the sediment. Staining of the sediment with a basic dye such as dilute toluidine blue or KOVA stain (I.C.L. Scientific, Fountain Valley, CA) demonstrated the bacteria in casts without difficulty. Blood tests may show leukocytosis with a predominance of neutrophils, increased erythrocyte sedimentation rate, elevated C-reactive protein levels, and elevated creatinine levels if renal failure is present. In addition, creatinine clearance may be decreased. Blood cultures may be positive.

Bacteriology. Urine cultures are positive, but about 20% of patients have urine cultures with fewer than 10^5 cfu/mL and therefore negative results on Gram staining of the urine (Rubin et al, 1992).

E. coli, which constitutes a unique subgroup that possesses special virulence factors, accounts for 80% of cases. If vesicoureteral reflux is absent, a patient bearing the P blood group phenotype may have special susceptibility to recurrent pyelonephritis caused by *E. coli* that have P pili and bind to the P blood group antigen receptors (Lomborg et al, 1983). Bacterial K antigens and endotoxins also may contribute to pathogenicity (Kaijser et al, 1977). Many cases of community-acquired pyelonephritis are caused by a limited number of multiantimicrobial-resistant clonal groups (Manges et al, 2004).

More resistant species, such as *Proteus*, *Klebsiella*, *Pseudomonas*, *Serratia*, *Enterobacter*, or *Citrobacter*, should be suspected in patients who have recurrent UTIs, are hospitalized, or have indwelling catheters, as well as in those who required recent urinary tract instrumentation. Except for *E. faecalis*, *S. epidermidis*, and *S. aureus*, gram-positive bacteria rarely cause pyelonephritis.

Blood cultures are positive in about 25% of cases of uncomplicated pyelonephritis in women, and the majority replicate the urine culture and do not influence decisions regarding therapy. Therefore blood cultures should not be routinely obtained for the evaluation of uncomplicated pyelonephritis in women. However, they should be performed in men and women with systemic toxicity or in those requiring hospitalization or with risk factors such as pregnancy (Velasco et al, 2003).

Renal Ultrasonography and Computed Tomography. These studies are commonly used to evaluate patients initially for complicated UTIs or factors or to reevaluate patients who do not respond after 72 hours of therapy (see later). Ultrasonography (Fig. 12-19) and CT show renal enlargement, hypoechoic or attenuated parenchyma, and a compressed collecting system. They also

may delineate focal bacterial nephritis and obstruction. When parenchymal destruction becomes pronounced, a more disorganized parenchyma and abscess formation associated with complicated renal and perirenal infections may be identified (Soulén et al, 1989).

Differential Diagnosis. Acute appendicitis, diverticulitis, and pancreatitis can cause a similar degree of pain, but the location of the pain often is different. Results of the urine examination are usually normal. Herpes zoster can cause superficial pain in the region of the kidney but is not associated with symptoms of UTI; the diagnosis will be apparent when shingles appear.

Management

Initial Management. Infection in patients with acute pyelonephritis can be subdivided into (1) uncomplicated infection that does not warrant hospitalization, (2) uncomplicated infection in patients

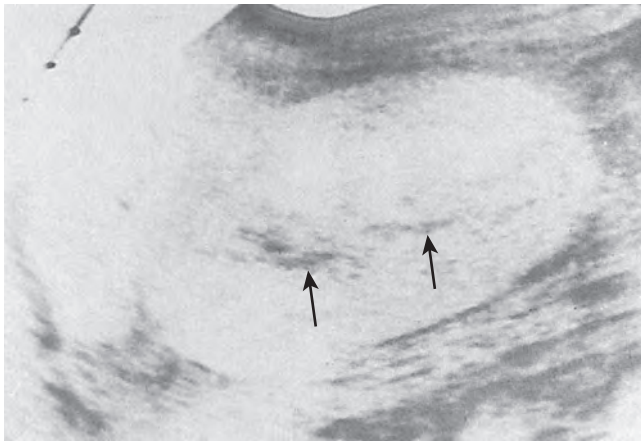


Figure 12-19. Acute pyelonephritis. Ultrasound image of the right kidney demonstrates renal enlargement, hypoechoic parenchyma, and compressed central collecting complex (arrows). (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JT, Grayhack JT, Howards SS, et al, editors. *Adult and pediatric urology*. Philadelphia: Lippincott William & Wilkins; 2002. p. 211–72.)

with normal urinary tracts who are ill enough to warrant hospitalization for parenteral therapy, and (3) complicated infection associated with hospitalization, catheterization, urologic surgery, or urinary tract abnormalities (Fig. 12-20).

It is critical to determine whether the patient has an uncomplicated or complicated UTI because significant abnormalities have been found in 16% of patients with acute pyelonephritis (Shen and Brown, 2004). In patients with presumed uncomplicated pyelonephritis who will be managed as outpatients, initial radiologic evaluation can usually be deferred. However, if there is any reason to suspect a problem or if the patient will not have reasonable access to imaging if there should be no change in condition, we prefer renal ultrasonography to rule out stones or obstruction. In patients with known or suspected complicated pyelonephritis, CT provides excellent assessment of the status of the urinary tract and the severity and extent of the infection.

For patients who will be managed as outpatients, single-drug oral therapy with a fluoroquinolone is more effective than TMP-SMX for patients with domiciliary infections (Talan et al, 2000). Many physicians administer a single parenteral dose of an antimicrobial agent (ceftriaxone, gentamicin, or a fluoroquinolone) before initiating oral therapy (Israel et al, 1991; Pinson et al, 1994). If a gram-positive organism is suspected, amoxicillin or amoxicillin/clavulanic acid is recommended (Warren et al, 1999).

If a patient has an uncomplicated infection but is sufficiently ill to require hospitalization (high fever, high WBC count, vomiting, dehydration, evidence of sepsis), has complicated pyelonephritis, or fails to improve during the initial outpatient treatment period, a parenteral fluoroquinolone, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside is recommended (Warren et al, 1999) (Table 12-15). If gram-positive cocci are causative, ampicillin/sulbactam with or without an aminoglycoside is recommended.

Hospitalization, IV fluids, and antipyretics are required.

An obstructed kidney has difficulty concentrating and excreting antimicrobial agents. Any substantial obstruction must be relieved expediently by the safest and simplest means.

A Gram stain of the urine sediment is helpful to guide the selection of the initial empirical antimicrobial therapy. In all cases,

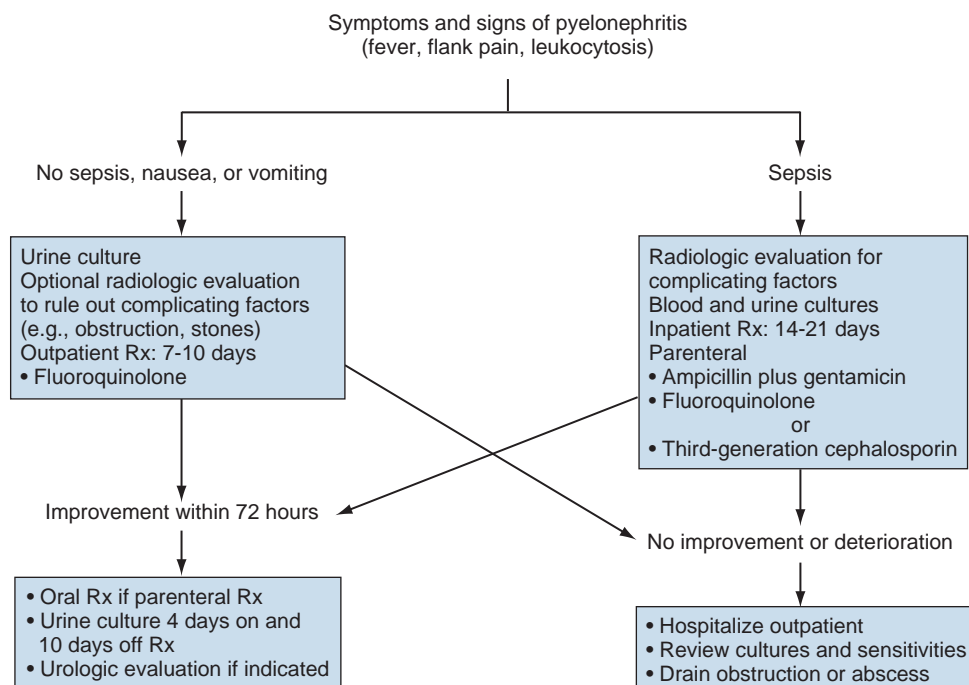


Figure 12-20. Management of acute pyelonephritis.

TABLE 12-15 Treatment Regimens for Acute Complicated and Uncomplicated Pyelonephritis in Women

CIRCUMSTANCES	ROUTE	DRUG	DOSAGE	FREQUENCY PER DOSE	DURATION (DAYS)
Outpatient—moderately ill, no nausea or vomiting	Oral	TMP-SMX DS	160-800 mg	bid	10-14
		Ciprofloxacin	500 mg	bid	3-7
		Levofloxacin	500 mg	qd	
Inpatient—severely ill, possible sepsis	Parenteral	Ampicillin and gentamicin	1 g	qid	14
			1.5 mg/kg	tid	
		Ciprofloxacin	400 mg	bid	10
		Levofloxacin	500 mg	qd	
		Ceftriaxone	1 to 2g	qd	
					Take until afebrile, then take oral
Pregnant	Parenteral	Ampicillin and gentamicin	1 g	qid	Take until afebrile, then take oral
			1 mg/kg	tid	
		Aztreonam	1 g	tid-qid	
	Oral	Cephalexin	500 mg	bid	

DS, double strength; TMP-SMX, trimethoprim-sulfamethoxazole.

Modified from Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med* 1993;329:1328-34. Copyright 1993, Massachusetts Medical Society. All rights reserved.

antimicrobial therapy should be active against potential uropathogens and achieve antimicrobial levels in renal tissue and urine.

Subsequent Management. Even though the urine usually becomes sterile within a few hours of starting antimicrobial therapy, patients with acute uncomplicated pyelonephritis may continue to have fever, chills, and flank pain for several more days after initiation of successful antimicrobial therapy (Behr et al, 1996). They should be observed.

Ambulatory patients should be treated with a fluoroquinolone for 7 days (Talan et al, 2000). Fluoroquinolone therapy is associated with greater bacteriologic and clinical cure rates than 14-day TMP-SMX therapy (Talan et al, 2000). Alterations in antimicrobial therapy may be made depending on the patient's clinical response and the results of the culture and susceptibility tests. Susceptibility tests should also be used to replace potentially toxic drugs, such as aminoglycosides, with less toxic drugs, such as the fluoroquinolones, aztreonam, and cephalosporins.

Patients with complicated pyelonephritis and positive blood cultures should be treated with parenteral therapy until clinically stable. If blood cultures are negative, 2- to 3-day parenteral therapy is sufficient. Following parenteral therapy, an appropriate oral antimicrobial drug (fluoroquinolone, TMP, TMP-SMX, or amoxicillin or amoxicillin/clavulanic acid for gram-positive organisms) should be continued in full dosage for an additional 10 to 14 days.

Unfavorable Response to Therapy. When the response to therapy is slow or the urine continues to show infection, an immediate reevaluation is mandatory. Urine and blood cultures must be repeated and appropriate alterations in antimicrobial therapy made on the basis of susceptibility testing. CT is indicated to attempt to identify unsuspected obstructive uropathy, abscess formation, urolithiasis, or underlying anatomic abnormalities that may have predisposed the patient to infection, prevented a rapid therapeutic response, or caused complications of the infectious process, such as renal or perinephric abscess. **In patients with fever lasting longer than 72 hours, CT is most helpful for ruling out obstruction and identifying renal and perirenal infections (Soulen et al, 1989).** Radionuclide imaging may be useful to demonstrate functional changes associated with acute pyelonephritis (decrease in renal blood flow, delay in peak function, and delay in excretion of the

radionuclide) (Fischman and Roberts, 1982) and cortical defects associated with vesicoureteral reflux.

Follow-Up. Repeat urine cultures should be performed on the fifth to the seventh day of therapy and 10 to 14 days after discontinuing antimicrobial therapy to ensure that the urinary tract remains free of infections. Between 10% and 30% of individuals with acute pyelonephritis relapse after a 14-day course of therapy. Patients who relapse usually are cured by a second 14-day course of therapy, but occasionally a 6-week course is necessary (Tolkoff-Rubin et al, 1984; Johnson and Stamm, 1987).

Depending on the clinical presentation and response and initial urologic evaluation, some patients may require additional evaluation (e.g., voiding cystourethrogram, cystoscopy, bacterial localization studies) and correction of an underlying abnormality of the urinary tract. Raz and colleagues (2003) evaluated the long-term impact of acute pyelonephritis in women. Scanning with ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) 10 to 20 years after acute pyelonephritis revealed scars in approximately 50% of the patients, but changes in renal function were minimal and not associated with renal scarring.

Acute Focal or Multifocal Bacterial Nephritis

Acute focal or multifocal bacterial nephritis is an uncommon, severe form of acute renal infection in which a heavy leukocyte infiltrate is confined to a single renal lobe (focal) or multiple lobes (multifocal).

Clinical Presentation. The clinical presentation of patients with acute bacterial nephritis is similar to that of patients with acute pyelonephritis but usually is more severe. About half of the patients are diabetic, and sepsis is common. Generally, leukocytosis and UTI resulting from gram-negative organisms are found; more than 50% of the patients are bacteremic (Wicks and Thornbury, 1979). There is growing evidence that acute focal bacterial nephritis (AFBN) represents a midpoint on the spectrum between pyelonephritis and renal abscess.

Radiologic Findings. The diagnosis must be made by radiologic examination. The mass has slightly less nephrographic density than the surrounding normal renal parenchyma.

Ultrasonography and CT establish the diagnosis. On ultrasonography, the lesion is typically poorly margined and relatively sonolucent with occasional low-amplitude echoes that disrupt the cortical medullary junction (Corriere and Sandler, 1982) (Fig. 12-21A). Enhancement with a contrast agent is necessary with CT studies because the lesion is difficult to visualize on the unenhanced study (Fig. 12-21B). Wedge-shaped areas of decreased enhancement are seen. No definite wall is evident, and frank liquefaction is absent. Conversely, abscesses tend to have liquid centers, are usually round, and are present both before and after contrast medium enhancement. More chronic abscesses may also show a ring-shaped area of increased enhancement surrounding the lesion (Corriere and Sandler, 1982). Gallium scanning reveals uptake that is in the region of and larger than the previously demonstrated mass (Rosenfield et al, 1979). In patients with multifocal disease, the findings are similar but multiple lobes are involved.

Management. Acute bacterial nephritis probably represents a relatively early phase of frank abscess formation. In a series of cases reported by Lee and coworkers (1980), a patient with acute focal bacterial nephritis progressed to abscess formation. McCoy and associates reported radiographically proven progression from acute nephritis to an abscess despite appropriate medical management (McCoy et al, 1985). Shimizu and colleagues presented a case of a 16-year-old female with CT imaging consistent with AFBN and no evidence of drainable fluid collection, which progressed by hospital day 13 to a hypodense large abscess in the area previously seen to be nephritis while being treated (Shimizu et al, 2005). Treatment includes hydration and IV antimicrobial agents for at least 7 days, followed by 7 days of oral antimicrobial therapy. Patients with bacterial nephritis typically respond to medical therapy, and follow-up studies will show resolution of the wedge-shaped zones of diminished attenuation. Failure to respond to antimicrobial therapy is an indication for appropriate studies to rule out obstructive uropathy, renal or perirenal abscess, renal carcinoma, or acute renal vein thrombosis. Long-term follow-up studies performed in a few patients with multifocal disease have demonstrated a decrease in renal size and focal calyceal deformities suggestive of papillary necrosis (Davidson and Talner, 1978).

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a urologic emergency characterized by an acute necrotizing parenchymal and perirenal

infection caused by gas-forming uropathogens. The pathogenesis is poorly understood. Because the condition usually occurs in diabetic patients, it has been postulated that the high tissue glucose levels provide the substrate for microorganisms such as *E. coli*, which are able to produce carbon dioxide by the fermentation of sugar (Schainuck et al, 1968). Although glucose fermentation may be a factor, the explanation does not account for the rarity of emphysematous pyelonephritis despite the high frequency of gram-negative UTI in diabetic patients, nor does it explain the rare occurrence of the condition in nondiabetic patients.

In addition to diabetes, many patients have urinary tract obstruction associated with urinary calculi or papillary necrosis and significant renal functional impairment. The overall mortality rate has been reported to be between 19% (Huang and Tseng, 2000) and 43% (Freiha et al, 1979).

Clinical Presentation. Nearly all of the documented cases of emphysematous pyelonephritis have occurred in adults (Hawes et al, 1983). Juvenile diabetic patients do not appear to be at risk. Women are affected more often than men.

The usual clinical presentation is severe, acute pyelonephritis, although in some instances a chronic infection precedes the acute attack. Almost all patients display the classic triad of fever, vomiting, and flank pain (Schainuck et al, 1968). Pneumaturia is absent unless the infection involves the collecting system. Results of urine cultures are invariably positive. *E. coli* is most commonly identified. *Klebsiella* and *Proteus* are less common.

Radiologic Findings. The diagnosis is established radiographically. Tissue gas that is distributed in the parenchyma may appear on abdominal radiographs as mottled gas shadows over the involved kidney (Fig. 12-22). This finding is often mistaken for bowel gas. A crescentic collection of gas over the upper pole of the kidney is more distinctive. As the infection progresses, gas extends to the perinephric space and retroperitoneum. This distribution of gas should not be confused with cases of emphysematous pyelitis in which air is in the collecting system of the kidney. Emphysematous pyelitis is secondary to a gas-forming bacterial UTI, often occurs in nondiabetic patients, is less serious, and usually responds to antimicrobial therapy.

Ultrasonography usually demonstrates strong focal echoes suggesting the presence of intraparenchymal gas (Brenbridge et al, 1979; Conrad et al, 1979). CT is the imaging procedure of choice in defining the extent of the emphysematous process and guiding management (Figs. 12-23 and 12-24). An absence of fluid in CT

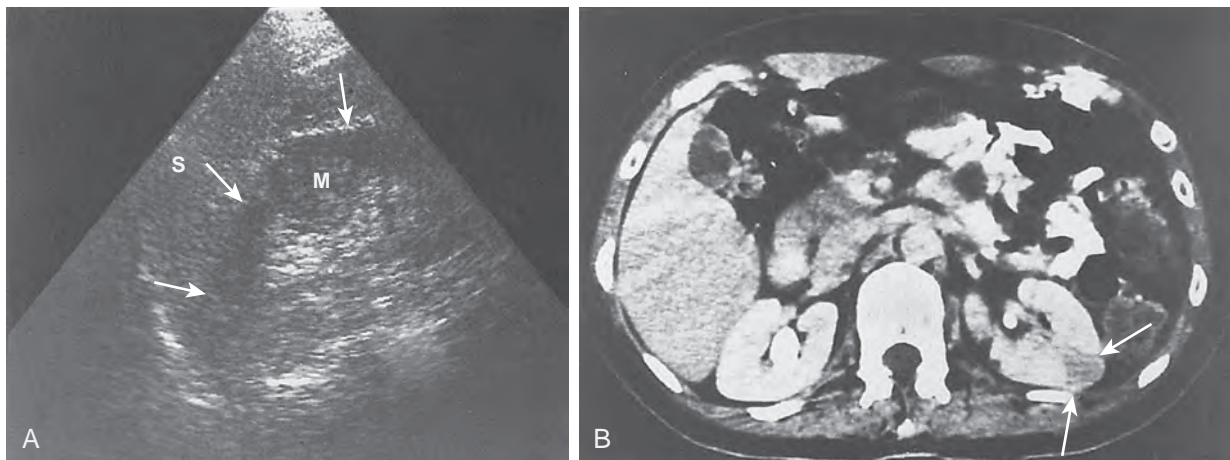


Figure 12-21. Acute focal bacterial nephritis. A, Ultrasound image; longitudinal view of the left kidney demonstrates spleen (S) and left kidney (arrows). Note irregular midpole mass (M) of slightly higher echo texture than surrounding normal renal parenchyma. B, Contrast medium-enhanced computed tomography scan demonstrates a wedge-shaped area of low density (arrows) in the middle portion of the left kidney. The findings resolved after antimicrobial therapy. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211-72.)

images or the presence of streaky or mottled gas with or without bubbly and loculated gas appears to be associated with rapid destruction of renal parenchyma and a 50% to 60% mortality rate (Wan et al, 1996; Best et al, 1999). The presence of renal or perirenal fluid, the presence of bubbly or loculated gas or gas in the collecting system, and the absence of streaky or mottled gas patterns



Figure 12-22. Emphysematous pyelonephritis; plain film. Extensive perinephric (*long arrows*) and intraparenchymal (*short arrows*) gas secondary to acute bacterial pyelonephritis. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott William & Wilkins; 2002. p. 211–72.)

are associated with a less than 20% mortality rate. Obstruction is demonstrated in approximately 25% of the cases. A nuclear renal scan should be performed to assess the degree of renal function impairment in the involved kidney and the status of the contralateral kidney.

Management. Emphysematous pyelonephritis is a surgical emergency. Most patients are septic, and fluid resuscitation and broad-spectrum antimicrobial therapy are essential. If the kidney is functioning, medical therapy can be considered (Wan et al, 1996; Best et al, 1999). Nephrectomy is recommended for patients who do not improve after a few days of therapy (Malek and Elder, 1978). If the affected kidney is nonfunctioning and not obstructed, nephrectomy should be performed because medical treatment alone is usually lethal. If a kidney is obstructed, catheter drainage must be instituted. If the patient's condition improves, nephrectomy may be deferred pending a complete urologic evaluation. Although there are isolated case reports of retention of renal function after medical therapy combined with relief of obstruction, most patients require nephrectomy (Hudson et al, 1986).

Renal Abscess

Renal abscess or carbuncle is a collection of purulent material confined to the renal parenchyma. Before the antimicrobial era, 80% of renal abscesses were attributed to hematogenous seeding by staphylococci (Campbell, 1930). Additionally, patients historically presenting with abscesses were young men with no prior renal disease. Although experimental and clinical data document the facility for abscess formation in normal kidneys after hematogenous inoculation with staphylococci, widespread use of antimicrobial agents since about 1950 appears to have diminished the propensity for gram-positive abscess formation (DeNavasquez, 1950; Cotran, 1969). The current index patient typically has a history of renal disease or obstruction, has no gender predominance and no laterality, and the infection is typically with a gram-negative organism.

Since about 1970, gram-negative organisms have been implicated in the majority of adults with renal abscesses. Hematogenous renal seeding by gram-negative organisms may occur, but this is not likely to be the primary pathway for gram-negative abscess formation. Clinically, there is no evidence that gram-negative septicemia antedates most lesions. Further, gram-negative hematogenous pyelonephritis is virtually impossible to produce in animals unless the kidney is traumatized or completely obstructed (Cotran, 1969; Timmons and Perlmutter, 1976). Like the normal kidney, the

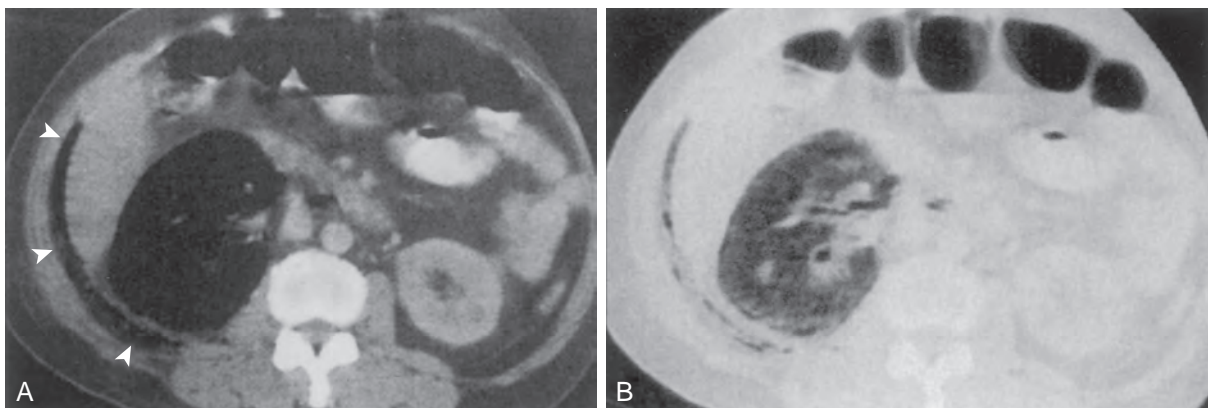


Figure 12-23. Type I emphysematous pyelonephritis with complete renal destruction in a 49-year-old woman. A, Computed tomography (CT) scan of the right kidney shows complete destruction with gas (*arrowheads*) extending beyond the renal fascia. B, CT scan with a modified lung window display shows the characteristic streaky gas in the completely destroyed kidney. The patient died on arrival in the emergency department. (From Wan YL, Lee TY, Bullard MJ, et al. Acute gas-producing bacterial renal infection: correlation between imaging findings and clinical outcome. Radiology 1996;198:433–8.)

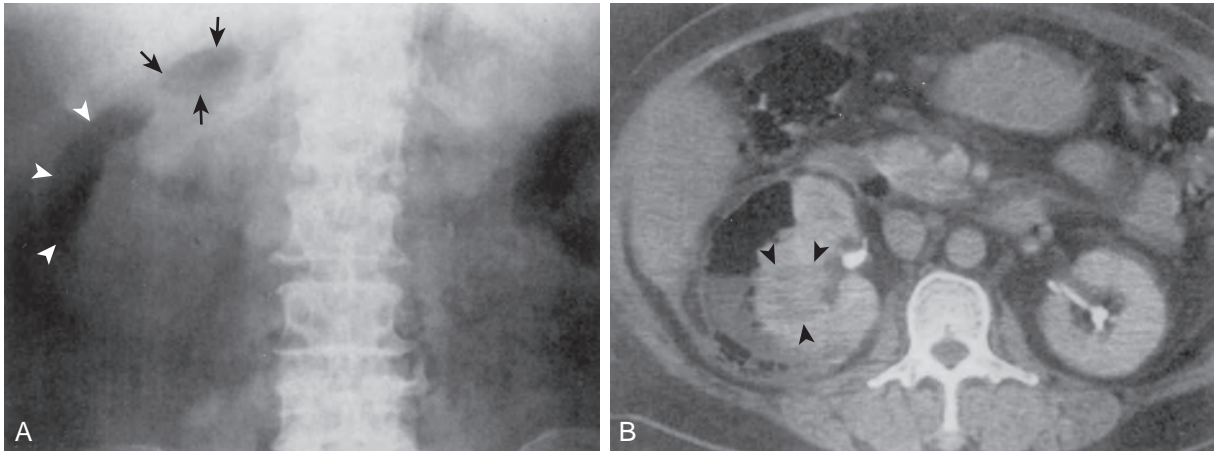


Figure 12-24. Type II emphysematous pyelonephritis in a 57-year-old woman. A, Radiograph shows crescent-shaped (white arrowheads) and loculated (black arrows) gas in the right renal area. B, Computed tomography scan obtained after administration of contrast material shows a low-attenuation area (arrowheads) in the right kidney due to acute pyelonephritis, as well as a subcapsular abscess with fluid and bubbly and loculated gas. The patient survived after percutaneous drainage was performed. (From Wan YL, Lee TY, Bullard MJ, et al. Acute gas-producing bacterial renal infection: correlation between imaging findings and clinical outcome. *Radiology* 1996;198:433–8.)

partially obstructed kidney rejects blood-borne gram-negative inocula. Thus ascending infection associated with tubular obstruction from prior infections or calculi appears to be the primary pathway for the establishment of gram-negative abscesses. Two-thirds of gram-negative abscesses in adults are associated with renal calculi or damaged kidneys (Salvatierra et al, 1967; Siegel et al, 1996). Although the association of pyelonephritis with vesicoureteral reflux is well established, the association of renal abscess with vesicoureteral reflux has been infrequently noted (Segura and Kelalis, 1973). Case reports in the pediatric literature exist, but literature within the adult population is sparse. More recent observations, however, indicate that reflux is frequently associated with renal abscesses and persists long after sterilization of the urinary tract (Timmons and Perlmutter, 1976; Anderson and McAninch, 1980).

Clinical Presentation. The patient may present with fever, chills, abdominal or flank pain, and occasionally weight loss and malaise. Symptoms of cystitis may occur. Occasionally, these symptoms may be vague and delay diagnosis until surgical exploration or, in more severe cases, autopsy (Anderson and McAninch, 1980). A thorough history may reveal a gram-positive source of infection 1 to 8 weeks before the onset of urinary tract symptoms or symptoms consistent with UTI or pyelonephritis in the weeks prior (Hung et al, 2007). The infection may have occurred in any area of the body. Multiple skin carbuncles and IV drug abuse introduce gram-positive organisms into the bloodstream. Other common sites are the mouth, lungs, and bladder (Lyons et al, 1972). Complicated UTIs associated with stasis, calculi, pregnancy, neurogenic bladder, and diabetes mellitus also appear to predispose the patient to abscess formation (Anderson and McAninch, 1980).

Laboratory Diagnosis. The patient typically has marked leukocytosis. In Siegel and associates' (1996) series of 52 patients, blood cultures were positive 28% of the time, while Yen and colleagues (1999) published a series of 78 patients, 25 of which (32%) had positive blood cultures. When comparing positive cultures in all three types of fluids (abscess, blood, urine) only 1 patient of the 78 had identical isolates in all three. Urine and abscess culture had a 15% identical culture rate, whereas blood and abscess had a 13% identical culture rate (Yen et al, 1999). Pyuria and bacteriuria may not be evident unless the abscess communicates with the collecting system. Because gram-positive organisms are most commonly blood-borne, urine cultures in these cases typically show no

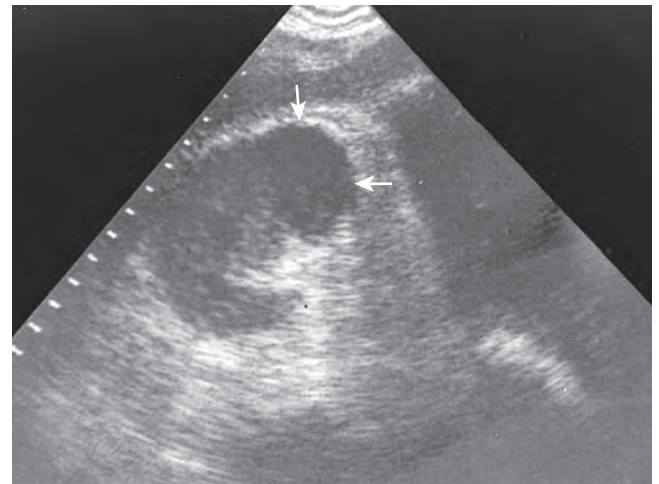


Figure 12-25. Acute renal abscess. Transverse ultrasound image of the right kidney demonstrates a poorly margined rounded focal hypoechoic mass (arrows) in the anterior portion of the kidney.

growth or a microorganism different from that isolated from the abscess. Another study showed not only a bacteremia rate of 26% but also that positive urine cultures were only present in roughly 30% of patients (Shu et al, 2004).

Ultrasonography and CT distinguish abscess from other inflammatory renal diseases. Ultrasonography is the quickest and least expensive method to demonstrate a renal abscess. An echo-free or low-echodensity space-occupying lesion with increased transmission is found on the ultrasound image (Fig. 12-25). The margins of an abscess are indistinguishable in the acute phase, but the structure contains a few echoes and the surrounding renal parenchyma is edematous (Fiegler, 1983). Subsequently, the appearance tends to be that of a well-defined mass. The internal appearance, however, may vary from a virtually solid lucent mass to one with large numbers of low-level internal echoes (Schneider et al, 1976). The number of echoes depends on the amount of cellular debris within the abscess. The presence of air results in

a strong echo with a shadow. Differentiation between an abscess and a tumor is impossible in many cases. Arteriography is used infrequently to demonstrate abscesses. The center of the mass tends to be hypervascular or avascular, with increased vascularity at the cortical margins and lack of vascular displacement and neovascularity.

CT appears to be the diagnostic procedure of choice for renal abscesses because it provides excellent delineation of the tissue. On CT, abscesses are characteristically well defined both before and after contrast agent enhancement. The findings depend in part on the age and severity of the abscess (Baumgarten and Baumgartner, 1997). Initially, CT shows renal enlargement and focal, rounded areas of decreased attenuation (Fig. 12-26). After several days of the onset of the infection, a thick fibrotic wall begins to form around the abscess. An echo-free or slightly echogenic mass caused by the presence of necrotic debris is seen. CT of a chronic abscess shows obliteration of adjacent tissue planes, thickening of the Gerota fascia, a round or oval parenchymal mass of low attenuation, and a surrounding inflammatory wall of slightly higher attenuation that forms a ring when the scan is enhanced with contrast material (Fig. 12-27). The ring sign is caused by the increased vascularity of the abscess wall (Callen, 1979; Gerzof and Gale, 1982).

Radionuclide imaging with gallium or indium is sometimes useful in evaluating patients with renal abscesses (see prior sections in this chapter and Chapter 2).

Management. Although the classic treatment for an abscess has been percutaneous or open incision and drainage, there is good evidence that use of IV antimicrobial agents and careful observation of a small abscess less than 3 cm or even 5 cm in a clinically stable patient is appropriate. Antibiotics, if begun early enough in the course of the process, may obviate surgical procedures (Hoverman et al, 1980; Levin et al, 1984; Shu et al, 2004). CT- or ultrasound-guided needle aspiration may be necessary to differentiate an abscess from a hypervascular tumor. Aspirated material should be cultured and appropriate antimicrobial therapy instituted on the basis of the findings.

All patients should be immediately started on IV antibiotic therapy. The selection of empirical antimicrobial therapy is dependent on the presumed source of the infection and the resistance patterns within the hospital. When hematogenous

dissemination is suspected, the pathogenic organism most frequently is penicillin-resistant *Staphylococcus*, and the antimicrobial of choice therefore is a penicillinase-resistant penicillin (Schiff et al, 1977). If a history of penicillin hypersensitivity is present, the recommended drug is vancomycin. Cortical abscesses that occur in the abnormal urinary tract are associated with more typical gram-negative pathogens secondary to ascending infection and should be treated empirically with IV third-generation cephalosporins, antipseudomonal penicillins, or aminoglycosides until specific therapy can be instituted. Patients should have serial examinations with ultrasonography or CT until the abscess resolves. The radiographic evolution or resolution of the abscesses will typically further dictate clinical management. The suspicion of misdiagnosis or an uncontrolled infection with the development of perinephric abscess or infection with an organism resistant to the antimicrobial agents used in therapy should be suspected with worsening clinical picture.

After patients are started on IV antibiotic therapy and there is radiographic confirmation of abscess, the size of the abscess typically dictates management. Abscesses 3 cm or less can be managed with antibiotics alone (Shu et al, 2004; Lee et al, 2010; Siegel et al, 1996). In a series from South Korea of 49 patients with normal urinary tracts and abscesses less than 5 cm, there was 100% resolution of abscesses confirmed with CT scan with antibiotics alone (Lee et al, 2010).

Though less data exist for patients with obstruction or anomalous urinary tracts, abscesses 3 to 5 cm in diameter should be

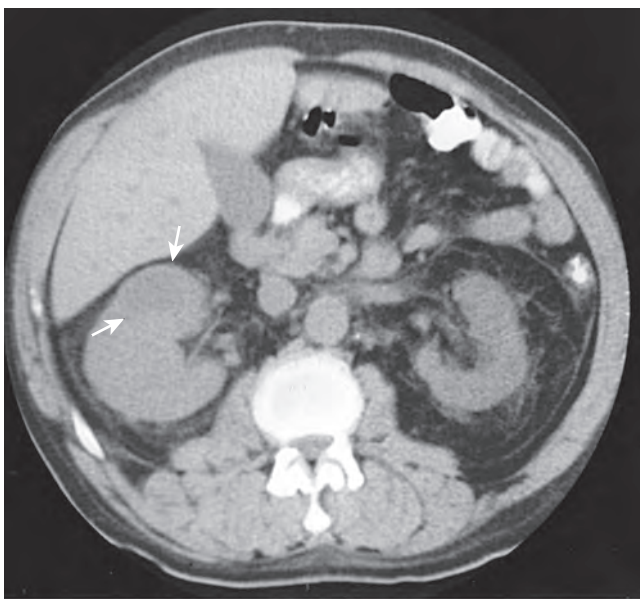


Figure 12-26. Acute renal abscess. Nonenhanced computed tomography scan through the mid pole of the right kidney demonstrates right renal enlargement and an area of decreased attenuation (arrows). After antimicrobial therapy, a follow-up scan showed complete regression of these findings.

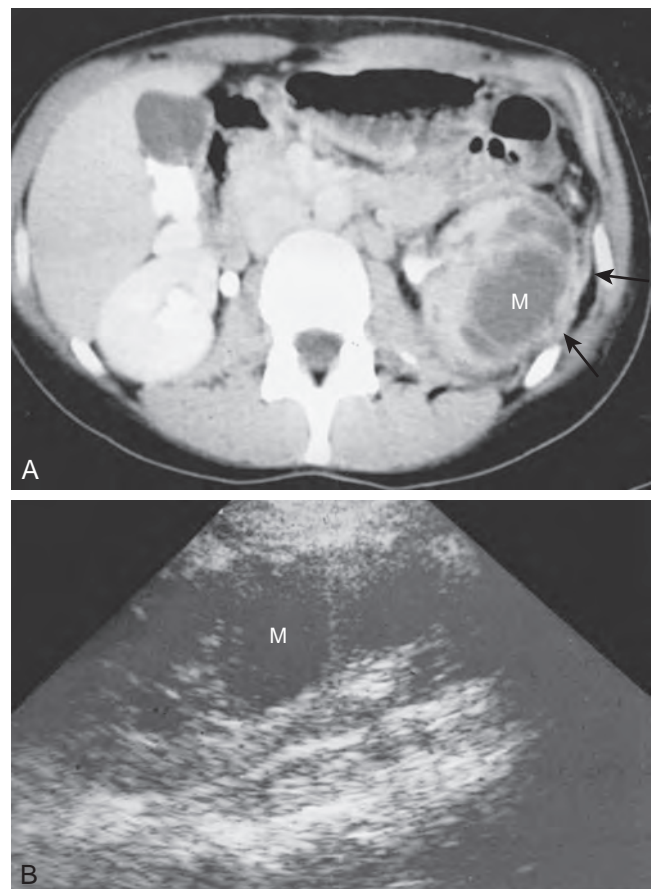


Figure 12-27. Chronic renal abscess. A, Enhanced computed tomography scan shows an irregular septated low-density mass (M) extensively involving the left kidney. Note thickening of perinephric fascia (arrows) and extensive compression of the renal collecting system. Findings are typical of renal abscess. B, Ultrasound longitudinal image demonstrates a septated hypoechoic mass (M) occupying much of the renal parenchymal volume.

conservatively managed initially in the setting of stable clinical parameters. We suggest following the clinical course and size of the abscess radiographically to assess for improvement. Should the patient progress, percutaneous drainage should be considered. Abscesses of all sizes in immunocompromised hosts or those that do not respond to antimicrobial therapy should be drained percutaneously (Fernandez et al, 1985; Fowler and Perkins, 1994; Siegel et al, 1996). Percutaneous drainage, however, remains the first-line procedure of choice for most renal abscesses greater than 5 cm in diameter. Typically, abscesses of this size require multiple drains, multiple drain manipulations, or eventual surgical washout and potential nephrectomy (Siegel et al, 1996).

Infected Hydronephrosis and Pyonephrosis

Infected hydronephrosis is bacterial infection in a hydronephrotic kidney. The term *pyonephrosis* refers to infected hydronephrosis associated with suppurative destruction of the parenchyma of the kidney, in which there is total or nearly total loss of renal function (Fig. 12-28). Where infected hydronephrosis ends and pyonephrosis begins is difficult to determine clinically. Rapid diagnosis and treatment of pyonephrosis are essential to avoid permanent loss of renal function and to prevent sepsis.

Clinical Presentation. The patient is usually very ill, with high fever, chills, flank pain, and tenderness. Occasionally, however, a patient may have only an elevated temperature and a complaint of vague gastrointestinal discomfort. A previous history of urinary tract calculi, infection, or surgery is common. Bacteriuria may not be present if the ureter is completely obstructed.

Radiologic Findings. The ultrasonographic diagnosis of infected hydronephrosis depends on demonstration of internal echoes within the dependent portion of a dilated pyelocalyceal system. CT is nonspecific but may show thickening of the renal pelvis, stranding of the perirenal fat, and a striated nephrogram. Ultrasonography demonstrates hydronephrosis and fluid debris levels within the dilated collecting system (Corriere and Sandler, 1982) (Fig. 12-29A). The diagnosis of pyonephrosis is suggested if focal areas of decreased echogenicity are seen within the hydronephrotic parenchyma.

Management. Once the diagnosis of pyonephrosis is made, the treatment is initiated with appropriate antimicrobial drugs and

drainage of the infected pelvis. A ureteral catheter can be passed to drain the kidney, but if the obstruction prevents this, a percutaneous nephrostomy tube should be placed (Camunez et al, 1989) (Fig. 12-29B). When the patient becomes hemodynamically stable, other procedures are usually needed to identify and treat the source of the obstruction.

Perinephric Abscess

Perinephric abscess usually results from rupture of an acute cortical abscess into the perinephric space or from hematogenous seeding from sites of infection. Patients with pyonephrosis,



Figure 12-28. Pyonephrosis: gross specimen. The kidney shows marked thinning of the renal cortex and medulla, suppurative destruction of the parenchyma (arrows), and distention of the pelvis and calyces. Previous incision released a large quantity of purulent material. The ureter showed obstruction distal to the point of section.

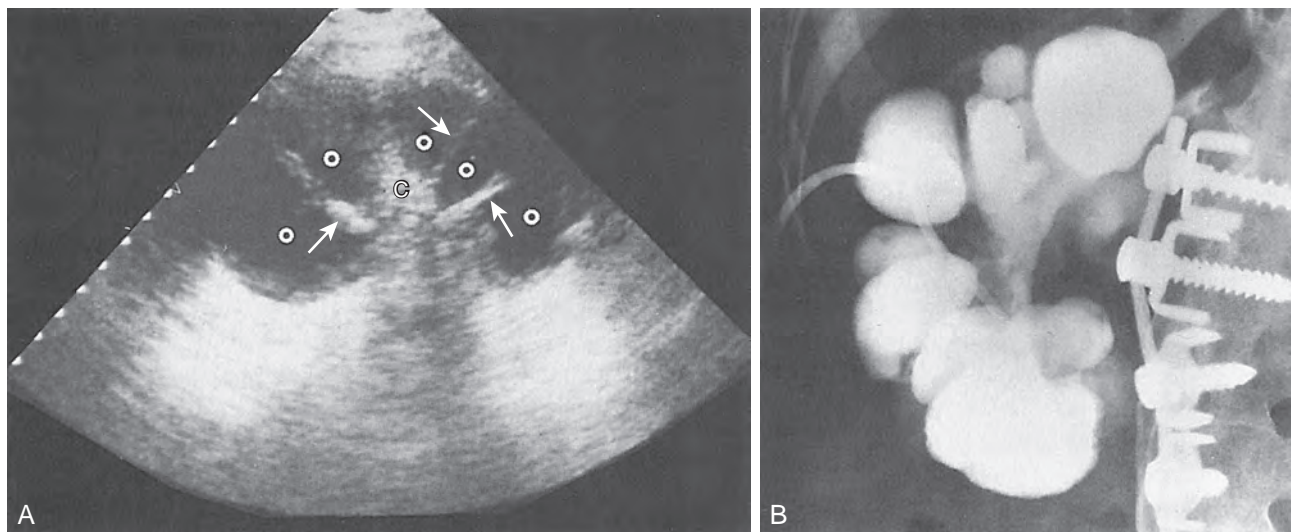


Figure 12-29. Pyonephrosis. A, Longitudinal ultrasound image of the right kidney demonstrates echogenic central collecting complex (C) with radiating echogenic septa (arrows) and thinned hypoechoic parenchyma. Multiple dilated calyces (o) with diffuse low-level echoes are seen. B, Antegrade pyelogram performed through a percutaneous nephrostomy catheter correlates well with the ultrasound image. Dilated pus-filled calyces are demonstrated. The renal pelvis is obliterated by chronic scarring and stone disease. The kidney did not regain function. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

particularly when a calculus is present in the kidney, are susceptible to perinephric abscess formation. Diabetes mellitus is present in approximately one third of patients with perinephric abscess (Edelstein and McCabe, 1988; Meng et al, 2002). In about one third of the cases, perinephric abscess is caused by hematogenous spread, usually from sites of skin infection (Gardiner et al, 2011). A perirenal hematoma can become secondarily infected by the hematogenous route or by direct extension of a primary renal infection. When a perinephric infection ruptures through the Gerota fascia into the paranephric space, the abscess becomes paranephric. Paranephric abscesses may also result from infectious disorders of the bowel, pancreas, or pleural cavity. Conversely, perinephric or psoas abscess may be the result of bowel perforation, Crohn disease, or spread of osteomyelitis from the thoracolumbar spine. *E. coli*, *Proteus*, and *S. aureus* account for most infections.

Clinical Presentation. The onset of symptoms is typically insidious. Symptoms are present for more than 5 days in most patients with perinephric abscess compared with only about 10% of patients with pyelonephritis. The clinical presentation may be similar to that of pyelonephritis; however, more than one third of patients may be afebrile. An abdominal or flank mass can be felt in about half of the cases; costovertebral angle tenderness is typically present. Psoas abscess should be suspected if the patient has a limp and flexion and external rotation of the ipsilateral hip. Laboratory features include leukocytosis, elevated levels of serum creatinine, and pyuria in more than 75% of cases. Edelstein and McCabe (1988) showed that results of urine cultures predicted perinephric abscess isolates in only 37% of cases; a blood culture, particularly with multiple organisms, was often indicative of perinephric abscess but identified all organisms in only 42% of cases. Meng et al (2002) showed that roughly 75% of patients had a positive culture. Urine was statistically significantly more sensitive than blood and abscess fluid collection in their study. Therefore caution should be exercised when choosing therapy based on the results of urine and blood cultures because data may sometimes be inadequate. Pyelonephritis usually responds within 4 to 5 days of appropriate antimicrobial therapy; perinephric abscess does not. Thus perinephric abscess should be suspected in a patient with UTI and abdominal or flank mass or persistent fever after 4 days of antimicrobial therapy. Perinephric abscesses are commonly seen concomitantly with renal abscesses.

CT is particularly valuable for demonstrating the primary abscess. In some cases, the abscess is confined to the perinephric space; however, extension to the flank or psoas muscle may occur (Fig. 12-30). CT is able to show with exquisite anatomic detail the route of spread of infection into the surrounding tissues (Fig. 12-31). This information may be helpful in planning the approach for surgical drainage. Ultrasonography demonstrates a diverse appearance ranging from a nearly anechoic mass displacing the kidney to an echogenic collection that tends to blend with normally echogenic fat within the Gerota fascia (Corriere and Sandler, 1982). Occasionally, a retroperitoneal or subdiaphragmatic infection may spread to the paranephric fat that is outside this fascia. The clinical symptoms of insidious onset of fever, flank mass, and tenderness are indistinguishable from those associated with perinephric abscess. UTI, however, is absent. Ultrasonography and CT can usually delineate the abscess outside the Gerota fascia.

Improved imaging techniques have decreased the mortality rate of 40% to 50% in early series to roughly 12%, but there is still an average of 3.4 days' lag time before appropriate diagnosis in a current series (Meng et al, 2002). Only 35% of patients were correctly diagnosed on presentation in the Meng series, and this lag time contributed to mortality in nearly all patients in that series. Having an appropriate threshold for imaging will continue to improve the rate of correct diagnoses.

Management. Antimicrobial agents should be immediately started upon diagnosis of perinephric abscess. Gram stain identifies the pathogenesis and guides antimicrobial therapy. An aminoglycoside together with an antistaphylococcal agent, such as methicillin or oxacillin, should be started immediately. If the

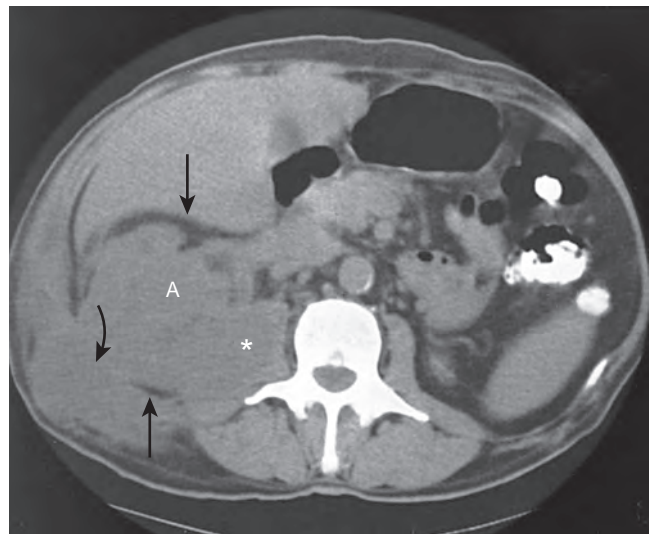


Figure 12-30. Nonenhanced computed tomography scan through the lower pole of the right kidney (previous left nephrectomy) shows extensive perinephric abscess. Extensive abscess (A) distorts and enlarges the renal contour, infiltrates perinephric fat (straight arrows), and also extends into the psoas muscle (asterisk) and the soft tissues of the flank (curved arrow). Also note that normal renal collecting system fat has been obliterated by the process.

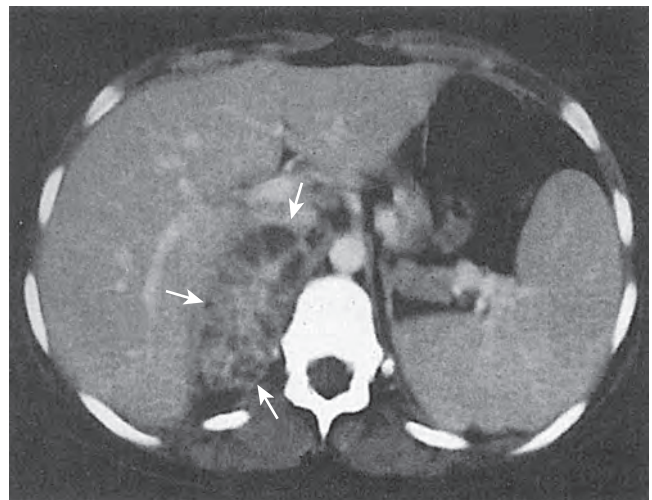


Figure 12-31. Perinephric abscess involving the right adrenal gland. Computed tomography scan shows large right pararenal mass (arrows) with multiple low-density areas within. At surgery, a large pararenal abscess with extensive involvement of the right adrenal was found. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

patient has a penicillin hypersensitivity, cephalothin or vancomycin may be used.

In addition to controlling sepsis and preventing further spread of infection, Meng and colleagues' series of 25 patients suggests that, for small perinephric abscesses (<3 cm), antibiotics alone can appropriately treat immune-competent patients (Meng et al, 2002). Eight out of the 10 patients treated with antibiotics alone had full resolution after a mean of 10 days in the hospital. The average size of abscess treated was 1.8 cm. Siegel and coworkers (1996) also showed good resolution of perinephric abscesses less than 3 cm, with cure seen in all five patients in their series.

For larger collections or those not responsive to initial antibiotic therapy, intervention is the next step in treatment. **Surgical drainage, or nephrectomy** if the kidney is nonfunctioning or severely infected, was the classic treatment for perinephric abscesses. However, with the advent of the field of interventional radiology and improvements in percutaneous drainage techniques, renal ultrasonography and CT- or ultrasound-guided percutaneous aspiration and drainage of perirenal collections is now a good option for therapy. In Meng's study, 11 of the 25 patients had percutaneous drainage in addition to antibiotics (Meng et al, 2002). The mean abscess size was 11 cm and the mean time to resolution was 25 days. Four of these patients eventually required open surgical exploration and drainage. All removed kidneys demonstrated hallmarks of minimal function. **Unlike in renal abscesses, early drainage of abscesses greater than 3 cm in diameter is recommended.**

Once the perinephric abscess has been drained, the underlying problem must be dealt with. Some conditions such as renal cortical abscess or enteric communication require prompt attention. Nephrectomy for pyelonephrosis may be performed concurrent with drainage of the perinephric abscess if the patient's condition is good. In other instances it is best to drain the perinephric abscess first and correct the underlying problem or perform a nephrectomy when the patient's condition has improved. Meng's series of 11 patients with abscesses greater than 11 cm had a roughly 33% need for nephrectomy (Meng et al, 2002). Although this is a high number in patients who are likely diabetic where the nephron-sparing approach is ideal, it is decidedly lower than the historical nephrectomy rate, likely secondary to more successful percutaneous drainage rates. In three of their patients with small perinephric abscesses and hydronephrosis, antibiotics and drainage of the obstructed urinary system led to cure.

Perinephric Abscess versus Acute Pyelonephritis. It has already been emphasized that the greatest obstacle to the treatment of perinephric abscess is the delay in diagnosis. In the series of Thorley and colleagues (1974), a common misdiagnosis was acute pyelonephritis; Meng's study showed a similar delay of roughly 3 to 4 days in appropriate diagnosis in a modern study (Meng et al, 2002). Thorley's study found that two factors differentiated perinephric abscess and acute pyelonephritis: (1) most patients with uncomplicated pyelonephritis were symptomatic for less than 5 days before hospitalization, whereas most with perinephric abscesses were symptomatic for longer than 5 days; and (2) no patient with acute pyelonephritis remained febrile for longer than 4 days once appropriate antimicrobial agents were started. All patients with perinephric abscesses had a fever for at least 5 days, with a median of 7 days. Similar results were noted by Fowler and Perkins (1994).

Patients with polycystic renal disease who undergo hemodialysis may be particularly susceptible to the progression from acute UTIs to perinephric abscess. Of 445 patients undergoing chronic hemodialysis at the Regional Kidney Disease Program in Minneapolis, 5.4% had polycystic kidney disease and 33.3% of these patients developed symptomatic UTIs (Sweet and Keane, 1979). Eight (62.5%) developed perinephric abscesses, and three of these patients died. According to the investigators, all UTIs, even those that progressed to perinephric abscesses, were promptly treated with appropriate antimicrobial agents, and all patients in this group became afebrile and asymptomatic when the agents were stopped. Yet later, after various times, symptoms attributable to perinephric abscess developed in eight of the patients. The mechanism of this process is not clear, but the limited bioavailability of some antimicrobial agents in cysts is variable and could contribute to the progression of renal infection.

Chronic Pyelonephritis

In patients without underlying renal or urinary tract disease, chronic pyelonephritis secondary to UTI is a rare disease and an even more rare cause of chronic renal failure. In patients with underlying functional or structural urinary tract abnormalities,

however, chronic renal infection can cause significant renal impairment. Thus it is essential that appropriate studies be used to diagnose, localize, and treat chronic renal infection.

The prevalence of chronic pyelonephritis has also been assessed in patients undergoing dialysis for end-stage renal disease. Despite a 2% to 5% prevalence of bacteriuria in women, pyelonephritis uncomplicated by obstruction or urinary tract malformation does not cause end-stage renal disease. Schechter and colleagues (1971) analyzed the cause for renal failure in 170 patients referred to them for dialysis. Chronic pyelonephritis was the primary cause of end-stage renal disease in 22 (13%) but was usually associated with an underlying structural defect. Unequivocal nonobstructive chronic pyelonephritis was not found. Symptomatic infections tended to occur before the onset of azotemia in most patients with chronic pyelonephritis. Similarly, Huland and Busch (1982) evaluated 161 patients with end-stage renal disease and found that 42 had chronic pyelonephritis. However, in addition to a history of UTIs, these 42 patients had complicating defects, such as vesicoureteral reflux, analgesic abuse, nephrolithiasis, or obstruction. Nonobstructive uncomplicated UTI alone was never found to be the cause of renal insufficiency. Thus, using end-stage renal disease seen at autopsy or at the dialysis clinic as an indicator, the prevalence of uncomplicated chronic bacterial pyelonephritis is rare.

In addition, the role of bacterial infection in development of chronic renal disease can be assessed in patients with renal interstitial and tubular damage similar to that which has classically been called chronic pyelonephritis. The frequency with which various potential causes of interstitial damage are operative in patients with interstitial nephritis was assessed by Murray and Goldberg (1975). These investigators not only concluded that UTI is rarely the sole cause of chronic renal disease in the adult but also observed that 89% of their azotemic patients had a readily identifiable primary cause of their interstitial nephritis. Thus, when patients with a clinical diagnosis of chronic interstitial nephritis are selected as the starting point, it is easy to associate many factors with this disease, but UTI does not seem to be one of them.

Clinical Presentation. There are no symptoms of chronic pyelonephritis until it produces renal insufficiency, and then the symptoms are similar to those of any other form of chronic renal failure. If a patient's chronic pyelonephritis is thought to be an end result of many episodes of acute pyelonephritis, a history of intermittent symptoms of fever, flank pain, and dysuria may be elicited. Similarly, urinary findings and the presence of renal infection correlate poorly. Bacteriuria and pyuria, the hallmarks of UTI, are not predictive of renal infection. Conversely, patients with significant renal infection may have sterile urine if the ureter draining the kidney is obstructed or the infection is outside of the collecting system.

The pathologic and radiologic criteria for diagnosing renal infection may also be misleading. Asscher (1980) has tabulated eight long-term follow-up studies from the literature on kidneys of adults with UTIs. The data from these reports on 901 patients show that bacteriuria present in otherwise healthy adults for long periods may be associated with nonexistent or extremely minimal evidence of kidney damage. Conversely, patients who have chronic pyelonephritis may have negative urine cultures.

Radiologic Findings. The diagnosis of chronic pyelonephritis can be made with the greatest confidence on the basis of pyelographic findings. The essential features are asymmetry and irregularity of the kidney outlines, blunting and dilation of one or more calyces, and cortical scars at the corresponding site (Fig. 12-32). In the absence of stones, obstruction, and tuberculosis, and with the single exception of analgesic nephritis with papillary necrosis (which can be readily excluded by history), chronic pyelonephritis is virtually the only disease that produces a localized scar over a deformed calyx (Stamey, 1980). In advanced pyelonephritis, calyceal distortion and irregularity together with cortical scars complete the picture. Regardless of the etiology of chronic pyelonephritis, CT findings will be consistent with atrophy, cortical/parenchymal thinning, calyceal clubbing, and possible hypertrophy of residual normal tissue and asymmetry (Craig et al, 2008). D'Souza and colleagues (1995) showed a linear relationship between renal

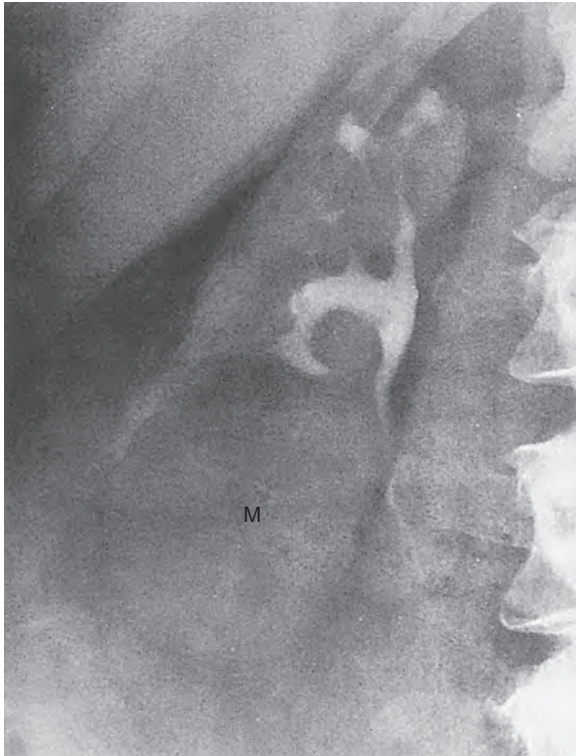


Figure 12-32. Chronic pyelonephritis. Ten-minute excretory urogram demonstrates irregular renal outline with upper pole parenchymal atrophy. Note significant loss of renal cortical thickness over blunted and dilated calyces. Lower pole mass (M) is a simple cyst. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. *Adult and pediatric urology*. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

parenchymal volume loss and function decline as assessed by DMSA scan. Hodson and Wilson (1965) pointed out that renal infarction, an extremely rare condition, may closely resemble pyelonephritic scars but that the renal pyramid remains with renal infarction in contradistinction to pyelonephritis.

Pathology. In chronic pyelonephritis, the gross kidney is often diffusely contracted, scarred, and pitted. The scars are Y-shaped, flat, broad-based depressions with red-brown granular bases. The scarring is often polar with underlying calyceal blunting. The parenchyma is thin, and the corticomedullary demarcation is lost. **Histologic changes are patchy.** There is usually an interstitial infiltrate of lymphocytes, plasma cells, and occasional polymorphonuclear cells. Portions of the parenchyma may be replaced by fibrosis, and, although glomeruli may be preserved, periglomerular fibrosis is often seen. In some affected areas, glomeruli may be completely fibrosed and tubules atrophied. Leukocyte and hyaline casts are sometimes present in the tubules; the latter may cause resemblance to the thyroid colloid, hence the description *renal thyroidization* (Braude, 1973). In general, the changes are nonspecific; they also may be seen in toxic exposures, postobstructive atrophy, hematologic disorders, postirradiation nephritis, ischemic renal disease, and nephrosclerosis.

Management. Management of radiographic evidence of pyelonephritis should be directed at treating infection if present, preventing future infections, and monitoring and preserving renal function. The treatment of existing infection must be based on careful antimicrobial susceptibility tests and selection of drugs that can achieve bactericidal concentrations in the urine and yet are not nephrotoxic. Achievement of acceptable bactericidal levels of a drug in the urine of a patient with chronic pyelonephritis may be difficult because the diminished concentrating ability of pyelonephritis may impair excretion and concentration of the antimicrobial agent. The

duration of antimicrobial therapy is often prolonged to maximize the chance of cure. With patients in whom renal damage develops or progresses in the presence of UTI, the working hypothesis should be that there is an underlying renal, usually papillary, lesion or underlying urologic condition, such as obstruction or calculus, which has increased susceptibility to renal damage. Appropriate nephrologic and urologic evaluation should be undertaken to identify and, if possible, correct these abnormalities.

Bacterial “Relapse” from a Normal Kidney

The concept that bacteria persist in the renal parenchyma between bacteriuric episodes and cause “relapsing” UTIs was based on a study by Turck and colleagues (1968) that suggested that bacterial persistence could be recognized by simply identifying two consecutive recurrent infections with the same organism. Unfortunately, this study did not indicate whether the urine was cultured during therapy to ensure that the original infection had actually been eradicated. It is possible that some of these so-called relapses were in fact unresolved initial infections and that ureteral edema associated with catheterization may have impeded clearance of the initial infecting strain.

Subsequent studies summarized by Stamey (1980) and Forland and associates (1977) have shown that in a normal urinary tract recurrent infections are not caused by relapse from bacterial persistence in the kidney. With ureteral catheterization techniques, Cattell and colleagues (1973) localized the site of bacteriuria in 42 patients who had follow-up for 6 months after therapy. He analyzed the response to antimicrobial therapy of 2 weeks’ duration. Of the 26 patients who were cured of their initial infection, 16 had recurrence with the same organism, 8 had upper tract infections, and 8 had bladder bacteriuria.

Most of the changes of chronic pyelonephritis seem to occur in infancy, probably because the growing kidney is most susceptible to scarring. A review that examined the long-term effect of UTIs in adults concluded that renal damage is rare in non-obstructive UTIs (Stamey, 1980), but it does occur (Bailey et al, 1969; Davies et al, 1972; Davidson and Talner, 1973; Feldberg, 1982).

The association between hypertension and the pyelonephritic kidney has been addressed by Pfau and Rosenmann (1978), who concluded that the association of chronic pyelonephritis and hypertension is usually coincidental. Their conclusion agrees with that of a study by Parker and Kunin (1973) that examined 74 women who had been admitted to the hospital 10 to 20 years previously for pyelonephritis. Only 14.5% of these women had hypertension, a rate similar to that found in a random female population of the same age.

Infectious Granulomatous Nephritis

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis (XGP) is a rare, severe, chronic renal infection typically resulting in diffuse renal destruction. Most cases are unilateral and result in a nonfunctioning, enlarged kidney associated with obstructive uropathy secondary to nephrolithiasis. XGP is characterized by accumulation of lipid-laden foamy macrophages. It begins within the pelvis and calyces and subsequently extends into and destroys renal parenchymal and adjacent tissues. It has been known to imitate virtually every other inflammatory disease of the kidney, as well as renal cell carcinoma, on radiographic examination (Malek and Elder, 1978; Tolia et al, 1980). In addition, the microscopic appearance of XGP has been confused with clear cell adenocarcinoma of the kidney on frozen section and has led to radical nephrectomy (Anhalt et al, 1971; Malek and Elder, 1978; Flynn et al, 1979; Lorentzen and Nielsen, 1980; Tolia et al, 1980). The entity is uncommon and is found in only about 0.6% (Malek et al, 1972) to 1.4% (Ghosh, 1955) of patients with renal inflammation who are evaluated pathologically.

Pathogenesis. The primary factors involved in the pathogenesis of XGP are nephrolithiasis, obstruction, and infection (Gregg et al, 1999). Nephrolithiasis has been noted in as many as 83% of the patients in various series; approximately half of the renal stones have been of the staghorn type (Parsons et al, 1983; Chuang et al, 1992; Nataluk et al, 1995). It has been proposed clinically and demonstrated experimentally that primary obstruction followed by infection with *E. coli* can lead to tissue destruction and collections of lipid material by macrophages (Povysil and Konickova, 1972). These macrophages (xanthoma cells) are distributed in sheets around parenchymal abscesses and calyces and are intermixed with lymphocytes, giant cells, and plasma cells. The bacteria appear to be of low virulence because spontaneous bacteremia has rarely been described. Other possible interrelated factors include venous occlusion and hemorrhage, abnormal lipid metabolism, lymphatic blockage, failure of antimicrobial therapy in UTI, altered immunologic competence, and renal ischemia (Friedenberg and Spjut, 1963; Mering et al, 1973; Goodman et al, 1979; McDonald, 1981; Tolia et al, 1981). The concept that XGP is related to incomplete bacterial degradation and altered host response has received mixed support (Nielsen and Lorentzen, 1981; Khalyil-Mawad et al, 1982). Thus it appears that there is probably no single factor that is instrumental in the pathogenesis of this disease. Rather, there is an inadequate host acute inflammatory response within an obstructed, ischemic, or necrotic kidney.

Pathology. The kidney is usually massively enlarged and has a normal contour. XGP may be diffuse, as in approximately 80% of the patients, or segmental. In the diffuse form of the disease, the entire kidney is involved, whereas in segmental XGP, only the parenchyma surrounding one or more calyces or one pole of a duplicated collecting system is involved. On sectioning, the kidney usually demonstrates nephrolithiasis and peripelvic fibrosis. The

calyces are dilated and filled with purulent material, but fibrosis surrounding the pelvis usually prevents dilation. The papillae are often destroyed by papillary necrosis (Goodman et al, 1979). In advanced stages of the disease, multiple parenchymal abscesses are filled with viscous pus and lined by yellowish tissue (Fig. 12-33A). The cortex is often thin and replaced by xanthogranulomatous tissue. The capsule is often thickened, and extension of the inflammatory process into the perinephric or paranephric space is common (Goodman et al, 1979; McDonald, 1981; Gregg et al, 1999).

On microscopic examination, the yellowish nodules that line the calyces and surround the parenchymal abscesses contain dark sheets of lipid-laden macrophages (foamy histiocytes with small, dark nuclei and clear cytoplasm) intermixed with lymphocytes, giant cells, and plasma cells (Fig. 12-33B). Xanthogranulomatous cells are not specific to XGP but may be present anywhere inflammation or obstruction coexists. The origin of the fatty substance is disputed. Cholesterol esters that make up a part of the lipid might be derived from lysis of erythrocytes after hemorrhage (Saeed and Fine, 1963).

Clinical Presentation. XGP should be suspected in patients with UTIs and a unilateral enlarged nonfunctioning or poorly functioning kidney with a stone or a mass lesion indistinguishable from malignant tumor. Most patients present with flank pain (69%), fever and chills (69%), and persistent bacteriuria (46%) (Malek and Elder, 1978). Additional vague symptoms, such as malaise, may be present. On physical examination, 62% of the patients had a flank mass and 35% had previous calculi (Malek and Elder, 1978). Less commonly, hypertension, hematuria, or hepatomegaly is the presenting complaint. The medical history is often positive for UTIs and urologic instrumentation (Malek and Elder, 1978; Flynn et al, 1979; Goodman et al, 1979; Grainger et al, 1982; Yazaki et al, 1982; Petronic et al, 1989; Eastham et al, 1994; Nataluk et al, 1995). Diabetics also appear to be at greater risk of

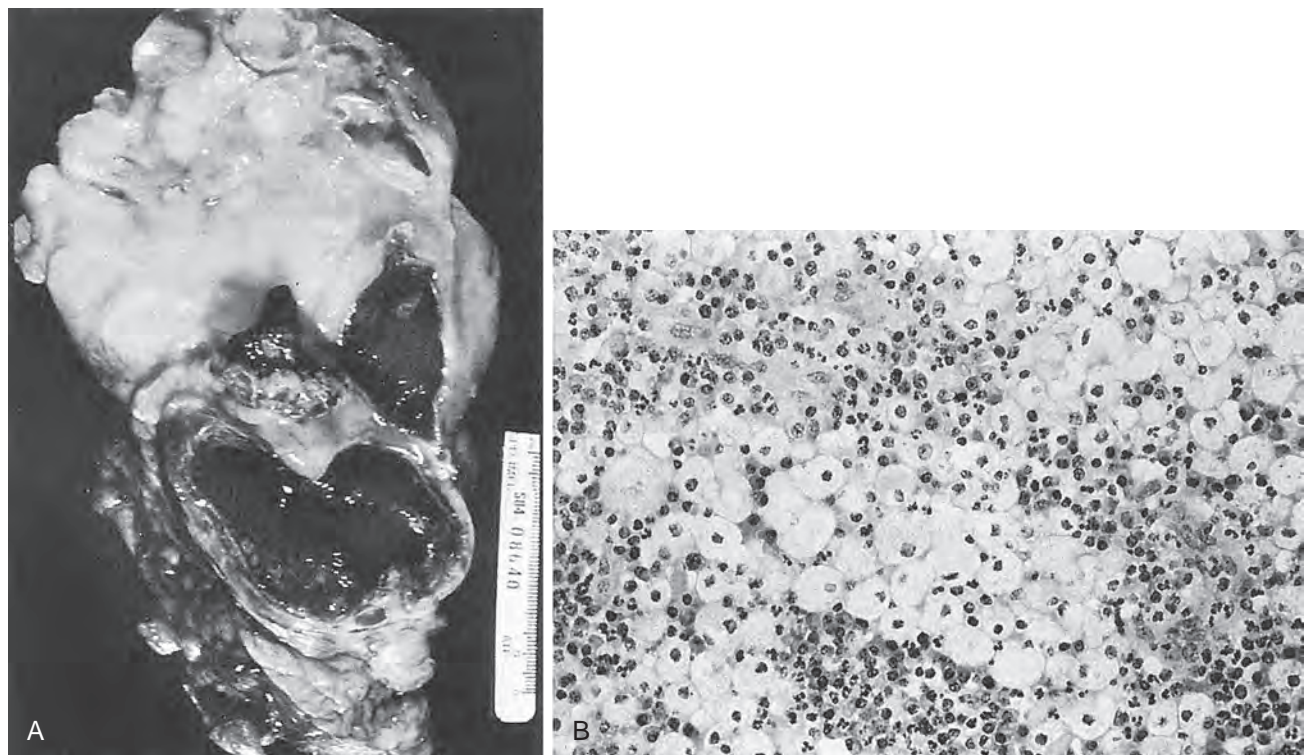


Figure 12-33. Xanthogranulomatous pyelonephritis. A, Gross specimen. Kidney is massively enlarged, measuring 23 × 12 cm; the normal architecture is replaced by a shaggy yellow upper pole mass corresponding to xanthogranulomatous inflammation and numerous distorted and dilated calyces. B, Microscopically, the shaggy yellow tissue is composed primarily of lipid-laden histiocytes mixed with other inflammatory cells. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

developing the disease (Eastham et al, 1994). Although it may occur at any age, the peak incidence of XGP is in the fifth to the seventh decade. Women are more commonly affected than men. There is no predilection for either kidney.

Bacteriology and Laboratory Diagnosis. Although review of the literature shows *Proteus* to be the most common organism involved with XGP (Anhalt et al, 1971; Tolia et al, 1981), *E. coli* is also common. The prevalence of *Proteus* organisms may reflect their association with stone formation and subsequent chronic obstruction and irritation. Malek and Elder (1978), in their analysis of 26 cases, found that renal tissue cultures grew bacteria in 22 of 23 cases. Anaerobes also have been cultured (Malek and Elder, 1978).

Approximately 10% of patients have mixed cultures. About one third of patients have no growth in their urine, probably because many patients have recently taken or are taking antimicrobial agents when cultures are obtained. The infecting organism may be revealed only by tissue cultures obtained during surgery. Urinalysis usually shows pus and protein. In addition, blood tests often reveal anemia and may show hepatic dysfunction in up to 50% of the patients (Malek and Elder, 1978).

XGP is almost always unilateral; therefore azotemia or frank renal failure is uncommon (Goodman et al, 1979; Gregg et al, 1999).

CT is probably the most useful radiologic technique in evaluating patients with XGP (Fig. 12-34). Fifty to eighty percent of patients show the classic triad of unilateral renal enlargement with little or no function and a large calculus in the renal pelvis (Elder, 1984). CT usually demonstrates a large, reniform mass with the renal pelvis tightly surrounding a central calcification but without pelvic dilatation (Solomon et al, 1983; Goldman et al, 1984; Hartman, 1985). Renal parenchyma is replaced by multiple water-density masses representing dilated calyces and abscess cavities filled with varied amounts of pus and debris. On enhanced scans, the walls of these cavities demonstrate a prominent blush owing to the abundant vascularity within the granulation tissue. The cavities themselves, however, fail to enhance, whereas tumors and other inflammatory lesions usually do. The CT scan is particularly helpful in demonstrating the extent of renal involvement and may indicate whether adjacent organs or the abdominal wall are involved by XGP (Eastham et al, 1994; Kaplan et al, 1997).



Figure 12-34. Xanthogranulomatous pyelonephritis. Enhanced computed tomography scan shows collecting system and parenchymal calculi (straight black arrows) with lower pole pyonephrosis (curved white arrow) and an irregular, predominantly low-density perinephric abscess (A) extending into the soft tissues of the flank.

Ultrasonography usually demonstrates global enlargement of the kidney (Merenich and Popky, 1991). The normal renal architecture is replaced by multiple hypoechoic fluid-filled masses that correspond to debris-filled, dilated calyces or foci of parenchymal destruction (Fagerholm, 1983; Hartman et al, 1984). With focal involvement, a solid mass involving a segment of the kidney is demonstrated with an associated calculus in the collecting system or ureter. Renal cell carcinoma and other solid renal lesions must be considered in the differential diagnosis (Elder, 1984).

Radionuclide renal scanning using ^{99m}Tc -DMSA is used to confirm and quantify the differential lack of function in the involved kidney (Gregg et al, 1999). MRI has not yet superseded CT in the evaluation of renal inflammation, but it provides some advantages in delineating extrarenal extension of inflammation (Soler et al, 1997). Lesions of XGP may appear as cystic foci of intermediate intensity signal on T1-weighted images and hyperintensity on T2-weighted images. Arteriography shows hypovascular areas, but there may be some hypovascular areas (Malek and Elder, 1978; Van Kirk et al, 1980; Tolia et al, 1981). Therefore radiologic studies, although distinctive, often cannot be used to differentiate between XGP and renal cell carcinoma.

Differential Diagnosis. Diagnosis of segmental XGP without calculi may be difficult. XGP in association with massive pelvic dilation cannot be distinguished from pyonephrosis. When XGP occurs within a small contracted kidney, the radiographic findings are nonspecific and nondiagnostic. Renal parenchymal malacoplakia may show renal enlargement and multiple inflammatory masses replacing the normal renal parenchyma, but calculi are usually not present. Renal lymphoma may be associated with multiple hypoechoic masses surrounding the contracted, nondilated pelvis, but lymphoma is usually clinically obvious, and renal involvement is usually bilateral and not associated with calculi (Hartman, 1985).

Management. The primary obstacle to the correct treatment of XGP is incorrect diagnosis. Today with CT technology, the diagnosis of XGP is made preoperatively nearly 90% of the time (Eastham et al, 1994; Nataluk et al, 1995). Antimicrobial therapy may be necessary to stabilize the patient preoperatively, and, occasionally, long-term antimicrobial therapy will eradicate the infection and restore renal function (Mollier et al, 1995). Because the renal abnormality may be diagnosed preoperatively as a renal tumor and/or is diffuse, nephrectomy is usually performed. If localized XGP is diagnosed preoperatively or at exploration, it is amenable to partial nephrectomy (Malek and Elder, 1978; Tolia et al, 1980; Osca et al, 1997).

The lipid-laden macrophages associated with XGP, however, closely resemble clear cell adenocarcinoma and may be difficult to distinguish solely on the basis of frozen section. Furthermore, XGP has been associated with renal cell carcinoma, papillary transitional cell carcinoma of the pelvis or bladder, and infiltrating squamous cell carcinoma of the pelvis (Schoborg et al, 1980; Pitts et al, 1981; Tolia et al, 1981); thus, if malignant renal tumor cannot be excluded, nephrectomy should be performed. When diffuse and extensive disease into the retroperitoneum exists, removal of the kidney and perinephric fat may be needed. Under these circumstances, the surgery may be difficult and may involve dissection of granulomatous tissue from the diaphragm, great vessels, and bowel (Malek and Elder, 1978; Flynn et al, 1979). It is important to remove the entire inflammatory mass because in nearly three fourths of patients, xanthogranulomatous tissue is infected. If incision and drainage alone are performed rather than nephrectomy, the patient may continue to suffer from protracted debilitating illness and may develop a renal cutaneous fistula; an even more difficult nephrectomy will then be necessary. One early case-matched series of laparoscopic nephrectomies performed for XGP concluded that the benefits of laparoscopic surgery do not extend to the treatment of this disease (Bercowsky et al, 1999); however, a larger review of a modern XGP experience suggests that laparoscopic nephrectomy is a reasonable treatment approach. Some studies suggest a retroperitoneal approach laparoscopically and, if transperitoneal, the use of a

hand-assist port (Tobias-Machado et al, 2005). High conversion rates were seen across multiple studies (Korkes et al, 2008)

Malacoplakia

Malacoplakia, from the Greek word meaning “soft plaque,” is an unusual inflammatory disease that was originally described to affect the bladder but has been found to affect the genitourinary and gastrointestinal tracts, skin, lungs, bones, and mesenteric lymph nodes. It is an inflammatory lesion described originally by Michaelis and Gutmann (1902). It was characterized by von Hansemann (1903) as soft, yellow-brown plaques with granulomatous lesions in which the histiocytes contain distinct basophilic lysosomal inclusion bodies or Michaelis-Gutmann bodies. Although its exact pathogenesis is unknown, malacoplakia probably results from abnormal macrophage function in response to a bacterial infection, which is most often *E. coli*.

Pathogenesis. The pathogenesis is unknown, but several theories are popular. In 93 patients who had cultures of urine, diseased tissue, or blood, 89.4% had coliform infections (Stanton and Maxted, 1981). Moreover, 40% of the patients in this review had an immunodeficiency syndrome, autoimmune disease, carcinoma, or another systemic disorder. This association of coliform infections and compromised health status in patients with malacoplakia is well recognized.

It is hypothesized that bacteria or bacterial fragments form the nidus for the calcium phosphate crystals that laminate the Michaelis-Gutmann bodies. Most investigations into the pathogenesis of this disease support theories that a defect in intraphagosomal bacterial digestion accounts for the unusual immunologic response that causes malacoplakia.

Pathology. The diagnosis is made by biopsy. The lesion is characterized by large histiocytes, known as *von Hansemann cells*, and small basophilic, extracytoplasmic, or intracytoplasmic calculospherules called *Michaelis-Gutmann bodies*, which are pathognomonic (Fig. 12-35). Electron microscopy has revealed intact coliform bacteria and bacterial fragments within phagolysosomes of the foamy-appearing malacoplakic histiocytes (Lewin et al, 1976; Stanton and Maxted, 1981). In their review of the subject, Stanton and Maxted (1981) and Esparza and associates (1989) emphasized that, although pathognomonic for the disease, Michaelis-Gutmann bodies may be absent in early malacoplakia and are not necessary for the diagnosis.

It has been shown that macrophages in malacoplakia involving the kidney and bladder contain large amounts of immunoreactive α_1 -antitrypsin (Callea et al, 1982). The amount of α_1 -antitrypsin remains unchanged during the morphogenetic stages of the pathologic process. Macrophages from other pathologic processes, closely resembling malacoplakia but without Michaelis-Gutmann bodies, do not contain α_1 -antitrypsin except for a few macrophages in

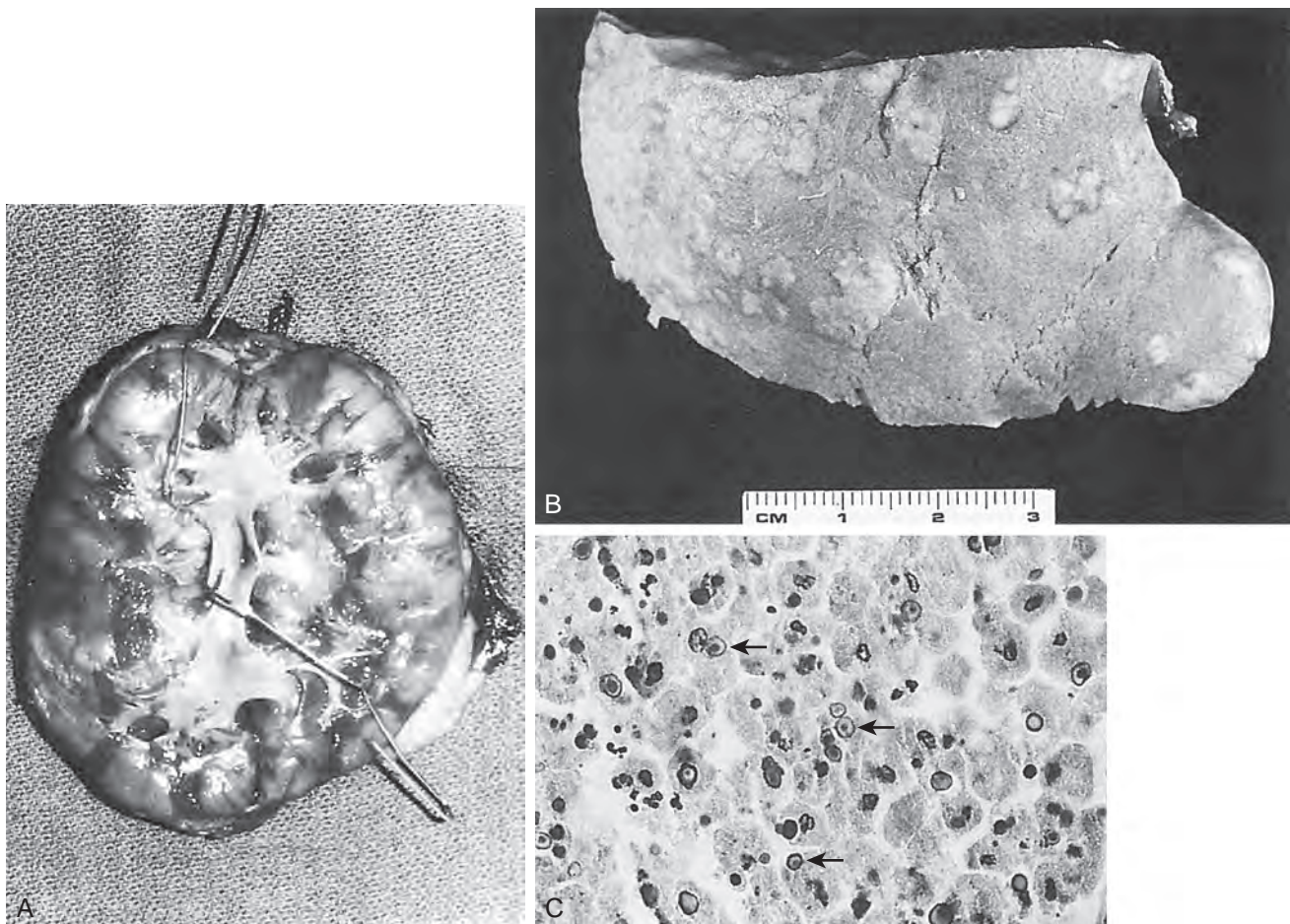


Figure 12-35. Renal parenchymal malacoplakia. A, Cut surface demonstrates extensive cortical and upper medullary replacement by multifocal, confluent, tumorlike masses. B, Cortical surface exhibits multiple, firm, plaque-like lesions. C, Hallmark of malacoplakia is demonstration of the Michaelis-Gutmann body (arrows), which represents incompletely destroyed bacteria surrounded by lipoprotein membrane (hematoxylin and eosin stain). (From Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney: I and II. *Monogr Urol* 1985;6:3.)

tuberculosis and XGP. Therefore immunohistochemical staining for α_1 -antitrypsin may be a useful test for an early and accurate differential diagnosis of malacoplakia.

Clinical Presentation. Most patients are older than 50 years. The ratio of females to males with malacoplakia within the urinary tract is 4:1, but this disparity does not occur in other body tissues (Stanton and Maxted, 1981). The patients often are debilitated and immunosuppressed and have other chronic diseases. The symptoms of bladder malacoplakia are bladder irritability and hematuria. Cystoscopy reveals mucosal plaques or nodules. As these lesions progress, they may become fungating, firm, sessile masses that cause filling defects of the bladder, ureter, or pelvis on excretory urograms. The distal ureter may become strictured or stenotic and cause subsequent renal obstruction or nonfunction (Sexton et al, 1982). A typical patient with renal parenchymal disease may have one or more radiographic masses and chronic *E. coli* infections. Renal parenchymal malacoplakia may be complicated by renal vein thrombosis and inferior vena cava thrombosis (McClure, 1983). When malacoplakia involves the testis, epididymo-orchitis is present. Malacoplakia of the prostate is rare, but, when it occurs, it may be confused with carcinoma clinically (Shimizu et al, 1981). Mortality can exceed 50%, and the morbidity can be substantial (Stanton and Maxted, 1981).

Radiologic Findings. Multifocal malacoplakia on excretory urography typically presents as enlarged kidneys with multiple filling defects. Renal calcification, lithiasis, and hydronephrosis are absent. The multifocal nature is best appreciated by using ultrasonography, CT, or arteriography. Ultrasound examination may demonstrate renal enlargement and distortion of the central echo complex. The masses are often confluent, resulting in an overall increase in the echogenicity of the renal parenchyma (Hartman et al, 1980). On CT, the foci of malacoplakia are less dense than the surrounding enhanced parenchyma (Hartman, 1985). Arteriography typically reveals a hypovascular mass without peripheral neovascularity (Cavins and Goldstein, 1977; Trillo et al, 1977).

Unifocal malacoplakia on excretory urography appears as a noncalcified mass that is indistinguishable from other inflammatory or neoplastic lesions. Ultrasonography and CT may demonstrate a solid or cystic structure, depending on the degree of internal necrosis. Angiography may demonstrate neovascularity (Trillo et al, 1977). Extension beyond the kidney, which can occur with either multifocal or uniform malacoplakia, is best demonstrated by CT.

Differential Diagnosis. The differential diagnosis includes renal cystic disease, neoplasia, and renal inflammatory disease (Hartman, 1985). Malacoplakia should be considered when one or more renal masses are observed, particularly in female patients with recurrent UTIs with *E. coli*, altered immune response syndromes, or cystoscopic evidence of malacoplakia or filling defects in the collecting system (Charboneau, 1980). Malacoplakia should also be suspected when these radiographic findings occur in a renal transplant patient who has persistent UTI despite appropriate antimicrobial therapy. Cystic disease generally can be excluded by careful sonographic and CT evaluations. Renal involvement with metastatic disease or lymphomas usually occurs late in the course of the disease, which is well established. Multifocal renal cell carcinoma is most often seen in the context of von Hippel-Lindau disease with its other clinical manifestations. Patients with XGP usually have signs and symptoms of UTI. As with malacoplakia, the involved kidney is enlarged but renal calculi and obstruction are common. Multiple renal abscesses are often associated with hematogenous dissemination resulting from cardiac disease.

Management. Management of malacoplakia should be directed at control of the UTIs, which should stabilize the disease process. This subject is well reviewed by Stanton and Maxted (1981). Although multiple long-term antimicrobial agents, including many antituberculosis agents, have been used, the sulfonamides, rifampin, doxycycline, and TMP are thought to be especially useful because of their intracellular bactericidal activity (Maderazo et al, 1979). Fluoroquinolones are taken up by macrophages directly and have

also proven effective in the management of malacoplakia (Vallorosi et al, 1999). Other investigators have used ascorbic acid and cholinergic agents such as bethanechol in conjunction with antimicrobial therapy and have reported good results (Abdou et al, 1977; Zornow et al, 1979; Stanton et al, 1983). Both agents are thought to increase intracellular cyclic guanosine monophosphate levels, which have been postulated as the biologic defect causing macrophage dysfunction. Surgical intervention, however, may be necessary if the disease progresses in spite of antimicrobial treatment. Nephrectomy is usually performed for the treatment of symptomatic unilateral renal lesions.

The long-term prognosis appears to be related to the extent of the disease. When parenchymal renal malacoplakia is bilateral or occurs in the transplanted kidney, death usually occurs within 6 months (Bowers and Cathey, 1971; Deridder et al, 1977). Patients with unilateral disease usually have a long-term survival after nephrectomy.

Renal Echinococcosis

Echinococcosis is a parasitic infection caused by the larval stage of the tapeworm *Echinococcus granulosus*. The disease is prevalent in dogs, sheep, cattle, and humans in South Africa, Australia, New Zealand, Mediterranean countries (especially Greece), and some parts of the former Soviet Union. In the United States, the disease is rare, but it is found in immigrants from Eastern Europe or other foreign endemic areas or as an indigenous infection among American Indians in the Southwest and in Eskimos (Plorde, 1977).

Pathogenesis and Pathology. Echinococcosis is produced by the larval form of the tapeworm, which in its adult form resides in the intestine of the dog, the definitive host. The adult worm is 3 to 9 mm long. The ova in the feces of the dog contaminate grass and farmlands and are ingested by sheep, pigs, or humans, the intermediate hosts. Larvae hatch, penetrate venules in the wall of the duodenum, and are carried by the bloodstream to the liver. Those larvae that escape the liver are next filtered by the lungs. Approximately 3% of the organisms that escape entrapment in the liver and lungs may then enter the systemic circulation and infect the kidneys. The larvae undergo vesiculation, and the resultant hydatid cyst gradually develops at a rate of about 1 cm/yr. Thus the cyst may take 5 to 10 years to reach pathologic size.

Echinococcosis cysts of the kidney are usually single and located in the cortex (Nabizadeh et al, 1983). The wall of the hydatid cyst has three zones: a peripheral zone of fibroblasts derived from tissues of the host becomes the adventitia and may calcify; an intermediate laminated layer becomes hyalinized; and a single inner layer is composed of nucleated epithelium and is called the *germinal layer*. The germinal layer gives rise to brood capsules that increase in number, become vacuolated, and remain attached to the germinal membrane by a pedicle. New larvae (scolecex) develop in large numbers from the germinal layer within the brood capsule (Fig. 12-36). The hydatid cyst is also filled with fluid. When brood capsules detach, they enlarge and move freely in the fluid and are then called daughter cysts. Hydatid sand is composed of free larvae and daughter cysts.

Clinical Presentation. The symptoms of echinococcosis are those of a slowly growing tumor. Most patients are asymptomatic or have a flank mass, dull pain, or hematuria (Gilsanz et al, 1980; Nabizadeh et al, 1983). Because the cyst is focal, it rarely affects renal function. Rarely, the cyst ruptures into the collecting system, and the patient may experience severe colic and passage of debris resembling grape skins in the urine (hydatiduria). The cyst may also rupture into an adjacent viscus or the peritoneal cavity. The fluid is extremely antigenic (Hartman, 1985).

Laboratory Diagnosis. If cyst rupture occurs, the definitive diagnosis can be established by identifying daughter cysts in the urine or by identifying the laminated wall of the cyst (Sparks et al, 1976). Fewer than half of the patients have eosinophilia. The most reliable diagnostic test uses partially purified hydatid arc 5 antigens in a double-diffusion test (Coltorti and Varela-Diaz, 1978). Complement fixation, hemagglutination (HA), and the Casoni

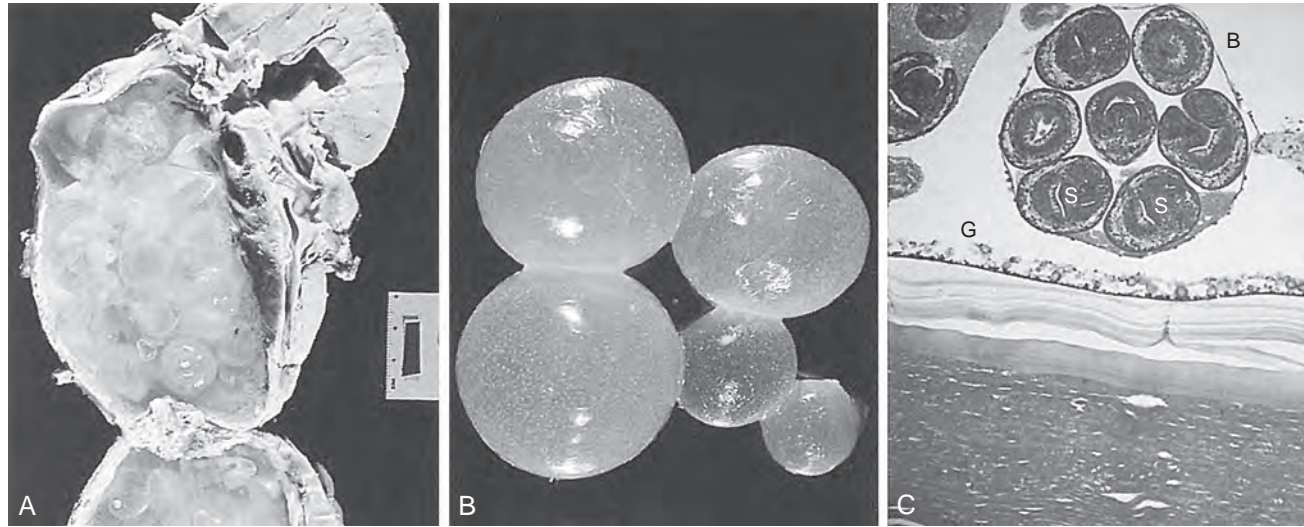


Figure 12-36. Echinococcosis. A, Gross specimen. A cystic mass measuring 7 × 11 cm in lower pole. Smaller daughter cysts are identified within the larger cystic mass. B, Gross specimen. Daughter cysts represent brood capsules that have detached and move freely. C, Photomicrograph. Brood capsules (B) arising from the germinal layer (G) contain viable and degenerating scoleces (S). (From Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney: III and IV. *Monogr Urol* 1985;6:26.)

intradermal skin tests are less reliable but, when combined, are positive in about 90% of patients (Sparks et al, 1976).

Radiologic Findings. Excretory urography typically shows a thick-walled cystic mass, occasionally calcified (Buckley et al, 1985). If the cyst ruptures into the collecting system, daughter cysts may be outlined in the pelvis as an irregular mass or as multiple solitary lesions (Gilsanz et al, 1980). Occasionally, direct filling of the cyst with contrast medium occurs.

Ultrasonography and CT are useful in characterizing the mass. Ultrasonography usually demonstrates a multicystic or multiloculated mass. A sudden change in position may demonstrate bright falling echoes corresponding to hydatid sand, which can be observed during real-time evaluation of hydatid cysts (Saint Martin and Chiesa, 1984).

On CT, several patterns of renal echinococcosis may be recognized. The most specific is a cystic mass with discrete, round daughter cysts and a well-defined enhancing membrane (Martorana et al, 1981). The less specific pattern is that of a thick-walled multiloculated cystic mass (Gilsanz et al, 1980). The presence of daughter cysts within the mother cyst differentiates the lesion from a simple renal cyst and from renal abscesses, infected cysts, and necrotic neoplasm.

Both CT and ultrasonography are useful in evaluating the liver. Angiography is seldom required. Diagnostic aspiration should not be performed because of the danger of rupture and spillage of the highly antigenic cyst contents and risk of fatal anaphylaxis. Nevertheless, Baijal and coworkers (1995) described a percutaneous management of renal hydatidosis as a minimally invasive diagnostic and therapeutic option.

Management. The prognosis of echinococcosis is good but depends on the site and size of the cysts. Medical treatment with benzimidazole compounds such as mebendazole or albendazole has shown limited success with significant side effects (Nabizadeh et al, 1983).

Surgery remains the mainstay of treatment of renal echinococcosis (Poulios, 1991). The cyst should be removed without rupture to reduce the chance of seeding, antigen reaction, and recurrence. If the cyst wall is calcified, the larvae are probably dead and the risk of seeding is low, although a daughter cyst may be viable. If the cyst ruptures or cannot be removed and marsupialization is required, the contents of the cyst initially should be aspirated and filled

with a scolicidal agent such as 30% sodium chloride, 0.5% silver nitrate, 2% formalin, or 1% iodine for approximately 5 minutes to kill the germinal portion (Sparks et al, 1976; Nabizadeh et al, 1983; Shetty et al, 1992).

KEY POINTS: KIDNEY INFECTIONS

- Acute pyelonephritis classically presents as the abrupt onset of chills, fever, and flank or costovertebral angle tenderness but can present as symptoms as mild as cystitis or as severe as sepsis.
- Emphysematous pyelonephritis is a life-threatening infection diagnosed radiographically by the presence of gas in the parenchyma or collecting system and managed surgically.
- Renal abscesses are well delineated by CT and are classically managed with IV antimicrobial agents and drainage. Smaller abscesses may be amenable to conservative treatment with medical management.
- Pyonephrosis is a bacterial infection in a hydronephrotic kidney. Prompt diagnosis is critical; treatment entails intravenous antimicrobial agents and drainage of the obstructed renal unit.
- XGP is a chronic renal infection that is often found in poorly functioning renal units obstructed secondary to nephrolithiasis. XGP can be mistaken for renal tumors.
- Malacoplakia is an unusual inflammatory disease thought to result from abnormal macrophage function. Michaelis-Gutmann bodies are lysosomal inclusion bodies that characterize this disease microscopically.

BACTEREMIA, SEPSIS, AND SEPTIC SHOCK

Sepsis is a clinical syndrome characterized by extremes of body temperature, heart rate, respiratory rate, and WBC count that occurs in response to an infection. A detailed list of potential characteristics can be found in Box 12-9. Severe sepsis and septic shock are extensions of the sepsis spectrum and involve acute organ dysfunction and life-threatening hypotension not

BOX 12-9 Potential Characteristics of Sepsis Spectrum**GENERAL**

Fever (core temperature $>38.3^{\circ}\text{C}$)
 Hypothermia (core temperature $<36^{\circ}\text{C}$)
 Heart rate >90 min, 1 or 2 SD above the normal value for age
 Tachypnea
 Altered mental status
 Significant edema or positive fluid balance (20 mL/kg/24 hr)
 Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes

INFLAMMATORY

Leukocytosis (WBC count $>12,000/\mu\text{L}$)
 Leukopenia (WBC count $<4000/\mu\text{L}$)
 Normal WBC count with $>10\%$ immature forms

ORGAN DYSFUNCTION

Arterial hypoxemia ($\text{PaO}_2/\text{FiO}_2 >300$)
 Acute oliguria (urine output 0.5 mL/kg in 1 hr for at least 2 hr)
 Creatinine increase of 0.5 mg/dL
 Coagulation abnormalities (INR 1.5 or aPTT >60 sec)
 Ileus (absent bowel sounds)
 Thrombocytopenia (platelet count $<100,000/\mu\text{L}$)
 Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)

TISSUE PERFUSION

Hyperlactatemia (>1 mmol/L)
 Decreased capillary refill or mottling

INR, international normalized ratio; aPTT, activated partial thromboplastin time.

From Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6.

responsive to fluid resuscitation (Dellinger et al, 2008). A typical host response to infection involves localized containment and elimination of bacteria and repair of damaged tissue. This process is facilitated by macrophages and dendritic cells and orchestrated by CD4^+ T helper cells via the release of both proinflammatory and anti-inflammatory molecules (cytokines, chemokines, interferons). Sepsis occurs when a local infectious process becomes an uncontrolled systemic blood-borne inflammatory response resulting in damage to tissues or organs remote from the initial site of infection or injury. The extremes of the spectrum are lethal in one in four patients, and there are an estimated 750,000 cases (3 cases per 1000 population) of sepsis or septic shock in the United States each year (Rivers et al, 2001; Dellinger et al, 2008). Much like other medical emergencies, including polytrauma, acute myocardial infarction, and stroke, early recognition and appropriate treatment significantly influence outcome; these are commonly known as “the golden hours.”

Definitions

- **Bacteremia:** the presence of viable bacteria in the blood
- **Systemic inflammatory response syndrome (SIRS):** a clinical syndrome characterized by the 2001 International Sepsis Definitions Conference (Levy et al, 2003) as extremes of body temperature, heart rate, ventilation, and immune response. SIRS can occur in response to multiple insults, including systemic infection, trauma, thermal injury, or a sterile inflammation.
- **Sepsis:** SIRS and infection either documented or strongly suspected
- **Severe sepsis:** sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion, typically systolic blood pressure (SBP)

less than 90 mm Hg or mean arterial pressure (MAP) less than 70 mm Hg

- **Septic shock:** an extreme form of sepsis with sepsis-induced hypotension persisting despite adequate fluid resuscitation; findings may include elevated lactic acid or oliguria

Pathophysiology

Initial studies of pathophysiologic features of septic shock concentrated on the interactions of lipopolysaccharides (LPS) from the gram-negative bacterial cell wall with various innate immune system pathways. More recent investigations now focus on understanding the activation and regulation of both the innate and acquired immune systems and the array of cytokines that are released during localized and systemic inflammatory responses.

Bacterial Cell Wall Components in Septic Shock

The exotoxins produced by some bacteria (e.g., exotoxin A produced by *P. aeruginosa*) can initiate septic shock. However, the bacteria themselves, and in particular their cell wall components, are primarily responsible for the development of septic shock. These components activate numerous innate immunologic pathways, including macrophages, neutrophils, and dendritic cells and the complement system. The prime initiator of gram-negative bacterial septic shock is endotoxin, an LPS component of the bacterial outer membrane. Endotoxin can directly activate the coagulation, complement, and fibrinolytic systems, leading to the release of small molecules that cause vasodilation and increased endothelial permeability (Tapper and Herwald, 2000).

Cytokine Network

Monocytic cells appear to have a pivotal role in mediation of the biologic effects of SIRS and septic shock. Monocytes can remove and detoxify LPS and be beneficial to the host. However, LPS-stimulated monocytes produce cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-1. The intravascular activation of inflammatory systems involved in septic shock is mainly the consequence of an overproduction of these and other cytokines. Production of these cytokines is modulated by CD4^+ T helper cells. Type I CD4^+ T helper cells release proinflammatory cytokines including TNF- α , interferon- γ , and IL-2. These cytokines are also produced by macrophages, endothelial cells, and other cells stimulated by microbial products. The systemic release of large amounts of the cytokine TNF is associated with death from septic shock in humans (Waage et al, 1987; Calandra et al, 1988; Girardin et al, 1988). However, despite the fact that TNF is classically regarded as a central mediator of pathophysiologic changes associated with sepsis, the role of attenuation of this and other proinflammatory cytokines remains unclear. For example, in one animal model of peritonitis, survival was worsened by the administration of antibodies blocking TNF (Eskandari et al, 1992). Also, patients suffering from rheumatoid arthritis treated with TNF- α agents remain susceptible to the development of septic shock. Lastly, a meta-analysis of clinical trials utilizing anti-inflammatory agents in sepsis suggested these agents were generally harmful in all but a small subset of patients (Hotchkiss and Karl, 2003). More recently, anti-inflammatory cytokines, including IL-4 and IL-10, released by type II CD4^+ T helper cells, have also been noted to be elevated in sepsis, further illustrating the complex regulation of both proinflammatory and anti-inflammatory cytokines in a septic patient. In summary, both proinflammatory and anti-inflammatory cytokines are elements of early sepsis; however, the role of cytokine modulation in the treatment of sepsis remains unclear.

Clinical Presentation and Diagnosis

Early signs of systemic inflammatory response syndrome include temperature extremes ($>38^{\circ}\text{C}$ [100.4°F] or $<36^{\circ}\text{C}$ [96.8°F]), tachycardia (heart rate >90 beats/min), tachypnea, and altered

mental status. The classic bedside findings differentiating septic shock from other types of shock include a warm patient, brisk capillary refill, and a bounding pulse reflecting pyrexia, peripheral vasodilation, and decreased systemic vascular resistance. Other diagnostic criteria include evidence of organ dysfunction such as hypotension, oliguria, or ileus and laboratory abnormalities including leukocytosis or leukopenia, hyperbilirubinemia, hyperlactatemia, hyperglycemia, coagulation abnormalities, and elevated C-reactive protein and procalcitonin (see Box 12-9). The classic clinical presentation of fever and chills followed by hypotension is manifest only in about 30% of patients with gram-negative bacteremia (McClure, 1983). Even before temperature extremes and the onset of chills, bacteremic patients often begin to hyperventilate. Thus the earliest metabolic change in septicemia is a resultant respiratory alkalosis. In critically ill patients, the sudden onset of hyperventilation should lead to blood drawing for culture and careful evaluation of the patient. Changes in mental status can also be important clinical clues. Although the most common pattern is lethargy or obtundation, an occasional patient may become excited, agitated, or combative. Cutaneous manifestations such as the bull's-eye lesion associated with *P. aeruginosa* may be identified.

Metastatic infections secondary to genitourinary tract bacteremia have been described (Siroky et al, 1976). In this review of 137 patients who developed metastatic infections from bacteremia with a genitourinary source, 79% had undergone prior urologic instrumentation, 59% developed skeletal infections, mainly of the spine, and 29% developed endocarditis, most commonly caused by *E. faecalis*.

Bacteriology

In classic studies of sepsis syndrome and septic shock, gram-negative bacteria were predominant organisms isolated in 30% to 80% of cases and gram-positive bacteria in 5% to 24% (Ispahani et al, 1987; Calandra et al, 1988; Bone, 1991). Although *E. coli* is the most common organism causing gram-negative bacteremia, many nosocomial catheter-associated infections are caused by highly resistant gram-negative organisms: *P. aeruginosa*, *Proteus*, *Providencia*, and *Serratia*. *Acinetobacter* and *Enterobacter* are also emerging as important nosocomial pathogens. In a large series, *E. coli* caused about one third of the cases; the *Klebsiella-Enterobacter-Serratia* family, approximately 20%; and *Pseudomonas*, *Proteus*, *Providencia*, and anaerobic species, approximately 10% each (Kreger et al, 1980). Anaerobic organisms may cause bacteremia when the source is a postsurgical intra-abdominal abscess or transrectal prostatic biopsy. More recent studies suggest the incidence of sepsis caused by both gram-positive bacterial and fungal organisms is increasing (Martin et al, 2003) and reinforce the need for initial broad-spectrum antimicrobial coverage.

Management

The principles of management of sepsis include resuscitation, supportive care, monitoring, administration of broad-spectrum antimicrobial agents, and drainage or elimination of infection (Sessler et al, 2004; Dellinger et al, 2008). Although the identification and early intervention of sepsis by the urologist is important, the use of expert consultants is also recommended because management of sepsis and the critically ill patient is complex and always evolving. Early goal-directed therapy remains the standard approach since it was shown to be significantly beneficial in a 263-patient study by Rivers and colleagues in 2001.

Principles of resuscitation include support of the airway and breathing and optimization of perfusion with the use of invasive pressure monitoring with central access (Rivers et al, 2001). Intubation and mechanical ventilation may be required in patients who are obtunded and unable to protect their airway. Supplemental oxygen may be instituted, but supranormal oxygen delivery is no longer considered a goal of therapy (Dellinger et al, 2008). Tissue perfusion should first be optimized with fluid resuscitation to

restore mean circulating filling pressures; this may include both crystalloid and or colloid/blood products. If additional blood pressure support is needed, vasoactive agents including phenylephrine, norepinephrine, vasopressin, and dopamine can be instituted; however, low-dose dopamine administration for renal protection is no longer recommended by critical care experts. Other principles of resuscitation and supportive care include optimization of oxygen delivery, correction of coagulopathies if clinically significant, maintenance of blood glucose levels below 110 mg/dL with intensive insulin therapy (Van den Bergh et al, 2001), and implementation of hemofiltration as needed (Schiffl et al, 2002). The use of hydrocortisone therapy in septic shock patients did not show a survival or disease-specific benefit in patients in a large study (Sprung et al, 2008).

Identification of the presumptive source of infection and cultures from corresponding fluids and blood should be obtained before the initiation of antimicrobial therapy. Multiple blood cultures for aerobic and anaerobic organisms should be obtained. In addition, all potential sources of bacteremia must be cultured (i.e., urine, sputum, and wounds). Careful attempts to identify the source of infection should be made because the choice of appropriate antimicrobial coverage depends on the organisms that are thought most likely to cause the infection. The severity of the underlying disease and the possibility of synergistic interactions are also important considerations. If the urinary tract is the most likely portal of entry, a broad spectrum antimicrobial either alone or in combination with an aminoglycoside should be administered. Three clinical factors have been predictive of the subsequent isolation of a resistant pathogen: (1) the use of an antimicrobial drug in the last month, (2) advanced age, and (3) male sex (Leibovici et al, 1992). If the infection is hospital acquired, or if the patient has had multiple infections or is immunocompromised or severely ill, an aminoglycoside and anti-*Pseudomonas* β -lactam or a third-generation cephalosporin should be used. When identification and drug susceptibilities of the offending organism are known, antimicrobial therapy should be changed to use the lowest cost, least toxic antimicrobial with the narrowest antimicrobial coverage. Antimicrobial treatment should be continued until the patient has been afebrile for 3 to 4 days and is clinically stable. Local infections that may have provided the focus for the bacteremia should be treated individually as appropriate. The surviving sepsis campaign suggests the initiation of broad-spectrum antibiotics within 1 hour of diagnosis of septic shock (Dellinger et al, 2008).

KEY POINTS: BACTEREMIA, SEPSIS, AND SEPTIC SHOCK

- Sepsis is a clinical syndrome characterized by extremes of body temperature, heart rate, respiratory rate, and WBC count that occurs in response to an infection.
- The principles of management of sepsis include resuscitation, supportive care, monitoring, administration of broad-spectrum antimicrobial agents, and drainage or elimination of infection.
- The surviving sepsis campaign and early goal-directed therapy has been shown to improve outcomes in critically ill patients.

BACTERIURIA IN PREGNANCY

Asymptomatic bacteriuria is one of the most common infectious issues encountered during pregnancy. The prevalence of asymptomatic bacteriuria does not change with the occurrence of pregnancy and ranges from 2% to 7% (Hooton et al, 2000). The risk of acquiring bacteriuria during pregnancy increases with lower socioeconomic class, multiparity, and sickle cell traits (Patterson and Andriole, 1987; Stenqvist et al, 1989).

The site of bacteriuria in pregnant female patients probably also reflects the situation before conception. In two studies that localized the origin of the bacteriuria, one using the Stamey ureteral catheterization technique and the other the Fairley bladder washout, upper tract infections were found in 44% and 24.5% of pregnant female patients, respectively (Fairley et al, 1966; Heineman and Lee, 1973). In nonpregnant females with recurrent bacteriuria, Stamey (1980) has reported about a 50% probability that the origin is in the upper tract. With other techniques, which may reflect the severity of tissue infection rather than the location of infection, the results are similar; approximately 50% of women with screening bacteriuria of pregnancy are fluorescent antibody-positive (Fa⁺) and thus have evidence of upper tract infection (Harris et al, 1976). Fairley and his group (1973) found that the site of infection is unrelated to the likelihood that pyelonephritis will develop during pregnancy.

Spontaneous resolution of bacteriuria in pregnant women is unlikely unless treated. Nonpregnant patients often clear their asymptomatic bacteriuria (Hooton et al, 2000), but pregnant women become symptomatic more frequently and tend to remain bacteriuric (Elder et al, 1971).

Pyelonephritis develops in 1% to 4% of all pregnant women (Sweet, 1977) and in 20% to 40% of pregnant women with untreated bacteriuria (Pedler and Bint, 1987; Wright et al, 1993). Of the women who develop pyelonephritis during pregnancy, 60% to 75% acquire it during the third trimester (Cunningham et al, 1973), when hydronephrosis and stasis in the urinary tract are most pronounced. From 10% to 20% of pregnant women who get pyelonephritis develop it again before or just after the delivery (Cunningham et al, 1973; Gilstrap et al, 1981). Moreover, a third of pregnant women who develop pyelonephritis have a documented prior history of pyelonephritis (Gilstrap et al, 1981).

The increased likelihood that bacteriuria may progress to acute pyelonephritis during pregnancy alters the morbidity of bacteriuria for this group. Treatment of screening bacteriuria of pregnancy decreases the incidence of acute pyelonephritis during pregnancy from a range of 13.5% to 65% to a range of 0% to 5.3% (Sweet, 1977).

Pathogenesis

The anatomic and physiologic changes induced by the gravid state significantly alter the natural history of bacteriuria (Patterson and Andriole, 1987). These changes may cause pregnant women to be more susceptible to pyelonephritis and may require alteration of therapy. These changes have been well summarized in several reviews (Davidson and Talner, 1978; Waltzer, 1981).

Anatomic and Physiologic Changes during Pregnancy

Increase in Renal Size

Renal length increases approximately 1 cm during normal pregnancy. It is thought that this does not represent true hypertrophy but is the result of increased renal vascular and interstitial volume. No histologic changes have been identified in renal biopsies (Waltzer, 1981).

Smooth Muscle Atony of the Collecting System and Bladder

The collecting system, especially the ureters, undergoes decreased peristalsis during pregnancy, and most women in their third trimester show significant ureteral dilatation (Davison and Lindheimer, 1978; Kincaid-Smith, 1978; Waltzer, 1981) (Fig. 12-37).

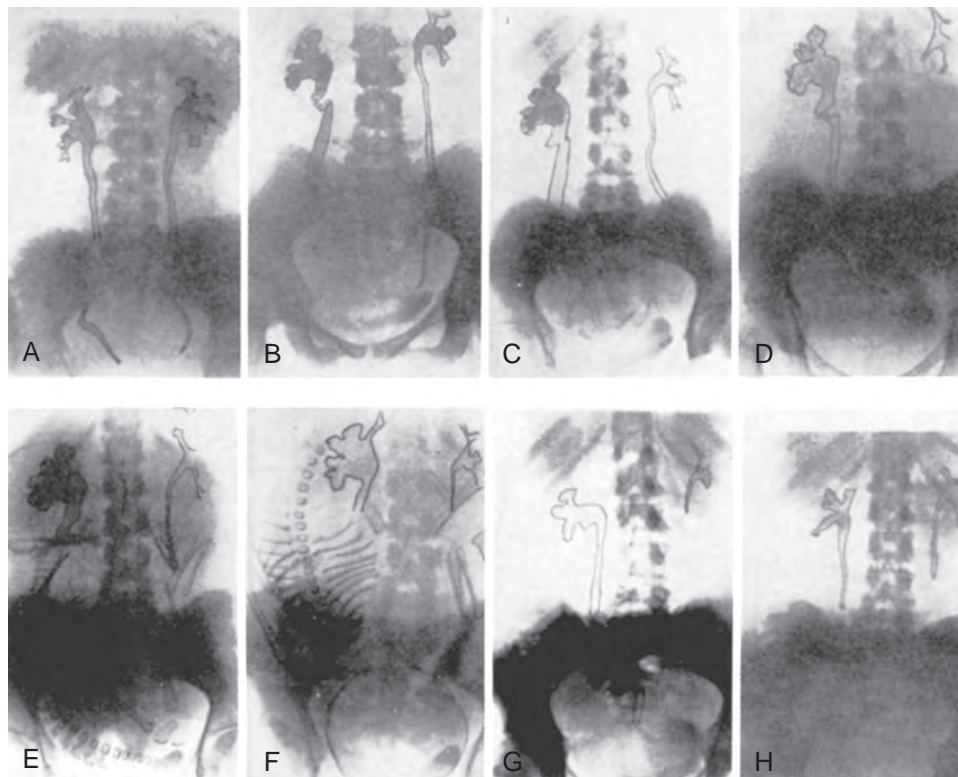


Figure 12-37. Progressive hydroureter and hydronephrosis observed on intravenous pyelogram during a normal pregnancy. A, 15 weeks; B, 18 weeks; C, 22 weeks; D, 26 weeks; E, 34 weeks; F, 39 weeks; G, 1 week postpartum; H, 6 weeks postpartum. Bilateral hydroureter and hydronephrosis are shown as early as 15 weeks (A). B to H, Successive urograms are from one patient during a normal pregnancy. Dilation occurs mainly on the right side, and both urinary tracts are normal by 6 weeks after delivery. (From Hundley JM, Walton HJ, Hibbits JT, et al. Physiologic changes occurring in the urinary tract during pregnancy. *Am J Obstet Gynecol* 1935;30:625-49.)

This hydroureter has been attributed both to the muscle-relaxing effects of increased progesterone during pregnancy and to mechanical obstruction of the ureters by the enlarging uterus at the pelvic brim. Progesterone-induced smooth muscle relaxation also may cause an increased bladder capacity (Waltzer, 1981). Later in pregnancy, the dilation may be the result of the obstructive effect of the enlarging uterus (Poole and Thorsen, 1999).

Bladder Changes

The enlarging uterus displaces the bladder superiorly and anteriorly. The bladder becomes hyperemic and may appear congested endoscopically (Waltzer, 1981). Estrogen stimulation probably causes bladder hypertrophy, as well as squamous changes of the urethra (Waltzer, 1981).

Augmented Renal Function

The transient increases in glomerular filtration rate and renal plasma flow during pregnancy have been well summarized by several authors and are probably secondary to the increase in cardiac output (Zacur and Mitch, 1977; Davison and Lindheimer, 1978; Kincaid-Smith, 1978; Waltzer, 1981). Glomerular filtration increases by 30% to 50%, and urinary protein excretion increases. The significance of these physiologic changes is apparent when the normal serum creatinine and urea nitrogen values for pregnant women are surveyed (Table 12-16). Values considered normal in nonpregnant women may represent renal insufficiency during pregnancy.

Davison and Lindheimer (1978) recommend that pregnant patients with serum creatinine levels greater than 0.8 mg/dL or urea nitrogen levels greater than 13 mg/dL undergo further evaluation of renal function. Similarly, urinary protein in pregnancy is not considered abnormal until greater than 300 mg of protein in 24 hours is excreted.

These significant physiologic changes in pregnancy, which may develop as early as the first trimester, lead to urinary stasis and mild hydroureteronephrosis and contribute to development of pyelonephritis.

Recent studies of *E. coli* adhesins and their respective specific tissue receptors have established an adhesin-based mechanism of pyelonephritis-induced preterm births and low birth weights in mice (Kaul et al, 1999). There is a higher incidence of *E. coli*-bearing Dr adhesins during the third trimester of pregnancy in women with gestational pyelonephritis (Nowicki et al, 1994) and an upregulation of Dr adhesin in the kidney, endometrium, and placenta during the third trimester of pregnancy (Martens et al, 1993). When infected intravesically with *E. coli*-bearing Dr adhesin, nearly 90% of mice that were hypo-responsive to bacterial lipopolysaccharide and had a deficient immune response delivered preterm, compared with 10% of mice infected with *E. coli* without Dr adhesin. Also, there was a significant reduction in fetal birth weight in the Dr adhesin-infected group. Bacterial tissue culture showed systemic spread of the *E. coli*-bearing Dr adhesins to the placentae and fetuses.

TABLE 12-16 Average Values for Serum Creatinine and Urea Nitrogen

	NONPREGNANT FEMALES (mg/dL)	PREGNANT FEMALES (mg/dL)
Serum creatinine	0.7	0.5
Urea nitrogen	13.0	9.0

Data from Davison JM, Lindheimer MD. Renal disease in pregnant women. Clin Obstet Gynecol 1978;21:411.

Complications Associated with Bacteriuria during Pregnancy

Prematurity and Prenatal Mortality

In the preantimicrobial era, pregnant women with symptomatic UTIs and bacterial pyelonephritis were reported to have a high incidence of prematurity, low birth weight, and death (Gilstrap et al, 1981). The relationship between asymptomatic bacteriuria and prematurity is less clear. Gilstrap and colleagues (1981) found no difference in pregnancy among patients treated for asymptomatic bacteriuria as compared with nonbacteriuric controls. However, Cunningham's review suggests that ascending GU tract infections may contribute to up to 50% of premature deliveries, especially before 30 weeks' gestation (Cunningham et al, 2013). Because women with asymptomatic bacteriuria are at higher risk for developing a symptomatic UTI that results in adverse fetal sequelae, complications associated with bacteriuria during pregnancy and pyelonephritis and its possible sequelae such as sepsis in the mother, all women with asymptomatic bacteriuria should be treated (Smail, 2001).

Maternal Anemia

Although several studies suggest that bacteriuria untreated during pregnancy is associated with maternal anemia, not all studies support this. Some difficulties in interpreting the results of these surveys have been caused by inadequate documentation of bacteriuria. In one survey in which urine cultures were obtained by suprapubic aspiration, the data suggest that pregnant patients requiring three or more treatments for bacteriuria have lower levels of serum hemoglobin and folate than controls (McFadyen et al, 1973). In another study from England, investigators showed a statistically significant difference in the incidence of anemia between 410 bacteriuric pregnant women and 409 control pregnant women (Williams et al, 1973). In this survey, 14.6% of bacteriuric women and 10% of control women were anemic at the first prenatal visit. This separation increased during the third trimester (32 weeks), when 25% of women treated with placebo alone had anemia, but only 16.8% of those women treated with antimicrobial agents had anemia. Furthermore, in the 31 untreated (placebo-treated) bacteriuric women who subsequently developed pyelonephritis, the incidence of anemia was 45.2%. These investigators concluded that "untreated bacteriuria increases the likelihood of developing anemia during pregnancy and that this risk is enhanced by the development of acute pyelonephritis, even if it is treated promptly."

Laboratory Diagnosis

Significant false-negative rates occur if screening is conducted by urinalysis or reagent strip testing (McNair et al, 2000; Preston et al, 1999). Therefore an initial screening culture should be performed in all pregnant women during the first trimester (Stenqvist et al, 1989). If the culture shows no growth, repeat cultures are generally unnecessary because patients who have no growth in their urine early in their pregnancy are unlikely to develop bacteriuria later (Norden and Kass, 1968; McFadyen et al, 1973). Pregnant women with a history of recurrent UTI or vesicoureteral reflux may benefit from antimicrobial prophylaxis (Bukowski et al, 1998).

Management

Selection of an antimicrobial agent to treat the bacteriuria must be made, however, with special considerations given to maternal and fetal toxicity. The physiologic changes of pregnancy may decrease tissue and serum drug concentrations. Maternal expanded fluid volume, the distribution of the drug in the fetus, increased renal blood flow, and increased glomerular filtration decrease the serum drug concentration. If the culture is positive, special consideration must be given to the selection of antimicrobial agents

TABLE 12-17 Oral Antimicrobial Agents Used in Pregnancy

DRUG	DOSAGE	COMMENTS
AGENTS CONSIDERED SAFE		
Penicillins		
Ampicillin	500 mg qid	Extensively used
Amoxicillin	250 mg tid	Safe and effective
Penicillin V	500 mg qid	Used less frequently but achieves excellent urinary levels
Cephalosporins		
Cephalexin	500 mg qid	Extensively used
Cefaclor	500 mg qid	Somewhat more effective against gram-negative organisms
Nitrofurantoin	100 mg qid	May be used during the first two trimesters; may result in hemolytic anemia in patients with G6PD deficiency
AGENTS THAT SHOULD BE AVOIDED		
Fluoroquinolones		Possible damage to immature cartilage
Chloramphenicol		Associated with “gray baby” syndrome
Trimethoprim		May cause megaloblastic anemia because of anti-folic acid action
Erythromycin		Associated with maternal cholestatic jaundice
Tetracyclines		May cause acute liver decompensation in the mother and inhibition of new bone growth in the fetus

G6PD, glucose-6-phosphate dehydrogenase.

Modified from Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.

chosen to treat infection to prevent fetal toxicity. The pathogens are similar to those seen in nonpregnant women (MacDonald et al, 1983). Table 12-17 lists the antimicrobial agents and dosing for use in pregnancy. The aminopenicillins and cephalosporins are considered safe and generally effective throughout pregnancy. In patients with penicillin allergy, nitrofurantoin is a reasonable alternative. It may be used safely during the first two trimesters in patients without glucose-6-phosphate dehydrogenase deficiency. Given the low efficacy of short-course β -lactam therapy in nonpregnant women, it is prudent to prescribe a full 3- to 7-day course of therapy in pregnant women. A recent Cochrane Review completed by Widmer and colleagues suggests that there is not adequate evidence at this time to suggest a single dose treatment to be noninferior to standard 7-day treatment (Widmer et al, 2011). Follow-up cultures should be obtained to document absence of infection. If the culture is positive, the cause of bacteriuria must be determined to be lack of resolution, bacterial persistence, or reinfection. If the infection is unresolved, proper selection and administration of another drug probably will solve the problem. If the problem is bacterial persistence or rapid reinfection, antimicrobial suppression of infection or prophylaxis (Pfau and Sacks, 1992) throughout the remainder of the pregnancy should be considered.

Pregnant women with acute pyelonephritis should be hospitalized and treated initially with parenteral antimicrobial agents. More than 95% of these patients respond within 24 hours using ampicillin and an aminoglycoside (Cunningham et al, 1973) or cephalosporins (Sanchez-Ramos et al, 1995). Appropriate oral agents should then be given for at least 14 days (Faro et al, 1984). After the treatment course is completed, low-dose prophylaxis with nitrofurantoin, amoxicillin, or cephalexin has been shown to be effective in preventing reinfection (Van Dorsten et al, 1987; Sandberg and Brorson, 1991). The efficacy of postcoital prophylaxis with either cephalexin (250 mg) or nitrofurantoin (50 mg) has been reported (Pfau and Sacks, 1992).

Drugs that are relatively contraindicated during pregnancy include the fluoroquinolones, TMP, chloramphenicol, erythromycin, tetracycline, sulfonamides, and sometimes nitrofurantoin (Nicolle, 1987). Fluoroquinolones are contraindicated because of their effects on immature cartilage. TMP may have teratogenic effects and should be avoided, especially in the first trimester. The “gray baby” syndrome is a toxic effect of chloramphenicol

on neonates resulting from the inability of the infant to metabolize or excrete the drug. Erythromycin may cause cholestatic jaundice in the mother. Tetracycline may cause fetal malformations and maternal liver decompensation. Sulfonamides may cause kernicterus and neonatal hyperbilirubinemia and should be avoided in the third trimester. As mentioned above, nitrofurantoin can cause hemolytic anemia in both mother and child when glucose-6-phosphate dehydrogenase deficiency is present (Nicolle, 1987).

Pregnancy in Women with Renal Insufficiency

With current management of recurrent UTIs, infections alone are no contraindication to pregnancy. In patients who have renal insufficiency with or without UTIs, Davison and Lindheimer (1978) emphasize that renal function should be carefully evaluated by both serum creatinine levels and creatinine clearance before a woman is counseled about conceiving or continuing a pregnancy. Although little is known about the outcome of pregnancies with differing degrees of renal insufficiency, it is known that normal pregnancy is rare if the preconception serum creatinine level exceeds 3 mg/dL (about 30 mL/min clearance).

The degree of renal function impairment is the major determinant for pregnancy outcome. The fetal survivors of pregnant women with mild or moderate renal disease (serum creatinine <1.4 mg/dL and from 1.4 mg/dL to 2.4 to 2.8 mg/dL, respectively) is only slightly diminished, and irreversible deterioration of maternal renal function is uncommon. However, the perinatal mortality is approximately four times higher with severe disease. The rate of perinatal morbidity caused by low birth weight or prematurity doubles from mild to moderate renal disease and again from moderate to severe disease (Vidaeff et al, 2008).

BACTERIURIA IN THE ELDERLY

UTIs in the elderly are a common and expanding health problem (Kaye, 1980). In 2003, there were almost 34 million Americans older than 65 years (U.S. Census Bureau, 2003). As the life expectancy increases, the diagnosis, treatment, morbidity, and mortality of UTIs in the elderly will assume increasing importance.

KEY POINTS: BACTERIURIA IN PREGNANCY

- Screening for bacteriuria with a culture should be performed in all pregnant women during the first trimester.
- The prevalence of bacteriuria does not change with the occurrence of pregnancy; however, unlike in nonpregnant women, spontaneous resolution of bacteriuria in pregnant women is unlikely.
- All pregnant women with bacteriuria should be treated.
- Bacteriuria more commonly progresses to acute pyelonephritis during pregnancy.
- Pyelonephritis develops in 1% to 4% of all pregnant women (Sweet, 1977) and in 20% to 40% of pregnant women with untreated bacteriuria.
- Pregnant women with acute pyelonephritis should be hospitalized and treated initially with parenteral antimicrobial agents.

Epidemiology

At least 20% of women and 10% of men older than 65 years have bacteriuria (Boscia and Kaye, 1987). In contrast to young adults, in whom bacteriuria is 30 times more prevalent in women than in men, the ratio in women to men with bacteriuria progressively decreases to 2 : 1. Most elderly patients with bacteriuria are asymptomatic; estimates among women living in nursing homes range from 17% to 55%, as compared with 15% to 31% for their male cohorts (Nicolle, 1994). The prevalence of bacteriuria in the elderly increases with age (Table 12-18) (Sourander, 1966; Brocklehurst et al, 1968) and concurrent disease (Fig. 12-38) and may exceed 50% in selective groups (Boscia and Kaye, 1987; Schaeffer, 1991). Risk factors can be compounded. In a study of 373 women and 150 men older than 68 years, 24% of functionally impaired nursing home residents had bacteriuria compared with 12% of healthy domiciliary subjects (Boscia et al, 1986). Longitudinal studies have clarified the dynamic aspect of bacteriuria in the elderly with frequent, spontaneous alteration between positive and negative urine cultures (Monane et al, 1995) (Fig. 12-39). There is only a small pool of elderly patients with persistent bacteriuria (Kaye, 1980). The incidence of asymptomatic bacteriuria is much more common than is apparent from a single survey, implying that most elderly will eventually have episodes of bacteriuria (Boscia et al, 1986).

Pathogenesis

The pathophysiology of increased susceptibility is multifactorial and poorly understood. Age-related changes include decline

in cell-mediated immunity, neurogenic bladder dysfunction, increased perineal soiling as a result of fecal and urinary incontinence, increased incidence of urethral catheter placement, and, in women, changes in the vaginal environment associated with estrogen depletion (Schaeffer, 1991; Raz and Stamm, 1993). Increased receptivity of uroepithelial cells (Reid et al, 1984) and a decrease in prostatic and vaginal antimicrobial factors associated with changes in pH and levels of zinc and hormones have been observed (Boscia et al, 1986). Bacteriologic characteristics of infection in the elderly differ from those in younger patients (Baldassarre and Kaye, 1991). *E. coli* remains the most common uropathogen, causing 75% of these infections. There is a significant increase in the incidence of *Proteus*, *Klebsiella*, *Enterobacter*, *Serratia*, and *Pseudomonas* species, as well as enterococci. Bacteriuria caused by gram-positive bacteria is much more common in elderly men than in elderly women (Jackson et al, 1962). *S. saprophyticus* is not seen in this population. Polymicrobial bacteriuria is more common among the elderly (Nicolle et al, 1987). The shift in the pattern of uropathogens, the high frequency of polymicrobial infections, and antimicrobial resistance in UTIs in the elderly are due in large part to the high frequency of institutionalization and hospitalization, catheterization, and antimicrobial usage in this population (Fig. 12-40).

Laboratory Diagnosis

Diagnosis of bacteriuria and UTIs in the elderly can be difficult. Urinary tract symptoms are often absent, and concomitant disease can mask or mimic UTI. Even severe upper tract infections may not be associated with fever or leukocytosis (Baldassarre and Kaye, 1991). Therefore a high index of suspicion is warranted, and diagnosis should rely on the results of a carefully obtained urinalysis and culture. The presence of greater than 10^5 cfu/mL of urine remains the standard for diagnosis in these patients. However, counts of 10^2 or more bacteria are clinically

TABLE 12-18 Bacteriuria in Two Population Surveys

AGE (yr)	MEN (%)	WOMEN (%)
65-70	2-3	20-21
>80	21-22	23-50

Data from Brocklehurst JC, Dillane JB, Griffiths L, et al. Prevalence and symptomatology of urinary infection in an aged population. *Gerontol Clin* 1968;10:242-53; and Sourander LB. Urinary tract infections in the aged: an epidemiological study. *Ann Med Intern Fenn* 1966;55:7-55.

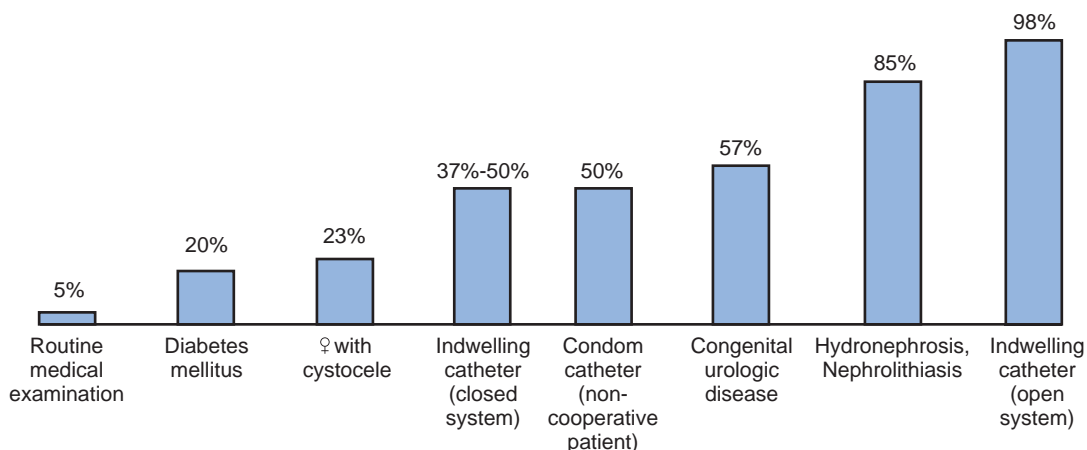


Figure 12-38. Frequency of significant bacteriuria related to underlying disease. (Modified from Jackson GG, Arana-Sialer JA, Andersen BR, et al. Profiles of pyelonephritis. *Arch Intern Med* 1962;110:63-75.)

significant in catheterized specimens (Kunin, 1987; Nicolle et al, 2005).

Pyuria alone is not a good predictor or an indication for antimicrobial treatment of bacteriuria in this population (Ouslander et al, 1996; Nicolle et al, 2005). Boscia and associates (1989) reported that more than 60% of women with pyuria of 10 WBCs/mm³ or greater (noted in midstream specimens) did not have a concurrent bacteriuria. However, the absence of pyuria was a good predictor of the absence of bacteriuria.

Because urinary tract abnormalities can often predispose and complicate bacteriuria in the elderly, a thorough urologic evaluation is warranted. Renal dysfunction, calculi, hydronephrosis, urinary retention, neurogenic bladder dysfunction, and other abnormalities should be identified by serum creatinine measurement, excretory urography, CT, ultrasonography, urodynamics, and/or cystoscopy. The timing and sequence of these tests should be dictated by the clinical setting.

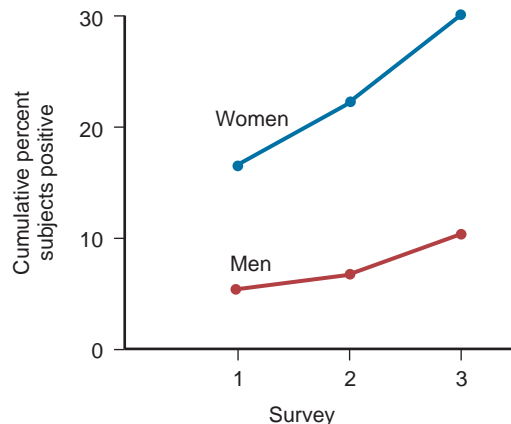


Figure 12-39. Cumulative percentage of subjects (age = 65 years) with at least one positive urine culture survey result over three surveys performed at 6-month intervals. (From Boscia JA, Kobasa WD, Knight RA, et al. Epidemiology of bacteriuria in an elderly ambulatory population. *Am J Med* 1986;80:208–14.)

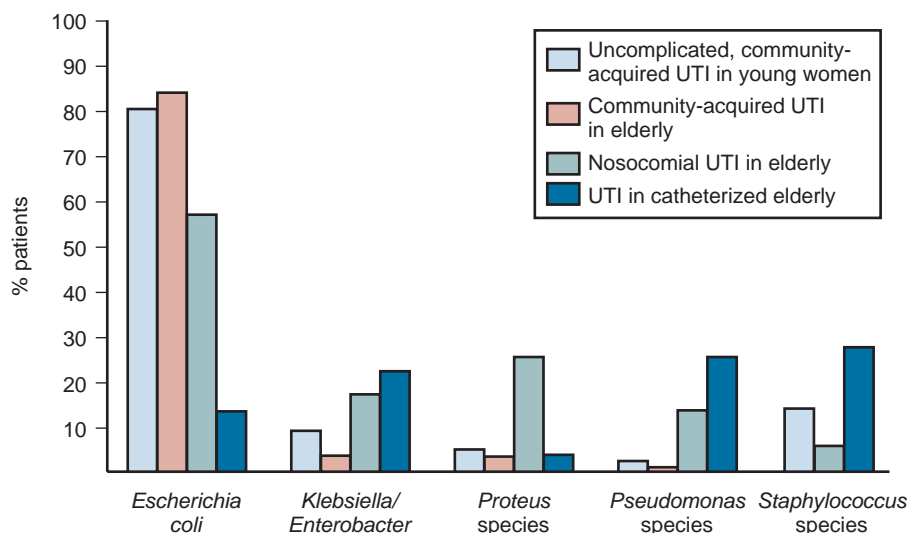


Figure 12-40. Microbiology of urinary tract infections (UTI). (Data from Stark RP, Maki DG. Bacteriuria in the catheterized patient: what quantitative level of bacteriuria is relevant? *N Engl J Med* 1984;311:560–4; Kunin CM. Detection, prevention, and management of urinary tract infections. 4th ed. Philadelphia: Lea & Febiger, 1978, p xiii; Nicolle LE, Bjornson J, Harding GK, et al. Bacteriuria in elderly institutionalized men. *N Engl J Med* 1983;309:1420–5; and Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. *J Infect Dis* 1983;148:57–62.)

Significance of Screening Bacteriuria

Screening for asymptomatic bacteriuria in elderly residents in the community or long-term care facilities is not recommended (Nicolle et al, 1983; Nordenstam et al, 1986; Boscia et al, 1987; Abrutyn et al, 1994). There is no documented relationship between asymptomatic bacteriuria and uncomplicated UTIs and worsening renal function in this population. The treatment of asymptomatic bacteriuria to improve incontinence has not been justified (Baldassarre and Kaye, 1991; Ouslander et al, 1995). Although studies have demonstrated decreased survival in bacteriuric patients compared with nonbacteriuric control subjects, it is unclear whether increased mortality rates and bacteriuria are causally related (Baldassarre and Kaye, 1991; Abrutyn et al, 1994).

Studies that have found a significantly increased mortality among persons with bacteriuria have looked at populations that were heterogeneous in terms of age and underlying disease (Dontas et al, 1981; Latham et al, 1985). An age difference of only 2 years increases mortality by 20% (Dontas et al, 1968). Therefore, in the studies mentioned previously (Dontas et al, 1968) and others (Abrutyn et al, 1994), it is not clear how much of the observed association between bacteriuria and mortality was due to differences in age between the bacteriuric and the abacteriuric groups. In a study of bacteriuria and mortality in a homogeneous 70-year-old population, the association between bacteriuria and mortality was weaker and linked to fatal diseases not attributable to bacteriuria (Dontas et al, 1968). Nicolle and associates (1987) randomized institutionalized women with bacteriuria to treatment or observation and followed these patients for more than 1 year. Treatment did not result in improved survival and was associated with a number of adverse effects.

Bacteriuria that leads to UTIs in elderly subjects in the presence of underlying structural urinary tract abnormalities (e.g., obstruction with hydronephrosis) or systemic conditions (e.g., severe diabetes mellitus) are clinically significant, can lead to renal failure, and require prompt therapy. In addition, UTIs caused by urea-splitting bacteria, such as *Proteus* or *Klebsiella* species that cause formation of infection stones, may also lead to severe renal damage.

Sepsis and its sequelae (sepsis syndrome and septic shock) are increasingly common in the elderly. This is in part due to the

aggressive use of catheters (Kunin et al, 1992) and other invasive equipment, implantation of prosthetic devices, and the administration of chemotherapy to cancer patients or corticosteroids in other immunosuppressed patients with organ transplants or inflammatory diseases. In addition, modern medical care has given longer life spans to the elderly and patients with metabolic, neoplastic, or immunodeficiency disorders, who remain at increased risk for infection.

Management

Prospective randomized comparative trials of antimicrobial or no therapy in elderly male and female nursing home residents with asymptomatic bacteriuria consistently document no benefit of antimicrobial therapy. There was no decrease in symptomatic episodes and no improvement in survival. In fact, treatment with antimicrobial therapy increases the occurrence of adverse drug effects and reinfection with resistant organisms and increases the cost of treatment. Therefore asymptomatic bacteriuria in elderly residents of long-term care facilities should not be treated with antimicrobial agents.

If patients present with lower tract symptoms, 7 days of therapy is recommended. For individuals presenting with fever or more severe systemic infection 10 to 14 days of therapy is recommended. The goal in this population is to eliminate symptoms but not sterilize the urine (McMurdo and Gillespie, 2000).

The 10% to 15% decrease in susceptibility of uropathogens to β -lactams, TMP-SMX, and fluoroquinolones in isolates from nursing home residents is disturbing and most likely due to a pattern of empirical prescribing in the nursing homes. In contrast, the susceptibility of isolates from patients with acute uncomplicated UTI in an outpatient setting has not changed appreciably in 10 years. The difference in susceptibility between the isolates from the outpatient and nursing home settings can be attributed to the presence of additional risk factors for antimicrobial resistance in the latter group. These risk factors include frequent antimicrobial usage, overcrowding, underlying pathology, and the presence of catheters and other invasive devices. Antimicrobial use needs to be guided by current surveillance studies of targeted uropathogenic bacteria and implemented (Vromen et al, 1999).

The elderly population is more susceptible than young patients to the toxic and adverse effects of antimicrobial agents (Grieco, 1980; Carty et al, 1981; Boscia et al, 1986) because the metabolism and excretion of antimicrobial agents may be impaired, and the resulting increased serum levels can further damage renal function. Interactions with other medications can occur (Stahlmann and Lode, 2003). The safety margin between therapeutic and toxic doses is significantly narrowed. Therefore antimicrobial agents must be used judiciously, and dosing and drug levels should be carefully monitored.

The fluoroquinolones are effective in this population, and the side effects are not more apparent than in a younger population. However, fluoroquinolones can cause QT interval prolongation, and therefore they should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia or hypomagnesemia, and patients receiving some antiarrhythmic agents (Stahlmann and Lode, 2003).

Chondrotoxicity of fluoroquinolones has led to restricted use in pediatric patients, but there is no indication that similar effects could occur in joint cartilage of adults. Tendinitis and tendon ruptures have occurred in rare cases. Chronic renal diseases, concomitant use of corticosteroids, and age older than 60 years have been recognized as risk factors for fluoroquinolone-induced tendon disorders (Stahlmann and Lode, 2003).

CATHETER-ASSOCIATED BACTERIURIA

Catheter-associated bacteriuria is the most common hospital-acquired infection, accounting for up to 40% of such infections and more than 1 million per year (Haley et al, 1985; Stamm,

KEY POINTS: BACTERIURIA IN THE ELDERLY

- Bacteriuria is very common in both elderly women and men.
- Screening for bacteriuria is not recommended in elderly patients because there is no relationship between asymptomatic bacteriuria and uncomplicated UTIs and deteriorating renal function; asymptomatic bacteriuria should not be treated.
- Infections of the urinary tract may present as subtle signs, and a high index of suspicion is often required for diagnosis.
- Treatment of symptomatic UTI requires modifications for physiologic and pathophysiologic conditions of the elderly.

1991). The development of bacteriuria in the presence of an indwelling catheter is inevitable and occurs at an incidence of approximately 10% per day of catheterization. Sterile and clean intermittent catheterization has been associated with rates of bacteriuria ranging from 1% to 3% per catheterization (Warren, 1997). The most important risk factors associated with increased likelihood of developing catheter-associated bacteriuria are duration of catheterization, female gender, absence of systemic antimicrobial agents, and catheter-care violations (Stamm, 1991). Most catheter-associated UTIs are asymptomatic. In patients with short-term catheter placement, only 10% to 30% of bacteriuric episodes produce typical symptoms of acute infection (Haley et al, 1981; Hartstein et al, 1981). Similarly, although patients with long-term catheters are bacteriuric, the incidence of febrile episodes occurs at a rate of only 1 per 100 days of catheterization (Warren, 1991). The financial impact of community-acquired UTIs is nearly \$1.6 billion in the United States alone (Foxman, 2002); the annual cost of nosocomial UTIs has been estimated to range from between \$515 million and \$548 million (Jarvis, 1996). Each catheter-associated urinary tract infection (CAUTI) is estimated to cost between \$589 and \$758 (Tambyah et al 2002; Anderson et al 2007). In patients requiring intensive care, the cost is roughly \$2,000 per nosocomial UTI (Chen et al, 2009). The nosocomial costs for *E. coli* infections with relatively susceptible strains are considerably lower than for those caused by resistant gram-negative bacteria, which often require expensive parenteral antimicrobial therapy (Tambyah et al, 2002). Recently, the Center for Medicare and Medicaid Services (CMS) announced that it will no longer reimburse hospitals for the extra costs resulting from catheter-associated UTIs.

Pathogenesis

Bacteria enter the urinary tract of a catheterized patient by several routes. Bacteria can be introduced at the time of initial catheter placement by either mechanical inoculation of urethral bacteria or contamination from poor technique. Subsequently, the bacteria most commonly gain access via a periurethral or intraluminal route (Stamm, 1991). In women, periurethral entry is the most prevalent. Daifuku and Stamm (1984) found that among 18 women who developed catheter-associated bacteriuria, 12 had antecedent urethral colonization with the infecting strain. Bacteria may also enter the drainage bag and follow the intraluminal route to the bladder. This route is particularly common in patients who are clustered among other patients with indwelling catheters (Maizels and Schaeffer, 1980; Tambyah et al, 1999).

The urinary catheter system provides a unique environment that allows for two distinct populations of bacteria: those that grow within the urine and another population that grows on the catheter surface. A biofilm represents a microbial environment of bacteria embedded in an extracellular matrix of bacterial products and host proteins that often lead to catheter encrustation (Stamm, 1991; Bonadio et al, 2001). Certain bacteria, particularly of the *Pseudomonas* and *Proteus* species, are adept at biofilm growth, which

may explain their higher incidence in this clinical setting (Moblely and Warren, 1987). The uropathogens isolated from the catheterized urinary tract often differ from those found in noncatheterized ambulatory patients. *E. coli* is still the most common organism isolated, but *Pseudomonas*, *Proteus*, and *Enterococcus* species are very prevalent (Warren, 1991). In patients with long-term catheterization of more than 30 days, the bacteriuria is usually polymicrobial and the presence of four or five pathogens is not uncommon (Warren et al, 1982). Although certain species may persist for long periods, the bacterial populations in these patients tend to be dynamic.

Clinical Presentation

Most patients are asymptomatic. Suprapubic discomfort and development of fever, chills, or flank pain may indicate a symptomatic UTI.

Laboratory Diagnosis

Significant bacteriuria in patients with catheters is present when greater than 100 cfu/mL is present because even this low level progresses to greater than 10^5 cfu/mL in almost all patients (Maizels and Schaeffer, 1980; Stark and Maki, 1984). Pyuria is not a discriminate indicator of infection in this population.

Management

Careful aseptic insertion of the catheter and maintenance of a closed dependent drainage system are essential to minimize development of bacteriuria. The catheter-meatal junction should be cleaned daily with water, but antimicrobial agents should be avoided because they lead to colonization with resistant pathogens, such as *Pseudomonas*.

Incorporation of silver oxide (Schaeffer et al, 1988) or silver alloy (Saint et al, 1998) into the catheter and hydrogen peroxide into the drainage bag has been reported to decrease the incidence of bacteriuria in some studies (Schaeffer et al, 1988) but not in other populations (Stamm, 1991). The major benefit of silver alloy is in decreasing the likelihood of bacteriuria in hospitalized adults catheterized for the short-term (Saint et al, 2000; Newton et al, 2002; Brosnahan et al, 2004). If an asymptomatic catheterized patient has had an indwelling catheter for 3 or more days and will have the catheter removed, a dipstick test can be used to rule out bacteriuria (Tissot et al, 2001). Concurrent administration of systemic antimicrobial agents transiently decreases the incidence of bacteriuria associated with short-term catheterization, but after 3 to 4 days the incidence of bacteriuria is similar to the rate in catheterized patients not taking systemic antimicrobials agents, and the prevalence of resistant bacteria and side effects is substantial. The concept of instilling nonvirulent bacteria into the bladder to completely block colonization and infection by pathogens has been tested in patients with spinal cord injuries (Hull et al, 2000). Patients successfully colonized with the nonvirulent strain had reduced symptomatic UTI and a subjective improvement in quality of life.

Patients with indwelling catheters should be treated only if they become symptomatic (e.g., febrile). Urine cultures should be performed before initiating antimicrobial therapy. The antimicrobial agent should be discontinued within 48 hours of resolution of the infection. If the catheter has been indwelling for several weeks, encrustation may shelter bacteria from the antimicrobial agent; therefore the catheter should be changed.

When a catheter is to be removed and there is a high probability of bacteriuria or the dipstick test is positive, a culture should be obtained 24 hours before removal (Tissot et al, 2001). If the probability is low or the dipstick is negative, a culture may not be necessary. The patient should be started on empirical antimicrobial therapy such as TMP-SMX or a fluoroquinolone just before decatheterization and maintained on therapy for 2 days. A post-therapy culture should be obtained 7 to 10 days later to confirm the eradication of the bacteriuria.

KEY POINTS: CATHETER-ASSOCIATED BACTERIURIA

- Careful aseptic insertion of the catheter and maintenance of a closed, dependent drainage system are essential to minimize development of bacteriuria.
- The development of catheter-associated bacteriuria is inevitable.
- If an infection is suspected in a catheterized patient, a culture should be obtained and antimicrobial therapy initiated before decatheterization.
- Only symptomatic catheter-associated UTIs require treatment.
- Antimicrobial therapy should be continued for 2 to 3 days and a post-therapy culture obtained 7 to 10 days later.

MANAGEMENT OF URINARY TRACT INFECTIONS IN PATIENTS WITH SPINAL CORD INJURY

Patients with spinal cord injury have unique concerns that affect the risk, diagnosis, and management of UTIs, which are all considered complicated.

Epidemiology

UTIs are among the most common urologic complications of spinal cord injury. It has been estimated that approximately 33% of spinal cord-injured patients have bacteriuria at any time (Stover et al, 1989) and that eventually almost all spinal cord-injured patients will become bacteriuric and many will suffer significant morbidity and mortality. One prospective study of patients on intermittent catheterization or condom catheterization reported an incidence of significant bacteriuria of 18 episodes per person per year and an annual incidence of febrile UTIs of 1.8 per person per year (Waites et al, 1993a). In addition, UTI is the most common cause of fever in the spinal cord-injured patient (Beraldo et al, 1993). The 1992 National Institute on Disability and Rehabilitation Research Consensus Conference examined the problems associated with UTIs in spinal cord-injured patients (National Institute on Disability and Rehabilitation Research, 1993). Among the risk factors identified were impaired voiding, overdistention of the bladder, elevated intravesical pressure, increased risk of urinary obstruction, vesicoureteral reflux, instrumentation, and increased incidence of stones. Other factors that have been implicated are decreased fluid intake, poor hygiene, perineal colonization, decubiti, and other evidence of local tissue trauma, and reduced host defense associated with chronic illness (Gilmore et al, 1992; Waites et al, 1993a).

Pathogenesis

The method of bladder management has profound impact on UTI. The National Institute on Disability and Rehabilitation Research Consensus Conference noted that indwelling catheters were most likely to lead to UTI and that the vast majority of patients with an indwelling catheter for 30 days are bacteriuric (National Institute on Disability and Rehabilitation Research, 1993). Suprapubic catheters and indwelling urethral catheters eventually have an equivalent infection rate (Kunin et al, 1987; Tambyah and Maki, 2000; Biering-Sorensen, 2002). However, the onset of bacteriuria may be delayed using a suprapubic catheter compared with a urethral catheter. During a 2-year period, 170 patients with spinal cord injury were evaluated regarding type of urinary drainage and infection (Warren et al, 1982). In patients using indwelling urethral catheters, all urine cultures were positive. The corresponding values for the suprapubic catheter group were 44%. Condom drainage systems are also associated with an incidence of bacteriuria from 63% (Dukes, 1928) to almost 100% (Pyrah et al, 1955).

Since its introduction by [Lapides and colleagues \(1972\)](#), clean (but not sterile) intermittent catheterization (CIC) has earned general recognition in the management of spinal cord injury patients ([National Institute on Disability and Rehabilitation Research, 1993](#)). Although never rigorously compared with indwelling urethral catheterization, CIC has been shown to decrease lower tract complications by maintaining low intravesical pressure and reducing the incidence of stones ([Stover et al, 1989](#)). CIC also appears to reduce complications associated with an indwelling catheter, such as UTI, fever, bacteremia, and local infections such as epididymitis and prostatitis. [Weld and Dmochowski \(2000\)](#) followed 316 patients with spinal cord injury with different bladder management for a mean of 18.3 years and recorded all complications. The CIC group had statistically significantly lower complication rates compared with the urethral catheterization group and no significantly higher complication rates relative to all other management methods for each type of complication studied. Thus it is generally agreed that CIC places patients with spinal cord injury at the lowest risk for significant long-term urinary tract complications ([Stamm, 1975](#)).

There is conflicting evidence over the value of sterile versus nonsterile or “no touch” methods of CIC. Some studies have reported a lower incidence of infection in patients treated with sterile techniques ([Foley, 1929](#)), whereas others have not ([Pyrah et al, 1955](#); [Nyren et al, 1981](#)). [Bennett and coworkers \(1997\)](#) reported on a sterile method of CIC that uses an introducer tip to bypass the distal 1.5 cm of the urethra and showed a significant decrease in UTI with the use of the urethral introducer tip. Different types of catheters have been used for CIC. The low-friction catheters might be less traumatic for the urethra ([Casewell and Phillips, 1977](#); [Garibaldi et al, 1980](#)), but their impact on bacteriuria and UTI has to be studied.

Clinical Presentation

The majority of patients with spinal cord injury with bacteriuria are asymptomatic. Because of a loss of sensation, patients usually do not experience frequency, urgency, or dysuria. More often, they complain of flank, back, or abdominal discomfort, leakage between catheterizations, increased spasticity, malaise, lethargy, and/or cloudy, malodorous urine. UTI is the most common cause of fever in spinal cord-injured patients ([Beraldo et al, 1993](#)).

Bacteriology and Laboratory Diagnosis

Urinalysis will show bacteriuria and pyuria. Pyuria is not diagnostic of infections because it may occur from the irritative effects of the catheter. The National Institute on Disability and Rehabilitation Research Consensus Statement recommended the following criteria for the diagnosis of significant bacteriuria in spinal cord-injured patients ([National Institute on Disability and Rehabilitation Research, 1993](#)). Any detectable bacteria from indwelling or suprapubic catheter aspirates was considered significant because the vast majority of patients with an indwelling catheter and low-level bacteriuria showed an increase to greater than 10^5 cfu/mL within a short period of time ([Cardenas and Hooton, 1995](#)). For patients on CIC, greater than or equal to 10^2 cfu/mL was considered significant. For catheter-free males, a clean voided specimen showing greater than or equal to 10^4 cfu/mL was considered significant.

Bacteriuria in patients with spinal cord injury differs from that in patients with intact spinal cords in its etiology, complexity, and antimicrobial susceptibility and is influenced by the type and duration of catheterization. *E. coli* is isolated in approximately 20% of patients. Enterococci, *P. mirabilis*, and *Pseudomonas* are more common among spinal cord-injured patients than patients with intact spinal cords. Other common organisms are *Klebsiella* species, *Serratia* species, *Staphylococcus*, and *Candida* species. Most bacteriuria in short-term catheterization is of a single organism, whereas patients catheterized for longer than a month will usually demonstrate a polymicrobial flora caused by a wide

range of gram-negative and gram-positive bacterial species ([Edwards et al, 1983](#)). Such specimens commonly have two to four bacterial species, each at concentrations of 10^5 cfu/mL or more ([Monson and Kunin, 1974](#); [Nickel et al, 1987](#)). Some may have up to six to eight species at that concentration ([Monson and Kunin, 1974](#)). This phenomenon is due to an incidence of new episodes of bacteriuria approximately every 2 weeks and the ability of these strains to persist for weeks and months in the catheterized urinary tract ([Edwards et al, 1983](#); [Gabriel et al, 1996](#)). Two of the most persistent species are *E. coli* and *Providencia stuartii*. *P. stuartii* is rarely found outside the long-term catheterized urinary tract and may use the catheter itself as a niche ([Lindberg et al, 1975](#); [Hockstra, 1999](#)).

Management

Because of the diverse flora and high probability of bacterial resistance, a urine culture must be obtained before initiating empirical therapy. For afebrile patients, an oral fluoroquinolone is the agent of choice ([Cardenas and Hooton, 1995](#)). β -Lactams, TMP-SMX, and nitrofurantoin are not recommended because of the high prevalence of bacterial resistance to these drugs. An indwelling catheter should be changed to ensure maximal drainage and eliminate bacterial foci in catheter encrustations. Spinal cord-injured patients with fever or chills are usually admitted and treated with a parenteral aminoglycoside and a penicillin or a third-generation cephalosporin ([Cardenas and Hooton, 1995](#)). In this patient population consultation with a physician with expertise in antimicrobial management may be necessary, especially in a patient with recurrent infections.

If clinical improvement does not occur within 24 to 48 hours, reculture and adjustment of antimicrobial therapy based on the initial culture and susceptibility should be performed. Imaging studies should be obtained to rule out obstruction, stones, and abscess. The duration of therapy is not established, but 4 to 5 days is recommended for the mildly symptomatic patient and 10 to 14 days for sicker patients ([Cardenas and Hooton, 1995](#)). Post-therapy cultures are usually not necessary because asymptomatic recolonization is common and not clinically significant. However, if a urea-splitting bacterium is identified, a follow-up culture should be obtained to ensure its eradication. Spinal cord-injured patients with recurrent symptomatic UTIs should undergo urinary tract imaging and urodynamic testing and a review of their bladder management program with particular attention to catheter drainage, intermittent catheterization techniques, and frequency of intermittent catheterization or voiding schedule ([Cardenas and Hooton, 1995](#)).

Antimicrobial prophylaxis is not supported for most patients who have neurogenic bladder caused by spinal cord injury ([Morton et al, 2002](#)). Antimicrobial prophylaxis did not significantly decrease symptomatic UTIs and resulted in an approximately twofold increase in antimicrobial-resistant bacteria.

Recurrent UTIs may be associated with high storage pressures, and intervention to decrease storage pressure may decrease the incidence of symptomatic UTI. Evidence from studies in spinal cord-injured patients suggests that bladder catheterization for longer than 10 years is associated with an increased risk of carcinoma of the bladder. [West and colleagues \(1999\)](#) examined two databases with more than 33,000 spinal cord-injured patients and identified 130 patients with bladder cancer (0.4%) during a 5-year period. Several risk factors for bladder cancer have been proposed. Vereczky and associates (cited in [Weyrauch and Bassett, 1951](#)) tested different risk factors based on the outcome of 153 spinal cord-injured patients in which 7 were diagnosed with bladder cancer. Of a total of 31 possible predictors, only duration of catheterization was significant. Chronic infection and inflammation of the bladder mucosa could be the carcinogenic stimulus in these patients ([Pyrah et al, 1955](#)). Nitrosamines produced in infected urine have also been implicated ([Najenson et al, 1969](#)).

For further discussion of spinal cord injury and urinary infection, see Chapter 75.

KEY POINTS: MANAGEMENT OF URINARY TRACT INFECTION IN PATIENTS WITH SPINAL CORD INJURY

- UTI in patients with spinal cord injury commonly presents as fever; flank, back, or abdominal discomfort; leakage between catheterizations; increased spasticity; malaise; lethargy; and/or cloudy, malodorous urine.
- The majority of spinal cord-injured patients with bacteriuria are asymptomatic.
- Only symptomatic patients require therapy.
- Urine culture before the initiation of empirical therapy is essential because spinal cord-injured patients often culture diverse flora with a high probability of bacterial resistance.
- Clean intermittent catheterization places patients with spinal cord injury at the lowest risk for significant long-term urinary tract complications.
- Chronic infection can be carcinogenic.

OTHER INFECTIONS

Fournier Gangrene

Fournier gangrene is a potentially life-threatening form of necrotizing fasciitis involving the male genitalia. It is also known as idiopathic gangrene of the scrotum, streptococcal scrotal gangrene, perineal phlegmon, and spontaneous fulminant gangrene of the scrotum (Fournier, 1883, 1884). As originally reported by Baurienne in 1764, and by Fournier in 1883, it was characterized by an abrupt onset of a rapidly fulminating genital gangrene of idiopathic origin in previously healthy young patients that resulted in gangrenous destruction of the genitalia. The disease now differs from these descriptions in that it involves a broader age range, including older patients (Bejanga, 1979; Wolach et al, 1989), follows a more indolent course, and has a less abrupt onset; and, in approximately 95% of the cases, a source can now be identified (Macrea, 1945; Burpee and Edwards, 1972; Kearney and Carling, 1983; Jamieson et al, 1984; Spirnak et al, 1984).

Infection most commonly arises from the skin, urethra, or rectal regions. An association between urethral obstruction associated with strictures and extravasation and instrumentation has been well documented. Predisposing factors include diabetes mellitus, local trauma, paraphimosis, periurethral extravasation or urine, perirectal or perianal infections, and surgery such as circumcision or herniorrhaphy. In cases originating in the genitalia, specifically as a result of urethral obstruction, the infecting bacteria probably pass through Buck fascia of the penis and spread along the dartos fascia of the scrotum and penis, Colles fascia of the perineum, and Scarpa fascia of the anterior abdominal wall. In view of the typical foul odor associated with this condition, a major role for anaerobic bacteria is likely. Wound cultures generally yield multiple organisms, implicating anaerobic-aerobic synergy (Meleney, 1933; Miller, 1983; Cohen, 1986). Mixed cultures containing facultative organisms (*E. coli*, *Klebsiella*, enterococci) along with anaerobes (*Bacteroides*, *Fusobacterium*, *Clostridium*, microaerophilic streptococci) have been obtained from the lesions.

Clinical Presentation

Patients frequently have a history of recent perineal trauma, instrumentation, urethral stricture associated with sexually transmitted disease, or urethral cutaneous fistula. Pain, rectal bleeding, and a history of anal fissures suggest a rectal source of infection. Dermal sources are suggested by history of acute and chronic infections of the scrotum and spreading recurrent hidradenitis suppurativa or balanitis.

The infection commonly starts as cellulitis adjacent to the portal of entry. Early on, the involved area is swollen, erythematous, and tender as the infection begins to involve the deep

fascia. Pain is prominent, and fever and systemic toxicity are marked (Paty and Smith, 1992). The swelling and crepitus of the scrotum quickly increase, and dark purple areas develop and progress to extensive gangrene. If the abdominal wall becomes involved in an obese patient with diabetes, the process can spread very rapidly. Specific genitourinary symptoms associated with the condition include dysuria, urethral discharge, and obstructed voiding. Alterations in mental status, tachypnea, tachycardia, and temperature greater than 38.3°C (101°F) or less than 35.6°C (96°F) suggest gram-negative sepsis.

Laboratory Diagnosis and Radiologic Findings

Anemia occurs secondary to a decreased functioning erythrocyte mass caused by thrombosis and ecchymosis coupled with decreased production secondary to sepsis (Miller, 1983). Elevated serum creatinine levels, hyponatremia, and hypocalcemia are common. Hypocalcemia is believed to be secondary to bacterial lipases that destroy triglycerides and release free fatty acids that chelate calcium in its ionized form.

Because crepitus is often an early finding, a plain film of the abdomen may be helpful in identifying air. Scrotal ultrasonography is also useful in this regard. Biopsy of the base of an ulcer is characterized by superficially intact epidermis, dermal necrosis, and vascular thrombosis and polymorphonuclear leukocyte invasion with subcutaneous tissue necrosis. Stamenkovic and Lew (1984) noted that the use of frozen sections within 21 hours after the onset of symptoms could confirm a diagnosis earlier and lead to early institution of appropriate treatment.

Management

Prompt diagnosis is critical because of the rapidity with which the process can progress. The clinical differentiation of necrotizing fasciitis from cellulitis may be difficult because the initial signs including pain, edema, and erythema are not distinctive. However, the presence of marked systemic toxicity out of proportion to the local finding should alert the clinician. Intravenous hydration and antimicrobial therapy are indicated in preparation for surgical debridement. Antimicrobial regimens include broad-spectrum antibiotics (β -lactam plus β -lactamase inhibitor) such as piperacillin-tazobactam, especially if *Pseudomonas* is suspected, ampicillin plus sulbactam, or vancomycin or carbapenems plus clindamycin or metronidazole (Morpurgo and Galandiuk, 2002).

Immediate debridement is essential. In the patient in whom diagnosis is clearly suspected on clinical grounds (deep pain with patchy areas of surface hypoesthesia or crepitation, or bullae and skin necrosis), direct operative intervention is indicated. Extensive incision should be made through the skin and subcutaneous tissues, going beyond the areas of involvement until normal fascia is found. Necrotic fat and fascia should be excised, and the wound should be left open. A second procedure 24 to 48 hours later is indicated if there is any question about the adequacy of initial debridement. Orchiectomy is almost never required, because the testes have their own blood supply independent of the compromised fascial and cutaneous circulation to the scrotum. Suprapubic diversion should be performed in cases in which urethral trauma or extravasation is suspected. Colostomy should be performed if there is colonic or rectal perforation. Hyperbaric oxygen therapy has shown some promise in shortening hospital stays, increasing wound healing, and decreasing the gangrenous spread when used in conjunction with debridement and antimicrobials (Paty and Smith, 1992). Once wound healing is complete, reconstruction (e.g., using myocutaneous flaps) improves cosmetic results.

Outcome

The mortality rate averages approximately 20% (Cohen, 1986; Baskin et al, 1990; Clayton et al, 1990) but ranges from 7% to 75%.

Higher mortality rates are found in diabetics, alcoholics, and those with colorectal sources of infection who often have a less typical presentation, greater delay in diagnosis, and more widespread extension. Regardless of the presentation, Fournier gangrene is a true urologic emergency that demands early recognition, aggressive treatment with antimicrobial agents, and surgical debridement to reduce morbidity and mortality.

Periurethral Abscess

Periurethral abscess is a life-threatening infection of the male urethra and periurethral tissues. Initially, the area of involvement can be small and localized by Buck fascia. However, when Buck fascia is penetrated, there can be extensive necrosis of the subcutaneous tissue and fascia. Fasciitis can spread as far as the buttocks posteriorly and the clavicle superiorly. Rapid diagnosis and treatment are essential to reduce the morbidity and high mortality historically associated with this disease.

Pathogenesis

Periurethral abscess is frequently a sequela of gonorrhea, urethral stricture disease, or urethral catheterization. Frequent instrumentation is also associated with periurethral abscess formation. The source of the infecting organism is the urine. Gram-negative rods, enterococci, and anaerobes are most frequently identified. The presence of multiple organisms is common. Anaerobes, normal residents of the male urethra, are also frequently found in wound cultures.

Clinical Presentation

Presenting signs and symptoms include scrotal swelling in 94% of patients, fever (70%), acute urinary retention (19%), spontaneously drained abscess (11%), and dysuria or urethral discharge (5% to 8%). The average interval between initial symptoms and presentation is 21 days. Urinalysis of the first glass specimen reveals pyuria and bacteriuria.

Management

Treatment consists of immediate suprapubic urinary drainage and wide debridement. Antimicrobial therapy with an aminoglycoside and a cephalosporin is usually adequate for empirical coverage. More selective antimicrobial therapy can be instituted when the antimicrobial susceptibility of the organisms is available. Perineal urethrostomy or chronic suprapubic diversion occasionally has been helpful to prevent recurrences, and it should be considered in patients with diffuse stricture disease. The presence of a malignancy is unusual, but biopsy is important.

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The complete reference list is available online at www.expertconsult.com.

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KEY POINTS: OTHER INFECTIONS

- Fournier gangrene is necrotizing fasciitis arising from the perineal skin, scrotum, urethra, or rectum.
- Emergent surgical debridement and broad-spectrum antimicrobial agents are the essentials of treatment of Fournier gangrene.
- Periurethral abscess can occur secondarily to urethral stricture or catheterization; treatment entails surgical debridement, suprapubic urinary drainage, and antimicrobial agents.

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Inflammatory and Pain Conditions of the Male Genitourinary Tract: Prostatitis and Related Pain Conditions, Orchitis, and Epididymitis

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Prostatitis and Chronic Pelvic Pain Syndrome

PROSTATITIS AND CHRONIC PELVIC PAIN SYNDROME

Historical Perspective

The clinical presentation, pathology, and microscopic evaluation of prostate-specific specimens of prostatitis patients were firmly established (Young et al, 1906) by the turn of the 20th century. Bacterial and cytologic localization studies of the lower urinary tract were described shortly thereafter (Hitchens and Brown, 1913) and standardized by 1930 (Von Lackum, 1927, 1928; Nickel, 1930, 1999c). The primary form of therapy for prostatitis during most of the 20th century was repetitive prostate massage (Farman, 1930; O'Connor, 1936; Henline, 1943; Campbell, 1957). Antimicrobial therapy became the mainstay of therapy with the introduction of sulfanilamide in the 1930s (Ritter and Lippow, 1938). However, even in the 1950s and 1960s, the significance of inflammatory cells and bacteria in the expressed prostatic secretion (EPS) was questioned (O'Shaughnessy et al, 1956; Bowers and Thomas, 1958; Bourne and Frishette, 1967), and it was even recognized that, in many cases, antibiotics were performing little better than placebo in the treatment of prostatitis (Gonder, 1963).

The next era of prostatitis management began in the 1960s with Meares and Stamey's (1968) description of the four-glass lower urinary tract segmented localization study. Prostatic massage as the mainstay of prostatitis therapy was abandoned, and antimicrobial therapy was rationalized for the very small percentage of patients with bacteria localized to prostate-specific specimens. Unfortunately, the vast majority of patients who were diagnosed with a nonbacterial cause continued to suffer the indignities of dismal urologic management (Nickel, 1998b). The establishment of new definitions and a classification system, better understanding of the etiopathogenesis, completion of randomized placebo-controlled trials with validated outcome indices, and the evolving insight that patients with prostatitis have variable clinical phenotypes have radically changed the way this condition is managed.

Epidemiology

Prostatitis is the most common urologic diagnosis in men younger than 50 years and the third most common urologic diagnosis in men older than 50 years after benign prostatic hyperplasia (BPH) and prostate cancer (Collins et al, 1998). As part of the International Consultation on Urologic Disease (ICUD) preparation for the male lower urinary tract symptoms (LUTS) guideline, the prevalence and incidence of prostatitis and/or chronic pelvic pain syndrome were estimated (Nickel et al, 2013b). Of 24 studies identified, 13 were from North America (Moon et al, 1997; Roberts et al, 1998; Collins et al, 1998, 2002; Nickel et al, 2001a;

Other Inflammatory and Pain Conditions of the Lower Urinary Tract

Roberts et al, 2002; Clemens et al, 2006, 2007; Daniels et al, 2007; Walz et al, 2007; Tripp et al, 2008; Wallner et al, 2009; Cheng et al, 2010); six from Asia (Ku et al, 2001; Tan et al, 2002; Cheah et al, 2003a; Kunishima et al, 2006; Liang et al, 2009; Lan et al, 2011); two from Europe (Mehik et al, 2000; Marszałek et al, 2007); two from Africa (Ejike et al, 2008; Tripp et al, 2012); and one from Australia (Ferris et al, 2010). Compiling the results of all studies, which included a total of 336,846 patients, a prevalence of 7.1% was estimated (range was from 2.2% to 16% with a median prevalence rate of 6.7%). Thirteen of these studies were population based and examined 48,824 patients. The prevalence overall was 7.7% with a range of 2.2% to 14.2% with a median prevalence rate of 8.4%. Five studies depended on physician diagnoses of prostatitis-like symptoms, including those using large databases to extract codes made by physicians for diagnosis. The reported prevalence ranged from 2.7% to 8.8%. The overall prevalence for these studies was 10,592 patients diagnosed out of 186,533 examined (mean 5.7%; median 8%). Five studies used patient recollection of a diagnosis of prostatitis. Of 101,489 patients, 9388 self-reported a diagnosis of prostatitis for a prevalence of 9.3%, ranging from 4.3% to 16%. The mean prevalence in studies according to continent of origin was 6.9% in North America, 7.5% in Asia, 7.6% in Australia, 8.6% in Europe, and 12.1% in Africa. A detailed discussion of this epidemiologic review can be found in the 2012 International Consultation report (Nickel et al, 2013b).

One study evaluated the incidence of male chronic pelvic pain syndrome (CPPS) in a managed care population (Clemens et al, 2005). The incidence was 3.30 cases per 1000 men per year, representing an incidence of 267,000 cases per year if these data can be extrapolated to the overall U.S. population. Prostatitis results in a substantial number of physician visits. The Urologic Diseases in America study reported an annualized visit rate of 1798 per 100,000 population for prostatitis (Pontari et al, 2007). Patients with symptoms of prostatitis appear to be at increased risk for persistent symptoms and for recurrent episodes. Participants with a previous diagnosis of prostatitis had a much higher cumulative probability of subsequent episodes of prostatitis (Roberts et al, 1998; Turner et al, 2004b).

In summary, the prevalence of prostatitis-like symptoms ranges from 2.2% to 16%, with a median prevalence rate approximating 7% for chronic prostatitis and CPPS.

Chronic prostatitis is associated with substantial costs and significant predicted resource consumption (Calhoun et al, 2004; Turner et al, 2004a; Duloy et al, 2007; Clemens et al, 2009). Overall spending in the United States for the diagnosis and management of prostatitis, exclusive of pharmaceutical spending, totaled 84 million dollars in 2000 and appears to be increasing (Pontari et al, 2007). This economic factor needs increased attention when evaluating the incidence and treatment of this prevalent condition.

KEY POINTS: EPIDEMIOLOGY

- Of men older than 18 years, 2% to 12% currently experience prostatitis-like symptoms.
- A median of 7% of men have chronic prostatitis or chronic pelvic pain syndrome.
- Prostatitis accounts for 6% to 8% of outpatient visits from men to urologists.

Histopathology

For the pathologist, prostatitis is defined as an increased number of inflammatory cells within the prostatic parenchyma (Cotran et al, 1999). Prostatic inflammation may or may not be noted in patients with a diagnosis of prostatitis (True et al, 1999), BPH (Nickel et al, 1999c), or prostate cancer (Zhang et al, 2000) and is noted in autopsy series in as many as 44% of prostate tissue samples from men without any definitive prostate disease (McNeal, 1968).

Consistently, fairly distinct although often coexisting patterns of chronic inflammation can be found in the prostate glands of patients with or without prostate disease. The most common pattern of inflammation is a lymphocytic infiltrate in the stroma immediately adjacent to the prostatic acini (Kohnen and Drach, 1979; Nickel et al, 1999c). The intensity of the inflammatory process varies considerably from only scattered lymphocytes to dense lymphoid nodules. Stromal lymphocytic infiltrates frequently coexist with periglandular inflammation. Sheets, clusters, and occasional nodules of lymphocytes and scattered plasma cells are seen within the fibromuscular stroma with no apparent relationship to the ducts and acini. Infiltrates of inflammatory cells restricted to the glandular epithelium and lumen are found in association with prostatitis and BPH but can be found in asymptomatic patients. The intraepithelial inflammatory cells may be neutrophils, lymphocytes, macrophages, or all of these, whereas neutrophils and macrophages are typically found in the lumen. A more detailed description of histologic inflammatory patterns in the prostate is available (Nickel et al, 2001d). Figure 13-1 illustrates the various inflammatory patterns seen in a prostate specimen from a patient with chronic prostatitis (CP).

Corpora amylacea, which may develop from the deposition of prostatic secretions around a sloughed epithelial cell or other irritant, are not usually associated with inflammation unless they become large enough to distend or obstruct the prostatic gland (Attah, 1975). Prostatic calculi may contribute to prostatic inflammation by obstructing central prostate ducts and thus preventing drainage or providing a nidus in which bacteria can survive host defenses and antibiotics (Meares, 1974; Roberts et al, 1997).

Granulomatous prostatitis presents a nonspecific and variable histologic pattern typified by heavy lobular, mixed, inflammatory infiltrates that include abundant histiocytes, lymphocytes, and plasma cells. Small, discrete granulomas may be present, or the pattern may be typified by well-defined granulomas. Granulomatous prostatic inflammation is a common consequence of surgery (Eyre et al, 1986) or bacille Calmette-Guérin (BCG) therapy (Lafontaine et al, 1997) and a rare event in patients with systemic tuberculosis (Saw et al, 1993).

Etiology**Microbiology**

Gram-Negative Uropathogens. Acute bacterial prostatitis is a generalized infection of the prostate gland and is associated with both lower urinary tract infection (UTI) and generalized sepsis. Chronic bacterial prostatitis is associated with recurrent lower UTIs (i.e., cystitis) secondary to areas of focal uropathogenic bacteria residing in the prostate gland. The most common cause

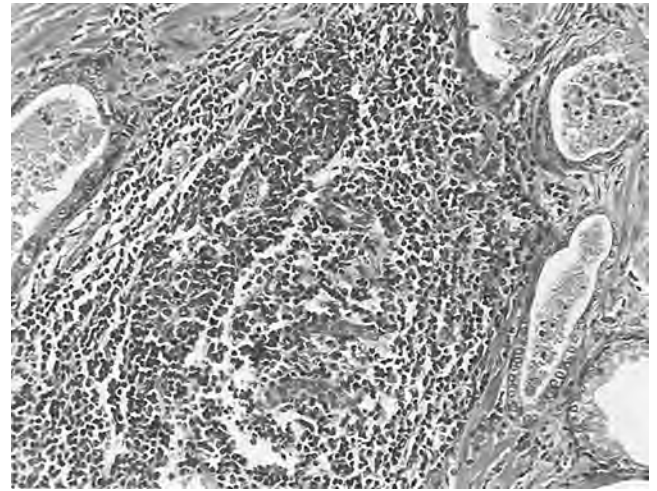


Figure 13-1. Histologic preparation of a prostate specimen demonstrating areas of glandular, periglandular, and stromal inflammation ($\times 400$). (Courtesy Dr. Alexander Boag.)

of bacterial prostatitis is the Enterobacteriaceae family of gram-negative bacteria, which originate in the gastrointestinal flora. The most common organisms are strains of *Escherichia coli*, which are identified in 65% to 80% of infections (Stamey, 1980; Lopez-Plaza and Bostwick, 1990; Weidner et al, 1991b; Schneider et al, 2003). *Pseudomonas aeruginosa*, *Serratia* species, *Klebsiella* species, and *Enterobacter aerogenes* are identified in a further 10% to 15% (Meares, 1987; Weidner et al, 1991b). However, in acute bacterial prostatitis, the organisms that result from previous manipulation of the lower urinary tract (including prostate biopsy) show different patterns of virulence and resistance (e.g., to quinolones and cephalosporins) compared with the organisms associated with spontaneous acute prostatitis (Millán-Rodríguez et al, 2006; Ha et al, 2008). Positive culture for extended-spectrum β -lactamase (ESBL) *E. coli* after prostate biopsy appears to be a risk factor for progression to CP (Oh et al, 2013).

Urovirulence factors play a significant role in the pathogenesis of bacterial prostatitis (Ruiz et al, 2002; Johnson et al, 2005). For instance, bacterial P fimbriae (or pili) bind to the urothelial receptors, and this subsequently facilitates ascent into the urinary tract as well as establishing deep infections in the prostate gland itself (Dilworth et al, 1990; Neal et al, 1990; Andreu et al, 1997). Colonization of the lower urinary tract by *E. coli* is also facilitated by the presence of type 1 fimbria, also known as *mannose-sensitive fimbria*. The receptor is a common moiety of the uroepithelial uromucoid; this association has been shown to be important in the development of cystitis in humans, and its presence in prostatitis has also been documented (Correll et al, 1996). Phase variation of type 1 pili during the establishment of acute bacterial prostatitis may occur in the setting of prostatitis (Schaeffer, 1991). Multiple virulence factors appear to be necessary to produce prostatitis (Mitsumori et al, 1999; Ruiz et al, 2002). Bacteria reside deep in the ducts of the prostate gland and when threatened with host defense and antimicrobial therapy tend to form aggregates (also called *biofilms*), which appears to be a protective mechanism allowing bacteria to persist in the prostate gland even when the cystitis is treated with antibiotics (Nickel and Costerton, 1993; Nickel et al, 1994). Hemolysin appears to be a virulence factor associated with *E. coli* acute prostatitis, but hemolysin may also be associated with increased ability of certain strains of *E. coli* to persist in the prostate as *biofilms* in patients with chronic bacterial prostatitis (Soto et al, 2007).

Gram-Positive Bacteria. Enterococci are believed to account for 5% to 10% of documented prostate infections (Drach, 1974a; Meares, 1987; Bergman, 1994). The role of other gram-positive organisms, which are also commensal organisms in the anterior urethra, is controversial (Fowler and Mariano, 1984a; Jimenez-Cruz

et al, 1984; Krieger et al, 2002). An etiologic role for gram-positive organisms such as *Staphylococcus saprophyticus*, hemolytic streptococci, *Staphylococcus aureus*, and other coagulase-negative staphylococci has been suggested by a number of authors (Drach, 1974a, 1986; Bergman, 1994). Nickel and Costerton (1992) have shown coagulase-negative *Staphylococcus* to be present in the EPS as well as transperineal prostate biopsy tissue of men with CP (microscopy and culture). Although this and other studies (Carson et al, 1982; Pfau, 1983; Bergman et al, 1989; Wedren, 1989) suggested that coagulase-negative staphylococci are involved in the pathogenesis of CP, these studies did not conclusively demonstrate that these bacteria were actually causing the inflammation and symptom complex rather than simply colonizing the prostate (Krieger et al, 2002). However, eradication of gram-positive bacteria in the prostate of men experiencing recent onset of prostatitis symptoms resulted in similar clinical results compared with men with gram-negative uropathogens localizing to the prostate (Magri et al, 2007a; Nickel and Xiang, 2008). In both cases, eradication of the bacteria localized to the prostate was strongly correlated with a good clinical outcome. However, the inconsistent localization of gram-positive bacteria in prostate-specific specimens from patients with CP suggests that this relationship may not be as strong as suggested (e.g., Krieger et al, 2005).

Anaerobic Bacteria. In studies in which the prostate-specific specimens were cultured anaerobically, anaerobic bacteria could be identified in a small number of patients (Nielsen and Justesen, 1974; Mardh and Colleen, 1975; Szoke et al, 1998). This has not been a consistent finding, and the role of anaerobic bacteria is essentially unknown.

Corynebacterium Infection. *Corynebacterium* species have usually been acknowledged as prostate nonpathogens but have been suggested as potential etiologic agents in this disease (Riegel et al, 1995; Domingue, 1998). Domingue and colleagues (1997) suggested that these difficult-to-culture coryneforms could be missed by routine culturing of EPS. Direct Gram staining of the EPS showed gram-variable pleomorphic coccobacillary rods that do not usually grow on routine media. The presence of these pleomorphic swollen rods was also shown by fluorescent acridine orange staining. Tanner and associates (1999), using polymerase chain reaction (PCR) techniques, were able to identify a bacterial signal (phylogenetically gram-positive organisms with predominance of *Corynebacterium* species) in 65% of 17 patients with CP. Approximately half these patients tended to respond to antimicrobial therapy, whereas patients in whom molecular signals for these bacteria could not be identified did not.

Chlamydial Infection. The evidence supporting the role of *Chlamydia trachomatis* as an etiologic agent in chronic prostatic inflammation is both confusing and conflicting. Mardh and Colleen (1972) found that one third of men with CP had antibodies to *C. trachomatis* compared with 3% of controls. Shortliffe and coworkers (1992) found that 20% of patients with nonbacterial prostatitis had antichlamydial antibody titers in the prostatic fluid. Koroku and associates (1995) detected *C. trachomatis*-specific immunoglobulin A (IgA) in 29% of men with chronic nonbacterial prostatitis. Bruce and colleagues (1981), on examination of early morning urine, prostatic fluid, or semen, found that 56% of patients with "subacute or chronic prostatitis" were infected with *C. trachomatis*. In a follow-up study, Bruce and Reid (1989) found that 6 of 55 men with abacterial prostatitis, including 31 believed to have chlamydial prostatitis, met strict criteria for positive diagnosis for chlamydial prostatitis based on identification of the organisms by culturing or immunofluorescence. Kuroda and colleagues (1989) identified *C. trachomatis* in the urethras of 20% of men with prostatitis. Other investigators have come to similar conclusions (Nilsson et al, 1981; Weidner et al, 1983). *Chlamydia* has also been isolated in prostate tissue specimens. Poletti and coworkers (1985) isolated *C. trachomatis* from prostate samples obtained by transrectal aspiration biopsy of men with "nonacute abacterial prostatitis." Abdelatif and colleagues (1991) identified intracellular *Chlamydia* through use of "in situ hybridization techniques" in transurethral prostate chips from 30% of men with histologic evidence of "chronic

abacterial prostatitis." Shurbaji and associates (1998) identified *C. trachomatis* in paraffin-embedded secretions in 31% of men with histologic evidence of prostatitis compared with none in patients with BPH without inflammation.

Although Mardh and Colleen (1972) suggested that *C. trachomatis* may be implicated in as many as one third of men with CP, their follow-up studies employing culturing and serologic tests could not confirm *C. trachomatis* as an etiologic agent in idiopathic prostatitis (Mardh and Colleen, 1975; Mardh et al, 1978). Shortliffe and Wehner (1986) came to a similar conclusion when their group evaluated antichlamydial antibody titers in prostatic fluid. Twelve percent of controls (compared with 20% of patients with nonbacterial prostatitis) had detectable antibodies. Berger and coworkers (1989) could not culture *C. trachomatis* from the urethras in men with CP, nor did they find a serologic or local immune response to *C. trachomatis* in such patients. Doble and associates (1989b) were not able to culture or detect by immunofluorescence *Chlamydia* in transperineal biopsy specimens of abnormal areas of the prostate in men with chronic abacterial prostatitis. Krieger and colleagues (1996b) were able to find *Chlamydia* in only 1% of prostate tissue biopsy specimens from men with CP. A further localization and culture series by Krieger and associates (2000) also failed to culture *Chlamydia* from either urethral or prostate specimens. Further elucidation of the role of chlamydial etiology of prostate infection is required before any definitive statement can be made regarding the association between isolation of this organism and its prostatic origin and effect (Weidner et al, 2002). That being said, antimicrobial therapy for presumed chlamydial prostate infection does result in amelioration of symptoms in many cases (Skerk et al, 2002b, 2003; Perletti et al, 2013).

Ureaplasma Infection. *Ureaplasma urealyticum* is a common organism isolated from the urethra of both asymptomatic men and men with nonspecific urethritis. Weidner and colleagues (1980) found high *U. urealyticum* concentrations in prostate-specific specimens in patients with signs and symptoms of abacterial prostatitis. Isaacs (1993) and associates cultured *U. urealyticum* from prostate secretions in 8% of patients with chronic nonbacterial prostatitis. Fish and Danziger (1993) found significant *U. urealyticum* concentrations in 13% of patients with prostatitis. Treatment with specific antimicrobial therapy cleared the organisms in all cases. Ohkawa and associates (1993a) isolated *U. urealyticum* cells from the prostates of 18 of 143 patients with CP. Antibiotics eradicated the organism in all, improved the symptoms in 10, and cleared the leukocytes in the EPS in 4 (Ohkawa et al, 1993b).

Other investigators (Mardh and Colleen, 1975), employing similar techniques, were unable to implicate *U. urealyticum* in patients with nonbacterial prostatitis. The problems encountered in all these studies include the absence of controls and the fact that it was difficult to account for possible urethral contamination in collecting specific prostate specimens. However, macrolides do appear to successfully improve CP symptoms when *Ureaplasma* or *Mycoplasma* organisms are identified in prostate specimens (Perletti et al, 2013).

Other Microorganisms. *Candida* (Golz and Mendling, 1991; Indudhara et al, 1992) and other mycotic infections such as aspergillosis and coccidioidomycosis (Schwarz, 1982; Chen and Schijj, 1985; Campbell et al, 1992; Truett and Crum, 2004) have been implicated in prostatic inflammation. However, in most cases it was usually an isolated finding in immunosuppressed patients or those with systemic fungal infection. Viruses (Doble et al, 1991; Benson and Smith, 1992) have also been implicated in prostatic inflammation, but no systematic evaluation of the role of these agents in prostatitis has been undertaken. *Trichomonas* has been described in the prostate glands of patients complaining of prostatitis-like symptoms (Kuberski, 1980; Gardner et al, 1996; Skerk et al, 2002a). *Helicobacter pylori* antibodies were positive in serum in 76% of men with CP compared with 62% in controls ($P < .05$). Although this is significantly greater, a large number of the patients without symptoms were seropositive (Karatas et al, 2010).

A newer concept is that it may not be the specific type of bacteria, but that the virulence of bacteria in men with CPPS may

be greater, resulting in symptoms or even causing symptoms that persist after eradication of the bacterial organism (Ivanov et al, 2009; Ivanov et al, 2010; Rudick et al, 2011; Galeone et al, 2013; Quick et al, 2013). It is interesting to note that the symptom patterns for patients who develop CPPS associated with previous bacterial infection may be different from those in patients who develop the syndrome not related to previous infection (Magri et al, 2013). **Nonculturable Microorganisms.** There are significant limitations to the culture techniques used to attempt to identify causative microorganisms associated with prostatitis (Lowentritt et al, 1995; Domingue et al, 1997; Domingue, 1998). Bacteria may exist in aggregated biofilms adherent to the prostatic ductal walls or within the obstructed ducts in the prostate (Nickel and MacLean, 1998). Nickel and Costerton (1993) observed that 60% of patients with previously diagnosed chronic bacterial prostatitis who progressed to sterile EPS cultures but continued to have symptoms despite antimicrobial therapy had positive cultures in prostate biopsy specimens showing an organism similar to the initial organism. As discussed earlier, such organisms appear to persist in small aggregates or biofilms in the ducts and acini of the prostate gland.

Berger and associates (1997) cultured urine specimens and transperineal prostate biopsies specifically for commensal and fastidious organisms. These investigators demonstrated that in prostate biopsy cultures men with evidence of inflammation in EPS are more likely to have bacteria isolated, positive cultures for anaerobic bacteria, higher total bacterial counts, and more bacterial species isolated than men without EPS inflammation. Krieger and colleagues (1996b), Riley and coworkers (1998) and Tanner and associates (1999), used a combination of clinical, culture, and molecular biologic methods (PCR) and found a strong correlation between inflammation and EPS and the detection of bacteria-specific 16S rRNA (gram-negative and gram-positive organisms) in the prostate tissue. But other researchers did not find any association between culture and PCR findings in men with nonbacterial prostatitis compared with men with prostatitis symptoms (Keay et al, 1999; Lee et al, 2003; Leskinen et al, 2003b). Nanobacteria are intriguing organisms that are difficult to isolate and culture, but may be implicated in some chronic urologic conditions including CP (Wood and Shoskes, 2006). A number of investigators (Shoskes et al, 2005; Zhou et al, 2008) have demonstrated the possibility that nanobacteria associated with and without prostatic calculi may be implicated in some cases of CP.

It has been estimated that less than 10% of all environmental bacteria have been identified (Domingue, 1998), so it is possible that fastidious and nonculturable microorganisms might be present in the prostate gland and that such organisms might be involved in the inflammatory process and subsequent development of symptoms.

Altered Prostate Host Defense

Risk factors that allow bacterial colonization or infection of the prostate with potentially pathogenic bacteria include intraprostatic ductal reflux (Kirby et al, 1982); phimosis (VanHowe, 1998); specific blood groups (Lomberg et al, 1986); unprotected penetrative anal rectal intercourse; UTI; acute epididymitis (Berger et al, 1987); indwelling urethral catheters and condom catheter drainage (Meares, 1998); and transurethral surgery, especially in men who have untreated, infected urine (Meares, 1989). Secretory dysfunction of the prostate characterized by an alteration in the composition of prostatic secretions can be diagnostic of patients with prostatitis—that is, a decrease in the levels of fructose; citric acid; acid phosphatase; the cations zinc, magnesium, and calcium; and the zinc-containing prostatic antibacterial factor—whereas pH, the ratio of isoenzymes lactate dehydrogenase-5 to lactate dehydrogenase-1, and inflammatory proteins such as ceruloplasmin and complement C3 are increased (Meares, 1989). These defined alterations in the prostate secretory function have also been blamed for adversely affecting the normal antibacterial nature of prostatic secretions. A decrease in prostatic antibacterial factor may reduce the intrinsic antibacterial activity of the prostatic fluid (Fair

et al, 1976), whereas the alkaline pH may hamper diffusion of certain basic antimicrobial drugs into the prostatic tissue and fluid (Fair and Cordonnier, 1978). However, caution is warranted because it is not known whether these compositional changes are a cause or a consequence of inflammation. It has further been suggested that the metabolic syndrome (Wang et al, 2013) and endothelial dysfunction with arterial stiffness (Shoskes et al, 2011) may be risk, mechanistic, or associated factors, likely through alteration of inflammatory pathways.

Dysfunctional Voiding

Anatomic or neurophysiologic obstruction resulting in high-pressure dysfunctional flow patterns has been implicated in the pathogenesis of prostatitis syndrome. Blacklock (1974, 1991) demonstrated that bladder neck, prostatic, and urethral anatomic abnormalities predisposed some men to developing prostatitis. Urodynamic studies confirm that many patients, particularly those with prostatodynia, have decreased maximal urinary flow rates and obstructive-appearing flow patterns (Barbalias et al, 1983; Ghobish, 2002). On video-urodynamic studies, many patients with prostatitis syndromes show incomplete funneling of the bladder neck as well as vesicourethral dyssynergic patterns (Kaplan et al, 1994, 1997; Hruz et al, 2003). Investigators (Dellabella et al, 2006) have described ultrasound alterations of the preprostatic sphincter in men with CP. In a study of 48 treatment-refractory CP patients with no associated infection, Hruz et al (2003) determined that 29 (60%) had bladder neck hypertrophy diagnosed by endoscopic and urodynamic criteria. This dyssynergic voiding may lead to an autonomic overstimulation of the perineal-pelvic neural system with subsequent development of a chronic neuropathic pain or neuromuscular state. Alternatively, this high-pressure, dysfunctional voiding may result in intraprostatic ductal reflux in susceptible individuals (see the next section).

Intraprostatic Ductal Reflux

Reflux of urine and possibly bacteria into the prostatic ducts has been postulated as one of the causative mechanisms involved in the pathogenesis of chronic bacterial and nonbacterial prostatic inflammation in some individuals. Anatomically, the ductal drainage of the peripheral zone is more susceptible than other prostatic zones to intraprostatic ductal reflux (Blacklock, 1974, 1991). Kirby and associates (1982) instilled a carbon particle solution into the bladders of men diagnosed with nonbacterial prostatitis. Carbon particles were found in the EPS macrophages and prostatic acini and ductal system after surgery in men with nonbacterial prostatitis. Persson and Ronquist (1996) noted high levels of urate and creatinine in EPS, which they postulated was caused by urine reflux into the prostatic ducts. Terai and colleagues (2000) provided molecular epidemiologic evidence for ascending infection in acute bacterial prostatitis.

Prostatic calculi are composed of substances found only in urine, not in prostatic secretions (Sutor and Wooley, 1974; Ramiraz et al, 1980), further evidence that urinary intraprostatic reflux occurs and likely contributes to the formation of prostatic calculi. If pathogenic bacteria reflux into the prostate gland, they may exist in protected aggregates within prostatic calculi themselves (Mazzoli, 2010). High culture counts of pathogens encrusted in prostatic calculi were demonstrated by Eykyn and colleagues (1974). This type of bacterial colonization in protective bacterial aggregates or biofilms associated with prostatic calculi may lead to recalcitrant CP and subsequent recurrent UTIs despite what seems to be adequate antibiotic therapy. Ludwig and coworkers (1994), employing transrectal ultrasonography, showed that men with chronic inflammatory prostatitis had a significantly increased frequency of prostatic calculi compared with men without prostate inflammation. It appears that prostatic calcification is common in patients with nonbacterial CP and is associated with greater inflammation, bacterial colonization, pelvic floor spasm, and symptom duration (Shoskes et al, 2007). The inflammation resulting from

chemical, bacterial, or immunologic stimulation has been shown to possibly cause an increase in intraprostatic pressures, measurable with transperineally inserted pressure transducers (Mehik et al, 2002).

Immunologic Alterations

The local prostatic immune system is activated by infection in bacterial prostatitis. In acute bacterial prostatitis, serum and prostatic fluid antigen-specific (i.e., bacterial antigen) IgG and IgA can be detected immediately after the onset of infection, and, after successful antibiotic therapy the levels decline to normal over the next 6 to 12 months (Meares, 1977; Fowler and Mariano, 1984b; Kumon, 1992; Meares, 1998). Prostate-specific antigen (PSA) levels can be markedly elevated during an acute episode of bacterial prostatitis (Dalton, 1989; Moon et al, 1992; Neal et al, 1992) and slowly resolve to normal levels over the course of 6 weeks to many months, provided there is no recrudescence of the infection. In chronic bacterial prostatitis, no serum Ig elevation is detected, whereas prostatic fluid IgA and IgG levels are both increased (Shortliffe and Wehner, 1986; Kumon, 1992). After successful antibiotic therapy, IgG levels return to normal after several months, but the IgA (particularly secretory IgA) levels remain elevated for almost 2 years (Shortliffe et al, 1981a, 1981b; Fowler and Mariano, 1984b). The presence of antibody-coated bacteria detected in urine, EPS, and semen is another prominent feature of chronic bacterial prostatitis (Riedasch et al, 1984, 1991).

Noninfectious inflammation (nonbacterial prostatitis or CPPS) might also be secondary to immunologically mediated inflammation caused by some unknown antigen or perhaps even related to an autoimmune process. IgA and IgM antibody levels (not microorganism specific) are elevated (Shortliffe and Wehner, 1986; Shortliffe et al, 1989, 1992), and similar antibodies as well as fibrinogen and complement C3 (Vinje et al, 1983; Doble et al, 1990) have been identified in prostatic biopsy samples from patients with CP. Both animal model studies (Donadio et al, 1998; Ceri et al, 1999; Lang et al, 2000; Breser et al, 2013; Chen et al, 2013; Quick et al, 2013) and human studies (Alexander et al, 1997; Batstone et al, 2002; Maake et al, 2003; Motrich et al, 2007) have suggested that prostatitis may be an autoimmune process. A number of candidates have been suggested for the self-antigen, including PSA (Ponniah et al, 2000). Other specific immunologic and neuroendocrine alterations such as cytokine production (Alexander et al, 1998; Jang et al, 2003), nerve growth factor (Miller et al, 2002), and mast cell activation (Done et al, 2012) have a subsequent role to play in the process of inflammation. Specifically, interleukin-10 (IL-10) has been implicated in the cause and clinical manifestations of CP (Miller et al, 2002; Shoskes et al, 2002), but other cytokines such as IL-1 β and tumor necrosis factor- α (TNF- α) have also been implicated (Nadler et al, 2000). IL-8 is the most common cytokine localized to the semen in men with CP (Khadra et al, 2006; Penna et al, 2007). There may be a genetic phenotype that promotes specific immunologic parameters that predispose to immunologically induced prostatic inflammation (Shoskes et al, 2002; Riley et al, 2002). These immunophenotypic patterns have even been observed in noninflammatory category IIIB CP/CPPS (Barghorn et al, 2001). One of the newest concepts emerging in the literature is that CPPS can exist through persistent immunologic mechanisms long after the bacteria have been eradicated (Ivanov et al, 2009, 2010; Rudick et al, 2011; Galeone et al, 2013; Quick et al, 2013). Whatever the initiating event, the immunologic cascade appears to have an important role in the development of prostatitis or CPPS in patients who develop prostatic inflammation (Moon, 1998; Kumon, 1999).

Chemically Induced Inflammation

Investigators have demonstrated that urine and its metabolites (e.g., urate) are present in the prostatic secretion of patients with CP (Persson and Ronquist, 1996). These investigators have hypothesized that the prostatic inflammation and subsequent symptoms

may be simply the result of a chemically induced inflammation secondary to the noxious substances in the urine that have refluxed into the prostatic duct.

Pelvic Floor Muscle Abnormalities

Investigators (Zermann et al, 1999) have proposed that the sensory or motor disturbances or both consistent with neural dysregulation of the lower urinary tract may be a consequence of acquired abnormalities in the central nervous system (CNS). Certainly, extraprostatic tenderness is identified in many patients with CP (Berger et al, 2007; Shoskes et al, 2008). Zermann and Schmidt (1999) described 103 patients with chronic pelvic pain whom they evaluated at a specialized neurourologic unit. They showed that a majority of the men had insufficient conscious control of their somatically innervated striated pelvic floor muscles. The patients showed various levels of identity with their pelvic floor muscles, but none were able to demonstrate the full range of pelvic floor contraction and relaxation repetitively and effortlessly. This was true whether or not there was evidence of inflammation. The researchers concluded that their findings reflect a functional disassociation between the CNS and the peripheral target, the pelvic floor muscles.

Other clinicians (Anderson, 1999; Potts, 2003; Hetrick et al, 2003; Shoskes et al, 2008; Anderson et al, 2009b) have proposed that the source of the pain is specifically at the pelvic musculature attachment area at the sacrum, coccyx, ischial tuberosity, pubic rami, and endopelvic fascia. These areas are immediately adjacent to the prostate and bladder and can be recognized by the demonstration of a hyperirritable spot or myofascial trigger point that is painful on compression. It is hypothesized that the formation of myofascial trigger points in this area results from mechanical abnormalities in the hip and lower extremities, chronic holding patterns such as those that occur during toilet training, sexual abuse, repetitive minor trauma and constipation, sports that create chronic pelvic stimulation, traumatic or unusual sexual activity, recurrent infections, and surgery (Anderson, 1999). More recently, it has been hypothesized that the pain experienced in some men with CPPS may be explained by pudendal nerve entrapment, which causes subsequent neuropathic pain (Antolak et al, 2002).

Neural Sensitization

The pain associated with the CP syndromes is similar in many respects to neuropathic pain. Objective autonomic nervous system changes can be observed in men with CP, suggesting that altered autonomic nervous system responses may be responsible for the pain associated with CPPS (Miller et al, 2002; Yang et al, 2003; Yilmaz et al, 2007, 2010). Pain that may have originated in the prostate or pelvic floor muscles, through mechanisms of cross-sensitization may have spread to adjacent organs and/or structures. Only recently have researchers begun to understand the complexity of overlapping neuropathways and possible mechanisms underlying pelvic organ crosstalk (Malykhina, 2007) including that from bowel (Takahashi et al, 2013). It now appears that actual measurable changes (functional and anatomic) in brain function can be observed in men with long-standing CPPS (Farmer et al, 2011; Moradasini et al, 2012).

It has recently been shown that men with CP showed evidence of dysfunctional hypothalamic-pituitary-adrenal axis function reflected in augmented awakening cortisol responses (Anderson et al, 2008), which can be further induced by stress (Anderson et al, 2009a). Another study evaluating adrenocortical hormone abnormalities in men with CP suggested that some men with this condition may even meet the diagnostic criteria for nonclassic congenital hyperplasia (Dimitrakov et al, 2008).

Psychosocial Associations

Psychological factors have always been considered to play an important role in the development or exacerbation of CP syndromes. Some researchers who have investigated the

psychopathology of these patients concluded that this syndrome should be viewed as a psychosomatic disorder (Mendlewich et al, 1971; Mellan et al, 1973; Keltikangas-Jarvinen et al, 1982). De la Rosette and associates (1993b) compared a group of 50 CP patients with a group of 50 patients seen for vasectomy and showed that although there were significant statistical differences between the groups (with CP patients demonstrating consistently higher personality disorder scores), these differences in scores were quite small compared with those between prostatitis and psychiatric patients. Berghuis and coworkers (1996) compared 51 prostatitis patients with a group of 34 men without any chronic pain condition and concluded that depression and psychological disturbances are common among prostatitis patients. Egan and Krieger (1994) compared prostatitis patients with those seeking treatment for chronic low back pain. Major depression was more common in prostatitis patients, but back pain caused more somatically focused depression and anxiety. Ku et al (2002) suggested that depression and weak masculine identity may be associated with an early stage of CP. A large case-control study confirmed that depression and panic disorders are significantly more common in men with chronic pelvic pain conditions than in controls (Clemens et al, 2008). These more recent studies demonstrate that psychological factors are involved in the disease, but it seems unjustified to label this group of patients as “neurotic” or as having a psychopathologic condition. However, recent analyses of the large prostatitis cohorts showed that psychological variables, such as depression, maladaptive coping techniques (e.g., pain catastrophizing, pain-contingent resting), poor social support, anxiety, and stress are important in CP outcomes (Tripp et al 2005; Ulrich et al, 2005; Tripp et al, 2006; Nickel et al, 2008c; Chung and Lin, 2013; Kwon and Chang, 2013). Factors such as catastrophizing are particularly important because they have been found to be stronger predictors of patient pain reports than depression (Tripp et al, 2006), indicating that negative cognitive appraisals of pain experience may be a primary target for psychosocial interventions. This may be especially important given the strong association that pain catastrophizing has been shown to have with elevations in depression, disability, and lower quality of life in patients with CP (Tripp et al, 2005, 2006; Nickel et al, 2008c; Hedelin, 2012; Tripp et al, 2013).

Association with Interstitial Cystitis or Bladder Pain Syndrome

Interstitial cystitis, now referred to by many as *bladder pain syndrome*, is an ill-defined CPPS occurring primarily in females, and a number of investigators have hypothesized that CPPS in men may have a similar cause (Pontari, 2006; Forrest et al, 2007). Unfortunately, the cause of interstitial cystitis remains unknown, but the

pathogenic mechanisms are theorized to be very similar to those that cause CP and/or chronic pelvic pain in men (Sant and Nickel, 1999; Eisenberg and Moldwin, 2003; Parsons 2003). Some researchers have proposed that in some patients diagnosed with prostatitis, a bladder-orientated interstitial cystitis mechanism actually accounts for the symptoms, and the prostate is only indirectly involved (Sant and Kominski, 1997). Certainly, the pain and voiding symptoms of interstitial cystitis and CP overlap to some extent (Miller et al, 1995; Novicki et al, 1998; Sant and Nickel, 1999; Forrest and Schmidt, 2004), and men with prostatitis diagnoses have cystoscopic (Berger et al, 1998), urodynamic (Siroky et al, 1981), and potassium sensitivity testing (Parsons and Albo, 2002; Parsons et al, 2005) findings very similar to those of patients with interstitial cystitis. However Yilmaz and coworkers (2004) did not confirm positive potassium sensitivity testing results in prostatitis patients, and Keay and colleagues (2004) showed that men diagnosed with CP (pain only) have normal antiproliferative factor (APF) activity whereas men diagnosed with interstitial cystitis (pain and irritative voiding symptoms) have detectable levels of urine APF.

Summary: Pathophysiology of Prostatitis and Related Syndromes

It is likely that nonbacterial prostatitis syndromes have a multifactorial cause—either a spectrum of causative mechanisms or, more likely, a progression or cascade of events that occur after one or more of the initiating factors described in the previous section. In a review on mechanisms involved in the pathogenesis of CP, Pontari and Ruggieri (2004) concluded that “the symptoms of chronic prostatitis/chronic pelvic pain syndrome appear to result from an interplay between psychological factors and dysfunction in the immune, neurological and endocrine systems.” Figure 13-2 describes a suggested pathophysiologic scenario that could potentially involve most of the proposed and interrelated causes described in this section.

KEY POINTS: ETIOLOGY

- Gram-negative Enterobacteriaceae and *Enterococcus* species are responsible for most cases of bacterial prostatitis.
- Other microorganisms might be implicated.
- Nonbacterial prostatitis and chronic pelvic pain syndromes are caused by an interrelated cascade of inflammatory, immunologic, endocrine, muscular, neuropathic, and psychologic mechanisms that begin with an initiator in a genetically or anatomically susceptible man.

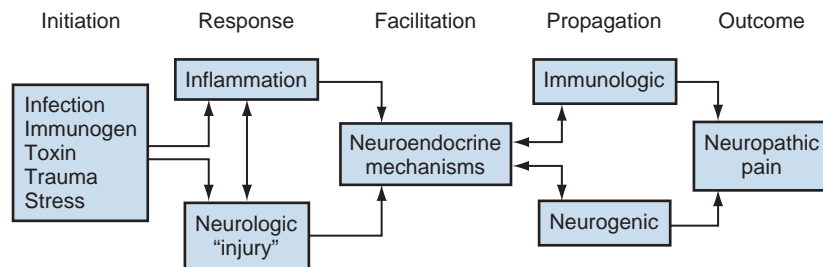


Figure 13-2. The cause and pathogenesis of chronic prostatitis/chronic pelvic pain syndrome (category III CPPS) appear to involve a pluricausal, multifactorial mechanism. An initiating stimulus, such as infection, reflux of some toxic or immunogenic urine substance, or perineal or pelvic trauma, starts a cascade of events in an anatomically or genetically susceptible man, resulting in a local response of inflammation or neurogenic injury or both. Further interrelated immunologic, neuropathic, endocrinologic, and psychologic mechanisms propagate or sustain the chronicity of the initial (or ongoing) event. The final outcome is the clinical manifestation of chronic perineal or pelvic pain and associated symptoms with local and central neuropathic mechanisms involving areas outside the prostate or pelvic area.

Definition and Classification

The traditional classification system is based on the landmark paper by Meares and Stamey (1968) describing the differential diagnosis of the prostatitis syndromes. This classic paper describes in great detail the serial cultures (and treatment) in four patients with CP and introduced the so-called *Meares-Stamey four-glass test*. This localization test, which segmentally assesses inflammation and cultures of the male lower urinary tract, is described in detail in the section on lower urinary tract evaluation. Based on 10 years of clinical experience with this test, a classification system describing four categories of prostatitis was described by Drach and colleagues in 1978. Differentiation of the four categories depended on an analysis of prostatic fluid, which included microscopy (examination for white blood cells (WBCs), inflammatory cell clumps, mucous debris, oval fat bodies, and macrophages) and culturing (identifying traditional uropathogens). This traditional classification system, which categorizes patients into those with acute bacterial prostatitis, chronic bacterial prostatitis, nonbacterial prostatitis, or prostatodynia, is described in Table 13-1.

The limitations of the traditional diagnostic algorithm and traditional classification system led to the development of the National

Institutes of Health (NIH) classification system (see Table 13-1) (Krieger et al, 1999). The new definition recognized that pain is the main symptom in “abacterial chronic prostatitis” (with variable voiding and sexual dysfunction), and it was the optimal criterion to differentiate CP patients from control patients or patients experiencing other genitourinary problems (e.g., BPH). The NIH classification differed from the traditional system in two main areas: the descriptions of category III CP/CPPS, and category IV asymptomatic inflammatory prostatitis.

Category I is identical to the acute bacterial prostatitis category of the traditional classification system. Category II is identical to the traditional chronic bacterial prostatitis classification, except that it now usually refers to patients with recurrent lower UTIs (with a prostate nidus of infection) (Schaeffer, 2006). Category III is defined as the “presence of genitourinary pain in the absence of uropathogenic bacteria detected by standard microbiological methodology.” This syndrome is further categorized into category IIIA, or inflammatory CP/CPPS (based on the presence of excessive leukocytes in EPSs or post-prostatic massage urine or semen), and category IIIB or noninflammatory CP/CPPS (no significant leukocytes in similar specimens). The inclusion of category IV, or asymptomatic inflammatory prostatitis, addressed one of the major problems and omissions of the traditional classification system. Patients are classified as having category IV prostatitis by the presence of significant leukocytes (or bacteria or both) in prostate-specific specimens (EPS, semen, and tissue biopsy specimens) in the absence of typical chronic pelvic pain.

The value of this classification system, not only in clinical research studies but also in clinical practice, has been generally accepted (Nickel et al, 1999d).

KEY POINT: CLASSIFICATION

- The National Institutes of Health classification of the prostatitis syndromes has now become recognized as the best system for research and clinical practice.

Clinical Presentation

Category I: Acute Bacterial Prostatitis

Acute bacterial prostatitis, category I, is a rare but important lower urinary tract infectious disease. It is characterized by an acute onset of pain combined with storage (irritative) and voiding (obstructive) urinary symptoms in a patient with manifestations of a systemic febrile illness. The patient typically reports urinary frequency, urgency, and dysuria. Obstructive voiding complaints including hesitancy, poor interrupted stream, strangury, and even acute urinary retention are common. The patient notes perineal and suprapubic pain and may have associated pain or discomfort of the external genitalia. In addition, there are usually significant systemic symptoms including fever, chills, malaise, nausea and vomiting, and even frank septicemia with hypotension. The combination and severity of symptoms in category I, acute bacterial prostatitis, vary from patient to patient. Approximately 5% of patients with acute bacterial prostatitis may progress to chronic bacterial prostatitis (Cho et al, 2005).

Category II: Chronic Bacterial Prostatitis

The most important clue in the diagnosis of category II, chronic bacterial prostatitis, is a history of documented recurrent UTIs. From 25% to 43% of patients diagnosed with chronic bacterial prostatitis through use of a four-glass test had a history of recurrent UTIs (Weidner and Ludwig, 1994; Wright et al, 1994). Patients may be relatively asymptomatic between acute episodes, or they may present with a long history of a CPPS, which is described extensively in the next section. The prevalence of bacterial prostatitis ranges

TABLE 13-1 Classification System for the Prostatitis Syndromes

TRADITIONAL	NATIONAL INSTITUTES OF HEALTH	DESCRIPTION
Acute bacterial prostatitis	Category I	Acute infection of the prostate gland
Chronic bacterial prostatitis	Category II	Chronic infection of the prostate gland
N/A	Category III Chronic pelvic pain syndrome (CPPS)	Chronic genitourinary pain in the absence of uropathogenic bacteria localized to the prostate gland employing standard methodology
Nonbacterial prostatitis	Category IIIA Inflammatory CPPS	Significant number of white blood cells in expressed prostatic secretions, post-prostatic massage urine sediment (VB3), or semen
Prostatodynia	Category IIIB Noninflammatory CPPS	Insignificant number of white blood cells in expressed prostatic secretions, post-prostatic massage urine sediment (VB3), or semen
N/A	Category IV Asymptomatic inflammatory prostatitis (AIP)	White blood cells (and/or bacteria) in expressed prostatic secretions, post-prostatic massage urine sediment (VB3), semen or histologic specimens of prostate gland

from 5% to 15% of prostatitis cases (Schaeffer et al, 1981; Krieger and Egan, 1991; Weidner and Ludwig, 1994). In one of the largest and most comprehensive clinical series, Weidner and associates (1991b) found significant bacteriuria (with uropathogenic organisms) in 4.4% of patients with symptoms of CP.

Category III: Chronic Prostatitis/Chronic Pelvic Pain Syndrome

The presenting symptoms of patients with inflammatory category IIIA CP/CPPS are indistinguishable from those of patients with noninflammatory category IIIB disease. The symptoms experienced by patients with CP/CPPS have been studied extensively by Krieger and colleagues (1996a). They evaluated 50 patients with CP/CPPS seen in a prostatitis clinic (compared with 75 control patients). Alexander and Trissel (1996) surveyed a cohort of 163 prostatitis patients on the Internet. These symptoms were best defined in the development of prostatitis symptom scores by Neal and Moon (1994), Krieger and colleagues (1996a), Nickel and Sorensen (1996), and Braehler and coworkers (1997). The predominant symptom in all these studies was pain, which was most commonly localized to the perineum, suprapubic area, and penis but can also occur in the testes, groin, or low back. Pain during or after ejaculation is one of the most prominent, important, and bothersome features in many patients (Shoskes et al, 2004). Storage and voiding urinary symptoms including urgency, frequency, hesitancy, and poor interrupted flow are associated with this syndrome in many patients. Erectile dysfunction and sexual disturbances have been reported in patients with CPPS (Mehik et al, 2001; Liang et al, 2004; Zaslaw et al, 2005; Muller and Mulhall, 2006; Smith et al, 2007a, 2007b; Lee et al, 2008b; Magri et al, 2008; Chung et al, 2012) but are not pathognomonic features of this syndrome. The best description of the CP/CPPS patient was provided by the NIH Chronic Prostatitis Cohort Study (Schaeffer et al, 2002). A detailed description of 488 men with CP/CPPS noted that the most frequently reported pain or discomfort was in the perineum, followed by pain or discomfort in the suprapubic area. Over half of the men had pain or discomfort during or after sexual climax (ejaculatory pain may be the most discriminatory symptom). A recent analysis of an international cohort of 1563 CP/CPPS patients was undertaken by Wagenlehner and colleagues (2013) to determine the prevalence and impact of pain locations and types to improve the strategy of individualized phenotypically guided treatment. This assessment confirmed that perineal pain or discomfort was the most prevalent pain symptom (63%), followed by testicular pain (58%), pain in the pubic area (42%), and pain in the penis (32%); reports of pain during ejaculation and voiding were 45% and 43%, respectively. Further study of this cohort showed that pain has more impact on quality of life than urinary symptoms; pain severity and frequency are more important than pain localization or type.

By definition, the syndrome becomes chronic after 3 months' duration. The symptoms tend to wax and wane over time; approximately one third of patients improve over 1 year (usually patients with a shorter duration of illness and fewer symptoms) (Nickel et al, 2002; Turner et al, 2004b; Probert et al, 2006b). An age-matched case-control study of risk factors in men with CP/CPPS (Pontari et al, 2005) showed that compared with asymptomatic controls, men with CP/CPPS reported a significantly greater lifetime prevalence of nonspecific urethritis (12% vs. 4%), cardiovascular disease (11% vs. 2%), neurologic disease (41% vs. 14%), psychiatric conditions (29% vs. 11%), and blood or infectious disease (41% vs. 20%).

The impact of this condition on health status is significant. The quality of life of many patients diagnosed with CP/CPPS is greatly diminished. Wenninger and associates (1996), employing a generic health status measure, the Sickness Impact Profile, showed that the mean scores were within the range of scores reported in the literature for patients with a history of myocardial infarction, angina, or Crohn disease. McNaughton Collins and coworkers

(2001b) employed similar quality-of-life assessment instruments in the NIH Chronic Prostatitis Cohort Study of almost 300 patients and confirmed this finding. These investigators noted that the mental health component was affected more than the physical component of the quality-of-life assessment. CP/CPPS patients' quality of life was lower than that observed in the most severely ill subgroups of men with congestive heart failure and diabetes mellitus. This significant impact on quality of life has also been reported in a cohort of CP/CPPS patients evaluated in a primary care setting (Turner et al, 2002). Patients with a diagnosis of CP/CPPS may have depression (Tripp et al, 2005, 2006), stress (Ulrich et al, 2005), or a history of abuse (sexual, physical, or emotional) (Hu et al, 2007). Depression, maladaptive coping techniques (e.g., catastrophizing and pain-contingent resting) and poor social support are associated with a poorer quality of life (Nickel et al, 2008c).

Category IV: Asymptomatic Inflammatory Prostatitis

Category IV, asymptomatic inflammatory prostatitis, by definition does not cause symptoms. The patients have BPH, an elevated PSA level, prostate cancer, or infertility. Subsequent microscopy of EPS or semen and/or histologic examination of BPH tissue, prostate cancer specimens, or prostate biopsy specimens disclose evidence of prostatic inflammation.

Evaluation

Symptom Assessment

For CP/CPPS, which is defined primarily by its symptom complex, analysis of specific prostatitis-like symptoms, the quality of life, the patient's functional status, and the patient's satisfaction with medical care will result in not only better evaluation of the prostatitis patient but also improved therapeutic follow-up. Scientifically validated symptom indices not only improve the care of patients but also optimize clinical decision making in terms of comparing clinical trial outcomes. Since the early 1990s, several different symptom indices have been described in clinical research (Neal and Moon, 1994; Krieger et al, 1996a; Nickel and Sorensen, 1996; Braehler et al, 1997; Chiang et al, 1997) and have been sporadically employed in clinical practice (McNaughton Collins and O'Leary, 1999). Although each of these symptom indices was successful at the time it was developed for the specific purpose or study, none was believed to be ideal for use in general research or clinical practice because they were not validated according to the rigorous standards that now must be met for an accepted urologic disease-specific index (O'Leary et al, 1992).

The NIH Chronic Prostatitis Collaborative Research Network (CPCRN) developed a reproducible and valid instrument to measure the symptoms and quality of life of patients with CP for use in research protocols as well as clinical practice (Litwin et al, 1999). The steps followed in the development of the NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) included a systematic literature review, focus groups, cognitive testing, an expert panel review, a validation test, and psychometric analyses. The final CPSI consists of nine questions that address the three most important domains of the CP experience. Pain (which is the primary symptom of CP/CPPS) was captured in four questions that focused on its location, severity, and frequency. Urinary function, the second most important component of patients' symptoms, was captured in two questions, one concerning storage (irritative) and the other voiding (obstructive) function. The quality of life or impact was captured in three additional questions that asked about the effect of symptoms on daily activities. The NIH-CPSI (Fig. 13-3) has now been accepted by the international prostatitis research community as an accepted outcome measure (Nickel et al, 1999d) and has shown validity and responsiveness in primary care samples (Turner et al, 2003) and clinical trials (Probert et al, 2006a). It has been translated and validated in many languages other than English (Collins et al, 2001; Kunishima et al, 2002; Leskinen et al, 2003a; Schneider et al, 2004; Karakiewicz

<u>NIH-Chronic Prostatitis Symptom Index</u>	<u>(NIH-CPSI)</u>																																														
<p><u>Pain or Discomfort</u></p> <p>1. In the last week, have you experienced any pain or discomfort in the following areas?</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 80%;"></td> <td style="text-align: right; width: 10%;">Yes</td> <td style="text-align: right; width: 10%;">No</td> </tr> <tr> <td>a. Area between rectum and testicles (perineum)</td> <td style="text-align: right;"><input type="checkbox"/> 1</td> <td style="text-align: right;"><input type="checkbox"/> 0</td> </tr> <tr> <td>b. Testicles</td> <td style="text-align: right;"><input type="checkbox"/> 1</td> <td style="text-align: right;"><input type="checkbox"/> 0</td> </tr> <tr> <td>c. Tip of the penis (not related to urination)</td> <td style="text-align: right;"><input type="checkbox"/> 1</td> <td style="text-align: right;"><input type="checkbox"/> 0</td> </tr> <tr> <td>d. Below your waist, in your pubic or bladder area</td> <td style="text-align: right;"><input type="checkbox"/> 1</td> <td style="text-align: right;"><input type="checkbox"/> 0</td> </tr> </table> <p>2. In the last week, have you experienced:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 80%;"></td> <td style="text-align: right; width: 10%;">Yes</td> <td style="text-align: right; width: 10%;">No</td> </tr> <tr> <td>a. Pain or burning during urination?</td> <td style="text-align: right;"><input type="checkbox"/> 1</td> <td style="text-align: right;"><input type="checkbox"/> 0</td> </tr> <tr> <td>b. Pain or discomfort during or after sexual climax (ejaculation)?</td> <td style="text-align: right;"><input type="checkbox"/> 1</td> <td style="text-align: right;"><input type="checkbox"/> 0</td> </tr> </table> <p>3. How often have you had pain or discomfort in any of these areas over the last week?</p> <p><input type="checkbox"/> 0 Never <input type="checkbox"/> 1 Rarely <input type="checkbox"/> 2 Sometimes <input type="checkbox"/> 3 Often <input type="checkbox"/> 4 Usually <input type="checkbox"/> 5 Always</p> <p>4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?</p> <table style="width: 100%; border: none;"> <tr> <td style="text-align: center;"><input type="checkbox"/> 0</td> <td style="text-align: center;"><input type="checkbox"/> 1</td> <td style="text-align: center;"><input type="checkbox"/> 2</td> <td style="text-align: center;"><input type="checkbox"/> 3</td> <td style="text-align: center;"><input type="checkbox"/> 4</td> <td style="text-align: center;"><input type="checkbox"/> 5</td> <td style="text-align: center;"><input type="checkbox"/> 6</td> <td style="text-align: center;"><input type="checkbox"/> 7</td> <td style="text-align: center;"><input type="checkbox"/> 8</td> <td style="text-align: center;"><input type="checkbox"/> 9</td> <td style="text-align: center;"><input type="checkbox"/> 10</td> </tr> <tr> <td colspan="11" style="text-align: center;">NO PAIN AS BAD AS YOU CAN IMAGINE</td> </tr> </table> <p><u>Urination</u></p> <p>5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?</p> <p><input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Less than 1 time in 5 <input type="checkbox"/> 2 Less than half the time <input type="checkbox"/> 3 About half the time <input type="checkbox"/> 4 More than half the time <input type="checkbox"/> 5 Almost always</p>		Yes	No	a. Area between rectum and testicles (perineum)	<input type="checkbox"/> 1	<input type="checkbox"/> 0	b. Testicles	<input type="checkbox"/> 1	<input type="checkbox"/> 0	c. Tip of the penis (not related to urination)	<input type="checkbox"/> 1	<input type="checkbox"/> 0	d. Below your waist, in your pubic or bladder area	<input type="checkbox"/> 1	<input type="checkbox"/> 0		Yes	No	a. Pain or burning during urination?	<input type="checkbox"/> 1	<input type="checkbox"/> 0	b. Pain or discomfort during or after sexual climax (ejaculation)?	<input type="checkbox"/> 1	<input type="checkbox"/> 0	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10	NO PAIN AS BAD AS YOU CAN IMAGINE											<p>6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?</p> <p><input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Less than 1 time in 5 <input type="checkbox"/> 2 Less than half the time <input type="checkbox"/> 3 About half the time <input type="checkbox"/> 4 More than half the time <input type="checkbox"/> 5 Almost always</p> <p><u>Impact of Symptoms</u></p> <p>7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?</p> <p><input type="checkbox"/> 0 None <input type="checkbox"/> 1 Only a little <input type="checkbox"/> 2 Some <input type="checkbox"/> 3 A lot</p> <p>8. How much did you think about your symptoms, over the last week?</p> <p><input type="checkbox"/> 0 None <input type="checkbox"/> 1 Only a little <input type="checkbox"/> 2 Some <input type="checkbox"/> 3 A lot</p> <p><u>Quality of Life</u></p> <p>9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?</p> <p><input type="checkbox"/> 0 Delighted <input type="checkbox"/> 1 Pleased <input type="checkbox"/> 2 Mostly satisfied <input type="checkbox"/> 3 Mixed (about equally satisfied and dissatisfied) <input type="checkbox"/> 4 Mostly dissatisfied <input type="checkbox"/> 5 Unhappy <input type="checkbox"/> 6 Terrible</p> <hr/> <p><u>Scoring the NIH-Chronic Prostatitis Symptom Index Domains</u></p> <p>Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3, and 4 = _____</p> <p>Urinary Symptoms: Total of items 5 and 6 = _____</p> <p>Quality of Life Impact: Total of items 7, 8, and 9 = _____</p>
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a. Area between rectum and testicles (perineum)	<input type="checkbox"/> 1	<input type="checkbox"/> 0																																													
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Figure 13-3. The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) captures the three most important domains of the prostatitis experience: pain (location, frequency, and severity), voiding (irritative and obstructive symptoms), and quality of life (including impact). This index is useful in research studies and clinical practice. (From Litwin MS, McNaughton Collins M, Fowler FJ, et al. The NIH Chronic Prostatitis Symptom Index [NIH-CPSI]: development and validation of a new outcome measure. *J Urol* 1999;162:369–75.)

et al, 2005). The symptom index has also proved its usefulness in the evaluation and follow-up of patients in general clinical urologic practice (Nickel, 1999d; Nickel et al, 2001c). Cut-off levels for pain severity categories were mild, 0 to 3; moderate, 4 to 6; and severe, 7 to 10 for CPSI item 4 (0 to 10); CPSI pain domain (0 to 21) scores were mild, 0 to 7; moderate, 8 to 13; and severe, 14 to 21 (Wagenlehner et al, 2013).

KEY POINT: SYMPTOM ASSESSMENT

- The validated National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) is a useful research and clinical tool for evaluating chronic prostatitis and chronic pelvic pain syndrome patients.

Physical Examination

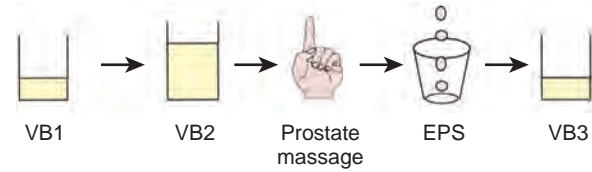
Physical examination is an important part of the evaluation of a patient with prostatitis, and although not confirmatory in making a definitive diagnosis, it is very helpful in further classifying the disorder and even directing therapy. It assists in ruling out other perineal, anal, neurologic, pelvic, or prostate abnormalities and is an integral part of the lower urinary tract evaluation by providing prostate-specific specimens (Nickel, 2002a).

In **category I**, acute bacterial prostatitis, the patient may be systemically toxic—that is, flushed, febrile, tachycardic, tachypneic, and even hypotensive. The patient usually has suprapubic discomfort and perhaps has clinically detectable acute urinary retention. Perineal pain and anal sphincter spasm may complicate the digital rectal examination. The prostate itself is usually described as hot, boggy, and exquisitely tender. The expression of prostatic fluid is believed to be totally unnecessary and perhaps even harmful.

The physical examination of a patient with **category II**, chronic bacterial prostatitis, and **category III** CPPS is usually unremarkable (except for pain). Careful examination and palpation of external genitalia, groin, perineum, coccyx, external anal sphincter (tone), and internal pelvic floor and side walls may pinpoint prominent areas of pain or discomfort (Shoskes et al, 2008; Anderson et al, 2009b). The findings of pelvic floor dysfunction and spastic pain, myofascial pain, or painful trigger points has significant implications for developing treatment plans. The digital rectal examination should be performed after the patient has produced preprostatic massage urine specimens (see later) and after the perineal and pelvic examination. The prostate may be normal in size and consistency, and it has also been described as enlarged and boggy (loosely defined by me as softer than normal). The degree of elicited pain during prostatic palpation is variable and is unhelpful in differentiating a prostatitis syndrome. The prostate should be carefully checked for prostatic nodules before a vigorous prostatic massage is performed to produce prostate-specific specimens (EPS and post-prostatic massage urine sample).

Lower Urinary Tract Cytologic Examination and Culture Techniques. In patients with category I, acute bacterial prostatitis, a urine culture is the only laboratory evaluation of the lower urinary tract required. It has been suggested that the vigorous prostatic massage necessary to produce EPS can exacerbate the clinical situation, although such fears have never been substantiated in the literature. A midstream urine specimen will show significant leukocytosis and bacteriuria microscopically, and culturing usually discloses typical uropathogens. Blood cultures may show the same organism.

In 1968, Meares and Stamey described the classic four-glass urine collection technique to distinguish urethral, bladder, and prostate infections in men with CP, and for three decades this has remained the gold standard for the evaluation of this lower urinary tract syndrome. The voided bladder-1 (VB1) specimen includes the first 10 mL of urine and represents the urethral specimen. The voided bladder-2 (VB2) specimen is similar to a midstream urine collection and represents the bladder urine. EPS should be collected directly into a sterile container during prostatic massage. The voided bladder-3 (VB3) specimen, the first 10 mL of urine voided after prostatic massage, includes any EPS trapped in the prostatic urethra. All four specimens are to be sent to the clinical microbiology laboratory for quantitative culture. Aliquots of the three urine specimens are centrifuged for 5 minutes and the sediment examined under high power for leukocytes (including aggregates of leukocytes), macrophages, oval fat bodies, erythrocytes, bacteria, and fungal hyphae. A wet mount of a drop of EPS can be examined under a coverslip in a similar manner. Some researchers (Muller et al, 2001; Krieger et al, 2003) point out that quantitative determination of the EPS WBC concentration by a counting chamber method is superior to the standard wet mount method but probably only indicated in research studies. In fact, the NIH Chronic Prostatitis Cohort Study (Schaeffer et al, 2002; Nickel et al, 2003a) suggested that leukocyte determination did not appear to add significant clinical information to the assessment of a patient with CP/CPPS.



4-Glass Test (Meares-Stamey Test)

Classification	Specimen	VB1	VB2	EPS	VB3
CAT II	WBC	–	+/-*	+	+
	Culture	–	+/-*	+	+
CAT IIIA	WBC	–	–	+	+
	Culture	–	–	–	–
CAT IIIB	WBC	–	–	–	–
	Culture	–	–	–	–

Figure 13-4. Technique and interpretation of the Meares-Stamey four-glass lower urinary tract localization test for chronic prostatitis and chronic pelvic pain syndrome. CAT, category; EPS, expressed prostatic secretion; VB, voided bladder; WBC, white blood cell.

Figure 13-4 illustrates the technique and interpretation of the four-glass test.

Category II, chronic bacterial prostatitis, is diagnosed if there is a 10-fold increase in bacteria in the EPS or VB3 specimen compared with the VB1 and VB2 specimens. In a patient who has acute cystitis this localization is impossible, and in this case the patient can be treated with a short course (1 to 3 days) of therapy with an antibiotic such as nitrofurantoin, which penetrates the prostate poorly but eradicates the bladder bacteriuria. Subsequent localization of bacteria in the post-prostatic massage urine or EPS is then diagnostic of category II prostatitis. Category IIIA CP/CPPS is diagnosed when no uropathogenic bacteria are cultured, but excessive leukocytosis (usually defined as more than 5 to 10 WBCs per high-power field [HPF]) is noted in the prostate-specific specimens (EPS or VB3 or both). Category IIIB CP/CPPS is diagnosed when no uropathogenic bacteria are cultured and there is no significant leukocytosis noted on microscopic examination of EPS or the sediment of VB3.

Although the four-glass test remains the gold standard diagnostic evaluation of prostatitis patients, numerous surveys (Moon, 1997; Nickel et al, 1998a; McNaughton Collins and O'Leary, 1999; McNaughton Collins et al, 2000a) have confirmed that clinicians have more or less abandoned this time-consuming and expensive rigorous evaluation. The pre-massage and post-massage test (or two-glass test), originally suggested by Weidner and Ebner (1985) and popularized by Nickel (1995, 1996, 1997a), is a simple, cost-effective screen to categorize patients with CP. The patient provides a midstream pre-massage urine specimen and a urine specimen (initial 10 mL) after prostatic massage. Microscopy (sediment) and culturing of these two screening urine specimens allows categorization of the majority of patients with a CP syndrome. Figure 13-5 illustrates the technique and interpretation of the two-glass pre-massage and post-massage test.

In a retrospective personal series and a review of series in the literature, Nickel (1997a) noted that this test had 91% sensitivity and specificity compared with the gold standard Meares-Stamey test. Its limitations were thought to be the result of the exclusion of the urethral and EPS specimen. However, in patients without clinical urethritis, Krieger and associates (2000) demonstrated that urethral swabs are more efficient in picking up urethral inflammation than the VB1 specimen. But in this series of 235 patients, only 3% had more than 1 WBC/HPF. Therefore the urethral specimens rarely resulted in detection of significant urethral inflammation, and in this series rarely did cultured organisms change the direction of clinical therapy in patients with prostatitis (without clinical urethritis). In the same study (Krieger et al, 2000) comparing EPS with post-prostatic massage urine, the investigators demonstrated that EPS examination detected 76%, whereas post-massage urine

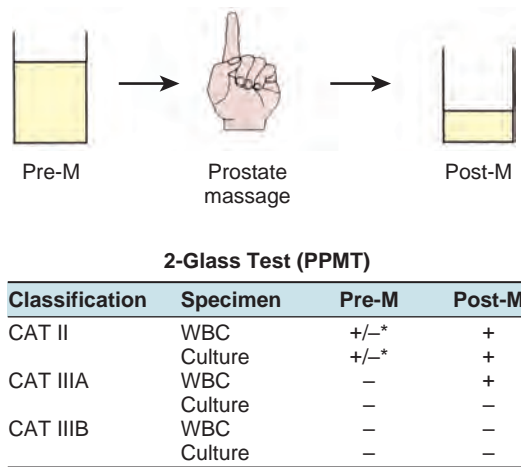


Figure 13-5. Technique and interpretation of the pre- and post-massage two-glass lower urinary tract localization test for chronic prostatitis and chronic pelvic pain syndrome. CAT, category; PPMT, pre- and post-massage test; WBC, white blood cell.

examination detected 82% of the patients who had inflammation on one or both tests. Ludwig and associates (2000), in a series of 328 patients in whom both EPS and a VB3 specimen were obtained, demonstrated that VB3 is almost as accurate as EPS (92% sensitivity; 99% specificity) in detecting prostate-specific inflammation. Seiler and associates (2003) came to the same conclusion in their study of 143 CP patients. Nickel and colleagues from the NIH CPCRN examined a cohort of 353 CP/CPPS men with complete four-glass data and noted that the two-glass test predicted a positive four-glass result with clinically acceptable accuracy (over 95% of men would have had the same diagnosis if the four-glass test were performed) (Nickel et al, 2006). This test, however, is only a screening test, and in patients in whom it is important to localize bacteria to the prostate versus the urethra (e.g., patients with recurrent UTIs, suspicion of urethral abnormality), a follow-up VB1 specimen or urethral swab may be very helpful. If typical urethral organisms are localized to the prostate when the pre-massage and post-massage test is used and the clinician is inclined to consider them pathogenic and subsequently treat the patients, urethral and EPS specimens to definitively localize the specific bacteria to the prostate are appropriate. As a general rule, it is always best to examine the EPS (if obtainable) microscopically.

The significance and diagnostic value of semen analysis in chronic bacterial prostatitis have been extensively debated and remain controversial. In a small study of 70 men with CP and 17 asymptomatic controls, Zagarra Montes and colleagues (2008) concluded that although a positive semen culture in a symptomatic patient may be useful to make a decision to start antibiotic treatment, a negative culture does not rule out the condition. Segmented lower urinary tract urine specimens are required for a definitive diagnosis. Data analyzed by Magri and associates (2009), in which 696 symptomatic patients were subjected to a four-glass test followed by semen culture and analysis, support the usefulness of semen analysis in the diagnostic workup of prostatitis patients but only when this test is used to complement the four-glass Meares and Stamey test.

Microbiologic Considerations

The Prostatitis Syndrome classification system depends on culturing for standard uropathogens. The Enterobacteriaceae (e.g., *E. coli*, *Serratia*, *Klebsiella*, *Proteus*, *Pseudomonas*) represent the most common uropathogens, followed by gram-positive enterococci. However, as discussed earlier in the section on etiology, other gram-positive organisms that typically colonize the urethra (*Staphylococcus epidermidis*, *S. saprophyticus*, *Streptococcus* species, *Corynebacterium*, and *Bacteroides*) can be localized to prostate specimens, including semen (>10-fold colony-forming unit count in prostate-specific specimens compared with pre-prostatic massage specimens), and their association with the prostatic inflammation symptom complex remains unclear. At this time, these patients are still considered to have category III CP/CPPS, but this may change as more research results become available and the current understanding of bacterial pathogenicity in the prostate gland evolves (Nickel and Moon, 2005; Nickel and Xiang, 2008). In patients with acute prostatitis, a blood culture should be considered, particularly if the patient has signs and symptoms of systemic infection (Etienne et al, 2010).

Cytologic Considerations

The differentiation of the two subtypes of category III CP/CPPS depends on cytologic examination of the urine or EPS or both. The urine specimens are centrifuged for 5 minutes; the sediment is resuspended under a coverslip and examined at high power (×300 to ×400), and the wet mount of a drop of EPS is examined under a coverslip at the same power. WBCs have traditionally been reported as numbers of leukocytes per high-power field (Fig. 13-6). There is no validated cutoff point for the level of WBCs per high-power field that is required to differentiate an inflammatory from a noninflammatory CP/CPPS. Although the suggested limits have ranged from as low as 2 (Anderson and Weller, 1979) to as high as 20 (Blacklock and Beavis, 1978), the consensus appears to favor 5 to 10 WBCs/HPF in EPS as the upper level of normal (Meares and Stamey, 1968; Pfau et al, 1978; Schaeffer et al, 1981). But inflammatory cells in the EPS fluctuate over time (Anderson and Weller, 1979; Schaeffer et al, 1981) and with the frequency of ejaculation (Jameson, 1967; Yavascaoglu et al, 1999). A disadvantage of looking at a drop of prostatic fluid or urine sediment is that the cells may clump or aggregate, which renders quantifying them virtually impossible. Also, an unstained specimen does not allow differentiation of the types of WBCs present (e.g., polymorphonuclear leukocytes, lymphocytes, monocytes, macrophages). If accuracy is required (e.g., for research), then the WBCs can be counted in a glass hemacytometer (so they may be quantified as cells per square millimeter) and subsequently stained to differentiate the inflammatory cell subtype (Anderson and Weller, 1979).

The clinical relevance of adding cytologic examination of semen specimens (which is difficult without special staining techniques) is unknown. Certainly, semen examination increases the percentage of patients identified as having inflammatory category IIIA CP/CPPS (Krieger et al, 2000).

Nickel and colleagues (2003a) compared the number of WBCs in the EPS in patients with CP/CPPS with the number in EPS specimens from normal asymptomatic control men and noted that although there was a statistically significant difference in WBC counts in the CP/CPPS men, the clinical significance was not apparent (i.e., 50% of CPPS men had >5 WBCs/HPF compared with 40% of control men). The relevance of examining urine and EPS for white cells in routine clinical practice has been challenged (Nickel et al, 2003a). In fact, my colleagues and I have not been able to confirm the association between histologically proven prostate inflammation and prostatitis symptoms (Nickel et al, 2007), further confusing the issue of whether it is necessary to determine prostate-specific specimen inflammation, which is really just a surrogate for prostate inflammation. However, some investigators (Nickel, 2002b) have recommended that a separate aliquot of urine be examined cytologically for malignant cells, particularly

KEY POINT: LOWER URINARY TRACT CULTURE TECHNIQUE

- The two-glass pre- and post-massage test is a simple, useful screen for inflammation and infection of the lower urinary tract in patients with chronic prostatitis.

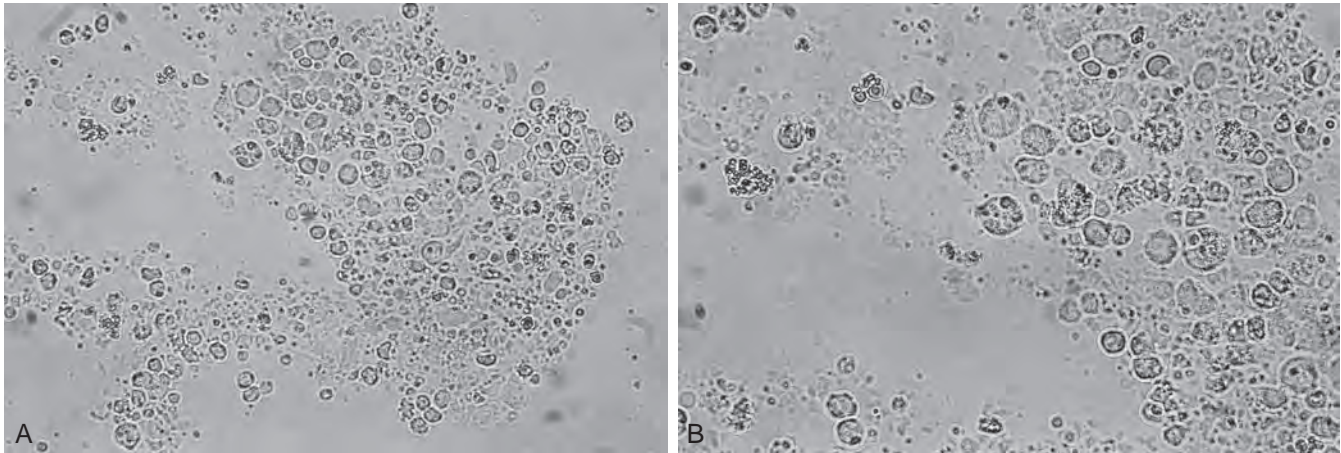


Figure 13-6. A and B, Unstained photomicrographs showing individual white blood cells, clumps of white blood cells, and lipid-laden macrophages in the expressed prostatic secretion of a patient with category IIIA chronic pelvic pain syndrome (A, $\times 250$; B, $\times 400$).

if the symptom complex includes storage urinary symptoms, dysuria, and/or suprapubic or bladder pain.

Urodynamics

Pain is the dominant symptom in patients with CP/CPPS, but a wide constellation of storage and voiding symptoms is associated with this syndrome. Proposed causes to account for the persistent urinary symptoms include detrusor vesical neck or external sphincter dyssynergia, proximal or distal urethral obstruction, and fibrosis or hypertrophy of the vesical neck (Blacklock, 1974; Bates et al, 1975; Orland et al, 1985; Blacklock, 1986; Theodorou et al, 1999). These abnormalities can often be clarified and diagnosed by urodynamics, particularly video-urodynamics. Others have suggested that men with defined primary voiding dysfunction have been misdiagnosed with CP (Webster et al, 1980; Siroky et al, 1981; Murnaghan and Millard, 1984). Siroky and associates (1981) noted that urodynamics revealed that 50% of 47 men with recurrent urinary symptoms, perigenital pain, or both who had previously been diagnosed as having CP had bladder acontractility during a study with nonrelaxing perineal floor (striated muscle spasm) and that another 36% had detrusor overactivity with appropriate striated sphincter relaxation. Barbalias (1990) and Barbalias and colleagues (1983) noted decreased peak and mean urinary flow rates, a significantly elevated maximal urethral closing pressure, and incomplete funneling of the bladder neck accompanied by urethral narrowing at the level of the external urinary sphincter during voiding with urodynamic evaluation of men diagnosed with CP. Hellstrom and colleagues (1987) also noted elevated urethral pressures, “hyperreflexia” of the external urethral sphincter, and intraprostatic reflux in three patients with unremitting symptoms of chronic nonbacterial prostatitis.

Kaplan and associates (1994, 1996, 1997) postulated that chronic lower urinary tract symptoms in young men are often misdiagnosed as chronic nonbacterial prostatitis when in fact they indicate a cohort of men with undiagnosed chronic voiding dysfunction. This conclusion is based on the video-urodynamic studies of 137 consecutive men 50 years of age or younger diagnosed with CP that did not respond to standard therapy (Kaplan et al, 1996). These researchers demonstrated a variety of urodynamic abnormalities in this selected population, including 54% of patients with primary vesical neck obstruction, 24% with functional obstruction localized to the membranous urethra (pseudodyssynergia), 17% with impaired bladder contractility, and 5% with an acontractile bladder. They noted detrusor overactivity in 49% of the men. Simple documentation of uroflowmetry and residual urine bladder scan abnormalities may suggest proceeding to more sophisticated urodynamics (Ghobish, 2000). Other groups dispute the benefits

of urodynamics and have noted very few urodynamic abnormalities in the typical patients with classic CP symptoms (Mayo et al, 1998).

Endoscopy

Clinical experience (rather than controlled clinical studies) suggests that lower urinary tract endoscopy (i.e., cystoscopy) is not indicated in the majority of men with CP/CPPS. However, cystoscopy is indicated in patients in whom the history (e.g., hematuria), lower urinary tract evaluation (e.g., VB1 urinalysis), or ancillary studies (e.g., urodynamics) indicate the possibility of a diagnosis other than CP/CPPS. In these patients, lower urinary tract malignancy, stones, urethral strictures, bladder neck abnormalities, and other lower urinary tract abnormalities that can be surgically corrected occasionally are discovered. Cystoscopy can probably be justified in men whose condition is refractory to standard therapy.

Ultrasonography

Transrectal ultrasonography has become one of the best radiologic methods to evaluate prostate disease and has become an especially helpful clinical tool for the assessment of prostate volume and ultrasound guidance of biopsy needles. The diagnostic value of ultrasonography in differentiating benign from malignant prostate disease is controversial, and the further differentiation of the various benign conditions of the prostate is even more so. Di Trapani and colleagues (1988) described inhomogeneous echo structures, constant dilatation of periprostatic venous plexus, elongated seminal vesicles, and thickening of the inner septa in patients with prostatitis. Doble and Carter (1989) described seven ultrasound signs associated with the presence of symptoms of CP compared with controls, and although the sensitivity increased with higher leukocyte counts, the signs were not sufficiently specific to differentiate clinical groups.

Peeling and Griffiths (1984) described the heterogeneity of the echo pattern and prostatic calculi as ultrasound features related to prostatitis. Ludwig and coworkers (1994) described the ultrasound features such as prostatic calcifications and seminal vesicle abnormalities that appear to be indicative of signs of inflammation but not proof of the presence of CP. Harada and associates (1980) concluded that the presence of stones is not related to a specific prostate disease process. De la Rosette and colleagues (1992b) performed ultrasonography in 22 patients with nonbacterial prostatitis and compared the results with those of a control group of 22 patients without lower urinary tract symptoms. This study indicated that there were no significant differences in ultrasound patterns of patients with nonbacterial prostatitis and the control group.

Others have employed color Doppler ultrasonography (Veneziano et al, 1995) and automated computer analysis (de la Rosette et al, 1995) in an attempt to improve the value of transrectal ultrasonography in the evaluation of prostatitis patients; however, the results are not conclusive enough to indicate that this is a clinically useful tool.

Transrectal ultrasonography can be valuable in diagnosing medial prostatic cysts in patients with prostatitis-like symptoms (Dik et al, 1996), diagnosing and draining prostatic abscesses (Granados et al, 1992), or diagnosing and draining obstructed seminal vesicles (Littrup et al, 1988). It is not required in all cases of acute bacterial prostatitis but rather only in those patients in whom appropriate antimicrobial therapy is failing (Horcajada et al, 2003).

Transabdominal (Khorasani et al, 2012) and pelvic floor (Davis et al, 2011) ultrasound have been suggested as modalities that could be used in assessing pelvic floor mobility; however, their use has not been standardized to a point at which it could be recommended in clinical practice.

Prostate Biopsy

Occasionally, because of an elevated PSA level or abnormal digital rectal examination findings, prostate biopsy is indicated (Kawakami et al, 2004). Some clinicians will consider starting patients with elevated screening PSA levels and a history of prostatitis or symptoms of CPPS on antibiotics, but this practice is reasonable only in patients with acute or chronic bacterial prostatitis (Nickel, 2002e), conditions that invariably lead to elevated PSA levels. The diagnosis of CP/CPPS should be used only as a reason against a prostate biopsy if the clinician is looking for an excuse not to perform a biopsy (Nickel, 2002e). Antimicrobial or anti-inflammatory treatment of category IV asymptomatic prostatitis detected on biopsy in men with elevated PSA is controversial, and no evidence-based recommendations can be made. Reviews on PSA and prostatitis are available (Kawakami et al, 2004, Hochreiter, 2008, Sandhu, 2009).

Out of desperation, urologists sometimes resort to prostate biopsy in an attempt either to demonstrate histologic evidence of prostatic inflammation or to culture an organism that cannot be cultured with the standard approach. The importance and interpretation of prostate biopsies in prostatitis performed for reasons other than prostate cancer screening are unclear. Doble and associates (1990) demonstrated immune complexes in the prostates of patients with prostatitis but found culture of the prostatic tissue unhelpful (Doble et al, 1989a). Nickel and Costerton (1993) were able to confirm the presence of potentially uropathogenic bacteria in patients with a documented history of chronic bacterial prostatitis in which EPS cultures became sterile after antibiotic therapy. Berger and associates (1997) also confirmed the presence of potential uropathogenic bacteria in prostate biopsy specimens (which correlated to some extent with prostatic inflammation in EPS) in patients in whom the same bacteria did not grow in standard prostatic specimens (e.g., EPS). Krieger and colleagues (1996b) demonstrated the possible presence of microorganisms in the prostate glands of a majority of men with CP syndrome through use of the molecular biologic technique of PCR. At this time, histologic, culture, and molecular biologic evaluations of prostate biopsy specimens in patients with CP/CPPS remain research tools only.

Evaluation of Suspected Seminal Vesiculitis

Occasionally, seminal vesiculitis can occur as a consequence of local bacterial infection in acute and chronic bacterial prostatitis (Zeitlin, 1999), and patients can develop seminal vesicle abscesses (Stearns, 1963; Kennelly and Oesterling, 1989). Seminal vesicle abscesses were traditionally diagnosed clinically by a positive ejaculate culture and seminal vesiculography (Dunnick et al, 1982; Baert et al, 1986) but are now imaged with computed tomography (Patel and Wilbur, 1987), transrectal ultrasonography (Littrup et al, 1988), magnetic resonance imaging (MRI) (Sue et al, 1989), or recently with

technetium-99m ciprofloxacin radioisotope scan (Choe et al, 2003).

Other Potential Markers

Wishnow and associates (1982) found that control patients (10 patients) and men with chronic abacterial prostatitis (4 patients) had no antibodies to gram-negative bacterial antigens, in contrast to men with bacterial prostatitis (6 patients). They hypothesized that immunologic analysis may provide a better diagnostic tool than culturing and microscopy. Shortliffe and coworkers (1981a, 1981b, 1986, 1989, 1992) found that the total IgA and IgG levels in the prostatic fluid in men with chronic abacterial prostatitis were higher than those in controls. They also discovered that prostatic fluid from control or abacterial prostatitis patients did not contain specific antibodies to gram-negative urinary pathogens (in contrast to men with bacterial prostatitis). Nickel and colleagues (2001b) used a similar antibody screening procedure in evaluation of 102 men with CP/CPPS who were subsequently treated with quinolone antibiotics. However, "antibody-positive" patients did not have a better response to antibiotic therapy than "antibody-negative" patients after 12 weeks of therapy. Li and associates (2001) demonstrated increased endotoxin concentrations in EPS and VB3 of men with bacterial prostatitis and inflammatory category IIIA CPPS and suggested that endotoxin levels might be used to identify these categories of patients with CP.

Alexander and colleagues (1998) discovered that men with chronic abacterial prostatitis had higher mean levels of the pro-inflammatory cytokines IL-1 α and TNF- α in seminal plasma compared with controls. Ruggieri and coworkers (2000) noted that levels of both IL-1 α and IL-8 were significantly higher in semen in category IIIA patients (leukocytes) than in category IIIB patients, but there was no statistically significant difference in levels of TNF- α , IL-1 α , or IL-6. This group found no correlation between cytokine levels and the number of leukocytes in EPS. The increased IL-8 levels in the semen of patients with prostatitis symptoms was confirmed by Khadra and coworkers (2006) and Penna and associates (2007), suggesting that this could be a surrogate marker for CP/CPPS. Nadler and colleagues (2000) found that mean levels of IL-1 α in EPS were higher in men with inflammatory chronic abacterial prostatitis and noninflammatory chronic bacterial prostatitis compared with controls. Hochreiter and associates (2000a) did find a direct significant correlation between the number of leukocytes in EPS and IL-1 α levels in EPS. One of the most intriguing possible biomarkers includes monocyte chemoattractant protein-1 and macrophage inflammatory protein-1 α detected in EPS. Both of these chemokines are elevated in category IIIA and IIIB CP/CPPS, and macrophage inflammatory protein-1 α may be a further marker for clinical pain in these patients (Desireddi et al, 2008). The sensitivity, specificity, and, more important, the clinical applicability of all these immunologic tests is really unknown, and none of them is yet indicated in clinical practice.

Marmar and associates (1980) hypothesized that zinc levels in EPS would be a useful marker for prostatitis and found that, indeed, zinc levels in men with chronic abacterial prostatitis and bacterial prostatitis were significantly lower than zinc levels in control patients and men with prostatodynia. However, Zaichick and colleagues (1996) found no differences in zinc levels between patients with chronic abacterial prostatitis, those with BPH, and controls. At this time the measurement of zinc levels in prostatic or semen specimens is clinically unhelpful.

Tanner and associates (1999) detected positive signals (rRNA-based molecular technique with prostatic fluid) in 65% of patients with CP. The condition of 7 of 11 patients with bacterial signals but none of 6 patients without bacterial signals was improved on antibiotic therapy. The same group (Shoskes and Shahed, 2000) subsequently confirmed this finding with a larger cohort of patients. These results are intriguing, and controlled studies evaluating the potential clinical significance of differentiating patients based on molecular biologic techniques are required.

An Approach to Diagnosis and Classification

A diagnostic algorithm that provides a practical approach to the workup of the majority of men with CP/CPPS is shown in Figure 13-7. Box 13-1 shows the tests recently recommended by the ICUD Guidelines for Male LUTS (Nickel et al, 2013b).

Phenotype Assessment in Chronic Prostatitis and Chronic Pelvic Pain Syndrome

Researchers and clinicians have become aware that patients with urologic CPPS, such as CP/CPPS, are not a homogeneous group of patients with identical causative mechanisms, genitourinary pain, urinary symptoms, and/or psychosexual problems but rather a

heterogeneous group of individual patients with widely differing clinical phenotypes. This realization led the NIH to fund the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) study group (www.mappnetwork.org) to explore basic science (particularly biomarker and causative studies) and epidemiology to

KEY POINTS: LOWER URINARY TRACT EVALUATION

- Mandatory evaluation includes history-taking, physical examination, urinalysis, and urine culture.
- Recommended evaluation includes lower urinary tract localization test, National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), sexual functioning assessment, flow rate, residual urine determination, and urine cytology.

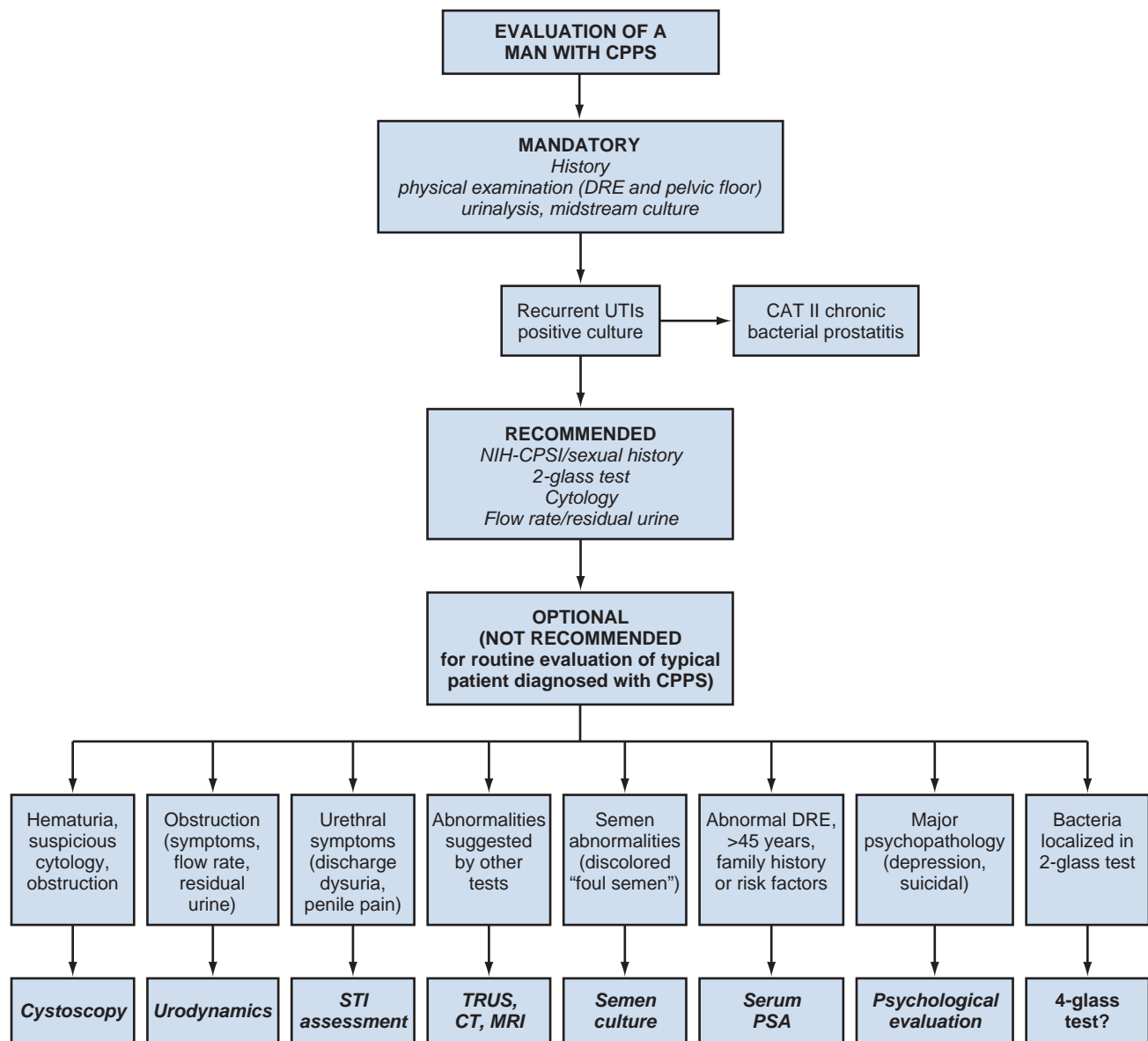


Figure 13-7. A suggested diagnostic algorithm from the 2012 International Consultation on Urological Diseases (ICUD) recommendations for the evaluation of patients with chronic prostatitis and chronic pelvic pain syndrome (CPPS). CAT, category; CT, computed tomography; DRE, digital rectal examination; MRI, magnetic resonance imaging; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; PSA, prostate-specific antigen; STI, sexually transmitted infection; TRUS, transrectal ultrasonography; UTIs, urinary tract infections. (Modified from Nickel JC, Wagenlehner F, Pontari M, et al. Male chronic pelvic pain syndrome (CPPS). In: Chapple C, Abrams P, editors. Male lower urinary tract symptoms (LUTS). An International Consultation on Male LUTS, Fukuoka, Japan, Sept 30-Oct 4, 2012. Montreal: Société Internationale d'Urologie (SIU); 2013. p. 331-72.)

BOX 13-1 Evaluation of the Typical Man with Chronic Pelvic Pain Syndrome**MANDATORY**

History
Physical examination, including digital rectal examination and pelvic floor assessment
Urinalysis and culture

RECOMMENDED

Two-glass lower urinary tract evaluation
Symptom inventory or index (National Institutes of Health Chronic Prostatitis Symptom Index [NIH-CPSI])
Sexual functioning assessment (questionnaire)
Flow rate
Residual urine determination
Urine cytology

NOT RECOMMENDED FOR ROUTINE INITIAL EVALUATION*

Four-glass lower urinary tract evaluation
Semen analysis and culture
Sexually transmitted infection evaluation or urethral culture
Pressure-flow studies
Video-urodynamics (including flow-EMG)
Transrectal ultrasound of the prostate
Pelvic imaging—ultrasound, CT scan, MRI
Prostate-specific antigen (PSA)

*Optional in selected patients.

CT, computed tomography; EMG, electromyography; MRI, magnetic resonance imaging.

Modified from Nickel JC, Wagenlehner F, Pontari M, et al. Male chronic pelvic pain syndrome (CPPS). In: Chapple C, Abrams P, editors. Male lower urinary tract symptoms (LUTS). An International Consultation on Male LUTS, Fukuoka, Japan, Sept 30-Oct 4, 2012. Montreal: Société Internationale d'Urologie (SIU); 2013. p. 331–72.

better understand the differences in this very heterogeneous group of patients. It is hoped that “phenotyping” patients may explain our very inconsistent therapeutic results and that the concept eventually may be applicable to direct better management strategies.

In 2009, a clinically practical phenotyping classification system for patients diagnosed with urologic CPPS (CP/CPPS and interstitial cystitis) was proposed (Nickel, 2009; Nickel and Shoskes, 2009; Shoskes et al, 2009a, 2009b). UPOINT is a 6-point clinical classification system that categorizes the phenotype of patients with urologic CPPS into one or more of six clinically identifiable domains: urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness (muscle) (Fig. 13-8). The UPOINT phenotypes can be differentially identified in individual patients through use of the standard clinical assessment described in the previous section and illustrated in Figure 13-7. UPOINT has become a new clinical tool for urologists to use to better understand their patients and direct individually based therapy. UPOINT has been evaluated and validated in female interstitial cystitis (Nickel et al, 2009) and male CP/CPPS (Shoskes et al, 2009a). For CP/CPPS, each domain has been clinically defined with standard clinical assessment, linked to specific mechanisms of symptom production or propagation, and associated with specific therapy (details described in the section on treatment).

In one study researchers determined the phenotype of a cohort of men with documented CP/CPPS through use of the UPOINT system and assessed the frequency of individual domains and their effect on symptom severity (Shoskes et al, 2009a). The percentages of patients positive for each domain were 52%, 34%, 61%, 16%, 37%, and 53% for the urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness domains,

UPOINT: THE “SNOWFLAKE HYPOTHESIS”

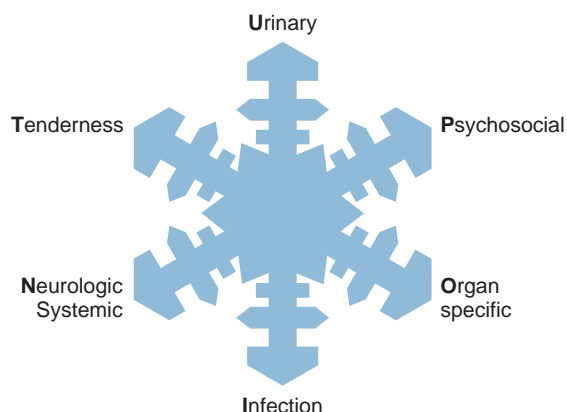


Figure 13-8. The UPOINT phenotypic classification system has six clinically defined domains (urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness). Because each individual patient has a unique phenotype, the six-point UPOINT system has been called the “snowflake hypothesis.”

respectively. Only 22% were positive for only one domain, and a significant stepwise increase was found in the total CPSI score as the number of positive domains increased (in other words, symptom severity was associated with the number of identified domains). As symptom duration increased, so did the number of positive domains (suggesting a phenotype progression). The domains with the most significant effect on symptoms included the urinary, psychosocial, organ-specific, and neurologic/systemic domains. For pain, the psychosocial, neurologic/systemic, and tenderness domains had significantly greater scores, whereas only the psychosocial and neurologic/systemic domains influenced the patients’ quality of life. This suggests that domains active outside the pelvis may have the most profound effect on symptoms and quality of life. Further evaluation of CP/CPPS patients (Samplaski et al, 2012) suggests clustering of domains specific to the pelvis (urinary, organ-specific, and tenderness) versus systemic domains (neurologic, infection, and psychosocial). This perspective implies two patient populations that may differ in pathophysiology and treatment response. It is postulated that identifying and managing these phenotypic domains may result in more effective amelioration of CP/CPPS symptoms and greater improvement in quality of life (Nickel, 2009; Nickel and Shoskes, 2009). Since this system was described, numerous investigators have assessed its implications (Hedelin, 2009; Magri et al, 2010; Samplaski et al, 2012) and suggested modifications (Hedelin, 2009; Davis et al, 2013a), including the inclusion of a sexual dysfunction (UPOINT“s”) phenotype (Magri et al, 2010; Davis et al, 2013b), although this addition has been contested by some researchers (Samplaski et al, 2011). This phenotype classification system has been used in English (Shoskes et al, 2009a, 2009b), German (Magri et al, 2010), Italian (Magri et al, 2010), Swedish (Hedelin, 2009), and Chinese (Liu et al, 2012; Zhao et al, 2013), and in each language and culture it has proved to be a useful clinical tool. Updated Canadian, European, and International guidelines for the management of CP/CPPS (Nickel, 2011; Engeler et al, 2013; Nickel et al, 2013b) have recommended that patients be clinically phenotyped during evaluation and treated according to individual phenotypes identified. This phenotype-directed therapy is discussed in the treatment section. My colleagues and I are currently testing specific questionnaires that will provide urologists with a clinical instrument to identify the six major phenotypes and also the further subclassifications that will likely be relevant within each specific domain. A better understanding of cause, mechanisms of disease, and disease progression and the discovery of specific biomarkers (e.g., from the NIH MAPP study) that will allow better phenotype identification will further improve our understanding and management of CP/CPPS.

KEY POINTS: PHENOTYPIC CLASSIFICATION OF CHRONIC PROSTATITIS AND CHRONIC PELVIC PAIN SYNDROME

- UPOINT classification of chronic prostatitis and chronic pelvic pain syndrome patients allows better descriptions of individual phenotypes.

Treatment

This section presents the rationale for each of the various treatments advocated for the prostatitis syndromes and reviews the clinical trial data that support (or not) the use of those specific therapeutic modalities in clinical practice. Recent rigorous prospective studies in chronic bacterial prostatitis and randomized placebo-controlled trials employing standardized definitions and validated outcomes in CP/CPPS have allowed us to develop best-evidence-based treatment strategies in a therapeutic field that used to be based on poor clinical data, dogma, and anecdotal experience (McNaughton Collins et al, 2000b, 2001a; Nickel, 2002c, 2002d, 2004; Schaeffer, 2006; Nickel, 2008b; Anothaisintawe et al, 2011; Nickel, 2011; Cohen et al, 2012; Thakkinstian et al, 2012; Engeler et al, 2013; Nickel et al, 2013b) (Tables 13-2 and 13-3).

Antimicrobials

Rationale. It is generally accepted that acute and chronic bacterial prostatitis are directly related to bacterial infection of the prostate gland. Many urologists further believe that, although bacteria are cultured in only 5% to 10% of cases of prostatitis, bacteria may be the cause of CP symptoms in a significant percentage of patients with this syndrome. Antimicrobial therapy is the most commonly prescribed treatment for the CP syndromes (Moon, 1997; Nickel et al, 1998a; McNaughton Collins et al, 2000b, 2001a; Taylor et al, 2008), independent of culture status.

Pharmacology and Pharmacokinetics. Most antimicrobial pharmacokinetic studies were performed in animal models (dogs and rats) (Madsen et al, 1978; Nickel, 1997b). Stamey (1980) and Stamey and associates (1970) found that acid antibiotic drugs can be detected in prostatic secretions only in very low concentrations, even when plasma concentrations of the drug are very high. Alkaline antibiotic drugs are found in concentrations greater than the simultaneous plasma levels. This phenomenon of ion trapping, and the fact that drug penetration was believed to be a passive transport mechanism based on diffusion and concentration, suggested that drug penetration is dependent on the lipid solubility, degree of ionization, degree of protein binding, and size and shape of the antimicrobial molecule. In dogs, the pH of plasma was found to be 7.4, whereas that of prostatic secretion is 6.4. Therefore, in this model, weak acids (low pKa) concentrate on the plasma side, whereas antibiotics with a higher pKa (weak bases) concentrate in the prostatic secretion.

Because infection may alter the local prostatic environment, thus changing the pharmacokinetic parameters, animal models were developed that introduced infection into the process (Baumueller and Madsen, 1977; Madsen et al, 1994; Nickel et al, 1995). All these animal studies (with and without infection) showed that trimethoprim concentrates in prostatic secretion and prostatic interstitial fluid (exceeding plasma levels), whereas sulfamethoxazole and ampicillin do not. The fluoroquinolones, which are neither pure acids nor bases but have characteristics of both, being zwitterionic drugs (i.e., those that have two pKa values) (Gasser et al, 1986), should allow drug concentration in the prostate at various pH ranges. Carbenicillin and the aminoglycosides did not concentrate in prostatic fluid in dog models.

It is difficult to extrapolate the animal pharmacokinetic studies to humans (Sharer and Fair, 1982). Fair and Cordonnier (1978) found that the prostatic secretion of normal men is

slightly alkaline (pH of approximately 7.3) but also that the pH of prostatic secretion in men with prostatic infection is markedly increased (pH of approximately 8.3). This has been confirmed in other studies (Anderson and Fair, 1976; Blacklock and Beavis, 1978; Pfau et al, 1978), and because the pH gradient is crucial to ion trapping, the results from animal studies should not be applied directly to humans. Unfortunately, drug diffusion studies are difficult to perform in humans, and most studies determine antibiotic concentrations in transurethraly resected BPH adenomas. These studies are further complicated because the high drug concentrations in urine can substantially alter the results. Employing a method to reduce urine contamination, Naber and Madsen (1999) demonstrated that for most fluoroquinolones the ratio of concentrations in prostatic fluid to concentrations in plasma is less than 1 (norfloxacin ratio 0.12, ciprofloxacin ratio 0.18 to 0.26, lomefloxacin ratio 0.48). Concentrations in seminal fluid usually exceed corresponding plasma concentrations of ciprofloxacin and ofloxacin, with ciprofloxacin demonstrating the highest ratio of seminal fluid to plasma (Naber, 1999). The numerous studies evaluating fluoroquinolone concentrations in prostatic tissue demonstrated that the fluoroquinolone concentration in the adenoma tissue is usually higher than that in plasma.

Clinical Trial Data. Unless the patient has a significant anatomic abnormality of the lower urinary tract or develops a prostate abscess, antimicrobial therapy is universally successful in eradicating the bacteria and curing the patient with acute bacterial prostatitis (Nickel and Moon, 2005). In the acutely inflamed prostate gland the pharmacokinetic considerations described in the previous section probably do not play a significant role in antibiotic penetration, and it is believed that most antibiotics achieve reasonable intraprostatic concentrations in the acute phase of the disease. Although prospective clinical trial data are unavailable, most experts suggest therapy initially with parenteral antibiotics (depending on the seriousness of the infection) followed by oral antibiotics with wide-spectrum antimicrobial activity (Becopoulos et al, 1990). The most common drugs suggested for initial therapy (Neal, 1999; Benway and Moon, 2008; Ludwig, 2008) are a combination of penicillin (i.e., ampicillin) and an aminoglycoside (i.e., gentamicin), second- or third-generation cephalosporins, or one of the fluoroquinolones. This traditional approach has changed recently because of the increasing risk of post-prostate biopsy prostate infection with ESBL microorganisms (Ozden et al, 2009; Oh et al, 2013). There are now identified risk factors for this shift, one of which is previous exposure to fluoroquinolones (Mosharafa et al, 2011; Ekici et al, 2012). Both the microorganisms (Bang et al, 2013) and the longer, more difficult clinical treatment course of the prostatitis after urologic intervention (Kim et al, 2012) illustrate the differences with spontaneous acute prostatitis. In patients with acute prostatitis with ESBL or suspected ESBL organisms (usually associated with transrectal prostate biopsies), treatment with a carbapenem (ertapenem, imipenem, or meropenem), amikacin, or colistin for at least 10 to 14 days is recommended (Paterson and Bonomo, 2005; Pallett and Hand, 2010; Fournier et al, 2013). Once the acute infection has settled down, therapy should be continued with one of the oral antimicrobial agents appropriate for the treatment of chronic bacterial prostatitis (e.g., trimethoprim or fluoroquinolones or ESBL-effective antimicrobial therapy based on sensitivity analysis). The duration of optimal therapy is unknown; between 2 and 4 weeks has been suggested (Bjerklund Johansen et al, 1998; Nickel, 1998a; Wagenlehner et al, 2007; Ludwig, 2008). It has been suggested that ineffective treatment of acute bacterial prostatitis may lead to the emergence of a CP category (Rudick et al, 2011; Galeone et al, 2013), particularly if the organism was post-prostate biopsy ESBL *E. coli* (Oh et al, 2013).

In the 1970s to 1990s the most commonly used antimicrobial agents in the treatment of CP were trimethoprim-sulfamethoxazole (co-trimoxazole) (Moon, 1997; Nickel et al, 1998a) and, to a lesser extent, trimethoprim alone. In patients with chronic bacterial prostatitis, eradication of pathogens (the only objective

TABLE 13-2 Randomized Placebo-Controlled Clinical Trials Evaluating Therapy for Chronic Prostatitis and Chronic Pelvic Pain Syndrome (CP/CPPS)*

ACTIVE AGENT	REFERENCE	DURATION	PATIENTS (N)		RESPONDERS (%)		CHANGE IN NIH-CPSI		TREATMENT EFFECT
			ACTIVE	PLACEBO	ACTIVE	PLACEBO	ACTIVE	PLACEBO	
Levofloxacin	Nickel et al, 2003b	6 wk	35	45	42	37	−5.4	−2.9	2.5
Tetracycline	Zhou et al, 2008	12 wk	24	24	NK	NK	−18.5†	−1.0	17.5†
Ciprofloxacin	Alexander et al, 2004	6 wk	49	49	22	22	−6.2	−3.4	2.8
Tamsulosin			49		24		−4.4		1.0
Ciprofloxacin and tamsulosin			49		10		−4.1		0.7
Terazosin	Cheah et al, 2003b	14 wk	43	43	NK	NK	−14.3†	−10.2	4.1†
Alfuzosin	Mehik et al, 2003	24 wk	17	20	65†	24	−9.9†	−3.8	6.1†
Tamsulosin	Nickel et al, 2004a	6 wk	27	30	52	33	−9.1†	−5.5	3.6†
Alfuzosin	Nickel et al, 2008c	12 wk	138	134	49.3‡	49.3‡	−7.1	−6.5	0.6
Doxazosin	Tugcu et al, 2007	24 wk	30	30	66†	33	−12.4†	−1.0	11.4
Tamsulosin (0.2 mg)	Chen et al, 2011	24 wk	50	50	50	50	−7.5†	−4.0	3.5†
Silodosin 4 mg	Nickel et al, 2011a	12 wk	45	54	63	35	−12.1†	−8.5	3.6†
Silodosin 8 mg			52		51		−10.2		1.7
Rofecoxib 25 mg	Nickel et al, 2003c	6 wk	53	59	46	40	−4.9	−4.2	0.7
Rofecoxib 50 mg	Nickel et al, 2003c	6 wk	49	59	63†	40	−6.2	−4.2	2.0
Prednisone	Bates et al, 2007	4 wk	6	12	50	50	NK	NK	No significant difference
Celecoxib	Zhao et al, 2009	6 wk	32	32	78†	32	−8.0†	−4.0	4.0†
Tanezumab	Nickel et al, 2012	Single IV dose	30	32	24	23.1	−4.3	−2.8	1.5
Pentosan polysulfate	Nickel et al, 2005a	16 wk	51	49	37	18	−5.9	−3.2	2.7
Finasteride	Nickel et al, 2004b	24 wk	33	31	33	16	−3.0	−0.8	2.2
Mepartricin	De Rose et al, 2004	8 wk	13	13	NK	NK	−15.0†	−5.0	10.0†
Quercetin	Shoskes et al, 1999	4 wk	15	13	67†	20	−7.9†	−1.4	6.5†
Pollen extract (Cernilton)	Wagenlehner et al, 2009	12 wk	70	69	62.9†	41.8	−7.5†	−5.4	2.1†
Pregabalin	Pontari et al, 2010	6 wk	103	106	47.2‡ (31†)§	35.8‡ (19)§	−6.6†	−4.2	2.4†

*These studies met the evidence-based criteria updated by the 2012 International Consultation on Urologic Disease (ICUD) committee (Nickel et al, 2013b), which included randomized, placebo-controlled design with National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) as one of the outcomes.

†Significant difference between active and placebo ($P < .05$).

‡Primary end point (CPSI responders—see text).

§Global Response Assessment responders.

NK, not known.

measurement in most CP studies) with trimethoprim-sulfamethoxazole or trimethoprim alone ranged from a low of 0% (Smith et al, 1979) to a high of 67% (Paulson and White, 1978), with most studies demonstrating an efficacy rate between 30% and 50% (Meares, 1973; Drach, 1974b; Meares, 1975; McGuire and

Lytton, 1976; Meares, 1978). It appears that longer-duration therapy (90 days) provides the best clinical results. Trimethoprim-sulfamethoxazole is less effective both in bacterial eradication and cost-effectiveness when compared with the newer fluoroquinolones (Kurzer and Kaplan, 2002).

TABLE 13-3 Sham Controlled Trials Evaluating Nonmedical Therapies Using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) as an Outcome Parameter

THERAPY	REFERENCE	DURATION OF THERAPY AND FOLLOW-UP (WEEKS)	PATIENTS (N)		CHANGE IN NIH-CPSI		TREATMENT EFFECT
			ACTIVE	SHAM	ACTIVE	SHAM	
Directed physiotherapy*	FitzGerald et al, 2009	12	10	11	-14.4	-6.8	7.6
Posterior tibial nerve stimulation	Kabay et al, 2009	12	45	44	-13.4	-1.4	12.0†
Acupuncture	Lee et al, 2008a	10	44	45	-10	-6	4.0†
Electroacupuncture	Lee and Lee, 2009	6	12	12	-9.5	-3.5	6.0†
Extracorporeal shock wave therapy	Zimmermann et al, 2009	4	30	30	-3.7	-0.1	3.6†
Extracorporeal shock wave therapy	Vahdatpour et al, 2013	4 (assessed at 12 weeks)	20	20	-7.1	-0.2	6.9†
Botulinum toxin A	Gottsch et al, 2011	4	13	16	+0.4	-2.2	2.6

*The randomized therapy was not sham but rather relaxation massage therapy.

†Statistically significant difference between groups.

Except for the well-studied fluoroquinolones, most antibiotics (including minocycline, cephalexin, and carbenicillin) do not demonstrate significant clinical efficacy in clinical studies in which patients were observed for sufficient time (Paulson and White, 1978; Oliveri et al, 1979; Mobley, 1981). One notable exception has been the macrolides erythromycin (Mobley, 1974), azithromycin (Skerk et al, 2003), and clarithromycin (Skerk et al, 2002b), particularly when *C. trachomatis* is implicated. A recent Cochrane review (Perletti et al, 2013) concluded that although the microbiologic and clinical cure rates were higher for the macrolides compared with fluoroquinolones for the treatment of intracellular pathogens (*Chlamydia* or *Mycoplasma*), there was no significant difference between azithromycin and clarithromycin.

The fluoroquinolones have demonstrated improved therapeutic results, especially in prostatitis caused by *E. coli* and other members of the Enterobacteriaceae but not necessarily in prostatitis caused by *P. aeruginosa* or enterococci. Naber (1999) analyzed the many studies available in the literature evaluating fluoroquinolones in the treatment of CP and found eight comparable studies in which the diagnosis was obtained by localization studies and in which the patients were observed for a sufficient time after completion of therapy (Weidner et al, 1987; Pust et al, 1989; Heidler, 1990; Schaeffer and Darras, 1990; Pfau, 1991; Weidner et al, 1991a; Ramirez et al, 1994; Koff, 1996); in these studies the researchers evaluated norfloxacin, ciprofloxacin, ofloxacin, and lomefloxacin. In 2005, Naber, reporting at the Sixth International Consultation on New Developments in Prostate Cancer and Prostate Disease, Paris, June, 2005 (Schaeffer et al, 2006), added three more recent studies that met these strict criteria (Naber et al, 2000; Naber and European Lomefloxacin Prostatitis Study Group, 2002; Bunderick et al, 2003) with a further addition from 2008 (Naber et al, 2008). The overall conclusion was that fluoroquinolones were the optimal antimicrobial agent for the treatment of chronic bacterial prostatitis. In a 2013 Cochrane review, Perletti and colleagues (2013) undertook an ambitious comprehensive review of antimicrobial therapy for chronic bacterial prostatitis by evaluating and comparing 18 clinical trials (Smith et al, 1979; Paulson et al, 1986; Cox, 1989; Ohkawa et al, 1993b; Koff 1996; Bustillo et al, 1997; Naber and European Lomefloxacin Prostatitis Study Group, 2002; Skerk et al, 2002a, 2002b; Bunderick et al, 2003; Skerk et al, 2003, 2004a, 2004b, 2006; Giannarini et al, 2007; Aliaev et al, 2008; Cai et al, 2009, 2010; Zhang et al, 2012) that met strict inclusion criteria including standardized microbiologic diagnoses and outcomes (microbiologic and clinical) in randomized controlled studies in which the comparison was with placebo, different administration schedules, or another antibiotic or combinations of antibiotics plus

other agents. The authors concluded that there are no significant differences in microbiologic and clinical efficacy or in adverse effect rates among the oral fluoroquinolones ciprofloxacin, levofloxacin, lomefloxacin, ofloxacin, and prulifloxacin. As mentioned previously, the macrolides appear to be superior to the fluoroquinolones for the treatment of proven chlamydial infection. The authors further concluded that there is inconclusive randomized controlled evidence regarding the role of combination treatments of chronic bacterial prostatitis with antimicrobial and nonantimicrobial substances, such as phosphodiesterase-5 inhibitors or herbal preparations.

For CP caused by *E. coli*, treatment duration of 1 month for the fluoroquinolones seems to be superior to the usual 3-month treatment with trimethoprim-sulfamethoxazole. It has been suggested that antibiotics should be continued only for 4 to 6 weeks if pre-treatment cultures are positive and/or the patient has reported positive effects from treatment (Wagenlehner et al, 2007); however, the duration of therapy cannot be confirmed from analysis of available studies (Perletti et al, 2013). Some clinicians have observed that as many as 20% of patients in whom an initial treatment period fails could be rescued with a second cycle of treatment with another antibiotic (Magri et al, 2007b). In microbiologically diagnosed chronic bacterial prostatitis, eradication of bacteria is associated with both short-term and long-term clinical success (Nickel and Xiang, 2008). This appears to be true in men with recent onset of prostatitis associated with bacterial localization with the traditional uropathogens (gram-negative uropathogens and *Enterococcus* species) as well as nontraditional bacteria (gram-positive bacteria such as coagulase-negative staphylococcal and streptococcal species) (Magri et al, 2007a; Nickel and Xiang, 2008). A number of investigators (Baert and Leonard, 1988; Jimenez-Cruz et al, 1988; Yamamoto et al, 1996; Guercini et al, 2005b) have advocated direct injection of antibiotics into the prostate gland, but this method has never been rigorously evaluated or become popular among urologists. It appears that men with chronic bacterial prostatitis and prostatic calculi are more difficult to cure (Zhao et al, 2012). Many physicians have resorted to prolonged therapy with low-dose prophylactic or suppressive antimicrobials for recurrent or refractory prostatitis, respectively, although this practice has not been confirmed with clinical studies.

Many studies evaluating physicians' practice patterns in prostatitis syndromes (de la Rosette et al, 1992a; Moon, 1997; Collins et al, 1998; Nickel et al, 1998a; McNaughton Collins et al, 2000a; Taylor et al, 2008) have confirmed that most patients diagnosed with CP, irrespective of culture results, are treated with antimicrobial therapy. Older studies have generally indicated that approximately 40% of patients with nonbacterial CP have some symptomatic

improvement with antimicrobial therapy (Berger et al, 1989; Weidner, 1992; de la Rosette et al, 1993a; Ohkawa et al, 1993b; Bergman, 1994; Bjerklund Johansen et al, 1998; Tanner et al, 1999; Nickel et al, 2001b). Antibiotic therapy may benefit CP/CPPS patients by three different mechanisms: a strong placebo effect, the eradication or suppression of noncultured microorganisms (Nickel et al, 2001b), or the independent anti-inflammatory effect of some antibiotics (Yoshimura et al, 1996; Galley et al, 1997). It has been suggested by a European consensus group evaluating the role of antibiotics in the treatment of CP (Bjerklund Johansen et al, 1998; Engeler et al, 2013) that antibiotics could be considered empirical treatment for category IIIA CP/CPPS, but the benefits should be appraised after a minimum of 2 to 4 weeks of therapy. The antibiotics could be continued for 4 to 6 weeks if the patient reports positive effects from treatment (Wagenlehner et al, 2007). These recommendations remain controversial (Taylor et al, 2008), particularly because new data appear to provide conflicting interpretations. Two multicenter randomized placebo-controlled studies have assessed the efficacy of 6 weeks of levofloxacin (Nickel et al, 2003b) and ciprofloxacin (Alexander et al, 2004) in men with CP/CPPS. In these trials the participants had chronic symptoms for a long duration (many years) and had been heavily treated (including treatment with antibiotics). In the study by Nickel and associates (2003b) 80 patients were randomized to levofloxacin or placebo, whereas in the NIH-sponsored study reported by Alexander and colleagues (2004) 196 men with CP/CPPS were randomized in a 2 × 2 factorial design to ciprofloxacin, tamsulosin, the combination of ciprofloxacin and tamsulosin, or placebo. In both of these prospective-designed controlled multicenter trials, no significant difference was reported between the fluoroquinolone and placebo in terms of symptom amelioration. **Antibiotics should not be prescribed for previously treated men with CP/CPPS of long duration.** However, two prospective trials comparing the effect of 4 to 6 weeks of antibiotics (Magri et al, 2007a; Nickel and Xiang, 2008) in men with localization of both traditional uropathogens and organisms not usually believed to be uropathogenic (and therefore classified as category III CP/CPPS) showed similar eradication and clinical success rates (75% to 80%). Furthermore, in the study by Nickel and Xiang (2008), the eradication of those organisms, whether or not they were considered to be uropathogens, correlated with both short- and long-term clinical success. Because the majority of patients in Nickel and Xiang's study (2008) had a short history of prostatitis and were antibiotic naive for that episode, it was concluded that **antibiotic treatment may be considered for antibiotic-naive patients with a recent diagnosis of prostatitis, regardless of culture status.**

α-Adrenergic Blocker Therapy

Rationale. Patients with CP/CPPS have significant lower urinary tract symptoms, which appear to be related to poor relaxation of the bladder neck during voiding (Barbalias et al, 1983; Murnaghan and Millard, 1984; Blacklock, 1986; Hellstrom et al, 1987; Barbalias, 1990; Kaplan et al, 1997). The subsequent turbulent "dysfunctional" voiding may predispose the patient to reflux of urine into the prostatic ducts, causing intraprostatic inflammation and subsequently pain (Kirby et al, 1982). **The bladder neck and prostate are rich in α receptors, and it is hypothesized that α-adrenergic blockade may improve outflow obstruction, improving urinary flow and perhaps diminishing intraprostatic ductal reflux.**

Clinical Trial Data. A number of older clinical trials suggested that the α-adrenergic blockers diphenoxylbenzamine (Dunzendorfer, 1983), phenoxybenzamine (Osborn et al, 1981), alfuzosin (de la Rosette et al, 1992c; Barbalias et al, 1998), terazosin (Neal and Moon, 1994; Barbalias et al, 1998; Lacquaniti et al, 1999; Gül et al, 2001), doxazosin (Evliyaoglu and Burgut, 2002), and tamsulosin (Lacquaniti et al, 1999) resulted in significant symptomatic improvement of prostatitis-related symptoms; however, these trials were small, most were uncontrolled, and outcome measures were not validated. Studies by Barbalias and associates (1998) and Youn et al (2008) further seemed to indicate that the combination of

antibiotics and α-adrenergic blockers improved the clinical result in patients with chronic bacterial prostatitis.

At least six randomized placebo-controlled trials with clearly defined CP/CPPS patients (NIH classification) and employing the NIH-CPSI as the outcome parameter appear to have confirmed the efficacy of α-adrenergic blockers but only in men who have recent-onset disease and have not been heavily pretreated and who are on therapy for longer than 6 weeks. Cheah and colleagues (2003b) randomized 86 patients with CP to either terazosin or placebo for 14 weeks. Patients on terazosin had a 50% reduction in mean symptom score compared with 37% in the placebo-treated group. Terazosin resulted in modest but significant improvement in all domains of the NIH-CPSI. Mehik and colleagues (2003) followed 19 patients randomized to 6 months of alfuzosin treatment and 20 patients on 6 months of placebo therapy, and both groups were followed for a further 6 months after discontinuing the active or placebo medication. Patients in the alfuzosin group had a significant amelioration of symptoms compared with the placebo therapy group that was evident at 4 months and became even more clinically significant by 6 months. At 6 months, 65% of alfuzosin patients were rated as responders compared with 24% of the placebo group. The beneficial effect appeared to wear off over the next 6 months after the alfuzosin was discontinued. Nickel and colleagues (2004c) randomized 57 men with CP/CPPS to tamsulosin, 0.4 mg, or placebo after a 2-week placebo run-in and observed the two groups for 6 weeks. Patients treated with tamsulosin had a statistically significant (but only modest clinically significant) treatment effect compared with patients taking a placebo. A significant treatment effect was not observed in patients who had mild symptoms, but patients with severe symptoms (75th percentile) had a statistically and clinically significant response compared with placebo. It appears that the response to α-adrenergic blockers is durable, for at least up to 24 to 38 weeks as long as the patient stays on the medication (Mehik et al, 2003; Cheah et al, 2004). Another study (Tugcu et al, 2007) included 90 treatment-naive patients with CP/CPPS randomized to receive doxazosin, 4 mg/day, alone or a triple therapy (doxazosin, 4 mg/day, plus an anti-inflammatory agent—ibuprofen, 400 mg/day—and a myorelaxant—thiocolchicoside, 12 mg/day) or placebo. Over 6 months, the total NIH-CPSI score significantly improved in the doxazosin group (from 23.1 to 10.5 points) and triple-therapy groups (from 21.9 to 9.2), and it remained stable in the placebo group (from 22.9 to 21.9). Chen and colleagues (2011) examined a total of 100 men diagnosed with CP/CPPS randomly allocated to receive either 0.2 mg of tamsulosin daily or placebo for 6 months. The tamsulosin patients had modest satisfactory improvements compared with the placebo group during treatment. Six months after initiation of treatment, the mean decrements of total NIH-CPSI score in the tamsulosin and placebo groups were 7.5 ± 1.9 and 4.0 ± 2.3, respectively ($P < .01$). After cessation of therapy, the significant difference waned gradually. Two years after cessation of therapy, the mean decrements in total NIH-CPSI score in the two groups were 3.0 ± 1.3 and 1.9 ± 0.9, respectively ($P > .05$). This suggests that in patients who respond to α blockers, the therapy must be continued long term. Finally, Nickel and coworkers (2011a) evaluated the efficacy and safety of two doses of silodosin versus placebo in 151 men with CP/CPPS who had not been treated previously with α blockers. Patients randomized to silodosin 4 mg experienced a significant decrease in total NIH-CPSI of −12.1 versus placebo (−8.5). At this dose, men also had a significant decrease in the urinary and quality of life subscore as well as the physical component of the Medical Outcomes Study Short Form 12 quality-of-life assessment. During global response assessment 56% of patients receiving 4 mg of silodosin versus 29% receiving placebo reported moderate or marked improvement (also significant). Increasing the dose of silodosin to 8 mg resulted in no incremental treatment effects.

In contrast, the results from the NIH CPCRN randomized controlled trial (Alexander et al, 2004) comparing 6 weeks of ciprofloxacin, tamsulosin, and the combination of ciprofloxacin and tamsulosin with placebo in very chronic and heavily pretreated patients failed to show any improvement in patients

treated with tamsulosin (with or without ciprofloxacin) compared with patients treated with placebo. A number of meta-analyses and comprehensive reviews of these data have suggested that α -adrenergic blockers provide significant symptom amelioration only after more than 6 weeks of therapy in less heavily treated patients with recent onset of moderate to severe symptoms (Yang et al, 2006; Mishra et al, 2007; Nickel, 2008a). To test this hypothesis, an NIH multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of 12 weeks of alfuzosin or placebo to reduce symptoms in 272 randomized men with CP/CPPS diagnosed within 2 years previously and who had not been previously treated with an α -adrenergic blocker (Nickel et al, 2008a). The rate of the primary outcome (reduction of at least 4 points in NIH-CPSI total score from baseline) was 49% in both treatment groups. The response rates at 12 weeks measured with a global response assessment were also similar: 34% and 35% for the placebo and alfuzosin groups, respectively ($P = .90$). These important findings did not support the use of α -adrenergic blockers in recently diagnosed α -adrenergic blocker-naïve men with CP/CPPS.

Anti-Inflammatory Agents and Immune Modulators

Rationale. Prostatic inflammation is associated with category IIIA CP/CPPS, and elevated cytokine levels are noted in the semen (Alexander et al, 1998; Ruggieri et al, 2000) and EPS (Hochreiter et al, 2000b; Nadler et al, 2000) of patients with inflammatory CPPS. Nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppressive drugs theoretically should improve the inflammatory parameters within the prostate and possibly result in a reduction of symptoms (Pontari, 2002).

Clinical Trial Data. Canale and associates (1993a) found that nimesulide (a nonsteroidal anti-inflammatory drug) quickly reduced inflammatory-type symptoms such as dysuria, strangury, and painful ejaculation. A second study by Canale and colleagues (1993b) found that, by the rectal route, ketoprofen was inferior to nimesulide (both drugs were used as suppositories). Prednisolone has been suggested as a potent anti-inflammatory for CP (Bates and Talbot, 2000), and a randomized study presented by Dimitrakov and associates (2004) indicates that high-dose methylprednisolone (followed by rapid tapering of dose) may have more efficacy than placebo, even after 12 months, but the side effect profile makes this type of therapy less attractive. A small randomized trial evaluating oral corticosteroids did not show superiority of the active therapy over placebo (Bates et al, 2007).

The new class of cyclooxygenase-2 inhibitors has proved successful for long-term treatment of other chronic inflammatory conditions such as rheumatoid arthritis and chronic osteoarthritis; many urologists have employed these medications for prostatitis patients, with some anecdotal successes reported. The results of a North American randomized controlled trial comparing the cyclooxygenase-2 inhibitor rofecoxib with placebo indicated that many men with CPPS benefited (in terms of pain and quality of life) from rofecoxib therapy compared with placebo. In this study, in which 161 patients were randomized to rofecoxib 25 mg, rofecoxib 50 mg, or placebo, only patients on the high dose showed any clinical improvement compared with the placebo. Very few patients, however, had complete resolution of their symptoms (Nickel et al, 2003c). Another study from China (Zeng et al, 2004) assessing the effectiveness of two doses of the cyclooxygenase-2 inhibitor celecoxib also demonstrated a dose-dependent response (200 mg twice a day for 6 weeks was more effective than 200 mg once a day). Zhao et al (2009) randomized 64 patients with category IIIA CPPS to celecoxib (200 mg daily) and placebo for 6 weeks with 8 weeks of follow-up. These researchers showed that celecoxib provides significant symptomatic improvement, but the benefit was limited to the duration of the therapy. At this time, high-dose, long-duration monotherapy with cyclooxygenase-2 inhibitors is not recommended.

Because the clinical and pathologic characteristics are similar to those of interstitial cystitis and there is evidence that pentosan

polysulfate, a glycosaminoglycan drug that has been used in the treatment of interstitial cystitis and provides significant anti-inflammatory effects (Sunaga et al, 2012), Wedren (1987) compared the efficacy of pentosan polysulfate with placebo. In this small study the treated group was noted to have a statistically significant improvement in symptoms, but the major symptom that improved was nonspecific myalgias and arthralgias. An uncontrolled pilot study evaluating oral pentosan polysulfate in 32 men with CPPS demonstrated amelioration of symptoms and improvement in the quality of life in over 40% after treatment for 6 months (Nickel et al, 2000). The results of a multicenter, randomized, placebo-controlled trial that randomized 100 men to pentosan polysulfate, 900 mg/day (three times the usual dose), or placebo indicated this medication provided modest benefit for some men with CPPS (Nickel et al, 2005a).

Thalidomide, a cytokine modulating drug, was assessed in 30 men with chronic bacterial prostatitis and abnormal semen cytokine levels (IL-2, IL-6, IL-8, IL-10, and TNF- α) in a randomized placebo-controlled trial (Guercini et al, 2005a). Despite a significant reduction in cytokine levels in semen, no difference in symptom relief was noted. A similar lack of efficacy was noted in a small placebo-controlled trial evaluating the leukotriene antagonist zafirlukast (Goldmeier et al, 2005).

The potential of various anti-inflammatory agents, immune modulators, and cytokine inhibitors makes these classes of drugs potentially useful as adjunctive therapy for the CP syndromes, but clinical trials suggest that they are not a useful monotherapy.

Muscle Relaxants

Rationale. Many investigators believe that CPPS is the ultimate reflection of a smooth and skeletal neuromuscular dysregulatory phenomenon in the perineum or pelvic floor (Osborn et al, 1981; Egan and Krieger, 1997; Anderson, 1999; Zermann and Schmidt, 1999). The use of α blockers to relax smooth muscle (see earlier discussion of α -adrenergic blockers) and skeletal muscle relaxants combined with adjuvant medical and physical therapies has been advocated and promoted (Anderson, 1999; Zermann and Schmidt, 1999).

Clinical Trial Data. In one of the few studies to compare muscle relaxants with placebo, Osborn and associates (1981) conducted a prospective double-blind study comparing phenoxylbenzamine, baclofen (a striated muscle relaxant), and placebo in 27 patients with prostatodynia (category IIIB). Patients were treated with each agent for 1 month in a crossover trial. Symptomatic improvement was seen in 37% of the patients treated with baclofen compared with 8% treated with placebo. Simmons and Thin (1985) compared diazepam with an antibiotic in patients with chronic abacterial prostatitis and found no difference in symptom improvement between the diazepam group (8 of 11 men improved) and the antibiotic group (7 of 12 men improved). Unfortunately these studies were hindered by a lack of controlled and defined entry criteria and no quantified measurement of patients' responses and therefore the role of muscle relaxants has yet to be determined.

Hormone Therapy

Rationale. Prostate growth and function are influenced by the local hormonal milieu, especially by androgens. Theoretically, anti-androgens (including 5 α -reductase inhibitors) could result in regression of prostatic glandular tissue (inflammation is believed to begin at the level of the ductal epithelium), decreased intraprostatic pressure (Mehik et al, 2002), improved voiding parameters (especially in older patients with BPH and prostatitis), and reduced intraprostatic ductal reflux (Nickel, 1999a).

Clinical Trial Data. Holm and Meyhoff (1996) were the first to note that the 5 α -reductase inhibitor finasteride had potential in alleviating symptoms by observing the effect of finasteride therapy in four patients with CP or prostatodynia. Leskinen and colleagues

(1999) randomized 41 patients with chronic idiopathic prostatitis (i.e., nonbacterial prostatitis and prostatodynia) to treatment with placebo (25%, or 10 patients) or finasteride (75%, or 31 patients) for 1 year. Compared with placebo, finasteride reduced prostatitis and BPH symptom scores; however, there was no statistically significant difference in pain between the two groups. The baseline characteristics of the two groups were not comparable, and the enrolled patients consisted of an unknown mixed population with inflammatory and noninflammatory prostatitis syndromes. A randomized open-label comparative trial in CP/CPPS men showed significantly more improvement in men treated for a year with finasteride compared with saw palmetto, an herbal therapy (Kaplan et al, 2004). A randomized controlled trial compared the reduction of NIH-CPSI in 64 men with CP/CPPS randomized to finasteride or placebo (Nickel et al, 2004b). Six months of finasteride resulted in a numerical but not statistically significant reduction in symptoms compared with the symptom reduction noted in the placebo group. In the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) prostate cancer reduction trial, dutasteride therapy produced statistically and possibly clinically significant benefits compared with placebo in the men with preexisting prostatitis or prostatitis symptoms (Nickel et al, 2011b). **Finasteride and dutasteride cannot be recommended as a monotherapy except in men with associated BPH.**

Testosterone and dihydrotestosterone are not the only hormones with a possible effect on prostate inflammation; estrogens may also play a role. A number of small, poorly controlled studies (Cavallini, 2001; Saita et al, 2001) suggested that mepartiricin (a drug that lowers estrogen levels in the prostate) may be useful in the treatment of CP/CPPS. A small prospectively designed trial randomized 26 men with CP/CPPS to 60 days of therapy with mepartiricin or placebo (De Rose et al, 2004). The study showed a statistical and perhaps clinically significant benefit (60% vs. 20% improvement, respectively) that should stimulate further research in the role of hormonal manipulation (in this case estrogens) in the treatment of CP/CPPS.

Phytotherapeutic Agents

Rationale. A number of plant extracts have been shown in many in vitro experiments to have 5 α -reductase activity, α -adrenergic blockade activity, effects on bladder contractility, and anti-inflammatory properties (Lowe and Fagelman, 1999; Shoskes, 2002).

Clinical Trial Data. Three specific phytotherapeutic agents have been tested in well-controlled clinical trials: Cernilton, a pollen extract (Buck et al, 1989; Rugendorff et al, 1993; Wagenlehner et al, 2009); Quercetin, a natural bioflavonoid (Shoskes et al, 1999); and *Serenoa repens* (saw palmetto berry) extract (Kaplan et al, 2004; Reissigl et al, 2004). Rugendorff and coworkers (1993) noted that over half of 72 patients with CP without other lower urinary tract abnormalities had favorable improvements in pain and irritative voiding symptoms when treated with Cernilton, but no control group was included in this study. A randomized study of pollen extract (Cernilton) in 122 men with category IIIA CP/CPPS showed that men receiving the active treatment had statistically significant improvements in the pain and quality-of-life components of the CPSI (Wagenlehner et al, 2009). A controlled, randomized study of a similar preparation, Prostat/Poltit (grass pollen extract, including rye pollen), in 60 patients showed greater improvement in patients receiving active therapy compared with placebo, but no validated outcome index was incorporated into the study design (Elist, 2006). Shoskes and associates (1999) randomized 15 patients to the bioflavonoid Quercetin and 13 patients to placebo for 1 month. Sixty-seven percent of the patients in the treatment group were considered responders compared with only 20% of the patients in the placebo arm. Kaplan and associates (2004) noted possible benefits with the use of saw palmetto but did not note any appreciable long-term improvement in any CP/CPPS parameters when compared with 12 months of finasteride in a randomized open-label comparative study. However, Reissigl and colleagues (2004) reported that there

was moderate to marked improvement in more than 60% of 72 CP/CPPS patients after 12 months of therapy with *S. repens* extract compared with less than 25% in the 70 men in the placebo-treated group. However, further follow-up did not support the durability of this therapy (Reissigl et al, 2005). **Phytotherapy for CP/CPPS may look promising, but further multicenter randomized controlled trials with well-characterized, standardized, and stable herbal components should be considered to assess their role in therapy.**

Neuromodulator Therapy

Rationale. One proposed mechanism is that CP/CPPS, particularly chronic, long-standing cases, represents a neurogenic pain syndrome and that the subsequent pain is actually a neuropathic pain (Pontari and Ruggieri, 2004). Patients with CP/CPPS have a history of neurologic disease that is almost five times more likely among cases than control subjects (Pontari et al, 2005), and men with CP/CPPS have been found to have abnormalities of both the afferent and efferent autonomic nervous systems (Yang et al, 2003; Yilmaz et al, 2007; Yang, 2013). This type of neuropathic pain related to CNS sensitization responds to gabapentinoids in other chronic pain conditions (Rosenstock et al, 2004; Crofford et al, 2005).

Clinical Trial Data. A recent NIH CPRN randomized placebo-controlled trial evaluated the effect of the gabapentinoid pregabalin on symptoms of men with long-standing, treatment-refractory CP/CPPS (Pontari et al, 2010). Among the 103 men assigned to pregabalin, 47% reported at least a 6-point decrease in total NIH-CPSI score at 6 weeks (primary end point) compared with 35.8% of 106 men assigned to placebo ($P = .072$). The NIH-CPSI total score decreased by a mean of 6.6 and 4.2 points (of 43) in the pregabalin and placebo groups, respectively ($P = .008$), whereas significantly more men in the pregabalin arm reported they were markedly or moderately improved compared with placebo (31% and 19%, respectively; $P = .023$). Although 6 weeks of pregabalin therapy was not superior to placebo for treating symptoms of CP/CPPS based on the primary end point, the impressive differences in secondary end points suggest that pregabalin may prove effective in some men with long-standing CP/CPPS. A recent well-powered study evaluating tanezumab (Nickel et al, 2012), a humanized monoclonal antibody directed against nerve growth factor, was not able to show significant benefit in a generally unselected population of men with CP/CPPS; however, a signal suggested that it might be beneficial in selected men (perhaps those with expression of nerve growth factor), a concept that should further explored (Watanabe et al, 2011). **It appears that for neuromodulatory therapy to be effective, it will need to be targeted toward a specific patient phenotype; however, biomarkers, either clinically or laboratory derived, have yet to be confirmed.**

Allopurinol

Rationale. Persson and Ronquist (1996) theorized that the intraprostatic ductal reflux of urine increases the concentration of metabolites containing purine and pyrimidine bases in the prostatic ducts, causing inflammation.

Clinical Trial Data. Persson and associates (1996) compared allopurinol therapy with placebo in a double-blind controlled study in 54 men. The allopurinol groups had lower levels of serum urate, urine urate, and EPS urate and xanthine. With variations in accepted statistical methodology, the investigators were able to show a difference in the mean patient-reported discomfort score between the study and the control groups at certain times in this trial with 330 days of follow-up. However, a re-examination of the data with use of more standardized statistical analyses did not convince other groups that changes in the urine and prostatic secretion of purine and pyrimidine bases resulted in significant amelioration of symptoms in this particular trial (Nickel et al, 1996). A follow-up randomized clinical trial further showed no advantage of allopurinol compared with placebo (Ziaee et al, 2006).

Prostatic Massage

Prostatic massage has been the principal therapy for prostatitis since the turn of the 20th century (O'Connor, 1936; Campbell, 1957). With the introduction of the scientific approach advocated by Meares and Stamey in 1968, prostatic massage became important only as a diagnostic tool, but as a therapy it was abandoned by urologists. It eventually regained some popularity, primarily because of the failure of standard medical therapy in patients with refractory symptoms of CP. Its benefits are believed to arise from draining theoretically occluded prostatic ducts and improving circulation and antibiotic penetration (Hennenfent and Feliciano, 1998). Independent but uncontrolled studies (Nickel et al, 1999b; Shoskes and Zeitlin, 1999) found clinical benefits in one third to two thirds of patients treated with repetitive prostatic massage (two to three times per week) for 4 to 6 weeks along with antibiotic therapy. However, another trial indicated that prostatic massage does not significantly improve the response of men with CP/CPPS treated with antibiotics (Ateya et al, 2006). It appears that some patients may improve with prostatic massage, but a panel of North American prostatitis experts (Nickel et al, 1999a) could not come to a consensus on the potential overall benefit or even the mechanism of achievement of that benefit if it does occur. A subsequent systematic review of the literature concluded that evidence for a role of repetitive prostatic massage as an adjunct in the management of CP is at most "soft" but that the practice could be considered as part of multimodal therapy in selected patients (Mishra et al, 2008). It has been suggested that frequent ejaculation may achieve the same function as prostatic massage (Yavascaoglu et al, 1999).

Pelvic Floor Physiotherapy (Including Directed Perineal and/or Pelvic Floor Massage and Myofascial Trigger Point Release)

Most clinicians recognize that men with prostatitis syndromes, especially category III CPPS, have specific anatomic areas that cause discomfort. Anderson (1999) believes that prolonged or chronic tension, distention, or distortion in the muscle bands (e.g., in the perineum) leads to a painful trigger point that is responsible for the pain. Predisposing factors leading to the formation of myofascial trigger points in the perineum or pelvis may include mechanical abnormalities in the hip and lower extremities, chronic urinary holding patterns (dysfunctional toilet training), sexual abuse, repetitive minor trauma, constipation, trauma, unusual sexual activity, recurrent infections or surgery, and perhaps stress and anxiety (Anderson et al, 2009a). Treatment of these trigger points includes heat therapy, physiotherapy massage, ischemic compression, stretching, anesthetic injections, acupuncture, electroneural modulation, and mind-body interactions such as progressive relaxation exercises, yoga, and hypnosis (Potts, 2003). Anderson and associates (2005) report that employing these techniques with a team consisting of a urologist, physiotherapist, and psychologist results in more than half of patients having or demonstrating a clinically detectable improvement. A case study analysis indicates that this may be an effective therapeutic approach in some patients (Anderson et al, 2005) and may result in improvement not just in pain but also in sexual function (Anderson et al, 2006). This technique has been further refined and modified by employing relaxation training (Anderson et al, 2011b). This technique has even been described as self-treatment using a "myofascial trigger point wand" (Anderson et al, 2011a). Certainly, many physicians managing CP/CPPS have found that directed physiotherapy results in significant benefits for selected patients with pelvic floor pathology diagnosed on physical examination (Van Alstyne et al, 2010). An NIH pilot study of men and women with chronic pelvic pain randomized to treatment with either relaxation massage or specific pelvic massage therapy demonstrated improvement; however, the beneficial effects were mainly found in women at 6 months, and the investigators could not corroborate these findings in the 23 randomized men (FitzGerald et al, 2009). In contrast, Marx and coworkers (2009), who randomized 35 men to osteopathic therapy, noted statistically significant

differences in favor of the osteopathy group ($P < .0005$). Long-term follow-up of 19 of the 20 men randomized to the treatment arm continued to show benefits for 5 years (Marx et al, 2013). Most clinicians with experience in the field believe that variations of pelvic floor physiotherapy can be extremely helpful in patients with demonstrable pelvic floor pathology that was found to be refractory to other therapies (Fitzgerald et al, 2013).

Pudendal Nerve Entrapment Therapy

It has been hypothesized that the symptoms of CPPS could be caused by entrapment of the pudendal nerve, perhaps between the sacrotuberous and sacrospinous ligaments, in the canal of Alcock or by the falciform process of the sacrotuberous ligament (Robert et al, 1998). Pudendal nerve blocks (Thoumas et al, 1999; McDonald and Spigos, 2000; Peng and Tumber, 2008) and neurolysis surgery (Robert et al, 1993; Mauillon et al, 1999) have been suggested for treatment. The role of the pudendal nerve in chronic perineal pain deserves more scientific scrutiny.

Biofeedback

It is possible that the voiding and pain symptoms associated with CP/CPPS may be secondary to some form of pseudodysynergia during voiding or repetitive perineal muscle spasm; biofeedback has the potential to improve this process. Kaplan and associates (1997), Nadler (2002), Ye and colleagues (2003), and Cornel and coworkers (2005) have demonstrated in small uncontrolled studies that biofeedback does ameliorate specific prostatitis-like symptoms in some men. Controlled clinical trials will be necessary to evaluate this mode of therapy.

Acupuncture

Acupuncture is an accepted traditional Chinese therapy for chronic pain, including pain from prostatitis (Ge et al, 1988; Katai, 1992; Ikeuchi and Iguchi, 1994). Chen and Nickel (2003) determined in a pilot study of 12 treatment-refractory men that acupuncture was safe and provided effective and durable symptom improvement. A subsequent study comparing 10 weeks of acupuncture versus sham acupuncture treatment indicated that the active acupuncture proved to be almost twice as likely as sham treatment to improve CP/CPPS symptoms (Lee et al, 2008a). A subsequent trial evaluating electroacupuncture versus sham therapy (Lee and Lee, 2009) also confirmed the efficacy of this approach. A 2011 analysis by Lee and associates further confirmed that sham therapy comparison in acupuncture trials was feasible (Lee et al, 2011). A subsequent systemic review (Posadzki et al, 2012) concluded that acupuncture is a reasonable choice of therapy for selected men with CP/CPPS.

Psychological Support

Data from the NIH Prostatitis Cohort (Tripp et al, 2004, 2005, 2006; Nickel et al, 2008c) support a biopsychosocial model that associates the chronic pain and poor quality of life of CP/CPPS with depression and suggest that physicians may be able to advise patients to avoid certain pain coping strategies that can be associated with greater depression. Nickel and colleagues (2008b) have developed an evidence-based cognitive behavioral treatment program for men with CP/CPPS (described in Tripp et al, 2011). This program specifically targets empirically supported biopsychosocial variables (e.g., pain catastrophizing, depressive thinking, social support) and encourages patients to critically evaluate their patterns of thinking and to entertain novel thinking and behavioral responses to their troublesome symptoms, with an end objective to improve overall quality of life. A pilot evaluation of the program demonstrated significant merit in this approach (Tripp et al, 2011).

Studies also show that the maladaptive pain coping technique of employing "pain-contingent resting" (using rest rather than more active behaviors to control pain) is reported by CP/CPPS patients

in response to their pain (Tripp et al, 2006; Nickel et al, 2008c). It was suggested by Tripp and coworkers (2006) that such sedentary behaviors in the presence of pain may be associated with elevated disability in men with CP/CPPS. A double-blind randomized study showed that men participating in aerobic exercise were significantly better than those who were randomized to stretching and motion exercise, suggesting that increased physical activity is a valid option in men with CP/CPPS (Giubilei et al, 2007). The results of a study examining perceived helpfulness of medical and self-management strategies suggested that clinicians may find it useful to support patients' use of safe, inexpensive self-management approaches, such as warm baths, increased water intake, exercise, and avoidance of prolonged sitting (Turner et al, 2006). It further appears that the support of a patient's partner can have a negative or positive impact on pain, disability, and sexual functioning (Smith et al, 2007b; Ginting et al, 2011).

Lifestyle Modification and Other Conservative Therapies

Conservative therapy should always be considered the primary therapy for CP/CPPS, despite the lack of evidence. Expert opinion and experience attest to the fact that conservative nonmedical and/or invasive therapies may provide the most benefit (Turner et al, 2006; Herati and Moldwin, 2013). My experience suggests that education (sometimes the only therapy required); avoidance of food, drink, and/or activities that exacerbate the symptoms; low-impact exercise (walking, elliptical machine, swimming, yoga, stretching); local heat therapy (hot water bottle, heating pad, hot tub or bath); and positive attitude and development of personal coping skills provide the basis on which all the other therapies rest. Most of these interventions, even diet modification (Herati et al, 2013), have not been proven in randomized clinical trials in CP/CPPS specifically; however, they have proven their worth in clinical practice (Turner et al, 2006) and in use with other pain syndromes (Giubilei et al, 2007).

Minimally Invasive Therapies

Balloon Dilatation. Lapatin and coworkers (1990) employed balloon dilatation in an uncontrolled trial of seven patients with nonbacterial prostatitis and prostatodynia and showed improvement in voiding symptoms during a 1- to 5-month follow-up. Pain and discomfort were not assessed. This treatment effect has never been substantiated, and balloon dilatation has not been routinely employed in clinical practice. Suzuki and coworkers (1995) combined the potential beneficial effects of balloon dilatation with prostatic hyperthermia in five men with CP/CPPS and demonstrated significant improvement in symptoms in one patient and partial improvement in three. Nickel and associates (1998b) were not able to duplicate this beneficial effect in a small pilot trial evaluating the "hot balloon" (heating by radiofrequency energy rather than laser energy).

Transurethral Needle Ablation. Chiang and associates (1997) employed transurethral needle ablation (TUNA) of the prostate in seven patients with chronic nonbacterial prostatitis, assessed the patients before and after therapy (6 months of follow-up) with a modification of the Symptom Severity Index (Nickel and Sorensen, 1996), and reported favorable results in four. A follow-up study by Chiang and Chiang (2004) showed significant improvement in symptoms in the majority of 32 patients treated with TUNA. However, Leskinen and colleagues (2002) investigated the effectiveness and durability of TUNA in 25 patients randomized to TUNA and eight patients randomized to sham treatment, and they reported that the efficacy of TUNA in CP/CPPS is comparable to that of sham treatment and so could not recommend TUNA as therapy for CP/CPPS.

Extracorporeal Shockwave Therapy. Extracorporeal shockwave lithotripsy has been suggested for the symptomatic relief of local perineal symptoms associated with CP/CPPS (Zimmerman et al, 2008). Zimmerman and colleagues (2009) randomized 60 men to perineal extracorporeal shockwave therapy (ESWT) or placebo and

showed statistically significant beneficial effects in comparison with placebo. Another study randomized 40 patients to ESWT or placebo (Vahdatpour et al, 2013), and this study again showed significant improvement in the treated group. This modality of therapy certainly should be further considered for a larger confirmatory clinical trial, especially because there seem to be few complications.

Minimally Invasive Neuromodulation Therapies. Neuromodulation techniques used for chronic pelvic pain conditions include sacral nerve stimulation (SNS), percutaneous tibial nerve stimulation (PTNS), and pudendal nerve stimulation (Yang, 2013). Ruedi and associates (2003) suggested that high-frequency electrostimulation may be harnessed to treat CP. Others (Schneider et al, 2013) have evaluated electrostimulation therapies and suggest that they might be beneficial. In a study published in the non-English literature, Yang and colleagues (2011) randomly divided a total of 140 patients with diagnosed CP/CPPS into a control group (n = 20), a biofeedback group (n = 40), an electrical stimulation group (n = 40), and a biofeedback plus electrical stimulation group (n = 40). Each treatment appeared to be better than the control group, with combination therapy being the most effective. In a study to evaluate posterior tibial nerve stimulation (Kabay et al, 2009), a total of 89 patients with therapy-resistant pelvic pain were randomized to receive either nerve stimulation (n = 45) or sham treatment (n = 44). The authors demonstrated that percutaneous PTNS may relieve pain in patients with category IIIB CP/CPPS. SNS has been studied in interstitial cystitis (bladder pain syndrome) (Yang, 2013), but the typical pain and lack of voiding symptoms in male CPPS make it much more difficult to treat and assess using this strategy (Yang et al, 2003). Yang (2013) reviewed the invasive neuromodulation literature and concluded that these modalities of therapy may eventually be proven to provide benefits for patients with CPPS. However, because of the paucity of data and the limitations of small studies, the conclusions of the existing literature must be carefully considered.

Microwave Hyperthermia and Thermotherapy. It is believed that the heat applied to the prostate gland by the microwave process could shorten the natural resolution of the inflammatory process, perhaps by accelerating the process of fibrosis or scar formation in the area of chronic inflammation. In addition, heat therapy, particularly with the higher temperatures achieved with transurethral microwave thermotherapy, could alter the afferent nerve fibers that convey the objective symptom of pain from the inflamed prostate gland (intraprostatic sympathectomy) (Perachino et al, 1993). It may even be possible that the microwave energy kills nonculturable or cryptic bacteria within the prostate gland (Sahin et al, 1998).

Although many uncontrolled trials employing heat therapy have shown benefit (Nickel, 1999b; Zeitlin, 2002), only three published studies have used sham controls, and unfortunately the NIH-CPSI was not available as an outcome parameter for these studies. Vassily and associates (1999) noted symptom improvement in 75% of men in a transrectal microwave hyperthermia-treated group compared with 52% of men in the sham-treated group. Shaw and colleagues (1993) documented treatment success (defined as a greater than 50% improvement in symptoms) in 55% of the men in a transrectal microwave hyperthermia group (15 patients) compared with 10% of patients treated with sham therapy (13 patients) at 3 months. Nickel and Sorensen (1996) examined the safety and efficacy of transurethral microwave thermotherapy in 20 men randomized to therapy or sham. At 3 months' follow-up, the transurethral microwave thermotherapy-treated patients had significantly improved symptom scores compared with sham-treated patients (7 of 10 men treated with transurethral microwave thermotherapy had a favorable result compared with 1 of 10 men treated with a sham therapy). A recently reported study in men with CP/CPPS treated with cooled transurethral microwave thermotherapy using the NIH-CPSI as an outcome (Kastner et al, 2004) again suggested that thermotherapy remains a promising treatment for intractable CP, particularly when it is associated with concomitant BPH. Although this prospective study showed a significant reduction in NIH-CPSI score compared with baseline in 35 men followed for 12 months, it was not a randomized sham controlled trial. Heat therapy appears to be a

promising therapeutic approach but, until larger-scale studies have been performed, should be restricted to patients with refractory or end-stage symptoms. In 2012, Gao and colleagues attempted to relate improvement they observed with transrectal hyperthermia with physiologic changes in the prostate.

Other Minimally Invasive Surgical Procedures. Serel and colleagues (1997) reported significantly meaningful beneficial effects of use of the neodymium:yttrium-aluminum-garnet laser in 30 patients with chronic abacterial prostatitis and prostatodynia. A number of other minimally invasive treatments have been examined in small pilot studies. These include pelvic and sacral electromagnetic therapy (Leippold et al, 2005; Rowe et al, 2005; Kim et al, 2013). It has been suggested that injection of botulinum toxin directly into the prostate may benefit some patients (Chuang and Chancellor, 2006). Botulinum toxin A (BTX-A) injection was evaluated in a small pilot study in which 29 patients were randomized to receive either BTX-A 100 U or normal saline injected into the perineal body and bulbospongiosus muscle (Gottsch et al, 2011). Total CPSI score did not reach significance in the BTX-A-treated group compared with controls; however, the CPSI pain subdomain score reached statistical significance in the BTX-A patients compared with controls ($P = .05$), with 30% of treated patients compared with 13% of placebo patients achieving at least minimal responder status ($P = .0002$).

Some minimally invasive surgical procedures (electrical neuromodulation, extracorporeal shock wave therapy, electroacupuncture, and perhaps transurethral microwave thermotherapy (TUMT) and botulinum toxin injection may be beneficial for treatment for CP/CPPS in selected patients (see Table 13-3); however, large, well-designed sham-controlled trials are required before these therapies can be considered recommended.

Traditional Surgery

In acute bacterial prostatitis (category I), urinary obstruction is a very common symptom. Traditionally it has been suggested that the insertion of a suprapubic cystostomy tube is the optimal therapy because an indwelling Foley catheter may further obstruct urethral ducts, resulting in the potential for development of prostate abscesses (Dajani and O'Flynn, 1968; Pai and Baht, 1972; Weinberger et al, 1988). In most patients, however, an in-and-out catheterization to relieve the initial obstruction or short-term (12 hours) indwelling catheterization with a small-caliber Foley catheter is appropriate. A developing prostate abscess, best detected with transrectal ultrasonography or computed tomography (Rovik and Doeblin, 1989), that fails to respond quickly to antibiotics is optimally drained by the transurethral incision route (Pai and Baht, 1972). However, transperineal incision and drainage (Granados et al, 1992) must be considered when the abscess has penetrated beyond the prostatic capsule or penetrated through the levator ani muscle. More recently it has been suggested that percutaneous drainage of the abscess is the most effective and less morbid procedure (Varkarakis et al, 2004).

Surgery does not have an important role in the treatment of most CP syndromes unless a specific indication is discovered during the evaluation of the patient (Kirby, 1999). These indications are usually noted during specific and ancillary investigations such as cystoscopy, transrectal ultrasonography, urodynamics, computed tomography, or MRI. Certainly, patients with urethral strictures benefit from surgical correction. Kaplan and associates (1994) have suggested that men with chronic nonbacterial prostatitis-like symptoms and urodynamic evidence of vesical neck obstruction benefit from endoscopic incision of the bladder neck.

Seminal vesicle abscesses can be managed with antibiotic therapy, transrectal aspiration, and, if necessary, an operation to remove the seminal vesicles. Traditionally, seminal vesiculectomy was performed as a difficult open procedure, but laparoscopic excision of the seminal vesicles was reported to be the least morbid procedure (Nadler and Rubenstein, 2001).

Radical transurethral resection of the prostate (Barnes et al, 1982; Sant et al, 1984) has been advocated in patients who have

either relapsing or refractory chronic bacterial prostatitis (category II) secondary to bacterial persistence within the prostate gland. Although prostatic calculi are not pathognomonic of prostatitis (Harada et al, 1980), it has been clearly shown that bacteria can persist in protective biofilms or aggregates within the interstices or on the surface of the calculus material (Meares, 1974; Nickel et al, 1994). Theoretically, removal of all the infected material, including potentially infected calculi, can be achieved (with appropriate intra-operative radiographs or ultrasound studies), but except for small anecdotal case series (Barnes et al, 1982; Sant et al, 1984) there is no substantial proof in the literature as to the efficacy of major prostate surgery in category II CP. Radical transurethral resection of the prostate has not been advocated for category III CP/CPPS, but open radical prostatectomy has been shown anecdotally to benefit a few patients with symptoms of nonbacterial prostatitis or prostatodynia or both (Davis and Weigel, 1990; Frazier et al, 1992). No definitive clinical series or long-term follow-up has ever been presented, and this type of surgery should not be encouraged or recommended at this time.

Phenotype Directed Multimodal Treatment Strategy

There are a number of reasons why the majority of randomized placebo- or sham-controlled trials reported in the literature and this chapter have been "negative" or only modestly "positive," making it difficult to develop evidence-based management guidelines. The first reason is that treatments based on a single causative mechanism may be doomed to fail when tested in the whole CP/CPPS population. As discussed earlier in the section on *etiology*, most of the mechanisms examined are based on sound scientific theory, and all are associated with at least some confirmatory clinical data. But it appears that patients have differing mechanisms and pathogenic progressions. We must accept that there is no one all-encompassing causative mechanism responsible for all cases of CP/CPPS. As further discussed in the section on *evaluation*, it is now evident that patients also have quite heterogeneous clinical phenotypes. In addition, one cannot be sure that the patients routinely managed in clinical practice are the same patients who have been enrolled in clinical trials. In fact, the most rigorously designed NIH-sponsored randomized controlled trials (Alexander et al, 2004; Nickel et al, 2008b; Pontari et al, 2010) did not enroll over 90% of the CP/CPPS patients who were screened. Finally, were the negative trials reported in the literature and this chapter really negative? A reappraisal of the study results would suggest otherwise. Antibiotics tended to work better in less chronic heavily pretreated patients (marginally significant improvement in levofloxacin trial [Nickel et al, 2003b] compared with ciprofloxacin trial [Alexander et al, 2004]), further substantiated by the 75% improvement seen with use of ciprofloxacin or levofloxacin treatment in patients with very early presentation (within 4 to 8 weeks of symptoms associated with that particular episode) (Nickel and Xiang, 2008). Whereas large NIH-sponsored multicenter studies failed to confirm the benefits of α -adrenergic blockers in both chronic heavily pretreated (Alexander et al, 2004) and recently diagnosed α -adrenergic blocker-naïve (Nickel et al, 2008b) CP/CPPS patients, at least six other randomized controlled trials (Cheah et al, 2003b; Mehik et al, 2003; Nickel et al, 2004b; Tugcu et al, 2007; Chen et al, 2011; Nickel et al, 2011a) with less rigorous selection criteria did show significant efficacy with α -adrenergic blockers. Although the results of trials examining anti-inflammatory agents (Nickel et al, 2003b), pentosan polysulfate (Nickel et al, 2005a), finasteride (Nickel et al, 2004b), celecoxib (Zhao et al, 2009), tanezumab (Nickel et al, 2012), and the neuro-modulator pregabalin (Pontari et al, 2010) were considered only marginally positive or even negative based on the primary end point analysis, these trials showed efficacy for many of the validated outcomes (including responder analyses using the validated subjective global or global response assessment scale) of statistical or marginal significance. In fact, when examined using a network meta-analysis approach, Anothaisintawee and colleagues (2011) evaluated all randomized controlled data for medical therapies and concluded that there was a statistically significant improvement compared with

placebo for almost all of these therapies. However, the clinical significance of this benefit and the disconnect between symptom score improvement and responder data indicate that these treatments are not very effective when used indiscriminately in the entire CP/CPPS population. It is very likely that we will never discover a single overall cure for all patients diagnosed with this condition. This reevaluation of trial results, however, strongly suggests that some patients do, in fact, respond to these various therapies. Multimodal therapy using multiple concurrent treatment strategies appears to offer the best results (Shoskes et al, 2003; Shoskes and Katz, 2005), at least compared with a sequential monotherapy approach (Nickel et al, 2004a; Nickel, 2008b). However, a number of well-controlled prospective studies did not demonstrate increased efficacy of combining α -adrenergic blockers and antibiotics (Alexander et al, 2004) or α -adrenergic blockers and anti-inflammatory agents (Batstone et al, 2005). The explanation for this difficulty in treating CP may be that the patients become peripherally and centrally sensitized and that treatment targeted to the local initiators of the early process may not work as well when the condition becomes chronic and outside the pelvis (Yang et al, 2003; Pontari and Ruggieri, 2004; Pontari, 2007). We must be able to identify patients who may respond to specific therapies, and at this time the UPOINT clinical phenotyping system comprehensively described in the evaluation section may be the best approach.

It has been suggested that UPOINT will be a new clinical tool for urologists to use to direct individually based therapy.

Each domain has been clinically defined using standard clinical assessment and linked to specific mechanisms of symptom production or propagation (see evaluation section for details). Each of these domains has been associated with specific therapy based on best evidence and expert experience (Fig. 13-9). One clinical trial assessing this approach in CP/CPPS showed what appeared to be a superior clinical benefit. In this study by Shoskes and associates (2010) almost 100 consecutive men referred to a tertiary CP clinic were categorized according to the UPOINT system and then treated according to an algorithm similar to that described in this chapter (see Fig. 13-9) and followed for 6 months. A 6-point decrease in NIH-CPSI total score is believed to be a clinically significant achievement in these chronic heavily pre-treated patients, and 84% of men reported this level of improvement at 6 months. The overall NIH-CPSI mean score in the group decreased from 25.2 (± 6.1) to 13.2 (± 7.2) a clinically and statistically significant ($P < .0001$) result. Based on previous clinical trial data, poor clinical experience with providing treatment benefits to CP/CPPS patients, initial studies, and ongoing experience in the clinic, the European (Engeler et al, 2013), Canadian (Nickel, 2011), and International Consultation on Urinary Disease (Nickel et al, 2013b) guidelines suggest that a phenotypic approach to therapy as described by the UPOINT system be considered for clinical practice. (Criteria for inclusion in the specific CP/CPPS domains and suggested directed therapies are shown in Fig. 13-9.)

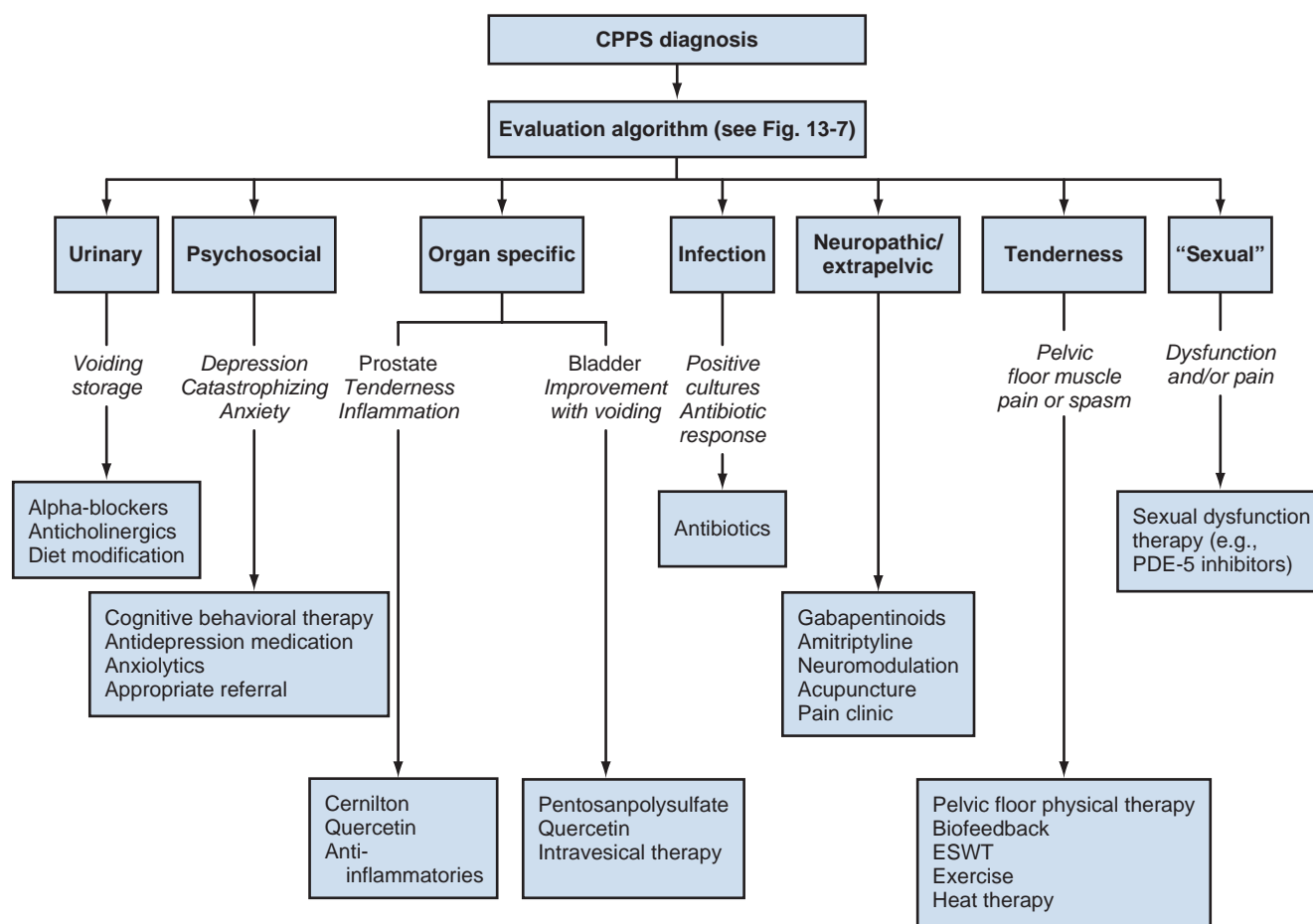


Figure 13-9. A suggested diagnostic and therapeutic algorithm for the treatment of patients with chronic prostatitis and chronic pelvic pain syndrome (CPPS) based on the UPOINT clinical phenotyping strategy. ESWT, extracorporeal shockwave therapy; PDE-5, phosphodiesterase type 5. (Modified from Nickel JC. Prostatitis. CUA Guideline. Can Urol Assoc J 2011;5:306–15; and Nickel JC, Wagenlehner F, Pontari M, et al. Male chronic pelvic pain syndrome (CPPS). In: Chapple C, Abrams P, editors. Male lower urinary tract symptoms (LUTS). An International Consultation on Male LUTS, Fukuoka, Japan, Sept 30-Oct 4, 2012. Montreal: Société Internationale d'Urologie (SIU); 2013. p. 331–72.)

Treatment Summary

Acute bacterial prostatitis is relatively simple to treat; the bacteria are eradicated with appropriate antibiotic therapy. However, ESBL infection related to prostate biopsy is becoming a worldwide problem. The objective for chronic bacterial prostatitis is similar—eradication of bacteria—but long-term symptom amelioration sometimes eludes us. Our standard therapies for CP/CPPS, when used as monotherapy, offer only modest improvement in symptoms (Nickel et al, 2004a, 2008b). Box 13-2 outlines a list of the various standard therapies that are currently recommended. Table 13-4 describes the standard doses of the various medical therapies.

To evaluate and compare the many clinical trials assessing the various therapies advocated for CP/CPPS it is important to clearly define and classify the patient population (NIH classification system), determine results by using a standardized outcome index (NIH-CPSI), prospectively compare a treated group with a similar group randomized to placebo, and fulfill the requirements of peer review for publication in a reputable

BOX 13-2 Suggested Therapies for Chronic Prostatitis and Chronic Pelvic Pain Syndrome (National Institutes of Health Category III)

RECOMMENDED

1. α -Blocker therapy as part of a multimodal treatment strategy for newly diagnosed, α blocker-naïve patients who have voiding symptoms.
2. Antimicrobial therapy trial for selected newly diagnosed, antimicrobial-naïve patients.
3. Selected phytotherapies: Cernilton and Quercetin.
4. Multimodal therapy directed by clinical phenotype.
5. Directed physiotherapy. Although level 1 evidence is not available, evidence from multiple weak trials and vast clinical experience strongly suggests benefit for selected patients.

NOT RECOMMENDED

1. α -Blocker monotherapy, particularly in patients previously treated with α -blockers.
2. Anti-inflammatory monotherapy.
3. Antimicrobial therapy as primary therapy, particularly for patients in whom treatment with antibiotics has previously failed.
4. 5 α -Reductase inhibitor monotherapy; can be considered in older patients with coexisting benign prostatic hyperplasia.
5. Most minimally invasive therapies such as transurethral needle ablation (TUNA), laser therapies.
6. Invasive surgical therapies such as transurethral resection of the prostate (TURP) and radical prostatectomy.

REQUIRING FURTHER EVALUATION

1. Low-intensity shock wave treatment.
2. Acupuncture.
3. Biofeedback.
4. Invasive neuromodulation (e.g., pudendal nerve modulation).
5. Electromagnetic stimulation.
6. Botulinum toxin A injection.
7. Medical therapies including meparticin, muscle relaxants, neuromodulators, immunomodulators.

Modified from Nickel JC, Wagenlehner F, Pontari M, et al. Male chronic pelvic pain syndrome (CPPS). In: Chapple C, Abrams P, editors. Male lower urinary tract symptoms (LUTS). An International Consultation on Male LUTS, Fukuoka, Japan, Sept 30-Oct 4, 2012. Montreal: Société Internationale d'Urologie; 2013. p. 331–72.

journal (Nickel et al, 1999b; Probert et al, 2002). In the past several years the results of a significant number of such trials have been published (Nickel, 2004; Schaeffer, 2006; Nickel, 2008a; Anothaisintawe et al, 2011; Nickel, 2011; Cohen et al, 2012; Thakkestian et al, 2012; Engeler et al, 2013; Nickel et al, 2013a), allowing the reader to assess and compare the efficacy of antibiotics, α -adrenergic blockers, anti-inflammatory agents, phytotherapies, hormonal agents, and minimally invasive approaches in CP/CPPS (see Tables 13-2 and 13-3). A patient-directed phenotypic strategy (such as the UPOINT approach), developing a unique best-evidence multimodal treatment plan for each individual, may be the optimal way to use the available clinical trial data to ultimately improve patient management in CP/CPPS (see Fig. 13-9).

KEY POINTS: THERAPY

- The following medical therapies have been evaluated in standardized randomized placebo-controlled trials in chronic pelvic pain syndrome (CPPS): antibiotics, α -adrenergic blockers, anti-inflammatory agents, hormonal therapies, phytotherapies, and pregabalin. The following minimally invasive therapies have been evaluated in randomized placebo- or sham-controlled trials in CPPS: extracorporeal shockwave therapy (ESWT), transurethral microwave therapy (TUMT), and neuromodulation (electrostimulation, botulinum toxin).
- The following therapies have shown benefits in placebo- or sham-controlled studies in CPPS: marked benefit—none; moderate benefit in some selected trials— α -adrenergic blockers and pregabalin; and modest benefit—anti-inflammatory agents, phytotherapies, ESWT, TUMT, selected neurostimulation.
- Specific multimodal therapy directed at individual UPOINT phenotypes may result in better management outcomes.

OTHER INFLAMMATORY AND PAIN CONDITIONS OF THE LOWER URINARY TRACT

Orchitis

Definition and Classification

By definition, orchitis is inflammation of the testis, but the term has been used to describe testicular pain localized to the testis without objective evidence of inflammation. Acute orchitis represents sudden occurrence of pain and swelling of the testis associated with acute inflammation of that testis. Chronic orchitis involves inflammation and pain in the testis, usually without swelling, persisting for more than 6 weeks. A classification (Nickel and Beiko, 2001) based on cause is presented in Box 13-3.

Pathogenesis and Etiology

Isolated orchitis is a relatively rare condition and is usually viral in origin. It spreads to the testis by a hematogenous route. Most cases of orchitis, particularly bacterial, occur secondary to local spread of an ipsilateral epididymitis and are referred to as *epididymo-orchitis*. UTIs are usually the underlying source in boys and elderly men. In young sexually active men, sexually transmitted diseases are often responsible (Berger, 1998). Truly noninfectious orchitis is often idiopathic or related to trauma, although autoimmune disease has rarely been implicated (Pannek and Haupt, 1997). It may be impossible to clinically distinguish chronic orchitis from chronic orchialgia.

Bacterial orchitis is usually associated with epididymitis and is therefore often caused by urinary pathogens, including *E. coli* and *Pseudomonas*. Less commonly, *Staphylococcus* species or *Streptococcus* species are responsible. The most common sexually transmitted

TABLE 13-4 Suggested Medical Therapy for Chronic Prostatitis and Chronic Pelvic Pain Syndrome

DRUG CLASS	SPECIFIC THERAPY	DOSE	DURATION OF THERAPY (WK)	EVIDENCE
Antibiotics	TMP-SMX	160/800 mg bid	12	See text for summary of clinical trial data.
	Norfloxacin	400 mg bid	4-12	
	Ciprofloxacin	500 mg bid	4-12	
	Ofloxacin	300 mg bid	4-12	
	Lomefloxacin	400 mg qd	4-12	
	Levofloxacin	500 mg qd	4-12	
α -Adrenergic blockers	Terazosin	5 mg qd	>14	Cheah et al, 2003b Mehik et al, 2003 Nickel et al, 2008b Nickel et al, 2004c Alexander et al, 2004 Nickel et al, 2011a
	Alfuzosin	10 mg qd	>12	
	Tamsulosin	0.4 mg qd	>6	
	Silodosin	4 mg qd	>12	
Phytotherapy	Pollen extract	1 tab tid	24	Buck et al, 1989 Rugendorff et al, 1993 Wagenlehner et al, 2009 Shoskes et al, 1999 Reissigl et al, 2004
	Quercetin	500 mg bid	4	
	Saw palmetto	150 mg qd	24	
Anti-inflammatory agents	Nimesulide	100 mg bid	2-4	Canale et al, 1993a Nickel et al, 2003c Evans, 1999
	Rofecoxib	25-50 mg qd	>6	
	Other NSAIDs	Various	2-4	
	Indomethacin			Wedren, 1987 Nickel et al, 2000 Nickel et al, 2005a
	Diclofenac			
	Ibuprofen			
	Pentosan polysulfate	100 mg tid	24	
Hormonal agents	Finasteride	5 mg qd	24	Leskinen et al, 1999 Nickel et al, 2004b De Rose et al, 2004
	Mepartricin	40 mg qd	8	
Gabapentinoids	Pregabalin	50-100 mg tid	6	Pontari et al, 2010

NSAIDs, nonsteroidal anti-inflammatory drugs; TMP-SMX, trimethoprim-sulfamethoxazole.

BOX 13-3 Classification of Orchitis

- Acute bacterial orchitis
 - Secondary to urinary tract infection
 - Secondary to sexually transmitted disease
- Nonbacterial infectious orchitis
 - Viral
 - Fungal
 - Parasitic
 - Rickettsial
- Noninfectious orchitis
 - Idiopathic
 - Traumatic
 - Autoimmune
- Chronic orchitis
- Chronic orchialgia

microorganisms responsible are *Neisseria gonorrhoeae*, *C. trachomatis*, and *Treponema pallidum*. Xanthogranulomatous orchitis, usually associated with *Proteus* and *E. coli*, is an extremely rare inflammatory destructive lesion of the testes that is treated with orchiectomy (Al-Said et al, 2007; Kang et al, 2007).

Mycobacterial infections, tuberculosis (Chen et al, 2004; Park et al, 2008; Gomez-Garcia et al, 2010), and BCG therapy (Hill et al,

2008) can also cause orchitis. The most common cause of **viral orchitis** is mumps (Jalal et al, 2004; Masarani et al, 2006; Emerson et al, 2007; Davis et al, 2010), but infectious mononucleosis has also been implicated (Weiner, 1997). **Fungal infections** occasionally involve the testis, with candidiasis, aspergillosis, histoplasmosis, coccidioidomycosis, blastomycosis, and actinomycosis all having been reported as causes of orchitis (Wise, 1998). **Parasitic infections** rarely cause orchitis in the Western Hemisphere, but filariasis (Hazen Smith and von Lichtenberg, 1998) and trypanosomiasis (Ehrhardt et al, 2006) have been described in some endemic areas of Africa, Asia, and South America.

Autoimmune orchitis can be a relevant cause of decreased fecundity in males with the concomitant presence of anti-sperm antibodies. Causes of this variant of orchitis and/or testicular vasculitis are associated with autoimmune diseases, mainly those with primary vasculitis such as polyarteritis nodosa, Behçet disease, and Henoch-Schönlein purpura (Hedger, 2011; Silva et al, 2012).

Diagnosis

In patients with **acute infectious orchitis**, history discloses a recent onset of testicular pain, often associated with abdominal discomfort, nausea, and vomiting. These symptoms may be preceded by symptoms of parotitis in boys or young men, by UTIs in boys or elderly men, or alternatively by symptoms of a sexually transmitted disease in sexually active men. Although the process is usually unilateral, it is sometimes bilateral, especially if viral. Physical examination may reveal a toxic and febrile patient. The skin of the

involved hemiscrotum is erythematous and edematous, and the testis is quite tender to palpation or can be associated with a transilluminating hydrocele. The patient should be clinically assessed for prostatitis and urethritis. For acute noninfectious orchitis the clinical picture resembles the just-presented description except that these patients lack the toxic appearance and fever.

For **chronic orchitis and orchialgia** there may have been a history of previous episodes of testicular pain, usually secondary to acute bacterial orchitis, trauma, or other causes. The patient has chronic testicular (and possibly epididymal) pain to a degree that could seriously affect his day-to-day functioning and quality of life. Patients with this diagnosis usually become very frustrated with this problem. On examination the patient does not appear toxic and does not have a fever. The scrotum is not usually erythematous, but the testis may be somewhat indurated and is almost always tender to palpation.

Laboratory tests employed to assist in the diagnosis include urinalysis, urine microscopy, and urine culture. For a patient in whom a sexually transmitted disease is suspected, a urethral swab should also be taken for culture. If the diagnosis is not evident from the history, physical examination, and these simple tests, scrotal ultrasonography should be performed (to rule out malignancy in patients with chronic orchitis or orchialgia). Color Doppler ultrasonography is a reasonably reliable method for evaluating patients with scrotal diseases, including swelling and pain (Rizvi et al, 2011), and MRI has been suggested as a second-line investigation (Parenti et al, 2009; Makela et al, 2011). The most important differential diagnosis in young men and boys is testicular torsion. Testicular torsion is often difficult to differentiate from an acute inflammatory condition. Scrotal ultrasound evaluations (with use of Doppler imaging to determine testicular blood flow) are especially helpful in differential diagnosis (Mernagh et al, 2004; Gunther et al, 2006), but occasionally the diagnosis will be missed (particularly with intermittent or partial torsion) and the clinician should err in favor of the surgically correctable diagnosis of torsion.

Treatment

General principles of therapy include bed rest, scrotal support, hydration, antipyretics, anti-inflammatory agents, and analgesics. **Antibiotic therapy** (specific for UTIs, prostatitis, or sexually transmitted diseases) should be employed for infectious orchitis and is ideally based on culture and sensitivity testing but may be based on microscopic or Gram stain results. Orchitis resulting from *Mycobacterium tuberculosis* infection requires treatment with antituberculous drugs (rifampin, isoniazid, and pyrazinamide or ethambutol) and rarely surgery (Gomez-Garcia et al, 2010). There are no specific antiviral agents available to treat orchitis caused by mumps, and the previously mentioned supportive measures are important. If early testing findings are negative or results are unavailable, empirical treatment should be initiated, directed at the most likely pathogens based on the available clinical information; a fluoroquinolone would be the best agent in this scenario. Most patients can be readily managed on an outpatient basis. Surgical intervention is rarely indicated, unless testicular torsion (or rarely xanthogranulomatous orchitis) is suspected (as discussed previously). Spermatic cord blocks with injection of a local anesthetic may sometimes be needed to relieve severe pain. Abscess formation is rare; if it does occur, then percutaneous or open drainage is necessary. Glucocorticoids and immunosuppressive drugs may be indicated in autoimmune orchitis-associated active systemic autoimmune diseases (Silva et al, 2012).

Treatment of chronic orchitis or orchialgia is supportive. Anti-inflammatory agents, analgesics, support, heat therapies, and nerve blocks all have a role in ameliorating symptoms. Neuromodulation, usually medical (tricyclic antidepressants or gabapentinoids), can be helpful, and SNS has been suggested as a potential treatment modality (McJunkin et al, 2009), but the evidence is not really available to justify this invasive procedure at this time. It is generally believed that the condition is self-limited but could take years (and sometimes decades) to resolve. **Orchidectomy is indicated only in**

cases in which pain control is refractory to all other measures (and even this might not be successful in alleviating the chronic pain) (Nariculam et al, 2007).

Epididymitis

Definitions and Classification

Epididymitis by definition is inflammation of the epididymis. **Acute epididymitis** represents sudden occurrence of pain and swelling of the epididymis associated with acute inflammation of the epididymis (Nickel et al, 2002). **Chronic epididymitis** refers to inflammation and pain in the epididymis, usually without swelling (but with induration in long-standing cases), persisting for over 6 weeks (Nickel et al, 2002). Inflammation is not always clinically evident in many cases of localized epididymal pain. Approximately 1 man in 100 attending a North American urology clinic has a diagnosis of epididymitis (Nickel et al, 2005b). In the late 1990s the average cost per episode of epididymitis managed in the United States was \$368 (Gift and Owens, 2006), a cost considerably less than that reported for men with a diagnosis of CP. A classification for epididymitis is presented in Box 13-4 (Nickel et al, 2002).

Pathogenesis and Etiology

Acute epididymitis usually results from the spread of infection from the bladder, urethra, or prostate via the ejaculatory ducts and vas deferens into the epididymis. The process starts in the tail of the epididymis and then spreads through the body of the structure to the head of the epididymis. In infants and boys, epididymitis is often related to a UTI and/or an underlying genitourinary congenital anomaly (Merlini et al, 1998) or even to the presence of a foreskin (Bennett et al, 1998). In elderly men, BPH and associated stasis, UTI, and catheterization are the most common causes of epididymitis. Bacterial prostatitis and/or seminal vesiculitis are associated with epididymal infection in postpubertal males of all ages (Furuya et al, 2004). In sexually active men younger than 35 years of age, epididymitis is commonly the result of a sexually transmitted infection (Berger, 1998). In most cases of acute epididymitis, the testis is also involved in the process and thus the condition is referred to as *epididymo-orchitis*.

Chronic epididymitis may result from inadequately treated acute epididymitis, recurrent epididymitis, or some other cause including associations with other disease processes such as Behçet disease (Cho et al, 2003; Arromdee and Tanakitviriul, 2006; Pektas et al, 2008) or treatment with amiodarone (Nikolaou et al, 2007). The cause of chronic epididymalgia is usually unclear. Certainly one of the best known and studied is the chronic epididymitis

BOX 13-4 Classification of Epididymitis

- Acute bacterial epididymitis
 - Secondary to urinary tract infection
 - Secondary to sexually transmitted disease
- Nonbacterial infectious epididymitis
 - Viral
 - Fungal
 - Parasitic
- Noninfectious epididymitis
 - Idiopathic
 - Traumatic
 - Autoimmune
 - Amiodarone-induced
 - Associated with a known syndrome (e.g., Behçet disease)
- Chronic epididymitis
- Chronic epididymalgia

or epididymalgia that occurs in some men after a vasectomy. About 1 in 100 men describe severe pain 6 months after a vasectomy that noticeably affects their quality of life (up to 15% of men report some discomfort 6 months after the procedure) (Leslie et al, 2007).

The most common causative microorganisms in the pediatric and elderly age groups are the coliform organisms that cause bacteriuria (Berger et al, 1979). In men younger than age 35 who are sexually active with women, the most common offending organisms causing epididymitis are the usual bacteria that cause urethritis, namely *N. gonorrhoeae* and *C. trachomatis* (Ito et al, 2012). In homosexual men who practice anal intercourse, *E. coli* and *Haemophilus influenzae* are most commonly responsible. Both tuberculosis (Liu et al, 2005; Tsili et al, 2008) and mycobacteria, such as BCG (Harada et al, 2006), can be associated with epididymitis. As with orchitis, viral, fungal, mycoplasmal, and parasitic microorganisms have all been implicated in epididymitis (Berger, 1998; Hazen Smith and von Lichtenberg, 1998; Wise, 1998; Scagni et al, 2008). Rarely, epididymitis as a complication of brucellosis has been described (Akinci et al, 2006; Queipo-Ortuno et al, 2006; Colmenero et al, 2007).

Diagnosis

Both acute infectious and acute noninfectious epididymitis manifest in much the same way as do acute infectious and acute noninfectious orchitis, respectively. Physical examination localizes the tenderness to the epididymis. However, in many cases the testis is also involved in the inflammatory process and subsequent pain; this is referred to as *epididymo-orchitis*. The spermatic cord is usually tender and swollen. Early in the process only the tail of the epididymis is tender, but the inflammation quickly spreads to the rest of the epididymis, and if it continues to the testis then the swollen epididymis becomes indistinguishable from the testis.

There may be no clinical or etiologic differentiation between chronic epididymitis and epididymalgia. The patient usually has a long-standing history of pain (waxing and waning or constant) localized to the epididymis, and, as with chronic orchitis and orchialgia, these symptoms may have a significant impact on the patient's quality of life (Nickel et al, 2002).

Laboratory tests should include Gram staining of a urethral smear and a midstream urine specimen. Gram-negative bacilli can usually be identified in patients with underlying cystitis. If the urethral smear reveals the presence of intracellular gram-negative diplococci, a diagnosis of infection with *N. gonorrhoeae* is established. If only WBCs are seen on the urethral smear, a diagnosis of *C. trachomatis* will be established two thirds of the time. A urethral swab and midstream urine specimen should be sent for culture and sensitivity testing. When an infant or young boy is diagnosed with epididymitis, he should be further evaluated with abdominopelvic ultrasonography, voiding cystourethrography, and possibly cystoscopy (Shortliffe and Dairiki, 1998; Al-Taheini et al, 2008). If the diagnosis is uncertain, duplex Doppler scrotal ultrasonography to look for increased blood flow to the affected epididymis may be performed (also to rule out torsion as described in the section on orchitis) (Mernagh et al, 2004; Rizvi et al, 2011). Ultrasonography can sometimes be helpful to rule out other epididymal and scrotal pathology (Lee et al, 2008). MRI can be considered a second-line investigation (Parenti et al, 2009; Makela et al, 2011).

Treatment

Management of acute infectious epididymitis depends on the likely cause and organism (Tracy et al, 2008). The Centers for Disease Control and Prevention's 2006 guidelines for the treatment of infectious epididymitis included ceftriaxone or doxycycline for men younger than age 35 years and levofloxacin or ofloxacin for men older than age 35 years (Centers for Disease Control and Prevention et al, 2006). The guidelines updated in 2010 (Centers for Disease Control and Prevention, 2010) have not changed the ceftriaxone recommendation but suggest that azithromycin could

be used instead of doxycycline. The recent U.K. guidelines (Street et al, 2011) are very similar.

For chronic epididymitis, a 4- to 6-week trial of antibiotics that would potentially be effective against possible bacterial pathogens and particularly *C. trachomatis* may be appropriate (Nickel, 2005). Anti-inflammatory agents, analgesics, scrotal support, and nerve blocks have all been recommended as empirical treatment (Nickel, 2005). It is generally believed that chronic epididymitis is a self-limited condition that will eventually "burn out," but this could take years (or even decades). Surgical removal of the epididymis (epididymectomy) should be considered only when all conservative measures have been exhausted and the patient accepts that the operation will have at best a 50% chance of curing his pain (Padmore et al, 1996; Tracy et al, 2008; Callear and Masood, 2009). Successful spermatic cord block (temporary pain relief) does seem to predict a better result with surgery (Benson et al, 2013). Better surgical results (up to 70%) have also been reported for epididymectomy for postvasectomy pain (Siu et al, 2007; Lee et al, 2011). It has recently been reported that inhibition of adhesion and fibrosis after epididymectomy with local application of hyaluronic acid and carboxymethylcellulose improves pain relief and patient satisfaction (Chung et al, 2013). Many clinicians have shown that microsurgical denervation of the spermatic cord may achieve the same results as a complete epididymectomy (Choa et al, 1992; Heidenreich et al, 2002; Strom and Levine, 2008; Parekattil et al, 2013).

KEY POINTS: ORCHITIS AND EPIDIDYMITIS

- Orchitis usually occurs with epididymitis (except for viral causation).
- The cause of epididymitis and orchitis is usually related to the age of the patient.
- Acute presentation is usually related to infection or ischemia.
- In the young patient the most important differential diagnosis is torsion of the testis.
- Treatment of chronic epididymitis or epididymo-orchitis is difficult.

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The complete reference list is available online at www.expertconsult.com.



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Definition

Historical Perspective

Epidemiology

Etiology

Pathology

Diagnosis

Classification

Treatment

Principles of Management

Bladder pain syndrome or interstitial cystitis (BPS/IC) is a **condition diagnosed on a clinical basis** and requiring a high index of suspicion on the part of the clinician. It is a deceptively intricate disorder that should be considered in the differential diagnosis of the patient with chronic pelvic pain, pressure, or discomfort often exacerbated by bladder filling, and associated with at least one other urinary symptom, often urinary frequency. One can argue that it is a *symptom complex* because it has a differential diagnosis that should be explored in a timely fashion before or at the time of initiation of empirical therapy (Blaiwas, 2007). It is a diagnosis of exclusion in a patient who has experienced the symptoms for at least 6 weeks. Once other conditions have been ruled out, it can be considered a syndrome that typically responds to one of a variety of therapeutic approaches in the majority of cases. Symptoms compatible with the diagnosis are now thought to affect up to 3% of the female population (Berry et al, 2011). Although the female-to-male ratio has historically been about 5 : 1, newer epidemiologic data suggest that male symptom prevalence may approach that of female symptom prevalence in the United States (Suskind et al, 2013a).

The perception that the original term, *interstitial cystitis*, was not at all descriptive of the clinical syndrome, or even the pathologic findings in many patients, led to the current effort to reconsider the name of the disorder and even the way it is positioned in the medical spectrum (Hanno, 2008a). What was originally considered a bladder disease is now considered a chronic pain syndrome (Janicki, 2003) that may begin as a pathologic process in the bladder in most but not all patients and eventually can develop into a condition that, in a small subset of those affected, even cystectomy may not benefit (Baskin and Tanagho, 1992). Its relationship to type 3 chronic pelvic pain syndrome (CPPS) or nonbacterial prostatitis is unclear (Chai, 2002; Hakenberg and Wirth, 2002). Its association with other chronic pain syndromes has taken on more importance recently as a promising clue in unlocking the challenging etiologic and therapeutic puzzle of this condition (Rodríguez et al, 2009).

BPS/IC encompasses a major portion of the “painful bladder” disease complex. Painful bladder disorders involve a large group of patients with bladder, urethral, and/or pelvic pain; irritative voiding symptoms (urgency, frequency, nocturia, dysuria); and sterile urine cultures. Painful bladder conditions with well-established causes include radiation cystitis, cystitis caused by microorganisms that are not detected by routine culture methodologies, ketamine cystitis (Winstock et al, 2012), and systemic

disorders that affect the bladder. In addition, many gynecologic disorders can mimic BPS/IC (Kohli et al, 1997; Howard 2003a, 2003b). BPS/IC has no easily discernible cause.

The symptoms are allodynic, an exaggeration of normal sensations. There are no pathognomonic findings on pathologic examination, and even the finding of petechial hemorrhages on the bladder mucosa during cystoscopy after bladder hydrodistention under anesthesia is no longer considered the *sine qua non* of BPS/IC (Erickson, 1995; Waxman et al, 1998; Erickson et al, 2005). BPS/IC is truly a diagnosis of exclusion. It may have multiple causes and represent a final common reaction of the bladder to different types of insult. Misdiagnosis as a psychological problem, an overactive bladder, or chronic urinary infection has plagued patients with the syndrome. A distinct subgroup of patients with discrete inflammatory lesions in the bladder lining (Hunner lesions) involves specific characteristics, and successful treatment of this subgroup is available (Nordling et al, 2012).

DEFINITION

“It resembles a constellation of stars; its components are real enough but the pattern is in the eye of the beholder” (Mäkelä and Heliövaara, 1991). This evocative description of fibromyalgia could equally apply to BPS/IC. Indeed, it has been argued, not necessarily convincingly, that each medical specialty has at least one somatic syndrome (irritable bowel syndrome, chronic pelvic pain, fibromyalgia, tension headache, noncardiac chest pain, hyperventilation syndrome) that might be better conceptualized as a part of a general functional somatic syndrome than with the symptom-based classification that we have now, which may be more reflective of professional specialization and access to care (Wessely and White, 2004).

BPS/IC is a clinical diagnosis based primarily on chronic symptoms of pain perceived by the patient to emanate from the bladder and/or pelvis associated with urinary urgency or frequency in the absence of another identified cause for the symptoms. It has been defined and redefined over the last century, and as the problem of definition has become more prominent lately, so have the number of definitions and attempts to crystallize just what the diagnosis means (Box 14-1). The International Continence Society (ICS) prefers the term *painful bladder syndrome*, defined as “the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection

BOX 14-1 History of Definitions of Bladder Pain Syndrome, Painful Bladder Syndrome, and Interstitial Cystitis Syndrome

- 1887, Skene (*Skene, 1887*): An inflammation that has destroyed the mucous membrane partly or wholly and extended to the muscular parietes.
- 1915, Hunner (*Hunner, 1915*): A peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment in patients with frequency and bladder symptoms (spasms).
- 1951, Bourque (*Bourque, 1951*): Patients who suffer chronically from their bladder—the ones who are distressed, not only periodically but constantly, having to urinate at all hours of the day and of the night and suffering pains every time they void.
- 1978, Messing and Stamey (*Messing and Stamey, 1978*): Non-specific and highly subjective symptoms of around-the-clock frequency, urgency, and pain somewhat relieved by voiding when associated with glomerulations on bladder distention under anesthesia.
- 1990, Revised National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria (*Wein et al, 1990*): Pain associated with the bladder or urinary urgency, and glomerulations or Hunner ulcer on cystoscopy under anesthesia, in patients with symptoms for 9 months or longer—at least eight voids per day, one void per night, and cystometric bladder capacity less than 350 mL.
- 1997, NIDDK Interstitial Cystitis Data Base study entry criteria (*Simon et al, 1997*): Unexplained urgency or frequency (seven or more voids per day) or pelvic pain, of at least 6 months' duration in the absence of other definable causes.
- 2008, European Society for the Study of Interstitial Cystitis (ESSIC) (*van de Merwe et al, 2008*): Chronic (longer than 6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded.
- 2009, Japanese Urological Association (*Homma et al, 2009*): A disease of the urinary bladder diagnosed by three conditions: (1) lower urinary tract symptoms such as urinary frequency, bladder hypersensitivity, and/or bladder pain; (2) bladder pathology proven endoscopically by Hunner ulcer and/or mucosal bleeding after overdistention; and (3) exclusion of confusable diseases such as infection, malignancy, or calculi of the urinary tract.
- 2009, Society for Urodynamics and Female Urology (SUFU) informal international dialogue consensus meeting (*Hanno and Dmochowski, 2009*): An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of longer than 6 weeks' duration, in the absence of infection or other identifiable causes.
- 2011, American Urological Association: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of longer than 6 weeks' duration, in the absence of infection or other identifiable causes.

or other obvious pathology" (*Abrams et al, 2002*). The ICS reserves the diagnosis of *interstitial cystitis* for patients with "typical cystoscopic and histological features," without further specifying these. This definition may miss 36% of patients, primarily because it confines the pain to a suprapubic location and mandates a relationship of pain to bladder filling (*Warren et al, 2006*).

In the absence of clear criteria for IC, this chapter will refer to BPS/IC and IC interchangeably, because all but recent literature terms the syndrome *interstitial cystitis*. The definition of the European Society for the Study of Interstitial Cystitis (ESSIC) is a clinically useful one, and changes made since its original iteration have likely made it more sensitive and inclusive (*Mouracade et al, 2008*). Minor modifications made at a meeting under the auspices of the Society for Urodynamics and Female Urology (SUFU) may be preferred by some clinicians. The SUFU definition was adopted in the guidelines of the American Urological Association (AUA) along with the nomenclature *interstitial cystitis/bladder pain syndrome* (*Hanno et al, 2011*). Perhaps more than for most diseases, how we arrived at this point is instructive and critical to an overall understanding of BPS/IC. The paradigm change that has resulted in morphing what was originally considered a bladder disease (aptly named *interstitial cystitis*) to a chronic pain syndrome (*bladder pain syndrome*) also merits discussion.

HISTORICAL PERSPECTIVE

Recent historical reviews confirm that IC was recognized as a pathologic entity during the 19th century (*Christmas and Sant, 1997; Parsons and Parsons, 2004*). Joseph Parrish, a Philadelphia surgeon, described three patients with severe lower urinary tract symptoms in the absence of a bladder stone in an 1836 text (*Parrish, 1836*), and termed the disorder *tic douloureux of the bladder*. Teichman argued that this may represent the first description of IC (*Teichman*

et al, 2000). Fifty years later Skene used the term *interstitial cystitis* to describe an inflammation that had "destroyed the mucous membrane partly or wholly and extended to the muscular parietes" (*Skene, 1887*).

Early in the 20th century, at a New England Section meeting of the AUA, Guy Hunner reported on eight women with a history of suprapubic pain, frequency, nocturia, and urgency lasting an average of 17 years (*Hunner, 1915, 1918*). He drew attention to the disease, and the red, bleeding areas he described on the bladder wall came to be called *Hunner ulcers*. As *Walsh (1978)* observed, this has proved to be unfortunate. In the early part of the 20th century, the very best cystoscopes available gave a poorly defined and ill-lit view of the fundus of the bladder. It is not surprising that when Hunner saw red and bleeding areas high on the bladder wall, he thought they were ulcers. For the next 60 years, urologists would look for ulcers and fail to make the diagnosis in their absence. The disease was thought to be focal, rather than a pancystitis.

Hand (1949) authored the first comprehensive review about the disease, reporting on 223 patients. In looking back, his paper was truly a seminal one, years ahead of its time. Many of his epidemiologic findings have held up to this day. His description of the clinical findings bears repeating. "I have frequently observed that what appeared to be a normal mucosa before and during the first bladder distention showed typical interstitial cystitis on subsequent distention." He noted "small, discrete, submucosal hemorrhages, showing variations in form ... dot-like bleeding points ... little or no restriction to bladder capacity." He portrayed three grades of disease, with grade 3 matching the small-capacity, scarred bladder described by Hunner. Sixty-nine percent of patients had grade 1 disease, and only 13% had grade 3.

Walsh (1978) later coined the term *glomerulations* to describe the petechial hemorrhages that Hand had described. But it was not until *Messing and Stamey (1978)* discussed the "early diagnosis" of IC that attention turned from looking for an ulcer to make the diagnosis to the concepts that (1) symptoms and glomerulations at

the time of bladder distention under anesthesia were the disease hallmarks, and (2) the diagnosis was primarily one of exclusion.

Bourque's "Aunt Minnie description" of IC (i.e., it is hard to define, but one knows it when one sees it) is more than 60 years old and is worth recalling. "We have all met, at one time or another, patients who suffer chronically from their bladder; and we mean the ones who are distressed, not only periodically but constantly, having to urinate often, at all moments of the day and of the night, and suffering pains every time they void. We all know how these miserable patients are unhappy, and how those distressing bladder symptoms get finally to influence their general state of health physically at first, and mentally after a while" (Bourque, 1951).

Although memorable, this description and others like it were not suitable for defining this disease in a manner that would help physicians make the diagnosis and design research studies to learn more about the problem. Physician interest and government participation in research were sparked through the efforts of a group of frustrated patients led by Dr. Vicki Ratner, an orthopedic surgery resident in New York City, who founded the first patient advocacy group, the Interstitial Cystitis Association, in the living room of her small New York City apartment in 1984 (Ratner et al, 1992, 1997). The first step was to develop a working definition of the disease. The modern history of BPS/IC is best viewed through the development of the modern definition.

Evolution of the Definition

There are data to suggest that true urinary frequency in women can be defined as regularly having to void at intervals of less than 3 hours, and that of women older than 40 years, 25% have nocturia at least once (Glennings, 1985; Fitzgerald and Brubaker, 2003). Whereas bladder capacity tends to fall in women by the eighth and ninth decades of life, bladder volume at first desire to void tends to rise as women age (Collas and Malone-Lee, 1996). Based on a 90th percentile cutoff to determine the ranges of normality, the highest "normal" frequency ranges in the fourth decade range from six for men to nine for women (Burgio et al, 1991). **Large variation in the degree of bothersomeness with varying rates of frequency (Fitzgerald et al, 2002) makes a symptomatic diagnosis of BPS/IC based on an absolute number of voids subject to question, and frequency per volume of intake or even the concept of "perception of frequency" as a problem may be more accurate than an absolute number.**

In an effort to define IC so that patients in different geographic areas and under the care of different physicians could be compared, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) held a workshop in August 1987 at which consensus criteria were established for the diagnosis of IC (Gillenwater and Wein, 1988). These criteria were not meant to define the disease, but rather to ensure that groups of patients included in basic and clinical research studies would be relatively comparable. After pilot studies were carried out to test the criteria, they were revised at another NIDDK workshop a year later (Wein et al, 1990). These criteria are presented in Box 14-2.

Although meant initially to serve only as a research tool, the NIDDK "research definition" became a de facto definition of this disease, diagnosed by exclusion and colorfully termed a "hole in the air" by Hald (George et al, 1986). Certain of the exclusion criteria serve mainly to make one wary of a diagnosis of IC, but should by no means be used for categoric exclusion of such a diagnosis. However, because of the ambiguity involved, these patients should probably be eliminated from research studies or categorized separately. In particular, exclusion criteria 4, 5, 6, 8, 9, 11, 12, 17, and 18 are only relative. The percentage of patients with idiopathic "sensory urgency" (hypersensitivity without decreased compliance or detrusor overactivity [DO]) who have BPS is unclear (Frazer et al, 1990). **The specificity of the finding of bladder glomerulations before or after distention has come into question (Erickson 1995; Waxman et al, 1998; Tomaszewski et al, 2001).** Similarly, the sensitivity of glomerulations is also unknown, but clearly patients with IC symptoms can demonstrate an absence

BOX 14-2 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Diagnostic Criteria for Interstitial Cystitis

To be diagnosed with interstitial cystitis, patients must have either glomerulations on cystoscopic examination or a classic Hunner ulcer, and they must have either pain associated with the bladder or urinary urgency. An examination for glomerulations should be undertaken after distention of the bladder under anesthesia to 80 to 100 cm H₂O for 1 to 2 minutes. The bladder may be distended up to two times before evaluation. The glomerulations must be diffuse—present in at least three quadrants of the bladder—and there must be at least 10 glomerulations per quadrant. The glomerulations must not be along the path of the cystoscope (to eliminate artifact from contact instrumentation). The presence of any one of the following excludes a diagnosis of interstitial cystitis:

1. Bladder capacity of greater than 350 mL on awake cystometry using either a gas or liquid filling medium
2. Absence of an intense urge to void with the bladder filled to 100 mL of gas or 150 mL of liquid filling medium
3. The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate just described
4. Duration of symptoms less than 9 months
5. Absence of nocturia
6. Symptoms relieved by antimicrobial agents, urinary antiseptic agents, anticholinergic agents, or antispasmodic agents
7. A frequency of urination while awake of fewer than eight times per day
8. A diagnosis of bacterial cystitis or prostatitis within a 3-month period
9. Bladder or ureteral calculi
10. Active genital herpes
11. Uterine, cervical, vaginal, or urethral cancer
12. Urethral diverticulum
13. Cyclophosphamide or any type of chemical cystitis
14. Tuberculous cystitis
15. Radiation cystitis
16. Benign or malignant bladder tumors
17. Vaginitis
18. Age younger than 18 years

From Wein AJ, Hanno PM, Gillenwater JY. Interstitial cystitis: an introduction to the problem. In: Hanno PM, Staskin DR, Krane RJ, et al, editors. Interstitial cystitis. London: Springer-Verlag; 1990. p. 13–5.

of glomerulations under anesthesia (Awad et al, 1992; Al Hadithi et al, 2002). Bladder ulceration has been considered rare (Sant, 1991). A California series found 20% of patients to have ulceration (Kozioł, 1994). Hunner lesions have been recognized more commonly as more urologists and gynecologists have become aware of the sometimes subtle findings suggesting a lesion and are present in up to 50% of patients in Scandinavia (Logadottir et al, 2012). Specific pathologic findings represent a glaring omission from the criteria because **there is a lack of consensus as to which pathologic findings, if any, are required for, or even suggestive of, a tissue diagnosis (Hanno et al, 1990, 2005a; Tomaszewski et al, 1999, 2001).**

The unexpected use of the NIDDK research criteria by the medical community as a definition of IC led to concerns that many patients with this syndrome might be misdiagnosed. The multicenter Interstitial Cystitis Data Base (ICDB) study through NIDDK accumulated data on 424 patients with IC, enrolling patients from May 1993 through December 1995. Entry criteria were much more

BOX 14-3 Interstitial Cystitis Data Base (ICDB) Study Eligibility Criteria

1. Informed consent to participate in the study
2. Willing to undergo a cystoscopy under general or regional anesthesia when indicated, during the course of the study
3. At least 18 years of age
4. Symptoms of urinary urgency, frequency, or pain for more than 6 months
5. Urinating at least seven times per day, or having some urgency or pain (measured on linear analog scales)
6. No history of current genitourinary tuberculosis
7. No history of urethral cancer
8. No history of bladder malignancy, high-grade dysplasia, or carcinoma in situ
9. Males: no history of prostate cancer
10. Females: no occurrence of ovarian, vaginal, or cervical cancer in the previous 3 years
11. Females: no current vaginitis, clue cells, or *Trichomonas* or yeast infection
12. No bacterial cystitis in the previous 3 months
13. No active herpes in the previous 3 months
14. No antimicrobials for urinary tract infections in previous 3 months
15. Never treated with cyclophosphamide
16. No radiation cystitis
17. No neurogenic bladder dysfunction (e.g., from spinal cord injury, stroke, Parkinson disease, multiple sclerosis, spina bifida, or diabetic cystopathy)
18. No bladder outlet obstruction (determined by urodynamic investigation)
19. Males: no bacterial prostatitis for previous 6 months
20. Absence of bladder, ureteral, or urethral calculi for previous 3 months
21. No urethritis for previous 3 months
22. No urethral dilation, cystometrogram, bladder cystoscopy under full anesthesia, or a bladder biopsy in previous 3 months
23. Never having had an augmentation cystoplasty, cystectomy, cystolysis, or neurectomy
24. No urethral stricture of less than 12 Fr

From Simon LJ, Landis JR, Erickson DR, et al. The Interstitial Cystitis Data Base study: concepts and preliminary baseline descriptive statistics. *Urology* 1997;49:64–75.

symptom driven than those promulgated for research studies (Simon et al, 1997) and are noted in Box 14-3. In an analysis of the defining criteria (Hanno et al, 1999a, 1999b), it appeared the NIDDK research criteria fulfilled their mission. Fully 90% of expert clinicians agreed that patients diagnosed with IC by those criteria in the ICDB indeed had the disorder. However, 60% of patients deemed to have IC by these experienced clinicians would not have met NIDDK research criteria. The ESSIC definition (pelvic pain for longer than 6 months; pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency; exclusion of confusable diseases as the cause of the symptoms) (van de Merwe et al, 2008) allows the inclusion of more patients in the IC/BPS syndrome, facilitating diagnosis and treatment in many patients who would otherwise remain undiagnosed (Proaño et al, 2013). Whereas IC symptom and problem indices have been developed and validated (O'Leary et al, 1997; Goin et al, 1998), these are not intended to diagnose or define IC but rather to measure the

severity of symptomatology and monitor disease progression or regression (Moldwin and Kushner, 2004).

IC/BPS is now viewed not only through the paradigm of a chronic pain syndrome that manifests through bladder-related symptoms, but as a syndrome that may not be a true disease of the bladder alone in many patients (Hanno, 2008b). This paradigm is reflected in the current Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network (mappnetwork.org), a 10-year ongoing research project of the National Institutes of Health. The subgroup of patients with Hunner lesions do seem to have a primary bladder disease, but their symptom complex is indistinguishable from that of the general IC/BPS population without the aid of endoscopic examination (Nordling et al, 2012). On average, these patients are two decades older than non-Hunner patients and have a smaller bladder capacity when under anesthesia (Logadottir et al, 2012).

Nomenclature and Taxonomy

In accordance with the guidelines of the AUA, this chapter uses the terminology of the International Consultation on Incontinence—*bladder pain syndrome*—but keeps the term *interstitial cystitis* to facilitate recognition and understanding. This change implies that it is the symptoms that drive treatment, and whether *interstitial cystitis* should refer to a distinct subgroup of the bladder pain syndrome (i.e., those with a Hunner lesion) is, as yet, unclear (Hanno et al, 2011; Fall and Peeker, 2013; Hanno et al, 2013).

The literature over the last 170 years has seen numerous changes in description and nomenclature of the disease. The syndrome has variously been referred to as *tic douloureux of the bladder*, *interstitial cystitis*, *cystitis parenchymatosa*, *Hunner ulcer*, *panmural ulcerative cystitis*, *urethral syndrome*, and *painful bladder syndrome* (Skene, 1887; Hunner, 1918; Powell and Powell, 1949; Bourque, 1951; Christmas and Sant, 1997; Teichman et al, 2000; Dell and Parsons, 2004). The term *interstitial cystitis*, which Skene is credited with coining and Hunner brought into common usage, is a misnomer; in many patients not only is there no interstitial inflammation, but histopathologically there may be no inflammation at all (Lynes et al, 1990a; Denson et al, 2000; Tomaszewski et al, 2001; Rosamilia et al, 2003). Focusing exclusively on the urinary bladder, the term *interstitial cystitis* furthermore does not do justice to the condition from both the physician's and the patient's perspectives. The textual exclusiveness ignores the high comorbidity with various pelvic, extrapelvic, and nonurologic symptoms and associated disorders (Clauw et al, 1997) that frequently precede or develop after the onset of the bladder condition (Wu et al, 2006).

With the formal definition of the term *painful bladder syndrome* by the ICS in 2002, the terminology discussion became an intense international focal point (Abrams et al, 2002).

- In Kyoto at the International Consultation on Interstitial Cystitis, Japan (ICICJ) in March 2003, it was agreed that the term *interstitial cystitis* should be expanded to *interstitial cystitis/chronic pelvic pain syndrome* when pelvic pain is at least of 3 months' duration and associated with no obvious treatable condition or pathology (Ueda et al, 2003).
- ESSIC held its first meeting in Copenhagen soon after Kyoto. Nomenclature was discussed but no decision was reached; the meeting concentrated on how to evaluate patients for diagnosis (Nordling et al, 2004).
- At the 2003 meeting of the NIDDK entitled "Research Insights into Interstitial Cystitis," it was concluded that "interstitial cystitis" would ultimately be replaced as a sole name for this syndrome. This was to be a gradual process over several years. At the meeting the condition was referred to as *interstitial cystitis/painful bladder syndrome* in keeping with ICS nomenclature (Hanno et al, 2005b).
- At the 2004 inaugural meeting of the Multinational Interstitial Cystitis Association in Rome, it was concluded that the syndrome should be referred to as *painful bladder syndrome/interstitial cystitis* or *PBS/IC* to indicate an intellectual and taxonomic hierarchy within the acronym (Hanno et al, 2005b).

TABLE 14-1 European Society for the Study of Interstitial Cystitis Classification System

BIOPSY	CYSTOSCOPY WITH HYDRODISTENTION			
	NOT DONE	NORMAL	GLOMERULATIONS*	HUNNER LESION†
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	2A
Inconclusive	XB	1B	2B	3B
Positive‡	XC	1C	2C	3C

*Cystoscopy granulations grade II to III.
†With or without glomerulations.
‡Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or tissue granulation and/or interfascicular fibrosis.
From van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 2008;53:60.

- The International Consultation on Incontinence in 2004, cosponsored by the ICS and the Société Internationale d’Urologie in association with the World Health Organization, included the syndrome as a part of its consultation. The chapter in the report was entitled “Painful Bladder Syndrome (Including Interstitial Cystitis),” suggesting that the IC formed an identifiable subset within the broader syndrome. Because such a distinction is difficult to define, within the body of the chapter, coauthored by nine committee members and five consultants from four continents, the syndrome was referred to as *PBS/IC* (one inclusive entity) (Hanno et al, 2005a). IC may be a subgroup that encompasses patients with typical histologic and cystoscopic features (Peeker and Fall, 2002a), but what these features are is still controversial and somewhat vague.
- In June 2006 Abrams and colleagues published an editorial focusing on the nomenclature problem (Abrams et al, 2006). They noted, “It is an advantage if the medical term has clear diagnostic features that translate to a known pathophysiologic process so that effective treatment may be given. Unfortunately, the latter is not the case for many of the pain syndromes suffered by patients seen at most pain, gynecologic, and urologic clinics. For the most part these “diagnoses” describe syndromes that do not have recognized standard definitions, yet imply knowledge of a pathophysiologic cause for the symptoms. Unfortunately the terminology used to describe the condition may promote erroneous thinking about treatment on the part of physicians, surgeons and patients. These organ based diagnoses are mysterious, misleading and unhelpful, and can lead to therapies that are misguided or even dangerous.” The editorial went on to note that use of a single pathologic descriptive term (*interstitial cystitis*) for a spectrum of symptom combinations ill serves patients. The umbrella term *painful bladder syndrome* was proposed, with a goal to define and investigate subsets of patients who could be clearly identified within the spectrum of PBS. It would fall within the rubric of CPPS. Affected patients would be identified according to the primary organ that appeared to be affected on clinical grounds. Pain not associated with an individual organ would be described in terms of the symptoms.
- One can see in this the beginnings of a new paradigm that might be expected to change the emphasis of both clinical and basic science research and that removes the automatic presumption that the end organ in the name of the disease should necessarily be the sole or primary target of such research.
- At the major biannual IC research conference in the fall of 2006, held by the NIDDK (“Frontiers in Painful Bladder Syndrome/Interstitial Cystitis”), the ESSIC group was given a block of time in which to present thoughts and conclusions. Because the term *painful bladder syndrome* (1) did not fit into the taxonomy of other pelvic pain syndromes such as urethral or vulvar pain syndromes, (2) as defined by the ICS missed more than a third of affected patients, and (3) is a term open to different interpretations, ESSIC suggested that *painful bladder*

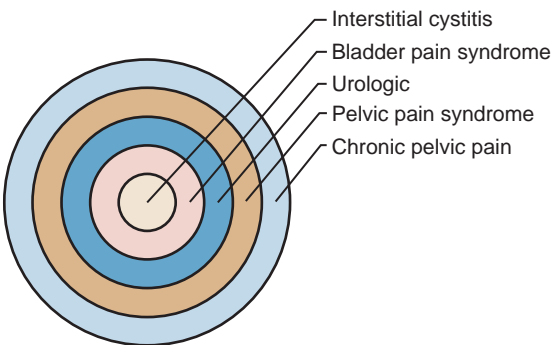


Figure 14-1. Conceptualization of pelvic pain syndrome classification. (From Hanno PM. Interstitial cystitis/painful bladder syndrome/ bladder pain syndrome: the evolution of a new paradigm, Proceedings of the International Consultation on Interstitial Cystitis, Japan: Comfortable Urology Network; 2008. p. 2-9.)

- syndrome* be redesignated as *bladder pain syndrome* followed by a type designation. BPS is indicated by two symbols: The first corresponds to cystoscopy with hydrodistention (CHD) findings (1, 2, or 3, indicating increasing grade of severity), and the second to biopsy findings (A, B, and C, indicating increasing grade of pathologic severity) (Table 14-1). Although neither CHD nor bladder biopsy was prescribed as an essential part of the evaluation, categorizing patients in terms of whether either procedure was performed, and, if so, the results, made it possible to follow patients with similar findings and study each identified cohort to compare natural history, prognosis, and response to therapy (van de Merwe et al, 2008).
- As Baranowski and colleagues conceived it in early 2008, BPS is thus defined as a pain syndrome with a collection of symptoms, the most important of which is pain perceived to be in the bladder (Baranowski et al, 2008). IC is distinguished as an end-organ, visceral-neural pain syndrome, whereas BPS can be considered a pain syndrome that involves the end-organ (bladder) and neurovisceral (myopathic) mechanisms. In IC, one expects end-organ primary pathology. This is not necessarily the case in the broader BPS.
- A didactically very demonstrative way to conceptualize the dawning shift in conception of the condition is with the drawing of a target (Fig. 14-1). There may be many causes of chronic pelvic pain. When a cause cannot be determined, the condition is characterized as pelvic pain syndrome. To the extent that it can be distinguished as urologic, gynecologic, dermatologic, and the like, it is further categorized by organ system. A urologic pain syndrome can sometimes be further differentiated based on the site of perceived pain. Bladder, prostate, testicular, and epididymal pain syndromes follow. Finally, types of BPS can be further defined as IC or simply

categorized by ESSIC criteria. Patient groups have expressed their concerns with regard to any nomenclature change that potentially drops the term *interstitial cystitis* because the U.S. Social Security Administration and private insurers recognize IC but not the term *bladder pain syndrome*, and benefits potentially could be adversely affected. Whether the term *interstitial cystitis*, as difficult as it is to define and as potentially misleading as it is with regard to cause and end-organ involvement, should be maintained is a subject of ongoing controversy (Hanno and Dmochowski, 2009).

KEY POINTS: DEFINITION

- The *painful bladder disease complex* includes a large group of patients with bladder and/or urethral and/or pelvic pain, irritative voiding symptoms, and sterile urine cultures, many with specific identifiable causes.
- *Bladder pain syndrome* comprises a part of this complex and is a clinical diagnosis based primarily on chronic symptoms of pain perceived by the patient to emanate from the bladder and/or pelvis associated with urinary urgency or frequency in the absence of other identified causes for the symptoms.
- Whether the older term *interstitial cystitis* should refer to a distinct subgroup of BPS (i.e., those with Hunner lesions) is, as yet, unclear.

Urgency is a common complaint of this group of patients. The ICS definition of urgency (Abrams et al, 2002), “the complaint of a sudden compelling desire to pass urine, which is difficult to defer,” could be interpreted as compatible with either DO or BPS/IC depending on the weight one attaches to the word *sudden*. There are those who see hypersensitivity or sensory urgency as bridging both overactive bladder and BPS/IC (Haylen et al, 2007; Yamaguchi et al, 2007), and the issue has been nicely addressed by Homma (2008). Pain and pressure are more involved in the frequency of BPS/IC, and fear of incontinence seems the reason for the urgency of overactive bladder (Abrams, 2005). Although BPS patients may have significantly higher voiding frequencies, smaller voided volumes, and narrower ranges of voided volume compared with overactive bladder patients (Kim et al, 2014), one cannot distinguish between the two syndromes based on a voiding diary. Urgency is not required to define BPS/IC, as it would tend to obfuscate the borders of overactive bladder and BPS/IC, and is unnecessary for definition purposes. The term *urgency* as it is comprehended by patients is not a well-defined and commonly understood symptom that can be used to clearly discriminate between BPS/IC and overactive bladder (Clemens et al, 2011). Figure 14-2 (Abrams et al, 2005)

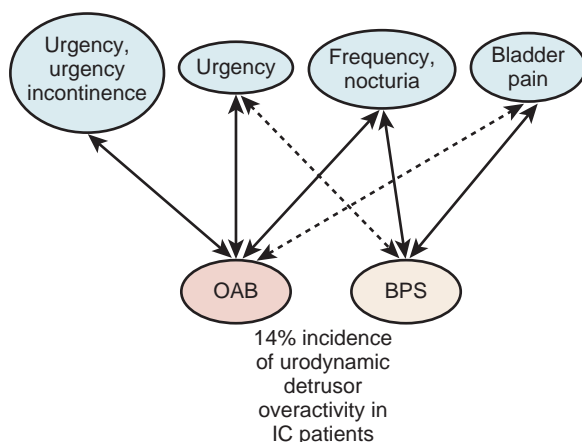


Figure 14-2. Overactive bladder (OAB) and its relationship to bladder pain syndrome (BPS). IC, interstitial cystitis. (From Abrams P, Hanno P, Wein A. Overactive bladder and painful bladder syndrome: there need not be confusion. *Neurourol Urodyn* 2005;24:149–50.)

is a graphic depiction of one view of the relationship between these two sometimes confused conditions. The 14% incidence of urodynamic DO in the BPS/IC patients (Nigro et al, 1997a) is probably close to what one might expect in the general population if studied urodynamically (Salavatore et al, 2003).

Still, there remains some ambiguity, and further research is necessary with regard to urgency (Hanno et al, 2009). Studies are hampered by the fact that patients tend to use words to describe lower urinary tract symptoms, but attribute different meanings to the words than do physicians and researchers (Digesu et al, 2008). An analysis of urgency by the University of Maryland group reported that 65% of patients with BPS experienced an urge to urinate to relieve pain, with 46% agreeing that they had an urge to relieve pain and not to prevent incontinence. Still, 21% reported that urgency arose from fear of impending incontinence and that this sensation was not present before the onset of BPS symptoms (Diggs et al, 2007). In some patients the term connotes an intensification of the normal urge to void, and in others it is a different sensation (Blaivas et al, 2009).

New efforts to phenotype the chronic urologic pain syndromes (BPS and chronic nonbacterial prostatitis and CPPS in men) are currently being explored (Shoskes et al, 2009). One of these is the MAPP Research Network, a 10-year ongoing research project of the National Institutes of Health (mappnetwork.org). Patients with Hunner lesions would seem to have a more bladder-centric disorder and are less likely to have comorbid conditions (Peters et al, 2011). The hope is that looking at psychological, physical, and organ-specific parameters of affected patients, and specifically focusing on associated disorders, will aid in proper selection of therapeutic agents that may have selective specificity for different symptom constellations, and also may improve productivity and results of research on etiology, prognosis, and new therapeutic agents.

KEY POINTS: URGENCY

- Urgency has been defined as the complaint of a sudden compelling desire to pass urine, which is difficult to defer.
- What the patient believes precipitates the sensation is not a part of the definition, and this has resulted in some ambiguity. Fear of incontinence is more consistent with overactive bladder, whereas pressure, pain, or discomfort suggests BPS.

EPIDEMIOLOGY

Prevalence

Epidemiology studies of BPS/IC have been hampered by many problems (Bernardini et al, 1999). The lack of an accepted definition, the absence of a validated diagnostic marker, and questions regarding etiology and pathophysiology make much of the literature difficult to interpret. This is most apparent when one looks at the variation in prevalence reports in the United States and around the world. These range from 1.2 to 4.5 per 100,00 females in Japan (Ito et al, 2000) to a figure in American women of 20,000 per 100,000 according to a questionnaire-based study (Parsons and Tatsis, 2004). Tea consumption and smoking were purported to be risk factors in a large Swedish twin study (Tettamanti et al, 2011); however the per capita consumption of tea in the United Kingdom is more than double that of the vast majority of the world's population, and no study reports a higher prevalence of BPS in that country.

It has been estimated that the prevalence in the population of chronic pain from benign causes is at least 10% (Verhaak et al, 1998). Numerous case series have, until recently, formed the basis of epidemiologic information regarding BPS/IC. Farkas and associates discussed IC in adolescent girls (Farkas et al, 1977). Hanash and Pool reviewed their experience with IC in men (Hanash and Pool, 1969). Geist and Antolak reviewed and added to reports of

disease occurring in childhood (Geist and Antolak, 1970). A childhood presentation is extremely rare and must be differentiated from the much more common and benign-behaving extraordinary urinary frequency syndrome of childhood, a self-limited condition of unknown cause (Koff and Byard, 1988; Robson and Leung, 1993). Nevertheless, there is a small cohort of children with chronic symptoms of bladder pain, urinary frequency, and sensory urgency in the absence of infection who have been evaluated with urodynamics, cystoscopy, and bladder distention and have findings consistent with the diagnosis of BPS/IC. In a review of 20 such children by Close and colleagues, the median age of onset was younger than 5 years, and the vast majority of patients had long-term remissions with bladder distention (Close et al, 1996).

A study conducted at the Scripps Research Institute (Koziol et al, 1993) included 374 patients at Scripps as well as some members of the Interstitial Cystitis Association, the large patient support organization. The findings of a more recent but similar study in England (Tincello and Walker, 2005) concurred with the Scripps findings of urgency, frequency, and pain in the vast majority of these patients, devastating effects on quality of life, and often unsuccessful attempts at therapy with a variety of treatments. Although such reviews provide some information, they would seem to be necessarily biased by virtue of their design.

Several population-based studies have been reported in the literature (Fig. 14-3), and these studies tend to support the reviews of selected patients or from individual clinics and the comprehensive follow-up case-control study by Koziol (1994). The first population-based study (Oravisto, 1975) included "almost all the patients with interstitial cystitis in the city of Helsinki." This superb, brief report from Finland surveyed all diagnosed cases in a population approaching 1 million. The prevalence of the disease in women was 18.1 per 100,000. The joint prevalence in both sexes was 10.6 cases per 100,000. The annual incidence of new cases in women was 1.2 per 100,000. Severe cases accounted for about 10% of the total. Ten percent of cases were in men. The disease onset was typically subacute rather than insidious, and full development of the classic symptom complex occurred over a relatively short time. IC does not progress continuously, but usually reaches its final stage rapidly (within 5 years in the Koziol study (Koziol et al, 1993) and then continues without significant change in symptomatology. Subsequent major deterioration was found by Oravisto to be unusual. The duration of symptoms before diagnosis was 3 to 5 years in the Finnish study. Analogous figures in a classic U.S. paper a quarter of a century earlier were 7 to 12 years (Hand, 1949).

Another early population study, this in the United States, first demonstrated the potential extent of what had been considered a very rare disease (Held et al, 1990). The following population groups were surveyed: (1) 127 board-certified urologists who completed a random survey; (2) 64 IC patients selected by the surveyed urologists and divided among the last patient with IC seen and the last patient with IC diagnosed; (3) 904 female patients belonging to the Interstitial Cystitis Association; and (4) 119 persons from the

U.S. population who completed a random phone survey. This 1987 study found the following:

1. 43,500 to 90,000 diagnosed cases of IC in the United States (twice the Finnish prevalence)
2. Up to a fivefold increase in IC prevalence if all patients with painful bladder and sterile urine had been given the diagnosis, yielding up to half a million possible cases in the United States
3. Median age of onset 40 years
4. Late deterioration in symptoms unusual
5. 50% temporary spontaneous remission rate, mean duration 8 months
6. 10 times higher incidence of childhood bladder problems in IC patients versus controls
7. Double the incidence of a history of urinary tract infection versus controls
8. 14% of IC patients were Jewish (15% in Koziol sample [Koziol, 1994]) versus 3% Jewish individuals in the general population sample
9. Lower quality of life than in dialysis patients
10. Costs including lost economic production in 1987 of \$427 million

Other population studies followed. Jones and colleagues obtained their data from self-report of a previous diagnosis of IC in the 1989 National Household Interview Survey (Jones and Nyberg, 1997). The survey estimated that 0.5% of the population, or more than 1,000,000 people in the United States, reported having had a diagnosis of IC. There was no verification of this self-report by medical records. Bade and colleagues performed a physician questionnaire-based survey in the Netherlands that yielded an overall prevalence of 8 to 16 per 100,000 females, with diagnosis heavily dependent on pathology and presence of mast cells (Bade et al, 1995). This prevalence in females compares with 4.5 per 100,000 in Japan (Ito et al, 2000). The Nurses' Health Study I and II (Curhan et al, 1999) showed a prevalence of IC of 52 to 67 per 100,000 in the United States, twice the prevalence in the Held study (Held et al, 1990) and threefold higher than in the Netherlands (Bade et al, 1995). It improved on previous studies by using a large sample derived from a general population and careful ascertainment of the diagnosis. If the 6.4% confirmation rate of these studies were applied to the Jones and colleagues National Health Interview Survey data, the prevalence estimates of the two studies would be nearly identical.

The most sophisticated population-based prevalence study was conducted by the Rand Corporation. With use of a case definition with an 83% specificity, a random sample of 146,231 households was contacted by telephone and 12,752 women completed the questionnaire; 2.7% met the high-specificity definition of BPS. Less than 10% of these women had a clinical diagnosis of BPS/IC. The figures correspond to 3.3 million women in the United States aged 18 or older with symptoms compatible with the diagnosis (Berry et al, 2011). When the same methodology was applied to men, the findings suggested that 1.9% of adult U.S. males have symptoms of IC/BPS, higher than the weighted prevalence of chronic prostatitis and CPPS (Suskind et al, 2013a). The Rand prevalence data are very high, yet the methodology is exceptionally sound for a population-based prevalence study (Konkle et al, 2012).

Leppilahti and colleagues used the O'Leary-Sant interstitial cystitis symptom and problem index (never validated for making a diagnosis per se) to select women with IC symptoms from the Finnish population register. Of 1331 respondents, 32 had moderate or severe symptoms involving a suspicion of BPS/IC (symptom score 7 or higher). Of 21 who consented to clinical evaluation, 7 had probable or possible BPS/IC. Corrected estimates yielded a prevalence of 300 per 100,000 women (Leppilahti et al, 2002, 2005). Similar studies without clinical confirmation suggested prevalence in Austrian women of 306 per 100,000 (Temml et al, 2007) and in Japanese women of 265 per 100,000 (Inoue et al, 2009). With use of the Bristol Female Lower Urinary Tract Symptoms questionnaire, prevalence of BPS symptoms of 100 per 100,000 Fuzhou Chinese women was reported (Song et al, 2009).

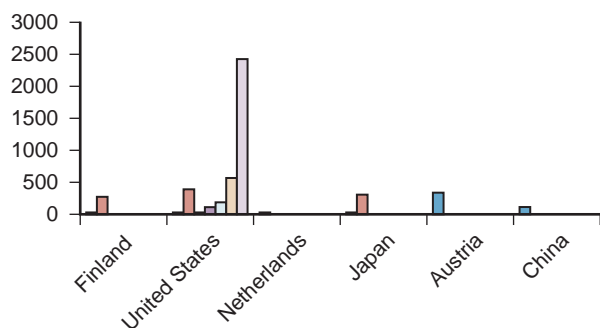


Figure 14-3. Prevalence of bladder pain syndrome per 100,000 females in reported studies from around the world. See text for details.

Roberts and colleagues, using a physician diagnosis as the arbiter of IC, found annual incidence in Olmsted County, Minnesota of 1.6 per 100,000 in women and 0.6 per 100,000 in men, a figure remarkably similar to that of Oravisto in Helsinki (Roberts et al, 2003). The cumulative prevalence by age older than 80 years in the Minnesota study was 114 per 100,000, a figure comparable to that in the Nurses' Health Study if one takes into account the younger age group in the Curhan data. Clemens calculated a prevalence of diagnosed disease in a managed care population of 197 per 100,000 women and 41 per 100,000 men, but when the diagnosis was tested by eliminating those who had not been evaluated with endoscopy or in whom exclusionary conditions existed, the numbers dropped considerably (Clemens et al, 2005). The Boston Area Community Health (BACH) Survey estimated a prevalence of BPS symptoms of 1% to 2% of the population depending on the definition used (Clemens et al, 2007). A population-based study in Korea found a prevalence in women of 0.26% (Choe et al, 2011). A Japanese study estimated the incidence of hospital admissions related to IC/BPS at 1.35 per 100,000 person-years (Sugihara et al, 2012).

With regard to office visits to practices with an interest in urologic problems, 2.8% of patients in Canadian urologist offices had BPS/IC (Nickel et al, 2005b), and probable BPS/IC was found in 0.57% of patients in a primary care office in Michigan (Rosenberg and Hazzard, 2005).

Until the Rand study, a reasonable prevalence estimate (recognizing that a consistent definition of the condition had not been used in epidemiologic studies) appeared to be about 300 per 100,000 in females, and in males 10% to 20% of the estimate in females. It now appears the problem may be 10 times greater.

Whether the considerable variability in prevalence in studies within the United States and around the world is related to methodology or true differences in incidence is an important question yet to be answered. One reason may be that pain that the patient perceives to be related to the bladder is a problematic concept, because most patients have different reasons for reaching that conclusion (Warren et al, 2011b). It is clear that the prevalence of BPS/IC symptoms is much greater than the prevalence of a physician diagnosis of the disease (Clemens et al, 2007). Familial occurrence of BPS/IC has been reported (Dimitrakov, 2001). A hereditary aspect to incidence has been suggested by Warren in a pioneering study. He found that adult female first-degree relatives of patients with IC may have a prevalence of IC 17 times that found in the general population. This, together with previously reported evidence showing a greater concordance of IC among monozygotic than dizygotic twins, suggests but does not prove a genetic susceptibility to IC that could partially explain the discord in prevalence rates in different populations (Warren et al, 2001b, 2004).

KEY POINT: PREVALENCE

- Prevalence studies show wide variation; however, more modern studies of the prevalence of BPS/IC per 100,000 women tend to show higher values.

Prevalence of BPS/IC per 100,000 Women

Oravisto, 1975 (Finland)	18
Jones and Nyberg, 1997 (United States)	500
Held et al, 1990 (United States)	30
Bade et al, 1995 (Netherlands)	12
Curhan et al, 1999 (United States)	60
Ito et al, 2000 (Japan)	4.5
Roberts et al, 2003 (United States)	1.6
Leppilahti et al, 2005 (Finland)	300
Clemens et al, 2007 (United States)	197
Temml et al, 2007 (Austria)	306
Song et al, 2009 (China)	100
Berry et al, 2011 (United States)	2700

Characteristics and Natural History

Before the Rand study (Suskind et al, 2013a), most studies had shown a female-to-male preponderance of 5:1 or greater (Clemens et al, 2005; Hanno et al, 2005a). In the absence of a validated marker, it is often difficult to distinguish BPS/IC from CPPS (nonbacterial prostatitis, prostatodynia) that affects males (Forrest and Schmidt, 2004), and the percentage of men with BPS/IC may actually be higher (Miller et al, 1995, 1997; Novicki et al, 1998). Men tend to be diagnosed at an older age and have a higher percentage of Hunner lesions in the case series reported (Novicki et al, 1998; Roberts et al, 2003). Costs of the disorder are not insignificant and can range from \$4000 to \$7000 dollars per year, not including lost wages, costs preceding diagnosis, costs of alternative therapies, and costs attributable to misdiagnosis (Clemens et al, 2008c, 2009b).

Patients with BPS/IC analyzed across a wide spectrum of ages at time of diagnosis show different symptom profiles. Those diagnosed at the youngest ages experienced significantly more urinary urgency, frequency, dysuria, dyspareunia, and pain in their external genitalia. Older patients had a higher incidence of nocturia, urinary incontinence, and Hunner lesions (Rais-Bahrami et al, 2012). Patients with mild disease symptoms at onset appear to show symptom stability at 3 years, whereas those with concomitant chronic fatigue syndrome at symptom onset tend to show symptom progression of BPS/IC over time (Warren et al, 2013a).

The ICDB cohort of patients has been carefully studied, and the findings seem to bear out those of other epidemiologic surveys (Proper et al, 2000). Patterns of change in symptoms with time suggest regression to the mean and an intervention effect associated with the increased follow-up and care of cohort participants. Although all symptoms fluctuated, there was no evidence of significant long-term change in overall disease severity. The data suggest that BPS/IC is a chronic disease, and no current treatments have a significant impact on symptoms over time in the majority of patients. Quality-of-life studies suggest that BPS/IC patients are six times more likely than individuals in the general population to cut down on work time because of health problems, but only half as likely to do so as patients with arthritis (Shea-O'Malley and Sant, 1999). There is an associated high incidence of comorbidity including depression, chronic pain, and anxiety and overall mental health issues (Michael et al, 2000; Rothrock et al, 2002; Hanno et al, 2005a). Disability may be partially explained by the impact of negative affect and catastrophizing (Katz et al, 2013). There seems to be no effect on pregnancy outcomes (Onwude and Selo-Ojeme, 2003).

Female patients with BPS/IC seem to report significant dyspareunia and other manifestations of sexual dysfunction. All domains of female sexual function including sexually related distress, desire, and orgasm frequency can be affected (Ottem et al, 2007; Peters et al, 2007b). Sexual function is an important predictor of physical quality of life and was the only strong predictor of mental quality of life in one study of patients with severe BPS/IC (Nickel et al, 2007).

The BACH Survey (Link et al, 2008) showed an overall prevalence of symptoms suggestive of BPS of 2%, with twice as many women as men affected. It was most common among middle-aged respondents, with an earlier peak in women. It was most common among minorities and those of lower socioeconomic status (SES), and SES seemed to overcome any effect of race or ethnicity. Emotional, sexual, and physical abuse was shown to be a risk factor in the BACH Survey (Link and Luftey, 2007), and this has been borne out in other studies. A Michigan study compared a control group of 464 women with 215 BPS/IC patients and found that 22% of the control group had experienced abuse versus 37% of the patient group (Peters et al, 2007b). Those with a history of sexual abuse may have more pain and fewer voiding symptoms (Seth and Teichman, 2008). How reliable these data are is not clear, and it would be wrong to jump to any conclusions about abuse in an individual patient. However, practitioners need to have sensitivity to the possibility of an abusive relationship history in all pain

patients, and BPS patients in particular. When patients are found to have multiple diagnoses, the rate of previous abuse also increases, and these patients may need referral for further counseling at a traumatic stress center (Fenton et al, 2008).

KEY POINTS: NATURAL HISTORY

- The female-to-male preponderance had been estimated at 5:1. Newer data suggest the prevalence may be similar in males and females.
- Symptoms tend to fluctuate, with the majority of patients showing no long-term deterioration.
- There is no deleterious effect on pregnancy outcomes.
- Men are diagnosed at an older age and have a higher prevalence of Hunner lesions.
- Quality of life in almost all domains is significantly affected.

Associated Disorders

Knowledge of associated diseases is relevant for the clues it engenders with regard to cause and possible treatment of this enigmatic pain syndrome. It is well known that patients with chronic pain syndromes including chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder share key symptoms and can often develop overlapping conditions including chronic pelvic pain (Aaron and Buchwald 2001; Aaron et al, 2001). Female patients with BPS/IC report significantly more nonpain symptoms and pain outside the pelvis than control female urology patients. In contrast to males with CPPS and nonbacterial prostatitis, females with BPS/IC are more likely to endorse multiple bothersome, medically unexplained symptoms across multiple organ systems (Lai et al, 2012). Bladder symptoms do not uniformly predate the nonbladder symptoms (Clemens et al, 2012). The number of functional somatic syndromes is perhaps the strongest risk factor for development of other non-bladder pain syndromes in the BPS/IC population. This is especially true for irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome (Warren et al, 2013a). These associated syndromes have an equivalent negative impact to BPS/IC in terms of quality of life (Suskind et al, 2013b).

In a case-control study Erickson found that patients with IC had higher scores than controls for pelvic discomfort, backache, dizziness, chest pain, aches in joints, abdominal cramps, nausea, palpitations, and headache (Erickson et al, 2001). Buffington theorizes that a common stress-response pattern of increased sympathetic nervous system function in the absence of comparable activation of the hypothalamic-pituitary-adrenal axis may account for some of these related symptoms (Buffington, 2004). Both depression and panic attacks have a high prevalence in patients with BPS/IC symptoms (Watkins et al, 2011). It has been suggested that panic disorder, a diagnosis associated with some BPS/IC patients (Clemens et al, 2008a), may sometimes be a part of a familial syndrome that includes IC, thyroid disorders, and other disorders of possible autonomic or neuromuscular control (Weissman et al, 2004; Subaran et al, 2012). Depression has been associated with BPS/IC in both men and women (Clemens et al, 2008a; Hall et al, 2008), but whether this is an association or effect of the disorder is uncertain (FitzGerald et al, 2007).

Newly diagnosed patients are most concerned with the possibility that BPS/IC could be a forerunner of bladder carcinoma. Until recently, no reports have ever documented a relationship to suggest that IC is a premalignant lesion. Utz and Zincke discovered bladder cancer in 12 of 53 men treated for IC at the Mayo Clinic (Utz and Zincke, 1974). Initial misdiagnosis was likely. Three of 224 women were eventually diagnosed with bladder cancer. Four years later, additional cases were reported (Lamm and Gittes, 1977). Tissot and colleagues reported that 1% of 600 patients previously diagnosed as having IC were found to have transitional cell carcinoma as the cause of symptoms (Tissot et al, 2004). Somewhat ominously, 2 of these patients had no hematuria. In all patients, irritative symptoms resolved after treatment of the malignancy. From this experience has

come the dictum that all patients with presumed IC should undergo cystoscopy, urine cytology, and bladder biopsy of any suspicious lesion to be sure that a bladder carcinoma is not masquerading as BPS/IC. It would seem that in the absence of microhematuria, and with negative cytology, the risk of missing a cancer is negligible, but not zero. A study from Taiwan reports a 2.95 relative risk of developing bladder cancer in BPS/IC patients compared with controls based on data analyzed from the Taiwan National Health Insurance Program (Keller et al, 2013b). This leaves the question still unresolved.

A large-scale survey of 6783 individuals diagnosed by their physicians as having BPS/IC studied the incidence of associated disease in this population (Alagiri et al, 1997). Data from the 2405 responders were validated by comparison with 277 nonresponders (Fig. 14-4). Allergies were the most common association, with over 40% affected. Allergy was also the primary association in Hand's study (Hand, 1949). Thirty percent of patients had a diagnosis of irritable bowel syndrome, a finding confirming that of Koziol (1994). Altered visceral sensation has been implicated in irritable bowel syndrome in that these patients experience intestinal pain at intestinal gas volumes that are lower than those that cause pain in healthy persons (Lynn and Friedman, 1993), strikingly similar to the pain on bladder distention in IC.

Fibromyalgia, another disorder frequently considered functional because no specific structural or biochemical cause has been found, is also overrepresented in the BPS/IC population. This is a painful nonarticular condition predominantly involving muscles; it is the commonest cause of chronic, widespread musculoskeletal pain. It is typically associated with persistent fatigue, nonrefreshing sleep, and generalized stiffness. Women are affected at least 10 times more often than men (Consensus document on fibromyalgia, 1993). The association is intriguing because both conditions have similar demographic features, modulating factors, associated symptoms, and response to tricyclic compounds (Clauw et al, 1997; Chelmsky et al, 2012).

Diagnosed vulvodynia, migraine headaches, endometriosis, chronic fatigue syndrome, incontinence, and asthma had similar prevalence as in the general population. Several publications have noted an association between BPS/IC and systemic lupus erythematosus (SLE) (Fister, 1938; Boye et al, 1979; de la Serna and Alarcon-Segovia, 1981; Weisman et al, 1981; Meulders et al, 1992). The question has always been whether the bladder symptoms represent an association of these two disease processes or rather are a manifestation of lupus involvement of the bladder (Yukawa et al, 2008) or even a myelopathy with involvement of the sacral cord in a small group of these patients (Sakakibara et al, 2003). The beneficial response of the cystitis of SLE to steroids (Meulders et al, 1992) tends to support the latter view. No association with discoid lupus has been demonstrated (Jokinen et al, 1972b). Overall, the incidence of collagen-vascular disease in the IC population is low. Parsons found only 2 of 225 consecutive IC patients to have a history of autoimmune disorder (Parsons, 1990).

The National Health Insurance Research Database of the Taiwan National Health Insurance Programme has yielded data on many associations with BPS, some of which await confirmation from further population-based research. These include depression, anxiety, urinary calculus, erectile dysfunction, reflux esophagitis, coronary heart disease, obstructive sleep apnea, rheumatoid arthritis, and ischemic stroke (Chung et al, 2013, 2014a, 2014b, 2015; Kang et al, 2013; Keller et al, 2013a, 2013c, 2013d; Chen et al, 2014b). A study using this database has looked at a multitude of other illnesses using a logistic regression analysis, and only metastatic cancer did not show a statistically higher prevalence rate in BPS patients, making the data somewhat difficult to interpret (Keller et al, 2012).

Inflammatory bowel disease was found in over 7% of the IC population Alagiri studied, a figure 100 times higher than in the general population and never corroborated by other epidemiologic studies (Alagiri et al, 1997). Although unexplained at this time, abnormal leukocyte activity has been implicated in both conditions (Bhone et al, 1962; Kontras et al, 1971).

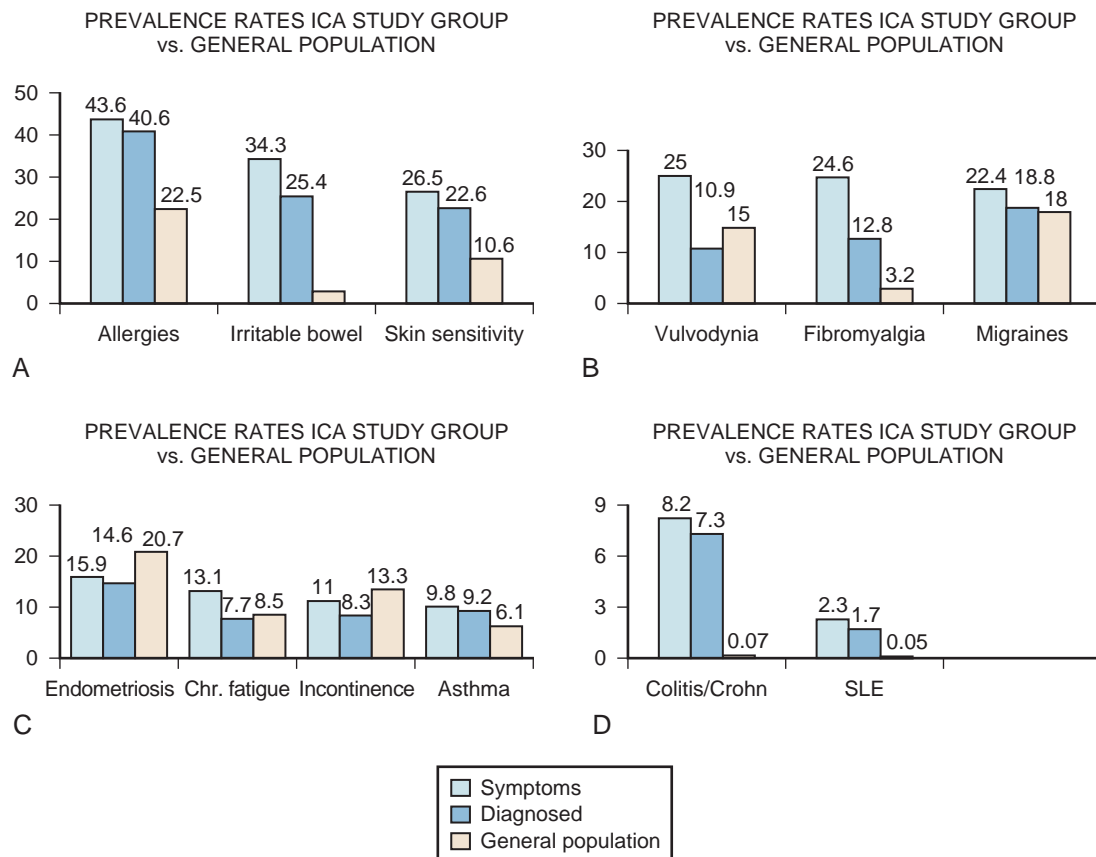


Figure 14-4. A through D, Comparison of disease prevalence rates among the Interstitial Cystitis Association (ICA) study group patients who report symptoms of a disorder, who have been diagnosed with a disorder, and the general population. Chr., chronic; SLE, systemic lupus erythematosus. (From Alagiri M, Chottiner S, Ratner V, et al. Interstitial cystitis: unexplained associates with other chronic pain syndromes. *Urology* 1997;49[Suppl. 5A]:52–7.)

The University of Maryland group sought antecedent nonbladder syndromes in 313 patients with incident BPS/IC and compared them with 313 matched controls (Warren et al, 2009). They found 11 antecedent syndromes were more often diagnosed in those with BPS/IC, and most syndromes appeared in clusters. The most prominent cluster (45%) comprised fibromyalgia–chronic widespread pain, chronic fatigue syndrome, sicca syndrome, and/or irritable bowel syndrome. Most of the other syndromes and identified clusters were associated with it. These researchers found probable chronic fatigue syndrome in 20% of BPS/IC patients, probable fibromyalgia in 22%, and probable irritable bowel in 27% of the BPS patients. Far fewer had physician-reported diagnoses of these syndromes, and odds ratios (ORs) for BPS/IC versus controls were 2.5 to 2.9. BPS/IC was significantly associated with previous female hormone use, a history of fewer pregnancies (in premenopausal women), and antecedent nonbladder syndromes (Warren et al, 2011a). Perhaps not surprisingly, in the month before the onset of BPS/IC, the approximated annual incidence of nonbladder pelvic surgeries was 15 times higher and of hysterectomy 25 times higher than the incidences in previous years and similarly higher than controls. The rate declined to preindex levels over the first 2 years of BPS/IC (Warren et al, 2013b). Although one could postulate that the surgery was an initiating factor, it may be more likely that the pelvic pain from undiagnosed BPS was what prompted the pelvic surgery in the first place.

Study of a managed care database in Portland, Oregon revealed that patients coded for gastritis (OR = 12.2), child abuse (OR = 9.3), fibromyalgia (OR = 3.0), anxiety disorder (OR = 2.8), headache (OR = 2.5), or depression (OR = 2.0) were commonly diagnosed with BPS/IC (Clemens et al, 2008b).

Women with BPS experience very high levels of sexual dysfunction (Bogart et al, 2011). An unexplained disorder that has been associated with IC is vulvodynia with focal vulvitis (Gardella et al, 2011; Reed et al, 2012). Vulvar vestibulitis syndrome is a constellation of symptoms and findings involving and limited to the vulvar vestibule and consisting of (1) severe pain on vestibular touch to attempted vaginal entry, (2) tenderness to pressure localized within the vulvar vestibule, and (3) physical findings confined to vulvar erythema of various degrees (Marinoff and Turner, 1991). McCormack reported on 36 patients with focal vulvitis, 11 of whom also had IC (McCormack, 1990). Fitzpatrick added 3 more patients (Fitzpatrick et al, 1993). Vulvodynia is associated not only with BPS/IC but also with irritable bowel syndrome and fibromyalgia (Nguyen et al, 2013). The concordance of these noninfectious inflammatory syndromes involving the tissues derived from the embryonic urogenital sinus and the similarity of the demographics argue for a common cause.

An association has been reported between IC and Sjögren syndrome (SS), an autoimmune exocrinopathy with a female preponderance manifested by dry eyes, dry mouth, and arthritis, but which can also include fever, dryness, and gastrointestinal and lung problems. Van de Merwe and colleagues (1993) investigated 10 IC patients for the presence of SS. Two patients had both keratoconjunctivitis sicca and focal lymphocytic sialoadenitis, allowing a primary diagnosis of SS. Only 2 patients had neither finding. He later reported an incidence of 28% of SS in patients with IC (van de Merwe et al, 2003). The incidence of symptoms of BPS/IC in patients with SS has been estimated to be up to 5% (Leppilähti et al, 2003). Patients with SS may have bladder symptoms from DO, and each patient requires careful individual evaluation before a diagnosis of BPS/IC is made (Lee et al, 2011a).

A negative correlation with diabetes has been noted (Parsons, 1990; Koziol, 1994; Warren et al, 2009). Although patients with multiple pain locations (increased pain phenotype) may have poorer psychosocial adjustment and diminished quality of life (Tripp et al, 2012), one cannot distinguish patients with Hunner lesions from those without Hunner lesions with regard to the number of painful areas or the location of pain (Killinger et al, 2013).

Further epidemiologic studies are warranted, because the epidemiology of this disorder may ultimately yield as many clues into cause and treatment as other avenues of research. The heterogeneity of causes and symptoms of CPPS suggests that proper clinical phenotyping could foster the development of better treatments for individual phenotypes and more successful treatments for all affected patients (Baranowski et al, 2008; Shoskes et al, 2009).

KEY POINTS: ASSOCIATED DISORDERS

- Look for symptoms of the following disorders, which may be associated with some cases of BPS: depression, SS, irritable bowel syndrome, allergies, fibromyalgia, chronic fatigue syndrome, inflammatory bowel disease, focal vulvitis.
- BPS has not been considered a premalignant condition.

ETIOLOGY

It is likely that BPS/IC has a multifactorial cause that may act predominantly through one or more pathways, resulting in the typical symptom complex (Holm-Bentzen et al, 1990; Mulholland and Byrne, 1994; Erickson, 1999; Levander, 2003; Keay et al, 2004b) (Fig. 14-5). There are an abundance of theories regarding

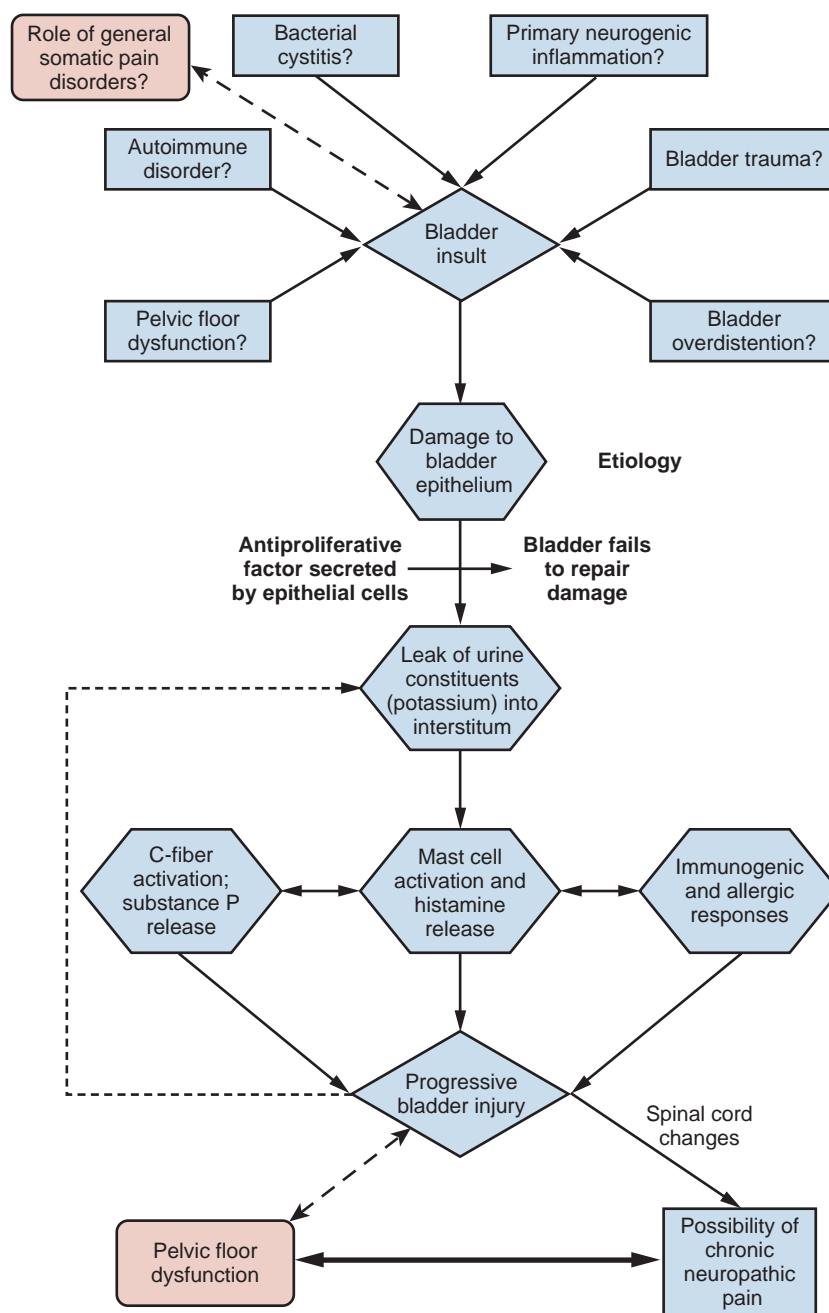


Figure 14-5. Hypothesis of causative cascade of bladder pain syndrome. (From Hanno P, Dinis P, Lin A, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence. Paris: International Consultation on Urological Diseases/European Association of Urology; 2013. p. 1583–649.)

its pathogenesis, but confirmatory evidence gleaned from clinical practice has proven sparse. Among numerous proposals that are further explored in this section are “leaky epithelium,” mast cell activation, and neurogenic inflammation, or some combination of these and other factors leading to a self-perpetuating process resulting in chronic bladder pain and voiding dysfunction (Elbadawi, 1997). Irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and various other chronic pain disorders may precede or follow the development of BPS/IC in some patients (Kim and Chang, 2012), but development of associated syndromes is not inevitable by any means, and their relationship to the cause is currently unknown (Warren et al, 2009). It has been postulated that neural cross-talk in the dorsal root ganglia, in the spinal cord, and at the level of the brain might play a role in the development of chronic pain disorders and their clinical associations through central sensitization (Furuta et al, 2012a). In rats, injection of hydrochloric acid into the gluteus can induce plantar hypersensitivity and urinary frequency for up to 2 weeks after the injection (Furuta et al, 2012b).



A discussion of animal models and the possible role of infection, autoimmunity, inflammation, mast cells, histamine, epithelial permeability, antiproliferative factor (APF), neurogenic factors, cross-sensitization, urine abnormalities, genetic factors, stress, and pelvic floor dysfunction can be found on the Expert Consult website.

PATHOLOGY

Pathology can be consistent with the diagnosis of BPS, but there is no histology pathognomonic of this syndrome. The role of histopathology in the diagnosis of BPS is primarily one of excluding other possible diagnoses. One must rule out carcinoma and carcinoma in situ, eosinophilic cystitis, and tuberculous cystitis, as well as any other entities with a specific tissue diagnosis (Hellstrom et al, 1979; Johansson and Fall, 1990; Tsiropoulos et al, 2006).

Although earlier reports described a chronic, edematous pancystitis with mast cell infiltration, submucosal ulcerations, and involvement of the bladder wall and chronic lymphocytic infiltrate (Smith and Dehner, 1972; Jacobo et al, 1974), these were cases culled from patients with severe disease and not representative of the majority of cases currently diagnosed. The pathologic findings in BPS are not consistent. There has been a great variation in the reported histologic appearance of biopsy specimens from BPS patients, and even variation among samples taken from the same patients over time (Gillenwater and Wein, 1988).

Lépinard and colleagues (1984) reported a pancystitis affecting the three layers of bladder wall. In nonulcerative disease the vesical wall was never normal, epithelium being thinned and muscle being affected. Johansson and Fall looked at 64 patients with ulcerative disease and 44 with nonulcerative IC (Johansson and Fall, 1990). The former group had mucosal ulceration and hemorrhage, granulation tissue, intense inflammatory infiltrate, elevated mast cell counts, and perineural infiltrates. The nonulcerative group, despite having the same severe symptoms, had a relatively unaltered mucosa with a sparse inflammatory response, the main feature being multiple, small mucosal ruptures and suburothelial hemorrhages that were noted in a high proportion of patients. As these specimens were almost all taken immediately after hydrodistention, how much of the admittedly minimal findings in the nonulcerative group was purely iatrogenic is a matter of speculation.

Completely normal biopsy specimens are not uncommon in the nonulcerative BPS group (Johansson and Fall, 1994). Transition from nonulcerative to ulcerative BPS is a rare event (Fall et al, 1987), and pathologically the two types of IC may be completely separate entities. Although mast cells are more commonly seen in the detrusor in ulcerative BPS (Holm-Bentzen et al, 1987a), they are also common in patients with idiopathic bladder instability (Moore et al, 1992). Mastocytosis in BPS is best documented by tryptase immunocytochemical staining (Theoharides et al, 2001). Larsen and colleagues recommend taking biopsy specimens from

the detrusor of patients with suspected BPS and examining them with tryptase-stained 3-micron-thick sections, with every seventh section used for quantification. They consider 27 mast cells/mm² indicative of mastocytosis (Larsen et al, 2008). Despite attempts to develop a diagnostic algorithm based on the detrusor-to-mucosa mast cell ratio and nerve fiber proliferation (Hofmeister et al, 1997), mast cell counts per se have no place in the differential diagnosis of this clinical syndrome.

Mast cells could be valuable in clinical phenotyping, but as yet that is unproven. Mast cells trigger inflammation that is associated with local pain, but the mechanisms mediating pain are unclear. In a murine model of neurogenic cystitis, Rudick and colleagues demonstrated that mast cells promote cystitis pain and bladder pathophysiology through the separable actions of histamine and TNF, respectively (Rudick et al, 2008). Therefore, pain is independent of pathology and inflammation, and histamine receptors may represent direct therapeutic targets for the pain of BPS and other chronic pain conditions.

Lynes and coworkers concluded that biopsy specimens are often not helpful in confirming the diagnosis (Lynes et al, 1990a). Although BPS patients in their study had a higher incidence and degree of denuded epithelium, ulceration, and submucosal inflammation, none of these findings was pathognomonic. In addition, these “typical” findings occurred only in BPS patients with pyuria or small bladder capacity. Epithelial and basement membrane thickness, submucosal edema, vascular ectasia, fibrosis, and detrusor muscle inflammation and fibrosis were not significantly different in the BPS and control patients.

Attempts to definitively diagnose BPS by electron microscopy have also been unsuccessful. Collan’s group, in the first such study (Collan et al, 1976), wrote that the similarity of the ultrastructure of epithelial cells in controls and IC patients makes it improbable that the disease process originates in the epithelium. Other investigators found no differences in the morphologic appearances of the glycocalyx and of urothelial cells in patients with IC when compared with controls (Dixon et al, 1986). Anderstrom and colleagues saw no surface characteristics specific for IC (Anderstrom et al, 1989), but believed that the mucin layer covering the urothelial cells seemed reduced in IC compared with controls, a fact disputed by Nickel in a very elegant paper (Nickel et al, 1993). Elbadawi and Light observed ultrastructural changes sufficiently distinctive to be diagnostic in specimens submitted for pathologic confirmation of nonulcerative IC (Elbadawi and Light, 1996). Marked edema of various tissue elements and cells appeared to be a common denominator of many observed changes. The wide-ranging discussion of the etiology of IC in his paper is fascinating, but the pathologic findings are potentially marred by the methodology, in that specimens were obtained after diagnostic hydrodistention (Elbadawi, 1997).

So what is the place of pathologic examination of tissue in BPS? Attempts to classify the painful bladder by the pathoanatomic criteria described by Holm-Bentzen (1989) are of questionable value. There is a group of patients with what she describes as *nonobstructive detrusor myopathy* (Holm-Bentzen et al, 1985). In her series, these patients with degenerative changes in the detrusor muscle often had residual urine, a history of urinary retention, and an absence of sensory urgency on cystometry with bladder capacities over 400 mL. Most of these signs would not be clinically confused with BPS. A similar English series (Christmas et al, 1996b), however, included patients who met NIDDK research criteria and associated detrusor myopathy with diminished detrusor compliance and ultimate bladder contracture.

The ICDB study worked backward from symptoms to pathology and concluded that certain symptoms are predictive of specific pathologic findings (Tomaszewski et al, 1999, 2001). Denson and colleagues analyzed forceps biopsy specimens from 65 females and 4 males with BPS (Denson et al, 2000). Ten percent of specimens showed vasodilatation or submucosal edema. Inflammation was absent in 30% of patients, and mild in another 41%. Cystoscopic changes did not correlate with degree of inflammation. Hanus and colleagues studied 84 biopsy specimens from 112 BPS

Animal Models

Until recently, lacking an easily available animal model of the naturally occurring disease, researchers have had to devise animal models to study isolated symptoms of BPS/IC, hoping to uncover the root causes of the symptomatology (Ruggieri et al, 1990). Although animal models can yield clues to cause, all theories must ultimately be tested in humans with the disease. Comparative and translational studies are required if the full potential of findings obtained with animal models is to be realized (Bjorling et al, 2011).

Bullock and associates reported a mouse model in which bladder inflammation could be induced by the injection of syngeneic bladder antigen (Bullock et al, 1992). The model demonstrated that a component in the Balb/cAN mouse is capable of inducing a bladder-specific, adoptively transferable, cell-mediated autoimmune response that exhibits many characteristics of clinical IC, but was difficult to reproduce (Klutke et al, 1997). In another mouse model, immunization of mice with recombinant mouse uroplakin II provoked an autoimmune response sufficient to induce an autoimmune cystitis (Altuntas et al, 2012). Injecting the Bartha strain of pseudorabies virus in the tail of mice causes female gender-specific pelvic pain (Rudick et al, 2012). In a pilot study, a mouse model using a synthetic APF intravesically has yielded histopathologic changes in the mouse similar to findings of IC/BPS patient biopsy specimens (Keay et al, 2012). Vascular endothelial growth factor (VEGF) instillation into the mouse bladder promotes a significant increase in peripheral nerve density with alterations in bladder function and visceral sensitivity (Malykhina et al, 2012).

In a guinea pig model, the instillation of a solution containing a protein to which the animal had been previously immunized resulted in bladder inflammation (Christensen et al, 1990; Kim et al, 1992), as did a rat model of allergic cystitis using a local challenge of ovalbumin in previously sensitized rats (Ahlwalia et al, 1998). Changes in the rat model were dependent on mast cell degranulation and activation of sensory C fibers. Induction of urinary symptoms after 7 days of repeated variate stress has been reported in a rat model (Merrill et al, 2013).

Ghoniem and coworkers studied four female African green monkeys challenged with intravesical acetone (Ghoniem et al, 1995). Not surprisingly, they exhibited symptoms of BPS. Rivas and associates performed similar experiments using dilute hydrochloric acid in a rat model (Rivas et al, 1997). A rat model for neurogenic cystitis using pseudorabies virus demonstrated that inflammatory changes in the spinal cord can result in dramatic, neurogenically mediated changes in the bladder (Doggweiler et al, 1998).

The problem with all these animal models relates to whether or not they mirror the human disease to any great extent. Buffington has described what appears to be a naturally occurring animal model of BPS/IC (Buffington, 2011) (Fig. 14-6). Two thirds of cats with lower urinary tract disease have sterile urine and no evidence of other urinary tract disorders (Kruger et al, 1991). A portion of these cats experience frequency and urgency of urination, pain, and bladder inflammation (Haupt, 1991). Glomerulations have been observed in the bladders of these animals. GP-51, a glycosaminoglycan (GAG) commonly found in the surface mucin covering the mucosa of the normal human bladder and decreased in IC, shows a decreased expression in cats with this symptom complex (Press et al, 1995), originally termed *feline urologic syndrome*. Bladder A δ afferents in these cats are more sensitive to pressure changes than are afferents in normal cats (Roppolo et al, 2005). They also demonstrate an increase in baseline nitric oxide production in smooth muscle and mucosal strips when compared with healthy cats, with evidence of altered mucosal barrier function (Birder et al, 2005).

Buffington now refers to this disorder as *feline interstitial cystitis* (FIC) (Buffington et al, 1999). It is associated with urinary urgency, frequency, and pain with sterile urine, bladder mastocytosis, increased histamine excretion, increased bladder permeability, decreased urinary GAG excretion (Buffington et al, 1996), and increased plasma norepinephrine concentrations (Buffington and Pacak, 2001).

Infection

Often, a diagnosis of BPS/IC is made only after a patient has been seen by a number of physicians and treated with antibiotics for presumed urinary tract infection without resolution of symptoms (Held et al, 1990). The symptom complex looks to the patient and physician like an infectious process (Porru et al, 2004). The epidemiology of urinary tract infection and its predominance in women mirror the BPS/IC data (Warren, 1994a). The acute to subacute onset in many patients has fascinated clinicians who often associate an insidious onset with a chronic condition such as BPS/IC.

Reverse logic led some to suspect that antibiotics may be instrumental in causing IC (Holm-Bentzen et al, 1990). Most patients have been treated with antibiotics once or several times before the diagnosis is made. Numerous antibiotics, primarily in the penicillin family, can induce cystitis (Bracis et al, 1977; Moller, 1978; Chudwin et al, 1979; Cook et al, 1979; Marx and Alpert, 1984), but no evidence has ever been documented that these antibiotics or the supposedly "surface active" nitrofurantoin or

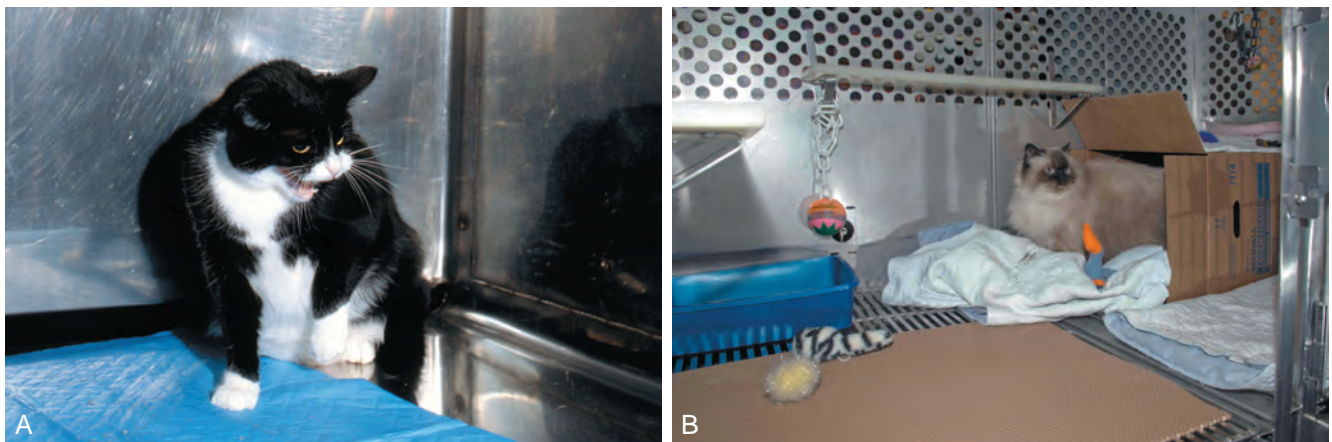


Figure 14-6. A, Photograph of a cat with feline interstitial cystitis (FIC). Note posture of defensive aggression in response to reflection in the stainless steel cage wall. B, Photograph of a cat with FIC in an enriched cage. Environmental modification intended to reduce perception of external threat has been found to be an effective approach to treatment of cats with FIC in both laboratory and clinical studies. (Courtesy Tony Buffington.)

tetracyclines have any involvement in pathogenesis (Ruggieri et al, 1987; Levin et al, 1988).

To determine whether there is an infectious cause of BPS, certain procedures are necessary (Warren, 1994b). Not just urine, but bladder epithelium as well must be cultured for appropriate microorganisms, including bacteria, viruses, and fungi. Because some organisms might be culturable yet fastidious, special culture techniques should be used. Because some organisms in urine or tissue might be viable but nonculturable, specific nonculture techniques for discovery and identification should be employed. Most important, the same procedures must be carried out in a control population.

Attempts to show an infectious cause go back to the dawn of the disease, but the case has never been a strong one (Duncan and Schaeffer, 1997). Hunner (1915) originally proposed that IC resulted from chronic bacterial infection of the bladder wall secondary to hematogenous dissemination. Harn proposed a relationship between IC and streptococcal and poststreptococcal inflammation (Harn et al, 1973). He produced a progressive chronic inflammation in rabbit bladders by injecting small numbers of *Streptococcus pyogenes* in the bladder wall. Studies of *Helicobacter pylori* have failed to demonstrate an association with IC (English et al, 1998; Agarwal and Dixon, 2003; Atug et al, 2004; Haq et al, 2004). Wilkins found bacteria in catheterized urine specimens and/or bladder biopsy samples in 12 of 20 patients with IC (Wilkins et al, 1989). However, 8 of the isolates were fastidious bacteria—*Gardnerella vaginalis* and *Lactobacillus* species—and no controls were included in the study. Polyomaviruses have been reported to cause a BPS/IC-like syndrome that responds to cidofovir treatment (Eisen et al, 2009). These viruses are excreted intermittently in the urine of healthy, asymptomatic adults, making diagnosis of a true infection problematic.

Negative studies far outnumber positive ones. Hanash and Pool performed viral, bacterial, and fungal studies on 30 IC patients and failed to substantiate an infectious cause (Hanash and Pool, 1970). Hedelin found only 3 of 19 IC patients to have urine cultures positive for *Ureaplasma urealyticum*, and indirect hemagglutination antibodies to *Mycoplasma hominis* to be no greater than in controls (Hedelin et al, 1983). Potts cultured *U. urealyticum* in 22 of 48 patients with “chronic urinary symptoms” and had great success in these patients (none of whom had established IC) with short courses of commonly prescribed antibiotics (Potts et al, 2000). Given the history of empirical antibiotics in the vast majority of IC patients, it is doubtful if this group represents even a small percentage of the IC-diagnosed population. Nevertheless, it illustrates that BPS/IC is a diagnosis of exclusion; urine culture is critical, and an empirical short course of antibiotics is certainly reasonable if the patient has not already been treated for presumed infection. Empirical doxycycline has been successfully used in this manner (Burkhard et al, 2004).

The development of highly sensitive, rapid, and specific molecular methods of identifying infectious agents by the direct detection of DNA or RNA sequences unique to a particular organism (Naber, 1994) resulted in a flurry of activity into the search for a responsible virus or microorganism. Hampson could find no evidence of mycobacterial involvement in 8 cases of BPS/IC with use of DNA probes (Hampson et al, 1993). Haarala confirmed an absence of bacterial DNA in the bladder of 11 BPS/IC patients with no documented history of urinary tract infection (Haarala et al, 1996). Hukkanen reported an absence of adenovirus and BK virus genomes in urinary bladder biopsy specimens of IC patients (Hukkanen et al, 1996). Domingue’s provocative finding of the presence of bacterial 16S rRNA genes in bladder biopsy specimens from 29% of IC patients but not from control bladders and his discovery of 0.22- μ m filterable forms in culture of biopsy tissue from 14 of 14 IC patients and 0 of 15 controls (Domingue et al, 1995) have never been confirmed or repeated.

A preliminary study found a statistically significant increase in urine polymerase chain reaction (PCR) to *Chlamydia pneumoniae* major outer membrane protein gene in patients with BPS/IC as compared with controls (Franke et al, 1999). Other studies have

shown that similar percentages of both IC and control patient populations have nonculturable bacteria in the bladder on the basis of PCR studies of bladder biopsy specimens (Heritz et al, 1997; Keay et al, 1998a). The spirochete *Borrelia burgdorferi* has been found in bladder biopsy specimens and urine of patients with Lyme disease and can cause frequency, urgency, and nocturia. DNA studies have failed to show a role for *Borrelia* in IC (Haarala et al, 2000). A study using high-throughput sequencing analysis of urine microbiota in BPS/IC patients compared with healthy females showed a reduced microbial diversity and richness accompanied by a higher abundance of the bacterial genus *Lactobacillus* in the BPS group (Siddiqui et al, 2012).

The role of infection in the pathogenesis of BPS/IC remains a mystery. At this time there are few data to support the role of an infectious cause, but investigators keep returning to an infectious theory. Insights into the mechanisms by which bacteria adhere, grow, and persist in association with host tissue and form intracellular pods capable of subverting host defense mechanisms and allowing replication within epithelial cells lay the foundation for a possible role of infection in initiating the BPS/IC pathologic cascade (Kau et al, 2005). The University of Maryland group proposed a model of BPS in which bladder epithelial damage such as that caused by bacterial cystitis may be the first step leading to a low-level inflammatory response (Keay and Warren, 1998). Domingue wrote, “It is logical to suggest that even if organisms are not causative agents, their presence may lead to immune and host-cell responses that could initiate or exacerbate an inflammatory state” (Domingue et al, 1997). In a case-control study, premenopausal women with a history of recurrent urinary tract infection had significantly greater urinary frequency, lower average voided volume, and a lower threshold of bladder sensitivity than controls (Arya et al, 2012).

If infection does play a role, it would be predicted that appropriate treatments to minimize microbial presence in the tissue would significantly improve the morbidity associated with BPS/IC. Durier’s incredible series (Durier, 1992) purporting to cure 27 out of 27 IC patients with the use of up to five sequential antibiotics covering the anaerobic spectrum has never been duplicated. Warren’s prospective, double-blind, placebo-controlled, randomized trial of 50 patients may well prove the end of long-term empirical antibiotic treatment in established BPS/IC (Warren et al, 2000). Eighteen weeks of placebo or antibiotics (sequential doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin, and ciprofloxacin for 3 weeks each) were administered. Most patients guessed the arm to which they were assigned. Of the 25 patients in the active arm, 80% had new nonurinary symptoms perceived as side effects. There was minimal improvement in some patients associated with the active arm, but the conclusion that intensive antibiotics do not represent a major advance in therapy for IC seems well justified.

Although the concept that a urinary tract infection may trigger BPS in some patients is appealing (Elgavish et al, 1995; Elbadawi, 1997), it is unlikely that active infection is involved in the ongoing pathologic process or that antibiotics have a role to play in treatment.

Autoimmunity and Inflammation

Immune and neuroimmune mechanisms may have an important role in the pathogenesis of BPS/IC. Excessive release of sensory nerve neurotransmitters and mast cell inflammatory mediators is thought by some to be responsible for the development and propagation of symptoms (Luo, 2005). Inflammation results in altered nerve growth factor content of the bladder and morphologic changes in sensory and motor neurons innervating the bladder. Inhibition of nerve growth factor with a monoclonal antibody showed preliminary efficacy in amelioration of BPS symptoms in phase 2 studies (Evans et al, 2011). Neuroplasticity may be a possible explanation for the association of bladder inflammation with long-term symptoms and pain after inflammation has subsided (Dupont et al, 2001). Up to one third of BPS/IC patients may have an acute urinary tract infection that immediately precedes the onset

of chronic symptoms (Warren et al, 2008). However, abnormal differentiation in the urothelium with a loss of barrier function markers and altered differentiation markers may be independent and occur independently of inflammation (Hauser et al, 2008).

The role of inflammation may stem from inflammation originating in organs other than the bladder. Pain syndromes such as irritable bowel syndrome and BPS, which are associated with visceral hyperalgesia, are often comorbid with endometriosis and chronic pelvic pain. Tirlapur concluded that in women with chronic pelvic pain, the mean prevalence of BPS is 61%, the mean prevalence of endometriosis is 70%, and the two problems coexist in 48% of this population (Tirlapur et al, 2013a). One of the possible explanations for this phenomenon is viscerovisceral cross-sensitization, in which increased nociceptive input from an inflamed pelvic organ sensitizes neurons that receive convergent input to the same dorsal root ganglion from an unaffected visceral organ. Visceral sensory integration in the dorsal root ganglia has been demonstrated in a rodent model and may underlie the observed comorbidity of female pelvic pain syndromes (Li et al, 2008).

For many years the possibility that BPS may represent some type of autoimmune disorder has been considered. Narrowly defined, autoimmune diseases are clinical syndromes caused by the activation of T cells, B cells, or both, in the absence of an ongoing infection or other discernible cause (Davidson and Diamond, 2001). To establish a disease as autoimmune, three types of evidence can be marshaled: (1) direct evidence from transfer of pathogenic antibody or pathogenic T cells; (2) indirect evidence based on reproduction of the autoimmune disease in experimental animals; and (3) circumstantial evidence from clinical clues (Rose and Bona, 1993). Circumstantial evidence would include (1) association with other autoimmune diseases in the same individual or same family; (2) lymphocytic infiltration of a target organ; (3) statistical association with a particular major histocompatibility complex haplotype; and (4) favorable response to immunosuppression.

Circumstantial evidence by itself cannot define an autoimmune disease, and **at this point the case for autoimmunity in BPS/IC is far from clear**. Three different possibilities exist: (1) BPS is caused by a direct autoimmune attack on the bladder; (2) some of the autoimmune symptoms and pathology of BPS arise indirectly as a result of tissue destruction and inflammation from other causes; and (3) autoimmune phenomena in BPS patients are coincident and unrelated to the disease (Ochs, 1997).

Silk found bladder antibodies in 9 of 20 IC patients and none in 35 pathologic or normal control patients (Silk, 1970). Gordon found antibladder antibodies present in biopsy specimens from 6 of 8 IC patients and in 3 of 5 control patients (Gordon et al, 1973). No control patient demonstrated antibodies in the muscle, whereas 3 of 5 IC patients with muscle in the biopsy specimen did. Jokinen looked at sera from 33 IC patients and found 28 with an antinuclear antibody (ANA) titer of 1:10 or greater, but no bladder-specific antibodies were detected with immunofluorescence. There was poor correlation between ANA titers and symptom severity (Jokinen et al, 1972a). He noted that elevated antibody titers against cell nuclei and crude kidney homogenate decreased within 12 months after cystectomy in 3 IC patients (Jokinen et al, 1973). All of this provided hints that BPS/IC could fall into the autoimmune group of diseases.

Oravisto summarized the world literature on this idea in 1980, concluding that the chronic course of disease, the absence of infection, the pathologic findings, the occurrence of ANAs, and the reported responses to steroids at that time provided strong circumstantial evidence of autoimmunity (Oravisto, 1980). He discounted the paucity of activated lymphocytes, which speaks against an autoimmune process. Studies on autoantibodies in BPS/IC have shown that these mainly consist of ANAs (Jokinen et al, 1972a), similar to the autoantibody profiles in some systemic diseases such as SS, well known to be of autoimmune origin (Tan, 1989; Leppilähti et al, 2003). Mattila presented evidence of immune deposits in the bladder vascular walls in 33 of 47 BPS/IC patients (Mattila, 1982). Studying sera from 41 patients with IC, he concluded that the classical pathway activation of the complement

system was involved, supporting the possibility that a chronic local immunologic process was indeed occurring (Mattila et al, 1983). The autoantibodies tested were found to be directed against cytoskeletal intermediate filaments. As the autoantibodies have to gain access to intracellular structures to cause *in vivo* deposits, primary tissue injury of unknown cause has to be postulated (Mattila and Linder, 1984).

Anderson and colleagues studied 26 patients with BPS/IC and compared them with a control group of similar age and sex with other urologic complaints (Anderson et al, 1989). They performed a standard autoimmune profile and looked for specific antibodies to normal human bladder in the serum. Sixty-five percent of IC patients and 36% of controls demonstrated non-organ-specific antibodies; 40% of IC patients had ANAs; and 75% of IC patients and 40% of controls had antibladder antibodies present in the serum. There was no increase in immunoglobulin deposition in the bladder epithelium in IC patients versus controls. Although IC patients demonstrated a nonspecific increase in antibody formation, this was not significantly different from a similar group of other urologic patients. The lack of specificity indicates the immunologic findings are likely secondary to inflammation rather than a primary cause.

In a study looking for active immune cellular deposition in BPS/IC patients, no statistically significant difference between controls and IC patients was identified (Harrington et al, 1990). In contrast, the ulcerative BPS group had focal sheets of plasma cells, aggregates of T cells, B cell nodules, a decreased or normal helper-to-suppressor cell ratio, and suppressor cytotoxic cells in germinal centers. Flow cytometry analysis of peripheral blood lymphocyte subsets showed increased numbers of secretory Ig-positive B cells and activated lymphocytes in the non-Hunner group, and increased numbers of secretory Ig-positive cells and activated lymphocytes in the Hunner group. These results may suggest a partial role for an immune mechanism in IC. Gamper and colleagues found elevated urinary antibody concentrations in patients with Hunner lesions (Gamper et al, 2013). Erickson and coworkers have noted a major difference in inflammatory cell types as well as clinical features in BPS/IC patients with severe inflammation, suggesting two different patient groups with two different underlying pathophysiologies (Erickson et al, 1997a).

Hanno and colleagues found CD4 cell predominance in all layers of the bladder in BPS/IC patients (Hanno et al, 1990). Christmas (1994) reported increased numbers of CD4⁺ and CD8⁺ T cells in bladder biopsy specimens from patients with IC and bacterial cystitis as compared with controls. These T cells were present in the urothelium and submucosa but not in the detrusor. Control bladder tissue demonstrated only CD8 cells in the urothelium and both CD4⁺ and CD8⁺ cells in the submucosa. The number of plasma cells was significantly greater in IC patients than in normal controls and controls with bacterial cystitis.

MacDermott and colleagues found a normal distribution of peripheral blood lymphocytes in IC patients, a finding not supportive of an autoimmune mechanism in the disease (MacDermott et al, 1991b). The lamina propria showed a predominance of CD4 lymphocytes (helper T cells) over CD8 cells in both IC and other cystitis patients. The same pattern was seen in the epithelium of patients with bacterial or mechanical cystitis, but patients with IC had a predominance of CD8 lymphocytes in the urothelium—identical to controls. The findings suggest that the urothelium is not involved in the inflammatory reaction, as is the lamina propria, making the urothelium an unlikely source for the initiating factor.

Miller and coworkers investigated the function of peripheral blood lymphocytes from nonulcerative IC patients, testing the proliferative response and cytokine production of T cells to nonspecific mitogenic stimulation and the proliferative response of T cells to urine components (Miller et al, 1992). Proliferation and cytokine production after mitogen stimulation were the same for controls and BPS/IC patients. Moreover, no immunologic response to IC urine by autologous peripheral blood lymphocytes *in vitro* assays was observed. These findings cast doubt on theories suggesting that IC is an autoimmune disease.

Numerous inflammatory mediators have been studied with regard to their relation to BPS (Elgebal et al, 1992; Felsen et al, 1994; Lotz et al, 1994; Steinert et al, 1994; Zuraw et al, 1994). There is a significant elevation of cytokines in BPS/IC bladder tissue when compared with controls (Corcoran et al, 2013) and an increase in urinary nerve growth factor (Liu and Kuo, 2012). The overexpression of genes related to immune and inflammatory responses, including T helper type 1-related chemokines and cytokines such as CXCR3 binding chemokines, may produce potential biomarkers of the disease (Ogawa et al, 2010). Urine sediment may be a substrate for gene expression analysis (Blalock et al, 2012).

Patients with BPS/IC exhibit varying degrees of inflammation that can separate them into clusters (Tomaszewski et al, 2001; Green et al, 2004). Bladder inflammation in IC is categorized by elevated urinary interleukin-6 (Erickson et al, 1997a) and activation of the kallikrein-kinin system (Rosamilia et al, 1999b). The absence of urinary interleukin-1 β in IC argues against an immunologic or autoimmune cause of the disorder (Martins et al, 1994). Neurogenic inflammation may play a role in the cause, as long-term exposure of afferent nerve terminals to inflammatory mediators can alter ion channels and result in bladder hyperalgesia (Buffington and Wolfe, 1998; Yoshimura and de Groat, 1999). Substance P itself does not seem to be the single initiator of inflammation in the bladder, and its blockade does not protect the bladder in animal models from inflammatory responses (Luber-Narod et al, 1997). Urinary nitric oxide synthase (NOS) activity is known to be elevated in patients with urinary infection and is thought to play a role in the bladder's response to infection and in the inflammatory process that follows infection. The finding that urinary NOS activity is decreased in BPS/IC patients has puzzled researchers but could explain the reduction in functional bladder capacity associated with the disorder (Smith and Christmas, 1996; Foster et al, 1997). However, patients with Hunner lesions have high levels of nitric oxide in the bladder. The production of nitric oxide in this entity may occur in different tissue compartments, because there is strong immunoreactivity for both inducible nitric oxide synthase (iNOS) in the urothelium and within the inflammatory infiltrates in the lamina propria of these patients (Logadottir et al, 2013).

Urothelial cell activation in IC may result in aberrant immune responses and immune activation within the bladder wall (Liebert et al, 1993) that could relate to pathogenesis of the disease but might not reflect the initiating cause (Ochs et al, 1994). It has been proposed that inflammatory and/or immune responses in IC could be exacerbated by persistent activation of nuclear factor- κ B (NF- κ B) (Abdel-Mageed and Choniem, 1998; Abdel-Mageed, 2003). Angiogenic factors such as platelet-derived endothelial cell growth factor/thymidine phosphorylase and transforming growth factor- β may be involved in the inflammatory process to induce painful symptoms in patients with IC or bladder carcinoma (Ueda et al, 2002).

The exact role of autoimmunity in IC remains controversial (Ochs, 1997). Suplatast tosilate, an immunoregulator, has shown efficacy in a small, uncontrolled IC study in which improvements in symptoms and bladder capacity were correlated with changes in autoimmune parameters (Ueda et al, 2000). Although the immune system remains a target for therapy, no clear indication of a primary role for autoimmunity as the cause of IC has been observed (Liebert and Sant, 1997).

Mast Cell Involvement

Although mast cells are thought of primarily in the context of allergic disorders and certain acute inflammatory responses, these cells have also been implicated in biologic responses as diverse as angiogenesis and wound healing, bone remodeling, peptic ulcer disease, atherosclerosis, and reactions to neoplasms (Galli, 1993). Mast cells remain one of the most enigmatic cells in the body. They secrete significant amounts of numerous proinflammatory mediators that contribute to a number of chronic inflammatory conditions, including stress-induced intestinal ulceration, rheumatoid arthritis, scleroderma, and Crohn disease. They have been described even among the lowest order of animals, having been

KEY POINTS: AUTOIMMUNITY AND INFLAMMATION

- Neuroplasticity may be a possible explanation for the association of bladder inflammation with long-term symptoms and pain after inflammation has subsided.
- Abnormal differentiation in the urothelium with a loss of barrier markers and altered differentiation markers may be independent and may occur independently of inflammation.
- Visceral sensory integration may result in inflammation originating in organs other than the bladder causing symptoms identified with BPS.

discovered in the frog mesentery over 100 years ago. Their *raison d'être* may be the initiation and coordination of the host's inflammatory and immune responses against microbial pathogens (Abraham and Malaviya, 1997). They have been implicated in a range of neuroinflammatory diseases, especially those worsened by stress (Theoharides, 2004; Theoharides and Cochrane, 2004). These include multiple sclerosis, migraines, inflammatory arthritis, atopic dermatitis, coronary inflammation, irritable bowel syndrome, and BPS/IC. They may be activated through their Fc receptors by immunoglobulins other than IgE, as well as by anaphylatoxins, neuropeptides, and cytokines, to secrete mediators selectively without overt degranulation.

Mast cells have frequently been reported to be associated with IC, both as a pathogenetic mechanism and as a pathognomonic marker (Simmons, 1961; Bhone et al, 1962; Smith and Dehner, 1972; Larsen et al, 1982; Hofmeister et al, 1997). The association of bladder mastocytosis, IC, and irritable bowel syndrome (Pang et al, 1996) and chronic urticaria (Sant et al, 1997) is intriguing. Evidence of their importance is mounting, suggesting that they may serve as the final common pathway through which the symptomatic condition is expressed. Mast cells produce, among other compounds, histamine. Histamine release in tissue causes pain, hyperemia, and fibrosis, all notable features of IC.

Simmons was the first to suggest mast cells as a cause of IC (Simmons, 1961). Contribution of mast cells to the cellular infiltrate in IC (Fig. 14-7) has been shown to vary from about 20% in nonulcer IC patients to 65% in patients with ulceration (Sant et al, 1988; Enerback et al, 1989). Mast cells participate in allergic reactions (hypersensitivity type I) during which IgE antibody is synthesized in response to specific antigens. IgE binds to mast cell receptors, and antigen binds to the IgE, leading to degranulation (Lagunoff et al, 1983). Other triggers of mast cell secretion include acetylcholine, anaphylatoxins, cationic peptides such as substance

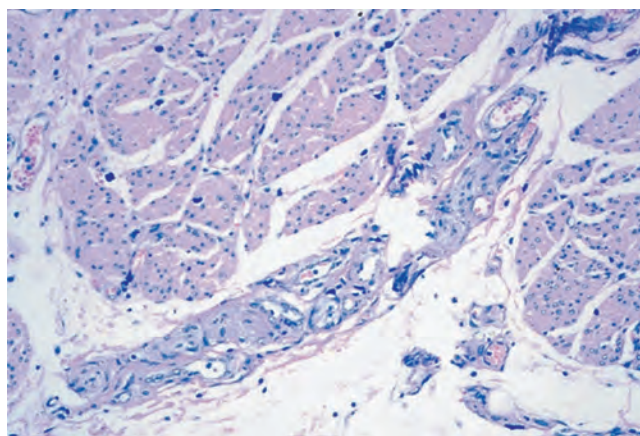


Figure 14-7. Giemsa stain shows detrusor mastocytosis and nerve hypertrophy in bladder pain syndrome (original magnification $\times 400$). (Courtesy John Tomaszewski, Hospital of the University of Pennsylvania, Department of Pathology).

P, chemicals, contrast, cytokines, opioids, antihistamines, exercise, hormones, viruses, and bacterial toxins (Sant and Theoharides, 1994). Mast cells promote infiltration of neutrophils, T and B lymphocytes, monocytes, and eosinophils. T lymphocytes secrete substances capable of activating mast cells, thus perpetuating the cycle of inflammation (Kaplan et al, 1985).

Since the presence of mast cells within the bladder wall was first recognized (Simmons and Bunce, 1958), numerous investigators have tried to determine whether there is an increase in the number of mast cells in the bladder of patients with IC, or differences in their location or functional state (Larsen et al, 1982; Kastrup et al, 1983; Fall et al, 1987; Feltis et al, 1987; Lynes et al, 1987; Christmas and Rode, 1991). An increase in urothelial mast cells appears to be part of the generalized inflammatory cell reaction regardless of cause, and not a specific feature of IC, whereas the presence of increased numbers of mast cells in the detrusor is more specific for IC. However, one study did report detrusor mastocytosis in 64% of IC patients and 80% of a control group with other urologic disease, with no statistically significant difference between the mean number of detrusor mast cells in the two groups (Hanno et al, 1990).

Aldenberg reported that mast cells are found predominantly in the detrusor muscle in patients with classic IC (Aldenberg et al, 1986), but there is also a secondary population of mast cells in the lamina propria and the bladder epithelium, with staining characteristics distinct from those in the detrusor. None of these epithelial mast cells were found in controls. These findings were interpreted to indicate a transepithelial migration of mast cells in patients with IC. This second population of mast cells does not appear to be involved in the nonulcer type of IC (Aldenberg et al, 1989). This mucosal population of mast cells can also differ from the mast cells found in deeper tissues in physiologic responses and release of secretory products (Sant, 1991). The “mucosal mast cells” are susceptible to aldehyde fixation and require special fixation and staining techniques for proper demonstration. Detrusor mast cells are not susceptible to fixation techniques. Recent studies have shown that although all human mast cells contain the proteinase tryptase, there is a population of mast cells that also contain the proteinase chymase. The mast cell expansion in IC involves both types (Yamada et al, 2000). Mast cell activation is far more pronounced in the ulcerative form, which in addition displays prominent inflammation, in contrast to nonulcer IC, in which it is sparse. Thus, the basic pathologic processes may differ (Peeker et al, 2000b). Because activated mast cells lose their histologically identifiable granules once degranulation has occurred, estimates of mast cell density using standard histologic techniques may underestimate mast cell numbers (Sant and Theoharides, 1994).

Electron microscopy has confirmed that mast cells in IC are more likely to be degranulated or activated than those found in other conditions (Larsen et al, 1982; Theoharides and Sant, 1991; Theoharides et al, 1995). In at least a subpopulation of IC patients, this may be explained by increased stimulation of mast cells by stem cell factor (Pang et al, 1998). A chronic exposure of detrusor muscle to histamine in IC patients is suggested by the finding that there is an impairment of the direct contractile response to histamine in detrusor muscle affected by IC in comparison with control detrusor, suggesting a receptor desensitization (Palea et al, 1993). The clinical relationship between an increased number of mast cells and symptoms of IC has not been definitively established. Some studies have found no correlation (Holm-Bentzen et al, 1987a; Lynes et al, 1987; Dondore et al, 1996). Although mast cell infiltration in intestinal segments used for augmentation has been associated with pain and failure of the procedure (Kisman et al, 1991), other researchers have shown that mast cell infiltration in intestine used in the urinary tract is the norm and not pathologic (MacDermott et al, 1990).

Many of the substances that have been shown to induce mast cell secretion are released from neurons that innervate the organ containing the mast cells (Christmas et al, 1990). The capsaicin-sensitive sensory neurons that innervate the bladder are thought to have a dual “sensory-efferent” function, in which an axon reflex-induced release of neuropeptides results in local inflammation

(Foreman, 1987; Barbanti et al, 1993). Hand (1949) reported an increase in the submucosal nerve density in IC, a phenomenon confirmed by Christmas and colleagues (1990), who showed an increase in nerve fiber proliferation in IC but not in patients with bacterial or lupus cystitis. Increased innervation by nerves releasing substances affecting mast cells could lead to increased mast cell secretion. Among these substances is acetylcholine. Mast cells can be stimulated by cholinergic agonists to secrete serotonin (Theoharides and Sant, 1991). Substance P-containing fibers have been found to be increased in bladders from IC patients and are found adjacent to mast cells (Pang et al, 1995b). In mice, mast cells modulate the inflammatory response of the bladder to substance P and to *Escherichia coli* lipopolysaccharide (Bjorling et al, 1999).

An increase in adrenergic but not cholinergic nerves in IC patients as compared with controls has been reported (Hohenfellner et al, 1992). Hohenfellner and colleagues also found increased numbers of neurons staining for vasoactive intestinal polypeptide and neuropeptide Y (NPY), both of which are associated with sympathetic nerves. Studies in rats have revealed that psychological stress can activate bladder mast cells via the action of sensory neuropeptides (Spanos et al, 1997; Alexacos et al, 1999). Diurnal cortisol variations have been associated with symptom levels in BPS/IC (Lutgendorf et al, 2002), and the mast cell may represent a pathway for stress to be reflected in bladder symptomatology.

Mast cells can alter their environment by regulating tissue gene expression (Saban et al, 2001). The finding of increased synthesis of urinary leukotriene E₄ in patients with IC and detrusor mastocytosis when compared with healthy controls suggests that cysteinyl-containing leukotrienes are involved in the inflammatory reaction observed in the urinary bladder of patients with IC and may be produced from tissue mast cells in the bladder wall, or macrophages (Bouchelouche et al, 2001a).

Could mast cell products be useful in diagnosing BPS/IC? They are not specific for BPS/IC and are increased in bladder carcinoma (Serel et al, 2004). Elevated histamine levels have been found in bladder biopsy specimens from IC patients (Kastrup et al, 1983; Lynes et al, 1987; Enerback et al, 1989) as well as from bladder washings (Lundeberg et al, 1993). Holm-Bentzen reported a significantly elevated urinary excretion of 1,4-methylimidazole acetic acid, the major metabolite of histamine (Holm-Bentzen et al, 1987c). Others have found no differences between IC and controls in random spot tests of urinary histamine (Yun et al, 1992). Levels were elevated after hydrodistention in IC patients but not in controls—a possible consequence of hydrodistention and resultant mast cell degranulation. El Mansoury found increased methylhistamine, a histamine metabolite, in spot and 24-hour urine samples from IC patients as compared with controls (El Mansoury et al, 1994). Although such an increase could still be interpreted as indicating a systemic rather than a bladder syndrome, subsequent findings of elevated mast cell tryptase in the urine of IC patients could come only from the bladder (Boucher et al, 1995). Erickson and colleagues reported that urine methylhistamine is not useful as an objective marker of response to bladder distention or as a predictor of response to distention or as a substitute for bladder biopsy to determine mast cell counts (Erickson et al, 2004).

The realization that mast cells are associated with the syndrome of BPS by no means diminishes the other multiple theories of causation. The poor clinical results with antihistamine therapy would argue against their being a primary factor. Their very presence could be related to injury from any of the proposed etiologic theories, and degranulation could likewise reflect a final common pathway resulting in pain and frequency from multiple causes. Rickard and Lagunoff proposed, based on results with mast cell granules and epithelial cells in tissue culture, that mast cells could contribute to failure of epithelialization of the bladder surface by two potential mechanisms after injury: (1) inhibition of epithelial cell replication, and (2) interference with epithelial cell spreading, thus resulting in the “leaky epithelium” found in some patients (Rickard and Lagunoff, 1995). Mast cell activation has been correlated significantly with the apoptotic cell number in BPS bladder tissue (Shie and Kuo, 2011). Mast cells may actually be the mediator through which

female hormones play a role, accounting for the 10:1 female-to-male preponderance of the disease (Vliagoftis et al, 1992; Pang et al, 1995a; Patra et al, 1995; Bjorling and Wang, 2001). Estradiol augments the secretion of mast cell histamine in response to substance P. It has been proposed that the symptoms of BPS/IC may depend on an imbalance between the relative number of estrogen receptors and progesterone receptors on bladder mast cells (Letourneau et al, 1996).

To summarize, much important IC research has centered on the mast cell. These cells are strategically localized in the urinary bladder close to blood vessels, lymphatics, nerves, and detrusor smooth muscle (Saban et al, 1997). **Studies to date strongly suggest that BPS is a syndrome with neural, immune, and endocrine components in which activated mast cells play a central, although not primary, pathogenetic role in many patients** (Elbadawi and Light, 1996; Filippou et al, 1999). Studies in a mast cell-deficient mouse model demonstrate that mast cells promote cystitis pain and bladder pathophysiology through the separable actions of histamine and tumor necrosis factor (TNF), respectively, suggesting that pain is independent of pathology and inflammation, and histamine receptors may represent direct therapeutic targets for pain in BPS/IC (Rudick et al, 2008).

KEY POINTS: MAST CELLS AND HISTAMINE

- Mast cells may be a pathognomonic marker for BPS and also represent a pathogenetic mechanism of the syndrome. They could serve as a final common pathway through which the symptomatic condition is expressed.
- Histamine, produced by mast cells, may cause pain, hyperemia, and fibrosis, all notable features of BPS.

Bladder Glycosaminoglycan Layer and Epithelial Permeability

Until the early 1970s, most investigators thought that the major barrier to free flow of urinary constituents was at the level of the epithelial cells. Tight junctions between urothelial cells, specialized “umbrella cells” lining the surface, and direct bactericidal activity of the vesical mucosa were thought capable of defense of the internal milieu from bacteria, molecules, and ions in the urine (Ratliff et al, 1994). Staehelin and colleagues proposed that lipid and other hydrophobically bonded materials were important in any barrier to permeability in the luminal membrane because permeants leaked through the interplaque regions if the particles alone limited transport (Staehelin et al, 1972). It has been shown that inflammation of the underlying muscle and lamina propria can disrupt the bladder permeability barrier by damaging tight junctions and apical membranes and causing sloughing of epithelial cells. Leakage of urinary constituents through the damaged epithelium may then exacerbate the inflammation in the underlying tissues (Lavelle et al, 1998, 2000).

It was Parsons who hypothesized and popularized the concept that IC in a subset of patients is the result of some defect in the epithelial permeability barrier of the bladder surface GAGs (Parsons and Hurst, 1990). The major classes of GAGs include hyaluronic acid, heparin sulfate, heparin, chondroitin 4-sulfate and chondroitin 6-sulfate, dermatan sulfate, and keratan sulfate. These carbohydrate chains, coupled to protein cores, produce a diverse class of macromolecules, the proteoglycans (Trelstad, 1985). GAGs exist as a continuous layer on the bladder urothelium (Dixon et al, 1986; Cornish et al, 1990). Except heparin, all the other types of GAGs have been found on the bladder surface (Ruoslahti, 1988). **The GAG layer functions as a permeability and antiadherence barrier.** When impaired, its functions can be duplicated by exogenous GAG (Hanno et al, 1978a, 1978b). In the absence of this protective layer in the urinary bladder, its susceptibility to infection

would increase, and the production of nitric oxide in the urothelial cells and of substance P in the intraepithelial afferent C-fiber terminals increases. Consequently, the permeability of both the urothelium and the blood vessels in the mucous membrane increases, and the blood flow slows as a result of vasodilatation (Hohlbrugger, 1999).

Parsons and Hurst reported a lower excretion of urinary uronic acid and GAGs in IC patients than in normal volunteers and hypothesized that a leaky transitional epithelium might be absorbing these substances to its surface (Parsons and Hurst, 1990). The data are interesting in that one might expect urinary GAG to increase with injury to the bladder and decrease with resolution (Uehling et al, 1988). Buzzega and coworkers noted a significant increase in total urinary hexosamines and in particular in glucosamine belonging to urinary heparin sulfate in BPS patients compared with controls (Buzzega et al, 2012). The San Diego group (Lilly and Parsons, 1990; Parsons et al, 1990;) went on to show experimentally that one can damage the GAG layer with protamine sulfate with resultant back-diffusion of urea through the bladder lumen, and that this urea loss can be prevented with a bladder instillation of exogenous GAG (heparin). By placing a solution of concentrated urea into the bladder of IC patients and measuring absorption versus controls, Parsons found support for his theory in patients with IC (Parsons et al, 1991). The rationale of the epithelial permeability school has been nicely summarized in four publications (Parsons, 1993, 1994; Hurst et al, 1997; Hohlbrugger and Riedl, 2000) and provides a comprehensive, if somewhat imperfect, theory of the disorder.

Support for an epithelial abnormality from a different perspective has come from Bushman, who found aneuploid DNA profiles on barbotage specimens from IC patients that may signal an underlying abnormality of the epithelial cell population in some patients with IC (Bushman et al, 1994). Wilson and colleagues identified a loss of type IV collagen in the urothelial basement membrane in 5 of 11 IC patients (Wilson et al, 1995). Hurst's group studied bladder biopsy specimens of IC patients and controls and concluded that there is a deficit of bladder luminal and basal proteoglycans associated with the disorder. The basal abnormality may reflect an altered urothelial differentiation program (Hurst et al, 1996). In a later study, IC bladder biopsy specimens showed abnormalities in 24 of 27 patients when examined by immunohistochemical assessment of E-cadherin, ZO-1, uroplakin, and chondroitin sulfate (Slobodov et al, 2004). Erickson and coworkers measured a glycoprotein (epitactin) in the urine of IC patients and found a decrease compared with a control population, although a significant overlap was detected (Erickson et al, 1996). Buffington and Woodworth gave 6 IC patients and 6 controls oral fluorescein dye. IC patients had higher levels of fluorescein in their plasma and lower urinary excretion of the dye, suggesting altered membrane permeability and increased fluorescein reabsorption in the bladder wall of IC patients (Buffington and Woodworth, 1997). Erickson and colleagues compared urinary levels of hyaluronic acid in IC patients and controls, reporting higher urinary hyaluronic acid in the patient group, possibly accounted for by leakage of this GAG across the epithelium (Erickson et al, 1998).

In FIC, the only naturally occurring animal model of the disorder, the urothelium has been shown to have decreased transepithelial resistance and increased water and urea permeability compared with controls in response to hydrodistention (Lavelle et al, 2000). This indicates that barrier function is compromised, which could lead to the sensitization of sensory nerves by irritants from urine crossing into the muscle layer. Bladder strip studies have shown that FIC bladders have significantly more spontaneous Ca^{2+} transients in the mucosal layer than control bladders. Coupled with increased sensitivity of muscarinic receptors in the mucosal layer, these bladders may manifest enhanced smooth muscle spontaneous contractions. This finding could play a contribution in the symptoms of BPS/IC (Ikeda et al, 2009). In fact, human cell culture studies comparing BPS/IC and normal bladder urothelial cells have shown greater sensitivity of IC bladder urothelial cells to carbachol, suggesting that BPS/IC pathobiology may also include alterations in

muscarinic signaling (Gupta et al, 2009). Neuhaus and colleagues have shown significantly upregulated M₂ (muscarinic), P2X₁ and P2X₂ (purinergic), and H₁ and H₂ (histaminergic) receptors in the tissue of BPS patients (Neuhaus et al, 2011).

Further data for an abnormal surface mucin came from Moskowitz and colleagues, who studied biopsy specimens from 23 IC patients with regard to the presence of a glycoprotein component of the surface mucin referred to as GP1 and compared the results with 11 normal controls. Qualitative GP1 changes in a majority of IC patients were identified. GP1 reactivity was noted in all controls but was absent in 35% of IC patients and diminished in 61% (Moskowitz et al, 1994). This study may provide evidence of an abnormal bladder urothelium, but the effects of bladder distention in the IC group are unknown and may have contributed to the results. There were no pathologic controls used, and no attempt was made to correlate GP1 reactivity with IC symptoms (Messing, 1994). Castration in female rabbits is associated with bladder mucosal changes resulting in increased mucosal permeability (Parekh et al, 2004). Birder and colleagues have shown that FIC results in increased baseline production of nitric oxide as a result of iNOS (Birder et al, 2005). These changes in transmitter release may have a role in altering mucosal barrier properties.

VEGF plays a key role in bladder inflammation and is closely associated with the vascular alterations observed in patients with BPS/IC. VEGF and coreceptors (neuropilins [NRPs]) are strongly expressed in human bladder urothelium. NRP-2 and VEGFR-1 are significantly downregulated in IC when compared with control subjects (Saban et al, 2008). GAG modification of NRPs plays a critical role in modulating VEGF/NRP signaling (Shintani et al, 2006), suggesting another possible mechanism whereby a GAG deficiency could act, by interfering with the functionality of this signaling system.

Some have cited the “potassium sensitivity test” as providing strong evidence for a population with mucosal leak (Parsons et al, 1994b). Parsons placed water or 0.4-M potassium chloride (KCl) intravesically into normal volunteers and IC patients. Water did not provoke pain in either group, but KCl provoked the symptom in 4.5% of normal subjects and 70% of IC patients. Symptomatic responses were reduced in patients on heparinoid therapy. Similar findings occur in patients with radiation cystitis (100%) (Parsons et al, 1994b), urinary infection (100%) (Parsons et al, 1998), detrusor instability (25%) (Parsons et al, 1998), and “urethral syndrome” (55%) (Parsons et al, 2001b) and in more than 80% of women with endometriosis, vulvodynia, and pelvic pain (Parsons et al, 2001a, 2002b). Up to 33% of unselected Turkish women may test positive (Sahinkanat et al, 2008). Eighty-four percent of men with prostatitis also have a positive test result (Parsons and Albo, 2002). The poor specificity of the potassium test suggests that it does not provide unequivocal evidence of a permeability dysfunction. Because it is known that the normal bladder epithelium can never be absolutely tight and that there is always some leak, however small (Hohlbrugger and Sant, 1997), it is conceivable that the findings of pain with KCl are related to a hypersensitivity of the sensory nerves in this condition rather than to pathologic epithelial permeability, at least in some patients. In fact, KCl administered intravesically to cats with FIC seems to *inhibit* afferent firing of peripheral A δ fibers. Heightened sensitivity of afferent nerve fibers can explain KCl results without necessarily evoking increased permeability (Lutgendorf and Kreder, 2005; Roppolo et al, 2005). Intravesical administration of KCl has since been proposed as a diagnostic test for IC (Parsons et al, 1998) (see later).

How central abnormal epithelial permeability is to IC is, however, by no means clear. Tamm-Horsfall protein (THP), a high-molecular-weight glycoprotein synthesized exclusively by the ascending loop of Henle and the distal tubule of the kidney, has been studied as a potential marker of urothelial permeability. Fowler provided graphic data that the urothelium might be leaky in IC. With immunohistochemical techniques, his group assayed the bladder biopsy specimens of 14 IC patients and 10 normal controls for intraurothelial THP to assess indirectly the *in vivo* permeability of the urothelium. Eight pathologic controls were also assessed. Ten of 14 IC patients

versus 1 of 18 controls demonstrated intraurothelial THP (Fowler et al, 1988). Serum THP autoantibody is higher in BPS/IC patients versus controls (Neal et al, 1991). It is known that excretion rates of THP vary widely, even in repeat samples taken from the same individual (Reinhart et al, 1990). Subsequent studies in IC have failed to show differences in the presence of intraurothelial THP in the IC population versus controls, and in antibody reactivity to THP (Stone et al, 1992; Stein et al, 1993). Parsons reported that the THP protein is qualitatively different in patients with IC than in controls, even if the urinary concentration of the protein is the same (Parsons et al, 2007, 2011; Argade et al, 2013). Bade and coworkers failed to find THP in bladder tissue from 10 IC patients (Bade et al, 1996). Others have suggested that when THP is seen in bladder tissue, it is an incidental finding of no clinical significance. The finding of intraurothelial THP has not been shown to be a harbinger of IC or any other bladder disorder (Truong et al, 1994).

Finally, we must look at a body of literature that has failed to find GAG abnormality or hyperpermeability. Ultrastructural, biochemical, and functional studies of bladder GAG have not supported this theory (Collan et al, 1976; Dixon et al, 1986; Johansson and Fall, 1990; Ruggieri et al, 1991). Nickel's group reported on use of sophisticated electron microscopy with a specific antimucus, antisera stabilization technique to study the ultrastructural morphologic appearance of the GAG layer (Nickel et al, 1993). No significant difference in the morphologic appearance of the mucus or GAG layer was noted in IC versus controls. Urinary chondroitin sulfates, heparan sulfate, and total sulfated GAGs normalized to creatinine are not altered in IC (Erickson et al, 1997b). Although an increased ratio of total GAGs to sulfated GAGs in IC may indicate an altered GAG layer, whether it reflects a cause or is a result of the primary pathologic process(s) is unknown (Wei et al, 2000). That leaves one to postulate an as-yet-unknown functional abnormality, rather than GAG deficiency, to account for any increase in permeability.

Chelsky and coworkers measured bladder permeability in IC using direct measurement by transvesical absorption of technetium-99m diethylenetriaminepentaacetic acid (DTPA). Although some IC patients had a more permeable bladder than others, the same was true for normal volunteers. Increased permeability in the IC group could not be demonstrated. However, 3 IC patients had marked absorption of DTPA and may represent a subpopulation of patients with increased epithelial permeability (Chelsky et al, 1994). Intravesical instillation of 10% and 20% ethanol in rabbits was reported to be a reliable quantitative measure of bladder hyperpermeability by the San Diego group (Monga et al, 2001), and subsequently failed to demonstrate bladder permeability in humans with IC (Gordon et al, 2003).

Overall, it does seem that there is a population of BPS/IC patients with increased epithelial permeability, but the issue is far from closed. Increased mucosal permeability is nonspecific and a consequence of bladder inflammation, and also occurs with cyclophosphamide-induced bladder injury, bacterial infection, and cystitis following intravesical challenge with antigen after sensitization (Engelmann et al, 1982; Kim et al, 1992). It may also be a consequence of aging itself (Jacob et al, 1978). Whether this represents a primary cause of IC or merely reflects the result of an as-yet-unidentified source of inflammation is unclear. Treatments that tend to damage GAG, including transurethral resection and laser of ulcerated areas, bladder distention, silver nitrate administration, Clorapactin administration, and administration of the organic solvent dimethyl sulfoxide (DMSO) have all been used with varying results to treat IC.

One does not need increased permeability of the mucosa as a foundation for the many potential causes or contributing factors to BPS/IC. Enhanced adenosine triphosphate (ATP) release from the urothelium of patients with BPS/IC has been described (Kumar et al, 2007). This non-neuronal ATP may act as a sensory neurotransmitter. Increased purinergic activity may thus lead to a condition in which the bladder is oversensitive to distention.

Increased permeability and epithelial dysfunction must be only a part of the story.

KEY POINTS: EPITHELIAL PERMEABILITY

- There is a population of BPS patients with increased epithelial permeability.
- Increased mucosal permeability is nonspecific and a consequence of bladder inflammation. It also occurs with cyclophosphamide-induced bladder injury, bacterial infection, and cystitis following intravesical challenge with antigen after sensitization.
- Whether this represents a primary cause of BPS or merely reflects the result of an as-yet-unidentified source of inflammation is unclear.

Inhibition of Uroepithelial Cell Proliferation: Antiproliferative Factor

The finding that cells from the bladder lining of normal controls grow significantly more rapidly in culture than cells from BPS/IC patients (Keay et al, 1996) led Keay and associates at the University of Maryland to the discovery of an APF produced by the urothelium of IC patients. Normal bladder cells were cultured in the presence of urine from patients with IC, asymptomatic controls, bacterial cystitis, and vulvovaginitis. Only urine from IC patients inhibited bladder cell proliferation (Keay et al, 1998b). The presence of APF was found to be a sensitive and specific biomarker for IC patients who met NIDDK criteria (Keay et al, 2001a) (Table 14-2). It was found in bladder urine but not in renal pelvic urine of IC patients, indicating production by the bladder urothelial cells (Keay et al, 1999). Subsequent studies indicated that APF is associated with decreased production of heparin-binding epidermal growth factor-like growth factor (HB-EGF) (Keay et al, 2000, 2003). APF activity was related to increased production of epidermal growth factor (EGF), insulin-like growth factor-1, and insulin-like growth factor binding protein-3 by the bladder cells from IC patients but not by the cells from healthy bladders. Studies of IC patients and asymptomatic controls showed urine levels of APF, HB-EGF, and EGF to reliably separate IC from controls (Erickson et al, 2002; Keay et al, 2001b).

TABLE 14-2 Prevalence of Urine Antiproliferative Factor Activity in Interstitial Cystitis Patients and Control Groups

GROUPS	NO. OF PATIENTS POSITIVE/TOTAL	PERCENT POSITIVE
PATIENTS		
Interstitial cystitis	206/219	94
CONTROLS		
Asymptomatic	10/113	9
Overactive bladder	2/32	6
Bacterial cystitis	7/58	12
Microscopic hematuria	2/19	11
Stress incontinence	1/10	10
Neurogenic bladder	0/11	0
Benign prostatic hypertrophy	1/14	7
Nonbacterial prostatitis	1/16	6
Vulvovaginitis	0/12	0
Miscellaneous	1/16	6

From Keay SK, Zhang CO, Shoenfelt J, et al. Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. *Urology* 2001;57:9.

APF levels in the urine were found to discriminate between men with IC versus those with CPPS or nonbacterial prostatitis (Keay et al, 2004a). APF activity dropped significantly in IC patients within 2 hours after hydrodistention (Chai et al, 2000b) and after 5 days of sacral neuromodulation (Chai et al, 2000a). Cell culture studies showed that APF actually caused a decrease in HB-EGF and an increase in EGF, mirroring the differences in urine levels of these growth factors between IC patients and controls and suggesting that APF is the primary abnormality (Keay et al, 2003a).

Whereas APF may prove to be a useful marker for BPS/IC, it may also unlock the cause of the syndrome. It has been hypothesized by Keay and colleagues that BPS/IC may result from an inhibition of bladder epithelial cell proliferation caused by APF, which is mediated by its regulation of growth factor production from bladder cells (Keay et al, 2003b). Conceivably, any of a variety of injuries to the bladder (infection, trauma, and overdistention) in a susceptible individual may result in BPS/IC if APF is present and suppresses production of HB-EGF (Keay and Warren, 1998). Theoretically, if production of APF could be “turned off” by genetic techniques or its effects were nullified by an APF antagonist (Keay et al, 2011) or exogenous HB-EGF, the clinical syndrome might be prevented (Yang et al, 2012a). HB-EGF functionally antagonizes APF activity via a mitogen-activated protein kinase pathway activation (Kim et al, 2009a).

APF has been purified (Fig. 14-8) and proved to be a frizzled 8 protein that belongs to a newly discovered family of proteins that seem to be important in the development of nerve tissues, skin, and the lining of organs (Keay et al, 2004b). The frizzled family of receptors is critically involved in embryogenesis, and there is substantial evidence that members of this family also regulate tissue homeostasis in many different organs in the adult (Schulte and Bryja, 2007).

It appears that the cell cycle regulatory protein p53 is an important mediator of APF-induced effects on bladder epithelial cells (Kim et al, 2007). APF treatment suppresses cell proliferation by cell cycle arrest of human bladder urothelial cells. Evidence shows that p53 levels increase significantly after APF stimulation; p53 down-regulation enhances the suppressive effect of APF on cell growth; and overexpression of p53 induces cell cycle arrest in the absence of APF. APF upregulates cellular p53 levels via functional attenuation of the USP2a-MDM2 pathway, resulting in p53 accumulation and growth arrest (Kim et al, 2012). It is possible that targeting of p53 could be a means of abrogating the pathologic effects of urinary APF and lead to new options for clinical therapy.

Studies are ongoing to confirm the research by Keay and colleagues and expand on its significance in diagnosis and development of a rational treatment approach (Rashid et al, 2004). The development of animal models with specific signaling abnormalities found in BPS/IC epithelial, endothelial, smooth muscle, neuronal, or immune cells to determine whether these animals develop a disease similar to the human disorder would be an extremely useful and potentially very productive pathway to learning more about potential therapeutic pathways (Keay, 2008).

KEY POINTS: ANTIPROLIFERATIVE FACTOR

- The frizzled 8 protein termed *antiproliferative factor* (APF) has been proposed as a marker to identify patients with BPS/IC.
- It is secreted by bladder epithelial cells of BPS patients and inhibits bladder epithelial cell proliferation through mediation of growth factor production. Thus, it could be a proximal cause of the syndrome in many patients.

Neurobiology

Nonadrenergic noncholinergic mechanisms play significant roles in mediating direct functional effects as well as indirect effects by affecting inflammation (Vesela et al, 2012).

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MEWGYLLEVT SLLAALALLQ RSSGAAAASA KELACQEITV PLCKGIGYNY TYMPNQFHD
TQDEAGLEVH QFWPLVEIQC SPDLKFFLCS MYTPICLEDY KKPLPPCRSV CERAKAGCAP
LMRQYGFAPW DRMRCDRLPE QGNPDTLCMD YNRTDLTTAA PSPRRRLPPP PPGEQPPSGS
GHGRPPGARP PHRGGGRGGG GGDAAPPAR GGGGGGKARP PGGAAPCEP
GCQCRAPMVS VSSERHPLYN RVKTGQIANC ALPCHNPFFS QDERAFTVFW IGLWSVLCFV
STFATVSTFL IDMERFKYPE RPIIFLSACY LFVSVGYLVR LVAGHEKVAC SGGAPGAGGA
GGAGGAAAGA GAAGAGGP GGRGEYELG AVEQHVRYET TGPALCTTVF LLVYFFGMAS
SIWWVILSLT WFLAAGMKWG NEAIGYSQY FHAAWLVPV VKSI AVLALS SVDGDPVAGI
CYVGNQSLDN LRGFVLAPLV IYLFITMFL LAGFVSLFRI RSVIKQDGP TKTHKLEKLM
IRLGLFTVLY TVPAAVVVAC LFYEQHNRP R WEATHNCPCL RDLQPDQARR PDYAVFMLKY
FMCLVVGITS GVWVWSGKTL ESWRSLCTRC CWASKGA AVG GGAGATAAGG
GGGPGGGGGG GPGGGGGPGG GGGSLYSDVS TGLTWRS GTA SSVSYPKQMP LSQV

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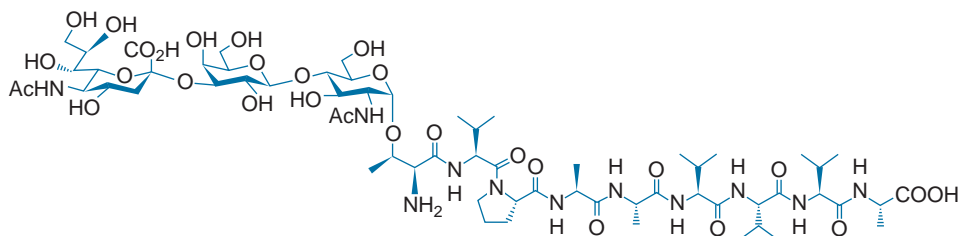


Figure 14-8. Composition and structure of antiproliferative factor (APF). (From Keay SK, Szekely Z, Conrads TP, et al. An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. *Proc Natl Acad Sci U S A* 2004;101:11803–8.)

Neuropeptides present in primary afferents and the dorsal horn of the spinal cord have an important role in the mediation of nociceptive input under normal conditions. Under pathologic conditions, such as during chronic inflammation or after peripheral nerve injury, the production of peptides and peptide receptors is dramatically altered, leading to a number of functional consequences (Wiesenfeld-Hallin and Xu, 2001). Inflammatory painful stimuli, especially if repeated, can chronically alter innervation, central pain-processing mechanisms, and tissue responses (Steers et al, 1997). It has been known for some time that the sensory nervous system can generate some of the manifestations of inflammation (Foreman, 1987; Dimitriadou et al, 1991, 1992). Activation of capsaicin-sensitive afferent neurons locally and centrally may be involved in stress-related pathologic changes in the rat bladder (Ercan et al, 2001). Activation of sensory nerves, specifically pain fibers, is known to trigger neurogenic inflammation through release of neuropeptides such as substance P, neurokinin A, and calcitonin gene-related protein, and subsequent increase in vascular permeability, with leukocyte adhesion and tissue edema. The neuropeptide mediators have been shown to also cause degranulation of mast cells with release of additional potent mediators of inflammation and to lead to injury and increased permeability of epithelial surfaces (Elbadawi and Light, 1996). An increase in nerve fibers within the suburothelium and detrusor muscle in ulcerative IC has been noted (Lundeberg et al, 1993). A correlation was found between the number of nerve fibers and numbers of mast cells as well as between the number of nerve fibers and the amount of histamine. Consolidating the leaky urothelium theory and mast cell activation, neurogenic inflammation is an attractive proposal for the cause and can readily accommodate infectious, immunologic, and autoimmunologic mechanisms as factors (Elbadawi and Light, 1996).

Harrison proposed that small-diameter sensory nerves in the bladder wall may have a role in the transmission of the sensation of pain and in the triggering of inflammatory reactions rather than forming the afferent limb of the micturition reflex (Harrison et al, 1990). Abelli demonstrated in the rat urethra that mechanical irritation alone can cause neuropeptide release from peripheral capsaicin-sensitive primary afferent neurons, resulting in neurogenic inflammation (Abelli et al, 1991). Extracellular ATP can act through the purinergic receptor subtype P2X₃ to transmit a pain signal to the central nervous system. These subunits expressed by

cultured IC bladder urothelial cells are upregulated during in vitro stretch and may phenotypically mimic sensory neurons (Sun and Chai, 2004). Purinergic receptor antagonists that are orally bioavailable may provide an avenue for a potential therapeutic strategy (Burnstock, 2012).

Several pieces of additional information support a theory of neurogenic inflammation. Levels of nerve growth factor are elevated in bladder biopsy specimens from IC patients (Lowe et al, 1997), providing another potential therapeutic target (Ochodnick et al, 2011). Studies in rats using pseudorabies virus clearly show that bladder inflammation can be induced from a somatic structure through a neural mechanism and that central nervous system dysfunction can bring about a peripheral inflammation (Doggweiler et al, 1998). Pelvic nerve stimulation in the rat increases urothelial permeability, which is antagonized by capsaicin, indicating both an efferent effect of afferent nerves and afferent mediated neuroepithelial interaction (Lavelle et al, 1999). Ca²⁺/calmodulin-dependent protein kinase II has been implicated in the neurogenic cystitis pelvic pain induced in a mouse model with pseudorabies virus infection (Yang et al, 2012b).

Numerous studies indicate increased sympathetic activity in IC. Hohenfellner suggested that IC is associated with increased sympathetic outflow into the bladder and altered metabolism of vasoactive intestinal polypeptide and NPY (Hohenfellner et al, 1992). NPY inhibits bladder afferents and therefore may be involved in autonomic disturbances affecting the bladder. Elevation of urinary catecholamines in IC patients and plasma catecholamines in cats with FIC has been observed (Stein et al, 1999; Buffington and Pacak, 2001), as has an increased density and number of nerve fibers immunoreactive for tyrosine hydroxylase in IC patients (Peeker et al, 2000a). Whether these changes reflect a cause of IC or are merely the result of long-standing intense pain and a severely pathological voiding pattern is unknown.

Galloway proposed that the changes in IC may be explained by an increase in sympathetic discharge, analogous to that seen in reflex sympathetic dystrophy (RSD) of limbs (Galloway et al, 1991). The pathology in RSD is the development of abnormal synaptic activity between sensory afferent and sympathetic efferent neurons. Nerve cells in the spinal cord become hypersensitive to sensory input, and this sustains abnormal sympathetic outflow and corresponding vasomotor dysregulation. The excess sympathetic outflow leads to constriction of blood vessels and tissue ischemia,

setting up further sensory changes and perpetuating the cycle. In RSD, there is usually a trigger event leading to these changes. With the acute phase of RSD, regional signs of inflammation are evident in the affected extremity. One school of thought believes an inflammatory response to an injury initiates RSD. Increased capillary permeability is a direct result (Goris and Jan, 1998). Perhaps a urinary infection could trigger such a pathologic cycle in some IC patients?

Herbst produced bladder lesions in a dog resembling the ulceration of IC by ligating the blood vessels to the posterior bladder wall and infecting the area with *Streptococcus viridans* (Herbst et al, 1937). Studies using laser Doppler flowmetry have shown that when the bladder is distended under anesthesia, blood flow increases in control patients to a statistically significant degree as compared with IC patients (Irwin and Galloway, 1993; Pontari et al, 1999). Another study has purported to show that topical heparin therapy can normalize urothelial permeability and vesical blood flow in IC (Hohlbrugger et al, 1998). Decreased microvascular density has been described in the suburothelium but not in the deeper mucosa in bladder biopsy specimens from women with IC (Rosamilia et al, 1999a). Hyperbaric oxygen has been suggested to have a limited effectiveness for the treatment of BPS/IC (van Ophoven et al, 2004b, 2006; Tanaka et al, 2007; Loran et al, 2011; Tanaka et al, 2011; Gallego-Vilar et al, 2013) as well as radiation-induced cystitis (Weiss and Neville, 1989). The mechanism of action has been postulated to be related to the overexpression of hypoxia-inducible factor-1 and VEGF in BPS/IC bladders (Lee and Lee, 2011).

If lumbar sympathetic blocks can decrease the pain of IC, a role of the sympathetic nervous system in IC pathogenesis is a reasonable supposition (Irwin et al, 1993; Doi et al, 2001). Buffington has demonstrated an increase in sympathetic activity in cats with FIC (Buffington and Pacak, 2001; Buffington et al, 2002). Similar findings have been reported in a small study of IC patients (Dimitrakov et al, 2001), and sympathetic activity may be an underlying common denominator in many disorders associated with PBS/IC (Buffington, 2004).

Nevertheless, no studies performed to date indicate that any case of IC is related to the syndrome of RSD (chronic regional pain syndrome) (Ratliff et al, 1994). No single test can be used to exclude sympathetically maintained pain, and there are no clear symptoms that predict sympathetically mediated pain (Baron, 2000). In the animal model, bladder ischemia is associated with DO or impaired detrusor contraction, not sensory urgency (Azadzi et al, 1999). Patients with RSD who have voiding symptoms rarely have a picture that would be confused with IC (Chancellor et al, 1996).

Before leaving the neurogenic causative theory, it is important to note that the nervous system itself almost surely contributes to the chronic nature of this pain syndrome, regardless of initiating cause (Vrinten et al, 2001). Repetitious stimulation of a peripheral nerve at sufficient intensity to activate C fibers results in a progressive buildup of the magnitude of the electrical response recorded in the second-order dorsal horn neurons. This "windup" phenomenon is central to the concept of chronic pain. Biochemically it is dependent on activation of *N*-methyl-D-aspartate (NMDA) receptors in the spinal cord (Bennett, 1999). With persistent NMDA receptor activation, spinal cord cells undergo trophic changes, and the pain resulting from subsequent stimulation becomes exaggerated and prolonged. This "pain memory" in the spinal cord may be what causes IC patients to become refractory to different therapies (Brookoff and Sant, 1997). NMDA-receptor-driven formation of new connections in the spinal cord may account for the expansion of the pain field.

Upregulation of the CNS and augmented sensory processing have been referred to as non-nociceptive pain (NNP) (Bennett, 1999). The four characteristic features of NNP would seem to apply very well to the clinical syndrome of IC (Box 14-4). Chronic neuropathic pain may continue after the resolution of tissue damage and persist on the basis of a maladaptive mechanism (Urban et al, 2002).

BOX 14-4 Non-Nociceptive Pain: Characteristic Clinical Features

1. The description of the pain seems inappropriate in comparison with the degree of tissue pathology, or no tissue pathology may be discernible.
2. Noxious stimuli result in a pain experience that is greater and more unpleasant than would normally be expected (hyperalgesia).
3. Normally non-noxious stimuli may result in pain (allodynia).
4. The extent of the pain boundary is greater than would be expected on the basis of the site of the original tissue pathology.

From Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. *Mayo Clin Proc* 1999;74:385–98.

Burnstock's observation that ATP has a role in mechanosensory transduction by the epithelial lining of hollow viscus organs such as bladder (Burnstock, 1999) has been followed up by Sun and colleagues. Stretched epithelial cells lining hollow organs release ATP, which acts on purinergic nociceptive receptors on subepithelial sensory nerve terminals. ATP was significantly elevated in the urine of PBS/IC patients, and the stretch-activated release of ATP was augmented in IC urothelium (Sun et al, 2001).

Neurogenic inflammation may be the cause of some cases of BPS or may be the result of other initiating causative events. It is not incompatible with the central role of the mast cell, or with the leaky epithelium theory. It conceivably could result in the appearance of autoimmune phenomena or result from an episode of infection. The central nervous system may also be implicated in dysregulation of the pelvic floor resulting in chronic pelvic pain and contributing to IC (Zermann et al, 1999), and perhaps in the rare cases of IC that chronologically seem to relate to trauma or pelvic surgery (Zermann et al, 1998). It is an etiologic theory that provides fertile ground for new treatment possibilities.

KEY POINTS: NEUROGENIC INFLAMMATION

- Numerous studies indicate increased sympathetic activity in BPS/IC. Activation of sensory pain fibers is known to trigger neurogenic inflammation through release of neuropeptides such as substance P, neurokinin A, and calcitonin gene-related protein.
- Neurogenic inflammation may be the cause of some cases of BPS/IC. Chronic neuropathic pain may continue after the resolution of tissue damage and persist on the basis of a maladaptive mechanism.

Pelvic Organ Cross-Sensitization

Clinical observations of viscerovisceral referred pain in patients with gastrointestinal and genitourinary disorders suggest an overlap of neurohumoral mechanisms underlying both bowel and urinary bladder dysfunctions. Close proximity of visceral organs within the abdominal cavity complicates identification of the exact source of chronic pelvic pain, where it originates, and how it relocates with time. Cross-sensitization among pelvic structures may contribute to chronic pelvic pain of unknown cause and involves convergent neural pathways of noxious stimulus transmission from two or more organs. **Inflammation, nerve injury, ischemia, peripheral hyperalgesia, metabolic disorders, and other pathologic conditions can dramatically alter the function of directly affected**

pelvic structures as well as organs located next to a damaged domain (Malykhina, 2007). It has been demonstrated in a rat model that acute colitis can sensitize lumbosacral spinal neurons receiving input from the urinary bladder (Qin et al, 2008). Acute colitis and acute cystitis in the rat model can each cross-sensitize the bladder and colon, respectively (Pezzone et al, 2005).

It is thought that chronic widespread pain in chronic fatigue syndrome and fibromyalgia (disorders associated with BPS/IC in many patients) can be a consequence of central sensitization. Central sensitization is an increased central neuronal responsiveness and causes hyperalgesia, allodynia, and referred pain and hyperalgesia across multiple spinal segments, leading to chronic widespread pain. Triggers include windup or temporal summation, dysregulated descending inhibitory pathways, and upregulated facilitatory modulation. Windup or temporal summation is the result of repetitive noxious stimuli, leading to an increase in electrical discharges in the dorsal horn. Inhibitory modulation can be impaired by abnormalities in the central nervous system, and the facilitatory pain pathways can be stimulated by certain behavioral and cognitive factors (Meeus and Nijs, 2007).

It is possible that a combination of central sensitization and pelvic cross-talk may account for the association of BPS/IC with bowel symptoms in some patients, and the use of dietary alterations for managing the severity of BPS symptoms. Relatively minor gut stimuli that otherwise cause no symptoms could exacerbate established, bladder-driven pelvic pain, because even slight increases of inputs from a second site such as the gut might lead to a sum of inputs that is considerably elevated above a threshold necessary to induce pain (Rudick et al, 2007; Klumpp and Rudick, 2008). Central pain amplification might also account for the increased startle responses described in female BPS/IC patients in the context of a threat of abdominal pain (Twiss et al, 2009).

KEY POINTS: SENSITIZATION OF NEURAL PATHWAYS

- Cross-sensitization among pelvic structures may contribute to CPPS.
- Neural pathways from two or more organs, one or both of which are carrying noxious stimuli transmissions, may converge. Theoretically, this could lead to alteration of the function of not only the directly affected pelvic structures, but organs located nearby as well.

Nitric Oxide Metabolism

Regulation of urinary NOS activity has been proposed to be of importance for immunologic responses in BPS. The oral administration of L-arginine, the substrate for nitric oxide production (Moncada and Higgs, 1993), has been shown to increase nitric oxide-related enzymes and metabolites in the urine of patients with BPS (Smith et al, 1996). It has been reported that differences in nitric oxide evaporation between ulcerative and nonulcerative BPS allows for subtyping of cases meeting the NIDDK criteria. This could potentially replace cystoscopy as a tool for identifying ulcerative BPS/IC (Logadottir et al, 2004). Increased levels of endogenously formed nitric oxide correspond to increased iNOS in mRNA expression and protein levels in BPS patients. iNOS has been found to be localized to the urothelium and has also been found in macrophages in the bladder mucosa. Whether high levels of endogenously formed nitric oxide are a part of the pathogenesis in BPS/IC and whether it has a protective or damaging role remains to be elucidated (Koskela et al, 2008).

Urine Abnormalities

In general, current theories of pathogenesis involve access of a component of urine to the interstices of the bladder wall, resulting in an inflammatory response induced by toxic, allergic, or

immunologic means. The substance in the urine may be a naturally occurring one—a substance that acts as an initiator only in particularly susceptible individuals—or may act like a true toxin, gaining access to the urine by a variety of mechanisms or metabolic pathways (Wein and Broderick, 1994). Clemmensen noted that 8 of 11 IC patients had positive skin reactions to patch tests with their own urine (Clemmensen et al, 1988). Immediate reactions were not observed, and the histology suggested a toxic rather than an allergic reaction. Lynes was unable to find a urinary myotropic substance unique to IC patients (Lynes et al, 1990b). The San Diego group found IC urine to result in higher cell death of cultured transitional cells than normal urine, suggesting a toxic compound in the urine of some IC patients (Parsons and Stein, 1990). They identified heat-labile, cationic components of low molecular weight that bind to heparin and that, when separated from the bulk of urinary wastes, are cytotoxic to urothelial cells as well as underlying smooth muscle cells (Parsons et al, 2000). They reported a 12% increase in 72-kDa stress protein in cells treated with urine from IC patients compared with controls (Ito et al, 1998).

Others have not been able to demonstrate in vitro cytotoxicity (Beier-Holgersen et al, 1994) or immunohistochemical changes in the nociceptive centers in the spinal cord or bladder wall when IC urine was compared with control urine (Baykara et al, 2003). Efforts to induce an IC-like picture in the rabbit bladder from exposure to urine of IC patients have failed to demonstrate conclusive changes (Perzin et al, 1991; Ruggieri et al, 1993; Kohn et al, 1998). Increased levels of soluble mediators associated with activation of sensory neurons and/or mast cells have been found in the urine of both IC and bladder cancer patients (Okragly et al, 1999).

Circumstantial evidence for the toxicity of IC urine is suggested by the failure of substitution cystoplasty and continent diversions in some of these patients because of the development of pain or contraction of the bowel segment over time (Nielsen et al, 1990; Baskin and Tanagho, 1992; Trinka et al, 1993; Lotenfoe et al, 1995), and by the histologic findings similar to IC found to occur in bowel used to augment the small-capacity IC bladder (McGuire et al, 1973; Singh and Thomas, 1996). Intestinal mucosa in contact with urine undergoes progressive changes for as long as 3 years after surgery, and the significance of the histologic IC-like changes has been questioned (MacDermott et al, 1990; Davidsson et al, 1996).

Role of Genetics in Bladder Pain Syndrome

Warren and colleagues (2001b) reported findings from a small cohort of twins in which a greater concordance of BPS was demonstrated among monozygotic than among dizygotic twins. This finding suggested that there could be a genetic susceptibility to BPS. A later study by the same research group (Warren et al, 2004) suggested that adult female first-degree relatives of patients with BPS may have a prevalence of IC 17 times that found in the general population. This, coupled with the previously reported twin data, suggests but does not prove that a genetic component adds to the susceptibility to BPS. Looking at an identical twin model with 246 twin sisters, Tunitsky and colleagues found that 9% were identified as having a moderate or high risk of BPS, with 5 twin sets in which both twins met the criteria. They concluded that BPS symptom scores within twin pairs were moderately correlated, implying some genetic component (Tunitsky et al, 2012).

A Swedish study that included more than 25,000 twins born from 1959 to 1985 compared monozygotic and dizygotic twins with symptoms of BPS. Overall BPS prevalence was 1.1% of men and 2.4% of women. In women, genetic factors contributed less than one third of the total variation in susceptibility to BPS. Lower male prevalence prevented determinations of genetic contribution. The authors concluded that the influence of environmental factors in the development of BPS in women is substantial, whereas genetic influences are of only modest importance (Altman et al, 2011).

The report by Weissman and colleagues (2004) of the increased frequency of BPS in patients and their first-degree relatives with panic disorder and other seemingly disparate disorders has suggested that there is a familial syndrome consisting of BPS and other

disorders of possible autonomic or neuromuscular dysfunction. A more recent case-control study by the same group (Talati et al, 2008) suggested that this syndrome might include other anxiety disorders as well, and that families with and without this collection of symptoms were genetically distinguishable on chromosome 13.

Gene expression profiles in cultured IC cells have been investigated and compared with controls (Erickson et al, 2008a). Few differences were appreciated, indicating that rather than being genetically based, the abnormal urothelium in BPS/IC may be caused by post-translational changes and/or to the bladder environment. It has been suggested that epigenetic reprogramming mechanisms in the bladder may provide an explanation for uroepithelial, mast cell, and nerve cell abnormalities in BPS/IC, as well as propagation of this altered state in the absence of the signal that may have triggered it (Elgavish, 2009). Viewing medically unexplained symptoms from the perspective of underlying developmental influences involving epigenetic modulation of gene expression that affect function of a variety of organs based on familial predispositions rather than from the traditional viewpoint of isolated organ-originating diseases may open up new areas of investigation for this class of “functional” disorders (Buffington, 2009).

Other Potential Causes

Various other etiologic theories have been proposed (Ratliff et al, 1994), but none has received much scientific support. Voiding almost hourly, always having to be aware of how far the nearest restroom facilities are, and suffering constant pain would be expected to lead to psychological stress. However, could there be individual differences in the propensity to develop BPS/IC that result from a dysregulation of anxiety and mood (Nesse, 1999; Bodden-Heidrich, 2004)? Childhood sexual trauma has been implicated as a causative factor for the disease (Mayson and Teichman, 2009; Tietjen et al, 2010; Nickel et al, 2011). **There are no data currently to suggest that stress itself initiates the chronic syndrome of BPS/IC, although it certainly can increase symptom severity (Lutgendorf et al, 2000).** Cats restricted to indoor living are five times more likely to have urinary problems than cats allowed outdoors (Buffington et al, 2002). Female patients with BPS/IC have been shown to have increased heart rate at baseline and throughout a laboratory mental stress challenge, but did not demonstrate greater autonomic reactivity to stress (Lutgendorf et al, 2004). Until stress can be shown to produce BPS/IC de novo in humans, it is just as reasonable to speculate that the stress is a result of the syndrome as a primary cause of it.

Speculation that abnormality in or obstruction of lymphatics or vascular structures is causative has never been borne out. The fact that some of these patients have had hysterectomy probably relates more to the attempt of the physician to treat chronic pelvic pain than to postsurgical change as a cause of the IC syndrome (Chung, 2004).

The knowledge that there is at least a 5:1 female-to-male preponderance immediately makes the role of the hormonal milieu potentially important (Bjorling and Wang, 2001). Paradoxically, it is known that estrogens can control hematuria in hemorrhagic cystitis, perhaps by decreasing the fragility of the mucosal microvasculature of the bladder (Liu et al, 1990). Estradiol augments whereas the estrogen receptor blocker tamoxifen inhibits mast cell secretion (Vliagoftis et al, 1992). Bladder mast cells express high-affinity estrogen receptors, and there is a higher number of such cells present in patients with IC compared with controls. Although this may help explain why IC is so common in women, the hormonal role can only account for the propensity of IC to occur in females, not the ultimate cause.

Pelvic floor dysfunction has been associated with BPS/IC for many years (Schmidt and Vapnek, 1991), and trials suggest that treatment of the pelvic floor can be effective in ameliorating symptoms (Lilius et al, 1973; Doggweiler-Wiygul et al, 2001; Holzberg et al, 2001; Weiss, 2001; Doggweiler-Wiygul et al, 2002; Oyama et al, 2004; FitzGerald et al, 2012). Speculation that abnormalities of the pelvic floor muscular function may contribute to the cause of some cases of CPPS in men is well accepted (Segura et al, 1979; Schmidt and Vapnek, 1991; Zermann et al, 1999), and a similar case might be made for patients with BPS/IC, though scientific support for a direct causative relationship is lacking.

One can understand the complexity of BPS/IC by looking at the myriad theories of etiology and the associated disorders that have been described. Complex functional disorders with patterns of comorbidity, in which there is overlap of what had once been regarded as independent syndromes, appear to fall outside the biomedical framework. It has been said that they “fully escape the profession’s divided and divisive grip. By their mere existence, they challenge the medical community’s view of the body, their understanding of what it is to be human and question whether present approaches to obtaining knowledge are adequate for helping people who suffer” (Kirkengen and Ulvestad, 2007).

KEY POINT: ETIOLOGY

- Both stress and pelvic floor dysfunction can contribute to BPS symptom severity and may be targets for treatment. Whether they can be contributing initiators of the syndrome complex is unclear at this time. The 5:1 female preponderance suggests hormonal involvement in the cause, but if recent data suggest that male prevalence is close to female prevalence, this conventional wisdom will need revision (Suskind et al, 2013a).

patients and reported a linear relationship between the mean bladder capacity under anesthesia and severity of glomerulations (Hanus et al, 2001). They did not find a correlation between severity of symptoms and histopathologic changes observed with light or electron microscopy.

Rosamilia reviewed the pathology literature pertaining to BPS and presented her own data (Rosamilia et al, 2003; Hanno et al, 2005a). She compared forceps biopsy specimens from 35 control and 34 BPS/IC patients, 6 with bladder capacities less than 400 mL under anesthesia. Epithelial denudation, submucosal edema, congestion and ectasia, and inflammatory infiltrate were increased in the BPS group. Submucosal hemorrhage did not differentiate the groups, but denuded epithelium was unique to the BPS group and more common in those with severe disease. The most remarkable finding in her study was that histologic parameters were normal and indistinguishable from control subjects in 55% of BPS subjects. Method of biopsy can be important in interpreting findings, because transurethral resection biopsy specimens tend to show mucosal ruptures, submucosal hemorrhage, and mild inflammation (Johansson and Fall, 1990), whereas histology is normal approximately half the time with cold-cup forceps biopsy specimens (Mattila, 1982; Lynes et al, 1990a; Rosamilia et al, 2003).

Histopathology plays a supportive diagnostic role at best (Johansson et al, 1997). Major reconstructive procedures appear to have better outcomes in patients with pathology consistent with Hunner lesions (Rössberger et al, 2007). Inflammatory features can be seen in 24% to 76% of patients without a visible Hunner lesion (Erickson et al, 2008b). Although studies have suggested that a severely abnormal pathology may be associated with poor prognosis (McDougald and Landon, 2003; Nordling et al, 2004), this is not necessarily the case (MacDermott et al, 1991a). At this point in time, excluding other diseases that are pathologically identifiable is the primary clinical use of bladder biopsy in this group of patients.

KEY POINTS: PATHOLOGY

- The role of histopathology is primarily to exclude other possible diagnoses that might be responsible for the symptoms.
- There is no histology pathognomonic of BPS, and one cannot make the diagnosis on pathology alone in the absence of the cardinal symptoms.
- Completely normal-appearing bladder biopsy specimens in symptomatic patients are not uncommon.

DIAGNOSIS

BPS/IC can be considered a functional pain disorder (Mayer and Bushnell, 2009) and one of the chronic visceral pain syndromes affecting the urogenital and rectal area, many of which are well described but poorly understood (Wessellmann et al, 1997; Wessellmann, 2001). These include vulvodynia, orchalgia, penile pain, perineal pain, and rectal pain. In men, many of the entities have now been included in the rubric of CPPS and can be difficult to distinguish from BPS/IC (Hakenberg and Wirth, 2002; Forrest and Schmidt, 2004). The diagnosis of BPS/IC is by its very nature based on the definition. In the past this was, by default, the symptom criteria enumerated by the NIDDK (Hanno et al, 1999a, 1999b) (see Box 14-2). It has now morphed largely into a diagnosis of chronic pain, pressure, or discomfort associated with the bladder, usually accompanied by urinary frequency in the absence of any identifiable cause (Hanno et al, 2005a, 2005b). Diagnostic approaches vary widely, and general agreement on a diagnostic algorithm remains a future goal (Chai, 2002; Nordling, 2004; Nordling et al, 2004). The disorder can be very difficult to diagnose until symptoms become well established, unless one has a high level of suspicion (Porru et al, 2004). Frequency and pelvic pain of long duration perceived to be related to the bladder unrelated

to other known causes establishes a working diagnosis. It is often difficult for patients to distinguish between sensations of pain, pressure, discomfort, and urgency. Ask a patient why he or she voids hourly, and the patient usually will state that it is because of discomfort rather than convenience. Heavy reliance on other aspects of the NIDDK research criteria will result in underdiagnosing more than half of patients (Hanno et al, 1999b). IC symptom scales (O'Leary et al, 1997; Goin et al, 1998; Moldwin and Kushner, 2004), such as the AUA symptom score for BPH, are designed to evaluate the severity of symptomatology and monitor disease progression or regression with or without treatment. They have not been validated as diagnostic criteria.

One must rule out infection and less common conditions including but not limited to carcinoma (Utz and Zincke, 1974; Tissot et al, 2004), eosinophilic cystitis (Hellstrom et al, 1979; Sidh et al, 1980; Littleton et al, 1982; Aubert et al, 1983; Abramov et al, 2004), malakoplakia, schistosomiasis, scleroderma (Batra and Hanno, 1997), and detrusor endometriosis (Sircus et al, 1988; Price et al, 1996). In men under the age of 50, video-urodynamics are useful to rule out voiding dysfunction resulting from vesical neck obstruction, "pseudo" dyssynergia, or impaired contractility (Kaplan et al, 1996). Musculoskeletal dysfunction may also play a role in causation or increasing symptom severity and should be looked for in the diagnostic phase of evaluation (Prendergast and Weiss, 2003). Reports of successful treatment of IC symptoms by laparoscopic adhesiolysis (Chen et al, 1997) or urethral diverticulum excision (Daneshgari et al, 1999) give credence to the fact that IC is a diagnosis of exclusion. Many drugs including cyclophosphamide, aspirin, nonsteroidal anti-inflammatory agents, and allopurinol have caused a nonbacterial cystitis that resolves with drug withdrawal (Bramble and Morley, 1997; Gheyi et al, 1999).

Ketamine hydrochloride, commonly used as an anesthetic agent, is an NMDA receptor antagonist. It has a rapid onset and short duration of action and produces a cataleptic-like state wherein the patient is dissociated from the surrounding environment by direct action on the cortex and limbic system. In some parts of the world such as Taiwan, it is an increasingly popular choice among young drug users, especially within dance club venues. It can cause dysuria, lower urinary tract symptoms, pelvic pain, and impaired bladder functional capacity. At endoscopy, ulceration with severe diffuse bladder hemorrhage and low capacity has been described (Chen et al, 2011; Middela and Pearce, 2011). Decreased E-cadherin and increased apoptosis are more severe in ketamine cystitis than BPS (Lee et al, 2013). Treatment is cessation of abuse of the drug.

Tarlov cysts are present in 4.6% of the population. When present at lumbosacral levels, symptoms may include perineal pressure and pain and voiding hallmarks of BPS. Successful treatment with epidural steroids has been reported (Freidenstein et al, 2012).

Various gynecologic problems can mimic the pain of IC (Kohli et al, 1997). The pelvic congestion syndrome, a condition of the reproductive years and equally prevalent among parous and nulliparous women, manifests with shifting location of pain, deep dyspareunia and postcoital pain, and exacerbation of pain after prolonged standing (Stones, 2003). Similar symptoms can be seen in BPS/IC. Other gynecologic disorders can include pelvic tumors, vaginal atrophy, vulvodynia, vestibulitis, pelvic relaxation, pelvic adhesive disease, levator ani myalgia, and undiagnosed chronic pelvic pain (Myers and Aguilar, 2002). Pelvic surgery is more common in women with a diagnosis of BPS/IC than in a control population (Ingber et al, 2008). In Ingber's series, the diagnosis of BPS/IC occurred 1 to 5 years after hysterectomy in most patients, suggesting that pelvic surgery may be performed for pain related to undiagnosed BPS.

Endometriosis can be a cause of pelvic pain (Evans et al, 2007), an idea largely based on findings of two randomized, placebo controlled studies of laser laparoscopy (Sutton et al, 1995, 1997; Abbott et al, 2004). Nevertheless, it is disconcerting that any claim linking endometriosis with pain fails to account for the common experience that identical lesions can be found in symptomatic and asymptomatic women (Vercellini, 1997). From 2% to 43% of

asymptomatic women are found to have endometriosis (Moen and Stokstad, 2002). Furthermore, there does not appear to be any risk for patients with asymptomatic mild endometriosis to develop symptoms even after more than 10 years (Moen and Stokstad, 2002). Although 70% to 90% of women with chronic pelvic pain have endometriosis, this does not definitively establish causation (Gambone et al, 2002). For these reasons, laparoscopy, which is not considered essential before initiation of hormonal treatment of endometriosis (Ling, 1999; Howard, 2003b), should not be considered a part of any routine evaluation of BPS/IC unless an experienced practitioner believes it is likely to benefit the patient.

A presumptive diagnosis can be made merely by ruling out known causes of frequency, pain, and urgency in a patient with compatible chronic symptoms (Box 14-5). This holds true for adolescents as well as adults (Yoost et al, 2012). Often this will involve a complete history, physical examination, appropriate cultures, and local cystoscopy. A finding of tenderness on examination

of the anterior vaginal wall with an empty bladder at the initial examination can lead one to suspect BPS (Paulson and Paulson, 2011). In the absence of microhematuria the value of cytology is questionable (Duldulao et al, 1997), but it is something we still consider important, especially if bladder carcinoma in situ is a serious possibility, as in patients older than 40 and those with a smoking history. The report of a large series of BPS/IC patients indicating that 1% actually had transitional cell carcinoma and that four of the six cancer patients did not have microhematuria provides evidence for the justification of local cystoscopic examination (Tissot et al, 2004).

It must be recognized that one may sacrifice a certain level of confidence in the diagnosis without the supporting evidence that can be furnished by additional studies. In a long-term illness such as BPS/IC, many patients and physicians ultimately want to base a diagnosis and treatment plan on the most complete data set possible (Rovner and Wein, 1999). A more thorough evaluation would also include a urodynamic evaluation and cystoscopy under anesthesia with hydrodistention of the bladder (Hanno et al, 1990; Hanno, 1994b). Bladder biopsy is indicated only if necessary to rule out other disorders that might be suggested by the cystoscopic appearance. Cystoscopy under anesthesia with bladder distention has been important in the identification of a Hunner lesion. Experimental data suggest that measurement of increased nitric oxide levels in the bladder can also accurately identify those with ulcerative disease (Logadottir et al, 2004). In general, the diagnosis is subject to more rigorous testing in Europe (Fall et al, 2008) than in North America, where symptoms in the absence of other obvious causes seems to be the gold standard (Nordling, 2004; Nordling et al, 2004; Hanno et al, 2005a). Japanese guidelines are listed in Box 14-6.

Although sensations reported during cystometric bladder filling are subjective, they have a normal pattern and may be helpful in distinguishing bladder pathology (Wyndaele, 1998). Many dispute the need for urodynamic study (Cameron and Gajewski, 2009), but Siroky and Kim argue that not only can it help to assess

BOX 14-5 International Consultation on Incontinence 2009: Diagnosis of Bladder Pain Syndrome

HISTORY

General thorough medical history emphasizing the following:

1. Previous pelvic surgery
2. Previous urinary tract infection
3. Bladder history and urologic diseases
4. Location of pelvic pain and relationship to bladder filling and emptying
5. Characteristics, onset, correlation of pain with other events
6. Previous pelvic irradiation
7. Autoimmune diseases
8. Associated syndromes (irritable bowel, fibromyalgia, chronic fatigue)

PHYSICAL EXAMINATION

Physical examination emphasizing the following:

1. Standing: kyphosis, scars, hernia
2. Supine: abduction and adduction of hips, hyperesthetic areas
3. Females: vaginal examination with pain mapping of vulvar region, vaginal palpation for tenderness of the bladder, urethra, levator and adductor muscles of the pelvic floor
4. Males: digital rectal examination with pain mapping of the scrotal-anal region and palpation of tenderness of the bladder, prostate, levator and adductor muscles of the pelvic floor and scrotal contents

LABORATORY TESTING

1. Urinalysis
2. Urine culture
3. Urine cytology in risk groups

SYMPTOM EVALUATION

1. Voiding diary
2. O'Leary-Sant symptom and problem index
3. Visual analog scale for pain in the last 24 hours

OTHER EVALUATIONS

Urodynamics (optional)
Cystoscopy with or without hydrodistention under anesthesia (optional)
Bladder biopsy (optional)

BOX 14-6 Recommended Tests for Diagnosis of Interstitial Cystitis from the Japanese Urological Association

MANDATORY

Clinical history
Physical examination
Urinalysis

RECOMMENDED

Urine culture
Urine cytology
Symptom scores
Quality-of-life scores
Frequency-volume chart
Residual urine measurement
Prostate-specific antigen
Cystoscopy
Hydrodistention

OPTIONAL

Ultrasonography
Urodynamic study
X-ray examination
Potassium test
Biopsy

From Hanno P, Lin AT, Nordling J, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence. Paris: Health Publication; 2009. p. 1459–518.

From Homma Y, Ueda T, Ito T, et al. Japanese guideline for diagnosis and treatment of interstitial cystitis. Int J Urol 2009;16:4–16. Copyright © Japanese Urological Association.

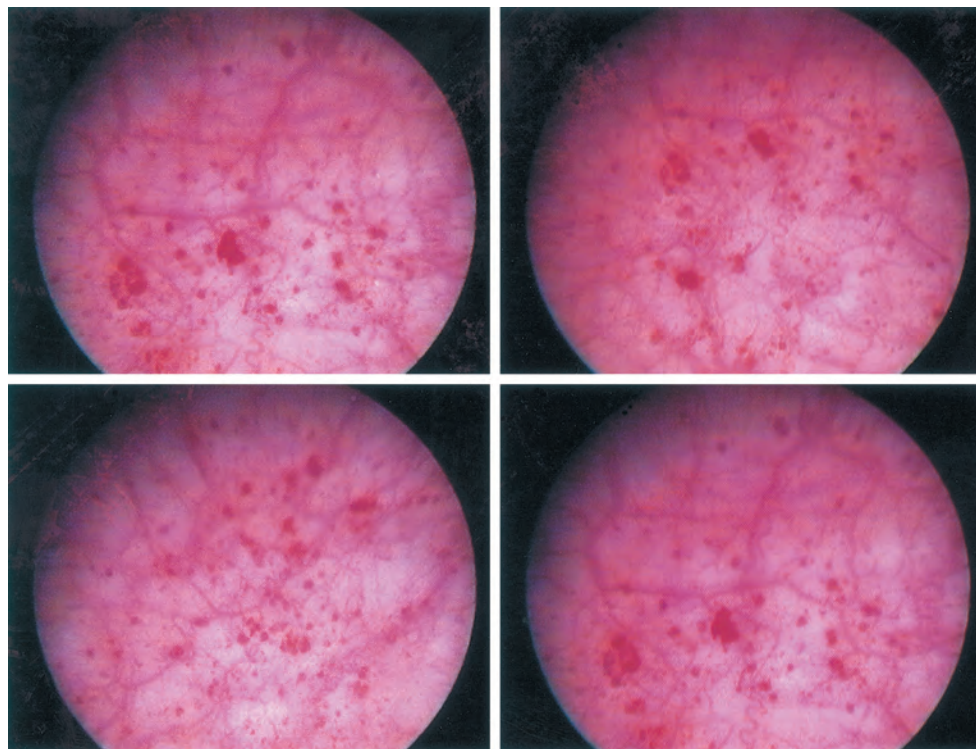


Figure 14-9. Typical appearance of glomerulations after bladder distention in a patient with nonulcerative bladder pain syndrome.

bladder compliance and sensation and reproduce the patient's symptoms during bladder filling, but it can help to rule out DO (Siroky, 1994; Kim et al, 2009b). Women with pain on filling can be indistinguishable from those with DO in their perception of bladder fullness (Creighton et al, 1991). One should be wary of diagnosing BPS/IC in patients with discrete, involuntary bladder contractions whose symptoms respond to antimuscarinic therapy. The two problems may coexist in 15% to 19% of patients (Gajewski et al, 1997; Kirkemo et al, 1997), but the pathophysiology is possibly very different. Patients who respond to anticholinergic medication tend not to respond to standard therapy for BPS (Perez-Marrero et al, 1987). If involuntary contractions are noted and the patient's symptoms of frequency and pain continue despite treatment for overactive bladder, one is on firmer ground in considering a diagnosis of BPS/IC. Complex cases may benefit from full video-urodynamic studies (Carlson et al, 2001).

Cystometry in conscious BPS patients typically demonstrates normal function, the exception being decreased bladder capacity and hypersensitivity. Pain on bladder filling that reproduces the patient's symptoms is very suggestive of the diagnosis. Volume at strong desire to void has been purported to be a predictor of treatment outcome (Kuo and Kuo, 2013). Bladder compliance in patients with BPS/IC is normal, as hypersensitivity would prevent the bladder from filling to the point of noncompliance (Siroky, 1994; Rovner and Wein, 1999). The possible addition of a second cystometrogram after instillation of intravesical lidocaine to help determine if pain is bladder related is a provocative issue worth further study (Teichman et al, 1997). It is not uncommon to find evidence of outlet obstruction in BPS/IC, presumably related to associated pelvic floor dysfunction (Cameron and Gajewski, 2009).

Long before it was considered a diagnostic tool, CHD was used as a therapeutic modality for BPS (Bumpus, 1930). CHD under anesthesia allows for sufficient distention of the bladder to afford visualization of either glomerulations (Fig. 14-9) or Hunner lesions (Fig. 14-10). After filling to 80 cm water pressure for 1 to 2 minutes, the bladder is drained and refilled. The terminal portion of the effluent is often blood tinged. Reinspection will reveal the pinpoint petechial hemorrhages that develop

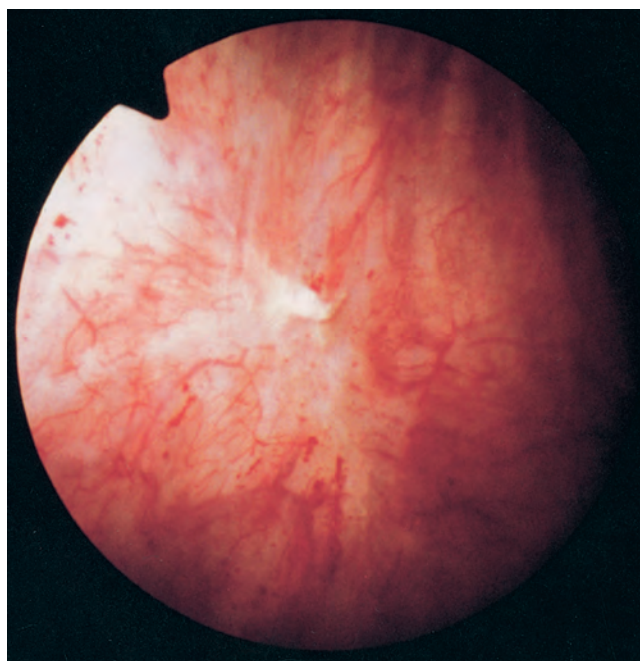


Figure 14-10. Typical appearance of Hunner lesion in a patient with bladder pain syndrome before bladder distention.

throughout the bladder after distention and are not usually seen during examination without anesthesia (Nigro et al, 1997b).

Glomerulations are not specific for BPS/IC (Erickson, 1995; Waxman et al, 1998), and only when seen in conjunction with the clinical criteria of pain and frequency can the finding of glomerulations be viewed as potentially significant. Glomerulations can be seen after radiation therapy, in patients with carcinoma, after exposure to toxic chemicals or chemotherapeutic agents, and

often in patients on dialysis or after urinary diversion when the bladder has not filled for prolonged periods. They have been reported in the majority of men with prostate pain syndromes, begging the question as to whether CPPS in men is closely linked with IC (Berger et al, 1998). They are observed in up to 20% of men undergoing transurethral prostatectomy for lower urinary tract symptoms (Furuya et al, 2007). We have speculated that they may simply reflect the response of the bladder to distention after a prolonged period of chronic underfilling because of sensory urgency, rather than resulting from a primary pathologic process. Although the presence of a Hunner ulcer has been associated with pain and urinary urgency, neither the finding of bloody irrigating fluid nor of glomerulations is strongly associated with any particular symptom in patients in the ICDB (Messing et al, 1997).

Further confusion arises when the patient demonstrates the symptoms of IC but the cystoscopic findings under anesthesia are completely normal. This occurred in 8.7% of patients undergoing CHD entered into the IC database (Messing et al, 1997). Awad and colleagues recognized this entity soon after the NIDDK research criteria had been described. They reported on a series of patients in whom the symptomatology, urodynamic evaluation findings, histology, and response to therapy were identical to IC but in whom findings on CHD were normal. It was termed *idiopathic reduced bladder storage* (Awad et al, 1992). Clinical, urodynamic, and cystoscopic data strongly suggest that the presence of glomerulations is not selecting out a meaningful difference in patients with symptoms of BPS/IC (Al Hadihi et al, 2002). The presence of cystoscopic abnormalities such as glomerulations on cystoscopy under anesthesia meeting the NIDDK criteria may identify a group of patients with worse daytime frequency and nocturia, lower mean voiding volumes, and lower bladder capacity under anesthesia, but does not have any relationship to biopsy findings, bladder pain, or urgency (Erickson et al, 2005; Boudry et al, 2013).

The Search for a Marker

What is the value of a “diagnostic test” in what is essentially a clinical syndrome defined by a symptom complex? If a patient has chronic pain associated with the bladder usually accompanied by urinary frequency with no discernible cause, we diagnose BPS/IC. In essence, once we have ruled out well-characterized pathologic entities, the patient makes the diagnosis by relating symptoms, much as a patient with impotence makes that diagnosis. Testing for impotence may give clues as to the cause, but we cannot rule out impotence by doing a test in a patient who cannot function sexually!

This is not to say that establishment of a valid diagnostic marker would not be a major advance in our understanding of IC. Just as with phenotyping, it will be important largely to the extent that it can predict prognosis in a given group of patients, predict response to therapy in a given group of patients, and/or distinguish between BPS/IC and another possible cause of the symptom complex that has been diagnosed. Ultimately, marker identification may enable us to stratify patients with the symptom complex in such a way that treatments will be specific to the specific cause (i.e., disease) the patient has. As various causes are identifiable, the diagnosis of BPS may itself become a rarity, much like what has happened to “acute urethral syndrome” (Stamm et al, 1980).

In just such an effort, numerous investigators have looked at the mast cell as a possible diagnostic marker for IC. The current standard involves detrusor muscle biopsy specimens examined with tryptase staining of 3- μ m thick sections, with every seventh section used for quantification (Larsen et al, 2008). Twenty-seven mast cells per cubic millimeter is considered indicative of mastocytosis. The results in the past have been very contradictory, and at this time, in terms of the use of mast cell criteria in diagnosis, the issue remains moot (Kastrup et al, 1983; Feltis et al, 1987; Holm-Bentzen et al, 1987a; Lynes et al, 1987; Hanno et al, 1990; Christmas and Rode, 1991; Moore et al, 1992; Dundore et al, 1996; Hofmeister et al, 1997). Methylhistamine, a histamine metabolite found in the urine and thought to reflect mast cell activation, was not associated

with symptom scores, response to bladder distention, cystoscopic findings, or bladder biopsy features including mast cell determination by tryptase staining (Erickson et al, 2004).

Attempts have been made to look at other markers (Erickson, 2001), including eosinophil cationic protein (Lose et al, 1987), GAG excretion (Hurst et al, 1993), and urinary histamine and methylhistamine (El Mansoury et al, 1994). Proposals for measuring smooth muscle isoactin expression (Rivas et al, 1997) and urinary levels of neurotrophin-3, nerve growth factor, glial cell line-derived neurotrophic factor, and tryptase (Okragly et al, 1999) have been suggested. Low levels of GP51, a urinary glycoprotein with a molecular weight of 5 kDa, have been documented in IC patients compared with normal controls and patients with other urinary tract disease (Byrne et al, 1999). Cell cultures (Elgavish et al, 1997) have been proposed as a screening technique.

The measurement of elevated nitric oxide levels in air instilled and incubated in the bladder has been proposed for office screening (Lundberg et al, 1996; Ehrén et al, 1999). Increased levels of endogenously formed nitric oxide in patients with IC correspond to increased iNOS mRNA expression and protein levels in these patients. Furthermore, iNOS was found to be localized to the urothelium, but it was also found in macrophages in the bladder mucosa (Koskela et al, 2008). The simple technique allows for discrimination of ulcer from nonulcer disease (Logadottir et al, 2004) and may provide an objective measure of treatment response (Hoseini et al, 2004).

The urine APF identified by Keay (see earlier) may prove to be an accurate marker of BPS/IC if it can be confirmed by other centers and become a biochemical rather than biologic assay. It appears to have the highest sensitivity and specificity of the variety of possible markers tested and fits nicely into an etiologic schema (Keay et al, 2001a, 2001b; Erickson et al, 2002). It has also been shown to differentiate men with BPS/IC symptoms from controls and to differentiate men with bladder-associated pain and irritative voiding symptoms from those with pelvic or perineal pain alone and other nonspecific findings compatible with CPPS in men (CPPS III), previously referred to as *nonbacterial prostatitis* (Keay et al, 2004a). This question—whether CPPS and BPS/IC are two different disorders—will doubtless be the subject of future research and is an integral question that the NIDDK is hoping to answer with current research (www.mappnetwork.org). Data regarding the reproducibility of APF and any practical clinical uses are lacking.

Much work in markers is ongoing. Uroplakin III-delta 4 is a potential marker for identifying nonulcerative IC (Zeng et al, 2007). The feasibility of diagnosing IC in humans and domestic cats from the spectra of dried serum films (DSFs) using infrared microspectroscopy has been reported (Rubio-Diaz et al, 2009).

Potassium Chloride Test

Parsons has championed an intravesical KCl challenge, comparing the sensory nerve provocative ability of sodium versus potassium using a 0.4-M KCl solution. Pain and provocation of symptoms constitutes a positive test result. Whether the results indicate abnormal epithelial permeability in the subgroup of positive patients or hypersensitivity of the sensory nerves is unclear. Normal bladder epithelium can never be absolutely tight, and there is always some leak, however small (Hohlbrugger and Sant, 1997). The concentration of potassium used is 400 mEq/L, far exceeding the physiologic urinary concentrations of 20 to 80 mEq/L depending on dietary intake (Vander, 1995). Healthy controls can distinguish KCl from sodium chloride, although they don't experience severe pain (Roberto et al, 1997). The hope is that this test may stratify patients into those who will respond to certain treatments (perhaps those designed to fortify the GAG layer), but to date this information is lacking (Teichman and Nielsen-Omeis, 1999).

Used as a diagnostic test for IC, the KCl test is not valid (Chambers et al, 1999). The gold standard in defining BPS/IC for research purposes has been the NIDDK criteria. These criteria are recognized to constitute a set of patients that virtually all researchers

can agree have BPS/IC, though they are far too restrictive to be used in clinical practice (Hanno et al, 1999b). Thus, this group of patients should virtually all be positive if the KCl test is to have the sensitivity needed to aid in diagnosis. Up to 25% of patients meeting the NIDDK criteria will have a negative KCl test result (Parsons et al, 1998). In the group of patients in whom it should perform best, it is lacking in sensitivity.

When we look at the specificity side of the equation, in the universe of unselected persons, studies reported a 36% false-positive rate in asymptomatic men (Yilmaz et al, 2004) and a 33% positive rate in a fixed population of Turkish textile workers (Sahinkanat et al, 2008). In the patient population with confounding conditions for which we would want help in sorting out BPS/IC from other disorders, 25% of patients with overactive bladder test positive and virtually all patients with irritative symptoms from radiation cystitis and urinary tract infection test positive (Parsons et al, 1994b, 1998). The results with chronic prostatitis and CPPS in men are variable, but 50% to 84% of men have been reported to test positive (Parsons and Albo, 2002; Yilmaz et al, 2004; Parsons et al, 2005). In women with pelvic pain the results are similar (Parsons et al, 2002b), and based on these findings Parsons has expressed the view that BPS/IC may affect over 20% of the female population of the United States (Parsons et al, 2002a). Another way to interpret the findings would be that the KCl test is very nonspecific, missing

a significant number of BPS/IC patients and overdiagnosing much of the population.

Prospective and retrospective studies looking at the KCl test for diagnosis in patients with symptoms of BPS/IC have found no benefit of the test in comparison with standard techniques of diagnosis (Chambers et al, 1999; Gregoire et al, 2002; Kuo, 2003), and it is not useful for monitoring results of treatment (Sairanen et al, 2007). The development of a painless modification of the KCl test (Daha et al, 2003) using cystometric capacity and a 0.2-M solution may improve acceptability among patients, but further research is needed to determine what place, if any, this test will have in the diagnostic or treatment algorithm.

Confusable Diseases (Differential Diagnosis)

The diagnosis of BPS can be made on the basis of exclusion of confusable diseases and confirmed by the recognition of the presence of the specific combination of symptoms and signs of BPS. If the main urinary symptoms are not explained by a single diagnosis, the presence of a second diagnosis is possible. One must remember that BPS may occur together with confusable diseases such as chronic or remitting urinary infections or endometriosis. Table 14-3 summarizes confusable diseases related to BPS and their mode of exclusion based on aforementioned diagnostic

TABLE 14-3 Diseases That May Be Mistaken for Bladder Pain Syndrome

CONFUSABLE DISEASE	EXCLUDED OR DIAGNOSED BY
Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with: Common intestinal bacteria <i>Chlamydia trachomatis</i> , <i>Ureaplasma urealyticum</i> , <i>Mycoplasma hominis</i> , <i>Mycoplasma genitalium</i> , <i>Corynebacterium urealyticum</i> , <i>Candida</i> species, <i>Mycobacterium tuberculosis</i> Herpes simplex and human papillomavirus	Routine bacterial culture Special cultures Dipstick; if “sterile” pyuria, culture for <i>M. tuberculosis</i> Physical examination
Radiation	Medical history
Chemotherapy, including immunotherapy with cyclophosphamide	Medical history
Anti-inflammatory therapy with tiaprofenic acid	Medical history
Bladder neck obstruction and neurogenic outlet obstruction	Uroflowmetry and ultrasonography
Bladder stone	Imaging or cystoscopy
Lower ureteral stone	Medical history and/or hematuria; upper urinary tract imaging (CT or IVP)
Urethral diverticulum	Medical history and physical examination
Urogenital prolapse	Medical history and physical examination
Endometriosis	Medical history and physical examination
Vaginal candidiasis	Medical history and physical examination
Cervical, uterine, and ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Postvoid residual urine volume measured by ultrasound evaluation
Overactive bladder	Medical history and urodynamics
Prostate cancer	Physical examination and PSA test
Benign prostatic obstruction	Uroflowmetry and pressure-flow studies
Chronic bacterial prostatitis	Medical history, physical examination, culture
Chronic nonbacterial prostatitis	Medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination; nerve block may prove diagnosis
Pelvic floor muscle-related pain	Medical history, physical examination

CT, computed tomography; IVP, intravenous pyelogram; PSA, prostate-specific antigen.

From van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol* 2008;53:60–7.

proposals and procedures as outlined by the ESSIC group (van de Merwe et al, 2008).

KEY POINTS: DIAGNOSIS

- BPS remains a diagnosis of exclusion in patients who meet the symptomatic criteria for diagnosis after confusable disorders have been ruled out.
- Cystoscopy with bladder distention under anesthesia aids in the diagnosis of a Hunner lesion but is not considered a prerequisite for beginning treatment.
- Cystoscopy and upper tract imaging are mandatory in patients with hematuria who have not been previously evaluated for this finding.
- Urodynamics are optional and usually reserved for complex cases. There are no commonly available laboratory markers that substantially contribute to diagnosis.

CLASSIFICATION

IC was originally described as a bladder disease with severe inflammation of the bladder wall described by Hunner as an ulcer (Hunner, 1915). The lesion is, however, not an ulcer, but a vulnus (weakness, vulnerability) that can ulcerate on distention, and the name of the bladder lesion has consequently been changed to *Hunner lesion* (van de Merwe et al, 2008). The finding of a Hunner lesion could therefore originally be regarded as a diagnostic criterion for IC. Messing and Stamey introduced glomerulations alone as another typical finding for IC, and this was included in the NIDDK criteria (Wein et al, 1990).

Magnus Fall proposed that patients with Hunner lesions (classic IC) and patients with glomerulations (non-Hunner type) represented two different subtypes (Fall et al, 1987). They may have different clinical pictures, different outcomes, and different responses to treatment (Peeker and Fall, 2002b). Patients with Hunner lesions were found to have a 5-fold to 20-fold increase in the chemokines CXCL-10 and CXCL-1, interleukin-6, and nerve growth factor when compared with BPS patients without Hunner lesions (Tyagi et al, 2012). Different expression patterns of the genes involved in proinflammatory reactions suggest distinct pathophysiologies for Hunner lesion patients compared with patients with BPS without Hunner lesions (Homma et al, 2013).

Thus, patients fulfilling the NIDDK criteria represent at least two (and possibly more) different patient populations. Moreover, up to 60% of patients clinically believed to have BPS by experienced clinicians do not fulfill the NIDDK criteria (Hanno et al, 1999b) and whether or not these patients are comparable to the patients fulfilling the NIDDK criteria is unknown. Finally, Japanese urologists consider that *interstitial cystitis* should be preserved as a disease name reserved for patients with urinary symptoms and cystoscopic findings of glomerulations or Hunner lesion as outlined in the NIDDK criteria (Homma, 2008).

In an attempt to unite these different philosophies into a coherent schema, ESSIC proposed a classification of BPS based on findings during CHD and morphologic findings in bladder biopsy specimens (van de Merwe et al, 2008) (see Table 14-1). The classification includes groups not having had CHD (group X) as well as groups not having had morphologic investigation of bladder biopsy specimens (group XX). By using this classification, future researchers will be able to identify whether findings of glomerulations and/or Hunner lesion as well as morphologic changes in bladder biopsy specimens do have significant importance for disease prognosis and/or treatment outcome (Geurts et al, 2011).

TREATMENT

Conservative Therapies

Once the diagnosis has been made, one must decide whether to institute therapy or employ a policy of conservative watchful

waiting. If the patient has not had an empirical course of antibiotics for their symptoms by the time the BPS/IC diagnosis is made, such a trial is reasonable. Doxycycline has been reported efficacious in a Swiss study (Burkhard et al, 2004). Further attempts to alleviate symptoms with antibiotics are unlikely to be worthwhile and are not recommended in the absence of positive cultures. **Stress reduction, exercise, warm tub baths, and efforts by the patient to maintain a normal lifestyle all contribute to overall quality of life (Whitmore, 1994).** In a large patient survey, dietary changes, application of heat or cold, and stress reduction all had positive response rates in over 80% of responders (O'Hare et al, 2013). In a controlled study of 45 PBS/IC patients and 31 healthy controls, higher levels of stress were related to greater pain and urgency in patients with IC but not in the control group (Rothrock et al, 2001). Maladaptive strategies for coping with stress may adversely affect symptoms (Rothrock et al, 2003).

Biofeedback, soft-tissue massage, and other physical therapies may aid in muscle relaxation of the pelvic floor (Mendelowitz et al, 1997; Meadows, 1999; Holzberg et al, 2001; Lukban, et al, 2001; Markwell, 2001). This is a reasonable intervention, given the strong association of pelvic floor dysfunction and BPS/IC (Peters et al, 2007a; Bassaly et al, 2011). A preliminary NIDDK trial demonstrated the feasibility of such a study and strongly suggested the efficacy of physical therapy when compared with global therapeutic massage (FitzGerald et al, 2009). This was confirmed in a randomized controlled trial comparing 10 scheduled treatments of myofascial physical therapy versus global therapeutic massage at 11 North American clinical centers. The Global Response Assessment (GRA) response rate was 26% in the global therapeutic massage group and 59% in the myofascial physical therapy group ($P = .0012$) (FitzGerald et al, 2012).

Mendelowitz and Moldwin had a 69% success rate in 16 patients treated with electromyographic biofeedback (Mendelowitz et al, 1997), but treatment response did not correlate to changes in muscle identification, and the placebo effect may have been considerable. **Acupuncture** has been used for BPS/IC and many other chronic pain syndromes. There is **limited evidence that it is more effective than nontreatment for chronic pain** and inconclusive evidence that acupuncture is more effective than placebo, sham acupuncture, or standard care (Ezzo et al, 2000). **BPS/IC results with acupuncture have been disappointing (Geirsson et al, 1993).**

Diet

Elaborate dietary restrictions are unsupported by any literature, but many patients do find their symptoms are adversely affected by specific foods and would do well to avoid them (Koziol et al, 1993; Koziol, 1994). Often these include caffeine, alcohol, artificial sweeteners, hot peppers, and beverages that might acidify the urine, such as cranberry juice (Shorter et al, 2007). Several acid-sensing ion channel subunits are expressed in human bladder, and the upregulation of some of these channels in BPS/IC patients suggests involvement in increased pain and hyperalgesia (Sanchez-Freire et al, 2011). Anecdotal association of IC with many foods has spawned the recommendation of various "interstitial cystitis diets" with little in the way of objective, scientific basis (Box 14-7). The only placebo-controlled dietary study, although small, failed to demonstrate a relationship between diet and symptoms (Fisher et al, 1993). Bade and colleagues found that IC patients tend to have a healthier diet than the general population but could discern no rationale for dietary or fluid intake change other than decreasing caffeine intake (Bade et al, 1997b). Nguan and coworkers performed a prospective, double-blind, crossover study consisting of crossover instillations of urine at physiologic pH (5.0) and neutral buffered pH (7.5) (Nguan et al, 2005). There was no statistically significant difference in subjective pain scores, suggesting that adjusting urine pH with diet or dietary supplements may have little influence on symptomatology. Orange and grapefruit juices, rich in potassium and citrate, tend to increase urinary pH (Wabner and Pak, 1993) but are avoided by many IC patients based on "IC diet" recommendations and their personal experience with food-related

BOX 14-7 Interstitial Cystitis Association Recommendations of Foods to Avoid**Milk and dairy products**

Aged cheeses
Sour cream
Yogurt
Chocolate

Vegetables

Fava beans
Lima beans
Onions
Tofu
Soybeans
Tomatoes

Fruits

Apples
Apricots
Avocados
Bananas
Cantaloupes
Citrus fruits
Cranberries
Grapes
Nectarines
Peaches
Pineapples
Plums

Fruits—cont'd

Pomegranates
Rhubarb
Strawberries
Juices from above fruits

Carbohydrates and grains

Rye bread
Sourdough bread

Meats and fish

Aged, canned, cured processed, smoked meats and fish

Nuts**Beverages**

Alcoholic beverages including beer and wine
Carbonated drinks
Coffee
Tea
Fruit juices

Seasonings

Mayonnaise
Ketchup
Mustard
Salsa

Seasonings—cont'd

Spicy foods (Chinese, Mexican, Indian, Thai)
Soy sauce
Miso
Salad dressing
Vinegar

Preservatives and additives

Benzyl alcohol
Citric acid
Monosodium glutamate
Artificial sweeteners
Preservatives
Artificial ingredients
Food coloring

Miscellaneous

Tobacco
Caffeine
Diet pills
Junk foods
Recreational drugs
Allergy medications with ephedrine or pseudoephedrine
Certain vitamins

Modified from Interstitial Cystitis Association. Understanding the interstitial cystitis/painful bladder syndrome diet, <<http://www.ichelp.org/document.doc?id=7>>; 2009 [accessed 29.10.14].

flares. Alkalinizing the urine may be worth trying, but supporting studies are lacking. Some patients have had benefit with calcium glycerophosphate, an over-the-counter food acid-reducing agent (Hill et al, 2008; O'Hare et al, 2013), but supporting controlled trials are lacking. A controlled method to determine dietary sensitivities, such as an elimination diet, may play an important role in patient management (Friedlander et al, 2012).

In a large National Institutes of Health study, patients with newly diagnosed BPS/IC were treated with a focus on four targeted areas: (1) controlling or managing symptoms, (2) controlling fluid intake, (3) changing the diet to one that might improve symptoms, and (4) bladder training and urge suppression. A behavioral approach to stress and pain management was also used to help patients learn skills to reduce stress in their lives. Of 135 patients randomized to this approach without additional medication, 45% were moderately or markedly improved at the 12-week end point (Foster et al, 2010). In another trial, hydrodistention followed by bladder training produced a statistically significant better response at 24 weeks post-procedure than hydrodistention alone (Hsieh et al, 2012).

Unfortunately, education and self-help are often not sufficient, and most patients will require one or more of a variety of therapies.

Oral Therapies (Table 14-4)**Amitriptyline**

Amitriptyline, a tricyclic antidepressant, has become a staple of oral treatment for BPS/IC. The tricyclics possess varying degrees of at least three major pharmacologic actions: (1) They have central and peripheral anticholinergic actions at some but not all sites, (2) they block the active transport system in the presynaptic nerve ending that is responsible for the reuptake of the released amine neurotransmitters serotonin and noradrenaline, and (3) they are sedatives, an action that occurs presumably on a central basis but perhaps is related to their antihistaminic properties. Amitriptyline, in fact, is one of the most potent tricyclic antidepressants in terms of blocking H₁-histaminergic receptors (Baldessarini et al, 1985).

There is also evidence that they desensitize α_2 receptors on central noradrenergic neurons. Paradoxically, they also have been shown to block α -adrenergic receptors and serotonin receptors. Theoretically, tricyclic agents have actions that might tend to stimulate predominantly β -adrenergic receptors in bladder body smooth musculature, an action that would further facilitate urine storage by decreasing the excitability of smooth muscle in that area (Barrett et al, 1987).

Hanno and Wein first reported a therapeutic response in IC after noting a "serendipitous" response to amitriptyline in one of their patients concurrently being treated for depression (Hanno and Wein, 1987). The following year, a similar report appeared relating a response to desipramine hydrochloride (Renshaw, 1988). Reasoning that a drug used successfully at relatively low doses for many types of chronic pain syndromes, that would also have anticholinergic properties, β -adrenergic bladder effects, sedative characteristics, and strong H₁-antihistaminic activity, would seem to be ideal for IC, the first clinical trial was carried out with promising results (Hanno et al, 1989). A subsequent follow-up study (Hanno, 1994a) reported that in 28 of 43 patients who could tolerate therapy for at least a 3-week trial at a dose of 25 mg at bedtime gradually increasing to 75 mg at bedtime over 2 weeks, 18 had total remission of symptoms with a mean follow-up of 14.4 months, 5 dropped out because of side effects, and 5 derived no clinical benefit. Benefits were apparent within 4 weeks. In all patients, hydrodistention and intravesical DMSO therapy had failed. Sedation was the main side effect. Kirkemo and colleagues treated 30 patients and had a 90% subjective improvement rate at 8 weeks (Kirkemo et al, 1990). Both studies noted that patients with bladder capacities over 450 to 600 mL under anesthesia seemed to have the best results. Another uncontrolled study of 11 patients with urinary frequency and pelvic pain (Pranikoff and Constantino, 1998) related success in 9 of the patients, with 5 reporting complete resolution of symptoms and 4 significant relief. Two patients could not tolerate the medication. In a 4-month intent-to-treat placebo-controlled double-blind trial of 50 patients, 63% on amitriptyline at doses of 25 to 75 mg (dose as tolerated) before bed reported good or excellent satisfaction versus

TABLE 14-4 Grade and Level of Evidence According to Oxford System for Oral and Intravesical Therapies

TREATMENT	ICI*	EAU†	GIANNANTONI‡
ORAL THERAPIES			
Amitriptyline	B: 2	A: 1	A: 1
Analgesics	C: 4	C: 2	
Hydroxyzine	D: 1	A: 1	
PPS	D: 1	A: 1	C: 1
Cyclosporine	C: 3	A: 1	A: 1
L-Arginine	—A: 1		A: 1
Antibiotics regimens	D: 4		
Azathioprine	D: 4		
Benzydamine	D: 3		
Chloroquine derivatives	D: 4		
Cimetidine	C: 3		
Doxycycline	D: 4		
Duloxetine	—C: 4		
Gabapentin	C: 4		
Methotrexate	D: 4		
Misoprostol	D: 4		
Montelukast	D: 4		
Nalmefene	—A: 1		
Nifedipine	D: 4		
Quercetin	D: 4		
Tanezumab	D: 1		
Suplatast tosilate	D: 3		
Vitamin E	D: 4		
INTRAVESICAL THERAPIES			
Lidocaine	C: 2		
DMSO	B: 2	A: 1	
Heparin	C: 3		
Hyaluronic acid	D: 1	B: 2	
Chondroitin sulfate	D: 4	B: 2	A: 1
PPS	D: 4	A: 1	
Capsaicin/RTX	—A: 1		
BCG	—A: 1		A: 1
Oxybutynin	D: 4		
BTX (intramural)	A: 1		A: 1

BCG, bacille Calmette-Guérin; BTX, botulinum toxin; DMSO, dimethyl sulfoxide; EAU: European Association of Urology; ICI, International Consultation on Incontinence, 2012; PPS, pentosan polysulfate; RTX, resiniferatoxin.

*Hanno P, Dinis P, Lin A, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence. Paris: International Consultation on Urological Diseases/European Association of Urology; 2013. p. 1583–649.

†Fall M, Baranowski AP, Elneil S, et al. EAU guidelines on chronic pelvic pain. *Eur Urol* 2010;57:35–48.

‡Giannantoni A, Bini V, Dmochowski R, et al. Contemporary management of the painful bladder: a systematic review. *Eur Urol* 2012;61:29–53.

From Committee on Bladder Pain Syndrome. Fifth International Consultation on Incontinence; 2012 Feb; Paris, France.

4% on placebo (van Ophoven et al, 2004a). At 19-month follow-up there was little tachyphylaxis, and good response rates were observed in the entire spectrum of BPS/IC symptoms (van Ophoven and Hertle, 2005).

The large, double-blind, randomized controlled trial by the NIDDK comparing education and behavioral modification with and without oral amitriptyline showed a 55% response in the arm that included both medication and conservative therapy compared with a 45% response to education and behavioral

therapy alone (Foster et al, 2010). The difference was not statistically significant. However, if only patients who could tolerate 25 mg or more of medication or placebo are included, the success compared with conservative therapy alone was 73% compared with 53% at 12 weeks. Frequency and O’Leary-Sant symptom and problem scores also showed significant improvement. Thus, on an intent-to-treat basis, there was not significant benefit from amitriptyline, but in the 62% of patients who could tolerate these relatively low doses of drug, the benefits appear substantial (Yang et al, 2014). Patients should be cautioned about fatigue, constipation, dry mouth, increased appetite, and dizziness. Slowly titrating the dose on a weekly basis, beginning at 10 mg before bed and increasing by 10 mg weekly to a maximum tolerated dose of 50 mg before bed seems to minimize side effects. Amitriptyline appears to have efficacy that is unrelated to the presence or absence of a Hunner lesion, and cystoscopy shows no predictive value for treatment outcome (Sun et al, 2014). It may also be beneficial in treating the vulvar pain syndrome that sometimes accompanies BPS (Ventolini, 2013).

Amitriptyline has proven analgesic efficacy with a median preferred dose of 50 mg in a range of 25 to 150 mg daily. This range is lower than traditional doses for depression of 150 to 300 mg. The speed of onset of effect is much faster (1 to 7 days) than reported in depression, and the analgesic effect is distinct from any effect on mood (McQuay and Moore, 1997). Tricyclic antidepressants are contraindicated in patients with long QT syndrome or significant conduction system disease (bifascicular or trifascicular block) after recent myocardial infarction (within 6 months), unstable angina, congestive heart failure, frequent premature ventricular contractions, or a history of sustained ventricular arrhythmias. They should be used with caution in patients with orthostatic hypotension (Low and Dotson, 1998). Doses greater than 100 mg are associated with increased relative risk of sudden cardiac death (Ray et al, 2004).

Other Antidepressants

Other tricyclic antidepressants have been used for BPS. One trial employed the combination of doxepin and piroxicam, a cyclooxygenase-2 (COX-2) inhibitor. Twenty-six of 32 patients (81%) experienced remission of symptoms (Wammack et al, 2002). Another study reported satisfactory outcome with desipramine (Renshaw, 1988). The safety and efficacy of duloxetine, a serotonin and norepinephrine reuptake inhibitor, for BPS/IC was assessed in an observational study of 48 women (van Ophoven and Hertle, 2007). Patients were prospectively treated for 2 months after an uptitration protocol to the target dose of 40 mg duloxetine twice daily. Five patients were identified as responders and 17 patients dropped out because of side effects including nausea in all 17 patients. No severe adverse events were reported. In the 5 responders, the 40-mg twice daily dose was required for efficacy to be seen. Overall, duloxetine did not result in clinically meaningful improvement of symptoms.

Antihistamines

The use of antihistamines goes back to the late 1950s and stems from work by Simmons, who postulated that the local release of histamine may be responsible for or may accompany the development of IC (Simmons, 1961). He reported on 6 patients treated with pyribenzamine. The results were far from dramatic, with only half the patients showing some response. The therapy is notable for this disease in that it was very logically conceived. It has been Theoharides who has spearheaded mast cell research in this field and been a major modern proponent of antihistamine therapy (Theoharides, 1994). He has used the unique piperazine H₁-receptor antagonist hydroxyzine, a first-generation antihistamine (Simons, 2004), which can block neuronal activation of mast cells (Minogianis et al, 1998). In 40 patients treated with 25 mg before bed increasing over 2 weeks (if sedation was not a problem) to 50 mg at night and 25 mg in the morning, virtually every symptom

evaluated improved by 30%. Only 3 patients had absolutely no response. As with many IC drug reports, these responses were evaluated subjectively and without blinding or placebo control. A subsequent study suggested improved efficacy in patients with documented allergies and/or evidence of bladder mast cell activation (Theoharides et al, 1997; Theoharides and Sant, 1997). No significant response to hydroxyzine was found in an NIDDK placebo-controlled trial (Sant et al, 2003).

Why an H₂-antagonist would be effective is unclear, but uncontrolled studies show improvement of symptoms in two thirds of patients taking cimetidine in divided doses totaling 600 mg (Seshadri et al, 1994; Lewi, 1996). It proved effective in a double-blind, placebo-controlled trial (Thilagarajah et al, 2001), but histologic studies show the bladder mucosa to be unchanged before and after treatment, and the mechanism of any efficacy remains unexplained (Dasgupta et al, 2001). Cimetidine is a common treatment in the United Kingdom, where over a third of patients reported having used it (Tincello and Walker, 2005).

Sodium Pentosan Polysulfate

Parson's suggestion that a defect in the epithelial permeability barrier, the GAG layer, contributes to the pathogenesis of IC has led to an attempt to correct such a defect with the synthetic sulfated polysaccharide sodium pentosan polysulfate (PPS), a heparin analogue available in an oral formulation, 3% to 6% of which is excreted into the urine (Barrington and Stephenson, 1997). It is sold under the trade name Elmiron. Study findings have been contradictory.

Fritjofsson treated 87 patients in an open multicenter trial in Sweden and Finland (Fritjofsson et al, 1987). Bladder volume with and without anesthesia was unchanged. Relief of pain was complete in 35% and partial in 23% of patients. Daytime frequency decreased from 16.5 to 13 and nocturia decreased from 4.5 to 3.5. Mean voided volumes increased by almost a tablespoon in the nonulcer group. Holm-Bentzen studied 115 patients in a double-blind, placebo-controlled trial (Holm-Bentzen et al, 1987b). Symptoms, urodynamic parameters, cystoscopic appearance, and mast cell counts were unchanged after 4 months. Bladder capacity under anesthesia increased significantly in the group with mastocytosis, but this had no bearing on symptoms or awake capacity.

Parsons had a more encouraging initial experience (Parsons et al, 1983), and subsequently the results of two placebo-controlled multicenter trials in the United States were published (Mulholland et al, 1990; Parsons et al, 1993). In the initial study, overall improvement of more than 25% was reported by 28% of the PPS-treated group versus 13% of the placebo group. In the latter study the respective figures were 32% on drug versus 16% on placebo. Average voided volume on PPS increased by 20 mL. No other objective improvements were documented. An NIDDK 2 × 2 factorial study to evaluate PPS and hydroxyzine looked at each drug used alone and in combination and compared results with a placebo group (Sant et al, 2003). Patients were treated for 6 months. No statistically significant response to either medication was documented. No significant trend was seen in the PPS treatment groups (34%) compared with non-PPS groups (18%). Of the 29 patients on PPS alone, 28% had a global response (the primary end point) of moderate or marked improvement versus 13% on placebo, a number remarkably similar to the results in the 3-month pivotal trials, although not reaching statistical significance in the 6-month study. A subsequent industry-sponsored trial showed no dose-related efficacy response in the range of 300 to 900 mg daily; however, adverse events were dose related (Nickel et al, 2005a). Another 6-month trial that compared PPS with cyclosporine A yielded a 19% response rate for PPS compared with a 75% global response to cyclosporine A (Sairanen et al, 2005).

Long-term experience with PPS in uncontrolled studies is consistent with efficacy in a subset of patients (Al-Zahrani and Gajewski 2011) that may drop below 30% of those initially treated (Jepsen et al, 1998). Tachyphylaxis seems to be uncommon in responders. A phase 4 study mandated by the U.S. Food and

Drug Administration (FDA) and initiated in July 2004 was terminated in January 2011. It evaluated the safety and efficacy of PPS, comparing 100 mg once a day, 100 mg three times a day, and placebo for 24 weeks in 66 study locations in 369 patients. The study was terminated when interim analysis showed that study continuation was futile and the drug was ineffective (<http://clinicaltrials.gov/ct2/show/results/NCT00086684?term=elmiron&rank=1>).

Adverse events with PPS occurred in less than 4% of patients at the dose of 100 mg three times daily (Hanno, 1997) and included reversible alopecia, diarrhea, nausea, and rash. Rare bleeding problems have been reported (Rice et al, 1998). It promotes cellular proliferation in vitro in the MCF-7 breast cancer cell line, and caution has been suggested in prescribing it in groups at high risk for breast cancer and premenopausal females (Zaslau et al, 2004). A 3- to 6-month treatment trial is usually required to see symptom improvement. In a small trial, PPS has shown efficacy when administered intravesically (Bade et al, 1997a). It may be of value in the management of radiation cystitis (Parsons, 1986; Hampson and Woodhouse, 1994) and cyclophosphamide cystitis (Toren and Norman, 2005), but its value in the treatment of BPS/IC seems marginal.

Immunomodulator Drugs

Cyclosporine. Cyclosporine, a widely used immunosuppressive drug in organ transplantation, was the subject of a novel BPS trial (Forsell et al, 1996). Eleven patients received cyclosporine for 3 to 6 months at an initial dose of 2.5 to 5 mg/kg daily and a maintenance dose of 1.5 to 3 mg/kg daily. Micturition frequency decreased, and mean and maximum voided volumes increased significantly. Bladder pain decreased or disappeared in 10 patients. After cessation of treatment, symptoms recurred in the majority of patients.

In a longer-term follow-up study, 20 of 23 refractory IC patients on cyclosporine therapy followed for a mean of 60.8 months became free of bladder pain. Bladder capacity more than doubled. Eleven patients subsequently stopped therapy, and in 9, symptoms recurred within months but responded to reinitiating cyclosporine (Sairanen et al, 2004). Sairanen and colleagues further found that cyclosporine A was far superior to sodium PPS in all clinical outcome parameters measured at 6 months (Sairanen et al, 2005). Patients who responded to cyclosporine A had a significant reduction of urinary levels of EGF (Sairanen et al, 2008). Data from three centers in the United States reported success in 23 of 34 patients with Hunner lesions and 3 of 10 patients without Hunner lesions (Forrest et al, 2012). A 3- to 4-month trial was suggested to gauge treatment success. Measurement of luminal nitric oxide has correlated lower levels with treatment response to cyclosporine (Ehrén et al, 2013). A case report highlighted success in a patient with primary SS and BPS (Emmungil et al, 2012).

Suplatast Tosilate. Suplatast tosilate (IPD-1151T) is an immunoregulator that selectively suppresses IgE production and eosinophilia via suppression of helper T cells that produce IL-4 and IL-5. It is used in Japan to treat allergic disorders including asthma, atopic dermatitis, and rhinitis. Ueda and colleagues reported a small study in 14 women with IC (Ueda, 2000). Treatment for 1 year resulted in a significantly increased bladder capacity and decreased urinary urgency, frequency, and lower abdominal pain in 10 women. Concomitant changes occurred in blood and urine markers, suggesting an immune system response. Larger, multicenter, randomized controlled trials in the United States and Japan have not led to the governmental approval of the BPS/IC indication or the introduction of the drug into the United States.

Azathioprine and Chloroquine Derivatives. In a single report in 1976, Oravisto and colleagues used azathioprine or chloroquine derivatives for BPS patients not responding to other treatments (Oravisto and Alfthan, 1976). About 50% of patients responded.

Mycophenolate Mofetil. In an aborted multicenter randomized placebo-controlled NIDDK trial, mycophenolate mofetil (CellCept) 1 to 2 g daily in divided doses failed to show efficacy in the treatment of symptoms of refractory BPS/IC. The trial, which included

59 patients randomized 2:1 to the active arm, was halted when the FDA issued a new black box warning for the drug (*miscarriage and congenital malformations have been associated with its use*), and an **interim analysis showed no benefit** (Yang et al, 2011).

Adalimumab. A randomized double-blind placebo-controlled trial of this TNF-inhibiting anti-inflammatory agent failed to demonstrate positive proof of concept for this drug, which is approved for use in the treatment of rheumatoid, psoriatic, and other types of arthritis; plaque psoriasis; Crohn disease; and ulcerative colitis (Bosch, 2014).

Miscellaneous Agents

L-Arginine. Foster and Weiss were the original proponents of L-arginine in the therapy of IC (Foster et al, 1997). Eight patients with IC were given 500 mg of L-arginine three times daily. After 1 month, urinary NOS activity increased 8-fold and 7 of the 8 patients noticed improvement in symptoms. An open-label study of 11 patients showed improvement in all 10 of the patients who remained on L-arginine for 6 months (Smith et al, 1997).

An open-label study of 9 women in Sweden failed to find any change in symptom scores or in nitric oxide production in the bladder (Ehrén et al, 1998). A placebo-controlled randomized trial of 53 BPS/IC patients could find no difference on an intention-to-treat analysis between drug- and placebo-treated patients (Korting et al, 1999). A smaller randomized placebo-controlled crossover trial of 16 BPS patients found no clinically significant improvement with L-arginine and concluded that it could not be recommended for IC treatment (Cartledge et al, 2000).

The body of evidence does not support the use of L-arginine for the relief of symptoms of IC.

Quercetin. Quercetin, a bioflavonoid available in many over-the-counter products, may have the anti-inflammatory effects of other members of this class of compounds found in fruits, vegetables, and some spices. Katske and colleagues administered 500 mg twice daily to 22 BPS patients for 4 weeks (Katske et al, 2001). All but 1 patient had some improvement in the O'Leary-Sant symptom and problem scores as well as in a global assessment score. Further larger studies with placebo controls are necessary to determine efficacy.

Antibiotics. Warren and colleagues (2000) randomized 50 patients to receive 18 weeks of placebo or antibiotics including rifampin plus a sequence of doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin, and ciprofloxacin for 3 weeks each. Intent-to-treat analysis demonstrated that 12 of 25 patients in the antibiotic and 6 of 25 patients in the placebo group reported overall improvement, whereas 10 and 5, respectively, noticed improvement in pain and urgency. The study was complicated by the fact that 16 of the patients in the antibiotic group underwent new BPS therapy during the study, as did 13 of the placebo patients. There was no statistical significance reached. What was statistically significant was the occurrence of adverse events in 80% of participants who received antibiotics compared with 40% in the placebo group. Nausea and/or vomiting and diarrhea were the predominant side effects. Most patients on antibiotics correctly guessed what treatment arm they were in, and those who guessed correctly were significantly more likely to note improvement after the study. No duration in improvement after completion of the trial of antibiotics was reported.

Burkhard and colleagues recorded a 71% success rate in 103 women with a history of urinary urgency and frequency and chronic urethral and/or pelvic pain often associated with dyspareunia and/or a history of recurrent urinary tract infection (Burkhard et al, 2004). This was a large, inclusive group and one that is probably broader than the BPS on which we are focusing. Nevertheless, Burkhard recommended empirical doxycycline in this group. The overwhelming majority of BPS patients have been treated with empirical antibiotics before diagnosis.

At this time there is no evidence to suggest that antibiotics have a place in the therapy of BPS in the absence of a culture-documented infection (Maskell, 1995). Nevertheless, it would not

be unreasonable to treat patients with *one* empirical course of antibiotic, if they have never been on an antibiotic for their urinary symptoms.

Methotrexate. Low-dose oral methotrexate significantly improved bladder pain in four of nine women with BPS but did not change urinary frequency, maximum voided volume, or mean voided volume (Moran et al, 1999). No placebo-controlled RCT has been done with this agent.

Montelukast. Mast cell triggering releases two types of proinflammatory mediators, including granule stored preformed types such as heparin and histamine and newly synthesized prostaglandins and leukotrienes B₄ and C₄. Classic antagonists, such as montelukast, zafirlukast, and pranlukast, block cysteinyl leukotriene-1 receptors. In a pilot study (Bouchelouche et al, 2001b), 10 women with IC and detrusor mastocytosis received 10 mg of montelukast daily for 3 months. Frequency, nocturia, and pain improved dramatically in 4 of the patients. Further study would seem to be warranted, especially in patients with detrusor mastocytosis, defined as more than 28/mm² (Traut et al, 2011).

Nifedipine. The calcium channel antagonist nifedipine inhibits smooth muscle contraction and cell-mediated immunity. In a pilot study (Fleischmann, 1994), 30 mg of an extended-release preparation was administered to 10 female patients and titrated to 60 mg daily in 4 of the patients who did not get symptom relief. Within 4 months, 5 patients showed at least a 50% decrease in symptom scores, and 3 of the 5 were asymptomatic. No further studies have been reported.

Misoprostol. The oral prostaglandin analogue misoprostol was studied in 25 patients at a dose of 600 µg daily (Kelly et al, 1998). At 3 months 14 patients were significantly improved, and at 6 months 12 patients still had a response. A cytoprotective action in the urinary bladder was postulated.

Dextroamphetamine. A single anecdotal series of six patients reported benefit from use of 30 mg of dextroamphetamine sulfate daily, with return of symptoms on discontinuation of medication (Check et al, 2013).

Phosphodiesterase Inhibitors. The use of phosphodiesterase (PDE) inhibitors for BPS has long been considered. PDE type 5 (PDE5) inhibitors are hypothesized to relax smooth muscle or structures involved in afferent signaling and suppress smooth muscle spontaneous activity (Truss et al, 2001; Hanna-Mitchell and Birdier, 2011; Chen et al, 2014a). Trials using them for BPS are underway.

Analgesics

The long-term, appropriate use of pain medications forms an integral part of the treatment of a chronic pain condition such as IC. Most patients can be helped markedly with medical pain management using pain medications commonly used for chronic neuropathic pain syndromes including antidepressants, anticonvulsants, and opioids (Wesselmann et al, 1997). Many nonopioid analgesics including acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs) and even antispasmodic agents (Rumman, 1994) have a place in therapy along with agents designed to specifically treat the disorder itself.

Studies on the use of analgesics for BPS are sparse, and most data have been inferred from non-BPS types of pain and expert opinion. Health professionals should ask about pain, and the patient's self-report should be the primary source of assessment. Clinicians should assess pain with easily administered rating scales and should document the efficacy of pain relief at regular intervals after starting or changing treatment.

Unlike opioids, with increasing doses acetaminophen, aspirin, and the other NSAIDs all reach a ceiling for their maximum analgesic effect (Drugs for pain, 1998). Gabapentin, introduced in 1994 as an anticonvulsant, has found efficacy in neuropathic pain disorders including diabetic neuropathy (Backonja et al, 1998) and postherpetic neuralgia (Rowbotham et al, 1998). It demonstrates synergism with morphine in neuropathic pain (Gilon et al, 2005). It may give some benefit in CPPS and BPS/IC (Sasaki et al, 2001). Pregabalin is also reported to be effective

for neuropathic pain and the pain of fibromyalgia (Freynhagen et al, 2005; Arnold et al, 2008).

With the results of major surgery anything but certain, the use of long-term opioid therapy in the patient in whom more conservative therapies have failed may also be considered (Box 14-8). Opiates are seldom the first choice of analgesics in chronic pain states, but they should not be withheld if less powerful analgesics have failed (Portenoy et al, 1997; Bennett, 1999). This is a difficult decision that requires much thought and discussion between patient and urologist, and involvement of a pain specialist is indicated. A single practitioner has to take responsibility for pain treatment and write all prescriptions for pain medications (Brookoff and Sant, 1997). Opioids are effective for most forms of moderate and severe pain and have no ceiling effect other than that imposed by adverse effects. The common side effects include sedation, nausea, mild confusion, and pruritus. In general, these are transient and easily managed. Respiratory depression is extremely rare if they are used as prescribed. Constipation is common and a mild laxative is typically necessary. The major impediment to the proper use of these drugs when they are prescribed for long-term nonmalignant

BOX 14-8 General Guidelines for the Use of Opioids in Chronic or Nonacute Urogenital Pain

1. All other reasonable treatments must have been tried and failed.
2. The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (preferably the patient's family doctor).
3. When there is a history or suspicion of drug abuse, a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.
4. The dose required needs to be calculated by careful titration.
5. The patient should be made aware of (and possibly give written consent regarding) the following:
 - a. Opioids are strong drugs and associated with addiction and dependency.
 - b. Opioids will normally be prescribed from only one source.
 - c. The drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period.
 - d. The patient will be subjected to spot urine and possibly blood checks to ensure that the drug is being taken as prescribed and that nonprescribed drugs are not being taken.
 - e. Inappropriate aggressive behavior associated with demanding the drug will not be accepted.
 - f. Hospital specialist review will normally occur at least once a year.
 - g. The patient may be requested to attend a psychiatric or psychological review.

Failure to comply with the above may result in the patient being referred to a drug dependency agency and the use of therapeutic, analgesic opioids being stopped.
6. Morphine is the first-line drug, unless there are contraindications to morphine or special indications for another drug. The drug should be prescribed in a slow-release or modified-release form. Short-acting preparations are undesirable and should be avoided where possible. Parenteral administration is undesirable and should be avoided when possible.

From Fall M, Baranowski A, Elneil S, et al. Guidelines on chronic pelvic pain. European Association of Urology; 2008. p. 1–99. www.uroweb.org/professional-resources/guidelines/.


pain is the fear of addiction. Studies suggest the risk is low (Gourlay, 1994). The long-acting narcotic formulations that result in steady levels of drug over many hours are preferable.

Chronic pain patients often receive inadequate doses of short-acting pain medications, which put them on cycles of short-term relief, anxiety, and pain. It leads to doctor-shopping and drug-seeking behavior confused by physicians with drug addiction. Although physical dependence on opioids will be unavoidable, physical addiction, a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user and the continued use despite that harm, is rare. Chronic opioid therapy can be considered in carefully selected patients. It is best administered in a pain clinic setting and necessitates frequent reassessment by both patient and physician (Portenoy and Foley, 1986).

KEY POINTS: ORAL THERAPIES

- Few of the oral therapies commonly used for the treatment of BPS have unequivocal evidence of efficacy in large, multicenter, randomized controlled clinical trials.
- There is little evidence that any of these therapies change the natural history of the disease, although many seem effective in individual patients.

Intravesical Therapies (see Table 14-4)

The use of silver nitrate and Clorpectin is described on the Expert Consult website. 

Dimethyl Sulfoxide

A mainstay of the treatment of BPS is the intravesical instillation of 50% DMSO (Sant, 1987). It is sometimes administered in a solution with sodium bicarbonate, heparin, and/or steroid, but its only FDA-approved use is as a stand-alone treatment (Stav et al, 2012; Gafni-Kane et al, 2013). DMSO is a byproduct of the wood pulp industry and a derivative of lignin. It has exceptional solvent properties and is freely miscible with water, lipids, and organic agents. One must be cognizant of systemic absorption of coadministered agents. Pharmacologic properties include membrane penetration, enhanced drug absorption, anti-inflammatory action (Kim et al, 2011), analgesic effects, collagen dissolution, muscle relaxation, and mast cell histamine release. In vitro effects on bladder function belie its positive effects in vivo (Freedman et al, 1989), where histamine release has not been demonstrated after treatment (Stout et al, 1995). It has been suggested that DMSO actually desensitizes nociceptive pathways in the lower urinary tract (Birder et al, 1997). Tests for DMSO for treatment of human illness began in the 1960s in the areas of musculoskeletal inflammation and the cutaneous manifestations of scleroderma.

Stewart and colleagues are credited for popularizing intravesical DMSO for BPS/IC (Stewart et al, 1967). In the mid 1960s he applied it to the skin over the suprapubic area in a group of patients refractory to conventional forms of therapy. Results were poor, but intravesical delivery of 50 mL of a 50% solution instilled for 15 minutes by catheter and repeated at intervals of 2 to 4 weeks showed positive effects lasting 2 to 12 months in six of eight patients. The absence of side effects, other than a garlic-like odor on the breath, and the lack of a need for inpatient administration were significant breakthroughs over previous treatments. Further reports by this group confirmed safety and efficacy (Stewart et al, 1971, 1972; Stewart and Shirley, 1976; Shirley et al, 1978) with symptom-free intervals of 1 to 3 months in 73% of patients. Ek reported a 70% success rate but found that most patients ultimately required retreatment or further therapy with other modalities (Ek et al, 1978). Prospective series of Fowler (Fowler, 1981) and Barker and colleagues (Barker et al,

Silver Nitrate

Although the evidence base for treating BPS/IC using intravesical preparations is limited and the potential for meta-analysis reduced by variation in the outcome measures used (Dawson and Jamison, 2007), intravesical lavage with one of a variety of preparations has remained a mainstay of treatment in the therapeutic armamentarium of BPS. Perhaps the oldest of the intravesical therapies is silver nitrate. The use of silver nitrate has been attributed to Mercier (Pool and Rives, 1944) who reported in 1855 that excellent results with bladder instillations had been obtained in patients with symptoms compatible with IC. Dodson advocated the use of solutions of silver nitrate in increasing strengths as the treatment of choice for this condition (Dodson, 1926). Pool and Rives (1944) reported on 74 patients with IC treated with intravesical silver nitrate. The treatment was carried out as follows:

A urethral catheter is inserted and the contents of the bladder are evacuated. The bladder is then irrigated with a saturated solution of boric acid. Then 30 to 60 cc of a 1:5000 solution of silver nitrate is instilled into the bladder and permitted to remain there for 3 or 4 minutes if it does not cause intolerable irritation. At the end of this period the solution is permitted to run out through the catheter, which is then withdrawn. The patient usually experiences some dysuria and vesical irritability for 2 or 3 hours. Treatments are repeated every other day. At subsequent treatments, the concentration of silver nitrate in the solution is increased to 1:2500, 1:1000, 1:750, 1:500, 1:400, 1:200, and finally 1:100. If at any time the reaction is too severe, the concentration is increased more slowly.

Although the initial treatments are performed with the patient under general anesthesia, later treatments are given on an outpatient basis. Ureteral reflux would be a contraindication, and it goes without saying that bladder biopsy would be contraindicated just before instillation for fear of extravasation. Twenty-three years later, Pool wrote that he still considered this treatment regimen the most efficacious form of treatment (Pool, 1967). Pool reported excellent results in 70% of patients with a mean response of 7.6 months. Burford reported a 14% cure rate and 79% improved figure (Burford and Burford, 1958). DeJuana had a 50% response rate in 102 patients (DeJuana and Everett, 1977).

Although silver nitrate is not used in the current treatment of BPS, an animal study showing that intravesical administration of nanocrystalline silver (1%) decreased urine histamine, bladder TNF- α , and mast cell activation in an experimental inflammation

model without any toxic effect, may restimulate interest in silver compounds (Boucher et al, 2008).

Clorpactin

O'Connor reported on the use of intravesical Clorpactin WCS 90 (O'Connor, 1955). *Clorpactin* is a term for closely related, highly reactive chemical compositions having a modified derivative of hypochlorous acid in a buffered base. Its activity is dependent on the liberation of hypochlorous acid and its resulting oxidizing effects, wetting and penetrating properties, and detergency. Wishard treated 20 patients with 0.2% Clorpactin gently lavaged in the bladder for 3 to 5 minutes without anesthesia; 14 patients reported subjective improvement (Wishard et al, 1957). Murnaghan noted improvement in 14 of 17 patients, although 10 required further treatment during the average 2-year follow-up (Murnaghan et al, 1970). Most commonly, the treatments are given as described by Messing and Stamey, using 0.4% solution administered at 10 cm water pressure under anesthesia (Messing and Stamey, 1978). Multiple instillations can be given, with a 1-month pause after the first two instillations to await a therapeutic response. Their success rate was 72% with an average 6-month duration of response. LaRock noted a 50% to 55% meaningful improvement rate occurring within 4 to 6 weeks of treatment (LaRock and Sant, 1995). A case of ureteral fibrosis complicating the treatment prompted the recommendation that vesicoureteral reflux be considered a contraindication to the procedure (Messing and Freiha, 1979). Our method of Clorpactin delivery is as follows:

1. Reflux is excluded with a cystogram.
2. Under anesthesia the bladder is distended for 2 minutes at 60 to 80 cm water pressure and emptied.
3. The perineum is shielded with a moistened towel.
4. A solution of 0.4% freshly prepared Clorpactin (4 g in 1000 mL of sterile water) is instilled by gravity drainage (the Foley catheter is held 10 cm above the level of the bladder) in 150- to 200-mL aliquots for a dwell time of 2 to 3 minutes and drained by gravity. This continues until the entire 1000 mL of solution has been used.
5. The bladder and introitus are then irrigated with normal saline and the catheter is removed.

Clorpactin is rarely used at the present time, and there is no current literature on this therapy. It is not a part of any guideline algorithm and has fallen out of favor.

1987) revealed symptomatic success rates higher than 80%, although relapse was not uncommon. Fowler noted only minimal improvements in functional bladder capacity and attributed the beneficial effects of DMSO to a direct effect on the sensory nerves of the bladder. Perez-Marrero compared DMSO with saline and showed a 93% objective improvement and 53% subjective improvement compared with 35% and 18%, respectively, for saline (Perez-Marrero et al, 1988). Patients with bladder instability do not respond (Emerson and Feltis, 1986). Stav and Hung reported 60% success rates and recommended it be considered a first-line therapy (Stav et al, 2012; Hung et al, 2012).

With its ease of administration (Biggers, 1986), low morbidity, and reasonable symptomatic results, DMSO certainly merits its place as a useful treatment for BPS/IC. In vivo studies on rat bladder strips exposed to various concentrations of DMSO for 7 minutes showed absence of electrical field stimulation contraction at a 40% concentration and diminished compliance at 30% concentration (Melchior et al, 2003). Concentrations of 25% or less had negligible effects in this model. How it relates to use of DMSO in humans is unknown. A rare case of eosinophilic cystitis has been reported after DMSO instillation (Abramov et al, 2004).

DMSO is often administered as part of an “intravesical cocktail” (50 mL Rimso-50 + 10 mg Kenalog + 44 mEq sodium bicarbonate + 20,000 to 40,000 units intravesical heparin) weekly for 6 weeks. If there is a good clinical response, maintenance therapy consisting of administration of the cocktail monthly for 6 months has been employed. There are no controlled studies as to the efficacy of this combined therapy, nor are there long-term safety studies reported. There is an inherent problem in doing placebo-controlled trials with DMSO because the strong garlic odor resulting from instillation quickly unblinds any trial.

Glycosaminoglycans

Exogenous GAGs have been shown to be effective in providing an epithelial permeability barrier in bladders in which the epithelium has been injured with protamine (Nickel et al, 1998). Heparin, which can mimic the activity of the bladder's own mucopolysaccharide lining (Hanno et al, 1978b), has anti-inflammatory effects as well as actions that inhibit fibroblast proliferation, angiogenesis, and smooth muscle cell proliferation. Because of its numerous effects, the possibility that heparin could be used for therapeutic reasons other than the control of coagulation has been the subject of much inquiry and speculation (Lane and Adams, 1993). Weaver first reported on the use of intravesical heparin for IC treatment (Weaver et al, 1963). Given intravesically, there is virtually no systemic absorption, even in an inflamed bladder (Caulfield et al, 1995). Although uncontrolled studies suggested some beneficial effect for subcutaneous administration (Lose et al, 1983, 1985), the obvious risks of anticoagulation and osteoporosis have prevented this form of administration from undergoing further trials and general usage. Ten thousand units can be administered intravesically in sterile water either alone or with DMSO at varying intervals with good results reported (Perez-Marrero et al, 1993; Parsons et al, 1994a). Kuo reported 50% or greater improvement in the International Prostate Symptom Score in 29 of 40 women with IC treated with 25,000 units intravesically twice weekly for 3 months (Kuo, 2001).

Parsons has used daily intravesical doses of 40,000 units of heparin in 20 mL of sterile water administered by the patient daily and held for 30 to 60 minutes. “Reasonable improvement of symptoms” can be expected between 6 months and 2 years after initiation of therapy (Parsons, 2000). Adding alkalized lidocaine to the heparin instillation provides better pain relief (Parsons, 2005). The addition of 8 mL of 2% lidocaine and 4 mL of 8.4% sodium bicarbonate may improve results (Welk and Teichman, 2008). In fact, a combination of 200 mg of lidocaine with 8.4% sodium bicarbonate (10 mL total solution) without heparin showed a 30% response rate 3 days after completion of daily intravesical administration for 5 days and was statistically superior to a placebo cocktail (Nickel et al, 2009b). A Japanese study reported high success rates with

weekly intravesical instillation of 20,000 units of heparin with 5 mL of 4% lidocaine and 25 mL of 7% sodium bicarbonate for 12 weeks (Nomiya et al, 2013). Intravesical administration of a solution of lidocaine and heparin has been proposed as a treatment for symptom flare (Parsons et al, 2012).

Another GAG analogue, PPS, administered intravesically (300 mg twice weekly in 50 mL of normal saline) showed some modest benefit in a small trial (Bade et al, 1997a). A 41-patient trial comparing oral PPS with oral and intravesical administration showed that the 24% reduction in O’Leary-Sant scores with oral therapy alone rose to a 46% reduction in the group that also received intravesical PPS (Davis et al, 2008).

The nonsulfated GAG hyaluronic acid has also been used intravesically. Trials using 40 mg dissolved in 40 mL of normal saline weekly for 4 to 6 weeks and then monthly treatments thereafter have had response rates varying from 71% (Morales et al, 1996) to 30% (Porru et al, 1997). In the summer of 2003 Bioniche Life Sciences and in the spring of 2004 Seikagaku Corporation reported double-blind, placebo-controlled, multicenter clinical studies of their hyaluronic acid preparations (40 mg or 200 mg per milliliter, respectively), and neither showed significant efficacy of sodium hyaluronate compared with placebo. These negative studies have not been published in peer-reviewed literature. Neither preparation has been approved for use for BPS/IC in the United States. An Austrian open-label study showed that 13 of 27 patients with BPS and a positive potassium test result responded to intravesical hyaluronic acid 40 mg weekly for 10 weeks, though initial nonresponders at 5 weeks also were treated with intravesical PPS 200 mg three times weekly for the remaining 5 weeks (Daha et al, 2008). The best results for hyaluronic acid come from Riedl, who studied 126 patients with a positive modified potassium test result who could hold the solution for 2 hours, using 40 mg weekly for a minimum 10 weeks; 84% had significant improvement (Riedl et al, 2008). Treatment-resistant cases have been managed with a combination of sequential bladder distention under anesthesia accompanied by a hyaluronic acid instillation every 1 to 3 months depending on response with a 74% success rate in 23 patients (Ahmad et al, 2008). Although hyaluronic acid has been seemingly efficacious in uncontrolled trials (Van Agt et al, 2011; Engelhardt et al, 2011; Figueiredo et al, 2011; Lv et al, 2012; Lai et al, 2013), the efficacy of hyaluronic acid for BPS/IC remains unproven in controlled and blinded trials (Iavazzo et al, 2007). It remains unapproved for BPS in the United States.

Chondroitin sulfate plays an important role for bladder barrier function (Janssen et al, 2013). Hurst has shown by immunohistochemistry a deficit of chondroitin sulfate from the luminal bladder surface in IC patients (Hurst, 2003). Intravesical chondroitin sulfate inhibited recruitment of inflammatory cells in an experimental “leaky bladder” model of cystitis (Engles et al, 2012). Small uncontrolled studies using intravesical chondroitin sulfate have shown success rates of 33% to 75% (Steinhoff et al, 2002; Sorensen, 2003; Tornero et al, 2013). A multicenter, open-label study using a 2% solution of sodium chondroitin sulfate weekly for 6 weeks and then monthly for 4 months had a 60% response rate with no safety issues (Nickel et al, 2009a). A larger follow-up study failed to demonstrate significant efficacy (Nickel et al, 2012; Thakkinstian and Nickel, 2013). A large open-label experience using the device for all forms of “chronic cystitis” concluded that it was effective in improving urgency, voided volumes, and nocturia, and well tolerated when administered weekly for a maximum of eight instillations (Nordling and van Ophoven, 2008).

The GAGs have been combined for instillation with good results reported in uncontrolled studies (Cervigni et al, 2008; Cervigni et al, 2012; Porru et al, 2012; Giberti et al, 2013).

A large analysis of GAG layer replenishment therapy with intravesical GAGs concluded that despite the fact that GAG intravesical therapy has been in use for over two decades, most of the studies have been uncontrolled, have been poorly done, and have had a small number of patients. Large-scale randomized controlled trials are urgently needed to underline the benefit of this type of therapy. Distinct patient groups (well phenotyped) need to be confirmed by

definite diagnostic findings (Madersbacher et al, 2013). Another review sadly concludes that “randomized controlled trials have suggested the GAG analogues are at best as good as placebo” (Chintea and Belal, 2013).

Other Intravesical Therapies



The use of doxorubicin, BCG, capsaicin, and resiniferatoxin (RTX) is described on the Expert Consult website.

KEY POINTS: INTRAVESICAL THERAPIES

- The potential for high efficacy combined with safety and a low side effect profile that is gained by applying a treatment directly to the bladder lining has made research into new methods of intravesical therapy a high priority of researchers and pharmaceutical companies.
- Patients in whom pain and other symptoms are not related directly to bladder pathology would not be expected to respond well to this type of organ-directed therapy.

Intradetrusor Therapies

The therapeutic value of **botulinum toxin type A (BTX-A)** stems partially from its ability to temporarily inhibit the release of acetylcholine and other neurotransmitters and to cause flaccid paralysis in a dose-related manner in skeletal muscle. It can correct focal dystonia when injected into a muscle. Intradetrusor BTX-A has now been approved for use in the United States in the management of refractory neurogenic and idiopathic DO. BTX-A also has analgesic properties (Rajkumar and Conn, 2004). Initially this effect was thought to be a result of relief of muscle spasm. However, botulinum has been shown to reduce peripheral sensitization by inhibiting the release of several neuronal signaling markers, including glutamate and substance P, and reducing *c-Fos* gene expression. It may affect the sensory feedback loop to the central nervous system by decreased input from the muscle tissue, possibly by inhibiting acetylcholine release from gamma motor neurons innervating intrafusal fibers of the muscle spindle (Rosales et al, 1996). It inhibits the release of sensory neurotransmitters from isolated bladder preparations in rat bladder models of both acute injury and chronic inflammation (Lucioni et al, 2008). Chronic inflammation and apoptosis is significantly reduced after repeated BTX-A injections in patients with BPS (Shie et al, 2013). BTX-A has been used effectively for years in different conditions with muscular hypercontractions. Intravesical BTX administration blocks the acetic acid-induced calcitonin gene-related peptide (CGRP) release from afferent nerve terminals in the bladder mucosal layer in rats (Chuang et al, 2004). In an animal model of bladder permeability barrier disruption, intravesical BTX-A minimized bladder irritability and restored afferent neural responses to baseline levels (Vemulakonda et al, 2005). These results support clinical trials of BTX-A for the treatment of BPS/IC and other types of visceral pain (Chancellor and Yoshimura, 2004).

A multi-institutional case series using Botox or Dysport intravesical injections in 13 patients with refractory BPS/IC reported improvement in 9 patients. Improvements in symptoms lasted a mean of 3.72 months (range 1 to 8 months). No systemic complications were observed, although 2 patients had a diminished flow with some need to strain to void (Smith and Chancellor, 2004). Rackley and colleagues at the Cleveland Clinic reported no change in objective or subjective outcome measures in a series of 10 BPS/IC patients in whom the trigone was spared in the injection technique (Rackley et al, 2005). A 1-year follow-up in 15 patients treated with 200 units of BTX-A in 20 mL of normal saline showed that the success rate fell from 86.6% at 3 months to 26.6% at 5 months and was 0 at 12 months (Giannantoni et al, 2008). Bladder biopsy 2 weeks after BTX-A intradetrusor injection showed that

nerve growth factor production levels fell to those of controls in patients who responded (Liu et al, 2009). It is hypothesized that treatment-refractory patients may have developed antibodies after initial BTX injection (Schulte-Baukloh et al, 2008).

The Portuguese group from Oporto has championed limiting injections to 100 units divided into 10 injection sites, all in the trigone. More than 50% of patients experienced efficacy with a duration of 9 months, and no voiding dysfunction was noted (Pinto et al, 2010). There appears to be little tachyphylaxis associated with the treatment, and repeated injections at regular intervals or when symptoms recur remain effective (Kuo, 2013; Pinto et al, 2013). Onabotulinum toxin A appears to be a reasonable treatment for BPS that is refractory to standard conservative, oral, and intravesical treatment (Mangera et al, 2011; Yokoyama et al, 2012). When injected into the trigone in 10-unit aliquots (100 units total), the risk of impaired bladder emptying seems to be minimized.

Submucosal injection of 10 mL of 40 mg/mL **triamcinolone acetonide** injected in 0.5-mL aliquots was used for the treatment of Hunner lesions in 30 patients (Cox et al, 2009). Seventy percent of patients were very much improved, and duration of improvement was estimated to be 7 to 12 months.

Neuromodulation

Because PBS/IC is a chronic pain syndrome, it is reasonable to consider therapeutic options that directly interface with the nervous system. This approach is further supported by the association of pelvic floor dysfunction with pelvic pain syndromes (Zermann et al, 1999).

Pain diversion by **transcutaneous electrical nerve stimulation (TENS)** is routine in a variety of painful conditions (Fall, 1987). Fall and colleagues were the first to use electrical stimulation in IC, reporting on 14 women treated successfully with long-term intravaginal nerve stimulation or TENS (Fall et al, 1980). Subsequently McGuire noted improvement in 5 of 6 patients treated with electrical stimulation (McGuire et al, 1983).

The primary intention in applying peripheral electrical nerve stimulation in IC is to relieve pain by stimulating myelinated afferents to activate segmental inhibitory circuits. As a secondary effect, urinary frequency may also be reduced. In the most complete review of the subject (Fall and Lindstrom, 1994), 33 patients with ulcerative IC and 27 patients with nonulcerative IC were treated by means of suprapubic TENS. Electrodes were positioned 10 to 15 cm apart immediately above the pubic symphysis. High- or low-frequency (2 to 50 Hz) TENS was employed. If there was no effect with high-frequency TENS after 1 month, low-frequency TENS was used. Application of 30 to 120 minutes of TENS was prescribed daily. Pain improved more than frequency. Good results or remission was described in 26% of nonulcerative IC patients and a surprising 54% of patients with ulcerative disease. Fall and Lindstrom (1994) caution that the experience is based on open studies, relatively few patients, and the knowledge of a significant placebo effect with peripheral pain stimulation.

Acupuncture has been used to treat frequency, urgency, and dysuria (Chang, 1988). Twenty-two of 26 patients treated at the SP 6 point had clinically symptomatic improvement. A study looking at both acupuncture and TENS in IC showed limited effects of both modalities (Geirsson et al, 1993). Lumbar epidural blockade was the subject of a positive case report (Pelaiez et al, 2004), but in an earlier series resulted in only short-term (mean 15 days) pain relief in IC (Irwin et al, 1993). Posterior tibial nerve stimulation was successful in 60% of 37 patients with symptoms of bladder overactivity in an uncontrolled Dutch study (van Balken et al, 2001). An Australian double-blind placebo-controlled study of transdermal posterior tibial nerve laser therapy showed no benefit in 56 patients when comparing active with placebo arms, but the placebo effect was remarkably strong, indicating the importance of such trials in evaluation of invasive therapies (O'Reilly et al, 2004). A Chinese study of posterior tibial nerve stimulation twice weekly for 5 weeks in BPS/IC patients failed to show improvement in pain scores, and

Doxorubicin (Khanna and Loose, 1990) and the mast cell stabilizer **cromolyn sodium** (Edwards et al, 1986; Kennelly and Konnak, 1995) have been tried in pilot trials with the promising results we have come to expect in such studies. Follow-up studies are lacking, and these drugs have not become a part of the intravesical pharmacopoeia.

The use of intravesical **bacillus Calmette-Guérin (BCG)** for IC was first reported by Zeidman and colleagues (1994). A subsequent randomized, prospective, double-blind, placebo-controlled trial of 30 patients treated weekly for 6 weeks and followed for a mean of 8 months noted a 60% response rate compared with a 27% placebo response (Peters et al, 1997). Surprisingly, BCG was tolerated as well as placebo. Even more surprisingly, 8 of 9 BCG responders continued to have an excellent response in all parameters measured at 27 months of follow-up (Peters et al, 1998). It is unclear how BCG achieved this result, but immunologic and/or anti-inflammatory mechanisms have been postulated (Peters et al, 1999). A double-blind crossover Swedish study comparing DMSO with BCG failed to substantiate BCG efficacy (Peeker et al, 2000c).

A large multicenter randomized controlled trial by NIDDK comparing BCG with placebo found a 12% response rate for placebo compared with a 21% response for BCG. Placebo responders in the trial had the same durability of response (up to 68 weeks) as the BCG responders (Propert et al, 2008). In a follow-up open-label phase of the trial, the response rate was 18% in both the group originally randomized to BCG and the group initially randomized to placebo, indicating that a second course of therapy does not improve response rate (Propert et al, 2007). The small response rate in the RCT failed to reach statistical significance at the $P = .05$ level, and this large study of 265 patients suggests that **BCG has no place in the treatment of moderate to severe BPS/IC** (Mayer et al, 2005). The BCG safety profile was considered acceptable in the NIDDK trial, but adverse events were not uncommon, and rare hypersensitivity reactions to intravesical BCG can occur (Parker et al, 2004). Although small uncontrolled trials showing efficacy of BCG have been reported (Aghamir et al, 2007; El-Bahnasy et al, 2009), the NIDDK trial dampened enthusiasm for this treatment modality.

Efforts to bring new therapies directly to the bladder continue to be the focus of investigators. Oxybutinin has shown efficacy in preliminary studies when administered intravesically at doses of 10 mg dissolved in saline (Bade et al, 2000; Barbalias et al, 2000). Electromotive drug administration, the active transport of ionized drugs by the application of an electric current, using lidocaine and dexamethasone has shown a 25% success rate up to 6 months after instillation (Rosamilia et al, 1997). A similar trial using repeated instillations noted success rates of 60% with a mean duration of 6.6 months (Riedl et al, 1997). **Capsaicin**, the main pungent ingredient in hot peppers of the genus *Capsicum*, is a specific neurotoxin that desensitizes C-fiber afferent neurons. **Resiniferatoxin (RTX)**, an ultra-potent analogue of capsaicin, appears to have similar effects with less of the acute pain and irritation associated with capsaicin application. Both compounds have been tested intravesically for the relief of bladder instability and hyperreflexia (Chancellor and de Groat, 1999). Clinical trials of the use of these compounds in bladder pain, urgency, and frequency could show this to be a new and viable treatment modality in the future, but **current data on efficacy in BPS are lacking** (Lazzeri et al, 1996; Lazzeri et al, 2000; Cruz et al, 1997). A phase 2 safety and proof-of-concept multicenter, placebo-controlled trial conducted by ICOS Corporation of Bothell, Washington found no significant efficacy of a single intravesical administration of RTX compared with placebo, although no safety issues were identified (Payne et al, 2005). Use of RTX and hydrodistention was effective in relieving the pain of BPS when compared with hydrodistention alone, but was not effective in improving lower urinary tract symptoms (Ham et al, 2012). Studies using other concentrations and multiple administrations may be worthwhile (Peng and Kuo, 2007).

Liposomes, vesicals composed of concentric phospholipid bilayers separated by aqueous compartments, adsorb onto cell surfaces and fuse with cells. They can be used for drug delivery and gene therapy. They are currently in testing as an intravesical therapy for BPS (Fraser et al, 2003; Lee et al, 2011b).

none of the 18 patients thought the treatment had a significant effect (Zhao et al, 2008).

Direct sacral nerve stimulation has been explored in the treatment of BPS and urgency and frequency and is referred to as **neuromodulation**, a technique whose urologic potential was developed through the basic and clinical research of Tanagho and Schmidt (Schmidt, 1993; Fandel and Tanagho, 2005). They and others have observed that patients who do best with this treatment modality are those who have identifiable pain and dysfunction in the pelvic muscles (Everaert et al, 2001; Siegel et al, 2001; Aboseif et al, 2002). Patients reporting pelvic pain in the absence of demonstrable pelvic floor dysfunction and levator tenderness did poorly (Schmidt, 2001). As initially practiced, trial stimulation was performed with a percutaneous temporary electrode for a 3- to 4-day temporary stimulation period to access efficacy. The S3 nerve was most frequently used. A wire electrode was inserted into the foramen and connected to an external pulse generator (Medtronic, Minneapolis, MN). If the trial was successful, the patient was considered for implantation of a permanent neural prosthesis. More recently, a staged procedure has supplanted the traditional percutaneous approach, as the response to stimulation can be better assessed with more accurate lead placement and stability than through the more hit-or-miss percutaneous lead placement (Peters et al, 2003). Peters's test-to-implant rate increased from 52% to 94%. Other reports have noted a test-to-implant rate with the percutaneous technique of 76% in 33 PBS/IC patients (Whitmore et al, 2003) to 40% in 211 patients with refractory urge incontinence, urgency-frequency syndrome, and urinary retention (Scheepens et al, 2002b).

Neuromodulation has been shown to be effective in treating refractory urinary urge incontinence (Schmidt et al, 1999; Spinelli et al, 2001). Studies on therapeutic potential in BPS/IC followed (van Kerrebroeck, 1999). The University of Maryland group described a decrease in antiproliferative activity and normalization of HB-EGF levels in patients with successful test stimulation (Chai et al, 2000a). Peters and coworkers reported success in two thirds of BPS/IC patients with sacral nerve stimulation (Peters et al, 2003). GRA score as determined by the patients correlated with objective findings (Peters et al, 2008). Another study (Comiter, 2003) noted that 17 of 25 patients were successful with test stimulation and went on to permanent implantation of the InterStim device (Medtronic, St. Paul, MN). Devices in 13 of 15 who underwent staged implantation were permanently implanted versus in 4 of 10 undergoing percutaneous test stimulation. With a mean follow-up of 14 months, 16 of 17 patients were judged to have a successful outcome, yielding an intent-to-treat success rate of 64%. Although sacral neuromodulation can decrease narcotic requirements significantly in refractory BPS/IC, the majority of patients taking chronic narcotics for pain will likely continue to use them for pain relief even after implantation (Peters and Konstant, 2004). One center reported a long-term improvement rate of 45% for the urgency and frequency indication (Elhilali et al, 2005). Treatment results do not appear to be age dependent (Peters et al, 2013b). Sexual functioning in women may improve as well (Yih et al, 2013). **Several studies now attest to the benefits of sacral neuromodulation for BPS (Ghazwani et al, 2011; Marinkovic et al, 2011; Vaarala et al, 2011; Tirlapur et al, 2013b).**

Unilateral stimulation should be performed before bilateral sacral stimulation is considered (Oerlemans and van Kerrebroeck, 2008). A bilateral test stimulation could be indicated when a unilateral test fails (Steinberg et al, 2007). The only prospective randomized crossover trial to compare the unilateral with bilateral sacral nerve stimulation found no significant differences comparing the results (Scheepens et al, 2002a). The presence of pain is a predictor of adverse events (White et al, 2009), and although sacral neuromodulation is effective in 56% of patients with urgency and frequency, when pain is the major complaint, caution is indicated. Nevertheless, **reviews of multiple, largely uncontrolled anecdotal studies show success rates of 60% to 80% for chronic pelvic pain (Marcelissen et al, 2011; Srivastava, 2012). Surgical revision rates are 7% to 0% (van Kerrebroeck et al, 2007; Gajewski and Al-Zahrani, 2011).** When used for BPS symptoms, frequent reprogramming is

often required (Maxwell et al, 2008). The presence of urgency may be a positive predictor of long-term success (Gajewski and Al-Zahrani, 2011).

KEY POINTS: NEUROMODULATION

- The association of pelvic floor dysfunction with pelvic pain syndromes makes neuromodulation a rational therapeutic alternative.
- Patients with pelvic pain in the absence of demonstrable pelvic floor dysfunction and levator tenderness may not respond as well as those with urgency and frequency associated with pelvic floor dysfunction. Controlled trials of sacral nerve stimulation for BPS are needed.

Surgical Therapy

Hydrodistention

Hydrodistention of the bladder under anesthesia, while technically a surgical treatment, is often the first therapeutic modality employed, often as a part of the diagnostic evaluation. **Because there have been no standard methods of distention (Turner and Stewart, 2005), results vary markedly.** Frontz first suggested hydraulic overdistention of the bladder for IC in 1922 (Frontz, 1922), and Bumpus reported the first series 8 years later (Bumpus, 1930). Simple bladder filling at cystoscopy will give relief to some patients (Hald et al, 1986); other researchers have reported use of an office-based procedure with intravesical lidocaine anesthesia and electromotive drug administration (Rose et al, 2005); and Dunn reported on 25 patients undergoing distention under anesthesia to the level of the systolic blood pressure for up to 3 hours (Dunn et al, 1977). Sixteen of the patients were symptom free with a mean follow-up of 14 months; 2 patients experienced bladder rupture. **The bladder in IC patients can be very thin, and the possibility of perforation or rupture must always be kept in mind and discussed with the patient (Badenoch, 1971; Hamer et al, 1992). Prolonged distention probably has little or no benefit over a short-term distention measured in minutes (Taub and Stein, 1994; McCahy and Styles, 1995).** Using epidural anesthesia and a balloon distention technique to the mean arterial pressure for 3 hours continuously, Glemain and colleagues reported good but transient efficacy in patients with a bladder capacity greater than 150 mL on predistention cystometry (Glemain et al, 2002). In their prospective series of 30 patients, 18 had maintained a therapeutic response at 6 months and 13 at 1 year of follow-up. Moderate hematuria was almost universal, worsening of symptoms occurred in 5% of patients, and low back and hypogastric pain were common sequelae. One bladder rupture, one episode of sepsis, and one episode of prolonged retention occurred.

Our method is to perform an initial cystoscopic examination (the findings of which are usually unremarkable), obtain urine for cytology, and distend the bladder for 1 to 2 minutes at a pressure of 80 cm H₂O. The bladder is emptied and then refilled to allow observation for glomerulations or ulceration. A therapeutic hydraulic distention follows for another 8 minutes. Biopsy, if indicated, is performed after the second distention. Therapeutic responses in patients with a bladder capacity under anesthesia of less than 600 mL showed 26% with an excellent and 29% with a fair result compared with 12% excellent and 43% fair in patients with larger bladder capacities (Hanno and Wein, 1991). Most favorable responses were extremely brief, however, with the exceptional patient noting improvement for 6 months, thus being a candidate for repeat therapeutic distention.

Acute hydrodistention does not seem to result in any long-term bladder dysfunction (Kang et al, 1992; Lasanen et al, 1992). Any efficacy is probably related to damage to mucosal afferent nerve endings (Dunn et al, 1977). It has no benefits in patients with DO

(Taub and Stein, 1994; McCahy and Styles, 1995). Over half of men with prostate pain and without bacteriuria may have glomerulations. Symptoms in this group have been reported to improve with hydrodistention (Berger et al, 1998). Although many patients with IC have sensory urgency at awake capacities of less than 100 mL, hydrodistention under anesthesia seems to allow for “staging” of the disease, giving the clinician some idea of the capacity he or she has to work with conservative therapies. A capacity under anesthesia of under 200 mL would not bode well for the likelihood of success of medical therapy. Fortunately, these cases are relatively rare.

Surgical Considerations

Major extirpative and/or reconstructive surgical therapy for BPS is an option after all trials of conservative treatment have failed—a point that cannot be overemphasized. BPS/IC, although a cause of significant morbidity, is a nonmalignant process with a temporary spontaneous remission rate of up to 50% (Held et al, 1990) that does not directly result in mortality. Deaths are either self-inflicted or the result of complications of therapy. Nowhere does the caveat *primum non nocere* bear more relevance; the treatment must be no worse than the disease process (Siegel et al, 1990). Surgery should be reserved for the motivated and well-informed patient who falls into the category of having extremely severe, unresponsive disease, a group that comprises less than 10% of patients (Irwin and Galloway, 1994; Parsons, 2000).

Historical Procedures

Many surgical approaches have been employed for IC, and it is worth mentioning a few for historical perspective alone. Sympathectomy and intraspinal alcohol injections have been used to treat pelvic pain (Greenhill, 1947). Differential sacral neurotomy was reported in 3 patients with good results (Meirowsky, 1969), but like most deinnervation procedures never gained popularity because of subsequent poor results. Transvesical infiltration of the pelvic plexuses with phenol failed in 5 of 5 patients with IC (Blackford et al, 1984). With a significant complication rate of 17% (McInerney et al, 1991), it is rarely if ever currently used for sensory urgency disorders or detrusor hyperreflexia. There are several reports on cystolysis going back to Richer in 1929 (Bourque, 1951). Worth and Turner-Warwick reported some short-term benefit, but unpredictable long-term results (Worth and Turner-Warwick, 1973; Worth, 1980). Freiha and Stamey used cystolysis in 6 IC patients with good results in 4 (Freiha and Stamey, 1979). Albers reported long-term follow-up in 11 IC patients and only 1 success (Albers and Geyer, 1988). Denervation procedures have a notoriously high late-failure rate, and the procedure is not justified for BPS/IC (Walsh, 1985; Stone, 1991). In fact, Rogers has concluded that there exist no convincing clinical studies to recommend surgical procedures to interrupt visceral nerve pathways in women with any type of chronic pelvic pain (Rogers, 2003).

Surgery for Hunner Lesion

Transurethral resection of a Hunner lesion as initially reported by Kerr can provide symptomatic relief (Kerr, 1971). Fall resected ulcerated lesions in 30 patients, resulting in initial disappearance of pain in all and a decrease in urinary frequency in 21 (Fall, 1985). Similar results have been attained with the neodymium-yttrium-aluminum-garnet (YAG) laser (Shanberg et al, 1985, 1989; Rofeim et al, 2001). The majority of patients require repeat fulguration as recurrence of the lesions and symptoms is to be expected over ensuing months to years (Hillelsohn et al, 2012). Extreme caution is critical with use of a laser in a BPS/IC bladder, because forward scatter through these thin bladders with resulting bowel injury is an ever-present danger. There would seem to be no justification in the literature for using the laser to treat areas of glomerulation or in the nonulcerative form of the disease (Shanberg et al, 1997).

Major Surgical Procedures

Supratrigonal cystectomy and the formation of an enterovesical anastomosis with bowel segments (substitution cystoplasty) has been a popular surgical procedure for intractable IC. The diseased bladder is resected in its entirety, sparing only a 1-cm cuff around the trigone to which the bowel segment is anastomosed (Worth et al, 1972; Irwin and Galloway, 1994). Although it is not always clear in the literature how much bladder has been resected, the results reported using these procedures for IC have been mixed at best. Badenoch operated on 9 patients, with 4 becoming much worse and 3 ultimately undergoing urinary diversion (Badenoch, 1971). Flood and colleagues reviewed 122 augmentation procedures, 21 of which were done for IC. Patients with IC had the poorest results of any group, with only 10 having an “excellent” outcome (Flood et al, 1995). Wallack reported 2 successes (Wallack et al, 1975); Seddon had success in 7 of 9 patients (Seddon et al, 1977); and Freiha ended up performing formal urinary diversion in 2 of 6 patients treated with augmentation cecocystoplasty (Freiha et al, 1980). Weiss had success in 3 of 7 patient treated with sigmoidocystoplasty (Weiss et al, 1984), and Lunghi had no excellent results in 2 patients with IC (Lungi et al, 1984). Webster reviewed his data in 19 patients and concluded that only patients with bladder capacities under anesthesia less than 350 mL should undergo substitution cystoplasty (Webster and Maggio, 1989). Hughes lowered the threshold to less than 250 mL (Hughes et al, 1995).

More recent series on subtotal cystectomy plus augmentation have been somewhat more positive (Costello et al, 2000; Chesa et al, 2001). Peeker had good results in all 10 patients with ulcerative IC but poor results in the 3 patients operated on with nonulcerative disease (Peeker et al, 1998). He no longer performs the procedure in the latter group. Linn had success in 20 of 23 patients (only 2 with ulcerative IC) treated with subtotal cystectomy and orthotopic bladder substitution with an ileocecal pouch (Linn et al, 1998). He recommends a supratrigonal cystectomy. A Spanish series reported success in 13 of 17 procedures with a mean follow-up of 94 months (Rodriguez Villamil et al, 1999). The University of Alabama group reported long-term success in 1 of 4 patients with orthotopic neobladders and 1 of 3 with augmentation cystoplasty (Lloyd, 1999). A German report on substitution cystoplasty sparing the trigone was quite enthusiastic, detailing a 78% pain-free rate in 18 patients treated with ileocecal augmentation (10) or ileal substitution (8) at a mean follow-up of 57 months (van Ophoven et al, 2002). Two patients failed to get any pain relief, and 4 required either long-term intermittent catheterization or suprapubic drainage to empty the neobladder.

Not all patients empty the bladder spontaneously after substitution cystoplasty. Although the need for clean intermittent catheterization would not obviate a successful outcome in the patient treated for bladder contraction from tuberculous cystitis, it can be a painful disaster in the IC patient. Nurse and colleagues have gone one step further, recommending trigone biopsy before substitution cystoplasty (Nurse et al, 1991). Diversion and/or total cystourethrectomy is recommended if the trigone is affected by IC. It is not clear how this is determined histologically, as IC has no pathognomonic findings by histology and in general is not a localized process. Nielsen and coworkers described eight women treated with substitution cystoplasty (Nielsen et al, 1990). Treatment in six patients failed, and the results of postoperative biopsies from the trigone showed no difference in the amount of fibrosis, degree of degenerative changes in the muscle, and mast cell density between the two cured patients and the others.

There has been a controversy over whether the IC process can occur in a transposed bowel patch (McGuire et al, 1973; Kisman et al, 1991; Singh and Thomas, 1996) or even in the ureter (Smith and Christmas, 1996). If so, not only would this be a relative contraindication to bladder augmentation, but it would also provide support for the view that a substance in the urine might be involved in pathogenesis. There is, however, evidence that inflammation and fibrosis are the usual reactions of bowel to exposure to urine;

therefore, pathologic findings alone would not be conclusive of spread of IC in such patients (MacDermott et al, 1990).

Augmentation cystoplasty has many potential complications, from the rare incidence of bladder neoplasm (Golomb et al, 1989) to the more common complication of upper tract obstruction (Cheng and Whitfield, 1990). In the best of hands, complications can involve almost 50% of patients, necessitating surgical intervention in 25% (Khoury et al, 1992; Bunyaratavej et al, 1993). Although problems are more common in patients operated on for disorders other than IC, the risk-benefit ratio of substitution cystoplasty seems to have discouraged its use in the last several years.

Urinary diversion with or without cystourethrectomy is the ultimate surgical answer to the dilemma of IC, akin to cutting the “Gordian knot.” If diversion alone is chosen, one must keep in mind potential problems that can befall the remaining bladder, including pyocystis, hemorrhage, severe pain, and unremitting feelings of incomplete emptying and spasm (Eigner and Freiha 1990; Adeyoku et al, 1996). Bladder carcinoma has also been reported after urinary diversion but is not specifically associated with BPS (Hanno and Tomaszewski, 1982). Consideration of cystourethrectomy is indicated only in patients who are miserable, in whom all other therapies have failed, and who have demonstrated chronicity such that remission is considered extremely unlikely. Fortunately, few patients fall into this category. Theoretically, conduit diversion seems to be reasonable if one is concerned about disease occurring in any continent storage type of reconstruction. The extended simple cystectomy performed for intractable IC may lend itself to anterior enterocele formation from weakening of the anterior vaginal wall, and prevention of this entity is warranted at the time of cystectomy (Anderson et al, 1998).

Bejany and Politano reported excellent results in 5 patients treated with total bladder replacement and recommended neobladder reconstruction (Bejany and Politano, 1995). Keselman and colleagues had 2 failures in 11 patients treated with continent diversion and attributed this to surgical complications (Keselman et al, 1995). A Finnish group noted failure in 2 of 4 patients treated with cystectomy and conduit diversion because of persistent pain (Lilius et al, 1973). Baskin and Tanagho also cautioned about persistence of pelvic pain after cystectomy and continent diversion, discussing 3 such patients (Baskin and Tanagho, 1992). A similar report followed (Irwin and Galloway, 1992). Webster and coworkers had 10 failures in 14 patients treated with urinary diversion and cystourethrectomy (Webster et al, 1992). Ten patients had persistent pelvic pain, and 4 of them also complained of pouch pain. Only 2 patients had symptom resolution. An English study of 27 patients who underwent cystectomy and bladder replacement with a Kock pouch noted successful treatment of pain in all patients, but follow-up was limited (Christmas et al, 1996a). Parsons suggests that pouch pain will occur in 40% to 50% of patients within 6 to 36 months of surgery (Parsons, 2000).

Attempts have been made to improve results by limiting the operation to those without detrusor mastocytosis (Trinka et al, 1993) and those without “neuropathic pelvic pain” (Lotenfoe et al, 1995). Based on the experience of the past decades, it is unclear if these efforts will prove any more successful. It would seem that risks of failure peculiar to IC include both the development of pain over time in any continent storage mechanism that is constructed, and the risk of phantom pain in the pelvis that persists despite the fact that the stimulus that initially activated the nociceptive neurons (diseased bladder) has been removed (Cross, 1994). Brookhoff has proposed trying a differential spinal anesthetic block before considering cystectomy (Brookhoff and Sant, 1997). If the patient continues to perceive bladder pain after a spinal anesthetic at the T10 level, it can be taken as an indicator that the pain signal is being generated at a higher level in the spinal cord and that surgery on the bladder will not result in pain relief. Some patients with intractable urinary frequency will opt for simple conduit urinary diversion alone, feeling that their quality of life will be improved independent of the pain piece of the puzzle. Despite all of the problems, many patients will do well after major surgery, and quality of life can measurably improve (Rupp et al, 2000). In the

event of neobladder pain after subtotal cystectomy and enterocystoplasty or continent diversion, it appears safe to retubularize a previously used bowel segment to form a urinary conduit for a straightforward urinary diversion without significant risk of conduit pain (Elzawahri et al, 2004).

The Gothenburg experience was recently reviewed, looking at results in 47 patients subjected to reconstructive or extirpative surgery (Rössberger et al, 2007). This included 23 substitution cystoplasties, 12 conduit diversions, and 10 Kock pouches. Twenty-eight of 34 patients with classic Hunner lesions had complete symptom resolution from the initial surgical procedure. Four of the remaining 6 required urinary diversion, cystectomy, or ulcer resection in a trigonal remnant, but ultimately did well. Only 3 of 13 patients with non-Hunner disease had successful symptom resolution after reconstructive surgery, 2 of whom required conduit diversion. Peeker's group concluded that only patients with Hunner lesions refractory to standard therapy could be expected to do well after major surgery.

A Thai experience using cystectomy and ileal neobladder in women in whom conservative therapy failed reported good results in all 35 patients treated (Kochakarn et al, 2007). Spontaneous voiding with minimal residual urine was found in 33 patients, and the remaining 2 patients had spontaneous voiding with residual urine requiring clean intermittent catheterization.

Forty years ago, Pool recognized that “surgical treatment has not been the boon many had hoped it would be” (Pool, 1967). “Diversion of the urine is not the entire answer to the situation. Removal of the lesion in the bladder has been of no benefit. Likewise, removal of almost the entire mobile portion of the bladder proved to be a failure.” Blaivas and colleagues (2005) described results of augmentation enterocystoplasty and continent diversion in 76 consecutive patients with benign disease with a mean 9-year follow-up. The procedures in all 7 patients with the diagnosis of IC were classified as failures, whereas 67 of the remaining 69 patients were cured or improved. When one of the deans of major urologic reconstruction writes, “I find it very difficult to justify such extensive surgery (continent diversion, cystourethrectomy) with such limited results and for these reasons have not been involved in surgery for IC over the past 3 years” (Webster, 1993), it is obvious that one should think carefully and proceed with surgery only after a complete discussion with a very motivated and well-informed patient. Recent reports seem to be more sanguine with regard to these procedures.

KEY POINTS: SURGICAL THERAPY

- Major surgery for BPS is a reasonable alternative for patients with severe symptoms in whom standard attempts at treatment have failed and when the disease course suggests that spontaneous remission of symptoms is unlikely.
- Patients with a small bladder capacity under anesthesia are less likely to respond to conservative attempts at therapy.
- Patients with a Hunner lesion may have the best results with major surgery.
- If one conceptualizes BPS as two disorders, one of pain and the other of frequency, it becomes easier for the patient and physician to rationalize the decision.
- Conduit urinary diversion can be relied on to resolve the frequency symptoms, and if the patient would consider this alone to make for a successful procedure, there is reason to seriously consider this option.
- Diversion, and even cystectomy with diversion, cannot guarantee a pain-free result, and it is critical for the patient to factor this into the decision about this often irrevocable step.

A simple ileal conduit without cystectomy or attempt at continent diversion can be an acceptable treatment choice with good clinical results and resulting quality-of-life improvement (Norus et al, 2014). Cystectomy may add complications and need for

reoperation (Peters et al, 2013a). Subtotal cystectomy with bladder augmentation may fail to give pain relief in more than one third of patients (Andersen et al, 2012).

Assessing Treatment Results

The diversity of BPS/IC therapies underscores the lack of understanding about the treatment of this syndrome (Rovner et al, 2000). It has been not only a difficult condition to diagnose, but also a difficult condition for which to assess therapeutic impact. There is a 50% incidence of temporary remission unrelated to therapy, with a mean duration of 8 months (Held et al, 1990). A recent meta-analysis of articles published from 1990 to 2010 on management of BPS/IC concluded that there is limited evidence proving efficacy of treatment and attributed the lack of definitive conclusions to the great heterogeneity in methodology, symptom assessment, duration of treatment, and follow-up in both randomized controlled trials and nonrandomized reports (Giannantonio et al, 2012). This should not be interpreted to conclude that all treatments for the affected individual are ineffective, but rather that demonstrating treatment effects in populations of patients has been problematic for the reasons noted. The lack of knowledge about how the syndrome should be best phenotyped stands out as an important missing piece.

A somewhat surprising finding from the ICDB was that although there was initial improvement in symptoms partially because of regression to the mean (Sech et al, 1998) and the intervention effect, there was no evidence of a long-term change in average symptom severity over the 4-year course of follow-up (Proper et al, 2000). In a chronic, devastating condition with primarily subjective symptomatology, no known cause, and no cure, patients are desperate and often seem to respond to any new therapy (Fig. 14-11). They are often victims of unorthodox health care providers with untested forms of therapy—some medical, some homeopathic, and some even surgical.

The Placebo Conundrum

Where possible, the results of randomized controlled studies should be used for decision making. Placebo-controlled, double-blind studies are optimal in this disorder for which there is no generally effective standard therapy.

Placebo effects influence patient outcomes after any treatment that the clinician and patients believe is effective, including surgery. Placebo effects plus disease natural history and regression to the mean can result in high rates of good outcomes, which may be misattributed to specific treatment effects (Gillespie et al, 1991; Gillespie, 1994; Turner et al, 1994; Proper et al, 2000). Unfortunately, too few BPS treatments have been subjected to a placebo-controlled trial. This is not to say that what seems effective is not, but rather that a high index of skepticism is healthy, even in treatments tested in controlled trials (Schulz et al, 1995).

Whereas in many diseases an argument can be made against using a true placebo control as opposed to an orthodox treatment of approved or accepted value (Rothman and Michels, 1994), a good case for true placebo comparison can readily be made for BPS. The vagaries of the natural history, the general lack of progression of symptom severity over time, and the fact that the condition is not life-threatening mean that there is little to lose and much to gain by subjecting new treatments to the rigorous scrutiny of placebo control. Many patients who volunteer for such trials have already run the gamut of accepted (although, in general, unproved) therapies. It has long been recognized in protocols that use subjective criteria for assessment that “improvement” may be expected in up to 35% of placebo-treated patients (Benson and Epstein, 1976). The spontaneous remission rate (although temporary) for BPS is 11% (Oravisto and Alfthan, 1976) to 50% (Held et al, 1990), and this in combination with the placebo improvement make efficacy difficult to prove.

Even in placebo-controlled trials, it is reasonable to surmise that some degree of unblinding may occur as a result of somatic or

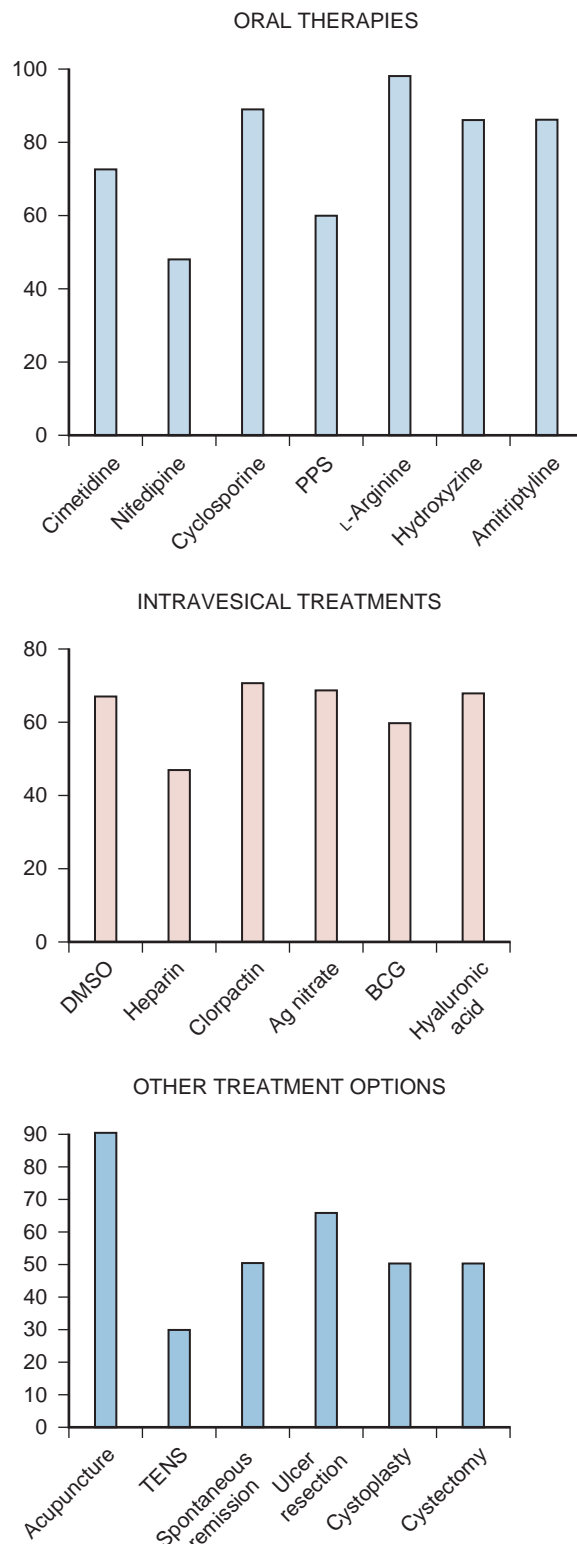


Figure 14-11. Selected reported treatment outcomes in uncontrolled studies in the bladder pain syndrome and interstitial cystitis literature: Percentage of patients initially improved. Ag nitrate, silver nitrate; BCG, bacillus Calmette-Guérin; DMSO, dimethyl sulfoxide; PPS, sodium pentosan polysulfate; TENS, transcutaneous electrical nerve stimulation.

psychological side effects of the active arm, impairing the validity of the trial results and giving the active arm a slight edge over placebo (DuBeau et al, 2005; Rees et al, 2005). Failure to recognize unblinding can easily bias results of a study and has not been routinely measured in clinical trials (Desbiens, 2002). When

occurring late in a study after one would expect onset of a therapeutic effect, unblinding could be the result of side effect profile or drug efficacy. Early in the trial it reflects poor placebo or study design. The degree of blinding needs to be ascertained throughout the trial. This is of specific concern in BPS and any disorder in which primary outcomes may be subject to patient-specific psychological and physiologic factors.

The ethics and necessity of placebo-controlled trials have been questioned, especially in situations in which an effective treatment exists and also in which delay in treatment has been shown to result in disease progression (Streiner, 1999; Anderson, 2006; Polman et al, 2008). However, there are methodologic concerns with equivalence and noninferiority active agent comparison trials (Streiner, 2007). These include an inability to determine if the treatments are equally good or equally bad and the possibility that successive noninferiority trials can lead to a gradual decrease in treatment efficacy. Although the use of placebo-controlled trials raises ethical concerns when proven effective treatment exists for the condition under investigation, they are ethically justified, provided that stringent criteria for protecting research subjects are satisfied (Miller et al, 2004).

The value of placebo-controlled trials is aptly illustrated by the recent decisions by pharmaceutical manufacturers not to pursue FDA approval in the United States for seemingly promising intravesical therapies for BPS/IC (Morales et al, 1996; Chancellor and de Groat, 1999) after placebo-controlled trials failed to establish efficacy. These include low-concentration hyaluronic acid (Bioniche, Canada), high-concentration hyaluronic acid (Seikagaku, Tokyo), and RTX (ICOS, Bothell, WA). Nalmefene, an initially promising oral therapy in the 1990s (Stone, 1994), also failed phase 3 trials (IVAX, Miami, FL). Placebo trials are impractical in surgery, and it can be difficult to evaluate surgical reports. The many older medications currently used off-label might not meet success if tested in the stringent manner in which new molecular entities are tested. The expense of testing therapies currently used off-label often requires dependence on the largesse of government agencies such as the National Institutes of Health (Probert et al, 2002; Sant et al, 2003; Mayer et al, 2005).

Finally, in considering objective changes, the concept of statistical versus clinical significance is paramount. Investigators should, but rarely do, point out differences between statistical improvement and what they consider to be clinically significant improvement (Wein and Broderick, 1994). As Gertrude Stein reportedly stated, "A difference, to be a difference, must make a difference." An increase in bladder capacity of 30 mL may be statistically significant but clinically irrelevant. Number-needed-to-treat and number-needed-to-harm data (McQuay, 2003) may be particularly important in BPS/IC and have not typically been included in efficacy analysis.

Clinical Symptom Scales

BPS/IC symptom questionnaires include the University of Wisconsin Interstitial Cystitis Inventory, the O'Leary-Sant IC symptom index and IC problem index, and the Pelvic Pain and Urgency/Frequency (PUF) scale.

The University of Wisconsin IC scale includes seven PBS/IC symptom items (Table 14-5). It has not been validated for identification or diagnosis of BPS/IC. It captures severity of symptom expression (Keller et al, 1994; Goin et al, 1998). BPS/IC patients do not appear to indiscriminately report higher scores than controls for different somatic and general complaints (Porru et al, 2005). Unlike the other two instruments, it addresses some quality-of-life issues, and this is an advantage when such issues are subject of investigation. Its most attractive aspects are its clinically apparent face validity and its ease of implementation.

The O'Leary-Sant indices (Table 14-6) are a validated questionnaire that was originally developed by focus groups, subjected to test-retest reliability analysis, and validated by administration to IC patients and asymptomatic controls (O'Leary et al, 1997; Lubeck

TABLE 14-5 University of Wisconsin Symptom Instrument

SYMPTOM	SCORE 1-6 (0 = NOT AT ALL, 6 = A LOT)
1. Bladder discomfort	—
2. Bladder pain	—
3. Other pelvic discomfort	—
4. Headache	—
5. Backache	—
6. Dizziness	—
7. Feelings of suffocation	—
8. Chest pain	—
9. Ringing in ears	—
10. Getting up at night to go to the bathroom	—
11. Aches in joints	—
12. Swollen ankles	—
13. Nasal congestion	—
14. Flu	—
15. Abdominal cramps	—
16. Numbness or tingling in fingers or toes	—
17. Nausea	—
18. Going to the bathroom frequently during the day	—
19. Blind spots or blurred vision	—
20. Heart pounding	—
21. Difficulty sleeping because of bladder symptoms	—
22. Sore throat	—
23. Urgency to urinate	—
24. Coughing	—
25. Burning sensation in bladder	—

From Sirinian E, Azevedo K, Payne CK. Correlation between 2 interstitial cystitis symptom instruments. *J Urol* 2005;173:835–40.

et al, 2001). The questionnaire centers on three questions related to urgency and frequency and one on bladder-associated pain. It does not address generalized pelvic pain or symptomatology associated with sexual activity. This is not because these questions were not considered in the formulation of the questionnaire. Of 73 questions in the preliminary instrument covering domains of urinary symptoms, pain, sexual function, menstrual variability, and general health, only the four questions now in the instrument were needed to reliably and validly describe the illness experience of those with IC and distinguish these patients from those without the disorder (O'Leary and Sant, 1997).

Another instrument is the PUF questionnaire (Parsons et al, 2002a) (Table 14-7). It was specifically designed to include questions that directly reflect a wide variety of the symptoms experienced by patients who are affected by this disorder. One third of the questions address pelvic pain, including pain anywhere in the pelvis: the vagina, labia, lower abdomen, urethra, perineum, testes, penis, or scrotum. A large study using the PUF questionnaire has concluded that up to 23% of female Americans have BPS/IC (Parsons et al, 2002a). This makes one wary as to the usefulness and face-validity of the PUF (Ito et al, 2003). A total score of 10 to 14 indicates a 74% likelihood of a positive potassium test (PST); 15 to 19 indicates 76%; 20+ indicates 91%. To the extent that the PST is suspect, the reliability of PUF data comes into question. Question 4 of the PUF is problematic. Patients who are sexually active can gain up to 6 more points than those who are not, and

TABLE 14-6 O'Leary-Sant Indices

INTERSTITIAL CYSTITIS SYMPTOM INDEX	INTERSTITIAL CYSTITIS PROBLEM INDEX
During the past month:	During the past month, how much has each of the following been a problem for you?
Q1. How often have you felt the strong need to urinate with little or no warning? 0. ___ Not at all 1. ___ Less than 1 time in 5 2. ___ Less than half the time 3. ___ About half the time 4. ___ More than half the time 5. ___ Almost always	Q1. Frequent urination during the day 0. ___ No problem 1. ___ Very small problem 2. ___ Small problem 3. ___ Medium problem 4. ___ Big problem
Q2. How often have you had to urinate less than 2 hours after you finished urinating? 0. ___ Not at all 1. ___ Less than 1 time in 5 2. ___ Less than half the time 3. ___ About half the time 4. ___ More than half the time 5. ___ Almost always	Q2. Getting up at night to urinate 0. ___ No problem 1. ___ Very small problem 2. ___ Small problem 3. ___ Medium problem 4. ___ Big problem
Q3. How often did you most typically get up at night to urinate? 0. ___ None 1. ___ Once 2. ___ 2 times 3. ___ 3 times 4. ___ 4 times 5. ___ 5 times	Q3. Need to urinate with little warning 0. ___ No problem 1. ___ Very small problem 2. ___ Small problem 3. ___ Medium problem 4. ___ Big problem
Q4. Have you experienced pain or burning in your bladder? 0. ___ Not at all 2. ___ A few times 3. ___ Fairly often 4. ___ Usually 5. ___ Almost always	Q4. Burning, pain, discomfort, or pressure in your bladder 0. ___ No problem 1. ___ Very small problem 2. ___ Small problem 3. ___ Medium problem 4. ___ Big problem
Add the numerical values of the checked entries.	Add the numerical values of the checked entries.
Total score: _____	Total score: _____

From O'Leary MP, Sant GR, Fowler FJ, et al. The interstitial cystitis symptom index and problem index. *Urology* 1997;49:58–63.

patients who over time begin sexual activity because they are feeling better can actually accumulate a falsely elevated PUF score because of this anomaly.

None of the questionnaires has been shown to be of value in diagnosis (Moldwin and Kushner, 2004), although they may suggest who should be screened further for the syndrome (Kushner and Moldwin, 2006). The O'Leary-Sant scales and University of Wisconsin instrument correlate strongly in a large population of patients with BPS/IC (Sirinian and Payne, 2001). Both the O'Leary-Sant and University of Wisconsin questionnaires are responsive to change over time and thus good for following the natural history of the disorder and the results of treatment.

Treatment outcome studies have also used the Global Response Assessment (GRA), a balanced patient self-report on overall response to therapy, developed for NIDDK-sponsored multicenter therapeutic trials (Sant et al, 2003) (Box 14-9). A one-category change in GRA correlates with a 1.2-point change in the O'Leary-Sant and a 3.1-point change in the University of Wisconsin instruments (Probert et al, 2006). More recently, the validated Genitourinary Pain Index (GUPI) has been used to assess the degree of symptoms in men and women with genitourinary complaints (Clemens et al, 2009a) (Figs. 14-12 and 14-13).

PRINCIPLES OF MANAGEMENT

The information currently available in the literature does not lend itself to easily formulating a diagnostic or treatment guideline that would be universally accepted. Different groups of experts would undoubtedly create different best practices. The algorithms for diagnosis and management constructed by the AUA (Hanno et al, 2011) and the International Consultation on Incontinence are presented in Figures 14-14 and 14-15. The compromise approach constructed by an experienced cross section of urologists and gynecologists from around the world at the International Consultation on Incontinence 2012 meeting in Paris seems reasonable and allows for significant latitude in individual practice and patient preference (Hanno et al, 2013). It is outlined in the following sections.

Definition of Bladder Pain Syndrome

(In the absence of a universally agreed-on definition, the ESSIC definition is given along with the definition of the AUA.)

ESSIC: Chronic pelvic pain, pressure, or discomfort of longer than 6 months' duration perceived to be related to the urinary

TABLE 14-7 Pelvic Pain and Urgency/Frequency Patient Symptom Scale

Patient's Name: _____ Today's Date: _____		Please circle the answer that best describes how you feel for each question.					SYMPTOM SCORE	BOTHER SCORE
	0	1	2	3	4			
1. How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+			
2. a. How many times do you go to the bathroom at night?	0	1	2	3	4+			
b. If you get up at night to go to the bathroom, does it bother you?	Never bothers	Occasionally	Usually	Always				
3. Are you currently sexually active? YES ____ NO ____								
4. a. If you are sexually active, do you now or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always				
b. If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always				
5. Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, penis, testes, or scrotum)?	Never	Occasionally	Usually	Always				
6. a. If you have pain, is it usually		Mild	Moderate	Severe				
b. Does your pain bother you?	Never	Occasionally	Usually	Always				
7. Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always				
8. a. If you have urgency, is it usually		Mild	Moderate	Severe				
b. Does your urgency bother you?	Never	Occasionally	Usually	Always				
Total Score (Symptom Score + Bother Score) Symptom Score (1, 2a, 4a, 5, 6a, 7, 8a) Bother Score (2b, 4b, 6b, 8b) Total score ranges are from 1 to 35.								

From Parsons CL, Dell J, Stanford EL, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology* 2000;60:573-8.

BOX 14-9 Global Response Assessment

- 3: Markedly worse
- 2: Moderately worse
- 1: Slightly worse
- 0: No change
- +1: Slightly improved
- +2: Moderately improved
- +3: Markedly improved

Data from Sant GR, Probert KJ, Hanno PM, et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. *J Urol* 2003;170(3):810-5.

bladder and accompanied by at least one other urinary symptom such as a persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.

AUA guideline definition: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of infection or other identifiable causes.

Nomenclature

The scientific committee of the International Consultation voted to use the term *bladder pain syndrome* for the disorder that has been commonly referred to as *interstitial cystitis*. The term *painful bladder syndrome* was dropped from the lexicon. The term *interstitial cystitis* implies an inflammation within the wall of the urinary bladder, involving gaps or spaces in the bladder tissue. This does not accurately describe the majority of patients with this syndrome. *Painful bladder syndrome* as defined by the ICS is too restrictive for the clinical syndrome.

Properly defined, the term *bladder pain syndrome* appears to fit in well with the taxonomy of the International Association for the Study of Pain (IASP) (see later) and focuses on the actual symptom complex rather than on what appears to be a long-held misconception of the underlying pathology.

Bladder Pain Syndrome (XXIII-2) (per IASP)

BPS is the occurrence of persistent or recurrent pain perceived in the urinary bladder region and accompanied by at least one other symptom, such as pain worsening with bladder filling and daytime and/or nighttime urinary frequency. There is no proven infection or other obvious local pathology. BPS is often associated with negative cognitive, behavioral, sexual, or emotional consequences as well

Female Genitourinary Pain Index

1. In the last week, have you experienced any pain or discomfort in the following areas?

a. Entrance to vagina	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
b. Vagina	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
c. Urethra	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
d. Below your waist, in your pubic or bladder area	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No

2. In the last week, have you experienced:

a. Pain or burning during urination?	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
b. Pain or discomfort during or after sexual intercourse?	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
c. Pain or discomfort as your bladder fills?	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
d. Pain or discomfort relieved by voiding?	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No

3. How often have you had pain or discomfort in any of these areas over the last week?

☐₀ Never ☐₁ Rarely ☐₂ Sometimes ☐₃ Often ☐₄ Usually ☐₅ Always

4. Which number best describes your AVERAGE pain or discomfort on the days you had it, over the last week?

<input type="checkbox"/> ₀	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> ₉	<input type="checkbox"/> ₁₀
No pain										Pain as bad as you can imagine

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

☐₀ Not at all ☐₁ Less than 1 time in 5 ☐₂ Less than half the time ☐₃ About half the time ☐₄ More than half the time ☐₅ Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

☐₀ Not at all ☐₁ Less than 1 time in 5 ☐₂ Less than half the time ☐₃ About half the time ☐₄ More than half the time ☐₅ Almost always

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

☐₀ None ☐₁ Only a little ☐₂ Some ☐₃ A lot

8. How much did you think about your symptoms, over the last week?

☐₀ None ☐₁ Only a little ☐₂ Some ☐₃ A lot

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

<input type="checkbox"/> ₀ Delighted
<input type="checkbox"/> ₁ Pleased
<input type="checkbox"/> ₂ Mostly satisfied
<input type="checkbox"/> ₃ Mixed (about equally satisfied and dissatisfied)
<input type="checkbox"/> ₄ Mostly dissatisfied
<input type="checkbox"/> ₅ Unhappy
<input type="checkbox"/> ₆ Terrible

Figure 14-12. Female Genitourinary Pain Index.

Male Genitourinary Pain Index

1. In the last week, have you experienced any pain or discomfort in the following areas?

a. Area between rectum and testicles (perineum)	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
b. Testicles	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
c. Tip of penis (not related to urination)	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
d. Below your waist, in your pubic or bladder area	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No

2. In the last week, have you experienced:

a. Pain or burning during urination?	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
b. Pain or discomfort during or after sexual climax (ejaculation)?	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
c. Pain or discomfort as your bladder fills?	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No
d. Pain or discomfort relieved by voiding?	<input type="checkbox"/> ₁ Yes	<input type="checkbox"/> ₀ No

3. How often have you had pain or discomfort in any of these areas over the last week?

☐₀ Never ☐₁ Rarely ☐₂ Sometimes ☐₃ Often ☐₄ Usually ☐₅ Always

4. Which number best describes your AVERAGE pain or discomfort on the days you had it, over the last week?

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
No pain										Pain as bad as you can imagine

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

☐₀ Not at all ☐₁ Less than 1 time in 5 ☐₂ Less than half the time ☐₃ About half the time ☐₄ More than half the time ☐₅ Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

☐₀ Not at all ☐₁ Less than 1 time in 5 ☐₂ Less than half the time ☐₃ About half the time ☐₄ More than half the time ☐₅ Almost always

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

☐₀ None ☐₁ Only a little ☐₂ Some ☐₃ A lot

8. How much did you think about your symptoms, over the last week?

☐₀ None ☐₁ Only a little ☐₂ Some ☐₃ A lot

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

<input type="checkbox"/> ₀ Delighted
<input type="checkbox"/> ₁ Pleased
<input type="checkbox"/> ₂ Mostly satisfied
<input type="checkbox"/> ₃ Mixed (about equally satisfied and dissatisfied)
<input type="checkbox"/> ₄ Mostly dissatisfied
<input type="checkbox"/> ₅ Unhappy
<input type="checkbox"/> ₆ Terrible

Figure 14-13. Male Genitourinary Pain Index.

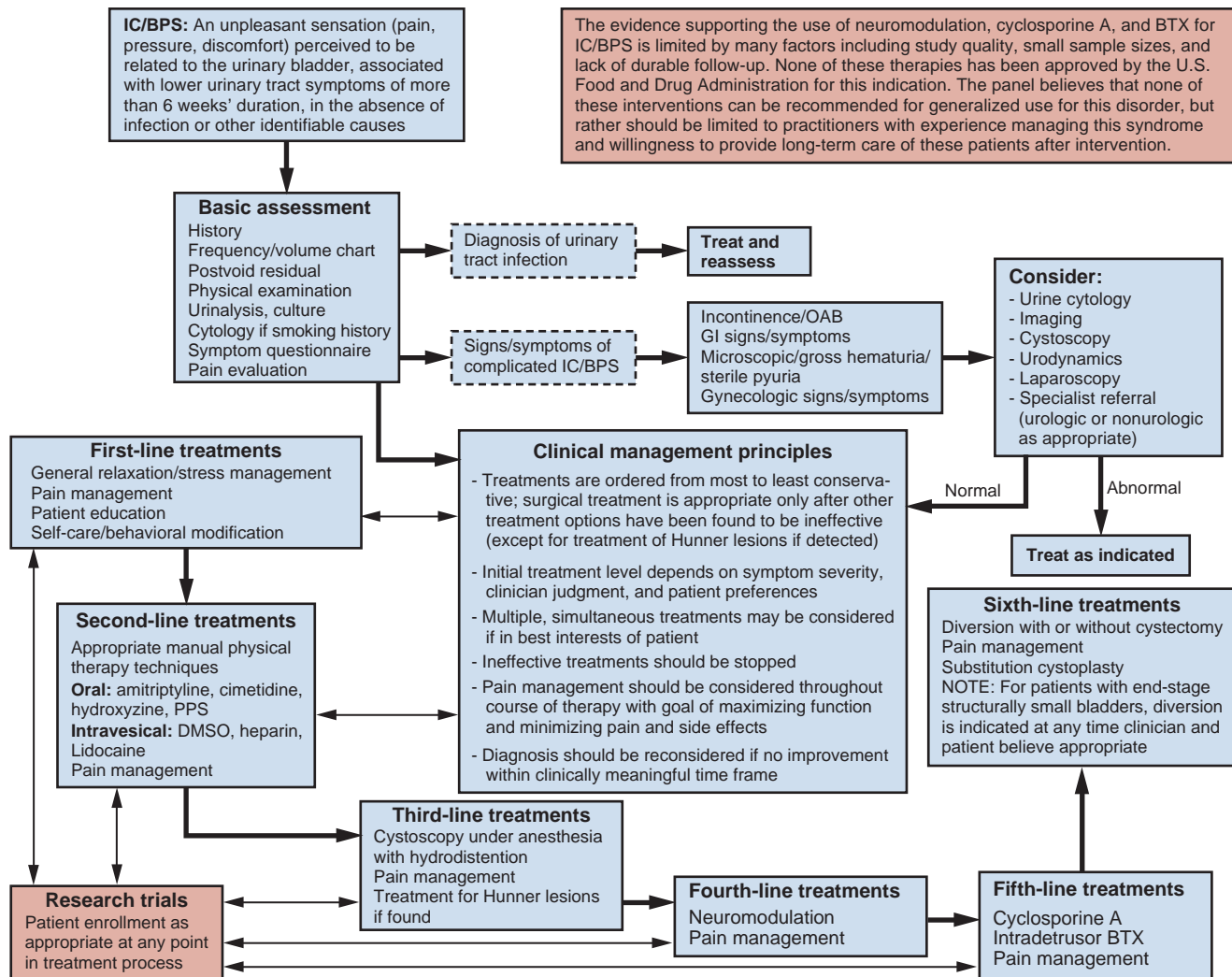


Figure 14-14. Diagnosis and treatment algorithm for interstitial cystitis/bladder pain syndrome (IC/BPS) of the American Urological Association. BTX, botulinum toxin; DMSO, dimethyl sulfoxide; GI, gastrointestinal; OAB, overactive bladder; PPS, pentosan polysulfate. (From Hanno PM, Burks DA, Clemens JQ, et al; Interstitial Cystitis Guidelines Panel of the American Urological Association Education and Research, Inc. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol* 2011;185[6]:2162–70. Copyright © 2010 American Urological Association Education and Research, Inc.)

as with symptoms suggestive of lower urinary tract and sexual dysfunction.

History and Initial Assessment

Patients whose symptoms meet the requirements of the definition of BPS should be evaluated. The presence of commonly associated disorders including irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia in the presence of the cardinal symptoms of BPS also suggests the diagnosis. Abnormal gynecologic findings in women and well-characterized confusable diseases that may explain the symptoms must be ruled out.

The initial assessment consists of a frequency and volume chart, focused physical examination, urinalysis, and urine culture. Urine cytology, cystoscopy, and urodynamic evaluation are recommended if clinically indicated and/or the diagnosis is in doubt. Patients with urinary infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and microscopic or gross hematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms are they diagnosed with BPS.

Initial Treatment

The initial treatment of BPS consists of the following:

- Patient education
- Dietary manipulation
- Nonprescription analgesics
- Stress reduction
- Pelvic floor relaxation techniques

In the patient with findings suggesting pelvic floor dysfunction, pelvic floor physical therapy with myofascial trigger point release and intravaginal Thiele massage is often an effective therapeutic intervention. The **treatment of pain** needs to be addressed directly, and in some instances referral to an anesthesia or pain center can be an appropriate early step in conjunction with ongoing treatment of the syndrome.

When conservative therapy fails or symptoms are severe and conservative management is unlikely to succeed, the following can be prescribed:

- Oral medication
- Intravesical treatment

It is recommended to initiate a single form of therapy and observe results, adding other modalities or substituting other

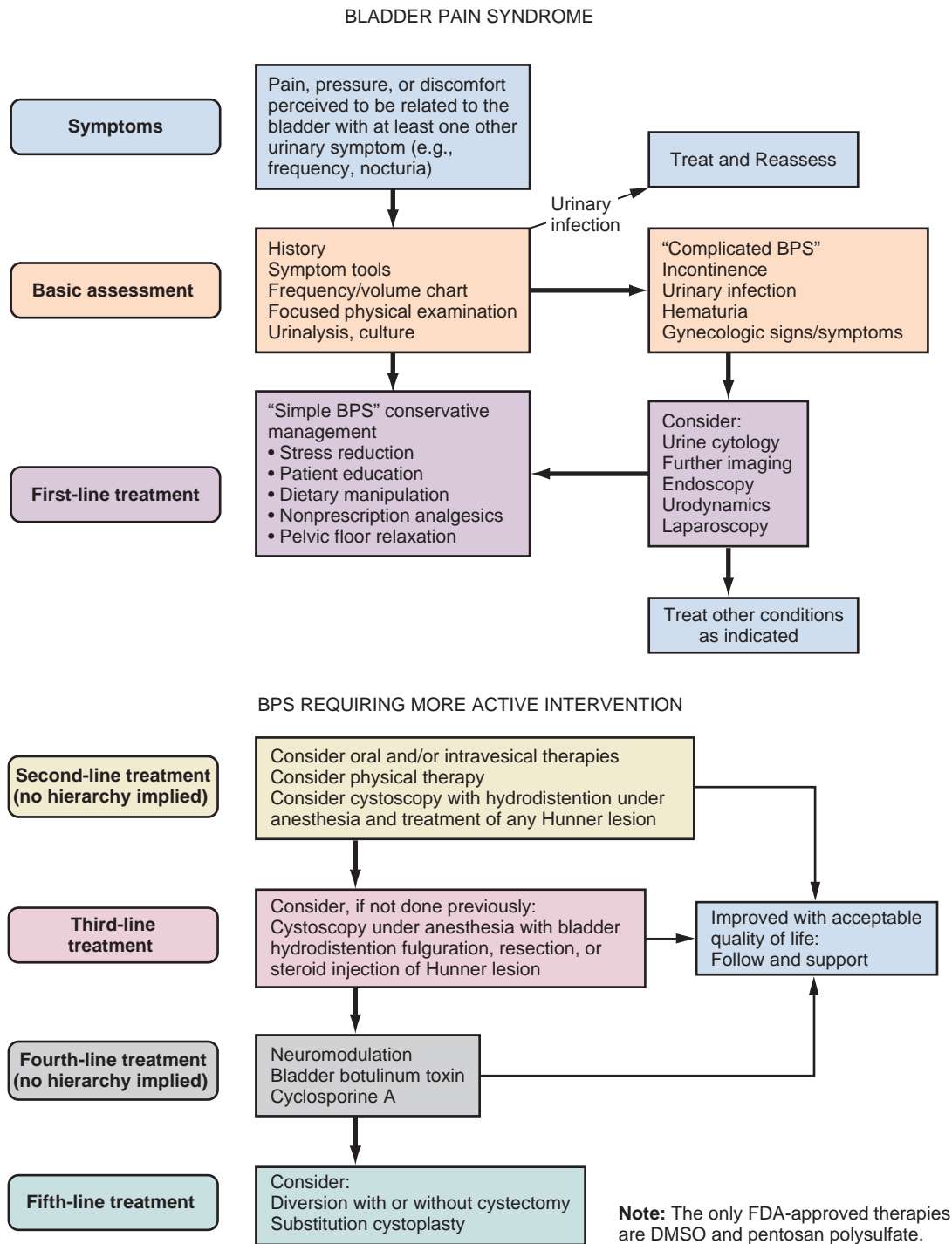


Figure 14-15. Algorithm for diagnosis and treatment of bladder pain syndrome (BPS) according to the Committee on Bladder Pain Syndrome of the Fifth International Consultation on Incontinence, held in Paris in February 2012, under the auspices of the International Consultation on Urological Diseases and enabled by the generous support of the European Association of Urology. Pain management is a primary consideration at every step of algorithm. Patient enrollment in an appropriate research trial is a reasonable option at any point. Evidence supporting neuromodulation, cyclosporine A, and botulinum toxin for BPS indication is limited. These interventions are appropriate only for practitioners with experience treating BPS and willingness to provide long-term care postintervention. DMSO, dimethyl sulfoxide; FDA, U.S. Food and Drug Administration. (From Hanno P, Dinis P, Lin A, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence. Paris: International Consultation on Urological Diseases/European Association of Urology; 2013. p. 1583–649.)

modalities as indicated by degree of response or lack of response to treatment.

Secondary Assessment

If initial oral or intravesical therapy fails, or before beginning such therapy based on clinician judgment, it is reasonable to consider further evaluation, which can include urodynamics, pelvic imaging, and cystoscopy with bladder distention and possible bladder biopsy under anesthesia.

- Findings of bladder overactivity suggest a trial of antimuscarinic therapy.
- The presence of a Hunner lesion suggests therapy with transurethral resection, fulguration of the lesion, or direct steroid injection into the lesion.
- Distention itself can have therapeutic benefit in 30% to 50% of patients, though benefits rarely persist for longer than a few months.
- Grade of recommendation: C

Refractory Bladder Pain Syndrome

Patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities. Many of these are best administered within the context of a clinical trial if possible. These may include the following:

1. Neuromodulation
2. Intradetrusor BTX
3. Oral cyclosporine A
4. Clinical trials of newly described pharmacologic management techniques

At this point, most patients will benefit from the expertise of an anesthesia pain clinic.

The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urinary stream.


- Urinary diversion with or without cystectomy has been used as a last resort with good results in selected patients.
- Augmentation or substitution cystoplasty seems less effective and more prone to recurrence of chronic pain in small reported series.

Philosophy of Management


I believe that, because of the natural history of the disorder, it is best to cautiously progress through a variety of treatments. Whereas the shotgun approach, starting newly diagnosed patients on a variety of simultaneous medications, seems to have many adherents, employing one treatment at a time makes the natural history of the disease itself an ally in the treatment process. One should encourage patients to maximize their activity and live as normal a life as possible, rather than becoming prisoners of the condition. Although some activities or foods may aggravate symptoms, nothing has been shown to negatively affect the disease process itself. Therefore patients should feel free to experiment and judge for themselves how to modify their lifestyle without the guilt that comes from feeling they have harmed themselves if symptoms flare.

Dogmatic restriction and diet are to be avoided unless they are shown to improve symptoms in a particular patient.

In the near future, phenotyping of patients with BPS/IC may improve treatment outcomes, but only time and future studies will determine if this is true (Baranowski et al, 2008). Foundational manuscripts from the MAPP Research Network (mappnetwork.org), an 11-year effort of the NIDDK, are in final preparation for submission in 2014 and underlie this massive effort, which will help to answer the phenotyping question (Clemens et al, 2014a, 2014b; Krieger et al, 2014; Landis et al, 2014). To answer the perennial query, "Can we, as health care providers, make evidence-based decisions for BPS/IC at this time?" the answer has not changed since the last edition of this text: *Sometimes* (Fall et al, 2008).

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Epidemiology of Sexually Transmitted Diseases

Urethritis

Epididymitis

Genital Ulcers

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome and the Urologist

EPIDEMIOLOGY OF SEXUALLY TRANSMITTED DISEASES

The Centers for Disease Control and Prevention (CDC) publishes annual reports on the number of cases of sexually transmitted diseases (STDs) in the United States (CDC, 2013). Data from 2012 are summarized in Tables 15-1 and 15-2. Overall, the estimate is that nearly 20 million new STDs occur every year in the United States, half among people aged 15 to 24 years. This group accounted for 58% of gonorrhea and 69% of chlamydia cases in 2012. Another group with disproportionate risk is men who have sex with men (MSM). This group now accounts for 75% of all primary and secondary syphilis cases. Factors that increase the risk of acquiring an STD include a higher number of lifetime sex partners, unprotected sex without use of a condom, risky sex partners, and the effect of alcohol or drugs on sexual decision making (Pollack et al, 2013).

Centers for Disease Control and Prevention Screening Recommendations

1. Annual chlamydia screening for all sexually active women age 25 and younger, as well as for women with risk factors such as new or multiple sex partners.
2. Annual gonorrhea screening for at-risk sexually active women, including women with new or multiple sex partners, or women who are living in areas with high rates of disease.
3. Syphilis, human immunodeficiency virus (HIV), and chlamydia screening for all pregnant women, and gonorrhea screening for at-risk pregnant women starting early in pregnancy, with repeat testing as needed.
4. At least once-per-year screening for syphilis, chlamydia, gonorrhea, and HIV for all sexually active gay, bisexual, and other MSM. Men who have multiple or anonymous partners should be screened more frequently for STDs, at 3- to 6-month intervals. More frequent screening is also recommended for MSM who use illicit drugs, particularly methamphetamine, or whose sex partners use them.

*The Centers for Disease Control and Prevention (CDC) provides national guidelines on the diagnosis and treatment of sexually transmitted diseases. The 2010 guidelines were used at the time this chapter was written (CDC, 2010c). These guidelines are periodically updated based on review of the most recent literature, and the reader is encouraged to check for updates from the CDC before treating patients with sexually transmitted diseases. Guidelines also include instructions for partner treatment and recommendations on follow-up.

Diseases That Must Be Reported to Local Health Authorities

Syphilis, gonorrhea, chlamydia, chancroid, HIV infection, and acquired immunodeficiency syndrome (AIDS) are reportable diseases in every state. Check requirements for reporting other STDs by state.

URETHRITIS

Urethritis, or urethral inflammation, can be the result of STDs. Symptoms include urethral discharge, pruritus, and dysuria. Several organisms can cause urethritis. Two broad classes are gonococcal urethritis (GU), caused by *Neisseria gonorrhoeae*, and nongonococcal urethritis (NGU), caused by all other organisms.

Diagnosis

Traditionally, urethritis is documented based on examination of the purulent discharge with Gram stain showing more than 5 white blood cells (WBCs) per high-power field (HPF), and documenting the presence or absence of white cells with intracellular gram-negative diplococci indicating GU. Looking at the urethral fluid can yield false-negative results, with reported sensitivity for more than 5 WBCs/HPF as low as 29% for chlamydial infection (Janier et al, 1995). Another criterion is a positive leukocyte esterase test result on first void urine or microscopic examination of first void urine sediment demonstrating more than 10 WBCs/HPF (CDC, 2010c). Nucleic acid amplification tests (NAATs) performed on urine can be used to look for *N. gonorrhoeae* and *Chlamydia trachomatis* (Geisler et al, 2005). Culture and hybridization tests that require urethral swab specimens are available. However, NAATs are preferred because of their higher sensitivity (Geisler, 2011), and urethral swabs are no longer recommended for evaluation of urethritis. All patients should be tested for both gonorrhea and chlamydia, given the high association of coinfection.

Gonococcal Infections

Neisseria gonorrhoeae is a gram-negative diplococcus. It is the second most common bacterial cause of STDs in the United States (CDC, 2013). The incubation period ranges from 3 to 14 days. Men will usually have symptoms that cause them to seek treatment soon enough to prevent transmission to others. This could include urethritis, epididymitis, proctitis or prostatitis. Women are frequently asymptomatic. Complications in women include pelvic inflammatory disease (PID), tubal scarring, infertility, ectopic pregnancy, and chronic pelvic pain (Short et al, 2009). Disseminated gonorrhea is rare today but can produce arthritis, dermatitis, meningitis, and

TABLE 15-1 Sexually Transmitted Disease Cases, 2012, Reported per 100,000 Population

	CASES REPORTED, 2012	RATE PER 100,000 PEOPLE	NOTES ON CHANGES
Chlamydia	1,422,976	456.7	Stable since 2011
Gonorrhea	334, 826	107.5	4.1% increase since 2011
Syphilis, primary and secondary	15, 667	5.0	11.1% increase since 2011
Chancroid	15		Decline 1987- 2001, steady fluctuation since then

TABLE 15-2 Sexually Transmitted Disease Cases, 2012, Reported by Initial Visits to Physicians' Offices

SEXUALLY TRANSMITTED DISEASE	NUMBER OF CASES REPORTED DURING INITIAL VISITS TO PHYSICIANS' OFFICES
Genital herpes	228,000
Genital warts	353,000
Vaginal trichomoniasis	219,000
Other vaginitis	3,452,000

endocarditis. Gonorrheal infection can also increase the risk of contracting and transmitting HIV (Cohen et al, 1997).

Treatment

Dual therapy is required for both *N. gonorrhoeae* and chlamydia because of the high rate of coinfection. Gonorrhea treatment is hindered by the ability of gonorrhea to develop antimicrobial resistance. As of 2007, quinolones are no longer recommended in the United States for treatment of gonorrhea and associated conditions such as PID (CDC, 2007). As of August 2012, because of high resistance, cefixime is no longer recommended as first-line therapy to treat gonorrhea (CDC, 2012; Kirkcaldy et al, 2013). Current treatment of uncomplicated gonococcal infections of the cervix, urethra, and rectum involves ceftriaxone 250 mg IM single dose plus azithromycin 1 gm orally in a single dose or doxycycline 100 mg orally twice per day for 7 days. Because NAATs cannot provide susceptibility results, in cases of treatment failure a culture test should be performed along with antimicrobial susceptibility testing. All persons with gonorrhea should be tested for other STDs including chlamydia, syphilis, and HIV. Treatment is no different in persons with HIV. In persons with a history of penicillin allergy, third-generation cephalosporins have a low incidence of cross-reactivity, lower than the 5% to 10% in first-generation cephalosporins.

Nongonococcal Urethritis

Chlamydia trachomatis accounts for 15% to 40% of cases of NGU, with less common causes including *Mycoplasma genitalium* (15% to 25%), *Trichomonas vaginalis*, adenoviruses, and herpes simplex virus type 1 (HSV-1); a pathogen is not identified in 20% to 50% of cases (Deguchi and Maeda, 2002; Bradshaw et al, 2006; Tabrizi et al,

2007). HSV-1 urethritis may be associated with oral sex (Bradshaw et al, 2006).

Chlamydia

Chlamydia is the most common bacterial sexually transmitted STD in the United States. The 1,422,976 cases of *C. trachomatis* infection reported to the CDC in 2012 comprised the largest number of cases ever reported to the CDC for any condition (CDC, 2013). The incubation period ranges from 3 to 14 days. The prevalence of chlamydia is highest in persons 25 years of age or older (Geisler, 2011). Other sequelae of chlamydial infection in males include epididymitis and Reiter syndrome (Geisler et al, 2008). One of the main concerns with untreated chlamydial infections in men is transmission to their female partners (Geisler, 2011). Up to 75% of women with chlamydial infection can be asymptomatic. Ascending chlamydial infection can result in scarring of the fallopian tubes, PID, risk for ectopic pregnancy, pelvic pain, and infertility. The risk of untreated chlamydial infection producing PID is estimated to be between 9.5% and 27% (Gottlieb et al, 2013).

Mycoplasma genitalium and Ureaplasma

Mycoplasmas are the smallest prokaryotes capable of autonomous replication. The genus *Mycoplasma* belongs to the class Mollicutes, along with *Ureaplasma*. Mycoplasmas lack a cell wall and cannot be Gram stained. They contain a terminal adhesion structure that helps them attach to epithelial cells (Cazanave et al, 2012). *M. genitalium* was first described as a pathogen in urethritis in 1980, and considerable evidence since has established this organism as a cause of acute NGU (Manhart et al, 2011). Most infected patients are symptomatic, but approximately 25% may have asymptomatic urethral infection (Taylor-Robinson and Jensen, 2011). *M. genitalium* can become intracellular, which can establish a chronic infection and aid in avoidance of both immune response and antibiotics (McGowin et al, 2009). The prevalence of *M. genitalium* in chronic urethritis is estimated at 12% to 41% (Manhart et al, 2011). Risk factors for infection with *M. genitalium* in men are young age, sexual intercourse in the past month, and a sex partner with a recent history of STD diagnosis or treatment (Mena et al, 2002). Culture is very difficult, and the diagnosis is made by nuclear amplification or polymerase chain reaction (PCR), but no commercially available test is available (Cazanave et al, 2012; Sena et al, 2012).

Other species of Mollicutes include *Ureaplasma urealyticum* and *Ureaplasma parvum* (Cazanave et al, 2012). The evidence for *Ureaplasma* as a causative agent in NGU is conflicting (Taylor-Robinson et al, 1979). In a case control study of 329 men with symptoms of urethritis and controls without symptoms, both *U. urealyticum* and *U. parvum* were found more often in controls than in cases and therefore were not considered to be associated with NGU in this population (Bradshaw et al, 2006). A more recent series reported *U. urealyticum* in 24% of cases of NGU (Wetmore et al, 2011a). An explanation for the difference among numerous studies has been proposed by Wetmore and colleagues (2011b). In a case control series of men with clinical signs and symptoms of NGU and controls from an STD clinic or emergency room, the overall association of *U. urealyticum* and NGU was marginal, and *U. parvum* was not associated with NGU. However, in men with fewer than 10 lifetime vaginal sex partners, *U. urealyticum* was significantly associated with NGU. The hypothesis proposed is that adaptive immunity by repeated or prolonged exposure to *U. urealyticum* through multiple sex partners may result in asymptomatic infection without signs of urethral inflammation.

Trichomonas

Trichomonas vaginalis is a flagellated parasite that exclusively infects the urinary tract (Muzny and Schwebke, 2013). *T. vaginalis* is a common vaginal pathogen but also can cause urethritis in men. Among men attending an STD clinic, the prevalence is reported at

3% to 17% (Schwebke and Hook, 2003; Bachmann et al, 2011). Wet mounts examined for *T. vaginalis* have been traditionally used for diagnosis, with a sensitivity of only 60%; culture has also been used as the gold standard of diagnosis. Both are being supplanted by NAATs (Schwebke et al, 2011).

Treatment of Nongonococcal Urethritis

Patients are treated initially for both *N. gonorrhoeae* and chlamydia. Treatment is azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice per day for 7 days.

Recurrent and Persistent Urethritis

Persons who were noncompliant with the initial regimen or reexposed to an untreated sex partner can be treated again with the initial medications. Persistent symptoms after doxycycline treatment could be caused by doxycycline-resistant *M. genitalium*, or by *T. vaginalis*. A urine specimen can be sent for testing (Schwebke and Hook, 2003). Alternative regimens include metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in single dose (if not used in initial episode). Another choice for second-line therapy is moxifloxacin 400 mg orally for 7 days, which is effective against *M. genitalium* (Bradshaw et al, 2008). The resistance rate for *M. genitalium* to azithromycin has been reported at 16% to 24% (Bradshaw et al, 2008; Twin et al, 2012). In men with persistent symptoms, urologic evaluation does not usually identify a specific cause for the urethritis. One consideration is to make sure there is not pain elsewhere in the pelvis, which could indicate chronic pelvic pain syndrome as opposed to localized urethritis (Nickel et al, 2003).

EPIDIDYMITIS

Acute epididymitis is characterized by pain, swelling, and inflammation of the epididymis that lasts less than 6 weeks (Tracy et al, 2008). The testis is usually involved (epididymo-orchitis). Among sexually active men younger than 35 years, acute epididymitis is frequently caused by *C. trachomatis* or *N. gonorrhoeae*. Among MSM, acute epididymitis can be caused by enteric organisms such as *Escherichia coli* and *Pseudomonas* as a result of anal intercourse. Sexually transmitted acute epididymitis is usually also accompanied by urethritis, although this can be asymptomatic. In men older than 35 years, a sexually transmitted cause is uncommon, and the infecting organism is usually associated with bacteriuria from obstruction or benign prostatic hyperplasia (BPH), with *E. coli* the most common organism (Berger et al, 1979). There can be atypical organisms in men with HIV, including cytomegalovirus (CMV), *Salmonella*, *Ureaplasma*, *Corynebacterium*, *Mycoplasma*, and fungi (Parr et al, 1993; Hohmann, 2001). Chronic epididymitis is characterized by more than 6 weeks of pain in the scrotum, testicle, and epididymis. Chronic infectious epididymitis is most commonly seen with tuberculosis (TB), as a consequence of hematogenous spread rather than seeding of the urinary tract from the kidneys (Heaton et al, 1989).

The diagnosis of acute epididymitis includes ruling out testicular torsion, especially in younger patients. Scrotal ultrasonography can be helpful but is not always diagnostic (Pontari, 2013). The evaluation of acute epididymitis should include either a Gram stain of urethral secretions as noted earlier for urethritis, a urine dip for leukocyte esterase on first-void urine, or microscopic examination of the first-void urine demonstrating more than 10 WBCs/HPF. Urine can be sent for NAAT (CDC, 2010c). Empirical therapy is indicated before laboratory test results are available. First-line therapy in men younger than 35 years is ceftriaxone 250 mg IM plus doxycycline 100 mg orally twice per day for 10 days. For patients with suspected enteric organisms, treatment is ceftriaxone plus levofloxacin 500 mg orally twice per day for 10 days (CDC, 2010c).

GENITAL ULCERS

In the United States, most young sexually active patients who have ulcers (Table 15-3) have either genital herpes or syphilis, with genital herpes being more common. Less common causes are chancroid and donovanosis. Ulcers may also be associated with noninfectious causes such as yeast, trauma, malignancy, aphthae, fixed drug eruption, and psoriasis (CDC, 2010c). In addition to a history and physical examination, all patients with ulcers need serologic testing for syphilis and a darkfield examination if possible, culture or PCR testing for HSV, and diagnostic serology for determining the specific type of HSV. In environments where chancroid is prevalent, a test for *Haemophilus ducreyi* should be performed. Patients who are not known to be HIV positive should be tested for HIV. Even after complete diagnostic evaluation, 25% of patients with genital ulcers will have no laboratory-confirmed diagnosis. Biopsy of ulcers is indicated if they are unusual or do not respond to initial therapy.

Syphilis

Syphilis is caused by *Treponema pallidum*, a coiled spirochete bacterium. *Treponema pallidum* cannot be easily cultured. Transmission is usually by sexual contact, through microabrasions in skin and mucosal membranes in patients with primary and secondary syphilis (Ho and Lukehart, 2011). The risk increases with increasing numbers of sexual partners (French, 2007). Syphilis replicates at the site of the infection and divides every 30 to 33 hours (Fieldsteel et al, 1981). It is estimated that 50% to 60% of sexual contacts of individuals with early syphilis will acquire syphilis (Schober et al, 1983).

Primary Syphilis

The lesions occur at the initial site of infection. The incubation is typically 2 to 3 weeks but can range from 9 to 90 days for the appearance of lesions after infection (French, 2007). The lesions are usually single and painless but can be multiple, and up to one quarter of chancres can be painful (Read and Donovan, 2012). Local nontender lymphadenopathy is common. Untreated lesions heal spontaneously in 3 to 8 weeks (Ho and Lukehart, 2011). In men,

TABLE 15-3 Genital Ulcer Disease

DISEASE	LESIONS	LYMPHADENOPATHY	SYSTEMIC SYMPTOMS
Primary syphilis	Painless , indurated, with a clean base, usually singular	Nontender, rubbery, nonsuppurative bilateral lymphadenopathy	None
Genital herpes	Painful vesicles, shallow, usually multiple	Tender, bilateral inguinal adenopathy	Present during primary infection
Chancroid	Tender papule, then painful , undermined purulent ulcer, single or multiple	Tender, regional, painful, suppurative nodes	None
Lymphogranuloma	Small, painless vesicle or papule progresses to an ulcer	Painful, matted, large nodes with fistulous tracts	Present after genital lesion heals



Figure 15-1. Syphilis with penile chancre.



Figure 15-2. Syphilis with vulvar chancre.

lesions are typically on the glans or the coronal or perineal area (Fig. 15-1), and on the labia or perianal area in women (Fig. 15-2).

Secondary Syphilis

Treponema pallidum eventually becomes a systemic infection with bacteremia. Secondary syphilis appears 3 to 5 months after the

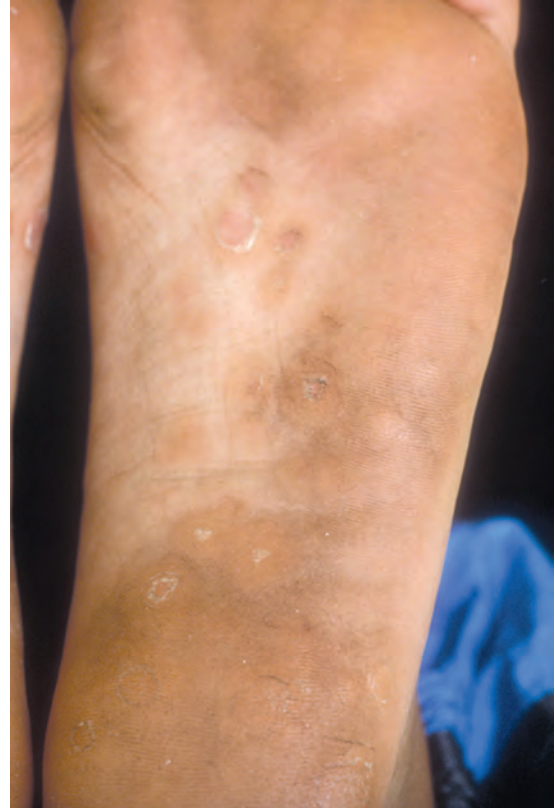


Figure 15-3. Secondary syphilis affecting the soles of the feet.

initial infection and is characterized by a maculopapular rash, which is often widespread and involves the scalp, palms, and soles of the feet in 75% of patients (Fig. 15-3) (Read and Donovan, 2012). The rash can ulcerate and lead to condyloma lata, which are wartlike lesions. Additional symptoms include fever, malaise, weight loss, patchy alopecia, and ocular inflammation (Mindel et al, 1989). There is also a broad vasculitis that in approximately 10% of patients may manifest as hepatitis, iritis, nephritis, and neurologic problems including headache and cranial nerve involvement, especially VIII (auditory). Relapses usually occur in the first year after infection and rarely after the second year. The infection then becomes latent and asymptomatic.

Latent Syphilis

Latent syphilis is defined as seroreactivity with no clinical evidence of disease and is arbitrarily divided into early and late latent infection. To be diagnosed with early latent syphilis, the patient must have no signs of primary or secondary disease and have positive syphilis serology, preceded by negative serology in the past year, or recent contact with an infectious patient (CDC, 2010c). Asymptomatic patients with no evidence of recent negative serology or previous treatment are classified as having syphilis of unknown duration and are considered to have late latent syphilis (Read and Donovan, 2012).

Tertiary or Late Syphilis

About 35% of individuals with late latent syphilis will develop the late manifestations of syphilis, which include neurosyphilis, cardiovascular syphilis, and gummatous syphilis. These are rare outside of developing countries. Neurosyphilis can be seen in secondary syphilis, and meningovascular syphilis also occurs in tertiary syphilis. The incubation period is usually 5 to 12 years. After 10 to 20 years, the spinal column and brain can also be involved. The spinal cord syndrome is called *tabes dorsalis*, and the brain syndrome is also called *general paralysis of the insane* (Danielsen et al, 2004;

French, 2007). Cardiovascular syphilis occurs 15 to 30 years after infection and may occur in any large vessel (French, 2007).

Tests for Syphilis

Darkfield Examination. Cultures of *T. pallidum* are not possible in vitro. Direct tests include identification of *T. pallidum* under a dark-ground microscope from samples taken from a lesion, with a sensitivity rate of up to 97% (Wheeler et al, 2004). This, however, requires trained personnel.

Serology

Nontreponemal Tests. Measurement of antibodies is important for the screening and diagnosis of syphilis. There are two categories of tests: nontreponemal, which are directed against phospholipids, and treponemal, which are directed against *T. pallidum* polypeptides. Nontreponemal antibodies bind lipids that have bound to the treponeme and become antigenic (Lafond and Lukehart, 2006). Nontreponemal antibodies are detected with the rapid plasma reagin (RPR) test, the Venereal Disease Research Laboratory (VDRL) test, and the toluidine red unheated serum test (TRUST). Results are positive within 21 days but sometimes as long as 6 weeks after infection. They are universally positive in secondary syphilis (Read and Donovan, 2012). Nontreponemal test results need confirmation with a treponemal test because they can be positive in other conditions such as viral infections, pregnancy, malignancies, autoimmune disease, and advanced age (Larsen et al, 1995). False-negative reactions occur if there is an excess of antibodies that overwhelm the assay, called the *prozone effect* (CDC, 2010c). Nontreponemal tests are used to monitor disease activity. A fourfold change in titer equivalent to a change of two dilutions (e.g., from 1:16 to 1:4) is considered necessary to demonstrate a clinically significant difference. The same test should be used in a given person because the tests are not directly comparable (CDC, 2010c). Nontreponemal tests usually become nonreactive with time after treatment, but in some patients levels of the antibodies can persist for a long time, including for the lifetime, a response referred to as the *serofast reaction* (CDC, 2010c).

Treponemal Tests. Treponemal antibodies are detected by immunofluorescence in the fluorescent treponemal antibody absorption (FTA-ABS) test or by agglutination in the microhemagglutination assay for *T. pallidum* (MHA-TP), the *T. pallidum* hemagglutination assay (TPHA), or the *T. pallidum* particle agglutination (TP-PA) test. False-positive results are uncommon but can occur in patients with collagen disease, systemic lupus erythematosus, and other infections (Hart, 1986). Treponemal test results remain positive for life except in 15% to 25% of patients treated early for primary syphilis (Young et al, 2009). Treponemal tests are not used to determine disease activity or treatment response.

Other Tests. Polymer chain reaction to identify *T. pallidum* may prove to be useful, with a sensitivity of 94.7% and specificity of 98.6% reported (Palmer et al, 2003). Rapid syphilis tests including enzyme-linked immunosorbent assays (ELISAs) are also available and are U.S. Food and Drug Administration (FDA) approved and cheaper than the nontreponemal tests usually used for initial diagnosis. They can give results in 5 to 20 minutes but cannot distinguish between active and treated syphilis (Ho and Lukehart, 2011). A newer paradigm of testing is to use the rapid test first, and if the result is positive, to perform a nontreponemal test with titers to guide management. If the nontreponemal test result is negative, a different treponemal test should be performed.

Coinfection with Human Immunodeficiency Virus

Of patients becoming infected with syphilis, up to 25% are HIV infected, and the incidence rate for syphilis in HIV patients has been reported as 77 times that of the general population (Chesson et al, 2005). The clinical course of syphilis in a person with HIV is similar to that in immunocompetent persons. However, HIV-positive patients may have larger ulcers in the primary phase and may be at risk for a more rapid progression to neurosyphilis with a CD4 count

of 350 or lower and/or a nontreponemal serologic test result of 1:32 or higher (French, 2007). Occasionally an unusual serologic response may occur with a false-negative result. If the clinical course strongly suggests syphilis and serologic test results are negative, consider other tests such as biopsy of lesion or rash (CDC, 2010c). All patients with syphilis should be tested for HIV.

Treatment of Syphilis

The standard treatment for all stages of syphilis is penicillin G. The stage and clinical manifestations of syphilis determine the preparation, dosage, and length of treatment. Treatment guidelines from the CDC are presented in Table 15-4 (CDC, 2010c). Not considered appropriate treatment are combinations of benzathine and procaine penicillin (Bicillin C-R), nor is oral penicillin. Patients with HIV receive the same treatment regimen as non-HIV-infected persons. A reaction consisting of fever, malaise, nausea, and vomiting, called the Jarisch-Herxheimer reaction, can occur. This is not an allergic reaction to penicillin but occurs with treatment of the treponemes, and more commonly with treatment with penicillin and in early syphilis. It may also be associated with chills and exacerbation of secondary rash. Treatment is with bed rest and nonsteroidal anti-inflammatory medications. Signs of treatment failure include persistent or recurring signs and symptoms of syphilis, and sustained fourfold increase in

TABLE 15-4 Treatment of Syphilis (Centers for Disease Control and Prevention 2010 Guidelines for Treatment of Sexually Transmitted Diseases)

STAGE OF SYPHILIS	PENICILLIN TREATMENT	PENICILLIN-ALLERGIC PATIENTS
Primary, secondary, and early latent syphilis, no neurologic involvement	Benzathine penicillin G 2.4 million units IM, single dose	Doxycycline 100 mg PO bid for 2 wk Tetracycline 500 mg PO qid for 2 wk
Late latent or latent syphilis of unknown duration, no neurologic involvement	Benzathine penicillin G 2.4 million units IM once per week for 3 wk	Doxycycline 100 mg PO bid for 28 days Tetracycline 500 mg PO qid for 28 days
Tertiary (late) syphilis without neurologic involvement	Benzathine penicillin G 2.4 million units IM once per week for 3 wk	Consult infectious disease specialist
Neurosyphilis Alternative regimen	Aqueous crystalline penicillin G 3-4 million units IV q4h, or continuous IV infusion for total 18-24 million units per day, for 10-14 days Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg PO qid, both for 10-14 days	

nontreponemal test result or failure to decrease fourfold within 6 months of therapy. Patients should be (1) retested for HIV, (2) evaluated for neurosyphilis with cerebrospinal fluid (CSF) examination, and (3) re-treated with weekly injections of benzathine penicillin G, 2.4 million units IM for 3 weeks, unless neurosyphilis is diagnosed.

Herpes

Herpes simplex virus type 1 and HSV-2 are double-stranded DNA viruses. They share 83% sequence homology of their protein coding regions and share similar structure of their genomes (Gupta et al, 2007). They can be distinguished serologically. HSV-1 causes mainly oral infections but now accounts also for at least half of first episodes of genital HSV infections (Roberts et al, 2003). This is thought to be a combination of later acquisition of oral HSV-1, which would confer immunity to the genital infection, and increase in oral sex in young adults (Halpern-Felsher et al, 2005). HSV-2 causes genital herpes and is transmitted by sexual contact. Women are more susceptible to HSV-2 infection than men and are more likely to have symptomatic infections (Langenberg et al, 1999). Most HSV-2 transmission thus occurs from individuals who do not know they are infected (Mertz, 2008). In a study of 5452 adults attending primary care offices in the United States, the seroprevalence of HSV-2 was 25.5%, but only 12% of these patients reported a history of prior infection (Leone et al, 2004). HSV-2 infection seems to protect against HSV-1 infection, but HSV-1 gives only a small amount of protection from infection with HSV-2 (Looker and Garnett, 2005).

Pathophysiology

Herpes simplex virus initiates replication in epithelial cells at the site of entry, damages the cells, and enters the ends of peripheral sensory nerves. It is then transported in a retrograde manner to the cell body in the sensory root ganglia. In the initial infection, herpes also spreads to the local and regional lymph nodes. Once in the nerve cell body, HSV enters a latent state (Jerome et al, 1998). Recurrence and reactivation of virus occur with transportation in the peripheral nerves back to the mucosal or skin surface. Events that trigger reactivation of HSV include local trauma such as surgery or ultraviolet light, immunosuppression, or fever (Gupta et al, 2007). Recurrence can lead to recurrence of lesions from mucosal or skin disruption or may occur in the absence of recognizable lesions. This is termed *asymptomatic* or *subclinical shedding* (Wald et al, 1995; Wald et al, 2000).

Natural History and Diagnosis

The classic first presentation of primary herpes is clusters of erythematous papules and vesicles on the external genitalia that do not follow a neural distribution (Figs. 15-4 and 15-5). This usually occurs 4 to 7 days after sexual intercourse (Looker and Garnett, 2005). Many herpetic lesions do not have the classic appearance and may look like fissures or furuncles, and in women may manifest as vulvar erythema (Koutsky et al, 1992). Patients have pain, burning, or itching, and 80% of women report dysuria. Other associated symptoms include fever, headache, malaise, and myalgias (Corey et al, 1983). Tender inguinal and femoral lymph nodes may be present. Primary genital HSV-1 infection cannot be distinguished from HSV-2 infection on clinical examination alone, but requires laboratory testing. Over the next 2 to 3 weeks, 75% of patients have new lesions, which can progress to vesicles and pustules and can coalesce into ulcers before crusting and healing (Corey et al, 1983). Possible complications include aseptic meningitis and autonomic dysfunction that can lead to urinary retention (Corey et al, 1983).

Recurrent Episodes

A primary genital herpes infection with either HSV-1 or HSV-2 is more severe in the absence of preexisting HSV-1 immunity (Corey



Figure 15-4. Herpes simplex virus infection on the penis.



Figure 15-5. Typical vesicular eruption of herpes simplex virus.

et al, 1983). Subsequent recurrent episodes with established immunity are milder than the initial infection. Genital HSV-1 recurs much less frequently (0.02 recurrences per month) than genital HSV-2 infections (0.23 recurrences per month), on the order of 10-fold less (Lafferty et al, 1987a). Although shedding is greatest in the first 6 to 12 months, it can continue for years (Schacker et al, 1998; Benedetti et al, 1999). Lesions heal in 5 to 10 days in the absence of antiviral treatment. HSV recurrences decrease after the first year, although some spike in recurrences in HSV-2 even after 4 years of follow-up have been noted (Benedetti et al, 1999).

Diagnosis and Testing for Herpes Simplex Virus

A definitive diagnosis of HSV subtype should be made both to confirm the diagnosis and to obtain important prognostic

TABLE 15-5 Recommended Oral Treatment for Genital Herpes Simplex Virus Infection

AGENT	FIRST CLINICAL EPISODE	EPISODIC THERAPY	SUPPRESSIVE THERAPY
Acyclovir	400 mg tid for 7-10 days or 200 mg 5 times/day for 7-10 days	400 mg tid for 5 days or 800 mg tid for 2 days or 800 mg bid for 5 days	400 mg bid
Famciclovir	250 mg bid for 7-10 days	125 mg bid for 5 days or 1000 mg bid for 1 day or 500 mg once, followed by 250 mg bid for 2 days	250 mg bid
Valacyclovir	1 g bid for 7-10 days	500 mg bid for 3 days or 1 g sid for 5 days	500 mg sid or 1 g sid

Modified from Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1–110.

information, given the clinical disparity between genital HSV-1 and HSV-2. In patients with lesions, fluid can be obtained from the base of the genital lesion and sent for viral culture, HSV antigen detection, or PCR of HSV DNA (Rose et al, 2008; Nguyen et al, 2010). The detection rate for HSV from lesions is 80% for primary infections but only 25% to 50% for recurrent lesions, and even less if the lesion has begun to heal (Lafferty et al, 1987b). In patients with no active lesions, serology must be used—that is, testing for antibodies. Specific immunoglobulin G (IgG) testing for glycoprotein G of HSV-1 or HSV-2 can distinguish the two types of HSV (Ashley, 2001). Serology is recommended for confirmation of a clinical diagnosis of genital herpes in patients with recurrent genital symptoms, atypical lesions, or healing ulcers and negative viral cultures. Type-specific antibodies to herpesvirus can take from 2 weeks to 3 months to develop; thus in a person with newly acquired herpes, an initial negative serology followed by a positive test after 12 weeks confirms a new infection (CDC, 2010c).

Treatment (Table 15-5)

Currently available medications to treat herpes do not eradicate the virus, but aim to reduce the signs and symptoms of infection and to prevent new lesions. Available drugs include acyclovir (intravenous only), valacyclovir, and famciclovir (CDC, 2010c). Treatment for a first clinical episode should be started on clinical grounds before laboratory confirmation of diagnosis. Treatment is usually 7 to 10 days but should be extended if lesions are not adequately healed (CDC, 2010c). Intravenous acyclovir (5 to 10 mg/kg every 8 hours) may be needed for those with neurologic complications, those unable to take oral medications, or those with widespread disease (e.g., immunocompromised patients) (Gupta et al, 2007). Treatment of recurrent episodes reduces their severity and duration. Oral therapy within 24 hours of the first signs or symptoms of recurrence increases the chance of resolving a recurrence without lesions (Leone et al, 2002; Wald et al, 2002; Aoki et al, 2006). In patients with frequent recurrences, daily suppressive therapy can be used to reduce recurrences by 70% to 80% (Wald et al, 2006). Patients with HIV can have prolonged or severe episodes of HSV infection, and HSV shedding is increased in HIV-infected persons. Doses and durations of medications are increased for suppression and treatment of episodic HSV infections in persons with HIV (CDC, 2010c).

Chancroid

Chancroid is caused by the gram-negative bacterium *H. ducreyi* (Lewis, 2003). Infection leads to anogenital ulceration and lymphadenitis with progression to bubo formation (Lewis and Ison, 2006). The incubation period is 3 to 10 days, with the initial



Figure 15-6. Chancroid with regional adenopathy.

presentation of a papule that may progress to form an ulcer (Fig. 15-6) (Lewis and Ison, 2006). Circumcised men are at lower risk of being infected with chancroid (Weiss et al, 2006). The prevalence of chancroid has declined in the United States (CDC, 2013), but chancroid is still endemic in other parts of the world such as Africa, Asia, Latin America, and parts of the Caribbean; a genital ulcer in a person with a history of travel to these areas should raise suspicion for chancroid (Lewis and Ison, 2006). Chancroid, like genital herpes and syphilis, is a risk factor for transmission of HIV (Magro et al, 1996).

A definitive diagnosis of chancroid requires culture on media not routinely available (Lockett et al, 1991). There are no FDA-approved tests. The CDC suggests that a probable diagnosis of chancroid can be made if (1) the patient has one or more painful ulcers;

(2) no evidence of *T. pallidum* is present on darkfield examination of ulcers or by serologic testing for syphilis performed at least 7 days after onset of the ulcers; (3) ulcers and lymphadenopathy, if present, are typical for chancroid; and (4) results of tests for HSV on the ulcer exudate are negative (CDC, 2010c). Treatment is with azithromycin 1 g in a single dose or ceftriaxone 250 mg IM in single dose or ciprofloxacin 500 mg orally twice per day for 3 days or erythromycin base 500 mg orally three times per day for 7 days. Patients should be tested for HIV at the time of diagnosis of chancroid. If initial test results were negative, repeat testing at 3 months for syphilis and HIV should be performed. Patients with HIV are less likely to respond to treatment, have slower healing of ulcers, and may require longer courses of therapy (CDC, 2010c).

Granuloma Inguinale

Granuloma inguinale is an infection by the intracellular gram-negative bacterium *Klebsiella granulomatis* (formerly called *Calymmatobacterium granulomatis*) that produces genital ulcers. Granuloma inguinale does not usually occur in the United States. The most common locations in the world for granuloma inguinale are Papua New Guinea, South Africa, parts of India and Brazil, and the aboriginal community in Australia (Lagergard et al, 2011). The incubation period averages 50 days (O'Farrell, 2002). The disease manifests as painless, slowly progressive ulcers on the genitals and perineum. Despite the name, inguinal involvement is uncommon (10%) (Velho et al, 2008). The lesions are described as beefy red because of high vascularity, and they bleed easily. The most common site of extragenital spread is the mouth, producing loss of teeth from bone destruction, but it can also occur in the pelvis, intra-abdominal organs, and other bones (especially the tibia) (Velho et al, 2008).

The bacterium is a strict human pathogen, which makes culture difficult. Diagnosis requires visualization of dark-staining Donovan bodies on crush preparation or biopsy, described by Donovan in 1905 (Richens, 2006). These are intracellular inclusions of the bacteria within the cytoplasm of macrophages and appear deep purple when stained with Wright, Giemsa, or Leishman stain (Lagergard et al, 2011). There are no FDA-cleared molecular tests for detection of *K. granulomatis*. Treatment is with doxycycline 100 mg orally twice per day for at least 3 weeks and until all lesions have healed (CDC, 2010c).

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is an infection by *Chlamydia*, specifically serovars L1, L2 or L3 (Mabey and Peeling, 2002). Traditionally, LGV is rare in developed countries but is endemic in parts of Africa, Asia, South America and the Caribbean (Mabey and Peeling, 2002). However, the incidence of LGV, especially in MSM, has been rising since the infection was first described in Western Europe in 2003, and LGV is occurring worldwide including in the United States (White, 2009). The incubation period is 3 to 30 days. A self-limited genital ulcer or papule sometimes is present at the site of infection but usually has disappeared by the time of presentation. The secondary stage is the most common presentation in heterosexuals and is marked by tender inguinal and/or femoral lymphadenopathy, typically unilateral (Fig. 15-7). Inguinal lymph nodes are more common in men because the lymph drainage of the cervix and vagina are to the retroperitoneal rather than the inguinal lymph nodes (Mabey and Peeling, 2002). Inguinal lymph nodes above and below the inguinal ligament can give rise to the "groove sign" in 10% to 20% of patients (Schachter and Osoba, 1983). Rectal exposure in women or MSM can result in proctitis with hemorrhoids, rectal or anal pain, rectal discharge, constipation, and fever (Arnold et al, 2013). A third stage can develop. If left untreated, LGV proctocolitis can develop into chronic colorectal fistulas and strictures. Chronic infection can also lead to lymphatic obstruction with elephantiasis of the genitalia in either sex. LGV does not appear to occur more frequently or with any more virulence in HIV-positive individuals (Jebbari et al, 2007).



Figure 15-7. Lymphogranuloma venereum with inguinal adenopathy.

Diagnosis is made by swab of lesions or aspiration of buboes from genitals or lymph nodes, sent for culture, direct immunofluorescence, or nucleic acid detection. NAATs are used for urethral specimens but are not FDA approved for rectal specimens. *Chlamydia* serology with complement fixation titers exceeding 1:64 can support the diagnosis of LGV (CDC, 2010c). When specific diagnostic testing is not available, the patient should be presumptively treated for LGV. Treatment is with doxycycline 100 mg orally twice per day for 21 days (CDC, 2010c).

Human Papillomavirus

Human papillomavirus (HPV) is a double-stranded DNA virus belonging to the Papillomaviridae family. More than 100 types of HPV exist, of which more than 40 types of HPV can infect the genital area and be sexually transmitted (Dunne et al, 2011). Types 6 and 11 are nononcogenic and are responsible for about 90% of anogenital warts (Gissmann et al, 1983; Garland et al, 2009). Other subtypes including 16 and 18 account for cervical cancer and other types of anogenital cancer including vulvar, vaginal, anal, and penile cancers (De Vuyst et al, 2009; Li et al, 2011). Although certain HPV types are associated with certain morphologic characteristics, the association is not absolute. The usual keratinizing squamous cell penile cancer is associated with HPV in only 11% of patients, with much higher rates of HPV DNA positivity strongly associated with either basaloid or warty changes (47%) or purely basaloid changes (75%) (Giuliano et al, 2008).

More than 50% of sexually active persons will become infected at least once in their lifetime (Myers et al, 2000). Approximately 70% of HPV infections resolve spontaneously in 1 year and 90% in 2 years, and HPV persistence develops in the remaining persons (Veldhuijzen et al, 2010). Transmission can occur from asymptomatic and subclinical patients. Among asymptomatic women in the general population, the prevalence of HPV infection ranges from 2% to 44%, and among men from 2.3% to 34.8% (Burchell et al, 2006). HPV infection starts at the basal cell layer of stratified squamous epithelial cells, which then stimulates cell proliferation in the epithelium. HPV warts can also occur in the urethra and can cause hematuria, dysuria, or difficulty voiding. Bowenoid papulosis involves reddish brown verrucous papules on the penis that are a low-grade carcinoma in situ with a chance of malignant transformation of 2% to 3% (Cubie, 2013). Buschke-Lowenstein tumors, or giant condyloma acuminatum, are large verrucous exophytic lesions on the penis or perineum, associated with HPV-6 or HPV-11. These tumors are considered a low-grade verrucous carcinoma, and in general only local invasion is present (Armstrong et al, 2009; Cubie, 2013).

Lesions such as warts can be seen clinically (Figs. 15-8 and 15-9), but HPV virus can also be present and subclinical. Latent viruses are detectable only through demonstration of HPV DNA in skin or



Figure 15-8. Meatal wart caused by human papillomavirus.



Figure 15-9. Penile warts.

mucosa (Cubie, 2013). The use of acetic acid to detect nonvisible skin lesions is not recommended because of the large number of false-positive results. HPV tests that detect viral nucleic acid (i.e., DNA or RNA) or capsid protein are available for women older than 30 years undergoing cervical cancer screening. These tests should not be used for men, for women younger than 20 years, or as a general test for STDs (CDC, 2010c). In the following situations, biopsy may be warranted to rule out a malignant lesion: (1) the diagnosis is uncertain; (2) the patient is immunocompromised; (3) the warts are pigmented, indurated, or fixed; (4) the lesions do not respond to or they worsen with standard treatment; (5) there is persistent ulceration or bleeding.

Treatment

The goal of treatment is removal of the warts; treatment will not eradicate the infection. Treatment is guided by wart size, number, and location, and patient preference. Treatment regimens are divided into patient-applied and provider-applied modalities (CDC, 2010c).

Patient-applied treatments for HPV (note: these are not approved for use during pregnancy):

1. Podofilox 0.5% solution or gel up to 0.5 mL/day, applied twice per day for 3 days, then no therapy for 4 days, up to four cycles. Total wart area should not exceed 10 cm².
2. Imiquimod cream 5% once daily at bedtime, three times per week up to 16 weeks; should be washed off 6 to 10 hours after application.
3. Sinecatechins 15% ointment (sinecatechins are major polyphenols found in green tea leaves) (Dunne et al, 2011), three times per day for up to 16 weeks. This should not be washed off after application. Avoid sexual contact with the ointment on the skin. Not recommended in patients with HIV, those

who are otherwise immunocompromised, or those with herpes.

Provider-administered treatments:

4. Podophyllin resin 10% to 25% in tincture of benzoin, applied to wart and allowed to dry. This can be repeated weekly. To avoid complications from systemic absorption and toxicity, ensure that (1) application is limited to an area less than 10 cm² or less than 0.5 mL of podophyllin is used and (2) the treatment area does not contain any open lesions or wounds.
5. Cryotherapy such as liquid nitrogen, which induces cytolysis. Application can be repeated every 1 to 2 weeks. Providers should be trained in the use of this method. Large warts may need local anesthesia because of possible pain with application.
6. Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80% to 90%; these acids destroy warts by chemical coagulation of wart proteins. Apply to wart and allow to dry before patient stands up; if intense pain ensues after administration, neutralize the acid with soap and water or sodium bicarbonate. Can be repeated weekly.
7. Surgical therapy including direct excision with scissors, tangential shave excision, curettage, or laser therapy using a CO₂ laser (Aynaud et al, 2008). Consider collaboration with a plastic surgeon for large lesions that require large areas of excision, especially on the penis or in the groin creases.

Urethral warts are usually caused by HPV subtypes at low risk for malignancy (Beutner et al, 1999). Treatments for urethral meatal warts include cryotherapy with liquid nitrogen and podophyllin 10% to 25% compounded in tincture of benzoin. The adjacent skin must be dry before treatment. Men with external urethral warts should undergo urethroscopy to rule out intraurethral warts (Fralick et al, 1994). Bladder warts may also be present. 5-Fluorouracil has been used intraurethrally, but its use is limited by the significant inflammation produced. Holmium laser can be used for lesions in the urethra and bladder. A biopsy is recommended to rule out any malignant or precancerous lesions.

Human Papillomavirus Vaccine

In June 2006, a quadrivalent HPV vaccine (Gardasil) was licensed for use in the United States in girls and women aged 9 to 26 years (Markowitz et al, 2007). In October 2009, this vaccine also was licensed for use in boys and men aged 9 to 26 years (CDC, 2010b). This vaccine provides protection against HPV types 6, 11, 16, and 18. In October 2009, a bivalent HPV vaccine (Cervarix) that provides protection against types 16 and 18 was licensed for use in girls and women aged 10 to 25 years (CDC, 2010a). Overall the bivalent vaccine prevents HPV types that cause 70% of cervical cancer and the quadrivalent vaccine prevents HPV types that cause 70% of cervical cancers and 90% of genital warts. Either vaccine is recommended for girls starting at age 11 to 12 and can be given to girls as young as age 9. Girls and women aged 13 to 26 who have not started or completed the vaccine series should also receive the vaccine. It is most effective if started before the onset of sexual activity. The vaccine is given as a three-dose series of intramuscular shots over a 6-month period. Women should still undergo regular cervical cancer screening because 30% of cervical cancer is caused by other HPV subtypes. The vaccines are not licensed for use in women older than 26 years in the United States (Dunne et al, 2011).

The quadrivalent vaccine is used in males to prevent genital warts and in both genders to prevent anal cancer (Dunne et al, 2011). MSM are particularly at risk for developing anal intraepithelial neoplasia and anal cancer (Burchell et al, 2006). As in women and girls, it is best started before the onset of sexual activity. The vaccines are designed to prevent infection and are not effective in clearing an infection once established (Markowitz, 2007). The use of the vaccine is still relatively low, with 49% of girls and women aged 13 to 19 having received at least one dose and 32% having received three doses in a 2010 survey. Despite



Figure 15-10. Scabies affecting the penis.

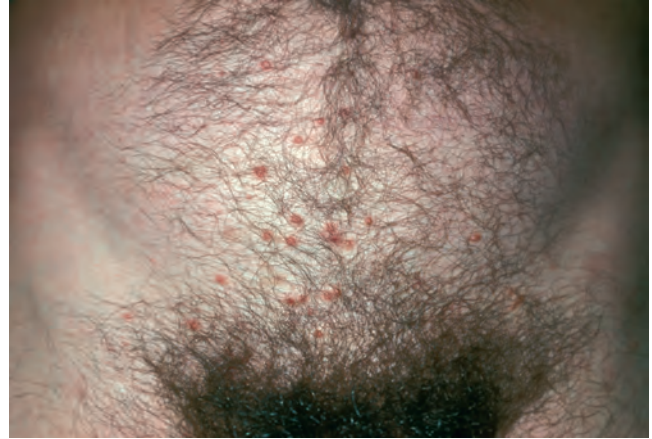


Figure 15-11. Molluscum contagiosum on the abdomen.

low rates of use, the prevalence of vaccine HPV subtypes in girls and women declined from 11.5% during the years 2003-2006 to 5.1% during the period 2007-2010 after initiation of the vaccine (Markowitz et al, 2013).

Scabies

Scabies is a skin infection caused by the mite *Sarcoptes scabiei* var. *hominis* and has been known for over 2500 years (Chosidow, 2000). The female lays eggs in the skin, and transmission is by person-to-person skin-to-skin contact with passage of pregnant female mites. This can occur during sexual contact (Fig. 15-10). Scabies also commonly passes from person to person in crowded conditions (Hay et al, 2013) and by contact with infected bedding or clothing. Symptoms usually do not appear for 2 to 6 weeks after infestation, and infected persons can pass the mites in the absence of symptoms (Chosidow, 2000). The most common symptoms are skin rash and itching, especially at night, from an allergic reaction to the mite proteins. Female scabies mites can tunnel under the skin, producing tiny raised and crooked or serpiginous lines on the skin. Scratching at a sore can lead to infection with *Staphylococcus aureus* or β -hemolytic streptococci. These secondary infections have been associated with poststreptococcal glomerulonephritis (Svartman et al, 1972).

A more concentrated area of mites can form a crust and is called *crusted* or *Norwegian scabies*. This may occur in persons who have difficulty scratching or are prevented from scratching, such as those with spinal cord injury or mental disability, and also occurs in elderly and immunocompromised persons, including those with HIV infection. These individuals are very contagious (Chosidow, 2000). Diagnosis is made by demonstration of mites, mite eggs, or fecal matter (scybala) on microscopic examination of a skin scraping. Treatment is with permethrin cream (5%) applied to all areas of the body from the neck down and washed off after 8 to 14 hours or ivermectin 200 μ g/kg orally, repeated in 2 weeks. An alternative is lindane (1%) lotion or cream, but this is used only if the patient cannot tolerate other therapies or if other therapies have failed, because lindane toxicity causes central nervous system (CNS) effects, seizures, and aplastic anemia (Chosidow, 2006). Bedding and clothing should be decontaminated by washing and drying on the hot cycles, or by removal and placement in a decontamination bag for longer than 72 hours. Scabies do not generally survive more than 2 or 3 days away from human skin.

Pediculosis Pubis (*Phthirus pubis*): Pubic or Crab Louse

Pediculosis (lice) has been known for 10,000 years (Orion et al, 2004). Lice are obligate bloodsucking parasites of humans. The pubic lice are much shorter than those that occur on the scalp or body. Transmission requires close contact. The female's life cycle

lasts for 1 to 3 months. Females lay eggs (nits) at the skin-hair junction; they mature into lice in 20 days. Pubic lice infestation is common in sexually active persons and tends to recur in gay men. Transmission is not prevented with use of condoms. Pubic lice specifically have a serrated surface on their claws to facilitate clinging to flat, hairless surfaces (Orion et al, 2006). In children, the presence of pubic lice does not imply a definite sexual contact, as they can be acquired by contact with an infected parent (Chosidow, 2000).

The typical presentation is pruritus, which is caused by a delayed hypersensitivity reaction to the lice. First exposure can result in symptoms in 2 to 6 weeks (Orion et al, 2004). Symptoms develop more quickly with subsequent exposures, on the order of 1 to 2 days. Eggs remain in situ after releasing their larvae (nymphs), and empty shells can remain on the hair for many months after the infection has been eradicated; therefore the diagnosis is only by identifying live lice or viable eggs (Chosidow, 2000). Treatment is permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes or pyrethrins with piperonyl butoxide applied to affected areas and washed off after 10 minutes (CDC, 2010c). Bedding and clothing should be decontaminated by dry cleaning; washing and drying at high temperature; or removal from body contact for 72 hours. Patients with pediculosis pubis should be evaluated for other STDs.

Molluscum Contagiosum

Molluscum contagiosum is a superficial skin disease caused by the pox virus. The virus contains double-stranded DNA and replicates entirely in the cytoplasm of infected cells, independent of the host nucleus (Myskowski, 1997). It can be sexually transmitted. Characteristic lesions are small, discrete waxy papules 3 to 5 mm in diameter, with a central depression (Fig. 15-11). The central core can be expressed, producing a white material. Localized eczematous dermatitis is commonly seen around the lesions (Chen et al, 2013). The infection is usually self-limited and spontaneously disappears in 6 to 12 months, but may take up to 4 years to resolve. However, infection in immunocompromised individuals, such as those with HIV, is typically more severe and extensive. Patients with HIV may develop widespread and large lesions including "giant" lesions larger than 15 mm in diameter (Cronin et al, 1996). Increase in the number of lesions can be seen in HIV patients as a manifestation of the immune reconstitution syndrome, which occurs shortly after the initiation of antiretroviral therapy (ART) in severely immunocompromised patients (Pereira et al, 2007). Diagnosis is generally on the basis of the characteristic appearance of skin lesions. Biopsy is indicated in cases of unclear diagnosis, especially in immunocompromised patients with unusual presentations in which malignancy must be excluded (Trobe and Lenzi, 2005). Skin biopsy will show typical "molluscum bodies" or Henderson-Patterson bodies,

which are eosinophilic inclusions in the epidermis (Eleftheriou et al, 2011).

One option for treatment is waiting, because the infection is generally self-limited. Rapid treatment options include cryotherapy (freezing the lesions), curettage with piercing of the lesion and removal of the contents, and laser therapy. Oral therapy with cimetidine has been used (Dohil and Prendiville, 1996). Topical therapies include podophyllotoxin cream 0.5% in men (this cannot be used in pregnant women because of fetal toxicity), iodine and salicylic acid, potassium hydroxide (KOH), cantharidin (a blistering agent), and imiquimod (Gottlieb and Myskowski, 1994). A first treatment in HIV patients is to use ART. The number of molluscum contagiosum lesions is inversely proportional to the CD4 cell count (Myskowski, 1997). Regression of recalcitrant molluscum contagiosum lesions after initiation of ART has been reported (Cattelan et al, 1999). Systemic and topical cidofovir may be beneficial in treating large molluscum contagiosum lesions associated with immunosuppression (Davies et al, 1999).

Vaginitis

Vaginal infections are characterized by discharge, itching, or odor. Three diseases most frequently associated with vaginal discharge are bacterial vaginosis (BV), trichomoniasis, and candidiasis. BV and trichomoniasis are sexually transmitted. The diagnosis can be made via Amsel's criteria: pH, a KOH test, and microscopic examination of fresh samples of the discharge (Table 15-6).

Bacterial Vaginosis

Bacterial vaginosis is caused by replacement of the normal hydrogen peroxide-producing *Lactobacillus* species in the vagina with high concentrations of anaerobic bacteria including *Prevotella*, *Mobiluncus*, *Gardnerella vaginalis*, *Ureaplasma*, *Mycoplasma*, and other fastidious anaerobes. Although BV is the most common diagnosis in women seeking care for vaginal symptoms, most women with BV are asymptomatic. Women with BV are at risk for acquisition of some STDs including HIV, *N. gonorrhoeae*, *C. trachomatis*, and HSV-2. Diagnosis can be made by Gram stain, evaluating for relative amounts of *Lactobacillus* and other bacteria characteristic of BV. Characteristic findings for BV on microscopic examination are clue cells, which are vaginal epithelial cells covered with bacteria. Recommended treatment regimens include metronidazole 500 mg orally twice per day for 7 days or metronidazole 0.75%, one full applicator (5 g) intravaginally once per day for 5 days or clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days (CDC, 2010c). Note that clindamycin is oil based and may weaken condoms and diaphragms for 5 days after use.

Trichomoniasis

Trichomoniasis is caused by the protozoan *T. vaginalis*. The discharge from trichomoniasis is diffuse, malodorous, and yellow

green with vulvar irritation; however, not all women infected are symptomatic. Diagnosis is usually by microscopy of vaginal secretions showing the *Trichomonas* organisms. The sensitivity of microscopy is only 60% to 70%. There are two FDA-approved rapid tests for *Trichomonas*: the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Lexington, MA), which uses immunochromatographic capillary flow dipstick technology, and the Affirm VPIII (Becton, Dickinson and Company, Sparks, MD), which is a nucleic acid probe test. Culture is also available for *T. vaginalis*. Treatment is metronidazole 2 g orally in a single dose or tinidazole 2 g orally in single dose (CDC, 2010c). **Patients are advised to abstain from alcohol consumption for 24 hours after taking metronidazole and 72 hours after tinidazole.** Evidence suggests interaction between HIV and *T. vaginalis* such that *T. vaginalis* infection in HIV-infected women might enhance HIV transmission by increasing genital shedding of the virus (Wang et al, 2001). In women with HIV, a multidose treatment regimen of metronidazole, 500 mg orally given twice per day for 7 days, is recommended instead of one 2-g dose (Kissinger et al, 2008; Kissinger et al, 2010).

Candidiasis

Vulvovaginal candidiasis is usually caused by *Candida albicans* but occasionally by other species of *Candida* or yeasts. Vaginal candidiasis is classified as complicated or uncomplicated based on clinical criteria (CDC, 2010c). Uncomplicated cases involve infections that are sporadic or infrequent, produce mild to moderate symptoms, are likely to be caused by *C. albicans*, and occur in immunocompetent women. Complicated cases involve recurrent candidiasis (four or more episodes of symptomatic vulvovaginal candidiasis in 1 year), severe infection, non-*C. albicans* cause, and women with uncontrolled diabetes, debilitation, or immunocompromise. Approximately 10% to 20% of cases of vulvovaginal candidiasis will be complicated. Vaginal cultures should be obtained in patients with recurrent vulvovaginal candidiasis because conventional antimycotic treatments are not as effective against atypical species such as *Candida glabrata*. The diagnosis is made via wet prep with saline or KOH; a Gram stain of vaginal discharge that demonstrates yeast, hyphae, or pseudohyphae; or a culture that shows *Candida* or other yeast species. Wet mounts should first be done for all patients, and culture used for those with symptoms with negative wet mounts.

Treatment for uncomplicated vulvovaginal candidiasis includes numerous over-the-counter intravaginal agents including butoconazole or clotrimazole creams, miconazole as a cream or intravaginal suppository, or tioconazole ointment. Prescription treatment formulations include butoconazole cream, terconazole cream or vaginal suppository, nystatin vaginal suppository, or one oral dose of fluconazole 150 mg (CDC, 2010c). A woman who has persistent symptoms or a recurrence 2 months after having used an over-the-counter treatment should be evaluated. In cases of recurrence, a longer duration of therapy such as 7 to 14 days of topical therapy or a dose of fluconazole every third day for a total of three doses is

TABLE 15-6 Differential Diagnosis of Vaginitis in Women

	VAGINAL DISCHARGE	pH	WHITE BLOOD CELLS	MICROSCOPY	SYMPTOMS
Normal	White, thick, smooth	≤4.5	Absent	Lactobacilli	None
Candidiasis	White, thick, curdlike	≤4.5	Absent	Mycelia	Vulvar pruritus, external or superficial dysuria
Trichomoniasis	Frothy or purulent	≥4.5	Present	Mobile trichomonads present Amine odor	Vulvar erythema and edema, punctate strawberry lesions on cervix
Bacterial vaginosis	Thin, white homogeneous	≥4.5	Absent	Paucity of lactobacilli (75% of patients) Amine odor Clue cells	Fishy odor and increased vaginal discharge

recommended (CDC, 2010c). Treatment for non-*C. albicans* vulvo-vaginal candidiasis is not standardized.

HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME AND THE UROLOGIST

HIV is a retrovirus that infects T cells and dendritic cells (Klasse, 2012). HIV spreads through blood, semen, vaginal fluid, or breast milk. The resultant immunosuppression leads to AIDS. The diagnosis of AIDS is made if the CD4 count is less than 200 cells/mm³ or if there is a serious opportunistic infection, neoplasm, or other life-threatening condition. A total of 26 conditions are AIDS defining, including cervical cancer, lymphomas, and infections with *Candida* and CMV (National Institutes of Health, 2013).

Estimates of the national HIV incidence in the United States are calculated by the CDC. At the end of 2010, approximately 1.1 million Americans were living with HIV, and it was estimated that 16% did not know they were infected (Lansky et al, 2010). Approximately 50,000 new infections occur each year, a number that has remained stable since the mid-1990s (Hall et al, 2008). HIV occurs more often in some populations. Of new infections, two thirds occur in MSM, with over half occurring in young black men. Heterosexuals accounted for one quarter of all new infections in 2010, two thirds of those being women. Injections drug users made up 8% to 10% of new cases (Lansky et al, 2010). The most affected age group was 25 to 34 years (31%), followed by 13 to 24 years (26%) and 35 to 44 years (24%) (CDC, 2014).

See Expert Consult website for details.

Diagnosis of Human Immunodeficiency Virus Infection

The CDC recommends HIV screening for all patients aged 13 to 64 in health care settings (Branson et al, 2006). Patients should be counseled and notified that testing will be performed and given the option to decline or defer testing. Written consent is not usually required. Diagnosis of HIV includes using serologic tests that detect antibodies against HIV-1 (and HIV-2) and virologic tests that detect HIV antigens or RNA. The initial test is a screening test for antibodies, the conventional or rapid enzyme immunoassay (EIA). The initial result can be obtained in 30 minutes. Positive or reactive screening tests must be confirmed by a supplemental antibody test, Western blot and indirect immunofluorescence assay (IFA), or virologic test, the HIV-1 RNA assay (CDC, 2004). A positive confirmation test result establishes the diagnosis. HIV is detectable in 95% of patients within 3 months after infection. During this initial 3-month period, the “window” period, the screening test

result may be negative but the person may still be infected. Virologic tests for HIV-1 RNA can be used to detect an acute infection in persons negative for HIV antibodies. This should be used with the initial antibody test in the setting of suspicion of acute retroviral syndrome (see the discussion of acute infection). A positive RNA test result should be confirmed by a subsequent antibody test. The majority of infections in the United States are HIV-1. HIV-2 infection should be suspected in persons with an unusual clinical presentation or with risk factors including having lived or having a sex partner from an endemic area (West Africa, Portugal), having a sex partner known to be HIV-2 positive, or having had a blood transfusion or nonsterile injection in an endemic area (CDC, 2004, 2010c).

See Expert Consult website for details.

Urologic Manifestations of Human Immunodeficiency Virus Infection

Interaction with other Sexually Transmitted Diseases

Testing for HIV is recommended in anyone with a diagnosed STD or who is at risk for an STD (CDC, 2010c). In many populations, the pattern of HIV acquisition parallels that of other STDs (Quinn et al, 1988; Clotney and Dallabetta, 1993); the presence of an STD increases the risk for both transmitting and acquiring HIV infection. STDs that produce ulcers are particularly associated with HIV; the adjusted OR for the effect of genital ulcer disease on increase in the risk of acquiring HIV is 2.2 to 11.3 (Quinn et al, 1990; Hook et al, 1992; Fleming and Wasserheit, 1999).

Several factors likely contribute to this association (Fleming and Wasserheit, 1999). Genital ulcers bleed frequently during intercourse, potentially leading to increased infectiousness. HIV has been detected in genital ulcer exudates (Kreiss et al, 1989). In HIV-seronegative individuals, ulcers may increase susceptibility to infection by disrupting mucosal integrity and by recruiting HIV-susceptible immune cells to the site of the ulcer, as in *H. ducreyi* infection (Magro et al, 1996). HSV infection may make keratinocytes also vulnerable to HIV, expanding the targets for infection (Heng et al, 1994). HSV also increases HIV replication in persons infected with both viruses (Van de Perre et al, 2008). Non-ulcer-producing STDs such as chlamydia and gonorrhea increase HIV shedding by recruiting HIV inflammatory cells in infected individuals (Moss et al, 1995). HIV shedding is associated with gonorrhea, cervicitis, and vaginitis in women (Mostad et al, 1997); higher levels are associated with concomitant infection with *M. genitalium* (Manhart et al, 2008). HIV-infected patients can also have larger lesions as in the case of HPV with giant condyloma (Fig. 15-16).



Figure 15-16. A and B, Acquired immunodeficiency syndrome patient with extensive genital condyloma.

Human Immunodeficiency Virus Virology

There are two types of HIV virus: HIV-1 and HIV-2. There are very few cases of HIV-2 infection in the developed world. HIV-2 is less virulent and is transmitted less readily (Campbell-Yesufu and Gandhi, 2011). Therefore this chapter deals exclusively with HIV-1. HIV is a retrovirus, in the family *Lentivirus* (Emerman and Malim, 1998). The genetic material in HIV is single-strand RNA. After entry into the targeted cell, the RNA is reverse transcribed by a reverse transcriptase into a double-stranded DNA. This new DNA is assembled into complexes, which then associate with the target cell chromatin and integrate via the action of viral integrase (Cavazza et al, 2013). The cell then translates and transcribes the viral genes to produce proteins that will assemble new copies of the virus. Copies of the virus are called *virions*.

Structure of the Human Immunodeficiency Virus

(Figs. 15-12 and 15-13)

Viral Envelope

The virus is shaped like a sphere. It is covered by an outer envelope, a lipid bilayer derived from the host cell when it buds out of the cell. Embedded in the envelope is a complex of proteins known as "Env." There is initially a precursor glycoprotein 160 (gp160) which is cleaved by a protease in the trans-Golgi network. It is cleaved into an outer subunit gp120 and a transmembrane subunit gp41. After proteolysis, the gp120 and gp41 remain coupled as noncovalent heterodimers (Klasse, 2012). These proteins protrude through the surface. The cap is made of three molecules of gp120, and the stem is three molecules of gp41. HIV must fuse its phospholipid bilayer surrounding the virus with a host membrane to be able to deliver the viral core (Grove and Marsh, 2011). The entry by fusion is mediated by the envelope glycoprotein (Env).

Viral Core

Within the envelope is a core or capsid, shaped like a cone, made of viral protein p24. Within the capsid are two copies of single-stranded RNA. Each RNA strand has a complete copy of the viral genes. Several structural genes are worth noting: *gag*, *pol*, and *env*. The *env* codes for a precursor protein gp160, which is then broken down to gp120 and gp41. There are regulatory genes including *tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu* that are involved with replication, virulence, and spread of disease (Emerman and Malim, 1998). Three core enzymes involved in later replication are reverse transcriptase, integrase, and protease.

Viral RNA

The ends of each strand of RNA contain a sequence called the *long terminal repeat* (LTR). Parts of the LTR function as switches to control production of new viruses. They are triggered by proteins from either HIV or the host cell.

Virus Entry and Replication (Fig. 15-14)

The virus enters a cell itself by endocytosis, with different forms of endocytosis depending on the cell type (Miyauchi et al, 2009). The HIV virion can infect a cell only if it has the necessary receptor. Glycoprotein gp120 has a high affinity binding site for the T-lymphocyte receptor CD4 (Sattentau et al, 1986; Sattentau and Weiss, 1988). Binding of gp120 to CD4 triggers conformational changes in Env that enable interactions with a coreceptor, a member of the chemokine family, usually CCR5 or CXCR4 (Alkhatib et al, 1996). This interaction in turn produces more changes in Env, releasing the fusogenic potential of gp41 (Platt et al, 2007). The native structure of gp41 is unknown, but its function is described. The N terminal 20 residues are called the *fusion peptide*. Fusion is dependent on areas called the *membrane proximal external region* (MPER) and the *transmembrane domain* (Pejchal and Wilson, 2010).



Figure 15-12. Human immunodeficiency virus (HIV) virion. HIV has a spheric shape, an outer envelope, variable surface projections, and an icosahedral capsid containing ribonucleoprotein complexed with a core shell. (Courtesy Centers for Disease Control and Prevention.)

The long cytoplasmic tail also modulates the confirmation of external Env and its ability to fuse (Bhakta et al, 2011). The cytoplasmic tail is next to the matrix protein, which forms a shell underneath the envelope after cleavage of the Gag precursor. Virions become fusion competent as they mature only by cleaving and rearranging the Gag. The tail also plays a role in fusion by Gag, and also in the noncovalent association of gp120 with gp41 (Davis et al, 2006).

Other cell surface molecules aid the attachment of the virus to specific cell surface receptors (Geijtenbeek et al, 2000a; Geijtenbeek et al, 2000b): (1) Heparin sulfate moieties interact with positively charged side chains of Env. (2) DC-SIGN and other lectins on dendritic cells anchor the virus via glycans on Env. (3) ICAM-1 on the virion binds to LFA-1 receptor on lymphocytes. Following fusion, the virion is uncoated by a virion encoded protease. Once in the cell, viral DNA is made by reverse transcriptase. This occurs within 4-6 hours of infection. The final product is double stranded viral DNA. It is then transported across the nucleus and integrates into the host DNA by viral integrase.

Virus Packaging and Assembly

New viral RNA and proteins are made by the host cell. Viral gene expression and replication are upregulated by the virion-encoded proteins Tat and Rev. The RNA and proteins are moved to the cell surface and form a new immature HIV form (National Institutes of Allergy and Infectious Diseases, 2014). Maturation occurs by a protease releasing individual HIV proteins. They are incorporated when

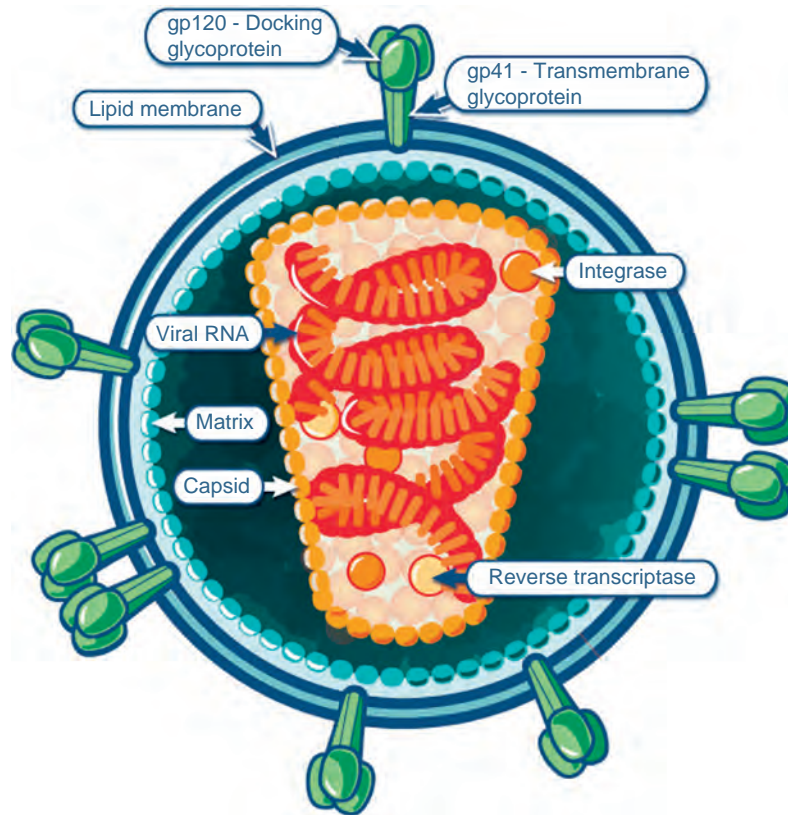


Figure 15-13. Human immunodeficiency virus virion. (Courtesy National Institute of Allergy and Infectious Diseases.)

virus particles, or virions, assemble and bud from the infected cell in a process driven by the viral Gag protein (Klasse, 2012).

Viral Synapse and Cell-to-Cell Transmission

An HIV-infected cell can establish contact with a target cell and transmit HIV infection across what is called a *virologic synapse*. This involves viral budding and Env-mediated virion fusion. It is not clear if mucosal infection is by virions (virus itself) or cell-to-cell transmission including T cells. During virologic synapse infection, virions accumulate within target cell endosomes. After transfer, the virion undergoes proteolytic maturation within the acceptor cell endosomes, and viral membrane fusion. Fusion with the other cell must await Gag cleavage; inhibitors of the viral protease block fusion after internalization (Dale et al, 2011). Particle maturation activates viral fusion in target T cells. Viral fusion can occur in compartments away from the synapse and may be a way for HIV to avoid antibody detection and neutralization (Dale et al, 2011).

Virus Heterogeneity and Mechanisms to Escape Therapy

Env has multiple defenses against neutralizing antibodies. Half of gp120 consists of high mannose glycans forming a dense shield (Klasse, 2012). It has hypervariable regions, V1, V2, and V3, with amino acid changes that affect glycosylation sites and produce escape from neutralization (Pejchal and Wilson, 2010). The three-dimensional structure also secludes the receptor binding sites from antibody binding (Klasse, 2012). Env has an unusual conformational flexibility (Pejchal and Wilson, 2010), and unliganded trimers are not conformationally identical (Liu et al, 2008). Binding different sites and ligands also produces variation in the quaternary structure of Env gp120 peptides (Tran et al, 2012). There is a high error rate of the reverse transcriptase resulting in diversity in the Env even in one cell infected by one virion. Variations in CD4 are less common. Common is variation in the coreceptors CCR5 or CXCR5, which has four tyrosine residues at its N terminus

extracellular region, that can be sulfated with various permutations with different effects on entry (Seibert et al, 2002). CXCR4 is also sulfated (Seibert et al, 2008).

Pathogenesis and Natural History of Human Immunodeficiency Virus Infection

Primary Infection

The initial infection with HIV resembles other infections such as mononucleosis or a nonspecific acute viral illness. The initial syndrome lasts approximately 14 days and occurs in 40% to 90% of patients, with variable severity. Common symptoms include fever, sore throat, fatigue, weight loss, and myalgia (Schacker et al, 1996). A maculopapular rash, usually occurring on the trunk, that is composed of CD4+ cells and local vasculitis is suggestive of acute HIV infection. The initial illness is associated with high plasma levels of the virus, often more than 1 million HIV RNA copies per milliliter, a decrease in CD4+ T-cell count, and a large increase in CD8+ T-cell count. The increase in CD8+ cells is the cellular immune attempt to limit virus replication and contain the infection (Musey et al, 1997). Neutralizing antibodies are not usually detectable until weeks to months after initial infection (Safrit and Koup, 1995). A marked decrease in plasma virus levels corresponds to resolution of the clinical symptoms. After the initial infection, the remaining viral load is prognostic of progression; those with the highest viral load or set point have the greatest risk of progression (Mellors et al, 1996; Kahn and Walker, 1998).

Chronic Asymptomatic Infection

After primary HIV infection, there can be a long phase of clinical latency, usually lasting around 10 years. Although viral and blood levels are relatively stable during this period, there is viral replication in the dendritic cell network in lymphoid tissue. Approximately 98% of the total T cells in the body are found in the

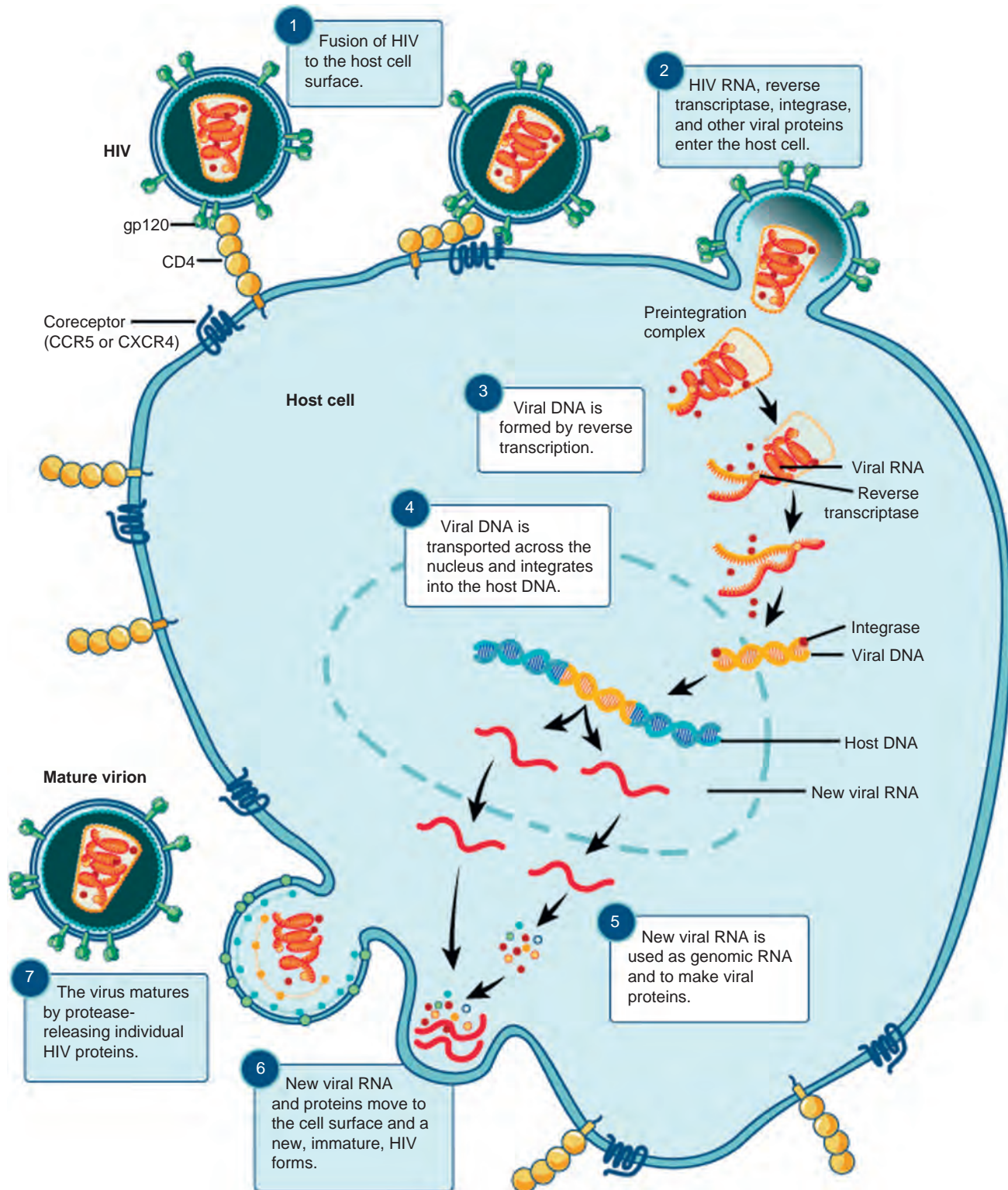


Figure 15-14. Viral replication cycle. HIV, human immunodeficiency virus. (Courtesy National Institute of Allergy and Infectious Diseases.)

secondary lymphoid organs and tissues including lymph nodes, spleen, and mucosal-associated lymphoid tissue such as gut-associated lymphoid tissue (GALT) and bronchial-associated lymphoid tissue (BALT) (Schacker, 2008). Despite relatively stable blood levels of virus, there is replication in this lymph tissue, leading to immunosuppression and progression of disease (Pantaleo et al, 1998). Eventually immunosuppression leads to increased viral loads, a drop in CD4⁺ cell counts, and conversion to AIDS.

Variation in Clinical Course

Several different clinical courses are observed in untreated patients with HIV infection (Sheppard et al, 1991, 1993; Haynes et al, 1996):

1. Typical progression (60% to 70%): Median time of development of AIDS is 10 to 11 years in the absence of treatment.

2. Rapid progression (10% to 20%): development of AIDS in less than 5 years. These patients have a persistently high viral load, rapid decline in CD4+ T cells within 2 to 3 years after infection, decreased levels of CD8+ cells, and lower levels of HIV antibodies (Janvier et al, 1993).
3. Slow progression (5% to 15%): This group remains free of AIDS for 10 to 15 years after infection, with stable CD4 counts. Genetic variation in the host may play a role in this lack of progression, including alleles for the coreceptors necessary for infection including CCR5 (Ioannidis et al, 2001).
4. Long-term nonprogressors (1%): no signs of disease progression after 8 to 10 years of infection. They generally have lower viral load and may be infected with a less virulent virus (Deacon et al, 1995).

Pathogenesis of Infection

The most common route of HIV transmission is sexual transmission at the genital mucosa (Royce et al, 1997). Dendritic cells, which are antigen presenting cells (Mellman and Steinman, 2001), are present in the vaginal epithelium (Spira et al, 1996). These cells can prime T cells. T cells that have not yet been exposed to antigen are called *naïve*. After presentation of antigen, these T cells are then programmed to respond to that particular antigen. Central memory T cells have limited effector function but can proliferate if reexposed to the antigen; the other class of memory T cells are effector memory T cells, which home to peripheral tissues and sites of inflammation to protect against pathogens (Schacker, 2008). Dendritic cells express specific chemokines that attract naïve T cells rather than memory T cells (Cameron et al, 1996). One is called "DC-SIGN," a specific membrane protein with an external mannose binding C-type lectin domain (Steinman, 2000). Dendritic cells subsequently migrate to lymph nodes, usually within 2 days, and then rapidly disseminate throughout the lymphoid tissue. Detectable virus in the blood is present 4 to 11 days after initial infection.

Overall there are variable rates of sexual transmission, and multiple factors including behavioral, biologic, genetic, and immunologic factors affect risk of transmission. A large review of this topic found several associations with risk of heterosexual transmission of HIV; the risk of transmission was greater for low-income countries, commercial sex exposure, presence of genitourinary ulcer disease, and higher viral load. Early- and late-stage HIV were associated with a greater risk of transmission than the asymptomatic

phase, on the order of 7 to 9 times increased risk (Boily et al, 2009).

Similar to findings in MSM, receptive anal intercourse had a higher rate of infection than vaginal sex (Boily et al, 2009). The risk of transmission during unprotected anal intercourse is greater than that of unprotected vaginal intercourse. Rectal mucosa lacks the protective humoral immune barrier found in secretions in the vagina and cervix (Belec et al, 1995) and is also more susceptible to traumatic abrasions that can break the epithelial barrier (Levy, 1993). The contribution of anal intercourse as well as increased risk with increased number of sex partners was recognized early in the study of HIV/AIDS (Winkelstein et al, 1987). The risk of transmission is not different for heterosexual male-to-female contact or for MSM (Baggaley et al, 2010). As a comparison, pooled samples of infectivity studies indicate per-act infectiveness for male-to-female vaginal intercourse of 0.08% (95% confidence interval [CI] 0.06 to 0.11) in developed countries and 0.30% (95% CI 0.14 to 0.063) in developing countries (Boily et al, 2009); for receptive anal intercourse of 1.4% (95% CI 0.2 to 2.5) (Baggaley et al, 2010); and for orogenital contact of 0.04% (95% CI 0.01 to 0.17) (Vittinghoff et al, 1999).

The Boily study (Boily et al, 2009) also confirmed findings of other studies that indicate a significant increase in infection in men who are uncircumcised. Overall the increase in transmission for uncircumcised status and genital ulcer disease was 3 to 8 times. This is somewhat higher than in three recent randomized controlled trials of circumcision (Auvert et al, 2005; Bailey et al, 2007; Gray et al, 2007). The efficacy rate of circumcision for reducing susceptibility to HIV transmission was 50% to 60% in these three clinical trials (Auvert et al, 2005; Bailey et al, 2007; Gray et al, 2007).

Several factors may facilitate heterosexual transmission by vaginal sex. Release of semen into the vagina triggers an influx of neutrophils to help remove excess spermatozoa; these neutrophils can be associated with a transient loss of epithelial barrier function (Southern, 2013). Semen also carries cytokines such as interleukin-8 (IL-8), which is chemoattractant for neutrophils, and also induces inflammation and immunologic changes in the cervix (Sharkey et al, 2012). Sexually active young women typically have mild to moderate cervicitis, and the ongoing inflammatory state is thought to be from repeated unprotected exposure to semen. Although hormonal contraceptives can change vaginal epithelium, their use does not appear to increase risk of HIV transmission (Heffron et al, 2013).

Treatment for Human Immunodeficiency Virus Infection

Because of persistence in reservoirs, treatment for HIV will not completely eradicate the virus. However, treatment will prevent or delay HIV-associated morbidity and mortality, because without treatment the vast majority of patients will develop progressive immunosuppression leading to AIDS and death. ART is used to inhibit the replication of HIV with the goal of keeping viral loads as measured by HIV RNA levels below the level detectable by commercial assays (National Institutes of Health, 2013). Measures of viral replication are predictive of disease progression, because time to clinical disease progression and mortality is fastest in those with the highest viral loads (Mellors et al, 1996). The concept of viremia copy-years as a measure of cumulative exposure to the virus is independently associated with mortality (Mugavero et al, 2011).

The benefit of treatment may depend on the starting CD4 count, but treatment guidelines recommend treatment for all patients regardless of CD4 count (U.S. Department of Health and Human Services Panel on Guidelines for Adults and Adolescents, 2013). In patients with CD4 counts below 200 cells/mm³ and/or a history of AIDS-defining illness, ART clearly improves survival and delays disease progression (Hammer et al, 1997; Zolopa et al, 2009). In patients with cell counts between 350 and 500 cells/mm³, starting ART reduces HIV-related disease progression, with an unclear effect on mortality (Kitahata et al, 2009; HIV-CAUSAL Collaboration et al, 2011). Some trials have not shown a benefit in starting ART in patients with CD4 cell counts above 500 cells/mm³ (When To Start Consortium et al, 2009), but other studies have shown that universal treatment of all increased the 1-year level of viral suppression in patients with a cell count above 500 cells/mm³ from 9% to 14% per year up to more than 52% (Geng et al, 2012).

ART may be beneficial even when started later in therapy. Reduction in viral levels can also prevent some of the known non-AIDS-defining complications, including renal disease, liver disease, cardiovascular disease, neurologic disease, and malignancies. HIV-associated nephropathy (HIVAN) specifically is discussed elsewhere; the risk of renal disease is on the order of threefold in persons with HIV (Islam et al, 2012b). HIV is associated with more rapid progression of viral hepatitis-related liver disease (Thein et al, 2008). Over time, HIV-infected individuals are at greater risk for cardiovascular disease, both heart disease and cerebrovascular events, with a relative risk of 1.6 (Islam et al, 2012a). Treatment of HIV reduces the risk of HIV-associated dementia (HAD) (Lescure

et al, 2011). The incidence of non-AIDS-defining cancers including liver, anal, oropharyngeal, and lung cancers, Hodgkin lymphoma, and melanoma is higher in HIV-infected persons than in matched controls (Bedimo et al, 2009). ART has been shown to be protective against development of HIV-associated malignancies (Guiguet et al, 2009). Another significant benefit to treatment is the prevention of sexual transmission of HIV. Lower levels of virus in the plasma are associated with lower levels in the genital secretions (Guiguet et al, 2009). Level of plasma virus load correlates with risk of HIV transmission in serodiscordant couples (Quinn et al, 2000; Tovanabutra et al, 2002).

One advancement in treatment has been the use of genetic testing to identify resistance-associated mutations in a given individual's HIV virus. Over 100 mutations involved in drug resistance have been described, and testing results are interpreted via one of the rule-based interpretation systems available on the Internet or through expert advice (Tang et al, 2012; Johnson et al, 2013). These data can predict the response to drug therapy including combinations in the range of 50% to 80% (Frentz et al, 2010). Given the limited resources in many countries with high rates of HIV infection, genotyping is not available for many infected people. Computational models have also been developed with results comparable to those of genotype testing; these models may be applicable in areas where genotyping is not available (Revell et al, 2013). Other testing for genetic variation in the CCR5 (R5) coreceptor is used to guide therapy with the drug maraviroc, a CCR5 antagonist, to help predict response and guide prescribing (Poveda et al, 2012). This can be used instead of the co-tropism receptor assay, which involves putting genetic sequences from the *env* gene of the virus into a vector and assessing for infection of cells expressing either the CXCR4 or the CCR5 co-receptor (Whitcomb et al, 2007).

Classes of currently available medications include the following (Fig. 15-15):

1. Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) act via two mechanisms: (1) as "chain terminators" that block viral DNA elongation, stopping addition of further nucleosides, and (2) by competition or binding of the reverse transcriptase.
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) act only by competition or binding of reverse transcriptase.
3. Protease inhibitors act by binding the aspartic protease, critical for post-translational processing of the polyprotein products into

POSSIBLE SITES OF INTERVENTION IN THE INHIBITION OF HIV REPLICATION

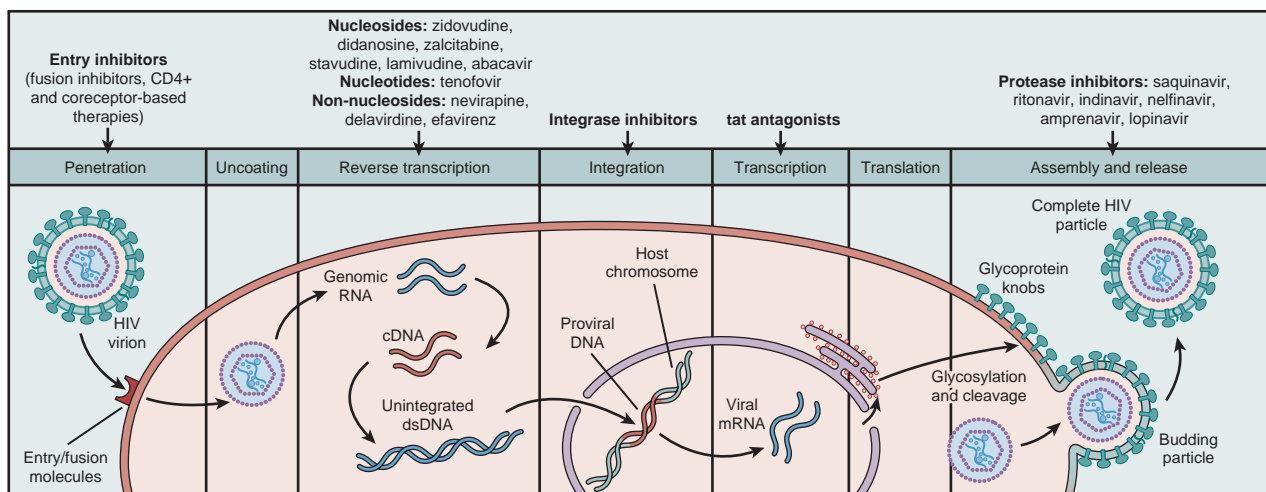


Figure 15-15. Antiretroviral therapy for human immunodeficiency virus (HIV): possible sites of intervention for drug therapy. (From Vella S, Florida M. HIV therapy: antiviral therapy. In: Cohen J, Powderly SF, Berkley SF, et al, editors. Infectious diseases. 2nd ed, vol. 2. Edinburgh: Mosby; 2004. p. 1387–98.)

the functional core proteins and viral enzymes. Inhibition of this step results in the release of immature, noninfectious viral particles. Protease inhibitors are also effective against chronically infected cells.

4. Integrase strand transfer inhibitors (INSTIs) block the enzyme integrase, used to integrate HIV viral DNA into the DNA of the host cell. Blocking integrase prevents HIV from replicating.
5. CCR5 antagonists block attachment to CCR5. These drugs are effective and durable only if the HIV molecule uses CCR5 and not CXCR4; thus receptor tropism screening is required before use (Thompson et al, 2012). A faster method of genetic tropism testing can also be used (Vandekerckhove et al, 2011).
6. Fusion inhibitors disrupt conformational changes in gp41 that drive membrane fusion.

Guidelines for the use of antiviral agents in HIV-1-infected adults and adolescents are available from the NIH on the aidsinfo.nih.gov website (U.S. Department of Health and Human Services Panel on Guidelines for Adults and Adolescents, 2013) and have also been published (Thompson et al, 2012). A synopsis of the treatment guidelines including level of evidence is as follows:

- ART should be started regardless of CD4 count. (For CD4 count below 350/ μ L, AI; for CD4 count between 350 and 500/ μ L, AII; and above 500/ μ L, BIII.)
- ART should be given during the acute phase of primary HIV infection regardless of symptoms (BIII).
- ART should be started within 2 weeks in persons with opportunistic infections (A1a).
- ART is recommended in HIV-infected persons with TB and should be started within 2 weeks of TB treatment when the CD4 count is below 50/ μ L and within 8 to 12 weeks for higher CD4 counts (A1a).
- Genotypic testing is recommended to guide therapy in ART-naïve patients. This includes testing in reverse transcriptase and protease genes; this may also be done when INSTI resistance is a concern (CIII). Gene therapy should also be used to guide a suboptimal response to therapy (AIII).
- A coreceptor tropism assay should be performed before starting a CCR5 receptor inhibitor.

As of the 2013 update, there were more than 20 approved antiretroviral drugs in the six classes just listed. Current treatment regimens for initial ART therapy consist of a combination of two NRTIs plus a third agent: an NNRTI, a ritonavir-boosted protease inhibitor, an INSTI, or an entry inhibitor (Thompson et al, 2012). Current regimens for first therapy and level of evidence for their use are as follows:

- Efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC), level AI
- Ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate/emtricitabine (ATV/r + TDF/FTC), level AI
- Ritonavir-boosted darunavir + tenofovir disoproxil fumarate/emtricitabine (DRV/r + TDF/FTC), level AI
- Raltegravir + tenofovir disoproxil fumarate/emtricitabine (RAL + TDF/FTC), level AI

Postexposure Prophylaxis

Occupational Exposure for Health Care Providers. The incidence of exposure incidents among hospital-based health care workers is estimated at 384,00 per year, or 1 in 10 health care providers with an exposure per year (Panlilio et al, 2004). An exposure that might put a health care provider at risk is defined as a percutaneous injury such as a needle stick or cut with a sharp object, or contact with mucous membrane or nonintact skin (e.g., contact between exposed skin that is chapped or abraded or affected by dermatitis and blood, tissue, or other body fluids that are potentially infectious). In addition to blood and visibly bloody bodily fluids, other potentially infectious fluids that may be encountered by a health care provider are CSF, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. Semen and vaginal secretions are also infectious but have not been implicated in the occupational transmission of HIV. The average risk of HIV

transmission with a percutaneous exposure is 0.32%, or one infection for every 325 exposures to a documented HIV-infected person (Bell, 1997; Henderson, 2012). The risk is estimated to be less for mucosal membrane exposures, at 0.03% or one infection for every 3300 exposures (Ippolito et al, 1993; Henderson, 2012).

Several factors are known to influence the inoculum risk. The amount of virus in the exposure comes from the concentration of virus in the fluid and the volume of fluid in the exposure. Volume increases with needle size and depth of penetration; thus hollow-bore needles carry a higher amount of virus than solid suture needles (Bennett and Howard, 1994). The patient's viral load is also important; circulating viral load is highest during the initial stage near the time of seroconversion and in advanced stages near death. A review of factors for increased risk of infection done by the CDC identified four that increased risk: deep as opposed to superficial exposure (odds ratio [OR] 15, 95% CI 6 to 41), visible blood on the injuring device (OR 6.2, 95% CI 2.2 to 21), prior placement of the injuring device in an artery or vein (OR 4.3, 95% CI 1.7 to 12), and patient dying within 2 months of the exposure (preterminal disease) (OR 5.6, 95% CI 2 to 16) (Panlilio et al, 2005).

Standard Precautions were introduced by the CDC in 1996. Methods such as announcing transfer of sharps and double gloving, among other precautions, are recommended (Panlilio et al, 2005; Siegel et al, 2007). Immediate steps after exposure are washing the wound or skin site with soap and water, flushing exposed mucous membranes with tap water, and rinsing exposed eyes with sterile water or a commercial eye irrigant (tap water is an acceptable alternative). If the infectious status of the source is not known, the source should be evaluated for HIV and hepatitis B and C. If the source is known to have HIV but has undetectable serum viral load, postexposure prophylaxis (PEP) should still be given because of the risk of infection from latently infected cells (Furtado et al, 1999). The exposed health care worker should be assessed for tetanus and get a booster of tetanus, diphtheria, and acellular pertussis booster if indicated (Henderson, 2012). The biologic effectiveness of postexposure chemotherapy has been demonstrated in a study that found that postexposure treatment with zidovudine was associated with an 81% reduction in the risk of infection (Cardo et al, 1997).

Previous treatment regimens recommended two or three drugs as therapy depending on the risk stratification (Panlilio et al, 2005). The 2013 update now recommends three medications to start treatment: emtricitabine (FTC) plus tenofovir (TDF) (these can be given as the combination pill Truvada) plus raltegravir (RAL). The guidelines also specify the following:

1. Persons receiving PEP should complete a full 4-week regimen.
2. If the source is determined to be HIV negative, PEP should be discontinued and no further testing is indicated.
3. PEP should be initiated as soon as possible, preferably within hours, and follow-up should occur within 72 hours.
4. Follow-up at a minimum should include HIV testing at baseline and at 6 weeks, 12 weeks, and 6 months (baseline, 6 weeks, and 4 months if a p24 antigen antibody test is used). To assess for toxicity of the medications, complete blood count and renal and hepatic function tests at baseline and 2 weeks should be performed.

Management of Sex Partners of Infected Persons

HIV-infected patients should be encouraged to notify their partners and to refer for counseling and testing. If patients are unwilling to notify their partners, physicians or health department personnel use confidential partner notification procedures. Partners who were exposed to genital secretions and/or blood of an HIV-infected partner in the preceding 72 hours should be offered PEP.

Preexposure Prophylaxis

Preexposure prophylaxis is the treatment of an uninfected person before he or she has sexual contact with an HIV-infected partner. In July 2012 the FDA approved daily oral tenofovir disoproxil fumarate

300 mg (TDF) and emtricitabine 200 mg (FTC) (Truvada [Gilead, Foster City, CA]) to reduce the risk of HIV transmission, including in both heterosexuals and MSM. Data come from several large-scale trials that showed benefit ([Grant et al, 2010](#); [Baeten et al, 2012](#); [Thigpen et al, 2012](#)), but not all trials have shown a benefit ([Van Damme et al, 2012](#)). Also, one of the trials raised concerns about decline in bone mineral density associated with taking the drug ([Thigpen et al, 2012](#)). Other side effects are impairment of renal and liver function. There are multiple other barriers to the effective use of preexposure prophylaxis in addition to the side effects of the

drugs, including the need for strict adherence to the regimen for the drug to be effective, additional testing to monitor HIV status, and knowledge of the HIV status of the partner ([Steinbrook, 2012](#)). A recent trial of prophylaxis in MSM indicated that adherence was good (87%) and side effects were not different from those of placebo ([Grohskopf et al, 2013](#)). **A complementary approach to preexposure prophylaxis is treatment for prevention, in which the infected partner is treated to try to prevent transmission to the uninfected partner.** A review of available trials indicates this can also be an effective strategy ([Baggaley et al, 2013](#)).

Renal Infections

Mycobacterial infection of the kidney is detected at autopsy in 6% to 23% of AIDS patients, and a significant number had no symptoms before death (Shindel et al, 2011a). Persons with HIV infection are more likely to develop clinical TB if infected, including renal and other extrapulmonary disease (Weiss et al, 1998). Treatment for TB may include rifampin, which induces cytochrome P450 and lowers concentrations of protease inhibitors and NNRTIs. HIV patients being treated for TB should be monitored carefully, and drug levels may have to be monitored and adjusted (Sterling et al, 2010). Other renal infections that occur in AIDS include CMV (van der Reijden et al, 1989) and *Aspergillus* and *Toxoplasma* infections. Abscesses may develop that require drainage, percutaneous or open, or nephrectomy.

Prostatitis

Prostate infection may be more common in men with HIV. One study of 209 hospitalized men with HIV reported bacterial prostatitis in 8%, with the incidence increasing from 3% in men with asymptomatic HIV infection to 14% in patients with AIDS (Leport et al, 1989). Most of the men were symptomatic with fever and urinary symptoms; prostate tenderness was not universal but was found on examination in 41%. Prostatitis is usually caused by *E. coli*, but in HIV-infected men many other organisms can cause prostate infection, including *S. aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Salmonella* Typhi, *Mycobacterium tuberculosis* and *Mycobacterium avium intracellulare*, and CMV (Weinberger et al, 1988; Benson and Smith, 1992). Fungal infections also can cause prostatitis, particularly in immunocompromised patients with T-cell counts below 200 cells/ μ L. Organisms include *C. albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, and *Histoplasma capsulatum* (Santillo and Lowe, 2006).

In men with HIV, cultures should be performed not only for the usual bacteria, but also for more atypical organisms including aerobes, anaerobes, fungi, and *M. tuberculosis* (Heyns and Fisher, 2005). The usual treatment in these men is a 4- to 6-week course of antimicrobials; in men with HIV, consideration should be given to low antimicrobial suppression for some time to reduce the risk of recurrence (Santillo and Lowe, 2006). In patients who are already being treated with ART and still persistently immunocompromised, lifetime suppressive antimicrobials have been recommended to reduce risk of progression to prostatic abscess (Lee et al, 2001). Prostate abscess can develop from relapsing or untreated infection and usually occurs in more severely immunocompromised patients. The incidence of prostate abscess in men with HIV has been reduced by use of ART, which has decreased the incidence of opportunistic infections (Murphy et al, 2001), and also by the use of long-term antibiotics in HIV men with bacterial or atypical urinary tract infections (UTIs). Diagnosis is made by transrectal ultrasound or computed tomography (CT) scan. It is important to prevent progression to sepsis by using broad-spectrum antimicrobials and performing surgical drainage.

Urinary Tract Infection

In a prospective study of urine cultures in a group of HIV-positive men, 30% of the group with CD4 counts below 200 had an episode of bacteriuria, which was significantly greater than in the group with CD4 counts of 200 to 500 (11%) and above 500 (0%) (Hoepelman et al, 1992). There was no association with age or practice of anal intercourse. Of the episodes of bacteriuria, 42% were asymptomatic. The incidence of bacteriuria also increases with progression to AIDS (De Pinho et al, 1994). The bacteria found in UTI in HIV-infected individuals may be different as well. Data from a single site showed that over a 9-year period, the most common organism causing UTI in HIV-infected patients, men and women, was *Enterococcus* (26%), whereas in uninfected controls it was *E. coli* (64.8%). *Proteus* was also found five times more often in the HIV-infected group (Schonwald et al, 1999). In severely immunocompromised

patients, unusual organisms may cause UTIs, including CMV (Benson et al, 1988). The mucosa may appear normal with a CMV infection, and deep biopsies may be needed to diagnose CMV interstitial cystitis (Whitaker et al, 2008). Other urinary infections include fungi such as *Cryptococcus*, *Candida*, or *Aspergillus* (Kiartiburanakul et al, 2004); other viruses including erythrovirus B19 (parvovirus B19) (Christensen et al, 2001) and adenovirus; and parasites such as *Toxoplasma gondii* and *Mycobacterium* (Heyns et al, 2009).

Overall, the incidence of bacteriuria does not appear to be greater in women with HIV but can be associated with the amount of viral load (Park et al, 2002). The management of UTI may be complicated by the concomitant use of other antibiotics for prophylaxis for other infections in HIV-infected patients. The use of co-trimoxazole as prophylaxis against pulmonary infection did not reduce the risks of UTI in a series of HIV-positive patients (Evans et al, 1995). However, the use of the other antibiotics may select out for antibiotic resistance. Among the bacterial isolates found in 350 episodes of symptomatic UTI in HIV-infected subjects, 29 of 36 *E. coli* isolates were multidrug resistant. Overall, 83% of bacterial isolates were resistant to trimethoprim-sulfamethoxazole (Vignesh et al, 2008). These findings should help inform empirical therapy for symptomatic UTI in these patients.

Testis, Epididymis and Seminal Vesicles

HIV in semen is the main vector for transmission and can persist despite high loads of ART (Roulet et al, 2006). The interstitium of the testis contains cells that have the receptors and coreceptors CXCR4, CCR5, CD4, and DC-SIGN, and is permissive to HIV infection. These cells appear to be macrophages (Roulet et al, 2006). The seminal vesicles also appear to be a reservoir for HIV, again with infection located in macrophages (Deleage et al, 2011).

The most common intrascrotal pathology in men with HIV/AIDS is testicular atrophy. This can arise from endocrine imbalances, febrile episodes, malnutrition, testicular infections, and toxic effects of therapy (Leibovitch and Goldwasser, 1994). A correlation has also been shown with body mass index (BMI); underweight HIV patients were 3.5 times more likely to have testicular atrophy on autopsy (Mhawech et al, 2001). The histology in men with HIV is peritubular interstitial inflammation, interstitial fibrosis, and thickening of the basement membrane (De Paepe et al, 1989). Spermatogenesis is decreased and maturation arrest is observed (Leibovitch and Goldwasser, 1994). HIV itself is thought to be cytotoxic to germ and Sertoli cells; on average, 30% of germ cells are infected (Shevchuk et al, 1998).

The testes may also be directly infected by opportunistic infections. Up to 39% of examined testes in autopsy series may have an opportunistic infection (Leibovitch and Goldwasser, 1994). The most common pathogens are CMV, *T. gondii*, and *M. avium intracellulare* (Lo and Schambelan, 2001). Treatment requires initial antibiotic therapy followed by a period of maintenance suppression, particularly if *Salmonella* is identified as the causative organism (Shindel et al, 2011a). Patients with AIDS are also prone to develop tuberculous epididymitis (Heyns et al, 2009). As a result of atrophy, infection, or other insult, testicular failure can occur. In combination with extratesticular causes, testosterone levels fall with progressive HIV disease (Lo and Schambelan, 2001; Moreno-Perez et al, 2010a).

Renal Function

Many factors affect renal function in patients with HIV/AIDS (Miro et al, 2012). HIVAN has received considerable attention because of the rapid clinical decline in these patients, the progression to irreversible renal failure, and the predilection for African Americans (Pardo et al, 1984; Rao et al, 1984). The classic clinical presentation is that of rapidly progressive azotemia with severe proteinuria, often nephrotic range, and little or no peripheral edema. The initial pathologic lesions described were global or focal segmental glomerulosclerosis (FSGS). Other features added to the description

include collapse of glomerular capillary loops, called “collapsing glomerulopathy” (Weiss et al, 1986). A recent review of a large case series of kidneys with HIVAN also described a new variant, termed the “fetal variant” because histologically it resembles a fetal glomerulus (Wearne et al, 2012). There appears to be a spectrum of histologic findings now associated with HIVAN, making the consensus definition in flux (Wearne et al, 2012).

The pathogenesis of HIVAN involves infection of renal epithelial cells by HIV virus, including podocytes, glomerular parietal epithelial cells, and tubular cells (Leventhal and Ross, 2008). Infection can be by cell free virus or by transfer of virus from infected T cells to renal tubular epithelial cells (Chen et al, 2011). The *vpr* and *nef* genes of HIV-1 are the most responsible for inducing HIVAN (Leventhal and Ross, 2008). Recently the genetic predisposition to HIVAN has been characterized. African-Americans carrying two variants of the *APOL-1* gene are at very high risk to develop HIVAN. These genes encode a secreted lipid binding protein called *apolipoprotein-1* (*apoL1*). The variants G1 and G2 are common in African chromosomes but absent in European chromosomes; these variants lyse trypanosomes, including *Trypanosoma brucei rhodesiense*, which causes African sleeping sickness (Genovese et al, 2010). Thus, these loci are thought to be selected out in this population. The presence of these two genes together increases the risk by 29-fold, resulting in a 50% risk of development of HIVAN in untreated individuals (Kopp et al, 2011) as compared with a 12% baseline risk (Shahinian et al, 2000). FSGS found in individuals with the two risk genes also occurs at an earlier age and progresses much more rapidly (Kopp et al, 2011). There also may be a contribution from the myosin heavy chain gene 9 (*MYH9*), which is a locus adjacent to the *APOL-1* gene on chromosome 22 and has been implicated in rare kidney disease producing glomerulosclerosis and podocyte effacement (Hays and Wyatt, 2012). Podocyte specific deletion of *Myh9* predisposes mice to renal injury (Johnstone et al, 2011). *APOL-1* and *MYH9* are likely contributors to HIVAN, but not the only contributors (Kopp et al, 2008).

The incidence of HIVAN can be decreased by treatment to reduce the viral load (Lucas et al, 2004). The study by Wearne and colleagues from South Africa (Wearne et al, 2012) included findings from a time when ART had not yet been endorsed or provided by the South African government. Therefore data are available on the untreated natural history of HIVAN. The 50% survival of those patients with HIVAN without ART was 4.47 months. The use of ART, no matter when started, reduced the mortality by 57%. Patients with better estimated glomerular filtration rate (eGFR) at presentation had better outcomes (adjusted hazard ratio [AHR] 0.72).

Voiding Dysfunction

Early series on voiding dysfunction in HIV-positive patients reported on neurogenic bladder in patients largely with AIDS and neurologic complications (Gyrtrup et al, 1995; Menéndez et al, 1995). Detrusor areflexia was commonly seen in patients with AIDS (Khan et al, 1992), but more patients with non-AIDS HIV had detrusor hyperreflexia (overactivity) (Kane et al, 1996). With the use of ART, patients are living longer and having less severe complications, and therefore it is expected that there will be an increase in incidence of voiding dysfunction as a result of aging in this group. In an Internet survey of MSM, HIV status was an independent risk factor for bothersome lower urinary tract symptoms (LUTS), and a history of AIDS was a risk factor for severe disease. Other risk factors for moderate but not severe LUTS were UTI, prostatitis, and gonorrhea. Although the cause of the association is not known, this study raised the question as to whether a direct toxic effect of the virus or ART leads to LUTS (Breyer et al, 2011).

Hematuria

A study from 1995 reviewed the records of 1326 patients with HIV in the U.S. Air Force. Urinalysis was performed and found a high rate of hematuria at 25%. Of the 67 patients with hematuria who underwent evaluation, management was affected in three patients

(4%). The recommendation at that time was that in young asymptomatic HIV-positive patients with microscopic hematuria, a urologic evaluation could be omitted (Cespedes et al, 1995). Of note in this study is that grade 1 hematuria was defined as 1 to 4 red blood cells (RBCs) per HPF; given the current definition of microhematuria as 3 or more RBCs per HPF, some of these patients who were diagnosed with microhematuria might not be diagnosed according to current criteria. Of the men with renal cell cancer in a recent series of patients with HIV, 44% had hematuria on presentation (Gaughan et al, 2008). Given the greater life expectancy of patients infected with HIV on ART, hematuria in the setting of HIV infection should be evaluated as in other individuals.

Erectile Dysfunction

The prevalence of mild, moderate, and severe erectile dysfunction (ED) is reported as being higher in HIV-infected than uninfected men for all decades of age. On multivariate analysis, HIV infection is the strongest predictor of ED, with an OR of 42.26 ($P < .001$) (Crum et al, 2005; Ende et al, 2006; Crum-Cianflone et al, 2007; Zona et al, 2012). Other studies have shown that progression to AIDS also leads to greater ED (Shindel et al, 2011b). ED is common in HIV-infected men under age 50, reported as 50% of infected men younger than age 30 years, 48% of those aged 31 to 40 years, and 53% of those aged 41 to 50 years (Zona et al, 2012). HIV also leads to an increased risk and earlier onset by 10 to 15 years of other comorbidities including coronary disease, diabetes, and bone fractures (Guaraldi et al, 2011). Thus, ED is thought to be one of the manifestations of an early aging phenomenon that is being seen in HIV-infected individuals. Other factors also influence the development of ED in this population, including depression (Crum-Cianflone et al, 2007), psychological distress associated with changes in body composition (lipodystrophy) (Guaraldi et al, 2012), hypogonadism (Crum et al, 2005; Zona et al, 2012), and diabetes (Shindel et al, 2011b). Endothelial dysfunction as measured by brachial artery flow-mediated dilation was not associated with ED in men with HIV (Guaraldi et al, 2012).

The role of ART in the development of ED in men with HIV is uncertain. Several studies have shown an association with ART, including duration of ART (Moreno-Perez et al, 2010b), and particularly protease inhibitors (Martinez et al, 1999; Lamba et al, 2004; Asboe et al, 2007). Other studies have not confirmed these associations (Ende et al, 2006; Zona et al, 2012). One consideration in treating ED in men with HIV is the possible interaction of phosphodiesterase type 5 (PDE5) inhibitors and antiretroviral medications. PDE5 inhibitors depend on CYP3A for clearance, and all protease inhibitors and NNRTIs are inhibitors of CYP3A to some extent (Rosen et al, 2006). This can lead to a significant increase in the serum dose of PDE5 inhibitors, and therefore they should be started at the lowest dose possible in patients taking these ART medications (Merry et al, 1999).

Stones and Human Immunodeficiency Virus

One of the complications of some medications for treatment of HIV is stone formation. The protease inhibitors specifically may cause stone formation. Indinavir can form crystals in the urine (Kopp et al, 1997). The incidence of indinavir stones is reported to be as high as 22% (Brodie et al, 1998). The risk has been reported to be greater in patients with hepatitis (Malavaud et al, 2000) or hemophilia (Brodie et al, 1998). Indinavir stones are typically radiolucent on both plain film and CT scan but can also be mixed with calcium and appear radiopaque (Sundaram and Saltzman, 1999). Newer inhibitors including lopinavir, atazanavir, amprenavir, and nelfinavir have also been associated with the development of stones, but with less frequency than reported for indinavir (Shindel et al, 2011a). The incidence of stones with atazanavir was 0.97% in one series (Couzigou et al, 2007). One possible risk factor for atazanavir stones is the discontinuation of tenofovir. Concomitant administration of tenofovir lowers circulating levels of atazanavir, so discontinuation increases plasma levels;

this was thought to play in a role in several cases of atazanavir stones (Fabbiani et al, 2011).

Hydration after taking protease inhibitors is suggested as means to reduce the risk of stone formation (Daudon et al, 1997). In patients with protease stones and in whom conservative management is possible as a first-line step, discontinuation of the drug and hydration should be tried. Success with these measures approaching 70% has been reported (Kohan et al, 1999). Patients with HIV can have other conditions that contribute to stone formation including dehydration with high specific gravity, low pH, hyperoxaluria, hypercalciuria, and hypocitraturia (Gagnon et al, 2000; Nadler et al, 2003). One other type of stone reported to be more common in HIV patients is ammonium acid urate stones, possibly reflecting chronic diarrhea and malnutrition of chronic disease (Nadler et al, 2003).

Human Immunodeficiency Virus and Neoplasms

In the earlier history of HIV infection, the predominant oncologic problems were AIDS-defining cancers, Kaposi sarcoma (KS), non-Hodgkin lymphoma, and, in women, invasive cervical cancer. With the advent of more effective therapies, ART has markedly improved life expectancy, turning HIV into a chronic disease. The emphasis has shifted to non-AIDS-defining cancers (Bonnet et al, 2009). Overall, patients with HIV compared with the general population still have a greater risk to develop not only non-AIDS-defining cancers with a viral pathogenesis but also non-virus-related cancers, estimated at a twofold risk in a recent study (Albini et al, 2013). Several factors have been suggested to explain this increased risk, including high-risk behaviors such as tobacco smoking, which is two to three times more prevalent in HIV-infected patients (Rahmanian et al, 2011); immunodeficiency (Grulich et al, 2007); inflammation (Borges et al, 2013); and age itself, because people are living longer with HIV infection (Albini et al, 2013). For the urologist, KS has the greatest relevance of the AIDS-defining cancers, given the possibility of KS lesions on the penis. There are increasing data regarding the rates and clinical course of non-AIDS-defining urologic malignancies.

Kaposi Sarcoma

Kaposi sarcoma was described in 1872 by Moritz Kaposi, who described three cases of fatal pigmented hemangiosarcomas in elderly men (Ruocco et al, 2013). Four forms are described: classic as described by Kaposi; an African endemic form occurring in young black men aged 25 to 40; an iatrogenic form first seen in the 1970s in patients on immunosuppressive therapy; and first reported in 1981 the form of KS in young homosexual men called the “epidemic form” (Hymes et al, 1981; Ruocco et al, 2013). KS is the second most common tumor in HIV-infected patients worldwide (Martellotta et al, 2009). However, the incidence of KS has decreased dramatically since the advent of the use of ART. In one recent prospective study, no new cases were noted in the period 1997 to 2000 (Speeckaert et al, 2011). Patients with KS typically have a CD4 cell count below 150 cells/mm³ and a viral load higher than 10,000 copies/mL (Gallafent et al, 2005). A cluster of patients having KS despite being on ART, and with CD4 cell counts above 300 cells/mm³ and viral loads below 300 copies/mL for at least 2 years, has been reported (Maurer et al, 2007).

The causative agent found in more than 90% of KS patients of all four types is human herpesvirus 8 (KSHV/HHV-8), a double-stranded DNA virus (Chang et al, 1994; Buonaguro et al, 1996). HHV-8 is now considered a necessary condition for the development of KS, but not all persons with HHV-8 get KS, and genetic, immunologic, and environmental factors are thought to be required as cofactors for KS to develop (Ruocco et al, 2013). KSHV infection leads to proliferation of both endothelial and spindle cells, the predominant cell type in KS, and angiogenesis (Martellotta et al, 2009; Ma et al, 2013). KS typically manifests with disseminated pigmented skin lesions, a few millimeters to several centimeters, from pink to purple or brown, often associated with edema and

lymph node and visceral involvement in up to 50% of patients. Other common sites of involvement are the oral cavity, gastrointestinal (GI) tract, and lungs (Mitsuyasu, 1993). The prognosis depends on the extent of the tumor, status of the immune system by CD4 count, and presence of systemic illness. The 3-year survival for patients with good risk is 80% to 88%, and for those with poor risk factors it is 53% (Nasti et al, 2003). Treatment depends on the type and is either local or systemic (Curatolo et al, 2012; Ruocco et al, 2013). For systemic therapy, one mainstay for epidemic KS is ART, which can produce a remission rate of 35% to 50% (Nguyen et al, 2008; Ruocco et al, 2013). Lesions typically start to decrease in size a few weeks to months after the initiation of treatment (Spano et al, 2008). KS may flare dramatically initially after the initiation of ART in what is called the *immune reconstitution inflammatory syndrome* (IRIS), seen in HIV-positive patients with initial low CD4 counts and high viral load (Leidner and Aboulafia, 2005). Onset of IRIS is as early as 3 weeks, with a mean onset of 5 weeks, and the syndrome can be fatal (Leidner and Aboulafia, 2005). First-line chemotherapy for advanced disease is liposomal anthracyclines (pegylated liposomal doxorubicin, daunorubicin citrate liposome DNX). Pegylated liposomes accumulate preferentially in highly vascularized KS lesions and are more effective than conventional chemotherapy regimens and with fewer side effects (Krown et al, 2004). Second-line therapy is paclitaxel or docetaxel (Lim et al, 2005; Cianfrocca et al, 2010).

Non-AIDS-Defining Urologic Malignancies

Testicular Tumors. The risk of testis tumors in early studies was reported to be 20 to more than 50 times greater in men with HIV than in uninfected men, and in general for seminoma. Later studies looking at men with HIV infection but after the development of ART have put the relative risk at a still significant level but much lower. Powles and colleagues found a relative risk for nonseminomatous germ cell tumors (NSGCTs) and seminoma of 4.36 (95% CI 2.71 to 6.55) and 5.45 (95% CI 3.35 to 8.10) (Powles et al, 2003). In a review of more than 260,000 men in the United States from 1980 to 2003, the risk for seminoma was 1.9 (95% CI 1.6 to 2.2) and there was no increased for NSGCTs (Goedert et al, 2007). An increased risk of 3.11 (95% CI 1.48 to 6.52) was recently reported from an Italian cohort, with no distinction between seminoma and nonseminoma tumors (Albini et al, 2013). The treatment for HIV-positive men with testes germ cell tumors is the same as for uninfected individuals (Powles et al, 2003). HIV-infected men are also at risk for testicular non-Hodgkin lymphoma, which may be disseminated at time of presentation, but tend to have the same response to therapy as uninfected individuals (Heyns et al, 2009).

Prostate Cancer. The relative risk of prostate cancer in men with HIV compared with uninfected individuals has been reported as either being no different or being even less, at 0.70 (Grulich et al, 2007; Bedimo et al, 2009; Albini et al, 2013). It has been postulated that ART may have a protective effect on prostate cancer independent of effect on increasing the CD4+ count (Chao et al, 2012). Radiotherapy in HIV-positive men is not associated with an increase in complications or effect on CD4 count (Ng et al, 2008). An increase in infectious complications with radical prostatectomy may be seen in patients with lower CD4 counts and higher viral loads, but no other adverse perioperative complications or differences in response to therapy (Huang et al, 2006). In a series of patients undergoing robot-assisted laparoscopic radical prostatectomy for prostate cancer, patients infected with HIV had a higher rate of transfusion and ileus compared with men without HIV; no other complications were different in the two groups, and prostate-specific antigen (PSA) was undetectable at 8 months in all HIV-positive men (Silberstein et al, 2010). PSA levels do not appear to be different in men based on their HIV status (Vianna et al, 2006; Pantanowitz et al, 2008). HIV-positive patients are reported to have a greater likelihood of a positive prostate biopsy compared with uninfected men (OR 3.9, 95% CI 1.3 to 11.5) (Hsiao et al, 2009), but the Gleason score on biopsies is not different (Pantanowitz et al, 2008). Overall, the evaluation and treatment of prostate cancer in patients

with HIV do not appear to be significantly different from those in uninfected men (Levinson et al, 2005). Given that the median survival after starting ART is estimated to be over 13 years (Walensky et al, 2006), patients with HIV should be screened and treated as uninfected men.

Kidney Cancer. An increased risk of renal cell carcinoma and HIV infection has been reported. In a study of more than 300,000 adults aged 15 to 69 years with HIV/AIDS in multiple geographic locations in the United States, compared with the expected population-based incidence rates, kidney cancer was 1.5 times more likely in the HIV population, similar to another large study of more than 444,000 patients (Frisch et al, 2001; Grulich et al, 2007). There was no increase in risk with progression to AIDS, arguing against immunosuppression as a contributing factor (Frisch et al, 2001). Much higher risks of developing renal cell cancer in HIV infection were reported in a single-site series from Cleveland (United States)—an increased risk of 8.5 times, as well as presentation 15 years younger than expected (Baynham et al, 1997)—and from Uganda (Africa), reporting a relative risk of up to 16 times (Mbulaiteye et al, 2006). A case series of nine men with renal cell carcinoma found diagnosis at a median age of 48, no association with immunosuppression, and a clinical presentation or response to treatment that appeared similar to that of uninfected individuals (Gaughan et al, 2008). The differential diagnosis of renal mass in an HIV-infected person should also include lymphoma.

Penile Cancer. The relative risk of penile cancer is reported to be approximately four times higher than in men without infection (Frisch et al, 2001; Grulich et al, 2007). Men with HIV have a high prevalence of high-risk HPV types, 16 and 18, in the anus, penis, and mouth, without evidence of any lesions in these areas (Sirera et al, 2006). This occurs in both MSM and heterosexual men (Videla et al, 2013). The risk of penile cancer increases the closer a man is to having AIDS or the longer he has had AIDS (Chaturvedi et al, 2009). Although squamous cell cancers can be more aggressive in HIV-positive individuals (Nguyen et al, 2002), early lesions such as penile intraepithelial carcinoma can still respond to treatment with local therapy (Ramoni et al, 2009).

Bladder Cancer. In large series reporting the incidence of cancer in HIV-positive patients compared with those without infection, bladder cancer is not more frequent than in uninfected persons (Frisch et al, 2001; Grulich et al, 2007; Mbulaiteye et al, 2006). A suggestion of a reduced risk has been reported (Layman and Engels, 2008). A case series of patients with bladder cancer and HIV indicated no difference in clinical course or response to treatment (Gaughan et al, 2009). One possible difference in treatment of HIV-positive patients is to use caution in deciding to use intravesical bacille Calmette-Guérin (BCG). The effectiveness of BCG is dependent on a functioning immune system, and therefore the agent is not typically used in immunocompromised patients. There is the theoretic risk of disseminated infection. One case report has documented bilateral interstitial pneumonitis in an HIV-infected patient after intravesical therapy with BCG (Kristjansson et al, 1993). However, in the case series by Gaughan and colleagues, one of their HIV patients received BCG without complications (Gaughan et al, 2009).

KEY POINTS

- Patients with urethritis need to be treated for both gonorrhea and chlamydia. In addition to microscopic examination of urethral discharge, urine should be sent for nucleic acid amplification testing for both gonorrhea and chlamydia. Urethral swab is no longer indicated.
- Most genital ulcers in the United States are either herpes or syphilis, with most being herpes. Chancroid occurs in some parts of the United States, but donovanosis usually does not. LGV is increasing in incidence in MSM, including in the United States.
- Vaccines to prevent HPV-associated disease such as genital warts and anal cancer in both genders and cervical cancer in females are now available and recommended for men and women younger than age 26, preferably to start before onset of sexual activity.
- Testing for HIV is recommended in anyone with an STD or at risk of acquiring an STD.
- Treatment of HIV with ART is indicated in all infected persons regardless of CD4 count.
- HIV is becoming a chronic disease, and many of the associated problems are from aging and chronic disease instead of immunosuppression.

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The complete reference list is available online at www.expertconsult.com.



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16

Cutaneous Diseases of the External Genitalia

Richard Edward Link, MD, PhD, and Theodore Rosen, MD

Introduction to Basic Dermatology

Dermatologic Therapy

Allergic Dermatitis

Papulosquamous Disorders

Vesicobullous Disorders

Noninfectious Ulcers

Infections and Infestations

Neoplastic Conditions

Benign Cutaneous Disorders Specific to the Male Genitalia

Common Miscellaneous Cutaneous Disorders

The diagnosis and treatment of cutaneous diseases of the external genitalia remain important elements of urologic practice. Often overlooked during formal urology residency training, this topic lies at the interface of multiple specialties, including urology, diagnosis of infectious diseases, rheumatology, allergy-immunology, and dermatology.

INTRODUCTION TO BASIC DERMATOLOGY

Dermatology is the clinical discipline focused on the normal biology and pathogenesis of diseases and disorders of the skin. The diagnosis of skin disease depends critically on the history and physical examination, with laboratory testing often relegated to a peripheral and confirmatory role. In many cases, visual inspection alone will suffice to narrow the diagnosis significantly. On the other hand, the skin has a limited repertoire of morphologic expression. Therefore one should not hesitate to perform a skin biopsy, when indicated, or to order a variety of laboratory investigations when needed to distinguish between two or more clinical mimics.

The skin is divided into three layers: the epidermis, dermis, and subcutaneous tissue. The epidermis, composed of stratified squamous epithelia, can vary in thickness from 0.05 to 1.5 mm depending on location. Melanocytes (pigment-producing cells) populate the lower layers of the epidermis. The dermis, composed of collagen, elastin, and reticular fibers, can be divided into two layers: the thin superficial layer (papillary dermis) and the thicker deeper layer (reticular dermis). Located within the dermis are mesenchymal structures, such as blood vessels and nerves. The bottom layer of the skin, known as subcutaneous tissue, is largely composed of fat.

Literally hundreds of cutaneous diseases exist that may involve the external genitalia. In addition, within each disease there may be significant variation in appearance and symptoms as the process for each condition evolves. For this reason, a methodical and systematic approach is essential to reach a rational diagnosis. The dermatologic history should focus on the duration, rate of onset, location, associated symptoms, family history, allergies, occupation, and previous treatment of the condition (Habif, 2004). Common symptoms include pruritus (itching), burning, stinging, and pain. The lack of symptoms, such as pain, can be important in arriving at the correct diagnosis and should therefore be noted.

The physical examination should address the distribution of primary and secondary skin lesions. **It is important to perform a thorough skin survey and not to focus solely on the area of affected genital skin.** Most skin conditions begin with a characteristic primary lesion that is an important key to diagnosis. A precise description of this lesion includes documenting its color (red,

brown, black, yellow, white, blue, or green) and morphology (macule, papule, plaque, nodule, pustule, vesicle, bulla, or wheal; Table 16-1) (Habif, 2004). Because of the mucosal nature of genital skin, papular and macular lesions may present as erosions in this area (Margolis, 2002). Secondary skin lesions develop as the skin condition evolves or are caused by scratching, rubbing, or superinfection. A secondary lesion should also be classified morphologically as a scale, crust, erosion, ulcer, atrophy, thickening, or scar (Table 16-2).

After gross morphology is determined, laboratory testing may serve to confirm the diagnosis. To identify cutaneous fungi such as dermatophytes and *Candida* species, potassium hydroxide (KOH) or periodic acid-Schiff staining may be applied to scraped or touched skin specimens. KOH dissolves keratin, leaving fungal hyphal walls prominently visible under the microscope. Likewise, Tzanck preparations may aid in identifying viral agents such as herpes simplex, varicella zoster, and molluscum contagiosum.

For difficult cases or those in which malignancy is suspected, skin biopsy may be indicated. A variety of techniques exist for this purpose, including curettage, punch, shave, and incisional and complete excisional biopsies. For small scrotal or phallic shaft lesions, these techniques can usually be performed in the office setting under local anesthesia. For larger lesions or those involving the urethral meatus, biopsy in the operating room is recommended. It is often possible to determine the correct diagnosis with a very small (2 to 3 mm) punch biopsy. The resultant defect can easily be closed with one or two 6-0 or 7-0 nylon sutures, thereby avoiding any substantial scar.

Additional diagnostic maneuvers that may prove invaluable in select situations include serologic testing (e.g., serologic tests for syphilis), culture (e.g., culture for *Pseudomonas aeruginosa*), and immunohistochemistry stains of biopsy specimens (e.g., examination for specific types of cytokeratins associated with different variants of lichen sclerosus).

DERMATOLOGIC THERAPY

Medical therapy for dermatologic conditions consists of a broad range of topical and systemic compounds.

For systemic therapy, useful drug classes include antibiotics, antifungals, antivirals, anti-inflammatories, and antipruritics. Less commonly used agents, including chemotherapeutic and biologic drugs (e.g., methotrexate, cyclophosphamide, adalimumab, etanercept, infliximab, and ustekinumab), immunosuppressants (e.g., azathioprine, cyclosporine, tacrolimus), and hydroxyurea, will be discussed within the specific disease entities.

TABLE 16-1 Primary Cutaneous Lesions

PRIMARY LESION	DESCRIPTION
FLAT	
Macule	A circumscribed, flat discoloration that may be brown, blue, red, or hypopigmented
ELEVATED, SOLID	
Papule	An elevated, solid lesion up to 0.5 cm in diameter of variable color. Papules may become confluent to become plaques
Nodule	A circumscribed, elevated solid lesion >0.5 cm in diameter
Plaque	A circumscribed, elevated , superficial, solid lesion >0.5 cm in diameter
FLUID-FILLED	
Vesicle	A circumscribed collection of free fluid ≤0.5 cm in diameter
Bulla	A circumscribed collection of free fluid >0.5 cm in diameter
Pustule	A circumscribed collection of leukocytes and free fluid (pus)
Wheal (hive)	A firm erythematous plaque resulting from infiltration of the dermis with fluid (may be transient)

From Habif TP. Clinical dermatology: a color guide to diagnosis and therapy. Edinburgh: Mosby; 2004.

TABLE 16-2 Secondary Cutaneous Lesions

SECONDARY LESION	DESCRIPTION
Scale	Excess dead epidermal cells that are produced by abnormal keratinization and shedding
Crust	A collection of dried serum and cellular debris (a scab)
Erosion	A focal loss of epidermis. Erosions do not penetrate below the dermoepidermal junction and they heal without scarring
Ulcer	A focal loss of epidermis and dermis, which heals with scarring
Fissure	A linear loss of epidermis and dermis with sharply defined, vertical walls
Atrophy	A depression in the skin resulting from thinning of the epidermis or dermis
Scar	An abnormal formation of connective tissue implying dermal damage

From Habif TP. Clinical dermatology: a color guide to diagnosis and therapy. Edinburgh: Mosby; 2004.

A lack of familiarity with cutaneous diseases affecting the genitalia may lower the threshold of urologists in prescribing systemic antibiotics for these conditions. Unfortunately, these agents carry significantly greater risks than topical preparations, including promotion of resistant organisms, interaction with other medications, and disruption of the normal bowel and vaginal flora. It is worth noting that alterations in bacterial flora or in their

antimicrobial susceptibility patterns may persist for protracted periods, thus emphasizing the need for truly appropriate antibiotic use (Jernberg et al, 2010). Similar caveats apply to systemic antifungal agents such as fluconazole, ketoconazole, and terbinafine. Superficial dermatophytes, such as those causing tinea cruris, generally respond well to diligent application of topical antifungal preparations. **Systemic antifungals are only indicated for very extensive cutaneous dermatophytosis, endemic mycoses with skin involvement, deep infection involving the hair follicles (Majocchi granuloma), or fungal infections in severely immunocompromised individuals (Leshner and McConnell, 2003).** In some cases, even in immunocompetent individuals, systemic antifungals are necessary to treat infections resistant to local therapy (Leshner, 1999). On the other hand, warnings have emphasized the need to avoid the routine use of some systemic antifungal medications (such as ketoconazole) for superficial cutaneous infections because of the unpredictable risk of life-threatening hepatotoxicity and adrenal insufficiency (U.S. Food and Drug Administration, 2013). Systemic anti-inflammatory agents, in particular the glucocorticosteroids (GCS), deserve additional attention. Oral GCS are absorbed in the jejunum with peak plasma concentrations occurring in 30 to 90 minutes (Lester, 1989). Despite short plasma half-lives of 1 to 5 hours, the duration of effect of GCS lasts between 8 and 48 hours, depending on the agent (Nesbitt, 2003). These drugs have **widespread anti-inflammatory effects.** They release neutrophils from bone marrow but they inhibit their movement to sites of inflammation in tissue. They also impair both T-cell activation and antigen presentation by dendritic cells (Nesbitt, 2003). **For short-term (≤3 weeks) treatment of dermatologic conditions such as allergic contact dermatitis (Feldman, 1992), a single morning dose of GCS is administered to minimize suppression of the hypothalamic-pituitary-adrenal axis (Myles, 1971).** Prednisone is generally the GCS of choice because of its low cost, intermediate duration of action, and variety of dosage forms, although methylprednisolone may be substituted to reduce the mineralocorticoid effects (Wolverton, 2001). **Longer-term treatment with systemic GCS may lead to a wide variety of adverse effects including osteoporosis, cataract formation, hypertension, obesity, hyperglycemia, aseptic necrosis of the femoral head, immunosuppression, and psychiatric changes (Nesbitt, 2003).** For this reason, the use of topical steroids (see later) is preferable to reliance on systemic GCS, whenever clinically feasible.

Topical preparations are the mainstay of therapy for a wide range of cutaneous diseases affecting the genitalia. Urologists tend to be less familiar with the use of these medications than are dermatologists. **Topical medications can be broken down into five general classes: emollients, anti-inflammatories, antibiotics, antifungals, and chemotherapeutic agents.**

Topical preparations include active ingredients and they also include a vehicle that determines the rate at which the active ingredients are absorbed by the skin. Emollients restore water and lipids to the epidermis and are useful for dry-skin diseases. Emollients should be applied to moist skin for maximal effect, such as after bathing. Preparations containing urea (e.g., Carmol, vanadine) or lactic acid (Lac-Hydrin, AmLactin) may be particularly potent hydrating agents (Habif, 2004). It has been noted that ceramides (combinations of a fatty acid and a sphingoid base), the main natural intercellular lipids in the outermost layer of skin, are critical for maintaining normal cutaneous hydration and barrier function (Weber et al, 2012). For this reason, new formulations containing ceramides (CeraVe) may also be particularly useful for skin conditions characterized by xerosis (dryness). Topical corticosteroids are potent anti-inflammatory agents available in a myriad of preparations and strengths. A detailed review of the use and dosing of topical corticosteroids is beyond the scope of this chapter, and the reader is directed to several excellent dermatology textbooks for more detail (Habif, 2004). It is important to recognize that even topical corticosteroids can include significant adverse effects, both from systemic absorption and also from the results of local application. Local effects include epidermal atrophy and the development of striae on the upper portion of the inner thigh,

dermal changes (telangiectasias, hypopigmentation), allergic reactions, and negative alterations in the usual course of skin infections and infestations (Burry, 1973). In most cases, atrophy is a reversible process that can be expected to resolve during the course of several months (Sneddon, 1976). Atrophy is particularly troublesome if corticosteroids are applied under the foreskin, which can serve as an occlusive “dressing” and can enhance penetration of the drug (Fig. 16-1) (Goldman and Kitzmiller, 1973).

A variety of physical modalities have also been applied to treat dermatologic problems, including ultraviolet light therapy, photodynamic therapy, laser therapy, and cryosurgery. Ultraviolet light therapy, with both broadband and narrow-band ultraviolet B (UVB), has been used to treat atopic dermatitis, psoriasis, seborrheic dermatitis, and vitiligo (Honigsmann and Schwarz, 2003). There are now several convenient single-wavelength UVB (308 nm) laser units with small spot sizes, which are particularly useful for treating vexing localized areas of genital psoriasis or vitiligo; such narrow spectrum machines are believed not to carry the risk of inducing the nonmelanoma skin cancer that is associated with broadband full-body light boxes. Psoralens, when combined with long-wave ultraviolet A radiation (psoralen ultraviolet A [PUVA] therapy), generate a phototoxic effect that is beneficial for treating psoriasis (Honigsmann, 2001; Stern, 2007), vitiligo (Honigsmann and Schwarz, 2003), atopic dermatitis (Morison, 1992), and lichen planus (Honigsmann and Schwarz, 2003). In general, the narrow-band UVB boxes and lasers have supplanted PUVA therapy, as the latter carries a substantial risk of squamous cell carcinoma (SCC) when performed throughout a prolonged period (Stern and PUVA Follow-Up Study, 2012). Photodynamic therapy involves the use of cytotoxic oxygen radicals generated from photoactivated molecules to achieve a therapeutic response (Tope and Shaffer, 2003; Braathen et al, 2007). Photodynamic therapy is a new arena of dermatologic therapy and holds promise for treating a variety of inflammatory, malignant, and infectious skin conditions. For example, photodynamic therapy is effective, both as monotherapy and in combination with cryosurgery, CO₂ laser ablation, and curettage, in the management of large or resistant condyloma acuminata or in genital warts occurring during pregnancy (Scheinfeld, 2013b). The downside to this promising modality is that there is not yet an

established optimum regimen for off-label use, including for genital warts. Laser and cryosurgery play a relatively small role in the management of genital lesions, although the CO₂ laser has been used effectively to manage genital condyloma acuminata, and cryosurgery may be useful for genital and suprapubic molluscum contagiosum.

ALLERGIC DERMATITIS

Allergic or “eczematous” dermatitis consists of a group of allergy-mediated processes leading to pruritic skin lesions (Box 16-1).

Atopic Dermatitis (Eczema)

Atopic dermatitis (AD) is a chronic relapsing dermatitis with a predilection for skin flexures that is associated with intense pruritus and damage to the epidermis (Williams, 2005). The characteristic lesions are erythematous papules and thin plaques with secondary excoriations (Fig. 16-2) (Kang et al, 2003). In

BOX 16-1 Differential Diagnosis of Allergic Dermatitis

- Eczema
- Allergic dermatitis
- Seborrheic dermatitis
- Intertrigo
- Contact dermatitis
- Irritant dermatitis
- Balanoposthitis
- Zoon balanitis
- Candidal-related illness
- Impetigo
- Herpes simplex
- Herpes zoster
- Drug reaction

From Margolis DJ. Cutaneous disease of the male external genitalia. In: Walsh PC, editor. Campbell's urology. Philadelphia: Saunders; 2002.



Figure 16-1. Steroid atrophy of penile shaft skin after application of corticosteroid under the foreskin for 8 weeks. (From Habib TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 36.)



Figure 16-2. Eczema involving the vulva. (From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 687.)

general, the lesions do not have a precise border as is common for papulosquamous disorders (Margolis, 2002). Although any age can be affected, 90% of AD patients manifest their condition before the age of 5 years (Rajka, 1989). AD is associated with susceptibility to a wide variety of substances that act as irritants (e.g., fragrances, preservatives, and various proteins). Patients suffering from AD also have a propensity to develop asthma and allergic rhinitis.

The genetic susceptibility to AD has been extensively explored. In a study of 372 AD patients, 73% had a positive family history for atopy. Likewise, twin concordance studies have demonstrated an AD risk of 0.86 for monozygotic twins compared to only 0.21 for dizygotic twins. These findings have spurred an intense search for genes involved in atopy and AD (Wollenberg and Bieber, 2000). Although no single gene has been found to be a unique marker for the disease, at least 11 genetic foci seem to be closely associated with AD (Kang et al, 2003; Ellinghaus et al, 2013). The single most important genetic defects confer an inability to synthesize functional filaggrin properly. This structural abnormality results in both a “leaky” epithelial barrier and chronic immune activation, which contribute to the pathophysiology of this common skin disease (Heimall and Spergel, 2012).

Intense pruritus is the hallmark of AD, and controlling the patient's urge to scratch is critical for successful treatment (Przybilla et al, 1994). Itching is often worse during evening hours and can be exacerbated by sweating, occlusive undergarments, or wool clothing (Kang et al, 2003). Scratching of lesions may contribute to the clinical complications of AD, including superinfection with *Staphylococcus aureus* species (Ogawa et al, 1994). There is growing evidence that bacterial toxins may serve as superantigens that drive an inflammatory cascade that sustains AD (Skov and Baadsgaard, 2000; Skov et al, 2000).

Clinically, there is no pathognomonic laboratory test, biopsy result, or single clinical feature that allows the definitive diagnosis of AD. The association with a personal or family history of atopy is a critical clue to the diagnosis (Kang et al, 2003). For patients presenting with genital findings, extragenital involvement is commonplace.

A variety of “trigger factors” have been implicated in the exacerbation of AD, including chemicals, detergents, and household dust mites. Removal of these factors from the environment may be beneficial on an individualized basis. Dust mite exposure, in particular, has received significant attention in the literature. Although several studies have demonstrated modest improvement in AD with mite reduction (Kubota et al, 1992; Tan et al, 1996), others report that reduction is associated with no significant clinical benefit (Colloff et al, 1989; Gutgesell et al, 2001).

Treatments for AD include gentle cleaning with nonalkali soaps or soap substitutes (e.g., Cetaphil, Aquanil) and the frequent use of emollients. Evaporation of liquid from the skin may trigger AD (Kang et al, 2003), so frequent bathing is not encouraged. Soaking may help during episodes of bacterial superinfection but should be discontinued after the infection has resolved (Margolis, 2002). Topical corticosteroids may be needed to control pruritus but should only be used for short courses with a rapid taper to avoid local complications of skin atrophy and dyschromia. Topical macrolide immunomodulatory agents such as tacrolimus and pimecrolimus have shown efficacy in the treatment of AD (Meagher et al, 2002; Nghiem et al, 2002; Luger and Paul, 2007; Leung et al, 2009), and these agents may decrease the need for corticosteroids during long-term therapy (Zuberbier et al, 2007). Antihistamines such as diphenhydramine or a variety of nonsedating agents, such as cetirizine, loratadine, and analogues of these, may be helpful in breaking the “itch-scratch cycle” in AD, particularly when administered before bedtime (Kang et al, 2003). Oral antistaphylococcal drugs have not been shown to significantly improve AD in a randomized, double-blind trial (Ewing et al, 1998). Systemic treatment with azathioprine, corticosteroids, cyclosporine, methotrexate, or mycophenolate mofetil may rarely be indicated for severe, widely disseminated cases (Cooper, 1993; Salek et al, 1993; Denby and Beck, 2012).

Contact Dermatitis

Contact dermatitis can be broken down into two distinct entities: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). Although the mechanisms differ significantly, the clinical presentation of ICD and ACD may be similar. Most notably, the affected area is usually sharply limited to an area of skin exposure to true allergen or irritating chemical. The primary mode of treatment is to identify and reduce exposure to the offending agent.

ICD results from a direct cytotoxic effect of an irritant chemical touching the skin and is responsible for approximately 80% of contact dermatitis cases (Marks et al, 2002). Examples of offending agents include soaps, solvents, metal salts, and acid- or alkali-containing compounds. Occupational ICD is a serious public health problem and contributes to costs on the scale of \$1 billion annually in the United States (Cohen, 2000). The clinical manifestations of ICD depend on the identity of the irritating substance as well as the duration of contact, concentration, temperature, pH, and location of exposure. Acute ICD, such as might result from an occupational accident, generally peaks within minutes to hours after exposure and then begins to heal. Symptoms of burning, stinging, and soreness may be accompanied by erythema, edema, bullae, or frank necrosis in a sharply defined area corresponding to the exposed skin (Cohen and Bassiri-Tehrani, 2003). There are also a variety of subacute forms of ICD that result from repeated subthreshold skin insults. Pruritus is much more common in these more chronic conditions, and the skin lesions are not as well demarcated. The mainstay of treatment for ICD lies in avoiding skin contact with the causative irritants through the use of protective clothing, safe occupational practices, and the use of skin barrier preparations such as ointments, emollient creams, or protective foams. Some commercially available barrier products include Atopiclair, Biafine, EpiCeram, Mimyx, Neosalus Foam, and PruMyx (Berndt et al, 2000; Draelos, 2012).

In contrast, ACD represents a local type IV hypersensitivity reaction to a skin allergen to which an individual has been previously exposed and sensitized. The typical appearance is a well-demarcated pruritic eruption, which may manifest blistering or weeping in the acute phase or the development of scaly plaques more chronically (Mowad and Marks, 2003). In 2003 and 2009, the North American Contact Dermatitis Group (NACDG) reported a long list of common allergens implicated in ACD based on patch testing results (Zug et al, 2009). Similar lists that were produced subsequently contain the same set of allergens, with only a few exceptions. Patch testing is a simple technique of exposing an area of skin to a variety of potential allergens at a known concentration in a grid template (Fig. 16-3). Generally performed by dermatologists, patch testing can help to confirm both the diagnosis of ACD and the allergen involved. The most common sensitizing allergen identified by the NACDG was nickel sulfate (Zug et al, 2009), which is a common component of costume jewelry and belt buckles (Fig. 16-4). Although traditionally a cause of earlobe dermatitis from pierced earrings, nickel sensitivity may be a potential cause of genital ACD resulting from the increasing prevalence of genital piercing. Other important allergens include textile dyes, topical antibiotics, perfumes and other fragrance materials, formaldehyde-releasing preservatives, the latex in condoms, and topical corticosteroids. When ACD is suspected, one should always inquire about the use of over-the-counter products such as genital moisturizers, antiyeast and anti-itch preparations, and lubricants used during sexual intercourse. Oral antihistamines may be helpful for the symptomatic control of ACD in combination with the removal of the inciting allergen. Severe ACD should *not* be treated with a short course of systemic steroids, but rather with a 3-week tapering dose of prednisone.

Erythema Multiforme and Stevens-Johnson Syndrome

Erythema multiforme (EM) is a generalized skin disease that may involve the genitalia. EM can be subdivided into minor and major forms.



Figure 16-3. An example of patch testing with a positive response to nickel. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 233.)



Figure 16-4. Contact dermatitis caused by a nickel allergy from a belt buckle. (From Habif TP. *Clinical dermatology*. Edinburgh: Mosby; 2004. p. 94.)

EM minor was first described in 1860 by an Austrian dermatologist, Ferdinand von Hebra ([von Hebra, 1860](#)). This condition is an acute, self-limited skin disease characterized by the abrupt onset of symmetrical fixed red papules that may evolve into target lesions ([Weston, 1996](#)). EM is a clinical rather than a histologic

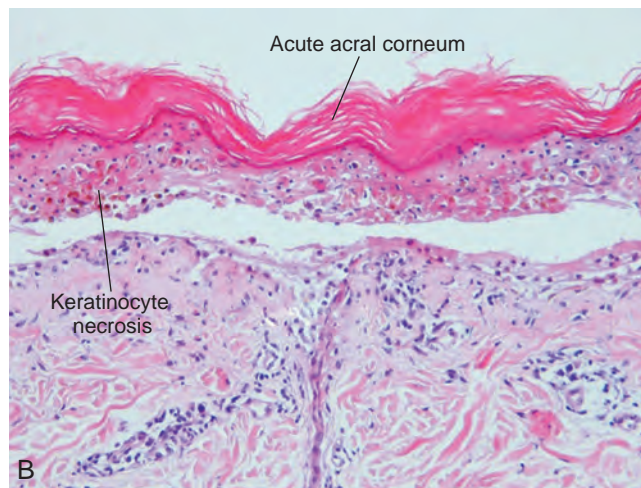


Figure 16-5. Erythema multiforme (EM). A, Targetoid lesions of the hands and penis. B, Typical microscopic picture of EM with a normal stratum corneum, necrotic keratinocytes in the epidermis and a lymphoid infiltrate. (A, From Korting GW. *Practical dermatology of the genital region*. Philadelphia: Saunders; 1981. p. 16; B, from Elston DM, Furrer T. *Dermatopathology*. Edinburgh: Saunders; 2009. p. 147.)

diagnosis. Papules and target lesions are usually grouped and can be present anywhere on the body, including the genitalia ([Fig. 16-5A](#)). There is also a predilection for involvement of the oral mucous membranes, as well as the palms and soles.

The majority of cases of recurrent EM minor are precipitated by human herpesvirus 1 and 2 ([Schofield et al, 1993](#); [Nikkels and Pierard, 2002](#)), with herpetic lesions usually preceding the development of target lesions by 10 to 14 days ([Lemak et al, 1986](#)). Although continuous suppressive acyclovir may prevent EM episodes in patients with herpes infection ([Tatnall et al, 1995](#)), administration of the drug after development of target lesions is of no benefit ([Huff, 1988](#)). The natural history of EM minor is spontaneous resolution after several weeks without sequelae ([Schofield et al, 1993](#)), although recurrences are common ([Huff and Weston, 1989](#)). Oral antihistamines may provide symptomatic relief. For immunosuppressed patients, the time course of EM minor outbreaks may be longer and the frequency of recurrence may be greater ([Schofield et al, 1993](#)).

The major form of EM has been called Stevens-Johnson syndrome (SJS) in the past, although there remains some controversy as to whether EM major and SJS are distinct entities or are part of a spectrum of disease ([Bachot and Roujeau, 2003](#); [Williams and Conklin, 2005](#)). SJS is a much more serious illness than EM minor and it includes features similar to extensive skin burns ([Parrillo, 2007](#)). In its more severe forms, SJS may mimic life-threatening toxic epidermal necrolysis. Admission to the intensive care unit or burn unit may significantly reduce the morbidity and mortality of



Figure 16-6. Labial erosions in a case of Stevens-Johnson syndrome. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 319.)

this condition (Wolf et al, 2005). Most patients with SJS exhibit a prodromal upper respiratory illness (fever, cough, rhinitis, sore throat, and headache), which progresses after 1 to 14 days to the abrupt development of red macules with blister formation and areas of epidermal necrosis. Genital involvement includes erythema and erosions of the labia (Fig. 16-6), penis, and perianal region.

A vast array of inciting factors has been implicated in the development of SJS, with drug exposures being the most commonly identified. Among the most common offending agents are non-steroidal anti-inflammatory agents, sulfonamides (particularly cotrimoxazole), tetracycline and doxycycline, penicillin and cephalosporins, and a wide range of anticonvulsants (Chan et al, 1990). In contrast to EM minor, there is rarely an association with an infectious agent (Weston, 2003). SJS generally presents a protracted course of 4 to 6 weeks and may include a mortality rate approaching 30%. Severe scarring of denuded skin may result in a range of complications including joint contractures, labial synechia, vaginal stenosis, urethral meatal stenosis, and anal strictures (Brice et al, 1990; Weston, 2003). Treatment involves immediate removal of the offending drug and supportive care similar to the management of severe burns. There is currently no strong evidence for any specific medical therapy for SJS (Weston, 2003), and the role of systemic corticosteroids in treating SJS remains controversial (Rasmussen, 1976; Tripathi et al, 2000; Weston, 2003). Newer modalities anecdotally reported to act as effective interventions include cyclosporine (3 to 5 mg/kg/day), tumor necrosis factor (TNF)- α inhibitors, plasmapheresis, and, especially noted, intravenous immunoglobulin (Mockenhaupt, 2011; Worswick and Cotliar, 2011). Care of the SJS patient is best accomplished via a multispecialty team approach.

PAPULOSQUAMOUS DISORDERS

Papulosquamous disorders are a disparate group of diseases that share a common primary lesion: scaly papules and plaques (Box 16-2).

Psoriasis

Psoriasis is a common disease affecting up to 2% of the population (Christophers, 2001; Nestle et al, 2009). For patients with a

BOX 16-2 Differential Diagnosis of Papulosquamous Lesions

- Psoriasis
- Seborrheic dermatitis
- Dermatophyte infection
- Erythrasma
- Secondary syphilis
- Pityriasis rosea
- Discoid lupus
- Mycosis fungoides
- Lichen planus
- Fixed drug eruption
- Reactive arthritis
- Pityriasis versicolor
- Bowen disease
- Extramammary Paget disease

From Margolis DJ. Cutaneous disease of the male external genitalia. In: Walsh PC, editor. *Campbell's urology*. Philadelphia: Saunders; 2002.

predisposition, which is likely polygenic in nature, triggering factors such as trauma, infection, psychological stress, or new medications can elicit a flare in the psoriatic phenotype. One third of affected patients have a family history of psoriasis (Melski and Stern, 1981; Hensler and Christophers, 1985; Margolis, 2002).

The characteristic lesion is a sharply demarcated erythematous plaque with silvery-white scales (van de Kerkhof, 2003). Its pattern can be limited to the elbows or knees or can be distributed on the entire surface of the skin. Although psoriasis can appear at any age, two peaks of onset have been identified: 20 to 30 and 50 to 60 years of age. Patients complain of a significant impairment in their quality of life as a result of pruritus and bleeding, as well as the cosmetic and psychosocial impact of these visible plaques.

Psoriatic involvement of the genitalia is relatively common although it is usually within the context of a generalized cutaneous disorder. Patients may present with concerns for malignancy or sexually transmitted disease (STD) when psoriatic lesions are present on the genitalia. Genital psoriasis leads to impaired self-esteem and reduced sexual self-image, thereby interfering with normal intimate relationships, particularly in women (Magin et al, 2010; Meeuwis et al, 2011). The presence of characteristic lesions on the elbows, knees, buttocks, nails, scalp, and umbilicus may help direct the diagnosis (Fig. 16-7A) (Margolis, 2002). When lesions are present in the inguinal folds and intergluteal cleft, scaling may be absent (so-called inverse psoriasis) (Goldman, 2000). When evaluating nonscaling erythematous plaques in the inguinal folds, the diagnosis of fungal involvement (i.e., tinea or *Candida*) should be considered and ruled out by KOH preparation or fungal culture. In circumcised men, psoriatic plaques are often present on the glans and corona whereas in uncircumcised men, lesions are commonly hidden under the preputial skin (Buechner, 2002). In some cases, however, psoriasis involves the entire penis and scrotum (Fig. 16-8).

Psoriasis is a chronic disease with a relapsing and remitting course. A variety of topical and systemic therapies have been developed and are applied to this difficult problem. Despite the variety of therapy, however, as many as 40% of psoriasis sufferers express frustration at the ineffectiveness of current treatments (Krueger et al, 2001). For genital psoriasis, the mainstay of therapy is the use of low-potency topical corticosteroid creams for short courses (Kalb et al, 2009). Examples include a preparation of 3% liquor carbonis detergens (a tar derivative) in 1% hydrocortisone cream or hydrocortisone butyrate 0.1% (Fisher and Margesson, 1998). These preparations should not be used for more than 2 weeks continuously on thin genital skin or in areas occluded by skin folds (Margolis, 2002). Other topical therapies for psoriasis include vitamin D₃ analogues (calcitriol, calcipotriene), topical

calcineurin inhibitors (pimecrolimus cream and tacrolimus ointment), and low-potency retinoids, although these agents are sometimes too irritating or not sufficiently effective. Photochemotherapy combining an ingested psoralen with ultraviolet radiation (PUVA) has been used extensively to treat psoriasis (Stern, 2007). However, a dose-dependent increase in the risk of genital SCC has been

associated with high-dose PUVA therapy for psoriasis elsewhere on the body (Stern, 1990; Stern et al, 2002). Genital shielding during PUVA therapy is strongly recommended; therefore this modality is contraindicated for treating psoriatic lesions localized to genital skin. For patients with extensive psoriasis, systemic therapy with methotrexate, cyclosporine, retinoids, or one of the approved TNF- α inhibitors (adalimumab, etanercept) or IL12/23 inhibitors (ustekinumab) may be appropriate. The 308-nm excimer laser (Gerber et al, 2003) is now approved for psoriasis treatment. Experimental therapies that have shown promise in treating psoriasis include vitamin D receptor ligands (Bos and Spuls, 2008) and antibodies or antisense oligonucleotides against T-lymphocyte surface molecules (Gottlieb et al, 2000b), TNF (Chaudhari et al, 2001; Bos and Spuls, 2008), or intracellular adhesion molecules (Gottlieb et al, 2000a).

Reactive Arthritis (Formerly Reiter Syndrome)

Reactive arthritis (formerly Reiter syndrome) is composed of urethritis, arthritis, ocular findings, oral ulcers, and skin lesions. Only about one third of all patients with this disorder demonstrate all of the manifestations. The skin findings, particularly when present on the genitalia, may be mistaken for psoriatic lesions (Fig. 16-9). Reactive arthritis is more common in men than in women and is rarely diagnosed in children. Reactive arthritis is generally preceded by an episode of either urethritis (*Chlamydia*, *Gonococcus*) or gastrointestinal infection (*Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, *Neisseria* or *Ureaplasma* species) and is more common in human immunodeficiency virus (HIV)-positive patients (Rahman et al, 1992; Margolis, 2002; Wu and Schwartz,



Figure 16-7. Psoriasis. A, Silver scales on an erythematous base. B, Alternating neutrophils and parakeratosis in the stratum corneum of plaque psoriasis (sandwich sign). (A, From Callen JP, Greer DE, Hood AF, et al. Color atlas of dermatology. Philadelphia: Saunders; 1993. p. 320; B, from Elston DM, Ferringer T. Dermatopathology. Edinburgh: Saunders; 2009. p. 152.)



Figure 16-8. Psoriasis involving the entire penis and scrotum. (From Bologna JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 130.)

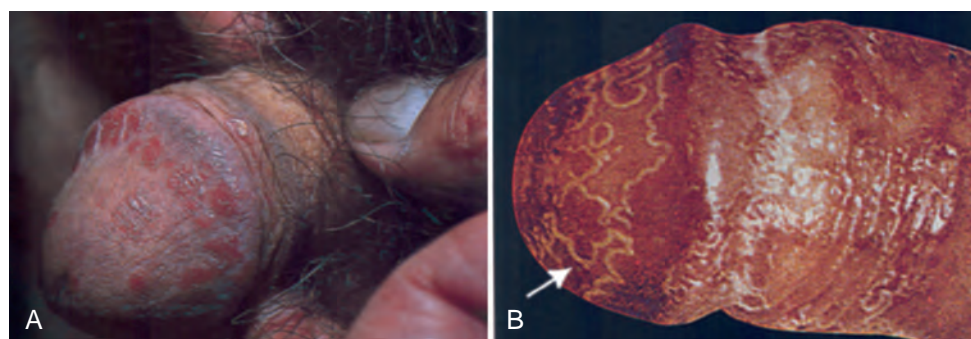


Figure 16-9. Comparison of psoriasis (A) and reactive arthritis (B) (balanitis circinata) involving the glans penis. Note the highly characteristic coalescence of lesions in this case of reactive arthritis forming a wavy pattern (arrow). (From Habib TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 217.)



Figure 16-10. Erosive psoriaform lesions of the glans penis (reactive arthritis; balanitis circinata) may also lack the wavy pattern, making them difficult to differentiate from genital psoriasis. (From Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993. p. 160.)

2008). There is a strong genetic association with the human leukocyte antigen (HLA)-B27 haplotype. Whether or not cross-reactivity between bacterial antigens and HLA-B27 leads to autoimmunity in reactive arthritis remains controversial (Ringrose, 1999; Yu and Kuipers, 2003).

Conjunctivitis is the most common ocular manifestation, although iritis, uveitis, glaucoma, and keratitis may occur. Polyarthritides and sacroiliitis are the most common orthopedic complaints and may lead to chronic disability in a small minority of cases (van de Kerkhof, 2003). Scaly, erythematous psoriaform skin lesions appearing on the penis are referred to as *balanitis circinata* (Fig. 16-10), and similar lesions on the soles are referred to as *keratoderma blennorrhagicum*. These lesions may be difficult to distinguish from psoriasis, and histologic analysis of biopsy specimens cannot consistently differentiate the two conditions (Margolis, 2002). The course of reactive arthritis involving the genitalia is usually self-limited, lasting a few weeks to months. Lesions may respond to low-potency topical corticosteroids, and systemic therapy is rarely required. Lesions on soles, however, are more persistent; these respond well to the application of potent topical retinoids such as tazarotene (Lewis et al, 2000).

Lichen Planus

Lichen planus (LP), the prototype of the lichenoid dermatoses, is an idiopathic inflammatory disease of the skin and mucous membranes. The characteristic “lichenoid tissue reaction” is characterized by epidermal basal cell damage that is associated with a massive infiltration of mononuclear cells in the papillary dermis (Shiohara and Kano, 2003). Cutaneous LP may affect up to 1% of the adult population (Boyd and Neldner, 1991) and oral lesions may be present in as many as 4% (Scully et al, 1998). The pathogenesis of LP appears related to an autoimmune reaction against basal keratinocytes, which express altered self-antigens on their surfaces (Morhenn, 1986).

The primary lesion of LP is a small, polygonal-shaped, violaceous, flat-topped papule. These lesions may be widely separated or may coalesce into larger plaques that may ulcerate, particularly on mucosal surfaces. LP commonly involves the flexor surfaces of the extremities, the trunk, the lumbosacral area, the oral mucosa, and the glans penis (Margolis, 2002). On the male genitalia, the clinical presentation of LP can be quite variable and includes isolated or grouped papules, a white reticular pattern, or an annular (ringlike) arrangement with or without ulceration (Fig. 16-11). In some cases, the lesions appear to form linear patterns related to skin trauma (the so-called Koebner phenomenon, which is also seen with psoriasis). On the female genitalia, painful erosion of erythematous plaques is common; in long-standing LP of the vulva, some areas of hyperhydrated hyperkeratosis (manifesting as white plaques) may surround shallow erosions. In women, more than in men, concomitant oral LP may be found on the buccal mucosa or tongue (Santegoets et al, 2010). The differential diagnosis of LP includes invasive and in situ SCC, Zoon balanitis, psoriasis, secondary syphilis, herpes and extramammary Paget disease, and lupus erythematosus. Biopsy may be necessary to establish the diagnosis, particularly when the lesions are small, multiple, and ulcerated (Shiohara and Kano, 2003). Lichenoid reactions can also occur in response to ingested drugs and contact allergens, and a careful search for potential offending agents is appropriate.

The natural history of LP is benign and the spontaneous resolution of cutaneous lesions has been observed in up to two thirds of cases after 1 year (Shiohara and Kano, 2003), although the oral form may persist significantly longer, and isolated cases of SCC arising within chronic genital LP have been reported (Mignogna et al, 2000). Although bothersome pruritus (more often in men) or pain/burning (more often in women) is common with LP, asymptomatic lesions on the genitalia do not require treatment. The primary modality of treatment for symptomatic genital LP is the application of an ultrapotent topical corticosteroid (such as clobetasol 0.05% or halobetasol 0.05%). There is also a role for topical calcineurin inhibitors (pimecrolimus cream, tacrolimus ointment) in the management of genital LP (Luger and Paul, 2007). For severe cases, systemic corticosteroids (15 to 20 mg/day; 2- to 6-week course) (Boyd and Neldner, 1991) have been shown to shorten the time course to clearance of LP lesions from 29 weeks to 18 weeks (Cribier et al, 1998). Other systemic therapies for severe LP include cyclosporine, tacrolimus, griseofulvin, metronidazole, and acitretin (Ho et al, 1990; Boyd and Neldner, 1991; Cribier et al, 1998; Buyuk and Kavala, 2000; Madan and Griffiths, 2007), although randomized trials demonstrating efficacy are generally lacking. In fact, as pointed out in an exhaustive meta-analysis, there is no overwhelmingly reliable evidence for the efficacy of any single treatment for erosive mucosal LP, including application of an ultrapotent topical steroid, which is the widely accepted first-line therapy (Cheng et al, 2012).

Lichen Nitidus

Lichen nitidus (LN) is an unusual inflammatory eruption characterized by tiny, discrete, flesh-colored papules arranged in large clusters. Although there is some debate as to whether LN may represent a variant of LP (Aram, 1988), the two entities are histologically distinct. LN has a dense, well-circumscribed, lymphohistiocytic infiltrate that is closely apposed to the epidermis (Shiohara and Kano, 2003). Commonly involved sites include the flexor aspects of the upper extremities, the genitalia, the trunk, and the dorsal aspects of the hands. Nail involvement is common. Similar to LP, the natural history of LN is one of spontaneous resolution, with the majority of patients (69%) manifesting the disease for less than 1 year (Lapins et al, 1978). Patients should be reassured that these genital lesions are not infectious and should resolve with time. For symptomatic pruritus, genital lesions usually respond to mid- to low-potency topical corticosteroids and oral antihistamines (Shiohara and Kano, 2003).

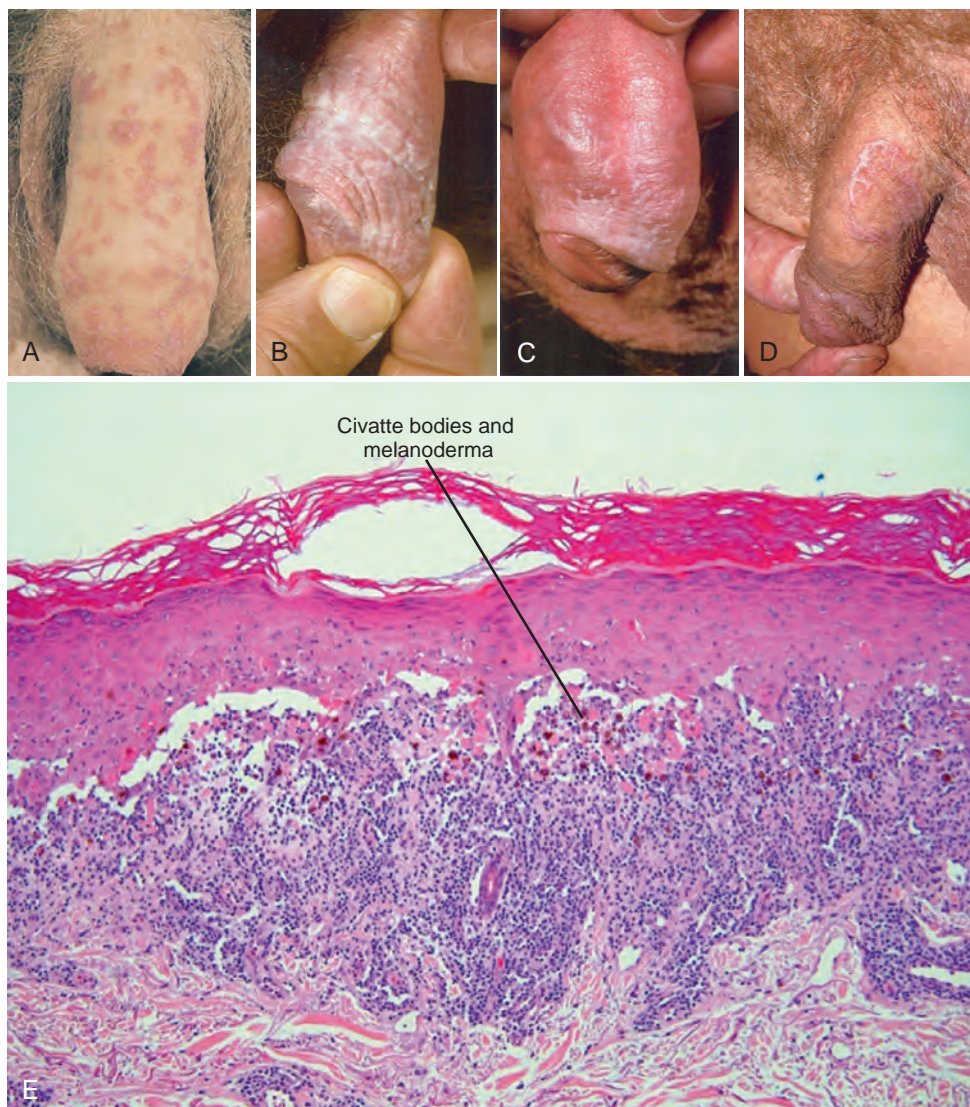


Figure 16-11. Lichen planus (LP). Various presentations of LP on the male genitalia. A and B, Both individual and grouped purple papules on the penile shaft, some oriented in a linear pattern. C, A white reticular pattern sometimes seen in LP. D, An annular (ringlike) arrangement with a shiny surface. E, Histologically, LP is characterized by destruction of the basal layer, a sawtooth rete ridge pattern, the presence of Civatte bodies and dermal melanocytes, and the absence of parakeratosis or eosinophils. (A, From Korting GW. *Practical dermatology of the genital region*. Philadelphia: Saunders; 1981. p. 29; B, C, and D, from du Vivier A. *Atlas of clinical dermatology*. London: Churchill Livingstone; 2002. p. 100; E, from Elston DM, Ferringer T. *Dermatopathology*. Edinburgh: Saunders; 2009. p. 137.)

Lichen Sclerosus

Lichen sclerosus et atrophicus (LS) is a chronic inflammatory disease of unknown etiology with a predilection for the external genitalia. LS is 6 to 10 times more prevalent in women than in men, generally presenting either around the time of menopause or in the prepubertal years (Wojnarowska and Cooper, 2003). It tends to affect older men (>60 years of age) (Ledwig and Weigand, 1989) and can be associated with pain during voiding or erection (Margolis, 2002). There is a strong familial predisposition for this disorder, suggesting a genetic contribution (Sherman et al, 2010). For patients with genital LS, 15% to 20% experience extragenital disease (Powell and Wojnarowska, 1999). LS is ultimately a scarring disorder characterized by tissue pallor, loss of architecture resulting from fibrosis, and hyperkeratosis (Fig. 16-12). Some cases of LS may demonstrate prominent purpura and fissuring; the former may be so severe as to obscure the typical “white” color of the disease. The

glans penis and foreskin are usually affected, and the perianal involvement common in women is usually absent. Preputial scarring from LS can lead to phimosis, and circumcision is usually curative, although recurrence in the circumcision scar may occur. The late stage of this disease is called *balanitis xerotica obliterans*, which can involve the penile urethra and result in troublesome urethral strictures. In women, the disease can eventually lead to vulvar adhesions, labial fusion, clitoral phimosis, and vaginal obstruction. LS can also be the cause of considerable genital itching, burning, pain, and dyspareunia in women.

Despite the similarities in name, LS shares little in common with LP and LN other than pruritus and a predilection for the genital region. Another critical distinction is that LS has been associated with SCC of the penis and vulva, particularly those variants not associated with human papillomavirus (HPV), and LS may represent a premalignant condition (Velazquez and Cubilla, 2003; Bleeker et al, 2009; van de Nieuwenhof et al, 2011).

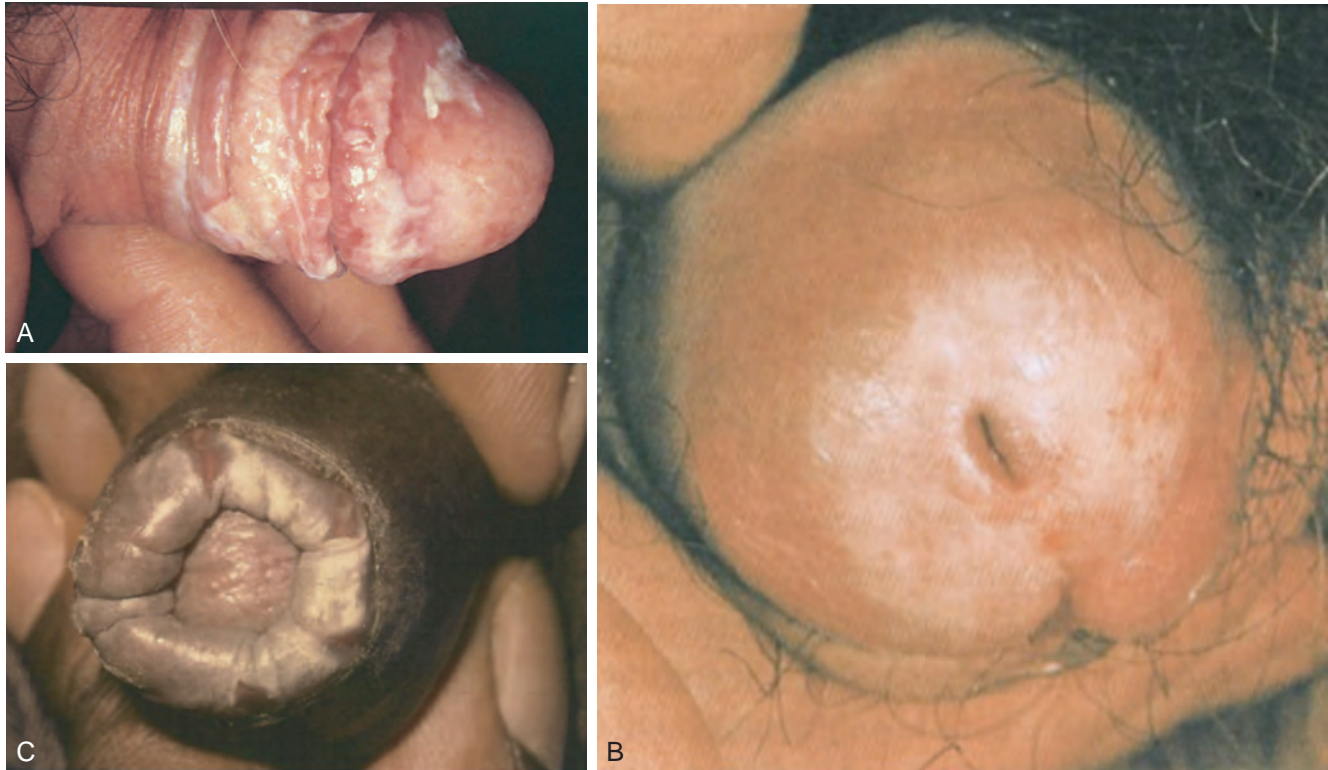


Figure 16-12. A to C, Lichen sclerosus et atrophicus (balanitis xerotica obliterans) of the penis. Note the erythematous and white plaques involving the penile shaft, preputial skin, and glans. (A, From Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993. p. 327; B, from du Vivier A. *Atlas of clinical dermatology*. London: Churchill Livingstone; 2002. p. 716; C, from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 1101.)

LS includes specific histologic features, including basal cell vacuolation, epidermal atrophy, marked dermal edema, collagen homogenization, focal perivascular infiltrate of the papillary dermis, and plugging of the ostia of follicular and eccrine structures (Margolis, 2002). Biopsy is worthwhile both to confirm the diagnosis and to exclude malignant change (Powell and Wojnarowska, 1999). It has been suggested that the expression of selected cellular markers (such as p53, survivin, telomerase, Ki-67, and cyclin D1) can help distinguish between indolent LS and LS with true malignant potential (Carlson et al, 2013). In the future, biopsy specimens may routinely be investigated for these (and other) protein markers to determine prognosis.

From a management standpoint, long-term follow-up of patients with LS is important because of the association with SCC. The application of potent topical steroids (such as clobetasol propionate 0.05% or halobetasol 0.05%) for long courses (3 months) is well established as a treatment for LS in women, and may both improve symptoms and reverse the disease process (Dalziel et al, 1991). This regimen is contrary to the usual policy of avoiding long courses of steroid application to genital skin. The efficacy of similar approaches has not been definitively confirmed in adult men, although benefits have been demonstrated in the pediatric age group (Kiss et al, 2001). A European, multicenter, phase II trial also supported the safety and efficacy of topical tacrolimus in the treatment of long-standing LS (Hengge et al, 2006). The application of topical and administration of systemic retinoids, as well as photodynamic therapy, may be therapeutic options in rare cases refractory to standard therapeutic interventions. Because of a high rate of recurrence (40% to 50%) after seemingly successful initial therapy, some experts suggest the routine use of proactive (prophylactic) maintenance therapy with either midpotency topical steroids (such as mometasone furoate 0.1%) or topical calcineurin inhibitors (Virgili et al, 2013).

Fixed Drug Eruption

A fixed drug eruption occurs in response to oral medications, usually 1 to 2 weeks after the first exposure, and commonly involves the lips, face, hands, feet, and genitalia, particularly the glans penis (Fig. 16-13). After subsequent re-exposure to the drug, the reaction presents in the exact same location, usually within 24 hours (hence the term “fixed”). The most common medications causing this reaction are sulfonamides, nonsteroidal anti-inflammatory agents, barbiturates, tetracyclines, carbamazepine, phenolphthalein, oral contraceptives, and salicylates (Kauppinen and Stubb, 1985; Stubb et al, 1989; Thankappan and Zachariah, 1991). There have been isolated reports of fixed drug eruption associated with urologic drugs, such as finasteride, tadalafil, and fluconazole (administered for vulvovaginal candidiasis).

When present on the penile shaft or glans, these lesions are usually solitary, violaceous-colored, inflammatory plaques, which may become erosive and painful (Margolis, 2002). On the genitalia, the differential diagnosis includes herpes simplex infection or an insect bite. Removing the offending agent usually results in resolution of the lesion, although a postinflammatory brown pigmentation may remain. There should be no long-lasting residual functional defect from this process.

Seborrheic Dermatitis

Seborrheic dermatitis (SD) is a common skin disease characterized by the presence of sharply demarcated pink-yellow to red-brown plaques covered with an adherent flaky scale. It shares a variety of features in common with eczematous dermatitis and could easily be grouped in that category. Common dandruff is a mild form of SD localized to the scalp. It has a predilection for areas rich in sebaceous glands and is generally present only during the

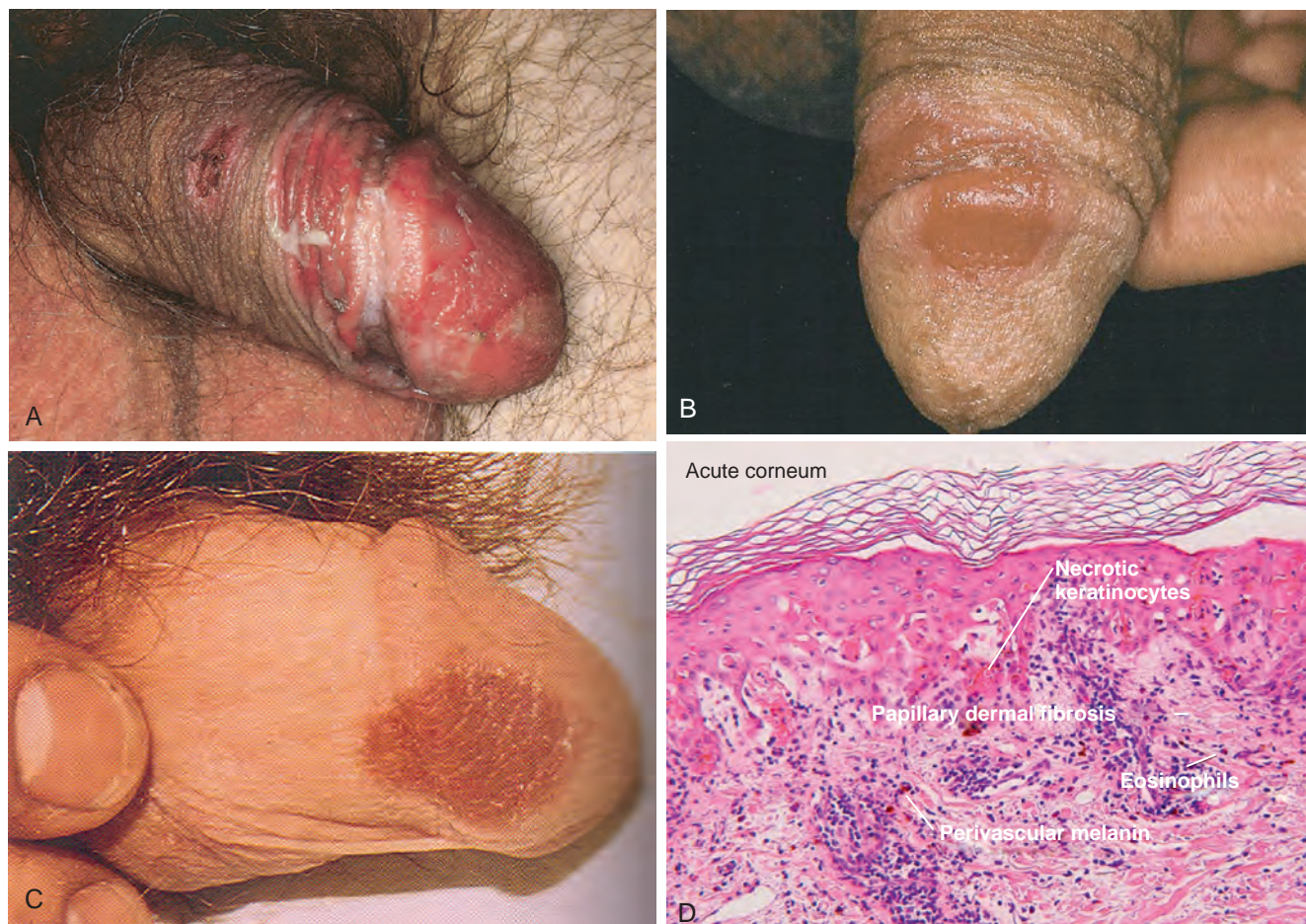


Figure 16-13. Fixed drug eruptions. A to C, Involvement of the penis. D, Histologic features include a normal stratum corneum with chronic changes in the superficial dermis including an eosinophilic infiltrate. (A, From Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993. p. 160; B, from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 345; C, from Habif TP. *Clinical dermatology*. Edinburgh: Mosby; 2004. p. 492; D, from Elston DM, Ferringer T. *Dermatopathology*. Edinburgh: Saunders; 2009. p. 149.)

first few months of life or postpuberty, when sebaceous glands are active. Commonly affected areas include the scalp, eyebrows, nasolabial folds, ears, and chest, although the anus, glans penis, and pubic areas may also be involved (Margolis, 2002). Circumcision may be somewhat protective against the development of SD. In one study of 357 patients, the risk of developing penile SD was 2.5 times greater in the uncircumcised state (Mallon et al, 2000).

Adult SD includes a chronic relapsing course (Webster, 1991). This condition is particularly common in patients with Parkinson disease, and up to 83% of acquired immunodeficiency syndrome (AIDS) patients may manifest SD (Froschl et al, 1990; Gupta and Bluhm, 2004). Particularly in immunosuppressed individuals, SD may involve a significant proportion of the body surface area. Extensive and/or severe SD should raise concerns for possible underlying HIV infection (Fritsch and Reider, 2003). SD may be pruritic, and differentiation from psoriasis may occasionally be problematic. Unlike psoriasis, however, SD rarely involves the nails and tends to have a thinner associated scale.

Controversy concerning the etiology of SD revolves around a possible autoimmune response to a component of normal skin flora, the yeast *Malassezia furfur* (*Pityrosporum ovale*). Although *M. furfur* can be isolated from the lesions of SD, the number of organisms is only about twice that observed in normal control skin (Nenoff et al, 2001). Likewise, severely SD-affected HIV patients do not harbor more organisms than HIV patients who do not manifest

SD (Pechere et al, 1999). Another factor potentially linked to SD is an elevated level of triglycerides and cholesterol at the skin surface (Fritsch and Reider, 2003).

Creams or foams containing topical antifungals (i.e., ketoconazole) are the mainstay of SD treatment on the body and include a 75% to 90% response rate (Faergemann, 2000; Fritsch and Reider, 2003; Elewski et al, 2007). For hair-bearing areas, "antidandruff" shampoos containing zinc, salicylic acid, selenium sulfide, tar, ciclopirox olamine, or 1% to 2% ketoconazole are effective (Margolis, 2002; Squire and Goode, 2002). Because of the chronic and relapsing nature of SD, treatment often must be repetitive and prolonged. Low-potency topical corticosteroids may play a role during the initial treatment of severe cases, but they should not be the primary mode of treatment for this condition because of the potential for local steroid side effects.

VESICOBULLOUS DISORDERS

Vesicobullous disorders are uncommon conditions often characterized by autoimmune damage to the epidermis or basement membrane (Box 16-3). Although intact blisters may be found on the groin and suprapubic skin per se, the rupture of vesicles and bullae on the genitalia may only leave behind residual erosions (Margolis, 2002).

BOX 16-3 Differential Diagnosis of Vesicobullous Disorders

Bullous pemphigoid
 Pemphigus vulgaris
 Pemphigus foliaceus
 Zoon balanitis
 Behçet syndrome
 Contact dermatitis
 Dermatitis herpetiformis
 Porphyria cutanea tarda
 Herpes zoster
 Herpes simplex
 Lymphangioma circumscriptum
 Impetigo
 Fixed drug eruption
 Factitial
 Innocent trauma
 Benign familial pemphigoid (Hailey-Hailey disease)

From Margolis DJ. Cutaneous disease of the male external genitalia. In: Walsh PC, editor. Campbell's urology. Philadelphia: Saunders; 2002.

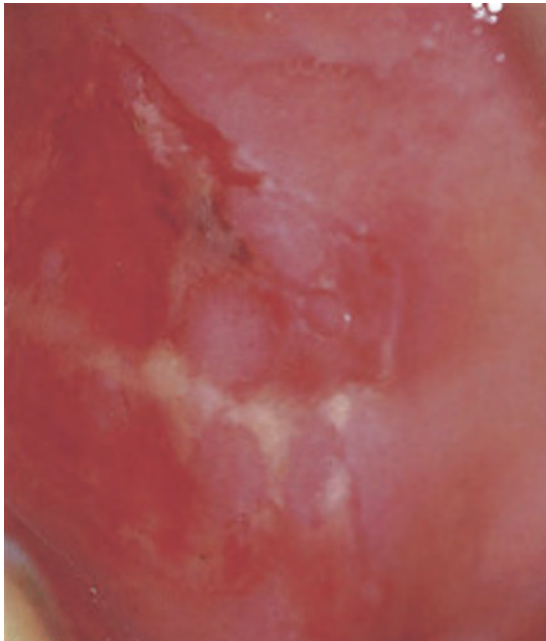


Figure 16-14. Characteristic painful oral mucosal erosions in pemphigus vulgaris. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 455.)

Pemphigus Vulgaris

Pemphigus is a family of autoimmune blistering diseases characterized by intraepidermal blisters resulting from the loss of keratinocyte cell-cell adhesion (Martel and Joly, 2001). These blisters are located in the deep epidermis close to the basal cell layer. The proposed immunopathology includes the development of autoantibodies directed against keratinocyte cell surface markers and desmosomes (Amagai et al, 1996; Zhou et al, 1997; Joly et al, 2000).

Almost all pemphigus patients will exhibit painful oral mucosal erosions and more than half will experience cutaneous blisters that may involve the genitalia. Characteristic oral lesions are therefore an important clue to the diagnosis (Fig. 16-14). The

cutaneous blisters are thin-walled and easily broken to leave behind a painful erosion. The loss of epidermal cohesion seen in pemphigus leads to the characteristic Asboe-Hansen sign: spreading of fluid under the adjacent normal-appearing skin away from the direction of pressure on the blister (Amagai, 2003). **In severe cases without appropriate treatment, pemphigus may lead to fatal septicemia as a result of the loss of the epidermal barrier function of large areas of affected skin.** Treatment for pemphigus traditionally depends on systemic corticosteroids, although minimization of steroid dose is an important goal to limit side effects. The addition of immunosuppressive agents such as azathioprine, cyclophosphamide, and mycophenolate mofetil may be beneficial because of their corticosteroid-sparing effect (Amagai, 2003). In recent years, the use of rituximab as monotherapy (1000 mg administered intravenously on days 1 and 15; repeated in 1 month if necessary) has gained considerable support because of high efficacy rates (>70% with a single cycle) and low relapse rates (22% at 8 to 12 months) (Leshem et al, 2013). The infusion of intravenous immunoglobulin may also prove effective and presents an inherent advantage of lowering infectious complication rates (Ruocco et al, 2013). The management of pemphigus is difficult and should always be performed in concert with a dermatologist or a rheumatologist who has experience with this disease.

Bullous Pemphigoid

Bullous pemphigoid (BP) is a subepidermal blistering disease that is more common in men and generally afflicts patients older than 60 years of age (Rzany and Weller, 2001). There is enrichment for specific HLA class II alleles in BP patients as compared to normal controls (Delgado et al, 1996), supporting an autoimmune mechanism of pathogenesis. In BP, autoantibodies against specific proteins involved in cell-cell adhesion (BP180, BP230) are present. These proteins are components of hemidesmosomes, which are structures that mediate epidermal-stromal adhesion. Binding of autoantibodies to these structures leads to complement activation and a cascade of events resulting in tissue damage, epidermal-dermal separation, and blister formation (Kitajima et al, 1994; Lin et al, 1997).

The clinical presentation of BP can be highly variable. It generally begins with a nonbullous phase characterized by severe itching and nonspecific skin findings. As the disease moves into the bullous phase, vesicles and blisters appear on normal skin or, most characteristically, on areas containing confluent erythematous plaques. The blisters are tense, tend to form on flexor surfaces, and may involve the inner thighs and genitalia (Fig. 16-15A). Mucous membranes may also be involved, although this is less common than in pemphigus. **The diagnosis is made by a combination of clinical, histologic, and, often most importantly, immunohistochemical features such as the deposition of IgG antibodies along the basement membrane (Fig. 16-15B) (De Jong et al, 1996).** Treatment of BP in the United States is traditionally similar to that described for pemphigus, with systemic corticosteroids and various immunosuppressives playing primary roles (Kirtschig and Khumalo, 2004). However, based on the results of several randomized comparative studies, the Europeans favor the use of superpotent topical steroids for the management even of extensive pemphigoid (Joly et al, 2002, 2009). Certainly, treatment of limited-extent pemphigoid should rely heavily on topical, rather than systemic, corticosteroids. For treatment-resistant cases, oral methotrexate, intravenous immunoglobulin, plasmapheresis, or intravenous rituximab may be beneficial (Hatano et al, 2003; Lee et al, 2003; Ruetter and Luger, 2004; Wetter et al, 2005; Shetty and Ahmed, 2013).

Dermatitis Herpetiformis and Linear IgA Bullous Dermatitis

Both of these entities are blistering autoimmune skin diseases associated with the deposition of IgA antibodies at the basement membrane.

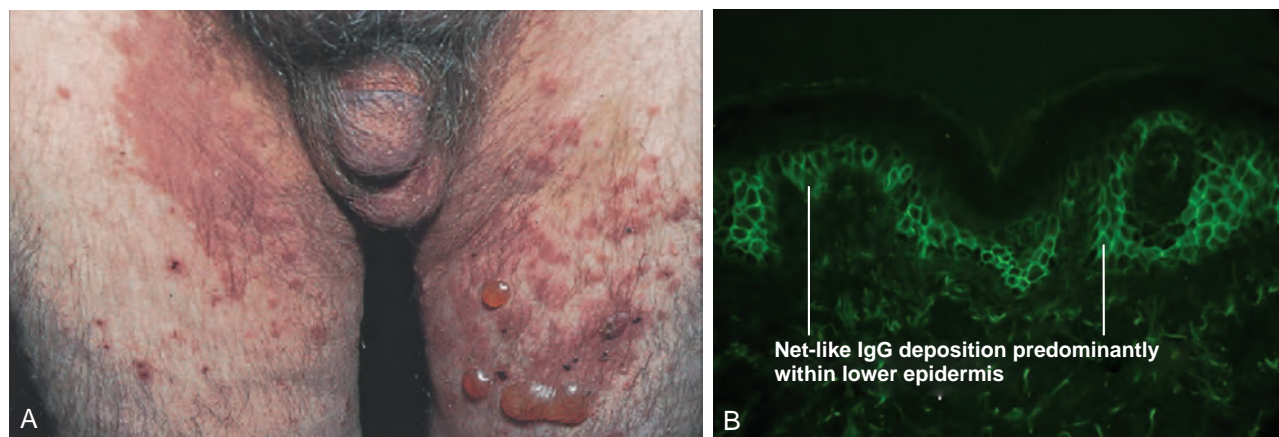


Figure 16-15. Bullous pemphigoid (BP). A, Involvement of the inner thighs. Note the confluent plaques and tense blisters in the inguinal area. B, Direct immunofluorescence of BP showing deposition of autoantibodies (IgG) at the dermoepidermal junction. (A, From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 465); B, from Elston DM, Ferringer T. *Dermatopathology*. Edinburgh: Saunders; 2009. p. 169.)

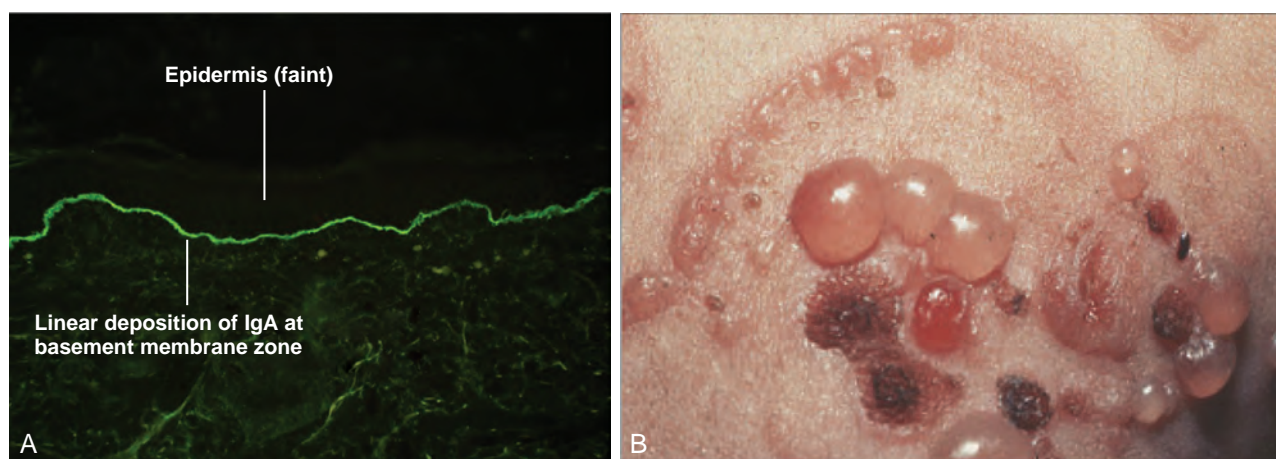


Figure 16-16. Linear IgA bullous dermatosis. A, Direct immunofluorescence showing linear deposition of IgA along the dermoepidermal junction. B, Typical circumferential and linear patterns of vesicles. (A, From Elston DM, Ferringer T. *Dermatopathology*. Edinburgh: Saunders; 2009. p. 170; B, from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 485.)

Dermatitis herpetiformis is a cutaneous manifestation of celiac disease and is generally associated with gluten sensitivity (Karpati, 2004). It is most common in people of northern European origin. There is a close association of dermatitis herpetiformis with certain HLA class II DQ2 alleles (DQA1*0501, DQB1*02) (Reunala, 1998). Pruritic plaques, papules, and vesicles in a symmetrical distribution characterize dermatitis herpetiformis. These vesicles may form “herpetiform” groups on an erythematous base. Patients may also complain of pain and burning over the lesions. Diagnosis can be confirmed by biopsy and direct immunofluorescence, which shows a granular pattern of IgA deposition at the basement membrane. Treatment includes the use of dapsone and a strict gluten-restricted diet (Frodin et al, 1981; Andersson and Mobacken, 1992).

Linear IgA bullous dermatosis (LABD), in contrast, is not associated with celiac disease. As the name implies, a linear pattern of antibody deposition at the basement membrane is found on immunohistochemistry in LABD (Fig. 16-16). Characteristic clinical features include vesicles and bullae arranged in a combination of circumferential and linear orientations. Treatment with either sulfapyridine or dapsone is usually effective in controlling LABD, and long-term spontaneous remission rates of 30% to 60% have been described (Wojnarowska et al, 1988). In contrast to both

pemphigus and BP, neither dermatitis herpetiformis nor LABD commonly affects genital or perigenital skin.

Hailey-Hailey Disease

Hailey-Hailey disease is an autosomal dominant blistering dermatosis related to various mutations in the ATP2C1 gene. The ATP2C1 gene encodes the protein product hSPCA1, which is a $\text{Ca}^{2+}/\text{Mn}^{2+}$ transporter. This protein is responsible for calcium homeostasis in the Golgi apparatus required for the post-translational processing of junctional proteins involved in proper epidermal cell-cell adhesion. Hailey-Hailey disease usually develops within the second or third decade of life (Burge, 1992). It has a characteristic predilection for the intertriginous areas including the neck, axillae, groin, and perianal region (Fig. 16-17). In women, disease in the inframammary folds is common although vulvar disease is unusual (Wieselthier and Pincus, 1993). Symptoms include an unfortunate combination of pruritus, pain, and a foul odor. As heat and sweating exacerbate the condition, Hailey-Hailey disease tends to worsen dramatically during the summer months (Burge, 1992). Skin findings include confluent areas of fragile vesicles and blisters, which form as a result of the



Figure 16-17. Genital presentations of Hailey-Hailey disease. A, The vulva and groin are covered in a vesicular eruption that has become confluent and macerated. B, Erythematous plaque with maceration of the inguinal canal and scrotum. (A, From du Vivier A. *Atlas of clinical dermatology*. London: Churchill Livingstone; 2002. p. 688; B, from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 830.)



BOX 16-4 Differential Diagnosis of Ulcers

Syphilis
Chancroid
Herpes simplex
Crohn disease
Aphthous ulcer
Behçet disease
Granuloma inguinale
Genital bite wound
Lymphogranuloma venereum
Factitial dermatitis
Wegener granulomatosis
Leukocytoclastic vasculitis
Pyoderma gangrenosum

From Margolis DJ. Cutaneous disease of the male external genitalia. In: Walsh PC, editor. *Campbell's urology*. Philadelphia: Saunders; 2002.

aberrant keratinocyte cell adhesion. Lesions may be confined to the axilla or groin, and superinfection with yeast, bacteria or herpes simplex virus may compound the problem. Histologic examination may be helpful in differentiating Hailey-Hailey disease from impetigo, pemphigus, intertrigo, and Darier disease (Margolis, 2002). Treatment includes wearing lightweight, breathable clothing to avoid friction and sweating. Lesions may respond to topical or intralesional corticosteroids, with the caveats mentioned previously about the use of these agents on intertriginous skin. For disease that is resistant to medical therapy, wide excision and skin grafting have been effective, as have local ablative techniques such as dermabrasion, photodynamic therapy, and CO₂ or erbium-YAG laser vaporization (Hamm et al, 1994; Christian and Moy, 1999; Hohl et al, 2003). An innovative approach to this disorder is to inject infected areas with botulinum toxin type A; this therapy greatly reduces sweating and thereby reduces disease severity (Bessa et al, 2010).

NONINFECTIOUS ULCERS

Genital ulcers can be a result of both infectious and noninfectious causes (Box 16-4).

Aphthous Ulcers and Behçet Disease

Aphthous ulcers are small, painful erosions that commonly involve the oral cavity (so-called canker sores) but they can occasionally be present on the genitalia. When oral and genital aphthous ulcers coexist, the clinician should seriously consider the diagnosis of Behçet disease (BD). BD is a generalized relapsing and remitting ulcerative mucocutaneous disease that likely involves a genetic predisposition and an autoimmune mode of pathogenesis (Sakane, 1997; Mendes et al, 2009). Although many genetic loci have been implicated, perhaps the strongest association is with HLA B51. Oxidative stress related to the overproduction of superoxide radicals by neutrophils has also been implicated in the development of this condition (Freitas et al, 1998; Najim et al, 2007). However, a large number of other etiopathogenetic mechanisms have been proposed and supported by experimental findings (such as IL-10 gene mutations) (Remmers et al, 2010). The notable variability in efficacy for any of the therapeutic interventions enumerated later suggests that pathways of inflammation in BD are unlikely to be uniform. BD has a high prevalence in Turkey (80 per 100,000), Israel (15 per 100,000), and Japan (10 to 12 per 100,000), but it is quite rare in the United States (0.12 to 5.0 per 100,000) (Arbesfeld and Kurban, 1988; Calamia et al, 2009). Affected individuals may also suffer from epididymitis, thrombophlebitis, aneurysms (particularly of the pulmonary artery), and gastrointestinal, neurologic, and arthritic problems (Koc et al, 1992; Tuzun et al, 1997; Cetinel et al, 1998; Krause et al, 1999; Aykutlu et al, 2002; Margolis, 2002). BD occurs with roughly similar frequency among males and females, although men typically experience a more severe course.

Mucocutaneous lesions of the oral cavity and genitalia (Fig. 16-18) and ocular involvement (uveitis) form a triad of clinical features in BD. The genital lesions are larger and generally more painful than the oral lesions. Optic involvement occurs in 90% of cases and may lead to blindness (Moschella, 2003). The Behçet International Study Group has defined the diagnosis as recurrent oral ulceration plus any two of the following: recurrent genital ulceration, eye lesions, cutaneous lesions, and skin sensitivity to needle puncture (pathergy test) (Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease, 1990). Other causes for genital ulceration, however, including simple aphthous ulcers, primary syphilis, herpes simplex, and chancroid, must be considered before a diagnosis of BD is made (Margolis, 2002). While using these accepted criteria, it should be noted that oral ulceration is the most sensitive lesion and genital ulceration is the most specific lesion. The latter therefore is the most clinically useful



Figure 16-18. Scrotal (A), perianal (B), and oral (C) ulcers seen in Behçet disease. (A, From du Vivier A. *Atlas of clinical dermatology*. London: Churchill Livingstone; 2002. p. 713; B and C, from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 419.)

lesion in diagnosing BD according to this schema. Nonetheless the diagnosis of BD depends exclusively on the aggregate clinical findings, as there are no specific laboratory, radiologic, genetic, or histologic findings that conclusively confirm this diagnosis (Hatemi et al, 2013).

The clinical course of BD is protean, and randomized controlled trials in support of specific therapy are currently limited (Kaklamani and Kaklamanis, 2001). A wide range of topical and systemic agents has been applied to treat BD with variable success, including corticosteroids, dapsone, colchicine, immunosuppressants, 5-aminosalicylic acid (5-ASA) derivatives, cyclosporine A, and TNF- α inhibitors (especially infliximab and adalimumab) (Moschella, 2003; Kose et al, 2009). It has become clear that earlier and more aggressive treatment of BD-associated significant organ involvement with immunosuppressives and biologics has improved the overall outcome. Rheumatologic consultation is advised when this diagnosis is suspected.

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a rare ulcerative skin disease associated with systemic illnesses including inflammatory bowel disease, arthritis, collagen vascular disease, chronic active hepatitis, HIV infection, and myeloproliferative disorders (Moschella, 2003). It most commonly affects women between the second and fifth decade of life and likely has an autoimmune pathogenesis given its association with other autoimmune diseases. Between 20% and 50% of cases, however, are idiopathic. The annual incidence of PG in the United States is about 1 case per 100,000 individuals.

The classic morphologic presentation of PG is painful cutaneous and mucous membrane ulceration, often with extensive loss of tissue and a purulent base (Fig. 16-19). Although unusual, PG can

involve the penis, scrotum, vulva, and peristomal sites (Cairns et al, 1994). As was the case in BD, no specific diagnostic laboratory test or histopathologic feature is pathognomonic for PG, although a history of an underlying systemic disease may raise suspicion. Aside from ulcerative STDs, the differential diagnosis of penile PG includes calciphylaxis, BD, necrotizing fasciitis, cutaneous metastatic Crohn disease, deep fungal infection, pemphigus vegetans, Fournier gangrene, neoplastic conditions, erosive LP, trauma, and factitious damage (Badgwell and Rosen, 2006). Treatment includes a combination of local and systemic corticosteroid therapy with or without adjunctive immunosuppressants (i.e., cyclosporine) (Chow and Ho, 1996). Minocycline, sulfasalazine, and thalidomide have been used in combination with corticosteroids in a small number of cases. Genital PG may also be amenable to topical treatment with calcineurin inhibitors (Lally et al, 2005).

Traumatic Causes

Cutaneous lesions of the genitalia, including ulceration, can be caused by local trauma, which should be included in the differential diagnosis. This can be either accidental ("innocent trauma") or self-inflicted ("factitial dermatitis" or "dermatitis artefacta"). Accidental injuries may be a result of trauma during sexual practices (including genital bite wounds), ornamentation (i.e., piercing), or unusual hygiene practices (i.e., cleaning) (Margolis, 2002). Factitial dermatitis is a psychocutaneous disorder in which the individual self-inflicts cutaneous lesions usually for an unconscious motive or because of an underlying mental illness (Fig. 16-20). Factitial lesions are occasionally produced deliberately with the hope of some secondary gain (such as product liability litigation). An association between factitial dermatitis and borderline personality disorder appears to exist (Koblentzer, 2000). Other disorders to be considered include Munchausen syndrome by proxy, body



Figure 16-19. Pyoderma gangrenosum involving the inner thigh of a woman with rheumatoid arthritis (A) and the penis and scrotum (B). (A, From du Vivier A. *Atlas of clinical dermatology*. London: Churchill Livingstone; 2002. p. 387; B, from Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993. p. 330.)



Figure 16-20. Factitial ulcer of the scrotum caused by repeated picking at the scrotal skin.

dysmorphic disorder, and malingering, if secondary-gain issues exist. Although rare, factitial dermatitis should always be considered in the differential diagnosis of unusual genital lesions, including oddly configured erosions and ulcerations (Verma et al, 2012).

INFECTIONS AND INFESTATIONS

Sexually Transmitted Diseases

STDs with genital cutaneous manifestations include lymphogranuloma venereum, granuloma inguinale, herpes simplex, chancroid, molluscum contagiosum, HPV, and syphilis (Fig. 16-21). These conditions are discussed in detail in Chapter 15.

Balanitis and Balanoposthitis

Balanitis is an inflammatory disorder of the glans penis. When the process involves the preputial skin in uncircumcised men, it is termed balanoposthitis. In children, bacterial infections are the predominant cause. In adult men, the cause may be intertrigo, ICD,

local trauma, or candidal and bacterial infections (Fig. 16-22). Treatment includes removal of irritating agents, improved hygiene, topical antibiotics and antifungals, and occasionally short courses of low-potency topical corticosteroids (Margolis, 2002). When treatment fails, the differential should include neoplastic diseases, Zoon balanitis, psoriasis, and alternative infectious agents such as HPV (Wikstrom et al, 1994). Balanoposthitis tends to occur in patients with phimosis and circumcision may be curative in select recurrent cases. Balanoposthitis may also result from bacterial superinfection in the setting of poor hygiene and neutropenia (Manian and Alford, 1987).

Cellulitis and Erysipelas

Cellulitis is an infection of the deep dermis and subcutaneous tissues most commonly caused by gram-positive organisms (*S. pyogenes* and *S. aureus*) (Lewis, 1998). In immunocompetent individuals, organisms usually gain entry to the site of infection through a break in the skin barrier. In immunocompromised patients, a blood-borne route of infection is more common. Systemic signs of illness include fever, chills, and general malaise. Local signs include erythema (rubor), warmth (calor), pain (dolor), and swelling (tumor) at the site with indistinct borders (Fig. 16-23). Treatment includes systemic antibiotics with activity against *S. pyogenes* and *S. aureus* species. The clinician may be forced to rely on known local antimicrobial sensitivity patterns, because obtaining satisfactory material for culture may be difficult. In cases associated with diabetes, mixed flora may be present and antibiotic coverage should be broadened. Marking the zone of cellulitis at the onset of therapy is an important step to allow progression and resolution of cellulitis to be monitored during therapy.

Erysipelas is a superficial bacterial skin infection limited to the dermis with lymphatic involvement. This disease commonly occurs at the extremes of age and often involves the face. In contrast to the cutaneous lesion of cellulitis, erysipelas generally exhibits a raised and distinct border at the interface with normal skin. The causative organism is usually *S. pyogenes*.

Fournier Gangrene (Necrotizing Fasciitis of the Perineum)

Fournier gangrene (FG) is a potentially life-threatening progressive infection of the perineum and genitalia (Morpurgo and Galandiuk, 2002). In the genital region, most cases of FG are caused by mixed



Figure 16-21. Genital lesions associated with sexually transmitted diseases. A, Herpes simplex virus. B, Molluscum contagiosum. C, Syphilitic chancre. D, Granuloma inguinale. E, Chancroid. F, Lymphogranuloma venereum. G, Condyloma accuminata. (From Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993.)

bacterial flora, which include gram-positive, gram-negative, and anaerobic bacteria. *Escherichia coli*, *Bacteroides* spp., *S. pyogenes*, and *S. aureus* are common etiologic pathogens. Risk factors for developing FG include underlying alcoholism, diabetes, cancer and malnutrition, advanced age, recent urogenital or colorectal instrumentation or trauma, and preexisting peripheral vascular disease. However, group A streptococcal necrotizing fasciitis can occur in healthy immunocompetent individuals.

The hallmark of FG is a rapid progression from the signs and symptoms of cellulitis (erythema, swelling, and pain) to blister formation, to clinically visible ischemia, and ultimately to foul-smelling necrotic lesions (Fig. 16-24). Infection may spread along fascial planes and hence the exterior skin findings may represent only a small proportion of the underlying infected and necrotic tissue. The diagnosis of FG is a surgical emergency, as progression from genitalia to perineum to abdominal wall may occur



Figure 16-22. Candidal balanoposthitis. (From Korting GW. *Practical dermatology of the genital region*. Philadelphia: Saunders; 1981. p. 159.)



Figure 16-23. Penoscrotal cellulitis. (From Korting GW. *Practical dermatology of the genital region*. Philadelphia: Saunders; 1981. p. 37.)

extremely rapidly (often within hours). Spread of tissue infection is accompanied by an ever-increasing risk of bacterial septicemia, usually the eventual cause of death. The exclusion of FG therefore should be a priority during every consultation for soft tissue infection of the genitalia. Pain out of proportion to

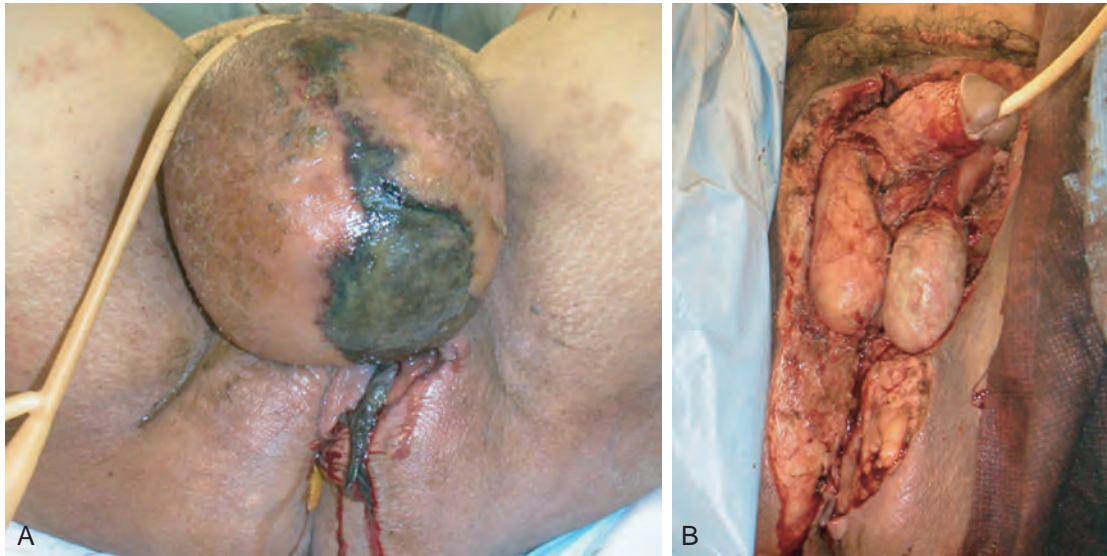


Figure 16-24. Fournier gangrene of the scrotum. A, Surface appearance of scrotum and perineum showing area of frank necrosis. B, Extent of soft tissue debridement required to achieve margins of viable tissue. Note that the testes within their tunica vaginalis compartment are spared.

the visible extent of infection should raise suspicion for FG. The skin may also exhibit a grayish cast or fetid odor uncharacteristic of uncomplicated genital cellulitis. Imaging of the genitalia with plain radiographs, computed tomography, and/or bedside ultrasonography (Amendola et al, 1994; Avery and Scheinfeld, 2013) may demonstrate gas bubbles within the tissue, although the delay associated with imaging should not postpone surgical intervention in obvious cases.

Treatment involves a combination of broad-spectrum antibiotics and extensive surgical debridement to margins of healthy bleeding tissue. These patients will often require a second-look operation after 24 to 48 hours to exclude further disease progression (Gurdal et al, 2003). During surgical debridement for scrotal FG, the testicles and other structures within the tunica vaginalis can almost always be spared, although loss of tissue in the abdominal wall may be extensive because of bacterial spread along fascial planes. The indications for adjunctive hyperbaric oxygen therapy in FG remain controversial, although several groups have reported favorable results (Dahm et al, 2000; Eke, 2000; Jallali et al, 2005). There may also be potential benefit to the use of vacuum-assisted closure devices in FG (Czymek et al, 2009). However, despite aggressive modern management, the mortality of FG may be as high as 16% to 40% (Dahm et al, 2000; Eke, 2000; Blume et al, 2003; Yenyol et al, 2004; Sorensen et al, 2009). A number of different numeric scoring scales have been applied to FG in an attempt to predict proactively the patients who are at the highest risk for mortality and who should receive the most aggressive intervention. These include the FG Severity Index and the Uludag FG Severity Index, as well as the more general Age-Adjusted Charlson Comorbidity Index (ACCI) and the recently introduced surgical Apgar Score (sAPGAR). A study verified that *all* of these scoring systems are valid methods for assessing patients in the setting of FG, and adoption of one may assist the clinician in making therapeutic decisions (Vyas et al, 2013).

Among patients who survive an episode of FG, there most likely will be ongoing disability and reduced functionality for months to years. Sexual dysfunction is quite common (~65%) (Czymek et al, 2013). Therefore FG survivors should expect to receive long-term care from a variety of specialists.

Folliculitis

Folliculitis is a common disorder characterized by perifollicular pustules on an erythematous base (Kelly, 2003). It occurs most



Figure 16-25. Pseudomonal folliculitis caused by the use of a hot tub. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 554.)

frequently in heavily hair-bearing areas such as the scalp, beard, axilla, groin, and buttocks and can be exacerbated by local trauma from prolonged occlusion (e.g., truck drivers), shaving, rubbing, or clothing irritation (Margolis, 2002). Patients may complain of pruritus or pain over the area; conversely, symptoms may be entirely absent. Cultures are generally negative, although a variety of infectious organisms have been associated with folliculitis including *S. aureus*, *Pseudomonas* spp., fungi, and herpes simplex virus. Folliculitis has also been associated with the use of contaminated hot tubs and swimming pools, with the offending organism usually *Pseudomonas aeruginosa* (Fig. 16-25) (Gregory and Schaffner, 1987; Rolston and Bodey, 1992). Treatment for folliculitis includes good hygiene, removal of offending irritants, and appropriate topical or systemic antiviral, antibiotic, or antifungal agents. The results of a

surveillance study indicate that 96% of *P. aeruginosa* isolates tested from swimming pools and hot tubs were multidrug resistant (Lutz and Lee, 2011). These results may have important implications for immune-suppressed individuals, where infection with multidrug-resistant *P. aeruginosa* has a greater potential impact. Failure to respond to conservative measures should lead to lesion culture with concomitant antimicrobial susceptibility testing.

Furunculosis

Both furuncles and abscesses are walled-off collections of pus. Although abscesses can occur anywhere on the body, a furuncle is by definition associated with a hair follicle. Furuncles tend to occur in areas prone to minor trauma including the groin and buttocks (Fig. 16-26). *S. aureus* is the most common causative organism although anaerobes may be present. Risk factors include diabetes mellitus, obesity, poor hygiene, and immunosuppression (Brook and Finegold, 1981). Warm compresses may be beneficial, and larger lesions may require incision and drainage, as for any abscess. When there is associated cellulitis, a systemic antibiotic with activity against staphylococci should be administered. In today's environment of methicillin-resistant staphylococci, coverage for such organisms is advisable if they are prevalent within the clinician's community.

Hidradenitis Suppurativa (Acne Inversa)

Hidradenitis suppurativa (HS) is a chronic disease of apocrine gland-bearing skin with a predilection for the axillae and anogenital regions (Kelly, 2003; Alikhan et al, 2009). The condition generally begins after puberty and a familial form with an autosomal dominant pattern of inheritance has been described (Von Der Werth et al, 2000). Originally believed to be a disease of apocrine glands, HS is now thought to be an epithelial disorder of hair follicles (Jansen et al, 2001). Although superinfection of HS lesions may occur, bacterial infection does not appear to be the primary initiator. During the pathogenesis of HS, hair follicles become plugged and swollen. Rupture of follicular contents (including bacteria and keratin) into the surrounding dermis initiates a marked inflammatory response with the formation of abscesses and sinus tracts (Slade et al, 2003).



Figure 16-26. A large furuncle located on the buttocks. (From Habib TP. Clinical dermatology: Edinburgh: Mosby; 2004. p. 284.)

The clinical features of HS include painful inflammatory nodules and sterile abscesses developing in the axillae, groin, perianal, and inframammary areas (Fig. 16-27) (Kelly, 2003). With time, draining sinus tracts and hypertrophic scars develop. Serious complications of HS can occur, including hypoproteinemia, secondary amyloidosis, the development of fistulae to the urethra (Gronau and Pannek, 2002), bladder, peritoneum and rectum (Nadgir et al, 2001), and SCC in areas of heavy scarring (Altunay et al, 2002; Rosenzweig et al, 2005).

Treatment of HS includes improvement in hygiene, weight reduction, and efforts to minimize friction and moisture in affected areas (i.e., loose undergarments, absorbent powder) (Kelly, 2003). No single therapeutic intervention is universally effective. Topical clindamycin or the combination of oral clindamycin or minocycline with oral rifampicin may be beneficial for some patients (Gener et al, 2009). In a double-blind randomized trial, systemic therapy with tetracycline was no more effective than topical clindamycin in HS (Jemec and Wendelboe, 1998). Other oral agents that sometimes prove beneficial include dapsone (50 to 200 mg/day), zinc (40 to 80 mg/day elemental zinc), retinoids (acitretin 25 to 50 mg/day or isotretinoin 1 mg/kg/day), cyclosporine (4 mg/kg/day), and hormone blockers (spironolactone and oral contraceptives in women and finasteride and dutasteride in men) (Scheinfeld, 2013a). Systemic corticosteroids may improve HS, but relapse is the rule after cessation of therapy (Slade et al, 2003). Lithium may exacerbate HS or limit its response to conventional medical therapy (Gupta et al, 1995). Although recurrent incision and drainage of HS lesions are discouraged, wide and deep excision with skin grafting has been effective (Rompel and Petres, 2000; Bocchini et al, 2003). A variety of new approaches, including the use of the CO₂ and Nd:YAG lasers to treat HS, are under investigation (Lapins et al, 1994; Madan et al, 2008; Tierney et al, 2009). Off-label administration of TNF- α blockers (particularly subcutaneous adalimumab: 40 mg/wk) has proven variably effective in the management of HS in select patients when surgery is simply not feasible (Shuja et al, 2010).

Corynebacterial Infection (Trichomycosis Axillaris and Erythrasma)

Trichomycosis axillaris is a superficial bacterial infection of axillary and pubic hair caused by corynebacteria. Yellow, red, or black nodules are visible on the hair shafts (Fig. 16-28) and there is frequently a characteristic odor (Blume et al, 2003). There is an association with hyperhidrosis (Margolis, 2002). The differential diagnosis includes infestation with pediculosis pubis or fungal infection (piedra) (Avram et al, 1987), although examination with magnification can generally distinguish trichomycosis axillaris from these conditions. Shaving can provide immediate improvement, and antibacterial soaps may prevent further infection (Blume et al, 2003). For pubic trichomycosis axillaris, clindamycin gel, bacitracin, and oral erythromycin have also proven effective (Bargman, 1984; Blume et al, 2003).

Erythrasma is a *Corynebacterium minutissimum* infection of the skin that results in sharply bordered, light red to dark brown, scaling patches in moist areas, particularly the groin and axilla. These lesions may be pruritic or asymptomatic and may be confused with dermatophyte infection (tinea cruris) (Sindhuphak et al, 1985). Under a Wood light, the lesions show a characteristic bright coral-red fluorescence (see Fig. 16-28) (Halprin, 1967). Effective treatments include antibacterial soaps, topical aluminum chloride, topical clindamycin 1% solution or gel, miconazole 1% cream, and oral erythromycin (500 to 1000 mg/day) (Cochran et al, 1981; Holdiness, 2002).

Ecthyma Gangrenosum

Ecthyma gangrenosum is a rare cutaneous manifestation of pseudomonal septicemia that presents most commonly on the



Figure 16-27. Hidradenitis suppurativa. A, Characteristic painful papules and draining sinus tracts. B, Histology shows follicular plugging and connection to a dilated apocrine duct. C and D, Examples of severe genital involvement of hidradenitis, which would make surgical management difficult. (A, From du Vivier A. *Atlas of clinical dermatology*. London: Churchill Livingstone; 2002. p. 712; B, from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Saunders; 2008. Fig. 39.13.)

anogenital area in debilitated, immunosuppressed, or neutropenic patients. The lesions of ecthyma gangrenosum are tender grouped erythematous macules that may progress to form bullae or rupture to produce a gangrenous ulcer covered by a thick, black eschar (Fig. 16-29) (Blume et al, 2003). On histologic examination, necrotizing vasculitis and gram-negative organisms are present. The differential diagnosis includes PG, necrotizing vasculitis, cryoglobulinemia, and septic emboli containing other organisms including *Candida*, *Aspergillus*, *Citrobacter*, *E. coli*, *Aeromonas hydrophila*, and *Fusarium* (Altwegg and Geiss, 1989; Martino et al, 1994; Gucluer et al, 1999; Reich et al, 2004). Consistent with the underlying sepsis, ecthyma gangrenosum carries a poor prognosis and immediate treatment with intravenous antipseudomonal antibiotics is

indicated. Wound debridement may also be necessary (Collini et al, 1986).

Genital Bite Wounds

Following deliberate or accidental bite wounds to the genitalia, a normal component of the human oral flora, *Eikenella corrodens*, may be implanted into genital skin. This results in the rapid development of extremely painful, necrotic ulcerations at the bite site(s) (Fig. 16-30) (Rosen and Conrad, 1999; Rosen, 2005). The rapidity of ulceration, extraordinary degree of discomfort, and a history of traumatic orogenital contact help distinguish this type of infection from the more common STDs and other genital ulcers. The



Figure 16-28. Corynebacterial infections of the skin. A, Trichomycosis axillaris. B and C, Erythrasma under white light (B) and Wood lamp (C) showing coral-red fluorescence. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003.)

treatment is high-dose oral amoxicillin-clavulanate (1500 mg/day) until healing occurs.

Candidal Intertrigo

Fungal infection of macerated skin folds can occur with candidal species and involve the finger webs and intertriginous areas. Affected pruritic skin is reddened and characteristic satellite lesions may be present (Fig. 16-31). The differential diagnosis includes dermatophyte infection (tinea cruris), pemphigoid, psoriasis, SD, and contact dermatitis (Margolis, 2002). Fungal forms (round yeast cells as well as elongate pseudohyphae) can be seen in scraped skin preparations after treatment with KOH, and culture is usually unnecessary. Daily topical treatment with any imidazole antifungal agent for at least 2 weeks is usually necessary for intertrigo, and oral antifungals (such as fluconazole 150 mg/day) are occasionally required (Cullin, 1977). Maneuvers to decrease moisture and skin maceration, such as the use of drying powders and loose clothing, may also help prevent relapse. Candida intertrigo may be a presenting sign of diabetes, and appropriate laboratory testing should be performed to rule this out as a predisposing condition.

Dermatophyte Infection

Dermatophytes are fungi of three genera (*Trichophyton*, *Microsporum*, *Epidermophyton*) that have the propensity to invade and grow within keratinized tissues such as the skin, hair, and nails. These fungi produce keratinases, which break down keratin and facilitate invasion (Viani et al, 2001). In addition, mannans in the cell wall of some dermatophytes produce immunoinhibitory effects (Dahl, 1994).

Tinea cruris is the term applied to dermatophyte infection of the groin and genital area and is commonly known as “jock itch.” More common in males than females, this condition is favored by hot, humid environments and concomitant dermatophyte infection of the feet (*tinea pedis*). Obesity may also be a significant risk factor (Scheinfeld, 2004). The inner thighs and inguinal region are the most commonly affected areas and the scrotum and penis are usually spared in men. However, isolated penile dermatophytosis has been well described (Pielop and Rosen, 2001). Conversely, significant scrotal involvement should raise suspicion for cutaneous candidiasis as an alternative diagnosis (Sobera and Elewski, 2003). Characteristic lesions in tinea cruris are sharply demarcated with a raised erythematous border

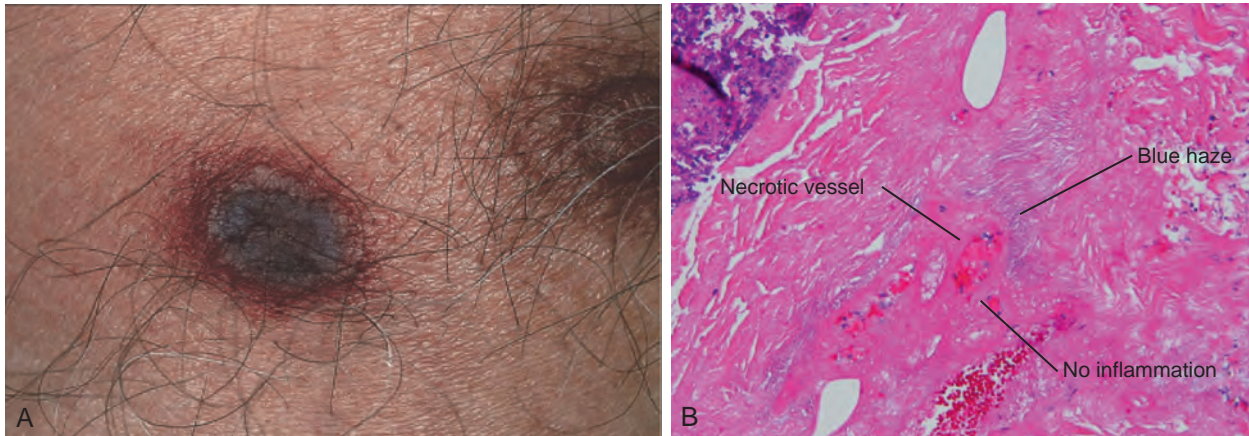


Figure 16-29. Ecthyma gangrenosum. A, Involvement on the chest wall. Note the necrotic center and erythematous border around the lesion. B, Histologically, necrotic vessels surrounded by a “blue haze” of organisms characterize ecthyma gangrenosum. (A, From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 1132; B, from Elston DM, Ferringer T. *Dermatopathology*. Edinburgh: Saunders; 2009. p. 263.)



Figure 16-30. Ulceration following a human bite wound to the penile shaft.



Figure 16-31. Candidal intertrigo with erythema, areas of tissue maceration, and satellite lesions. (From Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993. p. 318.)

(Fig. 16-32) and they may be intensely pruritic. A variety of disorders can mimic dermatophytes infection including SD, psoriasis, contact dermatitis and erythrasma. The diagnosis of fungal infection can be confirmed with skin scrapings and a KOH preparation. Culture is rarely required, as organisms are easily visualized microscopically.

Good hygienic practices can be beneficial in preventing recurrent disease, including wearing loose clothing, cleaning of contaminated garments, weight reduction, and the use of topical powders to keep the intertriginous areas dry (Sobera and Elewski, 2003). Topical antifungal preparations are the primary agents for treatment, with the powdered forms having the added benefit of drying moist areas. Care should be taken to treat only active disease and not the postinflammatory hyperpigmentation that can occur with recurrent chronic dermatophyte infection (Margolis, 2002). Systemic antifungals are rarely necessary to treat groin infection with dermatophytes. However, should this prove necessary, the current drug of choice is terbinafine in a dose of 250 mg/day for 1 week (Farag et al, 1994).

Infestation

Pediculosis pubis and scabies (*Sarcoptes scabiei*) are the most common infestations involving the genital region.

Infestation with the crab louse (*Phthirus pubis*) causes pediculosis pubis, a pruritic disorder of the genitalia, which may coexist with other STDs (Opaneye et al, 1993; Varela et al, 2003). In one study of adolescent males, patients with pediculosis pubis showed a risk of concomitant gonorrhea or chlamydial infection more than twofold higher than normal controls (Pierzchalski et al, 2002). Louse infestation is not limited to the genitals and may involve other hair-bearing areas such as the eyelashes, beard, and axillae (Meinking, 1999). The diagnosis is confirmed by



Figure 16-32. Dermato­phyte infection. A, *Tinea cruris* showing areas of postinflammatory hyperpigmentation and active infection at the border of the lesions. B, Histologically, fungal hyphae are localized within a compact stratum corneum layer. C, Potassium hydroxide preparation from a scraping showing fungal forms. (A, From Callen JP, Greer DE, Hood AF, et al. Color atlas of dermatology. Philadelphia: Saunders; 1993. p. 318; B and C, from Elston DM, Ferringer T. Dermatopathology. Edinburgh: Saunders; 2009. p. 275.)



Figure 16-33. Pediculosis pubis. Several crab lice are visible. (From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 338.)

identification of crab lice attached to hairs (Fig. 16-33), often with associated perifollicular erythema. Transmission of pediculosis pubis is usually through sexual contact, although contaminated clothing, bedding, and towels have also been implicated in some cases (Meinking, 1999). The standard treatment is the application of 5% permethrin cream overnight to all affected hair-bearing areas with a repeat application 1 week later (Meinking et al, 2003). Note that the second application of permethrin is important, as the rate of treatment success with

a single application may be as low as 57% (Kalter et al, 1987). For rare cases refractory to topical therapy or those involving the eyelashes (*tinea palpebrarum*), the addition of oral ivermectin may be curative (Burkhart and Burkhart, 2000). Interestingly, because of the adoption of the widespread removal of pubic hair among young adults of both genders ("Brazilian waxing"), the incidence of pubic louse infestation in industrialized countries has fallen dramatically in recent years.

Another important infestation involving the genitalia is scabies, caused by the female itch mite *Sarcoptes scabiei*. Scabies is a world-wide problem and factors such as overcrowding, delayed treatment of primary cases, and poor public awareness encourage spread (Meinking et al, 2003). Transmission is common between close contacts and family members (Burkhart et al, 2000). The number of mites living on an immunocompetent host is usually small (<100) (Arlan et al, 1988), although far greater numbers may be recovered in cases of immunosuppression (so-called crusted or Norwegian scabies). The incubation period before symptoms develop after infestation can vary from days to months in duration, but is most typically about 6 weeks.

Severe pruritus is the hallmark of scabies, often accentuated at night or after bathing (Meinking et al, 2003). In both genders, the genital areas are commonly affected. Small erythematous and pruritic papules are present, and excoriations with secondary bacterial infection may occur (Fig. 16-34). Thin, gray or white burrows may be visible and are pathognomonic for scabies infestation. Crusted scabies affecting genital skin presents as it does in other anatomic sites: with thickly crusted plaque(s) (Perna et al, 2004). In the absence of visible burrows, a broad differential must be considered including AD, pyoderma, psoriasis, and other insect bites. As in the case of pediculosis pubis, the

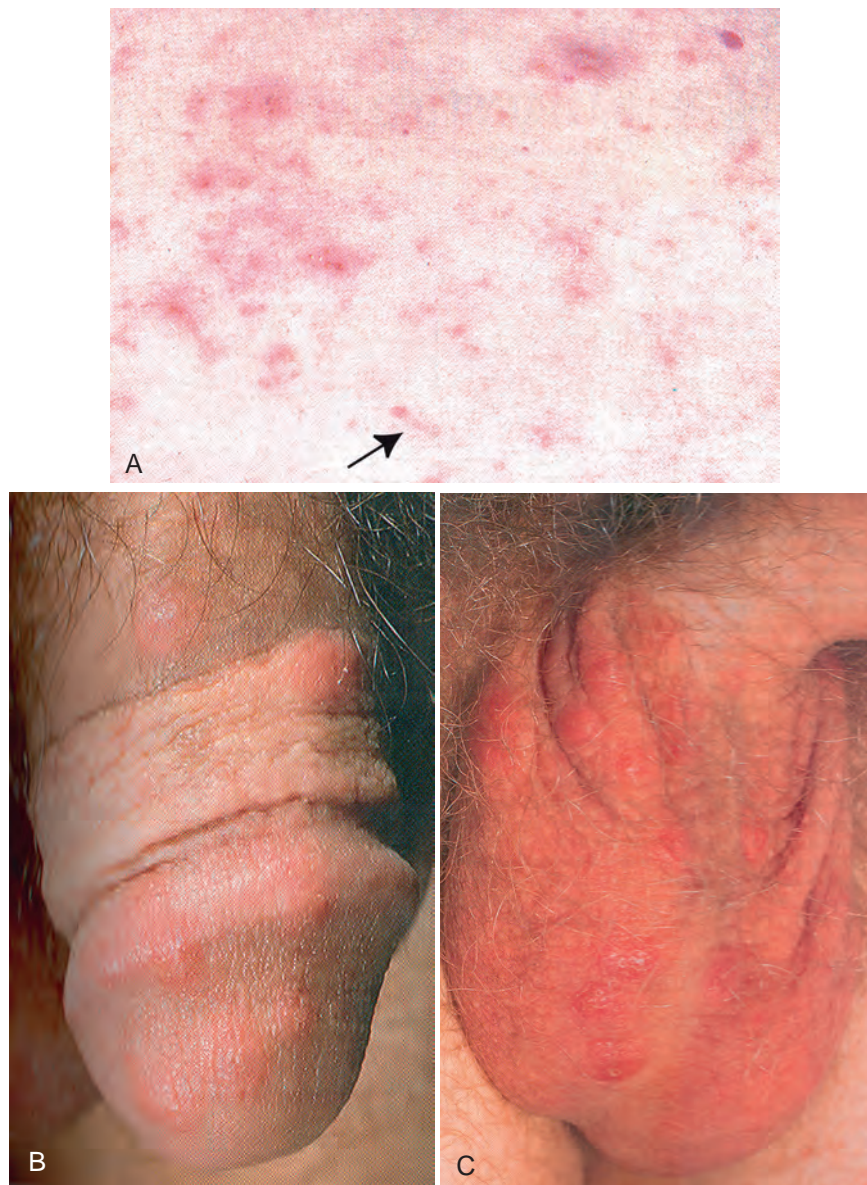


Figure 16-34. Scabies. A, A papular eruption with visible characteristic burrows (arrow). B and C, Classic established genital scabies with eroded papules on the glans penis and scrotum. (A, From du Vivier A. *Atlas of clinical dermatology*. London: Churchill Livingstone; 2002. p. 332; B and C, from Habif TP. *Clinical dermatology*. Edinburgh: Mosby; 2004. p. 501.)

treatment of choice for scabies is 5% permethrin cream applied to the entire body overnight with a second application 1 week later. An alternative topical scabicide, lindane, is not favored because of both central nervous system toxicity in children and a rising rate of resistance among mites (Purvis and Tyring, 1991; Elgart, 1996; Boix et al, 1997). Oral ivermectin (200 µg/kg/dose, 2 doses administered 2 weeks apart) is an alternate regimen that has been successfully used to treat scabies (Chouela et al, 2002; Heukelbach et al, 2004; Karthikeyan, 2005). A randomized comparative trial showed that permethrin was slightly more effective than ivermectin when the latter is only provided as a single dose (Goldust et al, 2012). Note that pruritus may persist for several weeks despite successful treatment and that all intimate contacts should also be treated to prevent reinfection. Even with effective treatment, itchy nodules may remain on the glans penis; intralesional injections of minute amounts of dilute triamcinolone acetonide (2 to 3 mg/mL) may facilitate resolution of these post-scabies nodules.

NEOPLASTIC CONDITIONS

Squamous Cell Carcinoma in Situ

Squamous cell carcinoma in situ (SCCis) is a full thickness intraepithelial carcinoma (Miller and Moresi, 2003). Bowen originally described this condition in 1912, hence the term “Bowen disease” (Bowen, 1912). On extragenital sites, there is a strong association between SCCis and ultraviolet light exposure (Reizner et al, 1994). Commonly presenting in the seventh decade of life with a slight female predominance (Hemminki and Dong, 2000; Arlette, 2003), SCCis usually has an indolent clinical course and rarely progresses to invasive disease. When it occurs on mucosal surfaces of the male genitalia, most notably the glans penis of uncircumcised men, this entity is referred to as erythroplasia of Queyrat (Fig. 16-35). Yet another name for this entity is penile intraepithelial neoplasia. In the female, the comparable SCCis on the vulva would be called vulvar intraepithelial neoplasia. In these locations,

coinfection with HPV types 8, 16 (70%), and other serotypes (30%) has been identified (Wieland et al, 2000). Other risk factors for SCCis include ionizing radiation, immunosuppression, thermal injury, arsenic exposure, chronic dermatoses (such as long-standing LP), and LS of the glans penis (Euvrard et al, 1995; Nasca et al, 1999; Powell et al, 2001; Centeno et al, 2002; Arlette, 2003).

SCCis lesions are sharply demarcated, solitary, pink to red scaly plaques, which may be confused with basal cell carcinoma, eczema, seborrhea, or psoriasis. SCCis on or near the vulva may be heavily pigmented and resemble both melanoma and external genital warts. When localized to the penile shaft, SCCis may have a more thickened, verrucoid appearance. Although usually asymptomatic, these lesions may also be pruritic or painful. The diagnosis is confirmed by histologic evaluation and several areas should be sampled to exclude the presence of dermal invasion (Margolis, 2002).



Figure 16-35. Erythroplasia of Queyrat. Squamous cell carcinoma involving the glans penis. (From Callen JP, Greer DE, Hood AF, et al. Color atlas of dermatology. Philadelphia: Saunders; 1993. p. 330.)

Primary treatment of SCCis involves either surgical excision or tissue ablation. For accessible areas, such as the scrotum, simple excision with a 5-mm margin is favored (Bissada, 1992; Margolis, 2002). For areas where tissue preservation is more critical, Mohs microsurgery, laser therapy, and cryoablation may play a role (Sonnex et al, 1982b; van Bezooijen et al, 2001; Leibovitch et al, 2005). Topical treatment with either 5-fluorouracil or imiquimod 5% has also proven effective for management of selected cases of SCCis involving the genitalia (Gerber, 1994; Orenge et al, 2002; Arlette, 2003; Micali et al, 2003).

Bowenoid Papulosis

Bowenoid papulosis is an uncommon condition found on the penis and vulva of sexually active adults, with a peak incidence in the third decade of life (Schwartz and Janniger, 1991). It histologically resembles Bowen disease except that the abnormal keratinocytes are spread discontinuously throughout the epidermis (Margolis, 2002). Typical lesions are multiple small erythematous papules that may coalesce to form plaques with a verrucous surface similar to a genital wart (Fig. 16-36). There is a clear association with HPV type 16. Female partners of men with bowenoid papulosis have an increased risk of cervical neoplasia and should receive close cervical follow-up (Rosemberg et al, 1991). In men, however, bowenoid papulosis generally has a benign course and spontaneous regression may occur (Eisen et al, 1983; Giam and Ong, 1986; Feng et al, 2013). Therefore, in a young and reliable patient, observation alone may be justified. If treatment is desired, conservative local therapy with topical agents (0.5% 5-fluorouracil, 0.5% tazarotene cream, or imiquimod 5%) or ablative measures (electrodessication, liquid nitrogen cryotherapy, laser ablation) is usually appropriate (Margolis, 2002).

Squamous Cell Carcinoma

Invasive SCC involving the genitalia (Fig. 16-37) is covered in detail in Chapter 37.

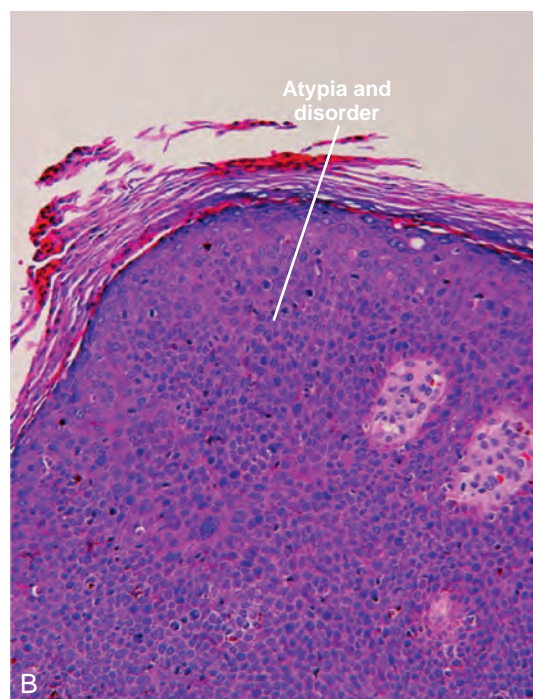
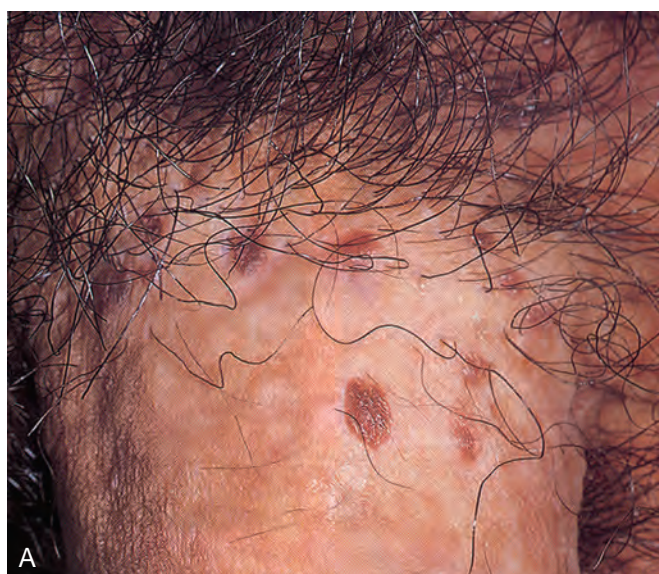


Figure 16-36. Bowenoid papulosis. A, Involvement of the penile shaft. Note multiple brown verrucous papules on the penile shaft. B, Characteristic full thickness atypia, which may be mistaken for Bowen disease. (A, From Habif TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 343; B, from Elston DM, Ferringer T. Dermatopathology. Edinburgh: Saunders; 2009. p. 293.)



Figure 16-37. Squamous cell carcinoma (SCC). A, Exophytic erosive lesion on the glans with evident keratinization. B, Atypical keratinocytes invading the dermis in SCC. (A, From Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993. p. 129; B, from Elston DM, Ferringer T. *Dermatopathology*. Edinburgh: Saunders; 2009. p. 57.)

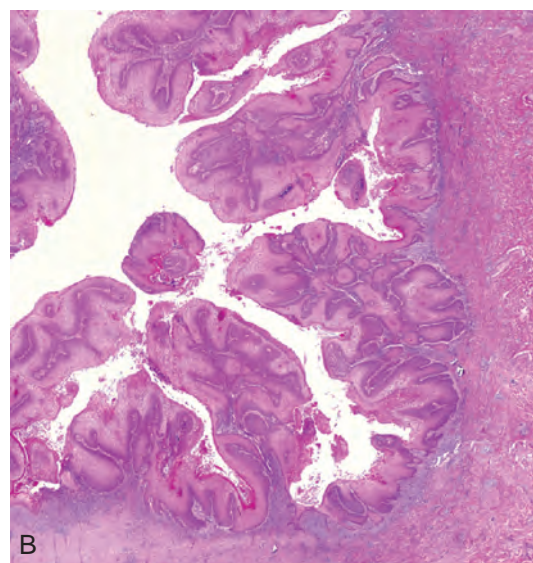
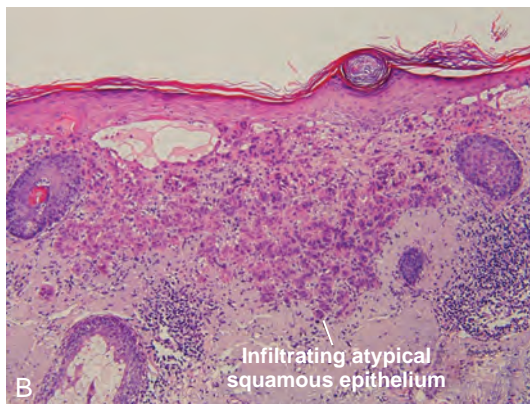


Figure 16-38. Verrucous carcinoma of the penis (Buschke-Lowenstein tumor). A, Note the exophytic and wartlike appearance. B, Histologic features of verrucous carcinoma. (A, From Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993. p. 330; B, from Elston DM, Ferringer T. *Dermatopathology*. Edinburgh: Saunders; 2009. p. 58.)

Verrucous Carcinoma (Buschke-Lowenstein Tumor)

Verrucous carcinoma is a locally aggressive, exophytic, low-grade variant of SCC that has little metastatic potential (Habif, 2004). The Buschke-Lowenstein tumor is a verrucous carcinoma of the anogenital mucosal surface and may represent up to 24% of all penile tumors (Schwartz, 1995). It most commonly occurs in uncircumcised men on the glans or prepuce, although similar lesions can be found on the vulva, vagina cervix, or anus. Verrucous carcinoma has been associated with HPV type 6 and 11 infection but not with the more classically oncogenic types 16 and 18 (Yasunaga et al, 1993; Chan et al, 1994; Margolis, 2002; Ahmed et al, 2006).

Verrucous carcinoma lesions have a warty appearance and are often large and fungating when presenting on the genitalia (Fig. 16-38). Aside from genital sites, these lesions can also present within the oral and nasal cavities and plantar surfaces of the feet. They are slow growing and locally destructive, often extending deeply into underlying tissue. Preferred treatment is by local excision. Mohs micrographic surgery may be helpful in tracing out the tumor and minimizing tissue loss. Primary radiotherapy is relatively contraindicated because of the potential for anaplastic transformation with a subsequent increase in metastatic potential (Stehman et al, 1980; Andersen and Sorensen, 1988; Fukunaga et al, 1994; Vandeweyer et al, 2001).

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common cutaneous neoplasm overall, arising most often on areas of chronically sun-exposed skin such as the head and neck. Genital BCC has also been described as a very rare entity, most commonly involving the scrotal skin in the male and the vulva in the female (Nahass et al, 1992; Benedet et al, 1997; Esquivias Gomez et al, 1999; Kinoshita et al, 2005). In the world medical literature, to date fewer than 100 total cases of BCC have been described involving all the potential genital sites (penis, scrotum, vulva). Several subtypes of BCC have been defined including nodular, superficial, micronodular morpheaform, and infiltrating. The nodular variant accounts for 60% of extragenital BCCs and virtually all genital BCCs, and this variant presents as a pearly, skin-toned papule or plaque often with telangiectasias overlying the tumor (Fig. 16-39) (Miller and Moresi,



Figure 16-39. Basal cell carcinoma involving the vulva. (From du Vivier A. *Atlas of clinical dermatology*. London: Churchill Livingstone; 2002. p. 688.)

2003). These lesions may ulcerate centrally and manifest a very low metastatic potential. Treatment is by local excision. Because preservation of genital skin is important, both for form and function, the use of Mohs micrographic surgery may be advisable for the rare genital BCC.

Kaposi Sarcoma

Kaposi sarcoma (KS) is a disease of endothelial cell origin. Whether KS is a neoplastic or hyperplastic process remains controversial, and evidence exists both for and against clonal expansion (Rabkin et al, 1997; Gill et al, 1998). Before the onset of the AIDS epidemic, KS was considered a chronic disease afflicting elderly men of Jewish, Mediterranean, or Eastern European descent ("classic KS") (Safai, 1987). However, infection with HIV-1 has increased the incidence of KS by more than 7000-fold (Miles, 1994; Margolis, 2002). KS generally affects HIV-infected patients with advanced immune impairment (CD4+ T-cell counts of <500 cells/mm) (Tappero et al, 1993). Approximately 40% of homosexual men with AIDS have developed KS as compared to less than 5% in other risk groups (Rogers et al, 1987; North et al, 2003). There is also a clear association between infection with human herpesvirus 8 and the development of KS (Boshoff and Weiss, 1997; Weiss et al, 1998). In this regard, the other group at risk for development of KS associated with human herpesvirus 8 infection includes recipients of solid organ transplants (Riva et al, 2012).

Classic KS in immunocompetent individuals presents as slowly growing, blue-red to overtly violaceous pigmented macules on the lower extremities. Although oral and gastrointestinal lesions may occur, the genitalia are seldom involved. This is in contrast to the case with AIDS ("epidemic KS") in which a solitary genital lesion may be the first manifestation of KS (Lowe et al, 1989). The clinical features of KS in both AIDS patients and solid organ transplant recipients are diverse, ranging from a single lesion to disseminated cutaneous and visceral disease (Fig. 16-40). Lesions may coalesce to cover large areas of skin and may result in lymphatic or venous blockage leading to local edema (Margolis, 2002). When these lesions involve the glans penis, they can cause obstruction at the urethral meatus or fossa navicularis (Swierzewski et al, 1993). It should be noted, however, that penile KS is still rare, even among those infected with HIV-1; only about 3% of AIDS patients will ever develop KS of the genitalia (Rosen et al, 1999).

Treatment must be tailored to the individual clinical case and complete cure may be an unrealistic goal. For solitary lesions, local



Figure 16-40. Kaposi sarcoma. Classic macular lesions seen on the back (A) and glans penis (B). (A, From Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993. p. 220; B, from du Vivier A. *Atlas of clinical dermatology*. London: Churchill Livingstone; 2002. p. 716.)



therapy such as surgical excision, laser ablation, cryotherapy, topical imiquimod 5%, or intralesional injection of chemotherapeutic agents (i.e., vinblastine) may be beneficial (Chun et al, 1999; Schwartz, 2004; Heyns and Fisher, 2005; Rosen, 2006). For extensive locoregional disease, radiotherapy (15 to 30 Gy) has an objective response rate of greater than 90% (Kirova et al, 1998; Cattelan et al, 2002). For widely disseminated KS, systemic chemotherapy with vincristine, doxorubicin, and bleomycin is the treatment of choice (Aversa et al, 1999). For KS associated with organ transplantation, reduction in the degree of postoperative immunosuppression or switching from a calcineurin inhibitor to an mTOR inhibitor may lead to KS resolution without any additional intervention (Riva et al, 2012).

Pseudoepitheliomatous, Keratotic, and Micaceous Balanitis

Pseudoepitheliomatous, keratotic, and micaceous balanitis (PEKMB) is a rare entity characterized by the development of a thick, hyperkeratotic plaque on the glans penis of older men (Fig. 16-41). The term *micaceous* refers to the white, scaly appearance of the lesions (Child et al, 2000). PEKMB was originally thought to be a purely benign process, although several case reports have documented the presence of concurrent verrucous carcinomas associated with this lesion (Child et al, 2000). Controversy remains as to whether PEKMB is a premalignant condition (Read and Abell, 1981; Beljaards et al, 1987; Jenkins and Jakubovic, 1988). Histologic examination is essential to exclude the presence of SCC and verrucous carcinoma (Margolis, 2002). PEKMB is characterized on histology by a hyperplastic epidermis with ridges extending deeply into the dermis (Jenkins and Jakubovic, 1988). These lesions should be treated locally either by surgical excision or ablative techniques, and close follow-up is essential (Read and Abell, 1981; Bargman, 1985). There are also anecdotal reports of successful treatment using topical 5-fluorouracil cream (Bargman, 1985; Kronic et al, 1996).

Melanoma

Malignant melanoma is a neoplasm arising from melanocytes. The incidence of melanoma has risen 3% to 7% during the past several decades (Nestle and Kerl, 2003). Risk factors for development of the disease include family history, certain genetic markers, fair skin, light eye color, and a history of excessive ultraviolet radiation exposure (especially multiple blistering sunburns as a child or adolescent). Primary melanoma of the male genitalia is an uncommon entity with only approximately 100 cases reported in the literature (Sanchez-Ortiz et al, 2005) and melanoma of the male urethra is even more rare (Oliva et al, 2000). The same cannot be said for



Figure 16-41. Pseudoepitheliomatous, keratotic, and micaceous balanitis. The glans becomes covered with mica (asbestos-like) scales and horny crusts. (From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 717.)

females, as melanoma comprises about 7% to 10% of all vulvar malignancies and remains the second most common such lesion after SCC (Suwandinata et al, 2007). Although vulvar melanoma is more common among Caucasian women, the prognosis is worse among African-American women (Mert et al, 2013).

Genital melanoma usually presents as a pigmented macule or papule with an irregular border, although unpigmented lesions and ulceration may also be present (Margolis, 2002). Early diagnosis is critical because local treatment of superficial lesions with wide local excision or partial penectomy can provide excellent disease control (Stillwell et al, 1988; Sanchez-Ortiz et al, 2005). The same caveats are true in female patients. In contrast, patients with biopsy-proven metastatic disease have traditionally had a universally poor prognosis despite aggressive surgical management and multiagent cytotoxic chemotherapy. In the last several years, however, several drugs have gained regulatory approval for the treatment of metastatic and unresectable melanoma as a result of an increase of knowledge in melanoma-specific molecular biology and immunology. The efficacy of small-molecule BRAF (e.g., vemurafenib, dabrafenib, trametinib) and MAP-ERK kinase (MEK) inhibitors, as well as the immune checkpoint inhibitors (e.g., ipilimumab and the anti-PD1/PDL1 antibodies lambrolizumab and nivolumab), have transformed the treatment of advanced melanoma.

Extramammary Paget Disease

Extramammary Paget disease (EPD) is an uncommon intraepithelial adenocarcinoma of sites bearing apocrine glands (Zollo and Zeitouni, 2000). The majority of patients with EPD are elderly Caucasian females, and involvement of the male penis and scrotum is exceedingly rare (Park et al, 2001; van Randenborgh et al, 2002; Yang et al, 2005). The vulva is the most commonly involved genital site in women followed by the perianal region in men (Wojnarowska and Cooper, 2003). There is an important association between EPD and another underlying malignancy in at least 10% to 30% of cases (Payne and Wells, 1994; Ng et al, 2001; Margolis, 2002). An investigation in a cancer specialty hospital suggested that this association might be even stronger in men than previously appreciated (Hegarty et al, 2011). In the male, associations between urethral, prostate, bladder, rectal, and apocrine malignancies with EPD have been described (Hayes et al, 1997; Salamanca et al, 2004; Hegarty et al, 2011). It is critical therefore to perform a systematic evaluation for underlying carcinoma in all cases of EPD.

The lesion in EPD is usually an erythematous plaque with a sharp border between normal and involved skin (Fig. 16-42). It may be asymptomatic, pruritic, or associated with burning pain. The diagnosis is confirmed histologically by the presence of vacuolated Paget cells in the epidermis that stain for glandular cytokeratins, epithelial membrane antigen, and carcinoembryonic antigen (Wojnarowska and Cooper, 2003). Treatment generally involves surgical excision or Mohs micrographic surgery, although radiotherapy, photodynamic therapy, and topical imiquimod 5% or 5-fluorouracil have also been used successfully (Sillman et al, 1985; Bewley et al, 1994; Brown et al, 2000; Brown et al, 2002; Guerrieri and Back, 2002; Moreno-Arias et al, 2003; Qian et al, 2003; Lee et al, 2009).

Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) represents a group of related neoplasms derived from T cells that home to the skin. CTCL includes a variety of conditions including mycosis fungoides, Sézary syndrome, lymphoid papulosis, and pagetoid reticulosis (Willemze, 2003). There is an increased risk of CTCL associated with HIV infection (Biggar et al, 2001). Although these disorders may involve the genitalia of both genders, extragenital disease is usually also present. CTCL accounts for the majority of primary cutaneous lymphomas with B-cell-derived lymphomas accounting for only 20% to 25% (Willemze et al, 1997, 2005). Definitive diagnosis depends on biopsy histopathology.

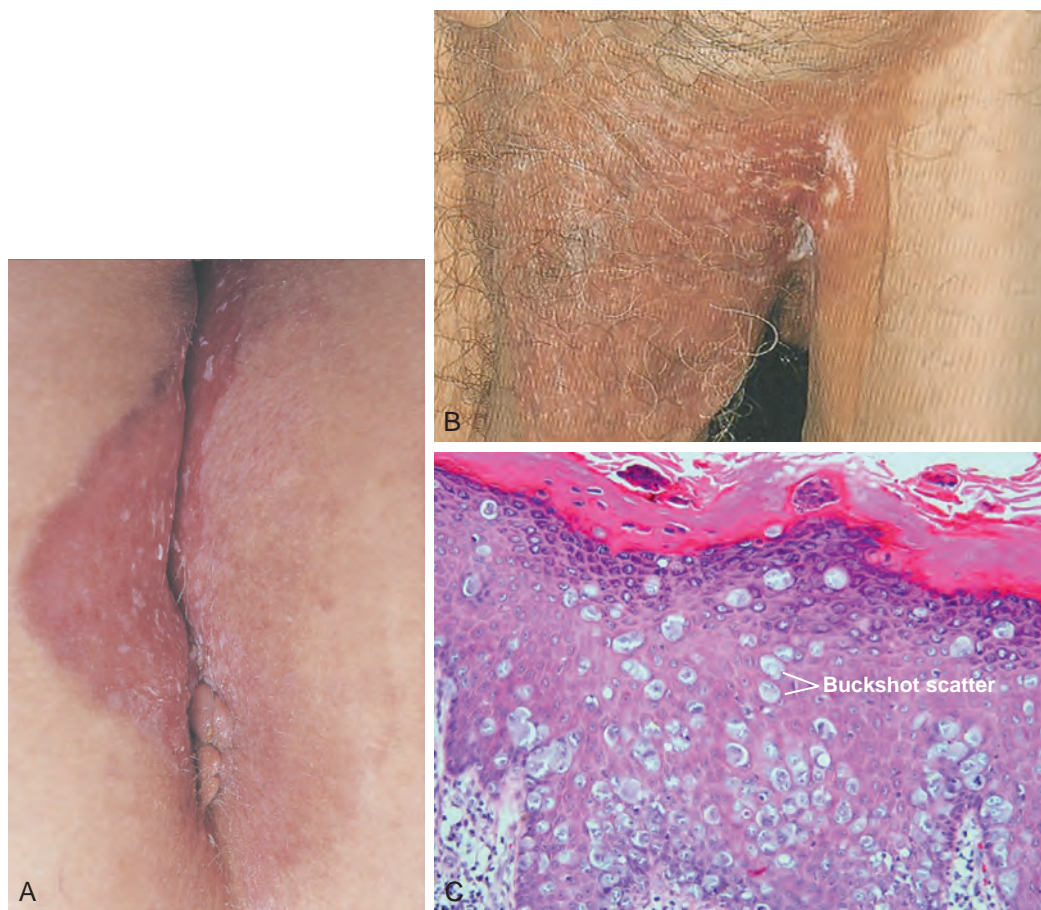


Figure 16-42. Extramammary Paget disease involving the vulva (A) and base of scrotum (B). Note the well-demarcated border between the lesion and normal adjacent skin. C, Tumor cells distributed throughout the epidermis (“buckshot scatter”). (A, From Habif TP. *Clinical dermatology*. Edinburgh: Mosby; 2004. p. 764; B, from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003. p. 1108; C, from Elston DM, Ferringer T. *Dermatopathology*. Edinburgh: Saunders; 2009. p. 66.)

CTCL generally presents initially as pruritic patches that must be differentiated from a variety of benign dermatoses including psoriasis, eczema, superficial fungal infections, and drug reactions. The initial lesions of CTCL have a strong predilection in both sexes to occur on suprapubic and/or buttock skin. Patients may subsequently develop hematologic involvement (Sézary syndrome) and cutaneous plaques, erosions, ulcers, or frank skin tumors (Fig. 16-43) (Margolis, 2002). CTCL is a chronic condition that may progress throughout many years. Topical treatments include application of ultrapotent corticosteroids, nitrogen mustard, and carmustine with complete remission rates of approximately 60% (Vonderheid et al, 1989; Zackheim et al, 1998). Other treatments include radiotherapy (including total body electron beam treatment), phototherapy (PUVA), and systemic treatment with chemotherapy, interferons, or retinoids (Hoppe et al, 1990; Olsen and Bunn, 1995; Diederer et al, 2003; Querfeld et al, 2005).

BENIGN CUTANEOUS DISORDERS SPECIFIC TO THE MALE GENITALIA

Angiokeratoma of Fordyce

Angiokeratomas of Fordyce are vascular ectasias of dermal blood vessels that may be visible on the penis and scrotum of adult men (Bechara et al, 2002). These lesions appear as 1- to 2-mm red or purple papules (Fig. 16-44A) and associated generalized scrotal redness may exist (Miller and James, 2002). This is usually a benign

condition without systemic manifestations, although it may rarely be a source of troublesome scrotal bleeding (Taniguchi et al, 1994; Hoekx and Wyndaele, 1998). Similar lesions can be observed in Fabry disease (Fig. 16-44B), which is a rare glycogen storage deficiency. Although treatment is usually unnecessary for angiokeratoma of Fordyce, several authors have reported success using erbium:YAG, Nd:YAG, KTP, and Argon laser photocoagulation in select cases (Occella et al, 1995; Bechara et al, 2004; Ozdemir et al, 2009).

Pearly Penile Papules

Pearly penile papules are white, dome-shaped or filiform, closely spaced small papules located on the glans penis (Fig. 16-44C). They are often arranged circumferentially at the corona. Pearly penile papules are common lesions found in up to 14% to 48% of young postpubertal adults, particularly if the penis is not circumcised (Rehbein, 1977; Khoo and Cheong, 1995; Sonnex and Dockerty, 1999). Although pearly penile papules may occasionally be misdiagnosed as condyloma, the available evidence does not support a role for HPV in causing pearly penile papules and no association with cervical intraepithelial neoplasia in female partners has been demonstrated (Hogewoning et al, 2003). Patients should be reassured that this is a benign condition that does not usually require treatment. If treatment is desired because of cosmetic concerns, local destruction with either the CO₂ laser or cryotherapy has been applied successfully (Ocampo-Candiani and Cueva-Rodriguez, 1996; Lane et al, 2002). Histologically,

these lesions are angiofibromas similar to the lesions seen on the face in tuberous sclerosis.

Zoon Balanitis

Zoon balanitis, also called plasma cell balanitis and balanitis plasmacellularis, occurs in uncircumcised men from the third decade onward (Pastar et al, 2004). Smooth, moist, erythematous, well-circumscribed plaques on the glans penis characterize the disease (Fig. 16-44D). Shallow erosions are often present (Yoganathan et al, 1994) and the lesions can be quite large (up to 2 cm in diameter) (Margolis, 2002). SCC and EPD must be excluded, typically by biopsy. Circumcision appears to be proof against development of the disease and can be performed to cure the majority of cases (Sonnex et al, 1982a; Ferrandiz and Ribera, 1984). For patients averse to circumcision, topical corticosteroids may provide symptomatic relief, and topical calcineurin inhibitors (tacrolimus or pimecrolimus) and laser therapy may also play a role in alleviation (Baldwin and Geronemus, 1989; Tang et al, 2001; Albertini et al, 2002; Retamar et al, 2003; Wojnarowska and Cooper, 2003; Rallis et al, 2007).



Figure 16-43. Mycosis fungoides (a cutaneous T-cell lymphoma) involving the buttocks. A shows the limited plaque stage, and B shows a more advanced case with plaques, patches, and tumors present. (From Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003.)

Sclerosing Lymphangitis

Nonvenereal sclerosing lymphangitis is a rare penile lesion consisting of an indurated, slightly tender cord involving the coronal sulcus and adjacent penile skin (Gharpuray and Tolat, 1991; Rosen and Hwang, 2003). It is usually flesh colored but may occasionally be red. A mechanism related to thrombosis of lymphatic vessels has been proposed. There is an association with vigorous sexual activity, and resolution usually occurs within several weeks (Sieunarine, 1987; Margolis, 2002). Although somewhat controversial, a search for concomitant gonococcal and nongonococcal urethritis may be advisable in these cases.

Median Raphe Cysts

Median raphe cysts occur in young men on the ventral aspect of the penis, most commonly near the glans (Stone, 2003). Although these cysts are believed to develop from aberrant urethral epithelium, they do not communicate with the urethra (Asarch et al, 1979). Treatment is accomplished by surgical removal.

Ectopic Sebaceous Glands

Ectopic sebaceous glands on the penile shaft may be visible as pin-sized, flesh-colored papular lesions that may be mistaken for verruca (Fig. 16-44E) (Margolis and Wein, 2002). There is no indication for treating these asymptomatic benign lesions and patient reassurance is sufficient.

COMMON MISCELLANEOUS CUTANEOUS DISORDERS

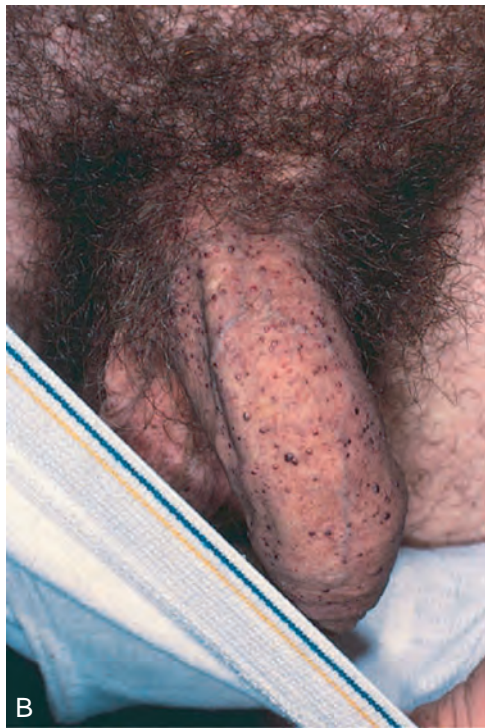
Skin Tag

Skin tags (acrochordons, fibroepithelial polyps) are soft, skin-colored, pedunculated lesions that can be present anywhere on the body but have a clear predilection for the neck, axillae, and inguinal folds. Although usually asymptomatic, these lesions may become painful secondary to local trauma or as a result of torsion and infarction in rare cases. These are common lesions, and up to 50% of all individuals may have at least one skin tag (Banik and Lubach, 1987). It is important to distinguish these lesions from the hamartomatous skin lesions (multiple fibrofolliculomas) associated with Birt-Hogg-Dube syndrome, which are histologically distinct from common skin tags (De la Torre et al, 1999). When skin tags cause either discomfort or cosmetic distress, they can easily be removed by snip excision and light electrocautery to the base to achieve hemostasis. When a large number of skin tags appear at a relatively young age (<40), there may be an association with both benign and malignant lower gastrointestinal tract polyposis, and gastroenterological referral for endoscopy should be considered (Piette et al, 1988).

Epidermoid Cysts

Epidermoid or epidermal-inclusion cysts are the most common cutaneous cysts, and these lesions can be found anywhere on the body including the genitalia. They are particularly common on the scrotum (Fig. 16-45E). The term “sebaceous cyst” should be avoided because the contents of these cysts are not sebaceous in origin (Stone, 2003). Although not painful at baseline,

Figure 16-44. Benign cutaneous disorders specific to the male genitalia. A, Angiokeratoma of Fordyce showing purple scrotal vascular malformations. B, Fabry disease: a glycogen storage deficiency with associated purple vascular malformations on the penile shaft. C, Pearly penile papules located on the corona of the glans penis. D, Zoon balanitis of the glans penis. E, Ectopic sebaceous glands on the penile shaft. (A, B, and E, From Callen JP, Greer DE, Hood AF, et al. *Color atlas of dermatology*. Philadelphia: Saunders; 1993; C and D, from Kortling GW. *Practical dermatology of the genital region*. Philadelphia: Saunders; 1981.)



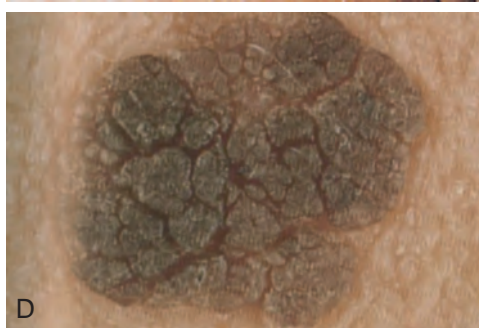
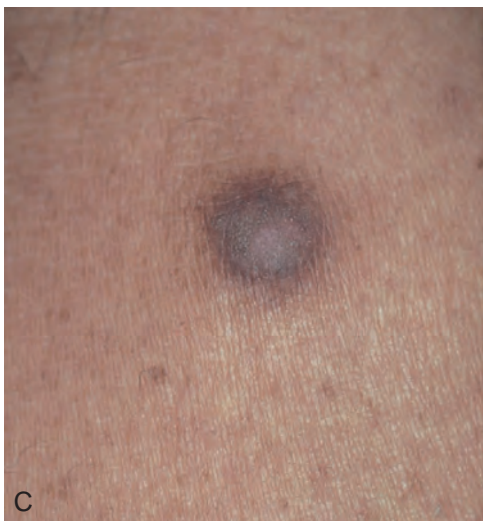
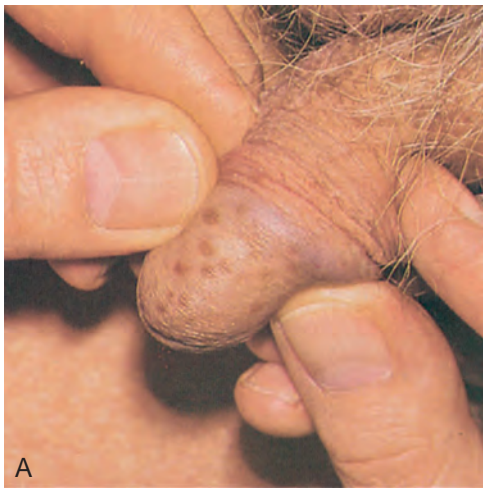


Figure 16-45. Miscellaneous cutaneous disorders. A, Lentigo simplex involving the glans penis (penile melanosis). B, A compound melanocytic nevus in the inguinal crease. C, A dermatofibroma on the lower extremity. D, A characteristic seborrheic keratosis showing the “stuck-on” waxy appearance. E, Epidermoid cysts of the scrotum. F, Pedunculated neurofibroma. G, Vitiligo involving the penile shaft. (A, B, E, and G, From Korting GW. *Practical dermatology of the genital region*. Philadelphia: Saunders; 1981; C, from Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. Edinburgh: Mosby; 2003; D, from Habif TP. *Clinical dermatology*. Edinburgh: Mosby; 2004.)

rupture of the cyst wall can lead to a severe inflammatory reaction that is extremely painful. Definitive treatment requires surgical excision of the entire cyst wall to prevent cyst recurrence. Inflamed or superinfected epidermoid cysts may require incision and drainage and antibiotic therapy if there is adjacent cellulitis. Dystrophic calcification of scrotal epidermoid cysts may be a cause of scrotal calcinosis (Dare and Axelsen, 1988; Michl et al, 1994).

Seborrheic Keratosis

Seborrheic keratoses are very common beige to dark brown macules, plaques, and papules affecting individuals older than 30 years, and the incidence increases in frequency with advancing age. They are most common on the face, neck, and trunk although any body site except the palms, soles, and mucous membranes may be affected. The degree of pigmentation can vary significantly, and darker lesions may be confused with melanoma or warts (Pierson et al, 2003). These lesions have a waxy, “stuck-on” appearance (Fig. 16-45D) and patients may note that they drop off spontaneously and then regrow (Margolis, 2002). Treatment by shave excision or destruction with liquid nitrogen is usually performed for cosmetic reasons. An abrupt increase in the size and number of multiple seborrheic keratoses has been termed the Sign of Leser-Trelat and has been implicated as a cutaneous marker of occult internal malignancy (Chiba et al, 1996; Heaphy et al, 2000; Vielhauer et al, 2000; Ginarte et al, 2001).

Lentigo Simplex

Lentigo simplex is a condition characterized by the presence of brown-pigmented macules unrelated to sunlight exposure (Fig. 16-45A). These lesions can be found anywhere on the body including the mucous membranes and nail beds. In the genital area (benign genital lentiginosis), these lesions present commonly on the labia, vaginal introitus, perineum, and glans penis (penile melanosis). The lesions of lentigo simplex are usually smaller than those seen in melanocytic nevi. Although usually benign, the lesions of lentigo simplex may deserve biopsy evaluation in cases demonstrating atypical shape or coloration. When present in a discontinuous manner at multiple sites, the diagnosis of genital melanoma becomes less likely compared to the probability of benign genital lentiginosis. Finally, the combination of multiple pigmented lesions associated with intestinal polyposis should raise suspicion for Peutz-Jeghers syndrome.

Mole (Nevus)

A mole or nevus of the skin is composed of slightly altered melanocytes called “nevus cells” arranged in a cluster. The location of the cluster determines the type of nevus. Junctional nevi are located between the epidermis and dermis and are usually flat, tan to black in coloration, small (<5 mm), and sharply bordered (Margolis, 2002). Intradermal nevi have clusters within the dermis and are usually small (<5 mm), lighter in coloration, with sharp borders. Compound nevi have clusters in both locations and are usually darker and raised as a papule (Fig. 16-45B). As is the case for any pigmented lesion, marked irregularity in coloration or border, and rapid morphologic change with time, are indications for excisional biopsy.

Dermatofibroma

Dermatofibromas are small hyperpigmented nodules that occur most commonly on the lower extremities and occasionally on the genitalia (Fig. 16-45C). Pinching of these lesions causes a downward movement of the tumor (the so-called dimple sign) (Kamino and Pui, 2003). These are benign lesions with a characteristic histologic pattern of spindle-shaped fibroblasts and myofibroblasts arranged in fascicles. Treatment by surgical excision is usually unnecessary and may leave a scar that is cosmetically inferior to the original lesion (Kamino and Pui, 2003).

Neurofibroma

Neurofibromas are common tumors composed of neuromesenchymal tissue with residual nerve axons. They can be present anywhere on the body including the labia and scrotum (Yoshimura et al, 1990; Singh et al, 1992; Mishra et al, 2002; Kantarci et al, 2005). They are usually skin-colored, soft or rubbery nodular lesions, which may be pedunculated (Fig. 16-45F). Digital pressure on the lesion causes invagination or so-called button-holing (Habif, 2004). These can be solitary lesions or multiple, which should raise suspicion for neurofibromatosis or von Recklinghausen disease.

Capillary Hemangioma

Capillary hemangiomas are proliferations of blood vessels that are either present at birth or develop rapidly during the neonatal period. These lesions can involve the anogenital region, can lead to bleeding, or can cause obstruction of the urethra, vagina, or anus (Sharma et al, 1981; Roberts and Devine, 1983). The majority will involute during childhood or early adolescence (Margolis, 2002). An innovation in the treatment of very large, persistent, and/or obstructive hemangiomas is the systemic administration of propranolol; because this treatment is not without some risk, it should be initiated and supervised by a clinician experienced with this modality (Izadpanah et al, 2013).

Vitiligo

Vitiligo is an acquired autoimmune disorder of the skin, leading to depigmentation, affecting 0.5% to 2% of the global population (Ortonne, 2003). It might present at any age and the precise pathogenesis of vitiligo remains a topic of intense research effort. Large patches of skin become completely amelanotic. Although the skin appears white, it is otherwise completely normal. The borders with unaffected skin are usually sharp and well defined (Fig. 16-45G). This condition is particularly noticeable in darker skinned individuals and on body sites that are normally hyperpigmented. Vitiligo limited to the genitalia has been observed in less than 0.3% of the male population (Moss and Stevenson, 1981). Lesions have a tendency to enlarge circumferentially with time and might develop at sites of local trauma (Koebner phenomenon). Genital vitiligo must be differentiated from LS and postinflammatory hypopigmentation (Margolis, 2002). Treatments include temporary

KEY POINTS

- The diagnosis of cutaneous diseases of the external genitalia depends critically on a thorough history and physical examination. Extragenital findings may provide the key to diagnosis. The urologist should perform a thorough skin survey and should not focus solely on the area of affected genital skin.
- The side effects of topical corticosteroids are significant, both from systemic absorption and locally. Adverse effects may be worsened if these agents are applied under the foreskin, which may serve as an occlusive dressing. In general, when applied to genital skin, only low-potency topical corticosteroids should be used for short treatment courses.
- Cutaneous disorders of the external genitalia can be broken down into the general categories of allergic, papulosquamous, vesicobullous, ulcerative, infectious, neoplastic, and miscellaneous diseases.
- Histopathologic analysis of biopsy specimens plays an important role in differentiating cutaneous diseases with similar clinical features and in excluding malignancy.
- Local treatment modalities including the use of laser energy, photodynamic therapy, ultraviolet radiation, and cryotherapy are being applied successfully to a variety of genital cutaneous disorders and offer an alternative to surgical excision in some cases.

repigmentation with topical cosmetics, ultraviolet light exposure, PUVA therapy, and skin grafting. Use of the excimer laser to induce melanin production is particularly suited to the genitalia. **The diagnosis of vitiligo should prompt a screening for autoimmune thyroid disease.**

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The complete reference list is available online at www.expertconsult.com.

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Genitourinary Tuberculosis

GENITOURINARY TUBERCULOSIS

Tuberculosis (TB) can affect any organ system of the body, including the genitourinary (GU) tract. Untreated, GU TB can lead to irreparable tissue damage with serious consequences such as renal failure and infertility, making it critical for clinicians to consider TB in the differential diagnosis of GU disorders. Described as the second “great imitator” (after syphilis) (Sievers, 1961), TB can mimic many other diseases and complicate the correct diagnosis and treatment of infected patients. As TB becomes less common in industrialized nations, the diagnosis of GU TB increasingly relies on clinical recognition and a high index of suspicion.

History

Genomic analyses suggest that *Mycobacterium tuberculosis* co-evolved with humans. Its early progenitor, *Mycobacterium prototuberculosis*, possibly infected early hominids more than 3 million years ago (Gutierrez et al, 2005). Bony lesions consistent with TB have been detected in a 500,000-year-old *Homo erectus* skeleton (Kappelman et al, 2008). The oldest microbiologic confirmation of *M. tuberculosis* infection in humans dates back to the Neolithic Period with use of DNA isolated from 9000-year-old skeletons of a woman and child found in a prehistoric site in the Eastern Mediterranean (Hershkovitz et al, 2008). Microscopic and molecular findings of tubercle bacilli have been documented in Egyptian mummies from circa 3000 BC (Zimmerman 1979; Nerlich et al, 1997). Descriptions of TB can be found in written records of civilizations from ancient East Asia, to New World cultures in the Americas, to Western Hemisphere societies such as the Greeks and Romans, and continuing into modern history (Daniel, 2006). It was not until the 18th and 19th centuries, however, that TB reached epidemic proportions and ravaged Europe and North America. “Consumption,” as it was known, was responsible for as many as 25% of deaths during the Industrial Age (Chalke, 1959). The turning point in the history of TB came on March 24, 1882, when Robert Koch famously presented to the scientific community the first successful isolation and identification of the tubercle bacillus (Sakula, 1982). In honor of Dr. Koch, March 24 has become World Tuberculosis Day.

Microbiology

Tuberculosis is caused by a group of closely related acid-fast bacteria referred to as the *Mycobacterium tuberculosis* complex (MTBC). The species that comprise the complex are *M. tuberculosis*, *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium canettii*, *Mycobacterium microti*, *Mycobacterium caprae*, *Mycobacterium mungi*, *Mycobacterium orygis*, and *Mycobacterium pinnipedii* (Alexander et al, 2010; Coscolla et al, 2013). *M. tuberculosis* and *M. africanum* infect only humans, whereas the others infect humans and additional mammals. By far, the most frequently isolated species in human

Parasitic Infections of the Urogenital Tract

TB is *M. tuberculosis*. This species has become synonymous with TB and is often used to represent the entire complex. Although the mycobacterial species in the complex are clinically indistinguishable, drug susceptibility among them may differ. *M. bovis*, for example, has innate resistance to pyrazinamide, which is one of the first-line agents against *M. tuberculosis*.

Epidemiology

The World Health Organization (WHO) estimates that one third of the world’s population is infected with MTBC in its latent form. In 2012 there were 8.6 million new cases of active TB and 1.3 million deaths from TB worldwide, a decline that has continued since the year 2000. TB mortality has fallen by 45% since 1990 (WHO, 2013). However, new obstacles in TB control have also surfaced. These include medical conditions that promote resurgence of TB such as the human immunodeficiency virus (HIV) epidemic in sub-Saharan Africa and the rapid increase in obesity and diabetes worldwide. The appearance of multidrug and extensive drug resistance also compromises TB control.

In the United States, 9945 cases of active TB were reported in 2012 (3.2 per 100,000 persons). TB incidence in the United States has been steadily declining since its resurgence in the 1980s and its peak in 1992. In the United States, TB disproportionately affects the foreign-born. In 2012, the incidence among foreign-born individuals was 11 times higher than among U.S.-born persons (Centers for Disease Control and Prevention [CDC], 2013d).

The frequency of GU involvement among patients who develop TB varies significantly depending on the population studied. In developed countries, GU TB has been found in 2% to 10% of patients with pulmonary TB. In contrast, the frequency in developing countries approaches 15% to 20% (Figueiredo and Lucon, 2008). In the developing world, the GU tract is the second most common extrapulmonary site after lymph nodes (Wong et al, 2013). In the United States, GU TB is the third most common form after pleural and lymphatic TB and is found in 27% of extrapulmonary cases (Daher Ede et al, 2013). Approximately two thirds of those affected are men. GU TB is generally a disease of adults, although it has been reported in children as young as 2 years of age (Merchant et al, 2013a).

Transmission and Host Immune Response

The initial mode of entry of MTBC into the host is via inhalation of cough-generated infectious aerosols, although there are reported cases of direct inoculation of MTBC into soft tissues (Angus et al, 2001). When the bacilli reach the alveoli, they are phagocytosed by alveolar macrophages. In some persons, MTBC organisms are killed by the macrophages at this point and effectively cleared from the body. These persons do not develop infection nor an adaptive immune response (Walzl et al, 2011). In others, MTBC bacilli escape killing, begin to replicate within macrophages, and establish

infection. Up to 12 weeks may pass before a cellular immune response is detectable (Dannenberg, 1994), and before this development the tubercle bacilli can spread through the lymphatics to the hilar lymph nodes and ultimately through the bloodstream to seed distant organs.

The host attempts to contain MTBC infection by forming granulomas. Infected macrophages secrete inflammatory cytokines such as interleukin-6 (IL-6), IL-12, IL-1 β , and tumor necrosis factor- α (TNF- α) and recruit a variety of immune cells to surround them. Foamy macrophages, epithelioid cells, and multinucleated giant cells (Langhans cells) cluster to the center of the granuloma and are surrounded by a cuff of lymphocytes (Silva Miranda et al, 2012). Antigen processing and presentation lead to T-cell activation and the mounting of an adaptive cellular response against MTBC (Schluger and Rom, 1998). T cells secrete cytokines such as IL-2, TNF- α , and, most important, interferon- γ (IFN- γ) to maintain the granuloma and to induce killing of the infected macrophages and the infectious bacilli. When killing is not achieved, the granuloma can still successfully sequester viable tubercle bacilli, which stop replicating and become dormant. In 90% to 95% of persons, TB is controlled at this point and enters latency (Boom et al, 2003). Latent TB is marked by cicatrization and granuloma calcification. In fewer than 5% of infected persons the initial infection fails to be controlled and progresses within the year to active TB (primary progression). After latency is established, MTBC can resurface years later to cause reactivation TB. The process of reactivation is not well understood. The development of some conditions such as old age, renal failure, diabetes mellitus, malnutrition, HIV infection, and other causes of immune suppression shifts the balance between host and pathogen in favor of the pathogen. A series of events then occur that lead to renewed bacillary replication and release, granuloma caseation (the pathognomonic lesion of TB), and reactivation. The lifetime risk of reactivation TB is estimated at 5% to 10%, although the risk is higher in patients with the medical comorbidities mentioned previously. Treatment of patients with latent TB with isoniazid (INH) for 9 months can decrease the risk of reactivation by up to 90%.

Development of Genitourinary Disease

There are four means by which GU TB develops. The principal route is via hematogenous spread of MTBC. Clinical disease may occur soon after bacilli reach the GU system, or they may enter a period of latency before becoming clinically active (Figueiredo and Lucon, 2008; Patterson et al, 2012). Typically, GU TB becomes evident after a prolonged latency, ranging up to 46 years (Christensen, 1974; Narayana, 1982). Hematogenous seeding may localize to only the GU tract or may widely disseminate to multiple organ systems. The typical sites for GU seeding are the kidneys and epididymis. Other organs of the GU tract become infected via contiguous spread from these initial landing sites.

Ascending or retrograde infection through the urinary system is the second route of infection, albeit significantly less common than hematogenous spread. This is the case in GU TB after bladder irrigation with bacille Calmette-Guérin (BCG) for the treatment of bladder cancer. BCG is a live, attenuated vaccine derived from *M. bovis*, a member of the MTBC. Although rare, GU TB complicates 0.9% of patients receiving BCG irrigation (Lamm et al, 1992). Cases described include pyelonephritis, renal abscesses, ureteric obstruction, cystitis, prostatitis, and epididymo-orchitis (Squires et al, 1999; Demers and Pelsser, 2012; Parker and Kommu, 2013).

Rarely, TB can also reach the GU system via contiguous spread from other organ systems or direct inoculation. TB is one of the few infectious diseases that do not respect anatomic boundaries. Extension of TB from the spine and psoas to the kidneys has been described (Kothari et al, 2001). Similarly, gastrointestinal (GI) TB can extend into the GU tract to form enterorenal and enterovesical fistulae (Ney and Friedenber, 1981; Merchant et al, 2013a). Direct inoculation is exceedingly rare. Cases include autoinoculation of external genitalia from infected stool or urine, and person-to-person

genital inoculation after contact with infected genital or oral lesions (Angus et al, 2001).

Clinical Manifestations and Pathologic Features

Symptoms and signs of GU TB are often nonspecific. Patients are often treated for other bacterial infections (sometimes repeatedly) or are evaluated for possible malignancy before GU TB is entertained. Symptoms correlate with the severity and location of disease. Renal TB, for example, can be progressive and destructive but symptomatically silent until it extends into the bladder. In developed countries, where patients with TB tend to seek medical attention earlier in the disease process, 8.4% of GU TB patients are asymptomatic (Figueiredo and Lucon, 2008). The typical TB constitutional symptoms of fever, weight loss, night sweats, and malaise are present in fewer than 20% of patients (Simon et al, 1977). Up to 50% of patients with GU TB have only dysuria on presentation, 50% have storage symptoms, and 33% have hematuria and flank pain (Figueiredo and Lucon, 2008). Renal colic occurs in fewer than 10% of patients and corresponds to the passage of necrotic papillary tissue, clots, stones, and caseous phlegmon in patients with severe pyelonephritis (Simon et al, 1977; Eastwood et al, 2001). Typical laboratory findings include sterile pyuria and/or hematuria. This combination is found in more than 90% of GU TB patients in developing countries.

Kidney

The kidney is the most common site of GU TB (Wong et al, 2013). Renal infection is progressive and highly destructive over time. The pathologic findings in the kidney vary greatly depending on disease severity.

The most insidious lesions are found in patients with pulmonary TB and renal failure, with or without pyuria, who have no changes visible on imaging of the GU tract. In these patients, kidney biopsies reveal TB-induced granulomatous interstitial nephritis (Ram et al, 2011). Renal histology shows granulomas, which are sometimes caseating. In some patients, treatment reverses the associated renal insufficiency (Eastwood et al, 2001). Other microscopic changes in the kidney include glomerulonephritis from immune complex deposition or amyloidosis secondary to TB (Sun et al, 2012). In these patients, the kidneys are collateral damage of pulmonary or systemic disease.

When renal infection is the outcome of widely disseminated TB in multiple organ systems, hematogenous spread of high numbers of bacilli leads to innumerable small (3-mm), pale clumps of granulomas that look like scattered millet seeds on gross pathologic examination of the kidney. This form of disseminated TB is known as *miliary TB* and carries a high mortality. In the kidney, the "milia" can be found studding the renal cortex and medulla and do not usually affect renal function (Eastwood et al, 2001).

In more localized infection of the kidney, tubercle bacilli become lodged first in the periglomerular capillaries. Granulomas form in the renal parenchyma and coalesce. When they caseate, cavities with necrotic material form. These can result in frank abscesses, chronic pyelonephritis, and parenchymal and papillary necrosis. Sinus tracts may emerge along the flanks (Bhatt and Lodha, 2012; Patterson et al, 2012). Examination findings at this stage can include costovertebral angle tenderness (Gokce et al, 2002). As infection advances, the calyces become inflamed and eventually calcify, resulting in calyceal distortion, dilatation, and stenosis (Merchant et al, 2013a).

With enough disease progression, the kidney becomes nonfunctional, a process called *autonephrectomy* (Teo and Wee, 2011). This complication is present in up to 33% of patients with GU TB. There are two types of autonephrectomy. The first is the caseo-cavernous type, in which viable tissue is replaced with granulomas and cavities filled with inflammatory exudate. This type of autonephrectomy occurs both with and without calcification. The second type is fibrotic, with severe scarring and calcification resulting in a shrunken kidney (Fischmann, 1951).

End-stage renal failure develops in approximately 7% of patients (Figueiredo and Lucon, 2008). Chronic inflammation may lead to squamous metaplasia in the renal pelvis that persists after treatment, posing a risk for squamous cell carcinoma (Byrd et al, 1976).

Ureter

TB in the ureters occurs via descent of infection from the kidneys. As bacilli pass in the urine through the ureter, granulomas can form along the walls. Infected calculi can also descend and lodge in the ureters. The ensuing inflammation leads to scarring and strictures, commonly in the distal end of the ureter at the vesicoureteral junction (Patterson et al, 2012). Strictures can also occur throughout the ureter in a “pan-ureteral” fashion leading to a “beaded corkscrew” appearance (Wong et al, 2013). When ureters are distorted from scarring, both obstruction and urinary reflux can develop (Eastwood et al, 2001). Urinary obstruction resulting from strictures is an important cause of renal failure in GU TB (Carl and Stark, 1997).

Bladder

Descending infection to the bladder usually begins near the ureteral orifices and spreads along the lymphatics to other areas. Similar to TB in the ureters, bacilli implant in the urothelium and cause a patchy cystitis. Ulcerations may develop in areas where large granulomas coalesce. The dome of the bladder is the most affected, whereas the trigone and neck usually remain normal. Mucosal inflammation, friability, and hematuria all follow (Wong et al, 2013). After approximately a year of chronic inflammation and mucosal scarring, bladder contracture develops (Singh et al, 2013). Urinary frequency, urgency, pain, and dysuria become prominent when bladder capacity shrinks to less than 100 mL. The severely contracted “thimble” bladder typically has a capacity of less than 20 mL. Bladder contraction is a late complication of GU TB and is more common in the developing world (12% vs. 4% of GU cases in developed countries), where diagnosis occurs after disease is more advanced (Figueiredo and Lucon, 2008).

Epididymis, Vas Deferens, Testes, and Scrotum

The epididymis, the second most common GU site of hematogenous seeding after the kidney, is involved in 10% to 55% of GU TB patients. Infection is bilateral in 34%. The disease initially affects the more vascular globus minor. Granulomas in the epididymal epithelium elicit chronic inflammation leading to fibrous narrowing and obliteration of the lumen. With disease progression, large caseous granulomas result in a nodular epididymis. On examination, the epididymis may appear swollen or hardened (Fraietta et al, 2003). In granulomas may adhere to the overlying skin and ulcerate, and in up to 50% of patients a tuberculous sinus tract develops on the posterior surface of the scrotum (Ferreira et al, 2011). After the infection spreads to the vas deferens, it becomes thickened and beaded on examination as a result of nodular scarring (Kulchavenya et al, 2012).

Isolated epididymis or testicular infections are rare but have been described (Kho and Chan, 2012; Shenoy et al, 2012). More commonly, epididymal TB extends into the testes. Granulomas form within the seminiferous tubular epithelium as well as in the connective tissue of the testis. Eventually, normal tissue becomes replaced with granulomatous tissue and fibrosis. The hardened masses that develop mimic testicular tumors. Approximately 5% of patients develop hydrocele.

Prostate and Seminal Vesicles

The prostate is infected via either hematogenous spread or urinary contamination. With hematogenous spread, prostatic lesions can be found in the periphery with sparing of the urethra. Disease then remains asymptomatic and progresses to calcification and gland hardening. Infection via the urinary route often involves the urethra and manifests more like bacterial prostatitis. Prostatic nodules or

fluctuation might be palpated on examination. TB should be suspected in patients with chronic prostatitis that persists despite antibiotics. Quinolones used to treat routine bacterial prostatitis are also active against MTBC. However, the shorter courses used for bacterial prostatitis are not sufficient for TB prostatitis, and the symptoms will not resolve or will quickly recur. Prostatic abscesses are rare but do occur, particularly in acquired immunodeficiency syndrome (AIDS) patients (Figueiredo and Lucon, 2008).

TB of the seminal vesicles may cause infertility, which can be the first symptom of GU TB (Lübbe et al, 1996). The bacilli reach the seminal vesicles through the vas deferens in patients with TB of the testis or epididymis, or through the urethra and ejaculatory ducts in patients with TB of the kidneys, bladder, or prostate. Granulomas develop in the walls of the seminal vesicles, and the lumen may be filled by caseation. Eventually calcification ensues. Patients may have low-volume ejaculate, oligospermia, azoospermia, or hematospermia. TB can rarely cause seminal vesicle abscesses (Eastham et al, 1999). Physical examination might reveal enlarged seminal vesicles with earlier detection, or hardened nodules with advanced disease.

Penis and Urethra

The urethra appears somewhat resistant to TB infection and is involved in only 1.9% to 4.5% of GU TB patients. It is typically associated with prostate infection and can manifest with urethroscrotal fistulae. Isolated urethral TB is very rare but has been reported (Bouchikhi et al, 2013). Similarly, primary TB in the penis is exceedingly rare. Penile lesions begin on the skin as an inflamed papule or a keratotic plaque (also known as *lupus vulgaris*). The lesions then ulcerate and spread to the cavernous tissue. Pea-sized nodules can be felt in the cavernous bodies and urethra corresponding to coalescing granulomas. These can be painless and hard, similar to malignancy. When fibrosis develops, the penis can become distorted (Angus et al, 2001; Gupta et al, 2008b; Kar and Kar, 2012).

Orificial TB, a rapidly necrotic form of penile TB, has also been reported (Ramesh and Vasanthi, 1989). It has been described in immunocompromised or severely debilitated patients. It arises from autoinoculation of the penile skin with infected stool or urine from the patient, or rarely from hematogenous or lymphatic spread (Wilkinson et al, 2010). Painful ulcers coated with pseudomembrane appear and can erode into deeper structures (Chen et al, 2000). Orificial TB is a presentation of very advanced and severe TB elsewhere in the GU or GI tract and carries a poor prognosis.

An exceedingly rare form of penile TB is papulonecrotic tuberculid (PNT) (Dandale et al, 2013). This is a cutaneous manifestation of TB on the glans penis and can occur in other skin areas as well. PNT of the penis has been described in Japan, South Africa, and India. The tuberculids are red papules that erupt on the skin, ulcerate, and undergo varioliform scarring. Unlike primary TB of the penis, these ulcers can be painless and do not contain tubercle bacilli. The tuberculids are hypersensitivity reactions to MTBC antigens that were disseminated to the skin from other infectious foci, and as such they are culture negative and typically polymerase chain reaction (PCR) negative. Histology is often inconclusive, as mature granulomas are not always seen. The recurrent lesions are easily confused with syphilis, Behçet disease, recurrent herpes simplex, balanitis, and squamous cell carcinoma. Recognizing this entity is the first step in diagnosis, and response to empirical TB treatment despite negative cultures confirms it.

Diagnosis

In developed countries, the primary goal of the diagnostic workup is isolation of MTBC in culture for drug susceptibility testing. In the right clinical context, tissue samples demonstrating caseating granulomas can support a diagnosis of TB when cultures or DNA test results are negative. Absent those, diagnosis of patients with GU TB relies on the constellation of consistent clinical findings in a patient with probable exposure and response to empirical medical treatment. Because up to 20% of GU TB occurs concurrently with

pulmonary TB (Figueiredo and Lucon, 2008), it is useful to also assess for the presence of pulmonary disease.

Culture

The current gold standard for the diagnosis of GU TB is urine acid-fast bacilli (AFB) culture. First-void urine is the best sample because urine is the most concentrated at that time. Three to five urine samples on consecutive days should be collected for maximum yield. These should be cultured immediately after collection because prolonged exposure to urine acidity can retard mycobacterial growth (American Thoracic Society, 2000a). The sensitivity of urine AFB cultures is as high as 80% when done in this manner. In real-world practice, however, sensitivity can be as low as 10% (Abbara and Davidson, 2011). Ziehl-Neelsen stains can be done on the urine as well, but the sensitivity is less than 50%. In addition, any tissue obtained from biopsy or surgery should also be cultured.

Mycobacterium tuberculosis complex has traditionally been cultured on solid, egg-based, Löwenstein-Jensen (LJ) medium. This method is laborious and time-consuming; usually 4 to 6 weeks are required before growth of MTBC can be detected. LJ remains the medium of choice in developing countries because it is the least expensive and requires no specialized equipment. In developed countries, urine is cultured on more expensive, agar-based, transparent, solid media, such as Middlebrook 7H10. With this medium, colonies can be visualized approximately 1 week earlier than with LJ media. Liquid-based detection systems such as the BACTEC Mycobacteria Growth Indicator Tube (MGIT) are also used in the developed world. The MGIT is a fully automated system that uses fluorescence quenching to detect mycobacterial growth in liquid media in as little as 10 days. Current guidelines recommend culturing on at least one solid medium concurrently with the liquid system to maximize yield (American Thoracic Society, 2000a). Other available detection methods include semiautomated systems that use radiometric liquid culture. Antibiotic susceptibility can be tested using any of the culture methods described earlier. Typically, susceptibility to first-line TB drugs is tested "in house" with use of the MGIT instrument. Susceptibility testing for second-line TB drugs is generally performed only at reference laboratories.

Nucleic Acid Amplification Tests

Several amplification tests have been developed to speed the detection of MTBC, providing results within 1 to 2 days. This can also aid detection in cases with low bacillary load, in which culture might fail to isolate the organisms. The tests have reported sensitivities ranging from 87% to 96% when compared with culture. However, nonsputum specimens such as urine contain natural inhibitors that interfere with the DNA or RNA amplification process, potentially resulting in false-negative test results (Moussa et al, 2000; Chawla et al, 2012; Mehta et al, 2012). The sensitivity of PCR tests for GU TB also depends on the type of sequence amplification used. Assays using the MTBC repetitive IS6110 insertion sequence perform better than those amplifying 16S-rRNA (Moussa et al, 2000).

In general, nucleic acid amplification tests (NAATs) are frequently underused in developed countries because culture is necessary for drug susceptibility testing. In developing countries, the cost and the need for expensive equipment have been the obstacles. Unlike cultures, NAATs cannot be used to monitor response to treatment because nucleic acids are shed from dead organisms and test results can remain positive despite adequate treatment (American Thoracic Society, 2000a).

In 2010, WHO enthusiastically endorsed the newest TB PCR assay on the market, the GeneXpert MTB/RIF. The system provides a self-contained platform that automates sputum processing, DNA extraction, and amplification in less than 2 hours. It simultaneously detects the presence of MTBC and rifampin resistance. Because more than 90% of rifampin-resistant strains are also INH-resistant, rifampin resistance serves as a surrogate marker for multidrug-resistant tuberculosis (MDR-TB) (Ioannidis et al, 2011). The assay

has been most studied with sputum samples and appears to have sensitivity similar to culture. Its use for GU TB is still being evaluated. In a small study of extrapulmonary TB that included 91 urine samples (only five of which were culture positive), the GeneXpert was 100% sensitive and 98.6% specific (Hillemann et al, 2011).

Histopathology

Histopathology shows findings consistent with TB in 38.3% of GU TB cases in developed countries and 21.9% of cases globally. Because urine cultures are sometimes negative, tissue biopsy can aid the diagnosis of GU TB (Kulchavenya et al, 2013). Although mycobacteria are often not seen, the finding of caseating granulomas in the appropriate clinical context can help establish a diagnosis of GU TB.

Screening Tests

The tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) do not differentiate between latent and active TB. They have limited usefulness in the diagnosis of active disease, although they are widely used and are approved by the U.S. Food and Drug Administration (FDA) for this purpose. A positive test result cannot rule in active TB, and a negative test result cannot rule it out. The ideal use for these tests is in the screening of individuals for the presence of latent TB infection. However, in the absence of other positive test results, the use of these screening tests can sometimes help sway the physician toward making a diagnosis of active TB disease.

Tuberculin Skin Test, Purified Protein Derivative, Mantoux Test. The TST evaluates the presence of an existing cellular immune response to MTBC antigens, which should be present in persons who have been infected. Tuberculin is a sterile suspension of protein extracted from cultures of *M. tuberculosis* and is injected intradermally into the volar aspect of the forearm. After 48 to 72 hours, delayed-type hypersensitivity will cause induration at the site of injection in those with prior immune priming. The CDC guidelines for interpretation of a positive test result depend on the risk factors of the patient. Three distinct cut-points for positivity have been defined according to risk. For persons with recent contact with a patient with TB, with fibrotic changes on chest radiographs that are consistent with prior TB, or who are immunosuppressed, 5 mm of induration or more is positive. For recent immigrants from high-prevalence countries, residents of or workers in high-risk institutions, injection drug users, and persons with medical comorbidities that increase risk of active TB, 10 mm of induration or more is positive. For the general public, 15 mm or more is positive (Box 17-1) (American Thoracic Society, 2000b).

Although initial training of personnel both in test placement and interpretation is necessary, the TST has many advantages. It is cheap, does not require a laboratory, and is easy to perform. The main disadvantage is that the TST is not specific for MTBC. Vaccination with BCG and infection with nontuberculous mycobacteria may elicit a positive reaction. In addition, the TST requires a second visit from the patient for test reading, which can be difficult to ensure. False-negative results can occur in 10% to 25% of persons with active TB (Huebner et al, 1993). In one study, the TST result was positive in 85% to 95% of patients with GU TB (Figueiredo and Lucon, 2008).

Interferon-Gamma Release Assays. IGRAs are blood tests that measure the level of IFN- γ (a surrogate of cellular immune reactivity) produced in response to MTBC-specific antigens, akin to an in vitro MTBC-specific TST. Persons infected with MTBC have circulating T cells that quickly recognize MTBC antigens and secrete IFN- γ on re-exposure. The antigens used in IGRAs are absent from all BCG strains and most nontuberculous mycobacteria, and thus exposure to these organisms does not result in a positive IGRA result. Results are available after 24 hours.

There are two IGRAs available in the United States: the QuantiFERON-TB Gold In-Tube test (QFT-GIT) and the T-SPOT.TB test. The QFT-GIT is simpler to run, whereas the T-SPOT.TB

BOX 17-1 Guidelines for Determining a Positive Tuberculin Skin Test Reaction**INDURATION ≥ 5 mm**

- HIV-positive persons
- Recent contacts of patient with active TB
- Fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of >15 mg/day prednisone for longer than 1 month, or TNF- α antagonists)

INDURATION ≥ 10 mm

- Recent arrivals (<5 yr) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings: prisons and jails, nursing homes and other health care facilities, residential facilities for AIDS patients, and homeless shelters
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that put them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss exceeding 10% of ideal body weight, gastrectomy, jejunoileal bypass
- Children younger than 4 years or infants, children, and adolescents exposed to adults in high-risk categories

INDURATION ≥ 15 mm

- Persons with no risk factors for TB; however, targeted skin testing programs should only be conducted among high-risk groups

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; TB, tuberculosis; TNF, tumor necrosis factor.

Modified from Diagnostic standards and classification of tuberculosis in adults and children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. *Am J Respir Crit Care Med* 2000;161(4 Pt. 1):1376–95; and Centers for Disease Control and Prevention. Tuberculosis (TB) fact sheets, <http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm>; September 1, 2012 [accessed 09.02.15].

IGRA requires more steps. In the QFT-GIT, whole blood is collected in three specialized test tubes, one containing the MTBC antigens ESAT-6, CFP-10, and TB7.7, and two controls (negative and positive). The blood is incubated directly in the collection tubes for 16 to 24 hours. Plasma is then separated and IFN- γ is measured using enzyme-linked immunosorbent assay (ELISA). Test results are read as positive, negative, or indeterminate, based on the level of IFN- γ produced in relation to the negative and positive controls. In the T-SPOT.TB assay, peripheral blood mononuclear cells are separated from whole blood and then incubated with ESAT-6 and CFP-10 in wells coated with antibodies that capture IFN- γ . Enzyme-linked immunospot (ELISPOT) assay is used to detect an increase in the number of cells (appearing as spots in each test well) that secrete IFN- γ in relation to a negative control. Spots are manually counted, and the test result is read as positive, negative, or borderline. Despite the increased difficulty of performing T-SPOT.TB over QFT-GIT, it is the more sensitive test. Pooled studies estimate a sensitivity of 83% for QFT-GIT and 91% for T-SPOT, versus 89% for TST in cases of culture-confirmed TB (Mazurek et al, 2010).



Figure 17-1. Kidney-ureter-bladder radiographic view in a patient with left renal tuberculosis with associated calcifications.

Radiography

GU TB generates a wide spectrum of imaging findings. The test of choice depends on disease location and should be driven by symptoms and other clinical data. Imaging is often the first test that indicates TB is the cause of a GU disorder.

Plain Radiography. The kidney-ureter-bladder (KUB) radiograph will frequently demonstrate calcifications caused by TB, which are present in more than 50% of patients (Merchant et al, 2013a). Initial renal lesions may appear as faint punctate calcifications within the parenchyma. As TB progresses, the KUB film may show globular calcifications that correspond to a tubercular mass (Fig. 17-1). Papillary necrosis appears as triangular ringlike calcifications in the collecting system. With fibrotic autonephrectomy, the KUB radiograph shows a small, shrunken, calcified “cement” or “putty” kidney, in which calcific rims outline the individual renal lobes; this lobar pattern is pathognomonic for end-stage renal TB.

A plain radiograph can also demonstrate renal and ureteral TB-infected calculi. Stones may take strange shapes as they form in a deformed and fibrosed renal pelvis. A stone in the shape of an upward arrowhead may indicate a renal pelvis that has been “hiked up” by contraction from scarring.

The KUB film can also show ureteral calcifications, which are characteristically intraluminal as opposed to the mural calcifications of schistosomiasis. Bladder wall calcifications are not very common except in late cases of bladder contraction. Calcifications of the prostate and seminal vesicles are seen in 10% of patients. Plain film findings suggestive of TB may be seen in surrounding tissues as well, appearing as erosions of the vertebral bodies or calcifications in cold abscesses of the psoas muscle (Teo and Wee, 2011; Merchant et al, 2013a).

Intravenous Urography. Intravenous urography (IVU) is the gold standard for imaging early renal TB. Initial erosive changes of the urothelium appear as loss of sharpness and edge irregularities (Figueiredo and Lucon, 2008). Calyceal erosions have a moth-eaten appearance (Patterson et al, 2012). Filling defects may be seen, caused by tuberculomas rupturing into the calyx or by papillary

necrosis. IVU can demonstrate medullary cavities that communicate with the collecting system. When a calyx or infundibulum is stenosed, contrast excretion by the renal parenchyma may fail, creating a “phantom calyx” in the location where the calyx should be visible (Eastwood et al, 2001). Ureteral TB can manifest as a rigid, calcified, straightened, pipestem ureter that is tubular and lacks normal peristaltic activity on IVU. The ureter may also take on the appearance of a beaded corkscrew as a result of nodular fibrosis along the entire ureter. The pipestem and corkscrew findings are highly suggestive of TB, particularly when seen concurrently with either kidney or bladder abnormalities. IVU can also detect nonfunctional kidneys resulting from autonephrectomy, as well as a fibrosed, contracted bladder (Fig. 17-2). On occasion, perinephric abscess might be suggested, particularly if there is restriction of renal movement with breathing, or ureteral displacement on IVU.

The most common findings on IVU, however, are obstructive changes resulting from scarring and distortion of the collecting system: calyceal obliteration, infundibular narrowing, hydrocalycosis, segmental or total hydronephrosis, and hydroureter (Figs. 17-3 and 17-4). Calyceal dilatation and distortion will present a typical cloverleaf pattern on film (Carl and Stark, 1997). Ureterovesical junction obstruction is caused by tuberculous cystitis or strictures of the distal third of the ureter (Fig. 17-5). The finding of a “hiked-up” renal pelvis, with sharp angulation of the ureteropelvic junction (UPJ), is known as “Kerr’s kink” (Merchant et al, 2013a).

Computed Tomography with Urography. Computed tomography (CT) with urography is the most frequently used modality for imaging TB in developed countries, where it has largely replaced IVU (Merchant et al, 2013b). High-end multidetector scanners can detect lesions as small as 3 to 4 mm. With the administration of intravenous contrast, CT can assess kidney function during different phases of excretion. Similar to KUB and IVU, CT reveals calcifications, scarring, and signs of obstruction (Fig. 17-6). CT is more sensitive than KUB in detecting calcifications and thickening of the collecting ducts. It is particularly useful in evaluating patients with complicated and extensive TB. Perinephric and psoas abscesses can

be seen, as well as any pathology in lymph nodes, vertebrae, spleen, or liver. Pathology in the prostate and seminal vesicles can also be visualized, including enlargement, necrosis, cavitations and abscesses, and calcifications.

CT does have disadvantages. CT is less sensitive for detecting the minimal urothelial thickening, subtle papillary necrosis, and other changes of early renal TB, for which IVU is still the preferred study. In addition, CT imparts a higher radiation dose than IVU.



Figure 17-3. Occluded calyx.



Figure 17-2. The cystogram portion of an intravenous pyelogram in a patient with left renal tuberculosis. Note the contracted left side of the bladder that is secondary to fibrosis from the tuberculosis.



Figure 17-4. Severe calyceal and parenchymal destruction.



Figure 17-5. Stricture at the distal left ureter.

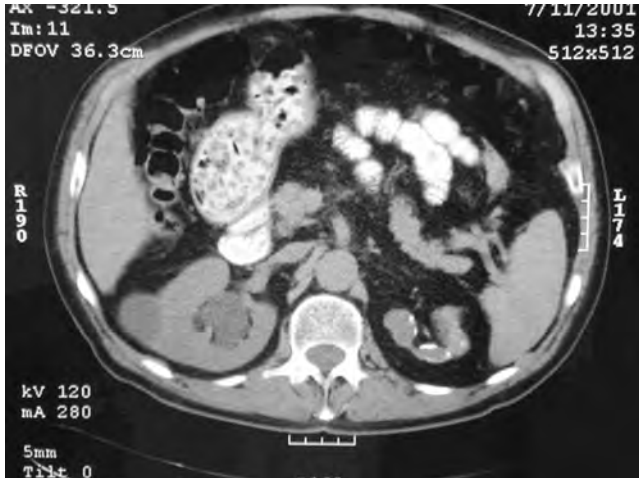


Figure 17-6. Computed tomography scan after oral contrast medium in a patient with bilateral renal tuberculosis. The right kidney is hydronephrotic secondary to infundibular stenosis but has retained good function. The left kidney is an end-stage nonfunctioning atrophic kidney with calcification.

Retrograde Pyelography and Antegrade Pyelography. Both retrograde and antegrade pyelography, with either percutaneously or endoscopically administered contrast, have been replaced by CT urography. However, when IVU or CT cannot be done because of renal insufficiency or contrast allergy, these modalities can be helpful in delineating the distortions in GU anatomy. In addition, these tests can be used in conjunction with IVU to determine whether cavitations are obstructive or nonobstructive, and whether they are in communication with the urinary collecting system or not (Merchant et al, 2013b).

Ultrasonography

Ultrasonography (US) has a limited role in the diagnosis of GU TB because findings are generally nonspecific and visualization is not as clear as with CT. It is useful in pediatric or pregnant patients because of the lack of radiation exposure. US is also less expensive than CT. US can be used to evaluate the testes, epididymis, and, with transrectal US, the prostate and seminal vesicles, which will appear thickened. US can also locate abscesses or cavities in the kidney. Cystic lesions with septations suggest chronic infection (Wong et al, 2013). Focal calcifications appear as highly echogenic areas with distal shadowing. Restriction of renal movement during breathing suggests a perinephric or psoas abscess. Like CT, US can provide concurrent information about the abdomen, such as the presence of ascites, lymphadenopathy, or omental caking. A primary use of US in GU TB is to follow hydronephrosis in patients who are receiving medical treatment because fibrosis during healing can worsen urinary obstruction.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is not commonly used in the workup of GU TB because of the many other imaging modalities available (Merchant et al, 2013b). Similar to US, it can be useful in pediatric or pregnant patients to avoid exposure to radiation. MRI can detect a single granuloma. Small lesions are hypointense on both T1 and T2 images. Larger lesions have central hyperintensity on T2 images because of the increased cellularity at the center of the granuloma. Larger TB lesions can mimic malignancy, and it is not always possible to differentiate the two.

A magnetic resonance urogram (MRU) can be more sensitive than IVU in showing urothelial thickening and caliectasis. The addition of diffusion-weighted imaging (DWI) can help distinguish hydronephrosis from pyonephrosis. Various techniques have been explored with MRI to study TB, including cine MRU and dynamic MRU, which can evaluate ureteral peristalsis. MRI with DWI can be used to monitor renal fibrosis. Apparent diffusion coefficients (ADCs) decrease with fibrosis and can be used to gauge the stage of TB, including the effect of treatment. Caution should be exercised with use of gadolinium in renal failure patients because of the risk of development of nephrogenic systemic fibrosis.

Cystoscopy and Ureteroscopy

Endoscopy plays a limited role in the diagnosis of TB. Although it allows direct visualization of lesions, findings can be nonspecific. They include local hyperemia, mucosal erosion, ulceration, granulomatous masses, and irregularity of the ureteral orifices. Ulcerative lesions may mimic malignancy. A "golf-hole" ureteric orifice is suggestive of TB, and, when found, upper tract imaging or endoscopy should be performed (Fig. 17-7). Biopsies should be performed when possible, especially if malignancy is a possibility. Although a positive urine culture for MTBC is sufficient for diagnosis, results may not be available quickly enough. Furthermore, in those with negative urine cultures, bladder biopsy can be 19% to 52% sensitive for TB (Figueiredo and Lucon, 2008).

Treatment

Before the development of antimicrobials, treatment of TB relied primarily on rest and nourishment in sanatoria; and in those with severe GU disease, extirpative surgery was the best hope for cure. With the development of streptomycin in 1944, followed by INH in 1952 and the rifamycins in 1957, medical treatment with antituberculous drugs replaced sanatoria and surgical procedures (Daniel, 2006). Today, most TB patients can be treated medically and in the ambulatory setting, even those with MDR-TB. Surgery now serves primarily to establish a diagnosis or as an adjunct to antibiotics in advanced cases (Abbara and Davidson, 2011).

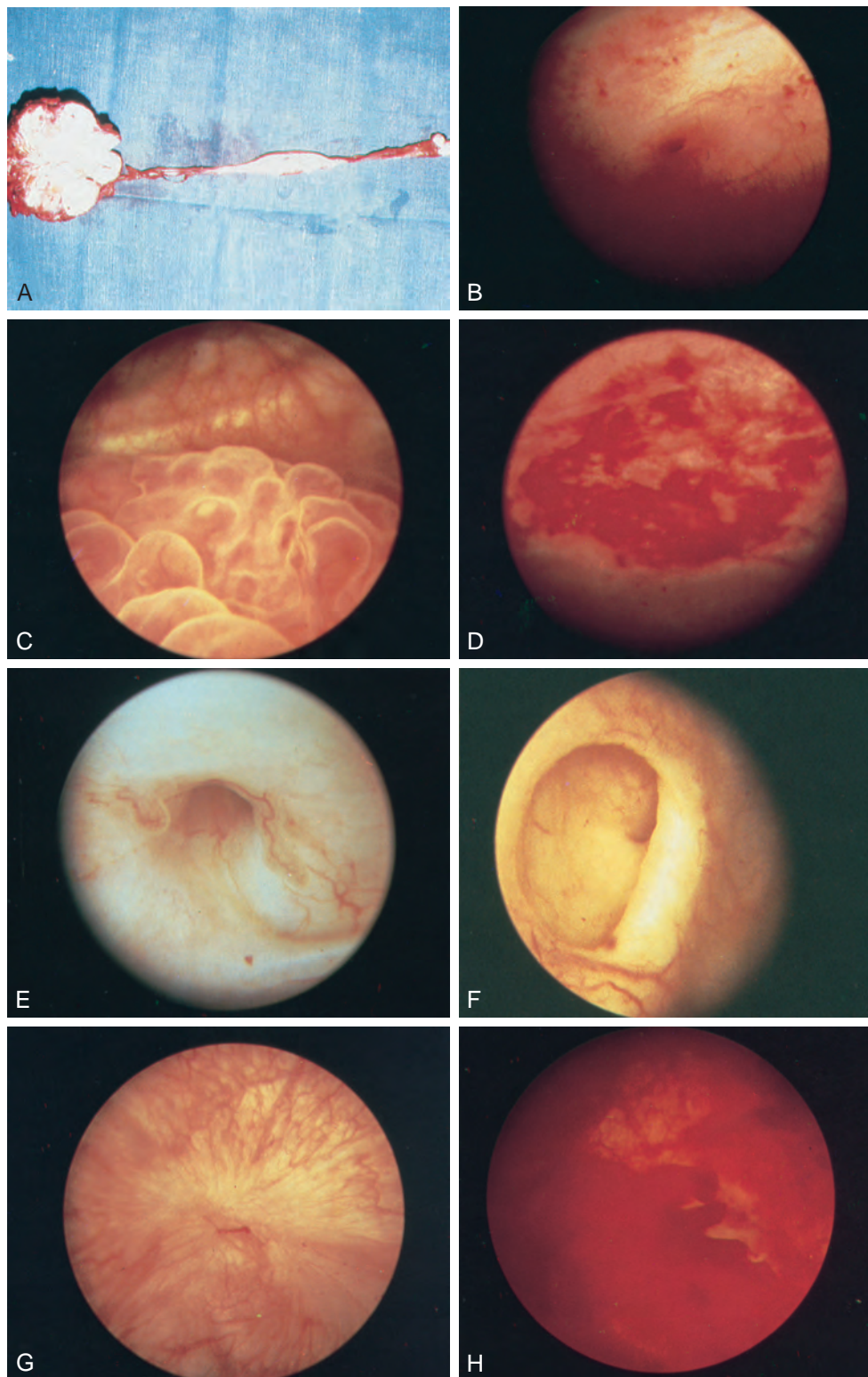


Figure 17-7. A, Extensive tuberculosis of the kidney and ureter with calcification and stricture formation. B, Acutely inflamed ureteric orifice. C, Tuberculous bullous granulations. D, Acute tuberculous ulcer. E, Tuberculous golf-hole ureter. F, Tuberculous golf-hole ureter, severely withdrawn. G, Healed tuberculous lesion. H, Acute tuberculous cystitis with ulceration.

Medical Therapy

Successful medical treatment of TB requires multiple drugs for several reasons (CDC, 2003). First, the tubercle bacilli exist in different microenvironments within the host. These apply different pressures on the organism and cause it to exhibit

different metabolic needs and replication speeds. The drugs vary in their activity against MTBC; some are bactericidal, whereas others are only bacteriostatic. Some drugs work best on rapidly replicating bacteria, whereas others are more effective against dormant bacilli. The drugs also penetrate differently into various tissues and perform optimally at different pHs. In addition,

TABLE 17-1 First-Line Antituberculous Drugs

DRUG/FORMULATION	ADULT DOSAGE (DAILY) ¹	ADULT DOSAGE (INTERMITTENT) ²	MAIN ADVERSE EFFECTS
Isoniazid (INH) ³ 100-mg, 300-mg tabs 50-mg/5-mL syrup 100-mg/mL injection	5 mg/kg (max 300 mg)	15 mg/kg (max 900 mg) 3 times/wk	Hepatic toxicity, peripheral neuropathy
Rifampin (Rifadin, Rimactane) ⁴ 150-mg, 300-mg caps 600-mg injection powder	10 mg/kg (max 600 mg)	10 mg/kg (max 600 mg) 3 times/wk	Hepatic toxicity, flulike syndrome, pruritus, drug interactions
Rifabutin (Mycobutin) ⁵ 150-mg caps	5 mg/kg (max 300 mg)	5 mg/kg (max 300 mg) 3 times/wk	Hepatic toxicity, flulike syndrome, uveitis, neutropenia, drug interactions
Rifapentine (Priftin) ⁶ 150-mg tabs		10 mg/kg/wk PO (max 600 mg) Continuation phase only in very select patients	Similar to rifampin
Pyrazinamide 500-mg tabs	40-55 kg: 1000 mg 56-75 kg: 1500 mg 76-90 kg: 2000 mg	3 times/wk: 40-55 kg: 1500 mg 56-75 kg: 2500 mg 76-90 kg: 3000 mg	Arthralgias, hepatic toxicity, pruritus, rash, hyperuricemia, gastrointestinal upset
Ethambutol (Myambutol) 100-mg, 400-mg tabs	40-55 kg: 800 mg 56-75 kg: 1200 mg 76-90 kg: 1600 mg	3 times/wk: 40-55 kg: 1200 mg 56-75 kg: 2000 mg 76-90 kg: 2400 mg	Decreased red-green color discrimination, decreased visual acuity, optic neuritis

1. Or 5 times/wk directly observed therapy (DOT).

2. Intermittent therapy (administered by DOT) only during the continuation phase of therapy. The World Health Organization (WHO) no longer recommends dosage intervals less frequent than 3 times/wk.

3. Pyridoxine 25 to 50 mg should be given to prevent neuropathy in malnourished or pregnant patients and those with human immunodeficiency (HIV) infection, renal failure, thyroid disease, alcoholism, or diabetes.

4. In general, cannot be taken by HIV-infected persons taking protease inhibitors or certain non-nucleoside reverse-transcriptase inhibitors (NNRTIs).

5. When taken with efavirenz, the rifabutin dose is increased to 450 mg/day or 600 mg 3 times/wk. When taken with fosamprenavir, nelfinavir or indinavir, the rifabutin dose is 150 mg/day or 300 mg 3 times/wk. With ritonavir, atazanavir, or ritonavir combined with other protease inhibitors, the rifabutin dose is 150 mg every other day or 3 times/wk; some experts believe this dose to be subtherapeutic and recommend 150 mg daily or 300 mg 3 times/wk with close monitoring for rifabutin toxicity, particularly uveitis.

6. Rifapentine is contraindicated in HIV-positive persons, in persons with cavitary pulmonary disease, and in persons with extrapulmonary tuberculosis. Use of once-weekly rifapentine is not advocated by WHO.

From Drugs for tuberculosis. Treat Guidel Med Lett 2012;10(116):29-36; and modified by Centers for Disease Control and Prevention (CDC). Treatment of tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR Recomm Rep 2003;52(RR-11):1-77.

multiple drug therapy prevents the emergence of drug-resistant strains.

Combination therapy with first-line antituberculous drugs achieves the best cure rates in the shortest time frame (Table 17-1). Treatment should start with these—namely, INH, rifampin, pyrazinamide, and ethambutol. Before the start of treatment, baseline measurements should include blood counts and liver and kidney function tests. Patients should also be tested for HIV and, when appropriate, hepatitis B and C. Medical therapy should be tailored according to drug susceptibility data when available. Directly observed therapy (DOT) should be employed to ensure medication adherence and minimize the likelihood of development of drug-resistant strains.

Second-line agents are reserved for patients in whom first-line agents fail or who experience side effects from first-line agents, and for cases of drug resistance. Second-line agents vary in tolerability and ease of administration (Table 17-2). Recent drugs added to the second-line agents are the fluoroquinolones and linezolid (Lee et al, 2012), both of which were developed to treat other bacterial infections, and bedaquiline—the first new drug in 40 years specifically developed for TB. It was fast-tracked by the FDA and approved for use on December 28, 2012 after completion of only phase 2b

studies. Currently, it is approved only as part of combination therapy for drug-resistant pulmonary TB (CDC, 2013b).

Genitourinary TB can be successfully treated with the standard short-course regimen of 6 months of first-line antituberculous drugs (CDC, 2003). Treatment begins with an intensive phase of 2 months of daily INH, rifampin, and pyrazinamide, followed by a continuation phase of 4 months of INH and rifampin given daily, or alternatively thrice weekly. Twice-weekly administration during the continuation phase is no longer recommended (WHO, 2010). Pyridoxine (vitamin B₆) administration minimizes the risk of INH-induced peripheral neuropathy. Ethambutol is added at the beginning of treatment pending drug susceptibilities and is discontinued if the strain is found to be susceptible to the other first-line drugs. First-line drugs reach high concentrations in the urine and work well in acidic environments. The intensive phase of treatment targets rapidly multiplying bacteria, whereas the continuation phase attempts to eradicate slow, sporadic multipliers and persistent bacteria.

Although 6 months is the duration of standard short-course therapy, clinical scenarios regularly arise that require prolongation of treatment. Both the type of clinical disease present and the antituberculous drugs used affect duration of treatment (CDC, 2003).

TABLE 17-2 Second-Line Antituberculous Drugs

DRUG/FORMULATION	ADULT DOSAGE (DAILY) ¹	MAIN ADVERSE EFFECTS
Streptomycin ²	15 mg/kg IM, IV (max 1 g)	Vestibular and auditory toxicity, renal damage
Capreomycin (Capastat) ²	15 mg/kg IM, IV (max 1 g)	Auditory and vestibular toxicity, renal damage, electrolyte imbalance
Kanamycin (Kantrex and others) ²	15 mg/kg IM, IV (max 1 g)	Ototoxicity, renal damage
Amikacin (Amikin and others) ²	15 mg/kg IM, IV (max 1 g)	Ototoxicity, renal damage
Cycloserine (Seromycin) ³	10-15 mg/kg in 2 doses (max 500 mg bid) PO	Psychiatric symptoms, seizures
Ethionamide (Trecator-SC)	15-20 mg/kg in 1 or 2 doses (max 500 mg bid) PO	Gastrointestinal and hepatic toxicity, hypothyroidism, optic neuritis, neurotoxicity
Levofloxacin (Levaquin)	500-1000 mg PO, IV	Gastrointestinal toxicity, central nervous system effects, rash, dysglycemia, QT prolongation, tendinitis or tendon rupture
Moxifloxacin (Avelox)	400 mg PO, IV	Gastrointestinal toxicity, central nervous system effects, rash, dysglycemia, QT prolongation, tendinitis or tendon rupture
Aminosalicylic acid (PAS; Paser)	8-12 g in 2 or 3 doses PO	Gastrointestinal disturbance, hepatitis, hypothyroidism
Linezolid (Zyvox)	600 mg PO bid	Bone marrow suppression, peripheral and optic neuropathy, hepatic toxicity
Bedaquiline (Sirturo) ⁴	400 mg PO	Headache, nausea, arthralgias, QT prolongation, hepatic toxicity

1. Dosage may need to be adjusted for patients with renal impairment.

2. In general, given 5 to 7 times/wk (15 mg/kg, or a maximum of 1 g per dose) for an initial 2 to 4 months, and then (if needed) 3 times/wk (20 to 30 mg/kg, or a maximum of 1.5 g per dose). Administration less frequently than 3 times/wk is no longer recommended. For patients older than 59 years, dose is reduced to 10 mg/kg (max 750 mg per dose). Dose should be decreased if renal function is diminished.

3. Some authorities recommend pyridoxine 50 mg for every 250 mg of cycloserine to decrease the incidence of adverse neurologic effects.

4. Bedaquiline is given at 400 mg orally with food, daily for 2 weeks, then 200 mg orally 3 times/wk.

From Drugs for tuberculosis. Treat Guidel Med Lett 2012;10(116):29-36; and modified by Centers for Disease Control and Prevention (CDC). Treatment of tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR Recomm Rep 2003;52(RR-11):1-77; Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med 2012;367(16):1508-18; and CDC. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR Recomm Rep 2013;62(RR-09):1-12.

For example, treatment for at least 9 months is recommended for extensive pockets of infection, concurrent smear-positive cavitary pulmonary disease, central nervous system involvement, or a delay in positive cultures converting to negative. If the patient is unable to take pyrazinamide for at least 2 months, because of either side effects or drug resistance, the duration of therapy should also be 9 months or longer. Some clinicians recommend 12 months of therapy for GU TB because of high relapse rates of up to 22% when therapy is given for only 6 months (Gokalp et al, 1990). Because of the complexities that often arise with regimen choice, drug interactions, and side effects, any deviation from standard short-course therapy should be discussed with specialists experienced in treating TB.

During therapy, liver enzymes should be monitored monthly in those with preexisting liver disease because all first-line agents except ethambutol can cause hepatic toxicity that can be reversed with drug discontinuation (CDC, 2003). Patients should be advised to abstain from alcohol and other hepatotoxic drugs. Although treatment is, in general, well tolerated, severe hepatic injury has occurred. Visual acuity and red-green color perception also should be monitored in patients taking ethambutol. Close follow-up of patients is necessary, not only to monitor for side effects, but also because renal lesions may worsen with drug treatment. The healing process is sometimes accompanied by new fibrosis, which can worsen urinary obstruction and bladder contraction (Psihramis and Donahoe, 1986). Steroids may help in the management of these patients (see later). Surgical intervention to relieve worsening or newly developed obstruction might be necessary.

Corticosteroids. The role of adjunctive corticosteroids for the treatment of active TB still needs to be fully elucidated. The

anti-inflammatory effects of corticosteroids are thought to prevent an unchecked host immune response from causing excessive tissue destruction and scarring. They are strongly recommended for TB meningitis and TB pericarditis, and they are sometimes used in patients with severe pulmonary TB, when antibiotic treatment leads to a paradoxical worsening of symptoms (Breen et al, 2004). Steroids have also been used in a few patients with GU TB to prevent ureteral strictures and bladder contraction, but these situations are anecdotal and no clinical trials have been conducted. A recent review and meta-analysis of published clinical trials of corticosteroid use in pulmonary, meningeal, pleural, pericardial, and peritoneal TB showed that regardless of which organ system was affected, steroids reduced mortality by 17% (Critchley et al, 2013).

Surgical Therapy

About 55% of patients with GU TB will require surgical management during the course of their disease (Wong et al, 2013). Intervention is more frequent as disease advances. Surgical procedures are performed to relieve urinary obstruction and drain infected material, to remove nonworking infected kidneys in cases resisting cure, to improve medically resistant hypertension secondary to a functionally excluded kidney, or to reconstruct the urinary tract. Currently, more than half of operations performed for TB are reconstructive (Gupta et al, 2008b). The optimal timing of surgery is 4 to 6 weeks after the initiation of medical therapy. This delay allows active inflammation to subside, the bacillary load to decrease, and lesions to stabilize.

Procedures to Relieve Obstruction. Prompt relief of obstruction is emergently required in cases of uremia or sepsis. Bilateral

obstruction or unilateral obstruction of a functionally solitary kidney is often the cause of renal failure. Early ureteral stenting or percutaneous nephrostomy (PCN) for tuberculous ureteral strictures limits the loss of renal function and increases the opportunity for later reconstructive surgery (Shin et al, 2002). Temporary and immediate drainage of obstruction is recommended, preferably by retrograde ureteric stenting. An indwelling double-J stent can be placed until the patient's condition has been optimized. Retrograde placement is successful in 41% of cases (Ramanathan et al, 1998). When this is not technically feasible, an antegrade, internalized or externalized ureteral stent is placed via percutaneous puncture of the obstructed kidney. If that also fails, a PCN is left in place until definitive management. Because strictures and fibrous scars may be present, more than one PCN may be necessary (Carl and Stark, 1997). PCN must be followed by correction of the cause of obstruction. A tuberculous cutaneous fistula can develop if the PCN is simply removed, although this is less likely to develop with effective concurrent medical therapy. If the kidney is unsalvageable, a nephrectomy may become necessary. High-contrast injection pressures during stent and PCN placement should be avoided to prevent possible dissemination of infection (Salem, 2008).

Nephrectomy. Organ preservation is the fundamental goal in surgical management of GU TB. However, total nephrectomy is considered in two settings. The first is the patient with a nonfunctional kidney and recalcitrant or recurrent TB despite optimal medical therapy. After nephrectomy of the infected kidney, relapse rates of less than 1% have been reported following short-course medical treatment (Figueiredo and Lucon, 2008). The second setting in which nephrectomy is considered is the patient with a nonfunctional kidney and medically resistant hypertension. Nephrectomy improves hypertension in 65% of patients (Flechner and Gow, 1980). Overall, nephrectomy is performed in 27% of GU TB patients, and the frequency is similar between developed and developing countries (Figueiredo and Lucon, 2008).

Because of the extensive fibrosis often present, the traditional approach to the kidney is through an oblique retroperitoneal incision that can be extended dorsally or ventrally as needed. In rare patients the perinephric fat may appear to have granulomatous masses or caseous cavities. These should be removed with the specimen. Individual ligation of the renal artery and vein is preferred to limit risk of late arteriovenous fistula. The ureters are usually not taken out concurrently. Care must be taken to minimize disruption of the surrounding lymphatics and to avoid entering the pleural or peritoneal space during the procedure.

More recently, laparoscopic nephrectomy has gained popularity (Lee et al, 2002; Hemal, 2011) despite concerns that extensive fibrosis associated with TB would render a laparoscopic approach suboptimal. Several investigators have reported good outcomes and suggest that it should be the preferred approach because of decreased blood loss and more rapid patient recovery (Chibber et al, 2005; Zhang et al, 2005; Gupta et al, 2008a). In experienced hands, laparoscopic nephrectomy for renal TB is a somewhat longer procedure than when it is done for other reasons, but in one study the procedure took only half an hour longer on average (Lee et al, 2002).

Ureteropelvic and Ureteral Surgery. Strictures of the UPJ and ureter may be temporarily stented to allow improvement of renal function before definitive management. Upper ureteric and mid-ureteric strictures are rare and may be amenable to endourologic treatment. Lower ureteric strictures are more common and often require open surgical intervention. The length and degree of the stricture, whether it can be passed by a guidewire or not, vascular supply to the lesion, and renal function are important factors to be considered in the management of patients (Kim et al, 1993).

Endoscopic Management. Tuberculous ureteric strictures are characterized by mucosal ischemia and dense fibrosis. Hence, success rates for endoscopic management of strictures from other causes may not necessarily apply to TB strictures. In general, short strictures with residual lumens in patients with good renal function yield the best outcome. Strictures forming during medical treatment and managed by early stenting (double-J placement) can stabilize and require no further treatment (Shin et al, 2002). Balloon dilatation

by retrograde or antegrade access has been described for TB strictures of the ureter, UPJ, ureterovesical junction, and calyceal infundibula (Murphy et al, 1982; Kim et al, 1993). A stent is often placed after dilatation. Because of high failure rates, repeated procedures are often needed.

Follow-up imaging (US or IVU) of all patients with ureteric strictures is needed, especially those managed endoscopically, because some strictures will worsen during the healing process as a result of fibrosis and cicatrization. Corticosteroids may be added if deterioration is detected. Failure to improve or progression after 6 weeks of medical treatment is an indication for open surgical management.

Open Surgical Options. Long, complex strictures require open surgical repair. Because of fibrosis, loss of elasticity, and reduced vascularity, mobilization of structures may be difficult. Repair of UPJ scarring is more challenging in patients with TB than in those with congenital stenosis. Dismembered pyeloplasty is feasible for extrarenal pelvis with short-segment scarring. Nondismembered (flap) pyeloplasty is preferred for longer strictures but may not be feasible because of excessive scarring of the pelvis. When anatomic reconstruction is not possible, ureterocalicostomy (anastomosis of the ureter to the lower pole calyx) is an option. The renal capsule should be preserved to cover the lower pole of the kidney. If not enough capsule is available, omentum can be used to avoid stenosis at the calicoureteral anastomosis (Carl and Stark, 1997).

Upper and middle ureteric strictures can be managed by excision of the diseased segment, and, with adequate mobilization, a primary tension-free ureteroureterostomy can be performed. Alternatively, lysis of adhesions and intubation (Davis intubated ureterotomy) may be done. Lower ureter strictures requiring surgery are best managed by complete excision of the entire affected ureteric segment back to healthy ureteric mucosa that has good blood supply. The resultant gap is bridged with a tension-free, well-vascularized anastomosis to healthy bladder (ureteroneocystostomy). Various procedures exist to bring the bladder closer to the ureteric end. Simple mobilization of the lateral attachments of the bladder on the contralateral side, accompanied by division of the superior vesical artery, may provide 2 to 3 cm of length to bridge a small gap. In patients with good bladder capacity, a psoas hitch may also be performed. Care must be taken to avoid the genitofemoral and femoral nerves when placing these sutures. A well-performed psoas hitch can bridge a gap of up to 5 cm. A Boari flap is another method of bridging a longer gap of 10 to 15 cm and may be performed in combination with a psoas hitch (Sankari, 2007). It is important to note that a poorly executed Boari flap can compromise bladder capacity. Contracted bladders from TB cystitis may not have sufficient surface area and elasticity to allow flap creation. Finally, ileal interposition (ileal ureteric replacement) can be done in patients with multiple or recurrent strictures when the native ureter is no longer an adequate conduit (Goel and Dalela, 2008).

Bladder Surgery. Augmentation cystoplasty and bladder substitution are options in the management of the tuberculous contracted bladder. First described in the 19th century for a tuberculous contracted bladder, augmentation is indicated when frequency, nocturia, urgency, pain, and hematuria become intolerable—typically when bladder capacity is less than 100 mL (Gupta et al, 2008b). For severely contracted bladders, ileocecum or sigmoid segments are most suitable. When only half the bladder is diseased, ileum is often used. Other segments used in augmentation include stomach and cecum. The general rules of incorporating the bowel into the urinary tract apply, such as thoroughly evaluating renal function, reconfiguring a low-pressure reservoir (de Figueiredo et al, 2006), performing patient education, and conducting long-term follow-up. Thimble bladders with capacity less than 20 mL are best managed by orthotopic bladder substitution (Hemal and Aron, 1999). Complications of either bladder augmentation or substitution include mucus production, electrolyte derangements, and secondary bacterial infection.

Urethra 1 Procedures. Bladder neck contracture is best managed endoscopically by transurethral incision of the contracture. Urethral

strictures are also managed endoscopically and often require repeated procedures. Tuberculous urethral fistulae are treated by initiation of medical therapy and suprapubic bladder drainage. Delayed reconstruction is preferred. Drainage of a seminal vesicle tuberculous cavity into the bladder by cold knife incision has been reported (Dewani et al, 2006).

Genital Surgery. Extirpative surgery for genital TB is considered only for patients in whom medical therapy has failed. When the epididymis is infected with sparing of the testis, every effort should be made to perform an epididymectomy alone without orchiectomy. Preserving testicular blood supply is important during dissection of the epididymis. Initiating dissection at the globus minor after ligation of the vas facilitates excision. If the testes are infected, a scrotal orchiectomy can be done. Involvement of the vas deferens by TB is usually distal to the external ring, and ligation at the level of the ring is possible and sufficient.

Monitoring for Tuberculosis Relapse

Even with optimized treatment, as with any infection, TB can relapse in 2% to 6% of pulmonary TB patients, particularly within the first year after treatment (CDC, 2003). A second, longer, or different drug course is then required. GU TB patients may relapse at a higher rate than pulmonary TB patients, in 6.3% to 22% of cases, even after 12 months of medical therapy (Figueiredo and Lucon, 2008). The extensively diseased kidney can contain innumerable foci of tubercle bacilli. Difficulty in achieving complete sterilization of all foci with antituberculous drugs may be the reason for the higher relapse rate. Viable bacilli have been identified in the kidneys even after 9 months of treatment (Figueiredo and Lucon, 2008). In all patients with recurrent TB, extra effort should be exerted to isolate the organism for drug susceptibility testing. Pulmonary TB patients are usually followed for 2 years after completing treatment; for GU TB patients, some investigators have recommended 10 years of follow-up, because the average time of relapse was 5.3 years (Gokce et al, 2002).

Management of Genitourinary Tuberculosis in Special Situations

Each of the special situations that follow require special handling of the antituberculous regimen because of side effects, interactions, and drug toxicities. Expert advice should be sought from infectious diseases specialists or physicians experienced in the treatment of TB.

Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

Persons with MTBC strains that are resistant to both INH and rifampin (the two most important first-line agents) have MDR-TB. Worldwide, approximately 3.7% of newly diagnosed patients and 20% of previously treated patients have MDR-TB (CDC, 2013b). Treatment is complicated by the need to use regimens longer than 18 months. The cure rate is 50% to 60% compared with 94% to 97% in patients with drug-susceptible TB (CDC, 2009). Among patients with MDR-TB, 9% have additional drug resistance, qualifying as extensively drug-resistant tuberculosis (XDR-TB) (CDC, 2013b). XDR-TB is resistant to INH, rifampin, any fluoroquinolone, and at least one of the injectable second-line aminoglycosides (amikacin, kanamycin, or capreomycin). XDR-TB is exceedingly difficult to cure, with complicated regimens involving five or six drugs for 2 years or more. As a result, the cure rate of patients with XDR-TB is only 30% to 50% (CDC, 2013c).

Pregnancy and Lactation

Women of childbearing age should be advised to avoid pregnancy while being treated for active TB. If the diagnosis is discovered

during pregnancy, prompt therapy should be initiated because the risk to the fetus from TB outweighs the risk of adverse drug effects. Treatment consists of INH, ethambutol, rifampin, and pyridoxine, for 9 months. Pyrazinamide is avoided because the effects on the fetus are unknown. Postpartum, women may breastfeed their infants because drug concentrations in breast milk are too low to cause toxicity.

Human Immunodeficiency Virus Infection

HIV infection increases the risk of active TB 30-fold. With HIV and TB coinfection, each disease accelerates the other. All TB patients should be tested for HIV. Among HIV-positive persons in the world, almost 25% of deaths are due to TB (WHO, 2013). This is reminiscent of TB mortality rates in 18th- and 19th-century Europe.

Extrapulmonary, and consequently, GU TB may be more common in HIV-positive patients. In a small study in India, GU TB was found postmortem in 49% of AIDS patients (Lanjewar et al, 1999). In HIV-positive patients, GU TB can be more disseminated, with more lymph node enlargement and bilateral renal disease. Usually, less caseation, necrosis, and fibrosis are present because a competent immune system is necessary for the vigorous inflammatory process that leads to fibrosis and scarring. As a result, among patients with GU TB, stenosis of the collecting system occurs less frequently (12.5% vs. 93.8% in HIV-negative persons), and there is a lower incidence of bladder contracture (12.5% vs. 65.3% in HIV-negative persons with GU TB) (Figueiredo et al, 2009). Despite the lower incidence of obstructive cicatricial lesions, GU TB in HIV-positive persons is associated with high mortality.

TB treatment in HIV-positive patients should not be delayed. Treatment guidelines are similar to those for persons without HIV infection. Short-course chemotherapy for 6 months is effective, and 9 months of treatment is no longer routinely recommended. Instead, duration of treatment is determined by the usual factors: disease location and severity, drugs tolerated, and response. During the continuation phase of therapy, however, HIV-positive patients should undergo daily or thrice-weekly administration, and nothing less frequent. Drug interactions with antiretrovirals can be complex and need to be considered. The rifamycins (rifampin and to a lesser degree rifabutin) may decrease serum levels of antivirals to suboptimal levels. Dose increases may be needed as a result (Kaplan et al, 2009).

Renal Transplant Recipients

Renal allograft TB is rare. Infection usually occurs in kidney transplant patients within 6 months of transplantation but can occur as late as 7 years after. The shorter interval from infection to presentation may be a result of the immunosuppression required for the graft or of preexisting TB in the donor kidney. Because patients are seen very early in the disease process, no changes are usually visible on imaging. Furthermore, the immunosuppression prevents much of the pathology that is part of the natural course of GU TB. Diagnosis is difficult because many of the symptoms and findings of GU TB are absent. Fever is the usual presenting symptom. Urinary symptoms are present in only 20% of cases (el-Agroudy et al, 2003). Chest x-ray findings are abnormal but not specific in 55% of patients. Regardless of chest x-ray findings, 56% of patients have positive sputum cultures. In one study, urine AFB culture was positive in 100% of patients (Dowdy et al, 2001). Many patients are diagnosed after graft nephrectomy with histopathology (Lorimer et al, 1999).

Treatment is complicated by drug interactions between the rifamycins and the immunosuppressive drugs, necessitating frequent monitoring of serum drug levels and dosage adjustments. Rifamycin-free regimens are possible but lengthen the duration of treatment to at least 12 to 18 months. Complications in transplant patients include graft rejection, disseminated TB, and death in up to 36% of patients (Dowdy et al, 2001).

PARASITIC INFECTIONS OF THE UROGENITAL TRACT

A number of parasitic infections affect the urogenital tract. Although urologists practicing in nonendemic areas may encounter patients with urogenital parasitic infections only rarely, it is nevertheless critical for physicians to understand these diseases to facilitate appropriate diagnosis and therapy of affected individuals. Parasitic infections relevant to urology include urogenital schistosomiasis, filariasis, amebiasis, enterobiasis, and echinococcosis.

Schistosomiasis

More than 200 million people globally are infected by *Schistosoma* species. The three species of primary medical importance are *Schistosoma mansoni* (found primarily in Africa, the Arabian Peninsula, and South America), *Schistosoma japonicum* (China and Southeast Asia), and *Schistosoma haematobium* (Africa and the Arabian Peninsula). Whereas *S. mansoni* and *S. japonicum* primarily affect the liver and GI tract, *S. haematobium* infection primarily affects the GU tract and is the focus of this chapter. Urogenital schistosomiasis is a disease featuring a complex parasite life cycle, multifaceted human disease, and close ecologic links to the environment. *S. haematobium* likely has co-evolved with humans and nonhuman

primates for millennia; as a result, even ancient civilizations realized the constellation of signs and symptoms associated with urogenital schistosomiasis.

History

The presence of schistosome antigens in Egyptian mummies (circa 3500 BCE), including more recent mummies with confirmed *S. haematobium* eggs in tissues (Deelder et al, 1990), confirms that urogenital schistosomiasis has been with *Homo sapiens* for millennia. Indeed, the Egyptians recognized this infection and named it "A-a disease," which was depicted hieroglyphically by a penis dripping with bloody urine (Hanafy et al, 1974; Shokeir and Hussein, 1999). Later, the German pathologist Theodor Bilharz, performing autopsies in Cairo in 1852, found worms in mesenteric veins and linked them to eggs found in human urine and stool.

Biology and Life Cycle

Human infection is initiated by the penetration of *S. haematobium* cercariae through (even intact) skin that is in contact with infested fresh water (Fig. 17-8). The average life span of cercariae is 1 day.

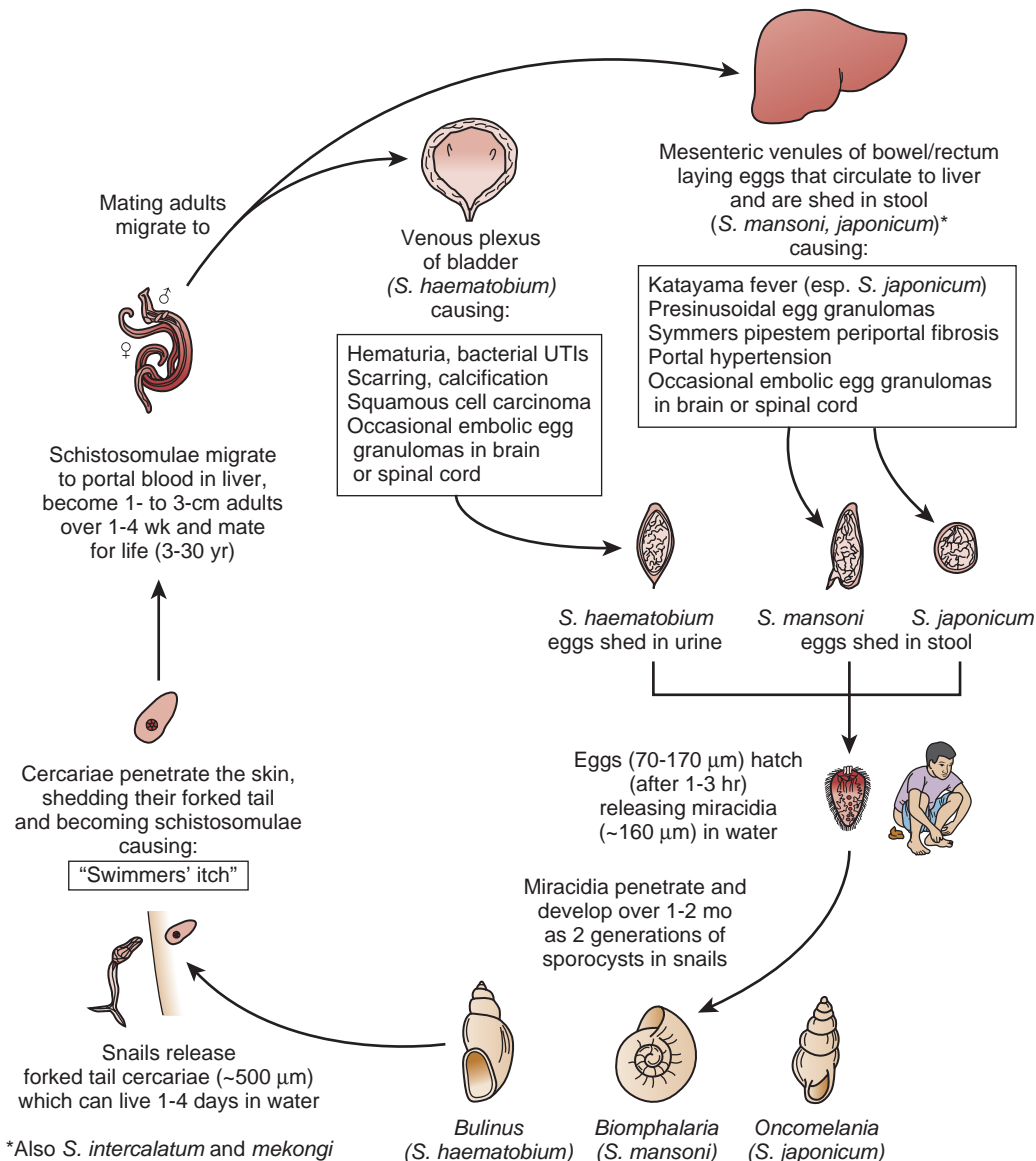


Figure 17-8. Life cycle of a schistosome. UTIs, urinary tract infections. (From King CH. Schistosomiasis. In: Guerrant RL, Walker DH, Weller PF, editors. Tropical infectious diseases, principles, pathogens, and practice. 2nd ed. Philadelphia: Churchill Livingstone; 2006. p. 1341-8.)

Penetration success rates fall off quickly within hours of cercarial shedding from the intermediate snail host (King, 2006).

After penetration, schistosomes transform from free-living cercariae into obligate parasites called *schistosomulae*, by first shedding their tails over approximately 90 to 120 minutes and then undergoing a series of structural changes (Melo and Pereira, 1985). The transformed schistosomulae migrate to the lungs via the bloodstream or lymphatics, and then the liver via the venous circulation (Wilson, 2009). Migration out of the skin and into the lungs takes several weeks (Rheinberg et al, 1998; Wilson, 2009).

The juvenile schistosomes then arrive at the liver sinusoids via the venous circulation, where they begin blood feeding. Soon thereafter, the now-mature worms preferentially migrate to the venous plexus of the bladder and other pelvic organs, where they live an average of 3 to 5 years. The developmental period from cercaria to adult worm ranges from 80 to 110 days. After worm pairing, males clasp the females in a ventral groove termed the *gynecophoric canal*, using their muscular bodies to help females pump host blood into their mouths and secreting chemical signals to stimulate oviposition (Gupta and Basch, 1987).

Eggs are laid by adult female worms in the pelvic venous circulation. Human schistosomes are very fecund, with egg-laying rates of hundreds to thousands of eggs per female per day. *S. haematobium* eggs are ovoid, measuring approximately 140 μm long and featuring a terminal spine (Loker, 1983; Ratard and Greer, 1991) (Fig. 17-9). Eggs must penetrate the endothelium to reach the lumen of bladder to exit via the urinary stream, reach fresh water, and hatch to become miracidia. Some *S. haematobium* eggs are also excreted into the feces after expulsion from the intestinal wall. It is estimated that less than half of the eggs produced are successfully excreted in urine. The rest are retained in the body where the immune response causes significant pathology.

Eggs can survive approximately 20 days as long as they remain wet. On contact with fresh water and light, the eggs hatch, releasing miracidia, which are the larval stage of the parasite. The ciliated miracidia of *S. haematobium* infect intermediate host snails of the

Bulinus genus. *Bulinus* snails prefer slow-flowing freshwater habitats and are able to withstand low-oxygen conditions.

The typical life span of a miracidium is 6 hours. If during this brief period a *Bulinus* snail is encountered, the miracidia will penetrate the snail tissue and form a primary sporocyst. After several days, 20 to 40 daughter sporocysts are generated by the primary sporocyst. These eventually mature into 200 to 400 cercariae (per sporocyst), which are released back into water. The prepatent period (the time between initial penetration of the snail by a miracidium and release of the first cercariae) varies with water temperature; at temperatures below 15°C or greater than 35°C, no cercariae are shed (Pflüger et al, 1984).

Epidemiology

The geographic distribution of urogenital schistosomiasis is dependent on the tropical conditions required by *S. haematobium* and its specific snail hosts. Consequently, *S. haematobium* is endemic throughout much of sub-Saharan Africa and in portions of North Africa and the Middle East. Approximately 112 million people worldwide have urogenital schistosomiasis (van der Werf et al, 2003). Up to 150,000 people die annually from *S. haematobium*-induced obstructive renal failure alone. It has been calculated that in a 2-week period in 2003, 70 million and 32 million individuals in sub-Saharan Africa experienced *S. haematobium*-induced hematuria and dysuria (respectively), and that major bladder wall pathology and major hydronephrosis were present in 18 and 10 million people (respectively) (van der Werf et al, 2003).

For individuals, the risk of contracting urogenital schistosomiasis is primarily driven by the nature and length of contact with contaminated fresh water. Rural women and children can be exposed during domestic chores when they use *S. haematobium*-infested ponds, rivers, and lakes as their water supply (e.g., for laundry and dishwashing). Children may also be infected while playing and swimming in infested water. Men and women can be exposed during freshwater fishing, washing cars, and working in agricultural areas with high-water-intensity crops such as rice and sugar cane (Hunter et al, 1993). In endemic areas, schistosomiasis prevalence is usually highly focal because of the localized nature of water-dependent transmission.

On a regional level, land-use patterns and ecologic changes can lead to a higher burden of schistosomiasis in some areas, sometimes even resulting in outbreaks. For instance, it has been recognized for at least a century that building dams and irrigation schemes can increase schistosomiasis transmission by creating year-round, slow-flowing, freshwater habitats for the intermediate snail hosts and by promoting increased human population density associated with expanded agriculture. Accordingly, data from Africa consistently show that populations living near dams and irrigation schemes have a greater risk of contracting schistosomiasis compared with populations living distantly from these schemes (Steinmann et al, 2006).

In the 1930s after the construction of the Aswan Low Dam in Egypt, which led to a conversion from ancient, flood-based irrigation to perennial irrigation, the prevalence of schistosomiasis increased from less than 11% to more than 75% in some regions (Hunter et al, 1993). Similar findings occurred after the construction of the Aswan High Dam in Egypt during the 1960s (Malek, 1975) and the Diama Dam in West Africa during the 1980s (Malek, 1975; Talla et al, 1990).

Communities with poor sanitation and a lack of access to clean, running water are generally at highest risk of harboring schistosomiasis (WHO, 2014b). Children are disproportionately affected, with the highest parasite loads occurring in those aged 5 to 15 (Anderson and May, 1992). It is unclear whether this age distribution results from higher exposure among children or a higher inherent susceptibility (Woolhouse et al, 1991).

Schistosomiasis is associated with poverty for a number of reasons. First, the aquatic snails that harbor the larval forms of schistosomes are distributed within tropical and subtropical developing countries, whereas they are not present in developed nations



Figure 17-9. Micrograph of *S. haematobium* eggs. Note the characteristic terminal spines of the eggs. (From Ray D, Nelson TA, Fu CL, et al. Transcriptional profiling of the bladder in urogenital schistosomiasis reveals pathways of inflammatory fibrosis and urothelial compromise. *PLoS Negl Trop Dis* 2012; 6(11):e1912.)

in temperate zones. Second, inadequate sanitation exacerbates the schistosomiasis problem because the schistosome life cycle requires an influx of eggs from human excreta into surface fresh waters. Moreover, prolonged contact with surface fresh water is promoted by lack of safe water supplies, leading to higher risk of infection (Soares Magalhães et al, 2011). Finally, schistosomiasis contributes to the perpetuation of poverty. Chronic infection adversely affects childhood growth, development, and learning, as well as worker productivity (Bonds et al, 2010).

Pathogenesis and Pathology

Cercarial skin penetration is facilitated by secreted molecules such as proteases, which initiate the cellular and humoral responses to schistosome infection (Curwen et al, 2006). However, likely as a result of the parasite strategy of modulating the host immune response from the moment of first contact, brief cercarial penetration does not typically induce an immune response beyond localized skin inflammation (Jenkins et al, 2005). Regardless, repeated exposure to schistosomes can lead to hypersensitization and the development of a maculopapular rash.

During subsequent maturation into adult worms, schistosomes begin to generate a double lipid bilayer outer surface (the tegument), which allows them to evade an immunopathologic response and remain in the host for years, facilitating chronic infection. As the survival of the worm within the host depends significantly on the tegument, numerous mechanisms are employed for immune evasion, including host antigenic mimicry, continual membrane turnover, immunomodulatory proteins and proteases, host-evading biophysical properties of the tegument, and modulation of expression of surface antigens (Abath and Werkhauser, 1996).

Because it is difficult to study the natural pathogenesis of egg-associated disease in humans, much of our knowledge stems from autopsy studies and animal models. In contrast to the relatively silent immune response to worms, the main immunopathologic responses raised against *S. haematobium* are triggered by oviposition in the walls of the bladder and other pelvic organs. With heavy worm burdens, egg deposition in the pelvic organs leads to granuloma development and eventual fibrosis, often obstructing the flow of blood or urine. Granulomas are characterized by a mixed leukocytic infiltration, including eosinophils, plasma cells, and lymphocytes. Because of continuous oviposition, all stages of granulomas are simultaneously present in individuals with chronic infection. Composite, coalescing granulomas are common, secondary to *S. haematobium* egg deposition in clusters. Grossly, granulomatous inflammation can form bulky, hyperemic, and polypoid masses projecting into the bladder lumen (Fig. 17-10). Other factors that have been shown to influence the host immune response and resulting disease severity include host genetics, in utero sensitization to parasitic antigens, and coinfection by other microbes or parasites (Pearce and MacDonald, 2002; Eriksson et al, 2007; Grant et al, 2011). *S. haematobium* eggs appear to rapidly induce bladder expression of type 2 inflammation-associated genes and suppress transcription of urothelial barrier function-related genes (Fu et al, 2012; Ray et al, 2012). These findings suggest that the parasite and human host may share the goal of expelling eggs from the bladder wall, across a temporarily lowered urothelial barrier, and out into the urinary stream.

Although *S. haematobium* has tropism for the pelvic organs, some oviposition occurs in the portal tract. As a result, portal hypertension occurs when eggs are swept into the liver, clog presinusoidal capillaries, induce granuloma formation, and consequently block the hepatic vasculature. Alternatively, embolized eggs can cause granulomatous and fibrotic portal areas and the dilation of collateral portosystemic shunts, permitting the lodging of eggs in these vessels and the formation of pipestem fibrosis (Symmer fibrosis) (Aubry et al, 1980). Hepatosplenomegaly is one clinical manifestation of Symmer fibrosis, although susceptibility to its development depends largely on the variability of individual immune responses. In addition to portal involvement, migration of worm pairs to the pulmonary vessels can result in oviposition in the lungs. In general,



Figure 17-10. Intravenous urogram in an Egyptian boy shows scalloping of the bladder and right lower ureter by schistosomal polypoid lesions.

pulmonary schistosomiasis develops only in very severe cases of infection and when pathogenesis in other organs (i.e., pelvic) has already occurred (Borgstein, 1964). When pulmonary oviposition occurs, eggs may obstruct the lung vasculature and lead to pulmonary fibrosis, pulmonary hypertension, and/or cor pulmonale (Bedford et al, 1946).

Naturally acquired immunity to urogenital schistosomiasis exists; some individuals maintain negative urine egg counts for at least 5 years despite never having received anthelmintics in the face of continual exposure to *S. haematobium* (McManus and Loukas, 2008). The resistance of these individuals to reinfection has been attributed to the involvement of both a T-helper type 1 (Th1) and a Th2 cytokine response, whereas chronically infected individuals exclusively mount a Th2 response (McManus and Loukas, 2008). In some individuals the activity of potentially protective immunoglobulin E (IgE) antibodies may be blocked by IgG4 antibodies generated against worm and egg antigens, possibly hampering the development of protective immunity to schistosomiasis (Hagan et al, 1991).

Because levels of IgE antibodies to worm antigens have been observed to increase with age (Roberts et al, 1993), many workers have suggested an immune-mediated development of resistance. This age-dependent trend, however, could be a result of either behavioral or immunologic changes, because studies in endemic communities have ascertained a general decline in contact with infected water with increasing age (Dalton and Pole, 1978). Nevertheless, recent analyses suggest that even when exposure to infected water is controlled for, age may play a role in the development of resistance.

Eggs that are not promptly expelled from pelvic organs calcify, including those in the bladder and ureters. The accumulation of eggs results in decreased compliance of the urinary tract and increases upper tract pressures. In turn, this promotes the development of urinary stasis, hydronephrosis, and hydroureter (Cheever et al, 1975). The extent of organ calcification can often be identified through radiologic imaging and is roughly correlated with the tissue

burden of calcified eggs (Cheever et al, 1975). The anatomic level of obstruction involves the ureteral meatus (1%), interstitial ureter (10% to 30%), juxtavesical ureter (20% to 60%), lower third of the ureter (15% to 50%), or a contiguous combination of these areas (30% to 60%) (Gelfand, 1948; Smith et al, 1977b; Al-Shukri and Alwan, 1983). Three patterns of hydroureter are associated with urogenital schistosomiasis: segmental (i.e., cylindric or fusiform), tonic, and atonic (Smith et al, 1977a). About one quarter of obstructive uropathy cases involve segmental ureteral dilation, with 80% of those cases occurring in the lower ureter. The dilations occur above areas of concentric ureteral muscular replacement by fibrosis and “sandy patches.” It is unusual for segmental lesions to cause significant hydronephrosis. Up to 30% of obstructive uropathy is caused by tonic hydroureter. This is characterized by dilated, tortuous, thick-walled, and trabeculated ureters with marked ureteral muscular hypertrophy and impaired peristalsis. Typically the entire ureter proximal to an obstructive lesion is involved, generating a functional stenosis. This is often accompanied by significant hydronephrosis, which is reversible if the obstruction is relieved (Smith et al, 1977a). Atonic hydroureters are found in the remaining patients with obstructive uropathy. These ureters are markedly dilated, very tortuous, and thin walled; lack peristalsis; and are associated with atrophic, fibrotic ureteral muscle.

Schistosomal hydroureter typically precedes hydronephrosis (Lehman et al, 1973; Cheever et al, 1978). Left untreated, schistosomal hydronephrosis progresses from worsening renal pelvic dilation to medullary atrophy to medullary effacement and cortical atrophy (Smith et al, 1974, 1977b). This pathophysiologic sequence accounts for the abrogation of tubular function (especially concentrating ability) before compromise of glomerular function (Lehman et al, 1971, 1973).

Patients with chronic *S. haematobium* are at increased risk of bacterial urinary tract superinfections, possibly because the bacteria can affix to the tegument of adult worms, or secondary to urinary stasis or immunomodulation. Patients infected with *S. haematobium* are also at higher risk for bladder cancer, especially squamous cell carcinoma. The relationship between *S. haematobium* and bladder cancer is perhaps the strongest of any helminthic infection–cancer association. This association is supported by both epidemiologic studies (particularly in Egypt) and experimental models (Mostafa et al, 1999). Rates of bladder cancer are linked with duration and severity of infection and are associated with a mortality rate as high as 10.8 per 100,000 males in Egypt (Mustacchi, 2003).

Female genital schistosomiasis (FGS) remains poorly understood. Sequestration of eggs in the female reproductive tract results in the formation of fibrotic nodules, or sandy patches, in the uterus, cervix, and lower genital tract (Badawy, 1962) (Fig. 17-11). Little is known about the mechanism through which *S. haematobium* generates female genital disease aside from the increased vascularization of the female genital mucosa that occurs as a result of the presence of eggs (Jourdan et al, 2011).

Other bladder sequelae of long-term *S. haematobium* infection include the development of urothelial hyperplasia, squamous metaplasia, urothelial dysplasia, and eventually urothelial or squamous cell carcinoma. Bladder cancer is the final pathologic sequela of schistosomiasis. Schistosomal bladder cancer features an early onset (40 to 50 years) and is often squamous cell carcinoma (60% to 90%) or adenocarcinoma (5% to 15%) (Cheever et al, 1978; Lucas, 1982; Al-Shukri et al, 1987; Thomas et al, 1990; Bedwani et al, 1998). Over 40% of schistosomiasis-associated bladder squamous cell carcinomas are well differentiated and verrucous and feature an overall good prognosis. Tumors are found on the posterior wall about half of the time and on the lateral wall approximately 30% of the time. Exophytic neoplasms account for roughly two thirds of schistosomal bladder cancers, and the remainder are ulcerative endophytic tumors. Mass drug administration (MDA) campaigns in Egypt have been associated with an overall reduction of bladder neoplasms from 28% to 12% and a shift from squamous cell carcinomas to transitional cell carcinomas (Gouda et al, 2007). Although transitional cell carcinomas of the bladder are less frequently associated with *S. haematobium* infection (Michaud, 2007),

some epidemiologists believe that the relatively high rate of smoking in schistosomiasis-endemic regions may further increase the risk of bladder cancer, possibly synergistically with *S. haematobium* infection (Bedwani et al, 1998). However, some unselected autopsy series from the same regions have reported similar frequencies of bladder cancers in patients without schistosomiasis (Smith et al, 1977a; Cheever et al, 1978).

Egg deposition into the bladder wall has been implicated as a major factor in carcinogenesis, and *S. haematobium* has been classified as a Class I agent (carcinogenic to humans) by the International Agency for Research on Cancer within WHO (International Agency for Research on Cancer, 2011). Vascular endothelial growth factor (VEGF) is increased in the bladder early after *S. haematobium* egg exposure (Fu et al, 2012; Ray et al, 2012; Salem et al, 2012). VEGF may promote tumor vasculogenesis and facilitate carcinogenesis and/or cancer progression. One potential pathway of schistosomal bladder oncogenesis may be initiated when papillomas merge with the basal transitional epithelium, forming benign fibroepithelial papillary growths. After successive episodes of inflammation and fibrosis, some of the urothelial cells may sequester together (or expand clonally) and form potentially precancerous lesions, including squamous metaplasia (Mustacchi, 2003). Molecular profiling of the mouse bladder indicates that *S. haematobium* egg exposure induces transcriptional alterations in bladder carcinogenesis-related signaling pathways (Ray et al, 2012). Bacterial urinary tract coinfections may also contribute to *S. haematobium*-associated bladder carcinoma, given that *S. haematobium* increases the ability of bacteria to reduce nitrates to nitrosamines, which can alkylate proteins and nucleic acids (Grisham and Yamada, 1992). Resulting mutations in oncogenes (i.e., p53) may then contribute to neoplasia (Mustacchi, 2003).

Clinical Manifestations

Acute schistosomiasis encompasses the transient human responses to cercarial penetration and the longer-lasting responses to schistosome tissue migration and maturation. Chronic schistosomiasis results from the immune response to protracted oviposition, often lasting for years and leading to organ damage. As a result, clinically apparent chronic schistosomiasis is limited to long-term residents of endemic areas, who are continually reinfected, have long-term, high worm burdens, and are re-exposed to eggs. As with most human helminths, *Schistosoma* species cannot complete their life cycle nor replicate in the human host. Thus, in tourists or short-term visitors who are exposed once to the parasite, even in the absence of efficacious chemotherapy, adult worms die of senescence within 3 to 5 years, limiting subsequent pathology.

Acute Schistosomiasis. The first clinical manifestation of schistosomiasis is often an itchy maculopapular rash (cercarial dermatitis), usually within 1 to 2 days of cercarial penetration. The rash usually resolves before travelers have returned from endemic areas, making the diagnosis more difficult (Stuiver, 1984).

Acute schistosomiasis is seen 2 to 8 weeks later in some patients during their primary infection (although it is silent in many). The well-known eponym for acute schistosomiasis, “Katayama fever,” is derived from early descriptions of the syndrome in the Katayama Valley in Japan; it occurs most commonly with heavy primary *S. japonicum* infections, less commonly with *S. mansoni*, and rarely with *S. haematobium*. The initial signs and symptoms of Katayama fever include fever, dry cough, fatigue, headache, diarrhea, eosinophilia, neck pain, and urticaria (Jauréguiberry et al, 2010). Acute schistosomiasis is seen rarely among people living in endemic areas (Meltzer et al, 2006). Because the signs and symptoms of acute schistosomiasis are nonspecific, cases often remain undiagnosed or confused with other endemic diseases such as malaria or enteric fever (Jensen et al, 1995).

Because acute schistosomiasis may be clinically silent, all individuals with exposure to potentially infested water should be aware of the possibility of infection, with considerations for accurate diagnosis and treatment based on these factors (Jauréguiberry et al, 2010).

Chronic Schistosomiasis. Adult *S. haematobium* worm pairs shed eggs into the bladder wall, beginning about 8 to 12 weeks after infection. This is sometimes heralded by painless, recurrent hematuria, dysuria, or urinary frequency (Mahmoud, 2001). In some highly endemic cultures, hematuria in males is seen as a sign of puberty and can be sufficiently severe as to result in anemia (Wilkins et al, 1985). Proteinuria is also often associated with urogenital schistosomiasis. Hematuria is a consistent and specific enough sign of infection that it is used as a primary diagnostic technique in endemic areas. However, given the many other possible causes of hematuria, urogenital schistosomiasis is often unsuspected and misdiagnosed in infected travelers returning to their nonendemic home countries (Raglio et al, 1995).

Long-term urogenital schistosomiasis results in fibrosis that may obstruct urinary drainage and result in organ dysfunction. Egg deposition in the ureters and subsequent granuloma, polyp, and ulcer formation increases the risk of hydronephrosis and hydroureter caused by impaired peristalsis of the walls of the renal pelvis and ureter, which in turn can result in obstruction, and vesicoureteral reflux. Recovery of renal function may be achieved through anthelmintic therapy in shorter-term infections, whereas surgical repair of the ureter or urinary diversion may be necessary during late-stage or more severe disease (Mahmoud, 2001).

FGS is another form of chronic schistosomiasis and occurs in 33% to 75% of females with *S. haematobium* infection as a result of egg deposition into the fallopian tubes, cervix, vagina, vulva, ovaries, and/or uterus (Kjetland et al, 2012). Friable mucosal lesions (sandy patches) can result, which often bleed on contact during pelvic examinations or sexual intercourse (Hotez and Fenwick, 2009). Dyspareunia, pelvic and abdominal pain, vaginal bleeding and discharge, urinary frequency, and infertility are common but resemble signs and symptoms of urinary tract infections (UTIs) and sexually transmitted diseases of other causes, so FGS is often misdiagnosed and left untreated (Hotez and Fenwick, 2009).

Men can carry high numbers of *S. haematobium* eggs in the ejaculatory ducts and seminal vesicles, and blood and/or schistosome eggs may be present in the ejaculate before they are detectable in the urine. Patients with involvement of these urogenital structures often have a testicular mass or scrotal pain. Egg burdens of the epididymis, ovaries, and fallopian tubes are generally higher than those of the testes, uterus, and vagina (Cheever et al, 1977, 1978; Helling-Giese et al, 1996a).

As infection progresses, a late, chronic, active stage develops when tissue egg burdens peak. Chronic suprapubic and pelvic pain with associated urinary urgency, frequency, and incontinence are classic for the schistosomal contracted bladder (Duvie, 1986). Frequently the trigone appears normal or somewhat hyperemic and edematous, whereas the remainder of the detrusor muscle is thickened and indurated, as is the entire bladder wall. Functional bladder capacity can be as low as 50 mL in adults.

Over years, active infection becomes more quiescent, and oviposition and egg excretion occur at a lower rate and symptoms are dampened. Over 30% of light infections become asymptomatic in some endemic regions (Rutasitara and Chimbe, 1985). In spite of this, clinically silent obstructive uropathy may evolve throughout this period as fibrosis replaces polypoid lesions and the bladder and ureters undergo sometimes irreversible damage. As a result, severe hydroureteronephrosis can develop insidiously.

Infected individuals can enter a chronic inactive phase, in which viable eggs are no longer detected in urine or tissues. Signs and symptoms at this stage are caused by sequelae and complications of the immune reaction to the calcified, dead eggs rather than the schistosomal infection itself. Unfortunately, among patients with schistosomal obstructive uropathy, 40% to 60% present to urologists at this end stage (Smith and Christie, 1986). In heavily endemic regions, poorly or nonfunctioning kidneys are common in patients who are asymptomatic. About half of patients will develop bacterial urinary tract coinfections superimposed on their schistosomal obstructive uropathy. The bacteria associated with urogenital schistosomiasis are the same organisms that cause UTIs in patients without schistosomiasis. There is evidence that these coinfections

may occur more readily because of parasite immunomodulation of the host (Hsieh et al, 2014). Some series have noted an association of chronic or recurring UTIs caused by *Salmonella*, often associated with intermittent bacteremia in some patients with urogenital schistosomiasis (King, 2001). This association suggests that *Salmonella* bacteriuria in this setting may actually be “spillover” of bacteremia into the urinary stream. *Salmonella* organisms reside in the apical invaginations of the schistosome tegument, where they are sheltered from host defenses and antibiotics. Awareness of this association can lead to treatment of both infections with good response. Antibiotics alone do not fully resolve this process.

Another manifestation of urogenital schistosomiasis is the development of bladder urothelial ulcers (Smith et al, 1977a). On presentation, acute schistosomal ulcers rarely are in the active stage, when necrotic polyps slough into the urine and leave behind a urothelial ulcer. The more common chronic bladder ulcer is a late sequela of heavy infection. This lesion is associated with a constant burning sensation and intense suprapubic and pelvic pain. The majority of these patients exhibit gross hematuria and pyuria.

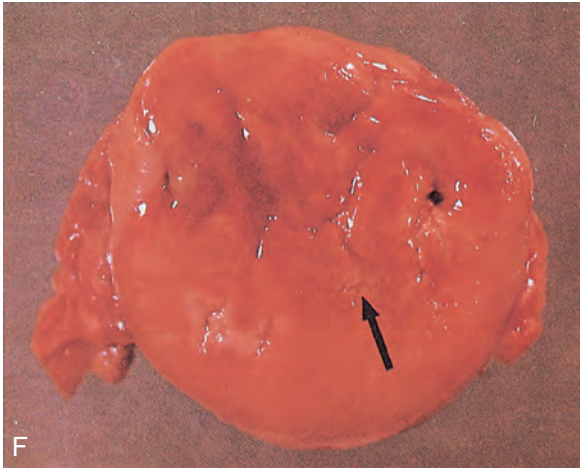
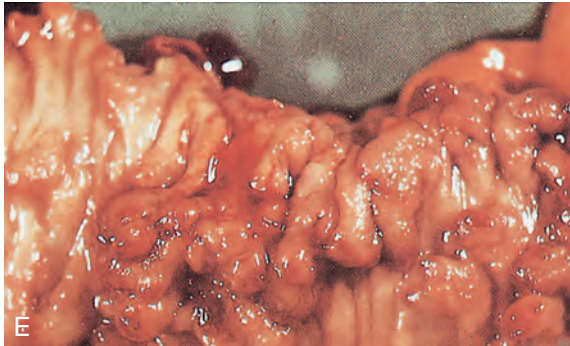
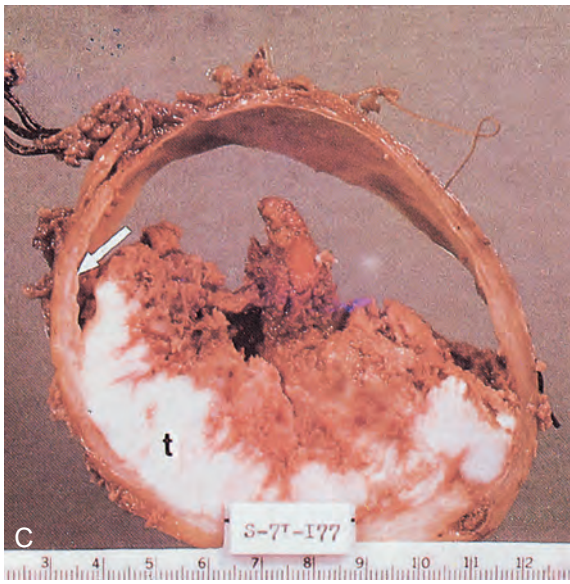
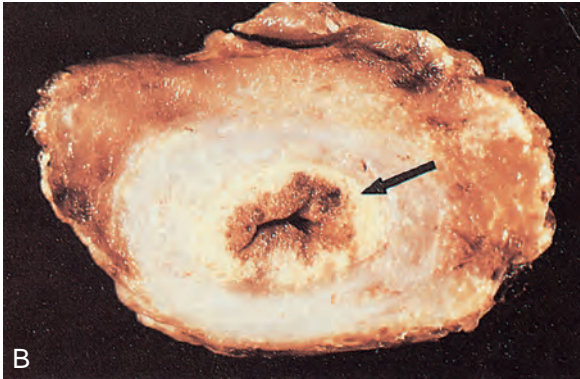
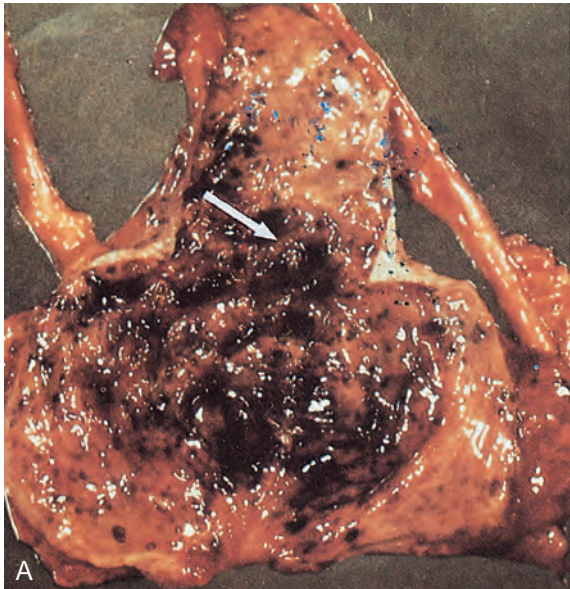
Eosinophilia is very common during acute schistosomiasis and is seen even during chronic infection. During chronic infection the eosinophilia is usually low grade, and although neither sensitive nor specific for schistosomiasis, its presence can be a clue that a parasitic infection such as schistosomiasis may be present. Exceptions to this usual sequence of acute and chronic infection may occur and sometimes manifest in the form of ectopic pulmonary schistosomiasis, neuroschistosomiasis, and FGS.

Diagnosis

Finding *S. haematobium* eggs in urine or stool remains the gold standard for diagnosis of active infection, although eggs do not appear until oviposition begins 8 to 12 weeks after initial infection. Because maximal egg shedding in the urine peaks at noon, urine samples should be ideally collected between 9 AM and 3 PM for examination (Doehring et al, 1983, 1985). Urine samples can be concentrated to increase sensitivity and detect low-intensity infections. If eggs are not found in the urine or stool but clinical suspicion remains high and serology is consistent with exposure, tissue biopsy can be considered. A rectal snip biopsy should be performed before a bladder biopsy, because eggs are common in the rectal mucosa and the risk of a bladder biopsy–related complication (e.g., infection, perforation) is avoided. A squash preparation of the biopsy specimen between glass slides is superior to histopathologic analysis, because it is more sensitive and allows determination of egg viability. In potential cases of FGS, microscopic inspection of biopsy samples from lesions on the vulva, vagina, or cervix may result in egg identification and diagnosis (Helling-Giese et al, 1996b). Visual and dipstick-based detection of gross or microscopic hematuria and urine turbidity are also used to indirectly diagnose urogenital schistosomiasis, although these methods are less sensitive and specific and best combined with already-established diagnostic tools; they are most commonly used in the developing world as part of control and elimination campaigns (Adesola et al, 2012).

Serologic tests that combine a Falcon assay screening test–enzyme-linked immunosorbent assay (FAST-ELISA) with a Western blot analysis are available at the CDC (Wilson et al, 1995; Al-Sherbiny et al, 1999). Together, the assays are over 90% sensitive and specific for *S. haematobium* infection. When the diagnosis is suspected but eggs are not present, serology can be useful, but it does not distinguish between acute and chronic infection because antibody titers remain positive even after curative chemotherapy. Other serologic assays are also available at commercial laboratories. Patients generally first become antibody positive about 4 to 6 weeks after infection (Schwartz et al, 2005).

Ultrasonography can also be useful and may demonstrate bladder or ureteral wall thickening, polypoid lesions, hydroureter, hydronephrosis, urinary tract calcifications, and even bladder carcinoma (Kardorff and Döhring, 2001). Plain abdominal radiographs may reveal urinary tract calcifications; a calcified bladder, which may resemble a fetal head in the pelvis, is characteristic of chronic



urogenital schistosomiasis (Fig. 17-12). The prostate, seminal vesicles, posterior urethra, distal ureters, and, occasionally, colon may also demonstrate calcifications.

The earliest radiographic changes on IVU appear to be striations in the ureters and renal pelvis (Hugosson, 1987). Ureteral calcification is typically intramural, and the ureters are dilated. This differs from the calcifications seen in TB, which form casts of nondilated

ureters. Other findings on IVU include hydronephrosis, hydroureter, nonfunctioning kidney, ureteral stenosis, and bladder and ureteral filling defects caused by polypoid lesions. Similar lesions can also be identified through US. With IVU, delayed films are often necessary in the presence of severe obstructive uropathy to discern distended ureters and kidneys. Postvoid views may reveal bladder neck obstruction with retention. Combining IVU with fluoroscopy can differentiate between tonic and atonic ureters (Abdel-Halim et al, 1985) and identify nonstenotic, immobile ureters.

CT can detect both obstructive uropathy and calcified lesions in the colon and urinary tract (Jorulf and Linstedt, 1985), a potential advantage over IVU. MRI does not yet seem to provide enough diagnostic superiority to warrant widespread use (Kohno et al, 2008). Fluoroscopic voiding cystourethrography can detect vesico-ureteral reflux, which occurs in 25% of infected ureters. Cystourethroscopy may reveal mucosal lesions in the bladder (Fig. 17-13). Retrograde fluoroscopic pyelography during cystourethroscopy may reveal important details regarding ureteral anatomy and drainage.

Antigen detection or PCR may be a more sensitive means of diagnosis. Serum or urine samples from infected individuals can be tested for the presence of circulating anodic antigens (CAAs) and circulating cathodic schistosome antigens (CCAs). CAAs and CCAs are specific for active infection because they are released only by viable adult worms and have the added benefit of producing quantitative measurements useful for determining infection severity (Kremsner et al, 1994; Agnew et al, 1995). Moreover, the development of an ELISA reagent strip test for urine samples has allowed for point-of-care detection of CCAs that is more user-friendly and field applicable (van Dam et al, 2004). However, in some hands the CCA test completely failed to detect *S. haematobium* infection (versus more than 80% sensitivity and specificity for detection of *S. mansoni* infection) (Stothard et al, 2006), and it is relatively expensive for wide-scale use in the developing world.

By far the most sensitive method for diagnosing urogenital schistosomiasis from urine or even stool samples is PCR (Obeng et al, 2008; ten Hove et al, 2008). PCR is also highly sensitive and specific for diagnosing FGS from vaginal lavage samples, although detection may vary based on patient age and length of infection (Kjetland et al, 2009). Unfortunately, PCR is difficult to use in the developing world and in the field because it requires highly trained technicians and the use of organic solvents and commercial kits. Still, in the context of transmission control and disease surveillance, especially in settings of low-intensity transmission, PCR is a useful option.

Globally, many cases of urogenital schistosomiasis remain undetected and untreated because most are diagnosed only through direct egg detection rather than more sensitive methods. The need for more reliable and accessible diagnostic tools is thus particularly important for the development of more effective schistosomiasis control strategies in the developing world.

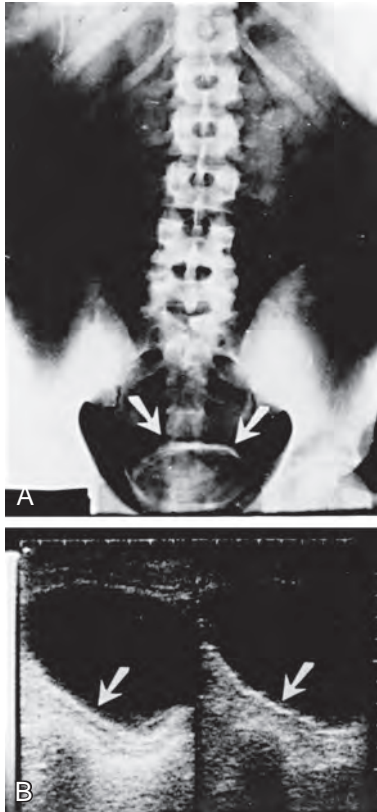


Figure 17-12. Bladder calcification in a 30-year-old Egyptian farmer. **A**, Plain x-ray film of the abdomen shows a rim of calcification surrounding the urinary bladder (arrows). **B**, Abdominal ultrasound study shows a bright line surrounding the bladder with a definite dark rim behind it (arrows). (A and B, Courtesy G. Thomas Strickland, MD. From Abdel-Wahab MF, Ramzy I, Esmat G, et al. Ultrasonography for detecting *Schistosoma haematobium* urinary tract complications: comparison with radiographic procedures. *J Urol* 1992;148:346.)

Figure 17-11. Macroscopic appearance of human urinary schistosomiasis. **A**, Urinary bladder opened with an anterior Y incision. The posterior and apical walls have many erythematous, granular, sessile, and pedunculated polyps (arrow), characteristic of the early active stage of urinary schistosomiasis. **B**, Coronal section through the apex of a formalin-fixed urinary bladder. The lamina propria has been expanded and is replaced by a yellow-tan, finely granular, sandy patch (arrow), which is characteristic of chronic inactive foci. Small sandy patches are sprinkled through the fibrotic, atrophic detrusor muscle, even in perivesical fat. The more superficial erythematous portion of the lamina propria contains some viable eggs with granulomatous response (chronic active stage of urinary schistosomiasis). **C**, Coronal section through the middle of a urinary bladder after formalin inflation and fixation. The lamina propria (arrow) has been replaced by a concentric sandy patch, most prominent at the margin of the exophytic, moderately differentiated squamous cell carcinoma. The bladder wall is attenuated except for the tumor (t). No evidence of recent oviposition was found in the lower urinary tract (chronic inactive stage of urinary schistosomiasis, usually found with the bilharzial bladder cancer syndrome). **D**, Urinary bladder opened with anterior Y incision shows several features of severe chronic inactive urinary schistosomiasis. The entire lamina propria has been replaced by a sandy patch. Foci of epidermization are seen at or near the white arrow. The left ureteral orifice (right) is markedly dilated (the so-called golf-hole ureter of schistosomal uropathy). The right ureteral orifice (point of black arrow) is markedly stenotic. **E**, Rectosigmoid colon with polyposis. Numerous sessile and pedunculated polyps are visible. Many are erythematous, indicative of active oviposition with granuloma formation. Some have necrotic hemorrhagic tips. **F**, Mucosal surface of partial cystectomy specimen (4- to 5-cm ellipse) from a patient with the chronic inactive stage of the disease. There is a stellate chronic schistosomal ulcer. Despite the inactivity of the disease, these ulcers may bleed profusely. Pale mucoid flecks at the margin of the ulcer (arrow) are areas of adenoid (goblet cell) metaplasia.

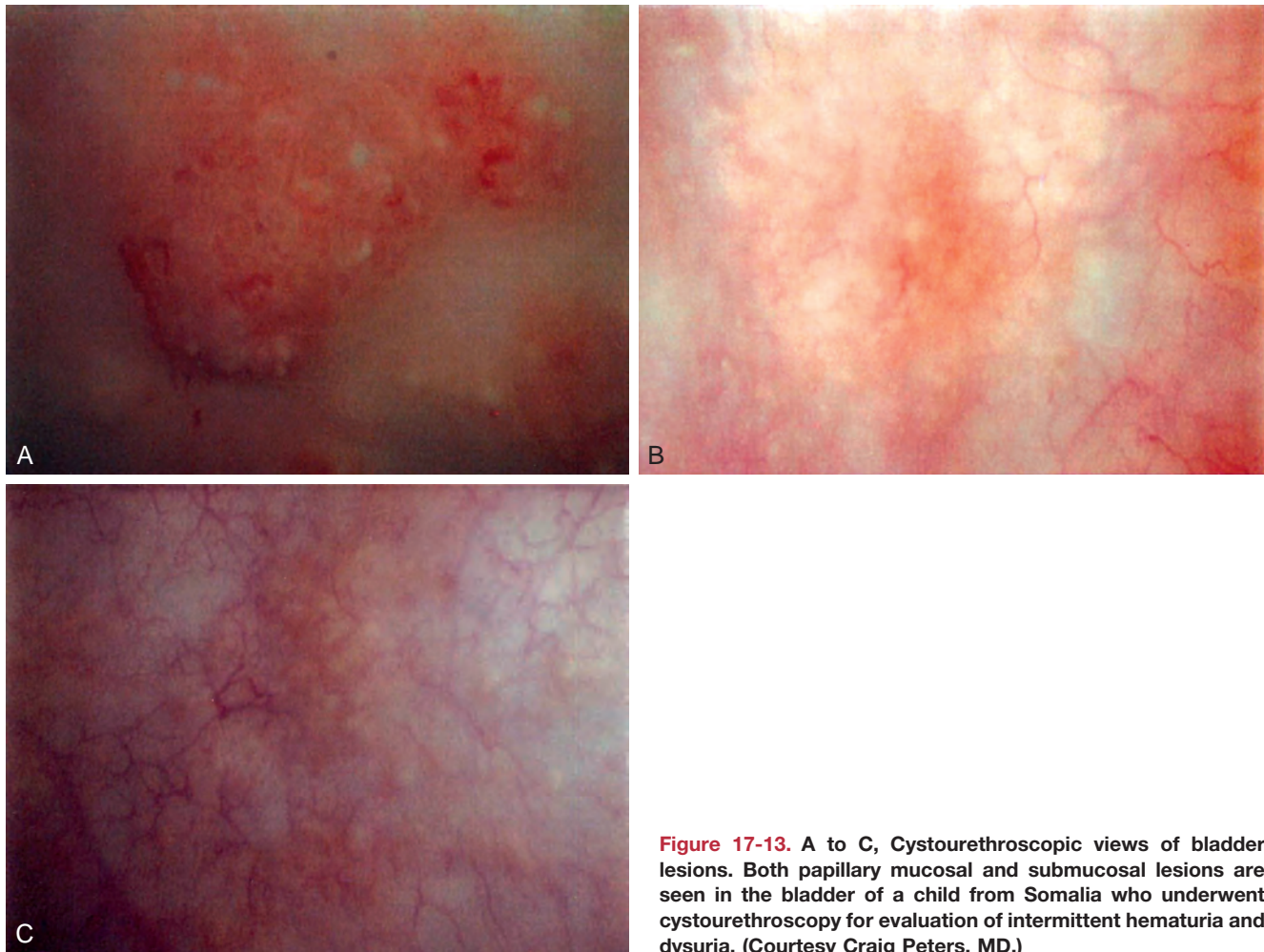


Figure 17-13. A to C, Cystourethroscopic views of bladder lesions. Both papillary mucosal and submucosal lesions are seen in the bladder of a child from Somalia who underwent cystourethroscopy for evaluation of intermittent hematuria and dysuria. (Courtesy Craig Peters, MD.)

Treatment

Medical Management. Praziquantel (PZQ) is currently the only WHO-recommended drug for schistosomiasis (WHO, 2014a) and has replaced metrifonate and oxamniquine as the main therapeutic agent. Although dependence on a single drug increases the potential for parasitic resistance, PZQ's efficacy, widespread availability, and low toxicity are favorable factors, and there has been little incentive for the development of alternative drugs. Two 20-mg/kg oral doses of PZQ are given on the same day, 6 to 8 hours apart (or alternatively, one 40- or 60-mg/kg dose) for *S. haematobium* infections. Corticosteroids are often added for the treatment of acute schistosomiasis (Katayama fever).

As measured by egg reduction and cure rate, PZQ's efficacy is 60% to 90% (Danso-Appiah et al, 2008; Doenhoff et al, 2008). Even in those not cured, the worm burden is likely substantially reduced, which significantly decreases the chances of development of further infectious sequelae. After treatment of a patient with PZQ, it is reasonable to monitor egg counts in urine and stool specimens and to perform serial ultrasonographic studies of the urogenital tract to assess response to drug therapy. Repeat PZQ courses can be given if there is a concern for persistent infection.

PZQ has a favorable pharmacokinetic and side effect profile. The most common side effects (abdominal pain, nausea, headache, and dizziness) are typically mild, generally occur within 3 to 4 hours after administration, and resolve spontaneously. Most patients experience few or no side effects (N'Goran et al, 2003). However, PZQ pills are large and bitter tasting, making oral administration difficult to tolerate, especially for children (Meyer et al, 2009). Perhaps because of its FDA classification as a Pregnancy Category B

drug (deemed safe in lactating and pregnant women based only on animal studies), many chemotherapy programs exclude pregnant and lactating women. However, there are few reports of adverse effects of PZQ among the millions of pregnant women treated with PZQ (Olds, 2003).

PZQ is less efficacious against schistosomulae than adult worms, which might partly explain the lower cure rates in areas with high rates of schistosomiasis transmission and reinfection. In addition, it means that PZQ cannot be used to abort infection shortly after exposure. Multiple PZQ doses administered several weeks apart can ensure that juvenile schistosomes missed by the first administration are eradicated after maturation (Doenhoff et al, 2008).

Whether schistosomes are developing resistance to PZQ is debatable. Most large studies conducted on *S. haematobium*-infected individuals suggest little drug resistance in endemic areas (King et al, 2000; Guidi et al, 2010). However, there have been reports of PZQ failures in the treatment of travelers or military personnel returning from endemic areas (Doenhoff et al, 2008). Even if resistance to PZQ is not already evolving, it could occur in the future. It is hoped that use of alternative drugs and combination of drug treatment programs with environmental control programs (snail control and sanitation improvement) may lower transmission and reduce the use of PZQ enough to prevent this.

Artemisinin and its analogues (artemether and artesunate, currently in use as antimalarials) are chemoprophylactic alternatives to PZQ because they specifically target the schistosomular stage of *S. haematobium*. Artemether and artesunate are 90% to 97% efficacious in preventing schistosomiasis but are poor treatments for established infections. Combined administration of PZQ and

artemisinin derivatives results in lower infection rates than PZQ alone and thus offers a valuable tool for MDA programs, especially in areas of high transmission and reinfection rates. However, a major concern regarding the use of artemisinins in this manner is the induction of malaria resistance to artemisinin derivatives. Because of this, widespread PZQ–artemisinin derivative combination therapy should not be used in schistosomiasis-malaria co-endemic areas (Liu et al, 2011).

Surgical Management. The efficacy and ease of PZQ therapy for urogenital schistosomiasis, together with the possible reversibility of early-stage disease (Richter et al, 1996; Richter, 2000), mean that in most patients trials of medical therapy should be undertaken before elective surgical approaches (Cioli et al, 1995). In general, surgery is reserved for complications that have not responded to adequate medical treatment within a reasonable follow-up period and for those settings in which immediate surgical intervention is necessary. For example, severe bladder hemorrhage is one common cause for urgent surgical intervention.

Prostatitis and prostatic enlargement are uncommon in schistosomiasis. Accordingly, numerous autopsy studies have failed to demonstrate evidence of anatomic bladder outlet obstruction (Smith et al, 1974; Cheever et al, 1977, 1978). However, clinical studies consistently report cystoscopic (Fam, 1964), urodynamic (Sabha and Nilsson, 1988), and elevated postvoid residual urine volumes, which are evidence of functional bladder outlet obstruction that occasionally requires surgical intervention in patients with severe inactive urinary schistosomiasis (Abdel-Halim et al, 1985). *S. haematobium* infection–associated scrotal induration, pain, and enlargement associated with epididymitis can lead to surgery being performed for the suspicion of a testicular tumor.

Surgery is indicated for irreversibly contracted bladders; procedures include vesical denervation, urinary diversion, ileocystoplasty, and hydrodistention. Any treatment, however, must be performed in conjunction with medical chemotherapy. Chronic, deep bladder ulcers may necessitate a partial cystectomy, because fulguration rarely produces either symptomatic relief or ulcer healing. Urothelial hyperplasia is strongly associated with severe urogenital schistosomiasis, whereas urothelial dysplasia and metaplasia commonly accompany schistosomal bladder cancer (Khafagy et al, 1972). Treatment of bladder cancer secondary to schistosomiasis is typically surgical and discussed elsewhere (see Chapters 92 to 96).

The most frequent sequelae of urinary schistosomiasis result from ureteral involvement causing obstructive uropathy (Lehman et al, 1973; Smith et al, 1974; Cheever et al, 1978; Smith and Christie, 1986). Hydroureter and hydronephrosis are linked to the intensity of *S. haematobium* infection. Because ureteral obstruction observed during schistosomiasis is most often caused by concentric or hemiconcentric polypoid lesions that “girdle” the ureteral muscle in the intramural and adjacent extravascular ureter, it often responds well to medical management alone. Complete resolution of deteriorated renal function caused by active infection–associated obstructive uropathy responds within 1 to 2 months of PZQ chemotherapy (Lehman et al, 1973). Chemotherapy not only reverses schistosomal obstructive uropathy but can also prevent it, even in persons who are continually reinfected (Subramanian et al, 1999). However, in late, chronic, active and inactive urinary schistosomiasis, anatomic obstruction may be less amenable to chemotherapeutic cure.

Anatomic ureteral stenosis, with or without calculi, has been identified in up to 80% of patients with ureteral obstruction (Lehman et al, 1973; Smith et al, 1977b; Al-Shukri and Alwan, 1983; El-Nahas et al, 2003). When residual ureteral stenosis persists after chemotherapy, it is usually amenable to surgical intervention. Depending on the location and extent of the stricture, procedures involving dilatation or excision have been employed. Balloon dilatation is efficacious with anatomic stenosis (Jacobsson et al, 1987), but mechanical dilatation is frequently plagued by recurrent stenosis (Wishahi, 1987). When the ureteral meatus, intramural ureter, ureterovesical junction, or distal ureter is involved, options to reconstruct a functional valve include a variety of plastic operations. Most of these procedures

are variants of the Politano-Leadbetter operation (Politano and Leadbetter, 1958; Leadbetter and Leadbetter, 1961). Although the procedures are highly efficacious for some patients (Smith et al, 1977b; Al-Shukri and Alwan, 1983), other authors have noted that restenosis can occur (Umerah, 1981).

In long or multifocal lesions of the ureter, excision of the affected portion may leave an inadequate residual ureter for reimplantation or simple ureteroureterostomy; in these patients, surgeons have successfully employed the Boari flap, ileal conduit, suprapubic intravesical ureterostomy (in which the obstructed ureteral segment is bypassed with use of a peritoneal dialysis catheter and drained into the bladder), and replacement of the ureter with ileal segments, taking care to maintain an isoperistaltic direction of the ileal segment (Abdel-Halim, 1980, 1984; Al-Shukri and Alwan, 1983; Abu-Aisha et al, 1985). Isolated meatal stenosis of the ureter may be amenable to simple meatoplasty (Al-Shukri and Alwan, 1983). When a ureter is hopelessly obstructed and cannot be reconstructed, long-term nephrostomy drainage is another option.

Prognosis

Approximately 112 million people are infected with *S. haematobium*, but most have mild infections and a good prognosis. The morbidity and mortality of urogenital schistosomiasis is determined by the overall intensity of infection and genetic polymorphisms for relevant immune response genes (Kouriba et al, 2005; He et al, 2008; Isnard and Chevillard, 2008; Isnard et al, 2011; Ouf et al, 2012). In regions of low *S. haematobium* prevalence, such as Nigeria, essentially no schistosomiasis-related mortality is observed and the frequency and severity of schistosomal obstructive uropathy are low. In contrast, when Egypt had a prevalence of 50%, schistosomiasis contributed to mortality in 10% of *S. haematobium*–infected individuals (Smith et al, 1974; Cheever et al, 1978). Among patients with severe disease, mortality approached 50% in 2 to 5 years (Lehman et al, 1970).

Patients who die of schistosomal obstructive uropathy (bilateral end-stage hydronephrosis or unilateral hydronephrosis with contralateral nonschistosomal end-stage renal disease) are typically in their 20s and have heavy total egg burdens. Patients who develop the complications of pyelonephritis and urothelial cancer are commonly older than age 40, consistent with time- and intensity-related pathology (Christie et al, 1986; Smith and Christie, 1986).

The prognosis for patients with urinary tract lesions has dramatically improved with PZQ therapy. In children with obstructive polyps, the uropathy usually completely resolves within 2 to 6 weeks of treatment. For patients with chronic obstructive uropathy from sandy patches and fibrosis, the prognosis is less clear. Some individuals tolerate advanced obstructive uropathy with little, if any, deterioration in renal function. Schistosomal obstructive uropathy, urolithiasis, bladder outlet obstruction, and bacterial cystitis all predispose to pyelonephritis. Bacterial superinfection can be life-threatening and should be treated aggressively and promptly. Finally, for those who develop a bladder malignancy, their prognosis is dependent on the aggressiveness of their tumor.

Prevention and Control

Travelers to endemic areas should be advised to avoid contact with potentially infested fresh water (streams, rivers, ponds, and lakes). Fast-flowing water can still harbor *S. haematobium*. Heating water to more than 125° F for 5 minutes kills the cercariae, as does chlorination and allowing the water to stand for more than 2 days in a setting free of snails. Since the advent of PZQ in the late 1970s and its subsequent mass distribution beginning in the 1980s, schistosomiasis has become relatively simple and affordable to treat, but it remains difficult to control. For the past three decades, control efforts have focused heavily on reducing morbidity using periodic, typically annual targeted mass drug treatments with PZQ, a strategy advocated by WHO. However, when access to safe water is not available, rural poor communities are

subject to vicious cycles of infection, treatment, and reinfection, making more frequent PZQ administration necessary. Sanitation improvements, health education, and snail control are approaches used to break the cycle of transmission, by slowing or halting the influx of eggs into the aquatic habitat, decreasing individual exposure, and reducing the availability of snail intermediate hosts, respectively. Although PZQ is inexpensive, the cost-effectiveness of chemotherapy fluctuates widely among MDA settings as a result of variations in the number of doses of PZQ given per person, variability in transportation and delivery costs, and the potential to take advantage of preexisting public health control programs or other infrastructure (Brooker et al, 2008). The per-person cost in control campaigns is typically under U.S. \$0.50—although even this modest cost, at sufficient scale, may exceed the available resources of many endemic countries (Hotez et al, 2009). Fortunately, a number of pharmaceutical companies and foundations are donating PZQ for use in MDA campaigns.

Because asexual reproduction in the snail host allows the parasite to amplify rapidly, sanitation programs and drug treatment campaigns must reduce egg input into the environment by nearly 90% before a substantial decrease in transmission can be achieved (Woolhouse, 1992). Reductions in snail populations, in contrast, can theoretically effect proportional decreases in disease transmission risk (Woolhouse, 1992). However, considering that adult worms can live for years in the human host, without concurrent mass treatment snail population control alone would need to persist for many years to eliminate transmission. Thus, integrated campaigns focusing on three aims (treating human patients, reducing contact of humans and their wastes with infested water, and controlling snails) offer the most promise.

Other control efforts include mollusciciding (Zhang and Jiang, 2011; Knopp et al, 2012, 2013), biologic control using snail predators or competitors (Roberts and Kuris, 1990; Mkoji et al, 1999; Pointier and Jourdan, 2000; Allen and Victory, 2003; Coelho et al, 2004; Sokolow et al, 2014), and vaccine development (although an efficacious vaccine currently remains out of reach) (Bethony et al, 2008; Gray et al, 2010). Water, sanitation, and hygiene (“WASH”) programs are also, once again, taking center stage and feature many additional benefits beyond potential schistosomiasis reduction (Soares Magalhães et al, 2011; Giné Garriga and Pérez Foguet, 2013).

Schistosomiasis has been eliminated in 10 countries to date (Iran, Japan, Lebanon, Malaysia, Martinique, Montserrat, Morocco, Thailand, Tunisia, and Turkey) (Amarir et al, 2011; Rollinson et al, 2013). At the 65th WHO World Health Assembly (May 2012), resolution WHA65.21 was passed, calling on the global community to “make available the necessary and sufficient means and resources ... to intensify control programmes in most disease-endemic countries and initiate elimination campaigns, where appropriate” (WHO, 2012). Representing a shift from morbidity control to a new focus on elimination, this marks an exciting and hopeful milestone in the global fight against schistosomiasis.

KEY POINTS: SCHISTOSOMIASIS

- *S. haematobium* worms can survive in human hosts for years to decades. A careful travel and social history is crucial to identify potential exposures, correlate them with urogenital symptoms, and determine the need to perform specific diagnostic assays.
- Praziquantel therapy of early stage urogenital schistosomiasis can reverse inflammatory lesions, including fibrosis, of the urinary tract caused by the host response to eggs deposited in tissues.
- The gold standard for diagnosis of active urogenital schistosomiasis is the identification of eggs in urine, stool, or bladder or rectal biopsy specimens. Serologic and PCR-based assays are highly sensitive but may not distinguish between active and resolved infection, and are impractical in endemic regions.

Filariasis

The filariae are vector-borne tissue nematodes. Human pathogens in this group include the agents of **lymphatic filariasis** (LF), *Onchocerca volvulus*, and *Loa loa*.

LF is caused by the mosquito-borne helminths *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. The symptoms of LF range from acute lymphatic inflammation to chronic lymphatic dilation with hydrocele, lymphedema, and elephantiasis of the limbs.

Organisms

W. bancrofti, *B. malayi*, and *B. timori* are threadlike nematodes. Infective (third-stage) larvae are transmitted to humans by mosquito bites. After entering humans, larvae migrate to central lymphatic vessels and eventually mature (over 6 to 9 months) into adult male or female worms. Adults (approximately 20 to 100 mm × 0.2 mm) are considerably larger than microfilariae (approximately 200 μm × 10 μm) (Fig. 17-14). Adult worms live primarily in the afferent lymphatics, especially in the lower extremities (inguinal, iliac, and periaortic lymphatics), and (for *W. bancrofti* only) male genitalia (epididymis, spermatic cord, testicles). Adult worms live approximately 5 to 7 years.

After mating with males, female worms release large numbers of microfilariae. In most endemic areas, *W. bancrofti* and *Brugia* microfilariaemia peaks in the middle of the night as an adaptation to facilitate transmission, coinciding with peak local mosquito vector activity. In some parts of the Pacific, the periodicity of *W. bancrofti* is diurnal rather than nocturnal. After mosquito ingestion, microfilariae mature over 10 to 14 days into infective third-stage larvae.

W. bancrofti and *Brugia* species harbor an obligate rickettsia-like endosymbiont (*Wolbachia*). These endosymbionts are involved in embryogenesis, and antimicrobial therapy (e.g., doxycycline) kills them, resulting in decreased microfilariae release and suppressed larval molting (Hoerauf et al, 2001).

Epidemiology

Globally, 120 million people are infected with LF. Over 90% of infections are caused by *W. bancrofti*, mostly in sub-Saharan Africa, South and Southeast Asia, and the western Pacific. In the Americas, *W. bancrofti* is endemic only to Haiti, the Dominican Republic, Guyana, and Brazil. Infection with *B. malayi* is limited to Asia and several Pacific islands (e.g., Indonesia and the Philippines). *B. timori* infection occurs only in southeastern Indonesia. Within a given



Figure 17-14. Microfilaria of *Wuchereria bancrofti* in peripheral blood. (Courtesy Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention.)

geographic area, the distribution of LF is often quite heterogeneous. Several genera of mosquitoes are capable of transmission, including *Anopheles* (rural Africa and the Pacific), *Culex* (urban areas, especially India), *Aedes aegypti* in some Pacific islands, and others.

Although varying among different locales and mosquito vectors, transmission of LF is relatively inefficient, and obstructive lymphatic disease is generally seen only in persons repeatedly infected over many years (i.e., usually long-term residents of endemic areas). In endemic communities, prevalence increases from childhood through the third or fourth decade of life, after which it remains fairly constant (because of the gradual accumulation of adult-stage worms in the population over time). Lymphedema and genital disease are rare before age 10 but increase in prevalence with age. Overall, about one third of infected persons have clinically overt disease. The likelihood of developing clinical manifestations is particularly high in India, Papua New Guinea, and Africa, whereas it is lower in the Americas (Kazura et al, 1997).

Pathology and Clinical Manifestations

The initial immune response to infective larvae and early adult worms is mostly proinflammatory (involving both Th1 and Th2 T-cell responses). The contribution of humoral immunity includes an increase in filaria-specific IgE titers. Eosinophil-mediated killing of microfilariae also likely plays a role. With the onset of microfilaremia, T-cell responses decrease, mediated by IL-10, IgG4-blocking antibodies, and antigen-specific suppressor T cells. Whether protective immunity develops has been difficult to determine, but groups of individuals have remained infection free despite long-term exposure in highly endemic settings (Steel et al, 1996).

Clinical manifestations in infected patients vary greatly, ranging from subclinical infection to severe disfigurement of the limbs and genitalia. Damage from established infection is cumulative because of progressive scarring and lymphatic obstruction. Medical therapy does not readily reverse such damage but can prevent further progression in patients with active LF infection. Although rarely fatal, LF can cause severe disability and among parasitic infections is responsible for the third highest number of disability-adjusted life years (DALYs) lost globally.

The mechanisms leading to lymphedema have been poorly established. However, parasite-derived factors are at least partly responsible for initial lymphatic dilatation, with subsequent contributions from secondary bacterial infections and inflammatory responses to dying or dead parasites. *Wolbachia* endosymbionts also appear to drive a proinflammatory response. Lesions vary from nodular inflammation to suppuration, histologically appearing as granulomas around worms, sometimes with tissue eosinophils (Fig. 17-15). A vicious cycle can result, with acute attacks worsening lymphedema, predisposing to more secondary infections, worsening lymphedema, and so on; episodic filarial inflammation eventually abates, leaving obliterated lymphatics surrounded by scar tissue. Elephantiasis or hydrocele is then the end stage in some patients.

Subclinical Infection. Most LF-infected persons have few overt clinical manifestations, even with high-grade microfilaremia. However, though the infection is clinically asymptomatic, virtually all persons with patent *W. bancrofti* or *B. malayi* infection have at least some subclinical disease (e.g., dilated lymphatics, scrotal lymphangiectasia, microscopic hematuria, or proteinuria). Eosinophilia is also very common with most forms of LF.

Acute Adenolymphangitis. Acute adenolymphangitis (ADL) is often the first clinical manifestation of LF, consisting of fever, lymphadenitis, lymphangitis, and edema that usually lasts days to a week. The lymphangitis is retrograde (extending peripherally), which distinguishes it from bacterial lymphangitis. Although all four extremities can be involved in both bancroftian and brugian filariasis, the genital lymphatics are affected almost exclusively by *W. bancrofti* infection. This can result in funiculitis, epididymitis, scrotal pain, tenderness, and lymph scrotum (ruptured lymphatic vesicles on the scrotal skin that yield a whitish discharge and secondary bacterial infections).

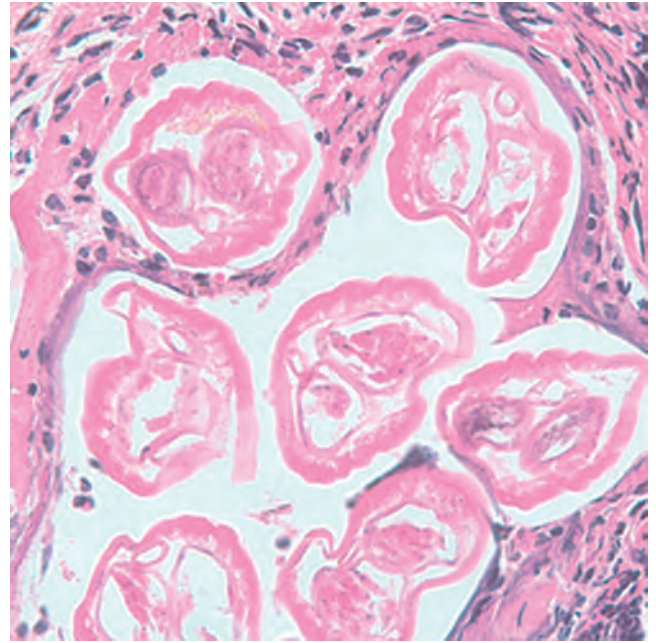


Figure 17-15. Section of an adult *Brugia* organism in a lymph node. (Courtesy Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention.)

Another acute manifestation, **dermatolymphangioadenitis** (DLA), is characterized by fever, chills, myalgias, and headache. Edematous inflammatory plaques occur, as well as hyperpigmentation, vesicles, and ulcers, often at the site of an inciting skin injury. Inflammation progresses proximally and is thought to be secondary to bacterial infections.

Lymphedema. Lower or upper extremity edema is the most common chronic manifestation of LF, with lower extremity edema being the more prevalent. Bancroftian filariasis typically involves the entire limb, whereas brugian filariasis usually involves only the leg below the knee. Although both lower extremities are often affected, asymmetrical involvement is most common. The overlying skin may exude serous fluid. Breast involvement can also occur in females.

Genitourinary Manifestations. Male genital involvement is very common with bancroftian filariasis but uncommon with *Brugia* infection. The prevalence of female genital involvement has not been well established, although anecdotal evidence suggests that it is uncommon (Nutman and Kazura, 2011). Genital disease is not usually experienced until at least the teenage years. Acute painful episodes of (usually unilateral) epididymitis or funiculitis accompanied by fever and malaise can last several days and are one of the most common consequences of bancroftian filariasis.

Funiculoepididymitis. Funiculoepididymitis is characterized by palpable cordlike swellings and edema. Although the condition is usually self-limited, recurrences and the subsequent development of chronic lymphedema are common. Filarial funiculitis rarely results in sterility or orchitis, because the spermatic cord usually remains uninvolved. This manifestation is often mistaken for malignancy, and many patients undergo surgery as a result (including orchiectomy). Varicocele may complicate inflammation, increasing pain and swelling. Bacterial superinfection is a rare but severe complication, with exquisite pain and septic thrombophlebitis often present.

Hydroceles. Chronic disease of the male genitals often results in hydroceles, which can be very large (Fig. 17-16). In endemic areas, differentiation of filarial from nonfilarial hydrocele is difficult, and parasites are rarely detected in the hydrocele fluid. Hydrocele accompanied by nodules in the cord or epididymis and a history of travel to or residence in an endemic area suggests LF. A thick,



Figure 17-16. Huge hydrocele and scrotal elephantiasis. (Courtesy Dr. B. H. Kean. From Zaiman H. A pictorial presentation of parasites, Valley City, ND.)

fibrous tunica, especially with cholesterol or calcium deposits, also suggests LF.

Hydroceles are usually painless unless complicated by acute epididymitis or funiculitis. The scrotal skin may also be thickened and brawny as a result of lymphedema, with oozing lymph. Patients with filarial hydrocele rarely experience bacterial superinfection, although those with elephantiasis and lymph scrotum are often superinfected.

Scrotal and Penile Elephantiasis. Mild scrotal edema is not unusual during early infection or with established hydrocele. Conversely, penile edema is unusual, and massive enlargement of the scrotum or penis occurs late, largely in individuals with poor access to medical care. Genital elephantiasis rarely arises from causes other than LF.

Chyluria. Chyluria occurs when GU tract lymphatics are damaged, resulting in lymph passage into the urine and massive fat and protein loss. Although rare, this can result in serious nutritional consequences. It usually occurs earlier in the natural history of filariasis than genital elephantiasis. Chyluria is usually intermittent and may spontaneously remit.

Tropical Pulmonary Eosinophilia. Tropical pulmonary eosinophilia (TPE) is a syndrome characterized by paroxysmal cough and wheezing (usually nocturnal), fever, adenopathy, high-grade eosinophilia, and elevated IgE levels. It is caused by an allergic response to microfilarial antigens and is seen most commonly in South and Southeast Asia. Chest radiographs range from normal to diffuse reticulonodular infiltrates, and pulmonary function tests show restrictive (and sometimes obstructive) defects. If done, lung biopsy reveals an eosinophilic interstitial pneumonitis. Microfilaremia is usually absent.

Diagnosis

In residents of endemic areas, lymphedema or male genital disease is epidemiologically more likely a result of LF than a similar presentation in the developed world (assuming no other cause of secondary edema is present). Still, tuberculosis, *S. haematobium* infection (urogenital schistosomiasis), and gonorrhea may also produce funiculoepididymitis and are in the differential diagnosis. In addition, nonfilarial hydrocele is common in both tropical and

nontropical areas. However, hydrocele occurs at an earlier age and with greater frequency in filariasis-endemic areas.

For parasitologic confirmation, it is difficult to visualize adult worms directly because they are localized in the lymphatics; they are usually seen only via histologic examination of surgical or biopsy specimens (in which visualizing adult worms is diagnostically definitive but insensitive). However, ultrasound examination of lymphatics has at least 80% sensitivity in some settings, in part because live adult worms have a distinctive pattern of movement (the “filaria dance sign”) (Amaral et al, 1994). Online examples can be found at www.youtube.com/watch?v=ER1BFx4_qGc, <http://www.filariajournal.com/content/2/1/3/figure/F1?highres=y>, and www.youtube.com/watch?v=d3KWh6xqQm0. Plain radiographs may reveal calcifications, which are also suggestive of LF in the appropriate clinical setting.

Microfilariae can be found in blood and occasionally in other body fluids; they are best detected by a Giemsa-stained blood smear. The timing of blood collection should be based on the periodicity of the microfilariae in the geographic location involved (highest at midnight in most cases). Microfilaremia is found in only 30% to 40% of all infections, and definitive diagnosis in amicrofilaremic cases can be more difficult. Detection of circulating *W. bancrofti* antigens is one means to detect such infections, and this can be done with both an ELISA and a point-of-care immunochromatographic card test (ICT). Recently, a new ICT (the Alere Filariasis Test Strip) has shown better sensitivity in field conditions than the BinaxNOW Filariasis ICT, which has been in use for the past 10 to 20 years (Weil et al, 2013). There are currently no tests for circulating antigens in brugian filariasis. PCR-based assays for *W. bancrofti* and *B. malayi* in blood are very sensitive but are not yet widely available.

Antibody-based assays for diagnosing LF have traditionally suffered from poor specificity. IgG4 antibodies are less cross-reactive to nonfilarial helminth antigens and thus are more specific. Specificity has also been improved with species-specific antigens for both brugian and bancroftian infection. A dipstick antibody test has been developed for brugian filariasis (Weil et al, 2011).

Patients with so-called burned-out infections (e.g., those who have received antiparasitic therapy or who departed endemic areas years previously and in whom the worms have now died) often have lasting damage (i.e., lymphedema, genital disease, and other clinical manifestations). In these patients, negative testing for microfilaremia and circulating antigens does not exclude the possibility that their lesions could be a result of LF. However, such patients are usually LF antibody positive.

Radionuclide lymphoscintigraphic imaging reliably demonstrates lymphatic abnormalities in patients with LF. Although helpful in documenting the degree of damage associated with infection, this is not useful for differentiating LF from other causes of lymphatic disease.

Treatment

Because most patients with microfilaremia have at least subclinical disease, treatment is recommended for both symptomatic and asymptomatic individuals with microfilaremia. Diethylcarbamazine (DEC, 2 mg/kg orally three times a day) is the treatment of choice for active LF (microfilaremia, antigen positivity, or live adult worms on ultrasound). A 1-day course appears to be as effective as the traditional 12-day regimen for most patients (CDC, 2013a), although those with TPE should receive a 2- to 3-week course. DEC kills microfilariae but has only modest activity against adult worms, and in the United States is available only through the CDC (phone: 404-718-4745). DEC should not be given to persons from areas co-endemic for onchocerciasis or *L. loa* (e.g., West and Central Africa) unless these infections have been excluded because of potentially serious side effects related to the killing of these parasites by DEC. Alternatives for LF include albendazole and ivermectin. Albendazole (400 mg orally twice daily for 21 days) has both microfilaricidal and macrofilaricidal activity, but the activity of ivermectin (150 to 400 µg/kg orally once) is limited mostly to microfilariae.

Side effects of DEC include fever, chills, arthralgias, headaches, nausea, and vomiting. In heavily infected patients, painful skin nodules, lymphadenitis, and epididymitis may occur as a reaction to dying parasites or *Wolbachia* endosymbionts, usually days to weeks after initiation of therapy. Ivermectin has a side effect profile similar to DEC when used for LF; it also must be used with caution if co-infection with *L. loa* is possible. Albendazole (when used in single-dose regimens; see later) has relatively few side effects when used for LF.

Doxycycline (200 mg daily) augments the suppression of microfilaremia induced by antifilarial drugs and has some macrofilaricidal activity. Prolonged courses (4 to 8 weeks) render adult worms sterile (Kappagoda et al, 2011). Individuals treated with doxycycline can experience substantial improvements in lymphedema and hydrocele. These benefits are seen even in lymphedema patients without active infection, suggesting that the benefit of doxycycline extends beyond the macrofilaricidal and anti-*Wolbachia* activity of this drug (Mand et al, 2012). The prolonged course is problematic for administration in the developing world, and doxycycline cannot be given to pregnant women or young children. However, in the United States a 6-week treatment course of this drug is a reasonable consideration in properly selected patients.

In persons with chronic lymphedema, prevention of secondary bacterial infections, good hygiene, elastic stockings, elevation, and physiotherapy are important for morbidity control. Antiparasitic therapy in these patients should be reserved for those with active infection. Surgical correction is challenging and often unnecessary. Lymphatic-venous and nodal-venous anastomoses for elephantiasis have been somewhat successful in decreasing leg swelling, as has reconstructive surgery for genital involvement. The long-term effects of these intensive surgical techniques have not been determined.

Genital elephantiasis is rarely amenable to surgery, and lymphadenectomy may further compromise lymph drainage and worsen symptoms. In some cases of funiculoepididymitis, surgery, such as decompression or excision of filarial nodules, might be indicated to preserve the testis and spermatic cord. When funiculoepididymitis is recurrent, painful, and deforming or complicated by blood vessel involvement, more radical surgery is warranted. Drainage of hydroceles provides immediate relief, although recurrence is common in the absence of medical and definitive surgical therapy. Hydrocelectomy is often indicated for large or symptomatic hydroceles. Excision of the intact hydrocele sac is the procedure of choice; alternatively, inversion with partial excision can be considered. When identified, leaking or dilated lymphatic vessels should be sutured or excised. Small hydroceles that do not enlarge usually do not require surgery. Reconstruction of the scrotum or vulva, with removal of redundant tissue, can also provide symptomatic relief to selected patients.

Prevention and Control

Individual protection against LF infection involves avoidance of infected mosquitoes through personal protective measures and long-lasting insecticide-treated bednets (LLINs); LLINs have recently been shown to be a valuable tool for the control and elimination of LF (Reimer et al, 2013). Elimination of microfilariae within communities can interrupt transmission because patent microfilaremia is necessary for mosquitoes to transmit the infection from person to person. However, because chemotherapy does not kill all of the adult worms, it is necessary to continue intermittent administration of antiparasitic drugs for many years, until the adult worms die of senescence. This strategy can be effective for *W. bancrofti* elimination (Molyneux, 2009) but is more challenging in *Brugia*-endemic areas because animals also serve as reservoirs of infection for the latter. MDA campaigns (involving distribution of single annual doses of albendazole plus either DEC or ivermectin, which have a sustained microfilaricidal effect, to most of the population) are the mainstay of control programs in Africa (albendazole/ivermectin) and elsewhere (albendazole/DEC). These campaigns have been successful in control and elimination of LF, especially in

many of the endemic middle-income countries of Asia, Latin America, and the Pacific.

Onchocerciasis, also known as **river blindness**, is a filarial infection caused by *O. volvulus*. The infection is transmitted by *Simulium* black flies; 99% of onchocerciasis cases are found in Africa, with limited foci in Latin America and the Arabian Peninsula. About 37 million people are infected globally (Taylor et al, 2010). As with LF, transmission is inefficient and highly focal. Adult worms live in subcutaneous nodules (mean life span, 9 to 10 years) and release microfilariae that travel through the skin (and eye). *O. volvulus* adults also harbor *Wolbachia* endosymbionts. Infection classically causes dermatitis, keratitis, and chorioretinitis, with blindness as an end result after many years, from corneal scarring. Diagnosis is confirmed by microscopically examining skin snips for microfilariae, finding adult worms in subcutaneous nodules, or seeing microfilariae in the anterior chamber of the eye via slit lamp. Antibody and antigen detection tests are less well developed than for LF.

In late stages, *Onchocerca* infection may produce “hanging groin” or scrotal elephantiasis as a result of recurrent lymphadenitis and loss of skin elasticity. Histology demonstrates atrophy and fibrosis of inguinal lymph nodes with subcutaneous edema and fibrosis. Onchocerciasis is also occasionally accompanied by massive inguinal lymphadenopathy.

Ivermectin is the treatment of choice (150 µg/kg orally once, repeated every 6 to 12 months until patient is asymptomatic), although it kills only microfilariae. Ivermectin must be used with caution if coinfection with *L. loa* is possible. Adverse effects include fever, rash, dizziness, pruritus, myalgias, arthralgias, and lymphadenopathy, mostly caused by dying filariae and *Wolbachia*. Six weeks of doxycycline (200 mg/day orally) kills more than 60% of adult female worms and sterilizes most of the remainder (Hoerauf, 2011). DEC should not be administered to persons infected with onchocerciasis because blindness and systemic toxicity can result from the resulting ocular and systemic inflammatory responses.

Loiasis is caused by *L. loa*, a filarial infection that is limited to Central and West Africa and transmitted by *Chrysops* flies. Adult worms migrate in subcutaneous tissues, and microfilariae circulate diurnally in the blood. *L. loa* does not harbor *Wolbachia*. Most infected persons have asymptomatic eosinophilia; some have urticaria, migratory subcutaneous lesions, and visible worms migrating across the conjunctivae (*eye worms*). Hematuria and proteinuria occur in 30% of patients; lymphadenitis and hydrocele also rarely occur. DEC (2 to 3 mg/kg orally three times a day for 14 to 21 days) is effective against loiasis, although multiple courses may be necessary (Klion and Nutman, 2011). Treatment can cause pruritus, arthralgias, migratory swellings, fever, eye worms, diarrhea, and renal failure. Patients with detectable microfilaremia (particularly more than 2500 to 8000 microfilariae per milliliter) are at risk of treatment-associated encephalopathy, which may be ameliorated by pretreatment apheresis. Albendazole (200 mg orally twice daily for 3 weeks) is associated with a lower risk of encephalopathy than DEC and may be safer in patients with high-grade parasitemia (Kappagoda et al, 2011).

Other Nonfilarial Genitourinary Parasites

Echinococcosis

Echinococcus granulosus is a cestode (tapeworm) that causes cystic echinococcosis. Infection results from ingestion of food or water contaminated with *Echinococcus* eggs or contact with infected dogs. Prevalence is high in pastoral communities, particularly in South America, the Mediterranean littoral, Eastern Europe, the Middle East, East Africa, Central Asia, China, Russia, and Australia. After infection the parasites encyst, usually in the liver or (less commonly) in the lungs. Although rare, cysts can grow ectopically in almost any organ in the body, with the kidneys being the third most common organ affected after the liver and lungs (<2% to 3% of cases) (Moscatelli et al, 2013). Initially, cysts are asymptomatic, but over time they enlarge (1 to 2 cm/yr) and eventually

cause pain or a palpable abdominal mass; hydatiduria and renal colic occur in a minority of patients. Renal function is usually unaffected. Imaging shows a thick-walled, fluid-filled spheric cyst, often with a calcified wall; the appearance helps define the stage of the disease and, in turn, management strategies. Serologic testing is adjunctive for diagnosis, with a sensitivity of only 60% to 90%. Although use of percutaneous puncture, aspiration, injection, and reaspiration (PAIR) is a good therapeutic option for liver cysts, this is not done for renal cysts, for which the only options are surgical resection or antiparasitic chemotherapy. Albendazole (400 mg orally twice per day for 1 to 6 months) is the recommended medical therapy (Kappagoda et al, 2011). Surgical excision is indicated in some patients because of the size or location of the lesions. Cyst rupture can cause anaphylaxis. Some evidence suggests that PZQ plus albendazole preoperatively and postoperatively may minimize secondary seeding and metastatic infection (Bygott and Chiodini, 2009).

Enterobiasis

Enterobius vermicularis (pinworm) causes enterobiasis, which occurs worldwide (common in both temperate and tropical countries). The worms live in the proximal colon and migrate to the perianal region to lay eggs, which become infectious after 6 hours. Transmission is mainly person to person, often via fecal-oral contamination of hands or fomites. Although most infections are asymptomatic, perianal pruritus can be severe. Rarely, pinworms can also migrate ectopically, including through the vagina, uterus, and fallopian tubes and into the peritoneal cavity of females. Dead worms and eggs incite granulomas and adhesions. Vulvar and cervical granulomas, salpingitis, oophoritis, tubo-ovarian abscess, appendicitis, and peritonitis can result. Epididymal involvement and inguinal hernias have been rarely reported in men (Moore and McCarthy, 2011).

Treatment with single-dose albendazole (400 mg orally) or mebendazole (100 mg orally) is highly effective. Alternatives include ivermectin (200 µg/kg orally once). Household and other close contacts should be treated, and treatment should be repeated after 2 weeks because of frequent reinfection and autoinfection (Kappagoda et al, 2011).

Amebiasis

Entamoeba histolytica, a protozoan transmitted by the fecal-oral route, is most common in tropical regions. Most infected persons remain asymptomatic, but 10% develop symptoms in other organs, including the kidneys. Cutaneous amebiasis can also occur, with painful ulcers often involving the perianal area and genitals (Peterson et al, 2011). Treatment is with tinidazole (2 g orally per day for 3 days) or metronidazole (750 mg orally three times a day for 10 days), followed by paromomycin (8 to 12 mg/kg orally three times a day for 7 days) or iodoquinol (650 mg orally three times a day for 20 days) (Kappagoda et al, 2011).

Trichomoniasis

Trichomonas vaginalis is a common sexually transmitted protozoan. See Chapter 15 for details.

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The complete reference list is available online at www.expertconsult.com.

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18

Basic Principles of Immunology and Immunotherapy
in Urologic Oncology

Charles G. Drake, MD, PhD

Basic Immunology

Chronic Inflammation and the Endogenous Immune Response to
Genitourinary Cancers

Immunotherapy for Genitourinary Cancers

Cancer Vaccines

Immune Checkpoint Blockade in Genitourinary Cancers

Conclusions

Immunotherapy is emerging as an important treatment modality for multiple tumor types, including melanoma, lung cancer, and kidney cancer (Drake et al, 2014b). What is often forgotten as the field moves forward is the prominent role that immunotherapy has long played in bladder cancer (Brandau and Suttman, 2007). In fact, the use of bacille Calmette-Guérin (BCG) in bladder cancer provides an ideal framework through which to understand immunotherapy for genitourinary (GU) cancers, although there are still many unanswered questions regarding its mechanism of action. In addition to BCG, which is a relatively nonspecific agent, immunotherapy for GU cancer has also involved the concept of inducing a specific anticancer immune response via a cancer vaccine. Vaccine approaches for prostate cancer and kidney cancer will be discussed at some length; more detailed clinical information is included in specific chapters dedicated to treatment. Finally, recent clinical and laboratory data support a novel approach to immunotherapy: in many patients, it appears that antigen-specific immune responses to cancer are restrained by a specific set of molecules expressed on CD4 and CD8 tumor-infiltrating lymphocytes (TILs) (Pardoll, 2012). These “checkpoint” molecules are critically important in restraining an antitumor immune response, so treatment with monoclonal antibodies blocking specific checkpoint molecules such as CTLA-4 (cytotoxic T-lymphocyte antigen-4) and PD-1 (programmed death-1) can lead to objective clinical responses (i.e., tumor shrinkage) in approximately 30% of patients with kidney cancer. These checkpoint molecules will be introduced, and some early clinical data highlighted as well.

BASIC IMMUNOLOGY

The Innate Immune System

For didactic purposes, the immune system is often parsed into two basic divisions, the **innate** and the **adaptive**. Evolutionarily, the innate immune system is the older of the two, and it is present in all vertebrate organisms. Functionally, the innate system recognizes its targets through repeated patterns associated with pathogens. These pathogen-associated molecular patterns (PAMPs) are recognized by a series of receptors related to Toll molecules in *Drosophila*, and are known as *Toll-like receptors* (TLRs) (Medzhitov and Janeway, 2000). The binding of PAMPs to TLRs is a fundamental immunologic mechanism through which the organism recognizes “danger.”

Urologists who treat bladder cancer with intravesical BCG employ these innate immune immunologic mechanisms clinically; peptidoglycans in the BCG cell wall are canonical PAMPs, which bind to the Toll-like receptor TLR2 on innate immune cells resident in the bladder wall, serving to activate them and to initiate a cascading immune response (Brandau and Suttman, 2007).

The initial immune cell that responds to an invading pathogen (or to instilled BCG) is most likely a tissue-resident macrophage (Table 18-1). Their name is derived from the Greek *makros* (“large”) and *phagos* (“to eat”); macrophages are large cells that have evolved to engulf and destroy pathogens. Recognition of PAMPs by tissue-resident macrophages leads to their activation and subsequent secretion of chemical messengers known as *cytokines* and *chemokines* (see later), which in turn recruit and activate additional immune cells important in controlling a local infection. Again, BCG therapy for bladder cancer provides an excellent example, as both recognition by macrophages and the adherence of bacteria to urothelial cells lining the bladder results in the secretion of a series of chemokines and cytokines (Fig. 18-1). Some of these secreted cytokines attract a second cell type of major importance in the innate immune system, the neutrophil (also known as a *polymorphonuclear neutrophil* [PMN]). PMNs are the most abundant immune cell in the periphery and comprise approximately 60% of the white cells in the blood. These cells have a half-life measured in hours in the peripheral blood but can survive for days when present in the tissue at a site of infection or inflammation. In that sense, PMNs are the major cellular constituent of pus, and the hallmark of acute inflammation. One remarkable feature of neutrophil biology is their ability to emigrate from the circulation into tissues; this occurs when they squeeze between cells in the vascular endothelium as they follow a chemokine concentration gradient toward an area of infection within tissues. The hypersegmented configuration of their nucleus likely helps in this process by presenting a less formidable structural barrier to deformation. Like macrophages, neutrophils synthesize a variety of secretory granules that are released on PAMP recognition and that serve to facilitate destruction of an invading pathogen.

Cytokines and Chemokines

Cytokines and chemokines are small-molecule chemical messengers through which epithelial cells communicate with key cells in the immune system, and through which cells in the immune system

TABLE 18-1 Selected Cell Types Involved in the Immune Response to Genitourinary Cancers

CELL TYPE	IMMUNOLOGIC ROLE
Epithelial or urothelial cell	Secrete type I interferons as well as chemokines in response to stress, inflammation, viral infection, or danger signals mediated by pathogen-associated molecular patterns (PAMPs).
Macrophage	An innate immune cell that engulfs both pathogens and dead or dying cells. Secretes cytokines and chemokines to amplify or initiate an immune response.
Neutrophil (polymorphonuclear neutrophil (PMN))	The most numerous of all innate immune cells in the peripheral blood, critically important in controlling bacterial infections. A collection of neutrophils (pus) is a characteristic of acute inflammation.
Dendritic cell (DC)	The cell type that bridges the innate and adaptive immune systems by presenting antigens (peptides) from dead or dying cells or debris to T cells in the lymph node. Like macrophages, DCs are activated by “danger” signals transmitted through PAMPs, or by cytokines in the microenvironment.
CD4 T cell	A “helper” T cell; can help CD8 T cells to kill or B cells to secrete antibodies.
CD8 T cell	A “killer” T cell; once activated, serially lyses specific targets.
Regulatory T cell (Treg)	A subset of CD4 T cells characterized by expression of the transcription factor FoxP3. Major role is to downregulate an ongoing immune response. In cancer, this is generally a detrimental function.

communicate with one another. There are a large number of such molecules, and their nomenclature can be confusing. However, these molecules have a critical role in both acute and chronic inflammation, in the innate immune response, and in the adaptive immune response to cancer, so understanding a few key players is important. In this regard, the term *cytokine* is a rather general one, referring to any small immunologically relevant molecule secreted by a cell. Because many (but not all) of these molecules are involved in the migration of cells, the name derives from *cyto* (“cell”) and *kinesis* (“movement”). Typical cytokines include the type I interferons (IFN- α and IFN- β), which are produced by virally infected or otherwise stressed epithelial cells. Immunologically, type I IFNs render epithelial cells more sensitive to immunologic attack, by increasing their recognition by cells of the adaptive immune system, and also by directly facilitating epithelial cell death through a number of mechanisms. As discussed later, intravesical instillation of IFN- α has been evaluated in a number of clinical trials in bladder cancer, with encouraging but somewhat mixed results (Askeland et al, 2012).

The term *chemokine* refers to a subset of cytokines whose primary function is to induce the migration of immune cells along a

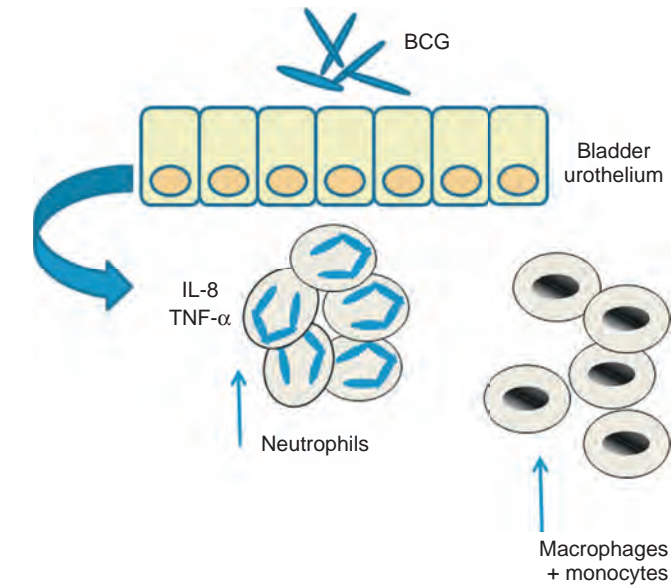


Figure 18-1. Activation of the innate immune system by bacille Calmette-Guérin (BCG). IL-8, interleukin-8; TNF- α , tumor necrosis factor- α . (Modified from Brandau S, Suttman H. Thirty years of BCG immunotherapy for non-muscle invasive bladder cancer: a success story with room for improvement. *Biomed Pharmacother* 2007;61:299–305.)

concentration gradient. The prototypic example is CXCL8, which can be secreted by most epithelial cell types, including bladder urothelium, in response to inflammatory signals. CXCL8 is a powerful chemoattractant for neutrophils and is likely important in the immune response to BCG in bladder cancer patients. The final subset of cytokines worth reviewing is a series of molecules originally described as facilitating communication between leukocytes, the interleukins. Interleukins were numbered in the order of their discovery, leading to an unfortunately complex situation in which an interleukin’s designation usually has very little to do with its functional role or cell of origin. Interleukin-1 (IL-1), for example, is really more of an innate cytokine than an interleukin; it is secreted from stressed epithelial cells, serves to attract a variety of immune cells, and in the systemic circulation is one of the primary mediators of an elevated temperature in response to infection. On the other hand, there are two discrete sets of cytokines associated with a broad polarization in the adaptive (T cell-mediated) immune response. These are termed the “Th1” and “Th2” family of cytokines (Tables 18-1 and 18-2; Fig. 18-2). These cytokines are secreted by CD4 (helper) T cells in response to various stimuli and are critically important in polarizing the immune system in one of several broad directions (Weaver et al, 2006). In bladder cancer, these patterns of response are especially important, because a Th1 response is associated with a successful response to BCG treatment whereas a Th2 response is associated with BCG failure (de Reijke et al, 1996; Thalmann et al, 2000; Saint et al, 2001, 2002). Mechanistically, this skewing occurs as naive CD4 helper cells are activated (see Fig. 18-2). In an environment rich in IL-12, they differentiate into Th1 CD4 T cells and in turn secrete IL-2, tumor necrosis factor- α (TNF- α), and IFN- γ . These Th1 cytokines, in turn, help to activate CD8 (killer) T cells and are important in a successful antitumor response. Conversely, when naive CD4 T cells recognize their targets in the context of IL-4, they differentiate into a phenotype associated with chronic inflammation and antibody production and in turn secrete IL-4, IL-5, IL-10, and IL-13. It is interesting to note that in bladder cancer these cytokines can be detected systemically after BCG treatment, so elevated serum IL-2 after treatment is associated with a favorable outcome. These are important data, showing that the immune effects of BCG are not merely local and illustrating the point that activation of the immune system in a single organ can have detectable effects throughout the entire organism.

TABLE 18-2 Selected Cytokines, Chemokines, and Interleukins Involved in the Immune Response to Genitourinary Cancers

CYTOKINE	CELL OF ORIGIN	ROLE
TYPE I INTERFERONS		
IFN- α	Urothelial cells Epithelial cells Macrophages	A type I interferon typically secreted by virally infected cells or cells sensing “danger” through Toll-like receptor (TLR) engagement. Upregulates class I MHC and antigen processing, rendering cells more susceptible to immunologic attack.
IFN- β	Urothelial cells Epithelial cells Macrophages	Similar to IFN- α , another type I interferon.
CHEMOKINES		
CXCL8	Urothelial cells Epithelial cells	A chemokine that is a powerful chemoattractant for neutrophils.
IL-1	Epithelial cells Macrophages	Like IL-8, also attracts other immune cells such as monocytes from the circulation.
SLC	Stromal cells in lymph nodes	Also known as CXCL21, SLC serves to attract activated dendritic cells and T cells into the lymph nodes. It is sensed by the receptor CCR-7.
INTERLEUKINS AND Th1 AND Th2 POLARIZATION		
IL-12	Dendritic cells	A Th1-inducing cytokine; when naive CD4 T cells are activated in the presence of IL-12, they differentiate into Th1 cells.
IL-4	Dendritic cells Natural killer T cells	A Th2 cytokine; when naive CD4 T cells are activated in the presence of IL-4, they differentiate into Th2 cells.
IL-2, TNF- α , IFN- γ	Th1 cells (CD4 T cells)	Canonical cytokines secreted by Th1 cells; associated with a favorable response to BCG in bladder cancer. These cytokines are also associated with inducing CD8 (killer) T-cell function.
IL-4, IL-5, IL-10, IL-13	Th2 cells (CD4 T cells)	Canonical cytokines secreted by Th2 cells; associated with an unfavorable response to BCG in bladder cancer. These cytokines are also associated with the induction of antibody production.

BCG, bacille Calmette-Guérin; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; SLC, secondary lymphoid chemokine; TNF, tumor necrosis factor.

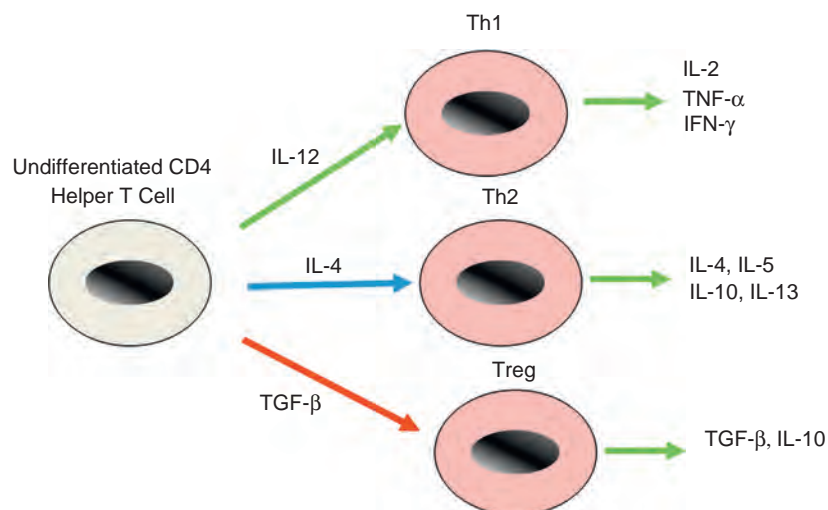


Figure 18-2. CD4 T-cell polarization and the Th1 and Th2 families of cytokines. IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor. (Modified from Weaver CT, Harrington LE, Mangan PR, et al. Th17: an effector CD4 T cell lineage with regulatory T-cell ties. *Immunity* 2006;24:677–88.)

The Adaptive Immune System

The adaptive immune system consists of CD4 (helper) T cells, CD8 (killer) T cells, and B cells. These cells are recruited into an immune response in response to activation of the innate immune system. They are important in two key facets of the immune response—its

specificity and its ability to “remember” antigen encounters and respond more robustly when an antigen is encountered again in the future. Before we expound on those properties, it is important to understand how information from the innate immune system is transferred to the adaptive immune system. This transfer depends on a unique cell type known as the *dendritic cell* (DC), which serves

as a bridge between an innate and an adaptive immune response. DCs get their name from their long and fine cytoplasmic projections, which microscopically resemble nerve cells. Functionally, DCs are scattered throughout the peripheral tissues, as exemplified by Langerhans cells in the skin. They spend the majority of their life span at rest, continually sampling their microenvironment, taking in fluid and protein antigens through the process of pinocytosis. In the absence of an activating or “danger” signal, DCs remain in situ and in a quiescent state. A danger signal can come in the form of cytokines such as $\text{TNF-}\alpha$ secreted from innate immune cells such as macrophages, or through direct contact with bacterial products through pattern receptors (TLRs) on DCs. When DCs are activated, a remarkable transition takes place. First, they cease taking in antigens, because their new role will be to present the antigens they have already taken up to T and B cells. Therefore their dendrites are retracted and the cells develop a more compact morphology. Second, they upregulate cell surface molecules important for presenting the antigens they are carrying to T cells. These include major histocompatibility complex molecules, which bind 9 to 12 amino acid peptide antigens in their grooves for interacting with specific receptors on T cells (TCRs), as well as a set of molecules designed to optimally stimulate T cells; these are called *costimulatory molecules* and include B7-1, B7-2, and others. Finally, DCs must solve a spatial problem: resting lymphocytes (T cells and B cells) reside in the secondary lymphoid structures—that is, in the lymph nodes—whereas resting DCs are situated in the tissues. Thus, DCs must migrate into the lymphatic system and enter into the lymph nodes through afferent lymphatic vessels. This is accomplished via chemotaxis; activated DCs follow a gradient of secondary lymphoid chemokine (SLC) using a receptor known as CCR7 into the lymph nodes. Once in the lymph nodes, DCs interact with (and activate) specific CD4, CD8, and B lymphocytes, facilitating the transfer of information from the innate to the adaptive immune system.

Thus, a CD4 T cell is activated when an antigen-presenting DC presents its cognate (specific) peptide antigen (usually 11 amino acids long) in the context of a class II major histocompatibility complex (MHC) molecule. These are helper cells; they either help CD8 T cells to become fully activated and exert their lytic function or assist B cells in making antibodies. As described earlier, CD4 T-cell responses fall into several basic categories, including a Th1 response, which serves to fully activate CD8 (killer cells), and a Th2 response, which serves to help B cells mature into antibody-secreting plasma cells. An additional CD4 T-cell subtype of interest is the

regulatory T cell (Treg). These cells suppress adaptive immune responses and appear to play a role in preventing a successful adaptive Th1- or CD8-driven anticancer response (Curiel, 2008). The origin of Tregs is complex; a population of “natural” Tregs arises de novo in the course of T-cell development in the thymus, and a second population is “induced” when naive CD4 T cells recognize their antigen in a microenvironment that is low in proinflammatory signals and rich in transforming growth factor- β (TGF- β) (see Fig. 18-2). The relative contribution of these two types of Tregs to the progression of GU cancers in humans is unclear; however, recent laboratory data point to a critical role for natural, thymus-derived Tregs (Savage et al, 2013).

Perhaps the most fascinating adaptive immune cell is the CD8 T cell. These cells recognize their specific cognate antigen 9 amino-acid long peptides in the context of class I MHC, which is present on almost all cell types but which is upregulated in the context of inflammation and on virally infected cells. When a specific CD8 T cell recognizes its target, it secretes a series of molecules that result in destruction of that cell type. This killing process is remarkably specific; in the autoimmune disease type 1 diabetes, CD8 T cells can lyse beta cells in the pancreas while leaving immediately adjacent alpha cells completely intact. The mechanism of killing is also exquisite; CD8 T cells employ multiple molecular mechanisms to induce their target cells to commit suicide—that is, to undergo programmed cell death or apoptosis. Finally, CD8 T cells are serial killers, able to lyse multiple specific targets in a sequential manner. As discussed later, the major goal of cancer vaccines is to activate antigen-specific CD8 T cells and to thereby eliminate an evolving tumor.

The Immune Editing Hypothesis

Before moving forward with a discussion of how the immune system may be manipulated to treat GU cancers, it is worthwhile to consider the immune system’s baseline role in either the promotion or the elimination of cancer. With the exception of certain virally mediated tumors that occur most commonly in immunocompromised individuals, most human cancers develop in immunologically intact hosts. As tumorigenesis proceeds from low-grade or localized disease to distant metastases, an interaction between the host immune system and the tumor mass occurs. This process has been well characterized in a number of animal models and can be divided into three distinct stages (Dunn et al, 2004) (Fig. 18-3). In

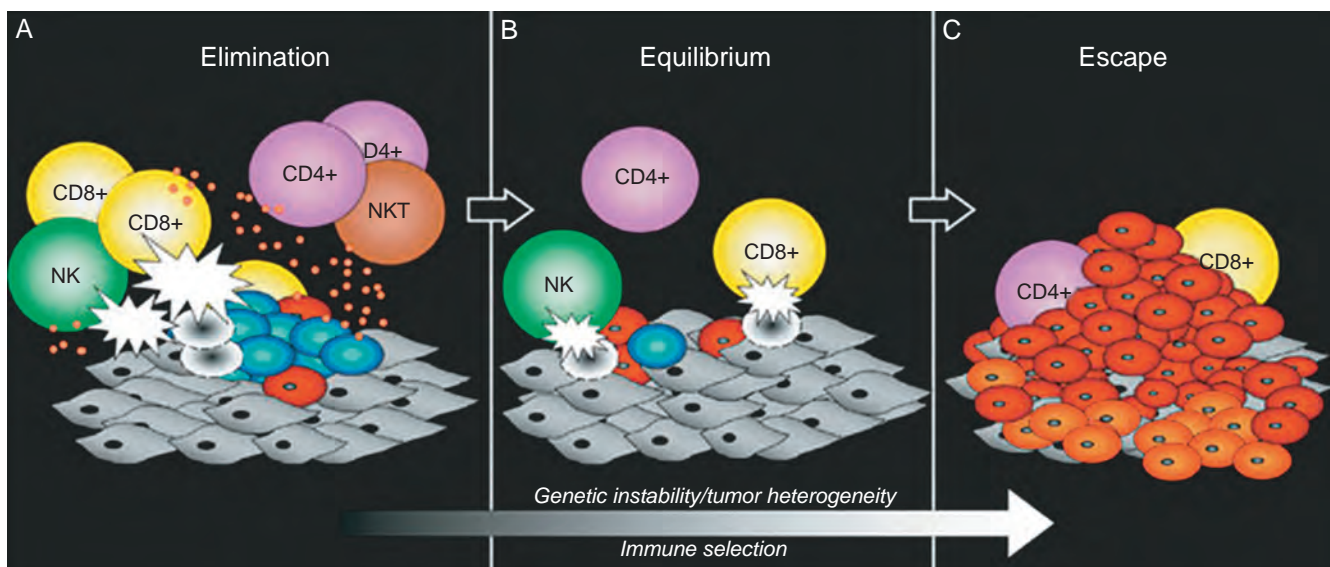


Figure 18-3. A–C, The immune editing hypothesis. NK, natural killer; NKT, natural killer T cell. (From Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity* 2004;21:137–48.)

the first stage of the process, early tumors are recognized by the immune system in a productive, proactive way, leading to **elimination** of small, clinically undetectable masses. Elimination is most likely mediated by a concerted effort between the innate (macrophages and DCs) and the adaptive immune system. As tumors progress, they acquire genetic and epigenetic alterations that render an antitumor immune response less efficacious. Therefore in the next phase of tumor-immune system interactions, tumors are able to exist in a sort of **equilibrium** with the host immune response, with progression slowed by an ongoing immune response, but in which tumors can no longer be successfully eliminated. Equilibrium may persist for a significant period of time, and some tumors may remain in the equilibrium stage for the life of the host. Eventually, though, many tumors proceed to **escape** the host immune response and become clinically apparent. The molecular mechanisms involved in the escape phase are multiple and include downregulation of tumor antigens against which a host response is directed (Drake et al, 2006), downregulation of MHC molecules, and the induction or expansion of Tregs that actively inhibit an immune response. The three phases of tumor-host interactions (elimination, equilibrium, and escape) collectively form the immune editing hypothesis, which serves as a valuable framework through which to understand the immune response to cancer. Indeed, subversion of a productive host antitumor response is now designated as one of the hallmarks of cancer (Hanahan and Weinberg, 2011).

KEY POINTS: BASIC IMMUNOLOGY

- An immune response begins with an innate response that is swift but relatively nonspecific then progresses to include the adaptive immune system, which is characterized by both specificity and memory.
- For an antitumor immune response, a Th1 response dominated by IFN- γ , IL-2, and TNF- α is desired.
- CD4⁺ regulatory T cells (Tregs) inhibit an adaptive immune response.
- The immune editing hypothesis explains how early tumors can be recognized and eliminated by the immune system, whereas clinically evident tumors must escape immune recognition to evolve.

CHRONIC INFLAMMATION AND THE ENDOGENOUS IMMUNE RESPONSE TO GENITOURINARY CANCERS

Although the immune editing hypothesis would leave one with the impression that antitumor immune responses are, in general, beneficial, those data need to be considered along with a great deal of apparently contradictory data suggesting that inflammation can promote tumor progression (Balkwill et al, 2005; de Visser et al, 2006). Human and animal studies indicate that inflammation has a clear role in the development of bladder cancer (Michaud, 2007) and likely plays a role in the development of prostate cancer, as well (De Marzo et al, 2007).

Chronic Inflammation and the Immune Response to Bladder Cancer

Among the various GU malignancies, bladder cancer provides the strongest evidence for a link between chronic inflammation and carcinogenesis (Michaud, 2007). The evidence linking inflammatory schistosomiasis infections to bladder cancer is particularly robust, and *Schistosoma haematobium* has been classified as a known carcinogen by the International Agency for Research on Cancer. Epidemiologically, countries with high rates of endemic infection have high rates of bladder cancer, and high levels of infestation are

associated with a squamous cell phenotype (Mostafa et al, 1999). Other sources of bladder inflammation that have been linked to carcinogenesis include chronic urinary tract infections (Kantor et al, 1984), chronic indwelling catheters (Groah et al, 2002), and cystitis induced by cyclophosphamide treatment (Talar-Williams et al, 1996). The cellular and molecular mechanisms by which chronic bladder infection leads to cancer have not been fully elucidated but likely involve mechanisms similar to those described in other cancers (Mantovani et al, 2008)—that is, dysfunctional (M2) macrophages that produce immune suppressive cytokines, a subset of myeloid cells that suppress an active immune response (myeloid suppressor cells [MSCs]) (Ostrand-Rosenberg and Sinha, 2009), and a polarization of the adaptive immune response toward a Th2 and Treg phenotype.

Once bladder tumors develop, the immune editing hypothesis (see Fig. 18-3) would suggest that early tumors might be recognized by the immune system and eliminated. That hypothesis is supported by data showing that CD8 T-cell infiltration correlates with outcome in patients with muscle-invasive bladder cancer (Sharma et al, 2007). Obviously a successful CD8-mediated antitumor response does not occur in all patients, and recent data describe an important mechanism by which bladder tumors may “escape” immune recognition (Sharpe et al, 2007; Zou and Chen 2008; Pardoll, 2012). This occurs through the interaction between immune checkpoint molecules expressed on cancer-specific T cells and their checkpoint ligands, expressed on either tumor cells or tumor-associated macrophages (Fig. 18-4). This interaction is profoundly inhibitory to T-cell efficacy, attenuating proliferation as well as effector function. In this regard, several tissue-based studies showed that the epithelial cells in bladder cancer express the immune checkpoint ligand PD-L1 (Inman et al, 2007; Nakanishi et al, 2007; Xylinas et al, 2014). In the first of these studies, PD-L1 expression was noted in approximately 15% to 35% of patients, and expression was associated with increased tumor grade (Nakanishi et al, 2007). It is interesting to note that in these patients, PD-L1 expression was more closely associated with prognosis than was World Health Organization (WHO) grade, pointing to a functional role for PD-1/PD-L1 interaction in bladder cancer progression. A second, related, study confirmed the relationship between PD-L1 expression and high-grade tumors and further demonstrated that PD-L1 expression was associated with tumor infiltration by immune cells (Inman et al, 2007). This group also showed that PD-L1 was highly expressed in BCG-induced granulomas in patients progressing on therapy, suggesting a possible escape mechanism. Mechanistically, these data support a model known as “adaptive immune resistance” (Fig. 18-5), which explains how PD-L1 expression may be a critical mechanism by which tumors evade the immune response (Topalian et al, 2012a). In this model, mutations arising as a tumor progresses lead to an adaptive immune response, characterized by CD8 T-cell recognition. These CD8 T cells migrate to the tumor, and in the course of their effector function they secrete the cytokine IFN- γ . IFN- γ is a powerful inducer of PD-L1 expression in both tumor cells and epithelial cells, and it is these induced PD-L1 molecules on tumor cells that interact with PD-1 on the infiltrating CD8 T cells to effectively curtail their antitumor effector function. These data would suggest that a monoclonal antibody that blocks either PD-1 or PD-L1 could potentially lead to objective tumor responses in patients with bladder cancer—a hypothesis that is currently being tested in several ongoing phase 1 and phase 2 trials.

The Immune Microenvironment in Kidney Cancer

Unlike with bladder and prostate cancer, a link between chronic inflammation and kidney cancer is less clear and is only weakly suggested by the associations of kidney cancer with proinflammatory risk factors such as smoking or obesity (Chow et al, 2010). Regarding the adaptive immune response to kidney cancer, data are somewhat conflicting as to whether CD4 T-cell infiltration is a positive or negative prognostic feature in renal cell carcinoma (RCC) patients. One early study reported that CD4 T-cell infiltration is associated with an improved outcome (in the context of IFN- α

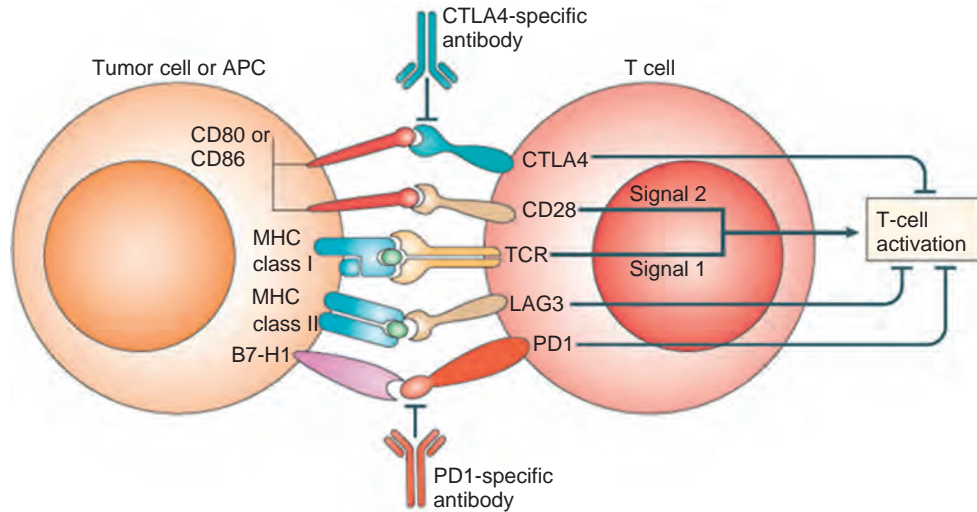


Figure 18-4. Immune checkpoint molecules. APC, antigen-presenting cell; MHC, major histocompatibility complex. (From Drake CG. Prostate cancer as a model for tumour immunotherapy. *Nat Rev Immunol* 2010;10:580–93.)

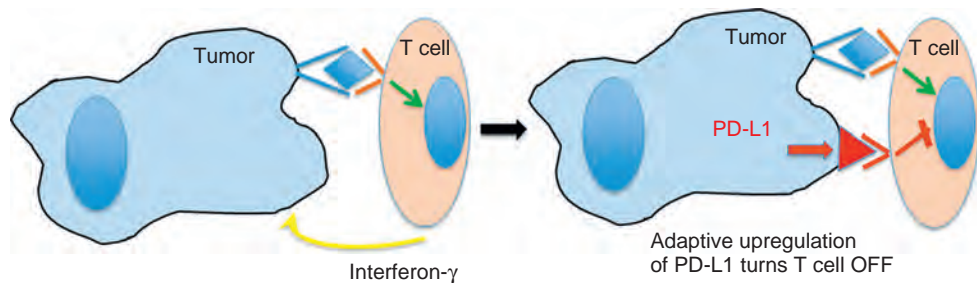


Figure 18-5. Adaptive immune resistance.

treatment) (Igarashi et al, 2002), but a more recent study suggested the opposite correlation (Hotta et al, 2011). Because neither study specifically examined whether the CD4 TILs were of the regulatory phenotype, differences in the number and/or function of CD4 Tregs could potentially explain that apparent contradiction. In this regard, as is the case in many other tumor types, tumor infiltration with Tregs has been described in RCC (Attig et al, 2009), and an association between both distant relapse and decreased overall survival with Treg infiltration has been reported in patients with clear cell RCC (Kang et al, 2013). Kidney tumors are also commonly infiltrated with CD8 T cells, suggesting an ongoing and potentially effective antitumor response, and the clonal nature of these infiltrating cells suggests an antigen-specific response (Sittig et al, 2013). As is the case for bladder cancer (Sharma et al, 2007), infiltration with proliferating CD8 T cells has been associated with an improved outcome in RCC (Nakano et al, 2001). Also similar to findings with bladder cancer, adaptive immune resistance is likely to play an important role in immune escape in kidney cancer, because PD-L1 expression has been associated with poor outcome (Thompson et al, 2007). Not unexpectedly, the CD8 T cells that infiltrate RCC express PD-1, suggesting that blocking PD-1 or PD-L1 in RCC could lead to clinical benefit. Several recent clinical trials support this concept, as is further described later.

Chronic Inflammation and the Immune Response to Prostate Cancer

Long before the appearance of clinical symptoms, the prostate microenvironment is frequently infiltrated by several types of

inflammatory cells including innate cells such as macrophages and adaptive cells such as T and B cells. This baseline inflammation is likely tumor promoting, and accumulating data from several groups support a model in which chronic prostatic inflammation drives the development of cancer (De Marzo et al, 2007). Multiple lines of evidence support this hypothesis. First, chronic inflammation in the prostate gland is frequently focused in the peripheral zone, the region in which more than 90% of tumors arise (McNeal et al, 1988). Second, epidemiologic studies show that Western nations, in which chronic prostatic inflammation is endemic, have a significantly increased incidence of prostate cancer as compared with Asian populations, in which inflammation is less prevalent (Sfanos and De Marzo, 2012). Finally, and perhaps most convincing, are data surrounding a prostatic lesion known as *prostatic inflammatory atrophy* (PIA) (De Marzo et al, 1999), a region characterized by flattened but proliferating epithelial cells and associated inflammatory cells. Morphologic studies showed that regions of PIA are located geographically proximal to high-grade prostatic intraepithelial neoplasia (PIN) lesions (Putzi and De Marzo, 2000), suggesting a possible etiologic link between PIA and the eventual development of cancer.

The adaptive T-cell environment of prostate cancer seems to be dominated by Tregs, which have been described both in the gland itself (Miller et al, 2006; Fox et al, 2007; Sfanos et al, 2008) and in the periphery (Yokokawa et al, 2008). A role for Tregs may extend even to metastatic lesions; recent studies by the Zhao group showed an increased prevalence of functional Tregs in the bone marrow of patients with prostate cancer (Zhao et al, 2012). In keeping with the notion of immunosuppression in prostate cancer, surprising data from both humans (Kiniwa et al, 2007) and animals

(Shafer-Weaver et al, 2009) suggest that in prostate cancer, CD8 T cells can also have a regulatory phenotype. In perhaps the most convincing of these studies, the McNeel group was able to show that regulatory CD8 T cells in the peripheral blood were sufficiently suppressive to mask an antigen-specific T-cell response driven by vaccination (Olson et al, 2012). Finally, as in other GU cancers, there is some evidence that the PD-1/PD-L1 axis may restrain an adaptive T-cell response to prostate cancer, because the CD8 T cells that infiltrate the prostate gland are clearly PD-1 positive (Sfanos et al, 2009). However, PD-1 blockade as a therapeutic maneuver for prostate cancer may be diminished by the finding that the tumor cells themselves do not appear to express PD-L1, suggesting either an intrinsic inability to upregulate the molecule or an absence of productive (IFN- γ) mediated inflammation. Taken together, these data suggest that prostate cancer develops in an environment characterized by chronic inflammation as well as a nonproductive adaptive CD4 and CD8 T-cell response (Bronte et al, 2005; Gannon et al, 2009).

KEY POINTS: CHRONIC INFLAMMATION AND THE ENDOGENOUS IMMUNE RESPONSE TO GENITOURINARY CANCERS

- Bladder cancer may be promoted by chronic inflammation initiated by infection or other stimuli.
- In kidney cancer, there is good evidence for an ongoing adaptive, T cell-mediated response, but that response is, in general, nonproductive.
- Prostate cancer may also be initiated through chronic inflammation.
- Expression of immune checkpoint molecules on TILs may attenuate the adaptive immune response to GU tumors.

IMMUNOTHERAPY FOR GENITOURINARY CANCERS

Bacille Calmette-Guérin in Bladder Cancer

The mechanism of action of BCG provides an excellent framework through which to understand the course of an induced immune response, an understanding that will be useful in appreciating the mechanisms of other immunotherapy modalities described later (Brandau and Suttman, 2007) (Fig. 18-6). The process begins with the instillation of 1 to 5×10^8 viable mycobacteria into the bladder. Most of these will be washed out with the first postinstillation void, but a significant fraction will adhere to the urothelial cells lining the bladder via a fibronectin attachment protein (Kavoussi et al, 1990). Repeated patterns (PAMPs) on the bacteria stimulate the urothelial cells to secrete cytokines, likely through the Toll-like receptors TLR-2 and TLR-4. Direct activation of resident macrophages and DCs by BCG components is also likely but has been less well described. The BCG-stimulated urothelial cells initiate a cascading immune response by secreting the chemokine IL-8 (among many others), and IL-8 is a powerful neutrophil attractant. TNF- α is also secreted, and in this setting this Th1 family cytokine recruits and activates macrophages. A few hours after BCG instillation, a wave of neutrophils migrates into bladder wall (de Boer et al, 1991). This wave of neutrophils is characteristic of acute inflammation, and neutrophils clear residual bacilli by secreting cytotoxic granules in addition to releasing a series of cytokines that help activate DC to potentiate the eventual involvement of the adaptive immune system. The next step in this inflammatory cascade occurs over several weeks as an adaptive immune response, primarily CD4 T cell driven, is recruited to the bladder. Although the precise mechanisms through which CD4 T cells are involved have not been well documented in bladder cancer, this most likely occurs in the same manner as it does in other immune responses: DCs are activated by neutrophil- and urothelial cell-derived cytokines (in addition to bacterial products) and traffic to the draining lymph nodes, where they present antigens to CD4 T cells to activate specific lymphocytes. The antigenic targets of CD4 T cells during BCG therapy for bladder cancer have not been well described but likely include bacterial

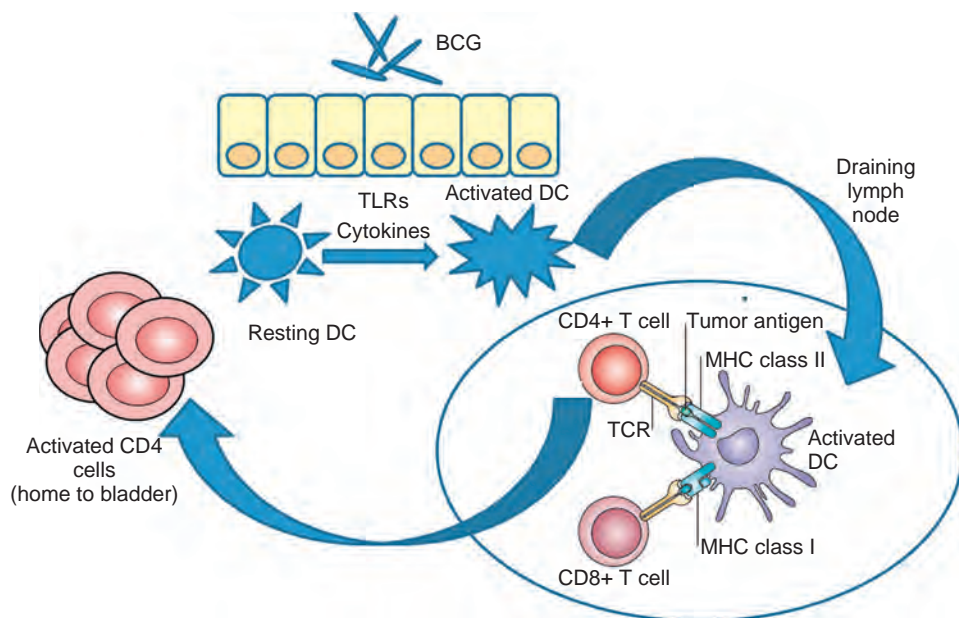


Figure 18-6. Bacille Calmette-Guérin (BCG) and an adaptive immune response. DC, dendritic cell; MHC, major histocompatibility complex; TCR, T-cell receptor; TLRs, Toll-like receptors. (Modified from Brandau S, Suttman H. Thirty years of BCG immunotherapy for non-muscle invasive bladder cancer: a success story with room for improvement. *Biomed Pharmacother* 2007;61:299–305; and Drake CG. Prostate cancer as a model for tumour immunotherapy. *Nat Rev Immunol* 2010;10:580–93.)

antigens as well as tissue- and tumor-specific antigens. Nevertheless, an adaptive immune response has been demonstrated to be required for successful BCG therapy of bladder cancer in laboratory studies (Ratliff et al, 1987), and the presence of CD4 T cell-rich granulomas in BCG-treated patients provides evidence that this may be the case in humans as well (Prescott et al, 1992). As mentioned earlier, the adaptive immune response is capable of generating long-lived memory T cells, which may persist for the life of a vaccinated patient. The generation of memory CD4 cells by BCG treatment of bladder cancer has not been well studied in patients, but their induction is strongly suggested by the significant fraction (approximately 50%) of patients whose non-muscle invasive disease remains in remission for years after BCG therapy. In summary, successful immunotherapy for bladder cancer represents a typical immune response, initially characterized by activation and involvement of the innate immune system (neutrophils and macrophages), which then transitions to an adaptive immune response driven by CD4 T cells polarized to secrete Th1 cytokines (IL-2, TNF- α , and IFN- γ), followed by eventual consolidation in the form of long-lived T-cell memory.

CANCER VACCINES

Like BCG, a “cancer vaccine” also aims to raise a T-cell response against cancer (Fig. 18-7). When a vaccine is injected into the skin, the components of the vaccine known as *pathogen-associated molecular patterns* (Medzhitov and Janeway, 2000) activate resting DCs and program them to migrate to a local lymph node. Thus, in general a vaccine includes some component(s) intended to activate DCs, although the precise substances employed vary among different vaccines. Another common term for these activating components is *adjuvant*, because they “add” immunogenicity to the protein or peptide components of a vaccine. The other key component of a vaccine is a target protein or proteins that are expected to be relatively overexpressed in a tumor relative to normal tissue. The choice of vaccine antigen(s) is somewhat empirical and, like adjuvant choice, varies widely among approaches. Once a resting DC has been loaded with antigen, has been activated, and has migrated to

a lymph node—it then displays fragments of antigen in the form of small peptides. Cellular recognition of these small peptide fragments (antigens) is complex; as introduced earlier, these peptides are not presented alone, but instead are bound within a genetically diverse set of host molecules collectively encoded by a set of genes within the MHC. Specific receptors on CD4 and CD8 T cells recognize a structure composed of both MHC molecules and a specific peptide. To increase specificity, simple recognition (a good fit) is insufficient for full T-cell activation; T cells must also receive additional costimulatory signals provided by mature DCs to proliferate and acquire effector function. In the case of CD8 T cells, the principal hoped-for effector function is the ability to lyse target cells expressing the same MHC-peptide complex that served to activate them—that is, their target antigen. For CD4 T cells, a Th1 response is desired. Once fully activated, CD8 T cells leave the lymph node and travel widely through the host in search of their targets. In the case of therapeutic cancer vaccines, the hoped-for goal is a clinically apparent reduction in tumor burden.

Vaccines for Kidney Cancer

Although an in-depth discussion of all the cancer vaccine approaches in GU cancers is beyond the scope of this chapter, several vaccines are highlighted. The chosen examples illustrate key immunologic principles, as well as the clinical challenges inherent in developing immunotherapy. In that regard, one interesting vaccine approach for kidney cancer focuses on targeting multiple, carefully selected antigens with a fairly simple adjuvant. To select relevant antigens, resected kidney tumors from a series of patients expressing the common class I MHC allele HLA-A2 were isolated, and the cell surface peptides residing in class I MHC molecules were eluted and analyzed with use of mass spectrometry (Walter et al, 2012). This approach identified a set of nine tumor-associated peptides, which were used to design a vaccine incorporating granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjuvant (Immunovax Biotechnologies, Tübingen, Germany). GM-CSF is a strong inducer of DC migration, but perhaps less robust than several of the TLR agonists in terms of inducing DC activation. In the phase 1 study of this agent (IMA901), 28 patients with RCC were enrolled; because

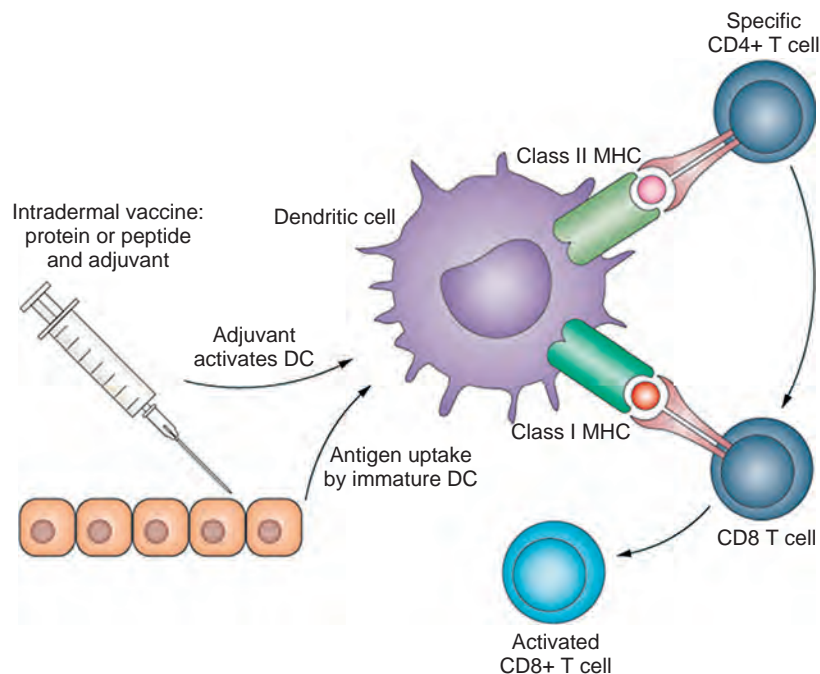


Figure 18-7. Cancer vaccines. DC, dendritic cell; MHC, major histocompatibility complex. (From Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer. *Nat Rev Clin Oncol* 2014b;11:24-37.)

the peptides in the vaccine are presented only by the MHC class I allele HLA-A2, patients were required to be A2 positive. These patients received up to eight multi-peptide vaccinations, each preceded by GM-CSF as an adjuvant. The vaccine was well tolerated, with no grade 3 or 4 adverse events reported. At a 3-month follow-up point, a single patient showed a partial response, 16 patients had disease progression, and 11 had stable disease. Immune responses to the targeted peptides were detected in several of the treated patients (Walter et al, 2012). To improve the clinical activity of this kidney cancer vaccine, investigators made use of well-established data showing that low doses of the alkylating agent cyclophosphamide have vaccine-potentiating immune effects (North, 1982); these effects are at least partially mediated by the depletion of the Tregs that turn off an immune response (Machiels et al, 2001; Wada et al, 2009). In a randomized phase 2 trial, 68 HLA-A2–positive patients with RCC were randomly assigned either to vaccine or to vaccine preceded by a single immunomodulatory dose of intravenous cyclophosphamide (300 mg/m²). As noted in many other cancer vaccine trials, objective tumor regressions were rare, with a single confirmed partial response among 64 patients. Subsequent immunologic analyses showed an increased T-cell response to the targeted peptides and verified that low-dose cyclophosphamide depletes Tregs in humans. There was a trend toward improved overall survival in the vaccine plus low-dose cyclophosphamide arm (hazard ratio [HR] 0.57, *P* = .090), but this was not statistically significant. Despite these less than optimal phase 2 results, a randomized phase 3 trial was initiated in which IMA901 was added to a first-line tyrosine kinase inhibitor in patients with metastatic RCC (NCT01265901). Enrollment of 330 patients to this trial was completed in 2012. A second illustrative vaccine approach involves autologous vaccines, in which antigens are derived from a patient's individual tumor lysate or whole cells. Such vaccines have been tested in RCC and lung cancer (Simons et al, 1997; Eager and Nemunaitis, 2005), but autologous vaccine approaches are complicated by the variability and complexity in generating a vaccine from variable amounts of patient material. To overcome these challenges, a novel approach was developed, whereby a vaccine was generated using RNA extracted from patient-derived tumor material rather than tumor lysate or cells (AGS-003, Argos Therapeutics, Durham, NC). With this approach, substantial quantities of vaccine can be manufactured using a relatively small amount of resected tumor. Rather than relying on the patient's endogenous DCs (which are often defective or dysfunctional) (Gabrilovich et al, 1997), the AGS-003 vaccine uses autologous DCs generated ex vivo through maturation of immature monocytes in the presence of the cytokines IL-4 and GM-CSF (Palucka et al, 2005). To manufacture AGS-003, patients undergo leukapheresis, and DCs are cultured. Simultaneously, tumor RNA is prepared and used to transfect those autologous DCs to generate a mature, cell-based vaccine, which is then frozen and stored for repeated intranodal injections. In a phase 2 trial using the AGS-003 vaccine, the incorporation of sunitinib, a standard therapy for RCC, was shown to result in proimmunogenic properties (Figlin et al, 2012). A phase 3 trial of AGS-003 is currently in progress; this trial will randomly assign 600 patients with metastatic high-risk RCC to receive either ongoing treatment with the standard-of-care tyrosine kinase inhibitor sunitinib, or one cycle (6 weeks) of sunitinib followed by AGS-003 coadministered along with sunitinib (NCT01582672). The primary end point of the study is progression-free survival (PFS), and enrollment has not yet been completed. Taken together, these two vaccine approaches for kidney cancer illustrate some basic principles of cancer vaccines but highlight the notion that vaccination alone is unlikely to achieve objective clinical responses in the majority of patients treated.

Vaccines for Prostate Cancer

As highlighted earlier, an adaptive immune response depends on DCs, and a cancer vaccine, like any other vaccine, depends on the presence of a population of host DCs that are numerically and functionally competent. As noted previously, this is often not the case in cancer patients, in whom DCs are dysfunctional

(Gabrilovich, 2004). One approach to overcoming DC dysfunction is to generate new DCs outside of the patient's tolerogenic environment. In prostate cancer, this approach is exemplified by Sipuleucel-T, which was the first cancer vaccine approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with a solid tumor (Kantoff et al, 2010a). Sipuleucel-T is individually manufactured for each patient with prostate cancer in a process that includes multiple steps. Briefly, patients undergo leukapheresis; peripheral blood mononuclear cells (PBMCs) are extracted and then incubated with PAP2024, a fusion protein that links the antigen prostatic acid phosphatase (PAP) to GM-CSF. After approximately 36 hours of incubation, cells are washed and resuspended for infusion back into the patient. In this approach, the GM-CSF serves as the adjuvant that helps to activate DCs. The process is repeated three times at 2-week intervals (Sonpavde et al, 2012). Of interest, the final Sipuleucel-T product is heterogeneous and includes mature antigen-presenting cells (APCs) as well as other cell types, including T cells, B cells, and natural killer cells (Sonpavde et al, 2012). Once infused, the autologous ex vivo–activated APCs are thought to prime PAP-specific CD4+ and CD8+ T cells in a manner similar to a classical vaccine-mediated prime-boost regimen, in which the first infusion primes the immune system and subsequent infusions boost the response (Drake, 2010). Recently, a combined analysis of immunologic data from several phase 3 trials of Sipuleucel-T (D9901, D9902A, and IMPACT) was completed (Sheikh et al, 2013). These combined data demonstrated that APC activation in the infused product occurred with the initial dose and increased with subsequent doses. Furthermore, antigen-specific T-cell activity (proliferation) was detectable in preculture cells obtained at weeks 2 and 4 (but not week 0). Finally, T-cell activation–associated cytokines were also noted in the second and third doses of Sipuleucel-T, supporting the idea that the first infusion of activated, antigen-loaded APCs primes T cells in patients in vivo. These results also show that the second and third doses of Sipuleucel-T are biologically different from the first and that each dose contains progressively more activated APCs and possibly a greater proportion of antigen-specific T cells with the capacity to recognize and kill prostate cancer cells. Finally, the authors demonstrated a positive correlation between overall survival and cumulative APC activation and antigen-specific immune responses. Taken together, these analyses showed that Sipuleucel-T induces an antigen-specific immune response and that the response appears to be associated with a survival benefit in treated patients.

A second prostate cancer vaccine that has reached late stages of clinical development is ProstVac-VF (Bavarian Nordic, Washington, DC) (Madan et al, 2009). This vaccine approach is quite different from the peptide- or cell-based vaccines discussed previously and relies on the incorporation of a target antigen into a virus to specifically activate the immune system (Fig. 18-8). The antigen chosen for this approach is prostate-specific antigen (PSA), and the viral backbone comes from poxviruses, which are related to the vaccine used in the successful worldwide eradication of smallpox. This technology has been honed over several decades, and the iteration in a phase 3 trial includes a number of important modifications designed to optimize immunogenicity. First, the vaccine involves a heterologous prime-boost regimen, in which the initial vaccine is based on a modified vaccinia Ankara (MVA) backbone, followed by a series of booster vaccines with a fowlpox backbone. This is necessary because the immune response to the MVA backbone is quite robust, so boosting with an identical vaccine is limited by the host's immune antibody response to the viral backbone itself. To further increase immunogenicity, the vaccine was engineered to incorporate a triad of costimulatory molecules designed to generate DCs with an enhanced potential for T-cell activation (Hodge et al, 1999). Finally, and similar to IMA901 in RCC, administration of GM-CSF at the vaccination site is used to help recruit local DCs and enhance antigen presentation. In patients, poxvirus vectors most likely infect epithelial cells, a proportion of which undergo cell death. Cellular debris, including encoded antigens, are then taken up by nearby immature DCs, which, when appropriately activated, can present these antigens to CD4+ and CD8+ T cells in a

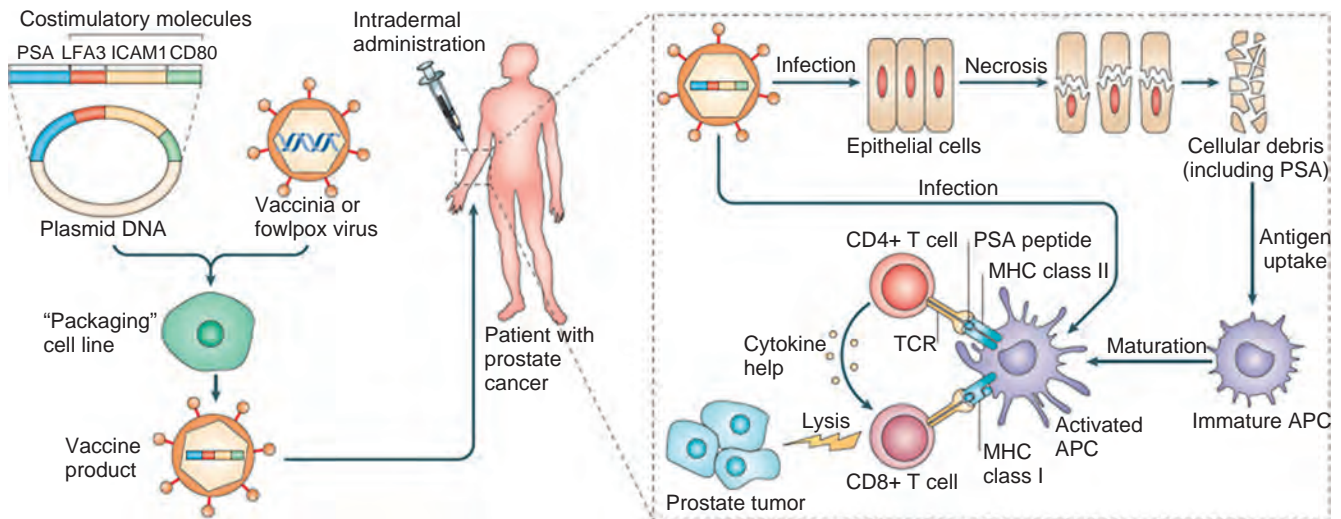


Figure 18-8. Virus-based cancer vaccines (ProstVac VF). APC, antigen-presenting cell; MHC, major histocompatibility complex; PSA, prostate-specific antigen; TCR, T-cell receptor. (From Drake CG. Prostate cancer as a model for tumour immunotherapy. *Nat Rev Immunol* 2010;10:580–93.)

proinflammatory context (Drake, 2010). Direct infection of DCs, particularly the Langerhans cells in the skin, is another mechanism by which poxvirus vectors can prime an immune response (Drake, 2010). The end result of ProstVac treatment is postulated to be activation and proliferation of PSA-specific CD8 and CD4 T cells, which was demonstrated in early correlative studies. In contrast to Sipuleucel-T (Sheikh et al, 2013), ProstVac-VF doesn't appear to prime much of an antibody response; indeed, antibodies specific for PSA have not been reported with this agent. Based on a potential survival benefit shown in a randomized phase 2 trial (Kantoff et al, 2010b), an international randomized phase 3 trial of ProstVac-VF was initiated (NCT01322490). This trial has enrolled 1200 patients and randomized them to placebo, ProstVac-VF plus subcutaneous GM-CSF, or ProstVac-VF alone. The primary end point of the trial is overall survival, and enrollment was limited to men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) who are chemotherapy naive.

Genitourinary Tumors

GVAX Prostate (Aduro BioTech, Berkeley, CA) is a cell-based immunotherapy based on irradiated allogeneic tumor cell lines genetically engineered to secrete GM-CSF (Dranoff et al, 1993). The product uses two prostate carcinoma cell lines: the androgen-sensitive line LNCaP, as well as the castration-resistant line PC3 (Simons and Sacks, 2006). The immunologic concept underlying whole-cell vaccines such as this is that these cells may provide a source of multiple tumor- and tissue-specific antigens, at least some of which will correlate with those expressed in an individual patient's tumor. So, like IMA901 in kidney cancer, GVAX vaccines are considered polyvalent. However, unlike IMA901, the precise antigens recognized when a prostate cancer patient is treated with GVAX are not known. The theoretic advantage to polyvalent vaccines such as GVAX prostate (or AGS-003 in RCC) is that it is possible that the inclusion of multiple antigens might prevent tumors from escaping immune pressure by downregulating the expression of any one tumor-associated antigen. The major disadvantage of cell-based vaccines is that they are relatively difficult to monitor immunologically, because the key target antigens are not known for any particular patient. Mechanistically, GVAX prostate is thought to function in a manner similar to ProstVac-VF: irradiated cells are administered intradermally, where they undergo necrosis and are taken up by resident DCs attracted by secreted GM-CSF. After uptake of cellular debris and processing, antigens are presented to host

CD4 and CD8 T cells in draining lymph nodes in the context of host MHC molecules on the APCs. This process, called *cross-presentation*, has been demonstrated to occur in the clinic (Thomas et al, 2004). Although phase 2 trials failed to demonstrate clear clinical benefit, two randomized phase 3 trials were launched. The first of these was a 626-patient trial in which men with asymptomatic mCRPC were randomized 1:1 to GVAX Prostate or to chemotherapy with standard doses of docetaxel administered every 3 weeks (Higano et al, 2009). The primary end point of the trial was overall survival, but the trial was halted prematurely based on an unplanned and underpowered futility analysis. Thus, it remains unknown whether GVAX Prostate provides a survival advantage in men with early-stage mCRPC. A second trial, comparing the combination of GVAX Prostate and chemotherapy versus docetaxel chemotherapy alone was initiated, but enrollment was halted based on a reported imbalance in deaths, with an interim analysis showing 67 deaths in the GVAX plus chemotherapy arm, versus 47 in the chemotherapy-alone arm. The trial was permanently closed on the basis of that "imbalance," but follow-up data showed that, in a final analysis, there was no statistical imbalance in deaths, with 85 on the combination arm and 76 in the chemotherapy-alone arm. Taken together, the two GVAX trials support the safety of these cell-based vaccines in prostate cancer, but unfortunately no conclusions can be drawn about efficacy because both trials were halted before meeting prespecified enrollment criteria. An interesting facet of both trials is the choice of chemotherapy as a comparator arm; no large randomized clinical trial of immunotherapy in GU cancer either before or after this has chosen chemotherapy as a comparator, and these data, although clearly incomplete, suggest that comparing a cancer vaccine with chemotherapy is challenging.

IMMUNE CHECKPOINT BLOCKADE IN GENITOURINARY CANCERS

As discussed earlier, most tumors have evolved multiple mechanisms to evade immune-mediated destruction (Drake et al, 2006), and one of the most important of these mechanisms involves T-cell expression of one or more of a series of molecules that effectively limit T-cell proliferation and killing capacity (Chen 2004; Keir et al, 2008; Pardoll, 2012). Collectively these molecules are referred to as *immune checkpoints*; perhaps the best known of them is CTLA-4 (Hoos et al, 2010). Critically important preclinical studies using transplantable murine colon carcinoma and fibrosarcoma lines

showed that blocking CTLA-4 with a monoclonal antibody permits antitumor T cells to acquire effector function (Leach et al, 1996), a finding that has recently been borne out in randomized phase 3 studies in patients with metastatic melanoma. In two large, randomized phase 3 trials involving a total of 1178 patients, blocking CTLA-4 with the monoclonal antibody ipilimumab (Bristol-Myers Squibb, Princeton, NJ) resulted in a significant survival benefit. In the first of these studies, which enrolled previously treated patients, the median overall survival with single-agent ipilimumab was 10.1 months versus 6.4 months for patients treated with a peptide vaccine on the control arm (Hodi et al, 2010). In the second of these studies, which enrolled treatment-naïve patients and randomized them to either ipilimumab plus chemotherapy with dacarbazine or dacarbazine alone, median overall survival was 11.2 months versus 9.1 months. Long-term follow-up from the first trial showed that approximately 15% of treated patients were alive 5 years after enrollment. As reviewed elsewhere, CTLA-4 blockade is moving forward in lung cancer and other tumor types (Drake et al, 2014b). Because the immune checkpoint molecule CTLA-4 likely evolved to protect self-tissues from autoimmunity, it is not surprising that clinical trials of anti-CTLA-4 (including the pivotal phase 3 trials) were associated with an approximate 20% incidence of grade 3 and 4 immune-related adverse events (IRAEs), including colitis and dermatitis (Attia et al, 2005; Blansfield et al, 2005; Weber 2009; Lipson and Drake 2011). As introduced earlier, blocking a second immune checkpoint, PD-1, has also led to objective responses in melanoma, kidney cancer, and, perhaps somewhat surprisingly, lung cancer (Brahmer et al, 2010; Topalian et al, 2013). Toxicity rates for the two agents are difficult to compare because PD-1 blocking antibodies have only recently entered phase 3 development. Nonetheless, the rate of grade 3 and 4 adverse events does seem to be lower with PD-1 blockade than with CTLA-4 blockade (Topalian et al, 2012b, 2013), possibly because the PD-1/PD-L1 pathway acts more peripherally than the CTLA-4/B7-1 pathway, which likely operates in the lymph nodes (Ribas, 2012). In contrast to the cancer vaccines discussed earlier, objective tumor regression and long-term complete responses have occasionally been observed with either PD-1 or CTLA-4 blockade (Lipson et al, 2013). Although it remains unclear why cancer vaccines rarely generate objective tumor shrinkage, accumulating clinical data suggest that current vaccines are likely unable to effectively circumvent the multiple immunosuppressive mechanisms operative in the tumor microenvironment (Drake et al, 2006).

Bladder Cancer

Because bladder cancers frequently express PD-L1, blocking PD-1 and/or PD-L1 in that disease would seem a logical approach. Currently the PD-1 blocking antibody pembrolizumab (Merck, Whitehouse Station, NJ) and the PD-L1 blocking antibody MPDL-3280A (Genentech, South San Francisco, CA) are both in early-phase trials, but no mature data on response rates have yet been reported.

Kidney Cancer

In addition to multiple trials in melanoma, CTLA-4 blockade has also been tested in patients with metastatic RCC; a phase 2 trial conducted mostly at the National Cancer Institute (NCI) treated 61 patients with 3-mg/kg doses of ipilimumab every 3 weeks, or with a single 3-mg/kg loading dose followed by 1-mg/kg doses every 3 weeks. In this trial sequential cohorts were assessed, with no planned comparative analyses (Yang et al, 2007). Partial responses were observed in 5 out of 40 patients receiving the higher dose. As expected, grade 3 or 4 IRAEs were observed in 33% of patients; this appears to be a higher rate than that observed in melanoma patients, but likely reflects the continuous every-third-week administration regimen. It is interesting to note that a clear association between immune-related toxicity and responses was observed in this trial. At this time, single-agent CTLA-4 blockade is not under study in RCC, most likely because of competition from the plethora of targeted agents for kidney cancer, both FDA approved and in clinical trials.

Because RCC is usually considered to be an immune-sensitive tumor type, the observation of single-agent objective responses in RCC patients treated with single-agent anti-PD-1 in phase 1 trials was not completely unexpected. Indeed, a patient with advanced RCC showed a stable partial response for over 4 years in the first-in-human dose-escalation study (Brahmer et al, 2010). Perhaps more noteworthy, this sustained partial response eventually evolved into a documented complete response, and the patient had remained off treatment for longer than 5 years at last follow-up (Lipson et al, 2013). This initial indication of clinical activity for PD-1 blockade in RCC was supported by data from the more dose-intensive phase 1b trial discussed previously (Drake et al, 2013). Here, the objective response rate was 30% to 35%, with an additional 10% of patients showing stable disease. Based on the activity seen in phase 1 trials, several phase 1 and 2 studies of PD-1 blockade using nivolumab in RCC were initiated. One interesting trial was a dose-ranging study (NCT01354431); this trial enrolled a total of 150 patients, randomized into treatment cohorts at doses of 0.3 mg/kg, 2 mg/kg, and 10 mg/kg, treated every 3 weeks (in contrast to the once every-2-week administration in the phase 1b study). Accrual to that trial has been completed, but final data have not yet been reported. A second trial (NCT01358721) mirrors that design but incorporates pretreatment and post-treatment biopsies in an effort to discover predictive biomarkers for PD-1 blockade in RCC. Because treatment with the tyrosine kinase inhibitor sunitinib appears to confer antitumor immune modulating effects (Finke et al, 2008), a phase 1 study combining PD-1 blockade with either of the tyrosine kinase inhibitors pazopanib and sunitinib was initiated; that study is currently ongoing (NCT01472081). Most important from a clinical standpoint is a potentially pivotal, randomized phase 3 study (NCT01668784); that study, which has completed accrual, randomized 820 previously treated RCC patients in a 1:1 ratio to receive either nivolumab at a dose of 3 mg/kg every 2 weeks or to standard second-line therapy with the mammalian target of rapamycin (mTOR) inhibitor everolimus given at a dose of 10 mg once daily. The primary end point of the study is overall survival. Overall, the clinical experience with immune checkpoint blockade in RCC has been thus far favorable, with a measurable rate of objective responses and a tolerable toxicity profile. Still, without randomized phase 3 data the overall clinical impact of these agents has yet to be determined.

Prostate Cancer

As was the case for RCC, immune checkpoint blockade using anti-CTLA-4 (ipilimumab) was evaluated in a number of early-phase studies in men with prostate cancer. These data were recently summarized by Slovin and colleagues and show that treatment is associated with a PSA response rate of approximately 15% to 20%, but with few objective (radiographic) responses (Slovin et al, 2013). In several of these studies, a low dose of radiation therapy (RT) was tested in an effort to “release antigen” and potentiate an immune response. However, in the small dataset accumulated to date, there was no evidence for such an effect; for example, the PSA response rate in patients treated with a dose of 10 mg/kg of ipilimumab was 12% in the presence of RT versus 25% without. Despite this relatively low PSA response rate and little evidence that low-dose RT applied to a single lesion in men with metastatic disease improved the PSA response rate to ipilimumab, a phase 3 trial combining RT and ipilimumab was launched in men with mCRPC who had progressed on or after treatment with docetaxel chemotherapy. This trial enrolled approximately 800 men and randomized them to a single low-dose treatment of RT alone versus RT followed by ipilimumab at a dose of 10 mg/kg every 3 weeks \times 4, with every-3-month maintenance for men who were not progressing. The primary outcome of this trial was overall survival, and results were recently reported (Drake et al, 2014a). The trial did not meet its primary overall survival end point, with a median overall survival of 11.2 months in the ipilimumab group versus 10.0 months for placebo. The prespecified secondary end point of PFS was met, with a PFS of 4.0 months in the ipilimumab group versus 3.1 months in the

placebo group (HR = 0.070, $P < .001$). These data provide additional evidence that ipilimumab may have clinical activity in prostate cancer but are clearly insufficient for regulatory approval. Retrospective analyses of the phase 3 data showed that men with more favorable disease characteristics (no visceral metastases, normal alkaline phosphatase, normal hemoglobin) appeared to potentially benefit from treatment, although post hoc analyses of that sort require verification in a prospective trial. One fascinating finding in these post hoc analyses was that men with visceral benefit appeared to derive absolutely no benefit from ipilimumab treatment, whereas in men with bone-only disease there was a clear suggestion of clinical benefit. The precise mechanisms underlying this dichotomy are unclear, but it may reflect a different immune microenvironment in bone versus soft tissue metastases in prostate cancer. Relevant to those findings, a second phase 3 trial in the prechemotherapy setting has also completed enrollment; that trial specifically excluded men with soft tissue disease, perhaps boding well for its success. In summary, these data suggest that ipilimumab may have some activity in mCRPC, but the results of the second phase 3 trial will be required for that clinical question to be answered in a definitive manner.

PD-1 blockade has also been evaluated in a small number of patients with mCRPC, the majority of whom were heavily pretreated (Brahmer et al, 2010; Topalian et al, 2012b). These data were, in general, disappointing; no objective responses were noted in approximately 20 men. Biologically, the lack of response to PD-1 blockade in prostate cancer might be explained by the notion that prostate cancer cells do not appear to express PD-L1, although the majority of CD8 T cells that infiltrate the gland do express PD-1 (Sfanos et al, 2009). Taken together, immune checkpoint blockade will likely play an important role in treating RCC and possibly in bladder cancer—but additional combinatorial efforts will almost certainly be required for achievement of objective responses in men with later-stage prostate cancer.

KEY POINTS: IMMUNOTHERAPY FOR GENITOURINARY CANCERS

- BCG therapy for bladder cancer stimulates both the innate and adaptive immune systems and is a prototype for successful cancer immunotherapy.
- Cancer vaccines have been evaluated in both kidney and prostate cancer, and a single vaccine (Sipuleucel-T) is FDA approved for metastatic prostate cancer.
- Cancer vaccines are usually well tolerated but result in few objective clinical responses.
- Blocking immune checkpoints with monoclonal antibodies shows significant clinical promise in both kidney cancer and bladder cancer, but for unclear reasons appears to be less effective in prostate cancer.

CONCLUSIONS

Cancer immunotherapy is a rapidly advancing field of both clinical and preclinical study, and progress in this area has been especially strong in the case of GU cancers. A more robust understanding of both basic immunology and immune resistance to tumors has driven recent progress, and a large number of trials are ongoing.

One should not lose sight of the fact that BCG immunotherapy for bladder cancer was one of the first immune-based treatments to enter into routine clinical practice in any cancer type. As discussed in other chapters, the future of immunotherapy will most likely involve combination approaches, anchored in immune checkpoint blockade but weaving in RT, conventional chemotherapy, and perhaps initial immune activation via cancer vaccines.

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The complete reference list is available online at www.expertconsult.com.



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Cell Cycle Deregulation

DNA Methylation

DNA Damage and Repair

Genomic Alterations

Telomeres and Telomerase

Apoptosis

Stem Cells and Cancer

Despite decades of intensive biomedical research, cancer remains a significant cause of morbidity and mortality worldwide. This situation is due in part to the complexity inherent in this disease, which is not truly a single disease at all but well over 100 separate subtypes, all grouped together under the single term “cancer.”

In the United States alone, cancer strikes more than half a million people annually and is currently the second leading cause of death; if more recent trends continue, it is poised to become the leading cause of death in the near future. According to statistics reported in 2013, genitourinary (GU) malignancies comprise 29% ($n = 480,240$) of all cancer cases in the United States (nonmelanoma skin cancers excluded) and 15% ($n = 88,270$) of all cancer deaths (Siegel et al, 2013). However, significant advances have been made in the diagnosis and treatment of certain GU cancers. For example, the cure rate for testicular cancer now approaches 100% (Einhorn, 2002; Horwich et al, 2006). Testicular cancer is unusual in its responsiveness to therapy and is relatively uncommon. There has been less success with the more prevalent GU malignancies such as prostate, bladder, and renal cancers—the first (prostate), sixth (bladder), and eighth (renal) most common cancers (Siegel et al, 2013). However, mortality figures for these malignancies have shown a slow but steady decline over the past decade, and these trends are likely to continue and even to accelerate in the future.

Much of the current understanding of cancer is the direct result of the molecular biology revolution that developed rapidly following the elucidation of the molecular structure of DNA by Watson and Crick in 1953. In subsequent years, the field of molecular genetics has complemented and greatly expanded on knowledge gleaned by other disciplines, such as biochemistry and cell biology, providing important insights at the molecular level regarding the abnormalities present in cancer cells. More recent years have seen a tremendous expansion in the tools available for studying the genetic basis of human cancer, including whole genome and whole “exome” (the coding regions of the genome) sequencing efforts that have become relatively affordable and routine. A great deal is now known concerning the numerous molecular signaling pathways that provide both positive and negative regulatory signals, which in normal cells stringently control cell proliferation such that any losses in cell number are precisely counterbalanced, maintaining tissue and organ homeostasis—processes that go awry in cancer cells. Renegade populations of autonomously proliferating cells represent a serious threat to survival of the organism, particularly to large, long-lived species such as humans, and we have evolved multiple barriers to prevent such outbreaks from occurring. Incipient cancer cells must overcome several hurdles on the way to becoming fully malignant—a multistep process that takes many years to decades to complete. Cancer cells need to acquire at least

eight key attributes to make the transition from a normal cell to a malignant one, including (1) genetic instability and mutation, (2) autonomous growth, (3) insensitivity to internal and external antiproliferative signals, (4) resistance to apoptosis and other forms of induced cell suicide, (5) unlimited cell division potential, (6) the ability to induce new blood vessel formation (angiogenesis), (7) locally invasive behavior that uniquely distinguishes malignant from benign neoplasms, and (8) evasion of the immune system. In addition, cancer cells need to deal with various cellular stresses that are by-products of their abnormal physiology and increase their energy metabolism required to fuel autonomous growth and unlimited replication. Also, tumor-associated inflammation may drive the development of early preneoplastic lesions into invasive cancers and promote tumor progression. Finally, many cancers develop an additional, lethal attribute—the ability to leave the site of the primary tumor to colonize and thrive in distant organs or tissues as metastases (Hanahan and Weinberg, 2000; Solimini et al, 2007; Luo et al, 2009; Hanahan and Weinberg, 2011).

This chapter outlines fundamental concepts of molecular genetics that are directly related to human cancer in general, with an emphasis on GU malignancies in particular. Spurred by more recent technologic advances such as high-throughput DNA sequencing, knowledge of the molecular genetics of cancer is rapidly expanding, providing new insights that are just beginning to be successfully exploited for use in novel diagnostic, prognostic, and therapeutic applications.

TUMOR SUPPRESSOR GENES AND ONCOGENES

For a detailed description of basic molecular genetics (DNA, RNA and transcription, protein synthesis, chromosomes, and gene structure) see the Expert Consult website.

Tumor Suppressor Genes

Tumor suppressor genes negatively regulate cellular growth and play a critical role in the normal processes of the cell cycle. These genes are also important for DNA repair and cell signaling. The absence of tumor suppressor gene function may lead to dysregulation of normal growth control and malignancy. Loss of function of both copies (alleles) of a tumor suppressor gene is typically required for carcinogenesis. This functional loss can occur via (1) homozygous gene deletion; (2) loss of one allele and mutational inactivation of the second allele; (3) mutational events involving both alleles; or (4) loss of one allele and epigenetic inactivation of the second allele, often involving DNA methylation, which suppresses expression

Basic Molecular Genetics

A glossary of molecular biology terms is presented in [Box 19-1](#).

DNA

The molecular characteristics of deoxyribonucleic acid (DNA) were first described in 1953 ([Watson and Crick, 1953](#)). This molecule serves as the blueprint for determination of structure and function of all living organisms. **DNA comprises three basic components: a pyrimidine or purine base, a sugar (2-deoxyribose), and a phosphate (Fig. 19-1).** The DNA structure exists as a double helix in which one strand of bases is ordered in one direction and the other strand is ordered in the opposite direction. The two strands are held together by hydrogen bonds and are organized

via complementary base pairing. The four bases that primarily constitute DNA are adenine, cytosine, guanine, and thymine. Uracil is substituted for thymine in ribonucleic acid (RNA). **Hydrogen bonding occurs specifically between the purine adenine (A) and the pyrimidine thymine (T) and between the purine guanine (G) and the pyrimidine cytosine (C) (Fig. 19-2).** In the RNA molecule, adenine base pairs with uracil (U).

During the process of replication, each strand of the DNA double helix acts as a template for generation of the new strand of DNA. The precise ordering of DNA base pairs results in a code that is processed ultimately to generate proteins responsible for various cellular functions. Each single-stranded DNA molecule has two nonidentical ends referred to as the 5' (5 prime) and 3' (3 prime) termini. The 5' and 3' numbering refers to the carbon atoms in the deoxyribose sugar. The 5' carbon of one deoxyribose is linked to

BOX 19-1 Glossary of Molecular Biology Terms

Allele: An alternative form of a gene.

Alternative splicing: A mechanism by which variations in the incorporation of a gene's coding regions during mRNA maturation leads to the production of multiple related forms of a gene.

Amplification: Additional copies of a chromosomal sequence; these sequences may include genes and may be extrachromosomal or intrachromosomal.

Aneuploid: Deviation in chromosomal number from the usual diploid state (e.g., tetraploidy)

Annealing: The pairing of two single strands of complementary DNA sequences to form a double helix.

Base pair: The physical relationship between adenine/thymidine and guanine/cytosine within the double helix of DNA. Abbreviated as *bp*, it provides the unit of measurement for DNA. Each base pair is stabilized by hydrogen bonds.

cDNA: A segment of DNA complementary to an RNA sequence.

Centromere: An essential structural element of chromosomes consisting of repetitive, noncoding DNA to which the spindle microtubules attach during mitosis.

Chromosome: A distinct segment of linear DNA containing a large number of genes. In humans, there are 23 such segments, each containing hundreds to thousands of genes.

Codon: Three sequential nucleotides in protein coding genes that specify a particular amino acid in the protein or a STOP translation signal.

Deletion: The removal of a segment of DNA, with rejoining of the ends.

Diploid: A set of chromosomes containing two complete copies of the organism's genomic DNA.

Dominant: Allele determining the phenotypic manifestation of a gene.

Endonuclease: An enzyme that cuts DNA or RNA within the nucleotide chain.

Epigenetic: Nongenetic information, such as methylation or acetylation of histone proteins, that modifies gene expression.

Exon: A sequence of DNA that is represented with a complementary RNA sequence, also known as the coding sequence.

Expression vector: A vector designed to encode a particular DNA sequence or gene for transcription and translation into RNA or protein.

FISH: Fluorescence in situ hybridization. A technique in which a fluorescently labeled nucleic acid probe is hybridized to its complementary target sequence in the genome allowing localization and enumeration of the target.

Frameshift mutation: A deletion or insertion of DNA that shifts the normal codons into a different order for translation into protein.

Gene: A segment of DNA that contributes to the formation of a protein, including both the introns (noncoding regions) and the exons (coding regions) and the regulatory regions preceding and following the coding regions.

Genetic code: The correspondence between triplets of DNA or RNA (codons) and amino acids making up proteins.

Genotype: The genetic makeup of an organism as reflected in its DNA sequence.

Haplotype: A group of alleles in relative close proximity on a chromosome that are inherited together.

Hemizygote: Having only one copy of a gene owing, for example, to the loss of chromosomal material or an entire chromosome.

Heterozygote: Having two different copies (alleles) of a gene.

Homozygote: Having two identical copies (alleles) of a gene.

Hybridization: The physical pairing of complementary RNA or DNA sequences.

Intron: A segment of DNA that is transcribed but is removed by the splicing together of the exons on either side; part of the noncoding sequences of a gene.

Karyotype: A catalog of all the chromosomes within a particular cell. Typically accomplished by isolation and staining of metaphase chromosomes.

Linkage: The tendency for genes in proximity to one another on a chromosome to be inherited together.

Locus: The position of a particular gene on a particular chromosome.

Loss of heterozygosity (LOH): Deletion or mutation of a gene creating a hemizygous state or, if the remaining allele is duplicated, a homozygous state. In cancers arising in cancer predisposition syndromes caused by an inherited gene mutation, the remaining wild-type allele is often lost via LOH.

Methylation: The addition of a methyl group to a molecule. Methylation of the nucleotide cytosine in the promoter regulatory region of a gene is often associated with decreased transcription of that gene.

MicroRNA (miRNA): Small, single-stranded RNA molecules 21 to 23 nucleotides in length that function to regulate negatively transcribed genes for which they have sequence complementarity.

Mutation: Any change in the sequence of genomic DNA.

Northern blotting: A technique of transferring RNA from an agarose gel to a nitrocellulose filter for hybridization with a complementary DNA.

BOX 19-1 Glossary of Molecular Biology Terms—cont'd

Oncogenes: Genes that encode for proteins that have the ability to transform normal cells into cancerous cells.

Phenotype: The appearance or function of an organism, reflecting the contributions of the genotype and the environment.

Ploidy: The number or copies of entire chromosome complements (genomes) within a cell; diploid has two copies, triploid has three copies, tetraploid has four copies, and so forth.

Point mutation: A change in a DNA sequence involving a single base pair.

Polymerase chain reaction (PCR): A technique using sequential temperature cycles favoring DNA denaturation, annealing of primer sequences, and primer extension with DNA polymerase to amplify a large number of copies of a particular sequence of DNA. This technique can be used to detect very small amounts of DNA by creating a huge number of identical copies.

Polymorphism: A difference in normal DNA sequence between individuals. It can be a repetitive element or a single nucleotide polymorphism (SNP).

Promoter: The region of DNA in a gene where RNA polymerase binds and gene transcription begins. This region is often the sequence of DNA 100 to 500 base pairs immediately before the initiation site of the protein coding portion of the gene.

Recessive: An allele that is not represented phenotypically in the presence of a dominant allele.

Reporter gene: A gene encoding for a new or foreign protein that can easily be detected. For example, the luciferase gene, encoding the light-producing proteins of the firefly, is introduced into cells that do not express this gene.

Restriction enzyme: Recognizing specific short sequences of DNA (e.g., four or six base pairs), these enzymes cut the DNA at a particular location.

Silent mutation: An alteration in a DNA sequence that does not change the protein product of the gene.

Small interfering RNA (siRNA): Small double-stranded RNA molecules 20 to 25 nucleotides in length that promote degradation of mRNA molecules to which they have complementarity, down-regulating expression of the corresponding gene. Often employed by researchers as a means of reducing expression of specific genes.

Southern blotting: A technique of transferring denatured DNA from an agarose gel to a nitrocellulose filter for hybridization with cDNA.

Splicing: The removal of introns (spliced out) and the connection of exons (spliced together) in mRNA.

Telomere: An essential structural element of chromosomes consisting of repetitive, noncoding DNA and associated telomere-specific binding proteins that cap and stabilize the chromosomal termini.

Transcription: Synthesis of RNA on a DNA template.

Transfection: The introduction of DNA sequences into a cell.

Transgenic animals: Animals created by the introduction of new DNA into the germline (into the egg).

Translation: Synthesis of protein from the mRNA template.

Vector: A plasmid, bacteriophage, or virus that carries new DNA into a cell. Vectors are often designed to produce large amounts of protein encoded by the gene within the host cell.

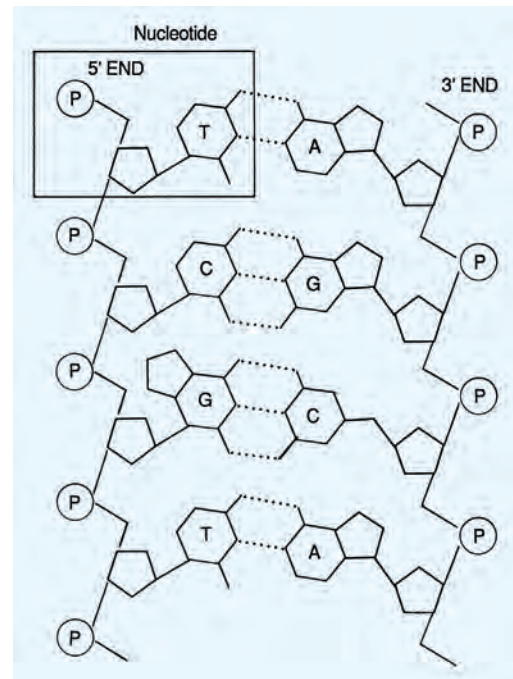
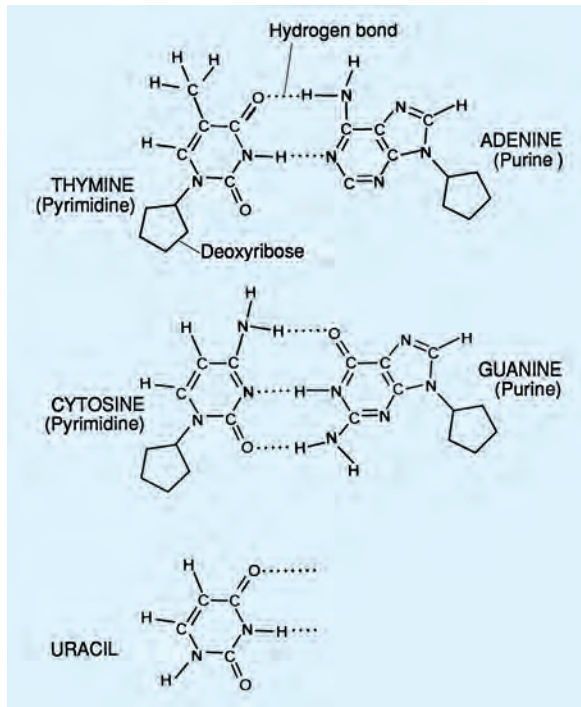


Figure 19-1. The nucleic acid alphabet consists of four bases: the purines adenine (A) and guanine (G) and the pyrimidines thymine (T) and cytosine (C). Uracil (U) is substituted for thymine in the case of RNA. The combination of a base and a sugar (deoxyribose) is referred to as a *nucleoside*.

Figure 19-2. The combination of a sugar phosphate group and a base constitutes a *nucleotide*. The double helix is made from two polynucleotide chains, each of which consists of a series of 5'- to 3'-sugar phosphate links that form a backbone from which the bases protrude. The double helix maintains a constant width because purines always face pyrimidines in complementary A-T and G-C base pairs.

the 3' carbon of another deoxyribose by a phosphate group. Each strand ends with part of the sugar ring exposed based on these connections.

Transcription

Transcription is the first step in converting information encoded in DNA into protein. During the process of transcription, linear DNA sequence is converted to linear RNA (messenger RNA [mRNA]). mRNA is later translated into a linear set of amino acids that form a functional protein (Fig. 19-3). RNA polymerase II is the enzyme that synthesizes mRNA, which is complementary to the DNA template. This primary strand of RNA is called a pre-mRNA and contains both protein coding sequences (exons) and intervening noncoding sequences (introns).

The pre-mRNA molecule undergoes three major modifications: 5' capping, 3' polyadenylation, and RNA splicing. These processes occur in the nucleus before the RNA molecule is translated into protein. RNA splicing is a dynamic process that can result in the formation of different peptide sequences having different functional properties. For example, alternatively spliced versions of the androgen receptor (AR) lacking the androgen binding domain have been identified in prostate cancer cells. Such AR splice variants are active in the absence of bound ligand and may contribute to the emergence of prostate cancer refractory to androgen ablative therapies (Dehm et al, 2008; Guo et al, 2009a; Hu et al, 2009). **Alternative RNA splicing is how a single gene can encode for multiple unique proteins by including or excluding certain exons in the mature mRNA transcript (Sharp, 1987).** The sequences contained within introns are not essential for protein synthesis; introns are spliced out and exons are spliced together to generate the functional mRNA.

Protein Synthesis

Translation of mRNA into protein occurs in the cytoplasm where ribosomes are located. The mRNA message is translated in segments of three adjacent nucleotides called a codon. Each codon is translated into 1 of 20 amino acids (Fig. 19-4). From the four bases

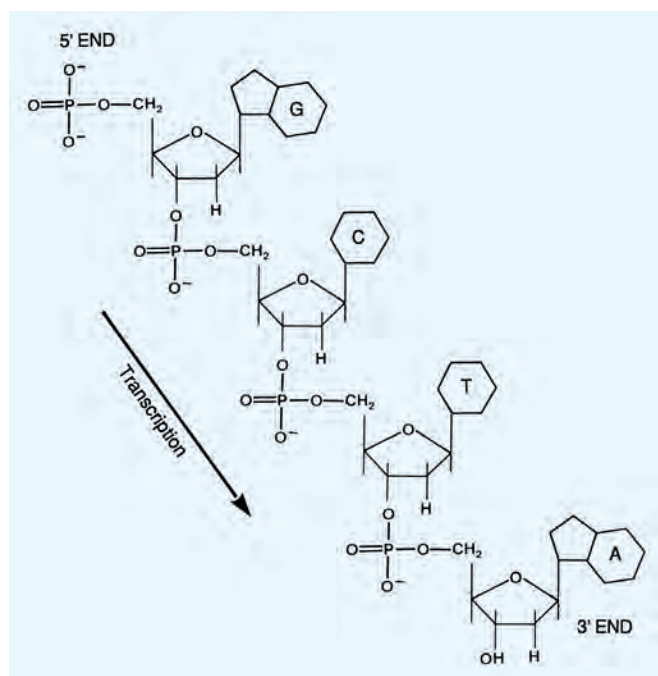


Figure 19-3. During transcription, a section of one DNA strand or the other is used as a template for the synthesis of messenger RNA. This synthesis always occurs in a 5'-to-3' direction.

found in RNA, 64 different codons can be generated. Because of redundancy, more than one codon can encode for a single amino acid (Fig. 19-5). Genetic mutations or alterations can have a profound effect on protein translation of mRNA. For example, a single base insertion or deletion results in a frame-shift mutation and often results in a nonfunctioning protein product. In contrast, a single base substitution may or may not result in a change in the amino acid sequence, which may or may not alter protein function.

Two other forms of RNA are important for protein translation: transfer RNA (tRNA) and ribosomal RNA (rRNA). tRNA is a small (75 to 85 bases long) adapter molecule that is covalently linked to a single amino acid at one end and an anticodon in the middle of the RNA chain. The anticodon comprises three nucleotides that are complementary to the mRNA codon representing a particular amino acid. rRNA comprises approximately 80% of the RNA within a cell and makes up part of the ribosome, which is the macromolecular structure responsible for protein synthesis.

The three major stages of protein synthesis are initiation, elongation, and termination. Initiation is frequently the rate-limiting step in translation (Merrick, 1992). During the process of initiation, the 40S ribosome binds to mRNA and forms an initiation complex that binds a tRNA with an amino acid attached. All new proteins start with methionine because the initiation codon is AUG. During elongation, amino acids are sequentially added to the peptide chain, and the ribosome moves along the mRNA chain similar to beads on a string. Elongation is the most rapid phase of protein synthesis. For any given mRNA transcript, multiple

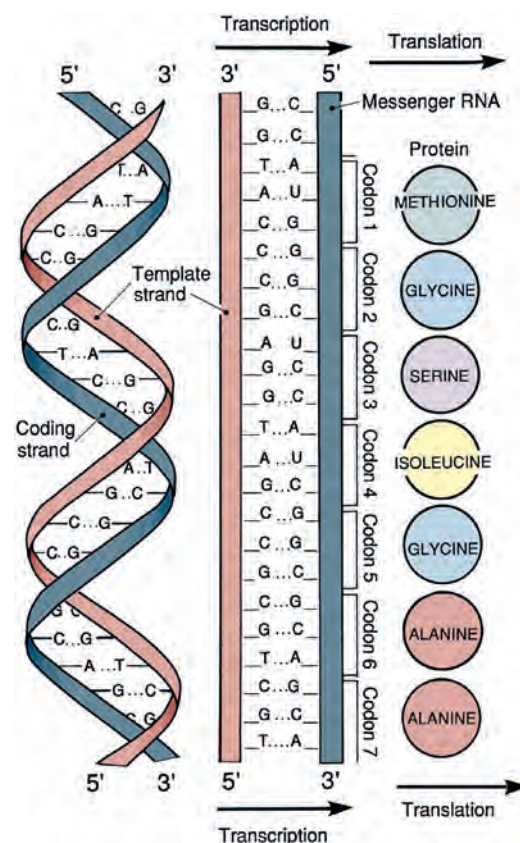


Figure 19-4. During transcription, the coding strand conveys its message through the template strand to make messenger RNA that is eventually translated into polypeptides by ribosomes. The relationship between DNA sequence and corresponding protein is called the **genetic code**, which is read in nucleotide triplets or codons specifying amino acids or protein translational start and stop signals. The code is degenerate, in that multiple codons may code for the same amino acid.

First base	Second base				Third base
	U	C	A	G	
U	Phenylalanine	Serine	Tyrosine	Cysteine	U
	Phenylalanine	Serine	Tyrosine	Cysteine	C
	Leucine	Serine	Stop	Stop	A
	Leucine	Serine	Stop	Tryptophan	G
C	Leucine	Proline	Histidine	Arginine	U
	Leucine	Proline	Histidine	Arginine	C
	Leucine	Proline	Glutamine	Arginine	A
	Leucine	Proline	Glutamine	Arginine	G
A	Isoleucine	Threonine	Asparagine	Serine	U
	Isoleucine	Threonine	Asparagine	Serine	C
	Isoleucine	Threonine	Lysine	Arginine	A
	Methionine	Threonine	Lysine	Arginine	G
G	Valine	Alanine	Aspartic acid	Glycine	U
	Valine	Alanine	Aspartic acid	Glycine	C
	Valine	Alanine	Glutamic acid	Glycine	A
	Valine	Alanine	Glutamic acid	Glycine	G

Figure 19-5. RNA codon table. The 20 amino acids found in proteins are listed. All 64 possible 3-letter combinations of the RNA coding units U, C, A, and G are used to encode an amino acid or one of the three stop codons. Note: The codon AUG codes for methionine and serves as an initiation site (the first AUG in the messenger RNA coding region where translation in protein is initiated).

ribosomes can simultaneously move along the chain to generate new polypeptides (Rich et al, 1963). Termination is the last stage of protein synthesis and is signaled by one of three stop codons (Tate and Brown, 1992).

Chromosomes and Gene Structure

The long strands of DNA responsible for the genetic makeup of eukaryotic cells (the genome) are organized together with

specialized proteins to form chromosomes. Eukaryotic cells contain large linear chromosomes that are packaged by histone proteins into a condensed structure called *chromatin*. The local chromatin structure has a great impact on gene expression and varies depending on the specific cell type. During interphase, chromatin can be classified into two forms. Euchromatin consists of DNA that is actively being expressed as protein, whereas heterochromatin consists of inactive DNA that may serve a structural support role.

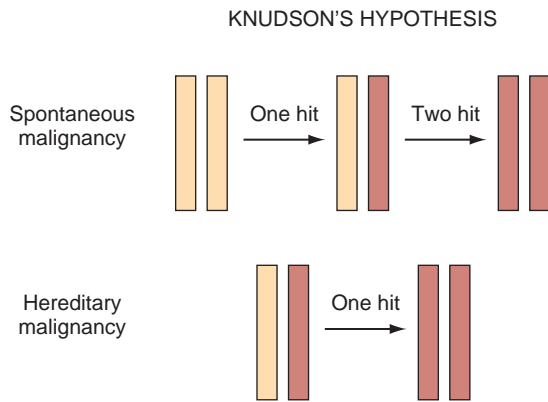


Figure 19-6. Knudson's hypothesis was that inactivation of the same gene was responsible for both sporadic and hereditary malignancies. Patients with sporadic tumors had two normal copies of the gene, and the sporadic tumors required inactivation of both copies of the gene. Patients with hereditary tumor syndromes were born with only one functioning copy of the gene of interest, and the hereditary tumors required inactivation of only one copy.

of the gene. Classic tumor suppressor genes discussed later in this chapter are the retinoblastoma gene (*RB1*) and the *TP53* gene (see [Cell Cycle Deregulation](#)).

The “two-hit” hypothesis was first proposed in cases of retinoblastoma, which required mutations in both alleles for disease manifestation (Knudson, 1971). This requirement is due to the fact that if just one allele is inactivated, the remaining allele could produce sufficient amounts of the correct protein to maintain the normal state (Fig. 19-6). However, specific types of mutations in certain genes may not follow this two-hit rule and can function in a dominant negative capacity when mutated, inhibiting the function of the normal protein from the unaltered allele. An example is when two or more of the same protein molecules act together (e.g., dimerization), as is the case for *TP53* (Baker et al, 1990). Alternatively, deletion or mutation of a single allele may result in insufficient protein production (haploinsufficiency) causing an increased carcinogen susceptibility as in the case of the *CDKN1B* (p27Kip1) gene (Fero et al, 1998).

Oncogenes

Oncogenes are positively associated with cellular proliferation and are the mutated form of normal genes (proto-oncogenes). Two oncogenes that have been found to be overexpressed in various cancers include *MYC* and *MET* (Wong et al, 1986; Bottaro et al, 1991). The proto-oncogene *MYC* encodes an early-response gene product that is a transcription factor responsible for regulating cellular proliferation. Amplification of *MYC* is a frequent event in prostate cancer, and expression of *MYC* in human prostate epithelial cells has been associated with immortalization (Gil et al, 2005).

Hepatocyte growth factor acts through a receptor that is encoded by the proto-oncogene *MET* (Bottaro et al, 1991). Increased expression of *MET* has been reported in renal cell carcinoma (RCC) and is more frequent in higher grade cancers (Pisters et al, 1997). Missense mutations of the *MET* proto-oncogene may also result in constitutive activation of the *MET* protein in tumors associated with hereditary RCC (Schmidt et al, 1997).

Mechanisms by which a proto-oncogene can be converted to an activated oncogene are via (1) mutation of the proto-oncogene resulting in an active form of the gene product, (2) gene amplification, and (3) chromosomal rearrangement. A mutation occurring within the protein coding sequence of a gene can lead to a continuous proliferation signal from the mutant protein. For example, mutation of the proto-oncogene *ERBB*, which encodes

for the epidermal growth factor receptor (EGFR), results in expression of a receptor that is constitutively active (Downward et al, 1984). Errors that occur during chromosomal replication may result in gene amplification and aneuploidy. Such an increase in gene copy number often results in an increased number of mRNA transcripts and overproduction of the corresponding protein. For example, certain types of bladder cancer overexpress *MYC* by this mechanism (Christoph et al, 1999). Immunohistochemical (IHC) staining of bladder cancer specimens has demonstrated overexpression of *MYC* protein in more than half of papillary and invasive tumors (Schmitz-Drager et al, 1997). Finally, chromosomal structural rearrangements such as translocation events can result in the formation of an oncogene; for example, genetic rearrangement leads to the fusion of a portion of the *TMPRSS2* gene and the *ERG* oncogene in a large proportion of prostate cancers (Tomlins et al, 2005).

KEY POINTS: TUMOR SUPPRESSOR GENES AND ONCOGENES

- Mutations in DNA can lead to changes in protein function or expression that increase the potential for cancer initiation, progression, or metastasis.
- Tumor suppressor genes normally negatively regulate and control cellular growth. Oncogenes normally promote cell growth.
- Loss of tumor suppressor gene function can occur primarily by (1) homozygous deletion, (2) loss of one allele and mutational inactivation of the second allele, (3) mutational events involving both alleles, and (4) loss of one allele and epigenetic inactivation of the second allele.
- Certain tumor suppressor genes do not follow the “two-hit” hypothesis and may be inactivated via dominant negative mutations or haploinsufficiency.
- Proto-oncogenes can be converted to oncogenes by (1) mutation of the proto-oncogene resulting in an activated form of the gene, (2) gene amplification, and (3) chromosomal rearrangement.

CELL CYCLE DEREGLATION

Apart from development and growth, cell division is tightly regulated such that the production of new cells precisely balances loss of cells during normal wear and tear, maintaining tissue and organ homeostasis. In contrast to single-celled eukaryotes, individual human cells are not allowed to make autonomous decisions regarding their proliferation. Rather, a complex series of external growth inhibitory and growth stimulatory signals are integrated by the cell, resulting in either cell division or quiescence. In cancer, activated oncogenes and inactivated tumor suppressor genes alter the balance between these signals such that net proliferation is continuously favored.

Quiescent cells are considered to be out of cycle, in a reversible state known as “*G*₀” that is the default state for most cells. When signaled to proliferate, cells activate their cell cycle machinery, initiating an orderly, unidirectional series of events resulting in duplication of the cell's genome during the DNA synthetic phase (S phase), followed by segregation of each genomic complement to each of two resulting daughter cells, a process referred to as mitosis (M phase). These two critical phases are separated by two so-called “gap” phases (*G*₁ and *G*₂). Throughout the cell cycle, which takes approximately 24 hours to complete, each step depends on completion of the prior step before progressing further (Hartwell et al, 1974). In addition, checkpoint mechanisms closely monitor DNA integrity and certain critical cell cycle events. If problems are detected (e.g., DNA damage), the cell cycle is paused to allow for repair (Hartwell and Weinert, 1989). If repair is impossible,

normal cells often commit cellular suicide through an active process termed *apoptosis*. Many oncogenes and tumor suppressors exert their effects by interfering with cell cycle checkpoints and apoptotic pathways, allowing cancer cells to divide continuously and accumulate. Loss of ability to respond appropriately to damaged DNA is particularly dangerous because it fosters genetic instability, a key attribute of cancer cells. Loss of DNA damage checkpoint controls results in an increased mutation rate, accelerating the mutation of cancer-associated genes and contributing to carcinogenesis and disease progression (Bartek et al, 1999).

Additional details of the eukaryotic cell cycle (cyclin-dependent kinases and cyclins, cell cycle entry, the retinoblastoma protein and the restriction point, S phase, mitosis, and cell cycle checkpoints) can be found on the Expert Consult website.

Retinoblastoma Protein and Genitourinary Malignancies

The retinoblastoma susceptibility protein, RB1 (formerly pRb), plays a central role in controlling the R-point—a decision point in late G₁, beyond which an irreversible commitment to divide is made. The inappropriate, continuous proliferation of cancer cells is largely due to a loss of R-point control, typically the result of functional inactivation of the RB1 pathway (Pardee, 1989). RB1 gene mutations have been identified in approximately one third of bladder tumors (Horowitz et al, 1990), and reintroduction of the RB1 gene into bladder carcinoma cell lines has been found to inhibit cell growth in vitro and tumor formation in vivo (Takahashi et al, 1991). Altered expression of RB1 protein also has been identified in approximately one third of bladder carcinomas (Logothetis et al, 1992), and altered expression has been correlated with higher stage disease and decreased patient survival (Cordon-Cardo et al, 1992).

Prostate carcinoma has not been as strongly linked to RB1. Although RB1 mutations are present in 10% to 30% of prostate cancer specimens (Bookstein et al, 1990; Kubota et al, 1995), decreased expression is not consistently identified with high-risk patients or recurrent disease (Kibel and Isaacs, 2000). In other studies, no correlation was found between expression and grade or stage (Ittmann and Wiczorek, 1996), but Theodorescu and colleagues (1997) reported that low RB1 protein expression correlated with decreased disease-specific survival in univariate and multivariate analysis.

Renal carcinoma has not been clearly linked to RB1. RB1 is rarely inactivated in renal carcinoma cell lines or tumors (Ishikawa et al, 1991). Analysis of clinical specimens has not demonstrated a clear association between prognosis and RB1 expression (Lipponen et al, 1995).

Cyclin-Dependent Kinase Inhibitors

The temporal sequencing of events occurring throughout the cell cycle is affected by cyclin-dependent kinases (cdks), a highly conserved set of protein kinases (Meyerson et al, 1992). The cdks phosphorylate specific protein substrates involved in executing the phase-specific activities of the cell cycle. The enzymatic activities of the cdks depend on cyclins, so named because their abundances are tightly linked to specific phases of the cell cycle, during which they physically associate with and activate the enzymatic activity of the cdks (Fig. 19-7) (De Bondt et al, 1993; Jeffrey et al, 1995). Another group of proteins termed *cyclin-dependent kinase inhibitors* (CDKIs) bind to and directly inhibit cdk activity or their activating phosphorylations (Peter and Herskowitz, 1994; Sherr and Roberts, 1995). Although cyclins play major regulatory roles in orchestrating cdk activities, cdks are subject to additional levels of control, and these processes are commonly altered in cancer cells. CDKIs belong to either of two different classes, the Cip/Kip family, which includes the proteins CDKN1A (p21), CDKN1B (p27), and CDKN1C (p57), and the INK4 (*inhibit cdk4*) family, which includes INK4B (p15), INK4A (p16), INK4C (p18), and INK4D (p19). The Cip/Kip proteins have broad actions, able to inhibit multiple cyclin-cdk complexes throughout the cell cycle (Clurman and Porter,

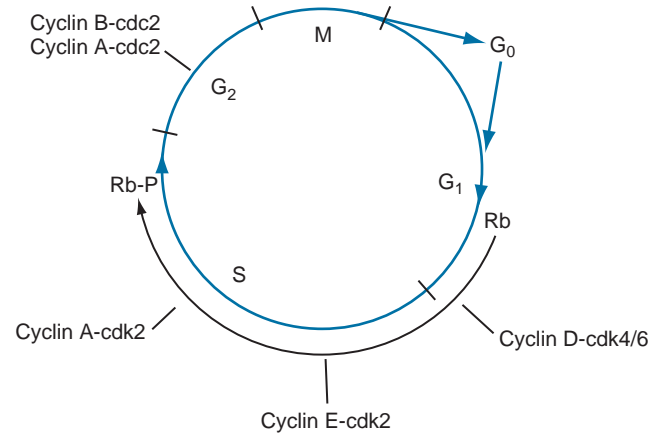


Figure 19-7. Schematic drawing of the cell cycle. Sequential activation of cyclin-cdk complexes is critical to the orderly progression of replication of the cell.

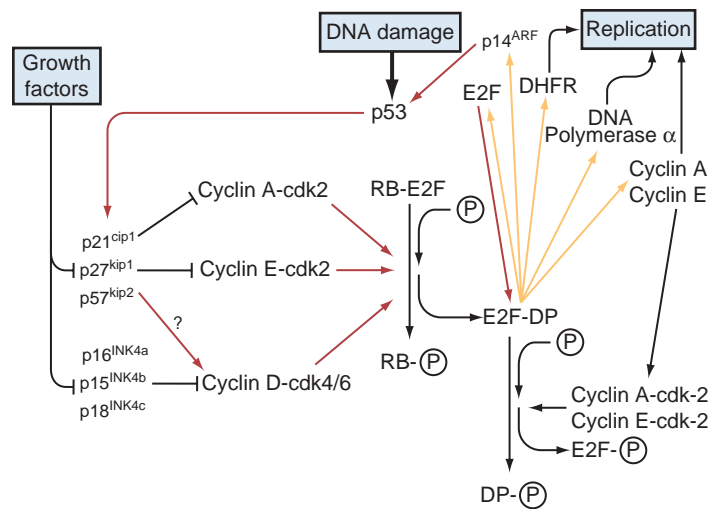


Figure 19-8. Schematic representation of the stimulatory and inhibitory cascade at the G₁/S boundary. This finely tuned system takes advantage of multiple negative and positive feedback loops.

1998). The INK4 proteins are more restricted in their activities, inhibiting cdk4-containing and cdk6-containing complexes; they are critical regulators of the R-point and the G₁/S transition because they can block RB1 phosphorylation (Fig. 19-8). The cell uses increased expression and accumulation of CDKIs as a means of halting the cell cycle in response to various stresses. For example, p21 expression is increased in response to DNA damage (el-Deiry et al, 1993). CDKIs function in nonstress situations as well. For example, p27 levels are high in quiescent cells, and all of the Cip/Kip proteins appear to play some role in maintenance of the G₀ state in terminally differentiated cells (Halevy et al, 1995; Matsuo et al, 1995; Parker et al, 1995).

Among the INK4 family, inactivating mutations and abnormal gene promoter methylation of p15 and p16 have been strongly implicated in cancer in general (Kamb et al, 1994; Hiram and Koeffler, 1995) and specifically in GU malignancies (Cairns et al, 1995; Herman et al, 1995). The best studied of the INK4 proteins is p16. The p16 protein binds to cdks 4 and 6 and inhibits their interaction with cyclin D1 that normally mediates passage through the G₁ phase of the cell cycle by phosphorylation of the RB1 protein (Serrano et al, 1993). The INK4A gene encoding p16 was initially found to be mutated and deleted in a wide variety of tumors

Cyclin-Dependent Kinases and Cyclins

The temporal sequencing of events occurring throughout the cell cycle are affected by a highly conserved set of serine-specific and threonine-specific protein kinases termed cyclin-dependent kinases (cdks) (Meyerson et al, 1992). The cdks phosphorylate specific protein substrates involved in executing the phase-specific activities of the cell cycle. As their name implies, the enzymatic activities of the cdks depend on a class of regulatory proteins called *cyclins*, of which there are 12 known in mammals (Morgan, 1995). The abundance of specific cyclins within the cell is highly dynamic and tightly linked to specific phases of the cell cycle, during which they physically associate with and activate the enzymatic activity of the cdks (see Fig. 19-7) (De Bondt et al, 1993; Jeffrey et al, 1995). Depending largely on the transitory presence of particular cyclins, which are rate-limiting, specific cyclin/cdk complexes form and act during restricted periods within the cell cycle to initiate and regulate the events required during these precise phases, after which each cyclin is typically degraded via polyubiquitination of specific lysine residues that serve as the signal for proteosomal degradation, inactivating its cdk partner (Sherr, 1993; van den Heuvel and Harlow, 1993). The cdks are also regulated by specific sites of phosphorylation on the cdks themselves (Lundgren et al, 1991). Finally, a group of proteins termed *cyclin-dependent kinase inhibitors* (CKIs) can bind to and inhibit cdk activity directly or their activating phosphorylations (Peter and Herskowitz, 1994; Sherr and Roberts, 1995). Although cyclins play major regulatory roles in orchestrating cdk activities, cdks are subject to additional levels of control, and these processes are commonly altered in cancer cells as well.

Cell Cycle Entry

Under normal conditions, a cell is induced to proliferate when the balance between growth-stimulatory signals received from its environment (e.g., soluble growth factors in the extracellular space) outweighs growth inhibitory signals (e.g., transforming growth factor- β). If a cell in the G_0 state is stimulated to proliferate, it will proceed into G_1 , the first gap phase of the active cell cycle, during which sufficient macromolecules and organelles are synthesized to support cell replication. Growth stimulatory signaling pathways (e.g., the Ras/Raf/MEK pathway) promote expression of the main G_1 cyclins, cyclin D and cyclin E, leading to their association with cdk4 and cdk6 kinases, activating these cdks (Baldin et al, 1993; Winston and Pledger, 1993; Sherr et al, 1994). Throughout early and mid G_1 , progression through the cell cycle remains sensitive to external signals, largely because persistent mitogenic stimulation is required for sustained expression of cyclin D (Matsushime et al, 1991).

Retinoblastoma Protein and Restriction Point

Because of the dependence of cyclin D on the continued presence of mitogens and other favorable conditions (e.g., attachment to the substratum), the cell cycle remains responsive to external signals throughout early and mid G_1 (Guadagno et al, 1993). However, if the decision is made in late G_1 to continue on with cell division, the subsequent phases of the cell cycle (S, G_2 , and M) proceed in an autonomous fashion. This key point in time in late G_1 , after which the cell cycle becomes insensitive to extracellular signals, is termed the *restriction point* (R-point) and is highly regulated (Pardee, 1974).

The retinoblastoma susceptibility protein, RB1 (pRb), plays a central role in controlling the R-point, and the inappropriate, continuous proliferation of cancer cells is largely due to a loss of R-point control, typically the result of functional inactivation of the Rb pathway (Pardee, 1989). RB1 is a substrate of G_1 cyclin/cdk complexes, and its activity is critically dependent on its phosphorylation state (Buchkovich et al, 1989; Mittnacht et al, 1994; Sherr, 1994). In nondividing cells, RB1 is unphosphorylated, and in this state RB1 physically associates with members of the E2F

family of transcription factors, inhibiting their transcriptional activation of target genes required for cell cycle progression into S phase (Lai et al, 1999b). In addition, RB1 recruits proteins such as histone deacetylases to E2F target genes promoting the formation of repressive heterochromatin at these sites, and RB1 itself may play a role in maintaining this repressive chromatin state, further suppressing E2F target genes (Lai et al, 1999a; Gonzalo and Blasco, 2005). However, during G_1 , RB1 becomes progressively phosphorylated on eight different sites by cyclin D-cdk4/6 and cyclin E-cdk2 complexes, creating hyperphosphorylated RB1, causing its dissociation from E2F (see Fig. 19-8). The liberated E2F proteins, of which there are at least seven, heterodimerize with one of three DP subunits (DP1-3) and activate transcription of target genes, including essential S phase genes (e.g., DNA polymerase and S phase cyclins) (Dyson, 1998). When the cell cycle is complete, RB1 returns to its unphosphorylated state, once more suppressing E2F until cell division is signaled again (Ludlow et al, 1993).

There are many ways, both direct and indirect, in which cancer cells inactivate function of RB1, including mutation or deletion of the RB1 gene itself; silencing of the RB1 gene via promoter DNA hypermethylation; overexpression of proteins such as cyclin D and E2F (in some cases as a result of increased copy number of the gene, or gene amplification), and mutational inactivation, deletion, or promoter methylation of genes encoding specific cdk inhibitors. It has been suggested that RB1 or components of the regulatory pathway with which it is associated (e.g., cyclins D and E, cdk4, E2F, p16 and p27) are likely to be altered in virtually all human cancers (Sherr, 1996; Hanahan and Weinberg, 2000).

Cell Cycle Progression through S Phase

During S phase, a normal cell replicates its diploid genome only once. S phase genes are activated as a result of cyclin A replacing cyclin E to form cyclin A-cdk2 complexes in early S phase and later by cyclin A associating with cdk1 forming cyclin A-cdk1 complexes in late S phase (Girard et al, 1991; Pagano et al, 1992). On completion of S phase, cyclin A-cdk2 phosphorylates E2F-DP heterodimers, terminating activity of E2F (Dylnacht et al, 1994). At the end of S phase, cyclin B replaces cyclin A, forming cyclin B-cdk1 complexes, which move the cell into the second gap phase of the cell cycle, G_2 , and on into mitosis (Pines and Hunter, 1989).

Mitosis

During mitosis, the two genomic complements present after S phase are precisely partitioned into what will become two separate daughter cells. The proper functioning of many of the proteins participating in mitosis depends on phosphorylation of these substrates by cyclin B-cdk1. Early in mitosis, the chromosomes condense through the activity of condensin proteins. Each chromosome is tightly associated along its length with its corresponding S phase copy, termed the *sister chromatid*, via cohesin proteins. Also during this time, two structures called centrosomes, which act as microtubule organizers, migrate to opposite poles of the nucleus and assemble spindle microtubules that radiate through the nucleus and attach to the condensed chromosomes at constriction sites termed *centromeres* via complex protein matrices termed *kinetochores*. The nuclear envelope and supporting intermediate filament proteins, the nuclear lamins, dissociate in response to phosphorylation by cyclin B-cdk1. Balanced tension along the spindle microtubules causes all of the chromosomes to align along the cell midline, creating a hallmark stage of mitosis termed *metaphase*. When all metaphase chromosomes are properly aligned, microtubule-associated motors on the spindle microtubules pull each diploid chromosome complement apart toward the centrosomes at opposite poles, a key mitotic event termed *anaphase*. Lastly, two new nuclei are assembled around the two separated chromosome complements, which decondense, and two separate daughter cells are formed in a cell-splitting process termed *cytokinesis*.

Mitotic abnormalities are commonly seen in human cancers and were noted by Hanseman in the late 1800s, soon after the

discovery of chromosomes. In 1914, the eminent German biologist Boveri proposed that such abnormalities might underlie tumor formation (Harris, 2008).

G₁/S Checkpoint

The expression of cyclin D during G₁ depends on the integration of both proliferative and antiproliferative signals received from the extracellular environment (e.g., mitogens, nutrient and oxygen availability). The cell does not fully commit to division unless it receives a sustained signal to do so and conditions remain favorable (Matsushime et al, 1991).

A critical contributor to the G₁/S checkpoint is the TP53 tumor suppressor protein. TP53 is a pleiotropic transcription factor that receives signals from multiple types of cell stress and damage and, in response, activates genes that function variously in cell cycle arrest, DNA damage repair, and apoptosis (programmed cell death), highlighting the link between cell cycle arrest and DNA repair (see Fig. 19-9) (Elledge, 1996). DNA damage has relevance for the G₁/S checkpoint because a normal cell would not wish to proceed to S phase if the genomic template DNA is damaged; intact checkpoint controls represent important antitumor mechanisms acting to limit the proliferation of cells bearing potentially oncogenic mutations. During the cellular response to DNA damage, specific kinases are activated that phosphorylate the TP53 protein protecting it from hdm2 ubiquitin ligase-mediated degradation (Momand et al, 1992). The accumulated TP53 protein undergoes further modifications that serve to activate it and facilitate its translocation to the nucleus, where it induces various checkpoint and DNA repair proteins, including CDKN1A (p21) and 14-3-3-sigma, which cause cell cycle arrest by inactivating or sequestering G₁ cdk complexes (Giaccia and Kastan, 1998). If the cell cannot arrest growth or repair the DNA damage, TP53 often induces apoptosis (Levine, 1997).

S Phase Arrest

Although S phase is not considered to have a checkpoint per se, such as the checkpoints recognized during G₁/S and G₂/M phases, the cell does maintain the ability to arrest the cell cycle and repair DNA damage through two mechanisms, both mediated through the ataxia-telangiectasia-mutated (ATM) kinase. First, in response to genotoxic insults, Cdc25A is targeted for destruction through an ATM-dependent cascade, resulting in a rapid decrease in Cdc25A levels. Because Cdc25 family members normally activate cdk2, the loss of Cdc25A maintains cdk2 in its inactive form. This cascade pauses the cell in S phase, ostensibly to allow time for DNA repair (Bartek et al, 2004).

The second mechanism mediated by ATM in response to DNA damage is phosphorylation of DNA repair enzymes (see DNA Repair Mechanisms). These two parallel pathways further highlight the interaction between DNA repair and checkpoint control. S phase control in response to DNA-damaging agents is the last opportunity to repair DNA damage before replication (Falck et al, 2002; Pichierri and Rosselli, 2004).

G₂/M Checkpoint

The G₂/M checkpoint is a second major point of control during cell division. In contrast to the G₁/S checkpoint, which responds to various extracellular signals in addition to DNA damage, the G₂/M checkpoint appears to be similar to S phase arrest and responds only to DNA damage. It serves as an important monitor of DNA replication errors (Weinert, 1997; Bartek et al, 1999).

DNA damage secondary to radiation is believed to induce G₂/M arrest through ATM. ATM activates CHEK1 and CHEK2 kinases in response to DNA damage, and these inactivate the Cdc25 family proteins through phosphorylation, which causes 14-3-3 sigma to bind and sequester it (Hermeking et al, 1997; Sanchez et al, 1997).

It has become apparent that, at least in part, G₂/M arrest may also be mediated by TP53 and the BRCA1 tumor suppressor (Bunz et al, 1998; Xu et al, 2001). Transcriptional upregulation of cell cycle inhibitors (e.g., p21, GADD45, 14-3-3 sigma) by TP53 helps maintain the cell in G₂/M arrest (Nyberg et al, 2002). As a result, TP53 appears to mediate both G₁/S and G₂/M arrest, consistent with its critical role in preserving genomic integrity.

Mitotic Arrest—Spindle Assembly Checkpoint

As detailed earlier, one of the key events in mitosis is the proper attachment of every chromosome to the spindle microtubule apparatus. It is critical that all chromosomes are attached before proceeding into anaphase, where the chromosome complements are pulled apart. Failure of one or more chromosomes to attach leads to chromosome nondisjunction, wherein one daughter cell receives an extra copy of the chromosome, becoming trisomic for that chromosome, while the other daughter cell receives one copy too few, becoming monosomic. Both cases are abnormal and fall under the category of aneuploidy, a nearly universal characteristic of human solid tumors. Gene expression patterns often correlate with gene copy number, and it has been proposed that aneuploidy may be a major contributor to cancer initiation and progression (Duesberg et al, 1999; Duesberg, 2005). The mitotic checkpoint (spindle assembly checkpoint) apparatus monitors chromosome attachment and receives a “not ready” signal from any unattached chromosomes, preventing activation of the anaphase-promoting complex, blocking the transition from metaphase to anaphase until all chromosomes are attached (Chan et al, 1999; Holland and Cleveland, 2009). Although mutations have been identified in specific mitotic checkpoint genes, such as *hBUBR1*, in some cancers (Cahill et al, 1998), subsequent studies have shown these to be relatively rare (Wang et al, 2008b). Additional studies have found aberrant expression levels of mitotic checkpoint proteins, which may better explain the mitotic instability frequently observed in cancer cells (Yuan et al, 2006), including reports of reduced levels of the checkpoint proteins MAD1 and MAD2 in RCC (Pinto et al, 2007) and reduced MAD2 in testicular cancer (Fung et al, 2007).

including bladder and kidney (Kamb et al, 1994). Subsequent analysis demonstrated that inactivation often occurs by DNA hypermethylation at the *INK4A* promoter—an alternative, epigenetic method of gene inactivation (Merlo et al, 1995).

The *INK4A* gene is frequently inactivated by deletion in bladder carcinomas (Cairns et al, 1995; Williamson et al, 1995). Despite its proximity, the *INK4B* gene was ruled out as the primary tumor suppressor at this site because it was not within the deletion interval. A study by Orlow and colleagues (1999) found that deletion and methylation of the gene encoding p16 occurred frequently in superficial bladder carcinoma, but only deletions that affect genes encoding both p16 and p14, which are located at the same locus, correlated with a decrease in disease-free survival. In contrast to bladder cancer, mutational inactivation of *INK4* family members appears to be rare in prostate carcinoma. However, inactivation of *INK4A* by promoter hypermethylation has been implicated in prostate cancer. Herman and associates (1995, 1996) demonstrated *INK4A* hypermethylation in 60% of prostate cancer cell lines, whereas *INK4B* was rarely inactivated. However, these results are tempered by the fact that silencing of the *INK4A* gene by promoter hypermethylation often occurs during the establishment of cell lines in vitro.

Despite the critical role that Cip/Kip family members play in G₁/S cell cycle arrest, they are rarely mutated in a wide variety of malignancies, including GU tumors, and there are only rare reports of promoter hypermethylation (Shiohara et al, 1994; Kawamata et al, 1995). However, expression of this family of CDKIs plays an important role in cancer in general (Catzavelos et al, 1997; Loda et al, 1997; Yatabe et al, 1998) and in GU carcinomas in particular. Stein and associates (1998) found increased expression of *CDKN1A* (p21) in 64% of bladder tumors and found that increased expression was associated with a decreased probability of tumor recurrence and improved patient survival. Decreased *CDKN1B* (p27) expression has also been linked to increasing tumor grade, pathologic stage, and poor survival in bladder carcinoma (Del Pizzo et al, 1999).

The expression of *CDKN1A* in prostate cancer has not shown a clear correlation with advanced disease or poor outcome (Kibel and Isaacs, 2000). However, specific genetic polymorphisms in *CDKN1A* and *CDKN1B* have been associated with advanced disease (Kibel et al, 2003), and altered expression of *CDKN1B* has been implicated in aggressive disease in multiple studies. Cordon-Cardo and colleagues (1998) examined radical prostatectomy specimens and found that absent or low *CDKN1B* production by immunohistochemistry was an independent risk factor for decreased disease-free survival by multivariate analysis. Cote and coworkers (1998) found that decreased *CDKN1B* nuclear staining correlated not only with decreased disease-free survival but also overall survival in patients undergoing radical prostatectomy, whereas Freedland and colleagues (2003) found that patients with *CDKN1B*-positive cells in the prostate needle biopsy specimen had a 2.5-fold increased risk of biochemical recurrence (prostate-specific antigen [PSA] relapse).

The relevance of *CDKN1B* to prostate cancer is also supported by studies of mouse models. For example, mice deficient in *CDKN1B* develop prostate hyperplasia, confirming the potential importance of this gene in prostate tissue homeostasis (Cordon-Cardo et al, 1998). Other studies have shown that mice deficient in both *CDKN1B* and *PTEN* have a high incidence of prostate cancer (Di Cristofano et al, 2001).

TP53 Tumor Suppressor

The TP53 tumor suppressor protein is a key player in cell cycle checkpoints, responding to DNA damage by signaling cell cycle arrest and repair of the damage (Fig. 19-9). If the DNA damage cannot be repaired, TP53 may trigger cell death (apoptosis). TP53 is the most commonly mutated gene in cancer and plays a prominent role in GU malignancies. Alterations to TP53 in regard to GU cancers are discussed in detail in the following sections.

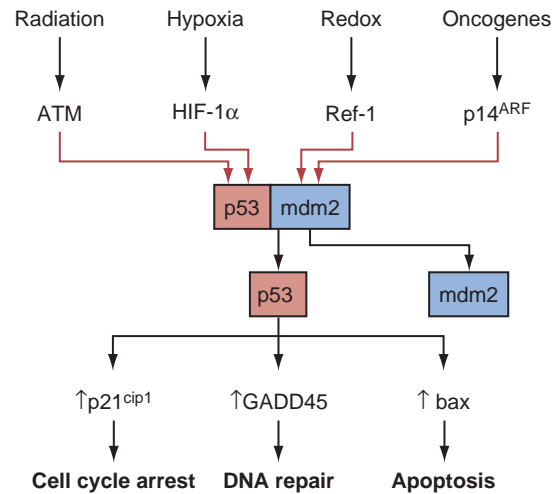


Figure 19-9. TP53 plays a central role in the cell's response to extra-cellular stimuli. Radiation, hypoxia, redox reactions, and oncogenes all can increase TP53 activity through different mechanisms. In response, the cell initially stops dividing and then attempts to repair the DNA damage. If it fails to repair the DNA, it undergoes apoptosis (programmed cell death). These functions are mediated through transcriptional activation of various genes, some examples of which are indicated in the figure.

KEY POINTS: CELL CYCLE Deregulation

- The cell cycle consists of an ordered, unidirectional series of events, the main goal of which is to replicate the cell's genome and partition one copy into each of two resulting daughter cells.
- The cell cycle is divided into four phases; G₁, S, G₂, and M. The transition from G₁ into S phase is critically dependent on phosphorylation of the RB1 tumor suppressor protein. Mutations in *RB1* are common in urologic malignancies.
- Phase-specific phosphorylation of substrate proteins by cdks orchestrates progression through the cycle.
- The activities of cdks depend on their association with specific cyclin proteins. Cyclins accumulate and are rapidly degraded in a phase-specific manner, ensuring the proper sequencing and irreversibility of key events throughout the cell cycle.
- Primary points of cell cycle control are the G₁/S and G₂/M checkpoints. Checkpoints employ CDKIs to pause the cell cycle in response to various signals, including DNA damage, cell-cell contact, cytokine release, and hypoxia.
- The TP53 tumor suppressor protein is a key player in cell cycle checkpoints, responding to DNA damage by signaling cell cycle arrest and repair of the DNA damage. If the DNA damage cannot be repaired, TP53 may trigger cell death (apoptosis).
- TP53 is the most commonly mutated gene in cancer and plays a prominent role in GU malignancies.
- Defects in cell cycle checkpoints lead to unregulated cell proliferation and genetic instability.

DNA METHYLATION

The covalent modification of the C-5 position of cytosine by a methyl group is mediated by DNA methyltransferase, resulting in the formation of 5-methylcytosine, an epigenetic modification of DNA that occurs in vertebrates and is essential for normal embryonic development (Jones, 1986; Bird, 1992). Methylation of cytosine occurs primarily at the CpG palindrome in DNA. The presence of 5-methylcytosine at CpG dinucleotides has resulted in a significant depletion of this sequence from the genome during the course

of vertebrate evolution (Schorderet and Gartler, 1992). This reduction in frequency of CpG dinucleotides in the genome is the result of spontaneous deamination of 5-methylcytosine to thymine (Rideout et al, 1990; Sved and Bird, 1990). Certain areas of the genome do not show a depletion of the CpG dinucleotides and contain the expected frequency of this sequence. These regions are referred to as CpG islands; although CpG islands constitute approximately 1% of vertebrate genomes, they account for approximately 15% of the total number of CpG dinucleotides in DNA (Bird, 1986; Gardiner-Garden and Frommer, 1987). CpG islands are typically located upstream of many ubiquitous housekeeping and tissue-specific genes. CpG island methylation affects the levels of gene transcription (Cedar, 1988). Hypermethylation of CpG islands usually results in transcriptional downregulation, whereas hypomethylation of these regions may increase gene expression.

CpG islands located in the promoter regions of tumor suppressor genes are normally unmethylated. Abnormal methylation of these regions may result in a progressive reduction in gene expression, altering normal cellular growth control in favor of proliferation. Methylation of CpG islands may lead to decreased gene expression by mechanisms including changes in local chromatin structure, inhibition of transcription factor binding, or exclusion of transcriptional machinery from methylated promoter DNA (Bird and Wolffe, 1999). The epigenetic properties of methylation may affect gene activity without altering the DNA sequence and represent an alternative means of gene inactivation apart from gene mutation or deletion.

Changes in global levels and regional patterns of DNA methylation are among the earliest and most frequent events known to occur in human cancer (Jones and Baylin, 2002). Alterations in DNA methylation have a direct impact on mutational and epigenetic components that may contribute to neoplastic transformation. Three major pathways by which DNA methylation may result in genetic dysregulation in human cancer include (1) inherent mutational effects of 5-methylcytosine, (2) epigenetic effects of promoter methylation on gene transcription, and (3) potential gene activation and induction of chromosomal instability by DNA hypomethylation (Gonzalzo and Jones, 1997; Jones and Gonzalzo, 1997).

DNA Methylation and Prostate Cancer

Glutathione-S-transferases belong to a superfamily of enzymes responsible for detoxification of a wide range of xenobiotics. These enzymes catalyze the nucleophilic attack of reduced glutathione on potentially damaging electrophilic compounds. **Aberrant methylation of the CpG island at the glutathione-S-transferase pi (*GSTP1*) locus is the most frequent somatic genome alteration reported in prostate cancer** (Lee et al, 1994; Jerónimo et al, 2001). Methylation of *GSTP1* has been detected in greater than 90% of prostate carcinomas and approximately 70% of prostatic intraepithelial neoplasia (PIN) lesions, but it is not present in normal prostate tissue or benign prostatic hyperplasia (Lee et al, 1994). In normal prostate tissue, expression of *GSTP1* is limited to basal cells, but it can be upregulated in columnar epithelial cells exposed to oxidative stress. Increased levels of DNA methylation have also been associated with worse clinical outcomes in patients with prostate cancer (Maruyama et al, 2002).

The ras association domain family protein 1 isoform A (*RASSF1A*) gene is located on chromosome 3p21. *RASSF1A* is a tumor suppressor gene that is frequently altered in various human cancers. Abnormal methylation of *RASSF1A* has been reported to occur in 60% to 70% of prostate carcinomas (Kuzmin et al, 2002). Loss of heterozygosity (LOH) of the 3p21 region is associated with methylation and silencing of the remaining *RASSF1A* allele during tumorigenesis. Methylation *RASSF1A* has been observed more frequently in higher grade prostate cancers compared with less aggressive tumors (Liu et al, 2002).

Genome-wide methylation analyses were conducted in prostate cancer more recently, and the results indicated that there are widespread changes in methylation patterns (both hypermethylation

and hypomethylation) that occur in both gene-associated and conserved intergenic regions. Although interindividual heterogeneity in DNA methylation patterns was observed among patients with prostate cancer, in individuals with metastatic prostate cancer, DNA methylation alterations were highly conserved across all of their metastases, suggesting that DNA methylation alterations undergo clonal selection (Yegnasubramanian et al, 2011; Aryee et al, 2013).

Role of DNA Methylation in Bladder Cancer

Mutations of the *TP53* gene are present in more than half of all human malignancies. Many of the mutational hot spots found in the *TP53* gene occur at CpG dinucleotides that are normally methylated, implicating 5-methylcytosine as an endogenous mutagen in the genome (Rideout et al, 1990; Greenblatt et al, 1994; Tornaletti and Pfeifer, 1995). Mutational inactivation of *TP53* is a frequent event in urothelial dysplasia, carcinoma in situ (CIS), and invasive bladder cancer (Spruck et al, 1994).

The contribution of DNA methylation to these mutational events varies depending on the type of bladder cancer and the etiologic agent believed to be responsible for tumor formation (Jones et al, 1998). Urothelial carcinomas in Western countries and Japan have relatively few mutations at CpG sites, suggesting that DNA methylation may not play a major role in inducing these changes. In contrast, a higher frequency of mutations at CpG dinucleotides consistent with 5-methylcytosine deamination is observed in patients with squamous cell carcinoma and urothelial carcinoma with a history of exposure to phenacetin or arsenic (Jones et al, 1998). These observations highlight the potential mutagenic effects of DNA methylation on the genome and the contribution of methylation to *TP53* inactivation during bladder carcinogenesis.

INK4A (p16) Methylation in Bladder Cancer

Inactivation of the *INK4A* gene may occur by various mechanisms, including deletion, mutation, and promoter methylation (Spruck et al, 1994; Gonzalez-Zulueta et al, 1995; Herman et al, 1995). Mutation or deletion of one *INK4A* allele and concurrent methylation of the remaining allele results in complete loss of functional activity. Methylation of *INK4A* has been reported in 27% to 60% of primary urothelial carcinomas (Chan et al, 2002; Chang et al, 2003). Such epigenetic changes are among the earliest molecular events associated with transformation and may precede morphologic alterations in cellular architecture.

The first detailed study investigating the effects of *INK4A* promoter methylation on transcriptional activity was performed in bladder cancer cells, where a reduction in *INK4A* expression was associated with higher levels of methylation in the upstream promoter region. Methylation of specific CpG sites in the *INK4A* promoter was shown to result in significant downregulation of transcriptional activity of the gene (Gonzalzo et al, 1998). Administration of the demethylating agent 5-aza-2'-deoxycytidine (5-Aza-CdR) was capable of reactivating *INK4A* expression in bladder cancer cells that were previously shown to contain methylated alleles of the gene. Methylation in exon 2 of the *INK4A* gene is also a frequent occurrence in various cancers and is an excellent marker for transformation, although the presence of methylation in this region of the *INK4A* gene does not affect *INK4A* transcription in bladder cancer cells (Gonzalzo et al, 1998).

Hypermethylation of Other Genes in Bladder Cancer

The E-cadherin (*CDH1*) gene encodes a transmembrane glycoprotein that modulates calcium-dependent intercellular adhesion in epithelial tissues. Methylation of the CpG island located in the *CDH1* promoter is associated with decreased gene expression in high-grade urothelial carcinoma, including disease associated with CIS (Graff et al, 1995; Horikawa et al, 2003). *CDH1* methylation has also been reported in histologically normal urothelium; however, many of these cases were from patients older than 70 years of age and may be related to a potential link between

methylation and aging (Ahuja and Issa, 2000; Bornman et al, 2001). Lower levels of CDH1 expression may increase β -catenin/T-cell factor/lymphocyte enhancer factor signaling activity and proliferation in urothelial carcinomas (Maruyama et al, 2002; Thievsen et al, 2003).

Methylation of *RASSF1A* has been reported in 97% of primary bladder tumors, suggesting that epigenetic inactivation of this gene may play an important role in bladder carcinogenesis (Lee et al, 2001). High tumor grade, nonpapillary growth pattern, and muscle-invasive disease are associated with *RASSF1A* promoter methylation in bladder cancer (Maruyama et al, 2001).

Hypomethylation in Bladder Cancer

Global DNA hypomethylation is also a frequent event in tumorigenesis (Jones and Baylin, 2002). Hypomethylation may result in genomic instability via alterations in chromatin structure, increased genetic recombination between repetitive elements, or derepression of retrotransposons (Baylin et al, 2001). Methylation of CpG sites is normally maintained by the enzymatic activities of DNA methyltransferase 1 (*DNMT1*), whereas de novo methylation of CpG sites is mediated by DNA methyltransferases 3A and 3B (*DNMT3A*, *DNMT3B*) (Jones and Baylin, 2002). One important role for methylation is genomic imprinting, which results in monoallelic gene expression without altering the genetic sequence. Loss of imprinting is a reduction in the methylation of the normally methylated allele that can lead to activation of the normally silent copy of a growth-promoting gene (Feinberg and Tycko, 2004). This phenomenon has been reported for the human insulin-like growth factor-2 gene (*IGF2*) in various cancers (Woodson et al, 2004; Sakatani et al, 2005).

Methylation of long interspersed nuclear element (L1 LINE) sequences is reduced in bladder cancer cell lines and primary tumors compared with normal bladder mucosa (Jürgens et al, 1996). However, DNA methyltransferase expression did not correlate with methylation status of cell lines, and methyltransferase activity was reduced in quiescent cells suggesting that aberrant expression of *DNMT1* does not account for the altered methylation patterns found in urothelial carcinoma (Jürgens et al, 1996). Decreased *DNMT1* expression and induction of *DNMT3A* and *DNMT3B* in bladder cancer have also been reported (Kimura et al, 2003). These data suggest that downregulation of *DNMT1* expression may be at least partly responsible for hypomethylation of repetitive elements in bladder cancer.

KEY POINTS: DNA METHYLATION

- Methylation occurs specifically at CpG dinucleotides in the genome. The presence of 5-methylcytosine in DNA can result in spontaneous deamination to thymine and the formation of C→T transition mutations.
- DNA methylation can affect gene function by subsequent mutational events or epigenetic mechanisms. Methylation of CpG islands associated with the promoter region of genes may result in suppression of gene expression.
- Loss of promoter methylation of normally methylated genes can lead to inappropriate gene expression (e.g., expression of oncogenes).

DNA DAMAGE AND REPAIR

Cancer is fundamentally a genetic disease. Alterations in numerous genes provide the malignant cell the means to activate cancer-associated pathways and inactivate tumor suppressive barriers, making possible the acquisition of the key set of attributes associated with the cancer phenotype. The intrinsic accuracy of DNA polymerase coupled with associated error-correction mechanisms keeps the error rate during DNA replication to an astonishingly low estimated value of approximately three incorrect

bases per cell division—in a genome of more than 3 billion bases! However, these processes are not perfect, and cancer-causing changes occur in oncogenes and tumor suppressor genes via epigenetic, mutational, and copy number alterations (CNAs), in addition to epigenetic abnormalities. Many of these genetic changes are thought to result from various endogenous (e.g., mitochondrial respiratory by-products) and exogenous (e.g., chemicals, radiation) DNA-damaging agents that constantly assault the genome (Ames and Gold, 1991, 1998). To counter these threats, cells employ a plethora of defensive mechanisms, including free radical scavengers such as α -tocopherol, vitamin C, carotenoids, bilirubin, and urate as well as protective enzymes such as superoxide dismutases, glutathione peroxidases, and glutathione transferases, which serve to detoxify a wide range of carcinogens (Mates and Sanchez-Jimenez, 1999; Finkel and Holbrook, 2000). Loss of expression, owing to promoter hypermethylation, of the glutathione-S-transferase pi enzyme encoded by the *GSTP1* gene is observed in most prostate cancer cases (Lee et al, 1994; Lin et al, 2001), and more recent studies have found associations between genetic polymorphisms in glutathione-S-transferases and the risk of biochemical recurrence in patients with prostate cancer (Nock et al, 2009). Epidemiologic and retrospective studies on prostate cancer risk have found a protective effect for selenium, which is used as a cofactor by glutathione peroxidases (Lowe and Frazee, 2006; Colli and Amling, 2009), raising hope that dietary intervention might be protective against prostate cancer. However, a large clinical trial showed no benefit for dietary supplementation with selenium (Hatfield and Gladyshev, 2009), and it now appears that observed protective effects of selenium may be limited to men with low baseline selenium levels. Results from other clinical chemoprevention trials in prostate cancer have been similarly disappointing (Gaziano et al, 2009).

In addition to DNA damage prevention, the cell employs a host of DNA repair systems. The set of pathways dealing with DNA damage recognition and repair is referred to as the DNA damage response (DDR) and encompasses a plethora of genes. The DDR includes the replication machinery itself (with its associated proof-reading capability) and the many components of specific DNA repair systems, such as base excision repair, nucleotide excision repair, double-stranded break repair, and mismatch repair described in detail further on (Loeb, 1998; Schmutte and Fishel, 1999).

As previously mentioned, the cell cycle and the DDR are closely integrated. In response to DNA damage, the first step is to arrest the cell cycle so that the DNA can be repaired. There is substantial overlap between the initiators of DNA repair and cell cycle arrest (Kastan and Bartek, 2004). For example, ATM and ATR kinases are both activated in response to DNA damage, and both activate TP53, CHK1, and other proteins critical to cell cycle arrest (Bartek and Lukas, 2003).

Considering the number of genetic changes calculated to be required for cancer development as well as the large number of changes actually observed in cancer cells and taking into account the very low spontaneous mutation rates in normal human cells, Loeb concluded that the spontaneous mutation rate is insufficient to explain the number of mutations observed in most human cancers. Loeb hypothesized that early in the process of tumorigenesis, preneoplastic cells might develop defects in one or more of the genes responsible for the fidelity of DNA replication (Loeb et al, 1974; Loeb, 1991; Cheng and Loeb, 1993). Such a defect would lead to an increased mutation rate resulting in a so-called mutator phenotype. This hypothesis gains further support from the fact that most cells in proliferating tissues, such as epithelial tissues, the source of most human cancers, are relatively short-lived, being eliminated either by cell shedding or by apoptosis. The target population of cells at risk for becoming cancerous is far less than the total number of cells in the body, yet cancers are common. In addition, cells with a “hypermutable” phenotype are often more difficult to treat because the selection pressure of therapy may rapidly select tumor cells with mutations conferring resistance (Tlsty et al, 1989).

The term *mutator phenotype* was originally used to refer to defects in the DNA replication and repair proteins, resulting in

small-scale errors in the DNA sequence, such as single base substitutions, deletions, and duplications. Despite (or perhaps because of) the many potential targets for mutator genes, few such genes have been found to be consistently mutated in significant proportions of common human cancers, a notable exception being the mismatch repair pathway. Mismatch repair defects are the underlying cause of hereditary nonpolyposis colorectal cancer (Aaltonen et al, 1993) and have been reported in 15% of sporadic colon cancers (Liu et al, 1995).

Although defects in DNA repair genes in sporadic malignancies, including GU tumors, have been identified, Loeb's concept of the mutator phenotype, as originally stated, has yet to be fully evaluated, and it currently appears that it may not be a major player in the development of most common sporadic human cancers. However, if one broadens the mutator concept to include systems involved in *chromosomal stability*, it may become widely applicable. At any rate, the current consensus is that *genetic instability of some sort is required for cancer development*.

Additional information on DNA repair mechanisms (nucleotide excision repair, base excision repair, mismatch repair, DNA double-stranded break repair, nonhomologous end joining) can be found on the Expert Consult website.



KEY POINTS: DNA DAMAGE AND REPAIR

- DNA damage does not often lead to malignancy because the cell possesses multiple repair mechanisms.
- Defects in DNA repair facilitate the accumulation of the mutations critical for tumor formation and progression.
- NER is a major defense against DNA damage caused by ultraviolet radiation and chemical exposure.
- BER repairs DNA damage caused by spontaneous deamination of bases, radiation, oxidative stress, alkylating agents, and replication errors.
- MMR removes nucleotides mispaired by DNA polymerase.
- Double-stranded break repair is a major defense against DNA damage caused by ionizing radiation, free radicals, and chemicals.
- Many syndromes that involve inherited defects in DNA repair exhibit marked increases in cancer susceptibility, strongly linking genomic instability and cancer.

GENOMIC ALTERATIONS

Although the ultimate source of genetic instability in cancer is still unclear, research by many different groups on several different tumor types has strongly implicated genetic instability as an important determinant of tumorigenesis (Loeb, 1991; Hartwell, 1992). As mentioned previously, although important in specific instances, such as inherited cancer susceptibility syndromes, deficiencies in genes involved in the replication, maintenance, and repair of DNA have not yet been shown to play a major direct role in the genesis of most sporadic human cancers. More recent studies on numerous human cancers found that the genomes of each cancer have numerous mutations (on average 33 to 66 somatic mutations in solid tumors) in gene coding sequences that are predicted to alter significantly the corresponding protein products (Vogelstein et al, 2013). Comprehensive sequencing efforts coupled with statistical methods to predict the effects of individual mutations have revealed that approximately 140 genes, when mutated, can “drive” tumorigenesis (e.g., “driver” genes). Most tumors contain only two to eight such driver mutations, whereas the remaining mutations in any particular cancer case are considered “passengers” that do not confer a selective growth advantage (Sjoberg et al, 2006; Wood et al, 2007; Vogelstein et al, 2013).

Apart from the sequence alterations predicted to arise from the original mutator phenotype concept, *chromosomal* instability leads

to gross changes in chromosome number and structure or both. The spectrum and severity of such chromosomal alterations may differ for different tumor types. For instance, **hematologic malignancies often manifest with simple diploid or near-diploid karyotypes with only one or very few detectable, often balanced, chromosomal rearrangements**. However, as a class, these cancers account for only about 10% of all human cancers. **In stark contrast, the presence of large variations in chromosome numbers and complex structural rearrangements as well as intratumoral variation in these aberrations are hallmarks of most human solid tumors**, which represent the bulk of human malignancies. Important exceptions include certain tumors deficient in MMR. **In prostate cancer as well as most human tumor types and transplantable tumor models, the extent of chromosomal abnormalities correlates with disease severity and aggressiveness**, pointing to a role for these changes in cancer progression—spanning from premalignant lesions to localized primary tumors to metastatic disease to which patients typically succumb (Brothman et al, 1990; Lundgren et al, 1992; Sandberg, 1992; Isaacs et al, 1995; Bostwick et al, 1996). For example, in a study that used a computational method to infer aneuploidy based on gene expression data of genes that are located in adjacent chromosomal regions, greater levels of aneuploidy were found to confer worse survival (Carter et al, 2006). Likewise, a study on prostate cancer performed unsupervised hierarchical clustering of copy number alterations (CNAs) in 218 tumor samples and found that tumors with the highest number of genome-wide CNAs had a significantly accelerated time to biochemical recurrence (Taylor et al, 2010).

The chromosomal changes seen in solid tumors can be broken down into two main classes: **changes in the number of whole chromosomes and changes in chromosomal structure**. Numerical chromosomal alterations can be subdivided further into changes in the numbers of specific individual chromosomes, aneusomies (e.g., monosomies and trisomies), and changes in the number of copies of the entire diploid set of chromosomes, ploidy changes (e.g., tetraploidy, octaploidy). Possible mechanisms responsible for such numerical changes include nondisjunction, endoreduplication (an abrupt doubling of the chromosome complement without cell division), cytokinesis defects, and cell fusion events. Likewise, structural changes can be subdivided into several distinct types of chromosomal aberrations as listed in Box 19-2. An additional mechanism

BOX 19-2 Gross Chromosomal Abnormalities Frequently Observed in Cancer

NUMERICAL ABNORMALITIES

- Aneuploidies
- Abnormal numbers of whole chromosome complement (e.g., triploidy, tetraploidy)
- Losses or gains of single chromosomes (e.g., monosomy, trisomy)

STRUCTURAL ABNORMALITIES

- Rearrangements
- Inversions
- Translocations (either balanced or unbalanced)
- Chromothripsis
- Chromosomal fusions
- End-to-end fusion = dicentric chromosome
- Intrachromosomal fusion = ring chromosome
- Deletions (from small segments up to entire chromosome arms)
- Duplications, amplifications
- Double minutes (often containing amplified sequences)
- Isochromosomes (loss of one chromosomal arm, replaced by duplication of the remaining arm)
- Complex (various combinations of the above-listed abnormalities)

DNA Repair Mechanisms

It has been estimated that each cell's genome experiences on the order of 10,000 lesions per day from reactions with oxidative species alone (Ames et al, 1993). Other processes, such as spontaneous loss of individual DNA bases (depurination and depyrimidination) and spontaneous deamination of bases, also occur at appreciable rates. In addition to damage prevention, the cell employs a host of DNA repair systems (Fig. 19-10). The relevance of DNA maintenance pathways to human cancer is borne out by the fact that many recessively inherited cancer predisposition syndromes (e.g., xeroderma pigmentosum, Bloom syndrome, Werner syndrome, ataxia telangiectasia, hereditary breast and colon cancer syndromes) are caused by defects in genes involved with DNA maintenance and repair, strongly implicating hypermutability in cancer causation (Modrich, 1994; Sancar et al, 1996; Patel et al, 1998). Three repair systems exist to deal with damage at the level of the DNA bases themselves. Such damage includes base modifications arising from reactive chemical species and from base mismatches secondary to rare misincorporation of incorrect bases or chemical conversions. The first of these, nucleotide excision repair (NER), is a major defense against DNA damage caused by ultraviolet radiation and chemical exposure. NER acts on a wide range of alterations that result in large local distortions in DNA, by recognizing distortions in the DNA helix, excising the damaged DNA, and replacing it with the correct sequence (Wood, 1997).

In base excision repair (BER), damage caused by various events, including spontaneous deamination of bases, radiation, oxidative stress, alkylating agents, or replication errors, is corrected. In particular, the pathway is critical for repair of oxidative lesions caused by reactive oxygen species. In contrast to NER, lesions recognized by BER do not tend to create major distortions in the DNA molecule.

In human cancers, mutations in the MUTYH glycosylase, a component of BER that removes damaged bases, are associated with colorectal carcinoma. This glycosylase functions with another glycosylase, OGG1, to correct A/G and A/C mismatches (Al-Tassan

et al, 2002). Polymorphic variants of OGG1 have been implicated in GU malignancies, including prostate cancer (Xu et al, 2002b). Mismatch repair (MMR) removes nucleotides mispaired by DNA polymerases and insertion/deletion loops (ranging from 1 to 10 or more bases) that result from slippage during replication of repetitive sequences or during recombination. The MMR pathway functions primarily to reverse incorporation errors made by DNA polymerase. Defects in MMR compromise DNA replication fidelity by approximately 2 orders of magnitude, dramatically increasing mutation rates. Genetic inactivation of MMR genes, particularly *MLH1*, is a frequent event in sporadic colon carcinoma (Veigl et al, 1998) and has been implicated in prostate (Boyer et al, 1995) and bladder (Christensen et al, 1998) carcinomas. The finding that MMR knockout mice are cancer prone provides additional evidence that defects in MMR repair can contribute substantially to tumorigenesis (Friedberg et al, 1998).

Double-Stranded Break Repair

DNA double-strand breaks (DSBs) arise from various causes, including ionizing radiation or radiographs, free radicals, and reactive chemical species as well as during replication of DNA containing single-strand breaks. After DSB detection, a complex cascade of reactions is triggered that halts the cell cycle and recruits specific repair factors (Kastan and Bartek, 2004). DSBs have the potential to be the most disruptive form of DNA damage. If they are not repaired, the cell often undergoes apoptosis. This apoptotic response to DNA DSBs is the basis of radiation therapy and many chemotherapeutic agents that function primarily by inducing DSBs. Cancer cells that have abrogated this response may exhibit increased resistance to such therapies. Incorrectly repaired DNA can lead to DNA mutations, deletions, and structural chromosomal rearrangements that are nearly ubiquitous in human solid tumors. There are two DSB repair pathways: homologous recombination (HR) and nonhomologous end joining (NHEJ) (Sancar et al, 2004).

The ATM kinase is a key player in DSB repair (Berkovich et al, 2007). By mechanisms that are still unclear, DSBs are quickly

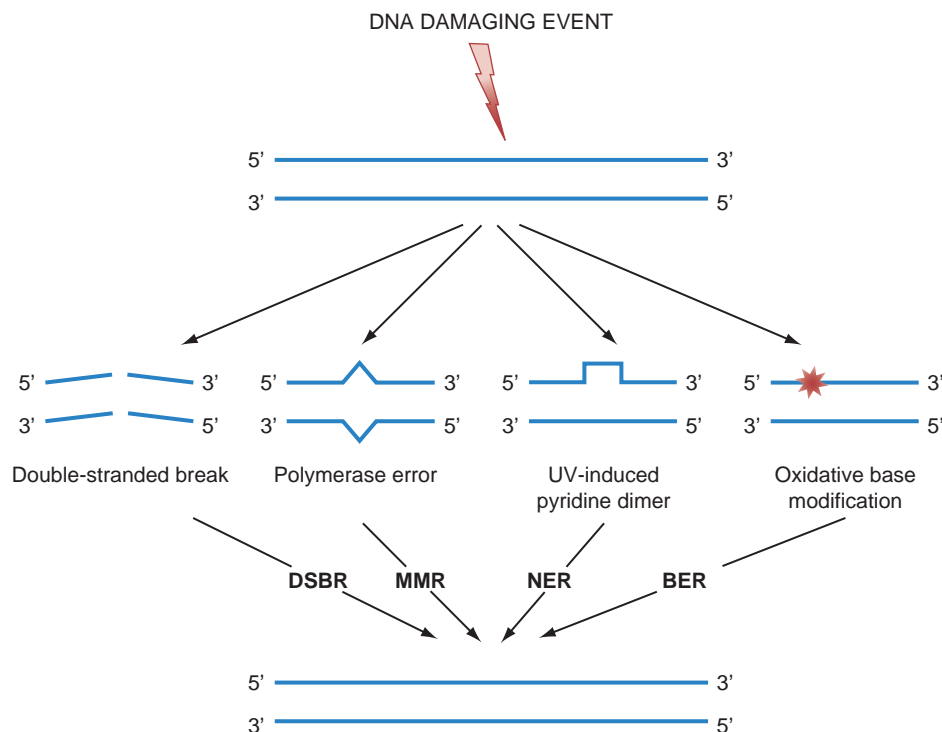


Figure 19-10. Schematic drawing of different DNA damaging events and repair mechanisms. BER, base excision repair; DSBR, double-stranded break repair; MMR, mismatch repair; NER, nucleotide excision repair.

recognized, leading to rapid ATM activation via phosphorylation. Activated ATM phosphorylates and activates TP53 and kinases CHECK1 and CHECK2, which, among other things, act to halt cell cycle progression to allow for DNA repair (Fig. 19-11 on the Expert Consult website). ATM also activates many proteins involved in

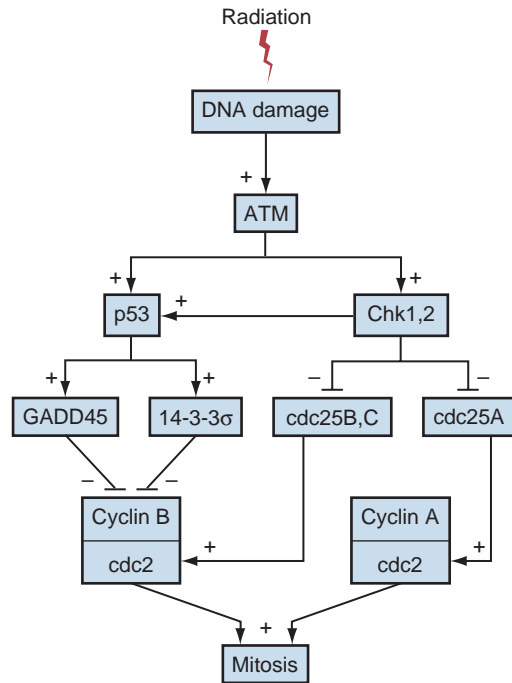


Figure 19-11. Schematic representation of the cascade at the G₂/M checkpoint in response to genotoxic events such as radiation. Increased ATM kinase activity eventually leads to inhibition of cyclin B through p53 and decreased stimulation of Cdc2 through Chk1 and Chk2; this leads to cell cycle arrest.

DSB repair, such as the histone H2A variant H2AX (Rogakou et al, 1998; Lukas et al, 2003), NBS1, BRCA1, and SMC1 (Kitagawa et al, 2004). Phosphorylated H2AX (also known as gamma H2AX) binds at the breakpoint and occupies a sizeable stretch of DNA (up to 30 Mbp) on either side of the break where it serves to recruit other DDR factors creating so-called repair foci (Rogakou et al, 1999; Bassal and El-Osta, 2005). Activated NBS1-MRE11-RAD50 (MRN) complex can then bind to Rad52 and the broken chromosomal ends (Lobachev et al, 2004). RAD51 along with the breast cancer susceptibility gene products, BRCA1 and BRCA2, plus the BRCA1-associated-RING-domain 1 protein (BARD1) participate in replicating the undamaged region from the sister chromosome template (Welch et al, 2000; Sancar et al, 2004). Homologous recombination involves the transfer of genetic information between sister chromatids. Essentially, homologous repair allows the normal undamaged sister chromatid to act as a template to allow precise repair of a damaged segment of DNA (Johnson et al, 1999). Use of the sister chromatid is only an option following S phase into G₂, before mitosis has occurred.

NHEJ is the more extreme of the two DSB repair pathways. In this instance, broken ends are brought together and ligated, often with a loss of some nucleotides at the resulting joint. In addition, the potential exists for incorrectly joining broken DNA ends that were not originally juxtaposed in the genome, creating chromosomal rearrangements such as chromosomal translocations. The Ku protein is a heterodimer consisting of XRCC6 (Ku70) and XRCC5 (Ku80) subunits that initiates NHEJ by binding to the broken ends of the DNA (Tuteja and Tuteja, 2000). Ku complexes with DNA-dependent protein kinase PRKDC (DNA-PK catalytic subunit) and in doing so activates kinase activity of PRKDC (Anderson, 1993). Active PRKDC phosphorylates numerous proteins involved in the repair process, including Ku and H2AX. Phosphorylated Ku uses its helicase activity to unwind the damaged DNA and allows the ligase 4/Xrcc4 heterodimer to repair the break (Tuteja and Tuteja, 2000).

Similar to other DNA repair mechanisms, defects in DSB repair have been linked to cancer. BRCA1 and BRCA2 are associated with familial breast and ovarian cancer (Miki et al, 1994; Wooster et al, 1995). Such inherited cancer predisposition syndromes further highlight the existing link between genomic instability and cancer causation.

for genomic rearrangement, termed *chromothripsis* (literally meaning “chromosome shattering”), has been described that was initially extrapolated from genomic sequencing studies on cancer cells (Stephens et al, 2011). Chromothripsis is evidenced by a large number (possibly hundreds) of chromosomal rearrangements in confined chromosomal regions that have occurred after apparent shattering and rejoining of a chromosomal region in a sometimes disordered fashion.

As previously mentioned, cancer-associated chromosomal changes were recognized in the 1900s by Boveri, who proposed that such abnormalities might be involved in cancer causation. Much later, Klein (1981) suggested that chromosomal rearrangements affect the expression of cancer-related genes located near the observed chromosomal breakpoints. This hypothesis has been validated over the ensuing years, in large part as a result of studies on what were observed to be consistent chromosomal changes found in hematologic malignancies and soft tissue sarcomas, eventually leading to the isolation and cloning of the resident genes involved (Nowell, 1994). Over the years, painstaking dissection of chromosomal regions that are repeatedly found to undergo alteration in specific tumor types or subtypes has led to the discovery of hundreds of individual cancer-associated genes. Typically, genomic loci that are frequently lost tend to harbor tumor suppressor genes, whereas loci exhibiting copy number gains (e.g., gene amplification) point toward oncogenes (Snijders et al, 2005). Examples of genes frequently amplified in cancers include members of the *MYC*, *RAS*, *EGFR*, and *FGF* gene families as well as cell cycle regulatory genes such as *CCND1* (cyclin D gene), *CDK4*, and *HDM2*. Gene amplifications in cancer are usually seen either as multiple small extrachromosomal copies, called *double minutes*, or as amplified regions within chromosomes, so-called homogeneous staining regions (Cowell, 1982).

Specific Chromosomal Rearrangements in Genitourinary Malignancies

Recurrent Gene Rearrangements in Prostate Cancer

Although they are much less frequently observed in common adult solid tumors, recurrent translocations do occur, often amid the backdrop of countless chromosomal abnormalities (Sandberg, 1985). One of the most exciting more recent findings in prostate cancer research has been the discovery of recurrent structural rearrangements in most prostate cancer cases, primarily involving oncogenic ETS transcription factor family members. The initial report by Tomlins and coworkers in 2005 described the use of a novel bioinformatic approach that led to the identification of recurrent gene fusions between the upstream regulatory region of the androgen-regulated gene *TMPRSS2* and *ERG*, an ETS family member previously known to be involved in Ewing sarcoma and various leukemias. These two genes reside 3 Mb apart on chromosome 21 (*TMPRSS2*, 21q22.3; *ERG*, 21q22.2), and detailed molecular analysis revealed that in most rearranged cases (approximately two thirds), the gene fusion occurs via deletion of the intervening sequence, with the remaining fusions resulting from more complex, translocation-type rearrangements (Tomlins et al, 2005; Perner et al, 2007). In either case, the net result is to place a known oncogenic transcription factor under the control of an androgen-regulated promoter, resulting in androgen-driven expression of the fusion transcript (Wang et al, 2008a). As expected, increased *ERG* transcription and *ERG* protein expression are positively correlated with presence of the gene fusion. In addition to various splice variants, there are multiple forms of the genomic rearrangement, the most common one being a fusion between exon 1 of *TMPRSS2* and exon 4 of *ERG*. These gene rearrangements can be readily detected, either by assaying for the presence of the fusion transcripts by reverse-transcription polymerase chain reaction (PCR) or by assaying for the rearrangement directly by multiprobe, multicolor fluorescence in situ hybridization (FISH). Such approaches are currently being evaluated for potential use in noninvasive diagnostic applications (e.g., in urine or blood).

More recently, detection of *ERG* protein expression by immunostaining has been shown to be an excellent surrogate marker for chromosomal rearrangements involving the *ERG* gene, providing a simpler method for their detection (Park et al, 2010; Chaux et al, 2011; Falzarano et al, 2011).

Since the publication of the initial report by Tomlins and coworkers, several large retrospective studies have been performed assessing these fusions in localized prostate cancers in PSA-screened cohorts. These studies confirmed the initial finding and found the prevalence of the *TMPRSS2-ERG* fusion in prostate cancer to be 40% to 60%, making this one of the most common somatic genetic alterations in prostate cancer (Mehra et al, 2007; Nam et al, 2007; Perner et al, 2007; Tu et al, 2007; Wang et al, 2008a; Gopalan et al, 2009b; Mosquera et al, 2009). One anatomic exception is cancer originating in the transition zone of the prostate, which appears to lack *TMPRSS2-ERG* gene rearrangements completely (Guo et al, 2009a).

As assessed by FISH in tissue sections, the *TMPRSS2-ERG* fusion has not been observed in benign prostate epithelial or stromal cells, although it has been reported to be present in high-grade prostatic intraepithelial neoplasia (PIN), the presumptive precursor lesion for prostate adenocarcinoma, at frequencies between 15% and 20%, which is about one half the frequency observed in localized PSA-detected cancers (Cerveira et al, 2006; Perner et al, 2007; Mosquera et al, 2008; Han et al, 2009). This finding implies that, at least in a subset of cases, the rearrangement may be an early event in prostate tumorigenesis. With the important exceptions of transition zone cancers and high-grade PIN, the prevalence and high degree of specificity of the *TMPRSS2-ERG* fusion for prostate cancer makes this a potentially useful biomarker for diagnosis and disease monitoring, one that could be used in conjunction with current markers such as serum PSA that have limited specificity. The detection of *TMPRSS2-ERG* fusion-driven *ERG* overexpression in prostate biopsy specimens from men found to have only high-grade PIN was shown to be predictive of cancer diagnosis on subsequent biopsy (Park et al, 2014), and multiple studies have demonstrated the utility of *TMPRSS2-ERG* detection in the blood or urine either alone or in combination with the non-protein-coding RNA prostate cancer antigen 3 (PCA3) in enhancing the sensitivity of prostate cancer diagnosis (Hessels et al, 2007; Tomlins et al, 2011; Leyten et al, 2014).

Apart from the promising potential of *TMPRSS2-ERG* as a diagnostic prostate cancer marker, it is unclear at the present time if additional clinical information might be provided by determining a patient's *TMPRSS2-ERG* gene fusion status. The prognostic significance of fusion status in prostate cancer remains uncertain. Although several studies have reported associations between *TMPRSS2-ERG* rearrangement and various indicators of disease aggressiveness, including higher stage, presence of metastases, and disease-specific death (Demichelis et al, 2007; Mehra et al, 2007; Nam et al, 2007; Perner et al, 2007; Rajput et al, 2007; Attard et al, 2008a; Cheville et al, 2008; Barwick et al, 2010; Leyten et al, 2014), several other published studies failed to observe such associations (Yoshimoto et al, 2006; Lapointe et al, 2007; Tu et al, 2007; Dai et al, 2008; Rouzier et al, 2008; Albadine et al, 2009; Darnel et al, 2009; Gopalan et al, 2009b; Lotan et al, 2009; Fine et al, 2010). A large prospective study of 1180 men treated by radical prostatectomy found that the presence of the *TMPRSS2-ERG* rearrangement was not predictive of recurrence or mortality but was associated with tumor stage (Pettersson et al, 2012). Studies examining the prognostic capabilities of *TMPRSS2-ERG* positivity in predicting treatment outcomes to androgen deprivation (Leinonen et al, 2010), abiraterone (Danila et al, 2011), or radiotherapy (Dal Pra et al, 2013) showed no association. In addition, one study reported a link between gene fusion and favorable prognosis (Saramaki et al, 2008), and Petrovics and colleagues (2005) reported that higher levels of *ERG* mRNA expression appeared to be positively associated with disease-free survival. Another study reported that *ERG* gene copy number gain without the presence of the gene fusion is prognostic for recurrence after radical prostatectomy (Toubaji et al, 2011). The precise reasons for these conflicting results are not

apparent. Numerous variables differ among many of these studies, including the nature of the study cohort, sample size, method of cancer detection, how the tissues were obtained, intratumoral heterogeneity in the presence of the fusion (Minner et al, 2013), how the gene fusions were detected (e.g., PCR or FISH), length of patient follow-up, and the clinical end points assessed. Further research in this area is warranted for better resolution of these issues.

Following the report of *TMPRSS2-ERG* rearrangements, further study revealed additional gene fusions in prostate cancer. The *TMPRSS2* gene can fuse to other ETS family member genes including *ETV1*, *ETV4*, and *ETV5* (Tomlins et al, 2005, 2006; Helgeson et al, 2008). These additional translocations are much rarer than the *TMPRSS2-ERG* rearrangement, which is estimated to represent greater than 90% of all fusions involving ETS genes in prostate cancer (Kumar-Sinha et al, 2008). In addition, fusions involving upstream fusion partners other than *TMPRSS2* have been found, including the fusions *SLC45A3-ETV5*, *SLC45A3-ERG*, *HNRPA2B1-ETV5*, and *SLC45A3-ELK4*; however, these are also relatively rare (Tomlins et al, 2007; Attard et al, 2008a, 2008b; Hermans et al, 2008; Maher et al, 2009; Rickman et al, 2009). Although the fusion events in prostate cancer are typically driven by genomic rearrangements, the *SLC45A3-ELK4* fusion was later found to be due to RNA cis-splicing events between these two genes (which are located adjacent to each other on chromosome 1 band q32) with no alterations to the DNA sequence (Zhang et al, 2012). To date, additional low-frequency gene fusions have been identified in prostate cancer that involve non-ETS family members, such as *CDKN1A*, *CD9*, *IKBK4*, the oncogene *PIGU*, the tumor suppressor *RSRC2*, and members of the RAF pathway (*BRAF*, *RAF1*) (Palanisamy et al, 2010; Pflueger et al, 2011; Ren et al, 2012). These studies have been facilitated by next-generation RNA sequencing (RNA-seq or whole “transcriptome” shotgun sequencing) technologies that unbiasedly sequence all RNA species in a sample, with an analysis that is not limited to “annotated” sequences. The results of RNA-seq studies indicate that some of the fusion events that occur in prostate cancer may be “private events” (e.g., occurring in only one patient), implying that the frequency and range of fusion events in prostate cancer may be far greater than what is currently understood (Pflueger et al, 2011).

Recurrent Gene Rearrangements in Renal Cancer

A novel subtype of RCC, MiTF/TFE family translocation carcinomas, has been described that features chromosomal translocations involving one of two members of the microphthalmia transcription factor (MiTF) family (Hemesath et al, 1994; Argani and Ladanyi, 2005). The first involves the *TFE3* gene on chromosome Xp11.2, which translocates to one of several partner genes including *PRCC* (1q21), *ASPL* (17q25), *PSF* (1p34), *NonO* (Xq12; rearranged via inversion), and an unknown gene at 3q12 (Sidhar et al, 1996; Weterman et al, 1996; Argani et al, 2001a, 2001b; Argani and Ladanyi, 2005; Argani et al, 2005; Martignoni et al, 2009). These translocations place the *TFE3* gene under the control of strong promoters that then drive inappropriate expression of *TFE3* (or a *TFE3*-containing fusion protein). In these cancers, *TFE3* protein is readily detectable in the nucleus by IHC staining with anti-*TFE3* antibody, aiding in diagnosis. *TFE3* RCCs are primarily found in children and adolescents and account for most pediatric cases of RCC (Argani and Ladanyi, 2005). Activation of the *MET* proto-oncogene may play a role with *TFE3* in these tumors (Tsuda et al, 2007), which is of interest because these tumors display papillary histologic architecture, and mutations in the *MET* gene are the underlying cause of hereditary papillary RCC (Jeffers et al, 1997).

A second class of MiTF/TFE family translocation carcinomas contains a specific translocation between the *TFEB* gene on 6p21 and the *ALPHA* gene on 11q12 (Argani et al, 2005). Similar to the Xp11 translocation RCCs, this entity is also most commonly found in children and adolescents and shares many other features with the *TFE3* translocation tumors. In addition to IHC staining for *TFE3* and *TFEB* proteins, it was demonstrated that these tumors are also marked by staining for the protein cathepsin K, a shared transcriptional target gene of these transcription factors (Martignoni et al,

2009). The use of such markers or PCR to detect these specific gene fusions may have clinical importance because, as the cathepsin K example shows, these tumors likely are controlled by a different transcriptional program than conventional RCC, and therapeutic targets used against these cancers may not be effective against translocation RCCs.

Recurrent Gene Rearrangements in Testicular Cancer

In testicular germ cell tumors (TGCTs), gain of the short arm of chromosome 12 is a nearly universal finding, with the notable exception of the rare spermatocytic seminoma subtype (Atkin and Baker, 1982; Rodriguez et al, 1993; Rosenberg et al, 1998; Verdorfer et al, 2004). In most cases (approximately 80%), this finding occurs through a structural rearrangement producing an isochromosome 12p—that is, a version of chromosome 12 consisting of 2 p arms and no q (long) arm. In the remaining cases, 12p material is gained through more complex chromosomal rearrangements (Rosenberg et al, 2000; Ottesen et al, 2003; Looijenga et al, 2007). More detailed analyses have revealed amplification of specific regions on 12p, including the area 12p11.2–12p13. One common region of amplification at 12p11.2–12p12.1 contains 22 potential genes, including *KRAS*, a promising candidate TGCT gene, which also undergoes activating mutations in TGCTs (Moul et al, 1992; Olie et al, 1995; Rodriguez et al, 2003; Zafarana et al, 2003; Goddard et al, 2007). An additional region of interest lies at 12p13.31, where the so-called stem cell cluster region is located. This region contains several stem cell–related genes including *CD9*, *EDR1*, *GDF3*, *SCNN1A*, *NANOG*, and *STELLAR*, which exhibit coordinate overexpression (Clark et al, 2004; Korkola et al, 2006).

Other Genomic Alterations in Genitourinary Malignancies

Apart from chromosomal translocations, which are primarily specific changes in the spatial organization of the genome, an overall derangement of the chromosomal complement is nearly universal in human cancer, particularly in carcinomas—cancers that originate from epithelial cells and represent most adult GU malignancies. Such abnormalities are wide-ranging, affecting the genome at multiple scales, including losses and gains of entire chromosomes or chromosomal arms as well as deletions and amplifications of large and small chromosomal regions. These changes are generically referred to as CNAs. In addition to mutations, structural rearrangements, and epigenetic changes, CNAs are yet another reflection of the underlying genomic instability in cancer cells, resulting in the large number of genetic changes required for malignant transformation. This instability generates a great degree of genetic heterogeneity. For instance, when metaphase chromosomes of tumor cells are examined during karyotypic analysis, a bewildering array of chromosomal aberrations is typically observed, such that no two karyotypes within a given cancer cell population are exactly the same. However, within this seemingly random assortment of alterations, some changes are seen in multiple different cells and multiple tumor samples, providing a strong indication that a gene or genes located in the region undergoing recurrent alteration is involved in the pathogenesis of the disease. Over the past several decades, using ever more sophisticated and higher resolution molecular methods, many such changes have been cataloged and candidate cancer genes have been identified. Two general approaches are used here. In the first, inherited (germline) defects in genes that cause hereditary cancer predisposition syndromes are sought, often by performing genetic linkage analysis in affected and nonaffected family members in an attempt to find genetic loci that track in a mendelian fashion with disease status. Several familial cancer predisposition syndromes are now understood in significant detail, some featuring GU malignancies and others not (Tables 19-1 and 19-2). In the second approach, various techniques are employed to discover disease-associated genes in sporadic cancers that lack a strong familial component (caused by somatic rather than germline genetic alterations). The detection of CNAs in a particular gene (or region containing the gene)

TABLE 19-1 Tumor Syndromes Associated with Genitourinary Malignancies

SYNDROME	TUMOR	CHROMOSOME(S)	GENE(S)	(FUNCTION)
Wilms tumor	Wilms tumor	11p13	<i>WT1</i>	(Transcriptional repressor)
Beckwith-Wiedemann	Wilms tumor	11p15	<i>CDKN1C</i>	(Cell cycle regulator)
von Hippel-Lindau	Clear cell renal carcinoma Pheochromocytoma	3p25	<i>VHL</i>	(Transcriptional elongation and ubiquitination)
Hereditary papillary renal cancer	Papillary renal carcinoma	7q31	<i>MET</i>	(Receptor tyrosine kinase)
Birt-Hogg-Dube	Papillary renal carcinoma Oncocytoma	17p11.2	<i>FLCN</i>	(Unknown function)
MEN type 2	Pheochromocytoma	10q11	<i>RET</i>	(Receptor tyrosine kinase)
Hereditary nonpolyposis colorectal cancer	Upper tract transitional cell carcinoma	2p22, 3p21.3, 2p18, 2q31-q33, 7p22, 14q24.3	<i>MSH2, MLH1, MSH6, PMS1, PMS2, MLH3</i>	(DNA mismatch repair)
Hereditary prostate cancer	Prostate cancer	1q24-25, 1p36, 1q42-43, 8p22-23, 17p11, 20q13, Xq27-28	<i>RNASEL, MSR1, ELAC2</i>	(Endoribonuclease, macrophage specific receptor, cell cycle regulator)

MEN, multiple endocrine neoplasia.

TABLE 19-2 Selected Tumor Syndromes Not Strongly Associated with Genitourinary Malignancies

SYNDROME	PRIMARY TUMOR	CHROMOSOME(S)	GENE(S)	(FUNCTION)
Familial retinoblastoma	Retinoblastoma	13q14	<i>RB</i>	(Transcriptional regulation)
Li-Fraumeni	Sarcoma, breast carcinoma	17p13, 22q12	<i>TP53, hCHK2</i>	(Transcription factor, serine kinase)
Familial adenomatous polyposis	Colorectal carcinoma	5q21	<i>APC</i>	(Regulates β -catenin activity)
Familial breast carcinoma	Breast carcinoma	17q21, 13q12	<i>BRCA1, BRCA2</i>	(DNA double-stranded break repair)
Cowden disease	Breast carcinoma	10q23	<i>PTEN</i>	(Phosphatase; PI3K antagonist)
MEN type 1	Pancreatic islet cell carcinoma	11q13	<i>MEN1</i>	(Transcription factor)

MEN, multiple endocrine neoplasia; PI3K, phosphatidylinositol-3'-kinase.

coupled with mutations in the other allele is persuasive evidence for that gene functioning as a disease-relevant oncogene (with activating mutations) or tumor suppressor gene (featuring inactivating mutations or promoter methylation). In the case of cancer-related genes identified in hereditary predisposition syndromes, one hopes that alterations of genes discovered in familial forms of the disease are also relevant to their more common sporadic counterparts. In many instances, this has been found to be the case; for example, gene abnormalities linked to certain familial forms of kidney cancer are also involved in sporadic forms of the disease. In the following sections, we describe some of the recurrent genetic changes identified in familial and sporadic forms of GU malignancies.

Hereditary Prostate Cancer

Family history is one of the strongest risk factors for prostate cancer (Steinberg et al, 1990), and criteria defining a hereditary form of the disease have been established (Carter et al, 1993). Twin studies have estimated a heritable risk for prostate cancer of approximately 50% (Page et al, 1997; Lichtenstein et al, 2000). Traditional linkage analysis is well suited to identify highly penetrant genetic alterations (Fig. 19-12). The overall low yield and irreproducibility seen in hereditary prostate cancer (HPC) linkage studies has led to the conclusion that rather than being caused by a few high-impact genes, HPC is instead likely to depend on

alterations in many genes, each of which has only a modest effect (Easton et al, 2003; Schaid, 2004).

Initial genome-wide searches in HPC families uncovered evidence for susceptibility loci on chromosomes 1q, 4q, 5p, 7p, 13q, and Xq (Smith et al, 1996). The first strong candidate locus, HPC1, was localized to the region 1q24.25 (Gronberg et al, 1997) and a gene, *RNASEL*, was later identified at this locus (Carpten et al, 2002; Rokman et al, 2002). Although this linkage was replicated in some studies, it was not confirmed in others (Cooney et al, 1997; McIndoe et al, 1997; Eeles et al, 1998; Berghthorsson et al, 2000). Similarly, a failure to confirm linkage consistently has plagued other candidate HPC loci and genes as well, highlighting the difficulty in conducting such studies. Because prostate cancer is a relatively common disease, HPC families are contaminated with sporadic cases ("phenocopies"). It has become apparent that familial prostate cancer may lack the type of high-risk susceptibility genes such as *BRCA1* or *BRCA2* that are clearly linked to hereditary forms of breast and ovarian cancers (Simard et al, 2003). Among other considerations, these facts underline the need for large, well-defined HPC cohorts, making genetic studies difficult to perform. One large HPC cohort of 175 pedigrees identified a region in chromosome 17q21-22 near *BRCA1* with linkage to prostate cancer susceptibility (Lange et al, 2003). This region has subsequently become one of the most intensively investigated regions of the genome for HPC susceptibility. More recently, targeted next-generation sequencing of exons in 202 genes on chromosome 17q21-22 from germline DNA

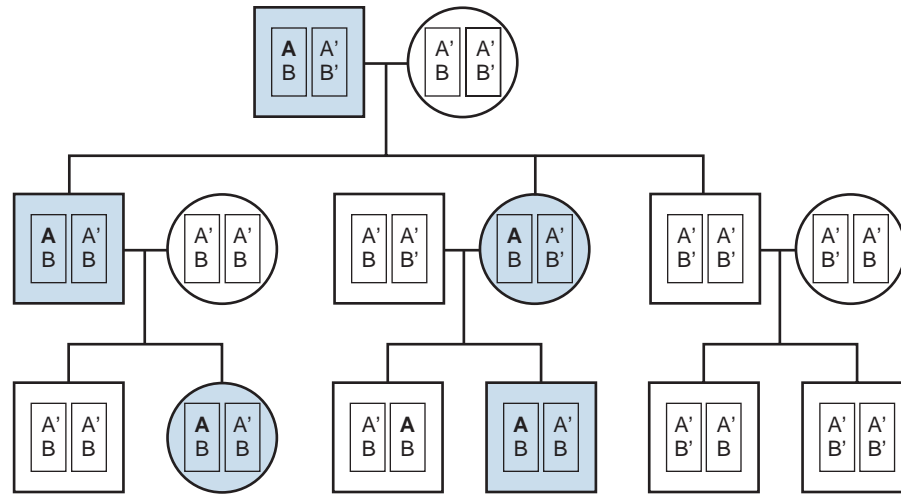


Figure 19-12. The familial tumor syndrome is passed from generation to generation. Genotyping demonstrates that the polymorphic marker **A** (marked in bold) is passed also from generation to generation in concert with the phenotypic disease. Presumably, a gene responsible for the syndrome is located near marker **A**. Linkage analysis is complicated by incomplete penetrance (not all members of the family with the allele get the disease), phenocopies (family members who have sporadic disease), inability to get DNA from all family members, and the large number of markers being simultaneously analyzed.

of unrelated patients with prostate cancer from families that were selected for linkage to the 17q22-22 region identified a variant in the *HOXB13* gene (*HOXB13* G84E) that significantly increased the risk of HPC (Ewing et al, 2012). The carrier frequency of the G84E allele was found in 0.1% of men without prostate cancer and 1.4% of men with prostate cancer. The frequency of the allele was much higher in men with early-onset, familial prostate cancer (3.1%) compared with men with late-onset, nonfamilial prostate cancer (0.6%) (Ewing et al, 2012). Although the carrier rate of the G84E allele is rare, the strong linkage to prostate cancer risk may warrant genetic testing for the variant, similar to testing that is currently performed for *BRCA1* or *BRCA2* in hereditary breast and ovarian cancers. Other candidate HPC susceptibility genes include *ELAC2* (HPC2), macrophage scavenger receptor-1 (*MSR-1*), and *PODXL* (Tavtigian et al, 2001; Xu et al, 2002a; Nupponen et al, 2004; Casey et al, 2006). It is intriguing that two of the HPC candidates, *RNASEL* and *MSR-1*, are both associated with functions of the immune response because inflammation is currently considered a likely contributor to the pathogenesis of prostate cancer (De Marzo et al, 2007; Sfanos and De Marzo, 2012).

Sporadic Prostate Cancer

In sporadic prostate cancer, initial studies found recurrent changes involving losses of genetic material at 6q, 7q, 8p, 10q, 13q, 16q, 17p, 17q, and 18q; however, in most cases, the precise genes involved have yet to be identified (Karan et al, 2003). Changes in chromosome 8, typically loss of the p arm and gain of the q arm, or portions of these arms, are the most frequently observed genetic alterations. At least two to three separate regions are deleted on 8p, implying the existence of multiple tumor suppressor genes. The region 8p22 is commonly deleted, with frequencies of 32% to 65% reported in primary tumors and 65% to 100% in metastases. *MSR-1* lies in this region, and sequence variants in *MSR-1* have been found to be associated with increased disease risk; however, mutations in *MSR-1* have not been reported in sporadic prostate cancers (Xu et al, 2002a; Nupponen et al, 2004; Wiklund et al, 2009). Another promising candidate tumor suppressor gene on 8p is the prostate-restricted homeobox gene *NKX3.1* at 8p21 (He et al, 1997). Mice engineered with a loss of a single allele of *NKX3.1* develop prostate hyperplasia and PIN, an example of haploinsufficiency, wherein a phenotypic effect is observed secondary

to the loss of a single allele (Bhatia-Gaur et al, 1999; Abdulkadir et al, 2002).

The most common chromosomal abnormality found in advanced prostate cancer (e.g., hormone-refractory lymph node metastases) is 8q gain, often involving the entire chromosomal arm leading to isochromosome 8q formation, and it is correlated with disease progression and resistance to hormone deprivation or blockade (Alers et al, 2000; Isaacs, 2002; van Dekken et al, 2003). The proto-oncogene *MYC* at 8q24 is a likely candidate gene on 8q, but the observed gains are large, and more work is required to assess this possibility properly. Elevated expression of another gene in this region, *EIF3S3*, has been documented in cancer compared with benign prostatic hyperplasia (Savinainen et al, 2004). Mouse models lend support for a linkage to *MYC*; transgenic mice with forced prostate-specific expression of human *MYC* develop PIN and invasive adenocarcinomas (Ellwood-Yen et al, 2003). Amplification at the *MYC* locus has been reported in some human prostate cancers and is associated with a poor prognosis (Jenkins et al, 1997; Sato et al, 1999).

Chromosome 7 abnormalities are also frequently observed in prostate cancer. Aneusomy of the entire chromosome (trisomy 7) has been reported in both PIN and cancer and has been associated with advanced stage and a poor prognosis (Arps et al, 1993; Macoska et al, 1993; Alcaraz et al, 1994; Zitzelsberger et al, 1994; Qian et al, 1995). Apart from whole chromosome gains, losses involving 7q31.1 have been documented, suggesting a tumor suppressor resides here (Zenklusen et al, 1994; Takahashi et al, 1995). A potential candidate tumor suppressor gene in this region is caveolin (*CAV1*), whose expression is reportedly decreased in cancer (Bender et al, 2000; Wiechen et al, 2001). However, positive IHC staining for caveolin has been associated with poor prognosis, and its role in prostate cancer remains unclear (Yang et al, 1999; Tahir et al, 2001). Another attractive candidate gene in this region is *EZH2*, which codes for a histone methyltransferase involved in gene silencing. In microarray analyses, *EZH2* has been found to be overexpressed in prostate cancer metastases, and its expression in primary tumors is associated with disease (PSA) recurrence (Varambally et al, 2002; Rhodes et al, 2003; Lapointe et al, 2004).

Chromosome 10 also undergoes alteration in prostate cancer, with deletions observed at 10p11.2 and 10q23-q24 (Ittmann, 1996; Trybus et al, 1996). The tumor suppressor gene *PTEN*, a phosphatidylinositol-3' (PI3) kinase antagonist, maps to this

second region and has been linked to human prostate cancer in many studies (Li et al, 1997a; Ayala et al, 2004). *PTEN* undergoes homozygous (both copies) deletion, LOH, and promoter hypermethylation and is mutated in prostate cancer. Overall, *PTEN* is more frequently altered in advanced disease (reported rates of 60% to 100%) compared with primary tumors (Cairns et al, 1997; Pesche et al, 1998; Whang et al, 1998; Han et al, 2009; Sarker et al, 2009). The frequency of *PTEN* LOH greatly exceeds *PTEN* mutation, and it is suggested that another gene or genes may be targeted for deletion in this region of chromosome 10. One possibility is the *MXI1* gene, whose protein product binds to and antagonizes *MYC*. In mice, *PTEN* deficiency exhibits synergy when combined with other mouse models of prostate cancer (Di Cristofano et al, 2001; Kim et al, 2002; Chen et al, 2006; Carver et al, 2009; King et al, 2009).

LOH on 13q has been reported in greater than 50% of prostate cases examined. Three separate regions of loss have been identified, containing the potential cancer genes *BRCA2*, *RB1*, *EDNRB*, and *KLF5* (Cooney et al, 1996b; Hyytinen et al, 1999; Chen et al, 2003). High rates of *RB1* loss (up to 80%) have been reported in advanced cancers (Cher et al, 1996); however, the *RB1* mutation rate is relatively low, and *RB1* expression is not well correlated with the gene dosage or disease status (Bookstein et al, 1990; Kubota et al, 1995; Ittmann and Wiczorek, 1996; Kibel and Isaacs, 2000). However, Theodorescu and associates (1997) reported that low *RB1* protein expression was correlated with decreased disease-specific survival in univariate and multivariate analysis.

Losses on 16q have been observed with reported frequencies ranging from 30% to 56% of prostate cancer cases, being more commonly seen in advanced cancer and associated with a poor prognosis (Carter et al, 1990; Bergerheim et al, 1991; Suzuki et al, 1996; Elo et al, 1997; Li et al, 1999). A common region of loss at 16q22-q24 contains two likely candidate genes, the *CDH1* gene at 16q22.1 that codes for the calcium-dependent cell-cell adhesion protein E-cadherin (Morton et al, 1993; Umbas et al, 1994; Murant et al, 2000; Rubin et al, 2001), and the *ATBF1* gene at 16q22, coding for an AT-sequence binding transcription factor (Sun et al, 2005). Loss of *CDH1* has been associated with metastatic prostate cancer; however, IHC staining studies have produced mixed results, and reports of mutation or LOH of E-cadherin are lacking; *CDH1* may not be the primary target of the 16q deletion. The *ATBF1* gene has been reported to be mutated in 40% of prostate cancers (Sun et al, 2005).

Reports of LOH on 6q range from 30% to 50%, with a minimal region of loss at 6q14-q22. No strong candidate gene has been identified in this region (Cooney et al, 1996a; Hyytinen et al, 2002).

Allelic losses of a region on 17p that includes the *TP53* gene have been documented but are infrequent in primary prostate cancer compared with more advanced disease (Brooks et al, 1996). This matches findings of mutational analyses in which *TP53* mutations are rarely found in primary tumors but are reported in 40% of advanced disease (Visakorpi et al, 1992; Bookstein et al, 1993; Navone et al, 1993). A recurrent region of loss on 17q is located near the *BRCA1* gene at 17q21; however, the identified common area of loss does not include this critical tumor suppressor gene (Brothman et al, 1995; Williams et al, 1996).

Deletions on 18q are mainly observed in advanced prostate cancer. A common region of deletion encompasses the known cancer-related genes *DCC*, *SMAD2*, and *SMAD4* (Ueda et al, 1997; Yin et al, 2001).

Loss of the cell cycle regulatory gene *CDKN2A* on 9p21, which encodes the CDKI p16, has been reported in 20% of prostate cancers and at twice this frequency in advanced disease (Cairns et al, 1995; Jarrard et al, 1997). As discussed previously, this locus also contains the p14 and p15 genes, making it difficult to pinpoint the exact target or targets of genetic loss in this region. Reduced expression and LOH of another CDKI gene, *CDKN1B* on 12p13.1-p12, which encodes the p27 protein, are also found in prostate cancer and are associated with more advanced disease (Guo et al, 1997; Kibel et al, 1998; Yang et al, 1998).

One additional locus that has particular relevance for prostate cancer is the androgen receptor (*AR*) gene located on Xq12. The region Xq11-q13 containing *AR* is amplified in 30% of cases of advanced disease failing hormonal ablation therapy, in stark contrast to untreated (hormonally naive) cases that do not show *AR* amplification (Visakorpi et al, 1995a; Chen et al, 2004; Linja and Visakorpi, 2004; Mellado et al, 2009). *AR* mutations, which often act to broaden the receptor's ligand specificity or otherwise provide a gain of function, occur in both advanced and lower stage cancer, although they are rarely found in cases untreated by androgen deprivation therapy (Newmark et al, 1992; Taplin et al, 1995; Tilley et al, 1996; Culig et al, 2001; Hara et al, 2003; Gottlieb et al, 2004). Even in the absence of gene amplification, *AR* protein levels have been seen to be elevated in prostate cancer (Latil et al, 2001; Linja et al, 2001), further emphasizing the importance of *AR* hyperactivation in this disease. In addition to mutation, alternatively spliced versions of the *AR* gene lacking the androgen ligand-binding domain have been identified in prostate cancer cells (Dehm et al, 2008; Guo et al, 2009b; Hu et al, 2009). Such *AR* splice variants are active in the absence of bound ligand and may contribute to the emergence of prostate cancer refractory to androgen ablative therapies.

Subsequent studies using the comparative genomic hybridization (CGH) technique, in which competitive reactions between differentially labeled tumor-derived versus normal-derived genomic DNA highlight regions lost or gained in the tumor sample, have largely confirmed as well as extended the genomic alterations previously uncovered using LOH analysis. These CGH studies indicate that the number of different alterations is increased in advanced disease and that losses are more frequent than gains in early stages of the disease, with gains and genetic amplifications more commonly seen in advanced hormone-refractory disease (Visakorpi et al, 1995b; Cher et al, 1996; Nupponen and Visakorpi, 2000). Sun and coworkers (2007) reviewed all published prostate cancer CGH studies and found that, overall, 13 regions were found to be altered in at least 10% of prostate cancer cases, with 8 regions showing deletion and 5 regions showing copy number gain. An additional six regions (three with gains, three with losses) were found to be altered in greater than 10% of advanced cancers. In agreement with earlier studies, 8p was the most frequent region of genomic loss (with a peak at 8p21.3), being observed in one third of all cases and one half of cases of advanced disease. Likewise, 8q was gained most often (bimodal peaks at 8q22.2 and 8q24.13), being observed in one quarter of all cases and one half of cases of advanced disease (Sun et al, 2007). The other regions commonly lost, in decreasing order of frequency, included 13q21.q31, 6q14.1-q21, 16q13-q24.3, and 18q12.1-q23; regions exhibiting gain included 7q11.21-q32.3, Xq11.1-q23, 17q24.1-q25.3, and 3q26.23-q33. Also in keeping with the general observation that more aggressive and advanced cancers typically harbor more genetic abnormalities than their lower grade and lower stage counterparts, advanced prostate cancers displayed twofold to threefold more CNAs.

The application of modern high-resolution methods for assessing CNA, such as representational oligonucleotide microarray analysis and single nucleotide polymorphism (SNP) mapping arrays, will vastly improve our ability to detect CNA, particularly smaller alterations below the resolution limit of CGH, as well as aid in the identification of the resident oncogenes and tumor suppressor genes (Lucito et al, 2003; Sebat et al, 2004; Slater et al, 2005; Zhao et al, 2005; Liu et al, 2006).

High-density SNP microarrays have been used in genome-wide association studies (GWAS), high-resolution association studies between common DNA sequence variants (SNPs) and prostate cancer risk. In contrast to the more traditional linkage analyses of the past, the new platform is amenable to very large cohorts and is better able to detect genetic variations with small to moderate effects on disease risk (Risch and Merikangas, 1996; Jorgenson and Witte, 2007; Manolio, 2010). To date, several GWAS have been published on prostate cancer, resulting in the identification of more than 70 germline variants (SNPs) that are associated

with the risk of developing prostate cancer (Amundadottir et al, 2006; Duggan et al, 2007; Gudmundsson et al, 2007; Haiman et al, 2007; Witte, 2007; Eeles et al, 2008; Gudmundsson et al, 2008; Thomas et al, 2008; Breyer et al, 2009; Eeles et al, 2009; Yeager et al, 2009; Nakagawa et al, 2012; Eeles et al, 2013). With larger meta-analyses being conducted worldwide, the number of prostate cancer SNPs is expected to increase to greater than 100 in the near future (Nakagawa, 2013). Most of the SNPs are not located in or even near genes previously shown to be involved in prostate cancer pathogenesis. Three independent loci were identified on 8q24, all contained within a 1-Mb DNA segment; however, no genes have been identified yet to account for these risk alleles (Cheng et al, 2008). A systematic review of replication studies in prostate cancer susceptibility loci identified from GWAS found that the 8q24 region continues to be the most implicated in prostate cancer risk and among different racial cohorts (Ishak and Giri, 2011). Although the *MYC* gene is in this vicinity, it is still 200 kb away from the nearest SNP, and its relevance, if any, remains uncertain. In contrast to the loci identified in earlier linkage studies in HPC families, the risk alleles identified in these GWAS have been independently confirmed. As predicted, the risk attributable to each locus is small to modest; however, because of the large cohorts studied, each association is highly statistically significant, and each has been shown to confer risk independent of the other loci. These risk alleles act in a fairly additive fashion (Kote-Jarai et al, 2008; Sun et al, 2008; Zheng et al, 2008; Witte, 2009). The clinical utility of using SNP “panels” for prostate cancer risk assessment is currently being investigated (Nam et al, 2009; Zheng et al, 2009; Chatterjee et al, 2013). However, although men in the top decile in terms of number of combined risk alleles have a twofold to fourfold increased risk for prostate cancer compared with the bottom decile, the numbers of men harboring such large numbers of risk alleles is small, and these SNPs are unlikely to have utility for population screening purposes. An important facet to these studies is that so far most of these prostate cancer risk alleles do not appear to be associated specifically with risk for aggressive disease (Kader et al, 2009; Wiklund et al, 2009). The lack of strong prognostic markers is a key shortcoming in the field that desperately needs to be resolved. Most current GWAS used case-control designs. New case-case studies comparing aggressive versus nonaggressive disease will likely be required to uncover new SNPs informative for disease aggressiveness. It is thought that the recently identified SNPs are more likely related to prostate cancer initiation rather than progression. One such study that compared SNP frequencies among patients with prostate cancer who were defined as having aggressive versus nonaggressive disease identified a region of 17p12 (TT genotype of SNP rs4054823) that was consistently higher among patients with more aggressive disease (Xu et al, 2010). The SNP in 17p12 resides in a region that does not contain any known genes; at the present time, the molecular mechanism by which it is associated with aggressive disease remains unknown. **Another approach that has had some early success in other cancers is to use gene expression array data to develop “gene signatures” able to predict aggressive behavior** (Cheville et al, 2008; Mucci et al, 2008; Setlur et al, 2008).

More recent rapid advances in next-generation sequencing technologies, allowing for whole genome sequencing and whole exome sequencing of multiple tumor samples at a time, have enabled comprehensive analyses of the complete landscape of genomic alterations (e.g., SNPs, CNAs, chromosomal rearrangements) present in human prostate cancer. One such study that conducted massively parallel sequencing of tumor and matched genomic DNA from seven patients with Gleason grade 7 or higher tumors identified a median of 3866 putative somatic base mutations (range 3192 to 5865) covering approximately 80% of the genome per tumor with a 10-fold higher mutation rate in CpG dinucleotides than in all other genomic positions (Berger et al, 2011). Of the somatic mutations identified, a median of 20 mutations per tumor that cause a change in amino acid sequence were found to occur within protein-coding genes. Specific genes found to be mutated in multiple tumors included the scaffold protein *SPTA1*; a modulator of

the transcriptional regulator DAXX called *SPOP*; chromatin modifiers *CHD1*, *CHD5*, and *HDAC9*; and members of the heat shock protein (HSP1) stress response complex *HSPA2*, *HSPA5*, and *HSP90AB1*. In addition to somatic mutations, a median of 90 chromosomal rearrangements were identified per tumor genome (range 43 to 213), all of which produced balanced translocations without genomic loss and with the generation of “chimeric” chromosomes. Additional genes found to be specifically targeted by mutation or rearrangements were the tumor suppressor *PTEN* and the *PTEN*-interacting protein *MAGI2*. In a separate study of whole exome sequencing of 112 prostate tumor and normal pairs, mutations in *SPOP* were again detected, and this was found to be the most frequently mutated gene (Barbieri et al, 2012). Barbieri and colleagues found that *SPOP* mutations occurred in the tumors that lacked ETS family gene rearrangements, possibly defining a new molecular subtype of prostate cancer. Additional recurrent mutations were identified in the forkhead transcription factor gene *FOXA1* and *MED12*, a protein involved in transcription initiation. As exome sequencing becomes increasingly more routine, attention has turned to the possibility of performing rapid high-throughput sequencing of patient samples that can inform therapeutic decisions on men with a new diagnosis of advanced prostate cancer (Roychowdhury et al, 2011).

In addition to novel gene fusions that have been identified via RNA-seq analyses, numerous novel noncoding RNA (ncRNA) species have been identified in prostate cancer samples. Much of the focus of ncRNA species in prostate cancer to date has been on microRNA (miRNA) species, which are small (approximately 22 nucleotides) molecules that function in gene silencing and may be linked to prostate cancer aggressiveness, may promote the development of castration resistance, or may serve as markers of prostate cancer stem cells (Bolton et al, 2014). Multiple novel long noncoding RNA (lncRNA) transcripts that may play a functional role in prostate carcinogenesis have also been discovered; lncRNAs are distinguished from small ncRNA species (e.g., miRNAs, small interfering RNAs, and small nucleolar RNAs) in that they are typically greater than 200 nucleotides in length. Although they do not encode for functional peptides, lncRNAs play a role in gene regulation and other cellular processes (Ulitsky and Bartel, 2013). One of the most clinically advanced biomarkers of prostate cancer, *PCA3* (also known as *DD3*), happens to be an lncRNA (Bussemakers et al, 1999). RNA-seq performed on a cohort of 102 prostate tissues and cell lines identified 106 unannotated intergenic RNAs that were differentially expressed between prostate cancer and benign prostate samples (Prensner et al, 2011). One of the top upregulated transcripts, an lncRNA called *PCAT-1*, was markedly upregulated in metastases and was found to act as a target of the Polycomb Repressive Complex 2 (PRC2). *PCAT-1* is located on chromosome 8q24—discussed previously in regard to susceptibility loci in prostate cancer—and is approximately 725 kb upstream of the *c-MYC* oncogene. Another lncRNA identified in this study, *SCHLAP1*, was found in a follow-up study to antagonize chromatin remodeling complex activity and serve as a prognostic indicator of poor prostate cancer outcome (Prensner et al, 2013).

Renal Cancer

RCCs include a spectrum of subtypes and can be subdivided into at least five different categories: clear cell RCC (ccRCC), which account for most adult cases (70% to 80%); papillary RCC, which accounts for most of the remaining adult cases (10% to 20%); chromophobe RCC; collecting duct RCC; and the MiTF/TFE family translocation carcinomas described earlier. In addition, there are more than four inherited forms of RCC. **The genes discovered to have germline mutations that cause these familial forms of the disease have been found to play important roles in sporadic RCC as well** (Coleman, 2008).

Patients with von Hippel-Lindau disease are predisposed to numerous tumor types, notably ccRCC (Coleman, 2008). The finding of consistent losses of 3p in this disease led to the identification of the *VHL* gene located at 3p25-p26; germline mutation of

this gene causes VHL disease (Zbar et al, 1987; Tory et al, 1989; Latif et al, 1993; Stolle et al, 1998). When the *VHL* gene was identified, its status was assessed in sporadic (nonfamilial) RCC, where it was found to be mutated in more than half of sporadic ccRCC cases (Gnarra et al, 1994; Shuin et al, 1994). To date, more than 300 different *VHL* mutations have been cataloged, and ccRCC cases not harboring *VHL* mutations often undergo LOH (deletion) or silencing of the gene by promoter hypermethylation. Altogether, most ccRCCs have compromised *VHL*. The *VHL* protein normally functions as part of a multiprotein complex with elonginB, elonginC, Cul-2 (cullin-2), and Rbx1 (ring box-1), which exhibits E3 ubiquitin ligase activity and targets subunits of the hypoxia-inducible factor-1 (HIF-1) transcription factor for ubiquitination and subsequent proteosomal destruction (Kibel et al, 1995; Iliopoulos et al, 1996; Pause et al, 1997; Kamura et al, 1999; Kaelin, 2002). HIF-1 functions as a master regulator of the cellular response to low oxygen levels. Under normal conditions, specific proline amino acid residues in the two HIF-1 subunits, HIF-1 alpha and HIF-1 beta, are hydroxylated by the oxygen-dependent proline hydroxylase enzymes *EGLN1-3*. This oxygen-dependent modification signals ubiquitination of HIF-1, and HIF-1 is rapidly turned over (Maxwell et al, 1999; Bruick and McKnight, 2001; Ivan et al, 2001; Jaakkola et al, 2001). Under conditions of oxygen deprivation (hypoxia), the prolyl hydroxylases fail to act, and HIF-1 is spared and accumulates, allowing its translocation to the nucleus where it activates numerous target genes, including the glucose transporter *GLUT-1*, the proangiogenic growth factors *PDGF* and *VEGF*, the chemokine *CXCL-1* and its receptor *CXCL4*, transforming growth factor- α , and the hepatocyte growth factor receptor *MET* (Wykoff et al, 2001; Igarashi et al, 2002; Hu et al, 2003; Staller et al, 2003; Linehan et al, 2007). That the HIF-1 pathway is activated in ccRCC is supported by the highly vascular nature of these tumors and the fact that expression of HIF-1 target genes is found to be elevated. In ccRCC, the loss of *VHL* function leads to a state of “pseudohypoxia,” in which the cells respond as if they are being starved for oxygen.

Several of the genes activated by HIF-1 have been singled out for therapeutic targeting, and positive results in clinical trials have led to U.S. Food and Drug Administration (FDA) approval of some of these agents (Linehan, 2002; Hansel and Rini, 2008). For example, the monoclonal anti-vascular endothelial growth factor (VEGF) antibody bevacizumab and the small molecule kinase inhibitors sunitinib and sorafenib, which inhibit both VEGF and platelet-derived growth factor, all have shown improvements in progression-free survival in clinical trials for metastatic RCC, leading in the latter two cases to FDA approval (Hansel and Rini, 2008).

The *VHL*/sporadic ccRCC example epitomizes the potential for translational application of cancer molecular genetics. Work began with studies on a familial cancer, which were translated to the sporadic form of the disease, culminating in the rational design of therapeutic agents against revealed molecular targets, having a positive impact in the clinic.

A second familial form of RCC is hereditary papillary renal carcinoma, the cause of which has been pinpointed to activation of the proto-oncogene tyrosine kinase *c-Met*, which is the cell surface receptor for hepatocyte growth factor (Jeffers et al, 1997). *MET* is located at 7q31-q34, which is notable because most sporadic papillary RCC cases show trisomy of chromosome 7 (Kovacs, 1993). In addition, activating mutations, typically affecting the tyrosine kinase domain and leading to a constitutively active receptor, have been found in sporadic cases (Schmidt et al, 1997).

A third type of hereditary RCC predisposition is Birt-Hogg-Dube (BHD) syndrome. Individuals with BHD syndrome most commonly develop chromophobe RCC, but other forms such as ccRCC, papillary RCC, and benign oncocytomas are also observed (Pavlovich et al, 2002, 2005). The *BHD* gene underlying the disease is located at 17p11.12 and codes for the protein folliculin (Schmidt et al, 2001). A spectrum of disruptive mutations and gene deletions supports a tumor suppressor gene function for folliculin (Khoo et al, 2002; Nickerson et al, 2002; Schmidt et al, 2005; Vocke et al, 2005). The precise function of this protein has not been elucidated,

although evidence indicates it affects both the ERK and Akt/mTOR signaling pathways (Baba et al, 2008).

A fourth, rare familial RCC subtype is hereditary leiomyomatosis renal cell carcinoma (HLRCC), featuring an aggressive form of papillary RCC (Kiuru and Launonen, 2004; Merino et al, 2007; Sudarshan et al, 2007). The cause of HLRCC has been traced to the Fumarate Hydratase gene at 1q42.3-q43, whose protein product acts to convert fumarate to malate in the Krebs cycle. The HIF-1 pathway is again implicated in RCC tumorigenesis because the resulting accumulation of fumarate acts as a competitive inhibitor of the prolyl hydroxylases *EGLN1-3*, preventing modification of HIF-1 subunits, prolonging their half-lives and leading to a pseudohypoxic state, as was the case for mutated *VHL*. In support of this pathogenetic scheme, increased expression of VEGF and a high microvessel density have been found in HLRCC tumors (Isaacs et al, 2005; Pollard et al, 2005).

In 2011, a germline missense substitution was discovered in microphthalmia-associated transcription factor (*MITE*, another member of the MiTF family discussed earlier in regard to MiTF/TFE family translocation carcinomas) that conferred a greater than five-fold increase in risk of developing RCC, melanoma, or both types of cancer (Bertolotto et al, 2011). The germline substitution in codon 318 (E318K) was found to impair SUMOylation of MITE, leading to transcriptional activation of genes that function in the hypoxia pathway (*HIF1A*, *CCR7*, *HMOX1*), the importance of which in RCC has already been discussed.

Bladder Cancer

Although first-degree relatives of patients with bladder cancer are at increased risk of developing the disease, high-risk families are very rare and lack clear mendelian inheritance patterns, precluding classic linkage analysis. Bladder cancer is not considered a familial disease. Instead, it has been proposed that many susceptibility genes likely exist with small to moderate effects on disease risk (Aben et al, 2006; Kiemeny, 2008). More recent attention has turned to the use of GWAS, which are better suited to the discovery of low-penetrance susceptibility loci. The first such studies have been published, and reported susceptibility loci include 8q24.21, near the *MYC* proto-oncogene; 3q28, associated with the *TP53* relative *TP63*; and 5p15.33, which is near the *HTERT* gene coding for the cancer-associated telomere maintenance enzyme telomerase (Kiemeny et al, 2008, 2009; Rafnar et al, 2009; Wang et al, 2009a). Gain of 5p15.33 had previously been identified as being associated with bladder cancer progression (Yamamoto et al, 2007), and reduced or absent *TP63* expression has been associated with disease progression and poor prognosis (Urist et al, 2002; Koga et al, 2003). An additional GWAS reported by Wu and coworkers (2009b) found a missense variant in the prostate stem cell antigen (*PSCA*) gene to be associated with bladder cancer risk in whites and was subsequently shown in a GWAS by Wang and associates (2010) to be associated with bladder cancer risk in a Chinese population. The rs2294008 variant of *PSCA* has also been shown to be significantly associated with gastric cancer in both Japan and China (Sakamoto et al, 2008; Matsuo et al, 2009; Wu et al, 2009a). This mutation is predicted to result in truncation of the first nine amino acids of the *PSCA* protein, and earlier studies reported that *PSCA* mRNA and protein levels are increased in bladder cancer compared with normal urothelium, with mRNA expression serving as an independent predictor of recurrence in superficial bladder cancer (Amara et al, 2001; Elsamman et al, 2006; Wang et al, 2010). Recent years have seen an explosion in large-scale GWAS in Europe and the United States that have now accounted for at least 11 extensively replicated urinary bladder cancer susceptibility loci: 1p13.3 (*GSTM1*), 2q37.1 (*UGT1A* cluster), 3q28 (*TP63*), 4p16.3 (*TMEM129* and *TACC3-FGFR3*), 5p15.33 (*HTERT-CLPTM1L*), 8p22 (*NAT2*), 8q24.21 (*MYC*), 8q24.3 (*PSCA*), 18q12.3 (*SLC14A1*), 19q12 (*CCNE1*), and 22q13.1 (*CBX6*, *APOBEC3A*) (García-Closas et al, 2005; Kiemeny et al, 2008; Rafnar et al, 2009; Wu et al, 2009b; Kiemeny et al, 2010; Rothman et al, 2010; García-Closas et al, 2011; Moore et al, 2011; Rafnar et al, 2011; Tang et al, 2012). Additional loci have been reported more

recently on 3q26.2 and 11p15.5 as well as two suggested regions on 20p12.2 and 6q22.3 (Figuerola et al, 2014). Pathway analysis of five GWAS conducted on bladder cancer cases and controls of European background found the genetic variants associated with bladder cancer to belong to three fundamental cellular processes: metabolic detoxification, mitosis, and clathrin-mediated vesicles (Menashe et al, 2012).

Most (75% to 85%) bladder cancer and cancer-associated lesions seen in the clinic are of superficial type (stages pTa, pTis, pT1). Recurrences after therapy are frequent, requiring diligent surveillance by urine cytology and cystoscopy resulting in frequent resections. In addition, the risk of progression is high. Accurate assessment of risk for recurrence and progression to muscle-invasive disease is critical, and current predictive schemes based on histopathologic features are suboptimal. It is hoped that information at the molecular level will help improve current methods of risk stratification.

Much work has been done to identify genetic alterations in bladder cancer. In general, observed changes fall into two groups: changes that are mostly unrelated to clinical subtype (e.g., changes in chromosome 9 and RAS mutations) and changes that are related to specific grades or stages of the disease (e.g., *FGFR3* mutations in superficial pTa disease, *TP53* and *RB1* alterations in muscle-invasive disease) (Knowles, 2008).

Greater than half of urothelial cell carcinomas of all grades show chromosome 9 alterations; these are commonly losses of the entire chromosome or entire chromosomal arms. LOH events of more restricted regions are also seen, leading to the current consensus that there are multiple tumor suppressor genes located on both chromosomal arms (Tsai et al, 1990; Cairns et al, 1993; Linnenbach et al, 1993). In otherwise near-diploid tumors, complete loss of one copy (monosomy 9) is the only karyotypic abnormality seen (Gibas et al, 1984; Fadl-Elmula et al, 2000). The region at 9p21 containing the genes for the CDKI proteins *INK4B* (p15) and *INK4A* (p16), which suppress the *RB1* pathway, as well as harboring the *TP53*-stabilizing gene *p14ARF* is a strong candidate for bladder cancer tumor suppressor gene locus. This region commonly undergoes LOH or homozygous deletion in bladder cancers, including low-grade and low-stage tumors (Devlin et al, 1994; Orlow et al, 1995; Williamson et al, 1995; Berggren et al, 2003), and mutations have been associated with high-grade disease and tumor progression (Orlow et al, 1999).

At least three different regions of loss have been mapped on 9q, and candidate bladder cancer tumor suppressor genes have been proposed including the patched gene, *PTCH*, at 9q22, which shows mutations and LOH in up to 40% of cancers (McGarvey et al, 1998; Aboulkassim et al, 2003); the region termed DBC1 at 9q32-q33, which exhibits deletion and silencing in approximately 50% of cases (Habuchi et al, 1998; Nishiyama et al, 1999); and 9q34, which exhibits LOH and contains the gene *TSC1* (tuberous sclerosis gene 1), a strong candidate bladder tumor suppressor gene owing to the finding of *TSC1* mutations in conjunction with LOH (Hornigold et al, 1999; Adachi et al, 2003; Knowles et al, 2003). The *TSC1* gene encodes the protein hamartin, which is a phosphorylation target of Akt and functions in negative regulation of mechanistic target of rapamycin (mTOR), a downstream target of the PI3 kinase pathway that is also dysregulated in bladder cancer via inactivation of the PI3 kinase antagonist *PTEN* as well as mutational activation of the p110 catalytic subunit of PI3 kinase, *PIK3CA* (Cairns et al, 1998; Aveyard et al, 1999; Wang et al, 2000).

Noninvasive (superficial, pTa) papillary urothelial cell carcinoma represents a major bladder cancer subgroup at diagnosis. Apart from changes involving chromosome 9, these tumors appear relatively stable with respect to chromosomal structural changes, with losses and gains reported for approximately 12 different chromosomal locations, most in 20% or less of cases examined (Koed et al, 2005; Knowles, 2008). More subtle genetic alterations in oncogenes and tumor suppressor genes also occur with varying frequencies. As reviewed by Knowles (2008), activating mutations in the RAS family of proto-oncogenes (H-RAS, K-RAS, and N-RAS) have been reported in 15% of cases; mutations in

PIK3CA have been reported in 16% of cases; and amplification/overexpression of *CCND1* and *HDM2* have been reported in 10% to 20% and approximately 30% of cases, respectively.

In addition to oncogene activation, inactivation of several tumor suppressor genes by either deletion or promoter hypermethylation has been reported in superficial papillary urothelial cell carcinoma. These genes include several genes on chromosome 9 such as *CDKN2A* (p16), affected in 30% to 60% of cases; *PTCH*, the *DBC1* locus; and *TSC1*, each reportedly affected in 60% of cases (Knowles, 2008).

The most frequently altered tumor suppressor gene in superficial stage Ta disease is the fibroblast growth factor receptor 3 (*FGFR3*), with mutation frequencies approaching 90% of cases reported (Cappellen et al, 1999; Billerey et al, 2001; Sibley et al, 2001; Tomlinson et al, 2007). The most common *FGFR3* mutation is a serine-to-cysteine mutation at amino acid 249, which has been shown to cause constitutive ligand-independent receptor activation secondary to induced receptor dimerization via intermolecular Cys-Cys disulfide bonding (Li et al, 2006). The frequency of *FGFR3* mutations is much lower in higher stage, invasive bladder cancers, and mutations are lacking in the superficial Tis stage (CIS) lesions, which have a high propensity for recurrence and progression to invasive disease. In addition, in stage Ta disease, there is a strong inverse correlation between mutation and tumor grade (Billerey et al, 2001). The high preferential prevalence of *FGFR3* mutations in stage Ta disease suggests an association with low-risk bladder cancer (Tomlinson et al, 2007). In this respect, it is noteworthy that *FGFR3* mutations are also associated with benign tumors of the skin (seborrheic keratoses) (Logie et al, 2005; Hafner et al, 2006). In a prospective study, Hernandez and colleagues (2006) concluded that *FGFR3* mutations are associated with a subgroup of tumors having a good prognosis, and Burger and associates (2008) reported *FGFR3* status is useful in risk stratification for patients with high-grade non-muscle-invasive urothelial cell carcinoma. Finally, there are indications that *FGFR3* mutations and RAS family mutations are mutually exclusive (Jebar et al, 2005; Logie et al, 2005; Hafner et al, 2006). These findings may be rationalized by considering that *FGFR3* itself is known to activate the RAS/RAF/MEK/ERK pathway (Choi et al, 2001). Likewise, reports of mutational exclusivity have been made regarding *FGFR3* and *TP53*, which is mutated in only about 5% of stage pTa cases and is associated with higher grade disease (Bakkar et al, 2003; Zieger et al, 2005). In stage pT1 disease, the frequency of *FGFR3* mutations is lower, and *TP53* mutation frequency is higher; in contrast to stage pTa disease, these mutations are not necessarily mutually exclusive (Bakkar et al, 2003; van Rhijn et al, 2004; Tomlinson et al, 2007).

Although the frequency of chromosome 9 alterations and RAS family mutations is comparable across all grades and stages of bladder cancer, muscle-invasive urothelial carcinomas (stage pT2 and higher) exhibit more genetic alterations (both qualitatively and quantitatively) than lower stage disease, in keeping with the general observation that more aggressive cancers tend to exhibit evidence of greater genetic instability than their less aggressive counterparts. Invasive bladder tumors exhibit a wide range of CNAs across virtually every chromosome, although the gene targets of these changes are largely unknown at the present time (Koed et al, 2005). In a similar vein, Blaveri and colleagues (2005) used cluster analysis of array CGH data to separate bladder tumors of differing stages and grades successfully from one another. In addition, a quantitative measure of the fraction of genome altered was shown to be inversely related to patient survival time in cases with muscle-invasive cancer (Blaveri et al, 2005). Ploidy, another reflection of genomic instability, has been found to be associated with progression from noninvasive to invasive bladder cancer (Holmang et al, 2001). Mutational inactivation of *TP53* is seen in greater than 40% of invasive pT2 tumors, in sharp contrast to the low mutational rate seen in pTa disease, where *TP53* mutation is associated with risk for progression (Fujimoto et al, 1992; Spruck et al, 1994; Uchida et al, 1995; George et al, 2007). Likewise, inactivation of *RB1*, either by LOH or through *INK4A* inactivation, is common in invasive bladder cancer but is infrequent in stage pTa tumors (Cairns et al, 1991;

Benedict et al, 1999; Chatterjee et al, 2004; Shariat et al, 2004). Loss of the region of 10q harboring the *PTEN* tumor suppressor gene is also more frequent in muscle-invasive bladder cancer than in lower stage pTa tumors (Cappellen et al, 1997; Kagan et al, 1998; Aveyard et al, 1999).

Genetic Alterations in Precursor Lesions to Bladder Neoplasia

Urothelial hyperplasias with flat or papillary histomorphology have been proposed to be precursors of low-grade bladder cancers, although this concept is controversial (Chow et al, 2000). In support, Hartmann and associates (1999) reported that, when present, genetic alterations (assayed at 9q21, 9q22, and 17p13) in hyperplasias were also found in superficial papillary tumors from the same patient. Genetic studies on hyperplasias have reported moderate to high frequencies of chromosome 9 alterations, whereas other genetic changes that are associated with aggressive forms of bladder cancer are reportedly infrequent (Chow et al, 2000). Dysplastic urothelial lesions have been found to have frequent changes of chromosome 9 and frequent aneuploidy, and approximately half are *TP53* mutated (Hartmann et al, 2002; Mallofre et al, 2003). The prevalence of changes seen in low-grade intraurothelial neoplasia was lower than that observed in high-grade (CIS) lesions (Hartmann et al, 2002). CIS lesions (pTis) are aggressive, high-grade precursor lesions, exhibiting high rates of recurrence and progression to invasive disease. In contrast to superficial papillary lesions, CIS exhibits frequent (50% to 70%) genetic alterations (LOH) of 4q, 8p, 11p, 13q, and 14q, in addition to several other chromosomal alterations observed at lower but still significant frequencies (Rosin et al, 1995). CIS lesions may be subdivided into primary lesions, which are isolated without associated cancer, and cancer-associated secondary lesions. It has been reported that chromosome 9 changes are infrequent in primary lesions, whereas most secondary lesions exhibit deletions on chromosome 9 (Spruck et al, 1994; Billerey et al, 2001; Hartmann et al, 2002; Hopman et al, 2002).

As expected, given their aggressive nature, *FGFR3* mutation rates are low in CIS, whereas the *TP53* pathway shows frequent alterations. *TP53* mutation occurs in more than half of CIS lesions and is correlated with strong nuclear *TP53* staining by IHC (Hartmann et al, 2002; Hopman et al, 2002). Nuclear *TP53* expression in transitional cell carcinoma has been associated with increased risk of recurrence and death, independent of tumor grade, stage, and lymph node status in patients with transitional cell carcinoma (Lipponen, 1993; Sarkis et al, 1993; Esrig et al, 1994).

Genetic Alterations in Normal and Benign Bladder Urothelium

Given the propensity of bladder cancer to recur, plus the fact that it is often multifocal, it has been proposed that there may be genetic changes in broad areas of the urothelium. Such a hypothesis would be in keeping with the “field cancerization” concept (also known as “field effect”), first put forward by Slaughter and associates in 1953 to help explain the multifocal nature and high local recurrence rates of cancers of the oral cavity as well as the finding of histologically abnormal epithelium in areas adjacent to cancer. These authors proposed that multiple cancer foci arose within a wider field of abnormal epithelium that had been preconditioned by some prior carcinogenic insult, a process they termed *field cancerization*. Genetic changes have been detected in samples of histologically normal-appearing urothelium obtained from surgical samples from patients with cancer. For example, Muto and colleagues (2000) found shared instances of LOH as well as promoter hypermethylation of the *INK4A* gene between normal-appearing areas and tumor areas from the same case. Likewise, Stoehr and coworkers (2005) performed LOH analyses on a large number of cases in which normal-appearing epithelium was isolated by laser capture microdissection. These authors also reported cancer-associated genetic changes in the

normal-appearing urothelium, which in some cases matched the changes found in concurrent cancers in the same case (Stoehr et al, 2005). However, caution is warranted when assessing such results given the possibility of contamination of the normal areas sampled by small multifocal cancer lesions or by pagetoid spread of tumor cells (Junker et al, 2003). A study by Obermann and colleagues (2004) using interphase FISH in tissue sections detected losses involving chromosome 9 in normal-appearing cells, which, from a technical standpoint, should be effective at excluding possible confounding microscopic foci of cancer cells.

Inverted papillomas of the urinary bladder are considered benign entities. In keeping with this benign status, they exhibit infrequent LOH at cancer-associated chromosomal loci as well as infrequent (<10%) mutations of *FGFR3* (Sung et al, 2006; Eiber et al, 2007). In contrast to inverted papillomas, papillary urothelial neoplasia of low malignant potential exhibits high rates (85%) of *FGFR3* mutation (van Rhijn et al, 2002)—a genetic alteration that, as described earlier, is strongly associated with bladder tumors of low stage and low grade. However, a study by Cheng and associates (2004) found frequent LOH at several loci that typically undergo LOH in advanced stages (pT2 or higher).

Molecular Genetics–Based Assays for Bladder Cancer Detection and Surveillance

The large amount of data concerning common genetic alterations in bladder cancer has been exploited to aid in detecting the presence of bladder cancer. One widely used test termed UroVysion (Abbott Molecular/Vysis, Abbott Laboratories, Abbott Park, IL) is a multiplex, multicolor FISH-based assay that features a cocktail of four hybridization probes that assess the status of four chromosomes (Bubendorf et al, 2001; Halling, 2003). Probes specific for the centromeres of chromosomes 3, 7, and 17 provide information on cancer-associated gains of these chromosomes; the fourth probe is specific for 9p21, which harbors the p14 and p16 genes that are often deleted in bladder cancers. This test, approved by the FDA in 2005, is used in conjunction with standard urine cytology in diagnosing suspected cases and monitoring for local recurrence in patients with previous diagnosis and treatment (Halling et al, 2000; Hajdinjak, 2008). In addition, the test may have utility in monitoring response in patients with superficial bladder cancer treated with intravesical bacillus Calmette-Guérin therapy (Kipp et al, 2005) and may be useful in distinguishing inverted papillomas from urothelial carcinoma with inverted growth pattern (Jones et al, 2007).

At the present time, there are six FDA-approved urine-based molecular tests for bladder cancer focused on either genetic or immunochemical targets, and many other potential markers are under development (van Rhijn et al, 2005; Herman et al, 2008; Zwarthoff, 2008; Sullivan et al, 2009). However, although these tests improve on standard urine cytology, they do not supplant it. Finally, Wang and colleagues (2009b) reported the development of a quantitative PCR gene signature for predicting progression in cases of non–muscle-invasive bladder cancer.

Testicular Cancer

TGCTs possess many unique features (Oosterhuis and Looijenga, 2005). These cancers appear to originate from totipotent stem cells, with evidence strongly supporting TGCT initiation in utero, whereby abnormal primordial germ cells (PGCs) or gonocytes are blocked in their differentiation, remaining dormant until puberty. This theory is supported by expression in TGCT of markers closely associated with PGCs, including placental alkaline phosphatase (PLAP), the stem cell factor tyrosine kinase receptor KIT (c-kit), and the transcription factors POU5F1 (Oct3/4) and NANOG that are involved in maintenance of pluripotency or “stemness.” The presumptive common precursors to TGCT are the intratubular germ cell neoplasia unclassified (ITGCNU), which closely resemble PGCs, sharing many of the same markers (PLAP, KIT, POU5F1) (Skakkebaek et al, 1987). ITGCNU, also traditionally referred to as

CIS, although this nomenclature is technically inaccurate, have a very high rate of progression to invasive disease, estimated to be essentially 100% if allowed sufficient time (Linke et al, 2005).

TGCTs are classified into two main categories: seminomas and nonseminomas. A third type, so-called spermatocytic seminomas, are extremely rare and are not discussed here (Ulbricht, 1993). Similar to the TGCT precursor ITGCNU, seminomas closely resemble PGCs/gonocytes, both morphologically and in their expression of molecular markers (positive expression of PLAP, KIT, POU5F1, NANOG, STELLAR, SOX17) (Sperger et al, 2003; de Jong et al, 2008). Nonseminomatous TGCTs resemble embryonic and extraembryonic tissues that have undergone varying extents of differentiation. Nonseminomas include four subtypes. Embryonal carcinomas are similar in many respects to embryonic stem cells, or perhaps primitive ectoderm, and express POU5F1, NANOG, and STELLAR as well as SOX2 (Gopalan et al, 2009a). Extraembryonic differentiation is apparent in yolk sac tumors and choriocarcinomas, whereas somatic tissue differentiation is found in teratomas.

Besides their unique pathogenesis, TGCTs are unique in their responsiveness to treatment modalities that induce DNA damage (e.g., ionizing radiation and cisplatin-based chemotherapy). Most patients are currently curable, including patients with advanced disseminated disease (Einhorn, 2002). This extreme sensitivity to DNA damage is thought to be related to the origins of TGCTs; their normal stem cell counterparts are poised to undergo apoptosis in response to DNA damage, and most TGCTs maintain wild-type *TP53* and apparently intact *DDR* (Kersemakers et al, 2002; Gorgoulis et al, 2005; Bartkova et al, 2007). Responsiveness to therapy in TGCT is inverse to responses seen in most other cancers—that is, sensitivity decreases with increasing differentiation state, such that ITGCNU are eliminated with low-dose radiation, whereas teratomas exhibit resistance to radiation and chemotherapy.

Family history is a strong risk factor for the development of TGCT, stronger than that found in most other cancers (Forman et al, 1992; Westergaard et al, 1996; Czene et al, 2002; Mai et al, 2010). Despite this fact, initial reports of an association between specific losses on Yq and risk were not confirmed later (Krausz and Looijenga, 2008). Genetic polymorphisms in CAG tract length, which codes for polyglutamine repeats in the androgen receptor, were assessed but were not found to be associated with disease risk (Rajpert-De Meyts et al, 2002; Giwercman et al, 2004; Garolla et al, 2005). Linkage analyses and more recent GWAS have not revealed evidence for major TGCT-related genetic loci, implying instead the existence of multiple loci having modest influence (Lutke Holzik et al, 2005; Crockford et al, 2006; Rapley, 2007). However, in two GWAS, Kanetsky and colleagues (2009) and Rapley and associates (2009) reported that common genetic variants at 5q31.3 near sprouty 4 (*SPRY4*, an inhibitor of the mitogen-activated protein kinase signaling pathway) and in the *KITLG* gene region (c-KIT ligand, also known as stem cell factor or steel factor) on 12q22 are significantly associated with TGCT risk, including both seminomas and nonseminomas. Rapley and associates (2009) additionally identified a susceptibility locus on chromosome 6 in an intron of *BAK1*, a gene that promotes apoptosis.

Spontaneous (as opposed to inherited) genetic alterations have been cataloged in TGCTs. Apart from aneuploidy, relatively few genetic changes or gene mutations are found in TGCTs, giving an overall picture of a relatively low level of genetic instability, which may be due largely to the aforementioned intact *DDR* and predominantly wild-type *TP53* status in these cancers (Bignell et al, 2006; Greenman et al, 2007). One recurrent, nearly universal genetic alteration in TGCTs (excluding the rare spermatocytic seminomas) is the previously described gain of 12p, which may involve the *KRAS* gene or genes such as *NANOG* and *STELLAR* located in the stem cell cluster region at 12p13.31. Additional evidence for *KRAS* involvement in TGCTs includes reports of activating mutations in 40% of cases as well as increases in expression in concert with increased gene copy number. *BRAF* mutations have also been identified in TGCTs but are seen to be mutually exclusive to K-Ras overexpression (McIntyre et al, 2005b; Sommerer et al, 2005).

Other changes that have been reported in sporadic TGCTs include gains of material on chromosomes 1, 5, 7, and X and losses on chromosome 18 in both ITGCNU and invasive cancer. Also, losses from chromosomes 4 and 13 plus gain of chromosome 2p are more restricted to invasive cancers (Summersgill et al, 2001).

In seminomas, recurrent gains of 4q12, 16p13, and Xq22 plus losses of 3q29, 11q12.1, and 14q13.2 have been reported (Goddard et al, 2007). The *KIT* gene, whose protein product is a receptor tyrosine kinase also known as CD117, is located at 4q12. *KIT* amplifications have been reported in 24% of seminomas, and gene-specific amplifications have been reported in 17%, but these changes were lacking in nonseminomas and ITGCNU (McIntyre et al, 2005a). Also, mutations in c-kit represent the most common somatic mutations found in seminomas (25% of cases) but are rarely found in nonseminomas (Forbes et al, 2006; Coffey et al, 2008). Despite the apparent lack of c-kit gene amplifications in ITGCNU, activating mutations in *KIT* have been reported, and IHC staining is positive for this entity as well as seminomas, although positive staining is not seen in nonseminomas or spermatocytic seminomas (Tian et al, 1999; Przygodzki et al, 2002; Looijenga et al, 2003; Kemmer et al, 2004; Goddard et al, 2007).

Gains of 17q11.2-q21 have been reported in TGCTs, and this region contains the *ERBB2* receptor tyrosine kinase gene as well as the *GRB7* adapter protein gene. *ERBB2* ties into the RAS pathway, whereas *GRB7* binds to and likely regulates KIT, *ERBB2*, and RAS and is reportedly overexpressed in TGCTs and ITGCNU precursor (Kraggerud et al, 2002; Skotheim et al, 2003).

The above-described results create an emerging picture of derangement of growth-stimulatory protein kinase signaling pathways in TGCT, including activations in the RAS and KIT pathways in most seminomas and nonseminomas (Kemmer et al, 2004; Sommerer et al, 2005). In keeping with the fact that both RAS and KIT activate the PI3 kinase/AKT pathway, activated Akt has also been observed (Kemmer et al, 2004). In addition, the PI3 kinase antagonist PTEN is reported to be frequently inactivated by either mutation or deletion in both seminomas and nonseminomas, further suggesting an important role for activated PI3 kinase/AKT pathway in TGCTs (Di Vizio et al, 2005; Teng et al, 1997).

Normal PGCs undergo programmed erasure of DNA CpG methylation marks and a loss of imprinting. IHC studies using an anti-5-methylcytosine antibody to assess global methylation status in situ confirmed and extended prior reports focusing on specific loci. The newer studies found very low to absent 5-methylcytosine in most ITGCNU and seminomas compared with robust detection of 5-methylcytosine in nonseminomas (Peltomaki, 1991; Smiraglia et al, 2002; Zhang et al, 2005; Netto et al, 2008). These results are supportive of a model for TGCT pathogenesis in which ITGCNU is derived from retained abnormal PGCs that have matured to the point of 5-methylcytosine erasure but before the point in normal PGC development where epigenetic marks are reestablished via de novo DNA methylation. Such observed changes in global methylation do not rule out the existence of hypermethylation at specific gene promoters. For instance, epigenetic silencing of specific genes, such as the tumor suppressor *RASSF1A*, has been reported in seminoma (Koul et al, 2002; Honorio et al, 2003).

TELOMERES AND TELOMERASE

As we have seen, cancer cells exhibit marked genetic, morphologic, and behavioral heterogeneity, a reflection of their underlying genetic complexity and instability. In addition, most cancers display a strong positive association with increasing age. As discussed previously, it has been persuasively argued that an increase over the extremely low baseline mutation rate (a mutator phenotype) is needed for accrual of sufficient mutations to bring about malignant transformation (Loeb, 1991).

Cancer genomes exhibit clear evidence of genetic instability; however, defective DNA maintenance and repair genes do not appear to be major contributors to the development of most sporadic cancers. The source of the genetic instability involved in most

KEY POINTS: GENOMIC ALTERATIONS

- Large variations in chromosome numbers and complex structural rearrangements as well as intratumoral variation in these aberrations are hallmarks of most human solid tumors.
- The extent of chromosomal abnormalities typically correlates with disease severity and aggressiveness.
- Recurrent structural rearrangements occur in prostate (*ETS* gene fusions), renal (MiTF/TFE family translocation carcinomas), and testicular cancers (isochromosome 12p).
- CNAs in a particular gene, coupled with changes in the other allele, are evidence for that gene functioning as a disease-relevant oncogene or tumor suppressor gene.
- Genes discovered to have germline mutations that cause familial forms of cancer may also be involved in the sporadic form of the disease (e.g., *VHL* in ccRCC).
- High-density SNP microarrays have been used in GWAS to identify DNA sequence variants associated with cancer risk.

cancers has been unclear; this has been particularly true of chromosomal instability, a nearly ubiquitous feature of carcinomas. Although alterations in chromosome number may arise via defects in centrosomes or the mitotic spindle checkpoint, little information exists regarding the origins of structural chromosomal abnormalities (Pihan et al, 2003; Roh et al, 2003). An attractive candidate for the source of chromosomal instability in cancer is telomere dysfunction. Telomeres may provide a common link between genetic instability, cellular proliferation, and aging (Shay, 1997; DePinho, 2000).

Telomeres and Chromosomal Instability

Telomeres are structures composed of specialized repetitive DNA complexed with telomere-specific binding proteins, located at the ends of every human chromosome where they function to stabilize and protect the ends (Blackburn, 1991). Telomeric DNA is noncoding and consists of tandem repeats of the 6-base pair sequence TTAGGG (Moyzis et al, 1988; Meyne et al, 1989). In normal human cells, telomere lengths typically range from 6 to 12 kb per chromosome. Telomeres that are too short are dysfunctional (“uncapped”), causing chromosomal destabilization (Karseder, 2003; Saldanha et al, 2003).

Telomeres are dynamic and shorten by approximately 100 base pairs each time a cell divides because of inability of DNA polymerases to replicate terminal DNA sequences completely (Harley et al, 1990; Lindsey et al, 1991). Telomere length is inversely correlated with the number of times a cell has divided (Hastie et al, 1990; Levy et al, 1992). Telomere shortening may also occur as a result of unrepaired single-strand breaks caused by oxidative damage to telomeric DNA (Kruk et al, 1995; von Zglinicki et al, 2000). Conversely, telomeres may be elongated through the action of the telomere synthetic enzyme telomerase or, uncommonly, via a telomerase-independent genetic recombination mechanism termed *alternative lengthening of telomeres* (ALT) (Greider and Blackburn, 1985; Reddel et al, 2001; Heaphy et al, 2011).

Chromosomes with short, dysfunctional telomeres are prone to fusion, leading to the formation of dicentric chromosomes that mis-segregate or break in mitosis during anaphase. The newly generated chromosomal breaks are themselves fusogenic, perpetuating a cycle of chromosome fusion and breakage (McClintock, 1941; Lo et al, 2002). In this way, critically short telomeres initiate chromosomal instability (Artandi and DePinho, 2000; Feldser et al, 2003; Vukovic et al, 2007). Numerous studies support the link between telomere dysfunction and chromosomal instability in human cancers. For example, in head and neck tumors, chromosomes bearing severely short telomeres are associated with chromosomal fusions, rearrangements, anaphase bridges, and multipolar mitoses (Gisselsson et al, 2000).

Telomere Shortening Acts as a Tumor Suppressive Mechanism in Normal Cells

Normal cells closely monitor their telomere lengths. Moderate telomere shortening either signals entry into an irreversible cell cycle arrest termed *replicative senescence* or initiates programmed cell death—responses thought to have evolved as tumor suppressive barriers against abnormal clonal expansion and the development of excessive telomere shortening that would accompany further cell division were it to be allowed to continue (Wright and Shay, 2001). **Progressive telomere shortening acts as a “mitotic clock” counting down cell divisions and signaling cell cycle exit when one or more telomeres reach a threshold length** (Harley et al, 1990).

Forced expression of the enzyme telomerase in presenescent cells counteracts telomere shortening, preventing replicative senescence and endowing the cells with unlimited cell division potential or “immortalization” (Bodnar et al, 1998; Vaziri and Benchimol, 1998). In normal somatic human cells, telomerase activity is stringently repressed, and telomere length will decrease in proliferating cells and can be used as a signal to halt further expansion. **Although the precise mechanisms by which short telomeres trigger senescence and apoptosis are still under study, evidence implicates the tumor suppressors TP53 and RB1 as being involved in the response to shortened telomeres** (Vaziri and Benchimol, 1999). Abrogation of this telomere length checkpoint allows continued cell division and, in the absence of telomerase, severe telomere shortening beyond the minimum length required for proper telomere function, causing telomere uncapping and chromosomal destabilization (Counter et al, 1992).

Telomere shortening presents two important barriers to incipient cancer cells. First, moderate shortening instigates the senescence cell cycle exit or apoptosis. Second, extreme telomere shortening causes chromosomal instability that, although it increases the mutation rate, also tends to result in genetic abnormalities lethal to the cell (Fig. 19-13).

Cancers and Premalignant Lesions Possess Abnormally Short Telomeres

Most human cancer tissues and cancer-derived cell lines examined to date have been found to contain abnormally short telomeres (Hastie et al, 1990; Mehle et al, 1996; Takagi et al, 1999; Furugori et al, 2000; Remes et al, 2000). For example, using a Southern blot technique for bulk telomere length assessment in radical prostatectomy specimens, Sommerfeld and colleagues (1996) and Koenen and colleagues (1998) observed substantial telomere shortening in primary prostate cancer tissues compared with matched adjacent normal-appearing and benign proliferative (benign prostatic hyperplasia) areas. Likewise, results from direct telomere length assessment in archival tissue samples using telomere-specific FISH revealed significantly shorter telomeres in prostate cancer cells compared with their normal epithelial cell counterparts within the same tissue samples (Meeker et al, 2002a).

When examined using high-resolution telomere-specific FISH, premalignant lesions, including lesions of bladder and prostate cancer, tend to have abnormally short telomeres (van Heek et al, 2002; Meeker and Argani, 2004; Meeker et al, 2004; Hansel et al, 2006; Kawai et al, 2007). This finding indicates that telomere loss occurs early in the disease process, at the intraepithelial neoplasia stage, strongly implying a causal role for telomere shortening in carcinogenesis through the initiation of chromosomal instability (O’Shaughnessy et al, 2002). In the prostate, the premalignant precursor is high-grade PIN (Bostwick and Cheng, 2012), most of which (93%) is found to harbor abnormally short telomeres by FISH (Meeker et al, 2002b). In this study, telomere shortening in high-grade PIN foci was restricted to the luminal secretory epithelial cells only, whereas the underlying basal epithelial cells and surrounding stromal cells displayed normal telomere lengths. In a separate study, Vukovic and coworkers (2003) reported significant telomere shortening in 63% of high-grade PIN lesions, with a

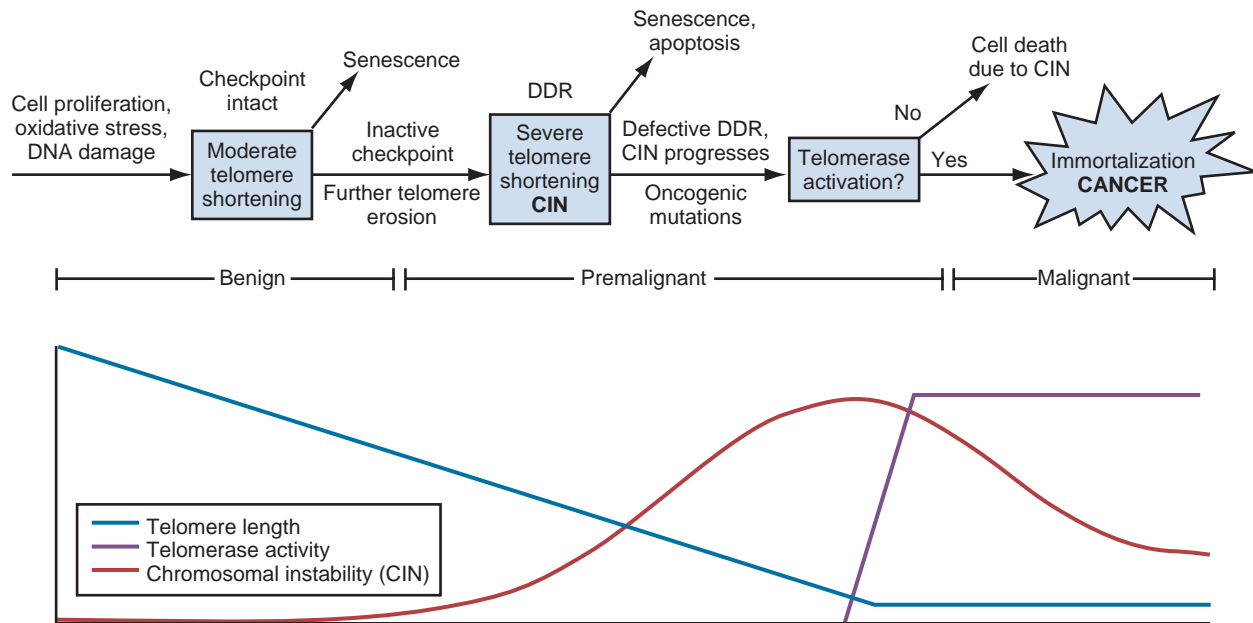


Figure 19-13. Contributions of telomere loss and telomerase activation to oncogenesis. Bypass of the normal telomere length–sensitive cell senescence checkpoint allows severe telomere loss, which initiates chromosomal instability (CIN). Defective DNA damage response (DDR) allows CIN to continue, generating potentially oncogenic mutations but also producing intolerable levels of genomic damage. Transformed cells may proceed through this second barrier by activating telomerase, which stabilizes the telomeres and provides an unlimited proliferative potential (“immortalization”).

higher rate of telomere shortening (80%) reported for foci situated near (within 2 mm) adenocarcinoma within the same tissue sample. Studying a cohort of men with a diagnosis exclusively of high-grade PIN in prostate needle biopsy specimens, Joshua and associates (2007) reported an association between short telomeres in the PIN lesions or surrounding stromal cells and eventual diagnosis of prostate cancer as well as time to diagnosis.

Because most PIN lesions are not thought to progress to invasive cancers, intact telomere-based replicative senescence or apoptosis checkpoints may represent a critical bottleneck restraining the outgrowth of most PIN lesions. Even if incipient cancer cells manage to abrogate these checkpoints, as described subsequently, they would still need to activate telomerase to avoid intolerable levels of genetic instability and provide an immortalized phenotype.

Telomerase Activity Restabilizes Chromosomes and Allows Unlimited Cellular Replication

Although dysfunctional telomeres may help initiate cancer formation, if left unchecked, continued telomere shortening in premalignant lesions and cancers would cause increasing levels of genetic instability ultimately becoming lethal to the tumor. Cancer cells overcome this problem by restabilizing their telomeres, primarily through activation of the enzyme telomerase, a specialized reverse transcriptase that adds back telomere DNA repeats to chromosome ends (Greider and Blackburn, 1987). Telomerase provides at least two critical functions to the tumor cell—quelling chromosomal instability and supplying the capacity for unlimited replication (“immortalization”) (Shay and Wright, 1996; Greider, 1998). Research has revealed that maintenance of telomere length appears to be a necessary step for human cells to become malignant, confirming the long-held belief that cellular immortalization is a key attribute of cancer cells (Hahn et al, 1999; Elenbaas et al, 2001). Although telomerase activity appears to be

the preferred way cancer cells stabilize their telomeres, 10% to 15% of cancer cases in human patients lack detectable telomerase activity. At least a subset of these, particularly certain central nervous system tumors and some cancers of mesenchymal origin, maintain their telomeres via a telomerase-independent genetic recombination pathway known as ALT (Reddel, 2003; Heaphy et al, 2011). With the exceptions of nonseminomatous TGCTs (15%), chromophobe RCC (9%), and small cell carcinoma of the bladder (23%), ALT is rarely if ever observed in common GU malignancies (Heaphy et al, 2011). However, almost all tissue samples assayed for ALT so far have been from primary tumors. Despite a lack of ALT in more than 1000 primary prostate cancers examined, ALT was found in all distant metastases assayed in a single patient with lethal prostate cancer. In this case, detailed genomic analysis indicated that ALT was acquired during the transition from local to disseminated growth, raising the possibility that ALT may play a role in advanced disease (Haffner et al, 2013).

Several studies have reported on telomerase activity in clinical prostate samples with positivity ranging from 47% to 100%, whereas normal and benign prostatic hyperplasia tissues taken from prostates without evidence of cancer are typically negative for telomerase activity (Kim et al, 1994; Sommerfeld et al, 1996; Engelhardt et al, 1997; Kallakury et al, 1997; Lin et al, 1997; Koeneman et al, 1998; Zhang et al, 1998; Wullich et al, 1999; Caldarera et al, 2000; Kamradt et al, 2003). Although two of these studies found a positive correlation between either the presence or the level of telomerase activity and tumor grade, four other studies found no correlation with grade, stage, or preoperative PSA levels. However, the number of cases in many of these studies was small.

Telomerase Activity as a Potential Diagnostic Marker

The high prevalence and relatively strong activity found in prostate cancers compared with normal tissue, plus the very high sensitivity of the standard telomerase activity assay, led to evaluation of the

telomerase activity assay as a potential diagnostic marker for cancer. However, the potential utility of aiding cancer diagnosis appears limited primarily because of problems with both false-negative and false-positive results seen with the technically demanding telomerase activity assay. False-negative results may occur because of inactivation of the labile enzyme during isolation, whereas false-positive results may stem from the presence of inflammatory cells in the sample (Meeker and Coffey, 1997). In addition, other molecular cancer biomarkers often outperform telomerase. For example, the detection of telomerase components by reverse transcriptase PCR in urine provides some improvement in the sensitivity and specificity over urine cytology in bladder cancer detection, particularly in low-grade disease (Eissa et al, 2007). However, a review of the literature on urinary molecular markers for bladder cancer detection concluded that other markers (e.g., microsatellites, FISH, and cytokeratin 20) outperform telomerase (van Rhijn et al, 2005).

Wu and colleagues (2003) found that shorter telomeres in peripheral blood leukocytes (PBLs), as measured with telomere-specific quantitative PCR, were associated with increased risk for many cancers, including bladder and renal cancer. Similar associations between short telomeres and bladder cancer risk were observed when comparing telomere lengths measured in buccal cells and PBLs (Broberg et al, 2005; McGrath et al, 2007). In contrast, no association was observed between PBL telomere length and prostate cancer risk in a study by Mirabello and coworkers (2009). The variations in the PBL telomere lengths measured in these studies are thought to be due to inherited interindividual differences in telomere lengths modified by changes occurring postnatally, perhaps as a result of diet and lifestyle factors.

Potential Prognostic Value of Telomere Length in Prostate Cancer

Telomere shortening has been found to be predictive of poor prognosis in several cancers, including cancers of the lung, endometrium, and breast and neuroblastoma (Smith and Yeh, 1992; Hiyama et al, 1995a; Hiyama et al, 1995b; Griffith et al, 1999; Bisoffi et al, 2006). A potential link between telomere length and prostate cancer prognosis was first reported by Donaldson and associates (1999). In this retrospective case-control study, both biochemical recurrence and overall survival were significantly correlated with tumor telomere content, a surrogate for telomere length. Specifically, all seven patients who underwent prostatectomy whose tumor telomeric DNA contents were less than that of control samples (placental DNA) showed evidence of biochemical recurrence (elevated PSA) within 10 years after surgery (Donaldson et al, 1999). Of the nine patients in this study with short tumor telomeres, seven died within 10 years, in contrast to 100% 10-year survival for patients with normal-to-long tumor telomeres. Additionally, these patients showed no evidence of biochemical recurrence. Potential drawbacks of this study include a small sample size (18 patients; only 7 of 9 men in the short telomere category underwent surgery) and the fact that it was unknown whether the deaths observed were due specifically to prostate cancer. In a more recent retrospective study using 77 prostatectomy samples and a more sensitive chemiluminescent slot blot assay, (Fordyce et al, 2002), it was reported that less-than-normal telomere content in primary prostate cancers was associated with recurrence, independent of patient age, grade (Gleason sum), and regional lymph node status (Fordyce et al, 2005). The magnitude of the relative hazard for disease recurrence associated with low telomere content (relative hazard = 5.02) was on par with that of Gleason grade and nodal status. A positive correlation was found between telomere content of the tumor and telomere content of the surrounding normal-appearing prostate tissue within the same prostatectomy samples. An association was also found between telomere content of these normal-appearing prostate tissues and 72-month recurrence-free survival. The authors postulated that telomere loss in morphologically normal tissue represents areas at heightened risk of experiencing genetic instability; this is reminiscent of the so-called field effect

phenomenon that has long been discussed in the cancer literature (Crissman et al, 1993; Bostwick et al, 1998; Foster et al, 2000; Yu et al, 2004). Fordyce and colleagues (2005) further proposed that cancers arising in such areas may show greater genotypic and phenotypic heterogeneity and be more prone to behave aggressively because of a greater level of chromosomal instability caused by short telomeres. Finally, in a more recent prospective population-based study of prostate cancer using telomere-specific FISH, short telomeres in tumor-associated stroma cells and greater cell-to-cell variability in telomere length among cancer cells were associated with higher risk of death from prostate cancer (Heaphy et al, 2013). These associations were found to be largely independent of other traditional poor prognostic indicators, and the risk associations were essentially additive, such that men with the shortest stromal telomeres and most variable cancer telomeres had a 14-fold increased risk of dying from cancer compared with men with the longest stromal telomeres and the least variable cancer cell telomeres (Heaphy et al, 2013).

Telomerase-Based Opportunities for Therapy

Given that most human tumors rely on telomerase for immortalization and genomic stabilization, this enzyme is an attractive target for anticancer therapy. There are two overall strategic paradigms for therapeutic targeting of telomerase in cancer. The first involves taking advantage of the tumor's dependence on telomerase enzymatic activity for survival. This strategy includes approaches aimed at directly inhibiting telomerase enzymatic activity or blocking its expression. The second approach attempts to exploit the fact that the telomerase gene (*HTERT*) promoter is selectively active in cancer cells, for example, by using the telomerase promoter to drive oncolytic virus or gene therapy vectors to limit their replication or expression to tumor cells or by directing immunotherapy against cells expressing hTERT protein.

Many of these approaches have undergone preclinical testing using prostate cancer cell lines and xenografts, and some are currently in early clinical trials. One point of concern with antitelomerase therapies has to do with the question of selectivity of action against tumor cells over normal telomerase-positive cells, such as the stem cells of the hematopoietic system and cells within tissues with high turnover rates. This question is of particular importance for approaches in which telomerase-positive cells are actively targeted for destruction, including immunotherapy, gene therapy, and oncolytic viral therapies. Work to date describing the treatment of human tumor xenografts in mice in general has not produced major toxicity in normal tissues.

KEY POINTS: TELOMERES AND TELOMERASE

- Telomeres contain stretches of terminal, noncoding, repetitive DNA that cap the ends of each chromosome, stabilizing them.
- Telomere DNA repeats are progressively lost as cells divide and as a result of oxidative DNA damage at the telomeres.
- Normal cells monitor their telomere lengths and permanently exit the cell cycle (cellular senescence) or commit suicide (apoptosis) in tumor suppressive responses to telomere shortening. This telomere length checkpoint involves *TP53* and *RB1*.
- Loss of telomere length checkpoints leads to critical telomere shortening, which initiates chromosomal instability contributing to cancer initiation.
- Most cancers and premalignant lesions have abnormally short telomeres.
- Most cancers express the enzyme telomerase, which restabilizes the telomeres and allows unlimited cell division potential (immortalization), making telomerase an attractive therapeutic target.

APOPTOSIS

Apoptosis, also known as programmed cell death, is a tightly regulated process used by multicellular organisms to eliminate unwanted cells. Apoptosis is used in tissue remodeling during development and in the immune system to eliminate self-reactive T cells (Kerr et al, 1972; Ashkenazi and Dixit, 1998). Apoptosis contrasts sharply with necrosis, a nonprogrammed form of cell death in which cells that are acutely injured (e.g., by physical trauma) swell and burst, abruptly releasing their contents, which act as potent inducers of the inflammatory response. Apoptosis is a more orderly, energy-requiring process in which the contents of the dying cell are degraded and neatly packaged into so-called apoptotic bodies, which are engulfed by neighboring cells or macrophages—a process that does not elicit a strong inflammatory response (Fadok et al, 1992).

Apoptosis and Cancer

In contrast to unicellular organisms, cancer poses a risk to multicellular life forms, and various potentially tumorigenic abnormalities can signal a cell to eliminate itself as a potential threat via apoptosis. For example, if a cell sustains DNA damage (potentially mutagenic) but fails to make repairs, it will be eliminated and replaced from the organism's pool of undamaged cells. Aberrations of apoptosis can be detrimental, and failure of dividing cells to initiate apoptosis contributes to cancer (Ashkenazi and Dixit, 1998).

Abnormalities in the apoptotic machinery have implications for malignancy beyond the ability of an individual cell to respond appropriately to cell physiologic stresses such as DNA damage. First, the apoptosis cascade is critical to the immune system's ability to eliminate cancer cells by inducing them to undergo apoptosis (Nagata, 1997); this has clear implications for both the organism's intrinsic immunosurveillance for malignancy and the tumor's response to extrinsic immunotherapy. Second, because cytotoxic cancer therapies also depend in large part on inducing apoptosis, defects in the apoptosis cascade can profoundly influence tumor responses to chemotherapy and radiotherapy (Walton et al, 1993; Minn et al, 1995; Thornberry and Lazebnik, 1998).

Apoptosis Is an Evolutionarily Conserved Process

Apoptosis is tightly regulated by an evolutionarily conserved system of positive and negative signals, the balance of which determines whether the cell will undergo apoptosis. These signals ultimately converge on an important family of proteases named *caspases* ("cysteine proteases with aspartic acid specificity"), key components of the apoptotic machinery (Thornberry, 1998). Caspases, of which there are at least 13, are broadly categorized as either initiator caspases (e.g., caspase-8, caspase-9, and caspase-10) or executioner caspases (e.g., caspase-3, caspase-6, and caspase-7). Caspases are synthesized as larger, inactive forms called procaspases, which require specific proteolytic cleavage to become active proteases themselves. Often a procaspase is activated by another caspase, setting in motion a sequential, amplifying, proteolytic cascade. Initiator caspases begin the cascade, which ultimately leads to activation of executioner caspases downstream. Once activated, the executioner caspases attack several intracellular protein targets. Executioner caspases cleave antiapoptotic proteins, such as Bcl-2 and Bcl-X_L, which not only destroys their antiapoptotic function but releases pro-apoptotic carboxyl-terminal fragments, further stimulating cell death (Wolf and Green, 1999). Executioner caspases target proteins critical to cell survival. Cleavage of DNA repair and replication proteins, such as DNA-PK ζ and replication factor C, leads to nuclear dysregulation. Nuclear structural proteins, such as lamins NuMa and SAF-A, are fragmented, contributing to dissolution of the nucleus and nuclear condensation, a hallmark of cells undergoing apoptosis. Proteolysis of cytoskeletal proteins such as keratin and actin leads to destruction of the internal structural integrity of the cell. Lastly, cleavage of proteins critical to cell-cell interaction, such as

beta-catenin and focal adhesion kinase, precipitates the specific and irreversible phenotypic changes associated with apoptosis (Orth et al, 1996; Wen et al, 1997; Wolf and Green, 1999). The end result is a stereotypic death in which the cytoplasm shrinks, the cell membrane blebs, and the nuclear chromatin condenses. The entire apoptotic process can be completed in 60 minutes (Thornberry and Lazebnik, 1998).

Additional details of the intrinsic and extrinsic apoptotic pathways can be found on the Expert Consult website.

Role of TP53 in Apoptosis

In addition to the key roles played by TP53 in cell cycle arrest and DNA damage repair, TP53 can also induce apoptosis (May and May, 1999). TP53-induced apoptosis is mediated through the Bcl-2 family, via the intrinsic pathway, and dysregulation of this apoptotic pathway has direct relevance to the etiology of cancer. TP53-induced apoptosis is mediated by transcriptional activation of genes that initiate the apoptotic cascade and inhibition of genes that block the cascade (Miyashita et al, 1994; Miyashita and Reed, 1995; Oda et al, 2000). TP53-induced apoptosis is dependent on the Apaf-1/caspase-9 activation pathway (Soengas et al, 1999). Although the Bcl-2 family member Bax has been implicated as the primary factor responsible for TP53 induction of this cascade (Miyashita and Reed, 1995), Bax is not essential for TP53-dependent apoptosis (Knudson et al, 1995). It is possible that inhibition of Bcl-2 (Miyashita et al, 1994) or upregulation of the pro-apoptotic Bcl-2 family member noxa may still allow cells lacking Bax to undergo TP53-dependent apoptosis (Oda et al, 2000). Considering the role of TP53 in multiple tumor suppressive pathways (DNA damage response, cellular senescence, and apoptosis), it is not surprising that it is so frequently mutated in cancer.

Apoptosis and Genitourinary Malignancies

Because the inability of a tumor cell to undergo apoptosis is a hallmark of malignancy, multiple groups have attempted to characterize the apoptotic response of GU malignancies. Because cells undergoing apoptosis exhibit a stereotypic death, global analysis of apoptosis is possible using assays designed to detect key hallmarks of the apoptotic process, such as the fragmentation of DNA characteristic of the process as well as assays designed to detect abnormalities in specific apoptotic proteins.

Global Defects in Apoptosis

Both high-grade PIN and prostate carcinoma have significantly higher levels of apoptosis than normal prostatic epithelium. The level of apoptotic activity is relatively low compared with other malignancies and is opposed by increased replication. Many prostate cancer cells can be induced to undergo apoptosis in response to androgen withdrawal, which represents a frontline therapy for patients with advanced disease (Kyprianou et al, 1990; Isaacs, 1994; Denmeade and Isaacs, 1996; Tu et al, 1996). However, not all of a patient's cancer cells succumb because recurrences inevitably arise. As the tumor progresses to androgen independence, it is unclear if the androgen-resistant cells have an increased or decreased rate of apoptosis because studies have demonstrated both in hormone-refractory disease (Berges et al, 1995; Koivisto et al, 1997). The conflicting data may reflect both the tumor's dynamics and the effect of therapy. There is a clear survival advantage for the advanced cancer cell that can protect itself from apoptosis. However, a rapidly growing, infiltrative, advanced tumor, which is outgrowing its blood supply and mutating its DNA, may have a high apoptotic rate despite protective mechanisms the tumor's cells have acquired.

Studies of apoptosis in bladder carcinoma have demonstrated an association with aggressive high-grade advanced disease but not with decreased disease-free survival (Lipponen and Aaltomaa, 1994; King et al, 1996). External-beam radiation therapy has been associated with a modest improvement in survival for tumors with high

Intrinsic Apoptotic Pathway

Apoptosis can be initiated via two different routes—the intrinsic and the extrinsic apoptotic pathways (Fig. 19-14). The intrinsic apoptotic pathway monitors conditions within the cell, responding to various forms of stress. Pro-apoptotic signals may arise secondary to unrepaired DNA damage or from a lack of prosurvival signals transduced from cell surface receptors, such as when cell-cell or cell–extracellular matrix contact is disrupted or soluble factors such as hormones or growth factors are withdrawn.

The mitochondrion is a main component of the intrinsic pathway, as is another conserved protein family, the Bcl-2 family. Bcl-2 family members include both pro-apoptotic and antiapoptotic proteins. The pro-apoptotic group consists of at least 12 members, including Bax, Bak, Bok, Bik, Bad, Bid, and Bim. There are at least six antiapoptotic (prosurvival) Bcl-2 family members, including Bcl-2 itself, Bcl-X_L, Bcl-W, and Mcl1 (Adams and Cory, 1998). All members contain one or more Bcl-2 homology domains (BH1 to BH4) that allow members of the family to heterodimerize with each other. Bcl-2 family members regulate each other's function through these BH domains (Chittenden et al, 1995; Cheng et al, 1996). Although each pro-apoptotic Bcl-2 member responds to different stimuli, the principal mechanism by which they induce cell death is by increasing mitochondrial membrane permeability (Kroemer and Reed, 2000). When apoptosis is signaled via the intrinsic pathway, the balance between Bcl-2 family members shifts in favor of pro-apoptotic proteins that increase the permeability of the mitochondrial outer membrane, facilitating the release of cytochrome *c* from the intermembrane space into the cytoplasm (Jurgensmeier et al, 1998; Wolf and Eastman, 1999). Once in the cytoplasm, cytochrome *c* molecules bind to Apaf-1 proteins, forming a complex termed the *apoptosome*. The apoptosome activates caspase-9, one of the initiator caspases, beginning the caspase cascade as described earlier (Li et al, 1997b).

Antiapoptotic Bcl-2 family members block apoptosis by inhibiting the pro-apoptotic family members and, in doing so, decreasing mitochondrial permeability (see Fig. 19-14 on the Expert Consult website) (Li et al, 1997b; Srinivasula et al, 1998).

Bax is the most well studied pro-apoptotic Bcl-2 family member. It is transcriptionally activated by TP53. When activated, Bax dimerizes at the mitochondrial membrane. The dimer forms a channel that facilitates the release of cytochrome *c* from the mitochondria. Bcl-2 is the best studied antiapoptotic Bcl-2 family member. It functions by binding to Bax and, in doing so, blocks Bax-induced mitochondrial permeability (Miyashita et al, 1994; Adams and Cory, 1998).

Other pro-apoptotic family members are activated by various stimuli. Often they function not by inducing mitochondrial permeability directly but by activating or inhibiting other Bcl-2 family members. The first example is Bid. Bid is regulated by initiator caspases. Cytosolic Bid is activated by caspase-8 (see Fig. 19-14); this allows dimerization of Bid with either Bax or Bcl-2. This dimerization activates Bax activity and inhibits Bcl-2. The net result is to tip the balance in favor of apoptosis (Li et al, 1998). Because Bid is activated by caspases, it provides a link between the ligand-induced apoptotic machinery of the extrinsic pathway (described subsequently) and Bcl-2 family members.

An additional level of regulation is provided by IAPs, a family of proteins that act to prevent apoptosis by inhibiting specific caspase proteases, either directly or by inhibiting the conversion from the procaspase to the active form (Deveraux et al, 1998).

Extrinsic Apoptotic Pathway

In addition to the intrinsic pathway, a second pathway termed the *extrinsic pathway* mediates apoptosis after receipt of extracellular signals from cell surface receptors called “death receptors,” such as the tumor necrosis factor receptor TNFR1 and the Fas receptor (Fig. 19-15). These receptors belong to the tumor necrosis factor superfamily and contain a ligand-specific extracellular domain and an intracellular “death domain.” The binding of extracellular signaling molecules to the receptor activates the receptor, which signals through the death domain located on the cytoplasmic portion of the receptor. The death domain allows the receptor to bind to intracellular adapter proteins that also contain a death

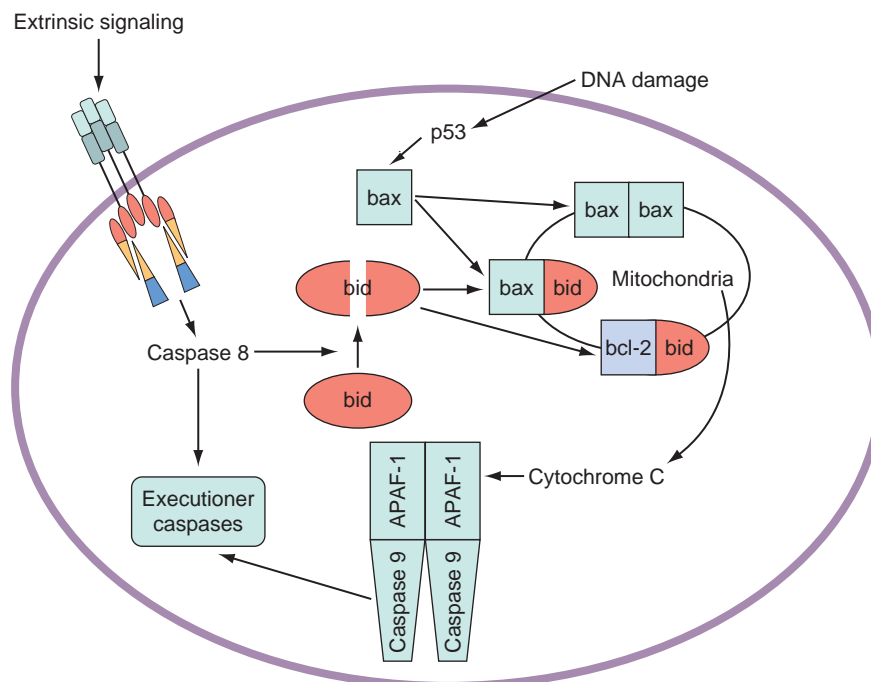


Figure 19-14. Cascade of extrinsic and intrinsic mechanisms of apoptosis. The extrinsic system depends on ligand-induced activation of executioner caspases, whereas the intrinsic system depends on the dimerization of BCL2 family members to alter mitochondrial membrane permeability.

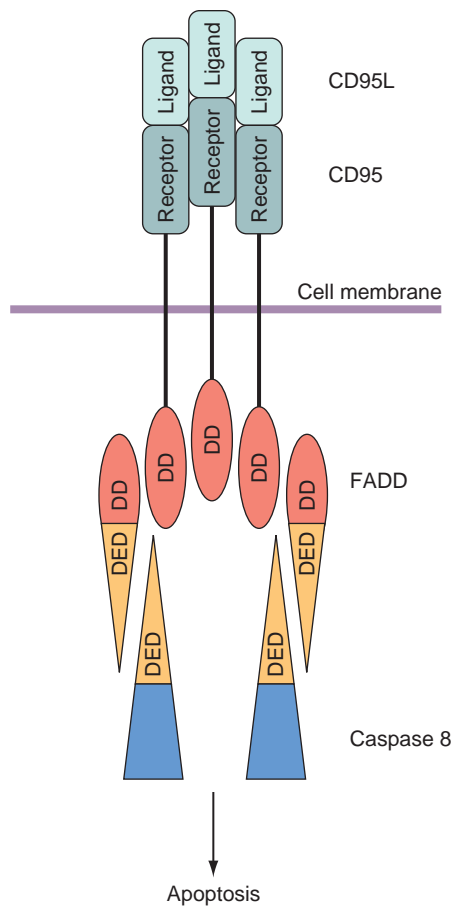


Figure 19-15. Example of death receptor-mediated activation of initiator caspases.

domain (e.g., RIP, TRADD, FADD). In addition to their own death domain, the adapter proteins have a death effector domain that allows the adapter protein to bind to the caspase recruitment domain (CARD) of initiator caspases (Ashkenazi and Dixit, 1998). Once bound, the initiator caspases undergo self-cleavage and are then capable of activating effector caspases via the caspase cascade (Li et al, 1998; Muzio, 1998).

The best-characterized death receptor is CD95, or FAS, which appears to play an important role in cancer immunosurveillance (Ashkenazi and Dixit, 1998). The ligand CD95L (also known as FAS ligand) forms a trimer that binds three CD95 receptors (Nagata, 1997). The clustering of CD95 allows the adapter protein FADD to bind to CD95 via their death domains (see Fig. 19-15). Procaspase-8, or FLICE, binds to FADD via the death effector domain. Procaspase-8 oligomerization promotes autoactivation to active caspase-8 (Muzio, 1998). Other initiator procaspases, such as procaspase-10, are activated through similar mechanisms (Vincenz and Dixit, 1997). Negative regulatory molecules, such as FLIP, bind to FADD and in doing so inhibit procaspase-8 binding and apoptosis (Irmeler et al, 1997).

The death receptor pathway does not appear to have a direct role in the etiology of cancer. Patients with hereditary defects in this system and knockout mice both are characterized by T-cell abnormalities and fatal autoimmune syndromes, not hereditary tumor syndromes (Nagata, 1997). However, the identification of ligand-dependent apoptosis receptors may have a profound impact on therapy. Most cancer therapies (i.e., chemotherapy and external-beam radiation therapy) depend on *TP53* to induce apoptosis in the cancer cell. Because *TP53* is mutated in more than half of malignancies (Hollstein et al, 1991), *TP53*-independent pathways for apoptosis are of great clinical interest. Because the ligand-dependent apoptosis described earlier is independent of *p53*, these receptors and ligands are attractive novel treatment targets. Compounds that bind to the receptors are extremely toxic (Nagata, 1997). It is hoped that novel compounds will have improved toxicity profiles.

apoptotic rates. This improved survival may reflect the fact that external-beam radiation therapy requires an intact apoptotic mechanism to be effective (Rodel et al, 2000).

As previously mentioned, most TGCTs maintain intact DDR and wild-type *TP53* and display high cure rates in response to therapies that induce DNA damage (Einhorn, 2002; Kersemaekers et al, 2002; Gorgoulis et al, 2005; Bartkova et al, 2007).

Individual members of the apoptotic machinery have been frequently studied. However, all studies are limited by an inability to assay all elements of the apoptotic machinery simultaneously and to assess globally the ability of the tumor to undergo programmed cell death.

TP53 mutations and abnormalities in expression are among the most frequent in cancer and have been identified in prostate, bladder, and renal cancers (Hollstein et al, 1991; Sidransky et al, 1991; Reiter et al, 1993). Abnormalities in *TP53* cause dysregulation of the cell cycle and DNA repair mechanisms in addition to apoptosis and are covered in more detail in Cell Cycle Deregulation.

Bcl-2 family members have been studied in GU malignancies. Elevated levels of Bcl-2 have been identified in most hormone-refractory prostate tumors, reflecting the tumor's relative resistance to apoptosis in the advanced state (McDonnell et al, 1992; Colombel et al, 1993). Both increased and decreased levels of Bcl-2 have been identified in localized prostate tumors, and a few studies have found a correlation with grade, stage, and progression (Byrne et al, 1997; Lipponen and Vesalainen, 1997; Theodorescu et al, 1997). Other antiapoptotic members of the Bcl-2 gene family, Bcl-X_L and Mcl1, may also be linked to prostate carcinoma (Krajewska et al, 1996). Analysis of bladder carcinoma has demonstrated similar results. Bcl-2 levels are higher in more aggressive bladder carcinoma, but expression of Bcl-2 had no effect on treatment outcome (King et al, 1996; Rodel et al, 2000). As noted earlier, phosphorylation of Bad by Akt can also tilt the scales toward cell survival, especially in concert with elevated levels of Bcl-2. Akt activation is commonly seen in many urologic malignancies and can result from loss of the tumor suppressor *PTEN*; mutation and constitutive activation of PI3 kinase; or activation of tyrosine kinase receptors such as HER2/NEU, EGFR, and insulin-like growth factor receptor.

Other Bcl-2 family members have not been as well studied. Loss of Bax expression is apparently an uncommon mechanism for the development of prostate carcinoma (Krajewska et al, 1996; Johnson and Hamdy, 1998), but it may play a role in progression of localized bladder carcinoma (Ye et al, 1998).

Deficiencies in signal transduction pathways leading to apoptosis play a role in the initiation and progression of malignancy. It is unclear if expression analysis of the apoptotic machinery will provide additional prognostic information than that provided by traditional histochemical analysis. However, it is clear that effective chemotherapy and radiation therapy are largely dependent on apoptosis. In addition, in the future the apoptotic machinery may be manipulated using novel ligands that bind to death receptors and promote *TP53*-independent cancer cell death.

Alternative Regulators of Apoptosis in Genitourinary Malignancies

In addition to the classic regulators of apoptosis, numerous other pathways for cell survival and death have been uncovered that play key roles in urologic cancer. Some of these pathways are being actively explored as targets for cancer therapy. The Vancouver group mapped out a detailed gene profile of prostate tumors treated with neoadjuvant hormonal ablation therapy to identify key regulators of cell death and survival after castration. In addition to Bcl-2, which is upregulated in surviving cancer cells, they also reported on clusterin and Hsp27. Clusterin, or TRPM2 (testosterone repressed prostate message-2), is upregulated both in patient samples after hormone ablation and in the Shionogi and CWR-22 xenograft models of hormone-sensitive tumors. Although its precise

function is unknown, a large body of evidence suggests that clusterin is induced by stress and functions to stabilize the cell during periods of stress (Miyake et al, 2000). In this model, clusterin is believed to act like heat shock proteins, whose role as a protein chaperone is also to stabilize client proteins. Clusterin is activated by HSP1. Functional evidence of the role of clusterin comes from studies in which clusterin is either overexpressed or knocked down using antisense strategies. In the first scenario, clusterin expression promotes hormone-refractory cell growth and prevents androgen withdrawal-induced apoptosis. In the second scenario, treatment of hormone-refractory cells with antisense clusterin promotes apoptosis (July et al, 2002; Miyake et al, 2004; Gleave and Miyake, 2005). This same group of investigators also reported that the heat shock protein HSP27 is frequently overexpressed in hormone-refractory prostate cancers. Similar experiments using overexpression and antisense strategies have suggested that targeting HSP27 may influence the course of hormone-refractory cancers, in particular in combination with cytotoxic chemotherapies (Rocchi et al, 2004).

Another family of cellular signaling molecules that play a role in the regulation of cell survival and apoptosis is the sphingolipids. Sphingolipids are one of three major constituents of the cell membrane, alongside phospholipids and cholesterol. Sphingolipid generation is regulated by a large cast of enzymes, notably the sphingomyelinases, ceramide synthase, and the ceramidases. Ceramide is produced from sphingomyelin by sphingomyelinase and from sphinganine by ceramide synthase. Ceramidases degrade ceramide and lead to formation of sphingosine and sphingosine-1-phosphate. Ceramide is a potent pro-apoptotic molecule that can promote apoptosis through the classic mitochondrial activation of caspases or through a nonclassic caspase-independent form of apoptosis (Kolesnick and Fuks, 2003). Sphingosine-1-phosphate, in contrast, is a powerful antiapoptotic molecule that may modulate the degree of apoptosis similar to a rheostat (Maceyka et al, 2002).

The importance of ceramide to GU tumors is that it appears to be a key modulator of radiation-induced tissue damage and apoptosis. Similar to clusterin and other heat shock proteins, ceramide appears to be a critical mediator of stress response in cells, in this case promoting apoptosis as opposed to cell survival. Studies supporting the role of ceramide in radiation-induced apoptosis are manifold, including studies demonstrating the direct cell death signal induced by exogenous treatment of cells with ceramide, studies of radiation response in mouse knockout models, and studies of radiation response in the presence and absence of inhibitors of sphingolipid metabolism. It is hoped that therapeutics that increase ceramide production and promote apoptosis can be developed. The role of sphingolipid-1-phosphate has also emerged from these studies, and work from several investigators suggests that this molecule is a promising target for cancer therapy (Gulbins and Kolesnick, 2003; Kester and Kolesnick, 2003; Perry and Kolesnick, 2003).

STEM CELLS AND CANCER

Stem cells are found in multicellular organisms and are characterized by the ability of self-renewal through mitotic cell division and differentiation into a diverse range of specialized cell types. Common properties of stem cells include the ability of self-renewal, generation of cellular progeny, localization within specialized niches, and the ability to give rise to all cell types within an organ. For example, human prostate stem cells are believed to be localized within the basal epithelium and give rise to a hierarchy of progenitor cells that may differentiate into secretory or neuroendocrine cells (Burger et al, 2005; Xin et al, 2005).

Studies suggest that neoplastic cells mimic normal tissue development and may arise from and are dependent on a small population of stem cells. The cancer stem cell hypothesis argues that cancers arise from transformation of stem or progenitor cells that are capable of multilineage differentiation. Cancer stem cells may account for only a small percentage of any tumor, but this

KEY POINTS: APOPTOSIS

- Apoptosis is a rapid, orderly programmed form of cell death that is used by multicellular organisms to eliminate unwanted cells.
- Apoptosis is believed to play an important role in tumor suppression because many of the signals that induce apoptosis arise from potentially tumorigenic cell stresses such as DNA damage.
- Cancer is characterized by interruptions in the normal process of apoptosis, resulting in inappropriate cell survival.
- Apoptosis is mediated by a conserved family of proteases known as caspases. Initiator caspases start caspase proteolytic cascades terminating in the activation of executioner caspases that target several cellular proteins.
- Two main apoptotic pathways have been identified. In the intrinsic pathway, Bcl-2 family members modulate the release of cytochrome *c* from the mitochondria, which participates in the activation of initiator caspases. The extrinsic pathway activates caspases in response to signals from extracellular “death receptors.”
- In addition to its functions in cell cycle arrest and DNA repair, *TP53* plays a key role in apoptosis.
- Bcl-2 is a classic inhibitor of the mitochondrial pathway of apoptosis and is overexpressed in some GU malignancies.
- Therapeutic response often depends on the integrity of apoptotic pathways in the cancer cells. Most TGCTs retain intact DDR, wild-type *TP53*, and apoptotic responses, providing high cure rates with DNA-damaging agents.
- Novel agonists and antagonists of apoptosis, such as ceramide and clusterin, may successfully be controlled to combat cancer.

small population of cells is critical for tumor survival. The most readily accepted experimental demonstration of cancer stem cells relies on serial transplantation of tumor cell populations isolated based on one or numerous putative cancer stem cell markers into immune-deficient mice or three-dimensional culture systems and recapitulation of the heterogeneous primary tumor. Using this experimental strategy, initial evidence to support the cancer stem cell hypothesis was discovered in leukemia, breast cancer, and neurologic cancers. For example, a CD44⁺/CD24^{low} population of cells in primary breast tumors was specifically capable of new tumor formation when engrafted into nude mice (Al-Hajj et al, 2003; Dontu et al, 2003). Similar reports in glioblastoma suggest that a CD133⁺ population is the putative stem cell (Singh et al, 2003; Dirks, 2005). One challenge in cancer stem cell research is the lack of any one marker that is exclusively expressed by cancer stem cells. For any given tumor type, typically many different markers can be identified that confer a cancer stem cell phenotype, and absence of the marker does not always imply that a cell is not a cancer stem cell. For example, in glioblastoma, both CD133⁺ and CD133⁻ cell populations have been shown to possess cancer stem cell-like properties (Beier et al, 2007).

A tumor-initiating cell (T-IC) subpopulation has also been identified in human bladder cancer. This group of cells was found to express CD44⁺/CK5⁺/CK20⁻ markers similar to normal bladder basal cells (Chan et al, 2009). The bladder T-IC subpopulation was also capable of forming xenograft tumors in vivo that recapitulated characteristics of the original tumor. CD47 was highly expressed in

this group of cells, and blockade of CD47 resulted in macrophage engulfment of bladder cancer stem cells in vitro. This finding suggests a potential role for therapeutic targeting of CD47 and the T-IC subpopulation in bladder cancer (Chan et al, 2009). To date, numerous other putative cancer stem cell populations have been identified in bladder cancer, including CK17⁺/67LR⁺/CAECAM⁻ cells, embryonic stem cell marker *POU5F1*⁺ cells, and high aldehyde dehydrogenase activity (ALDH^{hi}) cells (van der Horst et al, 2012).

KEY POINTS: STEM CELLS AND CANCER

- Stem cells are defined by their ability to differentiate along multiple lineages and their immortality.
- Cancer is believed to be a stem cell disease in which a small population of cancer stem cells maintains the larger tumor.
- Cancer may ultimately be eradicated by targeting only the cancer stem cell.

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The complete reference list is available online at www.expertconsult.com.

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The field of urology was the earliest to gain from the advent of transplantation, with the kidney being the first entire organ to be replaced in a human, in 1955 (Guild et al, 1955). In the early 1960s, Murray, who later received the Nobel Prize for his work, performed a nonrelated kidney transplantation from a non-genetically identical patient into another. This transplant, which overcame the immunologic barrier, marked a new era in medical therapy and opened the door for use of transplantation as a means of therapy for different organ systems. However, lack of good immunosuppression and the ability to monitor and control rejection, as well as a severe organ donor shortage, opened the door for other alternatives.

As times evolved, synthetic materials were introduced to replace or rebuild diseased tissues or parts in the human body. The advent of new manmade materials, such as tetrafluoroethylene (Teflon) and silicone, opened a new field that included a wide array of devices that could be applied for human use. Although these devices could provide for structural replacement, the functional component of the original tissue was not achieved.

Simultaneous with this development was an increased body of knowledge of the biologic sciences that included new techniques for cell harvesting, culture, and expansion. The areas of cell biology, molecular biology, and biochemistry were advancing rapidly. Studies of the extracellular matrix (ECM) and its interaction with cells and with growth factors and their ligands led the way to a further understanding of cell and tissue growth and differentiation. The concept of cell transplantation took hold in the research arena and culminated with the first human bone marrow cell transplant in the 1970s.

In the 1970s, a natural evolution occurred wherein researchers started to combine the fields of devices and materials sciences with cell biology, in effect starting a new field called *tissue engineering*. As more scientists from different fields came together with the common goal of tissue replacement, the field of tissue engineering became more formally established. Tissue engineering was defined as “an interdisciplinary field which applies the principles of engineering and life sciences towards the development of biological substitutes that aim to maintain, restore or improve tissue function” (Atala and Lanza, 2001). The first use of the term *tissue engineering* in the literature can be traced to a reference dealing with corneal tissue in 1985 (Wolter et al, 1985).

The field of stem cells also received a large boost with the discovery of mouse embryonic stem cells in the early 1980s (Martin, 1981). However, the field remained relatively dormant until the description of human embryonic stem cells (hESCs) in 1998 (Thomson et al, 1998). The description of these cells led to one of the most contested ethical debates in the field of medicine. Just a year later, in 1999, the world awoke to the startling media announcement of the creation of the first cloned mammal, a sheep named Dolly (Wilmut et al, 1997). Although cloning, or nuclear transfer, had been done in amphibians and other animal models for years, this accomplishment in a mammal showed once again that concepts believed to be scientifically prohibitive were indeed possible.

The fields of cell transplantation, tissue engineering and nuclear transfer all had one unifying concept—the regeneration of living tissues (organs). Thus in 1999, William Haseltine, then the Scientific Founder and Chief Executive Officer of Human Genome Sciences, coined the term *regenerative medicine*, in effect bringing all these areas under one defining field (Haseltine, 1999). Soon the first online journal in the field, *Regenerative Medicine*, was founded, along with the Regenerative Medicine Society.

Organ transplantation remains a mainstay of treatment for patients with severely compromised organ function. Despite initiatives to increase the availability of transplant organs, however, the number of patients in need of treatment far exceeds the organ supply, and this shortfall is expected to worsen as the global population ages. One alternative treatment approach is regenerative medicine. In the last two decades, scientists have attempted to grow native and stem cells, engineer tissues, and design treatment modalities using regenerative medicine techniques for virtually every tissue of the human body. This chapter reviews some of the progress that has been achieved in the field of genitourinary regenerative medicine.

REGENERATIVE MEDICINE: STRATEGIES FOR TISSUE AND ORGAN RECONSTITUTION

Regenerative medicine follows the principles of cell transplantation, materials science, and engineering toward the development of biologic strategies that can restore and maintain normal function. Regenerative medicine strategies usually fall into one of three categories: cell-based therapies; the use of biomaterials (scaffolds) alone, wherein the body's natural ability to regenerate is used to orient or direct new tissue growth; and the use of scaffolds seeded with cells to create tissue substitutes.

SOURCES OF CELLS FOR THERAPY

Stem Cells

The cells used for regenerative medicine can be autologous or heterologous, and from either native or stem cell sources. In general, there are three broad categories of stem cells obtained from living tissue that are used for cell therapies. Embryonic stem cells are obtained through the aspiration of the inner cell mass of a blastocyst or a single cell from this mass. Fetal and neonatal amniotic fluid and placenta may contain multipotent cells that may be useful in cell therapy applications. Cord blood cells have potency mainly limited to hematopoietic lineages, although differentiation to other cell types has also been reported. Adult stem cells, on the other hand, are usually isolated from organ or bone marrow biopsy specimens. Stem cells are defined as having three important properties: the ability to self-renew, the ability to differentiate into a number of different cell types, and the ability to easily form clonal populations (populations of cells derived from a single stem cell). Many techniques for generating stem cells have been studied over the past

TABLE 20-1 Summary of Alternate Methods for Generating Pluripotent Stem Cells

METHOD	ADVANTAGES	LIMITATIONS
Somatic cell nuclear transfer	Customized stem cells Has been shown to work in nonhuman primates	Requires oocytes Has not been shown to work in humans
Single-cell embryo biopsy	Patient specific to embryo Does not destroy or create embryos Has been done in humans	Allogeneic cell types Is not known if single cells are totipotent Requires coculturing with a previously established human embryonic stem cell line
Arrested embryos	Cells obtained from discarded embryos Has been done in humans	Allogeneic cell types Quality of cell lines might be questionable
Altered nuclear transfer	Customized stem cells	Ethical issues surround embryos with no potential Modified genome Has not been done with human cells
Reprogramming	Customized stem cells No embryos or oocytes needed Has been done with human cells	Retroviral transduction Oncogenes

few decades. Some of these techniques have yielded promising results, but others require further research. The main techniques are discussed in detail later, and their advantages and limitations are summarized in [Table 20-1](#).

Embryonic Stem Cells

In 1981 pluripotent cells were found in the inner cell mass of the human embryo, and the term *human embryonic stem cell* was coined ([Martin, 1981](#)). These cells are able to differentiate into all cells of the human body, excluding placental cells (only cells from the morula are totipotent—that is, able to develop into all cells of the human body). These cells have great therapeutic potential; their use is limited mostly by their biologic properties.

An ethical controversy surrounding stem cells was initiated in 1998 with the creation of hESCs derived from discarded embryos. hESCs were isolated from the inner cell mass of a blastocyst (an embryo 5 days after fertilization) using an immunosurgical technique. Given that some cells cannot be expanded *ex vivo*, hESCs could be an ideal resource for regenerative medicine because of their fundamental properties: the ability to self-renew indefinitely and the ability to differentiate into cells from all three embryonic germ layers, from skin to neurons. In addition, as further evidence of their pluripotency, embryonic stem cells can form embryoid bodies, which are cell aggregations that contain all three embryonic germ layers while in culture, and can form teratomas *in vivo* ([Itskovitz-Eldor et al, 2000](#)). These cells have demonstrated longevity in culture and can maintain their undifferentiated state for at least 80 passages when grown using current published protocols ([Thomson et al, 1998](#)). However, the clinical application of

embryonic stem cells is limited because they represent an allogeneic resource and thus have the potential to evoke an immune response. In addition, by definition the cells form teratomas, which may be problematic when treating patients. In October 2010, a phase 1 clinical trial was begun to assess the safety of hESC-derived oligodendrocyte progenitors for patients with thoracic spinal cord injuries. Unfortunately, the trial was discontinued in November 2011 ([Frantz, 2012](#)). hESC-derived retinal pigment epithelium has also been used in patients with macular degeneration and dystrophy ([Schwartz et al, 2012](#)). It might seem that we have waited too long to see hESCs in the clinic. However, this has been accomplished with incredible speed when it is considered that hESCs were first isolated just in 1998 ([Atala, 2012](#)).

A major objection to hESC research by some is that it results in the destruction of embryos. A method of isolating these cells without destroying the embryo would be advantageous. Three methods have been established experimentally for the generation of embryonic stem cell lines using alternate techniques whereby the embryos are not destroyed; these include performing a single-cell embryo biopsy ([Chung et al, 2006](#)), obtaining cells from arrested embryos ([Zhang et al, 2006a](#)), and using altered nuclear transfer ([Hurlbut, 2005](#); [Meissner and Jaenisch, 2006](#)).

A description of these techniques appears on the Expert Consult website.

Therapeutic Cloning (Somatic Cell Nuclear Transfer)

SCNT, or therapeutic cloning, entails the removal of an oocyte nucleus in culture, followed by its replacement with a nucleus derived from a somatic cell obtained from a patient. Activation with chemicals or electricity stimulates cell division up to the blastocyst stage.

It is important to differentiate between the two types of cloning that exist—reproductive cloning and therapeutic cloning. Both involve the insertion of donor DNA into an enucleated oocyte to generate an embryo that has identical genetic material to its DNA source. However, the similarities end there. In reproductive cloning, the embryo is implanted into the uterus of a pseudopregnant female to produce an infant that is a clone of the donor. A prominent example of this type of cloning resulted in the birth of a sheep named Dolly in 1997 ([Wilmut et al, 1997](#)). However, there are many ethical concerns surrounding such practices, and as a result, reproductive cloning has been banned.

Although therapeutic cloning also produces an embryo that is genetically identical to the donor, this process is used to generate blastocysts that are explanted and grown in culture rather than *in utero*. Embryonic stem cell lines can then be derived from blastocysts, which are allowed to grow only up to a 100-cell stage. At this time the inner cell mass is isolated and cultured, resulting in embryonic stem cells that are genetically identical to the patient. This process is detailed in [Figure 20-1](#). It has been shown that nuclear-transferred embryonic stem cells derived from fibroblasts, lymphocytes, and olfactory neurons are pluripotent and can generate live pups after injection into blastocysts. This shows that cells generated by SCNT have the same developmental potential as blastocysts that are fertilized and produced naturally ([Hochedlinger et al, 2002](#); [Eggan et al, 2004](#); [Brambrink et al, 2006](#)). In addition, the embryonic stem cells generated by SCNT are perfectly matched to the patient's immune system and no immunosuppressants would be required to prevent rejection should these cells be used in regenerative medicine applications.

Although embryonic stem cells derived from SCNT contain the nuclear genome of the donor cells, mitochondrial DNA (mtDNA) contained in the oocyte could lead to immunogenicity after transplantation. To assess the histocompatibility of tissue generated using SCNT, the nucleus of a bovine skin fibroblast was microinjected into an enucleated oocyte ([Lanza et al, 2002](#)). Although the blastocyst was implanted (reproductive cloning), the purpose was to generate renal, cardiac, and skeletal muscle cells, which were then harvested, expanded *in vitro*, and seeded onto biodegradable scaffolds. These scaffolds were then implanted into the donor steer

SOURCES OF CELL THERAPY: STEM CELLS

Single-Cell Embryo Biopsy

In 2006, Chung and colleagues were the first authors to report the generation of mouse embryonic stem cell lines via single-cell embryo biopsy (Chung et al, 2006). Their method was based on a technique used to obtain a single-cell embryo biopsy specimen for preimplantation genetic diagnosis. Cells were taken from eight-cell blastomeres rather than from blastocysts. The cells differentiated into derivatives of all three embryonic germ layers in vitro and as well as into teratomas in vivo. In addition, the mouse embryos that resulted from the biopsied blastomeres developed to term without a reduction in their developmental potential.

Obtaining Cells from Arrested Embryos

hESC lines can also be derived from arrested embryos. (Zhang et al, 2006a). During in vitro fertilization, only a small proportion of zygotes produced will develop successfully to the morula and blastocyst stages. Over half the embryos stop dividing (Hardy, 1993; Geber and Sampaio, 1999) and are therefore considered dead embryos (Landry and Zucker, 2004). Such embryos have unequal or fragmented cells and blastomeres and are usually discarded. Not all the cells within these arrested embryos, however, are abnormal (Martinez et al, 2002; Zhang et al, 2006a), and these embryos might be a source of hESCs. More studies are needed to characterize the full proliferation and differentiation potential of embryonic stem cells derived from arrested embryos.

Altered Nuclear Transfer

Altered nuclear transfer is a variation of somatic cell nuclear transfer (SCNT) in which a genetically modified nucleus from a somatic cell is transferred into a human oocyte. This embryo, which contains a deliberate genetic defect, is capable of developing into a blastocyst, but the induced defect prevents the blastocyst from implanting in the uterus. This process has the potential to generate customized hESCs from the blastocyst stage (Hurlbut, 2005). Human embryos with this genetic defect might lack the capacity to develop into viable fetuses as a result of their inability to implant, thus providing a source of stem cells without the destruction of viable embryos. Proof of concept was obtained in mice by Meissner and Jaenisch in 2006 using embryos lacking the *Cdx2* homeobox gene (Meissner and Jaenisch, 2006).

The viability of human embryos lacking the *CDX2* gene is unclear, as is whether this mutation restricts human developmental potential into certain lineages. Although much research must be done before therapeutic strategies based on this technique could ever enter the clinic, at this time hESCs derived from altered nuclear transfer can provide opportunities to study pluripotency in hESCs without the need for destruction of viable embryos. The exact effects of *CDX2* gene knockout on the development of human embryos are not well known. The effects of this gene, however, have been thoroughly investigated in the gastric and intestinal epithelium (Benahmed et al, 2008; Vauhkonen et al, 2008).

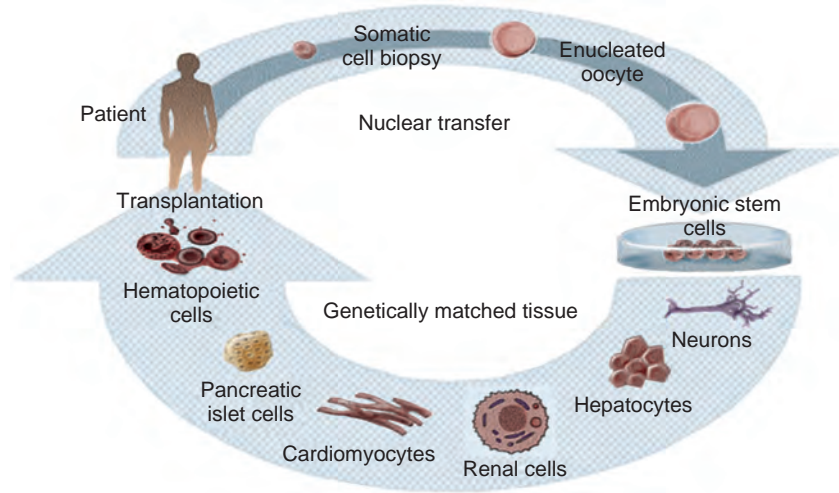


Figure 20-1. Therapeutic cloning strategy and its application to the engineering of tissues and organs.

from which the cells were cloned to determine if the cells were histocompatible. Analysis revealed that cloned renal cells showed no evidence of T-cell response, suggesting that rejection will not necessarily occur in the presence of oocyte-derived mtDNA. This finding represents a step forward in overcoming the histocompatibility problem of stem cell therapy.

Although promising, SCNT has certain limitations that require further improvement before its clinical application, in addition to the ethical considerations regarding the potential of the resulting embryos to develop into cloned embryos if implanted into a uterus. In addition, this technique has not been shown to work in humans to date. The initial failures and fraudulent reports of nuclear transfer in humans reduced enthusiasm for human applications (Simerly et al, 2003; Hwang et al, 2004, 2005), although nonhuman primate embryonic stem cell lines have been generated by SCNT of nuclei from adult skin fibroblasts (Byrne et al, 2007; Mitalipov, 2007).

Reprogramming (Induced Pluripotent Stem Cells)

Reprogramming is a technique that involves de-differentiation of adult somatic cells to produce patient-specific pluripotent stem cells, eliminating the need to create embryos. Cells generated by reprogramming would be genetically identical to the somatic cells (and therefore to the patient who donated these cells) and would not be rejected. Yamanaka was the first to discover that mouse embryonic fibroblasts (MEFs) and adult mouse fibroblasts could be reprogrammed into an “induced pluripotent state (iPS)” (Takahashi et al, 2006). These iPS cells possessed the immortal growth characteristics of self-renewing embryonic stem cells, expressed genes specific for embryonic stem cells, and generated embryoid bodies in vitro and teratomas in vivo. When iPS cells were injected into mouse blastocysts, they contributed to a variety of cell types. However, although iPS cells selected in this way were pluripotent, they were not identical to embryonic stem cells. Unlike with embryonic stem cells, chimeras made from iPS cells did not result in full-term pregnancies. Gene expression profiles of the iPS cells showed that they possessed a distinct gene expression signature that was different from that of embryonic stem cells. In addition, the epigenetic state of the iPS cells was somewhere between that found in somatic cells and that found in embryonic stem cells, suggesting that the reprogramming was incomplete.

These results were improved by Wernig and Jaenisch in July 2007 (Wernig et al, 2007). In this study, DNA methylation, gene expression profiles, and the chromatin state of the reprogrammed cells were similar to those of embryonic stem cells. Teratomas induced by these cells contained differentiated cell types representing all

three embryonic germ layers. Most important, the reprogrammed cells from this experiment were able to form viable chimeras and contribute to the germline-like embryonic stem cells, suggesting that these iPS cells were completely reprogrammed.

A major advance has been the reprogramming of human cells (Takahashi et al, 2007; Yu et al, 2007). Yamanaka generated human iPS cells that are similar to hESCs in terms of morphology, proliferation, gene expression, surface markers, and teratoma formation. Yamanaka received the Nobel Prize in Medicine for this work in 2012. Thompson’s group showed that retroviral transduction of the stem cell markers *OCT4*, *SOX2*, *NANOG*, and *LIN28* could generate pluripotent stem cells. Recently the cells have been noted to have the potential to be reversed to a ground state of pluripotency (Gafni et al, 2013). Since the discovery of iPS cells, work surrounding these cells has grown exponentially, with more than 6000 peer-reviewed papers listed in MEDLINE by 2014. The cells have shown great promise in the understanding of human disease, as well as the use of these cells for therapy. Like embryonic stem cells, the iPS cells also form teratomas, and this has limited their therapeutic potential, with no human trials to date. Direct in vivo reprogramming also leads to the formation of teratomas (Abad et al, 2013). Nonetheless, the potential of reprogramming remains exciting.

Perinatal Stem Cells

Various sources of perinatal stem cells have been reported, with varied potency. Umbilical cord blood is collected at the time of birth and provides a source of undifferentiated cells that may be banked at the time of birth to be available for autologous and allogeneic cell therapy. Umbilical cord blood stem cells were first used clinically in 1989 (Gluckman et al, 1989). Since then, the cells have been used in more than 25,000 patients worldwide. The cells are more immature than adult bone marrow stem cells (Tursky et al, 2012). Cord blood stem cells are mostly used for hematopoietic applications (Kurtzberg, 1996).

Early stem cell populations can be obtained from Wharton jelly, which surrounds the cord (Romanov et al, 2003; Hass et al, 2011). The cells are mesenchymal in origin, although limited multipotentiality has been demonstrated. The cells have not been used clinically.

The most recent perinatal stem cell type described was derived from both the amniotic fluid and placenta. The isolation of multipotent human and mouse amniotic fluid and placental-derived stem (AFPS) cells that are capable of extensive self-renewal and give rise to cells from all three germ layers was reported in 2007 (De Coppi et al, 2007b). AFPS cells represent a class of stem cells with

properties somewhere between those of embryonic and adult stem cell types; they are more agile than adult stem cells but less so than embryonic stem cells. Unlike embryonic and induced pluripotent stem cells, however, AFPS cells do not form teratomas, and if preserved for self-use, avoid the problems of rejection. The cells could be obtained either from amniocentesis or chorionic villous sampling in the developing fetus or from the placenta at the time of birth. The cells can be directed into all three germ layers, and they expand readily. Amniotic fluid stem cells have been used experimentally to treat bladder dysfunction (De Coppi et al, 2007a). Many different stem cell types can be obtained from the amniotic fluid or the placenta. There are more than 2500 references in the literature to studies involving these cells. The cells have varied properties and applications, depending on the specific source (Murphy and Atala, 2013).

Adult Stem Cells

Adult stem cells, especially hematopoietic stem cells from the bone marrow, are the best understood cell type in stem cell biology (Ballas et al, 2002). These cells have been used for decades for hematopoietic disorders. However, adult stem cell research remains an area of intense study, as the potential of these cells for therapy may be applicable to myriad degenerative disorders. Within the past decade, adult stem cell populations have been found in many adult tissues other than the bone marrow and the gastrointestinal tract, including the brain (Taupin, 2006; Jiao et al, 2008), skin (Jensen et al, 2008), and muscle (Crisan et al, 2008). Many types of adult stem cells have been identified in organs throughout the body and are thought to serve as the primary repair entities for their corresponding organs (Weiner, 2008) (Fig. 20-2). The discovery of such tissue-specific progenitors has opened up new avenues for research.

A notable exception to the tissue specificity of adult stem cells is the mesenchymal stem cell, also known as the *multipotent adult progenitor cell*. This cell type is also derived from bone marrow stroma (Devine, 2002; Jiang et al, 2002). Such cells can differentiate in vitro into numerous tissue types (Caplan, 2007; da Silva Meirelles et al, 2008). Some cells, such as those of the liver, pancreas, and nerve, have very low proliferative capacity in vitro, and the functionality of some cell types is reduced after the cells are cultivated. Isolation of cells has also been problematic because stem cells are present in extremely low numbers in adult tissue (Hristov et al, 2008; Mimeault et al, 2008). Bone marrow stem cells have been differentiated to both bladder urothelium and muscle (Anumanthan et al, 2008; Tian et al, 2010). The cells have also been used in experimental animal models for the enhancement of bladder function and regeneration (Soler et al, 2012; Sharma et al, 2013).

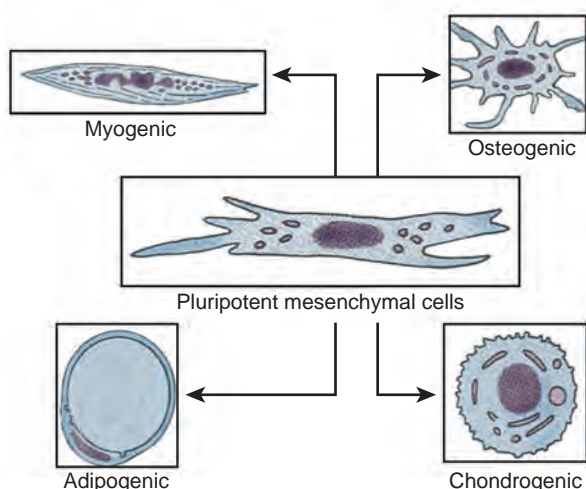


Figure 20-2. Schematic diagram of pluripotential stem cell lineages that can be derived from postnatal tissue.

Adipose-derived stem cells that could give rise to multiple lineages were first reported in 2001 (Zuk et al, 2001). The cells have been used for differentiation into urologic cells such as bladder smooth muscle (Jack et al, 2009; Zhang et al, 2012b) and urothelium (Zhang et al, 2013). The adipose-derived cells have also been used experimentally to improve bladder function (Zhang et al, 2012a; Song et al, 2013). Urine-derived stem cells have also been proposed for genitourinary reconstruction (Zhang et al, 2008; Bharadwaj et al, 2013).

Although the clinical usefulness of adult stem cells is currently limited, great potential exists for future use of such cells in tissue-specific regenerative therapies. The advantage of adult stem cells is that they can be used in autologous therapies, thus avoiding any complications associated with immune rejection. Composite adult cell populations from many sources, including bone marrow, fat, and fragments of peripheral blood have been used more extensively in patients for multiple indications more recently. These cells are currently being tested for urologic applications, such as erectile or voiding dysfunction. The mechanisms behind their mode of action need to be further elucidated.

Native Targeted Progenitor Cells

In the past, one of the limitations of applying cell-based regenerative medicine techniques to organ replacement was the inherent difficulty of growing certain human cell types in large quantities. Native targeted progenitor cells, or native cells, are tissue specific unipotent cells derived from most organs. The advantage of these cells is that they are already programmed to become the cell type needed, without any extra-lineage differentiation. By noting the location of the progenitor cells, as well as by exploring the conditions that promote differentiation and/or self-renewal, it has been possible to overcome some of the obstacles that limit cell expansion in vitro. One example is the urothelial cell. Urothelial cells could be grown in the laboratory setting in the past, but only with limited success. It was believed that urothelial cells had a natural senescence that was hard to overcome. Several protocols have been developed over the last two decades that have improved urothelial growth and expansion (Cilento et al, 1994; Liebert et al, 1997; Scriven et al, 1997; Puthenveetil et al, 1999). A system of urothelial cell harvesting was developed that does not use any enzymes or serum and has a large expansion potential. Using these methods of cell culture, it is possible to expand a urothelial strain from a single specimen that initially covers a surface area of 1 cm² to one covering a surface area of 4202 m² (the equivalent area of one football field) within 8 weeks (Cilento et al, 1994).

An additional advantage in using native cells is that they can be obtained from the specific organ to be regenerated, expanded, and used in the same patient without rejection, in an autologous manner. Bladder, ureter, and renal pelvis cells can equally be harvested, cultured, and expanded in a similar fashion. Normal human bladder epithelial and muscle cells can be efficiently harvested from surgical material and extensively expanded in culture, and their differentiation characteristics, growth requirements, and other biologic properties can be studied (Liebert et al, 1991; Cilento et al, 1994; Tobin et al, 1994; Harriss, 1995; Freeman et al, 1997; Liebert et al, 1997; Fauza et al, 1998; Lobban et al, 1998; Solomon et al, 1998; Nguyen et al, 1999; Puthenveetil et al, 1999; Rackley et al, 1999). Major advances in cell culture techniques have been made within the past several decades, and these techniques make the use of autologous cells possible for clinical application. However, even now, not all human cells can be grown or expanded in vitro. Liver, nerve, and pancreas are examples of human tissues for which the technology is not yet advanced to the point where these cells can be grown and expanded.

When cells are used for tissue reconstitution, donor tissue is dissociated into individual cells, which are either implanted directly into the host or expanded in culture, attached to a support matrix, and reimplanted after expansion.

BIOMATERIALS AND VASCULARIZATION FOR GENITOURINARY REGENERATIVE MEDICINE

For regenerative medicine purposes, there are clear advantages to use of degradable, biocompatible materials that can function as cell delivery vehicles and/or provide the structural parameters needed for tissue replacement. **Biomaterials in regenerative medicine function as an artificial ECM and elicit biologic and mechanical functions of native ECM found in tissues in the body.** Native ECM brings cells together into tissue, controls the tissue structure, and regulates the cell phenotype (Alberts et al, 1994). Biomaterials facilitate the localization and delivery of cells and/or bioactive factors (e.g., cell adhesion peptides, growth factors) to desired sites in the body; define a three-dimensional space for the formation of new tissues with appropriate structure; and guide the development of new tissues with appropriate function (Kim et al, 1998). Direct injection of cell suspensions without biomaterial matrices has been used in some cases (Ponder et al, 1991; Brittberg et al, 1994), but it is difficult to control the localization of transplanted cells. In addition, the majority of mammalian cell types are anchorage dependent and will die if not provided with a cell-adhesion substrate.

Design and Selection of Biomaterials

The design and selection of the biomaterial is critical in the development of engineered genitourinary tissues. The biomaterial must be capable of controlling the structure and function of the engineered tissue in a predesigned manner by interacting with transplanted cells and/or host cells. In general, the ideal biomaterial should be biocompatible, promote cellular interaction and tissue development, and possess proper mechanical and physical properties.

The selected biomaterial should be biodegradable and biore-sorbable to support the reconstruction of a completely normal tissue without inflammation. Such behavior of the biomaterials avoids the risk of inflammatory or foreign-body responses that may be associated with the permanent presence of a foreign material in the body. The degradation rate and the concentration of degradation products in the tissues surrounding the implant must be at a tolerable level (Bergsma et al, 1995).

The biomaterials should provide an appropriate regulation of cell behavior (e.g., adhesion, proliferation, migration, differentiation) to promote the development of functional new tissue. Cell behavior in engineered tissues is regulated by multiple interactions with the microenvironment, including interactions with cell-adhesion ligands (Hynes, 1992) and with soluble growth factors (Deuel, 1997). Cell adhesion-promoting factors (e.g., Arg-Gly-Asp [RGD]) can be presented by the biomaterial itself or incorporated into the biomaterial to control cell behavior through ligand-induced cell receptor signaling processes (Barrera et al, 1993; Cook et al, 1997). The biomaterials provide temporary mechanical support sufficient to withstand in vivo forces exerted by the surrounding tissue and maintain a potential space for tissue development. The mechanical support of the biomaterials should be maintained until the engineered tissue has sufficient mechanical integrity to support itself (Atala, 2007). This potentially can be achieved by an appropriate choice of mechanical and degradative properties of the biomaterials (Kim et al, 1998).

The biomaterials need to be processed into specific configurations. A large ratio of surface area to volume is often desirable to allow the delivery of a high density of cells. A high-porosity, interconnected pore structure with specific pore sizes promotes tissue ingrowth from the surrounding host tissue. Several techniques, such as electrospinning, have been developed that readily control porosity, pore size, and pore structure (Lee et al, 2007; Yoo et al, 2007; Choi et al, 2008; Lee et al, 2008a, 2008b, 2008c, 2010).

In general, three classes of biomaterials have been used for engineering of genitourinary tissues: naturally derived materials, such as collagen; acellular tissue matrices, such as bladder submucosa and small-intestinal submucosa; and synthetic polymers,

such as polyglycolic acid (PGA), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA). These classes of biomaterials have been tested with regard to their biocompatibility with primary human urothelial and bladder muscle cells (Pariente et al, 2001). Naturally derived materials and acellular tissue matrices have the potential advantage of biologic recognition. Synthetic polymers can be produced reproducibly on a large scale with controlled properties of strength, degradation rate, and microstructure. Combination scaffolds have also been used (Engelhardt et al, 2011).

Additional information on the general types of biomaterials used can be found on the Expert Consult website.

Vascularization

The goals in regenerative medicine include the replacement of damaged, injured, or missing body tissues with biologic-compatible substitutes. **A limiting factor for the engineering of tissues is that cells cannot be implanted in volumes exceeding 3 mm³ (Folkman and Hochberg, 1973).** Nutrition and gas exchange are limited by this maximal diffusion distance. If cells were implanted in volumes exceeding 3 mm³, only the cells on the surface would survive, and the central cell core would undergo necrosis resulting from a lack of vascularity. Therefore a critical obstacle in regenerative medicine is the ability to maintain large masses of cells alive, on transfer from the in vitro culture conditions into the host, in vivo (Mooney and Mikos, 1999). To achieve the goals of engineering large complex tissues, and possibly internal organs, vascularization of the regenerating cells is essential.

Formation of new blood vessels and capillaries is composed of two different processes: vasculogenesis, the in situ assembly of capillaries from undifferentiated endothelial cells (ECs), and angiogenesis, the sprouting of capillaries from preexisting blood vessels.

More information on these two processes is included on the Expert Consult website.

The understanding of the angiogenic process and the isolation of potent and specific angiogenic growth factors has encouraged the use of these factors therapeutically (Loges et al, 2009; Phelps and Garcia, 2009). Efforts have been aimed at incorporating the knowledge acquired in angiogenesis of ischemic tissues into practical approaches to vascularize bioengineered tissues (Stosich et al, 2009). Bioengineered tissues are usually supported by scaffolds of biocompatible matrices made from natural or artificial sources (Hubbell et al, 1991). Successful vascularization is dependent on the porosity of the supporting matrix. A positive correlation between the pore size of poly(L-lactic acid) (PLLA) implants and the rate of vascularization has been observed (Mikos et al, 1993).

Three approaches have been used for vascularization of bioengineered tissue: (1) incorporation of angiogenic factors in the bioengineered tissue; (2) seeding ECs with other cell types in the bioengineered tissue; and (3) prevascularization of the matrix before cell seeding. Angiogenic growth factors may be incorporated into the bioengineered tissue before implantation, to attract host capillaries and to enhance neovascularization of the implanted tissue. Angiogenic growth factors can be embedded in specific biomaterials and can be controlled to be released slowly (Eiselt et al, 1998). Cells can also be genetically engineered to secrete high levels of angiogenic proteins (Springer et al, 1998).

Another approach for enhancing angiogenesis employed cultured ECs, which are incorporated into the bioengineered tissue before implantation. Human penile corpus cavernosum-derived smooth muscle cells and ECs were seeded on biodegradable polymer scaffolds to reconstruct penile corporeal tissue in vitro and in vivo (Park et al, 1999). The use of ECs improved the formation of the engineered tissue. In another study the addition of both ECs and angiogenic growth factors (VEGF) accelerated the formation of engineered muscle tissue (De Coppi et al, 2005). An alternative direction in vascularization of bioengineered tissue is the prevascularization of the supporting polymer before cell seeding. In this manner, the bioengineered tissue will be organized around the vascular network, providing sufficient tissue perfusion (Fontaine et al, 1995).

Types of Biomaterials

Collagen is the most abundant and ubiquitous structural protein in the body, and it may be readily purified from both animal and human tissues with an enzyme treatment and salt and acid extraction (Li, 1995). Collagen has long been known to exhibit minimal inflammatory and antigenic responses (Furthmayr and Timpl, 1976), and it has been approved by the U.S. Food and Drug Administration (FDA) for many types of medical applications, including wound dressings and artificial skin (Cen et al, 2008). Intermolecular cross-linking reduces the degradation rate by making the collagen molecules less susceptible to an enzymatic attack. Intermolecular cross-linking can be accomplished by various physical (e.g., ultraviolet radiation, dehydrothermal treatment) or chemical (e.g., glutaraldehyde, formaldehyde, carbodiimides) techniques (Li, 1995). Collagen contains cell-adhesion domain sequences (e.g., RGD) that exhibit specific cellular interactions. This may help to retain the phenotype and activity of many types of cells, including fibroblasts (Silver et al, 1992) and chondrocytes (Sams and Nixon, 1995). This material can be processed into a wide variety of structures such as sponges (Fig. 20-3A), fibers, and films (Yannas et al, 1980a, 1980b; Cavallaro et al, 1994).

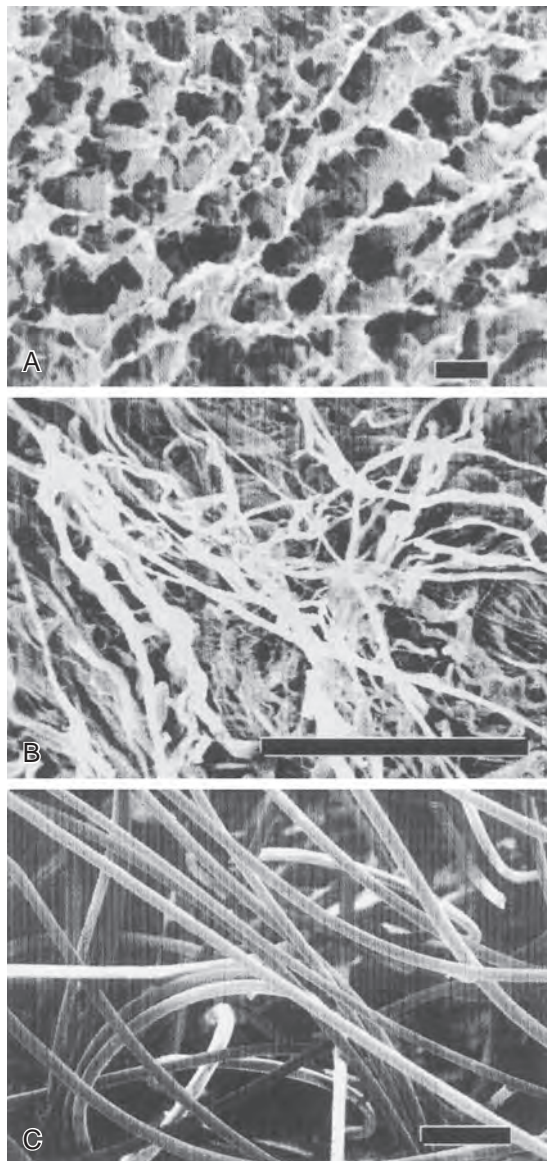


Figure 20-3. Scanning electron micrographs of biomaterials: collagen sponge (A), acellular matrix prepared from pig bladder submucosa (B), and polyglycolic acid fiber-based matrix (C). (Size bars = 100 μ m.)

Alginate, a polysaccharide isolated from seaweed, has been used as an injectable cell delivery vehicle (Smidsrod et al, 1990) and a cell immobilization matrix (Lim and Sun, 1980) owing to its gentle gelling properties in the presence of divalent ions such as calcium. Alginate is a family of copolymers of D-mannuronate and L-guluronate. The physical and mechanical properties of alginate gel are strongly correlated with the proportion and length of the polyguluronate block in the alginate chains (Smidsrod et al, 1990). Efforts have been made to synthesize biodegradable alginate hydrogels with mechanical properties that are controllable in a wide range by intermolecular covalent cross-linking and with cell-adhesion peptides coupled to their backbones (Rowley et al, 1999).

Natural materials such as alginate and collagen have been used as “bio-inks” in a newly developed bioprinting technique based on inkjet technology (Boland et al, 2006; Campbell and Weiss, 2007; Skardal et al, 2012; Murphy et al, 2013). With this technology, these scaffold materials can be “printed” into a desired scaffold shape using a modified inkjet printer. In addition, several groups have shown that living cells can also be printed using this technology (Lafamme et al, 2005; Xu et al, 2013). This exciting technique can be modified so that a three-dimensional construct containing a precise arrangement of cells, growth factors, and ECM material can be printed (Roth et al, 2004; Ilkhanizadeh et al, 2007; Xu et al, 2009). The bioprinting technology is currently being used to print several urologic structures, including miniature kidneys.

Acellular tissue matrices are collagen-rich matrices prepared by removing cellular components from tissues (Fig. 20-3B). The matrices are often prepared by mechanical and chemical manipulation of a segment of bladder tissue (Dahms et al, 1998; Piechota et al, 1998; Yoo et al, 1998b; Chen et al, 1999). The matrices slowly degrade after implantation and are replaced and remodeled by ECM proteins synthesized and secreted by transplanted or ingrowing cells. Acellular tissue matrices have been proved to support cell ingrowth and regeneration of genitourinary tissues, including urethra and bladder, with no evidence of immunogenic rejection (Probst et al, 1997; Chen et al, 1999). Because the structures of the proteins (e.g., collagen, elastin) in acellular matrices are well conserved and normally arranged, the mechanical properties of the acellular matrices are not significantly different from those of native bladder submucosa (Dahms et al, 1998).

Polyesters of naturally occurring α -hydroxy acids, including PGA, PLA, and PLGA, are widely used in regenerative medicine. These polymers have gained FDA approval for human use in a variety of applications, including sutures (Gilding, 1981). The degradation products of PGA, PLA, and PLGA are nontoxic, natural metabolites that are eventually eliminated from the body in the form of carbon dioxide and water (Gilding, 1981). Because these polymers are thermoplastics, they can easily be formed into a three-dimensional scaffold with a desired microstructure, gross shape, and dimension by various techniques, including molding, extrusion (Freed et al, 1994), solvent casting (Mikos et al, 1994), phase separation techniques, and gas foaming techniques (Harris et al, 1998). More recently, techniques such as electrospinning have been used to quickly create highly porous scaffolds in various conformations (Han et al, 2006; Choi et al, 2008; Lee et al, 2008a, 2008b).

Many applications in genitourinary regenerative medicine require a scaffold with high porosity and a high ratio of surface area to volume. This need has been addressed by processing biomaterials into configurations of fiber meshes (Fig. 20-3C) and porous sponges using the techniques described previously. A drawback of the synthetic polymers is lack of biologic recognition. As an approach toward incorporating cell recognition domains into these materials, copolymers with amino acids have been synthesized (Barrera et al, 1993; Intveld et al, 1994; Cook et al, 1997). Other biodegradable synthetic polymers, including poly(anhydrides) and poly(orthoesters), can also be used to fabricate scaffolds for genitourinary regenerative medicine with controlled properties (Peppas et al, 1994).

Nanotechnology, the ability to use small molecules that have distinct properties in a small scale, has been used to create “smart” biomaterials for regenerative medicine ([Boccaccini et al, 2005](#); [Harrison et al, 2007](#)). Nanoscaffolds have been manufactured specifically for bladder applications ([Harrington et al, 2006](#)). The manufacturing of biomaterials can also lead to enhanced cell alignment and tissue formation ([Choi et al, 2008](#)).

Vascularization for Genitourinary Regenerative Medicine

The formation of the first capillaries takes place mostly during the early stages of embryogenesis (Folkman and D'Amore, 1996; Yancopoulos et al, 1998). Vasculogenesis can be divided into five consecutive steps: (1) ECs are generated from precursor cells, called *angioblasts*, in the bone marrow; (2) ECs form the vessel primordia and aggregates, which establish cell-to-cell contact but have no lumen; (3) a nascent endothelial tube is formed, composed of polarized ECs; (4) a primary vascular network is formed from an array of nascent endothelial tubes; and (5) pericytes and vascular smooth muscle cells are recruited (Drake et al, 1998).

Angiogenesis is a morphogenic process—new blood capillaries are formed from ECs of preexisting vessels. There are six basic steps in angiogenesis: (1) vasodilatation of the parental vessel, reducing the contact between adjacent ECs; (2) degradation of

the basement membrane of a parental vessel by secretion and activation of a wide range of proteolytic enzymes; (3) EC migration and proliferation to form a leading edge of the new capillary; (4) generation of the capillary lumen and formation of a tubelike structure; (5) basement membrane synthesis; and (6) recruitment of pericytes and vascular smooth muscle cells (Folkman and Brem, 1992).

When converting to the angiogenic stage, ECs capture new properties that enable them to neovascularize the tissue (Hanahan and Folkman, 1996). When the new vessels are in place and the vascular network matures, the neovascular ECs resume their quiescent phenotype (Darland and D'Amore, 1999). Several growth factors serve as stimuli for EC conversion to the angiogenic phenotype (Battegay, 1995). Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are two well characterized and important angiogenic molecules that have a direct effect on ECs.

Despite the successes in bioengineering tissues consisting of thin layers of cells such as skin, a major challenge for regenerative medicine in the future is the production of larger organs with more complex structures, such as the kidney. Tissues with a large mass of cells require a vascular network of arteries, veins, and capillaries to deliver nutrients to each cell. The development of efficient methods to vascularize bioengineered tissues is critical for a successful outcome. There are many obstacles to overcome before large entire tissue-engineered solid organs are produced. Recent developments in angiogenesis research may provide important knowledge and are essential.

REGENERATIVE MEDICINE OF UROLOGIC STRUCTURES

Urethra

Various strategies have been proposed over the years for the regeneration of urethral tissue. Woven meshes of PGA without cells (Bazeed et al, 1983; Olsen et al, 1992) and with cells (Atala, et al, 1992) were used to regenerate urethras in various animal models. Naturally derived collagen-based materials such as bladder-derived acellular submucosa (Chen et al, 1999), acellular urethral submucosa (Sievert et al, 2000), and collagen gels (Micol et al, 2012) have also been tried experimentally in various animal models for urethral reconstruction.

The bladder submucosa matrix (Chen et al, 1999) proved to be a suitable graft for repair of urethral defects in rabbits. The neourethras demonstrated a normal urothelial luminal lining and organized muscle bundles. These results were confirmed clinically in a series of patients with a history of failed hypospadias reconstruction wherein the urethral defects were repaired with human bladder acellular collagen matrices (Atala et al, 1999). The neourethras were created by anastomosing the matrix in an onlay fashion to the urethral plate. The size of the created neourethra ranged from 5 to 15 cm. After a 3-year follow-up, three of the four patients had a successful outcome with regard to cosmetic appearance and function (Fig. 20-4). One patient who had a 15-cm neourethra created



Figure 20-4. Urethrogram 6 months after surgery in a patient who had a portion of his urethra replaced as an onlay with the use of an acellular bladder submucosa matrix.

developed a subglanular fistula. The acellular collagen-based matrix eliminated the necessity of performing additional surgical procedures for graft harvesting, and both operative time and the potential morbidity from the harvest procedure were decreased. Similar results were obtained in pediatric and adult patients with primary urethral stricture disease using the same collagen matrices (El-Kassaby et al, 2003). Another study in 30 patients with recurrent stricture disease showed that a healthy urethral bed (two or fewer prior urethral surgeries) was needed for successful urethral reconstruction using acellular collagen-based grafts (El-Kassaby et al, 2008). A clinical trial using tubularized nonseeded small intestinal submucosa (SIS) for urethral stricture repair was performed in eight evaluable patients. Two patients with short inflammatory strictures maintained urethral patency. Stricture recurrence developed in the other six patients within 3 months of surgery (le Roux, 2005). Many pediatric and adult patients with urethral disease have been successfully treated in an onlay manner with collagen-based matrices. One of the advantages of this method over nongenital tissue grafts used for urethroplasty is that the material is “off the shelf.” This eliminates the necessity of additional surgical procedures for graft harvesting, which may decrease operative time, as well as the potential morbidity from the harvest procedure.

The techniques previously described, involving the use of nonseeded acellular matrices, were applied experimentally and clinically in a successful manner for onlay urethral repairs. However, when tubularized urethral repairs were attempted experimentally, adequate urethral tissue regeneration was not achieved and complications ensued, such as graft contracture and stricture formation (De Filippo et al, 2002). Autologous rabbit bladder epithelial and smooth muscle cells were grown and seeded onto preconfigured tubular matrices. Entire urethra segments were resected and urethroplasties were performed with tubularized collagen matrices either seeded with cells or without cells. The tubularized collagen matrices seeded with autologous cells formed new tissue that was histologically similar to native urethra. Use of the tubularized collagen matrices without cells led to poor tissue development, fibrosis, and stricture formation (Orabi et al, 2013). These findings were confirmed clinically. In a pilot series of patients published in *The Lancet*, five patients with urethral injuries secondary to motor vehicle accidents had a small tissue biopsy specimen retrieved starting in 2004. The cells were expanded in vitro and seeded in two layers, muscle and epithelia, on tubularized scaffolds that were implanted surgically (Fig. 20-5). The tubularized engineered urethras were able to show adequate anatomy, both by urethroscopy and with urethrog-raphy (see Fig. 20-5), and function long term, currently with follow-up exceeding 10 years (Raya-Rivera et al, 2011). In another series of five patients, tissue-engineered oral mucosa was seeded in cadaveric dermis, mainly with fibroblasts and keratinocytes. All patients required instrumentation postoperatively because of strictures, but they all had the diagnosis of lichen sclerosis (Bhargava et al, 2008). Other cell types have also been tried experimentally in acellular bladder collagen matrices, including foreskin epidermal cells and oral keratinocytes (Fu et al, 2007; Li et al, 2008). VEGF gene-modified urothelial cells have also been used experimentally for urethral reconstruction (Guan et al, 2008).

The normal wound healing response to injury has been studied extensively, and this knowledge has been helpful in maximizing success for the engineering of tissues. At the time of tissue injury, cell ingrowth is initiated from the wound edges to cover the tissue defect. The cells from the edges of the native tissue are able to traverse short distances without any detrimental effects. If the wound is large, more than a few millimeters in distance or depth, increased collagen deposition, fibrosis, and scar formation ensue. Matrices implanted in wound beds are able to lengthen the distances that cells can traverse without initiating an adverse fibrotic response. However, these distances are also limited. The maximum distance that adjacent cells from the wound edge have to travel to create normal tissue over a biologic matrix is approximately 1 cm (Dorin et al, 2008). Tissue defects greater than 1 cm that are treated with a matrix alone, without cells, usually have increased collagen deposition, increased

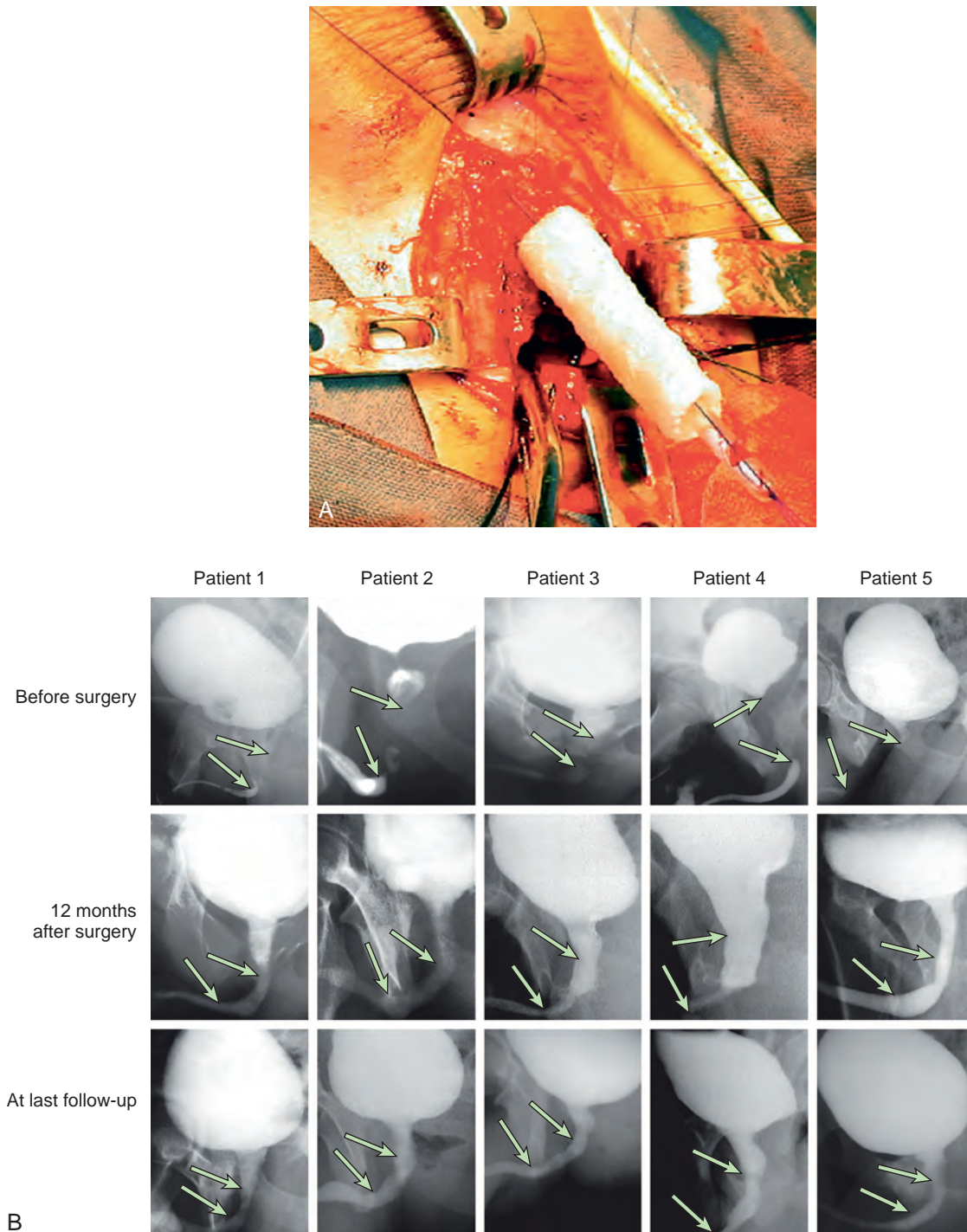


Figure 20-5. Tissue urethra implantation and clinical outcome in five patients after traumatic injury. **A**, An autologous cell-seeded graft sutured to the normal urethral margins from the first patient. **B**, Voiding cystourethrograms of five patients before surgery (arrows show the abnormal margins), 12 months after surgery (arrows show margins of tissue-engineered urethras), and at last follow-up to 7 years after surgery (arrows show margins of tissue-engineered urethras).

fibrosis, and scar formation. Cell-seeded matrices implanted in wound beds are able to further lengthen the distance for normal tissue formation without initiating an adverse fibrotic response. Studies in the field of regenerative medicine have shown that very large defects, greater than 30 cm, can be successfully treated using cell-seeded scaffolds. This explains the described experimental and clinical results noted with urethral repair. Nonseeded matrices are able to replace urethral segments when used in an onlay fashion because of the short distances required for tissue

ingrowth. However, if a tubularized urethral repair is needed, the matrices need to be seeded with autologous cells to avoid the risk of stricture formation and poor tissue development.

Bladder

Currently, gastrointestinal segments are commonly used as tissues for bladder replacement or repair. However, gastrointestinal tissues are designed to absorb specific solutes, whereas bladder tissue is

designed for the excretion of solutes. When gastrointestinal tissue is in contact with the urinary tract, multiple complications may ensue, such as infection, metabolic disturbances, urolithiasis, perforation, increased mucus production, and malignancy (McDougal, 1992). Because of the problems encountered with the use of gastrointestinal segments, numerous investigators have attempted alternative reconstructive procedures for bladder replacement or repair. These include autoaugmentation (Cartwright and Snow, 1989a, 1989b) and ureterocystoplasty (Adams et al, 1998). In addition, alternate methods for bladder reconstruction have been explored, such as the use of tissue expansion (Lailas et al, 1996; Satar et al, 1999) and regenerative medicine with cell transplantation.

Matrices for Bladder Regeneration

Over the last few decades, several bladder wall substitutes have been used in attempts at regeneration, with both synthetic and organic materials. Synthetic materials that have been tried in experimental and clinical settings include polyvinyl sponge, Teflon, collagen matrices, Vicryl (PGA) matrices, and silicone. Most of these attempts failed because of mechanical, structural, functional, or biocompatibility problems. Usually, permanent synthetic materials used for bladder reconstruction succumb to mechanical failure and urinary stone formation, and use of degradable materials leads to fibroblast deposition, scarring, graft contracture, and a reduced reservoir volume over time (Atala, 1995, 1998).

There has been a resurgence in the use of various collagen-based matrices for tissue regeneration. Nonseeded allogeneic acellular bladder matrices have served as scaffolds for the ingrowth of host bladder wall components. The matrices are prepared by mechanically and chemically removing all cellular components from bladder tissue (Probst et al, 1997; Yoo et al, 1998b). The matrices serve as vehicles for partial bladder regeneration, and relevant antigenicity is not evident.

Cell-seeded allogeneic acellular bladder matrices were used for bladder augmentation in dogs (Yoo et al, 1998b). Biomaterials preloaded with cells before their implantation showed better tissue regeneration compared with biomaterials implanted with no cells, in which tissue regeneration depended on ingrowth of cells from the surrounding tissue. The acellular collagen matrices can be enhanced with growth factors to improve bladder regeneration (Kikuno et al, 2009).

SIS, a biodegradable, acellular, xenogeneic collagen-based tissue-matrix graft, was first described in the early 1960s as an acellular matrix for tissue replacement in the vascular field (Rotthoff et al, 1964, 1969). The matrix is derived from pig small intestine in which the mucosa is mechanically removed from the inner surface and the serosa and muscular layer are removed from the outer surface. Animal studies have shown that the nonseeded SIS matrix used for bladder augmentation is able to regenerate in vivo (Kropp et al, 1996). Histologically, the transitional layer was the same as that of the native bladder tissue but, as with other nonseeded collagen matrices used experimentally, the muscle layer was not fully developed. In vitro contractility studies performed on SIS-regenerated dog bladders showed a decrease in maximal contractile response by 50% from that of normal bladder tissues.

Bladder augmentation using laparoscopic techniques was performed on minipigs with porcine bowel acellular tissue matrix, human placental membranes, or porcine SIS. At 12 weeks' postoperatively the grafts had contracted down to 60% of their original sizes, and histologically the grafts showed predominantly only mucosal regeneration (Portis et al, 2000). Hemicycstectomy and bladder replacement with SIS showed muscle at the graft periphery and center but it consisted of small fused bundles with significant fibrosis at 1 year. Compared with primary bladder closure after hemicycstectomy, no advantage in bladder capacity or compliance was documented (Landman et al, 2004).

In multiple studies using various materials as nonseeded grafts for cystoplasty, the urothelial layer was able to regenerate normally, but the muscle layer, although present, was not fully

developed (Kropp et al, 1996; Sutherland et al, 1996; Probst et al, 1997; Yoo et al, 1998b; Jayo et al, 2008b; Zhang, 2008). Studies involving acellular matrices that may provide the necessary environment to promote cell migration, growth, and differentiation are being conducted (Chun et al, 2007). With continued bladder research in this area, these matrices may have a clinical role in bladder replacement in the future.

Regenerative Medicine for Bladder Using Cell Transplantation

Regenerative medicine with selective cell transplantation may provide a means to create functional new bladder segments (Atala, 1997). The success of cell transplantation strategies for bladder reconstruction depends on the ability to use donor tissue efficiently and to provide the right conditions for long-term survival, differentiation, and growth. Various cell sources have been explored for bladder regeneration. Native cells are currently preferable because they can be used without rejection (Cilento et al, 1994). Amniotic fluid- and bone marrow-derived stem cells can also be used in an autologous manner and have the potential to differentiate into bladder muscle (De Coppi et al, 2007b; Shukla et al, 2008) and urothelium (Anumanthan et al, 2008). Embryonic stem cells also have the potential to differentiate into bladder tissue (Oottamasathien et al, 2007).

Formation of Bladder Tissue

Human urothelial and muscle cells can be expanded in vitro, seeded onto polymer scaffolds, and allowed to attach and form sheets of cells. The cell-polymer scaffold can then be implanted in vivo. Histologic analysis indicated that viable cells were able to self-assemble back into their respective tissue types, and would retain their native phenotype (Atala et al, 1993b). These experiments demonstrated, for the first time, that composite layered tissue-engineered structures could be created de novo.

It has been well established for decades that the bladder is able to regenerate generously over free grafts. Urothelium is associated with a high reparative capacity (de Boer et al, 1994). Bladder muscle tissue is less likely to regenerate in a normal fashion. Both urothelial and muscle ingrowth are believed to be initiated from the edges of the normal bladder toward the region of the free graft (Baker et al, 1958; Gorham et al, 1989). Usually, however, contracture or resorption of the graft has been evident. The inflammatory response toward the matrix may contribute to the resorption of the free graft. It was hypothesized that building the three-dimensional structure constructs in vitro, before implantation, would facilitate the eventual terminal differentiation of the cells after implantation in vivo and would minimize the inflammatory response toward the matrix, thus avoiding graft contracture and shrinkage. A dog study demonstrated a major difference between matrices used with autologous cells (tissue-engineered matrices) and those used without cells (Yoo et al, 1998b). Matrices implanted with cells for bladder augmentation retained most of their implanted diameter, as opposed to matrices implanted without cells for bladder augmentation, in which graft contraction and shrinkage occurred. The histomorphology demonstrated a marked paucity of muscle cells and a more aggressive inflammatory reaction in the matrices implanted without cells.

To better address the functional parameters of tissue-engineered bladders, a canine animal model was designed that required a subtotal cystectomy with subsequent replacement with a tissue-engineered organ (Oberpenning et al, 1999). Cystectomy-only and nonseeded controls maintained average capacities of 22% and 46% of preoperative values, respectively. An average bladder capacity of 95% of the original precystectomy volume was achieved in the cell-seeded tissue-engineered bladder replacements. These findings were confirmed radiographically (Fig. 20-6). Histologically, the nonseeded scaffold bladders presented a pattern of normal urothelial cells with a thickened fibrotic submucosa and a thin layer of muscle

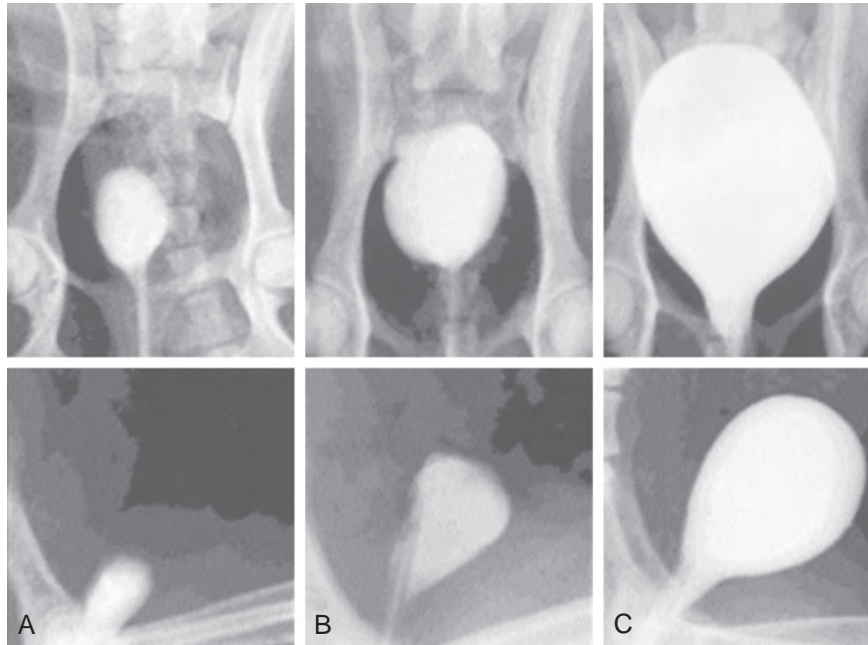


Figure 20-6. Radiographic cystograms in beagles 11 months after subtotal cystectomy without reconstruction (A); with reconstruction using a polymer without cells (B); and with reconstruction with a polymer and cell-seeded tissue-engineered organ (C). Organs after trigone-sparing cystectomy retained a small reservoir. Tissue-engineered neobladders showed a normal configuration and a larger capacity than the trigones grafted with polymer only.

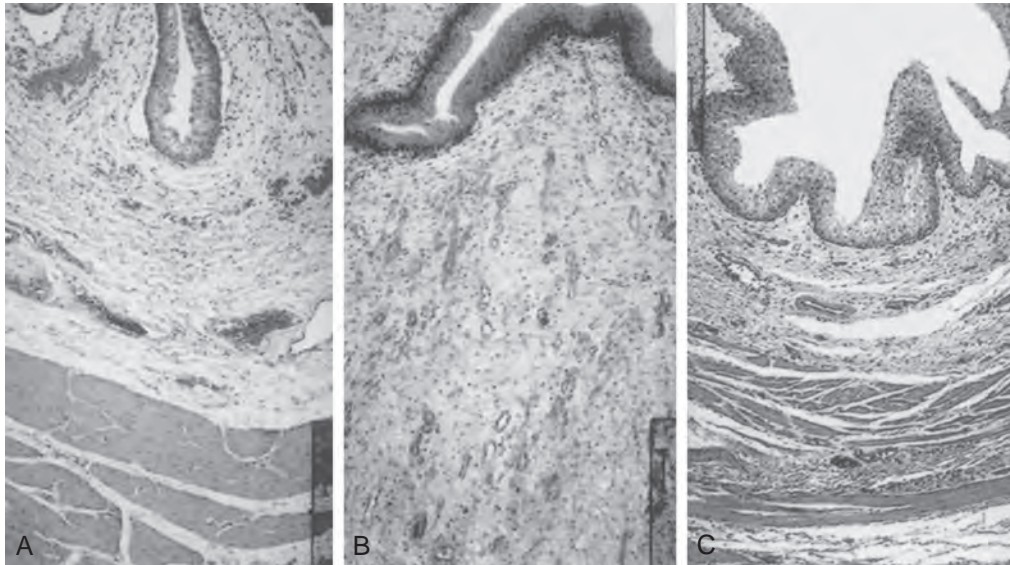


Figure 20-7. Hematoxylin and eosin staining shows histologic results 6 months after surgery (original magnification, $\times 250$). A, Normal canine bladder. B, The bladder dome of the bladder reconstructed with cell-free polymer consists of normal urothelium over a thickened layer of collagen and fibrotic tissue; only scarce muscle fibers are apparent. C, The tissue-engineered neo-organ has a histomorphologically normal appearance. A trilayered architecture consisting of urothelium, submucosa, and smooth muscle is evident.

fibers. The retrieved tissue-engineered bladders showed a normal cellular organization, consisting of a trilayer of urothelium, submucosa, and muscle (Fig. 20-7). These studies, performed with PGA-based scaffolds, have been repeated by other investigators, showing similar results in large numbers of animals long term (Jayo et al, 2008a, 2008b). However, not all scaffolds perform well if a large portion of the bladder needs replacement. In a study using SIS for subtotal bladder replacement in dogs, both the unseeded and

cell-seeded experimental groups showed graft shrinkage and poor results (Zhang et al, 2006b). The type of scaffold used is critical for the success of these technologies. The use of bioreactors, wherein mechanical stimulation is started at the time of organ production, has also been proposed as an important parameter for success (Farhat and Yeger, 2008; Bouhout et al, 2011).

A clinical experience involving engineered bladder tissue for cystoplasty reconstruction was conducted starting in 1998. A small

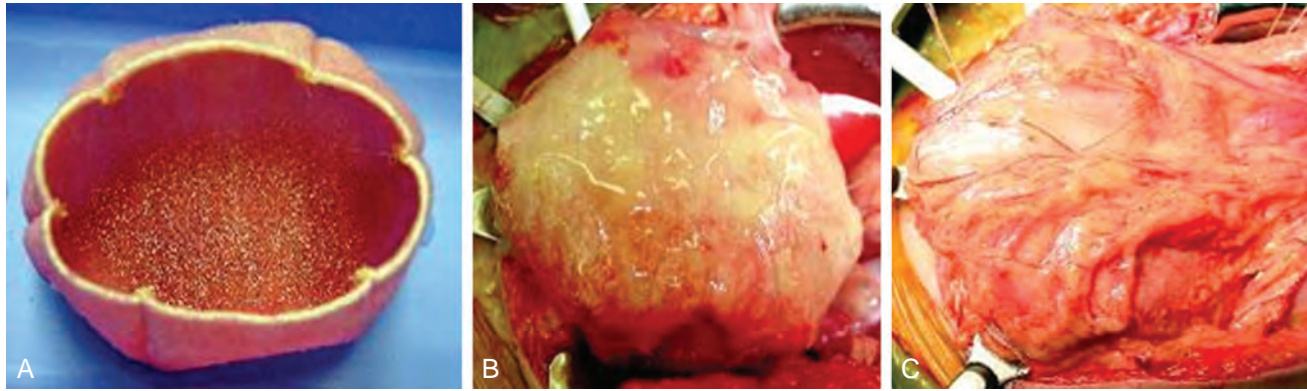


Figure 20-8. Construction of engineered bladder. A, Scaffold material seeded with cells for use in bladder repair. B, The seeded scaffold is anastomosed to native bladder with running 4-0 polyglycolic sutures. C, Implant covered with fibrin glue and omentum.

pilot study of seven patients was reported, using a collagen scaffold seeded with cells either with or without omentum coverage, or a combined PGA-collagen scaffold seeded with cells and omental coverage (Fig. 20-8). The patients who underwent reconstruction with the engineered bladder tissue created with the PGA-collagen cell-seeded scaffolds with omental coverage showed increased compliance, decreased end-filling pressures, increased capacities, and longer dry periods over time (Atala et al, 2006). Although the experience is promising in terms of showing that engineered tissues can be implanted safely, it is just a start in terms of accomplishing the goal of engineering fully functional bladders. This was a limited clinical experience, and the technology is not yet ready for wide dissemination; further experimental and clinical studies are required. FDA phase 2 studies have now been completed.

From the aforementioned studies it is evident, as with the urethral studies, that the use of cell-seeded matrices is superior to the use of nonseeded matrices for the creation of engineered bladder tissues. Although advances have been made with the engineering of bladder tissues, many challenges remain. Current research in many centers is aimed at the development of biologically active and “smart” biomaterials that may improve tissue regeneration. Also, similar engineering techniques are now being used for patients with bladder cancer, who are having engineered urinary conduits implanted after cystectomy (Hyndman et al, 2012). Stem cells derived from fat can be differentiated into smooth muscle for the conduits, thus avoiding native cells from bladder cancer patients (Basu et al, 2012).

Bladder Cell Therapies

Both urinary incontinence and vesicoureteral reflux are common conditions affecting the genitourinary system for which injectable therapy within the bladder may be useful. The ideal substance for the endoscopic treatment of reflux and incontinence should be injectable, nonantigenic, nonmigratory, volume stable, and safe for human use (Kershner et al, 1999). Toward this goal, long-term studies were conducted to determine the effect of injectable chondrocytes in vivo (Atala et al, 1993a). This system was adapted for the treatment of reflux in a porcine model (Atala et al, 1994).

The first human application of cell-based regenerative medicine technology for urologic applications occurred with the injection of chondrocytes for the correction of vesicoureteral reflux in children and for urinary incontinence in adults. Phase 1 trials showed an approximate success rate of 80% at both 3 and 12 months postoperatively (Bent et al, 2001). Patients with vesicoureteral reflux were treated at 10 centers throughout the United States. The patients had a similar success rate as with other injectable substances in terms of cure. The overall success rate in 29 children (47 ureters) was 86%. At 1-year follow-up, reflux correction was maintained in 70% of the

ureters. Chondrocyte formation was not noted in patients who had treatment failure (Diamond et al, 1999).

With cell therapy techniques, the use of autologous smooth muscle cells was explored for both urinary incontinence and vesicoureteral reflux applications (Cilento et al, 1995). In vivo experiments were conducted in minipigs, and reflux was successfully corrected. The potential use of injectable, cultured myoblasts for the treatment of stress urinary incontinence has been investigated in animal models (Chancellor et al, 2000; Yokoyama et al, 2000; Cannon et al, 2003; Lee et al, 2003; Strasser et al, 2004; Kwon et al, 2006; Mitterberger et al, 2007b). Intrinsic muscle precursor cells have also been shown to play an active role in the regeneration of injured striated urethral sphincter (Yiou et al, 2003a, 2003b). A canine model of irreversible urethral sphincter injury was also created to test these technologies (Eberli et al, 2008, 2012).

Other cell types have also been used for urinary incontinence. The use of amniotic fluid-derived stem cells has been tested experimentally (Chun et al, 2012; Kim et al, 2012a). The use of lipoaspirate cells has also been proposed for the treatment of urinary incontinence. The lipoaspirate cells were injected into mice bladders and urethras, and regenerated muscle tissue (Jack et al, 2005; Fu et al, 2010; Zhao et al, 2011). The cells were used in the clinical setting in patients in an autologous manner in a pilot study with adequate results (Yamamoto et al, 2012).

Several clinical trials using myoblast injection have been conducted in patients with stress urinary incontinence (Mitterberger et al, 2007a). The authors compared the effectiveness and tolerability of ultrasonography-guided injections of autologous cells with those of endoscopic injections of collagen for stress incontinence in 63 patients, showing improved results for the patients receiving the myoblasts. However, controversy surrounding the trial ensued and the paper was retracted. In another trial, myoblasts isolated from the abdominal wall vasculature were injected in a series of bladder exstrophy patients with urinary incontinence. The authors reported that 88% of patients were socially dry, described as daytime dryness lasting more than 3 hours. The patients were also on a pelvic floor electrical stimulation and pelvic floor exercise program (Kajbafzadeh et al, 2008). Another study described the use of autologous muscle-derived stem cell injection to treat stress urinary incontinence. After 1 year, one of eight women achieved total continence and five reported improvement (Carr et al, 2008). A 24% success rate was obtained in a patient trial using myoblasts delivered with ultrasound guidance (Blaganje and Lukianović, 2012). Activity has increased in the area of cell therapy for urinary incontinence in the last several years. Further trials and follow-up will be needed to determine long-term efficacy.

Cell therapy studies have also been conducted for radiation cystitis. Bone marrow cells have been injected in rats (Imamura et al, 2012). Both amniotic fluid and bone marrow stem cells have been used to ameliorate bladder dysfunction in a Parkinson animal

model (Soler et al, 2012). Also, recently, mechanisms are being elucidated for the regeneration of bladder stem cells in situ—for example, with a Hedgehog and Wnt feedback system (Shin et al, 2011). These studies are certain to advance with the generation of small molecules and pharmacologic agents for regenerative medicine (Lu and Atala, 2013).

Ureters

Various strategies have been used to engineer ureteral tissues experimentally, but these have not yet been implanted in patients.



Additional information on regenerative medicine efforts in the ureter appears on the Expert Consult website.

Male Genital and Reproductive Tissues

Reconstructive surgery is required for a wide variety of pathologic penile conditions, including penile carcinoma, trauma, severe erectile dysfunction, and congenital conditions such as ambiguous genitalia, hypospadias, and epispadias. One of the major limitations of genital reconstructive surgery is the availability of sufficient autologous tissue. Nongenital autologous tissue sources have been used for decades. Phallic reconstruction was initially attempted in the late 1930s, with rib cartilage used as a stiffener for patients with traumatic penile loss (Frumppkin, 1944; Goodwin and Scott, 1952). This method, involving multiple staged surgeries, was soon discouraged because of the unsatisfactory functional and cosmetic results. Silicone rigid prostheses were popularized in the 1970s and have been used widely (Small et al, 1975; Bretan, 1989). However, biocompatibility issues have been a problem in selected patients (Thomalla et al, 1987; Nukui et al, 1997).



Research has also been performed looking at the possibility of creating prostheses with cells; this information appears on the Expert Consult website.

Reconstruction of Penile Corpora

One of the major components of the phallus is corporeal smooth muscle. The creation of autologous functional and structural corporeal tissue de novo would be beneficial. Initial experiments showed that cultured human corporeal smooth muscle cells may be used in conjunction with biodegradable polymers to create corpus cavernosum tissue de novo (Kershen et al, 2002). When grown on collagen, corporeal cavernosal ECs formed capillary structures that created complex three-dimensional capillary networks. In a subsequent study, human corporeal smooth muscle cells and ECs seeded on biodegradable polymer scaffolds were able to form vascularized cavernosal muscle when implanted in vivo (Park et al, 1999). A naturally derived acellular corporeal tissue matrix that possesses the same architecture as native corpora was developed. Acellular collagen matrices were derived from processed donor rabbit corpora using cell lysis techniques. Human corpus cavernosal muscle and ECs were derived from donor penile tissue, and the cells were expanded in vitro and seeded on the acellular matrices. The matrices were covered with the appropriate cell architecture 4 weeks after implantation (Falke et al, 2003). The use of these tissue-derived matrices as cell-delivery scaffolds allowed for the development of adequate structural and vascular corpora cavernosa constructs.

To look at the functional parameters of the engineered corpora, acellular corporeal collagen matrices were obtained from donor rabbit penis and autologous corpus cavernosal smooth muscle, and ECs were harvested, expanded, and seeded on the matrices. An entire cross-sectional segment of protruding rabbit phallus was excised, leaving the urethra intact, and the cell-seeded matrices were interposed into the excised corporeal space. Functional and structural parameters (cavernosography, cavernosometry, mating behavior, and sperm ejaculation) were followed, and histochemical, immunocytochemical, and Western blot analyses were performed up to 6 months after implantation. The engineered corpora cavernosa achieved adequate structural and functional parameters (Kwon et al, 2002). This technology was further confirmed when the entire

rabbit phallus corpora were removed and replaced with the engineered scaffolds seeded with both corporeal endothelial and smooth muscle cells (Fig. 20-9). The experimental corporeal bodies demonstrated intact structural integrity by cavernosography and showed similar pressure by cavernosometry when compared with normal controls (Fig. 20-10). The control rabbits without cells failed to show normal erectile function throughout the study period. Mating activity in the animals with the engineered corpora appeared normal by 1 month after implantation. The presence of sperm was confirmed during mating, and sperm was present in all the rabbits with the engineered corpora. The female rabbits mated with the animals implanted with engineered corpora and also conceived and delivered healthy pups. Animals implanted with the matrix alone were unable to demonstrate normal mating activity and failed to ejaculate into the vagina. Grossly, the corporeal implants with cells showed continuous integration of the graft into native tissue. Histologically, sinusoidal spaces and walls, lined with endothelium and smooth muscle, were observed in the engineered grafts. Grafts without cells contained fibrotic tissue and calcifications with sparse corporeal elements. Each cell type was identified immunocytochemically and by Western blot analyses. The engineered corporeal tissues were able to contract and relax in response to electric field and pharmacologic stimulation, and the contractile response reached levels similar to normal corpora by 6 months after implantation (Chen et al, 2010).

The aforementioned series of studies demonstrates that penile corpora cavernosa tissue can be engineered. The engineered tissue is able to achieve adequate structural and functional parameters sufficient for erection, copulation, ejaculation, conception, and delivery experimentally. Further studies will be needed to confirm the long-term functionality of these organs. In addition, further studies are needed to show that human structures can also be engineered.

Penile Cell Therapy

Various cell therapies have been proposed and used experimentally for erectile dysfunction. ECs have been used in animal models to reverse erectile dysfunction (Gou et al, 2011). Mesenchymal stem cells have been used either alone or in combination with matrices (Lin et al, 2011; Kim et al, 2012b), showing an improvement in function in mice. The delivery of human bone marrow–derived stem cells to the periprosthetic region in rats led to improved response after the cells were injected in the corpora (Qiu et al, 2011; You et al, 2013). Muscle-derived stem cells showed the prevention of erectile dysfunction after cavernosal injury in rats (Kovanecz et al, 2012). Adipose-derived cells have also been used in rodents, showing reversal of corporeal damage, with or without growth factors (Orabi et al, 2012; Qiu et al, 2012; Ryu et al, 2012; Liu et al, 2013). Similar cells have also been used to treat Peyronie disease (Castiglione et al, 2013). Various cell populations are making a transition into the clinic. Long-term studies will be needed to gauge the full impact of these therapies.

Testis

Leydig cells are the major source of testosterone production in males. Patients with testicular dysfunction require androgen replacement for somatic development. Conventional treatment for testicular dysfunction consists of periodic intramuscular injections of chemically modified testosterone or, more recently, skin patch applications. However, long-term nonpulsatile testosterone therapy is not optimal and can cause multiple problems, including erythropoiesis and bone density changes.

A system was designed wherein Leydig cells were microencapsulated for controlled testosterone replacement. Microencapsulated Leydig cells offer several advantages, such as serving as a semipermeable barrier between the transplanted cells and the host's immune system, as well as allowing for the long-term physiologic release of testosterone. Purified Leydig cells were isolated and encapsulated in an alginate-poly-L-lysine solution. The encapsulated Leydig cells

Collagen tubular sponges have been used to transplant bladder cells for replacement of ureteral segments in dogs. The study showed severe stricture formation and papillary mucosal thickening at the anastomotic sites. In addition, muscle regeneration into the collagen grafts was not evident (Tachibana et al, 1985).

Ureteral decellularized matrices have been used as a scaffold both for the ingrowth of ureteral tissue (Dahms et al, 1997) and as a cell delivery vehicle using urothelial and bone marrow-derived cells (Matsunuma et al, 2006). Laparoscopic segmental ureteral replacement with an acellular matrix prepared from ureters and small-intestinal submucosa was performed in minipigs (Shalhav et al, 1999). At 12 weeks, all animals had complete obstruction at the level of the replacement. Ureteral replacement with polytetrafluoroethylene (Teflon) grafts was attempted in dogs, also with poor functional results (Baltaci et al, 1998). Nonseeded ureteral collagen acellular matrices were tubularized and used to replace 3-cm segments of canine ureters. At the time of sacrifice there was moderate to marked hydronephrosis above the level of the new tube in all dogs, with significant narrowing of the ureteral lumen up to complete occlusion (Osman et al, 2004).

Cell-seeded biodegradable polymer scaffolds have been used as cell transplantation vehicles to reconstruct ureteral tissues. In one study, urothelial and smooth muscle cells isolated from bladders and expanded in vitro were seeded onto PGA scaffolds with tubular configurations and implanted subcutaneously into athymic mice. After implantation, the urothelial cells proliferated to form a multilayered luminal lining of tubular structures, whereas the smooth muscle cells organized into multilayered structures surrounding the urothelial cells. Abundant angiogenesis was evident. The degradation of the polymer scaffolds resulted in the eventual formation of natural urothelial tissues (Atala et al, 1993b). This study suggested that it was possible to engineer urologic tissues containing multiple cell types. This approach was expanded to replacement of ureters in dogs by transplantation of smooth muscle cells and urothelial cells on tubular polymer scaffolds (Yoo et al, 1995). Amniotic membranes have also been used experimentally as a ureteral replacement (Ismail et al, 2009). The limitations of transferring this technology to humans are the small number of patients requiring this type of tissue, and the large investment that would be required for regulatory approval.

Engineered Penile Prostheses

Although silicone is an accepted biomaterial for penile prostheses, biocompatibility is a concern (Thomalla et al, 1987; Nukui et al, 1997). The use of a natural prosthesis composed of autologous cells may be advantageous. A feasibility study for the creation of natural penile prostheses made of cartilage was performed initially (Yoo et al, 1998a).

Cartilage harvested from the articular surface of calf shoulders was isolated, grown, and expanded in culture. The cells were seeded onto preformed cylindric PGA polymer rods and implanted in mice. At retrieval, all polymer scaffolds seeded with cells formed milky-white, rod-shaped, solid cartilage structures, maintaining their pre-implantation size and shape. In a subsequent study using an autologous system, the feasibility of applying the engineered

cartilage rods in situ was investigated (Yoo et al, 1999). Autologous chondrocytes harvested from rabbit ear were grown and expanded in culture. The cells were seeded onto biodegradable PLLA-coated PGA polymer rods and implanted into the corporeal spaces of rabbits. Examination at retrieval showed the presence of well-formed, milky-white cartilage structures within the corpora at 1 month. The animals were able to copulate and impregnate their female partners. In another study, human cartilage rods were engineered in vitro for potential use as penile prostheses. Chondrocytes isolated from human ear were seeded on rod-shaped biodegradable polymer scaffolds (1.2 cm in diameter, 6.0 cm long). The engineered human cartilaginous rods were flexible, elastic, and able to withstand high degrees of compressive forces. The mechanical properties were comparable to those of commercially available silicone prostheses (Kim et al, 2002).

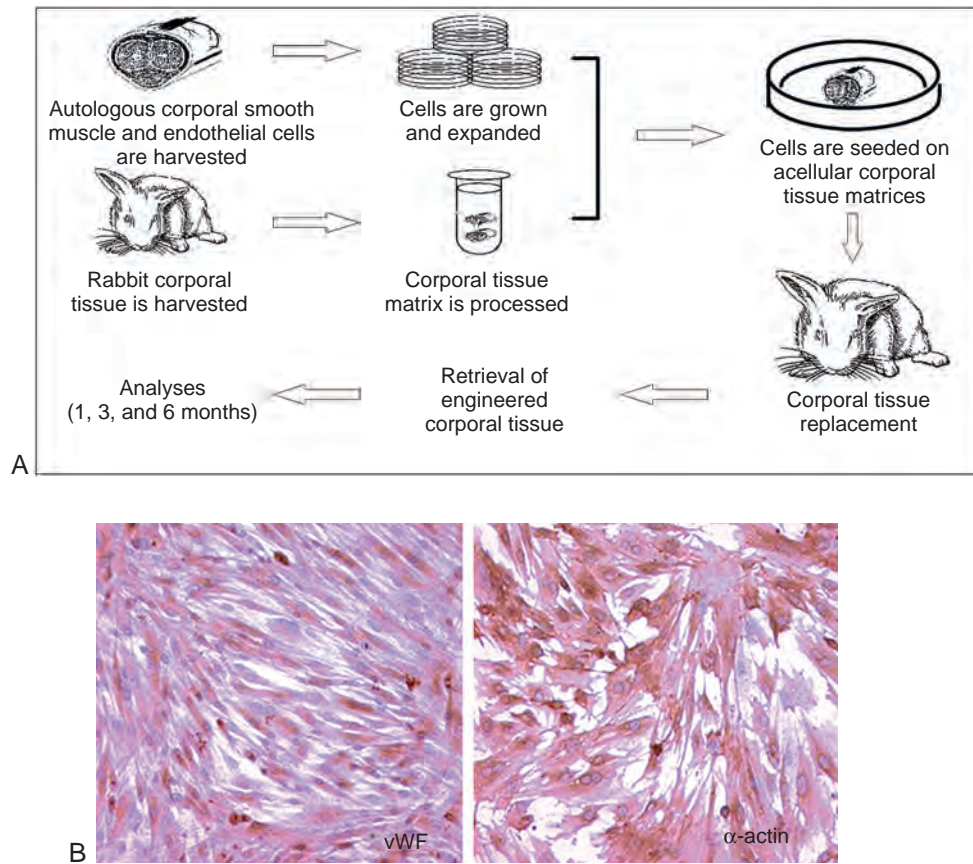


Figure 20-9. Isolation and culture of autologous corporeal cavernosal cells for tissue engineering. **A,** Overall study design. **B,** Culture expanded endothelial cells (*left*) show positive expression of cell-specific marker von Willebrand factor (vWF) protein, and smooth muscle cells show expression of smooth muscle-specific α -actin (*right*).

were injected into castrated animals, and serum testosterone was measured serially; the animals were able to maintain testosterone levels in the long term (Machluf and Atala, 1998). These studies suggest that microencapsulated Leydig cells may be able to replace or supplement testosterone in situations where anorchia or testicular failure is present. A novel technique to isolate Leydig stem cells and to study Leydig cell development has also been described (Lo et al, 2004). The successful transplantation of functional Leydig stem cells into a hypogonadal recipient showed that the *de novo* synthesis of testosterone is possible.

Further studies showed that testicular prostheses created with chondrocytes in bioreactors could be loaded with testosterone. The prostheses were implanted in athymic mice with bilateral anorchia, and testosterone was released long term, maintaining the androgen level at a physiologic range (Raya-Rivera et al, 2008). One could envision combining the Leydig cell technology previously described with engineered prostheses for the long-term functional replacement of androgen levels.

The ability to have spermatogenesis for infertility purposes has been a major area of interest in the last several decades. The introduction of spermatogonial stem cell transplantation in mice opened new avenues to the field of male infertility treatment (Brinster and Zimmermann, 1994). Since the discovery of the feasibility of spermatogonial stem cell isolation and autotransplantation, it has been demonstrated in several species including nonhuman primates. The first successful isolation of human spermatogonial stem cells in 2002 showed that the cells were able to colonize and survive for 6 months in mice recipient testes (Nagano et al, 2002). The same group had been able to show the restoration of fertility in mice with the transplantation of male germline stem cells (Ogawa et al, 2000). Sertoli cells, the main component of the testicular germ cell niche,

were also able to restore fertility in mice (Kanatsu-Shinohara et al, 2005). More recently, successful autologous and allogeneic spermatogonial stem cell transplantation was demonstrated in adult and prepubertal macaque testes that were previously rendered infertile with alkylating chemotherapy (Hermann et al, 2012). **In vitro** propagation of human spermatogonial stem cells from both adult and pubertal testes has been established (Sadri-Ardekani et al, 2009). In these systems, human spermatogonial stem cells are supported by a feeder layer from the same patient's testicular somatic cells. Human spermatogonial stem cells could be maintained *in vitro* for more than 15 weeks (Sadri-Ardekani et al, 2011). Optimization of this culture system based on FDA regulations and current good tissue practice (CGTP) requirements is imperative before use in a clinical application.

Female Genital and Reproductive Tissues

Congenital malformations of the uterus may have profound implications clinically. Patients with cloacal exstrophy and intersex disorders may not have sufficient uterine tissue present for future reproduction. The possibility of engineering functional uterine tissue using autologous cells was investigated (Wang et al, 2003). Autologous rabbit uterine smooth muscle and epithelial cells were harvested, grown, and expanded in culture. These cells were seeded onto preconfigured uterine-shaped biodegradable polymer scaffolds, which were then used for subtotal uterine tissue replacement in the corresponding autologous animals. On retrieval 6 months after implantation, histologic, immunocytochemical, and Western blot analyses confirmed the presence of uterine tissue components. Biomechanical analyses and organ bath studies showed that the functional characteristics of these tissues were similar to those of

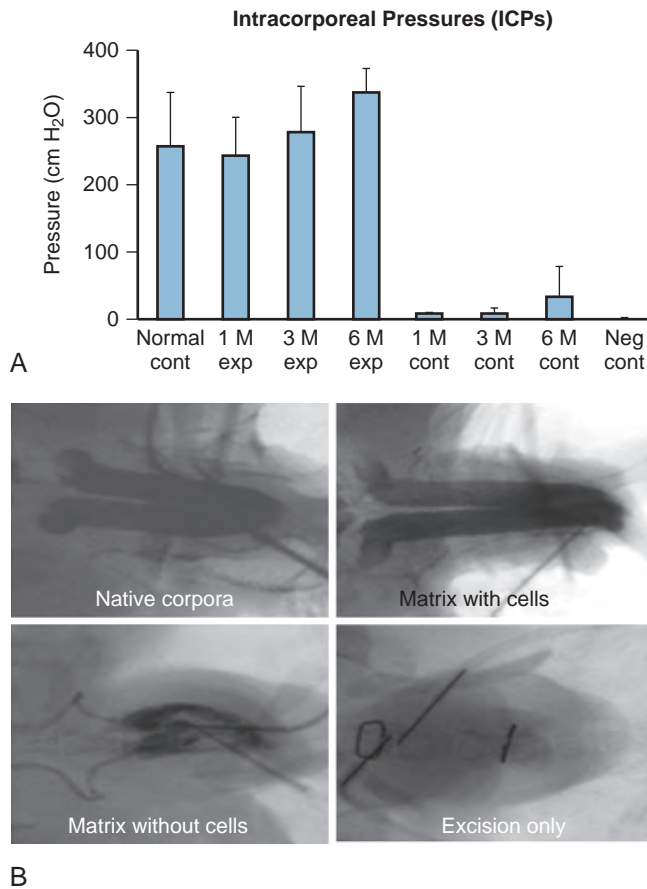


Figure 20-10. Cavernosometry and cavernosography. A, Cavernosometry shows that all rabbits implanted with the bioengineered corpora after complete penile corporeal excision had sufficient intracorporeal pressure (ICP) to attain erection ($n = 12$). The levels of ICP were comparable to native corpora ($n = 12$). B, Cavernosography shows a homogeneous appearance of corpora in the bioengineered group ($n = 12$) similar to the native corpora ($n = 16$), numerous filling defects in the unseeded control group ($n = 12$), and major filling gaps in the negative control group ($n = 3$).

normal uterine tissue. Breeding studies using these engineered uteri are currently being performed.

Similarly, several pathologic conditions, including congenital malformations and malignancy, can adversely affect normal vaginal development or anatomy. Vaginal reconstruction has traditionally been challenging because of the paucity of available native tissue.

Many techniques and materials can be used successfully for vaginal reconstruction. The most common surgical reconstructive approach involves creating a canal by dissecting the potential neovaginal space and subsequently lining the pelvic canal with a graft. Multiple materials have been used to line the surgically created cavity, including mostly full- or split-thickness skin grafts, but also cellulose (Dornelas et al, 2012), decellularized matrices derived from skin or intestinal mucosa (Ding et al, 2013; Zhu et al, 2013), and vaginal epithelia (Panici et al, 2007).

The feasibility of engineering vaginal tissue with cells in vivo was also investigated (De Filippo et al, 2003). Vaginal epithelial and smooth muscle cells of female rabbits were harvested, expanded, and seeded onto biodegradable polymer scaffolds, and the cell-seeded constructs were then implanted into both athymic mice ex situ and rabbits as a full replacement of the organ. Functional studies in the tissue-engineered constructs showed similar properties to those of normal vaginal tissue. When these constructs were used for autologous total vaginal replacement in a rabbit model, patent functional vaginal structures were noted

in the tissue-engineered specimens, whereas the non-cell-seeded structures were noted to be stenotic (De Filippo et al, 2008) (Fig. 20-11). These studies indicated that a regenerative medicine approach to clinical vaginal reconstruction would be a realistic possibility. Clinical trials are currently being conducted.

Ovarian tissue is essential for fertility. Recent studies have shown that ovarian cells can be derived from stem cell populations. The cells can lead to the production of oocytes and embryos (Choi et al, 2011). Implanted oocytes have shown full functionality, including fertility and live delivery in mice.

Cell therapies have also been used to enhance the functionality of the ovary experimentally in animal models. Adipose-, amniotic fluid-, umbilical cord-, and bone marrow-derived stem cells have all resulted in a return of experimentally damaged ovarian function in animal models (Fu et al, 2008; Abd-Allah et al, 2013; Lai et al, 2013; Sun et al, 2013; Wang et al, 2013).

Renal Structures

Although the kidney was the first organ to undergo substitution with an artificial device and the first successfully transplanted organ (Guild et al, 1955), current modalities of treatment are far from satisfactory. Dialysis remains the most common treatment for renal failure. Renal tissue is arguably one of the most difficult tissues to replicate in the laboratory. The kidney is a complex organ, and the unique structural and cellular heterogeneity present within this organ creates many challenges. The system of nephrons and collecting ducts within the kidney is composed of multiple functionally and morphologically distinct segments. For this reason, appropriate conditions must be provided to ensure the long-term survival, differentiation, and growth of many types of cells. Efforts in the area of kidney tissue regeneration have focused on the development of reliable cell sources (Prockop, 1997; Kale et al, 2003; Lin et al, 2003; Ikarashi et al, 2005; Lin et al, 2005; Yokoo et al, 2005). Moreover, optimal growth conditions have been extensively investigated to provide adequate enrichment to achieve stable renal cell expansion systems (Milici et al, 1985; Carley et al, 1988; Humes et al, 1992; Schena, 1998).

Isolation of particular cell types that produce specific factors may be a good approach for selective cell therapies. For example, renal cells that produce erythropoietin have been isolated in culture, and these cells could eventually be used to treat anemia that results from end-stage renal failure (AbouShwareb et al, 2008; Gyabaah et al, 2012). These cells have also been used to improve renal function in a model of chronic kidney disease (Yamaleyeva et al, 2012). Defined primary cells from the kidney have been studied extensively and used to reconstitute human function (Guimaraes-Souza et al, 2012). More ambitious approaches involve working toward the goal of total renal function replacement. To create kidney tissue that would deliver full renal function, a culture containing all of the cell types comprising the functional nephron units should be used. Optimal culture conditions to nurture renal cells have been extensively studied, and cells grown under these conditions have been reported to maintain their cellular characteristics (Lanza et al, 2002). Cells obtained through the initial process of nuclear transfer have been retrieved and expanded from cloned tissue. Moreover, renal cells placed in a three-dimensional culture environment are able to reconstitute into renal structures. In vitro generated kidney constructs were implanted in the renal capsule region in rats, and they vascularized and formed glomeruli (Joraku et al, 2009).

Recent investigative efforts in the search for a reliable cell source have been expanded to stem and progenitor cells. Use of these cells for tissue regeneration is attractive because of their ability to differentiate and mature into specific cell types needed. This is particularly useful when primary renal cells are unavailable as a result of extensive tissue damage. Bone marrow-derived human mesenchymal stem cells have been shown to be a potential source because of their ability to differentiate into several cell lineages (Ikarashi et al, 2005). The creation of adequate experimental models of renal failure has been critical for the testing of various cell therapies (Wang et al, 2013). Bone marrow-derived cells have been shown to

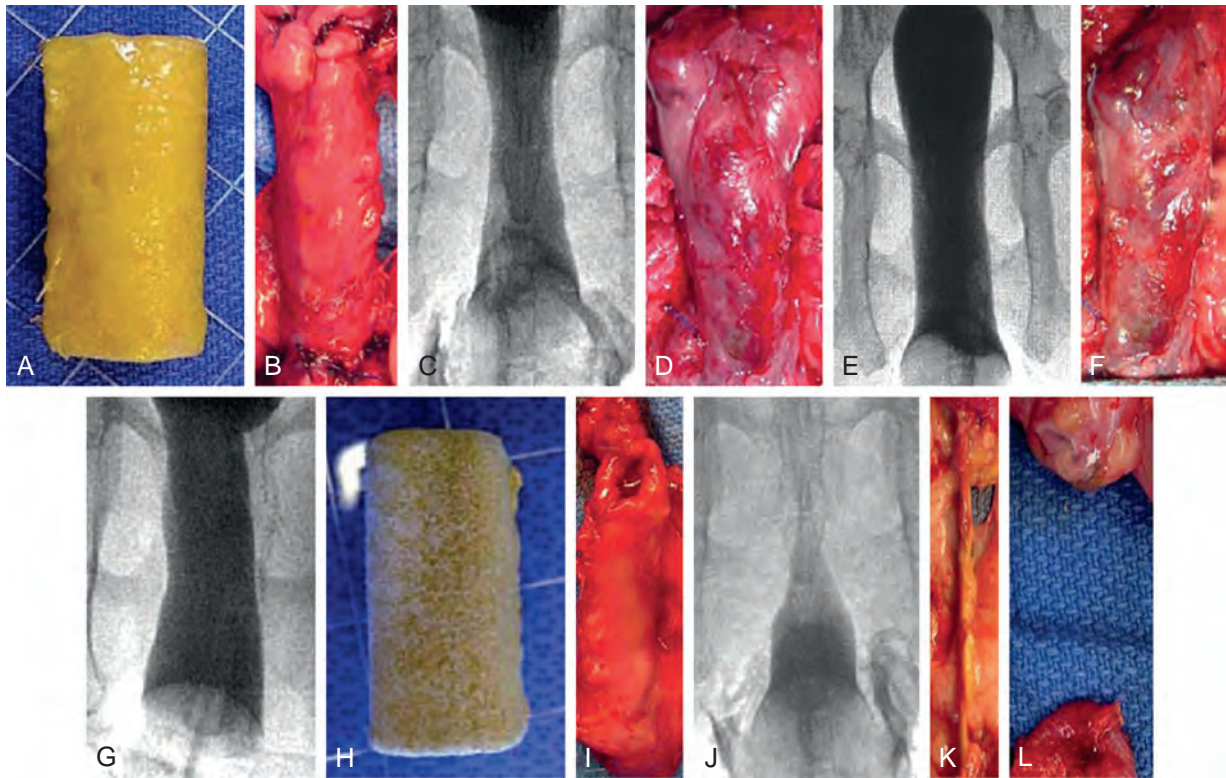


Figure 20-11. Appearance of tissue-engineered neovaginas. A, Tubular polymer scaffold after cell seeding and 1 week in vitro culture, before implantation in vivo. B, D, and F indicate gross appearance and C, E, and G show vaginography of cell-seeded constructs 1, 3, and 6 months postimplantation, respectively. H, Unseeded control scaffold before implantation. I, K, L, Gross appearance of unseeded construct at 1, 3, and 6 months postimplantation. J, Vaginography of unseeded graft at 1 month.

participate in kidney development when they are placed in a rat embryonic niche that allows for continued exposure to a repertoire of nephrogenic signals (Yokoo et al, 2005). The major cell source of kidney regeneration was found to originate from intrarenal cells in an ischemic renal injury model (Lin et al, 2005). Systemic administration of bone marrow–derived mesenchymal stem cells in mice has led to prevention of kidney damage in various animal models (Humphreys and Bonventre, 2008; Lin, 2008; Morigi et al, 2010). Autologous bone marrow cells have been used clinically for the treatment of allograft rejection after transplantation in a pilot study (Reinders et al, 2013). Other trials are also currently underway with bone marrow–derived stem cells and with primary renal cells, and it is still early to define the outcomes.

Other stem cell types, such as hESCs (Lin, 2006; Bruce et al, 2007), induced pluripotent stem cells (Osafune, 2010; Song et al, 2012), and human amniotic fluid and placental stem cells (Perin et al, 2007; Hauser et al, 2010) can also lead to renal differentiation and reversal of renal injury in animal models. Developmental approaches to kidney regeneration have also been studied, but these are mostly research-driven approaches without a direct clinical pathway.

Additional information can be found on the Expert Consult website.

Regenerative Medicine Approaches to Kidney Regeneration

The ability to grow and expand renal cells is one of the essential requirements in engineering tissues. The feasibility of achieving renal cell growth, expansion, and in vivo reconstitution using regenerative medicine techniques has been investigated (Atala et al, 1991). Donor rabbit kidney cells including distal tubules, glomeruli, and proximal tubules were plated separately in vitro and after expansion were seeded onto biodegradable PGA scaffolds.

Histologic examination demonstrated progressive formation and organization of the nephron segments within the polymer fibers with time. These results demonstrated that renal-specific cells can be successfully harvested and cultured and can subsequently attach to artificial biodegradable polymers. However, it was unclear whether the tubular structures reconstituted de novo from dispersed renal elements or if they merely represented fragments of donor tubules that survived the original dissociation and culture processes intact. Further investigation was conducted to examine the process (Fung et al, 1996). Mouse renal cells were harvested and expanded in culture. Subsequently, single isolated cells were seeded on biodegradable polymers and implanted into immune-competent syngeneic hosts. Renal epithelial cells were observed to reconstitute into tubular structures in vivo. Sequential analyses of the retrieved implants over time demonstrated that renal epithelial cells first organized into a cordlike structure with a solid center. Subsequent canalization into a hollow tube could be seen by 2 weeks. Histologic examination with nephron segment-specific lactins showed successful reconstitution of proximal tubules, distal tubules, loop of Henle, collecting tubules, and collecting ducts. These results showed that single suspended cells are capable of reconstituting into tubular structures, with homogeneous cell types within each tubule.

In a subsequent study mouse renal cells were harvested, expanded in culture, and seeded onto a tubular device constructed from polycarbonate (Yoo et al, 1996). The tubular device was connected at one end to a Silastic catheter that terminated into a reservoir. The device was implanted subcutaneously in athymic mice. Histologic examination of the implanted device demonstrated extensive vascularization as well as formation of glomeruli and highly organized tubulelike structures that were consistent with proximal and distal tubular cells and the cells of the thin ascending loop of Henle. The fluid collected from the reservoir suggested that the tubules are

Developmental Approaches to Kidney Regeneration

Transplantation of a kidney precursor, such as the metanephros, into a diseased kidney has been proposed as a possible method for functional restoration. In an animal study, human embryonic metanephroi transplanted into the kidneys of an immunodeficient mouse model have developed into mature kidneys (Dekel et al, 2003). The transplanted metanephroi produced urinelike fluid; however, they failed to develop ureters. This study suggests that development of an *in vitro* system in which metanephroi could be grown may lead to transplant techniques that could produce a small replacement kidney within the host. In another study, the metanephros was divided into mesenchymal tissue and ureteral buds, and each of the tissue segments was cultured *in vitro* (Steer et al, 2002). After 8 days in culture, each portion of the mesenchymal tissues had grown to the original size. A similar method was used for ureteral buds, which also propagated. These studies were expanded further by staging renal structure reconstitution *in vitro* and later implanting these structures *in vivo* in a mouse model (Rosines et al, 2007). These studies indicated that if the mesenchyme and ureteral buds were placed together and cultured

in vitro, a metanephros-like structure would develop, which suggests that the metanephros could be propagated under optimal conditions.

In another study, transplantation of metanephroi into a nonimmunosuppressed rat omentum showed that the implanted metanephroi were able to undergo differentiation and growth that was not confined by a tight organ capsule (Rogers et al, 1998). When the metanephroi with an intact ureteric bud were implanted, the metanephroi were able to enlarge and become kidney-shaped tissue within 3 weeks. The metanephroi transplanted into the omentum were able to develop into kidney tissue structure with a well-defined cortex and medulla. Mature nephrons and collecting system structures were shown to be indistinguishable from those of normal kidneys by light or electron microscopy (Hammerman, 2002a, 2002b). Moreover, these structures became vascularized via arteries that originate at the superior mesenteric artery of the host (Hammerman, 2002a, 2002b). It has been demonstrated that the metanephroi transplanted into the omentum survive for up to 32 weeks postimplantation (Rogers et al, 1999). These studies show that a developmental approach may be a viable option for regenerating renal tissue for functional restoration.

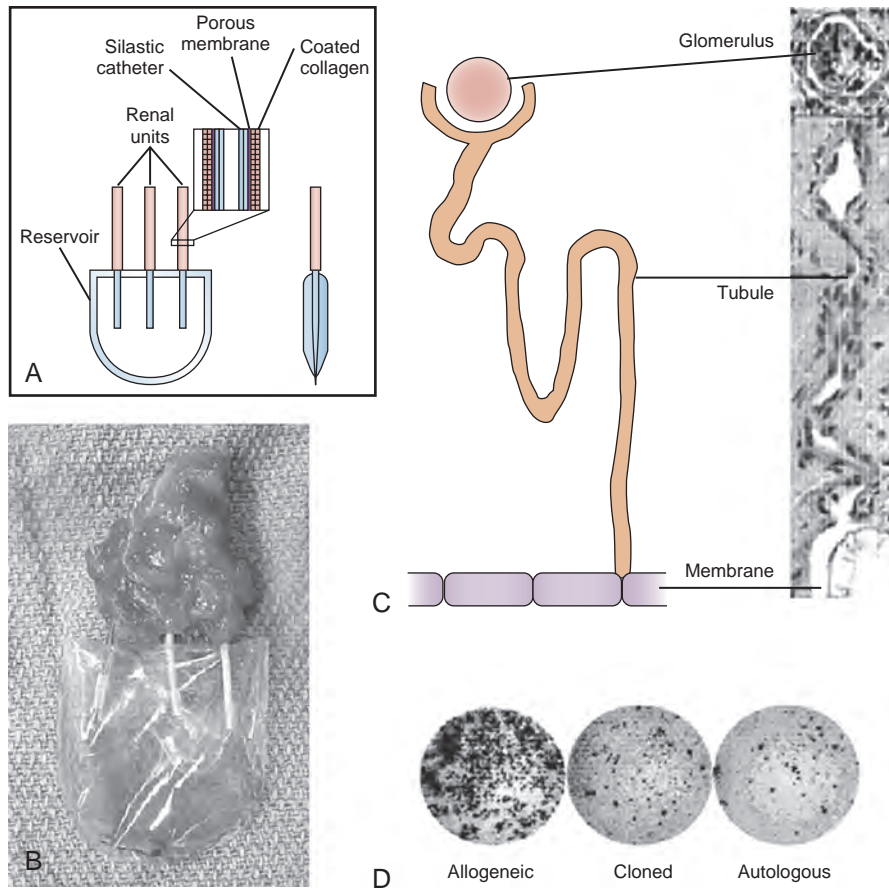


Figure 20-12. Production of kidney tissue by therapeutic cloning and regenerative medicine. **A,** Illustration of the tissue-engineered renal unit. **B,** Renal unit seeded with cloned cells, 3 months after implantation, showing the accumulation of urinelike fluid. **C,** There was a clear unidirectional continuity between the mature glomeruli, their tubules, and the polycarbonate membrane. **D,** ELISpot analyses of the frequencies of T cells that secrete interferon- γ after primary and secondary stimulation with allogeneic renal cells, cloned renal cells, or nuclear donor fibroblasts.

capable of unidirectional secretion and concentration of uric acid. The creatinine assay performed on the collected fluid showed an 8.2-fold increase in concentration as compared with serum. These results demonstrated that single cells from multicellular structures can become organized into functional renal units that are able to excrete high levels of solutes through a urinelike fluid (Yoo et al, 1996).

To determine whether renal tissue could be formed using an alternative cell source, nuclear transplantation (therapeutic cloning) was performed to generate histocompatible tissues, and the feasibility of engineering syngeneic renal tissues in vivo using these cloned cells was investigated (Lanza et al, 2002). Nuclear material from bovine dermal fibroblasts was transferred into unfertilized enucleated donor bovine eggs. Renal cells from the cloned embryos were harvested, expanded in vitro, and seeded onto three-dimensional renal devices. The devices were implanted into the back of the same steer from which the cells were cloned, and were retrieved 12 weeks later. This process produced functioning renal units (Fig. 20-12). Urine production and viability were demonstrated after transplantation back into the nuclear donor animal. Chemical analysis suggested unidirectional secretion and concentration of urea nitrogen and creatinine. Microscopic analysis revealed formation of organized glomeruli and tubular structures. Immunohistochemical and reverse-transcriptase polymerase chain reaction (RT-PCR) analysis confirmed the expression of renal messenger (m)RNA and proteins. These studies demonstrated that cells derived from nuclear transfer can be successfully harvested, expanded in culture, and transplanted

in vivo with the use of biodegradable scaffolds on which the single suspended cells can organize into tissue structures that are genetically identical to those of the host. These studies were the first demonstration of the use of therapeutic cloning for regeneration of tissues in vivo.

A naturally derived tissue matrix with existing three-dimensional kidney architecture would be preferable to the artificial matrix used in the aforementioned experiments because it would allow for transplantation of a larger number of cells, resulting in greater renal tissue volumes. Thus, an acellular collagen-based kidney matrix, which is similar to the native renal architecture, was developed. A subsequent study investigated whether these collagen-based matrices could accommodate large volumes of renal cells and form kidney structures in vivo (Amiel et al, 2000). Renal cells seeded on the matrix adhered to the inner surface and proliferated to confluency by 7 days after seeding. Renal tubular and glomerulus-like structures were observed 8 weeks after implantation. More recent data has confirmed that the creation of larger kidney structures using decellularized kidney matrices and repopulated with cells is possible (Orlando et al, 2012; Sullivan et al, 2012; Arenas-Herrera et al, 2013).

Summary

Regenerative medicine efforts continue to expand in the field of urology and are currently being undertaken for every type of tissue and organ within the urinary system. Most of the efforts expended

in the genitourinary field have occurred within the last several decades. Regenerative medicine strategies involve the use of biomaterials alone, as has been accomplished clinically in patients with urethral disease; biomaterials with cells, as is currently being tested clinically with bladder, urethral, and vaginal tissues; and cell therapies alone, as those applied clinically for erectile dysfunction, Peyronie disease, bladder dysfunction, urinary incontinence, and renal disease. The number of patients and the indications now amenable to regenerative medicine therapies keep increasing. Regenerative medicine is a multidisciplinary field that requires expertise in a wide variety of scientific disciplines, including cell and molecular biology, physiology, pharmacology, chemical engineering, biomaterials, nanotechnology, and clinical sciences. Although modest clinical success has been achieved to date in specific areas, technologies need to be further defined in terms of best patients to treat, because the field continues to be in its infancy. Long-term studies are still essential to ensure safety and efficacy before these technologies have widespread clinical application.

KEY POINTS

- New advances in the ability to expand cells in vitro and to use smart biomaterials and new techniques for vascularization are allowing more complex organs to be engineered.
- Tissue injury can be repaired with minimal fibrosis by the natural wound-healing response for small defects, by the use of nonseeded matrices for defects up to 1 cm from any edge, and by the use of cell-seeded matrices for defects larger than 1 cm.
- Stem cells may provide large repositories of different cell types for tissue and organ repair. Embryonic and induced pluripotent stem cells differentiate easily but may form tumors and may necessitate immunosuppression. Fetal stem cells replicate readily and do not form tumors but may be more limited than embryonic stem cells in their differentiation potential. Adult stem cells may not form tumors or necessitate immunosuppression, but they may not replicate readily.
- Both tissue engineering approaches and injectable cell therapy approaches are being used clinically. The types of cells used, the regenerative medicine strategies applied, the number of patients treated, and the indications for treatment continue to expand.

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The complete reference list is available online at www.expertconsult.com.

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21

Surgical, Radiographic, and Endoscopic Anatomy of the Male Reproductive System

Parviz K. Kavoussi, MD, FACS

Testis

Epididymis

Vas Deferens

Seminal Vesicles and Ejaculatory Ducts

Prostate

Urethra

Penis

Scrotum

A fundamental comprehension of male genital anatomy is necessary for understanding normal reproduction as well as pathology and treatment options. This chapter provides a general anatomic framework of the surgical, radiographic, and endoscopic anatomy of the normal male reproductive system. As this chapter is dedicated solely to the anatomy of the male reproductive system, please refer to Chapter 68 for further description of pelvic anatomy including bones, soft tissue, circulation, and innervation of the pelvis not directly related to reproduction.

TESTIS

Gross Structure

The testicles are paired organs within the scrotum that include both reproductive and endocrine functions. It is common for the right testis to be lower hanging compared to the left in approximately 85% of men. **The dimensions of the normal testis include a length of 4 to 5 cm, a width of 3 cm, and a depth of 2.5 cm; and the testis normally has a volume of 15 to 25 mL.** The organ is ovoid in shape and white in color (Prader, 1966; Tishler, 1971). There is a small pedunculated or sessile body at the upper pole of the testis, which is known as the appendix testis. A tough capsule envelops the testis, composed from external to internal of the visceral tunica vaginalis, the tunica albuginea, and the tunica vasculosa, before reaching the parenchyma of the testis. The tunica albuginea is composed of smooth muscle cells that pass through collagenous tissue (Langford and Heller, 1973). It is believed that these smooth muscle cells provide the testicular capsule with some ability to contract and may impact arterial flow into the testis. They may also promote the flow of seminiferous tubule fluid on its way out of the testis (Schweitzer, 1929; Rikmaru and Shirai, 1972; Davis and Horowitz, 1978). The attachment to the epididymis is on the posterolateral aspect of the testis (Figs. 21-1 and 21-2).

Microanatomic Architecture

The tunica albuginea invaginates into the testis to form the mediastinum testis, where vessels and ducts traverse the testicular capsule. The mediastinum testis sends septa that attach to the inner surface of the tunica albuginea to form 200 to 300 cone-shaped lobules,

each of which contains one or more convoluted seminiferous tubules. Each lobule contains a centrifugal artery. Seminiferous tubules are coiled and long, with both ends typically ending in the rete testis. The seminiferous tubules contain germ cells and supporting cells including Sertoli cells, fibrocytes, and myoid cells of the basement membrane. Each seminiferous tubule is U-shaped, but if a seminiferous tubule were stretched out from its convoluted form, each would measure nearly 1 m in length. **Each seminiferous tubule in the normal testis contains developing germ cells. The testosterone-producing Leydig cells are interdispersed in the loose tissue around the seminiferous tubules.** The interstitial tissue includes Leydig cells, mast cells, macrophages, nerves, blood vessels, and lymphatic vessels. This interstitial tissue makes up a total of 20% to 30% of the testicular volume (Setchell and Brooks, 1988). Sertoli cells line the seminiferous tubules and rest on the tubular basement membrane. The cellular characteristics of Sertoli cells include a low mitotic index, prominent nucleoli, and nuclei with irregular shapes. There are strong tight junctions between the Sertoli cells, which compartmentalize the seminiferous tubular space into adluminal and basal spaces. The seminiferous tubules straighten out and become tubuli recti toward the apex of each lobule, where they enter the mediastinum testis and anastomose with a network of tubules lined by flattened epithelia. This tubular network is the rete testis and forms 12 to 20 efferent ductules that anastomose into the caput of the epididymis. At this point, the efferent ductules convolute, enlarge, and form conical lobules. Each lobule produces a duct that drains into a single epididymal duct. The epididymal duct would be approximately 6 m in length if it were stretched out. It winds within the epididymis to form the body and the tail of the epididymis, all of which are surrounded by a fibrous sheath. The thickening and straightening of the duct forms the vas deferens as it reaches the tail of the epididymis (Figs. 21-3 and 21-4).

Arterial Supply

There are three arterial supplies to the testis: the testicular (internal spermatic) artery, the artery of the vas deferens (deferential artery), and the cremasteric (external spermatic) artery (Harrison and Barclay, 1948). The testicular artery is the main blood supply to the testis and its diameter is greater than the deferential and



Figure 21-1. The appearance of the testis with its shiny tunica albuginea layer.



Figure 21-2. The appearance of the testicular parenchyma when bivalved. The white nodule at the right inferior margin represents a sarcoid nodule.

cremasteric arteries combined (Raman and Goldstein, 2004). The testicular artery arises from the abdominal aorta and descends in the intermediate stratum of the retroperitoneum to enter the internal inguinal ring. From its aortic origin, it crosses the psoas muscle and the ureter to reach the inguinal ring to enter the spermatic cord. As the testicular artery descends toward the testis, it branches into an internal artery and an inferior testicular artery and into a capital artery to the caput epididymis. There may be variation at the level of this branching, which has been found to occur within the inguinal canal in 31% to 88% of cases (Beck et al, 1992; Jarow et al, 1992). In 56% of cases, a single artery enters the testis. In 31% of cases, there are two branches, and in 13% there are three or more branches of this artery (Korman and Suoranta, 1971). Arterial anastomosis occurs at the head of the epididymis, allowing for a rich blood supply between the testicular and capital arteries. At the tail of the epididymis, arterial anastomoses are formed between the testicular, epididymal, cremasteric, and vasal arteries. The testicular arteries pass into the mediastinum testis and supply the tunica vasculosa in the anterior portion of the upper pole of the testis and the anterior, medial, and lateral portions of the lower pole of the

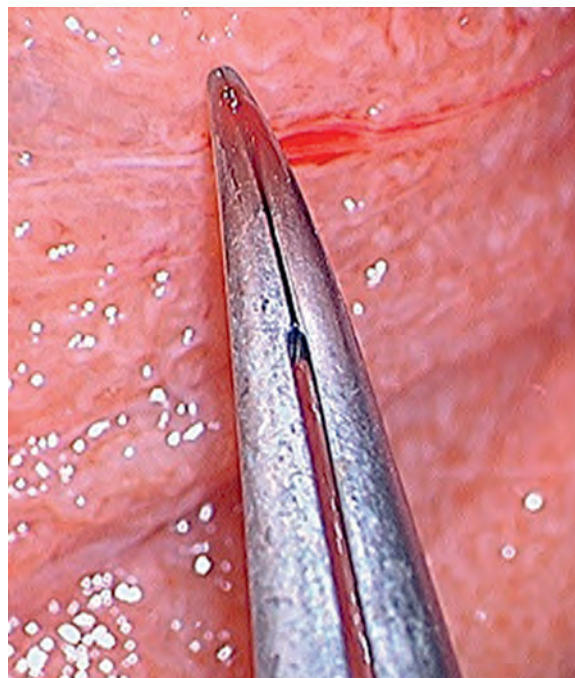


Figure 21-3. Appearance of the seminiferous tubules under magnification.

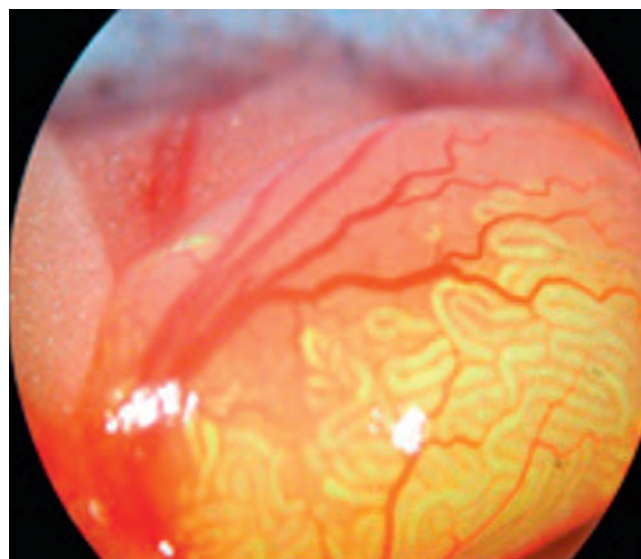


Figure 21-4. Microbeads injected retrograde through the rete testis into the seminiferous tubules demonstrating the tubular structure. This is a mouse testis that has very similar architecture to the human testis. (Courtesy Jeffrey Lysiak, PhD.)

testis. Therefore, care must be taken not to devascularize the testis by passing a traction suture through the lower pole, as well as by performing testis biopsies in the medial or lateral surfaces of the upper pole to minimize the risk of vascular injury. The middle of the testis has fewer vessels than the upper or lower poles. The deferential artery derives from the internal iliac artery or from the superior vesical artery. The cremasteric artery derives from the inferior epigastric artery and primarily supplies the tunica vaginalis, but it has branches going to the testis. Centrifugal arteries, which are the individual arteries supplying the seminiferous tubules, pass within the septa containing the seminiferous tubules and branch into arterioles that ultimately become intertubular and peritubular capillaries (Muller, 1957). Although in the case of testicular artery

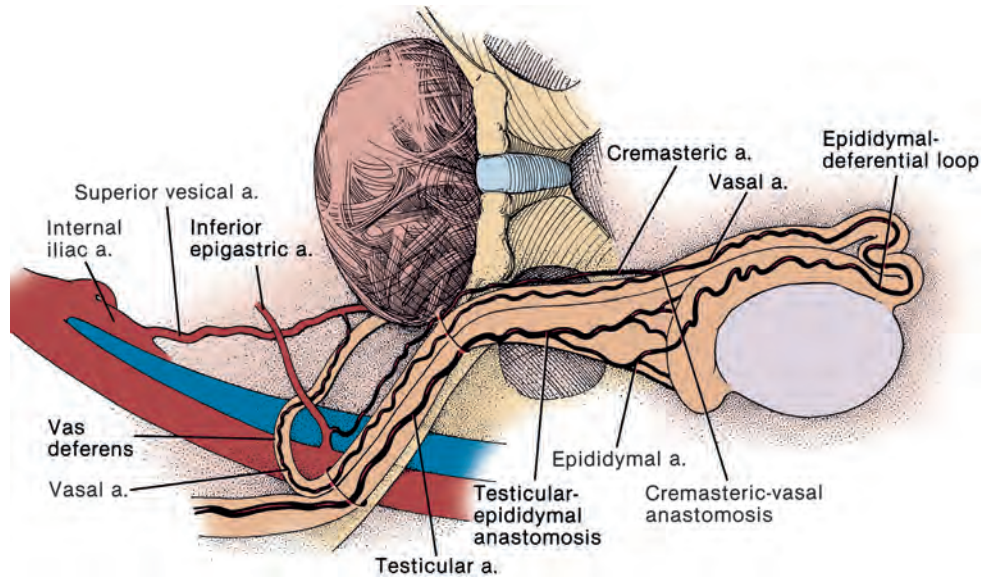


Figure 21-5. Collateral arterial circulation to the testis. (From Hinman F Jr. *Atlas of urosurgical anatomy*. Philadelphia: Saunders; 1993. p. 497.)

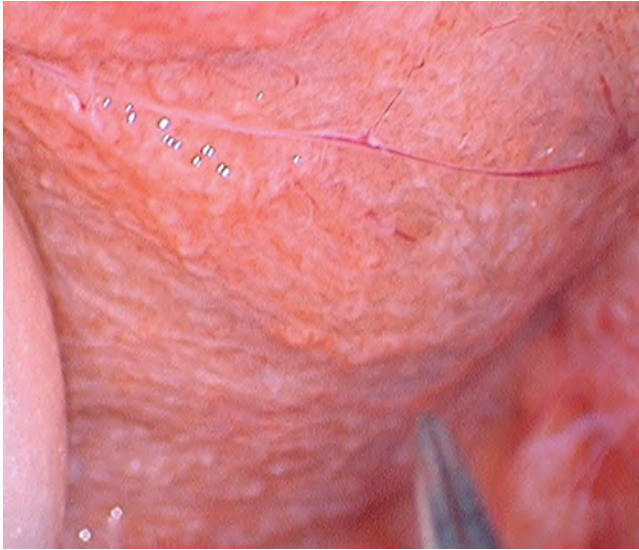


Figure 21-6. Microsurgical view of arterial supply to the testicular parenchyma.

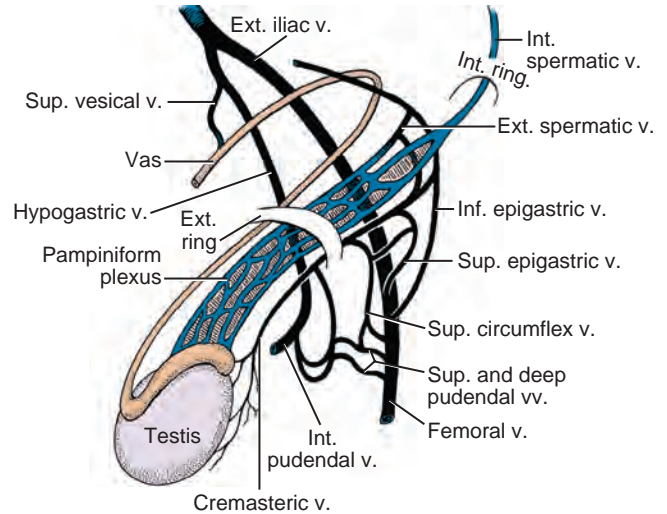


Figure 21-7. Venous drainage of the testis and epididymis. Note connections between the pampiniform plexus and the saphenous, internal iliac, and external iliac veins.

ligation, the deferential and cremasteric arteries can potentially provide adequate blood supply to the testis, atrophy and/or azoospermia has resulted from testicular artery ligation in adults and children. Men who have undergone vasectomy deserve special attention in preserving the testicular artery in future surgeries such as varicocele because of the risk of having had the deferential artery compromised at the time of vasectomy (Lee et al, 2007) (Figs. 21-5 and 21-6).

Venous Drainage

Unlike most other venous patterns in the human body, veins within the testis do not travel with their corresponding arteries. Small parenchymal veins either drain into a group of veins near the mediastinum testis, or they drain into veins on the surface of the testis (Setchell and Brooks, 1988). These two groups of veins anastomose with each other and the deferential veins to form the pampiniform plexus. The pampiniform plexus is a network of testicular veins that anastomose as they ascend surrounding the testicular artery. This

allows for a countercurrent heat exchange that cools the blood flow within the testicular artery. Ultimately, these veins join one another to form two or three veins at the level of the inguinal canal, and then they form one vein that ascends to drain into the inferior vena cava on the right and into the renal vein on the left side. There may be variations where the testicular veins can anastomose with the external pudendal, cremasteric, and vasal veins; this can allow varicocele ablations to result in recurrence (Figs. 21-7 and 21-8).

Lymphatic Supply

Lymphatic channels from the testis drain into the para-aortic and interaortocaval lymph nodes. These lymphatic channels ascend within the spermatic cord after leaving the testis (Hundeiker, 1969).

Nerve Supply

Visceral innervation to the testis and epididymis arise in the renal and aortic plexuses and course alongside the gonadal vessels. This is autonomic innervation, as the testis does not have

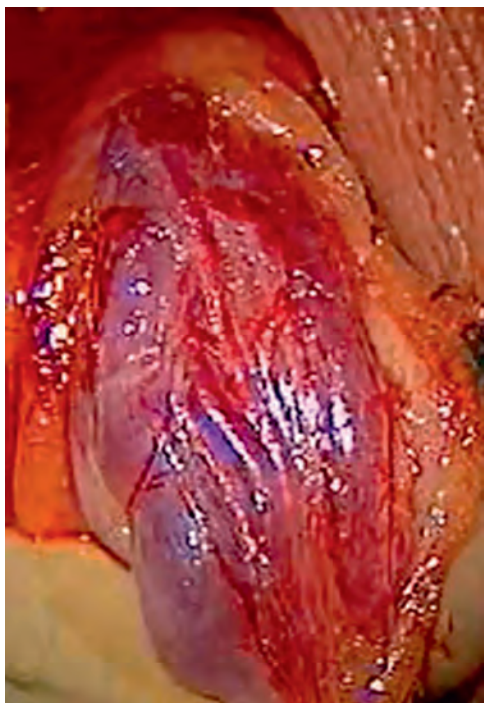


Figure 21-8. Microsurgical view of the veins of the pampiniform plexus during varicocele ligation through a subinguinal approach.

any known somatic innervation (Mitchell, 1935). The pelvic plexus, in association with the vas deferens, offers additional gonadal afferent and efferent nerves (Rauchenwald et al, 1995). Three distinct anatomic distributions of nerves have been isolated within the spermatic cord, and are thought to be the primary contributors in men with chronic orchialgia. These include a perivascular complex, posterior periaarterial/lipomatous complex, and intracremasteric complex (Parekattil et al, 2013). Some afferent and efferent nerves cross over to the contralateral pelvic plexus (Taguchi et al, 1999). This may account for pathology in one testis impacting the function of the contralateral testis, which has been reported with varicoceles and testicular tumors. The genital branch of the genitofemoral nerve primarily supplies sensation to the parietal and visceral tunica vaginalis and the overlying scrotum. These nerves travel along the testicular artery to reach the testis. These nerves ramify within the tunica albuginea, but do not enter the seminiferous tubules. Nerves are absent from the seminiferous epithelium.

Blood-Testis Barrier

The fluid passing from the seminiferous tubules and exiting from the testis has been found to have a substantially different fluid composition than that of blood plasma or lymphatics. This suggests that compounds do not freely diffuse to and from the tubules, indicating that a barrier exists, which is known as the blood-testis barrier (Setchell and Waites, 1975). There are extremely strong, tight junctions between Sertoli cells, which provide an intracellular barrier that allows for spermatogenesis in an immune privileged site. This is the barrier known as the blood-testis barrier (Ewing et al, 1980). This accounts for the anatomic component of the blood-testis barrier. The functional component will be further discussed in Chapter 22.

Ultrasonography

Ultrasonography is the primary imaging modality used to interrogate the scrotum and its contents. Scrotal ultrasound uses high-frequency transducers (7.5 to 10 MHz), grey scale real-time techniques, as well as color flow and power Doppler. The patient is

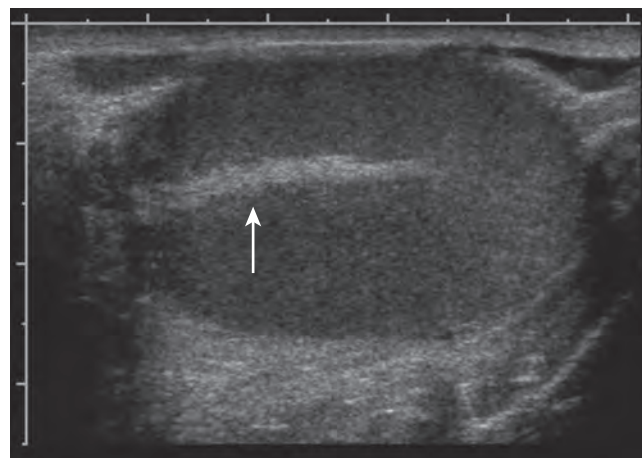


Figure 21-9. Testis ultrasound image demonstrating rete testis (arrow).

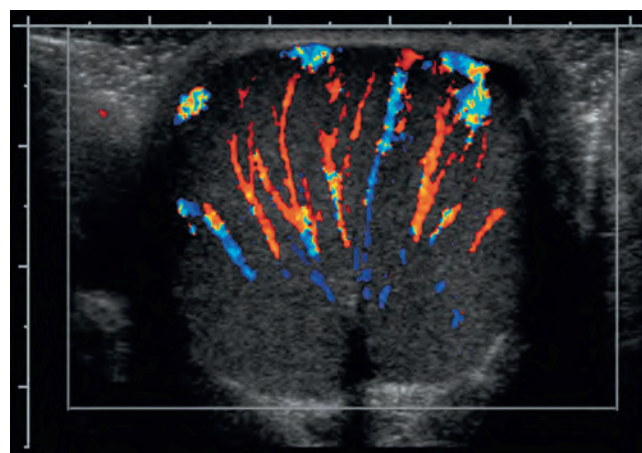


Figure 21-10. Doppler ultrasound image of testis demonstrating spokelike radiation of testicular vessels originating from the mediastinum testis.

placed in the supine position and a coupling gel is used with the transducer probe on the scrotal skin. The normal scrotal wall is 3 to 4 mm thick and is hypoechoic. An anechoic area between the echogenic scrotal wall and testicle is commonly visualized, which represents a small amount of physiologic fluid between the visceral and parietal layers of the tunica vaginalis. The mediastinum testis is visualized posteriorly as an echogenic band parallel to the epididymis. It may have variable lengths and thicknesses dependent on each patient's physiology (Dogra et al, 2003). The echo pattern of the normal testis is fine, uniform, with a medium-level echo pattern. Sonographically, the normal testis measures approximately 5 cm × 3 cm × 2 cm (Dogra et al, 2001). Color Doppler can identify testicular vessels in the majority of patients (Spimack and Resnick, 2002). Waveforms from intratesticular arteries and testicular capsular arteries demonstrate consistently low-impedance patterns with high levels of diastolic flow. This represents the lower vascular resistance of the testis. Supratesticular arteries are also sonographically identifiable and show low-impedance waveforms from the testicular, deferential, and cremasteric arteries (Middleton et al, 1989) (Figs. 21-9 and 21-10).

EPIDIDYMIS

Gross Structure

The epididymis is a duct or tubule that is attached to the posterolateral aspect of the testis and is nearest to the testis at its upper

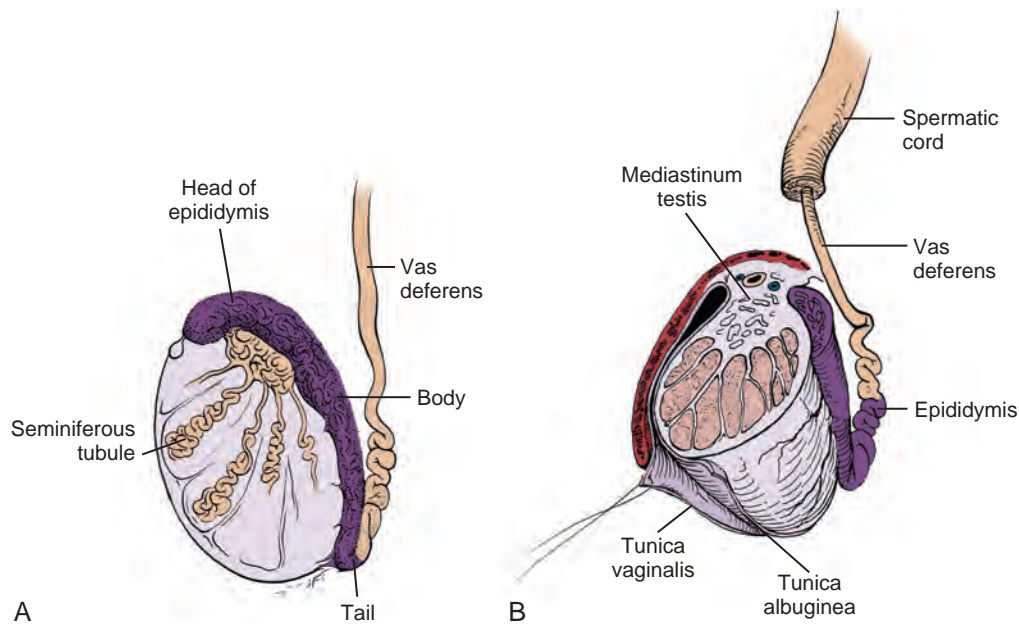


Figure 21-11. Testis and epididymis. A, One to three seminiferous tubules fill each compartment and drain into the rete testis in the mediastinum. Twelve to 20 efferent ductules become convoluted in the head of the epididymis and drain into a single coiled duct of the epididymis. The vas is convoluted in its first portion. B, Cross section of the testis, showing the mediastinum and septations continuous with the tunica albuginea. The parietal and visceral tunica vaginalis are confluent where the vessels and nerves enter the posterior aspect of the testis.

KEY POINTS: TESTIS

- The seminiferous tubules contain developing germ cells.
- The Leydig cells produce testosterone.
- There are three arterial supplies to the testis including the testicular artery, deferential artery, and cremasteric artery.
- Lymphatic channels from the testis drain into the para-aortic and interaortocaval lymph nodes.
- The nerves contributing to chronic orchialgia include a perivasal complex, posterior periarterial/lipomatous complex, and intracremasteric complex.
- Tight junctions between Sertoli cells comprise the anatomic component of the blood-testis barrier.
- Ultrasonography is the primary imaging modality for intra-scrotal content.

pole. Its lower pole is connected to the testis with fibrous tissue. The epididymis is comma shaped. The epididymis is tightly coiled and encapsulated within the tunica vaginalis sheath and would measure 3 to 4 m in length if stretched out (Von Lanz and Neuhaeuser, 1964; Turner et al, 1978). Septa form by extensions of the tunica vaginalis sheath into interductal spaces that divide the duct into histologically characteristic areas (Kormano and Reijonen, 1976). The three areas are characterized as the caput (head), the corpus (body), and the cauda (tail) of the epididymis. Eight to 12 ductuli efferentes from the testis comprise the caput epididymis. The caput epididymis is connected to the testis by multiple efferent ducts. The tightly coiled duct, which makes up the epididymis, is continuous with the vas deferens at the most distal portion of the cauda epididymis. Adjacent to the testis, this duct is irregularly shaped and comparatively large. The duct becomes more narrow and concentric near the junction with the ductus epididymis. The duct diameter remains unchanged throughout the corpus epididymis. The diameter of the duct enlarges and becomes irregular in shape in the cauda epididymis. The duct then progresses distally to form the vas deferens. A cystic body on the upper pole of the caput epididymis, which may be pedunculated or sessile, is known as the appendix of the epididymis (Figs. 21-11, 21-12, and 21-13).

Microanatomic Architecture

There are two primary types of cells throughout the epididymis: principal cells and basal cells (Holstein, 1969; Vendrely, 1981).

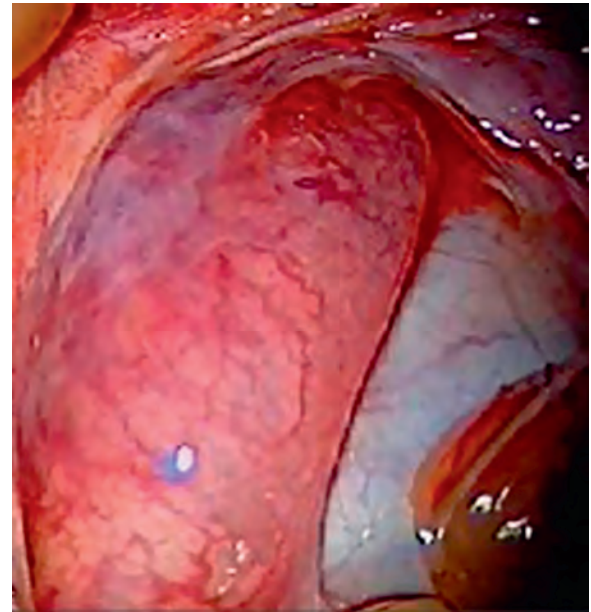


Figure 21-12. Gross microsurgical appearance of the epididymal caput and corpus.

From caput to cauda, the height of the epithelium decreases, whereas the diameter of the ductus and lumen increases. There are stereocilia that shorten progressively from the proximal to the distal epididymis. In the proximal epididymis, these stereocilia measure 120 μm in height and decrease to 50 μm in the distal epididymis. The principal cells contain elongated nuclei that are commonly clefted, and they contain one or two nucleoli. As the principal cells have absorptive and secretive functions, the apex of each of these cells contains multiple coated pits, membranous vesicles, multivesicular bodies, micropinocytic vesicles, and an extensive Golgi apparatus (Vendrely and Dadoune, 1988). There is a much larger number of principal cells in the epididymal epithelium than the number of basal cells that exist there. The basal cells are interdispersed between the principal cells. The basal cells are tear-shaped. They are positioned on the basal lamina and are 25 μm in length as they reach up toward the lumen. As opposed to the morphology of the principal cells, which varies throughout the epididymis, the basal cells' shape remains relatively consistent throughout the entirety of the

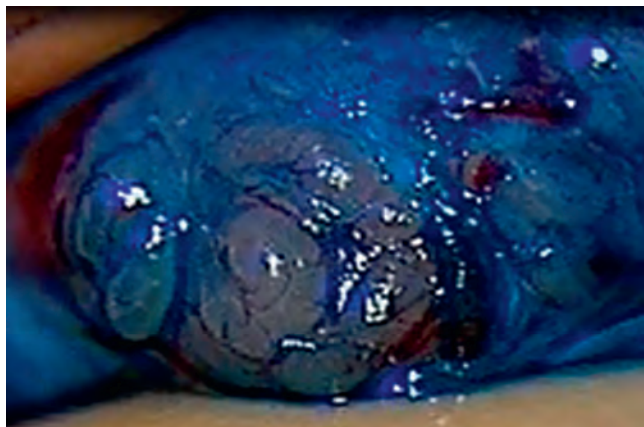


Figure 21-13. Microsurgical appearance of the epididymal duct after being stained with methylene blue.

epididymis. The basal cells are believed to be derived from macrophages and to be precursors of principal cells. There is a fair amount of variability in the nature of the epithelium of the epididymis, which is dependent on the region. There is a clear transition from a low to a high cuboidal epithelium where the rete testis and ductuli efferentes meet. The ductuli efferentes contain ciliated and nonciliated cells and the epithelium appears uneven (Holstein, 1969). The epithelium of the proximal ductuli efferentes primarily consists of nonciliated cells with extending apices thought to be for secretory function. The ciliated cells conduct sperm cells from the efferent duct to the epididymis, and they are widely dispersed throughout the epithelium (Vendrely, 1981). Junctional complexes join ciliated and nonciliated cells together at their apices, suggesting a blood-epididymis barrier (Suzuki and Nagano, 1978; Turner, 1979; Hoffer and Hinton, 1984). In the ductuli efferentes, the proximal corpus epididymis, and the distal caput epididymis there are contractile cells around the tubule in a loose, two-to-four cell-deep layer (Baumgarten et al, 1971). Nexuslike junctions connect these contractile cells to one another and each cell contains myofilaments. These cells are larger and appear like thin smooth muscle cells in the distal corpus epididymis, where they have fewer intracellular junctions. Thick smooth muscle cells are found in the cauda epididymis. The smooth muscle cells are organized in three layers. The cells have a longitudinal orientation in the two outer layers and a circular orientation in the central layer. The thickness of the distal contractile layer progressively increases as it forms the vas deferens.

Arterial Supply

A branch of the testicular artery supplies the caput and corpus epididymis. This arterial branch then further divides to supply the superior and inferior epididymal branches (Macmillan, 1954). The deferential artery also provides vascular supply to the epididymis. Branches from the deferential artery supply the cauda epididymis. As with the testis, the deferential and cremasteric arteries also supply the epididymis and can compensate for a ligated testicular artery. The connective tissue sheaths forming septa in the epididymis are the entry points for arterial supply within the epididymis. The coiled vessels ultimately straighten to form the microvascular bed within the epididymis (Kormano and Reijonen, 1976). The density of the microvasculature decreases progressively, with the caput containing the highest density of microvasculature and the more distal segments containing lower density (Clavert et al, 1981).

Venous Drainage

The corpus and cauda epididymis have their venous drainage through the vena marginalis of Haberer, draining into the

pampiniform plexus via the vena marginalis testis, or through deferential or cremasteric veins (Macmillan, 1954).

Lymphatic Supply

Similar to that of the testis, the caput and corpus epididymis have their lymphatic drainage through channels that travel with the internal spermatic vein, draining to the preaortic nodes. Lymphatic channels from the cauda epididymis join those leaving the vas deferens to drain ultimately into the external iliac nodes.

Nerve Supply

The superior portion of the hypogastric plexus and the pelvic plexus yield the intermediate and inferior spermatic nerves, respectively, which innervate the epididymis (Mitchell, 1935). Fibers from the sympathetic nervous system sparsely innervate the proximal portion of the epididymis as well as the ductuli efferentes (Baumgarten and Holstein, 1967; Baumgarten et al, 1971). These fibers form a peritubular plexus that is adjacent to the vasculature. The corpus epididymis includes sparse numbers of nerve fibers, and the density of nerve fibers increases progressively traveling toward the cauda epididymis. The density of fibers begins to increase at the midcorpus of the epididymis and the progressive increase in fibers is associated with the progressive proliferation of smooth muscle cells (Baumgarten et al, 1971).

Ultrasonography

The epididymis can be visualized ultrasonographically in its posterolateral position to the testis. The epididymis appears either hyperechoic or isoechoic in comparison to the testis (Spimak and Resnick, 2002). Compared to the testis, the caput epididymis is typically isoechoic, the corpus epididymis is hypoechoic, and the vas deferens is anechoic (Puttemans et al, 2006). The epididymis is typically homogeneous, with well-defined echoes surrounding the epididymis that represent the fascial lining (Black and Patel, 1996). By sonographic measurement, the normal caput epididymis diameter measures between 10 mm and 12 mm and the normal corpus epididymis measures between 2 mm and 5 mm (Pezzella et al, 2013). In 98% of men, the caput epididymis is above the upper pole of the testis, with the corpus epididymis typically lateral to the testis. The corpus epididymis is posterior to the body of the testis in 6% of men. The epididymis is inverted with the caput epididymis inferior to the lower pole of the testis in 2.4% of men (Puttemans et al, 2006). The appendix epididymis can be identified as an isoechoic structure attached to the caput epididymis (Black and Patel, 1996). Vascular flow is detectable with pulsed Doppler and color Doppler in all regions of the epididymis in nonpathologic states. The mean resistive index throughout the normal epididymis is approximately 0.55 (Keener et al, 1997) (Fig. 21-14).

KEY POINTS: EPIDIDYMIS

- The two primary cell types throughout the epididymis are principal cells and basal cells.
- The arterial supply to the caput and corpus epididymis is from a branch of the testicular artery and the cauda is supplied from deferential arterial branches.

VAS DEFERENS

Gross Structure

The vas deferens, also known as the ductus deferens, extends from the distal end of the cauda epididymis. It is tubular and its embryologic origin is the mesonephric (wolffian) duct. The vas deferens is tortuous for 2 to 3 cm as it leaves the epididymis (the convoluted vas deferens). From the cauda epididymis to its termination at the

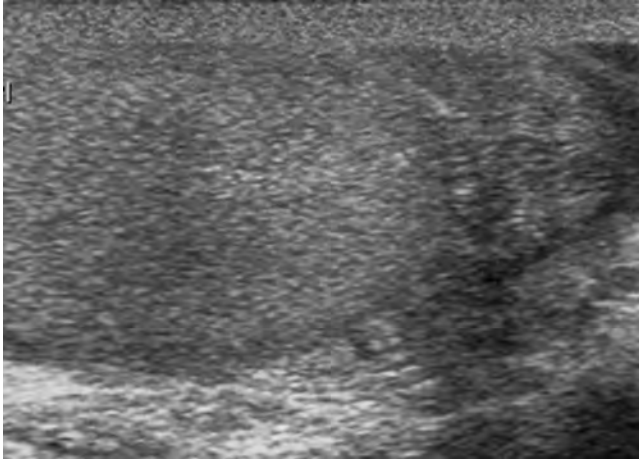


Figure 21-14. Ultrasound imaging of the caput epididymis, which appears hyperechoic to the testis and is at the right of the testis on this image.

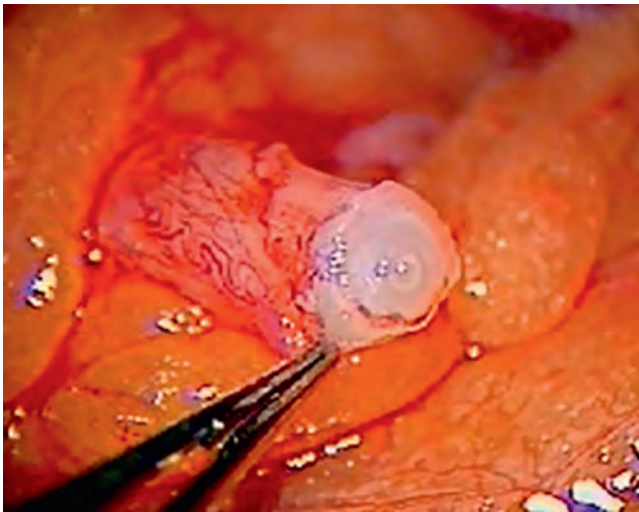


Figure 21-15. Microsurgical appearance of the transected vas deferens at the time of vasovasostomy.

ejaculatory duct, the vas deferens measures between 30 and 35 cm in length. The vas deferens travels posteriorly along the spermatic cord, behind the vessels in the cord. The vas deferens passes through the inguinal canal and enters the pelvis lateral to the epigastric vessels. On entering the pelvis, after passing through the internal inguinal ring, the vas deferens separates from the testicular vessels. The vas deferens ultimately reaches the posterior base of the prostate after traveling medial to the pelvic sidewall. The vas deferens is compartmentalized into five different regions. The first is the epididymal segment within the tunica vaginalis, which does not have a sheath. The second is the segment within the scrotum. The third segment is that within the inguinal canal. The fourth is the retroperitoneal segment, and the fifth is the ampulla of the vas deferens (Lich et al, 1978). The lumen of the vas deferens ranges between 0.2 and 0.7 mm in diameter, depending on the segment. The outer diameter of the vas deferens ranges between 1.5 and 2.7 mm (Middleton et al, 2009) (Figs. 21-15 and 21-16).

Microanatomic Architecture

There is an outer adventitial connective tissue layer surrounding the vas deferens that contains blood vessels and small nerves. Within

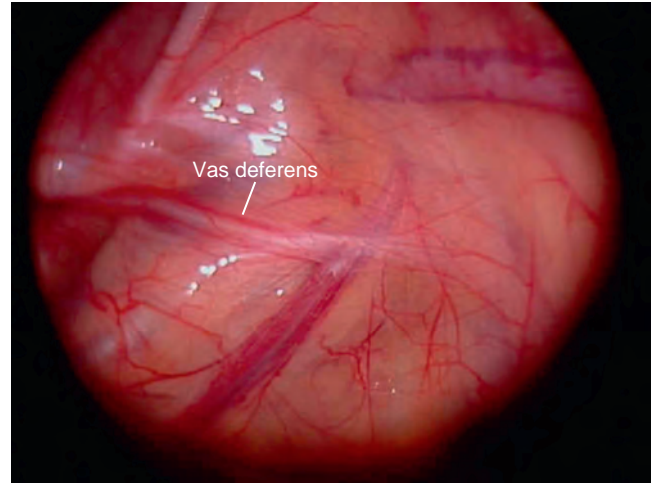


Figure 21-16. Laparoscopic visualization of the vas deferens.

this connective tissue layer, smooth muscle cells comprise the thick wall of the vas deferens. These smooth muscle cells are organized as an inner and outer longitudinal layer, a middle circular layer, and a pseudostratified columnar epithelial layer with nonmotile stereocilia as the inner lining, known as its mucosa (Neaves, 1975; Paniagua et al, 1981). The epithelial cell height decreases progressively throughout the length of the vas deferens from the testis to the seminal vesicle. There are three types of tall, thin columnar cells, as well as basal cells, comprising the pseudostratified epithelium of the vas deferens (Hoffer, 1976; Paniagua et al, 1981). Principal cells, pencil cells, and mitochondria-rich cells comprise the columnar cells that extend from the epithelial base to the lumen. The columnar cells have irregularly shaped convoluted nuclei and have stereocilia. In the proximal vas deferens, principal cells are the predominant cell type. Traveling more distally throughout the vas deferens, more pencil cells and mitochondria-rich cells are present. The muscular layer of the vas deferens progressively decreases from proximal to distal.

Arterial Supply

The superior vesical artery gives off the deferential artery, which supplies the vas deferens (Sjostrand, 1965).

Venous Drainage

The venous drainage of the scrotal vas deferens is via the deferential vein, which drains into the pampiniform plexus. The pelvic vas deferens' venous drainage is to the pelvic venous plexus.

Lymphatic Supply

Lymphatic drainage from the vas deferens travels to the external and internal iliac nodes.

Nerve Supply

The vas deferens receives sympathetic and parasympathetic innervation (Sjostrand, 1965). The sympathetic adrenergic nerves travel via the presacral nerve from the hypogastric nerve (Batra and Lardner, 1976; McConnell et al, 1982). All three layers of the vas deferens tunica muscularis contain adrenergic fibers, but the greatest density of these nerve fibers is found in the outer longitudinal layer (McConnell et al, 1982). Other types of neurotransmitters have been identified within neurons such as somatostatin, galanin, enkephalin, neuropeptide Y, vasoactive intestinal peptide, and nitric oxide. The function of these neurotransmitters in the vas deferens is not well understood (Dixon et al, 1998).

Vasogram

The vasogram was previously considered to be the radiographic test of choice to evaluate the prostate, ejaculatory duct, and seminal vesicles in the infertile male. The vasogram has been replaced by transrectal ultrasonography for the most part, and the vasogram is only used in conjunction with reconstructive surgery ([Honig, 1994](#)).

KEY POINTS: VAS DEFERENS

- The lumen of the vas deferens ranges between 0.2 and 0.7 mm in diameter, depending on the segment.
- The superior vesical artery gives off the deferential artery, which supplies the vas deferens.
- A vasogram should only be performed in conjunction with reconstructive surgery.

SEMINAL VESICLES AND EJACULATORY DUCTS

Gross Structure

The seminal vesicles are paired, viscous organs that are positioned posterior to the bladder and prostate. The seminal vesicle is a lateral outpouching of the vas deferens. It has the capacity for 3 to 4 mL of volume and the nonobstructed seminal vesicle typically measures 5 to 7 cm in length and 1.5 cm in width. The seminal vesicle is a single tube that is highly coiled, and it forms several outpouchings and would measure 15 cm in length if stretched out. The joining of the seminal vesicle with the vas deferens creates the ejaculatory duct. The smooth muscle sheaths from the seminal vesicle and the vas deferens combine with the capsule of the prostate at the prostatic base. The seminal vesicles' excretory duct joins the duct of the ampullary vas deferens as it enters the prostate.

The ejaculatory ducts are positioned at the junction of the vas deferens and the seminal vesicle. The ejaculatory ducts are paired visceral organs. **They ultimately empty through the verumontanum into the prostatic urethra.** The ejaculatory duct is divided into three distinct anatomic regions. These include the extraprostatic region (proximal), intraprostatic region (mid), and the distal region, which joins the lateral aspect of the verumontanum to empty into the prostatic urethra ([Nguyen et al, 1996](#)). In contrast to the first two regions, the third distal region is not surrounded by an outer muscular layer and does not form an anatomic sphincter at the ejaculatory duct orifice at the verumontanum ([Nguyen et al, 1996](#)).

Microanatomic Architecture

The seminal vesicle has a columnar epithelium with goblet cells. The seminal vesicle tube is surrounded by a thin layer of smooth muscle cells, which is enveloped by a loose adventitia. The three layers comprising the tubule of the seminal vesicle include an inner mucous membrane, a collagenous middle layer, and the outer circular and longitudinal muscle layers. The muscle layers account for 80% of the thickness of the wall of the seminal vesicle ([Nguyen et al, 1996](#)). The thin, folded mucosa of the seminal vesicle is comprised of nonciliated, pseudostratified cuboidal or columnar cells. The ejaculatory ducts have similar microanatomic architecture to the seminal vesicles, but they do not have the outer circular muscle layer that is found in the seminal vesicle ([Nguyen et al, 1996](#)). The inner epithelial layer of the ejaculatory duct is composed of simple and pseudostratified columnar cells in a folded pattern.

Arterial Supply

The arterial supply to the seminal vesicle originates from the superior vesical artery, which branches into the vesiculodeferential

artery. The vesiculodeferential artery supplies the anterior surface of the seminal vesicle in proximity to its tip. The internal iliac artery and inferior vesical artery provide additional arterial supply to the seminal vesicle via the prostatovesicular branch ([Clegg, 1955](#)). Variations of arterial supply include the prostatovesicular branch originating from the pudendal artery or the superior vesical artery. Arterial supply to the ejaculatory duct arises from branches of the inferior vesical artery.

Venous Drainage

The venous drainage of the seminal vesicle follows the arterial supply draining through the vesiculodeferential veins and the inferior vesical plexus to the pelvic venous plexus.

Lymphatic Supply

The lymphatic drainage from the seminal vesicle is to the internal iliac nodes ([Mawhinney and Tarry, 1991](#)).

Nerve Supply

Seminal vesicle parasympathetic innervation originates from the pelvic plexus with the sympathetic nervous system contributing fibers from the hypogastric nerves and the superior lumbar nerves ([Kolbeck and Steers, 1993](#)). The pelvic plexus innervates the ejaculatory ducts.

Transrectal Ultrasonography

The seminal vesicles can be imaged by transrectal ultrasonography, as they are positioned posteriorly at the base of the prostate. The seminal vesicles appear hypoechoic, compared to the prostate, and are crescent-shaped, paired, and symmetrical. The normal seminal vesicle measures 2 cm in width and 4.5 to 5.5 cm in length. They can be visualized as oriented horizontally in the transverse plane. Hypoechoic fatty tissue can be seen separating the seminal vesicles from the base of the prostate. The ejaculatory ducts may occasionally be seen by transrectal ultrasonography and they appear hypoechoic as they enter the prostate posteriorly.

Computed Tomography

Computed tomography (CT) can image the seminal vesicles. The mean measurements by CT of the seminal vesicles are 3 cm in length and 1.5 cm in width. No significant change is seen by CT in seminal vesicle length on the basis of age. However, the width of the seminal vesicle is smaller in men of increasing age. The pudendal venous plexus can be identified by CT as small punctuate densities along the lateral aspect of the seminal vesicle ([Silverman et al, 1985](#)).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the normal seminal vesicles demonstrate similar signal intensity to that of the bladder or muscle on T1 imaging. The seminal vesicles demonstrate a higher signal intensity than the surrounding fat on T2 imaging ([King et al, 1989](#); [Secaf et al, 1991](#)) (Fig. 21-17; also see Fig. 21-16).

KEY POINTS: SEMINAL VESICLES AND EJACULATORY DUCTS

- The nonobstructed seminal vesicle typically measures 5 to 7 cm in length and 1.5 cm in width.
- The ejaculatory ducts empty through the verumontanum into the prostatic urethra.
- Transrectal ultrasound, CT, and MRI can image the seminal vesicles.



Figure 21-17. Endoscopic view into the os of the ejaculatory duct transurethrally.

PROSTATE

Gross Structure

The normal prostate gland is ovoid in shape and measures 3 cm in length, 4 cm in width, and 2 cm in depth; it has a weight of 18 to 20 g. It is homologous to the Skene glands in females. The prostate is composed of glandular elements and fibromuscular stroma. The prostate is positioned just inferior to the bladder. The prostatic urethra travels through the prostate gland. The base of the prostate is at the bladder-prostate junction and the narrowed apex is the most inferior portion of the prostate gland, reaching the urogenital diaphragm. The prostate is palpable approximately 4 cm from the anus on digital rectal examination. **The apex of the prostate is continuous with the striated urethral sphincter.** The prostate is comprised of an anterior surface, a posterior surface, and lateral surfaces, and these are in relationship to the prostatic urethra traversing the prostate. A collagen, elastin, and smooth muscle capsule envelops the prostate. The capsule measures 0.5 mm in thickness posteriorly and laterally on average. There is no true prostatic capsule at the apex of the prostate, where normal prostate glands are seen blending into the striated muscle of the urethral sphincter. Similarly, there is no true capsule at the base separating the prostate from the bladder, where the detrusor muscle's outer longitudinal fibers fuse with the fibromuscular capsule of the prostate (Epstein, 1989). The prostate capsule blends with the continuation of the endopelvic fascia on the anterior and anterolateral aspects of the prostate. The prostate is fixed to the pubic bone anteriorly by the puboprostatic ligaments near the apex of the prostate. The superficial branch of the dorsal vein is positioned in the retropubic fat outside the prostatic fascia. It drains into the dorsal vein complex. The levator ani's pubococcygeal portion hugs the lateral aspects of the prostate and is related to its overlying endopelvic fascia. The prostate capsule and the pelvic fascia separate below the parietal and visceral endopelvic fascia juncture (arcus tendineus fascia pelvis). Fatty, areolar tissue and the lateral branches of the dorsal vein complex take up the space of this separation between the prostate capsule and the pelvic fascia. **The cavernosal nerves travel within the parietal pelvic fascia, also known as the lateral prostatic fascia, posterolateral to the prostate.** As more anatomic attention has been taken with higher-magnification robotic techniques at the time of radical prostatectomy, the lateral prostatic fascia has been defined in greater detail in an effort to preserve the cavernosal nerves. Nerve bundles have been identified traveling along the prostate laterally and anterior to the previously defined neurovascular bundle (Eichelberg et al, 2007; Raychaudhuri and Cahill, 2008) (Fig. 21-18).

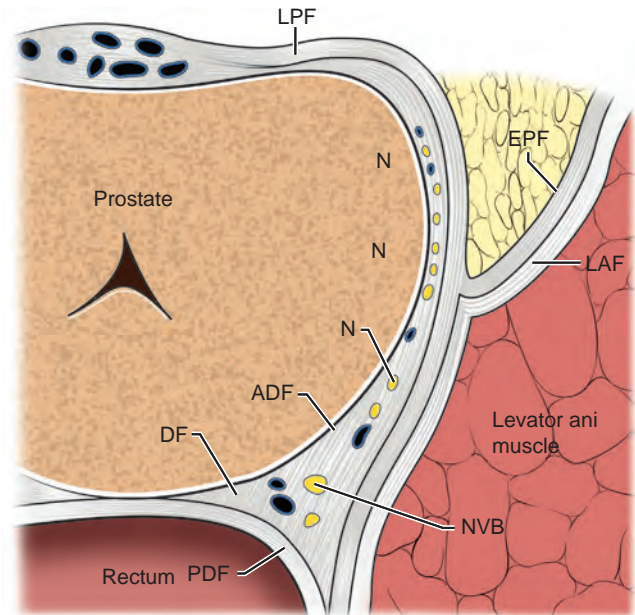
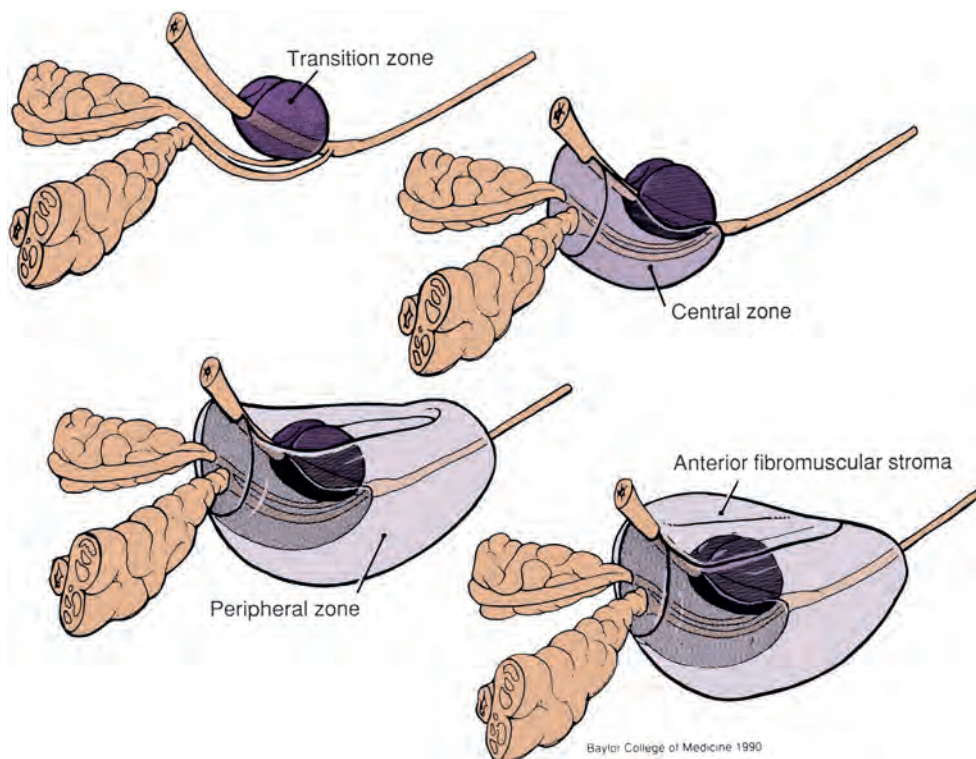


Figure 21-18. Cross section of prostate with prostatic fascial layers outlined, including the lateral prostatic fascia (LPF), endopelvic fascia (EPF), levator ani fascia (LAF), Denonvilliers fascia (DF), anterior lamina of Denonvilliers fascia (ADF), posterior lamina of Denonvilliers fascia (PDF), neurovascular bundle (NVB), and lateral nerves (N). (From Walz J, Graefen M, Huland H. Basic principles of anatomy for optimal surgical treatment of prostate cancer. *World J Urol* 2007;25:31–8.)

The prostate has been divided into distinct anatomic zones. These zones can be identified with transrectal ultrasonography. The transition zone is the smallest of the zones of the prostate. The ducts of the transition zone begin at the angle dividing the preprostatic and the prostatic urethra, and they travel beneath the preprostatic sphincter to course along its lateral and posterior sides. The transition zone comprises 5% to 10% of the glandular tissue of the normal prostate. The transition zone is separated from the rest of the glandular compartments of the prostate by a distinct fibromuscular band. Benign prostatic hyperplasia most commonly occurs in the transition zone. The central zone ducts are positioned circumferentially, surrounding the openings of the ejaculatory ducts. This zone expands toward the base of the bladder, surrounding the ejaculatory ducts, in the shape of a cone. The central zone comprises 25% of the glandular tissue of the prostate. The glands of the central zone are thought to be of wolffian duct origin, as they differ immunohistochemically and structurally from the other glands of the prostate (McNeal, 1988). **The peripheral zone of the prostate is the largest zone. Seventy percent of the glandular tissue of the prostate is comprised of the peripheral zone.** The peripheral zone makes up the posterior and lateral aspects of the prostate gland. The ducts of the peripheral zone drain into the prostatic sinus along the entire length of the post-sphincteric prostatic urethra. Seventy percent of prostate cancers are found in the peripheral zone. The nonglandular anterior fibromuscular stroma is found extending from the bladder neck to the striated sphincter, and it may comprise up to one third of the mass of the prostate. It is composed of collagen, smooth and striated muscle, and elastin. It is anatomically continuous with the anterior visceral fascia, the anterior preprostatic sphincter, and the prostatic capsule.

The prostate is also compartmentalized clinically, based on digital rectal examination and cystoscopic appearance. A central sulcus divides the two lateral lobes of the prostate and a middle lobe. The middle lobe may become hyperplastic and may extend into the bladder neck with age (Fig. 21-19).

Figure 21-19. Zonal anatomy of the prostate as described by McNeal (1988). The transition zone surrounds the urethra proximal to the ejaculatory ducts. The central zone surrounds the ejaculatory ducts and projects under the bladder base. The peripheral zone constitutes the bulk of the apical, posterior, and lateral aspects of the prostate. The anterior fibromuscular stroma extends from the bladder neck to the striated urethral sphincter. (© 1990, Baylor College of Medicine.)



Microanatomic Architecture

Seventy percent of the prostate's composition is glandular elements, whereas 30% is made up of fibromuscular stroma. The epithelial cells of the prostate glands are cuboidal or columnar. These secretory epithelial cells are terminally differentiated, have a low proliferative index, and measure 10 to 20 μm in height (De Marzo et al, 1998). These epithelial cells have abundant secretory granules and are organized in rows with their apices projecting into the lumen and their bases attached to a basement membrane (Knox et al, 1994). The nuclei of the cells are at their base, below the Golgi apparatus. The luminal apices have microvilli. The epithelial cells line the periphery of the acinus and secrete into the acinus, which drain into ducts to the urethra ultimately. The tubuloalveolar glands have simple branching patterns. Flattened, undifferentiated basal cells line each acinus beneath the epithelial cells. A thin layer of connective tissue and stromal smooth muscle surrounds each acinus. The secretory cells have scattered, terminally differentiated, non-proliferating neuroendocrine cells between them. Two types of neuroendocrine cells have been identified in the prostate. One is a closed cell with dendritelike processes that extend toward epithelial cells and basal cells in its proximity. The other type of neuroendocrine cell type seen is an open one with microvilli extending into the lumen (di Sant'Agnese and De Mesy Jensen, 1984; Abrahamsson, 1999; Vashchenko and Abrahamsson, 2005). The stroma is composed of smooth muscle, which is rich in α -actin, myosin, and desmin, and it is also composed of collagen and is continuous with the prostatic capsule. At the junction of the prostate gland, the prostatic urethra, the transitional cells of the prostatic urethra's epithelium, may extend into prostatic ducts. The preprostatic (internal urethral) sphincter encloses the small periurethral prostatic glands without periglandular smooth muscle, and these glands are positioned between fibers of longitudinal smooth muscle. Posterior to the prostate, microscopic smooth muscle bands fuse with Denonvilliers fascia after extending from the posterior aspect of the prostatic capsule. There is a plane of loose, areolar tissue between Denonvilliers fascia and the rectum.

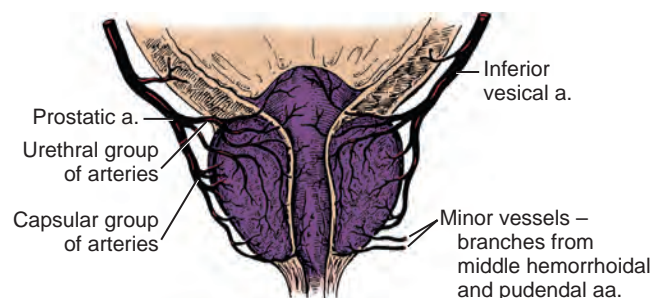


Figure 21-20. Arterial supply of the prostate. (Modified from Flocks RH. The arterial distribution within the prostate gland: its role in transurethral prostatic resection. J Urol 1937;37:527.)

Arterial Supply

The inferior vesical artery is the typical arterial supply to the prostate. The inferior vesical artery branches into urethral arteries that enter the prostatovesical junction posterolaterally and course in a perpendicular route to the urethra. They travel toward the bladder neck with the largest branches posteriorly, approaching the bladder neck in the one o'clock to five o'clock positions and the seven o'clock to eleven o'clock positions. They then supply the urethra after making a caudal turn to run parallel to the urethra. These branches supply the urethra, the periurethral glands, and the transition zone of the prostate (Flocks, 1937). The inferior vesical artery also branches into the capsular artery. The capsular artery yields small branches that supply the anterior prostatic capsule. The capsular branches enter the prostate at 90-degree angles and provide arterial supply to the glandular tissues, coursing along the reticular bands of the stroma. The majority of the inferior vesical artery travels posterolateral to the prostate to form the neurovascular bundles coursing with the cavernous nerves, terminating at the pelvic diaphragm. Branches from the internal pudendal artery and the middle rectal (hemorrhoidal) artery also contribute a supply to the prostate (Fig. 21-20).

Venous Drainage

The prostate includes abundant venous drainage through the periprostatic plexus. The periprostatic plexus anastomoses with the deep dorsal vein of the penis and the internal iliac (hypogastric) veins.

Lymphatic Drainage

The obturator and internal iliac nodes are the primary sites of lymphatic drainage from the prostate. The presacral group or, infrequently, the external iliac nodes may receive a small portion of the initial lymphatic drainage.

Nerve Supply

The cavernous nerves provide sympathetic and parasympathetic innervation to the prostate from the pelvic plexus. Innervations to the glandular and stromal elements of the prostate are found traveling with branches of the capsular artery. Sympathetic fibers innervate the smooth muscle of the capsule and stroma for contraction. The parasympathetic nerves promote secretory function by terminating in the acini. Prostate smooth muscle relaxation may be affected by peptidergic and nitric oxide synthase-containing neurons that have been identified in the prostate (Burnett, 1995). The pelvic plexuses carry afferent neurons from the prostate to the pelvic and thoracolumbar spinal centers.

Transrectal Ultrasonography of the Prostate

Transrectal ultrasonography of the prostate provides multiple diagnostic utilities including assessing prostate volume, locating focal abnormalities, assessing patients with infertility with suspicion of obstruction, and guiding prostate biopsies. The prostate is imaged with biplane, multiplane, and end-fire endorectal transducer probes with a frequency ranging from 6 to 8 MHz. The patient should be positioned either in the lateral decubitus or the dorsal lithotomy position, and a well-lubricated transrectal probe is gently passed into rectum above the anal verge. The prostate and seminal vesicles should be systematically examined in the longitudinal and transverse orientations. Pertinent images should be recorded and labeled (Terris et al, 1992). The normal prostate has a stipple grey echogenicity and appears homogeneous. The capsule appears echogenic, continuous, and well defined. The zonal compartments can be identified. A distinct layer of echogenic fibrous tissue separates the zones. The prostate presents a semilunar shape and appears symmetrical in the transverse orientation. The peripheral zone has a homogeneous, fine echo pattern. The periurethral tissue is centrally positioned and appears hypoechoic. The relation of the prostate to the surrounding structures such as the seminal vesicles, bladder neck, and prostatic urethra can be identified in the longitudinal orientation. The urethra will appear curved within the central portion of the prostate.

The prostate volume can be measured using transrectal ultrasonography with an accuracy of within 5% of its true weight (Hastak et al, 1982). Transverse and longitudinal orientations are used to measure the length, width, and height of the prostate. An ellipsoid formula is then used to estimate the volume of the prostate: $\text{Volume} = \frac{4}{3}\pi \times \text{length} \times \text{width} \times \text{height}$ (Roehrborn et al, 1986) (Fig. 21-21).

Magnetic Resonance Imaging of the Prostate

MRI of the prostate has been used to provide high-quality, clear images. MRI's direct multiplanar imaging has allowed for detailed demonstration of prostate anatomy (Dooms and Hricak, 1986). Zonal anatomy can be more clearly demonstrated by MRI using 0.5 cm slices. The peripheral zone showed higher signal intensity than the other zones and can be well visualized in the coronal, sagittal, and transverse planes. The central zone was well visualized in the coronal and sagittal planes and was of low signal intensity.

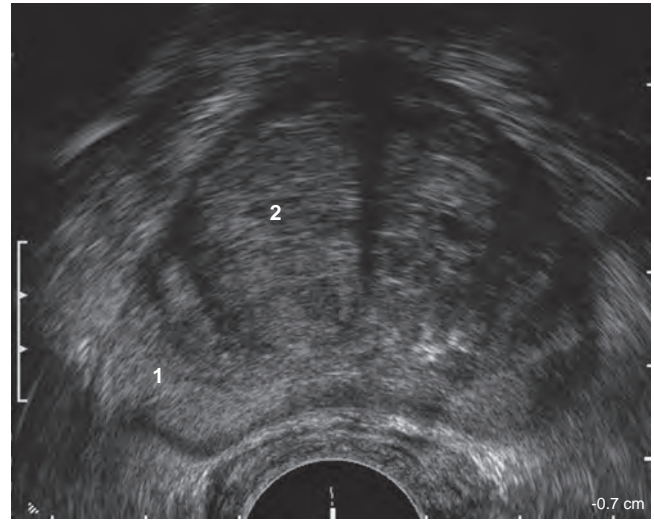


Figure 21-21. Transrectal ultrasound of the prostate demonstrating the peripheral zone (1) and the transition zone (2).

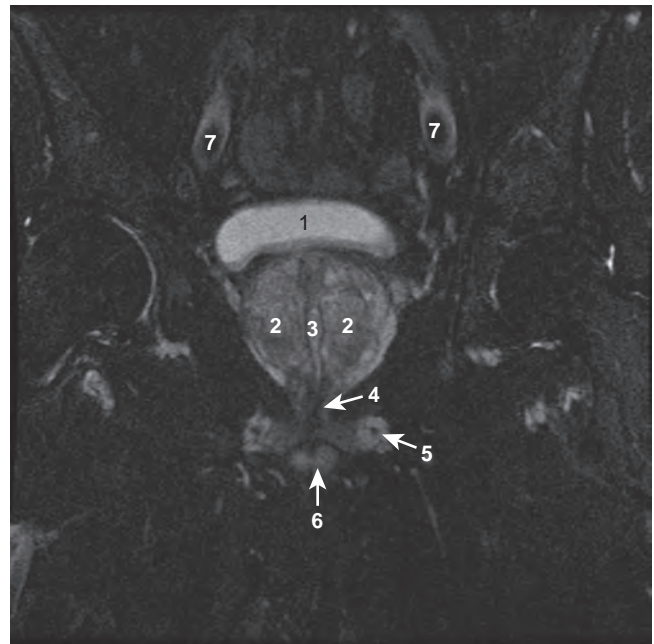


Figure 21-22. Axial T2-weighted magnetic resonance image of the male pelvis through the prostate gland and adjacent structures. 1, Urinary bladder; 2, lateral lobes of prostate; 3, verumontanum; 4, striated urethral sphincter; 5, inferior pubic ramus; 6, corpus spongiosum in cross section; 7, external iliac artery.

The transition zone showed similar MR parameters to the central zone (Hricak et al, 1987). Zonal anatomy is best demonstrated by T2-weighted images (Gevenois et al, 1990). Using a specific pulse sequence, the periprostatic venous plexus can be imaged (Poon et al, 1985). The endorectal surface coil has been used to enhance resolution (Schnall and Pollack, 1990). The use of MRI of the prostate has become more frequent for use with pathologic processes (Fig. 21-22).

URETHRA

The urethra is contained within the vascular corpus spongiosum and the glans penis. The normal urethral diameter is 8 to 9 mm. Anatomists have organized the urethra into multiple different

KEY POINTS: PROSTATE

- The normal prostate gland measures 3 cm in length, 4 cm in width, and 2 cm in depth, and it has a weight of 18 to 20 g.
- There is no true prostatic capsule at the apex of the prostate.
- The cavernosal nerves travel within the lateral prostatic fascia, posterolateral to the prostate.
- Benign prostatic hyperplasia most commonly occurs in the transition zone of the prostate.
- A total of 70% of the glandular tissue of the prostate is comprised of the peripheral zone and 70% of prostate cancers are found in the peripheral zone.
- Seventy percent of the prostate's composition includes glandular elements, whereas 30% is made up of fibromuscular stroma.
- The inferior vesical artery is the typical arterial supply to the prostate.
- The periprostatic plexus anastomoses with the deep dorsal vein of the penis and the internal iliac (hypogastric) veins.
- The obturator and internal iliac nodes are the primary sites of lymphatic drainage from the prostate.
- Transrectal ultrasonography of the prostate is useful for assessing prostate volume, locating focal abnormalities, assessing patients with infertility with suspicion of obstruction, and guiding prostate biopsies.

segmental divisions. It has been categorized in two broad segments: the anterior urethra and the posterior urethra. The **anterior urethra** begins at the perineal membrane and continues distally to the urethral meatus. The **posterior urethra** begins distal to the bladder neck and the transition to the anterior urethra is made at the perineal membrane. The segments have been further divided to characterize urethral anatomy more precisely. The **urethral epithelium** is transitional in type until the urethral epithelium becomes squamous where it traverses the glans penis. The submucosa contains smooth muscle, connective tissue, and elastic tissue. The glands of Littre are in the submucosa and their ducts empty into the urethral lumen. The arterial supply to the urethra is from the internal pudendal artery whose bulbourethral branches supply the urethra, the corpus spongiosum, as well as the glans penis. The venous drainage from the urethra drains to the pudendal plexus, which drains into the internal pudendal vein. The lymphatics from the urethra drain to the internal iliac (hypogastric) and common iliac nodes (Fig. 21-23).

Prostatic Urethra

The prostatic urethra travels the length of the prostate and is in greater proximity to the anterior surface of the prostate. A urethral crest extends inward from the posterior midline of the prostatic urethra and is present throughout the length of the prostatic urethra. This urethral crest is no longer present at the level of the striated sphincter. All glandular elements of the prostate drain into prostatic sinuses, which are positioned on either side of the urethral crest (McNeal, 1972). The urothelium of the prostatic urethra is made up of transitional epithelial cells. This transitional urothelium may extend into prostatic ducts. An angle at the mid-point of the prostatic urethra turns 35 degrees anteriorly and separates the prostatic urethra into anatomically and functionally distinct segments. These are termed the preprostatic (proximal) and prostatic (distal) segments of the prostatic urethra. This angle may range from zero to 90 degrees depending on variable anatomy (McNeal, 1972, 1988). All glandular elements of the prostate open into the prostatic urethra past the urethral angle. The **verumontanum** is formed by the widening and protrusion of the urethral crest from the posterior wall. The **prostatic utricle orifice** appears like a slit at the apex of the verumontanum. The utricle orifice is cystoscopically visible and measures 6 mm. The **prostatic utricle** is a müllerian remnant. The two small openings of the ejaculatory ducts are located on either side of the utricular orifice. After forming

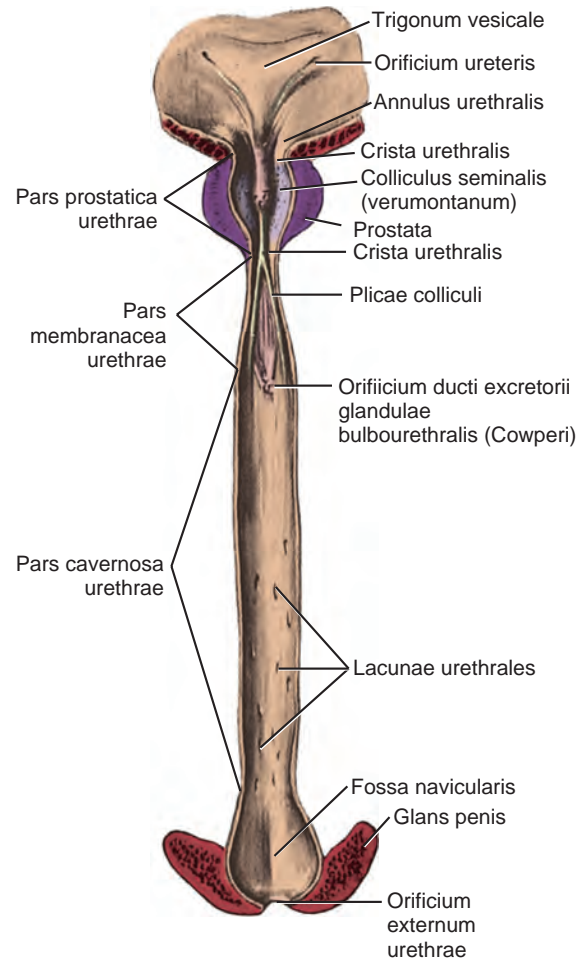


Figure 21-23. Posterior wall of the male urethra. (From Anson BJ, McVay CB. *Surgical anatomy*. 6th ed. Philadelphia: Saunders; 1984. p. 833.)

at the juncture of the vas deferens and seminal vesicles, the ejaculatory ducts travel approximately 2 cm through the prostate surrounded by circular smooth muscle, until they finally open into the distal prostatic urethra. The preprostatic sphincter is made up of thickened circular smooth muscle, synonymous with the internal urethral sphincter in the proximal segment. The prostatic segment is innervated by motor somatic fibers with an absence of any autonomic innervation (Figs. 21-24 and 21-25).

Membranous Urethra

On average the membranous urethra measures 2 to 2.5 cm in length and spans between the prostatic apex and the perineal membrane (Myers, 1991). A thin, smooth muscle layer spans across the membranous urethra. An outer layer of circularly arranged striated muscle in the shape of a horseshoe near the prostatic apex is found on the anterior surface of the urethra. The striated muscle reaches from the base of the bladder and the anterior aspect of the prostate extending the complete length of the membranous urethra. This signet ring-shaped striated sphincter is broad based and narrows as it courses through the urogenital hiatus of the levator ani to reach the prostatic apex. The posterior portion of the striated sphincter inserts into the perineal body throughout its length (Strasser et al, 1998). The striated sphincter is anterior to the dorsal vein complex and lateral to the levator ani. The band of fibrous tissue that suspends the urethra from the pubis anteriorly and that forms the suspensory ligament of the penis posteriorly, is made up of connective tissue from deep within the anterior and lateral walls. The striated sphincter's lumen consists of a pseudostratified columnar epithelium. There is a vascular submucosa that is surrounded by



Figure 21-24. Cystoscopic appearance of the verumontanum. (Courtesy David Leavitt, MD.)



Figure 21-26. Cystoscopic appearance of the striated sphincter. (Courtesy David Leavitt, MD.)

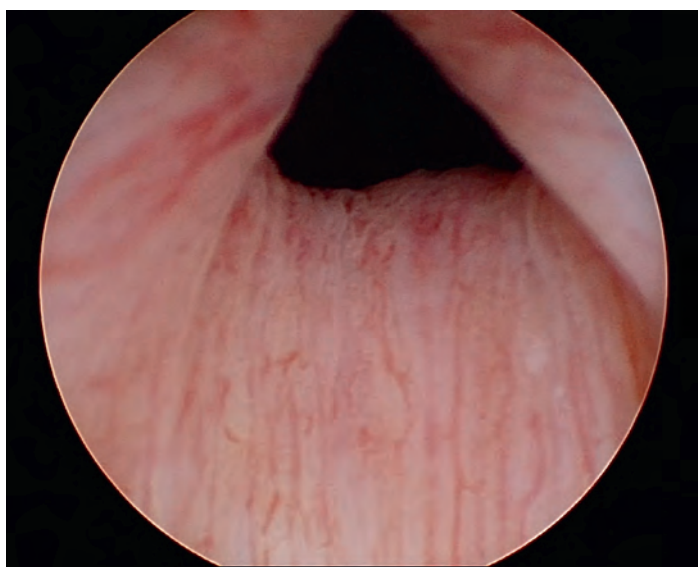


Figure 21-25. Cystoscopic appearance of the bladder neck. (Courtesy David Leavitt, MD.)

the longitudinal and circular urethral smooth muscle, which is the intrinsic component of the external sphincter (Raz et al, 1972). The pudendal nerve supplies innervation to the striated sphincter (Tanagho et al, 1982). A branch of the sacral plexus that travels along the surface of the levator ani provides another source of somatic innervation to the sphincter (Hollabaugh et al, 1997). The cavernous nerves are believed to supply autonomic innervation to the intrinsic smooth muscle of the membranous urethra (Steiner et al, 1991). The urethral stroma contains longitudinally organized collagen fibers and elastin fibers (Hickey et al, 1982). Lymphatic drainage from the membranous urethra travels in front of the prostate to join lymphatic channels draining the anteroinferior bladder. These channels terminate in the anterior or medial retrofemoral nodes and the middle node of the medial group of the external iliac nodes. Innervation is solely by motor somatic fibers without autonomic innervation. The ventral root of S3, with some contribution from S2, provides the somatic supply. The supply branches to the pelvic (splanchnic) nerve and passes to the pelvic (inferior hypogastric) plexus. Sensory innervation from the striated sphincter travels through the pudendal nerves via S2, and to a lesser extent S3, to travel to the node of Onuf centrally (Fig. 21-26).

Penile Urethra

The penile urethra, also known as the pendulous urethra and the spongy urethra, as it is surrounded by the corpus spongiosum,

comprises the urethra distal to the membranous urethra. The urethra is often subdivided even further at the junction of the membranous and penile urethra, and is termed the bulbomembranous urethra. This region comprises a 2-cm length of urethra within the urogenital diaphragm as well as being within the striated urethral sphincter and the first few proximal centimeters of the bulbous urethra, just distal to the sphincter within the penile bulb. The bulbospongy urethra begins a few centimeters distal to the membranous urethra and extends distally to the level of the suspensory ligament. The lumen widens to form the urethral bulb. The bulbourethral glands, also known as Cowper glands, empty into this region at the three o'clock and nine o'clock positions. The bulbourethral glands themselves are located more proximally on either side of the membranous urethra. The penile urethra measures approximately 15 cm in length in its entirety from the suspensory ligament to the meatus. It is positioned more dorsally than ventrally within the corpus spongiosum. The bulb and the fossa navicularis are the two segments of urethral lumen widening; otherwise the luminal diameter is relatively consistent throughout. The mucosa of the penile urethra includes a transitional epithelium until it reaches the fossa navicularis. The muscle layer is made up of an inner longitudinal, a middle circular, and an inconsistently characterized outer longitudinal stratum. The glands of Littre are composed of small mucus-secreting cells that lubricate the urethra before ejaculation, and they empty into orifices on the posterior wall of the penile urethra. The glands of Littre are rich in goblet cells and enter the spongy tissue between the vascular spaces and the trabeculae. **The penile urethra receives arterial supply from a branch of the internal pudendal artery, which enters at the level of the penile bulb, and is known as the bulbourethral artery.** Venous drainage of the bulbar urethra is by bulbar veins that drain into the prostatic plexus, which is the internal pudendal vein. The penile urethral lymphatics drain through a lymphatic network that is associated with the mucous membrane. These lymphatic channels course longitudinally but anastomose transversely and obliquely. The lymphatic channels drain proximally into trunks at the bulbomembranous urethra. The bulbomembranous lymphatic drainage may be variable. Some lymphatic drainage travels along the urethral artery or artery of the bulb, whereas others drain to the medial retrofemoral node after traveling behind the symphysis pubis. The penile urethral sensory innervation runs through submucosal axons that pass centrally through the dorsal nerve of the penis (Fig. 21-27).

Fossa Navicularis

The glanular portion of the urethra is known as the fossa navicularis, where its caliber dilates when compared to the urethra proximal to the fossa navicularis. It narrows again at the urethral meatus. **Unlike the transitional epithelium of the remainder of the urethra, the urethral mucosa that traverses the glans penis is a**

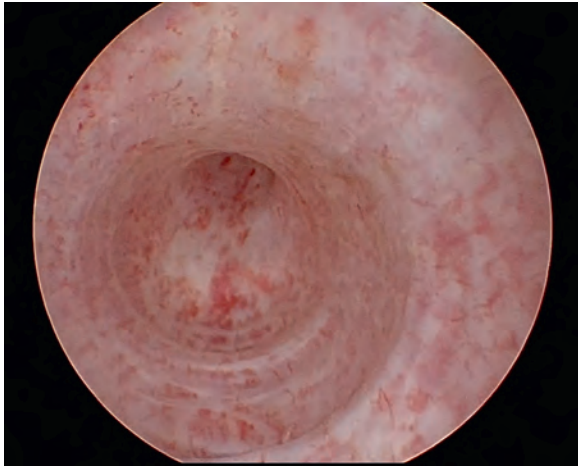


Figure 21-27. Cystoscopic appearance of the bulbar urethra. (Courtesy David Leavitt, MD.)

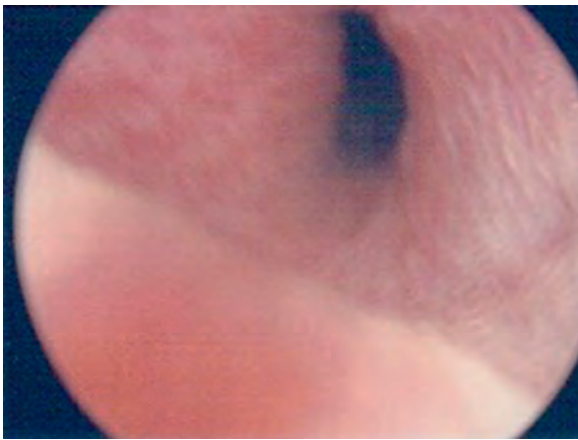


Figure 21-28. Cystoscopic appearance of the fossa navicularis.

squamous epithelium. These cells become keratinized near the meatus. The epithelium is separated from the smooth muscle of the spongy tissue by loose connective tissue, and a muscularis mucosa is absent. There are multiple pockets on the dorsal and lateral surfaces of the fossa navicularis. The lacuna magna (Morgagni) is a large pocket opening on the roof of the fossa navicularis (Figs. 21-28, 21-29, and 21-30).

KEY POINTS: URETHRA

- The urethra is contained within the corpus spongiosum and the glans penis.
- The anterior urethra begins at the perineal membrane and continues distally to the urethral meatus.
- The posterior urethra begins distal to the bladder neck and the transition to anterior urethra is made at the perineal membrane.
- The urethral epithelium is transitional in type until the urethral epithelium becomes squamous where it traverses the glans penis at the fossa navicularis.
- The arterial supply to the urethra is from the internal pudendal artery whose bulbourethral branches supply the urethra, the corpus spongiosum, and glans penis.
- The verumontanum is formed by the widening and protrusion of the urethral crest from the posterior wall.
- The prostatic utricle (müllerian remnants) orifice appears like a slit at the apex of the verumontanum.

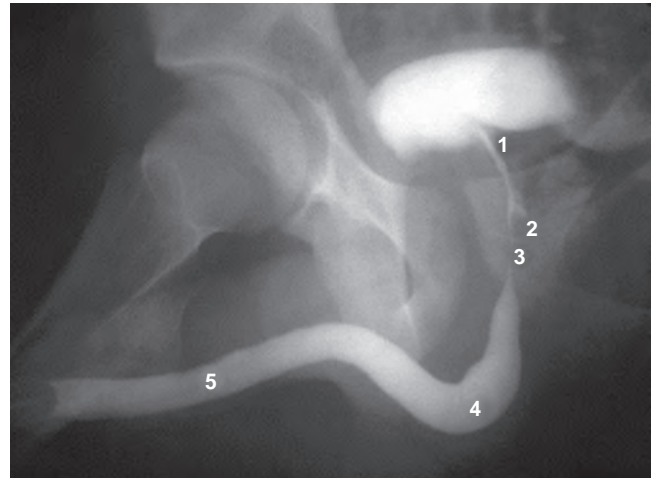


Figure 21-29. Retrograde urethrogram of the male urethra demonstrating urethral anatomy. 1, Prostatic urethra; 2, verumontanum, into which enter the ejaculatory ducts; 3, membranous urethra, note physiologic narrowing of urethral luminal diameter resulting from external striated sphincter; 4, bulbar urethra; 5, pendulous urethra.

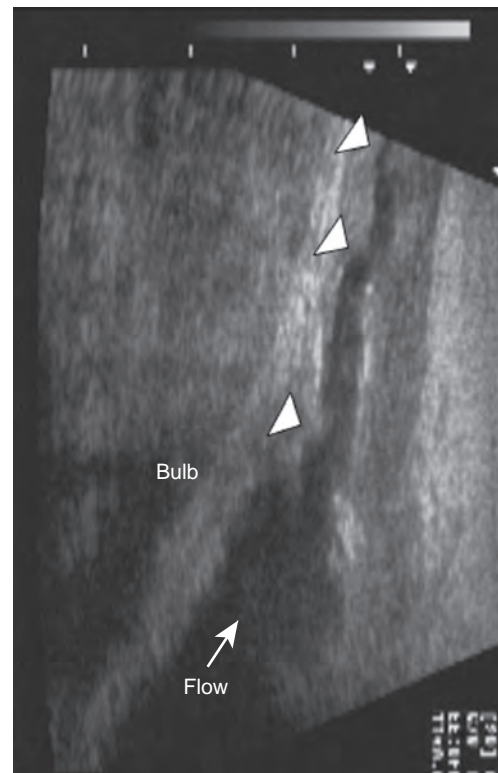


Figure 21-30. Urethral ultrasonography has been used to assist in assessing the urethra in a noninvasive fashion. The arrowheads indicate the direction of urine flow during voiding in a normal urethra without stricture. (Courtesy Jonathan Rhee, MD.)

PENIS

Structure

The gross structures of the penis can be divided into distinct anatomic compartments. The paired corpora cavernosa, which are the erectile bodies, prolongate proximally as the crus and attach to the pubic arch. The urethra travels through the corpus spongiosum, with its proximal segment known as the bulb. The glans

penis is an expansion of the corpus spongiosum. The superior surface of the penis during erection is known as the dorsum and the inferior surface during erection, containing the urethra, is known as the ventrum. The major portion of the body of the penis is formed by the corpora cavernosa as they join beneath the pubis (penile hilum). A **septum separates the corpora cavernosa but is permeable distally to allow for free communication between their vascular spaces.** The tunica albuginea is the tough connective tissue layer that envelops the corpora cavernosa and is primarily collagenous. With erection, the outer longitudinal layers and inner circular fibers of the tunica albuginea are tightly stretched, and in the flaccid state they form an undulating meshwork (Goldstein et al, 1982). Smooth muscle bundles traversing the corpora cavernosa form endothelial-lined cavernous sinuses. Myoendothelial junctions, which are cellular extensions through the internal elastic lamina, have been identified as connecting the vascular smooth muscle cells to the endothelial cells. Gap junctions have been identified at the point of cell-to-cell contact in the myoendothelial junction (Kavoussi et al, 2010). The corpus spongiosum tapers and

travels ventrally to the corpora cavernosa, distal to the bulb. The glans penis is the most distal expansion of the corpus spongiosum. The shaft of the penis and the base of the glans are separated by the corona. The corpora cavernosa are surrounded by Buck fascia dorsally. Buck fascia splits to surround the corpus spongiosum ventrally. The fundiform ligament of the penis is composed of collagenous and elastic fibers from the rectus sheath blending with and surrounding Buck fascia. The suspensory ligament of the penis is made up of deeper fibers from the pubis. Deep to the muscles of the corpora cavernosa, the tunica albuginea and the Buck fascia fuse (Uhlenhuth et al, 1949). Buck fascia joins the base of the glans at the corona distally. The penile shaft skin is very elastic and its only glandular elements are the smegma-producing glands, located at the base of the corona. The penile skin is very mobile as its dartos fascia backing is very loosely attached to Buck fascia. In uncircumcised men, the prepuce (foreskin) is the penile skin as it folds over the glans and attaches below the corona. The glans penis skin is immobile as it is attached to the tunica albuginea below it (Figs. 21-31 and 21-32).

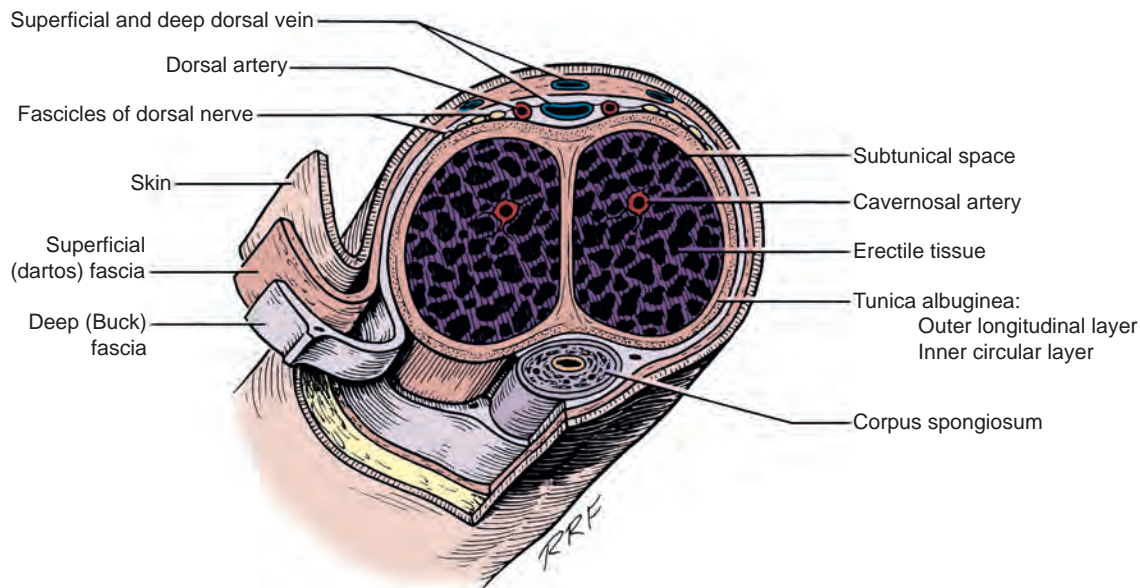


Figure 21-31. Cross section of the penis, demonstrating the relationship between the corporal bodies, penile fascia, vessels, and nerves. (From Devine CJ Jr, Angermeier KW. *Anatomy of the penis and male perineum*. AUA Update Series 1994;13:10–23.)

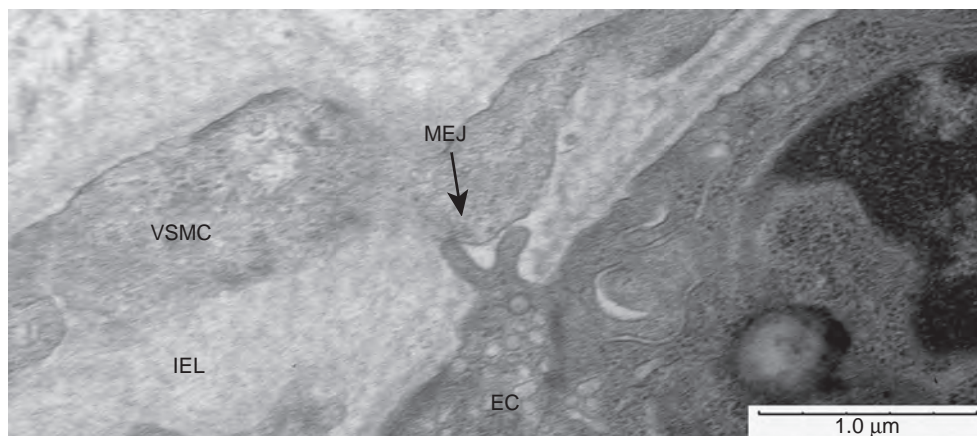


Figure 21-32. Electron microscopy of a myoendothelial junction (MEJ) in human corpus cavernosal tissue. The MEJ is extending from the endothelial cell (EC) through the internal elastic lamina (IEL) to communicate with the vascular smooth muscle cell (VSMC).

Arterial Supply

There is a superficial arterial system supplying the penis, which originates from the external pudendal arteries, and a deep arterial system that arises from each side from the internal pudendal arteries. The pudendal artery branches into a deep artery, supplying the corpora cavernosa, a dorsal artery, and the bulbourethral artery. Above the perineal membrane, the common penile artery travels in the Alcock canal, and it supplies the corpora cavernosa via three branches. The bulbourethral artery penetrates the perineal membrane where it enters the corpus spongiosum from above at its posterolateral border. This provides arterial supply to the corpus spongiosum, glans, and urethra. The cavernosal artery penetrates the corpus cavernosum in the penile hilum to nearly the center of the erectile tissue. It provides straight and helicine arteries that supply the cavernous sinuses. After it travels between the crus and the pubis, the dorsal artery of the penis supplies the dorsal surfaces of the corporeal bodies. The dorsal artery travels between the dorsal vein and the dorsal penile nerve, and they all attach to the underside of Buck fascia. The dorsal artery travels distally toward the glans and supplies cavernous branches and circumferential branches to the urethra and the corpus spongiosum (Devine and Angermeier, 1994). There can be a great deal of variability in penile arteries (Bare et al, 1994). A single cavernosal artery may supply both corpora cavernosa or it may be completely absent. In some cases, an accessory pudendal artery may supplement or completely take the place of branches of the common penile artery (Breza et al, 1989). The arterial supply to the penile skin is from the external pudendal branches of the femoral vessels. These vessels run longitudinally in the dartos fascia layer and provide a rich blood supply after entering the base of the penis (Fig. 21-33).

Venous Drainage

The superficial dorsal vein lies external to Buck fascia, whereas the deep dorsal vein is beneath Buck fascia and runs between dorsal arteries. A number of venous channels anastomose at the base of the glans to form the dorsal vein of the penis. **The dorsal vein travels between the corporeal bodies, in a groove, and drains into the preprostatic plexus.** In the distal two thirds of the penile shaft, the circumflex veins from the corpus spongiosum course around the corpora cavernosa to enter the deep dorsal vein perpendicularly. There are typically 3 to 10 circumflex veins. The cavernous sinuses form intermediary venules that empty into the subtunical capillary plexus. Emissary veins from these plexuses travel obliquely between the layers of the tunica and drain into the circumflex veins dorso-laterally. Emissary veins form two to five cavernous veins in the

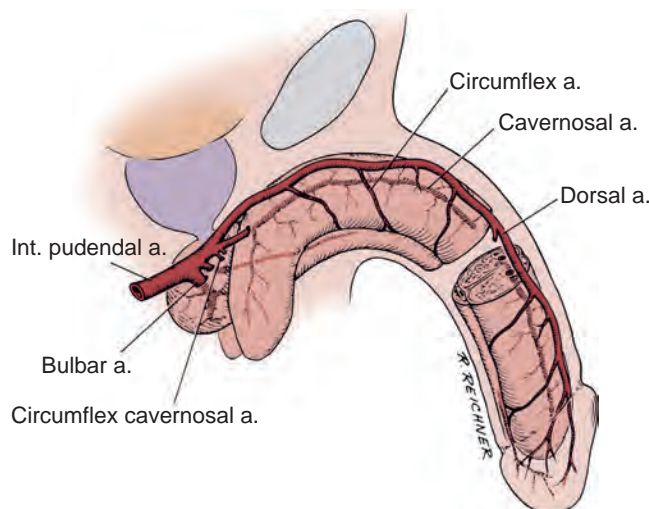


Figure 21-33. Arterial supply of the penis.

proximal third of the penis, joining on the dorsomedial surface of the corpora cavernosa. These veins travel between the bulb and crura at the hilum of the penis. They receive branches from the bulb and the crura and empty into the internal pudendal veins.

Lymphatic Supply

Lymphatics from the skin of the penis drain to the superficial inguinal and subinguinal lymph nodes. **Penile shaft lymphatics converge on the dorsum and ramify to both sides of the groin to drain into inguinal lymph nodes.** Lymphatics from the glans run deep to Buck fascia dorsally to drain to the superficial and deep inguinal nodes bilaterally. Some studies have suggested direct lymphatic channels from the glans to pelvic nodes as well as studies proposing lymphatic drainage through sentinel nodes positioned medial to the superficial epigastric veins. These models have been challenged (Catalona, 1988).

Nerve Supply

Sensory innervation of the penis is through the dorsal nerves. These nerves richly supply the glans. The dorsal nerves travel alongside the dorsal arteries. Small branches of the perineal nerve supply the ventrum of the penis as distally as the glans (Uchio et al, 1999). The somatic nerve supply originates from spinal nerves S2, S3, and S4 via the pudendal nerve. The pudendal nerve passes through the Alcock canal and continues as the dorsal nerve of the penis. The cavernous nerves supply sympathetic and parasympathetic innervation from the pelvic plexus to the corporeal bodies after penetrating them to ramify in the erectile tissue (Fig. 21-34).

Cavernosogram

Cavernosograms were primarily used historically to assist in the diagnosis of venous leak erectile dysfunction. Radiopaque contrast is injected into the corporal body with plain film imaging. This is not a commonly used diagnostic test any longer, but it is occasionally used at the time of penile fracture repair (Fitzpatrick and Cooper, 1975; Mydlo et al, 1998) (Fig. 21-35).

KEY POINTS: PENIS

- The paired erectile bodies are known as the corpora cavernosa.
- The glans penis is an expansion of the corpus spongiosum.
- A permeable septum separates the corpora cavernosa for free communication between their vascular spaces.
- The superficial arterial system to the penis originates from the external pudendal arteries, and a deep arterial system arises from the internal pudendal arteries.
- The dorsal vein runs between the corporeal bodies and drains into the preprostatic plexus.
- Penile shaft lymphatics converge on the dorsum and ramify to both sides of the groin to drain into inguinal lymph nodes.
- Sensory innervation of the penis is through the dorsal nerves, and the somatic nerve supply originates from spinal nerves S2, S3, and S4 via the pudendal nerve.

SCROTUM

Gross Structure

The scrotal skin is hair bearing, pigmented, with abundant sebaceous and sweat glands, and has an absence of fat. It is variable

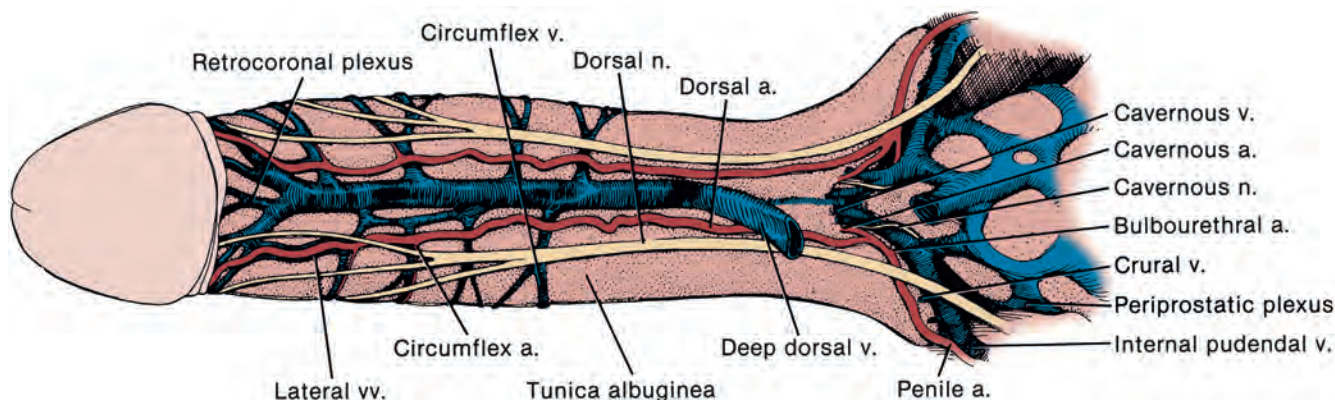


Figure 21-34. Dorsal penile arteries, veins, and nerves. (From Hinman F Jr. *Atlas of urosurgical anatomy*. Philadelphia: Saunders; 1993. p. 445.)

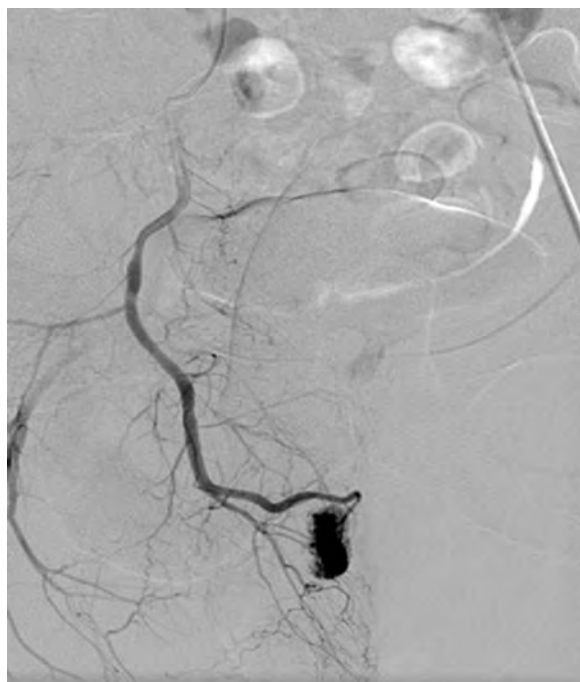


Figure 21-35. Angiogram of arteriocorporeal fistula in patient with nonischemic priapism showing filling of the right corpus cavernosum.

and may be folded with transverse rugae or it may appear loose and shiny. Its appearance depends on the tone of the underlying dartos smooth muscle. The median raphe runs longitudinally in the midline from the urethral meatus to the anus. Deep to the raphe, the scrotum is divided by a septum into two compartments, each containing a testis. The smooth muscle of the dartos fascia underlying the skin is continuous with Colles, Scarpa, and the dartos fascia of the penis. The spermatic fasciae are layers of the abdominal wall that extend to form parts of the scrotal wall. The external oblique extends to form the external spermatic fascia, which attaches to the borders of the external inguinal ring. The internal oblique extends to form the cremaster muscle and fascia, which attach to the inguinal ligament laterally, to the iliopsoas laterally, and to the pubic tubercle medially. The transversalis fascia continues to become the internal spermatic fascia in the scrotum. A peritoneal derivative known as the parietal and visceral tunica vaginalis surrounds the testis with a

mesothelium-lined pouch. The tunica vaginalis is continuous with the testis posterolaterally at its mesentery, where it is attached to the scrotal wall. The gubernaculum fixes the testis at its inferior pole (Fig. 21-36).

Arterial Supply

The external pudendal arteries supply the anterior wall of the scrotum. The arteries run parallel to the rugae and do not cross the median raphe. The posterior aspect of the scrotum has arterial supply from perineal branches. Arterial supply to the spermatic fascia is from the cremasteric, testicular, and deferential branches.

Venous Drainage

The external pudendal veins drain the anterior scrotal wall. The veins run parallel to the rugae and do not cross the median raphe.

Lymphatic Supply

Scrotal lymphatics do not cross the median raphe and drain into the superficial inguinal nodes on the ipsilateral side.

Nerve Supply

Branches of the ilioinguinal and genitofemoral nerves innervate the anterior scrotal wall. The nerves run parallel to the rugae and do not cross the median raphe. The posterior aspect of the scrotum receives innervation from scrotal branches of perineal nerves as well as from branches of the posterior femoral cutaneous nerve (S3).

KEY POINTS: SCROTUM

- The smooth muscle of the dartos fascia underlying the scrotal skin is continuous with Colles, Scarpa, and the dartos fascia of the penis.
- The scrotal wall arteries run parallel to the rugae and do not cross over the median raphe.
- Branches of the ilioinguinal and genitofemoral nerves innervate the anterior scrotal wall.

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The complete reference list is available online at www.expertconsult.com.



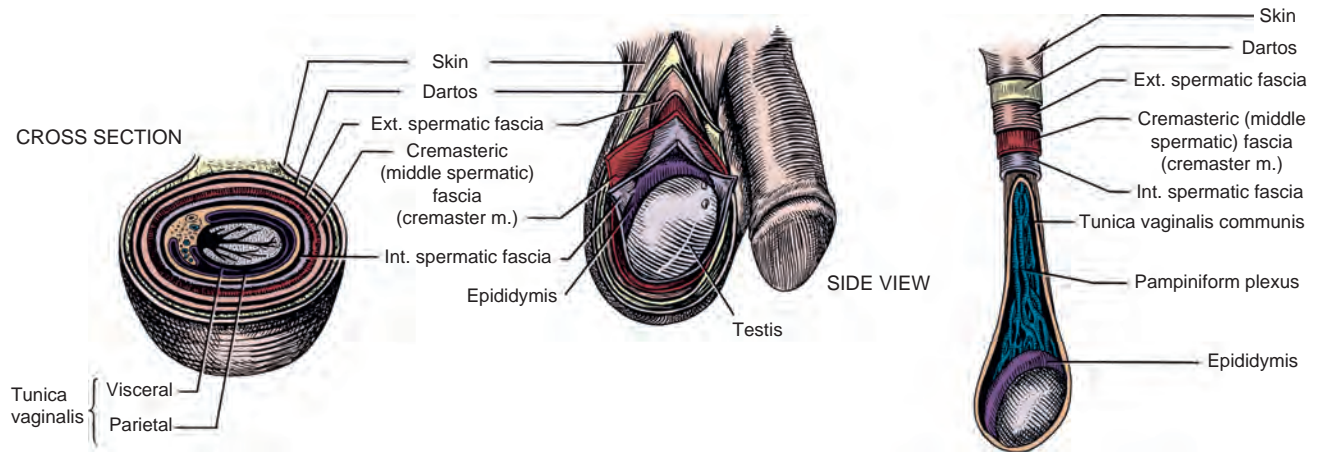


Figure 21-36. Scrotum and its layers. (From Pansky B. *Review of gross anatomy*. 6th ed. New York: McGraw-Hill; 1987.)

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Hypothalamic-Pituitary-Gonadal Axis

Testis

Epididymis

Ductus (Vas) Deferens

Seminal Vesicle and Ejaculatory Ducts

Spermatozoa

Summary

The male reproductive axis of hormones and organs is an efficient, well-orchestrated, and precisely managed biologic system that has evolved over millions of years. It is responsible for reproductive tract formation and development, fertility potential at puberty, and the maintenance of adult maleness. This chapter explores our current understanding of this complex system by defining the anatomy and physiology of its components, including the hypothalamic-pituitary-gonadal (HPG) hormonal axis, spermatogenesis and androgen production within the testicle, and maturation and transport of sperm in the ductal system. In addition, new concepts in genetic infertility, stem cell science, and ejaculatory physiology are explained. Through such rigorous intellectual dissection, the true beauty and sophistication of the reproductive process is appreciated.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS

The HPG axis plays a critical role during development and adulthood in four physiologic processes: (1) **phenotypic gender** development during embryogenesis, (2) **sexual maturation** at puberty, (3) testis endocrine function—**testosterone production**, and (4) testis exocrine function—**sperm production**.

Basic Endocrine Concepts

Two types of hormones mediate communication in the reproductive axis: peptide and steroid. **Peptide hormones are small, secretory proteins that act through cell surface receptors.** Hormone signals are transduced by one of several second-messenger pathways (Fig. 22-1). Ultimately, most peptide hormones induce phosphorylation of proteins that alter cell function. Examples of peptide hormones are luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In contrast, **steroid hormones are derived from cholesterol. They are not stored in secretory granules; consequently, steroid secretion directly reflects rates of hormone production.** In plasma, these hormones are usually bound to carrier proteins, and because they are lipophilic, steroid hormones are cell membrane permeable. After binding to intracellular receptors, steroids are translocated to nuclear DNA recognition sites and regulate target gene transcription. Examples of reproductive axis steroid hormones are testosterone and estradiol.

Hormonal signaling within the HPG axis is hierarchically governed by a free-running pulse generator within the hypothalamus. The amplitude and frequency with which hormone secretions occur within the reproductive axis determine downstream organ responsiveness. Feedback control is the principal mechanism through which hormonal regulation occurs in the HPG axis (Fig. 22-2). With feedback control, a hormone can regulate the synthesis and action

of itself or of another hormone. **In the HPG axis, negative feedback activity is primarily responsible for minimizing perturbations and maintaining homeostasis.**

Components of the Reproductive Axis

Hypothalamus

As the integrative center of the HPG axis, the hypothalamus receives neuronal input from the amygdala, thalamus, pons, retina, olfactory cortex, and many other areas (see Fig. 22-2). The pulse generator for the cyclic secretion of pituitary hormones, **the hypothalamus is anatomically linked to the pituitary gland by both a portal vascular system and neuronal pathways.** By avoiding the systemic circulation, the portal vascular system allows direct delivery of hypothalamic hormones to the anterior pituitary.

The most important hypothalamic hormone for reproduction is **gonadotropin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LHRH)**, a 10-amino acid peptide generated in the neuronal cell bodies in the preoptic and arcuate nuclei. **Currently, the only known function of GnRH is to stimulate the secretion of LH and FSH from the anterior pituitary.** GnRH has a plasma half-life of approximately 5 to 7 minutes and is almost entirely removed on the first pass through the pituitary either by receptor internalization or enzymatic degradation. GnRH secretion results from integrated input from the effects of stress, exercise, and diet from higher brain centers, gonadotropins secreted from the pituitary, and circulating gonadal hormones. Substances known to regulate GnRH secretion are listed in Table 22-1. In Kallman syndrome, characterized by congenital hypogonadotropic hypogonadism, the GnRH precursor neurons fail to migrate normally, with a subsequent absence of hypothalamic GnRH secretion (Bick et al, 1992; Dode et al, 2003). Affected individuals have delayed puberty or infertility owing to lack of testosterone production.

GnRH output exhibits several types of rhythmicity: seasonal, on a time scale of months and peaking in the spring; circadian, resulting in higher testosterone levels during the early morning hours; and pulsatile, with GnRH peaks occurring every 90 to 120 minutes on average. The importance of pulsatile GnRH secretions in normal HPG axis function is aptly demonstrated by the ability of exogenous GnRH agonists (e.g., leuprolide acetate) to stop testicular testosterone production by changing pituitary exposure to GnRH from a cyclic to a constant pattern.

Anterior Pituitary

Located within the bony sella turcica of the skull, the pituitary has two lobes: posterior and anterior. The posterior lobe, or

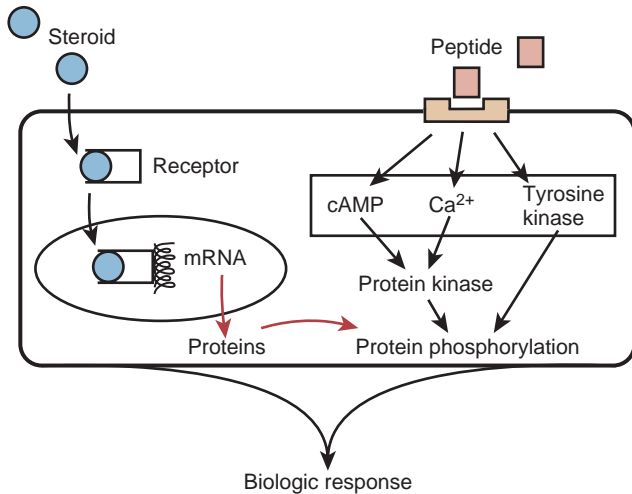


Figure 22-1. Two kinds of hormone classes mediate intercellular communication in the reproductive hormone axis: peptide and steroid. (Modified from Turek PJ. Male infertility. In: Tanagho EA, McAninch JC, editors. *Smith's urology*. 16th ed. Stamford [CT]: Appleton & Lange; 2008.)

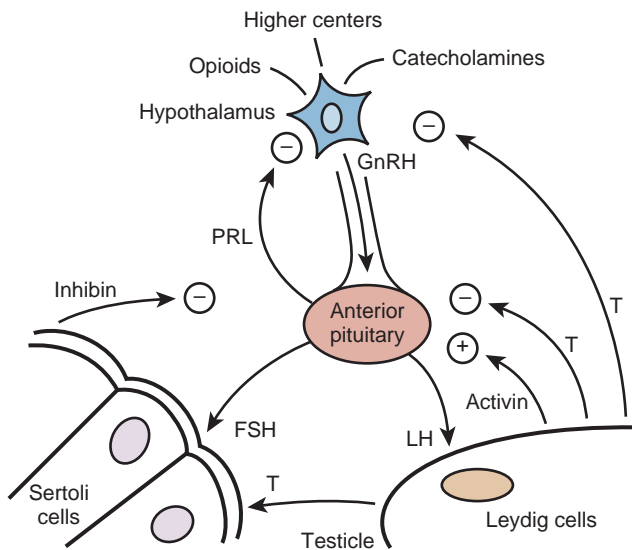


Figure 22-2. Diagram of the hypothalamic-pituitary-testis hormonal axis. +, Positive feedback; –, negative feedback; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PRL, prolactin; T, testosterone. (Modified from Turek PJ. Male infertility. In: Tanagho EA, McAninch JC, editors. *Smith's urology*. 16th ed. Stamford [CT]: Appleton & Lange; 2008.)

neurohypophysis, secretes two hormones, oxytocin and vasopressin, and is driven by neural stimuli. In contrast, the anterior pituitary, or adenohypophysis, is regulated by blood-borne factors and is the site of action of GnRH (see Fig. 22-2). GnRH stimulates the production and release of FSH and LH by a calcium flux-dependent mechanism. The sensitivity of pituitary gonadotrophs for GnRH varies with an individual's age and hormonal status. LH and FSH are the primary pituitary hormones that regulate testis function. They are glycoproteins composed of two polypeptide chain subunits, termed α and β , each coded by a separate gene. The α subunit of each hormone is identical and is similar to that of all other pituitary hormones; biologic and immunologic activities are conferred by the unique β subunit. Both subunits are required for endocrine activity. Sugars linked to these peptide subunits,

TABLE 22-1 Substances That Modulate Gonadotropin-Releasing Hormone (GnRH) Secretion

GnRH MODULATOR	TYPE OF FEEDBACK	EXAMPLES
Opioids	Negative	β -Endorphin
Catecholamines	Variable	Dopamine
Peptide hormones	Negative	FSH, LH
Sex steroids	Negative	Testosterone
Prostaglandins	Positive	PGE ₂
Insulin	Positive	Insulin
Kisspeptins	Positive	Kisspeptin (puberty)
Leptins	Positive	Leptin

FSH, follicle-stimulating hormone; LH, luteinizing hormone; PGE₂, prostaglandin E₂.

consisting of oligosaccharides with sialic acid residues, differ in content between FSH and LH and likely account for differences in their plasma clearance rates. Secretory pulses of LH vary in frequency from 8 to 16 pulses in 24 hours and vary in amplitude by onefold to threefold. These pulse patterns closely reflect GnRH release. Both androgens and estrogens regulate LH secretion through negative feedback. On average, FSH pulses occur approximately every 1.5 hours and vary in amplitude by 25%. The FSH response to GnRH is more difficult to assess than that of LH for two reasons: (1) FSH has a smaller amplitude response and a longer serum half-life, and (2) the gonadal proteins inhibin and activin may affect FSH secretion and are thought to account for the relative secretory independence of FSH from GnRH secretion.

FSH and LH are only known to act in the gonads. They activate adenylate cyclase, which leads to increases in intracellular cyclic adenosine monophosphate (cAMP). In the testis, LH stimulates steroidogenesis within Leydig cells by inducing the mitochondrial conversion of cholesterol to pregnenolone and testosterone. FSH binds to Sertoli cells and spermatogonial membranes within the testis and is the major stimulator of seminiferous tubule growth during development. FSH is essential for the initiation of spermatogenesis at puberty. In the adult, the major physiologic role of FSH is to stimulate quantitatively normal levels of spermatogenesis.

A third anterior pituitary hormone, prolactin, can also affect the HPG axis and fertility. Prolactin is a large, globular protein of 199 amino acids (23 kD) that is responsible for milk synthesis during pregnancy and lactation in women. No human mutations have been found in either the human prolactin gene or its receptor (Goffin et al, 2002). The normal role of prolactin in men is less clear, but it may increase the concentration of LH receptors on Leydig cells and sustain normal, high intratesticular testosterone levels. It may also potentiate the effects of androgens on the growth and secretions of the male accessory sex glands (Wennbo et al, 1997; Steger et al, 1998). Normal prolactin levels may be important to maintain libido. Although low prolactin levels are not necessarily pathologic, hyperprolactinemia abolishes gonadotropin pulsatility by interfering with episodic GnRH release. In addition, the anterior pituitary contains cells that secrete other glycoprotein hormones: adrenocorticotrophic hormone (ACTH), growth hormone (GH), and thyroid-stimulating hormone (TSH). These glycoprotein hormones can also have significant effects on male reproduction.

Testis

Normal male virility and fertility require the collaboration of the exocrine and endocrine testis (see Fig. 22-2). The interstitial compartment, composed mainly of Leydig cells, is responsible for steroidogenesis. The seminiferous tubules produce spermatozoa.

Normal testosterone production in men is approximately 5 g/day, and secretion occurs in a damped, irregular, pulsatile

manner (nyctohemeral). Testosterone is metabolized into two major active metabolites in target tissue: (1) the major androgen **dihydrotestosterone (DHT)** from the action of 5α -reductase, and (2) the estrogen **estradiol** through the action of aromatases. DHT is a much more potent androgen than is testosterone. In most peripheral tissues, testosterone reduction to DHT is required for androgen action, but in the testis and skeletal muscle, conversion to DHT is not essential for hormonal activity.

The primary site of FSH action is on Sertoli cells within seminiferous tubules. In response to FSH, Sertoli cells produce androgen-binding protein (ABP), transferrin, lactate, ceruloplasmin, clusterin, plasminogen activator, prostaglandins, and growth factors. Through these FSH-mediated factors, seminiferous tubule growth is stimulated during development, and sperm production is initiated during puberty. It is interesting to note that mice FSH knockout studies suggest that FSH is not essential for spermatogenesis, because affected mice can be fertile (Levallet et al, 1999). In humans, it is thought that FSH is required for normal spermatogenesis (Tapanainen et al, 1997).

The testis also produces the protein hormones **inhibin** and **activin** (Itman et al, 2006). Inhibin is a 32-kD protein made by Sertoli cells that inhibits FSH release from the pituitary. Within the testis, inhibin production is stimulated by FSH and acts by negative feedback at the pituitary or hypothalamus. Activin, a testis protein with close structural homology to transforming growth factor- β (TGF- β), exerts a stimulatory effect on FSH secretion. Activin receptors are found in a host of extragonadal tissues, suggesting that this hormone may have growth factor or regulatory roles in the body.

Negative feedback suppression of GnRH release by testosterone occurs through androgen receptors (ARs) in hypothalamic neurons and in the pituitary. In studies of genetic mutations, it is clear that both testosterone and estrogen participate in negative feedback (Shupnik and Schreihof, 1997). Steroid negative feedback results mainly from AR binding to testosterone, with a smaller contribution from estradiol binding. Testosterone feedback occurs mainly at the hypothalamus, whereas estrogen feedback is mainly in the pituitary (Santen, 1975). It also appears that although testosterone is the primary regulator of LH secretion, estradiol (along with inhibin from Sertoli cells) is the predominant regulator of FSH secretion (Hayes et al, 2001).

Development of the Hypothalamic-Pituitary-Gonadal Axis

Sex determination is genetically determined in humans. A critical gene for sex determination is **SRY** (sex-determining region Y gene) on the short arm of the Y chromosome. The SRY gene product is a protein with a high mobility group box (HMG) sequence, a highly conserved DNA-binding motif that kinks DNA. This DNA bending effect alters gene expression, leading to testis formation and subsequently to the male phenotype. However, the SRY gene does not act in isolation to determine human sex. **DAX1**, a nuclear hormone receptor gene, can alter SRY activity during development by suppressing genes downstream to SRY that would normally induce testis differentiation. A second gene, **WNT4**, largely confined to the adult ovary, may also serve as an "antitestis" gene. The discovery of these genes has significantly altered theories of sex determination. In the past, the female genotype was considered the "default," SRY-negative, developmental pathway. It is now clear that genes such as **WNT4** and **DAX1** can proactively induce female gonadal development, even in the presence of SRY (DiNapoli and Capel, 2008).

Once gonadal sex is determined, Leydig cells make **testosterone**, which induces development of the **internal genitalia** (Fig. 22-3). Leydig cells also synthesize **insulin-like growth factor-3** to promote **transabdominal testis migration** into the scrotum. DHT masculinizes the genital anlage to form the **external genitalia** (see Fig. 22-3). In addition, Sertoli cells within the developing testis synthesize **müllerian-inhibiting substance (MIS, or antimüllerian hormone [AMH])**, which prevents the müllerian duct from developing into uterus and fallopian tubes and keeps the early germ

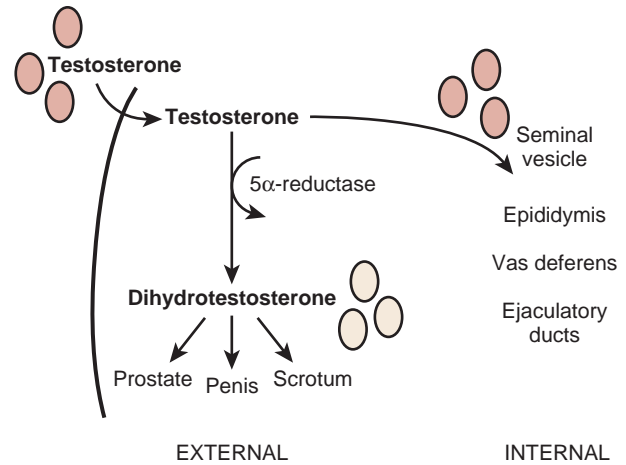


Figure 22-3. Diagram of internal and external genitalia development. Testosterone is the main androgenic steroid responsible for the developing male internal genitalia, whereas dihydrotestosterone is the main androgen responsible for development of male external genitalia.

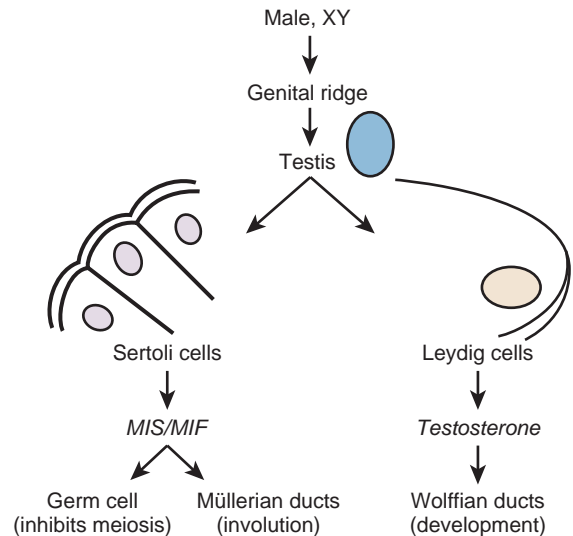


Figure 22-4. Early differentiation pathway of the male. MIS/MIF, müllerian inhibiting substance or factor. (Modified from Turek PJ. Male infertility. In: Tanagho EA, McAninch JC, editors. Smith's urology. 16th ed. Stamford [CT]: Appleton & Lange; 2008.)

cells quiescent in the testis (Fig. 22-4). In general, deficiencies in these developmental pathways result in either birth defects or intersex disorders.

The hormonal feedback relationships within the HPG axis become established during gestation. The expression of **kisspeptin** protein is in part responsible for activating GnRH neurons and triggering GnRH release. In addition, SF-1, an orphan nuclear receptor, is secreted by developing Sertoli cells and contributes to HPG axis development (Val et al, 2003). After the withdrawal of placental steroids at birth, there is a period of high gonadotropin secretion in the neonate. Subsequently, as axis sensitivity to gonadotropins increases, FSH and LH secretions fall to the low levels characteristic of childhood. Puberty begins with GnRH pulsing, leading gonadotropins to increase to adult levels and subsequently to increase sex hormones. The hypothalamic capacity to generate GnRH pulses arises at puberty, usually starting around the 12th year in males. Puberty begins at critical growth, weight, and nutritional rates for boys and girls and is likely initiated by

kisspeptin, melatonin, and leptin (Clement et al, 1998). The adipocyte hormone leptin is the body's regulatory signal governing the size of the fat stores, and there is increasing evidence that leptin modulates hypothalamic and pituitary activity (Caprio et al, 1999; Kiess et al, 1999; Quinton et al, 1999).

Aging and the Hypothalamic-Pituitary-Gonadal Axis

A progressive decline in testosterone and sperm production occurs with age, such that men in the seventh decade have mean plasma testosterone levels 35% lower than young men (Vermeulen et al, 1995). The consequence of this is a phenomenon that has been variously termed **male menopause**, **male climacteric**, **andropause**, or, more appropriately, **partial androgen deficiency in the aging male (PADAM)**. The changes to the seminiferous epithelium with age include decreases in seminiferous tubule volume and length. An age-related decrease in sperm production in older testes appears to stem from decreased germ cell proliferation rather than increased cellular degeneration. Correspondingly, FSH levels also increase with age, with mean values threefold higher in older than younger men. The cause of the age-related decline in HPG axis function is multifactorial. Testosterone production is reduced because of fewer Leydig cells and more testosterone-binding proteins. Diurnal variation of testosterone secretion is also lost in elderly men. With age, there is also evidence for a blunted HPG feedback response to low testosterone (despite generally high levels of gonadotropins) and to GnRH stimulation. Finally, normal pulsatile GnRH release is replaced by irregular pulses that are less effective in stimulating gonadotropin release (Mulligan et al, 1997). A combination of these effects is likely responsible for diminished HPG axis function with age.

KEY POINTS: HYPOTHALAMIC-PITUITARY-GONADAL AXIS

- Normal testosterone and sperm production depends on the pulsatile secretion of hypothalamic GnRH and LH and FSH from the anterior pituitary gland.
- Regulation of HPG axis hormones occurs primarily through negative feedback.
- The determination of maleness is derived from the SRY gene on the Y chromosome. However, developmental genes such as *WNT4* and *DAX1* are considered antitestis genes and can proactively induce female gonadal development.
- Changes to the HPG axis with paternal age include lower testosterone levels, blunted axis feedback, and irregular hormone pulsatility.

TESTIS

Gross Architecture

The testis is a white, ovoid organ that is normally 15 to 25 mL in volume (Prader, 1966) and has a length of 4.5 to 5.1 cm (Tishler, 1971; Winter and Faiman, 1972). The tunica albuginea has smooth muscle cells that course through predominantly collagenous tissue (Langford and Heller, 1973). Smooth muscle cells may impart contractile capability to the capsule (Rikmaru and Shirai, 1972), may affect blood flow into the testis (Schweitzer, 1929), and promote the flow of seminiferous tubule fluid from the testis (Davis and Horowitz, 1978).

The testis parenchyma is divided into compartments by septa. Each septum divides seminiferous tubules into lobes that each contain a centrifugal artery. Individual seminiferous tubules harbor developing germ cells. Interstitial tissue is composed of Leydig cells, mast cells, macrophages, nerves, and blood and lymph vessels. In humans, interstitial tissue comprises 20% to 30% of total testicular volume (Setchell and Brooks, 1988). The

relationship between seminiferous tubules and interstitial tissue anatomy is demonstrated in Figure 22-5. Seminiferous tubules are long, highly coiled, and looped. Both ends terminate in the rete testis. The combined length of the 600 to 1200 tubules in the human testis is estimated to be 250 meters (Lennox and Ahmad, 1970) (Fig. 22-6). The "hub" of the testis, also termed the rete testis, coalesces to form 6 to 12 ductuli efferentes that carry testicular fluid and spermatozoa into the caput epididymis (see Fig. 22-6).

The arterial supply to the testis and epididymis is derived from three sources: the internal spermatic artery, the deferential (vasal) artery, and the external spermatic (or cremasteric) artery (Harrison and Barclay, 1948). The internal spermatic artery arises from the abdominal aorta and is intimately associated with the pampiniform plexus of veins. The vascular arrangement within the pampiniform plexus, with the counterflowing artery and veins, facilitates the exchange of heat and small molecules. For example, testosterone passively diffuses from veins to the artery in a concentration-limited manner (Bayard et al, 1975). The counter-current heat exchange supplies arterial blood to the testis that is 2° C to 4° C lower than the rectal temperature in normal men (Agger, 1971). A loss of the temperature differential is associated with testicular dysfunction in men with varicocele (Goldstein and Eid, 1989) and cryptorchidism (Marshall and Edler, 1982). As the spermatic cord is commonly dissected during varicocele repair, it is surgically relevant to know that a single artery is observed in 50% of spermatic cords, with two arteries in 30% and three arteries in 20% of cases (Beck et al, 1992).

Inferior to the scrotal pampiniform plexus and near the mediastinal testis, the spermatic artery is highly coiled and branches before entering the testis. Extensive interconnections, especially between the internal spermatic and deferential arteries, allow maintenance of testis viability even after division of the internal spermatic artery (Fig. 22-7). From angiographic studies, a single artery enters the testis in 56% of cases; two branches enter in 31% of cases, and three

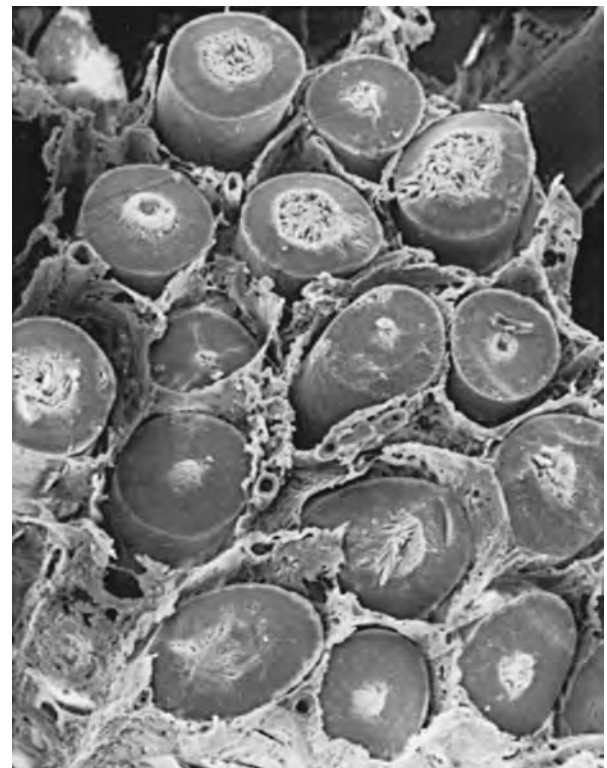


Figure 22-5. Scanning electron micrograph of the cut surface of the human testis. Note the relationship of interstitial tissue to seminiferous tubules. (From Christensen AK. Leydig cells. In: Greep RO, Astwood EB, editors. Handbook of physiology. Washington [DC]: American Physiology Society; 1975. p. 57–94.)

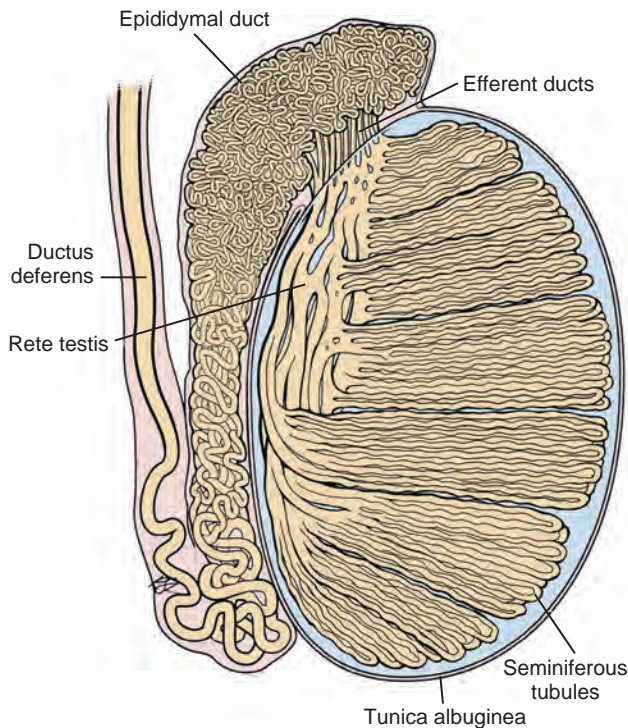


Figure 22-6. Drawing of the human testis showing the seminiferous tubules (250 meters in length), epididymis (3 to 4 meters in length), and vas deferens. (Based on Hirsh AV. The anatomical preparations of the human testis and epididymis in the Glasgow Hunterian Collection. *Hum Reprod Update* 1995;1:515–21.)

or more branches in 13% of testes (Kormano and Suoranta, 1971). In men with a single testicular artery, its interruption can result in testicular atrophy (Silber, 1979). The testicular arteries penetrate the tunica albuginea and then travel inferiorly along the posterior surface of the testis within the parenchyma. Branching arteries pass anteriorly over the testicular parenchyma. Major testicular artery branches also travel over the inferior pole of the testis, pass anteriorly, and branch out over the surface of the testis. The location of these vessels is clinically important, because they may be injured during orchiopexy or testis biopsy procedures (Jarow, 1991; Schlegel and Su, 1997). The midsection of the testis has relatively fewer vessels compared with superior or inferior areas. Individual arteries to the seminiferous tubules, termed *centrifugal arteries*, travel within the septa, which contain tubules. Centrifugal artery branches give rise to arterioles that supply individual intertubular and peritubular capillaries (Muller, 1957). The intertubular capillaries are located within the columns of interstitial tissue, whereas the ladder-like capillaries running near the seminiferous tubule are called *peritubular capillaries*. Through this vascular complex, the human testis is provided with 9 mL of blood per 100 g of tissue per minute (Pettersson et al, 1973).

Veins within the testis are unusual in that they do not run with the corresponding intratesticular arteries. Small parenchymal veins empty either into the veins on the testis surface or into a group of veins near the mediastinum testis that travels along the rete testis (Setchell and Brooks, 1988). These two sets of veins join together with deferential veins to form the pampiniform plexus as they ascend into the scrotum. Pampiniform plexus veins are thin walled, which likely contributes to the passive diffusion of testosterone and heat with the closely associated spermatic artery.

The testis has no known somatic innervation. It receives autonomic innervation primarily from the intermesenteric nerves and renal plexus (Mitchell, 1935). These nerves run along the testicular artery into the testis. It appears that testicular adrenergic innervation

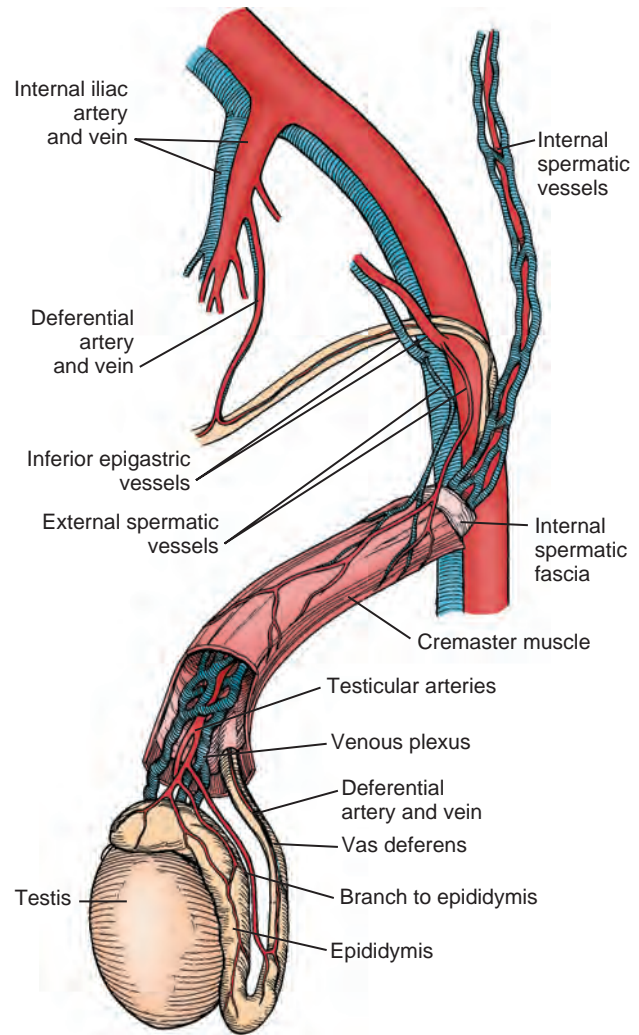


Figure 22-7. Schematic illustration of interconnections between internal spermatic, external spermatic (cremasteric), and deferential vessels in the peritesticular region and spermatic cord.

is restricted primarily to small blood vessels that supply Leydig cell clusters that may regulate Leydig cell steroidogenesis (Baumgarten et al, 1968; Turnbull and Rivier, 1997). It is thought that vascular tone in the testis may involve regulation at several levels (Linzell and Setchell, 1969), including autoregulation of capsular arteries (Davis et al, 1990), regional variation based on local metabolic need and governed by peptides such as atrial natriuretic peptide (Collin et al, 1997), and assisted transport of molecules such as LH across the vascular endothelium (Milgrom et al, 1997). Indeed, these observations suggest a highly specialized function for the microvasculature of the testis (see review by Desjardins [1989]).

Prominent lymphatics can be observed within the spermatic cord (Hundeiker, 1971). Obstruction of these ducts results in dilation of the testis interstitium but not the seminiferous tubules, suggesting that the interstitial space is drained by lymphatics, but the seminiferous tubules are not. Lymphatic obstruction can also result in hydrocele formation, a known complication of varicocelelectomy and herniorrhaphy procedures. The sperm-containing intratubular fluid that bathes Sertoli cells flows from the seminiferous tubules into the rete testis and subsequently into the caput epididymis. This fluid, isosmotic with plasma, is thought to be mainly of seminiferous tubule origin (Setchell and Brooks, 1988). Reabsorption of this fluid within the rete testis and efferent ductules is regulated by estrogens (Lee et al, 2000). Tubular fluid composition is markedly different from blood plasma or

lymphatics, suggesting that substances are not freely diffusible into and out of the tubules (Setchell and Waites, 1975). This has led to the concept of a “blood-testis barrier” to be discussed later.

Testis Cytoarchitecture

Interstitial

Leydig Cells. The testis interstitium contains blood vessels, lymphatics, fibroblasts, macrophages, mast cells, and Leydig cells (Fig. 22-8). Leydig cells are responsible for the bulk of testicular steroid production. Leydig cells differentiate from mesenchymal

precursor cells by the 7th week of gestation. The activation of Leydig cell steroidogenesis correlates with the onset of androgen-dependent differentiation of the male reproductive system. Although Leydig cells express steroidogenic enzymes before becoming responsive to LH (El-Gehani et al, 1998; Majdic et al, 1998), they also differentiate from precursors under the influence of LH and placental-derived human chorionic gonadotropin (hCG) and from the effect of local paracrine factors such as insulin-like growth factor-1 (IGF-1) (Huhtaniemi and Pelliniemi, 1992; Teerds and Dorrington, 1993; Le Roy et al, 1999). At 2 to 3 months after birth, a second wave of Leydig cell differentiation occurs in response to pituitary gonadotropin production, briefly elevating

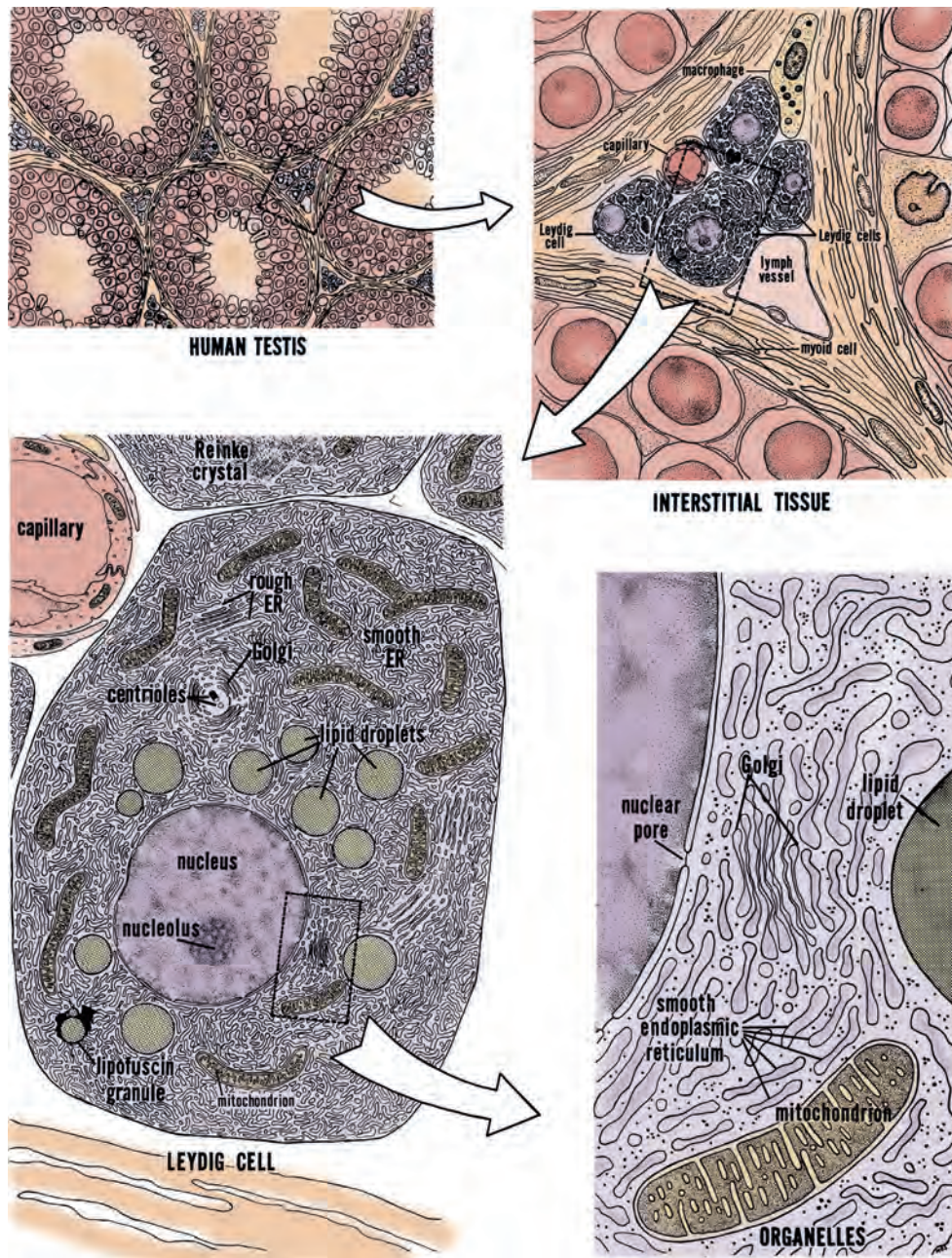


Figure 22-8. Fine structure of human Leydig cells. Leydig cells occur in clusters in the interstitium between seminiferous tubules (upper left). Interstitial tissue (upper right) contains macrophages and fibroblasts and capillaries and lymph vessels. The most abundant organelle within the Leydig cell cytoplasm is the smooth endoplasmic reticulum (lower left). Organelles seen in greater detail (lower right). (From Christensen AK. Leydig cells. In: Greep RO, Astwood WB, editors. Handbook of physiology. Baltimore: Williams & Wilkins; 1975. Copyright 1975, American Physiological Society, Bethesda, MD.)

testosterone levels. Androgen produced during the early male neonate's life is thought to hormonally imprint the hypothalamus, liver, and prostate such that they respond appropriately to androgen stimulation later in life. After reactivation of the HPG axis at puberty, stereologic analysis has revealed that a single testis from a young adult contains approximately 700 million Leydig cells (Kaler and Neaves, 1978).

Testosterone. Testosterone, synthesized from cholesterol, is the principal steroid produced by the testis (Lipsett, 1974). Numerous C18, C19, and C21 steroids are also produced (Lipsett, 1974; Ewing and Brown, 1977). Cholesterol must be transported into Leydig cell mitochondria, where the cholesterol side-chain cleavage enzyme converts it to pregnenolone. The three main sources of cholesterol in the Leydig cell are (1) external, from blood-borne lipoprotein and internalization of cholesterol-lipoprotein receptor complexes, (2) de novo synthesis from acetate, and (3) stored cholesterol esters in lipid droplets. Maintenance of cholesterol stores is part of normal Leydig cell function; LH stimulation evokes cholesterol mobilization through cholesterol esterase activity. Pregnenolone is transported out of the mitochondrial membrane into the smooth endoplasmic reticulum, where it is converted into testosterone. Testosterone diffuses across the cell membrane and is trapped within the extracellular fluid and blood plasma by steroid-binding proteins.

Cholesterol transport to the inner membrane of the mitochondrion is regulated by two transport proteins: steroid acute regulatory protein (StAR) and peripheral benzodiazepine receptor (PBR). LH binding elicits StAR synthesis in the Leydig cell, which then threads through the outer mitochondrial membrane to facilitate cholesterol transport (Stocco, 2000). PBR forms a channel

for cholesterol in the mitochondrial membrane (Culty et al, 1999), but it is not clear whether PBR functionally interacts with StAR (West et al, 2001).

The four major enzymes participating in testosterone biosynthesis from pregnenolone are cholesterol side-chain cleavage enzyme, 3β -hydroxysteroid dehydrogenase, cytochrome P450 17α -hydroxylase/C17-20-lyase, and 17β -hydroxysteroid dehydrogenase. The enzymology, chromosomal locations, and molecular genetics of these enzymes are well described (Payne and Hales, 2004). Mutations in the genes encoding these enzymes have been described and the resulting disorders of androgen biosynthesis are a relatively rare cause of sexual ambiguity in chromosomally normal males (Miller, 2002).

Control of Testosterone Synthesis. The control of Leydig cell steroidogenesis is complex and involves both pituitary and nonpituitary factors (Payne and Youngblood, 1995). The most important regulator of testosterone production is LH. After binding LH, through the second messenger cAMP, Leydig cells initiate transport of cholesterol into mitochondria. Pituitary peptides other than LH (e.g., FSH and prolactin) modify the response to LH (Ewing, 1983). Other, nonpituitary factors capable of modifying steroid production by Leydig cells include GnRH (Sharpe, 1984); inhibin and activin (Bardin et al, 1989); epidermal growth factor (EGF), IGF-1, and TGF- β (Ascoli and Segaloff, 1989; Saez et al, 1991); prostaglandins (Eik-Nes, 1975); and adrenergic stimulation (Eik-Nes, 1975). Moreover, direct inhibition of Leydig cell steroidogenesis may also occur through estrogens and androgens (Ewing, 1983; Darney et al, 1996).

Testosterone Cycles. Testosterone blood levels change dramatically during human fetal, neonatal, and adult life. Figure 22-9

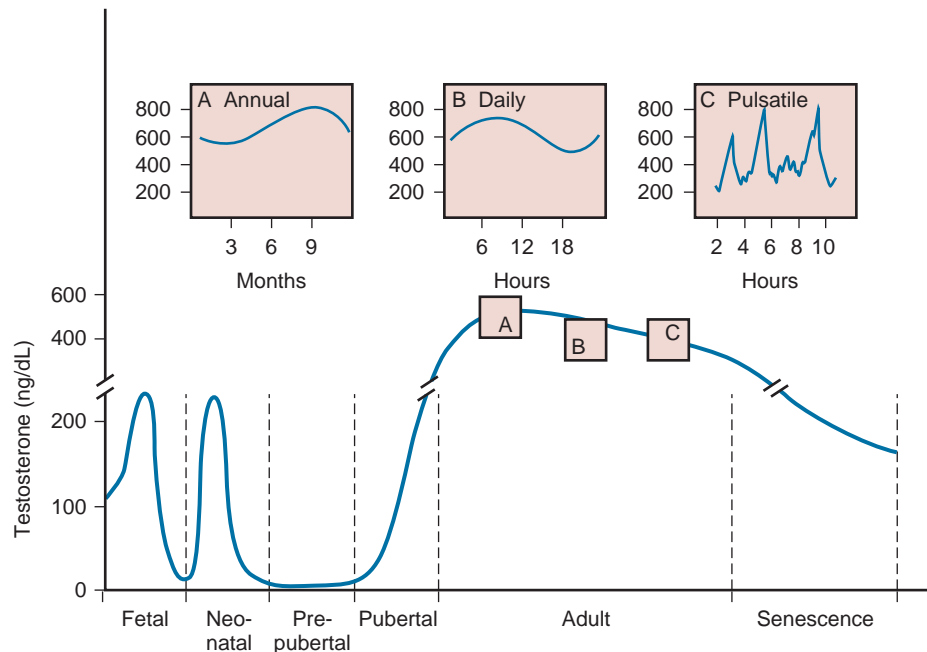


Figure 22-9. Peripheral blood testosterone levels in the human male during the life cycle. The fetal testosterone peak occurs at 12 to 18 weeks of gestation (*lower left corner; gestational age not shown*). The neonatal peak occurs at approximately 2 months of age. Testosterone declines to low levels during the prepubertal period. The pubertal increase in testosterone occurs at 12 to 17 years of age. Testosterone concentration in the adult reaches its maximum during the second or third decade of life and then declines slowly. Testosterone declines dramatically during senescence. *Inset A* shows the annual rhythm in testosterone concentration in the human male. The peak and nadir occur in the fall and spring, respectively. *Inset B* shows the daily rhythm in testosterone concentration. The peak and nadir occur in the morning and evening, respectively. *Inset C* shows the frequent and irregular fluctuations in testosterone concentration. (From Ewing LL, Davis JC, Zirkin BR. Regulation of testicular function: a spatial and temporal view. In: Greep RO, editor. International review of physiology. Baltimore: University Park Press; 1980. p. 41.)

shows that a testosterone peak occurs in the human fetus at 12 to 18 weeks of gestation. Another testosterone peak occurs at approximately 2 months of age. A third testosterone peak occurs during the second or third decade of life. After this, there is a plateau, and then a slow decline with age. Superimposed on this, there are annual and daily rhythms of testosterone production (see Fig. 22-9, insets A and B) and irregular daily fluctuations in testosterone (see Fig. 22-9, inset C). These temporal changes in testosterone production during human life reflect a complex interaction between the pituitary gland and testis. **The testosterone peaks correspond temporally to four developmental events: (1) the differentiation and development of the fetal reproductive tract, (2) the neonatal organization or "imprinting" of androgen-dependent target tissues, (3) the masculinization of the male at puberty, and (4) the maintenance of growth and function of androgen-dependent organs in the adult.** This topic has been reviewed thoroughly by Swerdloff and Heber (1981).

Seminiferous Tubules

The seminiferous tubules consist of germ cells and supporting cells and are a unique environment for gamete production. Support cells include Sertoli cells and fibrocyte and myoid cells of the basement membrane. The germ cells include a slowly dividing stem cell population, more rapidly proliferating spermatogonia and spermatocytes, and metamorphosing spermatids.

Sertoli Cells. The seminiferous tubules are lined with Sertoli cells that rest on the tubular basement membrane and extend cytoplasmic ramifications into its lumen (Fig. 22-10). The ultrastructural features of Sertoli cells are well described (Bardin et al, 1994). They have irregularly shaped nuclei, prominent nucleoli, and a low mitotic index and exhibit unique **tight junctional complexes** between adjacent Sertoli cells. **These tight junctions are the strongest intercellular barriers in the body. They divide the seminiferous tubule space into basal (basement membrane) and adluminal (lumen) compartments** (see Fig. 22-10). This anatomic arrangement forms the basis for the **blood-testis barrier** and allows spermatogenesis to occur in an immunologically privileged site. Sertoli cells serve as nurse cells for spermatogenesis, nourishing developing germ cells within and between Sertoli cell cytoplasmic projections. The undifferentiated spermatogonia are near the basement membrane of the tubule, whereas the more advanced spermatocytes and spermatids are near the luminal surface. Thus the Sertoli cell is a polarized epithelium in which the base approximates the plasma environment, and its apex harbors an environment unique to the seminiferous tubule (Ewing et al, 1980).

Sertoli cells nurture germ cell development by (1) providing a specialized adluminal microenvironment, (2) supporting germ cells through gap junctions between Sertoli and germ cells, and (3) allowing migration of developing germ cells within the tubule (see Fig. 22-10). The tight junctions between Sertoli cells are constantly remodeled to allow "opening" and "closing" necessary for germ cell interaction and migration (Mruk and Cheng, 2004). Ligand-receptor complexes, such as c-kit and kit ligand, are likely involved in mediating communication between germ and Sertoli cells. Sertoli cells also participate in germ cell phagocytosis and produce and secrete fluid and important effector molecules. ABP is one of earliest described Sertoli cell secretory products (Hansson and Djoseland, 1972). ABP is an intracellular carrier of androgen within the Sertoli cell. **By binding testosterone, ABP maintains high levels of androgen (50-fold higher than serum) within the seminiferous tubules.** Testosterone also plays an important role in the regulation of Sertoli cell function, including ABP production (Griswold et al, 1988). Inhibin is Sertoli cell derived and plays an important regulatory role in the negative feedback loop of FSH secretion. Inhibin B is emerging as an important endocrine marker of Sertoli cell function in the male infertility evaluation.

As keepers of the immunologic sanctuary in the testis, Sertoli cells maintain a germ cell microenvironment entirely distinct from that of plasma. As such, Sertoli cells secrete numerous other products including extracellular matrix components (lamin, collagen

type IV, and collagen type I) and proteins such as ceruloplasmin, transferrin, glycoprotein 2, plasminogen activator, somatomedin-like substances, T proteins, H-Y antigen, clusterin, cyclic proteins, growth factors, and somatomedin (Mruk and Cheng, 2004). Steroids, such as DHT, testosterone, androstenediols, 17 β -estradiol, and numerous other C21 steroids are also produced by Sertoli cells (Ewing et al, 1980; Mather et al, 1983). Although the function of many Sertoli cell and peritubular-derived substances is unclear, further research should enlighten our understanding of how Sertoli cells orchestrate and support spermatogenesis.

Germ Cells. Within the human seminiferous tubule, germ cells give rise to approximately 123×10^6 (range, 21 to 374×10^6) spermatozoa daily (Amann and Howards, 1980). This equates to the production of about 1200 sperm per heartbeat. Within the seminiferous tubule, germ cells are arranged in a highly ordered sequence from the basement membrane to the lumen. **Morphologic analysis of the various germ cells reveals at least 13 recognizable germ cell types in the human testis** (Clermont, 1963; Heller and Clermont, 1964) (Fig. 22-11). Each cell type is thought to represent a different step in the spermatogenic process. Proceeding from the least to the most differentiated, based on morphologic appearance, they have been named **dark type A spermatogonia (Ad); pale type A spermatogonia (Ap); type B spermatogonia (B); preleptotene (R), leptotene (L), zygotene (Z), and pachytene (P) primary spermatocytes; secondary spermatocytes (II); and Sa, Sb, Sc, Sd₁, and Sd₂ spermatids.** The tight junctions maintain spermatogonia and early spermatocytes within the basal compartment and all subsequent germ cells in the adluminal compartment.

Peritubular Structure

The human seminiferous tubule is surrounded by several layers of peritubular tissue (Hermo et al, 1977) (Fig. 22-12). The outer adventitial layer consists of fibrocytes. In the middle layer are myoid cells interspersed with connective tissue lamellae. The inner layer consists of a collagen matrix. In humans the peritubular myoid cells are thought to have contractile function (Toyama, 1977). Myoid cells actively secrete extracellular matrix components fibronectin and collagen type I, and produce the inner collagenous layer (Tung et al, 1984). Myoid cells may also affect Sertoli cell function and are known to associate with Sertoli cells in a precise mesenchymal-epithelial interaction. Skinner and coworkers (1988) isolated a paracrine factor produced by myoid cells, P-Mod-S (peritubular modifies Sertoli), that profoundly affects Sertoli cell synthetic and differentiation functions in vitro. Human peritubular cells have also been shown to secrete testosterone and may influence Sertoli cell activity (Cigorrage et al, 1994).

Blood-Testis Barrier

Dyes and other substances, when injected into the bloodstream of animals, will rapidly appear throughout all body tissues but fail to penetrate regions of the brain and testis. This led to the concept of the existence of a blood-testis barrier. **More appropriately termed the "blood-seminiferous tubule barrier," it has two components: an anatomic or mechanical element and functional elements.** The mechanical barrier is created, in part, by muscle-like myoid cells that surround seminiferous tubules (Dym and Fawcett, 1970; Fawcett et al, 1970). Regulation of molecular traffic also occurs at the level of capillary endothelial cells. However, the most important component of this barrier is the synaptic tight junctions between Sertoli cells that preclude the passage of large molecules and lymphocytes. These anatomic elements of the barrier are necessary but not sufficient for maintaining the immunologic "sanctuary" status within the tubule, because they are not observed in other protected areas of the reproductive tract (Tung et al, 1971; Brown et al, 1972).

Thus, although the mechanical barrier contributes to the isolation of the testis, other "functional" components must also exist to suppress the normal immune response. Several mechanisms likely work in concert to protect sperm from destruction. First, lymphocytes are excluded from anatomically vulnerable regions in the

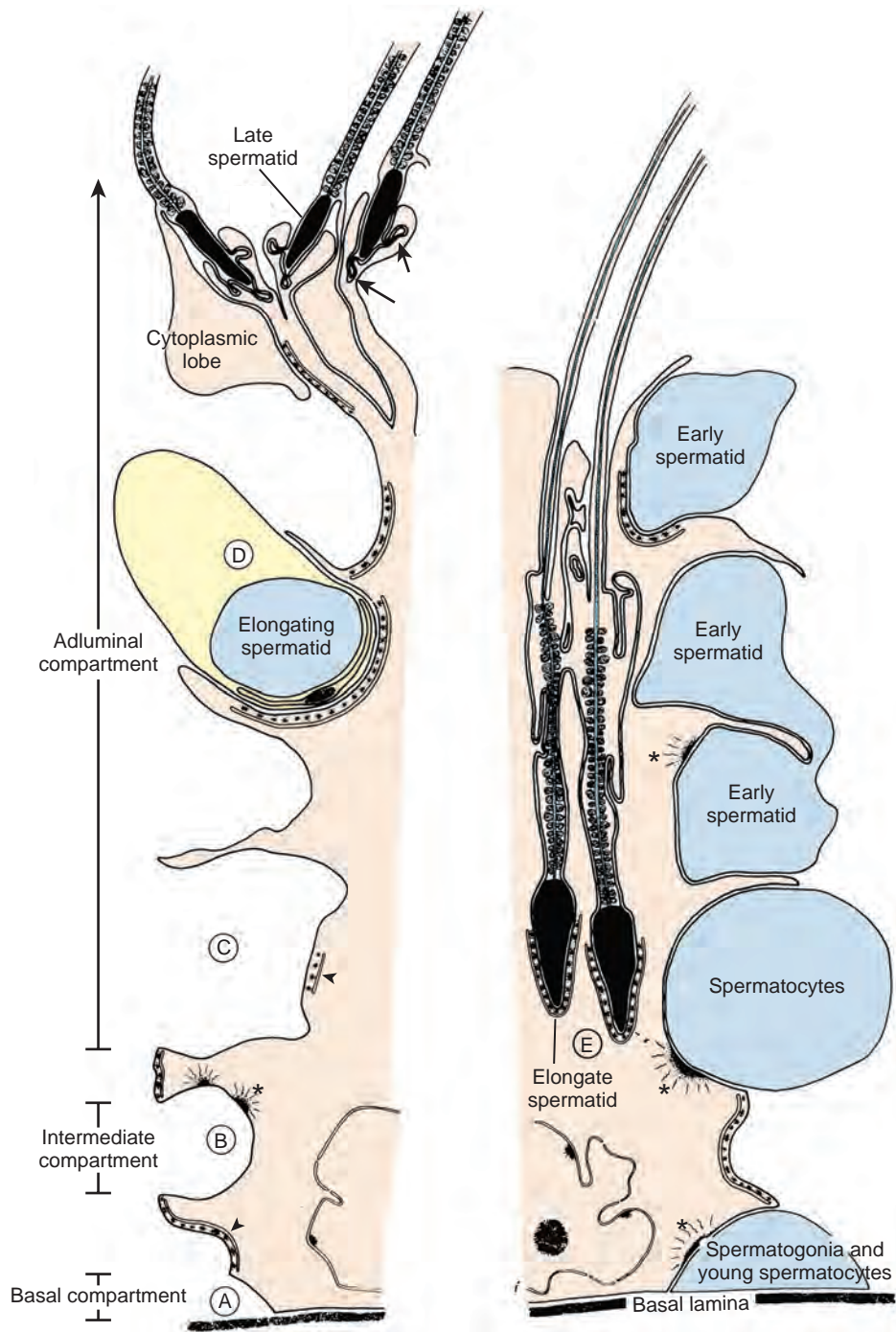


Figure 22-10. Representation of the tree-shaped Sertoli cell with a thickened central portion, or “trunk,” and more delicate processes, or “limbs.” Note the basal, intermediate, and adluminal compartments of the seminiferous epithelium. **A**, Spermatogonia and early spermatocytes share positions on the basal lamina and are enveloped by adjacent Sertoli cells that join to form tight junctional complexes (site of blood-testis barrier). **B**, Sertoli cells form junctional complexes both above and below leptotene-zygotene spermatocytes as they translocate from the basal to adluminal compartments. **C**, The spermatocytes enter the adluminal compartment when Sertoli tight junctions dissociate. **D**, The elongating spermatid is situated within a narrow recess of the Sertoli cell trunk. **E**, As the spermatid elongates further, the cell becomes lodged within the body of the Sertoli cell. The advanced spermatid moves toward the lumen of the epithelium in preparation for spermiation. Only the sperm head remains in intimate contact with the Sertoli cell. Specialized cell-to-cell contacts: *asterisks*, desmosome-gap junction complex; *arrowheads*, ectoplasmic specializations; *isolated arrows*, tubulobulbar complexes. (From Russell L. Sertoli-germ cell interactions: a review. *Gamete Res* 1980;3:179.)

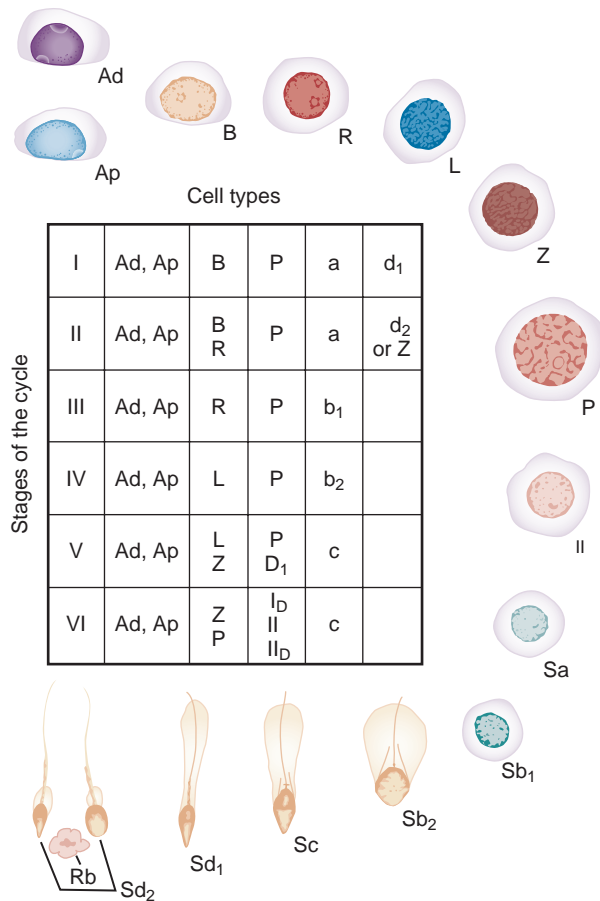


Figure 22-11. The steps of spermatogenesis in man. Ad, dark type A spermatogonium; Ap, pale type A spermatogonium; B, type B spermatogonium; II, secondary spermatocyte; L, leptotene spermatocyte; P, pachytene spermatocyte; R, resting or preleptotene primary spermatocyte; Rb, residual body; Sa(a), Sb₁(b₁), Sb₂(b₂), Sc (c), Sd₁(d₁), Sd₂(d₂), spermatids; Z, zygotene spermatocyte. The table shows cells that make up the six stages of the “cycle” of the seminiferous epithelium (I to VI): D₁, diakinesis; I_D and II_D, first and second maturation divisions of spermatocytes. (Modified from Clermont Y. Renewal of spermatogonia in man. *Am J Anat* 1966;118:509.)

germinal epithelium (Mahi-Brown et al, 1988). Second, these vulnerable regions harbor mainly T-suppressor cells (el-Demiry et al, 1985; Anderson and Hill, 1988). Owing to deficiencies in antigen–human leukocyte antigen association, there may be a lack of sperm antigen presentation to lymphocytes, impairing the immune response (Jenkins et al, 1987; Anderson and Hill, 1988). There is also evidence to suggest that immunologic tolerance plays a role in the functional blood–testis barrier. The leading theory proposes that within the anatomically weaker areas (rete testis, efferent tubule, epididymis) of the barrier, there is a small, continuous leak of sperm antigens (Tung, 1980). This leak generates T-suppressor cells and immune tolerance, similar to desensitization protocols for common environmental allergens. However, with larger antigenic challenges, a true immune response results (Turek, 1997). Cytokines may contribute to immune tolerance, including interferon- γ , soluble Fc receptor, and TGF- β (Perussia et al, 1987; Ben-Rafael and Orvieto, 1992; Turek, 1997). In addition, androgens have mild immunosuppressive activity and may regulate immunity (Diemer et al, 2003).

Why does the blood–testis barrier exist? Since it develops at spermatogenesis during puberty (Korman, 1967), it is likely important for meiosis. In addition, it may immunologically isolate developing male gametes that are not recognized as self by the adult male

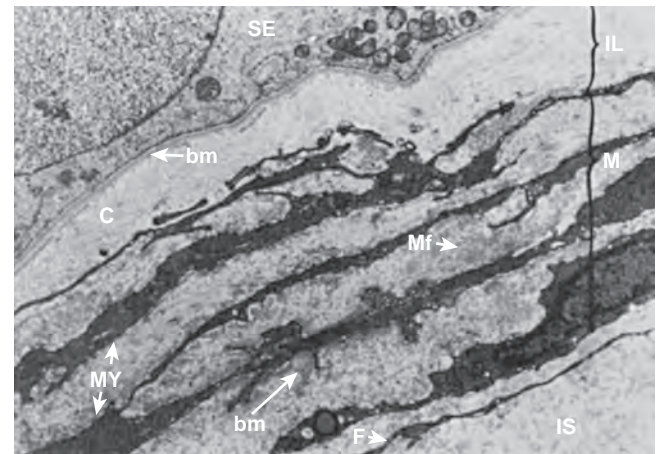


Figure 22-12. Low-power electron micrograph of human peritubular testis tissue. Peritubular tissue lies between the basement membrane (bm) of the seminiferous epithelium (SE) and the interstitial tissue (IS). Peritubular tissue has three zones: the inner lamella (IL); the myoid layer (M), containing myoid cells (MY) with abundant microfilaments (Mf); and an adventitial layer containing fibroblasts (F). (From Hermo L, Lalli M, Clermont Y. Arrangement of connective tissue elements in the walls of seminiferous tubules of man and monkey. *Am J Anat* 1977;148:433–46.)

immune system. In this sense, the value of a blood–testis barrier is fully realized after puberty, because foreign “antigens” on postmeiotic germ cells exist only after spermatogenesis. A testicular insult such as biopsy, torsion, or trauma will not induce anti-sperm antibodies if it occurs before puberty. After puberty, however, immunologic infertility is a known risk (Turek, 1997). Clinically, the blood–testis barrier may also limit chemotherapy access to cancer cells sequestered behind it and result in isolated cancer recurrence within the testis.

Spermatogenesis

Spermatogenesis is a remarkably complex and specialized process of DNA reduction and germ cell metamorphosis. Older studies have estimated that the entire process in humans requires approximately 64 days (Clermont, 1972). However, an *in vivo* kinetic study in healthy men revealed that the total time to produce an ejaculated sperm ranges from 42 to 76 days, suggesting that the duration of spermatogenesis can vary widely among individuals (Misell et al, 2006) (Fig. 22-13). Spermatogenesis involves (1) a proliferative phase as spermatogonia divide to replace their number (self-renewal) or differentiate into daughter cells that become mature gametes; (2) a meiotic phase when germ cells undergo a reduction division, resulting in haploid (half the normal DNA complement) spermatids; and (3) a spermiogenesis phase in which spermatids undergo a profound metamorphosis to become mature spermatozoa. (For excellent reviews, see Steinberger [1976] and de Kretser and Kerr [1988].)

A cycle of spermatogenesis involves the division of primitive spermatogonial stem cells into subsequent germ cells. Several cycles of spermatogenesis coexist within the germinal epithelium at any one time, and they are described morphologically as stages. If spermatogenesis is viewed from a single fixed point within a seminiferous tubule, six recognizable cellular associations or stages are predictably observed in humans (Heller and Clermont, 1964) (see Fig. 22-11). In addition, there is also a specific organization of spermatogenic cycles within the tubular space, termed *spermatogenic waves*. The best evidence suggests that human spermatogenesis exists in a spiral or helical cellular arrangement that ensures sperm production is a continuous and not a pulsatile process (Schulze, 1989) (Fig. 22-14).

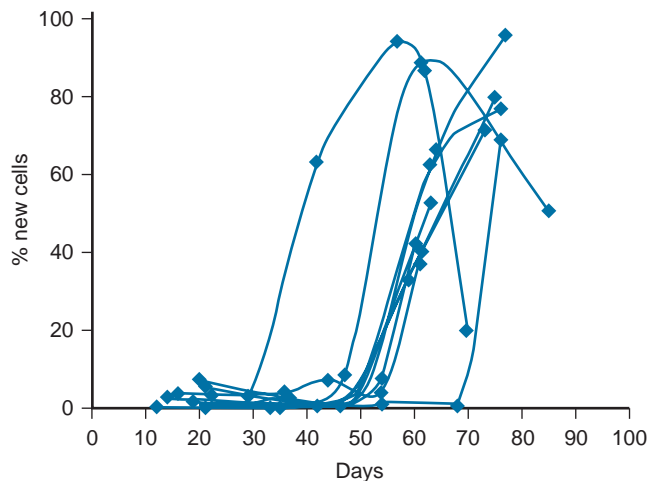


Figure 22-13. Time to make and ejaculate human sperm. Combined spermatocyte labeling curves for 11 individuals with normal semen quality who ingested 50 mL of $^2\text{H}_2\text{O}$ twice daily for 3 weeks. New ejaculated sperm was found as early as 42 days after ingestion of label, and there was considerable interindividual variation in the time to make and ejaculate sperm. (From Misell LM, Holochwost D, Boban D, et al. A stable isotope/mass spectrometric method for measuring the kinetics of human spermatogenesis in vivo. *J Urol* 2006;175:242–6.)

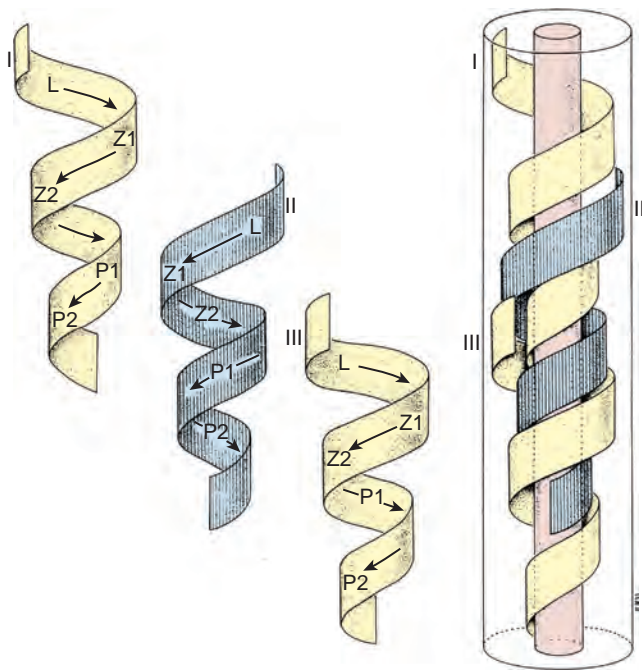


Figure 22-14. Helical configuration of seminiferous tubule epithelial cycles in man, forming overlapping waves of spermatogenesis that keep sperm production constant. (From Schulze W, Rehder U. Organization and morphogenesis of the human seminiferous epithelium. *Cell Tissue Res* 1984;237:395–407.)

Testis Stem Cell Migration, Renewal, and Proliferation

Testis Stem Cell Migration. During early prenatal development, primordial germ cells migrate to the gonadal ridge and associate with Sertoli cells to form primitive testicular cords (Witschi, 1948). These primitive germline stem cells are termed **gonocytes** after the gonad differentiates into a testis by forming seminiferous cords.

They are called **spermatogonia** after migration to the periphery of the tubule (Gondos and Hobel, 1971). It is interesting to note that these early migrating germ cells have properties very similar to embryonic stem cells and are likely the source of adult germ cell tumors (Ezeh et al, 2005).

Testis Stem Cell Renewal. Spermatogonia within the testis stem cell niche are replenished in a process termed *stem cell renewal*. The growth factor receptor kit ligand/c-kit receptor system and the niche factor glial cell line–derived neurotrophic factor (GDNF) appear to be involved in this process (Oatley and Brinster, 2008). In fact, the c-kit receptor is a marker of spermatogonial stem cells in rats (Dym, 1994), and spermatogenesis in the rat is a c-kit–dependent process, whereas spermatogonial stem cell renewal may be c-kit independent (Yoshinaga et al, 1991). Recent studies have also shown that human spermatogonial stem cells can be reprogrammed in vitro to become embryonic-like stem cells (Conrad et al, 2008; Kossack et al, 2009) (Fig. 22-15). Obtained from adult testis biopsy specimens, the embryonic-like cells express distinct markers of pluripotency (OCT-4, SOX-2, STELLAR, GDF-3), can form all three germ layers, maintain a normal karyotype, form teratomas, and express appropriate levels of epigenetic markers and telomerase (Kossack et al, 2009). This finding suggests that in the future the testis may be a source of patient-specific stem cells for cell-based therapy.

Testis Stem Cell Proliferation. In the human, pale type A (Ap) spermatogonia in the basal, stem cell niche of the seminiferous tubule divide at 16-day intervals (Clermont, 1972) to form B spermatogonia. B spermatogonia are committed to become spermatocytes, but the cytoplasm between spermatogonial daughter cells remains conjoined after mitosis, forming cytoplasmic bridges between adjacent cells. These cytoplasmic bridges are observed between germ cells of all classes throughout spermatogenesis (Ewing et al, 1980). These bridges could be important for synchronized cellular proliferation and differentiation and for regulation of gene expression.

Meiosis

Somatic cells replicate by mitosis, in which genetically identical daughter cells are formed. **Germ cells replicate by meiosis, in which the genetic material is halved to allow reproduction.** Meiosis generates genetic diversity, providing a richer source of material on which natural selection can act. Cell replication by mitosis is a precise, well-orchestrated sequence of events involving duplication of the genetic material (chromosomes), breakdown of the nuclear envelope, and equal division of the chromosomes and cytoplasm into daughter cells. **The essential difference between mitotic and meiotic replication is that a single DNA duplication step is followed by only one cell division in mitosis, but two cell divisions in meiosis (four daughter cells).** Consequently, daughter cells contain only half of the chromosome content of parent cells. Thus a diploid ($2n$) parent cell becomes a haploid (n) gamete. Other major differences between mitosis and meiosis are outlined in Table 22-2. Research has shown that small RNA molecules (small RNAs), including small interfering RNAs (siRNAs), microRNAs (miRNAs), and piwi-interacting RNAs (piRNAs), are important regulators of gene germ cell expression at the post-transcriptional or translation level (Tolia and Joshua-Tor, 2007; He et al, 2009).

Spermatogenesis begins with type B spermatogonia dividing mitotically to form primary spermatocytes within the adluminal compartment. Mature spermatocytes are the first germ cells to undergo meiosis (Kerr and de Kretser, 1981). In this process, a meiotic division is followed by a typical mitotic reduction division, resulting in daughter cells with a haploid chromosome complement. In addition, as a consequence of chromosomal recombination, each daughter cell contains different genetic information. The resultant cell is the Sa spermatid (see Fig. 22-11).

Chromosomal recombination, the defining feature of mammalian meiosis, ensures that haploid gametes differ genetically from their adult precursors and is the real engine of genetic diversity and evolution. During meiotic prophase, formation of a synaptonemal complex with pairing of homologous (maternal and

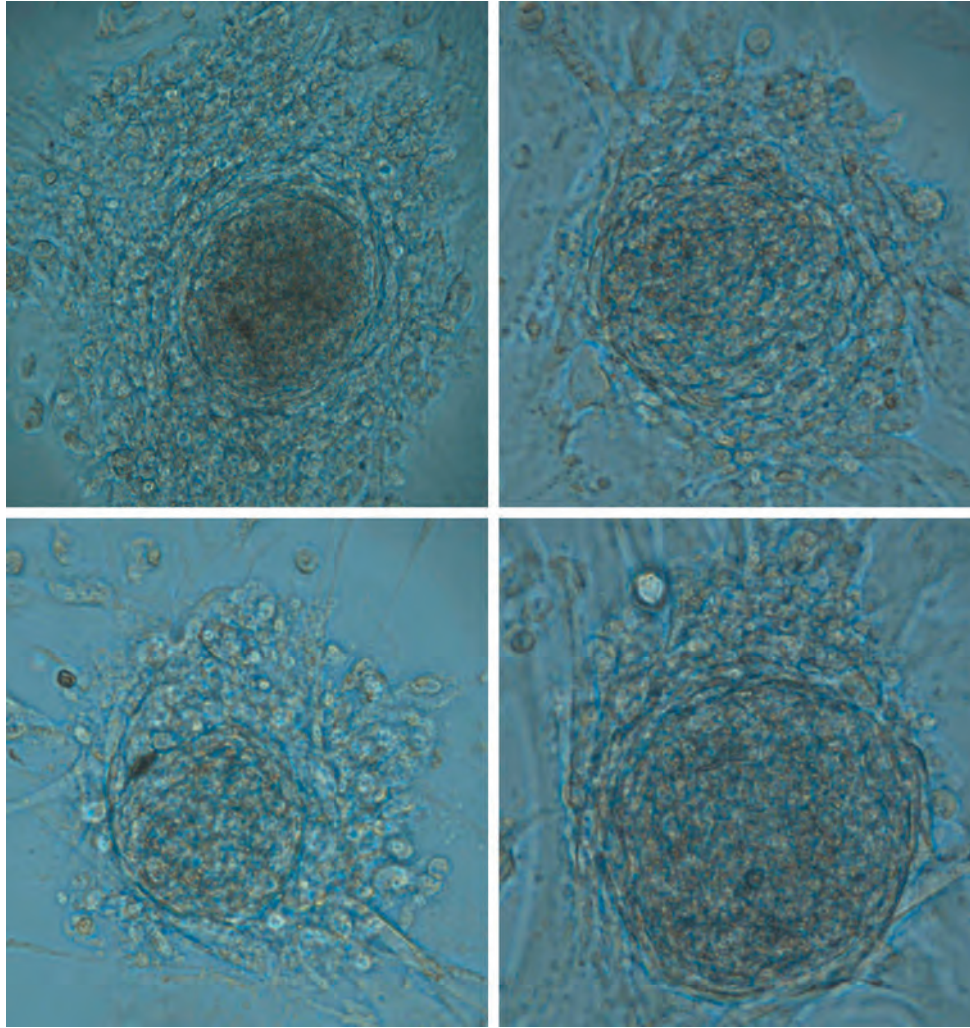


Figure 22-15. Microphotograph of four different colonies of adult testis spermatogonial-derived stem cells. Cell clusters are the result of reprogramming of adult spermatogonia in culture conditions used for human embryonic stem cells (HESCs). They exhibit the typical cobblestone appearance of HESCs and are functionally multipotent.

paternal) chromosomes occurs, along with physical interaction and exchange of DNA through reciprocal sites of crossing over (**chiasmata**) between homologs. Recent research has shown that defects in the fidelity of recombination within human male germ cells can cause azoospermia and male infertility (Walsh et al, 2009). In one study, 10% of nonobstructive azoospermic men had significant defects in recombination compared with men with normal spermatogenesis (Gonsalves et al, 2004). In addition, among men with maturation arrest pattern on testis biopsy, faulty recombination was observed in about half of cases, providing evidence that faulty recombination is linked to poor sperm production (Gonsalves et al, 2004). Variations in recombination also have implications for sperm aneuploidy, because alterations in crossover position are risk factors for chromosomal nondisjunction. Indeed, evidence suggests that the correlation of faulty recombination and sperm aneuploidy in azoospermic men is strong enough to explain the higher rate of chromosomal abnormalities in offspring conceived with in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (Sun et al, 2008).

Spermiogenesis

During spermiogenesis, round 4a spermatids mature into spermatozoa (see Fig. 22-11). During this maturation sequence, cell division does not occur, but there are extensive changes to the spermatid

TABLE 22-2 Essential Differences: Mitosis and Meiosis

MITOSIS	MEIOSIS
Occurs in somatic cells	Occurs in sexual cells
One cell division, two daughter cells	Two cell divisions, four daughter cells
Chromosome number maintained	Chromosome number halved
No pairing, chromosome homologs	Synapse of homologs, prophase I
No crossovers	More than one crossover per homolog pair
Centromeres divide, anaphase	Centromeres divide, anaphase II
Identical daughter genotype	Genetic variation in daughter cells

nucleus and cytoplasm. These include the loss of cytoplasm, migration of cytoplasmic organelles, formation of the acrosome from the Golgi apparatus, formation of the flagellum from the centriole, nuclear compaction to about 10% of former size, and reorganization of mitochondria around the sperm midpiece

(Kerr and de Kretser, 1981). The nucleus of the round spermatid changes from spheric to asymmetrical as chromatin condenses. Many cellular elements contribute to the reshaping process, including chromosome structure, associated chromosomal proteins, the perinuclear cytoskeletal theca layer, the manchette of nuclear microtubules, subacrosomal actin, and Sertoli cell interactions. With completion of spermatid elongation, the Sertoli cell cytoplasm retracts around the developing sperm, stripping it of all unnecessary cytoplasm and extruding it into the tubule lumen. The mature sperm has remarkably little cytoplasm and is produced in massive quantities—up to 300 per gram of testis per second.

Sertoli Cell–Germ Cell Interaction

A complex network of cell-cell interactions exists within the testis between Leydig cells and Sertoli cells, between Leydig cells and peritubular cells, between Sertoli and peritubular cells, and between Sertoli cells and germ cells. Several Sertoli cell–germ cell associations in mammalian testes are illustrated in Figure 22-10 (Russell and Clermont, 1976; Romrell and Ross, 1979; Skinner, 1995). In addition, there are factors that can reversibly disrupt the blood-testis barrier, including TGF- β 3 and tumor necrosis factor- α (TNF- α). These substances act by reducing the levels of occludin and zonula occludens-1 (ZO-1) in the barrier through a p38 mitogen-activated protein (MAP) kinase signaling pathway (Xia et al, 2009). This represents only a piece of the remarkably complex and highly interactive process that characterizes spermatogenesis.

Genetics

Genetic causes of abnormal spermatogenesis have been identified as point mutations in single genes inherited in mendelian fashion (e.g., cystic fibrosis), and as chromosomal disorders in which segments of (or entire) chromosomes have structural or numerical abnormalities. The reader is referred to Turek and Reijo Pera (2002) for a comprehensive review of such disorders. The postulation that deletions in the long arm of the Y chromosome cause azoospermia was made over three decades ago (Tiepolo et al, 1976). Based on cytogenetic analysis, this theoretic region was termed the *azoospermia factor* (AZF). Currently, the positional patterns of deletions (termed *microdeletions*) in the AZF region are used to subdivide this region into AZFa, AZFb, and AZFc subregions (Vogt et al, 1996). Regional deletions of the Y chromosome, termed *Yq microdeletions*, occur in 6% to 8% of severely oligospermic men and in 15% of azoospermic men (Reijo et al, 1996). Taken together, such deletions are the most commonly defined molecular cause of male infertility (Kostiner et al, 1998).

There is emerging literature addressing the prognostic value of specific AZF deletions. In sperm to partial and complete AZFc-deletion patients, in whom sperm is often found on semen analysis or testis biopsy, the chance of finding ejaculated or testis sperm in men with complete AZFa or AZFb deletions is highly unlikely (Hopps et al, 2003). Complete AZFa deletions are associated with germ cell aplasia or Sertoli cell–only histology. In general, complete AZFb deletions are associated with maturation arrest at the primary spermatocyte (early) or spermatid (late) stages. AZFc deletions are associated with hypospermatogenesis or a Sertoli cell–only pattern with foci of spermatogenesis. Sperm have been detected in ejaculates of men with presumed and confirmed partial AZFa and AZFb deletions (Foresta et al, 2001). Similarly, ejaculated sperm in men with AZFa + b, and AZFb + c deletions (presumably partial deletions) has also been reported, but the finding of AZFa – c deletions has been associated with azoospermia and no sperm on testis biopsy.

More recently, it has become clear that the X chromosome is also important for spermatogenesis, first postulated in rodent studies. In 2001, Wang and colleagues reported on a systematic search for genes expressed exclusively in mouse spermatogonia (Wang et al, 2001). Twenty-five genes were identified by complementary DNA (cDNA) subtraction, of which 10 localized to the X chromosome, suggesting that the X chromosome may have a key

role in premeiotic stages of spermatogenesis. A recent comparison of the mouse and human X chromosomes suggests that this chromosome may lead a double life and contribute significantly to both human male and female fertility (Mueller et al, 2013). Mutation studies of X-linked genes in male infertility patients have identified the SOX3 gene (sex determining region Y box 3) and the FATE gene as two potential candidate fertility genes (Olesen et al, 2003; Raverot et al, 2004). In the future, mutations in these and other X chromosome genes have the potential to define many currently unexplained cases of male infertility.

Genetics and Paternal Age

Age-Related Sperm Chromosomal Anomalies. The aneuploidy status and polyploidy status of sperm were first investigated owing to concern that advanced paternal age was associated with increased cases of trisomy, especially trisomy 21 or Down syndrome, in offspring. With fluorescence in situ hybridization (FISH) technology, subtle paternal-age effects on sperm aneuploidy are now evident. The paternal age effect appears to increase the fraction of sperm with sex chromosomal aneuploidies (Wyrobek et al, 1996). However, there is little evidence to support a paternal age–related increase in aneuploid births, except for possibly trisomy 21 and disomy 1 (very rare). Examining sperm chromosome structural abnormalities, Martin and Rademaker (1987) found that a significant linear relationship exists between paternal age and the frequency of structural anomalies in sperm ($r=0.63$). One explanation for this association may be that continued cell division during spermatogenesis places germ cells at risk for chromosomal injury, especially with advanced paternal age. Except for reciprocal translocations, however, there is little evidence to indicate that this association leads to an increased frequency of offspring with de novo structural chromosomal anomalies.

Age-Related Sperm Genetic Mutations. Single gene defects in sperm result from errors in DNA replication. To date, it has been difficult to assess the presence or absence of such defects in sperm. However, the effect of advanced paternal age on conditions in offspring associated with single-gene deletions is clear. These disorders are listed in Box 22-1 and consist of autosomal dominant diseases that have known associations with advanced paternal age. They are termed *sentinel phenotypes* because they are disorders of significant

BOX 22-1 Genetic Disorders in Offspring Associated with Advanced Paternal Age

- Achondroplasias
- Aniridia
- Apert syndrome
- Bilateral retinoblastoma
- Crouzon syndrome
- Fibrodysplasia ossificans
- Hemophilia A
- Lesch-Nyhan syndrome
- Marfan syndrome
- Neurofibromatosis
- Oculodentodigital syndrome
- Polycystic kidney disease
- Polyposis coli
- Progeria
- Treacher Collins syndrome
- Tuberous sclerosis
- Waardenburg syndrome
- Schizophrenia (postulated)
- Bipolar disorder (postulated)
- Autism (postulated)

frequency and low fitness, and stem from highly penetrant mutations. One mechanism for the development of new single-gene mutations with age implicates the characteristic and continuous process of spermatogonial cell division in spermatogenesis. By puberty, 30 cell divisions of spermatogonia have occurred, resulting in a large pool of undifferentiated cells. After puberty, 23 divisions per year occur in these cells. The simple fact that the spermatogonia of older men have undergone numerous cell divisions may make them more likely to harbor errors in DNA transcription, the source of single-gene defects. Formal risk estimates exist for the contribution of advanced paternal age to autosomal dominant mutations: In men younger than 29 years, the risk of a mutation occurring in offspring is 0.22 per 1000 births. This risk doubles (0.45 per 1000) at paternal ages 40 to 44, and then climbs to 3.7 per 1000 births at ages older than 45 (Friedman, 1981).

KEY POINTS: TESTIS

- The testis contains 250 meters of seminiferous tubules and 700 million Leydig cells in the young adult.
- Spermatogenesis occurs in stages, cycles, and waves to ensure constant sperm production.
- Genes on the X, as well as the Y, chromosome govern spermatogenesis and contribute to male infertility.
- With paternal age, there are increases in structural chromosomal abnormalities in sperm and autosomal dominant mutations leading to sentinel phenotypes in offspring.

EPIDIDYMIS

Gross Architecture

The epididymis is a comma-shaped organ located along the posterolateral surface of the testis. Passage through the epididymis induces many changes to newly formed sperm, including gains in functional motility, and alterations in surface charge, membrane proteins, immunoreactivity, phospholipids, fatty acid content, and adenylate cyclase activity. These changes improve cell membrane structural integrity, increase fertilization ability, and improve motility. Spermatozoa within the testis have very poor or no motility. They become progressively motile and functional only after traversing the epididymis. The transit time of sperm through the epididymis is thought to take 12 days in humans (Johnson and Varner, 1988).

The epididymis is a tubule or duct that is 3 to 4 meters in length and is tightly coiled and encapsulated within the sheath of connective tissue of the tunica vaginalis (Lanz and Neuhauser, 1964; Turner et al, 1978). Extensions from the sheath enter interductal spaces and form septa that divide the duct into histologically characteristic regions (Kormano and Reijonen, 1976). Anatomically, these are classically divided into three regions: caput or head, corpus or body, and cauda or tail (Fig. 22-16). The caput epididymis consists of 8 to 12 ductuli efferentes from the testis. The lumen of the ductuli efferentes is large and somewhat irregular in shape near the testis, becoming narrow and oval near the junction with the ductus epididymis. Distal to this junction, the duct diameter increases slightly and thereafter remains constant in the corpus epididymis. In the bulky cauda epididymis, the tubule diameter enlarges substantially and acquires an irregular shape. Progressing distally, the tubule gradually assumes the characteristic appearance of the vas deferens.

Vascular and Lymph Supply

In humans, the caput and the corpus epididymis receive arterial blood from a branch of the testicular artery (see Fig. 22-7). It subsequently divides into superior and inferior epididymal branches (MacMillan, 1954). The epididymis also receives blood from

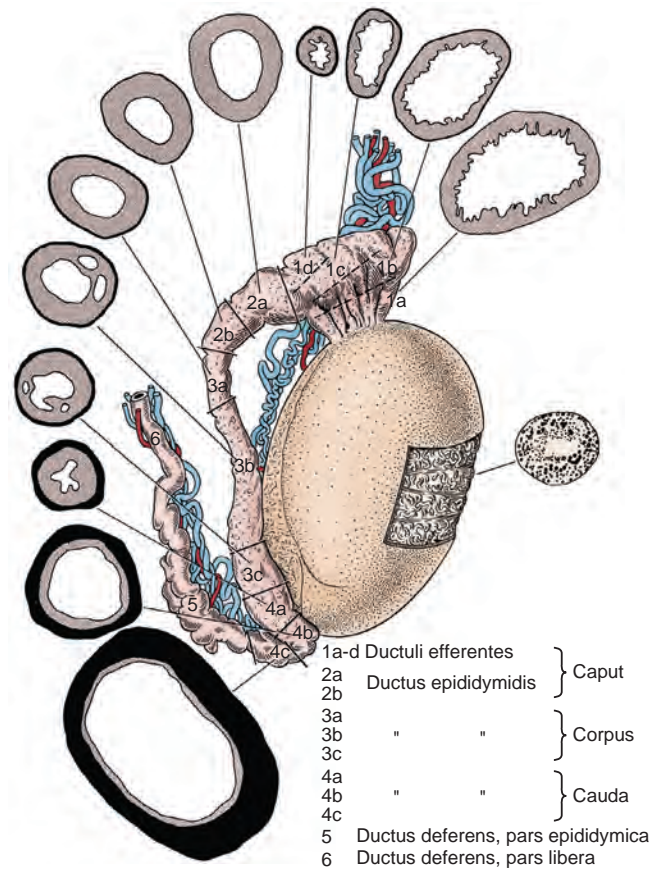


Figure 22-16. Drawing of the human epididymis showing regionalization of the ductal epithelium and muscle layer. Epididymal segment locations are shown in cross section and are identified by number. (From Baumgarten HG, Holstein AF, Rosengren E. Arrangement, ultrastructure, and adrenergic innervation of smooth musculature of the ductal efferentes, ductus epididymidis, and ductus deferens in man. *Z Zellforsch Mikrosk Anat* 1971;120:37.)

branches of the deferential arteries (artery of the vas deferens), and collateral vessels connect the deferential artery to the testicular blood supply. The cauda epididymis is supplied by branches of the deferential artery. The deferential and cremasteric arteries serve as collateral sources to the epididymis, when the main testicular artery is obstructed or ligated. The arterial branches within the epididymis enter along septa formed from the connective tissue sheath. These vessels coil extensively before transforming into the straight vessels of the microvascular bed (Kormano and Reijonen, 1976). Microvascularization density varies significantly along the length of the epididymis, with the proximal caput containing the densest subepithelial capillary network, and the more distal segments harboring less dense vascularization. From animal studies, the epididymal capillary network is under hormonal control. For example, in rabbits, bilateral hormonal castration results in progressive deterioration and eventual disappearance of the epididymal capillary network (Clavert et al, 1981). It is not clear whether vascularization in the human epididymis is similarly controlled.

According to MacMillan (1954), venous drainage from the corpus and cauda epididymis joins to form the vena marginalis epididymis of Haberer. These veins drain into the pampiniform plexus through the vena marginalis testis, or through the cremasteric or deferential veins. Lymphatic drainage of the epididymis occurs through two routes (Wenzel and Kellermann, 1966). Lymph from the caput and corpus epididymis is removed through the same route as that described for the testis. These vessels course beside the internal spermatic vein and ultimately terminate in the preaortic

nodes. Lymph vessels from the cauda epididymis join those draining the vas deferens and terminate in the external iliac nodes.

Innervation

The innervation of the human epididymis is derived primarily from the intermediate and inferior spermatic nerves that arise from the superior portion of the hypogastric plexus and pelvic plexus, respectively (Mitchell, 1935). The ductuli efferentes and the proximal segments of the epididymis are sparsely innervated by sympathetic fibers (Baumgarten and Holstein, 1967; Baumgarten et al, 1968). In these regions, the fibers are observed in a peritubular plexus and are principally associated with blood vessels. Many more fibers are observed in the midcorpus epididymis, and their density increases progressively with progression along the epididymis, coincident with the appearance and proliferation of smooth muscle cells in these areas (Baumgarten et al, 1971). The distribution of contractile cells and sympathetic nerves within the epididymis may explain the rhythmic peristaltic movements of the ductuli efferentes and initial epididymal segments, as well as the intermittent contractile activity of the cauda epididymis and the vas deferens during emission (Risely, 1963). These physiologic contractions are critical to the movement of sperm through the epididymis.

Cytoarchitecture

Epididymal Epithelium

The histology of the human epididymis has been reviewed by Holstein (1969) and Vendrely (1981). It consists of two main cell types: **principal cells** and **basal cells** (seen at low ultrastructural magnification in Figure 22-17). Principal cells vary in height along the length of the epididymis owing to the length of stereocilia (microvilli, not cilia). In general, tall stereocilia (120 μm) are found in the proximal epididymis, and smaller or shorter stereocilia (50 μm) are observed in more distal regions. The nuclei in principal cells are elongated and often possess large clefts and one or two nucleoli. Consistent with the idea that principal cells carry out both absorptive and secretive processes, their cellular apices have numerous coated pits, micropinocytotic vesicles, multivesicular bodies, irregularly shaped membranous vesicles, and an extensive Golgi apparatus. Because these cytologic features vary along the length of the epididymis, it suggests that there is varying absorptive and secretory capacity along the length of the duct (Vendrely and Dadoune, 1988).

There are far fewer basal cells than principal cells lining the epididymal epithelium, and they are dispersed among the more numerous principal cells. Tear-shaped basal cells rest on the basal lamina and extend toward the lumen, their apices forming threads between adjacent principal cells. They are thought to be derived from macrophages. Unlike the principal cells, the morphology of basal cells remains relatively constant throughout the epididymal duct. They are thought to be the precursors of principal cells.

The epithelium of the epididymis exhibits regional differences along its length. Within the epididymis proper, the epithelium is pseudostratified and consists of principal and basal cells as described earlier. Proximally, at the junction of the rete testis and ductuli efferentes, there is a distinct transition from a low to a high cuboidal epithelium. The epithelium in the ductuli efferentes consists of ciliated and nonciliated cells (Holstein, 1969). The ciliated cells conduct sperm from the efferent ducts into the epididymis. The nonciliated cells with protruding apices are likely secretory in nature and predominate in the proximal ductuli efferentes (Vendrely, 1981). Other nonciliated cells have microvilli suggestive of resorptive activity and predominate in the distal ductuli efferentes. Both nonciliated and ciliated cells are joined apically through junctional complexes. This suggests the existence of a blood-epididymis barrier analogous to the blood-testis barrier (Suzuki and Nagano, 1978; Hoffer and Hinton, 1984). Although not as dense as the blood-testis barrier, the blood-epididymis barrier extends from the caput to the cauda epididymis and may play an important role

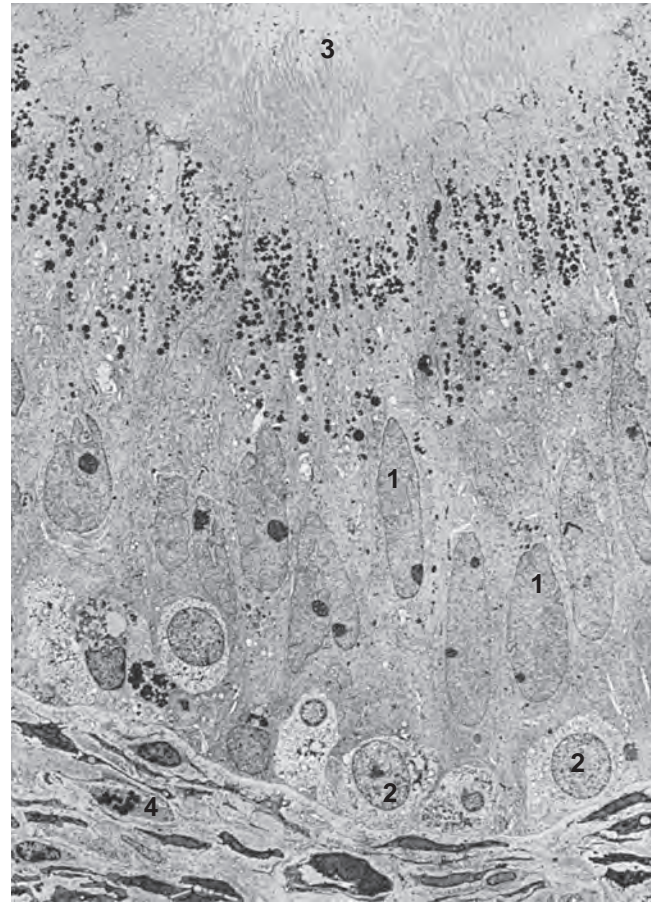


Figure 22-17. Electron micrograph of a human epididymis in cross section. Major components of the luminal epithelium are principal cells (1), basal cells (2), stereocilia (3), and myofilaments (4). Magnification approximately $\times 1800$. (From Holstein AF. In: Hafez ESE, editor. Human semen and fertility regulation in men. St. Louis: Mosby; 1976.)

in influencing the composition of fluid within different segments of the epididymal lumen (Turner, 1979).

Epididymal Contractile Tissue. Peripheral to the basal lamina of the ductuli efferentes and the epididymal tubule are various contractile cells (Baumgarten et al, 1971) (see Fig. 22-17). In the ductuli efferentes (distal regions of the caput and the proximal corpus epididymis), the contractile cells form a loose layer, two to four cells deep, around the tubule. These cells contain myofilaments and are connected by numerous nexus-like junctions. In the distal corpus epididymis, there are larger contractile cells with fewer nexus-like intracellular junctions that resemble smooth muscle cells. In the cauda epididymis, the thin contractile cells are replaced by thick smooth muscle cells that form three layers—the outer two layers oriented longitudinally and the central layer circularly. This distal contractile layer increases in thickness as it forms the vas deferens. The contractile tissue throughout the epididymis is likely involved in sperm transport.

Epididymal Function

Described variations in the anatomy and histology of the epididymal tubule from the caput to cauda regions suggest that the epididymis is actually several different functional tissues (Vendrely, 1981). It is clear that sperm transport and storage, fertilizing ability, and motility maturation are several consequences of epididymal passage. This is addressed more fully in reviews by Robaire and Hermo (1988) and Moore and Smith (1988).

Sperm Transport

Sperm transport through the human epididymis has been calculated to take from 2 to 12 days (Johnson and Varner, 1988). Sperm transit time through the caput-corpus epididymis is roughly similar to the transit time through the cauda epididymis and is more likely related to daily testicular sperm production rather than a man's age or the frequency of ejaculation (Amann, 1981; Johnson and Varner, 1988). In one study, sperm epididymal transit time averaged 2 days in men with a high daily rate of sperm production, compared with 6 days in men with low daily sperm production (Johnson and Varner, 1988). Although the frequency of sexual activity does not affect sperm transit time through the caput and corpus epididymis, "recent emissions" can reduce transit time through the cauda epididymis by 68% (Amann, 1981).

Because normal human testicular sperm are immotile as they enter the epididymis, and remain relatively immotile within the caput, mechanisms other than sperm motility must exist to transport sperm through the epididymis. Animal studies have been very revealing in this regard (Bedford, 1975; Hamilton, 1977; Courrot, 1981; Jaakkola and Talo, 1982; Jaakkola, 1983). Initially, sperm are carried into the ductuli efferentes by rete testis fluid, and fluid flow is facilitated by fluid resorption by ductal epithelial cells mediated by the estrogen receptor. Motile cilia and myoid cell contractions within the ductuli efferentes also assist with sperm movement. Within the epididymis proper, the principal mechanism responsible for sperm transport is likely the spontaneous, rhythmic contraction of the contractile cells surrounding the epididymal duct.

Sperm Storage

After migrating through the caput and corpus epididymis, sperm are retained in the cauda epididymis for varying lengths of time, depending on the frequency of sexual activity. In men 21 to 55 years of age, an average of 155 to 209 million sperm are present in each epididymis (Amann, 1981; Johnson and Varner, 1988), and approximately half are stored in the caudal region.

Spermatozoa stored in the cauda epididymis, unlike testicular sperm, are capable of progressive motility and are able to fertilize eggs. The exact amount of time that sperm can remain fertile within the epididymis is unclear, but animal studies have shown that sperm can remain viable for several weeks after vas deferens ligation (Hammond and Asdell, 1926; Young, 1929). However, it is also clear that sperm fertility measured *in vivo* diminishes when sperm are maintained in the epididymis for prolonged periods of time (Cooper and Orgebin-Crist, 1977; Cuasnicu and Bedford, 1989). In humans, sperm aging as a result of extended epididymal transit time and prolonged storage may contribute to reduced fertility (Johnson and Varner, 1988).

The exact fate of unejaculated epididymal sperm is unknown. In animals, sperm are lost through spontaneous seminal discharge, through oral self-cleaning (Martan, 1969), in urine (Lino et al, 1967), or by epididymal reabsorption (Amann and Almquist, 1961). Phagocytosis of spermatozoa by macrophages (spermio-phages) within the epididymal lumen has been observed in humans after ligation of the vas deferens (Alexander, 1972). However, whether this mechanism can remove large numbers of spermatozoa from the epididymis of unvasectomized men is unclear.

Sperm Maturation

Sperm Motility. Sperm gain an increased capacity for motility with migration through the epididymis. This is observed as both a change in the pattern of motility and as an increase in the proportion of sperm exhibiting "mature" motility patterns. Bedford and coworkers (1973) first observed that the majority of sperm from the ductuli efferentes, when placed in culture medium, are immotile or show only weak, twitching movement. Occasionally, they also observed sperm showing "immature" tail movements characterized by "thrashing" beats in wide arcs that result in little

forward progression. The proportion of sperm with this immature motility pattern increased within the initial epididymal segment. However, in the corpus region, the proportion of sperm exhibiting this motility pattern decreased. Within the corpus region, there was an increase in the fraction of sperm with a "mature" motility pattern characterized by high-frequency, low-amplitude beats that result in progressive motility (Fig. 22-18). Within the cauda epididymis, more than 50% of sperm had a mature motility pattern, with the remainder either immotile or showing the immature motility patterns described earlier. Moore and colleagues (1983) also formally demonstrated the increased capacity of human sperm to show progressive forward motility with epididymal transit. When placed in buffer *in vitro*, increasing proportions of sperm were motile as they progressed from the efferent ducts to the caput, proximal corpus, distal corpus, and cauda epididymis (Fig. 22-19).

The relative importance of overall epididymal contact time versus region-specific maturation to gains in mature sperm motility patterns is unknown. Animal studies indicate that motility maturation may, in part, be an intrinsic sperm process that occurs independent of specific epididymal interactions. For example, although hamster and rabbit sperm are in general immotile within the caput epididymis, motile sperm are found in this region (albeit developing motility far more slowly and persisting for shorter periods than in the normal system) after epididymal duct ligation within the corpus region (Orgebin-Crist, 1969; Horan and Bedford, 1972). Human studies in obstructed patients with congenital absence of the vas deferens or epididymal obstruction also frequently report poor motility in spermatozoa aspirated from the distal epididymis, and better sperm motility in the proximal epididymis (Silber, 1989; Matthews et al, 1995). When combined, these observations suggest that spermatozoa are able to develop motility based on contact time with the proximal epididymal epithelium. However, this maturation process may not be the same as that which occurs through sperm interaction with the epididymis during migration through all ductal regions.

Sperm Fertility. Testicular sperm are incapable of fertilizing eggs unless injected into them with micromanipulation (Orgebin-Crist, 1969; Bedford, 1974; Yanagimachi, 2005). In most animals, the ability of sperm to fertilize eggs is acquired gradually as the sperm pass through the distal epididymis (see Fig. 22-19). Indeed, it has

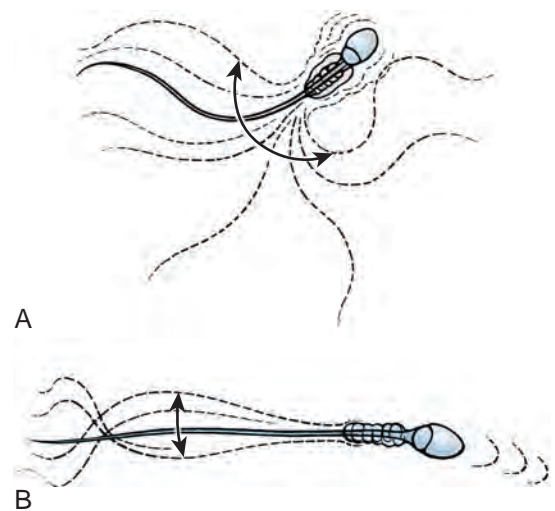


Figure 22-18. Patterns of tail movement of human epididymal sperm. **A,** The pattern shown by sperm taken from the proximal epididymis is characterized by high-amplitude, low-frequency beats producing little forward movement. **B,** In contrast, tail movement in a large proportion of sperm from the cauda epididymis is characterized by low-amplitude, rapid beats with forward progression. (From Bedford JM, Calvin HI, Cooper GW. The maturation of spermatozoa in the human epididymis. *J Reprod Fertil* 1973;18:199–213.)

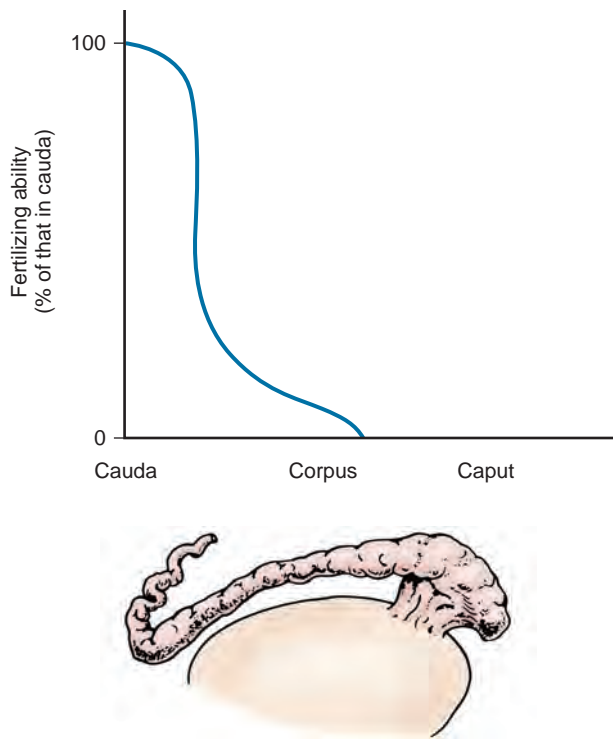


Figure 22-19. Sperm fertility maturation in the human epididymis. Sperm fertilizing ability was assessed using zona pellucida-free hamster eggs and by changes in motility. (From Bedford JM. The bearing of epididymal function in strategies for in vitro fertilization and gamete intrafallopian transfer. *Ann N Y Acad Sci* 1988;541:284–91.)

been shown in rabbits that sperm from the caput, corpus, and cauda epididymis can fertilize 1%, 63%, and 92% of rabbit eggs, respectively (Orgebin-Crist, 1969). Human in vitro experiments using zona pellucida-free hamster eggs have corroborated these findings (Moore et al, 1983). In a study that assessed the fertilizing capacity of human epididymal sperm, Hinrichsen and Blaquier (1980) demonstrated that although sperm from the proximal epididymis are able to bind to zona-free eggs, only sperm from the cauda epididymis can both bind and penetrate eggs. Thus sperm fertility maturation is, for the most part, achieved at the level of the late corpus or early cauda epididymis.

Recent clinical observations, however, challenge the idea that fertility maturation requires sperm migration through the entire epididymis. Indeed, patients with epididymal obstruction or congenital absence of the vas deferens can achieve natural pregnancies after vasoepididymostomy at the level of the ductuli efferentes (Schoysman and Bedford, 1986; Silber, 1989). This suggests that obstruction induces proximal skewing of the maturation sequence along the epididymal duct or that there may be a reduced flow of sperm through the epididymis after such bypass procedures, allowing more contact time and sperm maturation (Orgebin-Crist, 1969; Turner and Roddy, 1990). Despite this observation, it is generally believed that the likelihood of fertility is greater as the surgical anastomosis is performed more distally in the epididymis (Thomas, 1987). Additional findings from the reversal of older vasectomies (>15 years of obstruction) suggest that although post-operative ejaculated sperm concentrations are maintained after reversals with prolonged obstructive intervals, sperm motility is significantly decreased. This indicates that acquired epididymal dysfunction resulting from prolonged blockage may play an important role in the fertility potential of men after vasectomy reversal (Mui et al, 2014).

Sperm Biochemical Changes. Sperm undergo many biochemical changes with passage through the epididymis (Brooks, 1983). Epididymal sperm transit induces a net negative surface membrane

charge (Bedford et al, 1973), and sperm membrane sulfhydryl groups oxidize to disulfide bonds, improving sperm structural rigidity necessary for progressive motility and egg penetration (Bedford et al, 1973; Reyes et al, 1976). Other post-testicular modifications of sperm membranes include changes in sperm lectin-binding properties (Courtens and Fournier-Delpech, 1979; Olson and Danzo, 1981), phospholipid and lipid content (Nikolopoulou et al, 1985), glycoprotein composition (Brown et al, 1983), immunoreactivity (Tezón et al, 1985), and iodination characteristics (Olson and Danzo, 1981). Overall, these membrane modifications during epididymal passage may enhance sperm adherence to the egg zona pellucida (Orgebin-Crist and Fournier-Delpech, 1982; Blobel et al, 1990). Sperm also undergo numerous metabolic changes during epididymal transit (Dacheux and Paquignon, 1980). These include an increased capacity for glycolysis (Hoskins et al, 1975), changes in intracellular pH and calcium content, modification of adenylate cyclase activity (Casillas et al, 1980), and alterations in cellular phospholipid and phospholipid-like fatty acid content (Voglmayr, 1975).

Regulation of Epididymal Function

Sperm changes within the epididymis are likely influenced by fluids and secretions within the epididymal lumen (Robaire and Hermo, 1988; Blaquier et al, 1989). The biochemical composition of epididymal fluid differs from that of serum and also shows regional differences in osmolarity, electrolyte content, and protein composition (Robaire and Hermo, 1988). These differences are likely the consequence of variations in vascularization, blood-epididymis barrier activity, and selective absorption and secretion of substances such as glycerylphosphorylcholine (GPC), carnitine, and sialic acids along the epididymal duct. Proteins within epididymal fluid that are known to have physiologic effects on sperm in vitro include forward motility protein (Brandt et al, 1978), sperm survival factor (Morton et al, 1978), progressive motility sustaining factor (Sheth et al, 1981), sperm motility-inhibiting factor (Turner and Giles, 1982), acidic epididymal glycoprotein (Pholpramool et al, 1983), and the EP2-EP3 proteins that induce sperm binding to zona pellucida (Cuasnicu et al, 1984; Blaquier et al, 1988). Thus, variations in epididymal tubule fluid characteristics play an important role in sperm maturation during epididymal transit. It is not surprising, then, that the epididymis is a potentially important source of sperm dysfunction and male infertility.

Epididymal function is hormonally regulated. Testosterone and DHT are found in very high concentrations within the epididymis and do not show regional gradients in androgen levels (Leinonen et al, 1980). This suggests the importance of androgens for epididymal function (Brooks and Tiver, 1983). In animals, castration results not only in the loss of androgen-dependent epididymal proteins but also losses in epididymal weight, changes in luminal histology, and alterations in the synthesis and secretion of epididymal fluid GPC, carnitine, and sialic acid. Ultimately, the castrated epididymis loses the ability to sustain sperm motility, fertility maturation, and sperm storage capacities, processes that are reversed with androgen replacement.

Compared with other accessory sex glands, the epididymis requires relatively higher levels of androgen to maintain its structure and function (Prasad and Rajalakshmi, 1976). Androgen effects on the epididymis are mediated mainly through DHT, the primary androgen in epididymal tissue extracts (Pujol et al, 1976), and/or 5 α -androstane-3 α , 17 β -diol (3 α -diol) (Orgebin-Crist et al, 1975). Indeed, this is corroborated by the fact that the enzymes Δ 4-5 α -reductase (catalyzes DHT formation from testosterone) and 3 α -hydroxysteroid dehydrogenase (converts DHT to 3 α -diol), which produce testosterone metabolites, are also found in the human epididymis (Kinoshita et al, 1980; Larminat et al, 1980). It may also help to explain the recent observation that the clinical use of 5 α -reductase inhibitors is associated with impaired semen quality (Amory et al, 2007).

Epididymal function is also influenced by temperature (Foldes and Bedford, 1982; Wong et al, 1982). Chronic exposure

of the epididymis to elevated temperatures, for example by placing them within the abdomen, results in the loss of sperm storage and electrolyte transport functions. The effect of temperature on epididymal function may help explain how varicocele and cryptorchidism affect male infertility. Abnormalities in epididymal myoid cell contractility may also influence epididymal function. In the rat, partial surgical denervation of the epididymis results in an abnormal accumulation of sperm within the cauda epididymis and a decrease in the swimming speed of sperm (Billups et al, 1990). These findings have implications for infertility from neuropathic causes such as spinal cord injury and diabetes mellitus.

KEY POINTS: EPIDIDYMIS

- The epididymis consists of principal cells with absorptive and secretory function, basal cells derived from macrophages, and contractile cells that facilitate sperm transport.
- During epididymal passage, sperm mature by gaining progressive motility and the ability to bind to and penetrate the egg zona pellucida.
- Epididymal function is temperature and androgen (mainly DHT) dependent, important considerations for cryptorchidism, varicocele, and 5 α -reductase use.

DUCTUS (VAS) DEFERENS

Gross Architecture

The vas deferens is a tubular organ derived from the mesonephric (wolffian) duct. In humans, the vas deferens is 30 to 35 cm long, beginning at the cauda epididymis and terminating in the ejaculatory duct, medial to the seminal vesicle and posterior to the prostate. It is classically divided into five regions: (1) the sheathless epididymal segment contained within the tunica vaginalis, (2) the scrotal segment, (3) the inguinal segment, (4) the retroperitoneal or pelvic portion, and (5) the ampulla (Lich et al, 1978). In cross section, the vas deferens consists of an outer adventitial connective tissue sheet containing blood vessels and small nerves, a muscular coat that consists of a middle circular layer surrounded by inner and outer longitudinal muscle layers, and an inner mucosal layer with an epithelial lining (Neaves, 1975). The outer diameter of the vas deferens varies from 1.5 to 3 mm, and the lumen of the unobstructed vas deferens varies from 200 to 700 μ m in diameter (Midleton et al, 2009).

The vas deferens receives its blood supply from the deferential artery, a branch of the superior vesical artery. Venous drainage corresponds to arterial supply. The vas deferens receives innervation from both the sympathetic and the parasympathetic nervous systems (Sjostrand, 1965). The cholinergic supply does not appear important for motor activity of the vas deferens (Baumgarten et al, 1975). There is a rich supply of sympathetic adrenergic nerves derived from hypogastric nerve coursing via the presacral nerve (Batra and Lardner, 1976; McConnell et al, 1982). Adrenergic nerve fibers have been observed in all three layers of the vas muscularis, with the greatest concentration in the outer longitudinal layer (McConnell et al, 1982). The vas deferens also receives a short adrenergic nerve (Sjostrand, 1965) and has an abundance of ligand-gated, purinergic receptors in its smooth muscle membranes, suggesting sympathetic and purinergic cotransmission in sperm transport and ejaculation (Gur et al, 2007). Neurons containing other neurotransmitters, including neuropeptide Y, enkephalin, galanin, somatostatin, vasoactive intestinal polypeptide, and nitric oxide, have also been identified; however, their role in vas deferens function is unknown (Dixon et al, 1998). It is interesting to note that observations from human vas deferens specimens obtained at vasovasostomy after vasectomy show a marked reduction in the density of muscular noradrenergic and subepithelial secretomotor nerves in testicular compared with abdominal segments. These

changes may influence subsequent sperm transport processes, and hence procedural success, after vasectomy reversal (Dixon et al, 1998).

Cytoarchitecture

The human vas deferens is lined by pseudostratified epithelium (Paniagua et al, 1981). The height of the epithelium decreases along the length of the vas deferens from the testis to the seminal vesicle. In addition, the longitudinal epithelial folds are simpler near the testis and become more complex distally. The pseudostratified epithelium vasal lining is composed of basal cells and three types of tall, thin columnar cells (Hoffer, 1976; Paniagua et al, 1981). The columnar cells, extending from the epithelial base to the lumen, include principal cells, but also pencil cells and mitochondria-rich cells. All columnar cells exhibit stereocilia and irregular convoluted nuclei. Principal cells are the most frequent columnar cell type in the proximal vas deferens, whereas both pencil cells and mitochondria-rich cells increase in density distally. The thickness of the total muscle layer gradually decreases along the length of the vas deferens. This complex cytoarchitecture strongly suggests that the vas deferens is more than simply a passive conduit for sperm transport.

Vas Deferens Function

Sperm Transport

Sperm transport through the vas deferens is influenced by several physiologic processes. First, the human vas deferens exhibits spontaneous motility (Ventura et al, 1973). It also has the capacity to respond when stretched (Bruschini et al, 1977). Finally, fluid within the vas deferens can be propelled into the urethra by strong peristaltic contractions elicited either by electrical stimulation of the hypogastric nerve (Bruschini et al, 1977) or by adrenergic neurotransmitters (Bruschini et al, 1977; Lipshultz et al, 1981). This suggests that immediately before emission, with sympathetic stimulation, sperm is rapidly transported from the distal epididymis through the vas deferens to the ejaculatory duct. This rapid transport is consistent with the vas deferens having the highest muscle-to-lumen ratio (approximately 10:1) of any hollow viscus in the body.

Sperm reserves in the vas deferens have been estimated at approximately 130 million, suggesting that a significant proportion of human ejaculated sperm is stored in the vas deferens (Amann and Howards, 1980). In addition, vasal sperm quality, as assessed from fertile men at the time of vasectomy, is very similar to that of the ejaculate, with 71% motility and 91% viability (Bachtell et al, 1999). In the rabbit, it has been shown that during sexual rest, epididymal sperm are transported through the vas deferens and leak into the urethra in small amounts (Prins and Zaneveld, 1979, 1980a, 1980b). This suggests that the vas deferens is involved in ridding the epididymis of excess, stored sperm. On sexual stimulation, rabbit sperm are transported through the vas deferens similar to humans. After sexual stimulation, however, the vas deferens contents are propelled proximally toward the epididymis because the distal vas deferens contracts with greater amplitude, frequency, and duration than the proximal segment (Prins and Zaneveld, 1980a). Notably, with prolonged sexual rest, excess epididymal sperm are once again transported distally, supporting the idea that the vas deferens is important for sperm transport and for maintenance of epididymal sperm reserves.

Absorption and Secretion

Based on its cytoarchitecture, the human vas deferens likely has both absorptive and secretory functions (Hoffer, 1976; Paniagua et al, 1981). The principal cells are typical of cells that synthesize and secrete glycoproteins (Bennett et al, 1974; Gupta et al, 1974). The stereocilia, apical blebbing, and primary and secondary

lysosomes within principal cells are also characteristic of cells involved in absorptive function (Friend and Farquhar, 1967; Murakami et al, 1988). Lastly, spermophagy by epithelial cells in the ampullary vas deferens has been observed with scanning electron microscopy in both men and monkeys (Murakami et al, 1988). It is important to note that normal vas deferens function is likely to be androgen dependent because the vas deferens actively converts testosterone to DHT (Dupuy et al, 1979). Castration causes atrophy of—and testosterone treatment, restoration of—monkey vas cytoarchitecture (Dinakar et al, 1977), and spontaneous and α - and β -adrenergic-stimulated contractions of the rat vas deferens are altered by castration (Borda et al, 1981). Thus, although once thought to be a simple muscular conduit for sperm, the vas deferens is now viewed as a complex reproductive organ.

SEMINAL VESICLE AND EJACULATORY DUCTS

Gross Architecture and Cytoarchitecture

Seminal Vesicle

In the adult, the seminal vesicles are paired, elongated, hollow viscous organs located posterior to the prostate and bladder. Each seminal vesicle is 5 to 7 cm long and up to 1.5 cm wide. Each seminal vesicle actually consists of a tubule that is 15 cm long and highly coiled and convoluted. The tubule itself is composed of three layers: The inner lining is a moist and folded mucous membrane; the middle layer is largely collagenous; and the outer layer consists of circular and longitudinal muscle layers that constitute 80% of the wall thickness (Nguyen et al, 1996). The mucosa of the seminal vesicle, mainly nonciliated, pseudostratified columnar or cuboidal cells, is notable for many thin, complicated folds that produce numerous crypts. The excretory duct of the seminal vesicle opens into the ampullary vas deferens as it enters the prostate gland.

The blood supply to the seminal vesicle arises from the internal iliac artery and inferior vesicular artery through the prostatovesicular branch (Clegg, 1955). The prostatovesicular artery can also arise from the superior vesicular artery or from the pudendal artery. Most commonly, the prostatovesicular artery has anterior and posterior branches that supply the respective surfaces of the seminal vesicle. The lymphatic drainage of the seminal vesicle is through the internal iliac lymph nodes. The seminal vesicles are innervated through sympathetic nerves from the superior lumbar and hypogastric nerves. Parasympathetic innervation occurs through the pelvic plexus.

Ejaculatory Ducts

The ejaculatory ducts are paired, collagenous, tubular structures that commence at the junction of the vas deferens and seminal vesicle, course through the prostate, and empty into the prostatic urethra at the verumontanum. Histologically, the ejaculatory ducts are a continuation of the seminal vesicle, except that the outer circular muscle layer does not extend into the ducts (Nguyen et al, 1996). There are three distinct anatomic regions to the ejaculatory duct: the proximal, extraprostatic portion; the middle intraprostatic segment; and a short distal segment incorporating the lateral aspect of the verumontanum in the urethra (Nguyen et al, 1996) (Fig. 22-20). Although the ejaculatory duct contains an outer muscular layer in its extraprostatic and intraprostatic segments, as the duct courses distally the outer muscular layer dissipates, and there is no valvelike, muscular “sphincter” at the ejaculatory duct orifice, as was once thought (Nguyen et al, 1996) (Fig. 22-21). Instead, urinary reflux is prevented and ejaculatory continence is maintained by the acute angle of duct insertion into the urethra. The inner epithelial layer of the ejaculatory ducts is also complex and folded and consists of simple and pseudostratified columnar cells. The ejaculatory ducts receive their blood supply from branches of the inferior vesical artery and are innervated through the pelvic plexus.

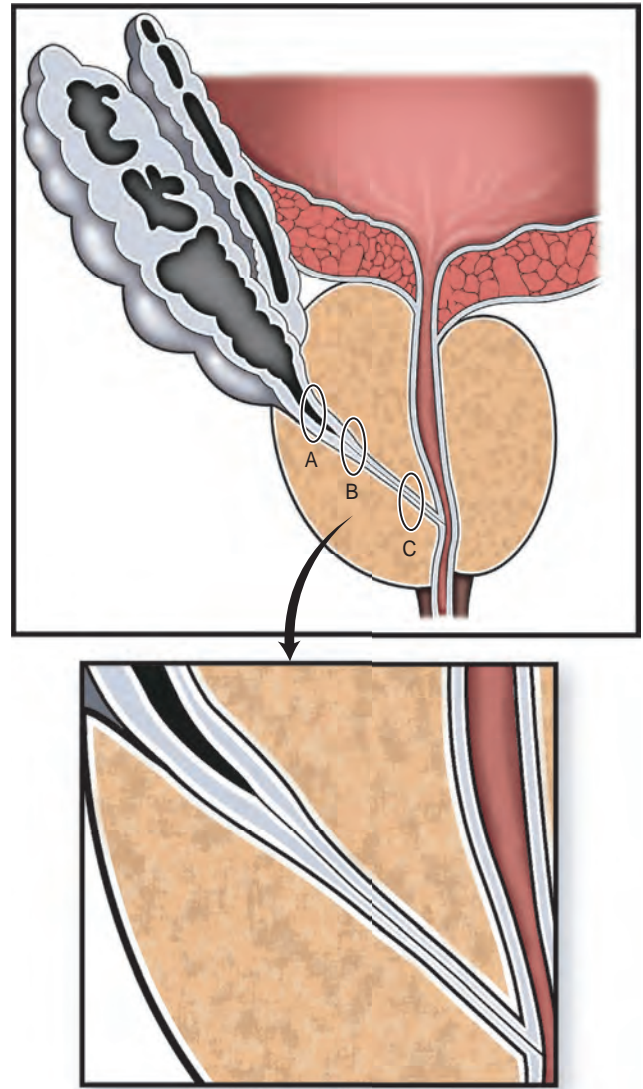


Figure 22-20. Schematic anatomy of the human ejaculatory duct complex. *A*, Proximal; *B*, intraprostatic or middle; and *C*, distal ejaculatory duct regions. The inset shows how the muscle layer thins out in the middle segment. (From Nguyen HT, Etzell J, Turek PJ, et al. Normal human ejaculatory duct anatomy: a study of cadaveric and surgical specimens. *J Urol* 1996;155:1639-42.)

Seminal Vesicle and Ejaculatory Duct–Unit Function

Animal studies suggest that the seminal vesicle and ejaculatory ducts are functionally similar to the bladder and urethra (Turek et al, 1998). The seminal vesicle is a contractile, compliant, smooth muscular organ with dynamic properties analogous to those of the bladder, and the ejaculatory ducts serve as a urethra-like conduit. This theory allows the classification of ejaculatory duct obstruction into two types of disorders, analogous to bladder outlet obstruction: (1) obstruction resulting from physical blockage of the ducts, similar to bladder outlet obstruction, and (2) “functional” obstruction of the seminal vesicle, similar to voiding dysfunction caused by bladder myopathy. In addition, this has implications for the diagnosis of ejaculatory duct disorders because “static” anatomic imaging, such as transrectal ultrasonography, may not be sufficient to differentiate between these disorders, and medications and conditions (such as diabetes) might predispose the system to seminal vesicle dysfunction (Smith et al, 2008).

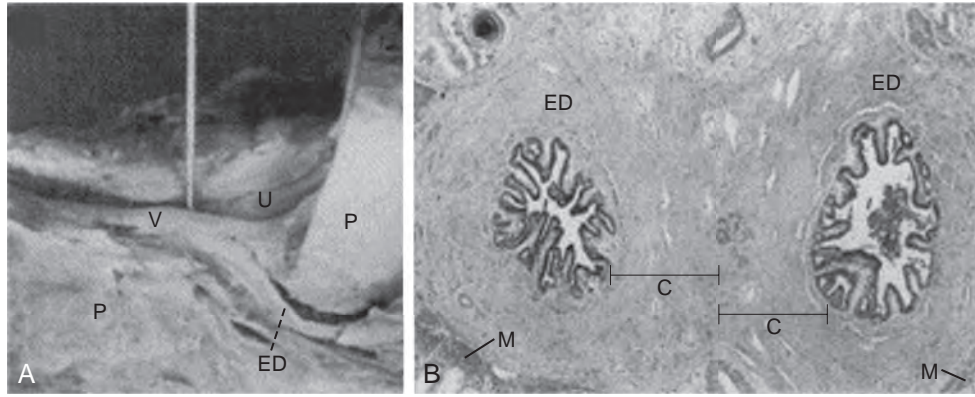


Figure 22-21. Human ejaculatory duct gross and microscopic anatomy from cadaver specimens. A, Sagittal section through the midline with pin in ejaculatory duct orifice and ejaculatory duct (ED) and veru (V), urethra (U), and prostate (P) visible. B, Microphotograph of the paired ejaculatory ducts in the middle intraprostatic segment showing the thick collagenous layer (C) surrounding the mucosa with a thin, outer muscular layer (M). (From Nguyen HT, Etzell J, Turek PJ, et al. Normal human ejaculatory duct anatomy: a study of cadaveric and surgical specimens. *J Urol* 1996;155:1639–42.)

Seminal Vesicle Function

The seminal vesicles secrete a significant proportion (80%) of the seminal fluid, and these secretions are found in later fractions of the ejaculate, after the sperm-rich epididymal and prostatic secretions. After ejaculation, sperm pass into and through the female cervical mucus and subsequently the uterus to enter the oviduct, where fertilization occurs. During residence in the female reproductive tract, sperm must undergo capacitation before oocyte fertilization. During capacitation, the acrosome reaction and development of hyperactivated motility occurs (Yanagimachi, 1994). It is not clear if prostatic or seminal vesicle secretions contribute to capacitation.

In fact, the exact physiologic role of seminal vesicle fluid is not clear, although in rodents it functions as a plug or barrier that reduces the chances for sperm from a subsequent male to fertilize the oocyte. Before ejaculation, semen is a liquid, and after all components mix with the seminal vesicle secretions, it coagulates. The major component of the coagulum is semenogelin I, a 52-kD protein expressed exclusively in the seminal vesicles (Robert et al, 1999). Through coagulating semen, seminal vesicle secretions may promote sperm motility, increase stability of sperm chromatin, and suppress immune activity in the female reproductive tract. The best-elucidated function of human semen appears to be its ability to provide antioxidative protection to sperm. Semen is rich in antioxidant enzymes, including glutathione peroxidase, superoxide dismutase, and catalase (Yeung et al, 1998). In addition, the antioxidant molecules taurine, hypotaurine, and tyrosine are present in high concentrations (van Overveld et al, 2000). Lipofuscin granules from dead epithelial cells give seminal vesicle secretions a yellow-white color. In addition, seminal vesicle secretions are alkaline and contain fructose, mucus, vitamin C, flavins, phosphoryl choline, and prostaglandins. High fructose levels provide nutrient energy for the sperm when studied in vitro. The mixing of seminal vesicle with prostatic secretions results in human semen having a mildly alkaline pH. Acidic ejaculate (pH <7.2) is associated with blockage or absence of seminal vesicles (Turek, 2005).

SPERMATOZOA

Anatomy and Physiology

The human spermatozoon is approximately 60 μm in length and is divided into three morphologic sections: head, neck, and tail (Fig. 22-22). The oval sperm head, about 4.5 μm long and 3 μm wide, contains a nucleus with highly compacted chromatin and an

KEY POINTS: VAS DEFERENS, SEMINAL VESICLE, AND EJACULATORY DUCTS

- The vas deferens is of wolffian (mesonephric) duct origin and serves to transport sperm from the cauda epididymis to the ejaculatory duct during seminal emission.
- The seminal vesicle and ejaculatory duct unit is analogous to the bladder and urethra and is subject to both physical blockage and functional disorders that result in infertility.

acrosome, a membrane-bound organelle that harbors enzymes required for penetration of the outer vestments of the egg before fertilization (Yanagimachi, 1978). The **sperm neck** maintains the connection between the sperm head and tail. It consists of the **connecting piece** and **proximal centriole**. The **axonemal complex** extends from the proximal centriole through the sperm tail. The **tail** harbors the **midpiece**, **principal piece**, and **endpiece** (Zamboni, 1992). The midpiece is 7 to 8 μm long and is the most proximal segment of the tail, terminating in the annulus. It contains the **axoneme**, with its characteristic microtubule arrangement, and surrounding **outer dense fibers** (Fig. 22-23). It also contains the **mitochondrial sheath**, which is helically arranged around the outer dense fibers. The outer dense fibers, rich in disulfide bonds, are not contractile proteins but are thought to provide the sperm tail with the elastic rigidity necessary for progressive motility (Okamoto and Clermont, 1990). Similar in structure to the midpiece, the principal piece has several columns of outer dense fibers that are replaced by the fibrous sheath. The fibrous sheath consists of **longitudinal columns** and **transverse ribs**. The sperm terminates in the endpiece, the most distal segment of the sperm tail, and contains axonemal structures and the fibrous sheath. Except for the endpiece region, the sperm is enveloped by a highly specialized plasma membrane that regulates the transmembrane movement of ions and other molecules (Friend, 1989).

The spermatozoon is a remarkably complex metabolic and genetic machine. The 75 sperm mitochondria that surround the axoneme contain enzymes required for oxidative metabolism and produce adenosine triphosphate (ATP), the primary energy molecule for the cell. Mitochondria are organelles that produce cellular energy and can also cause apoptotic cell death through the release of cytochrome *c*. Mitochondria are composed of outer and inner membranes. The inner membrane forms deep folds into the matrix, called the **cristae**, which make the surface area of the inner

membrane larger than that of the outer membrane. Five distinct respiratory chain complexes span the width of the inner membrane and are necessary for oxidative phosphorylation: nicotinamide adenosine diphosphate (NADPH) dehydrogenase, succinate dehydrogenase, cytochrome *bc1*, cytochrome *c* oxidase, and ATP synthase complexes. Contained within the matrix are citric acid cycle, fatty acid, and amino acid oxidative enzymes; newly made ATP; mitochondrial DNA (mtDNA); and ribosomes.

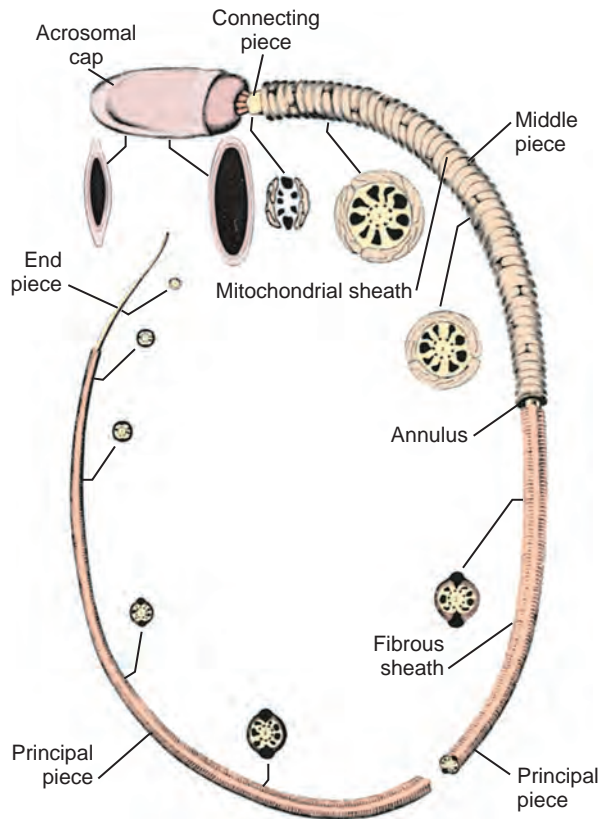


Figure 22-22. Diagram of a typical mammalian spermatozoon. The plasma membrane is omitted to illustrate the major cellular components. Cross-sectional insets show the orientation of the internal cell structures. (From Fawcett DW. The mammalian spermatozoon. *Dev Biol* 1975;44:394–436.)

Human mitochondria contain DNA (mtDNA) that is distinct from sperm nuclear DNA. mtDNA consists of a circular, histone-free chromosome of 16,569 base pairs of DNA arranged in a single heavy and single light strand and **encodes respiratory-chain-complex subunit proteins, mitochondrial rRNAs, and tRNAs used for protein synthesis.** These genes have no introns. mtDNA is also far more susceptible to mutations than is nuclear DNA (estimated 40 to 100 times higher). Reasons for this may include the fact that mitochondria are near respiratory-chain complexes and may be easily attacked by reactive oxygen species. **In addition, mtDNA is not coated with protective histones, and mitochondria have very limited DNA repair mechanisms (Hirata et al, 2002).** The fact that mitochondria rapidly accumulate mutations suggests the necessity of degrading all paternal mtDNA in the fertilized egg. This degradation is likely mediated by the small proteolytic polypeptide ubiquitin, which regulates proteolysis in many tissues (Sutovsky et al, 1999).

From animal studies, it is clear that the plasma membrane covering the sperm-head region harbors specialized proteins that participate in sperm-egg interaction (Saling, 1989). Indeed, carbohydrate-binding proteins on the sperm membrane interact with the species-specific ZP3 protein in the egg zona pellucida, resulting first in sperm binding to the zona and subsequently to induction of the acrosome reaction (Shabanowitz, 1990). Another sperm membrane protein, PH30, is present on testicular sperm, is modified during sperm migration through the epididymis, and functions as a fusion protein between the sperm and egg membranes at fertilization (Primakoff et al, 1987; Blobel et al, 1990).

Physiologically, the axoneme is the true motor assembly and requires 200 to 300 proteins for proper function. Among these, the “9 + 2” pattern of outer and inner doublets of microtubules is the best-understood component (see Fig. 22-23). The dynein proteins extend from one microtubule doublet to the adjacent doublet and form both the inner and outer arms of the axoneme. **The sperm axoneme contains the enzymes and structural proteins necessary for the chemical transduction of ATP into mechanical movement and motility.** Dynein is a large (2000 kD), Mg^{2+} -stimulated ATPase responsible for ATP-generated microtubule sliding that causes axonemal bending and, ultimately, sperm flagellar movement. The dynein structure has two or three globular, outer (heavy) chain heads (500 kD) joined to a common stem. The heads control movement along the microtubules. The inner (light) chain arms (14 to 120 kD) are the primary effectors of movement and are associated with the radial spokes of the dynein assembly. Sperm with outer arm mutants have reduced motility, and those with inner arm mutants have no motility. Radial links or spokes connect a microtubule of each doublet to the central inner doublet and consist of

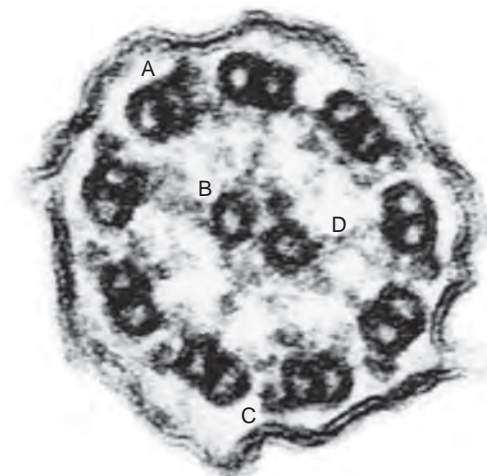
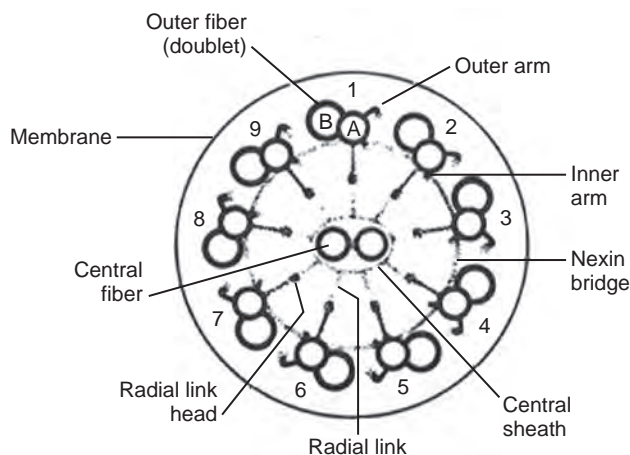


Figure 22-23. The “9 + 2” sperm axonemal structure. **Left,** Schematic cross section of axoneme, demonstrating microtubule arrangement. **Right,** Electron micrograph of axoneme. A, outer doublet; B, inner central doublet; C, outer dynein arm; D, radial link.

a complex of proteins. The central inner doublet is surrounded by a ringlike helical sheath to which the radial links from the outer doublets are attached. Tektins are proteins associated with the outer microtubular doublets, and nexin links are proteins that connect the outer doublets to one another and maintain the cylindric axonemal shape.

The phenotype of defective sperm structure has been recognized as ciliary dyskinesia. Although infertility is the rule with ciliary dyskinesias, ejaculated sperm can be motile and sperm concentrations can be normal. With ICSI, clinical pregnancies and live births have been reported after use of affected sperm (Cayan et al, 2001). Because the inheritance is usually recessive, normal offspring are likely. In general, patients suspected of harboring sperm structural defects exhibit severely compromised sperm motility (<10%). Sperm electron microscopy can reveal ultrastructural or functional sperm abnormalities. Sperm structural abnormalities are currently categorized by Chemes (2000) as follows:

1. **Nonspecific flagellar anomalies.** This is the most frequent flagellar anomaly underlying severely low motility and shows a structural phenotype of random, heterogeneous, microtubular alterations. These anomalies can arise from correctable disorders such as varicocele, reactive oxygen species, and gonadotoxin exposure. There is no evidence of familial occurrence.
2. **Dysplasia of the fibrous sheath.** This condition is a systematic sperm abnormality, usually associated with near-complete or total immotility. It has a more homogenous and distinctive phenotype characterized by sperm fibrous sheath, axonemal, and periaxonemal distortions. A subset of these patients exhibit the classic ciliary dyskinesia (formerly *immotile cilia syndrome*), in which sperm immotility is associated with respiratory disease and dextrocardia. There is a strong familial incidence, suggesting that such conditions are genetic in origin.

KEY POINTS: SPERM

- Sperm are ciliated cells that possess a “9 + 2” axonemal structure that allows motility.
- It is estimated that 200 to 300 genes regulate sperm motility.
- Sperm motility defects, termed *ciliary dyskinesias*, are common and can be either correctable (nonspecific flagellar anomalies) or genetic (dysplasia of the fibrous sheath).
- Human sperm mtDNA is a circular, histone- and intron-free DNA ring that encodes for respiratory-chain-complex proteins and is very susceptible to mutations.

SUMMARY

Spermatogenesis is a remarkably intricate and complex process that is driven by precisely regulated secretions of GnRH, LH, and FSH from the HPG axis. Perturbations in this hormonal milieu are common causes of male infertility. Sperm production in the testis functions optimally at 2°C to 4°C below body temperature and

generates a mature human sperm in 64 days. Well-integrated cycles and waves of spermatogenesis ensure that human sperm production is constant at about 1200 sperm per second. Spermatogenesis is an androgen-dependent process that occurs with very high intratesticular testosterone levels. The product of spermatogenesis, the spermatozoa, leave the testis as immotile cells with limited capacity to fertilize oocytes. After epididymal transit, sperm are typically motile and capable of fertilization. During ejaculation, sperm are rapidly transported through the ejaculatory ducts into the urethra from the distal epididymis. The ejaculate itself supports sperm metabolism and motility, serves as an antioxidant, and serves as a barrier to exclude subsequent gamete deposits from gaining access to the egg.

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**ANDROGEN DEFICIENCY:
AN EVIDENCE-BASED APPROACH****Introduction**

Testosterone is an essential male hormone. In utero, it serves a paramount role in the proper development of male genital organs. At puberty, it is important for the initiation of spermatogenesis and secondary sexual characteristics. During adulthood, testosterone continues to serve as a predominant circulating androgen, and the male hormonal reproductive axis is a finely controlled system with exquisite control of its biologic effects.

Lessons from androgen deprivation therapy (ADT) for prostate cancer have shown the detrimental effects of androgen deficiency (AD) on overall male health. AD has been associated with mortality in men and a significant decrease in quality of life, from sexual dysfunction to metabolic and musculoskeletal complications (Basaria, 2008). With an aging population, AD in the aging male, known as late-onset hypogonadism (LOH), has become a topic of increasing interest throughout the world.

Gonadal function decline has been recognized as part of normal male aging. It is estimated that testosterone levels in men older than 40 years decrease at a rate of 1% to 2% per year (Bremner et al, 1983). However, unlike female menopause, which is a universal process associated with aging, the exact rate of decline and presenting symptoms are highly variable in men. At the same time, biochemical measurements among assays also produce non-uniform reference ranges because of assay sensitivity variation, making diagnosis difficult (Lazarou et al, 2006).

Heightened awareness of AD has led to the development of many treatment options for LOH. Literature is limited regarding the long-term outcomes of LOH. Despite the wide recognition and adaptation to intervention, debate is ongoing regarding the benefit, and, most importantly, the risks associated with treatment (Connors and Morgentaler, 2013). Although more appears to be known about the aging female, men's health is a rapidly evolving field, and most physicians are actively engaged in bridging the significant knowledge and skill gaps in caring for the aging male population.

Definition

The International Society for the Study of the Aging Male has defined AD syndrome as "a biochemical syndrome associated with advancing age and characterized by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgen. It may result in significant alterations in the quality of life and adversely affects the function of multiple organ systems" (Morales and Lunenfeld, 2002). Precise definition of LOH has yet to be established in the literature, despite the fact that Professor Brown-Sequard

first reported it in the nineteenth century (Brinkmann, 2011). Without novel diagnostic markers, neither biochemical nor clinical parameters alone are sufficient for identifying affected individuals.

Epidemiology

According to data from the Organization for Economic Cooperation and Development and Centers for Disease Control and Prevention, U.S. life expectancy was 78.7 years in 2011 (76 for U.S. men and 81 for U.S. women). This represents a 9-year increase from the 1960s, and this increase is consistent with other observed trends in industrialized countries and signifies trends in the aging population around the world. Diseases associated with aging are now integral to the future of medicine, with AD playing an important role in men's health. The true prevalence of AD in the adult male is unknown because of differing definitions in the literature.

The Hypogonadism in Males study was a cohort analysis: Morning serum testosterone levels were obtained from men age 45 years and older who were visiting primary care practices in the United States (Mulligan et al, 2006). Using 300 ng/dL as a threshold for biochemical AD, the overall prevalence was 38.7%. A total of 52.4% of obese and 50% of diabetic men's testosterone values were found to be below the AD threshold. Even though AD symptoms were assessed, only the biochemical definition of AD was used in the study.

Studies that incorporated symptoms along with biochemical testing include Massachusetts Male Aging Study (MMAS) and the European Male Aging Study (EMAS). MMAS was a longitudinal cohort study: Men aged 40 to 70 years with three or more AD signs or symptoms were included (Araujo et al, 2004). Using a cut-off of total testosterone less than 200 ng/dL, the prevalence of AD was 6% and 12.3% at an approximate follow-up of 8.8 years. Researchers reported a crude incidence rate of 12.3 per 1000 person-years, or approximately 481,000 cases of AD in U.S. men aged 40 to 69 years.

In EMAS, the observed prevalence for AD was 2.1% in men aged 40 to 79 years (Wu et al, 2010). Men were categorized as having AD if their serum testosterone was below the threshold of less than 11 nmol/L (approximately 320 ng/dL) and three sexual symptoms were present (erectile dysfunction, decreased libido, and decreased frequency of morning erection). Without accounting for hypogonadal symptoms, the biochemical AD prevalence was 17% in the cohort.

The prevalence of AD associated with systemic disease is higher than for the normal aging process and is well documented (Box 23-1). Since the 1970s, AD has been described in acute illness associated with surgery, stroke, traumatic brain injury, myocardial infarction, respiratory illness, and burns (Kalyani et al, 2007). As many as 90% of men with a total of 15% or more body burns have

BOX 23-1 Systemic Illnesses Associated with Androgen Deficiency

Burn injury
 Traumatic brain injury
 Respiratory illness
 Surgical stress
 Chronic opioid exposure
 Chronic liver disease
 Human immunodeficiency virus
 Diabetes
 Stroke
 Myocardial infarction
 Sepsis
 Cancer
 Chronic renal failure
 Rheumatoid arthritis
 Chronic obstructive pulmonary disease
 Obesity

From Kalyani RR, Gavini S, Dobs AS. Male hypogonadism in systemic disease. *Endocrinol Metab Clin North Am* 2007;36:333–48.

been found to be AD (Vogel et al, 1985). Both free and total testosterone values decline rapidly 24 hours after injury and reach a nadir on average at day 11 (Lephart et al, 1987). Mean testosterone level among intensive-care patients has also been suggested to be a predictor for mortality: Surviving patients were shown to have significantly higher testosterone levels than nonsurvivors (Luppa et al, 1991).

Before highly active antiretroviral therapy (HAART), the prevalence of AD ranged from 30% to 50% in men suffering from acquired immunodeficiency syndrome (AIDS)–wasting (Crum et al, 2005). Currently, it still occurs in 20% to 25% of human immunodeficiency virus (HIV)–infected men undergoing HAART. Using a threshold of testosterone concentrations less than 300 ng/dL, AD is associated with AIDS-wasting syndrome and a decline in quality of life.

AD from chronic opioid exposure was first described in 1976 (Cicero et al, 1976). Testosterone levels can reach castration levels (reduced by >85% when compared to controls) within 24 hours after administration of a single opioid (Aloisi et al, 2005). Unlike other opiate-induced side effects, AD persists throughout treatment. In addition to its influence on sexual function, other physiologic changes such as fatigue, muscle wasting, osteoporosis, and changes in pain were also observed (Aloisi et al, 2009).

Testicular dysfunction is present in pretreatment and post-treatment oncologic patients. Approximately one third of patients with Hodgkin disease exhibit oligospermia and up to 70% of men experience abnormal semen parameters (Shekarritz et al, 1995). In testicular cancer, more than 50% of men have oligospermia before treatment (Meirow and Schenker, 1995). Although the exact mechanism of testicular dysfunction is unclear, both central and direct effects on the testis have been suggested (Kalyani et al, 2007).

About two thirds of men undergoing hemodialysis for end-stage renal disease (ESRD) show testosterone values in the AD range (Johansen, 2004). In nondialyzed men with chronic kidney disease, AD was associated with endothelial dysfunction and cardiovascular (CV) events (Yilmaz et al, 2011). In a cohort study of ESRD men, AD is independently associated with inflammation, CV comorbidity, and mortality (Carrero et al, 2011). Renal transplantation appears to reverse the hormonal abnormalities associated with ESRD (Prem et al, 1996). Further long-term study on the efficacy and safety of testosterone therapy (TT) in men with renal dysfunction is still warranted.

Physiology**Transport and Metabolism of Testosterone**

After testosterone is excreted into circulation, the majority of testosterone is bound to plasma proteins. The primary androgen-binding proteins are sex hormone binding globulin (SHBG) and albumin. The majority of testosterone is bound to albumin (54% to 68%); slightly less is bound to SHBG (30% to 44%), and only 0.5% to 3% remains unbound or as free testosterone (Pardridge, 1986). SHBG is produced by the liver and avidly binds to testosterone, rendering it biologically unavailable. Albumin's association with testosterone is much weaker; albumin-bound testosterone and the unbound testosterone compose what is termed *bioavailable testosterone*. These bioavailable testosterone molecules have the ability to enter target organs, bind to the androgen receptor (AR), and initiate protein synthesis.

Testosterone metabolism is important to maintain proper balance between production and to achieve appropriate androgen levels in the target organs. Testosterone metabolism occurs primarily in the liver (Luetjens and Weinbauer, 2012). Extratesticular aromatization results in the conversion of androstenedione to estrone with subsequent reduction to estradiol. The half-life of testosterone in plasma is only about 12 minutes; estrogen influences testosterone's effects by acting either synergistically or antagonistically. Bioavailable estrogen and testosterone are strongly associated with high bone turnover, low bone mineral density, and risk of osteoporotic fractures. The imbalance of the testosterone-to-estrogen ratio is thought to be responsible for the development of impaired glucose tolerance and insulin resistance in the setting of aromatase-deficient men (Maffei et al, 2004).

Testosterone gives rise to 5 α -dihydrotestosterone (DHT) through 5 α -reduction, mainly in the target organs. Although testosterone and DHT both bind to the same intracellular AR, they produce distinct biologic responses. Two isoforms of 5 α -reductase have been identified in humans. Type 1 5 α -reductase has been localized in the nongenital skin, liver, brain, prostate, and testis, whereas type 2 is mainly active in the classical androgen-dependent tissues, such as the epididymis, genitalia, seminal vesicle, testis, and prostate but also in liver, uterus, breast, hair follicles, and placenta (Luetjens and Weinbauer, 2012). DHT is responsible for normal sexual development and virilization in men and when combined with transactivation of AR leads to prostate gene transcription and growth (Penning et al, 2000).

A functional AR is crucial for the optimal action of the androgens. The AR is a ligand-activated transcription factor present in all tissues responsive to testosterone or DHT. The human AR gene was cloned and mapped to Xq11-12 more than 20 years ago (Chang et al, 1988). The N-terminal domain harbors two polymorphic repeats, including a polyglutamine repeat of 9-36 residues and a polyglycine repeat of 10-27 glycine residues, and the length of these repeats affects AR transactivation and sensitivity (Werner et al, 2006). The length of trinucleotide repeats cytosine, adenosine, and guanosine (CAG) has been implicated in various disease processes relating to hyperandrogenicity and hypoandrogenicity. The contribution of CAG repeat polymorphism to prostate cancer has been well described; either to age of onset (Latil et al, 2001) or to the general risk development (Balic et al, 2002). The longer the CAG repeat in the AR gene translates to decreased androgen sensitivity, the earlier the onset of the AD is observed and the more severe the symptoms of AD are (Dejager et al, 2002).

Etiology. AD can be a result of testicular failure (primary hypogonadism), or it can be caused by the disruption at the hypothalamic–pituitary–gonadal (HPG) axis level (secondary hypogonadism). It is important to identify defects in the central level, as it can be a consequence of pituitary pathology, which can be restored by hormonal stimulation in most patients with secondary hypogonadism (Table 23-1). The pathophysiology of these disorders is characterized by alteration of secretion or action of gonadotropin-releasing hormone (GnRH), resulting in impairment

TABLE 23-1 Forms of Hypogonadism

PRIMARY HYPOGONADISM	
DISEASE	CAUSES OF DEFICIENCY
Maldescended or ectopic testis	Failure of testicular descent, 85% idiopathic
Orchitis	Viral or bacterial etiology
Congenital anorchia (bilateral in 1 in 20,000 males, unilateral 4 times as often)	Probably intrauterine torsion
Acquired anorchia	Traumatic, torsion, inflammation, orchiectomy
Secondary testicular dysfunction	Medication, systemic disease, radiotherapy, or toxin exposure
46,XY disorders of sexual development (male pseudohermaphroditism)	Enzymatic defects of steroid biosynthesis
47,XXY syndrome	Nondisjunction in paternal meiosis
Gonadal dysgenesis	Genetic mutations
Leydig cell hypoplasia	Luteinizing hormone receptor mutation
Noonan syndrome	Autosomal dominant congenital disorder

From Dohle GR, Arver S, Bettocchi C, et al. Guidelines on male hypogonadism, <http://www.uroweb.org/gls/pdf/17_Male_Hypogonadism_LR.pdf>; 2013 [accessed 04.11.14].

of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion (Pitteloud et al, 2010).

As men age, testosterone serum levels progressively decrease (Harman et al, 2001). Despite the recognition of this phenomenon since the nineteenth century, the exact mechanism is yet to be elucidated. Circulating LH concentrations do not decline as men age (Harman and Tsitouras, 1980), suggesting that reduced testosterone results from primary gonadal hypofunction rather than changes at the hypothalamic-pituitary levels.

Reduction in testosterone levels might be caused by a reduced number of Leydig cells or by reduced androgenic activity of the cells. AD is also observed with aging in rodents. In the Brown Norway rat strain, similar hormonal changes were observed with aging, and they were studied extensively as models of aging testis (Chen et al, 1994). The number of Leydig cells per testis has been shown to remain unchanged, suggesting that changes in the steroidogenic machinery of the individual cells and not their reduced number are responsible for the declining serum testosterone concentrations. Furthermore, Leydig cells from aged Brown Norway rats have been shown to produce less cAMP and testosterone in response to LH when compared to young rats (Chen et al, 2002). Consistent with animal studies, the administration of human chorionic gonadotropin (hCG) has been shown to stimulate testosterone production to a lesser extent in older than in younger men (Liu et al, 2005), suggesting reduced responsiveness of Leydig cells to LH. Although serum LH levels do not change significantly with age, age-related changes in LH frequency and amplitude have been reported (Bonavera et al, 1997), and these changes could affect Leydig cell testosterone production.

In the setting of systemic illness, alterations in both HPG axis and testicular function have been demonstrated. HPG axis suppression was observed after acute injury: Significant falls of FSH and LH along with testosterone and estradiol were found in both genders (Woolf et al, 1985; Bonavera et al, 1997). In addition to declining

LH levels, decreased pulsatility of LH release in burn patients has also been found, suggesting another plausible mechanism for central hypogonadism (Semple et al, 1987). The degree of HPG suppression is related to the severity of illness in critically ill patients. Both APACHE (Acute Physiology and Chronic Health Evaluation) score and degree of burns in patients were shown to correlate with degree of AD (Kalyani et al, 2007). Severity of head trauma also correlated with AD, and patients who presented with the lowest Glasgow Coma Scale score displayed the lowest levels of baseline and peak FSH and testosterone (Dimopoulou et al, 2004).

Other illnesses also exhibit suppression of the HPG axis. Central hypogonadism is more common in HIV-positive patients. Malnutrition with acute and chronic illness can cause significant weight loss and can disrupt the HPG axis (Dobs et al, 1996). Cytokines have also been implicated in the AD of HIV-infected men: Interleukin (IL)-1 was shown to inhibit gonadotropin release and LH binding to Leydig cells, and tumor necrosis factor can also affect HPG axis (Mylonakis et al, 2001). Naturally occurring opiates (endorphins) inhibit GnRH, and the direct suppressive effect of chronic opioid exposure on the pituitary and testis was proposed (Blank et al, 1986). Uremia also diminishes the amplitude of pulsatile LH release leading to secondary hypogonadism (Palmer, 1999).

Many mechanisms of testicular injury from systemic illness have been demonstrated. Both the germinal epithelium and Leydig cells of the adult testis are more highly predisposed to cytotoxic damage than the prepubertal testis. In a cohort study of patients undergoing high-dose chemotherapy for a variety of hematologic malignancies, one third of the patients showed evidence of Leydig cell dysfunction and 90% of patients experienced germinal epithelial failure (Howell et al, 1999). Single-dose irradiation as low as 0.1 Gy can cause testicular dysfunction, and doses greater than 0.8 Gy result in azoospermia (Rowley et al, 1974). Factors affecting impairment and recovery of testicular function after cytotoxic therapy include the agent used, the dose received, and the maturation of testis at the time of insult (Pryzant et al, 1993). Testicular atrophy from opportunistic infections was also suggested; nonspecific interstitial inflammation and fibrosis were observed in 32% of AIDS patients during autopsy examination (De Paepe and Waxman, 1989). A serum factor present in uremia also exhibits inhibition of LH receptor resulting in decreased Leydig cell sensitivity to LH (Handelsman and Dong, 1993). In alcoholic liver disease, primary testicular failure resulting from defective morphology of Leydig cells caused by ethanol can occur even before any clinical sign and symptom of AD are present (Gursoy et al, 2004).

Systemic illness can also affect testosterone metabolism and transport. The prevalence of AD in chronic liver disease is unknown. Liver failure and other systemic illnesses are associated with elevated levels of sex hormone-binding globulin (SHBG) in liver failure, leading to the overestimation of bioavailable testosterone. Therefore a direct assay for free testosterone might be used in the initial evaluation of the patient's endocrine status, because AD is a

KEY POINTS: EPIDEMIOLOGY AND PHYSIOLOGY

- The true prevalence of AD in the adult male is unknown as a result of inconsistent definitions used in the literature. Population-based studies suggest the prevalence to be between 2.1% and 38.7%.
- The prevalence of AD in men suffering from systemic diseases is significantly higher than those not evincing these diseases. Physicians caring for these patients need to be aware of the increased prevalence and need to offer appropriate screening.
- AD can be a result of primary testicular failure or can be caused by the disruption at the HPG axis. Testosterone metabolism and transport can also be affected by systemic illnesses.
- A functional AR is critical for the action of androgens. AR polymorphism likely contributes to the clinical symptomatology, treatment response, and adverse reaction to therapy.

TABLE 23-2 Comparison of Available Questionnaires

AGING MALE SYMPTOM	ANDROGEN DEFICIENCY IN AGING MALE	MASSACHUSETTS MALE AGING STUDY
1. General well-being	1. Low libido	1. Age
2. Musculoskeletal symptoms	2. Lack of energy	2. Diabetes mellitus
3. Sweating	3. Decrease in strength	3. Asthma
4. Sleep problems	4. Loss of height	4. Sleep quality
5. Tiredness	5. Decreased enjoyment of life	5. Smoking habit
6. Irritability	6. Sadness	6. Headache
7. Nervousness	7. Sexual problems	7. Sexual problems
8. Anxiety	8. Reduced sports performance	8. Managing ability
9. Lacking vitality	9. Tiredness after dinner	9. Height and weight
10. Decreased muscular strength	10. Reduced work performance	
11. Depression		
12-13. Burnt-out feelings		
14. Reduction of beard growth		
15. Decreased sexual performance		
16. Reduced nocturnal erections		
17. Low libido		

From Corona G, Rastrelli G, Forti G, Maggi M. Update in testosterone therapy for men. *J Sex Med* 8:639–54.

significant risk factor for osteoporosis and for spinal fracture, and it is a predictor of mortality in men (Grossmann et al, 2012).

Diagnosis

Diagnosis of AD poses several challenges in men. Clinical signs and symptoms are often nonspecific, and modification by age, comorbid illness, severity and duration of AD, variation in androgen sensitivity, and previous TT can all lead to variable presentation. Multiple questionnaires were developed to screen and quantify the severity of AD in aging men (Table 23-2). Researchers at Saint Louis University first developed the **Androgen Deficiency in Aging Male (ADAM)** in 2000 (Morley et al, 2000). The standard ADAM questionnaire consists of 10 “yes or no” questions concerning symptoms of AD without severity of symptoms. The report initially presented a sensitivity of 88% and specificity of 60% in identifying men with serum biochemical AD as defined by bioavailable free testosterone that was less than 90 ng/dL. However, it was shown to be less specific at 60% in a study of Spanish men older than 50 years of age (Martinez-Jabaloyas et al, 2007). A modification of the original ADAM by quantifying each of the 10 symptoms into a Likert scale of 1 to 5 was shown to improve the questionnaire’s correlation with biochemical AD in a group of men with prostate cancer (Mohamed et al, 2010). The **Aging Male Symptom (AMS)** scale consists of a battery of 17 questions graded on a Likert scale of 1 to 5, which allows one to quantify the degree of improvement in AD symptoms after therapy. However, similar to standard ADAM, AMS lacks specificity. In a study of 1174 men with AD who were undergoing treatment for TT, authors found a sensitivity of 96% but a specificity of only 30% (Moore et al, 2004). The questionnaire from MMAS is mainly a risk questionnaire using a combination of symptom and epidemiologic findings. It was validated against AD as defined by serum total testosterone less than 12.1 nmol/L (Smith et al, 2000), with a sensitivity of 60% and specificity of 59% (Morley et al, 2006). These questionnaires mainly serve as screening tools; their usefulness in diagnosing and evaluating treatment efficacy remains to be determined.

Men with suspicious signs or symptoms or at risk for AD need confirmatory biochemical testing before the diagnosis is made. We do not yet know the exact biochemical threshold serum testosterone concentration below which symptoms of AD and adverse outcomes occur (Table 23-3). Age, target tissue, and androgen sensitivity all can affect threshold of testosterone levels producing various symptoms. The average testosterone threshold corresponding to the lower limit of the normal range for young men, approximately 300 ng/dL (10.4 nmol/L), was shown to be associated with

TABLE 23-3 Biochemical Definition of Hypogonadism Proposed by Various International Societies

	TOTAL TESTOSTERONE CONCENTRATION		
	nmol/L	ng/mL	ng/dL
EAA, ISA, ISSAM	Mild <12	<3.40	<340
EAU, ASA, ISSM	Severe <8	<2.31	<231
ES*	<10.4	<3.00	<300
AACE	7	<2.00	<200

*Pituitary imaging is required in the presence of severe secondary hypogonadism (total testosterone < 5.2 nmol/L or 150 ng/dL).

AACE, American Association of Clinical Endocrinologists; ASA, American Society of Andrology; EAA, European Academy of Andrology; EAU, European Association of Urology; ES, Endocrine Society; ISA, International Society of Andrology; ISSAM, International Society for the Study of the Aging Male; ISSM, International Society of Sexual Medicine.

From Corona G, Rastrelli G, Forti G, Maggi M. Update in testosterone therapy for men. *J Sex Med* 8:639–54.

greater likelihood of experiencing clinical symptoms (Zitzmann et al, 2006).

Serum testosterone levels peak in the morning and vary significantly as a result of circadian and circannual rhythm (Bremner et al, 1983). Most normal ranges for testosterone levels are established using morning blood samples, therefore diagnostic biochemical measurement for AD should be performed in the morning. Even though the effect of circadian rhythm is blunted with aging, a substantial fraction of men older than 65 years who had low serum testosterone levels in the afternoon was shown to have normal testosterone concentrations in the morning (Brambilla et al, 2007). It is important to confirm low testosterone concentrations in men with initial testosterone level less than the biochemical threshold range. In a cohort study of men aged 30 to 79 years, the day-to-day intraindividual variation in the level of testosterone exceeded the approximate 25% difference in half the men (Brambilla et al, 2007). Serum total testosterone concentration represents both protein-bound and unbound testosterone in circulation. Bioavailable testosterone refers to unbound testosterone and albumin-bound testosterone that is readily dissociable. Free or bioavailable testosterone concentrations should be measured when total testosterone levels are at the lower limit

BOX 23-2 Conditions Associated with Abnormal Sex Hormone Binding Globulin (SHBG)**CONDITIONS ASSOCIATED WITH DECREASED SHBG CONCENTRATIONS**

Obesity
 Nephrotic syndrome
 Hypothyroidism
 Use of glucocorticoids, progestins, and androgenic steroids
 Acromegaly
 Diabetes mellitus

CONDITIONS ASSOCIATED WITH INCREASED SHBG CONCENTRATIONS

Aging
 Hepatitis and cirrhosis
 Hyperthyroidism
 Use of anticonvulsants
 Use of estrogens
 Human immunodeficiency virus

From Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536–59.

of the normal range or when altered SHBG levels are suspected (Box 23-2). It is also important to assess gonadotropins and prolactin during confirmatory testing to exclude secondary hypogonadism. If abnormality of the HPG axis is suspected, magnetic resonance imaging (MRI) of the central nervous system is indicated.

Total testosterone concentrations can be measured by three methods: radioimmunoassay, immunometric assay, or liquid chromatography tandem mass spectrometry. In most laboratories, automated immunoassays for total testosterone are performed using chemiluminescence detection. A major problem exists when the standard reference range for the adult male does not correspond to values reported by clinical laboratories (Bhasin et al, 2008). There are significant variations among assay techniques and among different laboratories. An external quality-control program by the College of American Pathologists has shown that the interlaboratory variation of a control sample is in a range between 215 and 348 ng/dL (7.5 and 12 nmol/L) with coefficients of variation among laboratories using the same method ranging between 5.1% and 22.7% (Wang et al, 2004). Using liquid chromatography tandem mass spectrometry as the standard, both radioimmunoassay techniques and automated immunoassay techniques performed within the clinically acceptable limits of $\pm 20\%$ of the reference method in more than 60% of the samples at differentiating the eugonadal from the AD male with established reference ranges for the particular laboratory. However, with their lack of precision at low testosterone levels, the tested assays cannot be used to measure testosterone accurately in females or prepubertal subjects.

Equilibrium dialysis is the gold standard for measuring free testosterone; however, it is costly and is often unavailable in local laboratories. Many analog methods are frequently used in place of equilibrium dialysis, but these methods are heavily affected by SHBG levels and are often inaccurate (Rosner et al, 2007). Routine free testosterone testing using analog measurement is not recommended by the American Endocrine Society. Many calculations were developed to estimate free testosterone concentrations from total testosterone, SHBG, and albumen. The calculated free testosterone values are dependent on the quality of total testosterone and SHBG assays. Because calculations are systematically different from equilibrium dialysis measurements, a significant variability exists in the calculated free testosterone estimates (Sartorius et al, 2009).

Diagnosis for AD in men should begin with a general health evaluation to assess for clinical signs, symptoms, systemic illness, and medications that might contribute to transient depression of testosterone levels. Confirmatory biochemical testing should be performed to support any clinically suspected cases. Gonadotropins and prolactin evaluation is crucial to identify alteration of the HPG axis, and an appropriate imaging study should also be performed. Urologists must become familiar with the limitation of the biochemical assays and the reference range of their local laboratory. Health care providers must exercise clinical judgment in selecting appropriate patients for treatment, because no single modality is capable of providing an accurate diagnosis of AD (Fig. 23-1).

KEY POINTS: DIAGNOSIS

- All men suspected of having AD need to undergo confirmatory biochemical testing.
- The exact biochemical threshold testosterone concentration that correlates with symptoms of AD or adverse outcomes has yet to be elucidated.
- The gold-standard biochemical assay for testosterone is often unavailable; physicians need to be familiar with their local laboratory's protocol and the limitations of different methodologies.
- If testosterone levels are below or at the lower limit of the accepted normal values, a repeat confirmatory morning test along with an assessment of the pituitary function are required.
- In men with abnormal gonadotropins (secondary hypogonadism), MRI of the pituitary might be indicated.

Treatment

The goal of AD treatment is to restore physiologic testosterone levels in AD men while alleviating symptomatic AD. Given the nonspecific clinical presentation of AD, physicians must counsel patients on lifestyle modifications in addition to TT. Increased physical activity, reduction of total caloric intake, and tobacco cessation have all been shown to reduce the risk of cardiovascular disease (CVD) and are part of the first-line management of metabolic syndrome based on American Heart Association recommendations (Grundy et al, 2005). Only by combining lifestyle changes with the restoration of androgen balance can the optimal health of the aging male be achieved.

Randomized controlled studies have shown that TT provides several positive improvements in body composition, metabolic control, and psychological and sexual parameters. For a group of elderly men with stable congestive heart failure, those patients receiving long-acting TT in addition to optimal medical therapy experienced improved exercise capacity (peak oxygen consumption), quadriceps isometric strength, insulin sensitivity, and baroreflex sensitivity compared to the placebo-controlled group (Caminiti et al, 2009). In a meta-analysis of randomized placebo-controlled trials, intramuscular (IM) TT was associated with an 8% gain in lumbar bone mineral density score with mixed results on femoral neck bone mineral density (Tracz et al, 2006). Cohort studies on long-acting TT have demonstrated a clear decrease in waist circumference, a significant reduction in trunk adipose composition and body mass index (BMI), and improvement of lipid profile after 1 year of therapy (Saad et al, 2007; Haider et al, 2010). In a multicenter prospective study, AD men receiving long-acting TT showed a significant improvement in the International Index of Erectile Function (IIEF) score for libido, intercourse satisfaction, and overall satisfaction at 6 weeks of therapy (Moon du et al, 2010). Meta-analysis of randomized, placebo-controlled trials showed that TT in patients with borderline biochemical AD was associated with minimal improvement in erectile function (95% confidence interval [CI] 0.03 to 0.65), nonsignificant effect on libido (95% CI -0.01

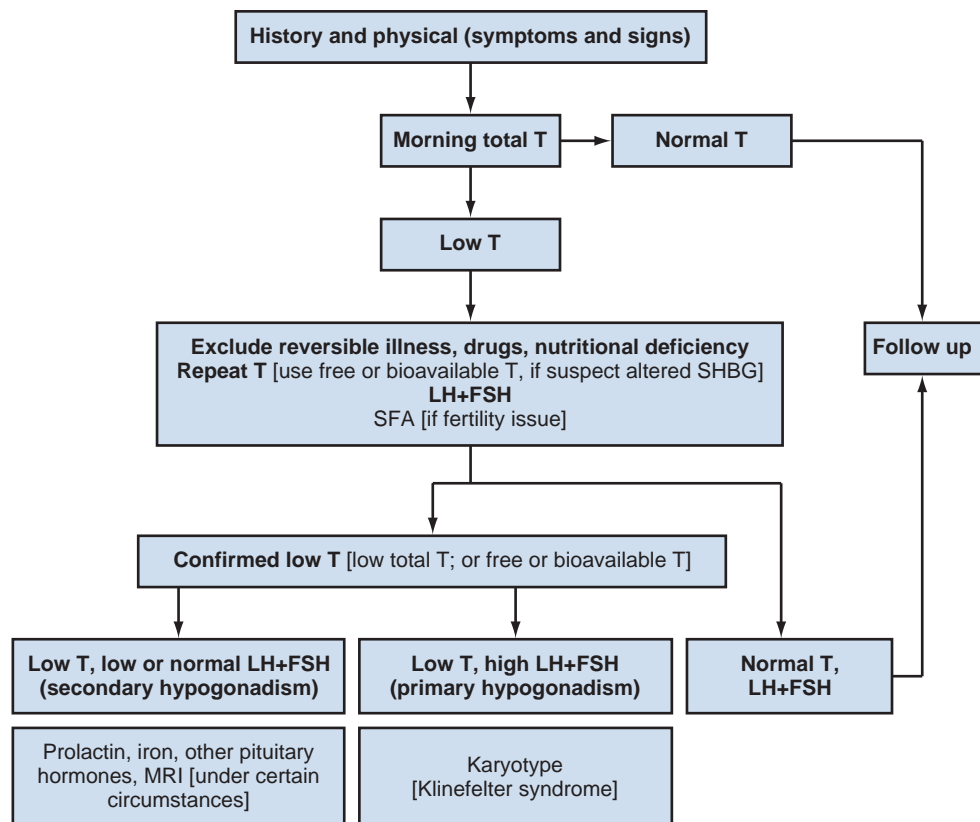


Figure 23-1. Approach for the evaluation for suspected androgen deficiency: endocrine guideline. FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging; SFA, sperm fine-needle aspiration; SHBG, sex hormone binding globulin; T, testosterone. (Modified from Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536–59.)

to 0.83), and no effect on overall sexual satisfaction (Bolona et al, 2007). In a randomized, placebo-controlled study of AD men with metabolic syndrome, long-acting TT administration significantly improved depressive symptoms (–2.5 points, Beck depression inventory), AD symptoms (–7.4 points, AMS), and sexual function (+3.1 points, IIEF) after 30 weeks of therapy as compared to the control group (Giltay et al, 2010). In placebo-controlled, randomized trials of aging men, TT failed to show significant improvement in cognitive function (Blackman et al, 2002; Kenny et al, 2004).

Randomized controlled studies also demonstrated the benefit of TT in patients suffering from systemic diseases. In a study of 70 HIV-positive men with symptomatic and biochemical confirmation of AD, biweekly IM TT was shown to improve libido, fatigue, depressive mood, and muscle mass compared to the placebo group (Rabkin et al, 2000). In a small randomized study of asthmatic men receiving long-term glucocorticoid treatment, TT increased bone density of the lumbar spine by 5% compared to no change in the placebo group after 1 year of therapy (Reid et al, 1996). In a double-blind, placebo-controlled trial of men with severe burn (40% to 70% of body surface), patients treated with a testosterone analogue, Oxandrolone, were found to decrease significantly both weight and net nitrogen loss while improving donor-site wound healing compared to the placebo group (Demling and Orgill, 2000).

Administration of native testosterone either orally or parenterally results in absorption by portal circulation and rapid metabolism by the liver, and only a small concentration reaches the systemic circulation (Qoubaitary et al, 2005). Advancement in chemical modification using esterification results in a series of testosterone analogues with improved bioavailability and pharmacokinetics (Corona et al, 2011) (Fig. 23-2).

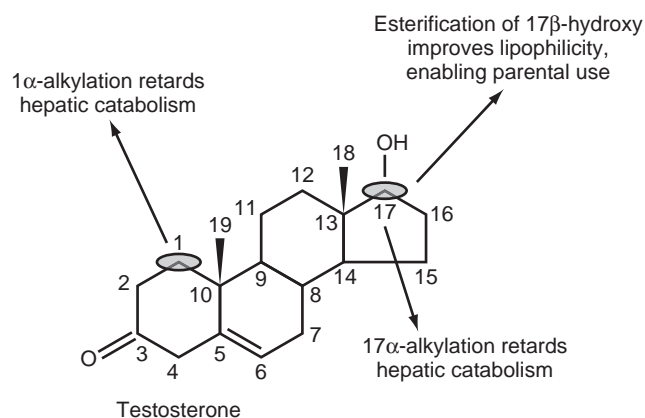


Figure 23-2. Biochemical structure of testosterone and potential site of modification: chemical structure of testosterone and possible site of structural modification to improve its bioavailability and pharmacokinetics. (Modified from Corona G, Rastrelli G, Forti G, et al. Update in testosterone therapy for men. *J Sex Med* 2011;8:639–54.)

TT is indicated in AD men who are demonstrating a decline in muscle mass and strength, a reduction of bone mineral density, and a decrease in sexual function (Boxes 23-3 and 23-4). TT is safe, and several preparations are available: oral, buccal, transdermal, IM injections, and subcutaneous implantation (Table 23-4 and Box 23-5). TT's goal and aim is to restore biochemical testosterone levels in a range for healthy young men. Physicians need to

be aware of the pharmacology of different TT formulations to avoid undertreatment and overtreatment when both are associated with increased adverse events. The principle of treatment with a short-acting formulation to assess efficacy and side effects before commitment to a long-acting preparation should be followed.

Oral Preparations

Oral alkylated testosterone preparations are associated with **hepatotoxicity**; use is considered obsolete and is no longer recommended. The only oral testosterone formulation available is testosterone undecanoate (TU), and its absorption is via the lymphatics,

bypassing liver metabolism to enable delivery (Seftel, 2007). This formulation is currently not available in the United States. The absorption via lymphatic route is highly dependent on the fat content of food intake: It must be taken with at least 20 mg of fat. Oral TU has a short half-life (approximately 4 hours) and it requires multiple dosing (2 to 3 times daily), resulting in irregular serum

BOX 23-3 Indications for Testosterone Therapy

Delayed puberty (idiopathic, Kallmann syndrome)
Klinefelter syndrome with hypogonadism
Sexual dysfunction with low testosterone
Low bone mass in hypogonadism
Adult men with signs and symptoms of hypogonadism
Hypopituitarism
Testicular dysgenesis with low testosterone

From Dohle GR, Arver S, Bettocchi C, et al. Guidelines on male hypogonadism, <http://www.uroweb.org/gls/pdf/17_Male_Hypogonadism_LR.pdf>; 2013 [accessed 04.11.14].

BOX 23-4 Contraindications for Testosterone Therapy

VERY HIGH RISK OF SERIOUS ADVERSE OUTCOMES

Metastatic prostate cancer
Breast cancer

MODERATE TO HIGH RISK OF ADVERSE OUTCOMES

Unevaluated prostate nodule or induration
Hematocrit greater than 50%
Severe lower urinary tract symptoms associated with benign prostatic hypertrophy (American Urological Association International Prostate Symptom Score >19)
Poorly controlled congestive heart failure
Unevaluated sleep apnea

From Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536–59.

TABLE 23-4 Available Testosterone Therapy Preparations

COMPOUND	DOSAGE	ADVANTAGES	DISADVANTAGES
ORAL AGENTS			
Testosterone undecanoate	120-240 mg, 2-3 times daily	Oral, adjustable dose	Variable testosterone levels and clinical response, must be taken with meals containing at least 20 g of lipids
INTRAMUSCULAR AGENTS			
Testosterone enanthate	200 mg every 1-2 wk	Low cost	Wide fluctuation in testosterone levels, multiple injections, increased risk for polycythemias
Testosterone cypionate	100-200 mg every 1-2 wk		
Testosterone propionate	100 mg every 2 days		
Testosterone undecanoate	750-1000 mg every 10-14 wk	Efficient testosterone normalization, long lasting, improved compliance	Injection site pain, requires injection training
SUBUTANEOUS AGENTS			
Surgical implants	450-700 mg every 4-6 mo	Efficient testosterone normalization, long lasting, improved compliance	Invasive placement, risk of extrusion and site infections
CONTROLLED-RELEASE BUCCAL FORMULATION			
Testosterone buccal	30 mg, twice daily	Oral	Mucosal irritation, twice daily administration
TRANSDERMAL AGENTS			
Testosterone patches	5-10 mg daily	Simple administration, mimics circadian rhythm	Skin irritation, daily administration, hygiene issues
Testosterone gel 1%-2%	40-80 mg daily	Efficient testosterone normalization, flexible doses, simple administration	Skin irritation, daily administration, possible transference during contact
Underarm Testosterone 2% solution	60-120mg daily		
Testosterone gel 1.62%	20.25-81 mg daily		

From Isidori AM, Buvat J, Corona G, et al. A critical analysis of the role of testosterone in erectile function, from pathophysiology to treatment—a systematic review. Eur Urol 2014;65:99–112.

BOX 23-5 Monitoring after Initiation of Testosterone Therapy

1. Evaluate the patient every 3 to 6 months after treatment initiation and then annually to assess symptom response and assess adverse effects.
2. Monitor testosterone level 3 to 6 months after treatment initiation with goal to raise serum testosterone level into the mid-normal range.
 Injectable formulations: Measure serum testosterone level midway between injections.
 Transdermal patch: Assess testosterone level 3 to 12 hours after application.
 Transdermal gels: Assess testosterone level any time after 1 week of treatment.
 Buccal testosterone: Assess testosterone level immediately before or after application.
 Oral agent: Monitor testosterone level 3 to 5 hours after ingestion.
 Testosterone pellets: Measure testosterone levels at the end of the dosing interval.
3. Check hematocrit at baseline, at 3 to 6 months, and then annually.
 If Hct is greater than 54%, stop therapy until Hct decreases to a safe level.
4. Measure bone mineral density of lumbar spine and/or femoral neck after 1 to 2 years of testosterone therapy in men with osteoporosis or low-trauma fracture.
5. Perform DRE and check PSA before initiation of therapy, at 3 to 6 months, and then in accordance with prostate cancer screening guidelines.
6. Additional urologic workup is indicated if there is abnormal DRE, elevation of PSA, worsening lower urinary tract symptoms, or an AUA/IPSS greater than 19.
7. Evaluate formulation-specific adverse effects at each visit.
 Buccal: alterations in taste and examination of gum and oral mucosa for irritation
 Injectable: fluctuations in symptom, fluid retention
 Testosterone patches: irritation at the application site
 Testosterone gels: Advise patient to cover the application sites with clothing, local hygiene before skin-to-skin contact with women or child. Serum testosterone levels are maintained when application site is washed 4 to 6 hours after application.
 Testosterone pellet: Check for signs of infection, fibrosis, or pellet extrusion.

AUA/IPSS, American Urological Association International Prostate Symptom Score; DRE, digital rectal examination; Hct, hematocrit; PSA, prostate-specific antigen.

From Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536–59.

testosterone levels throughout the day. Oral TU has the advantages of flexible dosage, self-administration, and immediate decrease in testosterone serum concentrations after cessation of therapy.

Transbuccal Preparation

A sustained-release mucoadhesive system offers an alternative preparation for oral TT. Transbuccal administration allows the absorption of testosterone through oral mucosa bypassing liver metabolism.

Softening and molding the tablet to the shape of the gum work to apply the system, and this tablet must be removed after 12 hours to avoid local irritation. This formulation was shown to restore testosterone to the physiologic levels while demonstrating efficacy similar to other testosterone formulations (Pfeil and Dobs, 2008).

Transdermal Preparations

A variety of transdermal formations is current available. They are normally to be used daily and they deliver consistent serum testosterone levels into the circulation during treatment. Available transdermal testosterone patches are frequently associated with local skin reactions and decreased compliance rate (Seftel, 2007). The patches can be scrotal and nonscrotal, and they can either include or not include enhancers to increase the skin absorption.

Transdermal testosterone gels were first introduced in the United States in 2000. The recommended starting dose is 50 mg/5 g per day, which provides the delivery of approximately 50 mg/day into circulation. The formulations are either 1% or 2% hydroalcoholic testosterone gels capable of continuous delivery of testosterone for 24 hours after a single daily application. **When transdermal gels are applied, testosterone is rapidly absorbed into the stratum corneum, which forms a reservoir and serves as a rate-controlling membrane (Corona et al, 2011).** It is recommended that testosterone gel be applied on intact dry skin over the shoulders, upper arms, axilla, abdomen, or inner thigh area. Dose adjustment might be needed after therapy because skin absorption is variable among men. Testosterone gels show an improved safety profile with a significant decrease in skin adverse reaction compared to the testosterone patch (Wang et al, 2000). **Transference to others during close contact with the skin's surface is a potential adverse event when using testosterone gels.** This risk can be avoided by wearing clothing or by removing the residue of gel on the skin by local hygiene or by showering after the mandatory residence time (2 to 4 hours based on the preparation).

Injectable Preparations

Injectable 17 β -hydroxyl esters are available in oil depot formulation. When administered into the muscle, testosterone is absorbed directly into the bloodstream. The frequency of injections is based on their half-lives. The propionate-testosterone ester is not widely used because of its short-term formulation, requiring 2 or 3 fractionated doses weekly. Cypionate and enanthate-testosterone esters are injected every 2 weeks. **After administration of injectable preparations, supraphysiologic levels of serum testosterone are reached after 24 hours, followed by a gradual decline to AD levels throughout the following 10 to 14 days (Matsumoto, 1994).** The “peak and valley” variation in serum testosterone concentration is often paralleled by variations of well-being and hypogonadal symptom recurrence. It is postulated that the wide fluctuation in testosterone concentrations contributes to the frequent side effects, including polycythemia, requiring dose adaptation, temporary interruption of therapy, and/or phlebotomy.

A longer-lasting injection preparation of TU is available, although not in the United States. It is administered into the gluteal muscle every 12 weeks following a 6-week loading dose. Testosterone is gradually released into systemic circulation at a consistent normal physiologic level while avoiding complications associated with the fluctuation of testosterone levels. Randomized, placebo-controlled studies have validated the clinical efficacy and the ability to maintain therapeutic testosterone levels of injectable TU (Caminiti et al, 2009; Corona et al, 2011).

Subcutaneous Implant Preparation

The testosterone pellet is the only long-acting testosterone formulation approved for the treatment of male AD in the United States, and it is also available as a different preparation in Europe and Australia. The crystalline testosterone pellets are inserted into subcutaneous tissue under local anesthesia, with complications of

infection or pellet extrusion. Serum testosterone reaches supra-physiologic levels approximately 1 month after implantation, with a gradual decline during the following 3 to 6 months (Kelleher et al, 2004). It offers the longest duration of action among the currently available TT preparations with a steady-state delivery in a multi-institution observational study (McCullough et al, 2012). The convenience of long-acting testosterone preparations has the potential to increase patient compliance, although long-term data on the testosterone pellet are still to be determined. In a randomized, crossover study comparing long-acting TT (testosterone pellet vs. injectable TU), patients preferred the injectable formulation despite no difference in clinical efficacy (Fennell et al, 2010). It should be noted that both formulations from the study are not available in the United States.

Any patient undergoing TT requires scheduled follow-up. During the first year of therapy, men should be monitored at 3- to 6-month intervals and at least annually thereafter (see Box 23-5). A complete clinical and andrologic evaluation is mandatory at each visit. Biochemical assessment of hormonal levels along with hematocrit (Hct) and prostate-specific antigen (PSA) are mandatory. Metabolic parameters can also be measured (e.g., lipid profile), whereas liver function testing is no longer required using the available testosterone formulations.

Complications and Controversies

Erythrocytosis

Testosterone appears to stimulate erythropoiesis. ADT and AD are both risk factors for anemia. In men with chronic kidney disease, AD was shown to be associated with reduced responsiveness to erythropoiesis-stimulating agents (Carrero et al, 2012). Despite the known association, the underlying mechanism of testosterone's role in erythropoiesis is poorly understood. One potential mechanism of action of testosterone is by improvement of iron bioavailability. Weekly administration of IM TT appeared to suppress hepcidin, an iron-regulating protein, resulting in erythrocytosis in a dose- and age-dependent manner (Bachman et al, 2010). Elderly men are at increased risk for developing post-treatment erythrocytosis. DHT has also been implicated at testosterone-induced erythrocytosis. In a randomized, placebo-controlled trial, men who received topical DHT experienced asymptomatic increases of Hct despite a decrease in serum testosterone concentrations, requiring the discontinuation of treatment per protocol (Idan et al, 2010).

Erythrocytosis is the most common side effect of TT with variable prevalence based on testosterone formulations; injection therapy is associated with a greater risk of erythrocytosis as compared to topical preparations. Comparing the testosterone patch with IM injections, the rate of erythrocytosis, as defined by Hct greater than 52%, was 15.4% and 43.8%, respectively (Dobs et al, 1999). Increased blood viscosity can aggravate vascular disease in the coronary, cerebrovascular, or peripheral vascular circulation, particularly in the elderly with pre-existing conditions (Jonathan, 2002). Therefore men receiving TT need to be monitored for erythrocytosis and appropriate measures: Dose reduction, withholding of therapy, therapeutic phlebotomy, or blood donation needs to be instituted in appropriate cases.

Benign Prostatic Hyperplasia

Androgen is important for the development of prostate tissue. Chemical or surgical castration results in the reduction of prostate volume. TT poses as a theoretic risk in men with known lower urinary tract symptoms (LUTS) relating to benign prostatic hyperplasia (BPH). Studies have shown a significant increase in prostate volume; measurement by transrectal sonography was associated with TT during the first 6 months of treatment (Pechersky et al, 2002). However, the increase in prostate volume did not translate into worsening LUTS. Multiple studies failed to demonstrate a significant increase in BPH-related voiding symptoms, measured by International Prostate Symptom Score (IPSS), urine

flow rates, postvoid residual volumes or complications, such as urinary retention, in men undergoing TT as compared to placebo-controlled groups (Fernandez-Balsells et al, 2010). Severe LUTS (IPSS >20) is a relative contraindication to TT and patients should consider evaluation and treatment before initiation of therapy. Urinary symptoms should be assessed as part of follow-up monitoring of men undergoing TT.

Prostate Cancer

Advancement in the understanding of androgen's effect on the prostate is the basis of modern ADT for prostate cancer. TT trials have shown a rise in serum PSA levels, which heightened the concern for the development of prostate cancer (Slater and Oliver, 2000). A collaborative analysis of 18 prospective studies showed no association between serum androgen concentrations and risk of prostate cancer (Roddam et al, 2008). Prospective trials on TT did not show an increase in the incidence of prostate cancer or the risk for prostate biopsy compared to placebo groups (Fernandez-Balsells et al, 2010). TT has emerged as a strategy for sexual function rehabilitation following treatment of prostate cancer. Multiple retrospective cohort studies of TT following prostate cancer treatment demonstrated an improvement in the recovery of sexual function without an increased rate of biochemical recurrence compared to matched controls (Pastuszak et al, 2013).

To date, no definitive evidence suggests that TT has a causative role in prostate cancer or that raising serum testosterone levels by exogenous TT increases the risk for prostate cancer. Both prostate cancer and AD are diseases of aging. Therefore a baseline measurement of PSA and a digital rectal examination should be performed during the evaluation of AD. Men with abnormal PSA or abnormal digital rectal examination require appropriate workup and counseling before TT. Careful monitoring of prostate pathology is critical after TT. Prostate biopsy is indicated in the presence of suspected prostate cancer following the established guidelines for eugonadal men.

Lipid Profile. Data on the relation of TT and lipid profile are inconsistent. Supertherapeutic dosage of androgens appears to lower high-density lipoprotein (HDL) levels (Singh et al, 2002). Multiple prospective studies using TT to restore testosterone in physiologic levels have shown either no change or minimal reduction in HDL (Whitsel et al, 2001). Both total cholesterol and low-density lipoprotein (LDL) levels were also unchanged or reduced compared to pretreatment levels. Transdermal preparation appears to have lesser effects on the lipid profile compared to injectable TT. In a double-blinded placebo-controlled study, there was no significant difference in serum lipids and apolipoprotein between healthy men receiving transdermal testosterone and a placebo group during 36 months of treatment (Snyder et al, 2001). Available data suggest that TT within a physiologic range is not associated with detrimental changes of the lipid profile.

Testicular Hypofunction

Testicular size and consistency often diminish after TT. Exogenous testosterone administration leads to excess negative feedback of the HPG axis, which results in suppression of endogenous testosterone production and spermatogenesis. An international multicenter male contraceptive study conducted by the World Health Organization showed that weekly administration of 100 mg IM testosterone enanthate in healthy men resulted in 98% suppression of spermatogenesis to severe oligospermic (<3 million sperm per mL) or azoospermic level (World Health Organization, 1996). Recovery after TT cessation usually occurs in 12 to 15 months, although normal spermatogenesis is not always observed (Gu et al, 2003). Despite existing literature on exogenous testosterone as male contraception, many physicians are unaware of the effect of exogenous testosterone on fertility. A survey of practicing urologists showed that 25% of respondents would use exogenous testosterone for the treatment of male infertility (Ko et al, 2012).

Strategies such as pretreatment sperm cryopreservation or concomitant administration of hCG have been shown to preserve spermatogenesis in men undergoing TT (Hsieh et al, 2013). **Be cautious when initiating TT in men who still desire to preserve fertility.** Physicians need to offer detailed counseling, monitoring of spermatogenesis, and appropriate strategy to preserve fertility.

Other Adverse Reactions

TT was shown to be associated with the development of sleep apnea (Attal and Chanson, 2010). This phenomenon generally occurs in men undergoing high-dosage TT with other identifiable risk factors for sleep apnea. Upper airway anatomy is unaffected by TT, suggesting a potential central mechanism of altered breathing during sleep rather than anatomical obstruction.

Dermatologic reactions are more common with transdermal patches (up to 66%) than with gel preparations (approximately 5%) (Wang et al, 2000). IM injections can cause local pain, ecchymosis, erythema, swelling, hematoma, abscess, or furuncles (von Eckardstein and Nieschlag, 2002). Acne, oily skin, changes in body hair, and flushing have also been observed but are generally well tolerated.

Fluid retention is uncommon and is generally mild. However, caution is needed when initiating TT in men with congestive heart failure or renal insufficiency.

Gynecomastia is a rare complication after TT. It is related to increased serum estradiol levels from aromatization of testosterone and is often managed by dose adjustment of TT.

Testosterone Therapy for Erectile Dysfunction

Erectile dysfunction (ED) has emerged as an important independent risk factor for CVD, and sexual dysfunction is the most specific symptom of LOH (Isidori et al, 2014). **Population-based studies have shown that the prevalence of AD in men experiencing ED ranges from 23% to 47% (Kohler et al, 2008). The association between ADT and sexual dysfunction is well documented but the role of TT as a monotherapy for ED is less clear.**

Testosterone is responsible for normal genital development, and the literature supports its role in erectile physiology. In the central nervous system, testosterone was shown to stimulate the release of excitatory neurotransmitters such as dopamine, oxytocin, and nitric oxide, which control sexual dimorphic development and mating behavior (Hull et al, 1999). Peripherally, testosterone modulates multiple components involved in erectile function: structure, function, and innervation of smooth muscle cells, endothelial function of penile vessels, and fibroelastic properties of the corpus cavernosum (Isidori et al, 2014). Unfortunately many available data derived from animal castration models, which are very different from AD in men, generate uncertainty, further complicated by the limited available human data.

Combination therapy with phosphodiesterase type 5 inhibitors (PDE5-I) and TT is a highly debated topic. PDE5-I monotherapy is effective at improving erection but is often inadequate in addressing other domains of sexual dysfunction, such as decreased libido, for the AD men. The concept of salvage therapy for nonresponders of PDE5-I was examined in a multicenter, double-blind, placebo-controlled study of 173 men (Buvat et al, 2011). Administration of topical TT resulted in additional beneficial effect only in AD men with total testosterone below the threshold of 10.4 nmol/L (300 ng/dL). The concept of combination therapy was further tested in a large randomized trial to address whether TT includes any additional benefit in AD men whose erectile function is already maximized by a PDE5-I (Spitzer et al, 2012). The study definitively confirmed that TT does not provide additional benefit when erectile function is already restored by PDE5-I. However, the study was not powered to assess the role of salvage therapy, because the overall number of PDE5-I failures was low.

In young men with symptomatic AD, TT should be the first-line treatment with high likelihood of improvement in all domains of sexual function, and PDE5-I can be added if necessary. In elderly

men with ED, PDE5-I should be first-line therapy with optimization of comorbid conditions. In the case of nonresponders, TT should be reserved only in men with biochemical confirmation of AD. Available evidence shows that there are no major safety concerns with combination therapy.

KEY POINTS: TESTOSTERONE THERAPY FOR ERECTILE DYSFUNCTION

- ED along with sexual dysfunction is the most specific predictor of AD.
- Testosterone acts peripherally to modulate multiple components responsible for normal erection.
- When erection is restored by PDE5-I, the addition of TT does not result in further benefit of erectile function.
- For ED refractory to PDE5-I, TT has the potential to improve the efficacy of therapy only in men with biochemical AD (<300 ng/dL).

CARDIOVASCULAR DISEASE AND TESTOSTERONE

CVD is the leading cause of death in most developed countries, with an estimated 17.3 million deaths worldwide per year (Laslett et al, 2012). The lifetime risk of coronary heart disease (CAD) at age 40 is one in two for men and one in three for women (Lloyd-Jones et al, 2004). Although mortality has decreased considerably in recent years, CVD and its complications remain highly prevalent and are significant burdens to the health system (Smolina et al, 2012). The American Heart Association projected that costs of CVD care would triple from \$272.5 billion in 2010 to an estimated \$818.1 billion in 2030 (Laslett et al, 2012). Men are at greater risk for CVD than premenopausal women, suggesting a possible influence of sex hormones (Yang and Reckelhoff, 2011).

Both CVD and AD are diseases of aging; they share many risk factors such as age, obesity, diabetes, alcohol consumption, and chronic diseases. **The association between AD and CVD has become evident in observational studies (Araujo et al, 2011). ADT is associated with an increased risk for CV events in patients with prostate cancer (Levine et al, 2010).** Prospective studies demonstrated that ADT increases CVD by affecting various risk factors: increased body weight, decreased insulin sensitivity, altered lipid profile, and increased fat mass. Two population-based studies reported that ADT is associated significantly with CAD and sudden cardiac death or life-threatening arrhythmia (Saigal et al, 2007). Data from the Cancer of the Prostate Strategic Urologic Research Endeavor also showed a significantly increased risk of CV death in men who underwent radical prostatectomy and received ADT compared with those undergoing surgery alone (Tsai et al, 2007). Endogenous testosterone has been suggested as CV-protective or as a secondary risk predictor of other processes, although the mechanism is still unclear.

Men with LOH commonly exhibit coexisting CVD risk factors; the safety of TT is often questioned, given the known adverse reaction of polycythemia. In 2004, the Institute of Medicine reviewed the evidence on TT and concluded that "there is not clear evidence of benefit for any of the health outcomes examined" (Xu et al, 2013). A randomized, placebo-controlled study on TT in elderly men with limitations in mobility was discontinued early because of an increase in CV-related events in the treatment arm despite showing an improvement in musculoskeletal parameters (Basaria et al, 2010). The generalizability of the results was often questioned, however, because the study population was elderly men (mean age of 74 years) with serious chronic illnesses. The number of CV adverse events was small and the trial was not originally designed to analyze CV outcomes. Meta-analysis of randomized studies on the adverse events associated with TT yielded mixed results on CV events and mortality (Fernandez-Balsells et al, 2010; Xu et al, 2013).

A retrospective study of 8709 male veterans showed a 29% increased risk of CV events in men undergoing TT (Vigen et al, 2013). However, the study was criticized for many flaws: improper patient exclusion, unbalanced comparison, and unusual complexity of statistical analysis. Another cohort study using a health care database (Truven Health MarketScan) suggested the risk of myocardial infarction doubled within 90 days after initiation of TT (Finkle et al, 2014). Researchers used prescription claim information, which does not accurately reflect initiation of TT when known patient compliance issues are considered. Additional statistical modeling was applied to the weighted data. Definitive assessment of CV risk associated with TT must await an ongoing large randomized, controlled trial.

Coronary Artery Disease

Traditionally, AD is not considered a risk factor for CAD. An earlier longitudinal case control study reported no significant difference in testosterone between low-risk men who developed CAD and those who did not (Heller et al, 1983). A growing body of evidence suggests a link between low endogenous testosterone levels and CAD. Several studies have demonstrated that patients with CAD as diagnosed by coronary angiography have lower levels of testosterone compared to control subjects (Chute et al, 1987; Sieminska et al, 2003; Cao et al, 2010). In addition to total testosterone, a significantly lower level of bioavailable testosterone was also found in patients with catheterization-proven CAD (Rosano et al, 2007).

In addition, the degree of AD has been reported as having an inverse relationship to the severity of CAD. Epidemiologic evidence reported a fivefold decrease in the risk of severe atherosclerotic CAD between the lowest and the highest quartiles of total testosterone (Chute et al, 1987). Four small studies have demonstrated independently that in men with CAD, lower levels of endogenous testosterone are associated with more severe CAD (Phillips et al, 1994; Rosano et al, 2007; Hu et al, 2011; Li et al, 2012). This correlation between low testosterone and CAD severity has also been demonstrated in both men and postmenopausal women with CAD (Phillips et al, 1997; Kaczmarek et al, 2003). Men with myocardial infarctions and ischemia have been reported as having lower testosterone and an increased estradiol-to-testosterone ratio when compared to controls (Sewdarsen et al, 1986; Lichtenstein et al, 1987).

Several population-based studies examined the association between mortality secondary to CVD and levels of total testosterone. Although some researchers found significantly greater CV mortality associated with lower testosterone concentrations, others did not (Oskui et al, 2013). A meta-analysis showed a trend toward increased CV mortality associated with lower levels of total testosterone, but statistical significance was not reached (Araujo et al, 2011). An analysis of 2416 Swedish men demonstrated that levels of endogenous total testosterone were significantly inversely associated with risk of adverse CV events (Ohlsson et al, 2011). Men in the fourth quartile of total testosterone showed significant improvement in event-free survival for both major adverse CAD events. Several studies also analyzed the association between bioavailable testosterone and CV mortality, and all indicated that a higher risk of CV mortality was associated with lower levels of bioavailable testosterone (Laughlin et al, 2008; Malkin et al, 2010; Menke et al, 2010).

Cerebral Vascular Disease

AD has also been implicated in the development of cerebral vascular disease. Low levels of total testosterone and bioavailable testosterone have been reported as predictive of an increased incidence of cerebral vascular accidents or transient ischemic attack, even after adjusting for conventional risk factors for cerebral vascular disease (Yeap et al, 2009). Multiple studies have demonstrated that low testosterone concentration is associated with increased carotid intimal-media thickness (IMT), which serves as a measure of cerebrovascular atherosclerosis (De Pergola et al, 2003; Fukui

et al, 2003; van den Beld et al, 2003). Several population-based studies reported an inverse association between total testosterone levels and carotid artery IMT that was present after excluding men with cerebral vascular disease; this relationship, however, was not independent of BMI (Svartberg et al, 2006; Debing et al, 2008). Similarly, a cross-sectional analysis of the Tromso cohort demonstrated an inverse association between testosterone levels and total carotid plaque area (Vikan et al, 2009). In studies without association with total testosterone, low levels of bioavailable testosterone were associated with carotid artery IMT after adjusting for age, BMI, and known cerebral vascular disease risk factors (Tsujimura et al, 2012). The association between testosterone and cerebral vascular disease appeared to be gender specific. No association was observed for free testosterone or total testosterone with carotid IMT in young to middle-aged women (Calderon-Margalit et al, 2010) or with progression of carotid IMT and adventitial diameter in perimenopausal women (El Khoudary et al, 2012).

Proposed Mechanism of Testosterone's Action on the Cardiovascular System

Endothelial Dysfunction

Endothelial dysfunction is the first step in the formation of atherosclerotic lesions. Testosterone has been demonstrated as having a protective effect on endothelial function (Fu et al, 2008). Testosterone has been inversely correlated with vascular cell adhesion molecule-1, which is produced by endothelial cells and is upregulated when endothelial cells undergo inflammatory and malignant stimulation. Investigators reported that hypogonadal men exhibited lower levels of endothelial progenitor cells, which are important in endothelial regeneration, and higher levels of an osteocalcin-positive subpopulation of endothelial progenitor cells, which are highly correlated with atherosclerosis progression, compared to eugonadal men (Foresta et al, 2010). Finally, testosterone has been shown to reduce significantly endoplasmic reticulum stress and superoxide generation in human umbilical vein endothelial cells, both of which have been implicated in atherosclerosis; however, when combined with aromatase inhibitors, the protective effect of testosterone was lost, suggesting an estradiol-mediated mechanism (Haas et al, 2012).

The antianginal and anti-ischemic effects of TT have been recognized since the late 1930s (Oskui et al, 2013). TT in AD men suffering from CAD has proven effective in increasing time to 1-mm ST-segment depression with an exercise stress test (Rosano et al, 1999; English et al, 2000). Although testosterone's vasodilatory effects are well recognized, the exact mechanism of action has yet to be elucidated. Testosterone has been reported to induce endothelium-independent relaxation of numerous vascular beds including human internal mammary arteries and radial arteries (Yildiz et al, 2005b). Both in vivo animal models and in vitro models provided evidence that testosterone induces coronary vasodilation by modulating the activity of ion channels. This direct relaxation response to testosterone has been attributed to conduction of non-adenosine triphosphate sensitive potassium channel (Yue et al, 1995), adenosine triphosphate-sensitive potassium channel (Seyrek et al, 2007), and large conductance calcium-activated potassium channel opening action (Yildiz et al, 2005a). Testosterone has also been reported to induce vasodilation by reducing calcium influx into vascular smooth muscle by acting as a selective and potent inhibitor of L-type calcium channels at physiologic levels and as an inhibitor of testosterone-type channels at supraphysiologic levels (Scrugg et al, 2004).

Contrarily, other studies have suggested an endothelium-dependent mediated mechanism behind testosterone's vasodilatory effect (Ong et al, 2000; Kang et al, 2002). Both acute and long-term administration of testosterone in men with CAD have been shown to increase brachial artery flow-mediated reactivity, which induces shear stress release of nitric oxide and subsequently leads to vasodilation. This relation has also been demonstrated in postmenopausal women (Montalcini et al, 2007).

Arterial wall stiffness is an independent predictor of CVD risk. Low testosterone levels have been associated with endothelial dysfunction (Laurent et al, 2006). This inverse relationship has been demonstrated using both pulse pressure and pulse wave velocity as reflections of arterial wall stiffness (Fukui et al, 2007; Corona et al, 2009). Interestingly, the association between testosterone and CVD mortality was lost in male hemodialysis patients after adjusting for pulse wave velocity, suggesting that endothelial dysfunction may be a possible explanation of testosterone's inverse association with CVD (Kyriazis et al, 2011). Contrarily, long-term (8-week) administration of testosterone increased myocardial perfusion in unobstructed coronary arteries and decreased radial and aortic augmentation indexes, indicating decreased arterial wall stiffness; however, no effect was observed on global perfusion or on endothelial function (Webb et al, 2008).

Inflammation

Atherosclerosis is mediated by an ongoing inflammatory response, which is induced by cytokines and other inflammatory markers. Cytokines cause cellular and local arterial wall inflammation and may lead to vascular smooth muscle apoptosis, degradation of the fibrin cap, and plaque rupture, thereby leading to platelet adhesion, thrombus formation, and ultimately angina or myocardial infarction (Malkin et al, 2003). An elevation in inflammatory markers or cytokines has been identified to be predictive of outcomes in patients with CVD (Libby et al, 2002). In a cross-sectional study, inflammatory markers, macrophage inflammatory protein 1- α , 1- β , and tumor necrosis factor- α , have been negatively associated with total testosterone levels in young healthy men, suggesting a low-grade inflammatory state (Bobjer et al, 2013).

TT was reported to suppress the expression of high-sensitivity C-reactive protein and IL-6 in patients who underwent coronary artery stent implantation, leading to the hypothesis that testosterone's anti-inflammatory property could potentially attenuate major CV events (Guler et al, 2006). In a randomized, placebo-controlled, crossover study of AD men, TT reduced levels of proinflammatory cytokines tumor necrosis factor- α and IL-1 β while suppressing levels of cytokine IL-10 (Malkin et al, 2004). However, the inverse relationship between cytokines and testosterone was not identified in AD men with congestive heart failure and in diabetic males compared to eugonadal controls (Pugh et al, 2005; Hernandez-Mijares et al, 2010).

Coagulation

The effect of testosterone on clotting factors including fibrinogen and plasminogen activator inhibitor-1 (PAI-1) has been studied previously. Fibrinogen is a known risk factor for CVD as well as an inflammatory biomarker (Danesh et al, 2005); it increases CVD risk through its effects on atherogenesis, thrombogenesis, and ischemia by the mechanism of increasing plasma and blood viscosity (Kaptoge et al, 2007). It was shown that endogenous testosterone levels were negatively correlated with fibrinogen (Phillips et al, 1994). In a study comparing patients with prostate cancer on ADT to healthy controls, patients on ADT presented with elevated levels of fibrinogen (Ziara et al, 2013). In addition to fibrinogen, PAI-1, another risk factor for ischemic heart disease, was also negatively correlated with endogenous testosterone levels (Yang et al, 1993; Phillips et al, 1994).

Contrarily, a double-blinded, randomized placebo-controlled trial of testosterone supplementation in men with chronic stable angina demonstrated no changes in fibrinogen or PAI-1, suggesting that testosterone supplementation does not affect blood coagulation status (Smith et al, 2005). Moreover, a study comparing chemically or surgically castrated males to eugonadal controls showed that castrated men had less platelet thromboxane A₂ (TXA₂) receptors, suggesting that the inhibition of testosterone production may attenuate platelet aggregation responses (Ajayi and Halushka, 2005).

KEY POINTS: CARDIOVASCULAR DISEASE AND TESTOSTERONE

- Increased awareness has been dedicated to the interplay between testosterone and various aspects of CV health. Existing literature suggests that lower levels of endogenous testosterone are associated with higher rates of all-cause and CV mortality.
- Negative correlation has been demonstrated among endogenous testosterone and severity of CAD, congestive failure, and IMT of the vasculature (Oskui et al, 2013).
- Normal testosterone levels play an important role in maintaining CV health.
- Exogenous TT in men with AD improves myocardial ischemia, exercise capacity, and CV risk factors.
- Current available guidelines do not recommend offering AD screening to patients with heart disease, nor do they recommend supplementing TT to improve outcome.
- Results from the Effects of Testosterone Replacement on Atherosclerosis Progressions in Older Men with Low Testosterone Levels trial have the potential to clarify any long-term adverse consequences and the role of exogenous testosterone in the survival of patients with heart disease.

METABOLIC SYNDROME AND UROLOGIC DISEASES

Introduction

Metabolic syndrome (MetS) is a constellation of clinical factors—including obesity, insulin resistance, hypertension (HTN), and abnormal serum lipid concentrations—associated with an increased risk of incident CVD and diabetes mellitus (DM). Other terms applied to this cluster include the obesity dyslipidemia syndrome, syndrome X, and the deadly quartet. The global prevalence and incidence of MetS have increased substantially since the mid-2000s, particularly in the developed world.

Epidemiologic studies have shown strong associations of MetS and its individual components with increased risks of developing a host of benign and malignant urologic diseases. These observations show novel pathways in the etiology of urologic diseases, underscore the links of urologic conditions with overall health, and suggest new interventions for their prevention and treatment.

These data also have promoted the idea of “men's health,” which, broadly speaking, represents the integration of male urologic care with the prevention and treatment of systemic CVD. However, the concept of men's health is an evolving paradigm with no clearly defined clinical parameters. In the absence of robust randomized clinical trial data and evidence-based guidelines, there are currently few, if any, clearly defined roles for the evaluation or treatment of MetS in the practical management of urology patients.

Definition and Epidemiology

Disagreement exists about the exact diagnostic criteria of MetS. At least five separate organizations have issued definitions, all of which contain the same five basic components (Table 23-5).

The National Cholesterol Education Program (Adult Treatment Panel [ATP] III) issued guidelines in 2001, which the American Heart Association/National Heart, Lung, and Blood Institute updated in 2005. This statement, one of the most commonly used, currently defines MetS as a condition in which at least three of the following factors are present:

- **Abdominal obesity**

Defined as a waist circumference greater than or equal to 88 cm in women and greater than or equal to 102 cm in men

TABLE 23-5 Metabolic Syndrome Definitions

	WHO (1998)	EGIR (1999)	AACE (2003)	IDF (2005)	NCEP ATP III (2005 REVISION)
Required component	IR (IGT, IFG, T2DM, or additional evidence of IR)	Hyperinsulinemia* (plasma insulin >75th percentile)	IR (IGT or IFG)	CO (WC)†	None
Criteria	Required component and $\geq 2/5$ below	Required component and $\geq 2/4$ below	Required component and any below, based on clinical judgment	Required component and $\geq 2/4$ below	$\geq 3/5$ below
Obesity	WHR >0.9 (M), >0.85 (F), or BMI >30 kg/m ²	WC ≥ 94 cm (M), ≥ 80 cm (F)	BMI ≥ 25 kg/m ²	—	WC >102 cm (M), >88 cm (F)
Hyperglycemia (mg/dL)	+	+	+	Fasting glucose ≥ 100	Fasting glucose ≥ 100 or Rx
Dyslipidemia (mg/dL)	TG ≥ 150 or HDL-C <35 (M), <39 (F)	TG ≥ 150 or HDL-C <39	TG ≥ 150 and HDL-C <40 (M), <50 (F)	TG ≥ 150 or Rx HDL <40 (M), <50 (F), or Rx	TG ≥ 150 or Rx HDL <40 (M), 50 (F), or Rx
Hypertension (mm Hg)	>140/90	>140/90 or Rx	>130/85	>130 (S), >85 (D) or Rx	>130 (S), >85 (D) or Rx
Other criteria	Microalbuminuria‡	—	Other features of IR§	—	—

*In patients without T2DM.

†Values are population dependent.

‡Urinary albumin excretion of 20 µg/min or albumin-to-creatinine ratio of greater than or equal to 30 mg/g.

§This includes family history of T2DM, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to T2DM.

+, criteria fulfilled with required component; AACE, American Association of Clinical Endocrinologists; BMI, body mass index; CO, central obesity; D, diastolic; EGIR, European Group for the Study of Insulin Resistance; F, female; HDL, high-density lipoprotein; IDF, International Diabetes Foundation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; M, male; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; Rx, pharmacologic intervention for that criterion; S, systolic; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference; WHO, World Health Organization; WHR, waist-to-hip ratio.

- **Elevated blood glucose**
Fasting plasma glucose greater than or equal to 100 mg/dL or drug treatment for elevated blood glucose
- **Elevated blood pressure**
Blood pressure greater than or equal to 130/85 mm Hg or drug treatment for elevated blood pressure
- **Elevated triglycerides**
Serum triglycerides greater than or equal to 150 mg/dL or drug treatment for elevated triglycerides
- **Decreased HDL cholesterol**
Serum HDL cholesterol less than 50 mg/dL in women and less than 40 mg/dL in men or drug treatment for decreased HDL cholesterol

Epidemiology of Metabolic Syndrome

MetS is common, and there is evidence that its prevalence is substantially increasing. Among 8814 U.S. adults participating in the third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994) the overall prevalence of MetS as defined by the 2001 ATP III criteria was 22%. Prevalence increased steadily with age; Mexican-Americans had the highest age-adjusted prevalence (31.9%). The age-adjusted prevalence for men (24.0%) was similar to women (23.4%) (Ford et al, 2002). An updated analysis among 1677 participants from NHANES 1999 to 2000 demonstrated that the overall prevalence had increased to 26.7% ($P = .043$), a trend driven primarily by a 23.5% increase in prevalence among women (Ford et al, 2004).

Similarly, among 3323 adult participants in the Framingham Heart Study, the baseline prevalence of MetS as defined by the 2005 revised ATP III criteria was 26.8% in men and 16.6% in women. After 8 years of follow-up, there was an age-adjusted 56% increase in prevalence among men and a 47% increase among women (Wilson et al, 2005).

Metabolic Syndrome and Clinical Urology

Although an emerging body of knowledge links MetS to the development of urologic diseases, and familiarity with these concepts is important, practical applications of these data to urologic practice are currently limited. At least two clinical issues remain unresolved with respect to MetS and the care of the urology patient.

First, because the management of MetS-related conditions primarily rests with cardiologists, endocrinologists, and primary care physicians, how urologists should approach urologic diseases in the context of MetS is currently unclear. Pathophysiologic links of MetS with urologic diseases, and a small number of clinical trials, imply that treating systemic manifestations of MetS will mitigate their effects on urologic conditions. Yet weight loss, lipid control, and other medical interventions do not typically fall within the purview of urologic practice; and without substantial changes in current care delivery paradigms, it is unlikely that urologists will oversee these therapies independent of other health care providers.

Second, because ED and male LUTS are potential markers for occult CVD (Thompson et al, 2005), some investigators have proposed that urologists routinely screen for CVD. This endeavor, too, is one that urologists do not normally pursue. Moreover, CVD screening is a discipline for which most urologists typically lack formal training, and it is therefore fraught with as-yet-unanswered practical, medical, and medicolegal questions.

Metabolic Syndrome, Benign Prostatic Enlargement, and Male Lower Urinary Tract Symptoms

MetS and its individual components have been associated with increased risks of benign prostatic enlargement (BPE) (formerly known as benign prostatic hyperplasia [BPH]) and

male LUTS. Definitions of BPE in the literature are heterogeneous and include radiographically determined prostate enlargement, decreased urinary flow rates, history of noncancer prostate surgery, physician diagnosis, and urinary symptoms.

LUTS describes a distinct phenotype of a group of disorders affecting the prostate and bladder that share a common clinical manifestation. In its evidenced-based report, the International Consultation on Urological Diseases (2012) used the term "LUTS" to classify the diagnosis, treatment, and study of these conditions. LUTS has also become the preferred term for studying urinary symptoms in populations. Most studies use the IPSS or the American Urological Association Symptom Index (AUASI) to quantify the severity of symptoms; older studies focused on specific symptoms, including nocturia and frequency.

Metabolic Syndrome and Cardiovascular Disease

A systematic review and meta-analysis of 8 studies involving more than 5400 men observed significant direct associations of a diagnosis of MetS with increased prostate volume (Gacci et al, 2015).

Other studies have shown that men with cardiac disease or who are receiving treatment for cardiac disease (and thus have a high likelihood of having at least one component of MetS) are at significantly increased risks of physician-diagnosed BPE and LUTS (De Nunzio et al, 2012).

Correlation between Metabolic Syndrome and Prostatic Diseases

Obesity

Increased adiposity is associated with increased ultrasound- and MRI-determined prostate volume as measured by body weight, BMI, and waist circumference. In the Baltimore Longitudinal Study of Aging (BLSA) cohort, each 1 kg/m² increase in BMI corresponded to a 0.41 mL increase in prostate volume, and obese (BMI ≥35 kg/m²) participants had a 3.5-fold increased risk of prostate enlargement compared to nonobese (BMI <25 kg/m²) participants (*P* trend = .06) (Parsons et al, 2006; Raheem and Parsons, 2014).

Obesity has been associated with increased risks of symptomatic BPE and LUTS in several different populations, including the U.S. Health Professionals Follow-up Study (*n* = 26,000), a study group in China (*n* = 500), a 7-year prospective analysis of the U.S. Prostate Cancer Prevention Trial (PCPT) (*n* = 4770), NHANES III (*n* = 2800), the second Nord-Trøndelag Health Study (HUNT-2) (*n* = 21,700), and the Prostate Study Group of the Austrian Society of Urology (*n* = 1500). Other studies have shown that obesity increases the risks of BPE surgery, initiation of BPE medical therapy, and LUTS (Raheem and Parsons, 2014).

Obesity also attenuates the efficacy of the 5 α -reductase inhibitors (5ARI) finasteride and dutasteride, which decrease serum concentrations of DHT, prevent clinical progression of BPE and LUTS, and prevent incident-symptomatic BPE. An analysis of the PCPT showed that obesity diminished the efficacy of finasteride for preventing symptomatic BPE. Similarly, a secondary analysis of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial concluded that obesity enhanced prostate volume growth and weakened the magnitude of prostate volume reduction by dutasteride. These observations likely highlight a balance between 5ARI-driven prostate volume reduction and obesity-driven prostate volume growth (Parsons, 2010, 2011; Raheem and Parsons, 2014).

Diabetes and Disruptions in Glucose Homeostasis

Higher serum concentrations of insulin-like growth factor-1 and insulin-like growth factor binding protein-3 were consistently associated with increased risks of BPE diagnosis and BPE surgery. DM, increased serum insulin, and elevated fasting plasma glucose have been associated with increased prostate volume and prostate enlargement, clinical diagnosis of BPE, BPE surgery, and LUTS in many different cohorts cumulatively involving tens of

thousands of men (Sarma et al, 2009; Parsons, 2010, 2011; Raheem and Parsons, 2014).

Diabetes and Disruptions in Glucose Homeostasis: The Epidemiology of Diabetes Interventions and Complications Study

The Epidemiology of Diabetes Interventions and Complications (UroEDIC) follow-up study of the Diabetes Control and Complications Trial (DCCT) was a post hoc analysis of 591 men enrolled in a randomized clinical trial comparing intensive to conventional glycemic control in type 1 DM (Van Den Eeden et al, 2009). The aim was to determine whether intensive glycemic control reduces LUTS severity in men with type 1 DM. Intensive treatment consisted of insulin administered three or more times daily by injection or by infusion pump coupled with rigorous monitoring of blood glucose levels. No associations were observed between LUTS, as measured by the AUASI, and intensive glycemic control. However, because these men were younger (mean age 45 years) and had type 1 rather than type 2 DM, these data may not apply to the broader population of older diabetic men with LUTS.

Elevated Blood Pressure

Associations of HTN with BPE and LUTS remain unclear. There have been at least six studies among men with HTN, three of which observed an increased risk of LUTS, one of which noted an increased risk of BPE surgery, and two of which observed no risk.

Elevated Triglycerides and Decreased High-Density Lipoprotein

Studies of BPE and LUTS with serum triglycerides and HDL are also conflicting. There have been at least six studies, including three showing positive and three showing null associations (Hammarsten et al, 1998; Zucchetto et al, 2005; Gupta et al, 2006; Lekili et al, 2006; Nandeeshia et al, 2006; Parsons et al, 2008; Parsons, 2011).

Metabolic Syndrome and Urinary Incontinence

MetS and some of its features, primarily obesity, were linked to a higher risk of urinary incontinence in women.

Metabolic Syndrome

One study of 400 women in Turkey observed an increased, albeit unadjusted, risk of stress urinary incontinence (SUI) in those with MetS compared to those without it in both the pre- and postmenopausal groups (*P* = .001 and *P* < .001, respectively) (Octuntemur et al, 2014).

Obesity

Multiple studies have noted strong associations of obesity with urinary incontinence in women across different populations. In a cross-sectional analysis of Taiwanese women, those who were obese (BMI >27 kg/m²) had a more than threefold (odds ratio [OR] 3.38, 95% CI 1.94 to 6.98, *P* < .001) increased adjusted risk of incontinence (stress, urge, or mixed) compared to those of normal weight (BMI ≤24 kg/m²) (Tsai and Liu, 2009).

In a study of more than 19,000 Chinese women, waist circumference greater than or equal to 80 cm was associated with an increased adjusted risk of SUI (OR 1.38, 95% CI 1.25 to 1.52) (Zhu et al, 2009); in another study by the same investigators that measured BMI, overweight (OR 1.31, 95% CI 1.12 to 1.55) and obese (OR 1.44, 95% CI 1.21 to 1.72) women were more likely to report SUI (Zhu et al, 2008).

In a randomized clinical trial of women with type 2 DM—the Action for Health in Diabetes (Look AHEAD) study—obese (BMI

>35 kg/m²) women were more likely to experience both SUI and overall incontinence (Phelan et al, 2009). In a randomized clinical trial of hormone replacement in postmenopausal women—the Heart and Estrogen/progestin Replacement Study (HERS)—BMI and waist-to-hip ratio were each directly associated with SUI risk; BMI was also associated with mixed incontinence (Brown et al, 1999).

In a survey of 6000 women living in the Pacific Northwest region of the United States, BMI greater than or equal to 30 kg/m² was associated with an increased risk of self-reported urinary incontinence (OR 2.39, 95% CI 1.99 to 2.87) (Melville et al, 2005). Finally, in a cross-sectional analysis of nearly 4000 women in southern California, obesity was associated with SUI in both nondiabetic (OR 2.62, 95% CI 2.09 to 3.30) and diabetic (OR 3.67, 95% CI 2.48 to 5.43) participants (Lawrence et al, 2007).

Obesity: Weight Loss and Urinary Incontinence

SUI in women is one of the few urologic conditions for which level I evidence exists favoring an intervention that, by targeting a feature of MetS, improves the urologic condition. The Program to Reduce Incontinence by Diet and Exercise (PRIDE) trial randomized overweight or obese women who experienced 10 or more incontinence episodes per week to either an intensive 6-month behavioral weight loss intervention or a structured educational program. Women in the behavioral intervention group lost more weight and showed significant improvements in SUI (but not urge incontinence) compared to those in the education group (Subak et al, 2009). Two systematic reviews also concluded that weight loss improves SUI in women (Hunskaar, 2008; Imamura et al, 2010).

Based on these data, the 2012 European Association of Urology Guidelines on Urinary Incontinence concluded that evidence in support of weight loss as an effective lifestyle intervention for incontinence was Grade A, and the recommendations also encouraged “obese women suffering from any urinary incontinence to lose weight (>5%)” (http://www.uroweb.org/gls/pdf/18_Urinary_Incontinence_LR.pdf). The extent to which urologists and other health care providers have adopted this recommendation, and routinely use weight loss as a first-line intervention for incontinence in obese women, is unknown. The American Urological Association guidelines have not as yet addressed the topic of lifestyle interventions and urinary incontinence (www.auanet.org).

Diabetes and Disruptions in Glucose Homeostasis

In the southern California study, nonobese women with type 2 DM were 80% more likely to report SUI (OR 1.81, 95% CI 1.09 to 3.00) (Lawrence et al, 2007). In HERS, DM was associated with a 49% increased risk of urge incontinence (OR 1.49, 95% CI 1.11 to 2.00) and a 32% increased risk of mixed incontinence (OR 1.04, 95% CI 1.11 to 2.00) (Brown et al, 1999).

Metabolic Syndrome and Urinary Stones

MetS has been associated with an increased risk of urinary lithiasis. Putative causal factors include decreased urine pH, hypercalciuria, hyperuricosuria, and hyperoxaluria (Gorbachinsky et al, 2010).

Metabolic Syndrome

Studies have shown robust associations of MetS with an increased prevalence of urinary stones in U.S., European, and Southeast Asian populations. In the U.S. NHANES, the prevalence of self-reported history of kidney stones in an analytic cohort of 14,870 men and women increased substantially with the presence of increased MetS components, with a prevalence of 3%, 7.5%, and 9.8% in participants with 0, 3, and 5 components, respectively. Multivariable adjustment showed further that the presence of greater than or equal to 2 components significantly increased the odds of kidney stones, and that the presence of greater than or equal to 4 components increased the odds approximately twofold (West et al, 2008).

In a study of a screened Korean population (n = 34,895), those with MetS showed a 25% increase in the multivariable adjusted odds (OR 1.25, 95% CI 1.03 to 1.50) in kidney-stone prevalence as detected with computed tomography or ultrasound.

Finally, in an Italian study (n = 2132) of hospitalized patients, MetS was associated with a twofold adjusted risk in the prevalence of ultrasound-detected kidney stones (OR 2.62, 95% CI 1.50 to 4.64) (Rendina et al, 2009).

Obesity

Increased waist circumference and BMI have been independently associated with an increased risk of urinary stones. In an analysis that combined the U.S. Health Professionals Follow-up Study (n = 45,988 men), the Nurses' Health Study I (n = 93,758), and the Nurses' Health Study II (n = 101,877), male participants with a BMI greater than or equal to 30 kg/m² showed a 33% increased risk of incident stone disease compared to those with a BMI of 21 kg/m² to 22.9 kg/m² (relative risk [RR] 1.33, 95% CI 1.08 to 1.63; *P* < .001 for trend). For the same categories of BMI in older and younger women, the increased risks were 90% (RR 1.90, 95% CI 1.61 to 2.25; *P* < .001 for trend) and more than twofold (RR 2.09, 95% CI 1.77 to 2.48; *P* < .001 for trend), respectively. Waist circumference was also positively associated with an increased risk of stones in both men (*P* = .002 for trend) and women (*P* < .001) (Taylor et al, 2005b).

In a study of 95,598 patients in a U.S. health administrative database, obesity was associated with a significantly increased risk of kidney-stone diagnosis at all stratifications comparing obese to nonobese patients. The odds generally increased with increasing BMI. Compared to men with BMI less than 20, those with a BMI of 45.0 to 49.9 had more than a threefold risk of stone diagnosis (OR 3.18, 95% CI 1.61 to 6.29; *P* < .0009) (Semins et al, 2010).

In the aforementioned Korean study, the adjusted odds for kidney stones increased with an increasing quintile of waist circumference (*P* < .001).

Diabetes and Disruptions in Glucose Homeostasis

In another analysis combining more than 200,000 participants in the Health Professionals Follow-up Study and Nurses' Health Studies I and II, DM was associated with an increased adjusted prevalence of stone disease in all groups, with increased risks of 38% (RR 1.38, 95% CI 1.06 to 1.79) in older women, 67% (RR 1.67, 95% CI 1.28 to 2.20) in younger women, and 31% (RR 1.31, 95% CI 1.11 to 1.54) in men.

Similarly, in a prospective analysis of the same cohorts, the adjusted stone incidence was greater in female participants with DM compared to those without: a 29% (1.29, 95% CI 1.05 to 1.58) and a 60% (1.60, 95% CI 1.16 to 2.21) increased risk in older and younger women, respectively. Although there was no association of DM with incident kidney-stone risk in men (RR 0.81, 95% CI 0.59 to 1.09), men with kidney stones at baseline were 49% more likely to develop incident DM (RR 1.49, 95% CI 1.29 to 1.72) than those without kidney stones, as were both older (1.33, 95% CI 1.18 to 1.50) and younger (1.48, 95% CI 1.14 to 1.91) women, respectively.

These investigators speculated that the association of stone disease with incident DM was potentially linked to subclinical insulin resistance (Taylor et al, 2005a).

Elevated Blood Pressure

In the Korean study, participants with HTN showed a 47% increased adjusted risk of kidney stones (1.47, 95% CI 1.25 to 1.71) compared to participants without HTN, and the multivariable-adjusted odds for kidney stones increased with increasing quintile of blood pressure (*P* < .001).

In a study of Italian male factory workers, those with HTN showed an unadjusted increased risk of a history of kidney stones compared to those without HTN (OR 2.11, 95% CI 1.17 to 3.81), which was even higher in men with treated HTN (OR 3.16, 95% CI

1.75 to 5.71). Men with treated HTN also had an increased, if slightly attenuated, age-adjusted kidney-stone risk (OR 2.63, 95% CI 2.23 to 3.10) (Cappuccio et al, 1990).

In a prospective study of the same population followed for 8 years, those with HTN at baseline were approximately twice as likely to develop kidney stones (Cappuccio et al, 1999).

Other studies have shown that nephrolithiasis is a risk factor for the development of HTN, suggesting that these associations are bidirectional (Madore et al, 1998a, 1998b).

Metabolic Syndrome and Erectile Dysfunction

The presence of MetS, each of the five individual components of MetS, and CVD all substantially increase the risk of ED. Several different etiologies are likely involved, including but not necessarily limited to the following: inhibition of nitric oxide synthase pathways; MetS-associated hypogonadism; atherosclerosis-mediated vasculopathy; disruption of autonomic signaling pathways; and promotion of corporal cavernosal fibrosis (Gorbachinsky et al, 2010).

Metabolic Syndrome and Cardiovascular Disease

Multiple studies worldwide have included observations showing a significantly increased prevalence of ED among men with a diagnosis of MetS, including a German health screening project of 2371 men ($P = .01$), a case control analysis of Italian men ($P = .03$), a cohort of 393 Turkish men ($P < .001$), a separate cohort of 268 Turkish men ($P < .001$), and a primary case-based population of 3921 Canadian men (Esposito et al, 2005; Grover et al, 2006; Bal et al, 2007; Heidler et al, 2007).

Moreover, ED appears to be an independent risk factor for incident CVD. In a study of more than 8063 men greater than or equal to age 55 years who were randomized to the placebo arm of the PCPT, those with incident ED experienced a 25% increased adjusted risk of incident CVD (defined as myocardial infarction or surgical treatment of coronary artery disease, angina, cerebrovascular accident, transient ischemic attack, congestive heart failure, or nonfatal cardiac arrhythmia requiring treatment) compared to those without ED (hazard ratio [HR] 1.25, 95% CI 1.02 to 1.53). Men with either incident or prevalent ED experienced a 45% increased adjusted risk (HR 1.45, 95% CI 1.25 to 1.69). The magnitudes of these risks were similar to those observed for current smoking or a family history of myocardial infarction (Thompson et al, 2005).

Similar conclusions were reported in other studies (Montorsi et al, 2006; Inman et al, 2009). ED has also been associated with subclinical atherosclerosis (Chiurlia et al, 2005), endothelial dysfunction (Yavuzgil et al, 2005), and reduced brachial artery vasodilation (Kaiser et al, 2004).

Nevertheless, although these data thus implicate ED as an independent risk factor for clinically significant CVD, the validity of routinely using ED for CVD screening has not been defined (Alhathal and Carrier, 2011; Ewane et al, 2012), and formal guidelines as yet do not exist.

Obesity

Obesity—including central obesity as measured by waist circumference—was one of the first modifiable risk factors linked to ED (Derby et al, 2000; Feldman et al, 2000; Bacon et al, 2003; Fung et al, 2004; Carvalho et al, 2013).

Obesity: Weight Loss, Exercise, and Erectile Dysfunction

Similar to SUI in obese women, level I evidence indicates that a lifestyle intervention aimed at weight loss improves erectile function in obese men. In an Italian randomized clinical trial, 110 obese men (BMI ≥ 30 kg/m²) aged 35 to 55 years with ED as determined by IIEF score and without DM, HTN, or hyperlipidemia were randomized to either an intensive weight loss intervention of caloric reduction and exercise or a control state that provided general

information about healthy food choices and exercise. After 2 years, men in the intervention group had lost more weight, were more physically active, and reported significantly larger increases in IIEF score than those in the control group. Moreover, in multivariate analyses, changes in BMI ($P = .02$) and physical activity ($P = .02$) were independently associated with changes in IIEF score (Esposito et al, 2004).

It is not clear to what extent these data are applied in the clinical management of ED. The American Urological Association Guidelines for the Management of Erectile Dysfunction did not formally address the use of weight loss or other lifestyle interventions in the management of ED (www.auanet.org).

Diabetes and Disruptions in Glucose Homeostasis

Although diabetes is a well-established risk factor for ED (Feldman et al, 1994, 2000; Maiorino et al, 2014), data have also shown links between ED and prediabetic states characteristic of MetS. In a cohort of Argentinian men, ED was associated with an increased risk of insulin resistance, defined as homeostasis model assessment greater than or equal to 3 ($P = .04$) (Knoblovits et al, 2010). Similarly, in a cohort of Chinese patients, ED was also associated with insulin resistance, defined as quantitative insulin sensitivity check index less than or equal to 0.357 (Chen et al, 2013).

Elevated Blood Pressure

Men with HTN are more likely to experience ED than those without HTN (Feldman et al, 1994; Saigal et al, 2006).

Metabolic Syndrome and Male Infertility

MetS and its components are associated with an increased risk of infertility. Several factors may potentially contribute to male infertility in the setting of MetS and its components, including associations of obesity with spermatic DNA damage, low ejaculate volume, and diminished sperm motility, volume, and count; associations of type 2 DM with lower sperm motility, semen volume, and ejaculatory dysfunction; and associations of MetS with hypogonadism (Fig. 23-3) (Gorbachinsky et al, 2010).

Obesity

A systematic review and meta-analysis of BMI and sperm count, which included 21 studies and 13,077 men, reported the conclusion that compared to men of normal weight, overweight (OR 1.28, 95% CI 1.06 to 1.55) and obese (OR 2.04, 95% CI 1.59 to 2.62) men were more likely to have oligozoospermia or azoospermia (Sermondade et al, 2013).

In a Norwegian study of 26,303 planned pregnancies, overweight (BMI 25 to 29.9 kg/m²) and obese (BMI 30 to 34.9 kg/m²) men were 20% (OR 1.20, 95% CI 1.04 to 1.38) and 36% (OR 1.36, 95% CI 1.13 to 1.63) more likely, respectively, to report infertility, defined as a need for up to 12 months to achieve pregnancy or a need for infertility treatment (Nguyen et al, 2007).

Similarly, in a prospective Japanese study of 74 healthy men, those with higher BMI were 20% less likely (HR 0.80, 95% CI 0.67 to 0.95) to father a child during a median follow-up period of 20 months (Ohwaki et al, 2009).

Finally, among an analytic sample of 1329 men enrolled in the U.S. Agricultural Health Study, a 3-unit increase in BMI was associated with a 12% increased adjusted risk (OR 1.12, 95% CI 1.01 to 1.25) of infertility, defined as not conceiving after 12 or more months of unprotected intercourse, regardless of whether or not a pregnancy subsequently occurred (Sallmén et al, 2006).

Diabetes and Disruptions in Glucose Homeostasis

In a cross-sectional study of 857 men in Qatar, those with type 2 DM were more likely to be diagnosed with infertility ($P = .003$).

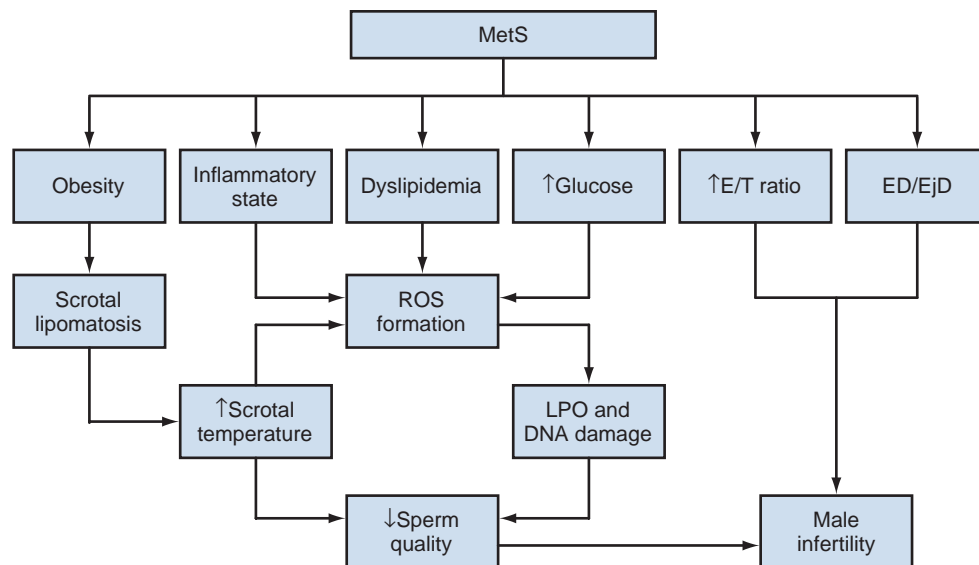


Figure 23-3. Possible mechanisms of male infertility in metabolic syndrome (MetS). DNA, deoxyribonucleic acid; ED/EjD, erectile dysfunction/ejaculatory dysfunction; E/T, estrogen/testosterone; LPO, lipid peroxidation; ROS, reactive oxygen species. (Modified from Gorbachinsky I, Akpinar H, Assimos G. Metabolic syndrome and urologic diseases. *Rev Urol* 2010;12:e157–e180.)

However, in reaching this conclusion, these investigators did not provide specific definitions for infertility nor did they control for potential confounders such as obesity. Indeed, the men with type 2 DM were more likely to be obese ($P = .073$), and in a multivariable-adjusted subgroup analysis of men with type 2 DM, obesity was strongly associated with infertility (OR 3.36, 95% CI 1.81 to 6.23), suggesting that obesity may have confounded the association of DM with infertility in these men (Bener et al, 2009).

Metabolic Syndrome and Urologic Cancers

Associations of MetS with urologic cancers are beginning to emerge, with epidemiologic studies indicating that some aspects of MetS may influence the natural histories of prostate, kidney, and bladder cancer. However, some of these data are conflicting, and not all risk patterns are entirely clear.

Prostate Cancer

The findings for prostate cancer are perhaps the most puzzling, with studies showing MetS associated with both increased and decreased risks of incident prostate cancer. In addition, obesity increases the risk of incident high-grade disease and biochemical recurrence after primary therapy, but decreases the risk of incident low-grade disease. DM decreases the risk of incident disease. Some investigators have speculated that these contradictory observations result from differential effects of different MetS components on the pathogenesis of prostate cancer (Buschemeyer and Freedland, 2007; De Nunzio et al, 2012).

Kidney Cancer

The most extensively studied MetS factor for kidney cancer is obesity, which has been associated with increased risks of disease prevalence and incidence (Chow et al, 2010; Ljungberg et al, 2011; Hakimi et al, 2013). In addition to obesity, at least one study—a cohort analysis of 560,388 men and women from Norway, Austria, and Sweden—indicated an increased risk of incident renal cell carcinoma with increased systolic or diastolic blood pressure, blood glucose, triglycerides, and a composite metabolic score that assessed the combined effects of adiposity, blood pressure, glucose, and triglycerides (Hägström et al, 2013).

Bladder Cancer

Several studies have focused on obesity, DM, and bladder cancer. A meta-analysis of 11 cohort studies noted a modest, but significant, increased risk of bladder cancer incidence and prevalence for obesity (Qin et al, 2013). A meta-analysis combining 36 studies observed an increased risk of bladder cancer among diabetics, with an overall increased risk of 35% compared with nondiabetics (RR 1.35, 95% CI 1.17 to 1.56), although men predominantly drove the risk (Zhu et al, 2013).

KEY POINTS: METABOLIC SYNDROME AND UROLOGIC DISEASES

- MetS is a constellation of clinical factors associated with an increased risk of incident CVD and diabetes.
- At least three of the following factors must be present to render a diagnosis of MetS:
 - Abdominal obesity
 - Elevated blood glucose
 - Elevated blood pressure
 - Elevated serum triglycerides
 - Decreased HDL cholesterol
- Men's health integrates male urologic care with the prevention and treatment of systemic CVD. It is an evolving paradigm with no clearly defined clinical parameters.
- There are no formal guidelines for the evaluation or treatment of MetS in the practical management of urologic conditions.
- MetS and its components are associated with increased risks of the following urologic conditions:
 - BPE and male LUTS
 - Female urinary incontinence
 - Urinary stones
 - ED
 - Male factor infertility
 - High-grade prostate cancer
 - Kidney cancer
 - Bladder cancer
- Weight loss improves continence in obese women with SUI.
- Weight loss improves erectile function in obese men with ED.

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The complete reference list is available online at www.expertconsult.com.

SUGGESTED READINGS

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"METABOLIC SYNDROME AND UROLOGIC DISEASES"

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Epidemiology

History

Physical Examination

Laboratory Evaluation of Male Infertility

Imaging in the Evaluation of Male Infertility

Testis Histopathology

Assisted Reproduction

Diagnoses and Therapies

EPIDEMIOLOGY

The disease of infertility affects approximately 15% of couples, rendering nearly one of six childless ([World Health Organization \[WHO\], 1991](#)). Multiple sources of bias historically have served to distort assessment of the contribution of each gender to infertility, but we can reasonably expect men to contribute equally to women when it comes to whose gametes are faulty ([Tielemans et al, 2002](#)). Hence, accurate evaluation and treatment of the man becomes of great importance in addressing a significant health care issue.

Unfortunately, much of infertility care for men is delivered outside of well-established reimbursement systems, frustrating accurate calculation of epidemiologic metrics ([Meacham et al, 2007](#)). Fortunately, the American Society for Reproductive Medicine's professional group, the Society for Assisted Reproductive Technologies (SART), compels in vitro fertilization (IVF), clinics to report outcomes in a systematic fashion, allowing limited evaluation of the impact of male infertility. However, this assessment is through the lens of women seeking the most evolved technology for female reproductive care and necessarily skews the appraisal of the incidence and prevalence of the male contribution to the disease.

The Urologic Diseases in America (UDA) Project included collection of male reproductive epidemiologic data from a variety of sources, which, albeit sparse, allowed for some limited analysis of the parameters of the disease of male infertility ([Meacham et al, 2007](#)). Considering ambulatory surgery for conditions associated with male infertility, it is unsurprising that men aged 25 to 34 years had higher usage with an average rate of 126 per 100,000 compared with men aged 35 to 44 with 83 per 100,000 and those aged 45 and older at 20 per 100,000 ([Meacham et al, 2007](#)). Thus, younger men represent over half of male infertility cases, and nearly one in 11 cases occurs in men in the fifth decade and older ([Meacham et al, 2007](#)). Considering geographic distribution in the United States, men living in the West had lower use of ambulatory surgery compared with those in the Northeast and Midwest (29 per 100,000, 104 per 100,000 and 72 per 100,000, respectively) ([Meacham et al, 2007](#)).

From an economic perspective, the UDA Project estimated total expenditures for treating primary male infertility at 17 million U.S. dollars (USD) in the year 2000, clearly an underestimate because of the delivered care absent from traditional databases ([Meacham et al, 2007](#)). Because a significant amount of male reproductive medical care delivery involves assisted technologies for the female partner, accounting for this care the assessed total cost is a sizable 18 billion USD ([Meacham et al, 2007](#)).

Complicating epidemiologic assessment is the fact that the primary assay for male infertility, the semen analysis, is a poor predictor with a low receiver operating characteristic (ROC) curve area for all available parameters ([Guzick et al, 2001](#)). Consequently, men with some presence of sperm on semen analysis may be inaccurately judged to be fertile and omitted from accurate accrual in a tabulation of insufficient reproductive potential.

HISTORY

The production and delivery of the male gamete requires high orchestration among endocrine, immune, and neural systems, passage through intricately constructed anatomy, complex orchestrated sequences of gene expression and chromosomal structural events, and the proper embryologic and postnatal development of all systems. It is consequently unsurprising that myriad disparate conditions contribute to male reproductive dysfunction. [Table 24-1](#) enumerates percentages of final diagnoses made in one infertility clinic ([Sigman et al, 2009](#)). As will become clear in this chapter, the percentages in [Table 24-1](#) for each condition are highly variable depending on how the individual conditions are assessed in published studies, and the data contained within the table are an indictment of how poorly male reproductive information is systematically collected. However, the table does demonstrate the wide variety of diagnoses associated with male infertility. To address all potential possibilities, the practitioner must approach inquiring about past history in a methodical fashion. For the sake of efficiency, the patient may complete a form at home or in the waiting area before the physician encounter.

Reproductive health is an unusual aspect of medicine in that two patients are required for a positive outcome. Several consequences arise from this unique circumstance, the first being that a probabilistic approach to diagnosing infertility is necessary. In the best circumstances, with intercourse timed to menstruation and a rigorous calculation of optimal timing including assessment of quality of cervical mucus and measurement of basal body temperature, cumulative pregnancy rates for all tracked subjects in one well-conducted study were 38% at one cycle, 68% at three cycles, 81% at six cycles, and 92% at 12 cycles ([Gnoth et al, 2003](#)). For those who ultimately became pregnant, the cumulative pregnancy rates were 42% at one cycle, 75% at three cycles, 88% at six cycles, and 98% at 12 cycles ([Gnoth et al, 2003](#)). Hence, a couple seeking treatment for infertility a month or two after discontinuing contraceptive measures should be counseled to continue to try for a few more months unless other significant conditions exist. A **minority of**

TABLE 24-1 Distribution of Final Diagnoses from a Male Infertility Clinic

CATEGORY	NUMBER	%
Immunologic	121	2.6%
Idiopathic	1535	32.6%
Varicocele	1253	26.6%
Obstruction	720	15.3%
Normal female factor	503	10.7%
Cryptorchidism	129	2.7%
Ejaculatory failure	95	2.0%
Endocrinologic	70	1.5%
Drug or radiation	64	1.4%
Genetic	56	1.2%
Testicular failure	52	1.1%
Sexual dysfunction	32	0.7%
Pyospermia	25	0.5%
Cancer	20	0.4%
Systemic disease	15	0.3%
Infection	10	0.2%
Torsion	5	0.1%
Ultrastructural	5	0.1%
TOTAL	4710	100.0%

From Sigman M, Lipshultz LI, Howards SS. Office evaluation of the subfertile male. In: Lipshultz LI, Howards SS, Niederberger CS, editors. Infertility in the male. 4th edition. New York: Cambridge University Press; 2009. p. 153–76.

couples who have not conceived after six cycles may still do so, and it is reasonable to initiate an evaluation after 6 months with the understanding that some couples will still conceive shortly afterward. It is useful to communicate to patients the probabilistic nature of reproduction by describing each month of trying as rolling a die or flipping a coin.

An important question to ask is how often the couple is having intercourse. In general, semen parameters peak after 1 or 2 days of abstinence and then decline (Levitas et al, 2005). Often in an attempt to accumulate sperm, men wait long periods before attempting to impregnate their partners. Data suggest that not only is this practice unhelpful, it actually results in poorer sperm quality (Levitas et al, 2005). For an optimal characterization of semen, a man should be instructed to wait 1 or 2 days after an ejaculation to submit a specimen for semen analysis (Levitas et al, 2005). However, for increasing the probability of conception and pregnancy, intercourse every day around the time of ovulation is likely the best strategy (Scarpa et al, 2007).

Another consequence of the fact that two patients are required for a positive outcome in this unique area of medicine is that consideration of the female partner's age is a critical component in judging reproductive potential and planning therapeutic strategies. Whereas the effects of male age on reproductive potential remain to be fully elucidated, advancing male age appears to affect bulk seminal parameters and sperm DNA packaging to only a limited degree, allowing a male to father children well into his later years (Henkel et al, 2005; Hellstrom et al, 2006; Moskovtsev et al, 2006; Schmid et al, 2007; Slotter et al, 2007; Yang et al, 2007; Cocuzza et al, 2008a; Colin et al, 2010; Silva et al, 2012). For the woman, age is a critical predictor of reproductive potential, especially when artificial reproductive technologies are used (te Velde and Pearson, 2002; Balasch and Gratacós, 2012). On average, female fecundity declines precipitously after age 35 (Balasch and Gratacós, 2012). In some geographic regions, female fertility appears to decline more rapidly than others (Zargar et al, 1997). Hence, determining the female partner's age and assessing it in the context of her locale are essential aspects of the reproductive history.

An important general question to ask is whether the man and his partner have previously conceived children, or if each has with other partners, and the age or ages of the offspring. Proven fertility at some point in time demonstrates a functioning reproductive system after puberty, which eliminates a number of concerns regarding congenital issues.

The typical enumeration of systemic diseases and past surgeries in taking the reproductive history reveals a number of conditions associated with reproductive dysfunction. Diabetes mellitus and multiple sclerosis interfere with normal coordinated ejaculatory function, as does spinal cord injury (Vinik et al, 2003; Kafetsoulis et al, 2006; Tepavcevic et al, 2008). Even before spermatotoxic chemotherapy, cancer itself appears to negatively affect spermatogenesis, especially if the cancer is of testicular origin (de Bruin et al, 2009). It is interesting to note that azoospermia may reveal cancer, and the physician considering a man with no sperm on semen analysis should regard testis cancer as a possible cause (Mancini et al, 2007). Surgeries such as transurethral resection of the prostate and minimally invasive therapies for prostatic enlargement are associated with ejaculatory dysfunction (Jaidane et al, 2010; Elshal et al, 2012). As discussed elsewhere in this text, retrograde ejaculation of varying degrees may occur after retroperitoneal lymph node dissection for testis cancer, depending on the type of dissection and the clinical context within which the dissection occurs.

Herniorrhaphy may result in obstruction of the vas deferens (Shin et al, 2005; Hallén et al, 2011, 2012; Tekatli et al, 2012). Mesh in particular appears to incite a dense foreign body inflammatory response that may entrap the vas deferens even if the placement of mesh is not be immediately adjacent to the vas (Maciel et al, 2007; Hallén et al, 2011, 2012; Tekatli et al, 2012). If vasal occlusion is the sole cause of infertility, then both vasa must be occluded, an expectedly infrequent event. However, occlusion of one vasa from herniorrhaphy with contralateral spermatogenic dysfunction of another source may serve as a cause of infertility in the male.

Aside from the typical questions regarding medical and surgical history, answers to a number of questions specifically related to male reproduction may elucidate causes of infertility. If the practitioner is not using a history form, a helpful mnemonic is *TICS*, as if one is ticking off items on a list. *T* stands for toxins, *I* for infectious disease, *C* for childhood history, and *S* for sexual history.

Spermatotoxicity

In the *TICS* mnemonic, *T* is for toxins. A variety of substances interfere with spermatogenesis, mature sperm function, and sperm delivery. Many common medications, prescribed and over the counter, can be associated with male reproductive dysfunction.

Endocrine Modulators

Medications may affect the ratio of estrogen to androgen through a variety of mechanisms, including a molecular similarity to estrogen, increased estrogen synthesis, increased aromatase activity, dissociation of steroids from sex hormone-binding globulin (SHBG), decreased testosterone synthesis, competitive and noncompetitive binding to steroid receptors, decreased synthesis of adrenal steroids, and induction of hyperprolactinemia (Bowman et al, 2012). Some of the more commonly encountered agents warranting inquiry include the antiandrogens bicalutamide, flutamide, and nilutamide; the antihypertensive spironolactone; the antiretroviral protease inhibitors such as indinavir; the nucleoside reverse transcriptase inhibitors such as stavudine; corticosteroids, especially in adolescence; and exogenous estrogen (Bowman et al, 2012).

Although a source of debate, the 5 α -reductase inhibitors finasteride and dutasteride appear to have only limited spermatogenic suppressive effects if at all (Overstreet et al, 1999; Amory et al, 2007). Occasional anecdotal case reports suggest that sperm parameters dramatically improve in an individual man after discontinuation of a 5 α -reductase inhibitor, but the substantial interassay

variability of semen parameters calls into question whether these effects could simply be the result of chance (Chiba et al, 2011).

Primarily through conversion to estradiol by aromatase and consequent inhibition of luteinizing hormone (LH) secretion by the pituitary, exogenous testosterone acts to decrease intratesticular testosterone synthesis and reduce spermatogenesis (Grimes et al, 2012). Agents with androgenic properties similarly diminish sperm production (de Souza and Hallak, 2011). In fact, investigators have studied testosterone and androgenic steroids as potential targets for male contraception since the 1970s (WHO Task Force, 1990; Gu et al, 2009; Grimes et al, 2012; Ilani et al, 2012). In general, these studies have a duration of 2 years or less of application of testosterone or androgenic steroid and demonstrate reversibility with return to sperm in the ejaculate after approximately 4 months or more of discontinuation of the contraceptive agent (WHO Task Force, 1990; Gu et al, 2009; Grimes et al, 2012; Ilani et al, 2012). However, whether and when spermatogenesis returns after longer periods of use is unknown.

Recreational Drugs

Although data are conflicting, most studies suggest that cannabis decreases plasma testosterone in a dose-dependent and duration-dependent manner (Gorzalka et al, 2010). More robust data associate chronic alcohol intake with decreases in androgens and sperm parameters (Villalta et al, 1997; Pasqualotto et al, 2004). Heavy chronic alcohol intake also appears to increase aromatization of testosterone to estradiol (Purohit, 2000). Investigators have observed that more moderate use of alcohol may decrease intracytoplasmic sperm injection (ICSI) outcomes (Braga et al, 2012).

Early studies suggested worsening of bulk seminal parameters with cigarette smoking (Stillman et al, 1986). Although the results of subsequent studies associating smoking and bulk parameters were conflicting, more recent cross-sectional analysis has supported deterioration of seminal parameters in a dose-dependent manner, arguing more strongly that cigarette smoking impairs male reproductive potential (Ramlau-Hansen et al, 2007). Investigators observed that cigarette smoking increased seminal oxidative stress parameters and decreased metrics of sperm DNA quality (Pasqualotto et al, 2008b; Taha et al, 2012). An abnormal ratio of protamines 1 and 2 was observed in smokers with evidence of atypical protamine 2 expression, pointing to DNA packaging as directly compromised by tobacco use (Hammadeh et al, 2010). The negative effects of cigarette smoking on sperm bulk parameters and DNA quality appear to be especially acute in the presence of a clinical varicocele, suggesting the possibility of additive toxicity (Fariello et al, 2012b). Researchers studied effects of an aryl hydrocarbon receptor ligand present in cigarette smoke and found that it induced apoptosis in fetal testis in a manner that was preventable with an aryl hydrocarbon receptor antagonist, providing evidence that maternal smoking may affect the reproductive potential of male offspring (Coutts et al, 2007). Consistent with these laboratory findings, epidemiologic data associated maternal cigarette smoking to smaller testes, lower sperm counts, and alterations in sex hormones in the adult male offspring (Jensen et al, 2005; Ravnborg et al, 2011). It is interesting to note that epidemiologic evidence supports that the secondary sex ratio, the ratio of boys to girls born, is altered in mothers who smoke (Beratis et al, 2008). One explanation is that cigarette smoking alters circulating testosterone concentrations in pregnant women (James, 2002).

Antihypertensives



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Antipsychotics

The most common mechanism of action for antipsychotic drugs is antagonism of dopamine, which causes loss of libido as a side effect in the majority of patients (Stimmel and Gutierrez, 2006). Another proposed reason for diminished libido with use of antipsychotics

is elevation of prolactin levels, which appears to be most acute for risperidone and to a lesser extent olanzapine (Melkersson, 2005). As discussed elsewhere in this text, selective serotonin reuptake inhibitors (SSRIs) are commonly associated with anorgasmia and delayed or absent ejaculation (Clayton and Montejo, 2006; Stimmel and Gutierrez, 2006).

Opioids

Opioid analgesics suppress LH release primarily through hypothalamic-mediated mechanisms and consequently reduce testosterone synthesis (Subirán et al, 2011). Experimental evidence in animals demonstrates endogenous opioid peptides, their precursors, and their receptors in various testis cell types (Subirán et al, 2011). Endogenous opioid peptides are primarily synthesized by Leydig and Sertoli cells and inhibit Sertoli cell function, via autocrine and paracrine mechanisms (Subirán et al, 2011). Hence, not only can opioids induce the hypogonadotropic hypogonadism commonly observed in chronic use, they may also diminish spermatogenesis directly in the testis (Brennan, 2013; Subirán et al, 2011). Evidence suggests that discontinuation of opioid analgesics may be associated with rapid return of androgen, perhaps as early as within 1 month (Brennan, 2013). With the widespread prescribing of opioid analgesics, their use as a cause of hypogonadotropic hypogonadism should be suspected in all such hypoandrogenic men.

Antibiotics

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Cytotoxic Chemotherapeutics

Because chemotherapeutic agents are most effectively applied to suppress a briskly proliferating population of cells, and the pathway of male gamete development primarily involves a rapidly dividing stem cell cohort, it is unsurprising that medical therapies directed toward cancers impair spermatogenesis. Alkylating agents such as the nitrogen mustard cyclophosphamide have been long identified to impair sperm production (Vaisheva et al, 2007). These spermatogenic suppressive effects were noted to be dose and time dependent, with lower doses and shorter durations of therapy leading to reversible dysfunction but ultimate return to male fertility potential, and higher doses and longer durations of therapies resulting in permanently impaired fertility (Vaisheva et al, 2007). Other chemotherapeutic agents commonly used in conjunction with cyclophosphamide to treat non-Hodgkin lymphoma, including doxorubicin, vincristine, and prednisone, have all been reported to impair spermatogenesis as individual agents (Vaisheva et al, 2007). Likewise, investigators reported that cisplatin, etoposide, and bleomycin were associated with diminished sperm parameters in a dose- and time-dependent manner (Gandini et al, 2006).

One concern of both patients and physicians is how much chemotherapy damages the DNA of sperm (Robbins, 1996; Spermon et al, 2006; Stahl et al, 2006; Delbes et al, 2007; O'Flaherty et al, 2008; Tempest et al, 2008; O'Flaherty et al, 2010; Smit et al, 2010). Evidence suggests that sperm DNA damage can be detected at least up to 2 years after chemotherapy, arguing that cryopreservation of sperm before treatment with cytotoxic chemotherapeutic agents is preferable to awaiting the return of sperm after chemotherapy (Tempest et al, 2008). The question is whether sperm is "safe" to use after a discrete amount of time after the induction of chemotherapeutic agents that might mutate cellular DNA in a way that may be translated through the germ line into offspring. An informed answer to that question based on well-conducted clinical trials is not yet available. This lack of knowledge frustrates male reproductive specialists who counsel patients on whether their own biologic material or donor sperm would be the best choice after cytotoxic chemotherapy. Questions about sperm DNA integrity and mutagenicity after chemotherapy serve as a second reason to encourage men undergoing such oncologic therapy to cryopreserve

The relationship between antihypertensive medication and erectile dysfunction is well known and discussed elsewhere in this text. The direct effects of antihypertensives on male reproductive function is less clear. Investigators have proposed that calcium channel blockers impair fertilization by inhibiting expression of mannose-ligand binding receptors and preventing sperm from attaching to the zona pellucida ([Benoff et al, 1994](#)). Although laboratory evidence supports this hypothesis, limited clinical data from IVF cycles question whether calcium channel blockers affect fertilization at all ([Katsoff](#)

[and Check, 1997](#)). It is interesting to note that angiotensin-converting enzyme inhibitors appear to improve sperm motility through a presumptive effect on seminal plasma kinins ([Somlev and Subev, 1998](#)). In a limited controlled clinical trial with cross-over design, 2.5 mg of lisinopril daily increased sperm count, motility, and morphology ([Mbah et al, 2012](#)). If these results are replicated in larger future studies, they suggest an effect beyond that of altering seminal plasma characteristics alone.

Data derived from animal studies indict drugs in each of the major classes of antibiotics as toxic to spermatogenesis or sperm function (Schlegel et al, 1991). However, evidence broadly suggesting male reproductive toxicity for antibiotics in humans is, in general, lacking. Animal studies and limited human data demonstrate testis dysfunction and reduced spermatogenesis with tetracycline, potentially through an oxidative stress mechanism (Kushniruk, 1973; Schlegel et al, 1991; Pasqualotto et al, 2004; Farombi et al, 2008). Because tetracycline binds mature sperm, direct toxicity on sperm function is also possible (Pasqualotto et al, 2004). It is

interesting to note that spermatotoxic effects of tetracycline may be paternally transmitted to male offspring (Zeh et al, 2012). Investigators observed in animals that high doses of nitrofurantoin reduced epididymal sperm density and sperm motility (Chapin et al, 1997). In humans, male reproductive toxicity of nitrofurantoin is unclear in the typical dose range for a discrete duration. Surgeons irrigating vasa with nitrofurantoin solution reported spermatotoxicity in the immediate postoperative period, but this experimental model does not accurately mimic the typical pharmacodynamic distribution of the drug (Albert et al, 1975).

sperm before induction, because cryopreservation presents a well-established means for fertility preservation in the setting of cancer (Anger et al, 2003; Meseguer et al, 2006; Crha et al, 2009). Proper cryopreservation of sperm results in long-term potential for reproductive success, and patients may be assured that should they store sperm in this way, it will be available when they need it (Rofeim and Gilbert, 2005). Although many patients may recover sperm in the ejaculate after cytotoxic chemotherapy, and it is very possible that, after a period as yet to be determined, ejaculated sperm after chemotherapy will be safe for conception, many men do not develop sufficient ejaculated sperm for fertility. These men do use cryopreserved sperm if available to successfully father offspring (Meseguer et al, 2006).

Systemic application of antitumor medication is not necessarily the only form of chemotherapy that may alter fertility potential. Investigators noted in a small series of young men that local instillation of bacille Calmette-Guérin into the bladder for superficial transitional cell carcinoma resulted in a significant decrease in sperm concentration and motility (Raviv et al, 2005).

A special case arises in peripubertal boys undergoing cytotoxic chemotherapy for cancer. Oncologists are often in a rush to apply lifesaving therapy, and parents may be uncomfortable discussing topics such as masturbation for semen collection with their children. However, if oncologic therapy is successful, it is precisely these patients with a potentially long life expectancy who would benefit from sperm cryopreservation as an option for future fertility. Peripubertal boys are capable of producing semen samples suitable for cryopreservation, and it is entirely feasible to obtain an ejaculate suitable for storage (van Casteren et al, 2008; Menon et al, 2009). The urologist need simply be comfortable enough to discuss the advantages of fertility preservation and the methods to achieve it.

Anti-Inflammatory Agents



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Phosphodiesterase V Inhibitors



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Environmental Toxicants



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Thermal Toxicity

For reasons not entirely clear but engendering much speculation, mammals evolved so that the scrotal container of the testis was housed outside the body cavity, keeping its contents at a temperature considerably cooler than that of the internal organs (Setchell, 1998; Thonneau et al, 1998). Scrotal temperature in humans is maintained to be 2° C to 4° C below core body temperature by mechanisms including a counter-current heat exchange between a central set of linear arteries directing blood toward the testis and a plexus of veins surrounding the arteries draining blood back toward the vena cava (Setchell, 1998; Thonneau et al, 1998). Many investigators have exhaustively studied the effects of heat on spermatogenesis in animals, observing depopulation of germ cells, perturbations in the various spermatogenic cell types, and apoptosis within specific cell types (Setchell, 1998; Absalan et al, 2010). Cryptorchidism provides a model by which the effects of heat can be studied on sperm production: increasing testis temperature to that of the abdominal cavity significantly impairs spermatogenesis (Setchell, 1998).

The degree to which scrotal temperature can be raised without affecting male fertility remains an open question. Clothing, physical activity, and body posture such as whether the legs are crossed or not in a sitting position all change scrotal temperature to an incremental degree, but whether that translates to alterations in spermatogenesis is purely speculative at this point (Jung et al, 2005; Miesusset et al, 2007). Researchers observed an increase in scrotal

temperature on the order of a half a degree Celsius with prolonged sitting on heated car seats, and speculated that such an effect may be additive to the intrascrotal temperature rise that occurs when sitting (Jung et al, 2008). One study observed that when a man was naked, mean scrotal temperature was significantly lower on the left than on the right, but when he was clothed, the temperature was significantly higher on the left than on the right (Bengoudifa and Miesusset, 2007). Clothing may thus confer a greater differential increase in left scrotal temperature than right scrotal temperature (Bengoudifa and Miesusset, 2007).

A number of studies associate occupational exposure resulting in a significant increase in intrascrotal temperature with detrimental effects on sperm (Thonneau et al, 1998; De Fleurian et al, 2009). However, other researchers have observed no significant negative effects on sperm in fertile men exposed to high heat at work, and postulated that in the normal state, compensatory mechanisms protect the testis when a prolonged rise in ambient temperature occurs (Momen et al, 2010).

Laptop computers radiate heat, and researchers have studied the effects of these devices on scrotal temperature. In one study, under controlled conditions, having a laptop computer resting on the lap for 1 hour raised the scrotal temperature an average 2.6° C on the left and 2.8° C on the right side (Sheynkin et al, 2005). However, simply sitting without a laptop raised the scrotal temperature an average of 2.1° C (Sheynkin et al, 2005). Whether the extra approximately half-degree Celsius imparts significant damage to spermatogenesis remains an open question. However, investigators have observed that a man sitting with his legs apart and for shorter periods of time experiences less of an increase in scrotal temperature (Sheynkin et al, 2011).

Radiation

Testes directly exposed to ionizing radiation suffer germ cell loss and Leydig cell dysfunction (Clermont, 1972; Castillo et al, 1990; Bahadur and Ralph, 1999; Gandini et al, 2006; Green et al, 2010). In one survey of boys with acute lymphoblastic leukemia who underwent testicular irradiation at 12, 15, and 24 Gray (Gy), all became azoospermic, but those receiving less than 24 Gy had normal testosterone production (Castillo et al, 1990). The investigators observed elevated gonadotropins and noted that this finding indicated the possibility of subclinical Leydig cell damage (Castillo et al, 1990). In a survey of childhood cancer survivors, chances of having future offspring were lessened by radiation doses to the testes of 7.5 Gy and above (Green et al, 2010). The testis need not be directly irradiated for spermatogenic impairment to occur; if the radiation field is proximal to the testis and the dose is sufficient, sperm production may be diminished even if the testis is shielded (Gandini et al, 2006).

With widespread use of radiofrequency devices for telecommunications and wireless networks, investigators have questioned the effects of this band of the electromagnetic spectrum on sperm (Erogul et al, 2006; Agarwal et al, 2008b; Baste et al, 2008; Falzone et al, 2008; Agarwal et al, 2009). Researchers observed negative effects on sperm motility parameters, viability, and reactive oxygen species (ROS) generation after electromagnetic radiation generated by 850- and 900- MHz cell phone transmission systems in vitro (Erogul et al, 2006; Falzone et al, 2008; Agarwal et al, 2009). However, in vitro exposure of sperm to electromagnetic radiation does not account for the distance and material, including biologic tissues, that separate a cell phone transceiver and sperm during common use. To address a more typical usage scenario, investigators have used epidemiologic data to gauge potential in vivo effects. In one questionnaire-based study of Norwegian sailors exposed to high-power electromagnetic fields in a military environment, researchers noted a significant linear relationship between increasing exposure and reported infertility (Baste et al, 2008). It is interesting to note that the offspring's sex ratio at birth also revealed a linear relationship, with a decreasing ratio of boys to girls with higher degrees of exposure to electromagnetic radiation (Baste et al, 2008). Researchers in another epidemiologic study divided men

The agent sulfasalazine prescribed for inflammatory bowel conditions is associated with oligoasthenospermia ([Stein and Hanauer, 2000](#)). If sulfasalazine is substituted with enteric-coated mesalazine, adverse effects on sperm are usually reversible ([Riley et al, 1987](#)). Should oligoasthenospermia be found in a patient prescribed sulfasalazine who has male infertility, substitution with mesalazine should consequently be recommended.

Because colchicine arrests cell division and inhibits cell motility dependent on microtubular function, it was suspected as a spermatotoxic agent ([Haimov-Kochman and Ben-Chetrit, 1998](#)). However, its actual role in male reproductive dysfunction is unclear.

In animal studies, the phosphodiesterase type 5 inhibitor sildenafil was observed to induce a premature acrosome reaction and to impair fertilization and early embryo development ([Glenn et al, 2007, 2009](#)). Sildenafil was also associated with an increase in sperm motility, whereas tadalafil was noted to decrease sperm

motility ([Glenn et al, 2007](#); [Mostafa, 2007](#); [Pomara et al, 2007](#)). Investigators observed vardenafil to increase motility and possibly sperm concentration ([Rago et al, 2012](#)). It is unclear whether these effects have significance in actual clinical use.

Researchers have investigated a large number of potential male reproductive environmental toxicants. A very concerning analysis projected that sperm counts declined between 1938 and 1991 (Carlsen et al, 1992). Whereas commentators noted a number of sources of error and bias in that analysis, the report spawned several investigations into an environmental basis for the putative cause of this phenomenon (Carlsen et al, 1992; Jørgensen et al, 2001; Fisch, 2008). One hypothesis explaining this observation was that an increase in pollutants with estrogenic activity was at fault (Carlsen et al, 1992). If that were the case, it would be expected that naturally occurring estrogenic substances should interfere with spermatogenesis. However, the limited data to date support that phytoestrogens, or plant compounds with estrogenic properties, do not display significant negative effects on male reproductive potential (Fraser et al, 2006; Hamilton-Reeves et al, 2010; Messina, 2010). Hinting at a more nuanced relationship, data correlated urine levels of the potent industrial endocrine disruptor bisphenol A and decreased sperm concentration and total sperm count, implying that environmental estrogens may play a role in hampering male reproductive potential (Li et al, 2011). Congruent with these observations, maternal beef consumption was correlated with decreased sperm concentration in the mothers' adult sons, with estrogenic xenobiotics as a possible causative mechanism (Swan et al, 2007).

Evidence supports insecticide and pesticide exposure as male reproductive toxicants. Investigators observed an association of increased DNA damage with urinary metabolites of the insecticides carbaryl and chlorpyrifos (Meeker et al, 2004). In a model system, researchers exposed human fetal testes to the insecticide and endocrine disruptor dieldrin and noted a variety of Leydig cell

dysfunctional effects, including reduced testosterone secretion and LH receptor and steroid regulatory protein concentrations (Fowler et al, 2007). Suggesting that a man consume locally grown produce to avoid ill effects of pesticides may not be in his best interest. In one study, men consuming locally produced vegetables had lower serum free testosterone, LH, and sperm concentration and normal sperm morphology (Dhooge et al, 2007).

Regarding metal and metalloid exposure, various reports suggest an array of potential male reproductive toxicities. **The heavy metal lead was associated with increased morphologic abnormalities and decreased metrics of DNA quality in sperm** (Hsu et al, 2009). These negative effects of lead on sperm DNA appear to be potentiated by cigarette smoking (Hsu et al, 2009). In one study, molybdenum was associated with a 37% reduction in circulating testosterone levels (Meeker et al, 2010). Environmental and workplace exposure to the metalloid boron was associated with decreased ratio of sperm bearing a Y chromosome to those with an X chromosome (Robbins et al, 2008).

Air pollution may also serve as a male reproductive toxin. Researchers observed an association of particulate air pollution with reduced sperm motility (Hammoud et al, 2010a). Exposure to episodes of high air pollution was also associated with increased sperm DNA fragmentation (Rubes et al, 2005). An animal model demonstrated a decrease in the secondary sex ratio with increased air pollution (Lichtenfels et al, 2007). The authors argued that as litter sizes were similar in exposed and nonexposed animals, the most likely explanation was alteration in the ratio of Y- and X-bearing sperm (Lichtenfels et al, 2007).

into four groups based on cell phone talking time: no use; less than 2 hours per day; 2 to 4 hours per day; and more than 4 hours per day (Agarwal et al, 2008b). The investigators observed that semen analyses in the four groups of increasing cell phone use revealed a linear decrease in sperm count, motility, viability, and normal morphology (Agarwal et al, 2008b).

Infections and Inflammation

In the *TICS* mnemonic, *I* stands for infectious and inflammatory disease leading to male reproductive dysfunction. Infections of the testis, epididymis, prostate, and urethra may lead to male infertility through anatomic and functional means (Kasturi et al, 2009). Common organisms affecting the prostate include *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella*, *Proteus*, and *Enterococcus* species (Kasturi et al, 2009). Typical epididymal organisms include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *E. coli* (Kasturi et al, 2009). Infectious urethral organisms in the context of impaired male reproduction include *N. gonorrhoeae*, *C. trachomatis*, *Mycoplasma* species, and *Trichomonas vaginalis* (Kasturi et al, 2009). Although relatively infrequently encountered, infections of the testis may include the Rubulavirus mumps, Coxsackievirus B, *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, *P. aeruginosa*, and *Klebsiella*, *Staphylococcus*, and *Streptococcus* species (Kasturi et al, 2009). Mumps orchitis is typically so painful and bizarre to the person so affected that even at a very young age, a boy with mumps traveling into his testis is unlikely to forget the event. Infrequently encountered in modern industrialized nations, *Mycobacterium tuberculosis* may affect any reproductive organ and cause scarring of the vas deferens and epididymis (Niederberger, 2011).

Infectious consequences may be anatomic, such as urethral infection leading to stricture, or functional, impairing sperm (Kasturi et al, 2009). Functional alterations may derive from direct effects of the infectious organism on sperm or through induction of immunologic responses in any male reproductive organ, leading to sperm dysfunction (La Vignera et al, 2011). As an example of direct effects, investigators observed that incubating sperm with increasing concentrations of *C. trachomatis* serovar E elementary bodies was associated with degradation of sperm DNA in a time-dependent manner (Satta et al, 2005). Although *in vitro* laboratory experiments have also demonstrated a negative effect of *E. coli* on sperm, the majority of bacteria including *E. coli* have limited or no effects on sperm motility *in vivo* (Diemer et al, 2003; Lackner et al, 2006). Whereas bacteria may coexist with sperm without significant pathologic consequence, sexually transmitted organisms may play a more virulent role (Bezold et al, 2007). The differential effects on sperm of common bacteria and sexually transmitted infectious agents remain far from clear.

Viruses proffer a potentially unique negative direct effect on sperm by integration into a man's genome and vertical transmission through his germ line (La Vignera et al, 2011). Although viral nucleic material appears to be present in the seminal plasma, neither hepatitis C nor human immunodeficiency virus appear to be correlated with a direct negative effect on sperm function (Garrido et al, 2005). Human papillomavirus was associated with impairment of bulk seminal parameters, and *in vitro* treatment of sperm in the laboratory with heparinase III appeared to diminish viral load without significantly altering functional semen parameters (Garolla et al, 2012).

Researchers have studied a wide variety of indirect negative effects of infection on sperm including through leukocytosis, ROSs, interleukins 1, 6, and 8, interferon- γ , macrophage migration inhibitory factor, tumor necrosis factor- α , epididymal macrophages, and dendritic cells (La Vignera et al, 2011). It is logical that any part of the immune system may lose self-recognition of sperm or in the presence of an active infection overwhelm sperm defenses.

Evidence suggests that noninfectious or postinfectious inflammatory processes of the prostate may lead to sperm alterations and male infertility, but the degree to which inflammation alters male reproductive potential beyond what infection imparts remains unknown (Schoor, 2002; Wagenlehner et al, 2008; Ausmees et al,

2013). One putative mechanism by which nonbacterial prostatitis may lead to male infertility is through seminal leukocytosis or pyospermia and the release of ROSs resulting in sperm damage (Schoor, 2002). Other possible means of sperm dysfunction via prostatic inflammation include generation of antisperm antibodies and biochemical alterations in prostatic ions such as zinc, magnesium, calcium, or selenium (Schoor, 2002). Prostatitis may itself damage sperm by inducing ROSs without leukocytosis as an intermediary (Pasqualotto et al, 2000; Schoor, 2002).

Childhood Diseases

The *C* in *TICS* stands for childhood diseases. Maladies of early development include anatomic maldevelopment leading to obstruction or misdirection of the male gamete as it traverses the journey from the testis to the female reproductive tract and disorders that lead to disturbed sperm production or to conditions that damage mature sperm.

Pediatric Surgery

Hydroceles and hernias repaired during childhood are associated with a low but discrete incidence of complications causing vasal obstruction (Lao et al, 2012). In one large series, the rate of testis atrophy after pediatric inguinal hernia was 0.3% (Ein et al, 2006). As hernias repaired during adolescence often include surgical mesh, vasal occlusion as a result of inflammation associated with this material should be considered in an infertile man with such a procedure in his surgical history (Shin et al, 2005; Hallén et al, 2011, 2012; Lao et al, 2012; Tekatli et al, 2012). Other surgical procedures during childhood may also affect future reproductive status. In earlier series, investigators associated scarring from posterior urethral valve ablation with male reproductive dysfunction, but in more recent series, fertility complications with urethral valve surgery are rarely observed (Caione and Nappo, 2011). Older procedures for restoring bladder neck anatomy in children were associated with retrograde ejaculation, but these surgeries are rarely performed today (Sigman et al, 2009).

Testis Torsion

For males 25 years and younger, testis torsion is more than three times more common than testis cancer, with an estimated incidence of 4.5 cases per 100,000 per year (Mansbach et al, 2005; Mellick, 2012). It is interesting to note that contralateral testicular biopsy findings are abnormal in 57% to 88% of males when torsion occurs, which suggests either that unnoticed torsion is damaging the testis before torsion becomes clinically evident or that some underlying pathology is present that manifests both as abnormal scrotal anatomy and as spermatogenic dysfunction (Visser and Heyns, 2003). Approximately half of men with torsion will develop adverse spermatogenic effects (Visser and Heyns, 2003). Overall after torsion, 36% to 39% of men will have sperm concentrations below 20 million/mL (Visser and Heyns, 2003). Because torsion is a traumatic event that disrupts intratesticular architecture including the tight junctions between the Sertoli cells that comprise the blood-testis barrier, it is unsurprising that up to 11% of men will develop antisperm antibodies after torsion (Visser and Heyns, 2003).

Cryptorchidism

As described elsewhere in this text, during the fifth week of gestation, cells destined to become gonads arise in the posterior abdominal wall of the developing embryo (Lewis and Kaplan, 2009). A complex set of highly orchestrated sequenced events occurs, including differentiation of the various testis cell types, organization into what will ultimately become histologic compartments within the testicle, and development of the outer container of the testis and its connection to the distal organs where sperm will be ultimately routed (Lewis and Kaplan, 2009). The most overt anatomic

change is migration of germ cells from the posterior abdominal wall toward the nascent inguinal canals and eventually into the scrotum, resulting in an extra-abdominal localization of the male gonads (Lewis and Kaplan, 2009). This process does not conclude until the third trimester (Lewis and Kaplan, 2009). Researchers have identified multiple regulatory triggers in animal models that direct descent of the testis, including the insulin-like 3 (*INSL3*) gene, the relaxin/insulin-like family peptide receptor 2 (*LGRF8*) gene, antimüllerian hormone (AMH), and members of the *HOX* gene family such as *HOX10* (Hughes and Acerini, 2008; Lewis and Kaplan, 2009). Dysfunction of certain of these genes may result primarily in arresting the mechanical journey of the germ cells, whereas aberrant expression of others may be involved in the processes of both spermatogenesis and descent, causing infertility in ways beyond the thermal toxicity to which undescended testes are subject in later reproductive life. **Androgens are required to induce regression of the cranial suspensory ligament during the fourth month of gestation to allow descent of the testis** (Hughes and Acerini, 2008; Lewis and Kaplan, 2009). Failure of any of these processes impedes descent of the testis into the scrotum, resulting in cryptorchidism, which is widely known to be associated with impaired reproductive potential in later life (Sigman et al, 2009).

Undescended testes occur in up to 4% of newborn boys at term (Barthold and González, 2003). The prevalence of cryptorchid testes decreases to less than 1.5% by 1 year of age (Barthold and González, 2003; Chung and Brock, 2011). Cryptorchidism concordance analysis in twins and siblings indicates a pattern of maternal inheritance, but also suggests that the intrauterine environment plays an important role (Jensen et al, 2010). In most series, the incidence of unilateral cryptorchidism is usually around twice that of bilateral undescended testes (Barthold and González, 2003). The distinction is important, because prognosis is related to whether cryptorchidism is unilateral or bilateral. The reproductive prognosis in later life is similar in men with no history of cryptorchidism and in those with a unilateral undescended testis who underwent orchidopexy as a child, regardless of age at surgery or the size of the undescended testis (Lee et al, 2001; Miller et al, 2001). In one large epidemiologic study of men who had orchidopexy during childhood, successful rates for those attempting paternity with a history of surgically treated unilateral cryptorchidism were 96% compared with a control population, but only 70% for those who had bilateral cryptorchidism (Lee, 2005). In that study, men with bilateral cryptorchidism had levels of the Sertoli cell product and marker of spermatogenesis inhibin B that were nearly one third of the levels in controls, compared with men with unilateral undescended testes repaired in childhood, who had inhibin B levels approximately two thirds that of controls (Lee, 2005). Differences in testosterone concentrations were less than those of inhibin B, arguing that fertility impairment caused by cryptorchidism is less based in Leydig cell steroidogenesis than in dysfunction of the seminiferous epithelium (Lee, 2005). Congruent with the identified differences in inhibin B between men with neither, one, or both testes undescended, researchers observed that sperm density on semen analysis is lower in men who had surgical repair of bilateral cryptorchidism than in those with a unilateral undescended testis, which in turn is lower than in men with normally descended testes (Lee, 1993; Lee and Coughlin, 2001; Moretti et al, 2007). With transmission electron microscopy, investigators also found a greater number of ultrastructural defects in men who had cryptorchidism surgically treated as a child compared with controls, and sperm from men with bilateral undescended testes had more defects than from those with unilateral disease (Moretti et al, 2007).

Conclusive data associating the timing of orchidopexy with reproductive outcomes in later life remain elusive. It is widely recognized that surgical correction of undescended testes after puberty likely has minimal effect on bulk semen analysis parameters (Grasso et al, 1991). However, the age before puberty at which orchidopexy results in optimal effect in reproductive potential has not been definitively established. Regression analysis demonstrated

that serum testosterone concentrations in men were negatively correlated to increasing age at orchidopexy, indicating that Leydig cell function is better spared by earlier age of surgical correction for cryptorchidism (Lee, 2005). Conventional wisdom contended that full germ cell development is arrested and remains quiescent before puberty, implying that orchidopexy performed at any earlier age would have similar outcomes. However, maturational alterations may occur in the hypothalamic, pituitary, and testicular endocrine axis much earlier than adolescence (Hadziselimovic, 2002). Likewise, a transition from the spermatogonial cell types of the fetal germ cell reservoir to that of the adult occurs at a very early age (Hadziselimovic, 2002).

Studies of men undergoing testis sperm extraction with the intent for use in ICSI and who had cryptorchidism and orchidopexy at an earlier time offer some information about the optimal timing of surgical correction of undescended testes, although results are conflicting. In an early study of 30 azoospermic men who had bilateral cryptorchidism, no correlation was found between the age at bilateral orchidopexy and the rate of successful surgical sperm retrieval, which was 73% overall (Negri et al, 2003). In a later study of 42 azoospermic men in whom all but two had bilateral cryptorchidism, no significant differences in surgical sperm retrieval rate were observed comparing men who had orchidopexy up to 10 years of age (61.9%) and men whose testes were brought into the scrotum after 10 years of age (57.1%) (Wiser et al, 2009). However, in an early study of 38 azoospermic men with 30 having had bilateral cryptorchidism, the successful surgical retrieval of sperm in 94% for men who had orchidopexy up to 10 years, 43% for 11 to 20 years, and 44% for older than 20 years, was statistically different at the selected threshold of 10 years ($P < .01$) (Raman and Schlegel, 2003). Congruent with these results, in 79 azoospermic men, 62% having had bilateral orchidopexy and 20.3% having had unilateral orchidopexy (with 17.7% unknown), ROC curve analysis revealed age at orchidopexy to have the second greatest area under the curve (AUC) after testosterone in discriminating successful surgical sperm retrieval (Vernaev et al, 2004). **It consequently appears prudent to recommend orchidopexy before 10 years of age from a reproductive perspective, recognizing that cryptorchid boys who pass that threshold still may have sperm surgically retrieved for use in ICSI later in life.**

Testes that change in position after descent and those that are nearly but not fully descended present special challenges in assessing potential alterations in reproductive potential. Numerous reports clearly document testes as being descended that are later observed to have ascended to varying degrees (Gracia et al, 1997; Barthold and González, 2003). Whereas most appear to ascend to a location distal to the inguinal canal, clinicians have reported ascent as high as to an intra-abdominal position (Gracia et al, 1997; Barthold and González, 2003). Unfortunately, the fertility potential for these patients has not yet been systematically studied, and their reproductive prognosis must be considered unknown at present. For men with retractile testes, limited data suggest that although sperm are often observed in the ejaculate in a man, sperm density is lower than would be expected in a man with normal fertility, approaching that of men with a history of cryptorchidism (Caroppo et al, 2005).

Testicular Dysgenesis Hypothesis

Please see the Expert Consult website for details.



Genetics

What is currently known of the genetic basis of male infertility will be discussed systematically later in this chapter. A good reproductive history should include whether any blood relatives experienced difficulty conceiving offspring. The evaluating physician should also inquire as to the presence in the patient's family of genetic syndromes known to be related to reproductive dysfunction such as cystic fibrosis and other entities detailed in the latter part of this chapter (Anguiano et al, 1992).

Investigators have noted an increase in the incidence of testis cancer and genitourinary abnormalities such as hypospadias and cryptorchidism and a concomitant decrease in seminal bulk parameters in general over time (Carlsen et al, 1992). The actual existence of each effect can be individually debated, and internal covariates are difficult to statistically assess (Akre and Richiardi, 2009; Thorup et al, 2010). However, the fact that sufficient evidence exists to posit the correlation of possible adverse male reproductive epidemiologic trends begs the question of what would be potentially responsible for a common “testicular dysgenesis syndrome” that would lead to multiple manifestations in reproductive dysfunction, cancer, and anatomic birth defects (Skakkebaek et al, 2001). Researchers have reported a paternal concordance, with fathers of boys with hypospadias having an increased probability of decreased sperm density

and of also having hypospadias (Asklund et al, 2007). This observation indicates a potential genetic component to a possible testicular dysgenesis syndrome. Investigators have also correlated environmental estrogenic compounds such as dichlorodiphenyltrichloroethylene, polychlorinated biphenyls, and dibutylphthalate exposure to cryptorchidism, suggesting that environmental toxicants may lead to testicular maldevelopment and potentially other reproductive system impairments (Brucker-Davis et al, 2008). These observations and conjectures must be tempered by the difficulties inherent in assessing male reproductive epidemiologic data (Akre and Richiardi, 2009; Thorup et al, 2010). However, it would seem prudent to continue to investigate whether such a testicular dysgenesis syndrome exists, and if so, what its root causes may be to ameliorate it.

Sexual History

The S in *TICS* is for the sexual history. Although it may seem intuitive that a couple would engage in a sufficient frequency of intercourse when attempting to conceive, lifestyle or proclivities may intervene and interfere. As discussed previously in this chapter, optimum timing for intercourse appears to be daily around the time of ovulation (Scarpa et al, 2007). Some women accurately predict the periovulatory period by symptoms, the so-called mittelschmerz (O'Herlihy et al, 1980). However, many women mistake bodily sensations as ovulation, and symptoms alone cannot reliably be used to assess optimal timing for intercourse. **Because ovulation is detectable by basal body temperature or home hormonal kits after it has occurred, a couple should be encouraged if possible to record the day of ovulation for two or three menstrual cycles, and begin daily intercourse several days before the earliest recorded day.** Such a method is impractical for women with advanced age, as it delays potential reproductive therapies. In the setting of advanced maternal age, more aggressive strategies in collaboration with the female fertility specialist should be considered.

Lubricants commonly used during sexual activity such as K-Y Jelly, Keri Lotion, Astroglide, and others are associated with impaired sperm motility (Sigman et al, 2009). Saliva should also be considered toxic to sperm (Sigman et al, 2009). Researchers incubated a variety of lubricants with sperm and observed that the isotonic preparation Pre-Seed did not result in a significant decrease in sperm motility or chromatin integrity as assessed by an acridine orange-based sperm chromatin structure assay (Agarwal et al, 2008a). In that study, FemGlide, Replens, and Astroglide lubricants resulted in a significant decrease in motility, and FemGlide and K-Y Jelly resulted in a significant decline in sperm chromatin quality (Agarwal et al, 2008a). Laboratory investigators have also provided evidence that use of Pre-Seed during semen collection for analysis does not affect assessment of bulk seminal parameters, sperm membrane functional integrity, levels of ROSs, total antioxidant capacity (TAC), and DNA integrity (Agarwal et al, 2013).

The urologist should inquire about erectile function, because obviously if intercourse is impeded or impossible, sperm will not be deposited successfully in the vaginal vault near the cervical os. The physiology, evaluation, and treatment of erectile dysfunction are discussed extensively elsewhere in this text.

The psychological weight of having a diagnosis of infertility and the stress of the therapy are significant (Schanz et al, 2005; Volgsten et al, 2008). One metric of whether infertility is exerting an adverse psychological effect on the male is frequency of intercourse, which may be altered in up to half of men being treated for infertility and is associated with libido and sexual satisfaction (Ramezanzadeh et al, 2006). A revealing question for a man undergoing male reproductive evaluation is whether the frequency of coitus has changed during the process.

Men and women adapt to the stress of infertility in different ways with different coping mechanisms (Peterson et al, 2006). Men tend to distance themselves and problem solve, whereas women are more likely to seek social support (Peterson et al, 2006). Men and women may consequently interpret their partner's natural adaptive strategy as problematic when in fact it is simply a different means of coping. **A common misconception is that men conflate fertility with masculinity, which in fact happens only infrequently (Fisher et al, 2010).**

Stress itself may impair semen quality, creating a vicious circle for men experiencing infertility and its related psychological distress (Gollenberg et al, 2010). Fortunately, evidence suggests that once men have entered into reproductive medical therapy including IVF with their partners, the diagnosis of male infertility does not disturb psychological well-being and well-adjusted relationships (Holter et al, 2007). The clinician treating male reproductive dysfunction should consider referral to a qualified psychologist to ease the transition from the fearsome diagnosis of infertility to the many effective therapies that are available. If the discussion is couched in terms of problem solving, many men are very willing to engage in psychological counseling.

KEY POINTS: MALE REPRODUCTIVE HISTORY

- The most important determinant of a couple's reproductive potential is maternal age.
- Many conditions may affect male reproductive function. The examining physician may organize the male reproductive history into toxicants, infectious processes, childhood conditions, and sexual history.

PHYSICAL EXAMINATION

General Physical Examination

Because male infertility may be related to many systemic and genetic conditions, the general physical examination often yields clues as to the source of reproductive dysfunction. Male and female faces are morphologically distinct, and female facial characteristics alert the examining physician to potential sex chromosomal and androgenization disorders (Veleminská et al, 2012). Alterations in secondary sexual characteristics such as facial, truncal, axillary, and pubic hair suggest inadequate androgenization (Sigman et al, 2009). If androgenization is significantly impaired through puberty, a high-pitched voice may result (Sokol, 2009). An overabundance of endogenous or therapeutically induced estradiol may lead to gynecomastia (Sigman et al, 2009). If testosterone production during puberty is so low that closure of the epiphyses of the long bones of the extremities fails to occur, typical body morphology will include an arm span 5 cm longer than the patient's height and a lower body segment as defined by pubic-to-heel distance more than 5 cm longer than the upper body segment as measured from the crown to the pubis (Sokol, 2009).

With the lack of virilization at the anticipated time of puberty, Klinefelter syndrome is classically detailed in textbooks as resulting in gynecomastia, a eunuchoid appearance, and tall height for age (Oates and Lamb, 2009). However, it should be noted that many men with a 47,XXY karyotype do not display the typical body morphology and habitus so described.

Obesity should be noted because substantial evidence associates it with male reproductive dysfunction. **It is well established that obese men have elevated estradiol as a result of peripheral conversion from testosterone by an overabundance of adipose cells that contain the enzyme aromatase (Hammoud et al, 2006; Aggerholm et al, 2008; Chavarro et al, 2010; Hammoud et al, 2010b; Hofny et al, 2010).** A TTTA aromatase polymorphism appears to be particularly related to increasing estradiol with increasing body mass, and those with the polymorphism are most likely to experience decreasing estradiol when they lose weight (Hammoud et al, 2010b). **Serum testosterone is also well known to be lower in obese men (Hammoud et al, 2006).** Four main causes are hypothesized: negative feedback of estradiol on the hypothalamic-pituitary axis resulting in decreased LH release; increased leptin; insulin resistance; and sleep apnea (Hammoud et al, 2006; Hofny et al, 2010). It should be noted that although some studies correlate increasing obesity with decreased LH, others do not, and the mechanism of reduced testosterone in obese men may be unrelated to gonadotropins (Hammoud et al, 2006; Aggerholm et al, 2008; Pauli et al, 2008; Hofny et al, 2010; Paasch et al, 2010; Teerds et al, 2011).

SHBG is typically reduced in obese men, in general ascribed to increased circulating insulin in obesity (Hammoud et al, 2006; 2008; Pauli et al, 2008; Teerds et al, 2011). The consequence of lowered SHBG is that bioavailable testosterone may be greater than what total testosterone predicts, and an obese man may be more androgenized than expected on superficial laboratory assessment.

Researchers observed an inverse correlation between serum inhibin B concentrations and body mass index (BMI) in men but not prepubertal boys (Winters et al, 2006). The association between decreasing inhibin B and increasing obesity in men potentially indicates decreased Sertoli cell number, and that the relationship is

not seen before puberty suggests that obesity exerts its negative effect on Sertoli cells during puberty (Winters et al, 2006).

Although these kinds of studies have associated obesity with altered male hormones that consequently result in infertility through an endocrine effect, researchers have also implicated increased BMI with decreased paternity in investigations that suggest that the adverse effects of obesity on male reproduction may be independent of the endocrine system (Pauli et al, 2008; Stewart et al, 2009). Some evidence suggests that only extreme obesity negatively affects male fertility through an endocrine pathway (Chavarro et al, 2010). Other published studies have observed a relationship only between sperm motility and BMI, but not an association with sperm concentration, suggesting that obesity may primarily interfere with epididymal function that imparts motility to sperm (Martini et al, 2010). Some studies indicate that obesity may degrade sperm DNA integrity and mitochondrial activity, whether through the final common pathway of the endocrine system or another hormonal-independent mechanism (Fariello, et al, 2012a). Although this evidence suggests that the endocrine system is a probable target for impairment of reproductive effects in the male, it is likely that the full elucidation of the means by which excess adiposity exerts its effects on male reproduction is beyond such a singular process.

Male Reproductive Physical Examination

Fortunately for the examining physician, much of the male reproductive system is located outside of the body cavity, where it can be easily palpated. Because much of the male reproductive physical examination is most effectively performed with the patient standing, it is important to put the patient both at ease and before a low examining table or chair, as some men will develop syncope during palpation of the scrotum. Asking a man about his work often serves to distract him from the male genital examination (Niederberger, 2011).

If the partner of the patient is present during the history, she may relate valuable information. However, the patient may also feel reluctant to divulge specific facts of reproductive significance before his partner, and the physical examination presents an opportunity to tactfully ask her to leave the room to allow the man time to discuss issues with his physician privately (Niederberger, 2011).

Examining the Scrotum

Visual observation of the scrotum may be revealing. One or both sides may be hypoplastic, indicating an absence of the scrotal contents since birth (Niederberger, 2011). One side may be substantially larger than the other, suggesting a reactive hydrocele or tumor. A varicocele may be so large as to be visible. Finally, proximity to the thighs in a large or obese male may indicate an insufficient difference between intrascrotal and body temperature.

Examining the Testis and Epididymis

The examiner first palpates the testis and epididymis through the scrotum, noting any abnormalities. The epididymis is typically difficult to appreciate; if it is easily palpated, it is likely engorged, which suggests obstruction. Segmentation of the epididymis is also worthwhile to note: If the portion near the upper pole is easy to discern but the lower pole is not, wolffian ductal development may have been incomplete (Lewis and Kaplan, 2009).

Testis size is well established to correlate with sperm production and is consequently an important assessment in the physical examination of the infertile male (Takahara et al, 1987; Bujan et al, 1989). The size of the testis may be assessed by calipers often referred to as the *Seager orchidometer* (Fig. 24-1) (Niederberger, 2011). The long axis of the testis is gently grasped between the jaws of the calipers, and a measurement of 4.6 cm or less is associated with spermatogenic impairment (Schoor et al, 2001). A second method to ascertain testis size is to compare the examiner's palpation findings with a string of ellipsoids of increasing size with marked



Figure 24-1. Caliper (Seager) orchidometer.



Figure 24-2. Prader orchidometer. (Courtesy Erler Zimmer GmbH and Co. KG, Germany.)

volumes as shown in Figure 24-2 (Niederberger, 2011). A volume of 20 mL or less is considered low (Sigman et al, 2009). Finally, testis volume may be more directly measured by ultrasonography of the scrotum (Sakamoto et al, 2007a, 2007b; Abdulwahed et al, 2013). However, it is unclear the degree to which the incremental increase in accuracy that testis ultrasound adds to that obtained by the caliper or Prader orchidometer translates to clinically useful information (Sakamoto et al, 2007a).

Examining the Spermatic Cord

Palpation of the spermatic cord yields two features of reproductive significance: whether the vas deferens is palpable, and whether a varicocele is present. The vas is a firm cordlike structure differentiated from vasculature within the spermatic cord by the compressibility of the vessels. Because the veins within the cord may be mistaken for the vas on manual examination of the upper scrotum, absence of the vas can be a difficult physical sign to identify. For the clinician with experience in vasectomy, one useful method of identifying whether the structure is absent is to search for the vas as if performing the first step of a vasectomy, bringing it to the surface of the skin. If what is presumed to be the vas disappears from the examiner's fingers three times, the clinician can be

confident that the vas is absent. This pearl is referred to as *Meacham's maxim* after Randall Meacham, who described the technique (Niederberger, 2011).

Unilateral absence of the vas deferens suggests the possibility of a complete lack of wolffian ductal development on that side, including renal agenesis. In such patients, a renal ultrasound may be considered to investigate whether the patient has a solitary kidney (Niederberger, 2011). If both vasa are absent, the man has a high likelihood of a cystic fibrosis gene mutation (Anguiano et al, 1992). In such patients, laboratory genetic assessment of the cystic fibrosis transmembrane conductance regulator gene sequence is indicated (Lyon and Miller, 2003; Bombieri et al, 2011). Because investigators have noted renal agenesis in 11% of men with congenital bilateral absence of the vas deferens (CBAVD), renal ultrasound may also be considered to investigate whether a solitary kidney is present (Schlegel et al, 1996).

In addition to assessing the presence, absence, and continuity of the vas deferens, the clinician examining the upper scrotum views its surface to determine if a plexus of varicose veins arising from the spermatic cord is visible and then gently palpates to identify whether a varicocele may be felt. Although sporadic reports before 1955 described cases in which surgery on varicocele yielded evidence of improved reproductive potential, W. Selby Tulloch was the first to systematically report a series of cases of infertile men undergoing high ligation of a varicocele and subsequent improvement in sperm counts (Tulloch, 1955). Lawrence Dubin and Richard Amelar studied varicocele and its treatment in larger series and broadly educated urologic surgeons on its pathology and the merits of therapy (Dubin and Amelar, 1975; Nagler and Grotas, 2009).

The varicocele is the most commonly encountered nonductal surgically addressable pathologic entity potentially affecting male reproductive potential (Nagler and Grotas, 2009). In general, incidence estimates in the general population range from one fifth to one sixth, whereas most studies suggest the incidence of varicocele in infertile males to be between one third and one half (Pryor and Howards, 1987; Fretz and Sandlow, 2002; Nagler and Grotas, 2009). That not all men with varicocele are infertile remains one of the most perplexing problems in male reproductive medicine today; the choice of therapy for a particular man with a varicocele is challenging.

Clinical studies of varicocele have used multiple grading systems to describe the severity of the entity, further complicating the task of the evaluating physician (Nagler and Grotas, 2009; Williams, 2011). Most systems use three or four grades, usually with the first being a varicocele that cannot be palpated but can be detected only by radiographic evaluation, typically ultrasound (Nagler and Grotas, 2009; Williams, 2011). Some systems differentiate varicoceles that can be palpated only during the Valsalva maneuver (Nagler and Grotas, 2009). Because the majority of studies concur that treatment of subclinical varicoceles does not significantly improve male reproductive potential, a sensible grading system would include these entities, which are best left untreated, to differentiate them from those that ought to be addressed with therapy (Niederberger, 2011). Likewise, the difference between varicoceles that can be seen and those that can only be felt is clinically obvious, and a reasonable grading system would differentiate the two (Niederberger, 2011). As the clinical significance of those varicoceles that can only be appreciated with the Valsalva maneuver is uncertain, a rational grading system would not include this feature as a major discriminator. Hence, the modern evidence-based clinical grading system for varicocele includes grade I, which is not palpable or visible and can only be detected by radiographic evaluation such as Doppler ultrasound; grade II, which is palpable but not visible; and grade III, a varicocele that is so large as to be visible by the examining physician through the rugae of the scrotum (Niederberger, 2011).

Examining the Phallus

In the typical setting of intercourse, semen must be deposited proximal to the cervical os for optimal chance of reproduction. Consequently, any abnormality of the phallus that may prevent placement

of the semen at that locale should be noted by the examining physician. These abnormalities include phimosis, meatal displacement in hypospadias or epispadias, and significant penile curvature (Niederberger, 2011).

Examining the Prostate and Seminal Vesicles

In general, examination of the prostate and seminal vesicles does not add a significant amount of information to the evaluation of the infertile male, and if the patient is sufficiently apprehensive about digital rectal examination, it may be prudently omitted. Should rectal examination be performed, the clinician notes the size of the prostate, as it may be aplastic or hypoplastic in cases of congenital malformation or significant hypogonadism (Niederberger, 2011). The seminal vesicles cannot typically be palpated; if they are palpable, it is an abnormal finding suggesting engorgement and possible ejaculatory ductal obstruction (Niederberger, 2011).

KEY POINTS: MALE REPRODUCTIVE PHYSICAL EXAMINATION

- Obesity impairs male reproductive potential by endocrine-dependent and endocrine-independent mechanisms.
- Testis size directly reflects spermatogenic mass.
- Unilateral absence of the vas deferens suggests a wolffian ductal anomaly; bilateral absence is associated with mutations in the gene responsible for cystic fibrosis. In both, renal agenesis may result.

LABORATORY EVALUATION OF MALE INFERTILITY

Like other aspects of urology, much can be learned about the condition of male infertility from blood tests, in this case, primarily of the endocrine system. Also similar to other urologic fields, genomic assessment of male reproductive function is a burgeoning area of research and increasing clinical usefulness. However, the laboratory inquiry into male infertility also includes a way of directly appraising the severity of the condition by observing the male gametes in the semen analysis. These three general laboratory assessments comprise the laboratory evaluation of male infertility: the endocrine evaluation, analysis of semen, and genomic assessment.

Endocrine Evaluation

As spermatogenesis is highly dependent on intratesticular testosterone synthesis, it is unsurprising that hypogonadism is associated with male infertility. Testosterone levels in men vary widely, and most investigators use either 280 ng/dL or 300 ng/dL as a threshold for adequate androgenization in a man (Petak et al, 2002; Sokol, 2009). Approximately 45% of men with azoospermia caused by spermatogenic dysfunction are observed to have testosterone less than 300 ng/dL, and serum testosterone below that threshold is found in 43% of men with oligospermia and 35% of men in an infertility clinic with sperm density greater than the threshold of 20 million/mL specified in the fourth edition of the WHO laboratory manual for the examination and processing of human semen (Sussman et al, 2008). Because 90% of men with sperm density of 22 million/mL or less will not have conceived with their partners within 1 year, many with sperm density less than that value are expected to have pathologic reproductive dysfunction, and consequently in approximately one third it is likely related to endocrinopathy (WHO, 2010). Androgenization should therefore be assessed by laboratory evaluation in all men presenting for infertility including those in whom sperm density is greater than 20 million/mL. An upper limit of sperm density has not been established above which endocrine dysfunction is unlikely to be discovered; clinicians may reasonably use the 50th percentile value

in the fourth edition of the WHO manual of 73 million/mL with time to pregnancy within 1 year as a guide, suggesting that a full endocrine evaluation is not necessary (WHO, 2010).

Testosterone circulates in three main forms: tightly bound to SHBG; loosely bound to protein, primarily albumin; and unbound or free (Matsumoto and Bremner, 2011). The forms inducing cellular activity are free and loosely bound, together comprising what is referred to as *bioavailable testosterone* (Matsumoto and Bremner, 2011). In the healthy man, 30% to 44% of circulating testosterone is bound to SHBG, 54% to 68% is loosely bound to albumin, and 0.5% to 3.0% is unbound (Matsumoto and Bremner, 2011). Using a threshold of 300 ng/dL for testosterone and the lower limit of 54.5% for percent bioavailable testosterone, a reasonable lower limit for the concentration of bioavailable testosterone would consequently be 164 ng/dL.

SHBG is altered in a variety of medical conditions and states such as obesity and aging (Box 24-1) (Bhasin et al, 2010). The clinician cannot rely on total testosterone to gauge bioavailable testosterone, and because obtaining an accurate laboratory assessment of free testosterone can be difficult, a practical method of determining bioavailable testosterone is to calculate it from total testosterone, SHBG, and albumin (Vermeulen et al, 1999). Internet-based and smartphone calculators are available; as of this writing, the International Society for the Study of the Aging Male hosts a calculator at www.issam.ch/freetesto.htm, and a calculator for iOS devices may be found at <http://itunes.apple.com/us/app/bioavailable-testosterone/id308770722>.

In young, healthy men, total serum testosterone exhibits a circadian rhythm, with a peak in the early morning and trough levels in the late afternoon (Plymate et al, 1989). SHBG displays an opposing circadian rhythm in men of all ages, with a peak in the late afternoon and a trough in the early morning (Plymate et al, 1989). Consequently, bioavailable testosterone demonstrates a marked circadian rhythm in young, healthy men, with a peak in the early morning and trough in the late afternoon (Plymate et al, 1989). In older men, total testosterone and its circadian rhythm are attenuated, and the circadian rhythm and concentration of bioavailable testosterone are substantially diminished (Plymate et al, 1989). To standardize sampling of total and bioavailable testosterone in all men, assays are typically performed in the morning, although the necessity of such timing is more important in younger men.

In the case of hypoandrogenism, a pituitary or testicular source is identified by assessing LH (Niederberger, 2011). If testicular Leydig cell dysfunction is the cause, LH is elevated to varying

degrees (Niederberger, 2011). In the case of pituitary dysfunction, LH is decreased (Niederberger, 2011). The clinician may assess LH after total or bioavailable testosterone returns with a low value, or, for efficiency, both assays may be performed simultaneously. Because testosterone and LH are released in a pulsatile fashion, borderline results may be investigated further by obtaining three morning samples at 20-minute intervals (Sokol, 2009). Historically, clinicians pooled these samples for a single measure, but three separate assay results may be determined and arithmetically averaged.

The Sertoli cell products inhibin B and activin regulate pituitary follicle-stimulating hormone (FSH) by respectively inhibiting and stimulating its release (Caroppo, 2011). Because the Sertoli cells are regulated by robust paracrine interaction with germ cells, with depopulation of the latter, inhibin levels decrease and FSH consequently increases (Niederberger, 2011). Clinicians have consequently used FSH as an indirect assessment of germ cell mass, with higher concentrations of FSH indicating increasing germ cell dysfunction and depopulation (Niederberger, 2011). Combined with testis size as measured by caliper orchidometer, FSH is an accurate predictor of whether azoospermia is a result of obstruction or spermatogenic dysfunction: 96% of men with obstructive azoospermia had FSH assay values of 7.6 IU/L or less and testis long axis greater than 4.6 cm, whereas 89% of men with azoospermia caused by spermatogenic dysfunction had FSH values greater than 7.6 IU/L and testis long axis 4.6 cm or less (Schoor et al, 2001). In the case of male reproductive dysfunction in which sperm is present in the ejaculate, the odds ratio of abnormal sperm concentration increased markedly at an FSH value of 4.5 IU/L, suggesting another threshold that the clinician may use to assess male reproductive dysfunction (Gordetsky et al, 2011).

Assays of inhibin B are clinically available, and investigators have investigated whether measuring inhibin B directly is a more accurate assessment of spermatogenic function than the indirect assay of FSH (Kumanov et al, 2006; Muttukrishna et al, 2007; van Beek et al, 2007; Myers et al, 2009; Jørgensen et al, 2010; Grunewald et al, 2013). In general, these studies include analyses of correlation between inhibin B or FSH and sperm parameters or testis parameters measured by physical examination. Many studies observe greater accuracy with measuring inhibin B than with FSH in these correlations, and some data suggest that lower ranges of inhibin B allow improved correlation (Kumanov et al, 2006; van Beek et al, 2007; Myers et al, 2009; Grunewald et al, 2013). However, the incremental improvement in accuracy is typically small, and inhibin and FSH both provide clinically useful markers of spermatogenic function (Myers et al, 2009). The clinician may consequently use either marker based on cost and availability.

Like inhibin B, AMH is a member of the transforming growth factor- β (TGF- β) family synthesized by Sertoli cells, and investigators have studied its use as an assay in assessing spermatogenic function (Fénelich et al, 1999; Fujisawa et al, 2002; Muttukrishna et al, 2007). Although results from pilot studies are encouraging, reported data sets remain small, and use of AMH is considered primarily experimental.

Aromatase enzymes convert cholesterol-based molecules such as testosterone to estrogens and are found in many organ systems including testis, adipose tissue, liver, and brain (Kim et al, 2013). Estradiol is consequently measurable in men, and investigators have proposed that elevated estradiol adversely affects male reproductive potential (Raman and Schlegel, 2002; Gregoriou et al, 2012; Schlegel, 2012). A ratio of total testosterone to estradiol below 10:1 is suggested to indicate reproductive dysfunction (Raman and Schlegel, 2002; Gregoriou et al, 2012; Schlegel, 2012).

The pituitary hormone prolactin is known to inhibit gonadotropins and suppress testosterone production in men, and it may be elevated in pituitary hyperplasia, adenoma, or tumors (Sokol, 2009). Clinically significant disease of the pituitary is typically associated with symptoms such as visual field changes, headache, or erectile dysfunction (Niederberger, 2011). Prolactin assay should be considered when these symptoms accompany male infertility, especially if total or bioavailable testosterone is low. However, the

BOX 24-1 Conditions Associated with Altered Sex Hormone-Binding Globulin (SHBG) Concentrations

CONDITIONS ASSOCIATED WITH DECREASED SHBG

Obesity
Nephrotic syndrome
Hypothyroidism
Glucocorticoids, progestins, and androgenic steroid therapy
Acromegaly
Diabetes mellitus

CONDITIONS ASSOCIATED WITH INCREASED SHBG

Aging
Hepatic cirrhosis and hepatitis
Hyperthyroidism
Anticonvulsant therapy
Estrogen therapy
Human immunodeficiency virus disease

Modified from Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536–59.

incidence of clinically significant prolactinoma is very low in infertile males, with only four detected in 1035 men in one large screening study, and prolactin need not be routinely included in the initial endocrine evaluation of an infertile man (Sigman and Jarow, 1997). Prolactin is commonly a labile assay; should it be found to be elevated, repetition of the test is warranted (Niederberger, 2011). Assessment of other pituitary hormones such as thyroid-stimulating hormone, adrenocorticotrophic hormone, or growth hormone is indicated if a space-occupying pituitary lesion is suspected or found on imaging examination (Sokol, 2009). Likewise, should signs of other endocrine disease, such as exophthalmos, striations, moon facies, or facial bony changes, be observed, thyroid hormone, cortisol, or growth hormone assays may be entertained. However, they need not be included in the initial screening evaluation of an infertile man. **A reasonable initial laboratory screen to assess an endocrine basis for male reproductive dysfunction should be performed in the morning and includes total testosterone, SHBG, and albumin to calculate bioavailable testosterone; LH and FSH to gauge pituitary function; and estradiol to evaluate aromatization.**

Men with a history of congenital adrenal hyperplasia (CAH) may develop testicular adrenal rest tumors and infertility later in life (Pierre et al, 2012; Aycan et al, 2013). In these patients, serum 17-hydroxyprogesterone, $\Delta 4$ -androstenedione, renin, and testosterone can be used to assess response to therapy (Pierre et al, 2012).

Evaluation of Semen

Reproduction is a probabilistic system: The more viable sperm that begin their journey in the female reproductive tract, the greater the chance that one will penetrate and fertilize the ovum. In this sense, there is only one definitive result of a semen analysis, and that is the condition in which no sperm are present; only in that case can a man be absolutely considered sterile.

In 1951, the physiologist John MacLeod published the first stringent statistical assessment comparing what could be observed under the light microscope in semen from men who had successfully impregnated their partners versus semen of men who had not done so (MacLeod, 1951). MacLeod applied a descriptive statistical approach, computing cumulative probability histograms for each observable parameter and determining quartiles for each of the two groups of men (MacLeod, 1951). Basic parameters studied included the concentration of sperm, their movement, and their shape (MacLeod, 1951). What is immediately evident from MacLeod's seminal publication is that the histograms for sperm parameters from fertile and infertile men are largely overlapping, meaning that a substantial range of values for any parameter do not discriminate between male fertility and infertility (MacLeod, 1951). MacLeod sensibly approached this problem by considering lower sperm parameter values to be more appropriate thresholds for suggesting male infertility; however, values above these lower thresholds do

not confirm fertility (MacLeod, 1951). This proved to be very difficult to grasp in clinical implementation, and the field of reproductive medicine is rife with the assumption that should a parameter be above a threshold—for example, sperm concentration greater than 20 million/mL—then the man is established to be fertile, which is incorrect. The only conclusion that may be drawn from such a comparison is that should the parameter be lower than the threshold, the man is likely to be infertile; the converse is not necessarily true.

One general approach to the problem of an assay for which the values representing disease and health are overly coincident is to establish two thresholds, beyond which health or disease is probable, and within which no predictive statement can be made. In one study to develop two such sets of thresholds for semen analysis, investigators applied the computational method classification and regression tree (CART) analysis to semen analyses from fertile men and those whose wives were undergoing intrauterine insemination (IUI) and for whom female infertility had been largely excluded (Guzick et al, 2001). As an example, for sperm concentration, 13.5 million/mL was found to be the lower parameter, and 48.0 million/mL was identified as the upper parameter (Guzick et al, 2001). Using these parameters, the clinician would counsel a man whose sperm concentration was less than 13.5 million/mL that he was likely infertile, and one with a concentration greater than 48.0 million/mL that he was likely fertile. Should the man's concentration be greater than 13.5 million/mL and less than 48.0 million/mL, no assessment of fertility potential could be accurately made.

Bulk Semen Parameters and the World Health Organization Criteria

Building on the original work by MacLeod and deriving consensus from a group of experts, WHO established criteria for semen analysis parameters in its laboratory manual for the examination and processing of human semen (Cooper et al, 2010; WHO, 2010; Niederberger, 2011; Murray et al, 2012). For the first four editions of the manual, criteria were set both by expert panel and survey data, and included such thresholds as sperm density of 20 million/mL, which would be judged as a reasonable number below which a man should be considered likely infertile (Cooper et al, 2010; WHO, 2010; Niederberger, 2011; Murray et al, 2012). The problems with such a set of criteria are manifestly evident: fertile men may be found below the thresholds and infertile men above.

The fifth edition of the WHO laboratory manual departed from the previous four by emphasizing the statistical description of the population of men on which it was based (Cooper et al, 2010; WHO, 2010). Values for percentiles of semen parameters from men whose partners became pregnant within 1 year of discontinuation of contraceptives are tabulated, allowing the clinician to compare an infertile patient's results with a fertile cohort (Table 24-2)

TABLE 24-2 Bulk Semen Analysis Parameter Percentiles

PERCENTILE	2.5	95% CI	5	95% CI	10	25	50	75	90	95	97.5
Semen volume (mL)	1.2	(1.0-1.3)	1.5	(1.4-1.7)	2	2.7	3.7	4.8	6	6.8	7
Sperm concentration (million/mL)	9	(8-11)	15	(12-16)	22	41	73	116	169	213	259
Total number (million/ejaculate)	23	(18-29)	39	(33-46)	69	142	255	422	647	802	928
Total motility (%)	34	(33-37)	40	(38-42)	45	53	61	69	75	78	81
Progressive motility (%)	28	(25-29)	32	(31-34)	39	47	55	62	69	72	75
Normal forms (%)	3	(2.0-3.0)	4	(3.0-4.0)	5.5	9	15	24.5	36	44	48
Vitality (%)	53	(48-56)	58	(55-63)	64	72	79	84	88	91	92

CI, confidence interval.

Modified from Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010;16(3):231-45.

(Cooper et al, 2010; WHO, 2010). Two limitations of such an approach are clear: First, the data are derived from a fertile population and not an infertile one, and second, the clinician cannot rely on descriptive statistics to predict outcomes. Nonetheless, the manual's tables offer the physician useful comparative information that would be otherwise unavailable in evaluating and treating infertile men.

Somewhat confusingly, the fifth edition of the manual published alongside the full percentile table a separate list of the 5th percentiles and their 95% confidence intervals (CIs) (Cooper et al, 2010; WHO, 2010). For example, the 5th percentile value for sperm density is 15 million/mL with a 95% CI range of 12 to 16 million/mL (Cooper et al, 2010; WHO, 2010). Although the authors of the companion publication to the manual very clearly describe the problems inherent in using thresholds derived from descriptive statistics of a fertile male population, the enumeration of the 5th percentile values has appeared to spur their use as new thresholds. The best use of the tables in the fifth edition of the manual would be for the urologist to present to a man alongside the patient's own parameters as a reference for an ultimately fertile population, but clinical reality dictates that both physicians and patients are interested in defining what represents infertility to consider when medical or surgical therapy is appropriately invoked. Communicating the 5th percentile value as one that likely represents infertility and the 50th percentile as typical for a man conceiving with his wife within 1 year is reasonable practice for clinical urology. As an example, for sperm density, that would be lower than 15 million/mL suggesting infertility, and 73 million/mL as typical (Cooper et al, 2010; WHO, 2010).

To complicate matters, semen analysis parameters are highly variable, and investigators typically recommend a minimum of two analyses separated by 2 to 3 weeks for assessment (Centola, 2011). Although data exist to the contrary, most investigators observe a linear decline in bulk seminal parameters with increasing days of abstinence, and variability in abstinence may be responsible for variability in semen analysis results (Levitas et al, 2005; Keel, 2006; Elzanaty, 2008). Consequently, the physician evaluating a man for his reproductive potential should ensure that the duration of abstinence before an ejaculated specimen is as constant as possible. Historically, men were instructed to wait 2 to 5 days after an ejaculation to submit a sample for semen analysis (WHO, 2010; Centola, 2011). More recent studies suggest that a single day of abstinence is optimal for assessing bulk seminal parameters (Levitas et al, 2005; Elzanaty, 2008).

A nontoxic wide-mouthed glass or plastic cup is used to collect the semen sample (WHO, 2010). In the case of religious or cultural stipulations that do not allow collection by masturbation, a special nontoxic condom may be used (WHO, 2010).

The physical and chemical characteristics of a semen sample are first assessed before microscopic examination. Ejaculated semen first forms a coagulum, and the sample is allowed to liquefy for 30 minutes before evaluation (Centola, 2011). Viscosity is assessed by aspiration into a pipette and measuring the length of the drop that forms, which should be no longer than 2 cm (WHO, 2010; Centola, 2011). The sample is then inspected visually for coloration. A normal ejaculate is white or light gray; a yellow or green hue may indicate infection, jaundice, or vitamins or medication; brown is often observed in spinal cord-injured men; and red suggests blood (WHO, 2010; Centola, 2011).

Historically, semen pH was reported, but its measurement is no longer recommended because environmental conditions may alter it, and the original intent of using pH to gauge whether obstruction exists is hampered by the vast difference in size between a hydrogen ion and sperm head (Centola, 2011). For bulk seminal parameters describing microscopic features, a specialized slide with a compartment with defined volume such as a hemocytometer or Makler counting chamber is typically used (Centola, 2011).

Semen Volume. Often unreported by laboratories infrequently performing semen analysis, semen volume is of significant clinical importance (Niederberger, 2011). Conditions causing seminal hypovolemia include anatomic factors, such as ejaculatory ductal

obstruction or hypoplasia of the prostate and seminal vesicles as may occur in severe androgen deficiency or CBAVD; functional issues, such as in retrograde ejaculation; neurologic conditions, such as in spinal cord injury, diabetes mellitus, or multiple sclerosis; and pharmacologic factors, which may occur in men prescribed α -adrenergic blocking agents such as tamsulosin (Sigman et al, 2009; Niederberger, 2011). The 5th percentile for volume according to the fifth edition of the WHO laboratory manual is 1.5 mL with a 95% CI of 1.4 to 1.7 mL, and the 2.5th percentile is 1.2 mL with a 95% CI of 1.0 to 1.3 mL (WHO, 2010). For practical purposes, the most frequently used threshold value for volume is 1.0 mL to initiate evaluation for seminal hypovolemia (Niederberger, 2011).

Aspermia, *dry ejaculate*, and *anejaculation* refer to the condition in which no fluid is discharged from the urethra during male orgasm (Sigman et al, 2009). It is caused by the same conditions associated with seminal hypovolemia (Sigman et al, 2009; Niederberger, 2011). If aspermia or seminal hypovolemia is observed, a postejaculatory urinalysis is performed to identify retrograde ejaculation, and some form of investigation such as transrectal ultrasonography (TRUS) is conducted to evaluate whether ejaculatory ductal obstruction may be present (Sigman et al, 2009; Niederberger, 2011). For postejaculatory urinalysis, the patient is instructed to void before ejaculation for a semen analysis and then to urinate after collection of the semen sample into separate containers (Sigman et al, 2009). The urine is reconstituted by centrifugation and the number of sperm in the pellet is counted (Sigman et al, 2009). A small number of sperm in the urine is of little consequence if the number of sperm in the antegrade sample is large. In general, if the number of sperm in the urine nears or exceeds that in the antegrade specimen, retrograde ejaculation is considered clinically significant (Sigman et al, 2009).

Seminal hypervolemia with an ejaculate volume exceeding 5 mL is a rare condition (Sigman et al, 2009). It is proposed to interfere with male reproduction by diluting sperm (Sigman et al, 2009). If a too-large seminal volume is of concern, the sperm may be reconstituted by processing into a smaller volume, and IUI performed (Sigman et al, 2009; Centola, 2011).

Sperm Density. Sperm density or concentration is typically recorded in millions per milliliter. The term *oligospermia* refers to low sperm density, and *cryptozoospermia* denotes sperm so few as to be difficult to reliably measure (Niederberger, 2011). The 5th percentile for sperm density according to the fifth edition of the WHO laboratory manual is 15 million/mL with a 95% CI of 12 to 16 million/mL, and the 50th percentile is 73 million/mL (Cooper et al, 2010; WHO, 2010). Previous editions of the WHO laboratory manual included a threshold for sperm density of 20 million/mL, and it was common in the past for practitioners to define oligospermia as lower than that value. With the descriptive tabulation of sperm parameters in the fifth edition of the WHO manual, oligospermia is more appropriately defined in a clinical context: A man with a single semen sample demonstrating 10 million/mL who has had no difficulty impregnating his wife may not be oligospermic, whereas one with small testes, an elevated FSH, and densities on several semen analyses ranging from 20 to 25 million/mL may be reasonably considered oligospermic. As previously written, a large CART analysis revealed 13.5 million/mL to be a lower parameter for sperm density and 48.0 million/mL to be an upper parameter (Guzick et al, 2001). In CART analysis, the ROC AUC for sperm density was 0.60, indicating relatively poor discriminating ability between fertile and subfertile subgroups (Guzick et al, 2001).

Total sperm count or number is calculated by multiplying semen volume and sperm density and is typically recorded in millions (Niederberger, 2011). The 5th percentile for total sperm number according to the fifth edition of the WHO laboratory manual is 39 million with a 95% CI of 33 to 46 million, and the 50th percentile is 255 million (Cooper et al, 2010; WHO, 2010).

Sperm Motility. Sperm motility is assessed optimally within 30 minutes of liquefaction and refers to a percentage of sperm observed with defined motion (WHO, 2010). Low motility is termed *asthenospermia* (Niederberger, 2011). The fifth edition of the WHO manual

classifies motility into three categories—progressive, nonprogressive, and immotility—replacing the four categories of older grading systems (a through d, where a and b indicated “rapid” and “slow” progressive motility) (WHO, 2010). *Progressive motility* is defined as sperm “moving actively, either linearly or in a large circle, regardless of speed,” and nonprogressive motility as “all other patterns of motility with an absence of progression” (WHO, 2010). The 5th percentile for progressive motility according to the fifth edition of the WHO laboratory manual is 32% with a 95% CI of 31% to 34%, and the 50th percentile is 55% (Cooper et al, 2010; WHO, 2010). **CART analysis revealed 32% to be a lower parameter for sperm motility and 63% to be an upper parameter (Guzick et al, 2001).** In CART analysis, the ROC AUC for sperm motility was 0.59, revealing low discriminating ability for this parameter (Guzick et al, 2001).

Sperm Morphology. Human sperm is highly pleomorphic with more bizarrely shaped sperm in any man’s ejaculate than those with configuration anticipated to successfully penetrate and fertilize an ovum (Niederberger, 2011). An overabundance of abnormal forms is termed *teratozoospermia* (Niederberger, 2011). Earlier editions of the WHO manual described fairly generous criteria as characterizing an acceptably shaped sperm, and even then, the majority of sperm were classified as misshapen in a normal semen analysis (Niederberger, 2011). **In an attempt to improve the predictive capability of sperm morphology, Kruger proposed a grading system in which several aspects of sperm were assessed, and if any one was out of range, the sperm was counted as abnormal (Kruger et al, 1987; van der Merwe et al, 2005).** This system is variably referred to as “strict” morphology, “Kruger” morphology, and “Tygerberg” morphology, and as a result of the more stringent criteria defining a normal sperm, thresholds in the range of 5% typically characterize a normal ejaculate (van der Merwe et al, 2005). The fifth edition of the WHO manual adopted strict morphology as its assessment of sperm shape (WHO, 2010). The 5th percentile for normal morphologic forms according to the fifth edition is 4% with a 95% CI of 3.0% to 4.0%, and the 50th percentile is 15% (Cooper et al, 2010; WHO, 2010). CART analysis revealed 9% to be a lower parameter for strict morphology and 12% to be an upper parameter (Guzick et al, 2001). In CART analysis, the ROC AUC for sperm motility was 0.66, as with the bulk parameters of density and motility revealing low discriminating capacity (Guzick et al, 2001).

The clinical predictive value of strict morphology is questionable. Although limited data suggest that the parameter may be associated with embryo formation, the majority of studies support that strict morphology is unassociated with sperm nuclear integrity and that it does not predict natural conception or IVF outcomes (Keegan et al, 2007; Dubey et al, 2008; Avendaño et al, 2009; Dayal et al, 2010; French et al, 2010; Sripathi et al, 2010; Morbeck et al, 2011). To complicate matters, evidence suggests that as laboratory technicians have learned to inspect each sperm more closely for eccentricities of shape, an increasing number of men are described as having lower percentages of sperm with normal morphology (Morbeck et al, 2011). The practical implication of this trend is that currently many men who seek evaluation are identified as having isolated teratozoospermia and are likely to have adequate reproductive potential.

Conditions exist in which specific biologic defects are associated with the majority of sperm. For example, should the acrosome fail to form, the preponderance of sperm will have small, round heads, a disorder referred to as *globozoospermia* (WHO, 2010). During spermiogenesis, if the basal plate does not attach to the nucleus opposite the acrosome, the heads are absorbed (WHO, 2010). This defect results in only tails observed and is termed *pinhead sperm* (WHO, 2010). Undoubtedly, these relatively uncommon specific morphologic conditions affect male reproductive potential.

Please see the Expert Consult website for further details.

Sperm Vitality. Vitality refers to the portion of sperm that are metabolically active living cells (WHO, 2010; Niederberger, 2011). *Necrozoospermia* is the condition describing a large number of nonliving sperm (Niederberger, 2011). **The assessment of whether or not sperm are living is essential if near or total asthenospermia is**

observed to discriminate whether the lack of motility is a result of cell death or of dysfunction of molecular processes involved in sperm motion (Niederberger, 2011; WHO, 2010). If the test is purely diagnostic and the sperm are not to be used in IVF, it is performed by staining with eosin Y and with or without nigrosin (WHO, 2010; Niederberger, 2011). A metabolically active sperm excludes the eosin Y dye, whereas a dead one cannot and absorbs the pigment (WHO, 2010; Niederberger, 2011). Nigrosin darkens the background and increases the contrast between it and the live sperm heads, allowing them to be identified more easily (WHO, 2010). The 5th percentile for sperm vitality according to the fifth edition of the WHO laboratory manual is 58% with a 95% CI of 55% to 63%, and the 50th percentile is 79% (Cooper et al, 2010; WHO, 2010).

A method of assessing sperm vitality in a nondestructive manner amenable to subsequent use in IVF is the hypo-osmotic swelling (HOS) test (Jeyendran et al, 1984). When incubated in hypo-osmotic medium, the tails of live sperm with unimpaired membranes swell within 5 minutes, allowing for identification of viable gametes (WHO, 2010).

Please see the Expert Consult website for further details.



Secondary Semen Assays

The haploid male gamete expresses different surface antigens than the remainder of diploid cells in the male body and consequently must be protected from the immune system by tight junctions between Sertoli cells (Walsh and Turek, 2009). Should this “blood-testis barrier” be disrupted, sperm exposed to the immune system may incite an immune response of varying severity involving secretory and humoral immunoglobulins and affecting multiple regions of the surface of the sperm cell (Walsh and Turek, 2009). **Conditions observed to be associated with antisperm antibody formation include vasectomy, testis trauma, orchitis, cryptorchidism, testis cancer, and varicocele (Walsh and Turek, 2009).**

Leukocytes may be harmful to sperm, with evidence suggesting that production of ROSs may be the destructive mechanism (Pasqualotto et al, 2000; Agarwal et al, 2006; Lackner et al, 2006; Desai et al, 2009; Domes et al, 2012; Aktan et al, 2013). Moderate levels of leukocytes in semen may be physiologic, and may even be beneficial for sperm function (Barraud-Lange et al, 2011).

Use of an assay for antisperm antibodies should be entertained if agglutination of sperm is observed or if sperm motility is decreased, especially if conditions associated with antisperm antibodies exist (Walsh and Turek, 2009; WHO, 2010; Brannigan, 2011; Niederberger, 2011). Two types of assays for antisperm antibodies are available; those that test for immunoglobulins on the surface of sperm are referred to as *direct* tests, and those that measure antibodies in fluid such as seminal plasma or serum are *indirect* assays (WHO, 2010; Brannigan, 2011). **Direct assays are preferred for clinical relevance, because antibodies in plasma or serum may not correlate to sperm surface binding (Walsh and Turek, 2009; Brannigan, 2011; Niederberger, 2011).** Owing to its large size, immunoglobulin M (IgM) is present in very low quantities if at all in semen, and consequently IgG and IgA are the primary assay targets (Walsh and Turek, 2009; Brannigan, 2011; Niederberger, 2011).

Two direct assays are available, the mixed antiglobulin reaction (MAR) test and the immunobead assay (WHO, 2010; Brannigan, 2011). The MAR test uses latex beads coated with an anti-IgG or anti-IgA “bridging” antibody incubated with sperm, whereas the direct immunobead test involves polyacrylamide beads coated with rabbit immunoglobulins against human IgG or IgA (WHO, 2010; Brannigan, 2011). **In both cases, after incubation the technician identifies the presence of antisperm antibodies by association of moving particles proximal to motile sperm, and thus some amount of sperm motion is essential for these assays; complete asthenospermia renders direct antisperm antibody assays unable to be performed (WHO, 2010; Brannigan, 2011; Niederberger, 2011).** The direct immunobead test is more laborious than the MAR assay but yields more precise information (WHO, 2010).



In an attempt to correlate sperm nuclear ultrastructure with reproductive outcomes, investigators examined sperm with an inverted light microscope outfitted with high-power Nomarski differential interference contrast optics, allowing for magnification of the field over 6000× (Bartoov et al, 2001). This technique was termed *motile sperm organelle morphology examination* (MSOME) (Bartoov et al, 2001). The theoretic advantage of MSOME is that it is a nondestructive method of assessing sperm nuclear morphology, and a sperm chosen by this method of high magnification visual inspection could be subsequently used in IVF techniques (Bartoov et al, 2001).

Early use of MSOME appeared to lead to improved pregnancy rates in IVF by screening those sperm with an overabundance of vacuoles in the sperm nucleus (Bartoov et al, 2001, 2003; Berkovitz et al, 2006). However, later studies questioned whether sperm so chosen actually led to improved IVF outcomes (Perdrix and Rives, 2013). In fact, one study argued that sperm nuclear vacuoles are a physiologic part of a normal sperm maturational process (Tanaka et al, 2012). At this point, MSOME is best considered primarily an investigational rather than a clinical tool.

Computer-Assisted Semen Analysis. Assessment of bulk seminal parameters is complex and laborious (Rothmann and Reese, 2009; WHO, 2010). The quality control mechanisms required for an accurate and reliable semen analysis performed by a capable laboratory technician are exacting and involved (Rothmann and Reese, 2009; WHO, 2010). Unfortunately, not all laboratories that offer semen analyses adhere to rigid quality assurance methods (Rothmann and Reese, 2009). It is consequently incumbent on the urologist to ensure that the semen analysis laboratory providing results uses sufficient quality standards to allow meaningful interpretation.

With the complexity associated with providing an accurate and reliable semen analysis, several manufacturers provide systems that automate the process of assessing sperm parameters such as motility, density, and morphology (Rothmann and Reese, 2009; WHO, 2010). Along with image motion analysis, these computer-assisted

semen analysis (CASA) systems also provide a variety of additional parametric assessments for moving sperm, including curvilinear velocity, rectilinear velocity, average path velocity, amplitude of lateral head displacement, linearity, wobble, straightness, beat-cross frequency, and mean angular displacement (WHO, 2010). Unfortunately, although CASA systems can rival or even exceed the precision and reproducibility of bulk semen analyses performed manually by a technician, they are still plagued by the same methodologic challenges such as optics and sample preparation, and their performance notably degrades at low sperm concentrations (Rothmann and Reese, 2009; WHO, 2010). Consequently, most high-quality laboratories combine some or much manual assistance if CASA is used (Rothmann and Reese, 2009). The highly specialized parametric assessments of motion such as curvilinear velocity are at this time primarily research rather than clinical tools (Rothmann and Reese, 2009).

The WHO laboratory manual loosely specifies 50% as a threshold for both the MAR and immunobead tests and notes that reference values are not established, leaving the interpretation of these assays to the physician considering the degree and localization of antisperm antibody binding and the clinical context (WHO, 2010). Sperm head binding is considered to be of greater clinical significance than tail binding (Niederberger, 2011).

Pyospermia Assays. Under phase contrast microscopy without staining, leukocytes and immature germ cells are indistinguishable (Brannigan, 2011). Consequently, when faced with a report indicating an abundance of cells resembling leukocytes observed only with phase contrast microscopy, the evaluating physician cannot accurately diagnose pyospermia (Brannigan, 2011). Fortunately, laboratory testing to evaluate the presence of leukocytes is not difficult. The Papanicolaou stain may be used to differentiate leukocytes from immature germ cells based on nuclear morphology (WHO, 2010). **The current consensus threshold for leukocytes according to the WHO laboratory manual is 1 million/mL (WHO, 2010).** Should pyospermia be excluded, the patient can be reassured that the presence of immature germ cells is common and not of pathologic significance (Brannigan, 2011).

Tertiary and Investigational Sperm Assays

The limitations of bulk seminal parameters spawned myriad additional means to assess sperm structure and function in hopes of better diagnosing male reproductive dysfunction, applying therapies, and predicting outcomes in techniques such as IVF. Most are promising, but few are even close to proven. Many provide insight into the biologic processes involved in reproduction, but similarly designed studies report conflicting results when these assays are applied to clinical problems. Emphasizing a lack of consensus on how they are to be used clinically, the fifth edition of the WHO manual details these assays in its “research procedures” chapter (WHO, 2010). The prudent practitioner will continue to follow the literature as it evolves and use these assays clinically should a clear consensus emerge regarding usefulness.

Sperm DNA Integrity Assays. Sperm DNA molecular and spatial organization is highly specific to cells of the male gamete. Sperm DNA is six times more compact than in somatic cells, and it is arranged with protamines to form tightly linear side-by-side sheets (Ward and Coffey, 1991). Investigators have hypothesized that fragmentation or disturbances in DNA arrangement lead to aberrations in sperm function, fertilization, implantation, and pregnancy. Conflicting data and opinions abound in testing this hypothesis, indicating that our understanding of the role of sperm DNA quaternary structure is limited, the assays available are imperfect, or both. In general, there are two types of test methods that assess DNA structural integrity (Sakkas and Alvarez, 2010). In one, DNA fragmentation is measured directly (Sakkas and Alvarez, 2010). In general, this type of assessment is preferred by andrology laboratories at present because it appears to more effectively correlate with clinical outcomes (Sakkas and Alvarez, 2010). In the other, DNA is denatured before analysis (Sakkas and Alvarez, 2010). In a comprehensive meta-analysis, higher rates of miscarriage were associated with an overall approximately double risk ratio with increasing sperm DNA fragmentation, but different assays yielded markedly different risk strengths (Robinson et al, 2012).

TUNEL Assay. The terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay represents a general method in widespread use in molecular biology to assess DNA fragmentation by labeling the terminal end of nucleic acid strands with a fluorescent marker, and it was adopted in the andrology laboratory with various modifications to detect sperm head DNA fragmentation (Gavrieli et al, 1992; Mitchell et al, 2011). Figure 24-3 details one method. In panels A and B, a fluorescent stain that binds to DNA regions rich in adenine and thymine, 4',6-diamidino-2-phenylindole (DAPI), identifies sperm heads containing packed DNA. Panel A is a brightfield image that allows sperm tails to be seen, confirming that the area under scrutiny is a sperm. Panel B is a fluorescent image, allowing comparison with TUNEL-positive sperm, which are

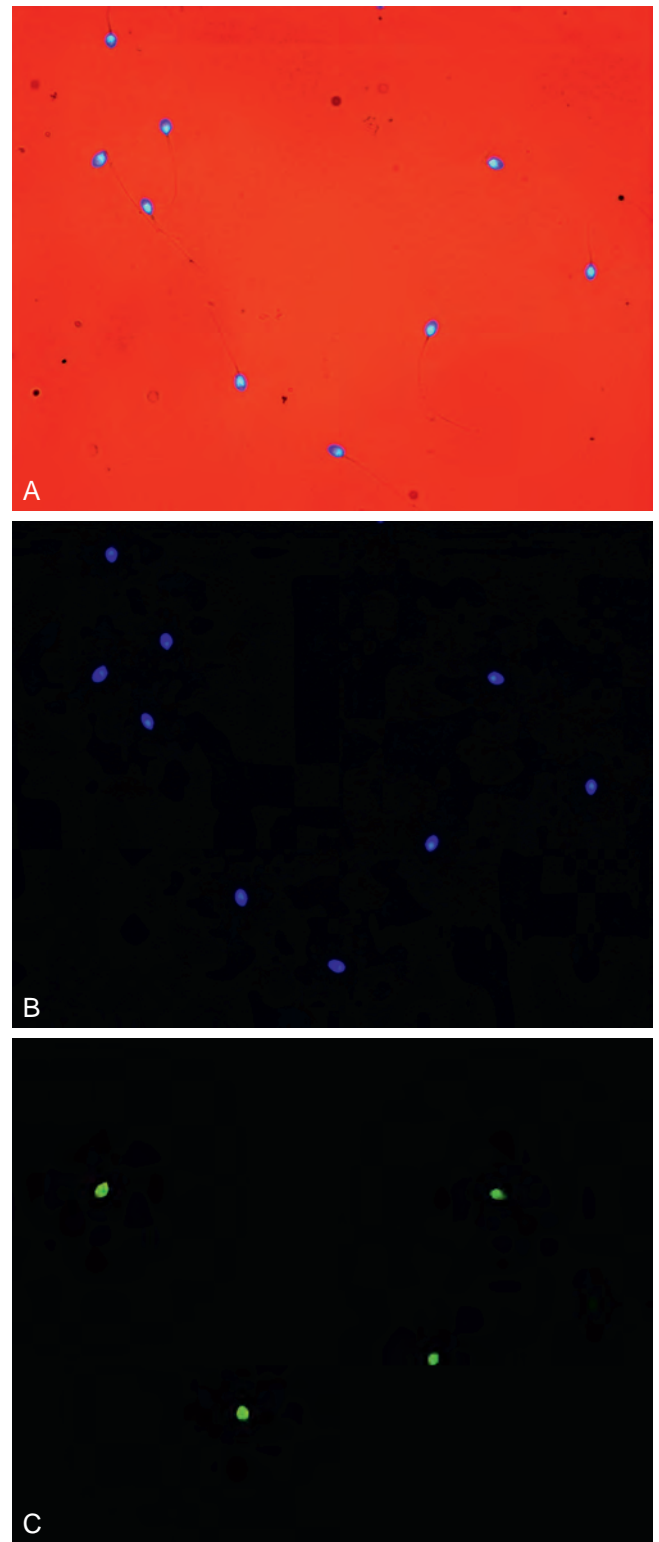



Figure 24-3. TUNEL assay. Bright field is shown in A. Sperm heads by fluorescence are demonstrated in B. TUNEL-positive sperm are identified in C.


identified in panel C. In general, results are reported as a DNA fragmentation index (DFI), which is calculated as the ratio of TUNEL-positive sperm to all sperm and expressed as a percentage. TUNEL is considered a direct measure of sperm DNA fragmentation, and in a meta-analysis of miscarriage rates, TUNEL had the highest associated risk ratio at nearly four (Sakkas and Alvarez, 2010; Robinson et al, 2012).


Comet Assay. Like the TUNEL assay, the comet assay, also referred to as the *single-cell gel electrophoresis assay*, is widely used in molecular biology laboratories to assess DNA fragmentation and has been adopted in the andrology laboratory for sperm (Tice et al, 2000; Sakkas and Alvarez, 2010). It is a simple assay that involves migration of single sperm head DNA in an electrophoretic agarose gel, and the tail resembling a comet indicates the degree of fragmentation (Tice et al, 2000). At neutral pH, this assay is considered a direct measure of sperm DNA fragmentation (Sakkas and Alvarez, 2010). Data are conflicting regarding its use as a tool for predicting clinical outcomes (Simon et al, 2010, 2011; Ribas-Maynou et al, 2012; Robinson et al, 2012). Investigators have used the comet assay in a variety of research settings to understand the effects of various entities on sperm DNA, including varicocele, toxins, male age, and testis cancer (Meeker et al, 2004; Bertolla et al, 2006; Delbes et al, 2007; Schmid et al, 2007; Blumer et al, 2008; Meeker et al, 2008; O'Flaherty et al, 2008; Wu et al, 2009; Lacerda et al, 2011; Fariello et al, 2012b).

Denatured Sperm DNA Assays. A number of assays denature sperm DNA before structural analysis (Sakkas and Alvarez, 2010). The comet assay performed in acidic or alkaline conditions denatures DNA, and like the comet assay, the sperm chromatin dispersion (SCD) assay allows visual identification of individual sperm head DNA structure by dispersion on agarose followed by nucleic acid staining (Fernández et al, 2003; Sakkas and Alvarez, 2010). The most established assay for sperm head DNA structure is the Sperm Chromatin Structure Assay (SCSA) (SCSA Diagnostics, Brookings, SD) (Evenson and Melamed, 1983; Evenson and Jost, 2000; Larson et al, 2000; Boe-Hansen et al, 2006; Chohan et al, 2006). The SCSA does not identify individual sperm but rather a population of cells by flow cytometry after denaturation in acidic conditions followed by staining with acridine orange (Evenson and Jost, 2000; Larson et al, 2000). Graphic analysis of flow cytometric data yields several outcome parameters for SCSA, with the DFI and high DNA stainability (HDS) being the two reported in common clinical use (Evenson and Jost, 2000; Larson et al, 2000). Although a number of studies have associated human reproductive outcomes with SCSA reported values, many failed to find statistically valid correlations (Evenson and Jost, 2000; Larson et al, 2000; Payne et al, 2005; Boe-Hansen et al, 2006; Bungum et al, 2007, 2008; Lin et al, 2008). In a meta-analysis of miscarriage rates, SCSA had a risk ratio of 1.47 with a 95% CI of 1.04 to 2.09, indicating a weak likely association.

Reactive Oxygen Species. Naturally occurring chemical reactions generate highly reactive molecules with unpaired electrons termed *free radicals*. Free radicals produced from oxidative reactions are referred to as *reactive oxygen species*. ROSs are involved in multiple physiologic processes important to sperm function, but investigators theorize that if present in excess, seminal ROSs may cause reproductive dysfunction (Agarwal et al, 2006, 2008c; Desai et al, 2009). TAC may be quantified in seminal fluid, and one popular method of quantifying how ROSs may affect sperm function is calculation of a ROS-TAC score (Rice-Evans and Miller, 1994; Sharma et al, 1999). Researchers have assessed ROS activity in aging, prostatitis, varicocele, lubricants, radiation, smoking, toxins, and obesity (Pasqualotto et al, 2000; Smith et al, 2005; Cocuzza et al, 2008a, 2008b; Farombi et al, 2008; Pasqualotto et al, 2008a; Agarwal et al, 2009; Hsu et al, 2009; Palmer et al, 2012; Taha et al, 2012; Agarwal et al, 2013).

 **Acrosome Reaction.** Please see the Expert Consult website for details.

 **Sperm Mucous Interaction.** Please see the Expert Consult website for details.

 **Sperm Ovum Interaction.** Please see the Expert Consult website for details.

Sperm Ultrastructural Assessment. MSOME involving sperm head morphologic inspection with high-power Nomarski differential interference contrast optics that magnify the field over 6000× is discussed in the section on sperm morphology in this chapter. Although electron microscopy is widely used in scientific research on the male gamete, it also has a place in the clinical assessment

of the infertile male (Chemes and Rawe, 2003). Sperm motility is dependent on the ultrastructural arrangement of microtubules in the tail with a peripheral array of nine pairs and a central two microtubules connected by dynein arms (Chemes and Rawe, 2003). This “9 + 2” architecture is shared with cilia, and genetic disorders affecting it can manifest as respiratory pathology associated with male reproductive dysfunction, referred to as the *immotile cilia syndrome*, *primary ciliary dyskinesia* (PCD), or *Kartagener syndrome* (Eliasson et al, 1977; Guichard et al, 2001; Chemes and Rawe, 2003). Kartagener syndrome results in sperm that are nearly totally or completely immotile but metabolically active (Peeraer et al, 2004). Semen samples with less than 10% motility and vitality demonstrated by testing may be investigated with electron microscopy to assess tail ultrastructural defects (Zini and Sigman, 2009). Electron microscopy is not available in all andrology laboratories.

Genomic Assessment

As odd as it may be to imagine that genes passed from parent to male offspring may be responsible for a condition that, if left untreated, would prevent those genes from being passed to future generations, evidence suggests that genetics plays a significant role in male reproductive dysfunction (Oates and Lamb, 2009). Known genetic conditions associated with the male sex are detailed in later sections of this chapter. In this section, clinically available assays are described.

Karyotype

Staining chromosomes with dyes binding to various moieties of the chemical structure of DNA resulting in banding patterns represents the classic means of cytogenetic analysis of chromosomes (Swansbury, 2003). Fluorescence in situ hybridization (FISH) uses fluorescent probes hybridizing to determined sequences on chromosomes, allowing for identification of specific regions or entire chromosomes depending on the specificity of the probe (Swansbury, 2003). One advantage of FISH is that it offers the ability to investigate the cytogenetics of both somatic and germ cells, which may differ beyond the expected halving of chromosomes (Martin, 2008). Other techniques, such as the spectral karyotype (SKY), use combinatorial methods to visualize all chromosomes in multiple colors (Swansbury, 2003). The American Urological Association Best Practice Statement on the Optimal Evaluation of the Infertile Male recommends that genetic testing including karyotype be performed in all males with azoospermia caused by spermatogenic dysfunction and in those with severe oligospermia defined as less than 5 million sperm/mL (Jarow et al, 2010). However, as numerical and structural chromosomal anomalies vary by geographic region, and obtaining a karyotype may represent a significant expense to the patient, the treating physician may judge whether this assay is indicated in his or her patient population.

Y Chromosome Microdeletion Testing

The Y chromosome is one of the smallest in humans at approximately 60 mega base pairs (Mb) (Tilford et al, 2001; Navarro-Costa, 2012). It is the determinant of the male gender and is the only chromosome passed directly from father to son (Navarro-Costa, 2012). It consists of a male-specific region with no homologous chromosomal mate and a pseudoautosomal region (Graves et al, 1998; Tilford et al, 2001; Navarro-Costa, 2012). In an elegant series of cytogenetic analyses for the time, Tiepolo and Zuffardi determined in 1976 that a region in the long arm of the Y chromosome was critical to the formation of sperm in man, which became known as AZF (azoospermia factor) (Tiepolo and Zuffardi, 1976; Chandley et al, 1989).

The portion of the Y chromosome that does not recombine represents approximately 95% of its sequence (Tilford et al, 2001). About one third of this nonrecombinant region consists of palindromic inner sequences present at least twice in forward and reverse

Functional sperm have an appendage at the head originating from the Golgi apparatus termed the *acrosome*, which primarily contains hydrolytic enzymes necessary for entering the ovum (Cross and Meizel, 1989). After binding to the zona pellucida of the ovum, the acrosome releases its contents, and the sperm penetrates the zona pellucida. Owing to its importance in normal fertilization,

investigators have devised ways of assessing acrosomal function, the first being fluorescent labeling of acrosomal contents (Cross and Meizel, 1989). Subsequent use of flow cytometry allowed real-time analysis of acrosomal function (Zoppino et al, 2012). Tests of acrosomal function are not in common clinical use and primarily serve as research tools.

Interaction with cervical mucus is a prerequisite for successful transit of sperm through the female reproductive tract. The postcoital test, also known as the *Sims-Huhner test*, assesses sperm interaction with mucus in two parts: first, it appraises mucus characteristics favorable to sperm penetration; and second, it gauges the number and motility of observed sperm ([Griffith and Grimes, 1990](#)). Although the postcoital test has been used by clinicians for a very long time, it suffers from a lack of standardization and reproducibility ([Griffith and Grimes, 1990](#)). Furthermore, researchers have demonstrated that medical history and semen analysis could accurately replace the postcoital test result in approximately half of couples ([van der Steeg et al, 2004](#)).

In an attempt to standardize and improve reproducibility of assessment of sperm interaction with cervical mucus, investigators

devised model systems in which sperm and mucus could be observed ex vivo ([Niederberger et al, 1993](#)). The Penetrak assay standardized the female component by replacing human with bovine cervical mucus and measuring the penetration of sperm in the latter, and the Tru-Trax assay provides two wells, allowing sperm penetration to be compared in either human and bovine cervical mucus or with either donor and patient sperm ([Niederberger et al, 1993](#)). Although bulk seminal parameters measure typical populations of sperm, evidence suggests that these standardized sperm-mucus interaction assays assessed motility of the unusual sperm that would ultimately fertilize the ovum ([Niederberger et al, 1993](#)). These assays are not presently in common clinical use.

Final structural barriers to the sperm on its journey through the female reproductive include the zona pellucida, the species-specific barrier to sperm, and the oolemma, and investigators have designed assays for both (Zini and Sigman, 2009). In the sperm penetration assay (SPA), hamster zona pellucida are removed, and human sperm are incubated with the denuded hamster ova, simulating IVF (Yanagimachi et al, 1976; Margalioth et al, 1986). Results of the SPA are reported as either percentage of ova penetrated or average number of sperm penetrating ova (Zini and Sigman, 2009). Before ICSI, clinicians used SPA results to counsel patients about the likelihood of IVF success; after the introduction of ICSI, clinicians used SPA results to decide whether ICSI was preferable to incubational IVF (Zini and Sigman, 2009). With widespread use of ICSI as a primary modality for IVF, the SPA is currently rarely used. Researchers also developed a modified SPA to predict ICSI outcomes in which sperm are microinjected directly into hamster ova and nuclear decondensation is assessed (Gvakharia et al, 2000). Because the majority of couples undergoing ICSI would do so independently of prognostication based on this assay, the SPA modified for ICSI is not in common clinical use.

Andrology laboratory investigators designed assays to investigate the initial union of sperm and ovum—the binding to the zona pellucida (Yanagimachi et al, 1979; Burkman et al, 1988; Liu and Baker, 1988; Coddington et al, 1991; Liu and Baker, 1992). These tests compare subject with control sperm binding to the zona pellucida (Burkman et al, 1988; Liu and Baker, 1988; Coddington et al, 1991; Liu and Baker, 1992). Either the zona can be halved, with each half subjected to subject or control sperm, or sperm may be labeled and differentiated visually with fluorescent microscopy (Burkman et al, 1988; Liu and Baker, 1988; Liu and Baker, 1992). The test using halves of ova is referred to as the *hemizona assay* (HZA) (Burkman et al, 1988; Coddington et al, 1991). Whereas ova may be stored in salt for use when needed, the fact that the zona pellucida is the species-specific barrier to sperm requires that human ova be used to assess zona binding (Yanagimachi et al, 1979; Burkman et al, 1988; Liu and Baker, 1988; Coddington et al, 1991; Liu and Baker, 1992). Owing to the paucity of human sources and readily available ova, the HZA is rarely used.

reading frames referred to as *amplicons* (Tilford et al, 2001). This sequence structure is believed to substitute in part in place of sexual recombination in repair of the Y chromosome but may also engender a particular fragility in increasing the likelihood of the loss of segments, or microdeletions (Oates and Lamb, 2009). Based on the work of Tiepolo and Zuffardi, investigators observed microdeletions of three regions on the Y chromosome to be commonly associated with azoospermia or oligospermia, which were termed AZFa, AZFb, and AZFc (Oates and Lamb, 2009). Once thought to be separate and distinct regions, AZFb and AZFc overlap, whereas AZFa is distant and isolated (Jobling and Tyler-Smith, 2003). The *DAZ* genes, believed to be integrally associated with spermatogenesis, are housed within the AZFc region (Saxena et al, 2000). Investigators have also referred to the proximal portion of AZFc as *AZFd*, but the usefulness of isolating this subregion remains unclear (Müslümanoğlu et al, 2005).

Some microdeletions of AZFc appear to be associated with spermatogenic impairment but not failure (Mulhall et al, 1997; Oates et al, 2002). Likewise, the clinical relevance of analysis of AZFc subregions such as gr/gr is unclear, because sperm may be present in the ejaculate and in the testis (Lardone et al, 2007; Wu et al, 2007; Giachini et al, 2008; Stouffs et al, 2008; Visser et al, 2009). However, evidence strongly suggests that AZFa and AZFb microdeletions cause significant pathology of the testis resulting in diminishing low likelihood of sperm retrieval by surgery (Hopps et al, 2003). **It is reasonable practice to recommend Y chromosomal microdeletion assessment to azoospermic men before surgical sperm extraction to counsel them on the likelihood of retrieval (Jarow et al, 2010).** However, it is also reasonable to omit testing based on the relative rarity of AZFa and AZFb microdeletions in clinical practice.

Genomic Sequence Assessment

A variety of technologies such as DNA microarrays allow multiple single nucleotide polymorphisms (SNPs) and mutations associated with known diseases to be screened for and reported (Schena et al, 1995; Hunter et al, 2008; Lizarin et al, 2013). These reports can be used to identify whether parents are carriers for a large number of genetic diseases and the probability of affected offspring. Whole genome sequencing as a clinical tool is also under current development (Moorthie et al, 2013). Although these technologies may ultimately be used to diagnose underlying causes of male reproductive dysfunction, use as general screening tools in evaluating male infertility is not yet warranted.

Cystic Fibrosis Transmembrane Conductance Regulator Mutation Assessment

The relationship between alterations in the cystic fibrosis transmembrane conductance regulator (CFTR) and maldevelopment of the vas is discussed in the section on developmental disorders in this chapter. This section describes what testing is available.

The protein encoded by CFTR forms a channel for chloride ions and possibly bicarbonate and may serve to regulate transport of other ions (Hampton and Stanton, 2010). More than 1600 CFTR mutations have been identified, and they may be mild or severe, defined by whether the full cystic fibrosis disease phenotype results from the mutation (Ratbi et al, 2007; Oates and Lamb, 2009; Hampton and Stanton, 2010; Bombieri et al, 2011; Yu et al, 2012). **The most common severe mutation is $\Delta F508$, which results from deletion of three base pairs that consequently remove the amino acid phenylalanine typically at position 508 of the encoded protein (Hampton and Stanton, 2010).** A high incidence of patients harbor more than one mutation; approximately 46% have two (Yu et al, 2012). A severe mutation such as $\Delta F508$ on each allele will result in a child with cystic fibrosis, making screening imperative for both the prospective father and mother for those suspected of harboring genetic alterations in CFTR.

Currently available CFTR screening panels typically include 25 to 40 of the most common mutations. Because a subset of known mutations is screened for, a negative result still carries a defined risk. Testing is commercially available for all known mutations but is expectedly more expensive. CFTR mutation prevalence varies by ethnicity and geography (Hamosh et al, 1998; Boyd et al, 2004; Foresta et al, 2005; Schulz et al, 2006; Ratbi et al, 2007; Havasi et al, 2010; Li et al, 2010; Bombieri et al, 2011). Consequently, the clinician should take into account location and ethnicity in interpreting results. Typically, CFTR screening panel reports are stratified by ethnicity.

KEY POINTS: LABORATORY EVALUATION OF MALE INFERTILITY

- Endocrine assessment of male reproductive status includes total testosterone, the portion of testosterone not bound to SHBG, estradiol, and the pituitary gonadotropins LH and FSH.
- The semen analysis represents a probabilistic assessment of male reproductive potential. Aside from azoospermia, no specific threshold applied to any parameter absolutely discerns infertility from fertility.
- The differential diagnosis for men with semen volumes less than 1.0 mL includes ejaculatory ductal obstruction, retrograde ejaculation, and vasal and accessory sex gland maldevelopment such as that occurring with CBAVD.
- Sperm vitality staining differentiates complete asthenospermia from necrospermia. Common laboratory staining methods differentiate pyospermia from immature germ cells.
- A preponderance of sperm with round heads, a condition referred to as *globozoospermia*, indicates deficient acrosome formation. The treatment is IVF with ICSI.
- Disruption in the blood-testis barrier formed by tight junctions between Sertoli cells results in antisperm antibodies, which have varying clinical significance depending on the degree of binding to sperm heads.
- Genetic screening of the CFTR in men with CBAVD and their partners identifies the presence of severe mutations such as $\Delta F508$ that may result in clinically overt cystic fibrosis in offspring.

IMAGING IN THE EVALUATION OF MALE INFERTILITY

Radiographic or ultrasonographic imaging is infrequently needed in the diagnosis of male reproductive dysfunction and should be **ordered cautiously**. Likely benign conditions such as testicular microlithiasis may be detected, resulting in patient distress and often unnecessary additional testing (Dagash and MacKinnon, 2007). The following descriptions of imaging in the evaluation of male reproductive dysfunction should not be interpreted as indicated in typical screening.

Scrotal Ultrasonography

Evaluation of the infertile male includes a detailed manual examination of the scrotum and its contents. As with the scrotal physical examination for any urologic evaluation, abnormalities may be detected that warrant scrotal ultrasonography for further investigation. In Figure 24-4, color duplex Doppler ultrasonography demonstrates a varicocele. Panel A reveals the varicocele to be adjacent to the testis, and the colored areas in panel B demonstrate the direction of flow. The diameter of the largest vein can be measured and reported.

Ultrasonography of the spermatic cord may be indicated if the evaluating physician is uncertain whether a varicocele is present on palpation (Nagler and Grotas, 2009). However, the varicoceles so identified are often so small as to be of questionable clinical

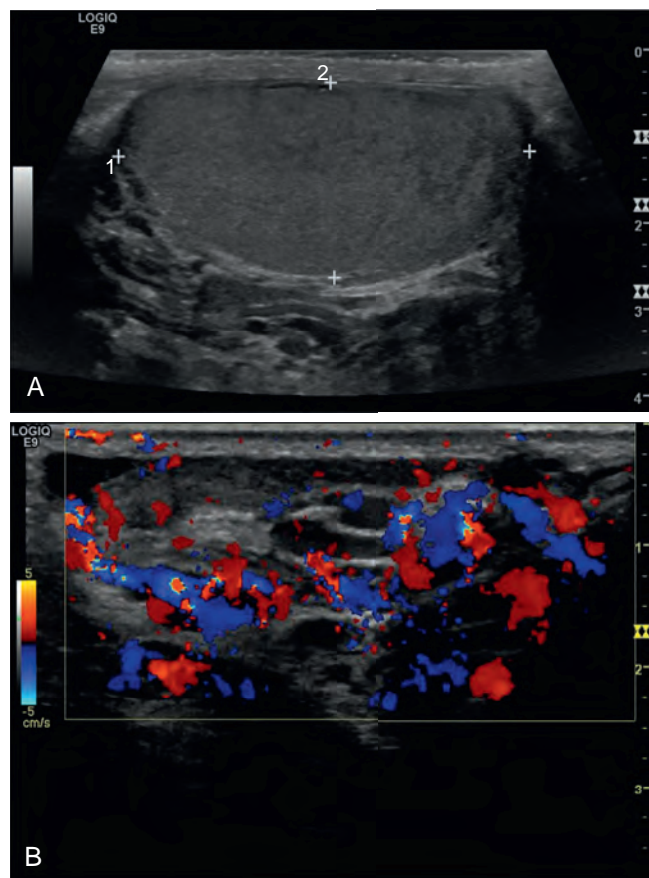


Figure 24-4. Color duplex Doppler ultrasonography of scrotum demonstrating varicocele. Dilated veins adjacent to the testis are exhibited in A, and directional flow in the vessels is revealed in B.

significance. Varicoceles become palpable at approximately 2.7 to 3.6 mm in diameter, and surgical treatment of varicoceles smaller than 3.5 mm that are not palpable on physical examination but observed on ultrasound does not result in improved seminal outcomes (Eskew et al, 1993; Hoekstra and Witt, 1995; Jarow et al, 1996; Schiff et al, 2006). Consequently, the most rational approach based on whether identification of a varicocele is likely to affect treatment outcomes is not to rely on ultrasound as a necessary diagnostic tool.

Direction of flow may be assessed by color Doppler ultrasound, and investigators have reported that reversal of flow is a positive prognostic sign that surgical treatment of varicocele may result in improved seminal parameters (Hussein, 2006; Schiff et al, 2006). At this time, insufficient numbers of men with nonpalpable varicoceles that are identified with reversal of flow are reported in studies investigating surgical treatment to conclude that color Doppler ultrasound is indicated as a screening modality for infertile men.

In conjunction with TRUS, investigators have observed sensitivity of 75% and specificity of 72% for diagnosing azoospermia caused by spermatogenic dysfunction and sensitivity of 29.8% and specificity of 87% for diagnosing azoospermia caused by obstruction (Abdulwahed et al, 2013). However, given the high accuracy in differentiating azoospermia caused by spermatogenic dysfunction versus obstruction yielded by measuring testis longitudinal axis and assaying serum FSH, it seems more prudent and cost-effective not to use ultrasonography in an attempt to diagnose the cause of azoospermia in men with adequate seminal volumes.

Vasography

Contrast vasography in the direction of the abdomen allows determination of patency of the vas deferens from the scrotum to the

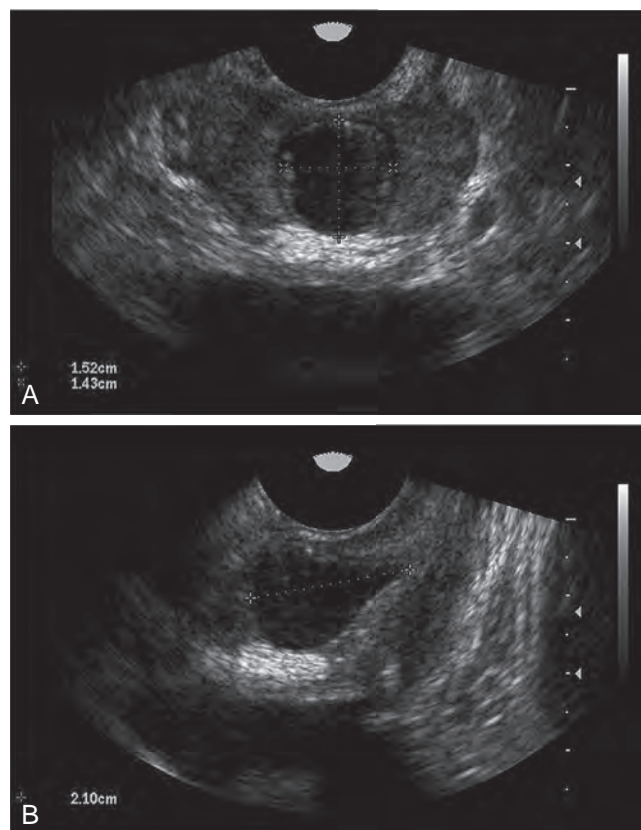


Figure 24-5. Transrectal ultrasonography revealing an intraprostatic cyst. A is transverse, and B is longitudinal. (Courtesy Marcelo Vieira.)

ejaculatory ducts (Ammar et al, 2012). It is currently rarely performed because image modalities such as TRUS and magnetic resonance imaging (MRI) have superseded it; it is invasive and may result in scar tissue formation in the vasal lumen and obstruction; and injection of saline into the vasal lumen during intended vasal reconstructive procedures with the manual feedback of whether fluid flows easily or backflow occurs offers similar information. Fluid, contrast or otherwise, should never be injected into the vasal lumen in the direction of the epididymis because it will rupture the delicate epididymal tubules. Should backflow be identified during intraoperative saline vasography, a monofilament suture such as 4-0 polypropylene may be inserted into the vasal lumen, advanced until resistance is encountered, and then withdrawn and the distance measured to determine the location of the obstruction.

Venography

Please see the Expert Consult website for details.

Transrectal Imaging

The diagnosis of ejaculatory ductal obstruction is considered when azoospermia in conjunction with low seminal volume is encountered (Niederberger, 2011). The earliest and still currently the most prevalent method of investigating whether ejaculatory ductal obstruction in present is TRUS (Jarow, 1996; Niederberger, 2011). TRUS imaging evidence of ejaculatory duct obstruction includes an anteroposterior seminal vesicle diameter of greater than 1.5 cm with or without a midline prostatic cyst (Jarow, 1996; Niederberger, 2011; Ammar et al, 2012). Figure 24-5 demonstrates an intraprostatic cyst, with panel A exhibiting the transverse view and panel B the longitudinal view. Unfortunately, although TRUS is convenient and common, its specificity is low compared with other modalities for identifying whether or not obstruction is



Venography is rarely performed for the diagnosis of varicocele. For the same reasons that scrotal ultrasound is infrequently necessary (i.e., clinically significant varicoceles are palpable and require no further imaging, and the treatment of varicoceles that are identifiable only by imaging and are not palpable does not improve

seminal outcomes), venography is usually not useful in assessing the import of a varicocele. If a clinically significant varicocele is to be treated by embolization, then venography is used to plan the radiographic interventional approach.

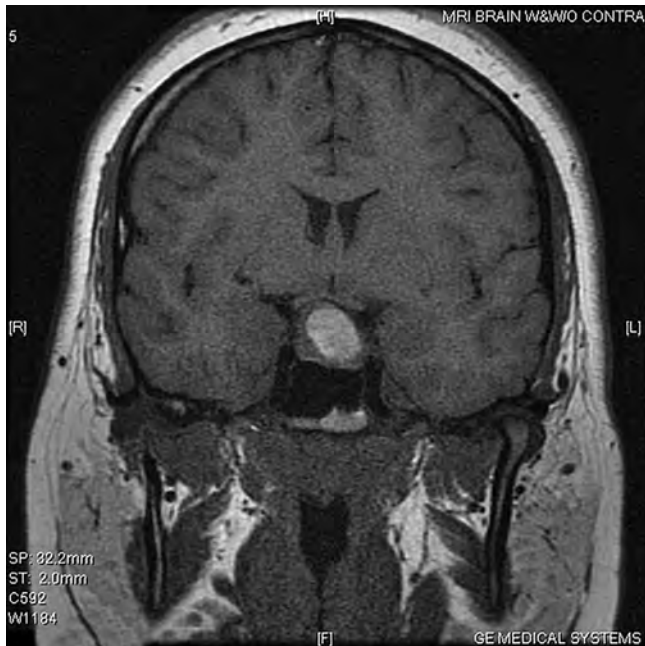


Figure 24-6. Large pituitary macroadenoma revealed by cranial magnetic resonance imaging.

present (Purohit et al, 2004). These other assessments include radiographic imaging after injection of contrast directly into the seminal vesicles, or vesiculography; aspiration of the seminal vesicles to determine whether sperm is present; and injection of diluted indigo carmine or methylene blue dye into the seminal vesicles and observation by cystoscopy of whether the colored dye flows from the ductal orifices at the verumontanum, a technique referred to as *chromotubation* (Purohit et al, 2004). In a small series, vesiculography and chromotubation were more accurate than TRUS by a margin of 25% (Purohit et al, 2004). However, these techniques are more invasive and expensive, and an incremental improvement in diagnostic accuracy compared with TRUS if conclusively demonstrated in larger studies may not justify the additional risk and cost.



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Abdominal Imaging



Please see the Expert Consult website for details.

Cranial Imaging

Cranial MRI allows assessment of whether hyperprolactinemia is associated with an anatomic pituitary lesion (Niederberger, 2011). MRI may distinguish between microadenomas and macroadenomas and may assist in judging whether medical or surgical therapy is indicated (Johnsen et al, 1991). Figure 24-6 demonstrates a cranial MRI revealing a large pituitary macroadenoma.

KEY POINT: IMAGING

- Imaging can reveal sequelae of genetic conditions such as congenital absence of the vas deferens and renal aplasia, and it can differentiate reasons for seminal hypovolemia such as ejaculatory ductal obstruction, but it is infrequently necessary to establish diagnoses such as varicocele or spermatogenic dysfunction.

ASSISTED REPRODUCTION

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DIAGNOSES AND THERAPIES

The understanding of the pathophysiology of male reproductive dysfunction has expanded in past years but remains manifestly incomplete. The difficulties inherent in the probabilistic nature of reproduction and its assessment pose challenges to the physician evaluating and consequently treating male infertility, but sufficient information is known for the treating physician to make reasoned assumptions about whether a pathologic explanation involving the man exists, its likely basis, and plausible therapy. This section reviews discrete diagnoses and possible medical therapies.

Genetic Syndromes

With the completion of sequencing of the human genome in 2004, knowledge of how the genes involved in human reproduction conspire to create fully formed and viable sperm will follow (International Human Genome Sequencing Consortium, 2004). As discussed in the section of this chapter describing genomic sequence assessment, broad panels are available that identify carrier risk of known genetic diseases, and whole genomic sequencing is under development. However, current use of the former and use of the latter, should it become immediately available, as general screening tools for male reproductive dysfunction are hampered by the lack of an understanding of how the majority of the genetic mechanisms involved in spermatogenesis function in concert to produce viable sperm. A certain number of genetic associations are known to be involved in male infertility, and these are detailed in subsequent sections. In this section, general genetic causes of male fertility involving chromosomal number, structure, and epigenetic mechanisms are discussed.

Chromosomal Numerical Disorders

The presence of a supernumerary X chromosome yielding 47,XXY, or Klinefelter syndrome, is the most commonly identified genetic cause of male infertility (Oates and Lamb, 2009; Sigman, 2012; Groth et al, 2013). A 47,XXY genotype is observed in 1 in 500 to 1000 live births, and in over 95% of affected adults results in azoospermia, small testes, and elevated gonadotropin levels (Maiburg et al, 2012; Groth et al, 2013). Approximately 75% of children have learning disabilities, and 63% to 85% of men have low testosterone levels (Groth et al, 2013). Body morphology features such as increased height are observed in only 30% of Klinefelter males, and consequently the condition cannot be excluded by physical examination and physical inspection alone (Groth et al, 2013). Increased incidence of other disorders related to the testis such as mediastinal germ cell tumors is documented in men with Klinefelter syndrome, suggesting broader testicular effects (Sokol, 2012).

A nonmosaic 47,XXY karyotype is observed in 80% to 90% of men with Klinefelter syndrome (Maiburg et al, 2012). The remainder are mosaic 46,XY/47,XXY or have additional or structurally abnormal X chromosomes (Maiburg et al, 2012). In the man, approximately 8% have sperm in the ejaculate, and the remainder are azoospermic (Oates, 2012). Within the testis, approximately half of men with Klinefelter syndrome have sufficient mature sperm amenable to surgical sperm retrieval for use with IVF and ICSI (Oates, 2012). Early age at diagnosis appears to offer a more favorable prognosis (Mehta and Paduch, 2012).

Until recently, fertility management of men with Klinefelter syndrome was limited to diagnosing the condition with karyotype analysis, assessing whether sperm was present in the ejaculate, and attempting to extract sperm from the testis if it was not. Many of these men are identified shortly after puberty with low testosterone levels and prescribed exogenous testosterone alone, suppressing native spermatogenesis if present. Citing the progressive decline

TESTIS HISTOPATHOLOGY



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MRI with an endorectal coil can be used to evaluate anatomic features consistent with ejaculatory ductal obstruction (Engin et al, 2000). It suffers from the same challenges as ultrasound, which is that ejaculatory ductal obstruction may not correlate with the observed anatomy. In one study comparing TRUS and MRI, MRI identified 23% of anatomic aberrations that were not discernible on TRUS (Engin et al, 2000). However, the clinical significance of these additional identified lesions is not established, and TRUS found anomalies not observed by MRI (Engin et al, 2000). Engin and coworkers concluded that TRUS is a good screening modality and that MRI should be reserved for situations in which TRUS results are ambiguous (Engin et al, 2000).

As with any hydraulic system, anatomic features may not correlate to resistance, which is ultimately a functional assessment of

flow and pressure. Investigators have described use of manometry to establish baseline functional characteristics of the ejaculatory ducts (Eisenberg et al, 2008). In one method, dye was injected into the seminal vesicles until it could be visualized with a cystoscope flowing from the ductal orifices at the verumontanum, and the pressure at that point was measured (Eisenberg et al, 2008). In another method, a constant infusion flow was applied to the seminal vesicles, and the pressure was measured (Eisenberg et al, 2008). Investigators have also injected technetium-99m-containing solution into the seminal vesicles and assessed emptying over time by scintigraphy (Orhan et al, 2008). These promising procedures should not yet be considered standard evaluation until further studies have established validity.

Abdominal imaging in the evaluation of the infertile male is primarily used to study whether renal sequelae of congenital vasal maldevelopment is present. As previously described, unilateral absence of the vas deferens may be associated with loss of wolffian

ductal development on that side and renal agenesis, and a solitary kidney was observed in one of nine men with CBAVD ([Schlegel et al, 1996](#); [Niederberger, 2011](#)). Renal ultrasound is typically sufficient to identify whether both kidneys are present.

Historically, men found to have azoospermia were subject to testis biopsy to diagnose whether the condition was caused by obstruction or spermatogenic dysfunction. However, as previously described, the majority of azoospermic men can be successfully diagnosed with a single laboratory assay and one measurement on physical examination (Schoor et al, 2001). The combination of the FSH assay result and testis size as measured by caliper or orchidometer accurately predicts whether azoospermia is the result of obstruction or spermatogenic dysfunction: 96% of men with obstructive azoospermia had FSH assay values of 7.6 IU/L or less and testis long axis greater than 4.6 cm, and 89% of men with azoospermia caused by spermatogenic dysfunction had FSH values greater than 7.6 IU/L and testis long axis 4.6 cm or less (Schoor et al, 2001). Coupled with the observation that a biopsy in one location of the testis does not predict histopathology and full spermatogenesis in other areas, the fact that the prognostic information afforded by biopsy could be supplanted with FSH and testis longitudinal axis called into question the value of testis biopsy in the evaluation of male reproductive dysfunction in general (Turek et al, 1997; Schoor et al, 2001; Ramasamy and Schlegel, 2007). Consequently, testis biopsy is not indicated in the initial diagnostic evaluation of the infertile man.

Men with infertility and azoospermia in particular appear to be at increased risk for certain diseases such as cancer (Walsh et al, 2010; Eisenberg et al, 2013). This observation is not unexpected, because azoospermia is likely to result from dysregulation of molecular systems that may be associated with oncogenesis. Hence, testis biopsy simultaneously with other procedures such as testis sperm extraction may yield pathologic information that can explain procedural outcomes as well as provide information about other related future diseases.

Testis biopsy should be considered as an incomplete sampling of testicular histology and germ cell development. In one series, one third of men who underwent testis biopsy that demonstrated no sperm were found to have sperm at a site distant from the biopsy location (Turek et al, 1997). In another series assessing outcomes of microsurgical testis sperm extraction in which the testis was globally and systematically visually explored for tubules likely to contain sperm, approximately two of five men with one or two prior biopsies demonstrating no germ cells were found to have mature sperm (Ramasamy and Schlegel, 2007). Even with three or four prior biopsies with only Sertoli cells seen, mature sperm was extracted in one of nine men (Ramasamy and Schlegel, 2007). These observations confirm that spermatogenesis may be highly focal in men with azoospermia, and a biopsy may not describe the entirety of the histology of a testis.

Should biopsy be performed in conjunction with testis sperm extraction to sample testis histology, spermatogenesis is typically characterized histologically by light microscopy as to whether germ cells are present at all, and if so, the volume of active spermatogenesis and the degree of development of the farthest advanced cell. In the most extreme case, germ cells are lacking entirely and only Sertoli cells are visible in the germinal epithelium. This condition is often referred to as *Sertoli cell-only syndrome* and is demonstrated by low-power light microscopy in Figure 24-7. For comparison, Figure 24-8 exhibits normal spermatogenesis on light microscopy. The low-power view in panel A reveals a robust and full seminiferous epithelium with a variety of germ cells in various stages of spermatogenesis. In the high-power view demonstrated in panel B, the arrow indicates the typical triangular shape of a mature sperm head. As sperm develop in a three-dimensional epithelial surface, it is unusual to find an entire mature sperm with its full tail in one single microscopic plane. Consequently, visualization of a mature sperm head is typically sufficient to confirm completion of the stages of spermatogenesis.

Figure 24-9 reveals general depopulation of the seminiferous epithelium. A variety of germ cells in differing stages of spermatogenesis are observed, but the seminiferous epithelium appears diminished in luminal caliber. This condition is referred to as *hypospermatogenesis*. In Figure 24-10, varying stages of spermatogenesis are observed but without completely formed sperm. This condition

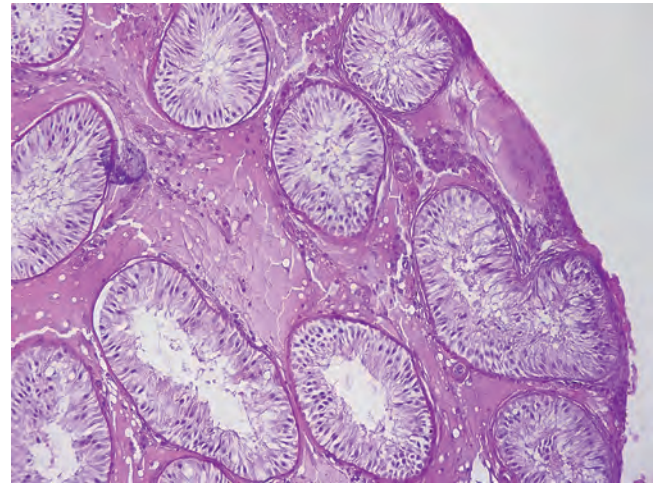


Figure 24-7. Low-power light microscopy demonstrating Sertoli cell-only syndrome.

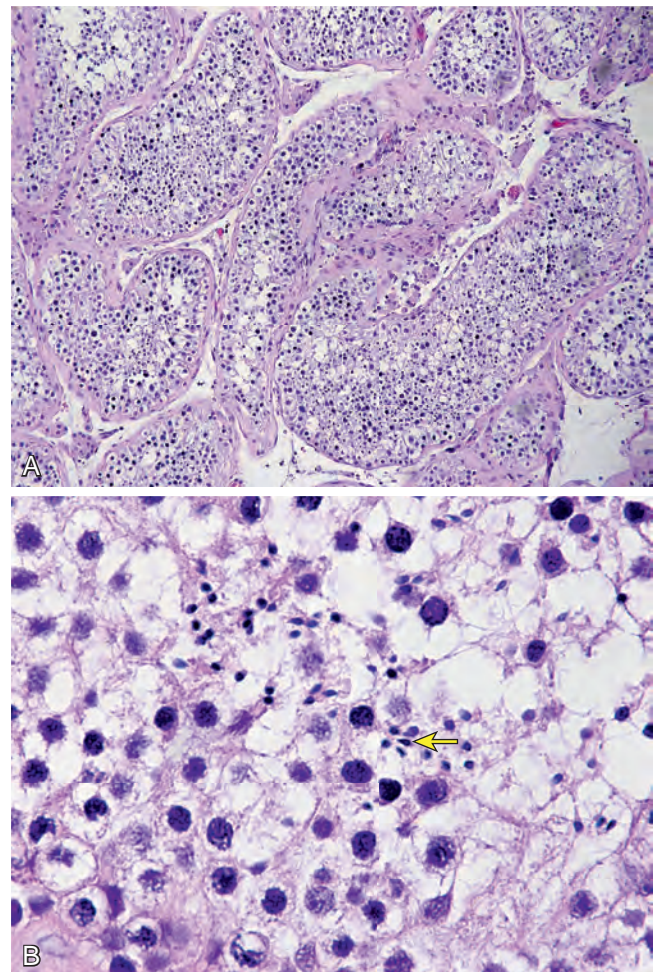


Figure 24-8. Light microscopy demonstrating normal spermatogenesis. A is low power, and B is high power. The arrow in B indicates a mature sperm head.

is referred to as *maturation arrest*. Spermatogenesis may be arrested before meiotic division, which is termed *early maturation arrest*, or during or after meiotic division, which is referred to as *late maturation arrest* (Alukal et al, 2009). In Figure 24-10, small nuclei consistent with postmeiotic germ cells are observed but not maturing or mature sperm; this is therefore considered late maturation arrest.

KEY POINT: TESTIS HISTOPATHOLOGY

- In general, testis biopsy is unnecessary to identify whether azoospermia is the result of spermatogenic dysfunction or obstruction; 96% of men with obstructive azoospermia have FSH assay values of 7.6 IU/L or less and testis long axis greater than 4.6 cm, and 89% of men with azoospermia caused by spermatogenic dysfunction have FSH values greater than 7.6 IU/L and testis long axis of 4.6 cm or less.

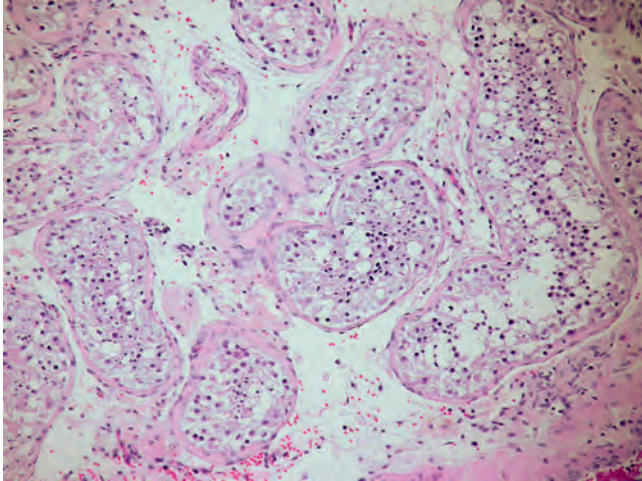


Figure 24-9. Low-power light microscopy demonstrating hypospermatogenesis.

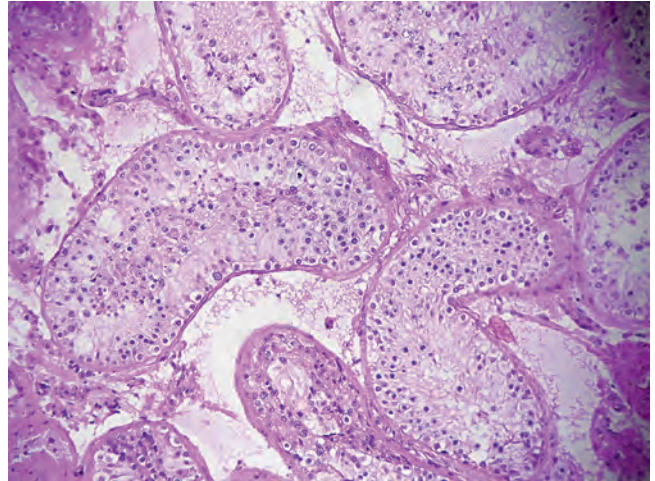


Figure 24-10. Low-power light microscopy demonstrating maturation arrest.

Reproductive medicine is unique in that it includes not one but two patients for a healthy outcome to occur. For natural conception, pregnancy, and delivery, a functional female reproductive system must be present, and coitus must be occurring at regular intervals. Several methods may be used by specialists in female fertility to control variables related to conception and the female reproductive tract. The urologist treating the infertile male works closely in integrated fashion with the gynecologist or reproductive endocrinologist caring for his partner. Even when the female reproductive system is fully functional and normal on evaluation, these methods may be used to overcome male factors impeding fertilization.

As previously described, chronologic age is a significant determinant of female reproductive potential, especially in the consideration of the use of more invasive reproductive techniques (te Velde and Pearson, 2002; Balasch and Gratacós, 2012). Female fecundity begins to decline after age 35, and this decline accelerates after age 37 (Van Voorhis, 2011; Balasch and Gratacós, 2012). The urologist must take into account maternal age and other female factors when planning therapy for the man. Because spermatogenesis is a lengthy process, treatment directed toward improving it and waiting to determine the effect may be appropriate with a female partner at age 30 years, but more aggressive therapy for the couple including more invasive techniques for the woman may be better suited should she be 38 years of age.

In assessing success rates for any therapy directed toward reproduction, outcomes must be carefully identified. If the embryo is cultured outside of the woman's body, a fertilization rate may be calculated. Pregnancy rate is different and greater than delivery rate, with the latter of greater interest to the couple.

Intrauterine Insemination

In general, external augmentation of reproduction takes two forms. In one form, semen is delivered by instrumentation into the female reproductive tract. The most common type of this form is IUI, during which a small catheter is placed through the cervical os to deliver sperm directly into the uterus, thus bypassing the cervical barrier (Van Voorhis, 2011). Often, sperm are processed in the laboratory to enrich the motile fraction before IUI. IUI decreases in effectiveness when the number of motile sperm in the ejaculate is low, in general considered to be in the range of less than 10 million, or if the motile sperm in the processed sample total fewer than 1 million (Van Voorhis, 2011).

Table 24-3 lists outcome data for various interventions for the female partner based on 2008 national data from SART (Van Voorhis, 2011). IUI alone results in an average per-cycle delivery rate of 5%; adding the oral medicine clomiphene citrate increases it to 8%, and adding the injectable medication human menopausal gonadotropin (hMG) increases the delivery rate to 15% to 18% (Van Voorhis, 2011).

The essential value of IUI is that it controls variables related to the initial voyage of sperm in the reproductive tract. Should the penile urethra, vaginal vault, and cervix be misaligned or hostile, IUI begins the journey of sperm at a point within the uterus. Sperm must then transit through the fallopian tubes to ultimately join the ovum, but a considerable barrier to reproduction is bypassed.

TABLE 24-3 Per-Cycle Success Rates of Various Forms of Intervention for the Female Partner and the Associated Multiple Birth Rate Based on 2008 National Data from the Society for Assisted Reproductive Technologies (SART)

TECHNIQUE	DELIVERY RATE OR CYCLE	MULTIPLE BIRTH RATE OR PREGNANCY
Timed intercourse	2%-3%	1%
IUI alone	5%	1%
Clomid alone	5%	10%
Clomid and IUI	8%	10%
hMG alone	12%-15%	15%
hMG and IUI	15%-18%	15%
In vitro fertilization	30%-32%	31%

hMG, human menopausal gonadotropin; IUI, intrauterine insemination. From Van Voorhis BJ. What to know about the infertile female. In: Niederberger CS, editor. An introduction to male reproductive medicine. New York: Cambridge University Press; 2011. p. 134–51.

In Vitro Fertilization

A variety of methods currently exist to manipulate gametes and embryos outside of a woman's body and to return the results into the female reproductive tract. These techniques are collectively known as *assisted reproductive technologies* (ART). With the culmination of a great body of scientific work leading to the first live birth reported in 1978 after incubation of sperm and ovum outside of a mother who had both fallopian tubes removed and replacement of the embryo into her uterus, an entirely new way of treating both female and male infertility was born (Stephens and Edwards, 1978). Later, investigators developed methods of inserting a single sperm into an ovum, dramatically lowering the number of male gametes needed for IVF (Palermo et al, 1992).

ICSI revolutionized IVF, allowing consideration of sperm that had not transited the epididymis for use in ART. Shortly after its introduction, investigators began to compare ICSI outcomes for sperm derived from the testis and epididymis, finding that fertilization and pregnancy rates were similar (Ubaldi et al, 1996; Watkins et al, 1997). Subsequent studies confirmed these initial observations and demonstrated that ICSI was equally effective with sperm from either testicular or epididymal origin (Nicopoullos et al, 2004; Kalsi et al, 2010). ICSI also made possible usage of cryopreserved testicular sperm for ART, which has the advantage of permitting the man and woman to undergo testicular sperm extraction and ova retrieval on separate days and also the benefit to the female reproductive specialist and couple of knowing whether biologic sperm could be procured before hormonal stimulation of the woman (Gil-Salom et al, 1996; Friedler et al, 1997; Prins et al, 1999). Investigators have observed similar outcomes when using ICSI with cryopreserved testicular sperm and sperm extracted from the testis on the day of ova retrieval (Nicopoullos et al, 2004; Kalsi et al, 2010).

in spermatogenesis over time, investigators have argued for aggressive management including surgical extraction of sperm at early to mid puberty before initiation of therapy with exogenous testosterone (Mehta and Paduch, 2012). This approach is primarily investigational at this time.

Structural Chromosomal Anomalies

As discussed in the section detailing Y chromosome microdeletion testing, investigators observed three regions on the Y chromosome, designated AZFa, AZFb, and AZFc, to be associated with azoospermia or oligospermia (Oates and Lamb, 2009). Microdeletions of AZFc currently have unclear clinical significance, whereas AZFa and AZFb microdeletions are nearly always associated with absence of retrievable sperm from the testis (Mulhall et al, 1997; Oates et al, 2002; Hopps et al, 2003; Lardone et al, 2007; Wu et al, 2007; Giachini et al, 2008; Stouffs et al, 2008; Visser et al, 2009). AZFa microdeletions have particular clinical significance, as spatially the AZFa region appears to be localized distinctly from AZFb and AZFc, with the latter two overlapping (Oates and Lamb, 2009).

Other structural anomalies of the Y chromosome may be identified by karyotypic analysis (Oates and Lamb, 2009). Two terminal breaks in both chromosome arms and subsequent fusion may lead to a ring Y chromosome, or r(Y), with variable phenotype depending on the amount of chromosomal material lost (Arnedo et al, 2005). Karyotypic anomalies in somatic chromosomes may also be associated with infertility (Mau-Holzmann, 2005).

Epigenetic Anomalies

Not only must the DNA sequence be intact for successful function of the male gamete, the DNA must be tightly coiled and packaged (O'Flynn O'Brien et al, 2010). As discussed in the section describing denatured sperm DNA assays, investigators have constructed various methods of interrogating sperm DNA structure with unclear prognostic outcomes at present. Other components of sperm DNA packaging may yield future diagnostic tools; for example, animal studies revealed that premature translation of protamine 1 resulted in postmeiotic maturational arrest in mouse spermatogenesis, and protamine 2 deficiency led to sperm DNA damage and embryo demise (Lee et al, 1995; Cho et al, 2003). In humans, evidence links protamine 2 precursors and the protamine 1–protamine 2 ratio to sperm DNA quality and IVF outcomes (Aoki et al, 2006; Torregrosa et al, 2006; de Mateo et al, 2009). Histones also offer a future target for clinical assessment. They are highly specifically localized along human sperm DNA, and researchers have observed histone variants to relate to fertility in bulls (Hammoud et al, 2009; de Oliveira et al, 2013).

DNA methylation allows coordination of gene expression in somatic cell development (Boissonnas et al, 2013). Once thought to be of little consequence in sperm, this epigenetic modification is now considered to play key roles in spermatogenesis and embryogenesis (Molaro et al, 2011; Carrell, 2012; Boissonnas et al, 2013). The pattern of gene promoter methylation is substantially different in somatic and sperm cell DNA and may have future clinical applicability in the assessment of male reproductive potential (Molaro et al, 2011).

Testicular Causes

The testis essentially consists of two compartments, the seminiferous tubules that house the developing male gametes and the interstitial spaces between the tubules, inhabited by Leydig cells. Both are required for sperm production, which then must conclude with transit of the male gamete outward. Testicular causes of male reproductive dysfunction may consequently be considered to derive from pathology in the production of sperm in the seminiferous epithelium or in the synthesis of testosterone by Leydig cells, or obstruction in the microductal system transporting sperm toward the ejaculatory ducts.

Spermatogenic Dysfunction

As discussed in the section describing testis histopathology, dysfunction in the seminiferous epithelium may be globally described as hypospermatogenesis, which indicates a decrease in sperm production; maturation arrest, which represents halting of the sequence of steps of the male gamete at some point through premeiotic, meiotic, and postmeiotic development; and Sertoli cell–only syndrome, which denotes a complete depopulation of spermatogonial cells. The molecular mechanisms leading to completion of spermatogenesis are still under investigation, and in the future it is likely that genomic, proteomic, and metabolomic markers will become available for clinical use to diagnose specific causes of spermatogenic dysfunction (Kovac et al, 2013). At present, the primary means of assessing deficiencies in spermatogenesis is histopathologic inspection. As previously described, should azoospermia be present, in 89% of cases spermatogenic dysfunction is identified as the cause with an FSH value greater than 7.6 IU/L and the testis long axis 4.6 cm or less (Schoor et al, 2001).

Another form of spermatogenic pathology arises in the testis and impedes sperm in the ejaculate. In the seminiferous epithelium, Sertoli cell tight junctions protect haploid germ cells from circulating immunologic cells, forming a blood–testis barrier (Brannigan, 2011). Pathologic conditions that disrupt this blood–testis barrier may expose the immunologically protected spermatids and spermatozoa to antibody formation, which may cause sperm agglutination, impeded sperm motility, and reduced fertilizing potential (Brannigan, 2011). These conditions include obstruction in the male reproductive tract such as that occurring after vasectomy; inflammation associated with orchitis, prostatitis, or sexually transmitted disease; exposure to heat with varicocele, cryptorchidism, or external sources such as hot tubs; trauma and testis torsion; and genetic associations including thymic maldevelopment and the HLA-B28 haplotype (Walsh and Turek, 2009). Assays for antisperm antibodies are detailed in the section describing the laboratory evaluation of semen.

For treatment of antisperm antibodies, simple measures include use of condoms and washing sperm. Neither has good evidence to substantiate its use (Walsh and Turek, 2009). Washing may remove unbound antibodies, but those that matter remain bound to sperm (Walsh and Turek, 2009). More direct treatments include immunosuppression with corticosteroids and ART. Two controlled trials of corticosteroids offer conflicting results, with one demonstrating improved fertility and the other not (Haas and Manganiello, 1987; Hendry et al, 1990). Whether because of a lack of compelling evidence or because of more direct results, IVF and ICSI have become common treatment for antisperm antibodies.

Steroidogenic Dysfunction

The terms hypergonadotropic hypogonadism, primary hypogonadism, and primary hypoandrogenism refer to impaired testosterone synthesis caused by Leydig cell dysfunction (Sokol, 2009). This entity is typically identified by elevated LH levels and decreased circulating testosterone (Sokol, 2009). However, Leydig cell dysfunction may exist concurrently with pituitary insufficiency, and these men will have decreased testosterone concentrations and variable LH levels that do not reflect the typical increase associated with primary Leydig cell insufficiency (Sokol, 2009). Increasing age is a condition associated with decreasing androgen and blunted pituitary response (Feldman et al, 2002; Sokol, 2009).

An absolute requirement for spermatogenesis is intratesticular steroidogenesis, which appears to be especially important for the postmeiotic maturation of sperm (Caroppo, 2011). Men with Klinefelter syndrome often have lower levels of circulating testosterone, but impaired Leydig cell function may not be the only mechanism responsible for a phenotype that resembles those of hypoandrogenic males (Sokol, 2009; Oates, 2012). Investigators have reported evidence of Leydig cell dysfunction in humans associated with mutations in the LH receptor gene and in FSH receptor–deficient mice, and as the genes responsible for steroidogenesis become

clinically available for assessment in humans, it is anticipated that more cases of Leydig cell dysfunction with genetic causes will be identified (Latronico et al, 1996; Baker et al, 2003). Other potential clinical causes of Leydig cell dysfunction include orchitis, cytotoxic chemotherapy, and exposure to environmental toxicants (Skakkebaek et al, 2001; Sokol, 2009).

There is currently no accepted therapy for hypoandrogenism caused by Leydig cell insufficiency (Sokol, 2009). Exogenous testosterone is not indicated, because insufficient testicular testosterone concentrations are achieved for spermatogenesis, and pituitary LH release is suppressed (Niederberger, 2011). **Should azoospermia be associated with low testosterone concentrations and significantly elevated LH levels, if the patient desires paternity, the treatment is surgical sperm extraction.**

Microductal Obstruction

Either by congenital or acquired means, the epididymis or scrotal vas deferens may be obstructed. If obstruction is bilateral, azoospermia typically results. As discussed in the section describing the endocrine evaluation, the physician may use the FSH level combined with the testis longitudinal axis as measured by calipers to predict whether azoospermia is associated with obstruction; 96% of men with obstructive azoospermia had FSH concentration of 7.6 IU/L or less and testis long axis greater than 4.6 cm (Schoor et al, 2001). **Figure 24-11** illustrates an algorithm for the evaluation of azoospermia. Microductal obstruction may also be unilateral: in that case, bulk seminal parameters may be reduced or not depending on the function of the contralateral testis. Should unilateral obstruction be present with adequate spermatogenesis present in the ipsilateral testis and the existence of spermatogenic pathology in the contralateral testis, impaired bulk seminal parameters may result and microductal reconstruction may be indicated.

As discussed in the section describing evaluation of the surgical history of an infertile male, herniorrhaphy especially with mesh may result in obstruction of the vas deferens in the inguinal canal (Shin et al, 2005; Maciel et al, 2007; Hallén et al, 2011, 2012; Tekatli et al, 2012). If both vasa are occluded, azoospermia likely results.

Pituitary Dysfunction

The pituitary hormones LH and FSH regulate spermatogenesis: LH directs Leydig cell steroidogenesis; and FSH controls spermatogenesis via the Sertoli cells (Caroppo, 2011). If by intrinsic dysfunction or external pathology LH, FSH, or both are suppressed, spermatogenesis suffers.

Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism refers to the condition of decreased pituitary hormonal secretion. Kallmann described anosmia associated with decreased pituitary function, and the syndrome bears his name (Kallmann and Schoenfeld, 1944). The incidence of the syndrome is approximately one in 10,000 males, and the mode of inheritance is most frequently autosomal recessive, but autosomal-dominant and X-linked recessive patterns are also observed (Bhagavath et al, 2006; Sokol, 2009). Investigators have identified associations with Kallmann syndrome and the *KAL1* gene encoding anosmin-1 responsible for neurotropic growth factors during embryogenesis, the *GNRHR* gene encoding gonadotropin-releasing hormone (GnRH) receptor, the pituitary-specific transcription factor *PIT1*, the *PIT1*-related transcription factor *PROP1*, the G protein-coupled Kisspeptin receptor *GPR54*, the homeobox genes *HESX1*, *LEX3*, and *LEX4*, and others (Dattani et al, 1998; Wu et al, 1998; de Roux et al, 2003; Kim et al, 2003; Sobrier et al, 2004; Bhagavath et al, 2006; Newbern et al, 2013). Researchers noted approximately 10% of men with Kallmann syndrome to harbor mutations in either the *GNRHR* or *KAL1* gene (Bhagavath et al, 2006).

Treatment includes replacement of LH with human chorionic gonadotropin (hCG) and replacement of FSH with recombinant FSH (rFSH) or hMG, which exhibits both LH and FSH-like activity (Sokol, 2009). Treatment with hCG alone may initiate spermatogenesis; if hMG or rFSH is prescribed, after spermatogenesis returns, these agents may be withdrawn after several months of therapy (Sokol, 2009). Men who are identified as having Kallmann syndrome later in life when reproductive interests occur have often been prescribed exogenous androgen since adolescence. These men may require gonadotropin therapy for 1 to 2 years before sperm becomes evident in the ejaculate. Typical doses for intramuscular or subcutaneous hCG are 1500 to 5000 international units two to three times weekly to a maximum of 10,000 international units per week and are titrated to serum testosterone results (Sokol, 2009; Hussein et al, 2013). The dose of hMG is 75 international units two to three times weekly, typically administered subcutaneously (Sokol, 2009).

Rarely, men may have isolated decreased secretion of either LH or FSH (Giltay et al, 2004; Sokol, 2009). Isolated LH deficiency was termed the “fertile eunuch syndrome” and characterizes men who have features of hypoandrogenism owing to low levels of LH but who produce sperm as a result of adequate FSH (Sokol, 2009). Conversely, men with isolated FSH deficiency have suppressed spermatogenesis but adequate androgenization (Giltay et al, 2004).

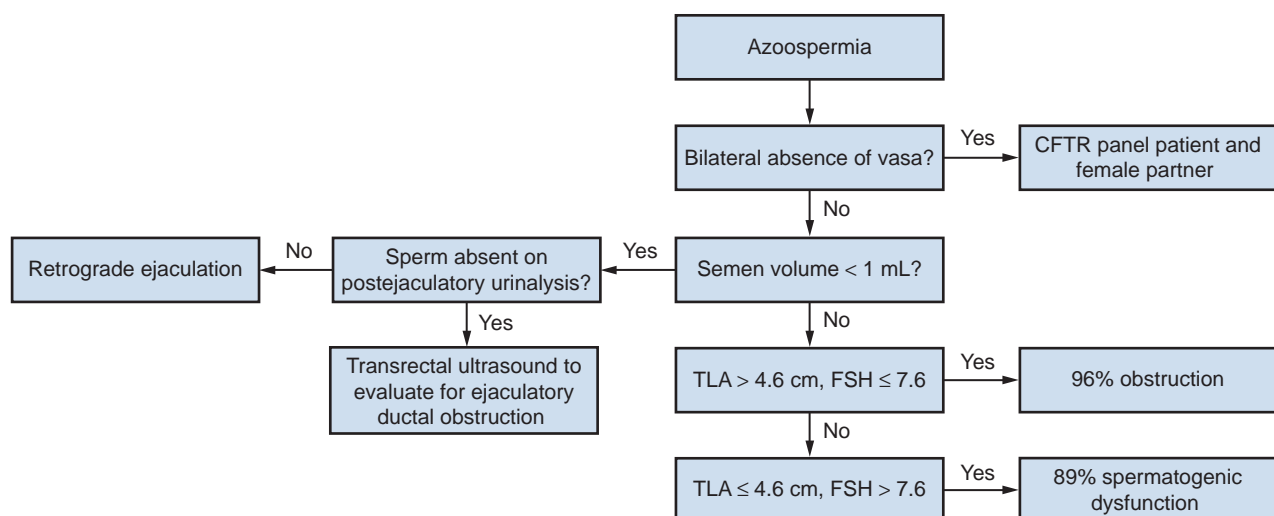


Figure 24-11. Algorithm for evaluation of azoospermia. CFTR, cystic fibrosis transmembrane conductance regulator; FSH, follicle-stimulating hormone; TLA, testis longitudinal axis measured by caliper orchidometer.

Treatment of these uncommon conditions includes replacement with the appropriate gonadotropin (Giltay et al, 2004; Sokol, 2009). Men may also infrequently have isolated hypothalamic GnRH deficiency (Nachtigall et al, 1997). Treatment includes GnRH administration by a subcutaneous portable mini-infusion pump every 2 hours, and, as with treatment for Kallmann syndrome, long-term courses of at least 6 months' duration may be required (Nachtigall et al, 1997).

Kallmann and the associated syndromes of hypogonadotropic hypogonadism are the most severe forms of conditions resulting in diminished pituitary hormonal secretion. **Incomplete forms with hypoandrogenism associated with serum LH concentrations above those observed with Kallmann syndrome but lower than expected for the diminished testosterone are common** (Bhagavath et al, 2006). For these men, pituitary stimulation with anti-estrogenic agents such as clomiphene or tamoxifen or with aromatase inhibitors such as anastrozole or letrozole may restore testosterone levels and possibly improve spermatogenesis (Raman and Schlegel, 2002; Siddiq and Sigman, 2002; Hussein et al, 2005; Ioannidou-Kadis et al, 2006; Whitten et al, 2006; Sussman et al, 2008; Katz et al, 2012; Moskovic et al, 2012; Hussein et al, 2013; Roth et al, 2013). The initial dose of clomiphene citrate is typically 25 mg every day or 50 mg every other day and is increased by titrating to serum testosterone to a maximum of 100 mg daily (Hussein et al, 2005; Sussman et al, 2008; Hussein et al, 2013). In some studies, the titration target is restoration of normal androgen levels; in others, it is elevated at 600 to 800 ng/dL (Hussein et al, 2005; Sussman et al, 2008; Hussein et al, 2013). The typical dose of anastrozole is 1 mg daily (Raman and Schlegel, 2002).

Prader-Willi syndrome is characterized by failure to thrive in infancy associated with a poor suck reflex followed by loss of satiety in early childhood, which may lead to marked obesity if poorly controlled (Cassidy and Driscoll, 2009). Its incidence is approximately 1 in 15,000 to 30,000 (Cassidy and Driscoll, 2009). Features associated with the syndrome include hypogonadism, small testes, dysmorphic facies, growth hormone deficiency with short stature and small hands and feet, pain insensitivity, and cognitive disorders such as obsessive-compulsive traits (Bervini and Herzog, 2013). Researchers have suspected that the association of growth hormone deficiency and hypogonadism with the syndrome derive from hypothalamic dysfunction, but the precise pathophysiology is still uncertain (Bervini and Herzog, 2013). Prader-Willi syndrome is typically caused by the loss of expression of genes located on human chromosome 15q11-q13 by means of failed imprinting, which is the epigenetic phenomenon that allows genes on only one chromosome to be active (Bervini and Herzog, 2013). In the healthy state, the genes located on the maternal chromosome 15q11-q13 are silenced, and those on the paternal chromosome are active; in Prader-Willi syndrome, the maternal genes are silenced and the paternal ones inactive (Bervini and Herzog, 2013).

Pituitary Tumors and Diseases

Space-occupying lesions in the sella turcica such as secretory and nonsecretory tumors and craniopharyngiomas may compress the anterior pituitary and result in varying degrees of LH and FSH suppression (Sokol, 2009). The most common kind of pituitary tumor resulting in male reproductive dysfunction secretes prolactin and is commonly associated with other symptoms such as erectile dysfunction (Sokol, 2009). These tumors are rare; as described in the section discussing the endocrine evaluation, in one series of 1035 men undergoing an infertility evaluation, only 4, or 0.4%, had hyperprolactinemia (Sigman and Jarow, 1997). This finding questions the value of including prolactin as a routine assay in screening infertile men, especially those who are otherwise asymptomatic (Sigman and Jarow, 1997; Sokol, 2009; Niederberger, 2011). In general, mild elevations of prolactin in the range of 20 to 50 µg/L do not warrant further evaluation; if prolactin is significantly elevated, cranial MRI is indicated (Niederberger, 2011). The dopamine agonists bromocriptine and cabergoline may be prescribed for

prolactin-secreting adenomas for which surgery is not indicated, with cabergoline exhibiting fewer side effects (Klibanski, 2010).

Other Pituitary Lesions

Diseases infiltrating the pituitary may also suppress its secretion of hormones, including granulomata of infection, sarcoidosis, and histiocytosis (Sokol, 2009). Deposition of iron by hemochromatosis or repeated blood transfusions may also invoke hypogonadotropic hypogonadism (Sokol, 2009). Systemic diseases such as morbid obesity, chronic malnutrition, and type 2 diabetes may also be associated with hypogonadotropic hypogonadism (Dhindsa et al, 2004; Sokol, 2009). Treatment of these disorders is aimed at ameliorating the underlying condition.

Extrapituitary Endocrine Modulators

As described in the section discussing the role of investigating endocrine modulators when taking the history of an infertile man, exogenous androgenic agents, especially testosterone, suppress pituitary gonadotropins (Grimes et al, 2012). Also discussed in that section are cannabis, antipsychotics, opioids, and environmental toxicants, which inhibit pituitary function via estrogenic and dopaminergic pathways (Carlsen et al, 1992; Stimmel and Gutierrez, 2006; Gorzalka et al, 2010; Subirán et al, 2011). Treatment is directed toward removing the offending agent when possible. CAH, especially in milder forms that manifest clinically in adolescence or adult life, may be associated with hypogonadotropic hypogonadism (Reisch et al, 2011). A high incidence of testicular adrenal rest tumors adds to the reproductive dysfunction present in these men (Claahsen-van der Grinten et al, 2008; Reisch et al, 2011). Fertility may be restored with corticosteroid therapy (Claahsen-van der Grinten et al, 2007). However, side effects such as weight gain and skin changes from the lengthy application of therapy required to address the long duration of spermatogenesis may prove problematic (Claahsen-van der Grinten et al, 2007).

Extratesticular Endocrine Dysfunction

Because estradiol inhibits gonadotropin release, conditions that increase its concentration may lead to hypogonadotropic hypogonadism. These include the pharmacologic agents described in the section discussing medications that alter the ratio of estrogen to androgen through a variety of means (Bowman et al, 2012). When possible, use of another agent may improve fertility. As described in the section discussing the general physical examination of the infertile male, elevated estradiol is associated with obesity by the mass of adipose cells containing aromatase (Hammoud et al, 2006; Aggerholm et al, 2008; Chavarro et al, 2010; Hammoud et al, 2010b; Hofny et al, 2010). Multiple factors are suspected to associate obesity with male infertility, and hypogonadotropic hypogonadism may or may not be involved (Hammoud et al, 2006; Aggerholm et al, 2008; Pauli et al, 2008; Hofny et al, 2010; Paasch et al, 2010; Teerds et al, 2011). The question remains regarding whether diet, exercise, and weight reduction improve male reproductive potential. Limited animal studies in an obese rodent model suggest that diet and exercise improve sperm parameters, but human studies are sparse and inconclusive (Nguyen et al, 2007; Braga et al, 2012; Palmer et al, 2012; Luconi et al, 2013). In the absence of conclusive data demonstrating a causative effect between weight loss and improved male fertility, it still seems prudent to recommend it in obese men because the ancillary health benefits are certain.

Researchers have investigated the use of aromatase inhibitors such as anastrozole, letrozole, and testolactone for elevated estradiol, demonstrating that for the typical male patient, testosterone levels increase and estradiol levels decline (Raman and Schlegel, 2002; Gregoriou et al, 2012; Schlegel, 2012). Limited data support that sperm parameters may concurrently improve (Raman and Schlegel, 2002; Gregoriou et al, 2012; Schlegel, 2012). As described in the section discussing the endocrine evaluation of male infertility, researchers have proposed that a testosterone-to-estradiol ratio

in nanograms per deciliter (ng/dL) to picograms per milliliter (pg/mL) of less than 10:1 indicates aromatase overactivity that would benefit from inhibitory therapy (Raman and Schlegel, 2002; Gregoriou et al, 2012; Schlegel, 2012). Prescribers should be cautious in the long-term use of aromatase inhibitors, because bone density in the male may be estradiol dependent, and long-term studies of this class of drug in men are lacking (Khosla et al, 2001; Kim et al, 2013).

Mutations in the androgen receptor (AR) gene located on the long arm of the X chromosome at banding region Xq11-12 lead to a spectrum of disorders from complete testicular feminization to male infertility (Dowsing et al, 1999; Davis-Dao et al, 2007; Sokol, 2009). Male reproductive dysfunction appears to be related to a longer cytosine-adenine-guanine (CAG) repeat length in exon one of the AR gene (Dowsing et al, 1999; Davis-Dao et al, 2007; Sokol, 2009). Male infertility associated with AR insensitivity is characterized by increased testosterone, estradiol, and LH to variable degrees with typical FSH levels; significantly elevated testosterone in the presence of impaired male fertility should consequently raise the suspicion of AR resistance (Sokol, 2009). High-dose testosterone therapy may result in improved spermatogenesis, but data on this form of treatment are limited (Tordjman et al, 2014). Pregnancy may be achieved by ICSI with ejaculated sperm or that derived by surgical extraction from the testis (Massin et al, 2012; Tordjman et al, 2014).

Because dihydrotestosterone regulates the anatomic development of external male genitalia, mutations in the gene encoding isozyme 2 of 5 α -reductase located on the short arm of chromosome 2 at banding region 2p23 result in a spectrum ranging from a female to a male phenotype (Johnson et al, 1986; Thigpen et al, 1993; Sokol, 2009). Phenotypic females with 5 α -reductase 2 mutations may harbor testes with intact spermatogenesis (Johnson et al, 1986; Thigpen et al, 1993). No medical treatment is currently available for this disorder. Pregnancies have been successfully attained with ICSI from sperm from men with 5 α -reductase-2 deficiency (Matsubara et al, 2010; Kang et al, 2011).

Developmental Disorders

Anatomic development that results in aberrant genital formation may manifest in later life as male infertility. Main areas of maldevelopment include the testes, the external genitalia, and the reproductive microductal system.

Intersex or Disorders of Sexual Development

Previously, intersex was divided into categories such as male pseudohermaphroditism, female pseudohermaphroditism, true hermaphroditism, and mixed or complete gonadal dysgenesis, with true hermaphrodites having components of both ovaries and testes (Oates and Lamb, 2009; Ono and Harley, 2013). Disorders of sex development (DSDs) are increasingly being understood as the consequence of specific aberrant genes, and the current nomenclature used to describe intersex now includes the karyotype, a clinically descriptive term, and the molecular basis of the disorder if it is known (Ono and Harley, 2013). An example of an intersex description using this nomenclature might be "46,XY DSD complete gonadal dysgenesis with SF1 mutation" (Ono and Harley, 2013). Genes identified to be involved in DSD are too numerous to be listed here, and the reader is referred to Ono and Harley for a current review (Ono and Harley, 2013). In general, the genes involved in DSDs that manifest as male infertility do so by developmental anatomic abnormalities, abnormal or absent spermatogenesis, general endocrinopathy, or encoding for defective endocrine receptors and target complexes (Oates and Lamb, 2009; Ono and Harley, 2013).

Hypospadias and Epispadias

Aberrant anatomic location of the urethra in hypospadias or epispadias may result in deposition of semen too distal in the vaginal

vault (Niederberger, 2011). These men may have adequate bulk seminal parameters, and if screening semen analysis is performed before physical examination of the man, the diagnosis may be missed. Hypospadias appears to have both genetic and environmental causes, with genetic polymorphisms playing a predominant role rather than isolated gene defects (Macedo et al, 2012). The pathophysiology of epispadias is different from that of hypospadias, and it is typically considered on the spectrum of bladder-exstrophy-epispadias complex (BEEC) disorders (Rasouly and Lu, 2013).

Cryptorchidism

The basis of cryptorchidism and the relationship of the disorder to male reproductive function is detailed in the section of this chapter describing childhood diseases in the reproductive history of the infertile male. The most significant feature related to the prognosis of cryptorchidism is whether the condition is unilateral or bilateral (Lee et al, 2001; Miller et al, 2001; Lee, 2005).

Microductal Aplasia

The vas deferens may fail to develop on one side or both. The distinction is significant, as the pathophysiologic basis of each is different.

Congenital Unilateral Absence of the Vas Deferens. As described in the section detailing the physical examination of the infertile male, unilateral absence of the vas deferens implies that wolffian, or mesonephric, ductal development on the ipsilateral side was aberrant. As these ducts become in embryogenesis the epididymis, vas deferens, and ejaculatory duct, the proximal and distal portions may be malformed or absent as well (Lewis and Kaplan, 2009). The most important consideration if unilateral absence of the vas is observed is that because renal development is coupled with wolffian ductal development, a solitary absent vas deferens may signal renal agenesis (Niederberger, 2011).

Congenital Bilateral Absence of the Vas Deferens. Oates and colleagues reported in the early 1990s that males with CBAVD had a high frequency of genetic sequence abnormalities associated with cystic fibrosis (Anguiano et al, 1992). Coupled with the observation that in nearly all men with cystic fibrosis the vasa are absent bilaterally, these findings suggested that CBAVD is frequently a phenotype for a spectrum of disorders involving mutations in the gene responsible for cystic fibrosis (Anguiano et al, 1992). As described in the section discussing genomic sequence assessment in the laboratory evaluation of the infertile male, that gene encodes a predominantly chloride ion channel termed the *cystic fibrosis transmembrane conductance regulator*, and currently more than 1600 mutations in the gene have been identified, which vary in the severity of the phenotype from CBAVD to cystic fibrosis (Ratbi et al, 2007; Oates and Lamb, 2009; Hampton and Stanton, 2010; Bombieri et al, 2011; Yu et al, 2012).

It is currently believed that two genetic causes of CBAVD exist: one that results from mutations in CFTR, and another that results from alterations in as-yet-unidentified other genes involved in mesonephric ductal development (Oates and Lamb, 2009). CFTR mutations represent a spectrum of disease severity; should both alleles harbor severe mutations, cystic fibrosis results, and if one or both alleles contain the milder forms, CBAVD may occur (Ratbi et al, 2007; Oates and Lamb, 2009; Hampton and Stanton, 2010; Bombieri et al, 2011; Yu et al, 2012). As described in the section detailing genomic sequence assessment, the most common mutation is $\Delta F508$, which is severe (Hampton and Stanton, 2010). The carrier frequency for cystic fibrosis gene mutations is high—approximately 1 in 20 in persons of Northern European descent—and it is consequently important to investigate the CFTR status of the female partner of a man identified to have CBAVD in addition to his genetic evaluation (Oates and Lamb, 2009). Symptoms such as chronic sinus or respiratory infections may be overlooked if mild, and the urologist diagnosing CBAVD might be the first to uncover an indolent form of cystic fibrosis (Oates and Lamb, 2009).

Spermatogenesis in men with CBAVD is typically normal, and ICSI with surgically extracted sperm is typically effective (Kamal et al, 2010). Genetic counseling taking into account the CFTR genetic assessment of the affected man and his female partner allows for the couple to understand the likelihood of cystic fibrosis in offspring and the implications of carrier status, and it may be performed by the urologist or a clinical geneticist.

Varicocele

The diagnosis of varicocele was discussed in the section detailing the physical examination of the infertile man: why imaging such as ultrasound is most rationally not recommended for the screening evaluation of a varicocele is discussed in the section describing imaging.

That most men with varicocele have sperm present on semen analysis has proved to be one of the most confounding aspects of its diagnosis and treatment. As discussed in the section describing the semen analysis, the results of this assay are assessed in a probabilistic context with substantial variability, making analytical statements concerning its effect on male reproductive potential difficult. Taking into account confounding factors involving the female partner that are often opaque and difficult to control in analyses, determining the effect of a varicocele on pregnancy, miscarriage, and birth becomes intractable. However, substantial evidence links varicocele to spermatogenic dysfunction and impaired male reproductive potential.

Because the left internal spermatic vein drains into the left renal vein approximately 8 to 10 cm superior to the entry of the right internal spermatic vein draining into the vena cava, the hydrostatic column of blood on the left predisposes that side to incompetence in its venous valves more so than on the right (Shafik and Bedeir, 1980; Gat et al, 2005; Masson and Brannigan, 2014). **As a result, varicose veins in the pampiniform plexus are more common on the left than on the right (Gat et al, 2005; Masson and Brannigan, 2014).** The incidence of bilateral varicoceles depends on the techniques involved in detection, with over 80% observed to be bilateral on contact thermography, Doppler sonography, and venography in one series (Gat et al, 2004). Whether these bilateral varicoceles so identified are clinically significant remains an open question. **One clinical consequence of the infrequency of solitary right varicoceles is that should one be identified, renal pathology such as tumor should be considered, especially if the right-sided varicocele is of abrupt onset (Masson and Brannigan, 2014).**

Varicoceles likely arise as most varicose veins do by intravenous valvular incompetence (Wishahii, 1991; Gat et al, 2005). Genetics may predispose to a valvular defect, as investigators have noted an increased incidence of varicoceles in first-degree relatives of men with a known varicocele (Raman et al, 2005).

Substantial evidence correlates the presence of palpable varicoceles to male reproductive dysfunction. Bulk seminal parameters are poorer in men with varicocele than in the fertile population (WHO, 1992; Al-Ali et al, 2010). Testis size, which reflects the mass of spermatogenesis, is smaller in men with varicocele, and investigators have documented progressive atrophy associated with the condition (Lipshultz and Corriere, 1977; Sakamoto et al, 2008; Patel and Sigman, 2010).

Most studies investigating how varicocele exerts deleterious effects on male reproductive function consider the primary event to be an increase in intratesticular temperature secondary to interruption in the counter-current heat exchange provided in the pampiniform plexus with opposing flow vectors in a central arterial system and surrounding veins (Zorgniotti and MacLeod, 1973; Goldstein and Eid, 1989; Masson and Brannigan, 2014). The proposed mechanisms by which male fertility is impaired by this effect mainly include DNA fragmentation and apoptosis, oxidative stress, predisposition to aneuploidy, and intracellular metabolic and ionic changes (Benoff et al, 2004; Smith et al, 2005; Baccetti et al, 2006; Bertolla et al, 2006; Enciso et al, 2006; Lima et al, 2006; Zucchi et al, 2006; Shiraishi and Naito, 2007; Agarwal et al, 2008c; Blumer et al, 2008; Pasqualotto et al, 2008a; Ghabili

et al, 2009; Wu et al, 2009; Abd-Elmoaty et al, 2010; El-Domyati et al, 2010).

Ejaculatory Dysfunction

Disorders of ejaculation may be anatomic, functional, or neuropathic in origin, resulting in absence of emission, resistance, or misdirection. The three main categories of ejaculatory dysfunction encountered in a clinical setting include ejaculatory ductal obstruction, retrograde ejaculation, and anejaculation.

Ejaculatory Ductal Obstruction

The ejaculatory ducts are primarily intraprostatic structures that originate at the terminus of the seminal vesicles and serve as their extensions but without their musculature, functioning within the prostate as simple conduits (Nguyen et al, 1996). The ampulla of the vas enters the prostate medially and at an acute angle with the terminating limb of the seminal vesicle (Nguyen et al, 1996). The intraprostatic conduit ends angled at the verumontanum, which contains two layers of longitudinal muscular bundles extending into the urethra (Nguyen et al, 1996).

Obstruction of the ejaculatory ducts is infrequent and is the cause of azoospermia in less than 5% of men without sperm in the ejaculate (Wosnitzer and Goldstein, 2014). It may occur at any point along the transit of the ducts within the prostate and result from infection, inflammation, prior surgery, or compression by congenital cysts (Wosnitzer and Goldstein, 2014). As detailed in the section discussing the semen analysis, an evaluation for ejaculatory ductal obstruction is indicated when the seminal volume is less than 1.0 mL. As noted in the section describing imaging to evaluate for ejaculatory ductal obstruction, techniques to investigate it include TRUS, MRI, chromotubation, and hydraulic pressure measurements. If clinically significant ejaculatory ductal obstruction is suspected and if the position of the obstruction is amenable to surgery, treatment is surgical resection.

Retrograde Ejaculation

Ejaculation is a multiphasic event that includes coordinated neural activity and muscular contraction and relaxation (Jefferys et al, 2012; Phillips et al, 2014). Afferent genital stimulation and cognitive ideation initiate the process, which induces emission through sympathetic stimulation of the bladder neck, vasal ampullae, seminal vesicles, and prostate (Jefferys et al, 2012; Phillips et al, 2014). **Essential to antegrade ejaculation, the bladder neck must first close while temporal neural sequencing first causes closure of the external sphincter to create a high pressure compartment that is emptied with its subsequent opening (Shafik, 1995).**

Failure of sufficient resistance at the bladder neck during generation of the high-pressure system within the prostatic urethra may redirect emission into the bladder, causing retrograde ejaculation. Pathologic causes include congenital abnormalities of or surgery to the bladder neck, spinal cord or neural injury during trauma or retroperitoneal lymph node dissection, diabetes mellitus, or idiopathic causes (Jefferys et al, 2012). **Like ejaculatory ductal obstruction, retrograde ejaculation is infrequent and is established as the diagnosis in less than 2% of infertile men (Jefferys et al, 2012).**

As detailed in the section discussing the semen analysis, an evaluation for ejaculatory ductal obstruction is indicated when the seminal volume is less than 1.0 mL and includes a postejaculatory urinalysis, which is considered significant if the number of sperm in the urine nears or exceeds that in the antegrade specimen (Sigman et al, 2009). **Primary treatment modalities include retrieval of retrograde ejaculated sperm and increasing resistance at the bladder neck with sympathomimetic agents.** In both cases, the sperm so obtained is processed for use in IUI or IVF. If retrieval is to be attempted, the urine is typically first alkalinized with oral bicarbonate or diluted by oral fluid intake, and then the voided urine or a catheterized specimen is obtained after masturbation and orgasm (Jefferys et al, 2012). Investigators have also described

ejaculation on a full bladder with successful results (Crich and Jequier, 1978; Templeton and Mortimer, 1982). Clinicians may also use sympathomimetic agents such as synephrine, pseudoephedrine, ephedrine, or phenylpropanolamine, with approximately one in four patients achieving antegrade ejaculation (Jefferys et al, 2012). Researchers have described other therapy such as anticholinergic agents, acupuncture, and surgery, but these should be considered investigational (Jefferys et al, 2012).

Anejaculation

Anejaculation refers to lack of seminal emission and projectile ejaculation, and it must be distinguished from anorgasmia, in which the absence of an ejaculation has a cerebral cause (Brackett et al, 2009). Conditions that result in anejaculation are primarily neurologic and include retroperitoneal lymph node dissection, pelvic surgery, multiple sclerosis, transverse myelitis, congenital neural tube defects, diabetes mellitus, and spinal cord injury (Brackett et al, 2009; Phillips et al, 2014).

For patients with sufficient peripheral neural function, neurostimulation with penile vibratory devices or application of current with a rectal electrode, or electroejaculation, may result in sufficient sperm for IUI or IVF (Brackett et al, 2009; Phillips et al, 2014). For men with spinal cord injuries at a level of T6 or above, stimulation may cause autonomic dysreflexia, an uninhibited sympathetic reflex accompanied by headache, diaphoresis, hypertension, bradycardia, and diaphoresis, which may be life-threatening. Autonomic dysreflexia can be addressed before stimulation by treatment with nifedipine and during the procedure with monitoring of cardiac activity and blood pressure (Brackett et al, 2009; Phillips et al, 2014).

The sperm achieved by stimulation in patients with spinal cord injury is typically characterized by adequate count but impaired motility (Brackett et al, 2009). Evidence supports impairment of sexual accessory gland function, a noxious seminal plasma milieu, and immunopathic mechanisms as causative (Brackett et al, 2009).

Stimulation with penile vibratory devices serves as first-line therapy, with electroejaculation used if the former is unsuccessful (Brackett et al, 2009). If electroejaculation does not yield sperm or if other factors prevent its use, surgical extraction is indicated (Brackett et al, 2009).

Structural Sperm Abnormalities

As discussed in the section describing evaluation of sperm morphology, the majority of sperm in fertile men are eccentrically shaped, and associating the typical variation of sperm shape to clinical relevance in a quantifiable manner has proved challenging. Investigators have characterized certain infrequent discrete structural abnormalities with overt clinical manifestations.

Evidence suggests genetic bases and consequences for two rare types of specific sperm head abnormalities, globozoospermia and macrocephaly. In globozoospermia, the majority of the sperm lack acrosomal caps, rendering the heads spheric rather than ovoid. Investigators have associated globozoospermia in humans with mutations in the genes *SPATA16* at chromosome band 3q26.32, *PICK1* at 22q12.3-q13.2, and *DPY19L2* at 12q14.2 (Perrin et al, 2013). Both *SPATA16* and *PICK1* localize to proacrosomal granules that are involved in formation of the acrosome during spermatogenesis (Perrin et al, 2013). It is debatable whether higher rates of aneuploidy are present in patients with globozoospermia or teratozoospermia in general; however, for men in whom nearly all sperm have enlarged heads, multiple tails, and abnormal acrosomes, a very high rate of aneuploidy is found (Machev et al, 2005; Sun et al, 2006). The treatment for globozoospermia is IVF with ICSI; owing to the high rate of aneuploidy in sperm associated with macrocephaly and multiple tails, ICSI is not recommended (Machev et al, 2005; Sun et al, 2006; Perrin et al, 2013).

As discussed in the section describing the ultrastructural assessment of sperm, *primary ciliary dyskinesia* refers to a rare condition in which the microtubular architecture of cilia is disrupted (Boon et al,

2013). Because structures such as the sperm tail share similar microtubular construction with cilia, conditions that affect this architecture frequently result in a variety of other clinical manifestations such as immotile sperm, congenital heart disease, chronic respiratory and otolaryngologic infections, and laterality defects (Ferkol and Leigh, 2012). PCD occurs in 1 in 15,000 to 30,000 live births and is typically inherited in an autosomal recessive manner, with occasional X-linked inheritance reported (Ferkol and Leigh, 2012; Boon et al, 2013). Investigators have associated numerous genetic mutations with PCD, with mutations in dynein axonemal heavy chain 5 (DNAH5) and intermediate chain 1 (DNAI1) accounting for 38% of patients with the condition (Hildebrandt et al, 2011; Zariwala et al, 2011; Davis and Katsanis, 2012; Ferkol and Leigh, 2012; Boon et al, 2013). ICSI may achieve pregnancy in cases of PCD (Peeraer et al, 2004).

Empirical Treatment

Please see the Expert Consult website for details.



KEY POINTS: DIAGNOSES AND THERAPIES

- Klinefelter syndrome, characterized by 47,XXY, is the most commonly identified genetic cause of male infertility. Bodily morphologic features cannot reliably exclude the presence of the condition.
- The clinical evaluation of a man identified with CBAVD includes CFTR assessment of both him and his female partner to determine risk of cystic fibrosis in offspring.
- Severe hypogonadotropic hypogonadism may be associated with anosmia and is treated with gonadotropin replacement. Less severe forms are more common, and patients may respond to antiestrogenic agents or aromatase inhibitors.

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The complete reference list is available online at www.expertconsult.com.



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In general, empirical treatment falls within two categories: either endocrine or nutraceutical based. The highly variable character of the semen analysis and its probabilistic nature make empirical treatments of male infertility difficult to assess without carefully conducted controlled clinical trials. Unfortunately, few exist. Investigators have reported results of many uncontrolled trials of selective endocrine receptor modulators such as clomiphene or gonadotropins in men, but the few available clinical trials usually do not demonstrate pregnancy rates to be greater than that expected by nature acting alone ([Vandekerckhove et al, 2000](#); [Siddiq and Sigman, 2002](#); [Attia et al, 2007](#)). **Consequently, should endocrine treatment be applied, identified endocrine dysfunction should be first demonstrated.**

Aside from endocrine therapy, nutraceuticals serve as the subject of many published reports, with antioxidant activity a common theme for proposed benefit. A Cochrane collaboration review concluded that results from small randomized controlled trials

supported that for subfertile couples undergoing ART, antioxidant supplementation in subfertile men may increase live birth rates, especially for vitamin E, zinc, and a multivitamin ([Vandekerckhove et al, 2000](#)). Investigators have studied the effects of Coenzyme Q10, or ubiquinone, a component of the mitochondrial electron transport chain, on semen analysis parameters in several small controlled trials, with improvement in sperm density and motility observed compared with placebo ([Balercia et al, 2009](#); [Safarinejad, 2009](#); [Safarinejad et al, 2012](#); [Lafuente et al, 2013](#)). Larger, blinded and randomized controlled trials will be required before definitive recommendations may be made regarding nutraceutical efficacy for improving male reproductive potential. The reproductive medical literature is rife with numerous noncontrolled trials of various nutraceuticals and sperm parameters, but, in general, owing to the highly variable nature of seminal metrics, the effect of regression to the mean prevents assessment of results.

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Surgical Anatomy

Testis Biopsy

Vasography

Vasovasostomy

Surgery of the Epididymis

Transurethral Resection of the Ejaculatory Ducts

Electroejaculation

Sperm Retrieval Techniques

Varicocelectomy

Orchiopexy in Adults

Since the 10th edition of this book was published, the indications for and techniques of surgery for male infertility have been significantly refined, resulting in substantially increased success in the management of male-factor infertility. These advances include (1) increasing use of genetic and molecular biologic markers (see Chapters 22 and 24) to better select patients for surgical treatment; (2) improved techniques for microsurgical reconstruction for obstruction; (3) the use of varicocelectomy for enhancement of spermatogenesis in azoospermic or severely oligospermic men (Inci et al, 2013; Kirac et al, 2013), for prevention of future infertility and androgen deficiency in young men, and for treatment of androgen deficiency in men of all ages (Tanrikut et al, 2011); and (4) refined microsurgical techniques for sperm retrieval combined with in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI) for men with nonobstructive azoospermia. Even men with nonobstructive azoospermia caused by Klinefelter syndrome, once regarded as hopeless cases, can now father biologic offspring with assisted reproductive techniques (Tournaye et al, 1996; Palermo et al, 1998; Ramasamy et al, 2009).

Use of transrectal high-resolution ultrasound as well as scrotal ultrasound with color flow Doppler has substantially improved our diagnostic and therapeutic abilities. Not only does transrectal ultrasound of the seminal vesicles provide diagnostic information, but ultrasound-guided aspiration of the seminal vesicles allows retrieval of sperm to be used for IVF with ICSI (Jarow, 1996). Power Doppler may allow identification of pockets of sperm production in the testis, which may help guide sperm retrieval in men with nonobstructive azoospermia (Har-Toov et al, 2004; Herwig et al, 2004; Tunc et al, 2005). Experimental use of multiphoton tomography in animals and human tissue has potential to further refine our ability to identify sperm in testes (Najari et al, 2012).

IVF with ICSI has expanded our ability to treat even the most severe forms of male-factor infertility such as unreconstructable reproductive tract obstruction and nonobstructive azoospermia. It is, however, a costly procedure and an intense process for the female partner, with associated risks of complications including ovarian hyperstimulation and multiple gestations, as well as complications of the procedures for oocyte retrieval. Furthermore, because ICSI bypasses all natural biologic barriers, it raises realistic concerns of passing genetic abnormalities to the offspring (Kim et al, 1998; Foresta et al, 2005) and is associated with an increased incidence of birth defects in resultant children (Davies et al, 2012). On the other hand, recent analyses clearly indicate that specific treatments for male-factor infertility, such as microsurgical reconstruction for obstructive azoospermia and varicocelectomy for impaired testis function, in properly selected patients remain the safest

and most cost-effective ways of managing infertile men (Kolettis and Thomas, 1997; Pavlovich and Schlegel, 1997; Marmar et al, 2007; Lee et al, 2008; Smit et al, 2010). Specific treatment aimed at correcting or enhancing male infertility can upgrade a couple from intensive levels of assisted reproduction to simpler methods such as intrauterine insemination (IUI) or even to naturally conceived pregnancies (Samplaski et al, 2013).

For men with unreconstructable obstruction as well as men with nonobstructive azoospermia, surgical retrieval of sperm to achieve fertilization, pregnancy, and live birth with IVF and ICSI is a feasible management option. The development and recent refinement of the various techniques of surgical sperm retrieval, from testes, epididymides, or seminal vesicles, with percutaneous or open surgical approaches, have expanded the armamentarium of urologists treating infertile men. In particular, use of the operating microscope to evaluate and identify individual seminiferous tubules more likely to contain sperm has significantly improved the success of testicular sperm extraction (TESE) (Schlegel, 1999; Dabaja and Schlegel, 2013) while minimizing morbidity significantly (Tsujimura et al, 2002; Ramasamy et al, 2005).

The use of microsurgical techniques has also been extended to varicocelectomy. Varicoceles have long been known to be associated with male infertility and have now clearly been shown to result in progressive, duration-dependent testicular injury (Russell, 1957; Lipshultz and Corriere, 1977; Nagler et al, 1985; Sigman and Jarow, 1997). Furthermore, microsurgical varicocelectomy, previously reserved only for men with oligospermia, has now been applied to men with nonobstructive azoospermia, resulting in induction of spermatogenesis and successful return of sperm to the ejaculate in many patients (Matthews et al, 1998; Kim et al, 1999; Pasqualotto et al, 2003, 2006; Ishikawa et al, 2008; Youssef et al, 2009). Although varicocelectomy has historically been reserved for the treatment of infertile men and varicocele-induced pain, there is an emerging concept of early repair of varicoceles to prevent both future infertility and Leydig cell dysfunction. Substantial evidence has accumulated suggesting that varicocele adversely affects Leydig cell function, resulting in lower serum testosterone levels when compared with age-matched controls without varicocele (Tanrikut et al, 2011). Varicocelectomy can halt and even partially reverse this decline (Castro-Magana et al, 1989; Su et al, 1995; Cayan et al, 1999; Tanrikut et al, 2011). In selected men, varicocelectomy may be an effective treatment for symptomatic, age-related androgen deficiency, a condition increasingly referred to as *andropause* or *testosterone deficiency syndrome* (TDS). Thus, with safer and more effective microsurgical techniques, early varicocelectomy has expanded the urologist's role from that of

salvaging remaining testicular function to that of preventing future infertility and TDS.

When surgery for male infertility is undertaken, only rarely is the life (or death) of the patient at stake. What is at stake when the surgery described in this chapter is undertaken is new life, with the potential for altering not only the quality of a couple's life but the future of our species. The responsibilities assumed by the surgeon in these circumstances demand the utmost in judgment and skill. Many of the procedures described in this chapter are among the most technically demanding in all of urology. Acquisition of the skills required to perform them demands intensive laboratory training in microsurgery and a thorough knowledge of the anatomy and physiology of the male reproductive system. Attempting such surgery only occasionally and without proper training would be doing a terrible disservice to the patient and his partner.

SURGICAL ANATOMY

The scrotal contents are unique in their accessibility for physical examination, imaging modalities, and surgical intervention. The success of surgery for male infertility and scrotal disorders is predicated on selection of the correct operation and the most appropriate surgical approach. The details of the history and careful physical examination followed by confirmatory, judiciously selected laboratory and imaging procedures are presented in Chapter 24. When surgical intervention for diagnostic or therapeutic purposes is indicated, a thorough understanding of the anatomy (see Chapter 21) and physiology (see Chapter 22) of the male reproductive system is requisite for planning and carrying out a surgical procedure with the highest probability of success and lowest morbidity.

The key points of surgical anatomy are discussed in the following sections.

Testicular Blood Supply (Box 25-1)

The main blood supply to the testis is from the testicular (internal spermatic) artery arising directly from the aorta. A second blood supply comes from the artery of the vas deferens (deferential artery), which derives from the hypogastric (internal iliac) artery or the superior vesical artery (also a branch of the hypogastric). The third blood supply, primarily to the tunica vaginalis, but with branches going to the testes, comes from the cremasteric (external spermatic) artery, which derives from the inferior epigastric artery. **The testicular artery is the main blood supply to the testes.** Its diameter exceeds the diameter of the deferential (vasal) artery and the cremasteric artery combined (Raman and Goldstein, 2004). Although the vasal and cremasteric arteries can provide adequate blood

supply to the testes in the event that the testicular artery is ligated, especially in children, **atrophy and/or azoospermia has resulted from testicular artery ligation both in adults and in children.** Experience with the one-stage Fowler-Stephens operation for orchiopepy, in which the testicular artery is intentionally ligated, indicates that 20% to 40% of such testes atrophy, although the rate of atrophy is lower in the staged procedure.

Special attention should be paid to men who have undergone vasectomy, in whom the vasal artery has likely been compromised. In these men, maintaining the integrity of the testicular artery in any future operations, such as varicocelectomy, is critical (Lee et al, 2007b).

Epididymal Blood Supply (see Box 25-1)

The epididymis has a rich blood supply. The superior and the medial epididymal arteries derive from the testicular artery. The blood supply to the cauda (inferior pole) of the epididymis derives from the vasal (deferential) artery. The two main blood supplies to the epididymis, running superiorly and inferiorly, form an extensive interconnection such that if the vasal artery is ligated from previous vasectomy, the blood supply to the epididymis from the testicular artery is more than adequate. In addition, in preparation for vaso-epididymostomy or vasovasostomy, the epididymis can be intentionally dissected off the testis and mobilized to the caput (see the discussion of long-term follow-up, evaluation, and results), with the inferior and medial epididymal arteries intentionally ligated without adverse consequence. **As long as the superior epididymal artery remains intact, the blood supply to the epididymis will be adequate.**

Blood Supply of the Vas Deferens (see Box 25-1)

The vas deferens obtains its blood supply from two sources. The seminal vesical (abdominal) end of the vas derives its blood supply from the deferential (vasal) artery. The testicular end of the vas receives additional blood supply from the inferior epididymal arterial interconnections, which extend onto the vas deferens. The two blood supplies to the vas deferens freely anastomose with each other. **After vasectomy, if the vasal vessels are ligated, the testicular end of the vas receives all of its blood supply from branches of the testicular artery and epididymal artery, whereas the seminal vesical (abdominal) end of the vas receives all of its blood supply from the deferential artery.** The vas deferens receives no blood supply from the surrounding cremaster muscle or from any blood vessels from the spermatic cord. Therefore, if the vas deferens is sectioned or obstructed in two different locations, the intervening segment will fibrose owing to lack of blood supply. **Therefore, two simultaneous vasovasostomies cannot be safely performed on the same vas if the vasal vessels have been interrupted in both locations.**

BOX 25-1 Blood Supply to Testis, Epididymis, and Vas Deferens

TESTIS

Testicular (internal spermatic) artery from aorta (main blood supply)
Deferential artery from internal iliac (hypogastric) artery and superior vesical artery
Cremasteric (external spermatic) artery from inferior epigastric artery

EPIDIDYMIS

Superior epididymal artery derived from testicular artery
Inferior epididymal artery derived from vasal (deferential) artery

VAS DEFERENS

Seminal vesical end: deferential artery
Testicular end: deferential artery and inferior epididymal artery

Anatomy of the Excurrent Ducts

Sperm and testicular fluid exit the testes through 7 to 11 tiny efferent ducts. These ducts become convoluted when they exit the testes and form the caput of the epididymis (see Chapters 21 and 41). At that level, they freely anastomose with one another. They all coalesce at the distal caput to form a single epididymal tubule from the caput-corpus junction all the way to the vas deferens. Therefore, **if the epididymis is accidentally injured or ligated distal to the caput, the entire system on that side will be completely obstructed.** This is an important consideration when performing epididymal surgery or surgery near the epididymis. **Hydrocelectomy** is a common surgical procedure that can result in **iatrogenic injury to the epididymis.** In long-standing large hydroceles, the epididymis is often splayed out and difficult to identify. Use of an operating microscope and transillumination of the hydrocele sac help avoid injury to the epididymis, vas, and testicular blood supply (Dabaja and Goldstein, 2014). **Generous margins from the epididymis should be allowed when performing hydrocelectomy (see Chapter 21 and 41).**

Orchiopexy for torsion can also result in inadvertent injury to the epididymis. A single stitch through an epididymal tubule in the corpus or cauda will result in complete obstruction of that side. Because there are multiple lobules at the levels of the caput, puncture of a single tubule for sperm aspiration can be safely performed at the most proximal region of the caput without significantly compromising the flow of sperm into the corpus. Multiple punctures of many tubules at the caput, or any puncture distal to the caput, however, can cause obstruction (Zhang et al, 2013).

Ejaculatory Ducts

The left and right ejaculatory ducts enter the prostatic urethra at the level of the utricle. Obstruction of ejaculatory ducts can lead to azoospermia. Transurethral resection (TUR) of the ejaculatory ducts (TURED) can relieve the obstruction. TURED should not be considered a benign procedure, as it is occasionally associated with significant morbidity (see the section on TURED). Normally, the ejaculatory ducts contain a valvelike mechanism that prevents reflux of urine into the ejaculatory duct. After TURED, a significant percentage of men develop reflux of urine up the excurrent ductal system (Vazquez-Levin et al, 1994) causing chemical and/or bacterial epididymitis.

TESTIS BIOPSY

Indications

The indications for testis biopsy are detailed in Chapter 24. Briefly, testis biopsy is indicated in azoospermic men with testis of normal size and consistency, palpable vasa deferentia, and normal serum follicle-stimulating hormone (FSH) levels, and a negative serum antisperm antibody assay (Lee et al, 2009). Under these circumstances, biopsy will distinguish obstructive from nonobstructive azoospermia. In men with congenital absence of vasa and normal serum FSH levels, biopsy always reveals spermatogenesis (Goldstein and Schlossberg, 1988) and biopsy is not necessary before definitive sperm aspiration and IVF with ICSI. Diagnostic biopsy should usually be performed bilaterally irrespective of the size discrepancy of the two testes. Good spermatogenesis is sometimes found in small, firm testes, and biopsies of large, healthy testes may reveal maturation arrest.

The ability to achieve pregnancy with only a single testicular sperm has turned biopsy into a potentially therapeutic, as well as diagnostic, procedure. Even men with markedly elevated serum FSH levels and small, soft testes, in whom testicular failure is certain, often harbor rare mature sperm in their testes. These sperm can be extracted using techniques described later in this chapter and used for IVF with intracytoplasmic injection of testicular sperm.

The recently discovered heterogeneity of the testes of men with nonobstructive azoospermia coupled with the ability of testicular sperm to acquire motility (Jow et al, 1993) has resulted in changes in the techniques of testis biopsy. Examination of fresh, unfixed tissue for the presence of sperm with tails and possible motility, and examination of multiple samples if sperm are not found initially, is now recommended. Furthermore, optimal care requires the availability, at the time of biopsy, of an andrology laboratory capable of processing and cryopreserving any sperm found at the time of biopsy.

Open Testis Biopsy: Microsurgical Technique

Open biopsy remains the gold standard because it provides an optimal amount of tissue both for accurate diagnosis and for retrieval of sperm for IVF (Rosenlund et al, 1998; Schlegel, 1999; Dardashti et al, 2000). Open testis biopsy may be performed using either general, spinal, or local anesthetic. Local anesthesia of just the skin and tunics without a cord block is uncomfortable; local anesthesia with spermatic cord block can be effective and comfortable. However, there are limitations to the cord block. In animal studies, the incidence of accidental damage to the testicular artery

during blind cord block is 5% (Goldstein et al, 1983). In addition, if there has been previous scrotal surgery with scar or adhesions and if more extensive dissection and manipulation may be required, I prefer to use general or spinal anesthetic.

The surgeon's goal when performing a testis biopsy is to provide an optimal tissue sample, avoid trauma to the specimen, and avoid injury to the epididymis or testicular blood supply. Open biopsy under magnification (preferably with an operating microscope) satisfies these requirements.

An assistant stretches the scrotal skin tightly over the anterior surface of the surface of the testis and confirms that the epididymis is posterior. Bilateral 1-cm transverse scrotal incisions within the scrotal skin folds provide good exposure with a minimum of scrotal bleeding. Alternatively, a single vertical incision in the median raphe may be used. The incision is carried through the skin and dartos muscle, and the tunica vaginalis is opened. If the anatomy is distorted from previous surgery, the epididymis cannot be clearly palpated posteriorly, or the tunica albuginea cannot be clearly identified, the incision should be enlarged and the testis delivered. The edges of the tunica vaginalis are held open with hemostats, and any bleeding vessels are cauterized. Use of loupes or, better yet, the operating microscope allows ready identification of a spot on the tunica albuginea relatively free of visible surface vessels. The wound should be dry before incision of the tunica albuginea to prevent saturation of the biopsy with blood. A 3- to 4-mm incision is made in the tunica albuginea with a 15-degree microknife (Fig. 25-1A). Small crossing vessels are cauterized with bipolar cautery and divided before excision of a pea-sized sample of seminiferous tubules with razor sharp iris scissors (Fig. 25-1B). When handling testis biopsy material for permanent fixation, avoid crushing tissue in any way (including with forceps) because this may traumatize and distort the testicular architecture. The specimen is then deposited directly into either Bouin, Zenker, or collidine buffered glutaraldehyde solution. Formalin fixation results in distortion of testicular histology and should not be used for testis biopsy. A "touch-prep" is made by blotting the cut surface of the testis several times with a glass slide (Fig. 25-1C) and adding a drop of saline, lactated Ringer solution, or human tubal fluid with IVF medium and a coverslip. Examination under high power using a light microscope with or without phase contrast will reveal the presence of sperm with tails and allow assessment of motility (Fig. 25-1D). If no sperm are found in the touch-prep, a second specimen may be cut for a wet "squash prep." In this case, the specimen is placed on a slide, a drop of saline is added, and the specimen is crushed under a coverslip (Jow et al, 1993). If no sperm are found, the tunica is closed with two or three interrupted sutures of 5-0 Vicryl (Fig. 25-1E), and biopsy of another area is performed through the same skin incision. As described later in this chapter, use of an operating microscope providing 10X to 25X magnification may allow selective sampling of larger seminiferous tubules more likely to contain sperm (Schlegel, 1999). If sperm are identified, the slide as well as additional tissue removed are sent for cryopreservation in the andrology laboratory. The location of the biopsy site where sperm were found is noted and the tunica albuginea is closed with two or three interrupted sutures of 6-0 nylon. This facilitates identification of sites of spermatogenesis for future TESE for IVF with ICSI.

The tunica vaginalis is closed with 5-0 monofilament nonabsorbable suture for hemostasis. Use of a nonabsorbable suture facilitates identification of the biopsy site if sperm were found at that site and subsequent TESE is required at the time of IVF with ICSI. The skin is closed with subcuticular 5-0 Monocryl. The wounds are covered with Bacitracin ointment and a fluff-type dressing secured with a snug scrotal support. Antibiotics are unnecessary.

Percutaneous Testis Biopsy

Percutaneous testis biopsy using the same 14-gauge biopsy gun used for prostatic biopsy is a blind procedure and could result in unintentional injury to either the epididymis or the testicular artery. This technique should not be used when previous surgery

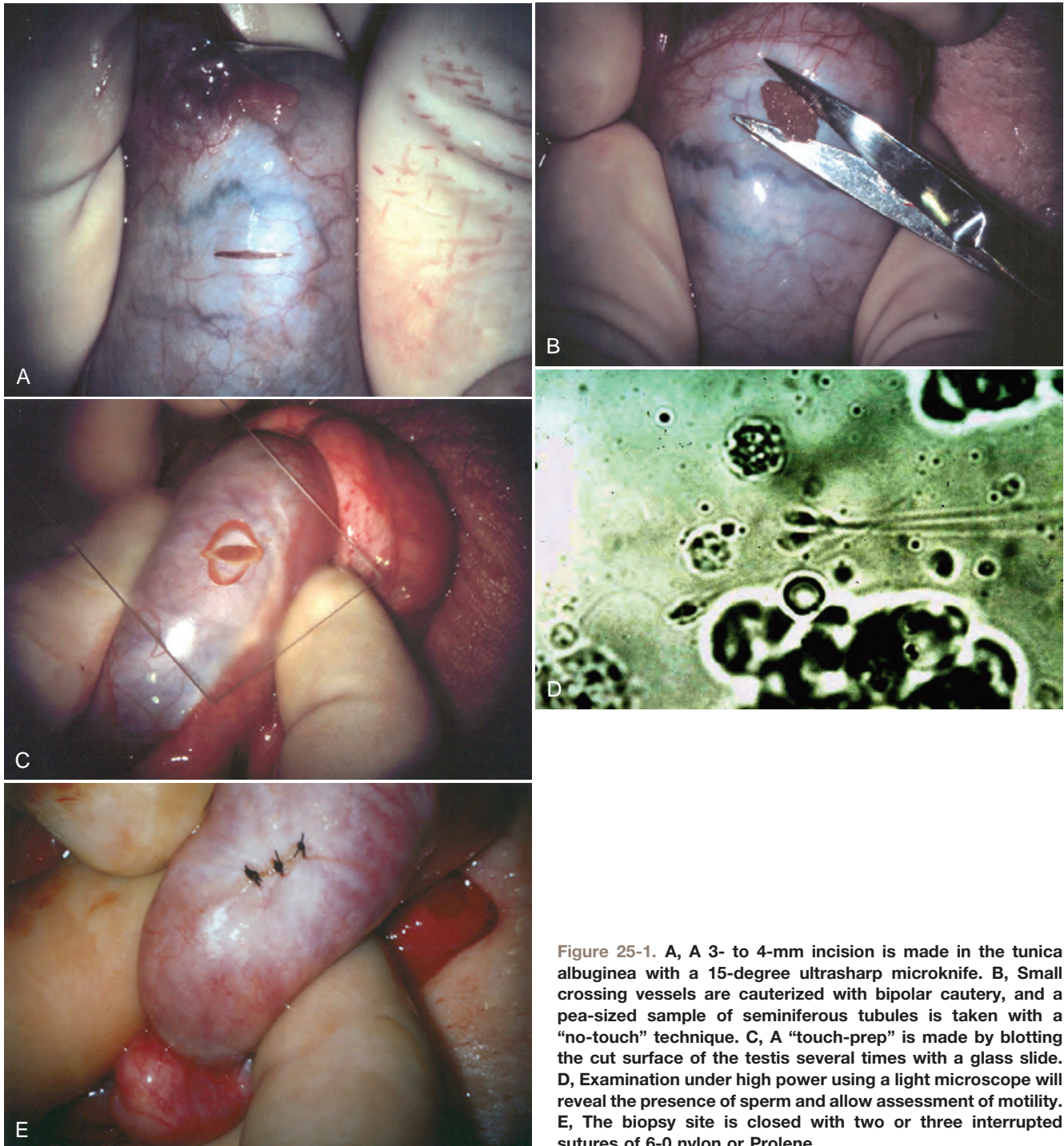


Figure 25-1. A, A 3- to 4-mm incision is made in the tunica albuginea with a 15-degree ultrasharp microknife. B, Small crossing vessels are cauterized with bipolar cautery, and a pea-sized sample of seminiferous tubules is taken with a “no-touch” technique. C, A “touch-prep” is made by blotting the cut surface of the testis several times with a glass slide. D, Examination under high power using a light microscope will reveal the presence of sperm and allow assessment of motility. E, The biopsy site is closed with two or three interrupted sutures of 6-0 nylon or Prolene.

has resulted in scarring and obliteration of normal anatomy. Fine-needle aspiration usually yields specimens that contain few tubules with poorly preserved architecture. When performed with the patient under local anesthesia, a cord block is necessary to minimize pain. The technique of percutaneous biopsy is described later in this chapter. As a therapeutic tool for sperm retrieval, percutaneous biopsy or aspiration is most useful for fresh sperm retrieval for IVF with ICSI in men with obstructive azoospermia and normal spermatogenesis.

Percutaneous Testicular Aspiration

Testicular aspiration performed with a 23-gauge needle or angiocath sheath (Marmar and Benoff, 2005) is probably less invasive

and less painful than percutaneous biopsy but usually yields few tubules with poorly preserved architecture. Although flow cytometric evaluation of this material can distinguish haploid from diploid cells and therefore confirm the presence or absence of late stages of spermatogenesis (Chan et al, 1984), direct wet examination of the aspirate for sperm and assessment of motility provide the most practical clinical information. Three or four aspirations can be performed until sperm are identified. In cases of obstructive azoospermia, these sperm can be used for IVF with ICSI (Craft et al, 1995) when sperm cannot be retrieved from the epididymis (see the section discussing TESE). Fine-needle aspiration has a significantly lower yield of sperm than open microsurgical TESE (micro-TESE) in men with nonobstructive azoospermia.

Complications of Testis Biopsy

Carefully performed, testis biopsy is associated with few complications (Schlegel and Su, 1997; Dardashti et al, 2000). The most serious complication associated with testis biopsy is inadvertent biopsy of the epididymis. If histologic evaluation of the biopsy material reveals epididymis with sperm within the epididymal tubule, obstruction of the epididymis at the site of the biopsy is certain. If, however, there are no sperm within the epididymal tubules, the patient is either obstructed above the level of the epididymal biopsy site or has primary seminiferous tubular failure and no harm has been done.

The most common complication of testis biopsy is hematoma. Hematomas can be quite large and may require drainage. Use of magnification to avoid vessels and bipolar cautery for hemostasis will help prevent this complication. Proper closure of the well-vascularized tunica vaginalis with a continuous 5-0 suture will minimize bleeding and adhesions.

With the rich blood supply of the scrotum and its contents, wound infection is rare in the absence of hematoma, and antibiotics are unnecessary.

VASOGRAPHY

Indications

The absolute indications for vasography are as follows:

1. Azoospermia, plus
2. Complete spermatogenesis with many mature spermatids on testis biopsy, plus
3. At least one palpable vas

Relative indications for vasography are as follows:

1. Severe oligospermia with normal testis biopsy
2. High level of sperm-bound antibodies, which indicates unilateral, bilateral, or partial obstruction (Lee et al, 2009)
3. Low semen volume and very poor sperm motility (partial ejaculatory duct obstruction)

Vasography should answer the following questions:

1. Are there sperm in the vasal fluid?
2. Is the vas obstructed?

If the testis biopsy reveals many sperm, then:

1. Absence of sperm in vasal fluid indicates obstruction on the testicular side of the vasotomy site, most likely an epididymal obstruction. Vasography is done in this case with saline or indigo carmine to confirm patency of the seminal vesical (distal) end of the vas before vasoepididymostomy.

2. Copious vasal fluid containing many sperm indicates vasal or ejaculatory duct obstruction, and formal contrast vasography is performed as described later to document the exact location of the obstruction.
3. Copious thick white fluid without sperm in a dilated vas indicates secondary epididymal obstruction in addition to a potential vasal or ejaculatory duct obstruction.

Vasography with radiographic contrast media and intraoperative radiography is rarely indicated. There is no need to perform vasography at the time of testis biopsy for azoospermia unless immediate reconstruction is planned and the touch or wet prep biopsy reveals mature sperm with tails. If not meticulously performed, vasography can cause stricture or even obstruction at the vasography site, which can complicate subsequent reconstruction (Howards et al, 1975b; Poore et al, 1997). In addition, vasography is of no value in making the diagnosis of epididymal obstruction, and the majority of nonvasectomy related obstructions are epididymal.

If testis biopsy reveals normal spermatogenesis and the vasa are palpable, vasography, if necessary, should be performed only at the time of definitive repair of obstruction. General anesthesia provides the most flexibility for scrotal exploration, vasography, and repair of obstruction. Although local anesthesia can provide adequate analgesia, patients are often unable to lie still through several hours of microsurgery. Long-acting hypobaric spinal or continuous epidural anesthesia can be a satisfactory alternative.

Technique of Vasography and Interpretation of Findings

Inguinal hernia repair, particularly when performed on children, is known to be associated with vasal injury leading to obstruction. If there is no previous inguinal incision and the side of obstruction is unknown, the testis is delivered through a high vertical scrotal incision (see the discussion of surgical scrotal approaches). The vas deferens is identified and isolated at the junction of the straight and convoluted portions of the vas deferens. Using an operating microscope and 10× magnification, the vasal sheath is longitudinally incised and the vasal vessels are carefully preserved (Fig. 25-2A).

A clean segment of bare vas is delivered and surrounded with a vessel loop. A straight clamp is placed beneath the vas to act as a platform. Under 25× magnification, a 15-degree microknife is used to hemitranssect the vas until the lumen is revealed (Fig. 25-2B). Any fluid exuding from the lumen is placed on a slide, mixed with a drop of saline, and sealed with a coverslip for microscopic examination. If the vasal fluid is devoid of sperm with repeated sampling after milking the epididymis and convoluted vas, epididymal

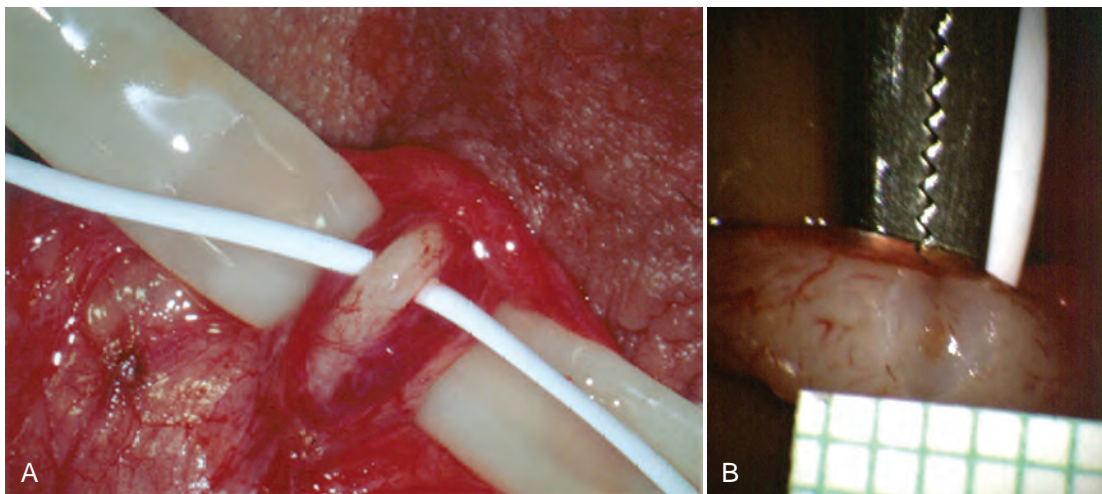


Figure 25-2. A, With use of an operating microscope and 10× magnification, the vasal sheath is longitudinally incised and vasal vessels are carefully preserved. B, Under 25× magnification, a 15-degree microknife is used to hemitranssect the vas until the lumen is revealed.

obstruction is present. The end of the vas toward the seminal vesicles is then cannulated with a 24-gauge angiocatheter sheath and is injected with 1 mL of lactated Ringer solution with a 1-mL tuberculin syringe to confirm its patency (Fig. 25-3). If the Ringer solution passes easily, formal vasography is not necessary. If further proof of patency of the vas deferens is desired, 1 mL of 50% dilute indigo carmine may be injected and the bladder catheterized. The presence of blue-green dye in the urine confirms patency of the vas. Indigo carmine diluted 50/50 with Ringer solution is preferred instead of methylene blue because even at low concentrations methylene blue kills sperm and renders them useless for cryopreservation or for immediate IVF and ICSI (Chang et al, 1998; Sheynkin et al, 1999b; Wood et al, 2003). If motile sperm are found in the vas, the testicular end should be gently barbotaged with 0.2 mL of human tubal fluid medium, and the fluid processed by the andrology laboratory for sperm cryopreservation for potential future use for IVF and ICSI. This should be done before injection with indigo carmine or x-ray contrast material (Sheynkin et al, 1999b).

If a large amount of fluid is found in the vasa lumen and microscopic examination reveals the presence of sperm, the obstruction is toward the seminal vesical end of the vas. In these cases, the vas is usually markedly dilated. A 2-0 Prolene suture can be passed toward the seminal vesical end of the vas and a clamp

placed on the Prolene when the suture passes no further. This is particularly useful for delineating the site of inguinal obstruction from prior groin surgery. If the obstruction is proximal to the inguinal scar, formal vasography is performed by passing a No. 3 whistle-tip ureteral catheter toward the seminal vesical end of the vas. A 16-Fr Foley catheter is placed in the bladder and the balloon is filled with 5 mL of air. Placing the balloon on gentle traction before vasography prevents reflux of contrast into the bladder, which can obscure detail (Fig. 25-4). The air-filled balloon also identifies the location of the bladder neck relative to any obstruction. After the vasa have been cannulated, vasograms are performed with the injection of 0.5 mL of water-soluble contrast media (Fig. 25-5). If vasography reveals obstruction at the site of the ejaculatory ducts (Fig. 25-6), indigo carmine is injected in both vasa to facilitate TURED (see the section on diagnosis of TURED). If both vasa are visualized after injection of contrast into only one vas (Fig. 25-7), it means that both vasa empty into a single cavity, usually a midline ejaculatory duct cyst.



Figure 25-3. The end of the vas toward the seminal vesicles is cannulated with a 24-gauge angiocatheter, and then injected with 1 mL of lactated Ringer solution with a 1-mL tuberculin syringe to confirm its patency.



Figure 25-5. Vasograms are performed with 0.5 mL of water-soluble contrast media.



Figure 25-4. Placing the balloon on gentle traction before vasography prevents reflux of contrast into the bladder, which can obscure detail.



Figure 25-6. Vasography reveals obstruction at the site of the ejaculatory ducts.



Figure 25-7. Both vasa are visualized after injection of contrast into one vas only, revealing distal obstruction.

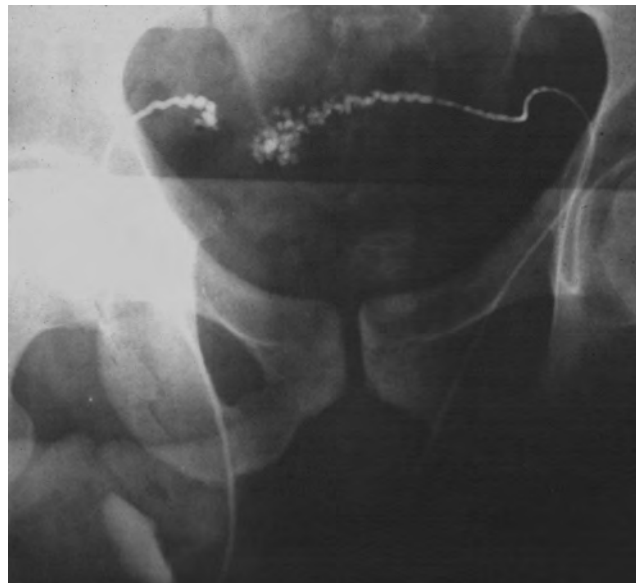


Figure 25-9. Vasogram demonstrating partial absence of the vas deferens.

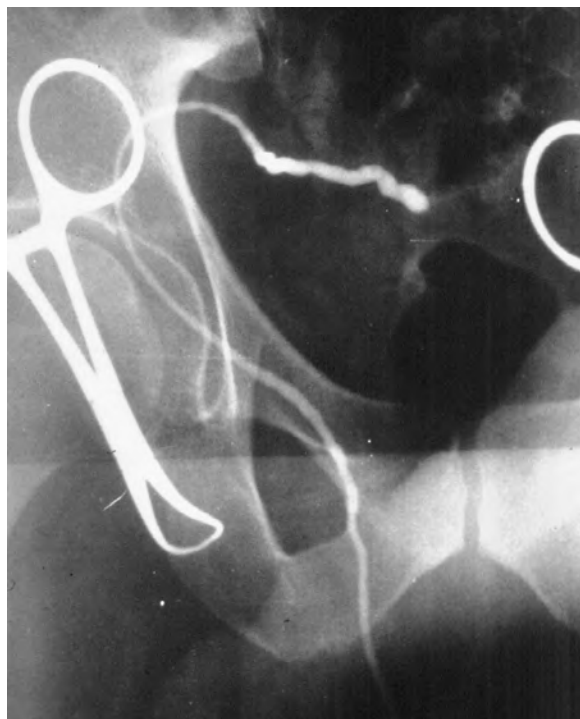


Figure 25-8. Vasography reveals a blind-ending vas deferens far from the ejaculatory duct.



Figure 25-10. Vasography reveals an obstruction in the inguinal region.

Vasography may reveal the vas deferens ending blindly, far from the ejaculatory ducts (Fig. 25-8). This finding indicates congenital partial absence of the vas deferens, and these patients should be tested for cystic fibrosis mutations (see Chapter 24). If this is found bilaterally (Fig. 25-9), reconstruction is impossible, but vasal or epididymal sperm can be aspirated into standard laboratory pipettes (see the section on [microsurgical epididymal sperm aspiration techniques](#)) and cryopreserved for future IVF with ICSI. If vasography reveals obstruction in the inguinal region (Fig. 25-10), either inguinal vasovasostomy or crossed transeptal vasovasostomy, using the contralateral unobstructed vas (see the section on [crossed vasovasostomy](#)), may be performed. The hemitranssected vasography sites are carefully closed microsurgically using two or three interrupted

10-0 monofilament nylon sutures for the mucosa and 9-0 for the muscularis and adventitia (see the discussion of the [microsurgical multilayer microdot method](#)).

If the vasal fluid reveals no sperm and vasography confirms patency of the seminal vesical end of the vas, the vas is completely transected, and the seminal vesical end is prepared for vasoepididymostomy (see later). If the vasal fluid reveals many sperm and vasography is normal, then retrograde ejaculation, lack of emission, or aperistalsis of the vas (Tiffany and Goldstein, 1985; Tillem and Mellinger, 1999) is the cause of the azoospermia.

Fine-Needle Vasography

Exposure of the vas in its straight portion may allow vasography to be performed with a fine needle, obviating the need for

hemitranssection of the vas. Dewire and Thomas (1995) used a 30-gauge lymphangiogram needle attached to Silastic tubing. When the sensation of puncture of the lumen is detected, 50% water-soluble contrast is injected to confirm patency radiographically. This has proven to be a difficult technique for even experienced microsurgeons to master. Accurate evaluation of vasal fluid for sperm is difficult because it is so scant. If barbotage with saline or lactated Ringer solution reveals the presence of sperm, then epididymal obstruction has been excluded and contrast can be injected. Collection of vasal sperm for cryopreservation is difficult with this technique. Percutaneous vasography through the scrotal skin has been successfully performed in China (Li, 1980) using the same ringed percutaneous fixation clamp as for the no-scalpel vasectomy. After fixation of the vas beneath the scrotal skin, the vas lumen is punctured with a 22-gauge sharp needle and cannulated with a 24-gauge blunt needle through which vasography is performed. This technique is even more difficult than the direct vision technique with a fine needle.

Complications of Vasography

Stricture

Multiple attempts at percutaneous vasography using sharp needles can result in stricture or obstruction at the vasography site. Imprecise closure of a vasotomy can also result in stricture and obstruction (Howards et al, 1975a; Poore et al, 1997). Use of non-water-soluble contrast agents may also result in stricture, and these agents should not be used for vasography.

Injury to the Vasal Blood Supply

If the vasal blood supply is injured at the site of vasography, vasovasostomy proximal to the vasography site may result in ischemia, necrosis, and obstruction of the intervening segment of vas.

Hematoma

Bipolar cautery should be used for meticulous hemostasis to prevent hematoma in the perivasal sheath.

Sperm Granuloma

Leaky closure of a vasography site may lead to the development of a sperm granuloma, which can result in stricture or obstruction of the vas. The microsurgical technique for closure of vasography sites is identical to that for vasovasostomy described later in this chapter.

Transrectal Vasography and Seminal Vesiculography

If transrectal ultrasound reveals markedly dilated seminal vesicles and/or a midline müllerian duct cyst in a man with obstructive azoospermia, transrectal aspiration followed by instillation of indigo carmine mixed with radiographic contrast is a useful diagnostic maneuver (Jarow, 1994; Katz et al, 1994; Riedenklaus et al, 1995; Eisenberg et al, 2008).

The same bowel preparation and antibiotic coverage used for transrectal prostate biopsy is employed. The fine-needle aspirate is examined for sperm. If sperm are present, it means that at least one vas and epididymis are patent. One-half milliliter of indigo carmine is diluted with 1.5 mL of 50% water-soluble contrast and instilled. If a flat plate reveals a potentially resectable lesion, TURED is performed (see later). Visualization of blue dye effluxing from the ejaculatory ducts or an unroofed cyst aids in determining the adequacy of the resection (Cornel et al, 1999).

This technique obviates the need for formal open scrotal vasography in men with transrectally accessible lesions. If sperm are found in the aspirate, TUR may immediately be undertaken without violating the scrotum. Sperm-laden aspirates may be frozen for future IVF with ICSI if surgery fails.

If no sperm are found in the aspirated fluid, it suggests that secondary epididymal obstruction exists. Simultaneous TURED and vasoepididymostomy is rarely successful. In the face of both ejaculatory duct obstruction and bilateral epididymal obstruction, the best option would be epididymal sperm aspiration for cryopreservation for future IVF and ICSI.

KEY POINTS: VASOGRAPHY

- Perform vasography only if testicular biopsy confirms spermatogenesis consistent with obstructive azoospermia.
- Perform vasography only at the time of planned reconstruction.
- Always sample vasal fluid first to allow cryopreservation of motile sperm if found.
- Use indigo carmine instead of methylene blue to confirm patency.
- Formal vasography with x-ray contrast is needed only to locate obstructions proximal to the internal inguinal ring.
- If transrectal ultrasound reveals dilated seminal vesicles and/or a midline (müllerian duct) cyst, transrectal fine-needle aspiration followed by instillation of contrast and indigo carmine should be performed. If motile sperm are found, they should be cryopreserved.

VASOVASOSTOMY

The number of American men who undergo vasectomy has remained stable at about 500,000 per year, as has the divorce rate of 50%. Surveys suggest that 2% to 6% of vasectomized men will ultimately seek reversal. Furthermore, obstructive azoospermia can be the result of iatrogenic injuries to the vas deferens, usually from hernia repair, in 6% of azoospermic men (Sheynkin et al, 1998a; Shin et al, 2005).

Preoperative Evaluation

Before attempted surgical reconstruction of the reproductive tract, adequate spermatogenesis should be documented. A prior history of natural fertility prevasectomy is usually adequate.

Physical Examination

Testis. Small or soft testes suggest impaired spermatogenesis and predict a poor outcome.

Epididymis. An indurated irregular epididymis often predicts secondary epididymal obstruction, necessitating vasoepididymostomy.

Sperm Granuloma. A sperm granuloma at the testicular end of the vas suggests that sperm have been leaking at the vasectomy site. This vents the high pressures away from the epididymis and is associated with a better prognosis for restored fertility regardless of the time interval since vasectomy (Wosnitzer and Goldstein, 2013).

Vasal Gap. When a very destructive vasectomy has been performed, most of the scrotal straight vas may be absent or fibrotic and the patient should be advised that inguinal extension of the scrotal incision will be necessary to mobilize adequate length of vas to enable a tension-free anastomosis.

Scars from Previous Surgery. Operative scars in the inguinal or scrotal region should alert surgeon to the possibility of iatrogenic inguinal obstruction (hernia repair) or vasal or epididymal obstruction (hydrocelectomy, orchiopexy) (Sheynkin et al, 1998a; Hopps and Goldstein, 2006).

Laboratory Tests

1. Semen analysis with centrifugation and examination of the pellet for sperm should be performed preoperatively.

Complete sperm with tails are found in 10% of preoperative pellets a mean of 10 years after vasectomy (Lemack and Goldstein, 1996). Under these circumstances sperm are certain to be found in the vas on at least one side, indicating a favorable prognosis for restored fertility. Men with a low semen volume should have a transrectal ultrasound to investigate the possibility of an additional ejaculatory duct obstruction.

2. Serum and antisperm antibody studies: The presence of serum antisperm antibodies corroborates the diagnosis of obstruction and the presence of active spermatogenesis (Lee et al, 2009).
3. Serum FSH: Men with small soft testes should have serum FSH measured. An elevated FSH predicts impaired spermatogenesis and a poorer prognosis.
4. Prostate-specific antigen (PSA): Vasectomy reversal candidates over age 40 should have serum PSA measured.

Anesthesia

General anesthesia is preferred. Slight movements are greatly magnified by the operating microscope and disturb performance of the anastomosis. In cooperative patients regional or even local anesthesia with sedation can be used if the vasal ends are easily palpable, a sperm granuloma is present, and/or the time interval since vasectomy is short, decreasing the likelihood of secondary epididymal obstruction. When large vasal gaps are present, extensions of the incisions high into the inguinal canal may be necessary. Furthermore, if vasoepididymostomy is necessary, the operating time could exceed 4 or 5 hours. Local anesthesia limits the options available to the surgeon. Hypobaric spinal anesthesia with long-acting agents such as bupivacaine (Marcaine) can provide 4 to 5 hours of anesthesia time and has the advantage of eliminating lower body motion. Epidural anesthesia with an indwelling catheter can be equally effective.

Surgical Approaches

Scrotal Incision

Bilateral high vertical scrotal incisions provide the most direct access to the obstructed site in cases of vasectomy reversal. Length is usually a problem on the abdominal end but not on the testicular end. Mark the location of the external inguinal ring (Fig. 25-11). If the vasal gap is large or the vasectomy site is high, this incision can easily be extended toward the external ring. If the vasectomy site is low, it is easy to pull up the testicular end. This incision should be made at least 1 cm lateral to the base of the penis. The testis should be delivered with the tunica vaginalis left intact. This provides excellent exposure of the entire scrotal vas deferens and, if necessary, the epididymis.

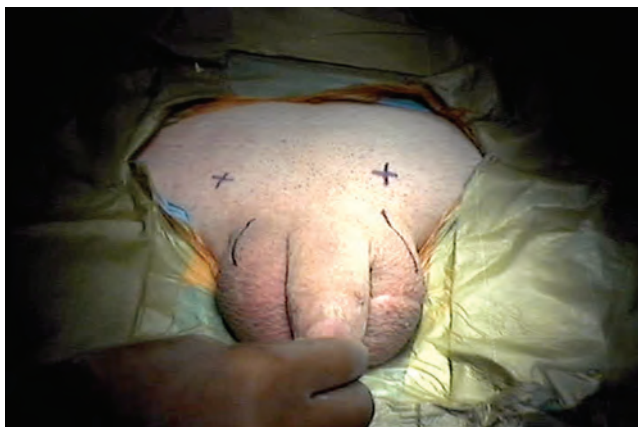


Figure 25-11. The Xs mark the locations of the external ring. Incisions are marked on the hemiscrotums.

Inguinal Incision

An inguinal incision is the preferred approach in men when obstruction of the inguinal vas deferens from prior herniorrhaphy or orchiopexy is strongly suspected. Incision through the previous scar usually leads directly to the site of obstruction. If the obstruction turns out to be scrotal or epididymal, it is a simple matter to deliver the testis through the inguinal incision or through a separate scrotal incision to perform the anastomosis.

Preparation of the Vasa

The vas is grasped above and below the site of obstruction with two Babcock clamps. Penrose drains replace the Babcock clamps and facilitate the dissection. The vasal vessels and periadventitial sheath are included. Transillumination of the periadventitial sheath by proper adjustment of the operating light allows clear visualization of the blood vessels, which facilitates dissection of the periadventitial sheath and prevents damage to the vasal vessels. The vas is mobilized enough to allow a tension-free anastomosis. To preserve good blood supply the vas should not be stripped of its sheath. The obstructed segment and, if present, sperm granuloma at the vasectomy site should be dissected out and excised. By staying right on the vas and/or sperm granuloma during this dissection, the surgeon reduces the risk of injuring the testicular artery. Injury to adjacent cord structures, especially the testicular artery, is likely to result in testicular atrophy because the vasal artery has usually been interrupted at the vasectomy site.

When large vasal gaps are present, a gauze-wrapped index finger is used to bluntly separate the cord structures from the vas. Blunt finger dissection through the external ring will free the vas to the internal inguinal ring if additional abdominal side length is necessary. These maneuvers will leave all the vasal vessels intact. When the vasal gap is extremely large, additional length can be achieved by dissecting the entire convoluted vas free of its attachments to the epididymal tunica (Fig. 25-12), allowing the testis to drop upside down. These maneuvers can provide an additional 4 to 6 cm of length. To maintain the integrity of the vasal vessels, this dissection is best performed using magnifying loupes or the

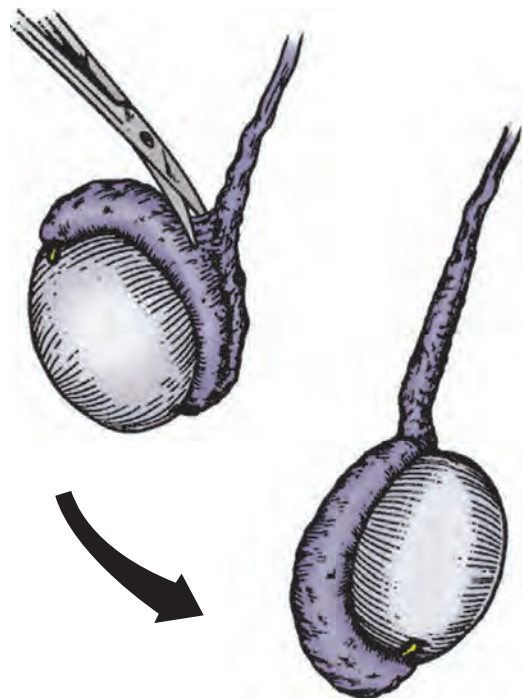


Figure 25-12. An additional 4 to 6 cm of length can be obtained by dissecting the epididymis off the testis from the vasoepididymal junction to the caput epididymis.

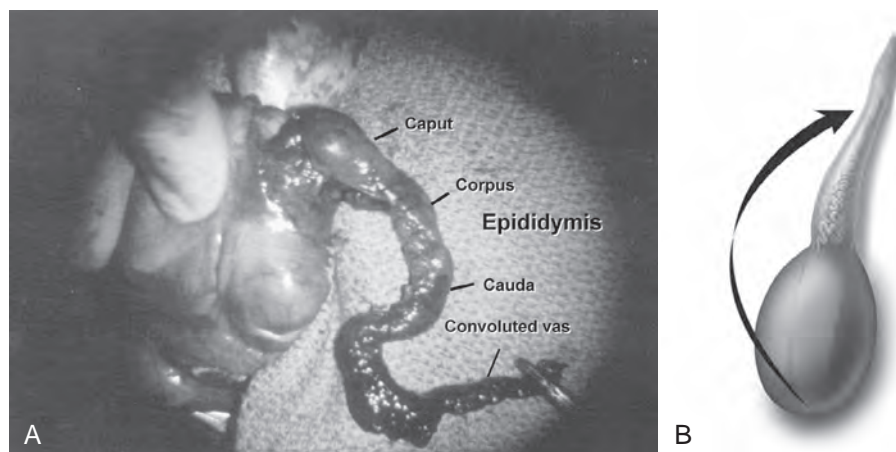


Figure 25-13. A and B, An additional 4 to 6 cm of length can be obtained by dissecting the epididymis off the testis from the vasoepididymal junction to the caput epididymis.



Figure 25-14. An ultrasharp knife drawn through a slotted 2-, 2.5-, or 3-mm diameter nerve-holding clamp (Accurate Surgical and Scientific Instrument Corp., Westbury, NY) yields a perfect 90-degree cut.

operating microscope under low power. If the amount of vas removed is so large that even these measures fail to allow a tension-free anastomosis, the incision can be extended to the internal inguinal ring, the floor of the inguinal canal cut, and the vas rerouted under the floor, as in a difficult orchiopexy. An additional 4 to 6 cm of length can be obtained by dissecting the epididymis off the testis from the vasoepididymal (VE) junction to the caput epididymis (Fig. 25-13). The superior epididymal vessels are left intact and provide adequate blood supply to the testicular end of the vas. With this combination of maneuvers, up to 10-cm gaps can be bridged.

After the vasa have been freed, the testicular end of the vas is cut transversely. An ultrasharp knife drawn through a slotted 2-, 2.5- or 3-mm diameter nerve-holding clamp (Accurate Surgical and Scientific Instrument Corp., Westbury, NY) yields a perfect 90-degree cut (Fig. 25-14). The cut surface of the testicular end of the vas deferens is inspected under 15× to 25× magnification. A healthy white mucosal ring should be seen and should spring back immediately after gentle dilation. The muscularis should appear smooth and soft. A gritty-looking muscularis layer indicates the presence of scar or fibrotic tissues. The cut surface should look like a bull's eye with the three valsal layers distinctly visible. Healthy bleeding

should be noted from both the cut edge of the mucosa and the surface of the muscularis. If the blood supply is poor or the muscularis is gritty, the vas is recut until healthy tissue is found. The valsal artery and vein are then clamped and ligated with 6-0 nylon. Small bleeders are controlled with microbipolar forceps set at low power. Once a patent lumen has been established on the testicular end, the vas is milked and a clean glass slide is touched to its surface. The valsal fluid is immediately mixed with a drop or two of saline or lactated Ringer solution and preserved under a coverslip for microscope examination. The abdominal end of the vas deferens is prepared in a similar manner and the lumen gently dilated with a microvessel dilator and cannulated with a 24-gauge angiocatheter sheath. Injection of saline or Ringer lactate confirms its patency. After injection of Ringer solution and a test dilation the vas is recut to obtain a fresh surface. **A minimum of instrumentation of the mucosa should be performed.**

After preparation, the ends of the vasa are stabilized with a Microspike approximator clamp (Goldstein, 1985) to remove all tension before the anastomosis is performed. Isolating the field through a slit in a rubber dam prevents microsutures from sticking to the surrounding tissue. A sterile tongue blade covered with a large Penrose drain is placed beneath the ends of the vasa to provide a platform on which to perform the anastomosis.

When to Perform Vasoepididymostomy

The gross appearance of fluid expressed from the testicular end of the vas is usually predictive of findings on microscopic examination (Table 25-1). If microscopic examination of the valsal fluid reveals the presence of sperm with tails, vasovasostomy is performed. If no fluid is found, a 24-gauge angiocatheter sheath is inserted into the lumen of the testicular end of the vas and barbotaged with 0.1 mL of saline while the convoluted vas is vigorously milked. The barbotage fluid is expressed onto a slide and examined. **Men with large sperm granulomas often have virtually no dilation of the testicular end of the vas and little or no fluid initially; however, with barbotage and vigorous milking, invariably sperm can be found in this scant fluid.** If there is no sperm granuloma, and the vas is absolutely dry and spermless after multiple samples have been examined, vasoepididymostomy is indicated. If the fluid expressed from the vas is found to be thick, white, water insoluble, and toothpaste-like in quality, microscope examination rarely reveals sperm. Under these circumstances, the tunica vaginalis is opened and the epididymis inspected. If clear evidence of obstruction is found—that is, an epididymal sperm granuloma with dilated tubules above and collapsed tubules below—vasoepididymostomy is performed. **When in doubt, or if not very experienced with vasoepididymostomy, vasovasostomy should be performed.** However, only 15% of men with bilateral absence of sperm in the

TABLE 25-1 Relationship between Gross Appearance of Vasal Fluid and Microscopic Findings

VASAL FLUID APPEARANCE	MOST COMMON FINDINGS ON MICROSCOPIC EXAMINATION	SURGICAL PROCEDURE INDICATED
Copious, crystal clear, watery	No sperm in fluid	Vasovasostomy
Copious, cloudy thin, water soluble	Usually sperm with tails	Vasovasostomy
Copious, creamy yellow, water soluble	Usually many sperm heads, occasional sperm with short tails	Vasovasostomy
Copious, thick white toothpaste-like, water insoluble	No sperm	Vasoepididymostomy
Scant white thin fluid	No sperm	Vasoepididymostomy
Dry spermless vas; no granuloma at vasectomy site	No sperm	Vasoepididymostomy
Scant fluid, granuloma present at vasectomy site	Barbotage fluid reveals sperm	Vasovasostomy

vasal fluid after barbotage and an intensive search will have sperm return to the ejaculate after vasovasostomy (Sheynkin et al, 2000).

When copious, crystal clear, water-like fluid squirts out from the vas and no sperm are found in this fluid, a vasovasostomy is performed because the likelihood is that sperm will return to the ejaculate after vasovasostomy is performed.

Multiple Vasal Obstructions

If saline injection reveals that the abdominal end of the vas deferens is not patent, a 2-0 nylon or polypropylene suture is gently threaded into the vas lumen to determine the site of obstruction. If the obstruction is within 5 cm of the original vasectomy site, the abdominal end of the vas deferens may be dissected to this site and excised. The incision should then be extended inguinally to free the vas up extensively toward the internal inguinal ring. The testicular end then should also be freed up to the VE junction. If the site of the second obstruction is so far from the vasectomy site that two vasovasostomies are necessary, a single crossed vasovasostomy should be performed to yield one good system (see the section on [crossed vasovasostomy](#)). If this is not possible, vasal or epididymal sperm is aspirated into micropipettes and cryopreserved for future IVF with ICSI (see the section on [sperm retrieval techniques](#)). **Simultaneous vasovasostomies at two separate sites will usually lead to devascularization of the intervening segment with fibrosis and necrosis.**

Varicocelectomy and Vasovasostomy

When men undergoing vasovasostomy or vasoepididymostomy are found to have significant varicoceles on physical examination, it is tempting to repair the varicoceles at the same time. **When varicocelectomy is properly performed, all spermatic veins are ligated and the only remaining avenues for testicular venous return are the vasal veins.** In men who have had vasectomy and are seeking reversal, the vasal veins are likely to be compromised from either the original vasectomy or the reversal itself. Furthermore the integrity of the vasal artery in those men is also likely to be compromised. Varicocelectomy in such men requires preservation of the testicular artery as the primary remaining testicular blood supply as well as preservation of some avenue for venous return.

Microscopic varicocelectomy can ensure preservation of the testicular artery in most cases. Deliberate preservation of small cremasteric or perivasal veins provides venous return. In one series of 570 men seeking vasectomy reversal, 19 had large varicoceles (20 left, 7 bilateral). Microsurgical varicocelectomy was performed at the same time as vasovasostomy. The cremasteric veins and the fine network of veins adherent to the testicular artery were left intact for venous return and to minimize the chances of injury to the testicular artery. Postoperatively, 5 of 26 varicoceles recurred (19%) (Goldstein, 1995). This compares with a recurrence rate of less than 1% in 3500 varicocelectomies I performed in nonvasectomized men in whom the vasal vessels were intact and the cremasteric veins and

periarterial venous network were ligated. However, Mullhall and colleagues performed a series of simultaneous microsurgical vasovasostomies and varicocelectomies without intentionally preserving the cremasteric and periarterial network. They reported a low recurrence rate and no cases of atrophy (Mulhall et al, 1997). It is interesting to note that the increase in recurrences when the cremasteric veins and periarterial venous network were left intact suggests that these veins contribute to a significant proportion of varicocele recurrences.

If varicocelectomy is performed at the same time as vasovasostomy or vasoepididymostomy, it is important that a microscope be used and the testicular artery preserved. Another approach, especially when the female partner is young, is to do the vasovasostomy or vasoepididymostomy first. The semen quality is then assessed postoperatively. **If necessary, varicocelectomy can be safely performed 6 months or more later when venous and arterial channels have formed across the anastomotic line.** This two-stage delayed approach has been completed a dozen times with no atrophy or recurrence.

Anastomotic Techniques: Keys to Success

All successful vasovasostomy techniques depend on adherence to surgical principles that are universally applicable to anastomoses of all tubular structures. These include the following.

1. **Accurate mucosa-to-mucosa approximation**
In human vasovasostomy, the lumen on the testicular side is usually dilated, often to a diameter two to five times that of the abdominal side. Techniques that work well with lumina of equal diameters may be less successful when applied to lumina of markedly discrepant diameters.
2. **Leakproof anastomosis**
Sperm are highly antigenic and provoke an inflammatory reaction when they escape from the normally intact lining of the excurrent ducts of the male reproductive tract. Extravasated sperm adversely influence the success of vasovasostomy (Hagan and Coffey, 1977). Unlike blood vessel anastomoses, in which platelets and clotting factors seal the gaps between sutures, vasal and epididymal fluid contain no platelets or clotting factors, so the water-tightness of the anastomosis is entirely dependent on the mucosal sutures.
3. **Tension-free anastomosis**
When an anastomosis is performed under tension, sperm may appear in the ejaculate for several months after surgery. Ultimately, sperm counts and motility will decrease and azoospermia may ensue. At re-exploration only a thin fibrotic band is found at the anastomotic site. This can be prevented by adequately freeing up the vasa and placing reinforcing sutures in the sheath of the vas.
4. **Good blood supply**
If the cut vas exhibits poor blood supply, it should be recut until healthy bleeding is encountered. If extensive resection is necessary, additional length should be obtained using the techniques previously described.

5. Healthy mucosa and muscularis

If the mucosa or cut surface of the vas exhibits poor distensibility after dilation, peels away from the underlying muscularis, or shreds easily, then the vas should be cut back until healthy mucosa is found. Surgeons should be aware that if needle electrocautery was used in vasectomy, the area of damage to the mucosa and muscularis by the electric current may extend far beyond the tip of the needle cautery. If the muscularis is found to be fibrotic or gritty, the vas must be recut until healthy tissue is found.

6. Good atraumatic anastomotic technique

If multiple surgical errors occur during the procedure, such as inadvertent cutting of the mucosa with the needles when placing sutures, tearing through of sutures, or back-walling of the mucosa, the anastomosis should be resected and redone immediately.

Setup

An operating microscope providing variable magnification from 6× to 32× is used. A diploscope providing identical fields for both surgeon and assistant is preferred. Foot pedal controls for a motorized zoom and focus leave the surgeon's hands free.

Both surgeon and assistant should be comfortably seated on microsurgical chairs that stabilize the chest and arms. This dramatically improves stability and accuracy. An inexpensive alternative is a simple rolling stool with a round bean bag (meditation pillow) taped on top for padding. Two armboards placed on both sides of the surgeon and built up to the appropriate height with folded blankets taped to the boards provide excellent arm support. A right-handed surgeon should sit at the patient's right side so that the forehead stitch is always on the smaller, more difficult abdominal side lumen.

Microsurgical Multilayer Microdot Method

The microsurgical multilayer microdot method of vasovasostomy can handle lumina of markedly discrepant diameters in the straight or convoluted vas. The microdot technique ensures precise suture placement by exact mapping of each planned suture. The microdot method separates the planning from the placement (Goldstein et al, 1998; Dabaja et al, 2013). This allows focus on only one task at a time and results in substantially improved accuracy.

A microtip marking pen (Devon Skin Marker Extra Fine No. 151) is used to map out planned needle exit points. Exactly six mucosal sutures are used for every anastomosis because it is easy to map out and always results in a leakproof closure even when the lumen diameters are markedly discrepant.

Immediately after drying of the cut surface of the testicular end of the vas with a Weck-Cel, a dot is made at the 3 o'clock position halfway between the mucosal ring and the outer edge of the muscle layer. A line is extended out from this dot to serve as a reference point. The second dot is made at the 9 o'clock position, and a line is extended from this dot as well. Additional dots are placed at the 11, 1, 5, and 7 o'clock positions for a total of six. The abdominal end of the vas is marked in the same way to exactly match the testicular end (Fig. 25-15). Monofilament 10-0 nylon sutures, double-armed with 70-micron diameter taper-point needles bent into a fish hook configuration (available from Sharpoint and Ethicon), are used. Double-armed sutures allow inside-out placement (Fig. 25-16), eliminating the need for manipulation of the mucosa and the possibility of back-walling. If the mucosal rings are not sharply defined, the cut surfaces of the vasal ends are stained with indigo carmine to highlight the mucosa (Sheynkin et al, 1999b). The anastomosis is begun with the placement of three 10-0 mucosal sutures anteriorly (Fig. 25-17). The small abdominal side lumen is gently and momentarily dilated with a microvessel dilator just before placement of the sutures. For accurate mucosal approximation, only a small amount of mucosa is included, but one third to one half the muscle wall thickness. Exactly the same amount of tissue is included in the bites on each side. The needle

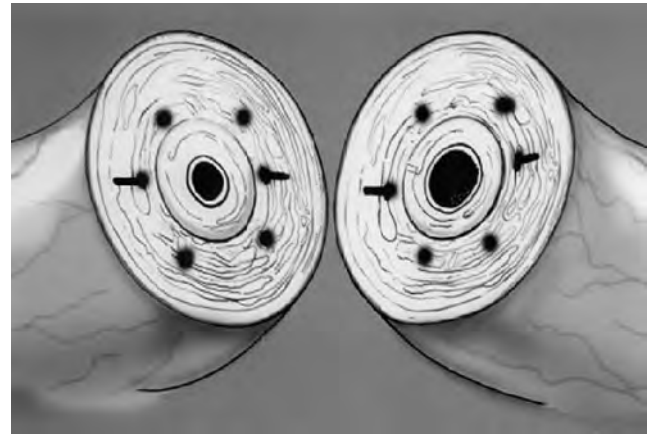


Figure 25-15. The abdominal end of the vas is marked in the same way to exactly match the testicular end.

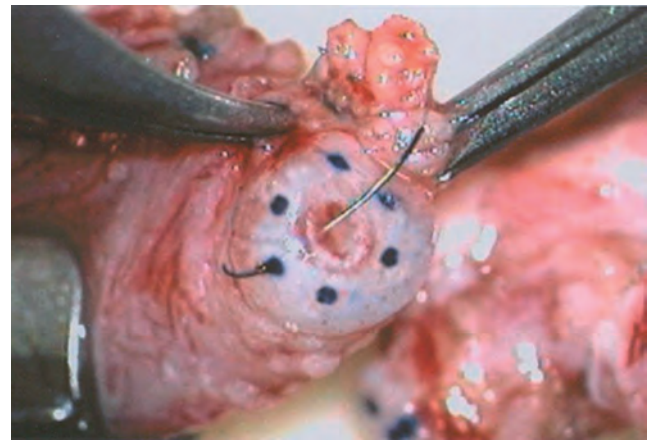


Figure 25-16. Double-armed sutures allow inside-out placement.

should exit through the center of each dot. After placement, the three mucosal sutures are tied. Two 9-0 monofilament nylon deep muscularis sutures are placed exactly between the previously placed mucosal sutures, just above but not through the mucosa (Fig. 25-18), and then are tied. These sutures seal the gaps between the mucosal sutures without trauma to the mucosa from the larger 100-micron diameter cutting needle required to penetrate the tough vas muscularis and adventitia. The vas is rotated 180 degrees (Fig. 25-19), and three additional 10-0 sutures are placed through each microdot and then tied to complete the mucosal portion of the anastomosis (Fig. 25-20). Just before the last mucosal suture is tied, the lumen is irrigated with heparinized Ringer solution to prevent the formation of clot in the lumen. After completion of the mucosal layer (Fig. 25-21), four more 9-0 deep muscularis sutures are placed exactly between each mucosal suture, just above but not penetrating the mucosa. Four to six 9-0 nylon interrupted sutures are placed between each muscular suture. This is a purely adventitial layer that covers the underlying mucosal suture. The anastomosis is finished by approximation of the vasal sheath with six to eight interrupted sutures of 8-0 nylon, completely covering the anastomosis and relieving it of all tension (Fig. 25-22).

Anastomosis in the Convoluted Vas

Vasovasostomy performed in the convoluted portion of the vas deferens is technically more demanding than anastomoses in the straight portion. Fear of cutting back into the convoluted vas to obtain healthy tissue may lead surgeons to complete an

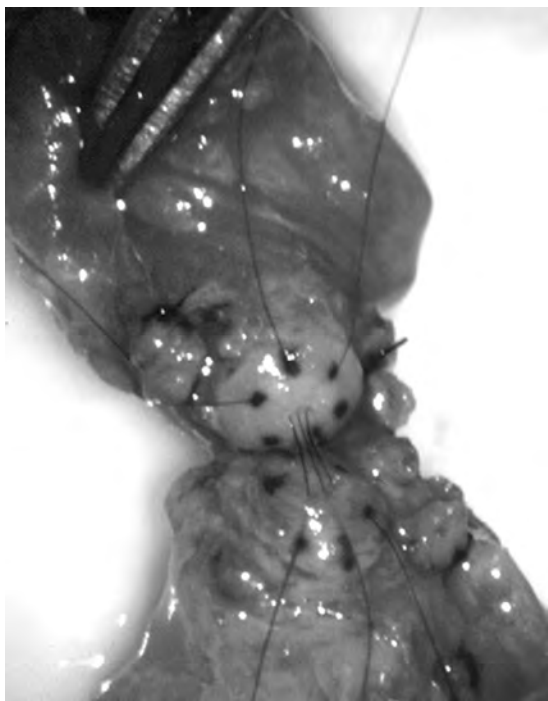


Figure 25-17. The anastomosis is begun with the placement of three 10-0 mucosal sutures anteriorly.

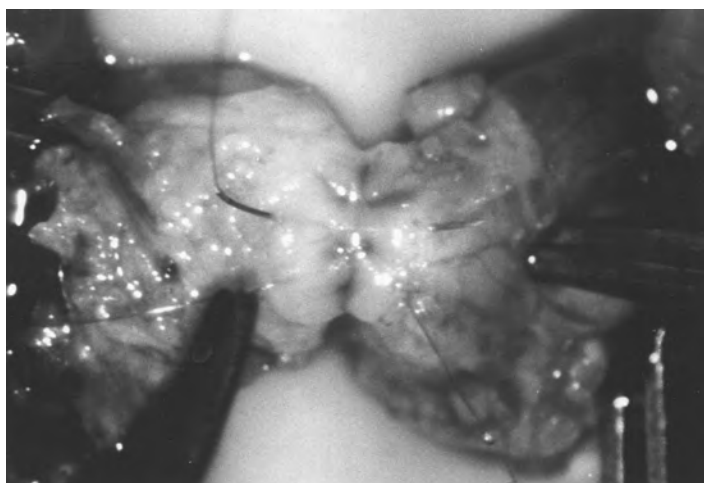


Figure 25-18. Place two 9-0 monofilament nylon deep muscularis sutures exactly between the previously placed mucosal sutures, just above but not through the mucosa.

anastomosis in the straight portion when the testicular end of the vas has poor blood supply, unhealthy or friable mucosa, or gritty fibrotic muscularis. Adherence to the following principles will enable anastomosis in the convoluted vas to succeed as often as those in the straight portion.

1. A perfect transverse cut yielding a round ring of mucosa and a lumen directed straight down is essential. A very oblique lumen with a thin flap of muscle and mucosa on one side is not acceptable (Fig. 25-23). The vas should be recut at 0.5-mm intervals until a perfect cut with good blood supply and healthy tissue is obtained. Use of a slotted nerve clamp 2.5 or 3 mm in diameter and an ultrasharp knife facilitates this part of the procedure (see Fig. 25-14). Often the vas must be recut two or three times until a satisfactory cut is obtained.
2. The convoluted vas should not be unraveled. This disturbs the blood supply at the anastomotic line.

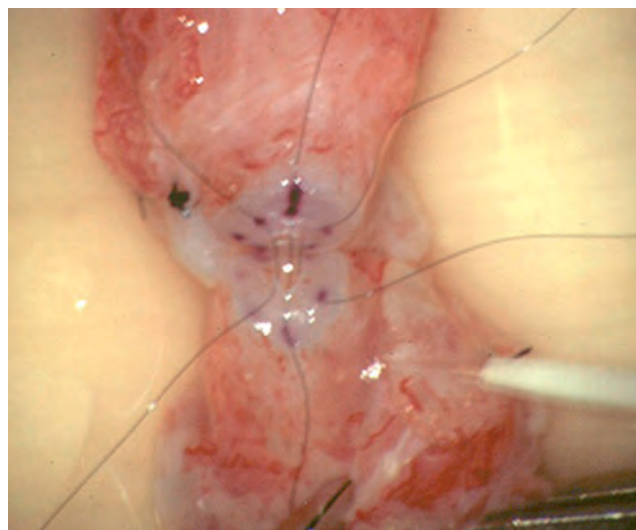


Figure 25-19. Rotate the vas 180 degrees, then place three more 10-0 sutures through the remaining microdots.



Figure 25-20. The mucosal layer is complete.

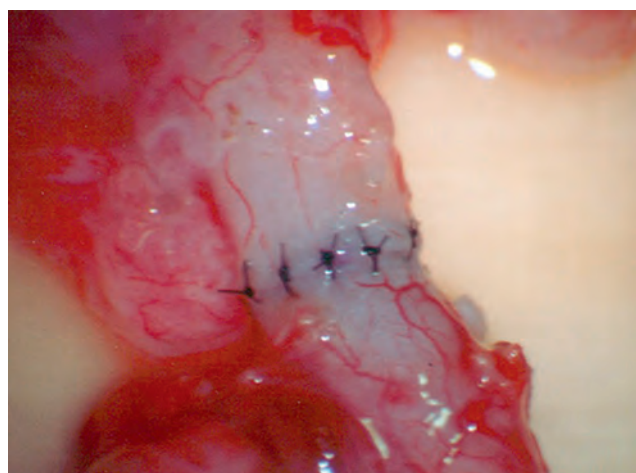


Figure 25-21. Additional sutures are placed between the mucosal sutures, completing the anastomosis.

3. The sheath of the convoluted vas may be carefully dissected free of its attachments to the epididymal tunica (see Fig. 25-12). This will minimize disturbance of its blood supply and provide the necessary length to perform a tension-free anastomosis.

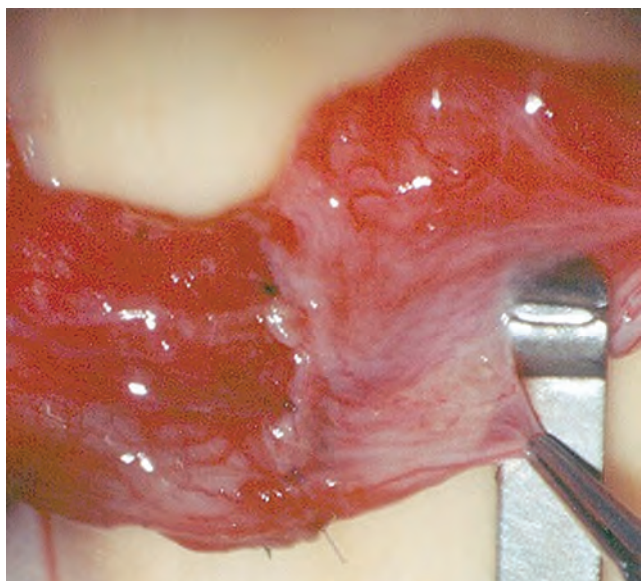


Figure 25-22. Finish the anastomosis by approximating the vasal sheath with six interrupted sutures of 8-0 nylon, completely covering the anastomosis and relieving it of all tension.

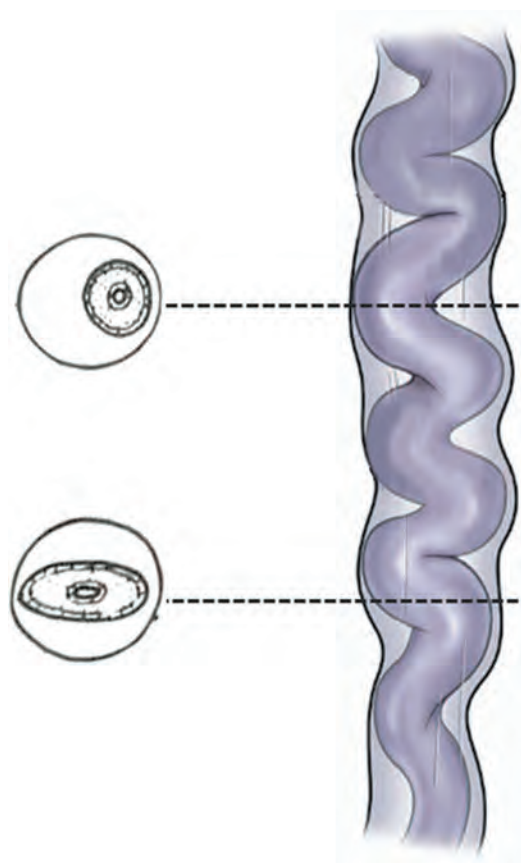


Figure 25-23. A very oblique lumen with a thin flap of muscle and mucosa on one side is not acceptable.

4. Care must be taken to avoid taking large bites of the muscularis and adventitial layers on the convoluted side to prevent inadvertent perforation of adjacent convolutions.
5. Reinforce the anastomosis by approximating the vasal sheath of the straight portion to the sheath of the convoluted portion with six interrupted sutures of 7-0 nylon. This will remove all tension from the anastomosis.

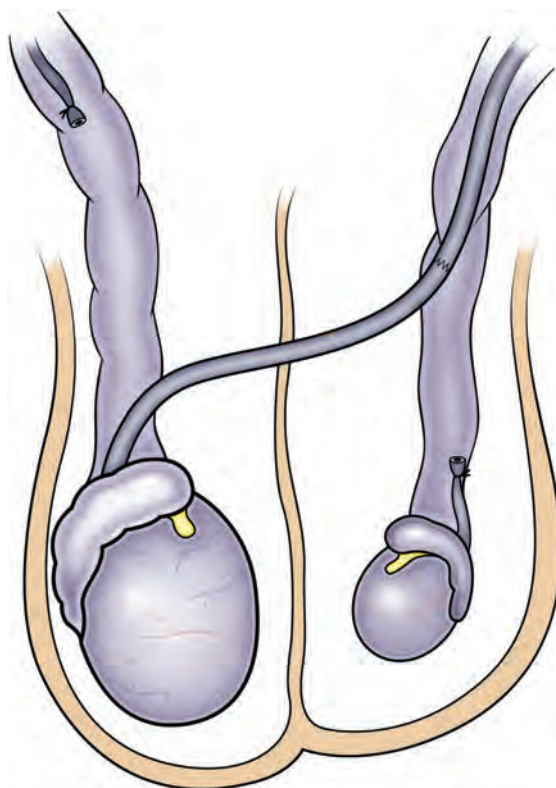


Figure 25-24. A crossed vasovasostomy can be done in patients with a unilateral atrophic testis.

Crossed Vasovasostomy

Crossed vasovasostomy is a useful procedure that often provides an easy solution for otherwise difficult problems (Lizza et al, 1985; Hamidinia, 1988; Sheynkin et al, 1998a). Crossover is indicated in the following circumstances:

1. Unilateral inguinal obstruction of the vas deferens associated with an atrophic testis on the contralateral side. A crossover vasovasostomy should be performed to connect a healthy testicle to the contralateral unobstructed vas.
2. Obstruction or aplasia of the inguinal vas or ejaculatory duct on one side and epididymal obstruction on the contralateral side.

It is preferable to perform one anastomosis with a high probability of success (vasovasostomy) than two operations with a much lower chance of success (e.g., unilateral vasaepididymostomy and contralateral TURED).

Technique (Fig. 25-24)

Transect the vas attached to the atrophic testis at the junction of its straight and convoluted portion and confirm its patency with a Ringer or indigo carmine vasogram. Dissect the contralateral vas with the normal testis toward the inguinal obstruction. Clamp and transect it as high up as possible with a right angle clamp. Cross the testicular end of the vas through a capacious opening made in the scrotal septum and proceed with vasovasostomy as described earlier. This procedure is much easier than inguinal vasovasostomy, which requires finding both ends of the vas within the dense scar of a previous inguinal operation.

Transposition of the Testis

Occasionally when vasal length is critically short, a tension-free crossed anastomosis can best be accomplished by testicular transposition (Fig. 25-25). The spermatic cord is always longer than the vas.

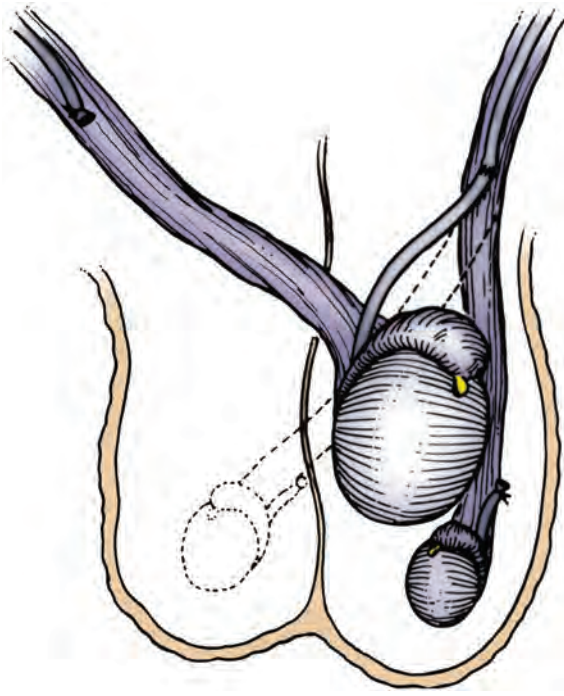


Figure 25-25. Occasionally when vasal length is critically short, a tension-free crossed anastomosis can best be accomplished by testicular transposition.

The testes will comfortably cross through a generous opening in the septum and sit nicely in the contralateral scrotal compartment.

Wound Closure

If the vasal dissection was extensive, Penrose drains are brought out the dependent portion of the right and left hemiscrota and fixed in place with sutures and safety pins, preferably before the anastomosis is begun. Placement of drains at the end of the procedure may potentially disturb the anastomosis. The dartos layer is approximated with interrupted 4-0 absorbable sutures and the skin with subcuticular sutures of 5-0 Monocryl. The wound heals with a fine scar. The use of through-and-through skin closures, which give an unacceptable "railroad track" scar, should be avoided. **Virtually all of our procedures are performed on an ambulatory basis.** If drains were placed, the patients are given detailed instructions (with explicit drawings) on how to remove the drains the next morning.

Postoperative Management

Sterile fluff gauze dressings are held in place with a snug-fitting scrotal supporter. Only perioperative antibiotics are used. Patients are discharged with a prescription for acetaminophen with codeine. They shower 48 hours after surgery. **They wear a scrotal supporter at all times (except in the shower), even when sleeping, for 6 weeks postoperatively.** Thereafter, a scrotal supporter is worn during athletic activity until pregnancy is achieved. Desk work is resumed in 3 days. No heavy work or sports are allowed for 3 weeks. **No intercourse or ejaculation is allowed for 3 weeks postoperatively.** Semen analyses are obtained at 1, 3, and 6 months postoperatively and every 6 months thereafter. If azoospermia persists at 6 months, a redo vasovasostomy or vasoepididymostomy will be necessary.

Postoperative Complications

The most common complication is hematoma. In 2500 operations, seven small hematomas occurred. None required surgical

drainage. Most were walnut sized and perivascular. They take 6 to 12 weeks to resolve. Wound infection has not occurred. Late complications include sperm granuloma at the anastomotic site (approximately 5%). This usually is a harbinger of eventual obstruction. Late stricture and obstruction are disappointingly common (see later). **Progressive loss of motility followed by decreasing counts indicates stricture.** Our recent change from Prolene to nylon sutures (Sheynkin et al, 1999a), use of the microdot system to prevent leaks, extensive dissection of the vas until healthy mucosa and muscularis are identified, constant attention to the preservation of good blood supply, and generous use of scrotal support until pregnancy is established have reduced the incidence of late obstruction from 12% (Matthews et al, 1995) to 5% (Kolettis and Thomas, 1997) at 18 months after surgery. Because of the risk of late stricture and obstruction, we strongly encourage cryopreservation of semen specimens as soon as motile sperm appear in the ejaculate.

Long-Term Follow-up Evaluation after Vasovasostomy

When sperm are found in the vasal fluid on at least one side at the time of surgery, the anastomotic technique described results in appearance of sperm in the ejaculate in 99.5% of men (Goldstein et al, 1998; Dabaja et al, 2013). Pregnancy has occurred in 52% of couples followed for at least 2 years and 63% when female factors are excluded, with outcomes dependent on the time since vasectomy and female partner age (Kolettis et al, 2003; Boorjian et al, 2004; Kolettis et al, 2005; Gerrard et al, 2007; Wosnitzer and Goldstein, 2013).

SURGERY OF THE EPIDIDYMIS

Detailed knowledge of epididymal anatomy and physiology (presented in Chapters 21 and 22) is essential before undertaking surgery of this delicate but important structure. Sperm motility and fertilizing capacity progressively increase during passage through the 200-micron diameter, 12- to 15-foot long, tightly coiled single tubule. When the epididymis is obstructed and functionally shortened after vasoepididymostomy, even very short lengths of epididymis are able to adapt and allow some sperm to acquire motility and fertilizing capacity (Silber, 1989a; Jow et al, 1993). Adaptation may gradually continue for up to 2 years after surgical reconstruction, with progressive improvement in the fertility and motility of sperm. Nevertheless, preservation of the greatest possible length of functional epididymis is most likely to result in the best sperm quality after vasoepididymostomy (Schoysman and Bedford, 1986; Schlegel and Goldstein, 1993). Furthermore, because the wall of the epididymis is thinnest in the caput region and gradually thickens, because of the increasing numbers of smooth muscle cells in its more distal (inferior) end, anastomoses are technically easier to perform and more likely to succeed in its distal regions. **Because the corpus and cauda epididymis is a single tubule with a very small diameter, injury or occlusion of a tubule anywhere along its length will lead to total obstruction of outflow at that level.** For these reasons, magnification, with loupes for macrodissection and with the operating microscope for anastomosis, is essential for performing all epididymal surgery.

Fortunately, the epididymis is blessed with a rich blood supply derived from the testicular vessels superiorly and the deferential vessels inferiorly (see the earlier section on **testicular blood supply** and Chapter 21). Because of the extensive interconnections among these branches, either the testicular or deferential branches (but not both) to the epididymis may be divided without compromising epididymal viability.

Conversely, because the epididymal branches of the testicular artery are medial to and separate from the main testicular artery and veins, surgical procedures may be performed on the epididymis without compromise to testicular blood supply.

TABLE 25-2 Comparison of Three Common Techniques for Vasoepididymostomy

TECHNIQUES	ADVANTAGES	DISADVANTAGES
Intussusception (longitudinal intussusception vasoepididymostomy)	Two sutures placed longitudinally in the dilated epididymal tubule provide four points of fixation. Virtually bloodless anastomosis.	Cannot assess tubular fluid for sperm before anastomosis setup.
End-side	Virtually bloodless anastomosis. Epididymal fluid can be examined before anastomosis.	Difficult suture placement to a collapsed tubule.
End-end	Epididymal fluid can be examined before anastomosis. Easy and rapid identification of the level of obstruction in the epididymis. Allows upward mobilization of epididymis to bridge a large vasal gap.	Difficult hemostasis on transected epididymis. Difficult to identify the proper tubule for anastomosis. Difficult outer layer closure. Vasal blood supply from inferior epididymal artery is sacrificed.

Vasoepididymostomy

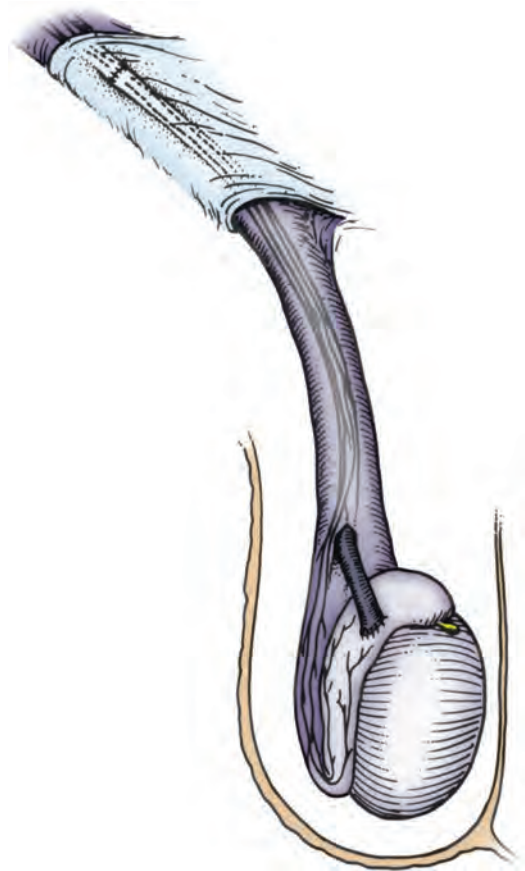
Before the development of microsurgical techniques, accurate approximation of the vasal lumen to that of a specific epididymal tubule was not possible. Vasoepididymostomy was performed by aligning the vas deferens adjacent to a slash made in multiple epididymal tubules and hoping a fistula would form. Results with this primitive technique were poor. Microsurgical approaches allow accurate approximation of the vasal mucosa to that of a single epididymal tubule (Silber, 1978), resulting in marked improvement in the patency and pregnancy rates (Schlegel and Goldstein, 1993; Chan et al, 2005). Microsurgical vasoepididymostomy, however, is the most technically demanding procedure in all of microsurgery. In virtually no other operation are results so dependent on technical perfection. Microsurgical vasoepididymostomy should be attempted only by microsurgeons who perform the procedure frequently.

Indications

The indications for vasoepididymostomy at the time of vasectomy reversal are reviewed in the earlier section on [vasovasostomy](#). For obstructive azoospermia not caused by vasectomy, vasoepididymostomy is indicated when the testis biopsy reveals complete spermatogenesis and scrotal exploration reveals the absence of sperm in the vasal lumen with no vasal or ejaculatory duct obstruction. The preoperative evaluation is identical to that described earlier for vasovasostomy.

Microsurgical End-to-Side Vasoepididymostomy

End-to-side techniques of vasoepididymostomy have the advantage of being minimally traumatic to the epididymis and relatively bloodless (Table 25-2) (Wagenknecht et al, 1980; Krylov and Borovikov, 1984; Fogdestam et al, 1986; Thomas, 1987; Chan et al, 2005; Schiff et al, 2005). The end-to-side technique does not disturb the epididymal blood supply. When the level of epididymal obstruction is clearly demarcated by the presence of markedly dilated tubules proximally and collapsed tubules distally, the site at which the anastomosis should be performed is readily apparent. The end-to-side approach has the advantage of allowing accurate approximation of the muscularis and adventitia of the vas deferens to a precisely tailored opening in the tunica of the epididymis. This is the preferred technique when vasoepididymostomy is performed simultaneously with inguinal vasovasostomy because it is possible to preserve the vasal blood supply deriving from epididymal branches of the testicular artery (Fig. 25-26). This provides blood supply to the segment of vas intervening between the two anastomoses. Maintenance of the deferential artery's contribution to the testicular blood supply is also important in situations in which the integrity of the testicular artery is in doubt owing to prior surgery

**Figure 25-26.** A diagram of a finished vasoepididymostomy.

such as orchiopexy, nonmicroscopic varicocelectomy, or hernia repair.

The testis is delivered through a 3- to 4-cm high vertical scrotal incision. The vas deferens is identified, isolated with a Babcock clamp, and then surrounded with a Penrose drain at the junction of the straight and convoluted portions of the vas deferens. Under 8× to 15× magnification provided by the operating microscope, the vasal sheath is longitudinally incised with a microknife, and a bare segment of vas stripped of its carefully preserved vessels is delivered. The vas is hemitranssected with the ultrasharp knife until the lumen is entered (Fig. 25-27). The vasal fluid is sampled. If microscopic examination of this fluid reveals the absence of sperm, the diagnosis of epididymal obstruction is confirmed. Patency of the vas and ejaculatory ducts is confirmed by cannulating the abdominal

end of the vas with a 24-gauge angiocatheter sheath and gently injecting lactated Ringer solution with a 1-mL tuberculin syringe (see Fig. 25-3). Further confirmation of patency may be obtained by injecting indigo carmine, catheterizing the bladder, and observing blue-tinged urine. The vas is then completely transected with use of a 2.5-mm slotted nerve clamp (see Fig. 25-27) and the vas is prepared as for vasovasostomy as described earlier.

After the tunica vaginalis has been opened, the epididymis is inspected under the operating microscope. An anastomotic site is selected above the area of suspected obstruction, proximal to any visible sperm granulomas, where dilated epididymal tubules are clearly seen beneath the epididymal tunica (Fig. 25-28). A relatively avascular area is grasped with sharp jeweler's forceps and the epididymal tunica tented upward. A 3- to 4-mm buttonhole is made in the tunica with microscissors to create a round opening that matches the outer diameter of the previously prepared vas deferens. The epididymal tubules are then gently dissected with a

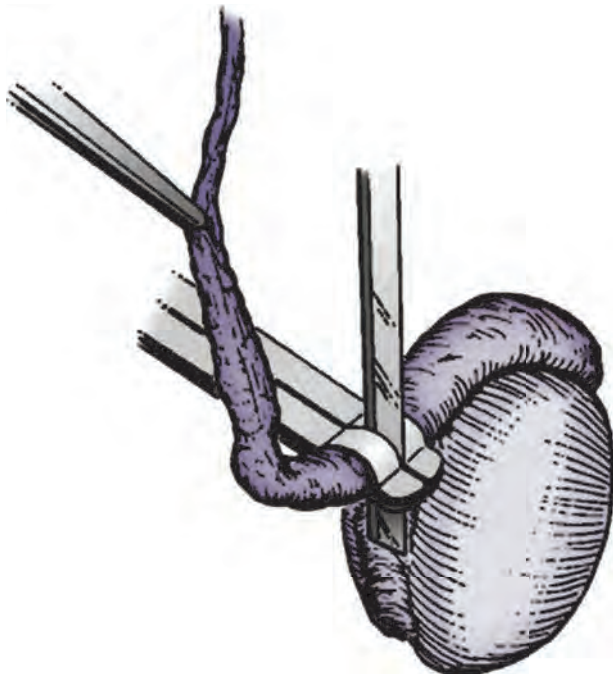


Figure 25-27. The vas is hemitransected with the ultrasharp knife until the lumen is entered.

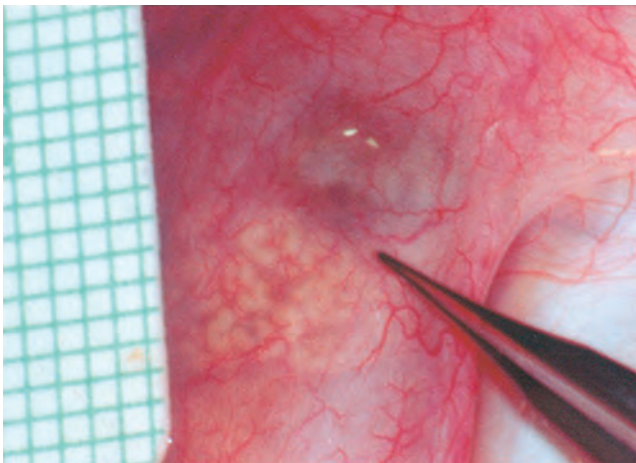


Figure 25-28. An anastomotic site is selected above the area of suspected obstruction, proximal to any visible sperm granulomas, where dilated epididymal tubules are clearly seen beneath the epididymal tunica.

combination of sharp and blunt dissection until dilated loops of tubule are clearly exposed (Fig. 25-29). If the level of obstruction is not clearly delineated, after the buttonhole opening has been made in the tunic, a 70- μ m diameter tapered needle from the 10-0 nylon microsuture is used to puncture the epididymal tubule beginning as distal as possible; fluid from the puncture site is examined under the 400-power magnification bench microscope. When sperm are found, the puncture sites are sealed with microbipolar forceps, a new buttonhole is made in the epididymal tunic just proximal, and the tubule is prepared as described previously.

The vas deferens is drawn through an opening in the tunica vaginalis and secured in proximity to the anastomotic site with two to four interrupted sutures of 6-0 polypropylene placed through the vasal adventitia and the tunica vaginalis. The vasal lumen should reach the opening in the epididymal tunica easily, with length to spare. The posterior edge of the epididymal tunica is then approximated to the posterior edge of the vas muscularis and adventitia with two to three interrupted sutures of double-armed 9-0 nylon (Fig. 25-30). This is done in such a way as to bring the vasal lumen in close approximation to the epididymal tubule selected for anastomosis.

Classic End-to-Side Technique

Under 25 \times to 32 \times magnification, with use of small curved microscissors or a 15-degree microknife, an opening about 0.3 to 0.5 mm

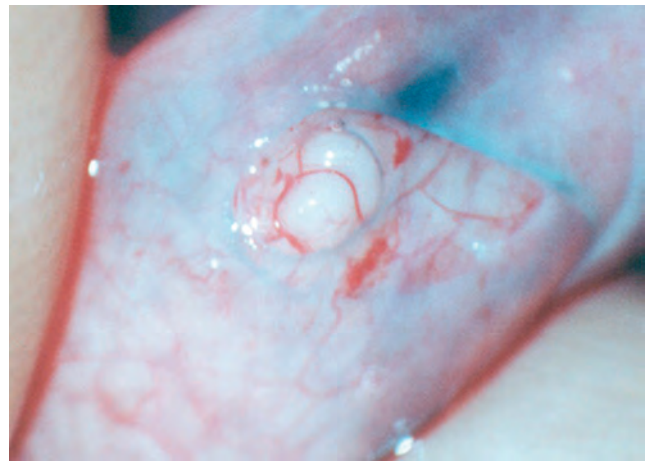


Figure 25-29. The epididymal tubules are then gently dissected with a combination of sharp and blunt dissection until dilated loops of tubule are clearly exposed.

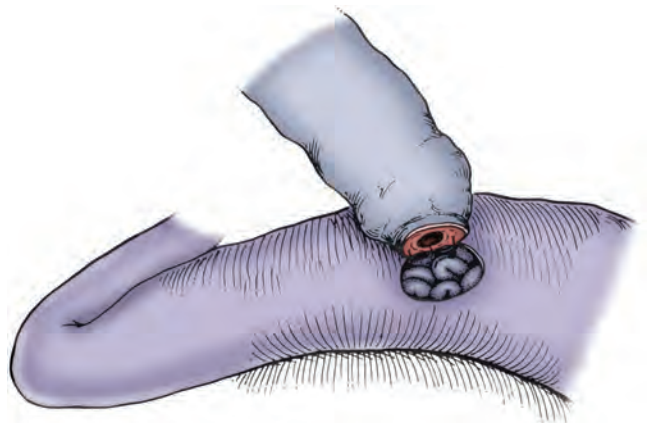


Figure 25-30. The posterior edge of the epididymal tunica is then approximated to the posterior edge of the vas muscularis and adventitia with two to three interrupted sutures of double-armed 9-0 nylon.

in diameter is made in the selected tubule. Epididymal fluid is touched to a slide, diluted with saline or Ringer solution, and inspected under the microscope for sperm. If no sperm are found, the opening in the tubule is closed with 10-0 sutures, the vas detached, and the tunica incision closed with 9-0 nylon. The procedure is then repeated more proximally in the epididymis.

Once sperm have been identified, they are aspirated into glass capillary tubes and flushed into media for cryopreservation (Fig. 25-31; see the section on the *open tubule technique* later in this chapter) (Matthews et al, 1995). Indigo carmine solution is dripped on the cut tubule to outline the mucosa. Methylene blue kills sperm instantly even when diluted, rendering the sperm useless for cryopreservation (Sheynkin et al, 1999b). Indigo carmine, diluted 50%, is safe for sperm. The posterior mucosal edge of the epididymal tubule is approximated to the posterior edge of the vasal mucosa with two interrupted 10-0 monofilament nylon sutures double-armed with fish hook 70-micron diameter tapered needles (Fig. 25-32). The lumen is irrigated with Ringer solution just before placement of each suture to keep the epididymal lumen open. The lumen is irrigated with heparinized saline just before the last mucosal suture is tied, to prevent clots from obstructing the lumen. Unlike with blood vessels, there are no platelets and fibrinogen to seal a leaky anastomosis and no clot lysis factor to dissolve clots. After these mucosal sutures are tied, the anterior mucosal anastomosis is completed with two to four additional 10-0 sutures.



Figure 25-31. Once sperm have been identified, they are aspirated into glass capillary tubes and flushed into media for cryopreservation.

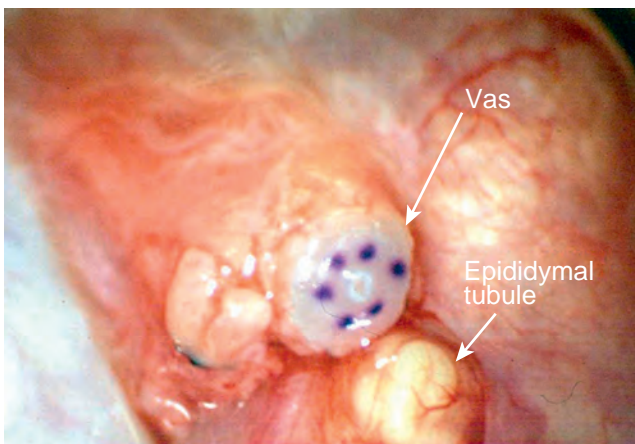


Figure 25-32. The posterior mucosal edge of the epididymal tubule is approximated to the posterior edge of the vasal mucosa with two interrupted 10-0 monofilament nylon sutures double-armed with fish-hook 70-micron diameter tapered needles.

The outer muscularis and adventitia of the vas are then approximated to the cut edge of the epididymal tunica with 6 to 10 additional interrupted sutures of 9-0 nylon double-armed with 100-micron diameter needles (Fig. 25-33). The vasal sheath is secured to the epididymal tunica with three to five sutures of 9-0 nylon. The testis and epididymis are gently returned to the tunica vaginalis, which is closed with 5-0 Vicryl. Penrose drains are usually not necessary. The scrotum is closed as previously described for vasovasostomy.

Two-Stitch Longitudinal Intussusception Vasoepididymostomy Technique

The original intussusception technique described by Berger (1998) used three double-armed 10-0 sutures placed in the epididymal tubule in a triangular fashion and a 9-0 needle to tear an opening in the middle of the triangle. We now use a two-stitch longitudinal intussusception (LIVE) technique for all vasoepididymostomies.

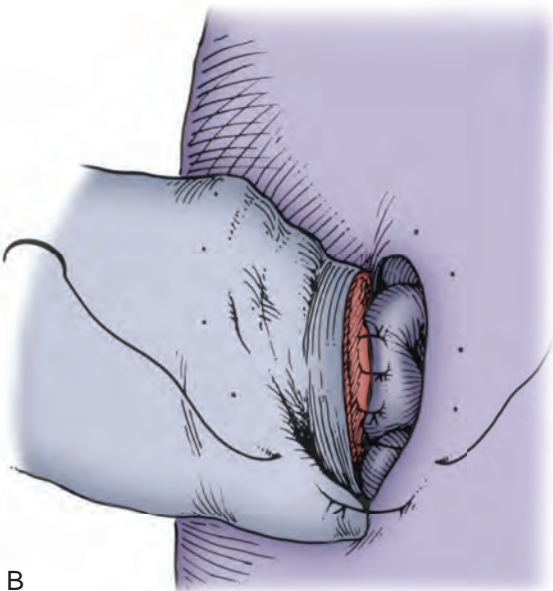
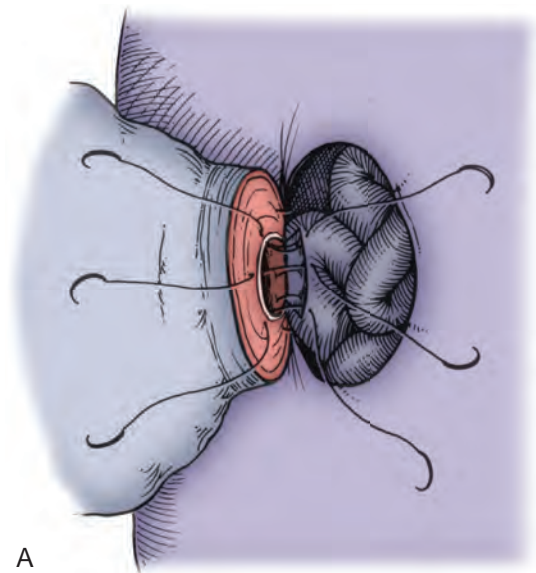


Figure 25-33. A and B, The outer muscularis and adventitia of the vas are then approximated to the cut edge of the epididymal tunica with 6 to 10 additional interrupted sutures of 9-0 nylon double-armed with 100-micron diameter needles.

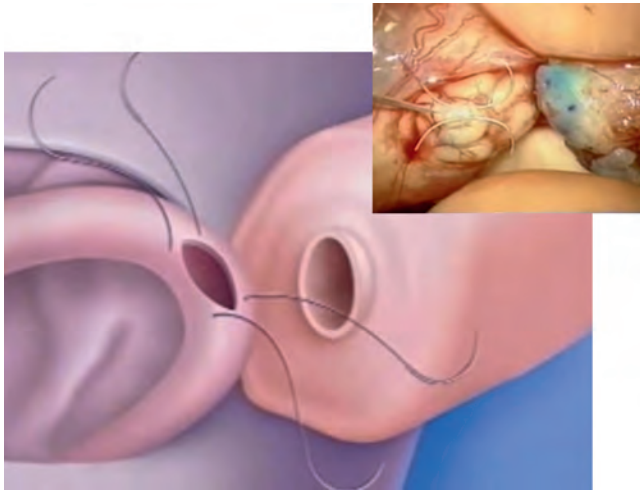


Figure 25-34. With this method, four microdots are marked on the cut surface of the vas deferens and two parallel sutures are placed in the distended epididymal tubule longitudinally, but not pulled through.

It is much easier to perform and is even more successful. With this method, four microdots are marked on the cut surface of the vas deferens and two parallel sutures are placed in the distended epididymal tubule longitudinally, but not pulled through (Fig. 25-34). Marmar (2000) suggests mounting two needles in the needle holder and placing them simultaneously transversely in the tubule. However, if the needles are not pulled through to avoid leakage of fluid and tubular collapse, they can be placed one at a time with greater control and accuracy (Chan et al, 2005; Schiff et al, 2005). Longitudinal placement also allows a larger opening to be made in the epididymal tubule without risk of completely transecting it. With a 15-degree microknife, an opening is made exactly between and parallel to the two previously placed sutures. Of note, we have also developed a single-arm technique of vasoepididymostomy that is almost as effective as the double-arm technique (Fig. 25-35) (Monoski et al, 2007). This technique may prove valuable when double-arm sutures are not available.

Technique When Vasal Length Is Severely Compromised (Fig. 25-36)

When there is inadequate length of the vas deferens to reach the dilated epididymal tubule without tension, the epididymis can be dissected down to the VE junction and then dissected off the testes as in the older end-to-end operation.

After the vas has been prepared, the tunica vaginalis is opened and the testis delivered. Inspection of the epididymis under the operating microscope may reveal a clearly delineated site of obstruction. Often, a discrete yellow sperm granuloma is noted, above which the epididymis is indurated and the tubules dilated and below which the epididymis is soft and the tubules collapsed. If the level of obstruction is not clearly delineated, a 70-micron tapered needle from the 10-0 nylon microsuture is used to puncture the epididymal tubule beginning as distal as possible, and fluid is sampled from the puncture site until sperm are found. At that level the puncture is sealed with microbipolar forceps and the epididymis is ligated just proximal to the puncture site with 6-0 nylon. The epididymis is then dissected off the testis and flipped up to obtain additional length. To do this, the epididymis is encircled with a small Penrose drain at the level of obstruction and, under 2.5× loupe magnification, dissected off the testis for 3 to 5 cm, yielding sufficient length to perform the anastomosis. Usually a nice plane can be found between the epididymis and testis, and injury to the epididymal blood supply can be avoided by staying

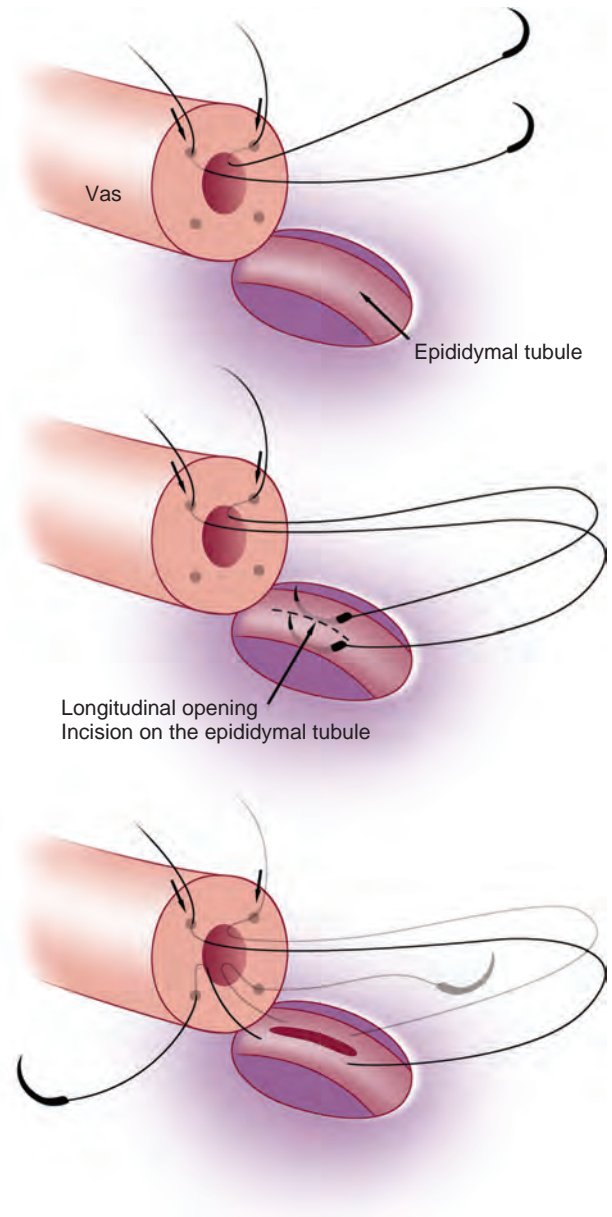


Figure 25-35. Of note, we have also developed a single-arm technique of vasoepididymostomy that is almost as effective as the double-arm technique.

right on the tunica albuginea of the testis. The inferior and, if necessary, middle epididymal branches of the testicular artery are ligated and divided to free an adequate length of epididymis. The superior epididymal branches entering the epididymis at the caput are always preserved and can provide adequate blood supply to the entire epididymis. The tunica vaginalis is then closed over the testis with 5-0 Vicryl. This prevents drying of the testis and thrombosis of the surface testicular vessels during the anastomosis. The dissected epididymis remains outside the tunica vaginalis.

If the epididymis is indurated and dilated throughout its length, the epididymis is dissected to the VE junction. This dissection is often facilitated by first dissecting the convoluted vas to the VE junction from below and then, after encircling the epididymis with a Penrose drain, dissecting the epididymis to the VE junction from above. In this way the entire VE junction can be freed up. This will allow preservation of maximal epididymal length in cases of distal obstruction near the VE junction. After the epididymis has been dissected off the testis and flipped up, a two-stitch end-to-side intussusception anastomosis is performed as described earlier.

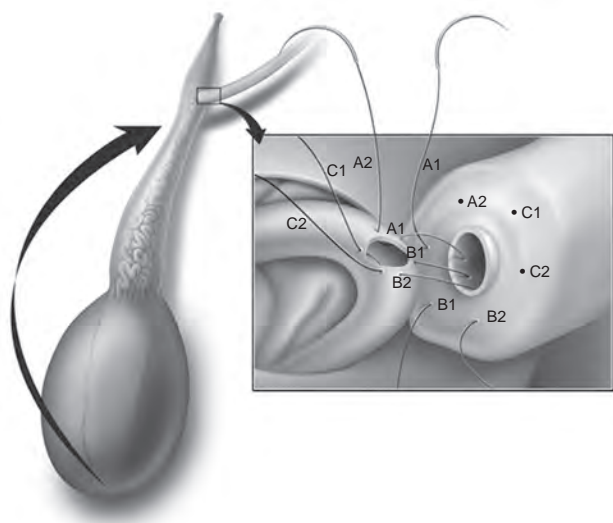


Figure 25-36. In addition, if vasal length is compromised, the epididymis can be dissected to the caput by ligating the inferior and medial epididymal vessels and flipping the epididymis up, providing additional length. A1, A2, B1, B2, C1, and C2 indicate needle exit points.

Long Term Follow-up: Evaluation and Results

Microsurgical vasoepididymostomy in the hands of experienced and skilled microsurgeons will result in the appearance of sperm in the ejaculate in 50% to 85% of men. Patency rates with the intussusception technique can exceed 80% (Berger, 1998; Brandell and Goldstein, 1999; Marmar, 2000). With the classic end-to-side or older end-to-end method, the patency rate is about 70%, and 43% of men with sperm will impregnate their partners after a minimum follow-up of 2 years (Schlegel and Goldstein, 1993; Pasqualotto et al, 1999). With the intussusception technique, patency rates are 70% to 90% (Kolettis and Thomas, 1997; Chan et al, 2005; Schiff et al, 2005). Regardless of technique, pregnancy rates are higher the more distally the anastomosis is performed (Silber, 1989b). With the older end-to-end or end-to-side methods, at 14 months after surgery 25% of initially patent anastomoses have shut down (Matthews et al, 1995). With the intussusception technique, the late shut-down rates appear to be less than 10%, but long-term follow-up with this technique has not been reported. Nevertheless, we recommend banking sperm both intraoperatively (Matthews and Goldstein, 1996) and as soon as they appear in the ejaculate postoperatively after vasoepididymostomy, regardless of technique used. In men with very low counts or poor sperm quality postoperatively and men who remain azoospermic, the sperm intraoperatively cryopreserved can be used for IVF with ICSI. Persistently azoospermic men without cryopreserved sperm can opt for either a redo vasoepididymostomy and/or microscopic epididymal sperm aspiration combined with IVF and ICSI (see the section on sperm retrieval techniques).

TRANSURETHRAL RESECTION OF THE EJACULATORY DUCTS

Ejaculatory duct obstruction is usually a congenital anomaly that represents the opposite end of the spectrum of excurrent ductal system anomalies that begins with congenital complete absence of the vas deferens and most of the epididymis. When the aplastic segment occurs at the terminal end of the vas, where the ejaculatory duct enters the urethra, it is potentially correctable by TUR (Paick et al, 2000; Schroeder-Printzen et al, 2000; Kadioglu et al, 2001; Ozgok et al, 2001; Yurdakul et al, 2008).

Occasionally, ejaculatory duct obstruction results from chronic prostatitis or extrinsic compression of the ejaculatory ducts by prostate or seminal vesical duct cysts (Cornel et al, 1999; Paick et al, 2000; Kadioglu et al, 2001). Higher ejaculatory duct pressures have been directly measured in men with ejaculatory duct obstruction (Eisenberg et al, 2008).

Diagnosis

The work-up leading to the diagnosis of probable ejaculatory duct obstruction is covered in Chapter 24. Briefly, ejaculatory duct obstruction is suspected in azoospermic or severely oligospermic and/or asthenospermic men with at least one palpable vas deferens, a low semen volume, acidic semen pH, and negative, equivocal, or low semen fructose levels. If these men have normal serum levels of FSH and testis biopsy reveals normal spermatogenesis, the diagnosis of ejaculatory duct obstruction is entertained.

Digital rectal examination may reveal a midline cystic structure. Transrectal sonography is key to the diagnosis and treatment of ejaculatory duct obstruction. A midline cystic lesion or dilated ejaculatory ducts and seminal vesicles can be visualized sonographically. As described in the section on transrectal vasography and seminal vesiculography earlier in this chapter, transrectal ultrasound-guided aspiration of the cystic or dilated ejaculatory ducts or seminal vesicles is performed (Jarow, 1994). The aspirate is examined microscopically; if motile sperm are found, they are cryopreserved and 2 to 3 mL of indigo carmine diluted with water-soluble radiographic contrast is instilled. If a radiograph confirms a potentially resectable lesion, TURED is performed without the need for prior vasography because the presence of sperm in the seminal vesicles indicates that at least one epididymis is patent and that the cyst or dilated ejaculatory duct communicates with a nonobstructed vas. The instillation of indigo carmine assists in localizing the opening of the ejaculatory duct and confirms when resection has successfully opened the obstructed system. Transrectal sonography with aspiration should be performed immediately before anticipated surgery and uses the same bowel preparation and antibiotic prophylaxis as for transrectal prostate biopsy.

If no sperm are found in the aspirate, vasography, as described in the earlier section on technique of vasography and interpretation of findings, is necessary. If no sperm are found in either vas when the vasotomy is made and vasography reveals ejaculatory duct obstruction, it is best to abandon attempts at reconstruction and simply perform microsurgical epididymal sperm aspiration and cryopreservation for future IVF and ICSI. Performance of simultaneous vasoepididymostomy and TURED has never worked in my experience. If ejaculatory duct obstruction is confirmed by vasography using a 50% water-soluble contrast medium and sperm are present in the vasa, the 3-Fr whistle tip ureteral vasography stents are left in place so that a dilute indigo carmine solution can be injected by the assistant to aid resection.

Technique

Cold knife incision alone almost always leads to reobstruction. The resectoscope, with the 24-Fr cutting loop, is engaged with a finger placed in the rectum providing anterior displacement of the posterior lobe of the prostate. The ejaculatory ducts course between the bladder neck and the verumontanum and exit at the level of and along the lateral aspect of the verumontanum (Fig. 25-37). Resection of the verumontanum will often reveal the dilated ejaculatory duct orifice or cyst cavity. Resection should be carried out in this region with great care to preserve the bladder neck proximally, the striated sphincter distally, and the rectal mucosa posteriorly. Efflux of indigo carmine from dilated orifices confirms adequate resection. Avoid excessive coagulation. If formal vasography was performed, the hemivasotomies are carefully closed using microsurgical technique. A Foley catheter is left overnight and the patient receives an additional 7 days of oral antibiotics.

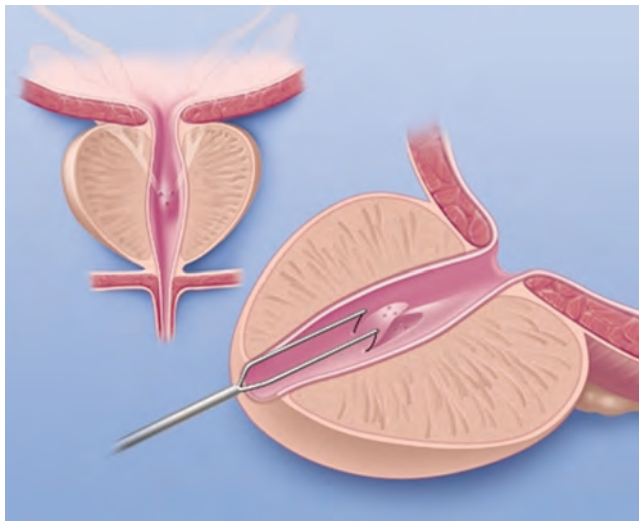


Figure 25-37. The ejaculatory ducts course between the bladder neck and the verumontanum and exit at the level of and along the lateral aspect of the verumontanum.

Complications

Reflux

Reflux of urine into the ejaculatory ducts, vas, and seminal vesicles occurs after a majority of resections. This can be documented by voiding cystourethrography or measurement of semen creatinine levels (Malkevich et al, 1994). Contamination of semen by urine impairs sperm quality.

Epididymitis

Reflux can lead to acute and chronic epididymitis. Recurrent epididymitis often results in epididymal obstruction. The incidence of epididymitis after TUR is probably underestimated. Symptomatic chemical epididymitis may occur from refluxing urine. Chronic low-dose antibacterial suppression, such as that used for vesicoureteral reflux, may be necessary until pregnancy is achieved. If epididymitis is chronic and recurrent, vasectomy or even epididymectomy may be necessary.

Retrograde Ejaculation

Even when care has been taken to spare the bladder neck, retrograde ejaculation is common after TUR. Pseudoephedrine 120 mg orally 90 minutes before ejaculation or Ornade Spansules (chlorpheniramine and phenylpropanolamine) twice a day for a week may prevent this. If this is not successful, sperm can be retrieved from alkalized urine and used for either IUI or IVF with ICSI.

Results

TURED results in increased semen volume about two thirds of the time and appearance of sperm in the ejaculate in about 50% of previously azoospermic men. Pregnancy rates are based on case reports and small series (Goldwasser et al, 1985; Paick et al, 2000; Ozgok et al, 2001; Fuse et al, 2003; Yurdakul et al, 2008). If viable sperm appear in the ejaculate but the quality is poor, IVF with ICSI is recommended and currently yields delivery rates of up to 38.5% per attempt. Because of the potential for serious complications, TUR should be performed only in azoospermic men or in severely oligoasthenospermic men and only after the male and female partners have stated they are unwilling to undergo IVF and have been fully apprised of the risks of TUR.

ELECTROEJACULATION

Men with neurologic impairments in sympathetic outflow, such as seen in traumatic spinal cord injury, demyelinating neuropathies (multiple sclerosis), and diabetes after retroperitoneal lymph node dissection, frequently have abnormalities in or absence of seminal emission. Ejaculation can be induced in most of these men, especially those with high spinal cord injury, with vibratory stimulation (Schellam, 1968; Brindley, 1981; Bennett et al, 1987; Brackett et al, 1997; Ohl et al, 1997). For men who do not respond to vibratory stimulation, electroejaculation has proven to be a safe and effective means of obtaining motile sperm suitable for assisted reproduction techniques (IUI, IVF with ICSI).

The procedure is performed with the patient under general anesthesia except for men with a complete spinal cord injury, who do not require anesthesia. In men with a high thoracic spinal cord lesion (above T6) or in men with prior history of autonomic dysreflexia, pretreatment, 15 minutes before the procedure, with 20 mg of sublingual nifedipine is used. These men should have intravenous access and their blood pressure and pulse should be monitored every 2 minutes before, during, and for 20 minutes after electroejaculation. In the event of a sympathetic outflow (autonomic dysreflexia), termination of the procedure should be sufficient to break the response; however, intravenous access allows for delivery of sympatholytic agents should they become necessary.

Before placing the patient in the lateral decubitus position, the bladder is catheterized and emptied. A 12-Fr or 14-Fr Silastic catheter lubricated with a small amount of mineral oil is used because common lubricants are spermicidal. Ten milliliters of buffer (HEPES-BSA) is instilled into the bladder. Before the electroejaculation sequence, a digital rectal examination and anoscopy are performed. A rectal probe with three large horizontal stripes is well lubricated, inserted with the electrodes facing anteriorly, and applied against the posterior aspect of the prostate and seminal vesicles. The probe is connected to a variable output power source which simultaneously records probe temperature through a thermistor in the rectal probe. Electrostimulation is started at 3 to 5 volts and increased in 1-volt increments with each stimulation (Ohl et al, 2001). An assistant records probe temperatures, number of stimulations to full erection, and ejaculation, and collects the ejaculate in a sterile wide mouth plastic container. The number of stimulations and maximum voltage required are variable and the ejaculate may be retrograde. If probe temperature rises rapidly or above 40°C, stimulation is suspended until the temperature falls below 38°C or the probes are changed. At the completion of stimulation, anoscopy is again performed to check for rectal injury. The bladder is recatheterized to obtain any retrograde-ejaculated sperm. The specimens are then delivered to the laboratory for processing. A second electroejaculation sequence can be immediately performed under the same anesthetic to obtain additional sperm.

With this technique, sperm can be recovered in more than 90% of men. Overall pregnancy rates of up to 40% can be achieved after multiple cycles with IUI. Use of IVF with ICSI will yield 50% live delivery rates for a single (albeit costly) procedure if motile sperm are obtained.

SPERM RETRIEVAL TECHNIQUES

Men with congenital absence or bilateral partial aplasia of vas deferens or those with failed or surgically unreconstructable obstructions can now be treated through use of sperm retrieval techniques in conjunction with IVF (Table 25-3) (Temple-Smith et al, 1985; Silber et al, 1990; Schlegel et al, 1994; Craft et al, 1995; Sheynkin et al, 1998b; Janzen et al, 2000; Levine et al, 2003; Qiu et al, 2003; Anger et al, 2004). These techniques are also useful for intraoperative retrieval of sperm during reconstructive procedures such as vasoepididymostomy, which have significant failure rates. The intraoperatively retrieved sperm may be used immediately if the female

TABLE 25-3 Surgical Techniques for Sperm Retrieval

	ADVANTAGES	DISADVANTAGES
MESA (microsurgical epididymal sperm aspiration)	Microsurgical procedure allows lower complication rate. Epididymal sperm has better motility than testicular sperm. Large number of sperm can be harvested for cryopreservation of multiple vials in a single procedure.	Requires anesthesia and microsurgical skills. Not indicated for nonobstructive azoospermia.
PESA (percutaneous epididymal sperm aspiration)	No microsurgical skill required. Local anesthesia. Epididymal sperm has better motility than testicular sperm.	Complications include hematoma, pain, and vascular injury to testes and obstruction of the epididymis. Variable success in obtaining sperm. Smaller quantity of sperm obtained than with MESA. Not indicated for nonobstructive azoospermia.
TESA (testicular sperm aspiration)	No microsurgical skill required. Local anesthesia. Can be used for obstructive azoospermia.	Immature or immotile testicular sperm. Small quantity of sperm obtained. Poor results in nonobstructive azoospermia. Complications include hematoma, pain, and vascular injury to testes and epididymis.
TESE (testicular sperm extraction)	Low complication rate if performed microsurgically. Preferred technique for nonobstructive azoospermia.	Requires anesthesia and microsurgical skills.

partner has been prepared for IVF or may be cryopreserved for a future IVF with ICSI cycle in the event the reconstructive surgery is unsuccessful. Sperm obtained from chronically obstructed systems usually have poor motility and decreased fertilizing capacity. **The use of ICSI combined with IVF is essential regardless of the count and motility of the aspirated sperm.**

Microsurgical Epididymal Sperm Aspiration Techniques

Open Tubule Technique

The technique described here can be used for either intraoperative sperm retrieval at the time of vasoepididymostomy or as an isolated procedure in men with congenital absence of the vas or unreconstructable obstructions (Matthews and Goldstein, 1996; Nudell et al, 1998). A median raphe approach through two small transverse scrotal incisions within the scrotal skin folds is made. After delivery of the testis, the tunica vaginalis is opened and the epididymis inspected under 16× to 25× magnification using the operating microscope. The epididymal tunica is incised over a dilated tubule as described previously for vasoepididymostomy. Meticulous hemostasis is obtained using bipolar cautery. A dilated tubule is isolated and incised with a 15-degree microknife. The fluid is touched to a slide, a drop of human tubal fluid media is added, a coverslip is placed, and the fluid examined. If no sperm are obtained, the epididymal tubule and tunica are closed with 10-0 and 9-0 monofilament nylon sutures, respectively, and an incision is made more proximally in the epididymis or even at the level of the efferent ductules until motile sperm are obtained.

As soon as motile sperm are found, a dry micropipette (5 μ L; Drummond Scientific, Broomall, PA) is placed adjacent to the effluxing epididymal tubule (Fig. 25-38). A standard hematocrit pipette is less satisfactory but can be used if micropipettes are not available. **Sperm are drawn into the micropipette by simple capillary action.** Negative pressure, as is generated by action of an in-line syringe, should not be applied during sperm recovery because this could disrupt the delicate epididymal mucosa. Two micropipettes may be employed simultaneously to increase speed of sperm recovery.

The highest rate of flow is observed immediately after incision of the tubule. Progressively better quality sperm are often found after the initial washout. **Gentle compression of the testis and epididymis enhances flow from the incised tubule.** With patience, 10 to 20 μ L of epididymal fluid can be recovered.



Figure 25-38. As soon as motile sperm are found, a dry micropipette (5 μ L; Drummond Scientific Co., Broomall, PA) is placed adjacent to the effluxing epididymal tubule.

The micropipette is connected to a short (3 to 5 cm) segment of medical grade silicone tubing (American Scientific Products, McGaw Park, IL). Alternatively, the tubing attached to a 25-gauge butterfly needle may be used. A 20-gauge needle fitted to a Luer-tip syringe is then placed in line. The fluid is flushed with IVF medium (0.5 to 1.0 mL) into a sterile container. Once a micropipette has been used, it is discarded. Residual fluid in the pipette will disrupt capillary action. A typical procedure requires 4 to 12 micropipettes. The sperm bank should be instructed to cryopreserve the aspirate in multiple vials (aliquots) so that several IVF cycles may be attempted if required (Janzen et al, 2000; Anger et al, 2004).

Experience with the technique has revealed that, paradoxically, in obstructed systems sperm motility is better more proximal in the epididymis, with the most motile sperm often found in the efferent ductules (Fig. 25-39). Motility immediately after aspiration and consequently fertilization rates are highest in men who have the longest length of epididymal tubule available. Even when packed with debris distally, the epididymal tubule may be capable of secreting substances that can diffuse proximally and benefit sperm motility and fertilizing capacity.

With use of ICSI, ongoing pregnancy or delivery rates exceeding 60% have been achieved with this technique using either

Packed sperm,
some macrophages

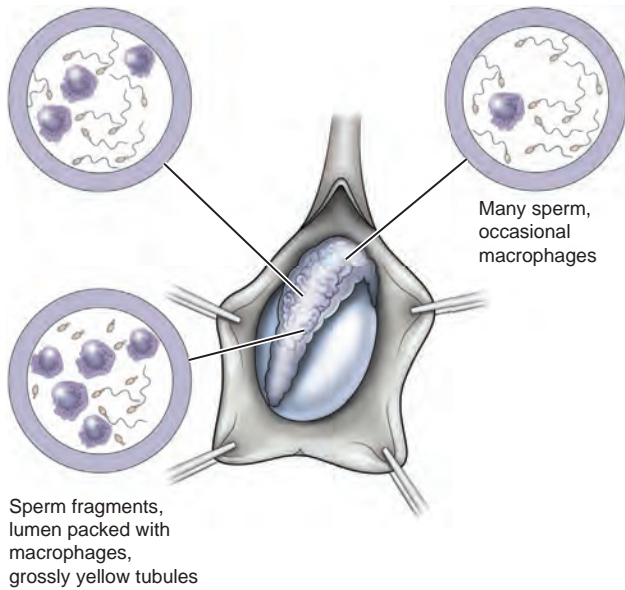


Figure 25-39. Experience with the technique has revealed that, paradoxically, in obstructed systems sperm motility is better more proximal in the epididymis, with the most motile sperm often found in the efferent ductules.

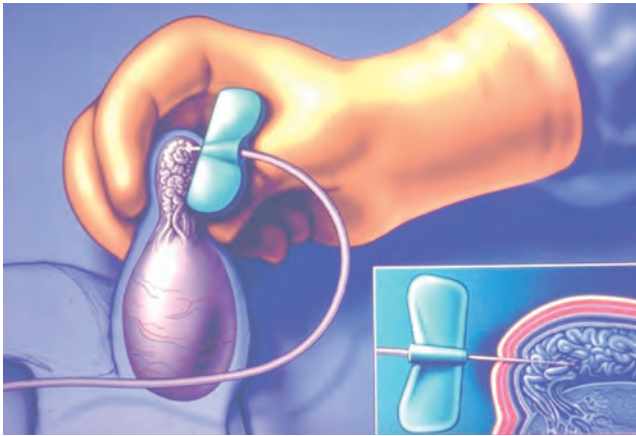


Figure 25-40. Percutaneous puncture of the epididymis with a fine needle.

fresh or cryopreserved epididymal sperm (Schlegel et al, 1995; Nudell et al, 1998). Epididymal sperm aspiration can be done electively, with the cryopreserved sperm used for multiple future IVF cycles (Janzen et al, 2000; Anger et al, 2004).

Percutaneous Epididymal Sperm Aspiration

Percutaneous puncture of the epididymis with a fine needle (Fig. 25-40) has been successfully used to obtain sperm and achieve pregnancies (Shrivastav et al, 1994; Craft and Tsigotis, 1995; Levine et al, 2003; Qiu et al, 2003; Lin et al, 2004). The technique is less reliable than open retrieval, and the small quantities of sperm obtained are sometimes inadequate for cryopreservation. Reported pregnancy rates are half those achieved with open techniques (Sheynkin et al, 1998b). It can also potentially obstruct the epididymis in men in whom future vasoepididymostomy is considered. In view of the enormous costs and effort involved in IVF, epididymal sperm retrieval under direct vision is the preferred technique (Zhang et al, 2013).

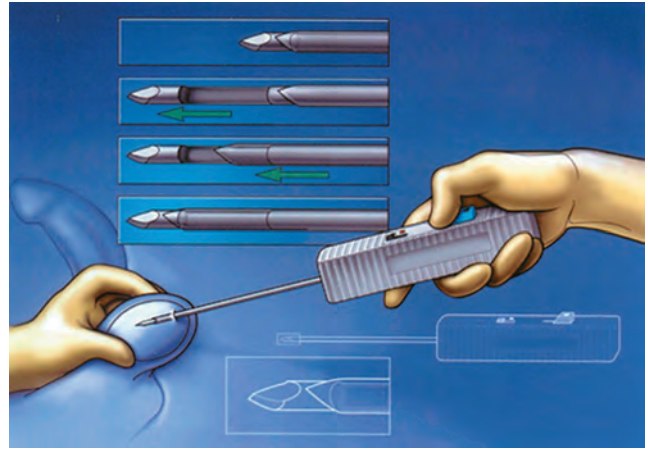


Figure 25-41. Percutaneous core biopsy; uses the same 14-gauge biopsy gun as prostate biopsy.

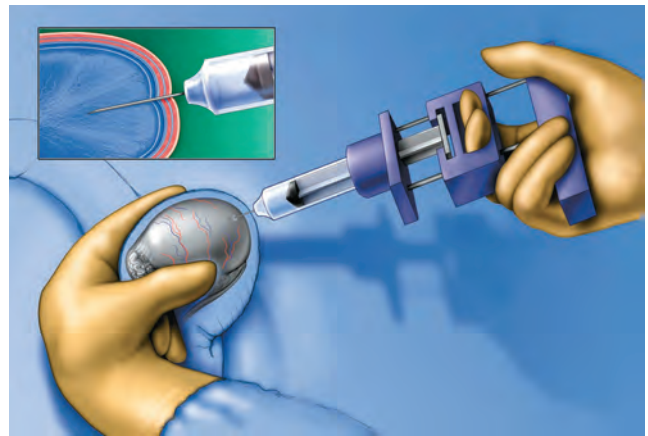


Figure 25-42. Percutaneous aspiration (testicular sperm aspiration) with a high-suction glass syringe and a 23-gauge needle. This is the least invasive procedure but requires 10 to 20 passes to obtain an adequate yield.

Testicular Sperm Extraction

The indications for TESE are as follows:

1. Failure to find sperm in the epididymis in the presence of the spermatogenesis or complete absence of the epididymis.
2. Nonobstructive azoospermia (Schlegel et al, 1997; Tsujimura et al, 2002; Ramasamy et al, 2013a, 2013b).
Testicular sperm has been retrieved via one of three techniques:
3. Open microsurgical TESE, preferably with an operating microscope (micro-TESE), which allows retrieval of the largest number of sperm with potential for cryopreservation; this is the best technique in men with nonobstructive azoospermia.
4. Percutaneous core biopsy; uses the same 14-gauge biopsy gun used for prostate biopsy (Fig. 25-41).
5. Percutaneous aspiration (testicular sperm aspiration [TESA]) with a high-suction glass syringe and a 23-gauge needle. This is the least invasive procedure but often requires 10 to 20 passes to obtain an adequate yield (Fig. 25-42) (Rajfer and Binder, 1989; Harrington et al, 1996; Friedler et al, 1997; Sheynkin et al, 1998b; Mercan et al, 2000; Carpi et al, 2005).

The percutaneous methods are most appropriate in men with normal spermatogenesis and obstructive azoospermia when adequate numbers of sperm can be retrieved in a small amount of tissue (Craft et al, 1995). The pros and cons of these three methods are discussed in the section on *testis biopsy*, earlier in this chapter.

Microsurgical Testicular Sperm Extraction

The use of an operating microscope for standard open diagnostic testes biopsy allows identification of an area in the tunica albuginea free of blood vessels (Fig. 25-43), minimizing the risk of injury to testicular blood supply and allowing a relatively blood-free biopsy specimen (Dardashti et al, 2000). Using the microscope for testis biopsy, Schlegel (1999) discovered that in men with nonobstructive azoospermia, some of the tubules were larger than others. The larger tubules are more likely to yield sperm. Previous studies had revealed that testicular biopsy specimens in men with nonobstructive azoospermia display considerable heterogeneity. Examination of permanently fixed biopsy specimens that display heterogeneity reveals that tubules with spermatogenesis are of considerably larger diameter than tubules that are Sertoli cell only. This difference can be readily observed under the operating microscope (Fig. 25-44).

Technique. With the patient under general or regional anesthetic, the testes are exposed through either a single midline median raphe incision or two transverse incisions within the skin lines and between the scrotal blood vessels. The testes is delivered into the wound. The tunica vaginalis is opened and the operating microscope is brought into the field. Under 10× magnification,



Figure 25-43. The use of an operating microscope for standard open diagnostic testes biopsy allows identification of an area in the tunica albuginea free of blood vessels.

an avascular plane is identified on the anterior surface of the tunica albuginea. Using a 15-degree microknife, a generous transverse incision is made between the blood vessels through the tunica albuginea. Small blood vessels that are seen coursing across the incision are coagulated with the microbipolar cautery before they are incised. This yields a blood-free field. The seminiferous tubules are observed. Sertoli cell-only tubules tend to be thin, white, and stringy. Tubules with active spermatogenesis are larger, plumper, and somewhat yellow. With a micro needle holder or microbipolar forceps, the seminiferous tubules are dissected in an attempt to identify larger tubules. If such a tubule is found, sharp curved iris scissors are used to selectively excise these tubules. The sample is placed in human tubal fluid medium, microdissected, and immediately examined by an andrology laboratory technician present in the operating room. After sperm have been found, hemostasis is obtained with the microbipolar cautery. The incision in the tunica albuginea is closed with a 6-0 nylon suture. The testis is returned to the tunica vaginalis, which is closed with a continuous suture of 5-0 Vicryl. If necessary, the opposite testis is explored.

Results. With use of the microdissection technique, sperm have been identified in 50% of men explored. (Schlegel, 1999; Dabaja and Schlegel, 2013). In men in whom sperm are found, a pregnancy rate of 45%, with a live delivery rate of almost 40%, has been achieved at Cornell using IVF with ICSI. The spontaneous abortion rate is 19%. The high rate of spontaneous abortion is probably a result of the increased incidence of chromosomal abnormalities and DNA damage in the sperm of men with nonobstructive azoospermia (Rucker et al, 1998). Even in severe cases of congenital or acquired testicular failure, as in Sertoli cell-only syndrome (Ramasamy et al, 2013a), postchemotherapy azoospermia (Chan et al, 2001), and nonmosaic (47,XXY) Klinefelter syndrome (Palermo et al, 1998; Ramasamy et al, 2009), sperm have been found and pregnancy and live births achieved (Table 25-4).

Postmortem Sperm Retrieval

Postmortem sperm retrieval and cryopreservation (but no pregnancies) were initially reported by Rothman in 1980 and involved removal and mincing of the epididymis. The retrieved sperm can be frozen and subsequently used to attempt to achieve pregnancy. Pregnancy has now been achieved with sperm retrieved postmortem using IVF with ICSI (reviewed in Benshushan and Schenker, 1998; Tash et al, 2003; Dostal et al, 2005).

Retrieval of sperm from the vas can be performed using the technique described for vasectomy (see earlier). Once the vas has

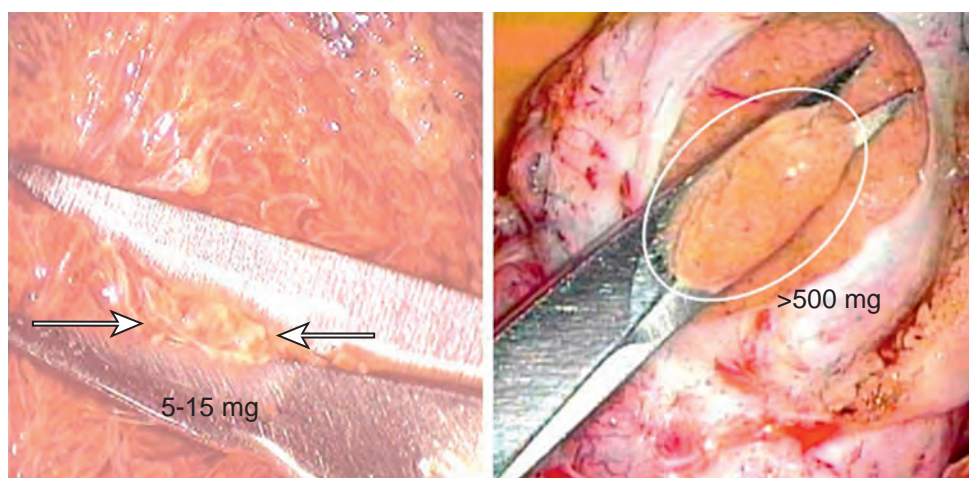


Figure 25-44. Tubules with spermatogenesis are of considerably larger diameter than tubules that are Sertoli cell only. This difference can be readily observed under the operating microscope.

been delivered, a hemivasotomy is made with a 15-degree microknife (as described in the section on [technique of vasography and interpretation of findings](#)). The testicular end of the vas is cannulated with a 22-gauge angiocatheter and the vas irrigated with a 0.2-mL volume of human tubal fluid medium while the convoluted vas and epididymis are massaged.

The ethical appropriateness of such retrieval is the most important issue surrounding its use, and current guidelines require the patient to have given permission for sperm retrieval and use before death ([Trinkoff and Barone, 2013](#)).

VARICOCELECTOMY

Varicocele is by far the most commonly performed operation for the treatment of male infertility. Varicocele is found in approximately 15% of the general population, 35% of men with primary infertility, and 75% to 81% of men with secondary infertility. Animal and human studies have demonstrated that varicocele is associated with a progressive and duration-dependent decline in testicular function ([Russell, 1957](#); [Lipshultz and Corriere, 1977](#); [Nagler et al, 1985](#); [Harrison et al, 1986](#); [Kass and Belman, 1987](#); [Hadziselimovic et al, 1989](#); [Chehval and Purcell, 1992](#); [Gorelick and Goldstein, 1993](#); [Witt and Lipshultz, 1993](#)).

Repair of varicocele will halt any further damage to testicular function ([Kass and Belman, 1987](#); [Gorelick and Goldstein, 1993](#)) and in a large percentage of men will result in improved spermatogenesis ([Dubin and Amelar, 1977](#); [Schlegel and Goldstein, 1992](#); [Marmar et al, 2007](#)) as well as enhanced Leydig cell function ([Su et al, 1995](#); [Tanrikut et al, 2011](#)). The potentially important role of urologists in preventing future infertility and/or androgen deficiency underscores the importance of using a varicocelectomy technique that minimizes the risk of complications and recurrence. [Table 25-5](#) summarizes the pros and cons of various methods of varicocele repair.

TABLE 25-4 Testicular Sperm Extraction Outcomes by Diagnosis

CONDITION	RETRIEVAL
Klinefelter syndrome	68%
AZFc deletions	70%
Sertoli cell only	30%
Postchemotherapy	53%
Cryptorchidism (postorchiopexy)	74%
Maturation arrest	40%
AZFa, AZFb deletions	0%

AZF, azoospermia factor (Y chromosome gene).
Data from [Chan et al, 2001](#); [Hopps et al, 2003b](#); [Raman and Schlegel, 2003](#); [Hung et al, 2007](#); [Ramasamy and Schlegel, 2007](#); [Ramasamy et al, 2009](#).

TABLE 25-5 Techniques of Varicocelectomy

TECHNIQUE	ARTERY PRESERVED	HYDROCELE (%)	FAILURE (%)	POTENTIAL FOR SERIOUS MORBIDITY
Retroperitoneal	No	7	15-25	No
Conventional inguinal	No	3-30	5-15	No
Laparoscopic	Yes	12	3-15	Yes
Radiographic	Yes	0	15-25	Yes
Microscopic inguinal or subinguinal	Yes	0	0.5-1.0	No

Scrotal Operations

A variety of surgical approaches have been advocated for varicocelectomy. The earliest recorded attempts at repair of varicocele date to antiquity and involved external clamping of the scrotal skin, including the enlarged veins. In the early 1900s an open scrotal approach was used, involving the mass ligation and excision of the varicose plexus of veins. At the level of the scrotum, however, the pampiniform plexus of veins are intimately entwined with the coiled testicular artery. Therefore, scrotal operations are to be avoided because damage to the arterial supply of the testis frequently results in testicular atrophy and further impairment of spermatogenesis and fertility.

Retroperitoneal Operations

Retroperitoneal repair of varicocele involves incision at the level of the internal inguinal ring ([Fig. 25-45](#)), splitting of the external and internal oblique muscles, and exposure of the internal spermatic artery and vein retroperitoneally near the ureter. This approach has the advantage of isolating the internal spermatic veins proximally, near the point of drainage into the left renal vein. At this level, only one or two large veins are present, and in addition the testicular artery has not yet branched and is often distinctly separate from the internal spermatic veins. Retroperitoneal approaches involve ligation of the fewest number of veins. This approach is still a commonly used method for the repair of varicocele, especially in children.

A disadvantage of a retroperitoneal approach is the high incidence of varicocele recurrence, especially in children and adolescents, when the testicular artery is intentionally preserved.

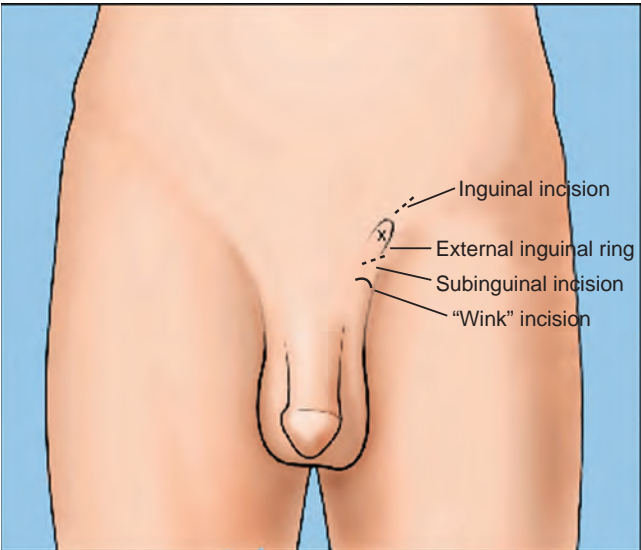


Figure 25-45. Retroperitoneal repair of varicocele involves incision at the level of the internal inguinal ring.

Recurrence rates after retroperitoneal varicocelectomy are in the range of 15% (Homonnai et al, 1980; Rothman et al, 1981; Watanabe et al, 2005). Failure is usually the result of preservation of the periaarterial plexus of fine veins (venae comitantes) along with the artery. These veins have been shown to communicate with larger internal spermatic veins. If left intact they may dilate and cause recurrence. Less commonly, failure is a result of the presence of parallel inguinal or retroperitoneal collaterals, which may exit the testis and bypass the ligated retroperitoneal veins, rejoining the internal spermatic vein proximal to the site of ligation (Sayfan et al, 1981; Murray et al, 1986). Dilated cremasteric veins (Sayfan et al, 1980) and scrotal collaterals (Kaufman et al, 1983) are also causes of varicocele recurrence and cannot be identified with a retroperitoneal approach. Positive identification and preservation of the 1.0- to 1.5-mm testicular artery via the retroperitoneal approach are difficult, especially in children in whom the artery is small. The operation involves working in a deep hole, and because at this level the internal spermatic vessels cannot be delivered into the wound, they must be dissected and ligated in situ in the retroperitoneum. In addition, the difficulty of positively identifying and preserving lymphatics while using this approach results in postoperative hydrocele formation after 7% to 33% of retroperitoneal operations (Szabo and Kessler, 1984). The incidence of recurrence appears to be higher in children, with rates of 15% to 45% reported in adolescents (Gorenstein et al, 1986; Levitt et al, 1987; Reitelman et al, 1987). Kass reports that recurrence can be markedly reduced in children and adolescents by intentional ligation of the testicular artery (Kass and Marcol, 1992). This ensures ligation of the periaarterial network of fine veins. Although reversal of testicular growth failure has been documented with intentional testicular artery ligation at the time of retroperitoneal repair in children, the effect of artery ligation on subsequent spermatogenesis is uncertain. In adults, bilateral artery ligation has been documented to occasionally cause azoospermia and testicular atrophy. At least, it is inarguable that testicular artery ligation will not enhance testicular function.

Laparoscopic Varicocelectomy

Laparoscopic repair is in essence a retroperitoneal approach, and many of the advantages and disadvantages are similar to those of the open retroperitoneal approach (Donovan and Winfield, 1992; Hagood et al, 1992; Enquist et al, 1994; Hirsch et al, 1998; Riccabona et al, 2003; Watanabe et al, 2005).

With use of the laparoscope, the internal spermatic vessels and vas deferens can be clearly visualized through the laparoscope as they course through the internal inguinal ring. The magnification provided by the laparoscope allows visualization of the testicular artery (Kobori et al, 2013). With experience, the lymphatics may be visualized and preserved as well (Glassberg et al, 2008). With laparoscopic varicocelectomy the internal spermatic veins are ligated at the same level as with the retroperitoneal (Palomo) approach described previously in the section on retroperitoneal operations. Laparoscopic varicocelectomy should allow preservation of the testicular artery in a majority of patients, as well as preservation of lymphatics. The incidence of varicocele recurrence would be expected to be similar to that associated with the open retroperitoneal operations. These recurrences would be the result of collaterals joining the internal spermatic vein near its entrance to the renal vein, or entering the renal vein separately.

Most series of laparoscopic varicocelectomy report a recurrence rate of 2.9% to 4.5% (May et al, 2006; Glassberg et al, 2008; Barroso et al, 2009), but up to 17% in some (Al-Said et al, 2008). An artery ligation but lymphatic-sparing laparoscopic technique has markedly reduced the incidence of postoperative hydrocele formation in children (Glassberg et al, 2008). The potential complications of laparoscopic varicocelectomy (injury to bowel, vessels, or viscera; air embolism; peritonitis) are significantly more serious than those associated with the open techniques. Furthermore, laparoscopic varicocelectomy requires a general anesthetic. The microsurgical techniques described next can be performed with local or regional

anesthesia and use an incision of 2 to 3 cm for unilateral repair. This is often no greater than the sum of incisions used for a laparoscopic approach. Postoperative pain and recovery from the laparoscopic technique are the same as those associated with subinguinal varicocelectomy (Hirsch et al, 1998). In the hands of an experienced laparoscopist, the approach is a reasonable alternative for the repair of bilateral varicoceles (Donovan and Winfield, 1992; Diamond et al, 2009; Mendez-Gallart et al, 2009; Tong et al, 2009.)

Microsurgical Inguinal and Subinguinal Operations: Preferred Approaches

Subinguinal varicocelectomy is currently the most popular approach. It has the advantage of allowing the spermatic cord structures to be pulled up and out of the wound so that the testicular artery, lymphatics, and small periaarterial veins may be more easily identified. In addition, an inguinal or subinguinal approach allows access to external spermatic and even gubernacular veins (Kaufman et al, 1983), which may bypass the spermatic cord and result in recurrence if not ligated. Lastly, an inguinal or subinguinal approach allows access to the testis for biopsy or examination of the epididymis for obstruction or repair of hydrocele (Dabaja and Goldstein, 2014).

Traditional approaches to inguinal varicocelectomy involve a 5-cm incision made over the inguinal canal, opening of the external oblique aponeurosis, and encirclement and delivery of the spermatic cord. The cord is then dissected and all the internal spermatic veins are ligated (Dubin and Amelar, 1977). The vas deferens and its vessels are preserved. An attempt is made to identify and preserve the testicular artery and, if possible, the lymphatics. In addition, the cord is elevated, and any external spermatic veins that are running parallel to the spermatic cord or perforating the floor of the inguinal canal are identified and ligated. Compared with retroperitoneal operations, conventional nonmagnified inguinal approaches lower the incidence of varicocele recurrence but do not alter the incidence of either hydrocele formation or testicular artery injury. Conventional inguinal operations are associated with an incidence of postoperative hydrocele formation varying from 3% to 15% with an average incidence of 7% (Szabo and Kessler, 1984). Analysis of the hydrocele fluid has clearly indicated that hydrocele formation after varicocelectomy is a result of ligation of the lymphatics (Szabo and Kessler, 1984). The incidence of testicular artery injury during nonmagnified inguinal varicocelectomy is unknown. Case reports, however, suggest that this complication may be more common than realized. It can result in testicular atrophy, and if the operation is performed bilaterally, azoospermia may ensue in a previously oligospermic man. Furthermore, Starzl and his transplant group reported a 14% incidence of testicular atrophy and 70% incidence of hydrocele formation when the spermatic cord was divided and only the vas and vasal vessels preserved (Penn et al, 1972).

The introduction of microsurgical technique to varicocelectomy has resulted in a substantial reduction in the incidence of hydrocele formation (Goldstein et al, 1992; Marmar and Kim, 1994; Matthews et al, 1998; Cayan et al, 2000). This is because the lymphatics can be more easily identified and preserved. Furthermore, the use of magnification enhances the ability to identify and preserve the 0.5- to 1.5-mm testicular artery, thus avoiding the complications of atrophy or azoospermia.

Advocates of nonmicrosurgical techniques contend that the deferential (vasal) artery and, if preserved, the cremasteric artery will provide adequate blood supply to the testes to prevent atrophy. However, anatomic studies have shown that the diameter of the testicular artery is greater than the diameter of the deferential artery and cremasteric artery combined (Raman and Goldstein, 2004). The testicular artery is the main blood supply to the testis. Experience with the one-stage Fowler and Stephens orchiopexy, in which the testicular artery is intentionally ligated, reveals that a substantial percentage of such procedures result in an atrophic testis. Also, animal models indicate that artery preservation varicocelectomy

results in improved testicular ultrastructure whereas artery ligation resulted in further deterioration of ultrastructure (Zheng et al, 2008). At the very least, it is inarguable that ligation of the testicular artery is unlikely to enhance testicular function.

Anesthesia

If the testis is delivered as described later, regional or light general anesthesia is preferred. If only the cord is delivered, local anesthesia with a 50%-50% combination of 0.25% bupivacaine and 1% lidocaine is satisfactory with adjunctive intravenous heavy sedation. After infiltration of the skin and subcutaneous tissues the cord is infiltrated before delivery. Blind cord block carries with it a small risk of inadvertent testicular artery injury (Goldstein et al, 1983). A 30-gauge needle should therefore be used for cord block to minimize the risk of injury and hematoma.

Inguinal and Subinguinal Approaches

The introduction of the subinguinal approach, just below the external inguinal ring (Marmar et al, 1985), obviates the necessity for opening any fascial layer and is associated with less pain and a rapid recovery comparable to laparoscopic procedures. At the subinguinal level, however, significantly more veins are encountered, the artery is more often surrounded by a network of tiny veins that must be ligated, and the testicular artery has often divided into two or three branches, making arterial identification and preservation more difficult (Hopps et al, 2003a).

Subinguinally, the arterial pulsations are often dampened by compression on the edge of the external ring, making its identification somewhat more difficult than when the external oblique is opened. Table 25-6 summarizes the criteria for performing the operation inguinally (external oblique opened) versus subinguinally (fascia intact). In general, it is best to use a subinguinal approach in men with a history of any prior inguinal surgery. Under these circumstances the cord is usually stuck to the undersurface of the external oblique, and opening the fascia risks injury to the cord. A subinguinal approach is easier in obese men in whom opening and closing the fascia is difficult through a small incision. A subinguinal approach is easier in men with high, lax, capacious external rings and in men with long cords and low-lying testes. In these men the level of the external ring is fairly proximal to the testis, and opening the fascia will not result in a significant diminution in the number of veins to be ligated or in the branching of the testicular artery.

I recommend always opening the external oblique in prepubertal children without prior inguinal surgery. In children the testicular artery is very small and systemic blood pressure is low, making identification of the artery very difficult in a subinguinal approach. The fascia could also be opened in men with a solitary testis in whom preservation of the artery is critical. Exposure of the cord more proximally (at the inguinal level) allows identification of the artery before it has branched, where clear pulsations are more readily observed.

Consider opening the fascia in men with prior failed subinguinal varicocelectomy to dissect proximal to the prior scarred ligation area. The microdissection will be quicker and easier. A subinguinal operation is significantly more difficult than a high inguinal operation and should be used only by surgeons who perform the operation frequently. Less experienced microsurgeons should start out doing inguinal operations because it is easier. An inguinal operation is used when simultaneous ipsilateral hernia repair is performed.

Before the incision is made the location of the external inguinal ring is determined by invagination of the scrotal skin and is marked. The size of the incision is determined by the size of the testis when delivery of the testis (see later) is planned. Atrophic testes can be delivered through a 2- to 2.5-cm incision. Larger testes require a 3-cm incision. The incision is made within the Langer lines to minimize scarring.

If the decision is made to perform an inguinal operation and thus to open the fascia, the incision is begun at the external ring and extended laterally 2 to 3.5 cm along the Langer lines (Fig. 25-46). If the operation is to be performed subinguinally, the incision is placed in the skin lines right over the external ring (Fig. 25-47).



Figure 25-46. If the decision is made to perform an inguinal operation and thus to open the fascia, the incision is begun at the external ring and extended laterally 2 to 3.5 cm along the Langer lines.

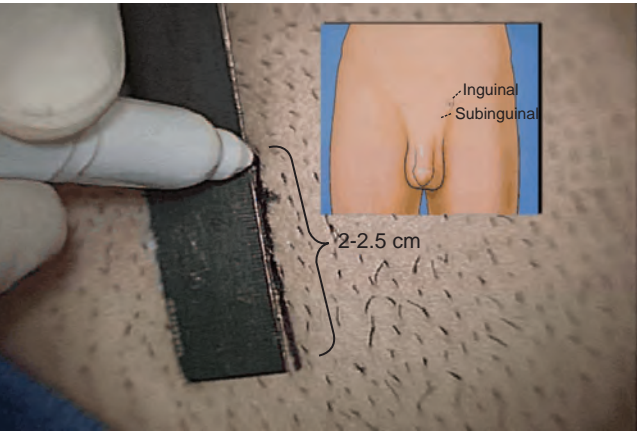


Figure 25-47. If the operation is to be performed subinguinally, the incision is placed in the skin lines just below the external ring.

TABLE 25-6 Indications for Inguinal (External Oblique Opened) Versus Subinguinal (Fascia Intact) Varicocelectomy

INGUINAL	SUBINGUINAL
Prepubertal children	Prior inguinal surgery
Solitary testis	Obesity
Tight, low external ring	Lax, capacious external ring
	High external ring
Short cord, high-lying testis	Long cord with low-lying testis
Less experienced with microsurgical repair	Very experienced with microsurgical repair

The Camper fascia and Scarpa fascia are divided with the electrocautery between the blades of a Crile clamp. The superficial epigastric artery and vein, if encountered, are retracted or alternately may be clamped, divided, and ligated.

If an inguinal approach is selected, the external oblique aponeurosis is cleaned and opened the length of the incision to the external inguinal ring in the direction of its fibers. A 3-0 absorbable suture placed at the apex of the external oblique incision facilitates later closure.

The spermatic cord is grasped with a Babcock clamp and delivered through the wound. The ilioinguinal and genital branches of the genitofemoral nerve are excluded from the cord, which is then surrounded with a large Penrose drain. If a subinguinal incision was made, the Camper and Scarpa fascia are incised as described earlier. An index finger is introduced into the wound and along the cord into the scrotum. The index finger is then hooked under the external inguinal ring, retracting it cephalad. A small Richardson retractor is slid along the back of the index finger and retracted caudad over the cord toward the scrotum (Fig. 25-48). The spermatic cord will be revealed between the index finger and retractor. The assistant grasps the cord with a Babcock clamp and delivers it through the wound. The cord is surrounded with a large Penrose drain.

Dissection of the Cord

The operating microscope is then brought into the field. Under 6× to 10× magnification the external spermatic fascia is opened with a

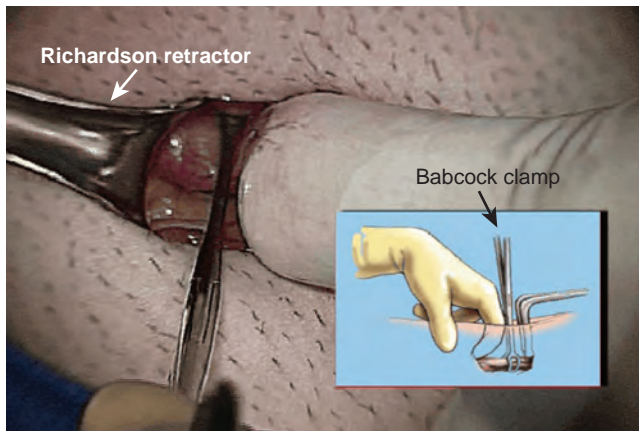


Figure 25-48. A small Richardson retractor is slid along the back of the index finger and retracted caudad over the cord toward the scrotum.

Bovie electrocautery instrument in the direction of the cremasteric fibers to avoid injury to the cremasteric arteries. A 5-0 Vicryl suture is placed at the apex of the opening to facilitate later closure. The relatively avascular internal spermatic fascia is opened with scissors as high as possible and held open with the straight mosquito forceps (Fig. 25-49). The magnification is increased to 10× to 25× and, after irrigation with 1% papaverine solution, the cord is inspected for the presence of pulsations revealing the location of the testicular artery. Micro-Doppler is extremely useful in identifying arteries (Fig. 25-50). Once the testicular artery has been identified, it is dissected free of all surrounding tissue, tiny veins, and lymphatics, using a fine-tipped nonlocking micro needle holder and microforceps. The artery is encircled with a vessel loop for positive identification and gentle retraction (Fig. 25-51). The suspected artery is tested by elevating the artery with the tips of the micro needle holder until it is completely occluded and then slowly lowering it until a pulsating blush of blood appears just over the needle holder. If the artery is not immediately identified, the cord is carefully dissected beginning with the largest veins. The veins are stripped clean of adherent lymphatics (Fig. 25-52) and the undersides of the largest veins inspected for an adherent artery. In approximately 50% of patients the testicular artery is adherent to the undersurface of a large vein (Beck et al, 1992). All veins within the cord, with the exception of the vasal veins, are doubly ligated either with hemoclips (Fig. 25-53) or by passing two 4-0 silk ligatures, one black and one white, beneath the vein (Fig. 25-54). These are then tied, and the vein is divided. Medium hemoclips are used for veins 5 mm or larger, small auto-hemoclips for veins 1 to 5 mm, and 4-0 silk for veins smaller than 2 mm. The use of an automatic clip applicator (Ligacip small size, Ethicon, Somerville, NJ) significantly reduces operating time. Bipolar cautery can be used for veins smaller than 0.5 mm. The vasal veins are preserved, providing venous return. If the vas deferens is accompanied by dilated veins greater than 2.5 mm in diameter, they are dissected free of the vasal artery and ligated. The vas deferens is always accompanied by two sets of vessels. As long as at least one set of deferential veins remains intact, venous return will be adequate. At the completion of the dissection, the cord is run over the index finger and inspected to verify that all veins have been identified and ligated. Small veins adherent to the testicular artery are dissected free and ligated or, if smaller than 1 mm, cauterized using a bipolar unit with a jeweler's forcep tip, and divided. Cremasteric arteries are found (usually between and adherent to two cremasteric veins) and preserved in at least 90% of patients. Recent studies using power Doppler imaging in men with nonobstructive azoospermia undergoing TESE have found that tubules containing sperm are most likely to be found in areas of the testis with the greatest blood supply. Therefore, logic would dictate that preservation of maximum testicular blood supply, including both testicular and cremasteric arteries, would be

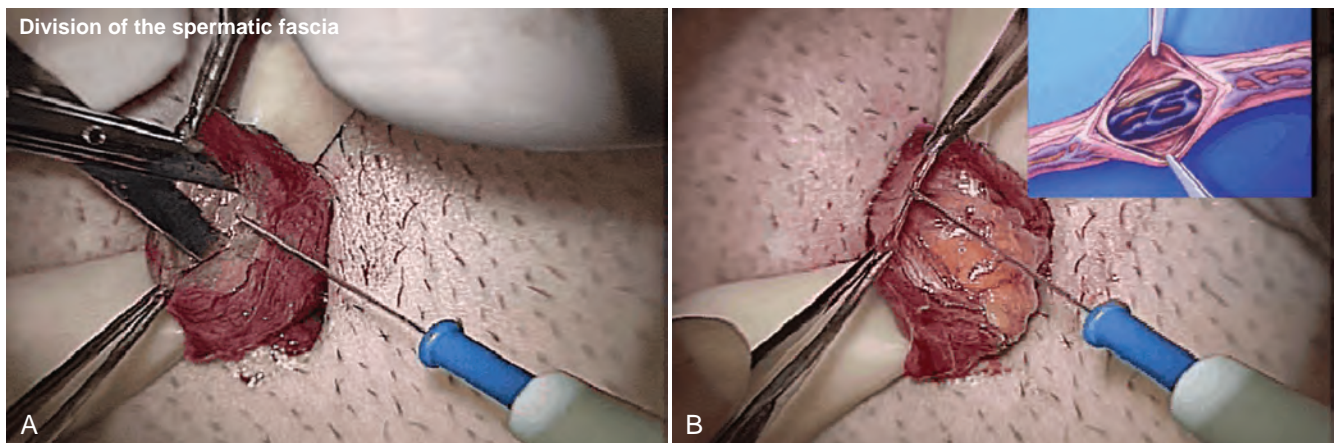


Figure 25-49. A and B, The operating microscope is then brought into the field. Under 4× to 6× magnification, the external and internal spermatic fasciae are opened.



Figure 25-50. Micro-Doppler is extremely useful in identifying arteries.

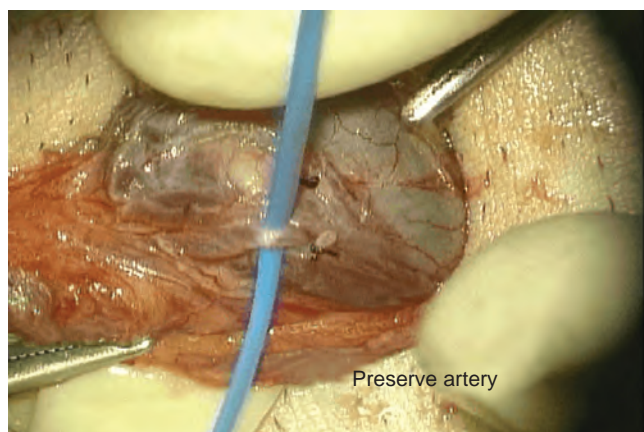


Figure 25-51. The artery is encircled with a vessel loop for positive identification and gentle retraction.

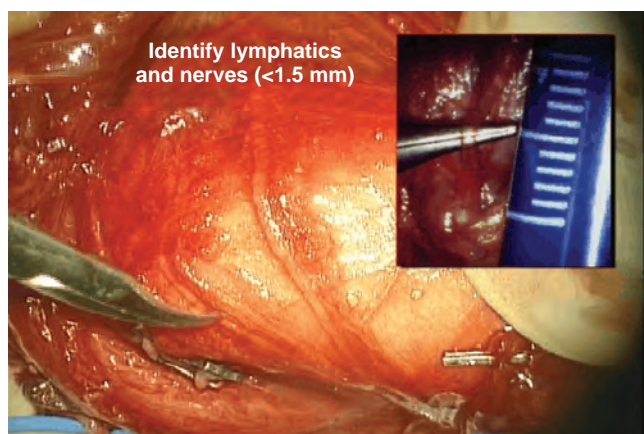


Figure 25-52. If the artery is not immediately identified, the cord is carefully dissected, beginning with the largest veins. The veins are stripped clean of adherent lymphatics.

beneficial to testicular function. At the completion of the dissection, only the testicular arteries, cremasteric arteries, lymphatics, and vas deferens with its vessels remain (Fig. 25-55). Dissection is not deemed complete until a run through the cord reveals no additional internal or external spermatic veins. Each time a vein is found and ligated, any remaining veins will dilate up.

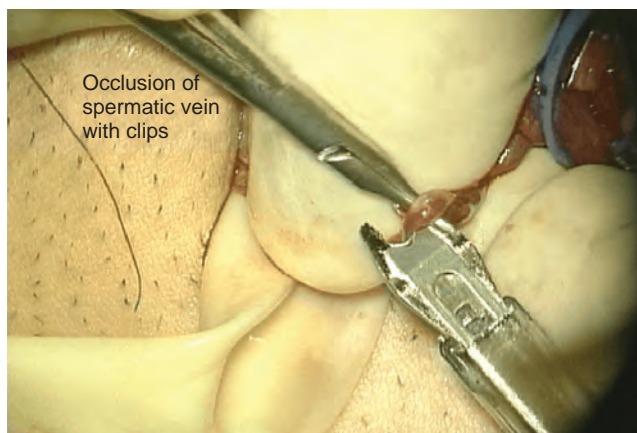


Figure 25-53. All veins within the cord, with the exception of the vasal veins, are doubly ligated, either with hemoclips or by passing two 4-0 silk ligatures, one black and one white, beneath the vein (see Fig. 25-54).

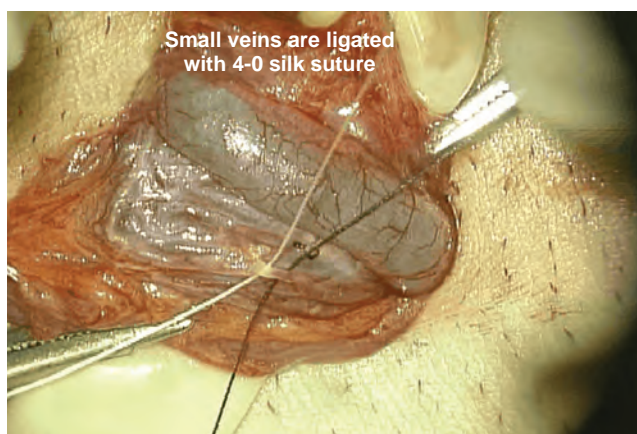


Figure 25-54. All veins within the cord, with the exception of the vasal veins, are doubly ligated, either with hemoclips (see Fig. 25-53) or by passing two 4-0 silk ligatures, one black and one white, beneath the vein.

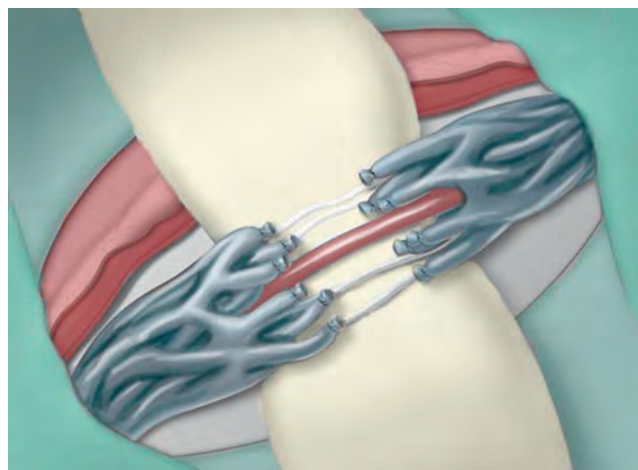


Figure 25-55. At the completion of the dissection, only the testicular arteries, cremasteric arteries, lymphatics, and vas deferens with its vessels remain.

Delivery of the Testis

Delivery of the testis through a small inguinal or subinguinal incision guarantees direct visual access to all possible avenues of testicular venous drainage. Delivery of only the cord allows

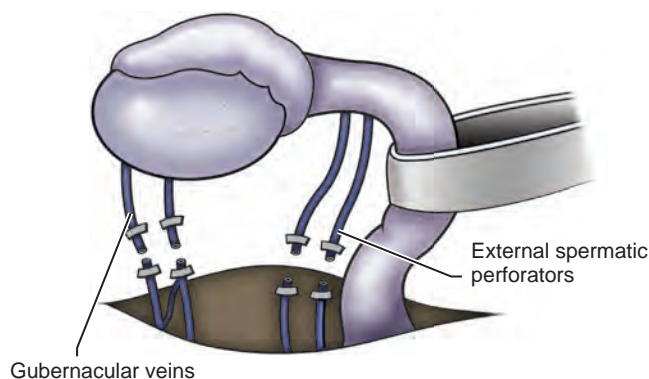


Figure 25-56. All external spermatic veins are identified and doubly ligated with hemoclips and divided.

access to most external spermatic collaterals but may miss those close to the testis and will not allow access to scrotal or gubernacular collaterals, which have been demonstrated radiographically to be the cause of 10% of recurrent varicoceles (Kaufman et al, 1983). With gentle upward traction on the cord and upward pressure on the testis through the invaginated scrotum, the testis is easily delivered through the wound. All external spermatic veins are identified and doubly ligated with hemoclips and divided (Fig. 25-56). The gubernaculum is inspected for the presence of veins exiting from the tunica vaginalis. These are either cauterized or doubly clipped and divided. **When this step is completed, all testicular venous return must be within the Penrose-surrounded cord.**

Hydroceles are found in 15% of testes associated with varicoceles. As little as 3 mL of hydrocele fluid can significantly alter testicular temperature regulation (Wysock et al, 2009). If a hydrocele is noted when the testis is delivered, it is repaired. Small ones may be treated with excision of a segment of the hydrocele sac and cauterization of the edges. Larger hydroceles are treated with either a bottleneck or excision technique. The temporary high venous pressure immediately after varicocelectomy can make good hemostasis difficult to achieve after excisional hydrocelectomy. Therefore, there should be no hesitation to use a scrotal Penrose drain placed in the dependent portion of the scrotum for 24 hours after combined varicocelectomy and excisional hydrocelectomy. The testis is then returned to the scrotum and the Penrose drain is left beneath the cord structures.

The external oblique aponeurosis, if opened, is reapproximated with continuous suturing using the previously placed 3-0 suture. The Scarpa and Camper fasciae are reapproximated with a single or continuous 3-0 plain catgut suture, and the skin is approximated with a 5-0 monofilament absorbable subcuticular suture reinforced by two or three Steri-Strips (Fig. 25-57). A scrotal supporter is applied and stuffed with fluff-type dressings. The patient is discharged on the day of surgery with a prescription for Tylenol with codeine. Light work may be resumed in 2 or 3 days.

If any large external or gubernacular veins are ligated after delivery of the testis, the cord is again run over the index finger to search for veins that may dilate after gubernacular or external spermatic veins are ligated. The external spermatic fascia is closed with interrupted 5-0 Vicryl, facilitated by the previously placed suture at the apex of the external spermatic fascia.

Radiographic Occlusion Techniques

Intraoperative venography has been used to visualize the venous collaterals, which if left unligated may result in varicocele recurrence (Sayfan et al, 1981; Belgrano et al, 1984; Levitt et al, 1987; Zaontz and Firlit, 1987). Intraoperative venography does reduce the incidence of varicocele recurrence, but the two-dimensional view afforded often does not enable the surgeon to identify the location of all collaterals.

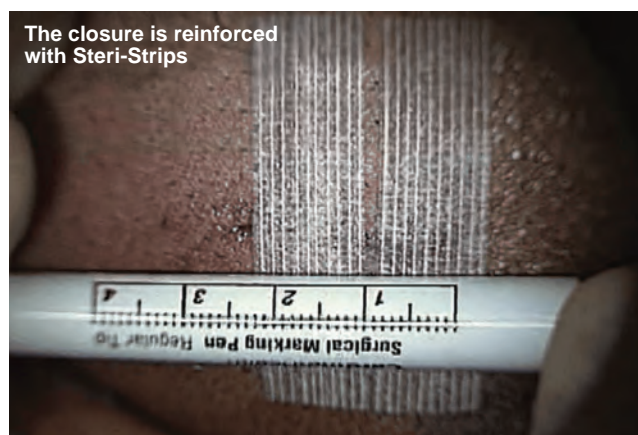


Figure 25-57. Scarpa and Camper fasciae are reapproximated with a single or continuous 3-0 plain catgut suture, and the skin is approximated with a 5-0 monofilament absorbable subcuticular suture, reinforced by two or three Steri-Strips.

Radiographic coil occlusion of the internal spermatic veins has been successfully used for varicoceles (Lima et al, 1978; Walsh and White, 1981; Weissbach et al, 1981). These techniques are performed under a local anesthetic through a small cut-down incision over the femoral vein. The recurrence rate after balloon occlusion was originally 11% and more recently was reportedly as low as 4% (Kaufman et al, 1983; Mitchell et al, 1985; Murray et al, 1986; Matthews et al, 1992). Failure to successfully cannulate small collaterals and external spermatic veins and scrotal collaterals results in recurrence. Venographic placement of a balloon or coil in the internal spermatic vein is successfully accomplished in 75% to 90% of attempts (White et al, 1981; Morag et al, 1984; Winkelbauer et al, 1994; Sivanathan and Abernethy, 2003); therefore a significant number of men undergoing attempted radiographic occlusion will ultimately require a surgical approach. In addition, the radiographic techniques take 1 to 3 hours to perform compared with 25 to 45 minutes for surgical repair. Although rare, serious complications of radiographic balloon or coil occlusion have included migration of the balloon or coil into the renal vein, resulting in loss of a kidney, pulmonary embolization of the coil or balloon (Matthews et al, 1992), femoral vein perforation or thrombosis, and anaphylactic reaction to radiographic contrast medium. Antegrade scrotal sclerotherapy via cannulation of a scrotal vein has been used in Europe (Tauber and Johnsen, 1994; Ficarra et al, 2002; Minucci et al, 2004). The recurrence rate is similar to that of balloon or coil techniques. Long-term follow-up is not available, and the consequence of escape of the sclerosing agent into the renal vein and vena cava is unknown. In addition, the larger the varicocele, the higher the failure and recurrence rate with this technique. We have seen many men referred with late (2 to 5 years) recurrence after radiographic occlusion. On presentation they typically have slow-filling veins that become prominent at the end of the day. Initial cursory physical examination can miss these recurrences. I believe these recurrences are likely the result of recanalization through the coils because, unlike with surgical repair, the veins are not ligated and divided. Although often initially successful, I believe that radiographic occlusion is less durable than microsurgical ligation.

Complications of Varicocelectomy

Hydrocele

Hydrocele formation is the most common complication reported after nonmicroscopic varicocelectomy. The incidence of this complication varies from 3% to 33%, with an average incidence of

about 7%. Analysis of the protein concentration of hydrocele fluid indicates that **hydrocele formation after varicocelectomy is caused by lymphatic obstruction** (Szabo and Kessler, 1984). At least half of postvaricocelectomy hydroceles grow to a size large enough to warrant surgical excision as a result of the discomfort and growth of the hydrocele to a large size. The effect of hydrocele formation on sperm function and fertility is uncertain. It is known that men with varicocele have significantly elevated intratesticular temperatures (Zorgniotti et al, 1979; Goldstein and Eid, 1989), and this appears to be an important pathophysiologic phenomenon mediating the adverse effects of varicocele on fertility (Saypol et al, 1981). The development of a large hydrocele creates an abnormal insulating layer that surrounds the testis. This may impair the efficiency of the counter-current heat exchange mechanism and therefore obviate some of the benefits of varicocelectomy (Wysock et al, 2009).

Use of magnification to identify and preserve lymphatics can virtually eliminate the risk of hydrocele formation after varicocelectomy (Goldstein et al, 1992; Marmar and Kim, 1994; Glassberger et al, 2008). The management of postvaricocelectomy hydrocele is identical to that for other hydroceles (see Chapter 41).

Testicular Artery Injury

The diameter of the testicular artery in humans is 1.0 to 1.5 mm. The testicular artery supplies two thirds of the testicular blood supply, and the vasal and cremasteric arteries the remaining one third (Raman and Goldstein, 2004). Microdissections of the human spermatic cord have revealed that the testicular artery is closely adherent to a large internal spermatic vein in 40% of men. In another 20% of men the testicular artery is surrounded by a network of tiny veins (Beck et al, 1992). During the course of cord dissection for varicocelectomy the artery may go into spasm and even in its uncontracted state is often difficult to positively identify and preserve. **Injury or ligation of the testicular artery carries with it the risk of testicular atrophy and/or impaired spermatogenesis.** Starzl's transplant group (Penn et al, 1972) reported a 14% incidence of frank testicular atrophy when the testicular artery was purposely ligated. The actual incidence of testicular artery ligation during varicocelectomy is unknown, but some studies suggest it is common (Wosnitzer and Roth, 1983). Animal studies have indicated that the risk of testicular atrophy after testicular artery ligation varies from 20% to 100% (MacMahon et al, 1976; Goldstein et al, 1983). In humans, atrophy after artery ligation is probably less likely a result of the contribution of the cremasteric as well as vasal arterial supply (Raman and Goldstein, 2004). **In children the potential for neovascularization and compensatory hypertrophy of the vasal and cremasteric vessels is probably greater than in adults, making atrophy after testicular artery ligation less likely.** Use of magnifying loupes, or preferably an operating microscope and/or a fine-tipped Doppler probe, facilitates identification and preservation of the testicular artery and therefore minimizes the risk of testicular injury. Radiographic balloon or coil occlusion techniques also eliminate this risk.

Varicocele Recurrence

The incidence of varicocele recurrence after surgical repair varies from 0.6% to 45% (Barbalias et al, 1998; Lemack et al, 1998; Cayan et al, 2000; Al-Kandari et al, 2007). Recurrence is more common after repair of pediatric varicoceles. Radiographic studies of recurrent varicoceles visualize periarterial, parallel inguinal, or midretroperitoneal collaterals or, more rarely, transscrotal collaterals (Kaufman et al, 1983). **Retroperitoneal operations miss parallel inguinal and scrotal collaterals.** Nonmagnified inguinal operations have a lower incidence of varicocele recurrence but fail to address the issue of scrotal collaterals or small veins surrounding the testicular artery. The microsurgical approach with delivery of the testis lowers the incidence of varicocele recurrence to less than 1% compared with 9% with use of conventional inguinal techniques (Goldstein et al, 1992; Marmar and Kim, 1994).

Results

Varicocelectomy results in significant improvement in semen analysis in 60% to 80% of men. Reported pregnancy rates after varicocelectomy vary from 20% to 60% (Marmar et al, 2007). A randomized controlled trial of surgery versus no surgery in infertile men with varicoceles revealed a pregnancy rate of 44% at 1 year in the surgery group versus 10% in the control group (Madgar et al, 1995). In our series of 1500 microsurgical operations, 43% of couples had achieved pregnancy at 1 year (Goldstein and Tanrikut, 2006) and 69% at 2 years when couples with female factors were excluded. **Microsurgical varicocelectomy results in return of sperm to the ejaculate in up to 50% of azoospermic men with palpable varicoceles** (Matthews et al, 1998; Kim et al, 1999; Pasqualotto et al, 2006; Lee et al, 2007a; Ishikawa et al, 2008).

The results of varicocelectomy are also related to the size of the varicocele. **Repair of large varicoceles results in a significantly greater improvement in semen quality than repair of small varicoceles** (Steckel et al, 1993; Jarow et al, 1996). In addition, large varicoceles are associated with greater preoperative impairment in semen quality than small varicoceles, and overall pregnancy rates consequently are similar regardless of varicocele size. Some evidence suggests that the younger the patient is at the time of varicocele repair, the greater the improvement after repair and the more likely the testis is to recover from varicocele-induced injury (Kass et al, 1987). Varicocele recurrence, testicular artery ligation, or postvaricocelectomy hydrocele formation are often associated with poor postoperative results. **In infertile men with low serum testosterone levels, microsurgical varicocelectomy alone results in substantial improvement in serum testosterone levels** (Su et al, 1995; Cayan et al, 1999; Younes, 2003; Rosoff et al, 2009; Tanrikut et al, 2011).

Summary

Varicocele is an extremely common entity, present in 15% of the male population. Varicoceles are found in approximately 35% of men with primary infertility but 75% to 81% of men with secondary infertility. Mounting evidence clearly demonstrates that varicocele causes progressive duration-dependent injury to the testis. Larger varicoceles appear to cause more damage than small varicoceles, and, conversely, repair of large varicoceles results in greater improvement of semen quality. **Varicocelectomy can halt the progressive duration-dependent decline in semen quality found in men with varicoceles.** The earlier the age at which varicocele is repaired, the more likely is recovery of spermatogenic function. **Varicocelectomy can also improve Leydig cell function, resulting in increased testosterone levels** (Su et al, 1995; Cayan et al, 1999; Younes, 2003; Tanrikut et al, 2011).

The most common complications after varicocelectomy are hydrocele formation, testicular artery injury, and varicocele persistence or recurrence. **The incidence of these complications can be reduced by using microsurgical techniques, inguinal or subinguinal operations, and exposure of the external spermatic and scrotal veins.** Use of these advanced techniques of varicocelectomy provides a safe, effective approach to elimination of varicocele, preservation of testicular function, and, in a substantial number of men, an increase in semen quality and likelihood of pregnancy, as well as increase in serum testosterone in men with androgen deficiency.

ORCHIOPEXY IN ADULTS

It is well known that cryptorchidism is associated with a high incidence of infertility even when unilateral. Long hot baths and saunas in humans, on a regular basis, have been shown to impair spermatogenesis. Elevated testicular temperature is also thought to be the primary pathophysiologic feature of varicocele (Zorgniotti, 1980; Saypol et al, 1981; Goldstein and Eid, 1989; Wright et al, 1997). Spermatogenesis is exquisitely temperature sensitive. Both



Figure 25-58. Instead of the testes being side by side, an ectopic testis is one behind the other, almost in the perineum.

animal and human studies have shown that artificial elevation of testicular temperature results in impaired spermatogenesis (Shin et al, 1997; Perez-Crespo et al, 2008; Shiraishi et al, 2010). It will also preserve testicular hormonal function. The technique of orchiopexy in adults is identical to that employed for children. Even with a normal contralateral testis, orchiopexy is worthwhile to bring down a unilateral undescended testis to, if possible, a scrotal location where it can be examined. Leydig cell function in undescended testis can be retained. Orchiopexy in adults with bilateral undescended testes can induce spermatogenesis and allow pregnancy (Shin et al, 1997). Even a solitary cryptorchid testis, when properly placed in the scrotum, can provide enough testosterone to obviate the need for hormone replacement. When orchiopexy is performed in adults, regular self-examination and yearly sonography are mandatory.

Retractile or Ectopic Testes in Adults

Retractile testes in boys are usually not surgically repaired if the testes can be manually manipulated to stay down in the scrotum either in the office or under anesthesia. The fate of persistently retractile testis in adults is unknown. A subset of infertile men have retractile testis (Caucci et al, 1997). The semen analyses of these men often demonstrate a typical stressed pattern similar to those of men with varicoceles. These men, however, do not have palpable varicoceles. They all have at least one and frequently both testes that retract out of the scrotum and into the abdomen and remain there for an hour or more a day. In some men these testes remain in the abdomen virtually all the time, except when in a warm shower or under anesthesia. It is likely that these testes will suffer from impaired temperature regulation and impaired spermatogenesis. Scrotal orchiopexy can improve the semen quality and fertility of some of these men. Some men have ectopic testis, in which instead of the testes being side by side, one testis is behind the other (Fig. 25-58), almost in the perineum. This is also likely to elevate testis temperature.

When scrotal orchiopexy is performed for retractile or ectopic testis in adults, a dartos pouch operation should be performed. Simple suture orchiopexy of the tunica albuginea of the testis to the dartos, as is performed sometimes to prevent torsion, will not prevent retraction of these testes into the groin. Creation of a dartos pouch will keep the testis well down in the scrotum and permanently prevent retraction. **This is also the most reliable and safest technique for the prevention of testicular torsion (Redman and Barthold, 1995).**

A 3- to 4-cm transverse incision is made in the low scrotal skin folds overlying the testis. **The incision is kept very superficial, just through the dermis and not into the dartos. A large pouch must be created to accommodate the adult testis.** The place of dissection is above the dartos and just below the skin, which is kept thin.

After a capacious pouch is created, the dartos and underlying tunica vaginalis are vertically incised and the testis delivered. The cremasteric fibers overlying the spermatic cord are divided and ligated to minimize the tendency of the testis to retract. The opening in the dartos is closed around the cord (but not too tightly) to prevent the testis from falling out of the pouch. The cut edge of the everted tunica is approximated to the opening in the dartos with interrupted synthetic monofilament absorbable sutures. This allows placement of the testis in the pouch without the need for fixation sutures in the tunica albuginea (Redman and Barthold, 1995). The skin is closed over the testis with interrupted sutures of 4-0 chromic catgut. This technique obviates the risk of inadvertent injury to and bleeding from the testicular artery, which courses just under the tunica albuginea (Jarow, 1990).

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Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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“The penis does not obey the order of its master, who tries to erect or shrink it at will. Instead, the penis erects freely while its master is asleep. The penis must be said to have its own mind, by any stretch of the imagination.”

– Leonardo da Vinci

PHYSIOLOGY OF PENILE ERECTION

Historical Aspects

The first description of erectile dysfunction (ED) dates from about 2000 BC and was set down on Egyptian papyrus. Two types were described: natural (“the man is incapable of accomplishing the sex act”) and supernatural (evil charms and spells). Later, Hippocrates reported many cases of male impotence among the rich inhabitants of Scythia and ascribed it to excessive horseback riding. Aristotle stated that three branches of nerves carry spirit and energy to the penis and that erection is produced by the influx of air (Brenot, 1994). His theory was well accepted until Leonardo da Vinci (1504) noted a large amount of blood in the erect penis of hanged men and cast doubt on the concept of the air-filled penis. However, da Vinci’s writings were kept secret until the beginning of the 20th century (Brenot, 1994). Nevertheless, in 1585, in *Ten Books on Surgery* and the *Book of Reproduction*, Ambroise Paré gave an accurate account of penile anatomy and the concept of erection. He described the penis as being composed of concentric coats of nerves, veins, and arteries and of two ligaments (corpora cavernosa), a urinary tract, and four muscles. “When the man becomes inflamed with lust and desire, blood rushes into the male member and causes it to become erect,” Paré wrote. The importance of retaining blood in the penis was stressed by Dionis (1718; quoted by Brenot, 1994), who attributed this to the muscles cramping the veins at the proximal end, and by Hunter (1787), who thought that venous spasm prevented the exit of blood.

Modern investigations of penile hemodynamics began in the 1970s with xenon washout and cavernosography studies in human volunteers exposed to audiovisual sexual stimuli. These studies yielded conflicting results: Shirai and associates (1978) concluded that penile venous flow is increased during erection, but markedly increased arterial flow compensates for this; Wagner (1981) also demonstrated increased arterial flow but concluded that venous drainage is decreased during erection.

Much of the current understanding of erectile physiology was gained in the 1980s and 1990s. In addition to the role of smooth muscle in regulating arterial and venous flow, the three-dimensional structure of the tunica albuginea and its role in venous occlusion were elucidated. An important breakthrough in the understanding

of neural influences was the identification of nitric oxide (NO) as the major neurotransmitter for erection and of phosphodiesterases (PDEs) for detumescence. The role of endothelium and nitric oxide synthase (NOS) in regulating smooth muscle tone and of the intercellular links affected by gap junctions has been uncovered. The importance of ion channels (potassium and calcium) and Rho/Rho-kinase pathways in contraction and relaxation of smooth muscle also has been shown. In regard to pathophysiology, changes in smooth muscle, nerve endings, endothelium, and the fibroelastic framework associated with many diseases have been identified. These developments are discussed in detail in this chapter.

Functional Anatomy of the Penis

The penis is composed of three cylindrical structures: the paired corpora cavernosa and the corpus spongiosum (which houses the urethra), covered by a loose subcutaneous layer and skin. Its flaccid length is controlled by the contractile state of the erectile smooth muscle and the amount of blood in the sinusoids and varies considerably, depending on emotion and outside temperature. In one study, penile length, measured from the pubopenile junction to the meatus, was 8.8 cm flaccid, 12.4 cm stretched, and 12.9 cm erect, with neither age nor the size of the flaccid penis accurately predicting erectile length (Wessells et al, 1996). In another study, Sparling (1997) concluded that about 15% of men have a downward curve during erection, erect angle is below horizontal in one quarter, and shorter erect lengths (from 4.5 to 5.75 inches) occur in 40% of men. Since then, more studies have been reported from several countries (Awwad et al, 2005) (Table 26-1). Regarding penile morphology and erection, one study showed that, during erection, the penile buckling forces are dependent not only on intracavernous pressures but also on penile geometry and erectile tissue properties. The authors concluded that in patients with normal penile hemodynamics but without adequate rigidity, structural causes should be investigated (Udelson et al, 1998).

Tunica Albuginea

The tunica affords great flexibility, rigidity, and tissue strength to the penis (Hsu et al, 1992) (Fig. 26-1). The tunical covering of the corpora cavernosa is a bilayered structure with multiple sublayers. Inner-layer bundles support and contain the cavernous tissue and are oriented circularly. Radiating from this inner layer are intracavernous pillars that act as struts to augment the septum and provide essential support to the erectile tissue. Outer-layer bundles are oriented longitudinally, extending from the glans penis to the proximal crura; they insert into the inferior pubic rami but are absent between the 5 o’clock and the 7 o’clock positions. Less abundant are oblique-oriented fibers that connect the two main layers. In contrast, the corpus spongiosum lacks an

TABLE 26-1 Penile Length in Adults

FIRST AUTHOR	YEAR OF REPORT	NO. SUBJECTS	AGE IN YEARS (RANGE)	FLACCID LENGTH (cm)	STRETCHED OR ERECT LENGTH (cm)	COUNTRY
Kinsey	1948	2770	20-59	9.7	15.5 (E)	United States
Bondil	1992	905	17-91	10.7	16.74 (S)	France
Wessells	1996	80	21-82	8.85	12.45 (S), 12.89 (E)	United States
Ponchietti	2001	3300	17-19	9	12.5 (S)	Italy
Ajmani	1985	320	17-23	8.16	NA	Nigeria
Schneider	2001	111	18-19	8.6	14.48 (E)	Germany
		32	40-68	9.22	14.18 (E)	
Awwad	2005	271 (N)	17-83	9.3	13.5 (S)	Jordan
		109 (ED)	22-68	7.7	11.6 (S)	

E, erect length; ED, erectile dysfunction; N, normal; NA, not available; S, stretched length.

Modified from Awwad Z, Abu-Hijleh M, Basri S, et al. Penile measurements in normal adult Jordanians and in patients with erectile dysfunction. *Int J Impot Res* 2005;17:191-5.

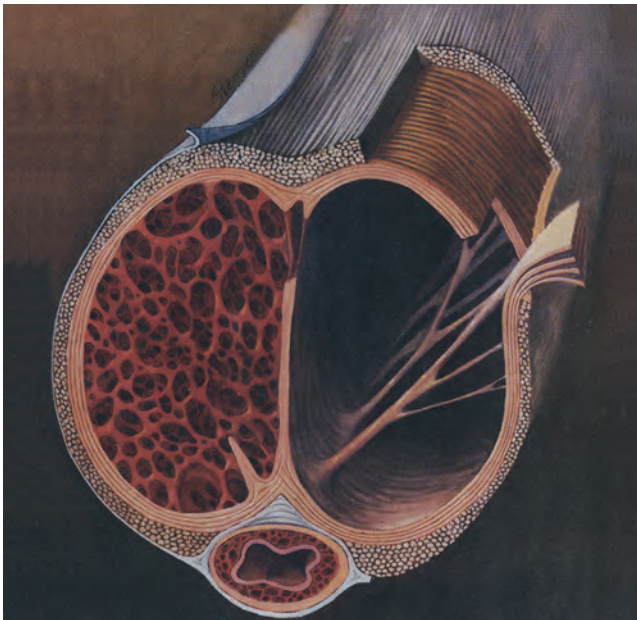


Figure 26-1. Artist's cross-sectional drawing of the penis, depicting the inner circular and outer longitudinal layers of the tunica albuginea and the intracavernous pillars. The longitudinal layer is absent in the ventral groove housing the corpus spongiosum. (From Lue TF, Akkus E, Kour NW. *Physiology of erectile function and dysfunction*. Campbell's Urology Update 1994;12:1-10.)

outer layer or intracorporeal struts, ensuring a low-pressure structure during erection.

The tunica is composed of elastic fibers that form an irregular, latticed network on which the collagen fibers rest (Fig. 26-2). The detailed histologic composition of the tunica varies with anatomic location and function. Emissary veins run between the inner and outer layers of the tunica for a short distance, often piercing the outer bundles obliquely. However, the cavernous artery and the branches of the dorsal artery that give additional blood supply to the corpus cavernosum take a more direct route and are surrounded by a periarterial soft-tissue sheath, which protects the arteries from occlusion by the tunica albuginea during erection.

The outer tunical layer appears to play an additional role in compression of the emissary veins during erection. It also determines, to a large extent, the variability in tunical thickness and strength (Hsu et al, 1992). Between the 6 o'clock and 7 o'clock positions, the tunical thickness is 0.8 ± 0.1 mm; at the 9 o'clock

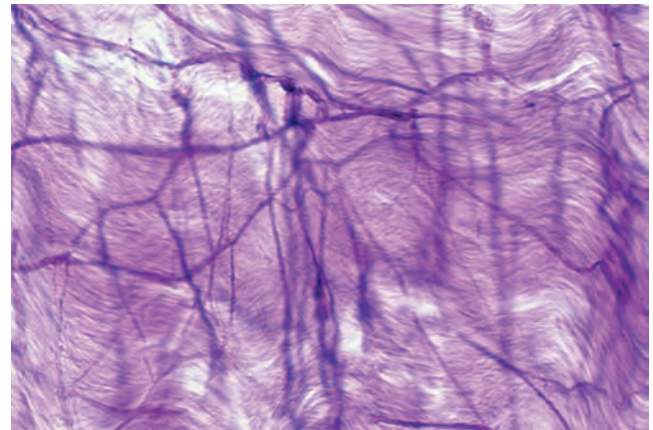


Figure 26-2. Micrograph of the human tunica albuginea, showing the interwoven elastic fibers and the finer collagen fibers (Hart stain $\times 100$).

position, 1.2 ± 0.2 mm; and at the 11 o'clock position, 2.2 ± 0.4 mm. At the 3 o'clock, 5 o'clock to 6 o'clock, and 1 o'clock positions, the measurements are nearly identical in mirror-image fashion. (Differences at specific locations have been found to be statistically significant.)

The stress on the tunica before penetration of a test object has been measured as $1.6 \pm 0.2 \times 10^7$ N/m² between the 6 o'clock and 7 o'clock positions, $3.0 \pm 0.3 \times 10^7$ N/m² at the 9 o'clock position, and $4.5 \pm 0.5 \times 10^7$ N/m² at the 11 o'clock position. The strength and thickness of the tunica correlate in a statistically significant fashion with location. The most vulnerable area is located on the ventral groove (between the 5 o'clock and 7 o'clock positions), where the longitudinal outer layer is absent; most prostheses tend to extrude here (Hsu et al, 1994).

The tunica albuginea is composed of fibrillar collagen (mostly type I but also type III) in organized arrays interlaced with elastin fibers. Although collagen has a greater tensile strength than steel, it is unyielding. In contrast, elastin can be stretched up to 150% of its length. The elastin content allows tunical expansion and helps to determine stretched penile length.

External penile support consists of two ligamentous structures: the fundiform and suspensory ligaments. The fundiform ligament arises from Colles fascia and is lateral, superficial, and not adherent to the tunica albuginea of the corpora cavernosa. The suspensory ligament arises from Buck fascia and consists of two lateral bundles and one median bundle, which circumscribe the dorsal vein of the penis. Its main function is to attach the tunica

albuginea of the corpora cavernosa to the pubis, and it provides support for the mobile portion of the penis (Hoznek et al, 1998). In patients with congenital deficiency or in whom this ligament has been severed in “penile elongation” surgery, the erect penis may be unstable or droop.

Corpora Cavernosa, Corpus Spongiosum, and Glans Penis

The corpora cavernosa comprise two spongy, paired cylinders contained in the thick envelope of the tunica albuginea. Their proximal ends, the crura, originate at the undersurface of the puboischial rami as two separate structures but merge under the pubic arch and remain attached up to the glans. The septum between the two corpora cavernosa is incomplete in men but is complete in some species such as dogs.

The corpora cavernosa are supported by a fibrous skeleton that includes the tunica albuginea, the septum, the intracavernous pillars, the intracavernous fibrous framework, and the periarterial and perineural fibrous sheath (Goldstein and Padma-Nathan, 1990; Hsu et al, 1992). Within the tunica are the interconnected sinusoids separated by smooth muscle trabeculae surrounded by elastic fibers, collagen, and loose areolar tissue. The terminal cavernous nerves and helicine arteries are intimately associated with the smooth muscle. Each corpus cavernosum is a conglomeration of sinusoids, larger in the center and smaller in the periphery. In the flaccid state, the blood slowly diffuses from the central to the peripheral sinusoids, and the blood gas levels are similar to those of venous blood. During erection, the rapid entry of arterial blood to both the central and the peripheral sinusoids changes the intracavernous blood gas levels to those of arterial blood (Sattar et al, 1995).

The structure of the corpus spongiosum and glans is similar to that of the corpora cavernosa except that the sinusoids are larger. The tunica is thinner in the spongiosum (with only a circular layer [see earlier]) and is absent in the glans (Table 26-2).

Arteries

The source of penile blood is usually the internal pudendal artery, a branch of the internal iliac artery (Fig. 26-3A). In many instances, however, accessory arteries exist, arising from the external iliac, obturator, and vesical and femoral arteries, and they may constitute the dominant or only arterial supply to the corpus cavernosum in some men (Breza et al, 1989). In a study of 20 fresh human cadavers, Droupy and colleagues (1997) reported three patterns of penile arterial supply: type I, arising exclusively from internal pudendal arteries (in 3 of 20 samples); type II, arising from both accessory and internal pudendal arteries

(in 14 of 20 samples); and type III, arising exclusively from accessory pudendal arteries (in 3 of 20 samples). Nehra and colleagues (2008) studied 79 consecutive patients with a history of ED and noted that 35% had an accessory pudendal artery, typically arising from the obturator artery. In these men, the accessory pudendal was the dominant blood supply in 54% and the only corporeal blood supply in 11%. The importance of accessory pudendal artery preservation during radical prostatectomy was demonstrated by Mulhall and colleagues (2008), who reported more rapid recovery of sexual function in men who underwent artery-sparing radical prostatectomy.

The internal pudendal artery becomes the common penile artery after giving off a branch to the perineum. The three branches of the penile artery are the dorsal, bulbourethral, and cavernous. Distally, they join to form a vascular ring near the

TABLE 26-2 Penile Components and Their Function during Penile Erection

COMPONENT	FUNCTION
Corpora cavernosa	Support corpus spongiosum and glans
Tunica albuginea (of corpora cavernosa)	Contains and protects erectile tissue Provides rigidity of the corpora cavernosa Participates in veno-occlusive mechanism
Smooth muscle	Regulates blood flow into and out of the sinusoids
Ischiocavernosus muscle	Pumps blood distally to hasten erection Provides additional penile rigidity during rigid erection phase
Bulbocavernosus muscle	Compresses the bulb to help expel semen
Corpus spongiosum	Pressurizes and constricts the urethral lumen to allow forceful expulsion of semen
Glans	Acts as a cushion to lessen the impact of penis on female organs Provides sensory input to facilitate erection and enhance pleasure Facilitates intromission because of its cone shape

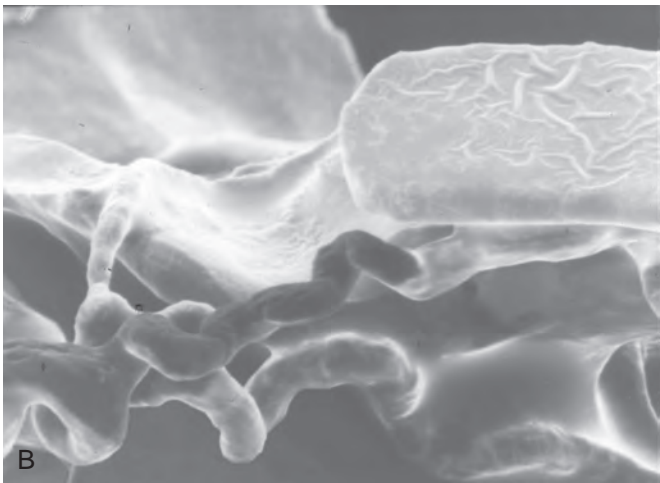
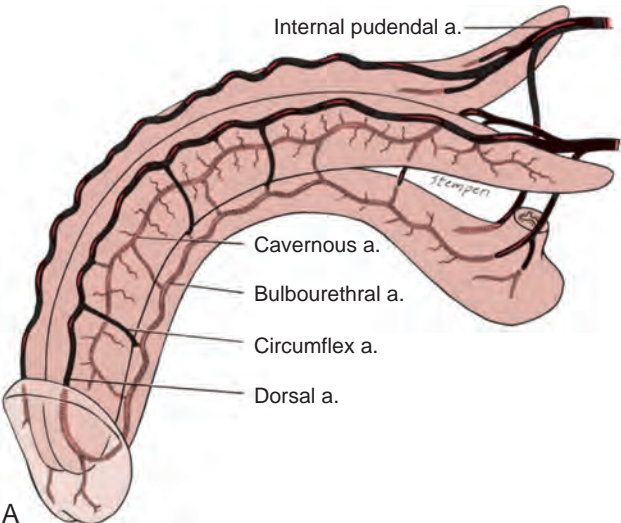


Figure 26-3. A, Penile arterial supply. B, Scanning electron micrograph of a human penile cast showing helicine arteries opening directly into the sinusoids without intervening capillaries.

glans. The dorsal artery is responsible for engorgement of the glans during erection. The bulbourethral artery supplies the bulb and corpus spongiosum. The cavernous artery effects tumescence of the corpus cavernosum and enters it at the hilum of the penis, where the two crura merge. It gives off many helicine arteries along its course, which supply the trabecular erectile tissue and the sinusoids (Fig. 26-3B). These helicine arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection. Diallo and associates (2013) noted that in four of their five cadaveric specimens, the dorsal artery sent two to four penetrating branches to join the cavernous artery and supply blood to the distal one third of the penis. The bulbourethral and urethral arteries are situated outside the tunica albuginea of the corpus spongiosum on the lateral and dorsal sides. Anastomosis of the cavernous and urethral arteries occurs outside the tunica of the spongiosum.

Veins

The venous drainage from the three corpora originates in tiny venules leading from the peripheral sinusoids immediately beneath the tunica albuginea. These venules travel in the trabeculae between the tunica and the peripheral sinusoids to form the subtunical venous plexus before exiting as the emissary veins (Fig. 26-4A). Outside the tunica albuginea, venous drainage is as follows.

Skin and Subcutaneous Tissue. Multiple superficial veins run subcutaneously and unite near the root of the penis to form a single (or paired) superficial dorsal vein, which drains into the saphenous veins. Occasionally, the superficial dorsal vein may also drain a portion of the corpora cavernosa.

Pendulous Penis. The emissary veins from the corpus cavernosum and spongiosum drain dorsally to the deep dorsal, laterally to the

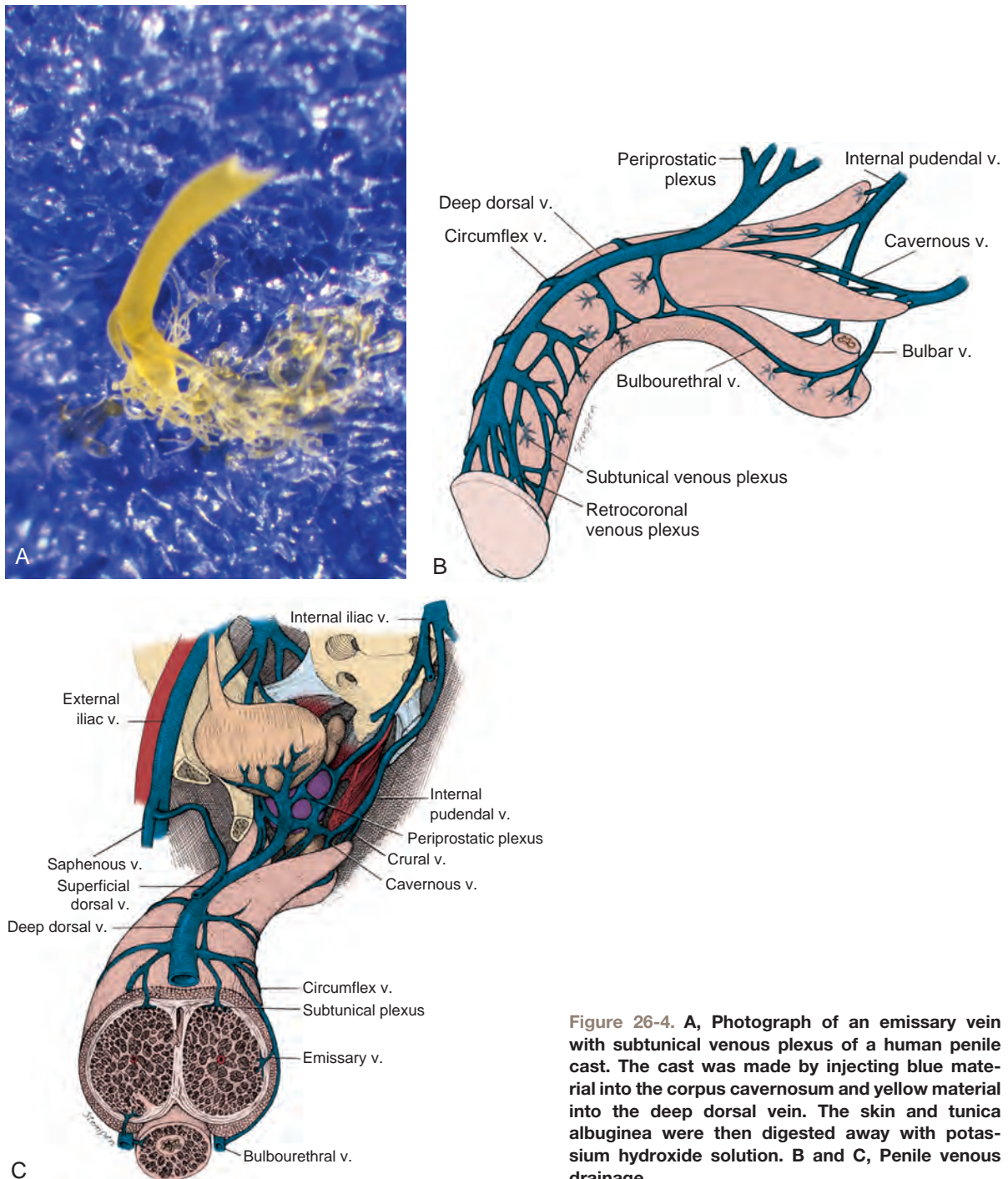


Figure 26-4. A, Photograph of an emissary vein with subtunical venous plexus of a human penile cast. The cast was made by injecting blue material into the corpus cavernosum and yellow material into the deep dorsal vein. The skin and tunica albuginea were then digested away with potassium hydroxide solution. B and C, Penile venous drainage.

circumflex, and ventrally to the periurethral veins. Beginning at the coronal sulcus, multiple venous channels coalesce to form the deep dorsal vein, which is the main venous drainage of the glans penis and distal two thirds of the corpora cavernosa. Usually a single vein, but sometimes more than one deep dorsal vein, runs upward behind the symphysis pubis to join the periprostatic venous plexus. There are also small venous channels accompanying the paired dorsal artery. Periarterial veins also travel longitudinally to join the dorsal vein or Santorini plexus proximally (Hsu et al, 2003). These become enlarged after the deep dorsal vein is ligated and may be the cause of recurrent leakage in venogenic ED (Chen et al, 2005). **Infrapubic Penis.** Emissary veins draining the proximal corpora cavernosa join to form cavernous and crural veins. These join the periurethral veins from the urethral bulb to form the internal pudendal veins.

The veins of the three systems communicate variably with each other. Variations in the number, distribution, and termination of these venous systems are common (Fig. 26-4B and C). In fresh cadavers, Hsu and coworkers (2012) determined the following percentage of venous flow from the corpora: deep dorsal vein, 65%; cavernous vein, 11.9%; periarterial vein, 11.4%; others, 15.6%. The study was performed in cadavers, and the cavernous vein is not the same as described by others.

Hemodynamics and Mechanism of Erection and Detumescence

Corpora Cavernosa

The penile erectile tissue, specifically the cavernous smooth musculature and the smooth muscles of the arteriolar and arterial walls, plays a key role in the erectile process. In the flaccid state,

these smooth muscles are tonically contracted, allowing only a small amount of arterial flow into the corpora. The blood partial pressure of oxygen (PO_2) is about 35 mm Hg (Sattar et al, 1995). The flaccid penis is in a moderate state of contraction, as evidenced by further shrinkage in cold weather and after phenylephrine injection.

Sexual stimulation triggers release of neurotransmitters from the cavernous nerve terminals. This release of neurotransmitters results in relaxation of these smooth muscles and the following events (Fig. 26-5): (1) dilation of the arterioles and arteries by increased blood flow in the diastolic and systolic phases; (2) trapping of the incoming blood by the expanding sinusoids; (3) compression of the subtunical venous plexuses between the tunica albuginea and the peripheral sinusoids, reducing venous outflow; (4) stretching of the tunica to its capacity, which occludes the emissary veins between the inner circular and outer longitudinal layers and further decreases venous outflow; and (5) increase in PO_2 (to about 90 mm Hg) and intracavernous pressure (around 100 mm Hg), which raises the penis from the dependent position to the erect state (the full-erection phase). A further pressure increase (to several hundred millimeters of mercury) can occur with reflex contractions of the ischiocavernosus muscles (rigid-erection phase) during sexual stimulation.

The angle of the erect penis is determined by its size and attachment to the puboischial rami (the crura) and the anterior surface of the pubic bone (the suspensory and funiform ligaments). In men with a long heavy penis or a loose suspensory ligament, the penis usually points downward, even with full rigidity.

Three phases of detumescence were reported in an animal study (Bosch et al, 1991). The first entails a transient intracorporeal pressure increase, indicating the beginning of smooth muscle

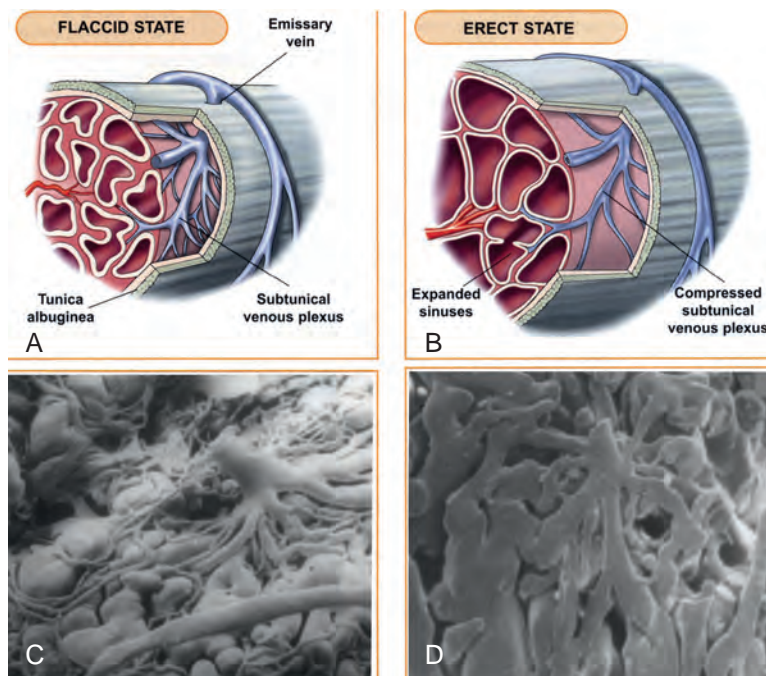


Figure 26-5. The mechanism of penile erection. A, In the flaccid state, the arteries, arterioles, and sinusoids are contracted. The intersinusoidal and subtunical venous plexuses are wide open, with free flow to the emissary veins. B, In the erect state, the muscles of the sinusoidal wall and the arterioles relax, allowing maximal flow to the compliant sinusoidal spaces. Most of the venules are compressed between the expanding sinusoids. The larger venules are sandwiched and flattened between the distended sinusoids and the tunica albuginea. This effectively reduces the venous capacity to a minimum. C and D, Scanning electron micrographs of casts of a canine subtunical venous plexus in the flaccid (C) and erect (D) states. (A and B, From Lue TF, Giuliano F, Khoury S, et al. Clinical manual of sexual medicine: sexual dysfunction in men. Paris: Health Publications; 2004.)

contraction against a closed venous system. The second phase shows a slow pressure decrease, suggesting a slow reopening of the venous channels with resumption of the basal level of arterial flow. The third phase shows a fast pressure decrease with fully restored venous outflow capacity.

Erection involves sinusoidal relaxation, arterial dilation, and venous compression (Lue et al, 1983). The importance of smooth muscle relaxation has been demonstrated in animal and human studies (Saenz de Tejada et al, 1989a; Ignarro et al, 1990). To summarize the hemodynamic events of erection and detumescence, seven phases have been observed in animal experiments that reflect the changes in and the relationship between penile arterial flow and intracavernous pressure (Fig. 26-6).

Corpus Spongiosum and Glans Penis

The hemodynamics of the corpus spongiosum and glans penis differ from those of the corpora cavernosa. During erection, the arterial flow increases in a similar manner; however, the pressure in the corpus spongiosum and glans is only one third to one half that in the corpora cavernosa because the tunical covering, which is thin over the corpus spongiosum and virtually absent over the glans, ensures minimal venous occlusion. During the full-erection phase, partial compression of the deep dorsal and circumflex veins between Buck fascia and the engorged corpora cavernosa contributes to glanular tumescence, although the spongiosum and glans essentially function as a large arteriovenous shunt during this phase. In the rigid-erection phase, the ischiocavernosus and bulbocavernosus muscles forcefully compress the spongiosum and penile veins, resulting in further engorgement and increased pressure in the glans and spongiosum (Table 26-3).

Neuroanatomy and Neurophysiology of Penile Erection

Spinal Centers and Peripheral Pathways

The innervation of the penis is both autonomic (sympathetic and parasympathetic) and somatic (sensory and motor) (Fig. 26-7). From the neurons in the spinal cord and peripheral ganglia, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa and corpus spongiosum to modulate the neurovascular events during erection and detumescence. The somatic nerves are primarily responsible for

sensation and the contraction of the bulbocavernosus and ischiocavernosus muscles.

Autonomic Pathways. The sympathetic pathway originates from the 11th thoracic to the 2nd lumbar spinal segments and passes through the white rami to the sympathetic chain ganglia. Some fibers travel through the lumbar splanchnic nerves to the inferior mesenteric and superior hypogastric plexuses, from which fibers travel in the hypogastric nerves to the pelvic plexus. In humans, the T10 to T12 segments are most often the origin of the sympathetic fibers, and the chain ganglia cells projecting to the penis are located in the sacral and caudal ganglia (de Groat and Booth, 1993).

The parasympathetic pathway arises from neurons in the intermediolateral cell columns of the second, third, and fourth sacral spinal cord segments. The preganglionic fibers pass in the pelvic nerves to the pelvic plexus, where they are joined by the sympathetic nerves from the superior hypogastric plexus. The cavernous nerves are branches of the pelvic plexus that innervate the penis. Other branches innervate the rectum, bladder, prostate, and sphincters. The cavernous nerves are easily damaged during radical excision of the rectum, bladder, and prostate. A clear understanding of the course of these nerves is essential to the prevention of iatrogenic ED (Walsh et al, 1990). Human cadaveric dissection has revealed medial and lateral branches of the cavernous nerves (the former accompanying the urethra and the latter piercing the urogenital diaphragm 4 to 7 mm lateral to the sphincter) and multiple communications between the cavernous and dorsal nerves (Paick et al, 1993) (Fig. 26-8). In addition to the cavernous nerve proper, pelvic ganglion cells exist in and along the nerve components and pelvic viscera. These are seen at the bladder/prostate junction, the dorsal aspect of the seminal vesicles, and along the prostate. Takenaka and colleagues (2005) reported

TABLE 26-3 Comparison of Corpus Spongiosum and Glans Penis

	CORPUS SPONGIOSUM	GLANS PENIS
Tunica albuginea	Thin (circular layer only)	Absent
Main blood supply	Bulbal and spongiosal arteries	Dorsal artery
Venous occlusion during erection	No	No
Compression by skeletal muscle	Yes (ischiocavernosus, bulbocavernosus)	No

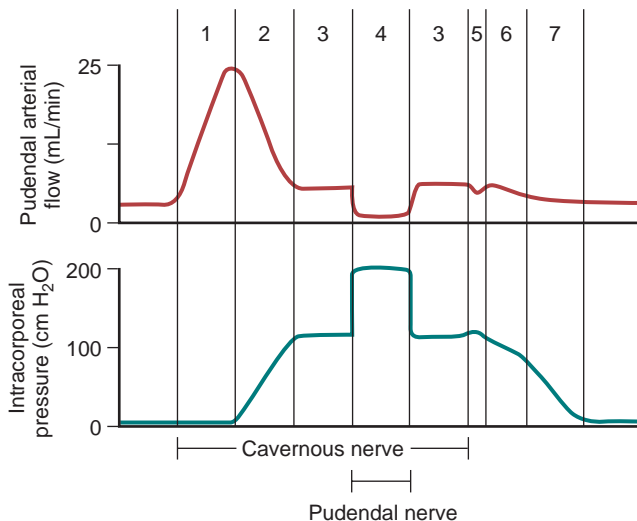


Figure 26-6. Blood flow and intracavernous pressure changes during the seven phases of penile erection and detumescence: 0, flaccid; 1, latent; 2, tumescence; 3, full erection; 4, rigid erection; 5, initial detumescence; 6, slow detumescence; 7, fast detumescence.

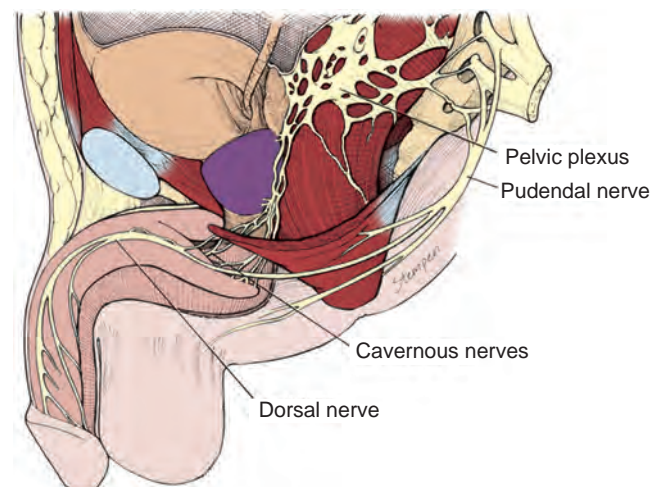


Figure 26-7. Penile neuroanatomy.



Figure 26-8. Drawing from a human cadaveric dissection shows the medial (red arrow) and lateral (green arrow) bundles of the cavernous nerve distal to the prostate. (From Paick JS, Donatucci EF, Lue TF. *Anatomy of cavernous nerves distal to prostate: microdissection study in adult male cadavers*. *Urology* 1993;42:145–9, with permission from Excerpta Medica, Inc.)

individual variations in distribution of these extramural ganglion cells in the male pelvis, which may complicate nerve-sparing efforts.

Stimulation of the pelvic plexus and the cavernous nerves induces erection, whereas stimulation of the sympathetic trunk causes detumescence. This clearly implies that the sacral parasympathetic input is responsible for tumescence, and the thoracolumbar sympathetic pathway is responsible for detumescence. In experiments with cats and rats, removal of the spinal cord below L4 or L5 reportedly eliminated the reflex erectile response, but placement with a female in heat or electrical stimulation of the medial preoptic area (MPOA) produced marked erection (Giuliano et al, 1996; Sato and Christ, 2000). Paick and Lee (1994) also reported that apomorphine-induced erection is similar to psychogenic erection in the rat and can be induced via the thoracolumbar sympathetic pathway in case of injury to the sacral parasympathetic centers. Many men with sacral spinal cord injury retain psychogenic erectile ability even though reflexogenic erection is abolished. These cerebrally elicited erections are found more frequently in patients with lower motoneuron lesions below T12 (Courtois et al, 1999); no psychogenic erection occurs in patients with lesions above T9. The efferent sympathetic outflow is suggested to be at the levels T11 and T12 (Chapelle et al, 1980). These authors also reported that in patients with psychogenic erections, lengthening and swelling of the penis are observed, but rigidity is insufficient.

It is possible that for production of rigid erection in normal men, cerebral impulses travel as follows: inhibiting the sympathetic pathway and decreasing norepinephrine release; through the parasympathetic pathway, releasing NO and acetylcholine; and through the somatic pathway, releasing acetylcholine. In patients with a sacral cord lesion, the cerebral impulses can still travel via the sympathetic pathway to inhibit norepinephrine release, and NO and acetylcholine can still be released through synapse with

postganglionic parasympathetic and somatic neurons. Because the number of these synapses is less than in men with an intact sacral spinal cord, the resulting erection will not be as strong.

Somatic Pathways. The somatosensory pathway originates at the sensory receptors in the penile skin, glans, and urethra and within the corpus cavernosum. There are numerous afferent terminations in the human glans penis: free nerve endings and corpuscular receptors in a ratio of 10:1. The free nerve endings are derived from thin myelinated A_δ and unmyelinated C fibers and are unlike any other cutaneous area in the body (Halata and Munger, 1986). The nerve fibers from the receptors converge to form bundles of the dorsal nerve of the penis, which joins other nerves to become the pudendal nerve. The latter enters the spinal cord via the S2–S4 roots to terminate on spinal neurons and interneurons in the central gray region of the lumbosacral segment (McKenna, 1998). Activation of these sensory neurons sends messages of pain, temperature, and touch by means of spinothalamic and spinoreticular pathways to the thalamus and sensory cortex for sensory perception.

Kozacioglu and associates (2014) reported a detailed study of the dorsal nerve. They noted that the dorsal nerve of the penis is composed of two to six branches, and in 16 of 22 adult cadaveric specimens, branches perforating the tunica albuginea to the corpus cavernosum were noted. The dorsal nerve of the penis previously was regarded as purely somatic; however, nerve bundles testing positive for NOS, which is autonomic in origin, have been demonstrated in humans by Burnett and colleagues (1993) and in rats by Carrier and colleagues (1995). These NOS-positive nerve bundles in the dorsal nerve are reduced after damage of the cavernous nerve near the rat prostate. Giuliano and coworkers (1993) have also shown that stimulation of the sympathetic chain at the L4–L5 level elicits an evoked discharge on the dorsal nerve and that stimulation of the dorsal nerve evokes a reflex discharge in the lumbosacral sympathetic chain of rats. These findings demonstrate that the dorsal nerve has somatic and autonomic components that enable it to regulate erectile and ejaculatory functions.

The Onuf nucleus in the second to fourth sacral spinal segments is the center of somatomotor penile innervation. These nerves travel in the sacral nerves to the pudendal nerve to innervate the ischiocavernosus and bulbocavernosus muscles. Contraction of the ischiocavernosus muscles produces the rigid-erection phase. Rhythmic contraction and compression of the bulbocavernosus muscle on the proximal corpus spongiosum helps semen expulsion, provided that the external sphincter is relaxed and the urethral lumen is compressed by the engorged spongiosum. In animal studies, direct innervation of the sacral spinal motoneurons by brainstem sympathetic centers (A5-catecholaminergic cell group and locus ceruleus) has been identified (Marson and McKenna, 1996). This adrenergic innervation of pudendal motoneurons may be involved in rhythmic contractions of perineal muscles during ejaculation. Oxytocinergic and serotonergic innervation of lumbosacral nuclei controlling penile erection and perineal muscles in male rats has also been demonstrated (Tang et al, 1998).

Depending on the intensity and nature of genital stimulation, several spinal reflexes can be elicited (Table 26-4). The best known is the bulbocavernosus reflex, which is the basis of genital neurologic examination and electrophysiologic latency testing. Although impairment of bulbocavernosus and ischiocavernosus muscles may impair erection, the significance of obtaining a bulbocavernosus reflex in overall sexual dysfunction assessment is controversial.

Supraspinal Pathways and Centers

Integration and processing of afferent inputs (e.g., visual, olfactory, imaginative, genital stimulation) in the supraspinal centers are essential in the initiation and maintenance of penile erection. A spinal transection study at the T8 level by Hubscher and associates (2010) revealed that ascending bilateral projections in the dorsal, dorsolateral, and ventrolateral white matter of the spinal cord convey information from the male external genitalia to the medullary reticular formation. The authors postulate that these multiple spinal pathways may correspond to different functions, including

TABLE 26-4 Spinal Reflexes Involved in Stimulation of Penile Dorsal Nerve

STIMULATION	SPINAL CENTER	EFFERENT	EFFECT
Noxious, abrupt stimulation	Sacral motor neurons	Pudendal nerve (motor)	Bulbocavernosus reflex
Low-intensity continuous (e.g., vibratory, manual)	Sacral parasympathetic neurons and interneurons	1. Pelvic nerves 2. Cavernous nerve	1. Bladder inhibition and closure of bladder neck 2. Penile erection
High-intensity continuous	Sacral motor and parasympathetic Thoracolumbar sympathetic neurons	Pudendal, pelvic, and cavernous nerves	Ejaculation

TABLE 26-5 Brain Centers Involved in Sexual Function

LEVEL	REGION	FUNCTION
Forebrain	Medial amygdala	Control sexual motivation
	Stria terminalis	
	Pyriform cortex	Inhibits sexual drive (hypersexuality when destroyed)
	Hippocampus	Involved in penile erection
	Right insula and inferior frontal cortex Left anterior cingulate cortex	Increased activity during visually evoked sexual stimulation (sexual arousal)
Hypothalamus	Medial preoptic area	Ability to recognize a sexual partner, integration of hormonal and sensory cues
	Lateral preoptic area	Control nocturnal penile tumescence in rats
	Paraventricular nucleus	Facilitates penile erection (via oxytocin neurons to lumbosacral spinal autonomic and somatic efferents)
Brainstem	Nucleus paragigantocellularis	Inhibits penile erection (via serotonin neurons to lumbosacral spinal neurons and interneurons)
	A5-catecholaminergic cell group	Major noradrenergic center
	Locus ceruleus	
Midbrain	Periaqueductal gray	Relay center for sexually relevant stimuli

functions processing affective, pleasure, and motivational; nociception; and mating-specific (e.g., for erection and ejaculation) inputs. In animal studies, the central supraspinal systems controlling sexual arousal are localized predominantly in the limbic system (e.g., olfactory nuclei, MPOA, nucleus accumbens, amygdala, and hippocampus) and hypothalamus (paraventricular and ventromedial nuclei). In particular, the medial amygdala, MPOA, paraventricular nucleus (PVN), periaqueductal gray, and ventral tegmentum are recognized as key structures in the central control of the male sexual response (Andersson, 2011; Melis and Argiolas, 2011).

In humans, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have allowed a greater understanding of brain activation during human sexual arousal by demonstrating increases in regional cerebral blood flow or changes in regional cerebral activity during a particular moment in time. Generally, in young heterosexual men, sexual arousal is triggered with sexually explicit pictures or videos. Scanned brain images taken during arousal are compared with images taken in response to sexually neutral media (e.g., documentaries or humorous video clips). Centers of activation and deactivation can be demonstrated. Although the simplicity of these study designs is elegant, multiple factors are involved in sexual arousal—especially when triggered by visual clues. The authors of these studies have placed many necessary conditions in experiments in an attempt to standardize the methods and participants; however, the complexity of human emotion and sexual response is extremely difficult to regulate (Table 26-5).

Kühn and Gallinat (2011) performed a quantitative meta-analysis of 11 fMRI studies that compared brain activity in response to erotic visual stimuli versus neutral visual stimuli. The meta-analysis identified a neural network that constitutes a core circuit of male sexual

arousal in humans and consists of the following components: cognitive (parietal cortex, anterior cingulate gyrus, thalamus, insula), emotional (amygdala, insula), motivational (precentral gyrus, parietal cortex), and physiologic (hypothalamus/thalamus, insula).

Using fMRI, detailed comparisons of brain activation in response to visual sexual stimuli have also been performed on varied groups. Stoléru and colleagues (2003) compared healthy men with men with hypoactive sexual desire disorder and reported that the left gyrus rectus, a portion of the medial orbitofrontal cortex, remained activated in the latter group in contrast to its deactivation in healthy men. This region is believed to mediate inhibition of motivated behavior, and its continued activation may help explain the pathophysiology of hypoactive sexual desire disorder. Montorsi and colleagues (2003) compared men with psychogenic ED and potent control subjects after the administration of apomorphine. During visual sexual stimulation, the men with psychogenic ED evidenced extended activation of the cingulate gyrus, frontal mesial, and frontal basal cortex, suggesting an underlying organic cause for psychogenic ED. However, fMRI images obtained after apomorphine were similar to the images of the potent control subjects. Apomorphine caused additional activation of foci in the patients with psychogenic ED (seen in the nucleus accumbens, hypothalamus, and mesencephalon), and it was significantly greater in the right hemisphere than in the left. This greater right-sided activation is a common finding in sexually evoked brain activation studies.

Brain scanning with PET and fMRI has become a powerful tool in the study of central activation of sexual arousal, with many brain regions of activation demonstrated in these studies (Table 26-6). Psychogenic ED, premature ejaculation, sexual deviations, and orgasmic dysfunction are just a few conditions that may accompany alterations in higher brain function and perhaps now can be

studied. As we begin to understand brain function with normal sexual response and arousal, the causes of dysfunction may be elucidated.

The structures discussed earlier are responsible for the three types of erection: psychogenic, reflexogenic, and nocturnal. **Psychogenic erection is a result of audiovisual stimuli or fantasy. Impulses from the brain modulate the spinal erection centers (T11-L2 and S2-S4) to activate the erectile process.** Reflexogenic erection is produced by tactile stimulation of the genital organs. The impulses reach the spinal erection centers; some then follow the ascending tract, resulting in sensory perception, whereas others activate the autonomic nuclei to send messages via the cavernous nerves to the penis to induce erection. This type of erection is preserved in patients with upper spinal cord injury. Nocturnal erection occurs mostly during rapid eye movement (REM) sleep. PET scanning of humans in REM sleep shows increased activity in the pontine area, the amygdalae, and the anterior cingulate gyrus but decreased activity in the prefrontal and parietal cortex. The mechanism that triggers REM sleep is located in the pontine reticular formation; the cholinergic neurons in the lateral pontine tegmentum are activated, whereas the adrenergic neurons in the locus ceruleus and the serotonergic neurons in the midbrain raphe are silent. In a brain stimulation study in rats, the sites for eliciting erection during REM sleep were located in the dorsal and intermediate parts of the lateral septum, whereas the ventral part of the lateral septum was the most effective site for eliciting erections during wakefulness (Gulia et al, 2008).

The brain centers activated during orgasm and ejaculation have also been studied. Holstege and colleagues (2003) used PET to

measure increases in regional cerebral blood flow during ejaculation versus sexual stimulation without orgasm in heterosexual volunteers. Manual penile stimulation was performed by the volunteer's female partner. Primary brain activation was found in the mesodiencephalic transition zone (including the ventral tegmental area), an area frequently activated with "reward" behaviors and with injection of opioids such as heroin. Other activated mesodiencephalic structures included the midbrain lateral central tegmental field; the zona incerta; the subparafascicular nucleus; and the ventroposterior, midline, and intralaminar thalamic nuclei. Increased activation was also observed in the lateral putamen and adjoining parts of the claustrum. Neocortical activity was found in Brodmann areas 7/40, 18, 21, 23, and 47, exclusively on the right side. Conversely, in the amygdala and adjacent entorhinal cortex, a decrease in activation was observed. Remarkably strong increases in blood flow were observed in the cerebellum. These findings corroborate the notion that the cerebellum plays an important role in emotional processing. Although activation of these particular areas is of great interest, further studies are necessary to understand completely the neurobiology of orgasm, ejaculation, and sexual satisfaction in men (Table 26-7).

Neurotransmitters

Peripheral Neurotransmitters and Endothelium-Derived Factors

Flaccidity and Detumescence. α -Adrenergic nerve fibers and receptors have been demonstrated in the cavernous trabeculae and surrounding the cavernous arteries, and norepinephrine has generally been accepted as the principal neurotransmitter to keep the penis in the flaccid state (Andersson, 2011; Dieckerichs et al, 1990). Both α_1 -adrenergic and α_2 -adrenergic receptors have been demonstrated in human corpus cavernosum tissue (Prieto, 2008). Research findings support a functional predominance of postjunctional α_1 -adrenergic receptors for contraction and of prejunctional α_2 -adrenergic receptors for downregulating not only release of norepinephrine but also NO (Prieto, 2008). Norepinephrine, released from adrenergic nerves, stimulates adrenergic receptors in the penile vessels and corpus cavernosum, producing a contraction that involves Ca^{2+} entry through calcium channels as well as calcium sensitization mechanisms mediated by protein kinase C, tyrosine kinases, and Rho-kinase (Andersson, 2011).

Endothelin-1, synthesized by endothelium, is a more potent vasoconstrictor than epinephrine and has been suggested to be a mediator for detumescence (Holmquist et al, 1990; Saenz de Tejada et al, 1991a). Endothelin-1 induces slowly developing, long-lasting contractions in different smooth muscles of the penis: corpus cavernosum, cavernosal artery, deep dorsal vein, and penile circumflex veins. Endothelin also potentiates the constrictor effects of catecholamines on trabecular smooth muscle (Christ et al, 1995b). Two receptors for endothelin, endothelin-A and endothelin-B, mediate the biologic effects of endothelin in vascular tissue: Endothelin-A receptors mediate contraction, whereas endothelin-B receptors induce relaxation.

TABLE 26-6 Common Brain Activation Regions with Visual Sexual Stimuli*

BRAIN ACTIVATION REGIONS	FUNCTIONAL ASSOCIATION
Bilateral inferior temporal cortex (right > left)	Visual association area
Right insula	Processes somatosensory information with motivational states
Right inferior frontal cortex	Processes sensory information
Left anterior cingulate cortex	Controls autonomic and neuroendocrine function
Right occipital gyrus	Visual processing
Right hypothalamus	Male copulatory behavior
Left caudate (the striatum)	Processes attention and guides responsiveness to new environmental stimuli

*These regions demonstrate activation with visual sexual stimuli in multiple studies.

TABLE 26-7 Brain Centers of Orgasm

	BRAIN AREAS	RELEVANCE
Increased activity: primary area	Mesodiencephalic transition zone (including the ventral tegmental area)	"Reward" center also activated by opioid
Increased activity: secondary areas	Midbrain lateral central tegmental field, the zona incerta, subparafascicular nucleus, ventroposterior, midline, and intralaminar thalamic nuclei Lateral putamen and adjoining parts of the claustrum Brodmann areas 7/40, 18, 21, 23, and 47, exclusively on the right side	
Increased activity: other area	Cerebellum	Emotional processing
Decreased activity	Amygdala and adjacent entorhinal cortex	

Several constrictor prostanoids, including prostaglandin I_2 (PGI_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), and thromboxane A_2 (TXA_2), are synthesized by the human cavernous tissue. In vitro studies demonstrated that prostanoids are responsible for the tone and spontaneous activity of isolated trabecular muscle (Christ et al, 1990). Functional characterization of prostanoid receptors in human trabecular and arterial penile smooth muscle revealed that only thromboxane A_2 (TP) receptors mediate contractile effects of prostanoids in these tissues (Angulo et al, 2002). Also, it has been observed in vitro that constrictor prostanoids, simultaneously released with NO, attenuate the dilator effect of NO (Azadzoi et al, 1992; Minhas et al, 2001).

The renin-angiotensin system (RAS) may also play a significant role in the maintenance of penile smooth muscle tone. The RAS comprises two major arms: a vasoconstrictor/proliferative arm, in which the main mediator is angiotensin II acting on angiotensin (AT1) receptors, and a vasodilator/antiproliferative arm in which the major effector is angiotensin-(1-7) acting via the G protein-coupled receptor Mas (Sousa et al, 2010). The mediators and receptors of both arms have been demonstrated in the corpus cavernosum. The RAS system may have a dual role in erectile function: pro-detumescence mediated by the angiotensin II-AT1 axis and pro-erection mediated by the angiotensin-(1-7)-Mas axis. Uckert and associates (2012) have also reported a decrease in cavernous blood level of neuropeptide Y during sexual arousal and suggested that neuropeptide Y may contribute to maintenance of a flaccid penis. In addition, the endothelium has been shown to release potent vasoconstrictors, including endoperoxides, TXA_2 , and superoxide anions.

The current consensus holds that the maintenance of the intracorporeal smooth muscle in a semicontracted (flaccid) state likely results from three factors: intrinsic myogenic activity (Andersson and Wagner, 1995); adrenergic neurotransmission; and endothelium-derived contracting factors such as angiotensin II, $PGF_{2\alpha}$, and endothelin-1. Detumescence after erection may be a result of cessation of NO release, the breakdown of cyclic guanosine monophosphate (cGMP) by PDEs, and/or sympathetic discharge during ejaculation.

Erection. Acetylcholine has been shown to be released with electrical field stimulation of human erectile tissue (Blanco et al, 1988). Traish and colleagues (1990) reported the density of muscarinic receptors in cavernous tissue to range from 35 to 65 fmol/mg protein and in endothelial cell membrane from 5 to 10 fmol/mg protein. However, intravenous or intracavernous injection of atropine failed to abolish erection induced in animals by electrical neurostimulation (Stief et al, 1989a) and in men by erotic stimuli (Wagner and Uhlenhuth, 1980). Although acetylcholine is not the predominant neurotransmitter, it contributes indirectly to penile erection by presynaptic inhibition of adrenergic neurons and stimulation of NO release from endothelial cells (Saenz de Tejada et al, 1989a).

Most researchers now agree that NO released from nonadrenergic/noncholinergic neurotransmission and from the endothelium is the principal neurotransmitter mediating penile erection. NO increases the production of cGMP, which relaxes the cavernous smooth muscle (Ignarro et al, 1990; Kim et al, 1991; Burnett et al, 1992; Rajfer et al, 1992; Trigo-Rocha et al, 1993; Andersson, 2011). The consensus is that NO derived from neuronal nitric oxide synthase (nNOS) in the nitrergic nerves is responsible for the initiation, whereby NO from endothelial nitric oxide synthase (eNOS) contributes to the maintenance of smooth muscle relaxation and erection (Hurt et al, 2002). (For a more detailed discussion of NO, see specific Nitric Oxide sections.)

Aside from its role in releasing vasoconstrictors, the endothelium can also release factors that induce smooth muscle relaxation, including carbon monoxide (CO), endothelium-derived hyperpolarizing factor (EDHF), prostacyclin (PGI_2), and endothelin (which may induce relaxation via activation of endothelin-B receptors).

Interactions among Nerves and Neurotransmitters. Acetylcholine, by acting on the presynaptic receptors on adrenergic neurons,

has been shown to modulate the release of norepinephrine (Saenz de Tejada et al, 1989b), which also can be inhibited by PGE_1 (Moldenings et al, 1992). In the human corpus cavernosum, noradrenergic responses are under nitrergic control. Conversely, adrenergic neurons, through prejunctional α_2 receptors, can also regulate the release of NO.

Several studies have demonstrated that the interaction between the two systems also occurs in the smooth muscle (Brave et al, 1993; Angulo et al, 2001a). The NO-cGMP-protein kinase G (PKG)-I pathway can lead to inhibition at several sites on the noradrenergic contractile pathway in the vascular smooth muscle, impairing inositol 1,4,5-triphosphate (IP3) production by phospholipase C (Hirata et al, 1990), IP3 receptor activity (Schlossmann et al, 2000), and the RhoA/Rho-kinase pathway (Sauzeau et al, 2000). However, interaction sites have not yet been identified in penile smooth muscle. A nitrergic-noradrenergic imbalance owing to defective nitrergic neurotransmission has been implicated in penile tissue from patients and in animal models with ED (Christ et al, 1995a; Celtek et al, 1999). Similar to the interaction between nitrergic and noradrenergic pathways, vasoconstrictive actions of endothelin have been shown to be inhibited by NO during erection (Mills et al, 2001).

Numerous factors have been reported to increase NOS activity and NO release, including molecular oxygen, androgen, long-term administration of L-arginine, and repeated intracavernous injection of PGE_1 (Kim et al, 1993; Escrig et al, 1999; Marin et al, 1999). Decreased NOS activity has been associated with castration, denervation, hypercholesterolemia, and diabetes mellitus. Interaction of different types of NOS may also occur. For example, nNOS activity has been shown to decrease and inducible nitric oxide synthase (iNOS) levels to increase after injection of transforming growth factor (TGF)- β 1 into the penis (Bivalacqua et al, 2000), and eNOS levels are reportedly significantly higher in nNOS-knockout mice (Burnett et al, 1996).

In a study of neurotransmitters in human corpus cavernosum and spongiosum, Hedlund and colleagues (2000b) reported that vesicular acetylcholine transporter, vasoactive intestinal polypeptide (VIP), and nNOS are found in the same nerve terminals. Tyrosine hydroxylase-positive nerves do not contain vesicular acetylcholine transporter, VIP, or NOS. Heme oxygenase (HO) enzymes HO-1 and HO-2 and eNOS are localized to the endothelium. Interaction of these neurotransmitters may modify the effect of parasympathetic and sympathetic activation on penile function.

Role of Caveolae. Caveolae are invaginated microdomains of plasma membrane that are rich in eNOS and caveolins as well as cholesterol, sphingolipids, and glycosylphosphatidylinositol-linked proteins. In addition, caveolae contain numerous other signaling proteins, such as receptors with seven-transmembrane domains, G proteins, adenylyl cyclase, phospholipase C, protein kinase C, calcium pumps, and calcium channels. Decreased caveolin-1 expression has been reported in the cavernous smooth muscle of aged rats (Bakircioglu et al, 2001). Linder and colleagues (2006) demonstrated that penile erection requires association of soluble guanylyl cyclase with endothelial caveolin-1 in rat corpus cavernosum. Shakhrova and colleagues (2009) reported that nerve-mediated relaxation of penile tissue from caveolin-1-deficient mice was impaired. Caveolin-1 in both the cavernous smooth muscle and the endothelium is decreased after bilateral cavernous nerve injury (Becher et al, 2009). In a rat model with diabetes induced by fructose and streptozotocin, Elcioglu and associates (2010) reported attenuation of erectile responses in both diabetic groups, an enhanced expression of caveolin-1, and a decrease in the eNOS activity with a concomitant decrease in NO synthesis. These reports strongly suggest that the caveolae and caveolin are involved in the regulation of penile function.

Central Neurotransmitters and Neuropeptides. Numerous neurotransmitters and neuropeptides have been implicated in regulation of sexual function. The major ones are dopamine, oxytocin, NO, norepinephrine, serotonin (5-hydroxytryptamine [5-HT]), and prolactin. In general, dopaminergic and adrenergic

receptors promote sexual function, and 5-HT receptors inhibit it (Foreman and Wernicke, 1990). Androgens also have an important role in modulating the effect of the transmitters.

Dopamine. There are many dopaminergic systems in the brain with ultrashort, intermediate, and long axons. The cell bodies are located in the ventral tegmentum, substantia nigra, and hypothalamus. One of these dopaminergic systems, the tuberoinfundibular system, secretes dopamine into the portal hypophysial vessels to inhibit prolactin secretion (Ganong, 1999a). Five different dopamine receptors have been cloned (D_1 to D_5), and several of these exist in multiple forms (Ganong, 1999b). In men, apomorphine, which stimulates both D_1 and D_2 receptors, induces erection that is unaccompanied by sexual arousal (Danjou et al, 1988). Neuroscientists have discovered that dopamine receptors (D_2 , D_3 , and D_4), nNOS, and oxytocin are coexpressed in the cell bodies of oxytocinergic neurons in the PVN and MPOA (Xiao et al, 2005; Baskerville et al, 2009). In male rats, injection of dopaminergic agonists to the PVN to stimulate D_2 , but not D_3 or D_4 , receptors, increases Ca^{2+} influx in cell bodies of oxytocinergic neurons. This increases the production of NO, which activates oxytocinergic neurotransmission in extrahypothalamic brain areas and spinal cord, leading to penile erection and yawning. The stimulation of D_4 receptors also increases Ca^{2+} influx and NO production leading to penile erection but not yawning. Nevertheless, D_4 receptors seem to play only a modest role in the pro-erectile effect (Melis and Argiolas, 2011).

Dopamine agonist in the form of sublingual apomorphine is available for the treatment of ED in many countries, but its utility is limited because of emetic side effects.

Oxytocin. Oxytocin is a neural hormone secreted by the neurons into the circulation. Oxytocin is found in the posterior pituitary gland, but because it is also found in the neurons projecting from the PVN to the brainstem and spinal cord, it can also function as a neurotransmitter. The blood level is increased during sexual activity in humans and animals. Oxytocin is a potent inducer of penile erection when injected into the central nervous system (CNS). In rats, the most sensitive brain area for the pro-erectile effect of oxytocin is the PVN of the hypothalamus. Oxytocin release after stimulation of dopamine receptors in the PVN influences the appetitive and reinforcing effects of sexual activity (Succu et al, 2007). As mentioned earlier, neurons in the paraventricular area contain NOS, and because NOS inhibitors prevent apomorphine-induced and oxytocin-induced erection, it is evident that oxytocin acts on neurons whose activity is dependent on certain levels of NO (Vincent and Kimura, 1992; Melis and Argiolas, 2011).

Nitric Oxide. NO mediates penile erection at the level of the PVN (Melis et al, 1998) and at other levels of the neural pathway supporting sexual response. The presence of NO and the soluble guanylyl cyclase needed to generate cGMP is seen throughout the human brain. The NO/cGMP pathway (see later) is affected by aging in the brain and offers a potentially significant but unexplored site for mediating the deleterious effects of age on sexual function (Ibarra et al, 2001). Reduced nNOS protein within the PVN leading to blunting of the erectile response has been reported in streptozotocin-induced diabetic rats (Zheng et al, 2007). In animals, testosterone increases NOS in the MPOA. NO increases basal and female-stimulated dopamine release, which facilitates copulation and genital reflexes. In rodents, dopamine receptor agonist-induced erections were abolished by castration, and testosterone replacement restored erectile function (Hull et al, 1999).

Serotonin. Neurons containing 5-HT have their cell bodies in the midline raphe nuclei of the brainstem and project to a portion of the hypothalamus, limbic system, neocortex, and spinal cord (Ganong, 1999a). At the present time, 5-HT receptors 1 to 7 have been cloned and characterized. Within the 5-HT₁ group are the 5-HT_{1A}, B, D, E, and F subtypes. Within the 5-HT₂ group are the 5-HT_{2A}, B, and C subtypes. There are two 5-HT₅ subtypes, 5-HT_{5A} and 5-HT_{5B} (Ganong, 1999b). General pharmacologic data indicate that 5-HT pathways inhibit copulation, but 5-HT may have both facilitatory and inhibitory effects on sexual function, depending on the receptor subtype, the receptor location, and the species investigated (de Groat and Booth, 1993). Andersson

and Wagner (1995) summarized the results of administration of selective agonists and antagonists as follows: 5-HT_{1A} receptor agonists inhibit erectile activity but assist ejaculation, stimulation of 5-HT_{2C} receptors cause erection, and 5-HT₂ agonists inhibit erection but assist seminal emission and ejaculation. Also, Steers and de Groat (1989) showed increased firing of the cavernous nerve and erection when *m*-chlorophenylpiperazine, a 5-HT_{2C} receptor agonist, was given to rats. Applying a novel 5-HT_{2C} receptor agonist (YM348) and antagonist SB242084, Kimura and colleagues (2006) confirmed the pro-erectile effect of the 5-HT_{2C} receptor stimulation in rats. In rats, 5-HT, dopamine, oxytocin, and melanocortin pathways are known to be involved in the induction of penile erections. Kimura and colleagues (2008) suggested that 5-HT_{2C} receptors in the lumbosacral spinal sites mediate not only dopamine-oxytocin-5-HT action but also melanocortin effects on penile erections and that the 5-HT pathway is located downstream from the melanocortin and the dopamine-oxytocin pathways.

5-HT is believed to be an inhibitory transmitter in the control of sexual drive (Foreman et al, 1989). Suppressed libido has been reported in patients taking fenfluramine, a 5-HT-releasing agent, but elevated libido occurred in patients taking buspirone, a 5-HT neuron suppressor (Buffum, 1982).

Norepinephrine. The cell bodies of the norepinephrine-containing neurons are located in the locus ceruleus and the A5-catecholaminergic cell group in the pons and medulla. The axons of these noradrenergic neurons ascend to innervate the paraventricular, supraoptic, and periventricular nuclei of the hypothalamus, thalamus, and neocortex. They also descend into the spinal cord and the cerebellum. Central norepinephrine transmission seems to have a positive effect on sexual function. In humans and rats, inhibition of norepinephrine release by clonidine, an α_2 -adrenergic agonist, is associated with a decrease in sexual behavior, and yohimbine, an α_2 -receptor antagonist, has been shown to increase sexual activity (Clark et al, 1985). β -Blockers have also been implicated in sexual dysfunction, probably because of their central side effects such as sedation, sleep disturbances, and depression.

Melanocortins. Melanocortin-4 receptor (MC4R), implicated in the control of food intake and energy expenditure, also modulates erectile function and sexual behavior. Evidence supporting this notion is based on several findings, as follows: (1) A highly selective nonpeptide MC4R agonist augments erectile activity initiated by electrical stimulation of the cavernous nerve in wild-type, but not MC4R-null, mice; (2) copulatory behavior is enhanced by administration of a selective MC4R agonist and is diminished in mice lacking MC4R; (3) reverse transcriptase polymerase chain reaction and non-polymerase chain reaction-based methods demonstrate MC4R expression in the rat and human penis and rat spinal cord, hypothalamus, brainstem, and pelvic ganglion (major autonomic relay center to the penis) but not in rat primary corpus cavernosum smooth muscle cells; and (4) in situ hybridization of glans tissue from the human and rat penis reveals MC4R expression in nerve fibers and mechanoreceptors in the glans. Collectively, these data implicate MC4R in the modulation of penile erectile function and provide evidence that MC4R-mediated pro-erectile responses may be activated through neuronal circuitry in spinal cord erectile centers and somatosensory afferent nerve terminals of the penis (Van der Ploeg et al, 2002).

Prolactin. Increased levels of prolactin suppress sexual function in men and experimental animals. In rats, high levels of prolactin decrease the genital reflex and disturb copulatory behavior (Rehman et al, 2000). It is suggested that the mechanism of action of prolactin is through inhibition of dopaminergic activity in the MPOA and decreased testosterone. In addition, prolactin may have a direct effect on the penis through its contractile effect on the cavernous smooth muscle (Ra et al, 1996). In a study of sexual activity of married men with ED, men with sexual inactivity were noted to have a significantly higher mean prolactin level (Paick et al, 2006) (Table 26-8).

γ -Aminobutyric Acid. γ -Aminobutyric acid (GABA) activity in the PVN provides a mechanism to balance (inhibit) pro-erectile signaling. Systemic administration or intrathecal injection at the

TABLE 26-8 Central Neurotransmitters and Their Function

NEUROTRANSMITTER	RECEPTOR AND FUNCTION
Dopamine	D1 and D4 receptor—enhances erection D2 receptor—enhances seminal emission
Serotonin (5-HT)	5-HT—inhibits sex drive and spinal sexual reflex 5-HT1A—inhibits erection, facilitates ejaculation 5-HT2C—enhances erection
Norepinephrine	Enhances sexual function
γ -aminobutyric acid	Inhibits erectile signals
Opioids	Inhibit penile erection
Cannabinoids	Inhibit sexual function
Oxytocin	Enhances appetitive and reinforcing effects of sexual activity
Nitric oxide	Mediates erection at paraventricular nucleus
Melanocortins	MCR4—enhances erection
Prolactin	Suppresses sexual function

lumbosacral level of the GABA_B receptor agonist baclofen decreased the frequency of erections in rats (Bitran and Hull, 1987). Activation of GABA_A receptors in the PVN reduced penile erection and yawning in male rats induced by apomorphine, *N*-methyl-D-aspartate, and oxytocin (Melis and Argiolas, 2002).

Opioids. Endogenous opioids are known to affect sexual function, but the mechanism of action is unclear. Injection of small amounts of morphine into the MPOA assists sexual behavior in rats. However, larger doses inhibit penile erection and yawning induced by oxytocin or apomorphine. It is suggested that endogenous opioids may exert an inhibitory control on central oxytocinergic transmission (Argiolas, 1992). Injection of morphine into the PVN of the hypothalamus prevents noncontact penile erections and impairs copulation in rats. It is speculated that intracellular NO may be involved in this process (Melis et al, 1999).

Cannabinoids. Cannabinoid CB₁ receptor activation inhibits sexual function by modulating the paraventricular oxytocinergic neurons, which mediate erection. Antagonism of CB₁ receptors in the PVN of male rats induces penile erection, which seems to involve glutamic acid and NO (Melis et al, 2004, 2006).

Smooth Muscle Physiology

In contrast to many other smooth muscles, corpus cavernosum smooth muscle is in a contracted state most of the time. In a study of myosin isoforms in smooth muscle cells in the corpus cavernosum, DiSanto and colleagues (1998) reported that their overall composition is between that in aorta and bladder smooth muscles, which generally express toniclike and phasiclike characteristics, respectively. Spontaneous contractile activity of cavernous smooth muscle has been recorded in vitro and in vivo. In a study in men, Yarnitsky and colleagues (1995) found two types of electrical activity recorded from the corpus cavernosum: spontaneous and activity induced. Berridge (2008) proposed that the rhythmic contractions of corpus cavernosum smooth muscle depend on an endogenous pacemaker driven by a cytosolic Ca²⁺ oscillator that releases Ca²⁺ from the sarcoplasmic reticulum periodically. This cytosolic oscillator can be modulated by neurotransmitters and hormones.

Molecular Mechanism of Smooth Muscle Contraction

Smooth muscle contraction is controlled by two major factors: cytosolic calcium concentration and Rho-kinase signaling (Berridge, 2008). Smooth muscle contraction can occur with or without change in membrane potential (Somlyo and Somlyo 2000; Berridge, 2008).

Cytosolic Free Calcium. Smooth muscle contraction is regulated by intracellular free calcium (Ca²⁺) acting through calmodulin. Calcium-bound calmodulin undergoes a conformational change, increasing its affinity for myosin light chain (MLC) kinase. MLC kinase is activated by binding of the calcium-calmodulin complex, leading to phosphorylation of the serine-19 residue of regulatory MLC₂₀. In the presence of adenosine triphosphate (ATP), this phosphorylation enables actin to activate the myosin ATPase and initiates cross-bridge cycling. Hydrolysis of ATP by ATPase supplies the energy for the contractile process (Fig. 26-9). The muscle contractile process ends when MLC₂₀ is dephosphorylated (inactivated) by myosin light chain phosphatase (MLCP). MLCP is a holoenzyme consisting of a type 1 phosphatase (PP1c), a myosin-targeting subunit (MYPT1), and a 20-kD subunit of unknown function (Hersch et al, 2004; Ito et al, 2004).

Rho Kinase Signaling Pathway (Calcium Sensitization Pathway). Theoretically, MLCP inhibition may lead to enhanced smooth muscle contraction. This is also termed the *calcium sensitization pathway*. The activity of MLCP can be modulated by Rho/Rho-kinase signaling (Fig. 26-10). Agonist activation causes dissociation of RhoA from Rho-guanine dissociation inhibitor and activates Rho-kinase. Phosphorylation of the regulatory subunit of MLCP by Rho-kinase inhibits phosphatase activity and enhances the contractile response (Hirano, 2007). RhoA and Rho-kinase are expressed in penile smooth muscle (Rees et al, 2002; Wang et al, 2002). The emerging consensus is that phasic contraction of penile smooth muscle is regulated by an increase in cytosolic Ca²⁺ and that tonic contraction is governed by the calcium-sensitizing pathways (Cellek et al, 2002). Several studies suggest that NO regulates RhoA/Rho-kinase activity (Bivalacqua et al, 2007; Priviero et al, 2010), and Chitale and coworkers (2001) reported that Rho-kinase antagonism stimulated rat penile erection.

Latch State: A Unique Characteristic of Smooth Muscle Contraction. Smooth muscle has the ability to maintain tension for prolonged periods with minimal energy expenditure. This efficiency has been termed the *latch* state and is critical for sustaining the “basal” tone of the smooth muscle. It has been proposed that dephosphorylated myosin remains bound to actin in the high-affinity state to help stabilize the latch state. Others have proposed that calponin participates in the latch state by simultaneously binding actin and myosin to stabilize cross-bridge interactions and slow the rate of detachment (Szymanski, 2004).

Pathways Involving Inositol 1,4,5-Triphosphate, 1,2-Diacylglycerol, and Protein Kinase C. Vasoconstrictor agonists such as norepinephrine (α_1 -adrenergic receptors), endothelin-1 (endothelin-A receptors), angiotensin II (AT1 receptors), prostaglandin F_{2 α} (FP receptors), and TXA₂ (TP receptors) bind their respective receptors to activate Gq, which stimulates phospholipase C beta. This membrane-bound enzyme hydrolyzes phosphatidylinositol 4,5-bisphosphate to liberate IP₃ and 1,2-diacylglycerol. IP₃ binds to specific receptors (IP₃ receptor) on the smooth endoplasmic reticulum to stimulate the release of Ca²⁺ from intracellular stores. Binding of IP₃ to these receptors not only activates the channel but also increases the sensitivity of the IP₃ receptor to Ca²⁺ and assists calcium-induced calcium release.

Another mechanism of increased intracellular Ca²⁺ is by permitting entry of extracellular Ca²⁺ through receptor-operated channels without a change in membrane potential (Large, 2002). Norepinephrine, endothelin, vasopressin, and angiotensin II cause the opening of Ca²⁺-permeable, nonselective cation channels.

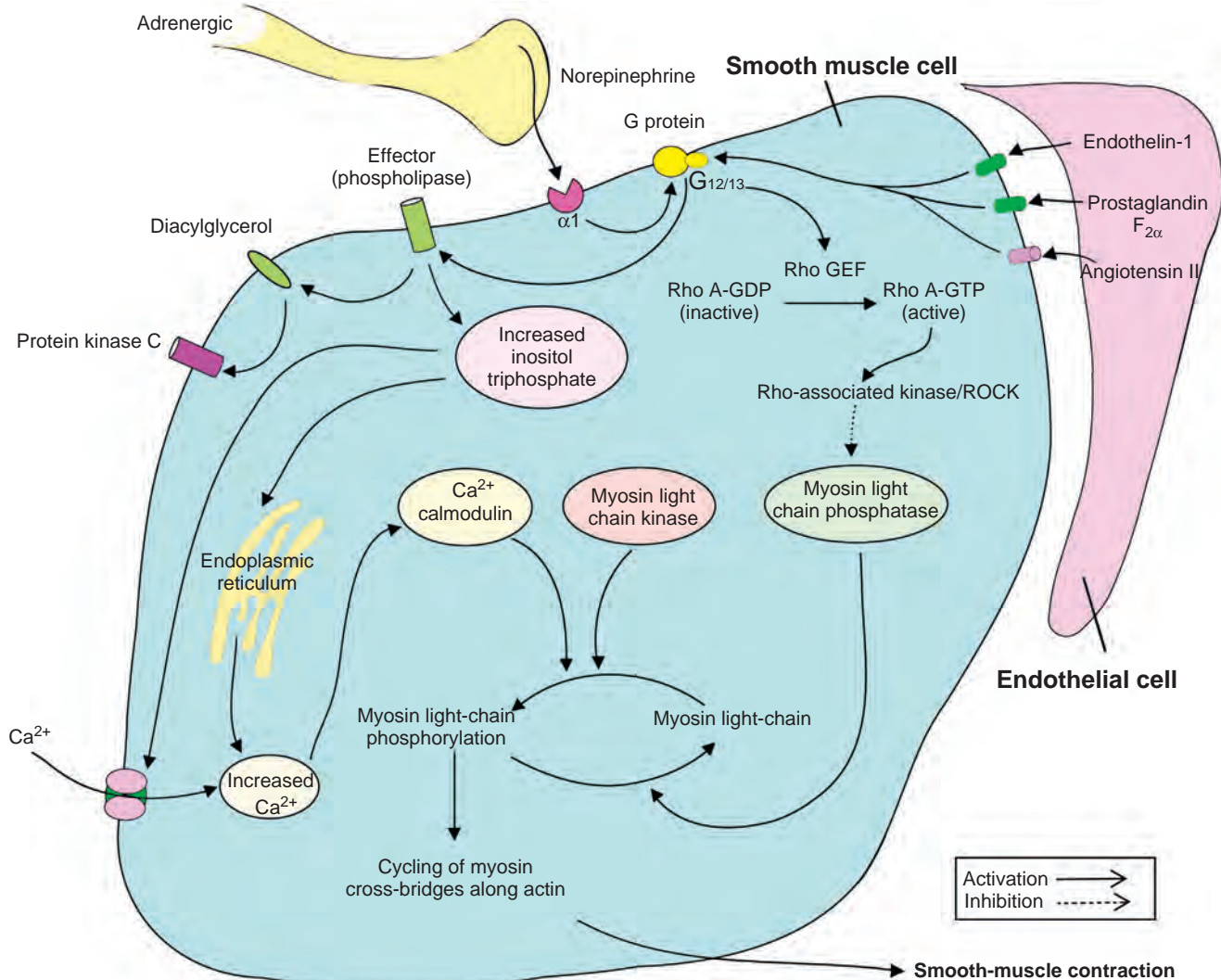


Figure 26-9. Molecular mechanism of penile smooth muscle contraction. Norepinephrine from sympathetic nerve endings and endothelins, angiotensin II, and prostaglandin $F_{2\alpha}$ from the endothelium activate receptors on smooth muscle cells to initiate the cascade of reactions that eventually result in elevation of intracellular calcium concentrations, activation of Rho-kinase, and smooth muscle contraction. Protein kinase C is a regulatory component of the Ca^{2+} -independent, sustained phase of agonist-induced contractile responses. GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate.

Molecular Mechanism of Smooth Muscle Relaxation

After contraction, relaxation of the muscle follows a decrease of free Ca^{2+} in the sarcoplasm. Calmodulin dissociates from MLC kinase and inactivates it. Myosin is dephosphorylated by MLCP and detaches from the actin filament, and the muscle relaxes (Fig. 26-11) (Walsh, 1991).

Another mechanism of smooth muscle relaxation is through cyclic adenosine monophosphate (cAMP) and cGMP, which are the two major second messengers involved in smooth muscle relaxation. They activate cAMP-dependent and cGMP-dependent protein kinases, which phosphorylate certain proteins and ion channels, resulting in (1) opening of the potassium channels and hyperpolarization; (2) sequestration of intracellular calcium by the endoplasmic reticulum; and (3) inhibition of voltage-dependent calcium channels, blocking calcium influx. The consequence is a decrease in cytosolic free calcium and smooth muscle relaxation.

Cyclic Guanosine Monophosphate–Signaling Pathway. Signaling molecules in the cGMP pathway include NO, CO, hydrogen sulfide (H_2S), and natriuretic peptides.

Nitric Oxide. Because of its small size, NO can diffuse inside its target cell, where it interacts with molecules that contain iron in either a heme or an iron-sulfur complex. The most physiologically relevant receptor for NO is soluble guanylyl cyclase (sGC), and the NO-sGC-cGMP pathway is responsible for the vasorelaxation effect of many endothelium-dependent vasodilators, including histamine, estrogens, insulin, corticotropin-releasing hormone, nitrovasodilators, and acetylcholine. This pathway is also principally responsible for physiologic penile erection.

Synthesis of NO is catalyzed by NOS, which converts L-arginine and oxygen to L-citrulline and NO. NOS exists as three isoforms in mammals: nNOS and eNOS are preferentially expressed in neurons/nerves and endothelial cells, respectively, and iNOS is expressed in virtually all cell types. All three NOS isoforms have been identified in the corpus cavernosum, with nNOS and eNOS being considered responsible for initiating and sustaining erection, respectively (Hurt et al, 2002; Musicki et al, 2009). A variant of nNOS (penile nNOS) has been identified as two distinct isoforms in the penis of rats and mice (Magee et al, 1996). eNOS has an indispensable role in penile erection, and its activity and bioavailability are regulated by multiple mechanisms,

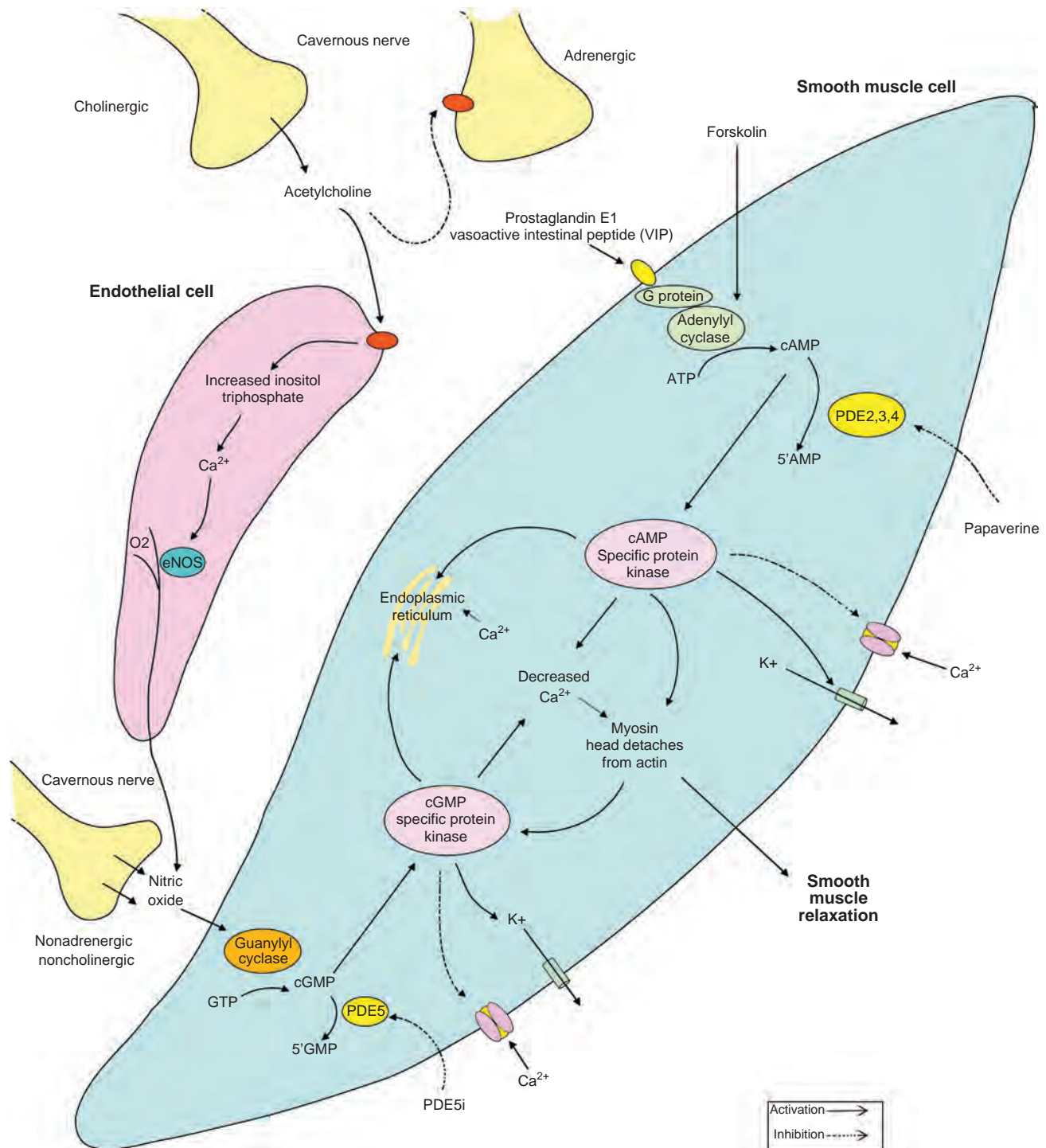


Figure 26-10. Molecular mechanism of penile smooth muscle relaxation. The intracellular second messengers mediating smooth muscle relaxation, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), activate their specific protein kinases, which phosphorylate certain proteins to cause opening of potassium channels, closing of calcium channels, and sequestration of intracellular calcium by the endoplasmic reticulum. The resultant decrease in intracellular calcium leads to smooth muscle relaxation. Sildenafil inhibits the action of phosphodiesterase (PDE) type 5 and increases the intracellular concentration of cGMP. Papaverine is a nonspecific phosphodiesterase inhibitor. ATP, adenosine triphosphate; eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate.

such as eNOS phosphorylation, eNOS interaction with regulatory proteins and contractile pathways, and actions of reactive oxygen species. Endothelial NO availability may be altered in vasculogenic ED. Downregulation of nNOS expression has been found in the corpus cavernosum of aging rats (Carrier et al, 1997),

castrated rats (Penson et al, 1996), and diabetic rats (Rehman et al, 1997).

Gene transfer of nNOS or eNOS to the penis has been shown to augment erectile responses in aging rats (Champion et al, 1999; Magee et al, 2002), and gene transfer of iNOS has enhanced

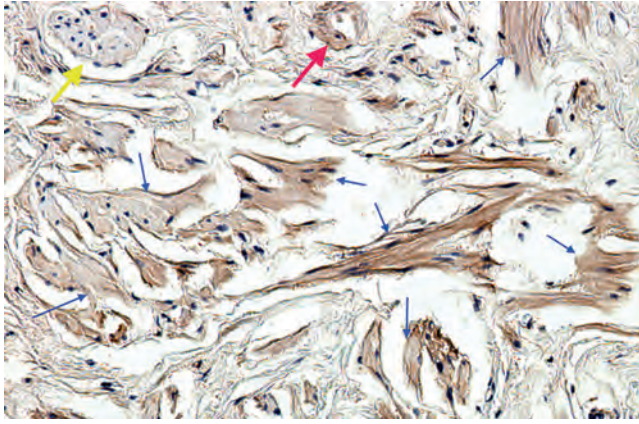


Figure 26-11. Immunohistochemistry of human penile tissue, showing positive phosphodiesterase type 5 staining of cavernous smooth muscle fibers (small blue arrows), nerve (yellow arrow), and blood vessel wall (red arrow) (x100).

intracavernous pressure (Chancellor et al, 2003). However, despite these encouraging results, mice with disrupted nNOS or eNOS gene have normal erectile function (Burnett et al, 1996, 2002). Compensatory mechanisms, alternative splicing of the disrupted gene (Ferrini et al, 2003), and/or other unknown mechanisms are possibly involved in the preservation of erectile function in NOS-knockout mice.

Carbon Monoxide. CO is a gaseous second messenger that occurs in biologic systems during the oxidative catabolism of heme by the HO enzyme. HO exists as constitutive (HO-2, HO-3) and inducible (HO-1) isoforms. HO-1 is upregulated in response to multiple stress stimuli. HO-1 confers protection in vitro and in vivo against oxidative cellular stress. CO regulates vascular processes, such as vessel tone, smooth muscle proliferation, and platelet aggregation, and may function as a neurotransmitter. The neurotransmitter effect of CO is dependent on the activation of guanylate cyclase by direct binding to the heme moiety of the enzyme, stimulating the production of cGMP.

Hydrogen Sulfide. L-Cysteine is a natural substrate for the synthesis of H₂S. Exogenous H₂S or L-cysteine causes relaxation of strips of human corpus cavernosum. Intracavernosal administration of either H₂S, sodium hydrosulfide (NaHS), or L-cysteine elicited penile erection in rats (d'Emmanuele di Villa Bianca et al, 2011). These observations indicate that a functional L-cysteine/H₂S pathway may be involved in mediating penile erection in men and some mammals.

Natriuretic Peptides. The natriuretic peptide family is involved in the regulation of cardiovascular homeostasis and consists of atrial (ANP), brain (BNP), and C-type (CNP) natriuretic peptides (Matsuo, 2001). ANP and BNP are ligands for the natriuretic peptide receptor NPR-A, whereas CNP is a ligand for the natriuretic peptide receptor NPR-B. Both receptors are members of the guanylyl cyclase family and are also called GC-A and GC-B.

The effects of ANP, BNP, and CNP on cGMP production and smooth muscle relaxation in isolated human and animal corpus cavernosum and in cultured cavernous smooth muscle cells have been investigated (Kim et al, 1998; Kuthe et al, 2003; Sousa et al, 2010). The results indicate that CNP is the most potent natriuretic peptide and that it relaxes the isolated cavernous smooth muscle by binding to NPR-B. However, whether CNP and NPR-B play a role in physiologic erection remains to be seen.

Guanylyl Cyclase. In mammals, seven membrane-bound (particulate) guanylyl cyclase isoforms (GC-A to GC-G) and one soluble isoform (sGC) have been identified (Andreopoulos and Papapetropoulos, 2000). Although the membrane-bound guanylyl cyclase system is not known to play a role in physiologic erection, expression of GC-B in human and rat corpus cavernosum and induction of cavernous smooth muscle relaxation by CNP (ligand for GC-B) have been demonstrated (Guidone et al, 2002; Kuthe et al, 2003).

The soluble isoform sGC plays a pivotal role in erectile function because it provides the link between NO and cGMP, which represent the extracellular and intracellular signaling molecules, respectively, in physiologic erection (Andersson, 2001). A heterodimeric protein, sGC consists of α and β subunits, each of which exists in two isoforms (α_1 , α_2 , and β_1 , β_2) that are encoded by two separate genes (Andreopoulos and Papapetropoulos, 2000). Nimmegeers and associates (2008) assessed the functional importance of the sGC $\alpha_1\beta_1$ isoform in corpus cavernosum from male sGC α_1 (–/–) and wild-type mice and concluded that the sGC $\alpha_1\beta_1$ isoform is involved in corpus cavernosum smooth muscle relaxation in response to NO and NO-independent sGC stimulators.

Protein Kinase G. PKG, also called cGMP-dependent kinase, is the principal receptor and mediator for cGMP signals. In mammals, PKG exists in two major forms, PKG-I and PKG-II, which are encoded by two separate genes. In smooth muscle, only PKG-I is expressed and exists as two splice variants (PKG-I α and PKG-I β).

cGMP and/or PKG-I may induce relaxation via activation of the plasma membrane Ca²⁺-ATPase pump, inhibition of IP₃ generation, inhibition of Rho-kinase, stimulation of MLCP, and phosphorylation of heat shock proteins (Carvajal et al, 2000; Lincoln et al, 2001). These mechanisms have been demonstrated in various cells, but their relevance to smooth muscle cells in genital tissues has not been explicitly shown.

Cavernous smooth muscle strips from PKG-I knockout mice cannot be relaxed by agents that raise cGMP levels, and these mice have a low ability to reproduce, presumably owing to ED (Hedlund et al, 2000a). This observation further affirms the essential role of the cGMP/PKG-I pathway in physiologic erection.

Cyclic Adenosine Monophosphate–Signaling Pathway. cAMP-signaling molecules include adenosine, calcitonin gene-related peptides (CGRPs), prostaglandins, and VIP.

Adenosine. Adenosine is released from various cells as a result of increased metabolic rates, and its actions on the vasculature are most prominent when oxygen demand is high (Tabrizchi and Bedi, 2001). However, the vascular response to the action of adenosine can be either relaxation or constriction, depending on which type of adenosine receptor is activated. Four adenosine receptor subtypes (A₁, A_{2A}, A_{2B}, and A₃) belonging to the GPCR superfamily have been recognized at the present time (Tabrizchi and Bedi, 2001). In general, the A₁ receptor is believed to be coupled to G_i and G_o proteins, and its activation results in inhibition of adenylyl cyclase and activation of phospholipase C, both of which lead to vasoconstriction. The A₂ receptors are coupled to the G_s proteins, and their activation stimulates adenylyl cyclase and vasorelaxation. The A₃ receptor is coupled to G_i and G_q proteins, and its activation results in the activation of phospholipase C/D and the inhibition of adenylyl cyclase, leading to vasoconstriction. The differential distribution of these adenosine receptor subtypes largely determines whether a particular vessel relaxes or contracts as a result of adenosine stimulation (Tabrizchi and Bedi, 2001). Whether adenosine plays a role in physiologic erection is unclear. Nevertheless, excessive adenosine accumulation in the penis, coupled with increased A_{2B} receptor signaling, contributes to priapism in two independent lines of mutant mice. One is adenosine deaminase-deficient mice (the animals display spontaneously prolonged penile erection), and the other is sickle cell disease transgenic mice, a well-accepted animal model for priapism (Bivalacqua et al, 2009; Dai et al, 2009).

Calcitonin Gene-Related Peptide Family. CGRP, amylin, and adrenomedullin are members of the CGRP family. These short-chain peptides are potent vasodilators released from perivascular nerve fibers. They act through the calcitonin receptor–like receptor, which belongs to the GPCR superfamily (Conner et al, 2002).

In rats, CGRP levels in the penis, bladder, kidney, testis, and adrenal gland were found to increase gradually up to maturity and then rapidly decline (Wimalawansa, 1992). In patients with ED given CGRP via intracavernous injection, a dose-related increase in penile arterial inflow (and erection) occurred (Stief et al, 1991). Adenovirus-mediated gene transfer of CGRP also enhanced erectile

responses in aged rats, apparently through an increase of cAMP levels in the corpora cavernosa (Bivalacqua et al, 2001).

Prostaglandins. Prostaglandins are a family of eicosanoids capable of initiating numerous biologic functions. The prime mode of prostaglandin action is through specific prostaglandin receptors that all belong to the GPCR family. There are at least nine known prostaglandin receptor subtypes in mice and humans and several additional splice variants with divergent carboxyl termini (Narumiya and FitzGerald, 2001). Four of the subtypes (EP1 to EP4) bind PGE₂, two (DP1 and DP2) bind PGD₂, and the other three subtypes (FP, IP, and TP) bind PGF_{2α} (FP), PGI₂ (IP), and TXA₂ (TP). On the basis of signaling attributes, the prostaglandin receptors are classified into three types. The “relaxant” receptors IP, DP1, EP2, and EP4 are coupled to an α_s-containing G protein and are capable of stimulating adenyl cyclase to increase intracellular cAMP. The “contractile” receptors EP1, FP, and TP are coupled to an α_i-containing G protein, which activates phospholipase C instead of adenyl cyclase. These contractile receptors do not signal through the cAMP pathway, and their signaling outcome is an increase of intracellular calcium. The EP3 receptor is also a contractile receptor, but it is coupled to an α_i-containing G protein that inhibits adenyl cyclase to result in a decrease of cAMP formation.

Animal and human corpora cavernosa produce several prostaglandins including PGF_{2α}, PGE₂, PGD₂, PGI₂, and TXA₂ (Moreland et al, 2001). In studies in isolated human penile tissue, different PGs have been shown to elicit different effects in human corpus cavernosum, corpus spongiosum, and cavernous artery (Hedlund and Andersson, 1985). Although PGF_{2α}, PGI₂, and TXA₂ contract the corpus cavernosum and corpus spongiosum, PGE₁ and PGE₂ (but not PGI₂) relax the corpus cavernosum and spongiosum that have been precontracted with noradrenaline or PGF_{2α}. Although PGI₂ is the predominant vasorelaxant in blood vessels, its action in the erectile tissue is either contractile or neutral. This disparity in the action of PGI₂ between blood vessels and the erectile tissue and the difference between the effects of PGI₂ and PGE₁ and PGE₂ in the erectile tissue are most likely due to differences in the distribution of prostaglandin receptors. Other studies have shown that in the corpus cavernosum, the relaxant effects of prostanoids are mediated by EP2 and/or EP4 receptors (for PGE₁ and PGE₂) but not IP receptor (for PGI₂) (Angulo et al, 2002).

Although the production of prostaglandins and the expression of prostaglandin receptors in the erectile tissue have been clearly demonstrated, their roles in physiologic erection are still undefined. The erectogenic effects of PGE₁ as a pharmaceutical agent have been extensively documented. First described in 1998, intracavernous injection of PGE₁ is one of the safest and most effective treatments for ED (Stackl et al, 1988). Transurethral application is an alternative.

Vasoactive Intestinal Peptide. The human or animal penis is richly supplied with nerves containing VIP and VIP-related peptides such as pituitary adenylate cyclase-activating polypeptide. Most of these nerves also contain immunoreactivity to NOS, and colocalization of NOS and VIP within nerves innervates the penises of both animals and humans (Andersson, 2001). Two subtypes of VIP receptors, VPAC1 and VPAC2, belonging to the GPCR family have been cloned from human and rat tissues. VPAC2, but not VPAC1, messenger RNA has been identified in cultured rat cavernous smooth muscle cells (Guidone et al, 2002). In dogs, intracavernous VIP injection has been found to induce penile erection (Juenemann et al, 1987b); in men, it has not produced rigid erection, but success rates are improved when VIP is combined with papaverine and phentolamine (Kiely et al, 1989). However, it has been shown that VIP release is not essential for neurogenic relaxation of human cavernous smooth muscle (Pickard et al, 1993), and the physiologic role of VIP in penile erection has not been resolved.

Adenylyl Cyclase. Signaling molecules in the cAMP pathway bind to and activate specific cytoplasmic membrane receptors that, through their coupled G proteins, activate adenylyl cyclases. To date, nine membrane-bound isoforms and one soluble form of mammalian adenylyl cyclase have been cloned and characterized (Patel et al, 2001). Although different membrane-bound adenylyl cyclases

are regulated differently, they all are stimulated by the GTP-bound form of the G_a subunit, and all (except AC9) are stimulated by forskolin.

In rabbits with alloxan-induced diabetes, cAMP formation in the corpus cavernosum in response to forskolin has been shown to be reduced. This suggests impaired adenyl cyclase function in diabetes mellitus (Sullivan et al, 1998).

Protein Kinase A. Protein kinase A (PKA), also called cAMP-dependent kinase, is the principal receptor for cAMP, and it mediates most of the cellular effects of cAMP by phosphorylating a wide variety of downstream targets in the cytoplasmic and nuclear compartments (Johnson et al, 2001). PKA is composed of two regulatory (R) and two catalytic (C) subunits that form a tetrameric holoenzyme R₂C₂. Binding of cAMP to the R subunits causes the holoenzyme to dissociate into an R₂(cAMP)₄ dimer and two free catalytically active C subunits. The presence of multiple C subunit genes further adds to the diversity and complexity of the various holoenzyme complexes, which differ in biochemical and functional properties as well as patterns of expression and localization. These differences among the isozymes contribute to the broad specificity of PKA in a wide variety of physiologic processes in response to cAMP signaling.

More than 100 different cellular proteins have been identified as physiologic substrates of PKA, with more than 90% (135 of 145) being phosphorylated at serine and the remainder at threonine (Shabb, 2001). The predominant target sequence (>50%) is Arg-Arg-X-Ser, in which Ser is the phosphate acceptor. Three PKA substrate proteins have been identified in penile tissue: PDEs, cAMP-responsive element-binding protein, and ATP-sensitive potassium (K_{ATP}) channel.

Cross-Activation. Increased levels of intracellular cAMP and cGMP cause the activation of cAMP-dependent and cGMP-dependent protein kinases (PKA and PKG). Each cyclic nucleotide-dependent kinase can be activated by either cAMP or cGMP, although cross-activation requires an approximately 10-fold higher concentration of cyclic nucleotide (Walsh, 1994). Although PKA and PKG may phosphorylate numerous common substrates, several lines of evidence indicate that the activation of PKG by cGMP and cAMP is the predominant mechanism by which cyclic nucleotides decrease intracellular Ca²⁺ to cause vascular smooth muscle relaxation (Lincoln et al, 1990; Jiang et al, 1992; Komalavilas and Lincoln, 1996).

Phosphodiesterase. In each episode of cyclic nucleotide signaling, the increase of intracellular cAMP or cGMP concentration is typically twofold to threefold baseline (Francis et al, 2001). Decline occurs rapidly and often during the continued presence of the signaling hormone (Francis et al, 2001). Termination of cyclic nucleotide signals is principally carried out by PDEs, which catalyze the hydrolysis of cAMP and cGMP to AMP and GMP, respectively. Feedback mechanisms that increase PDE activities and/or expression by the increased cyclic nucleotide level assist cyclic nucleotide degradation (Corbin et al, 2000; Lin et al, 2001a, 2001b).

The superfamily of mammalian PDEs consists of 11 families (PDE1 to PDE11) that are encoded from 21 distinct genes (Lin et al, 2003; Montorsi et al, 2004). Each PDE gene usually encodes more than one isoform through alternative splicing or from alternative gene promoters. PDE1, PDE3, PDE4, PDE7, and PDE8 are multi-gene families, whereas PDE2, PDE5, PDE9, PDE10, and PDE11 are unigene families. PDE1, PDE2, PDE3, PDE10, and PDE11 hydrolyze cAMP and cGMP; PDE4, PDE7, and PDE8 hydrolyze cAMP; and PDE5, PDE6, and PDE9 hydrolyze cGMP.

With the exception of PDE6, which is specifically expressed in photoreceptor cells, all PDEs have been identified in the corpus cavernosum (Küthe et al, 2001). However, there is ample evidence that PDE5 is the principal PDE for the termination of cavernous cGMP signaling (Fig. 26-12), and inhibition of the cGMP-catalytic activity by PDE5 inhibitors is highly effective in treating ED.

PDE5 also appears to play a role in erection, as demonstrated by the erectogenic effect of a PDE3-specific inhibitor, milrinone (Küthe et al, 2002). Although direct inhibition of PDE5 is the main mechanism through which sildenafil exerts its erectogenic effect, it has been shown that sildenafil also significantly increases cAMP

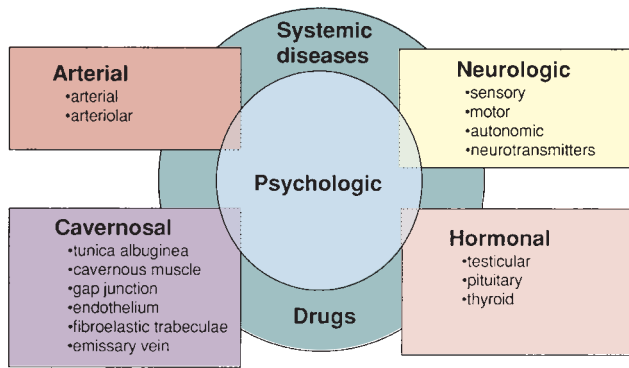


Figure 26-12. Functional classification of impotence. It is unlikely for impotence in an individual patient to derive solely from one source. Most cases have a psychogenic component of varying degree, and systemic diseases and pharmacologic effects can be concomitant and causative. (Modified from Carrier S, Brock G, Kour NW, et al. Pathophysiology of erectile dysfunction. Urology 1993;42:468–81, with permission of Excerpta Medica, Inc.)

concentration in isolated human cavernous tissue strips (Stief et al, 2000). This effect is thought to involve PDE3 because cGMP, which is accumulated as a result of PDE5 inhibition by sildenafil, is capable of preventing cAMP degradation by competing for the same catalytic sites on the PDE3 molecules (Francis et al, 2001). This attenuating effect of cGMP on the cAMP-catalytic activity of PDE3 is also believed to explain why inhibition of PKG could suppress the relaxing effect of forskolin in isolated human cavernous smooth muscle (Uckert et al, 2004).

Ion Channels. In general, there are four major types of ion channels: (1) external ligand-gated, which open to a specific extracellular molecule (e.g., acetylcholine); (2) internal ligand-gated, which open or close in response to an intracellular molecule (e.g., ATP); (3) voltage-gated, which open in response to a change in membrane potential (e.g., sodium, potassium, and calcium channels); and (4) mechanically gated, which open in response to mechanical pressure.

Smooth muscle has neither a T-tubule system nor a well-developed sarcoplasmic reticulum. Extracellular calcium plays an important role, and calcium must enter the cytoplasm through the plasma membrane during an action potential. Three transmembrane proteins are known to regulate calcium inflow and outflow: Calcium channels are the major inflow regulators, whereas the calcium-sodium exchanger and calcium-ATPase regulate calcium exit from muscle cells. The presence of voltage-dependent L-type calcium channels (long-duration current, slow calcium channel) in isolated cavernous smooth muscle and cultured muscle cells has been documented. Christ and colleagues (1993a) reported that both calcium influx through calcium channels and mobilization of intracellular calcium stores are involved during phenylephrine-induced and endothelin-induced contraction.

Studies have shown at least four types of potassium channel subtypes in the cavernous smooth muscle: (1) calcium-sensitive potassium channel (e.g., maxi-K); (2) metabolically regulated potassium channels (K_{ATP}); (3) delayed rectifier; and (4) fast transient A current (Christ et al, 1993a; Fan et al, 1995). The calcium-sensitive potassium channels may be involved in cAMP-mediated smooth muscle relaxation. Decreased intracytosolic potassium and altered potassium conductance have been shown to occur in corpus cavernosum smooth muscle treated with acetylcholine and sodium nitroprusside (Seftel et al, 1996). The movement of positively charged K^+ out of the cell causes hyperpolarization and relaxation of smooth muscle (Andersson, 2001).

Calcium-activated chloride channels on the smooth muscle cells of corpus cavernosum are thought to be involved in the maintenance of spontaneous tone and the contractile response to adrenaline and other agonists (Fan et al, 1999; Chu and Adaikan, 2008).

Hyperpolarization of Smooth Muscle Cells. Hyperpolarization causes closure of voltage-dependent calcium channels, a decrease in the intracellular free calcium concentration, and relaxation of the smooth muscle. One of the hyperpolarization mechanisms is through the opening of potassium channels. The opening of ATP-sensitive K^+ channels (K_{ATP}) and Ca^{2+} -activated K^+ channels (K_{Ca}) causes hyperpolarization and relaxation of vascular smooth muscle. These two types of channels are present in human corpus cavernosum smooth muscle (Christ et al, 1993b), and pharmacologic stimulation of K_{ATP} channels induces penile smooth muscle relaxation (Venkateswarlu et al, 2002). PNU-83757, an opener of K_{ATP} channels, has been shown to induce erection when administered intracavernously to patients with ED (Vick et al, 2002). The opening of large-conductance K_{Ca} channels, also known as maxi-K, has been found to hyperpolarize and relax human corpus cavernosum (Spekter et al, 2002). The opening of K^+ channels can be stimulated by PKA, PKG, or cGMP.

Hyperpolarization of penile smooth muscle is also important in endothelium-dependent relaxation of human penile arteries, in which significant relaxation remains despite blockade of NO and prostaglandin synthesis (Angulo et al, 2003b). This activity has been attributed to EDHF, which opens K_{Ca} channels and produces hyperpolarization and vasodilation. The nature of EDHF remains undetermined.

Molecular Oxygen as a Modulator of Penile Erection. The PO_2 level of cavernous blood in the flaccid state is similar to that of venous blood (≈ 35 mm Hg). During erection, the large inflow of arterial blood increases PO_2 to approximately 90 mm Hg (Sattar et al, 1995). Molecular oxygen is a substrate, together with L-arginine, for the synthesis of NO by NOS. In the flaccid state, the low oxygen concentration inhibits NO synthesis; during erection, the higher level of substrate induces NO synthesis. It has been estimated that the minimal concentration of oxygen in the cavernous bodies necessary to reach full NOS activity is 50 to 60 mm Hg (Kim et al, 1993).

Similarly, prostaglandin H synthase is also an oxygenase (cyclooxygenase) and uses oxygen as substrate for the synthesis of prostanooids. Production of PGE_1 has been shown to be inhibited in flaccidity and stimulated during erection. Endothelin synthesis is also modulated by oxygen: A low oxygen concentration promotes production, whereas a high concentration inhibits it.

Intercellular Communication. During erection and detumescence, communication should exist among cavernous smooth muscles to mediate synchronized relaxation and contraction (Christ et al, 1991). Several studies have demonstrated the presence of gap junctions in the membrane of adjacent muscle cells. These intercellular channels allow exchange of ions such as calcium and second-messenger molecules (Christ et al, 1993a). The major component of gap junctions is connexin-43, a membrane-sparing protein of less than 0.25 μm that has been identified between smooth muscle cells of human corpus cavernosum (Campos de Calvalho et al, 1993). Cell-to-cell communication through these gap junctions most likely explains the synchronized erectile response, although their pathophysiologic impact is still unclear.

Intracavernous Tissue Architecture

The trabeculae of the corpora cavernosa provide the structural support and regulatory mechanism for the endothelial-lined sinusoidal spaces as well as the conduit for blood vessels and nerves. Relaxation of the trabeculae allows the expansion and filling of the sinusoids by the incoming blood, whereas “recoil” of the trabeculae expels blood to the emissary veins and returns the penis to a flaccid state. In 24 men undergoing penile prosthesis implantation for severe ED, Nehra and colleagues (1996) categorized the smooth muscle content of the corpus cavernosum into four groups—high (39% to 42%), intermediate (30% to 37%), low (13% to 29%), and normal (42% to 50%)—and reported that increasing degree of venous leakage correlates with decreasing muscle content. In specimens from six men who died of nongenital causes, Costa and colleagues (2006) showed that the major constituents of the

trabeculae are collagen fibers (40.8%), smooth muscle (40.4%), and elastic fibers (13.2%). In seven men undergoing penile prosthesis implantation, the three components were composed of collagen fibers (41.6%), smooth muscle (42%), and elastic fibers (9.1%); the only significant change in men with ED compared with normal men was a reduction of elastic fibers. From these two reports, it seems likely that the histologic changes associated with ED consist primarily of decline in either smooth muscle or elastic fibers.

The complex architecture of the penis is maintained by the dynamic expression and interaction of numerous trophic factors. One is sonic hedgehog (SHH), which plays a key role in regulating vertebrate organogenesis, such as the growth of digits on limbs and organization of the brain. SHH remains important in adults. It controls cell division of adult stem cells and has been implicated in development of some cancers. SHH has been identified in the penis; inhibition of SHH in adult rats leads to rapid atrophy and disorganization of the corpus cavernosum (Podlasek et al, 2003, 2005). In addition, SHH has been shown to stimulate the expression of vascular endothelial growth factor (VEGF) and NOS in the penis (Podlasek et al, 2005) (Table 26-9).

KEY POINTS: SMOOTH MUSCLE PHYSIOLOGY

- Relaxation of the cavernous smooth muscle is the key to penile erection.
- NO released by nNOS contained in the terminals of the cavernous nerve initiates the erection process, whereas NO released from eNOS in the endothelium helps maintain erection.
- On entering the smooth muscle cells, NO stimulates the production of cGMP.
- cGMP activates PKG, which opens the potassium channels and closes the calcium channels.
- Low cytosolic calcium favors smooth muscle relaxation.
- The smooth muscle regains its tone when cGMP is degraded by PDE.

TABLE 26-9 Key Molecules Involved in Physiologic Regulation of Cavernous Smooth Muscle

CONTRACTION	
NAME	FUNCTION
High cytosolic calcium	Binds calmodulin to activate MLC kinase
MLC kinase	Converts MLC to active form, MLCP
Phosphorylated MLC (MLCP)	Cycling of myosin cross-bridges along actin results in muscle contraction
MLCP	Dephosphorylates MLCP to inactive form, MLC
Rho-kinase	Inhibits MLC phosphatase to enhance contraction (calcium sensitization pathway)
RELAXATION	
NAME	FUNCTION
Nitric oxide	Binds soluble guanylyl cyclase to produce cGMP
cGMP	Activates protein kinase G
Protein kinase G	Opens potassium channels and closes calcium channels
Low cytosolic calcium	Calcium dissociates from calmodulin, muscle relaxes

cGMP, cyclic guanosine monophosphate; MLC, myosin light chain; MLCP, myosin light chain phosphatase.

PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

"The Penis Poem"

*My nookie days are over, My pilot light is out.
What used to be my sex appeal, Is now my water spout.
Time was when, on its own accord, From my trousers it would
spring.
But now I've got a full time job, To find the gosh darn thing.
It used to be embarrassing, The way it would behave.
For every single morning, It would stand and watch me shave.
Now as old age approaches, It sure gives me the blues.
To see it hang its little head, And watch me tie my shoes!!*

– Willie Nelson

Incidence and Epidemiology

The increasing incidence of impotence with age was noted by Kinsey and colleagues in 1948: only 1 of 50 men at age 40 years, but 1 in 4 men by age 65. In 1990, Diokno and colleagues reported that 35% of married men 60 years old and older experienced erectile impotence.

Modern probability sampling techniques were used by two surveys obtaining prevalence data of ED in the United States: the Massachusetts Male Aging Study (MMAS) and the National Health and Social Life Survey (NHSLs). The MMAS consisted of 1709 non-institutionalized men between the ages of 40 and 70 years living in the greater Boston area first surveyed between 1987 and 1989 and resurveyed between 1995 and 1997 (Feldman et al, 1994; Johannes et al, 2000). Extensive physiologic measures, demographic information, and self-reported ED status (nine items related to potency on a questionnaire) were components of this report. The MMAS was the first cross-sectional, community-based, random-sample, multi-disciplinary epidemiologic survey on ED and its physiologic and psychosocial correlates in men in the United States. From the prevalence rates reported in the MMAS study, between the ages of 40 and 70 years, the probability of complete ED increased from 5.1% to 15%, the probability of moderate dysfunction increased from 17% to 34%, and the probability of mild dysfunction remained constant at about 17%.

The NHSLs was a national probability survey of men (N = 1410) and women between the ages of 18 and 59 years living in households in the United States in 1992 (Laumann et al, 1999) and was principally a broad-ranging inquiry into sexual practices and beliefs within that age group. The survey collected only limited information on sexual function broadly defined. The following prevalence rates for ED were reported (responses to questions regarding obtaining and maintaining erection): 7% for ages 18 to 29 years, 9% for ages 30 to 39, 11% for ages 40 to 49, and 18% for ages 50 to 59.

Regarding worldwide prevalence of ED, 24 international studies were reported between 1993 and 2003 (Lewis et al, 2004). All studies that were stratified by age showed an increasing prevalence of ED. For men younger than age 40, the rate was 1% to 9%; from 40 to 59, it ranged from 2% to 9% to 20% to 30%, with some studies showing marked differences between the 40 to 49 and the 50 to 59 age groups. The 50 to 59 age groups showed the greatest range of reported prevalence rates. For the 60 to 69 age group, most of the world showed a high rate (20% to 40%), with some showing increases after age 65 except for the Scandinavian reports, in which the 70s and older were the time of major rate change. Almost all of the reports showed high prevalence rates for men in their 70s and 80s, ranging from 50% to 75%.

Incidence Studies

The MMAS (Johannes et al, 2000) is the only longitudinal study conducted in the United States (1987-1989 and 1995-1997). Analyses were performed on 847 of the 1297 men without ED at baseline (1987-1989) and with follow-up information from 1995 to 1997. The average age of these men at baseline was 52.2 years (range 40 to 69 years). From this group of men, the crude incidence rate of impotence in white men in the United States was 25.9 cases/1000

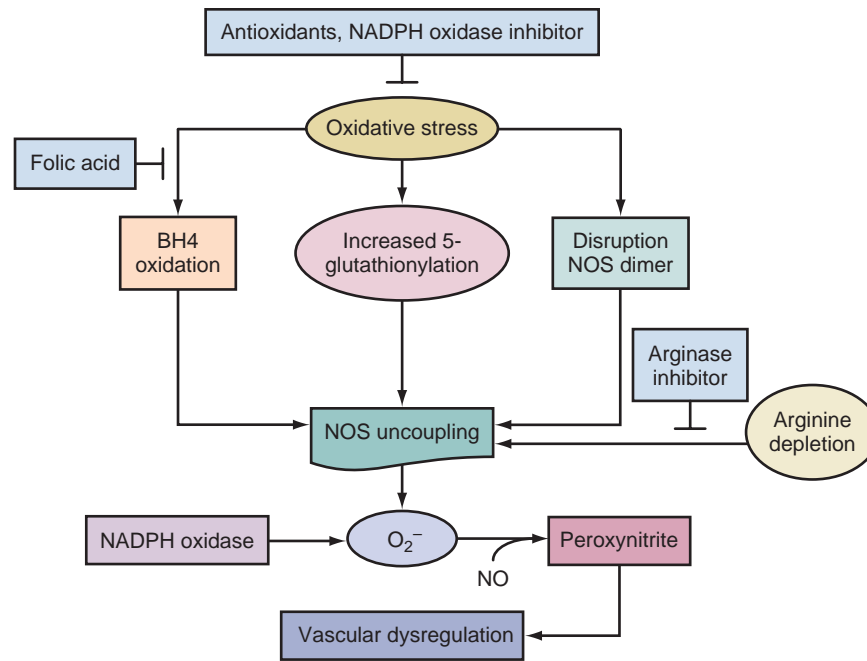


Figure 26-13. Factors contributing to nitric oxide synthase (NOS) uncoupling and the potential inhibitors. BH4, tetrahydrobiopterin; NADPH, reduced nicotinamide adenine dinucleotide phosphate.

man-years (95% confidence interval 22.5 to 29.9). The annual incidence rates increased with each decade (per 1000 man-years): 12.4 cases for 40 to 49 years, 29.8 cases for 50 to 59 years, and 46.4 cases for 60 to 69 years. Age-adjusted risk (per 1000 man-years) of ED was higher for men with diabetes mellitus (50.7 cases), treated heart disease (58.3 cases), and treated hypertension (42.5 cases). By using these data and the known population of the United States, it was estimated that, for white men, the new cases in the 40 to 69 age group would be 617,715 per year (Lewis et al, 2000). Rates reported from Europe and Brazil also suggest an incidence of 25 to 30 per 1000 man-years (Moreira et al, 2003; Schouten et al, 2005). A study using a validated questionnaire in a random sample of 2213 men conducted in Olmsted County, Minnesota, from 1996 to 2004 revealed that the five sexual function domains change together over time in this community-based cohort. Erectile function, ejaculatory function, and sexual drive decrease over time with greater rates of decline for older men. However, older men are less likely to perceive these declines as a problem and are less likely to express dissatisfaction referable to them (Gades et al, 2009).

Risk Factors

Common risk factor categories associated with sexual dysfunction include the following: general health status, diabetes mellitus, cardiovascular disease, concurrence of other genitourinary disease, psychiatric/psychological disorders, other chronic diseases, and sociodemographic conditions. In a study of race/ethnicity and socioeconomic status in 2301 men 30 to 79 years old from Boston, it was reported that men in the low socioeconomic status category had a greater than twofold increase in risk of ED (adjusted odds ratio 2.26, 95% confidence interval 1.39, 3.66). The increased risk of ED in black and Hispanic men in this study was thought to be associated with differences in socioeconomic status rather than biologic factors (Kupelian et al, 2008).

For ED, smoking, medications, and hormonal factors also serve as well-defined risk factors. In men, diabetes has been associated with a greater prevalence of decreased desire and orgasmic dysfunction as well as ED. A higher odds ratio is seen with insulin-dependent diabetes mellitus; diabetes present for more than 10

years; fair or poor control based on glycosylated hemoglobin; management by means other than diet; a history of diabetes-related arterial, renal, or retinal disease and neuropathy; and concurrent cigarette smoking. Endothelial dysfunction is a condition present in many cases of ED, and there are common etiologic pathways for other vascular disease states (Lewis et al, 2004).

Classification

Many classifications have been proposed (Fig. 26-13). Some are based on the cause (diabetic, iatrogenic, traumatic), and some are based on the neurovascular mechanism (failure to initiate [neurogenic], failure to fill [arterial], and failure to store [venous]) (Goldstein, personal communication, 1990). A classification recommended by the International Society of Impotence Research is shown in Box 26-1 (Lizza and Rosen, 1999).

Psychogenic

Previously, psychogenic impotence was believed to be the most common, thought to affect 90% of impotent men (Masters and Johnson, 1965). This belief has given way to the realization that ED is usually a mixed condition that may be predominantly functional or physical.

Sexual behavior and penile erection are controlled by the hypothalamus, limbic system, and cerebral cortex. Stimulatory or inhibitory messages can be relayed to the spinal erection centers to assist or inhibit erection. Two possible mechanisms have been proposed to explain the inhibition of erection in psychogenic dysfunction: direct inhibition of the spinal erection center by the brain as an exaggeration of the normal suprasacral inhibition (Steers, 2000) and excessive sympathetic outflow or elevated peripheral catecholamine levels, which may increase penile smooth muscle tone to prevent its necessary relaxation. Animal studies demonstrate that the stimulation of sympathetic nerves or systemic infusion of epinephrine causes detumescence of the erect penis (Diederichs et al, 1991a, 1991b). Clinically, higher levels of serum norepinephrine have been reported in patients with psychogenic ED than in normal controls or patients with vasculogenic ED (Kim and Oh, 1992).

BOX 26-1 Classification of Male Erectile Dysfunction**ORGANIC**

- I. Vasculogenic
 - A. Arteriogenic
 - B. Cavemosal
 - C. Mixed
- II. Neurogenic
- III. Anatomic
- IV. Endocrinologic

PSYCHOGENIC

- I. Generalized
 - A. Generalized unresponsiveness
 - 1. Primary lack of sexual arousability
 - 2. Aging-related decline in sexual arousability
 - B. Generalized inhibition
 - 1. Chronic disorder of sexual intimacy
- II. Situational
 - A. Partner-related
 - 1. Lack of arousability in specific relationship
 - 2. Lack of arousability owing to sexual object preference
 - 3. High central inhibition owing to partner conflict or threat
 - B. Performance-related
 - 1. Associated with other sexual dysfunction (e.g., rapid ejaculation)
 - 2. Situational performance anxiety (e.g., fear of failure)
 - C. Psychological distress or adjustment related
 - 1. Associated with negative mood state (e.g., depression) or major life stress (e.g., death of partner)

Bancroft and Janssen (2000) theorized that male sexual response depends on the balance between excitatory and inhibitory impulses within the CNS. One example is the high prevalence of sexual dysfunction/ED in men with psychiatric disorders. Mosaku and Ukpong (2009) surveyed patients (mean age 39.6, standard deviation 11.6 years) with a diagnosis of schizophrenia, bipolar affective disorder, recurrent depressive disorder, and/or substance use disorder with mean duration of illness of 10.24 years (standard deviation 8.2 years) who were attending a psychiatry clinic. In this population, the prevalence of ED was 83%; older age, unmarried status, use of medications, and the presence of comorbid medical conditions were significantly predictive of ED.

Neurogenic

It has been estimated that 10% to 19% of ED is neurogenic. If one includes iatrogenic causes and mixed ED, the prevalence is likely much higher. The presence of a neurologic disorder or neuropathy does not exclude other causes, and confirming that ED is neurogenic can be challenging. Because erection is a neurovascular event, any disease or dysfunction affecting the brain, spinal cord, and cavernous or pudendal nerves can induce dysfunction.

As discussed earlier, the MPOA, PVN, and hippocampus have been regarded as important integration centers for sexual drive and erection (Sachs and Meisel, 1988), and pathologic processes in these regions, such as Parkinson disease, stroke, encephalitis, or temporal lobe epilepsy, are often associated with ED. The effect of parkinsonism may result from the imbalance of the dopaminergic pathways (Chaudhuri and Schapira, 2009). Other brain lesions associated with ED are tumors, dementias, Alzheimer disease, multiple system atrophy, and trauma. In studies of sexual function in men after stroke, lack of sexual desire was found to be common (Jung et al, 2008). ED is more prevalent in patients who have cerebrovascular accident lesions in the thalamic area (Jeon et al, 2009).

In men with a spinal cord injury, the nature, location, and extent of the injury largely determine erectile function. In addition to ED, these men may have impaired ejaculation and orgasm. Reflexogenic erection is preserved in 95% of patients with complete upper cord lesions but in only about 25% of patients with complete lower cord lesions (Biering-Sørensen and Sønksen, 2001). Sacral parasympathetic neurons are important in the preservation of reflexogenic erection, although the thoracolumbar pathway may compensate for sacral loss through synaptic connections. In these patients, minimal tactile stimulation can trigger erection, albeit of short duration and requiring continuous stimulation. Other disorders at the spinal level (e.g., spina bifida, disk herniation, syringomyelia, tumor, transverse myelitis, and multiple sclerosis) may affect the afferent or efferent neural pathway in a similar manner.

Because of the close relationship between the cavernous nerves and the pelvic organs, the incidence of iatrogenic impotence from pelvic surgical procedures is reportedly high: radical prostatectomy, 43% to 100% (Walsh and Donker, 1982; Borchers et al, 2006), and abdominal perineal resection, 15% to 100% (Weinstein and Roberts, 1977).

An improved understanding of the neuroanatomy of the pelvic and cavernous nerves (Walsh and Donker, 1982) has resulted in modified surgery for cancer of the rectum, bladder, and prostate, producing a lower incidence of iatrogenic impotence. For example, the introduction of nerve sparing has reduced the incidence of impotence to 30% to 50% after radical prostatectomy (Catalona and Bigg, 1990; Quinlan et al, 1991) and less than 10% after radical rectal surgery (Liang et al, 2008).

In cases of pelvic fracture, ED can be a result of cavernous nerve injury or vascular insufficiency or both. In men with posterior urethral injury, early realignment has been associated with better potency preservation rate relative to delayed anastomosis (ED rate 34% vs. 42%) (Mouraviev et al, 2005). In diabetics, impairment of neurogenic and endothelium-dependent relaxation results in inadequate NO release (Saenz de Tejada et al, 1989a). Because autonomic penile innervation cannot be tested directly, clinicians should be cautious in diagnosing neurogenic ED. A corpus cavernosum electromyograph has been developed and refined for diagnosis of various conditions affecting the penis (including autonomic neuropathy), but the clinical utility of this device is still under investigation (Guiliano and Rowland, 2013).

A decrease in penile tactile sensitivity with increasing age was also reported by Rowland and colleagues (1993). Sensory input from the genitalia is essential to achieve and maintain reflexogenic erection, and the input becomes even more important when older people gradually lose psychogenic erection. Sensory evaluation should be an integral part of the evaluation for ED in all patients with or without an apparent neurologic disorder.

Endocrinologic

Hypogonadism is a frequent finding in impotent patients. Androgens influence the growth and development of the male reproductive tract and secondary sex characteristics; their effects on libido and sexual behavior are well established. In a review of published articles from 1975 to 1992, Mulligan and Schmitt (1993) concluded that testosterone (1) enhances sexual interest, (2) increases the frequency of sexual acts, and (3) increases the frequency of nocturnal erection but has little or no effect on fantasy-induced or visually stimulated erections. Granata and colleagues (1997) reported that the threshold level of testosterone for normal nocturnal erections is about 200 ng/dL. In a population-based, observational survey conducted in the Boston area, Araujo and colleagues (2007) reported a 5.6% prevalence of symptomatic androgen deficiency in men between the ages of 30 and 79 years, with older men at greater risk. Prevalence of symptoms was as follows: low libido, 12%; ED, 16%; osteoporosis/fracture, 1%; and two or more nonspecific symptoms, 20%. However, many men with low testosterone levels are asymptomatic. In a study of patients presenting with ED, Köhler and colleagues (2008) reported androgen

deficiency symptoms in 47% of men with testosterone levels of less than 200 ng/dL, 33% of men with levels less than 300 ng/dL, 23% of men with levels less than 346 ng/dL, and 7% of men with levels less than 400 ng/dL. Age, the presence of uncontrolled diabetes, high total cholesterol, and anemia all correlated with significantly decreased testosterone levels in men with ED. In another report from the same group, waist circumference was noted to be the most important predictor of low testosterone and symptomatic androgen deficiency (Hall et al, 2008). In men with a body mass index (BMI) of more than 30 kg/m², total testosterone was subnormal in 57.5%, and free testosterone subnormal in 35.6%. Most of these men had isolated hypogonadotropic hypogonadism (Hofstra et al, 2008). In a comprehensive literature review, Traish and colleagues (2009) noted that low testosterone precedes elevated fasting insulin, glucose, and hemoglobin A_{1c} values in men who develop diabetes, suggesting that hypogonadism may be a sentinel event in the development of diabetes. The authors further suggested that androgen deficiency is associated with insulin resistance, type 2 diabetes, metabolic syndrome, and increased deposition of visceral fat. Visceral fat may serve as an endocrine organ, producing inflammatory cytokines and promoting endothelial dysfunction and vascular disease.

The mechanism of androgen's effect has been examined by several investigators. Beyer and González-Mariscal (1994) reported that testosterone and dihydrotestosterone (DHT) are responsible for male pelvic thrusting and estradiol or testosterone is responsible for female pelvic thrusting during copulation. Androgens have beneficial effects on endothelial cells and smooth muscle cells: Androgens promote endothelial cell survival, reduce endothelial expression of proinflammatory markers, and inhibit proliferation and intimal migration of vascular smooth muscle cells. Low androgen levels are associated with apoptosis of endothelial cells and smooth muscle cells. Low androgen levels also impair proliferation, migration, and homing of endothelial progenitor cells as well as myogenic differentiation of mesenchymal progenitor cells (Mirone et al, 2009; Traish and Galoosian, 2013). Testosterone and DHT may also relax penile artery and cavernous smooth muscle through their nongenomic effects (Waldkirch et al, 2008). In rats, castration has been reported to decrease arterial flow, induce venous leakage, and reduce the erectile response to stimulation of the cavernous nerve by about 50% (Mills et al, 1994; Penson et al, 1996). Castration also increases α -adrenergic responsiveness of penile smooth muscle (Traish et al, 1999). Clinically, many men receiving long-term androgen ablation therapy for prostate cancer have reported poor libido and ED.

Any dysfunction of the hypothalamic-pituitary axis can result in hypogonadism. Hypogonadotropic hypogonadism can be congenital or caused by a tumor or injury. Hypergonadotropic hypogonadism may result from a tumor, injury, surgery, or mumps orchitis.

Hyperprolactinemia, whether secondary to a pituitary adenoma or drugs, results in both reproductive and sexual dysfunction. Symptoms may include loss of libido, ED, galactorrhea, gynecomastia, and infertility. Hyperprolactinemia is associated with low circulating levels of testosterone, which appear to be secondary to inhibition of gonadotropin-releasing hormone secretion by the elevated prolactin levels (Leonard et al, 1989). In a study of subjects consulting for sexual dysfunction, prolactin in the lowest quartile levels was noted to be associated with metabolic syndrome and arteriogenic ED as well as with premature ejaculation and anxiety symptoms (Corona et al, 2009).

ED may also be associated with hyperthyroidism and hypothyroidism. Hyperthyroidism is commonly associated with diminished libido (which may be caused by the increased circulating estrogen levels) and less often with ED. In hypothyroidism, low testosterone secretion and elevated prolactin levels contribute to ED.

Arteriogenic

Atherosclerotic or traumatic arterial occlusive disease of the hypogastric-cavernous-helicine arterial tree can decrease the

perfusion pressure and arterial flow to the sinusoidal spaces, increasing the time to maximal erection and decreasing the rigidity of the erect penis. In most patients with arteriogenic ED, the impaired penile perfusion is a component of the generalized atherosclerotic process. Common risk factors associated with arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, blunt perineal or pelvic trauma, and pelvic irradiation (Feldman et al, 1994; Martín-Morales et al, 2001). Shabsigh and colleagues (1991) reported that abnormal penile vascular findings increased significantly as the number of risk factors for ED increased. On arteriography, bilateral diffuse disease of the internal pudendal, common penile, and cavernous arteries has been found in ED patients with atherosclerosis. Focal stenosis of the common penile or cavernous artery is most often seen in young patients who have sustained blunt pelvic or perineal trauma (Levine et al, 1990). Long-distance cycling is also a risk factor for vasculogenic and neurogenic ED. There is a significant relationship between cycling-induced perineal compression leading to vascular, endothelial, and neurogenic dysfunction in men and the development of ED (Sommer et al, 2010). Nevertheless, ED does not commonly occur in men who engage in recreational bicycle riding (Kim et al, 2011).

ED and cardiovascular disease share the same risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, and smoking (Feldman et al, 1994; Martín-Morales et al, 2001). Lesions in the pudendal arteries are much more common in men with ED than in the general population of similar age. Natural remission and progression occur in a substantial number of men with ED. The association of BMI with remission and progression and the association of smoking and health status with progression offer potential avenues for facilitating remission and delaying progression using lifestyle intervention (Travison et al, 2007).

Cardiovascular Diseases. High prevalence of ED has been reported in men with coronary, cerebral, and peripheral vascular diseases (Bener et al, 2008; Chai et al, 2009). Among men with coronary arterial disease, the prevalence of ED increases as the severity of coronary arterial lesions increases (Montorsi et al, 2006). Several studies reported an association between ED and cardiovascular disease. The link between these conditions might reside in the interaction between androgens, chronic inflammation, and cardiovascular risk factors that determines endothelial dysfunction and atherosclerosis, resulting in disorders of penile and coronary circulation. Because penile artery size is smaller compared with coronary arteries, the same level of endothelial dysfunction causes a more significant reduction of blood flow in erectile tissues compared with that in coronary circulation. ED could be an indicator of systemic endothelial dysfunction (Gandaglia et al, 2014). In patients with chronic coronary disease who also had ED, onset of sexual dysfunction occurred before coronary artery disease onset in 93%, with a mean time interval of 24 months (range 12 to 36 months) (Montorsi et al, 2006). These data have led some authors to advocate screening for ED as a means to identify men at risk for cardiovascular disease (Gandaglia et al, 2014).

Hyperlipidemia. ED has been associated with a high prevalence of hyperlipidemia and coronary heart disease (Roumeguere et al, 2003). Hypercholesterolemia at baseline was also shown to be a predictor of subsequent ED over the course of 25 years in 570 male patients included in the Rancho Bernardo Study (Fung et al, 2004). A survey of 1899 men 30 to 79 years old in the Boston area did not show an association between untreated hyperlipidemia and ED (Hall et al, 2009).

The effect of hypercholesterolemia on erectile function has been studied in different experimental models. In hypercholesterolemic rabbits, examination of the corpus cavernosum ultrastructure revealed an early atherosclerotic process in the sinusoids (Kim et al, 1994). Although the endothelial NO/cGMP pathway is impaired in this model, neuronal vasodilation does not appear to be affected (Azadzoi et al, 1998). The NO/cGMP pathway effect likely is due to increased superoxide production (Kim et al, 1997) or endogenous NOS inhibitors such as NG-monomethyl-L-arginine monoacetate and asymmetrical dimethylarginine (ADMA).

L-Arginine supplementation reverses impairment of endothelium-dependent relaxation (Azadzo et al, 1998). VEGF is an important angiogenic factor for maintenance of endothelial health. Ryu and colleagues (2006) reported that VEGF and VEGF receptor 2 are downregulated in the corporeal tissue of rats eating a 4% cholesterol diet for 3 months. Xie and colleagues (2005) noted that levels of VEGF mRNA are reduced with subsequent observation of impaired endothelium-dependent relaxation in rabbits fed with a 1% cholesterol diet.

In a more severe ischemic experimental model, rabbits underwent balloon de-endothelialization of the iliac arteries followed by a high-cholesterol diet (Azadzo et al, 1992). The rabbits developed penile arterial insufficiency and veno-occlusive dysfunction owing to decreased expandability of the cavernous smooth muscle (Azadzo et al, 1997; Nehra et al, 1998). Changes in iliac and penile vasculature were noted, associated with decreased NOS activity and reduced endothelium-dependent and neurogenic NO-mediated relaxation of the cavernous tissue (Azadzo et al, 1999). As a result of the impaired NO activity, production of contractile thromboxane and prostaglandin increased, leading to potentiation of neurogenic contractions of the cavernous smooth muscle (Azadzo et al, 1998, 1999).

In large arteries in rabbits, oxidized low-density lipoproteins inhibited endothelium-dependent NO-mediated relaxation (Murohara et al, 1994). Enhanced corpus cavernosum muscle contractility by oxidized low-density lipoproteins has also been reported by Ahn and colleagues (1999).

Obesity. In a U.S. study of community-dwelling men 65 years old and older, Garimella and associates (2013) reported prevalence of complete ED of 42% in men who completed MMAS scale (N = 4108). In sexually active men who completed the five-item International Index of Erectile Function (IIEF-5) questionnaire (N = 1659) the prevalence of moderate to severe ED was 56%. In multivariate-adjusted analyses, high body weight, BMI, and total body fat percentage were independently associated with greater prevalence of moderate to severe and complete ED.

Perivascular adipose tissue (PVAT) is recognized as an active contributor to vascular function. Adipocytes and stromal cells contained within PVAT are sources of molecules with varied paracrine effects on the underlying smooth muscle and endothelial cells, including adipokines, cytokines, reactive oxygen species, and gaseous compounds. In obesity and diabetes, the expanded PVAT contributes to vascular insulin resistance. PVAT-derived cytokines may influence key steps of atherogenesis. The physiologic anticontractile effect of PVAT is severely diminished in hypertension. Above all, a common denominator of PVAT dysfunction in all these conditions is immune cell infiltration, which triggers the subsequent inflammation, oxidative stress, and hypoxic processes to promote vascular dysfunction (Szasz et al, 2013).

Hypertension. Hypertension is an independent risk factor for ED (Feldman et al, 1994; Johannes et al, 2000), and its consequent cardiovascular complications such as ischemic heart disease and renal failure are associated with even higher ED prevalence (Feldman et al, 1994; Kaufman et al, 1994; Johannes et al, 2000). However, in hypertension, the increased blood pressure itself does not impair erectile function; rather, the associated arterial biochemical and structural changes are thought to be the causes (Hsieh et al, 1989; Behr-Roussel et al, 2005). In two analyses including more than 270,000 men with ED from a U.S. care claim database, the prevalence of hypertension in men with versus without ED was 41.2% versus 19.2%, respectively (Seftel et al, 2004; Sun and Swindle, 2005).

The potential determinants for ED in hypertensive men include older age, longer duration of disease, greater severity of hypertension, and the use of antihypertensive medications (Dumas et al, 2006). Arterial hypertension is characterized by altered vascular tone and increased vascular contractility resulting in high blood pressure. It is accompanied by proliferation, migration of vascular smooth muscle cells, and varying levels of inflammation of the arterial wall. The Rho-kinase pathway plays a crucial role in the regulation of arterial blood pressure (Nunes et al, 2010).

Endothelial dysfunction, oxidative stress, and autoimmune diseases are also potential causes of arterial disease and ED. The Toll-like receptor activation on cells of the vasculature in response to the release of damage-associated molecular patterns and the consequences of this activation on inflammation, vasoreactivity, and vascular remodeling has been proposed as a novel link between inflammation and hypertension (McCarthy et al, 2014). In addition, endoplasmic reticulum stress leading to endothelium-dependent contractile responses in aorta has been proposed as a cause of hypertension in a spontaneously hypertensive rat (SHR) model (Spitler et al, 2013). Increased activity of angiotensin II-mediated reduced nicotinamide adenine dinucleotide phosphate oxidase in hypertensive rats is suggested to be the cause of increased superoxide anions (Jin et al, 2008).

Mechanism of Vascular Erectile Dysfunction

Structural Changes. In arteriogenic ED, oxygen tension in corpus cavernosum blood is less than that in psychogenic ED (Tarhan et al, 1997). Formation of PGE₁ and PGE₂ is oxygen dependent, and in rabbit and human corpus cavernosum, increased oxygen tension was associated with elevation of PGE₂ and suppression of TGF- β 1-induced collagen synthesis (Moreland et al, 1995; Nehra et al, 1999). A decrease in oxygen tension may diminish cavernous trabecular smooth muscle content and lead to diffuse venous leakage (Saenz de Tejada et al, 1991b; Nehra et al, 1998).

A narrowed lumen or increased wall/lumen ratio in the arteries contributes to increased peripheral vascular resistance in hypertension. Increased resistance has also been found in the penile vasculature of SHR—an alteration ascribed to structural changes of the arterial and erectile tissue (Gradin et al, 2006; Arribas et al, 2008). Mitochondrial damage (in smooth muscle and endothelial cells) and nerve degeneration have been described in SHR (Jiang et al, 2005). Partial success in the prevention or reversal of the structural changes has been described when rats were treated with a type 1 angiotensin II receptor (AT1) blocker; an AT1 blocker with a PDE5 inhibitor; and a selective β_1 blocker, nebivolol (Mazza et al, 2006; Toblli et al, 2006a, 2006b).

Enhanced Smooth Muscle Contraction and Vasoconstriction. In animal models, increased RhoA/Rho-kinase activity leading to increased contractility of the corporeal smooth muscle is proposed to contribute to ED in diabetes (Bivalacqua et al, 2004), hypercholesterolemia (Morikage et al, 2006), hypertension (Fibbi et al, 2008), hypogonadism (Vignozzi et al, 2007), and aging (Jin et al, 2006; Andersson, 2011). Park and coworkers (2006) found that the Rho/Rho-kinase pathway is substantially involved in the development of ED and pelvic atherosclerosis, both of which could be prevented by long-term treatment with fasudil, a Rho-kinase inhibitor.

Endothelin-1 levels are elevated in plasma of men with atherosclerosis, hypertension, and hypercholesterolemia. Men with organic ED have higher venous and cavernous blood levels of endothelin-1 as well (Nohria et al, 2003; El Melegry et al, 2005). Despite this, a pilot study using an endothelin-A receptor antagonist as a treatment for men with ED did not produce positive results (Kim et al, 2002). AT1 receptor antagonist and angiotensin-converting enzyme (ACE) inhibitor have shown promise in the treatment of men with ED and hypertension and men with ED and atherosclerosis, respectively (Speel et al, 2005; Baumhäkel et al, 2008).

Impaired Endothelium-Dependent Smooth Muscle Relaxation. Endothelial dysfunction has been proposed as the common link between cardiovascular disease and ED (Brunner et al, 2005). Impairment of endothelium-dependent flow-mediated dilation of the brachial artery has been reported in men with ED, and the degree of impairment correlates with the severity of ED (Kovacs et al, 2008). A plethysmography device designed to assess endothelium-dependent vasodilation of the penis did not find a correlation between brachial and penile arteries in men with ED (Vardi et al, 2009).

Endothelial progenitor cells are regenerative cells produced in bone marrow that migrate to peripheral vessels to repair endothelial defects. The number of endothelial progenitor cells is reduced in

TABLE 26-10 Vascular and Structural Changes Leading to Erectile Dysfunction

PENILE STRUCTURE	CHANGES IN ERECTILE DYSFUNCTION
Cavernous artery	Increased vascular resistance, narrow lumen
Smooth muscle	Increased tone (hypertonicity) Decreases muscle content Alteration of potassium channels and gap junctions
Erectile tissue	Fibrosis Impaired veno-occlusive mechanism
Endothelium	Impaired endothelium-dependent relaxation
Tunica albuginea	Alteration of elastic and collagen fibers
Neurotransmitters	Decreased nNOS, eNOS

eNOS, endothelial nitric oxide synthase; nNOS, neuronal nitric oxide synthase.

men with ED and coronary heart disease and in overweight men (Foresta et al, 2005; Baumhäkel et al, 2006; Esposito et al, 2009). Short-term and long-term administration of PDE5 inhibitors increases the number of circulating endothelial progenitor cells and improves endothelial and erectile function (Foresta et al, 2005, 2009).

In SHR, the relaxing effect of acetylcholine is blunted in corporeal strips (Behr-Roussel et al, 2003). Impairment of endothelium-dependent relaxation in arteries from SHR could be ascribed to angiotensin II (Rajagopalan et al, 1996), thromboxane, and superoxide (Cosentino et al, 1998) or to high blood pressure per se (Paniagua et al, 2000) (Table 26-10).

Cavernous (Venogenic)

Failure of adequate venous occlusion has been proposed as one of the most common causes of vasculogenic impotence (Rajfer et al, 1988). Veno-occlusive dysfunction may result from various pathophysiologic processes, including degenerative tunical changes, fibroelastic structural alterations, insufficient trabecular smooth muscle relaxation, and venous shunts.

Degenerative changes (e.g., Peyronie disease, old age, and diabetes) or traumatic injury to the tunica albuginea (e.g., penile fracture) can impair the compression of the subtunical and emissary veins (Gonzalez-Cadavid, 2009). In Peyronie disease, the inelastic tunica albuginea may prevent the emissary veins from closing (Metz et al, 1983). Chiang and colleagues (1992) postulated that a decrease in the elastic fibers of the tunica albuginea and an alteration in the tunica albuginea microarchitecture may contribute to impotence in some men. Changes in the subtunical areolar layer may impair the veno-occlusive mechanism, as is occasionally seen in patients after surgery for Peyronie disease (Dalkin and Carter, 1991).

Structural alterations in the fibroelastic components of the trabeculae, cavernous smooth muscle, and endothelium may result in venous leakage. Insufficient trabecular smooth muscle relaxation, causing inadequate sinusoidal expansion and insufficient compression of the subtunical venules, may occur in anxious individuals with excessive adrenergic tone or in patients with inadequate neurotransmitter release. It has been shown that alteration of an α adrenoceptor or a decrease in NO release may heighten smooth muscle tone and impair relaxation in response to endogenous muscle relaxant (Christ et al, 1990).

Acquired venous shunts—the result of operative correction of priapism—may cause persistent glans/cavernosum or cavernosum/spongiosum shunting.

Fibroelastic Component. Loss of compliance of the penile sinusoids associated with increased deposition of collagen and decreased elastic fiber may be seen in diabetes, hypercholesterolemia, vascular disease, penile injury, or old age. Sattar and colleagues (1994) reported significant differences in the mean percentage of penile elastic fibers: 9% in normal men, 5.1% in patients with venous leakage, and 4.3% in patients with arterial disease. In an animal model of vasculogenic ED, Nehra and colleagues (1998) demonstrated that cavernous expandability correlates with smooth muscle content and may be used to predict trabecular histology. Moreland and colleagues (1995) showed that PGE₁ suppresses collagen synthesis by TGF- β 1 in human cavernous smooth muscle, which implies that intracavernous injection of PGE₁ may be beneficial in preventing intracavernous fibrosis.

Smooth Muscle. Because corporeal smooth muscle controls the vascular events leading to erection, a change in smooth muscle content and ultrastructure can be expected to affect erectile response. In a study of human penile tissue, Sattar and colleagues (1996) demonstrated a significant difference between the mean percentage of cavernous smooth muscle in normal potent men, stained with antidesmin (38.5%) or antiactin (45.2%), and that in a venogenic group (antidesmin, 27.4%; antiactin, 34.2%) or an arteriogenic group (antidesmin, 23.7%; antiactin, 28.9%). An in vitro biochemical study showed impaired neurogenic and endothelium-related relaxation of penile smooth muscle in impotent diabetic men (Saenz de Tejada et al, 1989a). In vasculogenic and neurogenic ED, the damaged smooth muscle can be a key factor, aggravating the primary cause (Mersdorf et al, 1991). Pickard and colleagues (1994) also showed impairment of nerve-evoked relaxation and α -adrenergic-stimulated contraction of cavernous muscle and reduced muscle content in men with venous or mixed venous/arterial impotence.

Ion channels are intimately involved in the biochemical events of muscle function. Fan and colleagues (1995) reported an alteration of the maxi-K⁺ channel in cells from impotent patients and suggested that this might contribute to decreased hyperpolarizing ability, altered calcium homeostasis, and impaired smooth muscle relaxation. In animal studies, Jünemann and colleagues (1991) showed significant smooth muscle degeneration with loss of cell-to-cell contact in rabbits fed a high-cholesterol diet for 3 months. In a rabbit model of vasculogenic impotence, Azadzoi and colleagues (1997) demonstrated that veno-occlusive dysfunction could be induced by cavernous ischemia. Cavernous nerve injury may also affect cavernous smooth muscle relaxation, as demonstrated in neurotomized dogs (Paick et al, 1991).

Gap Junctions. Gap junctions, intercellular communication channels, are responsible for synchronization and coordination of the erectile response (Christ et al, 1991). In severe arterial disease, the presence of collagen fibers between cell membranes reduces or abolishes their contact (Persson et al, 1989). Suadicani and colleagues (2009) reported a significant decrease of gap junction protein connexin 43 in the corpus cavernosum in aged and streptozotocin-induced diabetic rats.

Endothelium. It is now recognized that the endothelium is an important source of not only NO but also many other signaling molecules, including EDHF, PGI₂, and hydrogen peroxide. In addition, the endothelium, via transferred chemical mediators, such as NO and PGI₂, and/or low-resistance electrical coupling through myoendothelial gap junctions, modulates flow-mediated vasodilation and influences mitogenic activity, platelet aggregation, and neutrophil adhesion. Disruption of endothelial function is an early indicator of the development of vascular disease (Triggle et al, 2012). Diabetes and hypercholesterolemia have been shown to alter the function of endothelium-mediated relaxation of the cavernous muscle (Azadzoi et al, 1991) and impair erection. In a study of cell junction proteins in hypercholesterolemic mice, Ryu and colleagues (2013) reported downregulation of endothelium-specific cell-to-cell junction proteins, including claudin-5, vascular endothelial-cadherin, and platelet endothelial cell adhesion molecule 1, as well as decreased endothelial content, which may contribute to ED in these mice.

Maintenance of Structural Integrity. SHH is one of three proteins in the mammalian hedgehog family, the others being desert hedgehog and Indian hedgehog. SHH plays a key role in regulating vertebrate organogenesis, such as in the growth of digits on limbs and organization of the brain. SHH is also important in adults. It controls cell division of adult stem cells and has been implicated in development of some cancers. SHH has been shown to regulate cavernous smooth muscle apoptosis in response to signals from cavernous nerve. In an animal model of neurogenic ED, SHH protein treatment of the penis prevents cavernous nerve injury-induced apoptosis and structural changes (Podlasek, 2009).

Markers of Erectile Function. Variable coding sequence protein A1 (Vcsa1) has been proposed as a marker of erectile function in rats. Vcsa1 is downregulated in animal models of neurogenic, diabetic, and aging-associated ED. The Vcsa protein product sialorphin is an endogenous neutral endopeptidase inhibitor. In humans, there are at least three homologues to the Vcsa1 gene (hSMR3A, hSMR3B, and PROL1). Downregulation of hSMR3A has been reported in men with ED (Davies and Melman, 2008).

Various cardiovascular risk factors have been associated with the onset and the severity of ED, including markers of endothelial function, thrombosis, and dyslipidemia. These markers can be used as a cardiometabolic risk profile in patients with ED. Although NO, ADMA, and endothelin and genetic polymorphisms hold some promise as biochemical markers of cardiovascular disease and ED, these are still in development (Lippi et al, 2012).

Drug-Induced

ED is common among older men and inevitably coexists with other conditions that are themselves risk factors for ED, such as depression, diabetes, and cardiovascular disease (Feldman et al, 1994). In addition, sexual symptoms related to medication can involve a combination of complaints concerning desire, arousal, and orgasm rather than being limited to impaired function. Self-reported and questionnaire data concerning ED as a side effect of medication should be interpreted with caution.

Antihypertensive Agents. Almost all antihypertensive drugs have ED listed as a potential side effect. Nevertheless, more recent well-designed controlled clinical trials have clarified some myths.

Diuretics. Thiazide diuretics are carbonic anhydrase inhibitors that alkalinize cells and cause vasodilation. The predominant activity of thiazide diuretics is to inhibit a directly coupled Na-Cl cotransporter along the distal convoluted tubule of the kidney. Acutely, when extracellular fluid volume depletion occurs because of salt wasting, cardiac output tends to decline, resulting in reactive vasoconstriction. However, on a long-term basis, cardiac output is regulated according to metabolic needs, and vasodilation supervenes, returning cardiac output toward baseline; this transforms hypotension from hypovolemic to vasodilatory (Ellison et al, 2009).

This class of drug has been extensively studied. Data from a large trial in the United Kingdom showed that twice as many men taking thiazides for mild hypertension reported ED than men taking propranolol or placebo—the most common reason for withdrawal from the bendrofluazide arm of the study (“Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension,” 1981).

Similar findings were documented from the Treatment of Mild Hypertension Study (TOMHS), where the prevalence of ED at 2 years in men taking low-dose thiazide was twice that of men taking placebo or alternative agents (Grimm et al, 1997). After 4 years of treatment, the prevalence of ED in the placebo group approached that of the thiazide group, a finding not fully explained by dropouts. It may be that thiazide therapy, rather than causing ED directly, unmasks it at an earlier stage. A study comparing sexual side effects of thiazide, placebo, or atenolol in hypertensive patients also found a higher rate of ED in the thiazide group, although this was ameliorated by weight loss (Wassertheil-Smoller et al, 1991). The mechanism of diuretic-induced ED remains to be elucidated.

β -Adrenergic Blockers. Receptor studies show that only 10% of adrenoceptors in the penile tissue are of the β type, and their

stimulation is thought to mediate relaxation (Andersson and Wagner, 1995). This response is attenuated *in vitro* by nonselective drugs such as propranolol, possibly via a prejunctional β_2 -receptor effect (Srilatha et al, 1999), but not by cardiac-selective agents such as practolol. β antagonists also exert an inhibitory effect within the CNS, perhaps leading to decreased sex hormone levels (Suzuki et al, 1988).

The differential effects of β -adrenoceptor antagonists on erectile function may be explained by whether they are general antagonists, are selective antagonists, or possess vasodilatory properties. Non-selective drugs such as propranolol are associated with higher prevalence of ED compared with prevalence of ED observed in patients treated with placebo or ACE inhibitors (Croog et al, 1986). Subsequent trials using agents with higher selectivity for the β_1 adrenoceptor such as acebutolol have shown a substantial reduction in ED with no difference between placebo and ACE inhibitor groups (Grimm et al, 1997). Carvedilol, a general β -adrenoceptor antagonist that also causes vasodilation by blocking α_1 adrenoceptors, has been associated with worsening sexual function (Fogari et al, 2001). Some more recently introduced β_1 -adrenoceptor antagonists, such as nebivolol, have vasodilatory effects mediated by release of NO (Reidenbach et al, 2007). In crossover studies using nebivolol versus the selective β_1 -adrenoceptor antagonists metoprolol and atenolol, nebivolol did not decrease sexual intercourse activity in hypertensive men and in some cases had positive effects on erectile function (Boydak et al, 2005; Brixius et al, 2007).

α -Adrenoceptor Blockers. Animal studies have demonstrated a positive effect on erection for α antagonists, particularly antagonists acting on the α_1 receptor, by increasing or prolonging the relaxant response of cavernous smooth muscle (Andersson and Wagner, 1995). In addition, prejunctional α_2 receptor activation modulates the release of noradrenaline, suggesting a putative relaxant role for α_2 blockers. In clinical observations, drugs such as doxazosin, used to treat hypertension (Grimm et al, 1997) or reduce urinary tract symptoms (Flack, 2002), were not associated with complaints of ED and had lower rates than in placebo groups. Drugs stimulatory to the α_2 receptor, such as clonidine, result in diminished erectile function clinically and experimentally by peripheral and central mechanisms (Srilatha et al, 1999). Methyldopa, a centrally acting drug, has also been associated with ED in controlled trials comparing it with placebo and other antihypertensive agents (Croog et al, 1988), and it may act by antagonizing hypothalamic α_2 adrenoceptors.

Angiotensin-Converting Enzyme Inhibitors. ACE inhibitors lack any easily appreciated peripheral or central effect that would interfere with sexual function. An *in vivo* experiment showed that the ACE inhibitor captopril did not cause any significant adverse effect on sexual function in awake normotensive rats (Srilatha et al, 1999). In three clinical studies of hypertensive patients comparing an ACE inhibitor with other agents and placebo, all found either no difference from placebo or improved sexual function over baseline compared with other agents (Croog et al, 1988; Suzuki et al, 1988; Grimm et al, 1997).

Angiotensin II Type 1 Receptor Antagonist. In studies of hypertensive or aging normotensive animals, the AT1 receptor antagonists (e.g., losartan, valsartan, candesartan) reverse structural changes in the penile vasculature and appear to conserve erectile function (Hale et al, 2001, 2002; Park et al, 2005; Hannan et al, 2006). In clinical cross-sectional studies, AT1 receptor antagonists, in contrast to other antihypertensive drugs, seem to improve erectile function (Doulmas et al, 2006). In a crossover study comparing valsartan with the β -adrenoceptor antagonist carvedilol, valsartan had a beneficial effect on preexisting sexual dysfunction and had no adverse sexual effects during 12 months of treatment (Fogari et al, 2001). Treatment with losartan for 3 months has also been reported to improve sexual function (Llisterri et al, 2001).

Calcium Channel Blockers. Clinical studies of calcium channel blockers have demonstrated no adverse effect on erection; ejaculatory complaints, which may be due to decreased force of bulbocavernosus muscles, seem short-lived (Suzuki et al, 1988). In

the TOMHS study, there was no increase in ED in the amlodipine group compared with placebo (Grimm et al, 1997). Another study also showed no increase in the prevalence of ED when hypertension was treated with diltiazem alone or in combination with an ACE inhibitor (Cushman et al, 1998).

Aldosterone Receptor Antagonist. Spironolactone and eplerenone are mineralocorticoid-blocking agents used for their ability to block the epithelial and nonepithelial actions of aldosterone. Spironolactone is a nonselective mineralocorticoid receptor antagonist with moderate affinity for progesterone and androgen receptors. The latter property increases the likelihood of endocrine side effects, including loss of libido, gynecomastia, and impotence. Eplerenone is a next-generation aldosterone receptor antagonist selective for aldosterone receptors alone. It has less affinity for progesterone and androgen receptors (Sica, 2005).

Summary. Treatment of mild to moderate hypertension requires agents with an acceptable side-effect profile to minimize noncompliance. Thiazide diuretics are associated with higher rates of ED, although this may be reduced by combination therapy and weight loss. α_1 -Blockers and angiotensin II receptor blockers tend to improve sexual functioning during treatment and may be useful when starting antihypertensive therapy in men with preexisting ED (Khan et al, 2002) (Table 26-11).

Psychotropic Medication. As with hypertension, the underlying disorder may be more relevant for ED than the medication. However, receptor complexity and interrelationship of pathways within the CNS make it extremely likely that neurons and ganglia involved in sexual functioning will be affected by psychotropic drugs, leading to functional changes that may be positive or negative. An example is the loss of sexual desire among nonmedicated patients with schizophrenia, whereas patients on antipsychotic drugs have shown greater desire but increased erectile and ejaculatory disturbance (Aizenberg et al, 1995).

Antipsychotics. Members of this class of drug have many effects on CNS receptors and may act peripherally. The therapeutic effect of antipsychotics is thought to relate to dopaminergic receptor blockade within the limbic and prefrontal areas of the brain. Their

unwanted effects are due to β -adrenergic blockade and anticholinergic properties and to antidopaminergic actions within the basal ganglia, causing extrapyramidal side effects that commonly produce sexual symptoms (Sullivan and Lukoff, 1990).

The occurrence of extrapyramidal effects differentiates older "typical" antipsychotics (frequent extrapyramidal effects) from newer "atypical" antipsychotics (less common extrapyramidal effects). This difference probably relates to differential affinities for particular classes of receptor (Strange, 2001) or avidity for particular areas of the cerebral cortex (Westerink, 2002). An additional effect of dopamine blockade, hyperprolactinemia, which also alters sexual function by reducing dopamine release in permissive cerebral centers, is more common with older "typical" agents (Smith and Talbert, 1986).

Animal experiments, chiefly in rats, show that D1 receptor activation in the MPOA of the hypothalamus facilitates erection through intermediary oxytocinergic and spinal cholinergic pathways. It is also possible that activation of D2 receptors in this area has the opposite effect (Zarrindast et al, 1992). Older agents such as haloperidol and flupenthixol have been shown to reduce apomorphine-induced erections in experimental animals by means of D1 receptor antagonism (Andersson and Wagner, 1995). In addition, systemic administration of antipsychotic agents in rabbits produced erection by a local nondopaminergic action, possibly involving antagonism of α_1 adrenoceptors (Naganuma et al, 1993). The clinical effect of antipsychotics on sexual function varies according to their affinity for particular receptors.

In a nonrandomized comparative study of antipsychotic medications, the prevalence of sexual dysfunction ranged from 40% to 70% (Wirshing et al, 2002). Newer agents such as clozapine showed a lower reduction in sexual desire, and the group taking risperidone had the greatest decrease in erectile frequency.

Antidepressants. Sexual side effects of antidepressants in men and women are varied but are important factors governing compliance because these drugs are commonly prescribed to younger and middle-aged adults. In a Cochrane review of 15 randomized trials, besides changing medications, addition of bupropion or a PDE5 inhibitor to an antidepressant seems to be an effective method to correct antidepressant-associated ED (Rudkin et al, 2004).

Tricyclics act by inhibiting the reuptake of catecholamines in the CNS. Their sexual side-effect profile is thought to relate to peripheral anticholinergic and β -adrenergic effects. It is also possible that they antagonize 5-HT receptors. Controlled clinical studies suggest that orgasmic disorders in both sexes are frequent, explaining the use of these drugs as inhibitors of ejaculation (Harrison et al, 1986; Monteiro et al, 1987).

Monoamine oxidase inhibitors are associated with higher rates of orgasmic dysfunction in controlled trials (Harrison et al, 1986), but the nature of the central or peripheral mechanisms involved is uncertain.

Selective serotonin reuptake inhibitors (SSRIs) are the class of drug commonly used to treat depression at the present time. They inhibit the reuptake of 5-HT into CNS neurons and can produce stimulatory effects on various 5-HT receptors. It is estimated that up to 50% of patients taking SSRIs experience a change in sexual function (Rosen et al, 1999; Keltner et al, 2002). Possible mechanisms include stimulation of 5-HT₂ and 5-HT₃ receptors, which may inhibit erectogenic pathways within the spinal cord (Tang et al, 1998); decreased dopamine release in the MPOA (Maeda et al, 1994); inhibition of NOS; and lower serum levels of luteinizing hormone, follicle-stimulating hormone, and testosterone (Safarinejad, 2008). A controlled clinical study suggested that the improvement in sexual function resulting from alleviation of clinical depression with use of SSRIs outweighed any negative effect (Michelson et al, 2001). However, other placebo-controlled randomized studies revealed increased sexual dysfunction, mainly anorgasmia, in the group treated with SSRIs (Labbate et al, 1998; Croft et al, 1999). Further studies have suggested that these adverse effects can be modified by cotreatment with other drugs such as sildenafil (Fava et al, 2006) or mianserin (Aizenberg et al, 1997).

SSRIs differ in their ability to cause ED. A high incidence has been observed in patients treated with paroxetine (Kennedy et al,

TABLE 26-11 Effect of Antihypertensive Agents on Sexual Function

AGENT	EFFECT	MECHANISM
Diuretics	ED (twice as common as placebo)	Unknown
β -Blocker (nonselective)	ED	Prejunctional α_2 -receptor inhibition
β_1 -Blocker (selective)	None	
α_1 -Blocker	Decreases ED rate but may cause retrograde ejaculation	Failure of sympathetically induced closure of internal sphincter and proximal urethra during ejaculation
α_2 -Blocker	ED	Inhibition of central α_2 receptor
Angiotensin-converting enzyme inhibitor	None	
Angiotensin II receptor blocker	Decreases ED rate	
Calcium channel blocker	None	

ED, erectile dysfunction.

2000), whereas a lesser impact has been reported with citalopram (Mendels et al, 1999). This difference suggests that mechanisms other than inhibition of serotonin reuptake may be involved, which is supported by a report that short-term or long-term administration of paroxetine, but not citalopram, caused ED in rats by inhibiting NO production (Angulo et al, 2001b). The inhibitory effects induced by short-term administration of paroxetine on erectile function in the rat can be prevented by inhibition of PDE5 with vardenafil (Angulo et al, 2003a).

Other Antidepressants. Animal experiments suggest that stimulation of 5-HT₁ receptors within the CNS modulates sexual function, with the 5-HT_{1A} subtype increasing ejaculation and the 5-HT_{1C} subtype improving erection. Recently developed antidepressants such as mirtazapine and nefazodone tend to have beneficial effects on sexual function, possibly by activating the 5-HT_{1C} receptor, which augments sexual response (Stancampiano et al, 1994), although they may also antagonize the 5-HT_{2C} receptor (Millan et al, 2000). The isolated reports of priapism seen with a prototype agent, trazodone, may be related to the 5-HT_{1C} erectogenic effect seen with its primary metabolite, *m*-chlorophenylpiperazine, in experimental animals (Andersson and Wagner, 1995). In a clinical study, trazodone was shown to increase nocturnal erectile activity, despite reducing REM sleep (Ware et al, 1994).

Anxiolytics. Although not previously associated with ED, anxiolytics have been implicated in sexual problems by the MMAS study (Derby et al, 2001). Benzodiazepines are thought to potentiate the action of GABA in the reticular and limbic system, but they may also affect the serotonin and dopaminergic pathways. Experimental studies suggest that GABAergic drugs inhibit erection induced by apomorphine, a dopamine agonist (Zarrindast and Farahvash, 1994). A controlled clinical study demonstrated that a combination of lithium and benzodiazepine was associated with a significantly higher rate of sexual dysfunction than treatment with lithium alone (Ghadirian et al, 1992). More recent anxiolytic agents, such as bupropion, acting mainly by inhibiting dopamine reuptake, and buspirone, acting on 5-HT_{1A} receptors, were not associated with sexual side effects in placebo-controlled trials (Coleman et al, 2001) and can be used to alleviate sexual symptoms caused by other antidepressant medication (Gitlin et al, 2002).

Anticonvulsants. Epileptic discharges may affect the function of the hypothalamic-pituitary axis and the level of hormones important for sexual function (Morris and Vanderkolk, 2005). Sexual function, bioavailable testosterone levels, and gonadal efficiency in men with epilepsy who take lamotrigine are comparable to control and untreated values and significantly greater than in men treated with carbamazepine or phenytoin (Herzog et al, 2004). Orgasmic dysfunction is common in patients who receive carbamazepine therapy, and loss of sexual desire is common in men treated with valproate (Kuba et al, 2006). There are reports of improved sexual function and hypersexuality in patients treated with lamotrigine (Gil-Nagel et al, 2006; Grabowska-Grzyb et al, 2006).

Antiandrogens

Androgens are believed to modify sexual behavior by modulating androgen receptors within the CNS. **Antiandrogens cause partial or near-complete blockade of androgen's action by inhibiting production of or antagonizing the androgen receptor.** The effects of androgen deficiency on sexual activity are variable, ranging from complete loss to normal function. Experimental studies in humans suggest that nocturnal erections during REM sleep are androgen dependent, whereas erections in response to visual sexual stimulation are independent (Andersson and Wagner, 1995). An additional peripheral effect has been suggested from animal experiments in which castration decreased NOS activity within the rat corpus cavernosum, leading to reduced erectile activity. Testosterone restored NOS activity, but treatment with finasteride prevented this recovery, suggesting that DHT may be the important androgen in penile tissue (Lugg et al, 1995).

The 5 α -reductase inhibitors, finasteride and dutasteride, are the antiandrogens with the least effect on circulating

testosterone. In randomized placebo-controlled studies of patients given finasteride (5 mg daily) for prostatic symptoms, approximately 5% complained of decreased desire and ED compared with 1% in the placebo group (Gormley et al, 1992). At the lower dose used to treat male-pattern alopecia (1 mg daily), no sexual dysfunction was seen (Tosti et al, 2001). However, persistent sexual dysfunction for months to years after discontinuation of finasteride for hair loss (Propecia; 1 mg) has been reported. The side effects include low libido, ED, decreased arousal, and difficulty with orgasm (Irwig and Kolukula, 2011).

More complete androgen ablation is achieved by competitive antagonism at the androgen receptor, preventing signal transduction of testosterone and DHT. Nonsteroidal drugs such as flutamide and bicalutamide have relatively pure effects on the androgen receptor. The steroidal antiandrogen cyproterone acetate also has inhibitory effects on the hypothalamus. These drugs are used in the palliative treatment of locally advanced and metastatic prostate cancer, either alone or in combination with a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist. When used alone, nonsteroidal antiandrogens are associated with an increase in serum testosterone levels. When nonsteroidal antiandrogen is combined with an LHRH agonist or antagonist, the combination reduces testosterone to the castrate range. The main side effect is a reduction of sexual desire, which occurs in up to 70% (Iversen et al, 2001).

In a clinical trial with larger sample size and longer duration, treatment with bicalutamide alone resulted in a smaller decrease in sexual desire than did castration (Iversen et al, 2000). However, in another large controlled trial, treatment with either flutamide or cyproterone resulted in a gradual loss of sexual desire over 2 to 6 years in approximately 80% (Schroder et al, 2000). In a placebo-controlled study, half of patients receiving bicalutamide therapy experienced loss of erectile function, even at a low dose of 50 mg (Eri and Tveter, 1994).

The near-complete androgen deprivation achieved by medical castration with LHRH antagonist (immediate testosterone suppression) or agonists (with an initial surge of testosterone) results in a profound loss of sexual desire, which is usually accompanied by ED (Basaria et al, 2002). In a small study, nocturnal penile tumescence (NPT) monitoring before and after initiation of therapy provided objective confirmation (Marumo et al, 1999).

Miscellaneous Drugs

Many other drugs are suggested to have sexual side effects, in particular, ED in men, but these contentions are usually based on anecdotal case reports or postmarketing drug alerts rather than controlled trials.

Digoxin. In an experimental in vitro study with isolated human corpus cavernosum tissue, digoxin attenuated the relaxant response to acetylcholine and intrinsic nerve stimulation; this was linked to findings of reduced penile rigidity not seen in men given a placebo after visual sexual stimulation (Gupta et al, 1998). A randomized clinical study confirmed a negative effect on general sexual functioning linked to a decrease in plasma testosterone (Neri et al, 1987). However, other investigators did not find change in sex and adrenal hormone levels in men taking digitalis (Kley et al, 1984).

Statins. Statins are used to reduce lipid levels and are commonly used in men likely to have established risk factors for sexual dysfunction, particularly ED. In a single placebo-controlled trial, the rate of ED was twice as high (12% vs. 6%) in men taking a statin, despite improvement in other parameters of hyperlipidemic endothelial dysfunction (Bruckert et al, 1996). In another study of 93 men attending cardiovascular risk clinics, after 6 months of statin therapy, the mean IIEF scores were reduced from 21 to 6.5 (range 0 to 25; $P < .001$), and 22% experienced new-onset ED. The authors suggest that ED after statin therapy is more likely in patients with severe endothelial dysfunction secondary to established cardiovascular risk factors including age, smoking, and diabetes (Solomon et al, 2006). In contrast, in the large Scandinavian simvastatin survival study, 4444 patients with coronary arterial disease were randomly assigned to treatment with simvastatin or placebo for up to

6 years. ED was found in 28 placebo-treated patients (8 resolved) and in 37 simvastatin-treated patients (14 resolved) (Pedersen and Faergeman, 1999). The underlying disease process appears to be the cause of ED in men treated with statins rather than the drug itself.

Regarding sexual side effects, the most studied statin is atorvastatin. In clinical studies, atorvastatin has been reported to have the following positive effects: (1) improvement in nocturnal penile activity and mean scores on the Sexual Health Inventory in Men questionnaire from 14.2 to 20.7 in hyperlipidemic patients treated for 4 months (Saltzman et al, 2004); (2) when combined with the ACE inhibitor quinapril, positive effects on ED in men with established penile disease and suboptimal response to PDE inhibitors (Bank et al, 2006); (3) improvement in the response to sildenafil in men with ED not initially responsive to sildenafil (Herrmann et al, 2006); (4) when combined with sildenafil, improvement in erectile function recovery in men who had undergone bilateral nerve-sparing radical prostatectomy (Hong et al, 2007); and (5) positive effect on IIEF questionnaire scores in patients with hyperlipidemia followed for 12 months (Dogru et al, 2008).

Statins are classified as natural (lovastatin), semisynthetic (simvastatin), and synthetic (atorvastatin, cerivastatin) and are structurally heterogeneous. The statins may have different effects on sexual function, which remain to be elucidated.

Histamine H₂ Receptor Antagonists. Cimetidine and ranitidine were widely prescribed for prophylaxis and treatment of peptic ulcer disease. Case reports suggested that cimetidine was associated with ED. A single in vitro animal study suggested that H₂ receptor stimulation causes cavernous relaxation, possibly via endothelial release of NO (Andersson and Wagner, 1995).

Opiates. Long-term intrathecal administration of opiates results in hypogonadotropic hypogonadism and associated sexual dysfunction that can be restored with appropriate supplementation (Abs et al, 2000). However, administration of opioid antagonists to older men with ED was not found to improve erectile function measured objectively by NPT monitoring (Billington et al, 1990). Opioids have a generalized depressant effect on sexual function when directly administered to the MPOA in rat brain, but treatment with the opioid receptor antagonist naloxone had no sexual effect on healthy male volunteers (Andersson and Wagner, 1995).

Antiretroviral Agents. Hypogonadism and ED appear to be more common among men infected with human immunodeficiency virus (HIV) compared with age-matched men in the general U.S. population (Crum et al, 2005). Sexual dysfunction seems to be a common event after the introduction of antiretroviral therapy. The average prevalence is ED, 46%; decreased libido, 44%; ejaculatory disturbances, 39%; and orgasmic disorders, 27% (Collazos, 2007). These disturbances seemed to be more common in patients treated with protease inhibitors. Because these patients may have diseases involving several organ systems and may be taking multiple drugs, the precise mechanism is difficult to determine.

Tobacco. Cigarette smoking may induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle (Juenemann et al, 1987a). In an NPT study in cigarette smokers, Hirshkowitz and colleagues (1992) reported an inverse correlation between nocturnal erection (rigidity and duration) and the number of cigarettes smoked per day: Men who smoked more than 40 cigarettes had the weakest and shortest nocturnal erections. The Boston Area Community Health (BACH) survey used a multistage stratified random sample to recruit 2301 men, 30 to 79 years to, from Boston. The authors' report indicates a dose-response association between smoking and ED with a statistically significant effect observed with 20 or more pack-years of exposure. Passive smoking is associated with a small, statistically insignificant increase in risk of ED comparable to approximately 10 to 19 pack-years of active smoking (Kupelian et al, 2007). In an experiment to elucidate the mechanisms of ED associated with tobacco use, nicotine-free and tar-free cigarette smoke extract was injected subcutaneously into adult male rabbits once a day for 5 weeks. The authors reported impaired NO production from blunted NOS activity, downregulation of nNOS protein,

accumulation of endogenous NOS inhibitors, enhanced arginase activity, and upregulation of arginase I protein in cavernous tissue. Cigarette smoke extract also caused accumulation of endogenous NOS inhibitors secondary to impaired dimethylarginine dimethylaminohydrolase activity and decreased expression of dimethylarginine dimethylaminohydrolase I protein. These alterations may be relevant to ED after administration of cigarette smoke extract (Imamura et al, 2007).

Alcohol. Alcohol in small amounts improves erection and sexual drive because of its vasodilatory effect and suppression of anxiety; however, large amounts can cause central sedation, decreased libido, and transient ED. In the Western Australia Men's Health Study, Chew and colleagues (2009) reported that compared with never-drinkers, the age-adjusted odds of ED were lower among current, weekend, and binge drinkers and higher among ex-drinkers.

Chronic alcoholism may result in liver dysfunction, decreased testosterone and increased estrogen levels, and alcoholic polyneuropathy, which may also affect penile nerves (Miller and Gold, 1988). In an in vitro study of rabbits given 5% alcohol for 6 weeks, Saito and colleagues (1994) reported augmented smooth muscle contraction and relaxation to both electrical field stimulation and vasoconstrictors such as phenylephrine and potassium chloride, but not to sodium nitroprusside, suggesting changes in neurovascular function. In a study of subacute alcohol effect, mice were exposed to alcohol vapor for 7 or 14 days. The authors reported impaired endothelium-dependent relaxation of cavernous smooth muscle and damage of endothelium in the group of mice exposed for 14 days but not the group exposed for 7 days (Aydinoglu et al, 2008) (Table 26-12).

TABLE 26-12 Drug-Induced Erectile Dysfunction and Suggested Alternatives

CLASS	KNOWN TO CAUSE ERECTILE DYSFUNCTION	SUGGESTED ALTERNATIVES
Antihypertensives	Thiazide diuretics General β blockers	α -Blockers Calcium channel blockers Specific β -blockers Angiotensin-converting enzyme inhibitors Angiotensin II receptor antagonists
Psychotropics	Antipsychotics Antidepressants Anxiolytics	Newer anxiolytics (bupropion, buspirone)
Antiandrogen	Androgen receptor antagonists Luteinizing hormone-releasing hormone agonists 5 α -Reductase inhibitors	
Opiates		
Antiretroviral agents		
Tobacco		Quit smoking
Alcohol	Large amount	Small amount

U.S. Community Survey of Prescription Drugs and Erectile Dysfunction. The BACH survey used a multistage stratified design to recruit a random sample of 2301 men 30 to 79 years old. To investigate the association of ED with commonly used medications, including antihypertensive agents, psychoactive agents, and pain and anti-inflammatory medications. ED was assessed using the IIEF-5 questionnaire. Multivariable analyses showed benzodiazepines and tricyclic antidepressants were associated with ED, whereas no association was observed for SSRIs/serotonin-norepinephrine reuptake inhibitors and atypical antipsychotics. The use of antihypertensive treatment, whether in monotherapy or in conjunction with others, and pain or anti-inflammatory medications was not associated with ED after accounting for confounding factors (Kupelian et al, 2013).

Aging, Systemic Disease, and Other Causes

Numerous studies have indicated a progressive decline in sexual function in “healthy” aging men. Masters and Johnson (1977) noted many changes in older men, including greater latency to erection, less turgidity, loss of forceful ejaculation and decreased volume, and a longer refractory period. Decreased frequency and duration of nocturnal erection with increasing age were reported in a group of men who had regular intercourse (Schiavi and Schreiner-Engel, 1988). Other research has also indicated a decrease in penile tactile sensitivity with age (Rowland et al, 1989). A heightened cavernous muscle tone may also contribute to the decreased erectile response in older men (Christ et al, 1990). In one study, a decrease in testosterone in aging impotent men in association with relatively normal gonadotropins was reported, suggestive of hypothalamic-pituitary dysfunction (Kaiser et al, 1988). Vascular endothelial dysfunction is regarded as a primary phenotypic expression of normal human aging. This senescence-induced disorder is the likely culprit underlying the increased cardiovascular and metabolic diseases associated with aging. Aging impairs endothelial function through reduced eNOS expression and action, accelerated NO degradation, increased PDE activity, inhibition of NOS activity by endogenous NOS inhibitors, increased production of reactive oxygen species, inflammatory reactions, decreased endothelial progenitor cell number and function, and impaired telomerase activity or telomere shortening (Toda, 2012).

Penile structural and functional changes have been documented in various animal studies. Costa and Venda (2008) reported progressive decline of smooth muscle content and increase in the caliber of vascular spaces in the corpus cavernosum with increasing age in Wistar rats. Suadicani and colleagues (2009) showed a significant decrease in gap junction protein connexin 43 and purinoceptor subtype P2X1R and an increase in purinoceptor subtype P2X7R in the corpus cavernosum of aging Fischer-344 rats. Ferrini and colleagues (2001a, 2001b) reported an increase of inducible NO, peroxynitrite formation, and elevation of apoptotic index in the corpus cavernosum and hypothalamic regions. The increased contractile property of the erectile tissue associated with aging may be due to elevated RhoA/Rho-kinase activity (Jin et al, 2006), enhanced renin-angiotensin system (Park et al, 2005), or impaired angiotensin-(1-7)-mediated relaxation (Yousif et al, 2007).

Diabetes Mellitus. Diabetes mellitus is a common chronic disease, affecting 0.5% to 2% of the worldwide population. The prevalence of ED is three times higher in diabetic men (28% vs. 9.6%) (Feldman et al, 1994), occurs at an earlier age, and increases with disease duration, being approximately 15% at age 30 and increasing to 55% at 60 years (McCulloch et al, 1980, 1984). ED among men with diabetes is more frequent in men with coexisting neuropathy. In a study of men presenting with ED, the authors found a twofold increase of hypogonadism in men with diabetes (24% vs. 12%) (Corona et al, 2006). The presence of ED is associated with more than 14 times higher risk for silent coronary artery disease, higher major cardiovascular morbidity, and mortality in diabetic men (Gazzaruso et al, 2004). This evidence indicates the presence of ED in diabetic patients could predict future major cardiovascular events. Diabetes mellitus may cause ED by

affecting one or a combination of the following: psychological well-being, CNS function, androgen secretion, peripheral nerve activity, endothelial cell function, and smooth muscle contractility (Dunsmuir and Holmes, 1996).

In 12% of diabetic men, deterioration of sexual function can be the first symptom. Duplex ultrasound after intracavernous injection has revealed a high prevalence (>75%) of penile arterial insufficiency among diabetic men with ED (Wang et al, 1993). Pathologic changes in the cavernous arteries (Michal, 1980), ultrastructural changes in the cavernous smooth muscle (Mersdorf et al, 1991), and impaired endothelium-dependent relaxation of the corporeal smooth muscle (Saenz de Tejada et al, 1989a) also have been noted in penile specimens from diabetic men with ED. Hirshkowitz and colleagues (1990) reported that impotent men with diabetes have fewer sleep-related erections, shorter tumescence time, diminished penile rigidity, decreased heart rate response to deep breathing, and lower penile blood pressure than age-matched nondiabetic men. Different severities of endothelial apoptosis between diabetic patients who are “responders” and “nonresponders” to sildenafil have also been reported (Condorelli et al, 2013).

Numerous type 1 and type 2 diabetic animal models have been used to study the basic mechanisms of diabetes-induced ED. In these animals, diabetes causes endothelial cell dysfunction, incompetent cavernous endothelial cell-cell junctions resulting in an increased prevalence of vascular disease (Ryu et al, 2013). Other effects include decreased nNOS, reduced activity of eNOS, oxidative stress, increased advanced glycation end products, decreased elastin, reduced VEGF, hypercontractility of cavernous erectile tissue, and decreased smooth muscle/collagen ratio leading to impairment of the veno-occlusive mechanism. Kilarkaje and associates (2013) reported that angiotensin II signaling is also involved in diabetes-induced structural changes and oxidative DNA damage in the corpus cavernosum of rats and that modulation of the signaling by captopril, losartan, and angiotensin-(1-7) restores the effects of diabetes mellitus. Activated Rho-kinase mediates diabetes-induced elevation of vascular arginase activation, and impaired corpora cavernosa relaxation has also been reported (Toque et al, 2013). Celtek and associates (2013) revisited the concept of “point of no return” in the course of diabetic ED and proposed that research focus on the role of vasa nervorum and advanced glycation end products. Summaries of mechanistic studies in humans and animal models, derived from the committee report of the Second International Consultation of Sexual Medicine (Saenz de Tejada et al, 2005), are shown in Tables 26-13 and 26-14.

Metabolic Syndrome. The metabolic syndrome includes glucose intolerance, insulin resistance, obesity, dyslipidemia, and hypertension. Higher prevalence of ED (26.7%) in men with metabolic syndrome relative to control subjects (13%) has been reported. The prevalence of ED increases as the number of metabolic syndrome components increases (Esposito et al, 2005). In an analysis of the Baltimore Longitudinal Study of Aging, in which men were followed for a mean of 5.8 years, Rodriguez and colleagues (2007) confirmed that the prevalence of metabolic syndrome increases with age and is associated with lower androgen levels. They also found that lower total testosterone levels, along with lower sex hormone-binding globulin levels, predicts a higher incidence of metabolic syndrome. Men with metabolic syndrome have an increased prevalence of ED, reduced endothelial function score, and higher circulating concentrations of C-reactive protein compared with men without metabolic disorders (Esposito et al, 2005). La Vignera and associates (2012) studied endothelial cell turnover by blood endothelial progenitor cells and endothelial microparticles and reported highest levels in men with both metabolic syndrome and arteriogenic ED, followed by men with metabolic syndrome without ED and then men without metabolic syndrome and ED. In a study of endothelial function in patients with metabolic syndrome and ED, Tomada and associates (2013) reported an imbalance of angiopoietins in patients with metabolic syndrome and ED and suggested that angiopoietins may be early markers of endothelial dysfunction in this population with higher cardiovascular risk. In insulin-resistant obese Zucker rats,

TABLE 26-13 Summary Findings of Studies in Diabetic Patients

FOCUS	FINDING
Anatomic	<ul style="list-style-type: none"> • More atheromatic lesions in large vessels and stenosis in pudendal and iliac arteries
Functional	<ul style="list-style-type: none"> • Decreased number and rigidity of nocturnal erections • Lower penile rigidity after intracavernous injection of vasodilators • High prevalence of penile arterial insufficiency studied with duplex ultrasound
CAVERNOUS TISSUE STUDIES	
Ultrastructural	<ul style="list-style-type: none"> • Decreased smooth muscle content, increased collagen, thickening of basal lamina, and loss of endothelial cells (more severe in men with diabetes)
Functional	<ul style="list-style-type: none"> • Reduced endothelial and neurogenic NO-mediated penile smooth muscle relaxation but not nitroprusside-induced relaxation (suggesting impaired NO release or synthesis) • Increased advanced glycation end products in cavernous tissue • Contractile response to α-adrenergic agonist is higher in type 1 but not type 2 diabetics • In human penile arteries, EDHF-mediated endothelium-dependent relaxation is significantly reduced in penile resistance arteries from diabetic patients • Exposure to hyperglycemia induces increased expression of collagen, decreased proliferation, and increased programmed cell death (apoptosis). Expression of tumor necrosis factor-α is also increased • Insulin is thought to enhance NOS activity by increasing transport of L-arginine into the cell and furnishing greater quantities of the essential cofactor NADPH. These effects are reversed in insulin deficiency or insulin resistance in diabetes • The inducible form (arginase II) of arginase, an enzyme that competes with NOS for the substrate L-arginine, is overexpressed in corpus cavernosum of diabetic patients, where inhibition of arginase restores NOS activity

EDHF, endothelium-derived hyperpolarizing factor; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase.

TABLE 26-14 Summary Findings of Studies in Diabetic Animal Models

MODEL	FINDING
Streptozocin-induced diabetic rats or mice	<ul style="list-style-type: none"> • Increased activity of AC and GC, resulting in production of more cAMP and cGMP in response to PGE₁ and nitroprusside, respectively • Decreased endothelial and neurogenic NO-mediated cavernous muscle relaxation • Increased prostacyclin synthesis • Increased cavernous muscle tone owing to upregulation of ET-A receptors • Increased contractile prostaglandins and free oxygen radicals in hyperglycemic state, resulting in reduced response to acetylcholine (reversed by indomethacin and antioxidants) • Increased levels of oxygen free radicals and oxidative stress injury. Preventive treatment with an antioxidant prevented the appearance of endothelial dysfunction in cavernosal tissue, whereas restorative treatment with same antioxidant only partially reversed the impairment of endothelium-dependent relaxation • Increased glycated hemoglobin, which impairs endothelium-dependent relaxation in aorta and corpus cavernosum from diabetic rats. This effect is reversed by SOD, the scavenger of superoxide anions • Inhibition of AGE formation improves endothelium-dependent relaxation and restores erectile function in diabetic rats • Impaired responses attributable to EDHF in the vasculature of diabetic animals • Plasma concentration and vascular content of L-arginine are reduced in diabetic rats • NO-dependent selective nitrergic nerve degeneration in diabetes
Diabetic rabbit	<ul style="list-style-type: none"> • Production of cAMP in response to PGE₁ or forskolin is reduced after 6 months, but not 3 months • Increased glucose-induced production of PKC mediated by oxidative stress in rabbit corpus cavernosum smooth muscle cells • Oxidative stress interferes with endothelial function in diabetic erectile tissue. This is supported by the potentiating effect of SOD or the natural antioxidant, vitamin E, on endothelium-dependent relaxation of corpus cavernosum from rabbits

AC, adenylyl cyclase; AGE, advanced glycation end product; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; EDHF, endothelium-derived hyperpolarizing factor; ET-A, endothelin-A; GC, guanylyl cyclase; NO, nitric oxide; PGE₁, prostaglandin E₁; PKC, protein kinase C; SOD, superoxide dismutase.

Sánchez and coworkers (2012) reported uncoupling of nNOS in the dysfunctional nitric oxide vasorelaxation of penile arteries (see Fig. 26-13).

Chronic Renal Failure. Sexual dysfunction is common in men with chronic renal failure. In a survey of 69 men on hemodialysis, only 55% were sexually active, and the predominant sexual dysfunctions were loss of or diminished sexual needs (84.7%), ED (44.5%), and inhibited or lack of ejaculation (51.5%) (Lew-Starowicz and Gellert, 2009). Similarly, ED was reported in 52% of men undergoing peritoneal dialysis (Lai et al, 2007). The presence of depressive symptoms, highly prevalent in hemodialysis patients, is an independent factor of sexual dysfunction in male hemodialysis patients (Peng et al, 2007). Significant improvement of sexual function has been reported after kidney transplantation (Tavallai et al, 2009). Nevertheless, in a report of 182 men who had undergone kidney transplantation, Espinoza and colleagues (2006) noted that 49% of men continued to have ED; 33% of men had normal sexual function, and 18% had no sexual activity. Many of the effects of uremia can potentially contribute to the development of ED, including disturbance of the hypothalamic–pituitary–testicular axis, hyperprolactinemia, accelerated atherosclerotic disease, and psychological factors (Ayub and Fletcher, 2000).

Bagcivan and colleagues (2003) suggest that ED may be due to either decreased production or reduced bioavailability of endogenous NO. Evidence from animal models of chronic uremia suggests that a decrease in functional NO may be responsible for vascular side effects including ED.

Evidence of autonomic neuropathy as a factor contributing to ED in men with chronic renal failure comes from studies that found a high rate of abnormality in vascular and bulbocavernosus reflexes, suggesting nerve dysfunction (Campese et al, 1982; Vita et al, 1999). Neuropathy is a common complication of end-stage kidney disease, typically manifesting as a distal symmetrical process with insidious onset progressing over months. Neuropathy has been estimated to occur in 60% to 100% of patients on dialysis. Nerves of uremic patients have been shown to exist in a chronically depolarized state before initiation of dialysis, with subsequent improvement and normalization of resting membrane potential after initiation of dialysis. The degree of depolarization correlates with serum K^+ , suggesting that chronic hyperkalemic depolarization plays an important role in the development of nerve dysfunction in end-stage kidney disease (Krishnan and Kiernan, 2007). Investigation of cavernous vascular function in 20 men undergoing renal replacement therapy showed that 80% had both arterial insufficiency and veno-occlusive dysfunction (Kaufman et al, 1994). A link between impairment of the NO–cGMP pathway relating to failure of cavernous relaxation is provided by the finding of increased serum levels of ADMA in uremic patients (Kielstein and Zoccali, 2005).

Patients with severe pulmonary disease often fear aggravating dyspnea during sexual intercourse. Patients with angina, heart failure, or myocardial infarction can become impotent from anxiety, depression, or arterial insufficiency. HIV infection itself is the strongest predictor of ED, and many factors related to the infection—fear of virus transmission, changes in body image, HIV-related comorbidities, infection stigma, obligatory condom use—impair erectile function (Santi et al, 2014). In two large European studies, Corona et al (2012) reported that overt hyperthyroidism was associated with an increased risk of severe ED. Conversely, no association between primary hypothyroidism and ED was observed. Other systemic diseases, such as cirrhosis of the liver, scleroderma, chronic debilitation, and cachexia, are also known to cause ED.

Primary Erectile Dysfunction

Primary ED refers to a lifelong inability to initiate and/or maintain erections beginning with the first sexual encounter. Although most cases are due to psychological factors, a few afflicted men have a physical cause resulting from maldevelopment of the penis or the blood and nerve supply. Primary psychological dysfunction is usually related to anxiety about sexual performance

stemming from adverse childhood events, traumatic early sexual experience, or misinformation. Endocrine abnormalities, particularly low testosterone levels, may also be implicated in primary ED, although decreased sex drive is likely to be the main symptom. Evidence to support these concepts is confined to observation studies with varying numbers of cases. The largest study described 67 patients, of whom 10 (15%) had a predominantly psychological cause (Stief et al, 1989b). Patients with physical abnormalities had a variety of neurologic, arterial, and veno-occlusive dysfunction.

Micropenis. Symmetrical hypoplasia of the phallus, micropenis, is often related to urethral developmental abnormalities such as hypospadias and epispadias (Reilly and Woodhouse, 1989) or endocrine deficiency. The erectile tissue in such cases often functions normally; sexual dysfunction usually relates to lack of penile length or the degree of chordee, rather than to ED (Woodhouse, 1998).

Vascular Abnormalities. Primary ED in the presence of an externally normal phallus is unusual. Authors have described structural abnormalities of the cavernous tissue, such as absence (Teloken et al, 1993) or replacement by fibrous tissue (Aboseif et al, 1992). Other authors have found vascular abnormalities, including hypoplasia of the cavernous arteries (Montague et al, 1995) or veno-occlusive dysfunction owing to aberrant cavernous venous drainage (Lue, 1999). The underlying cause of these congenital abnormalities is unknown. Treatment in most cases has been vascular surgery or implantation of a penile prosthesis.

KEY POINTS: OTHER CAUSES OF ERECTILE DYSFUNCTION

- Aging is the most important contributing factor to ED. The aging process can affect the central regulatory mechanism, hormonal and neural function, and penile structure.
- Diabetes mellitus and metabolic syndrome may affect multiple organ systems and cause premature aging of central and peripheral structures and molecules that regulate erectile process.
- The diseases that cause chronic renal failure may also cause ED, and the condition may persist despite successful renal transplantation.
- Primary ED may be due to psychogenic cause, inexperience, congenital arterial insufficiency, or abnormal venous channels.

KEY POINTS: PATHOPHYSIOLOGY

- The prevalence of ED increases with age and concomitant medical diseases. The incidence is about 25 to 30 cases per 1000 person-years.
- ED is a symptom of many underlying conditions and diseases.
- Any condition that affects penile nerve, artery, endothelium, smooth muscle, or tunica albuginea can cause ED.
- Endothelial dysfunction seems to be a common final pathway to ED in patients with hyperlipidemia, diabetes mellitus, hypertension, and chronic renal failure.
- Drugs most commonly associated with ED include antianesthetics, antidepressants, and antihypertensives.

PERSPECTIVES

The past two decades have seen a continuing explosion of new information on the physiology of penile erection and the pathophysiology of ED. These new discoveries not only enhance our understanding of the disease process but also provide a solid basis for improving diagnosis and treatment. We can expect that the application of new research tools and information in molecular

biology, signal transduction, growth factors, microarrays, and stem cells will bring the investigation of erectile function and ED to an even higher level in the near future.

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Historical Perspective

Public Health Significance

Management Principles

Diagnostic Evaluation

Specialized Evaluation and Testing

Treatment Considerations

Future Directions

HISTORICAL PERSPECTIVE

Erectile dysfunction (ED) management has evolved into a mature clinical discipline in the past few decades, owing to steady, considerable progress made in the basic science, epidemiology, clinical investigation, and health services research within this dynamic field. The field has advanced from its well-notioned beginnings of psychoanalysis and sex therapy, accompanied by the use of aphrodisiacs, herbal supplements, and hormonal treatments, typifying the knowledge and approach to clinical practice in the 1970s, to an increasingly structured, balanced, and evidence-based process of clinical evaluation and intervention of the contemporary era (Table 27-1).

Well-grounded ED management principles, premised on the highest clinical standards of ethics, quality, safety, and cost-effectiveness, are now well accepted by the scientific and clinical community in sexual medicine. These “guidelines” have derived from rigorous and timely review, organization, and reassessments of the constantly evolving body of knowledge in this field performed by assorted consensus bodies representing the spectrum of international and interdisciplinary authorities in sexual medicine. Most notably, the International Consultations on Sexual Medicine (ICSM), cosponsored variously by the World Health Organization, International Consultation on Urological Diseases, American Urological Association, Société Internationale D’Urologie, and the International Society for Sexual Medicine, have served this role and have published topical proceedings (Jardin et al, 2000; Lue et al, 2004; Montorsi et al, 2010).

PUBLIC HEALTH SIGNIFICANCE

ED is a medical condition of major health significance, with implications that extend beyond treating the occasionally presenting patient who possesses a problem of seemingly non-life-threatening magnitude. The value of properly assessing and managing ED relates not only to affected individuals and their partners but also to society as a whole, and its scope encompasses physical and mental wellness aspects related to addressing (or failing to address) the sexual dysfunction, concurrent disease management issues, as well as its socioeconomic burden.

Epidemiology

Epidemiologic investigation, which specifies that study results are readily generalized to the overall male population, has provided powerful information regarding the nature, etiology, and prognostic ramifications of ED. As the most thoroughly studied sexual

dysfunction in the context of epidemiologic research, ED is estimated to carry an overall adult male (older than 20 years of age) prevalence rate of 10% to 20% worldwide, with the majority of studies reporting a rate closer to 20% (Derogatis and Burnett, 2008; Lewis et al, 2010). It is acknowledged that an age correlation exists for the prevalence of ED, with a worldwide prevalence of 1% to 10% for men younger than the age of 40 years, as high as 15% for men age 40 to 49 years, as high as 30% for men age 50 to 59 years, as high as 40% for men 60 to 69 years, and 50% to 100% for men in their 70s and 80s (Lewis et al, 2010). It was estimated that there were more than 152 million men worldwide who experienced ED in 1995, with a projection of the prevalence reaching approximately 322 million men having ED by 2025 (Aytac et al, 1999). This trend is maintained irrespective of racial/ethnic background or geographic region.

Current data have also confirmed that the prevalence of ED mounts with the presence of comorbid medical conditions, which include type 2 diabetes mellitus, obesity, cardiovascular disease, hypertension, dyslipidemia, depression, and prostate disease/benign prostatic hyperplasia (Braun et al, 2000; Martin-Morales et al, 2001; Nicolosi et al, 2004; Rosen et al, 2004c; Saigal et al, 2006; Laumann et al, 2007; Selvin et al, 2007). This correlation has supported the premise that ED and comorbid medical conditions share pathophysiologic mechanisms, such as endothelial dysfunction, arterial occlusion, and systemic inflammation (Solomon et al, 2003; Montorsi et al, 2004; Billups, 2005; Ganz, 2005; Kloner, 2005; Guay, 2007).

Novel disease-risk relationships for ED have been described, likely also exhibiting such concomitant pathophysiologic mechanistic associations as endothelial dysfunction and systemic inflammation. These disease relationships include epilepsy (Keller et al, 2012b), sensorineural hearing loss (Keller et al, 2012a), open-angle glaucoma (Chung et al, 2012a), urinary calculi (Chung et al, 2011), psoriasis (Chung et al, 2012b), atopic dermatitis (Chung et al, 2012d), chronic periodontitis (Keller et al, 2012d), viral hepatitis (Chung et al, 2012c), varicocele (Keller et al, 2012c), and gastric ulcers (Keller et al, 2012e).

Although they are few in number, prospectively conducted longitudinal studies have documented the true incidence and disease-risk relationships for ED. In one study, a crude ED incidence rate was 25.9 cases/1000 man-years among men aged 40 to 69 years (Johannes et al, 2000). According to another study, incident ED statistics were 57% at 5 years and 65% at 7 years in men 55 years or older (Thompson et al, 2005). Such studies have uniquely affirmed predictors for the development of ED, which include age, lower education, diabetes, cardiovascular disease, hypertension, cigarette smoking, cigar smoking, passive exposure to cigarette smoke, and overweight condition (Feldman et al, 2000; Johannes et al, 2000; Inman et al, 2009).

TABLE 27-1 Evolution in the Management of Erectile Dysfunction

	DIAGNOSTICS	TREATMENTS	GUIDES
Pre-1970	Psychosexual history	Psychosexual therapy Herbal supplements	Studies of Masters and Johnson
1970s	Medical and psychosexual history Nocturnal penile tumescence testing	Penile prosthesis surgery Penile revascularization	International Conferences on Corpus Cavernosum Revascularization
1980s	Physical examination Endocrine evaluation Penile duplex ultrasonography, DICC	Oral medications Intracavernous pharmacotherapy Vacuum device therapy	Goal-directed management
1990s	Combined intracavernous injection and stimulation	Intraurethral pharmacotherapy Oral phosphodiesterase type 5 therapy	NIH Consensus Statement Process of Care Model
2000-Present	Biomarkers of vascular health neuroimaging	? Gene therapy ? Stemcell therapy ? Tissue engineering	ICUD algorithms (patient-centered approach) AUA Practice Guidelines (evidence-based approach)

AUA, American Urological Association; DICC, dynamic infusion cavernosometry and cavernosography; ICUD, International Consultation on Urological Diseases; NIH, National Institutes of Health.

However, the strength of the risk association is also gauged from the opposite analytic direction, and incident ED may indeed inform the risk of subsequent disease morbidity and mortality. This relationship has been best demonstrated so far with respect to cardiovascular disease. The placebo arm of the Prostate Cancer Prevention Trial found that ED is a sentinel for future risk of cardiovascular events, comparable to that of current cigarette smoking or a family history of myocardial infarction (Thompson et al, 2005). This study established that men with ED were 45% more likely than men without ED to experience a cardiac event after 5 years of follow-up (Thompson et al, 2005). In another population-based study of community-dwelling men followed longitudinally, ED was associated with an approximately 80% higher risk of subsequent coronary artery disease at 10 years (Inman et al, 2009). In a long-term follow-up (15 years) of the Massachusetts Male Aging Study (Feldman et al, 1994), ED was found to be positively associated with subsequent all-cause and cardiovascular disease mortality and constituted a risk in this regard similar to that of conventional risk factors, such as increased body mass index, diabetes, and hypertension (Araujo et al, 2009). It is an increasingly recognized and striking observation, made in epidemiologic studies demonstrating the risk association of ED with cardiovascular events, that the development of ED at a younger age heightens this particular risk (Chew et al, 2010; Miner et al, 2012; Vlachopoulos et al, 2013).

Recent meta-analyses of longitudinal studies have supported the findings of earlier reports and have provided relative risk estimates. A meta-analysis of seven prospective cohort studies provided adjusted relative risks for ED subjects compared with healthy subjects, calculating 1.47-fold increased cardiovascular disease events overall and 1.23-fold increased all-cause mortality (Guo et al, 2010). Another meta-analysis of 12 cohort studies calculated overall combined relative risk for men with ED compared with the reference group to be 1.48 with cardiovascular disease, 1.46 for coronary heart disease, 1.35 for stroke, and 1.19 for all-cause mortality (Dong et al, 2011). A further meta-analysis comprising 14 studies documented relative risk of 1.44 for cardiovascular mortality, 1.19 for myocardial infarction, 1.62 for cerebrovascular events, and 1.25 for all-cause mortality for men with ED versus those without ED (Vlachopoulos et al, 2013).

Besides a predictive relationship of cardiovascular disease based on incident ED, a similar relationship has been suggested with respect to carcinogenesis risk. The "Longitudinal Health Insurance Database" study in Taiwan showed that cancer risk was 1.42-fold higher in ED patients than in patients without ED during a 5-year follow-up, after adjusting for socioeconomic and comorbid health variables (Chung et al, 2011).

These compelling data regarding occurrence rates and risk factors for ED contribute greatly toward an understanding of the importance of this medical condition. **The subject of ED offers a veritable clinical barometer of overall male health status, and efforts geared toward advancing its management are immediately consequential for disease prevention, health promotion, and survival improvement.**

Health Policy

Sexual dysfunctions and ED specifically have taken on increasing importance with respect to their socioeconomic impact. **In addition to its medical comorbidity associations, ED is recognized to affect adversely quality of life, to decrease occupational productivity, and to increase the use of health care resources (Krane et al, 1989; Litwin et al, 1998).** Because of the heightened ease of use and availability of effective first-line treatments combined with a growing societal awareness of ED and an acceptance of its treatment, it is understandable that a trend toward increased use of health care services surrounding ED has been observed (Wessells et al, 2007; Polinski and Kesselheim, 2011).

ED can be included among a host of urologic diseases having a substantial burden on the public financially. Total expenditures for outpatient clinical management of ED (exclusive of pharmaceutical costs) in the United States in the year 2000 approximated \$330 million, ranking it the ninth most costly among the most frequent urologic diagnoses (Litwin et al, 2005). By contrast, this cost was approximately \$185 million in 1994 (Wessells et al, 2007). Individual-level expenditures on an annual basis associated with an ED diagnosis (inclusive of pharmaceutical costs) among affected 18- to 64-year-old males in the United States in 2002 were calculated to be \$1107 (Wessells et al, 2007). The Congressional Budget Office estimate of government expense for ED drugs in 2005 was \$2 billion for the subsequent 10 years (Polinski and Kesselheim, 2011). These data have enormous implications for governmental as well as nongovernmental agencies in the United States and worldwide, whose work must consider the practical distribution and fiscal allocation of health care services for ED. Some experts have accordingly urged an account of the medical necessity and cost of ED therapy when formulating grounds for insurance coverage (Polinski and Kesselheim, 2011). However, evidence points to rational coverage for ED therapy, and in fact a significantly lower use of this therapy has been shown as compared to ED prevalence (Hornbrook and Holup, 2011). Arguments support the fact that ED is not a frivolous indication for clinical intervention, having quality-of-life and well-being implications as well as importance with respect to health and life preservation.

KEY POINTS: EPIDEMIOLOGY AND HEALTH POLICY

- Approximately 20% of adult men worldwide experience ED.
- Risk factors for ED include increasing age and presence of comorbid medical conditions such as type 2 diabetes mellitus, obesity, cardiovascular disease, hypertension, dyslipidemia, depression, and prostate disease/benign prostatic hyperplasia.
- Outcomes research has shown that ED is meritorious for clinical intervention, having quality-of-life and well-being implications as well as importance with respect to health and life preservation.
- ED ranks among the top 10 most costly urologic diagnoses in the United States and must be included in considerations for fiscal allocation of health care services.

MANAGEMENT PRINCIPLES

The approach to the evaluation and treatment of ED is most assuredly different from that of many other urologic diseases in several basic respects. The diagnosis of ED customarily involves an acknowledgment of the subjective complaint of erectile inability by the patient (or patient and partner), and extensive diagnostic procedures are generally not required to proffer the diagnosis. Additionally, current first-line intervention in the form of effective oral pharmacotherapy is easily prescribed and administered and is frequently successful for the majority of patients. However, notwithstanding the semblance that the management of ED is fairly uncomplicated, it is a structured process that critically incorporates several clinical practice concepts for bringing the best therapeutic outcomes to patients.

Early Detection

Epidemiologic and clinical investigation has suggested that many patients with ED retain adverse clinical conditions and also lifestyle factors (e.g., diabetes, cardiovascular disease, prostate disease, overweight condition, current cigarette smoking, and physical inactivity) that potentially compromise erectile function (Saigal et al, 2006; Laumann et al, 2007; Selvin et al, 2007; Lewis et al, 2010). The extent of these risk factors comprises an increased global cardiometabolic risk profile in patients with ED (Miner et al, 2012; Nehra et al, 2012). Calculated odds ratios underscore the extent to which various ED risk factors correlate with ED (Table 27-2). These data support the contention that patients with identifiable ED risk factors likely experience the sexual dysfunction currently or will eventually develop it at some time. Clinical screening of such patients based on these indications is advantageous in allowing opportunities to diagnose and treat ED.

Growing evidence has also suggested that a patient's genotype influences the risk of developing ED, consistent with proposals that both molecular and genetic mechanisms account for the ED phenotype (Andersen et al, 2011; Lippi et al, 2012). This concept fits with the perspective that genetically determined biomarkers will eventually be defined to assess ED risk profile as well as level of responsiveness to a specific ED therapy in the advancing era of precision medicine.

Medication use has also been associated with ED in up to 25% of presentations (Keene and Davies, 1999; Francis et al, 2007). The most commonly implicated classes of drug include antihypertensive drugs, such as thiazide diuretics and β -adrenoceptor antagonists, and psychotherapeutic drugs, particularly selective serotonin reuptake inhibitor (SSRI) antidepressants. Table 27-3 lists several drug classes commonly associated with ED. It is important to recognize that medications may affect other components of the male sexual response cycle including sexual desire, arousal, and orgasm, which secondarily hampers erectile function. Of additional importance, the assignment of causation of ED for any particular medication is conditional, requiring that an increased prevalence exists in the

TABLE 27-2 Major Erectile Dysfunction Risk Factors

CONDITION	MULTIVARIATE ADJUSTED ODDS RATIO
Diabetes mellitus	2.9
Hypertension	1.6
Cardiovascular disease	1.1
Hypercholesterolemia	1.0
Benign prostate enlargement	1.6
Obstructive urinary symptoms	2.2
Increased body mass index (>30 kg/m ²)	1.5
Physical inactivity	1.5
Current cigarette smoking	1.6
Antidepressant use	9.1
Antihypertensive use	4.0

From Francis ME, Kusek JW, Nyberg LM, Eggers PW. The contribution of common medical conditions and drug exposures to erectile dysfunction in adult males. *J Urol* 2007;178:591–6; and Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med* 2007;120:151–57.

TABLE 27-3 Drugs Associated with Erectile Dysfunction

CLASS	SPECIFIC AGENTS
Antihypertensives	Thiazide diuretics, nonselective β -blockers
Antidepressants	Tricyclics; selective serotonin reuptake inhibitors
Antipsychotics	Phenothiazines
Antiandrogens	Nonsteroidal (flutamide); steroidal (cyproterone acetate); luteinizing hormone-releasing hormone analogues
Antiulcer drugs	Histamine H ₂ receptor antagonists (cimetidine)
Cytotoxic agents	Cyclophosphamide, methotrexate
Opiates	Morphine

target population compared with the placebo group after stratification for known risk factors or compared to another drug with an equivalent therapeutic effect, and, further, a credible physiologic mechanism should be established experimentally (Sáenz de Tejada et al, 2005).

Goal-Directed Management

A goal-directed approach to the management of patients with ED has largely been practiced in the field throughout the decades since Lue's original description (Lue, 1990). The approach dictates that the diagnostic evaluation and therapeutic plan relates to the individual patient's presentation and manner of deriving satisfaction, in accordance with a patient-centered framework (Hatzichristou et al, 2010). The basic aim of goal-directed management is to allow the patient or couple to make an informed selection of the preferred therapy for sexual fulfillment based on a sound understanding of all treatment options after completing a thorough discussion with the treating clinician. The approach recognizes that patients vary in their acceptance of their sexual disorders and in their interest in pursuing management. Their decisions accordingly follow individual preferences, needs, and expectations regarding management options. Evaluations of this approach have affirmed its utility and demonstrated that patient therapeutic preferences accord with the least invasive forms of therapy (Jarow et al, 1996; Hanash, 1997).

Role of Partner Interview

The partner interview is a critical component in initiating management of ED. Partner interviews have been shown to impact diagnosis and treatment in as much as 58% of cases (Tiefer and Schuetz-Mueller, 1995; Chun and Carson, 2001). The partner may be the source of important information that guides optimal intervention and response to therapy. The partner may share a new and different perspective on sexual issues affecting the couple, might provide insight into the quality of the couple's relationship, and might relate his/her role in the sexual dysfunction (Speckens et al, 1995; Fisher et al, 2009). The partner's involvement and attitude may also impact the patient's initiation of and adherence to therapy (Jackson and Lue, 1998; Fisher et al, 2005).

An important additional consideration is that partners' well-being may be affected by the patients' ED conditions. Studies have shown that women partners of men with ED are themselves more likely to have sexual dysfunction or to cease sexual activity entirely (Ichikawa et al, 2004; Montorsi and Althof, 2004; Fisher et al, 2005; Sand and Fisher, 2007). This observation further prompts the facilitatory role of the partner in ED management, which maximizes the success of therapy and inherently the satisfaction of the couple.

In practice, and as necessary, additional office visits, during which the partner accompanies the patient and the patient communicates educational information to the partner, are recommended techniques for involving partners in ED management (Dean et al, 2008).

Cardiac Risk Assessment

The frequent coexistence of ED and cardiovascular disease, as established by clinical epidemiologic study and by basic science research, has steered ED management to include procedures that account for the ED patient's cardiovascular health risks. The Princeton Consensus Conferences, a multidisciplinary forum convened successively on three occasions since the early 2000s, have emphasized the link between sexual activity and cardiac risk and have pronounced that all men with ED, even in the absence of manifesting cardiac symptoms, should be regarded as having potential risks for cardiovascular disease (DeBusk et al, 2000; Kostis et al, 2005; Jackson et al, 2006b; Nehra et al, 2012).

According to the Princeton Consensus expert panel guidelines, ED patients are recommended to undergo a full medical assessment with stratification of cardiovascular risk as high, medium, or low (Fig. 27-1). Patients classified as having a high risk would be those with unstable or refractory angina, a recent history of myocardial infarction, certain arrhythmias, or uncontrolled hypertension. For these patients, sexual activity with any particular ED therapy should be deferred until the cardiac condition is stabilized. Such patients should ideally undergo cardiologic referral for cardiovascular stress testing and subsequent risk-reduction therapy. Importantly, even patients at low risk for cardiovascular events should receive the minimum recommendations of cardiovascular disease management. Basic intervention includes counseling for lifestyle modifications such as increased physical activity and improved weight control combined with regular health monitoring by the patient's general practitioner (Kostis et al, 2005). A more comprehensive approach specifies cardiovascular risk reduction and affirmation of exercise tolerance for sexual activity following noninvasive cardiovascular risk assessment that may involve a specialist or collaborative medical team having such expertise (Nehra et al, 2012).

Step-Care Approach

Practitioners of ED management have always sought a rational approach for implementing diagnostic and therapeutic options. The "Process of Care Model for Erectile Dysfunction" was proposed as a stepwise methodology, combining processes, actions,

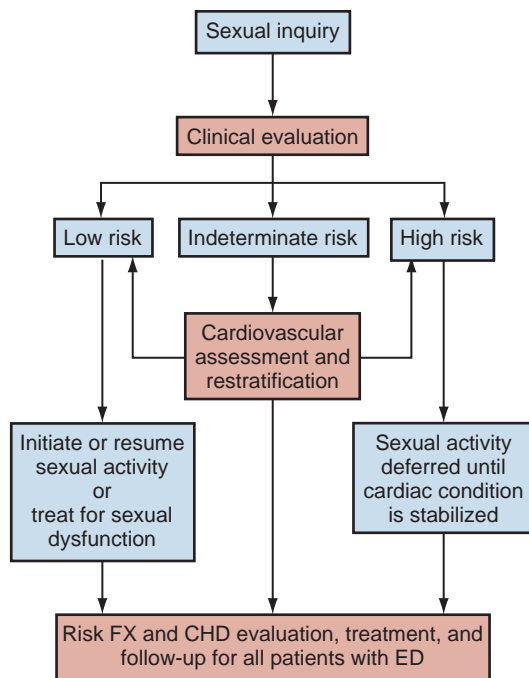


Figure 27-1. Algorithm for evaluation of the patient with cardiovascular disease recommended by the Second Princeton Panel. CHD, coronary heart disease; ED, erectile dysfunction; FX, factors.

and outcomes in the management of the ED patient (Process of Care Consensus Panel, 1999). It specified an algorithm for therapeutic decision making that takes into account patient needs and preferences (goal-directed management), although it was also based on specific criteria such as ease of administration, reversibility, relative invasiveness, and cost of therapies. This algorithm presented a strategy of staged therapy (i.e., first-, second-, and third-line interventions), which ranged from lifestyle modification to surgery. In concept, the scheme has been borrowed and endorsed by other consensus panels that acknowledged the purpose of patient education and counseling along with medical therapies as initial forms of ED management in common practice (Montague et al, 2005; Hatzichristou et al, 2010).

Shared Decision Making and Treatment Planning

The therapeutic plan may vary for every patient and couple and it ultimately depends on a host of factors including patient considerations as well as clinical indications and contraindications. An informed decision-making process should dictate the best therapeutic option. It follows a balanced and thorough discussion led by the clinician of all treatment options, both medical and nonmedical, and their expected advantages and disadvantages. Perceived risks and benefits, which may be influenced by the individual clinical situation, should be weighed. It is understood that the patient may appropriately select a preferred treatment option without necessarily adhering to a strictly prescribed succession of attempted therapies. Indeed, the patient may elect to defer treatment altogether. Whatever the patient (or couple) chooses, this option can then be pursued within the boundaries of safety, under the supportive partnership of his clinician.

Specialist Referral

The advent of effective oral pharmacotherapy for ED has enabled many primary practitioners to feel comfortable with managing the majority of clinical presentations of ED. At the same time, it is understood that situations arise in which the patient or primary

practitioner may request the assistance of a consultant/specialist (e.g., cardiologist, endocrinologist, psychologist, or urologist) for further diagnostic evaluation and treatment beyond the boundaries of initial management (*Process of Care Consensus Panel, 1999*). Such referrals may be required for individuals with complicated or atypical presentations of ED, representing diagnostic challenges that exceed common clinical practices of nonspecialists. Specialized evaluation and management potentially offer improved therapeutic outcomes for these presentations.

Generally recommended indications for specialized evaluations and associated consultants are: failure of initial treatment, referred to a urologist; younger patients with a history of pelvic or perineal trauma, referred to a urologist; patients with significant penile deformity (e.g., Peyronie disease, congenital chordee), referred to a urologist; complicated endocrinopathies (e.g., secondary hypogonadism, pituitary adenoma), referred to an endocrinologist; complicated psychiatric or psychosexual disorders (e.g., refractory depression, hypoactive sexual desire), referred to a psychiatrist; presentations requiring vascular or neurosurgical intervention (e.g., aortic aneurysm, lumbosacral disk disease), referred to a vascular surgeon or neurosurgeon, respectively; medical/legal reasons (e.g., workman's compensation claims), referred to a urologist.

A caveat is that effort should be made at the time of referral to ensure that patients are fully informed about the rationale, costs, potential risks, and potential outcomes of the referral and possible additional procedures. This recommendation is made in accordance with the principles of patient-centered medicine, by which patients (and partners where possible) should be included in the decision-making process.

Follow-up Care

Follow-up care is an essential part of ED management and should not be overlooked. The objectives of this action are manifold. A primary basis is to ensure continual success with the therapeutic outcome. It has been shown that treatment discontinuation occurs at high rates among patients who are not reassessed regularly (*Albaugh et al, 2002*). Additional purposes are to reassess medical and psychosocial conditions adversely impacting ED and success of therapy, evaluate the need for dosage titration or treatment substitution, and monitor adverse drug interactions or drug-interaction effects. As always, follow-up attention offers educational opportunities for patient and partner with regard to addressing sexual health concerns as well as lending guidance for related health care matters.

DIAGNOSTIC EVALUATION

The cornerstone in the evaluation of ED involves a detailed case history, preferably taken from patient and partner, physical examination, and proper laboratory tests (*Fig. 27-2*). The diagnosis can be submitted based on an individual's report of consistent inability to attain and maintain an erection of the penis sufficient to permit satisfactory sexual intercourse (*NIH Consensus Statement, 1992; Lewis et al, 2004*). It is noteworthy that the original National Institutes of Health definition did not specify a parameter for the duration of symptoms to accept the diagnosis. Subsequent organizational statements did apply a 3-month interval as a minimal requirement diagnostically, except for cases of trauma or surgically induced ED (*Lewis et al, 2004*).

Sexual, Medical, and Psychosocial History

The comprehensive assessment of any sexual problem begins with the performance of a detailed case history including sexual, medical, and psychosocial components. The clinician may use brief checklists or questionnaires for the purpose of recognizing the problem and initiating its evaluation, although he/she should routinely perform a detailed interview to understand the nature of the sexual complaint. The sexual history component in particular should be elicited with utmost sensitivity, given the intrapersonal and interpersonal aspects of sexual dysfunction (*Rosen et al, 2004; Althof et al, 2013*). Additional emphasis has been directed toward providing cultural competence when interacting with patients (*Hatzichristou et al, 2010*). All discussion of sexual matters is done privately and confidentially, and the clinician is required to express trust and concern as well as a nonjudgmental manner that epitomizes the doctor-patient relationship. The clinician should not assume that every patient is involved in a monogamous, heterosexual relationship. However, the situation may be presented whereby the partner can be interviewed, and this opportunity may be used, with the approval of the patient, to corroborate aspects of the clinical history and to confirm mutual therapeutic goals.

Sexual History

The sexual history is the central component of the clinical history and serves to confirm the patient's sexual dysfunction complaint of ED. Objectives of the interview are also to delineate the problem according to such features as its onset, duration, conditions, severity, and etiology. The conditions of the problem are often

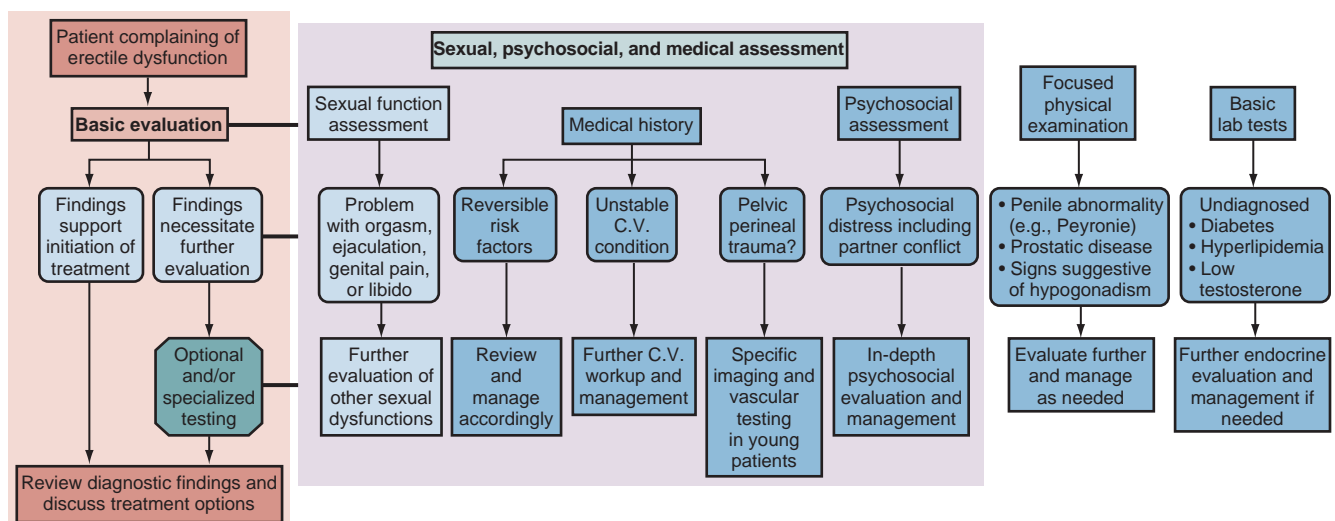


Figure 27-2. Diagnostic algorithm for erectile dysfunction (ED) recommended by the International Consultations on Sexual Medicine. C.V., cardiovascular.

determined by reviewing circumstances that facilitate or hinder erectile function. Circumstances for achievable erections include stimuli used during sexual encounters, erections on awakening, and the role of self-stimulation. Circumstances associated with erectile difficulty include performance anxiety, inability to perform with a designated partner, and motivational factors affecting lovemaking. Other pertinent issues include availability, interest and health of the partner, changes in medical status or other events relating to the onset of ED, and previous attempts to manage the problem by the patient or another caregiver.

The severity of ED can be defined as mild, moderate, or severe/complete, according to increasing degrees of loss of penile rigidity and the associated interference with sexual activity. For instance, mild ED may refer to a minimally decreased ability to attain and/or maintain an erection with intermittent satisfactory sexual performance, moderate ED may refer to a minimally decreased ability to attain and/or maintain an erection with infrequent satisfactory sexual performance, and severe ED may refer to a substantially decreased ability to attain and/or maintain an erection with rare or absent satisfactory performance.

The potential etiology of ED is commonly probed and may be categorized as psychogenic, organic, or mixed according to whether there is a presumed psychological or interpersonal determinant (psychogenic), a specific endocrinologic, neurologic, or cardiovascular cause (organic), or the coexistence of psychological or relationship factors and organic causes (mixed) (Table 27-4) (Ralph and McNicholas, 2000; Hatzichristou et al, 2010). It is accepted that many times ED cannot be fully dichotomized into psychogenic and organic categories. However, its characterization by a predominant etiologic basis may nonetheless facilitate therapeutic objectives. The interview should also assess whether ED is the primary source of the presenting complaint or secondary to some other aspect of the sexual response cycle (e.g., desire, ejaculation, orgasm) that may also relate to the clinical presentation (Rosen, 2004a). The association of decreased arousal, if present, may be explored as well and evaluated to determine whether it preceded or was incidental to the development of ED.

Medical History

The medical history primarily serves to identify and evaluate predictors and risk factors associated with ED. The main objective is to explore the role of possibly related or underlying medical conditions and to ascertain the existence of comorbidities. Recognition of the association between medical conditions and ED not only may lend insight into the possible basis for the ED, which may guide the choice of therapy, but it may also specify reversible or treatable factors associated with ED that may be corrected with an expectation of improving the level of erectile function.

Medical conditions associated with ED include disease states (e.g., type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, neurologic disease, hypogonadism, thyroid disorders), consequences of trauma involving aspects of the body, pelvis, or genitalia (e.g., spinal cord injury, pelvic surgery or radiation, sexual injury), and also side effects of medications or recreational substances that disturb biochemical processes of penile erection. Age is recorded, in accordance with the well-known association between aging and ED. It is important that comorbidities (e.g.,

depression, anxiety, anger) are registered because of their bidirectional relationship with ED.

Psychosocial History

The intake of psychosocial history is a necessary part of the clinical history. The very best sexual performance most assuredly implies wellness of mind and body acting together, and unstable psychosocial circumstances of both intrapersonal and interpersonal contexts may adversely affect sexual function. Accordingly, the presence and interaction of mental health problems, emotional stressors, and interpersonal relationship difficulties, both past and present, should be ascertained. Additional questions may be asked relating to occupational status, financial security, family life, and social support, which may also influence sexual function.

Physical Examination

The physical examination is a highly recommended component of the comprehensive assessment of sexual dysfunctions and complements the clinical case history (Ghanem et al, 2013). It may show possible etiologies for ED.

This evaluation consists of basic anthropometrics (i.e., height, weight, waist circumference), assessment of body habitus (appearance of secondary sexual characteristics), and examination of relevant body parts pertaining to cardiovascular, neurologic, and genital systems, with a particular focus on the external genitalia. The observation of a classically distinctive body habitus consistent with Kallman or Klinefelter syndrome or obvious physical signs of hypogonadism, such as gynecomastia and general poor masculine development, may suggest an endocrinologic basis for ED.

Findings of obesity, elevated blood pressure, or abnormal femoral or pedal pulses, all signs representative of cardiovascular disease, convey a potential vascular causation. Findings of abnormal genital and perineal sensation or bulbocavernosus reflex (squeezing of the glans penis resulting in contraction of the bulbocavernosus muscle detected by a finger in the anus) may indicate the presence of a peripheral neuropathy in association with a neurologic disorder or diabetes.

Detection of a penile deformity, such as micropenis, congenital chordee, or Peyronie disease-related fibrous plaques in the corpora cavernosa, supports the possibility that a physical impediment accounts for ED. Genital examination findings of abnormal position, size, and consistency of testes may also suggest hypogonadism and would indicate that ED exists on endocrinologic grounds.

Questionnaires and Sexual Function Symptom Scores

Self-administered ED questionnaires are extremely useful adjuncts to the case history, and they concur with the patient's self-report in establishing the diagnosis. Questionnaires supplied early in the field were very detailed, such as the Derogatis Sexual Function Inventory (245 items) (Derogatis and Melisaratos, 1979) and the Golombok Rust Inventory of Sexual Satisfaction (GRISS) (28 items) (Rust and Golombok, 1986), and they commonly aimed to differentiate psychogenic and nonpsychogenic ED or to evaluate sexual functioning in the context of the couple. Instruments developed more recently were implemented primarily in clinical trials associated with new drug development, and they particularly captured efficacy end points including sexual interest, performance, and satisfaction. However, as part of pattern shifts of practice that have occurred in ED management in recent years, there has been a growing emphasis on and application of patient self-reported instruments for clinical practice. These self-report measures have been meant to be brief and practical and to serve in documenting the presence and severity of ED, and the responsiveness of ED to treatment.

The most widely referenced instruments include the International Index of Erectile Function (IIEF) by Rosen and associates (1997), the Brief Male Sexual Function Inventory (BMSFI) by

TABLE 27-4 Classification of Erectile Dysfunction

PSYCHOGENIC	ORGANIC
Sudden onset	Gradual onset
Complete immediate loss	Incremental progression
Situational dysfunction	Global dysfunction
Waking erections present	Waking erections poor/absent

Modified from Ralph D, McNicholas T. UK management guidelines for erectile dysfunction. *BMJ* 2000;321:499–503.

O'Leary and colleagues (1995), the Center for Marital and Sexual Health Sexual Functioning Questionnaire by Glick and associates (1997), the Changes in Sexual Functioning Questionnaire by Clayton and associates (1997), and the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) by Althof and colleagues (1999). The IIEF, which contains 15 items that address and quantify

five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction, is the most widely used questionnaire (Fig. 27-3). An abridged 5-item version of this instrument, the IIEF-5, has been useful to clinicians in routine clinical practice specifically for the evaluation of ED (Rosen et al, 1999a). The instrument classifies ED severity into five categories: severe

Patient Name: _____ MR#: _____ Date: _____

OVER THE PAST 4 WEEKS

- | | |
|--|--|
| <p>1. How often were you able to get an erection during sexual activity?</p> <p>0 = No sexual activity
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always</p> <p>2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?</p> <p>0 = No sexual activity
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always</p> <p>3. When you attempted sexual intercourse, how often were you able to penetrate (enter)?</p> <p>0 = Did not attempt intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always</p> <p>4. During sexual intercourse, <u>how often</u> were you able to maintain your erection after you had penetrated (entered) your partner?</p> <p>0 = Did not attempt intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always</p> <p>5. During sexual intercourse, <u>how difficult</u> was it to maintain your erection to complete intercourse?</p> <p>0 = Did not attempt intercourse
1 = Extremely difficult
2 = Very difficult
3 = Difficult
4 = Slightly difficult
5 = Not difficult</p> <p>6. How many times have you attempted sexual intercourse?</p> <p>0 = No attempts
1 = One to two attempts
2 = Three to four attempts
3 = Five to six attempts
4 = Seven to ten attempts
5 = Eleven or more attempts</p> <p>7. When you attempted sexual intercourse, how often was it satisfactory to you?</p> <p>0 = Did not attempt intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always</p> | <p>8. How much have you enjoyed sexual intercourse?</p> <p>0 = No intercourse
1 = No enjoyment
2 = Not very enjoyable
3 = Fairly enjoyable
4 = Highly enjoyable
5 = Very highly enjoyable</p> <p>9. When you had sexual stimulation or intercourse, how often did you ejaculate?</p> <p>0 = No sexual stimulation/intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always</p> <p>10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?</p> <p>0 = No sexual stimulation/intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always</p> <p>11. How often have you felt sexual desire?</p> <p>1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always</p> <p>12. How would you rate your level of sexual desire?</p> <p>1 = Very low/none at all
2 = Low
3 = Moderate
4 = High
5 = Very high</p> <p>13. How satisfied have you been with your overall <u>sex life</u>?</p> <p>1 = Very dissatisfied
2 = Moderately dissatisfied
3 = About equally satisfied and dissatisfied
4 = Moderately satisfied
5 = Very satisfied</p> <p>14. How satisfied have you been with your <u>sexual relationship</u> with your partner?</p> <p>1 = Very dissatisfied
2 = Moderately dissatisfied
3 = About equally satisfied and dissatisfied
4 = Moderately satisfied
5 = Very satisfied</p> <p>15. How do you rate your <u>confidence</u> that you could get and keep an erection?</p> <p>1 = Very low
2 = Low
3 = Moderate
4 = High
5 = Very high</p> |
|--|--|

Figure 27-3. International Index of Erectile Function Questionnaire.

(5 to 7), moderate (8 to 11), mild to moderate (12 to 16), mild (17 to 21), and no ED (22 to 25). The Male Sexual Health Questionnaire offers another instrument that assesses core components of male sexual function (i.e., desire, erection, ejaculation, satisfaction) and is useful in both clinical and research settings (Rosen et al, 2004b). The Sexual Experience Questionnaire is a brief but comprehensive tool for evaluating health-related quality-of-life concepts, and it comprises erection, individual satisfaction, and couple satisfaction domains (Mulhall et al, 2008).

A known limitation of self-administered questionnaires is that they do not distinguish an etiologic basis for ED, that is, they do not differentiate among the various causes of ED (Blander et al, 1999; Kassouf and Carrier, 2003). Further, they may not sufficiently indicate the severity of ED that is evidenced on objective grounds (Tokatli et al, 2006). Although the exact nature of the ED diagnosis arguably is not absolutely necessary to initiate ED treatment today with current management options, it is understood that further clinical evaluation with diagnostic tests may be required to discern the basis and extent of the ED by system (e.g., vascular, neurologic, endocrinologic) and take action that may be most effective and possibly corrective.

Cardiovascular Risk Assessment Tools

A trend in ED assessment is the application of cardiovascular disease-risk prediction models, which are used as scoring instruments to aid in the assessment of any man evaluated for ED (Nehra et al, 2013). Such models as the Framingham Risk Score or an alternate global risk score, which incorporate such cardiovascular predictive variables as family history of coronary heart disease, body mass index, and metabolic laboratory biomarkers, offer a powerful initial step to characterize and possibly mitigate cardiovascular risk in this clinical setting.

Laboratory Tests

Appropriate laboratory testing can be considered part of a systematic clinical evaluation for individuals presenting with ED (Ghanem et al, 2013). Such evaluation may confirm or define etiologic medical conditions associated with the sexual dysfunction. At times, it may identify treatable conditions or previously undetected disease states that may contribute to ED. A standardized panel of tests can be offered for the man presenting routinely with sexual dysfunction including ED. Further laboratory testing can be tailored to the clinical situation. Similarly, specialized endocrinologic assessment can be performed when indicated for select clinical presentations.

Recommended laboratory tests for men with sexual problems typically include serum chemistries, fasting glucose, complete blood count, lipid profile, and serum total testosterone. Total testosterone, measured from a morning-time blood draw, serves to screen androgenic status, and, if abnormally low, serum-free (or bioavailable) testosterone and luteinizing hormone (LH) should be measured. Prolactin measurement may also be done for hormonal assessment. Thyroid function tests may be performed at the clinician's discretion. Serum prostate-specific antigen (PSA) testing is performed as needed if there is a suspicion of prostate pathology that might be promoted by exogenously administered testosterone. Dipstick analysis of urine may show glucosuria, which suggests the diagnosis of diabetes.

SPECIALIZED EVALUATION AND TESTING

The implicit goal of specialized evaluations in medicine in general is to improve diagnostic accuracy and direct successful therapy based on the specific diagnosis. A similar principle applies to sexual medicine. However, at the present time, despite the availability of various technologies that may specify and define the causation for ED (i.e., vasculogenic, neurogenic, endocrinogenic, psychogenic), the treatment plan for this sexual dysfunction can often be formulated without performing extensive diagnostic testing. Nonetheless,

such testing is frequently applied for diagnostic precision, typically by specialists, particularly in settings of complex clinical presentations. Table 27-5 summarizes the most frequently used evidence-based test procedures for diagnostic evaluations of ED (Rosen et al, 2004d).

Vascular Evaluation

The vascular evaluation for ED conceptually connotes surveying the vascular requirements of the sexual organ for the erectile response: arterial blood inflow, blood engorgement, and blood retention within the corporeal structures. From a diagnostic standpoint, the

TABLE 27-5 Evidence-Based Tests for Organic Erectile Dysfunction and Recommendations

TEST	RECOMMENDATION*
VASCULAR	
Dynamic infusion cavernosometry and cavernosography (DICC)	B
Intracavernous injection pharmacotesting (ICI)	B
ICI and color duplex ultrasound	B
Arteriography	C
Computed tomography angiography	D
Magnetic resonance imaging (MRI)	D
Infrared spectrophotometry	D
Radioisotope penography	D
AUDIOVISUAL SEXUAL STIMULATION (AVSS)	
Independent or jointly with vascular testing	C
With or without: pharmacologic stimulation (oral, ICI)	C
NEUROPHYSIOLOGIC	
Nocturnal penile tumescence and rigidity (NPTR)	B
Erectiometer/rigidometer	D
Biothesiometry (vibratory thresholds)	C
Dorsal nerve conduction velocity	C
Bulbocavernosus reflex latency	B
Plethysmography/electroimpedance	D
Corpus cavernosum electromyography (CC-EMG)	C
MRI or positron emission tomography scanning of brain (during AVSS)	D

*Grades of recommendation:
A: At least one meta-analysis, systematic review, or randomized controlled trial with a low level of bias and directly applicable to the target population.
B: A body of evidence including high-quality systematic reviews of case-control or cohort studies directly applicable to the target population and demonstrating overall consistency of results.
C: A body of evidence including well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal, directly applicable to the target population, with overall consistency of results.
D: Nonanalytic studies (e.g., case reports, case series, expert opinion).
Modified from Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *BMJ* 2001;323:334-6; and Rosen RC, Hatzichristou D, Broderick G, et al. Clinical evaluation and symptom scales: sexual dysfunction assessment in men. In: Lue TF, Basson R, Rosen F, et al, editors. *Sexual medicine: sexual dysfunctions in men and women*. Paris: Health Publications; 2004. p. 173-220.

studies aim to assist in deriving the classic diagnoses of arterial impairment and veno-occlusive dysfunction. As for all diagnostic testing, hemodynamic tests of the penis require patient counseling regarding the purpose, alternatives, risks, and benefits of any procedure before its implementation.

Combined Intracavernosal Injection and Stimulation

The combined intracavernosal injection and stimulation (CIS) test serves as a first-line evaluation of penile blood flow because of its very basic manner of administration and assessment. The test involves the intracavernosal injection of a vasodilatory drug or drugs as a direct pharmacologic stimulus, combined with genital or audiovisual sexual stimulation, and the erectile response is observed and rated by an independent assessor (Donatucci and Lue, 1992; Katlowitz et al, 1993). The test is designed to bypass neurologic and hormonal influences involved in the erectile response and allows the clinician to evaluate the vascular status of the penis directly and objectively.

The clinician may decide the protocol for using vasodilator drugs. Alternative regimens include alprostadil alone (Caverject or Edex, 10 to 20 µg), a combination of papaverine and phentolamine (Bimix, 0.3 mL), or a mixture of all three of these agents (Trimix, 0.3 mL). The procedure requires a syringe with a 5/8-inch needle (27 to 29 gauge), which is inserted at the lateral base of the penis directly into the corpus cavernosum for medication delivery. After needle withdrawal, manual compression is applied to the injection site for 5 minutes to prevent local hematoma formation. The assessment is done periodically subsequently with rating of both rigidity and duration of response. Repeated dosing may be performed if the initial erectile response is poor. Return to penile flaccidity is required before allowing the patient to leave the office, and if detumescence does not occur spontaneously in approximately an hour after dosing, intracavernosal injection of a diluted phenylephrine solution (500 µg/mL) can be administered every 3 to 5 minutes until flaccidity returns.

A normal CIS test, based on the assessment of a sustainably rigid erection, is understood to signify normal erectile hemodynamics. Alternative diagnoses of psychogenic, neurogenic, or endocrinogenic ED may then be considered. However, it is known that false-positive results might occur in as many as 20% of patients with borderline arterial inflow (as defined by the measurement of 25 to 35 cm/s peak cavernous artery systolic flow on duplex ultrasonography) (Pescatori et al, 1994). False-negative results are also possible and occur most commonly because of patient anxiety, needle phobia, or inadequate dosage.

Duplex Ultrasonography (Gray Scale or Color-Coded)

Duplex ultrasound of the penis following pharmacostimulation or CIS represents second-line evaluation of penile blood flow. However, it is the most reliable and least invasive diagnostic modality for assessing ED. The test adds an imaging dimension and a quantification component to the evaluation of blood flow in the penis distinct from first-line evaluation, which relies on the assessor's judgment alone.

The technique consists of high-resolution (7.5 to 12 MHz) real-time ultrasonography and color-pulsed Doppler, which serves to visualize the dorsal and cavernous arteries selectively and to perform hemodynamic blood-flow analysis (Lue et al, 1989; Sikka et al, 2013). Scanning is applied to the surface of the penis and may include the entire penis from the crura in the perineum to the tip. Color-coded duplex ultrasonography indicates the direction of blood flow within vessels, with red designating direction toward the probe and blue designating direction away from the probe (Broderrick and Arger, 1993; Herbener et al, 1994). Flow velocities are measured at baseline before injection and commonly every 5 minutes afterward up to 20 minutes. Cavernous arterial diameters may also be measured. Vascular anatomic communications between the paired cavernous arteries or between the dorsal and cavernous arteries should be noted (Fig. 27-4). Erection quality should also

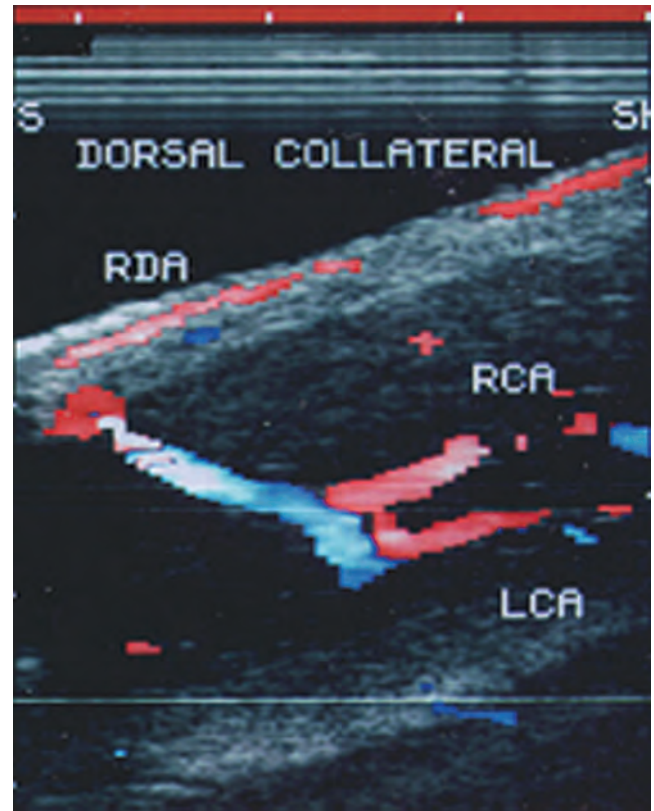


Figure 27-4. Collateral circulation connecting the right dorsal artery (RDA) to the right cavernous artery (RCA), and the left cavernous artery (LCA) is shown by color duplex ultrasonography in a longitudinal view.

be simultaneously assessed and rated. An observed poor erection, possibly associated with patient anxiety, should prompt vasodilator redosing as recommended for the CIS test.

A standard pattern of Doppler waveforms occurs with hemodynamic changes in corporeal pressure during progression to normal full erection (Fig. 27-5) (Schwartz et al, 1991). In the filling phase when sinusoidal resistance is low (within 5 minutes after vasodilator injection), the waveform increases in size consistent with high forward flow during both systole and diastole. As intracavernous pressure increases, diastolic velocities decrease. With full erection, the systolic waveforms sharply peak and may be slightly less than during full tumescence. At maximal rigidity, when intracavernous pressure exceeds systemic diastolic blood pressure, diastolic flow may be zero. The sonographic color pattern of the cavernous artery may demonstrate an impressive shift from red to blue in association with the reversal of diastolic flow.

Normative values have been described for peak systolic velocity (PSV) and diameter of the cavernous arteries during increases in arterial inflow to the penis. Early studies documented that the PSV of the cavernous arteries consistently exceeded 25 cm/s within 5 minutes of vasodilator injection in patients with nonarteriogenic causes of ED (i.e., psychogenic, neurogenic) (Lue et al, 1985; Mueller and Lue, 1988). Investigators subsequently confirmed mean PSV of cavernous arteries after pharmacostimulation to range from 35 cm/s to 47 cm/s in normal subjects (Benson and Vickers, 1989; Shabsigh et al, 1990). A cut point at 25 cm/s included a sensitivity of 100% and a specificity of 95% in patients with abnormal pudendal arteriography (Quam et al, 1989). Diameter changes of the cavernous artery after vasodilator injection were found to increase less than 75% and rarely to exceed 0.7 mm in patients with severe vascular ED (Lue and Tanagho, 1987; Mueller and Lue, 1988). Importantly, unlike PSV changes, a percentage of cavernous arterial vasodilation was not found to correlate well with findings on pudendal arteriography (Jarow et al, 1993).

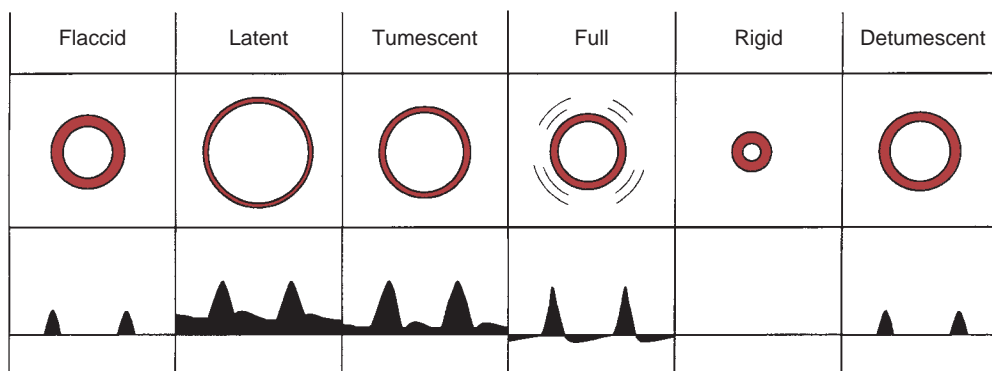


Figure 27-5. Artist's conception of the changes in diameter and flow waveform in the cavernous arteries induced by intracavernous injection of prostaglandin E₁ in a potent young man as demonstrated by duplex ultrasound. Forceful concentric pulsations are particularly noticeable during full erection.

Vascular arterial anatomic variants may confound the interpretation of duplex ultrasonography (Breza et al, 1989; Jarow et al, 1993). Early cavernous arterial branching or the presence of multiple such branches may affect blood-flow velocity determinations of the main cavernous artery. The presence of distal arterial perforators extending from the dorsal or spongiosal arteries also may alter the measurement of cavernous arterial blood-flow velocity. Accordingly, the clinician must recognize these variants to avoid making the incorrect diagnosis of arteriogenic ED. On the other hand, asymmetrical blood flow of the cavernous arteries may have diagnostic significance. The findings of dissimilar cavernous artery velocity measurements, which are greater than 10 cm/s between sides, or reversal of flow across a collateral may suggest a significant atherosclerotic lesion (Benson et al, 1993).

Duplex ultrasound measurements are informative for diagnosing vasculogenic ED (Rosen et al, 2004d). Cavernous arterial insufficiency is suggested when PSV is less than 25 cm/s; a PSV consistently greater than 35 cm/s defines normal cavernous arterial inflow. Cavernous artery acceleration time (i.e., PSV divided by systolic rise time) greater than 122 ms may also indicate this diagnosis. Cavernous veno-occlusive dysfunction, which refers to failure of erection maintenance despite adequate cavernous arterial inflow, is suggested by assorted sonographic parameters. Generally meaningful at 15 to 20 minutes after stimulatory onset, these parameters include persistent high systolic flow velocities (i.e., PSV >25 cm/s) and high end-diastolic flow velocities (EDV >5 cm/s), accompanied by rapid detumescence, following stimulatory onset. In addition, vascular resistive index (RI), based on the formula written as RI equals PSV minus EDV, which is then divided by PSV, has had tremendous diagnostic usefulness in this regard. The parameter is based on the concept that, as penile intracavernous pressure during erection achievement equals or exceeds diastolic pressure, diastolic flow in the corporeal bodies will approach zero and the value for RI will approach one. An RI greater than 0.9 has been associated with normal penile vascular function, and that less than 0.75 is consistent with veno-occlusive dysfunction (Naroda et al, 1996).

Several technical modifications of sonographic evaluation of the penis have been described. A portable Midus-pulsed Doppler unit connected to a laptop computer for in-office testing reliably records the Doppler waveform of the cavernous arteries despite the lack of a real-time ultrasound image (Metro and Broderick, 1999). Power Doppler offers an even more specialized technique to visualize distal ramifications of the main cavernous artery down to the level of arterioles (Sarteschi et al, 1998; Golubinski and Sikorski, 2002). A somewhat more invasive approach that evaluates the integrity of cavernous arterial flow involves the measurement of the cavernous artery systolic occlusion pressure (CASOP) by a Doppler transducer during saline intracavernosal infusion (Rhee et al, 1995). As a

variation on the stimulatory component of penile sonographic testing, a combination of an oral phosphodiesterase type 5 (PDE5) inhibitor in association with visual erotic stimulation has proven an effective, noninvasive method (Baçar et al, 2001; Speel et al, 2001). Sonographically measured postocclusive vasodilation of the cavernous arteries, which is believed to relate to the level of intact endothelial function in the penis, has been found diagnostic for organic ED (Virag et al, 2004). Cavernous artery intima-media thickness as demonstrated by high-resolution echo color Doppler ultrasound has been suggested as being more accurate than PSV in predicting vasculogenic ED (Caretta et al, 2009).

Dynamic Infusion Cavernosometry and Cavernosography

Cavernosometry and cavernosography, precisely referring to functional hemodynamic and radiographic assessments of the corpora cavernosa, represents third-line evaluation of the vascular integrity of the penis. The testing is indicated for select patients who are suspected of having a site-specific vasculogenic leak resulting from perineal or pelvic trauma or who have had lifelong ED (primary ED). When used, it generally precedes consideration for corrective penile vascular surgery.

The technique involves two needles inserted into the penis for simultaneous saline infusion and intracavernous pressure monitoring following intracavernosal pharmacologic injection (Glina and Ghanem, 2013). The testing requires complete trabecular smooth muscle relaxation to avoid erroneous results, and repeated and maximal pharmacologic dosing protocols are recommended (Hatzichristou et al, 1995). Measurements of maintenance flow rate, pressure drop, and CASOP are performed to verify complete smooth muscle relaxation (Fig. 27-6).

Dynamic infusion cavernosometry and cavernosography evaluates the penile venous outflow system. The existence of veno-occlusive dysfunction is indicated by the failure to increase intracavernous pressure to the level of the mean systolic blood pressure with saline infusion or the demonstration of a rapid drop of intracavernous pressure after cessation of saline infusion (Puyau and Lewis, 1983; Rudnick et al, 1991; Shabsigh et al, 1991; Motiwala, 1993). The flow rate required to maintain erection at an intracavernous pressure of more than 100 mm Hg is normally less than 3 to 5 mL/min, and the pressure decrease in 30 seconds from 150 mm Hg is normally less than 45 mm Hg. Cavernosography follows cavernosometric evaluation and is intended to show the site of venous leakage (Fig. 27-7). With normal veno-occlusive function, there should be opacification of the corpora cavernosa with minimal or no visualization of venous structures or corpus spongiosum. With impaired veno-occlusive function, leakage may be identified into such sites as the glans, corpus spongiosum, superficial dorsal veins, and cavernous and crural veins. More than one

site is visualized in the majority of patients (Lue et al, 1986; Rajfer et al, 1988; Shabsigh et al, 1991).

Penile Angiography

Penile angiography essentially refers to an anatomic study of the arterial vasculature of the penis and also represents third-line evaluation of the penile vascular system. It is commonly reserved for

the young patient with ED secondary to a traumatic arterial disruption or the patient with a history of penile compression injury, who is being considered for penile revascularization surgery (Sikka et al, 2013).

The procedure involves selective cannulation of the internal pudendal artery and injection of radiographic contrast. The intracavernosal injection of a vasodilating agent is optimally used to induce maximal vasodilation of the penile arterial supply. The anatomy and radiographic appearance of the iliac, internal pudendal, and penile arteries are then evaluated and documented (Fig. 27-8). The inferior epigastric arteries are frequently studied as well to determine their suitability for use in surgical revascularization. It should be recognized that significant variation of the intrapenile arterial anatomy exists, challenging the angiographer to differentiate congenital variations from acquired abnormalities and to establish their clinicopathologic relevance (Bähren et al, 1988; Benson et al, 1993).

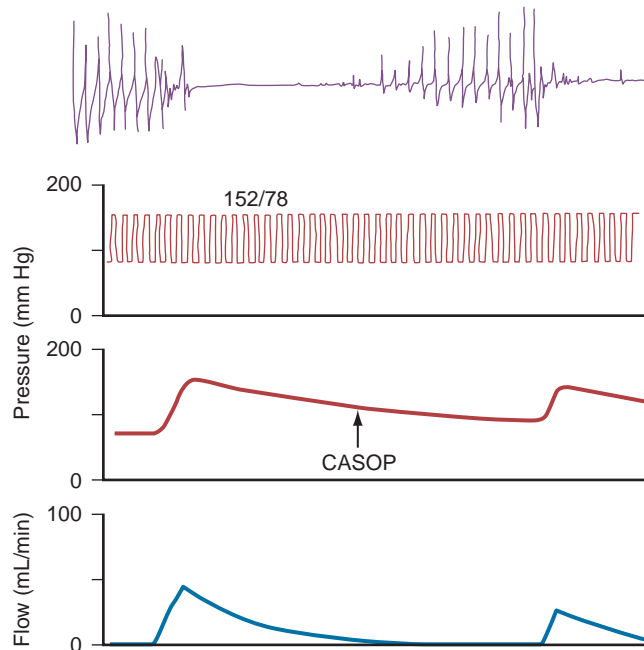


Figure 27-6. This tracing depicts four simultaneous variables obtained during the third phase of dynamic infusion cavernosometry and cavernosography. *Top to bottom:* Cavernosal artery flow recorded by using a continuous-wave Doppler ultrasound probe; systemic brachial systolic and diastolic arterial blood pressure (150/87 mm Hg); intracavernosal pressure, which varied from 70 to 160 mm Hg in this tracing; and intracavernosal heparinized saline inflow. The intracavernosal pressure at which the cavernosal artery pulsations returned, which is the effective cavernosal artery systolic occlusion pressure (CASOP), was 108 mm Hg. The gradient between the brachial and the cavernosal artery systolic occlusion pressures was 150 to 108, or 42 mm Hg, which is abnormal.

Historical and Investigational Studies of Penile Blood Flow

Penile Brachial Pressure Index

The penile brachial pressure index (PBI) test refers to the penile systolic blood pressure divided by the brachial systolic blood pressure. The technique involves applying a small pediatric blood pressure cuff to the base of the flaccid penis and measuring the systolic blood pressure with a continuous-wave Doppler probe. A PBI of 0.7 or less has been used to indicate arteriogenic ED (Metz and Bengtsson, 1981). The technique has not been found valid because it does not assess the hemodynamic properties of a functionally relevant, induced erection, and thus it is not recommended for use (Aitchison et al, 1990; Mueller et al, 1990).

Penile Plethysmography (Penile Pulse Volume Recording)

This test evaluates arterial pressure waveforms in the penis with an aggregate of the contributions of all penile vessels (Kedia, 1983). It requires the application of a 2.5- or 3-cm cuff connected to an air plethysmograph applied to the base of the penis, inflating the cuff to a pressure greater than brachial systolic pressure, and then decreasing the pressure by 10-mm Hg increments while recording pressure waveform tracings. Abnormal pressure waveforms by diagnostic criteria have been used to indicate vasculogenic ED (Doyle and Yu, 1986). Because this study is performed in the flaccid penis, as is the PBI, its clinical relevance has been questioned. Despite this concern, a technical modification that measures postischemic flow-mediated dilation was introduced as being

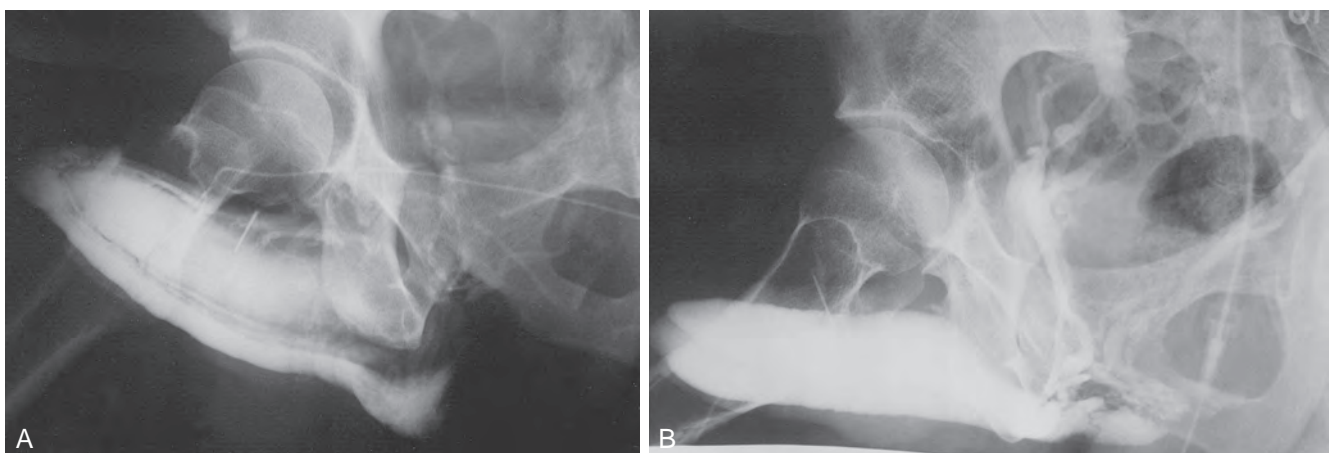


Figure 27-7. Pharmacologic cavernosography. **A**, In a patient 1 year after a penile fracture, a communication between the corpus cavernosum and the spongiosum is seen. **B**, In a 27-year-old man with primary impotence, venous leakage from the crura is seen.

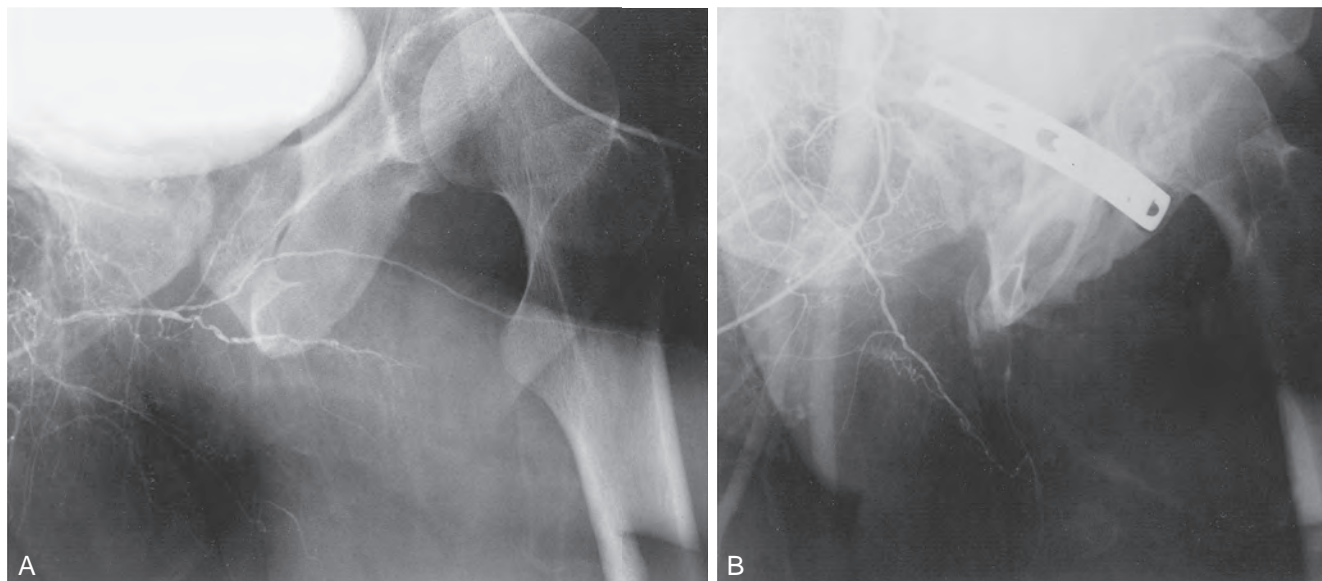


Figure 27-8. In this patient with a pelvic injury, pharmacologic penile arteriography (after intracavernous injection of 60 mg of papaverine) shows patent common penile, dorsal, and cavernous arteries (A) and nonvisualization of the common penile artery and its branches (B).

informative regarding penile vascular endothelial function (Dayan et al, 2005; Vardi et al, 2009).

Radioisotopic Penography

This test quantifies changes in penile blood volume after intracavernosal injection of a vasoactive agent using ^{99m}Tc -labeled red blood cells (Shirai et al, 1976). Extremely low flow is understood to mean arteriogenic ED (Smith et al, 1998). An evaluation comparing color duplex ultrasonography and radionuclide penography showed poor correlation (Glass et al, 1996).

Penile Magnetic Resonance Imaging

This test has significant potential applications for the assessment of anatomic details of the penis and penile microcirculation. Angiographic techniques may be combined with this test to evaluate the anatomic condition of the internal iliac and penile vasculature. Magnetic resonance angiography has been shown to correlate well with color duplex ultrasound testing (Stehling et al, 1997; John et al, 1999).

Penile Near Infrared Spectrophotometry

This test provides continuous, quantitative measurements of penile blood flow using a specialized near infrared spectrophotometry instrument (Burnett et al, 2000). It may be applied with an erectile stimulus and documents the hemodynamic phenomena of erection. Penile spectrophotometry has been further investigated in combination with intraurethral pharmacotherapy documenting blood-flow increase to the penis with this erectogenic modality (Padmanabhan and McCullough, 2007). Further investigation of this technique is needed to establish its clinical usefulness.

Cavernous Smooth Muscle Content

This test evaluates the smooth muscle composition of the corporeal tissue by light microscopic and computed morphometric assessment of biopsies of the penis and may serve adjunctively in the diagnosis of vasculogenic ED (Wespes et al, 1992). A reduced proportion of corporeal smooth muscle (and correspondingly increased collagen) has been observed in older men with veno-occlusive dysfunction (19% to 36% smooth muscle) and arteriogenic ED (10%

to 25%), compared with that of young, healthy men with normal erections and penile curvature (40% to 52%) (Wespes et al, 1991). In part because of its invasiveness, the test is controversial and thus it remains investigational at present.

Psychophysiologic Evaluation

The psychophysiologic evaluation of ED seeks to assess the erectile response by applying techniques that directly measure penile tumescence and rigidity. From the historical perspective of ED diagnostics, testing was applied primarily to differentiate psychogenic from organic ED. In general, the documentation of a full erection indicates functional integrity of the neurovascular axis regulating penile erection and thereby raises suspicion of a psychogenic etiology. There are several approaches to perform this evaluation. Importantly, the psychophysiologic evaluation does not currently represent first-line evaluation for ED, largely because of technical and cost limitations associated with current techniques. When considered to undergo any of these tests as part of a diagnostic plan, patients are counseled regarding the expected use, risks, and benefits of the tests.

Penile Tumescence and Rigidity Monitoring

Nocturnal penile tumescence (NPT) monitoring, which describes the study of erections that occur with nighttime sleep, was classically described as a technique offering the assessment of physiologic erectile ability (Wasserman et al, 1980). As a standard, sleep laboratory nocturnal penile tumescence and rigidity (NPTR) testing applies nocturnal monitoring devices that measure the number of episodes, tumescence (circumference change by strain gauges), maximal penile rigidity, and duration of nocturnal erections (Kessler, 1988). The conventional approach is to perform monitoring in conjunction with electroencephalography, electrooculography, and electromyography (EMG), with nasal airflow and oxygen saturation to document rapid eye movement (REM) sleep and the presence or absence of hypoxia (sleep apnea). It is important to note that documentation of REM sleep is undertaken because of the observation that true erectile phenomena occurring during sleep are associated with the REM sleep phase (Fisher et al, 1965). Sleep movement patterns are also monitored because periodic limb movement disorders are associated with abnormal NPT. Axial rigidity is measured along with photography of the erect penis when

awakening the patient at maximal tumescence; a buckling device is applied to the tip of the penis to measure resistance (500 g minimum for vaginal penetration, 1.5 kg suggestive of complete rigidity) (Karacan et al, 1977). NPT has traditionally been performed during 2 to 3 nights to overcome the so-called first-night effect when REM sleep is inconsistent. Formal testing, which involves a specially equipped sleep laboratory staffed with trained observers, is costly. The monitoring of diurnal penile tumescence, in reference to monitoring performed during daytime napping, has served alternatively as an in-office evaluation (Morales et al, 1994).

Rigiscan (Timm Medical Technologies, Inc., Minneapolis, MN) is an automated, portable device used for NPTR, which combines the monitoring of radial rigidity, tumescence, number, and duration of erectile events (Bradley et al, 1985). The device employs two loops, one placed at the base of the penis and the other placed at the coronal sulcus (respectively, base and tip recording sites), and these loops record penile tumescence (circumference) and radial rigidity with timed, standardized constrictions of the loops. A baseline initialization is performed with the patient in the office, and then it is calibrated for home use. At home, registrations of penile rigidity are done every 3 minutes and increased to every 30 seconds when the base loop detects a circumference increase of greater than 10 mm (Fig. 27-9). Recommended criteria for normal NPTR

include four to five erectile episodes per night, mean duration longer than 30 minutes, an increase in circumference of more than 3 cm at the base and more than 2 cm at the tip, and maximal rigidity greater than 70% at both base and tip (Cilurzo et al, 1992). A computerized program has yielded standardized data measurements according to cumulative distribution of time-intensity measures, defined as tumescence activity units (TAU) and radial rigidity activity units (RAU) (Burris et al, 1989; Levine and Carroll, 1994). Potential limitations of Rigiscan include the fact that radial rigidity does not accurately predict axial rigidity (Allen et al, 1993; Licht et al, 1995) and considerable variability apparently exists even in normal subjects (Levine and Carroll, 1994). Further, the manner of testing does not allow verification of the presence of REM sleep.

NPT electrobioimpedance (NEVA, American Medical Systems, Inc., Minnetonka, MN) is a device introduced more recently that assesses volumetric changes in the penis during nocturnal erections (Knoll and Abrams, 1999). The device consists of three small electrode pads applied to the hip and the penile base and glans and a small recording device attached to the patient's thigh. In operation, an undetectable alternating current is transmitted from the glans electrode to the hip ground, and the penile base electrode measures impedance and changes in penile length. Impedance measures decrease in concert with increases in cross-sectional area of the penis during nocturnal tumescence. Further investigation is needed to establish the relationship of volumetric changes and the rigidity of the penis. Similar to Rigiscan, the technique also does not include REM sleep monitoring and correlations.

In summary, NPTR monitoring is an attractive approach for objectively evaluating the somatic basis of erectile ability, theoretically devoid of psychological interference. However, it has several apparent shortcomings, which limit its routine use for diagnostic purposes (Jannini et al, 2009). Central issues are that the testing does not indicate the cause and severity of ED and that the results may be poorly reproducible. Another fundamental issue is whether the testing appropriately evaluates wakeful, sexually relevant erections. Indeed, erections observed during NPTR monitoring do not unequivocally equate with erections sufficient for sexual performance, and false-positive results are possible for various clinical situations (e.g., multiple sclerosis). False-negative results may occur in aging patients and in patients with depression or anxiety, which may conditionally affect the physiology of sleep-related erectile phenomena. Nonetheless, NPTR monitoring may be considered in special circumstances such as when the cause of ED is obscure and noninvasive testing is desirable.

Audiovisual and Vibratory Stimulation

Alternative erectogenic methods can be used in conjunction with diagnostic testing of erectile function. Erotic stimulation by explicit videotape material with monitoring has been used as a reliable as well as a time- and cost-effective alternative to NPTR for differentiating between organic and psychogenic ED presentations (Sakheim et al, 1987; Bancroft et al, 1991). It is also considered more physiologic, consistent with erectile behavior when awake. The testing has potential limitations, with possible false-negative responses occurring in the presence of endocrine abnormalities (Carani et al, 1992; Greenstein et al, 1995) and false-positive responses occurring in psychological situations such as erotic excitement inhibition (Chung and Choi, 1990). As one may infer, these methods can be applied in conjunction with other stimulatory conditions (e.g., pharmacologic erection testing) as well as erectile function assessment approaches (e.g., Rigiscan monitoring) (Katlowitz et al, 1993; Martins and Reis, 1997).

Neuroimaging

Diagnostic techniques to evaluate central mechanisms of male sexual arousal have contributed to the psychophysiologic investigation of ED. Positron emission tomography (Miyagawa et al, 2007) and functional magnetic resonance imaging (Park et al, 2001;

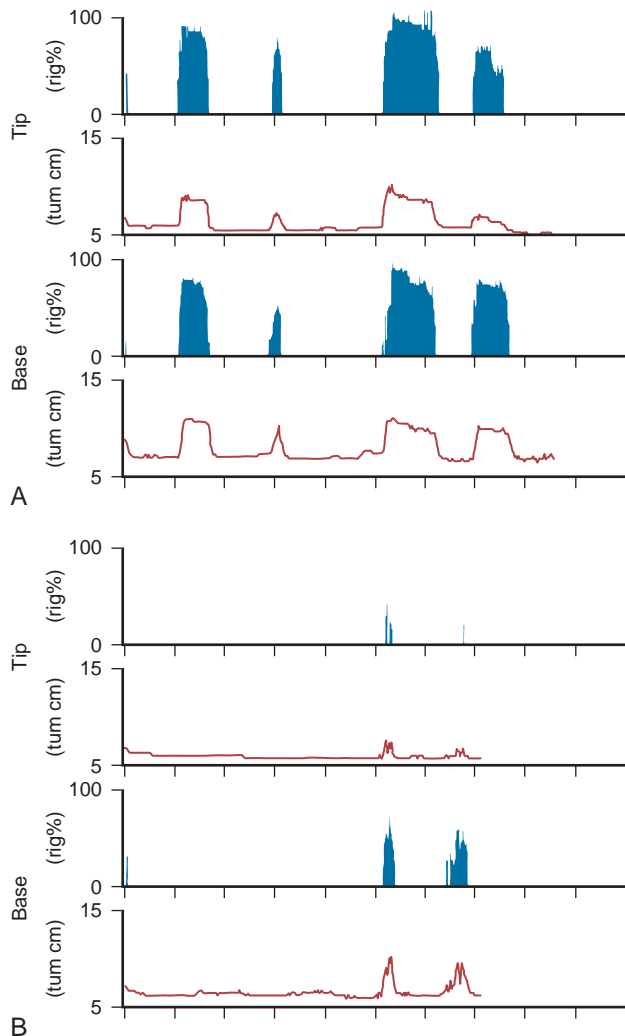


Figure 27-9. The RigiScan device has been designed to measure penile rigidity during home nocturnal monitoring. **A**, A study in a patient with at least two episodes of well-sustained, completely rigid nocturnal erections. **B**, A study with two episodes of poorly sustained, poorly rigid nocturnal erections. Such home studies fail to document sleep quality.

Montorsi et al, 2003; Mouras et al, 2003; Ferretti et al, 2005) have been used in association with video sexual stimulation or an erectogenic pharmacologic stimulus (e.g., oral apomorphine). Studies have documented key brain regions associated with sexual arousal that induce penile erection (i.e., anterior cingulate, insula, amygdala, hypothalamus, and secondary somatosensory cortices). Interestingly, functional abnormalities in the brain have been shown in patients with psychogenic ED, suggesting that this diagnosis may be attributable to an actual biologic basis. More investigation in this area is necessary before determining its clinical role.

Psychological Evaluation

The psychological evaluation of ED addresses psychogenic contributions to clinical presentations, essentially psychological and interpersonal factors interfering with erectile function. These aspects should not be underestimated, and it is well documented in population studies that ED is associated with anxiety, depression, low degrees of self-esteem, negative outlook on life, self-reported emotional stress, and a history of sexual coercion (Feldman et al, 1994; Laumann et al, 2007). The urologist's role in initiating a psychological evaluation is not necessarily complicated, and a basic attempt to use queries about a patient's psychological health is helpful in assessing sexual health (Rowland et al, 2005).

The diagnostic interview is central to the psychological evaluation, and this process should be straightforwardly handled. Readily discernible causes of sexual dysfunction may be elicited, such as fear of failure, performance anxiety (for widowers, this may include complex interactions of dating, new partners, and unresolved mourning/guilt), insufficient sexual stimulation, loss of attraction for the partner, adjustment to a chronic illness or surgery, and relationship conflicts. In addition, causes that are less immediately discernible may be identified to include unresolved parental attachments, sexual identity issues, history of sexual trauma, occurrence of extramarital affairs, and cultural-religious taboos (Leach and Bethune, 1996; Laumann et al, 2007).

The interviewer should be mindful of the possibility of a primary psychogenic ED presentation (Turnbull and Weinberg, 1983). In the absence of organic risk factors, a primary psychogenic ED causation may be suspected. Further support for the diagnosis may follow the confirmation of noncoital erections (i.e., masturbatory, nocturnal, or when awakening). Clinical subtypes of psychogenic ED may be further identified: (1) generalized versus situational, and (2) lifelong (primary) versus acquired (secondary, including substance abuse or major psychiatric illness).

The interviewer should also inquire about relationship factors (Rosen, 2001). Relationship conflicts may be the source of psychogenic ED or otherwise may exacerbate organic ED. A couple's issues include intimacy and trust, status and dominance, loss of sexual attraction, ability to achieve sexual satisfaction without erection, and communication problems. Important information may derive not just from interviewing the patient alone, and interviews both with the couple together and of partners separately may provide insight.

Complex intrapsychic causes of sexual dysfunction are often relevant for the ED presentation and may become evident during the diagnostic interview. The clinical history may show a significant traumatic life experience, cultural or religious strife, compulsive sexual behavior, or neurotic process. It may suggest the presence of serious psychiatric comorbidities such as substance abuse, depressive symptoms, anxiety disorder, or personality disorder. It is recognized that the urologist may not have the professional background, comfort, or time to address these issues definitively, and a referral to a psychological expert for further attention would certainly be appropriate.

Neurologic Evaluation

The neurologic evaluation of ED is concerned with neurogenic associations with ED presentations. The importance of testing for deficits in the neurologic system relates to the principal regulatory

role of this system for governing erectile function. Target sites for evaluation include peripheral, spinal, and supraspinal centers as well as both somatic and autonomic pathways involved in this biologic response. In line with this purpose, several diagnostic tests have been introduced. However, thus far they have had limited impact on routine clinical management decisions, and much of the available testing in this realm is reserved for research protocols and medicolegal investigations (Giuliano and Rowland, 2013). Additionally, fundamental problems surround the lack of sensitivity, reproducibility, reliability, and validity for many of these tests. This concern is particularly so for autonomic function tests, distinct from somatic function testing, which has been shown to be reproducible and valid. Otherwise, tests that could be most useful for evaluating penile erection, for example, neurotransmitter release, are altogether undeveloped.

Somatic Nervous System

Biothesiometry. This test represents a technique to assess afferent sensory function of the penis (Padma-Nathan, 1988). Testing involves a handheld electromagnetic device placed on the pulp of the index fingers, both sides of the penile shaft, and the glans penis. Measurements of sensory perception threshold are obtained in response to various amplitudes of vibratory stimulation. Investigators have questioned the usefulness of penile glans biothesiometry, which does not accurately portray neurophysiologic function of the dorsal penile nerve because of limitations in recording responses to vibratory stimuli of glanular skin (Bemelmans et al, 1995).

Sacral Evoked Response: Bulbocavernosus Reflex Latency. This test is used to assess the somatosensory reflexogenic mechanism of penile erection. Testing consists of a direct-current stimulator, which delivers square-wave impulses via two stimulating ring electrodes placed around the penis, one secured near the corona and the other secured 3 cm more proximally, and a recorder that gauges responses via concentric needle electrodes placed in the right and left bulbocavernosus muscles. Latency period is measured as the interval from the beginning of each stimulus to the beginning of each response. An abnormal latency time, defined as a value more than three standard deviations above the mean (30 to 40 ms), indicates a high probability of neuropathology (Padma-Nathan, 1988). However, the use of this test has been questioned, and it has been shown that a full battery of electrophysiologic tests evaluating limb nerve function is more sensitive in diagnosing neuropathy than such tests specific to pudendal nerve function alone (Vodusek et al, 1993; Ho et al, 1996).

Dorsal Nerve Conduction Velocity. This test in concept extends from pudendal nerve function reflex testing and involves electrophysiologic stimulation with two stimulating electrodes placed at the glans and the base of the penis for obtaining two bulbocavernosus reflex latency measurements. Conduction velocity of the dorsal nerve is represented by dividing the distance between the two stimulating electrodes by the difference in latency times recorded from both sites. An average conduction velocity of 23.5 m/s with a range of 21.4 to 29.1 m/s is found in normal subjects (Gerstenberg and Bradley, 1983). Abnormal nerve conduction velocities were found to be diagnostic for neurogenic ED in patients with diabetes (Kaneko and Bradley, 1987).

Genitocerebral Evoked Potential. This test is designed to assess afferent sensory mechanisms and stimulus processing at spinal and supraspinal nervous system levels. The testing requires complex electronic equipment for recording the evoked potential waveforms overlying the sacral spinal cord and cerebral cortex in response to dorsal penile nerve electrical stimulation (Spudis et al, 1989). Central conduction time is recorded as the difference between the latency times after stimulation of the first replicated spinal response and the first replicated cerebral response (Padma-Nathan, 1988). The test has been questioned as having poor discriminatory value of response latencies (Pickard et al, 1994). However, it may still serve as an objective tool to define characteristics of afferent penile sensory dysfunction in patients with subtle abnormalities on neurologic examination.

Autonomic Nervous System

Heart Rate Variability and Sympathetic Skin Response. The test of heart rate control (mainly parasympathetic) consists of measuring heart rate variations during quiet breathing, deep breathing, and in response to raising the feet. Normative parameters have been documented. The test of sympathetic skin response involves producing an electrical shock stimulus at a certain location, for example, median or tibial nerve, and recording the evoked potential elsewhere, for example, contralateral hand or foot or penis. Recording from the penis is considered to be a potentially useful method of testing penile autonomic innervation (Daffertshofer et al, 1994).

Penile Thermal Sensory Testing. This test serves to assess the conductance of small sensory nerve fibers, which are affected by autonomic disturbances consistent with neuropathy. The testing measures thermal threshold. In studies of the penis, it seems to correlate well with the clinical determination of neurogenic ED (Lefaucheur et al, 2001; Bleustein et al, 2003).

Corpus Cavernosum Electromyography and Single Potential Analysis of Cavernous Electrical Activity. This test offers a direct recording of cavernous electrical activity, which varies between penile flaccidity and tumescence (Wagner et al, 1989; Leddy et al, 2012). In the normally flaccid penis, electrical activity is described as exhibiting a rhythmic slow wave with intermittent bursts of activity. As penile tumescence occurs (such as in response to visual sexual stimulation or after intracavernosal injection of a smooth muscle relaxant), this activity ceases. During detumescence, the baseline electrical activity returns. Patients with suspected autonomic neuropathy were demonstrated to display a discordant pattern, having continued electrical activity during erectogenic stimuli (Wagner et al, 1989). Recording techniques have been standardized, and normative values have been defined to include maximum peak-to-peak amplitudes between 120 and 500 mV and mean potential durations of 12 seconds (Stief et al, 1994). However, the clinical utility of this test remains in question (Kellner et al, 2000; Jiang et al, 2003).

Hormonal Evaluation

The hormonal evaluation for ED explores an endocrinologic basis for the sexual dysfunction and recognizes accumulating evidence that endocrinopathies potentially impact the physiology of penile erection (Traish and Guay, 2006; Mironi et al, 2009). Several endocrine conditions are particularly relevant in this regard: hypogonadism (decrease or absence of hormonal secretion from the gonads), hyperthyroidism (excessive thyroid hormone release), and diabetes (altered modulation of androgen function (Wang et al, 2011; Maggi et al, 2013)). The diagnostic evaluation may be undertaken in view of their possible influences on erectile function. The clinical history may raise suspicion regarding the diagnosis, although the clinical presentation of an endocrinopathy may be variable. Several questionnaires have been proposed for use in screening, particularly with respect to hypogonadism (Morley et al, 2000; Daig et al, 2003; Heinemann, 2005). A new psychometrically validated hypogonadism screener has been developed to identify men with symptoms of hypogonadism (Rosen et al, 2011). However, their general lack of specificity for most presentations and the lack of sensitivity for some others has limited their widespread applications (Morales et al, 2007). The central feature of this evaluation involves biochemical testing for serum hormonal levels (Bhasin et al, 2010).

Serum Testosterone Measurements

Much focus in assessing the impact of endocrinopathies on male sexual function has centered on the role of androgens. Androgen deficiency or low testosterone levels are observed in as few as 2% and as many as 33% of men presenting clinically with ED (Korenman et al, 1990; Citron et al, 1996; Soran and Wu, 2005). Differences in patient populations under study likely account for the variation in statistics. In acknowledging that aging may represent

the primary cause of declining androgens, thought leaders have variously applied such terms as androgen deficiency of the aging male (ADAM), partial androgen deficiency of the aging male (PADAM), hypoandrogenism, symptomatic late-onset hypogonadism (SLOH), and andropause to designate this association.

It is important to understand the biology of testosterone production and function so as to proceed with its evaluation in laboratory. Testosterone circulates in three fractions: free (0.5% to 3%), tightly bound to sex hormone-binding globulin (SHBG) (~30%), and loosely bound to albumin and other serum proteins (~67%) (Basaria and Dobs, 2001; Freeman et al, 2001). Free testosterone and albumin-bound portions comprise the bioavailable testosterone fraction. The relative concentrations of the carrier proteins (SHBG and albumin) serve to modulate androgen function. Numerous conditions can alter the SHBG fraction and accordingly affect bioavailable testosterone to some extent even if the total testosterone measurement is unchanged (Bhasin et al, 2010). Decreased SHBG is associated with moderate obesity, nephrotic syndrome, hypothyroidism, and the use of glucocorticoids, progestins, and androgenic steroids, and it produces an elevation in bioavailable testosterone. Increased SHBG is associated with aging, hepatic cirrhosis, hyperthyroidism, human immunodeficiency virus infection, and the use of anticonvulsants and estrogens, and it produces a lowering in bioavailable testosterone. Despite the observation that lower levels of SHBG are associated with insulin resistance (Stellato et al, 2000), variable SHBG levels have been documented in diabetic men, possibly because of confounding obesity and aging factors, and the diagnosis of hypogonadism in this population should rely on the measurement of a low bioavailable testosterone level (see later) (Kapoor et al, 2007).

Theoretically, the unbound or free fraction measurement of testosterone offers the most relevant determination of testosterone bioavailability. However, commercial assays for free testosterone are known to be inconsistent and have been considered as invalid by some investigators (Vermeulen et al, 1999; Ly et al, 2010; Field and Wheeler, 2013). The best indicator of androgen status is the calculated bioavailable testosterone (free testosterone and albumin-bound testosterone). A formula for this calculation is found on the website of the International Society for the Study of the Aging Male at <http://www.issam.ch/freetesto.htm>, and this formula requires entries for the values of total testosterone and SHBG. In men with serious liver disease or hypoalbuminemia, entry of the serum albumin value may be useful for obtaining the best calculation.

For screening purposes, measurement of total serum testosterone level is generally sufficient. It is recommended that the blood draw be performed between 7:00 AM and 11:00 AM when there is a peak serum testosterone level, accounting for the fact that diurnal variation occurs in younger and middle-aged men (Wang et al, 2009). The typical reference range for the total testosterone measurement is 280 to 1000 ng/dL. Because of individual variability, it is recognized that the normal range for testosterone beyond which replacement therapy should be initiated remains unresolved. If the testosterone level is below or at the low limit of normal, blood draw should be repeated for confirmation. On the other hand, a mildly abnormal testosterone level might be found to be normal in 30% of patients on repeat testing (Bhasin et al, 2010). The clinical scenario, such as the presence of conditions that alter testosterone carrier proteins, may prompt further testing and assessment decisions.

Serum Gonadotropin Measurements

When proceeding with a second total testosterone determination, assessment of LH and prolactin should also be included. Measurement of serum gonadotropins will help to localize the source of the hypogonadism. It is understood that testosterone release involves the integrative activity of the hypothalamic-pituitary-gonadal axis and its regulatory feedback mechanisms, and disruption at any level of this axis may account for hypogonadism (Bhasin et al, 2010). A result of low testosterone is decreased

negative feedback to the hypothalamus and pituitary, causing increased secretion of LH and follicle-stimulating hormone (FSH). Elevated serum LH and FSH releases are appropriate pituitary responses to low serum testosterone levels, which is consistent with testicular failure (primary hypogonadism). In contrast, normal or low serum LH and FSH releases in the setting of low serum testosterone levels indicate an inappropriate response and suggest a central disorder (secondary hypogonadism).

Serum Prolactin Measurement

Hyperprolactinemia causes hypogonadism by suppression of gonadotropin-releasing hormone from the hypothalamus, which impairs the pulsatile LH secretion required for serum testosterone production by the gonads (Morales et al, 2004). An additional possible mechanism for sexual dysfunction, specifically loss of sexual libido, in patients with hyperprolactinemia independent of the circulating level of testosterone relates to an interference of the peripheral conversion of testosterone to dihydrotestosterone (DHT) (Lobo and Kletzky, 1983). Suspicion of hyperprolactinemia is raised in the patient with low serum testosterone and low or inappropriately normal LH. However, controversy surrounds the consideration of routine determinations of prolactin in men with ED, with some indicating the low yield in doing so (Johnson and Jarow, 1992; Govier et al, 1996) and others finding that low serum testosterone or low sexual desire does not always coincide with the diagnosis (Buvat and Lemaire, 1997; Johri et al, 2001). Causes of the condition include various medications such as antipsychotic agents, tricyclic depressants and opiates, prolactin-secreting tumors, hypothyroidism, hypothalamic lesions, renal insufficiency, cirrhosis, and chest wall lesions (Zeitlin and Rajfer, 2000; Molitch, 2005).

Magnetic Resonance Imaging Scans

Cases of central (hypogonadotropic) hypogonadism as well as unexplained hyperprolactinemia prompt central imaging of the pituitary. This evaluation commonly involves magnetic resonance imaging, which can identify structural abnormalities (Citron et al, 1996; Petak et al, 2002; Rhoden et al, 2003). Generally accepted guidelines provide indications for pituitary imaging: cases of severe central hypogonadism (testosterone <150 ng/dL) and suspicion of pituitary disease (i.e., panhypopituitarism, persistent hyperprolactinemia, or symptoms of tumor mass effect).

Serum Thyroid Function Tests

Hyperthyroidism is associated with ED, possibly by increasing aromatization of testosterone into estrogen (which raises levels of SHBG) (Morales et al, 2004) or by increasing adrenergic tone (which causes smooth muscle contractile effects or exerts psychobehavioral effects) (Carani et al, 2005). Symptoms of hyperthyroidism, such as hyperactivity, irritability, heat intolerance, palpitations, fatigue, and weight loss, are often reported, and physical signs such as tachycardia, tremor, goiter, and eyelid retraction are often identified. The diagnosis is made biochemically by measurement of high levels of thyroid hormone (total or free thyroxine [T₄] or triiodothyronine [T₃]) with a low-serum thyroid-stimulating hormone level.

TREATMENT CONSIDERATIONS

The treatment of ED axiomatically follows an appropriate diagnostic workup. Although current interventions are both etiologically specific and nonspecific, an intervention that is specific for the cause of ED ideally offers the opportunity to treat ED with a corrective purpose in mind. Current recommendations adhere to a patient goal-directed focus to therapy and specify that therapeutic options are presented according to a step-care clinical

KEY POINTS: DIAGNOSTIC EVALUATION

- The basic evaluation of ED consists of a detailed case history, physical examination, and proper laboratory tests.
- The sexual history should define the characteristics of the ED presentation according to such features as its onset, duration, conditions, severity, and etiology.
- Cardiac risk assessment and risk reduction interventions are appropriate when necessary for all patients presenting for ED evaluations.
- The hormonal evaluation for ED explores an endocrinologic basis for the disorder, with special consideration given to hypogonadism, hyperthyroidism, and diabetes as possible influences.
- Questionnaires and other patient self-report measures offer practical help in documenting the presence, severity, and responsiveness to treatment of ED.
- Specialized evaluation and testing may be required for individuals with complicated or atypical presentations of ED, and they potentially offer improved therapeutic outcomes for these presentations.

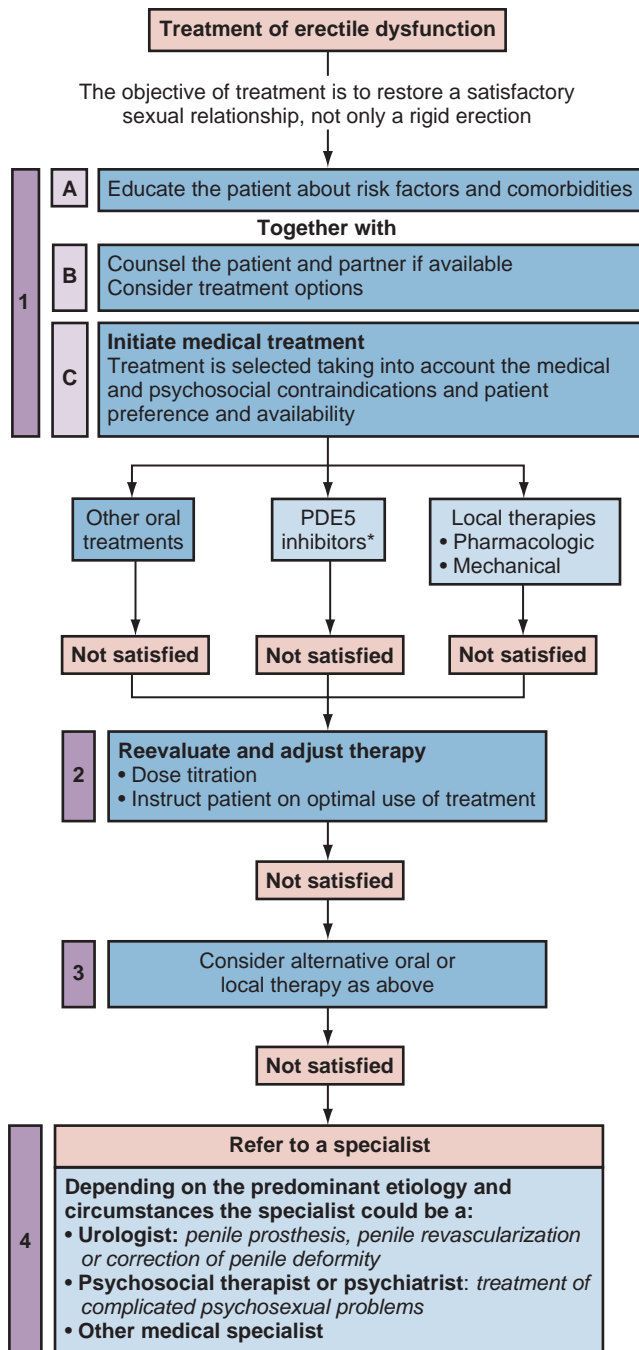
management approach (Fig. 27-10) (Montague et al, 2005; Hatzichristou et al, 2010).

Lifestyle Modification

The risk of developing ED is significantly associated with the presence of comorbid health conditions such as diabetes, cardiovascular disease, and metabolic syndromes that are either preventable or to a minimal extent treatable in endeavoring to optimize health status (Kostis et al, 2005). It stands to reason that optimization of these diseases offers opportunities to prevent the development of ED or to ameliorate its extent (Glina et al, 2013).

Epidemiologic studies have shown examinations of potentially modifiable risk factors and in some instances have provided support that risk modification may indeed improve erectile function. For instance, several reports have suggested that the discontinuation of cigarette smoking results in a recovery of functional erection status (Mannino et al, 1994; Feldman et al, 2000; Bacon et al, 2006). A beneficial role of increasing exercise for those with a sedentary lifestyle in men with ED was also evident (Feldman et al, 1994; Derby et al, 2000). In a prospective study, obese men with moderate ED and no overt symptoms of cardiovascular disease showed significant improvements in IIEF scores after exercise and weight control when compared with a control group that followed an educational program alone (Esposito et al, 2004). Significant changes in body mass index, C-reactive protein, and physical activity scores were observed in the intervention group compared with the control group. Mediterranean-style diets and a reduction in caloric intake have been found to improve erectile function in men with metabolic syndrome (Esposito et al, 2006). A change to a no-nose saddle from a conventional saddle was shown to recover erectile function, presumably by alleviating perineal trauma, in a short-term interventional study of men with ED associated with occupational bicycle riding (Schrader et al, 2008).

Reports indicating that ED is potentially ameliorated by lifestyle modifications of risk factors that predispose this sexual dysfunction are most illuminative. The role of lifestyle modifications to prevent or to treat ED has gained support by way of systematic reviews and meta-analysis (Kupelian et al, 2010; Gupta et al, 2011; Porst et al, 2013). The mechanisms of this effect may include reduced cardiovascular risk factors, increased serum testosterone levels, and overall improved mood and self-esteem (Gupta et al, 2011; Meldrum et al, 2012; Glina et al, 2013). Ongoing clinical and basic science investigation may further affirm the benefits of lifestyle modification and clarify its mechanistic basis.



*PDE5 inhibitors are the preferred treatment option in the large majority of patients.

Figure 27-10. Treatment algorithm for erectile dysfunction recommended by the International Consultations on Sexual Medicine. PDE5, phosphodiesterase type 5.

Medication Change

It is possible that a certain medication is an offending factor resulting in the clinical presentation of ED. After this inference is made, an appropriate next step would be to change to a different dose or type of medication entirely, considering that this action may reverse ED in some patients (Ralph and McNicholas, 2000). For instance, switching antihypertensive therapies from thiazide diuretics and β -blockers to calcium channel blockers and renin-angiotensin system inhibitors (i.e., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) may recover erectile function in men developing ED in this clinical setting.

Similarly, in patients suffering adverse sexual dysfunction effects from the use of SSRIs (e.g., ED, retarded ejaculation), treatment strategies such as drug substitution (e.g., bupropion, nefazodone, buspirone, mirtazapine), drug holidays, SSRI dosage reduction, watchful waiting, and administration of PDE5 inhibitors have enabled sexual function recovery (Rosen et al, 1999b; Nurnberg et al, 2001).

Psychosexual Therapy

Because of the frequent interplay of psychological and interpersonal factors in clinical presentations of ED, it is hardly surprising to consider that psychosexual therapy should be included in the therapeutic armamentarium for this sexual dysfunction. A strong limitation in this area is that evidence-based investigation and well-controlled, large-scale outcome research that documents the efficacy of interventions are generally lacking. In practice, psychosexual therapy does represent an ill-defined combination of interventions and interpretations, based on behavioral, relational, psychoanalytic, and cognitive psychology concepts. A variety of interventions are used: systematic anxiety reduction/desensitization, sensate focus, interpersonal therapy, cognitive-behavior therapy, sex education, couples' communication and sexual skills training, and masturbation exercises (Althof et al, 2005). Integrated treatments, which combine psychosexual interventions with medical therapies such as oral therapy, intracavernosal injection, or vacuum device therapy, have also proved successful in managing ED presentations, particularly those associated with motivational obstacles (Hawton, 1998; Althof et al, 2005). It is understandable that the common urologist may not feel comfortable or does not possess the necessary training to address complicated psychosocial concerns. However, for mild to moderate psychosocial matters, the urologist may be prepared to proceed with a "biopsychosocial" model that minimally involves awareness of psychosocial issues and preparedness to counsel a patient or couple about normal sexual function and acceptable sexual behaviors (Althof and Needle, 2011). Collaborative efforts with a mental health clinician who has expertise in psychosexual therapy may be necessary to implement intensive therapy techniques.

Hormonal Therapy

A prescription of hormonal therapy is considered so as to impact the clinical presentation of ED for the patient in whom a hormonal disturbance is identified. The urologist's role is fitting for the treatment of primary hypogonadism and hyperprolactinemia, whereas endocrinologists would be considered as the foremost consultants for other endocrinopathies.

Testosterone Replacement

Androgen replacement addresses straightforwardly the clinical complaint that is associated with hypogonadism. As a general principle of sex steroid replacement therapy, serum hormone levels to be achieved daily throughout 24 hours should ideally achieve normal reference values and resemble the normal diurnal pattern. Evaluating serum testosterone levels both before and during treatment is imperative, although the efficacy of testosterone supplementation is best judged by clinical response rather than a precise testosterone determination. Current recommendations suggest that a short (e.g., 3-month) therapeutic trial is justified, and, in the absence of a response, testosterone administration should be discontinued (Wang et al, 2009; Bhasin et al, 2010). Potential adverse effects of androgen therapy (i.e., erythrocytosis, sleep apnea, urinary symptoms, prostate cancer progression risk, gynecomastia, acne) should be recognized (Morales et al, 2004; Wald et al, 2006). Monitoring of patients on therapy consists of a baseline assessment that includes digital rectal examination and serum PSA testing along with laboratory evaluation (i.e., hemoglobin/hematocrit levels, liver function tests, cholesterol level, and lipid

profile) followed by the assessment of treatment efficacy after 3 to 6 months and annually thereafter to ascertain symptom response and any adverse events (Morales et al, 2004; Bhasin et al, 2010). Short-acting preparations may be preferred in favor of long-acting depot preparations in the initial treatment of patients, so that therapy can be discontinued on the occasion of an adverse event (Wang et al, 2009).

For the treatment of hypogonadism, several testosterone preparations are offered and can be delivered by various routes: intramuscular, subcutaneous, transdermal (patch and gel), buccal, and oral (Edelstein et al, 2006; Morgentaler et al, 2008; Wang et al, 2009; Bhasin et al, 2010; Corona et al, 2011). A brief description of available therapies follows (see also Table 27-6).

Intramuscular. Testosterone enanthate or cypionate, an injectable depot preparation of testosterone, is delivered by deep intramuscular injection (200 to 250 mg every 2 to 3 weeks). The schedule of therapy results in supraphysiologic levels of testosterone for 72 hours with a steady exponential decline to subphysiologic levels by 10 to 12 days. Alternative dosing of 100 mg every 7 to 10 days can be considered in situations when patients experience symptomatic mood changes or sexual fluctuations associated with documented early hypogonadal troughs. Another parenteral preparation, testosterone propionate, is also delivered intramuscularly at a dosage of 200 mg every 2 to 3 days because of its shorter half-life, and it may also display serum testosterone fluctuations. Testosterone undecanoate (TU), as a depot formulation consisting of 750- or 1000-mg dosages administered at 10-week dosing intervals, has been used in Europe since 2003 although it is not yet available in the United States.

Subcutaneous. Pellets offer a subcutaneous, long-acting depot formulation of testosterone. Testopel is a pellet containing 75 mg of testosterone. Dosing usually requires 2 to 6 pellets (150 to 450 mg testosterone) implanted subcutaneously every 3 to 6 months.

Transdermal. Transdermal delivery options comprise patches and gels, with a delivery approach that intentionally simulates normal circadian levels of testosterone. When patients apply medication in the morning, higher initial absorption will mimic normal diurnal variation.

Testoderm was approved initially as a scrotal patch administered daily without adhesive (4 to 6 mg), but it came under disuse because of difficulties with its application, the requirement for scrotal shaving, and the finding that it significantly produced high levels of DHT by conversion by 5 α -reductase activity that is plentifully present in the scrotal skin. Testoderm TTS represented an alternative formulation avoiding the inconveniences of the scrotal application. Its application is to the arm, back, or buttock as a 5-mg patch. Androderm, an alternative product, delivers 2.5 or 5 mg of testosterone daily. Both patches have been associated with itching, chronic skin irritation, and allergic contact dermatitis. The skin irritation is alleviated by the local application of cortisone cream. Patients are advised to alternate application sites and avoid sun-exposed areas.

AndroGel (testosterone 1% gel) is a topical gel pack that contains 50, 75, or 100 mg of testosterone, with only 10% of the drug being absorbed during a 24-hour period. Testim, also providing 1% testosterone, is an alternative product packaged as a 5-g tube containing 50 mg of testosterone. Both are similarly applied once daily in the morning to clean, dry skin on the shoulders, upper arms, or abdomen, and it is allowed to dry before dressing. Axiron (testosterone 2% solution) is another transdermal product approved by the U.S. Food and Drug Administration (FDA), consisting of 30 mg of testosterone applied to each axilla once daily using a metered applicator. Special considerations for axillary administration include the concealable location and high permeability of the axilla, which has a relatively high level of 5- α reductase activity.

Buccal. Striant refers to a tabletlike, mucoadhesive treatment system (30 mg of testosterone) that continuously delivers medication. It is applied twice daily to the gum tissue above the incisors allowing testosterone to be absorbed through the buccal mucosa.

Oral. Oral testosterone preparations are limited. Concern is associated with the liver toxicity of testosterone (i.e., hepatitis, cholestatic jaundice, hepatomas, hemorrhagic liver cysts, and hepatocellular carcinoma) related to the large doses necessary to achieve normal serum levels (Bagatell and Bremner, 1996). Large doses (>200 mg/day) are required orally because much of the administration is rendered metabolically inactive during the “first-pass” circulation through the liver. Chemical modifications of oral testosterone have been explored to overcome adverse reactions. Both 17 α -methyltestosterone and fluoxymesterone have been formulated, but because of their patient variability of effect with potential liver toxicity risk they should not be prescribed (Wang et al, 2009). TU, as an oral formulation in oleic acid, is safe by partly escaping hepatic inactivation (Köhn and Schill, 2003). However, it has shown a large individual variability for the time of maximal responses as well as when maximal serum testosterone is attained. Oral TU remains unapproved in the United States.

Alternative Hormone Treatments

Alternative hormonal replacement therapies have been suggested, and they have posed certain desirable features as well as caveats. DHT as a direct mode of therapy is attractive because of its action as a pure androgen that is not aromatizable to estradiol, and accordingly it has been demonstrated that the hormone does not exert adverse estrogenic effects on prostate growth or lipid profile measurements (Kunelius et al, 2002; Sakhri and Gooren, 2007). A therapeutic DHT gel is available at a dose of 125 to 250 mg/day, yielding plasma DHT levels comparable to physiologic testosterone levels (Kunelius et al, 2002). Dehydroepiandrosterone (DHEA), a hormone supplement with androgen-like and estrogen-like effects, has been used, although limited evidence exists showing it improves sexual function (Baulieu et al, 2000; Morales et al, 2004). It is important to note that the treatment cannot be considered harmless, and the potential exists for DHEA and other nontestosterone androgen precursor preparations (e.g., DHEA-S, androstenediol, androstenedione) to stimulate hormone-sensitive diseases such as breast or prostate cancer. Human chorionic gonadotropin (HCG) has been found to increase total and free testosterone and estradiol 50% above baseline, and it would conceivably be of benefit to hypogonadal men in a way similar to the effects of androgen administration. Clinical investigation of HCG has shown some anthropometric effects (i.e., decrease in fat mass, increase in lean body mass) and improvements in serum testosterone concentrations in androgen-deficient men without documented benefits for sexual function (Liu et al, 2002; Tsujimura et al, 2005). Antiestrogens and aromatase inhibitors have been shown to increase endogenous testosterone levels, and selective androgen receptor modulators are under development. Because of insufficient evidence about the therapeutic benefits and adverse effects of alternative replacement therapies in older men with hypogonadism, they are not currently recommended for use (Wang et al, 2009).

Hyperprolactinemia Treatments

The treatment of hyperprolactinemia is undertaken with the acknowledgment that testosterone replacement therapy is neither corrective nor sufficient to improve sexual function. The therapeutic objective, rather, is to identify and address the underlying cause, which may then ameliorate ED. Offending drugs, such as estrogens, morphine, sedatives, and neuroleptics, should be discontinued (Molitch, 2008). A prolactin-secreting adenoma should be treated medically and if necessary surgically. Bromocriptine, a dopamine agonist that lowers prolactin level and restores testosterone to normal, serves to reduce the size of the tumor. Neurosurgical ablation becomes necessary if the therapeutic response to medication does not occur or visual effects are noted in association with optic-nerve compression (Gillam et al, 2006). Erection recovery is most evident after treatment of men with significant serum elevations of prolactin (higher than 40 ng/mL) (Netto Júnior and Claro, 1993).

TABLE 27-6 Testosterone Preparations

Formulation	Chemical Structure	T _½	Standard Dosage	Advantages	Disadvantages
Oral Agents					
Testosterone undecanoate	17- α -hydroxyl-ester	4 hr	120-240 mg 2-3 times daily	Oral convenience Modifiable dosage	Serum testosterone levels and clinical responses vary Must be taken with meals Potential hepatotoxicity Treatment considered obsolete Nonaromatizable to estrogen
Methyltestosterone	17- α -alkylated	3.5 hr	20-50 mg 2-3 times daily	Oral convenience Modifiable dosage	
Mesterolone	1-alkylated	8 hr	100-150 mg 2-3 times daily	Oral convenience Modifiable dosage	
Intramuscular Agents					
Testosterone enanthate	17- α -hydroxyl-ester	4-5 days	250 mg every 2-3 wk	Low cost Modifiable dosage	Wide fluctuations in circulating T levels Multiple injections Relative higher risk of polycythemia Wide fluctuations in circulating T levels Multiple injections Wide fluctuations in circulating T levels Multiple injections Relative higher risk of polycythemia Pain at injection site
Testosterone cypionate	17- α -hydroxyl-ester	8 days	200 mg every 2-3 wk	Low cost Modifiable dosage	
Testosterone propionate	17- α -hydroxyl-ester	20 hr	100 mg every 2 days	Low cost	
Testosterone undecanoate	17- α -hydroxyl-ester	34 days	1000 mg every 10-14 wk	Testosterone levels maintained within normal range Long lasting Less frequent administration	
Subcutaneous Agents					
Surgical implants	Native testosterone	—	4-6 200-mg implants lasting \leq 6 mo	Treatment only twice per yr	Placement is invasive Risk of extrusion and site infections
Controlled-release T-buccal Formulation Agents					
Testosterone buccal	Native testosterone	12 hr	30 mg 2 times daily	Testosterone levels within physiologic range	Possible oral irritation Twice-daily irritation Unpleasant taste
Transdermal Agents					
Testosterone patches	Native testosterone	10 hr	5-10 mg/day	Mimics circadian rhythm Simple administration	Skin irritation Daily administration
Testosterone gel 1%-2%	Native testosterone	6 hr	5-10 g/day	Testosterone levels maintained within normal range Flexible dose modification Skin irritation less common than with patches	Possible transfer during intimate contact Daily administration
Testosterone solution 2%	Native testosterone	NA	60-120 mg/day	Testosterone levels maintained within normal range	Possible transfer during intimate contact Daily administration

NA, not available; T, testosterone; T_{1/2}, drug half-time.

Modified from Corona G, Rastrelli G, Forti G, et al. Update in testosterone therapy for men. J Sex Med 2011;8:639-54.

Pharmacologic Therapies

The premise of pharmacologic therapies is that they simulate the biochemical and molecular mechanisms of action naturally governing the erectile response. Conceptually, erectogenic therapies serve strategically either to promote proerectile mechanisms or to oppose antierection mechanisms, at both peripheral and central levels of the neurovascular axis responsible for penile erection (Rowland and Burnett, 2000). At a peripheral level, these mechanisms influence corporeal smooth muscle tone. Promotion of proerectile mechanisms is achieved by either inducing corporeal smooth muscle activation through cell-receptor agonists or effectors of tissue relaxant pathways (e.g., stimulating second messenger cyclic nucleotide [cyclic guanosine monophosphate {cGMP} or cyclic adenosine monophosphate {cAMP}] synthesis) or inhibiting the deactivation of smooth muscle relaxation pathways (e.g., inhibiting phosphodiesterases), whereas opposition of antierection mechanisms are achieved by decreasing smooth muscle contraction through receptor antagonists of tissue contractile pathways (e.g., α_1 -adrenergic inhibitors). At a central nervous system level (i.e., brain or spinal cord), neuronal pathways are affected, and potential opportunities exist to promote proerectile pathways (e.g., agonists of dopaminergic D₂ receptors in the medial hypothalamus) or to oppose antierection pathways (e.g., antagonists of 5-HT_{1A/2} [serotonergic] receptors in the spinal cord).

Diverse therapies have been touted throughout time, although their efficacy and safety characteristics have not always been clearly defined. Current standards of regulatory agency approval have helped to clarify the qualifications of commercially developed and marketed therapies (Hirsch et al, 2004).

Oral Therapy

Orally administered medication for ED meets many of the attributes of “ideal therapy,” which include convenience, simplicity, and noninvasiveness (Morales et al, 1995). Oral therapies are increasingly in demand to meet the therapeutic objective of clinical efficacy as well.

Phosphodiesterase Type 5 Inhibitors. This class of medication was famously inaugurated as an effective ED treatment in the United States following the FDA approval of sildenafil citrate (Viagra, Pfizer, Inc., New York, NY) in 1998, vardenafil hydrochloride (Levitra, Bayer Schering Pharma AG, Berlin, Germany), and tadalafil (Cialis, Lilly LLC, Indianapolis, IN) in 2003, and avanafil (Stendra, Vivus Inc., Mountain View, CA) in 2012 (Bruziches et al, 2013; Porst et al, 2013). PDE5 inhibitors similarly work to block the catalytic action of the enzyme that degrades cGMP, the downstream effector of the erection mediator nitric oxide, which

then facilitates the signal transductional mechanisms of corpus cavernosal smooth muscle relaxation required for penile erection. It is important to recognize that the medications augment but do not induce the erectile response and the induction of penile erection requires the release of nitric oxide from penile nerve endings and vascular endothelium under the influence of sexual stimulation (Burnett, 2005). The high concentration of PDE5 inhibitors in the smooth muscle of the penile corpora cavernosa accounts for the selectivity of their effect.

Despite their similar modes of actions, PDE5 inhibitors differ somewhat in their biochemical properties, pharmacokinetic profiles, and clinical performances (Table 27-7). The chemical structure of PDE5 inhibitors are similar, containing a guaninelike base, a riboselike or desoxyribose-like system, and a phosphate diester-like bond, which confers their ability to bind effectively to the catalytic site of the PDE5 enzyme. The chemical structures of sildenafil and vardenafil are similar, unlike that for tadalafil, and this difference serves to explain some phenomenologic distinctions observed between these agents (Corbin and Francis, 1999). The chemical structure of avanafil differs from the standard model of the other three agents, which may account for some of its selective actions (Kedia et al, 2013). Distinct from the actions of tadalafil and avanafil, sildenafil and vardenafil cross-react to a greater extent with phosphodiesterase (PDE) type 6, which is expressed in the retina, and this difference may explain the complaint of visual disturbances observed with sildenafil and vardenafil use. Tadalafil minimally cross-reacts with PDE type 11, unlike the other three PDE5 inhibitors, although the significance of this effect is unclear. The remaining side effects commonly observed with PDE5 inhibitor treatment are associated with inhibition of PDE5 localized in other target tissues, such as vascular and gastrointestinal smooth muscle. Tadalafil possesses a longer half-life of elimination than the other three PDE5 inhibitors. This feature suggests a longer therapeutic window uniquely afforded for tadalafil, which may translate into increased convenience for couples having sexual intercourse with this agent.

All four PDE5 inhibitors have demonstrated equivalent efficacy and tolerability in clinical trials for the treatment of ED of varying severity and cause (Carson and Lue, 2005; Hellstrom, 2007; Giuliano et al, 2010; Bruziches et al, 2013; Porst et al, 2013; Yuan et al, 2013). Trial designs for these agents have differed, limiting useful comparisons among them, and superiority cannot be claimed for any particular agent in the absence of directly comparative studies (Carson and Lue, 2005; Khara and Goldstein, 2011). In general, the agents effectively result in successful sexual intercourse rates of approximately 70% (Carson and Lue, 2005; Khara and Goldstein, 2011). A somewhat reduced intercourse success rate of 40% to 50% has been reported in diabetic patients with ED (Fonseca et al, 2004;

TABLE 27-7 Comparison of Four Phosphodiesterase Type 5 Inhibitors Currently Available in the United States

	SILDENAFIL	VARDENAFIL	TADALAFIL	AVANAFIL
Cmax (ng/mL)	450	20.9	378	2153
Tmax (hr)	0.8	0.7-0.9	2	0.3-0.5
Onset of action (min)	15-60	15-60	15-120	15-60
Half-life (hr)	3-5	4-5	17.5	3-5
Bioavailability	40%	15%	Not tested	30%
Fatty food	Reduced absorption	Reduced absorption	No effect	Reduced absorption
Recommended dosage	25, 50, 100 mg	5, 10, 20 mg	5, 10, 20 mg	50, 100, 200 mg
Side effects:				
Headache, dyspepsia, facial flushing	Yes	Yes	Yes	Yes
Backache, myalgia	Rare	Rare	Yes	Rare
Blurred/blue vision	Yes	Rare	Rare	No
Precaution with antiarrhythmics	No	Yes	No	No
Contraindication with nitrates	Yes	Yes	Yes	Yes

Cmax, maximal plasma concentration; half-life, time required for elimination of one half of the medication from plasma; Tmax, time required to attain Cmax.

Safarinejad, 2004) and in patients with ED associated with radical prostatectomy in general (Hatzimouratidis et al, 2009). However, the intercourse success rate for patients after bilateral nerve-sparing radical prostatectomy specifically is somewhat better than for the entire group, and reports have commonly documented rates that approach 60% to 70% for functional erections with therapy.

According to standard dosing recommendations, patients are instructed to take the medications on demand between 30 and 60 minutes before intended sexual activity. This lead-time interval is specified to take advantage of the duration by which the medications achieve peak serum concentrations (i.e., approximately ½ hour for avanafil, 1 hour for sildenafil and vardenafil, and 2 hours for tadalafil). Although the onset of activity has been documented to occur possibly within 20 minutes for each agent, this characteristic is less important to patients than erection hardness and maintenance of erections with therapy (Claes et al, 2008). A daily dosing regimen has been approved for tadalafil as an alternative treatment schedule to afford patients greater convenience in having sexual intercourse while using this agent (Porst et al, 2006; Shabsigh et al, 2010). Optimization of effect for all PDE5 inhibitors is also achieved by applying sexual stimulation properly as a prerequisite for nitric oxide release, by reducing food intake, which may delay drug absorption, by escalating drug dosing as needed, and by repeating attempts with the medications several times (up to nine or ten attempts affords maximal probability of success) (McCullough et al, 2002; Barada, 2003; Shindel, 2009). Correcting or improving adverse health conditions (e.g., glycemic control, hyperlipidemic control, androgen replacement), which affect drug efficacy, has also been demonstrated as potentially beneficial (Guay, 2003; Sadowsky et al, 2009). As evidence of therapeutic efficacy, patient and partner satisfaction with therapy (as shown for sildenafil) has been well demonstrated (Montorsi and Althof, 2004). Suboptimal acceptance or lack of long-term adherence to therapy (up to 47% of patients) has been reported, which may indicate the influence of psychosocial factors or challenges of a treatment that requires repeated dosing (Seftel, 2002; Al-Shaiji and Brock, 2009).

BOX 27-1 Warnings and Drug Interactions

The package inserts of all four phosphodiesterase type 5 (PDE5) inhibitors warn against their use in patients with severe cardiovascular diseases and left ventricular outflow obstruction (e.g., aortic stenosis, idiopathic subaortic stenosis), those with severely impaired autonomic control of blood pressure, and patients not studied in clinical trials (U.S. prescribing information of Viagra, Cialis, and Levitra and Stendra, September 2013). These include patients with:

- Myocardial infarction, stroke, or life-threatening arrhythmia within the previous 6 mo
- New York Heart Association class II or greater heart failure or coronary artery disease causing unstable angina
- Resting hypotension (<90/50 mm Hg) or hypertension (>170/100 mm Hg)
- Known hereditary degenerative retinal disorders including retinitis pigmentosa
- Severe hepatic impairment (Child-Pugh C) or end-stage renal disease requiring dialysis

Certain drugs such as ketoconazole and itraconazole and protease inhibitors such as ritonavir can impair the metabolic breakdown of PDE5 inhibitors by blocking the CYP3A4 pathway. Such agents may increase blood levels of inhibitors, requiring a PDE5 dose reduction. On the other hand, agents such as rifampin may induce CYP3A4, enhancing the breakdown of inhibitors and requiring higher PDE5 doses. Kidney or hepatic dysfunction may require dose adjustments or warnings.

Patients using PDE5 inhibitors should be thoroughly counseled regarding precautions (Box 27-1). Cardiovascular safety using this class of compounds has been well demonstrated, although it should be emphasized that given the cardiovascular risks of sexual activity and potential for adverse drug interactions with this therapy, cardiovascular risk assessment and stabilization should be considered for all men before the institution of PDE5 inhibitor therapy. **Controlled and postmarketing studies involving these agents have shown that they do not cause an increase in myocardial infarction or death rates when compared with expected rates in study control populations** (Jackson et al, 2006a; Hellstrom, 2007; Nehra, 2009). In addition, patients with known coronary artery disease or heart failure receiving PDE5 inhibitors did not exhibit worsening ischemia, coronary vasoconstriction, or worsening hemodynamics on exercise testing or cardiac catheterization. Caution is advised for the use of PDE5 inhibitors in patients with certain conditions: aortic stenosis, left ventricular outflow obstruction, hypotension, and hypovolemia. The agents have a minimal effect on QTc interval (Morganroth et al, 2004). Vardenafil among PDE5 inhibitors is not recommended in patients who take type 1A antiarrhythmics (e.g., quinidine or procainamide) or type 3 antiarrhythmics (e.g., sotalol or amiodarone) or in patients with congenital prolonged QT syndrome.

Nitrate use in any form (e.g., sublingual nitroglycerin, isosorbide dinitrate, other nitrate preparations used to treat angina, amyl nitrite, and amyl nitrate “poppers”) represents an absolute contraindication. Past use of nitrates, that is, more than 2 weeks before the use of PDE5 inhibitors, is not considered a contraindication. If angina occurs during sexual activity when using a PDE5 inhibitor, patients should cease this activity and seek emergency care immediately. They should inform medical personnel that a PDE5 inhibitor was taken and should avoid nitroglycerin use for a period of 24 hours for sildenafil and vardenafil and 48 hours for tadalafil (Cheitlin et al, 1999). If acute myocardial infarction occurs with the use of PDE5 inhibitors, usual therapies, with the exception of organic nitrates, may be administered. If hypotension results from PDE5 inhibitor use, patients should be placed in the Trendelenburg position and given intravenous fluids along with administration of α -adrenergic agonists (e.g., phenylephrine) as needed. Refractory hypotension warrants intra-aortic balloon counterpulsation, as specified by the American College of Cardiology/American Heart Association guidelines. **No pharmacologic antidote to the PDE5 inhibitor/nitrate interaction exists.** Caution is advised when PDE5 inhibitors are coadministered with α -adrenergic blockers, because both agents are vasodilators with blood pressure lowering effects.

Side effects observed with PDE5 inhibitor therapy include headache (7% to 16%), dyspepsia (4% to 10%), flushing (4% to 10%), myalgia/back pain (0% to 3%), nasal congestion (3% to 4%), and visual disturbances (e.g., photophobia, blue vision) (0% to 3%). Randomized, controlled trials have documented that flushing and visual side effects are more common in patients receiving sildenafil or vardenafil, whereas back pain/myalgia is more common in patients receiving tadalafil. These events have been found to be mild and to abate with time, and the side effects prompt discontinuation only in few patients (Hellstrom, 2007; Porst et al, 2013). The concern has been posed with PDE5 inhibitor therapy regarding the development of nonarteritic anterior optic neuropathy (NAION), which can cause blindness, although several systematic reviews of the safety of this class of compounds have not shown an increased risk of NAION or other adverse ocular events associated with their use (Laties, 2009; Porst et al, 2013). Affected patients in postmarketing reports possibly carried risk factors for blindness to include hypertension, diabetes, and hyperlipidemia. At this time, despite the absence of a proven link between PDE5 inhibitor use and serious ocular disorders, physicians should continue to advise patients to stop use of PDE5 inhibitors and to seek immediate medical attention as a safety measure in the event of a sudden loss of vision (Laties, 2009; Porst et al, 2013).

The interest in extending the use of PDE5 inhibitors beyond an on-demand erectogenic role and rather applying them to

recovery or maintenance of the natural vitality of the penis in the face of an ED-associated disease state or condition has been investigated. This proposal has been considered particularly in the clinical context of radical prostatectomy and has been introduced as a therapeutic strategy à la “penile rehabilitation,” by which the medications are taken in some regularly scheduled fashion to promote the recovery of spontaneous erectile function. Presently, this role remains unclear, owing to limited well-designed and conducted (i.e., randomized, controlled) clinical trials of PDE5 inhibitor use in this clinical setting (Mulhall et al, 2013). In one supportive trial involving sildenafil treatment of 36 weeks starting 4 weeks after the surgery, 27% of patients using the agent recovered erections defined as “good enough for sexual activity” compared with 4% of patients on placebo at about 1 year after surgery (Padma-Nathan et al, 2008). However, in another trial involving vardenafil treatment of 9 months either on-demand or daily starting 14 days after surgery, erection recovery was no different in patients using vardenafil by either form of administration or placebo at about 1 year after surgery (Montorsi et al, 2008). Another trial randomizing patients to the use of sildenafil nightly or on-demand for 12 months with a 1-month washout showed that erection recovery was not different between patient groups (Pavlovich et al, 2013). Randomized, controlled trials in other ED contexts have also failed to show sustained natural erectile function improvement after discontinuing continuous regimens of PDE5 inhibitor therapy (Zumbé et al, 2008; Burnett et al, 2009).

The notion of combining PDE5 inhibitors with other ED therapies such as vasoactive penile pharmacotherapies has been proposed (Lau et al, 2006; McMahon et al, 2006). This strategy is to be considered “off-label,” and clinical precautions are advised.

α -Adrenoceptor Antagonists. Phentolamine mesylate is a non-specific α -adrenergic receptor antagonist with equal affinity for blocking both α_1 - and α_2 -adrenoreceptors. Its mode of action presumably is to produce corporeal smooth muscle relaxation by blocking the (antierectile) postsynaptic α_1 -adrenergic receptor (Juenemann et al, 1986). Clinical trials suggested an efficacy rate in men with minimal ED of approximately 40% (Goldstein, 2000). The drug was considered to be relatively safe, with less than 10% of patients using the 40-mg dosage experiencing headaches, facial flushing, or nasal congestion. However, further investigation is required before determining whether it will produce erectile responses of sufficient quality for reliable sexual intercourse, particularly in men with more severe ED.

Yohimbine hydrochloride (Yocon), an indolalkylamine alkaloid derived from the bark of the yohimbe tree, reportedly exerts central effects on the mediation of penile erection operating as an α_2 -adrenoreceptor antagonist (Clark, 1991; Giuliano and Rampin, 2000). Originally proposed to be an erectogenic and aphrodisiac agent, the drug has been investigated as an authentic ED treatment. It is conventionally prescribed orally at a dosage of 5.4 mg three times daily with observation for improvement throughout at least a month. A meta-analysis of all randomized, placebo-controlled trials involving yohimbine suggested a superior effect for the medication compared to placebo (Ernst and Pittler, 1998). However, the drug does not appear to enable successful sexual intercourse any better than placebo in men with confirmed organic ED (Montague et al, 1996; Telöken et al, 1998). Adverse effects appear to be relatively infrequent but include hypertension, anxiety, tachycardia, and headache. Although yohimbine may be well tolerated, its modest results suggest that it may be best limited to men with psychogenic ED (Porst et al, 2013).

Dopaminergic Agonists. Apomorphine (Uprima, TAP Pharmaceutical Products Inc., Lake Forest, IL) is a dopaminergic agent activating D_1 and D_2 receptors at a central level within the paraventricular nucleus of the brain, indicating its particular relevance in the treatment of men with psychogenic ED (Lal et al, 1987). The medication is administered in sublingual form with a dosage range of 2, 4, and 6 mg, and it has no erectile efficacy if it is swallowed (Heaton, 2000). It has a rapid onset of action, with a mean time to erection of 12 minutes. Apomorphine achieves a maximal plasma concentration in 50 minutes, although its window of opportunity

extends for approximately 2 hours from administration. In clinical trials involving men with ED of varying severities and etiologies, the drug achieved a successful sexual intercourse rate of 50.6% at the 4-mg dosage compared with the 33.8% placebo rate (Heaton, 2000). Side effects include nausea (16.9%), dizziness (8.3%), yawning (7.9%), somnolence (5.8%), sweating (5%), and emesis (3.7%). Syncope occurred in 0.6% of patients using the medication at the highest recommended dosage, and this was accompanied by a prodrome consisting of nausea, vomiting, sweating, dizziness, and light-headedness but no cardiac sequelae. Side effects were minimized when patients were titrated from higher to lower dosages. The drug achieved regulatory approval for commercialization by European authorities in early 2001, but it has not been so approved in the United States.

Melanocortin-Receptor Agonists. Melanocortin analogues (e.g., melanotan II, PT-141) have been studied showing efficacy in inducing erectile responses in early clinical trials (Wessells et al, 2000; Diamond et al, 2004). These drugs operate centrally at melanocortin-4 receptors, which have been implicated in controlling food intake and energy expenditure as well as modulating erectile function and sexual behavior. Flushing and nausea have been reported as side effects. The drugs have not achieved regulatory approval for the treatment of ED.

Serotonin-Receptor Effectors. Trazodone (Desyrel) is an antidepressant that has been associated with priapism, prompting its “off-label” investigation as a possible treatment for ED (Lal et al, 1990). It is purported to work through mechanisms at the spinal-cord level with multiple serotonergic effects (Allard and Giuliano, 2001). The active metabolite of trazodone acts as an agonist of the proerectile 5-HT_{2C} receptor through reuptake inhibition, with some affinity for the 5-HT_{2A} receptor, although it may also operate as an antagonist of antierectile 5-HT_{1A} receptors (Andersson and Wagner, 1995). Rigorous evaluations have not shown clinical efficacy that exceeds placebo responses in eliciting penile erection (Costabile and Spevak, 1999). Given its potential side effects (i.e., drowsiness, nausea, emesis, blood pressure changes, urinary retention, and priapism) and general lack of effect, this medication would appear to have a limited role for ED treatment.

Other Oral Therapies. Additional possibilities for the oral treatment of ED, including L-arginine (the amino acid precursor of nitric oxide), L-dopa (dopamine precursor), limaprost (prostaglandin E₁), and naltrexone (opioid antagonist), have been proposed (Burnett, 1999). Each of these agents has a plausible mechanism of action to induce erections. However, they remain insufficiently studied, and their clinical roles remain unclear (Porst et al, 2013).

Intracavernosal Injection

The discovery in 1982 that vasoactive agents, delivered by injection into the penis, induced erections is credited with launching the movement toward medical therapies for the treatment of ED (Virag, 1982; Zorngiotti, 1985). Since that time, there has been an explosion of basic scientific and clinical research leading to the development and use of various locally administered vasoactive medications having mechanisms of action that result in corporeal smooth muscle relaxation. Although a host of medications have been explored for this purpose, three medications are used regularly in clinical practice: alprostadil, papaverine, and phentolamine (Table 27-8). These have been administered clinically as a single agent (i.e., monotherapy) or in various combinations (e.g., bimix, trimix). Combination therapy offers a synergistic mechanism of the vasoactive agents to elicit maximal erectile responses, particularly among patients who have failed monotherapy (Zorngiotti and Lefleur, 1985; Bennett et al, 1991; Floth and Schramek, 1991; Khera and Goldstein, 2011; Porst et al, 2013). This alternative may also be used to circumvent side effects of a certain agent (e.g., penile pain associated with alprostadil).

A general rule of thumb is to start with a small dose of medication, especially in patients with nonvasculogenic forms of ED. In-office self-injection training and education are recommended before home injection, and this opportunity may also be used to

TABLE 27-8 Intracavernosal Pharmacotherapies

TRADE NAME	DRUG	DOSAGES	EFFICACY (INTERCOURSE)
Caverject	Alprostadil (Prostin VR)	5–40 µg/mL	≈70%
Viradal/Edex	Alprostadil (Prostin VR)	5–40 µg/mL	≈70%
Bimix	Alprostadil + phentolamine	20 µg/mL + 0.5 mg/mL	≈90%
Bimix Androskat (EU)	Papaverine + phentolamine	30 mg/mL + 0.5 mg/mL	≈90%
Trimix	Alprostadil + papaverine + phentolamine	10 µg/mL + 30 mg/mL + 1.0 mg/mL	≈90%
Invicorp	VIP + phentolamine	NA	≈80%

EU, European Union; NA, not available; VIP, vasoactive intestinal polypeptide.

titrate medication toward a dosage that safely yields an erection of sufficient rigidity for sexual intercourse yet lasts no more than an hour (Bénard and Lue, 1990; Fallon, 1995). The therapy is contraindicated for men with psychological instability, a history or risk for priapism, histories of severe coagulopathy or unstable cardiovascular disease, reduced manual dexterity (although the partner can be trained in the injection technique), and use of monoamine oxidase inhibitors (because of the risk of precipitating a life-threatening hypertensive crisis in the event that an intracavernosal α -adrenergic agonist is used to reverse a priapic episode) (Sharlip, 1998).

Alprostadil. Alprostadil (Prostin VR) is a synthetic form of a naturally occurring fatty acid, prostaglandin E_1 , which binds with specific receptors on smooth muscle cells and activates intracellular adenylate cyclase to produce cAMP, which in turn induces tissue relaxation through a second messenger system (Palmer et al, 1994). It currently is the only FDA-approved injectable medication for ED, and it is marketed for this purpose under the trade names Caverject (Pfizer Inc., New York, NY) and Viradel/Edex (Schwarz Pharma, Milwaukee, WI) (Linnet and Ogrinc, 1996; Porst, 1996; Buvat et al, 1998). After intracavernosal injection, the medication is locally metabolized by 96% within 60 minutes and does not appreciably enter the peripheral circulation (van Ahlen et al, 1994). At dosages of 10 to 20 µg, alprostadil produces full erections in 70% to 80% of patients with ED (Linnet and Neff, 1994; Khera and Goldstein, 2011; Porst et al, 2013). The most common side effects of treatment are pain at the injection site or during erection (in 11% of patients), hematoma/ecchymosis (1.5%), prolonged erection/priapism (1% to 5%), and penile fibrotic lesions (2%) (Linnet and Ogrinc, 1996). Perceived advantages of alprostadil for intracavernosal pharmacotherapy relative to other agents are lower incidences of prolonged erection, systemic side effects, and penile fibrosis. Disadvantages include a higher incidence of painful erection and higher cost, and, after reconstitution into liquid from powder, alprostadil has a shortened half-life if not refrigerated.

Papaverine. Papaverine, an alkaloid isolated from the opium poppy, is a nonspecific PDE inhibitor that prevents the degradation of cAMP and cGMP so that these cyclic nucleotides accumulate in smooth muscle cells and thereby increasingly promote tissue relaxation (Kukovetz et al, 1975). The compound also blocks voltage-dependent calcium channels along the membrane wall, thus impeding calcium influx to the cell, a process known to trigger smooth muscle contraction (Brading et al, 1983; Sunagane et al, 1985). Papaverine is metabolized in the liver, and the plasma half-life is 1 to 2 hours. Its general efficacy in promoting penile erection after intracavernosal administration is approximately 60% (Porst et al, 2013). The drug is inexpensive and stable at room temperature. However, disadvantages include commonly observed liver enzyme elevations, priapism risk (up to 35%), and penile fibrosis risk (1% to 33%), which have led to its abandonment as monotherapy (Lakin et al, 1990; Fallon, 1995; Porst, 1996; Moemen et al, 2004).

Phentolamine. In addition to its purported oral role for ED therapy, phentolamine mesylate is more familiarly applied as an intracavernosal agent (Regitine). Although its erectogenic effect is mediated by blocking the (antierectile) postsynaptic α_1 -adrenergic

receptor (Sironi et al, 2000), because of its potential inhibition of the prejunctional α_2 -adrenergic receptor, which interferes with norepinephrine reuptake, the drug's tissue relaxant effect for penile erection is believed to be antagonized (Juenemann et al, 1986). This dual effect of the drug probably accounts for its limited success when administered intracavernosally as a sole agent (Blum et al, 1985). It has a short plasma half-life (30 minutes). Common side effects associated with the drug include systemic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset.

Vasoactive Intestinal Polypeptide. Vasoactive intestinal polypeptide (VIP), a hormone having 28 amino acids originally isolated from the small intestine, was proposed early on to be the elusive nonadrenergic noncholinergic (NANC) mediator of penile erection because of its potent vasodilatory effects in various tissues (Adaikan et al, 1986). Its mechanism of action in smooth muscle is achieved through specific protein receptor binding and activation of adenylate cyclase, thereby promoting synthesis of cAMP and subsequent tissue relaxation (Anderson and Wagner, 1995). The drug has had disappointing effects when administered alone, although when separately combined with other drugs such as papaverine and phentolamine, erection responses were elicited (Kiely et al, 1989; Dinsmore and Wyllie, 2008). VIP in combination with phentolamine (Invicorp) is currently being sought for regulatory approval in the United States.

Intraurethral Suppositories

The administration of vasoactive drugs via the urethral channel of the penis was introduced with the hope of affording a less invasive procedure than intracavernosal needle injections to induce penile erection. This technique relies on the absorption of the medication through the mucosal lining into the surrounding corpus spongiosum, with passage via small vascular channels into the main erectile bodies, the corpora cavernosa. The transfer of drug from the urethra to the cavernous tissue varies across men according to anatomic variability. Following an initial trial, which demonstrated that prostaglandin E_2 was effective in inducing full tumescence in 30% of patients and partial tumescence in 40% of patients (Wolfson et al, 1993), a synthetic formulation of prostaglandin E_1 was developed and the FDA approved it in November 1996 as MUSE (Medicated Urethral System for Erection, MEDA Pharmaceuticals, Inc., Somerset, NJ) (Hellstrom et al, 1996; Padma-Nathan et al, 1997). MUSE uses a suppository inserted into the urethral opening that dispenses a semisolid pellet (1 × 3 mm) of alprostadil (125, 250, 500, and 1000 µg dosages) into the distal urethra (3 cm from the external urethral meatus). Several technical procedures optimize the success of the treatment including properly depositing and manually distributing the medication into the penis and the patient's remaining in the upright position for several minutes after its application. In-office training and monitoring of initial response may afford advantages for optimizing technique and making dosage adjustments before performing the treatment at home.

A calculated final responder rate to MUSE is approximately 50%, and among responders approximately 70% of administrations result in sexual intercourse (Hellstrom et al, 1996;

Padma-Nathan et al, 1997; Guay et al, 2000; Khera and Goldstein, 2011; Porst et al, 2013). The combined use of an adjustable penile constriction band (ACTIS) was designed and was approved by the FDA to enhance the local retention and effect of the medication (Lewis, 2000). A transurethral bimix consisting of alprostadil and α_1 -adrenergic antagonist prazosin (ALIBRA) was introduced and in a multicenter trial of nearly 400 patients was shown to increase the at-home responder rate for successful sexual intercourse from 47% with alprostadil alone to 70% with ALIBRA (Qureshi, 2001).

Intraurethral therapy is perceived to have a niche role, associated with its inferior efficacy both with regard to PDE5 inhibitors and intracavernosal self-injection therapy (Khera and Goldstein, 2011; Porst et al, 2013). The main indications for this therapy are patients who are nonresponsive to PDE5 inhibitors resulting from damage of the autonomic penile nerve supply (e.g., radical prostatectomy, cystectomy, and trauma) or those who wish to use the therapy in combination with PDE5 inhibitors. Another rare indication for intraurethral therapy is patients complaining about a soft (cold) glans syndrome, which may occur after penile prosthesis implantation or as a clinical entity itself (Porst et al, 2013).

The most common side effects of MUSE include local urogenital pain (approximately one third of patients) and minor urethral bleeding (5%) (Padma-Nathan et al, 1997; Guay et al, 2000). Other complications such as hypotension (3%), dizziness (4%), and priapism (0.1%) have been observed as well. MUSE is contraindicated in patients with known hypersensitivity to alprostadil, abnormal penile anatomy, and conditions that increase the risk of priapism. MUSE seems safe for female partners, producing only a 5.8% incidence of vaginal burning or itching, although it should not be used without a condom for intercourse with a pregnant woman.

Transdermal/Topical Pharmacotherapy

The notion to apply vasoactive drugs directly to the surface of the penis is consistent with the general appeal of many transdermal therapies (e.g., gels and creams) in medicine based on their delivery route: convenience, simplicity, and putatively limited systemic adverse effects. Several topical therapies have been explored for ED treatments, although certain obstacles have limited their widespread use. Nitroglycerin, a nitric oxide donor formulated as a 2% paste, was found to produce tumescence but rarely penile rigidity sufficient for sexual intercourse (Owen et al, 1989). This relative inefficacy combined with its headache side effects for both patient and partner following absorption and action of the drug as a potent systemic vasodilator have precluded its use in clinical practice. Papaverine, formulated as a gel, was investigated but then abandoned as a topical ED treatment when it was found that its large molecular size (molecular weight 376 Da) interfered with its transdermal absorption (Kim et al, 1995).

Alprostadil has been a more promising prospect, subjected to commercial development for penile glans administration in combination with transdermal delivery enhancers: alprostadil 0.3% in combination with a proprietary permeation enhancer, referred to as Vitaros (Apricus Biosciences, San Diego, CA), and alprostadil combined with NexACT, referred to as Alprox-TD (NexMed, Inc., Robbinsville, NJ). Applied intrameatally, such agents in clinical trials have shown efficacy with rates of vaginal penetration and intercourse success that were small but significantly greater than placebo rates and caused minor side effects of site-specific burning or warmth that were comparable to placebo rates (McVary et al, 1999; Goldstein et al, 2001; McMahon, 2002; Padma-Nathan and Yeager, 2006; Rooney et al, 2009; Porst et al, 2013). Prostaglandin E_1 ethyl ester, which is a prodrug of prostaglandin E_1 , is believed to possess an improved transdermal permeation and less skin irritation than enhancing agents because of its esterification (Schanz et al, 2009). Applied to the shaft of the penis in early clinical trials, this drug achieved significantly higher rigidity scores than placebo. In general, transdermal therapy with alprostadil is likely to meet similar clinical roles as that assigned to transurethral pharmacotherapy. Further clinical trials will be useful to define and establish their place in the treatment of ED.

Medical Device

In patients who do not respond to or who decline oral or local vasoactive pharmacotherapeutic options, vacuum erection device therapy may be alternatively explored. The principle of vacuum erection device therapy is to mechanically create negative pressure surrounding the penis to engorge it with blood and then restrain blood egress from the organ to maintain the erection-like effect (Nadig et al, 1986; Broderick et al, 1992). Although the treatment does not produce a truly physiologic erection and the engorged blood predominantly consists of venous blood (Bosshardt et al, 1995), the effect resembles a normal erection and is sufficient for coitus. A particular feature is that the glans penis, and not solely the corpora cavernosa, is engorged with blood by the treatment, such that the treatment is further advantageous for patients experiencing glanular insufficiency (soft glans syndrome).

The standard vacuum erection device consists of a usually clear plastic suction cylinder and vacuum-generating source (manual or battery-operated pump) in one piece. It is placed directly over the flaccid penis and operated, and after the penis is erected an elastic constriction ring or band is positioned at the base of the penis; then the vacuum is released and the device is removed (Montague et al, 1996; McMahon, 1997). The cylinder has a pressure-release valve designed to prevent penile injury from excessive negative pressure. Sexual intercourse may then ensue, although it is recommended that the ring should not be left in place for longer than 30 minutes. Prescription devices are advised, and metal or other inelastic rings are contraindicated.

Efficacy rates as high as 90% have been reported for achieving satisfactory erections for ED associated with various severities and etiologies, but satisfaction rates with the device are lower, ranging commonly from 30% to 70% (Hellstrom et al, 2010; Porst et al, 2013). Attrition is reported to occur and may relate to lack of efficacy with more severe forms of ED, although long-term continuation rates have ranged up to 60% (Porst et al, 2013). Success is limited in patients with severe vascular abnormalities such as proximal venous leakage or arterial insufficiency or fibrosis secondary to priapism or prosthesis infection (Marmar et al, 1988). Patient preferences also dictate long-term success. The device is more acceptable to older men in a steady relationship compared to young, single men. Among basic expectations of the treatment, patients should be informed of possible local discomfort or pain associated with the constriction band, a pivoting effect of the penis because turgidity exists only distal to the band's location, a cyanotic discoloration and coolness of the penis resulting from extracorporeal congestion, and trapping of the ejaculation caused by urethral constriction (Witherington, 1989; Sidi et al, 1990; Cookson and Nadig, 1993). Common complications are minor and include penile pain and numbness, difficult ejaculation, ecchymosis, and petechiae, and major complications (e.g., penile skin necrosis, urethral varicosities, Fournier gangrene) are infrequent. Patients receiving anticoagulant therapy (e.g., aspirin, warfarin) and patients with bleeding disorders should use the device with caution (Limoge et al, 1996). Special uses for this therapy have been sought. It has been successfully combined with oral, intracavernosal, and intraurethral pharmacotherapies to produce erectile responses (Marmar et al, 1988; Chen et al, 1995; John et al, 1996; Chen et al, 2004; Canguven et al, 2009). The device has enhanced erectile effects in the presence of a malfunctioning penile prosthesis (Sidi et al, 1990; Korenman and Viosca, 1992). Further, it may offer a means to preserve the elasticity of penile tissues after priapism or penile prosthesis explantation (Moul and McLeod, 1989; Soderdahl et al, 1997) or after surgical correction of Peyronie disease (Yurkanin et al, 2001), and it has been suggested to facilitate erection recovery after treatments for prostate cancer (Raina et al, 2006; Köhler et al, 2007).

Surgery

Surgical interventions have always served an important role in the armamentarium of ED treatments. They are often applied in the

face of penile injury resulting from genital or pelvic trauma, penile structural deformity occurring in association with Peyronie disease, or possibly cavernosal fibrosis secondary to prolonged ischemic priapism or infection. They are also considered when medical therapy for ED is contraindicated, unsuccessful, or undesirable.

Penile Prosthesis Surgery

Penile prosthesis or implant surgery is a mechanism for creating penile rigidity that differs from a physiologic or pharmacologically induced erection. Malleable (semirigid) and inflatable (hydraulic) devices are both currently available for this purpose. Details of this treatment option are presented elsewhere.

Penile Revascularization Surgery

Based on the requirements of inflow of blood and its retention in the penis for penile erection to occur, it is hardly a wonder to think that vascular surgeries have aggressively been pursued to facilitate or restore these biologic processes.

Arterial Revascularization. In concept, arterial revascularization surgery was designed to create arterial inflow to the corpora cavernosa, in turn addressing the presentation of arteriogenic ED. Several procedures have been described to meet this objective, similarly creating an anastomosis of the inferior epigastric artery either to the corpus cavernosum directly or to vascular conduits of the penis such as the dorsal artery (i.e., revascularization), the deep dorsal vein (i.e., arterialization), or the deep dorsal vein with venous ligation (i.e., arterialization with venous reconstruction) (Hellstrom et al, 2010). Success of these surgeries has been variable and depends on careful patient selection. Penile arteriography is required to establish a penile arterial anatomic defect, and other organic causes of ED (e.g., venous incompetence) that would limit surgical success should be excluded. According to the current literature, the following inclusion criteria should be met when selecting patients for arterial surgery: age less than 55 years, nonsmoker, nondiabetic, absence of venous leakage, and radiographic confirmation of stenosis of the internal pudendal artery (Hellstrom et al, 2010; Sohn et al, 2013). The highest success rates are reported in young men (less than 30 years of age) with isolated arterial stenosis following perineal or pelvic trauma (Babaei et al, 2009). Complications of arterial revascularization surgery include glans hyperemia (13%), shunt thrombosis (8%), and inguinal hernias (6.5%) (Manning et al, 1998; Kawanishi et al, 2004).

Venous Reconstruction. Venous reconstruction was proposed to prevent the pathologic blood egress from the penis, understandably serving to correct veno-occlusive ED. Most surgical procedures have centered on ligating or embolizing penile veins (e.g., superficial dorsal vein, deep dorsal vein, crural vein) or surgically compressing the penile crura (e.g., crural plication/ligation, pericavernoplasty) (Hellstrom et al, 2010). Success with these surgeries has not been affirmed, owing primarily to inaccurate or deficient methods for diagnosing and correcting the relevant anatomic defect. The optimal surgical approach remains to be defined, and thus venous reconstructive surgery is presently considered investigational (Montague et al, 2005; Hellstrom et al, 2010; Sohn et al, 2013). Reported complications of this surgery include glanular hypo/anesthesia, skin necrosis, wound infections, penile curvature/shortening, and glans hyperemia.

Combination Therapies

It is well recognized that many patients with ED will not respond acceptably to monotherapy, with nonresponder rates documented as high as 40% of patients (Porst et al, 2013). Some patients indeed may achieve optimal therapeutic responses by combining treatment options. In addition, it is possible that a dose-limiting adverse effect is associated with ED monotherapy such that combined treatments may then seem advantageous. Multiple combinations may

certainly be proposed for ED treatment. The extant literature describes several successful combinations: oral PDE5 inhibitors with psychosocial counseling (Althof et al, 2005), oral PDE5 inhibitors with testosterone replacement therapy (Shabsigh et al, 2004), oral PDE5 inhibitors with transurethral alprostadil (Mydlo et al, 2000; Nehra et al, 2002), oral PDE5 inhibitor and intracavernosal pharmacotherapy (McMahon et al, 1999), oral PDE5 inhibitor and vacuum erection device (Chen et al, 2004; Canguven et al, 2009), intracavernosal pharmacotherapy and vacuum erection device (Chen et al, 1995), transurethral pharmacotherapy and vacuum erection device (John et al, 1996), and transurethral pharmacotherapy and penile prosthesis surgery (Benevides and Carson, 2000). Caution is advised when initiating combination therapy to observe for potential complications that may be compounded by combined treatments, and in-office evaluations before continuing treatments at home may be considered to offer an additional measure of safety.

Alternative Therapies

Alternative therapies have long been considered for the treatment of ED, from herbs, ointments, and concoctions of antiquity to vitamins, nutraceuticals, and dietary supplements in commercial supply today. The movement toward alternative medicines in this field actually gained momentum during the past decade with the emergence of effective oral therapy in the form of PDE5 inhibitors, which created avenues for producing PDE5 inhibitor-like counterfeit and imitation substances and promoting regulatory agency unapproved products in general. Indeed, the true efficacies of proposed alternative therapies (e.g., ginkgo biloba, L-arginine, Korean red ginseng) remain uncertain in the absence of evidenced benefit in rigorously performed, randomized, controlled clinical trials (Moyad et al, 2004; Khera and Goldstein, 2011). The success of these products is ascribed in some measure to the known placebo effect of agents to treat ED, which has been observed to amount to as much as 25% to 50% in properly conducted clinical trials. Before the use of alternative therapies can be advocated, further research that demonstrates their mechanisms of action and meaningful efficacies must be performed.

KEY POINTS: TREATMENT CONSIDERATIONS

- An informed decision-making process that combines goals and preferences of the patient (and partner) and balanced and thorough guidance of the clinician should dictate the best therapeutic option.
- Although definitive evidence is necessary to affirm the benefits of risk modification for preserving erectile health, recommendations are offered to maintain a healthy and fit lifestyle for this purpose.
- Patient education and counseling and application of medical therapies as initial forms of ED management constitute basic management in common practice.
- Psychosexual therapy offers a role in the integrative management of ED.
- Several pharmacotherapies administered by various modalities including oral, intracavernosal, intraurethral, and transdermal/topical routes are successfully applied or are under study as ED treatments.
- Vacuum erection device therapy offers an alternative to oral or local vasoactive pharmacotherapeutic options for ED.
- Surgical intervention, principally penile prosthesis surgery, represents an important ED treatment and may be considered when medical (nonsurgical) therapy is contraindicated, unsuccessful, or undesirable.
- Arterial revascularization surgery is offered only to selected patients with ED who meet stringent clinical and radiographic criteria for surgical success.

FUTURE DIRECTIONS

Impressive progress has been made in the field of ED management, encompassing all areas of epidemiology, basic scientific research, clinical investigation, and health services research. Future directions will assuredly continue with particular interest directed to new therapeutics. In the near future, pharmacotherapies will likely remain center stage, further driven by research discoveries in the molecular and cellular mechanisms responsible for the erectile response. Technologic advances in the way of interventional devices have rapidly gained interest. Alternatives such as implanting zotarolimus-eluting peripheral stents in atherosclerotic lesions of the internal pudendal arteries (Rogers et al, 2012) and low-intensity extracorporeal shockwave therapy applied to the penis (Vardi et al, 2012) are currently under study, supporting the idea that these and other such interventions may achieve the goal of restoring erectile function or improving it effectively for the long term. Futuristic approaches such as gene therapy, stem-cell therapy, and tissue engineering have been mainly advanced at the preclinical stage of development with the same long-term purpose, although their eventual roles remain eagerly anticipated. The future of this field looks excit-

ing and should foster the very best outcomes for patients experiencing ED.

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The complete reference list is available online at www.expertconsult.com.



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Defining Priapism

Priapism: Historical Perspectives

Epidemiology and Pathophysiology of Priapism

Molecular Basis of Ischemic and Stuttering Priapism

Evaluation and Diagnosis of Priapism

Medical Treatments

Surgical Management of Ischemic Priapism

Interventional Angiography in the Management of Arterial (Nonischemic, High-Flow) Priapism

Surgical Management of Arterial (Nonischemic, High-Flow) Priapism

Summary

Priapism is a persistent erection arising from dysfunction of the mechanisms regulating penile tumescence, rigidity, and flaccidity. A correct diagnosis of priapism is a matter of urgency requiring identification of the underlying hemodynamics.

Scientific organizations have recommended guidelines for the management of priapism, including the American Urological Association (AUA) in 2003 (www.auanet.org) and the International Society for Sexual Medicine in 2006 (www.issm.info). Both groups have noted that the literature on priapism is composed mainly of small case series and individual case reports and includes inconsistent definitions and methodologies with few long-term erectile function outcome data. Recent case series have included detailed methodology including duration of priapism, cause of priapism, and erectile function outcomes. The basic science on the pathogenesis of priapism and clinical research supporting the most effective treatment strategies are summarized in this chapter. Recommendations for best clinical practice and suggestions for research are made.

DEFINING PRIAPISM

Priapism is a full or partial erection that continues more than 4 hours beyond sexual stimulation and orgasm or is unrelated to sexual stimulation.

Ischemic Priapism (Veno-Occlusive, Low-Flow)

Ischemic priapism is a persistent erection marked by rigidity of the corpora cavernosa (CC) and little or no cavernous arterial inflow. In ischemic priapism there are time-dependent changes in the corporal metabolic environment with progressive hypoxia, hypercarbia, and acidosis. The patient typically reports penile pain after 6 to 8 hours, and the examination reveals a rigid erection. The condition is analogous to a muscle compartment syndrome, with initial occlusion of venous outflow and subsequent cessation of arterial inflows. Well-documented histologic changes occur within the corporal smooth muscle as a consequence of prolonged ischemia. Interventions beyond 48 to 72 hours of onset may help relieve erection and pain but have little benefit in preserving potency. Histologically, by 12 hours corporal specimens show interstitial edema, progressing to destruction of sinusoidal endothelium, exposure of the basement membrane, and thrombocyte adherence at 24 hours. After 48 hours thrombus can be found in the sinusoidal spaces, and smooth muscle necrosis

with fibroblast-like cell transformation is evident (Spycher and Hauri, 1986). Ischemic priapism is an emergency. When left untreated, resolution may take days and erectile dysfunction (ED) invariably results (Fig. 28-1A and B).

Stuttering Priapism (Intermittent)

Stuttering priapism is characterized by a pattern of recurrence. The term has historically described recurrent unwanted and painful erections in men with sickle cell disease (SCD) (Serjeant et al, 1985). Patients typically awaken with an erection that persists for several hours. Males with SCD may experience stuttering priapism from childhood; in these patients the pattern of stuttering may increase in frequency and duration, leading to a full episode of unrelenting ischemic priapism. Any patient who has experienced an episode of ischemic priapism is also at risk for stuttering priapism.

Nonischemic Priapism (Arterial, High-Flow)

Nonischemic priapism is a persistent erection caused by unregulated cavernous arterial inflow. Typically, the corpora are tumescent but not rigid and the penis is not painful. A history of blunt trauma to the penis or an iatrogenic needle injury is common. Whatever the mechanism of injury, the result is a disruption of the cavernous arterial anatomy creating an arteriolar-sinusoidal fistula. The cavernous environment does not become ischemic and cavernous blood gases do not show hypoxia, hypercarbia, or acidosis. This type of priapism, once properly diagnosed, does not require emergent intervention. Beyond the acute trauma, patients do not report pain. Normal erectile function has been reported after recovery from the initial event, despite persistence of nonsexual partial erection.

PRIAPISM: HISTORICAL PERSPECTIVES

The term *priapism* has its origin in reference to the Greek god Priapus, who was worshipped as a god of fertility and protector of horticulture. Priapus is memorialized in sculptures for his giant phallus. The first recorded account of priapism in English medical literature appears in the *Lancet* and is attributed to Tripe (1845). Historically, the most commonly cited observation on this condition in North American literature is Frank Hinman Sr's

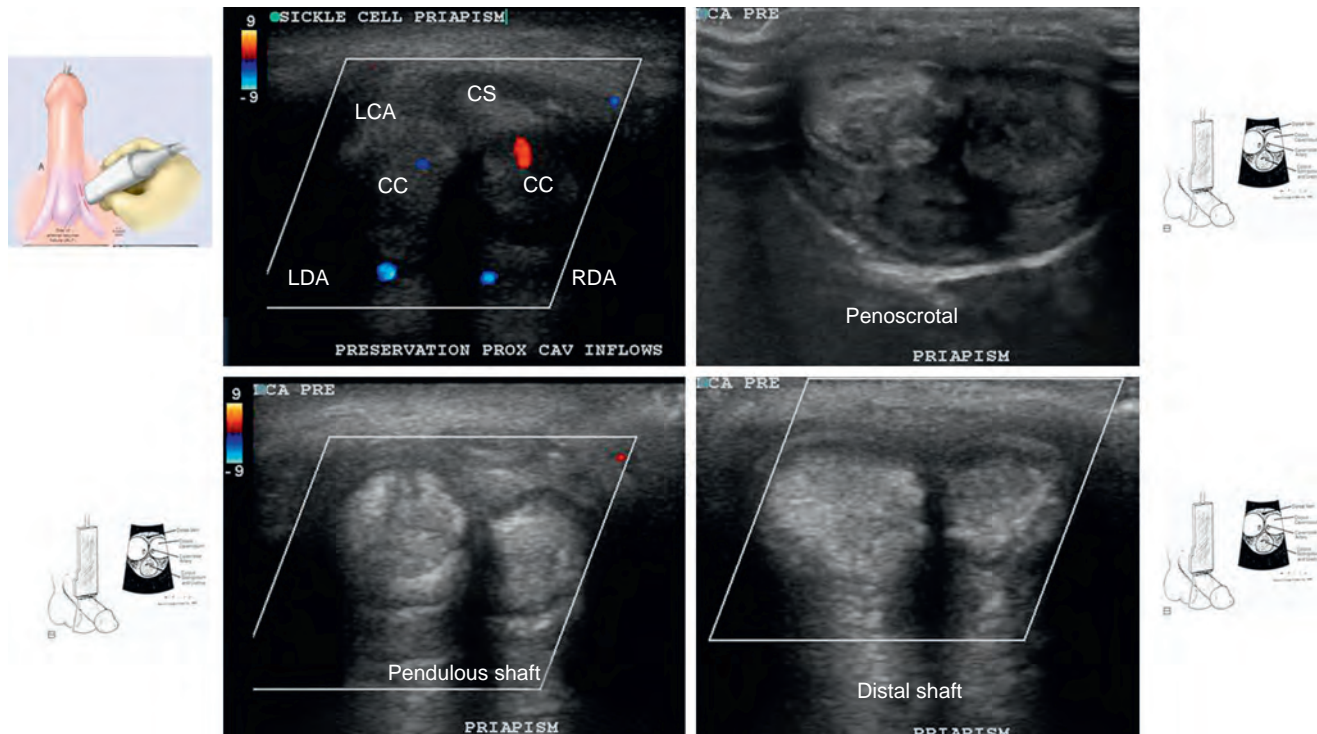


Figure 28-1. This 21-year-old Nigerian man had erectile dysfunction after recurrent episodes of sickle cell ischemic priapism. A, Transperineal imaging with color Doppler shows preservation of cavernous arterial inflow at the origin in the corpora cavernosa. B to D, Increasing echogenicity on gray-scale ultrasound of the penile shaft: penoscrotal, pendulous shaft, and distal shaft. These findings are the result of recurring ischemic priapism, which leaves the patient with distal corporal fibrosis. CC, corpora cavernosa; CS, corpus spongiosum; LCA, left cavernous artery; LDA, left dorsal artery; RDA, right dorsal artery.

landmark article describing the natural history of priapism (Hinman, 1914). Subsequently in 1960 his son, Frank Hinman Jr., proposed that venous stasis, increased blood viscosity, and ischemia were responsible for priapism and emphasized that failure to correct these abnormalities in the penile environment was essentially responsible for treatment nonresponse (Hinman, 1960). Advances in our understanding of the physiology of erection and the pathophysiology of ED substantiated early hypotheses that prolonged veno-occlusion within the corporal bodies is analogous to a compartment syndrome. Hauri and colleagues demonstrated the radiologic differences between veno-occlusive and arterial priapism (1983).

Frank Hinman (1914) first described “acute transitory attacks of priapism” as opposed to persistence or rapid recurrence of a single episode. The actual term *stuttering priapism* is attributed to Emond and colleagues (1980) in observations of patients with SCD in a Jamaican clinic. Stuttering priapism episodes were seen to increase in frequency and length, leading to major, unrelenting occurrence of ischemic priapism. Attempts to manage SCD patients with stuttering ischemic priapism resulted in the early recommendation for hormonal suppression of nocturnal erections and stuttering with estrogen (Serjeant et al, 1985).

Nonischemic priapism is described far less commonly than ischemic priapism in the urologic literature. Nonischemic priapism is invariably associated with antecedent perineal or penile trauma. It was first described in the English literature by Burt (Burt et al, 1960).

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF PRIAPISM

Etiology of Ischemic Priapism (Veno-Occlusive, Low-Flow)

Ischemic priapism accounts for the majority of cases described in the literature. The erection of ischemic priapism may begin with

KEY POINTS: PRIAPISM DEFINITIONS

- Priapism is a full or partial erection that continues more than 4 hours beyond sexual stimulation and orgasm or is unrelated to sexual stimulation.
- Ischemic (low-flow) priapism is a persistent erection marked by rigidity of the CC, with little or no cavernous arterial inflow.
- Nonischemic (arterial, high-flow) priapism is a persistent erection caused by unregulated cavernous arterial inflow. The corpora are tumescent but not rigid, and the erection is not painful.
- Stuttering priapism describes a pattern of recurrence. The term has traditionally described recurrent prolonged and painful erections in men with SCD.

sexual stimulation or the administration of pharmacologic agents. Once an erection persists beyond 4 hours and is not relieved by orgasm or pharmacologic reversal, the pathophysiologic phenomena of ischemic priapism have begun. Erections lasting up to 4 hours are by consensus defined as “prolonged”; manufacturers of erection-facilitating pharmacotherapies (oral, injectable, and intraurethral) recommend that the patient seek emergent medical consultation for prolonged erection.

Population-based studies estimate cases per 100,000 person-years (the number of patients with a first episode of priapism divided by the accumulated amount of person-time in the study population). Cases per 100,000 person-years have been calculated in several countries; these data depend on recording of presentations to clinics and hospitals where cases are registered. Kulmala and colleagues (1995) calculated the cases per 100,000 person-years

to be 0.34 to 0.52 from 1975 to 1990 in Finland; [Eland and colleagues \(2001\)](#) calculated the cases in the Netherlands to be 1.5 per 100,000 person-years; [Earle and colleagues \(2003\)](#) calculated 0.84 per 100,000 person-years in Australia from 1985 to 2000. These reported incidence rates were statistically significantly affected by the introduction and proliferation of intracavernous vasoactive injections for the management of ED; in Finland during the last 3 years of the study the incidence of priapism doubled to 1.1 cases per 100,000 person-years. These and other reports on the epidemiology and etiology of priapism are also greatly influenced by the prevalence of SCD in the populations described. **The lifetime probability of a man with SCD developing ischemic priapism ranges from 29% to 42%** ([Emond et al, 1980](#)). Two retrospective analyses—the Nationwide Inpatient Sample (NIS) and the Nationwide Emergency Department Sample—provide estimates of the incidence of priapism in the United States. [Chrouser and colleagues \(2011\)](#) accessed data from the NIS (1998 to 2006); the NIS database extrapolation suggests that 1868 to 2960 patients with priapism are admitted annually to hospitals in the United States. In the actual sample (4237 hospitalizations), 30% of patients were white, 61.1% were black, and 6.3% were Hispanic; 41.9% of patients had a diagnosis of SCD; and 36.2% of patients required penile surgery. The mean age at time of hospital admission for priapism associated with SCD was 23.8 years and for non-SCD was 40.8 years. [Roghamann and colleagues \(2013\)](#) looked at the Nationwide Emergency Department Sample. They estimated that from 2006 to 2009 there were 32,462 emergency department visits for priapism. The number of emergency department visits for priapism in the United States was higher during summer, and 13.3% of patients were admitted to the hospital.

In 1986 Pohl and colleagues reported on 230 cases. The cause of priapism was identified as idiopathic in the majority; 21% of cases were associated with alcohol or drug use or abuse, 12% with perineal trauma, and 11% with SCD ([Pohl et al, 1986](#)). Although SCD is a predominant cause of veno-occlusive priapism in the literature, there is a wide variety of reported associations from urinary retention to insect bites ([Hoover and Fortenberry, 2004](#)). Priapism has even been reported after spider bites and envenomation from the Brazilian banana spider, *Phoneutria nigriventer* ([Andrade et al, 2008](#); [Villanova et al, 2009](#)). The genus *Phoneutria* (from the Greek for “murderess”) has eight species. *P. nigriventer* is known to hide in dark and moist places, wander the jungle floor, and stow away within banana shipments. *P. nigriventer* is blamed for most cases of envenomation in Brazil; the venom contains a neurotoxin that has calcium channel blocking properties, inhibits glutamate release, and inhibits calcium reuptake and glutamate reuptake. Bites can cause intense pain, loss of muscle control—paralysis, breathing problems—asphyxiation, and priapism. Two peptides isolated from the venom of *P. nigriventer* have been directly linked with the induction of persistent and painful erections in mammals (Tx2-5 and Tx2-6) ([Leite et al, 2012](#)). The protein has been named *eretina* and has been shown to have a highly specific interference at the molecular level with the nitric oxide pathway (NO). Penile erection has been induced in vivo with *eretina* by direct intraperitoneal injection with a minimum effective dose of 0.006 µg/kg ([Andrade et al, 2008](#)).

Hematologic dyscrasias are a major risk factor for ischemic priapism. Priapism has been described as a complication of SCD, thalassemia, hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria, glucose-6-phosphate dehydrogenase deficiency, glucose-6-phosphate isomerase deficiency, and congenital dyserythropoietic anemia ([Burnett, 2005](#); [Kato, 2012](#)). **Thrombotic disease states have also been cited as precipitants of ischemic priapism;** these conditions include asplenia, erythropoietin use, hemodialysis with heparin use, and cessation of Coumadin therapy. Intracavernous heparin given as a therapy for priapism caused by rebound hypercoagulable states has actually worsened the condition ([Fassbinder et al, 1976](#); [Bschleipfer et al, 2001](#)). Priapism may occur in patients with excessive white blood cell (WBC) counts. The incidence of priapism in adult male patients with leukemia is 1% to 5% ([Chang et al, 2003](#)). Hyperleukocytosis causes priapism in these patients; it

is believed that mechanical pressure on abdominal veins secondary to splenomegaly causes congestion of cavernous outflow and sludging of leukemic cells within the CC. When priapism occurs in the oncology setting, evaluation and management of the predisposing condition must accompany interventions directed at the penis. In hematologic malignancies, leukapheresis and cytotoxic therapy (hydroxyurea, cytosine arabinoside) may reduce the numbers of circulating WBCs ([Ponniah et al, 2004](#); [Manuel et al, 2007](#)). **Priapism secondary to metastatic infiltrating solid lesions rather than leukemoid reaction is extremely rare.** In most case reports of metastatic priapism, the primary malignancy is genitourinary (prostate and bladder). Metastatic infiltration of the penis may proceed with solid replacement or focal deposits within the CC, glans, and corpus spongiosum. Theoretically, metastatic deposits within the corpora could obstruct venous outflow, resulting in ischemic priapism. Depending on the status of the patient, metastatic lesions may be managed expectantly, with partial or total penectomy, chemotherapy, or irradiation. These cases are too rarely and poorly described to define best practice recommendations ([Robey and Schellhammer, 1984](#); [Chan et al, 1998](#); [Guvel et al, 2003](#); [Celma Doménech et al, 2008](#)) (Box 28-1).

Sickle Cell Disease

Blood dyscrasias are a risk factor for ischemic priapism. SCD priapism has traditionally been ascribed to stagnation of blood within the sinusoids of the CC during physiologic erection, secondary to obstruction of venous outflow by sickled erythrocytes ([Lue, 2002](#)). [Nelson and Winter \(1977\)](#) described a series of cases in which SCD was the primary cause of ischemic priapism in 23% of adults and 63% of children. **Sickle cell hemoglobinopathy accounts for at least a third of all cases of priapism,** and, indeed, prevalence of ischemic priapism varies significantly within the population of males in a community with SCD. From [Emond and colleagues' 1980](#) observational study comes the most commonly quoted incidence: Among 104 men attending an outpatient sickle cell clinic in Kingston, Jamaica, the incidence of priapism in men with homozygous sickle cell (SS) disease was 42% ([Emond et al, 1980](#)). In a U.S. clinical series, [Tarry and associates \(1987\)](#) found that 6.4% of male children in an outpatient sickle cell clinic had a history of priapism. [Adeyoju and colleagues \(2002\)](#), in an international multicenter observational study of SCD, mailed or interviewed 130 patients attending SCD clinics in the United Kingdom and Nigeria. Respondents ranged in age from 4 to 66 years old, with a mean age of 25. The authors cited mean age of onset of priapism as 15 years, with 75% of patients having their first episode before age 20 and rare first-time presentations by the third decade of life. In the questionnaires a clear distinction was made between acute severe prolonged priapism lasting longer than 24 hours requiring emergency attention and stuttering recurrent priapism of shorter and self-limiting duration. In this population the incidence of acute priapism was 35%; of these patients, 72% gave a history of stuttering priapism. The median frequency of occurrence of stuttering priapism was three times per month; the median duration of each episode was 1.2 hours, with the longest being 8 hours. Precipitating events reported from greatest to least were sexual arousal or intercourse, fever, sleep, cold weather, and dehydration. Self-administered regimens were analgesics, drinking water, and exercise. Twenty-one percent of patients reporting a history of priapism also reported ED. Only 7% of young men who had not experienced priapism were even aware that priapism was a potential complication of their SCD. On the basis of the World Health Organization global prevalence map of SCD, [Aliyu and colleagues \(2008\)](#) estimated that 20 to 25 million individuals worldwide have homozygous SCD: 12 to 15 million in sub-Saharan Africa, 5 to 10 million in India, and 3 million in other world regions. They also found that 70,000 patients with SCD live in the United States ([Aliyu et al, 2008](#)).

The sickle cell genetic mutation is the result of a single amino acid substitution in the β -globin subunit of hemoglobin S (HbS). The clinical features are seen in homozygous SCD patients: chronic hemolysis, vascular occlusion, tissue ischemia, and

BOX 28-1 Causes of Priapism **α -ADRENERGIC RECEPTOR ANTAGONISTS**

Prazosin, terazosin, doxazosin, tamsulosin

ANTI-ANXIETY AGENT

Hydroxyzine

ANTICOAGULANTS

Heparin, warfarin

ANTIDEPRESSANTS AND ANTIPSYCHOTICS

Trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thioridazine, phenothiazines

ANTI-HYPERTENSIVES

Hydralazine, guanethidine, propranolol

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AGENTSMethylphenidates (Concerta, Daytrana, Focalin, Metadate, Methylin, Quillivant, Ritalin)
Atomoxetine (Strattera)**RECREATIONAL DRUGS**

Alcohol, cocaine (intranasal and topical), crack cocaine, marijuana

GENITOURINARY CONDITIONS

Straddle injury, coital injury, pelvic trauma, kick to penis or perineum, arteriovenous or arteriocavernous bypass surgery, urinary retention

HEMATOLOGIC DYSCRASIAS

Sickle cell disease, thalassemia, granulocytic leukemia, myeloid leukemia, lymphocytic leukemia, multiple myeloma, hemoglobin Olmsted variant, fat emboli associated with hyperalimentation, hemodialysis, glucose-6-phosphate dehydrogenase deficiency

HORMONES

Gonadotropin-releasing hormone, testosterone

INFECTIOUS (TOXIN-MEDIATED) CAUSES

Scorpion sting, spider bite, rabies, malaria

METABOLIC CONDITIONS

Amyloidosis, Fabry disease, gout

NEOPLASTIC CAUSES (METASTATIC OR REGIONAL INFILTRATION)

Prostate, urethra, testis, bladder, rectum, lung, kidney

NEUROGENIC CONDITIONS

Syphilis, spinal cord injury, cauda equina compression, autonomic neuropathy, lumbar disk herniation, spinal stenosis, cerebral vascular accident, brain tumor, spinal anesthesia, cauda equina syndrome

VASOACTIVE ERECTILE AGENTSPapaverine, phentolamine, prostaglandin E₁, oral phosphodiesterase type 5 inhibitors, combination intracavernous therapy

Modified from Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction and priapism. In: Walsh PC, Retik AB, Vaughan ED, et al, editors. Campbell's urology. Philadelphia: Saunders; 2002. p. 1610–96.

end-organ damage. HbS polymerizes when deoxygenated, injuring the sickle erythrocyte, activating a cascade of hemolysis and vaso-occlusion. Membrane damage results in dense sickling of red cells, causing adhesive interactions among sickle cells, endothelial cells, and leukocytes. Hemolysis releases hemoglobin into the plasma. Free hemoglobin reacts with NO to produce methemoglobin and nitrate. This is a scavenging reaction; the vasodilator NO is oxidized to inert nitrate. Sickled erythrocytes release arginase-I into blood plasma, which converts L-arginine into ornithine, effectively removing substrate for NO synthesis. Oxidant radicals further reduce NO bioavailability. The combined effects of NO scavenging and arginine catabolism result in a state of NO resistance and insufficiency termed *hemolysis-associated endothelial dysfunction* (Morris et al, 2005; Rother et al, 2005; Kato et al, 2007; Aliyu et al, 2008).

Contemporary science implicates hemolysis and reduced NO in the pathogenesis of pulmonary hypertension, leg ulcers, priapism, and stroke in SCD patients, whereas increased blood viscosity is believed to be responsible for painful crises, osteonecrosis, and acute chest syndrome (Kato, 2012; Kato et al, 2006). SCD patients with priapism have a fivefold greater risk of developing pulmonary hypertension. SCD priapism is also associated with reduced hemoglobin levels and increased hemolytic markers: reticulocyte count, bilirubin, lactate dehydrogenase, and aspartate aminotransferase. Cerebral vascular accidents are more frequent, close to episodes of full-blown priapism; the ASPEN syndrome (association of SCD, priapism, exchange transfusion, and neurologic events) describes cerebral vascular accidents in SCD patients who have received exchange transfusions (Siegel et al, 1993; Merritt et al, 2006). Sickle cell trait is considered a benign condition; a few complications have been associated with

extreme physical exertion. There have been case reports of sickle cell trait as the predisposing factor to ischemic priapism (Larocque and Cosgrove, 1974; Birnbaum and Pinzone, 2008).

Iatrogenic Priapism: Intracavernous Injections

Prolonged erection is more commonly reported than is priapism after therapeutic or diagnostic injection of intracavernous vasoactive medications (Broderick and Lue, 2002). Despite the introduction of effective oral medications for ED in 1998, intracavernous injection (ICI) remains an important therapeutic option for men with severe ED in whom a phosphodiesterase type 5 (PDE5) inhibitor fails or who cannot take PDE5 inhibitors because they require or include nitrates. In many communities patients receiving intracavernous medications for ED will outnumber patients with SCD. Priapism after ICI is a problem all urologists will encounter and must be prepared to manage. In a review of worldwide reports on ICI programs, Junemann and colleagues (1990) noted that diagnostic injection resulted in 5.3% of men getting ischemic priapism, and 0.4% of men reported priapism after injecting at home. In papaverine-based ICI programs, reports of prolonged erections and priapism are poorly distinguished and range from 0% to 35% (Broderick and Lue, 2002). In worldwide clinical trials of the Alprostadil Study Group, prolonged erection (defined as 4 to 6 hours) was described in 5% of patients, and priapism (longer than 6 hours) in 1% (Porst, 1996). In the United States the approved label and package insert for one product (alprostadil [Caverject]) cites the frequency of prolonged erection (4 to 6 hours) as 4% and frequency of priapism as 0.4%. The label recommends that “to minimize chances of prolonged erection or priapism Caverject

should be titrated slowly to the lowest effective dosage." In papaverine/phentolamine/alprostadil ICI programs, prolonged erections have been reported in 5% to 35% of patients (Broderick and Lue, 2002).

Idiopathic Priapism: Oral Phosphodiesterase Type 5 Inhibitors and Medications for Attention-Deficit/Hyperactivity Disorder

All PDE5 inhibitors have similar side effects related directly to their mode of action, tissue content of substrate, and pharmacologic selectivity for type 5 inhibition versus other phosphodiesterase enzymes. Side effects occurring in 2% or more of patients include headache, flushing, dyspepsia, rhinitis, light sensitivity, and myalgia. Morales and colleagues (1998) analyzed data from 4274 men who received double-blind treatment with sildenafil or placebo for up to 6 months and 2199 who received long-term open-label sildenafil for up to 1 year. No cases of priapism (erection lasting longer than 4 hours) were reported. No cases of priapism were reported by Montorsi and colleagues (2004) in a multicenter, open-label, 24-month extension of 8- or 12-week double-blind, placebo-controlled studies assessing the long-term efficacy, safety, and tolerability of tadalafil in 1173 men with ED. Nonetheless, the indications and usage section of the U.S. Food and Drug Administration (FDA)-approved product labeling (U.S. prescribing information [USPI]) for PDE5 inhibitors does contain this warning: "There have been rare reports of prolonged erection greater than 4 hours and priapism (painful erections >6 hours duration) for this class of compounds." Both the USPI and European Summary of Product Characteristics label information contain warning or precautionary language about the use of these agents in men who have conditions predisposing them to priapism. The FDA approved Cialis (tadalafil) as an oral treatment for ED (2.5 mg, 5 mg, 10 mg, and 20 mg) in 2003. Once-daily tadalafil (2.5 mg and 5 mg) was approved for oral treatment of ED in 2008, and subsequently in 2011 tadalafil (2.5 mg and 5 mg) was approved for the signs and symptoms of benign prostatic hyperplasia (BPH) and treatment of ED. Tadalafil 5 mg daily caused no priapism in a phase 2 clinical study of 281 men with history of lower urinary tract symptoms secondary to BPH for 6 weeks, followed by dosage escalation to 20 mg once daily for 6 weeks (McVary et al, 2007). The 2013 label for the most recently approved PDE5 inhibitor, Stendra (avanafil 50 mg, 100 mg, 200 mg), contains virtually identical precautionary wording as prior labels for as-needed (PRN) oral forms of sildenafil, vardenafil, and tadalafil: "There have been rare reports of prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours)."

From 1999 to 2007 there were at least nine case-based reports of oral PDE5 inhibitor use and adult priapism and at least one pediatric patient (Aoyagi et al, 1999; Kassim et al, 2000; Sur and Kane, 2000; Goldmeier, 2002; McMahon, 2003; Wilt and Fink, 2004; Galatti et al, 2005; King et al, 2005; Kumar, et al 2005; and Wills et al, 2007). Most case reports detailing priapism after use of a PDE5 inhibitor reveal histories of increased risk for priapism: SCD, spinal cord injury, use of a PDE5 inhibitor recreationally, use of a PDE5 inhibitor in combination with ICI, history of penile trauma, use of psychotropic medications, or use of recreational drugs. Wills and coworkers (2007) described a 19-month-old boy weighing 10 kg who accidentally ingested up to six tablets of sildenafil 50 mg. The child had persistent sinus tachycardia and partial erection for 24 hours; the authors presume this was a high-flow priapism (HFP) because the shaft was neither completely rigid nor painful. Erection in the child subsided spontaneously after overnight intravenous hydration and observation.

In 2013 the FDA issued a warning that methylphenidate medications used in the treatment of attention-deficit/hyperactivity disorder (ADHD) may result in prolonged erection or priapism. The FDA also warns that atomoxetine, another ADHD drug, has been linked to reports of priapism in children, teens, and adults. Drug therapy in ADHD is used in children, adolescents, and adults

to increase the ability to pay attention and decrease impulsiveness and hyperactivity. The 2012 Summary Health Statistics for U.S. Children: National Health Interview Survey (Bloom et al, 2013) estimated that more than 6.4 million children ages 4 to 17 have been diagnosed with ADHD; this represents a 41% increase over a decade. The Centers for Disease Control and Prevention (CDC) further estimate that two thirds of these children are prescribed methylphenidate medications (Centers for Disease Control and Prevention, 2013).

Methylphenidate is a central nervous system stimulant; atomoxetine is a selective norepinephrine reuptake inhibitor. The FDA cautions that physicians may be tempted to switch patients from methylphenidate medications to atomoxetine but that priapism is actually more common in patients taking atomoxetine (U.S. Food and Drug Administration, 2013). The median age of male patients taking methylphenidate who developed priapism (erection lasting longer than 4 hours) was 12.5 years.

KEY POINTS: ISCHEMIC PRIAPISM AS A COMPLICATION OF ERECTILE DYSFUNCTION THERAPY

- Prolonged erection is more commonly reported than priapism after therapeutic or diagnostic injection of intracavernous vasoactive medications.
- In worldwide clinical trials of alprostadil, prolonged erection (defined as 4 to 6 hours) occurred in 5% of administrations, and priapism (longer than 6 hours) in 1%.
- In clinical practice, ICI of Trimix (papaverine, phentolamine, and alprostadil) results in prolonged erections in 5% to 35% of administrations.
- Few case reports have documented priapism after PDE5 inhibitor therapy. These reports suggest that men were at increased risk for priapism because of SCD, spinal cord injury, use of a PDE5 inhibitor recreationally, use of a PDE5 inhibitor in combination with ICI, history of penile trauma, use of psychotropic medications, or abuse of narcotics.
- Methylphenidate medications and atomoxetine used in the treatment of ADHD may result in prolonged erection or priapism.

Etiology of Stuttering (Intermittent) Priapism

Stuttering (intermittent) priapism describes a pattern of recurrent priapism. The term has traditionally been used to describe recurrent unwanted and painful erections in men with SCD. Patients typically awaken with an erection that persists up to 4 hours and becomes progressively painful secondary to ischemia. SCD patients may experience stuttering priapism from childhood. Any patient who has experienced ischemic priapism is at risk for stuttering priapism. Patients with stuttering priapism will experience repeated painful intermittent attacks up to several hours before remission. Affected young men suffer embarrassment, sleep deprivation, and performance anxiety with sexual partners (Chow and Payne, 2008). In a study of 130 patients with SCD, Adeyoku and colleagues (2002) reported that 46 (35%) had a history of priapism and, of these, 33 (72%) had a history of stuttering priapism. In 75% of patients the first episode of stuttering priapism occurred before the age of 20. Two thirds of males with SCD ischemic priapism at presentation will describe prior stuttering attacks (Jesus and Dekermacher, 2009). Commonly reported precipitants of full-blown SCD priapism are stuttering nocturnal or early morning erections, dehydration, fever, and exposure to cold (Broderick, 2012).

Etiology and Pathophysiology of Nonischemic (Arterial, High-Flow) Priapism

HFP is a persistent erection caused by unregulated cavernous arterial inflow. The epidemiologic data on nonischemic priapism is almost

exclusively derived from small case series or individual case reports. Nonischemic priapism is much rarer than ischemic priapism, and the cause is largely attributed to trauma. Forces may be blunt or penetrating, resulting in laceration of the cavernous artery or one of its branches within the corpora. The cause most commonly reported is a straddle injury to the crura. Other mechanisms include coital trauma, kicks to the penis or perineum, pelvic fractures, birth canal trauma to the newborn male, needle lacerations, complications of penile diagnostics, and vascular erosions complicating metastatic infiltration of the corpora (Witt et al, 1990; Brock et al, 1993; Dubocq et al, 1998; Burgu et al, 2007; Jesus and Dekermacher, 2009). Although accidental blunt trauma is the most common cause, HFP has been described after iatrogenic injury from cold-knife urethrotomy, Nesbitt corporoplasty, and deep dorsal vein arterialization (Wolf and Lue, 1992; Liguori et al, 2005). Any mechanism that lacerates a cavernous artery or arteriole can produce unregulated pooling of blood in sinusoidal space with consequent erection. Nonischemic priapism is typically delayed in onset compared with the episode of blunt trauma (Ricciardi et al, 1993). Sustained partial erection may develop 24 hours after perineal or penile blunt trauma. It is believed that the hemodynamics of a nocturnal erection disrupts the clot and the damaged artery or arteriole ruptures; the unregulated arterial inflow creates a sinusoidal fistula. As healing progresses with clearing of clot and necrotic smooth muscle tissue, the fistula forms a pseudocapsule. Formation of a pseudocapsule at the site of fistula may take several weeks to months.

Contemporary reports suggest that HFP may have a unique subvariety. Several authors have noted that after either aggressive medical management of ischemic priapism or surgical shunting, priapism may rapidly recur with conversion from ischemia to high flow. HFP has been reported after aspiration and injection of α -adrenergics in the management of ischemic priapism (McMahon, 2002; Rodriguez et al, 2006; Bertolotto et al, 2009). Color Doppler ultrasonography (CDU) has shown formation of an arteriolar-sinusoidal fistula at the site of intervention (needle laceration or shunt site) (Fig. 28-2). On rare occasions after reversal of ischemic priapism, a new high-flow hemodynamic state of the cavernous arteries occurs with no evidence of fistula. This presentation of HFP should be suspected in patients in whom rapid recurrence, persistence of erection with partial penile rigidity, or stuttering priapism not associated with pain is evident. Nonfistula type of arterial priapism is the result of dysregulation of cavernous inflows. Nonfistula arterial priapism is a rare complication after management of ischemic priapism (Seftel et al, 1998; Cruz Guerra et al, 2004; Wallis et al, 2009). Penile tenderness to palpation is easily confused with the ongoing ache of persistent ischemia. Soft-tissue edema and ecchymosis render the physical examination findings equivocal after medical and surgical maneuvers to alleviate priapism. Dysregulated arterial inflows with or without a fistula can best be distinguished from persistent ischemic priapism by CDU.

KEY POINTS: HIGH-FLOW PRIAPISM

- Nonischemic priapism is much rarer than ischemic priapism.
- HFP results from laceration or disruption of a cavernous artery or arteriole.
- The most common cause is a straddle injury to the crura.
- Other mechanisms include coital trauma, kicks to the penis or perineum, pelvic fractures, birth canal trauma to the male newborn, needle lacerations, complications of penile diagnostics, and vascular erosions complicating metastatic infiltration of the corpora.
- HFP has been described after iatrogenic trauma from cold-knife urethrotomy, corporoplasty, and penile revascularization procedures.

Priapism in Children

Priapism in children and adolescents is most commonly related to SCD. The literature suggests that the incidence of priapism in pediatric sickle cell clinics is 2% to 6% (Tarry et al, 1987; Jesus and Dekermacher, 2009). The majority of SCD priapism is ischemic. In the newborn period, fetal hemoglobin predominates, not HbS (Burgu et al, 2007). SCD phenotypes related to ischemic or occlusive crises are unlikely to be evident while fetal hemoglobin persists. Newborn priapism is an extremely rare phenomenon with only limited case reports and rare application of contemporary diagnostic modalities. Erection is frequently elicited in males during the newborn period. In male newborns, simple tactile stimulation such as diaper changing, bathing, and urethral catheterization may result in erection; the erection quickly subsides after cessation of stimuli. Fewer than 20 cases of newborn priapism have been reported in the literature, and rarely has the cause been defined; causes have included polycythemia, blood transfusion, and birth canal trauma (Amlie et al, 1977; Leal et al, 1978; Shapiro, 1979; Walker and Casale, 1997). The majority of cases have been conservatively managed with spontaneous resolution reported from hours to days. Minimally invasive diagnostics (CDU) should be performed (Pietras et al, 1979; Meijer and Bakker, 2003). In children who develop priapism after straddle trauma, every effort should be made to localize the arteriolar-sinusoidal fistula. Hatzichristou and colleagues (2002) reported that identification of the fistula by Doppler ultrasound coupled with direct manual compression softens the high-flow erection and may speed spontaneous resolution. They suggested that this noninvasive therapy likely works in children and not adults because the perineum has considerably less subcutaneous fat and because crural bodies are more easily compressed.

MOLECULAR BASIS OF ISCHEMIC AND STUTTERING PRIAPISM

Advances in our understanding of the molecular basis of priapism have drawn significantly from both in vitro and in vivo experimental studies using animal models. Data on the true inciting mechanisms involved in ischemic priapism are emerging. Ischemic priapism consists of an imbalance of vasoconstrictive and vasorelaxatory mechanisms predisposing the penis to hypoxia and acidosis. In vitro studies have demonstrated that when corporal smooth muscle strips and cultured corporal smooth muscle cells are exposed to hypoxic conditions, α -adrenergic stimulation fails to induce corporal smooth muscle contraction (Broderick and Harkaway, 1994; Saenz de Tejada et al, 1997; Muneer et al, 2005). Extended periods of severe anoxia significantly impair corporal smooth muscle contractility and cause significant apoptosis of smooth muscle cells and, ultimately, fibrosis of the CC.

In experimental animal models of ischemic priapism, lipid peroxidation, an indicator of injury induced by reactive oxygen species (ROSs), and increased hemo-oxygenase expression occur in the penis during and after ischemic priapism (Munarriz et al, 2003; Jin et al, 2008). Additional pathophysiologic mechanisms involved in the progression of ischemia-induced fibrosis are the upregulation of hypoxia-induced growth factors. Transforming growth factor- β (TGF- β) is a cytokine that is vital to tissue repair. However, excess amounts may induce tissue damage and scarring. Upregulation of TGF- β occurs during hypoxia and in response to oxidative stress (Moreland et al, 1995; Jin et al, 2008). It is hypothesized that TGF- β may be involved in the progression of the corporal smooth muscle to fibrosis (Bivalacqua et al, 2000; Jeong et al, 2004).

Transgenic mouse models of SCD manifest priapism (Beuzard, 1996; Bivalacqua et al, 2009b). There have been two major discoveries in elucidation of the molecular mechanism of ischemic priapism. Mi and colleagues (2008) have shown that transgenic sickle cell mice CC have enhanced smooth muscle relaxation to electrical field stimulation. Transgenic sickle cell mice and mice lacking endothelial NO synthase (eNOS) gene expression display

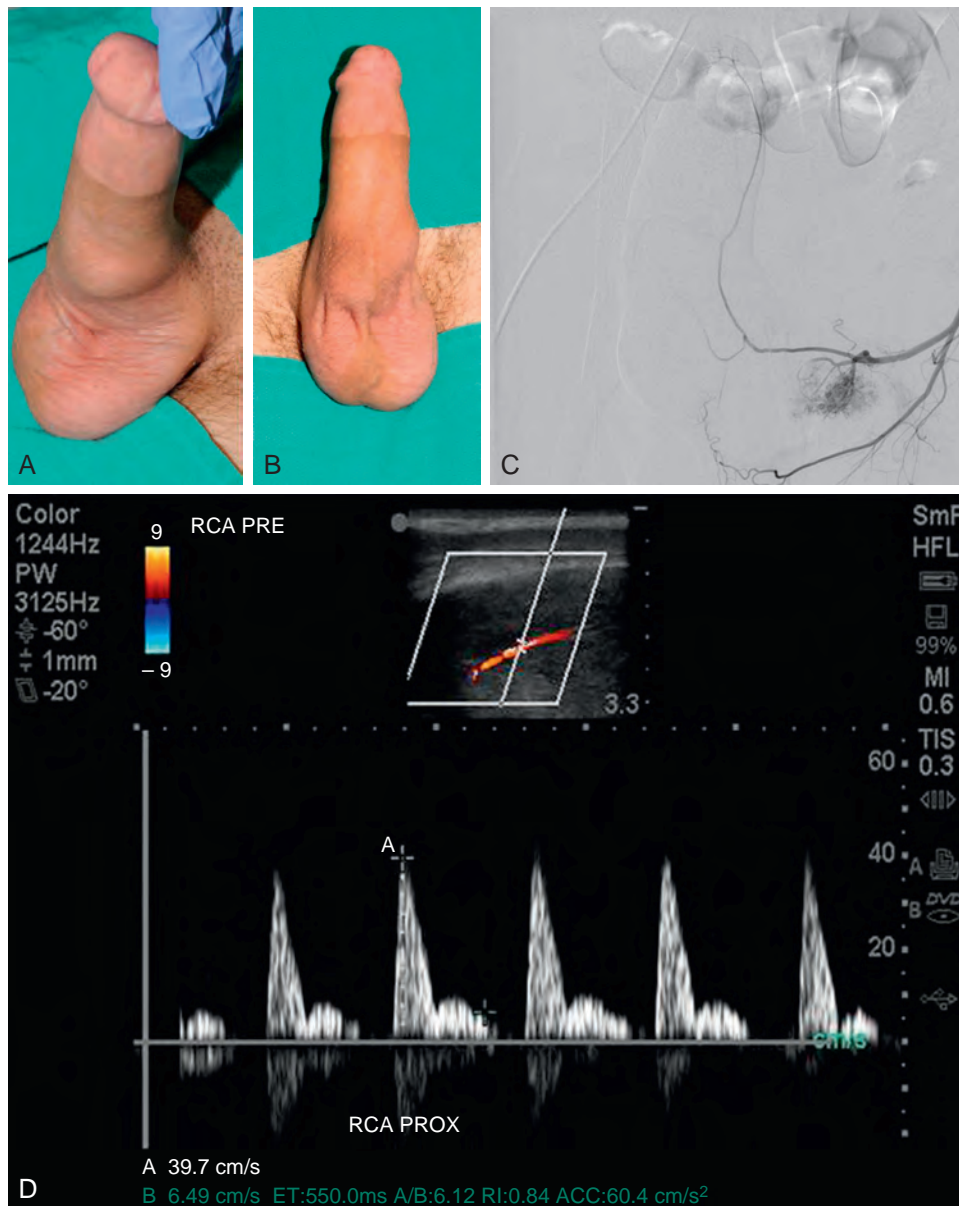


Figure 28-2. A, A 21-year-old white man with a history of ischemic priapism after binging with alcohol, marijuana, and energy drinks. Patient had a series of penile shunt procedures in attempts to reverse ischemic priapism: Winter, Al-Ghorab, bilateral corpora cavernosa to spongiosum. Six months later he sought evaluation for embarrassing persistent partial erection; consistent with converting from ischemic to high-flow priapism, he had no pain. A, Tumescent shaft with glans scar. B, Penoscrotal bulging at site of cavernospongiosal shunts. C, Angiogram of fistula originating at the bulbourethral artery. D, Doppler flows with peak systolic velocity of 39 cm/sec and 6 cm/sec; end diastolic flow and resistive index, 84.

supraphysiologic erections and spontaneously phasic priapic activity in vivo (Bivalacqua et al, 2006, 2007).

Endothelial cells actively regulate basal vascular tone and vascular reactivity by responding to mechanical forces and neuro-humoral mediators with the release of a variety of relaxing and contracting factors. In the penis the vascular endothelium is a source of vasorelaxing factors such as NO and adenosine, as well as vasoconstrictor factors such as RhoA/Rho-kinase. Recent evidence suggests that in states of priapism there may be aberrant NO and adenosine signaling, thus identifying a potential role for NO/cyclic guanosine monophosphate (cGMP), as well as adenosine and RhoA/Rho-kinase signaling in the pathophysiology of ischemic priapism (Champion et al, 2005; Mi et al, 2008; Bivalacqua et al, 2009a).

eNOS^{-/-} mutant mice have an exaggerated erectile response to cavernous nerve stimulation and have phenotypic changes in erectile function consistent with priapism (Champion et al, 2005; Bivalacqua et al, 2006). Mice lacking the *eNOS* gene manifest a priapism phenotype through mechanisms involving defective PDE5 regulatory function in the penis, resulting from altered endothelial NO/cGMP signaling in the organ (Lin et al, 2003; Bivalacqua et al, 2006). Supporting this hypothesis, PDE5 expression is significantly reduced in corpora cavernosa smooth muscle cells (CCSMCs) grown under anoxic and hypoxic cell culture conditions (Lin et al, 2003). In the context of molecular dysregulation, the cyclic nucleotide cGMP is produced in low steady-state amounts under the influence of priapism-related destruction of the vascular endothelium and thus reduced endothelial NO activity; this

situation downregulates the set point of PDE5 function, secondary to altered cGMP-dependent feedback control mechanisms (Champion et al, 2005; Bivalacqua et al, 2006; Burnett and Bivalacqua, 2007). When NO is neuronally produced in response to an erectogenic stimulus or with nocturnal erections, cGMP production surges in a manner that leads to excessive erectile tissue relaxation because of basally insufficient PDE5 enzyme to degrade the cyclic nucleotide. In addition, reduced Rho-kinase activity (contractile mediator) may contribute to the susceptibility of corporal tissue to excessive relaxation via two distinct molecular mechanisms. Two distinct molecular mechanisms appear to act in concert to promote stuttering ischemic priapism: enhanced vasorelaxation by uninhibited cGMP and diminished contractile effects of Rho-kinase. Transgenic sickle cell mice also have significant reductions in penile NO/cGMP signaling leading to deficient PDE5 expression and activity, as well as reduced RhoA/Rho-kinase expression, which causes them to manifest enhanced erectile responses and recurrent priapism (Champion et al, 2005). Another potential cause of enhanced corporal smooth muscle relaxation in SCD-associated priapism is elevated penile adenosine levels, which cause the CC to be in a chronically vasodilated state (Mi et al, 2008). Taken together, these data suggest that ischemic priapism and, most important, stuttering priapism are direct results of NO imbalance resulting in aberrant molecular signaling, PDE5 dysregulation, adenosine overproduction, and reductions in Rho-kinase activity, translating into enhanced corporal smooth muscle relaxation and inhibition of vasoconstriction in the penis.

KEY POINTS: SICKLE CELL DISEASE AND PRIAPISM

- Sickle cell hemoglobinopathy accounts for at least a third of all cases of ischemic priapism.
- The sickle cell genetic mutation is the result of a single amino acid substitution in the β -globin subunit of hemoglobin.
- Clinical features are seen in homozygous SCD patients: chronic hemolysis, vascular occlusion, tissue ischemia, and end-organ damage.
- Hemolysis and reduced NO are central in the pathogenesis of pulmonary hypertension, leg ulcers, priapism, and stroke in SCD patients.
- Increased blood viscosity is responsible for painful crises, osteonecrosis, and acute chest syndrome.
- SCD patients may experience stuttering priapism from childhood.
- SCD patients with stuttering priapism will experience repeated painful intermittent attacks up to several hours before remission.
- Stuttering priapism in SCD is the result of molecular dysregulation with enhanced corporal smooth muscle vasorelaxing forces and inhibition of vasocontractile forces in the penis.

EVALUATION AND DIAGNOSIS OF PRIAPISM

History

In order to initiate appropriate management, the physician must determine whether the underlying priapism hemodynamics are ischemic or nonischemic. **Emergency management of ischemic priapism is recommended.** Ischemia should be suspected when the patient has progressive penile pain associated with the duration of erection; has used a known drug associated with priapism; has SCD or another blood dyscrasia; or has a known neurologic condition, especially those affecting the spinal cord. Stuttering priapism history is one of recurrent episodes of prolonged erections, usually nonresolving morning erections. **Nonischemic priapism should be**

BOX 28-2 Elements in Taking the History of Priapism

Duration of erection
 Presence of pain
 Previous episodes of priapism and method of treatment
 Baseline erectile function
 Use of any erectogenic therapies (both prescription and nutritional supplements)
 Medications and recreational drugs
 Sickle cell disease, hemoglobinopathies, hypercoagulable states
 Trauma to the pelvis, perineum, or penis

suspected when there is no pain and the erection duration has not been accompanied by progressive discomfort. There is a history of straddle injury, coital trauma, blunt trauma to the penis or perineum, penile injection, penile surgery, or a diagnostic procedure of the pelvic and penile vessels. The onset of post-traumatic HFP in adults and children may be delayed by hours to several days after the initial injury (Box 28-2).

Physical Examination

Inspection and palpation of the penis are recommended to determine the extent and degree of tumescence and rigidity; the involvement of the cavernous bodies; the presence of pain; and the evidence of trauma to the perineum. **In ischemic priapism the corporal bodies will be completely rigid; the glans penis and corpus spongiosum are not.** Although malignancies rarely cause priapism, examination of the abdomen, testicles, perineum, rectum, and prostate may help identify a primary cancer. Malignant infiltration of the penis causes indurated nodules within or replacing corporal tissue. The subtle differences in the penile examination findings may be apparent to the experienced urologist but can be overlooked by emergency personnel on initial evaluation (Fig. 28-3A to F). If physical examination reveals the penis to be nontender, tumescent, or partially erect, nonischemic priapism should be suspected. **In nonischemic priapism the corpora will be tumescent but not completely rigid.** In children and adults with HFP, depending on the location of trauma and time since the traumatic event, there may be residual bruising at the perineum from straddle injury (Table 28-1).

Laboratory Testing

Evaluation should include a complete blood count (CBC), WBC count with blood cell differential, platelet count, and coagulation profile to assess anemia, rule out infection, detect hematologic abnormalities, and ensure that the patient can safely tolerate surgical interventions should initial medical management fail. In African-Americans, a sickle cell preparation and hemoglobin electrophoresis should be requested. Other hematologic abnormalities may cause priapism, including leukemia, platelet abnormalities, and thalassemia, and these should be sought if the cause is not evident. An elevated reticulocyte count is nonspecific and may be present in both priapism caused by SCD and thalassemia. Urine and serum toxicology panels should be done if recreational narcotic or prescription psychoactive drugs are suspected from the history. A corporal blood gas by aspiration is recommended in the emergency evaluation of priapism. The corporal blood aspirate differentiates ischemic from nonischemic priapism. Aspiration may be both diagnostic and therapeutic. Visual inspection of the color and consistency of an initial penile aspirate will reveal dark deoxygenated blood with a "crankcase oil" appearance in ischemic priapism. The initial corporal aspirate may be sent for blood gas testing to document pH, PO₂, and PCO₂ (Table 28-2). CDU should be initiated if the history

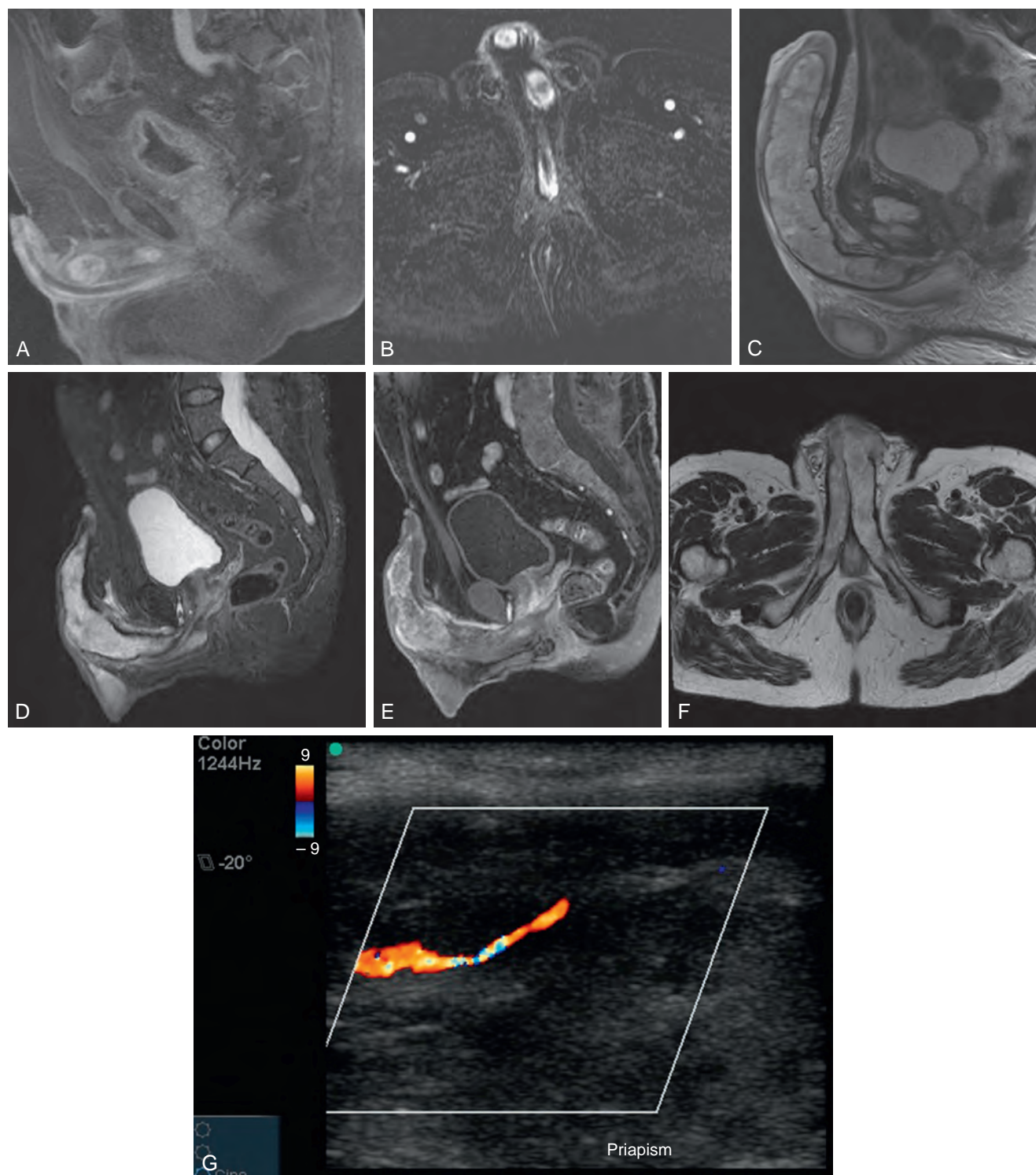


Figure 28-3. A, Sagittal magnetic resonance imaging (MRI) scan of the penis showing metastatic deposits of prostate cancer to the corpus cavernosum. B, Coronal MRI image from the same patient. Note the proximal and distal metastatic deposits of prostate cancer. C, T2-weighted MRI showing chondrosarcoma replacing corpus cavernosum. D to F, A 50-year-old white man with neurofibromatosis with a 6- to 12-month history of partial erection and progressive penile deformity. He was referred with a diagnosis of Peyronie disease. Penile biopsies showed malignant peripheral nerve sheath tumor or neurofibrosarcoma. T2- and T1-weighted MRI images show large irregular masses replacing corpora cavernosa. G, Color Doppler imaging shows irregular right cavernous artery with high flow. (C, Courtesy David Ralph.)

suggests penile or perineal trauma or if the corporal aspirate reveals well-oxygenated blood (Fig. 28-4).

Penile Imaging

CDU of the penis and perineum is recommended in the evaluation of priapism. CDU is an adjunct to the corporal aspirate

TABLE 28-1 Key Findings in Priapism

FINDINGS	ISCHEMIC PRIAPISM	NONISCHEMIC PRIAPISM
Perineal trauma	Seldom	Usually
Hematologic abnormalities	Usually	Seldom
Recent intracorporal injection	Sometimes	Sometimes
Corpora cavernosa fully rigid	Usually	Seldom
Penile pain	Usually	Seldom
Abnormal penile blood gas	Usually	Seldom
Cavernous inflow (on Doppler)	Seldom	Usually

Modified from Montague DK, Jarow J, Broderick GA, et al. American Urological Association guideline on the management of priapism. J Urol 2003;170:1318–24.

TABLE 28-2 Typical Blood Gas Values

SOURCE	Po ₂ (mm Hg)	Pco ₂ (mm Hg)	PH
Normal arterial blood (room air)	>90	<40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischemic priapism (first corporal aspirate)	<30	>60	<7.25

Modified from Montague DK, Jarow J, Broderick GA, et al. American Urological Association guideline on the management of priapism. J Urol 2003;170: 1318–24.

in differentiating ischemic from nonischemic priapism. Patients with prolonged ischemic priapism will have no blood flow in the cavernous arteries; the return of the cavernous artery waveform will accompany successful detumescence. Patients with nonischemic priapism have normal to high blood flow velocities detectable in the cavernous arteries; an effort should be made to localize the characteristic blush of color emanating from the disrupted cavernous artery or arteriole (Broderick and Lue, 2002). Examination of the entire penile shaft and perineum is recommended; this can be done with the patient supine but frog-legged (Fig. 28-5). Penile arteriography should be reserved for the management of HFP, when embolization is planned; arteriography is too invasive as a diagnostic procedure to differentiate ischemic from nonischemic priapism (Burnett, 2004). The data from penile blood gas assessments become confusing after interventions. CDU should always be considered in the evaluation of a full or partial erection after treatments for ischemic priapism. The differential diagnosis includes resolved ischemia with penile edema, persistent ischemia, and conversion to high-flow state. Chiou and colleagues (2009a) have recommended that to accurately categorize presentations as nonischemic or ischemic, careful interpretation of CDU hemodynamics must be done in conjunction with the clinical assessment. They describe eight patients with priapism after ICI (duration ≤7 hours), all of whom showed presence of cavernous arterial inflows with varied peak systolic velocities and end-diastolic velocities. They concluded that most patients with priapism after ICI (and duration <7 hours) have a hemodynamic picture of mixed arteriogenic and veno-occlusive priapism. In their series, men with idiopathic ischemic priapism longer than 20 hours showed no detectible cavernous arterial inflows.

There have recently been reports on the use of magnetic resonance imaging (MRI) in priapism. Kirkham and colleagues (2008) noted that there are three possible roles for MRI to help in the assessment of priapism; the primary role would be in the imaging of a well-established arteriolar-sinusoidal fistula. The authors acknowledge that a limitation of MRI is resolution; MRI cannot demonstrate small vessels as clearly as high-frequency Doppler sonography or angiography. The second role would be in ischemic priapism to demonstrate the presence and extent of tissue thrombus and corporal smooth muscle infarction. Ralph and coworkers (2009) used MRI to assess 50 patients presenting with refractory ischemic priapism. All patients had priapism lasting from 24 to 72

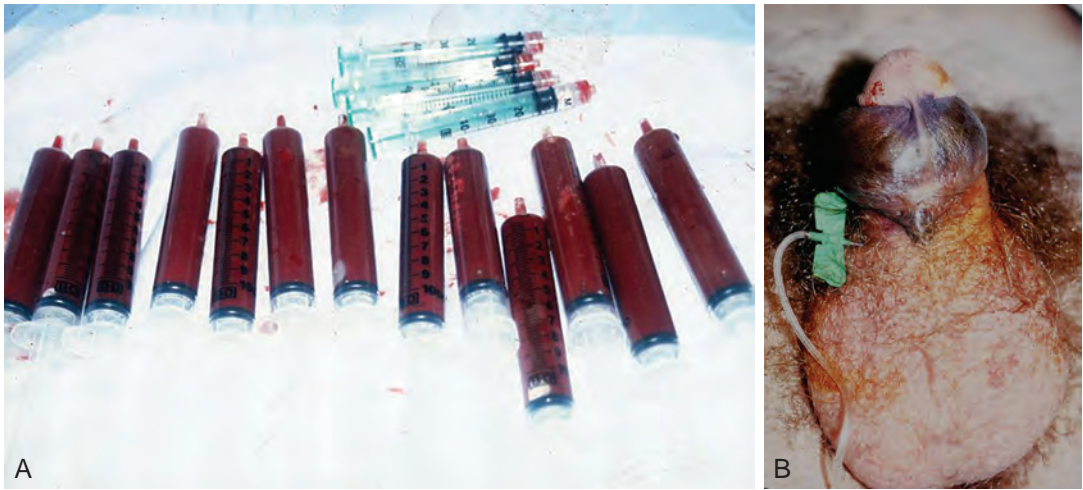


Figure 28-4. A, The initial corporal aspirate in ischemic priapism shows dark, deoxygenated blood. Subsequent aspirations will show brighter blood as corpus cavernosum is reoxygenated by inflow. Empty syringes are from successive injections of phenylephrine. B, A butterfly needle for aspiration and injection should be placed at the penoscrotal junction. Initial attempts in the emergency department failed to reverse priapism because of distal placement of the butterfly needle and failure to repeat aspiration and injections of an α -adrenergic agent.

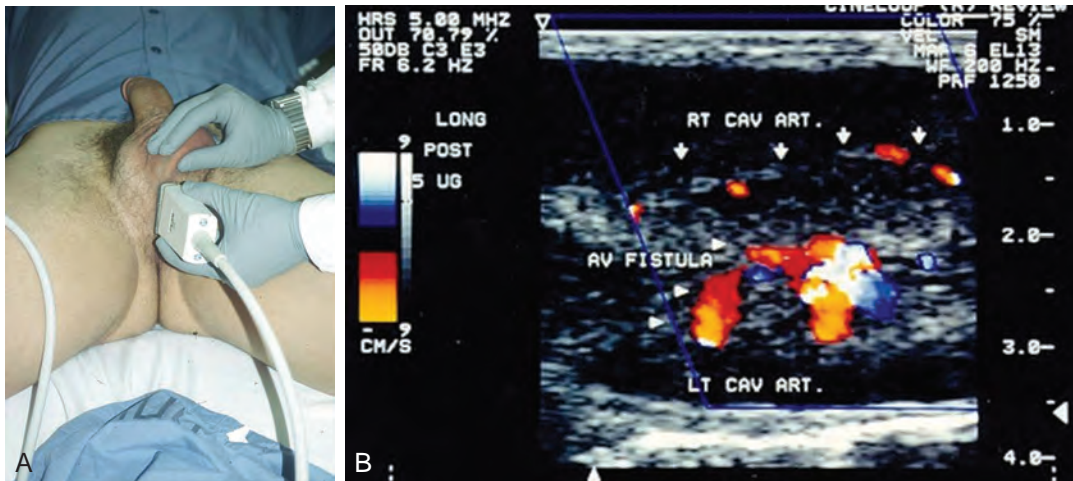


Figure 28-5. A, Examination of the crural bodies is required when searching for arterial sinusoidal fistula after straddle injury. B, Color Doppler image of arterial sinusoidal fistula of left cavernous artery.

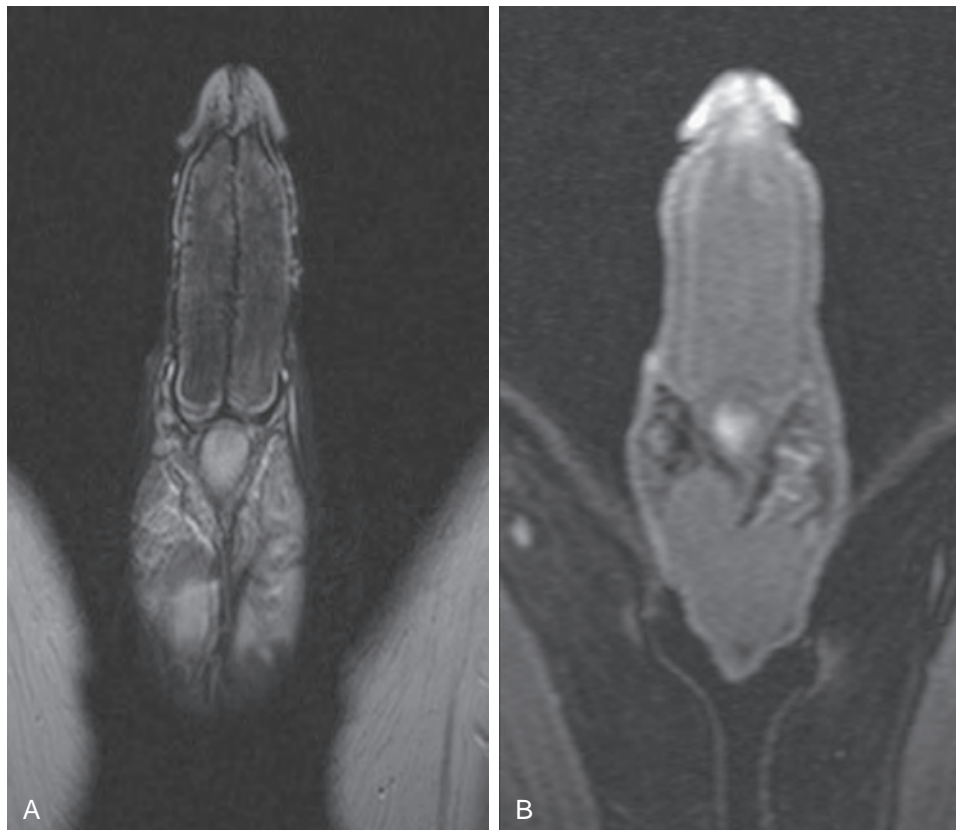


Figure 28-6. A, T2-weighted magnetic resonance image showing cavernous body thrombosis. B, Same patient. There is no enhancement after gadolinium infusion. At operation, extensive smooth muscle necrosis and thrombus were found. Patient had untreated ischemic priapism lasting several days. (Courtesy David Ralph.)

hours, and each had failed medical and surgical interventions. Patients underwent MRI to characterize the extent of smooth muscle necrosis before placement of penile prosthesis (Fig. 28-6). The third role for MRI would be in the imaging of corporal malignancy or metastasis with corporal smooth muscle replaced by malignant tissue or with true ischemic priapism caused by obstruction of venous outflow.

MEDICAL TREATMENTS

Ischemic Priapism

Historically, first aid was applied by the patient or recommended by a health practitioner unfamiliar with the hemodynamics of priapism; these interventions included ejaculation, ice packs, cold

KEY POINTS: PRIAPISM IMAGING

- CDU is an adjunct to the corporal aspirate in differentiating ischemic from nonischemic priapism.
- CDU imaging should include corporal shaft and transperineal assessment of the crural bodies when there is a history of penile trauma or straddle injury.
- CDU should always be considered in the evaluation of a persistent or partial erection after treatments for ischemic priapism.
- Penile arteriography is too invasive as a diagnostic procedure to differentiate ischemic from nonischemic priapism.
- MRI has three possible roles: imaging of a well-established arteriolar-sinusoidal fistula, identifying corporal thrombus, and identifying corporal metastasis.

baths, and cold water enemas. Each of these remedies was thought to end erection by inducing vasoconstriction. Some historical reports advised voiding and exercise. Oral sympathomimetic drugs (etilefrine, pseudoephedrine, phenylpropanolamine, and terbutaline) have been reported to effectively reverse prolonged erection (<4 hours) initiated by ICI therapies with efficacies of 28% to 36% (Lowe and Jarow, 1993). Lowe and Jarow (1993) compared oral terbutaline with pseudoephedrine or placebo in 75 patients with prolonged erection induced by ICI of alprostadil; they reported detumescence in 38% of cases with terbutaline, 28% with pseudoephedrine, and 12% with placebo. In a follow-up study Priyadarshi (2004) specifically investigated the efficacy of oral terbutaline in the management of prolonged erection after ICI (papaverine/chlorpromazine); he administered oral terbutaline 5 mg or placebo to men with persisting erection for more than 2.5 hours. Detumescence was achieved in 42% and 15% of cases, respectively, treated with terbutaline or placebo. Terbutaline treatment was unsuccessful in 58% of cases; all of those patients responded to ICI of an α -adrenergic agent.

Every practice administering diagnostic ICI or teaching ICI must be prepared to manage priapism. In my experience, when a vasoactive injection results in a prolonged erection with duration longer than 1 hour but shorter than 4 hours, aspiration may not be necessary. Phenylephrine (200 μ g) injected with an ultrafine needle and 1-mL syringe may reverse the erection. Reversing a prolonged erection will spare the patient and the office staff the complexity of treating full-blown ischemic priapism.

Oral agents are not recommended in the management of acute ischemic priapism (>4 hours). The recommended initial treatment of ischemic priapism is the decompression of the CC by aspiration. Aspiration will immediately soften the erection and relieve pain. Aspiration alone may relieve priapism in 36% of cases. The AUA Guidelines Panel (2003) advised that there were not sufficient data to conclude that aspiration followed by saline intracorporal irrigation was any more effective than aspiration alone (Montague et al, 2003). Subsequently, Ateyah and colleagues (2005) reported that a combination of corporal blood aspiration and cold saline irrigation effectively terminated priapism in 66% of cases compared with aspiration alone (24%). Data to support the efficacy of cold saline are limited. Aspiration should be repeated until no more dark blood can be seen coming out from the corpora and fresh bright red blood is obtained. This process leads to a marked decrease in the intracavernous pressure, relieves pain, and resuscitates the corporal environment, removing anoxic, acidotic, and hypercarbic blood. A single, large-bore, 19-gauge needle should be inserted at the penoscrotal junction at the 3 or 9 o'clock position to avoid piercing the dorsal neurovascular bundle. The surgeon should compress the penile shaft between the thumb and first digit, just below the 19-gauge needle, aspirating the shaft until it is soft. With the needle left in place, the shaft is permitted to refill. Compression is reapplied and aspiration repeated. These maneuvers may need to be serially

repeated. Several small, empty syringes should be available (3-mL to 12-mL syringes).

Corporal aspiration, if unsuccessful, should be followed by α -adrenergic injection or irrigation. Aspiration followed by the ICI of sympathomimetic drugs was recommended by the AUA Guidelines Panel in 2003 (Montague et al, 2003; Broderick et al, 2010). Sympathomimetic drugs (phenylephrine, etilefrine, ephedrine, epinephrine, norepinephrine, metaraminol) cause cavernous smooth muscle contraction. In the laboratory, normal cavernous smooth muscle preparations from humans, rabbits, and rodents show concentration-dependent contractions on exposure to phenylephrine, if the corporal environment is well oxygenated and has a normal pH (Broderick et al, 1994). In patients, time-dependent changes in the corporeal environment begin within 6 hours of persistent erection (Broderick and Harkaway, 1994). Animal models of ischemic priapism have demonstrated impairment in smooth muscle contraction with progressive acidosis, hypoxia, and glucopenia (Broderick, 1994; Saenz de Tejada et al, 1997; Munnarriz et al, 2006; Muneer et al, 2008). Corpus cavernosum specimens from patients with prolonged priapism show no contractions to high-dose phenylephrine in vitro.

Phenylephrine is a relatively selective α_1 -adrenergic receptor agonist with minimal β -mediated inotropic and chronotropic cardiac effects; it is the agent of choice according to AUA consensus recommendation (2003), the International Consultation on Sexual Medicine (2010), and the European Association of Urology guideline on priapism (2014) (Montague et al, 2003; Broderick et al, 2010; Salonia et al, 2014). There are no comparative trials of sympathomimetics in the management of priapism, nor are there studies of dosage tolerance to report. In terms of corporal physiology, α -adrenergic agonists are vasoconstrictors of cavernous artery and arterioles. Intracavernous administration of an α -adrenergic agent should contract cavernous smooth muscles, allowing sinusoidal blood to egress from subtunical veins. On the other hand, a β -adrenergic agonist, which would relax cavernous smooth muscle and dilate the cavernous artery and arterioles, could promote oxygenated arteriolar blood to enter the cavernous spaces and wash out deoxygenated blood. Metaraminol is a pure α -adrenergic agent; etilefrine, phenylephrine, and epinephrine are mixed α - and β -adrenergic agonists. Terbutaline is a pure β agonist. Case reports with these agents show varying efficacy from 43% to 81%. In addition to the specific reversal agent, there is clearly a time-dependent efficacy for pharmacologic reversal of priapism. For acute pharmacologic management of ischemic priapism, the intracavernous administration of dilute solutions of phenylephrine or epinephrine is most commonly described in the United States. In Europe etilefrine is commonly described. Etilefrine is a phenylephrine related β -adrenergic and α -adrenergic agonist. It is available in oral and parenteral formulations internationally (effortil, ethyladrianol, ethylphenylephrine, phetanol, ethyl nor-adrianol). Currently, pseudoephedrine, phenylpropanolamine, and ephedrine are the orally active adrenergic agents available in the United States. Pseudoephedrine (Sudafed) is regulated under the Combat Methamphetamine Epidemic Act of 2005, which banned over-the-counter sales of cold medicines containing pseudoephedrine. It is available "behind the counter" without a prescription. Neither Sudafed (pseudoephedrine) nor Sudafed PE (phenylephrine) have been evaluated as oral agents for the reversal or prevention of priapism in the United States. Phenylephrine is typically diluted in normal saline to a concentration of 100 to 200 μ g/mL; it is administered intracavernously as a 1-mL injection every 3 to 5 minutes. Administration should be intermittent over the course of an hour. In my experience, phenylephrine can be concentrated as 200 μ g/mL in saline and administered intermittently as 0.5 mL to 1.0 mL every 5 to 10 minutes to a maximum dosage of 1 mg. This will permit up to 10 separate injections of 0.5 mL (100 μ g each) or 5 separate injections of 1 mL (200 μ g each). The penis is aspirated between successive injections by tightly pinching the shaft at the penoscrotal junction, just below the site of needle insertion. Aspiration should continue until the distal shaft is empty and collapses. This removes deoxygenated

acidic blood. Then phenylephrine is injected. Gradually the compression at the penoscrotal junction is released, allowing the shaft to refill with fresh blood. Extremes of age and preexisting cardiovascular diseases should be taken into consideration before intracavernous sympathomimetic administration. Serial monitoring of blood pressure and pulse should be performed during and immediately after ICI of sympathomimetic drugs. Potential side effects of intracavernous sympathomimetics include headache, dizziness, hypertension, reflex bradycardia, tachycardia, and irregular cardiac rhythms. Davila and colleagues (2008) reported subarachnoid hemorrhage in a patient with SCD ischemic priapism. The patient was a 24-year-old African-American man who reported sudden and severe headache immediately after intracorporal administration of phenylephrine 500 µg/mL repeated every 3 minutes for a total of 4 mL (2000 µg = 2 mg). In 2005 the Pennsylvania Patient Safety Authority published an advisory, *Let's Stop This "Epi"demio! Preventing Errors with Epinephrine*. The report

describes a case of a 16-year-old boy who received 4 mL of undiluted 1:1000 epinephrine solution intracavernously to treat priapism. The physician thought the 1:1000 ratio on the epinephrine 1 mg/mL label meant the solution had been prediluted with 1000 mL of fluid (Pennsylvania Patient Safety Authority, 2006). Whichever intracavernous sympathomimetic agent is chosen for the management of ischemic priapism, urologists are well advised to consult their pharmacies and develop clear mixing and dosage protocols for safe administration (Fig. 28-7).

SCD and hematologic malignancies are rare but important causes of ischemic priapism. Classically, treatment of SCD-induced ischemic priapism involved analgesics, hydration, oxygen, bicarbonate, and exchange transfusion. Unfortunately, acute neurologic complications may follow exchange transfusions. Hematologists have begun to question the emphasis on intravenous hydration, sodium bicarbonate for alkalization, and exchange transfusion as first line therapy for SCD-associated priapism (Kato, 2012).

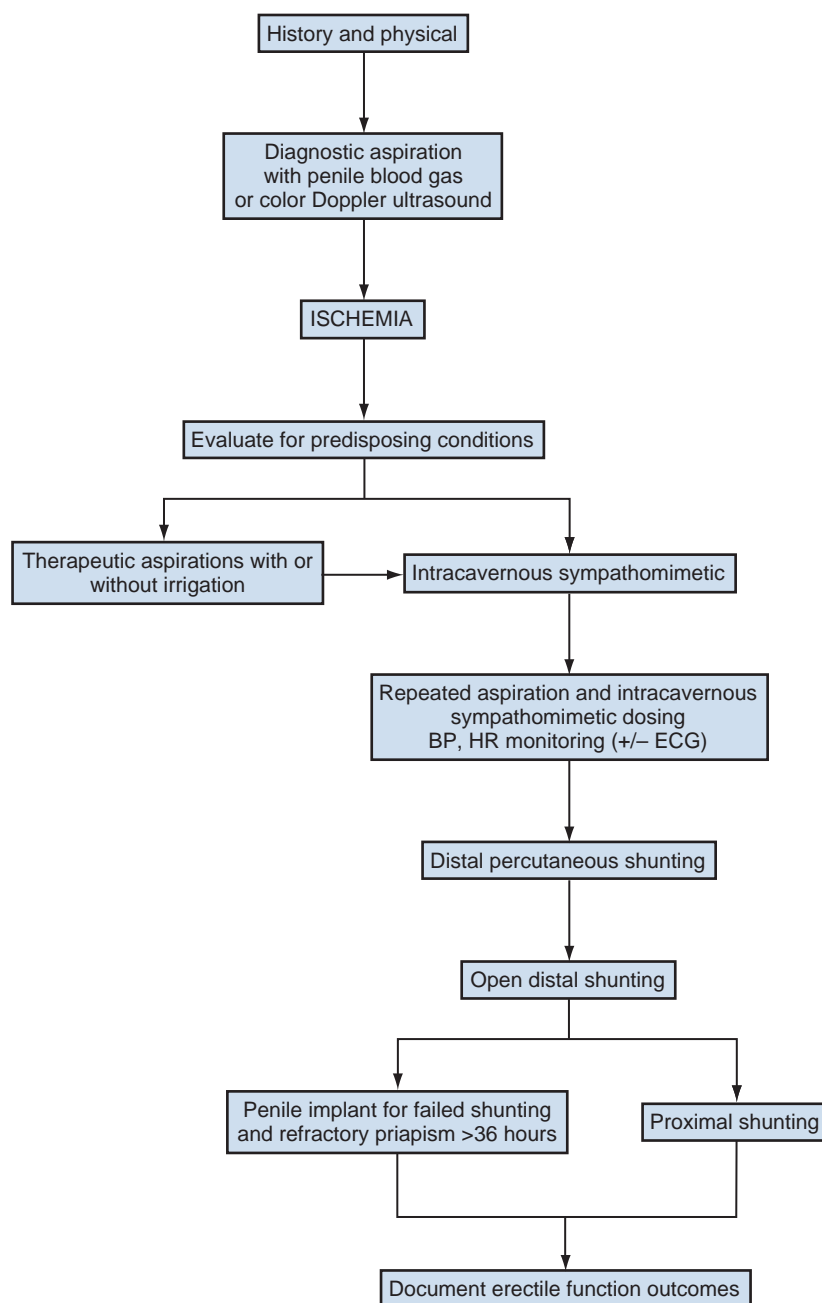


Figure 28-7. Algorithm for managing ischemic priapism. BP, blood pressure; ECG, electrocardiogram; HR, heart rate.

Hydroxycarbamide (hydroxyurea) is a hematologic agent used in the management of vaso-occlusive crises in sickle cell patients (Saad et al, 2004; Morrison and Burnett, 2012). The proposed mechanisms of action are increase in production of hemoglobin F; reduction of leukocytes, platelets, and reticulocytes; and promotion of release of NO. **In the best interests of the patient, the urologist should seek hematologic consultation in the management of boys and men with SCD priapism but remain assertive that hematologic therapy alone is not effective management of SCD priapism (Rogers, 2005).** A 2006 report suggested that blood transfusion may have no effective role in the treatment of sickle cell-induced priapism (Merritt et al, 2006). **Reports from hematology centers suggest high success rates with use of penile aspiration, injection, and irrigation with intracavernous sympathomimetics for SCD priapism (Mantadakis et al, 2000).** Mantadakis and colleagues (2000) conducted a prospective trial for the management of children with SCD with prolonged erection, ages 3 to 18 years (no placebo group). For erections lasting longer than 4 hours and less than 12 hours, emergency department interventions were local anesthetic, cavernous aspiration, and irrigation with 10 mL of a 1:1,000,000 solution of epinephrine. If detumescence lasted for 30 minutes, patients were discharged to home. They described 15 patients receiving 39 interventions, of which 37 were successful; 67% required only one aspiration and irrigation treatment. **In the management of SCD pediatric patients with stuttering priapism, several levels of escalating intervention are necessary, with parental and emergency department staff education being the first level.** Gbadoe and colleagues (2001) described the treatment of 11 SCD patients (ages 30 months to 15 years) with acute ischemic priapism or stuttering priapism. In their series of cases, if the patient had priapism lasting less than 6 hours, aspiration and injection of 5 mg of etilefrine was given in the emergency department; for stuttering priapism, patients were given oral etilefrine 0.5 mg/kg nightly for 1 month, or 0.25 mg/kg twice daily. Patients (parents) also administered injections at home to reverse painful erection lasting longer than 1 hour. The authors reported no significant hypertension and only one case of "agitation" attributed to daily administration.

Stuttering Priapism

Various factors need to be considered in treating stuttering priapism. **Although an episode may last less than 4 hours, increasing frequency or duration of stuttering episodes may herald a major ischemic priapism.** Multiple frequent visits to the emergency department to resolve the priapism are disruptive to the patient's life and embarrassing. If attacks follow sexual activity, patients may become sexually avoidant (Adeyolu et al, 2002; Chow and Payne, 2008). Safety and efficacy of various treatments are poorly characterized in the literature. The side effects of recommended medications should be understood by the patient. Patients on chronic medical therapy to decrease the frequency of stuttering episodes may significantly benefit from performing a single sympathomimetic intracorporal injection at home as part of a personal treatment algorithm (Virag et al, 1996; Teloken et al, 2005). Multiple treatment options have been described: oral and injectable α -adrenergic agonists, terbutaline, digoxin, the antisickling agent hydroxycarbamide (hydroxyurea), estrogens, gonadotropin-releasing hormone (GnRH) analogues, antiandrogens, baclofen, gabapentin, and recently PDE5 inhibitors (Chow and Payne, 2008).

Etilefrine is available as an oral or injectable treatment in some European countries. The maximum oral dose is 100 mg in 24 hours (Okpala et al, 2002). Okpala and colleagues (2002) followed 18 adults (17 SCD patients and 1 with sickle trait), all with a history of stuttering priapism. Patients were given oral etilefrine in escalating doses from 25 mg at bedtime to a maximum of 100 mg each day. Stuttering episodes were reduced in frequency and duration in 72%. A small series of 6 SCD children were followed with administration twice daily with 0.25 mg of etilefrine per kilogram (Gbadoe et al, 2002). **The experience of multiple**

KEY POINTS: MEDICAL MANAGEMENT OF ISCHEMIC PRIAPISM

- Oral therapy is not recommended for the treatment of acute ischemic priapism.
- The initial treatment of ischemic priapism is decompression by aspiration.
- Aspiration should be repeated until oxygenated blood is seen to refill the corpora.
- Aspiration should be followed by the ICI (or irrigation) of a diluted α -adrenergic drug.
- Worldwide availability of adrenergic agents varies; effective reversal of priapism has been documented with dilute injections of ephedrine, epinephrine, etilefrine, metaraminol, or phenylephrine. Phenylephrine is the agent of choice recommended by AUA, International Consultation on Sexual Medicine, and European Association of Urology guidelines.
- Clinicians are advised to consult their pharmacies and develop clear mixing and dosage protocols for safe administration of adrenergic solutions.
- Phenylephrine is a sympathomimetic drug with selective α_1 adrenergic receptor actions; it has minimal β -mediated ionotropic and chronotropic cardiac effects.
- Phenylephrine should be concentrated as 200 μ g/mL in normal saline and administered intracavernously as 0.5 mL to 1 mL. Lower concentrations should be used in children and adults with cardiovascular disease. Administration and aspiration may need to be repeated. No recommendations can be made about maximum safe dosage. Hypertensive stroke has been reported as a complication of cumulative administration of 2 mg.
- Physicians should monitor patients for subjective complaints and objective findings consistent with known undesirable effects: headache, chest discomfort, acute hypertension, reflex bradycardia, tachycardia, palpitations, and cardiac arrhythmia. Patients and parents should be informed about these potential complications.
- Blood pressure monitoring is recommended with repeated sympathomimetic administration. In patients with significant cardiovascular risks, electrocardiogram monitoring is recommended.
- Ischemic priapism associated with SCD requires intracavernous treatment. A hematologist may provide concurrent systemic therapies (oxygen, hydration, transfusion), but the best resolution rates are achieved with therapies directed at the penis.

investigators using oral α -adrenergics in the management of SCD stuttering ischemic priapism suggests that limited daily administration should be considered in the management of stuttering priapism; drug therapy is typically initiated at bedtime. Oral α -adrenergic administration is a preventative strategy for stuttering priapism.

Hormonal Therapies

The primary action of systemic hormonal therapy in stuttering priapism is the suppression of the androgenic effects on penile erection. Attempts to treat stuttering priapism with hormones have exploited known regulators of male sexual function by targeting the pituitary gland (GnRH agonists), suppressing pituitary function through feedback inhibition (diethylstilbestrol [DES]), blocking androgen receptors (antiandrogens), and reducing testicular and adrenal synthesis (ketoconazole). The common goal of hormonal therapy in the prevention of stuttering priapism is to reduce serum testosterone to hypogonadal levels or block testosterone's effects on the penis. In the only randomized placebo-controlled trial, a synthetic estrogen, DES, caused termination of the stuttering

episodes in all patients who received treatment (Chinegwundoh and Anie, 2004). However, in more than 50% of patients (5 of 9) priapism recurred after treatment cessation. Similar results have been described by others in case reports (Gbadoe et al, 2002; Shamloul and el Nashaar, 2005). Long-term estrogen therapy is not recommended because of the potential cardiovascular side effects. **GnRH analogues**, goserelin acetate and leuprolide acetate, have been described in case reports (Levine and Guss, 1993; Shamloul and el Nashaar, 2005). Chronic therapy with GnRH analogues in combination with penile injection of α -adrenergics as needed has been reported in the management of ischemic stuttering priapism (Steinberg and Eyre, 1995). Discontinuation of GnRH analogues typically leads to stuttering resumption. **Antiandrogens** including flutamide, bicalutamide, and chlormadinone have been used to interrupt stuttering priapism, and their use has been detailed in case reports. Antiandrogens may have benefit to patients over the GnRH analogues because they are orally administered and because some patients continue having sexually stimulated erections (Costabile, 1998; Dahm et al, 2002; Yamashita et al, 2004). **Abern and Levine (2009)** used nightly administration of the antifungal agent **oral ketoconazole** and **prednisone** to suppress nocturnal erections as a preventive strategy for recurrent ischemic priapism in 8 patients followed for 1.5 years. The protocol required titrating dosages and monitoring of nocturnal erections and serum testosterone levels; mean testosterone levels fell from a baseline of 475 ng/dL to 275 ng/dL. The fall in testosterone levels appeared to be a surrogate for efficacy in preventing significant episodes of priapism. Ketoconazole inhibits steroidogenesis in the adrenal and gonadal tissues; it has a half-life of 8 hours. Ketoconazole inhibits cortisol production, necessitating concomitant prednisone administration. In the Abern and Levine protocol, men with recurring ischemic priapism were treated with ketoconazole 200 mg given orally (PO) every 8 hours and prednisone 5 mg at bedtime for 2 weeks, followed by ketoconazole nightly without prednisone supplementation. **Rachid-Filho and colleagues (2009)** have described the efficacy of oral **5 α -reductase inhibitors** (finasteride) in the management of sickle cell stuttering priapism. They administered finasteride to 35 patients over 120 days in doses that decreased monthly from 5 mg/day to 3 mg/day and then 1 mg/day in the final month. This was not a controlled trial, but careful observation of stuttering episodes was made. They found at the beginning of treatment that the mean number of episodes of stuttering priapism per patient was 22.7, and at the end of 4 months the mean number of episodes per patient was 2.1. The optimal effects were found at 5- and 3-mg daily doses. Six of 35 patients in this study developed painless gynecomastia. Finasteride is a 5 α -reductase inhibitor approved in the United States for management of symptomatic BPH (Proscar 5 mg) and male pattern alopecia (Propecia 1 mg); finasteride and dutasteride are type II 5 α -reductase inhibitors. This class of drugs reduces conversion of testosterone to dihydrotestosterone, which is believed to be many times more potent at the cellular level. Paradoxically, when measured during clinical trials, serum testosterone levels go up in healthy controls and patients administered finasteride or dutasteride. Neither drug is approved for use in patients with stuttering ischemic priapism.

Baclofen

Studies in both rats and humans suggest that baclofen inhibits penile erection and ejaculation, through γ -aminobutyric acid (GABA) receptor activity. In rats, stimulation of GABA_B receptors in the lumbosacral spinal cord inhibits erection (Bitran et al, 1988; Paredes and Agmo, 1995; Vaidyanathan et al, 2004). **Denys and colleagues (1998)** reported on nine men with multiple sclerosis or spinal cord injuries who were treated for 44 months with intrathecal baclofen for muscle spasticity; eight of nine reported decreased erectile function, which reversed on cessation of baclofen. **Rourke and colleagues (2002)** first reported on the use of oral nightly baclofen 40 mg in the management of recurrent priapism in patients with neurologic lesions. **D'Aleo and colleagues (2009)** were the first to report on the use of an intrathecal pump to administer baclofen

180 μ g daily for the management of skeletal muscle spasm and recurrent priapism in a patient with spinal cord injury; the patient was refractory to treatment with oral administration of 75 mg/day but responded to a test dose of 25 μ g intrathecally. The neurologic literature generally fails to categorize these erectile events as ischemic or nonischemic. Triggering events may be tactile nonsexual stimulation causing repeated reflexogenic erections. Better characterization of these unwanted erections in men with upper motor neural lesions is necessary to appreciate hemodynamics, inciting events, duration, and impact on erectile function. There have been reports to the FDA that men with baclofen infusion pumps experience a withdrawal syndrome when those pumps fail. The withdrawal syndrome has been characterized by return of spasticity, agitation, sleeplessness, and priapism. Advanced symptoms resemble autonomic dysreflexia and may include rhabdomyolysis. The syndrome responds to oral baclofen dosing until intrathecal therapy can be resumed. In non-neurogenic patients, daily administration of baclofen is associated with drowsiness, nausea, complaints of fatigue, and ED. Recurrent reflexogenic erections are clearly an unwanted condition associated with muscle spasticity in men with spinal cord lesions and neurologic disease, but it remains to be demonstrated whether the duration and hemodynamics of such erectile events are similar to ischemic stuttering priapism typical in SCD.

Phosphodiesterase Type 5 Inhibitors in the Management of Stuttering Priapism: A Counterintuitive Treatment Strategy

Bialecki and Bridges (2002) first reported on sildenafil having a paradoxical effect in controlling stuttering priapism in three patients with SCD. Although this proposal would immediately seem illogical on the basis of the understanding that PDE5 inhibitors exert erectogenic effects, there is a scientific basis for using these agents to treat priapism.

In a small case series, Burnett and colleagues showed that daily sildenafil or tadalafil therapy reduces ischemic priapism episodes in men with stuttering priapism (Burnett et al, 2006a). When used in long-term regimens unassociated with erection stimulatory conditions, PDE5 inhibitor therapy alleviates recurrent priapism episodes in men with SCD-associated priapism without affecting normal erectile capacity (Burnett et al, 2006b; Bivalacqua et al, 2009a). The working theory is that surges of cGMP go unchecked because of downregulated levels of PDE5; this results in stimuli such as nocturnal erection, which causes unchecked corporal smooth muscle relaxation. In initial series, the short-acting PDE5 inhibitor sildenafil citrate was given at a dose of 25 mg oral daily, with escalation to 50 mg daily. Subsequently these investigators reported on tadalafil at a dose of 5 or 10 mg taken orally three times weekly. Multicenter, randomized, double-blind, placebo-controlled clinical trials are underway. PDE5 inhibitors should be started under conditions of complete penile flaccidity, not during a stuttering episode. Efficacy is seen after a week or more of administration.

SURGICAL MANAGEMENT OF ISCHEMIC PRIAPISM

Surgical management of ischemic priapism is indicated after repeated penile aspirations and injections of sympathomimetics have failed or if such an attempt has resulted in a significant cardiovascular side effect. At present there is a paucity of data regarding the timing of surgical intervention following initiation of medical treatment, although the 2004 International Consultation on Sexual Medicine in Paris recommended corporal aspiration and α -adrenergic agonists for at least 1 hour before consideration of shunting (Pryor et al, 2004). Early surgical intervention may be preferable in patients with malignant or poorly controlled hypertension or for men who are using monoamine oxidase inhibitor medications contraindicating α -adrenergic therapies. A comprehensive discussion and documentation that includes baseline erectile function, duration of priapism, risks and benefits

KEY POINTS: MEDICAL MANAGEMENT OF STUTTERING PRIAPISM

- The goals of managing a patient with stuttering priapism include prevention of future episodes, preservation of erectile function, and balancing the risks versus benefits of various treatment options.
- A trial of daily oral α -adrenergic therapy may be used in the management of patients (adults and children) with stuttering priapism associated with hemoglobinopathies. Efficacy should be monitored through frequency and duration of stuttering episodes, blood pressure, and normal erectile capacity.
- A trial of daily oral PDE5 inhibitor therapy may be used in the management of patients (adults and children) with stuttering priapism associated with hemoglobinopathies. Treatment should be initiated under conditions of complete penile flaccidity. Efficacy should be monitored through frequency and severity of stuttering episodes, as well as PDE5 inhibitor side effects and normal erectile capacity.
- A trial of GnRH agonists or antiandrogens may be used in the management of adult patients with stuttering priapism. Hormonal agents should not be used in patients who have not achieved full sexual maturation and adult stature. Chronic GnRH or antiandrogen administration in men may affect libido or fertility, cause gynecomastia, cause hot flashes, promote osteoporosis, increase the risks of cardiovascular disease, and worsen sexual function.
- When administered at home for prolonged morning erections, an injection of an intracavernous α -adrenergic agent may avert a full-blown episode of ischemic priapism. ICI of phenylephrine (by the adult patient or parent) should be considered as an adjunct to daily systemic therapies in patients with stuttering priapism.

of the surgery, and ED should be held with the patient or guardian and an informed consent form signed by the patient or guardian.

Shunting

It is generally accepted that the longer an episode of ischemic priapism lasts, the greater the likelihood of compromised erectile function in the future. Early reviews concluded that priapism lasting longer than 24 hours was associated with a 90% ED rate (Pryor and Hehir, 1982). Kulmala and colleagues (1996) reported 92% erectile function preservation among patients with ischemic priapism reversed in less than 24 hours, but only 22% preservation of erectile function among men with priapism lasting longer than 7 days. Recommendations based on well-documented erectile function outcomes are few. One recent study does document erectile function outcomes by contemporary standards (International Index of Erectile Function [IIEF]). Bennett and Mulhall (2008) carefully documented 39 patients with SCD priapism who came to their emergency department over 8 years; men were routinely interviewed for erectile function status within 4 weeks of priapism and interventions. Of the 39 African-American men followed, 73% acknowledged prior episodes of stuttering; 85% had previously been diagnosed with SCD; but only 5% had been counseled in SCD clinics or were aware that priapism was a complication of SCD. A standard protocol of aspiration and phenylephrine injection was performed; shunting for failure of medical management was performed in 28%. In patients in whom priapism was reversed, spontaneous erections (with or without use of sildenafil) were reported in 100% of men when priapism was reversed by 12 hours; 78% when reversed by 12 to 24 hours; and 44% when reversed by 24 to 36 hours. In this contemporary series of SCD patients, no men reported the return of spontaneous erections after priapism lasting 36 hours or more. The International Society for Sexual Medicine

Standards Committee (expert opinion) stated that shunting is to be considered for ischemic priapism events lasting 72 hours or less. Consideration should be given to foregoing a shunt in priapism events lasting longer, in particular when cavernous thrombosis is evident and no blood can be aspirated from the corporal bodies (Pryor et al, 2004; Mulhall, 2006).

The objective of shunt surgery is reoxygenation of the cavernous smooth muscle. The shared principle of shunt procedures is to reestablish corporal inflow by relieving venous outflow obstruction; this requires creation of a fistula between the CC and glans penis, CC and corpus spongiosum, or CC and dorsal or saphenous veins. Shunt procedures are subdivided on the basis of anatomic location on the penis (Lue and Pescatori, 2006) (Fig. 28-8).

- Percutaneous distal shunts—Ebbehoj (1974), Winter (1976), or T shunt (Brant et al, 2009)
- Open distal shunt—Al-Ghorab (Hanafy et al, 1976; Borrelli et al, 1983) or corporal snake (Burnett and Pierorazio, 2009)
- Combined T shunt and corporal snake maneuver—Zacharakis and colleagues (2014b)
- Open proximal shunt—Quackles (1964) or Sacher and colleagues (1972)
- Saphenous vein—Grayhack and colleagues (1964)
- Deep dorsal vein shunt—Barry (1976)

A distal cavernoglanular shunt should be the first choice of shunting procedures because it is technically easier to perform than proximal shunting. Percutaneous distal shunting is less invasive than open distal shunting and can be performed with local anesthetic in the emergency department. The most recently described distal shunt (Brant et al, 2009) creates a T-shaped shunt between the CC and glans penis. Brant and associates (2009) describes 13 men with priapism durations longer than 24 hours (in 6 of 13, other distal or proximal shunt procedures had failed). All T shunts were performed after penile anesthetic block; in 12 of 13 patients, the priapism was successfully reversed by initial intervention. In T shunting a No. 10 blade is placed vertically through the glans 4 mm away from the meatus; the blade pierces through the glans to the CC and is rotated 90 degrees away from the urethra and removed (Fig. 28-9). Deoxygenated blood is milked out of the wound. The glans is then sutured with absorbable suture. The authors recommend discharge home if the penis remains flaccid for 15 minutes (Brant et al, 2009). If erection returns or persists, a second T shunt is recommended on the opposite side of the meatus. When ischemic priapism has been present for more than 36 hours, immediate placement of bilateral T shunts is recommended, with passage of 20-Fr dilators into the fistula tract and well into the CC down to the crus. This technique is more traumatic and will require general anesthesia. Burnett and Pierorazio (2009) have described a similar technique to resolve ischemic priapism refractory to first-line interventions. Their procedure, known as the *corporal snake*, is a modification of the Al-Ghorab corporoglanular shunt (see Fig. 28-8B and Fig. 28-10). With the patient under general anesthesia, a 2-cm transverse incision is made on the glans; the distal tips of the rigid CC are incised and grasped with 2-0 stay sutures or Kocher clamps. Deoxygenated blood is milked out of the CC, but rather than excising a wedge of tunica and underlying CC muscle, a 7/8 Hegar dilator is advanced through each of the tunica windows proximally several centimeters to release blood and thrombus. The penis is made flaccid by repeated manual compression and release; the glans skin is then approximated with 4-0 chromic sutures; a urethral catheter is placed, and lightly compressive dressing is applied to the genitalia.

Segal and associates (2013) retrospectively reviewed the Johns Hopkins Hospital experience with the corporal snake maneuver. Ten patients with ischemic priapism with a mean duration of 75 hours (range 24 to 288 hours) refractory to medical intervention and simple distal shunting (Winter or Ebbehøj) were treated surgically with the corporal snake maneuver; in 8 the priapism resolved, and they had no postoperative recurrence during 6-month follow-up. In 2 patients the priapism did not respond; they were treated by insertion of inflatable penile implant at time of presentation. Complication rates were significant (20%); complications

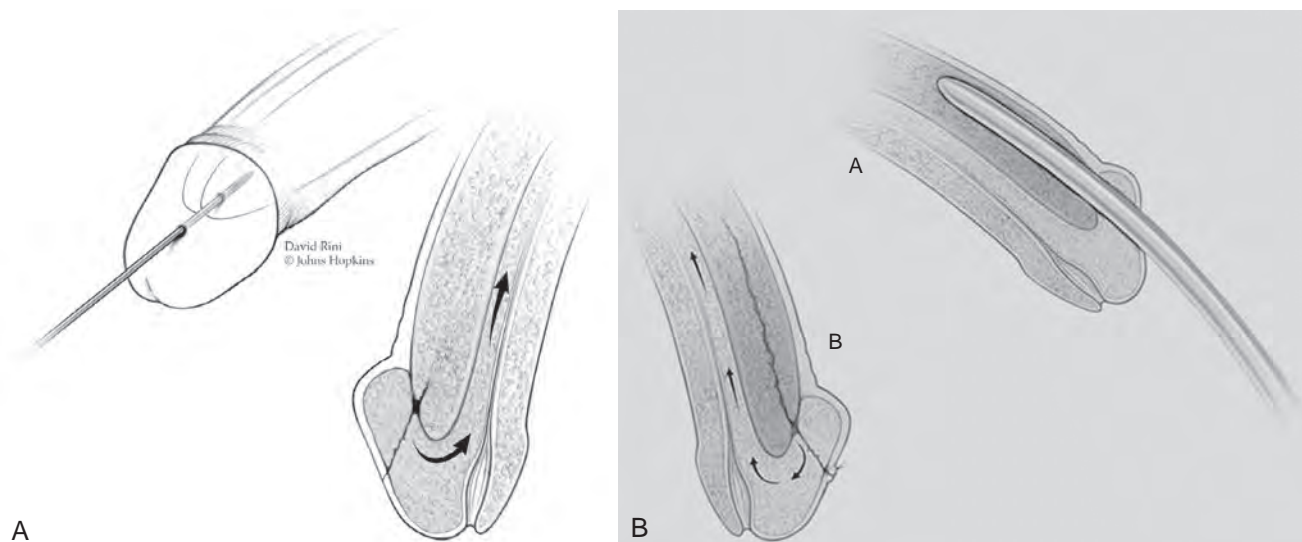


Figure 28-8. A, Winter shunt. The distal cavernoglanular shunt procedure is depicted by the transglanular placement of a large-bore needle or angiocatheter in the distal glans and corpus cavernosum. B, Corporal snake maneuver is a modification of the Al-Ghorab shunt. After excision of a 5-mm circular core of distal tunica albuginea, a 7/8 Hegar dilator is inserted down each corporal body through the tunica window. (A, © Brady Urological Institute; B, from Burnett AL, Pierorazio PM. Corporal “snake” maneuver: corporoglanular shunt surgical modification for ischemic priapism *J Sex Med* 2009;6:1171–76.)



Figure 28-9. A, A No. 11 blade is used for an Ebbehoj percutaneous cavernoglanular shunt, and a No. 10 blade is used for a T shunt. B and C, Note the differences between the Ebbehoj and T shunts. In the Ebbehoj technique the No. 11 blade leaves a straight incision into the glans and corpus cavernosum. In the creation of a T shunt the No. 10 blade is rotated 90 degrees after insertion and is withdrawn. In both the percutaneous techniques deoxygenated blood is milked out of the open wounds; once bright red blood is seen, the skin is closed, leaving the deeper incision of the open fistula. In either procedure the maneuver may be repeated on the opposite corpus. (Courtesy Dr. Tom Lue.)

included wound infection, penile skin necrosis, and urethrocutaneous fistula. The authors documented sexual health function outcomes in these patients treated for refractory priapism lasting 24 to 288 hours; all had significant complaints of ED at 6 months, with 2 of 8 receiving subsequent penile implants (Segal et al, 2013). Zacharakis and colleagues (2014b) described the efficacy and outcomes of combining the T shunt (Brant et al, 2009) with the corporal snake maneuver in 45 patients. All were refractory to medical reversal of ischemic priapism. The combined distal surgical technique was successful in resolving the acute priapism if duration was less than 24 hours but had limited efficacy in cases of priapism exceeding 48 hours. Corporal needle biopsies were performed in

each patient and documented smooth muscle necrosis, worsening as a function of time and uniform in all men with more than 48 hours of ischemia. At 6 months, erectile function outcomes were assessed by the erectile function domain score from the IIEF-5. T shunt with corporal snake tunneling successfully reversed ischemic priapism in all patients with less than 24 hours' duration, but at 6 months ED was reported by 50% of men. The authors (Zacharakis et al, 2014b) conclude that the cutoff for reversing ischemic priapism in the hopes of preserving future erectile function is 48 hours. They advise that management of refractory ischemic priapism of longer than 48 hours' duration should include discussion of immediate insertion of a penile implant.

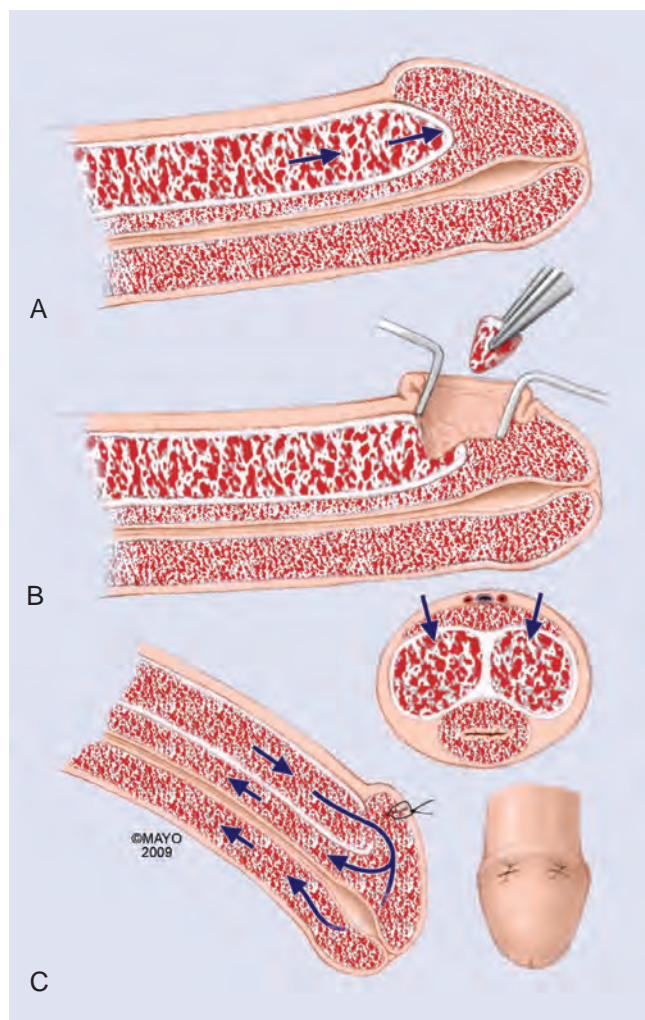


Figure 28-10. An open corporoglanular shunt is indicated if percutaneous shunting fails to reestablish cavernous blood inflow. The Al-Ghorab shunt requires the excision of circular cone segments of the distal tunica albuginea (5 × 5 mm). (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

The key factors determining successful surgical reversal of ischemic priapism are evacuation of thrombus, reestablishing cavernous inflow, and patency of shunt. Theoretically, larger open shunt procedures are likely to result in higher shunt patency rates; there are no data comparing percutaneous and open distal shunts. The surgeon must be guided by familiarity with various techniques: percutaneous shunting, open distal shunting, proximal shunting, and vein shunting. Although distal shunting can be performed with penile block and sedation in the emergency department, open shunting, especially that requiring passage of dilators into the CC, will likely require general anesthesia and an operating room suite. At the completion of the shunt, patency can be verified in the operating room and subsequently the recovery room in a number of ways: bright oxygenated blood should be seen emanating from the corporal bodies; intracavernous pressures should fall; the penis should detumescence and refill with sequential compression and release; and CDU should show resumption of cavernous artery inflow (Lue, 2002; Nixon et al, 2003; Chiou et al, 2009a) (Box 28-3). Complications of shunting include penile edema, hematoma, infection, urethral fistula, penile necrosis, and pulmonary embolism. Distal shunt failures may be the consequence of inadequate size and/or formation of a clot at the site. Distal shunt failure invariably leads to further surgical interventions. Shunts cut through the collagen-rich tunica albuginea; collagen-activated platelets and fibrin form as a reaction to surgical injury and will work to seal off

BOX 28-3 Assessing Corpora Cavernosa Shunt Patency

Visualization of bright red blood in corporal aspirate
Corporal blood gas
Color Doppler ultrasonography
Measurement of intracavernous pressure
Penile compression maneuver (squeeze and release)

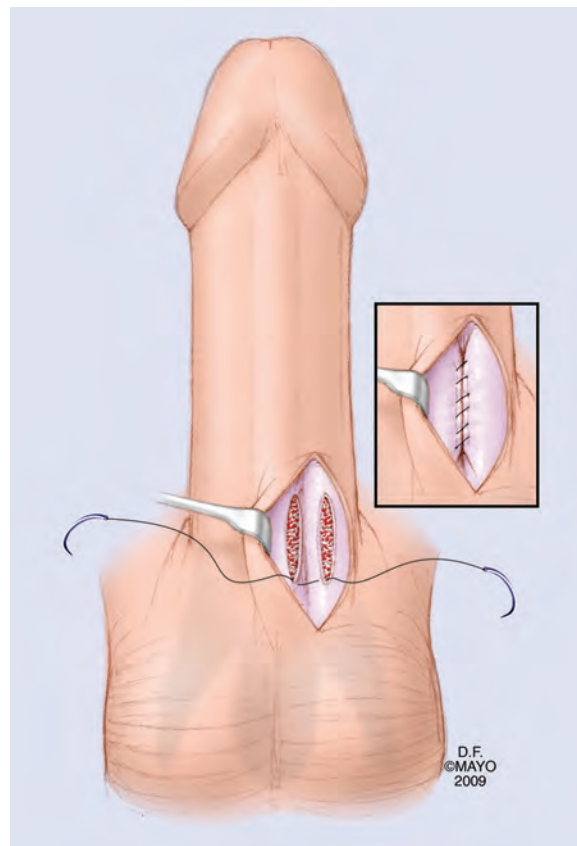


Figure 28-11. The proximal open shunt technique to establish communication between the corpus spongiosum and corpus cavernosum was first described by Quackles in 1964. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

the shunt. Premature thrombosis of the site could lead to shunt failure. Three suggestions have been made to prevent shunt obstruction and subsequent failure: (1) compressive penile dressings should be avoided; (2) the patient should periodically squeeze and release the distal penis to “milk” the shunt maintaining patency; and (3) anticoagulation should be considered with shunting. The literature contains only one such recommendation for perioperative anticoagulation for the prevention of premature shunt obstruction in ischemic priapism. That regimen includes preoperative aspirin 325 mg coupled with subcutaneous heparin 5000 units and postoperative aspirin 81 mg daily for 2 weeks (Lue and Garcia, 2013).

The most commonly described proximal shunt is the unilateral shunt, described by Quackles in 1964 (Fig. 28-11). Proximal corpus cavernosum to spongiosum (CC-CS) shunt procedures require a trans-scrotal or transperineal approach (Quackles, 1964). There are no data comparing bilateral (Sacher et al, 1972) and unilateral CC-CS shunts (Quackles, 1964). Typically, bilateral shunts are staggered; the right side and left side are separated by a distance of at least 1 cm in an effort to minimize the risk of urethral stricture at the point of CC-CS communication (Fig. 28-12). If

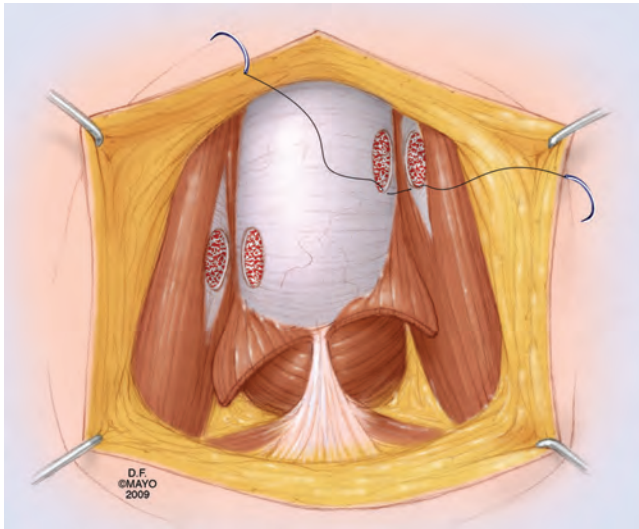


Figure 28-12. Bilateral shunts are staggered. The right and left sides are separated by a distance of at least 1 cm in an effort to minimize the risk of urethral stricture at the point of corpus cavernosum to spongiosum communication (Sacher et al, 1972). (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

proximal shunting fails, some have advocated saphenous vein bypass or deep dorsal vein shunt (Fig. 28-13). A wedge of tunica albuginea is removed and the vein is anastomosed end to side of CC. There are no comparative trials of vein shunting for ischemic priapism. Authors have described a significant risk of saphenofemoral vein thrombus and pulmonary embolism with vein shunting (Kandel et al, 1968).

Immediate Implantation of Penile Prosthesis

Unfortunately, the natural history of untreated ischemic priapism or priapism refractory to interventions is severe fibrosis, penile length loss, and complete ED (see Fig. 28-1). Kelami (1985) described the implantation of the Small-Carrion penile prosthesis through an infrapubic incision in the management of postpriapic ED. Bertram and colleagues (1985) described six postpriapic cases of penile prosthesis; five of the six men had successful implantation of semirigid prostheses. Both groups described extensive corporal fibrosis and suggested that semirigid implants were preferable because inflatable implants would not overcome the corporal fibrosis sufficiently to erect the penis. Douglas and colleagues (1990) reported on penile prosthesis in five SCD postpriapic men; they described a surgical technique of tunneling and corporal excavation. Inadvertent damage to the tunica albuginea was common, as was subsequent migration of hardware; 11 additional procedures were required after the initial implants. The average time from priapism to implant in Douglas's series was 4 years. Monga and

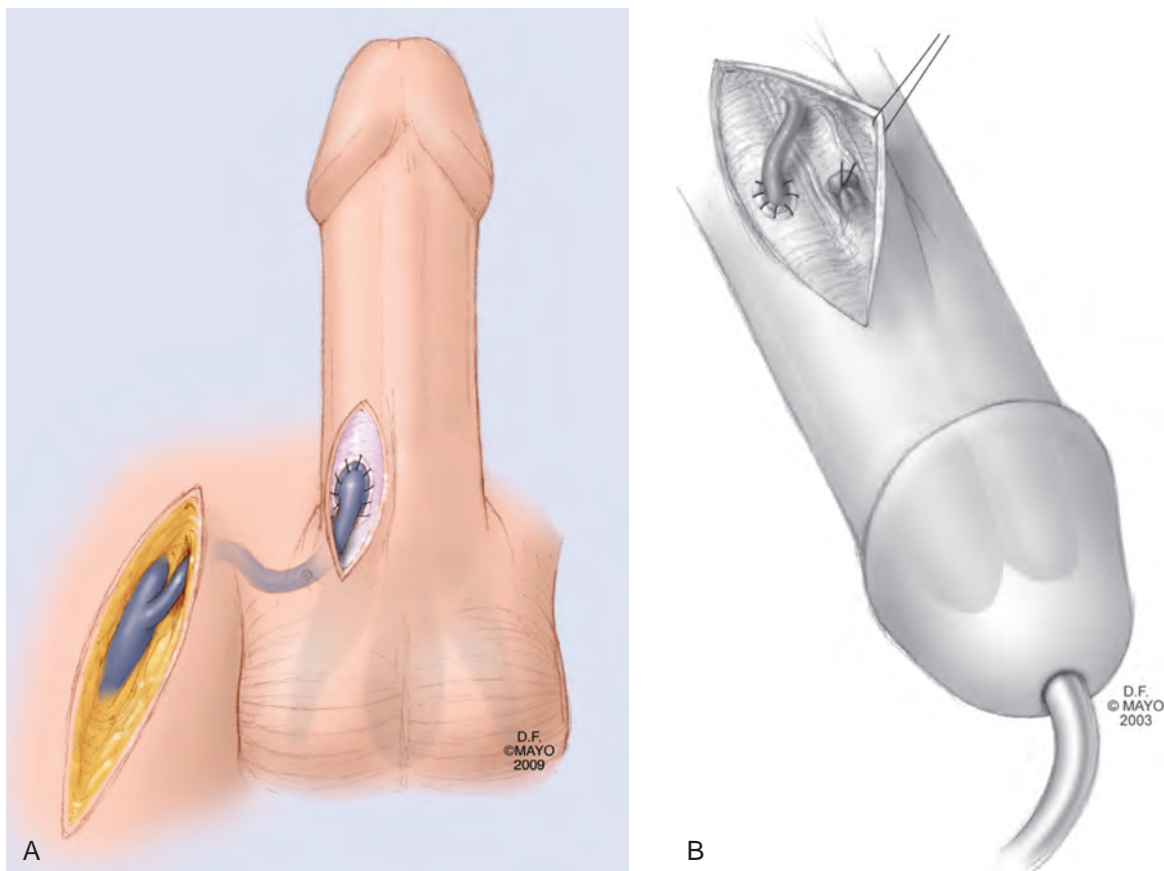


Figure 28-13. A, Venous bypass to control ischemic priapism was first described by Grayhack and colleagues in 1964. The Grayhack shunt mobilizes the saphenous vein below the junction of the femoral vein and anastomoses the vein end to side into the corpus cavernosum. B, Deep dorsal vein (DDV) shunt with distal ligation of DDV and anastomosis of proximal DDV to corpus cavernosum. A wedge of tunica albuginea is removed. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

KEY POINTS: SURGICAL MANAGEMENT OF ISCHEMIC PRIAPISM

- Shunt surgery should be considered for all patients with ischemic priapism in whom aspiration and ICI of α -adrenergics has failed.
- Patients should be counseled that erectile function outcomes decline significantly when ischemic priapism has lasted longer than 24 hours and that complete ED is anticipated if ischemic priapism persists for longer than 36 hours.
- The objective of shunt surgery is reoxygenation of the cavernous smooth muscle.
- The key factors determining successful surgical reversal of ischemic priapism are evacuation of thrombus, patency of shunt, and resumption of cavernous inflow.
- A distal cavernoglanular shunt should be the first choice of shunting procedures.
- Percutaneous distal shunting is less invasive than open distal shunting and may be performed with local anesthetics.
- There are a number of distal shunting procedures, and the surgeon should be familiar with these procedures and their complications.
- Open distal shunting should be considered if percutaneous shunting fails. There are no comparative trials of safety, efficacy, or erectile function outcomes for percutaneous versus open distal shunting techniques.
- If distal shunting fails, then proximal shunting is recommended. Proximal shunting establishes a communication between the CC and corpus spongiosum at the base of the penis. The surgeon must be aware of the unique anatomic relationship between the corpus spongiosum and urethra.
- Shunting may also be accomplished with vein grafting to the CC. Venous shunts have increased the risk of thromboembolism.
- After medical or surgical reversal of ischemic priapism, penile tumescence rather than complete flaccidity may be evident. A phenomenon of conversion from ischemic priapism to HFP has been described. In cases in which the examination findings may be equivocal, CDU or cavernous blood gas is recommended to demonstrate patency of the shunt and restoration of cavernous inflows.
- After shunting, follow up with the patient regarding erectile function and any subsequent ED therapies.

colleagues (1996) described implants in young SCD patients (six patients, average age 26); inflatable implants were placed to both treat ED and circumvent ongoing episodes of stuttering priapism. These researchers suggested that both potency and recurrent episodes of ischemic priapism could be managed by “early” implantation. Some have suggested performing an immediate penile prosthesis procedure in the acute management of ischemic priapism in patients in whom sympathomimetic intracavernous therapies and shunting have failed (Rees et al, 2002). There are two distinct advantages to immediate implantation: corporal fibrosis is not yet established, and penile length may be preserved. The exact time point at which prosthetic insertion becomes a reasonable option for managing ischemic priapism is unclear. Should medical management of ischemic priapism be followed by distal percutaneous shunt, by open distal shunt, and subsequently by proximal shunting before penile implant? Should men with delayed presentation of ischemic priapism and evident corporal thrombus be triaged to an immediate penile implant procedure? What is clear is that any discussion pertaining to early prosthesis insertion should be documented and should include a comprehensive review of the theoretic advantages and actual risks. Compared with prosthesis insertion in a typical patient with ED, there are significantly higher rates of complications noted in priapism cases: infection, urethral injury, device migration, device erosion, and revision surgeries. The surgeon must be familiar with the additional technical concerns posed by weaknesses in the tunica albuginea in the region of prior shunts.

The advantages of early penile implantation in the acute management of ischemic priapism are preservation of penile length and technically easier implant insertion. Delayed placement of penile prosthesis is technically challenging because of corporal fibrosis (see Fig. 28-1B to D). Ralph and colleagues (2009) reported on 50 patients with ischemic priapism. In all patients, conservative management with the instillation of α -adrenergic agents (200 μ g phenylephrine repeated to a maximum dose of 1500 μ g) failed. Unsuccessful shunts were performed in 13 of 50 cases (Ralph et al, 2009). Mean duration of priapism was 209 hours (range 24 to 720 hours). All patients had evidence of cavernous thrombus and smooth muscle necrosis on MRI, and all 50 underwent insertion of penile prosthesis in the acute setting of refractory ischemic priapism. Revision rates were significantly high, at 24% (12 of 50 patients). The infection rate of 6% was also notably high and likely related to multiple factors including ischemic tissues and preceding penile interventions (Fig. 28-14). The same surgical group recently

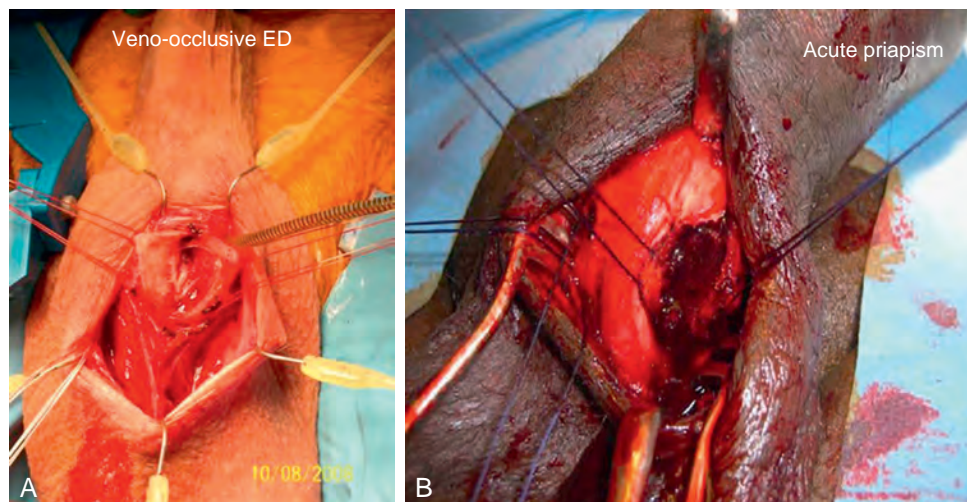


Figure 28-14. A penoscrotal surgical approach for insertion of inflatable penile implant in a white male patient with severe veno-occlusive erectile dysfunction (ED) (A) and a sickle cell disease patient with acute ischemic priapism refractory to pharmacologic interventions and shunting for 48 hours (B). (A, Courtesy G. A. Broderick, MD; B, courtesy David J. Ralph, MD.)

KEY POINTS: SURGICAL MANAGEMENT OF ISCHEMIC PRIAPISM WITH IMMEDIATE PENILE IMPLANT

- The natural history of untreated ischemic priapism or priapism refractory to interventions is severe fibrosis, penile length loss, and complete ED.
- The advantages of early penile implantation in the acute management of ischemic priapism are preservation of penile length and easier insertion.
- Document baseline erectile function, duration of priapism, history of stuttering, and prior interventions.
- Consider penile prosthesis in the following circumstances:
 - Aspiration and sympathomimetic ICI have failed.
 - Distal and proximal shunting procedures have failed.
 - Ischemia has been present for longer than 36 hours.
- Consider an MRI before surgery or corporal biopsy at the time of implant to document corporal smooth muscle necrosis.
- There are higher rates of revision surgery and complications noted in priapism cases resulting from infection, urethral injury, device migration, and device erosion.

compared two cohorts of patients undergoing penile implant for refractory ischemic priapism. An early insertion cohort was operated on at a mean of 7 days after onset of priapism, and the delayed cohort was operated on at a mean of 5 months after priapism. In the early insertion group, satisfaction and ability to have intercourse was 96%; in the delayed group, corporal fibrosis made surgery technically more difficult and overall patient satisfaction was 60% (Zacharakis et al, 2014a).

INTERVENTIONAL ANGIOGRAPHY IN THE MANAGEMENT OF ARTERIAL (NONISCHEMIC, HIGH-FLOW) PRIAPISM

Arterial priapism is not an emergency. Spontaneous resolution or response to conservative therapy has been reported in up to 62% of published series (Montague et al, 2003; Pryor et al, 2004). Persistent partial erection from HFP may be evident for months to years, without adverse impact on erectile function (Bastuba et al, 1995). Kumar and colleagues (2006) described a case of HFP in a 24-year-old patient 10 days after straddle injury on a bicycle. The patient had no erection for the first 4 days after injury. Examination revealed a tumescent penis that was compressible. Penile aspiration and blood gas analysis revealed oxygenated corporal blood. CDU of the cavernous artery revealed arteriosinusoidal fistula. Partial erection spontaneously resolved 4 days after diagnostic evaluation, with the patient reporting normal erections 2 weeks later. The authors hypothesized that in patients with blunt penile and perineal trauma, an arteriolacunar fistula forms; these fistulae, unlike arteriovenous communications, may spontaneously resolve because the less rigid walls of the lacunae are prone to spontaneous thrombosis. Onset of HFP is typically delayed for 72 hours after injury. The erection is partial, not rigid, and not painful. Although the site of perineal trauma may have hematoma, spreading of the hematoma to the shaft should raise suspicion of rupture of tunica albuginea; this would be highly unusual in blunt perineal (straddle) injury. The pathophysiology of HFP is unregulated arteriolacunar fistula from disruption or crush injury to terminal branches of the cavernous artery. Fistula is typically unilateral. Because there is no restriction of venous outflow, erection is partial and bendable. Patients do report additional engorgement with sexual stimulation, with return to partial erection after climax.

There are no comparative outcome studies of intervention versus conservative management in HFP; there are sufficient case descriptions, especially in children, to recommend initial watchful

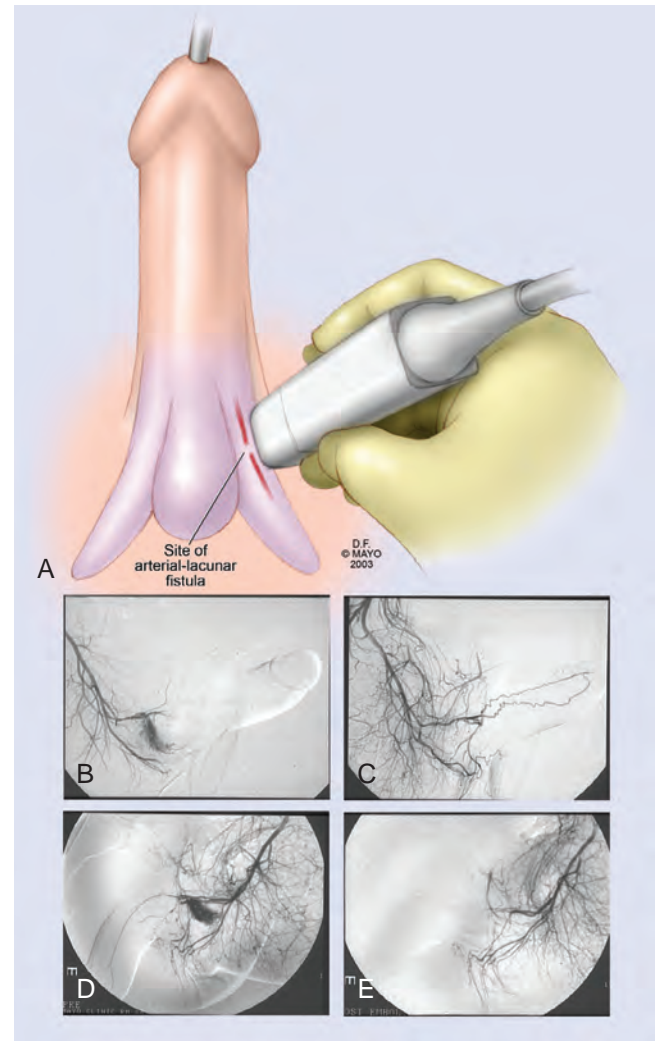


Figure 28-15. Color Doppler ultrasonography of the penis and perineum is recommended in the evaluation of priapism when the history or examination findings suggest penile trauma (A). Doppler sonography for localization of a fistula correlates well with selective pudendal angiography (B to E); a characteristic fistula blush is shown (B and D), along with normal arteriograms (C and E). (A, By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

waiting (Nehra, 2006). Initial observation is recommended for this type of priapism. Conservative measures include ice applied to the perineum and site-specific compression. Cavernous aspiration has only a diagnostic role in HFP. Repeated aspirations, injection, and irrigation with intracavernous sympathomimetics have no role in the treatment of nonischemic priapism.

Patients demanding immediate relief can be offered selective arterial embolization. The pathognomonic arteriographic finding is an arteriolacunar fistula; a characteristic intracavernosal cone-shaped blush of contrast is seen at the site of the cavernous artery or arteriole laceration (Fig. 28-15). Selective internal pudendal catheterization and subsequent embolization have been reported with various agents: microcoils, polyvinyl alcohol, *N*-butylcyanoacrylate, gel-foam, and autologous blood clot (Kuefer et al, 2005). Permanent materials pose a greater theoretic risk of ED; many authors recommend use of autologous blood clot and absorbable gels (Pryor et al, 2004; Kim et al, 2007). Autologous blood clot has a low risk of foreign body reaction, or antigenicity; it is a temporary occlusive agent and should permit recanalization of the cavernous artery (Park et al, 2001). The success rates with selective pudendal

artery catheterization followed by embolization are quite high (89% to 100%), regardless of the embolization material used (Kuefer et al, 2005; Numan et al, 2008). Similar results have been reported by others (Savoca et al, 2004; Alexander Tønseth et al, 2006). Normal postembolization erectile function has been reported in 75% to 86% of patients (Cakan et al, 2006; Numan et al, 2008). It should be noted that a single treatment of embolization carries a recurrence rate of 30% (Ciampalini et al, 2002; Gandini et al, 2004; Ozturk et al, 2009). Although ultimately successful, embolization of HFP may require retreatment. The most notable side effect of bilateral arterial embolization is ED. Recurrence of HFP after embolization may be caused by recanalization of the embolized fistula or unmasking of a fistula in the contralateral cavernous artery. Although it was previously reported that non-permanent embolization materials cause less ED than permanent ones (5% vs. 39%), reports describing use of the IIEF in evaluation of postembolization erectile function note similar rates of ED—15% and 20% (Savoca et al, 2004; Alexander Tønseth et al, 2006). Other reported adverse effects include penile gangrene, gluteal ischemia, purulent cavernositis, and abscess of the perineum (Hakim et al, 1996; Sandock et al, 1996).

Puppo and colleagues (1985) compared perineal duplex ultrasound and selective internal pudendal arteriography, showing excellent sensitivity of ultrasound in detecting arteriolacunar fistulae that were seen angiographically (12 of 12 cases). Several reports have described combined ultrasound-guided compression with selective arterial embolization to increase success rates in the treatment of nonischemic priapism (Hatzichristou et al, 2002; Bartsch et al, 2004; Cakan et al, 2006). If the follow-up clinical examination is equivocal for recurrence of HFP, a perineal duplex Doppler ultrasound can determine the need for repeat arteriography and embolization (Kim et al, 2007).

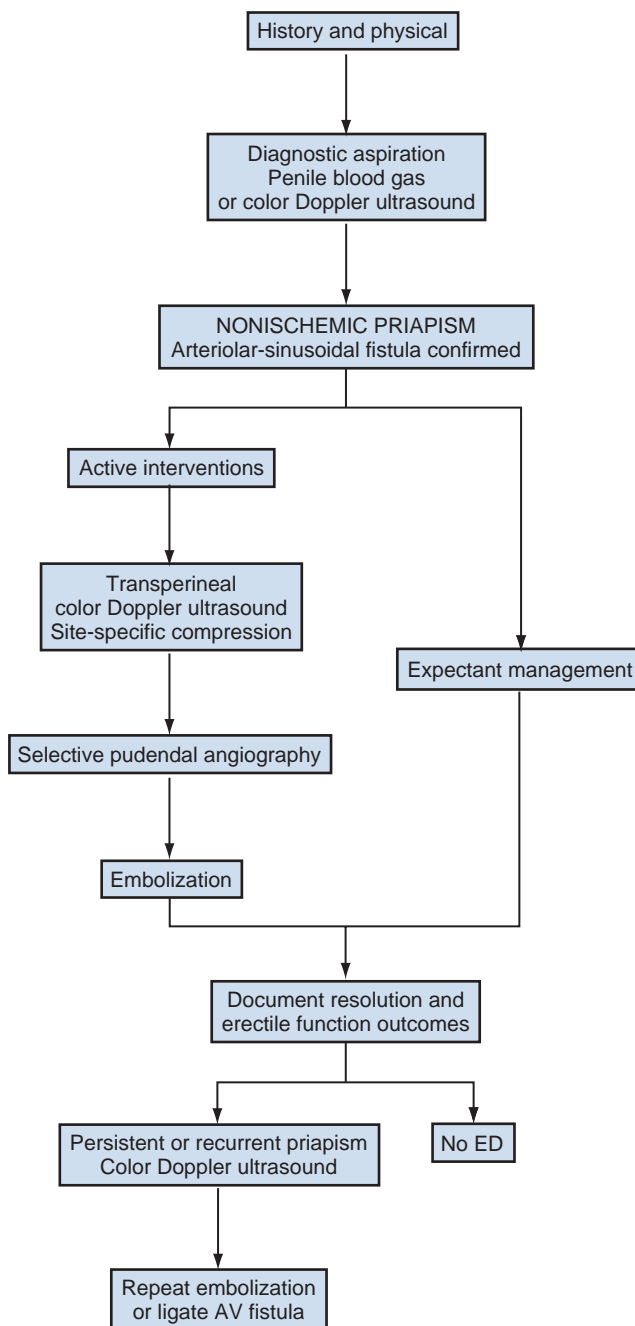
SURGICAL MANAGEMENT OF ARTERIAL (NONISCHEMIC, HIGH-FLOW) PRIAPISM

Arterial priapism is not a urologic emergency. HFP is painless, and there have been reports of partial erection persisting for years (Nehra, 2006). Any intervention must follow a comprehensive discussion with the patient regarding risks and benefits of any of the procedures advocated by the clinician. In cases of long-standing arterial priapism in which a pseudocapsule around the fistula has developed, surgical ligation has been reported to be successful. Formation of a pseudocapsule may take weeks to months after trauma. Corporal exploration before the formation of a pseudocapsule may result in ligation of the cavernous artery

rather than selective ligation of the fistula. Currently this intervention is reserved for patients who do not wish to pursue expectant management or who are poor candidates for angioembolization. It is also reserved for patients who refuse the procedure; for patients in places where technology is not available; and for patients in whom angioembolization has failed (Ji et al, 1994; Berger et al, 2001; Mulhall, 2006). The surgical approach is transcorpal. Intraoperative Doppler ultrasound guidance is recommended (Fig. 28-16).

SUMMARY

Priapism is a full or partial erection that persists more than 4 hours beyond sexual stimulation and orgasm or is unrelated to sexual stimulation. Prompt diagnosis and appropriate management are



KEY POINTS: EVALUATION AND MANAGEMENT OF HIGH-FLOW PRIAPISM

- Arterial priapism is not an emergency and may be managed expectantly.
- Diagnosis of HFP is best made by penile or perineal CDU.
- Penile aspiration and injection of α -adrenergic agents is not recommended for HFP.
- Angioembolization should be preceded by a thorough discussion of chances for spontaneous resolution, risks of treatment-related ED, and lack of significant consequences expected from delaying interventions.
- Overall success rates with embolization are high, although a single treatment carries a recurrence rate of 30% to 40%.
- When angioembolization fails or is contraindicated, surgical ligation is reasonable.
- Formation of a pseudocapsule at the site of a sinusoidal fistula may take weeks to months after trauma.
- CDU guidance is recommended during exploration to locate fistulae.

Figure 28-16. Algorithm for managing high-flow priapism. AV, arteriovenous; ED, erectile dysfunction.

necessary to spare patients ineffective interventions and optimize erectile function outcomes. Ischemic priapism (veno-occlusive, low-flow) is a persistent erection marked by rigidity of the CC. In ischemic priapism there are time-dependent changes in the corpora with progressive hypoxia, hypercarbia, and acidosis. Ischemic priapism is a urologic emergency. Treatment for ischemic priapism is administered in stepwise manner: decompression of the corpora by needle aspiration, injection and irrigation with a dilute sympathomimetic drug, surgical shunting, and consideration of immediate penile implant in refractory cases. Ischemic priapism is a common pathologic consequence of SCD. Stuttering ischemic priapism describes a pattern of prolonged morning erections that are unwanted and painful in boys and adolescents with SCD. Any patient who has experienced an episode of ischemic priapism is also at risk for stuttering priapism. HFP (nonischemic priapism, arterial priapism) is a persistent erection caused by unregulated cavernous arterial inflow. Typically, the corpora are tumescent but not rigid and the penis is not painful. A history of blunt trauma (a straddle injury) or an iatrogenic needle injury to the penis is common. The cavernous environment in HFP does not become ischemic, and cavernous blood gases do not show hypoxia, hypercarbia, or acidosis. HFP, once properly diagnosed, does not require emergent treatment. Urologists intervening to treat priapism should use standardized questionnaires to document the history of the prolonged erection: onset, trauma, medical history of blood dyscrasias, use of illicit substances, prior events, prepriapism erectile function, recurrence after each intervention, and recovery of erectile function. Documenting erectile function outcomes on the basis of duration of ischemic priapism, time to interventions, and types of interventions will establish evidence-based guidance on how and when to apply those interventions.

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Anatomy and Physiology of the Ejaculatory Response

Premature Ejaculation

Delayed Ejaculation, Anejaculation, and Anorgasmia

Retrograde Ejaculation

Painful Ejaculation

Postorgasmic Illness Syndrome

Conclusion

Ejaculatory dysfunction is one of the most common male sexual disorders. The spectrum of ejaculatory dysfunction extends from premature ejaculation (PE), through delayed ejaculation, to a complete inability to ejaculate (known as anejaculation) and includes retrograde ejaculation, painful ejaculation, and the recently described postorgasmic illness syndrome (POIS).

The sexual response cycle comprises the four interactive stages of desire, arousal, orgasm, and resolution. During sexual activity, increasing levels of sexual arousal reach a threshold that triggers the ejaculatory response, which then typically terminates the sexual episode for the male. The perception of the striated muscle contractions and resulting semen expelled during ejaculation, mediated through sensory neurons in the pelvic region, gives rise to the experience of orgasm, a distinct cortical event, experienced phenomenologically both cognitively and emotionally.

Ejaculatory latency, the time extending from the onset of penile stimulation to the moment of ejaculation, represents a continuum of time that shows variation across men and, within men, across situations. Although the great majority of men appear to reach ejaculation and orgasm after several minutes of penile vaginal stimulation and are, along with their partners, quite satisfied with the latency of their ejaculatory response, others report dissatisfaction. Specifically, some men ejaculate very rapidly after, or sometimes even before, penetration and do so with minimal stimulation. Others may ejaculate only with great difficulty or not at all, even after prolonged stimulation.

ANATOMY AND PHYSIOLOGY OF THE EJACULATORY RESPONSE

The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centers, spinal motor centers, and efferent pathways (Fig. 29-1). Neurochemically, this reflex involves a complex interplay between central serotonergic and dopaminergic neurons, with secondary involvement of cholinergic, adrenergic, oxytocinergic, and γ -aminobutyric acid (GABA) neurons.

Based on functional, central, and peripheral mediation, the ejaculatory process is typically subdivided into three phases: emission, ejection (or penile expulsion), and orgasm. Emission consists of contractions of seminal vesicles and the prostate, with expulsion of sperm and seminal fluid into the posterior urethra, and is mediated by sympathetic nerves (T10 to L2). Ejection is mediated by somatic nerves (S2 to S4), and involves pulsatile contractions of the bulbocavernosus and pelvic floor muscles together with relaxation of the external urinary sphincter. Ejection also involves a

sympathetic spinal cord reflex, on which there is limited voluntary control. The bladder neck closes to prevent retrograde flow; the bulbocavernosus, bulbospongiosus, and other pelvic floor muscles contract rhythmically, and the external urinary sphincter relaxes. Intermittent contraction of the urethral sphincter prevents retrograde flow into the proximal urethra (Yeates, 1987). Orgasm is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from the verumontanum, and contraction of the urethral bulb and accessory sexual organs.

Many neurotransmitters are involved in the control of ejaculation, including dopamine, norepinephrine, serotonin, acetylcholine, oxytocin, GABA, and nitric oxide (McMahon et al, 2004a). Of the many studies conducted to investigate the role of the brain in the development and mediation of sexual functioning, dopamine and serotonin have emerged as essential neurochemical factors. Whereas dopamine promotes seminal emission/ejaculation via D_2 receptors, serotonin is inhibitory. Serotonergic neurons are widely distributed in the brain and spinal cord and are predominantly found in the brainstem, raphe nuclei, and the reticular formation. Currently, multiple serotonin (5-HT) receptors have been characterized: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, etc. (Peroutka and Snyder, 1979). Stimulation of the 5-HT_{2C} receptor with 5-HT_{2C} agonists results in delay of ejaculation in male rats, whereas stimulation of postsynaptic 5-HT_{1A} receptors results in shortening of ejaculation latency (Ahlenius et al, 1981), leading to the hypothesis that men with PE may have hyposensitivity of 5-HT_{2C} and/or hypersensitivity of the 5-HT_{1A} receptor (Waldinger, 2002; Waldinger and Oliver, 2005).

PREMATURE EJACULATION

Classification of Premature Ejaculation

In 1943 Schapiro proposed classification of PE into two types, B and A (Schapiro, 1943). In 1989 Godpodinoff renamed both types as lifelong (primary) and acquired (secondary) PE (Godpodinoff, 1989). Over the years, other attempts to specify subtypes have occurred (e.g., global vs. situational, the effect of a substance, etc.).

Lifelong PE is a syndrome characterized by a cluster of core symptoms, including early ejaculation at nearly every intercourse within 30 to 60 seconds in the majority of cases (80%) or between 1 to 2 minutes (20%), with every or nearly every sexual partner and from the first sexual encounters onward (Waldinger, 1998; McMahon, 2002).

Acquired PE differs in that men develop early ejaculation at some point in their life, which is often situational, having previously had normal ejaculation experiences. The main distinguishing features between presentations of these two syndromes are the

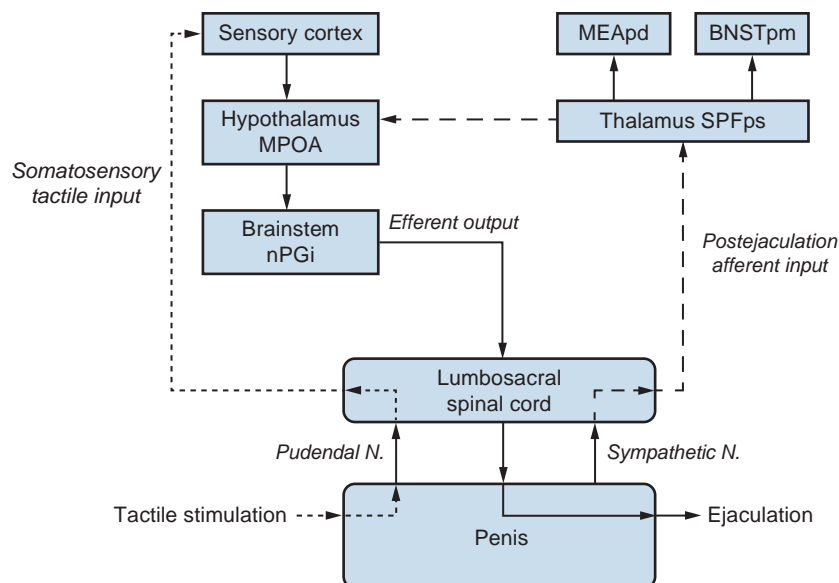


Figure 29-1. Central nervous system areas involved before, during, and after ejaculation. Somatosensory tactile input from the penis/genitals ascends to the cerebral cortex. Efferent pathways project from the hypothalamus to the sacral spinal cord and genitals. After ejaculation, information is returned from the genitals to several brain areas. BNSTpm, posteromedial bed nucleus of stria terminalis; MEApd, posterodorsal medial amygdala; MPOA, medial preoptic area; N, nerve; nPGi, nucleus paragigantocellularis; SPFPs, medial parvocellular subparafascicular nucleus of thalamus. (From Waldinger MD. The neurobiological approach to premature ejaculation. *J Urol* 2002;168:2359–67.)

time of onset of symptoms and the reduction in previously normal ejaculatory latency of acquired PE.

Community-based normative intravaginal ejaculation latency time (IELT) research and observational studies of men with PE demonstrated that although IELTs of less than 1 minute have a low prevalence of approximately 2.5% in the general population, a substantially higher percentage of men with normal IELT report PE (Patrick et al, 2005; Waldinger et al, 2005a, 2009). To take account of this diversity, Waldinger and Schweitzer (2006b, 2008) proposed a new classification of PE in which four PE subtypes are distinguished on the basis of the duration of the IELT, frequency of reports, and course in life. In addition to lifelong PE and acquired PE, this classification includes natural variable PE (or variable PE) and premature-like ejaculatory dysfunction (or subjective PE). Men with variable PE occasionally experience an early ejaculation. It should not be regarded as a disorder, but as a natural variation of the ejaculation time in men (Waldinger, 2013). On the other hand, men with subjective PE report PE while actually having a normal or even extended ejaculation time (Waldinger, 2013). The report of PE in these men is probably related to psychological and/or cultural factors. In contrast, the consistent early ejaculations of lifelong PE suggest an underlying neurobiologic functional disturbance, whereas the early ejaculation of acquired PE is more related to underlying medical causes. Serefoglu and colleagues (2010, 2011) confirmed the existence of these four PE subtypes in a cohort of men in Turkey. Recently, Zhang and associates (2013) and Gao and colleagues (2013) using a similar methodology confirmed similar prevalence rates of the four PE subtypes in China to that reported by Serefoglu and associates (2010, 2011). This new classification and continued research into the diverse phenomenology, cause, and pathogenesis of PE are expected to provide a better understanding of the four PE subtypes (Waldinger and Schweitzer, 2008). Although the pathogenesis of lifelong and acquired PE differs, the presence of shared dimensions, such as a lack of ejaculatory control and the presence of negative personal consequences, suggests a potential for a single unifying definition of both lifelong and acquired PE. With

continued research into the two other PE subtypes, variable PE and subjective PE, it may be appropriate to expand this unifying definition in the future.

Definition of Premature Ejaculation

Research into the treatment and epidemiology of PE depends heavily on how PE is defined. The medical literature contains several univariate and multivariate operational definitions of PE (Masters and Johnson, 1970; American Psychiatric Association, 1994; World Health Organization, 1994; Metz and McCarthy, 2003; Colpi et al, 2004; McMahon et al, 2004b; Montague et al, 2004; Jannini et al, 2005; Waldinger et al, 2005b; McMahon et al, 2008b) (Table 29-1). Each of these definitions characterizes men with PE using all or most of the accepted dimensions of this condition: ejaculatory latency, perceived ability to control ejaculation, reduced sexual satisfaction, personal distress, partner distress, and interpersonal or relationship distress. **None of these definitions was supported by evidence-based clinical research.**

These authority-based definitions are discussed in detail on the Expert Consult website.

International Society for Sexual Medicine Definition of Premature Ejaculation

In the last decade, substantial progress has been made in the development of evidence-based methodology for PE epidemiologic and drug treatment research using the objective IELT and subjective validated patient-reported outcome (PRO) measures. In October 2007, the International Society for Sexual Medicine (ISSM) convened an initial meeting of the first Ad Hoc ISSM Committee for the Definition of Premature Ejaculation to develop the first contemporary, evidence-based definition of lifelong PE. Evidence-based definitions seek to limit errors of classification and thereby increase the likelihood that existing and newly developed therapeutic strategies are truly effective in carefully selected dysfunctional

Traditional Definitions of Premature Ejaculation

During the period of 1920 to 1960, the absence of any scientific publications proposing a definition of PE reflects the scarcity of prevalence data. Based on the limited published literature, a man was considered to have PE when he ejaculated within seconds or within approximately a minute of vaginal penetration (Waldinger, 2006). In the 1970s, despite an absence of empirical data, Masters and Johnson (1970) rejected this ejaculation latency proposal and defined PE as a man's inability to satisfy his female partner on more than 50% of sexual events. Their rejection of the ejaculation time criterion has led to debate on "objective criteria" and "subjective criteria" of PE (Waldinger and Schweitzer, 2008). Typical "objective" criteria include the ejaculation latency time and the number of penile thrusts. "Subjective" criteria are measures of self-efficacy, including "diminished feelings of control" and "ejaculation at moments without wishing it."

These opposing constructs have served as the framework for the development of the various definitions proposed in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) by the American Psychiatric Association (Waldinger and Schweitzer, 2006a, 2006b).

The first official definition of PE was established in 1980 by the American Psychiatric Association in the DSM-III. PE was defined as "Ejaculation that occurs before the individual wishes it, because of recurrent and persistent absence of reasonable voluntary control of ejaculation and orgasm during sexual activity" (American Psychiatric Association 1980). However, because of disagreement on the criterion of "reasonable voluntary control," this criterion was removed in the subsequent DSM-III-R and DSM-IV definitions (American Psychiatric Association, 1987, 2000) and replaced by the criterion of a "short ejaculation time." The DSM-IV-TR defined PE as a "Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect the duration of the excitement phase such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity" and requires for the diagnosis that "the disturbance causes marked distress or interpersonal difficulty" (American Psychiatric Association, 2000). Thus DSM-III contains the criterion of control but not time, whereas subsequent DSM-III-R, DSM-IV, and DSM-IV-TR definitions contained the criterion of time but not control (Waldinger and Schweitzer, 2006a, 2006b).

The DSM III/IV definitions of PE were largely accepted with little discussion, despite having no evidence-based medical support (St. Lawrence and Madakasira, 1992). After the introduction of evidence-based PE pharmacotherapy, the validity of the DSM definitions was the subject of debate with a substantial polarization of opinion. The inclusion of words such as *persistent*, *recurrent*, *minimal*, and *shortly after* rendered the DSM definitions vague, multi-interpretable, and lacking quantification (O'Donohue et al, 1993; Waldinger, 2002; Althof and Symonds, 2007). Concerns about the validity and application of the DSM-IV-TR definition were also expressed by regulatory agencies such as the U.S. Food and

Drug Administration, which regarded the lack of evidence-based criteria as a potential obstacle to interpret and assess data from clinical trials of PE investigational drugs.

The World Health Organization 1992 ICD-10 defines PE as "The inability to control ejaculation sufficiently for both partners to enjoy sexual interaction" and as "an inability to delay ejaculation sufficiently to enjoy lovemaking, and manifest as either of the following: (1) occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) and (2) ejaculation occurs in the absence of sufficient erection to make intercourse possible" (World Health Organization, 1994). The ICD-10 uses both the criterion of "control" and a "very short" ejaculation time, and quantifies the ejaculation time to maximally 15 seconds after penetration. Although the ICD-10 provides an objective definition of PE, evidence to support a latency cutoff of 15 seconds was not provided (Waldinger and Schweitzer, 2006a, 2006b). Furthermore, the ICD-10 use of the criterion of ejaculation that occurs within 15 seconds restricts the application of the criterion of control (Waldinger and Schweitzer, 2006a, 2006b).

The lack of consensus as to what constitutes PE hampered clinical practice and basic and clinical research into the cause and management of this condition. The results of PE epidemiologic and drug treatment clinical trials are reliable, interpretable, and capable of being generalized to patients only when consistent objective physiologic measures or sensitive, validated outcome assessment instruments are used as study end points (McMahon, 2008a) in well-defined and consistent populations in whom lifelong PE, acquired PE, or PE with comorbid erectile dysfunction (ED) are treated as separate PE subgroups.

The absence of a specific ejaculation time cutoff point to operationalize "shortly after penetration or before the person wishes" led to the incorrect application of the DSM definitions in epidemiologic and clinical research (Waldinger et al, 1998; Patrick et al, 2005; Giuliano et al, 2008; McMahon, 2008b). Giuliano and colleagues (2008) reported the IELT of men with DSM-IV-TR–diagnosed PE ranged from 0 seconds (antiportal ejaculation) to almost 28 minutes, with 44% of subjects having an IELT of 2 minutes or longer and 25% of 4 minutes or longer. This study demonstrates that a subject with DSM-IV-TR–diagnosed PE has a 44% risk for not having PE if a PE diagnostic threshold IELT of 2 minutes, as suggested by community-based normative IELT trial, is used (Waldinger et al, 2005a).

Waldinger and associates (1998), in a number of studies in cohorts of heterosexual men with lifelong PE with prospective stopwatch IELT measurement, showed that approximately 90% of men seeking treatment for lifelong PE ejaculated within 1 minute after penetration and approximately 10% ejaculated between 1 and 2 minutes. These data were confirmed by McMahon (2002) in a retrospective questionnaire analysis of a large cohort of men with lifelong PE. These data support the proposal that lifelong PE is characterized by an IELT of less than or approximately 1 minute after vaginal penetration.

TABLE 29-1 Definitions of Premature Ejaculation (PE)

DEFINITION	SOURCE
PE is a male sexual dysfunction characterized by ejaculation that always or nearly always occurs before or within 1 min of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to $\sim \leq 3$ min (acquired PE), the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.	International Society of Sexual Medicine, 2014
Lifelong PE is a male sexual dysfunction characterized by ejaculation that always or nearly always occurs before or within 1 min of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.	McMahon et al (ISSM), 2008b
A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within ~ 1 min after vaginal penetration and before the individual wishes it. This symptom must have been present for at least 6 mo and must be experienced on almost all or all ($\sim 75\%$ -100%) occasions of sexual activity. It causes clinically significant distress in the individual.	American Psychiatric Association (DSM-5), 2013
Persistent or recurrent ejaculation with minimal sexual stimulation, before, on, or shortly after penetration and before the person wishes it. The condition also must cause marked distress or interpersonal difficulty and cannot be due exclusively to the direct effects of a substance.	American Psychiatric Association (DSM-IV-TR), 2000
For individuals who meet the general criteria for sexual dysfunction, the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction, manifest as either the occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required, before or within 15 secs) or the occurrence of ejaculation in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity.	World Health Organization (ICD-10), 1994
The inability to control ejaculation for a “sufficient” length of time before vaginal penetration. It does not involve any impairment of fertility, when intravaginal ejaculation occurs.	Hatzimouratidis et al (EAU Guidelines on Disorders of Ejaculation), 2010
Persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration and before the person wishes it, over which the man has little or no voluntary control, which causes the man and/or his partner bother or distress.	McMahon et al (ICUD), 2004b
Ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to one or both partners.	Montague et al (AUA Guideline on the Pharmacologic Management of PE), 2004
The man does not have voluntary, conscious control or the ability to choose in most encounters when to ejaculate.	Metz and McCarthy, 2003
The Foundation considers a man a premature ejaculator if he cannot control his ejaculatory process for a sufficient length of time during intravaginal containment to satisfy his partner in at least 50% of their coital connections.	Masters and Johnson, 1970
Men with an IELT < 1 min (belonging to the 0.5th percentile) have “definite” PE, and men with IELTs between 1 and 1.5 min (0.5th to 2.5th percentile) have “probable” PE (see Fig. 29-2). In addition, a grading of severity of PE should be defined in terms of associated psychological problems. Thus both definite and probable PE need further psychological subclassification in asymptomatic, mild, moderate, and severe PE.	Waldinger et al, 2005c
PE is diagnosed on the basis of the pathologic IELT, as measured by the stopwatch method, with a feeling of loss of voluntary control and/or distress or relational disturbances, as measured by PRO.	Jannini et al, 2005

AUA, American Urological Association; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders* (4th edition, Text Revision); DSM-5, *Diagnostic and Statistical Manual of Mental Disorders* (5th edition); EAU, European Association of Urology; ICUD, International Consultation on Urological Diseases; IELT, intravaginal ejaculation latency time; ISSM, International Society of Sexual Medicine; PRO, patient-reported outcome.

populations (Metz and McCarthy, 2003). After critical evaluation of the published data, the committee unanimously agreed that the constructs that are necessary to define lifelong PE are time from penetration to ejaculation, inability to delay ejaculation, and negative personal consequences from PE, and they recommended the following definition (McMahon et al, 2008a):

Lifelong PE is a male sexual dysfunction characterized by the presence of all of these criteria: 1) ejaculation that always or

nearly always occurs prior to or within about 1 minute of vaginal penetration; 2) the inability to delay ejaculation on all or nearly all vaginal penetrations; and 3) negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

However, the committee was unable to identify sufficient published objective data to craft an evidence-based definition of acquired PE. The committee anticipated that future studies would


generate sufficient data to develop an evidence-based definition for acquired PE.

In April 2013 the ISSM convened a second Ad Hoc ISSM Committee for the Definition of Premature Ejaculation in Bangalore, India. The brief of the committee was to evaluate the current published data and attempt to develop a contemporary, evidence-based definition of acquired PE and/or a single unifying definition of both acquired and lifelong PE. Members unanimously agreed that although lifelong and acquired PE are distinct and different demographic and etiologic populations, they can be jointly defined, in part, by the constructs of time from penetration to ejaculation, inability to delay ejaculation, and negative personal consequences from PE. The committee agreed that the presence of these mutual constructs was sufficient justification for the development of a single unifying definition of both lifelong and acquired PE. Finally, the committee determined that the presence of a clinically significant and bothersome reduction in latency time, often to approximately 3 minutes or less, was an additional key defining dimension of acquired PE.

The second Ad Hoc ISSM Committee for the Definition of Premature Ejaculation (2013) defined PE (lifelong and acquired PE) as a male sexual dysfunction characterized by the following:

- Ejaculation that always or nearly always occurs before or within approximately 1 minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to approximately 3 minutes or less (acquired PE)
- The inability to delay ejaculation on all or nearly all vaginal penetrations
- Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy

The unified ISSM definition of lifelong and acquired PE represents the first evidence-based definition for these conditions. This definition should form the basis for the office diagnosis of lifelong PE and the design of PE observational and interventional clinical trials. It is limited to men engaging in vaginal intercourse because few studies are available on PE research in homosexual men or during other forms of sexual expression. This definition intentionally includes a degree of diagnostic conservatism and flexibility. The 1-minute IELT cutoff point for lifelong PE should not be applied in the most absolute sense, because approximately 10% of men seeking treatment for lifelong PE have IELTs of 1 to 2 minutes. The phrase “within approximately 1 minute” must be interpreted as giving the clinician sufficient flexibility to diagnose PE also in men who report an IELT as long as 90 seconds. Similarly, a degree of flexible clinical judgment is key to recognition and interpretation of a bothersome change in ejaculatory latency with reduction of premorbid latency to 3 minutes or less in men with acquired PE. Men who report these ejaculatory latencies but describe adequate control and no personal negative consequences related to their rapid ejaculation do not merit the diagnosis of PE.

 The rationale for the ISSM definition of lifelong and acquired PE is fully explored on the Expert Consult website.

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Definition of Premature Ejaculation

Based on the same data that supported the ISSM definition of lifelong PE, the recently published DSM-5 definition of PE (American Psychiatric Association, 2013) now includes an objective ejaculatory latency criterion. DSM-5 defines PE as follows:

A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it. This symptom must have been present for at least 6 months and must be experienced on almost all or all (approximately 75%-100%) occasions of sexual activity. It causes clinically significant distress in the individual.

The DSM-5 definition of PE requires clinicians to specify PE as either lifelong or acquired and as generalized or situational. In addition, the DSM-5 definition of PE distinguishes between mild PE (ejaculation occurring within ~30 seconds to 1 minute of vaginal penetration), moderate PE (ejaculation occurring within ~15 to 30 seconds of vaginal penetration), and severe PE (ejaculation occurring before sexual activity, at the start of sexual activity, or within ~15 seconds of vaginal penetration).

Prevalence of Premature Ejaculation

Reliable information on the prevalence of lifelong and acquired PE in the general male population is lacking. PE has been estimated to occur in 4% to 39% of men in the general community (Reading and Wiest, 1984; Nathan, 1986; Spector and Boyle, 1986; Spector and Carey, 1990; Grenier and Byers, 1997; Laumann et al, 1999; Porst et al, 2007) and is often identified as the most common self-reported male sexual disorder (Jannini and Lenzi, 2005). However, a substantial disparity exists between the incidence of PE in epidemiologic studies that rely on patient self-report of PE and/or inconsistent and poorly validated definitions of PE (Laumann et al, 1999; Patrick et al, 2005; Giuliano et al, 2008) and, as suggested by community-based stopwatch studies of the IELT, the interval between penetration and ejaculation (Waldinger et al, 2005a). The latter demonstrates that the distribution of the IELT is positively skewed, with a median of 5.4 minutes (range, 0.55 to 44.1 minutes), decreases with age, varies across countries, and supports the notion that IELTs of less than 1 minute are statistically abnormal compared to those in men in the general Western population (Fig. 29-2) (Waldinger et al, 2005a).

Prevalence data derived from patient self-report will be appreciably higher than prevalence estimates based on clinician diagnosis using the more conservative ISSM definition of PE. The following studies demonstrate the varying prevalence estimates ranging from 30% down to 3%. Data from The Global Study of Sexual Attitudes and Behaviors (GSSAB), an international survey investigating the attitudes, behaviors, beliefs, and sexual satisfaction of 27,500 men and women 40 to 80 years of age, reported the global prevalence of PE (based on subject self-report) to be approximately 30% across all age groups (Nicolosi et al, 2004; Laumann et al, 2005). Perception of “normal” ejaculatory latency varied by country and differed when assessed by either the patient or the partner (Montorsi, 2005). A core limitation of the GSSAB survey stems from the fact that the youngest participants were 40 years of age, an age when the incidence of PE might be different from that of younger males (Jannini and Lenzi, 2005). Contrary to the GSSAB study, the Premature Ejaculation Prevalence and Attitude Survey found the prevalence of PE among men 18 to 70 years of age to be 22.7% (Porst et al, 2007). The real prevalence of PE is difficult to assess in clinical practice (Jannini and Lenzi, 2005).

Basile Fasalo and associates (2005) reported that 2658 of 12,558 men (21.2%) attending a free andrologic consultation self-diagnosed PE, the majority describing acquired PE (14.8%) and 4.5% describing lifelong PE. In contrast, Serefoglu and colleagues (2010) reported that the majority of PE treatment-seeking patients described lifelong PE (62.5%) compared to acquired PE (16.1%). Similar findings were reported by Zhang and coworkers (2013) who found that the majority of 1988 Chinese outpatients described lifelong PE (35.6%) or acquired PE (28.07%). These data provide evidence that patients with lifelong and acquired PE comprise the majority of the patients who seek treatment for PE. In addition, a disparity appears to exist between the incidence of the various PE subtypes in the general community and in men actively seeking treatment for PE.

Consistent with this notion, Serefoglu and colleagues (2011) subsequently reported an overall PE prevalence of 19.8% comprising lifelong PE (2.3%), acquired PE (3.9%), variable PE (8.5%), and subjective PE (5.1%). Using similar research methodology, Gao and associates (2013) reported that 25.80% of 3016 Chinese men reported PE, with similar prevalence of lifelong (3.18%), acquired (4.84%), variable PE (11.38%), and subjective

Rationale for ISSM Definition of Lifelong and Acquired Premature Ejaculation. The multivariate ISSM evidence-based definition of PE captures the key PE constructs of ejaculatory latency, perceived (ejaculatory control), and presence of negative personal consequences from PE (McMahon et al, 2008b). Although men with lifelong and acquired PE appear to share the dimensions of short ejaculatory latency, reduced or absent perceived ejaculatory control, and the presence of negative personal consequences from PE, they remain distinct and different demographic and etiologic populations (Porst and McMahon, 2010).

Rationale for Inclusion of “ejaculation always or nearly always occurs before or within approximately 1 minute of vaginal penetration IELT less than approximately 1 minute (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to approximately 3 minutes or less (acquired PE).” Operationalization of PE using the length of time between penetration and ejaculation, the IELT, forms the basis of most current clinical studies on PE (Waldinger et al, 1994). IELT can be measured by a stopwatch or estimated. Several authors report that estimated and stopwatch IELT correlate reasonably well or are interchangeable in assigning PE status when estimated IELT is combined with PROs (Althof et al, 1995; Pryor, 2005; Rosen et al, 2007).

Several studies suggest that 80% to 90% of men seeking treatment for lifelong PE ejaculate within 1 minute (Waldinger et al, 1998, 2007; McMahon, 2002). Waldinger and colleagues (1998) reported IELTs of less than 30 seconds in 77% and less than 60 seconds in 90% of 110 men with lifelong PE, with only 10% ejaculating between 1 and 2 minutes. These data are consistent with normative community IELT data, support the notion that IELTs of less than 1 minute are statistically abnormal, and confirm that an IELT cutoff of 1 minute will capture 80% to 90% of treatment-seeking men with lifelong PE (Waldinger et al, 2005a). Further qualification of this cutoff to “approximately 1 minute” affords the clinician sufficient flexibility to also diagnose PE in the 10% to 20% of PE treatment-seeking men who ejaculate within 1 to 2 minutes of penetration without unnecessarily stigmatizing the remaining 80% to 90% of men who ejaculate within 1 to 2 minutes of penetration but have no reports of PE.

Porst and associates (2010) reported that both the arithmetic (1.1 vs. 0.9 min, $P < 0.001$) and geometric mean IELT (0.9 vs. 0.7 min, $P < .001$) were slightly (but significantly) greater for patients with acquired PE. Several authors confirmed this preliminary finding by demonstrating that self-estimated IELT is higher in men with acquired PE than in those with lifelong PE.

However, a post hoc analysis of the dapoxetine phase 3 COUPLE trial data confirms a statistically significant higher IELT in men with acquired PE and comorbidity compared to men with lifelong PE with comorbid ED (52.2 years vs. 45.5 years) (McMahon et al, 2013). Serefoglu and coworkers (2010) reported that self-estimated IELT was lowest in men with lifelong PE and highest in men with subjective PE (lifelong PE: 20.47 ± 28.90 seconds (2 to 120 seconds); acquired PE: 57.91 ± 38.72 seconds (90 to 180 seconds); variable PE: 144.17 ± 22.47 seconds (120 to 180 seconds); subjective PE: 286.67 ± 69.96 seconds (180 to 420 seconds, $P = .001$). Gao and associates (2013) and Zhang and colleagues (2013) confirmed that self-estimated IELT follows a continuum among the four PE syndromes and reported a mean self-estimated IELT of 1.65 ± 0.82 minutes and 1.84 ± 1.02 minutes, respectively, in patients with acquired PE. These data suggest 3 minutes as a valid cutoff for either self-estimated or stopwatch IELT for the diagnosis of acquired PE.

Rationale for Inclusion of “the inability to delay ejaculation on all or nearly all vaginal penetrations.” The ability to prolong sexual intercourse by delaying ejaculation and the subjective feelings of ejaculatory control make up the complex construct of ejaculatory control. Virtually all men report using at least one cognitive or behavioral technique to prolong intercourse and delay ejaculation, with varying degrees of success, and many young men reported using multiple different techniques (Grenier and Byers, 1997). Voluntary delay of ejaculation is most likely exerted either before or in the early stages of the emission phase of the reflex but

progressively decreases until the point of ejaculatory inevitability (McMahon et al, 2006b; Perelman, 2006).

Several authors suggest that an inability to voluntarily defer ejaculation defines PE (Kaplan et al, 1974; Zilbergeld, 1978; Vandereycken, 1986; McCarthy, 1988). Patrick and associates (2005) reported ratings of “very poor” or “poor” for control over ejaculation in 72% of men with PE, compared to 5% in a group of normal controls. Lower ratings for control over ejaculation were associated with shorter IELT with “poor” or “very poor” control reported by 67.7%, 10.2%, and 6.7% of subjects with IELT less than 1 minute, longer than 1 minute, and longer than 2 minutes, respectively. However, Grenier and Byers (1997, 2001) failed to demonstrate a strong correlation between ejaculatory latency and subjective ejaculatory control. Several authors report that diminished control is not exclusive to men with PE and that some men with a brief IELT report adequate ejaculatory control and vice versa, suggesting that the dimensions of ejaculatory control and latency are distinct concepts (Grenier and Byers, 1997; McMahon et al, 2005; Patrick et al, 2005). Furthermore, a greater variability exists in changes in control compared to IELT in men treated with selective serotonin reuptake inhibitors (SSRIs) (Waldinger et al, 2004a). Contrary to this, several authors report a moderate correlation between the IELT and the feeling of ejaculatory control (Rowland et al, 2000; Patrick et al, 2005; Rosen et al, 2007; Giuliano et al, 2008). Rosen and colleagues (2007) report that control over ejaculation, personal distress, and partner distress were more influential in determining PE status than IELT. In addition, the effect of IELT on satisfaction and distress appears to be mediated by its direct effect on control (Patrick et al, 2007). However, despite conflicting data on the relationship between control and latency, the balance of evidence supports the notion that the inability to delay ejaculation appears to differentiate men with PE from men without PE (Rowland et al, 2004a; Patrick et al, 2005; Giuliano et al, 2008).

Consistent with these findings, several recent studies report that the majority of patients with acquired and lifelong PE, regardless of comorbid ED, reported perceived control over ejaculation as “poor” or “very poor” (Porst et al, 2010; McMahon et al, 2013).

Rationale for Inclusion of “negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.” Several authors have reported an association between lifelong or acquired PE and negative psychological outcomes in men with lifelong or acquired PE and their female partners (McCabe, 1997; Dunn et al, 1999; Byers and Grenier, 2003; Symonds et al, 2003; Rowland et al, 2004a; Hartmann and colleagues, 2005; Patrick et al, 2005; Riley and Riley, 2005; Althof, 2006a, 2006b; Brock et al, 2007; Porst et al, 2007; Rowland et al, 2007; Giuliano et al, 2008; Rosen and Althof, 2008; McMahon et al, 2013). Patrick and colleagues (2005) reported significant differences in men with and without PE in the PRO measures of personal distress (64% vs. 4%) and interpersonal difficulty (31% vs. 1%), suggesting that this personal distress has discriminative validity in diagnosing men with and without PE. The personal and/or interpersonal distress, bother, frustration, and annoyance that result from PE may affect men’s quality of life and partner relationships, have an impact on their self-esteem and self-confidence, and can act as an obstacle to single men forming new partner relationships (McCabe, 1997; Dunn et al, 1999; Byers and Grenier, 2003; Symonds et al, 2003; Rowland et al, 2004a, 2007; Hartmann et al, 2005; Patrick et al, 2005; Riley and Riley, 2005; Althof, 2006a, 2006b; Brock et al, 2007; Porst et al, 2007; Giuliano et al, 2008; Rosen and Althof, 2008). McCabe (1997) reported that sexually dysfunctional men, including men with PE, scored lower on all aspects of intimacy (emotional, social, sexual, recreational, and intellectual) and had lower levels of satisfaction compared to sexually functional men ($P < .001$ or $P < .01$). Rowland and colleagues (2007) showed that men with PE had significantly lower overall health-related quality of life and total Self-Esteem and Relationship Questionnaire (SEAR) scores and lower confidence and self-esteem compared to non-PE groups. Men with PE rated their overall health-related quality of life lower than men without PE ($P \leq .001$).

Rationale for Exclusion of Sexual Satisfaction

Men with PE report lower levels of sexual satisfaction than men with normal ejaculatory latency (McCabe, 1997; Dunn et al, 1999; Byers and Grenier, 2003; Symonds et al, 2003; Rowland et al, 2004a; Hartmann et al, 2005; Patrick et al, 2005; Riley and Riley, 2005; Althof, 2006a, 2006b; Brock et al, 2007; Porst et al, 2007; Rowland et al, 2007; Giuliano et al, 2008; Rosen and Althof, 2008; Porst et al, 2010; McMahon et al, 2013). Patrick and coworkers (2005) reported ratings of “very poor” or “poor” for sexual satisfaction in 31% of subjects with PE compared to 1% in a group of normal controls. However, caution should be exercised in

assigning lower levels of sexual satisfaction solely to the effect of PE and contributions from other difficult-to-quantify issues such as reduced intimacy, dysfunctional relationships, poor sexual attraction, and poor communication should not be ignored. This is supported by the report of Patrick and colleagues (2005) that despite reduced ratings for satisfaction, with shorter IELTs, a substantial proportion of men with an IELT of less than 1 minute report “good” or “very good” satisfaction ratings (43.7%). The current data are limited but suggest that sexual satisfaction is of limited use in differentiating individuals with PE from those without PE and was not included in the ISSM definition of PE (Patrick et al, 2005).

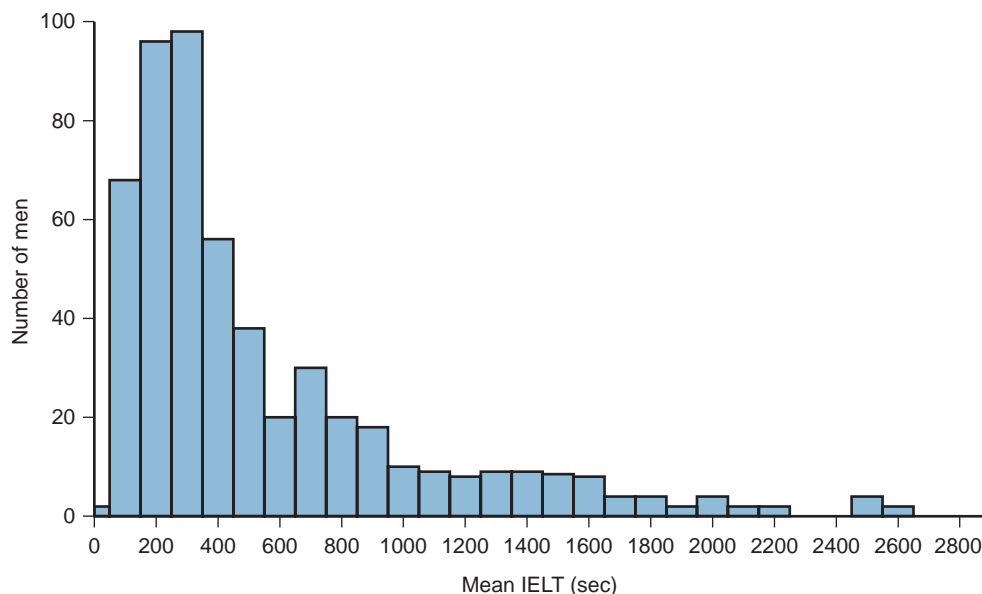


Figure 29-2. Distribution of intravaginal ejaculatory latency times (IELT) values in a random cohort of 491 men. (From Waldinger M, Quinn P, Dilleen M, et al. A multinational population survey of intravaginal ejaculation latency time. *J Sex Med* 2005;2:492–7.)

PE (6.4%). Of particular interest is the report of [Serefoglu and colleagues \(2011\)](#) that men with acquired PE are more likely to seek medical treatment than men with lifelong PE (26.53% vs. 12.77%). This finding was confirmed by [Gao and coworkers \(2013\)](#), who demonstrated that patients with acquired PE were more likely to seek (17.12% vs. 14.58%) and plan to seek (36.30% vs. 27.08%) treatment for their PE than men with lifelong PE. These data suggest that the prevalence of acquired PE in the community is approximately 4% among sexually active adults and that these patients are more likely to seek medical treatment.

Causes of Premature Ejaculation

Historically, attempts to explain the cause of PE have included a diverse range of biologic and psychological theories. Most of these proposed causes are not evidence based and are speculative at best. Although men with lifelong and acquired PE appear to share the dimensions of short ejaculatory latency, reduced or absent perceived ejaculatory control, and presence of negative personal consequences from PE, they remain distinct and different demographic and etiologic populations ([Porst et al, 2010](#)).

Lifelong Premature Ejaculation

[Waldinger and colleagues \(1998\)](#) hypothesized that lifelong early ejaculation in humans may be explained by either a hyposensitivity of the 5-HT_{2C} and/or hypersensitivity of the 5-HT_{1A} receptor. Recent studies suggest that in some men, neurobiologic and genetic variations could contribute to the pathophysiology of lifelong PE, as defined by the ISSM criteria and that the condition may be maintained and heightened by psychological/environmental factors ([Janssen et al, 2009](#)).

Acquired Premature Ejaculation

Acquired PE is commonly due to sexual performance anxiety ([Hartmann et al, 2005](#)), psychological or relationship problems ([Hartmann et al, 2005](#)), ED ([Laumann et al, 2005](#)), occasionally prostatitis ([Screponi et al, 2001](#)), or hyperthyroidism ([Carani et al, 2005](#)) or during withdrawal/detoxification from prescribed ([Adson and Kotlyar, 2003](#)) or recreational ([Peugh and Belenko, 2001](#)) drugs. Consistent with the predominant organic cause of acquired

PE, men with this problem are usually older, have a higher mean body mass index (BMI), and have a greater incidence of comorbid disease, including hypertension, sexual desire disorder, diabetes mellitus, chronic prostatitis, and ED, than men with lifelong, variable, and subjective PE ([Basile Fasolo et al, 2005](#); [Porst et al, 2010](#); [Serefoglu et al, 2010](#); [Serefoglu et al, 2011](#); [Gao et al, 2013](#); [McMahon et al, 2013](#); [Zhang et al, 2013](#)).

Premature Ejaculation and Sexual Performance Anxiety, Psychological Problems, and Relationship Problems

Anxiety has been reported as a cause of PE by multiple authors and is entrenched in the folklore of sexual medicine as the most likely cause of PE despite scant empirical research evidence to support any causal role ([Jern et al, 2007](#); [Janssen et al, 2009](#)). Several authors suggest that anxiety activates the sympathetic nervous system and reduces the ejaculatory threshold as a result of an earlier emission phase of ejaculation ([Janssen et al, 2009](#)).

Hypoactive sexual desire may lead to PE, as a result of an unconscious desire to abbreviate unwanted penetration. Similarly, diminished sexual desire can be a consequence of chronic and frustrating PE.

Female sexual dysfunctions (such as anorgasmia, hypoactive sexual desire, sexual aversion, sexual arousal disorders, and sexual pain disorders, such as vaginismus ([Dogan and Dogan, 2008](#))) also may be related to acquired PE.

Premature Ejaculation and Comorbid Erectile Dysfunction

Recent data demonstrate that as many as half of subjects with ED also experience PE ([Basile Fasolo et al, 2005](#); [Laumann et al, 2005](#); [Porst et al, 2007](#)).

Premature Ejaculation and Prostate Disease

Acute and chronic lower urogenital infection, prostatodynia, or chronic pelvic pain syndrome (CPPS) is associated with ED, PE, and painful ejaculation ([Waldinger et al, 2005c](#); [Donatucci, 2006](#); [Zohdy, 2009](#); [Rowland et al, 2010](#)). Several studies report PE as the main sexual disorder symptom in men with chronic prostatitis or CPPS, with a prevalence of 26% to 77% ([Rowland et al,](#)

2010). The exact pathophysiology of the links among chronic prostatitis, ED, and PE is unknown. It has been hypothesized that prostatic inflammation may result in altered sensation and modulation of the ejaculatory reflex, but evidence is lacking (Donatucci, 2006; Shamloul and El-Nashaar, 2006; Sharlip, 2006). It has been reported that antibiotic treatment of microbiologically confirmed bacterial prostatitis in men with acquired PE resulted in a 2.6-fold increase in IELT and improved ejaculatory control in 83.9% of subjects (El-Nashaar and Shamloul, 2007).

Premature Ejaculation and Hyperthyroidism

The majority of patients with thyroid hormone disorders experience sexual dysfunction. Studies suggest a significant correlation between PE and suppressed thyroid-stimulating hormone (TSH) values in a selected population of andrologic and sexologic patients. The 50% prevalence of PE in men with hyperthyroidism fell to 15% after treatment with thyroid hormone normalization (Carani et al, 2005). Although occult thyroid disease has been reported in the elderly hospitalized population, it is uncommon in the population who present for treatment of PE and routine TSH screening is not necessary unless clinically indicated (Atkinson et al, 1978).

Evaluation of Men Reporting Premature Ejaculation

Medical History

Men presenting with self-reported PE should be evaluated with a full medical and sexual history, a focused physical examination, inventory assessment of erectile function, and any investigations suggested by these findings. Inclusion of the partner in the management process is an important but not mandatory ingredient for treatment success. Some patients may not understand why the clinician wishes to include the partner, and some partners may be reluctant to join the patient in treatment. However, if partners are not involved in treatment, they may be resistant to changing the sexual interaction (Donahey and Miller, 2000). A cooperative partner can enhance the man's self-confidence, skills, self-esteem, and sense of masculinity and more generally assist the man to develop ejaculatory control (Perelman, 2003). This is in turn likely to lead to an improvement in the couple's sexual relationship, as well as the broader aspects of their relationship. No controlled studies have been done on the impact of involving partners in treating PE. However, a review of treatment studies for ED demonstrated the important role of including a focus on interpersonal factors on treatment success (Mohr and Bentler, 1990).

Patients expect clinicians to inquire about their sexual health (Schein et al, 1988). Often patients are too embarrassed, shy, and uncertain if sexual complaints belong in the health care professional's office (Humphrey and Nazareth, 2001). Inquiry into sexual health gives patients permission to discuss their sexual concerns and also screens for associated health risks (e.g., cardiovascular risk and ED). Box 29-1 lists recommended and optional questions that patients who report PE should be asked (McMahon et al, 2004b; Althof et al, 2010). The recommended questions establish the diagnosis and direct treatment considerations and the optional questions gather detail for implementing treatment. Finally, the committee recommends that the health care providers take a medical and psychosocial history.

Diagnosis of Premature Ejaculation

The ISSM definition of PE should form the basis for the diagnosis of PE. A significant population of men with self-reported PE fails to satisfy the criteria of the ISSM definition of PE. This parallels the substantial disparity between the self-reported incidence of PE in epidemiologic studies (Laumann et al, 1999) and that suggested by community-based normative stopwatch IELT studies (Waldinger et al, 2005a). This population has recently been categorized as having either variable PE or subjective PE (Waldinger et al, 2006b;

BOX 29-1 Recommended and Optional Questions to Establish the Diagnosis of Premature Ejaculation (PE) and Direct Treatment

RECOMMENDED QUESTIONS FOR DIAGNOSIS OF PE

What is the time between penetration and ejaculation (coming)?
Can you delay ejaculation?
Do you feel bothered, annoyed, and/or frustrated by your PE?

OPTIONAL QUESTIONS

Differentiate Lifelong and Acquired PE

When did you first experience PE?
Have you experienced PE since your first sexual experience on every/almost every attempt and with every partner?

Assess Erectile Function

Is your erection hard enough to penetrate?
Do you have difficulty in maintaining your erection until you ejaculate during intercourse?
Do you ever rush intercourse to prevent loss of your erection?

Assess Relationship Impact

How upset is your partner with your PE?
Does your partner avoid sexual intercourse?
Is your PE affecting your overall relationship?

Previous Treatment

Have you received any treatment for your PE previously?

Impact on Quality of Life

Do you avoid sexual intercourse because of embarrassment?
Do you feel anxious, depressed, or embarrassed because of your PE?

From Althof SE, Abdo CH, Dean J, et al. International Society for Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation. *J Sex Med* 2010;7:2947–69.

Waldinger and Schweitzer, 2008). Men with subjective PE report PE but have a normal ejaculatory latency typically of 2 to 6 minutes but on some occasions as long as 25 minutes. It is characterized by a preoccupation with a subjective but false perception of PE with an ejaculation latency time (ELT) within the normal range but often with reduced ejaculatory control.

Determination of Intravaginal Ejaculation Latency Time

Self-estimation by the patient and partner of IELT should be used to determine IELT in clinical practice. Stopwatch measures of IELT are widely used in clinical trials and observational studies of PE, but have not been recommended for use in routine clinical management of PE. Despite the potential advantage of objective measurement, stopwatch measures have the disadvantage of being intrusive and potentially disruptive of sexual pleasure or spontaneity. More recently, studies have indicated that patient or partner self-report of ejaculatory latency correlate relatively well with objective stopwatch latency and might be useful as a proxy measure of IELT (Althof, 1998; Pryor et al, 2005; Rosen et al, 2007; McMahon, 2008a). Because patient self-report is the determining factor in treatment seeking and satisfaction, it is recommended that self-estimation by the patient and partner of ejaculatory latency be accepted as the method for determining IELT in clinical practice.

Patient-Reported Outcome Measures

Standardized assessment measures such as validated questionnaires and PRO measures can be used as an adjunct to a full medical and sexual history and self-estimation of ejaculatory latency in the evaluation of men presenting with self-reported PE. These measures are all relatively new and were developed primarily for use as research tools. Some have shown good psychometric properties and are potentially valuable adjuncts for clinical screening and assessment.

Several PE measures have been described in the literature (Yuan et al, 2004; Althof et al, 2006; Arafa and Shamloul, 2007; Symonds et al, 2007a, 2007b; Patrick et al, 2008; Serefoglu et al, 2009), although only a small number have undergone extensive psychometric testing and validation. Five validated questionnaires have been developed and published to date. Currently, two questionnaires have extensive databases and meet most of the criteria for test development and validation: the **Premature Ejaculation Profile (PEP)** and the **Index of Premature Ejaculation (IPE)** (Althof et al, 2006; Patrick et al, 2008). A third brief diagnostic measure, the **Premature Ejaculation Diagnostic Tool (PEDT)**, has a modest database and is available for clinical use (Symonds et al, 2007a). Two other measures, the Arabic and Chinese PE Questionnaires, have minimal validation or clinical trial data available and are not recommended for clinical use.



Further details of PRO measures are available on the Expert Consult website.

Assessment of Erectile Function

The presence of comorbid ED should be evaluated using a validated instrument such as the **International Index of Erectile Function (IIEF)** or the **IIEF-5 (SHIM)**. Normal erectile function should be defined as an **IIEF Erectile Function Domain** of 26 or greater or **IIEF-5** greater than 21 (Rosen et al, 1997; Cappelleri et al, 2001). Recent data demonstrate that as many as half of subjects with ED also experience PE (Jannini et al, 2005). In the European Premature Ejaculation Study (PEPA), ED was present in 31.9% of men with PE compared to 11.8% of men without PE (Porst et al, 2007). In the GSSAB, the odds ratio for ED in men with PE ranged from 6.0 in Europe and as high as 11.9 in South America (Laumann et al, 2005). Consistent with this, ED is more prevalent in men with acquired PE than lifelong PE (Basile Fasolo et al, 2005). PE is also more common with increasing severity of ED after adjustment for age (Corona et al, 2004; El-Sakka, 2006, 2008). Men with ED may either require higher levels of stimulation to achieve an erection or intentionally “rush” intercourse to prevent early detumescence of a partial erection, resulting in ejaculation with a brief latency (Jannini et al, 2005). This may be compounded by the presence of high levels of performance anxiety related to their ED, which serves to only worsen their prematurity. However, caution should be exercised in the diagnosis of comorbid ED in men with PE, because 33.3% of potent men with PE confuse the ability to maintain erections before and after ejaculation, record contradictory response/s to some/all questions of the SHIM, especially Q3 and Q4, and receive a false-positive SHIM diagnosis of ED (McMahon, 2009).

Physical Examination

Current literature suggests that the diagnosis of lifelong PE is based purely on the medical history because there are no predictive physical findings or confirmatory investigations (McMahon, 2005). As differentiation of lifelong PE and acquired PE may be difficult in either young men or men with no or few previous sexual partners and/or limited sexual experience, a physical examination is highly desirable and represents an opportunity for screening for cardiovascular or gender-specific diseases. However, in men with acquired PE, a physical examination is mandatory in an effort to identify the cause of the PE and to alleviate its possible cause (Jannini et al, 2006b). The presence of ED should be evaluated either by medical history or with the assistance of a validated instrument. Laboratory

or imaging investigations are occasionally required based on the patient's medical history. A digital prostate examination, routine in an andrologic setting for all men over 40, is useful in identifying possible evidence of prostatic inflammation or infection (Jannini et al, 2006a).

Treatment of Premature Ejaculation

Figure 29-3 is a flow chart for the management of PE (Rowland et al, 2010). **Multiple psychosexual and pharmacologic treatments are available for PE.** Men with lifelong PE are best managed with PE pharmacotherapy alone or in combination with graded levels of patient and couple psychosexual therapy. Men with acquired PE should receive cause-specific treatment (e.g., psychosexual counseling or ED pharmacotherapy, alone or in combination with PE pharmacotherapy). Men with natural variable PE or PE-like ejaculatory dysfunction should be primarily treated with psychosexual education and graded patient and couple psychotherapy.

Psychosexual Therapy

All men seeking treatment for PE should receive basic psychosexual education or coaching (Althof, 2006c, 2007; Perelman, 2003, 2006). This may include providing information on the prevalence of PE and general population IELT to dispel myths about PE, information on enjoyable sexual activities to extend the man and his partner's sexual repertoire, as well as strategies to address avoidance of sexual activity or unwillingness to discuss sex with his partner. These educational strategies are designed to give the man the confidence to try the medical intervention, reduce performance anxiety, and modify his maladaptive sexual scripts.

Additional information on the role of psychosexual therapy in the management of PE is available on the Expert Consult website.



Pharmacologic Treatment

Several forms of pharmacotherapy have been used in the treatment of PE (Giuliano and Clement, 2012). These include the use of **topical local anesthetics, SSRIs, tramadol, phosphodiesterase type 5 (PDE5) inhibitors, and α -adrenergic blockers**. The use of topical local anesthetics, such as lidocaine, prilocaine, or benzocaine, alone or in association, to diminish the sensitivity of the glans penis is the oldest known pharmacologic treatment for PE (Schapiro, 1943). The introduction of the SSRIs paroxetine, sertraline, fluoxetine, and citalopram and the tricyclic antidepressant (TCA) clomipramine has revolutionized the treatment of PE. These drugs block axonal reuptake of serotonin from the synaptic cleft of central serotonergic neurons by 5-HT transporters, resulting in enhanced 5-HT neurotransmission and stimulation of postsynaptic membrane 5-HT receptors.

Treatment with Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants. PE can be treated with on-demand SSRIs such as dapoxetine or off-label clomipramine, paroxetine, sertraline, and fluoxetine or with daily dosing of off-label paroxetine, clomipramine, sertraline, fluoxetine, or citalopram.

Dapoxetine. Dapoxetine has received approval for the treatment of PE in over 50 countries worldwide. Dapoxetine has not received marketing approval for the United States by the U.S. Food and Drug Administration. It is a rapid-acting and short-half-life SSRI with a pharmacokinetic profile supporting a role as an on-demand treatment for PE (Pryor et al, 2006). No drug-drug interactions associated with dapoxetine, including phosphodiesterase inhibitor drugs, have been reported. In randomized controlled trials (RCTs), dapoxetine 30 mg or 60 mg taken 1 to 2 hours before intercourse is more effective than placebo from the first dose, resulting in 2.5- and 3.0-fold increases in IELT, increased ejaculatory control, decreased distress, and increased satisfaction. Dapoxetine was comparably effective in men with lifelong and acquired PE (Porst et al, 2010) and was similarly effective and well tolerated in men with PE and comorbid ED treated with PDE5 inhibitor drugs (McMahon et al, 2013). Treatment-related side effects were

Premature Ejaculation Profile

A four-item, self-report measure of PE has been developed by Patrick and colleagues (2008). The PEP comprises single-item constructs of (1) perceived control over ejaculation, (2) satisfaction with sexual intercourse, (3) personal distress related to ejaculation, (4) interpersonal difficulty related to ejaculation, and (5) an index or total score. Each of the four individual items is assessed on a 5-point scale, which are averaged to provide an index PE score. The measure has been used in observational studies and clinical trials of PE (Patrick et al, 2005). It also has been recommended for clinical use in evaluating the subjective components of the disorder. Validation studies have been performed in comparison to stopwatch measures of intravaginal latency and other PRO measures of sexual function and distress (Patrick et al, 2005, 2008). The scale has adequate test-retest reliability (total scale = 0.80) and moderate to strong correlations with stopwatch-measured IELT. A major limitation of the scale is the lack of validated cutoff scores, which make it less suitable for use as a diagnostic or clinical screening tool. On the positive side, it is very brief and easy to administer and may be valuable for use in a clinical setting as a measure of treatment responsiveness.

Index of Premature Ejaculation

The IPE was developed by Althof and colleagues (2006). It is a 10-item self-administered questionnaire designed to evaluate sexual satisfaction, control, and distress in men with PE. It was developed using four stages: item pool development, initial psychometric

analyses, patient interviews, and final psychometric analyses. The IPE contains three factor analytically derived domains: control, sexual satisfaction, and distress. All three domains have shown adequate internal consistency and reliability, as well as known group validity in comparing men with and without PE. Convergent validity against IELT was also strong for all three domains (control [$r = .75$], sexual satisfaction [$r = .60$], and distress [$r = .68$]).

The IPE has the advantages of also being relatively brief and easy to administer, although the measure is not as brief as the PEP. It also assesses clinically relevant domains and has adequate known group validity data. However, similar to the PEP, it lacks norms and diagnostic cutoffs and has limited value as a diagnostic or screening measure for PE.

Premature Ejaculation Diagnostic Tool

The two measures (PEP, IPE) discussed previously are available for use as treatment change or outcome measures of PE treatment. The PEDT, in contrast, was developed specifically for use as a screening questionnaire (Symonds et al, 2007a, 2007b; Serefoglu et al, 2009). This questionnaire is a brief, 5-item measure used to screen men for potential presence of PE based on DSM-IV-TR criteria of lack of control, frequency, minimal stimulation, distress, and interpersonal difficulty.

Depending on the specific need, the PEP and IPE are currently the preferred questionnaire measures for assessing PE, particularly when monitoring responsiveness to treatment. Overall, these measures may serve as useful adjuncts, but should not substitute for a detailed sexual history performed by a qualified clinician.

Graded levels of patient and couple counseling, guidance, and/or relationship therapy, either alone or ideally in combination with PE pharmacotherapy, should be offered as a treatment option for most men with PE. PE exerts a significant psychological burden on men, their partners, the male/partner relationship, and their overall relationship (Rust et al, 1988; Symonds et al, 2003). Men with PE show other negative effects, including a general negative affect associated with sexual situations, as well as more intense feelings of embarrassment/guilt, worry/tension, and fear of failure (Sotomayor, 2005). These individuals indicate decreased self-confidence, increased distress and interpersonal difficulty, and mental preoccupation with their condition (Hartmann et al, 2005; Patrick et al, 2005). Partner satisfaction may play a greater role in PE than ED, so it is not surprising that relationship dysfunction is reported as the second most common negative effect of PE (Hartmann et al, 2005; Symonds et al, 2003). Not only is PE associated with marital discord (Rust et al, 1988), but the insecurity of men with PE about satisfying the partner also serves as an obstacle to initiating and maintaining new relationships (Symonds et al, 2003; Sotomayor, 2005).

Until recently, treatment options have been limited to behavioral and psychological procedures. Psychological factors such as anxiety and negative affect have frequently been associated with sexual dysfunctions such as PE (Kaplan, 1983, 1989), and treatment addressing such issues has represented a logical approach. Psychological-behavioral strategies for treating PE have been at least moderately successful in alleviating the dysfunction in the short term (Golden et al, 1978; De Amicis et al, 1984; Hawton et al, 1986; Levine, 1992; de Carufel and Trudel, 2006).

Psychological interventions are designed to achieve more than simply increasing the IELT. Targeted factors focus on the man, his partner, and their relationship. Psychotherapy and behavioral interventions improve ejaculatory control by helping men/couples to (1) learn techniques to control and/or delay ejaculation, (2) gain confidence in their sexual performance, (3) lessen performance anxiety, (4) modify rigid sexual repertoires, (5) surmount barriers to intimacy, (6) resolve interpersonal issues that precipitate and maintain the dysfunction, (7) increase communication (Althof, 2003; Althof

and Wieder, 2004), and (8) come to terms with feelings/thoughts that interfere with sexual function.

Present-day psychotherapy for PE most often represents an integration of behavioral (e.g., the well-known start-stop and pause-squeeze methods) and cognitive approaches within a short-term psychotherapy model (Golden et al, 1978; De Amicis et al, 1984; Hawton et al, 1986; Levine, 1992; Althof and Wieder, 2004; de Carufel and Trudel, 2006). The guiding principles of treatment are to learn to control ejaculation while understanding the meaning of the symptom and the context in which it occurs.

Although the new and often more expedient pharmacologic therapies are overshadowing traditional psychological-behavioral methods in the treatment of PE, the psychological-behavioral approach remains an attractive option for several reasons. The treatment is specific to the problem; is neither harmful nor painful; depends less on the man's medical history; produces minimal or no adverse side effects; and encourages open communication about sexuality in the couple, which is likely to lead to a more satisfying sexual relationship (Verhulst and Heiman, 1988; Wincze and Carey, 1991). Once the techniques have been learned and incorporated into lovemaking, men with PE continue to have access to strategies that help them control their ejaculation. At the same time, there are drawbacks to the psychological-behavioral approach: it is time-consuming, often requires substantial resources of both time and money, lacks immediacy, requires the partner's cooperation, and has mixed (and less well-documented) efficacy. Furthermore, data to support long-term efficacy are lacking.

Combining a medical and psychological approach may be especially useful in men with acquired PE in whom there is a clear psychosocial precipitant or lifelong if the individual or couple's responses to PE are likely to interfere in the medical treatment and ultimate success of therapy. Similarly, in men with PE and comorbid ED, combination therapy also may be helpful to manage the psychosocial aspects of these sexual dysfunctions. Once the man's self-confidence and sense of control have improved, it may then be possible to reduce or discontinue the medical intervention (McMahon, 2002).

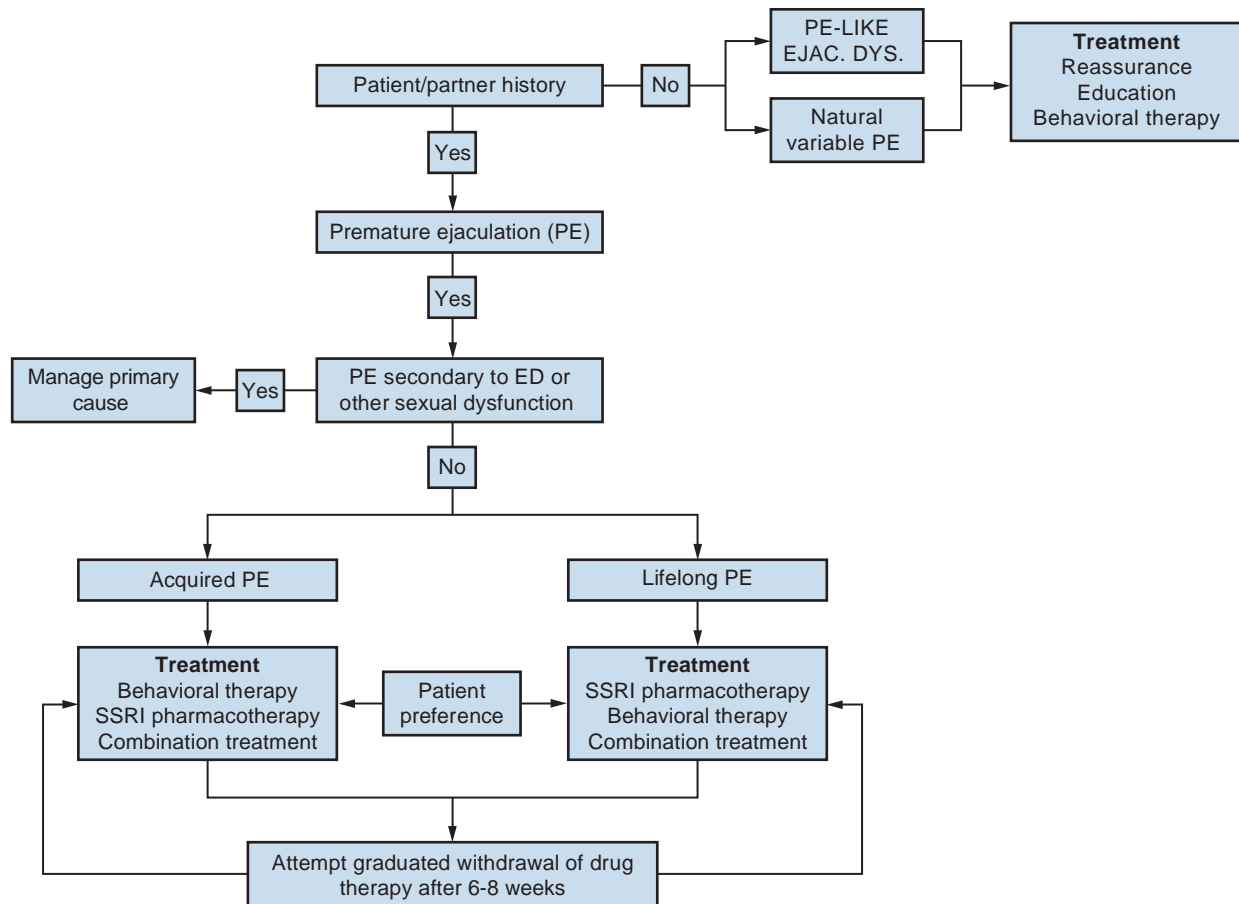


Figure 29-3. Algorithm for the office management of premature ejaculation (PE). ED, erectile dysfunction; EJAC. DYS., ejaculation dysfunction; SSRI, selective serotonin reuptake inhibitor.

uncommon and dose dependent and included nausea, diarrhea, headache, and dizziness (McMahon et al, 2011). They were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects. There was no indication of an increased risk for suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation (Levine, 2006).

Off-Label Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants. Daily treatment with off-label paroxetine 10 to 40 mg, clomipramine 12.5 to 50 mg, sertraline 50 to 200 mg, fluoxetine 20 to 40 mg, and citalopram 20 to 40 mg is usually effective in delaying ejaculation. A meta-analysis of published data suggests that paroxetine exerts the strongest ejaculation delay, increasing IELT approximately 8.8-fold over baseline (Waldinger et al, 2004b).

Ejaculation delay usually occurs within 5 to 10 days of starting treatment, but the full therapeutic effect may require 2 to 3 weeks of treatment and usually is sustained during long-term use (McMahon, 2002). Adverse effects are usually minor, start in the first week of treatment, and may gradually disappear within 2 to 3 weeks. They include fatigue, yawning, mild nausea, diarrhea, or perspiration. Anecdotal reports show that decreased libido and ED are less frequently seen in nondepressed men with PE treated by SSRIs compared to depressed men treated with SSRIs (Waldinger, 2007). Neurocognitive adverse effects include significant agitation and hypomania in a small number of patients, and treatment with SSRIs should be avoided in men with a history of bipolar depression (Marangell et al, 2008).

Platelet serotonin release has an important role in hemostasis (Li et al, 1997) and SSRIs, especially with concurrent use of aspirin and nonsteroidal anti-inflammatory drugs, may be associated with

increased risk for upper gastrointestinal bleeding. Priapism is a rare adverse effect of SSRIs and requires urgent medical treatment. Long-term SSRI use may be associated with weight gain and an increased risk for type 2 diabetes mellitus (Fava et al, 2000). In men with normal semen parameters, paroxetine has been reported to induce abnormal sperm DNA fragmentation in a significant proportion of subjects, without a measurable effect on semen parameters. The fertility potential of a substantial number of men on paroxetine may be adversely affected by these changes in sperm DNA integrity (Tanrikut et al, 2010).

Systematic analysis of RCTs of antidepressants (SSRIs and other drug classes) in patients with depressive and/or anxiety disorders indicates a small increase in the risk for suicidal ideation or suicide attempts in youth but not adults. In contrast, the risk for suicidal ideation has not been found in trials with SSRIs in nondepressed men with PE. Caution is suggested in prescribing SSRIs to young adolescents with PE aged 18 years or less, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation (Khan et al, 2003). Patients should be advised to avoid sudden cessation or rapid dose reduction of daily dosed SSRIs, which may be associated with an SSRI withdrawal syndrome (Black et al, 2000).

On-demand administration of clomipramine, paroxetine, sertraline, and fluoxetine 3 to 6 hours before intercourse is modestly efficacious and well tolerated but is associated with substantially less ejaculatory delay than daily treatment in most studies (Kim and Paick, 1999; McMahon and Touma, 1999; Strassberg et al, 1999; Waldinger et al, 2004a). On-demand treatment may be combined with either an initial trial of daily treatment or concomitant low-dose daily treatment (McMahon and Touma, 1999).

Patients are often reluctant to begin off-label treatment of PE with SSRIs. [Salonia and associates \(2009\)](#) reported that 30% of patients refused to begin treatment (paroxetine 10 mg/day for 21 days followed by 20 mg as needed) and another 30% of those who began treatment discontinued it ([Salonia et al, 2009](#)). Similarly, [Mondaini and colleagues](#) reported that in a clinic population, 90% of patients either refused to begin or discontinued dapoxetine within 12 months of beginning treatment ([McMahon, 2002](#)). Reasons given included not wanting to take an antidepressant, treatment effects below expectations, and cost.

The decision to treat PE with either on-demand dosing of dapoxetine (where available) or daily dosing of off-label SSRIs should be based on the treating physician's assessment of individual patient requirements. Although many men with PE who engage in sexual intercourse infrequently may prefer on-demand treatment, many men in established relationships may prefer the convenience of daily medication. Well-designed preference trials will provide additional insight into the role of on-demand dosing. In some countries, off-label prescribing may present difficulties for the physician because the regulatory authorities strongly advise against prescribing for indications in which a medication is not licensed or approved. Obviously this complicates treatment in countries where there is no approved medication and the regulatory authorities advise against off-label prescription.

Off-Label Topical Local Anesthetics. The use of topical local anesthetics such as lidocaine and/or prilocaine as a cream, gel, or spray is well established and is moderately effective in delaying ejaculation. Data suggest that diminishing the glans sensitivity may inhibit the spinal reflex arc responsible for ejaculation ([Wieder et al, 2000](#)). [Dinsmore and associates \(2007\)](#) reported on the use of PSD502, a lidocaine-prilocaine spray currently in clinical trials that is applied to the penis at least 5 minutes before intercourse. The treated group reported a 6.3-fold increase in IELT and associated improvements in PRO measures of control and sexual satisfaction ([Dinsmore et al, 2007](#); [Henry et al, 2008](#)). Minimal reports have been made of penile hypoanesthesia and transfer to the partner as a result of the unique formulation of the compound. Other topical anesthetics are associated with significant penile hypoanesthesia and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used ([Busato and Galindo, 2004](#)).

Phosphodiesterase Type 5 Inhibitors. Off-label on-demand or daily dosing of PDE5 inhibitors is not recommended for the treatment of lifelong PE in men with normal erectile function. ED pharmacotherapy alone or in combination with PE pharmacotherapy is recommended for the treatment of lifelong PE or acquired PE in men with comorbid ED. PDE5 inhibitors sildenafil, tadalafil, and vardenafil are effective treatments for ED. Several authors have reported experience with PDE-5 inhibitors alone or in combination with SSRIs as a treatment for PE ([Abdel-Hamid et al, 2001](#); [Chia, 2002](#); [Erenpreiss and Zalkalns, 2002](#); [Linn et al, 2002](#); [Salonia et al, 2002](#); [Chen et al, 2003](#); [Li et al, 2003](#); [Lozano, 2003](#); [Tang et al, 2004](#); [Mattos and Lucon, 2005](#); [McMahon et al, 2005](#); [Sommer et al, 2005](#); [Zhang et al, 2005](#); [Atan et al, 2006](#); [Sun et al, 2007](#); [Mattos et al, 2008](#); [Aversa et al, 2009](#); [Mathers et al, 2009](#); [Jannini et al, 2011](#)). The putative role of PDE5 inhibitors as a treatment for PE is speculative and based only on the role of the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) transduction system as a central and peripheral mediator of inhibitory nonadrenergic, noncholinergic nitrergic neurotransmission in the urogenital system ([Mamas et al, 2003](#)). Although systematic reviews of studies on the PDE5 inhibitor drug treatment of PE have failed to provide robust empirical evidence to support a role of PDE5 inhibitors in the treatment of PE, with the exception of men with PE and comorbid ED ([McMahon et al, 2006a](#); [Asimakopoulos et al, 2012](#)), recent well-designed studies do support a potential role for these agents, suggesting a need for further evidence-based research ([Aversa et al, 2009](#)).

Some evidence supports the efficacy and safety of off-label, on-demand, or daily dosing of PDE5 inhibitors in the treatment of lifelong PE in men with normal erectile function (level of

evidence 4D). Treatment of lifelong PE with PDE5 inhibitors in men with normal erectile function is not recommended, and further evidence-based research is encouraged to understand conflicting data.

Table 29-2 is a summary of recommended pharmacologic treatments for PE.

Treatment of PE with tramadol, α_1 -adrenoceptor antagonists, intracavernous injection of vasoactive drugs, acupuncture, surgical neurotomy, cryoablation, and neuromodulation of the dorsal penile nerve is discussed in detail on the Expert Consult website.



Conclusion

Recent epidemiologic and observational research has provided new insights into PE and the associated negative psychosocial effects of this dysfunction. Recent normative data suggest that 80% to 90% of treatment-seeking men with lifelong PE will ejaculate within 1 minute and form the basis of the ISSM definition of lifelong. Although insufficient empirical evidence exists to clearly identify the cause of PE, limited evidence suggests that men with PE may have a genetic predisposition toward rapid ejaculation, high levels of sexual anxiety, and comorbid ED.

The use of dapoxetine and off-label SSRIs, clomipramine, and topical anesthetics has drawn new attention to this common and often ignored sexual problem. PE pharmacotherapy fails to directly completely address causal psychological or relationship factors, and data are either lacking or scarce on the efficacy of combined psychosexual counseling and pharmacologic treatment and the maintenance of improved ejaculatory control after drug withdrawal.

KEY POINTS: PREMATURE EJACULATION

- PE is a common sexual dysfunction.
- PE is associated with negative psychological consequences, including distress, bother, and frustration that may affect quality of life, partner relationships, self-esteem, and self-confidence and can act as an obstacle to single men forming new partner relationships.
- The evidence-based ISSM definition of lifelong and acquired PE should form the basis of the office diagnosis of lifelong PE.
- Limited evidence suggests lifelong PE has a genetic basis and acquired PE is most often the result of sexual performance anxiety, psychological or relationship problems, and/or ED.
- Oral SSRI drugs and topical anesthetic drugs are effective and safe treatments for PE.
- Psychosexual cognitive behavioral therapy has a limited role as a first-line treatment for PE but has an important role as an adjunct to pharmacotherapy, especially in men with acquired PE resulting from sexual performance anxiety.
- Men with acquired PE, most often secondary to comorbid ED, hyperthyroidism, chronic lower urogenital infection, prostatodynia, or CPPS, should receive appropriate cause-specific treatment alone or in combination with an SSRI.

DELAYED EJACULATION, ANEJACULATION, AND ANORGMASIA

Any psychological or medical disease or surgical procedure that interferes with either central control of ejaculation or the peripheral sympathetic nerve supply to the vas and bladder neck, the somatic efferent nerve supply to the pelvic floor, or the somatic afferent nerve supply to the penis can result in delayed ejaculation, anejaculation, retrograde ejaculation, and/or anorgasmia. Thus the

On-Demand Treatment with Off-Label Tramadol. Tramadol is a centrally acting synthetic opioid analgesic with an unclear mode of action that is thought to include binding of parent and M1 metabolite to μ -opioid receptors and weak inhibition of reuptake of GABA, norepinephrine, and serotonin (Frink et al, 1996). The efficacy of on-demand tramadol in the treatment of PE was recently reported (Salem et al, 2008; Alghobary et al, 2010; Xiong et al, 2011; Kaynar et al, 2012). Most studies are poorly designed open-label trials with a wide range of efficacy. The only double-blind, well-designed trial demonstrates a superiority to placebo but a mediocre-fold increase in IELT of 2.49, consistent with the weak serotonin reuptake inhibitor activity of tramadol (Bar-Or et al, 2012). The unclear safety profile and the potential for addiction discourage use of tramadol in PE clinical practice.

Tramadol may be an effective option for the treatment of PE. However, it may be considered when other therapies have failed because of the risk for addiction and side effects. It should *not* be combined with an SSRI because of the risk for serotonin syndrome, a potentially fatal outcome (Takeshita and Litzinger, 2009). Further well-controlled studies are required to assess the efficacy and safety of tramadol in the treatment of patients with PE (level of evidence 2).

Daily Treatment with Off-Label α_1 -Adrenoceptor Antagonists. Ejaculation is a sympathetic spinal cord reflex that could theoretically be delayed by α_1 -adrenergic blockers. Several researchers have reported their experience with the selective α_1 -adrenergic blockers alfuzosin and terazosin in the treatment of PE. Both drugs are approved only for the treatment of lower urinary tract symptoms (LUTS) in men with obstructive benign prostatic hyperplasia (BPH). In a double-blind placebo-controlled study, Cavallini (1995) reported that both alfuzosin (6 mg/day) and terazosin (5 mg/day) were effective in delaying ejaculation in approximately 50% of the cases. Similarly, Basar and colleagues (2005) reported that terazosin was effective in 67% of men. However, both studies were limited by the use of subjective study end points of patient impression of change and sexual satisfaction, and they did not evaluate actual ejaculatory latency. Additional controlled studies are required to determine the role of α_1 -blockers in the treatment of PE.

Intracavernous Injection of Off-Label Vasoactive Drugs. Intracavernous self-injection treatment of PE has been reported but is currently without any evidence-based support for efficacy or safety. In one study, which included eight patients with PE, a mixture of phentolamine mesylate 1 mg/mL and papaverine hydrochloride 30 mg/mL was injected. All patients reported satisfaction with the results of this treatment, but ejaculation delay was not objectively measured (Fein, 1990). Intracavernosal injection of vasoactive drugs is not recommended for the treatment of PE (level of evidence 4).

Acupuncture

One randomized placebo-controlled clinical study compared effectiveness of acupuncture therapy (twice per week) with paroxetine 20 mg/day and placebo (sham acupuncture) in the treatment of PE (Sunay et al, 2011). The authors included 90 patients with PE and demonstrated that acupuncture had a significantly stronger ejaculation-delaying effect than placebo (65.7 vs. 33.1 seconds), although it was less effective than daily paroxetine (82.7 seconds) ($P = .001$). Similarly, the patient-reported outcome measures showed an improvement in the acupuncture and paroxetine groups.

Surgical Neurotomy, Cryoablation, and Neuromodulation of the Dorsal Penile Nerve

Selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation is not recommended for the treatment of PE. Surgery may be associated with permanent loss of sexual function and is contraindicated in the management of PE. Several authors have reported the use of surgically induced penile hypoanesthesia via selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation in the treatment of lifelong PE refractory to behavioral and/or pharmacologic treatment (Kim et al, 2004; Perelman, 2006; Kwak et al, 2008; Shi et al, 2008; Basal et al, 2010). The role of surgery in the management of PE remains unclear until the results of further studies have been reported.

TABLE 29-2 Drug Therapy for Premature Ejaculation (PE)

DRUG	DOSE	DOSING INSTRUCTIONS	INDICATION	COMMENTS	LEVEL OF EVIDENCE
Dapoxetine	30-60 mg	On demand, 1-3 hr before intercourse	Lifelong PE Acquired PE	Approved in >50 countries	High
Paroxetine	10-40 mg	Once daily	Lifelong PE Acquired PE		High
Sertraline	50-200 mg	Once daily	Lifelong PE Acquired PE		High
Fluoxetine	20-40 mg	Once daily	Lifelong PE Acquired PE		High
Citalopram	20-40 mg	Once daily	Lifelong PE Acquired PE		High
Clomipramine	12.5-50 mg	Once daily	Lifelong PE Acquired PE		High
	12.5-50 mg	On demand, 3-4 hr before intercourse	Lifelong PE Acquired PE		High
Tramadol	25-50 mg	On demand, 3-4 hr before intercourse	Lifelong PE Acquired PE	Potential risk for opiate addiction	Low
Topical lignocaine/prilocaine	Patient titrated	On demand, 20-30 min before intercourse	Lifelong PE Acquired PE		High
Alprostadil	5-20 µg	Patient administered intracavernous injection 5 min before intercourse	Lifelong PE Acquired PE	Risk for priapism and corporal fibrosis	Very low
PDE5 inhibitors	Sildenafil 25-100 mg Tadalafil 10-20 mg Vardenafil 10-20 mg	On demand, 30-50 min before intercourse	Lifelong and acquired PE in men with normal erectile function	? Improved efficacy if combined with SSRI	Very low
			Lifelong and acquired PE in men with ED		Moderate

ED, erectile dysfunction; PDE5, phosphodiesterase type 5; SSRI, selective serotonin reuptake inhibitor.

causes of delayed ejaculation, anejaculation, and anorgasmia are manifold.

Definition, Terminology, and Characteristics of Men with Delayed Ejaculation

Delayed ejaculation (DE), retarded ejaculation (RE), or inhibited ejaculation (IE) are probably the least common, least studied, and least understood of the male sexual dysfunctions. Yet their impact is significant in that it typically results in a lack of sexual fulfillment for both the man and his partner, an effect further compounded when procreation is among the couple's goals of sexual intercourse.

Problems with "difficulty" in ejaculating may range from varying delays in the latency to ejaculation to complete inability to ejaculate (anejaculation). Reductions in the volume, force, and sensation of ejaculation may occur as well. At the extremes are anejaculation (time) and retrograde ejaculation (direction), but more commonly encountered are IE, RE, and DE. A final disorder, anorgasmia, refers to a perceived absence of the orgasm experience, independent of whether any or all of the physiologic concomitants of ejaculation have taken place.

Terminology and Definition

RE, DE, IE, inadequate ejaculation, idiopathic anejaculation, primary impotentia ejaculations, and psychogenic anejaculation all

have been used synonymously to describe a delay or absence of male orgasmic response. If a distinction is to be made, usually IE is characterized by the complete absence of ejaculation, although no clear consensus exists. Herein, the preferred terminology DE is meant to describe any and all of the ejaculatory disorders resulting in a delay or absence of ejaculation.

DSM-IV-TR defines DE as follows ([American Psychiatric Association, 2000](#)):

The persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase during sexual activity that the clinician, taking into account the person's age, judges to be adequate in focus, intensity, and duration. The disturbance causes marked distress or interpersonal difficulty; it should not be better accounted for by another Axis I (clinical) disorder or caused exclusively by the direct physiologic effects of a substance or a general medical condition.

Similarly, the Second International Consultation on Sexual Dysfunction defines DE as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm after sufficient sexual stimulation, which causes personal distress ([McMahon et al, 2004a](#)).

No clear criteria exist as to when a man actually meets the conditions for DE, because operationalized criteria do not exist. Given that most sexually functional men ejaculate within approximately 4 to 10 minutes after intromission ([Patrick et al, 2005](#)), a clinician might assume that men with latencies beyond 25 or 30 minutes (21 to 23 minutes represents approximately 2 standard

deviations above the mean) who report distress or men who simply cease sexual activity because exhaustion or irritation qualify for this diagnosis. Such symptoms, together with the fact that a man and/or his partner decide to seek help for the problem, are usually sufficient for a DE diagnosis.

Epidemiology of Delayed Ejaculation

The prevalence of ejaculatory disorders is unclear, partly because of the dearth of normative data for defining the duration of “normal” ejaculatory latency, particularly regarding the right “tail” of the distribution (i.e., beyond the mean latency to orgasm). Furthermore, larger epidemiologic studies have not subdivided various types of ejaculatory disorders (e.g., delayed vs. absent), further limiting our knowledge. In general, DE is reported at low rates in the literature, rarely exceeding 3% (Laumann et al, 1999; Simons and Carey, 2001; Perelman, 2004). The prevalence of DE appears to be moderately and positively related to age, which is not surprising in view of the fact that ejaculatory function as a whole tends to diminish as men age.

Failure of ejaculation can be a lifelong problem or an acquired problem. It may be global and happen in every sexual encounter or be intermittent or situational. Normative descriptive data from large samples of men with DE have not been available, but a recent analysis identified 25% of a clinical sample with lifelong DE, with the remainder reporting a secondary problem (Perelman, 2004). Although coital anejaculation is frequently the treatment driver (especially for extremely religious individuals referred for fertility problems), men also seek treatment when distressed by their inability to achieve orgasm in response to manual, oral, or vaginal stimulation by their partner. Many men with acquired DE can masturbate to orgasm, whereas others, for multiple reasons, will not or cannot. Loss of masturbatory capacity secondary to emotional or physical trauma also is seen. Approximately 75% of one clinical sample could reach orgasm through masturbation, whereas the remainder either would not or could not (Perelman, 2004).

Similar to men with other types of sexual dysfunction, men with DE indicate high levels of relationship distress, sexual dissatisfaction, anxiety about their sexual performance, and general health issues—significantly higher than sexually functional men. In addition, along with other sexually dysfunctional counterparts, men with DE typically report lower frequencies of coital activity (Rowland et al, 2005). A distinguishing characteristic of men with DE—and one that has implications for treatment—is that they usually have little or no difficulty attaining or keeping erections; in fact they are often able to maintain erections for prolonged periods. But despite their good erections, they report low levels of subjective sexual arousal, at least compared with sexually functional men (Rowland et al, 2004b).

Cause of Delayed Ejaculation and Anejaculation

DE and anejaculation may be lifelong or acquired, global, or situational. A number of pathophysiologic conditions have been associated with ejaculatory problems (Box 29-2). These include congenital disorders as well as ones caused by psychological factors, treatment of male pelvic cancers with surgery or radiotherapy, neurologic disease, endocrinopathy, infection, and treatment for other disorders. When a medical history or symptomatology so indicates, investigation of such possible causes may be necessary. The most common causes of DE seen in clinical practice are psychogenic IE, degeneration of penile afferent nerves and pacinian corpuscles in the aging male, hypogonadism, diabetic autonomic neuropathy, treatment with SSRI antidepressants and major tranquilizers, radical prostatectomy or other major pelvic surgery, or radiotherapy.

Psychological Delayed Ejaculation

Psychogenic DE, often described as IE, is usually related to sexual performance anxiety, which may draw the man’s attention away

BOX 29-2 Causes of Retrograde Ejaculation, Delayed Ejaculation, Anejaculation, and Anorgasmia

AGING MALE

Degeneration of penile afferent nerves

PSYCHOGENIC

Inhibited ejaculation

CONGENITAL

Müllerian duct cyst
Wolffian duct abnormality
Prune belly syndrome

ANATOMIC CAUSES

Transurethral resection of prostate
Bladder neck incision

NEUROGENIC CAUSES

Diabetic autonomic neuropathy
Multiple sclerosis
Spinal cord injury
Radical prostatectomy
Proctocolectomy
Bilateral sympathectomy
Abdominal aortic aneurysmectomy
Para-aortic lymphadenectomy

INFECTIVE

Urethritis
Genitourinary tuberculosis
Schistosomiasis

ENDOCRINE

Hypogonadism
Hypothyroidism

MEDICATION

α-Methyldopa
Thiazide diuretics
Tricyclic and SSRI antidepressants
Phenothiazine
Alcohol abuse
SSRI, selective serotonin reuptake inhibitor.

from erotic cues that normally serve to enhance arousal. Other psychodynamic explanations emphasize psychosexual development issues and have attributed lifelong DE to a wide range of conditions, including fear, anxiety, hostility, orthodoxy of religious belief, and relationship difficulties (Munjack and Kanno, 1979; Waldinger and Schweitzer, 2005). Although some of these factors may contribute to DE in individual men, no well-controlled studies provide broad support, at this point, for any of the various hypotheses mentioned previously (Waldinger and Schweitzer, 2005).

Masters and Johnson (1970) were the first to suggest that DE in some men might be associated with orthodoxy of religious belief. Such beliefs may limit the sexual experience necessary for learning to ejaculate or may result in an inhibition of normal function. Many devoutly religious men have masturbated only minimally or not at all, and, for some, guilt and anxiety about “spilling seed” may have led to idiosyncratic masturbatory patterns, which in turn resulted in DE. Such men often had little contact with women before marriage and, although they may have dated, were less likely than their

secular counterparts to experience orgasm with a partner, especially through intercourse.

Idiosyncratic and vigorous masturbation styles that cannot be replicated during intercourse with a partner, or an “autosexual” orientation in which men derive greater arousal and enjoyment from masturbation than from intercourse, are risk factors for DE (Perelman, 2005; Perelman and Rowland, 2006). These men precondition themselves to possible difficulty attaining orgasm with a partner and, as a result, experience acquired DE. They appear able to achieve erections sufficient for intercourse despite a relative absence of subjective arousal (Apfelbaum, 1989), and their erections are taken as erroneous evidence by both the man and his partner that he was ready for sex and capable of achieving orgasm. Disparity between the reality of sex with the partner and the sexual fantasy used during masturbation may inhibit sexual arousal and thus represent another contributor to DE (Perelman, 2001).

Endocrinopathy

Hypothyroidism is commonly strongly associated with DE, whereas hyperthyroidism is rarely associated with PE (Carani et al, 2005; Corona et al, 2006). Similarly, **hypogonadism** and low testosterone are associated with DE or anejaculation (Corona et al, 2008, 2011, 2012). **Hyperprolactinemia**, via inhibition of hypothalamic gonadotropin-releasing hormone GnRH is associated with low testosterone, reduced sexual desire, ED, and DE. The effect of prolactin on ejaculation is possibly mediated via its action on the serotonergic system (Corona et al, 2006, 2009).

Iatrogenic Causes

Any prescribed or recreational drug that changes the levels of neurotransmitters such as serotonin, dopamine, or oxytocin that are involved in the central or peripheral neurocontrol of ejaculation may affect ejaculatory latency.

SSRIs are commonly used for the treatment of depression and are associated with a high incidence of sexual dysfunction, with up to 60% reporting some form of treatment-related sexual dysfunction, most commonly ejaculatory dysfunction (Montejo et al, 2001; Delgado et al, 2005; Madeo et al, 2008). Treatment with **antipsychotics**, probably resulting from either a direct and/or indirect dopamine antagonism (Hull et al, 2004) or increased prolactin levels (Roke et al, 2012), is also commonly associated with DE and retrograde ejaculation (Madhusoodanan and Brenner, 1996; Raja, 1999). Retrograde ejaculation associated with antipsychotics is thought to be due to antagonistic effects on the α -adrenergic system at the level of the bladder neck (Holtmann et al, 2003).

Treatment of Male Pelvic Cancers

Overall quality of life and sexual functioning have evolved as key issues in the management of patients with cancer. Because of modern surgical techniques, improved quality of drugs for chemotherapy, and modern radiation techniques, more patients can be successfully treated without largely compromising sexual functioning.

Prostate Cancer

Prostate cancer has become the most common nonskin malignancy in men in Western countries. External-beam radiotherapy (EBRT) and brachytherapy (BT) are, together with the open or robotic radical prostatectomy (RP/RALP), the most common and effective treatments for localized prostate cancer. Despite the introduction of very modern radiotherapy (RT) techniques, sexual functioning after prostate cancer treatment remains problematic for many patients. **After RP/RALP, men no longer ejaculate, but maintain a sense of orgasm** that can vary from less to more intense than preoperatively and may experience arousal urinary incontinence or climacturia—that is, urinary incontinence at orgasm.

Ejaculatory disturbances after RT of prostate cancer were reported as early as the 1980s (Van Heeringen et al, 1988). More recent

studies have evaluated the impact of RT on sexual desire, ejaculation, and orgasm. **After EBRT, a decline in sexual desire was reported by 43% of 64 patients and a decreased frequency of orgasm by 57%; all men reported a decrease in ejaculate volume (Helgason et al, 1995).** Using a validated questionnaire, Borghede and Hedelin (1997) reported a decrease in the ability to ejaculate in 56% of the patients. Good prognostic factors for sexual functioning preservation after RT were low age and higher frequency of intercourse.

Early RT studies also assessed sexual functioning. Herr (1979) reported already in 1979 on 51 patients treated with retropubic iodine-125 seeds, with loss of ejaculate experienced by 6% of the patients. In a later study, dry ejaculation was reported by 16% of the patients after BT (Kwong et al, 1984). In both studies, all patients had previously undergone a transurethral resection of the prostate (TURP). For the first time a discomfort with ejaculation was mentioned in two studies (up to 25% of the patients) (Kleinberg et al, 1994; Arterbery et al, 1997). This result is quite common in clinical practice after BT, because of edema of the prostate possibly reducing the elasticity of the urethra and inducing discomfort with ejaculation. In some patients, discomfort with ejaculation did not disappear even 18 to 24 months after BT (Beckendorf et al, 1996). Also, decreased interest in sex, sexual desire, and libido was mentioned in up to 50% of the patients evaluated (Beckendorf et al, 1996; Arterbery et al, 1997; Borghede and Hedelin, 1997; Joly et al, 1998).

Several studies on the cause of post-RT decreased libido and ejaculatory disorders have been reported. Daniell and associates (2001) studied retrospectively levels of testosterone and other hormones after RT of prostate cancer. Testosterone was found to be low 3 to 8 years after EBRT, with lower levels found in older patients. Although testes are very sensitive to radiation, spermatogenesis is more easily affected than androgen productions. The radiation dose calculated in the testes of men irradiated for prostate cancer is only 3% to 8% of the dose that could possibly affect androgen production and could explain a decrease in testosterone. A TURP carries a high incidence of retrograde ejaculation because it is thought to disrupt the closure mechanism of the vesical neck; this could explain ejaculatory disturbances in most patients after previous TURP.

Rectal Carcinoma

Not much is known about sexual functioning after RT of rectal carcinoma. Preoperative RT for rectal cancer has been associated with a reduction in the rate of local relapse and possibly an advantage in survival. Preoperative RT with the total mesorectal excision in low-stage rectal cancer has become a common procedure in Europe. **A sharp dissection of the mesorectum associated with visualization and preservation of the pelvic autonomic nerve leads to excellent results regarding erectile and ejaculatory functioning.** Only one study has specifically studied the effects of preoperative RT for rectal carcinoma on male sexual functioning and concluded that it may impair male sexual functioning (Bonnell et al, 2002). However, numbers were too small to draw final conclusions.

Testicular Cancer

Germ cell tumors of the testis are relatively rare, accounting for approximately 1% of all male cancers. The long-term survival for early disease approaches 100%. Because testicular cancer affects mainly young men in their sexual and fertile life, sexual functioning and ejaculatory disorders are particularly important. The side effects of retroperitoneal lymph node dissection (RPLND) for residual mass after chemotherapy for nonseminomatous cancer are better documented than sexual sequelae of elective abdominal RT for seminoma. **Anejaculation occurs in the majority of the patients in non-nerve-sparing techniques.** As a result of careful anatomic studies, the technique of RPLND has been modified with nerve sparing so that antegrade ejaculation is now maintained in 80%

TABLE 29-3 Correlation of Erection, Ejaculation, and Intercourse with Level and Severity of Spinal Cord Injury

CORD LESION		REFLEXOGENIC ERECTIONS (%)	PSYCHOGENIC ERECTIONS (%)	SUCCESSFUL COITUS (%)	EJACULATION (%)
Upper motor neuron	Complete	92	9	66	1
	Incomplete	93	48	86	22
Lower motor neuron	Complete	0	24	33	15
	Incomplete	0	1	100	100

From Comarr AE. Sexual function among patients with spinal cord injury. *Urol Int* 1970;25:134–68.

to 100% of patients (van Basten et al, 1997). Libido and orgasm seem to be normal in these patients.

After RT, deterioration in sexual functioning has been reported in 1% to 25% of the patients (Schover et al, 1986; Tinkler et al, 1992; Jonker-Pool et al, 1997; Caffo and Amichetti, 1999; Incrocci et al, 2002). Tinkler and colleagues (1992) reported on 237 patients after orchiectomy and abdominal RT and compared these data to 402 age-matched controls. In almost all parameters studied, including erection, ejaculation, and libido, patients scored less than controls (reduction in orgasm, in libido, and interest in sex). Specifically, there was no difference in the ability to ejaculate during sexual activity, but the patients undergoing RT reported a noticeable reduction in the amount of semen compared to before treatment. Caffo and Amichetti (1999) evaluated toxicity and quality of life in 143 patients treated for early-stage testicular cancer. Of these, 23% reported a decreased libido, 27% problems with getting an orgasm, and 38% ejaculation disturbances, including PE. A decrease in sexual desire, orgasm, and volume or semen was negatively correlated with age (Schover et al, 1986). Jonker-Pool and associates (1997) reported on three groups of patients, after RT, wait and see, and chemotherapy. Patients undergoing RT reported decreased libido in 22% compared to 12% in the wait-and-see group and 30% in the chemotherapy group. Decrease or absence of ejaculate was reported in 15%, 7%, and 21% in the three groups, respectively; decreased orgasm was found in 15%, 12%, and 30%, respectively. Although the differences were not statistically significant, in the RT group, ejaculation and orgasm disturbances were higher than in the wait-and-see group. Similar results were reported by Arai and coworkers (1997). PE was reported in up to half of the patients (Arai et al, 1997; Incrocci et al, 2002), but it was the same as recalled before treatment (Incrocci et al, 2002).

The superior hypogastric plexus is responsible for ejaculation and is mediated by the sympathetic system; it is a fenestrated network of fibers anterior of the lower abdominal aorta. The hypogastric nerves exit bilaterally at the inferior pole of the superior hypogastric plexus and have connections with the S1 to S2 roots. Normal emission requires integrity of this system. During RPLND, these nerves are difficult to recognize and might be damaged, resulting in decreased semen volume or dry ejaculation. Pathways for ejaculation are included in the RT fields for rectal and prostate carcinomas. Damage of the sympathetic nerves could be caused by radiation, but the dose does not seem enough to completely explain the dysfunction. Orgasm is even more complex than ejaculation, because it is also affected by cortical input.

Neurologic Disorders

Degeneration of penile fast-conducting afferent nerves and pacinian corpuscles in the aging male, diabetic autonomic neuropathy, multiple sclerosis, and spinal cord injury are often associated with DE/anejaculation.

Spinal Cord Injury

The ability to ejaculate is severely impaired by spinal cord injury (SCI). Bors and Comarr highlighted the impact of the level and completeness of SCI on the postinjury erectile and ejaculatory

capacity (Bors and Comarr, 1960; Comarr, 1970) (Table 29-3). Unlike erectile capacity, the ability to ejaculate increases with descending levels of spinal injury. Fewer than 5% of patients with complete upper motor neuron lesions retain the ability to ejaculate. Ejaculation rates are higher (15%) in patients with both lower motor neuron lesions and an intact thoracolumbar sympathetic outflow. Approximately 22% of patients with an incomplete upper motor neuron lesion and almost all men with incomplete lower motor neuron lesions retain the ability to ejaculate. In patients capable of successful ejaculation, the sensation of orgasm may be absent and retrograde ejaculation often occurs.

Several techniques for obtaining semen in men with SCI with ejaculatory dysfunction have been reported. Vibratory stimulation is successful in obtaining semen in up to 70% of men with SCI (Brindley, 1984). The use of electroejaculation to obtain semen by electrical stimulation of efferent sympathetic fibers of the hypogastric plexus is an effective and safe method of obtaining semen. Brindley (1986) reported that 71% of men with SCI who underwent electroejaculation achieved ejaculation. However, both vibratory stimulation and electroejaculation are associated with a significantly high risk for autonomic dysreflexia. Pretreatment with a fast-acting vasodilator such as nifedipine minimizes the risk for severe hypertension, should autonomic dysreflexia occur with either form of treatment (Steinberger et al, 1990).

Semen collected from men with SCI is often initially senescent and of poor quality with a low sperm count and reduced sperm motility but may improve with subsequent ejaculations. This poor semen quality may be due to chronic urinary tract infection, dilution of sperm content with urine, chronic use of various medications, elevated scrotal temperature as a result of prolonged sitting, and stasis of prostatic fluid. Testicular biopsies in men with SCI demonstrate a wide range of testicular dysfunction including hypospermatogenesis, maturation arrest, atrophy of seminiferous tubules, germinal cell hypoplasia, interstitial fibrosis, and Leydig cell hyperplasia. In addition, prostatitis secondary to prolonged catheterization, epididymitis, and epididymo-orchitis can precipitate obstructive ductal lesions and testicular damage. Ohl and associates (1989) reported that sperm density and motility were higher in those with incomplete lesions. In a recent collective analysis of 40 paraplegic patients, 22 successfully produced pregnancies by natural insemination or assisted reproductive techniques (Dahlberg et al, 1995).

Congenital Disorders

Typical congenital problems include müllerian duct obstruction, caused by failure of complete absorption of müllerian duct remnants in males; wolffian duct abnormalities, which may compromise vas deferens, ejaculatory duct, and seminal vesicle functioning; and prune belly syndrome.

Infective Disorders

Sexually transmissible infections such as gonorrhea or nonspecific urethritis can produce cicatrization and obstruction anywhere in the male reproductive tract, especially if treatment is delayed. Urinary infection, especially if complicated by epididymitis, also

can produce obstruction that may be situated at the ejaculatory duct level. Schistosomiasis is endemic in large parts of Africa and is seen with increasing frequency in tourists returning from Africa who have contracted the disease while enjoying water sports. The disease may manifest with hemospermia (McKenna et al, 1997), and fibrosis and calcification may lead to genital obstruction. Genitourinary tuberculosis can cause great damage to the male reproductive tract, and because healing occurs with calcification, the lesions may be irreparable.

Evaluation of Men with Delayed Ejaculation

Evaluation of men presenting with DE or anejaculation should include a **full medical and sexual history, a focused physical examination, determination of serum testosterone levels, and any additional investigations suggested by these findings.**

Assessment begins by determining whether DE is lifelong or acquired, global or situational (Box 29-3). Evaluation includes establishment of how often a man can ejaculate during intercourse and the time elapsed between penetration and ejaculation, the IELT. If ejaculation fails to occur, the duration of thrusting before suspension of intercourse, the reasons for suspension of intercourse (e.g., fatigue, loss of erection, a sense of ejaculatory futility, or partner request), and whether ejaculation can occur during postcoital

BOX 29-3 Recommended and Optional Questions to Establish the Diagnosis of Delayed Ejaculation (DE) and Direct Treatment

RECOMMENDED QUESTIONS FOR DIAGNOSIS OF DE For Diagnosis

How often can you ejaculate during sexual intercourse?
During intercourse, how long after penetration does it take for you to either ejaculate or stop intercourse?
When you cannot ejaculate during sexual intercourse, how often do you feel that you are close to ejaculation?
If you cannot ejaculate, why do you stop intercourse?
Do you ever feel that you have ejaculated but fail to release semen?
Do you feel bothered, annoyed, and/or frustrated by your DE?
How often can you ejaculate during masturbation by yourself or with your partner?

OPTIONAL QUESTIONS

Differentiate Lifelong and Acquired DE

When did you first experience DE?
Have you experienced DE since your first sexual experience on every/almost every attempt and with every partner?

Assess Erectile Function

Is your erection hard enough to penetrate?
Do you have difficulty in maintaining your erection during intercourse?

Assess Relationship Impact

How upset is your partner with your DE?
Do you or your partner avoid sexual intercourse?
Is your DE affecting your overall relationship?

Previous Treatment

Have you received any treatment for your DE previously?

Impact on Quality of Life

Do you feel anxious, depressed, or embarrassed because of your DE?

self- or partner-assisted masturbation must be determined. The presence or absence of premonitory ejaculatory sensation during intercourse or masturbation suggests achievement of sufficient arousal to almost attain the ejaculation threshold. Variables that improve or worsen performance are noted. The man's ability to relax, sustain, and heighten arousal and the degree to which he can concentrate on sensations are noted.

The presence and extent of patient, partner, or interpersonal related negative psychological consequences such as bother, distress, frustration, or the avoidance of sexual contact should be established. The frequency of intercourse and the identity of the initiator of sexual contacts are useful surrogate measures for these negative psychological consequences. The quality of the nonsexual relationship also should be explored.

In men with acquired DE, previous illness, surgery, medications, or life events or circumstances should be reviewed. The events may include a variety of life stressors and other psychological factors (e.g., after his wife's mastectomy the man is afraid of hurting her and therefore is only partially aroused). Societal and religious attitudes that may interfere with excitement are noted, such as the "spilling of seed as a sin."

A **focused physical and genital examination** to determine whether the testes and epididymes are normal and whether the vasa are present or absent on each side, supported by a screening morning total testosterone level and any other hormonal or imaging investigations indicated by either history or physical examination, will identify or exclude organic disease. Digital rectal examination to determine prostate size, anal sphincter tone, and quality of the bulbocavernosus reflex is indicated in most men, with the exception of young men with situational and clear psychogenic IE. The presence of a neuropathy may require electrophysiologic evaluation of neural pathways controlling ejaculation, pudendal somatosensory and motor evoked potentials, sacral reflex arc testing, and sympathetic skin responses.

The occurrence of orgasm in the absence of prograde ejaculation suggests retrograde ejaculation and can be confirmed by the presence of spermatozoa in postmasturbation first-void urine. If the cause of DE is unclear, culture of expressed prostatic secretion and urine, urine cytology, and serum prostate-specific antigen will exclude prostatitis and bladder and prostatic cancer. Ultrasound scan of the testicles and epididymes may define any local disease.

Patients with unilateral or bilateral ejaculatory duct obstruction or congenital absence of vasa usually present with thin/runny low-volume semen, aspermia, and infertility. Seminal analysis demonstrates azoospermia or oligospermia with low concentration of fructose and a low pH. Ultrasound scanning of the entire urinary system and referral to a urologist is indicated because coexisting renal anomalies may be present. Bilateral absence or malformation of the vasa may be associated with the cystic fibrosis gene (Mickle et al, 1995).

Treatment of Men with Delayed Ejaculation or Anejaculation

Figure 29-4 is a flow chart for the management of DE (Rowland et al, 2010). Treatment should be cause specific, address the issue of infertility in men of reproductive age, and may include **patient/couple psychoeducation and/or psychosexual therapy, pharmacotherapy, or integrated treatment.** Men/partners of reproductive age undergoing pelvic surgery should be informed of the risk for infertility as a result of anejaculation and the availability of sperm harvesting and assisted reproductive techniques.

Whether a clear pathophysiologic cause is present or absent, patients might be counseled to consider **lifestyle changes, including enjoying more time together to achieve greater intimacy, minimizing alcohol consumption, making love when not tired, and practicing techniques that maximize penile stimulation such as pelvic floor training (Waldinger and Schweitzer, 2005).** Neuro-pathic DE is usually irreversible, and therefore the patient might be counseled to seek alternative methods to achieve mutual sexual satisfaction with his partner.

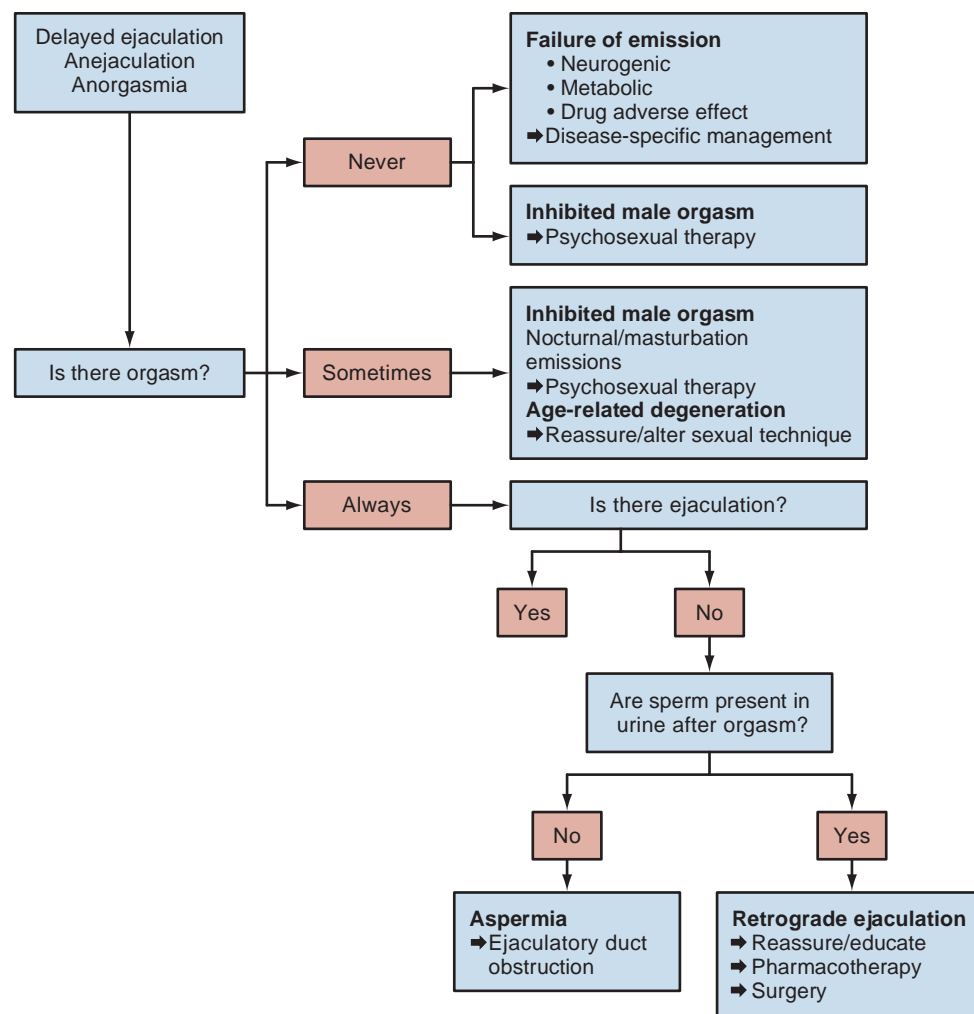


Figure 29-4. Algorithm for the office management of delayed ejaculation, anejaculation, and anorgasmia.

Psychological Strategies in the Treatment of Delayed Ejaculation

If organic and pharmacologic causes have been eliminated, referral to an expert psychosexual therapist is usually indicated to evaluate the causative psychological and behavioral issues. Beneficial effects through psychotherapy depend on the severity of the DE and the individual's receptiveness to engage in counseling and adhere to the counselor's recommendations.



Additional information on the role of psychosexual therapy in the management of DE is available on the Expert Consult website.

Pharmacotherapy in the Treatment of Delayed Ejaculation

Drug treatment of DE or IE ejaculation has met with limited success (Table 29-4). These drugs facilitate ejaculation by either a central dopaminergic, antiserotonergic, or oxytocinergic mechanism of action or a peripheral adrenergic mechanism of action. However, no drugs have been approved by regulatory agencies for this purpose and most drugs that have been identified for potential use have limited efficacy, impart significant side effects, or are as yet considered experimental in nature. Results are relatively poor in men with psychogenic DE and neuropathic DE.

α_1 -Adrenergic receptor agonists such as on-demand precoital pseudoephedrine (60 to 120 mg 1 to 2 hours before intercourse) or the selective norepinephrine reuptake inhibitor (SNRI) antidepressant reboxetine (4 to 8 mg daily) which inhibits synaptic noradrenaline reuptake have limited efficacy. The antihistamine cyproheptadine, a central serotonin antagonist, is anecdotally

TABLE 29-4 Drug Therapy for Delayed Ejaculation and Anejaculation

DRUG	DOSAGE	
	AS NEEDED	DAILY
Cabergoline	—	0.5-2 mg every 3 days
Amantadine	100-400 mg (for 2 days before coitus)	100-200 mg twice daily
Pseudoephedrine	60-120 mg (1-2 hr before coitus)	—
Reboxetine	—	4-8 mg
Oxytocin	24 IU intranasal during coitus	—
Bupropion	—	150 mg/day or twice daily
Buspirone	—	5-15 mg twice daily
Cyproheptadine	4-12 mg (3-4 hr before coitus)	—

The partner and the quality of the relationship warrant exploration. Numerous psychotherapeutic processes are described for the management of DE or IE (McCarthy, 1981; Apfelbaum, 1989) and some appear to be effective, but none has been properly evaluated in large-scale samples (McMahon et al, 2006b). Among these strategies are: (1) sex education; (2) reduction of goal-focused anxiety; (3) increased, more genitally focused stimulation; (4) patient role-playing an exaggerated ejaculatory response on his own and in front of his partner; (5) masturbatory retraining; and (6) realignment of sexual fantasies and arousal strategies.

Most current sex therapy approaches to DE emphasize the importance of masturbation in the treatment of DE, with most of the focus on “masturbatory retraining” integrated into sex therapy (Kaplan, 1995). Typically, self-stimulation techniques incorporating fantasy can be used to achieve incremental increases in arousal that eventually enable orgasm. Fantasy can serve the purpose of increasing arousal and blocking inhibiting thoughts that might otherwise interfere. Once the man’s ejaculatory ability is established through masturbation, the same skill set can be incorporated into sex with the partner.

An important component in the treatment of any type of DE is the removal of the “demand” (and thus anxiety-producing) characteristics of the situation (Apfelbaum, 1989). “Ejaculatory performance” anxiety can interfere with the erotic sensations of

genital stimulation and may result in levels of sexual excitement insufficient for climax (although they may be more than adequate to maintain an erection). To reduce anxiety, treatment may include recognition of the overeagerness of men with DE to please their partners, validation of (though not necessarily encouragement of) the man’s autosexual orientation, removal of stigmas suggesting hostility or withholding toward their partner, and general anxiety reduction techniques such as relaxation and desensitization.

The partner also needs to collaborate in the therapeutic process, finding ways to enhance the man’s arousal and accepting the use of erotica and various (harmless) sexual fantasies that also might be incorporated into the couple’s lovemaking. Furthermore, because interventions used in the treatment of DE may be experienced by the female partner as mechanistic (e.g., using a stepwise program) and insensitive to her sexual needs, the therapeutic challenge is to facilitate the rapport between the partners, while maintaining a therapeutic alliance with both partners and simultaneously optimizing his response to her manual, oral, and vaginal stimulation.

The success of treating DE is difficult to assess from the literature (McMahon et al, 2006b) because the evidence on the effectiveness of various treatments is limited (Heiman and Meston, 1997) and both successful and unsuccessful case reports have been cited (Apfelbaum, 1989).

associated with the reversal of anorgasmia induced by the SSRI antidepressants, but no controlled studies have been reported (McCormick et al, 1990; Ashton et al, 1997). These studies suggest an effective dose range of 4 to 12 mg 3 to 4 hours before intercourse, with administration on a chronic or on-demand basis. However, significant dose-related sedative effects are likely to diminish its overall efficacy.

Amantadine, an indirect stimulant of dopaminergic nerves both centrally and peripherally, has been reported to stimulate sexual behavior and ejaculation in SSRI antidepressant-induced anorgasmia when administered on demand (100 to 400 mg 2 days before coitus) or chronically (100 to 200 mg twice daily) (Balogh et al, 1992).

A variety of other pharmacologic agents, including **cabergoline**, **bromocriptine**, **bupropion**, and **buspirone** have been anecdotally reported as potential DE pharmacotherapy, despite an absence of large-population RCTs. Of interest is the recent single case report of the **intracoital administration of intranasal oxytocin** in a case of treatment-resistant anorgasmia (Ishak et al, 2008). However, in the absence of robust RCT data, oxytocin cannot be recommended as a treatment for DE.

KEY POINTS: DELAYED EJACULATION

- The causes of DE and anejaculation are manifold.
- Failure of ejaculation can be a lifelong problem (25%) or an acquired problem (75%). It may be global and occur in every sexual encounter or be intermittent or situational.
- Treatment of men with DE should be cause specific and address the issue of infertility in men of reproductive age.
- Drug treatment of men with DE or anejaculation has had limited success.

RETROGRADE EJACULATION

Antegrade (normal) ejaculation requires a closed bladder neck (and proximal urethra). **Surgical procedures that compromise the bladder neck closure mechanism may result in retrograde ejaculation.** Transurethral incision of the prostate (TUIP) results in retrograde ejaculation in 5% (Hedlund and Ek, 1985) to 45% (Kelly et al, 1989) of patients and is probably related to whether one or two incisions are made and whether the incision includes primarily the bladder neck or extends to the level of the verumontanum. The importance of contraction of the urethral smooth muscle at the level of the verumontanum has been hypothesized to be important in preventing retrograde ejaculation (Reiser, 1961). TURP carries a higher incidence of retrograde ejaculation than does TUIP. The reported incidence of retrograde ejaculation after TURP ranges from 42% (Edwards and Powell, 1982) to 100% (Quinlan et al, 1991). Although these men may have some antegrade ejaculation and usually experience orgasmic sensation, both events may be reduced as part of the changes that occur in the male sexual response as a man ages. Retrograde ejaculation is more common in diabetes mellitus than in age-matched controls ($P < .01$), has been reported in 30% of men with diabetes mellitus, and is not statistically associated with duration of diabetes mellitus, BMI, waist circumference, or hemoglobin A1c or total testosterone levels (Waldinger et al, 2005a).

Retrograde ejaculation and failure of emission can be distinguished by examination of a postmasturbatory specimen of urine for the presence of spermatozoa and fructose. The finding of more than 5 to 10 sperm per high-power field in a postejaculation urine specimen confirms the presence of retrograde ejaculation. In patients with low-volume ejaculate, the finding of more sperm in the urine than in the antegrade ejaculate indicates a significant component of retrograde ejaculation (Sigman and Howards, 1998).

Treatment of Retrograde Ejaculation

Retrograde ejaculation can be surgically treated with bladder neck reconstruction but results remain consistently poor (Abrahams et al, 1975; Lipshultz et al, 1981). Drug treatment is the most promising approach. As mentioned earlier, α -adrenergic sympathetic nerves mediate both bladder neck closure and emission. Several sympathomimetic amine agents have been described as useful with mixed results (Kedia and Markland, 1975). These drugs include **pseudoephedrine**, **ephedrine**, **midocrine**, and **phenylpropanolamine**. These agents work by stimulating the release of noradrenaline from the nerve axon terminals but also may directly stimulate both α - and β -adrenergic receptors. The most useful is pseudoephedrine, which is administered at a dose of 120 mg 2 to 2.5 hours precoital. The TCA **imipramine**, which blocks the reuptake of noradrenaline by the axon from the synaptic cleft is also occasionally useful. The usual dose is 25 mg twice daily. The current feeling is that long-term treatment with imipramine is likely to be more effective. Although medical treatment may not always produce normal ejaculation, it may result in some prograde ejaculation. In patients who do not achieve antegrade ejaculation with either surgery or medication, sperm retrieval and artificial insemination is an alternative approach. The basic method of sperm retrieval involves recovery of urine by either catheter or voiding after masturbation and then centrifugation and isolation of the sperm.

KEY POINTS: RETROGRADE EJACULATION


- TURP and diabetic autonomic neuropathy are the most common causes of retrograde ejaculation.
- Retrograde ejaculation and failure of emission can be distinguished by examination of a postmasturbatory specimen of urine for the presence of spermatozoa and fructose.
- Pharmacotherapy is associated with variable degrees of success and includes agents such as pseudoephedrine, midodrine, and imipramine.

PAINFUL EJACULATION

Painful ejaculation, or **odynorgasmia**, is a poorly characterized syndrome. It may be associated with **urethritis**, **BPH**, **acute or chronic prostatitis**, **CPPS**, **seminal vesiculitis**, **seminal vesicular calculi**, or **ejaculatory duct obstruction** (Weintraub et al, 1993; Corriere, 1997; Kochakam et al, 2001; Nickel et al, 2005). Often, no obvious etiologic factor can be found. **Painful ejaculation occurs in 17% to 23% of men with LUTS/BPH** (Frankel et al, 1998; Tubaro et al, 2001; Brookes et al, 2002; Vallancien et al, 2003). Men with BPH and painful ejaculation have more severe LUTS and report greater bother. In addition, they report a higher incidence of ED and a reduced ejaculation volume, compared to men with LUTS only (Rosen et al, 2003). Treatment of men with LUTS with α -blocking drugs may be associated with painful ejaculation. A lower incidence of pain has been reported with the uroselective α_1 -blocking drug, alfuzosin (van Moorselaar et al, 2005). Management should focus on treatment of the underlying cause.

POSTORGASMIC ILLNESS SYNDROME

POIS is a recently described but poorly characterized “orphan” disease comprising a **collection of symptoms that include severe myalgia and fatigue associated with a flulike state that occurs within 30 minutes of orgasm.**

Additional information on POIS is available on the Expert Consult website. 

People engage in sexual activity for a number of reasons. The feelings of calmness, contentment, and sedation after orgasm have been described as inducements for intercourse, particularly in men (Meston and Buss, 2007).

In 2002, Waldinger and Schweitzer described a collection of symptoms following orgasm in two males that were qualitatively similar but more extreme and prolonged than the expected state of relaxation and somnolence that would normally occur. The symptoms consisted of severe myalgia and fatigue associated with a flulike state after orgasm. The symptoms were severe enough that the individuals avoided ejaculating to try to prevent the symptoms. Waldinger and Schweitzer (2002) named this cluster of symptoms after ejaculation postorgasmic illness syndrome (POIS). To date, POIS is a rarely described syndrome, and despite having a significant impact on quality of life for individual sufferers, little is known about its epidemiology and cause.

Although POIS may appear to be an orphan disease, it may be more common than reported in the literature. In the *New York Times* in January 2009, Richard Friedman, a New York City psychiatrist, describes several patients who experience low mood and somatic symptoms after orgasm, whose symptoms improved with the use of SSRIs. Evidence of many more undiagnosed individuals with POIS is seen in the existence of an extremely active Internet forum in which more than 100 people have self-reported symptoms of POIS.

More recently, Waldinger and colleagues (2011b) reported 45 males with suspected POIS in whom symptoms did not occur during sexual contact without ejaculation. POIS symptoms started within 30 minutes after ejaculation in 87% of men. All men reported a gradual intensity peak of symptoms, most of which were experienced on day 2. Reports of POIS were categorized in seven clusters of symptoms: (1) a sensation of a flulike state; (2) extreme fatigue or exhaustion; (3) weakness of musculature; (4) experiences of feverishness or perspiration; (5) mood disturbances and/or irritability; (6) memory difficulties, concentration problems, incoherent speech; and (7) congestion of nose or watery nose, itching eyes. All symptoms occur immediately (e.g., seconds), soon (e.g., minutes), or within a few hours after ejaculation that is initiated by coitus, and/or by masturbation, and/or spontaneously (e.g., during sleep). Symptoms occur always or nearly always—that is, in more than 90% of ejaculation events. Most of these symptoms last for approximately 2 to 7 days and disappear spontaneously.

Waldinger and associates (2011b) proposed a type 1 hypersensitivity immunogenic mechanism as local allergic reactions of eyes and nose were reported in 44% and 33% of subjects, 58% had an atopic constitution, and 88% had a positive skin-prick test with their own semen. He suggested that autologous seminal peptides or peptides released from the disrupted urethral lining cells contact the inner mucosal epithelium of the urethra, are recognized and taken up by dendritic cells in the epithelium, and migrate to the T-cell zones of lymph nodes, where contact between the seminal fluid antigen(s) and naive T cells initiate the cascade of events of a hypersensitivity reaction. This may parallel the reports of an alloallergic reaction to specific protein fractions of seminal plasma in female partners of males if symptoms are localized but may include generalized urticaria and, rarely, anaphylactic shock (Ohman et al, 1990; Lee et al, 2008).

Of particular interest was the observation that 56% of this POIS study population also had lifelong PE with an IELT of 1 minute or less. In men with POIS, the relative risk for PE is 22.4-fold higher than in healthy individuals. This may be related to forced abstinence of, and therefore low frequency of, sexual activity.

In a third study, two men with POIS with positive autologous semen skin testing underwent a prolonged hyposensitization program with multiple subcutaneous injections of autologous semen and reported a gradual reduction of complaints and 60% and 90% amelioration of POIS complaints at 31 and 15 months, respectively (Waldinger et al, 2011a).

KEY POINTS: POST ORGASMIC ILLNESS SYNDROME

- The symptoms of POIS occur after ejaculation and are severe myalgia, fatigue associated with a flulike state, nasal congestion, and itching eyes.
- POIS symptoms commence within 30 minutes of ejaculation in 87% of men and increase in intensity to a peak on day 2.
- A type 1 hypersensitivity immunogenic reaction has been proposed as the underlying mechanism.
- A prolonged hyposensitization program with multiple subcutaneous injections of autologous semen has been suggested as a possible treatment.

CONCLUSION

Recent epidemiologic and observational research has provided new insights into PE and the associated negative psychosocial effects of this dysfunction. The recently developed multivariate evidence-based ISSM definition of lifelong and acquired PE provides the clinician a more discriminating diagnostic tool and should form the basis of the office diagnosis of lifelong PE.

Although insufficient empirical evidence exists to unequivocally identify the cause of PE, limited evidence suggests that lifelong PE may have a genetic basis and that acquired PE is most often due to sexual performance anxiety, psychological or relationship problems, and/or ED and to a lesser extent, chronic prostatitis, CPPS or hyperthyroidism.

Current evidence suggests that psychosexual cognitive behavioral therapy has a limited role in the contemporary management of PE and confirms the efficacy and safety of oral SSRI drugs and topical anesthetic drugs. It is likely that dapoxetine, despite its modest effect on ejaculatory latency, has a place in the management of PE, which will eventually be determined by market forces once the challenge of regulatory approval has been met. Treatment with tramadol, intracavernous injection therapy, or alternative methods of drug delivery cannot be recommended until the results of large, well-designed RCTs are published in major international peer-reviewed medical journals.

DE and anejaculation are more common as men age and have manifold organic and psychogenic causes. They have a significant impact on sexual fulfilment for both the man and his partner and may result in infertility. Treatment of men with DE represents one of the most significant challenges in sexual medicine and outcome results are often disappointing.

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The complete reference list is available online at www.expertconsult.com.



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Types of Prostheses

Preoperative Patient Evaluation and Preparation

Surgical Preparation and Approach

Postoperative Care

Complications

Special Cases

Patient Satisfaction

Conclusion

Penile prostheses have been used to treat erectile dysfunction (ED) since the mid 1970s (Scott et al, 1973; Small et al, 1975). In the United States, approximately 20,000 penile prosthetic devices are implanted annually, accounting for 75% of the global market (Mulcahy and Wilson, 2006; Garber, 2008). The primary goal of penile implant surgery is to restore erections that most closely resemble normal function in terms of rigidity, girth expansion, and length expansion. Because ED is often associated with feelings of inadequacy, disappointment, and loss of self-confidence, an additional goal of implant surgery is to improve a patient's quality of life and self-esteem. **Men who experience ED constantly think about their dysfunction. After prosthetic surgery for ED, they experience a sense of freedom that is very similar to being cured. This feeling is not reported by men who use other temporary treatment options for ED (Rajpurkar and Dhabuwala, 2003).**

Indications for a penile prosthetic device include failure or rejection of more conservative therapy for ED, Peyronie disease in which ED and erectile deformity coexist, irreversible organic etiology of ED, penile fibrosis, post priapism and unresponsive to more conservative treatment, phalloplasty following radical penile cancer surgery or gender change, and psychological impotence after failure of all other treatment (Anderson et al, 2007; Al-Enezi et al, 2011). Prosthetic implants are considered the most effective method for obtaining an artificial erection in patients with ED who are unresponsive to or cannot tolerate other treatment (Bettocchi et al, 2010).

TYPES OF PROSTHESES

There are two broad categories of penile implants, semirigid rods and inflatable devices, both of which were introduced almost 40 years ago and have undergone significant design improvements since that time (Scott et al, 1973; Small et al, 1975). The devices in both categories can be used to achieve penile rigidity, but there are differences in cosmetic appearance, and semirigid rods do not permit flaccidity. **The selection of a device may depend on a physician's surgical experience, insurance coverage, and patient preference and anatomy and/or history.**

Semirigid Rods

Semirigid rods are paired, solid cylinders that fill each corpus cavernosum. They can be further subdivided into malleable and positional devices (Figs. 30-1 and 30-2). A malleable device has a central core that allows a patient to position the penis upward for sexual intercourse and downward at other times. A positional device incorporates a series of articulating polyethylene discs with a central

metal cable support, which make it better able to maintain upward and downward positions. Semirigid rods are typically available in several diameters and lengths. Advantages of these prostheses are that they are relatively inexpensive, easy to implant (although a larger incision of the tunica albuginea is required), and easy to use. They also have a relatively low mechanical failure rate. Drawbacks are that they simulate a constant erection, may be difficult to conceal, and do not increase penile girth (Jain and Terry, 2006; Montague, 2011). Also, with semirigid rods, the capsule of scar tissue that forms around the device loosens up over time, decreasing the quality of the erection. Because the elastic tunica albuginea wants to retract when stretched to the erect length, the distal tip of the rigid device is more likely to atrophy or migrate toward the distal portion of the glans and potentially to erode through the meatus (see Figs. 30-1 and 30-2).

Inflatable Prostheses

Inflatable prostheses are designed to approximate normal function more closely by permitting girth and length expansion during erection and penile flaccidity when not in use. They consist of two hollow intracorporeal cylinders, each of which fills a corpus cavernosum. The cylinders are inflated with saline solution to produce penile rigidity during sexual activity and are deflated after intercourse. Inflatable prostheses can be subdivided further into two-piece and three-piece devices. The two-piece device consists of the two cylinders and a scrotal pump (Fig. 30-3). Reservoirs in the proximal portion of the cylinders are prefilled with saline and preconnected to the pump via silicone tubing. Pressing a valve mechanism in the pump transfers the solution from the reservoirs into the distal, inflatable portion of each cylinder. Bending the cylinders down for several seconds activates a release valve that deflates the device by allowing the fluid to flow back to the reservoirs. Cylinders are typically available in several widths and lengths to permit a more customized fit. Rear tip extensions allow the length of a two-piece prosthesis to be further tailored to each patient.

The three-piece device consists of the two hollow cylinders, a scrotal pump, and a saline-filled reservoir (Fig. 30-4). Silicone tubing connects the cylinders to the pump and the pump to the reservoir. Repeatedly squeezing the pump transfers saline from the reservoir to the cylinders until adequate rigidity is achieved, and pressing a valve mechanism in the pump causes the fluid to flow back to the reservoir. Similar to the two-piece devices, three-piece devices are also typically available in several widths and lengths and come with optional rear tip extensions. One-touch release models and other more recent innovations in pump design facilitate deflation.



Figure 30-1. Coloplast Genesis malleable prosthesis. (Courtesy Coloplast Corp., Minneapolis, MN.)



Figure 30-3. Ambicor two-piece prosthesis. (Courtesy American Medical Systems, Minnetonka, MN.)



Figure 30-2. Spectra positional prosthesis. (Courtesy American Medical Systems, Minnetonka, MN.)



Figure 30-4. Coloplast Titan Zero Degree angle cylinders with Touch pump and reservoir with lockout valve prosthesis. (Courtesy Coloplast Corp., Minneapolis, MN.)

An advantage of a two-piece device over a three-piece device is that there is no need to implant a separate reservoir; this facilitates the surgery for the urologist and may be useful with patients in whom placement of the reservoir is extremely difficult because of colostomy, ileostomy, kidney transplant, or extensive pelvic surgery. A two-piece device also reaches full inflation with fewer squeezes of the pump. However, the pump is very small and hard, making it difficult for patients to manipulate. Also, implantation of a two-piece device requires a larger incision of the tunica albuginea. In comparison, a three-piece device acts and feels more like a natural erection. It is more rigid when inflated and is more flaccid when deflated (Fig. 30-5).

Initially, semirigid prostheses were more popular than inflatable devices, primarily because they were easier to implant and rarely required mechanical revision (Wilson and Mulcahy, 2006). However, this preference diminished as mechanical reliability improved. At the present time in the United States, 70% of patients are implanted with three-piece inflatable devices, 20% are implanted with two-piece devices, and 10% are implanted with semirigid rods. Elsewhere, approximately half of all patients are implanted with

semirigid rods, and half are implanted with inflatable devices, primarily owing to cost considerations (Mulcahy and Wilson, 2006).

PREOPERATIVE PATIENT EVALUATION AND PREPARATION

Although penile prosthetic surgery is a highly effective treatment for ED, it is an irreversible procedure accompanied by numerous risks, which makes careful patient evaluation and preparation critical. Thorough preoperative assessment and education can help ensure that a patient is a good candidate for the procedure. It also helps identify the best type of prostheses for any specific circumstance. See Table 30-1 for more details about selection of a prosthesis.

The patient's first visit should be informational in nature; the focus should not be on decision making. It is important that the patient understand the efficacy of the various treatment options available for ED and potential contraindications for penile prosthetic surgery (Box 30-1). Giving a patient the opportunity to

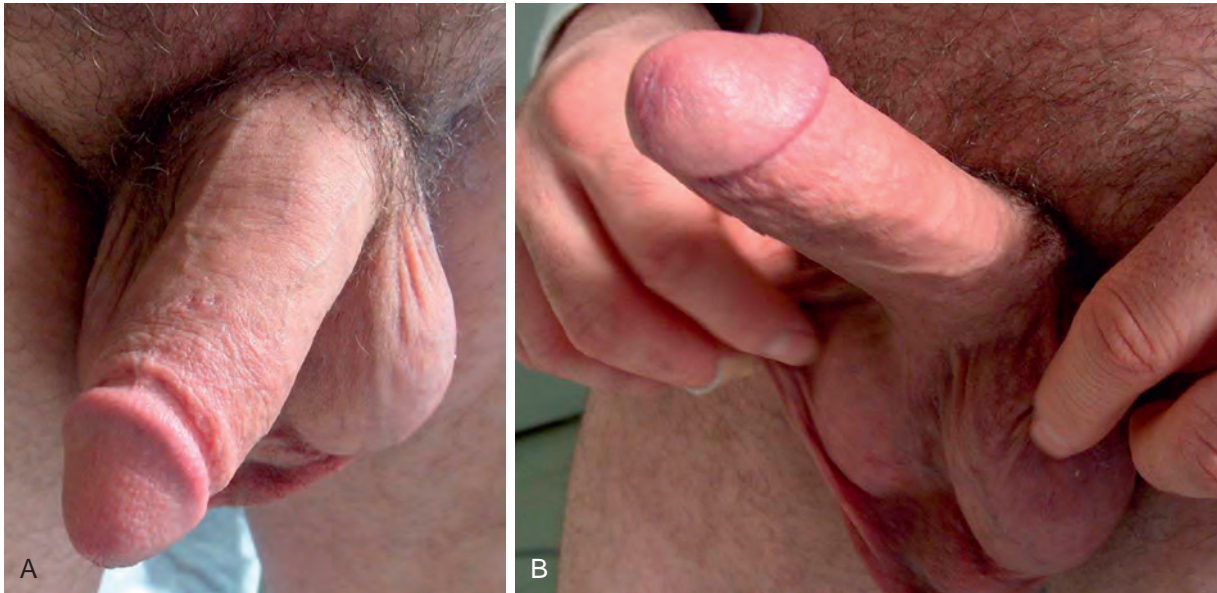


Figure 30-5. A and B, Patient with Coloplast Titan Zero Degree angle cylinders and Touch pump showing the flaccid and erect penis.

TABLE 30-1 Selection of a Prosthesis

CIRCUMSTANCE	RECOMMENDED PROSTHETIC	RATIONALE
Fibrosis (e.g., secondary to priapism)	Narrow-cylinder AMS CXR* or Coloplast Narrow†	Inadequate corporeal space
Peyronie disease/penile curvature	AMS CX*, Coloplast Titan†, or malleable	Allows girth expansion but no length expansion so will not exacerbate curvature
Limited manual dexterity or mentally disabled	Malleable or semirigid rods	Easier to manipulate
Penis length <20 cm	AMS CX*, AMS LGX*, or Coloplast Titan†	Allows for maximum amount of fluid transfer between cylinders and reservoir for best rigidity and flaccidity
Small narrower penis	AMS LGX*	Cylinder lengthens by 18% and narrow corporeal cavity prevents deformity of cylinders on inflation
Abdominoperineal resection Femora-femoral bypass Cystectomy with neobladder	Two-piece device—AMS Ambicor*	Avoids reservoir placement
Extensive abdominal/pelvic surgery Open and post-robotic prostatectomy	AMS Ambicor* or three-piece device—AMS CX or LGX with Conceal Reservoir*	Place reservoir in a submuscular location above the transversalis fascia
Neurologic impairment	AMS CX with soft cylinders	Lower risk of erosion
Atrophic tunica albuginea	AMS CX*	
Older patients with frail tissues and weak hands	AMS CX with Momentary Squeeze Pump*	AMS cylinders are softer, and Momentary Squeeze Pump is easier to deflate
Younger patients with larger, more robust penises	Coloplast Titan with Zero Degree Angle cylinders with Touch pump†	Rounder and wider shaft when cylinders are inflated Smaller, more discreet pump
Penis length >20 cm in length and >21 mm in girth	Coloplast Titan 20, 22 cm or XL 24-28 cm Zero Degree Angle cylinders†	Titan cylinders expand to 22 mm girth vs. 18 mm girth for AMS CX

*American Medical Systems (AMS), Minnetonka, MN.

†Coloplast Corp., Minneapolis, MN.

BOX 30-1 Potential Contraindications for Penile Prosthetic Surgery

Situational ED
 ED resulting from relationship conflict
 Potentially reversible ED
 Inability to follow instructions
 Hygiene issues and skin cleanliness
 Noncompliance with concurrent medication (e.g., for hypertension or diabetes)
 Spinal cord injury
 Uncontrolled diabetes mellitus

ED, erectile dysfunction.

From Garber BB. Inflatable penile prostheses for the treatment of erectile dysfunction: an update. *Expert Rev Med Devices* 2008;5(2):133–44; and Al-Enezi A, Al-Khadhari S, Al-Shaiji TF. Three-piece inflatable penile prosthesis: surgical techniques and pitfalls. *J Surg Tech Case Rep* 2011;3(2):76–83.

handle a sample prosthesis and see how it works facilitates actual use of the device after it is implanted (Bettocchi et al, 2010); however, seeing the entire three-piece device on the first visit can be intimidating and overwhelming. It is best for patients first to see a video and photos of implanted patients to appreciate the look and function of a prosthesis. Next, the patient can be given the opportunity to handle a model of the pump only, without having to handle the reservoir and cylinders. It is important to ensure patients understand that sensation, orgasm, and ejaculatory function are not altered by a penile prosthesis and that nothing is removed to insert the implant. On seeing the device, patients are often concerned about the size of the incision required to implant it, and they should be reassured that only a 1-inch incision is necessary.

A thorough review of the patient's medical, surgical, and sexual history is critical to evaluating the efficacy of previous nonsurgical treatment, selecting the most appropriate type of prosthesis, identifying contraindications, and mitigating risk factors for potential adverse events (Ulloa et al, 2008; Wilson and Mulcahy, 2006). For example, any detected infection should be eradicated before surgery, and glycemic control should be optimized in diabetic patients. Box 30-1 contains a list of potential contraindications for penile prosthetic surgery.

The appointment should also include a complete urologic examination, including a penile Doppler ultrasound study after intracorporeal injection of a vasodilator agent to assess severity of ED, vascular flow, tumescence, and penile anatomy. After a penile injection, the penis is more easily stretched, and abnormalities such as shortening, hourglass deformity, and curvature are revealed and can be evaluated. This is also a good time to measure and record the length of the stretched penis and show the patient what size he should expect from the implant. These measurements can be recorded on a flow sheet and made available during the surgery to confirm that intraoperative measurements of the penis with the cylinders inflated match the measurements obtained in the office.

Finally, informed consent should be obtained from the patient after a discussion that addresses the surgical procedure and postoperative recovery, potential complications (especially complications that may require surgical intervention), and expected outcome. Ensuring that the patient (and, ideally, his partner) has realistic expectations is essential to a positive outcome (Anderson et al, 2007). It is important for the patient to understand that the procedure is irreversible and that positioning the device permanently alters the corpora cavernosa, resulting in the loss of any preexisting erectile capability. Patients should also be made aware that the preoperative length of the fully stretched flaccid

penis is typically the maximal length that can be obtained after prosthetic surgery and that the procedure may result in a degree of penile shortening and glans softening (Montague and Angermeier, 2003).

To help reduce the incidence of postoperative infection, patients are instructed to wash with chlorhexidine soap for 3 days before the surgery. The American Urological Association also recommends preoperative administration of prophylactic antibiotics for both gram-positive and gram-negative organisms for any open procedures involving prosthetic implantation (Wolf et al, 2008). Finally, patients should be instructed to avoid taking aspirin and nonsteroidal anti-inflammatory drugs for 7 days before surgery because such medication can increase the risk of postoperative bleeding. Patients with drug-eluting stents or a history of coronary artery disease are exceptions to this rule and should continue taking low-dose aspirin (81 mg) including on the day of the surgery.

KEY POINTS: PREOPERATIVE PATIENT PREPARATION

- Patients are often concerned about the size of the incision required to implant the device and should be reassured that only a 1-inch incision is necessary.
- It is important the patient understands that the procedure is irreversible and that positioning the device permanently results in the loss of any preexisting erectile capability.
- Patients should know that the preoperative length of the fully stretched flaccid penis is typically the maximal length that can be obtained after prosthetic surgery.
- Ensuring that the patient (and, ideally, his partner) has realistic expectations is essential to a positive outcome.

SURGICAL PREPARATION AND APPROACH

The surgical approach varies depending on the surgeon's preference and on the type of prosthetic device implanted. This section focuses on implantation of a three-piece inflatable device because this type is most commonly used in the United States. The three-piece device can be inserted through a scrotal or infrapubic incision. Each approach offers the surgeon and the patient advantages and disadvantages. Reservoir placement is easier when choosing the infrapubic approach. More precise pump positioning and better cylinder input pump tube concealment are achievable through the scrotal approach, which is described in this section. When planning to implant a standard three-piece device (i.e., 12 to 14 mm), it is recommended also to have a narrower or semirigid device (i.e., 9 to 11 mm) available at the time of surgery; this provides the flexibility to use the narrower option if implanting a multicomponent device becomes difficult because of unanticipated anatomic constraints. For example, it is better to implant a narrower device than attempt vigorous dilation of a fibrotic, scarred corpora and risk urethral perforation. Over time, the narrower device will dilate the corpora, and it may be possible to replace it with a three-piece device 3 to 6 months later.

To the extent possible, it is important to minimize the duration of the surgery, decreasing the risk of infection. This can be facilitated by using a dedicated surgical instrument set that, along with sutures and other necessary equipment, is kept close at hand. The specific instruments, sutures, needles, and cylinder sizes that should be available in the operating room have been described elsewhere (Eid, 2003). It is critical that all instruments are thoroughly scrubbed of all potential debris before undergoing final sterilization. Infection risk is reduced further by using as few instruments as possible and limiting the extent to which they must be passed back and forth with the scrub nurse. Ideally, operating room traffic should be minimized, and laminar flow ventilation should be used to reduce surgical site infection further.

General, local, spinal, or regional anesthesia is administered at the discretion of the anesthesiologist. A benefit of spinal anesthesia

is that it blocks the parasympathetic and sympathetic nervous systems, causing penile dilation and facilitating the surgery. Blood flow to the legs is also increased, which decreases the risk of deep vein thrombosis. A disadvantage of spinal anesthesia is that it necessitates a longer stay in the recovery room and the placement of an indwelling urinary catheter, which needs to be removed within 24 to 48 hours. A risk with general anesthesia is that the typical cough reflex after extubation could potentially herniate the reservoir.

The patient is admitted for a penile implant on the day of surgery and discharged the same day. (Admission to an outpatient surgery center is preferable to hospital admission because the latter increases the risk of cross-contamination from sick patients.) The patient showers before surgery with an antiseptic chlorhexidine scrub and is placed in a supine position on the operating room table. The table should be flexed in a manner that elevates the pelvis and flattens the lower abdomen; this permits a more proximal exposure of the crura and stretches the lower abdominal muscles to provide countertraction for placement of the reservoir. The patient is shaved and undergoes a presurgical chlorhexidine soap scrub of the genital area. The skin is painted with a chlorhexidine/70% alcohol preparation, and intravenous antibiotics are administered to protect against gram-positive and gram-negative organisms, based on the profile of antibiotic-resistant bacteria most commonly found in the institution. An iodophor drape with a small fenestration is used to cover exposed skin while permitting access to the penis and scrotum. A Foley catheter is inserted, capped, and palpated to identify the urethra, which is then avoided for the remainder of the surgery. Finally, a Scott retractor is secured with tubing across the base of the penis. The use of large, blunt yellow hooks instead of the smaller, sharp blue hooks provides better exposure and minimizes the risk of damaging the device or surgical gloves.

From this point forward and depending on the surgeon's preference, it is possible to use a novel "no touch" surgical technique designed to reduce penile prosthesis infection (Eid et al, 2012). With this technique, all surgical instruments used to make the skin incision before cylinder placement are considered contaminated and removed from the surgical field, and everyone on the operating field who has touched skin replaces their surgical gloves (Fig. 30-6).

A study evaluating the no touch technique reported a 0.46% infection rate (Eid et al, 2012). However, regardless of the technique used, exposure of all of the components of the device to the patient's skin must be minimized because most penile prosthesis infections are caused by skin flora that attach to the device and are then introduced into the patient.

Cylinder Placement

A high scrotal approach on the median raphe, approximately 1 inch inferior to the junction with the penis, is preferable to the classic

penoscrotal approach because it allows the incision to be limited to 1 inch, which permits quick closure without scarring and less postoperative bleeding, swelling, and pain. This approach also facilitates access to the penis in obese or thin men. The high scrotal approach is also preferable to an infrapubic approach because the latter increases the tendency of the pump to migrate to a high scrotal position, making it more visible in the anterolateral aspect of the scrotum and leaving the tubing easily palpable at the base of the penile shaft. Scrotal skin is mobilized over the shaft of the base of the penis, and surrounding tissue is pushed laterally by securing the Foley catheter and urethra between the thumb and index finger (see Fig. 30-6).

Dissection can be minimized by making the incision straight down toward the urethra. This incision reduces postoperative swelling and edema and results in a thick layer of subcutaneous tissue allowing for complete isolation of tubing from skin suture line and better incision closure. The scrotal location of the incision also allows for deeper placement and concealment of input tubing to the pump (see Fig. 30-6). A small fenestration is then made in the 3M Steri-Drape 1012 that is placed to cover the operative field and the Scott retractor loosely. Four additional blunt hooks are used to secure the opening in the drape to the edges of the scrotal incision, retracting the cut edges of the skin and drape by securing the hooks on the retractor frame (Fig. 30-7). The remainder of the procedure is performed through the opening, eliminating all direct and indirect contact between the implant and the skin.

The tunica albuginea of each corpus cavernosum is identified on either side of the urethra (Fig. 30-8), secured with 3-0 polydioxanone suture (PDS) RB-1, and incised 1 cm lateral to the urethra (Fig. 30-9). The incision should be limited to the tunica albuginea and avoid cavernosal muscle tissue. Positioning the corporotomy close to the urethra allows direct downward orientation of the tubing between the cylinder and the pump and makes it less likely that the patient will be able to palpate the tubing at the base of his penis.

Blunt scissors are used to develop a space between the tunica albuginea and cavernosal muscle (Fig. 30-10) in both directions to

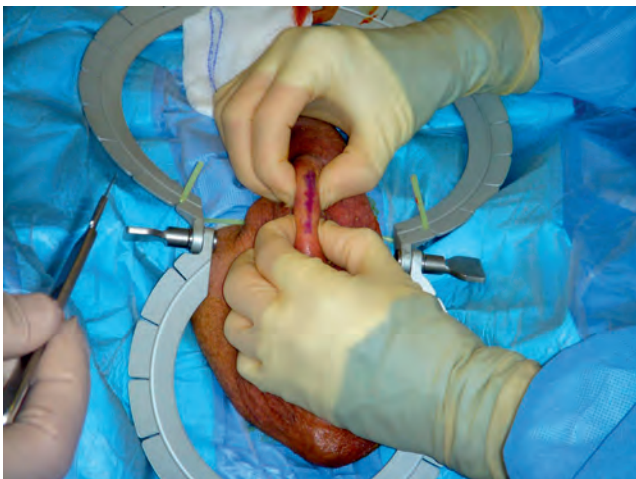


Figure 30-6. Securing the Foley catheter and urethra.



Figure 30-7. The 3M Steri-Drape 1012 Fluoroscope Drape with opening secured to scrotal incision with yellow hooks.



Figure 30-8. Left tunica albuginea is marked 1 cm lateral to the urethra.

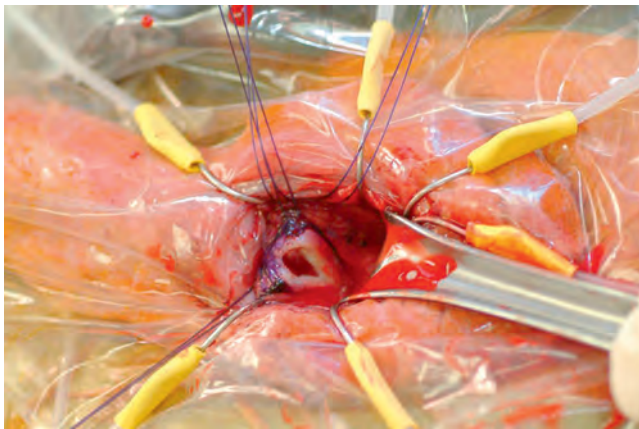


Figure 30-9. Position and size of corporotomy.

allow sequential dilation of the corpora using Dilamezinsert (Lone Star Medical Products, Stafford, TX) or Hegar dilators. More than half of surgery-related complications when implanting cylinders occur during this part of the procedure (Henry and Wilson, 2007). The use of force is unnecessary and should be avoided to prevent perforation of the tunica albuginea and damage to the urethra at the meatus or the crus, which can occur during either distal or proximal dilation (Sadeghi-Nejad, 2007). The use of special dilators (e.g., Rossello [Coloplast Corp., Minneapolis, MN] or Uramix [Uramix, Inc., Lansdowne, PA] double-blade cavernotome dilators or Otis urethrotome) can help decrease the risk of perforation in the presence of corporeal fibrosis (Bettocchi et al, 2008).

To prevent distal or proximal crossover into the contralateral corpus during initial dilation, constant traction should be applied to the shaft of the penis by pulling on the glans, and the curvature of the scissors should be maintained away from the midline of the penis, with the tips next to the tunica albuginea (see Fig. 30-10). It is preferable to dilate at the level of the venous plexus at



Figure 30-10. Initial dilation with blunt-tip Mayo curved scissors.

the periphery of cavernosal muscle tissue (vs. centrally through cavernosal muscle). If crossover occurs, it is usually preferable to recognize it and correct it during this part of the procedure, rather than after further dilation or insertion of the cylinders.

To correct a distal perforation, the damaged corpus apex should first be exposed through a transverse incision of the skin and tunica albuginea near the glans. A small hole can usually be located distally on the medial aspect of the cavernosal cavity and repaired using separate PDS stitches. The distal apex of the corpora needs to be closed with a second running suture, and a slightly shorter prosthetic cylinder is selected for the perforated side; this is necessary to prevent the distal tip of the cylinder from resting on the urethral suture repair. A more conservative approach would be to terminate the procedure and bring the patient back for implantation 3 months later. The disadvantage of this strategy is that the length of the shaft is foreshortened, and dilation of the scarred corpora is much more difficult. If the perforation occurs after both corpora are dilated, a semimalleable cylinder can be placed in the nonperforated side to preserve penile length. Use of a Dacron or Gore-Tex sleeve should be avoided because of the markedly increased risk of infection and ingrowth into the graft, which makes it impossible to remove. To evaluate proximal perforation during surgery, a dilator can be placed in each crura, and their heights can be compared to confirm that one has penetrated too deeply inside the perineum. Repair involves anchoring the cylinders to the surrounding corpora tissue by placing stitches above and below the input tubing, which prevents the cylinder from proximal migration and allows the perforation to heal. Alternatively, nonabsorbable sutures can be used to create a sling through the solid portion of the inflatable cylinder (Bettocchi et al, 2008). A study comparing prosthetic implantation with or without corpora dilation suggested that dilation is unnecessary in primary implantation cases. The investigators reported that patients receiving an implant without the use of dilation experienced less postoperative pain and increased penile length compared with patients in whom dilators were used to facilitate cylinder insertion (Moncada et al, 2010).

To select an optimally sized cylinder, the corporeal lengths should be measured distally and proximally with respect to a fixed

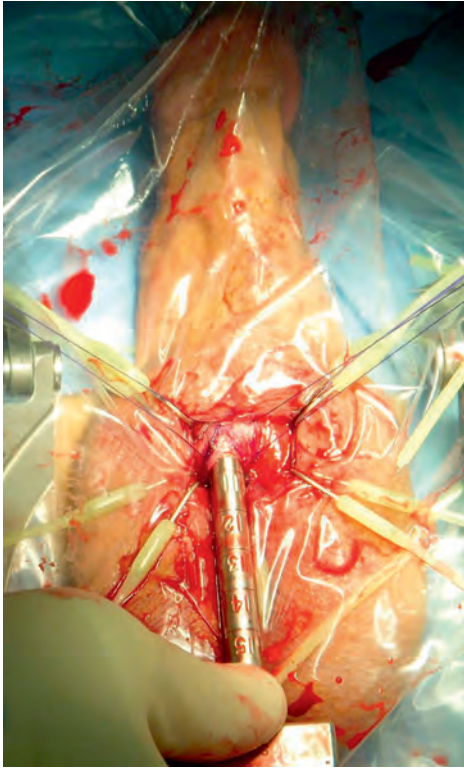


Figure 30-11. Dilamezin insert is used to obtain distal measurement.



Figure 30-12. Furlow introducer is used to pass right cylinder traction suture.

point of reference, such as a traction suture (Fig. 30-11). Oversized cylinders can result in erosion and an S-shaped penile deformity, which can cause increased wear at the flexion point of the curve and lead to mechanical failure (Wilson et al, 1996; Montague, 2011). Conversely, an undersized cylinder may not adequately support the glans; this can be easily addressed by adding rear tip extenders. It is important not to overstretch the penis over the measuring instrument, especially when measuring the proximal portion. Creating an artificial erection by irrigating the corpora with saline can help assess if the penis is straight or curved. Noting the presence or absence of irrigant leakage from the meatus around the catheter can also help evaluate the possibility of urethral injury.

When a cylinder is selected, the device is opened on the surgical field and prepared for implantation by purging air from the cylinders and pump. The traction suture from the distal tip of each cylinder is secured to a Keith needle and passed into the distal aspect of the penile shaft and through the glans penis with the Furlow introducer (Fig. 30-12).

Damage to the device is avoided by passing both sutures and Keith needle before placing a cylinder into a corpora (Bettocchi et al, 2010). Because most cylinders are preconnected to the pump, it is important to orient the cylinders such that the two input tubes to the pump do not cross over each other. After each traction suture has been passed through the glans penis, the proximal portion of each cylinder is inserted first. The cylinder is folded on itself, and when the distal tip is placed in the corporeal orifice, the traction suture is pulled to insert the rest of the cylinder.

Each cylinder must lay flat in the corpora when traction is applied on the suture. Any folds observed in the cylinder indicate that it may be too long or that the rear tip is not properly positioned.

When both cylinders have been inserted, a 60-mL syringe filled with saline is used as a surrogate reservoir to inflate the cylinders to evaluate erection size and quality. The cylinders are then deflated, and the penis is reexamined to ascertain correct cylinder sizing. This test can also help identify cylinder malfunction or damage should it occur. If the cylinder length needs adjustment, the saline should

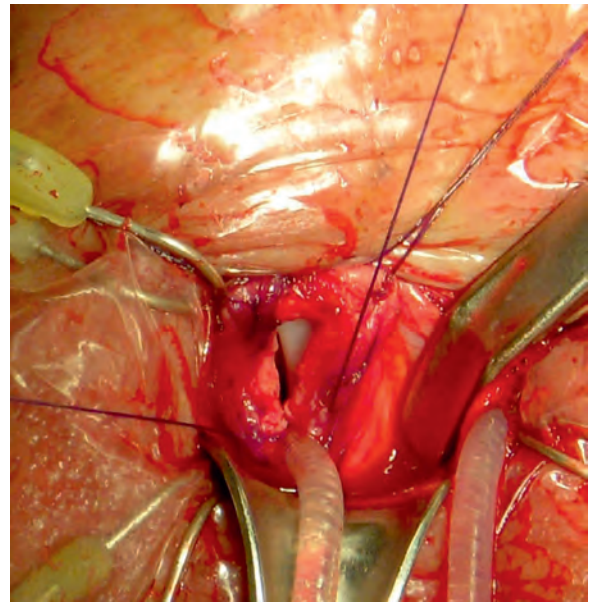


Figure 30-13. Watertight closure of right corporotomy.

be completely removed from the cylinder before removing the cylinder from the corpora and changing or removing the rear tip extender; this facilitates the adjustment and decreases the chance of damaging the cylinder. Each time a cylinder is removed, adjusted, and repositioned into the corpora, it can become contaminated and its sterility can be compromised, especially if it comes into contact with skin.

A watertight closure of the corporotomy can be achieved with a running 3-0 PDS using a hemostatic stitch or by approximating the previously placed tagging 3-0 PDS (Fig. 30-13). Although the former

approach takes more time and can potentially cause needle injury to the cylinder, it is preferable because it creates a watertight closure. When the corporotomy is closed, the pump should be activated and deactivated several times while assessing cylinder size and integrity. **If the latter approach is used, and a watertight closure is not achievable, a drain should be placed at the end of the procedure to evacuate bleeding and prevent scrotal hematoma.**

Pump Placement

Placement of the pump before the reservoir minimizes skin contact time while the reservoir is being placed. Allis clamps are used to provide gentle traction to the scrotal fascia, and a flap is developed beneath the urethra for a distance of 2 to 3 cm. A long, closed nasal speculum is introduced into a 1-cm incision made in the scrotal fascia, approximately 1 to 2 cm from the urethra, and directed upward between both testicles and toward the bottom of the scrotum. The speculum is used to form a pocket in the scrotal sac, in the fatty layer between the testicular tunica vaginalis and slightly behind the testicles (Fig. 30-14).

It is important to keep the blades of the speculum closed until the tips reach the bottom of the scrotal sac to prevent excessive dilation of the pouch, which should fit snugly around the pump. This prevents posterior pump migration, which renders it less accessible to the patient. **The pump should be positioned such that the deflation footprint is easily accessible to the patient yet unobtrusive, and the tubing between the pump and the cylinders should be placed so that it cannot be detected by the patient and sexual partner.** After obtaining complete hemostasis, the opening in the scrotal fascia can be closed. Bleeding around the pump causes an inflammatory reaction and hematoma formation, and a thick capsule develops around the pump. Use of the implant is delayed, and it is difficult to activate the device.

Reservoir Placement

Before reservoir placement, it is important to ensure the bladder is empty to avoid bladder perforation. While applying upward traction to the penis, the base of the crus is palpated, and Scarpa fascia is bluntly divided. In this manner, a defect is created between the crus of the penis medially and the spermatic cord laterally. Next, the operator's finger is oriented toward the pubic ramus, and the external inguinal ring is identified. The tip of a large blunt Mayo curved scissors is placed over the pubic ramus by sliding it between the base of the penis and the operator's finger. After tilting the scissors at a 90-degree angle with the plane of the abdominal wall and positioning the tip of the scissors just over the pubic ramus, a small 0.5-cm defect is made in the floor of the inguinal canal with the

blunt Mayo scissors. **It is important to limit the excursion of the scissors to a 1-cm depth and to maintain the scissors on the pubic ramus.** Incomplete perforation of the floor of the inguinal canal should be avoided because it will cause separation of transversalis fascia from the undersurface of the internal oblique muscle. This will cause a decrease in the countertraction of the transversalis fascia, making it more difficult to puncture the floor of the inguinal canal and access the space of Retzius. When the defect of the floor is made, the scissor is removed and exchanged for a nasal speculum with 8-cm-long blades (Fig. 30-15). **It is unnecessary to dilate the space of Retzius vigorously, and great care must be taken not to make a large defect in the floor of the inguinal canal resulting in reservoir herniation or migration.**

This part of the procedure may be difficult in a patient after hernia repair and transversalis fascia thickening owing to mesh and previous surgery. In such cases, it may be necessary instead to make a separate incision for adequate reservoir placement or to implant the reservoir in a submuscular location. The latter approach may make the reservoir palpable and possibly visible (Henry and Wilson, 2007; Al-Enezi et al, 2011). Catastrophic outcomes, such as injury to bowel or a major blood vessel or placing the reservoir into the bladder, colon, and vena cava, have occurred in the past when attempting to place the reservoir in this manner in patients with previous pelvic surgery. **Placement of the reservoir in the space of Retzius should be performed only in patients who have not undergone surgery previously.** Submuscular reservoir placement with a flat reservoir (AMS Conceal; American Medical Systems [AMS], Minnetonka, MN) or a separate incision (Fig. 30-16) should always be performed in all patients after robotic prostatectomy, radical cystectomy, and abdominoperineal resection and in patients with history of pelvic fracture with bladder rupture and pelvic surgery. However, positioning the reservoir above the transversalis fascia in a submuscular position can lead to autoinflation of the device, which occurs when the fluid pressure within the reservoir is greater than the back-pressure limits of the pump (Levine and Hoeh, 2012).

When the space of Retzius is entered with the long nasal speculum, it is opened, and the surgeon's index finger is used to confirm



Figure 30-14. Placement of pump into scrotal sac.

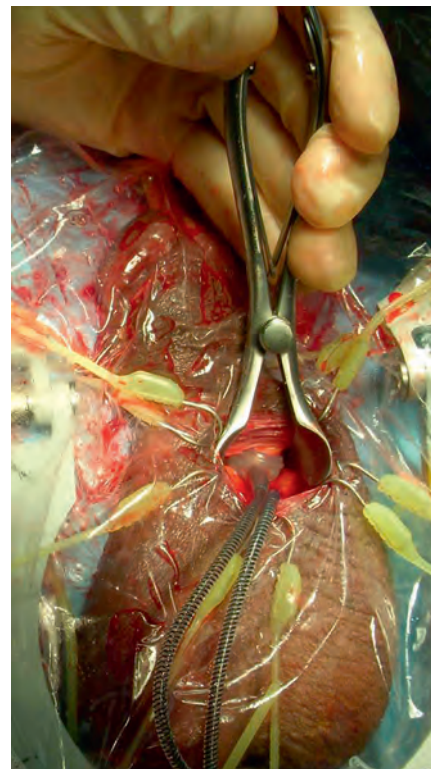


Figure 30-15. Placement of reservoir into space of Retzius.



Figure 30-16. Right lower quadrant incision for submuscular placement of reservoir in a patient after robotic prostatectomy. Coloplast Titan 24-cm XL cylinders are shown inflated 2 weeks postoperatively.

its position. An empty reservoir is placed through the nasal speculum next to the bladder, the speculum is removed, and the reservoir is filled with the appropriate amount of saline. A back-pressure test performed by applying gentle pressure on the lower abdominal wall. A palpable reservoir or back-pressure of saline noted into the syringe is an indication that it has not been properly positioned. A surrogate test should then be performed, using a syringe as the reservoir, to confirm proper reservoir placement and check for back-pressure. It is important that the prosthesis is completely deflated before tubing from the pump is trimmed and connected to tubing from the filled reservoir. **Every effort must be made to maintain the reservoir full during the immediate postoperative period to prevent autoinflation of the device later on.** Allowing healing to occur over a partially filled reservoir limits its ability to store an adequate volume of saline. If hematuria is present at this point, it could potentially indicate injury to the bladder wall, which must be ruled out before closing.

Closure

At this point, the surgical site should be irrigated and reexamined for hemostasis. When hemostasis is confirmed, Buck fascia and the dartos muscle are closed, followed by closure of the skin. A benefit of using nonabsorbable sutures are the warm baths (lying flat, not sitting) started on postoperative day 3, which help relieve pain, decrease any swelling or edema, and keep the scrotum clean. The catheter can be removed the morning after the surgery by the patient at home, and the stitches are removed after 14 days.

The use of a closed-suction drain to reduce the risk of hematoma after inflatable penile implant surgery is controversial. Two retrospective studies investigating the use of drains did not produce conclusive results, and there have been no randomized controlled clinical trials evaluating the efficacy of using a drain after implant surgery (Wilson et al 1996; Sadeghi-Nejad et al, 2005; Kramer et al, 2011). Proponents posit that draining the scrotum can decrease edema, increase comfort, and decrease the time to initiation of device cycling. Opponents argue that draining increases the risk of infection, drain fracture, bleeding during placement, and damaging the device and inconveniences the patient, who then has to return to the clinic the following day to have the drain removed (Sadeghi-Nejad et al, 2005; Kramer et al, 2011). A review of articles addressing penile prosthetic infection published in Medline and EMBASE

databases from 2000 to 2012 concluded that no recommendation can be made about the use of surgical drains to reduce infection rates associated with penile prosthetic surgery (Elmussareh et al, 2013). **If the surgeon is not satisfied with hemostasis, the surgical area should be drained.**

KEY POINTS: SURGICAL PREPARATION AND APPROACH

- Minimizing surgery duration decreases the risk of infection.
- Exposure of all of the components of the device to the patient's skin should be minimized.
- During dilation, the use of force is unnecessary and should be avoided to prevent perforation of the tunica albuginea.
- Narrower inflatable and semirigid devices should be available for all cases in the event that implanting a three-piece device becomes difficult.
- Placement of the reservoir in the space of Retzius should not be performed in patients with prior pelvic surgery.
- A closed-suction drain should be used if the surgeon is not satisfied with hemostasis.

POSTOPERATIVE CARE

When implanting a penile prosthesis, the outcome is very dependent on the nature of postoperative care. Because the surgery is typically an outpatient procedure or involves a 23-hour stay, the Foley catheter and drain (if used) are removed the morning after surgery (Garber, 2008). The efficacy of postoperative prophylactic antibiotics has not been demonstrated in prospective studies and remains controversial. Although there is no consensus regarding the type or duration of antibiotic administration postoperatively, a survey of 216 urologists found that most prescribed antibiotics for 7 days after surgery and favored quinolones (Koves et al, 2011; Wosnitzer and Greenfield, 2011; Elmussareh et al, 2013).

During the first week, the patient should avoid sitting on the scrotum (this can push the pump upward) and lifting more than 15 pounds or any other activities that could cause displacement of the reservoir into the inguinal canal. **Brief-style underwear should be worn for the first month, with the penis placed on the lower abdomen and oriented toward the umbilicus until the device is first inflated.** Such positioning promotes capsule formation around the cylinders and will orient the erection in an upward direction. It also helps prevent downward curvature during the healing process (Wilson and Mulcahy, 2006; Montague, 2011).

If the type of device implanted does not include a lock-out valve on the reservoir, the patient should be warned about the potential for postoperative autoinflation, which typically occurs following intra-abdominal pressure increase. This autoinflation can be embarrassing and increases the risk of cylinder erosion (Abbosh et al, 2012). Should autoinflation occur, the patient may need to return to the clinic earlier than usual for instruction about how to deflate the device. At 3 months, the capsule that forms around the reservoir typically protects it from any pressure increase and decreases the incidence of autoinflation (Wilson and Mulcahy, 2006). **It is important for the patient to understand that capsule formation should occur when the reservoir is full, and the reservoir should not be left in a partially filled state for extended periods.** If the capsule forms around a partially filled reservoir, the capsule will restrict future expansion of the reservoir, prohibit complete cylinder emptying, and potentially cause autoinflation, resulting in a need for surgical revision. Abbosh and colleagues (2012) described the use of outpatient laparoscopic capsulotomy to treat this problem.

The extent to which a patient experiences postoperative pain varies depending on his tolerance and any preexisting conditions (e.g., neuropathy). Scrotal bruising and swelling are common, with

scrotal hematoma typically receding without surgical intervention (Wilson and Mulcahy, 2006). An oral narcotic is often required the first week, followed by nonsteroidal anti-inflammatory medication as needed. Ice packs may be used intermittently.

The first postoperative visit typically occurs at 2 weeks to assess wound healing and manage any signs of autoinflation. During this visit, it is critical to identify early signs or symptoms of local infection. The patient again returns to the clinic at approximately 4 weeks after surgery for an appointment focusing on how to operate the device. Initial inflation of the prosthesis may be difficult, and the patient should be instructed to cycle the device (i.e., inflate and deflate it) during warm baths twice each day for the next month to facilitate its use. The patient can then attempt sexual intercourse as soon as he feels comfortable using the device. Additional postoperative instructional visits may be necessary, depending on each patient's experience. Subsequent follow-up at 3 months, 6 months, and then annually should be scheduled to assess healing, particularly cylinder tip position in the glans; device functioning; and patient satisfaction.

COMPLICATIONS

Complications can occur during surgery or postoperatively. Complications that can occur during surgery include organ injury/perforation, cylinder crossover, and damage to the device during implantation. These are addressed in Surgical Preparation and Approach. Complications that can occur postoperatively are addressed in the following sections.

Infection

Infection is a serious complication of prosthetic surgery and represents significant pain and suffering for an elective procedure. The incidence of infection is estimated to be approximately 4% for primary implants before the introduction of specially coated devices and 10% for revision implants (Henry et al, 2004); however, this may reflect underreporting because of discontinuity of care (Muench, 2013). Research suggests that most infections are caused by bacteria on the skin that attach to the device and are then introduced into the patient. Because infections are infrequent and evidence suggests that skin bacteria are relatively innocuous, physicians tend to assume that such contamination is inevitable and focus their efforts on managing the contamination by irrigating, using antibiotic-coated implants, and administering IV antibiotics (Henry et al, 2008; McKim and Carson, 2010), overlooking surgical technique (i.e., avoiding touching the skin) as an adjunct to decrease the potential source of infection further.

Knowing the time line of presentation of a suspected infected prosthesis can help guide early management and diagnosis. For example, at the 2-week postoperative interval, if the patient does not seem to improve and reports persistent or increased pain, one must resist the temptation to prescribe oral antibiotics. If the device is not infected, the patient should experience a clinical improvement within the next 7 to 14 days. If the device is infected, antibiotics are useless at this point and may delay diagnosis. Fever, erythema, swelling, elevated white blood cell count, and incision drainage are late signs and symptoms of infection and are usually not observed at this postoperative visit. The sooner an infection is diagnosed, the better the chance for successful salvage. Imaging studies such as scrotal sonography, computed tomography scan, and magnetic resonance imaging are not helpful in making an early diagnosis. Tethering of the pump may also be a sign of infection but can sometimes be caused by inflammation and capsule formation from a hematoma. Capsule formation improves over time, whereas inflammation persists or becomes more pronounced. Close patient follow-up and weekly examinations with evaluation of white blood cell count are important when an infection is suspected. Clinical deterioration with persistence of pain and tethering at 3 to 4 weeks postoperatively signals an infection, and aggressive early salvage should be considered before systemic symptoms,



Figure 30-17. Tethering of pump consistent with early infection of prosthesis.

such as fever, elevated white blood count, erythema, and abscess formation of scrotum, occur (Fig. 30-17).

The bacterial contamination that causes infection most often occurs at the time of surgery and typically involves organisms that colonize the skin, such as *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Candida albicans*. These organisms can persist despite perioperative antibiotics. When they reach a critical mass, they excrete a biofilm in which they can live in a decreased metabolic state, causing no clinical symptoms until at least 4 to 6 weeks and sometimes years after implantation (Wilson and Mulcahy, 2006). Because of the biofilm, the use of systemic antibiotics to treat symptomatic patients is typically insufficient, and infection necessitates the removal of all device components as well as any permanent sutures or graft material used during corporeal reconstruction. Attempts to remove only part of an infected device typically result in persistent infection (Garber, 2008).

Traditionally, after removal of an infected implant, a surgeon waited several months before considering replacement. However, severe cavernosal fibrosis after explantation complicates replacement surgery, contributing to a 50% success rate even for experienced surgeons. The fibrosis also causes significant penile shortening and potential loss of sensation, which has a negative impact on patient satisfaction (Muench, 2013). Introduction of a "salvage" procedure involving removal of the infected prosthesis, wound washout, and immediate device replacement helped facilitate reimplantation and preserve penile length (Brant et al, 1996; Jain and Terry, 2006). When indicated (i.e., for chronic and nonpurulent infection), salvage success rates can exceed 84% if the procedure includes thorough wound irrigation with a series of antibiotic and antiseptic solutions, followed by a change of surgical gowns, gloves, drapes, and instruments; placement of a new device; wound closure without drains; and oral antibiotics for 1 month (Mulcahy, 2000; Henry et al, 2005; Garber, 2008). More recent research suggests that aggressive washout with normal saline combined with meticulous sterile technique may further improve postsalvage infection and reoperation rates (Masson, 2012). The salvage technique can also

be used when a device requires replacement for reasons other than infection (Henry et al, 2005). Salvage is contraindicated in patients presenting with enterococcus, tissue necrosis, sepsis, diabetic ketoacidosis, or cylinder erosion into the urethra (Mulcahy 2003; Wilson and Mulcahy, 2006).

When malfunctioning penile prostheses are removed, they are often found to be colonized with pathogenic bacteria, even in the absence of clinical infection. For example, Silverstein and colleagues (2006) used scanning laser microscopy to determine that 80% of prostheses explanted because of mechanical malfunction were colonized with gram-positive rods, cocci, and fungal elements, and Henry and associates (2004) reported that culture-positive bacteria were found in 70% of patients with clinically uninfected penile prostheses. However, according to a study by Kava and colleagues (2011), less than 10% of devices removed because of malfunction or rerouted because of extrusion were colonized with pathogenic bacteria. The authors also found that there was no correlation between culture-positive patients and postoperative infection. They suggested that their findings may differ from findings of other investigators because of their use of a preoperative, adjuvant, alcohol-based skin preparation.

More recently, a novel surgical technique has been developed to facilitate delayed implantation of a replacement device. Swords and coworkers (2013) described the insertion of a temporary filler consisting of an antibiotic cast of synthetic high-purity calcium sulfate into the corpus cavernosum when an infected device is removed. This “spacer” provides constant delivery of local antibiotic to the infected area and reabsorbs within 30 to 60 days, at which time a new prosthetic device can be implanted.

Specially coated three-piece devices have been developed by both AMS (Minnetonka, MN) and Coloplast Corporation (Minneapolis, MN) to inhibit bacterial adhesion and proliferation. The AMS 700 devices are impregnated with InhibiZone, a coating on the external surface of the device that elutes rifampin and minocycline to inhibit bacterial growth. The Coloplast Titan prosthesis has a hydrophilic polyvinylpyrrolidone coating that absorbs and elutes any antibiotic solution in which it is soaked. The introduction of these coatings within the past decade has decreased the incidence of infection by 50% to 70%, even after 11 years of follow-up (Carson et al, 2011; Mandava et al, 2012; Serefoglu et al, 2012). This decreased incidence confirms our hypothesis that infections are caused by contamination of the prosthesis at the time of implantation. It appears that the antibiotics eluting from the devices and/or the slippery surfaces of the implant reduce the proliferation and attachment of the relatively milder, late-appearing types of bacteria noted earlier. However, although such coatings have significantly decreased overall infection rates, more aggressive and earlier-appearing bacteria, such as *Enterococcus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, are now causing infection at increasing rates (Eid et al, 2012).

Risk factors for infection may be related to patient history, intraoperative conditions, or postoperative variables. Risk factors related to patient history include poor patient hygiene, spinal cord injury, urinary tract infection, distant sites of infection, and revision surgery performed for previous device infection; however, it is unclear whether revision surgery for mechanical failure is associated with higher rates of infection (Cakan et al, 2003; Kava et al, 2011; Selph and Carson, 2011; Elmussareh, 2013; Muench 2013). Diabetes mellitus may also be a risk factor, although studies report conflicting results. For example, a large retrospective study with a follow-up period of up to 7.7 years found a higher incidence of first revisions owing to infection in diabetic patients compared with nondiabetic patients; however, other studies have not found a difference in the incidence of infection between the two groups (Lotan et al, 2003; Mulcahy and Carson, 2011). It is also unclear whether poorly controlled diabetes and immunosuppression are associated with an increased infection risk (Bishop et al, 1992; Wilson et al, 1998; Elmussareh et al, 2013). Intraoperative risk factors for infection may include inadequate skin preparation with alcohol/chlorhexidine; prolonged surgical time (i.e., >2 hours); prolonged and repeated exposure of components of the

prosthesis to patient’s skin; frequent repositioning and resizing of the cylinder, pump, or reservoir; scrotal hematoma (particularly if liquefied); and not changing gloves before handling the device. A postoperative variable associated with infection risk is prolonged hospitalization.

A review of studies focusing on penile prosthetic infection between 2000 and 2012 suggested that the most important factors to minimize the risk of device infection include the use of antibiotic-coated prostheses and procedures that decrease inoculating bacteria into the surgical wound (i.e., alcohol skin preparation, a no touch surgical technique, and perioperative antibiotic use) (Elmussareh et al, 2013). Although the use of perioperative antibiotics reduces infection, there are no specific guidelines recommending antibiotic protocols, and a wide range of practice patterns exists among urologists performing prosthetic surgery (Wosnitzer and Greenfield, 2011).

KEY POINTS: INFECTION

- Knowing the time line of presentation of a suspected prosthetic infection can help guide early management and diagnosis.
- Infection necessitates the removal of all device components as well as any permanent sutures or graft material used during corporeal reconstruction.
- Factors that minimize the risk of device infection include the use of antibiotic-coated prostheses and procedures that decrease inoculating bacteria into the surgical wound (i.e., alcohol skin preparation, a no touch surgical technique, and perioperative antibiotic use).

Device Malfunction

Device malfunction is becoming less common as prosthesis design improves over time (Bettocchi et al, 2010). A historical prospective study estimating long-term survival rates of first-time implants (N = 2384) found that freedom from mechanical breakage was 79.4% at 10 years and 71.2% at 15 years (Wilson et al, 2007). The most common types of malfunction in a three-piece prosthetic device depend on the manufacturer and include cracks in the silicone tubing, leaks at the site where the tubing connects to the pump, leaks within the cylinder, cylinder aneurysm, and pump disruption (Garber, 2008). Autoinflation, which is discussed elsewhere in this chapter, has been observed to occur in 2.4% to 11% of devices overall, but this incidence decreased to 1.3% in devices with lock-out valves (Carson et al 2000; Wilson et al, 2002). Reservoir-related mechanical malfunction is also rare, and it is unclear whether a functioning reservoir should be replaced during revision surgery to address other issues (Levine and Hoeh, 2012).

If malfunction occurs within a few months after implantation, replacement of only the defective component should be considered, especially if this avoids a repeat corporeal incision. After the device has been in place for more than 2 years, complete replacement is indicated (Jain and Terry, 2006). Other options following malfunction include no treatment or device removal without replacement. When choosing the latter, it is important for the patient to understand that because the cavernosal space is now empty, the tunica albuginea will retract, scar tissue will form inside the penis, and the penis will become permanently shorter.

Other Complications

Postoperative complications occurring less frequently than infection and device malfunction include erosion, S-shaped penile deformity, poor glans support, and scrotal hematoma. Erosion typically occurs months or years after implantation and can manifest in several different locations. For example, an oversized cylinder, especially the semimalleable type, is most likely to erode into the

meatus at the level of the glans. The pump and input tubes to the cylinders can erode at the level of the scrotal skin if placed too superficially, although an indolent low-grade bacterial infection is most often the reason for this (Natali, 2010; Talib et al, 2013). Similarly, the reservoir can erode into the bowel or bladder if either is fixed in place by adhesions resulting from previous surgery or radiation; however, this is very uncommon (Levine and Hoeh, 2012). **Regardless of the location, erosion always necessitates complete removal of all the components of the device and possible salvage replacement.** If only one of the cylinder tips has eroded through the meatus, the entire device needs to be removed, including the pump and reservoir, and a malleable cylinder is placed in the noneroded side only, to prevent shortening of the penis. The perforation must be allowed to heal for 8 to 12 weeks before reimplantation is attempted (Natali, 2010).

An S-shaped penile deformity can occur after incomplete distal dilation of the corpora cavernosa and/or implantation of an oversized cylinder (Wilson et al, 1996; Bettocchi et al, 2008). This complication also necessitates device replacement. In contrast, implantation of an undersized cylinder can result in poor glans support; however, this can be treated by adding rear tip extenders or by replacing the cylinders with the correct size without disturbing the scrotal pump.

Because blood collects in dependent areas of the body, scrotal hematoma can follow implantation of a three-piece prosthesis, with reported incidence ranging from 0.7% to 3.6%. Attempts to decrease the development of scrotal hematoma include keeping corporotomies small, closing with a running watertight suture, and using hemostatic sealant (Cohen and Eid, 2014). Kramer and colleagues (2011) published an analysis of the risks and benefits related to the use of closed-suction drains. In the absence of a large, prospective, randomized trial, it is unclear which course of action is most beneficial, and the final decision is largely a matter of surgeon preference. **In my opinion, it is better to use a drain than to risk hematoma. Blood in the scrotal sac causes significant inflammation and formation of a thick fibrous capsule around the pump, which makes it very difficult for the patient to manipulate the pump when healed.** Additionally, a liquefying hematoma provides iron and nutrients, making it an ideal setting for bacterial growth and infection.

SPECIAL CASES

Several situations make implantation of a penile prosthesis particularly challenging. These include previous pelvic surgery (which is addressed in Surgical Preparation and Approach), Peyronie disease, priapism, scleroderma and lupus, and previous radical prostatectomy.

Peyronie disease is characterized by focal fibrotic replacement of healthy tunica albuginea; this most commonly causes curvature of the penis toward the location of the scar and results in ED (Mulcahy and Wilson, 2006). A prosthetic implantation procedure similar to that described in Surgical Preparation and Approach has been found to straighten the erection adequately in approximately 40% of patients (Chaudhary et al, 2005). Otherwise, penile straightening may be required and typically involves manual modeling during which the tunical plaque is fractured over an inflated cylinder at the time of implantation by forcibly bending the penis in a direction opposite the curvature. Plication or tunical incision/excision with or without grafting may rarely be necessary (Hudak et al, 2013; Segal and Burnett, 2013). Mulhall and associates (2005) developed an algorithm for the surgical treatment of Peyronie disease and ED that involves objective assessment of penile deformity using dynamic infusion cavernosometry and cavernosography, followed by administration of erectogenic therapy. The authors found that patients who did not respond to erectogenic therapy and underwent penile prosthetic surgery had excellent results. Other studies subsequently reported that surgical placement of an inflatable penile prosthesis is an effective treatment option for Peyronie disease (Levine et al, 2010; Chung et al, 2013). However,

another study suggested that Peyronie disease compromises inflatable prosthetic device durability and increases malfunction rates, possibly owing to stress on the device during surgery, use, or both (DiBlasio et al, 2010).

Priapism is defined as a full or partial erection that continues for more than 4 hours beyond intercourse or is unrelated to sexual stimulation (Tausch et al, 2013). If left untreated, the resulting fibrosis is usually distal, extensive, and dense, making it very difficult to dilate with conventional instruments (Wilson and Mulcahy, 2006; Martinez-Salamanca et al, 2011). A review of surgical procedures to facilitate prosthetic implantation and improve outcomes in such situations suggests that scar incision should include a combination of techniques (i.e., extensive wide excision, multiple incisions minimizing excision, corporeal counterincisions, corporeal excavation technique, or Shaeer technique) as well as cavernotomies and smaller prostheses (Shaeer and Shaeer, 2007; Martinez-Salamanca et al, 2011). A retrospective analysis of prosthetic implantation in 17 patients with postpriapism ED found that although all patients were successfully implanted without major postoperative complications, 2 patients experienced urethral injury secondary to extensive corporeal fibrosis (Durazi and Jalal, 2008).

The use of radical prostatectomy to treat prostate cancer often results in ED. Some clinicians assume that implantation of a three-piece prosthetic device is contraindicated in such situations because of a perceived increased risk of intraoperative injury. To address these concerns, two studies investigated the use of penile prostheses after radical prostatectomy. In the first, Lane and colleagues (2007) reported that of 115 consecutive patients receiving a three-piece inflatable penile prosthesis after prostatectomy, none experienced intraoperative complications, including injury to the bladder or iliac vessels, with successful blind entry into the retropubic space in all cases. In the second study, Menard and associates (2011) examined surgical complication and patient satisfaction rates in subjects receiving a penile implant after radical prostatectomy and found that the procedure was associated with low morbidity and high satisfaction, especially with respect to erectile function; however, they noted that fibrosis in the retropubic space may necessitate a second incision for reservoir placement or use of a two-piece device instead of a three-piece device. Nevertheless, there have been several catastrophic mishaps related to implantation of a penile prosthesis after prostatectomy, such as placing the reservoir in the bladder, sigmoid colon, or vena cava and injury to the bladder or bowel. **In my opinion, the reservoir should always be placed through a separate incision (if the implant is performed via a penoscrotal approach) and placed in a submuscular position.** Although robotic prostatectomy can be performed through an extraperitoneal approach, most prostatectomies are performed transabdominally, and the peritoneum is not closed after the prostate is removed. Under this circumstance, a second incision (preferably on the right side to avoid the sigmoid) or submuscular reservoir placement must always be performed.

PATIENT SATISFACTION

In general, patient satisfaction with penile prosthetic implantation for ED has increased over the past 40 years, seemingly at least partly as a result of mechanical and design enhancements (Trost et al, 2013). **Patient satisfaction with penile prosthetic implantation is currently the highest among all of the treatments for ED** (Mulcahy, 2010; Rajpurkar and Dhabuwala, 2003). Bernal and Henry (2012) reviewed all relevant research published over the past two decades and identified nine studies meeting their inclusion criteria (e.g., >30 subjects, three-piece device, written in English), all of which indicated that patients report high satisfaction rates. This seems to be the case regardless of device manufacturer or older age (Brinkman et al, 2005; Villarreal and Jones, 2012; Chung et al, 2013).

In a study designed to identify specific factors that affect overall satisfaction, 21 patients were surveyed preoperatively about their


expectations and asked to rate their satisfaction 4 months postoperatively (Kramer and Schweber, 2010). The investigators found an inverse correlation between patients' expectations and postoperative satisfaction, suggesting that helping patients have realistic expectations and providing them with an accurate description of the procedure result in higher satisfaction after implantation.

Factors associated with postoperative dissatisfaction include a diagnosis of Peyronie disease, a history of radical prostatectomy, and a body mass index of 30 (Akin-Olugbade et al, 2006). The most common postoperative complaint associated with the reduction of overall satisfaction is loss of penile length (Lee and Brock, 2013). Strategies to preserve penile size after prosthetic implantation can be implemented before insertion, intraoperatively, or after insertion. Henry and colleagues (2012) conducted a prospective, multicenter study to assess patient satisfaction and axial rigidity of a cylinder that is longer in length than other available prostheses. The investigators concluded that the longer cylinders had great rigidity based on objective and subjective assessment. They also reported that patients had excellent satisfaction rates after implantation of the longer cylinders.


CONCLUSION

Penile prosthetic surgery is a highly effective treatment option for patients with ED who fail first-line and second-line therapy. Over the past 40 years, refinements in surgical technique have

significantly reduced the rates of infection and other complications, and innovations in prosthetic design have had a positive impact on device malfunction rates. High levels of patient and partner satisfaction exceed that of many other, less invasive treatment options and reflect the fact that penile implants have become the "gold standard" for the treatment of advanced ED.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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General Considerations

Natural History

Epidemiology

Penile Anatomy and Peyronie Disease

Etiology of Peyronie Disease

Symptoms

Evaluation of the Patient

Treatment Protocols

Nonsurgical Treatment of Peyronie Disease

Surgical Management

Conclusion

GENERAL CONSIDERATIONS

Peyronie disease (PD) was first known as *induratio penis plastica*. It was subsequently named after Francois Gigot de la Peyronie because he was the first to describe and offer treatment for it in a paper published in 1743 (Peyronie, 1743). But Guilielmus de Saliceto in the 13th century and Gabriele Falloppio in the 15th century had previously reported on this abnormality of the penis (Musitelli et al, 2008).

PD is currently recognized as a wound-healing disorder of the tunica albuginea (Devine and Horton, 1988) that results in the formation of an exuberant scar, occurring presumably after an injury to the penis activates an abnormal wound-healing response (Van De Water, 1997; Greenfield and Levine, 2005; Ralph et al, 2010; Levine and Burnett, 2013). The resulting scar or plaque is inelastic and therefore results in penile deformity including curvature, indentation, hinge effect, and shortening and is frequently accompanied by erectile dysfunction (ED). One of the most important characteristics of this particular wound-healing disorder is that once the scar has occurred, it does not undergo normal remodeling and therefore the scar and deformity persist (Del Carlo et al, 2008). Progress with treatment of PD has been limited by an incomplete understanding of its pathophysiology, and this lack of understanding has resulted in an inability to prevent the disease from starting and to prevent progression once it has occurred. This, combined with the fact that there is no known reliable treatment to reverse the scarring process, makes PD a challenging disorder to treat.

Multiple misconceptions have been held for decades about PD. Many of these misconceptions have been carried forward and appear to have compromised the proper assessment and early treatment of men with PD (LaRochelle and Levine, 2007). These include that Peyronie is a rare disorder. On the contrary, we now know that the prevalence of PD is somewhere between 3% and 20%, and in certain populations such as those with diabetes mellitus and ED the prevalence may be even higher (Lindsay et al, 1991; La Pera et al, 2001; Rhoden et al, 2001; Schwarzer et al, 2001; Sommer et al, 2002; Mulhall et al, 2004b; El-Sakka, 2006; Arafa et al, 2007; DiBenedetti et al, 2011). Another misconception is that PD has a reasonable likelihood of resolving spontaneously. As a result, men are often told by their physicians that nothing can be done during the acute phase and they should wait 6 months to a year, because there is a "good chance" that the disease process will resolve. We now know from multiple natural history studies that

full spontaneous resolution is extremely rare and that it is more likely that within the first 12 to 18 months after presentation, if no treatment is offered, up to 50% of patients will experience worsening of their deformity (Mulhall et al, 2006). Another misconception is that PD is a disorder that occurs only in middle-aged men. Multiple studies have demonstrated that it can occur in teenagers to men in their late 70s (Levine and Dimitriou, 2000; Kadioglu et al, 2002; Tal et al, 2012). Why this process occurs more commonly in middle-aged men is unclear, but theories include that the aging tunica is more apt to be injured in men who are susceptible to the disease, which activates the abnormal wound-healing process (Devine and Horton, 1988; Jarow and Lowe, 1997).

It is also a disorder that appears to go through an active phase during which the scar can grow, resulting in progressive deformity and pain. However, once it stabilizes, there is rarely further progression (Box 31-1).

NATURAL HISTORY

An understanding of the natural history of PD is critical to counseling patients and selection of treatment options. There are two phases. The first is the active (acute) phase, which is commonly associated with painful erections and changing deformity of the penis. This is followed by a stable (chronic) phase, which is characterized by stabilization of the deformity and disappearance of painful erections (Devine et al, 1997; Jalkut et al, 2003; Ralph et al, 2010; Kadioglu et al, 2011a). It would seem intuitive that once the scarring process has begun, there would be a progressive increase in deformity; but we have found that up to 20% of patients will experience a sudden onset of deformity that can be as great as 90 degrees.

It has been reported that PD can completely resolve in some patients, but this is probably a misconception. It is more likely that some men who traumatize their penises develop curvature secondary to the local inflammatory process. In some of these patients the inflammation resolves before scarring sets in. Thus the patient who has resolution of his deformity may not have had PD at all, but rather a slow-healing wound that simply takes longer to undergo the proper remodeling found with normal wound healing. Spontaneous regression has been looked at in several contemporary natural history studies that have suggested that no more than 13% of patients will have some improvement of their deformity over the first 12 to 18 months after onset of the disease process

BOX 31-1 Peyronie Disease Caveats

- Peyronie disease is not rare.
- It does not have a high likelihood of spontaneous resolution.
- It is not a disease of only middle-aged men.
- It is not a disease of only Caucasian men.
- Trauma to the flaccid and erect penis appears to activate the scarring process in susceptible men.
- Erectile dysfunction is frequently found in men with Peyronie disease.
- Plaque calcification is not an indication of mature, chronic-phase disease.

when not treated (Kadioglu et al, 2002; O'Brien et al, 2004; Mulhall et al, 2006; Hatzimouratidis et al, 2012). The key point to remember is that complete spontaneous resolution of PD is a rare occurrence. Recently, Berookhim and associates (2014) reported on a group of men who elected to have no treatment of their PD. In this study it appeared that the later the man sought evaluation in the first year after the onset of symptoms, the less likely that he would experience further deformity when left untreated (Berookhim et al, 2014).

EPIDEMIOLOGY**Incidence**

The incidence of PD varies widely depending on the population being screened—from 0.39% to 20.3%, with most current estimates of the incidence of PD being between 3% and 9% and the peak age of onset of PD in the early 50s (Schwarzer et al, 2001; Mulhall et al, 2004a). It was previously held that this was a disorder primarily of Caucasian men of northern European descent. It is now recognized that men of every race can develop PD. The variation in recognition of and reporting on this disorder in certain populations may be a result of the interest and presence of physicians with expertise in PD, as well as cultural mores that may make it more or less comfortable for men to share information about changes in their sexual function with a health care provider (Lindsay et al, 1991; Arafa et al, 2007). A recent Japanese study looked at a total of 1090 men undergoing a routine health check and demonstrated the prevalence of PD in healthy men to be quite low at 0.6% (Shiraishi et al, 2012). In a large U.S. Web-based survey, 16,000 randomly selected men over the age of 18 years were asked to self-report the symptoms, diagnosis, or treatment of PD. In this study, 0.5% to 0.8% of respondents had received a diagnosis of or treatment for PD, whereas 13% of respondents admitted to having symptoms of PD such as penile deformity or palpable plaque (DiBenedetti et al, 2011). The estimated number of unknown cases seems to be much greater than the number of symptomatic patients seeking treatment because autopsy data demonstrate that 22 out of 100 men have at least a mild form of the disease (Smith, 1969). Therefore the prevalence of PD seems to be equivalent to if not greater than that of important public diseases such as diabetes and urolithiasis, both established to be present in 3% to 4% of the general population (Sommer et al, 2002). It is worthwhile to note that the actual rates of PD may be higher than self-reported studies would suggest, because men with PD may be reluctant to discuss the signs and symptoms of this embarrassing condition.

The incidence of symptomatic PD may be increasing, which is perhaps explained by an increasing tendency to obtain medical help, increasing awareness that may be secondary to people seeking information on the Internet, or increasing use of pharmacologic treatments for ED (e.g., phosphodiesterase inhibitors, intracavernosal injectable agents) (Hellstrom, 2003). Phosphodiesterase inhibitors have not been suggested to directly contribute

to the development of PD; rather, their associated use in those with medical conditions such as diabetes that contribute to ED is the likely explanation, because these men now experience erections with deformities they would not have realized were present. At this time there is no suggestion that use of phosphodiesterase type 5 (PDE5) inhibitors should worsen or provoke PD. On the other hand, more recent in vitro and animal model studies have suggested that use of PDE5 inhibitors, as nitric oxide (NO) donors, has an antifibrotic effect that may be beneficial for the patients with PD (Valente et al, 2003; Ferrini et al, 2006; Gonzalez-Cadavid and Rajfer, 2009; Chung et al, 2011a). Treatments for ED, including intracorporeal injection therapy and vacuum devices, have also been implicated as a cause of PD (Carrieri et al, 1998; Jalkut et al, 2003; Bjekic et al, 2006). What seems more likely is that these treatments are designed to create a stronger erection, which can then be injured during a sexual encounter, activating the disease process in the susceptible individual. To date there is no evidence that any medicines such as beta blockers or phenytoin cause PD.

Associated Conditions**Aging**

PD is most commonly diagnosed in the fifth decade of life. A linear increase in prevalence can be seen from ages 30 to 49 with an exponential increase in prevalence at age 50 and up (Sommer et al, 2002). Mulhall and associates (2004b) demonstrated an increased prevalence of 8.9% in a population being screened for prostate cancer in a study in which the mean patient age was 68 years (Mulhall et al, 2004b). PD may also occur in young men. PD patients under age 40 tend to be seen during the acute phase after rapid onset of disease with a penile deformity and pain on erection (Tefekli et al, 2001). Studies have shown that approximately 10% of men with PD are younger than 40 years (Levine and Dimitriou, 2000). In addition, Tal and associates (2012) reported on 32 teens diagnosed with PD over a 10-year period with a mean age of 18 (Tal et al, 2012). Sixteen percent reported antecedent trauma, and 37% reported subsequent ED. A high level of distress was reported by 94% of these young men, with 34% seeking treatment for an anxiety or mood disorder (Tal et al, 2012). The increased prevalence of PD with age is likely a reflection of the increased likelihood of comorbid medical conditions contributing to the development of ED such as hypertension, hyperlipidemia, diabetes, and low testosterone, all of which have been suggested as possible causative factors associated with PD. Hypothetically, it could also reflect the reduced tissue elasticity that naturally occurs with aging, predisposing this tissue to stretch-related injury.

Diabetes

One of the more interesting recently studied associations is that of diabetes mellitus and PD. The prevalence of diabetes in men with PD has been reported to be as high as 33.2%, which is much higher than in the general population (Kadioglu et al, 2002; Bjekic et al, 2006; Cowie et al, 2010). Conversely, the prevalence of PD among diabetics has been shown to be increased when compared with the general population, with a reported rate of 8.1% to 20.3% depending on the specific population being screened (El-Sakka and Tayeb, 2005; Tefekli et al, 2006; Arafa et al, 2007). This may reflect particular patient populations, ethnic groups, referral patterns, and expertise of the physicians treating the disorder. Longer duration of diabetes and poor glucose control have also been shown to significantly increase the severity of PD with respect to duration of PD, deformity, curvature, and erectile function (El-Sakka and Tayeb, 2005; Kendirci et al, 2007). A recent retrospective study suggested that plaque size and pain may decrease as underlying diabetes is treated (Cavallini and Paulis, 2013). This was a small retrospective study, and further prospective studies are necessary to confirm these results.

One theory for the apparent association between PD and diabetes is that men with diabetes are at a higher risk for ED, which may

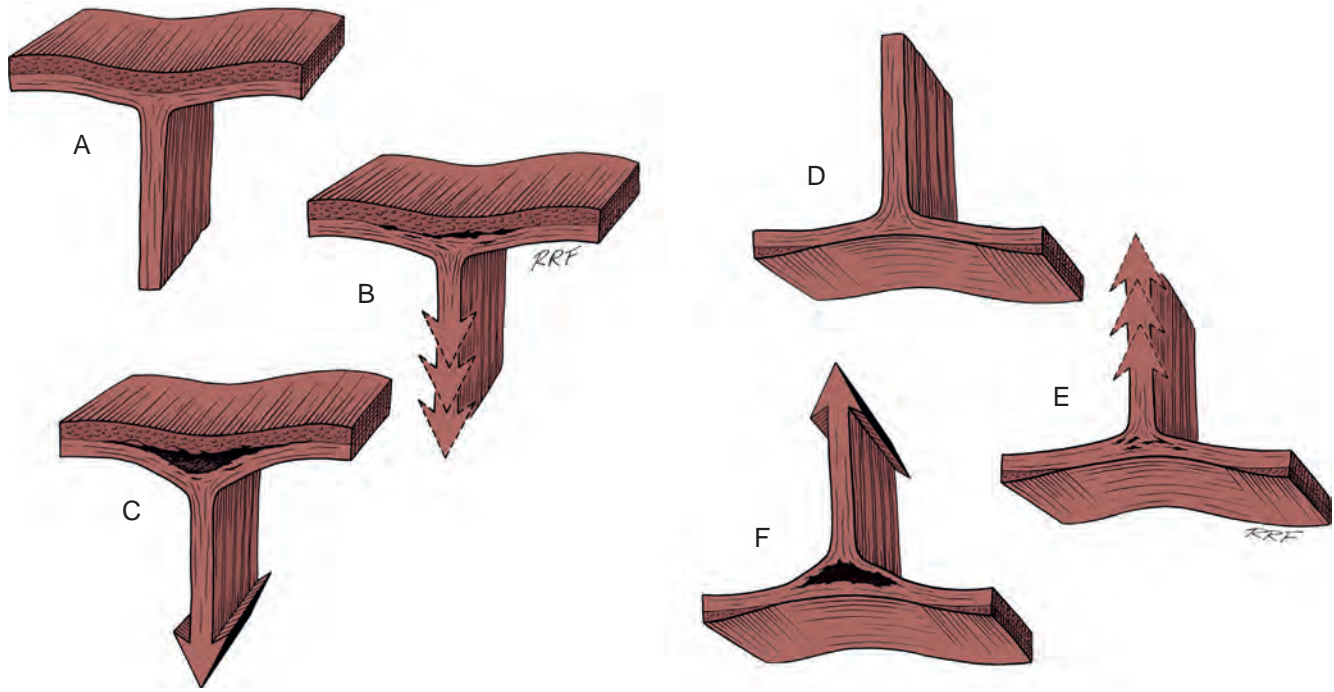


Figure 31-1. Demonstration of the mechanism of injury during buckling injuries to the penis. **A**, Fibers of the septal strands dorsally fan out and are interwoven with the inner circular lamina fibers of the tunica albuginea. The outer lamina consists of longitudinal fibers. **B**, In the chronic mechanism of Peyronie disease, less turgid erections allow flexion of the penis during intercourse, producing elastic tissue fatigue, further reducing elasticity of the tissue and leading to multiple smaller ruptures of the fibers of the tunica with smaller collections of blood, possibly producing multiple scars. **C**, In the acute mechanism of Peyronie disease, bending the erect penis out of column produces tension on the strands of the septum, delaminating the layers of the tunica albuginea. Bleeding occurs, and the space fills with clot. The scar generated by the response of the tissue to this process becomes the Peyronie disease plaque. **D**, Illustration of the situation on the ventrum of the penis, where the bilaminar arrangement of the tunica albuginea becomes thinned, with the midline being monolaminar. The fibers of the septal strands fan out and are interwoven with the inner circular layer. There is no outer circular layer. **E**, In the chronic mechanism of Peyronie disease, less turgid erections allow buckling of the penis as in **B**. **F**, In the acute mechanism of Peyronie disease, buckling of the erect penis out of column produces tension on the strands of the septum, causing the septal fibers to tear.

predispose to injury during intercourse because of the less rigid penis pivoting back and forth, potentially resulting in a tissue fatigue-type fracture, activating the scarring disorder (Devine and Horton, 1988) (Fig. 31-1). Another theory suggests that diabetes may lead to decreased compliance of tissues as a result of increased collagen cross-linking (Aronson, 2003). This may make minor injuries less prone to normal remodeling.

Erectile Dysfunction

ED appears to be more common in men with PD than in the general population (Ralph et al, 2010). The prevalence of ED in men with PD has been reported to be 37% to 58% (Kadioglu et al, 2002; Usta et al, 2004; Casabé et al, 2011; Chung et al, 2011b). In a duplex ultrasound study of 76 men with PD and ED, 36% had evidence of penile arterial insufficiency and 59% had veno-occlusive disease as the cause of their ED (Lopez and Jarow, 1993). In our review of their own clinical experience, approximately 80% of men with PD also have reported diminished rigidity. Half of these men had ED before the onset of PD, usually as a result of the typical vascular risk factors for ED (e.g., smoking, diabetes, hypertension, dyslipidemia), whereas the other half developed ED subsequent to the onset of the PD. The prevalence of associated comorbidities is higher in patients with PD and ED than in patients with PD, which may indicate that hypertension, smoking,

hypercholesterolemia, diabetes mellitus, and hyperlipidemia are more likely related to ED than to the pathogenesis of PD (Usta et al, 2004). This later onset may be attributable to changes in penile geometry and/or psychological inhibition, which is difficult to determine even in studies in which duplex ultrasound and cavernosometry are used (Levine and Coogan, 1996; Kadioglu et al, 2002).

Psychological Aspects

PD is not only a physically deforming but also a psychologically devastating disorder. Multiple studies have now demonstrated the frequent association of psychological distress in men with PD including diminished self-esteem, shame, embarrassment, self-disgust, anxiety, loss of sexual confidence, and depression, all of which can compromise the man's relationships at home, at work, and in the bedroom (Gelbard et al, 1990; Jones, 1997; Rosen et al, 2008; Smith et al, 2008a). Penile shortening and the inability to have intercourse are the two most common and consistent risk factors for emotional distress and relationship problems associated with PD (Rosen et al, 2008; Smith et al, 2008a).

Psychosocial stress is reported by 77% to 94% of men with PD (Gelbard et al, 1990; Tal et al, 2012; Nelson and Mulhall, 2013). Contemporary studies using a validated measure of depression (Center for Epidemiologic Studies Depression Scale [CESD]) have

demonstrated moderate to severe depression in 48% of PD patients, and these rates typically increase with the duration of PD (Nelson et al, 2008). PD also commonly affects the patient's sexual partner, causing feelings of helplessness as well as feelings of personal responsibility for the PD caused by trauma during intercourse, and sadness over loss of intimacy (Rosen et al, 2008).

In an effort to develop a valid outcome measure for assessing psychosocial and sexual consequences of PD, Rosen and associates (2008) conducted a study composed of a series of focus groups with 28 PD patients and identified common concerns. These concerns were grouped into four core domains: (1) physical appearance and self-image, (2) sexual function and performance, (3) PD-related pain and discomfort, and (4) social stigmatization and isolation (Rosen et al, 2008). With these data, a validated Peyronie's Disease Questionnaire (PDQ) was developed; patient-reported estimates of penile curvature severity correlated with PDQ domains, whereas objective measures of penile curvature did not. Thus for some patients even a lesser degree of curvature may be highly bothersome or provoke distress (Hellstrom et al, 2013). This is also evidenced by the fact that self-estimates of penile curvature in men with PD differ from objective measures by an average of 20 degrees, with 54% of patients overestimating their curvature (Bacal et al, 2009). It is important to remember that despite "successful treatment" that may allow the patient to be sexually functional again, there is often persistent psychological distress, presumably because of the residual changes to the patient's pre-PD penis (Gelbard et al, 1990; Jones 1997). It is critical that the physician recognize these psychological effects, not only to enhance the trust between the patient and physician, but also to identify more advanced indicators of depression, which should initiate referral to a sex therapist, psychologist, or psychiatrist (Levine, 2013).

Radical Prostatectomy

Both prostate cancer and PD are most prevalent in men after their fifth decade of life. The evidence to support or refute a link between radical prostatectomy and PD is limited. In a study of 1011 post-radical prostatectomy patients, Tal and associates (2010) demonstrated an incidence of PD of 15.9% with a mean time to development of disease of 13.9 months (Tal et al, 2010). Although postoperative erectile function was not a predictor of development of PD, younger age at time of prostatectomy and white race were reported risk factors for developing PD after radical prostatectomy. The authors concluded that prospective controlled studies are needed to elucidate the incidence of PD after radical prostatectomy and determine if radical prostatectomy has a causative role in the pathogenesis of PD (Tal et al, 2010).

Ciancio and Kim (2000) also examined the effects of prostatectomy on penile fibrosis and sexual dysfunction. Eleven percent of all patients undergoing prostatectomy developed fibrotic changes in the penis. This fibrosis led to penile curvature in 93%, "waist-band" deformity in 24%, and palpable plaques in 69%. Therefore, it does appear that men undergoing radical prostatectomy by an open or robotic approach have a higher risk of developing PD than the general population. The mechanism responsible for this is not known but may include perioperative penile trauma, neurogenic consequences, or as we believe is local release of cytokines that activate the abnormal wound-healing process in men susceptible to PD.

Hypogonadism

The possibility that low serum testosterone may be associated with PD has also been investigated. Results of studies have varied on this topic. Moreno and Morgentaler (2009) demonstrated that severity of curvature was worse in men with low free and total testosterone. Rhoden and associates could demonstrate no such association and concluded in their study that androgen serum levels and sexual dysfunction had no association to PD (Rhoden et al, 2010).

The presence of hypogonadism in patients with PD has been suggested to exaggerate the severity of PD. Nam and associates (2011) showed in a study of 106 patients with PD that curvature, plaque size, ED, and response to medical therapy were worse in patients with testosterone deficiency and concluded that further studies are needed to confirm this relationship. Cavallini and associates (2012) investigated whether testosterone replacement in hypogonadal men with PD would affect treatment with intraleisional verapamil injection. In these patients, supplementation with testosterone improved the efficacy of intraleisional verapamil compared with those who did not receive testosterone replacement. Plaque area and penile curvature were also more severe in hypogonadal men with PD (Cavallini et al, 2012).

Collagen Disorders

There does appear to be an association of PD with other collagen disorders such as Dupuytren disease (DD). DD is believed to be transmitted in an autosomal dominant manner. The prevalence of DD in different geographic locations is extremely variable (0.2% to 56%), and it is not clear whether this is because of genetic or environmental factors. The literature concerning coexisting DD in patients with PD also demonstrates a very large range (0.01% to 58.8%) (Nugteren et al, 2011). As with PD, the prevalence of DD increases with age, from 7.2% among men in the age group of 45 to 49 years up to 39.5% in those 70 to 74 years old (Gudmundsson et al, 2000). Other studies have demonstrated DD in 21% to 22.1% of PD patients, as well as 6.7% who reported having a first-degree relative with DD (Carrieri et al, 1998; Nugteren et al, 2011). Other associated fibrotic conditions are contracture of the plantar fascia (Ledderhose disease) and tympanosclerosis, both of which are uncommon disorders (Box 31-2).

KEY POINTS: EPIDEMIOLOGY

- The incidence of PD varies widely depending on the population being screened and is likely much higher than once thought. Current estimates are between 3% and 9%, and the peak age of onset of PD is the early 50s.
- A linear increase in prevalence can be seen from ages 30 to 49, with an exponential increase in prevalence at age 50.
- PDE5 inhibitors have not been suggested to directly contribute to the development of PD; rather, their associated use in those with medical conditions that contribute to ED likely unmasks deformities that would have otherwise gone unrecognized.
- The prevalence of PD among diabetics has been shown to be 8.1% to 20.3% depending on the population screened, which is higher than in the general population. This may reflect particular patient populations, ethnic groups, referral patterns, and expertise of the physicians treating the disorder.
- The prevalence of ED in men with PD has been reported to be 37% to 58%.
- PD is not only a physically deforming but also a psychologically devastating disorder, with 48% of patients showing signs of moderate to severe depression; in general, these rates increase with the duration of PD. Penile shortening and inability to have intercourse are the two most common and consistent risk factors for emotional and relationship problems associated with PD.
- There appears to be an increased incidence of PD in men who have undergone radical prostatectomy, although further prospective studies are required to confirm this association.
- Although hypogonadism may be associated with PD, there is no clear evidence that it is a risk factor. Further study is indicated, and assessment of serum testosterone is recommended.

BOX 31-2 Associated Conditions

Aging
 Diabetes
 Erectile dysfunction
 Psychological distress
 Radical prostatectomy
 Hypogonadism
 Collagen disorders

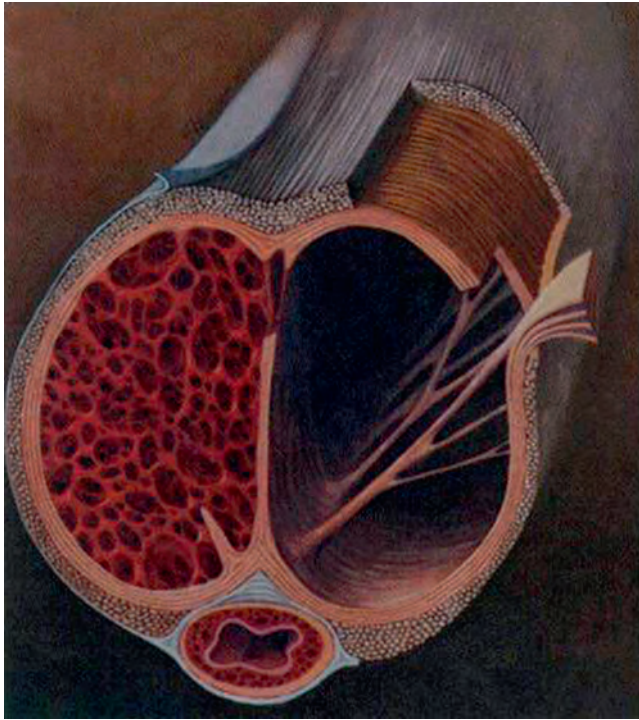


Figure 31-2. The outer layer bundles, which are coarser and directed in a longitudinal manner, often form an incomplete layer (regions 4 to 5 o'clock, 7 to 8 o'clock, and 11 to 1 o'clock) and condense to form ligament-like structures. Artist's drawing of penis depicts dorsal and ventral thickening and pillars. (Data from Brock G, Hsu GL, Nunes L, et al. The anatomy of the tunica albuginea in the normal penis and Peyronie's disease. *J Urol* 1997;157:276–81.)

PENILE ANATOMY AND PEYRONIE DISEASE

The exact cause of PD remains to be determined. Ongoing studies continue to clarify this disorder on the genetic, molecular, and anatomic level. The corpora cavernosa, the erectile bodies of the penis, surrounded by the tunica albuginea possess the ability to become rigid by becoming engorged with blood. The tunica albuginea is a multilayered structure predominantly composed of type 1 collagen that is oriented with an inner circular and outer longitudinal layer interlaced with elastin fibers separated by an incomplete septum (Gentile et al, 1996; Brock et al, 1997; Kelly, 2007). This septum is anchored into the inner circular layer and is key to the structural integrity of the tunica; without it, computer models have demonstrated that the stress generated by a full erection of one contiguous corporeal body would be sufficient to rupture the tunica albuginea (Mohamed et al, 2010). These anchor sites are susceptible to microvascular trauma and tunical delamination, which may be one of the triggers leading to this disease (Devine et al, 1997). The structure is further reinforced by intracavernous pillars, which anchor the tunica albuginea across the corpora cavernosa at the 2 to 6 o'clock and 10 to 6 o'clock positions, with finer pillars at the 5 and 7 o'clock positions (Fig. 31-2) (Brock et al, 1997). It is

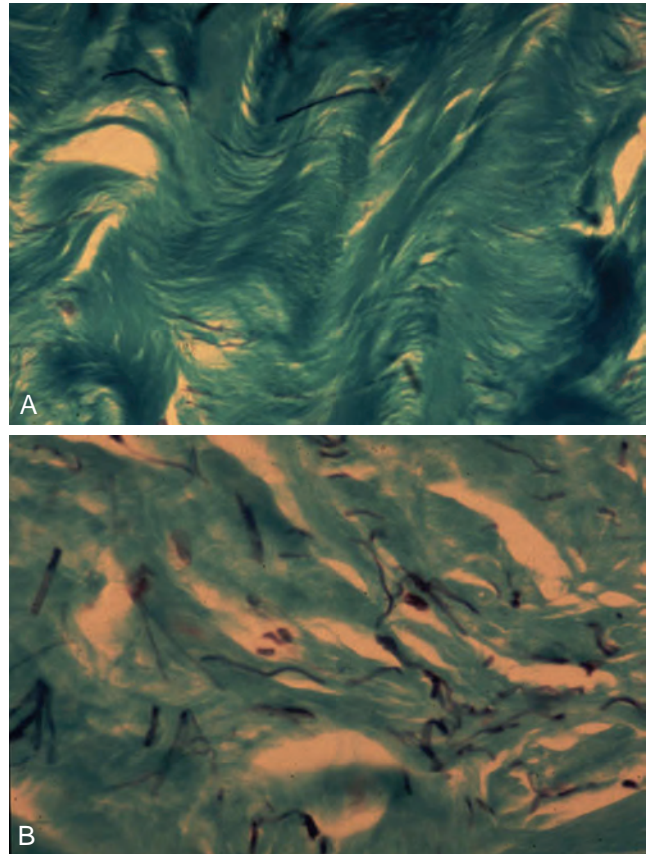


Figure 31-3. Photomicrographs of the tunica albuginea. A, Normal tunica albuginea demonstrating the polarized arrangement of collagen. B, Peyronie plaque demonstrating the nonpolarized arrangement of collagen and the haphazard arrangement of elastin. Collagen stains green; elastin stains black.

interesting to note that 60% to 70% of plaques are located on the dorsal aspect of the penis and are usually associated with the septum (Pryor and Ralph, 2002). It is possible that pressures on the penis during intercourse may cause a delamination between the two layers, activating the abnormal wound-healing process, which is trapped within the tunic, fostering the progressive scarring.

The longitudinal layer of the tunica albuginea is thinnest at the 3 and 9 o'clock positions of the corpora; it is completely absent between the 5 and 7 o'clock positions (Brock et al, 1997). This may contribute to greater ease of dorsal buckling and may explain why most PD patients exhibit dorsal curvature (Devine and Horton, 1988; Border and Ruoslahti, 1992; Brock et al, 1997; Devine et al, 1997; Jarow and Lowe, 1997). In normal tunical tissue, each layer appears to be distinct and is able to slide on the adjacent layer. The normal three-dimensional structure of the tunica affords great flexibility, rigidity, and tissue strength to the penis despite the fact that the tunica albuginea is quite thin—1.5 to 3.0 mm, depending on the position around the circumference. Normal architecture is essentially lost consequent to this disease, resulting in what is known as a Peyronie “plaque,” which when examined histologically demonstrates disorganization of collagen fibrils as well as a decrease in and disorganization of elastin resulting in penile deformity caused by asymmetrical expansion of the corpora (Figs. 31-3 and 31-4) (Akkus et al, 1997; Brock et al, 1997; Devine et al, 1997; Costa et al, 2009). When expansion is limited at one point along the circumference of the corpora by the inelastic scar of the Peyronie plaque, deviation to that side occurs; a circumferential plaque may lead to an hourglass deformity (Akkus et al, 1997; Devine et al, 1997).

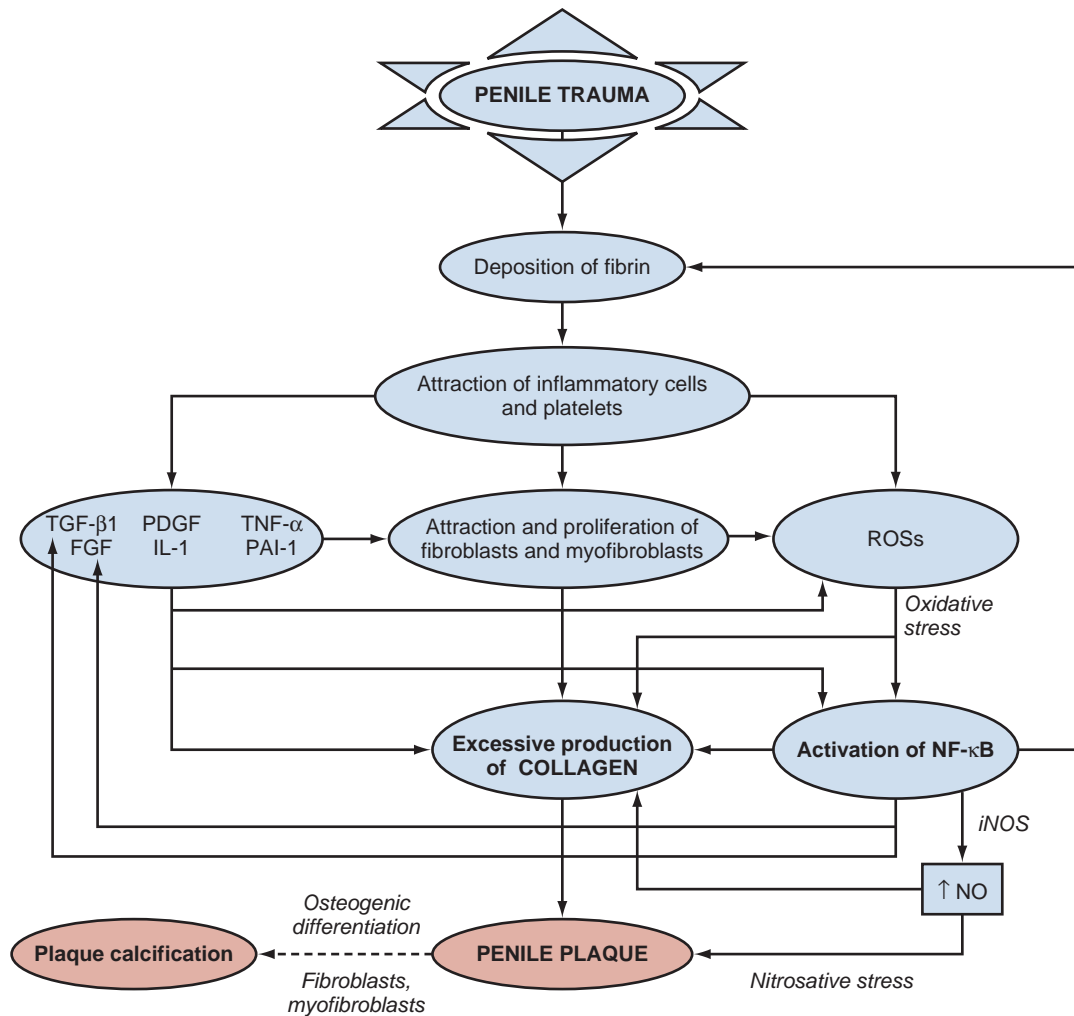


Figure 31-4. Pathogenetic mechanisms of Peyronie disease. FGF, fibroblast growth factor; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor-κB; NO, nitric oxide; PAI, plasminogen activator inhibitor; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor necrosis factor. (Data from Paulis G, Brancato T. Inflammatory mechanisms and oxidative stress in Peyronie's disease: therapeutic "rationale" and related emerging treatment strategies. *Inflamm Allergy Drug Targets* 2012;11:48–57.)

Impact of Wound Healing on the Development of Peyronie Disease

In general, PD has been described as a wound-healing disorder of the tunica albuginea. Recent investigations have focused on the mechanisms of wound healing, fibrosis, and scar formation and have correlated the findings with the PD population. Normal wound healing involves three phases: an acute phase, a proliferative phase, and a remodeling phase. These are not to be confused with the acute and chronic phases of PD previously described. By understanding the wound-healing process, one gains a better understanding of PD, targets for drugs used to treat PD, and the animal models that have been developed for the study of PD. In general, during the **acute phase**, blood vessel injury leads to extravasation of blood and aggregation and activation of platelets that release chemotactic agents that act as promoters in the wound-healing cascade by activating and attracting neutrophils during the first 24 hours after clot formation, macrophages after 48 hours, and finally lymphocytes after 72 hours (DiPietro, 1995). Macrophages phagocytose dead or potentially injurious material and destroy bacteria or other foreign cells via oxygen free radical reactions. In addition, macrophages activate keratinocytes, fibroblasts, and endothelial cells by releasing potent tissue growth factors, particularly transforming growth

factor-β (TGF-β), as well as other mediators such as TGF-α, heparin binding epidermal growth factor, fibroblast growth factor (FGF), and collagenase (DiPietro, 1995; Ravanti and Kahari, 2000).

The next phase of normal wound healing is the **proliferative phase**, which marks the shift toward tissue repair beginning at approximately 72 hours after injury and persisting for approximately 2 weeks. It is characterized by fibroblast and myofibroblast migration in response to TGF-β and platelet-derived growth factor (PDGF), as well as deposition of newly synthesized extracellular matrix (ECM) composed of type I and type III collagen, hyaluronan, fibronectin, and proteoglycans (Velnar et al, 2009). At this point, fibroblasts are stimulated by TGF-β to change into myofibroblasts, which contain thick actin bundles allowing for wound contraction. TGF-β also signals fibroblasts and myofibroblasts to synthesize types I and III collagen (Tomasek et al, 2002; Gelbard, 2008).

Finally, the **remodeling phase** begins and in the normal situation may last up to 1 or 2 years. The remodeling of an acute wound is tightly regulated by mechanisms that balance the simultaneous degradation and synthesis of collagen as well as other ECM macromolecules. Any alterations in this process may lead to abnormal wound healing with excessive scarring (Velnar et al, 2009). Matrix metalloproteinases (MMPs) (collagenases), produced by neutrophils, macrophages, and fibroblasts in the wound, are responsible for the degradation of collagen. They are subsequently

held in check by inhibitory factors called tissue inhibitors of metalloproteinases (TIMPs). As the activity of TIMPs increases, there is a drop in matrix breakdown by metalloproteinase enzymes, thereby promoting new matrix accumulation (Ravanti and Kahari, 2000). This balance between TIMPs and MMPs has also been studied in the pathogenesis of PD and is described later in this section.

Over time the highly disorganized initial deposition of collagen matrix becomes more oriented and cross-linked during the final stages of the remodeling phase. The process is regulated by a number of factors, with PDGF, TGF- β , and FGF being the most important (Velnar et al, 2009), but also including MMPs, TIMPs, fibrin or plasminogen activator inhibitor-1 (PAI-1) (Taylor and Levine, 2007; Velnar et al, 2009). Having accomplished this task, redundant fibroblasts and myofibroblasts are eliminated by apoptosis. A fundamental understanding of the elements of normal wound healing provides a foundation for understanding which components may go awry in PD. It does appear that most basic science research in this field has focused on the development of the scarring process resulting in the exuberant scar found in men with PD. More recent research has focused on the dysregulation of remodeling that may be responsible for why the fibrosis does not resolve.

ETIOLOGY OF PEYRONIE DISEASE

The exact cause of PD has not yet been defined, although most would agree that some injurious stimulus is necessary to trigger the cascade of events that leads to PD in the susceptible individual (Devine et al, 1997; Jarow and Lowe, 1997; Carrieri et al, 1998; Jalkut et al, 2003; Bjekic et al, 2006; Nachtsheim and Rearden, 1996). Trauma may be perceived as a single event experienced by the patient or may take the form of repetitive microtrauma to the penis. Furey (1957) initially suggested that trauma was the primary cause of PD (Furey, 1957).

The proposed mechanism is that in the erect state, the pressures inside the penis can get quite high and acutely higher when external forces are placed on the penis during intercourse in particular. These pressures may exceed the elasticity and strength of the tunica tissues, resulting in a microfracture. A commonly held misconception is that the trauma to the penis must occur only when it is erect; however, in our experience we have noted that trauma to the flaccid penis may also trigger this process. In a recent review of our database of 228 patients who had recognized trauma to the penis shortly before the onset of PD, 16% reported a traumatic event to the flaccid penis (e.g., motor vehicle accident, sports-related injury). As the scar develops, there may also be an inflammatory response, resulting in the pain that can be present in the flaccid penis or when pressure is placed on the penis. Dorsal and ventral shear stresses occurring during sexual activity may account for the more common dorsal location of plaques (Devine et al, 1997). Investigators have suggested that repetitive microtrauma to the penis leads to delamination of the tunica albuginea and vessels between the layers of the tunica (Somers and Dawson, 1997). This leads to microhemorrhage and initiates the wound-healing cascade described previously.

Carrieri and associates (1998) reported a 16-fold increase in PD in those who had undergone prior invasive procedures as well as a nearly 3-fold increase in PD in patients who had experienced genital and/or perineal trauma (Carrieri et al, 1998). It is also important to note that although trauma has been considered the most likely trigger activating PD, in our clinical experience no more than 30% of men recall a specific event involving injury to the penis close to the time when the scarring or pain began. Other investigators have reported 16% to 40% of patients having had antecedent trauma (Bjekic et al, 2006; Tal et al, 2012). An injury occurring during sexual activity appears to be the most common recognized event associated with the onset of PD. An association with trauma and position of intercourse has been proposed for some time, based on the assumption that certain positions may be more apt to cause injury. This has not been verified but it does appear from anecdotal experience that the most common sexual

position noted to precede the onset of PD is with the partner on top. In this position, a sudden “faux pas de coit” or missed thrust may lead to high intracorporeal pressures (Bitker et al, 1988).

Although trauma undoubtedly plays a pivotal role in the development of disease, it alone cannot explain why some men develop deformity whereas others do not. This is no better illustrated than by a study of 193 penile fracture patients in whom none went on to develop PD (Zargooshi, 2004). Several underlying factors have been considered responsible for PD; genetic predisposition, autoimmune factors, an aberration of localized wound healing, and even infection have been proposed as possible causes (Devine et al, 1991; Ralph et al, 1996; Mulhall et al, 2002; Jalkut et al, 2003; Taylor and Levine, 2007). Therefore, we should be careful about the medicolegal implications of referring to PD as the result of treatments for ED, trauma to the flaccid penis, or catheterization or endoscopy, which are more likely just providing an opportunity for the forces at hand to activate the abnormal wound-healing response in the “genetically” susceptible man rather than being the cause of PD (Carrieri et al, 1998; Levine and Latchamsetty, 2002). The following discussion focuses on specific research into the pathophysiology of PD.

Role of Oxygen Free Radicals and Oxidative Stress

Oxidative stress has a well-documented role in tissue fibrosis and has been studied in the pathogenesis of PD (Gonzalez-Cadavid and Rafjer, 2005). As stated previously, microvascular trauma leads to extravasation of blood, with thrombus formation that leads to deposition of fibronectin and fibrin. Inflammation ensues with accumulation of inflammatory cells and production of reactive oxygen species (ROSs). During the early phase of PD an increase in oxidative stress in the form of free radicals induces overexpression of fibrogenic cytokines and augmented transcription and synthesis of collagen. ROSs are increased by TGF- β 1, which also directly inhibits collagenase and promotes collagen synthesis (Magee et al, 2002). ROSs include superoxide anion, hydrogen peroxide, hydroxyl radical, organic hydroperoxide, alkoxy radicals, and peroxy radicals. Although NO seems to play an antifibrotic role, nitrosative stress as well as oxidative stress can lead to macromolecular damage, cytotoxic effects, lipid peroxidation, DNA fragmentation, collagen accumulation, and cellular dysfunction (Paulis and Brancato, 2012).

Role of Nitric Oxide in Peyronie Disease

NO is a small reactive free radical that acts as both an intracellular and an extracellular regulatory molecule. Wound cells, including monocytes, macrophages, and fibroblasts, have been shown to synthesize NO through a nuclear factor- κ B (NF- κ B)-activated inducible NO synthase (iNOS)-dependent mechanism after injury. The iNOS isoform produces NO; it is usually considered a defense mechanism against infection or cancer, is associated with inflammation, and is significantly increased in human and animal PD plaques (Gonzalez-Cadavid, 2009). NO synthesized by iNOS reacts with ROSs, thus reducing ROS levels and presumably inhibiting fibrosis. The antifibrotic effects of NO may be mediated at least in part by the reduction of myofibroblast abundance and may lead to a reduction in collagen I synthesis (Vernet et al, 2005). NO may also play an antifibrotic role by activating guanylyl cyclase, thus producing cyclic guanosine monophosphate (cGMP), which has been suggested to inhibit plaque formation (Ferrini et al, 2002; Valente et al, 2003).

Role of Myofibroblasts in Peyronie Disease

The excessive deposition of collagen and ECM accompanied by the loss of functional cells that characterizes tissue fibrosis is caused in some cases by the appearance and accumulation of myofibroblasts (Gonzalez-Cadavid, 2009). Twenty percent of cells cultured from PD tunica albuginea are in fact myofibroblasts, suggesting that they may be one of the primary factors leading to fibrosis in PD (Mulhall

et al, 2002). Proposed mechanisms for the presence and persistence of myofibroblasts include a decrease in myofibroblast apoptosis, as well as stimulation of fibroblast transformation to myofibroblasts by TGF- β and mechanical stress, which has been associated with hypertrophic scarring (Darby and Hewitson, 2007; Gelbard, 2008). Myofibroblast activation is a key event in the development of fibrosis. Trauma to the tunica albuginea secondary to microscopic delamination increases the adherence of fibroblasts to their surroundings, exposing them to changes in ECM tension, and in the presence of appropriate cytokines initiates their differentiation into myofibroblasts (Gelbard, 2008). When tension diminishes, myofibroblasts tend to undergo apoptosis. Gelbard postulated that if myofibroblasts are continuously exposed to tension in the form of rigid corpora during erections, they may fail to undergo apoptosis and subsequently contribute to what appears to be a hallmark of PD—inappropriate and persistent stimulation of the wound-healing process (Gelbard, 2008).

Role of Transforming Growth Factor- β 1 in the Etiology of Peyronie Disease

TGF- β 1 has been shown to be significantly associated with PD (El-Sakka et al, 1997). TGF- β is a strong activator of myofibroblasts and is known to be a potent fibrotic growth factor by stimulating the deposition of ECM. TGF- β binds cell surface receptors and through a signal transduction cascade leads to the deposition and remodeling of ECM by stimulating cells to simultaneously (1) increase the synthesis of most matrix proteins (Ihn, 2002); (2) decrease production of matrix-degrading proteases while increasing the production of inhibitors of these proteases (Knittel et al, 1999); and (3) modulate the expression of integrins (Margadant and Sonnenberg, 2010). The action of TGF- β in tissue repair has been shown to involve an initiation of complex sequences of monocyte chemoattraction, induction of angiogenesis, and control of the production of cytokines and other inflammatory mediators (Border and Ruoslahti, 1992). Moreover, TGF- β stimulates the synthesis of individual matrix components including fibronectin, tenascin, collagens, and proteoglycans, while simultaneously blocking matrix degradation by decreasing the synthesis of proteases and increasing levels of protease inhibitors (Balza et al, 1988). All these events can be beneficial in tissue repair; however, the deposition of ECM at a site of tissue injury can lead to scarring and fibrosis. Furthermore, the ability of TGF- β to induce its own production may be the key to the development of scarring and fibrosis (Border and Ruoslahti, 1992). TGF- β 1 is not the only member of the large TGF- β superfamily of growth and differentiation factors (GDFs) that have been implicated as fibrotic agents. Myostatin, also known as GDF-8, has been proposed not only as an inhibitor of myofiber formation but also as an inducer of fibrosis. Myostatin is expressed in the normal human tunica albuginea (TA) and overexpressed in PD plaque. Myostatin stimulates myofibroblast generation and collagen deposition in normal tunic and is upregulated by TGF- β 1. Myostatin seems to potentiate the effects of TGF- β 1 (Cantini et al, 2008).

Fibrotic Gene Expression in Peyronie Disease

A variety of profibrotic and antifibrotic factors contribute to the development of PD plaque that leads to deformity (Grazziotin et al, 2004). Qian and colleagues performed DNA microarray analysis of PD tissue obtained from patients undergoing surgery for PD. The most highly upregulated gene found in the PD plaque, *PTN* or *OSF1*, codes for a secreted heparin-binding protein thought to stimulate mitogenic growth of fibroblasts and osteoblast recruitment, and is possibly related to plaque ossification. Proteins responsible for cell proliferation, cell cycling, and apoptosis were found to be increased, whereas Id-2, an inhibitor of myofibroblast differentiation, was downregulated. The second most upregulated gene, *MCP-1*, is critical to the inflammatory response and ossification (Graves, 1999; Graves et al, 1999). Genes related to myogenic

conversion during wound healing and fibroblast differentiation into myofibroblasts were upregulated, whereas collagenase IV, which is critical for collagen degradation and is decreased in fibrosis, was downregulated (Magee et al, 2002). Qian and associates (2004) performed a study comparing gene expression profiles of PD patients with those of DD patients. A series of 15 genes were upregulated and none were downregulated in the PD plaque versus the normal TA. Of the genes upregulated, the ones most prominently increased were MMPs involved in collagen breakdown, specifically MMP-2 or MMP-9 in one half of the PD plaques, in addition to genes involved in actin-cytoskeleton interactions required for fibroblasts and myofibroblasts to generate the contractile forces (Qian et al, 2004). According to the findings of another study, the lower expression of apoptotic genes may cause the persistence of collagen-producing cells that are upregulated, consequently resulting in plaque formation. Similar expression levels of apoptotic genes in both tunica albuginea and Peyronie plaques may be caused by the generalized physiopathologic alterations in the tunica albuginea that lead to plaque formation at a vulnerable region subjected to recurrent trauma (Zorba et al, 2012).

Del Carlo and colleagues (2008) investigated the role of MMPs and TIMPs in the pathogenesis of PD by using harvested plaque from patients who had PD. PD tissue samples were found to have diminished or absent levels of MMP-1, MMP-8, and MMP-13 compared with matched perilesional tunica and non-PD controls. PD fibroblasts were cultured with soluble MMPs and TIMPs after treatment with TGF- β or interleukin-1 β (IL-1 β). They found that IL-1 β stimulation increased the production of MMP-1, MMP-2, MMP-8, MMP-9, MMP-10, and MMP-13 in PD fibroblasts, whereas TGF- β increased the production of only MMP-10 and decreased the production of MMP-13, suggesting that PD fibroblasts can be induced to make MMPs (Del Carlo et al, 2008). Baseline aberrant expression of p53, a cell cycle-regulating protein, has been demonstrated in PD fibroblasts as well as an absent response to sublethal DNA damage. This suggests a role for an aberration in the p53 pathway in the pathogenesis of this condition (Mulhall et al, 2001a).

When all this information is taken together, it is not hard to understand why there are myriad clinical presentations and treatments for this very complex disease. A variety of alterations may be present in a given patient, which may manifest as fibrosis with penile deformity (see Box 31-2). This has been demonstrated by Qian and colleagues, who found marked heterogeneity in gene expression profiles among men with PD (Qian et al, 2004). As suggested by the ensuing section on medical therapy, different medical treatments that target different disease mechanisms may not work uniformly among the PD population (see Fig. 31-4).

KEY POINTS: ANATOMY AND ETIOLOGY

- The longitudinal layer of the tunica albuginea is thinnest at the 3 and 9 o'clock positions of the corpora; it is completely absent between the 5 and 7 o'clock positions. This absence of the longitudinal layer ventrally may contribute to greater ease of dorsal buckling and may explain why most PD patients exhibit dorsal curvature.
- Normal architecture is essentially lost consequent to this disease, resulting in what is known as a Peyronie plaque, which when examined histologically demonstrates disorganization of collagen fibrils as well as a decrease and disorganization of elastin, resulting in penile deformity caused by asymmetric expansion of the corpora.
- Antecedent trauma has been reported in 16% to 40%; most would agree that some injurious stimulus is necessary to trigger a cascade of events that lead to PD in the susceptible individual.
- Oxygen free radicals, oxidative stress, NO, myofibroblasts, TGF- β 1, and fibrotic gene expression all play a key role in the development of PD and are key avenues for future research to further elucidate the exact mechanism behind the development of PD.

SYMPTOMS

The most frequent presenting symptoms of patients with PD include penile pain, erect deformity, and palpable plaque, as well as ED (Pryor and Ralph, 2002; Smith et al, 2008b; Chung et al, 2011a). Many men who have PD visit the doctor with a self-misdiagnosis of ED. Not all patients experience pain or are able to palpate a plaque, but the shortening, hinge effect, distal softening, and curvature, when present, are readily recognized. Pain, when present in the acute phase, can occur in the flaccid condition with palpation of the plaque, with erection, or during intercourse. Once the disease process is stable, most pain will resolve, but in some men the pain persists with what has been referred to as “torque” pain associated with a pulling sensation on the plaque when a strong erection occurs (Levine and Larsen, 2013). This should not be confused with the inflammatory pain of the acute phase.

Although curvature can be one of the most recognized and distressing deformities associated with PD, many men are capable of sexual activity with curvature up to 60 degrees, particularly if the curvature is dorsal and more gradual along the shaft. Men with ventral or lateral curvatures may have a more difficult time with intromission because of discomfort. Yet, it is not uncommon to hear that the partner does not complain of discomfort during coitus, regardless of the degree or direction of curvature. Patient estimates of curvature are unreliable. One study demonstrated that 50% of patients overestimated their degree of curvature by an average of 20 degrees (Bacal et al, 2009). Classification by degree of curvature was introduced by Kelami (1983). One center reported on the distribution of curvature by the Kelami classification and found that 39.5% of patients had 30 degrees (mild) or less, 35% had 31 to 60 degrees (moderate), and 13.5% had more than 60 degrees of curvature (severe); 12% had no curvature but did experience an hourglass deformity resulting in an unstable erection (Kadioglu et al, 2011b).

The PD plaque can manifest in a variety of configurations including cords; simple nodules; coinlike, irregular dumbbell shapes; or I-beam plaques. It appears that virtually all plaques have a septal component, which supports the concept of delamination of tunical fibers as a result of axial forces on the septum (Jordan, 2007). Pure septal plaques have also been reported and may result in narrowing, shortening, or no recognized deformity at all (Bella et al, 2007).

The orientation of the plaque usually defines the deformity. Therefore patients with a simple dorsal plaque are most apt to have dorsal curvature; but if there is transverse or spiraling scarring, which can be partial or circumferential, this could result in varying degrees of indentation including an hourglass deformity, which can result in an unstable penis, or a hinge effect as a result of the inability to tolerate axial forces in the erect condition (Pryor and Ralph, 2002). The distal softening of the shaft beyond the plaque is also difficult to understand, because dynamic infusion cavernosometry and cavernosography (DICC) studies have found that the pressures within the corpora cavernosa are equal, when measured, proximal and distal to the plaque (Jordan and Angermeier, 1993). The cause of distal flaccidity remains speculative and includes local cavernosal fibrosis extending from the involved tunic (Ralph et al, 1992) and site-specific venous leak.

EVALUATION OF THE PATIENT

As with all medical conditions, a detailed history is a critical part of the evaluation of the man with PD (Levine and Greenfield, 2003). The intake interview should focus on presenting signs and symptoms such as pain, deformity, and palpable plaque. The assessment should also include whether onset was gradual or sudden and the estimated time that symptoms began; it should be determined whether there was any inciting event that may have triggered the process, including direct external penile trauma to the



Figure 31-5. This patient had physical evidence of Dupuytren, Ledderhose, and Peyronie diseases.

flaccid or erect penis or instrumentation. The patient should be asked whether there is any personal or family history of other fibrotic disorders including DD and Ledderhose disease (Fig. 31-5). Patients should be carefully queried as to their erectile capacity, but ultimately the question is whether the patient is capable of intromission or incapable because of deformity and/or diminished rigidity. A useful question that has been shown to be an effective predictor of postoperative erectile function is “If your penis was straight with the same quality of rigidity that you have now, do you think it would be adequate for penetrative sexual activity?” (Levine and Greenfield, 2003; Taylor et al, 2012). Clearly if the patient does not feel his erections would be satisfactory with or without pharmacotherapy, this can help direct the patient to treatment with a penile prosthesis and straightening maneuvers; nonsurgical or other surgical approaches could result in improvement of deformity, but if there is persistent ED, such treatment would likely not give the patient a sexually functional erection.

Further information to be obtained from the sexual history will be whether there are any vascular risk factors for ED, including a history of diabetes, hypertension, elevated cholesterol, and smoking. This is also a useful time to determine if there are issues with premature or delayed ejaculation. A list of medications may also indicate underlying medical conditions that may predispose to ED.

The recently validated PD questionnaire (PDQ) (Rosen, 2008; Hellstrom et al, 2013) addresses not only the concerns of the patient regarding structural changes of the penis but also how PD affects his overall psychological condition. The current questionnaire has 15 questions assessing three domains, including (1) Peyronie psychological and physical symptoms (six items), (2) penile pain (three items), and (3) the effects of PD symptoms (six items). Each domain is intended to be an independent measure, and the scores are not summed for a total instrument score. Higher scores indicate a greater negative impact. With further experience, it may prove to be a useful assessment tool for patients making treatment decisions. The PDQ can be downloaded at www.auxilium.com/PDQ.

The value of a photograph taken at home of the erect penis has been controversial because of the inability to adequately represent and measure a three-dimensional deformity (Ohebshalom et al, 2007; Bacal et al, 2009). At the current time, with the prevalence of smartphones, a photograph can be taken by the patient from above and from the side in the erect state, which can

be useful during the initial consultation to get a general impression of the direction and severity of the deformity.

The physical examination should include a general assessment of the femoral pulses, appearance of the flaccid penis, and whether it is circumcised. To assess the Peyronie plaque, the penis should be examined on stretch, which allows easier identification of the plaque (Fig. 31-6). The location of the plaque may be useful to



Figure 31-6. Palpation of penis on stretch facilitates identification of plaque.

record, but measurement of the size of the plaque with any modality has been found to be inaccurate because the plaque is rarely a discrete lesion (Bacal et al, 2009; Ralph et al, 2010; Hatzimouratidis et al, 2012; Levine and Burnett, 2013). It has irregular borders and often extends into a septal cord (Levine and Greenfield, 2003; Ralph et al, 2010). Furthermore, there is no evidence that a reduction in plaque size as a result of treatment is at all associated with improvement of deformity (Levine and Burnett, 2013). The stretched penile length (SPL) is also a critical parameter to measure at the initial consultation. This is performed by placing the penis on stretch by grasping the glans and pulling at a 90-degree angle away from the body (Wessells et al, 1996). It is our preference to measure from the pubis to the corona dorsally, as these are two fixed points and facilitate repeated measurement during the course of treatment and follow-up. The consistency of the plaque may be recorded. A “rock hard” plaque may be an indicator of calcification but will need to be confirmed with some form of imaging, preferably ultrasonography (Fig. 31-7). A calcified plaque is readily identified on ultrasonography because of the hyperdensity of the plaque with shadowing behind it. Computed tomography and magnetic resonance imaging have little value in the evaluation of the man with PD, but further investigation is ongoing to determine whether these modalities can provide prognostic information (Andresen et al, 1998; Hauck et al, 2003).

Only recently has it been recognized that calcification may occur early after the onset of the scarring process, and therefore the previously held notion that calcification is an indication of chronic, severe, and/or mature disease appears untrue (Levine et al, 2013). Calcification is most likely the result of a different genetic subtype of PD in which there is activation of genes involved in osteoblastic activity (Vernet et al, 2005). Why some plaques undergo mineralization and others do not remains unknown, but it does appear that the extent of mineralization may have a bearing on a successful response to nonsurgical therapy; men with more extensive calcification are less likely to benefit from nonsurgical treatment (Chung et al, 2011a). Several investigators have indicated that intralesional injection therapy with verapamil and interferon (IFN) is less likely to be successful in men with significant calcification (Levine et al, 2002; Hellstrom et al, 2006). This is because the drug will not be able to get into or effect change within this

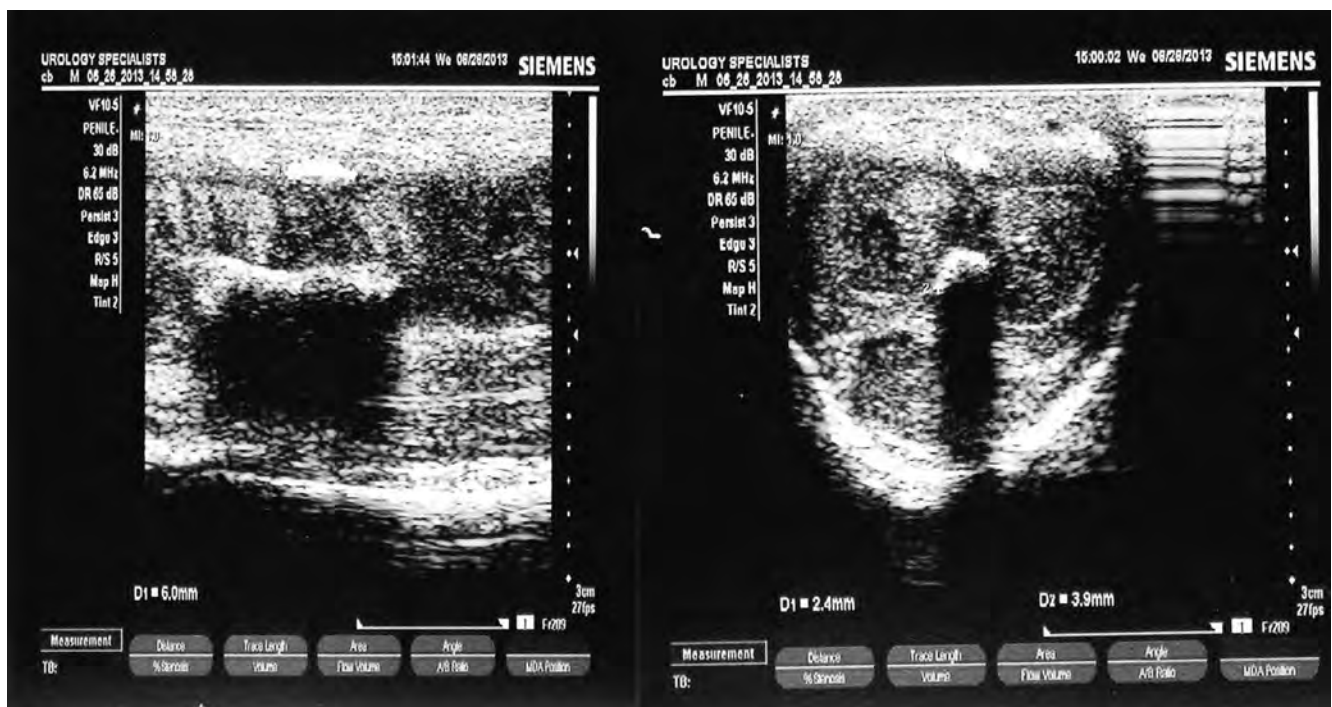


Figure 31-7. This ultrasound image demonstrates areas of dorsal and ventral calcification. Note shadowing behind calcified plaques.

mineralized tissue. Furthermore, investigators have also suggested that patients with extensive calcification are more apt to proceed to placement of a penile prosthesis (Breyer et al, 2007; Chung et al, 2012b). Recently a calcification grading system was published. The investigators found that patients with grade 3, or the most extensive, calcification (>1.5 cm in any dimension or multiple plaques ≥ 1.0 cm) were more likely to undergo surgery when they also had satisfactory erectile function. This is in contradistinction to those who had less severe calcification of grade 1 (<0.3 mm) or grade 2 (0.3 to 1.5 cm) or no calcification in whom there was no evidence of an increased likelihood of proceeding to surgery (Levine et al, 2013).

The role of vascular testing has not been clearly defined. In centers that see many men with this disorder, duplex ultrasound analysis is routinely performed as part of the initial evaluation, especially for those who are considered surgical candidates (Ralph et al, 2010; Hatzimouratidis et al, 2012; Levine and Burnett, 2013). Assessment of penile deformity in the erect state is critical to the evaluation. This has been shown to be most accurately measured after an office vasoactive injection as compared with a home photograph or vacuum-induced erection (Ohebshalom et al, 2007). The benefits of a complete duplex ultrasound assessment include identification of calcification during initial surveillance in the flaccid state, assessment of penile vascular flow parameters after intracavernosal injection of vasoactive agent, observation of the erectile response to the vasoactive injection compared with the patient's sexually induced erection at home, and provision of the best opportunity to objectively assess deformity (Figs. 31-8

and 31-9; Box 31-3). These parameters are absolutely critical to the decision process for the patient who is considering surgery (Fig. 31-10).

Several studies have demonstrated that preoperative erectile function correlates strongly with postoperative results (Jordan and Angermier, 1993; Levine and Greenfield, 2003; Taylor et al, 2012). In an analysis of the relationship of penile deformity to the vascular status of PD, patients with ventral curvature were most likely to have cavernous veno-occlusive dysfunction, which further confirms the concern about postoperative ED after grafting of ventral curves (Lowsley and Boyce, 1950; Kendirci et al, 2005).

Some authors have reported the use of DICC as a tool to assess penile vascular integrity and in particular venous leakage before surgery (Jordan, 2007; Alphs et al, 2010). This test appears to add unnecessary invasiveness and expense and provides little value to the diagnostic evaluation over a well-done dynamic penile duplex ultrasonography. Although no standard evaluation for assessment of penile sexual sensitivity has been established, light touch and biothesiometry can be used (Levine and Burnett, 2013). Biothesiometry has been suggested to be an indirect measure of penile sexual sensation. This is controversial because no definitive controlled studies have been reported (Padma-Nathan, 1988). The assumption is that the vibratory nerves travel with the unique sexual nerves of the penis. Therefore, vibratory appreciation with the index fingers used as the positive control and anterior thighs as the negative control can be a surrogate assessment of sexual sensation, which may be compromised by scar infiltration into the sensory nerves or because of other underlying systemic disorders such as diabetes mellitus. In response to the proposed increased prevalence of hypogonadism with PD, we recommend obtaining a morning serum total testosterone level during the initial evaluation (Moreno and Morgentaler, 2009).



Figure 31-8. Measurement of curvature with goniometer.

BOX 31-3 Value of Penile Duplex Ultrasonography for Peyronie Disease

- Identification and measurement of plaque calcification
- Identification of corporeal fibrosis
- Observation of erectile response to vasoactive intracavernosal injection
- Measurement of penile vascular parameters (peak systolic velocity, end-diastolic velocity, and resistive index)
- Optimum objective measurement of erect penile deformity (curvature, girth irregularities, hinge effect)



Figure 31-9. Instability or a hinge effect of the erect penis caused by indentation is demonstrated in this severely dorsally bent penis with application of axial pressure.

KEY POINTS: EVALUATION

- Detailed history includes onset of symptoms, vascular risk factors for ED, patient estimated degree of deformity, and patient assessment of quality of erection with respect to rigidity.
- Validated questionnaires include the PDQ to document the degree of effect associated with PD.
- The physical examination focuses on palpability of plaque with the penis on stretch to enhance appreciation of plaque, stretched flaccid penile length, and presence of pain during palpation.
- Deformity (e.g., curve, indentation) is assessed during a vasoactive drug injection–induced erection using goniometer and duplex ultrasound, particularly for assessment of plaque mineralization and especially if surgery is contemplated.

NONSURGICAL TREATMENT OF PEYRONIE DISEASE

Myriad nonsurgical treatments for PD have been offered since the time of de la Peyronie. Medical therapy until very recently has been compromised by suboptimal studies that failed to demonstrate meaningful results owing to small numbers of subjects, lack of a control group, lack of randomization, and limited objective measurements (Schaeffer and Burnett, 2012). In addition, the variety of disease presentations and its poorly understood cause contribute to treatments that have not addressed the underlying pathophysiology of this wound-healing disorder. In this section, we review the contemporary treatments and focus on placebo-controlled studies when possible.

Some patients require only reassurance, particularly if there is no difficulty or pain for the patient or his partner in accomplishing penetrative sex. Patients should also be reassured that this is not a disorder that will degenerate into a cancer and is therefore not life-threatening.

TREATMENT PROTOCOLS

Multiple treatment protocols have been developed and published. It should be recognized that these algorithms serve only as guidelines and that individualization is key to patient success, which depends on specific findings from the history, physical examination, duplex ultrasonography, and patient goals (Levine and Lenting, 1997; Levine and Greenfield, 2003; Bokarica et al, 2005; Ralph et al, 2010; Hatzimouratidis et al, 2012).

Oral Medications**Potaba**

Potassium aminobenzoate (Potaba) is a member of the vitamin B complex. Its mechanism of action has not been studied since 1959, when Zarafonitis and Horrax demonstrated in fibroblast cell cultures that potassium aminobenzoate can reduce the formation of collagen. According to this in vitro study, it is believed that this drug decreases serotonin levels by increasing monoamine oxidase

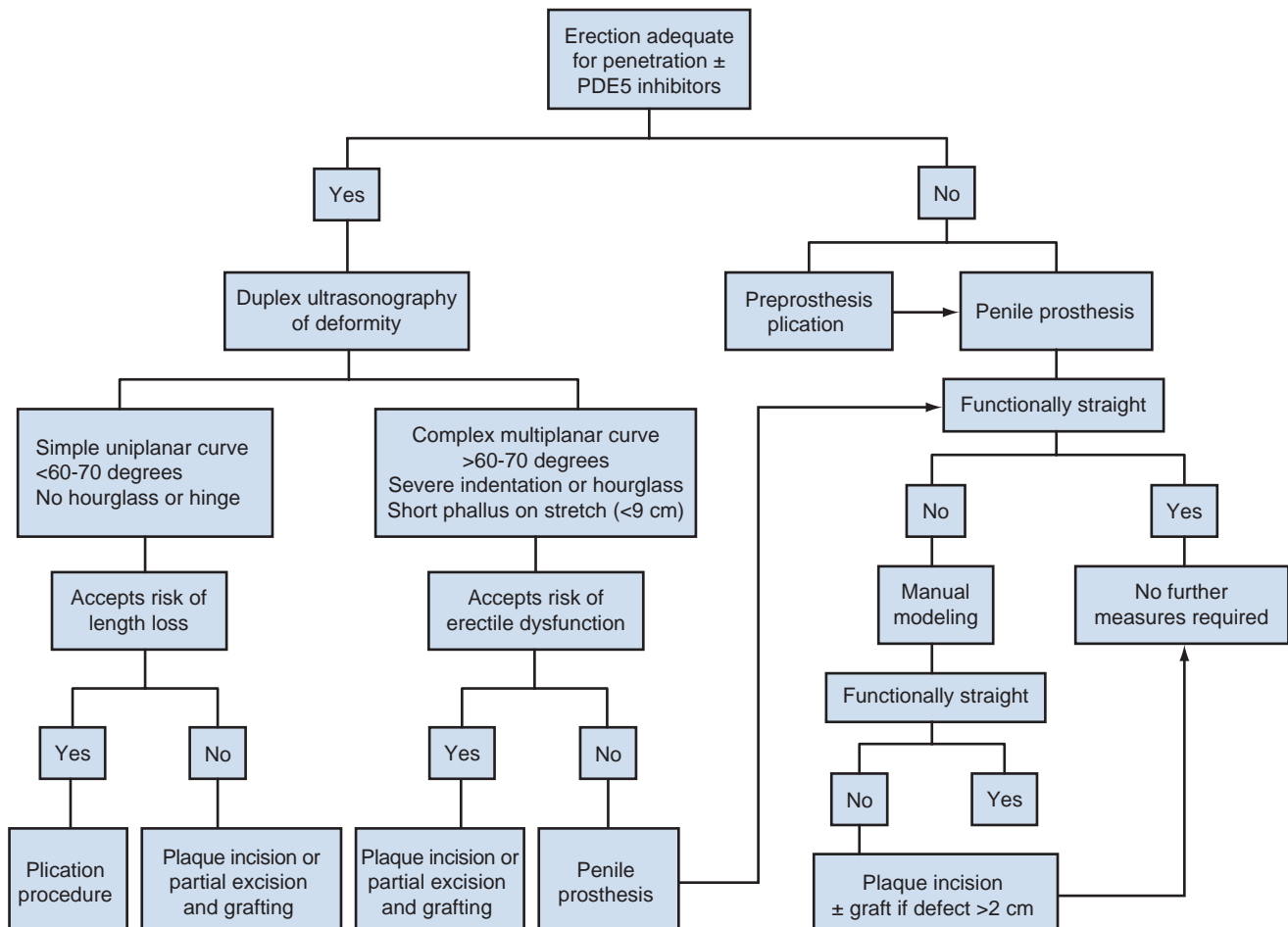


Figure 31-10. Algorithm for the surgical management of Peyronie disease. PDE5, phosphodiesterase type 5.

activity, resulting in enhancement of the endogenous antifibrotic properties of tissues (Zarafonitis and Horrax, 1959).

In a randomized double-blind placebo-controlled trial of 103 treatment-naïve PD patients with noncalcified plaque, 51 patients were assigned to treatment with potassium *p*-aminobenzoate and 52 to placebo. Mean plaque size decreased in the treatment arm, whereas plaque size remained stable over 12 months of follow-up in the placebo arm. Penile deviation remained stable in those receiving active drug; penile curvature deteriorated significantly in 32.5% of those receiving placebo. No significant differences concerning decrease in pain could be observed between the two groups. The authors concluded, "Potassium paraaminobenzoate appears to be useful to stabilize the disorder and prevent progression of penile curvature" (Weidner et al, 2005). No severe adverse events occurred in the study; however, acute hepatitis associated with administration of potassium aminobenzoate for PD has been reported (Roy and Carrier, 2008). Because there is little evidence of benefit with potassium amino benzoate in placebo-controlled trials and it is expensive and difficult to consume (24 tablets daily), we do not recommend its use.

Vitamin E

Vitamin E is one of the oldest described oral treatments for the treatment of PD (Scardino and Scott, 1949). Vitamin E, a fat-soluble vitamin metabolized in the liver and excreted in bile, is an antioxidant that is thought to limit oxidative stress of ROSs known to be increased during the acute and proliferative phases of wound healing. Increased free-radical expression and a prolonged inflammatory phase of wound healing have been demonstrated in PD. Treatment with vitamin E inactivates circulating free radicals that otherwise would inhibit NO from exerting its positive effects on vascular smooth muscle (Safarinejad et al, 2007).

Several well-designed studies have demonstrated no significant improvement in pain, curvature, and plaque size when compared with placebo (Ralph et al, 2010). Pryor and Farrell (1983) conducted a double-blind, placebo-controlled crossover study evaluating vitamin E for the treatment of PD in 40 subjects. No significant improvements were noted in plaque size or penile curvature (Pryor and Farrell, 1983). Gelbard and associates (1990) compared treatment with vitamin E with the natural history of PD in 97 subjects with disease duration ranging from 3 months to 8 years; no significant differences were found between the two groups in terms of curvature, pain, or the ability to have intercourse (Gelbard et al, 1990). In a randomized double-blind placebo-controlled study of a total of 236 men with PD, vitamin E failed to show benefit with respect to pain, curvature, or plaque size when compared with placebo (Safarinejad et al, 2007). Although there were no significant observed adverse effects reported in this study, there is evidence that vitamin E may increase the risk of cerebrovascular events (Brown et al, 2001). Vitamin E is the most frequently recommended oral agent in spite of studies showing no benefit over placebo (LaRochelle and Levine, 2007; Shindel et al, 2008).

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator that has both agonist and antagonist effects on target tissues depending on tissue-specific estrogen receptor expression. It has also been demonstrated that tamoxifen can induce the production of TGF- β in an estrogen receptor-independent fashion (Colletta et al, 1990). The use of tamoxifen for the treatment of PD is truly fascinating and underscores how complex the role of TGF- β is in the development of PD. TGF- β released by platelets and activated macrophages plays a central role in the inflammatory response and wound healing. In normal healing it promotes matrix synthesis by fibroblasts and is self-regulated in an autocrine fashion. However, higher concentrations of TGF- β in the cellular environment inhibit the inflammatory response, causing macrophage deactivation and T-lymphocyte suppression, thus preventing further fibrogenesis (Wahl et al, 1989). This was the initial reasoning for Ralph and associates (1992) to

report in a nonrandomized study on the initial use of tamoxifen for the treatment of PD (Ralph et al, 1992).

The initial beneficial effects previously reported were not confirmed in a randomized placebo-controlled trial of 25 patients with PD (Teloken et al, 1999). The study demonstrated no significant improvement with respect to pain, penile deformity, or plaque size when compared with placebo (Teloken et al, 1999).

Colchicine

Colchicine has been demonstrated to have several different potential mechanisms of action in the treatment of PD. By binding to tubulin and causing it to depolymerize, colchicine inhibits cell mitosis, mobility, and adhesion of leukocytes; inhibits transcellular movement of collagen; and stimulates the production of collagenase (Taylor, 1965; Ehrlich and Bornstein, 1972; El-Sakka et al, 1999).

In a randomized double-blind placebo-controlled study to determine the effectiveness and safety of colchicine, 84 PD patients with noncalcified plaque were randomized to colchicine or placebo. Objective measurements did not demonstrate any difference in plaque size or penile curvature. There were no substantial differences in response to treatment based on duration of disease or within the three Kelami classification groups (Kelami, 1983). Significant drug-related adverse effects in the colchicine group included gastrointestinal upset with diarrhea (Safarinejad, 2004).

Carnitine

Carnitine is a trimethylamine molecule that plays a unique role in cell energy metabolism (Reda et al, 2003). L-Carnitine is hypothesized to act by increasing mitochondrial respiration and decreasing free radical formation (Bremer, 1983).

In the same double-blind placebo-controlled study mentioned previously, Safarinejad and colleagues compared the effects of L-carnitine with placebo (Safarinejad et al, 2007). Fifty-nine PD patients were randomized to receive propionyl-L-carnitine and 59 were randomized to placebo during the 6-month treatment period. This study again did not show significant improvement in pain, curvature, or plaque size in patients with PD treated with propionyl-L-carnitine as compared with those treated with placebo.

Pentoxifylline

Pentoxifylline has been shown to block the TGF- β 1-mediated pathway of inflammation and to prevent deposition of collagen type I and is a nonspecific phosphodiesterase inhibitor with combined anti-inflammatory and antifibrogenic properties. In an animal model of PD, pentoxifylline reduced the expression of collagen I, α -smooth muscle actin (ASMA), and plaque size by 95% (Valente et al, 2003). Pentoxifylline inhibits tunica albuginea-derived fibroblast proliferation in vitro and attenuates TGF- β -mediated elastogenesis and collagen type I deposition (Shindel et al, 2010). Elastogenesis is inhibited not by decreasing the amount of elastin produced but by inhibiting its deposition through an α_1 -antitrypsin-related mechanism (Lin et al, 2010). Pentoxifylline has also been shown to downregulate TGF- β and increases fibrinolytic activity (Schandené et al, 1992; Raetsch et al, 2002). Pentoxifylline has been used successfully for the treatment of experimental autoimmune diseases, the presence of which has been suggested as a cause of PD (Ralph et al, 1996). Pentoxifylline downregulates the release and the production of the profibrotic cytokine tumor necrosis factor (TNF), suppresses the production of platelet-activating factor, and inhibits its action on neutrophils (Safarinejad et al, 2010).

In a randomized double-blind placebo-controlled study, 114 PD patients were randomized to receive pentoxifylline and 114 were randomized to placebo for 6 months. Of patients in the pentoxifylline group, 12 (11%) had disease progression, versus 46 (42%) in the placebo group. Improvement in penile curvature and plaque volume was significantly greater in patients treated with

pentoxifylline than with placebo. The increase in International Index of Erectile Function (IIEF) total score was significantly higher in the pentoxifylline group. One patient discontinued the medication because of adverse effects. There were no adverse effects in any of the vital signs or in the laboratory data. Pentoxifylline is a peripheral vasodilator and could induce hypotension; consequently, blood pressure should be monitored during treatment with this drug. The most common side effects include nausea, vomiting, dyspepsia, malaise, flushing, dizziness, and headache (Safarinejad et al, 2010).

Phosphodiesterase Type 5 Inhibitors

PDE5 inhibitors have been shown to be safe and effective in treating ED in patients with PD (Levine and Latchamsetty, 2002). Recently tadalafil was shown to significantly improve IIEF and quality-of-life (QoL) scores when used in conjunction with extracorporeal shock-wave therapy (ESWT) as compared with ESWT alone (Palmieri et al, 2012). There was no advantage with respect to deformity.

PDE5 inhibitors have also been suggested as treatment for PD. By increasing the levels of cGMP, PDE5 inhibitors can inhibit collagen synthesis and induce fibroblast and myofibroblast apoptosis, thus acting as antifibrotic agents by inhibiting scar development (Valente et al, 2003; Gonzalez-Cadavid and Rajfer, 2010).

In a study by Chung and associates (2001), 35 men with an isolated septal scar received tadalafil 2.5 mg daily over a 6-month period, after which 24 patients (69%) had resolution of the septal scar. The authors concluded that low-dose daily tadalafil is a safe and effective treatment option in septal scar remodeling (Chung et al, 2011a).

Intralesional Injection

Verapamil

Calcium channel blockers were originally found to inhibit the incorporation of proline into ECM protein, thus leading to the conclusions that cellular calcium metabolism appears to regulate ECM production and that hypertrophic disorders of wound healing may respond to therapy with calcium channel antagonist drugs (Lee and Ping, 1990).

Verapamil is a calcium channel blocker that has been shown to significantly affect fibroblast function on several levels, including cell proliferation, ECM protein synthesis and secretion, and collagen degradation. In vitro Peyronie plaque fibroblast proliferation is inhibited by 65% by verapamil at a concentration of 100 to 1000 mg/mL (Anderson et al, 2000). These changes may allow intralesional verapamil to retard, prevent, or possibly reverse plaque formation and progression of PD (Levine and Estrada, 2002). Recently a study demonstrated the mechanism of action of intralesional verapamil injection versus normal saline in a rat model. After verapamil injection there were histologic changes as well as reduced plaque size and penile curvature. Verapamil injection also resulted in decreased collagen and elastin fibers, as well as reduced ASMA, an indicator of myofibroblast activity (Chung et al, 2013b).

The first reported use of verapamil for the treatment of PD was by Levine and associates and was the first new intralesional treatment since steroid injection was introduced in 1957 (Furey, 1957; Levine et al, 1994). This was a nonrandomized dose-escalating study in 14 men who received biweekly injections of verapamil for 6 months. Subjectively, there was significant improvement in plaque-associated penile narrowing (100%) and curvature (42%). Objectively, a decreased plaque volume of more than 50% was noted in 30% of the subjects. Plaque softening was noted in all patients, and 83% noticed that plaque-related changes in erectile function had arrested or improved. There was no toxicity, nor did symptoms recur when improvement was noted. This preliminary study suggested that intralesional verapamil may be an economical and sensible nonoperative approach to the treatment of PD warranting further study (Levine et al, 1994). In a larger noncontrolled study, verapamil injection resulted in a reduction of pain in 97%

of the patients, an improvement in sexual function in 72%, a subjective reduction of deformity in 86%, an improvement in distal rigidity in 93%, and an objective reduction of curvature in 54% (mean curve reduction of 25 degrees) (Levine, 1997).

Rehman and associates (1998) performed a single-blind study on 14 PD patients who were randomly assigned to injection with verapamil or saline. This study demonstrated a significant improvement in plaque size, plaque-associated penile narrowing, and quality of erection in the verapamil-treated men versus the control group. There was no significant difference with respect to penile curvature. There was no local or systemic toxicity except for an occasional ecchymosis or bruise at the injection site (Rehman et al, 1998). Bennett and colleagues showed in a shorter 3-month trial of 94 patients improvement in curvature in 18%, no change in 60%, and worsening in 22% and concluded that intralesional verapamil can at a minimum stabilize penile deformity (Bennett et al, 2007).

Currently, intralesional verapamil is one of the leading treatment options for the conservative management of PD despite the fact that some studies have not shown as favorable a response as described earlier (Shindel et al, 2008). In a recent randomized single-blind placebo-controlled trial, Shirazi and associates (2009) randomized 80 patients to receive intralesional verapamil and 40 patients to receive local saline injection. This study demonstrated no significant difference with respect to plaque size, pain, curvature, plaque softening, or improvement in sexual dysfunction in the active drug and control groups. This study concluded that although some trials have demonstrated intralesional verapamil to be an effective treatment for PD, further larger-scale studies are warranted given these negative findings to assess the effectiveness of intralesional verapamil for the treatment of PD (Shirazi et al, 2009). This study highlights the potential for inconsistent results for men with PD, which may vary because of patient selection, presence of calcification, plaque location, drug administration technique, and sample size. Drug concentration has also been evaluated, and although 10 mg/10 mL is the most commonly used dose and volume, Cavallini and associates (2007) showed a greater response to injection when 10 mg of verapamil was diluted with 20 mL of injectable saline (Cavallini et al, 2007). Poor candidates for this treatment include those with extensive calcification, curvature of greater than 90 degrees, or ventral curvature, in which it is difficult to adequately infiltrate the plaque (Levine et al, 2002). Predictors of success with intralesional verapamil include younger age (below age 40) and curvature greater than 30 degrees (Moskovic et al, 2011).

Nicardipine

Nicardipine is a dihydropyridine (DHP) type of calcium channel blocker. An in vitro study has suggested that it is more effective than a non-DHP type, verapamil, in reducing glycosaminoglycan biosynthesis and ECM production (Gürdal et al, 1992). Soh and associates (2010) performed the only study on the effectiveness of nicardipine for the treatment of PD. A total of 74 patients were assigned randomly to nicardipine versus saline. Nicardipine demonstrated a significant reduction of pain, improvement in IIEF-5 score, and reduction of plaque size when compared with placebo. Penile curvature was significantly improved in both the active drug and placebo groups without significant difference. There were no severe side effects, such as hypotension or other cardiovascular events (Soh et al, 2010).

Interferon Alfa-2b

IFN alfa-2b was first investigated as a treatment for PD in 1991 in the in vitro studies by Duncan and associates (1991). In fibroblasts derived from Peyronie plaques, the addition of IFN alfa-2b decreased their rate of proliferation in a dose-dependent fashion, decreased the production of extracellular collagen, and increased the production of collagenase (Duncan et al, 1991).

In a single-blind, multicenter, placebo-controlled, parallel study to assess the safety and efficacy of intralesional IFN alfa-2b,

Hellstrom and associates (2006) randomized a total of 117 consecutive PD patients to IFN alfa-2b or saline. Improvement in penile curvature, plaque size and density, and pain resolution was significantly greater in patients treated with IFN alfa-2b versus placebo. The treatment group demonstrated a mean decrease in curvature of 27% or 13.5 degrees versus 9% or 4.5 degrees in the placebo group. Although these results were statistically significant, the question arises whether the small difference between the IFN and saline is clinically significant when taking into account the significant cost of the drug and its side effect profile, which frequently includes flulike symptoms (fever, chills, and arthralgia) and minor penile swelling with ecchymosis. All these symptoms were effectively treated with over-the-counter nonsteroidal anti-inflammatory agents ingested before the injection procedure, and none lasted longer than 36 hours (Hellstrom et al, 2006). This study was important because it was the first multicenter randomized placebo-controlled trial of intralesional injection for PD. It also was important because it showed that saline injection had little to no effect on penile deformity.

Clostridial Collagenase

The first U.S. Food and Drug Administration (FDA)-approved drug for the treatment of PD, collagenase *Clostridium histolyticum* (CCH), is produced by the bacterium *C. histolyticum* and selectively degrades collagen types I and III in connective tissues despite the presence of TIMPs, which have been shown to be elevated in PD as well as to increase apoptosis of fibroblasts (Morales et al, 1983; Matsushita et al, 2001; Del Carlo et al, 2008; Syed et al, 2012). The recent flurry of investigation on this drug has come many years after the first time it was examined as a treatment for PD by Gelbard and associates (1982), who demonstrated that CCH significantly reduced the size of PD plaques, whereas elastic fibers, vascular smooth muscle, and axonal sheaths were not affected (Gelbard et al, 1982).

In the first prospective, randomized, double-blind, placebo-controlled study of CCH, 49 men with PD were treated with CCH, resulting in significant improvements in plaque size and penile deformity (Gelbard et al, 1993). All patients with a penile bend of 30 degrees or less and/or palpable plaque less than 2 cm responded ($N = 3$); 36% of patients with a penile bend of 30 to 60 degrees and/or 2 to 4 cm of palpable plaque responded; and 13% of patients with a penile bend of greater than 60 degrees and/or greater than 4 cm of palpable plaque responded. CCH was well tolerated, with no allergic reactions and no significant changes in laboratory parameters (Gelbard et al, 1993). Further investigation was encouraged but took years owing to absence of industry support.

In a phase 2 trial, 25 patients with PD received three intralesional injections of 10,000 units of CCH over 7 to 10 days, with a repeat of treatment at 3 months to assess change from baseline in penile deviation angle and plaque size (Jordan, 2008). A decrease in deviation angle of at least 25% was achieved in 58% of patients, and 95% of patients experienced a reduction in plaque size (Jordan, 2008). More than 50% of patients in this series were considered "very much improved" or "much improved" at all time points in the study; approximately one third were considered to show minimal improvement or no change, resulting in an investigator's assessment of "worse."

In a phase 2b trial, 147 patients with PD were enrolled in a randomized, double-blind, placebo-controlled trial of CCH or placebo, with a second randomization to modeling or nonmodeling (Gelbard et al, 2012). Patients receiving CCH and modeling had a significant change in curvature of the penis and decrease in the PD symptom effect score compared with placebo (Gelbard et al, 2012).

The phase 3 IMPRESS (Investigation for Maximal Peyronie Reduction Efficacy and Safety Studies) I and II trials examined the clinical efficacy and safety of CCH intralesional injections in subjects with PD (Gelbard et al, 2013). A total of 417 and 415 subjects, respectively, went through a maximum of four treatment cycles, each separated by 6 weeks. Men received up to eight injections of

0.58 mg CCH, two injections per cycle separated by approximately 24 to 72 hours with the second injection of each followed 24 to 72 hours later by penile plaque modeling. Men were stratified by baseline penile curvature (30 to 60 degrees versus 61 to 90 degrees) and randomized to CCH or placebo 2:1 in favor of active drug. Post hoc meta-analysis of IMPRESS I and II data revealed that men treated with CCH showed a mean 34% improvement in penile curvature, representing a mean change of -17.0 degrees ± 14.8 degrees per subject, compared with a mean 18.2% improvement in placebo-treated men, representing a mean change of -9.3 ± 13.6 degrees per subject ($P < .0001$). The mean change in PD symptom effect score was significantly improved in treated men versus men on placebo (-2.8 ± 3.8 vs. -1.8 ± 3.5 , $P = .0037$). Patients with extensive calcification, ventral plaques, and disease duration less than 12 months were excluded. Although serum antibodies to CCH developed in virtually all patients studied, no adverse events were noted as a result. The primary and frequently noted side effect was varying degree of ecchymosis and local penile bruising. Serious adverse events included corporeal rupture in three patients and penile hematoma in three patients. All three corporeal ruptures and one of the three penile hematomas were successfully repaired surgically; another hematoma was successfully drained percutaneously (Gelbard et al, 2013). Further experience will help determine which patients may benefit most from CCH. This may depend on direction of curve, size of plaque, prevalence of calcification, and duration of disease, among other factors to be determined. A recent presentation did demonstrate that surgical correction with plication or grafting could be successfully performed after CCH injection without added technical difficulty (Larsen and Levine, 2012). CCH received FDA approval for the treatment of PD in December 2013.

Topical Drug Application

Several studies have evaluated the effectiveness of topically applied agents for the treatment of PD. Topical application avoids the pain and trauma of intralesional injection therapy. The first study of topical application of a drug, β -aminopropionitrile, showed no benefit with respect to deformity change (Gelbard et al, 1983).

Topically applied liposomal recombinant human superoxide dismutase (IrhSOD) has also been studied in a randomized placebo-controlled trial (Riedl et al, 2005). This substance is proposed to act as an oxygen free radical scavenger, which might interrupt inflammatory cascades and thereby limit further disease progression. Penile curvature was improved by 5 to 30 degrees in 23% of patients and pain was significantly reduced as well ($P = .017$) compared with placebo after 4 weeks. The authors concluded that IrhSOD is an easily given, safe, and effective local therapeutic for the painful phase of PD (Riedl et al, 2005). No further studies have been performed regarding the use of IrhSOD. Therefore at this time the data are insufficient to recommend its use.

Fitch and associates (2007) reported on the use of topical verapamil for the treatment of PD (Fitch et al, 2007). Two simultaneous three-armed, double-blind, placebo-controlled studies were conducted in this pilot study. In this study topical verapamil improved curvature in 14 of 18 patients (77.8%) with mean curvature improvement of 43.6%. This study also boasted reduction in plaque size in 100% of participants, as well as improvement in erectile function in 72.7%. This study was originally aimed at comparing verapamil to topical trifluoperazine, but because of the severity of side effects (anxiety, agitation, blurred vision, insomnia, and depression), topical trifluoperazine was discontinued before completion of randomization. The results of this study have been called into question given the small sample size, lack of a true placebo, and absence of objective measures (Levine, 2007). In addition, simple topical administration of verapamil has been shown to be ineffective in achieving tissue levels within the tunica albuginea sufficient for therapeutic effect (Martin et al, 2002).

At this time, no topically applied agent has been shown to be effective in the treatment of PD.

Electromotive Drug Administration

Transdermal drug delivery was proposed to be superior to oral or injection therapy because it bypasses hepatic metabolism and minimizes the pain of injection. Unlike topical verapamil gel, electromotive drug administration (EMDA) with verapamil has been found to deliver detectable levels of the drug to the tunica albuginea (Martin et al, 2002; Levine et al, 2003).

A double-blind, placebo-controlled trial to determine the effectiveness of verapamil delivered through EMDA randomized a total of 42 PD patients to verapamil versus saline. Treatments were performed twice weekly for 3 months. Both verapamil and saline groups demonstrated essentially equivalent reduction of curvature. The study concluded that further research is necessary to determine whether electric current alone may have a role in the treatment of PD (Greenfield et al, 2007). Overall, EMDA was well tolerated in each group and it was noted by all patients to be easy and convenient to perform at home. The only adverse event reported by patients was temporary mild erythema at the treatment site (Greenfield et al, 2007).

In another prospective placebo-controlled study with transdermal EMDA, Di Stasi and associates (2004) randomized patients to receive verapamil and dexamethasone versus placebo. Those receiving active drug demonstrated significant decreases in plaque volume as well as penile curvature from 43 degrees to 21 degrees, which was significant when compared with placebo. Significant pain relief occurred in both groups, transient in the control group and permanent in the study group. All patients experienced temporary erythema at the electrode site. There were no other side effects (Di Stasi et al, 2004). Although this approach has limited evidence of benefit, it has not been adopted in most centers.

Extracorporeal Shockwave Therapy

The mechanism of action involved in ESWT for PD is unclear. However, there are two purported hypotheses: (1) Shock waves cause direct damage to the penile plaque, and (2) ESWT increases the vascularity of the targeted area by generating heat, which leads to the induction of an inflammatory reaction, resulting in lysis of the plaque and removal by macrophages (Gholami et al, 2003).

In the first prospective randomized double-blind placebo-controlled clinical trial evaluating ESWT for the treatment of PD, 100 treatment-naïve PD patients with disease duration less than 12 months were randomly allocated to either ESWT ($n = 50$) or placebo ($n = 50$). For the placebo group, a nonfunctioning transducer was employed. Patients randomized to ESWT demonstrated improvements in pain, IIEF-5 score, and mean QoL score. Plaque size and penile curvature were not significantly different in the treatment and placebo groups. After 24 weeks, mean IIEF-5 score and mean QoL score were stable in the ESWT group, whereas mean visual analog scale (VAS) score was significantly lower when compared with baseline in both groups. It is interesting to note that after 24 weeks, mean plaque size and mean curvature degree were significantly worse in the placebo group when compared with both baseline and ESWT values. This difference was less than 3 degrees, which, although statistically significant, is of no clinical significance (Palmieri et al, 2012).

Recently a second placebo-controlled, prospective randomized single-blind study was performed in which 102 PD patients were randomly assigned ($n=51$) to ESWT or placebo (Hatzichristodoulou et al, 2013). Pain decreased in 17 of 20 (85.0%) patients in the ESWT group and in 12 of 25 (48.0%) patients in the placebo group. Penile deviation was not reduced by ESWT and worsened in 40% and 24.5% of patients in the ESWT and placebo groups, respectively ($P=.133$). Change in sexual function and plaque size reduction was not different between the two groups. In addition, plaque size increased in five patients (10.9%) receiving ESWT only. The authors concluded that despite some potential benefit of ESWT with regard to pain reduction, it should be emphasized that pain usually resolves spontaneously with time. Given this and the fact

that deviation may worsen with ESWT, the treatment cannot be recommended.

Penile Traction

Controlled stretching of the penis, or "penile traction," by a device that holds the penis in a cradle and subjects it to tension appears to meet a previously unmet need within the population of PD patients for a noninvasive, nonsurgical first-option treatment modality.

Traction has been shown in nonpenile tissue models to induce cellular proliferation by several pathways (Ilizarov, 1989; Sun et al, 1996; Molea et al, 1999; Assoian and Klein, 2008; Bueno and Shah, 2008). It can also trigger scar remodeling; it has been shown that tension applied to tissues leads to a reorientation of collagen fibrils parallel to the axis of stress (Molea et al, 1999; Shapiro, 2008). These changes are the result of a process referred to as *mechanotransduction* whereby mechanical stimuli are converted into chemical responses within the cell (Alenghat and Ingber, 2002). Several signaling cascades are activated by tension on the cytoskeleton, which leads to a proliferative response as well as activation of various genes (Assoian and Klein, 2008). An *in vitro* study to determine the cellular effects of traction on PD cells demonstrated a significant decrease in ASMA in the strained compared with nonstrained PD cell cultures, whereas an increase in MMPs involved in collagen degradation was observed. In contrast, cytokines and proteins involved in fibroblast replication and inflammation such as ASMA, heat shock protein 47 (HSP47), and TGF- β 1 receptor were not upregulated (Chung et al, 2013a). Several studies have been performed examining the clinical effects of traction for the treatment of PD, although none have been controlled trials.

Levine and associates (2008) first demonstrated the use of penile traction for the treatment of PD in a pilot study of 10 men. In nearly all (90%), prior medical therapy had failed. Traction was applied as the only treatment for 2 to 8 hr/day for 6 months. All subjects underwent pretreatment and post-treatment physical examination including measurement of stretched flaccid penile length and biotensiometry. Subjectively, all men noted reduced curvature estimated at 10 to 40 degrees, increased penile length (1 to 2.5 cm), and enhanced girth in areas of indentation or narrowing. Objective measures demonstrated reduced curvature in all 10 men of up to 45 degrees; average reduction for the group was 33%, from 51 degrees to 34 degrees. SPL increased 0.5 to 2.0 cm, and erect girth increased 0.5 to 1.0 cm with correction of hinge effect in four out of four men. It is important to note that results were maintained at 6 months after completion of therapy. The IIEF erectile function domain score increased from 18.3 to 23.6 for the group. There were no adverse events including skin changes, ulcerations, hypoesthesia, or diminished rigidity (Levine et al, 2008).

Gontero and associates (2009) performed a phase 2 prospective study on 15 PD patients with a curvature not exceeding 50 degrees with mild or no ED. Penile curvature decreased from an average of 31 degrees to 27 degrees at 6 months, which was not statistically significant. Mean stretched and flaccid penile length increased by 1.3 and 0.83 cm, respectively, at 6 months. Results were maintained at 12 months. Overall treatment results were subjectively scored as acceptable in spite of limited curvature improvements, which varied from "no change" to "mild improvement." The investigators concluded that the use of a penile extender device provided only minimal improvements in penile curvature but a reasonable level of patient satisfaction, probably attributable to increased penile length. The selection of patients with stabilized disease, many with calcified plaques, and penile curvature not exceeding 50 degrees may have led to outcomes underestimating the potential efficacy of the treatment (Gontero et al, 2009).

Recently a prospective nonrandomized study was conducted administering traction to PD patients in the acute phase, defined as progressive penile curvature exceeding 15 degrees and/or pain at rest or at erection in the last 12 months (Martínez-Salamanca et al, 2014). A total of 55 patients underwent traction for 6 months and were compared with 41 patients also in the acute phase who did

not. Patients were advised to use the device at least 6 hours a day and no more than 9 hours, preventing its use during sleep. Mean duration of use was 4.6 hours per day (3.1 to 9.2 hours). Also, patients were taught to remove the device for at least 30 minutes every 2 hours to prevent glans ischemia. **The mean curvature decreased from 33 degrees at baseline to 15 degrees at 6 months and 13 degrees at 9 months with a mean decrease of 20 degrees in the traction group.** VAS score for pain decreased from 5.5 to 2.5 after 6 months ($P < .05$). The percentage of patients who were not able to achieve penetration decreased from 62% to 20% ($P < .03$). Without this intervention, deformity increased significantly, stretched flaccid penile length decreased, VAS score for pain increased, and erection hardness worsened. **Furthermore, the need for surgery was reduced in 40% of patients who would otherwise have been candidates for surgery and simplified the complexity of the surgical procedure (from grafting to plication) in one of every three patients.** Treatment-related adverse events included two cases of erythema in the balanopreputial sulcus, which resolved with stopping traction for 24 to 48 hours. Fourteen patients (25.5%) reported some degree of discomfort. Worsening of erectile function over the treatment period was not observed, **and the overall satisfaction rate was 85% (range 60% to 90%) at 9 months.** No case of sensory change after traction was reported (Martínez-Salamanca et al, 2014). **In our opinion, traction therapy has the potential to be the most effective nonsurgical treatment to recover lost length, reduce curvature, and enhance girth.** It is critical that the patient wear the device for 3 or more hours per day to get satisfactory results.

Vacuum Therapy

Application of a penile vacuum device to mechanically straighten the penis has been evaluated in one published noncontrolled study in which subjects wore the vacuum device for 10 minutes twice per day for 12 weeks. This study demonstrated a reduction in the angle of curvature by 5 degrees to 25 degrees in 21 of 31 patients. Three patients' curvature worsened, and in seven the curvature remained unchanged. Fifty-one percent were satisfied with this outcome; the other 49% went on to surgical correction (Raheem et al, 2010). Although vacuum erection devices are usually considered safe, it would seem that the short-term duration of stretching forces on the penis would not induce the desired physical changes known to occur with mechanotransduction with prolonged stretch therapy. Several complications such as the development of PD, urethral bleeding, skin necrosis, and penile ecchymosis have been reported with concomitant use of constriction rings and when inappropriately elevated pressures are applied to the penis for an extended period of time (Kim et al, 1993; Ganem et al, 1998).

Combination Therapy

One study investigated whether the combination of the mechanical effects of penile traction with the chemical effects of intralesional verapamil and oral medications (pentoxifylline and L-arginine) could have a synergistic effect on the tunica albuginea and Peyronie plaque (Abern et al, 2012). All patients were given oral pentoxifylline and L-arginine, with 39 electing to undergo traction and 35 choosing not to use traction. Both treatment groups had a statistically significant reduction in erect penile curvature. The traction group had a reduction from a mean of 44.4 degrees (standard deviation [SD] 27.5 degrees) at baseline to a mean of 33.4 degrees (SD 25.3 degrees) after the 24-week protocol ($P = .03$). Patients not using traction had a reduction from a mean of 36.6 degrees at baseline (SD 18.5 degrees) to a mean of 21.5 degrees (SD 19.3 degrees) after treatment ($P < .01$). There were no statistically significant differences in curvature outcomes between the two groups. In patients using traction, SPL increased overall by a mean 0.3 cm (SD 0.9 cm) after treatment, which trended toward statistical significance ($P = .06$), whereas the men not using traction lost an average of 0.7 cm (SD 1.1 cm) of length, which was not statistically different ($P = .46$) (Abern et al, 2012). Unfortunately, this

study did not control for duration of traction therapy, and some men included in the traction group applied the device for only 1 to 2 hr/wk, whereas others wore it for over 50 hr/wk. An analysis of traction duration and deformity change demonstrated that wearing the device on average three or more hours per day allowed reliable measured deformity improvement, which occurred in a dose-response fashion.

Another combination study examined the effects of combining verapamil injection and verapamil iontophoresis with or without the use of a combination pill that contained vitamin E (36 mg), *p*-aminobenzoic acid (100 mg), propolis (as galangin 100 mg), blueberry anthocyanins (80 mg), soy isoflavones (50 mg), *Muirapauama* (25 mg), damiana (25 mg), and *Persea americana* (50 mg). Intergroup analysis revealed greater plaque size reduction (−30.8% vs. −18.0%) and greater percentage with reduction of curvature (85% vs. 53.5%) with use of the combination pill (Paulis et al, 2013b).

Radiation Therapy

Radiation therapy has been proposed as a treatment for PD since 1964 (Duggan, 1964). **In vitro studies suggest that low-dose radiation therapy has a potent anti-inflammatory effect, inhibiting leukocyte-endothelium interactions** (Arenas et al, 2012). In recent years, radiation therapy has been proposed as a treatment for pain that was thought to be "abnormally persistent." In 1975 a retrospective study examined the use of radiation therapy and found it to be no more effective than no treatment (Incrocci et al, 2000). **It is the consensus of multiple experts in the field that radiation should be avoided because of potential risk of malignant change and increase in the risk of ED in aging patients** (Ralph et al, 2010; Hatzimouratidis et al, 2012; Mulhall et al, 2012).

Conclusion

At this time it is our opinion that combination therapy will offer the best opportunity for improvement by creating a synergy between the chemical effects of the oral and/or injectable agents and the mechanical effects of external forces on the penis. The recent addition of an FDA-approved treatment (injectable CCH) provides what appears to be a sensible nonsurgical treatment option for PD. Further experience will allow better discrimination as to the optimum candidates. Clearly, it appears that the goal of nonsurgical treatment at a minimum should be to prevent progression of deformity during the acute phase. Reducing deformity to improve sexual function and reduce the effects of the scarring is the ultimate goal of all treatment for PD (Tables 31-1, 31-2, and 31-3).

SURGICAL MANAGEMENT

Indications

Surgical reconstruction is indicated for men with deformity that precludes satisfactory sexual intercourse or causes pain for themselves or their partner during sexual relations or because of distress as a result of the appearance of the erect penis (Kadioglu et al, 2006).

Surgery remains the gold standard treatment to most rapidly and reliably correct the deformity associated with PD; and for men who also have ED, placement of a penile prosthesis can provide rigidity for penetrative sexual activity. The indications for surgical correction include stable disease, which is defined as disease that is at least 1 year from onset, and at least 6 months of stable deformity. These indications have not been formally studied but appear to be generally accepted by experts in the field (Jordan, 2007; Ralph et al, 2010; Levine and Burnett, 2013). Other indications include a deformity that compromises or makes impossible the patient's ability to engage in sexual intercourse because of the nature of the deformity and/or inadequate rigidity, and patients in whom conservative therapy has failed (Box 31-4). No single surgical approach is universally defined as the

KEY POINTS: NONSURGICAL TREATMENT OF PEYRONIE DISEASE

- Patients who have no pain or difficulty in accomplishing penetrative sex may require only reassurance, because this is not a disorder that will degenerate into a cancer and is not life-threatening.
- A poor understanding of the cause of this wound-healing disorder contributes to the fact that to date, conservative treatments often yield inconsistent and clinically insignificant improvements in deformity.
- Currently, no oral agent has been shown in placebo-controlled trials to result in clinically meaningful improvement in curvature.
- Topical therapy and ESWT have not been shown to reduce penile deformity.
- Intravesical verapamil and IFN alfa-2b have shown evidence of reduced curvature and improved sexual function. Yet most studies are not controlled trials. These agents at a minimum appear to result in deformity stabilization during the acute phase.
- The first FDA-approved drug for the treatment of PD, CCH is produced by the bacterium *C. histolyticum* and selectively degrades collagen types I and III. Mean curvature reduction in the phase 3 trials in the treatment arm was 34% (17 degrees) vs. 18.2% (9.3 degrees) for placebo. Further experience will help determine which patients may benefit most from CCH, which may depend on direction of curve, size of plaque, prevalence of calcification, and duration of disease. The volume of patients seeking treatment for PD may increase over the coming years as public awareness increases with the advent of use of this drug.
- Combination therapy, also known as a “three-armed approach” using daily pentoxifylline and L-arginine, biweekly verapamil injections, and daily traction likely provides the best opportunity for deformity improvement by creating a synergy between the chemical effects of the oral and/or injectable agents with the mechanical effects of external forces on the penis.

standard of care (Kendirci and Hellstrom, 2004; Gur et al, 2011) because there are multiple factors to consider, including severity of curvature, direction of curvature, presence of a hinge effect, erection quality, and patient goals. An algorithm for surgical decision making is presented in Figure 31-10 (Levine and Larsen, 2013).

Preoperative consent is critical because patients with PD are distressed and frequently emotionally devastated. It has been reported that men who have undergone treatment for PD are often not satisfied with their results because of their expectation for recovery of their pre-Peyronie penile appearance (Jones, 1997). It is therefore important to have a frank discussion with the patient so that he understands the limitations of the operation, as well as to set appropriate expectations regarding outcomes to optimize patient satisfaction (Jordan and McCammon, 2007; Ralph et al, 2010). The patient should understand that there is a possibility of persistent or recurrent curvature, reduction of penile erect length, diminished rigidity, and decreased sexual sensation (Box 31-5). Persistent or recurrent curvature is unusual but has been shown in up to 16% of men, the great majority of whom do not require another operation (Taylor and Levine, 2007; Ralph et al, 2010). The patient should understand that the goal is to make the penis “functionally straight,” which expert opinion defines as a residual deformity of 20 degrees or less (Ralph et al, 2010; Levine and Burnett, 2013). The European Association of Urology (EAU) guidelines committee on PD defines successful curvature correction as 15 degrees or less of residual curvature (Hatzimouratidis et al, 2012). Change in penile erect length is more likely with plication than with grafting, although all surgical correction procedures have been associated with some length loss. This is extremely important for the patient to understand preoperatively because 70% to 80% of patients initially have loss of length as a result of the fibrotic disease process (Pryor and Ralph, 2002; Jordan and McCammon, 2007; Ralph et al, 2010). Thus, further loss of length can be a major concern. Having stretched flaccid penile length documented preoperatively permits comparison with postoperative length. Diminished rigidity has long been reported after surgery, and studies have demonstrated that up to 50% of men may have some degree of postoperative reduction in rigidity, which may respond to a PDE5 inhibitor. Rigidity will not likely be

TABLE 31-1 Oral Agents for Peyronie Disease (PD)

TREATMENT	MECHANISM OF ACTION	STUDY OUTCOMES	ADVERSE EFFECTS
Potaba	Decreases serotonin levels by increasing monoamine oxidase activity, resulting in enhancement of the antifibrotic properties of tissues	Decreased plaque size, no decrease in curvature	Anorexia, nausea, fever, skin rash, hypoglycemia, acute hepatitis
Vitamin E	Antioxidant, limits oxidative stress of reactive oxygen species shown to be increased in PD	No benefit	Possible cerebrovascular events, nausea, vomiting, diarrhea, headache, dizziness
Tamoxifen	Induces the production of TGF- β in an estrogen receptor-independent fashion, theoretically causing macrophage deactivation and T-lymphocyte suppression, thus preventing further fibrogenesis	No benefit	Alopecia, retinopathy, thromboembolism, pancytopenia
Colchicine	Microtubule depolymerization; inhibits cell mitosis, mobility, adhesion of leukocytes, and transcellular movement of collagen and stimulates the production of collagenase	No benefit	Myelosuppression, diarrhea, nausea, vomiting
Carnitine	Increases mitochondrial respiration; decreases free radical formation	No benefit	Seizures, diarrhea, nausea, stomach cramps, vomiting
Pentoxifylline	Blocks the TGF- β 1-mediated pathway of inflammation; prevents deposition of collagen type I; is a nonspecific phosphodiesterase inhibitor; decreases platelet-activating factor	Decreased curvature in 33% of patients, mean 23 degrees	Nausea, vomiting, dyspepsia, malaise, flushing, dizziness, and headache

TGF, transforming growth factor.

TABLE 31-2 Intralesional Agents for Peyronie Disease (PD)

TREATMENT	MECHANISM OF ACTION	STUDY OUTCOMES	ADVERSE EFFECTS
Verapamil	Calcium channel blocker inhibits fibroblast proliferation, extracellular matrix protein synthesis and secretion; increases collagenase activity.	Reduction of curvature and plaque-associated penile narrowing, improvement in quality of erection	Nausea, lightheadedness, penile pain, ecchymoses
Nicardipine	DHP type of calcium channel blocker. In vitro study demonstrated that it is more effective than a non-DHP type, verapamil, in reducing glycosaminoglycan biosynthesis and production of extracellular matrix, such as collagen.	Reduction of pain, improvement in IIEF-5 score, and reduction of plaque size; no benefit in curvature	No severe side effects, such as hypotension or other cardiovascular events
Interferon alfa-2b	Decreases plaque fibroblast proliferation in dose-dependent fashion, decreases the production of extracellular collagen, and increases the production of collagenase.	Decrease in curvature of 27% (13.5 degrees) vs. 9% (4.5 degrees) in the placebo group	Sinusitis, flulike symptoms (fever, chills, and arthralgia), and minor penile swelling with ecchymosis
Clostridial collagenase	Selectively degrades collagen types I and III in connective tissues despite the presence of TIMPs, which have been shown to be elevated in PD and to increase apoptosis of fibroblasts.	Decrease in penile curvature by 34%, mean decrease of 17 degrees vs. 18%, mean decrease 9.3 degrees in placebo; PD symptom bothersomeness score significantly improved vs. placebo	Contusions, ecchymoses, corporeal rupture

DHP, dihydropyridine; IIEF, International Index of Erectile Function; TIMPs, tissue inhibitors of metalloproteinases.

TABLE 31-3 External Force Application for Peyronie Disease

TREATMENT	MECHANISM OF ACTION	STUDY OUTCOMES	ADVERSE EFFECTS
Electromotive drug administration	Bypasses hepatic metabolism, increases concentration of drug to target tissues compared with topical application alone	Verapamil alone: no benefit Verapamil + dexamethasone: decreases in plaque volume as well as penile curvature from 43 degrees to 21 degrees	Temporary erythema at the electrode site
Extracorporeal shockwave therapy	Direct damage to the penile plaque; increases vascularity of the targeted area inducing an inflammatory reaction, resulting in lysis of the plaque and removal by macrophages	Improvements in pain, IIEF-5 score, and mean QoL score; no curvature reduction	Local petechiae and ecchymoses
Penile traction	Decreases α -smooth muscle actin, increases matrix metalloproteinases involved in collagen degradation	Length increased 0.5-2.0 cm; girth increased 0.5-1.0 cm; curvature mean decrease of 20 degrees; pain decreased; softening or shrinking of plaque; overall satisfaction 85%	Erythema in the balanopreputial sulcus, discomfort
Vacuum therapy	Unknown; mechanical effects similar to traction have been suggested	Reduction in the angle of curvature by 5-25 degrees in 21 of 31 patients	Development of PD, urethral bleeding, skin necrosis, and penile ecchymosis
Radiation therapy	Anti-inflammatory effects via functional modulation of the adhesion of white blood cells to activated endothelial cells and modulation of the induction of nitric oxide synthase in activated macrophages	No clinical benefit	Possible malignant change, increased risk of ED in elderly

ED, erectile dysfunction; IIEF, International Index of Erectile Function; QoL, quality of life.

BOX 31-4 Indications for Surgery

- Stable deformity for at least 6 months from onset of symptoms
- Inability to engage in satisfactory penetrative sexual intercourse because of deformity and/or inadequate rigidity
- Failed conservative treatment
- Desire for most rapid and reliable result

BOX 31-5 Preoperative Consent

Set expectations regarding outcome.

- Persistent or recurrent curvature: The goal is “functionally straight” (curvature <20 degrees)
- Change in length: The result is more likely shorter with plication than with grafting.
- Diminished rigidity
 - $\geq 5\%$ in all studies—grafting more than plication
 - $\geq 30\%$ if suboptimal preoperative rigidity—dependent on preoperative erectile quality
- Decreased sexual sensation
 - Typically resolves in 1 to 6 months
 - Rarely compromises orgasm or ejaculation

improved by penile straightening, and therefore in patients who already have significant ED that does not respond to oral medication, placement of a penile prosthesis should be offered (Taylor and Levine, 2007; Ralph et al, 2010). Men who are considering penile straightening procedures without a penile prosthesis should be carefully evaluated for the quality of their preoperative erections, which does appear to be the most reliable predictor of postoperative ED (Flores et al, 2011; Taylor et al, 2012). In some men with PD and ED the correction of the penile geometry resulted in improved rigidity (Pescatori et al, 2003). Regardless, it is of critical importance that the patient understand that any operation done on the penis to correct PD may result in diminished rigidity, and that this may subsequently be treated successfully with oral PDE5 inhibitors, injection therapy, or a vacuum device; and those in whom these approaches fail can have a penile prosthesis implanted with little to no additional difficulty (Kendirci and Hellstrom, 2004; Levine et al, 2010; Chung et al, 2012c). Decreased sexual sensation has been examined and reported on infrequently, but it does appear that around 20% of men will describe some reduction in penile sensitivity, rarely interfering with orgasm or ejaculation. During the acute postoperative period there can be hyperesthesia or hypoesthesia, which tends to resolve and stabilize within 6 to 12 months postoperatively (Taylor and Levine, 2008; Ralph et al, 2010). The primary determinants for the choice of surgical approach are based on two factors, including quality of the preoperative erection hardness and severity of deformity, including curvature and indentation. In men who have rigidity that is adequate for coital activity with or without pharmacotherapy, tunica plication techniques and plaque incision or partial excision with grafting may be used. Tunica plication techniques are recommended for those who have a simple curvature of less than 70 degrees, those with absence of an hourglass or hinge effect, and those in whom the anticipated loss of length would be less than 20% of the total erect length (Levine and Lenting, 1997; Ralph and Minhas, 2004; Mulhall et al, 2005). The estimated penile length loss can be determined during preoperative testing while the penis is erect by measuring the difference in length between the long and short sides of the penis. Grafting procedures are recommended for those with more complex curves of greater than 60 to 70 degrees and/or a destabilizing hourglass resulting in a hinge effect. This hinge effect results in

a buckling or unstable penis, which makes penetrative sex difficult. These men must have strong, sexually induced rigidity to reduce the likelihood of postoperative ED (Flores et al, 2011; Taylor et al, 2012) (Table 31-4). For the man who has PD and ED that is refractory to medical therapy, published algorithms have indicated that penile prosthesis placement is the procedure of choice (Levine and Dimitriou, 2000; Mulhall et al, 2005; Ralph et al, 2010; Levine and Burnett, 2013). This procedure allows for correction of the deformity while also addressing the ED. If curvature is not satisfactorily corrected with the prosthesis inflated during surgery, additional straightening maneuvers may be performed. We recommend manual modeling as the first step as initially reported by Wilson and Delk (1994). If there is residual curvature in excess of 30 degrees after modeling, then a relaxing incision in the tunica albuginea overlying the area of maximum curvature can be made. It is recommended that if the incisional defect is greater than 2 cm, a biograft (i.e., pericardium or small intestine submucosa) should be placed over the defect to prevent cicatrix contracture of the incision or herniation of the prosthesis (Levine and Dimitriou, 2000; Ralph et al, 2010). Plication techniques have been recommended to be performed before placement of the prosthesis to correct curvature in lieu of manual modeling (Rahman et al, 2004; Dugi and Morey, 2010). In this circumstance, if the curvature is dorsal, the erectile deformity can be defined with injection of a vasoactive drug and infusion of saline, then sutures are placed in a Lambert fashion to cause ventral shortening and correction of the curve.

Tunical Shortening Procedures

Penile plication aims to shorten the longer (or convex) side of the tunica albuginea to match the length to the shorter side (Syed et al, 2003; Ralph, 2006). Advantages to these approaches include shorter surgical time, good cosmetic outcomes, minimal effect on rigidity, simple and safe surgery, and effective straightening (Hudak et al, 2013; Hatzimouratidis et al, 2012). Disadvantages include shortening and failure to correct an hourglass or hinge. A study of failures with the Nesbit procedure identified three factors associated with an unsatisfactory outcome, including impaired preoperative erectile function, penile shortening of greater than 2 cm, and penile deformity greater than 30 degrees (Andrews et al, 2001). Multiple surgical plication techniques have been offered for PD, beginning with the Nesbit procedure (Nesbit, 1965) (Fig. 31-11). This technique uses excision of an elliptical segment of the tunica on the contralateral side of the curvature. In the setting of a ventral curvature, once Buck's fascia has been elevated, small wedges of the dorsal tunica albuginea are excised and then the defect is closed, typically with permanent suture. Multiple variations on this approach have evolved, including the Yachia procedure, which uses the Heineke-Mikulicz technique (Yachia, 1990; Yachia, 1993). In the setting of a dorsal curvature, a short (0.5 to 1.5 cm), full-thickness vertical incision is made on the ventral shaft tunic, opposite the area of maximum curvature, which is then closed transversely to shorten the ventral aspect and correct the curvature (Fig. 31-12). This approach must be used carefully so that the length of the incision is not too long, such that transverse closure could result in further narrowing of the shaft, possibly resulting in an unstable erection. Several authors have suggested that this approach has a lower risk of perceived penile shortening (Klevmark et al, 1994; Nooter et al, 1994; Sulaiman and Gingell, 1994; Kümmerling and Schubert, 1995; Poulson and Kikeby, 1995; Ralph et al, 1995; Savoca et al, 2000; Savoca et al, 2004).

Imbrication procedures are used to avoid making a full-thickness tunical incision and fold the tunica to correct curvature. The techniques of tunical plication without incision were introduced in 1985 by Essed and Schroeder, who used nonabsorbable sutures placed in a figure-of-eight fashion to enable the knots to be buried (Essed and Schroeder, 1985). Two years later, Ebbehøj and Metz (1987) described their plication technique using multiple rows of sutures to shorten the longer side for congenital curvature (Ebbehøj and Metz, 1987). The 16-dot procedure has become a popular variation

TABLE 31-4 Outcomes for Plaque Excision or Incision and Grafting

GRAFT MATERIAL	AUTHOR AND DATE	PATIENTS (N)	MEAN FOLLOW-UP (MONTHS)	STRAIGHT AT LATEST FOLLOW-UP (%)	ED (%)	SATISFACTION RATES (%)
Dermal grafts	Wild et al, 1979	10	11	60	6	70
	Levine, 1997	15	11	73	12	70
	Chun et al, 2001	48	19.6	80	25	73
	Kovac and Brock, 2007	50	45	94	NR	NR
	Chung et al, 2011a	6	102	50	NR	35
Saphenous vein grafts	El-Sakka et al, 1998	113	9.72	96	12	92
	Kadioglu et al, 1999	20	13.2	75	5	NR
	Montorsi et al, 2000	50	12	80	6	96
	Akkus et al, 2001	58	16	86	7	92
	Adeniyi et al, 2002	51	32	82	8	88
	Hsu, 2003	24	31.2	96	4	100
	Kalsi et al, 2005	113	>60	80	23	60
	Kim et al, 2008	20	>12	85	35	NR
Buccal mucosa	Shiohvili et al, 2005	26	38	92	8	NR
	Cormio et al, 2009	15	13	100	0	93
Proximal crura	Teloken et al, 2000	7	6	86	0	86
	Schwarzer et al, 2003	31	NR	84	19	94
	Da Ros et al, 2012	27	NR	96	4	70
Tunica vaginalis	Das, 1980	15	4-16	87.5	0	100
	O'Donnell, 1992	25	42.2	88	68	NR
Dura mater	Fallon, 1990	40	12-72	95	25	NR
	Sampaio et al, 2002	40	12-24	95	15	NR
Temporalis fascia	Gelbard and Hayden, 1991	12	NR	100	0	100
Fascia lata	Kalsi et al, 2006	14	31	79	7	93
Small intestinal submucosa (SIS 4-layer)	Breyer et al, 2007	19	15	63	53	Score of 2.7/5.0
	Kovac and Brock, 2007	13	7.8	77	NR	85
	Lee et al, 2008	13	14	100	54	NR
	Staerman et al, 2010	33	14	67	11	79
	Chung et al, 2010	17	75	77	13	NR
Bovine pericardium	Egydio et al, 2002	33	19	88	0.0	NR
	Knoll, 2007	162	38	91	21	NR
Tutoplast pericardial graft	Hellstrom and Reddy, 2000	81	58	79	20	78
	Leungwattanakij et al, 2001	19	22	84	16	74
	Usta et al, 2003	11	14	91	NR	NR
	Levine et al, 2003	40	22	98	30	92
	Kovac and Brock, 2007	13	30	100	NR	NR
	Chung et al, 2011a	81	58	91	32	75
	Taylor and Levine, 2008	23	79	87	NR	NR
Acellular dermis	Adamakis et al, 2011	5	6	100	0	100
Synthetic materials	Faerber and Konnak, 1993	9	17.5	100	0	100
TachoSil	Licht et al, 1997	28	22	61	18	30
	Horstmann et al, 2011	43	63	41	9	20

ED, erectile dysfunction; NR, not reported.

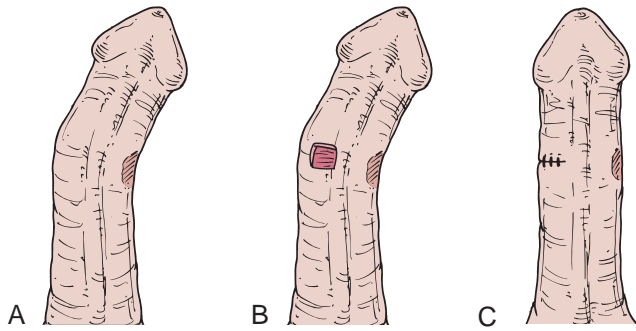


Figure 31-11. A, The Nesbit procedure employs a transverse elliptical incision of the tunica albuginea. B, This is done contralateral to the area of greatest curvature. C, The defect is closed transversely with permanent suture with or without the addition of absorbable suture.

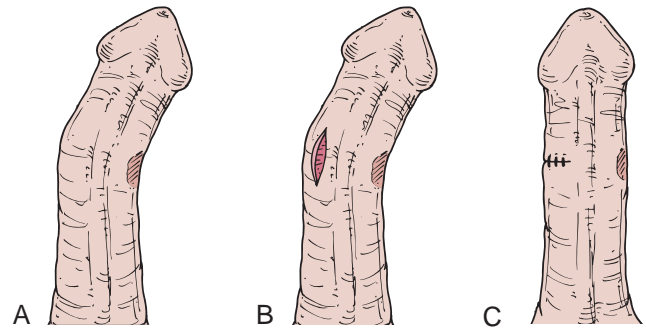


Figure 31-12. A, The Yachia procedure employs a full-thickness vertical incision (B) in the tunica albuginea contralateral to the area of greatest curvature and is closed transversely (C) without removal of tunica albuginea.

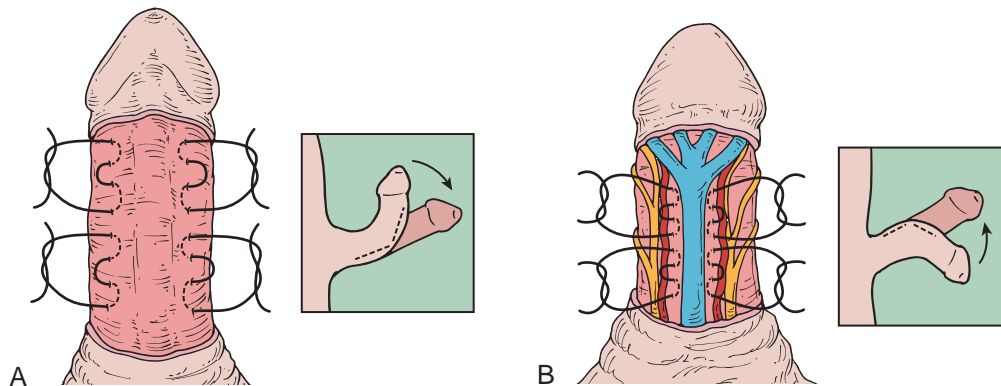


Figure 31-13. The dot procedure employs no incision. The tunica albuginea is pliated with permanent suture using an extended Lambert-type suture placement following four dots per plication. A, Suture placement for dorsal curve. B, Suture placement for ventral curve.

of tunical shortening in which there is no incision into the tunic but the tunica albuginea is pliated with permanent suture using an extended Lambert-type suture placement technique (Gholami and Lue, 2002; Brant et al, 2007; Rolle et al, 2005) (Fig. 31-13). Another plication variation is the Levine modification of the Duckett-Baskin tunica albuginea plication (TAP), which was originally used for children with congenital curvature. Here, a partial-thickness incision is made transversely on the contralateral side to the point of maximum curvature (Baskin and Duckett, 1994; Levine, 2006). A pair of transverse parallel incisions 1 to 1.5 cm in length are made through the longitudinal fibers but do not violate the inner circular fibers of the tunic. As a result, the underlying cavernosal tissue is not disturbed, which is thought to reduce the likelihood of postoperative ED. These incisions are separated by 0.5 to 1.0 cm depending on the desired amount of shortening. The longitudinal fibers between the two transverse incisions are excised so as to reduce the bulk of the plication. This procedure is now done with a single central permanent suture (2-0 Tevdek suture, Teleflex Medical, Research Triangle Park, NC, or TiCron suture, Medline, Mundelein, IL) placed in an inverting vertical mattress fashion to bury the knot and then supported with absorbable suture (3-0 polydioxanone [PDS], Ethicon, Somerville, NJ) placed in a Lambert fashion to reduce the palpable nature of the plication and knots (Fig. 31-14).

The key is that all plication procedures shorten the long side of the penis and therefore can result in loss of length on that aspect of the penis. Studies have examined the loss of penile length after use of the TAP technique. The expected factors that predicted loss of length included the direction of curvature and the degree of curvature (Greenfield et al, 2006). Greenfield and colleagues (2006) found that men who had a ventral curvature of

greater than 60 degrees tended to have the greatest potential loss of penile length. Preoperative penile length and degree and direction of curvature deformity appear to correlate with postoperative satisfaction (Mulhall et al, 2005; Greenfield et al, 2006).

The drawbacks of any tunica plication procedure for PD are that it does not correct shortening and it potentially may enhance loss of penile shaft length. It does not address hinge or hourglass effect and may exacerbate it, resulting in an unstable penis. The plaque is also left in situ. Penile narrowing or indentation has been reported in up to 17% with these techniques. In addition, there can be pain associated with the knots and suture granulomas (Tornehl and Carson, 2004; Taylor and Levine, 2008; Ralph et al, 2010). Surgical straightening with plication procedures can be expected in 79% to 100% of patients, with a reported satisfaction rate of 65% to 100% (Van der Horst et al, 2004; Ding et al, 2010; Larsen and Levine, 2013). Recurrence of penile curvature deformity (greater than 30 degrees) has been reported in up to 12% in a limited number of long-term studies (Taylor et al, 2008; Levine and Burnett, 2013). The reported risk of new ED ranges from 0% to 38%, and diminished sensation has been reported in 4% to 21% with follow-up of up to 89 months. Other, less common complications include hematoma in up to 9% of patients, urethral injury in less than 2%, and phimosis in up to 5% (Tornehl and Carson, 2004; Kadioglu et al, 2011b; Larsen and Levine, 2013). The most recent International Consultation on Sexual Medicine (ICSM) published recommendations regarding plication procedures in 2010 and reported that there was “no evidence that one surgical approach provides better outcomes over another, but curvature correction can be expected with less risk of new ED” when compared with grafting procedures (Ralph et al, 2010) (see

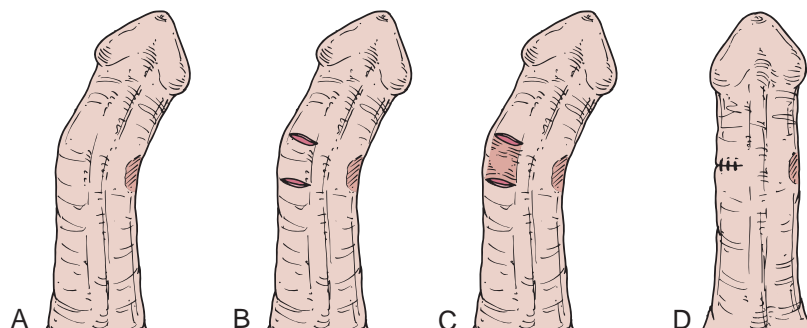


Figure 31-14. The tunica albuginea plication (TAP) procedure (A) employs a pair of transverse parallel incisions (B) separated by 0.5 to 1.0 cm. The incision is made through the longitudinal fibers but does not violate the inner circular fibers of the tunic. C, The longitudinal fibers between the two transverse incisions are removed to reduce the bulk of the plication. D, The defect is then brought together transversely.

TABLE 31-5 Outcomes of Tunical Shortening Procedure for Peyronie Disease (PD)

PROCEDURE	AUTHOR AND DATE	PATIENTS (N)	MEAN FOLLOW-UP (MONTHS)	STRAIGHT AT LATEST FOLLOW-UP (%)	SHORTENING (% OF PATIENTS)	ED (%)	SATISFACTION RATES (%)
Nesbit	Licht et al, 1997	28	22	79	37	4.0	79
	Schneider et al, 2003	48	25	23	44	0	75
	Syed et al, 2003	42	84	91	50	2.0	76
	Savoca et al, 2004	218	89	86.3	17.4	12.9	83.5
	Bokarica et al, 2005	40	81	88	15,* 100**	5.0	NR
	Ralph, 2006	9	31	NR	NR	NR	67
Plication	Geertsen et al, 1996	28	34	57	NR	3.5	82
	Levine and Lenting, 1997	22	20	91	9	9	NR
	Thiounn et al, 1998	29	34	79	NR	38	81,* 62**
	Schultheiss et al, 2000	61	39.8	70.5	45.9	3.3	NR
	Chahal et al, 2001	44	49	29	90	36	NR
	Gholami and Lue, 2002	124	31	85	41	6	96
	Van der Horst et al, 2004	28	30	83	NR	0	67.8
	Paez et al, 2007	76	70	42	NR	60	NR
	Kim et al, 2008	26	≥12	65	69	11	65
	Kadioglu et al, 2008	15	21	87	NR	NR	93
	Taylor and Levine, 2008	61	72	93	18	10	84
Yachia	Dugi and Morey, 2010	34	6	98	NR	2.9	93
	Licht et al, 1997	30	12	100	NR	NR	83
	Rehman et al, 1997	26	32	92	100	7.7	78
	Daitch et al, 1999	14	24.1	93	57	7	79

*Patient perceived shortening

**Objectively measured shortening

ED, erectile dysfunction; NR, not reported.

Table 31-5 for a summary of outcomes of tunical shortening procedures).

Tunical Lengthening Procedures (Plaque Incision or Partial Excision and Grafting)

Indications for plaque incision and grafting (PIG) or partial plaque excision and grafting (PEG) for surgical correction of PD includes greater complexity of disease with several (or

all) of the following: curvature greater than 60 to 70 degrees, shaft narrowing, hinging, and extensive plaque calcification (Levine and Lenting, 1997; Kendirci and Hellstrom, 2004; Ralph et al, 2010; Kadioglu et al, 2011b; Levine and Burnett, 2013). Most important, for the patient to be a candidate for incision or PEG, he must have strong preoperative erections (Taylor et al, 2012). This can be determined during the patient interview, when he is asked directly, "If your penis was straight, would the quality of rigidity that you currently have allow penetrative sex?" Should the patient hesitate or note suboptimal-quality erections,

a grafting procedure should not be performed unless the patient fully understands the risk of more advanced postoperative ED and the possible need for subsequent prosthesis placement to obtain optimal rigidity. Some men simply reject the idea that they need a prosthesis as a first-line surgical treatment. Others who might be considered candidates for tunica plication reject this approach because of fear of penile length loss. These men may be offered a grafting repair with the understanding that a penile prosthesis can be placed with minimal added difficulty at a later time. The advantage of performing the grafting procedure is that it would likely correct curvature and reestablish more normal shaft caliber while increasing the likelihood of some length recovery in the range of 0.5 to 3.0 cm.

Other factors have been reported in the literature as possible predictors of postoperative ED, including age older than 55 years, evidence of corporeal veno-occlusive dysfunction on duplex ultrasound analysis with a resistance index of less than 0.80, large tunica defect and graft size, ventral curvature, and curvature greater than 60 degrees (Leungwattanakij et al, 2001; Levine et al, 2005; Alphs et al, 2010; Flores et al, 2011). These predictors have been suggested as a result of single-center studies, with a limited number of patients in each cohort. Larger-scale studies indicate that the most critical criterion for any grafting procedure is the quality of preoperative erections (Flores et al, 2011; Taylor et al, 2012). In fact, Jordan and Angermeier found that there was a linear association between preoperative and postoperative ED (Jordan and Angermeier, 1993). Expert opinion has been consistent that patients with ventral deformity do not do well with grafting procedures. In fact, Hellstrom's analysis of the relationship of penile deformity to the vascular status of PD patients showed that men with ventral curvature had the greatest likelihood of having cavernous veno-occlusive dysfunction (Lowsley and Boyce 1950; Jordan and Angermeier, 1993).

Surgical grafting techniques include PIG and PEG. Historically, total excision of the plaque was practiced to "cut out the disease," resulting in onlays of large grafts with an unacceptably high rate of ED (Kendirci and Hellstrom, 2004; Kadioglu et al, 2006). Therefore, plaque incision was introduced in which a modified-H or double-Y incision is made in the area of maximum curvature (Gelbard, 1995). This allows the tunic to be expanded in this area, thereby correcting the curvature and shaft caliber but minimizing the underlying exposure of the cavernous tissue and thereby reducing the potential fibrosis of the cavernosal tissue and/or interrupting the delicate veno-occlusive mechanism, which has been considered the most likely contributor to postoperative ED with these grafting procedures (Dalton et al, 1991; Hatzimouratidis et al, 2012). Using the modified-H incision allows the correction of the curvature and shaft caliber. Gelbard (1995) has suggested that using multiple incisions and filling them with grafts would result in a smoother correction of curvature and potentially less injury to the underlying cavernosal tissue (Gelbard, 1995).

We favor PEG in which the area of maximum deformity is excised, particularly if it is associated with severe indentation. An increasing number of patients with severe deformity have indentation that if not addressed may result in a straightened penis but with residual narrowing causing instability. The corners of the defect are darted in a radial fashion to enhance correction of the narrowing in that area (Levine, 2011). Geometric principles have been applied to the grafting technique so as to obtain a properly sized graft with excellent correction of deformity (Egydio et al, 2004). This approach has been considered unnecessarily complex, and there have been reports of a higher rate of postoperative ED when this technique has been used (Flores et al, 2011). It appears intuitive that to reduce the risk of postoperative ED, the key is to limit the trauma to the underlying cavernosal tissue to maintain the veno-occlusive relationship between the cavernosal tissue and the overlying tunica graft.

Graft Materials

The ideal graft should approximate the strength and elastic characteristics of normal tunica albuginea; should have minimal

morbidity and tissue reaction; should be readily available, not too thick, pliable, easy to size and suture, inexpensive, and resistant to infection; and should preserve erectile capacity (Gur et al, 2011; Kadioglu et al, 2007). Multiple autologous grafts have been used historically, including fat, dermis, tunica vaginalis, dura mater, temporalis fascia, saphenous vein, crura or albuginea, and buccal mucosa (Lowsley and Boyce, 1950; Devine and Horton, 1974; Das, 1980; Lue and El-Sakka, 1998; Teloken et al, 2000; Sampaio et al, 2002; Leungwattanakij et al, 2003; Kargi et al, 2004; Shiosh-vili et al, 2005; Kadioglu et al, 2007). These have fallen out of favor because of a need for extended surgery to harvest the graft as well as a second surgical site, which possesses its own potential complications of healing, scarring, and possible lymphedema. Crural and buccal grafts are compromised by the inability to get enough graft material for large defects (Hatzichristou and Hatzimouratidis, 2002; Schwarzer et al, 2003; Shiosh-vili et al, 2005). Synthetic polyethylene terephthalate (PETE, Dacron) and polytetrafluoroethylene (PTFE, Teflon) grafts have been used historically and are not recommended now because of the potential risk of infection, localized inflammatory response, and fibrosis (Devine et al, 1997; Brannigan et al, 1998). Finally, "off-the-shelf" allografts and xenografts have emerged, including processed pericardium from a bovine or human source, porcine intestinal submucosa, and porcine skin. The two most common grafts currently used are Tutoplast (Coloplast US, Minneapolis, MN), processed human and bovine pericardium, and porcine small intestinal submucosa (SIS) grafts (Surgisis ES, Cook Urological, Spencer, IN) (Hellstrom, 1994; Hellstrom and Reddy, 2000; Knoll, 2001; Levine and Estrada, 2003). These packaged processed grafts are being used with increased frequency because of their ease of use and reduction in operating times. The pericardial grafts are thin, are strong, do not contract, and have no reports of infection or rejection. Chun and associates (2001) performed a comparison of dermal and non-Tutoplast processed human cadaveric pericardial grafts in the modified Horton-Devine procedure. Overall, 92% of patients were able to achieve successful coitus with or without assistance. These researchers reported a 33% overall recurrence rate, with 26% of patients who received dermal grafts and 44% of patients who received pericardial grafts experiencing recurrence. However, this study did not report on the severity of recurrence, and all these patients were able to achieve erections suitable for coitus. Satisfaction rates were similar, and those who underwent pericardial grafting had shorter operative times as well as decreased morbidity associated with the absence of a graft donor site (Chun et al, 2001). The SIS grafts have similar advantages to pericardium, except there have been reports of graft contraction, particularly with one-ply grafts, with associated recurrent curvature in the 37% to 75% range (Santucci et al, 2005; John et al, 2006; Breyer et al, 2007; Kovac and Brock, 2007; Taylor and Levine, 2008). Other reported postoperative complications with SIS grafts include subgraft hematoma in 26% and an infection rate of 5% (Breyer et al, 2007).

Tissue-engineered graft materials have been considered more recently and potentially offer the advantage of having a graft seeded with cellular material, which may enhance the take of the graft and potentially reduce local tissue fibrosis with diminished postoperative ED. Adipose tissue-derived stem cell-seeded SIS, human acellular matrix tunica albuginea grafts, and autologous tissue-engineered endothelialized tunica albuginea grafts have been investigated for incision and excision procedures (Schultheiss et al, 2004; da Silva et al, 2011; Imbeault et al, 2011; Ferretti et al, 2012; Ma et al, 2012). Imbeault and associates (2011) demonstrated in vitro creation of artificial tunica albuginea using human dermal fibroblast and human endothelial cells. They concluded that this tissue-engineered endothelialized tubular graft was structurally similar to normal tunica with a high burst pressure and adequate mechanical resistance. Furthermore, the autologous property of this model could represent an advantage compared with other available grafts (Imbeault et al, 2011). Such studies may help elucidate future medical treatments for PD using tissue-engineered grafts for the reconstruction of the tunica albuginea. The biomechanical properties, compatibility with the tunica albuginea, and effective neovascularization of the

tissue-engineered grafts need to be investigated further before such basic research can be applied in practice.

Grafting Surgical Technique

Once the patient has achieved satisfactory general anesthesia, it is advised that the patient receive a dose of intravenous antibiotics and that the deep venous thrombosis protection apparatus be applied. The dorsal SPL should be measured. An artificial erection is then created by injecting a vasoactive drug (papaverine, Trimix, prostaglandin E₁) via a 21-gauge butterfly needle placed through the glans into the corpus cavernosum. Saline can be infused to create a full rigid erection, which allows visualization and measurement of the deformity, including curvature and areas of indentation with or without hinge effect. The preferred approach for grafting procedures is a circumcising incision made approximately 1.5 to 2 cm proximal to the corona, or through a previous circumcision site. The penis is degloved down to the Buck fascia, at which point hemostasis is obtained with bipolar cautery. It is advisable for the surgeon to use loupe magnification to reduce the likelihood of injury to neurovascular structures. With the shaft exposed, the erection can again be re-created, demonstrating the area of maximum deformity. In the circumstance of a dorsal or dorsal-lateral curvature, the Buck fascia, with the enclosed neurovascular bundle, is elevated by making a pair of parallel incisions just lateral to the urethral ridge, through the Buck fascia to the tunica albuginea. The Buck fascia is carefully elevated off the tunic. Typically this can be done with delicate, sharp dissection, but occasionally, if there is significant adhesion between the Buck fascia and the tunic, bipolar cautery can be used to elevate this with minimal risk of permanent nerve injury. Once the Buck fascia is elevated off the area of maximum deformity, a full erection is re-created. The area of maximum deformity is marked for incision or partial plaque excision. This allows excision and expansion of areas of severe indentation. It should be noted that even with a pure lateral curvature, the tunic to be excised must traverse through the dorsal septum, because this is the anchor point of the scar and if it is not taken, substantial residual curvature will likely remain (Jordan, 2007). When extensive calcification extends beyond the area of partial plaque excision, the calcified component can be removed, leaving the outer lamina intact because the calcification involves the inner circular fibers. Once the rectangular defect is established, the corners are darted in a radial fashion so as to help to recover normal shaft caliber in the area of indentation. We have simplified the geometric principle technique by ensuring that the lateral sides of the defect are of equal length (Egydio et al, 2004; Levine, 2011). In doing this, we create a uniform-sized square or rectangle, which virtually always allows satisfactory correction of lateral and dorsal curvature. Often the proximal transverse length will be longer than the distal transverse length because of distal tapering of the shaft. The penis can now be measured on stretch again; typically there will be increased dorsal length from 0.5 to 3.0 cm. Stay sutures of 4-0 PDS (Ethicon, Somerville, NJ) are placed in the four corners of the defect and at the midpoint transversely, distally, and proximally. With these stay sutures on stretch, the defect can be measured longitudinally and transversely. Our preference is to use a Tutoplast processed pericardial graft (Coloplast, Minneapolis, MN), because there is usually little graft contraction. The graft should be sized no more than 10% larger than the measured defect on stretch. Porcine SIS grafts (Cook Urological, Spencer, IN) need to be oversized by 25%. Once the graft has been cut to size, it is secured in place with the previously placed stay sutures; then, with 4-0 PDS placed in a running fashion, the graft is secured to the defect. If a large defect is created, it may be advisable to place several interrupted 4-0 PDS sutures in the area of the septum to reduce the volume of blood that can accumulate under the graft. An artificial erection is again reestablished; if there is significant residual curvature, this can be addressed with tunica plication. We have found that this is necessary in up to 25% of patients. In patients who have a more prolonged curve or in those who have substantial indentation in one area as well as a more distal curvature, the grafting should be performed in the area of indentation, and plication is used to address any residual

dorsal or lateral curve once grafting has been completed. In this circumstance a single graft can be used, which has not been shown to have a higher rate of postoperative ED than when multiple grafts are used but does have the advantage of shorter operative time. Once satisfactory deformity correction has been accomplished, the Buck fascia is reapproximated with running 4-0 chromic, and the shaft skin is reapproximated to subcoronal skin with interrupted 4-0 chromic in a horizontal mattress fashion. Of note, for those patients who are uncircumcised and do not have any evidence of phimosis, a circumcision is not necessary (Garaffa et al, 2010); but if there is any question of excessive redundant foreskin and/or phimosis, then circumcision should be performed to reduce the likelihood of postoperative paraphimosis (Garaffa et al, 2010). The penis is dressed with Xeroform gauze (3M, St. Paul, MN) placed over the circumcising incision, and then a Coban wrap (3M, St. Paul, MN) is placed distal to proximal, providing gentle compression. Typically the dressing is left in place for 3 days and then removed, at which point the patient may shower. Submersion of the wound is not advised because this may encourage wound separation.

Postoperative Management

The postoperative rehabilitation period is critical to reduce the risk of postoperative ED and length loss as well as to optimize straight healing. We find it useful to liken the importance of postoperative rehabilitation after penile surgery to the importance of the rehabilitation needed for successful orthopedic joint replacement. Typically a patient is seen 2 weeks after surgery, at which point massage and stretch therapy are initiated (Horton et al, 1987). The patient is instructed to grasp the penis by the glans and gently stretch it away from the body and then with his other hand to massage the shaft of the penis for 5 minutes twice per day for 2 to 4 weeks. The massage and stretch can be performed by the patient's partner for the second 2 weeks if possible. This will reinitiate the sexual experience for the couple and hopefully diminish the fear of reinjuring the penis, for which the partner may feel responsible. Investigators have recommended the use of nocturnal PDE5 inhibitors to enhance postoperative vasodilation, which may help support graft take, reduce cicatrix contraction, and theoretically preserve cavernosal tissue, thereby reducing postoperative ED (Levine et al, 2005). Finally, external penile traction devices have been encouraged and have been recently shown to reduce length loss postoperatively and can even enhance length gain after both grafting and plication procedures (Levine et al, 2013). In a recent report, SPL in patients who used postoperative traction therapy was shown to increase after plication and PEG procedures by +0.85 cm and +1.48 cm, respectively, versus length changes of -0.53 cm and +0.24 cm in the plication and PEG groups in which postoperative traction was not used. In fact 50% of the plication and 89% of the PEG patients using postoperative traction had measured length gain. The reported average daily use was 2.5 hours for 4.5 days per week for an average duration of 3.8 months. There was no patient reported with postoperative length loss among those who used postoperative traction therapy, and although not statistically significant, there was a trend of higher satisfaction for erect length in the groups in which postoperative traction was used. Traction is recommended to be used for 3 or more hours per day, beginning 3 to 4 weeks after surgery, once the wound can tolerate the pressures of the stretching device for 3 months (Rybak et al, 2012).

In a review of the published reports on grafting for PD over the past 12 years, satisfactory straightening was found in 74% to 100% of patients, but postoperative ED, which does not have a uniform definition in the literature and may include reduced rigidity, compared with preoperative rigidity, to complete loss of rigidity, has been reported in 5% to 54% of patients. Diminished sensation after grafting has been reported in a few series with a follow-up of less than 5 years (Taylor and Levine, 2008). In the few single-center surgical outcome reviews with 5 or more years of follow-up, ED has been reported in up to 24%, with recurrent or persistent curvature in the 8% to 12% range (Montorsi et al, 2004; Kalsi et al, 2005; Chung et al, 2011a; Usta et al, 2003). See Table 31-4 for a summary

of the outcomes for penile straightening with plaque incision or excision and grafting.

Penile Prosthesis for Men with Peyronie Disease

Indications

In men with PD and concurrent ED refractory to PDE5 inhibitors, penile prosthesis placement is the procedure of choice (Levine and Lenting, 1997; Levine and Dimitriou, 2000; Kendirci and Hellstrom, 2004; Ralph and Minhas, 2004; Mulhall et al, 2005). Additional straightening maneuvers may be necessary, including manual modeling and incising of the tunica albuginea with or without grafting. Recently, transcorporeal approaches have been used before modeling or relaxing incisions; the plaque is incised or stretched from within the corporeal body (Shaer, 2011; Perito and Wilson, 2013).

Techniques for Straightening When Placing a Penile Prosthesis for Peyronie Disease

An inflatable penile prosthesis (IPP) appears to be the preferred surgical implant, as the pressure within the cylinders allows for superior correction of curvature with manual modeling, as well as improved girth enhancement. Malleable prostheses, when used for PD historically, were associated with narrow, cold, and less than natural erections (Montorsi et al, 1993; Ghanem et al, 1998; Marzi et al, 1997).

Manual modeling via the penoscrotal approach is recommended with a high-pressure inflatable cylinder, but all available three-piece and two-piece devices have been used successfully to correct deformity (Wilson and Delk, 1994; Montague et al, 1996; Montorsi et al, 1996; Levine et al, 2001; Chung et al, 2012c). Our approach is to place the prosthesis cylinders first, followed by closing of the corporotomies. With use of a surrogate reservoir attached to the pump tubing, the prosthesis can be filled to full rigidity, which will allow visualization of the deformity. To protect the pump from the high pressures that may occur during manual modeling, shodded hemostat clamps are applied to the tubing between the pump and the cylinders. The penis is then bent in the contralateral direction to the curvature. It is recommended to try to hold the penis in this position for 60 to 90 seconds, but experience has suggested that around 30 seconds may be all that is possible. Once the modeling has been performed, the penis can be reassessed by instilling more fluid, reapplying the hemostats, and then performing the modeling procedure repeatedly until satisfactory curvature correction has been attained. **The modeling technique should be a gradual bending rather than a violent maneuver, because this will reduce the likelihood of inadvertent tearing of the tunic or injury to the overlying neurovascular bundle.** Urethral injuries during performance of this technique as a result of distal extrusion of the prosthetic cylinders at the fossa navicularis have been reported (Wilson and Delk, 1994; Wilson et al, 2001). To reduce the likelihood of this occurring, the bending hand should be placed on the shaft of the penis rather than on the glans, to avoid downward pressure on the tips of the cylinders. The other hand should be grasping the base of the penis with pressure over the corporotomies, which will provide support to this area and reduce the likelihood of disruption of the suture line.

Published reports on the use of modeling have indicated that successful straightening can be expected in 86% to 100% with no higher incidence of device revision; sensory deficit after manual modeling is rare but remains a potential complication that should be discussed with the patient preoperatively (Wilson and Delk, 1994; Montague et al, 1996; Wilson et al, 2001; Levine et al, 2010; Chung et al, 2012c). Although it would appear that for more severe curvature more advanced techniques are necessary, published experience has suggested that manual modeling may be used as first-line therapy for correction of curvature after prosthesis implantation (Levine et al, 2010; Chung et al, 2012c). An alternative to this would be to perform a tunic plication contralateral to the curvature before

placement of the prosthesis to correct the curvature (Rahman et al, 2004; Dugi and Morey, 2010). When there is residual curvature of greater than 30 degrees or residual indentation causing the inflated cylinder to buckle, tunical incision is recommended after elevation of the Buck fascia in that area (Levine and Dimitriou, 2000).

The transverse penoscrotal skin incision will allow access to virtually the entire shaft, except when the curvature is distal and dorsal on the shaft, so degloving the penis is not always necessary. The tunical incision is made with the cylinders deflated, using the cautery to release the tunic with an effort to preserve cavernosal tissue over the implant. When Titan cylinders (Coloplast, Minneapolis, MN) are used, the energy should be less than 30 watts to reduce potential cylinder thermal injury (Hakim et al, 1996). Once the incision has been made, the cylinders are reinflated and further modeling can be performed to optimize deformity correction. Although there is not a clearly accepted approach, grafting is recommended when the defect measures greater than 2 cm in any dimension to reduce cicatrix contracture and cylinder herniation (Levine and Dimitriou, 2000; Carson and Levine, 2014). Historically, synthetic grafts were used, but currently biografts of pericardium or porcine SIS are recommended. Use of locally harvested dermal grafts is not recommended, because there is risk of transferring bacteria to the prosthesis.

There have been limited publications looking at the long-term results with regard to outcomes and satisfaction with inflatable penile prostheses in men with PD and ED. Levine and associates (2010) reported on 90 consecutive men undergoing placement of an IPP, with 4% having satisfactory straightening with prosthesis placement alone, 79% having satisfactory curvature correction with prosthesis and modeling, 4% requiring tunical incision, and 12% having incision and pericardial grafting for correction of curvature. There was no evidence that the additional maneuvers increased the rate of mechanical failure or infection with up to 8 years of follow-up. In the nonvalidated questionnaire used in this study, overall patient satisfaction was 84%, whereas only 73% were satisfied with curvature correction. This may indicate a flaw in the design of the questionnaire, but may also reflect the general disappointment and frustration of patients with PD (Levine et al, 2010). Thus, preoperative counseling and setting appropriate expectations as with any prosthesis placement are critical (Akin-Olugbade et al, 2006). It is recommended that preoperative discussion also be focused on the goal of obtaining "functional straightness," in which a residual curvature of 20 degrees or less in any direction would likely not compromise sexual activity and may correct in time as a result of tissue expansion caused by the cylinders. A comparison of outcomes between the two three-piece inflatable devices in North America found no significant advantage with respect to device reliability, infection, or patient satisfaction (Chung et al, 2012c).

By far the most common postoperative complaint heard from men who have undergone penile prosthesis placement is length loss (Montague, 2007). The first to objectively evaluate penile length change after prosthesis implantation were Wang and associates, who demonstrated decreases of 0.8, 0.75, and 0.74 cm at 6 weeks, 6 months, and 1 year after surgery, respectively (Wang et al, 2009). This is of particular concern in the PD population, who often already have loss of penile length. Any additional length loss as a result of the implant may be distressing to the patient and should be addressed preoperatively. For those men who cannot tolerate any further length loss, a recent small pilot study using traction therapy before penile prosthesis placement in men with PD as well as other disorders causing penile shortening (e.g., prosthesis explants, radical prostatectomy) did demonstrate that after 3 to 4 months of daily traction for an average of 3 hours or more per day, there was no further loss of length after prosthesis placement, and the majority had gained some length (0.5 to 2.0 cm) compared with the pretraction SPL (Levine and Rybak, 2011). Postoperative prolonged cylinder inflation has been recommended to maintain penile length and decrease residual curvature; the device is kept inflated for 10 to 30 minutes daily for 3 months starting 6 weeks after surgery. See Table 31-6 for a summary on the outcomes of penile straightening with penile prosthesis placement.

TABLE 31-6 Outcomes of Penile Prosthesis Implantation for Peyronie Disease

AUTHOR AND DATE	PROSTHESIS TYPE	PATIENTS (N)	MEAN FOLLOW-UP (MONTHS)	ADDITIONAL STRAIGHTENING MANEUVERS (%)	SATISFACTION RATES (%)
Garaffa et al, 2011	Inflatable	129	NR	37	86
	Malleable	80	NR	16	72
Levine et al, 2010	Inflatable	90	49	96	84
DiBlasio et al, 2010	Inflatable	79	20	11	NR
Wilson and Delk, 1994	Inflatable	138	NR	8	NR
Montague et al, 2007	Inflatable	72	NR	8	67
Chaudhary et al, 2005	Inflatable	46	12	61	93
Rahman et al, 2004	Inflatable	5	22	100	100
Levine and Dimitriou, 2000	Inflatable	46	39	NR	NR
Akin-Olugbade et al, 2006	Inflatable	18	≥6	22.2	60
Usta et al, 2003	Inflatable	42	21 (12-48)	30	84
Wilson et al, 2001	Inflatable	104	60	0	99
Carson et al, 2000	Inflatable	63	NR	NR	88
Morganstern et al, 1997	Inflatable	309	42	NR	NR
Montorsi et al, 1996	Inflatable	33	17	40	79

NR, Not reported.

KEY POINTS: SURGICAL MANAGEMENT

- Surgical correction of PD with or without penile prosthesis placement remains the gold standard to correct deformity and is indicated when deformity or rigidity compromises or prevents penetrative sexual activity.
- Surgical candidates need to undergo a detailed and comprehensive consent process so that the patient will understand the potential limitations of the surgery and will have appropriate personal expectations, thereby improving postoperative satisfaction.
- For the man with satisfactory preoperative rigidity with curvature less than 60 to 70 degrees without significant indentation, some form of tunica plication is indicated. There does not appear to be any one plication technique that has been demonstrated to be superior to others, as no head-to-head comparative trials have been published.
- Men who have more severe, complex deformity but who have strong preoperative erectile function and no evidence of venous insufficiency on duplex ultrasound analysis should be considered candidates for straightening with plaque incision or PEG.
- The complications associated with these operations include incomplete straightening, recurrent curvature, shaft shortening, diminished penile sexual sensation, and ED.
- It appears that the nature of the graft is less likely the determining factor with respect to postoperative ED. On the other hand, optimum outcomes are most likely a result of proper patient selection with respect to preoperative erectile status as well as operative technique.
- For men who have inadequate rigidity and PD, penile prosthesis placement with straightening maneuvers as necessary should be considered first-line surgery.

CONCLUSION

PD is far more common than previously thought and is a growth area in urology, not only for clinical practice but also for basic science research. The mysteries of this wound-healing disorder need to be clarified, and this will likely yield better treatment options as well as potential strategies to prevent progression. It should be recognized that there are acute and stable phases and that surgery should be offered only after the scarring process has been stable for 3 to 6 months. Patients with PD should be counseled that complete

correction of the deformity, including curvature, indentation, and shortening, is not likely and that the goal is to allow the patient to function sexually again. The devastating psychological impact of this disease is important to recognize, and psychological counseling is occasionally indicated and should be offered. For patients in the acute phase, not offering any therapy does little for their emotional and physical distress and may allow progression of deformity. Offering nonsurgical treatment including oral, injection, and/or mechanical therapy may stop progression and possibly improve deformity and sexual function. When surgery is indicated, the goal is to correct the deformity and prevent worsening of ED so that penetrative sexual activity is possible. The patient must understand that recovery of his pre-PD penis is not likely and that surgery carries the risk of incomplete straightening and recurrent curvature, further shaft shortening, change in sexual sensitivity, and, most important, diminished postoperative rigidity. For men with drug-refractory ED and PD, placement of a penile prosthesis with straightening maneuvers is the best approach to address both problems with one operation.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Sexual Wellness

Female Sexual Response

Mental Aspects of Sexual Response in Women

Evaluation of Sexual Wellness in Women

Special Populations

Female Sexual Dysfunction

Hypoactive Sexual Desire Disorder

Female Sexual Arousal Disorder

Persistent Genital Arousal Disorder

Female Orgasmic Disorder

Sexual Pain Disorders

Conclusions

SEXUAL WELLNESS

At a technical consultation on sexual health sponsored by the World Health Organization, sexual wellness was defined as (World Health Organization, 2006):

1. A state of physical, emotional, mental, and social well-being in relation to sexuality
2. Not merely the absence of disease, dysfunction, and/or infirmity
3. An important and integral aspect of human development and maturation
4. A human right

Diminished sexual function is associated with impaired quality of life and well-being (Laumann et al, 1999; Davison et al, 2009). Many urologists underestimate the prevalence of female sexual concerns and do not routinely make the assessment of sexual wellness a part of their practice (Bekker et al, 2009) despite evidence that many women in urologic clinics have sexual issues (Elsamra et al, 2010).

Relatively few women discuss sexual issues with their provider (Lindau et al, 2007). There are myriad reasons for this failure to address the issues; an important example is failure of the physician to broach the subject with the patient (MacLaren, 1995; Sadowsky et al, 2006; Sobocki et al, 2012). Despite a common perception that sexuality is not of importance to older women, studies have indicated that sex remains a concern even for a substantial number of elderly women.



Data referable to this may be found on the Expert Consult website.

A basic understanding of female sexual response is important, as urologic conditions and procedures have the capacity to markedly influence female sexual wellness. The astute urologist will be aware of how sexual function may influence or be influenced by urologic conditions and will address these issues with patients.

FEMALE SEXUAL RESPONSE

The Sexual Response Cycle

William Masters and Virginia Johnson were among the first to report on the physical aspects of sexual response (Masters and Johnson, 1966). According to their observations, sexual response begins with the arousal phase. The arousal phase is characterized by vulvar and clitoral swelling, vaginal lubrication and lengthening, nipple erection, increased genital sensitivity, tachycardia,

tachypnea, and subjective pleasure and excitement (Masters and Johnson, 1966; Basson et al, 2010b). The sexual arousal phase is followed by the plateau phase during which sexual excitement/arousal continues (Masters and Johnson, 1966).

Orgasm may follow a variable period of arousal and sexual stimulation. Orgasm is a “variable, transient peak sensation of intense pleasure, creating an altered state of consciousness usually accompanied by involuntary, rhythmic contraction of the pelvic striated circumvaginal musculature, with concomitant uterine and anal contractions and myotonia, usually with an induction of well-being and contentment” (Masters and Johnson, 1966; Meston et al, 2004).

Female orgasm has a long and controversial history; for centuries there was denial that such an entity even existed in healthy women. Female orgasm (and how it can and should be obtained) continues to be a highly controversial topic (Colson, 2010). Many women climax from direct or indirect stimulation of the clitoris; others may experience orgasm during vaginal penetration with or without stimulation of the clitoris or vulva. Some healthy women do not experience orgasm during vaginal penetration under any circumstances (Masters and Johnson, 1966; Wallen and Lloyd, 2011). Anal stimulation may also play a role in attaining orgasm for a minority of women (Herbenick et al, 2010b).

After orgasm(s) there is a resolution phase as sexual excitement declines back to baseline levels. In women this involves reduction in pelvic blood flow, relaxation of nipple erection, and restoration of heart rate to resting levels. Sexual excitement declines to resting levels; a sense of sexual satiety and lack of desire for additional sexual activity is typical of this phase (Masters and Johnson, 1966).

There is a wide range of normal sexual response in women (Bancroft and Graham, 2011). Some women may not experience orgasm during partnered sex; others may have one or several orgasms before a return to the resting state (Fig. 32-1) (Masters and Johnson, 1966). This heterogeneity in sexual response is not necessarily associated with differing levels of sexual satisfaction.

In the 1970s, Kaplan added the concept of sexual desire to the linear response model. Sexual desire was postulated to precede the development of arousal (Kaplan, 1977). In the early 2000s, Basson stated that a linear response may not be reflective of what women experience during sex. An alternative hypothesis is that intrinsic, active sexual desire is not an essential component of sexual health for all women. Some women may have a reactive desire that occurs in response to sexual initiation by a partner or by other external stimuli. In such women, sexual response may

A study sponsored by the American Association of Retired Persons indicated that 61% of women older than 45 years report that a satisfying sexual life is important to them; almost 40% of women older than 70 years continued to view sex as at least somewhat important in their lives (Fisher et al, 2010). Data from the National Social Life, Health, and Aging study indicated that 62%, 40%, and 17% of women aged 57 to 64, 65 to 74, and 75 to 85 reported having sex in the previous year, respectively. Of these sexually active

persons, more than 50% of all age groups reported sex at least twice a month with coital intercourse occurring on at least 75% of sexual encounters (Waite et al, 2009). The Global Survey of Sexual Attitudes and Beliefs (GSSAB) included more than 13,000 women aged 40 to 80 years from around the world and the survey reported that up to 25% of women aged 70 to 80 years engaged in sexual activity at least once a week; the prevalence of sexual activity did vary a great deal by region (Nicolosi et al, 2005, 2006a, 2006b).

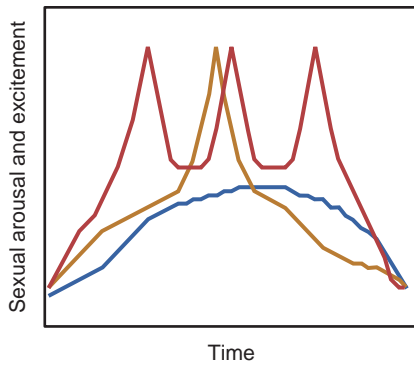


Figure 32-1. This linear sexual response cycle corresponds approximately to the models of [Masters and Johnson \(1966\)](#) and [Kaplan \(1977\)](#). Sexual arousal/excitement increases during sexual activity, reaching a peak with orgasm and eventually declining to baseline. Heterogeneity is present in female sexual response, with some women experiencing a single orgasm during a sexual encounter (orange line). Other women may experience multiple orgasms (red line) or no orgasm (blue line). Each of these patterns may be normal in a given woman.

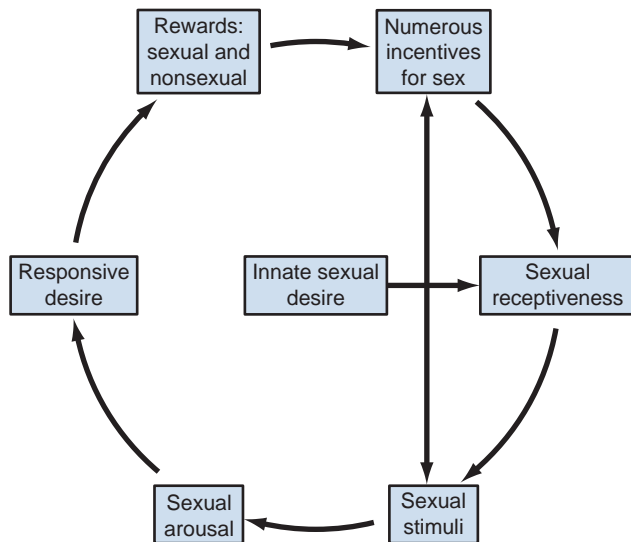


Figure 32-2. This circular sexual response cycle corresponds to the model of [Basson \(2002\)](#). In this model, sexual activity may occur in response to sexual desire or to previous rewards from sexual activity. With positive reward, sexual incentives are increased and sexual activity becomes more likely.

follow a circular model in which sexual activity leads to intra- and interpersonal rewards. This prompts sexual interest and receptiveness to additional sexual experiences ([Fig. 32-2](#)) ([Basson, 2002](#)). The various sexual response models are useful as a means of classification but should not be interpreted as a fixed pattern applicable to every woman and/or in every circumstance ([Bancroft and Graham, 2011](#)).

Studies on models of sexual response are discussed in more detail on the Expert Consult website.

Pelvic Anatomy and Genital Sexual Response

A detailed discussion of pelvic anatomy can be found on the Expert Consult website.

Pelvic anatomy relevant to female sexual response includes the clitoris (glans and crura), labia major and minora, the vulvar vestibule, the vagina, the vestibular bulbs, and the LA muscle ([O'Connell et al, 2008](#)). Engorgement with blood of genital tissues is the

unifying theme of the genital events underlying female sexual arousal ([Suh et al, 2004](#); [Yang et al, 2006](#)). The clitoris (both glans and bulbs) is composed of erectile tissue with large dilated vascular spaces. The vascular spaces of the vagina, labia minora, and urethra are spongy but lack the large sinusoidal spaces of the clitoris; these structures may swell but do not become rigid with arousal ([Yang et al, 2006](#)).

Increased blood flow leads to attenuation of sodium reabsorption and increased oncotic pressure within the vaginal walls ([Munarriz et al, 2002a](#)). Increased oncotic pressure produces a transudative ultrafiltrate that crosses into the vaginal lumen, producing vaginal lubrication ([Fig. 32-4](#) on the Expert Consult website) ([Martin-Alguacil et al, 2006](#)). Aquaporins are critical for the translocation of fluid across the vaginal mucosa. These soluble proteins translocate between the cytoplasm and the cell membrane, permitting efflux of transudate fluid through the vaginal epithelium ([Kim et al, 2009](#)). There are no glandular elements in the vagina itself. There may be some contribution to vaginal lubrication from small cervical glands and to external lubrication from vestibular (also known as Bartholin) glands around the vaginal introitus and/or the urethral Skene glands; these contributions are thought to be relatively minor ([Woodard and Diamond, 2009](#)).

Genital responses are controlled in large part by the autonomic nervous system. Generally, the parasympathetic nervous system enhances sexual response by vasodilation. The sympathetic nervous system opposes sexual responses by vasoconstriction but does play an important role in pelvic contractions with orgasm ([O'Connell et al, 2008](#)). The somatic nervous system plays a role in transmission of sensation and control of motor neurons to the pelvic floor ([Schober and Pfaff, 2007](#)).

Details on nongenital sites relevant to sexual arousal are included on the Expert Consult website.

Molecular Mechanisms

Molecular mechanisms and neuroanatomic information relevant to female sexual response are discussed on the Expert Consult website.

Neurophysiology

Serotonin

Serotonin is an important CNS neurotransmitter and is intimately linked to sexual response. Serotonergic receptors are present in the peripheral nervous system, vasculature, and vestibular glands ([Fetisov et al, 1985](#); [Frohlich and Meston, 2000](#)). Serotonergic agonists induce vascular smooth muscle contraction by action on the 5-HT_{2A} receptor ([Yang and Mehta, 1994](#)). Generally, serotonergic drugs (e.g., selective serotonin reuptake inhibitors [SSRIs]) have an inhibitory effect on sexual desire, arousal, and orgasm ([Balon, 2006](#)).

More information is available on the Expert Consult website.

Dopamine and Oxytocin

Centrally, dopamine and oxytocin have been implicated as pro-organic. Oxytocinergic and dopaminergic agonists increase sexual arousal and initiate sexual solicitation when released in the MPOA ([Caldwell et al, 1989](#); [Graham et al, 2012](#)).

Oxytocin is synthesized in the PVN of the hypothalamus ([Jenkins and Nussey, 1991](#)) and has central and peripheral effects; it appears to mediate pair bonding in some species ([Moscovice and Ziegler, 2012](#)). In humans, oxytocin is released with orgasm and the intensity of sensation appears to correlate with the amount released ([Blaicher et al, 1999](#); [Meston and Frohlich, 2000](#)).

Norepinephrine

Norepinephrine is the predominant sympathetic nervous system neurotransmitter in the peripheral nervous system. Tonic

In a study of 129 female nurses, there was a relatively even split between endorsement of the three aforementioned sexual response cycles (Masters and Johnson, 1966; Kaplan, 1977; Basson, 2002) as most representative of their experience. Interestingly, women at higher risk of sexual dysfunction were significantly more likely to endorse the Basson model (Sand and Fisher, 2007). Giles and McCabe (2009) reported a similar result in a study of 404 women; in this study the linear models were a good fit for the mixed population of women but the circular model was a better fit for women with lower sexual function scores. These authors

determined that many women reported desire preceded arousal, implying that intrinsic sexual desire occurs in women (Giles and McCabe, 2009).

These controversies do not necessarily indicate fundamental defects in the circular model. However, they do imply that secondary gain from sexual activity (e.g., mate guarding, emotional intimacy, etc.) may be important driving factors for sexual activity in women with lower sexual desire, decreased subjective/objective arousal response, and/or difficulty attaining orgasm with partnered sexual activity.

External Genitalia

The external-most portion of the female genital tract is collectively known as the *vulva*. The *mons pubis* is the fleshy area anterior to the pubic bone and superior to the *vaginal introitus*. The mons contains subcutaneous fat and the suspensory ligaments of the *clitoris* (O'Connell et al, 2008).

Labia

The *labia major* are paired, rugated organs located inferior to the mons pubis and extending to the perineum (O'Connell et al, 2008). The labia majora contain abundant adipose tissue with a dual blood supply, making these tissues useful as local flaps for reconstructive surgery in the female pelvis (Given and Acosta, 1990). The labia majora contain numerous sebaceous glands (Salonia et al, 2010), are derived from embryonic ectoderm, and are hence keratinized (Farage and Maibach, 2006). The labia majora are innervated anteriorly by the anterior labial branch of the ilioinguinal nerve and posteriorly by the labial branch of the pudendal nerve (O'Connell et al, 2008).

Between the paired labia majora are the *labia minora*. The labia minora lie on either side of (in descended order) the clitoris, *urethral meatus*, and the *vaginal vestibule* (Puppo, 2013). Inferiorly, the labia minora coalesce to the *posterior fourchette*, the midline skin at the posterior margin of the vaginal introitus.

The labia minora are derived from embryonic endoderm (Farage and Maibach, 2006). The labia minora are thinly or not at all keratinized and consist of vascular tissue in a fibrous stroma (Yang et al, 2006). The labia minora are very sensitive to the presence or absence of sex steroids. There is a wide variation of normal in the appearance of the labia minora (Puppo, 2013). The *vestibular* (also known as Bartholin) glands are paired structures located near the labia minora that produce lubrication during sexual arousal (Levin, 1980).

Labial branches of the external pudendal artery (derived from the femoral artery) supply the labia major and minora. External labial veins drain to the great saphenous vein (O'Connell et al, 2008).

The perineal neurovascular bundles are branches of the pudendal nerve and originate near the takeoff point of the clitoral nerves. The perineal neurovascular bundles are responsible for innervations to the external genitalia (O'Connell et al, 2005) as well as the urethra (O'Connell et al, 2008).

Clitoris

The clitoris is composed of two erectile bodies that extend bilaterally along the ischium lateral to the vagina (Yang et al, 2006). The clitoral bodies contain spongy erectile tissue consisting of lacunar spaces, endothelium, and smooth muscle, which become engorged with blood during arousal (Toesca et al, 1996; Yang et al, 2006; Martin-Alguacil et al, 2008). A fibroelastic sheath called the tunica albuginea covers each corporal body (Yang et al, 2006). The tunica albuginea of the clitoral corpora cavernosa and corpus spongiosum/glans clitoris is relatively thin. This has the effect of reducing the veno-occlusive force during engorgement of the clitoris. Furthermore, the clitoris does not contain a dense network of venous tissue immediately deep to the tunica albuginea (Toesca et al, 1996). The thinness of the tunica albuginea and absence of subtunical venules differs from what is observed in the male phallus. These structural differences account for the less turgid erectile response observed during clitoral erection compared to penile erection.

The majority of clitoral length is located inside the pelvis; the visible glans of the clitoris represents only a small portion of this organ. In the nonerect state the clitoris is partially or completely obscured by the labia minora, which fuse to form the clitoral prepuce (O'Connell et al, 2008). Depending on the size of the clitoris and state of arousal, a portion of the clitoris may protrude beyond the prepuce. In rare cases, fibrosis or atrophy of the superior

margins of the labia may produce entrapment of the glans clitoris, a condition known as clitoral phimosis (Fig. 32-3) (Goldstein and Burrows, 2007).

The glans clitoris is attached to the symphysis pubis by the suspensory ligament (Rees et al, 2000). The suspensory ligament maintains the clitoris in a "bent" position with the glans and distal elements oriented inferiorly. The principal blood supply to the glans clitoris is via the dorsal clitoral arteries, a branch of the pudendal artery. Additional blood supply to the erectile bodies of the clitoris is derived from perineal arteries (bulbar and urethral branches) and the deep arteries of the clitoral bodies (O'Connell et al, 2008). The deep dorsal vein drains the erectile tissues of the clitoris. The clitoral prepuce derives its blood supply from the external pudendal arteries (O'Connell et al, 2008).

The dorsal clitoral nerves are derived from the pudendal nerve and originate near the pelvic sidewall (O'Connell et al, 2005) lateral to the rectum where they branch off from the pudendal neurovascular bundles (Yucel and Baskin, 2004). The paired clitoral nerves travel along the ischium and coalesce superior to the glans clitoris (O'Connell et al, 2005). These nerves extend along the surface of the clitoral tunica but most terminate in the glans clitoris (O'Connell et al, 2005). There is some redundancy of innervations for the glans clitoris via the cavernous nerves (Yucel and Baskin, 2004; Martin-Alguacil et al, 2008). Sympathetic fibers to the clitoris are derived from the hypogastric nerve, which is in turn derived from the paravertebral sympathetic chain ganglia (Giuliano et al, 2002).

The dorsal nerve of the clitoris is the principal somatic sensory innervation of the clitoris and surrounding tissues. The distal clitoral nerves stain positive for cholinergic, nitrergic fibers as well as substance P and calcitonin gene-related peptide (CGRP). Cavernous nerves (containing S2 to S4 parasympathetic fibers from the pelvic ganglia) provide innervations to the erectile bodies of the clitoris (O'Connell et al, 2008). These fibers are positive for cholinergic and nitrergic neurons (Yucel and Baskin, 2004).

Interestingly, in the glans clitoris itself the fibers stain positive only for the sensory neuropeptides substance P and CGRP (Yucel and Baskin, 2004). It is implied that the vasoactive neuronal innervations from cholinergic and nitrergic fibers are relevant primarily to the erectile portions of the clitoris, whereas sensory neurons are of primary importance in the clitoral glans. Nerve endings in the glans clitoris consist of free nerve endings (sensitive to temperature and light touch) and Pacini corpuscles (sensitive to vibration and pressure) in addition to a number of nerve endings (O'Connell et al, 2005; Martin-Alguacil et al, 2006, 2008).

Clitoral stimulation is typically pleasurable for women and may lead to orgasm; the nature of desirable stimulation however varies from woman to woman and may vary for a woman in different circumstances (Leff and Israel, 1983). Because the clitoris is densely innervated, direct contact may sometimes be uncomfortable for some women (O'Connell et al, 2008).

Internal Genitalia

Like the labia minora, the *vulvar vestibule* is derived from embryonic endoderm (Woodruff and Friedrich, 1985). The vulvar vestibule consists of mucosal tissue that surrounds the vaginal orifice circumferentially from the hymenal ring to the paired labia minora (O'Connell et al, 2008).

The hymen is a circumferential skin structure located immediately proximal to the vaginal introitus. There is variability in hymen appearance but in most cases it has fenestrations to permit passage of menstrual blood. The hymen may rupture with bleeding during vigorous physical activity or with vaginal penetration (O'Connell et al, 2008).

The urethra, although not technically a sexual organ, is in close approximation to the vagina and clitoris, and periurethral tissue may engorge during sexual arousal. The distal urethra also contains glandular elements known as Skene glands, which may produce some fluid during sexual arousal (Goldberg et al, 1983). The content of this fluid has been shown to include prostate-specific

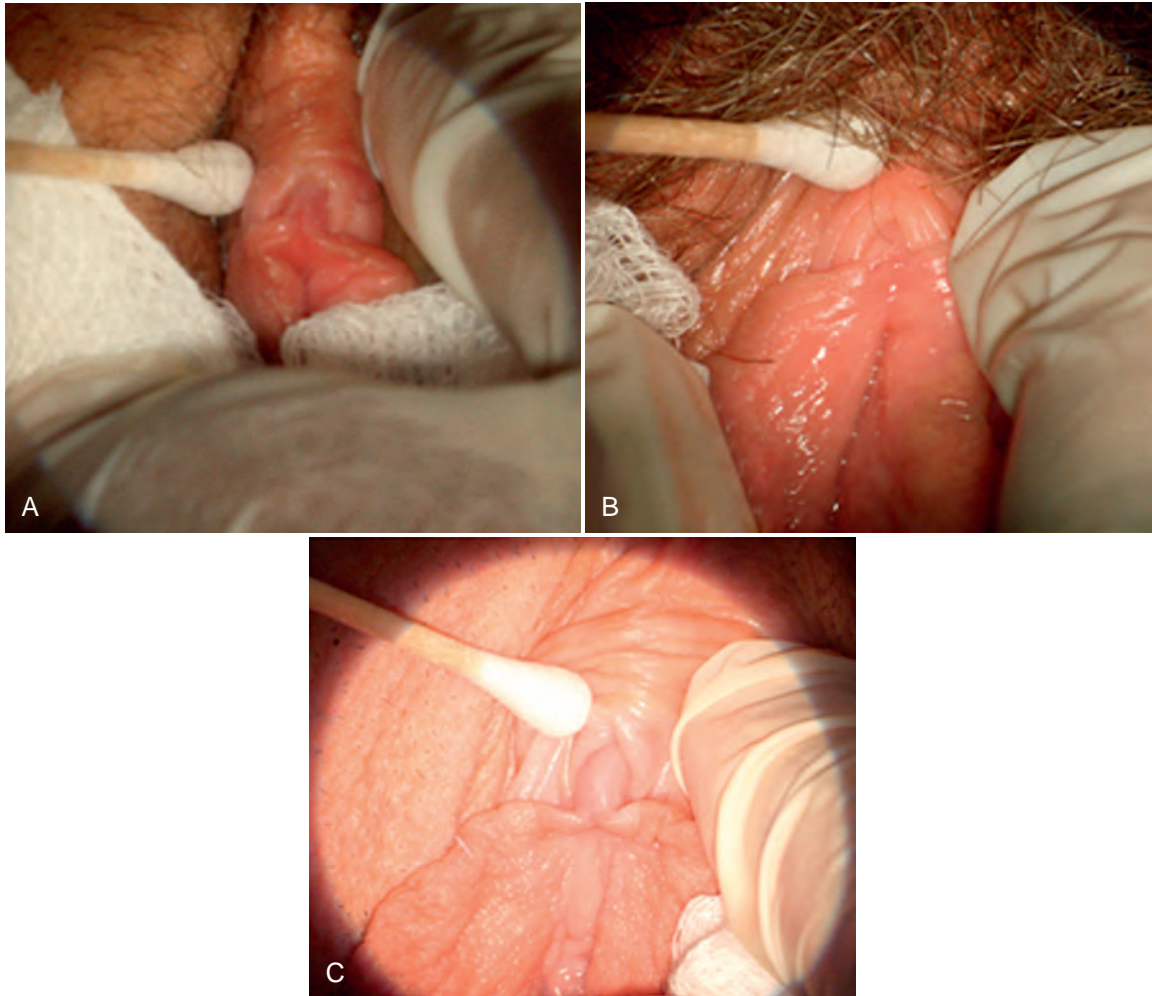


Figure 32-3. A and B, Vulvoscopy photos from two women, ages 27 years and 35 years, who presented with clitoral pain. Both were found to have moderate clitoral phimosis with an inability to visualize the remaining portion of the glans and especially the corona of the glans. Both were diagnosed with glans balanitis secondary to phimosis of the prepuce. Conservative strategies failed to resolve the clitoral pain; both women underwent a dorsal slit procedure that resolved the glans balanitis. C, A 24-year-old woman with no vulvar pathology.

antigen (PSA) (Tepper et al, 1984; Ziviatic and Ablin, 2000) and serum levels of creatinine (Wimpissinger et al, 2007). Some reports have suggested that these glands may be the source for female ejaculate (Goldberg et al, 1983; O'Connell et al, 2008).

Vagina

The vagina is a tubular structure with a mucosal surface that connects to the endodermal tissue of the vulvar vestibule. The vagina extends from the vestibule to the cervix.

The vaginal introitus is the opening from the exterior into the vaginal canal. The vaginal introitus is highly elastic and has a tremendous capacity to stretch during sexual activity and childbirth (O'Connell et al, 2008). The distal one third of the vagina is derived from the urogenital sinus (O'Connell et al, 2008). The proximal two thirds of the vagina is a mesodermal derivative of the müllerian duct (O'Connell et al, 2008).

There are four layers to the vagina; from superficial to deep, these include the mucosa, lamina propria, muscularis, and areolar connective tissue rich in collagen and elastin. There is a rich network of vascular tissue in the lamina propria, which permits engorgement of the vagina with blood during sexual arousal (Musicki et al, 2009). The muscularis layer is composed of outer longitudinal fibers and inner circular fibers (Munarriz et al, 2002a). In premenopausal women, the vagina has a baseline level

of moisture that may allow for sexual intercourse even without additional production of vaginal transudate fluid (van Lunsen and Laan, 2004).

The vagina is acidic at baseline with a pH between 4 and 5 and is colonized with a variety of micro-organisms, predominately *Lactobacillus* and/or other lactic acid-producing species (Eschenbach et al, 2000; Zhou et al, 2004). The acidity of the vagina is maintained in part by the metabolism of glycogen from the vaginal mucosa into lactic acid (Goldstein and Alexander, 2005). More recent evidence has suggested that vaginal epithelial cells may also contribute to vaginal acidity by direct secretion of hydrogen ions by an estrogen sensitive mechanism (Gorodeski, 2005). Perturbations of vaginal pH may be cause or effect of bacterial overgrowth, infection, and vaginal discomfort (Bachmann et al, 1999). Changes in pH and the absence of *Lactobacilli* have been associated with a loss of estradiol (E) effect after menopause; this may predispose women to bladder or vaginal infection with enteric organisms (Bachmann, 1995). Estrogen replacement may reduce these effects (Henriksson et al, 1994).

There appears to be ethnic variability between women with respect to vaginal microbiome (Zhou et al, 2004). These variations are not necessarily pathologic and there may be a cultural/dietary component to some of the variability (Ravel et al, 2011). These differences may also explain (or be explained by) ethnic variations in vaginal pH that have been reported (Ravel et al, 2011).

The vagina is innervated by the pelvic nerves (Schober and Pfaff, 2007), parasympathetic fibers derived from S2 to S4 (Giuliano et al, 2002), and also by the vagus nerve. The vagus is purported to serve as a “bypass mechanism,” by which women who have had spinal cord injury may still experience vaginal and cervical sensation (Komisaruk et al, 2004). Sympathetic fibers to the vagina are derived from the hypogastric nerve, which is in turn derived from the paravertebral sympathetic chain ganglia (Giuliano et al, 2002). In rodent studies the sympathetic fibers to the vagina are localized to the lower thoracic and upper lumbar spinal roots (Nadelhaft and Booth, 1984). The density of nerve receptors is greatest in the distal portion of the vagina (Pauls and Berman, 2002) and on the anterior vaginal wall (Hilliges et al, 1995).

Vaginal blood supply is derived from the vaginal branches of the uterine and hypogastric arteries proximally and from the middle hemorrhoidal and clitoral arteries distally (Salonia et al, 2010).

Cervix and Uterus

The cervix is located at the proximal portion of the vagina and is the inferior-most portion of the uterus. The cervix contains small glands that contribute to vaginal lubrication with arousal. In coital intercourse with intravaginal ejaculation, spermatozoa are transported through the cervical os, which also dilates at parturition to permit passage of the fetus.

The role of the cervix in sexual response is unclear and controversial (Grimes, 1999); some women may enjoy contact with the cervix during sex but many find it uncomfortable. Studies of women after total versus subtotal (i.e., cervix-sparing) hysterectomy are subject to multiple confounders and have not uniformly shown convincing results that support or refute a role for the cervix in sexual function (Grimes, 1999).

The uterus is a muscular pelvic organ that carries the fetus during pregnancy. Uterine contractions occur during orgasm. The hypogastric nerves innervate the uterus and cervix (Berkley et al, 1990; Schober and Pfaff, 2007); there are also fibers of the vagus nerve that appear to innervate the cervix (Komisaruk et al, 2004, 2011).

The uterus is attached to the bilateral fallopian tubes, which terminate in the vicinity of the ovaries. Although not immediately germane to sexual response, the ovaries are obviously essential in reproduction and may lead to sexual problems in disease states (e.g., polycystic ovarian syndrome, etc.) (Goldstein and Burrows, 2008).

Clitoral Bulbs

The clitoral (also known as vestibular) bulbs are bilateral organs located caudad to the clitoris and on either side of the vagina (O’Connell et al, 2005). The clitoral bulbs are confluent in the vicinity of the urethral meatus and track posteriorly along the crura of the clitoris superficial to the pelvic diaphragm and medial to the bulbocavernosus muscles. It does not appear that these structures merge with the glans clitoris (Yang et al, 2006). The clitoral bulbs are erectile tissue but lack a dense tunica albuginea; hence, they may expand a great deal during sexual arousal but do not become rigid because of the lack of an ability to coapt and trap blood.

“G Spot”

In 1950 Dr. Ernst Grafenberg reported the existence of an area on the anterior vaginal wall that was associated with intense sexual pleasure when stimulated (Grafenberg, 1950). This area was subsequently named the “G spot” in his honor and has been the subject of intense societal interest since that time (Goldberg et al, 1983).

For many years the existence of the G spot as a distinct anatomic region has been controversial; anatomic and imaging studies have generally not demonstrated a discrete anatomic region corresponding to a specific gland or organ (O’Connell et al, 2005). However, there is evidence to suggest that the anterior vaginal wall does have a greater density of sensory neurons than the

posterior wall, providing some credence to the idea that this area is erotically sensitive (Hilliges et al, 1995).

More recently, some authors have reported the presence of distinct periurethral tissues that are more developed in women who report pleasure from G-spot stimulation and/or female ejaculation (Wimpissinger et al, 2007). Female ejaculation is itself a controversial topic in that glandular elements capable of producing significant volumes of fluid are difficult to locate radiographically or anatomically in women. Despite this ambiguity, many authors have documented female ejaculation and reported enrichment of PSA (Zavaiacic and Ablin, 2000) and serum levels of creatinine in “female ejaculate” (Wimpissinger et al, 2007). This suggests a glandular source potentially analogous to the male prostate and argues against female ejaculate as urine (Goldberg et al, 1983; Davidson et al, 1989).

The derivation and even the existence of the G spot and female ejaculation are likely to remain controversial. Regardless, some women find direct stimulation of this area pleasurable and others do not. The determination of whether a “G spot” exists is something of an academic question. A woman should be encouraged to determine for herself if stimulation of the anterior vaginal wall (or any other part of her body) is particularly pleasurable.

Pelvic Floor Musculature

The pelvic floor musculature plays a critical role in sexual arousal and response. The pubococcygeus and iliococcygeus muscles are collectively known as the levator ani (LA). The iliococcygeus attaches to the coccyx posteriorly and to the pubic bone anteriorly. The pubococcygeus is anterior to the iliococcygeus and inserts bilaterally at the pubic ramus and forms a muscular sling around the bladder, urethra, vagina, and rectum (Strohbehn, 1998). Some authors divide the pubococcygeus into segments based on visceral attachment; these subdivisions are known as the pubovaginalis, pubourethralis, puboanalis, and puborectalis for the portions attached to the vagina, urethra, anus, and rectum, respectively (Lawson, 1974). The pubococcygeus may also be divided into a transverse portion called the levator plate and a vertical portion called the suspensory sling (Shafik, 2000). The semantic variations in published reports on female pelvic muscle anatomy can complicate interpretation of published research.

The general action of the LA is to draw the urogenital structures of the female pelvis ventrally toward the pubic bone. The LA plays an important role in fixing urogenital organs to the pelvic sidewall. The LA is composed primarily of slow twitch fibers that serve to fix pelvic viscera and to prevent prolapse with exertion. Fast twitch fibers are also present and may serve a role in reacting to sudden increases in intra-abdominal pressure with the Valsalva maneuver (Critchley et al, 1980; Gilpin et al, 1989). Innervation of the LA is primarily derived from the pudendal nerve and S2 to S4 nerve roots (Lawson, 1974).

Genital Anatomy and Self-Image

Any discussion of genital anatomy in women must include an acknowledgment that there is a tremendous diversity of normal vulvar/labial appearance (Lloyd et al, 2005). Many women are unfamiliar with their own genital anatomy and/or have concerns about the “normalcy” of their external genitalia; these concerns may be exacerbated by exposure to “idealized” female genitalia in explicit media and/or by partner criticisms (Boynton, 1999; Herbenick et al, 2011b).

Education and reassurance are often of great benefit when discussing with women the normal variations in genital anatomy. In most cases of distress associated with genital appearance, reassurance is all that is required. In some rare cases, variations of external genital anatomy may predispose women to particular sexual concerns (e.g., redundant labia being tugged on painfully during intercourse, clitoral phimosis, etc.) and these concerns may be amenable to adaptation in sexual practices. In cases where adaptation fails, surgical intervention may be an option (Goldstein and Burrows, 2007).

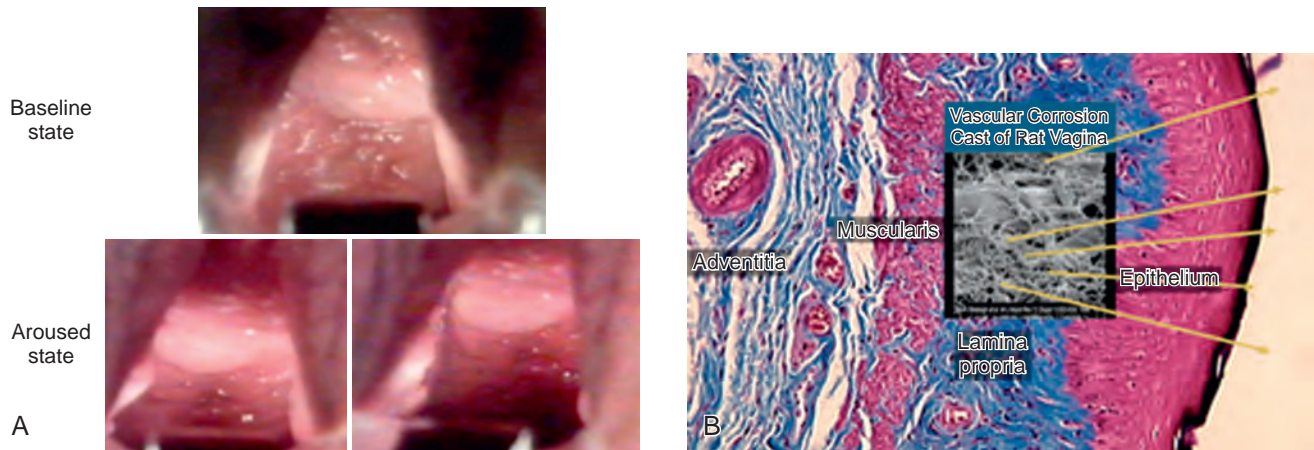


Figure 32-4. A, Three images showing vulvoscopy examination of the vaginal mucosa at baseline and following sexual arousal. Multiple beadlike droplets of exudative plasma can be seen on the vaginal mucosa following arousal. B, Multiple layers of the vaginal wall.

The female breasts are often linked to sexual responses; physical changes including nipple erection and increased sensitivity are commonly observed in studies of sexual arousal in women. **Studies indicate that the majority of women enjoy stimulation of the breasts and nipples as part of sexual activity** (Levin and Meston, 2006). The nature of breast stimulation that is pleasurable varies greatly from woman to woman and may change for a given woman dependent on context. Breast stimulation may be uncomfortable for some women, particularly during pregnancy or lactation (Leeman and Rogers, 2012).

Stimulation of the anus is pleasurable for some women, and slightly more than one third of women in studies report a history of anal sex (Chandra et al, 2011; Mercer et al, 2013). This

stimulation may take the form of external stimulation of the anus or anal penetration with a penis, finger, or other object. As the anal sphincter is normally tightly coapted and the anus does not produce lubrication, application of some form of lubricant and gentle, slow stimulation is advisable during sexual activity involving the anus (Herbenick et al, 2011a). Caution should also be exercised to avoid transfer of coliform bacteria from the rectum to the vagina, as this may increase the risk of urinary tract or vaginal infection.

Individual women may have intense arousal response to stimulation of parts of their body that are not generally deemed erogenous. Self-exploration can be a powerful means of discovering ways to intensify sexual pleasure and is recommended for sexual problems by the majority of sex therapists (Basson et al, 2010b).

The nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway contributes to clitoral erection and vaginal vasodilation with sexual arousal (Burnett et al, 1997; Kim et al, 2003). The cavernous nerves to the clitoris and the vaginal tissues stain positive for neuronal nitric oxide synthase (nNOS) (Burnett et al, 1997; Yucel and Baskin, 2004). NO activates guanylate cyclase, which produces cGMP. cGMP activates numerous downstream effectors, the net effect of which is to sequester calcium and to reduce contraction of smooth muscle in the clitoral and vaginal circulation and within the vaginal wall. The production of NO in genital tissues may also be mediated by the activity of endothelial nitric oxide synthase (eNOS). The expression of eNOS in genital tissues is under the regulation of E (Musicki et al, 2009).

Nitric oxide synthase (NOS) uses the amino acid arginine as a substrate; the enzyme arginase breaks arginine into ornithine and thus reduces the available pool of substrate for NOS. Based on this, it has been hypothesized that arginase may oppose vascular engorgement in the female genital response but the precise mechanisms of this are unclear (Kim et al, 2004). Preliminary data have suggested that arginase inhibitors may enhance genital responses in vitro but in vivo studies are scant (Cama et al, 2003).

Vasoactive intestinal polypeptide (VIP) is also involved in genital vasodilation (Blank et al, 1986). VIP has also been detected in the clitoris and plays a role in clitoral erection (Martin-Alguacil et al, 2006).

Prostaglandins and other local tissue effectors (histamine, tachykinins, etc.) play a role in female genital response, particularly with respect to sensation (Martin-Alguacil et al, 2006). This modulation of sensation may account for changes in the nature of genital stimulation desirable to a given woman during sexual response.

Phosphodiesterase type 5 (PDE5) is present in human female genital tissue and is responsible for the breakdown of cGMP. Inhibitors of PDE5 (PDE5I) promote vasoconstriction and decreased vaginal blood flow. PDE5I are active in human female genital tissue and promote vascular engorgement. Side effects of PDE5I include flushing, congestion, headache, and visual changes (Park et al, 1998).

Although PDE5I will reliably exert genital effects in women (Laan et al, 2002; Basson and Brotto, 2003), published literature supporting the clinical use of PDE5I for the management of sexual arousal problems in women is not robust (Chivers and Rosen, 2010). Lack of predictable concordance between genital and subjective measures of female sexual response may partially explain this observation (Laan et al, 1995; Chivers et al, 2004, 2007, 2010). Ambiguity regarding the appropriate classification of female sexual dysfunction (FSD) has also plagued clinical trials of PDE5I in women with sexual concerns (Chivers and Rosen, 2010). Finally, the marked placebo response noted in most trials of medications for sexual function also contributes to a difficulty in demonstrating the superiority of PDE5I to placebo in controlled trials (Rosen et al, 2007; Bradford and Meston, 2009, 2011; Bradford, 2013).

Additional molecules relevant to sexual response in the female genitalia include neuropeptide Y, galanin, calcitonin gene-related peptide, substance P, peptide histidine methionine, and histidine valine (Jorgensen et al, 1989). The role of these various cellular messengers has not been clearly elucidated (Giuliano et al, 2002; Traish et al, 2010).

Neuroanatomy

Current understanding of the neurophysiology of female sexual response is somewhat limited. Extrapolation to women of neurobiologic findings in men is scientifically unsound (Giuliano et al, 2002; Schober and Pfaff, 2007). Any parallels between female and

male sexual response should be treated as hypothetical until they have been investigated.

Central Nervous System

Processing of erotic stimuli and regulation of sexual response occurs in the central nervous system (CNS). Psychogenic arousal is typically derived from visual, aural, and/or olfactory stimuli that are interpreted as arousing (Schober and Pfaff, 2007); this may include the presence of an attractive partner, exposure to erotic visual or auditory materials, erotic thoughts or memories, or scents that are linked to arousal or sexual response (Schober and Pfaff, 2007).

Brain centers deemed particularly important to the integration of sexual desire and arousal responses for women include the medial amygdala, the stria terminalis, the ventromedial nucleus of the hypothalamus, and the paraventricular nucleus (PVN) (Veening and Coolen, 1998; Schober and Pfaff, 2007). A connection has been demonstrated between the clitoris and the PVN in female rats (Marson, 1995) and activation of this brain region has been demonstrated during copulation studies (Flanagan-Cato and McEwen, 1995). Visual sexual stimuli appear to be processed by relays from the vision centers to the lateral geniculate nucleus (Schober and Pfaff, 2007).

It is postulated that some brain regions important in male sexual response (e.g., the medial preoptic area [MPOA]) are less important in female sexual response (Schober and Pfaff, 2007). However, it has been demonstrated that the MPOA is important in mate selection by female rats (Whitney, 1986), and a study reported that stimulation of the MPOA in female rats leads to an excitatory genital response (Giuliano et al, 2001).

Brain centers activated in orgasm include the medial amygdala, the anterior cingulate, the frontal, parietal, and insular cortices, and the cerebellum (Komisaruk et al, 2004). The left anterior insula has been linked to sensations and intensity of orgasm; it is thought that this region is linked to feelings of closeness and attachment to the partner (Ortigue et al, 2007). It has been hypothesized that reduction in CNS activity in brain regions is associated with embarrassment or suppression of sexual response (e.g., the superior and middle temporal gyri) (Maravilla and Yang, 2008). Decreased activity in these regions may facilitate sexual response by removing CNS inhibition (Salonia et al, 2010).

The spinal cord receives sensory afferent information from the pelvic, hypogastric, and pudendal nerves (Martin-Alguacil et al, 2006). Information is transmitted via interneurons within the spinal cord gray matter and to the thalamus and brain stem via ascending spinothalamic and spinoreticular columns (Lee and Erskine, 1996; Marson and Foley, 2004). Integration of these ascending pathways occurs in the medullary reticular formation and the lateral vestibular nucleus; from these centers, signals are relayed to the ventromedial hypothalamus and other brain areas (Schober and Pfaff, 2007). Brain centers including the nucleus paragigantocellularis and the locus caeruleus are projected to the lumbar spinal cord and they modulate spinal cord responses (Martin-Alguacil et al, 2006). The lumbosacral spinal cord is an important center for integrating and coordinating central and peripheral nervous system responses into a coordinated sexual response (Schober and Pfaff, 2007).

A variety of molecular messengers, likely relevant to genital and sexual function, have also been localized to the lumbar spine. Interestingly, expression of these molecular messengers appears to vary between men and women (Martin-Alguacil et al, 2006). It should not be assumed that the regulation of female sexual response is of necessity entirely similar to male sexual response. Further research is needed (Giuliano et al, 2002).

In animal models, stimulation of the serotonergic 5-HT_{1A} receptors in the MPOA and/or midbrain tends to inhibit lordosis behavior, suggesting a suppressive effect on sexual activity (Uphouse et al, 1992). Interestingly, activation of other peripheral serotonin receptors (5-HT₁ and 5-HT₃) may induce vasodilation (Cappelli-Bigazzi et al, 1991; Skop and Brown, 1996). The serotonin-mediated control of vasculature tone is complex and incompletely understood, particularly as it pertains to female sexual function (Frohlich and Meston, 2000).

Serotonin also plays a role in peripheral neurotransmission involving the genital organs (Berkley et al, 1993), reflex contraction of uterine smooth muscle (Maigaard et al, 1986; Frohlich and Meston, 2000), and serotonin levels have been shown to fluctuate throughout the menstrual cycle (Schreiner-Engel et al, 1981; Rapkin et al, 1987).

contraction of genital vasculature and suppression of arousal response are mediated by norepinephrine (Giuliano et al, 2002).

The administration of the adrenergic antagonist phentolamine has been shown to increase objective parameters of female sexual response (Rosen et al, 1999b); adrenergic agents have also been shown to reduce clitoral engorgement (Pescatori et al, 1993). Hence, there is indirect evidence of a role for the adrenergic neurotransmitter norepinephrine in opposing genital vasodilatory responses in humans as well. This effect is parsimonious with the known effects of adrenergic neurotransmitters in other vascular tissues, and this suggests that basal sympathetic tone to the female genital organs is mediated in large part by norepinephrine (Giuliano et al, 2002).

Other Neurotransmitters Relevant to Sexual Response

VIP plays a role in the CNS with respect to pair bonding during noncoital sexual intimacy (Eriksson and Uvnas-Moberg, 1990). This relationship is in addition to the important peripheral effects of VIP in the female genitalia. γ -Aminobutyric acid (GABA) and glutamate are neurotransmitters (inhibitory and excitatory, respectively) (Giuliano et al, 2002) that play a role in regulating interneuronal fibers at the level of the lumbar spinal cord. These interneurons integrate sexual stimuli (Schober and Pfaff, 2007). Acetylcholine plays a relatively minor excitatory role in female genital response. Anticholinergics have little effect on vaginal blood flow in humans (Wagner and Levin, 1980) and animals (Giuliano et al, 2001).

Hormonal Aspects of Sexual Response

Estrogens

Estrogens are the primary “female” sex steroids and estradiol (E) is the most significant of these. Estrogens act by binding to estrogen receptors (ERs). The alpha subtype (ER- α) is the most common isoform in the genitalia, although the beta subtype (ER- β) has also been detected (Hodgins et al, 1998; Saunders et al, 2000).

Estrogens have CNS effects relevant to sexual response (Rachman et al, 1998). Estrogens maintain female genital tissue integrity and thickness (Martin-Alguacil et al, 2006). Peak E levels occur at the midpoint of the menstrual cycle and are associated with maximal vaginal mucosal thickness and glycogen content; it is parsimonious to hypothesize that this is an evolutionary adaptation to facilitate sexual activity during the fertile window (Farage and Maibach, 2006). With menopause there is a marked decline in genital sensitivity, vaginal thickness, collagen content, baseline moisture, and acidity (Fig. 32-5 on the Expert Consult website). This may occur because of downregulation of VIP activity in the hypoestrogenic environment (Farage and Maibach, 2006; Martin-Alguacil et al, 2006).

Women with serum E levels less than 50 pg/mL have a markedly increased risk of vaginal dryness and pain during sexual activity (Sarrel, 2000). Menopausal women who start E hormone replacement (vaginal or systemic) typically report increased sexual interest and enjoyment, less sexual pain, and greater orgasmic potential (Nathorst-Boos et al, 1993; Dennerstein et al, 2005). Similar findings have been reported in women using selective estrogen receptor modulators (SERMs) and the novel synthetic hormone tibolone (Laan et al, 2001). The benefit of estrogenic therapies in nonselected menopausal women is less clear (Nastri et al, 2013). E replacement has been associated with increased risk of venous thromboembolism; some reports have also suggested that E replacement may predispose women to carcinogenesis (breast or endometrial) and cardiac disease. The issue of E replacement remains controversial (Utian et al, 2008).

E has been shown to enhance sensory fields, nerve density, and tissue mechanical properties that drive sensitivity in the genital tissues of experimental animals (Komisaruk et al, 1972; Kow and Pfaff, 1973; Pfaff et al, 1977). This effect may be mediated by E modulation of local sensory mediators important in genital sensation (Martin-Alguacil et al, 2006). E has also been shown to effect

recovery of pudendal nerves after trauma in animal models (Kane et al, 2004).

Although hypoestrogenism is associated with changes in sexual function and activity, many women with low serum estrogen report sexual interest and sexual activity that is satisfying (Cawood and Bancroft, 1996; Avis et al, 2009). Furthermore, postmenopausal women often maintain the capacity for vaginal lubrication; change in vaginal blood flow with sexual arousal is similar in healthy pre- and postmenopausal women (Laan and van Lunsen, 1997). With adequate sexual stimulation, vaginal lubrication may compensate for decreased baseline vaginal moisture (Berman et al, 1999). Postmenopausal sexual satisfaction is most strongly predicted by satisfactory sexual activity before menopause (Bachmann and Leiblum, 1991). Ergo, estrogen status is important but not entirely predictive of sexual satisfaction in women (van Lunsen and Laan, 2004). Sexual distress in older women may also be lower in some cases because of declines in sexual interest, which reduces the psychoemotional toll of declines in sexual functionality common in aging (Hayes and Dennerstein, 2005).

Testosterone

Testosterone (T) is the “male” sex hormone, but it is present in small quantities in women. Approximately 50% of circulating T in premenopausal women is produced by the adrenal glands with the remaining 50% produced by the ovaries (Judd et al, 1974). Activity of T is influenced by binding to sex hormone-binding globulin (SHBG) and weak binding to albumin. T bound to SHBG tends not to exert biologic effects (Bachmann and Oza, 2006).

Androgen receptors (ARs) are present in female genital tissues (Hodgins et al, 1998). The activity of the AR is of critical import in determining androgenic response to circulating T. Variations in AR activity result from a variety of factors; there has been intense interest on the trinucleotide (CAG) repeats on the AR primer (Chamberlain et al, 1994). Longer CAG repeats tend to reduce activity of the enzyme; this may influence the efficacy of serum T in producing clinically meaningful effects, although evidence to support this hypothesis in women is currently scant (Davison and Davis, 2011).

There is evidence that T plays a role in sexual appetitive behavior, maintenance of genital tissue integrity, and sexual arousal responses in women (Van Goozen et al, 1997; Riley and Riley, 2000; Traish et al, 2010). Low androgen levels are associated with a decline in sexual activity and desire (Bachmann and Leiblum, 1991). However, the relationship between T and sexuality in women is inconsistent (Davis et al, 2005; Brotto et al, 2010).

T levels decline with age in women although the rate of decrease slows after age 35. Because a substantial proportion of women's androgens are derived from adrenal sources, the decline in T production with menopause is gradual. The postmenopausal ovary produces T; women who are surgically menopausal after oophorectomy experience a more marked decline in T compared to women who are naturally menopausal (Davison et al, 2005). As SHBG levels rise with age, many postmenopausal women will experience a decline in bioavailable T, particularly if they use supplemental estrogen (another common cause of rising SHBG) (Bachmann and Oza, 2006).

Exogenous androgen increases sexual desire, arousal, and orgasmic response in women with low baseline serum androgen levels (Braunstein et al, 2005; Somboonporn et al, 2005; Shifren et al, 2006; Blumel et al, 2008; Davis et al, 2008b). A role for exogenous T in management of vulvovaginal atrophy has been demonstrated in some small studies (Witherby et al, 2011). Potential adverse effects of T treatment include application site reactions, hirsutism, acne, vaginal bleeding, and dyslipidemia (Braunstein et al, 2005; Braunstein, 2007). There have also been substantial concerns about the risk of increased incidence of carcinogenesis, particularly hormone-sensitive tumors such as breast and endometrial (Braunstein, 2007). The majority of long-term observation studies have not suggested a significant increase in cancer risk for women taking exogenous T for as long as 2 years (Braunstein, 2007; Davis et al, 2009; Jick et al, 2009).

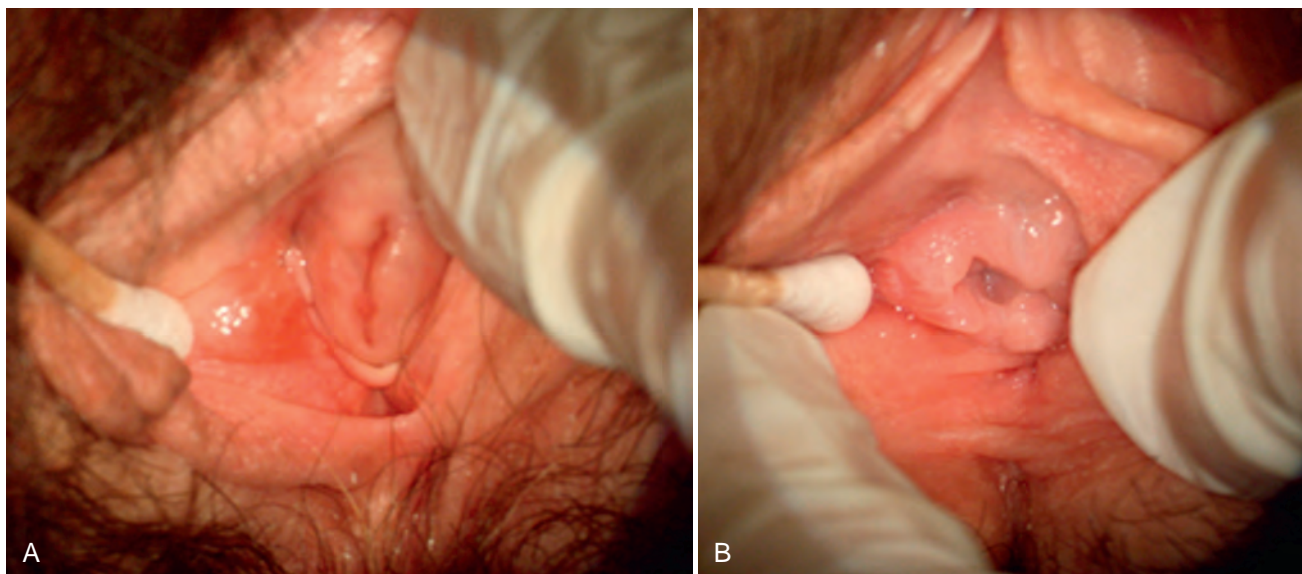


Figure 32-5. A, Vulvoscopy photo of a 59-year-old woman in menopause for 8 years without hormone replacement. She presented with dyspareunia, burning, itching, and dryness of the vulva consistent with vulvovaginal atrophy. In vulvovaginal atrophy, there is genitourinary atrophy with vaginal pH greater than 5.0, blanching of the vaginal mucosa, diminished introital elasticity, telescoped and patulous urethral meatus, as well as urethral glans tissue, concavity, and involution of the vestibule and increased erythema of the posterior fourchette. B, For comparison, a normal vulvoscopy photo of a 38-year-old woman with a healthy reproductive cycle who presented for discussion of contraceptive options.

An association has been reported between high serum androgen level and cardiovascular disease in women (Janssen et al, 2008). However, a 19-year longitudinal study in postmenopausal women did not detect any link between sex hormone levels and cardiovascular mortality (Barrett-Connor and Goodman-Gruen, 1995). Additionally, a long-term study in 365 female-to-male (FtM) transgender persons receiving supplemental androgen did not detect an increase in risk of cardiovascular disease (Asscheman et al, 2011). Additional data on long-term safety are needed (White et al, 2012).

T for women is off-label use in the United States. Careful discussion and documentation between patient and provider are essential if T supplementation is considered in women (Shifren et al, 2006; Wierman et al, 2010).

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a weak androgen produced by the adrenal cortex. DHEA may be converted into androstenedione, a precursor to both T and E. Like T, DHEA levels tend to decline with increasing age (Davison et al, 2005).

In a study of more than 1000 Australian women, those with sulfated DHEA levels in the bottom 10th percentile experienced an increased risk for lower sexual desire, arousal, and responsiveness (Davis et al, 2005). However, the role of supplemental DHEA in female sexual function is not established (Arlt, 2004; Davis et al, 2011).

The Menstrual Cycle and Sexuality

Menstruation is under the regulation of several hormones, principally E (Bancroft and Graham, 2011). E gradually increases during the follicular phase and causes endometrial proliferation. Stability of the endometrium is maintained by the action of progesterone (P). E leads to a surge in LH production from the pituitary, triggering ovulation and initiating the luteal phase. T levels rise during the follicular phase to a peak around the time of ovulation (Roney and Simmons, 2013). In many women sexual desire peaks during the ovulatory phase (Burlinson et al, 2002); these data are subject to several limitations (Brown et al, 2011) and there is substantial variability among women (Burlinson et al, 2002; Sheldon et al, 2006; Wallen and Lloyd, 2011). After ovulation, E, P, and T gradually decline, leading to sloughing of the endometrium and the beginning of the menstrual phase (Wallach, 1970).

Hormonal contraceptives (oral, subcutaneous, injectable) modulate E to prevent ovulation. Hormonal contraceptives tend to reduce serum T (Coenen et al, 1996; Kovalevsky et al, 2010; Battaglia et al, 2012) and raise serum SHBG (Warnock et al, 2006). This synergistically lowers bioavailable T and may contribute to sexual side effects (Coenen et al, 1996). **Specific changes reported in some women using hormonal contraception include decreased sexual desire, atrophy and pain in the labia and genital tissues, decreased intercourse frequency, and decreased orgasmic function** (Fig. 32-6 on the Expert Consult website) (Battaglia et al, 2012). Some women tolerate hormonal contraception without discernible perturbation of their sexual life; several studies have reported no objective or subjective changes in sexual function in women using hormonal contraceptives (Shirtcliff et al, 2002; Greco et al, 2007; Flyckt et al, 2009; Kovalevsky et al, 2010; Lee et al, 2011). However, some women may be particularly sensitive to the androgen-lowering effects of hormonal contraception (Bancroft and Graham, 2011). The benefits of hormonal contraceptives for birth control and other concerns (e.g., dysmenorrhea, acne, etc.) should be balanced against these potential risks. Use of an agent with androgenic effects may be of benefit in women with sexual issues related to hormonal contraception (Davis et al, 2013).

Pelvic Floor Musculature

Contraction of the LA produces straightening and dilation of the vagina and elevation of the cervix (Shafik, 2000). The bulbospongiosus and ischiocavernosus muscles, located superficially and

circumferential to the distal vagina, contract to increase distal vaginal tone and pressure during sexual arousal and orgasm (Shafik, 1993).

Kegel and Graber reported that the strength of the LA is directly related to sexual pleasure and orgasmic response in women (Kegel, 1952; Graber and Kline-Graber, 1979). Hypotonicity of these muscles may impair sexual response (Graziottin, 2005) and contribute to sexual problems resulting from pelvic organ prolapse and incontinence (Strohbehn, 1998). Hypertonicity of the LA may predispose women to pain with vaginal penetration (Rosenbaum and Owens, 2008).

MENTAL ASPECTS OF SEXUAL RESPONSE IN WOMEN

Mental and physical arousal may occur independently of one another in women. Women exposed to erotic imagery consistent with sexual orientation and preference typically experience subjective arousal and increased vaginal blood flow. Women may also have genital responses to sexual imagery that is mentally unappealing (e.g., images of the nonpreferred gender, images of nonpreferred sexual activities, etc.) despite the absence of subjective arousal (Laan et al, 1995; Chivers et al, 2007).

Additional information on sexual arousal in women is available on the Expert Consult website.

KEY POINTS: FEMALE SEXUAL RESPONSE

- Sexual response in women may be triggered by a number of intrinsic or extrinsic factors.
- NO, VIP, and a variety of other cellular messengers play important roles in female genital arousal responses.
- The CNS integrates erotic stimuli and exerts control of genital responses during arousal.
- E and T play important roles in maintaining genital tissues and modulating sexual response.
- Psychological, emotional, and mental factors play a substantial role in sexual response.

EVALUATION OF SEXUAL WELLNESS IN WOMEN

History

Sexuality and sexual health are sensitive topics and many patients (particularly older women) are hesitant to discuss these topics with their health care providers (Roos et al, 2012). Discomfort may stem from personal embarrassment or shame about sexuality, fear of embarrassing the provider, a sense that nothing can be done, a sense that sexual dysfunction is not a medical problem and/or not a significant problem to be addressed, or a simple lack of time during health care encounters (Nicolosi et al, 2006b). Unfortunately, many providers also have difficulty initiating conversations about sex for reasons similar to those given by patients (Merrill et al, 1990; Tsimtsiou et al, 2006). Many providers also report a lack of training in how to appropriately address sexuality with patients (Parish and Rubio-Aurioles, 2010; Shindel et al, 2010).

Sexual health inquiry can be incorporated into a general urologic clinic visit. Normalizing statements (e.g., "Many patients have questions or concerns about their sexual life") may help the patient to feel at ease discussing sex issues (Sadovsky et al, 2006). A simple, open-ended question (e.g., "What concerns or questions do you have about sexuality?") is recommended as an initial screen (Kingsberg and Althof, 2009). Yes/no questions (e.g., "Are there any problems with your sexual life that you wish to discuss with me?", "Are you satisfied with your sexual life?", "Are you having any bothersome sexual issues?") may be a more expedient and practical means to screen for sexual concerns in some contexts (Roos et al, 2012); if an affirmative response is provided to these

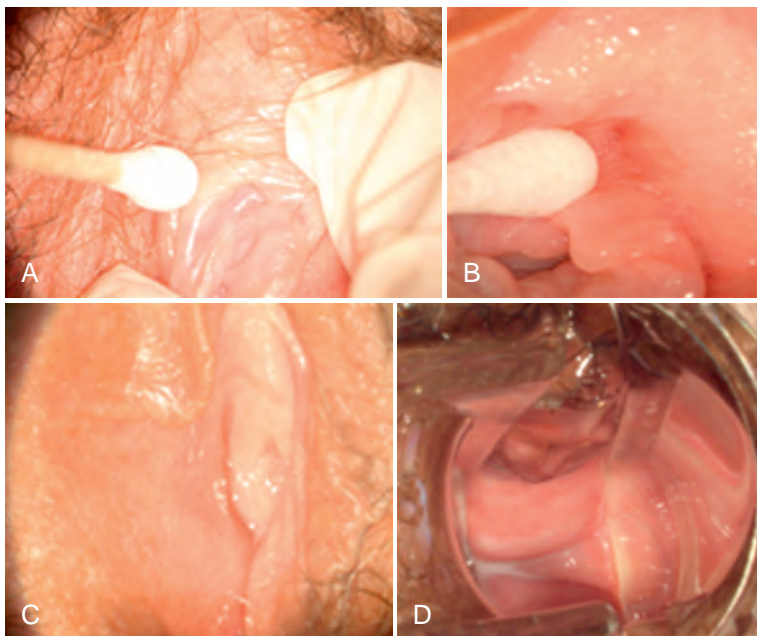


Figure 32-6. Hormonal contraceptive users often show four vulvoscopy findings. Shown are vulvoscopy photographs of a 22-year-old woman on hormonal contraceptive agents. Hormonal contraceptives may cause elevation of sex hormone-binding globulin and a reduction of free testosterone. This may result in glans clitoris atrophy (A), erythema of the minor vestibular glands (B), and limited robust periurethral tissue (D). C, Labial resorption.

A meta-analysis of studies on sexual arousal indicated that there is robust correlation between subjective arousal and penile erection in the male (correlation coefficient = 0.66), whereas the correlation between subjective arousal and genital vasoengorgement (correlation coefficient = 0.26) in women is much less (Chivers et al, 2010). These observations indicate a substantial potential for a disconnect between subjective and objective sexual arousal in women. In a forensic sense, these data may explain why some women experience genital responses such as vaginal lubrication in the context of non-consensual sexual activity (e.g., rape) (Levin and van Berlo, 2004). Various theories have been advanced on how this may be an evolutionary adaption to ensure adequate lubrication (and hence reduced risk of vaginal trauma) even in the context of undesired sexual activity (Chivers and Rosen, 2010).

Despite this biologic observation, interpersonal and psychosocial factors are tremendously important in the sexual response for women. Psychological and emotional responses modulate

how a woman expresses her sexuality and how she responds to sexual initiation from a partner. Women with sexual issues are more likely to have dysfunctional sexual beliefs (e.g., “I’m not turned on” or “sex always hurts”) compared to sexually healthy women (Klaassen and Ter Kuile, 2009; Nobre, 2009). These responses are rooted in psychology but exert physical effects by sympathetic and CNS processes. Interpersonal issues are frequently more important than biologic issues in women’s sexual response (Avis et al, 2000; Dennerstein et al, 2005). Other reports have confirmed the primacy of the marital relationship and general health over menopausal status as predictors of satisfying sexual function (Avis et al, 2000; Dennerstein et al, 2005). Historically these issues have been considered central to sexuality in women and of lesser import in men; one may hypothesize that the dearth of biomedical understanding about female sexuality (and subsequent dearth of nonpsychological treatment options) may play a role in fostering this concept.

screeners, follow-up with open-ended questions will likely produce more nuanced and informative responses (Kingsberg and Althof, 2009).

Allowing the woman to voice any concerns she has about her sexual life and satisfaction is one of the most basic but critical interventions that providers may make on behalf of sexual wellness. **The opportunity to discuss sexuality issues with a professional may substantially decrease sex-related distress (Goldstein and Alexander, 2005).**

Additional advice on taking a sexual history is available in the online supplement.

Surveys

Validated sexuality surveys are simple, unobtrusive, and reliable (Rosen, 2002; Kingsberg and Althof, 2009). In clinical practice, these instruments are useful as means to initiate a conversation about sexual issues (Clegg et al, 2012). **Survey instruments cannot replace a detailed history and physical examination (Kingsberg and Althof, 2009).** A 2010 study indicated that some female partners of men with ED had persistently low survey metric scores despite increases in sexual satisfaction (Conaglen et al, 2010).



Information on survey instruments is available on the Expert Consult website.

Evaluation of the Partner

Sexual distress is linked to incompatibility with the partner (Witting et al, 2008). **Hence involvement of the sexual partner is critical in the management of any sexual health concern.** Education of the partner may be of particular importance given the generally low knowledge of female sexual response in the community (Goldstein and Alexander, 2005).

Additional information on partner evaluation is available in the online supplement.

Physical Examination

A general physical examination including vital signs is required. The patient should be assessed for evidence of endocrinopathy, nerve injury, diabetes, or obesity (Goldstein and Alexander, 2005; Basson et al, 2010b). **Evaluation of the genitals should start with careful inspection of the external genitalia including mons pubis, labia majora, labia minora, clitoris, and vulvar vestibule. This superficial examination may show genital lesions, erythema that may predispose to sexual pain disorders, redundancy of the labia, or atrophy of the external genitalia (Fig. 32-7 on the Expert Consult website) (Goldstein and Alexander, 2005; Basson et al, 2010b).** Vulvar skin conditions are common and can lead to a variety of sexual concerns. Examples include eczema, psoriasis, contact dermatitis, fungal infections, aphthous ulcers, and drug reactions.



Some dermatoses are specific to the vulva and are described on the Expert Consult website.

Testing for genital neuropathy may be accomplished by application of heat/cold stimuli, vibration, and/or application of a toothpick or small pin. A simple assessment for urinary incontinence (cough test, Q-tip test, etc.) is warranted. Urinary symptoms are associated with sexual problems and are within the scope of practice for urologists to manage.

Bimanual examination of the vagina is performed to assess for pelvic organ prolapse and ovarian pathology (Goldstein and Alexander, 2005). Assessment of the LA should be included as part of the bimanual examination (Rosenbaum and Owens, 2008). A speculum examination should be considered.

Assessment of vaginal pH is a simple, inexpensive test. High pH implies E deficiency and/or disruption of the normal vaginal microbiome; this may have relevance to recurrent infection, vulvovaginal atrophy, or other issues and should be performed routinely (Bachmann et al, 1999).

Serum and Other Laboratory Studies in the Evaluation of Sexual Wellness

The role of serum studies in evaluation of female sexual wellness is controversial (Goldstein and Alexander, 2005; Basson et al, 2010b). Serum chemistry, lipids, and glycosylated hemoglobin should be assayed, as these are low-risk tests for common problems potentially relevant to female sexual function. **Assessment of sex steroids, particularly serum E and T, should be considered if there is concern for significant endocrinopathy (Utian et al, 2008; Kingsberg, 2009).**

Serum T testing is controversial because of questions of relevance and precision of results; most widely available assays for T are not precise at the levels typical in women (Stanczyk et al, 2003; Bancroft and Graham, 2011). The timing of assay with respect to menstrual cycle should be clearly defined. T should be assayed in the morning between days 8 and 14 of a 28-day menstrual cycle (Davison and Davis, 2011). Mass spectroscopy is a preferred means for assessing T levels in women but is typically not available outside of research settings (Stanczyk, 2006). Radioimmune assay (RIA) has been shown to possess acceptable precision in quantifying androgen levels in women. The decision to measure serum T should only be made after consultation with the patient about the unknowns and with a clear sense of what will be done with the data if the test result is concerning for androgen insufficiency (Bachmann et al, 2002; Bachmann and Oza, 2006).

In the setting of very low sex steroid levels, prolactin may be assessed. Elevated prolactin is associated with decreased sexual desire and suppression of serum T levels (Atis et al, 2010). Assay of hormones such as DHEA (Munarriz et al, 2002b) and dihydrotestosterone (DHT) may be considered, but the usefulness of these tests is unclear (Davis et al, 2011).

Additional information on physiologic and sensory testing is available on the Expert Consult website.



KEY POINTS: EVALUATION OF SEXUAL WELLNESS IN WOMEN

- A complete history (medical, sexual, partner, etc.) and thorough physical examination (particularly of the genitals) is fundamental to evaluation of sexual wellness in women.
- Many patients are reticent to ask questions about sex; providers should initiate conversations about sexuality.
- Questionnaires and adjunctive testing are of benefit in some cases but do not replace history and physical examination.

SPECIAL POPULATIONS

Pregnancy

Pregnancy has biologic and psychological ramifications for a woman's sexuality (Farage and Maibach, 2006; Pauleta et al, 2010). **Sexual activity is generally safe in pregnancy.** Adaptation to the physical and emotional challenges of gravidity influence a woman's experience of her sexuality. Obstetrical involvement and advice are critical (Millheiser, 2012).

Sexual problems are generally most common in the third trimester (Leite et al, 2009). Women in the later stages of pregnancy may find some sexual positions uncomfortable; these may in some cases be resolved by use of alternative sexual positions or assistive cushions/furniture. Caution should be exercised when considering sexual activity in women with a history of cervical incompetence; repeated trauma to the cervix from vaginal penetration and prostanoids in semen may theoretically contribute to increased risk of preterm labor.

Delivery may be traumatic to the vulva and perineum. Vaginal tears, operative vaginal delivery, and episiotomy may be a source of persistent pain during intercourse with larger tears portending

A thorough history is the cornerstone of evaluation for a woman with sexual concern(s). Sexual, medical, and psychological issues should be assessed; in the situation where the clinician does not have training for in-depth discussion of sexuality, an appropriate referral should be considered (Goldstein and Alexander, 2005; Basson et al, 2010b).

The precise nature of the sexual concern, any associated symptoms, chronology, presumed or defined trigger events, exacerbating or relieving factors, and previously attempted treatments should be elicited (Kingsberg and Althof, 2009; Basson et al, 2010b). It is prudent to avoid assumptions about sexual orientation and/or partner status. Gender-neutral pronouns should be used until the gender of the patient's partner(s) is elucidated. Even in the absence of intent, assumptions about partner gender may make patients uncomfortable and/or fearful to disclose the nature of their sexual lives, particularly if they have a non-normative sexual orientation.

It is desirable to be aware of the patient's perceptions and beliefs on sexuality as this may markedly influence their perception of any sexual issues; women from deeply religious backgrounds are likely to have conservative beliefs on sexuality (Ahrold et al, 2011) and may be more reticent about discussing these issues with a provider. It is always desirable to be sensitive to the patient's sexuality-related beliefs, be they conservative or liberal. Means to improve patient/provider communication about sex is a fertile ground for further research and development but is beyond the scope of this chapter.

An assessment of sexually transmitted infections (STIs) risk behaviors should be included in any sexual wellness consultation (Sadeghi-Nejad et al, 2010). Pre- or perimenopausal women who are involved with a male partner(s) should be asked what (if any) means they are using for contraception.

Female Sexual Function Index

The most widely used and cited research in urologic sexual medicine is the Female Sexual Function Index (FSFI). The FSFI is a 19-item questionnaire that assesses 6 domains of female sexual experience (desire, arousal, lubrication, orgasm, satisfaction, and pain). Each domain is scored on a scale of 0 to 6 points with the exception of the desire domain (scored from 1.2 to 6) and the satisfaction domain (scored from 0.8 to 6). The instrument thus has a range of 2 to 36, with 36 representing a “perfect” score (Rosen et al, 2000). An abbreviated six-item version of the FSFI has been reported (Isidori et al, 2010). The FSFI was validated for use in heterosexual women; versions of the FSFI have been validated for use in lesbian women (Tracy and Junginger, 2007), although these have not been widely used in research (Shindel et al, 2012).

In most studies, a total FSFI score of less than 26.55 has been used as a marker for a higher risk of sexual dysfunction (Wiegel et al, 2005). A specific cutoff for the diagnosis of hypoactive sexual desire disorder (HSDD) using the two-item desire domain of the FSFI was reported; on a scale of 2 to 10, women with a score of 6 or higher on this domain were unlikely to carry the diagnosis (Gerstenberger et al, 2010). Domain-specific cutoff scores for the diagnosis of specific types of sexual “dysfunction” have not been validated for other domains, although various authors have reported arbitrary cutoffs based on speculation.

The FSFI has been shown to be more reliable in predicting treatment success in studies of sexual dysfunction relative to objective measures such as sexual-event logs and vaginal plethysmography (Rellini and Meston, 2006). The FSFI does not specifically assess sexual distress. As sexual distress is an important diagnostic criterion for sexual dysfunction, a sexual dysfunction should not be diagnosed strictly on the numeric criteria of the FSFI. At most, women with low FSFI scores should be considered “at risk” for sexual dysfunction pending complete evaluation.

Profile of Female Sexual Function and Personal Distress Scale

The Profile of Female Sexual Function (PFSF) is a validated, 37-item instrument developed primarily for the assessment of sexual function in postmenopausal women with low sexual desire. It consists of seven domains (sexual desire, arousal, orgasm, sexual pleasure, sexual concerns, sexual responsiveness, and sexual self-image) (Derogatis et al, 2004). The PFSF and a related scale called the personal distress scale (PDS) were combined/adapted into a seven-item brief version (B-PFSF) that also shows good discriminant validity for decreased sexual desire in postmenopausal women (Rust et al, 2007); out of a total possible score of 35, women who score 20 or less on the B-PFSF are at greater risk of low sexual desire.

A follow-up study derived from investigations on T therapy for HSDD indicated that an increase in the sexual desire domain of the PFSF and a 20-point change in the PDS were associated with clinically meaningful changes in HSDD (Derogatis et al, 2009).

Pelvic Organ Prolapse–Urinary Incontinence Sexual Function Questionnaire (PISQ) and PISQ-12

The Pelvic Organ Prolapse–Urinary Incontinence Sexual Function Questionnaire (PISQ) is a validated, 31-item instrument

designed specifically to assess sexual function in women with pelvic organ prolapse and/or urinary incontinence. The PISQ consists of three domains (behavioral emotive, physical, and partner-related) (Rogers et al, 2001). A validated short form of the PISQ (PISQ-12) is more commonly used in clinical research (Rogers et al, 2003).

Female Sexual Distress Scale

The Female Sexual Distress Scale (FSDS) is a 12-item scale that specifically measures sexuality-related distress (Derogatis et al, 2002). This scale differs from some other scales in that it may assess subjective or relationship-based sexual distress in addition to distress related to physical issues in sexual response. A score of greater than 15 is suggestive of significant sexual distress (Meston and Derogatis, 2002). This scale may be of greater use in assessing the subjective components of sexual problems in women but it still cannot be used as a substitute for careful and meticulous history and physical examination.

Arizona Sexual Experience Scale

The Arizona Sexual Experience (ASEX) scale is a validated five-item gender-specific scale that assesses sex drive, arousal, vaginal lubrication, ability to orgasm, and satisfaction from orgasm. Lower scores indicate better levels of sexual function (McGahuey et al, 2000).

Brief Index of Sexual Functioning for Women

The Brief Index of Sexual Functioning for Women (BISF-W) is a 22-item questionnaire that assesses seven domains of female sexual function (sexual thoughts/desires, arousal, frequency of activity, receptivity/initiation, pleasure/orgasm, relationship satisfaction, and sexual problems) (Taylor et al, 1994).

Golombok Rust Inventory of Sexual Satisfaction

The Golombok Rust Inventory of Sexual Satisfaction (GRISS) is a 28-item questionnaire that assesses seven domains of sexual function (avoidance, nonsensuality, infrequency, vaginismus, anorgasmia, noncommunication, and dissatisfaction) (Rust and Golombok, 1986). This scale addresses psychosocial issues primarily and has not been used extensively in biomedical research.

Sexual Function Questionnaire

The Sexual Function Questionnaire (SFQ) is a 31-item questionnaire assessing seven domains of female sexual response (desire, physical arousal, lubrication, enjoyment, orgasm, pain, and partner relationship) (Quirk et al, 2002).

Decreased Sexual Desire Screener

The Decreased Sexual Desire Screener (DSDS) is a brief screening tool designed primarily for use in a clinical setting specifically to assess for symptoms of decreased sexual desire (Clayton et al, 2009). This tool may be of increased use in routine clinical practice related to more comprehensive instruments such as FSFI.

The partner of a woman who has sexual issues is likely to have sexual issues of his/her own (Fisher et al, 2005; Chedraui et al, 2009). There is robust evidence that treatment of erectile dysfunction in the male partner of heterosexual couples leads to positive changes in the female partner's sexual life (Chevret-Measson et al, 2009; Conaglen et al, 2010). Treatment or referral should be considered for a partner with sexual issues. Data on improvement in the sexual lives of same-sex partners are generally lacking but it is logical to hypothesize that similar effects may exist in same-sex relationships.

If there is a significant discrepancy in patient/partner perceptions, or disagreement about the presence of a problem at all, it

may be of value to involve a mental health professional, ideally a qualified sex therapist (Althof, 2010; McCabe et al, 2010). There is a great deal of heterogeneity among self-identified sex therapists so it is beneficial to establish a working relationship with one or more established therapists who have extensive experience and/or training in sexual health issues. A variety of professional organizations certify therapists/counselors for their expertise on matters of sexuality (e.g., the American Association of Sexuality Educators, Counselors and Therapists [AASECT], the Society for Sex Therapists and Researchers [SSTAR], etc.).

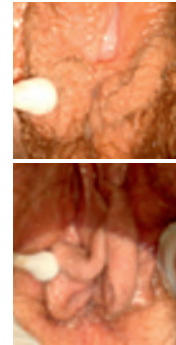
Vulvoscopic assessment of two estradiol-dependent organs: (1) labia minora and (2) vaginal epithelium (rugae), and vaginal pH before and after estradiol therapy.



Low Estrogen State

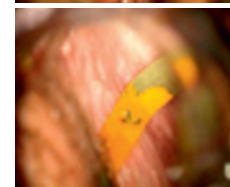
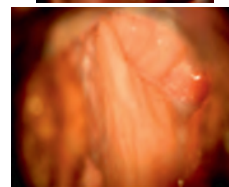
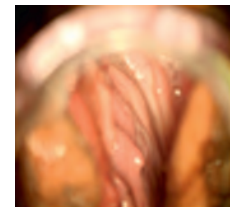
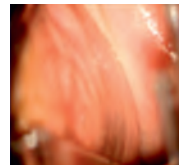


Robust Estrogen State



Labia Minora Normally Meet at Posterior Fourchette

Resorption of Labia Minora



Reduced vaginal rugae. pH >5

Robust vaginal rugae. pH 4

Figure 32-7. Vulvoscopy with photography involves examination of external female genitalia using a binocular vulvoscope/colposcope with magnification and light source. Vulvoscopic photographs show two estradiol-dependent organs in the vestibule before and after estradiol treatment. *Top to bottom*, estradiol-dependent organs including the labia minora and the vagina. In particular, estrogenization of the vagina will show abundant rugae and a pH around 4.0.

Lichen simplex is a condition of skin thickening, erythema, and excoriation that may occur across the labia majora; it is attributable to recurrent pruritus, leading to itching with excoriation and subsequent worsening of the pruritic reaction from recurrent scratching (Salim and Wojnarowska, 2005). Lichen sclerosus is an inflammatory condition thought to include an autoimmune component. The vulvar skin tends to be whitish and atrophy and labial resorption is not uncommon (Fig. 32-8). There is a small but finite risk of malignant transformation in lichen sclerosus (Salim and

Wojnarowska, 2005). Lichen planus (LP) is a condition of violaceous papules and plaques across the genital area. There is an erosive variant of this condition that involves loss of the outer skin layers and development of painful, eroded areas on the labia minora and vulvar vestibule (Fig. 32-9) (Salim and Wojnarowska, 2005). If a lesion is ambiguous or of concern for malignancy, a biopsy should be considered. It is advisable to send a biopsy with a specific diagnostic entity in mind to help guide the dermatopathologist in making an appropriate diagnosis (Salim and Wojnarowska, 2005).

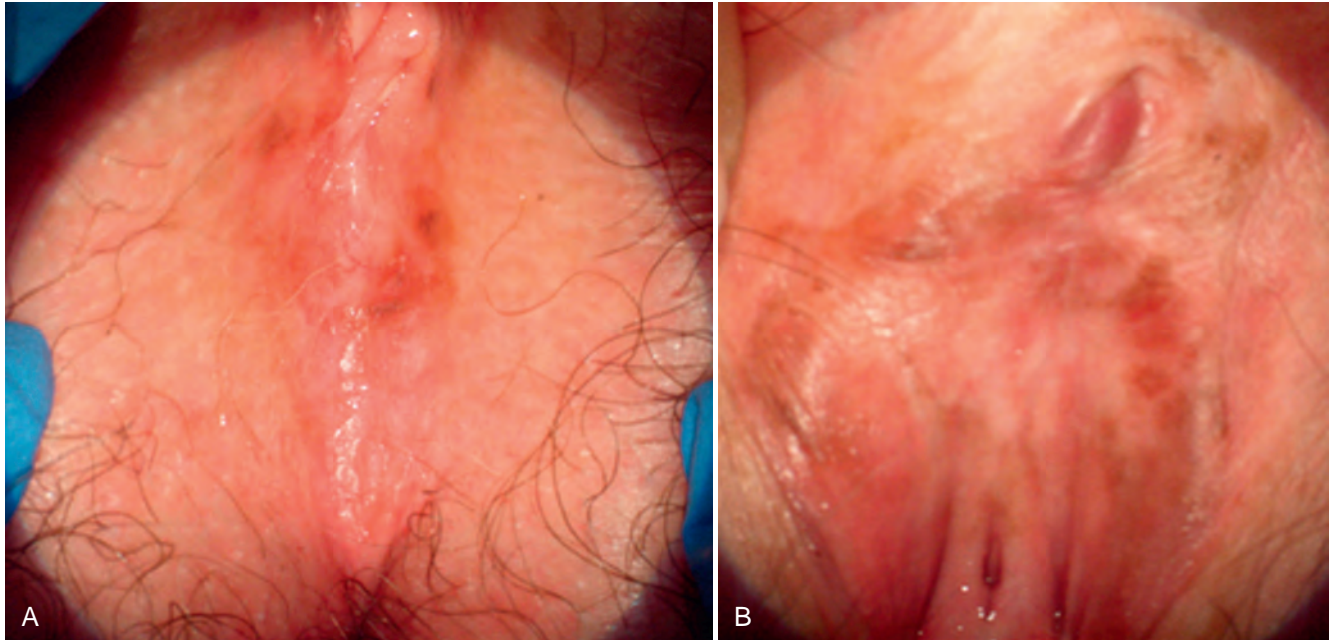
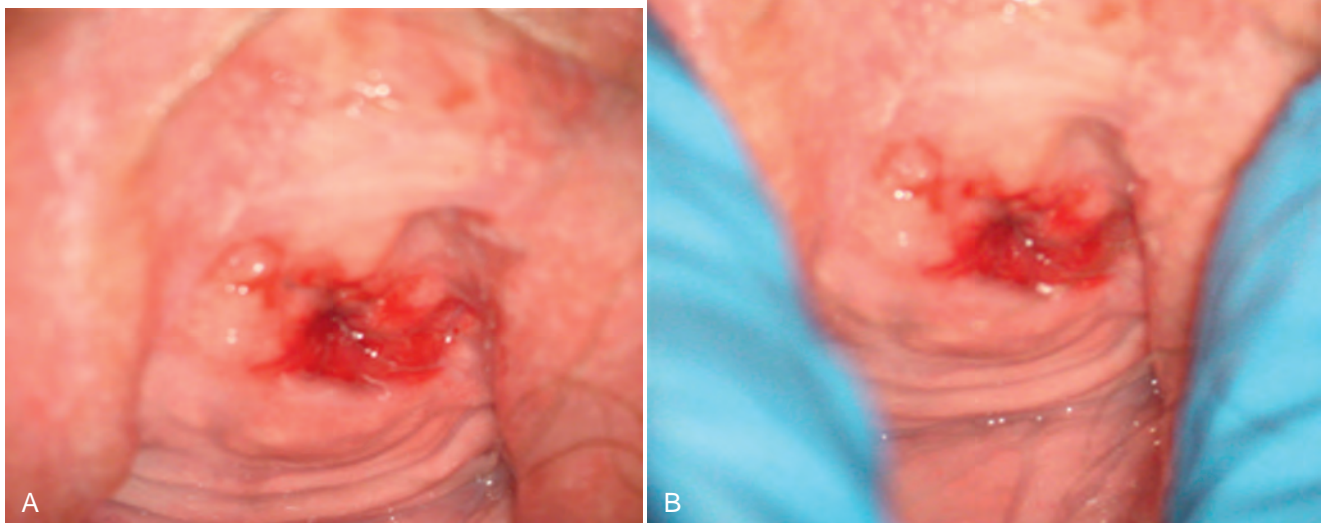


Figure 32-8. A and B, Vulvoscopy photographs from a 43-year-old woman who experienced lichen sclerosus and dyspareunia for more than 15 years.

Figure 32-9. A and B, Vulvoscopy image of a 59-year-old woman with severe dyspareunia and biopsy-proven lichen planus (LP). LP is a disease of the skin caused by inflammation and can affect the vulva and the vagina. Common symptoms include burning, soreness, and itching. LP is also associated with whitish eruption or ulcers in the mouth. LP is thought to be an autoimmune reaction that may have started from an infection or a medication.



Physiologic and/or imaging studies may provide information on sexual response. Whether such testing changes the management of such responses is unclear (Woodard and Diamond, 2009). Sensory testing of the genitals may be accomplished by application of cotton swabs or pins. A biothesiometer (device that applies quantifiable heat and/or vibration) is a more objective means, but the additional information may not change management (Fig. 32-10) (Berman et al, 2001; Woodard and Diamond, 2009).

A 2009 study did suggest that “abnormal” findings were common on genital sensory testing in women with sexual concerns (Helpman et al, 2009). Whether this reliably differentiates women with and without sexual concerns has not been established. Electromyography and biofeedback may be used for assessment of pelvic floor muscles; these technologies are primarily useful in the hands of

specially trained physical therapists (Woodard and Diamond, 2009).

Vaginal plethysmography, Doppler ultrasound, thermography, and angiography have been used to characterize the vascular integrity of the female genitalia (Woodard and Diamond, 2009). Vaginal plethysmography (measurement of vaginal microcirculation) is the most widely used research measure of genital sexual response in women (Geer et al, 1974). Color Doppler ultrasound has been proposed as a means to assess vascular integrity of the clitoris (Lavoisier et al, 1995). Standard parameters for clitoral ultrasound have not been established. Cross-sectional imaging studies such as computed tomography and magnetic resonance imaging may be indicated in certain select cases (e.g., MRI for assessment for urethral diverticulum as a cause for sexual pain) (Suh et al, 2003).

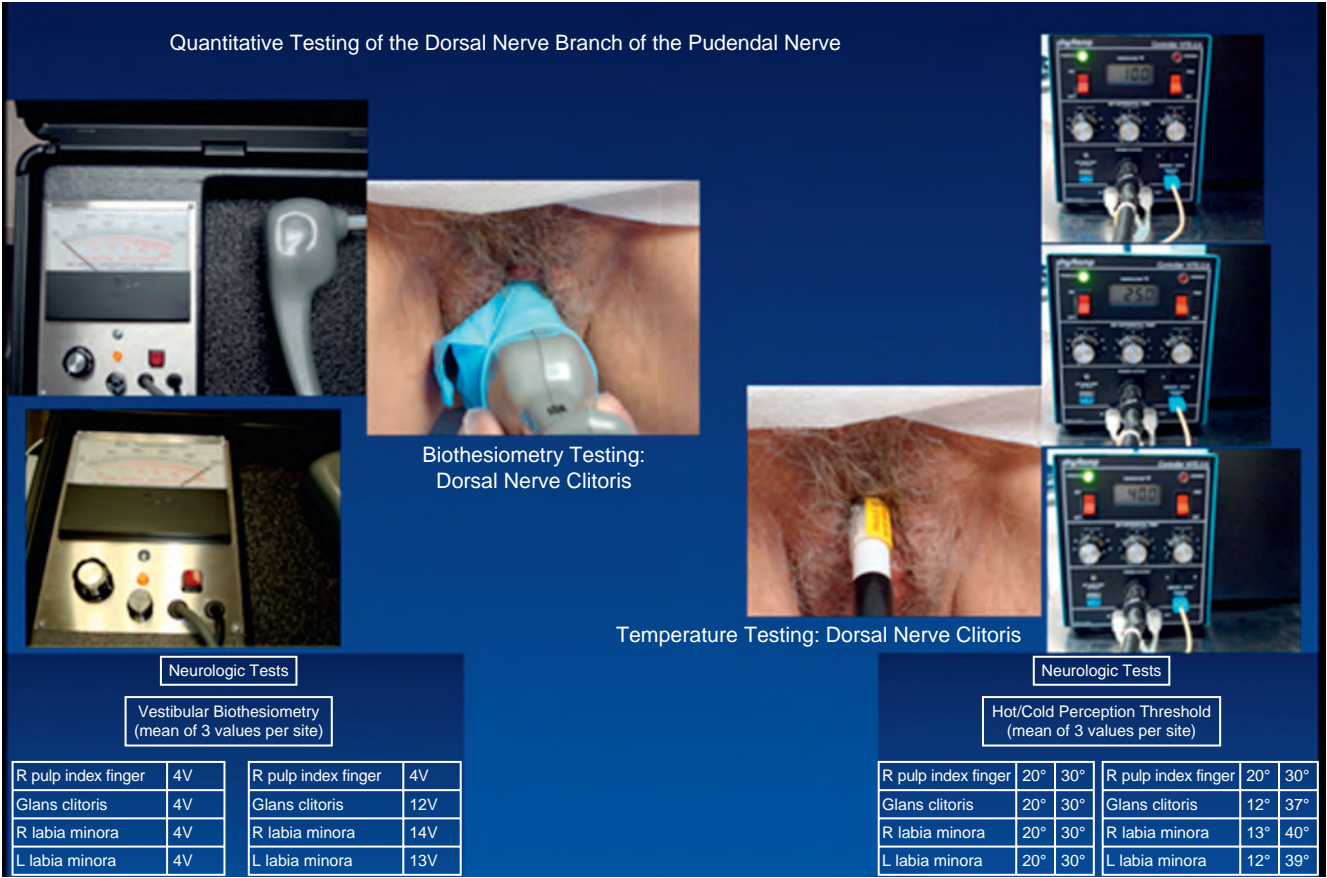


Figure 32-10. Objective sensory nerve testing may be performed using a biothesiometer to determine vibratory perception thresholds (expressed in volts) as displayed (left). Objective sensory nerve testing may be also performed using temperature testing to determine hot and cold perception threshold values (expressed in degrees centigrade) as displayed (right). Quantitative sensory testing measures and values are obtained in a nongenital reference site (pulp index finger) as well as in multiple genital sites such as the glans clitoris (dorsal nerve branches of the pudendal nerve), and the right and left labia minora (the perineal nerve branches of the pudendal nerve)—these latter locations are not shown on the photographs.

greater risk (Signorello et al, 2001; Leeman and Rogers, 2012). There is evidence of pelvic floor denervation and loss of pelvic floor strength in as many as 80% of women giving birth (Allen et al, 1990). It does not appear that there is a significant difference in postpartum sexual function between women who deliver by Caesarean section and those who deliver vaginally (Leeman and Rogers, 2012).

Although about 90% of women have resumed sexual activity by 3 months postpartum (Brubaker et al, 2008), several studies indicate that FSFI scores have not returned to baseline by that time point (Pauls et al, 2008). A major risk factor for this change may be dyspareunia, which has been reported in approximately half of postpartum women at 3 months (Barrett et al, 2000); the prevalence of dyspareunia after 3 months is generally lower (Lal et al, 2011), suggesting a decline in postdelivery dyspareunia with time.

Lactation involves robust production of the hormone prolactin, which tends to suppress estrogens and androgens; this may contribute to declines in sexual desire and dyspareunia from loss of hormone effect on genital tissues (Leeman and Rogers, 2012). The stressors of parenting a newborn and recovery from delivery are short-term barriers to sexual activity, which in some cases may lead to long-term sexuality issues (Pauleta et al, 2010).

Racial/Ethnic Minorities

Some differences in the prevalence of sexual concerns likely stem from cultural factors (Laumann et al, 2005). Perceptions of what is normal will dictate whether a woman believes the sexual issues she is experiencing are problematic (Anderson et al, 2011). Women from conservative or repressive environments tend to report lower levels of sexual satisfaction (Laumann et al, 2006). Awareness of cultural paradigms is useful; however, individual women may not conform to stereotypes of their culture.

A 2005 study reported on differences in sexual concerns of American women of Asian, European, and African ancestry. There was a high prevalence of concerns in women of all racial groups; however, the nature of those specific concerns differed. Compared to white women, African-American women were less likely to express concerns about vaginal lubrication and attractiveness but were more likely to be concerned about sexually transmitted diseases. Asian-American women were less likely than white women to report issues of sexual desire, arousal, orgasm, and dissatisfaction with sexual life although there was a slightly higher rate of concern about vaginal penetration (Nusbaum et al, 2005).

The Boston Area Community Health Study reported a lower odds ratio for sexual issues in women of black race compared to Latino and white women (Rosen et al, 2009a). A study of low-income breast cancer survivors indicated that Latino women had higher prevalence of a variety of sexual concerns (low desire, low arousal, lack of satisfaction, difficulty with orgasm) compared to Caucasian women even after controlling for covariables (Christie et al, 2010).


Physiologic differences may exist between racial/ethnic groups; these may be driven by genetics, cultural factors, and physical factors (Ravel et al, 2011). For example, serum T tends to be lower in women of African and Latino backgrounds relative to Caucasians and East Asians (Randolph et al, 2003). Whether these differences are clinically meaningful is fertile ground for future research.

Women Who Have Sex with Women and Transgender Persons

Between 1% and 2% and between 1% and 4% of women in the United States identify as lesbian or bisexual, respectively (Aaron et al, 2003; Conron et al, 2010; Herbenick et al, 2010b). Transgender persons account for 1% or less of the population but are increasingly visible in Western nations. Transgender persons include

female to male (FtM or “transmen”), male to female (MtF or “transwomen”), and individuals who elect not to categorize themselves into a gender category. A person may identify as transgender without using cross-gender hormonal replacement or having gender reassignment surgery (Persson, 2009).

A provider who is not generally familiar with women who have sex with women (WSW) and transgender persons should take time to develop rapport and ask respectful questions to elucidate fully the precise nature of sexual concerns. Tactful questions and avoidance of assumptions about sexual proclivity are essential. The majority of patients will respond well to questions for clarification if such questions are asked in a respectful and non-judgmental fashion (Stott, 2013). Care must be individualized to the patient's gender identity, sexual orientation, and sexual concerns (Wierckx et al, 2014).

Additional information on WSW and transgender persons is available on the Expert Consult website. 

Disabled Women

Disabilities are mental and/or physical impairments (congenital or acquired) that limit an individual's capacity to function independently. Physical disabilities such as chronic pain, back injury, arthritis, spinal cord injury, multiple sclerosis (MS), cerebrovascular injury, amputations, and/or metabolic diseases may make sexual activity difficult or uncomfortable (Basson et al, 2010a). However, many persons with even severe disabilities are able to adapt their sexual lives and practices to obtain a satisfying expression of their sexuality. Providers should not assume that disabled persons cannot or should not enjoy a healthy sexual life (Tepper et al, 2001; Kreuter et al, 2011).

CNS injury or lesion can be particularly damaging to sexuality. Women with lesions of the spinal cord often report diminished genital sensation, loss of sexual self-esteem, difficulty with orgasm, and dissatisfaction with sexual responses (Tepper et al, 2001). Interestingly, genital sensation is preserved in some women with spinal cord injury. This appears to be mediated by vagus nerve fibers that bypass the spinal cord and project to the nucleus tractus solitarius region of the medulla oblongata (Komisaruk et al, 2004).

The issue of sexual activity in mentally disabled persons is an ethically and legally challenging issue (Appel, 2010). Respect for human rights warrants that a person with mental disability should not be denied the right to sexual pleasure (Greenspan, 2002); at the same time, issues of consent and coercion are difficult to resolve in persons with cognitive impairments (Spiecker and Steutel, 2002). Careful consideration and ethics consultation should be considered when such cases arise (Kennedy, 2003).

Victims of Sexual Violence

The lifetime prevalence of rape (forcible sexual penetration) or attempted rape in American women is estimated at 18% (Black et al, 2011). Data from other regions of the world suggest about 1 in 3 women globally will experience intimate partner violence or sexual violence perpetrated by a nonpartner (World Health Organization, 2013). The prevalence of sexual abuse/violence against women underscores the importance of provider education on addressing sexuality in survivors.

Sexual dysfunction is a common consequence of sexual violence and/or coercion (Nusbaum et al, 2005). Physical trauma to the genitals may predispose to pain from injury or muscle dysfunction (Postma et al, 2013). More relevant for the majority of cases is the psychological toll of having been forced into unwanted sexual contact. Multidisciplinary management is recommended; the primary goals of therapy are to empower the woman to feel in control of her sexuality and to dissociate consensual sexual activity from traumatic experiences (Basson et al, 2010b; Daglieri and Andelloux, 2013).

Female genital cutting is a special case of sexual violence that is addressed on the Expert Consult website. 

The percentage of women who report sexual contact with another woman is higher in contemporary series compared to historical data (Chandra et al, 2011; Mercer et al, 2013). In a study of almost 6000 women aged 18 to 44 from the United Kingdom, 14% stated that they had experienced sexual activity with another woman (Burri et al, 2012). Data from the National Social Life, Health, and Aging study indicated a 4%, 7%, and 3% rate of lifetime same-gender sexual activity in women aged 57 to 65, 65 to 74, and 75 to 85, respectively (Waite et al, 2009). A 2010 study in American women indicated that 7% of women aged 18 to 59 had engaged in sexual activity with a female partner with a higher prevalence in the younger age groups (Xu et al, 2010). Reasons for engaging in same-gender sexual activity in these women may include curiosity, attraction to a particular individual, or restriction of contact with partners of the preferred gender (e.g., incarceration in a women's prison). About 50% of women with previous same-sex sexual experience identify as heterosexual (Xu et al, 2010). Interestingly, the converse situation is also true in that many lesbian-identified women have a historical or current history of sexual activity with male partners (Diamant et al, 1999). The behavioral term *women who have sex with women* (WSW) is often applied in contemporary research.

It is hypothesized that women are more likely than men to report flexibility in sexual attraction and behavior (Baumeister, 2000). This hypothesis is supported by increased likelihood of change in professed orientation as time passes (Diamond, 2000; Kinnish et al, 2005) and nonorientation-congruent sexual behavior in women compared to men (Rust, 1992; Baumeister, 2000). The central role of social and emotional factors in mediating many aspects of female sexual response is one hypothesis as to why/how women may experience greater flexibility in sexual attraction (Diamond, 2003). Lack of specificity in genital response may also explain arousal in response to erotic stimuli not necessarily congruent with professed orientation in women (Laan et al, 1995; Chivers and Bailey, 2005; Chivers et al, 2007). These responses could motivate some women to explore same-sex sexual activity.

Functional MRI studies have elucidated interesting differences in brain activation between heterosexual and lesbian women; there appears to be some degree of congruence between lesbian women and heterosexual men with respect to the activation of the dorso-medial area and PVN during sexual arousal (Berglund et al, 2006). This situation differs from what is observed with sexual arousal in heterosexual women, in whom activation of the MPOA and ventromedial hypothalamus is observed with sexual arousal (Savic et al, 2001). There also appear to be differences in connections to and from the amygdala between heterosexual and lesbian women (Savic and Lindstrom, 2008).

The genital physiology of sexual response is similar between WSW and non-WSW females. Common sexual activities in WSW include kissing, whole body contact, breast stimulation, stimulation of the genitals by hand, vaginal penetration with fingers or sexual toys, cunnilingus, and tribadism (genital to genital contact)

(Schick et al, 2012). Compared to their non-WSW peers there is some evidence that WSW have a greater diversity of sexual experiences (Burri et al, 2012) and are more likely to engage in bondage and domination/sadomasochism (BDSM) or to have consensually nonmonogamous relationships (Richters et al, 2008).

Studies on the prevalence of sexual dysfunction in WSW are scant. Tracy et al reported on the validation of the FSFI for use in a lesbian population (Tracy and Junginger, 2007). In an Internet study, Shindel et al reported on a population of 1566 WSW. Using a modified version of the FSFI it was estimated that 25% of respondents were at risk of sexual dysfunction based on previously validated cutoffs for the total FSFI score in non-WSW females. The FSFI cutoff showed reasonable correlation to the single-item FSFI question on sexual satisfaction. Risk factors for high risk of sexual dysfunction in these women included overactive bladder symptoms, lower sex frequency, and nulligravidity (Shindel et al, 2012).

Attention to the unique health care needs of WSW and transgender persons is a priority. The urologist may be called on to address sexual wellness issues in transgender persons as part of comprehensive urology care. Many transgender persons report a history of discrimination from both the general public and from health care providers, so it is critically important to establish sensitive rapport early when interacting with transgender patients (Makadon, 2011). Lesbian and bisexual women are also at greater risk of poor health. Numerous studies have indicated a higher rate of unhealthy behaviors in WSW and transgender persons, including obesity and tobacco use. Safer sex practices may not be widely used by WSW (Schick et al, 2012; Kerr et al, 2013). A 2013 study reported that 62% of WSW do not use a barrier for sexual toys, between 83% and 87% do not use a barrier for cunnilingus, and 88% have never used barriers for manual stimulation of the genitalia. In the 316 women from this study with more than one partner, 57% sometimes or never used barriers (Rowen et al, 2013).

Low adherence to safer sex practices and gynecologic cancer screening may result in part from the absence of concern about conception and a common misperception (all too often shared by health care providers) that STIs are not likely to be transmissible between women (Matthews et al, 2004). WSW are at risk of human papillomavirus (HPV) infection by transfer of vaginal fluids between female partners and also by sexual contact with men (Koh et al, 2005). Male sexual partners of WSW are more likely to be at risk for human immunodeficiency virus (HIV) and HPV infection. Between 13% and 17% of WSW report a history of STI; indeed, Singh and colleagues (2011) reported that the rate of chlamydia infection in WSW was slightly higher than the prevalence in women who have sex exclusively with men (7% vs. 5%, respectively). STI including HPV may be transmitted between female partners directly or by sexual toys or by intercourse with male partners. The prevalence of HIV infection appears to be higher in lesbians versus heterosexual women. Education on safer sex practices should be a part of sexual health consultation in WSW (Diamant et al, 1999; Matthews et al, 2004; Marrazzo et al, 2005).

Special mention is warranted regarding women who have been victims of female genital cutting (FGC). FGC is a nonspecific term encompassing a wide variety of cultural practices performed on the genitals of girls and young women, ranging from removal of the clitoral prepuce to removal of the clitoris and resection of sewing together of the labia majora (infibulation), leaving a small aperture for passage of menstrual fluids ([World Health Organization, 2008](#)). FGC is classified by the World Health Organization on a three-point scale ([World Health Organization, 2008](#)):

1. Partial or total removal of the clitoris and/or prepuce
2. Partial or total removal of the clitoris and the labia minora
3. Infibulation; narrowing of the vaginal orifice by suturing of the labia majora with or without clitoral removal

FGC is most prevalent in portions of East Africa including Egypt ([World Health Organization, 2008](#)). It is estimated that as many as 120 million women and girls have been subjected to FGC ([Elchalal et al, 1999](#)). This practice may be carried out in a variety of settings, from surgical suites using sterile technique or in traditional village ceremonies using crude instruments from the environment. While the practice is most common in Islamic cultures it is not an Islamic mandate and most proponents do not explicitly link the practice to religious requirements ([Shafer and Shafer, 2013](#)).

Dyspareunia is common in women who have had FGC. In addition to physical concerns survivors of FGC may have substantial post-traumatic stress disorder and/or cultural beliefs on sexuality that will interfere with their ability to enjoy sexual activity. Women who have undergone FGC have lower levels of sexual functioning in comparison to women from similar cultural backgrounds who have not undergone FGC ([Andersson et al, 2012](#)). The degree of sexual impairment in FGC survivors is variable and dependent in large part on the degree of tissue manipulation; as would be expected women with type III FGC are most likely to have impaired sexual response ([Andersson et al, 2012](#)).

Sensitivity to these issues is critical in the care of these patients; referral to specialists with particular expertise in addressing the needs of women who have undergone FGC is warranted and may yield benefit for the patient ([Fazari et al, 2013](#)). Some women who have undergone FGC support the practice and are content with their genital appearance/function (Johnson, personal communication). Although one need not be supportive nor tolerant of the practice of FGC, the preferences of adult women who have undergone FGC should be respected as they pertain to their own personal sexual life and experience.

Women with Urologic Concerns

Overactive bladder, stress urinary incontinence, and incontinence with sexual activity have been identified as independent risk factors for FSD in numerous studies (Rosen et al, 2009b; Wehbe et al, 2010). The prevalence of sexual dysfunction and/or decreased sexual activity in women with lower urinary tract symptoms varies between 19% and 50% depending on population and means of assessment. Women with urinary issues are twice as likely to report disruption of sexual life compared to their peers (Chen et al, 2013). Painful bladder syndromes and interstitial cystitis have also been linked to impairment of sexual response, sexual avoidance, and sexual pain in up to 88% of affected women (Bogart et al, 2011; Gardella et al, 2011).

Management of overactive bladder and/or stress incontinence has been clearly linked to positive changes in sexual response for women (Rogers et al, 2008; Wehbe et al, 2010). However, placement of transvaginal mesh for pelvic organ prolapse or stress incontinence may contribute to dyspareunia, alteration of vaginal lubrication, and/or discomfort for sexual partners (Helstrom and Nilsson, 2005; Boyles and McCrery, 2008). Procedures that involve placement of slings may disrupt neurovascular innervations to the genital organs (Benson and McClellan, 1993). While the risks of pelvic surgery for prolapse and/or incontinence are real several studies have reported improvements in sexual function after mesh placement; in many cases improvement is driven by resolution of incontinence and/or prolapse-related sexual dysfunction (Roovers et al, 2006; Altman et al, 2009).

Gynecologic Surgery Patients

The effects of hysterectomy on sexual function are mediated in large part by the indication for the procedure (Roovers et al, 2003); women who experience sexual dysfunction from gynecologic conditions (e.g., leiomyoma, endometriosis, etc.) (Helstrom, 1994; Grimes, 1999) are more likely to benefit from surgery whereas those without sexual issues at baseline may experience worsening of sexual function (Dennerstein et al, 1977; Carlson, 1997).

Cancer Patients

Sexual issues are common in women after pelvic cancer surgeries such as cystectomy/urethrectomy, vulvectomy, colectomy, abdominoperineal resection, and proctectomy (Raina et al, 2007; Donovan et al, 2010; Philip et al, 2013). Sexual dysfunction is also a risk of pelvic radiotherapy as a primary or adjuvant treatment (Incrocci and Jensen, 2013). Disruption of pelvic neurovasculature, side effects of treatment, and body image issues may predispose to impairment of sexual responses and pain (Raina et al, 2007).

In cystectomy and/or urethrectomy the anterior vaginal wall may be partially resected or otherwise compromised, leading to difficulty with vaginal penetration (Yang et al, 2006). Disruption of the nerve innervation to the external genitalia, vagina and clitoris is a common risk during cystectomy/urethrectomy (Stenzl et al, 1995). A 2004 study indicated that difficulty with orgasm, desire, and arousal are very common in women after radical cystectomy. Slightly less than half of female cystectomy patients engage in coital intercourse after cystectomy and slightly over half report a decline in sexual life satisfaction (Zippe et al, 2004).

Issues in cancer survivorship are discussed in more detail on the Expert Consult website.



KEY POINTS: SPECIAL POPULATIONS

- A woman's sexuality may be affected by medical, sociocultural, and life factors.
- Sensitivity to the sexual wellness needs of minority populations and/or women who have suffered trauma is an essential component of professionalism.

FEMALE SEXUAL DYSFUNCTION

Semantics and Controversy

Female sexual dysfunction (FSD) is an umbrella term that encompasses distressing situations that interfere with a woman's ability to enjoy a satisfying sexual life. FSD is not truly a diagnosis but rather an umbrella term that may encompass one or more distressing situations that interfere with a woman's ability to enjoy a satisfying sexual life.

Controversies regarding FSD are addressed on the Expert Consult website.



Epidemiology

There is marked variability in the prevalence of sexual issues between regions (Laumann et al, 2006). Prevalence of sexual issues in the general female population is ambiguous due to selection bias, limited data collection, and variation/disagreement about what constitutes a sexual problem. Studies on the prevalence of FSD are presented in Table 32-1.

Disruption of sexual response and sexuality-related distress may occur independently. In a U.K. study of female twins only 37% of women with sexual dysfunction (assessed by Female Sexual Function Index [FSFI]) had concomitant sexual distress (assessed by the Female Sexual Distress Scale [FSDS]) (Burri et al, 2011). It is also important to note that not every sexually distressing situation is a sexual dysfunction; a woman may have distress about sexuality that is related to interpersonal issues rather than a disturbance in her own sexual response. The same twin study from the United Kingdom demonstrated that up to 16% of women who had "normal" sexual function per the FSFI still reported significant sexual distress. In cases of sexual distress without sexual dysfunction, interpersonal and/or psychological issues (Burri et al, 2011) were the principal bothersome issues. In a study of over 31,000 women in the United States, 43% of women had a sexual concern but just 22% endorsed sexual distress; just 12% had a sexual problem and distress (Shifren et al, 2008). A similar Finnish study reported a 34% prevalence of FSD, 36% prevalence of sexual distress, and a 20% prevalence of concomitant sexual dysfunction and distress (Witting et al, 2008).

Due to ambiguity in terminology, Raina et al (2007) have suggested a tripartite classification system:

1. *Sexual complaints* are expressions of discontent associated with sexual function. Women with sexual complaints are likely to have issues related to their partner and/or their personal experience of sexuality. Education on the anatomy and physiology of sexual response as well as communication and interpersonal skills may be sufficient to resolve many sexual complaints.
2. *Sexual dysfunction* is a disturbance in one more or more phases of the sexual response cycle and/or pain during sexual activity. Women with sexual dysfunction may compensate for it in some fashion and thus preserve a sense of sexual satisfaction or at least contentment.
3. *Sexual disorder* is the combination of sexual dysfunction and personal distress relating to the sexual dysfunction. These women merit complete evaluation to assess for etiology and treatment options.

Whether one adheres to this classification scheme or not, it is always important when evaluating research or seeing a patient to gauge personal distress as this is a very important determinant of which treatments are indicated/desired.

Sexual dysfunction is more frequent in older women; *sexual complaints* may be more frequent in younger women (Roos et al, 2012). Similarly, distress related to sexual issues appears to be higher in premenopausal versus menopausal women (Berra et al, 2010); this may be due in part to adaptation on the part of some older women. The highest prevalence of sexual concerns with attendant distress is in women aged 45-64 (Shifren et al, 2008). It is reasonable to hypothesize that this is an age group in whom sexual activity remains a priority despite physical changes of menopause and advancing age, which may compromise sexual response. Distress is

Cancers of nongenital sites may influence sexual function due to alteration in body image, genital and systemic side effects of chemotherapy and radiation, and/or psychological distress ([Perez et al, 2009](#)). Particular interest has been dedicated to sexuality and breast cancer survivorship; breast cancer survivors may be treated with estrogen-blocking drugs that may cause genital atrophy and premature symptoms of menopause. Psychosocial issues are also of great importance in breast cancer patients due to the sexual context

of the female breast in many cultures ([Schover, 1991](#); [Bredart et al, 2011](#); [Kedde et al, 2013](#)).

In recent years concern for quality of life and cancer survivorship have increased interest in promoting sexual wellness for cancer survivors ([Raina et al, 2007](#); [Perez et al, 2009](#)). Oncologists of all disciplines should prioritize sexual quality of life as part of their patient's overall holistic treatment plan.

Some critics have contended that constructs of FSD are derived too heavily from “male” models of sexual response; such proponents may be supportive of the concept of FSD but concerned that the paradigms mediating contemporary concepts of FSD are flawed and can be improved upon (Basson, 2002). Others have contended that FSD is mediated by emotional, mental, or social factors and that these issues are of greater relevance to sexual function than biomedical issues (Tiefer et al, 2002; Tiefer, 2007). Bancroft and colleagues (2003) demonstrated that the best overall predictors of sexual distress in women were emotional relationship with partner and general well-being. Physical issues also played a role but these effects were relatively minor (Bancroft et al, 2003). The most concerning allegations against the concept of FSD are that it does not reflect women’s experience of sex and/or is a “medicalization” of female sexual response for the purpose of financial gain (Tiefer, 2002; Moynihan, 2004).

It is legitimate to challenge current concepts in human sexuality with novel ideas. Similarly, it is prudent to be concerned about the

potential victimization of women and their partners for financial gain (Bancroft, 2002). However, sexuality is a biologic process and medical issues may interfere with a woman’s capacity to enjoy her sexuality (Basson and Leblum, 2003). In the ideal future, optimization of a given woman’s sexual health will be tailored to her unique preferences and needs and will include biomedical, psychological, and/or interpersonal interventions as indicated (Basson et al, 2010b).

As physicians are in the best position to understand the physical (and in some cases mental) processes of sexual response, involvement of the medical community in optimization of sexual wellness is of critical importance for many women. Individual providers will best serve their patients by integrating medical assessment and therapies (when appropriate) with psychosocial intervention in a holistic approach that recognizes the rich complexity of human sexual response (Althof, 2011).

TABLE 32-1 Epidemiology of Female Sexual Dysfunction (FSD) in General Populations

STUDY	REGION	POPULATION	FSD DEFINITION	FSD PREVALENCE	NOTES
Laumann et al, 1999	USA	1749 women aged 18-59	Yes on ≥ 1 PRO	43%	
Oksuz and Malhan, 2006	Turkey	518 women aged 18-55	FSFI ≤ 25	48%	
Nicolosi et al, 2005	Asia	3350 women aged 40-80	Sometimes or occasionally experiencing >1 PRO	32% to 82%	Lack of interest most common
Nicolosi et al, 2006b	Anglophone Countries	3006 women aged 40-80	Sometimes or occasionally experiencing >1 PRO	28% to 57%	Lack of interest most common
Nicolosi et al, 2006a	Europe	5023 women aged 40-80	Sometimes or occasionally experiencing >1 PRO	23% to 46%	Lack of interest most common
West et al, 2008	USA	1944 women aged 30-70	PFSF ≥ 40 = low desire PFSF* < 40 + PDS† ≥ 60 = HSDD	Low desire 36%; HSDD 8%	Assessment of sexual desire only
Valadares et al, 2008	Brazil	315 women aged 40-65 with 11+ years of school	PEQ score ≤ 7	36%	
Shifren et al, 2008	USA	31,581 women aged 18+	CSFQ response of “never” or “rarely”	43%	Sexual distress was 22% with combined distress and FSD in 12%
Witting et al, 2008	Finland	6601 women aged 18-33	FSFI < 26.55	35%	
Chedraui et al, 2009	Ecuador	409 women aged 40-59	FSFI < 26.55	56%	Lubrication and pain domains were lowest
Rosen et al, 2009b	USA	3202 women aged 30-79	FSFI < 26.55	40%	Only 51% sexually active in past 4 wk
Blumel et al, 2009	Latin America	7243 women aged 40-59	FSFI < 26.55	57%	74% sexually active
Ishak et al, 2010	Malaysia	163 women aged 18-65	Malaysian FSFI ≤ 55	26%	
Echeverry et al, 2010	Colombia	410 women aged 18-40	FSFI < 26.5	30%	
Shindel et al, 2011	USA	1241 women aged 25 ± 3	FSFI < 26.55	50%	
Mezones-Holguin et al, 2011	Peru	335 women aged 40-59	FSFI < 26.5	35%	
Shindel et al, 2012	North America	1566 WSW aged 18-86	Modified FSFI < 26.55	25%	
Moghassemi et al, 2011	Iran	149 women aged 43-64	FSFI < 26.5	87%	
Zhang and Yip, 2012	Hong Kong	1410 women aged 19-49	Face-to-face interview using DSM-IV-TR criteria	38%	

*From Derogatis L, Rust J, Golombok S, et al. Validation of the profile of female sexual function (PFSF) in surgically and naturally menopausal women. *J Sex Marital Ther* 2004;30:25-36.

†From Derogatis L, Rust J, Golombok S, et al. A patient-generated multinational inventory to measure distress associated with low desire (PDS). International Society for the Study of Women's Sexual Health (ISSWSH) 2004 Annual Meeting, Atlanta, Georgia, October 28-31, 2004.

CSFQ, Changes in Sexual Functioning Questionnaire; DSM-IV-TR, *Diagnostic and statistical manual for mental disorders*, fourth edition, text revision; FSFI, female sexual function index; HSDD, hypoactive sexual desire disorder; PDS, personal distress scale; PEQ, personal experiences questionnaire; PFSF, profile of female sexual function; PRO, patient reported outcomes; WSW, women who have sex with women.

TABLE 32-2 Prevalence and Definition of Female Sexual Dysfunctions

	PREVALENCE*	DEFINITION†
Hypoactive sexual desire/low libido	9%-60%	Diminished feelings of sexual interest or desire, absence of sexual thoughts, and/or lack of receptivity to sexual activity‡
Sexual arousal disorder/sex not pleasurable	5%-51%	Genital Female Sexual Arousal Disorder: Disruption of clitoral erection, vaginal vasocongestion, vaginal lubrication
Difficulty with genital lubrication	8%-60%	Psychological Female Sexual Arousal Disorder: Absent or markedly diminished feelings of excitement or pleasure in response to sexual stimuli
Persistent genital arousal disorder	~1%	Mixed Female Sexual Arousal Disorder: GFSAD and PFSAD
Female orgasmic disorder	7%-65%	Persistent, recurrent, intrusive, and/or distressing sensations of genital arousal not related to sexual stimulation and that do not resolve after orgasm
Sexual pain disorders	4%-42%	Lack of experience of orgasm or diminished orgasm intensity despite high sexual arousal after a period of sufficient sexual stimulation and arousal
		Dyspareunia: Persistent/recurrent pain with attempted/complete vaginal entry with a penis, finger, or other object
		Vaginismus: as vaginal spasm or pain in response to penetration with a penis, finger, or other object despite a desire for penetration to occur‡
Anxiety about sexual performance	6%-16%	N/A

*Laumann et al, 1999; Nicolosi et al, 2005, 2006a, 2006b; Shifren et al, 2008; West et al, 2008; Witting et al, 2008; Garvey et al, 2009.

†Waldinger et al, 2009; Basson et al, 2010b.

‡The term *vaginismus* is no longer preferred, as it includes significant semantic baggage as a psychological disorder.

also more frequent in women who are partnered; a woman who is unpartnered may not be concerned with sexuality and will not have bother stemming from being unable to satisfy her partner.

FSD has been linked to increasing age (Hisasue et al, 2005; Ponholzer et al, 2005; Oksuz and Malhan, 2006; Valadares et al, 2008; Blumel et al, 2009; Chedraui et al, 2009), menopausal symptoms (Oksuz and Malhan, 2006; Valadares et al, 2008; West et al, 2008; Chedraui et al, 2009; Nappi and Lachowsky, 2009), absence of partner (Valadares et al, 2008), age of partner (Chedraui et al, 2009), partner sexual dysfunction (Hisasue et al, 2005; Blumel et al, 2009; Chevret-Measson et al, 2009; Zhang and Yip, 2012), marital discord (Zhang and Yip, 2012), urinary incontinence (Rosen et al, 2009b; Kim et al, 2011), urinary symptoms (Blumel et al, 2009; Rosen et al, 2009b; Mezones-Holguin et al, 2011; Shindel et al, 2012), depression (West et al, 2008; Rosen et al, 2009b; Echeverry et al, 2010), tobacco use (Oksuz and Malhan, 2006; Roos et al, 2012), sedentary lifestyle (Esposito et al, 2010), infertility (Millheiser et al, 2010), HIV infection (Wilson et al, 2010), hypothyroidism (Atis et al, 2010), diabetes (Giraldi and Kristensen, 2010), sleep apnea (Subramanian et al, 2010), and poor general health (Valadares et al, 2008; Blumel et al, 2009; Ishak et al, 2010; Navaneethan et al, 2010).

Several factors have conflicting data on association with FSD. Estrogen replacement has been linked to both better (Chedraui et al, 2009) and worse (Blumel et al, 2009) sexual function in postmenopausal women. Similarly, both higher (Chedraui et al, 2009) and lower (Blumel et al, 2009; Echeverry et al, 2010) educational achievement have been linked to risk of FSD. Conflicting data have been reported on the role of obesity in FSD. Some studies have reported lower rates of sexual activity and sexual desire (Smith et al, 2012) in obese women and in women with metabolic syndrome (Martelli et al, 2012); however other studies (Christensen et al, 2011) have suggested that among women who are sexually active, obesity (Christensen et al, 2011) and metabolic syndrome (Kim et al, 2011) are not linked to sexual dysfunction. Although data are ambiguous, concern for general health dictates that practitioners should encourage patients to maintain healthy body weight (Goldstein and Alexander, 2005).

Classification

Linear sexual response cycles have served as the foundation for most modern classification systems for FSD (Masters and Johnson, 1966).

While the linear model may not perfectly reflect sexual response in every woman it does represent a convenient means to organize diagnostic criteria. A summary of specific female sexual issues and their estimated prevalence is presented in Table 32-2. There is substantial comorbidity between sexual issues in women (Giles and McCabe, 2009).

The fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5) incorporated several changes to diagnostic criteria for FSD. DSM-5 emphasizes that FSD should be categorized as lifelong versus acquired and generalized versus situational. Duration of at least 6 months is required to apply a diagnosis except in the case of medication-induced sexual dysfunction.

In the DSM-5 sexual desire and arousal disorders in women have been combined into “female sexual interest/arousal disorder.” This change was to address concerns that active sexual desire is not present in all sexually healthy women (Basson, 2002) and that some women do not differentiate sexual arousal from desire (Graham et al, 2004; Brotto et al, 2009). Similarly, the DSM-IV terms “vaginismus” and “dyspareunia” have been combined into “genito-pelvic pain/penetration disorder” in DSM-5. These reorganizations were controversial (Derogatis et al, 2010).

There has been scant research using these new diagnoses; in the interest of simplicity we will outline this chapter according to previous diagnostic categories (Basson et al, 2004).

KEY POINTS: FEMALE SEXUAL DYSFUNCTION

- FSD is a controversial topic but one of great importance to many women.
- A variety of medical and psychosocial issues have been clearly linked to risk of sexual concerns in women.
- Classification of female sexual disorders remains controversial; however, most classification schemes recognize disorders of sexual desire/interest, arousal, orgasm, and sexual pain.

HYPOACTIVE SEXUAL DESIRE DISORDER

Etiology

There are numerous causes for low sexual desire in women. Hubin and colleagues (2011) proposed five axes relevant to hypoactive

TABLE 32-3 Risk Factors for Hypoactive Sexual Desire Disorder

Cognitive	Lack of knowledge, negative anticipation, distractions, negative body image, depression
Physiologic	Neurologic, hormonal, surgical, iatrogenic, age
Behavioral	Avoidance, detachment linked to routine, habituation to infrequent sex
Emotional	Guilt, anxiety, insecurity, conflict
Environmental	Work/family obligations, poor communication, decreased attraction, societal influence

Modified from Hubin A, De Sutter P, Reynaert C. Etiological factors in female hypoactive sexual desire disorder sexologies. 2011;20:149–57.

sexual desire disorder (HSDD): cognitive, physiologic, behavioral, emotional, and environmental (Table 32-3). Women who do not experience desire at baseline but who respond to sexual initiation and are not distressed do not meet criteria for HSDD (Basson, 2002).

It is important to clarify that many early studies characterized sexual desire in terms of spontaneous sexual interest and desire. There is increasing evidence that for many women absence of sexual desire may be typical and not associated with distress. This relationship may be compounded by the self-attribution theory, which articulates that individuals may determine personal beliefs based on their personal behaviors rather than vice versa. For example, a woman who does not think about or initiate sex but who is receptive to sexual stimuli and enjoys sexual activity may (mistakenly) conclude that she is not interested in sex (Eccles and Wigfield, 2002).

Events or issues that occurred prior to onset of decreased sexual desire should be assessed. Common precipitating factors include hormonal changes, medication use, changes in relationship status, or life stressors (Brotto et al, 2010). It is very common for women to experience a reactive decline in sexual desire in the presence of other impediments to sexual activity. It may also be helpful to elucidate whether the decline in sexual interest is mental, emotional, or both. A subtle but important distinction may exist between absence of visceral desire for sex (nonspecific and colloquially referred to as “being horny”) and absence of intellectual interest in sexual pleasure/intimacy (which may be related to psychosocial and partner issues). Patients may not be able to differentiate but this inquiry could provide valuable insights.

Hypoestrogenism has been clearly linked to decreased sexual desire in women, primarily in association with menopause. Women who are surgically menopausal report more severe perturbation of sexual desire relative to nonmenopausal women (de Almeida et al, 2011) and naturally menopausal women (West et al, 2008). Androgen deficiency has also been linked to decreased sexual interest in women (Warnock et al, 1997).

Psychosocial stressors have a marked effect on sexual interest in women. Depression is prevalent and includes a well-known association with HSDD. The HSDD Registry for women reported that up to one third of women with HSDD also report clinically significant depressive symptoms (Clayton et al, 2012). Sexual interest also declines with increasing relationship duration and/or with partner conflict (Segraves, 2002). Interestingly, although aging is associated with declines in sexual desire, associated distress may also decrease; this may account for the relatively lower rate of HSDD in older women compared to younger women (West et al, 2008).

The use of medications, particularly antidepressants of the SSRI class, is associated with HSDD (Montejo et al, 2001; Clayton et al, 2006). Other classes of medication commonly associated with HSDD in women are presented in Box 32-1; virtually every

BOX 32-1 Medications Associated with Female Sexual Dysfunction

Antiandrogens
 Spironolactone
 LHRH agonists
 Anticonvulsants
 Anticholinergics
 Antidepressants
 Antiestrogens
 Tamoxifen
 Raloxifene
 LHRH agonists
 Antihistamines
 Antihypertensives
 Diuretics
 β -blockers
 Calcium channel blockers
 Chemotherapy
 Cyclophosphamide
 Corticosteroids
 Hormones
 Contraceptives
 GnRH agonists
 Metoclopramide
 Metronidazole
 Recreational drugs
 Alcohol
 Amphetamines
 GnRH, gonadotropin-releasing hormone; LHRH, luteinizing hormone-releasing hormone.

Modified from Jha S, Thakar R. Female sexual dysfunction. Eur J Obstet Gynecol Reprod Biol 2010;153:117–23.

medicine has at least anecdotally been linked to a risk for sexual problems.

Treatment

At the time of this writing, there is no approved pharmacotherapy for HSDD in women. Attention to psychosocial issues and partner variables is of critical import. Stress reduction strategies, maintenance of general health, and addressing relationship issues are generally regarded as positive interventions, although empiric studies are scant.

Sexual interest can be an end unto itself and sexual desire can be positively perceived even in the absence of sexual activity (Wallen and Lloyd, 2011). This finding argues against the regulatory agency mandate that the end point of greatest interest in the treatment of HSDD is “satisfying sexual events” (Derogatis et al, 2011). Many women endorse satisfaction from sexual desire or a “desire to be desired”; this does not require a sexual encounter (satisfying or otherwise) to yield benefit (Meana, 2010; Bancroft and Graham, 2011). These topics remain controversial and speak to the need for more focused qualitative research on the fundamental underpinnings of women’s sexual function.

Psychosexual Therapy

There are numerous mental health approaches to addressing HSDD in women. The general goals of therapy include education on sexual physiology and response, determination of type and frequency of sexual activity that is personally desired, and developing interpersonal communication skills (Kingsberg and Althof, 2009; Althof, 2010).

Cessation/Modulation of Medical Therapy

The ideal resolution of sexual problems related to a medication is cessation or substitution with a less side-effect-prone medication that produces similar effects. This is a preferred management strategy for SSRI-associated sexual dysfunction. Alternative strategies include “drug holidays,” decreased dosages, and alternative agents acting as replacements or adjuncts (Ahrold and Meston, 2009; Fabre et al, 2011; Clayton et al, 2013; Taylor et al, 2013).

A meta-analysis of adjunctive treatments for SSRI-induced sexual dysfunction confirmed that twice-daily dosing with bupropion 150 mg improved sexual function outcomes; benefit was not realized with a single daily dose (Taylor et al, 2013). The 5-HT_{1A} partial agonist buspirone (20 to 60 mg/day) has also shown superior efficacy compared to placebo (50% remission for buspirone vs. 20% for placebo) for the management of sexual symptoms in women taking an SSRI for major depression (Landen et al, 1999). A randomized study of women taking SSRIs for depressive symptoms indicated that on-demand use of sildenafil (50 to 100 mg on demand) enhanced orgasmic function relative to placebo (Nurnberg et al, 2008).

Estrogens

E plays an important role in sexual desire for women (Nappi and Polatti, 2009). Correction of E deficiency has been associated with improvement in female sexual function, including desire (Gast et al, 2009; Nastri et al, 2013). This may occur by direct action on libido or by improvement in sexual arousal response and reduction in genital pain resulting from vulvovaginal atrophy.

Androgens

Supplementation with T increases sexual desire in women with low libido and low serum androgen levels (Lobo et al, 2003; North American Menopause Society, 2005). Studies on androgen for the management of HSDD in women are presented in Table 32-4. T has also been shown to improve other aspects of sexual function such as orgasm, pleasure concerns, responsiveness, and self-image (Davis et al, 2006; Shifren et al, 2006; Davis et al, 2008a, 2008b). Although most studies have investigated T as an adjunct to estrogen (in premenopausal women or in postmenopausal women already taking an estrogen supplement), a number have also investigated T monotherapy and have shown similar benefit with respect to sexual interest, desire, and sexual events (Davis et al, 2008b). T supplementation may work in part by increasing general markers for quality of life such as feelings of health, energy, and sense of well-being (Shifren et al, 2000). Mood and affect are crucially important in sexual response, and enhancement of these parameters may be of great benefit (Middleton et al, 2008).

A T patch was approved in Europe as a treatment for HSDD in women; the product was subsequently withdrawn (European Medicines Agency, 2012). The T-patch treatment did not achieve approval in the United States because of concerns about long-term safety and a perceived lack of clarity regarding the concept of female androgen insufficiency. Currently there is no approved androgen-based treatment for sexual-interest disorders in women in the United States (Wierman et al, 2006). Off-label T is used in women by some clinicians (Bachmann et al, 2002; Goldstein and Alexander, 2005).



Use of tibolone, flibanserin, bremelanotide, and other drugs for HSDD is detailed on the Expert Consult website.

FEMALE SEXUAL AROUSAL DISORDER

Female sexual arousal disorder (FSAD) may refer to the disruption of genital responses (GFSAD), to psychological arousal responses (PFSAD), or mixed FGSAD and PFSAD (Basson et al, 2010b).

Etiology

Atherosclerotic lesions reduce genital blood flow and responsiveness in animal models of FSD (Park et al, 2000; Traish et al, 2010). Vascular or neurologic disease may also contribute to GFSAD (Goldstein and Berman, 1998; Traish et al, 2010). Pelvic surgery (gynecologic, urologic, or colorectal) may also perturb genital innervations (particularly the autonomic innervation of the pelvic nerve) and vascular supply (Raina et al, 2007). Nicotine is associated with impairment of genital response (Harte and Meston, 2008). Diabetes represents a special risk factor for FSD, as it may be associated with neurologic, vascular, and/or hormonal defects (Kim et al, 2009; Giraldi and Kristensen, 2010) in addition to marked psychological morbidity (Bitzer and Alder, 2009).

In addition to their known effects on sexual desire, antidepressants may also impair genital arousal responses. Animal models have demonstrated inhibition of genital vasodilation from pelvic nerve stimulation after administration of antidepressant medications including SSRIs and serotonin/norepinephrine reuptake inhibitors (Angulo et al, 2004). In this same study there was some difference within class, suggesting that effects may not be universal for all antidepressants or in all women. Furthermore, as depression itself is a risk factor for sexual dysfunction, some women may experience improvement in sexual satisfaction when treated with antidepressant drugs (Ishak et al, 2013).

The hormonal milieu may have a profound influence on genital tissues; hence endocrinopathy is an important cause of GFSAD. Perturbation of genital response (thinning of vagina, dryness, rise in pH) is often attributable to hypoestrogenism from menopause (Bachmann et al, 1999).

PFSAD typically originates from psychological causes. Common examples include dissatisfaction with a sexual partner, nonsexual stressors that reduce mental energy required for fostering of sexual interest, and depression (Basson et al, 2010b).

Evaluation of Female Sexual Arousal Disorder

Appropriate characterization of FSAD is required to determine etiology and potential avenues for intervention. A precise history is critical to this process. Time of onset and associated factors should be assessed. Attention to the woman's feelings and relationship status is also of critical import (Brotto et al, 2010).

Treatment of Female Sexual Arousal Disorder

Psychosocial

Attention to psychosocial factors mediating FSAD is always an important component of treatment. These issues may or may not be primary in causing FSAD but they will be present to some extent in virtually every case. These issues should be addressed, or appropriate referral to a therapist should be made early in treatment.

Devices

The Eros Clitoral Therapy Device (Eros-CTD) is a battery-powered vacuum-driven suction device designed to be applied to the clitoris. In a validation study it was shown to enhance sensation, arousal, and orgasmic potential in women with and without sexual concerns (Billups et al, 2001).

Outside the realm of medical devices there exists a wide variety of sexual enhancement products. Examples include vibrators/massagers, dildos, and devices used for erotic/fantasy role-play (Queen, 2013). These devices may be of great usefulness in improving sexual response. Studies have indicated that many women use and have used vibrators for sexual stimulation; vibrator use has been associated with better scores on the FSFI (Herbenick et al, 2009, 2010a). Fantasy role-play and power exchange activities such as consensual bondage/dominance/sadomasochism (BDSM) are used for sexual stimulation by small but significant numbers of women (Moser and Kleinplatz, 2006; Richters et al, 2008).

Tibolone

Tibolone is a synthetic hormone that is metabolized to several forms with estrogenic activity; tibolone also has the capacity to bind and activate ARs. Tibolone is superior to placebo in enhancing sexual desire in premenopausal women (Laan et al, 2001). In a randomized controlled study of postmenopausal women with sexual dysfunction (defined by FSFI criteria) tibolone produced greater increases in FSFI score (driven primarily by the desire, arousal, and satisfaction domains) compared to a combined estrogen/P patch. Interestingly, there was no significant difference in sex-related distress between treatment groups (Nijland et al, 2008).

Flibanserin

Flibanserin is an agonist against the 5HT_{1A} receptor and antagonist against the 5HT_{2A} receptor (D'Aquila et al, 1997). Flibanserin also exerts dopaminergic and noradrenergic action (Invernizzi et al, 2003; Gelez et al, 2013a). These CNS effects may enhance sexual interest (Stahl et al, 2011; Gelez et al, 2013b).

Flibanserin was initially investigated as a treatment for major depressive disorder. Four randomized studies of flibanserin for

depression (enrolling 523 women) did not demonstrate acceptable efficacy compared to active treatment; however, there was a slight improvement in sexual function in treated women. This improvement did not reach statistical significance although the studies were not designed/powerd to assess sexual function outcomes (Kennedy, 2010).

High doses of flibanserin (100 mg/day) are consistently associated with statistically significant positive changes in sexuality (particularly desire), whereas 50-mg doses are less consistent (Goldfischer et al, 2011; Derogatis et al, 2012; Thorp et al, 2012; Katz et al, 2013; Simon et al, 2014). There is also a slight but significant superiority of flibanserin over placebo based on patient-reported efficacy in all studies. Highlights of published trials on flibanserin are summarized in Table 32-5. Unpublished randomized controlled studies in other populations have yielded similar results.

Adverse events associated with flibanserin include somnolence, headache, vertigo, and nausea. A 52-week open-label study in 962 women reported an 11% discontinuation rate as a result of adverse events, most of which were minor in nature (Jayne et al, 2012). At the time of this writing, flibanserin has not been approved for management of FSD in the United States after being rejected by U.S. Food and Drug Administration (FDA) advisory boards in 2010 and 2013 (Lenzer, 2010).

TABLE 32-5 Randomized Controlled Trials of Flibanserin for Hypoactive Sexual Desire Disorder (HSDD)

STUDY	N	DESIGN	TREATMENT	DIFFERENCE VS. PLACEBO IN				
				SSE	FSFI	FSFI-DESIRE	FSDS	AE
Goldfischer et al, 2011	333 women, premenopausal	Randomized withdrawal of women previously responsive* to flibanserin	Flibanserin 50-100 mg/day	NR	2.1†	0.3†	-0.3†	-1.6%
Thorp et al, 2012	1584 women, premenopausal	Randomized controlled dose escalation trial of women with HSDD	Flibanserin 50-100 mg/day	0.3-0.8†	1.3-1.5†	0.2-0.3†	-0.1 to -0.2†	2% to 13%
Derogatis et al, 2012	880 women, premenopausal	Randomized controlled trial of women with HSDD	Flibanserin 50 or 100 mg/day	0.6-0.8†	1.5-2.6†	0.3-0.4†	-0.1 to -0.3†	6%-8%
Katz et al, 2013	1090 women, premenopausal	Randomized controlled trial of women with HSDD	Flibanserin 100 mg/day	1.0†	1.8†	0.3†	-0.3†	11.7%
Simon et al, 2014	949 women, postmenopausal	Randomized controlled trial of women with HSDD	Flibanserin 100 mg/day	0.4†	1.5†	0.3†	-0.2†	11.7%

*Responsive women reported an increase of at least 2 SSE and/or 4 days/mo of feeling sexual desire.

†Statistically significant ($P < .05$).

AE, adverse events; FSDS, Female Sexual Distress Scale; FSFI, Female Sexual Function Index; NR, not reported; SSE, satisfying sexual event/mo.

Bremelanotide (also Known as PT-141)

Bremelanotide is an analogue of α -melanocyte-stimulating hormone (MSH) (Wikberg et al, 2000). MSH is active in the hypothalamus of female rodents and induces sexual solicitation behavior (Pfaus et al, 2004). In a placebo-controlled randomized trial, 18 premenopausal women with female sexual arousal disorder were treated with intranasal bremelanotide 20 mg. Women who received treatment reported greater levels of sexual arousal in response to sexually explicit material compared to women receiving placebo; there was no significant difference in genital arousal response (Diamond et al, 2006).

The nasal route of administration for bremelanotide has been associated with an increase in systemic blood pressure. A subcutaneous, on-demand route of administration is under investigation.

Other Medical Therapy

Several small studies have suggested beneficial changes in sexual desire in women treated with a proprietary blend of herbals and vitamins (Ito et al, 2006). Use of any herbal therapy should be approached with caution given the lack of regulation for manufacturer and efficacy claims.

TABLE 32-4 Randomized Controlled Trials of Testosterone Therapy for Hypoactive Sexual Desire Disorder (HSDD)

STUDY	N	TREATMENT	DIFFERENCE VS. PLACEBO					AE
			SSE	PFSF-AROUSAL	PFSF-DESIRE	PDS	BISF-W	
Braunstein et al, 2005	447 women with HSDD, surgically menopausal, on estrogen	T transdermal patch (150-450 µg/day)	NR	8*	~5*	NS	NR	6%
Simon et al, 2005	562 women with HSDD, surgically menopausal, on estrogen	T transdermal patch (300 µg/day)	1.1†	5†	5†	-7.7†	NR	-2%
Davis et al, 2006	77 women with HSDD, surgically menopausal, on estrogen	T transdermal patch (300 µg/day)	0.5	19†	10†	-19.3†	NR	-1%
Shifren et al, 2006	238 women with HSDD, naturally menopausal on estrogen	T transdermal patch (300 µg/day)	1.6†	26%†	5.8†	-9†	NR	6%
El-Hage et al, 2007	36 women with HSDD, surgically menopausal, on estrogen	T transdermal cream (10 mg/day)	NR	NR	NR	NR	8.2†	NR
Davis et al, 2008a	261 women with decrease in satisfying sex, premenopausal	T transdermal spray (2.8-9 mg/day)	0.4-0.8†	NR	NR	NR	NR	11%-16%
Davis et al, 2008b	814 women with HSDD, menopausal, not on systemic estrogen‡	T transdermal patch (150 or 300 µg/day)	1.4*	~10†	~8†	~-11†	NR	0%
Panay et al, 2010	272 women with HSDD, naturally menopausal (26% on estrogen)	T transdermal patch (300 µg/day)	1.2†	~14†	7.6†	11.5†	NR	9%

AE, incidence of adverse events; BISF-W, Brief Index of Sexual Functioning for Women; NR, not reported; NS, not significant; PFSF, profile of female sexual function; PDS, personal distress scale; SSE, satisfying sexual event/mo; T, testosterone.

*Significant differences only with 300 µg/day patch.

†Statistically significant ($P < .05$).

‡Women taking vaginal estrogens continued on stable dosing regimens.

Some sexual enhancement products are marketed as “novelty items” not actually for use in sexual contexts to limit manufacturer liability for potential injuries. Urologists need not be experts in such devices but should advise patients to use reasonable cautions to prevent trauma (e.g., laceration, electric shock, numbness, loss inside a body cavity, etc.) (Aaronson and Shindel, 2010).

Oral Pharmacotherapy

PDE5I have been of great interest in treating FSAD because of the similarities in the mechanisms of vascular engorgement between men and women (Kim et al, 2003; Munarriz et al, 2003). Taken in aggregate, the data are conflicting on the efficacy of sildenafil (50 to 100 mg) for FSAD (Chivers and Rosen, 2010). The greatest efficacy of these drugs has been demonstrated in women with clearly defined etiologies for impairment of genital response, typically

neurologic lesions such as spinal cord injury, MS, or diabetes (Sipski et al, 2000; Dasgupta et al, 2004; Caruso et al, 2006). PDE5 inhibitors are not approved for use in women and hence any use of these drugs in women is off label.

Details on apomorphine, transdermal agents, lubricants, and hormones are detailed on the Expert Consult website.



PERSISTENT GENITAL AROUSAL DISORDER

Persistent genital arousal disorder (PGAD) is persistent, recurrent, intrusive, and/or distressing sensations of genital arousal that are not related to sexual stimulation and that do not resolve after orgasm (Basson et al, 2010b). Genital sensations associated with PGAD include throbbing, lubrication, pelvic congestion, sense of imminent orgasm without climax, and unprovoked orgasm (Waldinger and Schweitzer, 2009). The degree of distress is apparent

In a randomized controlled study in 24 women with orgasmic disorder, apomorphine 3 mg sublingual was superior to placebo in enhancing objective and subjective arousal and lubrication after application of a vibrator to the genitals. Nausea and vertigo were the most common side effects (Bechara et al, 2004). An open-label study demonstrated no benefit in 80% of women taking apomorphine 2 or 3 mg sublingual for HSDD or arousal disorders; in a follow-up randomized study, improvements in various spheres of sexual life were reported (Caruso et al, 2004). The unusual methodology of this study warrants caution in interpreting results.

A variety of other oral agents have been used in small randomized controlled studies of FSAD with some evidence of benefit for objective arousal responses. Examples include L-arginine with yohimbine (Meston and Worcel, 2002) and Korean red ginseng (Oh et al, 2010). Data on these therapies is scant and they should hence be viewed as experimental.

Topical Agents

One of the simplest approaches to GFASD is use of a sexual lubricant (Herbenick et al, 2011a). There are innumerable brands and formulations of sexual lubricants; they vary in terms of lubricity, additives, durability, and cost. Women who report dissatisfaction with one lubricant should be encouraged to investigate alternatives (Queen, 2013).

There are a variety of lubricants available that may be divided into three main categories.

1. Water-based (e.g., saliva and water-based commercial lubricants): safe for use with latex condoms and easy to wash off. May dry out and require repeat application.
2. Silicone-based: safe for use with latex condoms and easy to wash off. Less likely to dry out but more difficult to wash off. May have an unpleasant taste.
3. Oil-based (e.g., vegetable oils, butter, etc.): not safe for use with latex condoms. Less likely to dry out but more difficult to wash off.

It is important to note that most lubricants have spermatotoxic properties and may interfere with conception (Vargas et al, 2011). Couples that are attempting to conceive should avoid the use of most commercially available lubricants and saliva. Sperm-safe alternatives are available.

Transdermal Agents

Transdermal agents are designed to be absorbed through the skin and modulate the physiology of deep tissues. These differ in that respect from topical agents, which are designed to remain on the skin surface (e.g., sexual lubricants).

Transdermal prostaglandin E₁ (PGE₁) applied to the vulva and/or clitoris has been reported as a therapy for GFASD. One gram of ointment containing 0.2% PGE₁ applied to the external genitalia produced a more robust genital response when compared to placebo ointment (Bechara et al, 2003). A 2008 study demonstrated a significant improvement in survey scores and overall satisfaction with sexual arousal in women treated with PGE₁ versus placebo (Liao et al, 2008). Side effects of PGE₁ include localized irritation, soreness, and burning (Padma-Nathan et al, 2003; Liao et al, 2008).

A 16-week randomized, placebo-controlled study included 256 women with a variety of sexual concerns (including HSDD, FSAD, and orgasmic disorder) and sexual distress (per the FSDS) in response to on-demand vaginal treatment with a proprietary botanical agent. Women receiving the herbal compound reported higher mean FSFI desire and arousal scores compared to women receiving placebo. Scores for other domains did not reach statistical significance and overall FSFI score was not significantly different between treatment and placebo groups (mean increase of 2.1 vs. 0.9, respectively) (Ferguson et al, 2010).

In a single study the use of the adrenergic antagonist phentolamine as an oral pill or vaginal solution in 40 postmenopausal women with FSAD was investigated. In women receiving hormone therapy, a 40-mg dose of phentolamine led to significantly greater improvement in subjective arousal and vaginal blood flow as assessed by plethysmography. The most common side effects were rhinitis and headache (Rubio-Aurioles et al, 2002).

Hormones

Hormonal modulation may play an important role in the management of GFASD related to hypoestrogenic and/or hypoandrogenic states (Bachmann and Oza, 2006; Utian et al, 2008). Estrogens, SERMs, and the synthetic hormone tibolone may prove efficacious in treating FSAD (Laan et al, 2001; Gast et al, 2009).

from the fact that more than 20% of women presenting with PGAD in one series requested clitorrectomy for management (Waldinger and Schweitzer, 2009). On the other hand, unprovoked sexual arousal may engender positive feelings in some women (Leiblum and Chivers, 2007).

Reliable data on the prevalence of PGAD are scant (Leiblum and Nathan, 2001; Waldinger et al, 2009). A survey of 96 women presenting to a sexual health clinic indicated that just one patient met the full five-point criteria for PGAD. Importantly, about one third reported at least one symptom of PGAD (Garvey et al, 2009). Whether this represents a continuum of PGAD severity or a difference in subjective perception of bother is unclear.

Etiology

PGAD has been associated with a dysfunction of sexual beliefs (Carvalho et al, 2013) and restless legs syndrome (Waldinger and Schweitzer, 2009). PGAD has also been associated with anxiety and obsessive-compulsive symptoms (Leiblum and Chivers, 2007), dietary soy intake (Amsterdam et al, 2005), sleep disturbances (Wylie et al, 2006), periclitoral masses (Bedell et al, 2014), spinal tumors, withdrawal of SSRI medications (Goldmeier et al, 2006; Leiblum and Goldmeier, 2008), and pelvic arteriovenous malformations (Goldstein et al, 1995).

The largest series of women with confirmed PGAD included 18 Dutch women. It was reported that two thirds of the women presenting with PGAD were menopausal. Also noted was a high (55%) prevalence of pelvic varices; it is unclear whether or not menopause and the prevalence of pelvic varices are related, as varices are common in older women (Waldinger et al, 2009). Additional evaluations (brain MRI, pelvic MRI, electroencephalogram, transvaginal ultrasound, and serum hormone levels) were not conclusively demonstrative of any abnormalities (Waldinger et al, 2009). However, clinical examination of these women demonstrated that two thirds of them had restless legs syndrome and/or overactive bladder (Waldinger and Schweitzer, 2009). Many women also reported exacerbation of PGAD symptoms with stress. The authors hypothesized that PGAD may be a manifestation of nonsexual "hyperexcitability" of the genitals.

Evaluation

A careful physical examination may show genital anomalies that predispose to recurrent and unwanted sexual stimulus. Hormonal evaluation is warranted. If there are other neurologic signs, spinal MRI may be of some use.

Treatment

Waldinger and colleagues (2009) reported durable efficacy of the benzodiazepine drug clonazepam (0.5 to 1.5 mg/day) in reducing PGAD symptoms in 56% of treated subjects; benefit was also reported in some women from treatment with tramadol 50 mg or oxazepam 10 mg (Waldinger and Schweitzer, 2009).

Cognitive/behavioral treatments have been proposed, including training to direct attention away from genital sensations and the reduction of overall anxiety (Leiblum and Chivers, 2007). Women with this poorly understood disorder have very positive responses to empathy and support from their providers (Waldinger and Schweitzer, 2009).

FEMALE ORGASMIC DISORDER

Etiology

For diagnosis of female orgasmic disorder (FOD), the term "sufficient sexual stimulation" must be kept in mind. A substantial number of healthy women do not climax from vaginal penetration; others may experience climax from penetration but only after prolonged stimulation. These are normal variants of female sexual response.

There is a widespread cultural belief (derived in large part by the theories of Sigmund Freud) that vaginal penetration should lead to orgasm and that an absence of orgasm from penetration is indicative of psychopathology (Freud, 1905). Some authors have reported superior sexual and life functioning in women who climax from vaginal penetration (Nicholas et al, 2008; Brody and Costa, 2011). Although coitus-associated orgasms may be physically possible but inhibited in some women, there is no reliable data indicating that women who rely on stimulation of the glans clitoris for sexual climax are abnormal (Colson, 2010). Such women should be encouraged to explore nonpenetrative sexual stimuli that lead to climax without being informed that they are frigid or otherwise dysfunctional.

The quality of the relationship influences a woman's capacity to experience orgasm during sex. Poor communication (Kelly et al, 2004) and relationship conflict (Dennerstein et al, 1999) are associated with a lower likelihood of orgasm in women. Psychosocial issues and depression also exert a substantial negative influence on orgasmic capacity in women (Laumann et al, 1999). Antidepressant drugs are associated with FOD (Rosen et al, 1999a).


There are conflicting data on whether orgasm problems are more frequent based on sociodemographic variables. No definite trends have been identified based on age, ethnicity, or menopausal status (Graham, 2010). Similarly, there has been investigation of genetic or hereditary factors; preliminary results have suggested that there may be some genetic component related to difficulty with orgasm but further studies are needed (Witting et al, 2009). Surgical therapy or disruption of the genitals has been linked to FOD in women; this is most likely a result of psychological distress and/or disruption of the earlier phases of sexual response (Graham, 2010).

Evaluation

The general evaluation of sexual health should be performed. It should be determined whether or not the woman is receiving the adequate sexual stimulation that leads to orgasm for her (Basson et al, 2000). Assessment of patient/partner perceptions is essential.

Treatment

Directed masturbation is one of few therapies that has been shown efficacious for FOD (Andersen, 1981; Heiman and Meston, 1997). Frank and honest discussion between partners on preferred erotic activity is essential. This may require education of the woman and her partner on the normalcy of variations in sexual preferences and responses. Incorporation of clitoral or other erotic stimulation may be a satisfactory means to resolve FOD in some women.

Other behavioral interventions are detailed on the Expert Consult website. 

There are no approved pharmacotherapies for FOD. PDE5I enhance orgasmic response in women with decreased sexual desire related to the use of SSRI drugs (Nurnberg et al, 2008) and in postmenopausal women with orgasmic dysfunction (Cavalcanti et al, 2008). Use of these drugs in women is off label. Estrogens and androgens may be of benefit for women with FOD (Gast et al, 2009). These effects are likely driven by enhancement of earlier phases of sexual response and no study groups have investigated hormone manipulations with a primary end point of orgasm.

SEXUAL PAIN DISORDERS

Etiology

Genital and sexual pain disorders are often complex and multifactorial (Pauls and Berman, 2002). Regardless of initial etiology, pain with intercourse is likely to trigger a number of physical and psychological defense mechanisms that will further increase pain with sexual activity (Pauls and Berman, 2002). For instance, a woman with neuroproliferative vestibulodynia who experiences pain with

A 2008 report suggested that masturbation was more frequent in women who report frequent coital intercourse, a pattern that was reversed in men. A number of other sexual behaviors and a greater number of partners were also associated with more frequent masturbation ([Gerressu et al, 2008](#)). It may be inferred that masturbation is a supplement rather than a replacement for partnered sexual activity in women; it may also be a means to reach orgasm in women who do not routinely climax during partnered sex.

Sensate focus is a learning process of progressive body exploration; attention in sensate focus is directed away from genital

stimulation and the goal-oriented pursuit of orgasm and is directed toward full-body sensation and mutual pleasure. A graduated sequence of steps is performed throughout several weeks, leading eventually to penetrative intercourse. The general principle is to reduce anxiety and the goal-oriented pursuit of orgasm that may be self-defeating. This technique was introduced by Masters and Johnson and has been widely advocated by sex therapists, although long-term outcome data are sparse ([Masters and Johnson, 1966](#)).

BOX 32-2 Conditions Commonly Associated with Sexual Pain**SUPERFICIAL**

Neuroproliferative vestibulodynia
 Vulvar dermatoses
 Vulvovaginal atrophy
 Condyloma

DEEP

Endometriosis
 Interstitial cystitis
 Pelvic floor muscle dysfunction
 Uterine leiomyoma
 Pelvic inflammatory disease
 Pelvic fracture
 Pelvic radiation
 Vulvovaginal atrophy

Modified from Boardman LA, Stockdale CK. Sexual pain. Clin Obstet Gynecol 2009;52:682–90; and Vallier HA, Cureton BA, Schubeck D. Pelvic ring injury is associated with sexual dysfunction in women. J Orthop Trauma 2012;26:308–13.

intercourse will likely experience anxiety and impairment of genital arousal/lubrication with her next sexual encounter. Enhanced pelvic muscle tone may occur as a defense mechanism. This constellation of downstream effects will generally compound on one another. There is often a substantial delay between the onset of symptoms and the presentation for evaluation, and many presenting women have experienced genital pain as a result of numerous contributing factors (Pauls and Berman, 2002).

A list of conditions known to be associated with sexual pain disorders is presented in Box 32-2. Studies in adolescent and young adult women (<25 years of age) indicated that between 20% and 57% report pain with intercourse (Landry and Bergeron, 2009). Sexual pain is also prevalent in older women, most commonly from vulvovaginal atrophy (Farage and Maibach, 2006). The most common cause of vulvovaginal atrophy is estrogen deficiency related to menopause (surgical or natural) (North American Menopause Society, 2013). Pelvic radiation may also contribute to vaginal atrophy (Incrocci and Jensen, 2013).

Superficial dyspareunia may result from neuroproliferation of the vulvar vestibule. The vulvar vestibule is of endodermal origin and is hence embryologic and histologically distinct from the adjacent vaginal mucosa and vulvar squamous epithelium (O'Connell et al, 2008). This area may become hypersensitive, with tactile allodynia prohibitive of sexual contact (Zolnoun et al, 2006). Vulvar dermatoses are common and may be frequently missed as causes of superficial dyspareunia (Burrows et al, 2008). A retrospective review of patients seen in a tertiary referral center for vulvovaginal disorders reported that more than 60% of women had some form of vulvar dermatosis (Bowen et al, 2008). Deep dyspareunia has been associated with other gynecologic conditions such as uterine leiomyoma, ovarian cysts, and endometriosis (Vercellini et al, 2012).

The importance of mental, cognitive, and partner-related factors cannot be overlooked in any pain disorder. Anxiety and mood disorders are common in women with dyspareunia; attention to these factors is an essential part of treatment (Basson et al, 2010b). Women with high levels of relationship intimacy and partner support generally report less bother related to sexual pain disorders (Bois et al, 2013). Women from conservative, religious, and/or sexually repressive backgrounds are more likely to report sexual pain (Yasan and Gorgen, 2009). Pain that is prohibitive of sexual activity may also occur in victims of sexual abuse or trauma (Nusbaum et al, 2005; World Health Organization, 2013). Fear of pain, catastrophizing

thoughts (i.e., exaggerated negative thoughts about pain), and loss of self-efficacy (e.g., thoughts such as “I’ll never be able to have good sex” or “there is nothing I can do to make it hurt less”) have all been linked to worse pain with sexual activity. Loss of self-efficacy has been reported as the most influential mental variable in patients with genital pain during sex (Desrochers et al, 2009).

Evaluation

The onset of sexual pain is very relevant; a woman who experienced lifelong difficulty with sexual activity may have a congenital or psychological etiology for pain. A woman who previously enjoyed sexual activity but now finds it painful is likely to have a musculo-skeletal, pelvic, genital, dermatologic, or psychological etiology.

Evaluation of sexual pain relies heavily on physical examination. Careful inspection of the entirety of the external genitalia is essential, as subtle pathology may be easily missed. Inspection of the vulva and labia majora may show dermatologic conditions such as lichen planus (LP), lichen simplex chronicus, lichen sclerosus, vulvar intraepithelial neoplasia (VIN), genital condyloma, contact dermatitis, or other lesions (Fig. 32-11 on the Expert Consult website). A biopsy may be warranted but should only be ordered to rule in or rule out a specific diagnosis.

After inspection of the vulva and labia majora, the labia minora, clitoris, and vulvar vestibule should be examined. Some degree of erythema is normal along the crease of the labia minora. Bartholin gland cysts, inflammation of Skene glands, clitoral phimosis, vulvar erythema, and labial fissures may be detected (Goldstein and Burrows, 2008). The endodermally derived vulvar vestibule is a site for superficial dyspareunia resulting from neuroproliferation (Fig. 32-12 on the Expert Consult website) (O'Connell et al, 2008). The line of demarcation between the endodermal vestibule, the ectodermal vulva, and the mesodermal vagina is subtle; precise examination is key to appropriate diagnosis. Regression/resorption of the labia minora is an important and often overlooked anomaly that is most commonly observed in women who are hormonally deficient (Goldstein and Burrows, 2008).

Assessment for vulvar sensation and tactile allodynia is recommended. This may be accomplished by application of a cotton swab, heat/cold, or a biothesiometer. Women with neuroproliferative vestibulodynia will have marked pain with even light contact against the vestibular tissue (Goldstein and Burrows, 2008).

Transvaginal palpation of the levator ani (LA) is essential. Transanal palpation may be an option in women unable to tolerate vaginal penetration. The patient should be asked to characterize palpation as pressure (normal) or pain (abnormal). Localization of pain permits more focal physical therapy and/or trigger-point injections. Palpation of the adnexa, uterus, and the pudendal nerves in the vicinity of the ischial tuberosity completes the examination (Goldstein and Burrows, 2008).

Treatment

The clitoris may not be involved in pain syndromes of the vestibule and vagina. Hence women with a sexual pain disorder may be able to experience sexual pleasure and bonding with a partner by means of clitoral stimulation. This may be a useful means to foster or maintain sexual intimacy while issues of vaginal and/or pelvic pain with intercourse are being addressed. A multimodal approach to the management of sexual pain is advisable. Psychobehavioral intervention to reduce anxiety surrounding sexual activity is crucial (Rosenbaum, 2011). Cognitive behavioral therapy, psychodynamic, and other therapeutic approaches have been used (Bergeron et al, 2001).

Treatment of Abdominopelvic Processes

Gynecologic conditions (uterine leiomyoma, cystic ovarian disease, endometriosis, labial fusion, vaginal septum, etc.) and other

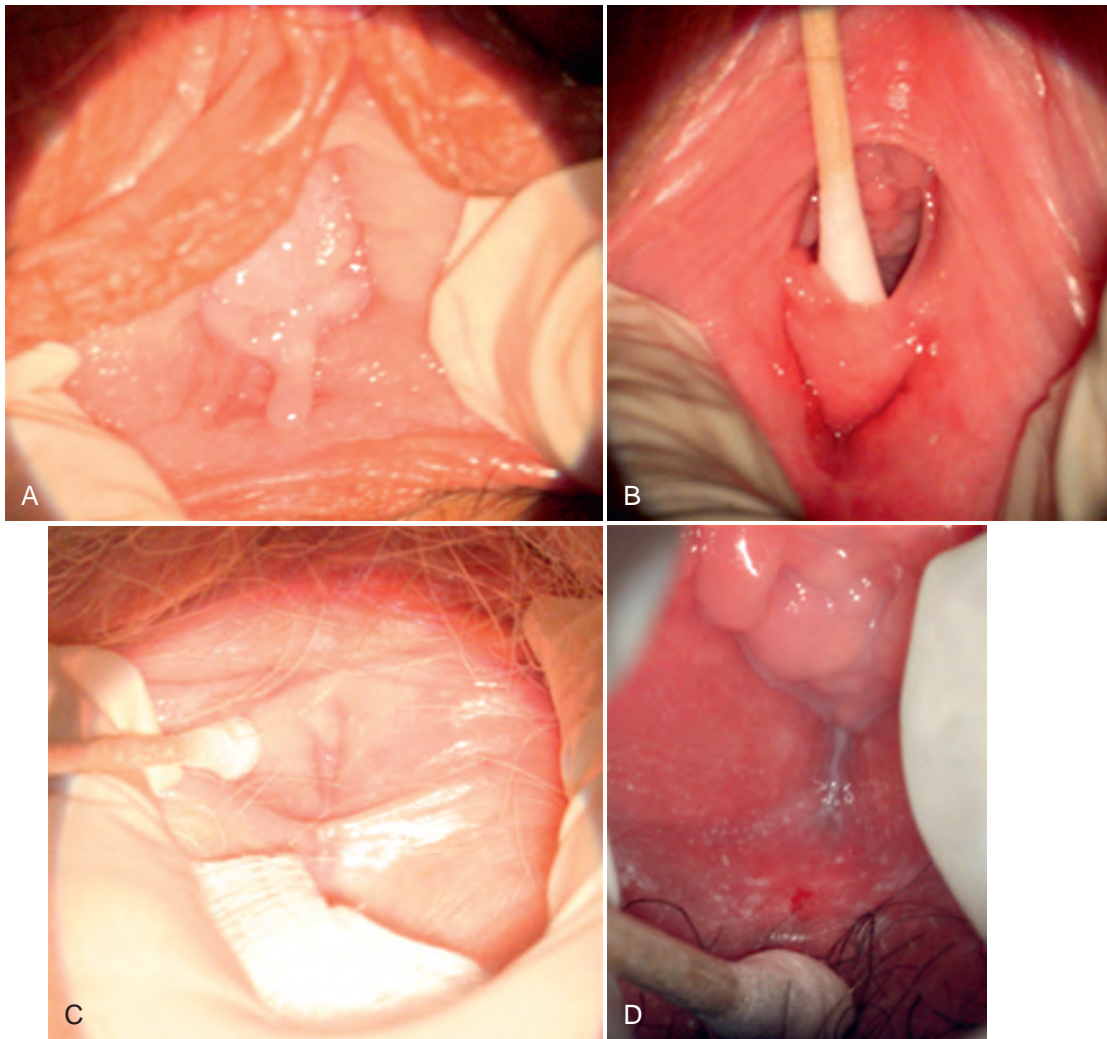


Figure 32-11. A variety of vulvar conditions. A, Fibroadenoma of the hymen that caused dyspareunia. B, Persistent hymenal tissue in a young woman with dyspareunia. C, Stenosis of the introitus in a sexually inactive menopausal woman with pain wearing tight clothing and during sitting. D, Painful tearing of the posterior fourchette from sexual intercourse.

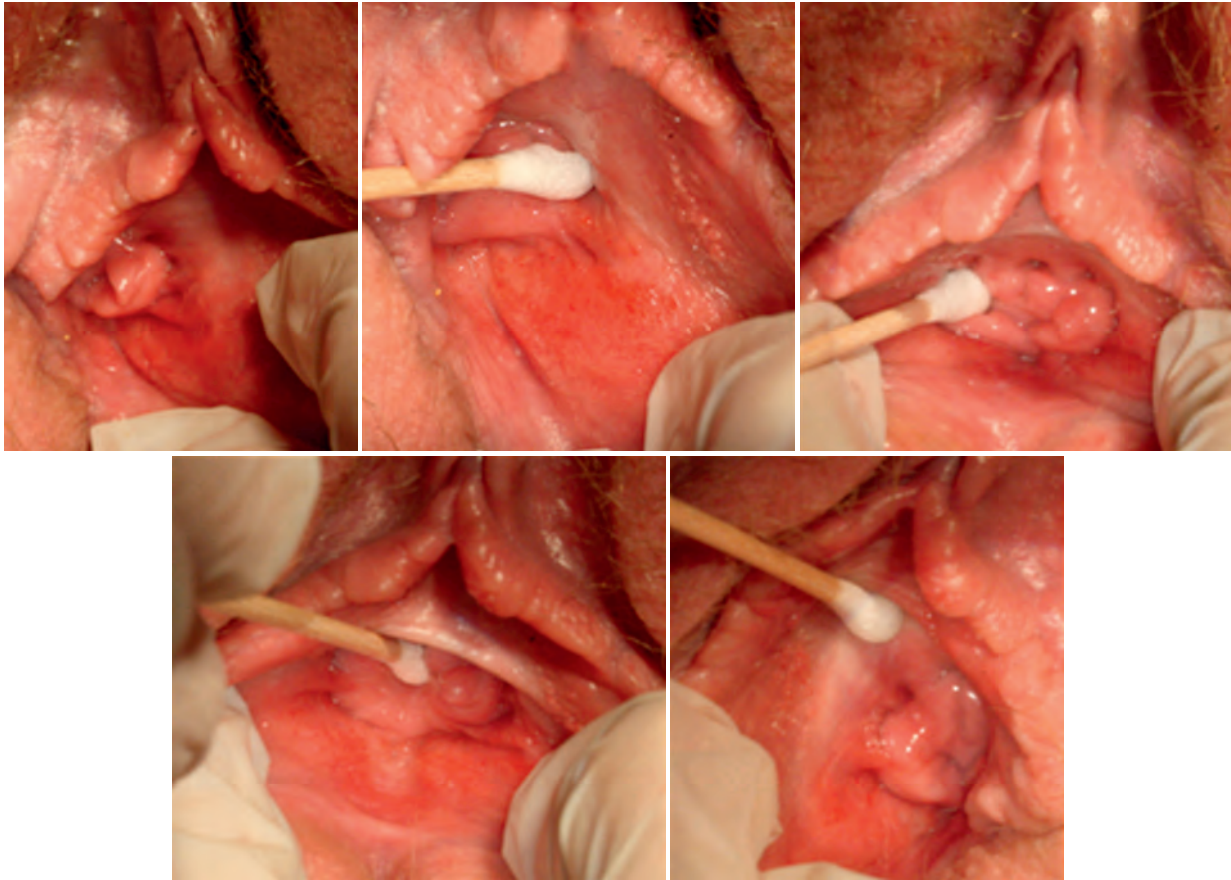


Figure 32-12. Neuroproliferative vestibulodynia. In some women with vestibulodynia and extreme allodynia, the following abnormalities have been found in the vestibular mucosa: (1) an increased density of C-afferent nociceptors, (2) a marked increase in mast cells, and (3) an increased expression of heparinase. It has been postulated that activated mast cells release nerve growth factor and heparinase, which leads to the proliferation of nociceptors. This form of vestibulodynia has been called neuroproliferative vestibulodynia and may be congenital or acquired. In some of these women, polymorphisms in genes have been found that code for various interleukins, a group of cytokines expressed by the immune system, and involved in wound healing. When neuroproliferative vestibulodynia is identified, complete vestibulectomy and vaginal advancement flap reconstruction may be considered.

pelvic disorders (irritable bowel, Crohn disease, etc.) may predispose women to dyspareunia. Appropriate medical or surgical treatment may be of benefit in addressing sexual dysfunction although adjunctive therapies may be required (Basson et al, 2010b).

Empiric Medical Therapy

Empiric therapies advanced for sex-related pain include fluconazole, cromolyn sodium, botulinum toxin injection, capsaicin, local anesthetics, desipramine, tricyclic, and novel antidepressants, anticonvulsants, montelukast, enoxaparin, monoclonal antibodies to tumor necrosis factor- α , sacral nerve stimulation, and combination therapies. The level of evidence supporting these interventions as empiric therapy is generally sparse (Kamdar et al, 2007; Koninckx et al, 2008; Bertolasi et al, 2009; Ramsay et al, 2009; Basson et al, 2010b).

Vulvar Dermatoses

Vulvar dermatoses are best managed with reassurance and routine hygiene. Antihistamines may be beneficial to break the cycle of warranted itching that exacerbates the condition of lichen simplex and contributes to other entities. Steroids should not be used empirically for the management of any sexual pain disorder without a diagnosis. Steroid therapy may be indicated in some specific cases; before treatment with steroids is initiated it is prudent to consider biopsy, particularly because there is a small but finite risk of malignant transformation in lichen sclerosus and LP (Salim and Wojnarowska, 2005).

Vulvovaginal Atrophy

Vaginal moisturizers are agents designed to restore baseline lubriciousness of the vagina. Such agents may be of use in addressing uncomfortable vaginal dryness and have been shown to enhance sexual pleasure for many women. It is important to note that such agents are not designed for use as sexual lubricants; they tend to dry out from friction during intercourse. There are numerous commercially available lubricants intended for use during sexual contact (see *Female Sexual Arousal Disorder*) (Herbenick et al, 2011a).

Systemic or local administration of estrogens has been linked to improvements in vaginal atrophy related to hypoestrogenism (North American Menopause Society, 2007). Local estrogen therapies need not be combined with progestins for endometrial protection when used at low doses (North American Menopause Society, 2013). A variety of estrogen preparations are available for local use; these may be administered as vaginal creams, suppositories, rings, pessaries, or tablets. Systemic absorption of vaginal estrogen preparations is generally very low (Weisberg et al, 2005; Simon et al, 2010; North American Menopause Society, 2013) and hence local therapy may be preferable for patients and providers who are concerned primarily with genital effects. Systemic estrogens may be of use in some women (Bachmann, 1995) but their use must be carefully considered in light of some controversy about long-term health risks (Utian et al, 2008; Jick et al, 2009).

Local and systemic androgens have also been investigated for the management of vaginal symptoms in women. Pilot studies have suggested improvements in symptoms of dyspareunia and vaginal pH after administration of local androgens with no changes in systemic T or E levels (Witherby et al, 2011). A meta-analysis of T therapy has confirmed a generalized benefit with respect to sexual function (arousal, lubrication, and pain) in women who received T supplementation, although safety data are limited (Somboonporn et al, 2005).

Intravaginal DHEA has also been used for treatment of dyspareunia related to vulvovaginal atrophy and has been shown to be superior to placebo for improvement in vaginal histology, pH, and pain with intercourse (Labrie et al, 2011). Further research on the

safety and efficacy profile of T and DHEA for vulvovaginal atrophy is warranted (Nappi and Davis, 2012).

Ospemifene is the first nonestrogen treatment approved by the FDA for the management of dyspareunia in postmenopausal women. Ospemifene is a SERM that includes estrogenic activity in bone and in the vaginal epithelium (Rutanen et al, 2003). Randomized controlled trials of oral ospemifene, 30 to 60 mg/day, have demonstrated superiority to placebo for improving vaginal histology, vaginal pH, and dyspareunia (Bachmann et al, 2010; Portman et al, 2013). The most common side effects of ospemifene are hot flashes, candidiasis, and urinary tract infection (Bachmann et al, 2010). In 1-year extension studies of ospemifene, continued benefits were noted with respect to dyspareunia. There was a low rate (0% to 1%) of endometrial proliferation; no carcinomas of the breast or endometrium were identified (Goldstein et al, 2013; Simon et al, 2013).

Musculoskeletal Dysfunction/Scarring

Pelvic floor physiotherapy is a treatment for pelvic/sexual pain related to musculoskeletal disorders. Directed massage, exercise, and pelvic floor biofeedback may durably ameliorate some forms of sexual pain (Rosenbaum, 2005; Bergeron et al, 2008). Progressive dilator therapy may be conducted in the office or at home for management of pain associated with penetration. The patient receives a set of progressively larger polymer dilators that can be inserted into the vagina. The size of the dilators inserted is increased gradually with the eventual goal of comfort with vaginal penetration. Compliance tends to be low without support and involvement from the provider (Rosenbaum, 2011).

Vaginal suppositories containing the benzodiazepine drug diazepam (10 mg) have been advocated by some experts for pelvic pain syndromes including dyspareunia. The FDA has not approved these medications for this indication, but several case reports have suggested efficacy as part of a multimodal treatment regimen (Rogalski et al, 2010). Muscle relaxants have also been used with the intent of decreasing somatic muscle contraction. These may be administered systemically or locally. Botulinum toxin may be effective as an injection for high-tone pelvic floor muscle dysfunction with vaginal spasm (Bertolasi et al, 2009; Goldstein et al, 2011; Nesbitt-Hawes et al, 2013).

Provoked/Neuroproliferative Vestibulodynia

Vulvar vestibulectomy is efficacious in the management of pain in the superficial external vulva related to neuroproliferation (Goldstein et al, 2006). A randomized study indicated superior results (based on intention to treat) of vestibulectomy compared to cognitive-behavioral therapy and biofeedback for dyspareunia (Bergeron et al, 2001). Benefits of treatment were maintained up to a follow-up of 2½ years post-treatment (Bergeron et al, 2008). Experienced and/or well-trained providers may offer vulvar vestibulectomy to patients who are carefully selected. **Patient selection is critical; this procedure should only be offered in the setting of neuroproliferative vestibulodynia affecting the vulvar vestibule** (Goldstein et al, 2006). Complete excision of all tissue between the Hart's line (junction between keratinized skin and mucosa) and the hymenal ring, with reapproximation of the vaginal mucosa to the vulvar skin, permits a satisfactory cosmetic result with removal of all affected tissue (Fig. 32-13 on the Expert Consult website) (Goldstein, 2006).

CONCLUSIONS

Female sexual function and dysfunction are important aspects of urologic practice. Urologists should be aware of the urologic ramifications of sexual issues and vice versa. Appropriate treatment (or referral) of women with sexual concerns will improve patient satisfaction and treatment compliance.



COMPLETE VESTIBULECTOMY REMOVING ALL VESTIBULAR TISSUE,
EVEN 1 TO 2 MM FROM THE URETHRAL MEATUS

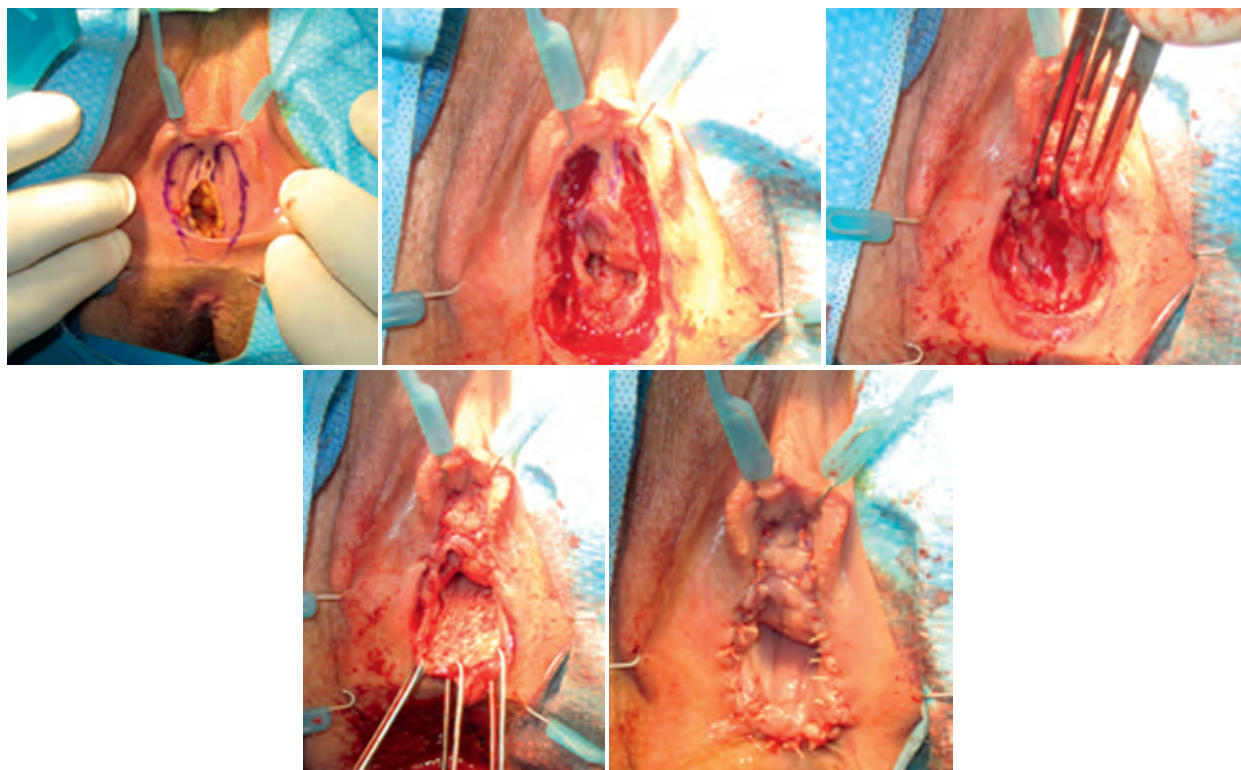


Figure 32-13. A complete vestibulectomy may be considered for neuroproliferative vestibulodynia. The tissue for excision is marked with a blue pen intraoperatively and involves (1) the right and left anterior vestibule bounded by the urethral meatus and Hart's line of the labia minora and (2) the posterior vestibule bounded by Hart's line, the tissue just inside the hymen, and the perineum. After the tissue has been excised, reconstruction of the posterior fourchette defect is fashioned with a vaginal advancement flap. It is critical to remove the entire vestibule as the neuroproliferative process is a field disease.

KEY POINTS: FEMALE SEXUAL CONCERNS

- The etiology of sexual concerns in women is often multifactorial.
- There is substantial overlap between sexual concerns in women.
- There are few approved pharmacotherapies for female sexual concerns; there are a number of treatments, but many of these are off label.
- A multidisciplinary approach to sexual concerns with sensitivity to the woman's unique situation is most likely to be effective.
- Psychosocial support is critical in the management of any sexual concern.

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The complete reference list is available online at www.expertconsult.com.

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33

Surgical, Radiographic, and Endoscopic Anatomy of the Retroperitoneum

Drew A. Palmer, MD, and Alireza Moinzadeh, MD

Body Surface Landmarks

Posterior Abdominal Wall

Lumbodorsal Fascia

Retroperitoneal Fasciae and Spaces

Gastrointestinal Viscera

Vasculature

Lymphatic System

Nervous Structures

To the astute urologist, anatomic knowledge of the retroperitoneum is critical for success. This chapter provides a thorough description of retroperitoneal anatomy, including the genitourinary organs, musculature, bony structures, fasciae, vessels, lymphatics, neural structures, and gastrointestinal viscera. See [Table 33-1](#) on the Expert Consult website for a review of the anatomic and surgical history of the retroperitoneum.

The retroperitoneum can be described as the entirety of the structures contained anteriorly by the posterior reflection of the peritoneum, posteriorly by the abdominal wall, cranially by the diaphragm, and caudally by the extraperitoneal pelvic structures ([Fig. 33-1](#)). The last term must be distinguished from *extraperitoneal space*, which includes the retroperitoneum and the space that circumferentially surrounds the abdominal cavity ([Miralis and Skandalakis, 2009, 2010a, 2010b, 2010c, 2010d](#)).

The contents of the retroperitoneum include the **kidneys, ureters, adrenals, pancreas, portions of the duodenum, ascending colon, descending colon, arterial structures including the aorta and its branches, venous structures including the inferior vena cava (IVC) and its tributaries, lymphatics, lymph nodes, sympathetic trunk, and lumbosacral plexus** ([Fig. 33-2](#) on the Expert Consult website and [Box 33-1](#); also see [Fig. 33-1](#)).

BODY SURFACE LANDMARKS

The ability to identify abdominal organs using physical examination has great utility for clinical diagnosis and operative planning. The location of the kidneys can be estimated based on their relationship to the bony structures of the posterior abdominal wall ([Fig. 33-3](#)). The upper pole of the left kidney is typically located at the level of the 11th rib. The right kidney lies lower than the left, with its upper pole at the level of the 12th rib. The lower poles of the kidneys are between the L3 and L4 vertebrae, and the **renal hila** are approximately at the level of L1.

POSTERIOR ABDOMINAL WALL

Flank Muscles ([Figs. 33-4 to 33-7](#) and [Table 33-2](#))

The most superficial of the flank muscles is the **external oblique**, which lies beneath the subcutaneous fascia. It originates from ribs

5 through 12, and its muscle fibers travel inferomedially inserting at the iliac crest and ending in the midline at the linea alba. **The inferior border of the aponeurosis of the external oblique forms the inguinal ligament.** Deep to the external oblique lies the **internal oblique**, which originates from the lumbodorsal fascia and the

BOX 33-1 Organs and Structures of the Retroperitoneum

ORGANS

Kidneys (PR)
Ureters (PR)
Adrenal glands (PR)
Portions of the duodenum (SR)
Ascending colon (SR)
Descending colon (SR)
Pancreas (SR)

VESSELS

Abdominal aorta (and its branches)
Inferior vena cava (and its tributaries)
Ascending lumbar veins
Portal vein
Lumbar lymph nodes
Lumbar lymphatic trunks
Cisterna chyli

NERVES

Branches of the lumbosacral plexus
Sympathetic trunk
Autonomic plexuses
Autonomic ganglia

PR, primarily retroperitoneal; SR, secondarily retroperitoneal.

Modified from Miralis P, Skandalakis JE. Surgical anatomy of the retroperitoneal spaces—part I: embryogenesis and anatomy. *Am Surg* 2009;75(11):1091–7.

TABLE 33-1 Anatomic and Surgical History of the Retroperitoneum

Morgagni	1761	Described retroperitoneal lipoma found at autopsy
Cloquet	1817	Studied perirenal fascia
Bogros	1823	Studied surgical anatomy of iliac area
Lobstein	1829	First use of term <i>retroperitoneal tumor</i>
Broca	1850	Discovered retroperitoneal tumors at autopsy
Moynier	1850	Discovered retroperitoneal tumors at autopsy
Treitz	1853	Stated theory of “absorption”; described retroduodenopancreatic fascia
Dickinson	1871	Described teratomatous tumor similar to dermoid teratomas commonly found in the ovary
Toldt	1879, 1893	Theory of conjoined visceral fasciae
Zuckerkindl	1883	Described posterior renal fascia
Bassini	1889	Described retroperitoneal cystadenoma that resembled pseudomucinous cystadenoma of ovary
Rogie	1894	Described retroperitoneal anatomy
Gerota	1895	Described anterior renal fascia
Poirer et al	1923	Studied lobulation of adipose tissue in pararenal and perirenal areas
Drouet	1941	Studied subperitoneal area
Baumann	1945	Described embryology of renal area
Altmeir and Alexander	1961	Described extraperitoneal compartments above pelvic brim
Stevenson and Ozeran	1969	Subdivided anatomy of extraperitoneal pelvis into posterior, anterior, inferior, and superior spaces
Meyers et al	1972	Descriptions of anterior and posterior pararenal and perirenal spaces
Wickham	1979	Operated in a pneumoretroperitoneum for endoscopic removal of ureteric stone
Hureau et al	1990, 1991	CT study of extraperitoneal spaces
Korobkin et al	1992	Used CT to study anatomy and fluid collections in retroperitoneal space
Gaur	1992	Performed retroperitoneal videoscopic renal surgery
McDougall et al	1994	Performed retroperitoneal videoscopic renal surgery

CT, computed tomography.

Modified from Skandalakis JE, Colborn GL. Skandalakis' surgical anatomy: the embryological and anatomic basis of modern surgery. Athens, Greece: Paschalides Medical Publications; 2004.



Figure 33-2. A, Dissected retroperitoneum. The anterior perirenal (Gerota) fascia has been removed. B, 1, Diaphragm. 2, Inferior vena cava. 3, Right adrenal gland. 4, Upper pointer, celiac artery; lower pointer, lower pointer, right gonadal artery. 5, Right kidney. 6, Pararenal retroperitoneal fat. 7, Gerota fascia. 8, Pararenal retroperitoneal fat. 9, Perinephric fat. 10, Upper pointer, right gonadal vein; lower pointer, right gonadal artery. 11, Lumbar lymph nodes. 12, Retroperitoneal fat. 13, Right common iliac artery. 14, Right ureter. 15, Sigmoid colon (cut). 16, Esophagus (cut). 17, Right crus of diaphragm. 18, Left inferior phrenic artery. 19, Upper pointer, left adrenal gland; lower pointer, left adrenal vein. 20, Upper pointer, superior mesenteric artery; lower pointer, left renal artery. 21, Left kidney. 22, Upper pointer, left renal vein; lower pointer, left gonadal vein. 23, Aorta. 24, Perinephric fat. 25, Aortic autonomic nervous plexus. 26, Upper pointer, Gerota fascia; lower pointer, inferior mesenteric ganglion. 27, Inferior mesenteric artery. 28, Aortic bifurcation into common iliac arteries. 29, Left gonadal artery and vein. 30, Left ureter. 31, Psoas major muscle covered by psoas sheath. 32, Cut edge of peritoneum. 33, Pelvic cavity. (Reproduced from the Bassett anatomic collection, with permission from Dr. Robert A. Chase.)



Figure 33-2, cont'd. C, Dissected retroperitoneum. The kidneys and adrenal glands have been sectioned, and the inferior vena cava has been excised over most of its intra-abdominal course. **D,** 1, Inferior vena cava (cut). 2, Diaphragm. 3, Right inferior phrenic artery. 4, Right adrenal gland. 5, Upper pointer, celiac artery; lower pointer, superior mesenteric artery. 6, Right kidney. 7, Upper pointer, right renal artery; lower pointer, right renal vein (cut). 8, Lumbar lymph node. 9, Transversus abdominis muscle covered with transversalis fascia. 10, Right ureter. 11, Anterior spinous ligament. 12, Inferior vena cava (cut). 13, Right common iliac artery. 14, Sigmoid colon (cut). 15, Right external iliac artery. 16, Esophagus (cut). 17, Left adrenal gland. 18, Celiac ganglion. 19, Left kidney. 20, Upper pointer, left renal artery; lower pointer, left renal vein (cut). 21, Left renal pelvis. 22, Aorta. 23, Aortic autonomic nervous plexus. 24, Inferior mesenteric ganglion. 25, Left ureter. 26, Inferior mesenteric artery. 27, Psoas major muscle covered by psoas sheath. (Reproduced from the Bassett anatomic collection, with permission from Dr. Robert A. Chase.)

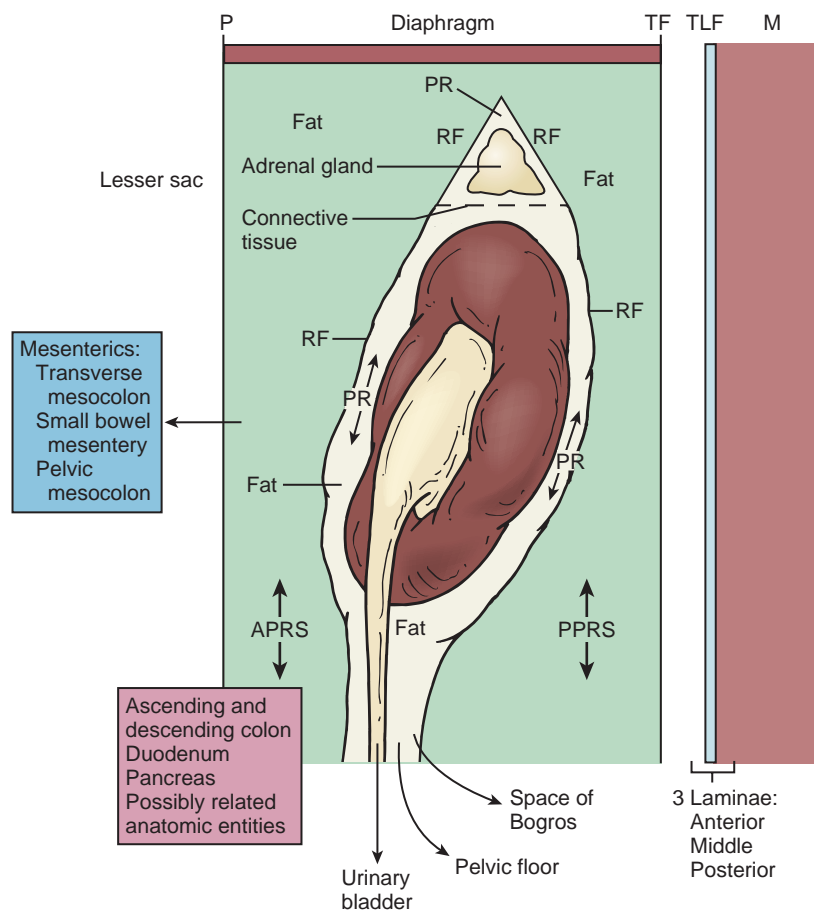


Figure 33-1. Diagram of retroperitoneal spaces. APRS, anterior pararenal space; M, muscles; P, peritoneum; PPRS, posterior pararenal space; PR, perirenal space; RF, renal fascia (Gerota fascia); TF, transversalis fascia; TLF, thoracolumbar fascia. (Modified from Skandalakis JE, Colborn GL. Skandalakis' surgical anatomy: the embryological and anatomic basis of modern surgery. Athens, Greece: Paschalides Medical Publications; 2004. p. 155.)

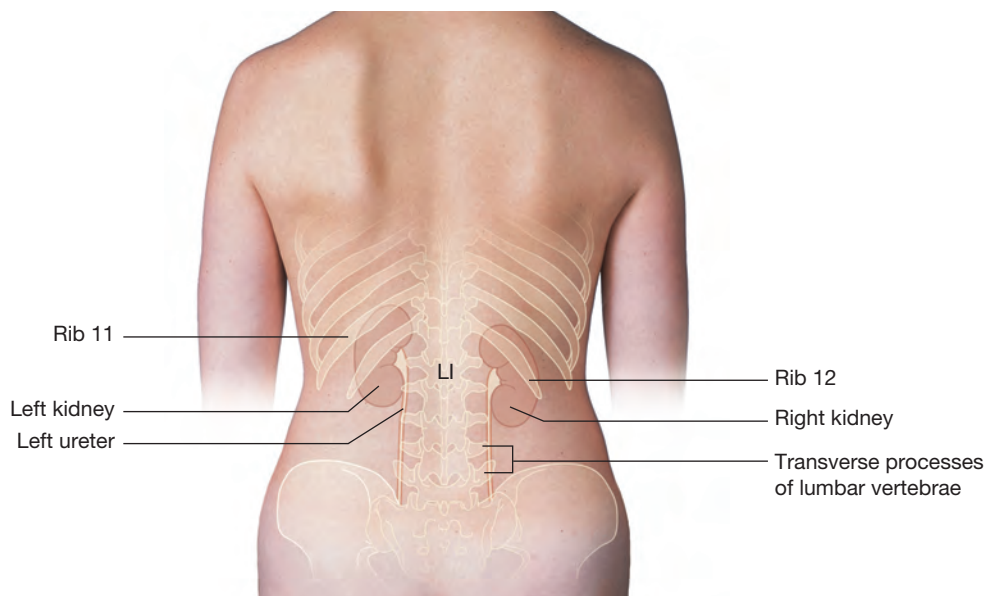


Figure 33-3. Posterior view of the abdominal region of a woman with projections of the kidneys and ureters. (From Drake RL, Vogl AW, Mitchell AWM. Gray's anatomy for students. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

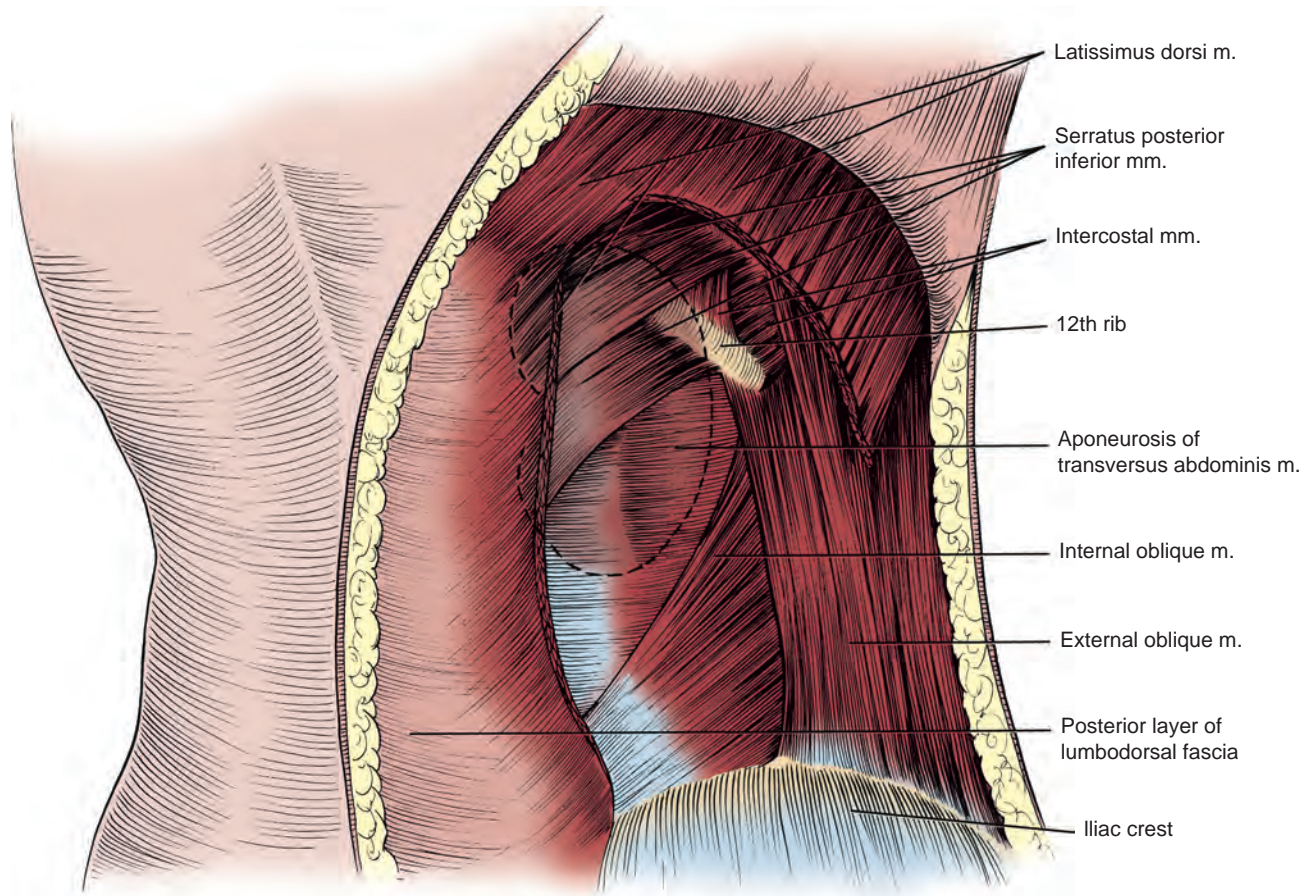


Figure 33-4. Posterior abdominal wall musculature, superficial dissection. A section of the latissimus dorsi muscle has been removed. The location of the right kidney within the retroperitoneum is shown by the *dashed outline*.

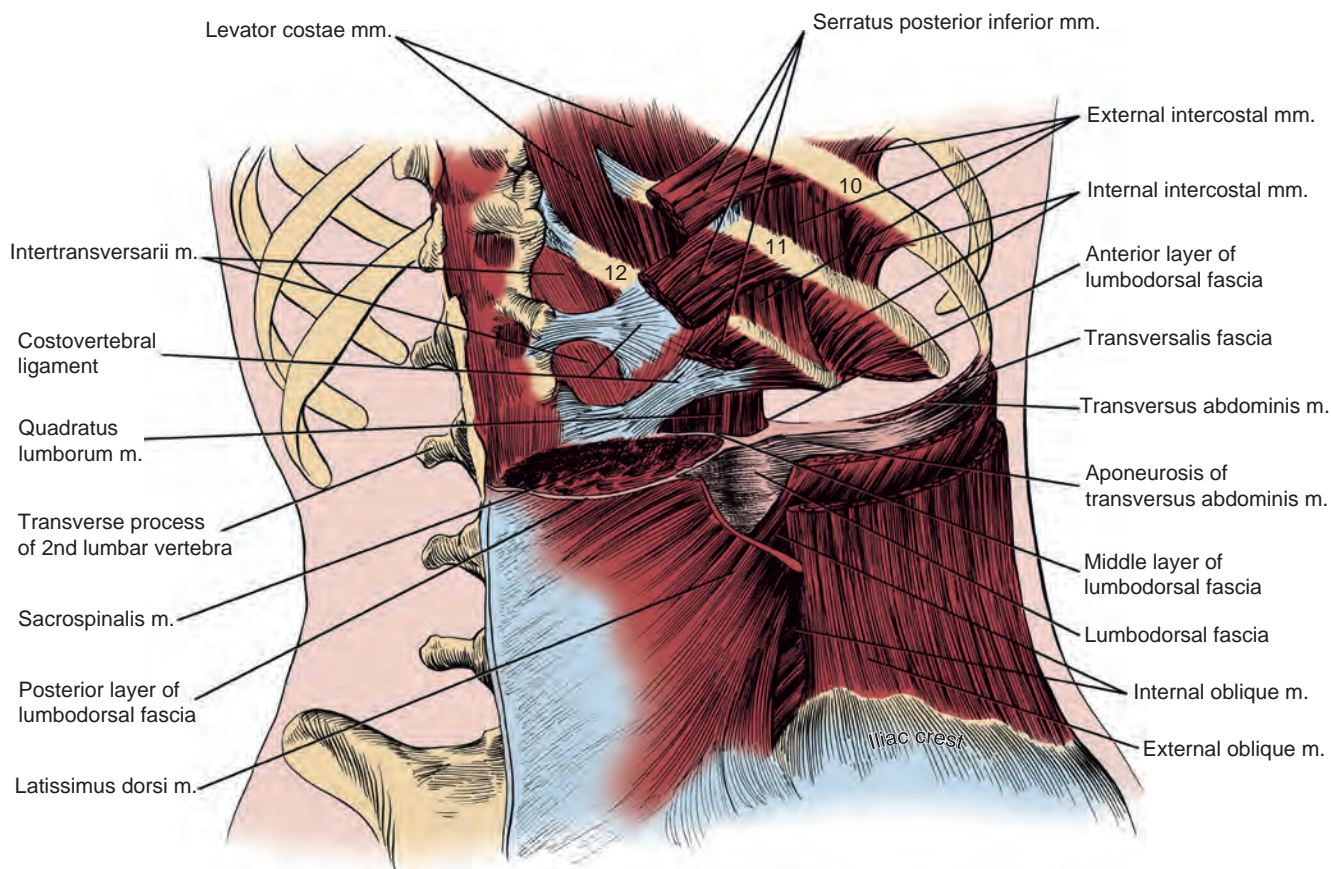


Figure 33-5. Posterior abdominal wall musculature, intermediate dissection. The sacrospinalis muscle and three anterolateral flank muscle layers are seen in cut section, and the three layers of the lumbodorsal fascia posteriorly can be appreciated.

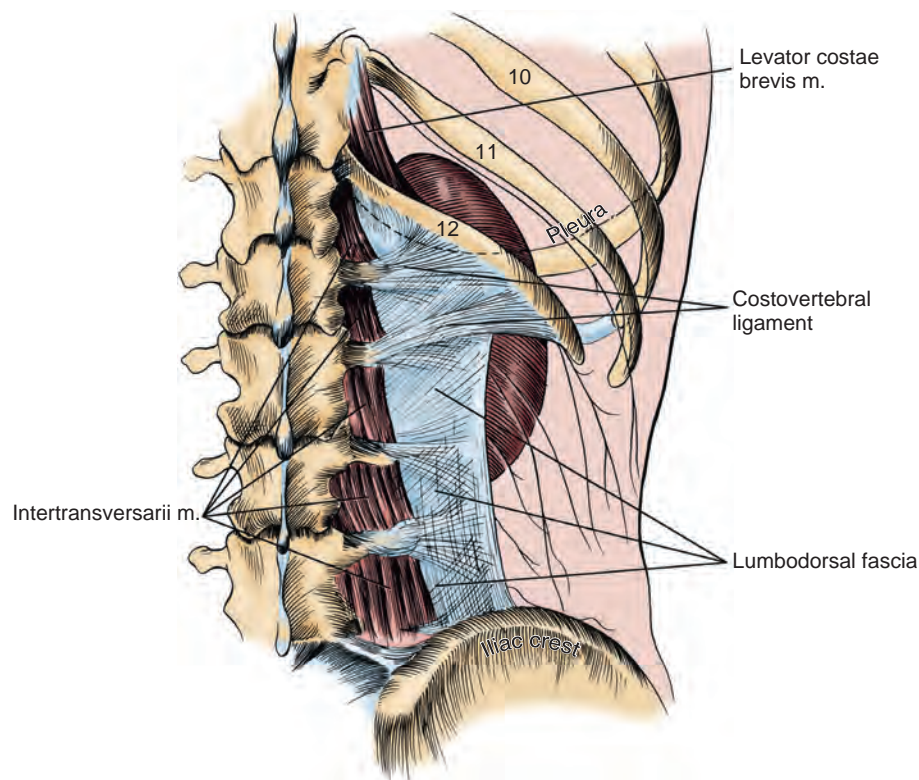


Figure 33-6. Posterior abdominal wall musculature, deep dissection. The lumbodorsal fascia and costovertebral ligament are visualized arising from the transverse processes of the lumbar vertebrae. The relationship of the kidney and pleura is also shown.

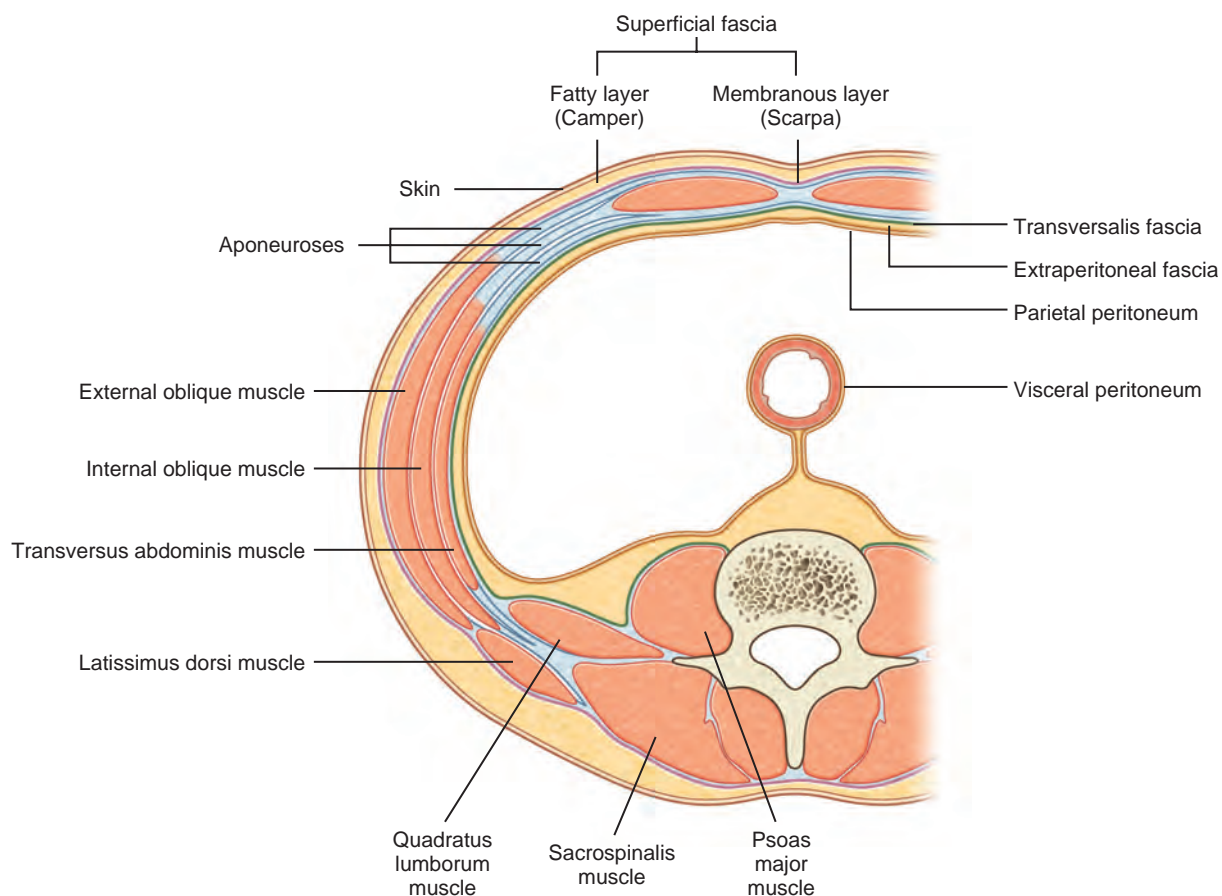


Figure 33-7. Transverse section showing layers of the lateral flank musculature. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

TABLE 33-2 Musculature of the Posterior and Lateral Abdominal Wall

MUSCLE	ORIGIN	INSERTION	FUNCTION
Erector spinae	Sacrum and vertebrae	Lower ribs and vertebrae	Extension of spine
External oblique	Ribs 5-12	Lateral lip of iliac crest, aponeurosis ending in linea alba	Compress abdominal contents, flexion of trunk
Internal oblique	Lumbodorsal fascia, iliac crest, inguinal ligament	Lower four ribs, aponeurosis ending in linea alba, pubic crest	Compress abdominal contents, flexion of trunk
Transversus abdominis	Lumbodorsal fascia, medial lip of iliac crest, ribs 7-12	Aponeurosis ending in linea alba, pubic crest	Compress abdominal contents
Psoas major	T12-L5 vertebrae	Lesser trochanter of femur	Flexion of hip
Psoas minor	T12 and L1 vertebrae	Pelvic brim, iliopubic eminence	Weak flexion of lumbar vertebral column
Iliacus	Iliac fossa, sacrum	Lesser trochanter of femur	Flexion of the hip
Quadratus lumborum	5th lumbar vertebra, iliac crest	L1-L4 vertebrae, 12th rib	Depress and stabilize 12th rib, lateral bending of trunk

Modified from Drake RL, Vogl AW, Mitchell AWM. Gray's anatomy for students. Philadelphia: Churchill Livingstone; 2005.

iliac crest. It travels superomedially inserting at the lower ribs and linea alba. Each of these muscle layers is invested in a layer of fascia. The **transversus abdominis** muscle, named because of the *transverse* direction of its muscle fibers, lies deep to the internal oblique. Deep to the transversus abdominis muscle lies the **transversalis fascia**, which crosses the midline anteriorly and fuses with the lumbodorsal fascia posteriorly. These flank muscles function to flex, extend, and rotate the trunk and provide compression of the abdominal contents.

Psoas, Iliacus, Quadratus Lumborum, and Erector Spinae (Fig. 33-8; also see Figs. 33-4 to 33-7 and Table 33-2)

The **psoas major** muscle arises from the 12th thoracic vertebra to the 5th lumbar vertebra to attach to the lesser trochanter of the femur after traveling along the pelvic brim posterior to the inguinal ligament. The psoas minor muscle, which may be absent in some individuals, originates at T12 and L1 and inserts at the pelvic brim and iliopubic eminence. The psoas major functions in flexion of the thigh at the hip joint and is innervated by the anterior rami of L1, L2, and L3. The **iliacus** muscle originates at the caudal aspect of the iliac fossa and the lateral sacrum to insert at the lesser trochanter of the femur. It functions in flexion of the thigh at the hip joint along with the psoas major. The **quadratus lumborum** lies posterior and medial to the psoas muscle and assists with lateral bending of the trunk and stabilization of the 12th rib. Its origin is at L5 and the iliac fossa, and it attaches to the inferior border of the 12th rib and the transverse processes of L1-L4. The **erector spinae (sacrospinalis)** is a large group of back muscles that function to extend the spine.

Spine

The spine consists of 7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, the sacrum, and the coccyx. Each vertebra has a large weight-bearing area called the **vertebral body** and a posterior and lateral arch that forms the vertebral foramen (Fig. 33-9 on the Expert Consult website). The **spinous process** projects posteroinferiorly, and the **transverse processes** project posterolaterally. The lumbar vertebrae are the most clinically significant in regard to the retroperitoneum. They are larger than the other vertebrae with generally long, thin transverse processes.

The vertebral column levels have different relationships with the spinal cord segmental levels at different locations within the

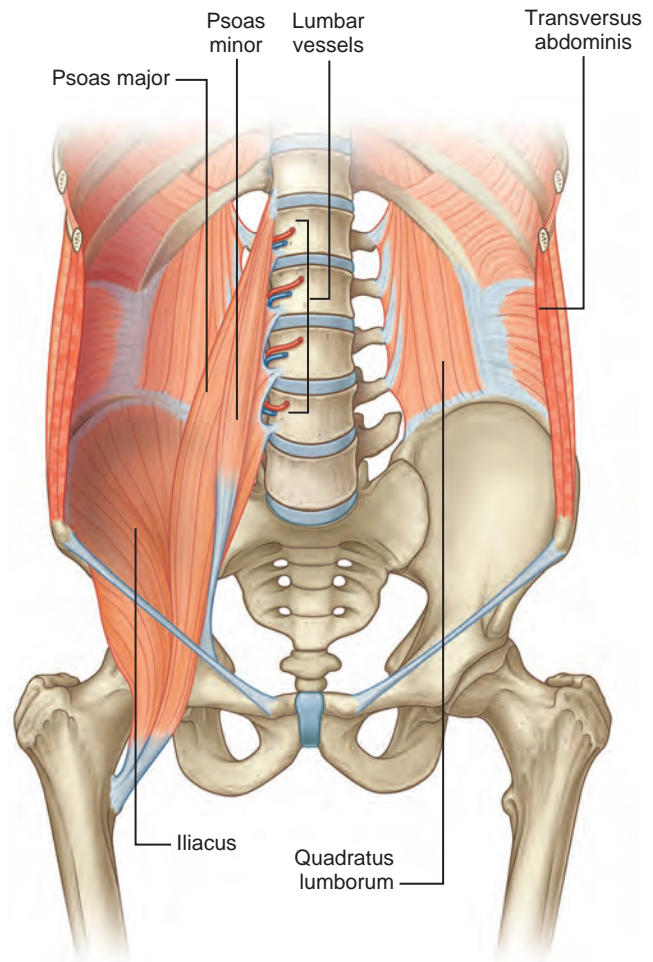


Figure 33-8. Muscles of the posterior abdominal wall. (From Drake RL, Vogl AW, Mitchell AWM. Gray's anatomy for students. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

spinal column. For example, the sacral spinal cord segmental levels typically begin between vertebral column level T12 and L1 in adults. When discussing spinal cord injury, one must be careful to specify vertebral column level versus spinal segmental level.

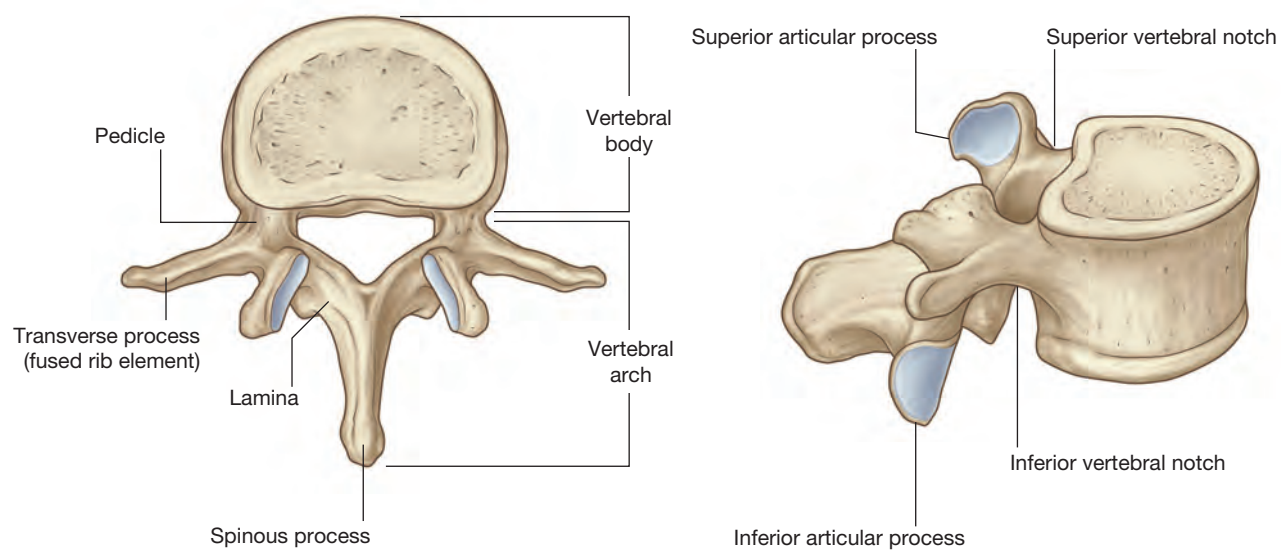


Figure 33-9. Typical vertebrae. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

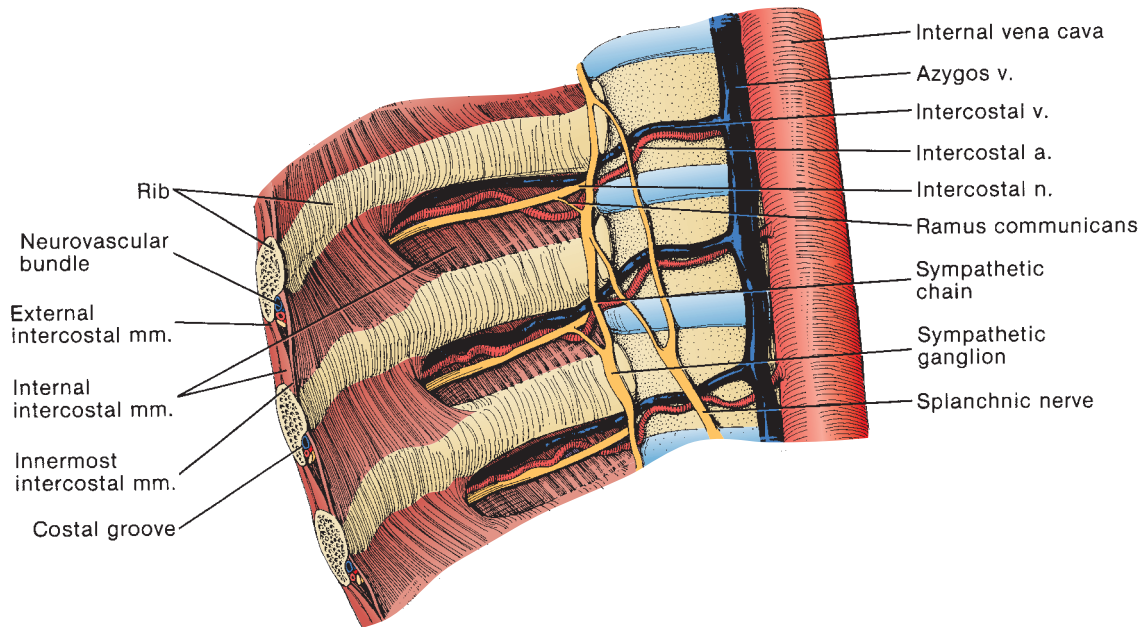


Figure 33-11. Intercostal neurovascular bundle. (From MacLennan GT. *Hinman's atlas of uro-surgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

10th, 11th, and 12th Ribs

The lower ribs function to protect the retroperitoneal structures from traumatic injury. Fracture of these lower ribs should lead to a high clinical suspicion for injury to the retroperitoneal structures (Fig. 33-10 on the Expert Consult website). The lower ribs differ from the upper ribs given their shorter length with less pronounced angulation. The 10th rib articulates with the body of the vertebra at its head and the transverse process at its neck. The 11th rib lacks a neck and does not articulate with the transverse process. The angle of the 11th rib is less pronounced than that of the upper ribs. The 12th rib has no angle and is shorter than the other ribs. Its inferior border is attached to the transverse processes of L1 and L2 by the costovertebral (lumbocostal) ligament, which can be incised to allow for increased mobility for greater exposure of the upper retroperitoneum during posterior approaches. Similar increased mobility may be achieved by dividing a thick fibrous band known as the intercostal ligament found between other ribs.

The 11th and 12th ribs must be distinguished from the other ribs because they have no anterior connection with the sternum and are often referred to as *floating ribs*. These ribs are of clinical significance during palpation for the marking of a surgical incision.

The intercostal vessels and nerves travel between the internal intercostal and innermost intercostal muscles within the costal groove on the caudal margin of the superior rib (Fig. 33-11). The vein is the most superior structure with the artery running inferior to it. The intercostal nerve is the most inferior of the three structures and is often not protected by the costal groove.

LUMBODORSAL FASCIA

The lumbodorsal (thoracolumbar) fascia is composed of three distinct layers that invest the posterior abdominal wall musculature (Fig. 33-12). These three layers merge into one as they travel laterally. A common access point to the retroperitoneum is near the tip of the 12th rib, where all layers have merged into one. This single layer of lumbodorsal fascia merges with the aponeurosis of the transversus abdominis muscle anterolaterally. The **posterior lamella** originates medially from the spinous process of the lumbar vertebrae and covers the erector spinae muscles. The **middle lamella**

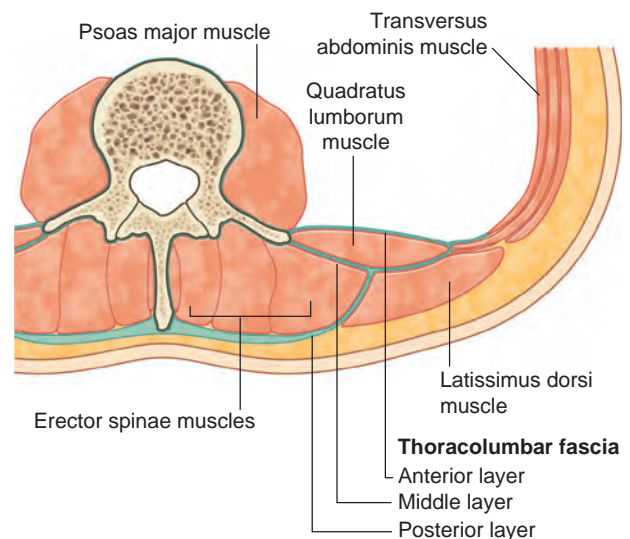


Figure 33-12. Lumbodorsal fascia and the deep back muscle. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

separates these erector spinae muscles from quadratus lumborum. The anterior lamella covers the ventral surface of quadratus lumborum. Extending medially, the **anterior lamella** attaches to the vertebral transverse process and is continuous with the fascia that invests the psoas muscle.

The retroperitoneum can be entered without incising muscle using a dorsal lumbotomy incision (Fig. 33-13). This approach uses a vertical incision through the lumbodorsal fascia lateral to the erector spinae and quadratus lumborum muscles (Fig. 33-14 on the Expert Consult website).

RETROPERITONEAL FASCIAE AND SPACES

Derived from the mesoderm, the primitive mesenchyme differentiates to form a subcutaneous layer, body layer, and retroperitoneal

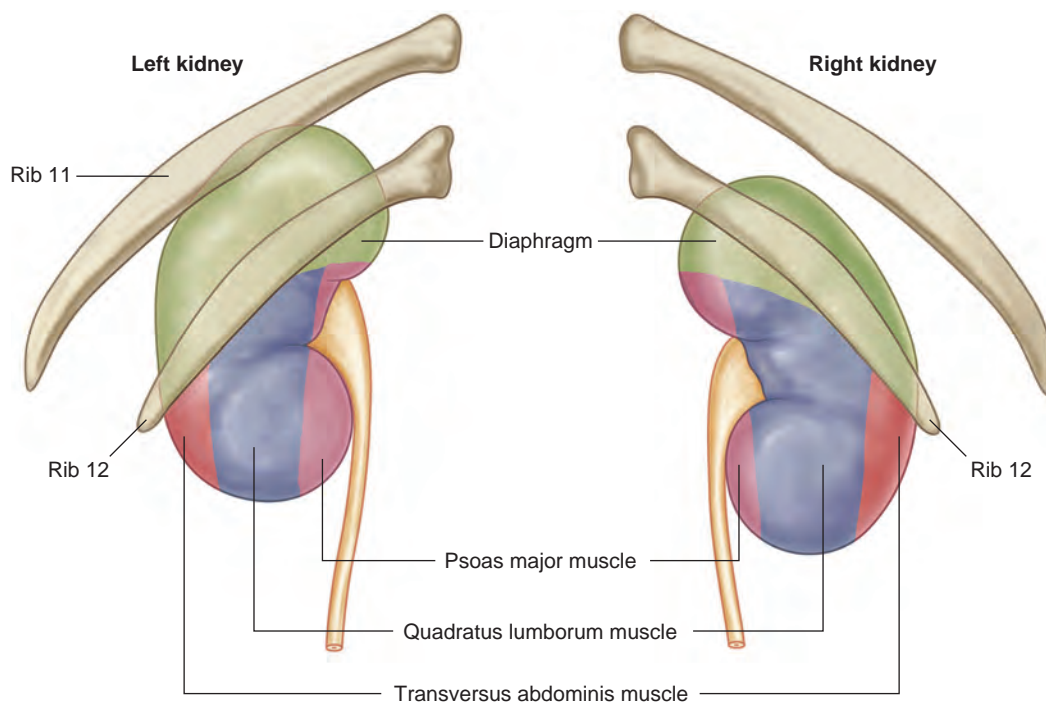


Figure 33-10. Structures related to the posterior surface of the kidney. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

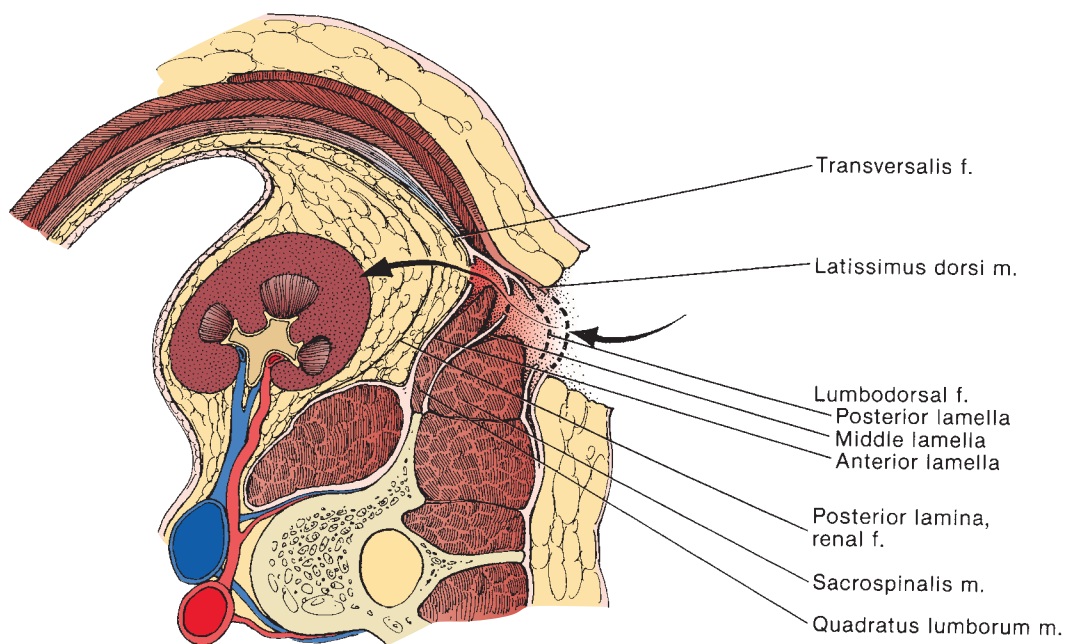


Figure 33-14. Posterior approach to the kidney through the lumbodorsal fascia. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

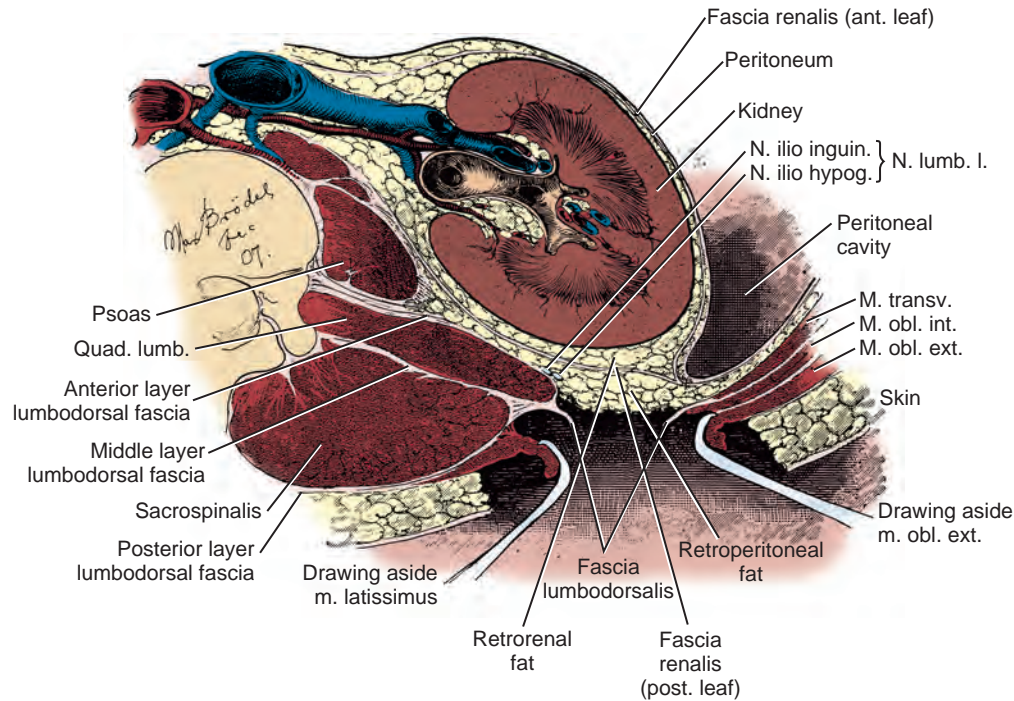


Figure 33-13. Transverse section through the kidney and posterior abdominal wall showing the lumbodorsal fascia incised. Through such a lumbodorsal incision, the kidney can be reached without incising muscle. (After Kelly and Burnam, from McVay C. Anson & McVay surgical anatomy. 6th ed. Philadelphia: Saunders; 1984.)

layer. The retroperitoneal layer forms three strata in late fetal development: the outer stratum, intermediate stratum, and inner stratum (Fig. 33-15 on the Expert Consult website). Historically, the retroperitoneum has been divided embryologically based on these three strata (Tobin, 1944). The **outer stratum** covers the epimysium of the abdominal wall muscles and becomes the transversalis fascia. The **intermediate stratum** is associated with the urinary organs, and the **inner stratum** is associated with the gastrointestinal organs (MacLennan, 2012). The aim is not to have the reader memorize what each embryologic stratum becomes during development. Rather, these embryologic strata serve to categorize the retroperitoneal fasciae, which compartmentalize various spaces within the retroperitoneum.

Transversalis Fascia and Posterior Pararenal Space

The outer stratum forms the **transversalis fascia**, which lies deep to the transversus abdominis muscle and superficial to the preperitoneal fat and peritoneum. Posterior to the kidney, the transversalis fascia remains anterior to the fascia surrounding the quadratus lumborum and psoas muscle (Fig. 33-16). It may fuse medially with the posterior lamina of Gerota fascia, which is of clinical significance during retroperitoneal dissection because this fascia must be incised to allow access to the renal hilum. This fusion creates the medial boundary of the posterior pararenal space. The anterior boundary is formed by the posterior lamina of Gerota fascia, and the posterior and lateral boundaries are formed by the transversalis fascia (Tobin, 1944).

Gerota Fascia (Renal Fascia) and Perirenal Space (Figs. 33-17 and 33-18; also see Fig. 33-16)

The anterior lamina (fascia of Toldt or prerenal fascia) and the posterior lamina (fascia of Zuckerkandl or retrorenal fascia) of the renal fascia are derived from the intermediate stratum, which embeds the genitourinary organs. They help to form the boundaries of the retroperitoneal spaces: the posterior pararenal space,

perirenal space, and anterior pararenal space. The two laminae together form the **renal fascia**, eponymously named *Gerota fascia*, after the Romanian anatomist Dimitrie D. Gerota (1867-1939). The **perirenal space** contains the adrenal, kidney, ureter, perirenal fat, renal vascular pedicle, and gonadal vessels. The perirenal fat is finer and lighter yellow in color compared with the coarser yellow-orange pararenal fat. The anatomy of the adrenal, kidney, and ureter is discussed in detail in their respective chapters.

The posterior lamina of Gerota fascia is thicker and more frequently visualized radiographically than the anterior lamina. These two layers merge laterally to form the **lateroconal fascia**, which separates the anterior and posterior pararenal spaces and continues anterolaterally deep to the transversalis fascia. There is some controversy regarding the medial and inferior extents of the perirenal space. Historically, it was assumed that there was no communication between the right and left perirenal spaces. However, based on in vivo cases and cadaveric injection studies, **there may be some communication across the midline below the level of the renal hilum** (Lim et al, 1998).

In addition, there has been no consensus on the patency and caudal extent of the perirenal space. Previously, it was suggested that the perirenal space is closed inferiorly by the fusion of Gerota fascia. However, in vivo cases and cadaveric injection studies demonstrated that the **perirenal space has a conelike shape that is open at its inferior extent in the extraperitoneal pelvis** (Lim et al, 1998). These boundaries are of tremendous clinical significance in the pathology of urologic disease because they function to contain perinephric fluid collections, which include urine (traumatic or iatrogenic urinary extravasation, obstructive uropathy with calyceal rupture), blood (traumatic or iatrogenic perinephric hematoma, ruptured aneurysm), or purulence (perinephric abscess or infected urinoma).

Anterior Pararenal Space and Inner Stratum

The **anterior pararenal space** is formed by the anterior lamina of the renal fascia posteriorly and the posterior layer of parietal peritoneum anteriorly (Fig. 33-19 on the Expert Consult website).

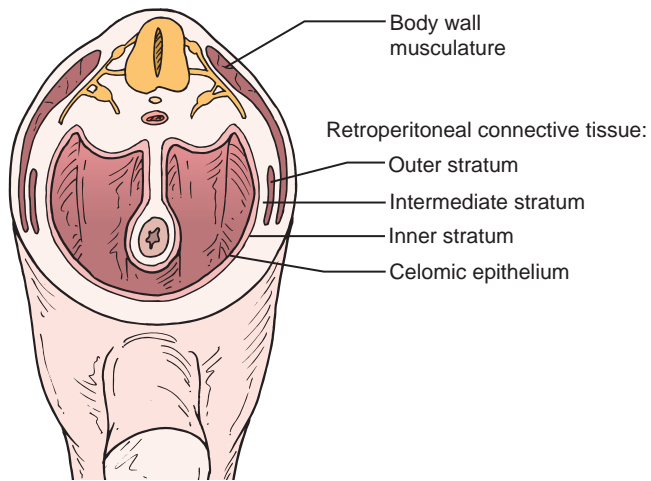


Figure 33-15. Retroperitoneal fascial development at 5 weeks. (Modified from Skandalakis JE, Colborn GL. *Skandalakis' surgical anatomy: the embryological and anatomic basis of modern surgery*. Athens, Greece: Paschalides Medical Publications; 2004.)

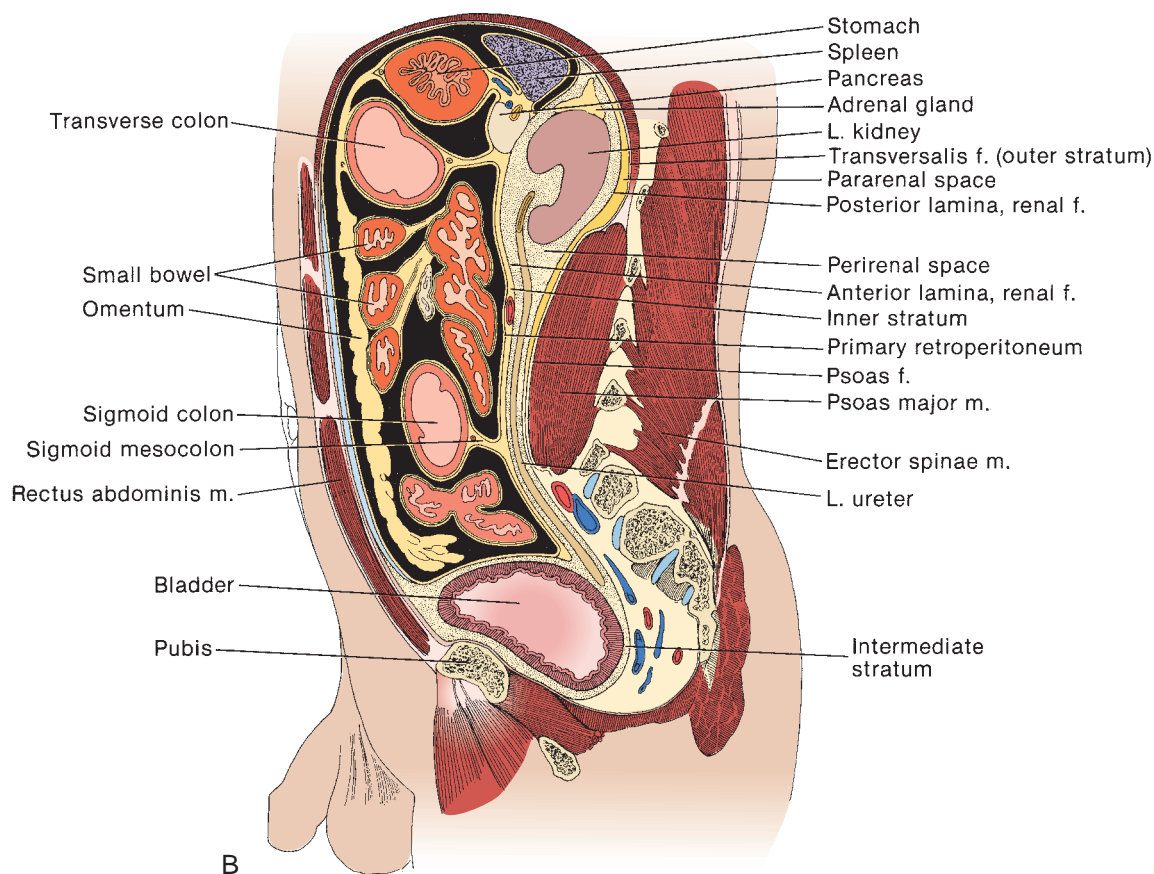
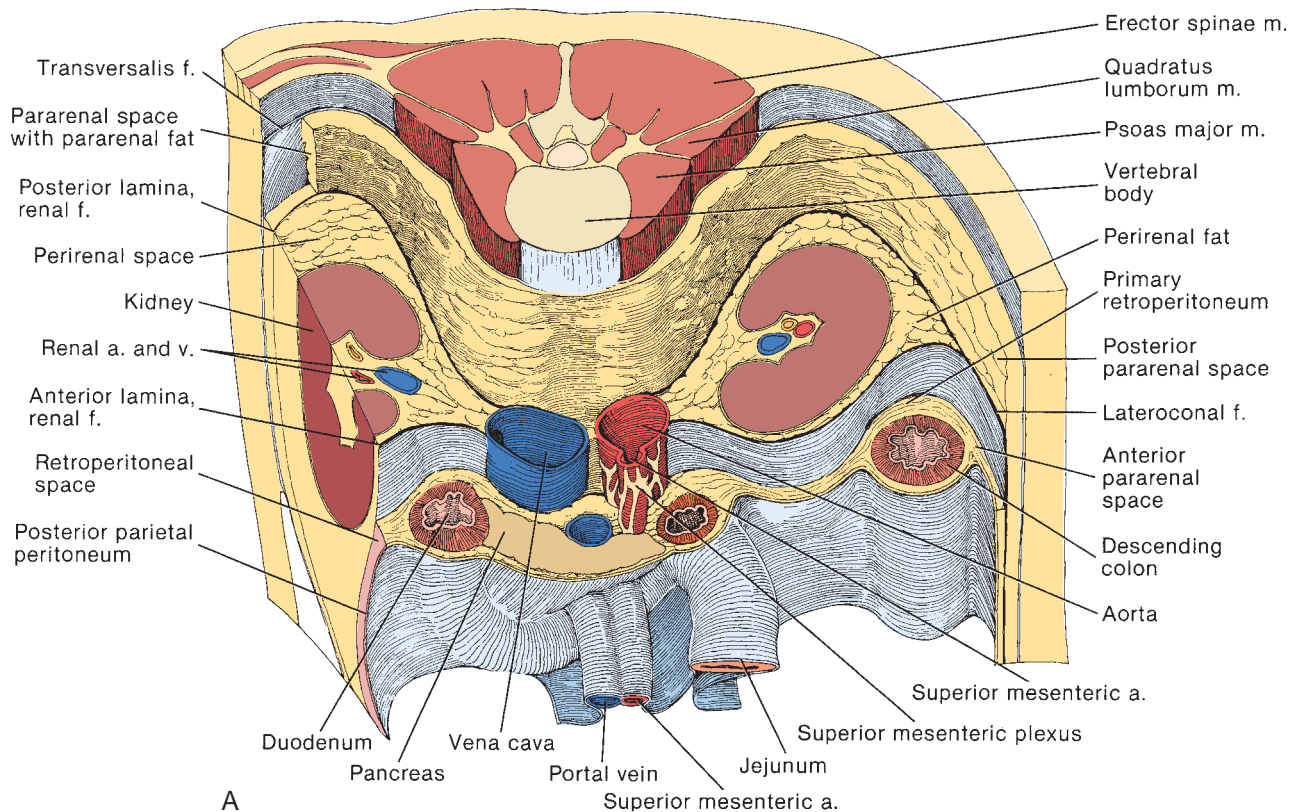


Figure 33-19. Retroperitoneal spaces. A, Transverse-oblique view. B, Sagittal view. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

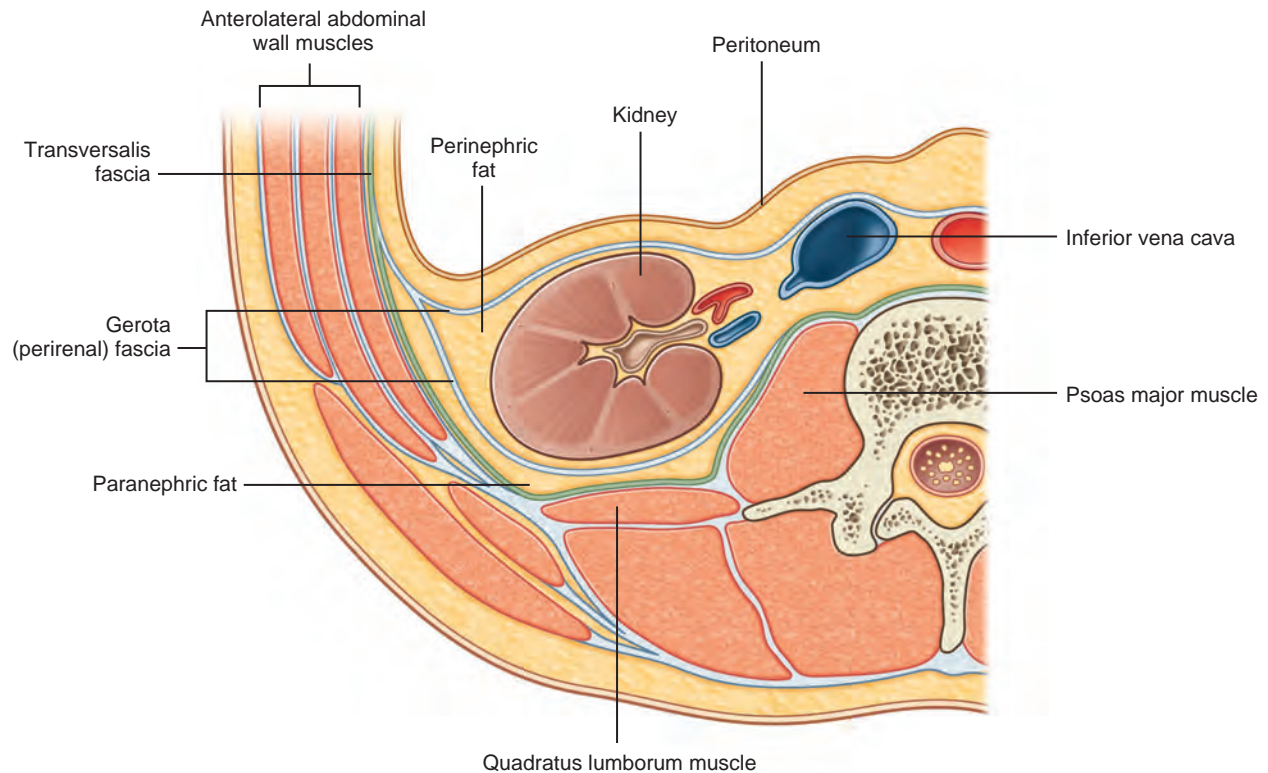


Figure 33-16. Organization of the fasciae and fat surrounding the kidney. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

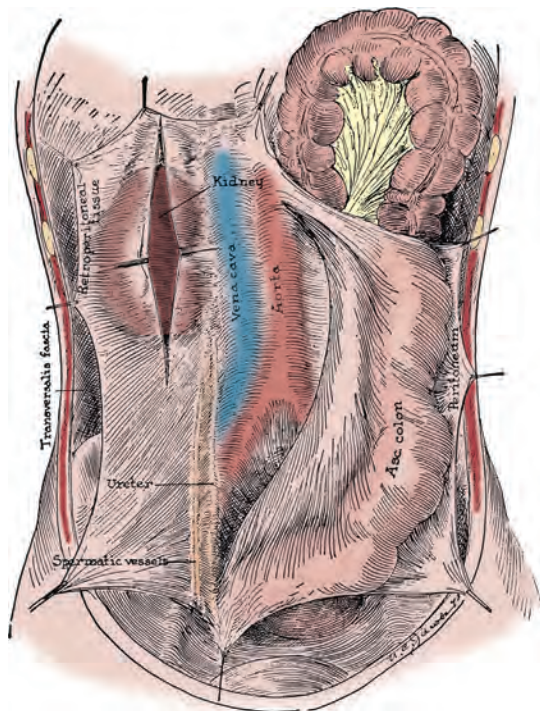


Figure 33-17. Anterior view of Gerota fascia on the right side, split over the right kidney (which it contains) and showing inferior extension enveloping the ureter and gonadal vessels. The ascending colon and overlying peritoneum have been reflected medially. (From Tobin CE. The renal fascia and its relation to the transversalis fascia. *Anat Rec* 1944;89:295–311.)

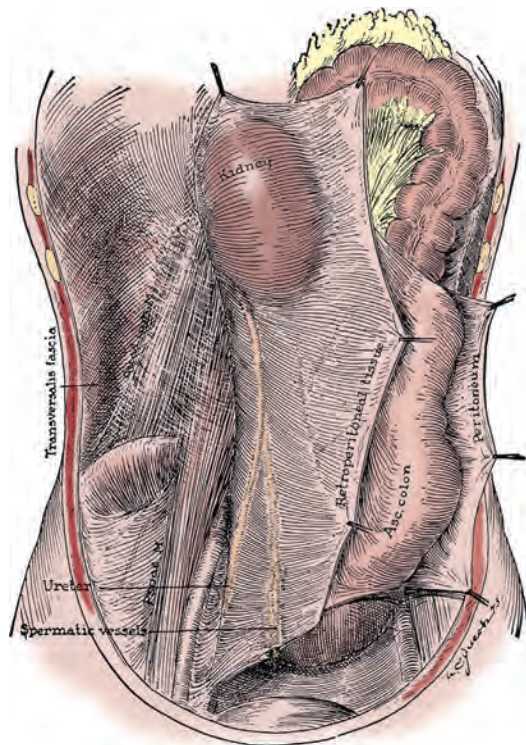


Figure 33-18. Posterior view of Gerota fascia on the right side, rotated medially with the contained kidney, ureter, and gonadal vessels, exposing the muscular posterior body wall covered by the transversalis fascia. (From Tobin CE. The renal fascia and its relation to the transversalis fascia. *Anat Rec* 1944;89:295–311.)

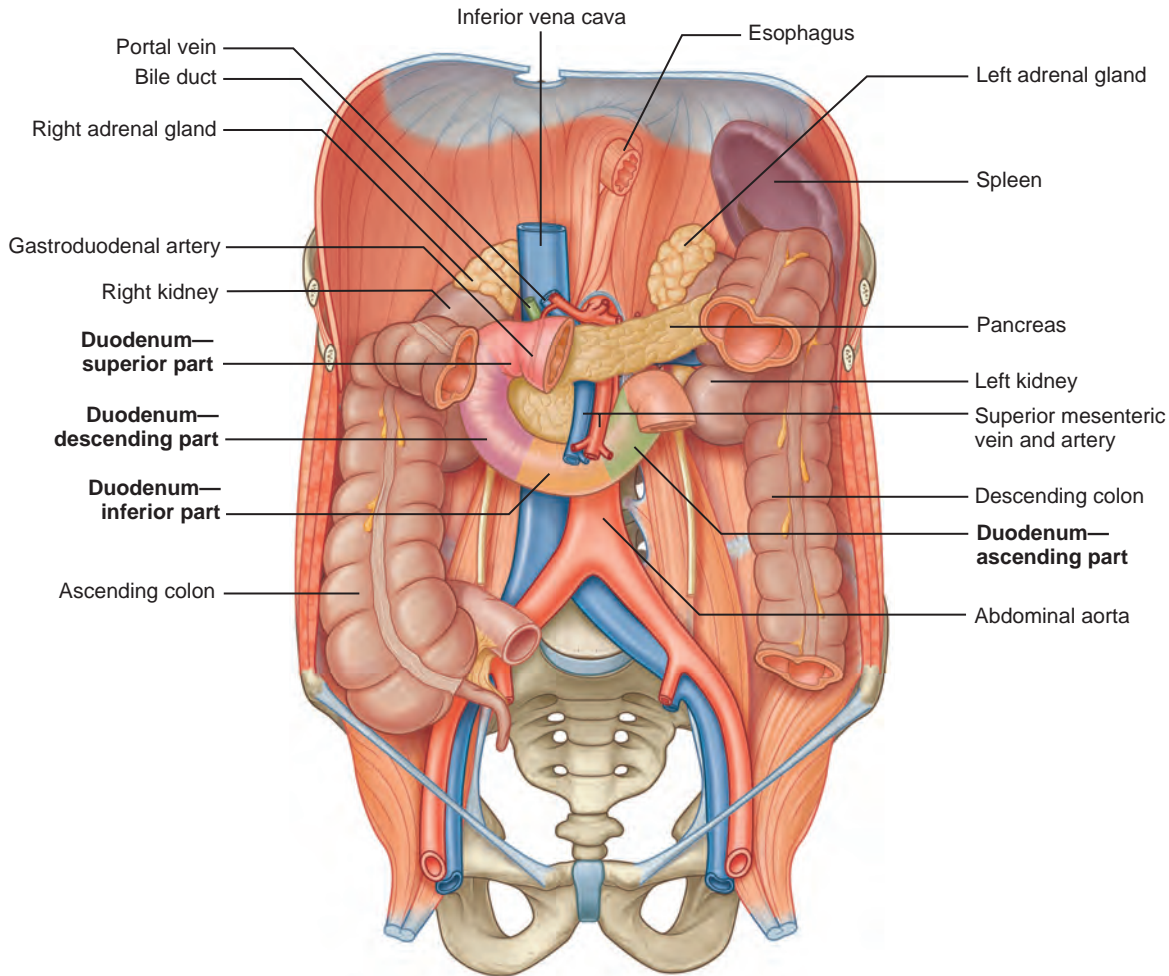


Figure 33-21. Colon, duodenum, and pancreas within the retroperitoneum. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

Clinically, this space is significant because it can be developed to gain access to the kidney anteriorly when followed medially from the **white line of Toldt**. This classic landmark is created during embryogenesis when the inner stratum forms a multilayer fusion fascia with the primary dorsal peritoneum during the rotation and posterior attachment of the gastrointestinal viscera (Fig. 33-20 on the Expert Consult website). **During this event, the white line of Toldt is formed at the lateral border of the fusion of the colonic mesentery with the posterior peritoneum.**

The anterior pararenal space contains the secondarily retroperitoneal organs: the ascending and descending colon, pancreas, and second and third portions of the duodenum. These organs are intraperitoneal at one point during embryogenesis; however, they become retroperitoneal secondarily as they attach to the posterior abdominal wall when the inner stratum fuses with the primary dorsal peritoneum.

GASTROINTESTINAL VISCERA

The nonurologic viscera within the retroperitoneum includes the pancreas and parts of the duodenum and the colon (Figs. 33-21 and 33-22). The **pancreas** consists of four parts and has endocrine and exocrine functions. The head lies anterior to the IVC and is surrounded by the second portion of the duodenum. This portion is of concern for potential injury during right kidney procedures. The neck connects the head to the body, which crosses the abdomen anterior to the aorta and the origin of the superior mesenteric artery (SMA).

The tail of the pancreas is closely associated with the spleen and must be accounted for during left retroperitoneal surgery because of its proximity to the upper pole of the left kidney and left adrenal. In addition, the stomach is anterior to the upper pole of the left kidney and must be accounted for during transperitoneal left renal surgery (Fig. 33-23 on the Expert Consult website).

The **duodenum** is 20 cm to 25 cm in length and can be divided into four distinct parts. The first (superior) portion is intraperitoneal and extends from the pylorus to the neck of the gallbladder. The second (descending) and third (horizontal or inferior) portions of the duodenum are contained within the retroperitoneum. **The second, descending portion of the duodenum is of critical importance to the urologist because of its proximity to the right renal hilum.** The duodenum may be mobilized medially using a **Kocher maneuver** to expose these right-sided retroperitoneal structures. The common bile duct and the main pancreatic duct combine to enter the second portion of the duodenum at the ampulla of Vater (hepatopancreatic ampulla). The third portion of the duodenum crosses the body from right to left and lies posterior to the SMA and anterior to the aorta. The fourth and final portion ascends and becomes intraperitoneal as it transitions into the jejunum.

As with the duodenum, portions of the colon are secondarily retroperitoneal because they developed intraperitoneally but fused with the posterior abdominal wall during embryogenesis. The **ascending colon** and hepatic flexure overlie the right-sided retroperitoneal structures, and the splenic flexure and **descending colon** cover the left-sided retroperitoneal structures. To gain access

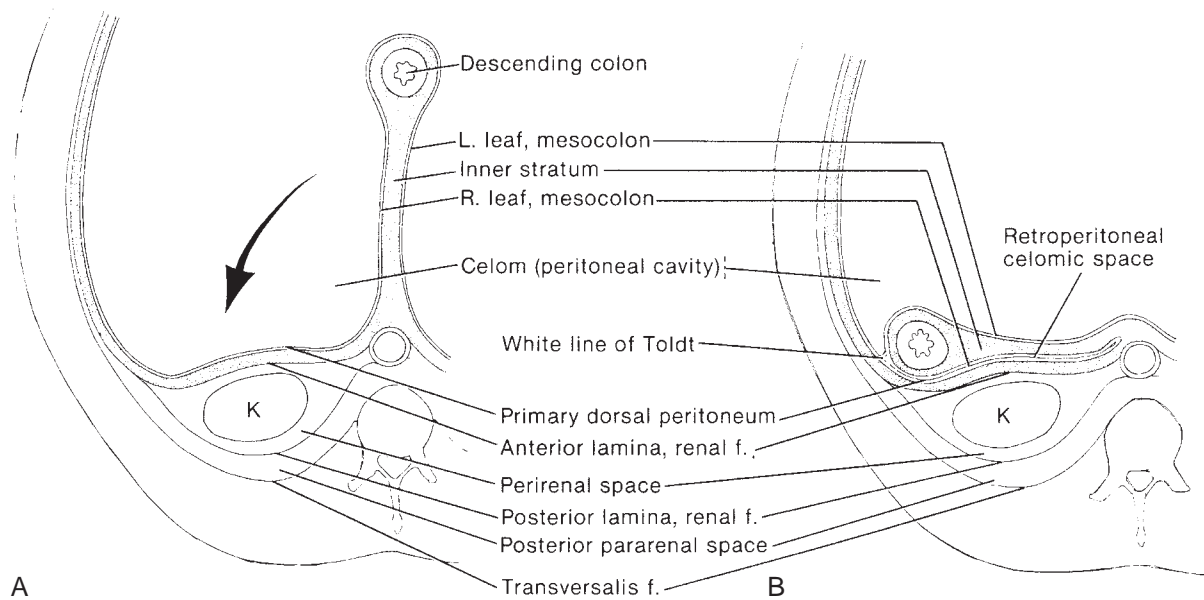


Figure 33-20. A and B, Colonic rotation and formation of the white line of Toldt. K, kidney. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

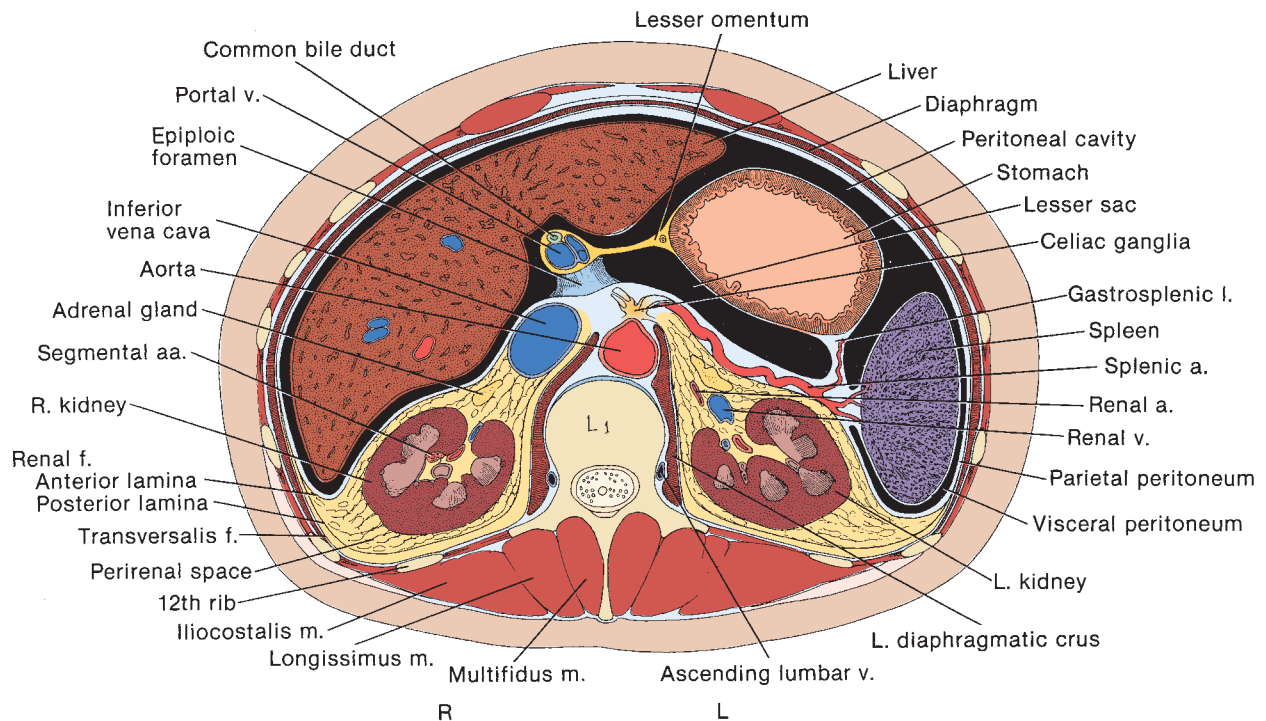


Figure 33-23. Transverse section at L1. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

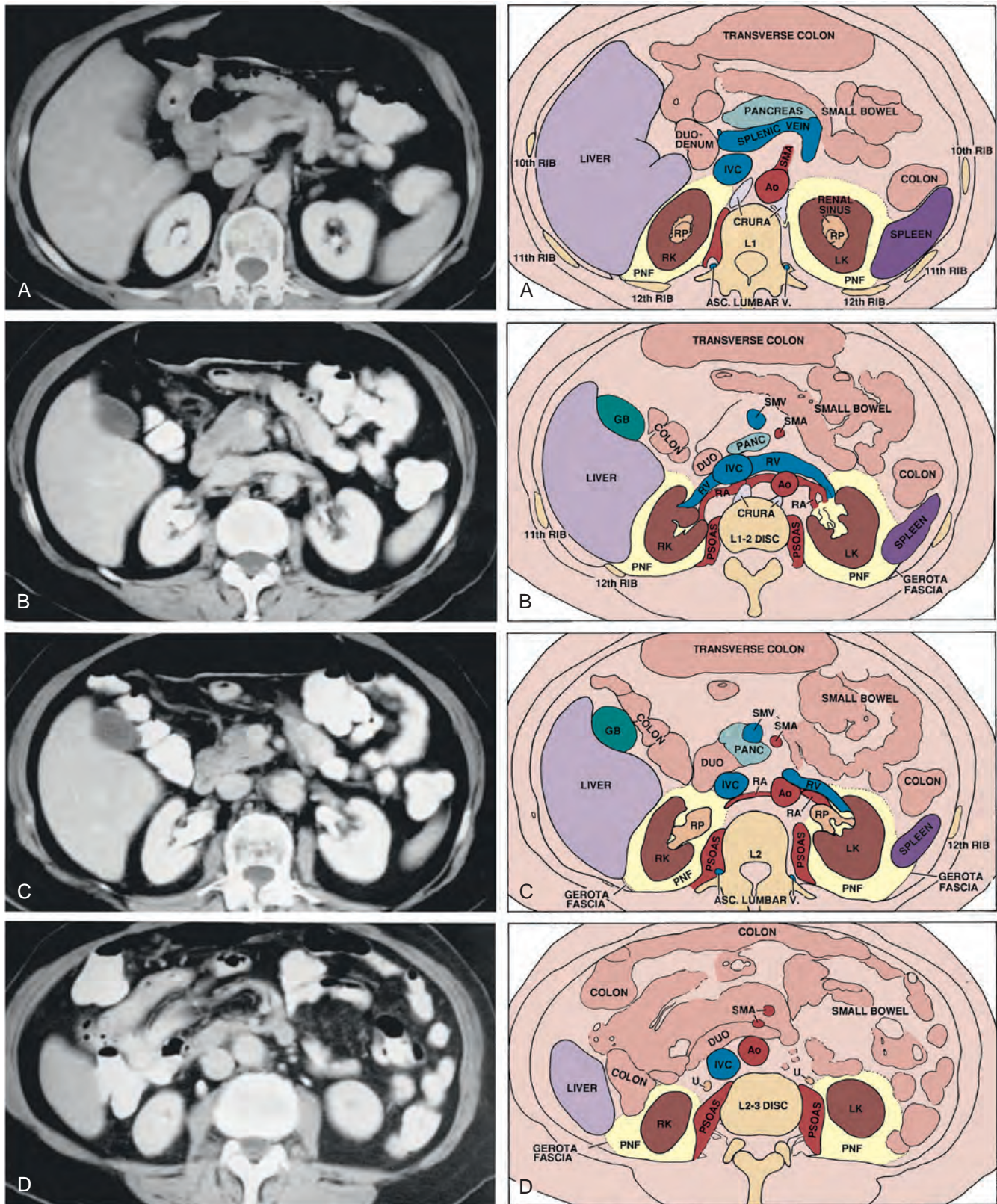


Figure 33-22. Cross-sectional anatomy of the upper abdomen at the level of the kidneys demonstrated with transverse sections obtained by computed tomography. Sections are arranged from most cephalic to caudal. A, Section through the upper poles of the kidneys, superior to the renal vascular pedicles. B, Section through the level of the renal arteries and veins. C, Slightly more inferior section showing the renal pelvis and relationship of the duodenum to the right renal hilum. D, Section through the lower poles of the kidneys showing the upper ureters. Ao, aorta; DUO, duodenum; GB, gallbladder; IVC, inferior vena cava; LK, left kidney; PANC, pancreas; PNF, perinephric fat; RA, renal artery; RK, right kidney; RP, renal pelvis; RV, renal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; U, ureter.

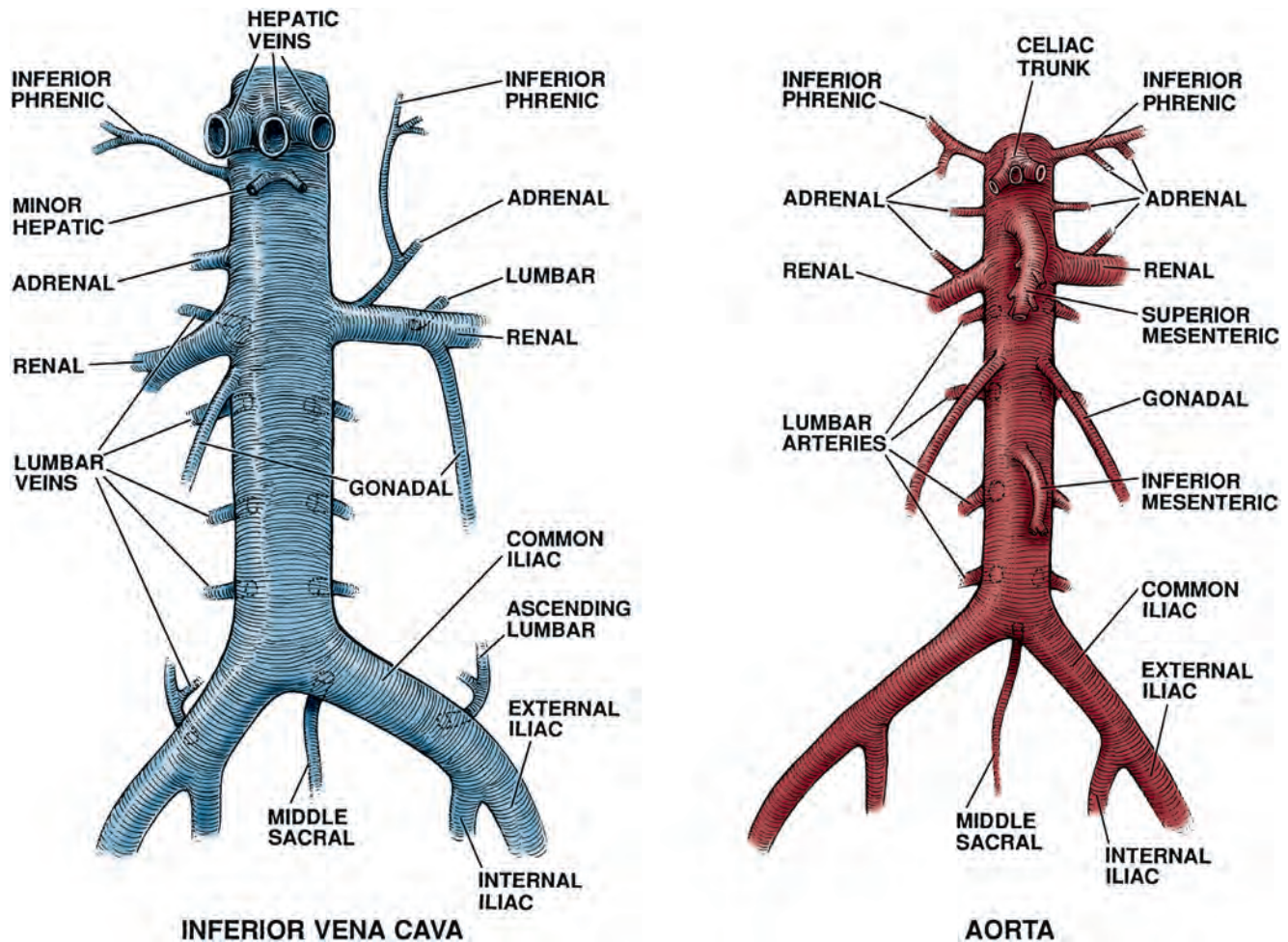


Figure 33-27. Inferior vena cava and its tributaries and abdominal aorta and its branches.

to the kidneys transperitoneally, the ipsilateral colon must be reflected medially in most instances. This can be performed by mobilizing the colon at the white line of Toldt, which visually represents the transition from the colonic visceral peritoneum to the posterior parietal peritoneum. Care must be taken to divide the hepatocolic and splenocolic ligaments sharply when necessary to avoid iatrogenic injury to the liver and spleen, which is often due to excessive retraction during attempts to obtain adequate exposure.

VASCULATURE

Arterial System

Arterial structures have three layers: the tunica intima (intima), tunica media (media), and tunica externa (tunica adventitia or adventitia) as shown in Figure 33-24 on the Expert Consult website. The **intima** consists of a layer of endothelial cells surrounded by subendothelial connective tissue. The **media** layer contains vascular smooth muscle cells and elastic connective tissue that control the caliber of the vessel. This layer is surrounded by the internal and external elastic laminae. The **adventitia** is the connective tissue sheath surrounding the vessel. It contains the nerves that control vasomotor tone and the vasa vasorum (Latin, “vessels of the vessels”), which are smaller vessels that supply the walls of larger vessels.

The major arterial structures of the retroperitoneum include the abdominal aorta (Figs. 33-25 and 33-26 on the Expert Consult website) and its branches (Fig. 33-27 and Table 33-3). Entering the abdomen through the aortic hiatus of the diaphragm at the level of

T12, the **abdominal aorta** courses centrally and to the left of the IVC. The first branches are the paired **inferior phrenic arteries**, which supply the inferior surface of the diaphragm (Fig. 33-28 on the Expert Consult website). The **superior adrenal artery** branches from the inferior phrenic artery and supplies the ipsilateral adrenal gland. The superior arterial blood supply to the adrenal is constant; however, the middle and inferior arteries to the adrenal are variable. These arteries vary in number and location with the most common variant being the middle adrenal artery arising from the aorta and the inferior adrenal arising from the renal artery.

The next branch of the abdominal aorta is the **celiac artery** (celiac trunk or truncus coeliacus) which is a short, unpaired artery that arises anteriorly at the midline at the level of T12. It gives origin to the left gastric, splenic, and common hepatic arteries, which supply the abdominal esophagus, stomach, duodenum, spleen, liver, and pancreas. Of surgical anatomic significance, the splenic vessels course on the cephalad aspect of the body and tail of the pancreas. When the inferior pancreatic edge is mobilized off the anterior renal fascia during adrenal or renal transperitoneal surgery, knowledge of the anatomic relationship between the splenic vessels and the pancreas is paramount to prevent vascular injury. The next branches are the paired middle adrenal arteries, which supply the ipsilateral adrenal gland as noted earlier.

The SMA branches next off the aorta, arising anteriorly in the midline at approximately the level of the middle adrenal arteries at L1-L2. It supplies the pancreas (inferior pancreaticoduodenal artery), small intestine, and most of the large intestine (ileocolic, right colic, and middle colic arteries). The **middle colic artery** anastomoses with the left colic artery off the inferior mesenteric

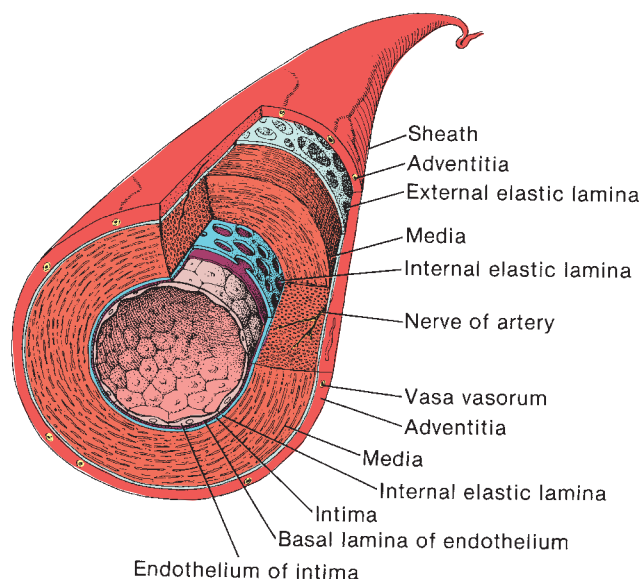


Figure 33-24. Structure of the arterial wall. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

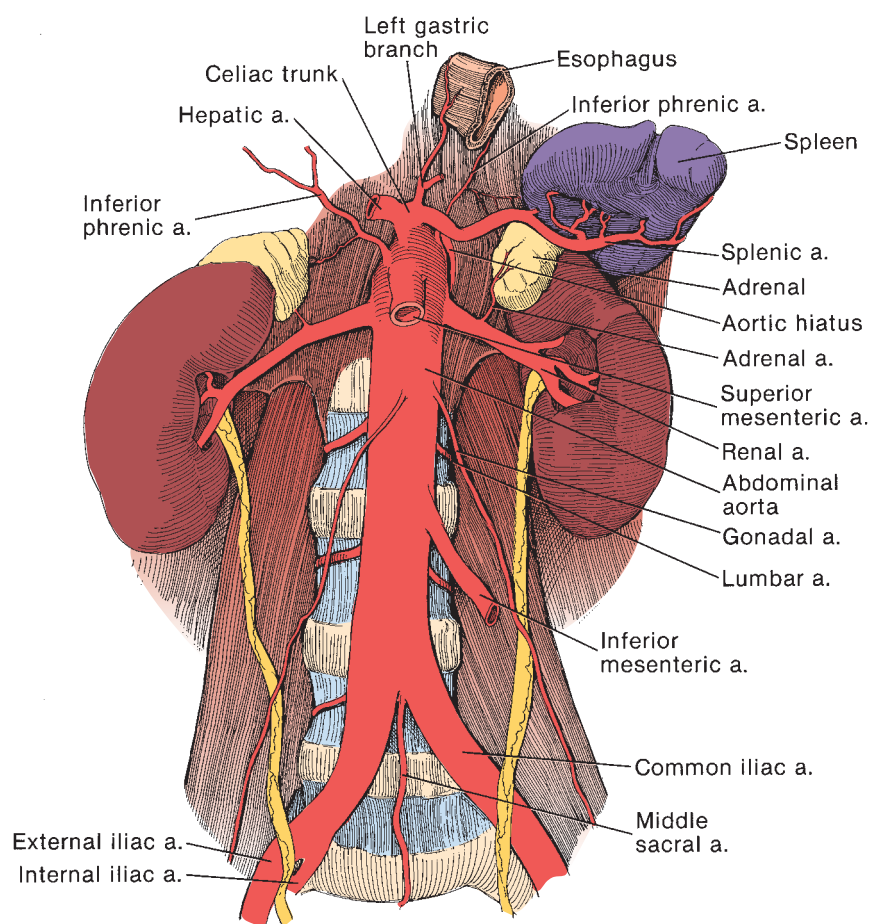


Figure 33-25. Abdominal aorta and its branches. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

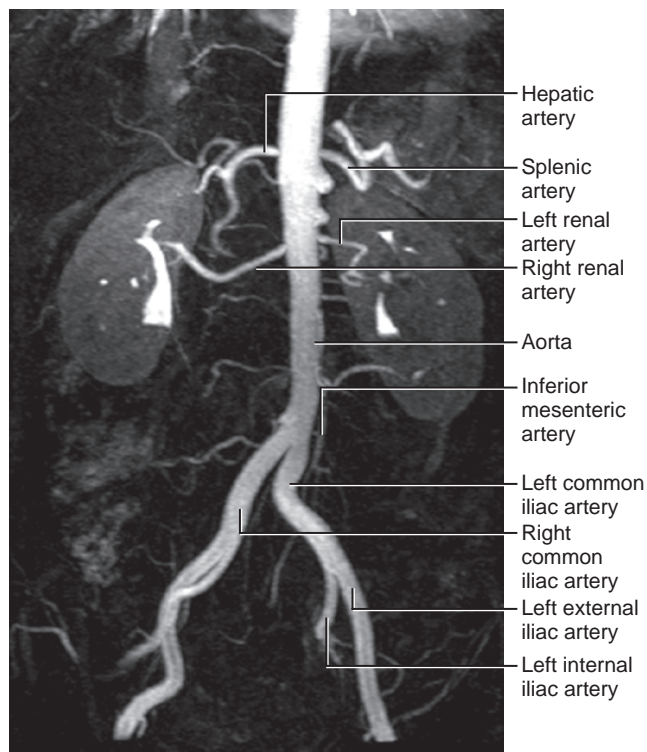


Figure 33-26. Computed tomography angiogram of the abdominal aorta and its branches. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

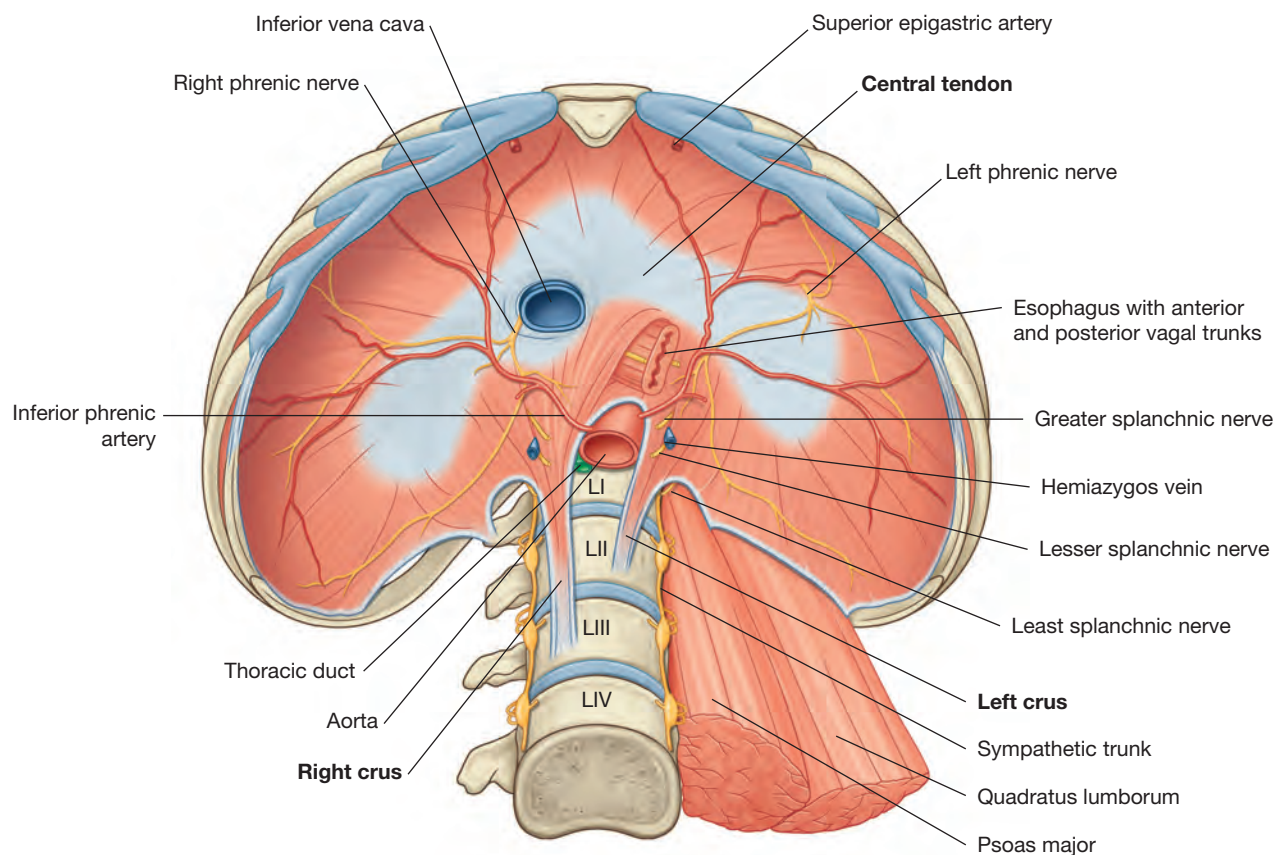


Figure 33-28. The abdominal surface of the diaphragm. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

TABLE 33-3 Branches of the Abdominal Aorta

ARTERY	BRANCH	ORIGIN	SUPPLIES
Celiac trunk	Anterior	Immediately inferior to aortic hiatus of diaphragm	Abdominal foregut
Superior mesenteric artery	Anterior	Immediately inferior to celiac trunk	Abdominal midgut
Inferior mesenteric artery	Anterior	Inferior to renal arteries	Abdominal hindgut
Middle adrenal arteries	Lateral	Immediately superior to renal arteries	Adrenal glands
Renal arteries	Lateral	Immediately inferior to superior mesenteric artery	Kidneys
Testicular or ovarian arteries	Paired anterior	Inferior to renal arteries	Testes in male and ovaries in female
Inferior phrenic arteries	Paired lateral	Immediately inferior to aortic hiatus	Diaphragm
Lumbar arteries	Posterior	Usually four pairs	Posterior abdominal wall and spinal cord
Median sacral arteries	Posterior	Just superior to aortic bifurcation, pass inferiorly across lumbar vertebrae, sacrum, and coccyx	
Common iliac arteries	Terminal	Bifurcation usually occurs at level of L4 vertebra	

Modified from Drake RL, Vogl AW, Mitchell AWM. Gray's anatomy for students. Philadelphia: Churchill Livingstone; 2005. p. 331.

artery (IMA) via the marginal artery of Drummond. This anastomosis forms an important SMA-to-IMA collateral circulation that allows for the IMA to be sacrificed without colonic ischemia (Walker, 2009). However, despite the presence of this collateral circulation, injury to the SMA during left-sided retroperitoneal surgery may lead to severe bowel ischemia.

At L1, the paired renal arteries are the next branch of the aorta (Fig. 33-29 on the Expert Consult website). The inferior adrenal arteries branch off the renal arteries to supply the ipsilateral adrenal gland. There is considerable variation in the location, size, and number of renal arteries, with one quarter of cases manifesting with supernumerary renal arteries, which are more common on the right. The specific anatomic variations are discussed in depth in Chapter 42.

The gonadal arteries are the next paired branch of the aorta, typically arising anterolaterally from the aorta below the renal arteries. They may emerge from the renal artery in some variations, in which case they course with the gonadal vein. In males, the gonadal arteries are called the testicular arteries, and in females, they are called the ovarian arteries. The testicular arteries typically run anterior to the psoas, IVC, genitofemoral nerve, and ipsilateral ureter as they travel toward the internal inguinal ring.

The ovarian arteries arise from the anterolateral aspect of the aorta below the renal arteries. They travel anterior to the ureter and course medially as they pass through the infundibulopelvic ligament (suspensory ligament of the ovary) to the ovary. There are extensive collaterals to the gonads in both sexes, allowing for ligation of the testicular and ovarian arteries without gonadal ischemia.

The paired lumbar arteries arise posteriorly, adjacent to the bodies of the upper four lumbar vertebrae. They supply the posterior body wall and spine. In some instances, a fifth pair of lumbar arteries is present, arising from the middle sacral artery.

The IMA arises from the anterior aorta in the midline at the level of L3-L4 and supplies the colon from the splenic flexure to the upper rectum. The branches of the IMA are the left colic, sigmoid, and superior hemorrhoidal (rectal) arteries. The sigmoid artery branches into two to three inferior left colic arteries. As previously mentioned, the colonic branches of the IMA anastomose with the SMA via the marginal artery of Drummond and preclude colonic ischemia with IMA ligation. The superior hemorrhoidal artery has collateral circulation with the inferior and middle hemorrhoidal arteries, which branch off the internal iliac arteries. These collaterals provide blood supply to the rectum and prevent ischemia during IMA ligation.

Before bifurcation, the median sacral (middle sacral) artery arises from the posterior aspect of the aorta and courses over the fifth lumbar vertebra and sacrum. This vessel may be sacrificed if necessary without end-organ ischemia. At the fourth lumbar vertebra, the aorta bifurcates to form the common iliac arteries. No named branches are given off as these arteries enter the pelvis and divide to form the internal and external iliac arteries.

The ureter has a variable arterial supply that changes proximally and distally. Most often, the renal artery supplies the proximal ureter, and the internal iliac artery including its branches, the superior and inferior vesical arteries, supply the distal ureter. The middle ureter is typically supplied by the aorta; however, it may also be supplied by the common iliac, gonadal, uterine, middle rectal, and vaginal arteries. In general, the abdominal (proximal) ureter receives its blood supply medially, and the pelvic (distal) ureter receives its blood supply from a lateral direction.

Venous System

Although not as well defined, the layers of the venous system are similar to that of the arterial system. The layers from innermost to outermost are the intima, internal elastic lamina, media, external elastic lamina, and adventitia. As in the arterial system, the intima is composed of a layer of endothelial cells with subendothelial connective tissue. In the venous system, the internal and external elastic laminae are often poorly defined even in larger caliber vessels. The media layer of veins is significantly smaller than that of arteries and contains less vascular smooth muscle. Conversely, the venous adventitia is larger than the venous media and functions similar to the adventitia of the arterial system.

The venous system also differs from the arterial system with the presence of valves that prevent retrograde flow. These valves are typically bicuspid and they function to maintain the full venous blood flow toward the heart.

The major retroperitoneal venous structure is the IVC, formed from the confluence of the common iliac veins, inferior and to the right of the aortic bifurcation (see Fig. 33-27). The IVC ascends anterior to the vertebral bodies and to the right of the aorta through the retroperitoneum (Figs. 33-30 and 33-31 on the Expert Consult website). The infrarenal portion runs parallel and inferior to the aorta. On its ascent, the IVC becomes more anterior, and at the level of the diaphragm the great vessels are separated by the right crus of the diaphragm. The IVC then enters the thorax through the central tendon of the diaphragm at the level of T8 and drains into the inferior aspect of the right atrium.

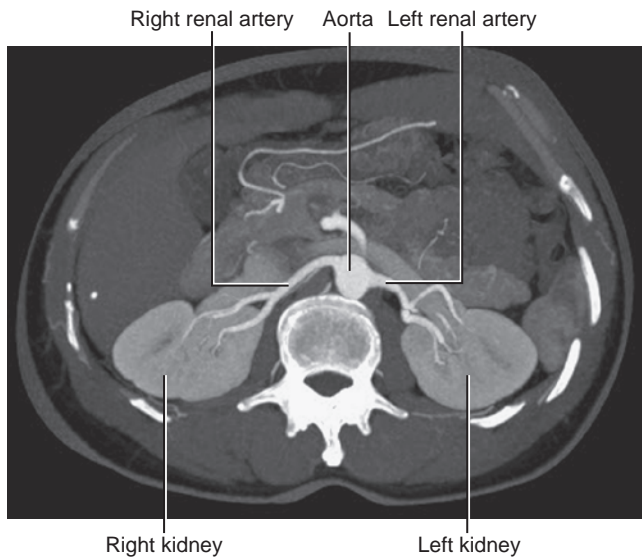


Figure 33-29. Magnetic resonance angiogram, transverse section, right and left renal arteries arising from the aorta and supplying the kidneys. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

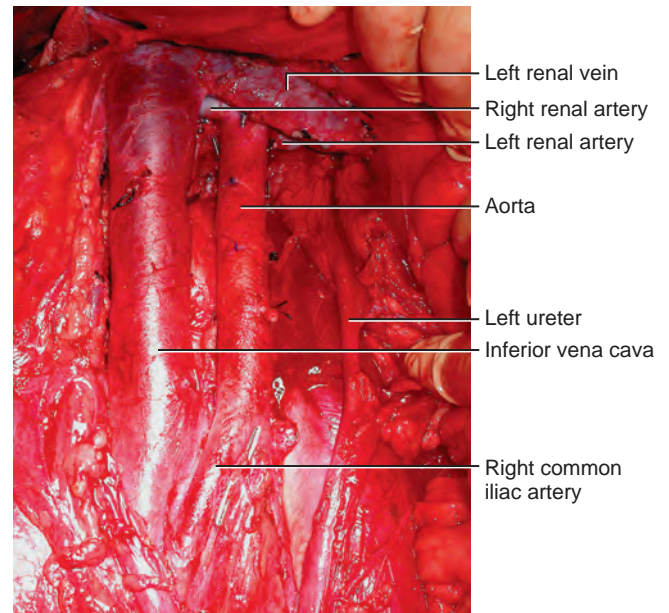


Figure 33-31. Intraoperative photograph of inferior vena cava and its tributaries. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

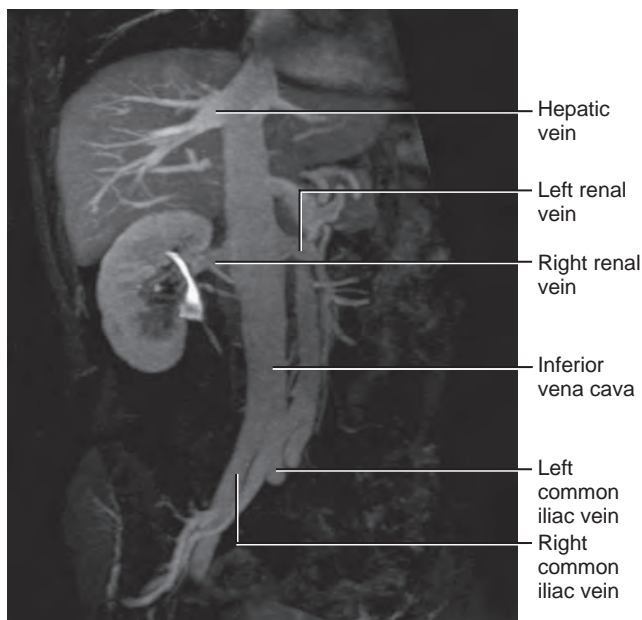


Figure 33-30. Radiograph showing inferior vena cava and its tributaries. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

The venous system is more variable than the arterial system; however, many venous structures run parallel with their arterial equivalent. The **median (middle) sacral vein** runs with its respective artery and typically drains into the left common iliac vein; however, it may enter into the angle created by convergence of the two common iliac veins. Avoiding these veins during fixation of the proximal limb of mesh during sacral colpopexy procedures is critical.

The ascending lumbar veins drain the posterior abdominal wall and run posterior to the psoas muscle and lateral to the spinal column (Fig. 33-32 on the Expert Consult website). They connect with the ipsilateral lumbar veins, which are variable in number and location compared with their arterial equivalents. These veins may assume a plexiform arrangement anterior to the vertebral bodies. As the ascending lumbar veins enter the thorax, they become the hemiazygos vein on the left and the azygos vein on the right.

In males, the gonadal veins (testicular veins) receive drainage from the pampiniform plexus, which is the venous complex that emerges from the testes. The testicular veins ascend through the retroperitoneum medially, running lateral to the respective artery and anterior to the ipsilateral ureter. The left testicular vein typically enters the inferior aspect of the left renal vein at a right angle; however, it may enter the IVC directly. The right testicular vein typically enters into the right anterolateral aspect of the IVC; however, it may enter into the right renal vein in 10% of cases. **These anatomic differences have clinical significance because the increased length and perpendicular entry of the left testicular vein into the left renal vein may account for the increased incidence of left-sided varicoceles.** This anatomic configuration may result in some element of increased back pressure in the left testicular vein compared with the right side. With the relative rarity of unilateral right-sided varicocele, a sudden-onset right varicocele should increase suspicion for a renal or retroperitoneal malignancy causing obstruction and poor venous outflow (e.g., right side renal cell cancer with venous thrombus). This clinical scenario should warrant retroperitoneal imaging to rule out malignancy.

The ovarian veins receive drainage from the pampiniform plexus adjacent to the ovarian hilum and travel through the infundibulopelvic ligament. As with the gonadal veins in males, the left ovarian vein enters the left renal vein, and the right ovarian vein empties into the anterolateral wall of the vena cava.

The renal veins course anteriorly to the renal arteries and empty into the lateral aspects of the vena cava at the level of L1. The right and left renal veins differ in length and tributaries with the right being shorter and typically having no tributaries. In rare cases, the right gonadal vein or a lumbar vein may empty into the right renal vein. In one sixth of cases, the renal vein is duplicated on the right side. The left renal vein is longer and typically receives the left gonadal vein at its caudal margin. At least one lumbar vein enters the left renal vein at or near the ostia of the gonadal vein. **The left adrenal vein is situated at the superior margin of the renal vein and in most patients inserts into the renal vein just medial to the gonadal vein.** The left adrenal vein occasionally is joined by the left inferior phrenic vein. The right adrenal vein is short, is single in number, has no tributaries, and drains directly into the posterolateral aspect of the vena cava. Although variable, the right inferior phrenic vein also typically drains into the superior portion of the IVC.

The gastrointestinal venous drainage does not mirror the arterial system as directly as the aforementioned venous structures. The portal venous system receives venous blood from the bowel, spleen, pancreas, and gallbladder to be emptied into the liver (Fig. 33-33 on the Expert Consult website). The superior mesenteric vein (SMV) receives venous drainage from the small intestine and the large intestine proximal to the splenic flexure. Tributaries of the SMV include the right gastro-omental, anterior and posterior inferior pancreaticoduodenal, jejunal, ileal, ileocolic, right colic, and middle colic veins. The SMV is joined by the splenic vein to form the portal vein. The tributaries of the splenic vein are the short gastric, left gastro-omental, pancreatic, and typically inferior mesenteric veins. The inferior mesenteric vein receives the venous

drainage from the colon distal to the splenic flexure. The portal vein splits into right and left branches, and the venous blood enters the endothelial lined hepatic sinusoids. After passing through these sinusoids, the venous blood leaves the liver through the hepatic veins, which enter the anterior aspect of the IVC before it crosses the diaphragm into the thorax. There are two groups of hepatic veins: the upper group, typically larger in caliber, and the lower group, which are typically smaller. **Occlusion of these hepatic veins can lead to Budd-Chiari syndrome, which is a form of progressive liver failure that often manifests rapidly with jaundice, ascites, abdominal pain, and hepatomegaly.**

LYMPHATIC SYSTEM

The lymphatic channels line tissue spaces and transport lymph to specialized areas of lymphoid tissue called lymph nodes. **The nodes typically have multiple afferent lymphatics and a single efferent lymphatic that drains into larger lymphatic vessels. Lymph generally flows cephalad from right to left until it returns to the venous circulation at the left innominate (brachiocephalic) vein.** Lymphatic fluid from the head, neck, right thorax, right arm, and right heart drains into the right innominate vein.

The lymphatic fluid from the pelvis and lower extremities drains into the internal iliac, external iliac, common iliac, obturator, and sacral nodes. These nodal regions then drain cephalad toward the lumbar nodes, whose efferent lymphatics form the lumbar trunks (Parker, 1935). The lumbar nodes are of considerable interest to the urologist because they provide the primary lymphatic drainage for structures supplied by lateral aortic arterial branches: the kidneys, adrenals, ureters, and gonads (Fig. 33-34). **For anatomic classification, three groups of lumbar nodes can be defined: left lumbar (aortic), interaortocaval (interaortocaval), and right lumbar (caval) nodal groups.**

The left lumbar group includes the preaortic, left para-aortic (periaortic), and retroaortic nodes. The preaortic nodes are located anterior to the abdominal aorta, around the major anterior arterial branches that supply the gastrointestinal tract. The celiac, superior mesenteric, and inferior mesenteric nodes receive lymphatic drainage based on the anatomy of the similarly named arteries that supply the corresponding abdominal viscera. The efferents of these lymphatics coalesce to form the intestinal trunk. The left para-aortic region includes the nodes lateral to the midline of the aorta and medial to the left ureter. The retroaortic nodes are variably present and located between the aorta and vertebrae. The interaortocaval nodal group extends from the midline of the IVC to the midline of the aorta.

The right lumbar group includes the precaval, right paracaval, and retrocaval nodes. The precaval nodes are located on the anterior wall of the IVC. The right paracaval region includes the area lateral to the midline of the IVC, extending to the right ureter. The retrocaval nodes are present between the vena cava and the psoas muscle.

The testes are significant because they are embryologically retroperitoneal and have retroperitoneal blood supply and primary lymphatic drainage. When practically discussing testis malignancy, the three significant nodal regions are the left para-aortic, interaortocaval, and right paracaval. Elegant studies of early metastasis demonstrated the drainage pattern of the testes. **The left testis drains to the left para-aortic nodes with some drainage to the interaortocaval nodes.** There is no significant drainage to the right paracaval nodes, which is consistent with the general direction of lymphatic flow from right to left. **The right testis drains primarily to the interaortocaval nodes with some drainage to the right paracaval nodes. The left para-aortic region receives a small but appreciable amount of lymphatic drainage from the right testis, consistent with the aforementioned right-to-left flow.**

The efferent lymphatics of the lateral lumbar nodes coalesce to form the right and left lumbar trunks. Posterior to the right side of the abdominal aorta and anterior to the L1 and L2 vertebrae, these trunks come together at a saccular dilated structure known as the

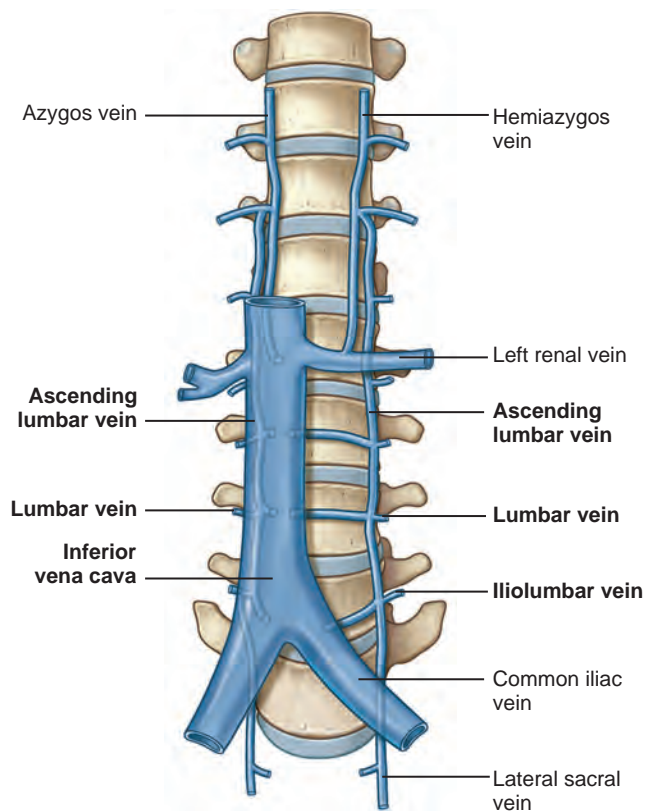


Figure 33-32. Lumbar, azygos, and hemiazygos veins. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

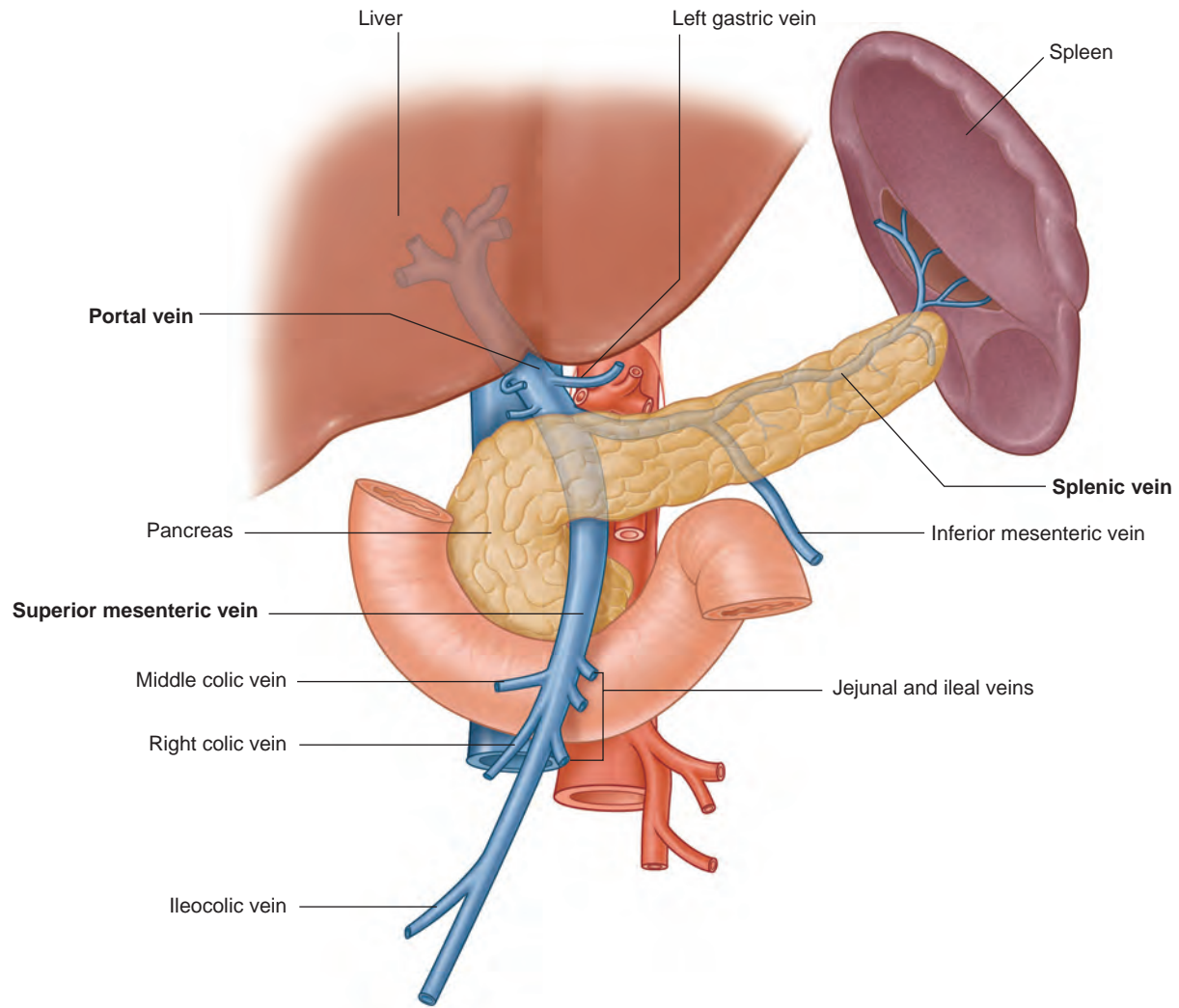


Figure 33-33. Portal vein and its tributaries. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

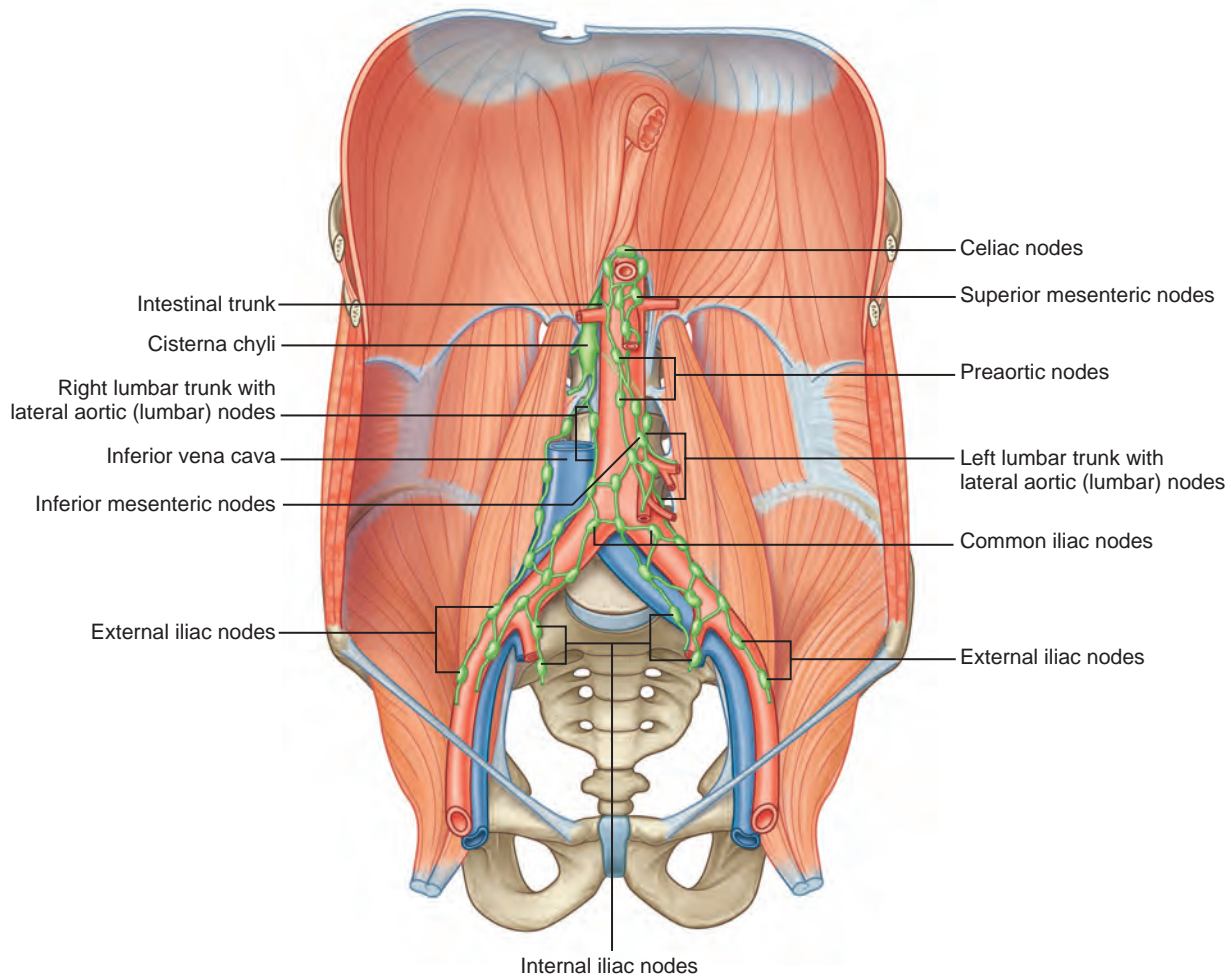


Figure 33-34. Retroperitoneal lymphatics. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

cisterna chyli. This marks the beginning of the **thoracic duct**, which runs cephalad posterior to the aorta and empties into the left innominate vein.

NERVOUS STRUCTURES

The nervous structures of the retroperitoneum can be divided into the **autonomic nervous system** and the **somatic nervous system**. The autonomic system supplies efferent and afferent innervation to the abdominal viscera, blood vessels, and smooth muscle. The somatic system supplies efferent and afferent innervation to skeletal muscle, skin, and peritoneum.

Autonomic Nervous System

The general structure of the **autonomic nervous system** consists of two nerves with two cell bodies. The **preganglionic neuron** has a cell body within the central nervous system and an axon that extends into the peripheral nervous system, synapsing with another neuron within a ganglion. The second neuron is referred to as a **postganglionic neuron**, and its axon enters the structure in which it provides innervation. One caveat to this general structure is the neural anatomy of the adrenal gland. The **preganglionic fibers synapse directly with the cells of the adrenal medulla resulting in release of catecholamines**. The adrenal can be considered a specialized ganglion of the autonomic nervous system.

The autonomic system can be divided further into the **parasympathetic** and **sympathetic nervous systems**. The **parasympathetic nervous system** has craniosacral outflow because the preganglionic fibers originate from cranial nerves III, VII, IX, and X and from the ventral rami of the second, third, and fourth sacral nerves. The preganglionic fibers from S2-S4 form the pelvic splanchnic nerves, which provide parasympathetic innervation to the pelvic and abdominal viscera, which often contain the postganglionic parasympathetic fibers within their walls. The vagus nerve (cranial nerve X) also provides preganglionic parasympathetic fibers to the thoracic, abdominal, and pelvic viscera.

In contrast to the parasympathetic system, the preganglionic fibers of the **sympathetic nervous system** originate between the first thoracic and the second lumbar vertebral levels. These fibers exit the spinal cord from T1 to L2 through the ventral root and course through the corresponding spinal nerve and anterior rami into the ipsilateral sympathetic trunk (Fig. 33-35). The fibers then run medial to the psoas muscle along the anterolateral aspect of the spine. The **paired sympathetic trunks are in close proximity to the lumbar arteries and veins, which cross them perpendicularly**. The preganglionic fibers can synapse within the ganglia of the sympathetic trunk and send forth postganglionic fibers to the body wall and lower extremities. The preganglionic fibers also may leave the trunk as splanchnic nerves to synapse with the ganglia of the autonomic plexuses of the aorta (Fig. 33-36).

The first and largest of these plexuses is the celiac plexus, which contains paired ganglia that lie lateral to the celiac artery. Much of the autonomic innervation to the kidney, adrenal, renal

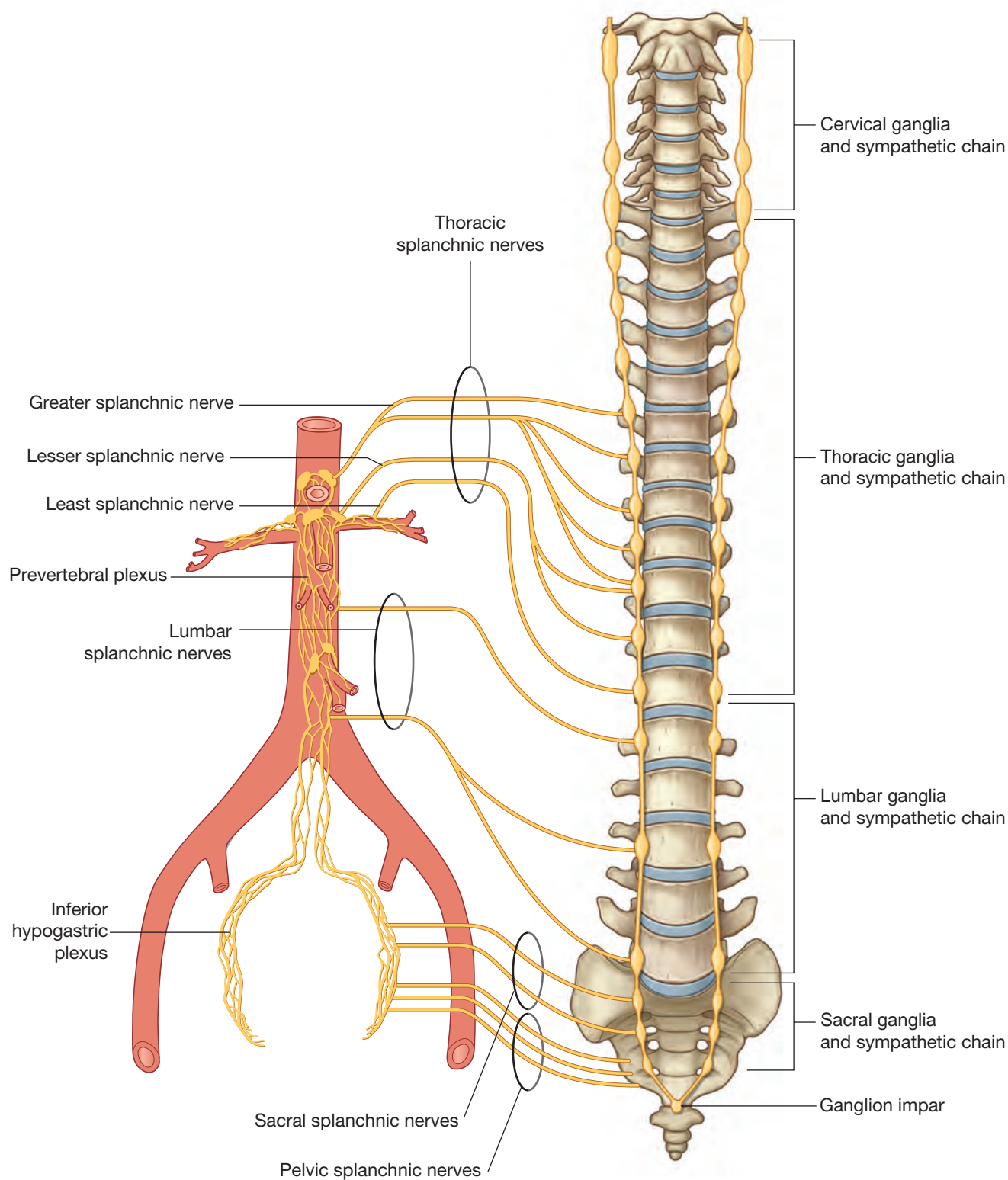


Figure 33-35. Sympathetic chain and splanchnic nerves. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

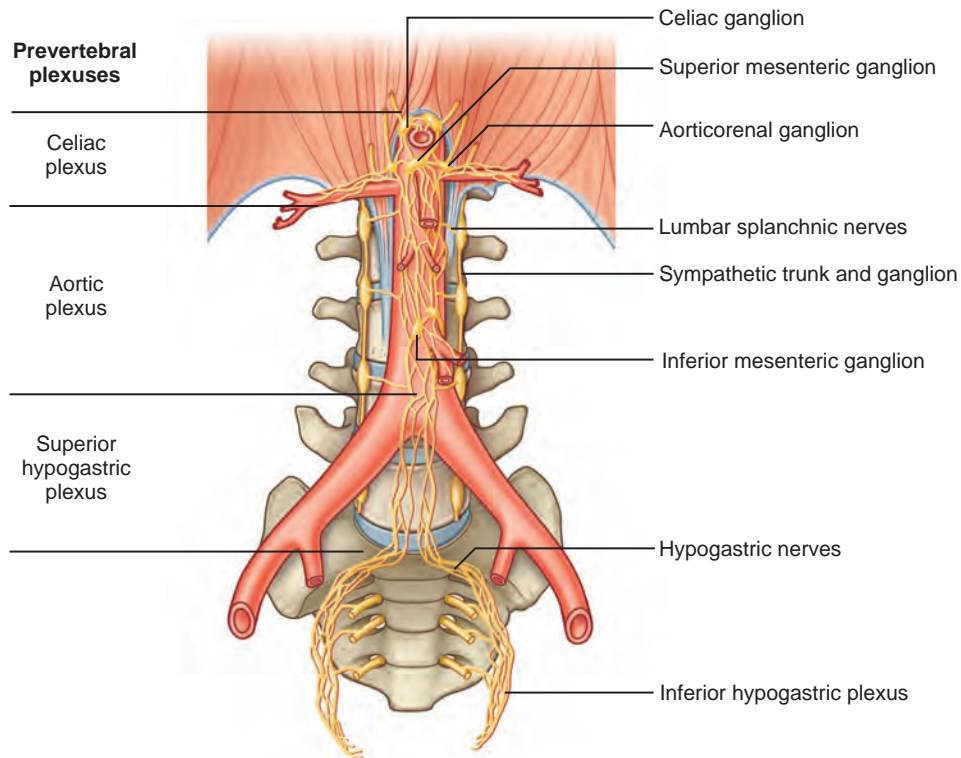


Figure 33-36. Autonomic plexuses associated with branches of the aorta. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

pelvis, and ureter runs through this plexus. Some of the autonomic innervation for the testes passes through this plexus and travels caudally with the testicular artery. The renal autonomic plexus is continuous with the celiac plexus and forms adjacent to the renal arteries. It contains the aorticorenal ganglion, which is an inferior extension of the celiac ganglion.

Much of the sympathetic innervation to the pelvic viscera travels through the superior and inferior hypogastric plexuses, which are contiguous. The superior hypogastric plexus originates at the caudal extent of the abdominal aorta and extends to the anterior surface of the fifth lumbar vertebra. **Extensive retroperitoneal dissection that causes disruption of these plexuses may result in loss of seminal vesicle emission or failure of bladder neck closure resulting in retrograde ejaculation.**

Confusion may arise with the term *splanchnic* used for nerves of both the parasympathetic and the sympathetic systems (see Fig. 33-35). For clarification, the thoracic splanchnics (greater, lesser, and least), lumbar splanchnics, and sacral splanchnics carry sympathetic fibers from the paired sympathetic trunks to the autonomic plexuses, whereas the pelvic splanchnics carry parasympathetic fibers from the sacral outflow.

Somatic Nervous System

The somatic sensory and motor nerves of the lower abdomen and lower extremities originate in the retroperitoneum. They form the lumbosacral plexus from the anterior rami of the lumbar and sacral nerves along with T12 (Fig. 33-37 on the Expert Consult website). The nerves arising from this plexus are in close proximity to the psoas muscle, with the superior nerves piercing the muscle, while the inferior nerves travel medial to the muscle body (Fig. 33-38). This plexus provides the cutaneous sensory innervation to the lower extremities (Fig. 33-39 and Table 33-4).

The **subcostal nerve** is an extension of the 12th thoracic nerve and runs inferior to the 12th rib. The **ilioinguinal and iliohypogastric nerves** arise from the anterior ramus of L1. These three nerves run laterally over the anterior aspect of the quadratus lumborum and travel through the transversus abdominis to run deep to the internal oblique muscle. They provide innervation to the muscles of the abdominal wall and sensory innervation to the posterolateral gluteal skin, upper medial thigh, and genitalia.

The **genitofemoral nerve** originates from L1 and L2 and courses anterior and parallel to the psoas muscle. The nerve typically divides near the level of the inguinal ligament. The **femoral branch** passes under the inguinal ligament and enters the femoral sheath to supply sensation to the upper anterior thigh. The **genital branch** enters the inguinal canal at the deep internal ring to provide motor innervation to the cremaster muscle. This motor component allows for contraction of the muscle during the cremasteric reflex. In addition to the motor component, the genital branch supplies sensation to the anterior scrotum in males and the mons pubis and labium majus in females. The genitofemoral nerve may be injured during a psoas hitch procedure (suture placement) and laparoscopic varicocelectomy (ligation). The **lateral cutaneous nerve of the thigh** (lateral femoral cutaneous nerve) arises from L2 and L3 and provides sensory innervation to the anterior and lateral thigh.

The **obturator nerve** originates from the anterior rami of L2-L4 posterior to the psoas muscle and courses inferiorly to the obturator canal. The function of the obturator nerve includes **hip adduction via motor innervation to the medial thigh compartment, which is of clinical significance during lateral transurethral resection and pelvic lymph node dissection.** Electrocautery employed during a transurethral resection of bladder tumor (TURBT) procedure may result in obturator nerve stimulation with

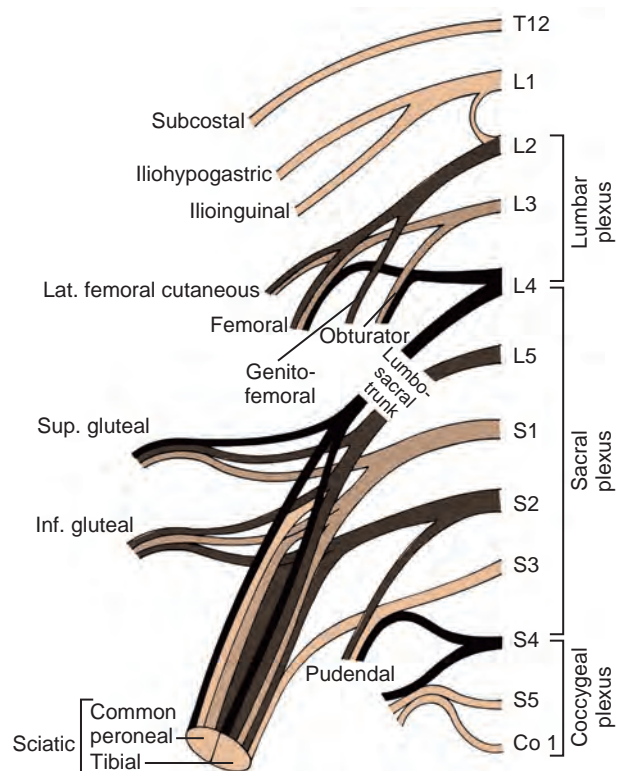


Figure 33-37. Diagrammatic representation of the lumbosacral nervous plexus.

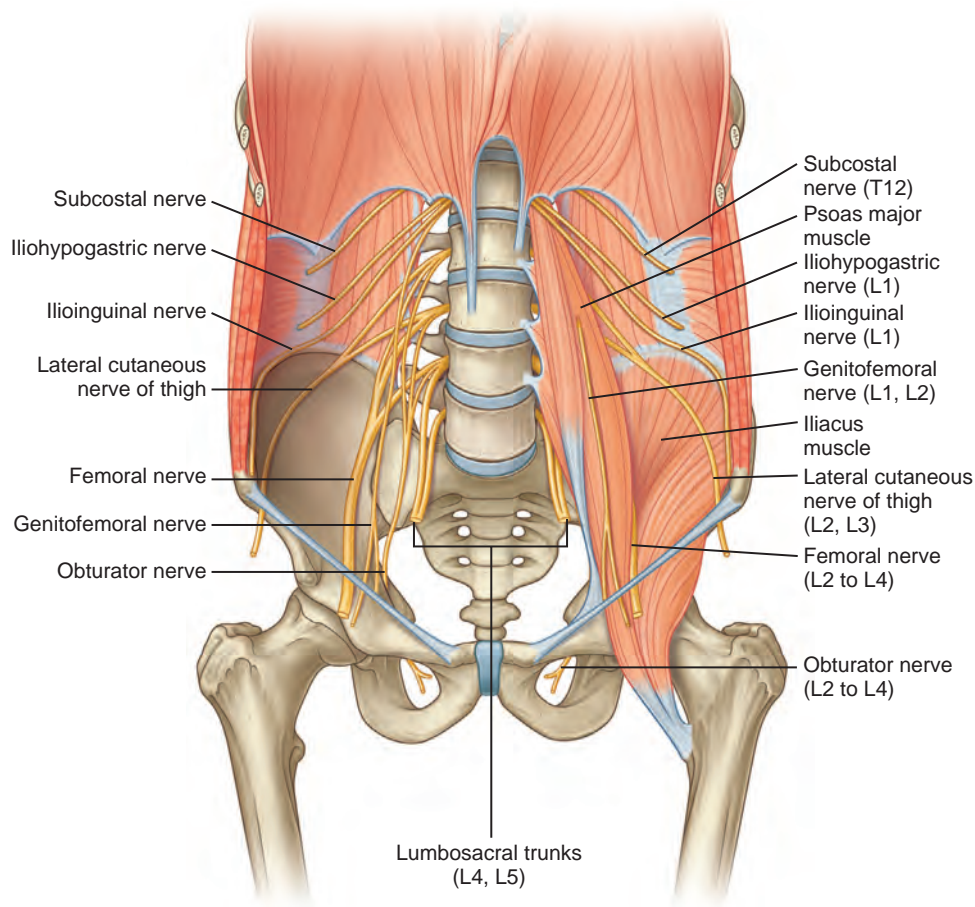


Figure 33-38. Lumbar plexus in the posterior abdominal region. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

TABLE 33-4 Branches of the Lumbosacral Plexus

BRANCH	ORIGIN	SPINAL SEGMENTS	MOTOR FUNCTION	SENSORY FUNCTION
Subcostal	Anterior ramus T12	T12	Muscles of abdominal wall	Skin over hip
Iliohypogastric	Anterior ramus L1	L1	Internal oblique and transversus abdominis	Posterolateral gluteal skin and skin in pubic region
Ilioinguinal	Anterior ramus L1	L1	Internal oblique and transversus abdominis	Skin in upper medial thigh and the skin over either the root of the penis and anterior scrotum or the mons pubis and labium majus
Genitofemoral	Anterior rami L1 and L2	L1, L2	Genital branch: male cremasteric muscle	Genital branch: skin of anterior scrotum or skin of mons pubis and labium majus Femoral branch: skin of upper anterior thigh
Lateral cutaneous nerve of the thigh	Anterior rami L2 and L3	L2, L3	None	Skin on anterior and lateral thigh to the knee
Obturator	Anterior rami L2-L4	L2-L4	Obturator externus, pectineus, and muscles in medial compartment of thigh	Skin on medial aspect of thigh
Femoral	Anterior rami L2-L4	L2-L4	Iliacus, pectineus, and muscles in anterior compartment of thigh	Skin on anterior thigh and medial surface of leg

Modified from Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. Philadelphia: Churchill Livingstone; 2005.

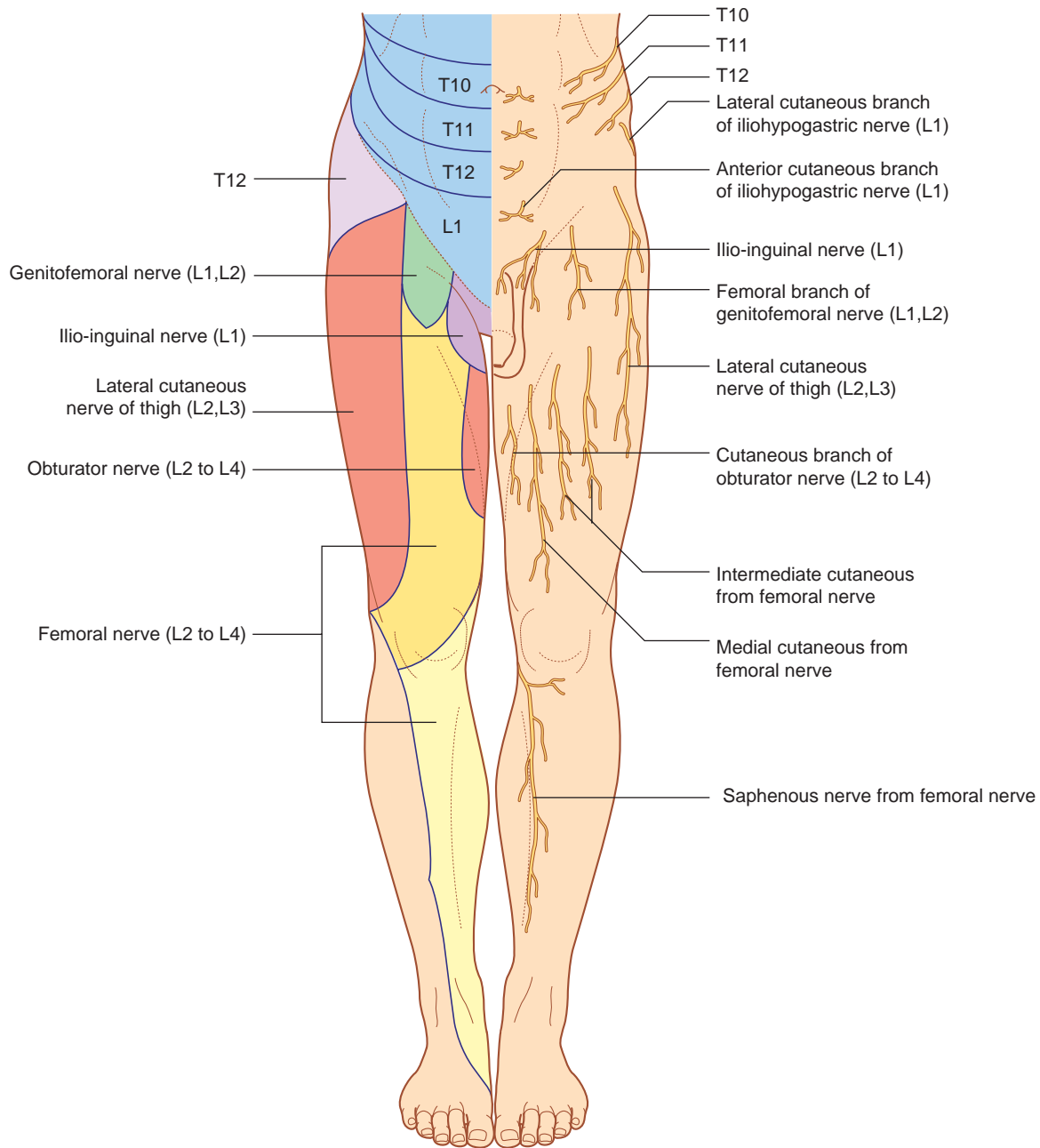


Figure 33-39. Cutaneous distribution of the nerves from the lumbar plexus. (From Drake RL, Vogl AW, Mitchell AWM. *Gray's anatomy for students*. 2nd ed. Philadelphia: Churchill Livingstone; 2010.)

subsequent rapid, forceful hip adduction. If this potential event is not anticipated and accounted for, severe bladder perforation may occur.

With its origin from the anterior rami of L2-L4, the **femoral nerve** provides efferent motor input to the muscles of the anterior thigh as well as the iliacus and pectineus, which are responsible for knee extension and hip flexion, respectively. The femoral nerve also gives sensory innervation to the skin over the anterior medial lower extremity. Compression of the femoral nerve may occur intraoperatively with placement of retractor blades inferolaterally against the inguinal ligament. Compression injury may result in a motor palsy to the quadriceps muscle, impairing extension at the knee.

Additionally, a stretch injury to the femoral nerve may occur with prolonged hip flexion in low lithotomy position used during minimally invasive pelvic surgery.

The **sciatic nerve** receives input from L4-S3 and provides the bulk of motor and sensory input to the lower extremities, including motor innervation to the posterior thigh compartment and all muscles in the leg and foot. Injury to this nerve may occur secondary to prolonged hip hyperflexion used during a high lithotomy position for vaginal and urethral procedures.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.



KEY POINTS

- The retroperitoneum is contained anteriorly by the posterior reflection of the peritoneum, posteriorly by the abdominal wall, cranially by the diaphragm, and caudally by the extraperitoneal pelvic structures.
- The lumbodorsal fascia merges anterolaterally with the transversus abdominis muscle and is composed of three layers that cover the posterior abdominal wall musculature.
- The anterior and posterior laminae of Gerota fascia form the boundaries of the perirenal space, which has a conelike shape that is open caudally in the extraperitoneal pelvis.
- The retroperitoneal gastrointestinal structures are the pancreas, the second and third portions of the duodenum, the ascending colon, and the descending colon.
- The renal hila are at the level of L1, and the renal veins are anterior to the renal arteries.
- The lymph of the left testis drains to the left para-aortic nodes with some to the interaortocaval nodes, and the right testis drains primarily to the interaortocaval nodes with some to the right paracaval nodes and a small amount to the left para-aortic region. This drainage is consistent with global lymphatic flow from right to left.
- The parasympathetic autonomic nervous system has craniosacral outflow and the postganglionic fibers are often contained within the walls of the innervated viscera.
- The preganglionic sympathetic nervous system fibers exit from the spinal cord from T1 to L2 and may synapse within the sympathetic trunk or within the autonomic plexuses.
- The somatic nervous system provides sensory and motor innervation to the pelvis and lower extremities through the lumbosacral plexus.

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Germ Cell Tumors

Non-Germ Cell Tumors

Neoplasms of the testis constitute a morphologically and clinically diverse group of tumors, of which more than 95% are germ cell tumors (GCTs). GCTs are broadly categorized as seminoma and nonseminoma germ cell tumor (NSGCT) because of differences in natural history and treatment. GCT is a relatively rare malignancy, accounting for 1% to 2% of cancers among men in the United States. Approximately 95% of GCTs arise in the testis, and 5% are extragonadal in origin. With the development of cisplatin-based chemotherapy and the integration of surgery, GCTs have become a model of a curable neoplasm and serve as a paradigm for multidisciplinary treatment of cancer (Einhorn, 1981). In the era before cisplatin-based chemotherapy, the cure rate for patients with advanced GCT was 5% to 10%. At the present time, the long-term survival for men with metastatic GCT is 80% to 90%. With the successful cure of patients, an important treatment objective is minimizing treatment-related toxicity without compromising curability. Mortality from GCT is due to inherent resistance to cisplatin chemotherapy and the failure to eradicate fully residual disease elements in the early course of therapy.

Non-GCT tumors of the testis are rare and include sex cord-stromal tumors, lymphoid and hematopoietic tumors, tumors of the collecting duct and rete testis, and tumors of the testicular adnexa. A classification of testis neoplasms is presented in Box 34-1.

GERM CELL TUMORS

Epidemiology

In 2014, an estimated 8820 men were expected to develop testis cancer in the United States, and 380 were expected to die from this disease (Siegel et al, 2014). In the United States, testis cancer is the most common malignancy among men 20 to 40 years old and the second most common cancer after leukemia among adolescent boys and young men 15 to 19 years old (Horner et al, 2009). Testis tumors have three age peaks: infancy, age 30 to 34 years, and approximately age 60. The incidence of bilateral GCT is approximately 2.5% (0.6% risk of synchronous and 1.9% risk of metachronous contralateral tumors) (Fossa et al, 2005).

The incidence of testis cancer varies significantly according to geographic region. Rates are highest in Scandinavia, Western Europe, and Australia–New Zealand; intermediate in the United States and United Kingdom; and lowest in Africa and Asia (Weijl et al, 2000). The incidence of testis cancer in the United States in non-Hispanic whites is five times higher than the incidence in blacks, four times higher than the incidence in Asians, and 78% higher than in Hispanics (Horner et al, 2009).

The incidence of GCT appears to be increasing worldwide (McKiernan et al, 1999; McGlynn et al, 2005; Purdue et al, 2005). In the United States, the age-adjusted incidence rate for adolescent boys and men 15 to 49 years old increased from 2.9 per 100,000 in 1975 to 5.1 per 100,000 in 2004 (Holmes et al, 2008). Over this time period, incidence rates increased substantially more for seminoma than NSGCT (McGlynn et al, 2005; Powles et al, 2005). A

Tumors of the Testicular Adnexa

stage migration of GCT has been observed in several countries partly secondary to increased awareness and earlier diagnosis. Between 1973 and 2001, the percentage of tumors diagnosed at a localized stage increased from 55% to 73% in the United States among white men. The stage distribution for African-American men remained stable during this time (McGlynn et al, 2005). Only about 10% to 30% of men present with distant metastatic disease. In the United Kingdom, the change in stage distribution over time is largely restricted to an increase in localized seminoma and a decrease in metastatic NSGCT; rates of localized NSGCT and metastatic seminoma are largely unchanged (McGlynn et al, 2005). At the present time, localized seminoma is the most common presentation of GCT, representing approximately 50% of all men with GCT (Powles et al, 2005).

Risk Factors

There are four well-established risk factors for testis cancer: cryptorchidism, family history of testis cancer, a personal history of testis cancer, and intratubular germ cell neoplasia (ITGCN). Infertile men also have a higher incidence of testis cancer. Numerous studies have reported that more recent increases in testis cancer incidence can be largely attributed to birth-cohort effects, which implies that diet and/or other environmental factors play a major role in GCT carcinogenesis (Liu et al, 1999; Huyghe et al, 2003; McGlynn et al, 2003; Richiardi et al, 2004; Bray et al, 2006; Verhoeven et al, 2008).

Men with cryptorchidism are four to six times more likely to have testis cancer diagnosed in the affected gonad, but the relative risk decreases to two to three times more likely if orchidopexy is performed before puberty (Dieckmann and Pichlmeier, 2004; Wood and Elder, 2009). A meta-analysis of cryptorchidism studies reported that the contralateral descended testis is also at slightly increased risk (relative risk 1.74 [95% confidence interval 1.01 to 2.98]) (Akre et al, 2009). Men with a first-degree relative with testis cancer have a substantially increased risk of testis cancer, and the median age at diagnosis in these men is 2 to 3 years younger than in the general population (Mai et al, 2009). A man's relative risk for testis cancer is 8 to 12 with an affected brother compared with 2 to 4 in men with an affected father (Westergaard et al, 1996; Sonneveld et al, 1999b; Hemminki and Chen, 2006). Men with a history of testis cancer have a 12-fold increased risk of developing GCT in the contralateral testis, but the 15-year cumulative incidence is only 2%.

Most GCTs arise from a precursor lesion, ITGCN (which is also referred to as carcinoma in situ). ITGCN is present in adjacent testicular parenchyma in 80% to 90% of cases of invasive GCT and is associated with a 50% risk of GCT within 5 years and 70% within 7 years (Skakkebaek et al, 1982; Dieckmann and Skakkebaek, 1999; Montironi, 2002). Of patients with GCT, 5% to 9% have ITGCN within the unaffected contralateral testis, although the incidence of contralateral ITGCN increases to about 36% in men with testicular atrophy or cryptorchidism (Dieckmann and

BOX 34-1 World Health Organization Classification of Testicular Tumors

Germ cell tumors	Lymphoid and hematopoietic tumors
Precursor lesions—intratubular malignant germ cells (carcinoma in situ)	Lymphoma
Tumors of one histologic type (pure forms)	Plasmacytoma
Seminoma	Leukemia
Variant—seminoma with syncytiotrophoblastic cells	Tumors of collecting ducts and rete
Spermatocytic seminoma	Adenoma
Variant—spermatocytic seminoma with sarcoma	Carcinoma
Embryonal carcinoma	Tumors of the tunica, epididymis, spermatic cord, supporting structures, and appendices
Yolk sac tumor	Adenomatoid tumor
Polyembryoma	Mesothelioma
Trophoblastic tumors	Benign
Choriocarcinoma	Malignant
Choriocarcinoma with other cell types	Adenoma
Placental site trophoblastic tumor	Carcinoma
Teratoma	Melanotic neuroectodermal
Mature teratoma	Desmoplastic small round cell tumor
Dermoid cyst	Soft-tissue tumors
Immature teratoma	Unclassified tumors
Teratoma with malignant areas	Secondary tumors
Tumors of more than one histologic type (mixed forms)—specify types and estimate percentage	Tumorlike lesions
Sex cord–gonadal stromal tumors	Nodules of immature tubules
Pure forms	Testicular lesions of adrenogenital syndrome
Leydig cell tumor	Testicular lesions of androgen-insensitivity syndrome
Sertoli cell tumor	Nodular precocious maturation
Large-cell calcifying Sertoli cell tumor	Specific orchitis
Lipid-rich Sertoli cell tumor	Nonspecific orchitis
Granulosa cell tumor	Granulomatous orchitis
Adult-type granulosa cell tumor	Malakoplakia
Juvenile-type granulosa cell tumor	Adrenal cortical rest
Tumors of thecoma/fibroma group	Fibromatous peritonitis
Incompletely differentiated sex cord–gonadal stromal tumors	Funiculitis
Mixed forms	Residue of meconium peritonitis
Unclassified forms	Sperm granuloma
Tumors containing germ cell and sex cord–gonadal stromal elements	Vasitis nodosa
Gonadoblastoma	Sclerosing lipogranuloma
Mixed germ cell and sex cord–gonadal stromal tumors, unclassified	Gonadal splenic fusion
Miscellaneous tumors	Mesonephric remnants
Carcinoid tumor	Endometriosis
Tumors of ovarian epithelial types	Epidermal cyst
	Cystic dysplasia
	Mesolithial cyst
	Others

Data from Vogelzang NJ, Scardino PT, Shipley WU, et al, editors. Genitourinary oncology. Philadelphia: Lippincott Williams & Wilkins; 1999.

Loy, 1996; Dieckmann and Skakkebaek, 1999). Gene expression profile analysis indicates that ITGCN develops before birth from an arrested gonocyte (Hussain et al, 2008; Sonne et al, 2009). In men with a history of GCT, the finding of testicular microlithiasis on ultrasound of the contralateral testis is associated with an increased risk of ITGCN (Karellas et al, 2007). However, the significance of microlithiasis in the general population is unclear; a study of 1500 Army volunteers found a 5.6% prevalence of microlithiasis, yet less than 2% of men with microlithiasis developed GCT within 5 years (DeCastro et al, 2008).

Pathogenesis and Biology

The carcinogenesis of GCTs is poorly understood (Looijenga et al, 2011; Turnbull and Rahman, 2011; Sheikine et al, 2012). As noted earlier, testicular GCTs develop from a precursor lesion,

ITGCN, which appears to develop from arrested primordial germ cells or gonocytes that failed to differentiate into prespermatogonia (Rajpert-de Meyts and Hoei-Hansen, 2007; Hussain et al, 2008; Looijenga et al, 2011). These cells are thought to lay dormant until after puberty, when they are stimulated by increased testosterone levels.

The increased incidence of testis cancer that started in the first half of the 20th century has been accompanied by an increased incidence of other male reproductive disorders, such as hypospadias, cryptorchidism, and subfertility (Rajpert-de Meyts and Hoei-Hansen, 2007; Sonne et al, 2008). These findings led to the hypothesis that testis cancer and these other disorders all resulted from a testicular dysgenesis syndrome, which resulted from environmental and/or lifestyle factors and genetic susceptibility. The specific environmental or lifestyle factors have not been defined. Increased prenatal estrogen exposure has been hypothesized as a

risk factor, but this is controversial (Martin et al, 2008). There is stronger evidence that reduction in androgen activity can result in features of testicular dysgenesis syndrome, including cryptorchidism, hypospadias, and impaired spermatogenesis, but a direct link between reduced androgen signaling and ITGCN remains hypothetical (Sonne et al, 2008; Hu et al, 2009).

Evidence of environmental and lifestyle factors contributing to testis cancer includes the rapid increase in its incidence and findings that risk of second-generation immigrants is similar to their country of birth. In addition, mothers of children with testis cancer (but not the patients with testis cancer themselves) have been found to have higher blood levels of certain organic pollutants compared with other mothers (Sonne et al, 2008). Evidence for genetic factors includes the clustering of testis cancer in some families; the extreme difference in the rate of testis cancer in black and white Americans; and the finding of susceptibility loci on chromosomes 5, 6, and 12 in case-control studies (Mai et al, 2009). In addition, specific polymorphisms of certain genes, including the gene encoding c-KIT ligand, have been associated with an increased risk of testis cancer (Blomberg Jensen et al, 2008; Kanetsky et al, 2009; Turnbull and Rahman, 2011; Sheikine et al, 2012). Gonocytes depend on KIT ligand for survival, and the gene for this protein is located on the short arm of chromosome 12. An increased number of copies of genetic material from the short arm of chromosome 12 is a universal finding in testicular and extragonadal germ cell tumors. Of GCTs, 70% to 80% have an extra copy of chromosome 12 in the form of an isochromosome 12p ([i(12p)]), whereas the remainder show gain of 12p sequences detectable with fluorescence in situ hybridization (Looijenga et al, 2003). A connection between mutations or polymorphisms in c-KIT ligand and GCT has biologic plausibility.

One of the most striking features of GCTs is their sensitivity to cisplatin-based chemotherapy, which enables cure in most patients with widely metastatic disease. The specific biologic basis of this acute vulnerability to chemotherapy is incompletely understood but is thought to derive from the close relationship between GCTs and embryonal stem cells and gonocytes, which have a low threshold for undergoing apoptosis in response to DNA damage (Mayer et al, 2003; Schmelz et al, 2010). Gene expression analysis has found an upregulation of numerous genes that facilitate apoptosis, including *FasL*, *TRAIL*, and *Bax*, whereas *BCL-2* is downregulated (Schmelz et al, 2010). Expression patterns of genes controlling the G₁/S-phase checkpoint in GCTs appear to promote induction of apoptosis (Schmelz et al, 2010). In addition, GCTs lack transporters to export cisplatin from the cell and have a reduced ability to repair cisplatin-induced DNA damage (Mayer et al, 2003). GCTs have high intrinsic levels of wild-type p53 protein (which plays a role in mediating cell cycle arrest and apoptosis), and p53 mutations in GCTs are rare, yet differences have not been consistently found in p53 status when comparing chemosensitive and chemoresistant GCTs (Burger et al, 1998; Houldsworth et al, 1998). Similarly, expression of the antiapoptotic protein BCL-2 is low in GCTs, but BCL-2 levels do not distinguish chemosensitive and chemoresistant cell lines (Mayer et al, 2003). A small fraction of GCTs are resistant to chemotherapy, and the basis of that resistance remains obscure (Veenstra and Vaughn, 2011). Impaired DNA mismatch repair and activating *BRAF* mutations have been associated with treatment failure (Honecker et al, 2009; Looijenga et al, 2011; Veenstra and Vaughn, 2011; Sheikine et al, 2012).

Approximately 5% of GCTs are extragonadal in origin and develop in midline anatomic locations (retroperitoneum and mediastinum are most common). There are two main competing theories regarding the pathogenesis of extragonadal GCTs. The first hypothesizes that they originate from germ cells that mistakenly migrated along the genital ridge and were able to survive in an extragonadal environment. The second theory proposes a reverse migration from the testis to extragonadal locations (Chaganti and Houldsworth, 2000).

Primary mediastinal NSGCTs differ in several ways from NSGCTs originating in the testis or retroperitoneum (Moran and Suster, 1997a; Moran et al, 1997a, 1997b; Moran and Suster, 1998).

First, they are less sensitive to chemotherapy and have a poor prognosis with a 5-year overall survival of about 45% (Bokemeyer et al, 2002b). Mediastinal NSGCTs are more likely to have yolk sac tumor components and to be associated with elevations in serum α -fetoprotein (AFP) (Moran et al, 1997a; Bokemeyer et al, 2002b; Kesler et al, 2008). They are also associated with Klinefelter syndrome and with hematologic malignancies that carry extra copies of the short arm of chromosome 12, as seen in adult GCT (Bokemeyer et al, 2002a; McKenney et al, 2007). In contrast, mediastinal seminomas have a prognosis similar to testicular seminomas, and mature teratomas of the mediastinum have low metastatic potential and can generally be cured surgically (Lewis et al, 1983; International Germ Cell Consensus Classification, 1997; Allen, 2002). Primary retroperitoneal GCTs are indistinguishable biologically from testicular GCTs and carry the same prognosis.

Histologic Classification

The histologic classification of GCTs is outlined in Box 34-2 (Sobin and Wittekind, 2002). GCTs are broadly classified as seminoma and NSGCT, and the relative distribution is 52% to 56% and 44% to 48%, respectively (McGlynn et al, 2005; Powles et al, 2005). NSGCTs include embryonal carcinoma (EC), yolk sac tumor, teratoma, and choriocarcinoma subtypes, occurring either alone as pure forms or in combination as mixed GCT with or without seminoma (Ulbright, 2005). Most NSGCTs are mixed tumors that are composed of two or more GCT subtypes. GCTs that contain both NSGCT subtypes and seminoma are classified as NSGCTs.

Intratubular Germ Cell Neoplasia

With the exception of spermatocytic seminoma, all adult invasive GCTs arise from ITGCN. ITGCN consists of undifferentiated germ cells that have the appearance of seminoma that are located basally within the seminiferous tubules. The tubule usually shows decreased or absent spermatogenesis, and normal constituents are replaced by ITGCN. The presence of ITGCN in an orchiectomy specimen in men with testis cancer does not have any prognostic implications with regard to the risk of relapse (von Eyben et al, 2004). ITGCN is much less frequent in GCTs in pediatric patients (Cheville, 1999).

BOX 34-2 World Health Organization Classification of Germ Cell Tumors

- Intratubular germ cell neoplasia
- Tumors of one histologic type (pure forms)
 - Seminoma
 - Seminoma with syncytiotrophoblastic cells
 - Spermatocytic seminoma
 - Embryonal carcinoma
 - Yolk sac tumor
 - Trophoblastic tumors
 - Choriocarcinoma
 - Trophoblastic neoplasms other than choriocarcinoma
 - Monophasic choriocarcinoma
 - Placental site trophoblastic tumor
 - Teratoma
 - Dermoid cyst
 - Monodermal teratoma
 - Teratoma with somatic type malignancy (malignant transformation)
- Tumors of more than one histologic subtype (mixed forms)

From Sobin LH, Wittekind CH. UICC: TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss; 2002.

Seminoma

Seminoma is the most common type of GCT. On average, seminomas occur at an older average age than NSGCTs, with most cases diagnosed in the fourth or fifth decade of life (Cheville, 1999). Grossly, seminoma is a soft tan-to-white diffuse or multinodular mass (Fig. 34-1A). Necrosis may be present but is usually focal and

not as prominent as in other GCTs. Seminomas consist of a sheet-like arrangement of cells with polygonal nuclei and clear cytoplasm, with the cells divided into nests by fibrovascular septa that contain lymphocytes (Fig. 34-1B) (Ulbright, 2005). Syncytiotrophoblasts, which stain positive for human chorionic gonadotropin (hCG), can be identified in about 15% of cases but are of no clear prognostic significance (Cheville, 1999). Lymphocytic infiltrates and

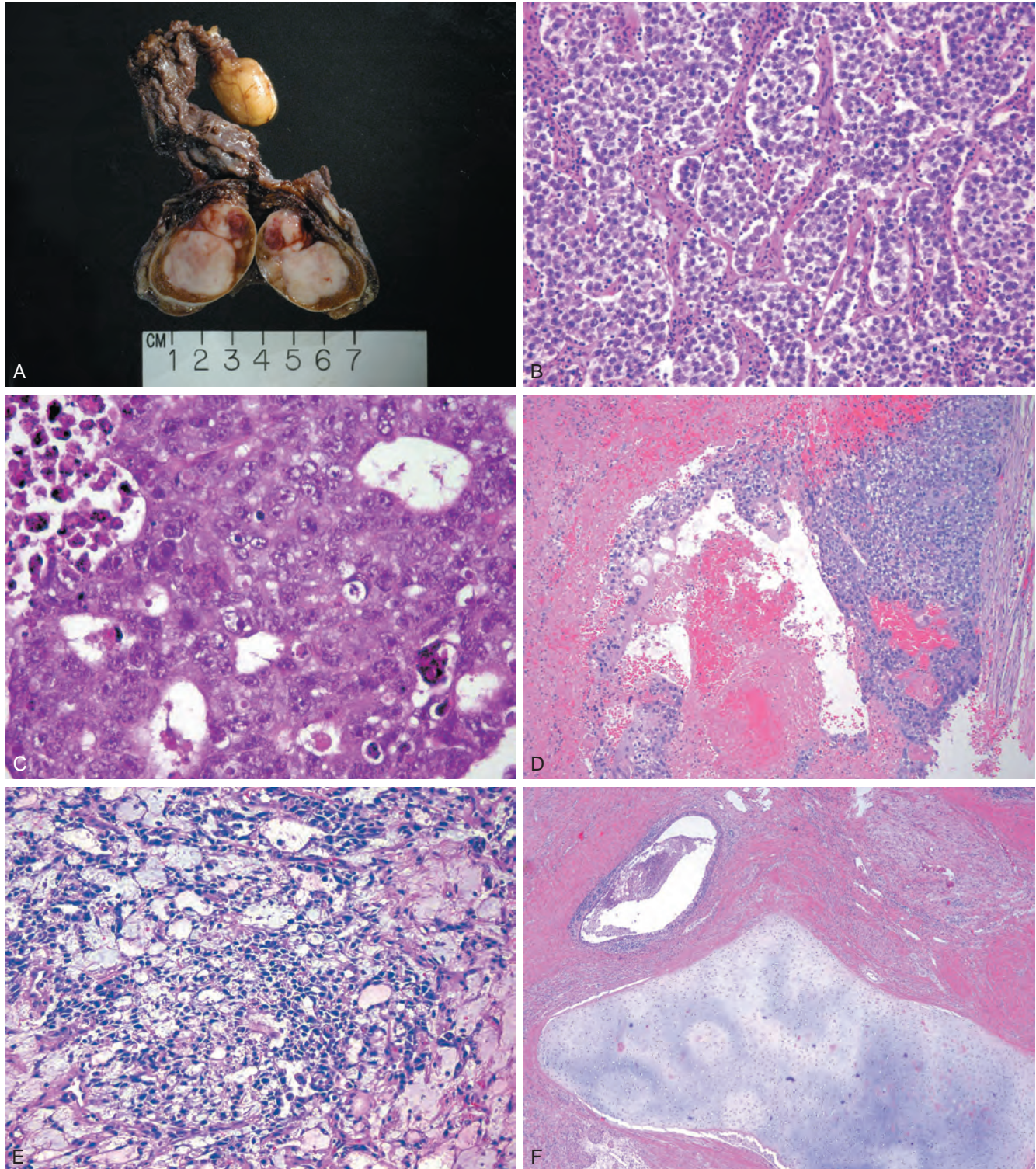


Figure 34-1. A, Gross section of testis containing seminoma. B, Seminoma (hematoxylin-eosin [H&E] stain). C, Embryonal carcinoma (H&E stain). D, Choriocarcinoma (H&E stain). E, Yolk sac tumor (H&E stain). F, Teratoma (H&E stain).

granulomatous reactions are often seen, and seminomas appear to be associated with an increased incidence of sarcoidosis (Rayson et al, 1998; Tjan-Heijnen et al, 1998). Seminomas may be confused with solid-pattern EC, yolk sac tumor, or Sertoli cell tumors (Ulbright and Young, 2008). Although immunohistochemical staining has a limited role in diagnosing GCTs, seminomas are typically negative for CD30, positive for CD117, and strongly positive for placental alkaline phosphatase (PLAP). Anaplastic seminoma was a previously recognized subtype of seminoma, but this distinction is of no clear biologic or clinical significance and is no longer recognized. **Seminoma arises from ITGCN and is considered to be the common precursor for the other NSGCT subtypes (Ulbright, 2004).** This ability of seminoma to transform into NSGCT elements has important therapeutic implications for the management of seminoma (discussed later) (Ulbright, 2004).

Spermatocytic Seminoma

Spermatocytic seminoma is rare and accounts for less than 1% of GCTs. Although classified as a variant of seminoma, these tumors represent a distinct clinicopathologic entity from other GCTs. In contrast to other GCTs, spermatocytic seminomas do not arise from ITGCN, are not associated with a history of cryptorchidism or bilaterality, do not demonstrate i(12p), and do not occur as part of mixed GCTs (Ulbright, 2005). Histopathologically, they differ from seminoma in that they do not stain for PLAP or glycogen (periodic acid–Schiff stain); nuclei are round; minimal lymphocytic infiltration is present; and three distinct cell types are present, including small lymphocyte-like cells, medium-size cells with dense eosinophilic cytoplasm and a round nucleus, and large mononucleated or multinucleated cells (Aggarwal and Parwani, 2009). The peak incidence is the sixth decade of life (Eble, 1994; Chung et al, 2004a). It is a benign tumor (only three documented cases of metastases) and is almost always cured with orchiectomy (Chung et al, 2004a; Horn et al, 2011). An exception to this rule are the rare cases of spermatocytic seminoma with sarcoma, which exhibit elements of sarcomatous differentiation, and anaplastic variant of spermatocytic seminoma; both of these entities are associated with widely metastatic chemotherapy-resistant disease and poor prognosis (Dundr et al, 2007; Narang et al, 2012; Wetherell et al, 2013).

Embryonal Carcinoma

EC consists of undifferentiated malignant cells resembling primitive epithelial cells from early-stage embryos with crowded pleomorphic nuclei (Ulbright, 2005). Grossly, EC is a tan-to-yellow neoplasm that often exhibits large areas of hemorrhage and necrosis. The microscopic appearance of these tumors varies considerably, and they may grow in solid sheets or in papillary, glandular-alveolar, or tubular patterns (Fig. 34-1C). In some cases, syncytiotrophoblasts are identified. EC is an aggressive tumor associated with a high rate of metastasis, often in the context of normal serum tumor markers. EC is the most undifferentiated cell type of NSGCT, with totipotential capacity to differentiate to other NSGCT cell types (including teratoma) within the primary tumor or at metastatic sites. As discussed subsequently, the presence and proportion of EC have been associated with an increased risk of occult metastases in clinical stage (CS) I NSGCT. EC typically stains for AE1/AE3, PLAP, and OCT3/4 and does not stain for c-KIT.

Choriocarcinoma

Choriocarcinoma is a rare and aggressive tumor that typically manifests with extremely highly elevated serum hCG levels and disseminated disease. These tumors are typically deemed poor risk (stage IIIC) at diagnosis because of the serum hCG level and/or nonpulmonary organ metastases (Alvarado-Cabrero et al, 2014). **Choriocarcinoma commonly spreads by hematogenous routes,** and common sites of metastases include lungs, liver, and brain (Tinkle et al, 2001; Allen, 2002; Osada et al, 2004; Yokoi et al, 2008;

Alvarado-Cabrero et al, 2014). Microscopically, the tumor is composed of syncytiotrophoblasts and cytotrophoblasts, and the former stain positively for hCG (Fig. 34-1D) (Cheville, 1999). Seminoma and EC may also contain syncytiotrophoblasts. Areas of hemorrhage and necrosis are prominent. Similar to gestational trophoblastic disease, testicular choriocarcinoma is prone to hemorrhage, sometimes both spontaneously and immediately after chemotherapy is initiated, and such bleeding can be catastrophic, particularly when it occurs in the lungs or brain (Motzer et al, 1987; Yokoi et al, 2008; Kandori et al, 2010). In addition, choriocarcinomas are associated with hormonal disturbances, most likely as a result of highly elevated serum hCG. Stimulation of receptors for thyroid-stimulating hormone and luteinizing hormone by hCG (which shares an identical α subunit) can result in hyperthyroidism and elevated androgen production (Ulbright, 2005). Hyperprolactinemia also has been reported.

Yolk Sac Tumor

Pure yolk sac tumors (sometimes called endodermal sinus tumors) represent a very small fraction of adult gonadal and retroperitoneal GCTs but are more common in mediastinal and pediatric GCTs (Moran et al, 1997a; Moran and Suster, 1997b; Ross et al, 2002; Ulbright, 2005; Cao and Humphrey, 2011). Mixed GCTs often include elements of yolk sac tumor, which consists of a reticular network of medium-sized cuboidal cells with cytoplasmic and extracytoplasmic eosinophilic, hyaline-like globules (Epstein, 2010). Yolk sac tumors may grow in a glandular, papillary, or microcystic pattern. Schiller-Duval bodies, which resemble endodermal sinuses, are a characteristic feature and are seen in roughly half of cases (Fig. 34-1E). Cytoplasmic and extracellular eosinophilic hyaline globules are another characteristic histologic feature and can be present in 84% of cases. **Yolk sac tumors almost always produce AFP but not hCG.**

Teratoma

Teratomas are tumors that contain well-differentiated or incompletely differentiated elements of at least two of the three germ cell layers: endoderm, mesoderm, and ectoderm. Characteristically, all components are intermixed. Well-differentiated tumors are labeled mature teratomas, whereas tumors that are incompletely differentiated (i.e., similar to fetal or embryonal tissue) are labeled immature teratomas. **In adolescent boys and men, there is no clinical significance to the distinction between mature and immature teratomas, and histopathologists do not typically distinguish between the two entities.** Mature teratomas may include elements of mature bone, cartilage, teeth, hair, and squamous epithelium (a fact that most likely explains the name teratoma, which roughly means “monster tumor” in Greek) (Fig. 34-1F). The gross appearance of teratoma depends largely on the elements within it, with most tumors having solid and cystic areas. **Teratomas are generally associated with normal serum tumor markers, but they may cause mildly elevated serum AFP levels.** Approximately 47% of adult mixed GCTs contain teratoma; pure teratomas are uncommon (Leibovitch et al, 1995b; Simmonds et al, 1996).

In men, teratomas have a histologically benign appearance but are frequently found at metastatic sites in patients with advanced NSGCT. **Teratoma is resistant to chemotherapy.** Given its frequent presence at metastatic sites in advanced NSGCT, patients with residual masses after chemotherapy require consolidative surgical resection. The inherent chemoresistance of teratoma is a limitation to treatment strategies for NSGCT that use chemotherapy alone.

Despite their benign histologic appearance, teratomas contain many genetic abnormalities frequently found in malignant GCT elements, including aneuploidy, i(12p), and widely variable proliferative capacity (Castedo et al, 1989; Sella et al, 1991). Studies have also shown that cystic fluid from teratoma frequently contains hCG and AFP, confirming its malignant potential (Sella et al, 1991; Beck et al, 2004). The genetic instability of teratoma has

important clinical implications. Teratomas may grow uncontrollably, invade surrounding structures, and become unresectable (termed *growing teratoma syndrome*) (Logothetis et al, 1982). Rarely, teratoma may transform into a somatic malignancy, such as rhabdomyosarcoma, adenocarcinoma, or primitive neuroectodermal tumor (Little et al, 1994; Comiter et al, 1998; Motzer et al, 1998). These tumors are called teratoma with somatic-type malignancy or teratoma with malignant transformation. These tumors frequently have abnormalities of i(12p), indicating their origin from GCT. Malignant transformation is highly aggressive, resistant to conventional chemotherapy, and associated with a poor prognosis (Comiter, 1998; El Mesbahi et al, 2007). Lastly, unresected teratoma in patients with advanced NSGCT may result in late relapse (Sheinfeld, 2003). All of these events may result in death.

KEY POINTS: GERM CELL TUMORS

- GCT is the most common solid malignancy among men 20 to 40 years old.
- Bilateral GCT occurs in 2% of men. A metachronous lesion is the most common presentation.
- The incidence of GCT is highest in whites and lowest in African-Americans.
- Cryptorchidism, personal or family history of GCT, and ITGCN are known risk factors for GCT.
- Orchidopexy for cryptorchidism performed before puberty is associated with a decreased risk of GCT.
- Approximately 70% of GCTs have an extra copy of chromosome 12 or i(12p), and this genetic marker may be used in the histopathologic diagnosis of GCT and non-GCT somatic malignancy arising from malignant transformation of teratoma.
- Approximately 5% of GCTs originate at extragonadal sites, most commonly mediastinum and retroperitoneum. Primary mediastinal NSGCTs are associated with a poor prognosis.
- Teratoma is histologically benign. Teratoma at metastatic sites arises from differentiation of metastatic embryonal carcinoma.
- Teratoma is resistant to chemotherapy.
- Teratoma is histologically benign but genetically unstable. It has unpredictable biology. Although uncommon, teratoma has the capacity to grow rapidly or undergo malignant transformation of ectodermal, mesodermal, or endodermal elements to form a non-GCT somatic malignancy.

Initial Presentation

Signs and Symptoms

The most common presentation of testis cancer is a **painless testis mass**. Acute testicular pain is less common and is caused by rapid expansion of the testis secondary to intratumor hemorrhage or infarction caused by rapid tumor growth. Pain is more commonly associated with NSGCT because these tumors tend to be more vascular and exhibit more rapid growth compared with seminomas. Patients frequently report a history of testicular trauma; incidental trauma is likely responsible for bringing the testis mass to the patient's attention for the first time. Patients may also complain of vague scrotal discomfort or heaviness. **Regional or distant metastasis at diagnosis is present in approximately one third of cases of NSGCT and 15% of cases of pure seminoma, and symptoms related to metastatic disease are the presenting complaint in 10% to 20% of patients** (Sonneveld et al, 1999a; Enewold et al, 2011). Bulky retroperitoneal metastasis may cause a palpable mass, abdominal pain, flank pain secondary to ureteral obstruction, back pain owing to involvement of the psoas muscle or nerve roots, lower extremity swelling secondary to compression of the inferior vena cava, or gastrointestinal symptoms. Pulmonary

metastasis may manifest with dyspnea, chest pain, cough, or hemoptysis. Metastasis to supraclavicular lymph nodes may manifest as a neck mass. **Approximately 2% of men have gynecomastia**, resulting from elevated serum hCG levels, decreased androgen production, or increased estrogen levels (most commonly seen in men with Leydig cell tumors). **Although approximately two thirds of men with GCT have diminished fertility, it is an uncommon initial presentation.**

Physical Examination

The physician should carefully examine the affected and the normal contralateral testis, noting their relative size and consistency and palpating for any testicular or extratesticular masses. Atrophy of the affected or contralateral testis is common, particularly in patients with a history of cryptorchidism. Any firm area within the testis should be considered suspicious for malignancy and should prompt further investigations. A hydrocele may accompany a testis cancer and impair the examiner's ability to evaluate the testis. In this case, a scrotal ultrasound scan to evaluate the testis is warranted. The patient also should be examined for any evidence of palpable abdominal mass or pain, inguinal lymphadenopathy (particularly if he has had prior inguinal or scrotal surgery), gynecomastia, and supraclavicular lymphadenopathy. Auscultation of the chest for intrathoracic disease should be done.

Differential Diagnosis

The differential diagnosis of a testis mass includes epididymo-orchitis, torsion, hematoma, or paratesticular neoplasm (benign or malignant). Other diagnostic possibilities include hernia, varicocele, or spermatocele, although these usually can be distinguished from a testis mass by physical examination. **A firm intratesticular mass should be considered cancer until proved otherwise and should be evaluated further with a scrotal ultrasound scan. Patients with a presumptive diagnosis of epididymo-orchitis should be re-evaluated within 2 to 4 weeks of completion of an appropriate course of oral antibiotics.** A persistent mass or pain should be evaluated further with scrotal ultrasonography.

Diagnostic Delay

Diagnostic delay is a well-recognized phenomenon of this disease, with patients and physicians contributing to this delay. Patients with testis cancer are typically young and may be less inclined to seek medical evaluation for symptoms because of denial, ignorance, or limited access. **In prior studies, up to one third of testis tumors were initially misdiagnosed as epididymitis or hydrocele** (Bosl et al, 1981). For patients who present with signs or symptoms resulting from metastatic GCT, these may become the focus of the treating physician, who fails to diagnose GCT. These patients may be subjected to inappropriate treatment, diagnostic tests, and unnecessary surgery with subsequent delays in definitive therapy. Case reports describe patients undergoing exploratory laparotomy, neck dissection, or mastectomy for unsuspected metastatic GCT. The interval of delay is associated with advanced clinical stage, suboptimal response to chemotherapy, and diminished survival. **Moul and colleagues (1990) reported a decrease in survival in patients with GCT treated during the period 1970 to 1987 with a diagnostic delay greater than 16 weeks, although a significant survival difference was not observed among patients treated in the cisplatin era.** **Stephenson and coworkers (2004) reported a higher proportion of men requiring intensive chemotherapy (multiple regimens, high-dose chemotherapy, and salvage chemotherapy) among men with a treatment delay greater than 30 days owing to unnecessary exploratory laparotomy.**

Diagnostic delay can be avoided by efforts to improve patient and physician education. Physicians must consider the diagnosis of GCT in any adolescent boy or man from age 15 to 50 years with a firm testis mass, midline retroperitoneal mass, or mass in the left supraclavicular fossa.

Diagnostic Testing and Initial Management

Scrotal Ultrasonography

In men presenting with a testis mass, hydrocele, or unexplained scrotal symptoms or signs, scrotal ultrasonography should be considered an extension of the physical examination because it is widely available, inexpensive, and noninvasive. With high-frequency transducers (5 to 10 MHz), intratesticular lesions a few millimeters in size can be identified and readily distinguished from extratesticular pathology. On ultrasound scan, a typical GCT is hypoechoic, and two or more discrete lesions may be identified (Fig. 34-2). Heterogeneous echotexture within a lesion is more commonly associated with NSGCT because seminomas usually have a homogeneous echotexture. The presence of increased flow within the lesion on color Doppler sonography is suggestive of malignancy, although its absence does not exclude GCT. The association between testicular microlithiasis and GCT is not clearly defined, and this finding alone should not prompt further evaluation (DeCastro et al, 2008). Given the 2% incidence of bilateral GCT, both testes should be evaluated with ultrasonography, although bilateral tumors at diagnosis are rare (0.5% of all GCTs), and metachronous presentation is more common (Fossa et al, 2005).

In men with advanced GCT and a normal testicular examination, scrotal ultrasonography should be performed to rule out the presence of a small, impalpable scar or calcification, indicating a “burned-out” primary testis tumor. GCTs are among the most common neoplasms to undergo spontaneous regression, with seminoma being the most frequent subtype (Balzer and Ulbricht, 2006). Radical orchiectomy should be performed in patients with sonographic evidence of intratesticular lesions (discrete nodule, stellate scar, coarse calcification) because ITGCN and residual teratoma are frequently encountered. Men with advanced GCT with normal testes on physical examination and ultrasound scan are considered to have primary extragonadal GCT.

The presence of small (<10 mm), impalpable intratesticular lesions in the absence of disseminated GCT or elevated serum tumor markers represents a diagnostic dilemma. Most of these lesions are benign (testicular cysts, small infarcts, Leydig cell nodules, or small Leydig cell or Sertoli cell tumors), although 20% to 50% may represent small GCTs (usually seminomas) (Hindley et al, 2003; Connolly et al, 2006; Muller et al, 2006; Shilo et al, 2012). The risk of malignancy increases with the size of the lesion, from 50% for lesions less than 1 cm to 80% or more for lesions 1 to 2 cm (Carmignani et al, 2005). Management options include inguinal orchiectomy, testis-sparing surgery involving inguinal

exploration and excision (with frozen-section analysis to rule out GCT), and close observation with serial ultrasound scans (with exploration of growing lesions). Intraoperative ultrasonography is useful during surgical exploration of the testis to locate the lesion.

Serum Tumor Markers

Testis cancer is one of the few malignancies associated with serum tumor markers (lactate dehydrogenase [LDH], AFP, and hCG) that are essential in its diagnosis and management (Gilligan et al, 2010). Serum tumor marker levels should be obtained at diagnosis, after orchiectomy, to monitor for response to chemotherapy, and to monitor for relapse in patients on surveillance and after completion of therapy.

At diagnosis, AFP levels are elevated in 50% to 70% of low-stage (CS I, IIA, and IIB) NSGCT and 60% to 80% of advanced (CS IIC and III) NSGCT. EC and yolk sac tumors secrete AFP. Choriocarcinomas and seminomas do not produce AFP. Patients with pure seminoma in the primary tumor with an elevated serum AFP are considered to have NSGCT. The half-life of AFP is 5 to 7 days. AFP levels may also be increased in patients with hepatocellular carcinoma; cancers of the stomach, pancreas, biliary tract, and lung; nonmalignant liver disease (infectious, drug-induced, alcohol-induced, autoimmune); ataxic telangiectasia; and hereditary tyrosinemia.

hCG levels are elevated in 20% to 40% of low-stage NSGCT and 40% to 60% of advanced NSGCT. Approximately 15% of seminomas secrete hCG. hCG is also secreted by choriocarcinoma and EC. Levels greater than 5000 IU/L are usually associated with NSGCT. The half-life of hCG is 24 to 36 hours. hCG levels may be elevated in cancers of the liver, biliary tract, pancreas, stomach, lung, breast, kidney, and bladder. The α subunit of hCG is common to several pituitary tumors, and so immunoassays for hCG are directed at the β subunit. Cross-reactivity of the hCG assay with luteinizing hormone may cause false-positive hCG elevations in patients with primary hypogonadism. Elevated serum hCG results caused by hypogonadism normalize within 48 to 72 hours after administration of testosterone, and this can be done to distinguish between true-positive and false-positive hCG results. Marijuana use may also cause false-positive hCG results.

LDH levels are elevated in approximately 20% of low-stage GCT and 20% to 60% of advanced GCT. LDH is expressed in smooth, cardiac, and skeletal muscle. Lymphoma may also cause elevated LDH levels. Of the five isoenzymes of LDH, LDH-1 is the most frequently elevated isoenzyme in GCT. LDH-1 levels are correlated with the chromosome arm 12p copy number, which is frequently amplified in GCT. The magnitude of LDH elevation correlates with the bulk of disease. As a nonspecific marker for GCT, its main use is in the assessment of prognosis of GCT at diagnosis. The serum half-life of LDH is 24 hours.

Patients suspected to have a GCT should have blood drawn for serum AFP, hCG, and LDH before orchiectomy to aid in the diagnosis and to help interpret tumor marker levels after orchiectomy. For staging purposes, it is relevant to know whether serum tumor marker levels obtained before orchiectomy are declining after orchiectomy and, if so, how quickly. The results of serum tumor marker assays should not be used to guide decision making about whether or not to perform a radical orchiectomy because AFP or hCG levels in the normal range do not rule out GCT. A significantly elevated serum AFP can establish the diagnosis of NSGCT in a patient whose histopathologic diagnosis is pure seminoma because seminomas do not produce AFP. However, borderline-elevated values should be interpreted cautiously. In rare patients who present with a testis, retroperitoneal, or mediastinal primary tumor and whose disease burden has resulted in a need to start treatment very urgently, substantially elevated serum AFP and/or hCG may be considered sufficient for diagnosis of GCT. For such rare, medically unstable patients, treatment need not be delayed until histology results permit a tissue diagnosis. However, these patients should undergo radical orchiectomy after the completion of chemotherapy because the testis is a sanctuary site for

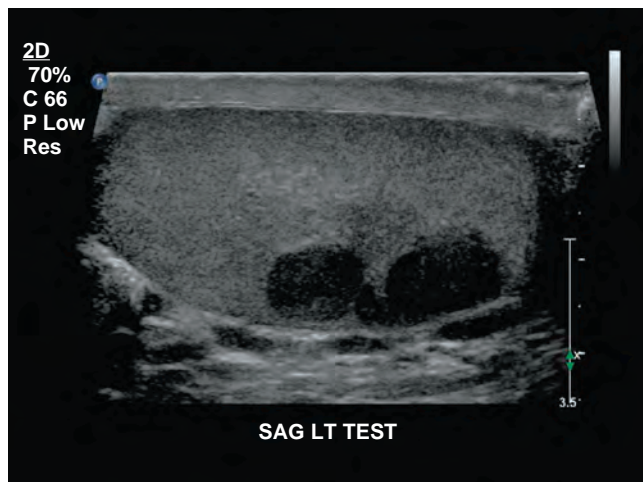


Figure 34-2. Sagittal view of ultrasound of left testis showing multi-nodular hypoechoic intratesticular lesion confirmed to be pure seminoma at orchiectomy.

malignant GCT owing to the blood-testis barrier, and the testis frequently contains residual invasive GCT, teratoma, or ITGCN (Geldart et al, 2002).

Radical Inguinal Orchiectomy

Patients suspected to have a testicular neoplasm should undergo a radical inguinal orchiectomy with removal of the tumor-bearing testicle and spermatic cord to the level of the internal inguinal ring. A trans-scrotal orchiectomy or biopsy is contraindicated because it leaves the inguinal portion of the spermatic cord intact and may alter the lymphatic drainage of the testis, increasing the risk of local recurrence and pelvic or inguinal lymph node metastasis. Because of the rapid growth of GCTs, orchiectomy should be performed in a timely manner; delays greater than 1 to 2 weeks should be avoided. Radical orchiectomy establishes the histologic diagnosis and primary T stage, provides important prognostic information from the tumor histology, and is curative in 80% to 85% of CS I seminoma and 70% to 80% of CS I NSGCT.

Histopathologic examination of the testis should identify the histologic type of the tumor (see Box 34-2) (Sobin and Wittekind, 2002), tumor size, multifocality, local tumor invasion (rete testis, tunica albuginea, tunica vaginalis, epididymis, spermatic cord, scrotum), primary T stage (Table 34-1) (Greene et al, 2002; Sobin and Wittekind, 2002), presence of ITGCN, invasion of blood or lymphatic vessels (termed *lymphovascular invasion*), and surgical margin status. For patients with mixed GCT, each individual tumor subtype should be identified including its relative proportion. Because of the relative rarity of GCT and the importance of primary tumor histology for treatment decision making, review of primary tumor specimens by experienced pathologists is recommended (Krege et al, 2008a, 2008b). In a randomized, multicenter clinical trial, 5 of 382 NSGCT specimens (1.3%) were reclassified as seminomas by centralized pathologic review (Albers et al, 2008).

Testis-Sparing Surgery

Testis-sparing surgery (or partial orchiectomy) is highly controversial and has no role in the treatment of a patient suspected to have a testicular neoplasm with a normal contralateral testis.

However, it may be considered for organ-confined tumors less than 2 to 3 cm in size (30% of testicular volume) in patients with synchronous bilateral tumors or tumor in a solitary testis with sufficient testicular androgen production. It may also be considered for suspected benign tumor or indeterminate lesion less than 3 cm when serum AFP, hCG, and LDH are normal because the incidence of benign histology is 80% (Giannarini et al, 2010). Testis-sparing surgery is seldom feasible for larger tumors (>3 cm) because a complete excision frequently leaves insufficient residual testicular parenchyma for preservation. When testis-sparing surgery is performed, intraoperative frozen-section analysis can distinguish between benign and malignant histology in most cases (Tokuc et al, 1992; Elert et al, 2002). Biopsy of the adjacent testicular parenchyma should be performed to rule out the presence of ITGCN. For patients with ITGCN, adjuvant radiotherapy to the residual testis using doses of 20 Gy or greater is usually sufficient to prevent the development of a GCT, while preserving Leydig cell function (and testicular androgen production). Radiation at these doses causes permanent sterility of the treated testis. Leydig cell function may decline over time, and 40% of men who receive radiation therapy require supplemental testosterone (Petersen et al, 2002). The German Testicular Cancer Study Group reported no cases of local recurrence over a median follow-up of 91 months in 46 patients with small, organ-confined tumors who underwent testis-sparing surgery and received adjuvant radiotherapy for ITGCN (Heidenreich et al, 2001). In contrast, recurrent testis cancer developed in four of five men who did not receive adjuvant radiotherapy. Adjuvant radiotherapy may be delayed after testis-sparing surgery if fathering a child is desired, although close follow-up is mandatory (Giannarini et al, 2010).

Contralateral Testis Biopsy

Of patients with GCT, 5% to 9% have ITGCN in the normal contralateral testis (Dieckmann and Skakkebaek, 1999). In patients with an atrophic testis, history of cryptorchidism, or age younger than 40 years, the prevalence of ITGCN in the contralateral testis has been reported to be 36% (Dieckmann and Loy, 1996). An open inguinal biopsy of the contralateral testis may be considered in patients with risk factors for ITGCN or patients with suspicious lesions on preoperative ultrasound scan (Motzer et al, 2006).

TABLE 34-1 TNM Staging of Testicular Tumor: American Joint Committee on Cancer and Union Internationale Contre le Cancer

PRIMARY TUMOR (T)*

The extent of primary tumor is usually classified after radical orchiectomy and, for this reason, a *pathologic* stage is assigned.

pTx	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g., histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade into tunica albuginea but not tunica vaginalis
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion or tumor extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion

REGIONAL LYMPH NODES (N)

Clinical (as Determined by Noninvasive Staging)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with lymph node mass ≤ 2 cm in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with lymph node mass, >2 cm, but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass >2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with lymph node mass >5 cm in greatest dimension

Continued

TABLE 34-1 TNM Staging of Testicular Tumor: American Joint Committee on Cancer and Union Internationale Contre le Cancer—cont'd

Pathologic (pN) (as Determined by Pathologic Findings of RPLND without Prior Chemotherapy or Radiotherapy)				
pNX	Regional lymph nodes cannot be assessed			
pN0	No regional lymph node metastasis			
pN1	Metastasis with lymph node mass ≤2 cm in greatest dimension and ≤5 nodes positive, none more than 2 cm in greatest dimension			
pN2	Metastasis with lymph node mass >2 cm but not more than 5 cm in greatest dimension; or >5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor			
pN3	Metastasis with lymph node mass >5 cm in greatest dimension			
DISTANT METASTASIS (M)				
MX	Distant metastasis cannot be assessed			
M0	No distant metastasis			
M1	Distant metastasis			
M1a	Nonregional nodal or pulmonary metastasis			
M1b	Distant metastasis at site other than nonregional lymph nodes or lung			
SERUM TUMOR MARKERS (S)				
SX	Marker studies unavailable or not performed			
S0	Marker study levels within normal limits			
S1	LDH <1.5 × N† and hCG (mIU/mL) <5000 and AFP (ng/mL) <1000			
S2	LDH 1.5-10 × N or hCG (mIU/mL) 5000-50,000 or AFP (ng/mL) 1000-10,000			
S3	LDH >10 × N or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000			
STAGE GROUPING				
GROUP	T	N	M	S (SERUM TUMOR MARKERS)
Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/Tx	N0	M0	S1-3
Stage II	Any pT/Tx	N1-3	M0	SX
Stage IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
Stage IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
Stage IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
Stage III	Any pT/Tx	Any N	M1	SX
Stage IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
Stage IIIB	Any pT/Tx	N1-3	M0	S2
	Any pT/Tx	Any N	M1a	S2
Stage IIIC	Any pT/Tx	N1-3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

*Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. Tx may be used for other categories in the absence of radical orchiectomy.

$\dagger N$ indicates the upper limit of normal for the LDH assay.

AFP, α -fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; RPLND, retroperitoneal lymph node dissection.

From AJCC. Testis. In: Edge SE, Byrd DR, Compton CC, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. p. 469-73. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, Seventh Edition (2010), published by Springer Science and Business Media, LLC, www.springer.com.

Suspected Extragenadal Germ Cell Tumor

Approximately 5% of GCTs are of extragenadal origin (Bokemeyer et al, 2002b). Of patients with metastatic GCT without a testis mass, only one third definitively have a primary extragenadal GCT; one third have ITGCN in the testis, and one third have sonographic evidence of a “burned-out” primary tumor (Scholz et al, 2002). GCT should be considered in any male under 40 years with a midline mass. The presence of elevated serum AFP and/or hCG with a normal testicular evaluation is sufficient for the diagnosis of GCT, and histologic confirmation by biopsy is unnecessary before starting treatment. In cases of normal serum tumor markers, a biopsy of the mass should be performed to confirm the diagnosis of GCT before beginning treatment. A biopsy specimen showing poorly differentiated carcinoma represents a diagnostic dilemma if a primary tumor site cannot be confirmed. In this scenario, the diagnosis of extragenadal GCT with malignant transformation may be considered and supported by the expression of i(12p) in biopsy specimens. Patients with suspected extragenadal GCT should undergo inguinal orchiectomy at some point during their treatment course if the pattern of metastasis is consistent with a right-sided or left-sided testicular primary tumor or if there is sonographic evidence of a “burned-out” primary tumor.

KEY POINTS: DIAGNOSIS AND INITIAL MANAGEMENT OF GERM CELL TUMOR

- A solid intratesticular mass in a postpubertal male patient should be considered a GCT until proved otherwise.
- With rare exceptions, inguinal orchiectomy with high ligation of the spermatic cord should be performed in men suspected to have GCT. Trans-scrotal orchiectomy and biopsy should be avoided.
- Testis-sparing surgery for GCT is a consideration in highly selected patients who have a small tumor in either a solitary testis or synchronous bilateral testis masses, in whom preservation of the affected testis would provide sufficient testicular androgen production.
- Diagnostic delay is common in GCTs, and approximately one third of cases are initially misdiagnosed.
- If serum tumor marker levels were elevated before orchiectomy, they should be measured after orchiectomy to determine if levels are declining, stable, or rising. Serum tumor marker levels obtained before orchiectomy should not be used in management decisions.

Clinical Staging

The prognosis of GCT and initial management decisions are dictated by CS of the disease, which is based on the histopathologic findings and pathologic stage of the primary tumor, serum tumor marker levels measured after orchiectomy, and the presence and extent of metastatic disease as determined by physical examination and staging imaging studies. In 1997, an international consensus classification for GCT was developed by the American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC) (see Table 34-1). The AJCC and UICC staging systems for GCT are unique because, for the first time, a serum tumor marker category (S) based on postorchiectomy AFP, hCG, and LDH levels is used to supplement the prognostic stages as defined by anatomic extent of disease. **The AJCC and UICC staging systems were updated in 2002, and the new systems consider the presence of LVI in the primary as pT2 in an otherwise organ-confined tumor. CS I is defined as disease clinically confined to the testis, CS II indicates the presence of regional (retroperitoneal) lymph node metastasis, and CS III represents nonregional lymph node and/or visceral metastasis.**

Staging Imaging Studies

GCT follows a predictable pattern of metastatic spread, which has contributed to its successful management. With the exception of choriocarcinoma, the most common route of disease dissemination is via lymphatic channels from the primary tumor to the retroperitoneal lymph nodes and subsequently to distant sites. Choriocarcinoma has a propensity for hematogenous dissemination. The retroperitoneum is the initial site of metastatic spread in 70% to 80% of patients with GCT. Detailed mapping studies from retroperitoneal lymph node dissection (RPLND) series have increased understanding of the testicular lymphatic drainage and identified the most likely sites of metastatic spread (Sheinfeld, 1994). For right testis tumors, the primary drainage site is the inter-aortocaval lymph nodes inferior to the renal vessels, followed by the paracaval and para-aortic nodes. The primary “landing zone” for left testis tumors is the para-aortic lymph nodes, followed by the inter-aortocaval nodes (Donohue et al, 1982). The pattern of lymph drainage in the retroperitoneum is from right to left. Contralateral spread from the primary “landing zone” is common with right-sided tumors but is rarely seen with left-sided tumors and usually is associated with bulky disease. More caudal deposits of metastatic disease usually reflect retrograde spread to distal iliac and inguinal lymph nodes secondary to large-volume disease and, more rarely, aberrant testicular lymphatic drainage. Retroperitoneal lymphatics drain into the cisterna chyli behind the right renal artery and right crus of the diaphragm. Retrocaval lymph node metastasis may be visible in patients with retroperitoneal disease. From there, lymphatic spread occurs via the thoracic duct to the posterior mediastinum and left supraclavicular fossa.

Clinical Staging of the Abdomen and Pelvis. All patients with GCT should undergo staging imaging studies of the abdomen and pelvis. Computed tomography (CT) imaging with oral and intravenous contrast material is the most effective, noninvasive means of staging the retroperitoneum and pelvis. CT imaging also provides a detailed anatomic assessment of the retroperitoneum to identify anatomic anomalies that may complicate subsequent RPLND, such as a circum-aortic or retro-aortic left renal vein, lower pole renal artery, or retrocaval right ureter. Magnetic resonance imaging is an alternative to CT, although it is associated with longer examination times, higher cost, and less availability.

Enlarged retroperitoneal lymph nodes are found on CT in approximately 10% to 20% of seminomas and 60% to 70% of NSGCTs. The retroperitoneum is the most difficult area to assign CS accurately. A consistent 25% to 35% rate of pathologically involved retroperitoneal lymph nodes has been reported for CS I NSGCT in the presence of a “normal” CT scan despite the improvements in CT imaging over the last four decades (Fernandez et al, 1994). There is no consensus regarding size criteria for retroperitoneal lymph nodes that constitutes a “normal” CT scan. A size cutoff of 10 mm is frequently used to identify enlarged lymph nodes, but false-negative rates up to 63% have been reported when this size criterion is used. Among patients with CS IIA and IIB disease, clinical overstaging by CT (i.e., pathologically negative lymph nodes at RPLND despite enlarged lymph nodes on CT) is reported in 12% to 40% of patients.

An understanding of the primary drainage sites for left-sided and right-sided tumors has led to efforts to increase the sensitivity of abdominopelvic CT imaging by decreasing the size criteria for clinically positive lymph nodes in the primary landing zone. Leibovitch and colleagues (1995a) showed that using a size cutoff of 4 mm in the primary landing zone and 10 mm outside this region was associated with sensitivity and specificity for pathologic stage II disease of 91% and 50%, respectively. In a similar study, Hilton and associates (1997) reported sensitivity and specificity of 93% and 58%, respectively, using a cutoff of 4 mm for lymph nodes in the primary landing zone that were anterior to a horizontal line bisecting the aorta. **Based on this evidence, retroperitoneal lymph nodes 5 to 9 mm in size in the primary landing zone should be viewed with suspicion for regional lymph node metastasis, particularly if they**



Figure 34-3. Postorchiectomy computed tomography image of the abdomen and pelvis in a patient with right testicular nonseminoma germ cell tumor showing a 7-mm lymph node in a primary landing zone. The lymph node was involved with teratoma at retroperitoneal lymph node dissection.

are anterior to the great vessels on transaxial images (Fig. 34-3). Because of the rapid growth of GCTs, it is advisable to base management decisions on CT imaging studies performed within 4 weeks of the initiation of treatment.

Malignant GCTs accumulate fluorodeoxyglucose (FDG), and several studies have investigated positron emission tomography with FDG (FDG-PET) in the staging of GCTs at diagnosis and assessing response after chemotherapy. Several small pilot studies suggested that FDG-PET can identify retroperitoneal metastasis in low-stage seminoma and NSGCT more precisely than CT (Albers et al, 1999). In a prospective trial of centrally reviewed FDG-PET studies in 111 contemporary patients with CS I NSGCT on surveillance, relapse was observed in 33 of 87 patients who were PET-negative with an estimated relapse-free rate of 63% (Huddart et al, 2007). The investigators concluded that FDG-PET is not sufficiently sensitive to stage CS I NSGCT accurately. *de Wit and colleagues* (2008) also reported that FDG-PET yielded only slightly better results than CT as a primary staging tool for low-stage NSGCT. **There is currently no role for FDG-PET in the routine evaluation of NSGCT and seminoma at the time of diagnosis.**

CS II disease is subclassified based on the size of regional lymph nodes as determined by abdominopelvic imaging into IIA (enlarged retroperitoneal lymph nodes ≤ 2 cm), IIB (enlarged retroperitoneal lymph nodes >2 cm but ≤ 5 cm), and IIC (enlarged lymph nodes >5 cm).

Pathologic Staging of the Abdomen and Pelvis. In selected European centers performing open RPLND and most laparoscopic RPLND series, RPLND is performed in patients with CS I or IIA NSGCT largely as a staging procedure without curative intent to identify the presence of regional lymph nodes and determine the need for subsequent chemotherapy (Nelson et al, 1999; Janetschek et al, 2000; Albers et al, 2003; Bhayani et al, 2003; Nielsen et al, 2007; Albers et al, 2008). Pathologic N stage differs from clinical N stage in that the former considers the number of lymph nodes involved: pN0, no regional lymph node metastasis; pN1, five or fewer lymph nodes involved, none larger than 2 cm; pN2, more than five lymph nodes involved and/or any lymph node 2 to 5 cm; pN3, any lymph node larger than 5 cm. In patients with pathologic stage II disease (pTany, pN1-3, M0), the risk of occult metastases (and relapse after RPLND) is closely related to the burden of regional lymph node metastasis (10% to 30% of pN1 vs. 50% to 80% for pN2-3). The pathologic N stage cannot be applied to RPLND specimens from patients who have received prior chemotherapy.

Chest Imaging

All patients with GCTs should undergo chest imaging before management decisions are made. Thoracic metastasis in the absence of retroperitoneal disease and/or elevated serum tumor markers is uncommon, particularly for seminomas. Routine chest CT imaging may be associated with a high rate of false-positive findings, which may complicate subsequent therapy (Horan et al, 2007). It is reasonable to obtain chest radiographs at the time of diagnosis as an initial staging study, and CT should be performed in patients with elevated serum tumor markers after orchiectomy, evidence of metastatic disease by physical examination or abdominopelvic CT imaging, or abnormal or equivocal findings on chest radiograph. It may be reasonable to order chest CT in patients with CS I NSGCT with evidence of LVI or EC predominance because some studies have reported a high rate of hematogenous metastasis to lung in the setting of a negative CT scan for retroperitoneal metastasis (Hermans et al, 2000; Sweeney et al, 2000). Mediastinal or hilar lymphadenopathy in the absence of retroperitoneal disease should raise the index of suspicion of non-GCT etiology such as lymphoma or sarcoidosis, and histologic confirmation of GCT by mediastinoscopy and biopsy should be performed before initiating systemic therapy (Hunt et al, 2009).

Visceral metastasis to bone and brain is uncommon in GCT in the absence of symptoms or other clinical indicators of disease. There is no role for routine bone scintigraphy or brain CT imaging at the time of diagnosis. A notable exception is brain CT imaging for patients with a highly elevated hCG ($>10,000$ mU/mL) because these levels are often associated with metastatic choriocarcinoma, which has a propensity for brain metastases.

Serum Tumor Markers

AFP, hCG, and LDH levels measured after orchiectomy are important for staging, prognosis, and treatment selection. All patients should have serum tumor markers drawn after orchiectomy to assess for appropriate decline according to half-life in patients with elevated levels before orchiectomy. Newly elevated and/or rising serum tumor marker levels after orchiectomy indicate the presence of metastatic disease, and these patients should receive induction chemotherapy. In the setting of a negative metastatic evaluation and slowly declining markers (i.e., not according to half-life), patients should be monitored closely and have levels checked periodically until the levels normalize or begin to rise. Stable AFP or hCG levels slightly above the normal range should be interpreted cautiously, and other causes for serum tumor marker elevation should be ruled out before management decisions are made. As with staging imaging studies, management decisions should be based on serum tumor marker levels measured within 4 weeks of the initiation of treatment.

Prognostic Classification of Advanced Germ Cell Tumors

An international, retrospective pooled analysis of 5202 patients with advanced NSGCT treated between 1975 and 1990 with platin-containing chemotherapy regimens (cisplatin or carboplatin) identified AFP, hCG, and LDH levels at the initiation of chemotherapy; the presence of nonpulmonary visceral metastasis; and primary mediastinal NSGCT as significant and independent prognostic factors for progression and survival (International Germ Cell Consensus Classification, 1997). In 660 patients with advanced seminoma, only the presence of nonpulmonary visceral metastasis was an important predictor of progression and survival (International Germ Cell Consensus Classification, 1997).

Based on these analyses, the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification for advanced GCT was developed (Table 34-2) (International Germ Cell Consensus Classification, 1997). The IGCCCG risk group should be determined for each patient with metastatic GCT, and this should be used to guide treatment decision making on the choice of chemotherapy (discussed later). This classification applies only to

TABLE 34-2 International Germ Cell Cancer Collaborative Group Risk Classification for Advanced Germ Cell Tumor

NONSEMINOMA	SEMINOMA
GOOD PROGNOSIS	
Testicular/retroperitoneal primary <i>and</i> No nonpulmonary visceral metastases <i>and</i> Good markers—all of: AFP <1000 ng/mL <i>and</i> hCG <5000 IU/L (1000 ng/mL) <i>and</i> LDH <1.5 × upper limit of normal (N) 56% of nonseminomas 5-year PFS 89% 5-year survival 92%	Any primary site <i>and</i> No nonpulmonary visceral metastases <i>and</i> Normal AFP, any hCG, any LDH 90% of seminomas 5-year PFS 82% 5-year survival 86%
INTERMEDIATE PROGNOSIS	
Testicular/retroperitoneal primary <i>and</i> No nonpulmonary visceral metastases <i>and</i> Intermediate markers—any of: AFP ≥1000–10,000 ng/mL <i>and</i> ≤10,000 ng/mL <i>or</i> hCG ≥5000–50,000 IU/L <i>and</i> ≤50,000 IU/L <i>or</i> LDH ≥1.5 × N <i>and</i> ≤10 × N 28% of nonseminomas 5-year PFS 75% 5-year survival 80%	Any primary site <i>and</i> Nonpulmonary visceral metastases <i>and</i> Normal AFP, any hCG, any LDH 10% of seminomas 5-year PFS 67% 5-year survival 72%
POOR PROGNOSIS	
Mediastinal primary <i>or</i> Nonpulmonary visceral metastases <i>or</i> Poor serum markers—any of: AFP >10,000 ng/mL <i>or</i> hCG >50,000 IU/L (10,000 ng/mL) <i>or</i> LDH >10 × upper limit of normal 16% of nonseminomas 5-year PFS 41% 5-year survival 48%	No patients classified as poor prognosis

AFP, α -fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; PFS, progression-free survival.

From International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol* 1997;15:594–603.

patients with advanced GCT at the time of diagnosis and is not applicable to patients with relapsed GCT. It is also based on the postorchietomy serum tumor marker levels at the start of chemotherapy, not levels measured before orchietomy.

According to IGCCCG criteria, approximately 56% of patients with advanced NSGCT are classified as good risk, 28% are classified as intermediate risk, and 16% are classified as poor risk, and the

5-year progression-free and overall survival rates for these patients are 89% and 92% (good risk), 75% and 80% (intermediate risk), and 41% and 48% (poor risk). There is no poor risk category for seminoma. Approximately 90% and 10% of patients with advanced seminoma are classified as good and intermediate risk by IGCCCG criteria, respectively, and the 5-year progression-free and overall survival rates for these patients are 82% and 86% (good risk) and 67% and 72% (intermediate risk). [Van Dijk and colleagues \(2006\)](#) published a meta-analysis of 10 studies of 1775 patients with NSGCT treated after 1989 and reported pooled 5-year survival estimates of 94%, 83%, and 71% for good-risk, intermediate-risk, and poor-risk patients by IGCCCG criteria. These results represent significantly improved survival compared with the original study (particularly for patients classified as poor risk) and are attributed to more effective therapy and more experience in treating patients with NSGCT.

The TNM system incorporates marker levels (S0-3) and nonpulmonary visceral metastasis in the staging of testis cancer. However, this system does not consider the differences in prognosis between seminomas and NSGCTs with nonpulmonary visceral metastasis. In the TNM system, both of these entities would be classified as stage IIIC, but IGCCCG would classify the former as intermediate risk and the latter as poor risk. The IGCCCG system is preferentially used for prognostic assessment and the selection of chemotherapy.

Sperm Cryopreservation

Although infertility is an uncommon presentation for GCT, up to 52% of men have oligospermia at diagnosis and 10% are azoospermic ([Williams et al, 2009a](#)). The limited data that exist suggest that roughly half of these men recover normospermia after orchietomy ([Carroll et al, 1987](#); [Jacobsen et al, 2001](#)). The germinal epithelium is exquisitely sensitive to platin-based chemotherapy and radiation therapy. Virtually all patients become azoospermic after chemotherapy, and 50% and 80% of patients with normal semen parameters at diagnosis return to these levels within 2 and 5 years, respectively ([Bokemeyer et al, 1996a](#); [Feldman et al, 2008](#)). Recovery of spermatogenesis after radiation therapy for seminoma may take to 2 to 3 years or longer ([Fossa et al, 1999b](#)). RPLND may result in ejaculatory dysfunction in 80% or more of patients undergoing a full, bilateral template dissection without nerve sparing. Most men are able to father children after standard chemotherapy for GCTs; radiotherapy appears to have a more deleterious effect on fertility than chemotherapy ([Huyghe et al, 2004](#)). Given the impact of treatments for testis cancer on fertility, men who are undecided or are planning future paternity are recommended to undergo sperm cryopreservation before treatment is initiated. Sperm banking can be done before or after radical orchietomy.

Treatment

Therapeutic Principles

The management of GCTs is governed by the potential for rapid growth and for cure in essentially all patients; this translates into a need for rapid diagnosis and staging and expeditious application of appropriate treatment so as not to have patients die unnecessarily or experience side effects from treatment that would not have been required with earlier diagnosis and proper management. After orchietomy, staging imaging studies, serum tumor marker status should be performed and treatment plans should be developed as rapidly as can be reasonably accomplished.

The probability of cure even in the presence of metastatic disease has led to an aggressive approach with regard to the administration of chemotherapy and the performance of surgery after chemotherapy to resect residual masses. Chemotherapy is generally administered regardless of low white blood cell counts or thrombocytopenia, and nephrotoxic chemotherapy (cisplatin) is often administered even in the presence of moderate to severe renal

KEY POINTS: CLINICAL STAGING

- Testicular GCT follows a predictable pattern of spread from the primary tumor to retroperitoneal lymph nodes and then to distant metastatic sites.
- The primary landing zone for left-sided tumors is the para-aortic and left renal hilar lymph nodes and for right-sided tumors is the inter-aortocaval and paracaval lymph nodes.
- CT imaging is the optimal modality for staging the retroperitoneum, although false-negative scans occur in 25% to 35% and 14% to 20% of patients with CS I NSGCT and seminoma, respectively, when a 1-cm cutoff is used.
- Chest radiograph and chest CT scan are acceptable staging modalities in the absence of retroperitoneal lymphadenopathy or elevated serum tumor marker levels.
- Increasing serum tumor marker levels after orchiectomy indicate the presence of metastatic GCT, and these patients should receive chemotherapy.
- The IGCCCG risk classification is used to evaluate the prognosis of patients with metastatic GCT and dictates the selection of chemotherapy. For NSGCT, IGCCCG risk is assigned based on postorchiectomy serum tumor marker levels, mediastinal primary tumor, and the presence of nonpulmonary visceral metastases. For seminoma, IGCCCG risk is assigned based on the presence of nonpulmonary visceral metastases only.
- Sperm cryopreservation should be offered to all patients before RPLND, chemotherapy, or radiation therapy because of the potential effects of these treatments on fertility.

insufficiency (Williams et al, 1987; Einhorn et al, 1989; Bajorin et al, 1993; Loehrer et al, 1995; Bokemeyer, et al, 1996b; Nichols et al, 1998; de Wit et al, 2001). Similarly, an aggressive surgical approach is taken to resect all sites of residual disease after chemotherapy for NSGCT even if this involves multiple anatomic sites. The young age and generally good health of patients with GCTs permits an aggressive treatment approach if needed.

Serum tumor markers strongly influence the management of GCTs, particularly NSGCTs. As discussed, **elevated serum AFP or hCG after orchiectomy indicates the presence of metastatic disease, and these patients are preferentially given chemotherapy.** For patients receiving chemotherapy, increasing serum tumor marker levels during or after therapy generally indicate refractory or relapsed disease, respectively. As discussed earlier, serum AFP, hCG, and LDH levels at the initiation of chemotherapy are important prognostic factors and influence the selection and duration of chemotherapy regimens (*International Germ Cell Consensus Classification, 1997*).

Testis cancer is a relatively rare disease, and general urologists and general oncologists do not typically treat a large volume of patients with GCTs. In addition, the treatment algorithms are complex and nuanced, and the data supporting certain treatments, such as RPLND, are based on data from a relatively small number of surgeons who have performed a large number of these operations (Donohue et al, 1993, 1995; Heidenreich et al, 2003; Stephenson, et al, 2005b; Williams et al, 2009b). Most urology residents in the United States complete their training having performed two or fewer RPLND procedures (Lowrance et al, 2007). Several studies reported improved survival when the treatment was provided at high-volume institutions (Aass et al, 1991; Harding et al, 1993; Feuer et al, 1994; Collette et al, 1999; Joudi and Konety, 2005; Suzumura et al, 2008). Whenever possible, patients with GCTs should be treated at high-volume centers, and RPLND should be performed by surgeons who are experienced with this operation.

Contrasting Seminoma and Nonseminoma Germ Cell Tumor

For treatment purposes, the distinction between seminoma and NSGCT is very important. Compared with NSGCT, seminoma has

a more favorable natural history. In general, seminoma tends to be less aggressive, to be diagnosed at an earlier stage, and to spread predictably along lymphatic channels to the retroperitoneum before spreading hematogenously to the lungs or other organs. **At diagnosis, the proportion of patients with CS I, II, and III disease is 85%, 10%, and 5% for seminoma and approximately 33%, 33%, and 33% for NSGCT (Powles et al, 2005).** Seminoma is also associated with a lower incidence of occult metastasis among patients with CS I (10% to 15% vs. 25% to 35% for NSGCT) and a lower risk of systemic relapse after treatment of the retroperitoneum (1% to 4% after radiotherapy for seminoma vs. 10% after RPLND for NSGCT), which has important implications for the use of chemotherapy. Seminoma is less likely to have elevated serum tumor markers, and serum tumor markers do not range as high as in NSGCT. Also, serum tumor markers are not used in the IGCCCG risk classification of seminoma.

Compared with NSGCT, **seminoma is exquisitely sensitive to radiation therapy and platin-based chemotherapy.** Substantially lower radiation doses are required to eradicate seminoma compared with other solid tumors. **Radiation therapy is a standard treatment option for CS I, IIA, and IIB seminoma but has no role in NSGCT,** with the exception of treatment for brain metastases. Seminoma accounts for only 10% of advanced GCT cases despite the fact that it accounts for 52% to 56% of all GCTs. A poor prognosis IGCCCG risk category does not exist for advanced seminoma, and greater than 90% of metastatic cases are classified as good risk (compared with 56% for NSGCT) (*International Germ Cell Consensus Classification, 1997*). **The risk of teratoma at metastatic sites is generally not a consideration for advanced seminoma, which has important implications for the management of residual masses after chemotherapy.** However, the potential for seminoma to transform into NSGCT elements is an important consideration in the management of patients who fail to respond to chemotherapy or who relapse after radiation therapy. Of patients with metastatic seminoma who relapse after treatment, approximately 10% to 15% have NSGCT elements at the site of relapse. An autopsy study showed that 30% of patients who die of seminoma have NSGCT elements at metastatic sites (Bredael et al, 1982).

The risk of teratoma at metastatic sites has a substantial effect on treatment algorithms for NSGCT and necessitates the frequent use of postchemotherapy surgery (PCS) in patients with advanced disease. The risk of teratoma in the retroperitoneum in low-stage NSGCT has also influenced many clinicians to favor RPLND over chemotherapy in situations where the risk of occult distant metastases is low. As discussed earlier, teratoma is not sensitive to chemotherapy, and the outcome of patients with metastatic teratoma is related to the completeness of surgical resection.

Because GCTs are almost always cured, numerous clinical trials have been conducted in an attempt to minimize treatment and avoid unnecessary therapies in an effort to reduce short-term and particularly long-term side effects and toxicity. One approach has been to limit the number of patients who receive two interventions ("double therapy"): either surgery or chemotherapy and not both. However, because NSGCTs are usually mixed tumors, and teratoma often exists at metastatic sites with other GCT elements, **"cure" often requires chemotherapy to kill the chemosensitive components and surgery to remove teratomatous components.** It is widely accepted that the successful integration of systemic therapy and PCS is a major contributing factor to the improved cure rates for metastatic GCT seen over the past several decades. Although minimizing unnecessary treatment is an important goal, chemotherapy, radiation therapy, and CT imaging are associated with an increased lifetime risk of secondary malignant neoplasms (SMN) and/or cardiovascular disease (Meinardi et al, 2000; Zagars et al, 2004; Brenner and Hall, 2007; van den Belt-Dusebout et al, 2007; Tarin et al, 2009). In contrast, RPLND when performed by experienced surgeons is associated with a substantially more favorable long-term toxicity profile.

KEY POINTS: CONTRASTING SEMINOMA AND NONSEMINOMA GERM CELL TUMOR

- Compared with NSGCT, seminoma is associated with an indolent natural history with a lower incidence of metastatic disease and lower rates of occult retroperitoneal and distant metastases in patients with CS I, IIA, and IIB.
- No poor-risk prognostic category exists for metastatic seminoma, and substantially more patients are classified as good risk by IGCCCG criteria compared with NSGCT.
- Seminoma is associated with increased sensitivity to radiation therapy and platin-based chemotherapy compared with NSGCT.
- Serum hCG is elevated in only 15% of patients with metastatic seminoma, and serum tumor marker levels are not used to guide treatment decisions.
- Teratoma at metastatic sites is less of a concern for seminoma compared with NSGCT but should be considered in patients who fail to respond to conventional therapy.

Intratubular Germ Cell Neoplasia

ITGCN is diagnosed by testicular biopsy performed for the investigation of infertility, contralateral testis biopsy in patients with GCT, or within the affected testis in a patient undergoing testis-sparing surgery. The rationale for treatment of ITGCN is based on the high risk of developing invasive GCT (Skakkebaek et al, 1982; Dieckmann and Skakkebaek, 1999). Treatment options include orchiectomy, low-dose radiotherapy, and close observation. The choice of therapy should be individualized based on the patient's desire for future paternity, the presence or absence of a normal contralateral testis, and the patient's desire to avoid testosterone replacement therapy. Radical orchiectomy is the most definitive treatment, although low-dose radiotherapy (≥ 20 Gy) is associated with similar rates of local control with the prospect of preserving testicular endocrine function owing to the relative radioresistance of Leydig cells compared with germinal epithelium (Heidenreich et al, 2001; Montironi, 2002; Dieckmann et al, 2003). However, testosterone replacement therapy is ultimately required in up to 40% of patients, and patients should be monitored after radiotherapy for adequate testicular androgen production (Heidenreich et al, 2001; Petersen et al, 2002). To preserve testicular endocrine function, dose reductions to less than 20 Gy have been investigated, but cases of recurrent ITGCN have been observed (Classen et al, 2003a; Dieckmann et al, 2003). For patients with a normal contralateral testis who desire future paternity, radical orchiectomy is preferred because scatter to the contralateral testis from radiotherapy may impair spermatogenesis. For patients with abnormal semen parameters but sufficient for assisted reproductive techniques, close surveillance with periodic ultrasound evaluation of the testis is a reasonable strategy with deferred therapy until successful pregnancy and/or development of GCT. Another option for these patients is testis exploration, sperm harvesting, and cryopreservation for assisted reproductive techniques and radical orchiectomy followed by testosterone replacement therapy.

Patients with ITGCN who are scheduled to receive cisplatin-based chemotherapy represent a unique circumstance because chemotherapy may reduce (but not eliminate) the risk of GCT. A study estimated the risk of testicular GCT after chemotherapy in a patient with ITGCN to be 21% at 5 years and 45% at 10 years (Christensen et al, 1998). These patients may be treated by low-dose radiotherapy after completion of chemotherapy, or they may undergo testis biopsy 2 years or more after chemotherapy with therapy reserved for patients with evidence of ITGCN (Krege et al, 2008a, 2008b).

Nonseminoma Germ Cell Tumor

Clinical Stage I Nonseminoma Germ Cell Tumor. Approximately one third of patients with NSGCT have CS I with normal

KEY POINTS: INTRATUBULAR GERM CELL NEOPLASIA

- ITGCN is a precursor lesion for GCT and is associated with a 50% risk of developing an invasive GCT within 5 years.
- Radical orchiectomy and low-dose (≥ 20 Gy) radiation therapy are effective treatment options for ITGCN.

serum tumor markers after orchiectomy. The optimal management of these patients continues to generate controversy because the long-term survival associated with surveillance, RPLND, and primary chemotherapy approaches 100%. Contributing to the controversy is the fact that occult metastases in the retroperitoneum or at distant sites are present in only 20% to 30% of patients overall. Any intervention after orchiectomy, with the potential for short-term and long-term morbidity, represents overtreatment for the 70% to 80% of patients with disease limited to the testis. Most centers employ a risk-adapted approach based on the probability of occult metastasis, although surveillance is the preferred approach at selected centers, regardless of a man's risk.

Risk Assessment. Numerous studies have attempted to identify histopathologic factors within the primary tumor that are predictive of the presence of occult metastasis. The most commonly identified risk factors for occult metastasis are LVI and a predominant component of EC. The definition of EC predominance in the literature varies from 45% to 90%. The reported rate of occult metastasis (based on observed relapses on surveillance or lymph node metastasis at RPLND) with LVI and EC predominance varies from 45% to 90% and 30% to 80%, respectively (Heidenreich et al, 1998; Sogani et al, 1998; Hermans et al, 2000; Sweeney et al, 2000; Alexandre et al, 2001; Roelleveld et al, 2001; Albers et al, 2003; Vergouwe et al, 2003; Nicolai et al, 2004; Stephenson et al, 2005a). In the absence of these two risk factors, the risk of occult metastasis is less than 20%. Other identified risk factors include advanced pT stage, absence of mature teratoma, absence of yolk sac tumor, presence of EC (regardless of the percent composition), percentage of MIB-1 staining, tumor size, and patient age. In a pooled analysis of 23 studies assessing predictors of occult metastasis in CS I NSGCT, Vergouwe and associates (2003) identified LVI (odds ratio 5.2), MIB-1 staining greater than 70% (odds ratio 4.7) and EC predominance (odds ratio 2.8) as the strongest predictors, and these factors were present in 36%, 55%, and 51% of patients.

As discussed previously, the results of abdominopelvic CT imaging should be considered when formulating treatment recommendations because a size cutoff of 1 cm is associated with a high false-negative rate. Retroperitoneal lymph nodes greater than 5 to 9 mm in the primary landing zone should be viewed with suspicion for regional lymph node metastasis.

Numerous risk groups and prognostic indices have been proposed based on the presence or absence of several of these risk factors, most commonly on the basis of LVI and EC predominance (Freedman et al, 1987; Read et al, 1992; Heidenreich et al, 1998; Sogani et al, 1998; Hermans et al, 2000; Alexandre et al, 2001; Albers et al, 2003; Nicolai et al, 2004; Stephenson et al, 2005a). Classification of patients as low versus high risk based on LVI and EC predominance applies to the risk of occult metastatic disease in patients with CS I and should not be confused with the IGCCCG risk classification for metastatic NSGCT (discussed previously). Only one of these prognostic models has been prospectively validated, and none have considered the results of staging CT imaging (Freedman et al, 1987; Read et al, 1992). Three prospective studies suggest that LVI and EC predominance may be associated with a risk of metastasis between 35% and 55%, not between 50% and 70% as has been reported in most older studies. A surveillance series from Princess Margaret Hospital reported a relapse rate of 52% among patients with LVI and/or pure EC (Sturgeon et al, 2011). Similarly, a series from British Columbia and Portland, Oregon, reported that LVI was associated with a relapse rate of 50%, whereas EC predominance was associated with a relapse rate of 33% (Kollmannsberger et al, 2010b). Likewise, a population-based

surveillance study from Scandinavia reported a 42% relapse rate in patients with LVI (Tandstad et al, 2009). Lastly, only 18% of patients with CS I NSGCT treated by RPLND in a randomized trial had retroperitoneal lymph node metastasis despite the fact that 42% had evidence of LVI in the primary tumor (Albers et al, 2008). This lower than expected rate of occult metastasis may be due to greater scrutiny of staging CT imaging for abnormal lymph nodes and/or stage migration.

Surveillance. The rationale for surveillance is based on the fact that 70% to 80% of patients with CS I NSGCT are cured by orchiectomy alone and the ability to salvage virtually all relapsing patients with chemotherapy based on the long-term cure rates achieved for chemotherapy for good-risk metastatic NSGCT (International Germ Cell Consensus Classification, 1997). Surveillance offers the potential of reducing treatment-related toxicity by restricting treatment to patients with a proven need for it. Surveillance series have reported overall and disease-specific survival rates indistinguishable from rates seen with RPLND and primary chemotherapy. As a result, initial surveillance is regarded as a standard treatment option for CS I NSGCT. The disadvantages of surveillance are that it is associated with the highest risk of relapse, the need for long-term (>5 years) surveillance, the potential for SMN owing to intensive surveillance CT imaging (Brenner and Hall, 2007; Tarin et al, 2009), and the more intensive therapy required to treat patients at the time of relapse than if they had received treatment at diagnosis.

Published surveillance series have reported results on more than 3000 men, with a mean relapse risk of 28% and 1.2% cancer-specific mortality. The 11 largest series are summarized in Table 34-3 (Freedman et al, 1987; Read et al, 1992; Gels et al, 1995; Sogani et al, 1998; Colls et al, 1999; Sharir et al, 1999; Francis et al, 2000; Daugaard et al, 2003; Ernst et al, 2005; Tandstad et al, 2009; Kollmannsberger et al, 2010b; Tandstad et al, 2010; Sturgeon et al, 2011). More than 90% of relapses occur within the first 2 years, but late relapses (>5 years) are seen in 1% of patients (5% in some reports) (Daugaard et al, 2003; Sturgeon et al, 2011). In more contemporary series, 65% to 75% of relapses are contained in the retroperitoneum, with or without elevated serum tumor markers (Tandstad et al, 2009; Sturgeon et al, 2011). Induction chemotherapy is the most common treatment used for patients with relapses because most have bulky (>3 cm) retroperitoneal lymphadenopathy, elevated serum tumor markers, or distant metastasis. However, patients with normal serum tumor markers and relapses limited to nonbulky (<3 cm)

retroperitoneal lymphadenopathy may be managed initially with RPLND (Stephenson et al, 2007).

The surveillance schedule employed in published series is highly variable, and no schedule has been demonstrated to be superior to another in terms of survival. Given that most relapses occur within the first 2 years, surveillance imaging and testing is intense in years 0 to 2, with less frequent testing in years 3 to 5. The risk of late relapse mandates surveillance beyond 5 years, but whether such surveillance should include CT scans is controversial. The frequency of abdominopelvic CT imaging varies across multiple series from 2 to 13 or more scans within the first 5 years of follow-up. A randomized trial of two versus five CT scans in years 1 to 2 reported no significant differences in survival, IGCCCG risk category at relapse, or CS at relapse (Rustin et al, 2007). Noncompliance with the prescribed surveillance schedule has been reported in 35% to 80% of patients in published series (Howard et al, 1995; Hao et al, 1998; Ernst et al, 2005).

Retroperitoneal Lymph Node Dissection. The rationale for RPLND for CS I NSGCT is based on the following factors: (1) retroperitoneum is the most common site of occult metastatic disease, with low risk of associated systemic disease; (2) 15% to 25% incidence of retroperitoneal teratoma (which is resistant to chemotherapy) in patients with occult metastasis; (3) low risk of abdominopelvic recurrence after full, bilateral template RPLND, obviating the need for routine surveillance CT imaging; (4) high cure rates after RPLND alone for patients with low-volume (pN1) retroperitoneal malignancy and teratoma (pN1-3); (5) avoidance of chemotherapy in greater than 75% or more of patients if adjuvant chemotherapy is restricted to patients with extensive retroperitoneal malignancy (pN2-3); (6) high salvage rate of relapses with good risk and induction chemotherapy; and (7) low short-term and long-term morbidity when nerve-sparing RPLND is performed by experienced surgeons. In low-stage NSGCT, the therapeutic focus is the retroperitoneum, for which RPLND provides the most effective control with the lowest rates of serious long-term morbidity. The disadvantages of RPLND are that all patients undergo major abdominal surgery, it requires the availability of experienced surgeons and may not be deliverable to all patients, and it is associated with the highest rate of double therapy.

The seven largest RPLND series for CS I NSGCT are summarized in Table 34-4 (Richie, 1990; Donohue et al, 1993; Hermans et al, 2000; Nicolai et al, 2004; Stephenson et al, 2005b; Albers et al, 2008; Williams et al, 2009b). The rate of pathologic stage II in these series ranges from 19% to 28%, and an estimated 66% to 81% of

TABLE 34-3 Surveillance Series for Clinical Stage I Nonseminoma Germ Cell Tumor

STUDY	NO. PATIENTS	RELAPSES (%)	MEDIAN FOLLOW-UP (mo)	MEDIAN TIME TO RELAPSE (mo)	SYSTEMIC RELAPSE*	GCT DEATHS (%)
Freedman et al, 1987	259	70 (32)	30	NR	61%	3 (1.2)
Read et al, 1992	373	100 (27)	60	3 (1.5-20)	39%	5 (1.3)
Gels et al, 1995	154	42 (27)	72	4 (2-24)	71%	2 (1)
Sogani et al, 1998	105	27 (26)	136	5 (2-24)	37%	3 (3)
Sharir et al, 1999	170	48 (28)	76	7 (2-21)	79%	1 (0.5)
Colls et al, 1999	248	70 (28)	53	NR	73%	4 (1.6)
Francis et al, 2000	183	52 (28)	70	6 (1-12)	54%	2 (1)
Daugaard et al, 2003	301	86 (29)	60	5 (1-171)	66%	0
Ernst et al, 2005	197	58 (29)	54	6 (2-135)	22%	0
Kollmannsberger et al, 2010b	223	59 (26)	52	NR	NR	0
Sturgeon et al, 2011	371	104	76	7	33	3 (0.8)
Tandstad et al, 2009†	350	44 (13)	56	8	27%	1 (0.3)
Tandstad et al, 2010‡	129	19 (15)	123	8	37%	0

*Relapse with elevated serum tumor markers and/or relapse in tissue other than retroperitoneal lymph nodes.

†97% were lymphovascular invasion and low risk.

‡96% were lymphovascular invasion and low risk.

GCT, germ cell tumor; NR, not reported.

TABLE 34-4 Published Series of Retroperitoneal Lymph Node Dissection for Clinical Stage I Nonseminoma Germ Cell Tumor

STUDY	NO. PATIENTS	PS II (%)	TERATOMA IN RETROPERITONEUM	RELAPSE, PS I	RELAPSE, PS II	ADJUVANT CHEMOTHERAPY	GCT DEATHS (%)
Donohue et al, 1993	378	113 (30)	15%	12%	34%	13%	3 (0.8)
Hermans et al, 2000	292	67 (23)	NR	10%	22%	12%	1 (0.3)
Nicolai et al, 2004	322	61 (19)	NR	NR	27%	NR	4 (1.2)
Stephenson et al, 2005b	297	83 (28)	15%	6%	19%	15%	0
Williams et al, 2009b	76	37 (49)	NR	5%	11%	NR	0
Albers et al, 2008	173	31 (19)	NR	9%	NR	19%	0
Richie, 1990	99	35 (35)	NR	6%	15%	15%	0

GCT, germ cell tumor; NR, not reported; PS, pathologic stage.

these patients were cured after RPLND alone (Donohue et al, 1993; Hermans et al, 2000; Sweeney et al, 2000; Rabbani et al, 2001; Nicolai et al, 2004; Stephenson et al, 2005a, 2005b). The long-term cancer-specific survival with RPLND (with or without adjuvant chemotherapy) approaches 100%, and the risk of late relapse is negligible. Most RPLND series have reported retroperitoneal recurrences in less than 2% of patients, demonstrating its efficacy for control of disease of the retroperitoneum (Donohue et al, 1993; Hermans et al, 2000; Stephenson et al, 2005b).

A full, bilateral template dissection is associated with the lowest risk of abdominopelvic recurrence (<2%) and the highest rate of antegrade ejaculation (>90%) when nerve-sparing techniques are employed (Jewett, 1990; Donohue and Foster, 1998; Stephenson et al, 2005b; Eggener et al, 2007b; Subramanian et al, 2010). For this reason, it is now considered by many to be the standard of care for primary RPLND (Stephenson et al, 2011). A randomized trial of primary RPLND (plus adjuvant bleomycin-etoposide-cisplatin [BEP]×2 for pathologic stage II) versus BEP×1 chemotherapy for CS I NSGCT showed a significant improvement in 2-year progression-free survival with chemotherapy (99% vs. 92%), although no GCT deaths were observed in either arm (Albers et al, 2008). The local recurrence rate was 11% in patients with histologically negative retroperitoneal lymph nodes at RPLND, which was substantially higher than the local recurrence rate among all patients from experienced centers. The patients in this trial were treated at 61 different centers in Germany. The relative inexperience of surgeons and unilateral templates likely contributed to these poor results. Patients who opt for RPLND should have this procedure performed by an experienced surgeon with a full, bilateral template dissection. Otherwise, patients should go on surveillance or receive primary chemotherapy.

RPLND is a curative procedure in 60% to 90% of patients with pN1 disease and up to 100% of patients with teratoma only (regardless of the extent of lymph node involvement) (Pizzocaro and Monfardini, 1984; Williams et al, 1987; Richie and Kantoff, 1991; Rabbani et al, 2001; Sheinfeld et al, 2003; Stephenson et al, 2005b). The risk of relapse in patients with pN2-3 disease is greater than 50% (Vogelzang et al, 1983; Williams et al, 1987; Socinski et al, 1988; Stephenson et al, 2005b). With two cycles of adjuvant chemotherapy (most commonly BEP×2 or etoposide-cisplatin [EP]×2), relapses are reduced to 1% or less (Behnia et al, 2000; Albers et al, 2003; Kondagunta et al, 2004). A randomized trial of adjuvant chemotherapy versus observation after RPLND for pathologic stage II showed a significant reduction in the risk of relapse (6% vs. 49%) but no difference in overall survival (Williams et al, 1987). Adjuvant chemotherapy and observation are acceptable treatment options for patients with pathologic stage II disease, and patients should be informed of the risk of relapse after RPLND and the potential benefits and risks of these approaches.

Primary Chemotherapy. In contradistinction to adjuvant chemotherapy given for pathologic stage II disease after RPLND, primary

chemotherapy refers to treatment administered to men with CS I NSGCT after orchiectomy. The goal of primary chemotherapy is to minimize the risk of relapse and to allow men to avoid RPLND and induction chemotherapy (for patients who relapse on surveillance). The rationale for primary chemotherapy is based on the efficacy of two cycles of chemotherapy to eradicate micrometastatic disease when given as adjuvant therapy after RPLND and the 20% to 25% need for chemotherapy despite RPLND (either as adjuvant therapy or for treatment of relapse) (Donohue et al, 1993; Hermans et al, 2000; Nicolai et al, 2004; Stephenson et al, 2005a). Primary chemotherapy offers patients the greatest chance of being relapse-free with any single treatment modality, and it can be delivered at community-based institutions (Tandstad et al, 2009, 2010). The disadvantages of primary chemotherapy are as follows: (1) it does not treat retroperitoneal teratoma and exposes patients to the potential for chemoresistant and/or late relapse (discussed later), (2) long-term surveillance CT imaging of the retroperitoneum is required, and (3) all patients are exposed to chemotherapy and the potential risk of late toxicity (e.g., cardiovascular disease and secondary malignancies). The risk of late toxicity from two cycles of chemotherapy is poorly defined, although there appears to be no safe lower limit.

Primary chemotherapy has been investigated in 12 published series, most of which have used BEP×2 (Table 34-5) (Abratt et al, 1994; Cullen et al, 1996; Pont et al, 1996; Ondrus et al, 1998; Bohlen et al, 1999; Amato et al, 2004; Chevreau et al, 2004; Oliver et al, 2004; Dearnaley et al, 2005; Albers et al, 2008; Tandstad et al, 2009, 2010). In men with LVI and/or EC predominance, it is possible to reduce the recurrence rate from 30% to 60% to about 2% to 3%. In 8 of the 12 series, no deaths from GCT were reported over an average median follow-up of 5 years. In the other four studies comprising 406 patients, 13 relapses (3%) were observed, and 6 (46%) of these relapsing patients died of GCT. Although primary chemotherapy is associated with the lowest risk of relapse, these relapses are less amenable to salvage therapy because they are chemoresistant, particularly if they have received a regimen other than standard dose BEP. In contrast, patients who relapse after RPLND or on surveillance are chemotherapy-naïve and are cured with chemotherapy in virtually all cases. Although relapses are uncommon with primary chemotherapy, virtually all occur in the retroperitoneum; this mandates the use of surveillance abdominopelvis CT imaging in the follow-up of these patients. Many European institutions prefer BEP×2 to RPLND because the latter is primarily used as a staging procedure, performed without curative intent (Krege et al, 2008a, 2008b; Schmoll et al, 2009b).

A randomized trial and a population-based study investigated the use of BEP×1 as primary chemotherapy for CS I NSGCT (Albers et al, 2008; Tandstad et al, 2009). Over a median follow-up of less than 5 years in both studies, the risk of relapse after BEP×1 ranged from 1% to 3%, and cancer-specific survival approached 100% in

TABLE 34-5 Published Series of Primary Chemotherapy for Clinical Stage I Nonseminoma Germ Cell Tumor

STUDY	NO. PATIENTS	REGIMEN*	MEDIAN FOLLOW-UP (mo)	RELAPSES (%)	TIME TO RELAPSE (mo)	GCT DEATHS (%)
Abratt et al, 1994	20	BEP×2 (E: 360)†	31	0	NR	0
Cullen et al, 1996	114	BEP×2 (E: 360)	48	2 (1.8)	7, 18	2 (1.8)
Pont et al, 1996	29	BEP×2 (E: 500)	79	2 (2.7)	8, 27	1 (3.5)
Ondrus et al, 1998	18	BEP×2 (E: 360)	36	0	NR	0
Amato et al, 2004	68	CEB×2 (E: 360)	38	1 (1.5)	21	0
Bohlen et al, 1999	58	BEP×2 (E: 360); PVB×2 (20 pts)	93	2 (3.4)	22, 90	0
Chevreau, et al, 2004	40	BEP×2 (E: 360)	113	0	NR	0
Oliver et al, 2004	148	BEP×1 (n = 28); BEP×2 (n = 46); BOP×2 (n = 74) (E: 360)	33	6 (4.1)	NR	2 (1.4)
Dearnaley et al, 2005	115	BOP×2	70	3 (1.7)	3, 6, 26	1 (0.9)
Albers et al, 2008	191	BEP×1 (E: 500)	56	2 (1.0)	15, 60	0
Tandstad et al, 2009	382	BEP×1 (n = 312); BEP×2 (n = 70) (E: 500)	56	7 (1.8)	Range: 8-36	0
Tandstad et al, 2010	100	PVB×1 (n = 40) or PVB×2 (n = 60)	116	5	1, 9, 10, 27, 126	0

*Chemotherapy regimens: BEP, bleomycin-etoposide-cisplatin; BOP, bleomycin-vincristine-cisplatin; CEB, carboplatin-etoposide-bleomycin; PVB, cisplatin-vinblastine-bleomycin.

†E: 360 refers to an etoposide dose of 360 mg/m²/cycle; E: 500 refers to an etoposide dose of 500 mg/m²/cycle.

GCT, germ cell tumor; NR, not reported; pts, patients.

both studies. BEP×1 needs to be compared with BEP×2 in a randomized trial to verify its safety and efficacy.

Treatment Selection for Clinical Stage I Nonseminoma Germ Cell Tumor. There are no randomized trials that compare the standard treatment approaches for CS I NSGCT. A phase III, randomized trial compared BEP×1 versus unilateral, modified-template RPLND (with BEP×2 for patients with pathologic stage II disease) (Albers et al, 2008). Although a statistically significantly reduced risk of relapse was reported with BEP×1 (hazard ratio [HR] 0.13, 95% confidence interval 0.02 to 0.55), no cancer-specific deaths were reported in either arm. This trial has been criticized because it compared two nonstandard treatment approaches for CS I NSGCT (Sheinfeld and Motzer, 2008).

Given the excellent long-term survival with surveillance, RPLND, and primary chemotherapy, it is inappropriate to recommend any specific treatment option because there are relative advantages and disadvantages of each approach in terms of treatment-related toxicity, the need for subsequent treatment, and intensity of surveillance testing and imaging. Likewise, patient preferences may vary and should be considered. Several clinical practice guidelines for CS I NSGCT have been published, and surveillance is generally recommended to low-risk patients, and surveillance, RPLND, or primary chemotherapy is recommended to high-risk patients (Albers et al, 2005; Motzer et al, 2006; Hotte et al, 2008; Krege et al, 2008a, 2008b; Schmoll et al, 2009b; Stephenson et al, 2011). Nguyen and colleagues (2010) developed a decision-analysis model that considered cancer outcomes, treatment-related toxicity, and patient preferences for important post-treatment outcomes to define the optimal treatment for CS I NSGCT. Surveillance is associated with the highest quality-adjusted survival when the estimated risk of relapse is less than 33% to 37%, and active treatment (RPLND or primary chemotherapy) is favored when the risk of relapse is greater than 46% to 54%.

Clinical Stage IS Nonseminoma Germ Cell Tumor. CS IS is defined as the presence of elevated serum tumor markers after orchiectomy without clinical or radiographic evidence of metastatic disease. Studies of primary RPLND for CS IS NSGCT reported that 37% to 100% of patients subsequently required chemotherapy for retroperitoneal metastasis, persistently elevated serum tumor

markers, or relapse (Davis et al, 1994; Saxman et al, 1996). There is consensus that these patients should be treated similarly to patients with CS IIC and III and receive induction chemotherapy. The cancer-specific survival after chemotherapy for CS IS is greater than 90% (Culine et al, 1996; International Germ Cell Consensus Classification, 1997). Slightly elevated and stable serum tumor marker levels after orchiectomy in patients without clinical evidence of disease should be interpreted cautiously because they may represent false-positive findings for disseminated NSGCT.

Clinical Stage IIA and IIB Nonseminoma Germ Cell Tumor. The optimal management of CS IIA and IIB NSGCT is controversial. RPLND (with or without adjuvant chemotherapy) and induction chemotherapy (with or without postchemotherapy RPLND) are accepted treatment options with survival rates exceeding 95%. No randomized trials have compared these treatment approaches. In a prospective, multicenter, nonrandomized trial of RPLND and two cycles of adjuvant chemotherapy versus induction chemotherapy, no significant differences in recurrence (7% for RPLND vs. 11% for chemotherapy) or overall survival were observed (Weissbach et al, 2000). A single-institution, nonrandomized, retrospective comparison of RPLND (and two cycles of adjuvant chemotherapy for pathologic stage II) and induction chemotherapy reported a significant reduction in the risk of recurrence with induction chemotherapy (98% vs. 79%), but cancer-specific survival approached 100% with both modalities (100% vs. 98%), patients undergoing RPLND received fewer cycles of chemotherapy (mean 4.2 vs. 1.4), and 51% of patients undergoing RPLND avoided chemotherapy (Stephenson et al, 2007).

The arguments in favor of RPLND for CS IIA and IIB are as follows: (1) 13% to 35% of patients have pathologically negative lymph nodes and avoid chemotherapy (Pizzocaro, 1987; Donohue et al, 1995; Weissbach et al, 2000; Stephenson et al, 2007); (2) approximately 30% have retroperitoneal teratoma, which is resistant to chemotherapy (Foster et al, 1996; Stephenson et al, 2007); (3) long-term cancer-specific survival is 98% to 100% with RPLND with or without adjuvant chemotherapy (Pizzocaro, 1987; Donohue et al, 1995; Weissbach et al, 2000; Stephenson et al, 2007); (4) 10% to 52% avoid any chemotherapy (Pizzocaro, 1987; Donohue et al, 1995; Weissbach et al, 2000; Stephenson et al, 2007); and (5)

ejaculatory function is preserved in 70% to 90% of patients (Richie and Kantoff, 1991; Donohue et al, 1995; Weissbach et al, 2000). The disadvantages of RPLND are as follows: (1) additional therapy is required in 48% or more of patients, (2) 13% to 15% have persistence of disease after RPLND and require a full induction chemotherapy regimen, and (3) high-quality RPLND may not be deliverable at all institutions (Weissbach et al, 2000; Stephenson et al, 2007).

The arguments in favor of induction chemotherapy are the following: (1) a complete response is achieved and PCS is avoided in 60% to 78% of patients, (2) treatment can be delivered at community-based institutions, and (3) cancer-specific survival is 96% to 100% (Peckham and Hendry, 1985; Logothetis et al, 1987; Socinski et al, 1988; Ondrus et al, 1992; Horwich et al, 1994; Lerner et al, 1995; Culine et al, 1997; Debono et al, 1997; Weissbach et al, 2000; Stephenson et al, 2007). The disadvantages of chemotherapy are the following: (1) all patients are exposed to the risk of long-term toxicity of chemotherapy, and (2) patients who do not undergo postchemotherapy RPLND are at risk of relapse with chemorefractory GCT.

Given that 13% to 35% of patients with CS IIA NSGCT have pathologically negative lymph nodes (a false-positive CT result), patients with indeterminate lesions on staging abdominopelvic CT imaging who are at otherwise low risk for metastatic disease may be observed closely initially to clarify subsequent treatment decisions. Treatment considerations for CS IIA and IIB NSGCT include the risk of occult systemic disease, risk of retroperitoneal teratoma, short-term and long-term treatment-related morbidity, and need for double therapy. The last consideration is of least importance but has strongly influenced opinion regarding the optimal treatment of these patients. As discussed earlier, because metastatic NSGCT frequently exists as chemosensitive malignant GCT and chemoresistant teratoma, "cure" often requires the combination of chemotherapy and surgery.

Experience with primary RPLND in low-stage NSGCT over the last two decades has identified parameters associated with systemic relapse. As with CS IS NSGCT, the presence of elevated AFP and hCG levels after orchiectomy is associated with an increased risk of systemic relapse after RPLND. Rabbani and colleagues (2001) reported relapses after RPLND in 4 of 5 patients (80%) with elevated postorchiectomy AFP or hCG levels compared with 7 of 45 patients (16%) with normal serum tumor markers. Stephenson and associates (2005b) identified the presence of elevated serum tumor markers (HR = 5.6, $P < .001$) and retroperitoneal lymphadenopathy greater than 3 cm (HR = 12.3, $P < .001$) as significant predictors of systemic relapse after RPLND. There is consensus that patients with CS IIA and IIB NSGCT and elevated AFP or hCG levels or bulky lymph nodes (>3 cm) should receive induction chemotherapy.

The presence of retroperitoneal teratoma is a limitation to any strategy for metastatic NSGCT that uses chemotherapy alone because it is resistant to chemotherapy. Overall, approximately 20% of patients with CS IIA and IIB have retroperitoneal teratoma, and this increases to 30% to 35% in patients with teratoma in the primary tumor (Donohue et al, 1995; Foster et al, 1996; Stephenson et al, 2005b). Residual microscopic teratoma may remain dormant and clinically silent throughout a patient's lifetime. It may also exhibit slow growth, which can be detected on surveillance CT imaging and is amenable to cure by surgical resection. However, growing teratoma syndrome, malignant transformation, and late relapse are the most serious (although rare) sequelae of unresected teratoma. RPLND is preferred as initial therapy in patients at risk for retroperitoneal teratoma who are at otherwise low risk for systemic disease (normal serum tumor markers, lymphadenopathy <3 cm).

Clinical Stage IIC and III Nonseminoma Germ Cell Tumor. Induction chemotherapy with cisplatin-based regimens is the initial approach used for the treatment of CS IIC and III NSGCT. As discussed previously, induction chemotherapy is also the preferred approach for CS IS and CS IIA and IIB with elevated AFP and hCG levels after orchiectomy. The specific regimen and

number of cycles are based on IGCCCG risk stratification (see Table 34-2) (International Germ Cell Consensus Classification, 1997).

The development of cisplatin-based chemotherapy represents the most important advancement in the treatment of GCT. Before the identification of cisplatin, complete responses to chemotherapy were achieved in 10% to 20% of patients, and the cure rate was only 5% to 10% (Einhorn, 1990). Long-term cure is now anticipated in 80% to 90% of patients with metastatic GCT. Randomized trials have evaluated the efficacy and safety of various drug combinations to determine the optimal regimen based on IGCCCG risk (Debono et al, 1997).

The initial landmark study was conducted at Indiana University using cisplatin-vinblastine-bleomycin (PVB)×4 in the 1970s and reported complete responses in 74% of patients and more than 70% long-term survivors (Beck et al, 2005). When it was demonstrated that etoposide could cure some patients with relapse after PVB chemotherapy, PVB×4 was compared with BEP×4 in a multicenter randomized trial. No significant difference in overall survival was seen between the two regimens (2-year survival 80%, $P = .11$), but BEP×4 was associated with less neuromuscular toxicity and was subsequently adopted as the standard regimen (Williams et al, 1987).

Chemotherapy for Good-Risk Nonseminoma Germ Cell Tumor

After BEP×4 became the standard regimen for advanced GCT, subsequent trials focused on reducing toxicity for patients with good-risk features and improving outcomes for patients with intermediate-risk and poor-risk disease. For good-risk patients, two randomized trials showed that BEP×3 is not inferior to BEP×4 (Einhorn et al, 1989; Saxman et al, 1998; de Wit et al, 2001). With 184 patients enrolled in the U.S. study, 92% of patients in each arm were continuously disease-free with a minimum follow-up of 1 year, and four deaths in each arm at 10 years were reported in a later analysis (Einhorn et al, 1989; Saxman et al, 1998). An international European trial comparing BEP×3 versus BEP×4 in more than 800 IGCCCG good-risk patients reported similar outcomes with respect to 2-year progression-free survival (90% vs. 89%) and overall survival (97% in each arm) (de Wit et al, 2001). As a result of these studies, BEP×3 became the standard regimen for good-risk GCT.

To reduce toxicity, investigators have studied the effect of omitting bleomycin and substituting carboplatin for cisplatin. All of the randomized trials in which a cisplatin regimen has been compared with a carboplatin regimen have reported superior outcomes with cisplatin (Bajorin et al, 1993; Bokemeyer et al, 1996b; Horwich et al, 1997, 2000; Bokemeyer et al, 2004). The issue of whether bleomycin can be safely omitted from cisplatin-based regimens in good-risk patients is much less clear and is one of the few remaining controversies in the management of advanced GCT. The rationale for omitting bleomycin is based on the risk of pulmonary complications (including pulmonary fibrosis) and Raynaud phenomenon. All of these studies have shown a trend toward superiority for the bleomycin-containing regimen, although no significant survival advantage has been shown in any of the trials (Bosl et al, 1988; Levi et al, 1993). EP×3 is inferior to BEP×3 (Loehrer et al, 1995). A European randomized trial comparing BEP×4 with EP×4 (with reduced doses of etoposide) reported a significantly higher complete response rate (95% vs. 87%, $P = .008$) with BEP×3 but no difference in overall survival (de Wit et al, 1997). More recently, a French randomized trial comparing BEP×3 with EP×4 (using conventional doses of etoposide) failed to show a statistically significant difference in the risk of relapse or survival between the two regimens (Culine et al, 2007). BEP×3 and EP×4 are both accepted regimens for patients with advanced GCT and good-risk features by IGCCCG criteria, and the 5-year overall survival is 91% to 94% (International Germ Cell Consensus Classification, 1997; van Dijk et al, 2006).

Chemotherapy for Intermediate-Risk and Poor-Risk Nonseminoma Germ Cell Tumor

BEP×4 has been the standard regimen for advanced GCT with intermediate-risk and poor-risk features since 1987, and the corresponding 5-year survival rate is 79% for intermediate-risk patients and 48% for poor-risk patients (*International Germ Cell Consensus Classification, 1997*). Ifosfamide-based regimens using either etoposide-ifosfamide-cisplatin (VIP×4) or vinblastine-ifosfamide-cisplatin (VeIP×4) have been investigated in randomized trials and compared with BEP×4 (*de Wit et al, 1998; Nichols et al, 1998; Hinton et al, 2003*). The multicenter U.S. trial reported results on nearly 300 men with advanced GCT, with 13%, 23%, and 64% classified as good, intermediate, and poor risk by IGCCCG criteria (*Nichols et al, 1998; Hinton et al, 2003*). Comparing BEP×4 with VIP×4, the 2-year survival was 71% versus 74%, and the 5-year survival was 57% versus 62%; neither 2-year survival nor 5-year survival was significantly different (*Nichols et al, 1998*). The European study closed prematurely when the results of the U.S. study became available. Nevertheless, with 84 patients enrolled and more than 7 years' median follow-up, there were two deaths in the BEP×4 arm and one death in the VIP×4 arm, and overall survival at 5 years was greater than 80% (*de Wit et al, 1998*). In both BEP×4 versus VIP×4 trials, there were more deaths with BEP×4, but the differences were not significant. Because VIP×4 resulted in more high-grade hematologic and urologic toxicity, BEP×4 has remained the standard regimen for intermediate-risk and poor-risk GCT. However, these trials showed that comparable cancer outcomes could be achieved when ifosfamide is substituted for bleomycin. VIP×4 may be substituted for BEP×4 in patients with compromised pulmonary function and in patients in whom extensive chest surgery is likely to be performed to remove residual disease after chemotherapy (*Kesler et al, 2008*).

High-dose chemotherapy (HDCT) using carboplatin-etoposide-based regimens with autologous stem cell support (also termed *stem-cell rescue*) has been investigated as an alternative to BEP×4 in patients with GCT with a poor prognosis. The rationale for HDCT is the hypothesis that increasing dosage may overcome chemotherapy resistance. The most widely studied regimens have included carboplatin-etoposide alone or in combination with cyclophosphamide, ifosfamide, paclitaxel, or thiotepa (*Beyer et al, 1996; Bokemeyer et al, 2002a; Einhorn et al, 2007; Kondagunta et al, 2007; Lorch et al, 2007; Kollmannsberger et al, 2009*). Carboplatin is used in HDCT regimens because of dose-limiting nephrotoxicity and neuropathy with cisplatin. A randomized trial in 219 patients with intermediate-risk (21%) and poor-risk (79%) GCT randomly assigned to BEP×4 versus BEP×2 followed by two cycles of high-dose carboplatin-etoposide-cyclophosphamide and autologous stem cell support showed no significant difference in the 1-year durable complete response rate (48% vs. 52%, $P = .5$) or overall survival (*Motzer et al, 2007*). For patients in both arms, the 2-year survival was 83%, and the 5-year survival was 71%. However, toxicity was more severe for patients receiving HDCT. A smaller randomized trial also failed to demonstrate improved survival with HDCT compared with standard-dose regimens as first-line therapy for patients with metastatic GCT with poor prognosis (*Droz et al, 2007*). As a result, BEP×4 remains the standard first-line regimen in patients with intermediate-risk and poor-risk disease.

Although the standard chemotherapy for men with poor-risk disease has not changed in more than 20 years, the outcome of these men appears to have improved over time. In the original IGCCCG analysis, the 5-year overall survival for poor-risk patients was 48%, whereas survival rates of 60% or greater have been reported in subsequent multicenter randomized trials (*Hinton et al, 2003; Droz et al, 2007; Motzer et al, 2007; Culine et al, 2008*). A meta-analysis of 10 studies enrolling 1775 patients with disseminated NSGCT (including 456 poor-risk patients) reported that the pooled 5-year survival estimate for poor-risk patients was 71% (*van Dijk et al, 2006*).

Management of Residual Masses in Nonseminoma Germ Cell Tumor after Chemotherapy

To assess the response to first-line, cisplatin-based chemotherapy, patients are restaged with serum tumor markers and imaging studies of the chest, abdomen, and pelvis (including other sites of disease if present before chemotherapy). Patients are classified into the following categories based on their response to chemotherapy: (1) complete response, defined by normalization of serum tumor markers and resolution of radiographic disease (usually defined as residual masses ≤ 1 cm); (2) normalization of serum tumor markers with persistent radiographic tumor (partial remission—marker negative); (3) partial remission—marker positive; and (4) disease progression. Approximately 5% to 15% of patients fall into categories 3 and 4 and are typically managed with second-line (also termed *salvage*) chemotherapy (*Einhorn et al, 1989; Mead et al, 1992; de Wit et al, 1997; Debono et al, 1997*). There is clear consensus that patients with residual masses larger than 1 cm should undergo PCS (*Albers et al, 2005; Motzer et al, 2006; Krege et al, 2008a, 2008b; Schmoll et al, 2009b*). The management of patients with complete serologic and radiographic response is controversial, with some guidelines advocating close observation and others recommending PCS if the mass size before chemotherapy is greater than 3 cm (*Albers et al, 2005; Motzer et al, 2006; Krege et al, 2008a, 2008b; Schmoll et al, 2009b*).

The role of PCS for residual masses in patients with metastatic NSGCT is well established, and its rationale is based on several factors. Multiple large series of patients undergoing PCS for residual masses after first-line chemotherapy have consistently reported evidence of persistent GCT elements in the resected specimens in 50% or more. On average, histology of resected specimens demonstrates necrosis, teratoma, and viable malignancy (with or without teratoma) in 40%, 45%, and 15% of cases (*Table 34-6*) (*Toner et al, 1990; Gerl et al, 1995; Steyerberg et al, 1995; de Wit et al, 1997; Debono et al, 1997; Hartmann et al, 1997b; Sonneveld et al, 1998; Stenning et al, 1998; Steyerberg et al, 1998; Hendry et al, 2002; Albers et al, 2004; Spiess et al, 2006b; Carver et al, 2007a*). The 5-year overall survival of patients with complete resection of viable malignancy (with or without further chemotherapy) ranges from 45% to 77% (*Toner et al, 1990; Fox et al, 1993; Gerl et al, 1995; Hartmann et al, 1997b; Donohue et al, 1998; Stenning et al, 1998; Fizazi et al, 2001; Spiess et al, 2006a; Carver et al, 2007a; Fizazi et al, 2008*). In contrast, if left unresected, residual viable malignancy is destined to relapse, and only 25% to 35% of patients achieve durable remissions to second-line chemotherapy.

As discussed earlier, teratoma is resistant to chemotherapy and is present at metastatic sites in 15% or more of patients with disseminated NSGCT. The presence of metastatic teratoma is a limitation to any strategy for NSGCT that employs chemotherapy alone and necessitates the integration of chemotherapy and PCS in most patients with metastatic GCT. Unresected teratoma has the potential to exhibit rapid growth (growing teratoma syndrome), undergo malignant transformation, or cause late relapse, all of which may have lethal consequences. The outcome of metastatic teratoma is related to the completeness of surgical resection, and long-term survival is reported in 75% to 90% of patients who undergo PCS for residual teratoma (*Toner et al, 1990; Hartmann et al, 1997b; Sonneveld et al, 1998; Stenning et al, 1998; Carver et al, 2007c*). Lastly, in-field retroperitoneal relapse occurs in less than 2% of patients after a full, bilateral template RPLND, largely eliminating the need for radiographic surveillance of the abdomen and pelvis (*Carver et al, 2007b*).

Approximately 6% to 8% of PCS specimens contain evidence of non-GCT malignancy arising from malignant transformation of teratoma (*Toner et al, 1990; Little et al, 1994; Carver et al, 2007c*). The most common histology is rhabdomyosarcoma, and the presence of i(12p) or abnormalities of chromosome 12 in most specimens confirm its origin from GCT (*Motzer et al, 1998*). As with teratoma, the outcome of patients with malignant transformation is related to the completeness of surgical resection

TABLE 34-6 Histology of Postchemotherapy Residual Masses

STUDY	NO. PATIENTS	NECROSIS	VIABLE MALIGNANCY ± TERATOMA	TERATOMA ONLY
Steyerberg et al, 1995	556	45%	13%	42%
Carver et al, 2007a	504	49%	11%	39%
Hendry et al, 2002	330	25%	9%	66%
Debono et al, 1997	295	25%	7%	67%
Spiess et al, 2006b	236	41%	17%	42%
Albers et al, 2004	232	35%	31%	34%
Toner et al, 1990	185	47%	16%	37%
Steyerberg et al, 1998	172	45%	13%	42%
Stenning et al, 1998	153	29%	15%	55%
de Wit et al, 1997	127	35%	9%	56%
Oeschle et al, 2008	121	45%	21%	34%
Sonneveld et al, 1998	113	46%	9%	45%
Gerl et al, 1995	111	47%	12%	41%
Hartmann et al, 1997a	109	52%	21%	27%

TABLE 34-7 Histology of Postchemotherapy Residual Masses Less Than 20 mm in Size

STUDY	NO. PATIENTS	SIZE (mm)	NECROSIS	VIABLE MALIGNANCY ± TERATOMA	TERATOMA ONLY
Steyerberg et al, 1995	275	≤20	65%	5%	30%
Steyerberg et al, 1995	162	≤10	72%	4%	24%
Oldenburg et al, 2003	87	≤20	67%	7%	26%
Fossa et al, 1992	78	<20	68%	4%	29%
Fossa et al, 1989b	37	≤10	67%	3%	30%
Stephenson et al, 2007	36	≤5	69%	6%	25%
Toner et al, 1990	21	≤15	81%	7%	12%
Stomper et al, 1991	14	≤20	36%	14%	50%

because they are generally resistant to GCT-specific chemotherapy regimens. With complete resection, approximately 50% to 66% of patients survive, whereas most patients with incomplete resection experience rapid progression and death from GCT (Little et al, 1994; Comiter et al, 1998; Motzer et al, 1998; Lutke Holzik et al, 2003; Carver et al, 2007c). Chemotherapy specific to the transformed histology (e.g., sarcoma-specific regimen) has been investigated in two small series in selected patients with measurable disease limited to one histology. Partial responses were observed in 11 of 24 patients, 6 of whom are alive (Donadio et al, 2003; El Mesbahi et al, 2007).

Patients with necrosis only in the PCS specimens have a favorable prognosis, with relapse rates of 10% or less reported in most series (Toner et al, 1990; Hartmann et al, 1997b; Stenning et al, 1998; Carver et al, 2007a). Investigators have sought to identify factors that are reliably predictive of a high probability of necrosis to obviate the need for PCS in all patients with residual masses. In an early study, Donohue and coworkers (1987) reported that 0 of 15 patients without teratoma in the primary tumor and who achieved a 90% or greater reduction in the size of the residual mass with chemotherapy had no evidence of viable malignancy or teratoma at PCS. In contrast, seven of nine patients (78%) with teratoma in the primary tumor experiencing a similar reduction in the size of the metastasis with chemotherapy had evidence of viable malignancy and/or teratoma. The absence of teratoma in the primary tumor, the percentage reduction in the retroperitoneal mass with chemotherapy, and the size of the residual mass have consistently been identified as predictors of necrosis in PCS specimens (Toner et al, 1990; Stomper et al, 1991; Fossa et al, 1992; Steyerberg et al, 1995, 1998; Albers et al, 2004). However, despite statistical modeling using these and other factors, a consistent false-negative rate for necrosis of 20% has been reported (Steyerberg et al, 1995, 1998; Vergouwe et al, 2001). The presence of

necrosis only in the retroperitoneum cannot be predicted with sufficient accuracy to obviate safely the need for PCS in patients with residual masses. An important concept is that the absence of teratoma in the primary tumor does not reliably exclude its presence in the retroperitoneum (Toner et al, 1990; Beck et al, 2002). Investigators have also studied the utility of FDG-PET in the prediction of the histology of residual masses after first-line chemotherapy. The utility of FDG-PET in the prediction of retroperitoneal histology for NSGCT is limited by the fact that teratoma is not FDG-avid. In a prospective study of 121 patients with residual masses after induction chemotherapy, the predictive accuracy of FDG-PET (56%) for viable malignancy or teratoma was no better than CT (55%) or postchemotherapy serum tumor markers (56%) (Oechsle et al, 2008). FDG-PET has no role in the assessment of patients with NSGCT and residual masses after chemotherapy.

Approximately 26% to 62% of patients experience a serologic and radiographic complete response to first-line chemotherapy (Einhorn et al, 1989; Dearnaley et al, 1991; Mead et al, 1992; Debono et al, 1997; Stenning et al, 1998; Ehrlich et al, 2010; Kollmannsberger et al, 2010a). The optimal management of these patients is controversial. Advocates of PCS for these patients argue that residual mass size (or percentage reduction with chemotherapy) cannot be used to exclude reliably the presence of residual disease within the retroperitoneum. Numerous studies have demonstrated that, on average, patients with residual masses 20 mm or smaller have a 30% and 6% incidence of teratoma and viable malignancy, respectively (Table 34-7) (Fossa et al, 1989b; Toner et al, 1990; Stomper et al, 1991; Fossa et al, 1992; Steyerberg et al, 1995; Beck et al, 2002; Oldenburg et al, 2003; Stephenson et al, 2007). In an analysis of 295 patients with GCT managed at Indiana University after induction chemotherapy, 77 (26%) experienced a complete serologic and radiographic response to chemotherapy; 92% were alive at 5 to 10 years with an observational strategy

(Debono et al, 1997). This result highlights the therapeutic benefit of PCS for patients with residual masses. However, patients with complete serologic and radiographic response after induction chemotherapy represent a small minority of the overall population, indicating that observation is a reasonable option for only a select group of patients. Two studies have confirmed the low risk of relapse (4% to 10%) and 97% to 100% cancer-specific survival in patients with residual masses less than 1 cm who were observed without PCS (Ehrlich et al, 2010; Kollmannsberger et al, 2010a). However, most of these patients were good risk by IGCCCG criteria and did not have teratoma in the primary tumor, highlighting their select nature.

Approximately one third of patients have residual masses at multiple anatomic sites (retroperitoneum, chest, and left supraclavicular fossa are the most common), and these patients should undergo resection of all sites of measurable residual disease (Toner et al, 1990; Gerl et al, 1994; Hartmann et al, 1997a; McGuire et al, 2003). Although some centers have described performing simultaneous RPLND, thoracotomy, or neck dissection, our practice is to perform infradiaphragmatic and supradiaphragmatic resections as separate procedures. **Discordant histology between anatomic sites is reported in 22% to 46% of cases (Toner et al, 1990).** In general, the histology of PCS specimens from nonretroperitoneal sites is more likely to show necrosis (60%) and less likely to show viable malignancy (10%) and teratoma (30%) (Toner et al, 1990; Gerl et al, 1994; Hartmann et al, 1997a; Steyerberg et al, 1997). In addition to the size of residual masses and the number of anatomic sites, the presence of necrosis in postchemotherapy RPLND specimens is highly predictive of necrosis at other sites (Steyerberg et al, 1997). Of patients undergoing PCS for residual masses at different sites, only 19 of 159 (12%) who had necrosis in the RPLND specimen had either viable malignancy or teratoma at other sites (Tiffany et al, 1986; Gerl et al, 1994; Brenner et al, 1996; Steyerberg et al, 1997; Tognoni et al, 1998; McGuire et al, 2003). RPLND should be performed before PCS at other sites because the probability of residual disease in the retroperitoneum is highest, and RPLND histology is a strong predictor of histology at other sites. Observation of small residual masses at other sites is a reasonable option if the histology of the RPLND specimen is necrosis.

As mentioned earlier, the 5-year survival for patients with viable malignancy in PCS specimens is 45% to 77%. The role of postoperative chemotherapy in this setting is controversial. Fox and colleagues (1993) reported that 14 of 27 patients (70%) undergoing PCS for viable malignancy were free of recurrence with adjuvant chemotherapy versus 0 of 7 patients who were observed. In an international pooled analysis of 238 patients with viable malignancy in PCS specimens, Fizazi and colleagues (2001) identified prechemotherapy IGCCCG intermediate-risk and poor-risk disease, incomplete resection, and greater than 10% viable malignancy in PCS specimens as important prognostic factors. Patients with zero, one, and two to three risk factors had a 5-year overall survival of 100%, 83%, and 51%. Overall, a significant improvement in 5-year relapse-free survival was observed with postoperative chemotherapy (73% vs. 64%, $P < .001$), but there was no difference in 5-year overall survival (74% vs. 70%, $P = .7$). In a subset analysis, patients with one risk factor had an improved 5-year survival with postoperative chemotherapy (88% vs. 56%, $P = .02$), but patients with zero (100% survival, with or without chemotherapy) and two to three risk factors (55% vs. 60%) did not. In a confirmatory study, this prognostic index was validated for relapse-free and overall survival, and no significant difference in these end points was observed among the patients who did and did not receive postoperative chemotherapy (Fizazi et al, 2008). **A complete resection of residual masses is the most critical determinant of outcome for patients with viable malignancy in PCS specimens after first-line chemotherapy.** Immediate postoperative chemotherapy and surveillance may be reasonable options depending on the completeness of resection, IGCCCG risk group, and percent of viable cells. There is no consensus on the appropriate chemotherapy regimen and the number of cycles that should be used in this setting.

The importance of PCS was highlighted in a randomized trial of BEP×3 versus EP×4 in 257 men with good-risk metastatic NSGCT (Culine et al, 2007). As part of this trial, PCS was not dictated by protocol, and only 52% underwent PCS, which frequently involved resection of residual mass only. Overall, 14 of 20 (70%) relapsing patients and 7 of 14 (50%) patients who died of GCT either did not undergo PCS or relapsed in the retroperitoneum after inadequate RPLND. **These results suggest a substantial proportion of deaths from GCT may be prevented by the appropriate integration of chemotherapy and surgery.**

Relapsing Nonseminoma Germ Cell Tumor

The treatment of relapsing NSGCTs depends on what treatment the patient previously received and, in certain cases, the location of the relapse. Patients who have never received chemotherapy have a much more favorable prognosis than patients who have already been treated with chemotherapy for disseminated disease.

Chemotherapy-Naive Nonseminoma Germ Cell Tumor Relapse.

Chemotherapy-naive relapses occur in men with CS I NSGCT managed with either surveillance or RPLND and in men with CS IIA and IIB NSGCT treated with RPLND alone. Serum tumor markers are elevated 60% to 75% of the time in patients with CS I NSGCT who relapse on surveillance (Read et al, 1992; Gels et al, 1995; Sharir et al, 1999; Alexandre et al, 2001). **In general, these patients are treated with induction chemotherapy, with the specific regimen and duration of therapy determined by IGCCCG risk, and cure rates exceed 95%.** Select CS I patients on surveillance who relapse in the retroperitoneum with nonbulky (<3 cm) tumor and normal serum tumor markers may be treated by induction chemotherapy or RPLND (particularly if teratoma was present in the primary tumor) (Stephenson et al, 2007). The rationale for RPLND is to avoid or minimize the toxicity of chemotherapy, and long-term cure rates approach 100% with RPLND with or without adjuvant chemotherapy (Stephenson et al, 2007). CS I, IIA, and IIB patients who relapse after RPLND usually have involvement in the lungs or mediastinum. Virtually all of these patients are cured with first-line chemotherapy. Most relapses during surveillance or after RPLND occur within the first 2 years (Freedman et al, 1987; McLeod et al, 1991; Read et al, 1992; Albers et al, 1995; Gels et al, 1995; Sogani et al, 1998; Colls et al, 1999; Sharir et al, 1999; Francis et al, 2000; Daugaard et al, 2003; Stephenson et al, 2005b; Albers et al, 2008; Williams et al, 2009b; Zuniga et al, 2009; Kollmannsberger et al, 2010a). For the rare patient relapsing more than 2 years after orchiectomy or RPLND with normal tumor markers, biopsy or surgical resection should be strongly considered because of the likelihood of teratoma (Michael et al, 2000; Oldenburg et al, 2006). **Although the time to relapse is an important determinant of outcome in relapsing patients who have received prior chemotherapy, chemotherapy-naive patients who relapse more than 2 years after initial treatment have a prognosis similar to patients who relapse earlier.**

Nonseminoma Germ Cell Tumor Relapse Early after Chemotherapy.

Men who relapse after previously receiving first-line chemotherapy are treated with second-line (salvage) chemotherapy. Most relapses occur within 2 years of completing initial treatment, and these are classified as early relapse (de Wit et al, 1998; Nichols et al, 1998; Michael et al, 2000; Culine et al, 2007; Motzer et al, 2007). Relapses occurring more than 2 years after completion of initial therapy are classified as late relapse and differ substantially in terms of prognosis and therapy (discussed later). Early relapsing patients who appear to have a particularly unfavorable prognosis are patients who fail to achieve a complete response to first-line therapy or who relapse within 6 months of achieving a complete response; these patients are frequently termed *incomplete responders* (Fossa et al, 1999c). In an international pooled analysis of 1984 patients from 38 centers with relapse after first-line chemotherapy who received second-line chemotherapy, median progression-free survival was 10 months, and overall survival was 41 months (Lorch et al, 2010). Incomplete response to induction chemotherapy (HR = 1.4 to 1.9), primary mediastinal NSGCT

(HR = 3.0), nonpulmonary visceral metastasis (HR = 1.3), and elevated AFP (HR = 1.3 to 2.0) and hCG (HR = 1.5) were associated with increased risk of progression with second-line chemotherapy.

As discussed earlier, etoposide and ifosfamide were demonstrated to have substantial activity in patients with relapse after first-line chemotherapy, and this led to investigation of VIP×4 as a second-line regimen for relapsed GCT after PVB×4 (Loehrer et al, 1986; Einhorn, 1990). VeIP×4 was also studied as a second-line regimen in men who had received prior etoposide from BEP regimens (Loehrer et al, 1998). Studies of VIP×4 and VeIP×4 reported long-term remission rates of 23% to 35% and overall survival rates of 32% to 53% (McCaffrey et al, 1997; Loehrer et al, 1998; Pico et al, 2005). Studies of paclitaxel in the early 1990s showed activity in relapsed GCT, which led to development of the paclitaxel, ifosfamide, and cisplatin (TIP) regimen, and relapse-free survival has been reported in 36% to 47% of patients (Kondagunta et al, 2005; Mardiak et al, 2005; Mead et al, 2005). TIP×4, VIP×4, and VeIP×4 have never been compared in a randomized trial, and all are considered standard second-line regimens.

HDCT has also been investigated as a second-line (and third-line) regimen in patients with GCT relapse, although its role as second-line therapy is controversial. Indiana University has amassed the largest, single-institution series comprising 184 consecutive patients with metastatic GCT that progressed after first-line (73%) or second-line (27%) chemotherapy; 94% of these patients received two or more courses of HDCT (Einhorn et al, 2007). Over a median follow-up of 4 years, 63% of patients were continuously disease-free, including 70% and 45% of patients who received HDCT as second-line and third-line therapy, respectively. An international matched-pair analysis comparing 74 patients treated at a single institution who received two to three cycles of VIP followed by one cycle of HDCT using carboplatin-etoposide-ifosfamide with 119 patients treated at multiple centers throughout Europe who received standard-dose, second-line chemotherapy using various regimens reported a 10% improvement in event-free and overall survival with HDCT (Beyer et al, 2002). HDCT was compared with standard-dose, second-line chemotherapy in a randomized controlled trial enrolling 280 patients from 43 institutions. Patients in the standard-dose arm received VIP×4 or VeIP×4, depending on whether they received prior etoposide during first-line therapy. Patients in the HDCT arm received VIP/VeIP×3 followed by one cycle of high-dose carboplatin-etoposide-cyclophosphamide (Pico et al, 2005). Over a median follow-up of 45 months, there were no significant differences in complete and partial response rates (56% in both arms) or 3-year event-free (35% vs. 42%, $P = .16$) and overall (53% in both arms) survival.

There are several potential explanations for the lack of benefit of HDCT in the randomized trial despite the favorable results reported in the two nonrandomized studies. First, the results from single-arm trials may be subject to selection bias from differences in case mix. In addition, the results achieved at high-volume institutions with unique experience with HDCT may not be reproducible at other institutions. Alternatively, the treatment strategy employed in the randomized trial may have been suboptimal in that three cycles of standard-dose chemotherapy and only one cycle of HDCT were given. The treatment philosophy at Indiana University is to take patients to HDCT as quickly as possible, limit the number of cycles of standard-dose chemotherapy so that patients are able to tolerate HDCT better, and to give two cycles of HDCT. In the randomized trial, only 73% of patients assigned HDCT were able to receive it, and deaths resulting from toxicity on the HDCT arm were twice as common as on the standard-dose arm (7% vs. 3%). In the Indiana University series, 94% of patients were able to receive two cycles of HDCT, and the treatment-related death rate was 2.7%. Although HDCT as second-line therapy can cure a significant number of patients, the failure to demonstrate an improvement in survival compared with standard-dose regimens in three randomized trials (two as first-line therapy and one as second-line therapy) suggests it should not be considered a standard approach. At the present time, HDCT

should be offered only at specialized centers with extensive experience.

Treatment options for high-risk patients with relapse (e.g., incomplete responders) include standard-dose, second-line chemotherapy or HDCT (if administered at a specialized, high-volume institution). Standard-dose, second-line chemotherapy is the preferred approach for patients who relapse more than 6 months after first-line chemotherapy. Special mention is made of patients with declining or normalized serum tumor markers during first-line chemotherapy with enlarging (usually cystic) masses. These patients are considered to have growing teratoma syndrome. In these rare cases, chemotherapy is temporarily interrupted, and patients are taken for surgical resection. With complete surgical resection, the long-term prognosis for these patients is favorable (Logothetis et al, 1982; Andre et al, 2000; Spiess et al, 2007).

For patients relapsing after second-line chemotherapy, subsequent options are HDCT (if not given previously) and regimens including various combinations of the following agents: gemcitabine, paclitaxel, oxaliplatin, and irinotecan (Pectasides et al, 2004; De Giorgi et al, 2006; Bokemeyer et al, 2008; Nicolai et al, 2009; Oechsle et al, 2011; Veenstra and Vaughn, 2011).

Management of Residual Masses after Salvage Chemotherapy. Patients with serologic complete response to second-line chemotherapy with residual masses should undergo surgical resection after salvage chemotherapy. Patients undergoing surgical resection after salvage chemotherapy differ from patients undergoing PCS of residual masses after first-line chemotherapy in several ways. A complete resection of residual masses is feasible in only 56% to 72% of patients (compared with ≥85% after first-line therapy) (Fox et al, 1993; Debono et al, 1997; Hartmann et al, 1997b; Stenning et al, 1998; Eggener et al, 2007a). The histology of post-salvage chemotherapy surgical specimens is characterized by higher rates of viable malignancy (53%) and lower rates of necrosis (26%) and teratoma (21%) compared with surgical specimens after first-line chemotherapy. The long-term survival of patients is also substantially poorer with 5-year survival rates of 44% to 61% in most series (Fox et al, 1993; Hartmann et al, 1997b; Donohue et al, 1998; Stenning et al, 1998). Patients with viable malignancy in post-salvage chemotherapy surgical specimens have a particularly poor prognosis, and their survival is not improved with the use of postoperative chemotherapy.

Desperation Surgery. Most patients with progressive disease despite first-line and second-line chemotherapy have a dismal prognosis. However, a highly select group of patients with rising serum tumor markers who are deemed to have resectable disease limited to a single site (usually the retroperitoneum) may be candidates for salvage surgery, commonly referred to as desperation surgery. Although published studies are limited to small, single-institution case series, 47% to 60% have normalization of serum tumor markers postoperatively, and long-term survival is reported in 33% to 57% of patients after desperation surgery with or without postoperative chemotherapy (Wood et al, 1992; Murphy et al, 1993; Eastham et al, 1994; Albers et al, 2000; Beck et al, 2005).

Nonseminoma Germ Cell Tumor Relapse Late after Chemotherapy. Late relapse after chemotherapy is defined as relapse occurring more than 2 years after treatment. Roughly 3% of patients with NSGCT experience a late relapse (Ronnen et al, 2005; Oldenburg et al, 2006). Because late relapse is rare, a biopsy should be performed to confirm the diagnosis, particularly when serum AFP and hCG are normal. Late relapses can be divided into three histopathologic categories: viable malignancy (54% to 88%, yolk sac tumor most common), teratoma (12% to 28%), and malignant transformation (10% to 20%, adenocarcinoma most common) (Baniel et al, 1995; Gerl et al, 1997; Michael et al, 2000; George et al, 2003; Sharp et al, 2008).

Risk factors for late relapse have not been definitively identified, but a history of prior relapse and the presence of teratoma in PCS specimens (potentially for incomplete resection) are associated with an increased risk (Gerl et al, 1997; Shahidi et al, 2002). Most men with a late relapse have only one site of disease.

Most late relapses occur in the retroperitoneum (50% to 72%), 17% occur in the lungs, 9% occur in the mediastinum, 7% occur in the neck, and 4% occur in the pelvis (Baniel et al, 1995; Gerl et al, 1997; George et al, 2003; Dieckmann et al, 2005; Oldenburg et al, 2006; Sharp et al, 2008). Failure to control the retroperitoneum in the initial treatment phase is a major risk factor for late relapse. Serum AFP and hCG levels are elevated in about 50% and 25% of late relapses, respectively (Oldenburg et al, 2006). Patients with elevated serum tumor markers as the only manifestation of late relapse should be monitored closely until there is measurable disease (George et al, 2003).

Until more recently, late relapse was associated with a worse prognosis than early relapses, although contemporary data suggest these patients may have a similar probability of cure. In general, late relapse is resistant to chemotherapy, and the outcome is related to the ability to render patients disease-free by complete surgical resection (Gerl et al, 1997; Shahidi et al, 2002; George et al, 2003; Dieckmann et al, 2005; Oldenburg et al, 2006; Sharp et al, 2008).

The importance of surgery is related to the fact that teratoma and malignant transformation are inherently chemoinensitive, and viable malignancy is usually present in the setting of prior chemotherapy (platin-resistant). Of 32 patients with late relapse at Indiana University who received chemotherapy, only 6 (19%) achieved a complete response. Of the 49 patients treated initially with surgery, 45 (92%) were rendered disease-free (22 [45%] by surgery alone), and 29 (59%) are in complete remission. Overall, 69 (85%) patients achieved a disease-free state, and 58% were disease-free over a median follow-up of 25 months (George et al, 2003). In the Memorial Sloan-Kettering experience, the 5-year cancer-specific survival was 60%, and patients who had a complete surgical resection at the time of late relapse (60%) had significantly improved survival compared with patients without complete resection (40%) (79% vs. 36%, $P < .001$) (Sharp et al, 2008). The presence of symptoms and multifocal disease at late relapse were associated with inferior survival. In a German study of 72 patients with NSGCT and late relapse, 35 (49%) were in complete remission at last follow-up, most of whom were treated with a combination of chemotherapy and surgery (Dieckmann et al, 2005). The most favorable chemotherapy results for late relapse are with the TIP regimen (Kondagunta et al, 2005). An aggressive surgical approach to resect all disease is appropriate either as the primary treatment or, in the setting of unresectable disease, after chemotherapy.

Seminoma

Clinical Stage I Seminoma. Approximately 80% of patients with seminoma are CS I, and this is the most common presentation of testis cancer. The management of these patients has undergone substantial changes over the past two decades, and surveillance, primary radiotherapy, and primary chemotherapy with single-agent carboplatin are now accepted treatment options. More recent efforts have focused on reducing the therapeutic burden. Platinum-based chemotherapy and infradiaphragmatic radiotherapy are associated with an increased risk of late cardiovascular toxicity and SMN (Zagars et al, 2004; Travis et al, 2005; van den Belt-Dusebout et al, 2007; Beard et al, 2013). Minimizing target volume and dose has been investigated to reduce the toxicity of radiotherapy. Carboplatin is associated with less neurotoxicity, ototoxicity, and nephrotoxicity compared with cisplatin, but the risks of cardiovascular disease and SMN are largely unknown. In many instances, the short-term efficacy and safety of these approaches have been validated by randomized trials. Long-term cancer control with each of these modalities approaches 100%.

Primary Radiotherapy. The mainstay of treatment for CS I seminoma for the past four decades had been primary radiotherapy to the retroperitoneum and ipsilateral pelvis, termed *dog-leg configuration*. Published series of radiotherapy for CS I are listed in Table 34-8 (Fossa et al, 1989a; Warde et al, 1995; Fossa et al, 1999b; Classen et al, 2004; Jones et al, 2005; Oliver et al, 2005; Warde et al, 2005; Tandstad et al, 2011). The optimal radiation dose has

KEY POINTS: NONSEMINOMA GERM CELL TUMOR

- The optimal management of CS I NSGCT is controversial. Surveillance, primary RPLND, and primary chemotherapy with BEP×2 are accepted treatment options with long-term survival rates approaching 100% for each.
- A risk-adapted approach based on the presence of LVI and EC predominance is recommended. Surveillance is recommended for patients without these risk factors, and active treatment (RPLND or BEP×2) is recommended for patients with LVI and/or EC predominance. A non-risk-adapted approach, which includes surveillance as the recommended approach for all patients, is employed at some centers.
- Surveillance is not recommended for patients who are anticipated to be poorly compliant with follow-up imaging and clinical evaluation. The standard treatment approach for patients who relapse on surveillance is induction chemotherapy based on IGCCCG risk. However, selected patients with normal serum tumor marker levels and nonbulky (<3 cm) retroperitoneal adenopathy may also be managed with RPLND.
- BEP×2 is the standard regimen used for patients with CS I NSGCT who choose to receive chemotherapy. There is insufficient evidence at the present time to support BEP×1 as an acceptable alternative.
- A full, bilateral template with nerve sparing is the recommended approach for primary RPLND. Attempts to preserve ejaculatory function should not compromise oncologic efficacy. RPLND should be performed only by surgeons experienced with the procedure.
- Adjuvant chemotherapy after primary RPLND for pathologic stage II disease is associated with a substantial reduction in the risk of relapse but no difference in long-term survival compared with a strategy comprising observation with induction chemotherapy at the time of relapse. Adjuvant chemotherapy is usually recommended for patients with extensive retroperitoneal metastasis (pN2-3) and patients anticipated to be noncompliant with postoperative cancer surveillance imaging and testing.
- Induction chemotherapy and primary RPLND are accepted treatment options for patients with CS IIA and IIB NSGCT, with long-term cure in 95% or more. Induction chemotherapy is favored in patients with a high risk of occult metastatic disease on the basis of elevated serum tumor markers after orchiectomy and/or bulky (>3 cm) retroperitoneal lymphadenopathy.
- The management of patients with CS IS, IIC, and III NSGCT is induction cisplatin-based chemotherapy. The specific regimen and number of cycles is dictated by IGCCCG risk criteria. Patients with good-risk disease should receive BEP×3 or EP×4, and patients with intermediate-risk and poor-risk disease should receive BEP×4. With risk-appropriate chemotherapy and PCS, the survival of patients with good-risk disease is 89% to 94%, with intermediate-risk disease is 75% to 83%, and with poor-risk disease is 41% to 71%.
- Resection of all residual masses after chemotherapy is based on the incidence of residual cancer (either viable malignancy or teratoma) in 50% or more of patients.
- The use of adjuvant chemotherapy is controversial in patients with viable malignancy in residual masses after first-line chemotherapy.

not been defined; most centers use 20 to 30 Gy over 10 to 15 daily fractions (Fossa et al, 1989a; Warde et al, 1995; Fossa et al, 1999b). Long-term cancer-specific survival approaches 100%, and progression-free probability between 95% and 97% is reported (Fossa et al, 1989a; Warde et al, 1995; Fossa et al, 1999b; Warde et al, 2005; Kollmannsberger et al, 2010; Tandstad et al, 2011). In-field recurrence after dog-leg radiotherapy is less than 1%,

TABLE 34-8 Radiation Therapy Series for Clinical Stage I Seminoma

STUDY	NO. PATIENTS	MEDIAN FOLLOW-UP (mo)	TARGET VOLUME	MEDIAN DOSE (Gy)	GCT DEATHS (%)	RELAPSE (%)	IN-FIELD RELAPSE (%)	PELVIC RELAPSE (%)
Fossa et al, 1989a	365	109	Dog-leg	40	4 (1)	13 (4)	1 (0.3)	0
Warde et al, 1995	194	97	Dog-leg	25	0	11 (6)	0	0
Warde et al, 2005	282	106	Dog-leg	25	0	14 (5)	—	—
Fossa et al, 1999b	242	54	Dog-leg	30	0	9 (4)	0	0
Fossa et al, 1999b	236	54	Para-aortic	30	1	9 (4)	2 (0.8)	4 (1.7)
Classen et al, 2004	721	61	Para-aortic	26	2 (0.3)	26 (4)	8 (1.1)	13 (1.8)
Jones et al, 2005	313	61	Para-aortic	30	1 (0.3)	10 (4)	3 (1)	6 (2)
Jones et al, 2005	312	61	Para-aortic	20	0	11 (4)	2 (0.6)	3 (1)
Oliver et al, 2005, 2011	904	78	Para-aortic	20-30	1 (0.1)	32 (4)	3 (0.3)	10 (1.6)
Tandstad et al, 2011	481	73	Dog-leg	25	0	4 (1)	2 (0.6)	—
Kollmannsberger et al, 2010c	159	65	Para-aortic	25	0	4 (2)	—	2(1)

GCT, germ cell tumor.

obviating the need for routine surveillance abdominopelvic CT imaging. Inguinal metastases are uncommon in patients without prior inguinal or scrotal surgery. **The most common sites of recurrence are the thorax and left supraclavicular fossa. Virtually all recurrences are cured with first-line chemotherapy.** Selected patients with isolated inguinal relapse may be salvaged with radiotherapy or surgical resection. **The surveillance of patients after dog-leg radiotherapy consists of regular clinical assessment, chest radiography, and serum tumor markers.**

Most patients experience some acute side effects with adjuvant radiotherapy, which typically include transient nausea, vomiting, and diarrhea, which are usually mild and self-limited. Acute grade II to IV hematologic toxicity occurs in 5% to 15% of patients (Fossa et al, 1999b). Moderate and severe late gastrointestinal toxicity (usually chronic dyspepsia or peptic ulcer disease) is reported in 5% and less than 2% of patients, respectively. The testicular germinal epithelium is exquisitely sensitive to ionizing radiation, and scatter dose to the contralateral testis may be significant despite protective shielding. After dog-leg radiotherapy, persistent oligospermia is reported in 8% (Fossa et al, 1999b). The issue of late cardiac toxicity and SMN is particularly germane for these patients given the long anticipated life expectancy. **The actuarial risk of developing SMN is estimated to be 18% at 25 years after radiotherapy for seminoma, and there is a 2.64% risk of dying of SMN at 15 years, representing an 89% increased risk of death from nontesticular cancer (Travis et al, 2005; Beard et al, 2013).** Secondary leukemia is linked with radiotherapy and chemotherapy, whereas an increased incidence of upper gastrointestinal tract, bladder, and possibly pancreas cancers is associated with radiotherapy.

To reduce the toxicity of radiotherapy, efforts to minimize the target volume and dose have been evaluated in randomized trials. The Medical Research Council (MRC) in the United Kingdom conducted a randomized trial of dog-leg versus para-aortic radiotherapy for CS I seminoma (Fossa et al, 1999b). The rationale for omitting radiotherapy to the ipsilateral pelvis is based on the low rate (1% to 3%) of pelvic lymph node involvement in patients without prior inguinal or scrotal surgery. Restricting radiotherapy to the para-aortic strip may reduce the risk of SMN and improve recovery of spermatogenesis. The 3-year relapse-free survival (96% vs. 97%) and overall survival (99% vs. 100%) in the para-aortic versus dog-leg

arms were similar, but patients receiving para-aortic radiotherapy had an improved short-term recovery of spermatogenesis (although no difference was seen at 3 years). However, the para-aortic arm experienced a significant increase in the rate of pelvic recurrence (2% vs. 0%, $P = .04$). The small but significant risk of pelvic recurrence necessitates the use of routine surveillance pelvic CT imaging with the associated increased cost and radiation exposure (Brenner and Hall, 2007).

The MRC and the European Organisation for the Research and Treatment of Cancer (EORTC) also conducted a randomized trial of 20 Gy versus 30 Gy para-aortic radiotherapy for CS I seminoma (Jones et al, 2005). The 5-year relapse-free survival (96% vs. 97%) and overall survival (99.6% vs. 100%) were similar, but patients receiving 20 Gy experienced less acute gastrointestinal toxicity, leukopenia, and lethargy (although results were similar at 12 weeks). Further follow-up is necessary to assess the durability of these results. **Surveillance.** Given the potential for late toxicity with dog-leg radiotherapy, the 80% to 85% cure rate after orchiectomy, and the greater than 90% cure rates achieved with platin-based chemotherapy for advanced seminoma, surveillance has been evaluated at several centers. **Compared with NSGCT, surveillance for CS I seminoma is complicated by the limited utility of serum tumor markers to detect relapse and the need for long-term surveillance CT imaging because 10% to 20% of relapses occur 4 years or more after diagnosis (Chung et al, 2002).**

The largest surveillance series for CS I seminoma are listed in Table 34-9 (Horwich et al, 1992; von der Maase et al, 1993; Warde et al, 1995; Aparicio et al, 2003; Daugaard et al, 2003; Aparicio et al, 2005; Choo et al, 2005; Warde et al, 2005; Kollmannsberger et al, 2010c; Tandstad et al, 2011). **The 5-year relapse-free survival ranges from 80% to 86%, and cancer-specific survival approaches 100%. Of patients, 84% to 100% relapse in the retroperitoneum, and 18% to 24% have bulky retroperitoneal disease and/or distant metastases at the time of recurrence (Horwich et al, 1992; von der Maase et al, 1993; Warde et al, 1995; Aparicio et al, 2003; Choo et al, 2005).** Dog-leg radiotherapy is employed for treatment of relapse in 73% to 88% of patients, and cure rates of 70% to 90% are reported. Virtually all patients who relapse outside the retroperitoneum are cured with first-line chemotherapy.

TABLE 34-9 Surveillance Series for Clinical Stage I Seminoma

STUDY	NO. PATIENTS	MEDIAN FOLLOW-UP (mo)	GCT DEATHS (%)	RELAPSE (%)	RPN RELAPSE (%)	CS IIC-III RELAPSE (%)	SYSTEMIC RELAPSE (%)
Daugaard et al, 2003	394	—	0	69 (17)	—	—	—
Warde et al, 2005	348	106	1 (0.3)	55 (16)	—	—	—
Warde et al, 1995	172	50	1 (0.6)	27 (16)	24 (89)	5 (19)	1 (4)
von der Maase et al, 1993	261	48	1 (0.4)	49 (19)	46 (94)	12 (24)	1 (2)
Aparicio et al, 2003	143*	52	0	23 (16)	19 (84)	—	3 (13)
Horwich et al, 1992	103	62	0	17 (17)	17 (100)	3 (18)	1 (6)
Choo et al, 2005	88	145	0	17 (19)	15 (88)	3 (18)	2 (12)
Aparicio et al, 2005	100†	34	0	6 (7)	6 (100)	—	0
Tandstad et al, 2011	512	60	0	65 (14)	65 (100)	—	—
Kollmannsberger et al, 2010c	313	34	0	47 (19)	—	—	—

*Patients with lymphovascular invasion or clinical stage \geq T2 excluded.

†Patients with tumor size >4 cm or rete testis invasion excluded.

CS, clinical stage; GCT, germ cell tumor; RPN, retroperitoneal.

TABLE 34-10 Adjuvant Chemotherapy Series for Clinical Stage I Seminoma

STUDY	NO. PATIENTS	MEDIAN FOLLOW-UP (mo)	NO. CYCLES	GCT DEATHS (%)	RELAPSE (%)
Oliver et al, 2005, 2011	573	78	1	0	27 (5)
Steiner et al, 2002	108	60	2	0	2 (2)
Reiter et al, 2001	107	74	2	0	0
Dieckmann et al, 2000	93	48	1	0	8 (9)
Dieckmann et al, 2000	32	48	2	0	0
Oliver et al, 1994	78	51	2*	0	2 (2)
Aparicio et al, 2003	60	52	2	0	2 (3.3)
Aparicio et al, 2005	214	34	2	0	7 (4)
Tandstad et al, 2011	188	62	1	0	7 (4)
Kollmannsberger et al, 2010c	73	33	1-2	0	1 (2)

*33% of patients received 1 cycle of carboplatin.

GCT, germ cell tumor.

To detect and treat recurrences at an early stage, patients on surveillance should be followed with clinical assessment, chest radiography, serum tumor markers, and abdominopelvic CT imaging. Surveillance schedules employ assessments every 2 to 4 months in years 1 to 3, every 6 months in years 4 to 7, and annually thereafter. The necessary frequency of CT imaging is poorly defined; centers obtain CT imaging every 4 to 6 months in years 1 to 3, every 6 months in years 4 to 7, and annually thereafter. A trial from the MRC suggested that the frequency of surveillance CT imaging in low-risk CS I NSGCT in years 0 to 2 may be safely reduced from five times to two times without affecting survival or burden of therapy (Rustin et al, 2007). It is unclear whether these findings can be safely applied to surveillance for seminoma. Long-term follow-up is mandatory given the higher incidence of relapse after 5 years compared with NSGCT (Chung et al, 2002).

To select patients for active treatment better, investigators have endeavored to identify prognostic factors for occult metastasis. In a pooled analysis of three large surveillance series from the 1980s, tumor size larger than 4 cm and rete testis invasion were significant predictors of relapse in multivariable analysis (Warde et al, 2002). In contrast to NSGCT, LVI has not been identified as a significant predictor of relapse for CS I seminoma. The 5-year

relapse rates for patients with zero, one, and two risk factors were 12%, 16%, and 32%. In this cohort, 21% of patients had both rete testis invasion and tumor size larger than 4 cm. Primary radiotherapy or carboplatin for all “high-risk” patients would still expose two thirds of patients with CS I seminoma (who are cured by orchiectomy) to unnecessary therapy. However, prospective validation of these risk factors is currently lacking.

Primary Chemotherapy with Single-Agent Carboplatin. Primary chemotherapy with one to two cycles of single-agent carboplatin has also been investigated as an alternative to primary radiotherapy with the potential for reduced late toxicity. The rationale for single-agent carboplatin is based on the 65% to 90% reported complete response rates observed among patients with advanced seminoma (Horwich et al, 2000) and its reduced toxicity compared with cisplatin. Oliver and colleagues (1994) first described the use of one to two cycles of carboplatin in 78 patients and reported only two relapses and no deaths. The published studies of carboplatin in CS I seminoma are listed in Table 34-10 (Dieckmann et al, 2000; Reiter et al, 2001; Steiner et al, 2002; Aparicio et al, 2003, 2005; Oliver et al, 2005; Kollmannsberger et al, 2010c; Aparicio et al, 2011; Tandstad et al, 2011). No deaths from seminoma have been observed, and 3- to 5-year relapse-free rates are 91% to 100%.

The MRC and EORTC conducted a randomized, phase III clinical trial of one cycle of carboplatin versus 20 to 30 Gy para-aortic radiotherapy in 1477 patients with CS I seminoma (Oliver et al, 2005, 2011). Over a median follow-up of 6.5 years, the 5-year relapse-free survival was similar (94.7% vs. 96%), and only one death was observed in the para-aortic radiotherapy arm. In this trial, patients receiving carboplatin experienced less lethargy and time away from work than patients receiving radiotherapy, and acute grade III to IV hematologic toxicity was observed in 4% of patients. Carboplatin was associated with a reduction in the rate of contralateral second-primary testis cancers (0.3% vs. 1.7%, $P = .03$).

A concern with one cycle of carboplatin is the potential for inadequate dosing leading to an increased risk of relapse. A higher relapse rate with one versus two cycles has been seen when comparing different studies, and a higher risk of relapse was reported among patients receiving an inadequate dose of carboplatin in the MRC/EORTC trial (Dieckmann et al, 2000; Oliver et al, 2008). The optimal dosing of carboplatin is calculated by the formula $7 \times (\text{glomerular filtration rate [mL/min]} + 25) \text{ mg}$ (Calvert and Egorin, 2002). Carboplatin dosing should not be based on estimated glomerular filtration rate. It is recommended to base one cycle of carboplatin dosing on the results of radioisotope renal scans or administer two cycles of therapy.

Given the low overall risk of relapse with CS I seminoma, the lack of prospectively validated markers to identify a high-risk population, and the potential for late toxicity with radiotherapy and carboplatin, many clinical practice guidelines now recommend surveillance as the preferred approach (Krege et al, 2008a, 2008b; Schmoll et al, 2009a). Surveillance enables 80% to 85% of patients to avoid treatment-related toxicity, and relapses are effectively salvaged with dog-leg radiotherapy in most cases. However, surveillance must be continued more than 5 years, and frequent CT imaging is required. For noncompliant patients or patients unwilling to accept surveillance, primary radiotherapy or primary chemotherapy with one to two cycles of carboplatin is recommended.

Clinical Stage IIA and IIB Seminoma. Approximately 15% to 20% of patients with seminoma have CS II disease; 70% of these patients have CS IIA and IIB. Dog-leg radiotherapy using 25 to 30 Gy (including a 5- to 10-Gy boost to involved areas) is employed at most centers. The higher radiation doses administered to CS IIA and IIB patients is generally well tolerated with acute grade III to IV gastrointestinal toxicity reported in 8% to 10% of patients (Classen et al, 2003b). Prophylactic radiation to the left supraclavicular fossa is no longer practiced because less than 3% of patients are likely to benefit (Zagars and Pollack, 2001; Chung et al, 2003). Long-term disease-free survival rates of 92% to 100% for CS IIA and 87% to 90% for CS IIB have been reported, with in-field recurrences reported in 0% to 2% and 0% to 7% of cases, respectively (Zagars and Pollack, 2001; Classen et al, 2003b; Chung et al, 2004b). Adding single-agent carboplatin to 30 Gy dog-leg radiotherapy reduced the relapse rate from 30% to 6% in one series, although further data are required to assess the utility of this approach (Patterson et al, 2001). Relapses are cured in virtually all cases with first-line chemotherapy, and disease-specific survival approaches 100%. Routine surveillance CT imaging is unnecessary after complete resolution of disease.

Induction chemotherapy using first-line regimens (BEP \times 3 or EP \times 4) is an accepted alternative to dog-leg radiotherapy. The Spanish Germ Cell Cancer Study Group reported on the use of BEP \times 3 or EP \times 4 in 72 patients with CS IIA and IIB seminoma (Garcia-del-Muro et al, 2008). Overall, 83% of patients achieved a serologic and radiographic complete response; only one patient (1.3%) had residual mass larger than 3 cm, and the two patients who underwent PCS for residual masses had necrosis only in the resected specimens. The 5-year relapse-free survival was 90%, and overall survival was 90% to 95%. The SWENOTECA group similarly reported that there were no relapses among 73 CS IIA and IIB patients treated with cisplatin-based chemotherapy, whereas there were three relapses (10%) among 29 patients treated with radiotherapy. Induction chemotherapy is preferentially given to

patients with bulky (>3 cm) and/or multiple retroperitoneal masses because the risk of relapse is lower than with dog-leg radiotherapy (Patterson et al, 2001; Chung et al, 2004b; Garcia-del-Muro et al, 2008).

Clinical Stage IIC and III Seminoma. As with NSGCT, patients with CS IIC and III seminoma are treated with induction chemotherapy, with the regimen and number of cycles determined by IGCCCG risk. Of patients with advanced seminoma, 90% are classified as good risk and should receive either BEP \times 3 or EP \times 4 chemotherapy. Complete radiographic responses are reported in 70% to 90% of patients, and the 5-year overall survival is 91% (Loehrer et al, 1987; Mencil et al, 1994; International Germ Cell Consensus Classification, 1997; Gholam et al, 2003). Only 10% of advanced seminomas have nonpulmonary visceral metastasis (classified as intermediate risk by IGCCCG criteria). With BEP \times 4 chemotherapy, the 5-year overall survival is 79% and progression-free survival is 75 (International Germ Cell Consensus Classification, 1997). Single-agent carboplatin in advanced seminoma is associated with inferior survival compared with cisplatin-based regimens (Bokemeyer et al, 2004).

Management of Residual Masses after Chemotherapy. After first-line chemotherapy, 58% to 80% of patients have radiologically detectable residual masses (Motzer et al, 1987; Puc et al, 1996; Duchesne et al, 1997; Fossa et al, 1997; Herr et al, 1997; Flechon et al, 2002; De Santis et al, 2004). Spontaneous resolution of these masses is reported in 50% to 60% of cases, and the median time to resolution is 13 to 18 months (Flechon et al, 2002; De Santis et al, 2004). The histology of residual masses is necrosis and viable malignancy in 90% and 10% of cases, respectively (Puc et al, 1996; Herr et al, 1997; Ravi et al, 1999; Flechon et al, 2002; De Santis et al, 2004). PCS for seminoma is technically difficult (and frequently not feasible) because of the desmoplastic reaction that occurs after chemotherapy with resultant increased perioperative morbidity (Mosharafa et al, 2003). Surgical complete resections in seminoma after chemotherapy are reported in only 58% to 74% of patients (compared with $\geq 85\%$ after first-line chemotherapy for NSGCT) (Puc et al, 1996; Herr et al, 1997; Ravi et al, 1999; Flechon et al, 2002; De Santis et al, 2004). Teratoma and malignant transformation are much less of a concern with advanced seminoma. The management of postchemotherapy residual masses differs substantially for seminoma compared with NSGCT.

Investigators have endeavored to identify factors associated with a high risk of viable malignancy to justify PCS. Postchemotherapy radiotherapy has no role in the management of residual masses (Duchesne et al, 1997). The size of residual masses is an important predictor of viable malignancy; 27% to 38% of discrete residual masses larger than 3 cm contain viable malignancy compared with 0% to 4% for masses smaller than 3 cm (Puc et al, 1996; Herr et al, 1997; Flechon et al, 2002; De Santis et al, 2004). FDG-PET has been found to be a useful adjunct to CT imaging to select patients for PCS (De Santis et al, 2004). The specificity and sensitivity of a positive FDG-PET scan for masses larger than 3 cm were 100% and 80%, respectively. Patients with discrete residual masses larger than 3 cm should be evaluated further with FDG-PET, and patients with positive PET scans should undergo PCS. PET-negative residual masses larger than 3 cm and masses less than 3 cm should be observed. Inflammation and residual nonviable malignancy may cause a false-positive PET result if patients are scanned too soon after completing chemotherapy. FDG-PET should be delayed until at least 4 weeks after completion of chemotherapy.

Relapsed Seminoma

Chemotherapy-Naive Seminoma Relapse. Chemotherapy-naive relapse occurs in men with CS I seminoma on surveillance and in men with CS I and IIB seminoma treated with primary radiotherapy. For the former patients, dog-leg radiotherapy is employed for treatment of relapse in 73% to 88% of patients, and cure rates of 70% to 90% are reported. Patients with bulky (>3 cm) retroperitoneal masses and systemic relapse should receive first-line chemotherapy, and salvage rates approach 100%.

First-line chemotherapy cures virtually all patients who relapse outside the retroperitoneum after primary radiotherapy. Patients who relapse after single-agent carboplatin are considered to have chemotherapy-naïve relapse and should receive first-line cisplatin-based chemotherapy.

Early Relapse of Seminoma after Chemotherapy. An estimated 15% to 20% of patients with advanced seminoma relapse after induction chemotherapy, including 10% who achieve an initial complete response (Loehrer et al, 1987; Mencil et al, 1994; International Germ Cell Consensus Classification, 1997). In general, patients with incomplete response to first-line chemotherapy or relapse after an initial major clinical response have a poor prognosis with long-term survival rates of 20% to 50% (Miller et al, 1997; Vuky et al, 2002; Gholam et al, 2003). The small number of patients with seminoma who require second-line chemotherapy has limited the evaluation of unique treatment strategies, and relapsing patients are treated on regimens that were largely developed for NSGCT relapse. In two small studies, the efficacy of Velpx4 as second-line chemotherapy was evaluated in 36 patients with relapsed seminoma. Overall, 30 patients (83%) achieved a complete response to chemotherapy (with or without PCS), and 21 (53%) were continuously free of recurrence over a median follow-up of 72 to 84 months (Miller et al, 1997; Vuky et al, 2002). Vuky and coworkers (2002) also evaluated HDCT in 12 patients with advanced seminoma and an incomplete response to first-line chemotherapy, and 6 patients (50%) achieving a complete response remained free of recurrence. An important consideration for patients with advanced seminoma who relapse after first-line chemotherapy is the potential for teratoma at the site of relapse. Patients with normal serum tumor markers should undergo biopsy before starting second-line chemotherapy.

Late Relapse of Seminoma after Chemotherapy. In most published series, pure seminoma accounts for less than 8% of late relapse events (Baniel et al, 1995; George et al, 2003; Ronnen et al, 2005; Sharp et al, 2008). However, Dieckmann and colleagues (2005) reported a series of 122 patients with late relapse, of whom 50 (41%) had pure seminoma at diagnosis. Only 6 (12%) of these patients had received prior first-line chemotherapy, and most had received single-agent carboplatin or radiation therapy at diagnosis. Long-term control of cancer was achieved in 88% of patients. Late relapse of seminoma may have a favorable prognosis, particularly in patients without prior exposure to cisplatin.

Brain Metastases

About 1% of men with disseminated GCT have brain metastases detected before initiating chemotherapy, and between 0.4% and 3% develop brain metastases after first-line chemotherapy (Raina et al, 1993; International Germ Cell Consensus Classification, 1997; Fossa et al, 1999a). Brain metastases are associated with choriocarcinoma and should be suspected in any patient with a very high serum hCG level (Fossa et al, 1999a; Kollmannsberger et al, 2000; Salvati et al, 2006; Gremmer et al, 2008; Nonomura et al, 2009). Choriocarcinomas are highly vascular and tend to hemorrhage during chemotherapy, and death rates of 4% to 10% secondary to intracranial hemorrhage have been reported (Kollmannsberger et al, 2000; Nonomura et al, 2009). This risk must be considered in management of these patients, and neurologic changes need to be evaluated expeditiously.

The 5-year overall survival in patients with brain metastases is 33% for patients with disseminated NSGCT and 57% for patients with seminoma (International Germ Cell Consensus Classification, 1997). Men who relapse in the brain after achieving a complete response to chemotherapy appear to have a worse prognosis than patients with brain involvement at diagnosis, with overall survival rates of 39% to 44% for isolated brain metastases and 2% to 26% for brain metastases associated with other sites of disease (Fossa et al, 1999a; Kollmannsberger et al, 2000; Hartmann et al, 2003; Salvati et al, 2006; Gremmer et al, 2008; Nonomura et al, 2009). Case studies and pooled analyses of patients with GCT and brain metastases have reported outcomes with various

KEY POINTS: SEMINOMA

- The optimal management of CS I seminoma is controversial. Surveillance, primary radiotherapy (20 to 30 Gy to the para-aortic region with or without ipsilateral pelvis), and primary chemotherapy with carboplatin (one to two cycles) are accepted treatment options with long-term survival rates approaching 100% for each.
- Prognostic factors for occult metastases in CS I seminoma are not as well developed as for NSGCT. Given the overall low risk of occult metastases (15% to 20%), the inability to identify a high-risk population on the basis of histopathologic factors in the primary tumor, and the potential for late toxicity with primary radiotherapy, surveillance has become the recommended treatment approach for CS I seminoma.
- Surveillance is not recommended to patients who are anticipated to be poorly compliant with follow-up imaging and clinical evaluation. The standard treatment approach to patients who relapse on surveillance is dog-leg radiotherapy (25 to 35 Gy), although patients with bulky retroperitoneal lymphadenopathy or distant metastases should receive IGCCCG risk-appropriate first-line chemotherapy.
- Primary radiotherapy and primary chemotherapy with single-agent carboplatin are associated with similar rates of cure and survival. Patients who receive para-aortic radiotherapy and patients who receive carboplatin require periodic CT imaging in the surveillance of recurrent disease after treatment; this is not required for patients who receive dog-leg radiotherapy.
- Dog-leg radiotherapy (25 to 35 Gy) and first-line chemotherapy (BEPx3 or EPx4) are accepted treatment options for patients with CS IIA and IIB seminoma and nonbulky (<3 cm) retroperitoneal lymph node metastasis. First-line chemotherapy (BEPx3 or EPx4) is recommended for bulky (>3 cm) and/or multifocal retroperitoneal metastases.
- The first-line treatment of patients with CS IIC and III seminoma is cisplatin-based chemotherapy, and the specific regimen and number of cycles are dictated by IGCCCG risk criteria. Patients with good-risk disease should receive BEPx3 or EPx4, and patients with intermediate-risk disease should receive BEPx4.
- Patients with discrete, residual masses larger than 3 cm after first-line chemotherapy should undergo further evaluation with FDG-PET imaging. Patients with PET-positive residual masses should undergo PCS. Residual masses that are PET-negative or less than 3 cm can be safely observed after chemotherapy.

treatment strategies, but there are no randomized trials to define optimal management clearly (Spears et al, 1992; Fossa et al, 1999a; Kollmannsberger et al, 2000; Hartmann et al, 2003; Salvati et al, 2006; Gremmer et al, 2008; Nonomura et al, 2009). Treatment strategies include chemotherapy, surgical resection, whole-brain radiation therapy, and stereotactic radiosurgery, with most patients receiving multimodal therapy. **Patients with brain metastases at diagnosis should receive BEPx4 chemotherapy followed by resection of residual masses.** The benefit of radiation therapy in this setting is unclear (Fossa et al, 1999a; Kollmannsberger et al, 2000; Hartmann et al, 2003). At our institution, radiation therapy is considered only for patients with unresectable residual lesions not amenable to stereotactic radiosurgery because of concerns of radiation-induced neurotoxicity (Doyle and Einhorn, 2008). **Patients who relapse in the brain after first-line chemotherapy should be treated with second-line chemotherapy followed by resection and/or radiation therapy** (Fossa et al, 1999a; Hartmann et al, 2003). For men who relapse in the brain and at other anatomic sites, the prognosis is very poor, particularly if it is not the first relapse.

KEY POINT: BRAIN METASTASES

- Brain metastases are associated with choriocarcinoma and should be suspected in any patient with a very high serum hCG level. Choriocarcinomas are highly vascular and tend to hemorrhage during chemotherapy, causing intracranial hemorrhage.

Treatment-Related Sequelae

Sequelae of treatment of testis cancer can be divided into late and early complications. Complications from orchiectomy and RPLND are discussed in Chapter 35 and are not reviewed here except to note that the main issues after RPLND are midline scar, ejaculatory dysfunction, small bowel obstruction, and perioperative complications. Also, there is an increased incidence of hypogonadism after orchiectomy for GCT.

Early Toxicity

Cisplatin-based chemotherapy is associated with numerous early complications and side effects, including fatigue, myelosuppression, infection, peripheral neuropathy, hearing loss, diminished renal function, and death. The death rate from toxicity has ranged from 0% to 2.4% during chemotherapy for good-risk disease and from 3% to 4.4% during standard first-line chemotherapy for intermediate-risk and poor-risk disease (de Wit et al, 1998; Nichols et al, 1998, 2001; Toner et al, 2001; Culine et al, 2007, 2008). The impact of chemotherapy and radiation therapy on spermatogenesis has been discussed previously. Most men are able to father children after treatment for GCT but paternity rates are lower for men treated with radiation therapy and/or chemotherapy (Huyghe et al, 2004; Brydoy et al, 2005). Early complications of radiation therapy include fatigue, nausea and vomiting, leukopenia, and dyspepsia (Fossa et al, 1999b; Jones et al, 2005; Oliver et al, 2005).

Late Toxicity

Numerous long-term sequelae have been reported in GCT survivors, including peripheral neuropathy, Raynaud phenomenon, hearing loss, hypogonadism, infertility, SMN, and cardiovascular disease (Brydoy et al, 2009; Fossa et al, 2009; Rossen et al, 2009; Gilligan, 2011). Symptoms of Raynaud phenomenon and peripheral neuropathy have been reported in 20% to 45% and 14% to 43%, respectively, of GCT survivors (Brydoy et al, 2009; Rossen et al, 2009). Significant hearing loss and/or tinnitus after cisplatin-based chemotherapy is reported in 20% to 40% of patients and can be documented via audiometry in 30% to 75%. Hypogonadism has been documented in about 10% to 20% of patients treated with orchiectomy alone, 15% to 40% of patients treated with radiation therapy, and 20% to 25% of patients treated with first-line chemotherapy regimens (Nord et al, 2003; Lackner et al, 2009).

Large population-based studies of GCT survivors have reported an increased risk of death from gastrointestinal and cardiovascular diseases after radiation therapy and an increased risk of death from infections, cardiovascular diseases, and pulmonary diseases after chemotherapy (Fossa et al, 2007). Patients treated with both radiation and chemotherapy have the highest risk of death from nonmalignant causes. The increased cardiovascular disease incidence and mortality in GCT survivors is particularly well documented (Meinardi et al, 2000; Huddart et al, 2003; Fossa et al, 2007; van den Belt-Dusebout et al, 2007; Fossa et al, 2009). The etiologies of these cardiovascular complications are not well understood, but putative contributing factors are radiation-induced or chemotherapy-induced vascular injury and chemotherapy-induced cardiac injury and metabolic syndrome (Nuver et al, 2005; Altena et al, 2009).

The risk of SMN is a particular concern. The incidence of non-germ cell malignancies is 60% to 100% higher in GCT survivors treated with cisplatin-based chemotherapy or radiation

therapy compared with the general population and 200% higher in patients who received both radiation and chemotherapy (Travis et al, 2005; Richiardi et al, 2007). The risk of death from non-germ cell malignancies in GCT survivors treated with radiation or chemotherapy is less well defined but appears to be doubled compared with the general population (Fossa et al, 2004). The frequent use of body CT imaging in the surveillance of patients after therapy is another source of radiation that may increase the risk of SMN (Brenner and Hall, 2007; Chamie et al, 2008; Tarin et al, 2009).

KEY POINT: TREATMENT-RELATED SEQUELAE

- All treatments for GCT (surgery, radiotherapy, and chemotherapy) are associated with risks of early and late toxicity. The most concerning late complications are cardiovascular disease and SMN. With the successful cure of patients (including patients with advanced disease), an important treatment objective is minimizing treatment-related toxicity without compromising curability.

NON-GERM CELL TUMORS**Sex Cord–Stromal Tumors**

Sex cord–stromal tumors are rare, comprising approximately 4% of testis neoplasms. The term *sex cord–stromal tumor* refers to neoplasms containing Leydig cells, Sertoli cells, granulosa cells, or thecal cells. **Approximately 90% of these tumors are benign, and 10% are malignant.** Histologic criteria have been developed to help distinguish between benign and malignant histology and include tumor size larger than 5 cm, necrosis, vascular invasion, nuclear atypia, high mitotic index, increased MIB-1 expression, infiltrative margins, extension beyond the testicular parenchyma, and DNA ploidy (Kim et al, 1985; Cheville et al, 1998). Most malignant cases are associated with two or more of these features. **However, the presence of metastatic disease is the only reliable criterion for making this distinction.**

Leydig Cell Tumors

Leydig cell tumors account for 75% to 80% of sex cord–stromal tumors. There is no association with cryptorchidism. Most of these tumors occur in men 30 to 60 years old, although approximately one fourth occur in children. Adults may present with painless testis mass, testicular pain, gynecomastia (as a result of androgen excess and peripheral estrogen conversion), impotence, decreased libido, and infertility. Boys usually present with a testis mass and isosexual precocious puberty (prominent external genitalia, pubic hair growth, and masculine voice).

Diagnostic workup should include serum tumor markers and testicular ultrasound examination. The ultrasound appearance of these tumors is variable and is indistinguishable from GCT. In the presence of gynecomastia, infertility, depressed libido, or precocious puberty, luteinizing hormone, FSH, testosterone, estrogen, and estradiol should also be drawn (these should be measured after orchiectomy if the diagnosis is not suspected preoperatively). When the diagnosis is confirmed, patients should undergo chest-abdomen-pelvis CT imaging for staging purposes.

In the past, radical inguinal orchiectomy was the initial treatment of choice. If the diagnosis is suspected preoperatively, given the 90% incidence of benign histology, testis-sparing surgery may be considered for lesions less than 3 cm with intraoperative frozen-section histologic confirmation (Carmignani et al, 2006, 2007). Completion orchiectomy should be performed if GCT histology is seen (either on intraoperative frozen section or on final pathology) or if malignant features (listed earlier) are present on final pathologic examination of the resected tumor.

Given the rarity of these tumors, they are often not suspected preoperatively, and most patients undergo radical orchiectomy. Benign lesions are usually small, yellow to brown, and well circumscribed, without areas of necrosis or hemorrhage. Histologically, the tumors consist of uniform, polygonal cells with round nuclei. Reinke crystals are present in 25% to 40% of cases and appear as densely eosinophilic, needlelike or rhomboid structures within the cytoplasm. These tumors must be distinguished from Leydig cell hyperplasia that occur in atrophic testes and adjacent to GCTs, in which Leydig cells infiltrate between seminiferous tubules without displacing or obliterating them. Malignant behavior has not been reported in a prepubertal patient. Older patients are more likely to have malignant tumors.

The most frequent metastatic sites are the retroperitoneum and lung. RPLND is reasonable in selected cases with adverse features, although high rates of progression are observed in cases with pathologically involved nodes, suggesting a staging role only for RPLND (Mosharafa et al, 2003). Metastatic Leydig cell tumors are resistant to chemotherapy and radiation therapy, and survival is poor (Mosharafa et al, 2003). Ortho,para-DDD, a potent inhibitor of steroidogenesis, may produce partial responses in patients with metastasis and excess androgen production, but cure is impossible (Schwarzman et al, 1989). Surveillance is recommended for patients without clinical or pathologic features suggestive of malignancy. There are no widely accepted criteria for follow-up, but patients should be monitored at regular intervals with clinical assessment, hormonal profile (including luteinizing hormone, FSH, testosterone, estrogen, and estradiol), and CT imaging of the chest, abdomen, and pelvis for 2 years. Persistent Leydig cell dysfunction and hypogonadism may occur after excision of the primary tumor, and 40% of men may require testosterone supplementation postoperatively (Conkey et al, 2005).

Sertoli Cell Tumor

Sertoli cell tumors constitute less than 1% of testis neoplasms. The median age at diagnosis is 45 years, but rare cases in boys have been reported. Rarely, these tumors are associated with Peutz-Jeghers syndrome and androgen insensitivity syndrome and are frequently bilateral (either synchronous or metachronous). There is no association with cryptorchidism. Gynecomastia is evident in one third of patients. As for Leydig cell tumors, testis-sparing surgery can be considered for tumors less than 3 cm given the high incidence of benign histology (90%). For tumors larger than 3 cm or if intraoperative frozen-section or final pathologic analysis reveals GCT or malignant features, radical inguinal orchiectomy should be performed. The tumors are well circumscribed, yellow-white or tan, with uniform consistency. Microscopically, the tumors contain epithelial elements resembling Sertoli cells with varying amounts of stroma organized into tubules. These tumors may be misinterpreted as seminomas leading to errors in the selection of treatment. Diagnostic workup; staging studies; and criteria for treatment, surveillance, and follow-up are similar to Leydig cell tumors.

Granulosa Cell Tumors

Granulosa cell tumors of the testis are exceedingly rare. The juvenile type is benign and is the most frequent congenital testis tumor (most frequently occurring in infants <6 months old), accounting for 7% of all prepubertal testicular neoplasms. The adult type resembles granulosa cell tumors of the ovary. Gynecomastia and increased estrogen secretion are common. Testis-sparing surgery may be considered for tumors less than 3 cm if the diagnosis is suspected preoperatively. Otherwise, radical inguinal orchiectomy is recommended. Treatment of the primary tumor is curative because these tumors appear to have limited metastatic potential.

Gonadoblastoma

Gonadoblastoma is a mixed germ cell–sex cord–stromal tumor composed of seminoma-like germ cells and sex cord cells showing

Sertoli differentiation. They occur almost exclusively in patients with gonadal dysgenesis and intersex syndromes. Of affected individuals, 80% are phenotypic females, usually presenting with primary amenorrhea. The remaining patients are phenotypic males, almost always presenting with cryptorchidism (with the dysgenetic gonad in the inguinal or abdominal location), hypospadias, and some form of female internal genitalia. **These tumors should be considered an in situ form of malignant GCT because approximately 50% of patients develop an invasive GCT (usually seminoma, although yolk sac tumor and EC can occur) (Ulbright, 2004).** Gonadoblastomas do not metastasize, but metastasis of the malignant GCT elements may occur. **Bilateral orchiectomy is required because of the risk of bilateral tumors (40%) (Scully, 1970).** For patients with malignant GCT, subsequent workup for metastatic disease with or without treatment should be initiated.

Miscellaneous Testis Neoplasms

Dermoid and Epidermoid Cyst

Dermoid and epidermoid cysts are rare benign neoplasms that are thought to arise from benign germ cells with retained embryonic properties or from displaced metaplastic mesothelial cells (Ye and Ulbright, 2012). Grossly, they are well-circumscribed, unilocular cystic masses filled with keratinized debris that may have a laminated appearance, which gives them the characteristic “onion peel” appearance on ultrasound scan. Dermoid cysts are differentiated from epidermoid cysts by the presence of adnexal structures such as glandular elements, adipose tissue, and cartilage. Dermoid and epidermoid cysts are distinguished from teratoma by the absence of ITGCN in the adjacent testis. Enucleation or partial orchiectomy may be performed, although the lesion should be thoroughly sampled by a pathologist to rule out GCT or ITGCN.

Adenocarcinoma of the Rete Testis

Adenocarcinoma of the rete testis is a rare but highly malignant neoplasm arising from the collecting system of the testis. The usual presentation is a painless testis mass with hydrocele. More than 50% of patients present with metastatic disease, and the overall median survival is 1 year. RPLND may be curative in patients with limited retroperitoneal lymph node metastasis. Chemotherapy and radiation therapy are ineffective.

Secondary Tumors of the Testis

Lymphoma

Primary testicular non-Hodgkin lymphoma is a rare tumor representing only 1% to 2% of all cases of lymphoma. Most commonly, lymphoma involves the testis through dissemination from extratesticular sites (Ulbright, 2004). Of cases, 85% occur in men older than 60 years. Non-Hodgkin lymphoma is the most common testicular neoplasm in men older than age 50. Bilateral testicular involvement occurs in 35% of cases. It usually manifests as a painless testicular mass in an older man. Approximately 25% of men have systemic symptoms (fever, night sweats, weight loss). Central nervous system involvement at diagnosis is reported in 10% of men. The initial treatment is radical inguinal orchiectomy. Men with testicular non-Hodgkin lymphoma should be referred to a hematologist-oncologist for staging investigations and subsequent therapy. Most cases are associated with systemic disease, and the overall prognosis is poor.

Leukemic Infiltration

The testis is a frequent site of relapse in boys with acute lymphocytic leukemia. Most boys are in complete remission at the time of testicular enlargement. The diagnosis can usually be made by biopsy, and orchiectomy is unnecessary. Local control can be achieved with low-dose radiotherapy (20 Gy), and treatment

should include the contralateral testis because of the frequent risk of bilateral involvement. Overall, the prognosis is poor because most patients have associated systemic disease.

Metastases

Metastases to the testis are rare. Bilateral involvement occurs in 15% of patients. The most common primary tumors are prostate, lung, melanoma, colon, and kidney. Although treatment is largely dictated by the primary tumor, orchiectomy may be considered for palliative reasons.

TUMORS OF THE TESTICULAR ADNEXA

Paratesticular tumors are rare and account for approximately 5% of intrascrotal neoplasms, roughly 75% of which arise from the spermatic cord.

Adenomatoid Tumor

Adenomatoid tumor is the most common paratesticular tumor, most commonly involving the epididymis (although these tumors may also arise within the testicular tunicae or the spermatic cord). The most common presentation is a small (0.5 to 5 cm), painless paratesticular mass detected on routine examination in a man in his third or fourth decade. **These tumors are benign and managed by inguinal exploration and surgical excision.** On microscopic examination, tumors are composed of epithelial-like cells that contain vacuoles and fibrous stroma.

Cystadenoma

Cystadenoma of the epididymis corresponds to benign epithelial hyperplasia. The lesions are usually multicystic, and the walls are studded with nodules of epithelial cells arranged in a glandular or papillary configuration. **Approximately one third of cases occur in patients with von Hippel-Lindau disease, which are usually bilateral.** The lesions are usually small and painless and are detected on routine examination in a young man.

Mesothelioma

Paratesticular mesothelioma arises from the tunica vaginalis and usually manifests as a painless scrotal mass in association with a hydrocele. These tumors most commonly occur in older adults but may be encountered in any age group. **Benign and malignant cases have been described, with the distinction based on atypia, mitotic activity, and invasion (Ulbright, 2004).** Malignant cases may be associated with asbestos exposure. **Treatment is radical inguinal orchiectomy.** RPLND may be considered in patients with malignant tumors without widespread metastatic disease. The role of chemotherapy for these tumors is poorly defined.

Sarcoma

Sarcomas of the spermatic cord, epididymis, and testis are the most common genitourinary sarcomas in adults. **Liposarcoma is the most common histologic subtype in adults,** followed by leiomyosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, and fibrosarcoma (Coleman et al, 2003; Ulbright, 2004; Dotan et al, 2006; Rodriguez et al, 2014). **Embryonal rhabdomyosarcoma is the most common histologic subtype in men younger than age 30.** Sarcomas most commonly arise from the spermatic cord and are located in the intrascrotal region; primary mesenchymal tumors of the testis are exceedingly rare. These tumors usually manifest as a painless, palpable mass, and most are large (>5 cm in size) (Dotan et al, 2006). Ultrasonography demonstrates a solid mass, although it cannot distinguish between benign and malignant pathology. **Any solid mass in the scrotum external to the tunica albuginea should be explored through an inguinal approach, and a biopsy should**

be performed. Liposarcomas of the spermatic cord in the inguinal canal may be mistaken for inguinal hernia or lipoma, and CT or magnetic resonance imaging is helpful to distinguish between these entities.

Most patients have localized disease at diagnosis. **Sarcomas should be managed initially through an inguinal approach with wide excision of the spermatic cord and testis with high ligation.** Patients with an initial incomplete resection should undergo repeat wide excision (Coleman et al, 2003). The primary pattern of failure is local, particularly for liposarcoma (Ballo et al, 2001; Montgomery and Fisher, 2003; Khandekar et al, 2013). Some authors have advocated for postoperative radiation therapy for all paratesticular sarcomas, particularly for liposarcomas and for tumors for which the adequacy of local control is in doubt (Ballo et al, 2001; Hazariwala et al, 2013). However, the efficacy of this approach is debated (Fagundes et al, 1996; Coleman et al, 2003; Khandekar et al, 2013). Systemic chemotherapy should be given to patients with evidence of retroperitoneal or distant metastases. **In the presence of a normal metastatic evaluation, patients with sarcomas other than liposarcoma should undergo RPLND, and postoperative chemotherapy should be given to patients with retroperitoneal lymph node metastasis (Dang et al, 2013).** Given that the lymphatic drainage of the spermatic cord includes the ipsilateral pelvis, inguinal, and retroperitoneal lymph nodes, treating these areas with lymphadenectomy or radiation therapy should be considered. The long-term survival of men with paratesticular sarcoma is approximately 50%, with liposarcoma having the most favorable prognosis and malignant fibrous histiocytoma and leiomyosarcoma having the least favorable prognosis (Coleman et al, 2003; Rodriguez et al, 2014).

REFERENCES

The complete reference list is available online at www.expertconsult.com.



SUGGESTED READINGS

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Management of Testis Mass

Retroperitoneal Lymph Node Dissection

Auxiliary Procedures

Surgical Decision Making

Histologic Findings at Postchemotherapy Retroperitoneal Lymph Node Dissection and Survival Outcomes

Postchemotherapy Retroperitoneal Lymph Node Dissection in High-Risk Populations

Surgical Outcomes, Functional Considerations, and Complications of Retroperitoneal Lymph Node Dissection

Retroperitoneal Lymph Node Dissection in Unique Situations

Conclusion

In addition to its remarkable chemosensitivity, testicular germ cell tumor (GCT) is among the most surgically curable malignancies. Before the development of effective chemotherapeutic regimens for testicular GCT, investigators at Walter Reed Army Hospital were able to achieve a nearly 50% durable cure rate for patients demonstrating node-positive disease at primary retroperitoneal lymph node dissection (RPLND) (Patton et al, 1959). At the present time, nearly 80% of patients presenting with clinical stage I (CS I) testicular nonseminomatous germ cell tumor (NSGCT) are cured with orchiectomy alone (Warde et al, 2002; Hotte et al, 2010), whereas 60% to 80% of patients with pathologic stage II (PS II) NSGCT can be cured with primary RPLND (Donohue et al, 1993a; Stephenson et al, 2005). In the setting of larger volume metastatic disease requiring induction chemotherapy, approximately 90% of patients with residual retroperitoneal masses are cured by postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) (Donohue et al, 1990). This chapter describes the management decision-making processes, operative techniques, and outcomes for testicular cancer surgery. This chapter provides the urologist with the foundation necessary to manage surgically the primary tumor as well as regional retroperitoneal metastases for all stages of testicular cancer.

MANAGEMENT OF TESTIS MASS

History and Physical Examination, Ultrasonography, and Preorchietomy Evaluation

The presentation of a testicular mass warrants a prompt and thorough investigation. Principal to this evaluation is understanding the temporal development of any associated symptoms, characterizing the scrotal contents with careful physical and ultrasound examination, and obtaining appropriate serologic tests (Robson et al, 1965; Sandeman, 1979; Bosl et al, 1981; Thornhill et al, 1987; Richie, 1993; Honig et al, 1994; Petersen et al, 1999; Jacobsen et al, 2000; Simon et al, 2001). Timely recognition and diagnosis are paramount in the treatment of a given cancer at its earliest and most curable stage (Post and Belis, 1980; Oliver, 1985; Gascoigne et al, 1999; Chapple et al, 2004; Moul, 2007). Physical examination is the most crucial part of the evaluation of the testis mass. Although not mandatory, ultrasound examination can provide important details of tumor characteristics and document radiographically the laterality of the lesion (Horstman et al, 1992; Shah et al, 2010; Goddi et al, 2012). Additionally, documentation

of the characteristics of the contralateral testicle is essential because synchronous testicular masses have been reported in approximately 1% of patients (Bokemeyer et al, 1993; Coogan et al, 1998; Che et al, 2002; Holzbeierlein et al, 2003; Pamentier et al, 2003; Fossa et al, 2005; Hentrich et al, 2005). Obtaining serum tumor marker (STM) values, including α -fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase, aids in solidifying a diagnosis of GCT and serves as a baseline to compare serologic trends after orchiectomy. Placement of a testicular prosthesis at the time of radical orchiectomy should be discussed before surgery.

Radical Orchiectomy

In patients in whom a testicular malignancy is suspected, radical orchiectomy is the diagnostic and therapeutic treatment of choice. The approach is via an inguinal incision, allowing for complete removal of the ipsilateral testis, epididymis, and spermatic cord to the level of the internal inguinal ring.

Technique

The patient is positioned supine on the operating room table. Proper preparation of the skin should encompass the abdomen above the umbilicus cranially, the bilateral mid-to-lower thigh caudally, and the external genitalia through to the perineum posteriorly. After sterile draping of the surgical field, exposure of the ipsilateral anterior superior iliac spine, pubic tubercle, and scrotum is required. Palpation and marking the overlying skin of the external inguinal ring can facilitate orientation of the medial extent of the inguinal canal.

The incision, typically 3 to 5 cm in length, is made with a transverse orientation overlying the inguinal canal following the lines of Langer. In circumstances in which a mass is too large to be delivered through the standard incision, the incision can be extended down along the anterior scrotum in a hockey-stick fashion. When the external oblique fascia is exposed and the external ring is identified, the inguinal canal should be opened along its course laterally for approximately 4 cm. In an obese patient, self-retaining instruments such as a Weitlaner or Gelpi retractor often prove helpful or necessary to provide exposure. With the external oblique fascia open, care should be taken to identify the ilioinguinal nerve for prospective preservation. This structure courses parallel to spermatic cord, typically along the cephalad aspect of its anterior surface. When the nerve is safely displaced, the spermatic cord is mobilized within the canal at the level of the pubic tubercle, where it can be encircled

with a Penrose drain. After division of the external spermatic fascia and cremasteric fibers that surround the spermatic cord, gentle traction can be placed in the cephalad direction to draw the testicle toward the incision. Delivery of the testicle can be facilitated by applying external pressure to the ipsilateral hemiscrotum. After division of the gubernaculum, the spermatic cord is mobilized to the level of the internal inguinal ring until the peritoneal reflection is visualized. At this level, the vas deferens and gonadal vessels are dissected out, ligated, and divided separately. Ligation and division are typically performed with nonabsorbable suture, leaving a 1- to 2-cm suture tail on the stump of the gonadal vessels to facilitate identification at RPLND. Individually ligating the vas deferens from the remainder of the spermatic cord facilitates retrieval of the distal spermatic cord stump during subsequent RPLND because the vas deferens is not taken as part of this specimen.

After irrigation of the wound and close inspection for hemostasis, the ilioinguinal nerve is positioned safely in the floor of the inguinal canal, and closure of the external oblique aponeurosis is performed. A two- or three-layer closure of the subcutaneous and skin layers is completed, and sterile dressings are applied. In general, scrotal support and fluff dressings are helpful to avoid unnecessary scrotal swelling and hematoma formation for the first 48 to 72 hours.

Partial Orchiectomy

Because of the high rate of long-term survivors after testis cancer therapy, functional issues pertaining to treatment-related side effects and preservation of quality of life have emerged (Skakkebaek, 1975; Jacobsen et al, 1981; Klein et al, 1985; Haas et al, 1986; Kressel et al, 1988; Robertson, 1995; Carmignani et al, 2004). **Partial orchiectomy should be considered in patients with a polar tumor measuring 2 cm or less and an abnormal or absent contralateral testicle.** In circumstances in which the malignant nature of the tumor is uncertain, inguinal exploration and excisional biopsy can be done. In general, these operations should be performed in very select patients in whom the benefits of organ preservation are thought to outweigh the risks of local tumor recurrence. In patients with a normal contralateral testis, elective testis-sparing surgery is not advised.

Technique

The approach to partial orchiectomy is identical to the approach of a radical inguinal orchiectomy. The use of ischemia with or without hypothermia has been questioned by some authors and can be omitted if the resection time is limited to less than 30 minutes (Giannarini et al, 2010). With sterile towels draping the field to avoid contamination, intraoperative ultrasonography can be used to facilitate localization of the mass. When the mass is identified, a scalpel can be used to incise the tunica albuginea overlying the mass. When the approach is from the ventral midline, a vertical incision along the long axis of the testis is preferred. Otherwise, incisions localized medial or lateral to the ventral midline should be oriented horizontally to follow the course of the segmental arteries beneath the tunica albuginea.

Once identified, the tumor is enucleated preferably with a small rim of surrounding seminiferous tubules insulating the mass. In the presence of a confirmed GCT, the association of concomitant intratubular germ cell neoplasia in the surrounding parenchyma of the ipsilateral testis warrants consideration for completion radical orchiectomy or adjuvant radiotherapy to the remnant testis to reduce the risk of recurrent disease. Because of this risk, some clinicians choose to omit parenchymal biopsies in the setting of confirmed GCT and recommend treatment of all remnants with radical orchiectomy or adjuvant therapy. If radical orchiectomy is not performed, the tunica is closed with absorbable suture, and the testis is placed back into the dependent portion of the scrotal compartment and secured at three points of internal fixation to the gubernaculum or medial septum of the scrotum.

Adjuvant radiotherapy with a dosage of 18 to 20 Gy is recommended to prevent local tumor recurrence in all patients treated with partial orchiectomy for the management of GCT in a functionally solitary testis (Heidenreich et al, 2001; Krege et al, 2008; Giannarini et al, 2010). In these patients, the only benefit of partial orchiectomy is preservation of Leydig cell function. **Any local recurrence within the ipsilateral testis occurring with or without adjuvant therapy should be managed with completion radical orchiectomy.**

Delayed Orchiectomy

Most testicular cancers are initially diagnosed at the time of orchiectomy. However, in a small subset of patients with widespread and/or symptomatic GCT, the diagnosis is made based on biopsy of a metastatic lesion or empirically based on clinical and serologic features. In these unique settings, initiation of systemic chemotherapy supersedes diagnostic orchiectomy (Ondrus et al, 2001). **Because of high discordance of pathologic response rates within the testis, a delayed orchiectomy is recommended for all patients with NSGCT after induction chemotherapy, even in the setting of a complete response in the retroperitoneum** (Snow et al, 1983; Simmonds et al, 1995; Leibovitch et al, 1996; Ondrus et al, 2001).

The role of delayed orchiectomy is more controversial in patients with presumed primary retroperitoneal/extragenadal GCT. In studies in which biopsy of the testis was performed in these cases, intratubular germ cell neoplasia was seen in 42% of patients (Daugaard et al, 1992). Among such patients who are observed after chemotherapy, approximately 5% develop a metachronous testicular cancer (Hartmann et al, 2001). **Radical orchiectomy has been advocated when the metastatic pattern of retroperitoneal disease lateralizes to the expected distribution of a testicular primary.** In a small cohort series at Indiana University, 71% of patients with presumed extragenadal GCT undergoing a post-chemotherapy delayed orchiectomy had histologic evidence of teratoma or necrosis within the testis, the latter suggesting a burned-out primary or complete response to chemotherapy (Brown et al, 2008). If observation of the testis is elected, monthly self-examinations and periodic physician assessment are warranted.

Postorchiectomy Evaluation

After orchiectomy, review of the pathologic findings along with incorporation of appropriate radiographic and serologic studies is necessary to determine clinical stage. Contrast-enhanced computed tomography (CT) with intravenous and oral contrast agents is the most effective means to accomplish this; however, magnetic resonance imaging may serve as a suitable alternative. Fluorodeoxyglucose-labeled positron emission tomography (PET) and lymphoangiography serve little to no role in the staging of GCTs after initial diagnosis. Similar to the evaluation before orchiectomy, assessment of STM (α -fetoprotein, human chorionic gonadotropin, lactate dehydrogenase) values and trends after orchiectomy completes the initial evaluation before patient counseling regarding management options.

KEY POINTS: MANAGEMENT OF THE TESTIS MASS

- Radical inguinal orchiectomy with high ligation of the spermatic cord is the definitive diagnostic and initial therapeutic step for management of testicular cancer in most cases.
- Partial orchiectomy should be considered only in selected patients with a polar mass measuring 2 cm or less and an abnormal or absent contralateral testicle.
- In the rare patient whose disease is sufficiently advanced/symptomatic to warrant immediate initiation of systemic chemotherapy, delayed orchiectomy should be performed given the potential for residual disease.

RETROPERITONEAL LYMPH NODE DISSECTION

All GCT subtypes demonstrate a propensity for predictable lymphatic spread to the retroperitoneum. Choriocarcinoma has also demonstrated a predilection for hematogenous spread. Depending on the presence and bulk of retroperitoneal disease and STM status, RPLND may be incorporated into management of the testicular GCT in the primary or postchemotherapy setting. Although the approaches and techniques of primary RPLND and PC-RPLND are similar, these are fundamentally distinct surgeries. The rationale for primary RPLND is that, in contrast to most malignancies, testicular GCT is surgically curable in most patients with low-volume regional (retroperitoneal) lymphatic metastases. Conversely, the rationale for performing PC-RPLND in patients with residual retroperitoneal masses is that unresected teratoma and/or viable malignancy predispose the patient to disease progression and death. In this section, we discuss similar technical considerations and exposure for primary RPLND

and PC-RPLND. However, the surgeon must be aware of the aforementioned basic philosophical distinctions between these two surgeries. The retroperitoneal lymph node regions are illustrated in Figure 35-1.

The following list provides definitions of the different subtypes of RPLND that are discussed throughout this chapter:

- **Primary RPLND**—RPLND performed after orchiectomy for CS I or low-volume CS II NSGCT with normal postorchiectomy STMs.
- **PC-RPLND**—RPLND performed after completion of induction systemic chemotherapy. This procedure is generally performed when there is a residual retroperitoneal mass and normal postchemotherapy STMs. At some centers, PC-RPLND is performed even when there is a clinical complete remission (CR) to chemotherapy (discussed later).
- **Salvage PC-RPLND**—PC-RPLND performed after completion of induction and salvage (standard or high-dose) chemotherapy.

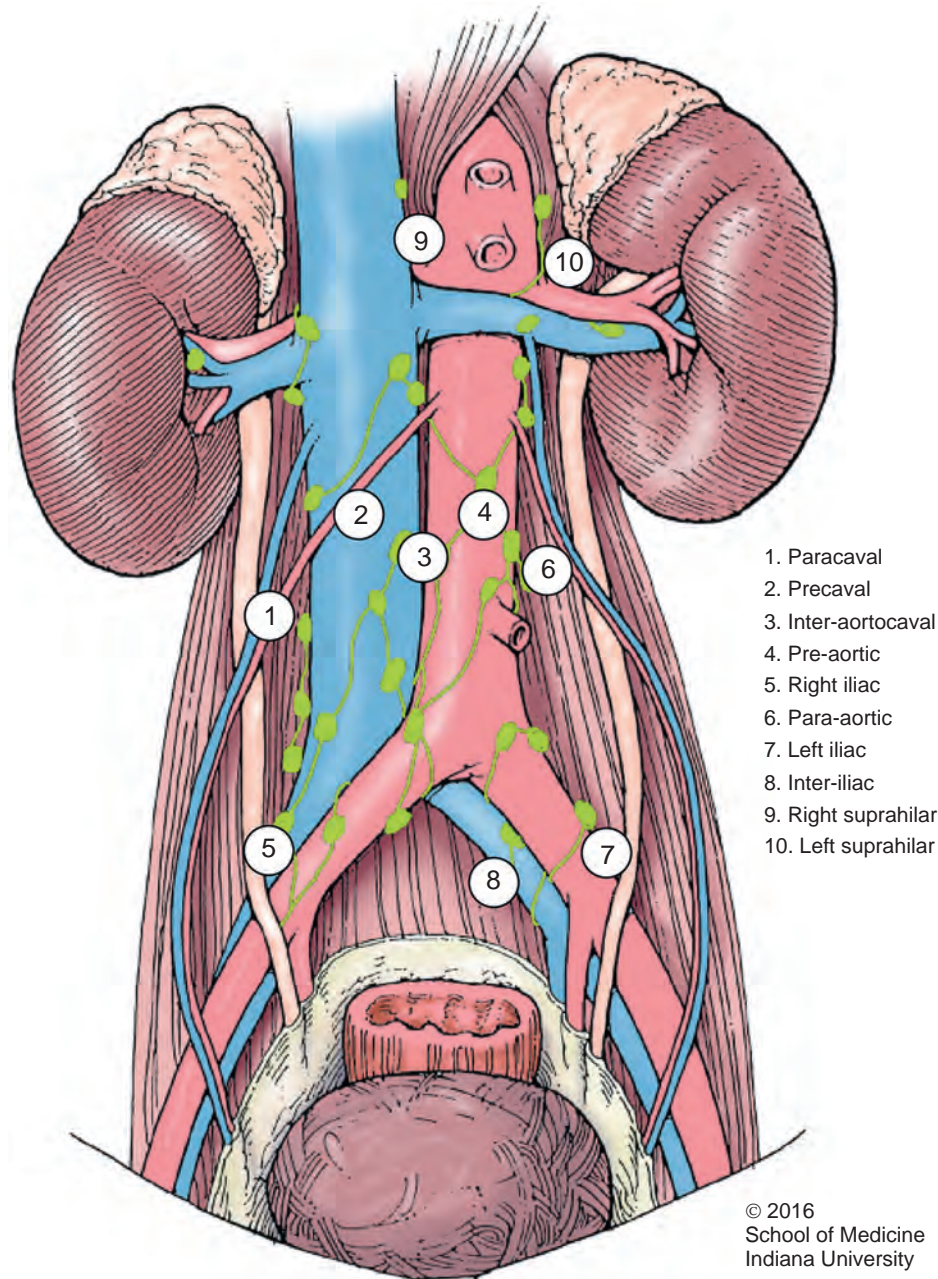


Figure 35-1. Retroperitoneal lymph node regions. (© 2016 Section of Medical Illustration in the Office of Visual Media at the Indiana University School of Medicine. Published by Elsevier Inc. All rights reserved.)

- **Desperation PC-RPLND**—PC-RPLND performed despite STM elevation.
- **Reoperative RPLND**—PC-RPLND performed in a patient who has undergone prior primary RPLND or PC-RPLND.
- **Resection of late relapse**—PC-RPLND performed for retroperitoneal recurrence 24 months or later after CR to primary therapy (which may or may not have included RPLND).

Preoperative Planning

We do not recommend bowel preparation or dietary modifications before RPLND. STMs should be checked within 7 to 10 days of surgery. Increased quantities of blood products should be considered for patients requiring more complex resections. Preoperative sperm banking should be offered to patients who desire future paternity if retroperitoneal masses are in the path of the postganglionic sympathetic nerve fibers. It is important for the urologist to have a medical oncology partner who possesses the clinical ability to assess bleomycin toxicity, to limit the dose when necessary and to obtain pulmonary function testing when appropriate before sending the patient to surgery to minimize risk of postoperative acute respiratory distress syndrome. Additionally, the surgeon should ensure that the anesthesia provider is aware of any prior receipt of bleomycin and that he or she is familiar and comfortable with management of these patients. Specifically, low fraction of inspired oxygen (FiO_2) and conservative intraoperative fluid resuscitation are important in minimizing the risk of postoperative lung toxicity (Goldiner et al, 1978; Donat and Levy, 1998).

Preoperative CT scan of the abdomen and pelvis should be thoroughly reviewed at initial consultation and immediately before surgery. A current CT scan of the chest is also required in patients with a history of pulmonary masses, planned concurrent resection of thoracic disease, or other radiographic/serologic evidence of disease progression. We prefer that preoperative imaging be performed within 6 weeks of that surgery date. Careful inspection of imaging can usually prevent unplanned intraoperative consultations of other surgical specialists. Preoperative identification of total inferior vena cava (IVC) thrombosis is important because the operation is made simpler by resection of the IVC (Beck and Lalka, 1998). Patients with incomplete occlusion requiring IVC resection may require reconstruction with a cadaveric allograft.

Surgical Technique

An orogastric tube is sufficient for intraoperative gastric decompression. Nasogastric tubes are generally reserved for patients with duodenal invasion that requires resection/repair or high-volume retroperitoneal masses that require complete mobilization of the mesentery and placement of the bowels on the patient's chest for the duration of the surgery.

The patient is placed in the supine position, and a ventral midline incision is made. When the peritoneal cavity is entered, a thorough inspection of abdominal viscera is performed. The falciform ligament is identified, ligated, and divided to minimize risk of hepatic retraction injury. A self-retaining retractor is then placed.

Exposure of the Retroperitoneum

For smaller paracaval and interaortocaval masses, the root of the mesentery is opened from the inferior tip of the cecum to the medial aspect of the inferior mesenteric vein (Fig. 35-2, green dotted line). In the case of large interaortocaval and/or paracaval masses, the mesenteric incision can be continued around the inferior portion of the cecum to the right white line of Toldt and up to the foramen of Winslow to permit placement of the bowels on the chest (see Fig. 35-2, right purple dotted line). In the case of larger left para-aortic masses, the inferior mesenteric vein is often ligated and divided to improve exposure of the left retroperitoneum (see Fig. 35-2, left purple dotted line). Alternatively, in the case of a modified left template dissection for CS I disease, the para-aortic packet can

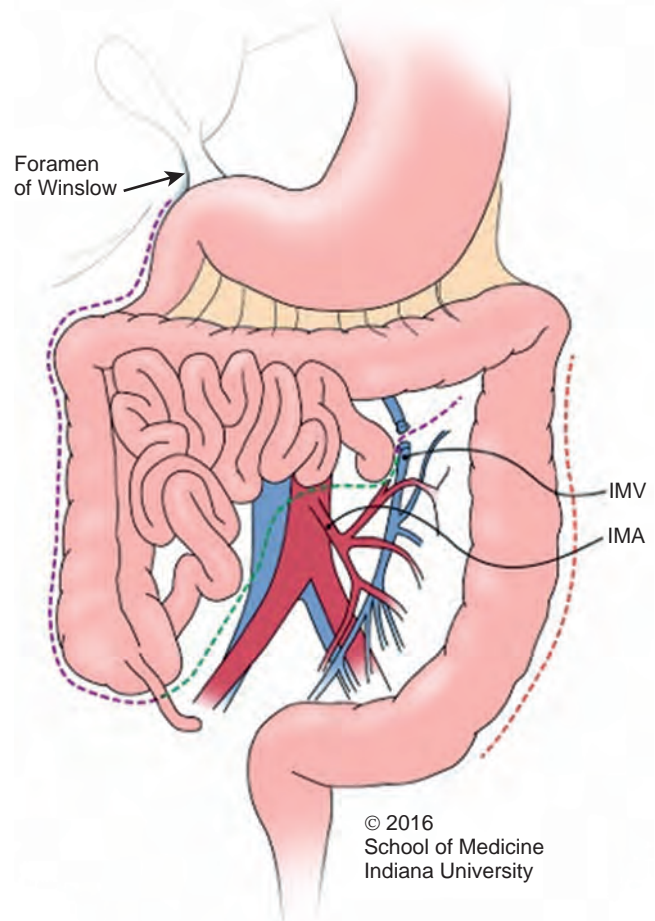


Figure 35-2. Exposure of the retroperitoneum. IMA, inferior mesenteric artery; IMV, inferior mesenteric vein. (© 2016 Section of Medical Illustration in the Office of Visual Media at the Indiana University School of Medicine. Published by Elsevier Inc. All rights reserved.)

be approached through the left white line of Toldt (see Fig. 35-2, red dotted line).

The plane between the mesentery and the retroperitoneal fat is developed by identifying the gonadal vein and developing the plane along its anterior surface. The duodenum is dissected off of the IVC and left renal vein. Before placing retractors in this region, the superior mesenteric artery must be identified (usually by palpation). The blades of the retractors should then be placed on either side of the superior mesenteric artery.

Split and Roll Technique

The large lymphatics coursing over the left renal vein should be ligated and divided. When the chosen template includes splitting over both great vessels, we prefer to perform the split on the aorta first rather than the IVC to avoid precaval right-sided accessory lower pole renal arteries. The advantage of performing the IVC split first is that the right-sided postganglionic sympathetic nerve fibers can be identified and traced to the superior hypogastric plexus minimizing risk of injury during the aortic split. The split is started at the 12 o'clock position of the aorta, immediately inferior to the left renal vein (Fig. 35-3), and continued caudally taking care to identify prospectively the inferior mesenteric artery (IMA) and (1) preserve it in cases of right modified template RPLND or (2) doubly ligate and divide this structure to expose the left para-aortic region in cases of full bilateral dissection. If a nerve-sparing technique is to be performed, the split should be stopped at the IMA, and postganglionic sympathetic fibers should be identified before proceeding caudally.

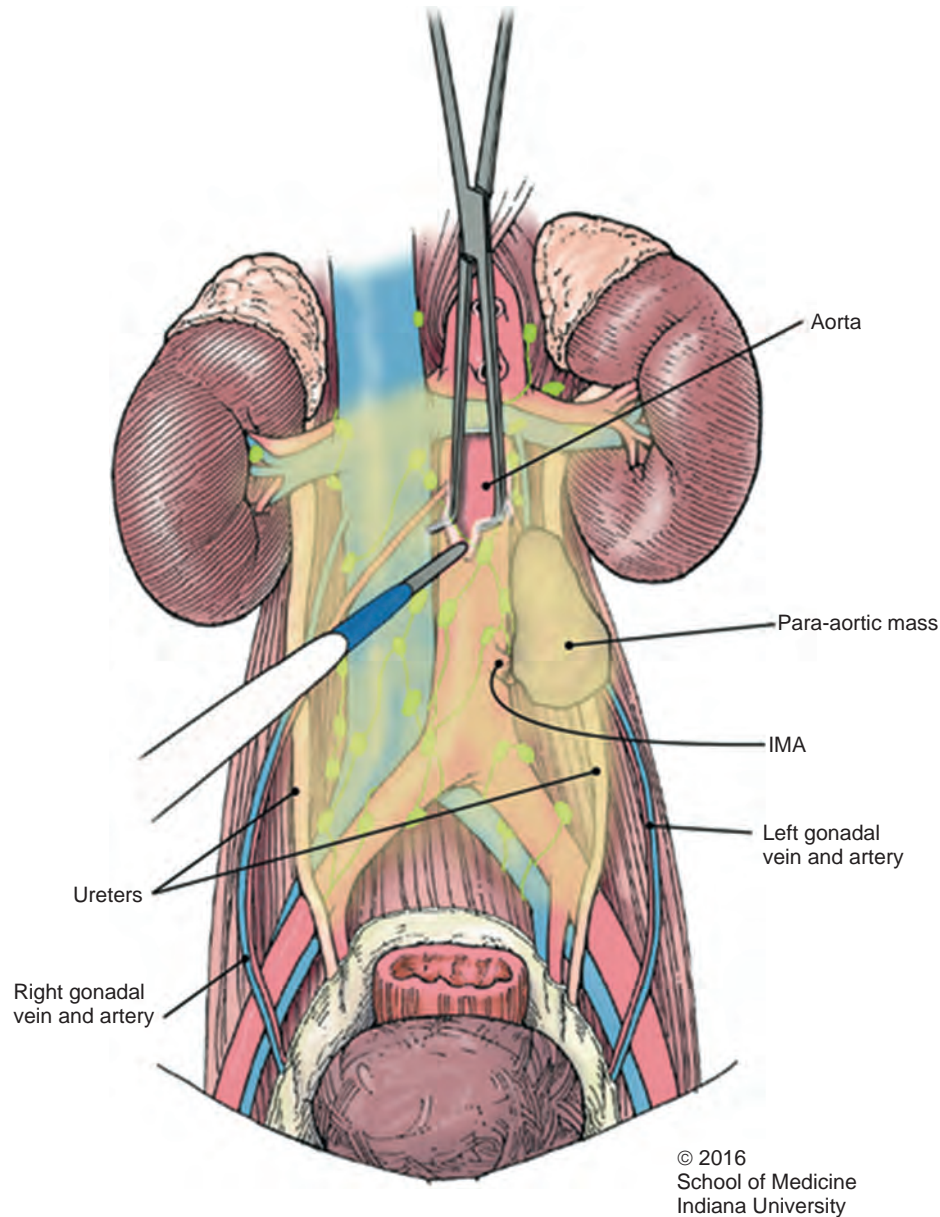


Figure 35-3. The split-and-roll technique. IMA, inferior mesenteric artery. (© 2016 Section of Medical Illustration in the Office of Visual Media at the Indiana University School of Medicine. Published by Elsevier Inc. All rights reserved.)

Left Para-aortic Packet

As mentioned previously, the left para-aortic packet can be approached laterally through the left white line of Toldt or medially through the mesenteric root depending on which template is used. The left gonadal vein is doubly ligated and divided where it crosses the left ureter. The ureter is swept laterally and placed behind a retractor to minimize risk of subsequent injury. The split is continued down the 12 o'clock position of the aorta and left common iliac artery until the left ureter is reached. The lymphatic tissue is rolled laterally off of the aorta and left common iliac artery. The three left-sided lumbar arteries located between the renal hilum and aortic bifurcation are identified, doubly ligated, and divided.

The packet is rolled inferiorly off of the left renal vein. The left gonadal and lumbar vein (when present) are doubly ligated and divided where they drain into the left renal vein. The lateral aspect of the packet is dissected off of the lower pole of the kidney and ureter.

The caudal extent of the packet is rolled superiorly off of the posterior body wall. The left genitofemoral nerve and sympathetic

trunk should be identified and preserved when possible. The lumbar veins and body wall ends of the divided lumbar arteries should be identified and controlled. The packet is rolled up to the crus of the diaphragm. Lymphatics should be ligated as they course through the crus and into the retrocrural region. When the para-aortic resection is complete, tension on the ureteral retractor should be released to prevent prolonged ischemia.

Interaortocaval Packet

If a right-sided nerve-sparing technique is to be performed, the IVC split and roll is performed next. Otherwise, the medial side of the aorta can be controlled first. The IVC split is performed from the renal hilum to the crossover of the right common iliac artery where it is continued inferolaterally until the right ureter is reached. The right gonadal vein is doubly ligated and divided at the IVC. The lymphatic tissue is rolled medially off of the IVC. The nerves are visible running obliquely along the lateral edge of the packet as it is peeled off the medial border of the IVC. The lumbar veins located between the renal hilum and the

common iliac veins are identified, doubly ligated, and divided. In contrast to the lumbar arteries, the number and positions of the veins are unpredictable. When the medial aspect of the IVC has been controlled, lymphatic tissue is rolled laterally off of the IVC, and any lumbar veins encountered are ligated and divided. Before harvesting the interaortocaval packet, the right gonadal vein is ligated and divided where it crosses the right ureter. The ureter is placed behind a retractor to keep it out of the field of dissection.

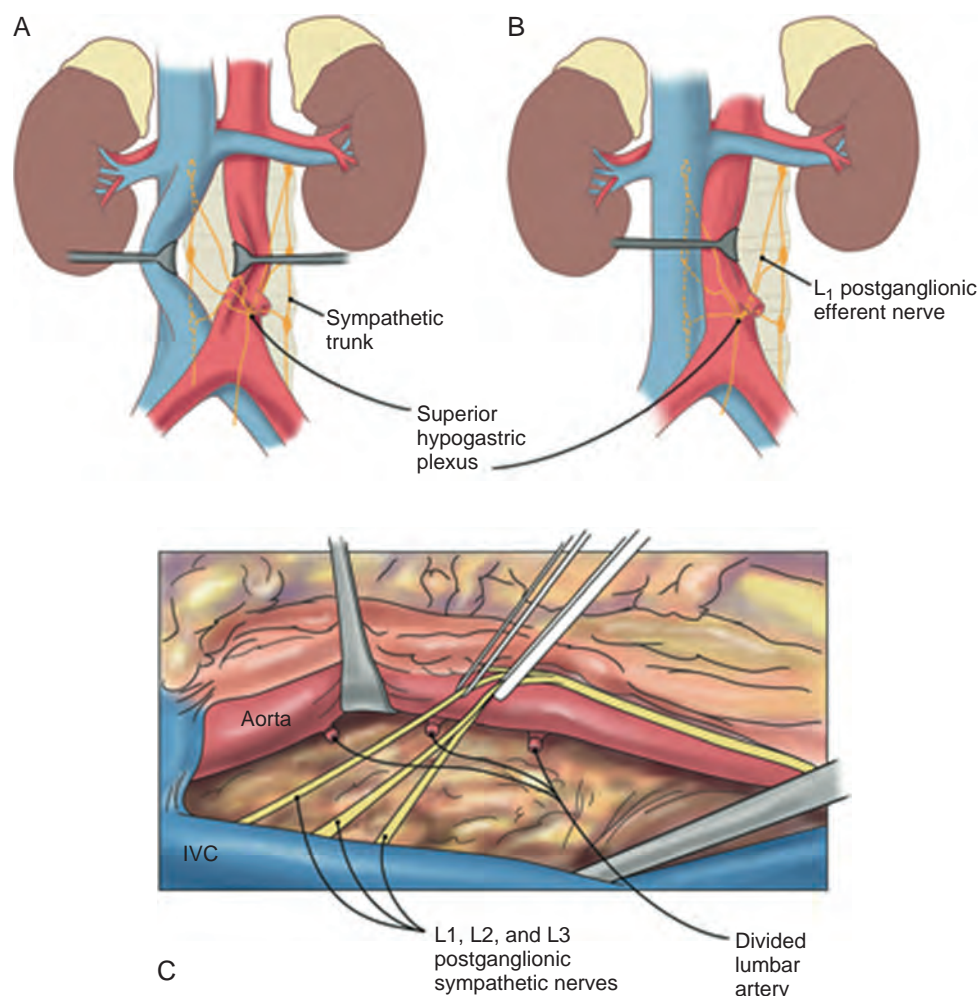
Lymphatic tissue is rolled medially off of the aorta. The medial three lumbar arteries are identified, ligated, and divided (Fig. 35-4C). The interaortocaval lymph node packet is harvested off of the anterior spinous ligament. The right sympathetic trunk is encountered at the right lateral border of the interaortocaval packet and should be preserved when possible. As the packet is rolled off of the anterior spinous ligament, the cut ends of the lumbar vessels should be controlled as they enter and exit the body wall. The superior aspect of the packet is rolled inferiorly off of the renal vessels exposing the crus of the diaphragm. Taking care to avoid injury to the renal artery, the lymphatics coursing into the retrocrural region must be ligated to prevent postoperative lymph leak and chylous ascites.

Right Paracaval Packet

The right paracaval packet tends to be the smallest of the three major lymph node packets because the right kidney and ureter are located very close to the lateral border of the IVC. The lymphatic tissue is rolled laterally and superiorly off of the right common iliac artery until the crossover of the right ureter is reached. The tissue is rolled superiorly off of the psoas fascia, taking care to preserve the right sympathetic trunk and the genitofemoral nerve. This roll is continued superiorly toward the right renal hilum and crus of the diaphragm. This packet often tapers to nothing and crosses under the IVC before the actual renal hilum is reached.

Gonadal Vein

The peritoneal lining is opened immediately over the gonadal vein. The ureter should be swept posteriorly off of the vein. The gonadal vein is placed on gentle traction and bluntly dissected down to the internal ring. If the orchiectomy was performed properly, the distal cut end of the gonadal vein and suture ligature should be easily retrievable. When the left gonadal vein is approached through the mesenteric root, it must be passed under



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Figure 35-4. Nerve-sparing technique. A, Location of right-sided postganglionic sympathetic nerves. B, Location of left-sided postganglionic sympathetic nerves. C, Right-sided nerve-sparing technique with ligated lumbar arteries. IVC, inferior vena cava. (© 2016 Section of Medical Illustration in the Office of Visual Media at the Indiana University School of Medicine. Published by Elsevier Inc. All rights reserved.)

the mesentery of the sigmoid colon before it is resected down to the left internal inguinal ring.

Nerve-Sparing Technique

The anatomy of the four postganglionic efferent sympathetic fibers (L1 through L4) involved in antegrade ejaculation demonstrates significant variability from patient to patient. The L2 and L3 fibers are usually fused. Although the L2 through L4 fibers tend to take a more anterior course along the aorta and common iliac vessels, the L1 fiber takes a more shallow, caudal, and oblique course, exiting the sympathetic trunk near the level of the ipsilateral renal hilum. An intraoperative photograph of the bilateral nerve-sparing technique is shown in [Figure 35-5](#).

The left-sided postganglionic sympathetic nerves are first identified as they course along the lateral border of the aorta and left common iliac artery and onto the anterior surface of these vessels immediately caudal to the IMA (see [Fig. 35-4B](#)). A Kittner sponge can be used to sweep the fatty connective tissue gently away revealing the shiny off-white nerve fibers running obliquely over the aorta and joining the contralateral postganglionic fibers in the superior hypogastric plexus. Fibers can be tagged with vessel loops to provide continued gentle traction as they are dissected to their origins at the sympathetic trunk. Alternatively, the left sympathetic trunk can be identified first distal to the level of the IMA and traced cranially until the postganglionic fibers are sequentially encountered.

The right-sided postganglionic nerve fibers are best identified as the precaval and interaortocaval lymphatic tissue is rolled medially off of the IVC. The postganglionic fibers can be seen coursing obliquely in an anterior and inferior direction toward the superior hypogastric plexus (see [Figs. 35-4A and 35-5](#)). These can be cleared of overlying tissue using a Kittner sponge. As described previously, the individual fibers should be encircled with vessel loops to place them on traction as they are traced down to their origins in the right sympathetic trunk.

When the nerve fibers have been dissected free for the entirety of their courses through the RPLND template, the lymphatic packets

around the fibers should be dissected. The specimen must be sequentially passed through the web of postganglionic fibers as it is released from the body wall. Care must be taken to avoid injuring the fibers during specimen harvest and obtaining hemostasis. The nerve fibers often exit the sympathetic trunks in close proximity to the lumbar vessels, which puts them at particular risk of collateral injury if lumbar bleeding is encountered.

Closure and Postoperative Care

When the RPLND is complete, the resection bed should be carefully inspected for any residual lymphatic tissue, lymph leaks, and hemostasis. Lymph leaks can be controlled with placement of metal clips. The abdomen should be copiously irrigated with warm sterile water in an attempt to discover any bleeding vessels in spasm. The posterior parietal peritoneum should be reapproximated with a simple running 2-0 chromic suture. This maneuver is designed to prevent the small bowel from scarring to the great vessels and retroperitoneum. Additionally, in the setting of full mobilization of the root and ascending colon, reapproximation of the mesentery is thought to decrease the risk of volvulus. When the retroperitoneum is closed, the small bowel should be run for its entire length to rule out unrecognized retractor injuries. Additionally, the liver, colon, and stomach should be inspected. Surgical drains are not routinely placed. However, large-volume retroperitoneal, retrocrural, or duodenal resections may require a drain. We leave a Penrose drain for large-volume resections, given the propensity of postoperative abdominal third spacing. This drain is typically removed after the patient has resumed a regular diet and drainage remains serous and less than 100 mL for 24 hours.

In the absence of bowel repair/anastomoses, patients are given sips of ice chips on the evening of surgery. On postoperative day 1, patients are advanced to unlimited clear liquids, and they are encouraged to spend most of the day in a chair and ambulating. If patients tolerate clear liquids, they are advanced to a regular diet and transitioned off of intravenous pain medications on postoperative day 2. Patients are typically discharged between postoperative days 3 and 5 depending on how quickly they are able to tolerate a

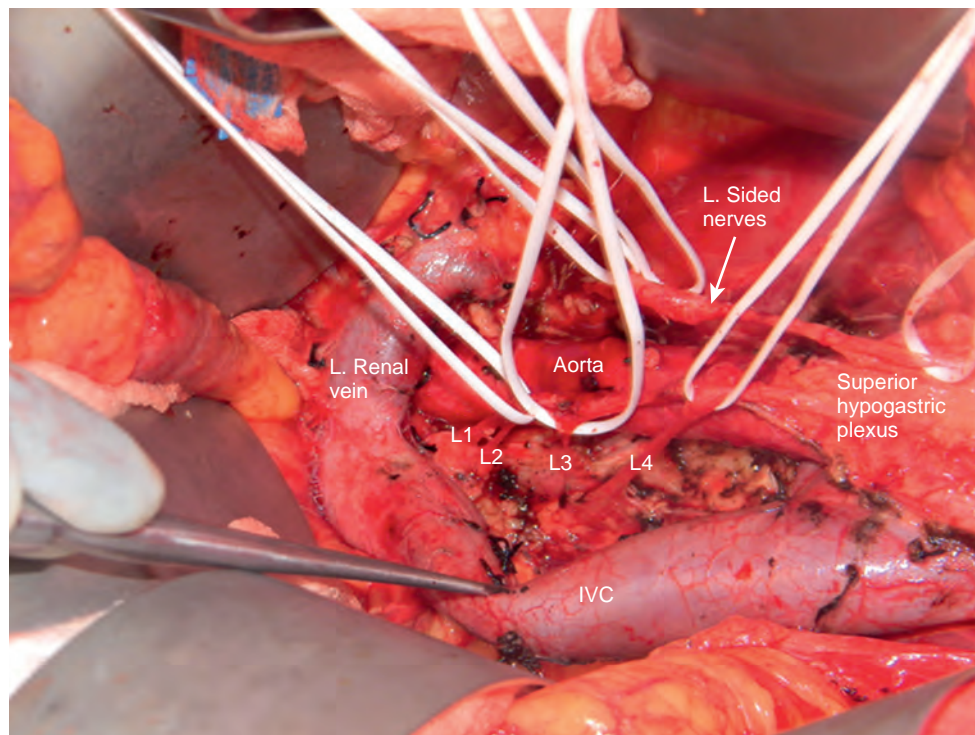


Figure 35-5. Bilateral nerve-sparing technique. IVC, inferior vena cava; L., left; L1 through L4, right-sided postganglionic sympathetic nerves.

regular diet. Patients undergoing larger resections tend to have longer inpatient stays.

AUXILIARY PROCEDURES

The following discussion of auxiliary procedures applies to PC-RPLND because these procedures are rarely, if ever, required during primary RPLND. The incidence of auxiliary procedures at the time of PC-RPLND ranges from 24% to 45% in the literature (Beck et al, 2009; Heidenreich et al, 2009; Winter et al, 2012). The most common auxiliary procedure is a nephrectomy, followed by vascular reconstruction or resection. As the volume of retroperitoneal disease increases, so does the likelihood of requiring resection of adjacent organs and/or structures.

Nephrectomy

Nephrectomy at the time of PC-RPLND is the most commonly performed auxiliary procedure. The incidence of nephrectomy at PC-RPLND ranges from 5% to 31% (Base and Navratil, 1984; Beck and Lalka, 1998; Nash et al, 1998; Stephenson et al, 2006; Djaladat et al, 2012; Cary et al, 2013). Table 35-1 summarizes studies reporting on simultaneous nephrectomy and associated risk factors.

Recognition of preoperative risk factors associated with nephrectomy at PC-RPLND is vital for surgical planning and patient counseling. Nephrectomy is usually needed in high-risk settings such as salvage RPLND, desperation RPLND, resection of late relapse, or reoperative RPLND. Additional risk factors include retroperitoneal mass size and location of primary tumor (i.e., left vs. right testicle). In the Indiana University study, men with retroperitoneal mass size greater than 10 cm had a ninefold increase in odds of nephrectomy compared with men with retroperitoneal mass less than 2 cm. Left-sided primary tumors with left para-aortic retroperitoneal masses had significantly increased odds of nephrectomy compared with right-sided tumors (odds ratio 5.44, $P < .0001$) (Cary et al, 2013). Other reports supported this finding (Heidenreich et al, 2009; Djaladat et al, 2012). This finding is due to the fact that left-sided primary tumors metastasize to the para-aortic region near the renal hilum compared with metastasis of right-sided primary tumors to the interaortocaval landing zone.

It is important to consider postoperative renal function after nephrectomy because these patients may require postoperative

adjuvant chemotherapy. Studies from Indiana University and Memorial Sloan-Kettering Cancer Center (MSKCC) reported a decline in renal function after nephrectomy (Nash et al, 1998; Stephenson et al, 2006). However, this decreased renal function neither resulted in the need for renal replacement therapy nor compromised subsequent adjuvant or salvage chemotherapy when necessary. Despite changes in renal function, most patients are able to tolerate subsequent chemotherapy if needed and avoid renal replacement therapy.

Major Vascular Reconstruction

Inferior Vena Cava Resection

Most cases requiring IVC resection have bulky stage disease (stage IIb or higher). The incidence of IVC resection reported in the literature ranges from 5% to 10% (Beck and Lalka, 1998; Nash et al, 1998; Winter et al, 2012). In 1991, Donohue and colleagues reported 40 patients who underwent IVC resection without reconstruction. In this study, the three indications for caval resection were necessity for tumor clearance (38%), vena caval scar occlusion (14%), and vena caval tumor thrombus (48%). The decision for en bloc caval resection was justified by the adverse nodal pathology, which included active cancer in 63% and teratoma in 31% of the specimens. For patients with lower extremity edema and imaging concerning for IVC compression/occlusion, venacavography, ultrasonography, or magnetic resonance imaging is helpful to assess for flow through the IVC and guide intraoperative decision making.

A German study reported on 34 patients with IVC interventions during PC-RPLND (Winter et al, 2012). There were 23 complete IVC resections performed with four patients having an IVC reconstruction using a polytetrafluoroethylene graft. The authors found that retroperitoneal mass size ($P < .0001$) and International Germ Cell Cancer Collaborative Group (IGCCCG) intermediate/poor risk ($P = .005$) were associated with the need for an IVC intervention on univariate analysis. The probability for an IVC intervention was 20.4% for patients with retroperitoneal mass size 5 cm or larger and IGCCCG intermediate/poor risk. Conversely, patients with retroperitoneal mass size smaller than 5 cm and good-risk disease had only a 2.7% probability for an IVC intervention.

Routine reconstruction of the vena cava after resection is not required. Data on 65 infrarenal IVC resections without reconstruction by Beck and Lalka (1998) support this approach. This study

TABLE 35-1 Risk Factors and Indications for Nephrectomy at Postchemotherapy Retroperitoneal Lymph Node Dissection*

STUDY	PATIENTS UNDERGOING Nx, N (INCIDENCE %)	TIME PERIOD	INDICATIONS/RISK FACTORS
Cary et al, 2013	265 (14.8)	1980-1997	RP mass size Year of surgery Primary tumor site Salvage chemotherapy Elevated markers
Djaladat et al, 2012	12 (14.1)	2004-2010	Left-sided hilar mass
Heidenreich et al, 2009	7 (4.6)	1999-2007	Encasement of renal vessels/ureter
Stephenson et al, 2006	32 (5)	1989-2002	Salvage RPLND Desperation RPLND Redo RPLND Late relapse
Nash et al, 1998	162 (19)	1974-1994	Involvement of renal structures Venous thrombus Poor renal function Combination of above

*Not all studies performed formal statistical analyses for predictive risk factors because of small sample size.
Nx, nephrectomy; RP, retroperitoneal; RPLND, retroperitoneal lymph node dissection.

evaluated the long-term sequelae of IVC resection using a survey developed by an international consensus conference on chronic venous disease held by the American Venous Forum (Beebe et al, 1996). The median follow-up for these patients was 89 months. Of patients, 75% had a disability score of 0 to 1 (none or mild disability). Only one patient had the highest possible disability score. Although these patients are at higher risk for chylous ascites and other periprocedural complications (Baniel et al, 1993), long-term venous congestion seems to be less of an issue; this is particularly true if there is complete occlusion with development of collateral circulation present preoperatively. Slow progressive retroperitoneal tumor growth with accompanying desmoplastic reaction to chemotherapy likely results in a gradual occlusion of caval blood flow allowing for adequate development of venous collateral circulation. The development of this collateral venous return likely results in less morbidity from caval resection in patients with testis cancer compared to patients with acute IVC occlusion.

Aortic Resection and Reconstruction

In some cases, retroperitoneal tumor encasement of the aorta requires en bloc aortic resection with reconstruction to remove the retroperitoneal mass adequately. **When this clinical situation occurs, it is crucial to alert additional surgical teams (i.e., vascular surgery) preoperatively to ensure successful clinical outcomes.** It is ideal to anticipate the need for aortic replacement preoperatively to allow proper patient counseling and time to coordinate between surgical services. An aortic tube graft is most commonly used for reconstruction; however, an aortobi-iliac graft may be used depending on the extent of tumor involvement.

Several studies evaluated the indications for aortic resection and its morbidity. In 2001, Beck and colleagues reported 15 patients who underwent aortic replacement during PC-RPLND. **Over a 30-year span involving more than 1200 patients, approximately 1% required this procedure.** Two thirds of these patients had received at least one course of salvage chemotherapy and/or had elevated STMs at the time of surgery. The indication for aortic replacement in these patients was tumor fixation to the aorta, with en bloc resection of the aorta deemed necessary for complete tumor removal. The retroperitoneal pathology in this group revealed active cancer in 80% and teratoma in 20%. At a median follow-up of 34 months, 33% of these patients were disease-free. Given the chemoresistant nature of the disease and bulky tumor burden surrounding the aorta in most of these patients with advanced GCT, aortic resection is a worthwhile undertaking and may provide a therapeutic benefit in a significant proportion of patients. In a multi-institutional German study of 402 patients who underwent PC-RPLND, 6 patients required aortic resection with graft placement (Winter et al, 2012). Although not statistically significant, there was a trend toward aortic replacement occurring more commonly in patients with residual mass size 5 cm or larger and having IGCCCG intermediate/poor risk.

When the decision for aortic resection has been made, the principles of the operation do not change substantially. The IVC should be dissected away from the mass and aorta using the split-and-roll technique with division of lumbar veins. The left ureter should be freed from the retroperitoneal mass. If the tumor does not encroach on the left renal hilum, this is also dissected free. The vascular surgery team assists with this dissection to ensure adequate length of the aorta cranial and caudal to the tumor, which allows for proximal and distal vascular control and ease of graft anastomoses. The aorta is cross-clamped and resected en bloc with the retroperitoneal mass. Lumbar arteries are divided during this process. Before cross clamping, the patient is usually administered intravenous heparin to minimize the risk of arterial thrombosis. The graft is sewn into place using standard vascular surgery principles.

Hepatic Resections

Patients with hepatic involvement at initial presentation fall into the IGCCCG poor-risk classification. Based on the initial 1997

publication of the IGCCCG risk stratification scheme, patients in this risk category have a 5-year overall survival (OS) of 48%. Patients with liver metastasis represent approximately 6% of patients with advanced GCTs (International Germ Cell Consensus Classification, 1997).

Jacobsen and colleagues (2010) evaluated the concordance between retroperitoneal and liver histology in patients who largely underwent simultaneous resections. The authors identified 59 patients with advanced GCT who underwent a liver resection. Of all hepatic specimens, 73% contained necrosis only, and the histologic concordance between retroperitoneal and liver necrosis was 94%. The authors concluded that management of hepatic lesions must be individualized, but that observation may be warranted for liver lesions requiring complicated hepatic surgery. Conversely, other groups found the histologic concordance between the retroperitoneum and liver less reliable (Hartmann et al, 2005; You et al, 2009). Nevertheless, necrosis is the most common histology found in the liver after chemotherapy in these studies. **Observation of liver lesions is warranted in some cases, particularly when hepatic involvement may require extensive resection.** Use of intraoperative frozen-section analysis of core biopsy specimens of liver lesions may provide additional information when deciding whether or not to resect hepatic lesions.

Pelvic Resections

Pelvic lymph node dissection is rarely needed during PC-RPLND. The largest series to date on pelvic metastases among patients undergoing RPLND was presented as an abstract on 137 (5%) of 2722 patients treated from 1990 to 2009. Mean pelvic mass size was 6.5 cm. The pelvic mass was managed by pelvic excision alone in 28%, pelvic excision with primary RPLND in 3%, and pelvic excision with PC-RPLND in 69%. Pelvic pathology revealed necrosis, sarcoma, teratoma, and active cancer in 16%, 5%, 55%, and 24%. **Factors associated with pelvic metastases were initial clinical stage, extragonadal primary, and prior groin surgery (e.g., inguinal hernia repair) (all $P < .001$) (Mehan et al, 2011).**

MSKCC reported their findings on 44 (2%) patients who underwent pelvic lymph node dissection during the course of management (Alanee et al, 2013). Mean pelvic mass size was 4 cm. Pelvic histology in this series revealed active cancer in 19 (43%) and teratoma in 17 (39%). No patient reported a history of prior scrotal or inguinal surgery. Overall, the need for pelvic lymph node dissection is rare; approximately 80% of patients with a pelvic mass had either teratoma or active cancer on final histology warranting resection in patients with pelvic disease.

Management of Supradiaphragmatic Disease

Approximately 10% to 20% of patients with a diagnosis of testicular cancer have evidence of supradiaphragmatic disease at presentation or go on to manifest intrathoracic spread at some point in the course of their illness (Kesler et al, 2011). Pulmonary metastases of testicular GCT represent disease spread via the hematogenous route, whereas mediastinal and cervical metastases represent lymphatic spread. Approximately 80% of mediastinal metastases are confined to the lower (retrocrural) and middle visceral mediastinum (Kesler et al, 2011). GCT found in the anterior mediastinum usually indicates a mediastinal primary GCT.

Studies evaluating comparative histology of retroperitoneal and thoracic disease have demonstrated pathologic discordance ranging from 25% to 50%. Most of these patients harbor the more aggressive pathology in the retroperitoneum (Gerl et al, 1994; Gels et al, 1997; Steyerberg et al, 1997; Besse et al, 2009). Steyerberg and colleagues (1997) reported on a multi-institutional study of 215 patients undergoing thoracotomy after cisplatin-based induction chemotherapy in an attempt to predict thoracic histology. RPLND histology was a strong predictor of histology at thoracotomy with 89% of patients with necrosis at RPLND having necrosis only in the chest. **It is generally recommended that if these resections are to be staged, RPLND should be performed first because the finding**

of retroperitoneal necrosis/fibrosis may spare select patients unnecessary thoracic resection. Determining if and when to proceed with resection of thoracic disease in the setting of retroperitoneal necrosis is a decision that needs to be based on the expertise of a multidisciplinary testicular cancer team that has extensive experience in dealing with this disease. Kesler and colleagues (2011) recommended resection of any residual postchemotherapy thoracic mass larger than 1 cm. The exception to this rule would be a patient with extensive residual masses requiring a potentially morbid resection in the setting of necrosis only at RPLND.

Resection of Retrocrural Disease

Description of the surgical approach to most supradiaphragmatic disease is beyond the scope of this chapter. However, the surgical approach to and timing of resection of retrocrural disease is often intimately related to RPLND. The retrocrural space presents a surgical challenge given its anatomic location, and surgical approaches to retrocrural disease have evolved over time. Most of these cases are performed in combination with the thoracic surgery team. At Indiana University, early efforts employed a thoracoabdominal incision or a separate midline laparotomy and posterior thoracotomy. A more recent technique used for residual lower retrocrural disease is a midline laparotomy employing a transabdominal transdiaphragmatic approach that can be performed at the same time as RPLND (Fig. 35-6). This approach was first described by Fadel and associates (2000) in 18 patients who had simultaneous resection of masses located in the retroperitoneum and lower mediastinum. The rationale for this approach was to minimize the morbidity of a thoracotomy when feasible. Kesler and colleagues (2003) published results on 268 patients with mediastinal metastases who underwent mediastinal dissection for NSGCT. A transabdominal transdiaphragmatic approach was used in 60 (13.2%) of these patients. Operative morbidity was low with three (1.1%) operative deaths in the entire cohort, which represented patients with extensive/bulky residual disease.

The timing of retrocrural resection depends in part on whether there is contiguous disease in the retroperitoneum. Generally, if

small-volume retrocrural disease exists concurrently with a retroperitoneal mass, this is approached through a single transabdominal and transdiaphragmatic incision simultaneously. If large-volume retroperitoneal teratomatous disease exists requiring a prolonged surgical time for RPLND, the retrocrural and mediastinal resection can be staged. If the mediastinal disease is not contiguous, the timing of mediastinal dissection is guided in part by the pathology of the retroperitoneum. This rationale is based on studies evaluating concordance between retroperitoneal and thoracic pathology discussed earlier.

KEY POINTS: AUXILIARY PROCEDURES

- Nephrectomy is the most commonly required auxiliary procedure. It is more common with large left-sided masses and when PC-RPLND is performed in high-risk settings.
- Routine IVC reconstruction is unnecessary when en bloc resection is performed in the setting of complete or near-complete IVC occlusion.
- Given the complex vascular reconstruction required, every effort must be made preoperatively to identify patients who require en bloc aortic resection.
- Given the high incidence of necrosis, the decision to proceed with hepatic resection needs to be based on retroperitoneal pathology (when available) and predicted morbidity of hepatic resection as determined by hepatic surgical specialists.
- Pathologic discordance between retroperitoneal and thoracic disease is common, with more aggressive histology being found more commonly in the retroperitoneum. If procedures are to be staged, RPLND should be performed first.
- When patients harbor residual masses in the retroperitoneum and the retrocrural region, consideration should be given to simultaneous PC-RPLND and retrocrural resection using a transabdominal, transdiaphragmatic approach to the latter.

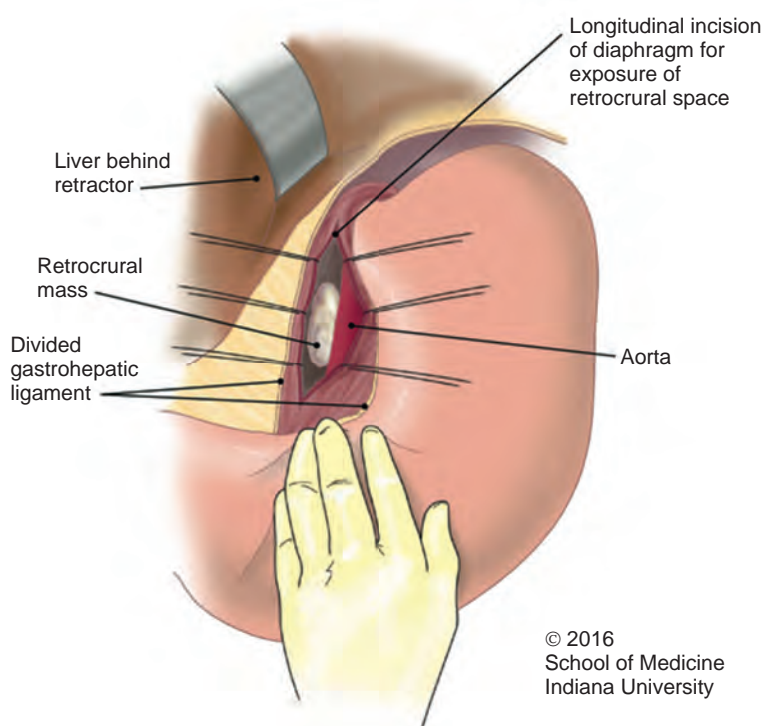


Figure 35-6. Transabdominal, transdiaphragmatic approach to retrocrural mass. (© 2016 Section of Medical Illustration in the Office of Visual Media at the Indiana University School of Medicine. Published by Elsevier Inc. All rights reserved.)

SURGICAL DECISION MAKING

This section discusses the decision-making process involved in determining when to perform RPLND, the extent of dissection, and when to administer postoperative chemotherapy. The indications for, advantages of, and disadvantages of primary RPLND are discussed in Chapter 34 and are not repeated here.

Management of Clinical Complete Remission to Induction Chemotherapy

There is little debate that patients with disseminated testicular cancer who achieve a complete serologic remission but harbor a residual retroperitoneal mass after induction chemotherapy require PC-RPLND. However, the management of patients who achieve complete radiographic (no residual mass >1 cm) and serologic remission of metastatic GCT is controversial. Approximately 70% of men who receive cisplatin-based chemotherapy for stage II or higher testicular cancer can be expected to demonstrate complete resolution of measurable disease. Management options for these patients include observation or PC-RPLND.

Proponents of observation cite the excellent long-term survival demonstrated by patients managed nonoperatively. In a study of 141 men observed after demonstrating clinical CR to induction chemotherapy alone, Ehrlich and associates (2010) reported 15-year recurrence-free survival (RFS) of 90% and cancer-specific survival (CSS) of 97%. In a similar study of 161 patients with median 4.5-year follow-up, Kollmannsberger and colleagues (2010) reported RFS of 93.8% and CSS of 100%.

Investigators at MSKCC recommended performing PC-RPLND on all patients with a history of retroperitoneal metastases even in the setting of a clinical CR because of the potential for residual microscopic disease. In 2006, Carver and coworkers reported on 532 patients undergoing PC-RPLND at MSKCC. Of 154 patients demonstrating a residual mass 1 cm or smaller on cross-sectional imaging performed after chemotherapy, 22%, 1%, and 5% demonstrated teratoma, teratoma/GCT, and GCT at PC-RPLND.

The main issue at the center of this debate is the natural history of microscopic residual teratoma. The concerns expressed by proponents of PC-RPLND in patients with clinical CR is that microscopic teratoma left in the retroperitoneum may lead to growing teratoma syndrome, late relapse, or malignant transformation to somatic-type malignancy. Proponents of observation propose that microscopic teratoma is biologically inert in most cases. Table 35-2 lists the results of three retrospective studies evaluating these two management strategies for patients with clinical CR to chemotherapy alone. Survival outcomes were excellent using either approach (Karellas et al, 2007; Ehrlich et al, 2010; Kollmannsberger et al, 2010). The two questions that remain to be answered are: (1) Does performing PC-RPLND in these patients prevent cancer-specific deaths? (2) Would the number needed to treat to prevent one death be low enough to justify this approach?

Use of Modified Templates in Primary Retroperitoneal Lymph Node Dissection

As the patterns of lymphatic spread of GCT have been defined, various RPLND templates have been proposed with the goal of balancing therapeutic efficacy with potential morbidity. Historically, RPLND involved removal of all lymphatic tissue contained in a contemporary bilateral infrahilum template in addition to resection in the interiliac region down to the bifurcation of the common iliac vessels (Ray et al, 1974). Full bilateral suprahilum dissections were performed routinely at some centers as well (Donohue et al, 1982a). Sometimes performed through a large thoracoabdominal incision, these resections were necessary to provide the best chance for durable cure because of the absence of curative chemotherapy for GCT and were associated with significant perioperative morbidity as well as rendering most patients anejaculatory (Donohue and Rowland, 1981).

In the 1970s and 1980s, the development of curative cisplatin-based chemotherapeutic regimens (Einhorn and Donohue, 1977), elucidation of distinct lymphatic spread for right-sided versus left-sided testicular tumors (Ray et al, 1974; Donohue et al, 1982b; Weissbach and Boedefeld, 1987), and description of surgical techniques to preserve the postganglionic sympathetic nerve fibers involved in seminal emission and antegrade ejaculation (Jewett et al, 1988; Colleselli et al, 1990; Donohue et al, 1990) significantly altered management of the retroperitoneum in patients with testicular GCT. In 1974, Ray and colleagues presented a series of 283 patients undergoing RPLND at MSKCC from 1944 to 1971. Dissections were predominantly infrahilum and evolved from a full bilateral dissection to a “modified bilateral” dissection as the primary landing zones of right-sided versus left-sided primaries became apparent. These modified bilateral templates were very similar to modified unilateral templates with the exception that lymphatic tissue below the IMA was routinely resected. The detailed description of distinct templates based on the laterality of the testicular primary was the first of its kind and set the stage for further refinement.

Donohue and colleagues (1982b) published a pathologic lymph node mapping study performed at Indiana University on 104 patients found to have pathologically positive nodes (pN+) at primary RPLND. Full bilateral dissections to include bilateral suprahilum dissections were performed on every patient. Investigators found that left-sided tumors were most likely to metastasize to the left para-aortic lymph nodes, whereas right-sided tumors were most likely to metastasize to interaortocaval and precaval regions. Spread to contralateral retroperitoneum and suprahilum regions was rare but increased with tumor bulk. Metastasis to the interiliac region was rare. This study confirmed the relatively predictable pattern of the lymphatic spread of testicular GCTs and provided strong pathologic evidence for the use of “modified bilateral” templates proposed by Ray and colleagues (1974) in patients with low-stage retroperitoneal disease. Omission of the contralateral retroperitoneum and interiliac regions resulted in the preservation of antegrade ejaculation in most patients. Omission of suprahilum regions decreased the risk of

TABLE 35-2 Management of Patients Experiencing a Clinical Complete Remission to Induction Chemotherapy

	EHRlich ET AL, 2010	KOLLMANNsBERGER ET AL, 2010	KARELLAS ET AL, 2007
Management	Observation	Observation	PC-RPLND
No. patients	141	161	147
Follow-up (yr)	15.5	4.3	3
Good risk (%)	77	94	98
DFS (%)	91	94	97
CSS (%)	97	100	NR

CSS, cancer-specific survival; DFS, disease-free survival; NR, not reported; PC-RPLND, postchemotherapy retroperitoneal lymph node dissection.

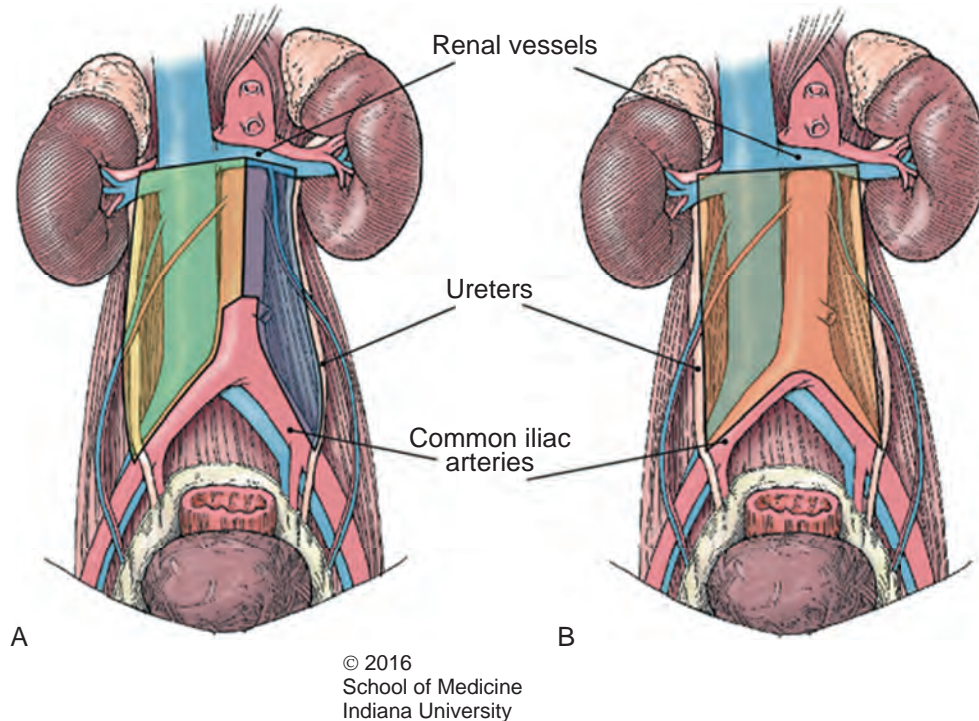


Figure 35-7. Retroperitoneal lymph node dissection templates. A, Modified unilateral templates—right-sided shaded in yellow, left-sided shaded in purple. B, Modified bilateral template—shaded area. (© 2016 Section of Medical Illustration in the Office of Visual Media at the Indiana University School of Medicine. Published by Elsevier Inc. All rights reserved.)

postoperative chylous ascites, renovascular injuries, and pancreatic complications.

In 1987, Weissbach and Boedefeld reported a multi-institutional retrospective review of 214 patients with nonbulky PS II disease. The authors recommended a more reduced left-sided template including the para-aortic and upper preaortic nodes. The authors also proposed that a frozen section be sent from the primary landing zone; if the section was positive, a full bilateral infrahilar RPLND should be performed.

The end result of these template studies has been a more efficient, less morbid, and maximally effective RPLND. There is still significant debate among experts regarding the ideal extent of surgical templates. Most experts agree that suprahilar/retrocruar and interiliac resections can safely be omitted from the standard RPLND template. However, controversy exists regarding the need to resect the contralateral retroperitoneal lymphatic tissue. The boundaries of the modified unilateral templates and a full bilateral template are demonstrated in Figure 35-7.

Eggner and colleagues (2007b) reviewed a series of 500 patients undergoing primary RPLND for CS I or IIA testicular cancer at MSKCC. Bilateral infrahilar dissection was usually performed. The authors analyzed the 191 patients (38%) with PS II disease for the anatomic distribution of positive-node packets and applied five modified templates to these results. They reported that 3% to 23% of patients with pathologically positive nodes were found to have disease outside of the modified unilateral template depending on which one was applied. Extratemplate disease was seen more commonly with right-sided than left-sided tumors. Given these results, the authors recommended full bilateral infrahilar nerve-sparing RPLND for patients with CS I or IIA testicular cancer.

To date, no prospective or retrospective studies have compared the modified unilateral templates with the full bilateral templates. As discussed earlier, CSS and OS approach 100% in all series. Expanding the templates cannot be expected to improve either of these outcomes. The question is whether performance of a full bilateral infrahilar RPLND would prevent

retroperitoneal relapses that would occur after a properly performed modified unilateral template. When comparing series from centers that use the modified unilateral templates with series from centers that use the bilateral infrahilar templates, outcomes are very similar (Table 35-3) (Donohue et al, 1993a; Hermans et al, 2000; Nicolai et al, 2004; Stephenson et al, 2005). Although the MSKCC series reported an increased proportion of patients being cured by surgery alone, patients with pN2 disease routinely receive adjuvant postoperative chemotherapy at that center (Stephenson et al, 2005). In the first Indiana study, most of the node-positive patients were randomly assigned to observation versus adjuvant chemotherapy on protocol (Donohue et al, 1993a). In the more recent Indiana study, pN1 patients and most pN2 patients were observed with chemotherapy reserved for patients who experienced recurrence and pN3 patients (Hermans et al, 2000).

The appropriate boundaries of the primary RPLND template are controversial. Use of the templates recommended in the studies by Ray, Donohue, Weissbach, and Eggner and their colleagues will undoubtedly result in excellent survival outcomes. The question of which template offers greatest balance of oncologic control and minimization of morbidity remains unanswered.

Use of Modified Templates in Retroperitoneal Lymph Node Dissection after Chemotherapy

Donohue and colleagues first reported their experience performing consolidative RPLND after cisplatin-based chemotherapy in 1982. Most tumors containing teratoma and/or viable malignancy were located in their respective primary landing zones. However, given the frequent contralateral crossover in the setting of bulky disease and the inability to obtain reliable confirmation of histology intraoperatively, the authors stressed the importance of the PC-RPLND being "as complete as possible" (Donohue et al, 1982a). The standard PC-RPLND became resection of all macroscopic disease

TABLE 35-3 Selected Primary RPLND Series

STUDY	NO. PATIENTS	NO. pN+ (%)	RECURRENCE RATE FOR pN0 (%)	RECURRENCE RATE FOR pN+ MANAGED WITH RPLND ALONE (%)	FOLLOW-UP (yr)	CSS (%)
Donohue et al, 1993a	378	112 (29.6)	31 (12)	22 (34)	6.2	99.2
Stephenson et al, 2005	308	91 (29.5)	NR (7)	NR (34)	4.9	99.7
Hermans et al, 2000	292	66 (22.4)	23 (10.2)	7 (22.6)	3.8	100.0
Nicolai et al, 2004	322	60 (20)	NR	NR	7.2	98.8

CSS, cancer specific survival; NR, not reported; pN+, histologically positive lymph nodes; pN0, histologically negative lymph nodes; RPLND, retroperitoneal lymph node dissection.

along with a full bilateral infrahilar dissection. This approach provides excellent local control of the retroperitoneum, but is associated with significant morbidity including anejaculation in patients in whom a nerve-sparing technique is not possible.

Several groups investigated whether modified unilateral templates can safely be applied to appropriately selected patients in the postchemotherapy setting (Wood et al, 1992; Herr, 1997; Rabbani et al, 1998; Ehrlich et al, 2006; Beck et al, 2007; Carver et al, 2007a; Steiner et al, 2008; Heidenreich et al, 2009). Table 35-4 lists the results from several studies examining distribution of positive lymph nodes (teratoma and/or viable malignancy) and/or reporting outcomes after selective use of the modified unilateral templates in the postchemotherapy setting. When bilateral dissections were performed, rates of disease outside the unilateral template ranged from 18% to 32% (Carver et al, 2007a). However, rates of disease outside of the unilateral template and outside of macroscopic disease ranged from 2% to 18.6%. Variability in these percentages is likely a function of patient selection and the specific template used. Safe use of the unilateral modified templates in the postchemotherapy setting relies on selection of the correct template as well as appropriate patient selection. **Patients meeting the following criteria may be considered for modified unilateral template PC-RPLND according to data emerging from centers performing these surgeries:**

1. Well-defined lesion measuring 5 cm or less confined to the primary landing zone of the primary tumor on imaging before and after chemotherapy
2. Normal postchemotherapy STMs
3. IGCCCG good/intermediate risk

Figure 35-8 shows representative CT images for candidates for modified unilateral versus bilateral template PC-RPLND. Use of these selection criteria has resulted in in-field retroperitoneal recurrence rates of 0% to 1%, antegrade ejaculation rates of 85% to 94%, and CSS of 98% to 100% at postoperative follow-up times of 2.6 to 7.8 years (Beck et al, 2007; Steiner et al, 2008; Heidenreich et al, 2009). Although these data are encouraging with regard to the use of the modified unilateral templates in PC-RPLND, the standard of care for patients requiring postchemotherapy resection remains resection of all macroscopic disease and a full bilateral infrahilar template RPLND. To date, there have been no prospective studies comparing outcomes in patients undergoing bilateral versus modified unilateral template PC-RPLND. If unilateral modified templates are to be used at PC-RPLND, strict adherence to the above-listed selection criteria is important.

Adjuvant Chemotherapy for Pathologic Stage II Disease at Primary Retroperitoneal Lymph Node Dissection

Primary RPLND alone is curative in approximately 70% of patients with pN1-2 disease, and nearly all patients who experience recurrence are successfully salvaged at the time of recurrence (Donohue et al, 1993a, 1995; Nicolai et al, 2004; Stephenson et al, 2005). Evaluation of two cycles of adjuvant cisplatin-based

chemotherapeutic regimens has consistently demonstrated near-complete elimination of post-RPLND recurrences (Williams et al, 1987; Behnia et al, 2000; Kondagunta et al, 2004). However, pro forma use of adjuvant chemotherapy for pN+ patients would result in overtreatment of approximately 70% of patients without any change in OS. Conversely, treating patients with pN1 and pN2 disease in the adjuvant rather than salvage setting spares patients with recurrent disease full-induction chemotherapy (in most cases one additional cycle of bleomycin, etoposide, Platinol or two additional cycles of etoposide, Platinol). Investigators have attempted to determine which PS II patients are most likely to experience recurrence after primary RPLND.

Although the bulk of retroperitoneal disease encountered at primary RPLND has traditionally been viewed as a predictor of disease recurrence in the absence of adjuvant chemotherapy, this predictive value has not been consistently demonstrated when examining outcomes in patients with PS IIA and IIB disease. Most data demonstrating a direct relationship between retroperitoneal tumor burden and relapse come from early reports in which microscopic disease was separated out from low-volume macroscopic disease (both of which are now grouped together in PS IIA) (Vugrin et al, 1981; Fraley et al, 1985). When evaluating recurrences in the observation arm of a prospective randomized multi-institutional trial evaluating adjuvant cisplatin-based chemotherapy, Williams and coworkers (1987) reported recurrence rates of 40% for patients with microscopically positive nodes, 53% for patients with macroscopic nodal disease smaller than 2 cm, and 60% for patients with disease larger than 2 cm. However, this numeric trend did not reach statistical significance. Several retrospective studies reported no difference in recurrence rates when comparing PS IIA and IIB patients managed with postoperative observation (Pizzocaro and Monfardini, 1984; Donohue et al, 1993b; Nicolai et al, 2010; Al-Ahmadie et al, 2013). In two reports on patients with CS II NSGCT managed with primary RPLND, larger retroperitoneal tumor bulk was associated with increased recurrence rates (Donohue et al, 1995; Weissbach et al, 2000). It is unclear from these retrospective series what selection factors were used to determine which PS II patients were given adjuvant chemotherapy.

Additional histologic characteristics such as number and proportion of positive lymph nodes removed (Beck et al, 2005a; Al-Ahmadie et al, 2013), histology of viable GCT (Beck et al, 2005a; Al-Ahmadie et al, 2013), and extranodal extension (Beck et al, 2007; Al-Ahmadie et al, 2013) have failed to predict reliably patients who are more likely to experience recurrence when managed on post-RPLND surveillance. Patients with PS II disease demonstrating teratoma only in the retroperitoneal specimen demonstrate very low recurrence rates. Given this finding and the chemoresistance of teratoma, adjuvant chemotherapy is not recommended in these patients.

There is general agreement that compliant patients with pN1 disease can be safely observed after RPLND. The management of patients with pN2 disease is controversial. Some investigators recommend two cycles of adjuvant chemotherapy in these patients (Kondagunta and Motzer, 2007). The practice at Indiana University

TABLE 35-4 Studies Evaluating the Use of Modified Unilateral Templates in Postchemotherapy Retroperitoneal Lymph Node Dissection

STUDY	NO. PATIENTS	N+ OUTSIDE TEMPLATE (%)	N+ OUTSIDE TEMPLATE AND MACROSCOPIC DISEASE (%)	IN-FIELD RP RECURRENT AFTER B/L RPLND (%)	IN-FIELD RP RECURRENT AFTER U/L RPLND (%)	PRESERVATION OF EJACULATION IN TEMPLATES	FOLLOW-UP (yr)	CSS
Wood et al, 1992	113	14 (21.4)	9 (8)	NA	NA	NA	NA	NA
Herr, 1997	62	NR	NR	1 (4)	1 (2.7)	NR	6	89%
Rabbani et al, 1998	50	12 (24)	1 (2.6)	1 (2.6)	1* (9.1)	50%	4-5	96%-100%
Ehrlich et al, 2006	50	9 (18)	1 (2)	0	0	NA	4.4	NR
Beck et al, 2007	100	NA	NA	NA	0	NR	2.6	100%
Steiner et al, 2008	102	NA	NA	NA	1 (1)	94%	7.8	99%
Carver et al, 2007a	269	20-86 (7-32)	50 (18.6)	NR	NR	NR	3.75	NR
Heidenreich et al, 2009	152	NA	NA	1 (1.9)	0	85%	3.25	98%

*Occurred in patient who underwent tumorectomy only.
B/L, bilateral; CSS, cancer-specific survival; NA, not applicable; N+, histologically positive lymph nodes; NR, not reported; RP, retroperitoneal; RPLND, retroperitoneal lymph node dissection; U/L, unilateral.

KEY POINTS: SURGICAL DECISION MAKING

- Patients experiencing a clinical CR to induction chemotherapy generally should be observed. There is some debate regarding the benefit of PC-RPLND in these patients because of the potential for microscopic residual disease.
- The predictable lymphatic spread of testicular GCT has allowed for the establishment of the modified templates for use in patients with low-stage disease.
- The standard of care for PC-RPLND in patients with residual masses includes resection of all macroscopic residual disease and a full bilateral infrahilar template dissection. When modified unilateral templates are used in this setting, strict adherence to the above-outlined criteria is necessary to ensure proper patient selection.
- Administering two cycles of adjuvant cisplatin-based chemotherapy to patients with PS II disease demonstrating viable GCT nearly eliminates postoperative recurrences without affecting OS.

is to offer postoperative surveillance to patients with pN2 disease at primary RPLND.

HISTOLOGIC FINDINGS AT POSTCHEMOTHERAPY RETROPERITONEAL LYMPH NODE DISSECTION AND SURVIVAL OUTCOMES

The report from Indiana in 1982 on postcisplatin cytoreductive surgery was important in that it established the three major histologic categories encountered at PC-RPLND ([Donohue et al, 1982a](#)). In that report, teratoma, fibrosis, and viable GCT were encountered in roughly equal proportions. Since that time, refinement in primary chemotherapeutic regimens and clearer indications for resection have resulted in a decreasing number of patients demonstrating viable malignancy at PC-RPLND. The relative frequencies of fibrosis, teratoma, and viable GCT reported in more contemporary series have generally been 40%, 45%, and 15% ([Steyerberg et al, 1995](#); [Donohue et al, 1998](#); [Hendry et al, 2002](#); [Albers et al, 2004](#); [Carver et al, 2006](#); [Spiess et al, 2007](#)).

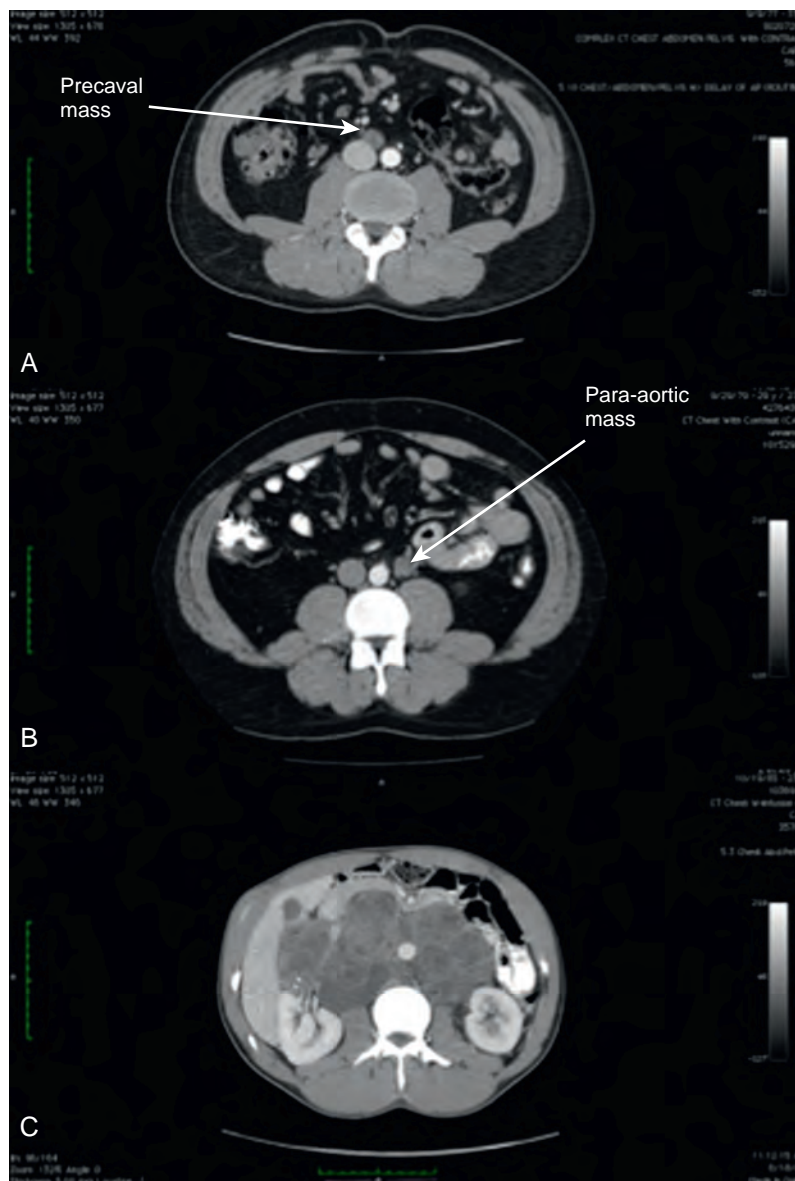


Figure 35-8. Computed tomography images of postchemotherapy residual retroperitoneal masses. A, This patient could be considered a candidate for modified right template postchemotherapy retroperitoneal lymph node dissection (PC-RPLND). B, This patient could be considered a candidate for modified left template PC-RPLND. C, This patient would require an extensive bilateral PC-RPLND.

Outcomes by Histology

Fibrosis, teratoma, and viable malignancy are associated with distinct survival outcomes when encountered at PC-RPLND. Survival outcomes as reported in the literature can be found in [Table 35-5](#). The variability of figures within each histologic group is a function of era of treatment, level of pretreatment, study inclusion criteria, and length of follow-up.

Fibrosis/Necrosis

The finding of fibrosis/necrosis only at postchemotherapy resection is associated with favorable RFS and CSS because it indicates a total malignant cell kill in most patients. It can be inferred that the retroperitoneal metastatic deposits harbored no chemoresistant germ cell elements and that any other subclinical metastatic deposits were likely cleared by chemotherapy. CSS and RFS can be expected to approach 95% in these patients ([Donohue and Foster, 1994](#); [Carver et al, 2007c](#); [Maroni et al, 2008](#)).

Teratoma

In 1986, Loehrer and colleagues published the first report dedicated to examining outcomes in patients found to have teratoma only at PC-RPLND. With RFS of 61% and CSS of 82.3%, this series reported poorer outcomes than would be seen in later studies. According to more contemporary outcomes, patients demonstrating teratoma only at PC-RPLND can be expected to demonstrate 80% to 90% RFS and 85% to 95% CSS ([Jansen et al, 1991](#); [Donohue and Foster, 1994](#); [Carver et al, 2006](#)). Investigators found larger mass size after chemotherapy, presence of somatic-type malignancy, and mediastinal primaries to be associated with increased risk of recurrence ([Loehrer et al, 1986](#); [Jansen et al, 1991](#); [Carver et al, 2007b](#)). However, even in the setting of massive retroperitoneal teratoma (>10 cm), 98% CSS has been reported ([Beck et al, 2009](#)).

Viable Malignancy

Persistent viable malignancy encountered at PC-RPLND is associated with a poorer prognosis than teratoma or fibrosis. Reported long-term survival in this group typically ranges from 50% to 70% ([Jansen et al, 1991](#); [Donohue et al, 1998](#); [Fizazi et al, 2001](#); [Spiess et al, 2007](#); [Kundu et al, 2010](#)).

In a multi-institutional review of 238 patients with viable malignancy at PC-RPLND, [Fizazi and associates \(2001\)](#) determined three factors associated with poorer prognosis: (1) incomplete resection, (2) 10% or greater viable malignancy, and (3) IGCCCG intermediate/poor risk stratification at initial diagnosis. Patients with none of these risk factors were classified as “favorable” and demonstrated a 90% 5-year progression-free survival (PFS) and 100% 5-year OS. Patients with one risk factor were classified as “intermediate risk” (5-year PFS 76%, 5-year OS 83%), and patients with two or more risk factors were classified as “poor risk” (5-year PFS 38%, 5-year OS 51%). In a review of 41 patients treated at M.D. Anderson Cancer Center who were found to have viable GCT at PC-RPLND, larger tumor dimension and IGCCCG intermediate/poor risk were associated with increased recurrence rate, whereas persistently elevated α -fetoprotein and prior receipt of salvage chemotherapy were associated with poorer CSS ([Spiess et al, 2007](#)).

Adjuvant Chemotherapy

Adjuvant chemotherapy for viable malignancy at PC-RPLND has never been evaluated in a prospective randomized controlled trial. However, early experience revealed a very poor prognosis when these patients were observed postoperatively ([Einhorn et al, 1981](#)). It was recommended that patients demonstrating viable GCT at PC-RPLND receive postoperative adjuvant cisplatin-based chemotherapy. Although the specific regimen has varied, the number of courses administered in the adjuvant setting after PC-RPLND has generally been two.

TABLE 35-5 Survival Outcomes by Histologic Findings at Postchemotherapy Retroperitoneal Lymph Node Dissection

STUDY	NO. PATIENTS	FOLLOW-UP (yr)	RFS	CSS
FIBROSIS				
Donohue and Foster, 1994	150	>2	NR	93
Egger et al, 2007a*	36	4.3	NR	85
Carver et al, 2007c	113	NR	95	NR
Maroni et al, 2008	184	4	92.1	NR
TERATOMA				
Loehrer et al, 1986	51	NR	61	82.3
Jansen et al, 1991	26	7.7	88.5	88.5
Donohue and Foster, 1994	273	>2	NR	93.4
Egger et al, 2007a*	15	4.3	NR	77
Carver et al, 2006	210	3	85.4	94
Beck et al, 2009	99	3.5	76.8	98
VIALE MALIGNANCY				
Jansen et al, 1991	23	7.9	54.5	64
Fox et al, 1993	133	3	30.8	42.8
Donohue et al, 1998	122	9	39	51.5
Fizazi et al, 2001	238	7.2	64	73
Egger et al, 2007a*	10	4.3	NR	56
Spiess et al, 2007	41	3.9	50	71
Kundu et al, 2010	90	NR	62	71

*All patients received salvage chemotherapy before postchemotherapy retroperitoneal lymph node dissection.
CSS, cancer-specific survival; NR, not reported; RFS, recurrence-free survival.

Fizazi and colleagues (2001) found that adjuvant chemotherapy was associated with statistically superior PFS without statistical improvement in OS. When dividing patients into the aforementioned viable GCT risk categories, only patients in the intermediate-risk group demonstrated statistically significant improvements in 5-year PFS and OS. Adjuvant chemotherapy seemed to be unnecessary in favorable-risk patients and ineffective in poor-risk patients. In the absence of randomization, these outcomes were likely heavily influenced by selection bias. Similarly, when evaluating patients with viable GCT after salvage RPLND, patients did not appear to benefit from two postoperative cycles of cisplatin-based chemotherapy (Fox et al, 1993; Kundu et al, 2010). Adjuvant chemotherapy is generally not recommended in this setting.

KEY POINTS: HISTOLOGIC FINDINGS AT POSTCHEMOTHERAPY RETROPERITONEAL LYMPH NODE DISSECTION AND OUTCOMES

- Approximately 90% long-term survival can be expected among patients with fibrosis and/or teratoma only at PC-RPLND. This number decreases to 50% to 70% for patients demonstrating viable GCT at PC-RPLND.
- Two cycles of adjuvant chemotherapy are generally recommended in patients with viable GCT at PC-RPLND after induction chemotherapy.

POSTCHEMOTHERAPY RETROPERITONEAL LYMPH NODE DISSECTION IN HIGH-RISK POPULATIONS

Salvage Retroperitoneal Lymph Node Dissection

Patients undergoing PC-RPLND after salvage chemotherapy demonstrated higher rates of persistent viable malignancy and worsened survival outcomes compared with patients who received first-line chemotherapy only (see Table 35-5). Typically, OS and CSS ranged from 60% to 75% in this group (Fox et al, 1993; Donohue et al, 1998; Eggener et al, 2007a). When comparing only patients found to have viable malignancy at PC-RPLND, Fox and associates (1993) reported CSS of 58.5% in patients having received induction chemotherapy only versus 36.7% in patients having received salvage chemotherapy.

Reported experience with RPLND after high-dose chemotherapy (HDCT) is limited (Table 35-6). In 2004, Rick and colleagues reported results in 57 patients undergoing PC-RPLND after HDCT. They observed 59% RFS and 65% CSS at a median follow-up of 7.3 years. Similarly, Cary et al (2011) reported 71% OS at a median follow-up of 4.2 years in 77 patients undergoing RPLND after HDCT.

Desperation Retroperitoneal Lymph Node Dissection

In general, patients with elevated STMs after chemotherapy are not considered candidates for RPLND and are given standard or high-dose salvage chemotherapy. However, a surgical cure remains

TABLE 35-6 Postchemotherapy Retroperitoneal Lymph Node Dissection in High-Risk Populations

STUDY	NO. PATIENTS	TERATOMA (%)	FIBROSIS (%)	VIALE MALIGNANCY (%)	FOLLOW-UP (yr)	CSS OR OS
SALVAGE						
Fox et al, 1993	163	NR	NR	55	5	36.7*
Donohue et al, 1998	166	NR	NR	NR	9.7	61.4
Eggener et al, 2007a	71	21	51	28	5	74
HDCT						
Rick et al, 2004	57	16	38	46	7.3	65
Cary et al, 2011	77	33.8	27.3	39	4.2	71
DESPERATION						
Donohue et al, 1998	150	NR	NR	NR	9.7	66
Ravi et al, 1998	30	26.7	27.6	46.7	4.8	57
Albers et al, 2000	30	11	25	64	11	57
Beck et al, 2005c	114	34.2	12.3	53.5	6	53.9
Ong et al, 2008	48	25	17	58	4.3	69
REDO						
McKiernan et al, 2003	56	37.5	28.6	33.9	4.1† 2.4‡	56
Sexton et al, 2003	21	67	24	24	4.7	63
Heidenreich et al, 2005	18	33.3	44.4	22.2	1.9	89
Willis et al, 2007	54	35	9	56	5	94.2
Pedrosa et al, 2014	203	34	14.8	51.2	5	61.2
LATE RELAPSE						
Baniel et al, 1995a	81	19	0	81	4.8	56.8
George et al, 2003	83	17	0	78	2.4	74.7
Dieckmann et al, 2005	72	NR	NR	NR	NR	58.3
Sharp et al, 2008	75	19	3	78	4.5	61

*Includes only patients with viable malignancy in the survival analysis.

†Follow-up for postchemotherapy retroperitoneal lymph node dissection.

‡Follow-up for primary retroperitoneal lymph node dissection.

CSS, cancer-specific survival; HDCT, high-dose chemotherapy; NR, not reported; OS, overall survival.

possible in selected cases in which chemotherapy has failed to normalize STMs. **Desperation RPLND is resection performed in the setting of elevated STMs.** Pathologic findings at desperation RPLND are listed in Table 35-6. In a review of 114 selected patients undergoing desperation RPLND, Beck and colleagues (2005c) reported a 5-year OS of 53.9% at a median follow-up of 6 years. OS was poorest in patients with viable malignancy demonstrated in the resection specimen, patients who had previously received salvage chemotherapy, patients with increased human chorionic gonadotropin before surgery, or patients who underwent repeat RPLND. Patients who received first-line chemotherapy only and demonstrated declining (but not normalizing) STMs were most likely (>75%) to demonstrate fibrosis and/or teratoma at RPLND. Further chemotherapy would not likely have benefited most of these patients. The authors recommended use of the following selection criteria for desperation RPLND: declining or plateauing STMs after chemotherapy, slowly rising STMs after initial clinical CR to chemotherapy, resectable disease at one or two sites, and as a last resort in a patient with resectable disease and rising STMs after exhausting all reasonable chemotherapeutic options. In a subsequent report on 48 patients by Ong and colleagues (2008), patients with fibrosis at PC-RPLND demonstrated poorer OS than patients with viable malignancy or teratoma likely indicating systemic metastases outside of the retroperitoneum. Patients with postoperative normalization of STMs demonstrated significantly improved OS. This finding was the only prognostic factor that remained robust to multivariable analysis. Outcomes reported in several retrospective desperation series are listed in Table 35-6 (Donohue et al, 1998; Ravi et al, 1998; Albers et al, 2000).

Reoperative Retroperitoneal Lymph Node Dissection

Repeat resection of retroperitoneal recurrence after primary or PC-RPLND has been termed *reoperative* or *redo* RPLND. CSS has been reported to range from 55% to 65% (Donohue et al, 1998; McKiernan et al, 2003; Sexton et al, 2003; Heidenreich et al, 2005; Willis et al, 2007). The reported histologic findings and survival outcomes in reoperative series are listed in Table 35-6. There appears to be a high incidence of GCT with somatic-type malignancy in this population, with a reported incidence of 15% to 20%. Given the technical difficulty of reoperative resections, complications have been reported to occur in approximately one third of patients (McKiernan et al, 2003; Pedrosa et al, 2014). Poorer survival outcomes have been reported in patients demonstrating viable GCT at reoperative RPLND and patients with prior receipt of salvage chemotherapy (McKiernan et al, 2003; Pedrosa et al, 2014).

In most cases, the need for reoperative RPLND likely represents an inadequate primary resection. Several reported findings support this idea. Most patients experience recurrence within the primary landing zone (McKiernan et al, 2003; Heidenreich et al, 2005). Pedrosa and colleagues (2014) reported that ipsilateral recurrence was associated with incomplete ipsilateral lumbar vessel ligation and an unresected ipsilateral gonadal vein. Similarly, Willis and colleagues (2007) reported that 46% of reoperative cases demonstrated retroaortic and/or retrocaval disease, indicating that these regions were omitted from prior RPLND. Using good technique at initial RPLND decreases the likelihood of having to perform a reoperative RPLND.

Late Relapse

Late relapse is defined as recurrence of GCT 24 or more months after CR to primary treatment modalities. This is a rare phenomenon that occurs in 2% to 4% of patients with GCT (Baniel et al, 1995a; Gerl et al, 1997). The retroperitoneum is the most common site of late relapse (Baniel et al, 1995a). Approximately 80% of cases of late relapse contain viable GCT with yolk sac tumor predominating (Baniel et al, 1995a; Michael et al, 2000; George et al, 2003; Sharp et al, 2008). Additionally, there appears to be a disproportionately high incidence of GCT with somatic-type malignancy. When late relapse occurs in patients who previously received

chemotherapy, it is rarely cured by chemotherapy. **Surgical extirpation should be the initial management of all patients with resectable disease at late relapse.** Patients with widespread and/or unresectable disease should be offered chemotherapy in an effort to downsize the tumor burden and render the disease resectable. Reported OS is usually around 60%. Predictors of poorer survival outcomes include viable malignancy or somatic-type malignancy at late relapse, prior chemotherapy, and incomplete resection (Baniel et al, 1995a; George et al, 2003; Sharp et al, 2008).

KEY POINTS: POSTCHEMOTHERAPY RETROPERITONEAL LYMPH NODE DISSECTION IN HIGH-RISK POPULATIONS

- PC-RPLND performed as a salvage, desperation, or reoperative procedure or in the setting of late relapse is associated with significantly poorer survival outcomes than PC-RPLND performed after complete serologic response to induction chemotherapy.
- Viable GCT is encountered in an increased proportion of patients within all of these subpopulations. Additionally, somatic-type malignancy is seen with increased frequency in patients undergoing reoperative RPLND and patients undergoing resection of late relapse disease.
- In general, patients with elevated STMs after induction chemotherapy should receive salvage chemotherapy. Only patients satisfying the above-outlined selection criteria should be considered for desperation RPLND.
- Reoperative RPLND generally indicates an inadequate prior RPLND. Increased complication rates and poorer survival outcomes in this setting highlight the importance of proper surgical technique at initial RPLND.
- Late relapse in patients who previously received chemotherapy is generally chemoresistant. First-line management of late relapse in all patients with resectable disease should be surgical extirpation.

SURGICAL OUTCOMES, FUNCTIONAL CONSIDERATIONS, AND COMPLICATIONS OF RETROPERITONEAL LYMPH NODE DISSECTION

Lymph Node Counts

Higher lymph node counts have been associated with improved oncologic outcomes in various malignancies (Herr et al, 2002; Le Voyer et al, 2003; Schwarz and Smith, 2006, 2007). Given these findings, some investigators have proposed that node counts be used as surrogates for adequacy of lymphadenectomy. In recent years, several groups have investigated lymph node counts in primary and PC-RPLND (Carver et al, 2010; Risk et al, 2010; Thompson et al, 2010, 2011). Although investigators at MSKCC reported a direct correlation between node count and node positivity when evaluating patients with primary RPLND (Thompson et al, 2010), no such association was appreciated in two other studies (Lieberman et al, 2010; Risk et al, 2010). Significant variability in lymph node counts, demonstrated by wide interquartile range and large standard deviation, indicates that node counts are not useful when assessing adequacy of an individual surgery (Risk et al, 2010; Thompson et al, 2010). However, surgeons and treatment centers may consider reviewing their own mean or median lymph node counts to determine if their numbers reflect those reported in the literature for the templates used. If lymph node counts are consistently lower than published standards, there may be a problem related to thoroughness of surgery and/or pathologic processing of specimens obtained.

Retroperitoneal Lymph Node Dissection and Fertility

Fertility in Patients Undergoing Retroperitoneal Lymph Node Dissection

Preserving fertility in men undergoing RPLND is more complex than simply sparing their postganglionic sympathetic nerves. Subfertility in a significant proportion of patients presenting with newly diagnosed testicular cancer is well documented. When including all stages of disease, approximately 40% to 60% of patients presenting with testicular GCT have been reported to demonstrate abnormal parameters on semen analysis (Fossa et al, 1985; Lange et al, 1987; Hansen et al, 1991; Foster et al, 1994). Baseline subfertility needs to be taken into account when evaluating paternity rates after RPLND.

Ejaculatory Dysfunction and Retroperitoneal Lymph Node Dissection

For successful antegrade ejaculation of sperm-containing semen to occur, several processes need to occur in coordinated fashion, as follows: (1) smooth muscle contraction in the vasa deferentia, seminal vesicles, and prostate resulting in seminal emission and prostate glandular secretion along with (2) closure of the bladder neck to prevent retrograde ejaculation and (3) rhythmic contractions of the ischiocavernosus, bulbospongiosus, and levator ani muscles expelling semen from the urethra. Processes 1 and 2 require efferent neurologic input from the L1 through L4 postganglionic sympathetic fibers, which coalesce with their contralateral counterparts in the superior hypogastric plexus. From the hypogastric plexus, these nerve fibers continue caudally to the seminal vesicles, ampulla of the vasa deferentia, vasa deferentia proper, bladder neck, and prostate (Donohue et al, 1990).

Before the development of unilateral modified RPLND templates and nerve-sparing techniques, most patients undergoing bilateral RPLND were rendered anejaculatory (Donohue and Rowland, 1981). In light of the successful nerve preservation techniques established for radical retropubic prostatectomy by Walsh and Donker (1982), testicular cancer surgeons sought to refine the surgical technique of RPLND with the goal of preserving antegrade ejaculation without compromising diagnostic and therapeutic efficacy. Techniques were altered in two ways: (1) changing the boundaries of dissection (Pizzocaro et al, 1985; Weissbach et al, 1985) and (2) prospectively identifying postganglionic sympathetic fibers and the superior hypogastric plexus so that these structures could be preserved during subsequent lymphadenectomy (Jewett et al, 1988).

Early studies on ejaculatory outcomes after modified unilateral template RPLND without nerve-sparing technique reported postoperative antegrade ejaculation in 75% to 87% of patients (Fossa et al, 1985; Pizzocaro et al, 1985; Weissbach et al, 1985). However, in a more recent series, Beck and colleagues (2010) reported preservation of antegrade ejaculation in 97% of men undergoing modified unilateral template dissection without ipsilateral nerve-sparing technique. These superior outcomes likely reflect improved understanding of the anatomy of postganglionic sympathetic nerve fibers allowing for the avoidance of damage to contralateral fibers caudal to the IMA.

Nerve-sparing RPLND results in preservation of antegrade ejaculation in 90% to 100% of patients (Jewett and Torbey, 1988; Donohue et al, 1990; Heidenreich et al, 2003; Beck et al, 2010). Although Jewett and Torbey (1988) reported temporary postoperative anejaculation in most patients, Donohue (1993) observed no such anejaculatory period. In the study by Jewett and Torbey (1988), bilateral template RPLND was performed in all patients, whereas ipsilateral nerve-sparing and modified unilateral template dissections were performed in most patients in the study by Donohue (1993). Neurapraxia likely accounted for the temporary anejaculation reported by Jewett and Torbey (1988).

In addition to demonstrating the efficacy of unilateral template dissection and nerve-sparing techniques in preserving antegrade ejaculation, these studies provided evidence that these new techniques did not compromise oncologic outcomes. With follow-up ranging from 10 months to nearly 5 years, only one retroperitoneal recurrence was reported in the aforementioned series. However, heterogeneous indications for use of post-RPLND adjuvant chemotherapy almost certainly affected recurrence rates.

Over the last 30 years, refinements in the technique of primary RPLND and PC-RPLND have resulted in a significant decrease in the incidence of postoperative ejaculatory dysfunction. Through the use of modified unilateral dissection templates and/or nerve-sparing techniques, preservation of antegrade ejaculation can be expected in greater than 90% of patients in whom at least one of these modalities can be employed. Postoperative paternity can be expected in approximately 75% of men undergoing primary nerve-sparing RPLND (Beck et al, 2010). Fertility after PC-RPLND has not been established because chemotherapy-induced disruption of spermatogenesis can persist for several years after completion of therapy (Lampe et al, 1997).

Complications of Retroperitoneal Lymph Node Dissection

The overall complication rate for primary RPLND has been reported to range from 10.6% to 24% (Baniel et al, 1994; Heidenreich et al, 2003; Subramanian et al, 2010). Reported complication rates for PC-RPLND range from 20% to 30% (Baniel et al, 1995b; Subramanian et al, 2010). Given the paucity of studies on this topic, predictors of complications after RPLND have been inconsistent. When evaluating primary RPLND, investigators at Indiana University reported lower complication rates associated with unilateral dissection and more recent era of surgery. The German Testicular Cancer Study Group found no such correlation between RPLND template and complications. However, investigators reported increased complication rates when RPLND was performed by surgeons with a lower volume of cases and/or at lower volume centers, leading to a recommendation to centralize RPLND to high-volume centers and to minimize the number of surgeons performing these surgeries at each center.

Table 35-7 summarizes reported complications in primary RPLND and PC-RPLND. A review of the incidence, prevention, and management of select complications follows.

Pulmonary Complications

Major pulmonary complications are extremely rare after primary RPLND but have been reported to occur in approximately 3% to 5% of patients after PC-RPLND (Baniel et al, 1994, 1995b; Heidenreich et al, 2003; Subramanian et al, 2010). Because most patients who undergo PC-RPLND have received bleomycin-containing induction chemotherapy, acute respiratory distress syndrome and prolonged postoperative ventilation account for most of these major complications. The incidence of bleomycin-related perioperative pulmonary complications can be minimized by avoiding aggressive intraoperative and postoperative intravenous fluid resuscitation and keeping FiO_2 as low as is safely possible (Goldiner et al, 1978; Donat and Levy, 1998). The importance of working with an anesthesiologist who has experience in managing patients who previously received bleomycin cannot be overstated. Pulmonary complications are most likely to be encountered in patients with large-volume pulmonary disease, particularly if simultaneous retroperitoneal and thoracic resections are to be performed (Baniel et al, 1995b).

Ileus

The reported rates of postoperative paralytic ileus range widely in the primary RPLND (0% to 18%) and PC-RPLND (2.2% to 21%) settings. This variation likely stems from differences in the definitions of ileus. In relatively low-volume PC-RPLND, an orogastric tube is used and removed at the conclusion of the procedure. In

TABLE 35-7 Complications of Retroperitoneal Lymph Node Dissection

	PRIMARY RPLND			PC-RPLND	
	BANIEL ET AL, 1994	HEIDENREICH ET AL, 2003	SUBRAMANIAN ET AL, 2010	BANIEL ET AL, 1995b	SUBRAMANIAN ET AL, 2010
No. patients	478	239	112	603	96
Overall complications (%)	10.6	19.7	24	20.7	32
Major complications (%)	8.2	5.4	3	NS	8
Mortality (%)	0	0	0	0.8	1
Major pulmonary (%)	1.9	0.8	0.9	5.1	3.1
Minor pulmonary (%)	0.2	0.4	3.6	5.1	3.1
Chylous ascites (%)	0.2	2.1	2	2	2
Symptomatic lymphocele (%)	0.2	1.7	0	1.7	1
Ileus (%)	NR	2.1	17.9	2.2	20.8
Wound infection (%)	4.8	5.4	0.9	4.8	4
Pulmonary embolism (%)	0	0.8	0.9	0.1	3.1
Ureteral injury (%)	0.2	0.4	0.9	0.9	0
Small bowel obstruction (%)	2.3	0.4	2.7	2.3	1.8
Postoperative hemorrhage (%)	0	0.8	0	0.3	1

NR, not reported; NS, not studied; PC-RPLND, postchemotherapy retroperitoneal lymph node dissection; RPLND, retroperitoneal lymph node dissection.

higher volume disease, the probability of significant ileus is greater, and a nasogastric tube should be used.

Lymphocele

The incidence of subclinical lymphocele after RPLND is unknown. However, it is thought that lymphoceles are relatively common and clinically insignificant in most cases. Symptomatic retroperitoneal lymphoceles are extremely rare with reported rates ranging from 0% to 1.7% (Baniel et al, 1994, 1995b; Heidenreich et al, 2003; Subramanian et al, 2010). Symptoms can be related to ureteral compression, displacement of abdominal viscera (if very large), or secondary infection. CT scan demonstrates a thin-walled cystic lesion in the resection bed. Air within the lymphocele and/or rim enhancement should raise concern for an infection. **Meticulous attention to ligation of large-caliber lymphatics during resection likely decreases the risk of developing a symptomatic lymphocele.** Treatment of symptomatic and/or infected lymphoceles includes percutaneous drainage with systemic antibiotics reserved for infected lymphoceles. Additionally, in the setting of infected lymphocele, one should consider leaving an indwelling drain rather than simple percutaneous aspiration.

Chylous Ascites

Chylous ascites refers to the accumulation of chylomicron-containing lymphatic fluid in the peritoneal cavity. **Chylous ascites has been reported to occur in 0.2% to 2.1% of patients undergoing primary RPLND and 2% to 7% of patients undergoing PC-RPLND** (Baniel et al, 1994, 1995b; Heidenreich et al, 2003; Evans et al, 2006; Subramanian et al, 2010). Patients typically present with complaints of increasing abdominal fullness, anorexia, nausea, vomiting, abdominal pain, and dyspnea. Patients often have a fluid wave on abdominal examination, which can help distinguish ascites from an ileus. Additionally, accumulated peritoneal fluid results in significant weight gain. Fluid has a milky color if paracentesis is performed. Chylous ascites is alkaline, stains positive for Sudan black, and demonstrates a triglyceride concentration greater than that of serum. However, these tests are usually unnecessary because clinical examination and/or gross inspection of aspirating fluid should be enough to confirm the diagnosis.

Suprahilar resections are thought to carry a higher risk for chylous ascites because of disruption of the cisterna chyli and

its contributing lymphatics. The cisterna chyli is located at the level of the L1-2 vertebral bodies, medial to the posterior surface of the aorta in the retrocrural space. The association of IVC resection and chylous ascites is thought to be related to increased venous pressure below the level of the IVC producing increased capillary leak and ultimately third spacing of lymphatic fluid into the retroperitoneum (Baniel et al, 1993). In a review of the M.D. Anderson Cancer Center experience, Evans and colleagues (2006) found increased number of preoperative cycles of chemotherapy, increased estimated blood loss, and longer operative time to be associated with development of chylous ascites.

We recommend a graduated approach to the management of chylous ascites. In general, patients with symptomatic chylous ascites should first be managed with paracentesis. Although an indwelling drain can be left, we recommend simple paracentesis with consideration of low-fat/medium-chain triglyceride diet and intramuscular octreotide. If ascites reaccumulates, an indwelling drain should be placed. If these dietary modifications have already been instituted, patients should be given nothing by mouth, and total parenteral nutrition should be initiated. Although the use of octreotide in the setting of chylous ascites has not been studied in the urologic literature, it has demonstrated efficacy in minimizing chylous leaks after hepaticopancreaticobiliary surgery (Shapiro et al, 1996; Kuboki et al, 2013). Persistent high-volume chylous drainage (>100 mL/24 hr) despite these modifications is exceedingly rare. When it does occur, options include continued observation with conservative management, placement of a peritoneovenous (LeVeen) shunt, or surgical exploration with attempted ligation of the lymphatic leak. The latter two options should be reserved as last resorts. Peritoneovenous shunts have been reported to be associated with a significant incidence of occlusion and/or malfunction often requiring revision after placement, sepsis, and potentially fat embolization (Evans et al, 2006). Regardless of treatment modality that ultimately results in resolution of chylous ascites, consideration should be given to a continued low-fat diet with medium-chain triglycerides for 1 to 3 months after resolution of lymph leak.

Venous Thromboembolism

Venous thromboembolism (VTE) rates reported after primary RPLND and PC-RPLND are consistently low; this is likely the result

of a young, otherwise healthy patient population. The rate of pulmonary embolism after primary RPLND has been reported to be less than 1% (Baniel et al, 1994; Heidenreich et al, 2003; Subramanian et al, 2010). After PC-RPLND, the rates range from 0.1% to 3.1% (Baniel et al, 1995b; Subramanian et al, 2010). The incidence of deep venous thrombosis is more difficult to determine because these cases are not consistently reported in the literature and are likely most often asymptomatic. Reported rates range from 0% to 1% in primary RPLND and PC-RPLND (Heidenreich et al, 2003; Subramanian et al, 2010).

All patients undergoing RPLND should have sequential compression devices placed before induction, which should be maintained throughout the hospital course. Ambulation should be resumed on postoperative day 1 in virtually all cases. The use of pharmacologic prophylaxis has never been evaluated in patients undergoing RPLND. Prophylactic subcutaneous low-dose unfractionated heparin or low-molecular-weight heparin has demonstrated efficacy in decreasing VTE rates in postoperative patients (Collins et al, 1988; Kakkar et al, 1993). The potential disadvantages are an increased risk for postoperative hemorrhage and anecdotal reports of increased risk for lymphocele. Retrospective studies on patients undergoing radical prostatectomy reported conflicting results with regard to the effect of postoperative pharmacologic thromboprophylaxis on pelvic lymphocele formation (Bigg and Catalona, 1992; Koch and Jr, 1997; Schmitges et al, 2012). The decision to use pharmacologic thromboprophylaxis needs to be made based on the low incidence of VTE in patients undergoing RPLND and extrapolation of data based on risk/benefit data from other surgeries and specialties. Pharmacologic thromboprophylaxis is likely most important in patients who are at an increased risk for postoperative VTE, such as patients with a personal history of VTE, obesity, known hypercoagulable condition, or older age.

Neurologic Complications

In the Indiana PC-RPLND review, no cases of paraplegia were noted. Seven cases of peripheral nerve injury were reported (Baniel et al, 1995b). All of these cases were secondary to patient positioning and potentially retractor placement (femoral neurapraxia). Careful attention to appropriate patient positioning by the surgical and anesthesia teams is important in minimizing peripheral nerve damage. In a review of 268 patients undergoing postchemotherapy resection of mediastinal disease for testicular or primary retroperitoneal GCT, Kesler and colleagues (2003) reported 6 patients (2.2%) with paraplegia. Patients with bulky mediastinal and retroperitoneal disease are at an increased risk of developing paraplegia. The likelihood of neurologic complications increases with the scale of para-aortic resection.

Mortality

Reported mortality after primary RPLND is essentially zero (Baniel et al, 1994; Heidenreich et al, 2003; Capitanio et al, 2009; Subramanian et al, 2010). Mortality after PC-RPLND is extremely rare and generally reported to be less than 1% (Baniel et al, 1995b; Capitanio et al, 2009; Subramanian et al, 2010). In a review of the Indiana University experience, 5 of 603 patients (0.8%) died after PC-RPLND (Baniel et al, 1995b). Causes of death were severe respiratory distress in two patients, multiple organ failure in one patient, fungal sepsis in one patient, and myocardial infarction after aorticoduodenal fistula in one patient. In a population-based study of 882 patients having undergone RPLND, Capitanio and colleagues (2009) used the Surveillance, Epidemiology, and End Results (SEER) database to determine if mortality rates previously reported by centers of excellence were applicable to the community. Although receipt of chemotherapy was not reported, there were no mortalities among patients with localized disease, whereas mortality rates of 0.8% and 6% were reported among patients with retroperitoneal disease and distant metastases, respectively.

KEY POINTS: SURGICAL OUTCOMES, FUNCTIONAL CONSIDERATIONS, AND COMPLICATIONS OF RETROPERITONEAL LYMPH NODE DISSECTION

- Through the use of modified unilateral templates and nerve-sparing techniques, preservation of antegrade ejaculation can be expected in nearly all patients undergoing primary RPLND. Similar success rates are possible in patients undergoing PC-RPLND when one or both of these techniques can be safely performed. However, this is often impossible in patients with large retroperitoneal masses.
- Major complications are rare after primary RPLND and PC-RPLND. A significant proportion of major complications at PC-RPLND are pulmonary and are related to prior bleomycin and thoracic disease burden. Anesthesia providers play a key role in minimizing these events.
- Although very rare, chylous ascites can be a challenging complication to manage. Careful attention to retroperitoneal lymphatic anatomy with ligation of large-caliber lymphatics is thought to minimize the risk of this complication.
- A graduated approach to the management of chylous ascites is recommended.
- Paraplegia after RPLND is vanishingly rare. However, patients undergoing resection of large-volume retroperitoneal and visceral mediastinal disease should be counseled regarding the potential for this devastating complication.

RETROPERITONEAL LYMPH NODE DISSECTION IN UNIQUE SITUATIONS

Postchemotherapy Retroperitoneal Lymph Node Dissection for Seminoma

Pure seminoma is a particularly chemosensitive tumor with CR rates of 70% to 90% being reported in patients with disseminated disease treated with cisplatin-based chemotherapy (Loehrer et al, 1987; International Germ Cell Consensus Classification, 1997; Gholam et al, 2003). Residual masses are relatively common after treatment of seminoma owing to the intense desmoplastic reaction occurring in response to chemotherapy. In most series of PC-RPLND performed for pure seminoma, viable malignancy is encountered in approximately 10% of cases, with remaining patients demonstrating only fibrosis (Herr et al, 1997; Ravi et al, 1999; Flechon et al, 2002). Additionally, PC-RPLND for seminoma has been associated with increased perioperative morbidity compared with PC-RPLND for NSGCT (Friedman et al, 1985; Fossa et al, 1987; Mosharafa et al, 2003b). Various thresholds for operative intervention have been derived with the common goal of avoiding an often unnecessary and potentially morbid surgery.

In a review of 55 patients treated at MSKCC with pure testicular seminoma and available postchemotherapy retroperitoneal pathology (RPLND or biopsy), 30% of patients with masses 3 cm or larger had viable retroperitoneal seminoma or teratoma at resection, whereas none of the patients with smaller masses harbored residual disease (Herr et al, 1997). Investigators recommended RPLND in patients with pure seminoma with residual masses 3 cm or larger. Conversely, investigators at Indiana University reported no association between residual mass size and disease recurrence/progression on observation in their experience with 21 patients. The authors recommended observing all residual masses with resection reserved for patients demonstrating serologic or radiographic evidence of progression (Schultz et al, 1989).

More recently, PET has been used to assess for the presence of viable seminoma in residual masses. In this capacity, PET scans have a negative predictive value approaching 100%. However, false-positive PET scans have resulted in inconsistent positive predictive values ranging from 67% to 100% in two studies (De Santis et al,

2004; Lewis et al, 2006). In light of these findings, some guidelines propose that patients without residual masses or a residual mass less than 3 cm be observed and patients with larger masses be evaluated with a PET scan 6 weeks after completing chemotherapy. Patients with PET-avid masses are managed with RPLND, standard-dose salvage chemotherapy, or HDCT. Of these three modalities, HDCT has demonstrated the best survival outcomes with 92% OS when it is used in the second-line setting (Agarwala et al, 2011). In a review of 36 patients with pure seminoma demonstrating viable seminoma at PC-RPLND, Rice and colleagues (2012) reported a 54% CSS with only 9 patients (25%) remaining continuously disease-free after resection. Given the superior survival outcomes associated with HDCT, this modality is preferred for most patients with pure seminoma who relapse after induction chemotherapy. However, PC-RPLND may continue to have a role for management of patients who relapse with focal, easily resectable masses to avoid the potential morbidity of HDCT. Ultimately, the decision needs to be made based on predicted morbidity of resection versus HDCT.

Retroperitoneal Lymph Node Dissection for Sex Cord–Stromal Tumors

Sex cord–stromal tumors (SCSTs) account for 4% to 5% of all testicular neoplasms and include Leydig, Sertoli, and granulosa cell tumors as well as various combinations of these histologies. It is estimated that 10% to 20% of adult SCSTs are malignant (Kim et al, 1985; Grem et al, 1986; Kratzer et al, 1997). Although the presence of metastatic disease is the only reliable indicator of malignant phenotype, various primary tumor characteristics have been evaluated for their ability to predict aggressive behavior. Features seeming to correlate with aggressive behavior have been fairly similar when examining the distinct subtypes of SCSTs. These characteristics include older age, primary tumor size larger than 4 to 5 cm, necrosis, mitotic rate greater than three to five per 10 high-power fields, moderate-to-severe nuclear atypia, infiltrative tumor margins/invasion of adjuvant structures, and lymphovascular invasion (Kim et al, 1985; Dilworth et al, 1991; Kratzer et al, 1997; Young et al, 1998). Multiple features predictive of malignant phenotype frequently occur in the same patients, with patients demonstrating a malignant disease course often possessing two or three malignant characteristics (Kim et al, 1985; Young et al, 1998). Some experts recommended that tumors possessing two or more such features be categorized as malignant (Kratzer et al, 1997; Silberstein et al, 2013). However, prediction of malignant behavior based on histology is not as accurate as in GCT.

The role of RPLND in the treatment of SCST is unclear. Arguments for use of RPLND in treatment of this disease are as follows: (1) Retroperitoneal nodes are consistently the most common (and likely the first) site of metastases in reported series (Kim et al, 1985; Kratzer et al, 1997; Young et al, 1998); (2) CS I patients can go on to develop retroperitoneal metastases at widely ranging time intervals indicating that early primary RPLND could perhaps prevent these recurrences (Mosharafa et al, 2003a); (3) there have been isolated reported cases of surgically cured patients with microscopic deposits of SCST in RPLND specimens (Lockhart et al, 1976; Gohji et al, 1994; Mosharafa et al, 2003a; Silberstein et al, 2013); and (4) although these tumors have been reported to demonstrate partial responses to chemotherapy, cures have not been documented.

Arguments against performing RPLND are as follows: (1) Primary tumor histologic predictors of malignant behavior have demonstrated inconsistent performance making patient selection difficult (Mosharafa et al, 2003a; Silberstein et al, 2013), and (2) although there have been some surgical cures reported in the literature, follow-up is often too short to confirm cure, and most patients with positive retroperitoneal nodes die of their disease. At the present time, no conclusive recommendation can be made regarding the use of RPLND in managing patients with SCST. The aforementioned advantages and disadvantages should be discussed with


the patient to allow him to make an informed decision regarding management.

KEY POINTS: RETROPERITONEAL LYMPH NODE DISSECTION IN UNIQUE SITUATIONS


- PC-RPLND is rarely performed in the setting of seminoma given the chemosensitivity of this histology, the technical difficulty of these resections, and the excellent response to HDCT.
- The role of RPLND in the treatment of SCST has not been definitively demonstrated given the rarity of malignant forms of these tumors.

CONCLUSION

Over the last 50 years, the field of testicular cancer has undergone a striking evolution through the parallel development and integration of more effective and less toxic chemotherapeutic regimens and the continued refinement of techniques for surgical resection. These advances have resulted in delivery of durable cures to more than 90% of patients with testicular cancer, while minimizing acute and long-term morbidity. These excellent outcomes can be achieved only through strict adherence to established therapeutic principles. Although treatment of patients with testicular cancer often requires an experienced multidisciplinary team, the successful management of nearly every patient with testicular cancer begins with his urologist. All urologists should have a thorough and nuanced understanding of the appropriate treatment of testicular cancer. This understanding helps to ensure expeditious delivery of appropriate medical and surgical treatment with early referral to high-volume centers when necessary. The success of surgical management of testicular tumors is measured not only by survival outcomes but also by minimizing morbidity through avoidance of unnecessary surgeries and functional preservation whenever possible.

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Rationale and Evolution

Staging Laparoscopic Retroperitoneal Lymph Node Dissection and Controversy

Duplication of Open Retroperitoneal Lymph Node Dissection

Development of Robotic-Assisted Retroperitoneal Lymph Node Dissection

Surgical Technique

Postoperative Care

Prospective Nerve-Sparing Techniques

Complications

Results and Current Status

Summary

Germ cell tumors (GCTs) are the most common malignancy in men between the ages of 15 and 35 (Carver and Sheinfeld, 2005). Testicular cancer is also one of the most curable solid-organ neoplasms, owing in large part to an excellent multimodal treatment paradigm that includes effective platinum-based chemotherapy and surgery (Einhorn, 1981). **Although contemporary survival rates for GCTs are more than 90%, cure rates and patient morbidity depend on selection of the management options.** Retroperitoneal lymph node dissection (RPLND) plays a major role in the management of patients with GCTs. The role of surgery continues to evolve owing to advances in chemotherapy regimens, clinical staging modalities, and continued surgical innovation (Sheinfeld and Herr, 1998; Allaf et al, 2005; Albers et al, 2008).

Primary chemotherapy is favored in Europe, whereas RPLND traditionally has been the management strategy of choice in the United States for high-risk patients with clinical stage I nonseminomatous germ cell tumor (NSGCT). RPLND can accurately stage the retroperitoneum and positively identify patients harboring metastases. In addition, patients with pathologic stage I disease are spared the toxicity and morbidity of any additional therapy because 90% or more experience long-term disease-free survival with surgery alone. Patients with pathologic stage II disease can learn more about the extent of their disease and make informed decisions regarding further therapy after RPLND. For patients in this group who harbor small-volume retroperitoneal disease (pN1), a properly performed RPLND can be curative in approximately 70% of men, so chemotherapy also can be avoided in this setting (Richie and Kantoff, 1991; Donohue et al, 1993; Rabbani et al, 2001). Because the retroperitoneum is the most frequent site of chemoresistant malignant GCT and teratoma, both of these processes are minimized with RPLND (Baniel et al, 1995). Some groups advocate RPLND as the treatment of choice for all men with clinical stage I NSGCT with teratoma in the orchiectomy specimen given the increased propensity of harboring teratoma in the retroperitoneum (Sheinfeld et al, 2003). RPLND eliminates these chemoresistant elements and maximizes therapeutic efficacy.

Traditionally, RPLND for GCTs has been performed via an open transabdominal or thoracoabdominal approach. Over the past two decades, minimally invasive approaches for the treatment of various malignancies have emerged and become popular. Since the early

1990s, retroperitoneal laparoscopic surgery has been used with proven benefits related to reducing perioperative morbidity, improving cosmesis, and shortening convalescence without compromising oncologic efficacy (Cadeddu et al, 1998; Allaf et al, 2004; Permpongkosol et al, 2005). Laparoscopic RPLND (L-RPLND) and more recently robotic-assisted RPLND (RA-RPLND) are technically demanding procedures that are increasingly being performed by experienced surgeons aiming to minimize morbidity while duplicating the open technique. **Given that untreated retroperitoneal disease and late relapses in the retroperitoneum are fatal and can be chemorefractory, it is of paramount importance that, as in open RPLND, a complete “cleanout” of lymph nodes is performed** (Whitmore, 1979; Borge et al, 1988; Baniel et al, 1995; Carver et al, 2005).

In this chapter, the evolution of L-RPLND and RA-RPLND is summarized. Controversies surrounding their use, surgical techniques, outcomes, and associated complications are discussed. The focus is on the management of low-stage NSGCTs and the role of these minimally invasive approaches after chemotherapy.

RATIONALE AND EVOLUTION

In an effort to decrease the morbidity associated with open RPLND, shortly after the introduction of laparoscopic renal surgery in 1991, several reports emerged documenting the feasibility of L-RPLND in the management of clinical stage I NSGCT (Rukstalis and Chodak, 1992; Stone et al, 1993; Klotz, 1994). Larger retrospective series followed suggesting decreased blood loss, shorter hospital stays, and faster return to normal activity compared with open RPLND, with preservation of antegrade ejaculation in more than 95% of patients (Gerber et al, 1994; Janetschek et al, 1994, 1996). An early multi-institutional retrospective analysis demonstrated preservation of antegrade ejaculation in all patients, short hospital stays (<3 days), and return to normal activity at 2 to 3 weeks postoperatively (Gerber et al, 1994). **The abbreviated convalescence allows patients who are candidates to receive chemotherapy with minimal delay.** These attractive early results encouraged others to investigate L-RPLND as a viable treatment option for low-stage NSGCT.

STAGING LAPAROSCOPIC RETROPERITONEAL LYMPH NODE DISSECTION AND CONTROVERSY

Of all laparoscopic applications to surgical urology, L-RPLND has raised the most controversy. This controversy is due to the technical difficulty of RPLND in general, the limited number of cases, and lack of interest at traditional centers of excellence. Laparoscopy is an access technique with the internal procedure being performed the same as with an open incision. Experience drives an equivalent dissection. In all early series and some contemporary studies, L-RPLND was used as a staging procedure (Bianchi et al, 1998; Janetschek et al, 2000). Patients not harboring occult metastases were identified and spared exposure to chemotherapy without undergoing open RPLND. In this form, L-RPLND was performed without retrocaval or retroaortic dissection, and chemotherapy was given to all patients harboring metastatic disease (including patients with pN1 disease). The decision to omit dissection behind the great vessels was based on the belief of a lack of isolated positive lymph nodes in this area (Holtl et al, 2002). Within this paradigm, the procedure was routinely aborted if positive lymph nodes were encountered, and chemotherapy was instituted in these cases (Bianchi et al, 1998; Nelson et al, 1999). In contemporary series, this approach has been abandoned, and L-RPLND has evolved into a therapeutic procedure duplicating the open approach in its intent (Allaf et al, 2005; Steiner et al, 2008; Hyams et al, 2012).

The use of restrictive template boundaries coupled with the universal use of chemotherapy in men harboring pathologic stage II disease generated criticism of published L-RPLND series. The controversy regarding the use of “staging” L-RPLND hinges on mapping studies demonstrating increased multifocality and contralateral disease in the presence of positive retroperitoneal nodes (Ray et al, 1974; Donohue et al, 1982; Weissbach and Boedefeld, 1987; Eggener et al, 2007). Critics argue that the liberal use of chemotherapy would not prevent relapses and compensate for incomplete resection.

DUPLICATION OF OPEN RETROPERITONEAL LYMPH NODE DISSECTION

At experienced centers at the present time, an exact replication of the open template is performed on all patients with NSGCT undergoing L-RPLND with wide templates and complete excision of retroaortic and retrocaval tissue, rendering the procedure both a staging and a therapeutic operation. Some groups perform a bilateral dissection on all patients, whereas others reserve bilateral dissection for patients with lymph node involvement (Allaf et al, 2005; Steiner et al, 2008).

DEVELOPMENT OF ROBOTIC-ASSISTED RETROPERITONEAL LYMPH NODE DISSECTION

Robotic technology has become ubiquitous within the urologic oncology community, and it is believed to have facilitated a minimally invasive approach to complex urologic operations such as radical prostatectomy and partial nephrectomy. Robotic technology has been shown to increase use of partial nephrectomy, likely owing to perceived ease in facility of this complex laparoscopic procedure (Patel et al, 2013). Given the wide range of robotic procedures performed by urologists and given that L-RPLND requires a complex laparoscopic skill set, small case series of RA-RPLND have emerged demonstrating safety and feasibility (Daval et al, 2006; Williams et al, 2011).

SURGICAL TECHNIQUE

L-RPLND is a technically challenging procedure associated with a steep learning curve and should be undertaken by experienced laparoscopic surgeons who are comfortable and adept with advanced

vascular techniques and open surgery in case of conversion. The indications for primary L-RPLND are identical to the indications for open RPLND and include clinical stage I or IIA disease, negative serum tumor markers, and the absence of comorbidities that would preclude safe surgery. In the postchemotherapeutic setting, L-RPLND has been limited mainly to small-volume residual disease; however, experienced surgeons have excised bulky tumors. **The surgical template for the procedure is dictated by laterality and intraoperative findings. Surgical margins should not be compromised to minimize morbidity, to preserve ejaculation, or because of technical constraints. The extent of the node dissection can be expanded based on intraoperative findings.**

Preoperative Patient Preparation and Technical Considerations

All patients considered candidates for L-RPLND must be fully informed of all treatment options, including open RPLND, chemotherapy, and surveillance. All potential complications including bleeding requiring blood transfusion; injury to adjacent organs (liver, bowel, gallbladder, kidney, ureter, pancreas, major vascular structures); and orthopedic, neurologic, or pulmonary complications as well as conversion to open surgery because of complications or incomplete resection should be discussed (Allaf et al, 2005; Winfield, 1998). Patients interested in future fertility are educated regarding preoperative sperm banking. Some surgeons advocate a low-fat diet 1 to 2 weeks before surgery to reduce the risk of chylous ascites, but data regarding this practice are not definitive. Patients undergo a mechanical bowel preparation the afternoon before surgery and take only clear liquids until midnight to decompress the bowels. Preoperative antibiotics are given before surgery, and antiembolism devices are placed on the lower extremities to minimize deep vein thrombosis.

Standard laparoscopic instruments are used throughout this procedure (e.g., atraumatic graspers, scissors, clip appliers, irrigation/suction device, and laparoscopic paddle retractor). Radiolucent polypropylene clips (Hem-o-lok; Weck Closure Systems, Triangle Park, NC) may minimize artifact on postoperative imaging of the retroperitoneum. In addition, a needle driver loaded with suture and adjunct hemostatic agents such as gelatin matrix (FloSeal Matrix Hemostatic Sealant; Fusion Medical Technologies, Fremont, CA) or oxidized cellulose (Surgicel; Ethicon, Piscataway, NJ) should be readily available in case of vascular injury. Sealing devices such as ultrasonic shears and bipolar devices should be used with caution and can be unreliable in sealing large lymphatic channels. A laparoscopic retractor is particularly useful for medial retraction of the bowel and alleviates the need to position the patient in a modified flank position. A gauze sponge placed in the abdomen can be helpful in tamponading bleeding.

Approach

Although some surgeons use an extraperitoneal approach (Hsu et al, 2003; Hara et al, 2004), most prefer a transperitoneal approach owing to the larger and more familiar working space. **Additionally, a transperitoneal approach facilitates bilateral dissection when warranted by allowing access to all four quadrants.**

Patient Positioning and Port Placement for Laparoscopic Retroperitoneal Lymph Node Dissection

After general anesthesia is induced, an orogastric tube and Foley catheter are inserted. The patient may be placed in the modified flank position (45 degrees) with the side of dissection elevated, but we prefer the supine position because it makes transitioning to a bilateral dissection less cumbersome and does not require patient repositioning (Fig. 36-1). Great care is taken to pad all pressure points to minimize the risk of nerve injury or rhabdomyolysis because these surgeries may require a longer time than their open

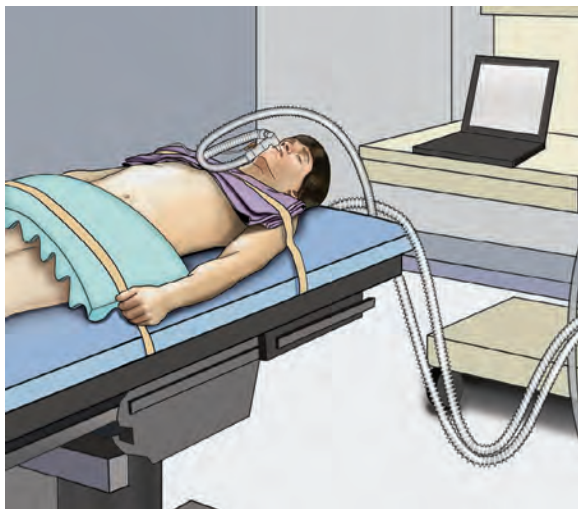


Figure 36-1. Patient positioning during laparoscopic retroperitoneal lymph node dissection. The arms are tucked, and the patient is padded and secured in a relatively supine position.

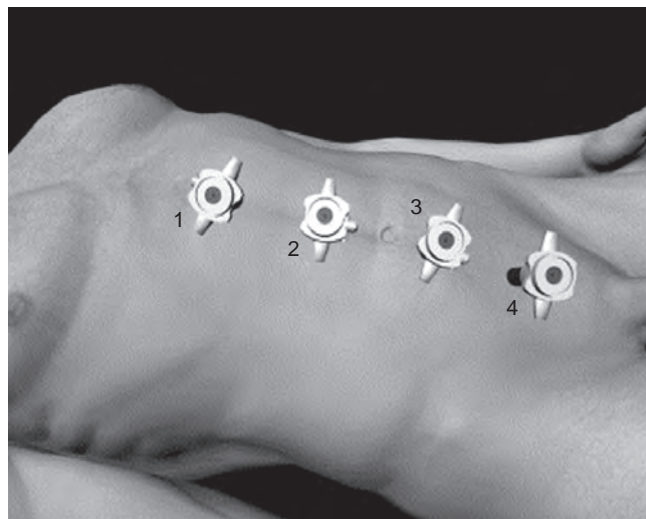


Figure 36-2. Port placement for laparoscopic retroperitoneal lymph node dissection. Four 10/12-mm, equally spaced trocars are placed in the midline.

counterpart. The patient must be secured to the operating table because tilt is needed to use gravity to help shift the bowel out of the operative field.

After intraperitoneal access is achieved (via a Veress needle or Hasson technique), four equally spaced, 10/12-mm laparoscopic ports are placed in the midline beginning 1 cm below the xiphoid process (Fig. 36-2). The umbilicus may not be incorporated as a port site. The large port size is essential to allow for the convenient introduction of larger (10/12-mm) instruments from varying angles. An additional 5-mm port may be placed in the midaxillary line midway between the iliac crest and ribs for additional retraction if needed. The bed is rotated maximally to allow optimal medialization of the bowel away from the operative field.

Right-Sided Dissection

The ascending colon is mobilized by incising the white line of Toldt from the pelvis and around the hepatic flexure. The second portion of the duodenum is identified and Kocherized, providing exposure of the retroperitoneum including the medial para-aortic space on the left.

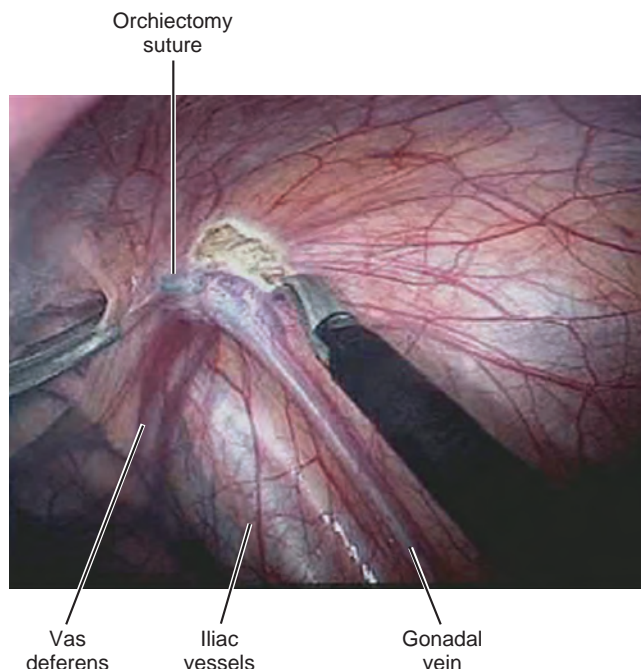


Figure 36-3. Incision of posterior peritoneum circumferentially around the inguinal ring.

Spermatic Cord Dissection

The camera is moved to the second to the bottom trocar (trocar 3 in Fig. 36-2) to facilitate visualization during dissection of the spermatic cord stump. The peritoneum medial to the spermatic cord is incised, and the vas deferens is transected. The peritoneum is incised circumferentially around the inguinal ring (Fig. 36-3). With gentle traction on the cord, fibrous attachments and scar are incised until the suture on the spermatic cord is identified. The attachments are cut, and the cord is followed proximally along with surrounding nodal and fibroadipose tissue to the inferior vena cava (IVC). The ureter must be identified at all times to prevent inadvertent thermal injury. The spermatic vein and artery are ligated proximally and transected. The specimen is placed in an endobag and dropped on the contralateral side of the abdomen.

Lymphadenectomy

Although templates should be individualized to each case, we advocate removal of the right common iliac, paracaval, interaortocaval, preaortic, and medial para-aortic nodes (Fig. 36-4). Occasionally in obese patients (or when performing a full bilateral dissection), the left-most border of the dissection must be performed after rotating the table contralaterally to optimize exposure. The camera should be moved to the port second from the top. A paddle retractor is placed in the lowest trocar to protect and sweep the bowel medially.

The testicular vein stump is identified and minimally manipulated to prevent pseudoaneurysm formation with subsequent rupture. The tissues overlying the IVC are gently lifted and carefully incised longitudinally (Fig. 36-5). It is swept off the IVC in a “split and roll” fashion. Blunt dissection aids in further separating these lymphatic tissues toward and overlying the common iliac vessels inferiorly and renal hilum superiorly. Care must be taken to avoid injury of lower pole renal arteries, which are present in approximately 20% of cases, and accessory vessels crossing anterior to the IVC. The renal hilum is dissected to separate all fibroadipose tissue from the renal vein and artery as far under the IVC as possible. Next, the ureter is traced to its crossing over the common iliac vessels, and the lymphatic packet is separated from both of these structures.

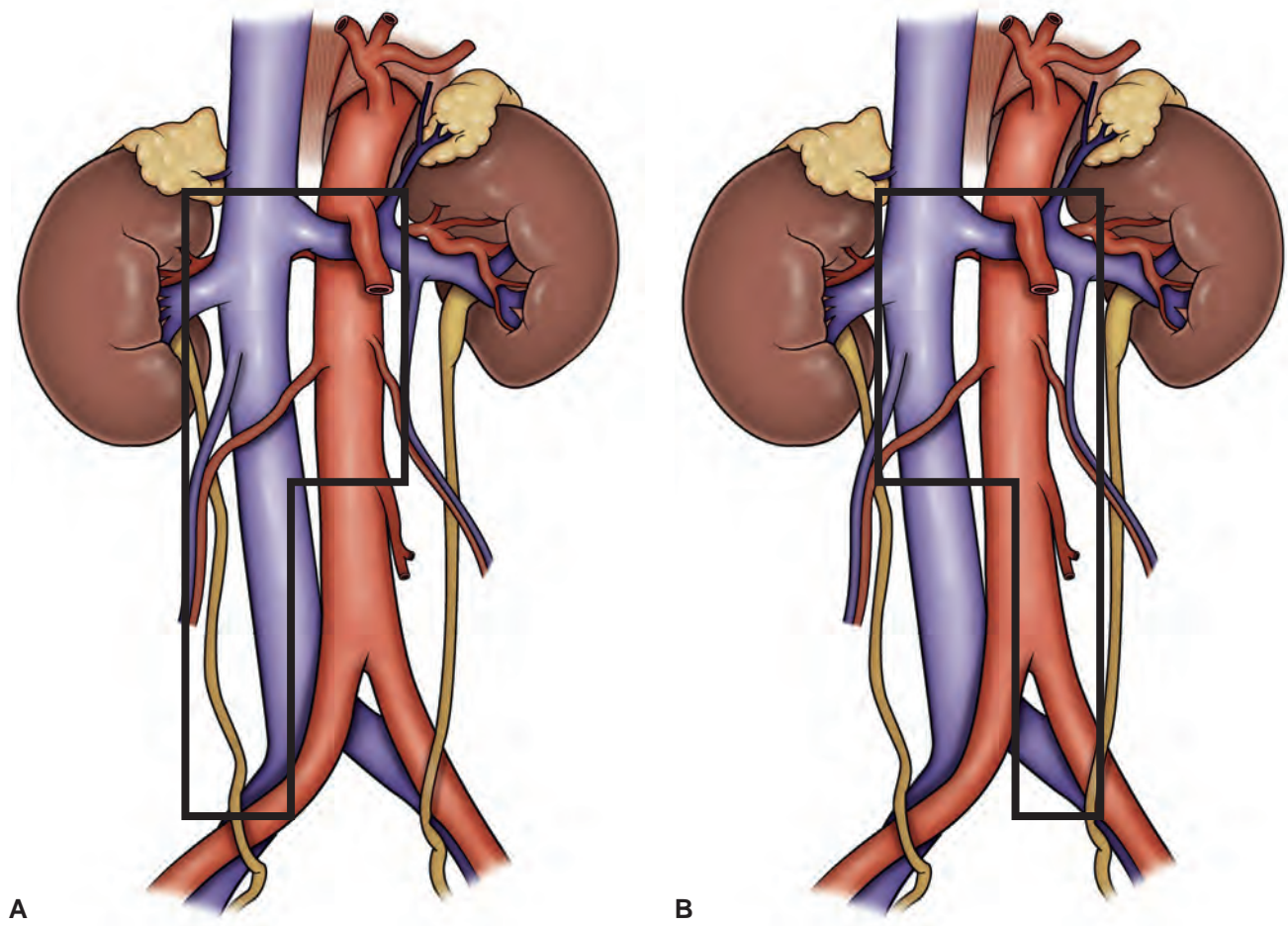


Figure 36-4. Suggested templates for right (A) and left (B) therapeutic laparoscopic retroperitoneal lymph node dissection. These templates can be expanded or contracted based on each patient's tumor.

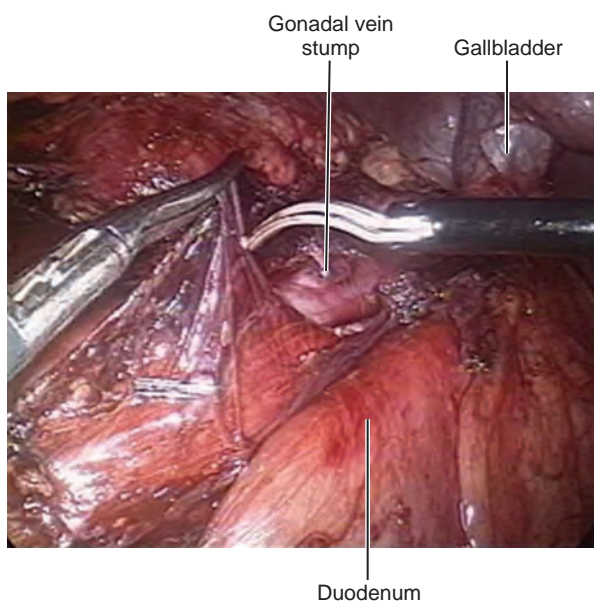


Figure 36-5. Fibrofatty tissue overlying the inferior vena cava being incised to initiate the “split and roll” technique. The duodenum has been reflected medially, and the spermatic vein stump has been clipped and divided.

The “split” tissue along the IVC is “rolled” medially to expose the retrocaval space. Lumbar vessels are identified, clipped, and divided to allow splitting of the posterior lymphatic tissues (Fig. 36-6). After this splitting is accomplished, the tissues are released from their attachment to the spine and delivered laterally. Great care is taken to separate the lymph nodes from the sympathetic chain and post-ganglionic nerve fibers. The aorta is identified next, and the tissues overlying it are similarly split to the level of the inferior mesenteric artery and rolled medially to enter the retroaortic space. The lumbar arteries may be controlled if additional mobility is needed to mobilize the interaortocaval packet posteriorly. The aorta can be medially retracted, facilitating para-aortic node excision with careful preservation of the sympathetic chain laterally. The interaortocaval nodes finally are removed to complete the dissection.

An important technical point is to leave a long stump on the aorta/vena cava side when ligating lumbar vessels such that they can be grasped and controlled in the event a clip dislodges. Lumbar vessels that retract into the iliopsoas uncontrolled usually can be managed with pressure or a figure-of-eight suture placed deep into the muscle. Lacerations of the IVC and aorta may occur during this operation but in most cases do not mandate open conversion. Direct pressure usually prevents excessive hemorrhage and can achieve hemostasis without the need for additional maneuvers. Adjunct hemostatic agents also can be used successfully in this circumstance. If the bleeding persists, or in the case of arterial bleeding, direct pressure can be used temporarily before definitive repair is undertaken with intracorporeal suturing.

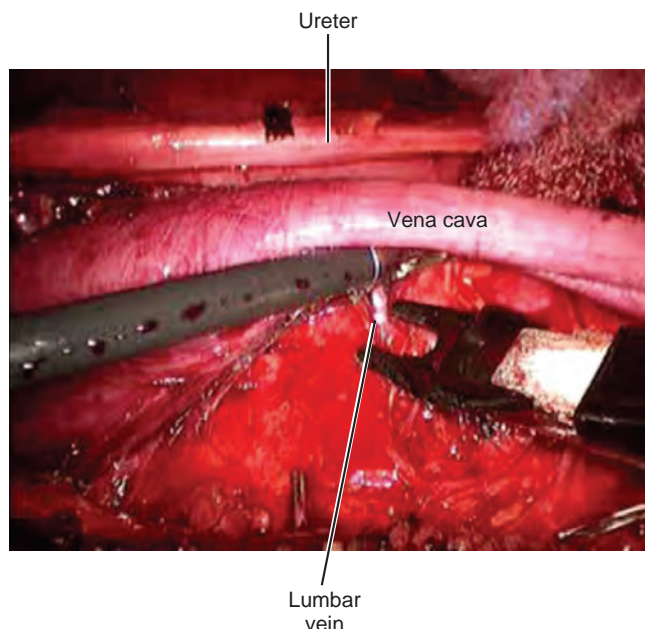


Figure 36-6. The inferior vena cava is retracted to allow for lumbar vein ligation. Paracaval and precaval lymph nodes have been cleared.

Left-Sided Dissection

The peritoneum is incised lateral to the descending colon and along the splenic flexure. The colorenal ligaments are severed, and the bowel is bluntly dissected medially. The lateral attachments of the spleen are incised, and the tail of the pancreas is swept medially to ensure wide exposure of the retroperitoneum, including the medial paracaval space.

Spermatic Cord Dissection

Analogous to what is done on the right side, the spermatic cord stump suture is identified after circumscribing the peritoneum at the inguinal ring. The spermatic vein along with adjacent lymph nodes is traced proximally to the renal vein and the artery to the aorta where they are ligated and cut. The cord is placed in an endobag for removal at the conclusion of the procedure.

Lymphadenectomy

We advocate removal of the left common iliac, para-aortic, preaortic, interaortocaval, and medial paracaval lymph nodes (see Fig. 36-4). The dissection can be expanded as needed. Lumbar veins draining into the renal vein are clipped and divided to allow full dissection of the renal hilum. The vein is cleaned off medially to the junction of the vena cava. A paddle retractor in the lowest trocar aids in dissection. The renal artery is completely freed of all lymphatic tissues. Clips are generously used to avoid postoperative leakage of lymph. The tissues overlying the aorta are split from the renal hilum to the level of the inferior mesenteric artery. Care should be taken to identify the right spermatic artery to avoid avulsion. In contrast to the tissues overlying the vena cava, the preaortic space may include postganglionic sympathetic nerves; care must be taken to separate the nodal tissue while preserving these nerves (Fig. 36-7). The ureter and common iliac vessels are separated from all fibroadipose tissue. The preaortic tissues are rolled medially down to the lumbar arteries. The lumbar vessels are controlled and cut, allowing excision of the retroaortic lymph nodes. The vena cava is identified, and using a “split and roll” approach, the paracaval, precaval, and interaortocaval lymph nodes are removed in the same manner as for a right-sided dissection. Care should be taken to identify any right-sided renal arteries to avoid inadvertent ligation.

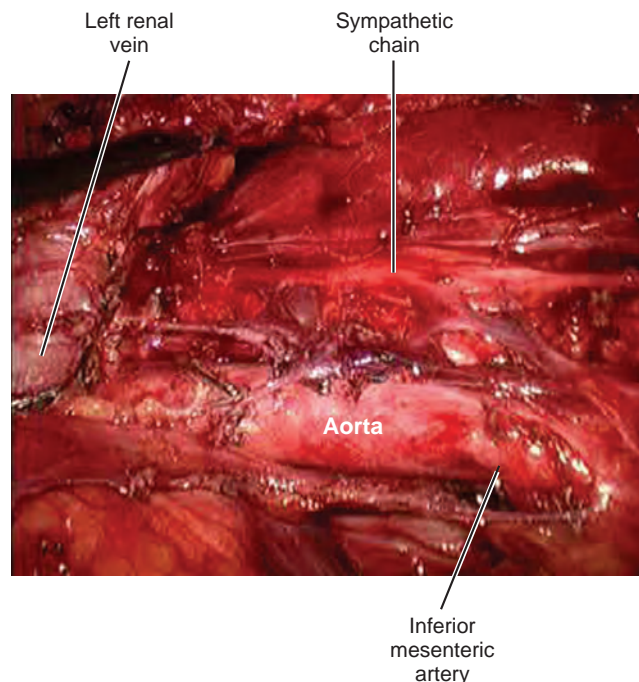


Figure 36-7. The sympathetic chain and efferent nerves are seen spared, while para-aortic and preaortic lymph nodes have been removed.

In patients who have had chemotherapy, it may be necessary to ligate and transect the inferior mesenteric artery. If suspect nodes are detected, the node dissection can be expanded to perform a complete bilateral dissection; this can be performed from the same side using retraction.

At the conclusion of the operation, the lymph nodes are placed in an endobag and extracted. Each packet should be placed in a separate sac during dissection to help increase yield of nodal evaluation and count. The retroperitoneum is irrigated with warm water, and lymphostasis and hemostasis are ensured. The bowel and adjacent organs (liver, gallbladder, kidneys, ureters, pancreas, and spleen) are inspected carefully for injury. The trocar sites are closed with fascial sutures using a Carter-Thomason device. A drain is not routinely used.

Bilateral Laparoscopic Retroperitoneal Lymph Node Dissection

Bilateral dissections may be performed when necessary and usually can be undertaken without a change in patient positioning. When the side of primary tumor is completed with the templates described, a small amount of tissue is left just medial to the contralateral ureter and inferiorly toward the common iliac vessels. These tissues are dissected free, and a bilateral dissection is completed. It is easier to approach a bilateral dissection from the right side.

Robotic-Assisted Retroperitoneal Lymph Node Dissection Port Placement and Technique

For RA-RPLND, we place the patient in a modified flank position, and the port locations are similar to the locations used in robotic renal surgery, with the ports shifted slightly caudally to assist in the iliac nodal dissection (Fig. 36-8). Use of the robotic fourth arm is preferred for improved retraction leaving the surgeon two working instruments. One or two 12-mm assistant ports may be used depending on surgeon preference. The general steps of the operation mirror the open and laparoscopic techniques. The robotic clip

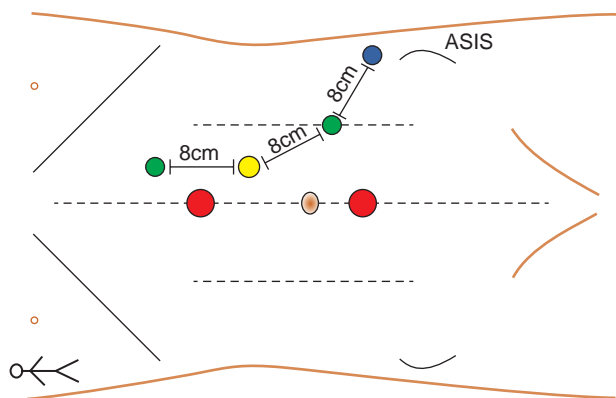


Figure 36-8. Port placement for robotic-assisted retroperitoneal lymph node dissection. Yellow indicates camera port, green indicates 8-mm robotic ports, and red indicates 12-mm assistant ports. ASIS, anterior superior iliac spine.

applier allows the surgeon to articulate the instrument while placing clips and can be particularly helpful in securing lumbar vessels. Depending on body habitus, dissection of the spermatic cord to the orchiectomy suture may require re-docking of the robotic arms and triangulating them toward the inguinal ring for a more direct approach to this area. An alternative technique has been described and entails placement of the patient in a steep Trendelenburg supine position with the robot docking from the patient's head (de Cobelli et al, 2013). The ports are placed in positions similar to robotic-assisted radical prostatectomy, but the field of dissection is reversed (toward the head).

POSTOPERATIVE CARE

Patients are extubated and transferred to the recovery area without nasogastric tube drainage. The patient may ambulate and resume a liquid diet the night of surgery. Postoperative tachycardia may occur secondary to sympathetic stimulation (Bahnon et al, 1989). Most patients can be discharged on postoperative day 1. Some surgeons advocate consumption of a low-fat diet for 1 to 2 weeks postoperatively.

PROSPECTIVE NERVE-SPARING TECHNIQUES

As in open RPLND, nerve-sparing techniques involve prospectively identifying, dissecting, and preserving the sympathetic chains, hypogastric plexus, and postganglionic fibers. With experience, these tissues can be readily identified as more fibrous compared with lymphatic tissue. On the right side, the postganglionic sympathetic fibers are most easily identified behind the IVC as they cross anterior to the aorta to insert in the hypogastric plexus. Their takeoff from the sympathetic chains is always near lumbar veins, so great care should be taken in clipping lumbar vessels. On the left side, it is easiest to identify the postganglionic sympathetic nerves at the ganglia as they leave the sympathetic chain and dissect them prospectively as they course anterior to the aorta before joining the hypogastric plexus. Care should be taken to avoid energy sources such as electrocautery when dissecting nerve fibers (Peschel et al, 2002; Bhayani et al, 2003; Abdel-Aziz et al, 2006; Steiner et al, 2008).

COMPLICATIONS

The most common reason for conversion to an open procedure is uncontrollable bleeding, and vascular injury is cited as the most common intraoperative complication (Bhayani et al, 2003;

Abdel-Aziz et al, 2006; Neyer et al, 2007; Kenney and Tuerk, 2008). Although bleeding and open conversion occurred frequently in older series, it is less common in more recent series. In most contemporary series, the open conversion rate is less than 5%, but it has been reported as high as 11.8% (Rassweiler et al, 2000; Neyer et al, 2007; Nielsen et al, 2007; Cresswell et al, 2008; Skolarus et al, 2008). Conversion to an open procedure should never be viewed as a failure, and surgeons should be familiar with open RPLND should it be required. Injury to major abdominal viscera also has been reported but appears to be a rare event (Neyer et al, 2007; Kenney and Tuerk, 2008).

Postoperative complication rates of 9% to 25% have been reported in contemporary series (Albqami and Janetschek, 2005; Neyer et al, 2007; Nielsen et al, 2007; Cresswell et al, 2008; Skolarus et al, 2008). Reported complications include chylous ascites, ileus, lymphocele, nerve injury, pulmonary embolus, *Clostridium difficile* colitis, retroperitoneal hematoma, and ureteral injury (Kenney and Tuerk, 2008). Retrograde ejaculation is a potential long-term source of morbidity for patients undergoing open RPLND and L-RPLND. The rates of retrograde ejaculation have been consistently low with the laparoscopic approach and range from 0% to 14% (Albqami and Janetschek, 2005; Neyer et al, 2007; Nielsen et al, 2007; Cresswell et al, 2008; Skolarus et al, 2008; Steiner et al, 2008). With meticulous ligation of lymphatic channels, the incidence of chylous ascites should be less than 2%. A summary of the morbidity of L-RPLND in the management of clinical stage I NSGCT is provided in Table 36-1. Although it is difficult to compare these data retrospectively with published open RPLND series, they appear to compare favorably. In one study of open primary RPLND, a 6% transfusion rate with a mean length of stay of 6 days was reported (Subramanian et al, 2010). Similar to L-RPLND, vascular injury was the most common intraoperative complication (4.5% of cases); 2 patients developed chylous ascites (1.8%) and 14 (12.5%) had an ileus. Antegrade ejaculation in this group of patients was 80%, and seven patients (6.3%) required reoperation (for small bowel obstruction [two patients], incisional hernia repair [four patients], and ureteral reconstruction [one patient]). Two patients required nephrectomy, one for a dysplastic kidney and the other for oncologic reasons.

The morbidity and open conversion rate of L-RPLND after chemotherapy is higher and seems to be experience dependent as well. Early series cited major complication rates of more than 50% (Palese et al, 2002) and high conversion rates (Rassweiler et al, 1996). However, similar to primary L-RPLND, more recent series from experienced centers show improvement in these parameters (Steiner et al, 2004; Permpongkosol et al, 2007). Steiner and colleagues (2004) reported on 68 L-RPLND procedures performed after chemotherapy and reported no open conversions. In another more limited report including 17 patients who underwent L-RPLND after chemotherapy, the authors reported no complications, transfusions, or open conversions (Maldonado-Valadez et al, 2007). Studies report preservation of antegrade ejaculation with experience (LeBlanc et al, 2001; Albqami and Janetschek, 2005; Corvin et al, 2005).

RESULTS AND CURRENT STATUS

There are no randomized trials comparing open RPLND and L-RPLND. Retrospective assessments suggest that patients undergoing L-RPLND have a significantly shorter hospital stay, decreased blood loss, greater quality-of-life scores, and faster return to normal activities (Janetschek et al, 1996; Abdel-Aziz et al, 2006; Poulakis et al, 2006). Results of RA-RPLND are limited to early reports demonstrating safety and feasibility.

Laparoscopic Retroperitoneal Lymph Node Dissection for Clinical Stage I Disease

Published reports of L-RPLND with long-term follow-up suggest that it is an effective treatment option for patients with low-stage

TABLE 36-1 Perioperative and Morbidity Outcomes of L-RPLND for Clinical Stage I NSGCT

STUDY	NO. PATIENTS	OR TIME (MEAN, MIN)	OPEN CONVERSION	EBL (mL)	LENGTH OF STAY (DAYS)	MAJOR INTRAOPERATIVE COMPLICATIONS	MAJOR POSTOPERATIVE COMPLICATIONS	ANTEGRADE EJACULATION
Hyams et al, 2012	91	NA	4	200	2.1	7	2	87 (95.7%)
Steiner et al, 2008	42*	323	0	125	4.8	0	2 (lymphoceles)	36 (85.7%)
Skolarus et al, 2008	19	250	0	145	1.5	0	4 (lymphoceles)	23/26† (88.5%)
Cresswell et al, 2008	79	177	1	NR	6	1 (bleeding with open conversion)	7 (1 lymphocele, 5 ureteral stenosis/injury, 1 pulmonary embolus)	78 (98.7%)
Albqami and Janetschek, 2005	103	217	3	144	3.6	3 (bleeding with open conversion)	0	217 (100%)
Bhayani et al, 2003	29	258	2	389	2.6	2 (bleeding with open conversion)	2 (1 lymphocele, 1 compartment syndrome)	28 (96.6%)
LeBlanc et al, 2001	20	230	0	<50	1.2	0	0	20 (100%)

*Data include 21 patients with clinical stage II disease.

†Ejaculation data given only as percentage of all patients (included are 7 patients with nonclinical stage I disease).

EBL, estimated blood loss; L-RPLND, laparoscopic retroperitoneal lymph node dissection; NA, not available; NR, not reported; NSGCT, nonseminomatous germ cell tumor; OR, operating room.

NSGCTs (Table 36-2). The staging accuracy of L-RPLND has been documented and consistent with open series in that 25% to 30% of men with clinical stage I NSGCT are found to harbor occult nodal disease. A study with a mean follow-up of 7 years included 87 patients with clinical stage I disease and revealed a 9% and 0% relapse rate for patients with pN0 and pN+ disease, respectively, with all patients alive and free of disease at last follow-up (Cresswell et al, 2008). The two retroperitoneal recurrences (2.5%) in this series occurred outside the dissection template, and all patients with pN+ disease were administered adjuvant chemotherapy. Examination of other large L-RPLND series confirms these findings, and recurrence rates and their patterns in this patient population are comparable to those of open RPLND series. The recurrence rate of patients found to have negative lymph nodes at L-RPLND is reported between 0% and 10%, which compares favorably with open RPLND series (Donohue et al, 1993; Hermans et al, 2000).

Despite the favorable long-term outcomes, the practice of universal chemotherapy in the adjuvant setting in patients with clinical stage I disease who are also harboring metastatic disease at L-RPLND has been the focus of critics who question the therapeutic efficacy of the technique. Approximately 70% of men found to have pN1 disease and who undergo a properly performed RPLND are cured and can avoid chemotherapy (Richie and Kantoff, 1991; Donohue et al, 1993; Rabbani et al, 2001). However, patients found to have pN1 disease can opt to receive two cycles of chemotherapy in the adjuvant setting with excellent long-term results rather than risk receiving three or four cycles of chemotherapy should they experience relapse. The decision to administer chemotherapy to patients with pN1 disease is a matter of preference and factors in the philosophy of the urologist and medical oncologist as well as the patient.

A report of 120 patients undergoing L-RPLND at one of four institutions in the United States included 10 patients with pathologic stage II disease who underwent surveillance (Nielsen

et al, 2007). At a mean follow-up of 34.8 months, none of the patients had experienced a retroperitoneal recurrence. **Additional reports omitting chemotherapy for patients with pN1 disease who underwent L-RPLND support its therapeutic efficacy, but further studies and follow-up are required (Skolarus et al, 2008; Steiner et al, 2008).**

The adequacy of L-RPLND also can be evaluated by examining patients found to have pathologic stage I disease. If L-RPLND was inadequate, certain patients with pathologic stage II disease would be mislabeled as having pathologic stage I disease, and a retroperitoneal recurrence would result. This supposition has not occurred because no retroperitoneal recurrence has resulted in a series of therapeutic L-RPLND where a full dissection has been performed (Bhayani et al, 2003; Porter and Lange, 2003; Nielsen et al, 2007; Skolarus et al, 2008; Steiner et al, 2008). The therapeutic efficacy of L-RPLND will continue to be tested as more patients found to have pathologic stage II disease are choosing observation after this technique with good results.

Laparoscopic Retroperitoneal Lymph Node Dissection for Clinical Stage II

Fewer reports exist examining the role of L-RPLND for patients with clinical stage II NSGCTs as a primary modality or in the postchemotherapeutic setting. Data regarding the use of primary L-RPLND in patients with clinical stage IIA disease are limited. Several authors have reported on the use of L-RPLND in the postchemotherapeutic setting (see Table 36-2). Albqami and Janetschek (2005) reported their experience with 59 patients with stage IIB or IIC disease who underwent L-RPLND after chemotherapy: Of the 43 patients with preoperative stage IIB disease with a mean follow-up of 53 months, 1 experienced a recurrence 24 months postoperatively along the external iliac nodes, outside the original template. Another group

TABLE 36-2 Oncologic Outcomes of Published L-RPLND Series for Patients with Clinical Stage I NSGCT

STUDY	NO. PATIENTS	FOLLOW-UP (MEAN, MONTHS)	NODE YIELD	NO/N+	NO. pN+ RECEIVING ADJUVANT CHEMOTHERAPY	NO. RECURRENCES*	DISEASE-FREE SURVIVAL
Hyams et al, 2012	91	38	26.1	N0: 63 N1: 21 N2: 7	21 (75%)	N0: (2 PU, 1 BC, 2 distant) N+: 0	100%
Steiner et al, 2008	21	17	22	N0: 16 N+: 5	0 (0%)	N0: 1 (PU) N+: 0	100%
Skolarus et al, 2008	19	23.7	23.8	N0: 13 N1: 6	5 (83.3%)	N0: 0 N+: 0	100%
Cresswell et al, 2008	79	84	14	N0: 60 N+: 19	19 (100%)	N0: 8 (3 PU, 2 RP, 1 PS, 1 BC) N+: 0	100%
Albqami and Janetschek, 2005	103	62	NR	N0: 77 N+: 26	26 (100%)	N0: 5 (3 PU, 1 RP, 1 BC) N+: 0	100%
Bhayani et al, 2003	29	72	20	N0: 17 N+: 12	10 (83.3%)	N0: 2 (PU, BC) N+: 1 (M)	100%
LeBlanc et al, 2001	20	15	9.8 (Rt) 17.7 (Lt)	N0: 14 N+: 6	6 (100%)	N0: 0 N+: 0	100%

*Recurrences: PU, pulmonary; RP, retroperitoneal, outside of template; BC, isolated biochemical; PS, port site.

L-RPLND, laparoscopic retroperitoneal lymph node dissection; Lt, left; NSGCT, nonseminomatous germ cell tumor; pN+, histologically positive lymph nodes; Rt, right.

(Maldonado-Valadez et al, 2007) reported on 17 patients and demonstrated the feasibility of L-RPLND after chemotherapy: Viable tumor was found in 3 patients, 2 of whom experienced retroperitoneal recurrences. Full bilateral RPLND, which is typically recommended in this setting, was not performed in these series (Stephenson and Sheinfeld, 2004).

Keeping in line with the goals of open RPLND performed after chemotherapy, Steiner and associates (2008) performed bilateral nerve-sparing L-RPLND on 19 postchemotherapy patients with stage IIB disease. The authors found teratoma in 4 patients, necrosis/fibrosis in 14 patients, and active tumor in 1 patient. This study included two patients with clinical stage IIA disease who underwent L-RPLND without adjuvant chemotherapy. No retroperitoneal recurrences were noted in either group at 17 months of follow-up. Longer follow-up and larger series are required to evaluate the efficacy of L-RPLND in the postchemotherapeutic setting.

SUMMARY

L-RPLND has been demonstrated to be a feasible, safe, and effective treatment option for men with clinical stage I NSGCT when performed at large-volume institutions by experienced laparoscopic surgeons. L-RPLND has evolved into a therapeutic operation duplicating the open procedure, with reports demonstrating efficacy and minimal morbidity. Data regarding L-RPLND for clinical stage II disease and for patients who have received chemotherapy are limited and associated with a longer learning curve. Early reports suggest that robotic-assisted surgery is emerging as yet another minimally invasive alternative to RPLND.

KEY POINTS

- L-RPLND aims to decrease operative morbidity while duplicating the open approach.
- The most common reason for conversion to an open procedure is bleeding, although this is a rare complication (<5%).
- L-RPLND is an effective treatment option for patients with low-stage NSGCTs.
- Reports omitting chemotherapy for patients with N1 disease who underwent L-RPLND support its therapeutic efficacy, but more studies and follow-up are required.
- RA-RPLND is emerging as another minimally invasive alternative to open RPLND.

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Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.



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Premalignant Cutaneous Lesions

Squamous Cell Carcinoma

Surgical Management of the Primary Tumor

Treatment of the Inguinal Nodes

Radiation Therapy

Chemotherapy

Nonsquamous Penile Malignant Neoplasms

Cancers of the penis are uncommon tumors that are often devastating for the patient and frequently diagnostically and therapeutically challenging for the urologist. Although rare in North America and Europe, penile malignant neoplasms constitute a substantial health concern in many African, South American, and Asian countries.

Any discussion of penile cancers must begin by addressing both premalignant and malignant tumors of the penis. A description of these lesions serves to establish their anatomic, etiologic, and histologic relationship to squamous cell carcinoma, which is the most common malignant tumor of the penis, as well as to other malignant neoplasms that involve the penis. Developments in the etiologies of various premalignant and malignant penile tumors are reviewed in this chapter.

In this chapter, we review the epidemiology, etiology, and natural history of squamous carcinoma and its contemporary management. Reports have confirmed the importance of pathologic stage and histologic features of the primary tumor as well as the presence and extent of lymph node metastasis in determining prognosis and treatment planning for penile squamous carcinoma (Ravi, 1993a; McDougal, 1995; Theodorescu et al, 1996; Pizzocaro et al, 1997; Slaton et al, 2001). In addition, developments in staging of the disease, including novel imaging modalities and the use of dynamic sentinel node biopsy (DSNB), and modified surgical approaches to improve staging accuracy and reduce potential morbidities are presented. The selection of patients for organ-preserving surgical strategies is discussed.

The role of radiation therapy as both a primary treatment and a palliative measure is reviewed. Contemporary developments in chemotherapy as well as in combination therapy with multiple therapeutic modalities are also discussed. A contemporary scheme for the management of the inguinal region, based on histologic and clinical features, is presented.

Finally, the various nonsquamous malignant neoplasms that may involve the penis are reviewed and discussed.

PREMALIGNANT CUTANEOUS LESIONS



Please see the Expert Consult website for a discussion of premalignant cutaneous lesions (including Fig. 37-1), and virus-related dermatologic lesions.

SQUAMOUS CELL CARCINOMA

Carcinoma in Situ

Carcinoma in situ (Tis) of the penis is called *erythroplasia of Queyrat* by urologists and dermatologists if it involves the glans penis and prepuce or Bowen disease if it involves the penile shaft or the remainder of the genitalia or perineal region. This nomenclature has served to separate carcinoma in situ from the mainstream of thinking and reporting of penile carcinoma. However, the epidemiology and natural history of this lesion parallel those of early carcinoma of the penis, and carcinoma in situ can progress to invasive carcinoma.

The erythroplasia originally described by Queyrat in 1911 consists of a red, velvety, well-marginated lesion of the glans penis or, less frequently, the prepuce of the uncircumcised man (Aragona et al, 1985). It may ulcerate and may be associated with discharge and pain. On histologic examination the normal mucosa is replaced by atypical hyperplastic cells characterized by disorientation, vacuolation, multiple hyperchromatic nuclei, and mitotic figures at all levels. The epithelial rete extends into the submucosa and appears elongated, broadened, and bulbous. The submucosa shows capillary proliferation and ectasia with a surrounding inflammatory infiltrate that is usually rich in plasma cells. These microscopic features distinguish erythroplasia of Queyrat from chronic localized balanitis. HPV has been identified in penile carcinoma in situ (Pfister and Haneke, 1984). Progression to invasive carcinoma can occur in 10% to 33% of patients (Buechner, 2002; Bleeker et al, 2009).

In 1912 Bowen described an intraepithelial neoplasm of the skin associated with a high occurrence of subsequent internal malignant disease as a distinct entity. Bowen disease and erythroplasia of Queyrat are histologically similar (Graham and Helwig, 1973) (see Fig. 37-1C on the Expert Consult website). Both tumors are characterized by the noninvasive changes of carcinoma in situ. Visceral malignant disease is not associated with erythroplasia of Queyrat, and subsequent case-control studies have shown no association of Bowen disease with internal malignant tumors (Anderson et al, 1973). Thus penile carcinoma in situ does not in itself warrant a specific search for internal malignant tumors. Bowen disease is characterized by sharply defined plaques of scaly erythema on the penile shaft. Crusted or ulcerated variants can occur. The appearance can be confused with Bowenoid papulosis, nummular eczema, psoriasis, and superficial basal cell carcinoma. If it is not treated, then invasive carcinoma may arise in about 5% of patients (Buechner, 2002). When all cases of carcinoma in situ



- When in doubt, biopsy of penile lesions should be considered to establish a diagnosis.
- Lesions associated with the development of penile carcinoma that require treatment or close follow-up include cutaneous horn, balanitis xerotica obliterans, and pseudoepitheliomatous micaceous and keratotic balanitis.

Some histologically benign penile lesions have been recognized as having malignant potential or close association with the development of squamous carcinoma. In one large series, 42% of patients with squamous cell cancer had a history of preexisting penile lesions (Bouchot et al, 1989). Although the incidence of progression of these lesions to squamous cell carcinoma is not known, all have been associated with the disease. Premalignant penile lesions have now been divided into two broad categories based on their potential causation by human papillomavirus (HPV) or inflammatory pathways (reviewed in Shabbir et al, 2011b).

Non-Human Papillomavirus-Related Penile Premalignant Lesions

Cutaneous Horn

The penile cutaneous horn is a rare lesion. It usually develops over a preexisting skin lesion (wart, nevus, traumatic abrasion, or malignant neoplasm) and is characterized by overgrowth and cornification of the epithelium, which forms a solid protuberance. On microscopic examination, extreme hyperkeratosis, dyskeratosis, and acanthosis are noted. It is associated with HPV type 16. Treatment consists of surgical excision with a margin of normal tissue about the base of the horn. These lesions may recur and may demonstrate malignant change on subsequent biopsy, even when initial histologic appearance is benign (Fields et al, 1987). Because this tumor may evolve into a carcinoma or may develop as a result of an underlying carcinoma, careful histologic evaluation of the base and close follow-up of the excision site are essential (Fig. 37-1A) (Pressman et al, 1962; Hassan et al, 1967; Solivan et al, 1990).

Pseudoepitheliomatous Micaceous and Keratotic Balanitis

Pseudoepitheliomatous micaceous and keratotic balanitis is an unusual lesion that manifests as hyperkeratotic, micaceous growths on the glans and may have some of the microscopic features of verrucous carcinoma (see Chapter 16, Fig. 16-41). They tend to recur and may represent an early form of that tumor (Jenkins and Jakubovic, 1988; Gray and Ansell, 1990). Treatment includes excision, laser ablation, or cryotherapy. These lesions require aggressive treatment and close follow-up. Fibrosarcoma of the glans after treatment of a pseudoepitheliomatous micaceous and keratotic balanitis lesion with cryotherapy has been reported (Irvine et al, 1987).

Male Lichen Sclerosus (Balanitis Xerotica Obliterans)

Male lichen sclerosus (LS) (balanitis xerotica obliterans), a genital variation of lichen sclerosus et atrophicus, manifests as a whitish patch on the prepuce or glans, often involving the meatus and sometimes extending into the fossa navicularis (see Chapter 16, Fig. 16-12). The lesions may be multiple and may assume a mosaic appearance. The meatus may appear white, indurated, and edematous. Glanular erosions, fissures, and meatal stenosis may occur. The disorder is most common in uncircumcised men and occurs most commonly in middle-aged men, but it does occur in boys (McKay et al, 1975). Symptoms include pain, dyspareunia, pruritus, painful erections, and urinary obstruction (Bainbridge et al, 1971).

On histologic examination, these lesions show an atrophic epidermis with loss of the rete pegs and homogenization of collagen on the upper third of the dermis combined with a zone of lymphocytic and histiocytic infiltration. They resemble the lesions of lichen sclerosus et atrophicus found elsewhere (Laymon and Freeman, 1944). There are reports documenting the association of male LS with squamous cell carcinoma as well as with the development of carcinoma long after a lesion of LS has been treated (Laymon

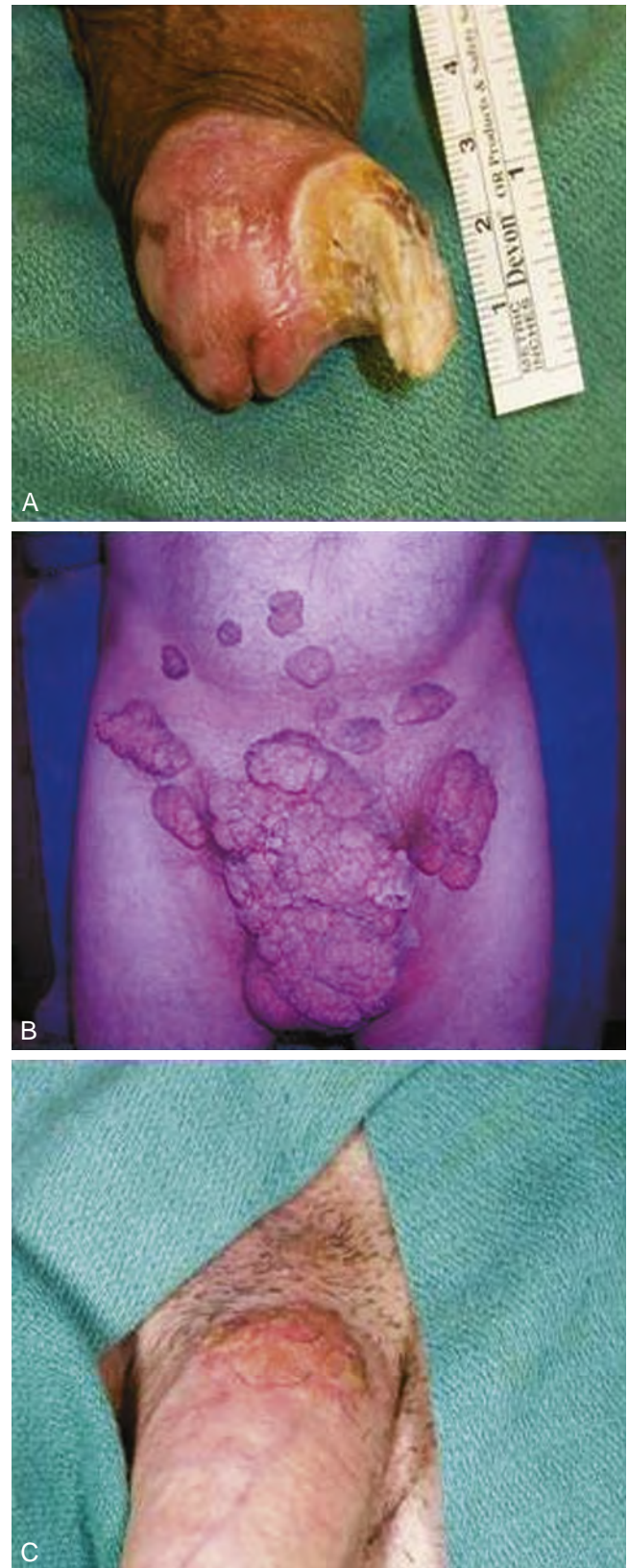


Figure 37-1. A, Cutaneous horn with underlying well-differentiated squamous carcinoma. B, Buschke-Löwenstein tumor. C, Bowen disease involving penile shaft skin.

and Freeman, 1944; Bart and Kopf, 1978; Jamieson et al, 1986; Dore et al, 1990; Simonart et al, 1998; Velazquez and Cubilla, 2003; Kumaran and Kanwar, 2004). It is a frequent finding in conjunction with squamous penile cancer, noted in 28% to 50% of patients. Penile cancer was subsequently diagnosed in 2.3% to 5.8%

of men with LS in two different series (Nasca et al, 1999; Powell and Wojnarowska et al, 1999; Depasquale et al, 2000; Pietrzak et al, 2006). Cubilla and coworkers (2004) describe a well-differentiated nonverruciform variant of squamous cell carcinoma associated with lichen sclerosus et atrophicus that preferentially involves the prepuce. The cause of male LS is unknown; however, a recent study identified *Borrelia burgdorferi* infection in affected tissues in the early course of the disease. Floating microscopy was used to examine specimens from 60 patients with LS, and *B. burgdorferi* species were identified in 63% of the LS tissues and none of the controls (Eisenle et al, 2008). Whether this organism is causative is unproven at this time and requires additional study.

Treatment involves clobetasol propionate cream for 2 to 3 months (Pugliese et al, 2007). Meatal stenosis is a common problem often requiring repeated dilations, corticosteroid injection, or even formal reconstructive surgery (Poynter and Levy, 1967). Close follow-up is essential, with biopsy if a change in appearance or behavior occurs.

Virus-Related Penile Lesions

There is increasing evidence to suggest that a number of penile lesions share viral causes. Condyloma acuminatum and bowenoid papulosis appear to be related to infection with HPV. Human herpesvirus 8, also known as *Kaposi sarcoma-associated herpesvirus*, is strongly suspected of being the causative agent of epidemic (acquired immunodeficiency syndrome [AIDS]-related) Kaposi sarcoma (Miller et al, 1996; Simpson et al, 1996; Jaffe and Pellett, 1999; Dianzani et al, 2004).

Human Papillomavirus in Malignant Transformation

Condylomata acuminata are soft, papillomatous growths typically considered to be benign (see Chapter 16, Fig. 16-21G). Also known as *genital warts* or *venereal warts*, they have a predilection for the moist, glabrous areas of the body and the mucocutaneous surfaces of the perineal and genital areas. The lesions are soft and friable and may occur singly on a pedicle or in a moruloid cluster on a broad base. These lesions are rare before puberty (Redman and Meacham, 1973; Copulsky et al, 1975) and when encountered may suggest sexual abuse (Handly et al, 1993).

In the male, condylomata occur most commonly on the glans, the penile shaft, and the prepuce. The meatus should also be carefully inspected. Lesions recur frequently, both in new and in previously treated sites. Approximately 5% of patients will demonstrate urethral involvement, which may extend to the prostatic urethra (Culp et al, 1944). Rarely, extreme involvement of the urethra may require urethroplasty (Feneley et al, 1992). Bladder involvement, although rare, is extremely difficult to treat effectively (Bissada et al, 1974).

On microscopic examination, condylomata acuminata demonstrate an outer layer of keratinized tissue covering papillary fronds, which are supported by connective tissue stroma. The epithelial layer consists of well-ordered rows of squamous cells. A dermal lymphocytic infiltrate is usually present. Treatment of these lesions with podophyllin may induce histologic changes suggestive of carcinoma (King and Sullivan, 1947). Consequently, preliminary biopsy of large lesions that appear to be condylomata acuminata should precede any treatment with topical podophyllin.

Interest in genital condylomata has increased dramatically, stimulated by an increased understanding of the relationship between HPV infection and certain human cancers. The terms *genital condyloma*, *venereal warts*, *genital warts*, and *genital HPV infection* all refer to a sexually transmitted disease caused by HPV. Although HPV is not a reportable sexually transmitted disease, a current estimate puts the number of new infections at 500,000 to 1 million annually (Stone, 1989). A study of 463 men aged 18 to 40 years analyzed samples from the glans and corona, penile shaft, scrotum, urethra, perianal area, anal canal, and semen and detected HPV in 51.2% (Nielson et al, 2007). Giuliano and colleagues (2009) found the prevalence of HPV in U.S. males to be

51.7%, in Brazilian men to be 69.4%, and in Mexican men to be 56.1%. In a study of 379 adult heterosexual males, HPV infection was localized to the penile shaft (52%), scrotum (40%), glans or corona (32%), urine (10%), and semen (6%) (Hernandez et al, 2008). In a cohort of 379 adult heterosexual males, the overall incidence of HPV infection was 52%, with 60% of the uncircumcised and 50% of the circumcised males found to have HPV infection. There was a higher prevalence of oncogenic HPV in the uncircumcised group (Hernandez et al, 2008). Factors associated with higher rates of infection with HPV include presence of foreskin, increasing numbers of sexual partners, lack of condom use, and smoking (Giuliano et al, 2009).

The overall prevalence of HPV in females was found to be 26.8% among U.S. females aged 14 to 59 years and highest among women aged 20 to 24 years (44.8%) (Dunne et al, 2007). HPV is recognized as the principal causative agent in cervical dysplasia and cervical cancer (Lancaster et al, 1986; Alani and Munger, 1998; Gross and Pfister, 2004). Significant numbers of male partners of women with cervical condylomata will have lesions not identified on simple inspection and may not be aware that they are infected or have the potential to infect others (Sedlacek et al, 1986).

On histologic examination, the koilocyte—a cell characterized by an empty cavity surrounding an atypical nucleus—is pathognomonic for HPV infection (Schneider, 1989). DNA hybridization techniques have been used to identify and classify HPV infections, and some 60 genotypes of HPV virus have been identified that involve the genital tract (Nielson et al, 2007). Virus types 6, 11, and 42 to 44 are associated with gross condylomata and low-grade dysplasia. Types 16, 18, 31, 33, 35, and 39 have a higher association with malignant disease (Smotkin, 1989). More recently, reports have suggested that tumor virus transforming proteins from HPV types 16 and 18, particularly the E6 and E7 proteins, may target tumor suppressor gene products pRB and TP53 and may be the causative agents in a subset of penile cancers (Levi et al, 1998; Griffiths and Mellon, 1999). E6 appears to bind to cellular tumor suppressor protein TP53, leading to its rapid degradation, resulting in chromosome instability, DNA mutations, and aneuploidy. E7 binds to and phosphorylates the pRB retinoblastoma protein, leading to the release of transcription factor E2F that activates mitosis (zur Hausen, 1996). Human immunodeficiency virus (HIV) infection may predispose affected patients to rapid development of squamous carcinoma from preexisting condyloma infection (Sanders, 1997).

Subclinical disease may be detected by the application of 5% acetic acid solution to the penis, followed by inspection with a magnifying glass. Lesions will turn white, and flat lesions often invisible on regular inspection may be detected. These acetowhite lesions are not always caused by HPV, and biopsy must be performed to confirm the diagnosis (Krebs and Schneider, 1987). Careful inspection of the base of the shaft, the scrotum, and the inguinal folds is essential. The meatus should be examined; if lesions are present, urethroscopy should be performed (Culp et al, 1944; Barrasso et al, 1987).

A variety of treatments for genital warts are available, but none has been proven to reduce transmission to sexual partners nor to prevent progression to dysplasia or cancer. In addition, recurrence after treatment is quite common. The more commonly used treatments include (1) podophyllotoxin 0.5% solution or gel, (2) trichloroacetic acid 35% to 85%, (3) cryotherapy with liquid nitrogen, (4) electrofulguration, (5) CO₂ laser therapy, and (6) imiquimod 5% cream (Buechner, 2002; Dupin, 2004).

The goal of surgical therapies is to either remove or ablate condylomata. Circumcision will remove preputial lesions, gain exposure for treatment, and allow post-treatment monitoring. Fulguration and excision may be advisable to avoid large areas of maceration, ulceration, and secondary infection.

Surgical therapy with use of a pediatric resectoscope may be helpful in debulking large intraurethral lesions. The lowest power required to resect the lesions should be used, and electrocautery should be minimized to avoid the development of urethral stricture. Whether laser therapy, electrocautery, or cryotherapy is used,

significant rates of recurrence have been noted within the first 6 months after treatment (i.e., 40% to 80%; Dupin, 2004).

Topical podophyllin (Condylox 0.5%) or trichloroacetic acid has been a well-established and often successful treatment for small condyloma lesions (Culp et al, 1944; Kinghorn et al, 1993). More recently, however, imiquimod cream (5%) has become the topical treatment of choice for condyloma. Imiquimod is an immune modulator that enhances natural killer cell activity (Buechner, 2002; Sanchez-Ortiz and Pettaway, 2003). It is important to note that immune modulators and antiviral agents have the potential to affect the viral load.

Various interferons have been used in condyloma treatment (Geffen et al, 1984). A randomized study has shown that short-term intralesional interferon alfa-2b has activity against condyloma (Eron et al, 1986). The outcome of studies using other interferons has been less clear (Zouboulis et al, 1991). Interferon therapy continues to be reserved for extensive and recalcitrant lesions (Krebs, 1989a, 1989b; Ferenczy, 1990).

Another recent antiviral agent shown to have activity against HPV includes (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine (cidofovir), an acyclic nucleoside phosphonate with broad-spectrum antiviral activity against DNA viruses. A 1% gel preparation of cidofovir applied daily every other week for six cycles was shown to be superior to placebo in a double-blind placebo-controlled trial, with a complete response of 47% in treated patients (Snoeck et al, 2001).

Intraurethral lesions may be extremely difficult to treat. 5-Fluorouracil cream applied weekly for 3 weeks has been successful in eliminating urethral lesions (Bissada et al, 1974; Dretler and Klein, 1975; Boxer and Skinner, 1977). Care must be taken to work the cream down the urethra and to avoid exposure of the scrotal skin. Use of a scrotal support or zinc oxide cream may be helpful. The addition of 5-fluorouracil cream to laser therapy did not improve the success rate in one study (Carpiniello et al, 1987).

HPV infection is common and, as noted earlier, potentially carcinogenic. Condylomata have been associated with squamous cell carcinoma of the penis (Beggs and Spratt, 1964; Dawson et al, 1965; Rhatigan et al, 1972). Malignant transformation of condyloma to squamous cell carcinoma has been reported (Boxer and Skinner, 1977; Coetzee, 1977; Malek et al, 1993). Condylomata acuminata located in the perianal, scrotal, and oral areas have also demonstrated malignant degeneration (Siegel, 1962; Burmer et al, 1993). An increased incidence of penile intraepithelial neoplasia has been found in the male partners of women with cervical intraepithelial neoplasia (Barrasso et al, 1987; Iversen et al, 1997). Thus preventive strategies are relevant. A quadrivalent vaccine (Gardasil, approved by the U.S. Food and Drug Administration [FDA], June 2006) that protects against HPV types 5, 11, 16, and 18 in women ages 9 to 26 years (Watson et al, 2008) has become available. In 2010 the same vaccine was approved for use in males ages 9 to 26 for the prevention of both anal and genital lesions (Sun, 2010). In one study the efficacy of preventing HPV-related genital lesions was 65% (Giuliano et al, 2011). Vaccination consists of a series of three injections over 6 months (Hoffner, 2009). In 2010 it was estimated that only about one third of eligible females received the vaccine (Centers for Disease Control and Prevention, 2011).

Bowenoid Papulosis

Carcinoma in situ of the penis has been well recognized since its first description by Queyrat in 1911. Kopf and Bart described bowenoid papulosis, a condition having a histologic appearance similar to that of carcinoma in situ but a benign course, in 1977.

Bowenoid papulosis manifests as multiple papules on the penile skin or female vulva, usually during the second or third decade of life. The lesions are usually pigmented and range from 0.2 to 3.0 cm in diameter, and smaller lesions may coalesce into larger ones (Patterson et al, 1986). Pigmented lesions occur on the penile skin, whereas glanular lesions tend to be flat papules (Gross et al, 1985). Diagnosis is confirmed by biopsy (Peters and Perry, 1981). These lesions meet all the histologic criteria of carcinoma in situ but

display differing growth patterns relative to flat, endophytic, or exophytic clinical appearance (Wade et al, 1978; Peters and Perry, 1981; Gross et al, 1985; Patterson et al, 1986; Bhojwani et al, 1997). DNA sequences suggestive of HPV-16 have been found in specimens of bowenoid papulosis, and a causative role for HPV is suspected (Gross et al, 1985; Endo et al, 2003). Whereas histologically this condition is a carcinoma in situ, the clinical course of bowenoid papulosis is invariably benign (Su and Shipley, 1997).

Treatment has included electrodesiccation, cryotherapy, laser fulguration, topical 5-fluorouracil cream, and excision with skin grafting.

Kaposi Sarcoma

Kaposi sarcoma, first described in 1972, is a tumor of the reticuloendothelial system (Kaposi, 1982). It appears as a cutaneous neovascular lesion, a raised, painful, bleeding papule or ulcer with bluish discoloration. On histologic examination the tumor is vasoformative with endothelial proliferation and spindle cell formation.

Initially, Kaposi sarcoma occurred rarely in Europe and North America. It was characterized by a slowly progressive tumor affecting the lower extremities of older men, usually of Eastern European Jewish or Italian descent. Kaposi sarcoma was also found in young black African men and patients receiving immunosuppressive therapy. The disease is now closely linked with patients who have AIDS and takes a much more aggressive clinical course in this group.

Kaposi sarcoma is now subcategorized as follows: (1) classic Kaposi sarcoma, which occurs in patients without known immunodeficiency and has an indolent and rarely fatal course; (2) immunosuppressive treatment-related Kaposi sarcoma, which occurs in patients undergoing immunosuppressive therapy for organ transplantation or other indications and is often reversed with dosage modification of the immunosuppressive agents; (3) African Kaposi sarcoma, which occurs in young men and may be indolent or aggressive in course; and (4) epidemic or HIV-related Kaposi sarcoma, which occurs in the patient with AIDS.

The classic and immunosuppressive forms of the disease are considered nonepidemic. Nonepidemic Kaposi sarcoma limited to penile involvement should be aggressively treated because it is rarely associated with diffuse organ involvement. Localized surgical excision or small-field external-beam or electron beam radiation has been effective (Lands et al, 1992). With wider areas of involvement, partial penectomy is indicated. In the immunosuppressed patient Kaposi sarcoma will often regress with the discontinuation of immunosuppressive therapy. If regression does not occur, local excision or radiation should be considered. Systemic management for multisystem involvement has employed interferon and cytotoxic therapy (National Cancer Institute Position Statement, 1990).

In the patient with AIDS, the underlying immunodeficiency predisposes the host to Kaposi sarcoma by a factor of 7000 (Miles, 1994). The first case of HIV-related epidemic Kaposi sarcoma was reported in 1981 (Friedman-Kien, 1981) and the first with penile involvement in 1986 (Seftel et al, 1986). Subsequently, Kaposi sarcoma of the penis has become a relatively common lesion in the patient with AIDS. Penile involvement is more common in homosexual men than in others with AIDS. In the first 1000 cases of AIDS reported by the Centers for Disease Control and Prevention, incidence of penile Kaposi sarcoma was 44% in homosexual and bisexual patients compared with only 16% in intravenous drug abusers with AIDS and 0% of hemophiliac patients with AIDS (Jaffe et al, 1983; Bayne and Wise, 1988). Several reports suggest a strong relationship between infection with human herpesvirus 8, also known as *Kaposi sarcoma-related herpesvirus*, and the development of Kaposi sarcoma lesions in patients with HIV infection (Jaffe and Pellett, 1999; Sitas et al, 1999). Some studies have found epidemic Kaposi sarcoma in patients who are HIV negative, which suggests that certain sexual practices and a separate sexually transmitted agent may be responsible for this form of the disease (Miles, 1994; Chitale et al, 2002). Human herpesvirus 8 has been isolated

from penile Kaposi lesions in patients who were HIV negative, which supports the notion that this disease may be sexually transmitted potentially via homosexual practices (Morelli et al, 2003).

Whereas Kaposi sarcoma may be the presenting sign of the disease in many patients with AIDS, early involvement of the penis is rare in this group (Grunwald et al, 1994). Treatment is directed toward palliation (Lowe et al, 1989). Glans penis or corpus spongiosum involvement may produce urethral obstruction, necessitating proximal urethrostomy. This will usually allow voiding in the upright position. With large lesions involving the penis, partial or total penectomy may be necessary. Radiation therapy and use of the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser to alleviate distal urethral obstruction have also been reported (Wishnow and Johnson, 1988; Ruszczak et al, 1996).

KEY POINTS: VIRUS-RELATED DERMATOLOGIC LESIONS

- HPV infection among men has been associated with penile carcinoma as well as with cervical dysplasia and carcinoma among female partners.
- Imiquimod cream has now become the standard topical treatment of choice for condyloma.
- Bowenoid papulosis, although appearing histologically similar to carcinoma in situ, occurs on the shaft of young men in most cases and does not progress to invasive disease.
- A diagnosis of penile Kaposi sarcoma is often associated with human herpesvirus 8 and should prompt an investigation into whether the patient is also infected with HIV or otherwise immunosuppressed.

Buschke-Löwenstein Tumor (Verrucous Carcinoma, Giant Condyloma Acuminatum)

The Buschke-Löwenstein tumor was initially described by Buschke and Löwenstein in 1925 and later by Löwenstein in 1939 in the United States. Ackerman (1948) described a histologically similar tumor occurring in the oral cavity. Verrucous carcinomas of the larynx, vulva, and penis were described by Goethals and colleagues (1963) (Fig. 37-1B).

The true incidence of the Buschke-Löwenstein tumor is unknown, but it is probably higher than reported because many cases have been labeled low-grade squamous carcinoma of the penis. Retrospective analyses of several reports have revealed a number of cases of verrucous cancer or giant condylomata under the category of low-grade squamous cell carcinomas (Davies, 1965; Hanash et al, 1970; Grussendorf-Conen, 1997).

The Buschke-Löwenstein tumor differs from condyloma acuminatum in that condylomata, regardless of size, always remain superficial and never invade adjacent tissue. Buschke-Löwenstein tumor displaces, invades, and destroys adjacent structures by compression. Aside from this unrestrained local growth, it demonstrates no signs of malignant change on histologic examination and does not metastasize. On microscopic examination, the tumor forms a luxuriant mass composed of broad rounded rete pegs, often extending far into underlying tissue. The pegs are composed of well-differentiated squamous cells that show no cellular anaplasia. These epithelial pegs are characteristically surrounded by a dense band of acute and chronic inflammatory cells. As with condyloma acuminatum, the cause may be viral (Dawson et al, 1965; Ubben et al, 1979; Antony et al, 2003). DNA from HPV types 6 and 11 has been identified in these tumors (Boshart and zur Hausen, 1986).

Lymph node metastases are rare with verrucous carcinoma (Ackerman, 1948; Davies, 1965; Seixas et al, 1994), and their presence probably reflects malignant degeneration in the primary lesion. Such changes are known to occur in verrucous carcinoma of nonpenile sites (Davies, 1965; Dawson et al, 1965). Anecdotal cases of malignant degeneration in association with penile carcinoma have been reported (Youngberg et al, 1983).

Either excisional biopsy or multiple deep biopsies are required to distinguish the lesion from true penile carcinoma. Treatment consists of excision, sparing as much of the penis as possible. Large lesions may necessitate total penectomy. Recurrence is common, and close follow-up is essential. Topical therapy with either podophyllin or 5-fluorouracil has been unsuccessful, probably because the characteristic thickened stratum corneum is impervious to the medication (Bruns et al, 1975).

Radiation therapy is ineffective for verrucous carcinoma (Lepor and Leffler, 1960; Kraus and Perez-Mesa, 1966; Proffitt et al, 1970; Fukunaga et al, 1994). Bleomycin has been used in both a primary and an adjunctive mode for verrucous carcinoma (Mishima and Matunaka, 1972). Successful treatment of a Buschke-Löwenstein tumor with systemic interferon therapy combined with Nd:YAG laser therapy has been reported (Gilbert and Beckert, 1990). Cryosurgery has also been employed with success (Michelman et al, 2002).

KEY POINTS: VERRUCOUS CARCINOMA

- Verrucous penile carcinoma exhibits progressive local growth but does not metastasize.
- It often requires surgical excision for definitive treatment.
- Treatment with radiation therapy is ineffective.

are considered, metastasis is extremely rare but has been reported (Eng et al, 1995).

Treatment is based on proper histopathologic confirmation of malignancy with multiple biopsies of adequate depth to rule out invasion. When lesions are located on the foreskin, circumcision or excision with a 5-mm margin is adequate for local control (Bissada, 1992). In this regard, lesions on the glans penis are more difficult to treat by excisional strategies while maintaining normal penile anatomy. Recently several groups have described the technique of glans resurfacing for penile squamous carcinoma of the glans penis. In this technique the epithelium and subepithelial tissue of the glans penis are completely dissected off the underlying spongiosal tissue. The resulting defect is then closed with a skin graft. Early follow-up reveals very low rates of local recurrence (Hadway et al, 2006; Shabbir et al, 2011b). Alternative strategies include topical 5-fluorouracil cream (Lewis and Bendl, 1971; Graham and Helwig, 1973; Goette, 1974), 5% imiquimod cream (Danielson et al, 2003), and ablation with Nd:YAG (Landthaler et al, 1986; Frimberger et al, 2002a), potassium titanyl phosphate (KTP) 532-nm, or carbon dioxide lasers (Rosemberg and Fuller, 1980; Tietjen and Malek, 1998; van Bezooijen et al, 2001). Such strategies have been shown to produce excellent cosmetic and functional results. Radiation therapy can be used to treat tumors that are resistant to topical treatment, especially among patients who are not surgical candidates (Kelley et al, 1974; Grabstald and Kelley, 1980; Mazoner et al, 1984; McLean et al, 1993).

KEY POINTS: CARCINOMA IN SITU

- Carcinoma in situ (Tis) is an intraepithelial malignant process.
- Progression to invasive carcinoma may occur in 5% to 33% of patients if it is not treated.
- Metastasis has rarely occurred.
- Cancer eradication with organ-preserving strategies is the goal of therapy.

Invasive Carcinoma

Penile carcinoma accounts for 0.4% to 0.6% of all malignant neoplasms among men in the United States and Europe; it may represent up to 10% of malignant neoplasms in men in some Asian, African, and South American countries (Gloeckler-Ries et al, 1990; Vatanasapt et al, 1995). However, reports suggest that the incidence of penile cancer is decreasing in many countries, including Finland, the United States, India, and other Asian countries (Maiche, 1992; Frisch et al, 1995; Vatanasapt et al, 1995; Yeole and Jussawalla, 1997). The reasons are unclear but may be related in part to increased attention to personal hygiene.

Penile cancer is a disease of older men, with an abrupt increase in incidence in the sixth decade of life (Persky, 1977). In two studies the mean ages were 58 years (Gursel et al, 1973) and 55 years (Derrick et al, 1973). The tumor is not unusual in younger men; in one large series, 22% of patients were younger than 40 years and 7% were younger than 30 years (Dean, 1935); the disease has also been reported in children (Kini, 1944; Narasimharao et al, 1985). The Surveillance, Epidemiology, and End Results (SEER) database reveals no racial difference in incidence of penile cancer between black and white men in the United States (incidence for white men, 0.8 per 100,000; for black men, 0.7 per 100,000) (Vatanasapt et al, 1995).

However, a study using SEER data suggested that race is associated with outcome. Rippentrop and colleagues (2004) noted there were 1605 patients diagnosed with penile cancer from 1973 to 1998, with 22.4% (360) dying of the disease. They found factors independently predictive of worsened survival to be higher stage at diagnosis, age older than 65 years, African-American ethnicity, and disease within lymph nodes. These researchers demonstrated a statistically significant disease-specific risk of death that was

2.2-fold higher in African-American patients than in white patients. Although the reason for this disparity is likely to be multifactorial, possibilities include differences in cancer biology, in health care access, or in treatment. These provocative findings clearly deserve further study.

Etiology

The incidence of carcinoma of the penis varies according to circumcision practice, hygienic standard, phimosis, number of sexual partners, HPV infection, exposure to tobacco products, and other factors (Barrasso et al, 1987; Maiche, 1992; Maden et al, 1993; Misra et al, 2004).

Neonatal circumcision has been well established as a prophylactic measure that virtually eliminates the occurrence of penile carcinoma because it eliminates the closed preputial environment where penile carcinoma develops. The chronic irritative effects of smegma, a byproduct of bacterial action on desquamated cells that are within the preputial sac, have been proposed as a causative agent. Although definitive evidence that human smegma itself is a carcinogen has not been established (Reddy and Baruah, 1963), its relationship to the development of penile carcinoma has been widely observed. Improper hygiene can lead to buildup of smegma beneath the preputial foreskin, with resulting inflammation. Healing by fibrosis leads to phimosis of the preputial skin, which tends to perpetuate the cycle. Phimosis is found in 25% to 75% of patients described in most large series. Reddy and associates (1984) studied the foreskins of 26 men undergoing circumcision because of phimosis and found epithelial atypia in one third of the specimens.

Carcinoma of the penis is rare among the Jewish population, for whom neonatal circumcision is a universal practice (Licklider, 1961). Similarly, in the United States, where neonatal circumcision is widely practiced, penile cancer represents less than 1% of male malignant neoplasms. Among noncircumcising tribes of Africa and within Asian cultures in which circumcision is not practiced, penile cancer may amount to 10% to 20% of all male malignant neoplasms (Dodge, 1965; Narayana et al, 1982). Data from most large series show that penile cancer is rare among neonatally circumcised individuals but more frequent when circumcision is delayed until puberty (Frew et al, 1967; Gursel et al, 1973; Johnson et al, 1973). Adult circumcision appears to offer little or no protection from subsequent development of the disease (Maden et al, 1993). These data suggest that the critical period of exposure to certain causative agents may have already occurred at puberty and certainly by adulthood, rendering later circumcision relatively ineffective as a prophylactic tool for penile cancer.

Population-based data reveal that although neonatal circumcision is highly protective for invasive penile cancer, it does not afford the same level of protection for carcinoma in situ. Schoen and colleagues (2000) evaluated the incidence of invasive penile cancer or carcinoma in situ during a 10-year period and found only 2 cases of 89 (2.3%) occurring among neonatally circumcised men, whereas of 118 men with carcinoma in situ, 16 cases were noted among 102 men who were circumcised at birth for an incidence of 15.7%. Considering that the protective effects of circumcision on invasive penile cancer are likely to be mediated by avoidance of phimosis, it is noteworthy that another study associated phimosis with the development of invasive penile cancer but not carcinoma in situ (Hung-fu et al, 2001).

Male circumcision has also been shown to be effective against HIV type 1 (HIV-1) infection. This effect was shown to be specific by Reynolds and colleagues (2004). There was no protective effect of circumcision for other sexually transmitted diseases, such as herpes simplex virus type 2 infection, syphilis, or gonorrhea.

HPV infection and exposure to tobacco products appear to be associated with development of penile cancer. Epidemiologic data provided the first clues to a relationship between a sexually transmitted agent and cancer by demonstrating that the wives or ex-wives of men with penile cancer had a threefold higher risk of cervical carcinoma (Graham et al, 1979). Further investigation revealed that

the male partners of women with cervical intraepithelial neoplasia had a significantly higher incidence of penile intraepithelial neoplasia (Barrasso et al, 1987). These same male patients were also found to have a greater incidence of HPV infection.

Polymerase chain reaction and *in situ* hybridization have provided increased evidence for a causative role of HPV by identifying specific DNA sequences from different HPV types in primary penile lesions (malignant and benign) but not in normal foreskins (Varma et al, 1991; Iwasawa et al, 1993). More than 25 types of HPV infect genital sites. HPV types 6 and 11 are most commonly associated with nondysplastic lesions such as genital warts, but these are also noted in nonmetastatic verrucous carcinomas. In contrast, HPV types 16, 18, 31, and 33 are associated with *in situ* and invasive carcinomas (Wiener and Walther, 1995). HPV-16 appears to be the most frequently detected type in primary carcinomas and has also been detected in metastatic lesions (Varma et al, 1991; Iwasawa et al, 1993; Wiener and Walther, 1995). As noted previously, the HPV genome encodes oncoprotein E6, which complexes with the tumor suppressor protein TP53, and oncoprotein E7, which binds the retinoblastoma (RB) protein, thus affecting cell cycle regulation (Munger et al, 1989; zur Hausen, 1996; Levi et al, 1998; Griffiths and Mellon, 1999) via the p14ARF/MDM2/p53 and p15INK4a/cyclin D/Rb pathways (Bleeker et al, 2009). Maden and colleagues (1993) found that the incidence of HPV infection directly correlated with the number of lifetime sexual partners, which was also related to risk of penile cancer. Furthermore, Castellsague and colleagues (1997) noted a direct correlation between the number of sexual partners, HPV-infected men, and incidence of cervical neoplasia among their female partners. Thus, for both cervical and penile cancer, HPV infection represents a preventable cause.

Poblet and coworkers (1999) reported on two patients with coexisting HIV-1 and HPV infection and postulated that HIV-1 could synergize with HPV to increase the progression of HPV penile lesions into penile carcinoma. Although there is evidence supporting this effect in cervical and anal neoplasia, definitive proof for penile cancer awaits further study (Northfelt, 1994).

Although HPV infection is probably an important factor in the development of penile cancer, its presence is not invariable (31% to 63% of patients with penile carcinoma test positive) (Wiener and Walther, 1995), indicating that additional factors may be involved in the development of the disease or its subtypes. Additional evidence includes a study by Rubin and associates (2001), who performed a sensitive polymerase chain reaction assay on penile cancer specimens from the United States and Paraguay and wrote their hypothesis-based essay. Overall, 42% of penile carcinomas were HPV positive. However, only 34.9% and 33.3% of keratinizing and verrucous carcinomas, respectively, were positive, whereas 80% and 100% of basaloid and warty tumor subtypes, respectively, exhibited HPV DNA. Other non-HPV-dependent molecular events leading to penile carcinogenesis have been described, including silencing of the CDK2NA locus via promoter hypermethylation, the expression of genes that target the INK4a/ARF locus, other gene mutations affecting TP53, and p14ARF, and MDM2 overexpression (reviewed in Ferreux et al, 2003; Bleeker et al, 2009).

Four studies have shown a significant association between exposure to cigarette smoke and development of penile cancer (Hellberg et al, 1987; Daling et al, 1992; Maden et al, 1993; Harish and Ravi, 1995). Hellberg and colleagues (1987) studied the smoking history of 244 men with penile cancer and matched controls. They found a significantly increased odds ratio for penile cancer based on whether an individual had smoked, and the risk increased with the number of cigarettes smoked. This observation held even when the presence of phimosis was controlled. Harish and Ravi (1995) extended these observations by showing that all forms of tobacco products, including cigarettes, chewing tobacco, and snuff, were significantly and independently related to the incidence of penile cancer subsequent to multivariate regression analysis. It has been hypothesized that tobacco products can act in the presence of HPV infection or bacteria associated with chronic inflammation to promote malignant transformation. These same risk factors are also

common to other anogenital carcinomas (Daling et al, 1992; Maden et al, 1993).

Penile trauma may be another risk factor for penile cancer. The development of carcinoma in the scarred penile shaft after mutilating circumcision has been reported as a distinct entity (Bissada et al, 1986). Furthermore, Maden and colleagues (1993) found a greater than threefold risk of penile cancer in men with penile tears and rashes. A case-control study also revealed an odds ratio of 18:1 for the development of penile cancer for those men reporting a penile injury 2 years before the onset of the disease (Hung-fu et al, 2001).

Genital ultraviolet radiation, alone and combined with 8-methoxypsoralen, increases the risk of squamous carcinoma at genital sites. A 12-year follow-up study reported that the risk of penile and scrotal cancer was increased 286 times that of the general population for those exposed to ultraviolet A photochemotherapy and 8-methoxypsoralen (PUVA) (Stern, 1990). The risk was dose related. For those treated with ultraviolet B exposure, the risk was 4.6-fold enhanced. Another long-term follow-up study of PUVA-associated malignant neoplasia from Sweden revealed a 30-fold increased risk for skin cancer (but not for penile cancer) among males. In this study, PUVA was also associated with respiratory and pancreatic cancers (Lindelof et al, 1991). Lichen sclerosus (also known as balanitis xerotica obliterans) is a risk factor for the development of penile cancer. Studies have shown the incidence of subsequent cancer with long-term follow-up to be between 2.3% and 9% of men with LS (Depasquale et al, 2000; Micali et al, 2001). Velazquez and Cubilla (2003) studied LS occurring in association with penile cancer and noted its presence distinctly among the subset of penile carcinomas that were not associated with HPV.

Larger studies performed in areas where the disease is endemic, incorporating the many risk factors for penile cancer into a multivariate analysis, are clearly needed to define which factors independently confer risk. Thus far, no convincing evidence has been found linking penile cancer to other factors such as occupation, other venereal diseases (gonorrhea, syphilis, and herpes), marijuana use, or alcohol intake (Maden et al, 1993).

Prevention

The role of routine neonatal circumcision as a preventive strategy for penile cancer has been, to say the least, a controversial topic. The position of the American Academy of Pediatrics has changed over time with accumulating evidence from one of denial of any medical benefits (Schoen et al, 1989) to the more moderate position stating, "There are potential medical benefits of newborn circumcision" (Shapiro, 1999) to the most recent statement published in August 2012, which states, "Evaluation of current evidence indicates that the health benefits of newborn male circumcision outweigh the risks and that the procedure's benefits justify access to this procedure for families who choose it." Specific benefits in their data review included prevention of urinary tract infections, penile cancer, and transmission of sexually transmitted infections including HIV (American Academy of Pediatrics Task Force on Circumcision, 2012).

Any argument against circumcision must consider that penile carcinoma represents the only neoplasm for which there exists a predictable and simple means of prophylaxis to spare the organ at risk (Dagher et al, 1973). Although circumcision can obviate the disease, especially where facilities for daily hygiene may be lacking, it may not be as important in countries where good hygiene is practiced. Frisch and colleagues (1995) reported a falling incidence of penile cancer (from 1.15 per 100,000 men to 0.82 per 100,000 men) in the Danish population, which has a circumcision rate of only 1.6%. They attributed this trend to improved hygiene because the incidence of dwellings having a bath facility increased from 35% in the 1940s to 90% in the 1990s. Thus, considering the benefits of circumcision (including the prevention of infections, HIV infection and its transmission, and penile and cervical cancer), enhanced education about the potential benefits of circumcision, especially in developing countries, seems rational (Schoen et al, 1989; Reynolds et al, 2004; Kinkade et al, 2005).

Although neonatal circumcision and good hygiene to prevent the occurrence of phimosis represent important prevention strategies, additional efforts to prevent malignant transformation include avoidance of HPV infection potentially through condom use, of ultraviolet light exposure, and of tobacco products. Thus, modifiable behaviors can potentially prevent penile cancer (Munger et al, 1989; Maden et al, 1993; Harish and Ravi, 1995; Levi et al, 1998; Griffiths and Mellon, 1999; Bleeker et al, 2009).

As mentioned previously, HPV vaccination could play an emerging role in the future with respect to preventing transmission of HPV between males and females and potentially penile cancer. To date two prophylactic HPV vaccines are available (HPV 16/18 vaccine Cervarix [GlaxoSmithKline] and the quadrivalent HPV 16/18/6/11 vaccine Gardasil [Merck Sharp & Dohme]), and the efficacy of preventing HPV infection among HPV-negative young women and men has been demonstrated (Harper et al, 2004; Villa et al, 2005; Block et al, 2006; Bleeker et al, 2009; Giuliano et al, 2011).

KEY POINTS: EPIDEMIOLOGY, ETIOLOGY, AND PREVENTION

- Penile cancer is rare in developed countries and varies worldwide with age, circumcision, and hygiene practices.
- Recent epidemiologic data from the United States suggest a disparity in outcome, with African-Americans exhibiting poorer survival.
- Risk factors for development of penile cancer include lack of neonatal circumcision, phimosis, HPV infection, exposure to tobacco products, penile LS, and potentially penile trauma and exposure to PUVA.
- Histologic subtypes of penile cancer are correlated with HPV infection.
- Penile cancer represents a preventable disease in most cases via neonatal circumcision and/or behavior modification.

Natural History

Carcinoma of the penis usually begins with a small lesion that gradually extends to involve the entire glans, shaft, and corpora. The lesion may be papillary and exophytic or flat and ulcerative; if it is untreated, penile autoamputation may occur as a late result. The rates of growth of the papillary and ulcerative lesions are similar, but the flat, ulcerative tumor has a tendency toward earlier nodal metastasis and is associated with poorer 5-year survival rates (Dean, 1935; Marcial et al, 1962; Ornellas et al, 1994). Lesions larger than 5 cm (Beggs and Spratt, 1964) and those extending over 75% of the shaft (Staubitz et al, 1955) are also associated with an increased incidence of metastases and a decreased survival rate. However, others have not found a consistent relationship among lesion sizes, presence of metastases, and decreased survival (Ekstrom and Edsmyr, 1958; Puras et al, 1978).

Buck fascia acts as a temporary natural barrier to local extension of the tumor, protecting the corporeal bodies from invasion. Penetration of Buck fascia and the tunica albuginea permits invasion of the vascular corpora and establishes the potential for vascular dissemination. Urethral or bladder involvement is rare (Riveros and Gorostiaga, 1962; Thomas and Small, 1968).

The earliest route of dissemination from penile carcinoma is metastasis to the regional femoral and iliac nodes. A detailed description of lymphatic drainage of the penis is found elsewhere in this text and is well documented in the literature (Dewire and Lepor, 1992). Briefly, the lymphatics of the prepuce form a connecting network that joins with the lymphatics from the skin of the shaft. These tributaries drain into the superficial inguinal nodes (the nodes external to the fascia lata). The lymphatics of the glans join

the lymphatics draining the corporeal bodies, and they form a collar of connecting channels at the base of the penis that drain by way of the superficial nodes. The superficial nodes drain to the deep inguinal nodes (those deep to the fascia lata). From there, drainage is to the pelvic nodes (external iliac, internal iliac, and obturator). Penile lymphangiographic studies demonstrate a consistent pattern of drainage that proceeds from superficial inguinal to deep inguinal to pelvic node sites without evidence of ipsilateral drainage (Cabanias, 1977, 1992). Multiple cross-connections exist at all levels of drainage, so that penile lymphatic drainage is bilateral to both inguinal areas.

Metastatic enlargement of the regional nodes eventually leads to skin necrosis, chronic infection, and death from inanition, sepsis, or hemorrhage secondary to erosion into the femoral vessels. Clinically detectable distant metastatic lesions to the lung, liver, bone, or brain are uncommon and are reported to occur in 1% to 10% of patients in most large series (Staubitz et al, 1955; Riveros and Gorostiaga, 1962; Beggs and Spratt, 1964; Derrick et al, 1973; Johnson et al, 1973; Kossow et al, 1973; Puras et al, 1978, reviewed in Pettaway et al, 2010). Such metastases usually occur late in the course of the disease after the local lesion has been treated. Distant metastases in the absence of regional node metastases are unusual.

Carcinoma of the penis is characterized by a relentless progressive course, causing death for the majority of untreated patients within 2 years (Beggs and Spratt, 1964; Skinner et al, 1972; Derrick et al, 1973). Rarely, long-term survival occurs, even with advanced local disease and regional node metastases (Furlong and Uhle, 1953; Beggs and Spratt, 1964). No report of spontaneous remission of carcinoma of the penis is known. Five percent to 15% of patients have been reported to develop a second primary neoplasm (Buddington et al, 1963; Beggs and Spratt, 1964; Gursel et al, 1973), and one series reported secondary carcinoma in 17% of patients (Hubbell et al, 1988).

Modes of Presentation

Signs

It is the penile lesion itself that usually alerts the patient to the presence of penile cancer. The presentation ranges from a relatively subtle induration or small excrescence to a small papule, pustule, warty growth, or more luxuriant exophytic lesion. It may appear as a shallow erosion or as a deeply excavated ulcer with elevated or rolled-in edges. Phimosis may obscure a lesion and allow a tumor to progress silently. Eventually, erosion through the prepuce, foul preputial odor, and discharge with or without bleeding call attention to the disease.

Penile tumors may arise anywhere on the penis but occur most commonly on the glans (48%) and prepuce (21%). Other tumors involve the glans and prepuce (9%), the coronal sulcus (6%), or the shaft (<2%) (Sufrin and Huben, 1991). This distribution of lesions may be the result of constant exposure of the glans, coronal sulcus, and interior prepuce to irritants (e.g., smegma, HPV infection) within the preputial sac, whereas the shaft is relatively spared.

Rarely, a mass, ulceration, suppuration, or hemorrhage in the inguinal area may be caused by nodal metastases from a lesion concealed within a phimotic foreskin. Urinary retention or urethral fistula from local corporeal involvement is a rare presenting sign.

Symptoms

Pain does not develop in proportion to the extent of the local destructive process and usually is not a presenting complaint. Weakness, weight loss, fatigue, and systemic malaise occur secondary to chronic suppuration. On occasion, significant blood loss from the penile lesion, the nodal lesion, or both may occur. Because local disease and regional disease are usually far advanced by the time distant metastases occur, presenting symptoms referable to such metastases are rare.

Diagnosis

Delay

Patients with cancer of the penis, more than patients with other types of cancer, seem to delay seeking medical attention (Lynch and Krush, 1969). In large series, 15% to 50% of patients delayed medical care for more than a year (Dean, 1935; Buddington et al, 1963; Hardner et al, 1972; Gursel et al, 1973). Explanations include embarrassment, guilt, fear, ignorance, and personal neglect. This level of denial is substantial, given that the penis is observed and handled on a daily basis.

Delay on the part of the physician in initiating both diagnosis and treatment may also be considerable. In some instances patients have been given prolonged courses of antibiotics or topical antifungal preparations before being referred for biopsy. Although some studies show that the difference in survival rates between patients with early presentation and those with later presentation is negligible (Ekstrom and Edsmyr, 1958; Johnson et al, 1973), other series show decreased survival with longer delay (Hardner et al, 1972). It appears logical that earlier diagnosis and treatment should improve outcome.

Examination

At presentation most lesions are confined to the penis (Skinner et al, 1972; Derrick et al, 1973; Johnson et al, 1973). The penile lesion is assessed with regard to size, location, fixation, and involvement of the corporeal bodies. Inspection of the base of the penis and scrotum is necessary to rule out extension into these areas. Rectal and bimanual examination provides information about perineal body involvement and presence of a pelvic mass. Careful bilateral palpation of the inguinal area for adenopathy is extremely important.

KEY POINTS: NATURAL HISTORY AND PRESENTATION

- Penile cancer often begins on the surface of the glans penis or in the preputial area, where it progressively enlarges.
- Delay both in seeking medical attention and then in subsequent definitive biopsy is common.
- Examination of both the penile primary tumor and the inguinal region is critical to treatment planning.
- Metastasis occurs by embolization of tumor deposits from the penile tumor through penile lymphatics to the inguinal lymph nodes.
- Distant metastases occur late in the history of the disease.

Biopsy

Confirmation of the diagnosis of carcinoma of the penis and assessment of the depth of invasion, the presence of vascular invasion, and the histologic grade of the lesion by microscopic examination of a biopsy specimen are mandatory before the initiation of any therapy. This provides insight into the therapeutic options for treatment of the primary lesion as well as the likelihood of nodal metastases in patients with no palpable adenopathy (McDougal, 1995; Lopes et al, 1996; Theodorescu et al, 1996).

Biopsy may be a separate procedure from definitive surgical treatment. A dorsal slit is frequently necessary to gain adequate exposure of the lesion for satisfactory biopsy. An alternative approach to treatment is biopsy with frozen-section confirmation followed by partial or total penectomy. Full informed consent must be obtained before the procedure. Velazquez and colleagues (2004) demonstrated the shortcomings of superficial diagnostic biopsies in a study evaluating specimens from 57 patients. There was difficulty in delineating the extent of depth in 91% of patients, discordance with the histologic grade in 30% of patients (specifically with

verrucous and mixed histologic patterns), and failure to detect any cancer in 3.5% of patients with well-differentiated cancers. The importance of obtaining an adequate biopsy specimen cannot be overemphasized.

Histologic Features

Most tumors of the penis are squamous cell carcinomas demonstrating keratinization, epithelial pearl formation, and various degrees of mitotic activity. The normal rete pegs are disrupted. Invasive lesions penetrate the basement membrane and the surrounding structures. Cubilla and associates (1993) originally divided penile cancers by growth pattern into superficially spreading squamous carcinoma, vertical growth carcinoma, verrucous carcinoma, and multicentric carcinoma. The superficially spreading carcinoma occurred most frequently, and inguinal lymph node metastases were found in 42% of patients. However, lymph node metastases were noted in 82% of patients with a vertical growth pattern, in none of those with a verrucous pattern, and in 33% of those with multicentric carcinomas. Subsequent to review of 61 cases from Memorial Sloan Kettering Cancer Center, Cubilla and colleagues (2001) classified the histologic types as follows: usual type, 59% of cases; papillary, 15%; basaloid, 10%; warty (condylomatous), 10%; verrucous, 3%; and sarcomatoid, 3%. Of note, both the basaloid and sarcomatous types were associated with aggressive behavior; 5 of 7 patients with these histologic patterns exhibited metastasis, and 5 of 8 (63%) died. In contrast, the verruciform histologic patterns were more favorable (1 patient with metastasis and no deaths). The typical squamous histologic type was intermediate in biologic potential; 14 of 26 patients exhibited metastases, and 13 of 36 (36%) died.

The basaloid variant, in addition to its aggressive behavior as noted previously, is associated with HPV expression in approximately 80% of cases (Gregoire et al, 1995; Cubilla et al, 1998, 2001; Rubin et al, 2001).

Squamous cell carcinomas have classically been graded using the Broders classification to define the level of differentiation on the basis of keratinization, nuclear pleomorphism, number of mitoses, and several other features (Broders, 1921; Lucia and Miller, 1992). This grading system was originally designed for squamous carcinoma of the skin and has been adapted by pathologists for penile squamous carcinoma. Four grades were originally described, but it is common for authors to modify this to a three-grade system by combining grades (Maiche et al, 1991). Low-grade lesions (grade 1 and grade 2) constitute 70% to 80% of the reported cases at diagnosis, whether a three- or four-grade system is used (Maiche et al, 1991). These well-differentiated lesions show cords of atypical squamous cells projecting downward from a hyperkeratotic epidermis. The lower-grade carcinomas typically demonstrate keratin, prominent intercellular bridges, and keratin pearls, characteristics that are absent in high-grade tumors. Almost half the tumors originating in the shaft are poorly differentiated (grade 3 and grade 4, depending on scale), whereas only 10% of tumors located in the prepuce are high-grade tumors (Maiche et al, 1991). Thus, grade and stage are often correlated.

Several studies have emphasized the association of high-grade disease with regional nodal metastases (Fraleigh et al, 1989; Ravi, 1993a; McDougal, 1995; Theodorescu et al, 1996; Heyns et al, 1997). Overall, there is a significant body of agreement as to the histologic features that characterize high tumor grade (grade 3 and grade 4) and its correlation with nodal metastasis. However, as noted previously, most tumors are of lower grades. Histologic features that would better stratify the prognosis for patients with invasive, low- to intermediate-grade penile cancers would be of value for management of patients.

Slaton and colleagues (2001) found that describing the percentage of poorly differentiated cancer in the primary penile tumor specimen correlated with lymph node metastasis. In this study, a semiquantitative system that estimated the amount of high-grade cancer (i.e., $\leq 50\%$ vs. $>50\%$) was significantly associated with nodal metastases and was more predictive than the Broders

three-grade system in stratifying those with or without nodal metastasis.

However, [Chaux and colleagues \(2009\)](#) questioned these findings as they examined 117 specimens among patients undergoing primary tumor therapy and lymph node dissection. Over 50% of the tumors were actually heterogeneous with respect to grade, and among these tumors any proportion of grade 3 cancer was associated with lymph node metastasis. These disparate findings point to at least three problems with respect to grading and prognosis, including (1) lack of a uniform system, (2) reproducibility of interpretation, and (3) intratumoral heterogeneity of tumor components.

Vascular invasion by tumor cells has significant prognostic importance but may not be specifically mentioned in pathology reports. When vascular invasion is present, it provides valuable information. Four studies have assessed its presence or absence, and it was an important predictor of nodal metastasis in all the reports ([Fraleigh et al, 1989](#); [Lopes et al, 1996](#); [Heyns et al, 1997](#); [Slaton et al, 2001](#)). Thus the pathologist should specifically comment on the presence or absence of vascular invasion in the surgical specimen.

Perineural invasion was recently found to be present in 36% of cases analyzed in a multi-institutional data set of 134 patients and was a strong predictor of lymph node metastasis ([Velazquez et al, 2008](#)).

KEY POINTS: BIOPSY AND HISTOLOGIC FEATURES

- Adequate tumor biopsy is essential to diagnosis and treatment planning.
- Squamous carcinoma histologic subtypes include usual type, papillary, basaloid, warty, verrucous, and sarcomatoid. They vary with respect to metastatic potential.
- Pathologic description of anatomic structures invaded (i.e., stage), the grade, and the status of vascular and perineural invasion provide important information to assess the risk of metastasis.

Laboratory Studies

The results of laboratory tests in patients with penile cancer are often normal. Anemia, leukocytosis, and hypoalbuminemia may be present in patients with chronic illness, malnutrition, and extensive suppuration at the area of the primary and inguinal metastatic sites. Azotemia may develop secondary to urethral or ureteral obstruction.

Hypercalcemia without detectable osseous metastases has been associated with penile cancer ([Anderson and Glenn, 1965](#); [Rudd et al, 1972](#)). In a review from Memorial Sloan Kettering Cancer Center ([Sklaroff and Yagoda, 1982](#)), 17 of 81 patients (20.9%) were hypercalcemic. Hypercalcemia seems to be largely a function of the bulk of the disease. It is often associated with inguinal metastases and may resolve after excision of involved inguinal nodes ([Block et al, 1973](#)). **Parathyroid hormone and related substances may be produced by both tumor and metastases that activate osteoclastic bone resorption** ([Malakoff and Schmidt, 1975](#)). Medical treatment of hypercalcemia includes aggressive saline hydration to restore the extracellular fluid volume and to promote both sodium and calcium excretion. The administration of diuretics is performed if volume overload is suspected. Bisphosphonates (e.g., pamidronate, etidronate, and zoledronic acid) have become first-line therapy because they possess demonstrated efficacy as antiresorptive agents and are relatively safer than mithramycin, an older agent ([Videtic et al, 1997](#); [Morton and Lipton, 2000](#)). For severe hypercalcemia associated with neurologic manifestations, the antiresorptive bisphosphonates can be combined with an

agent that produces calciuria, such as calcitonin, to rapidly lower serum calcium levels.

Radiologic Studies

Primary Penile Tumor. In patients with penile cancer both the primary tumor and the inguinal lymph nodes are readily assessed by palpation. However, [Horenblas and associates \(1991\)](#) found that physical examination incorrectly established the actual pathologic stage in 26% of cases, with understaging in 10% and overstaging in 16%. It is clear that more accurate means of staging for penile tumors is needed.

Penile ultrasonography was performed on 16 patients referred for primary therapy by [Horenblas and colleagues \(1994\)](#). With use of a 7.5-MHz linear array small parts transducer they found that the ultrasound appearance of cancer was invariably hypoechoic. However, ultrasound examination often underestimated the thickness of tumors and could not delineate invasion into the subepithelial connective tissue of the glans penis from corpus spongiosum involvement (i.e., glanular stage T1 vs. glanular stage T2). However, the tunica albuginea separating the corpus cavernosum from the glans was easily identified in all patients, and the sensitivity for detecting corpus cavernosum invasion was 100%. This study confirmed the value of ultrasonography in assessing the primary tumor, as reported by others ([Yamashita and Ogawa, 1989](#); [Dorak et al, 1992](#)).

Several studies have assessed the role of magnetic resonance imaging (MRI) in evaluating both the normal penis and its involvement by cancer. [Vapnek and associates \(1992\)](#) described the MRI appearance of the normal corpus cavernosum, corpus spongiosum, tunica albuginea, and Buck fascia. Of six patients with urethral cancer, the disease was accurately staged in five (83%). [De Kerviler and colleagues \(1995\)](#) used gadolinium contrast-enhanced MRI to compare both clinical and MRI findings with tumor pathologic stage. Clinical examination correctly staged six of nine tumors: MRI was correct in seven of nine cases but was not useful for clinical T1 lesions. Compared with MRI and ultrasonography, computed tomography (CT) has poor soft-tissue resolution and has not been useful for imaging the extent of the primary tumor ([Vapnek et al, 1992](#)).

[Lont and associates \(2003\)](#) directly compared physical examination with ultrasonography and MRI to assess their ability to determine the tumor stage. They evaluated 33 patients with penile squamous cell carcinoma, all of whom underwent ultrasound examination, MRI, and physical examination of the primary tumor. Findings were correlated with histologic evaluation of the specimens obtained at surgery with a focus on determining the invasion of the corpus cavernosum. The respective positive predictive value, sensitivity, and specificity for the study were as follows—physical examination: 100%, 86%, 100%; ultrasound examination: 67%, 57%, 91%; and MRI: 75%, 100%, 91%. This comparative study concluded that physical examination is reliable in determining corporeal invasion and that additional tests are mainly of value when physical examination cannot be properly performed.

The technique of artificial erection (by intracorporeal injection of prostaglandin E₁) may augment the use of contrast-enhanced MRI in staging of the primary tumor. A study by the European Institute of Oncology evaluated nine patients to compare clinical, pathologic, and MRI staging ([Scardino et al, 2004](#)). MRI aided by artificial erection and contrast enhancement was shown to be of value because it correlated with pathologic stage in eight of nine cases, whereas physical examination correlated with only five of nine cases. These data suggest that this novel MRI approach could be beneficial in staging of glanular tumors, specifically when physical examination findings are equivocal. Thus, for small-volume glanular lesions, imaging studies add virtually no additional information to palpation in most patients. However, for lesions thought to invade the corpus cavernosum, contrast-enhanced MRI (perhaps augmented with artificial erection) may provide unique information, especially when physical examination

findings are equivocal and organ-sparing techniques are being considered.

Inguinal and Pelvic Region

Current Imaging Strategies among Clinical Node-Negative Patients. The ability to noninvasively determine the presence or absence of inguinal and pelvic metastases in patients with penile cancer remains problematic because physical examination exhibits varying reliability based on the grade and stage of the primary tumor as well as body habitus of the patient. Both CT and MRI techniques have depended on lymph node enlargement for detection of metastases but are unable to define the internal architecture of normal-sized nodes. Because CT and MRI have similar accuracy in determining lymphadenopathy in other cancers, CT has often been the imaging modality chosen in penile cancer to examine the inguinal and pelvic areas as well as to rule out more distant metastases.

Horenblas and associates (1991) compared the ability of physical examination, CT, and lymphangiography to assess the inguinal region in patients who were surgically staged or had prolonged follow-up. In 102 patients with a 39% prevalence of positive nodes, the sensitivity and specificity of physical examination were 82% and 79%, respectively. Of note, both CT and lymphangiography were performed in patients who were thought to have metastases. The sensitivity of lymphangiography was only 31%, but there were no false-positive results. Similarly, the sensitivity and specificity of CT were 36% and 100%, respectively. The combination of CT and lymphangiography performed simultaneously demonstrated equally poor sensitivity. Only one fifth of patients had positive nodes detected with either test. On the basis of these data the authors concluded that CT and lymphangiography offer no useful additional information over physical examination, especially in patients with no palpable adenopathy. An important caveat is that CT may have a role in examination of the inguinal region in obese patients or in those who have had prior inguinal surgery, in whom the physical examination may be unreliable.

Insights in the field of nanoparticle technology have been applied to imaging of genitourinary malignant neoplasms to enhance detection of microscopic metastases. Ferumoxtran-10 particles (size, 35 nm), administered at a dose of 2.6 mg of iron per kilogram of body weight intravenously combined with MRI, were capable of imaging microscopic metastasis in lymph nodes that were by size criteria normal (1 cm). Tabatabaei and colleagues (2005) evaluated lymphotropic nanoparticle-enhanced MRI (LNMRI) in seven patients with penile cancer who subsequently underwent groin dissection. Five of seven patients had no palpable adenopathy. LNMRI was highly sensitive and detected positive nodes in all five of these patients. Of note, the size range of the metastases was less than 1 cm in four patients. Unfortunately, no confirmatory studies were performed using this agent, and the compound is not currently available for routine use.

Squamous carcinoma was shown to take up the radiopharmaceutical fluorodeoxyglucose (FDG) and to be amenable to detection using combination positron emission tomography (PET) and CT. Scher and associates (2005) evaluated PET/CT among 13 patients with penile cancer who received injections of FDG. Five of the 13 patients had metastatic disease, and FDG-PET/CT detected it in 4 of them (80% sensitivity). However, in a follow-up study from the Netherlands, PET/CT was used in patients who were clinically node negative to determine the sensitivity among patients scheduled to undergo inguinal staging procedures. Among 5 patients with proven nodal metastasis, PET/CT was positive in only 1 (i.e., sensitivity of 20%) (Leijte et al, 2009a).

Among a similar cohort reported from this same group, ultrasound-guided needle aspiration was also shown to have limited sensitivity as well, detecting only 9 of 23 patients with proven metastases (sensitivity of 39%; Kroon et al, 2005a). Thus, among clinically node-negative patients, no current imaging modality has been shown to be sufficiently sensitive to detect microscopic metastases.

Current Imaging Strategies among Clinical Node-Positive Patients. Recent data among patients with proven inguinal

metastases suggest that additional imaging may be of value in determining those patients with advanced disease who might do poorly when treated with surgery alone or could in fact exhibit occult distant metastases.

Graafland and colleagues (2011) evaluated the CT scan findings among a cohort of biopsy-proven patients with metastatic inguinal adenopathy to define if scan parameters could determine those with poor prognostic features subsequent to lymphadenectomy. They found that central necrosis or an irregular nodal border was highly sensitive and specific for any of the poor prognostic features including three or more positive nodes, extranodal extension (ENE) of cancer, or positive pelvic nodes.

In contrast to the clinically node-negative disease setting, one study has shown the potential value of PET/CT among patients with proven inguinal metastases. Graafland and coworkers (2009) studied PET/CT among 18 patients with biopsy-proven inguinal metastases and found PET/CT to have a sensitivity and specificity of 91% and 100%, respectively, for detecting pelvic lymph node metastases. In that study, PET/CT also identified several patients with distant metastases that were unsuspected. Thus, if confirmed, PET/CT may become an important study for detecting pelvic and distant metastasis.

In general, distant metastases occur late in the course of the disease, usually in patients with recognized significant inguinal and pelvic adenopathy. The most common metastatic sites are the lung, bone, and liver. Currently, in addition to chest, abdominal, and pelvic CT, radionuclide bone scintigraphy may be indicated to stage the extent of disease in patients thought to have widespread metastases (Vapnek et al, 1992).

KEY POINTS: RADIOLOGIC STUDIES

- Soft-tissue detail of penile tumors is best imaged by MRI.
- Physical examination provides the most reliable staging information for small distal lesions.
- Penile MRI performed in combination with artificial erection may provide unique staging information when physical examination findings are equivocal.
- Physical examination of the inguinal region remains the clinical gold standard for evaluating the presence of metastasis in the nonobese patient.
- CT or MRI can be useful in evaluating the inguinal region of obese patients and in those who have had prior inguinal surgery.
- Among patients with proven inguinal metastases, CT scan of the abdomen and pelvis may help to determine those patients with poor prognostic features for cure with surgery alone.
- PET/CT may be useful among patients with clinically detected inguinal metastases to define the presence of pelvic or distant metastasis.

Penile Cancer Staging

Seventh Edition TNM Penile Staging System. The seventh edition of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) TNM staging system was published in 2010 and has become the consensus method for staging penile cancer (Table 37-1, Fig. 37-2) (Edge et al, 2010). With respect to the primary tumor, because grade and the presence of vascular invasion are established prognostic markers in predicting the risk of subsequent inguinal metastasis, the seventh edition TNM stratifies pT1 stage by their presence (i.e., high-grade tumors, vascular invasion present is pT1b) or absence (pT1a) (Slaton et al, 2001; Solsona et al, 2004; Ficarra et al, 2005). In addition, prostatic invasion (a rare finding) is now included in the pT4 designation.

Of considerable importance is that the seventh edition has both clinical and pathologic nodal staging descriptors to facilitate both

TABLE 37-1 American Joint Committee on Cancer (AJCC) Staging for Penile Cancer

PRIMARY TUMOR (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
Ta	Noninvasive verrucous carcinoma*		
T1a	Tumor invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated (i.e., grade 3-4)		
T1b	Tumor invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated		
T2	Tumor invades corpus spongiosum or cavernosum		
T3	Tumor invades urethra		
T4	Tumor invades other adjacent structures		
LYMPH NODES (N)			
NX	Regional nodes cannot be assessed†		
pNX	Regional nodes cannot be assessed‡		
N0	No palpable or visibly enlarged inguinal lymph nodes†		
pN0	No regional lymph node metastasis‡		
N1	Palpable mobile unilateral inguinal lymph node†		
pN1	Metastasis in a single inguinal lymph node‡		
N2	Palpable mobile multiple or bilateral inguinal lymph nodes†		
pN2	Metastasis in multiple or bilateral inguinal lymph nodes‡		
N3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral†		
pN3	Extranodal extension of lymph node metastasis or pelvic lymph node(s), unilateral or bilateral‡		
DISTANT METASTASIS (M)			
M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
M1	Distant metastasis§		
STAGE GROUPING			
Stage 0	Tis	N0	M0
	Ta	N0	M0
Stage I	T1a	N0	M0
Stage II	T1b	N0	M0
	T2	N0	M0
	T3	N0	M0
Stage IIIa	T1-3	N1	M0
Stage IIIb	T1-3	N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

*Broad pushing penetration (invasion) is permitted; destructive invasion is against the diagnosis.

†Based on palpation and imaging.

‡Based on biopsy or surgical excision.

§Lymph node metastasis outside the true pelvis in addition to visceral or bone sites.

From Edge SB, Byrd DR, Compton CC, et al. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.

clinical and pathologic staging to better predict prognosis before definitive therapy. As pointed out by [Leijte and colleagues \(2008\)](#), the prognosis worsens for patients exhibiting greater degrees of palpable adenopathy (i.e., unilateral vs. bilateral vs. a fixed mass) or positive nodes on imaging versus those with clinically negative inguinal lymph nodes. Considering pathologic nodal factors further,

the seventh edition stratifies patients with a single positive node from those with multiple or bilateral nodes and further recognizes the ominous prognosis (5% to 18% 5-year survival) associated with ENE of cancer ([Srinivas et al, 1987](#); [Ravi, 1993a](#); [Lont et al, 2007](#)).

Considering that the pathologic status of inguinal nodes is the driving factor determining survival, stage groupings (i.e., stage 0 to

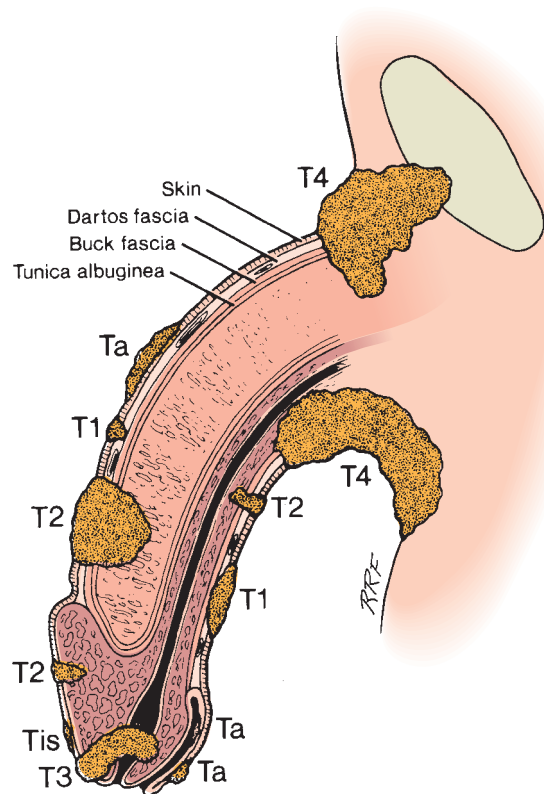


Figure 37-2. Because treatment decisions for inguinal node dissections are based on the characteristics of the primary lesion (see section on [treatment of inguinal nodes](#)), a careful assessment of the depth of invasion of the primary tumor is required. This diagram illustrates the importance of depth of invasion in assigning tumor (T) stage.

stage IV [see [Table 37-1](#)]) in the seventh edition TNM use the extent of nodal involvement as the major consideration. Thus the strength of the unified AJCC-UICC seventh edition TNM system (2010) is that it provides not only an accurate assessment of the primary tumor based on clinical staging (examination, biopsy) but also clinical and improved pathologic descriptors of lymph node status to predict outcome. Furthermore, the nodal status of the new TNM version has been externally validated among node-positive patients in a recent study from Shanghai ([Zhu et al, 2011](#)). In that study, stratification of recurrence-free survival among N1 to N3 categories was significantly better when comparing the seventh edition TNM to the prior sixth edition system.

Another recent important prognostic variable, lymph node density (LND), has been described. This variable describes the number of positive inguinal or pelvic nodes removed at surgery as a function of the total number of nodes removed. Thus, in addition to describing the number of positive lymph nodes, it also includes a potential quality variable in incorporating the total lymph node yield. [Svatek and colleagues \(2009\)](#) described this initially in a small series of 45 patients with proven inguinal metastasis, finding that LND was the strongest predictor of disease-specific survival, even when considering TNM stage and extracapsular extension. [Zhu and colleagues \(2011\)](#) confirmed this finding subsequently and also showed that LND retained its independent prognostic ability even when considering the improved seventh edition TNM staging system. Larger series of node-positive patients will be required to more precisely determine clinically useful cutoff values for LND as well as what constitutes an adequate lymph node yield at lymphadenectomy.

In the TNM staging system the primary tumor stage is assigned by biopsy (or even more reliably by complete resection) and

BOX 37-1 Minimal Diagnostic Criteria for Carcinoma of the Penis

PRIMARY TUMOR (T)

Clinical examination

Incisional-excisional biopsy of lesion (or complete resection) and histologic examination for grade, anatomic structure invaded, and presence of vascular invasion

REGIONAL AND JUXTAREGIONAL LYMPH NODES (N)

Clinical examination

CT, if inguinal adenopathy is palpable*

CT/PET may be considered for bulky inguinal adenopathy†

Superficial inguinal node dissection or dynamic sentinel node biopsy (as indicated for high grade, vascular invasion, or invasive histologic pattern)

Aspiration cytology (as indicated)

DISTANT METASTASES (M)

Clinical examination

Biochemical determinations (liver functions, calcium)

CT scan of the chest, abdomen, pelvis; bone scintigraphy; or CT/PET scan (as indicated)

*CT should also be performed in obese patients and those who have had prior inguinal surgery, whose physical examination findings may be unreliable.

†CT/PET scans coregistered to correlate uptake with anatomic location. CT, computed tomography; PET, positron emission tomography.

additional prognostic factors within the primary tumor now included in the TNM system (i.e., tumor grade and the presence of vascular invasion). In most cases the presence of palpable adenopathy, along with the histologic features of the primary tumor, determines the need for additional imaging studies. Positive fine-needle aspiration of palpably enlarged inguinal nodes or fine-needle biopsy of pelvic adenopathy identified by CT can assist in assigning nodal stage before therapy. In patients requiring surgical staging (palpable lymph nodes or those with adverse primary tumor histologic features), pathologic nodal status assigned according to seventh edition TNM stage provides valuable prognostic information. The suggested diagnostic criteria for current TNM staging are listed in [Box 37-1](#).

KEY POINTS: STAGING

- Both clinical and pathologic factors related to the presence and extent of lymph node involvement determine survival and should be recorded.
- The current, seventh edition unified TNM staging system represents a consensus document that includes both clinical and pathologic descriptors that provide important prognostic information.

Differential Diagnosis

A number of penile lesions must be considered in the differential diagnosis of penile carcinoma. They include condyloma acuminatum, Buschke-Löwenstein tumor, and balanitis xerotica obliterans, as well as a number of infectious lesions (e.g., chancre, chancroid, herpes, lymphopathia venereum, granuloma inguinale, and tuberculosis). These diseases can be identified by appropriate skin tests, tissue studies, serologic examinations, cultures, or specialized staining techniques.

SURGICAL MANAGEMENT OF THE PRIMARY TUMOR

Organ Preservation

Surgical amputation of the primary tumor remains the oncologic gold standard for rapid definitive treatment of the penile primary tumor; local recurrence rates range from 0% to 8% (de Kernion et al, 1973; McDougal et al, 1986; Horenblas et al, 1992). Whereas amputation is often necessary for bulky stage T2 to T4 tumors, it has been shown to decrease sexual quality of life (Opjordsmoen and Fossa, 1994). This is relevant because approximately 55% of penile cancer patients are 60 years of age or younger and 30% are 55 years of age or younger (Narayana et al, 1982).

It is generally accepted that patients with penile primary tumors exhibiting favorable histologic features (stages Tis, Ta, T1; grade 1 and grade 2 tumors) are at a lower risk for metastases. These patients are also best suited for organ-sparing or glans-sparing procedures (Solsona et al, 2004). The goal of treatment is to preserve glans sensation where possible or at least to maximize penile shaft length. Such approaches include topical treatments (5-fluorouracil or imiquimod cream for Tis only), radiation therapy, Mohs surgery, limited excision strategies, and laser ablation (Sanchez-Ortiz and Pettaway, 2003; Solsona et al, 2004; Minhas et al, 2005; Crook et al, 2009; Alnajjar et al, 2012). This section focuses on novel insights into surgical strategies to achieve organ preservation. Radiation-based strategies are discussed later in the section on radiation therapy for the primary lesion.

Circumcision and Limited Excision Strategies

Circumcision, limited excisions of the glans, and glans removal with sparing of the penile shaft represent surgical strategies to maintain function and penile length. Historically, data on circumcision and limited excision of glanular lesions have been associated with recurrence rates from 11% to 50% (Hanash et al, 1970; Skinner et al, 1972; McDougal et al, 1986). However, the grade, size, and exact location of the lesion and the status of surgical margins were often unavailable in such reports.

Recent reports have suggested that conservative surgery may be performed safely in well-selected patients with discrete tumors by intraoperative frozen-section analysis (Davis et al, 1999; Bissada et al, 2003; Pietrzak et al, 2004; Minhas et al, 2005). In addition, several studies have challenged the dictum establishing that a 2-cm surgical margin is required for all patients undergoing partial penectomy (Hoffman et al, 1999; Agrawal et al, 2000). After performing a prospective histologic analysis of 64 penectomy specimens, Agrawal and associates (2000) concluded that tumor grade highly correlated with microscopic tumor spread. The maximum proximal histologic extent was 5 mm for grade 1 and grade 2 tumors and 10 mm for grade 3 tumors. Furthermore, "skip" lesions were not encountered. After performing a retrospective pathologic review of 12 penectomy specimens, Hoffman and colleagues (1999) also found 7 patients with disease of pathologic stage T1 or greater with microscopic margins measuring less than 10 mm. None of these patients had disease recurrence at a mean follow-up of 32.4 months. Pietrzak and colleagues (2004) documented the use of various techniques in a series of 39 patients to excise the tumor and to reconstruct or graft the glans and distal penis. With a mean follow-up of 16 months, only 1 patient (2.5%) who underwent a partial glans resection had a local recurrence. There were two early complications with grafts and two late complications with graft overgrowth intruding on the urethral meatus. Minhas and associates (2005) similarly performed either wide local excision or glans penis removal in 51 patients with margins of 0 to 10 mm in 48% and less than 2 cm in 98% of patients. With a median follow-up of 26 months, a local recurrence rate of 4% to 6% was noted. Limitations of this approach include proximal and distal deeply invasive tumors, high-grade tumors, and patients with poor health status who would not be candidates for salvage procedures if they experienced recurrence. A follow-up series from this same group that included 179 patients having undergone a variety

of organ-sparing procedures including glansectomy, excisions, and distal corporectomy was recently reported (Philippou et al, 2012). With a mean follow-up of 43 months, the incidence of recurrence was 8.9% (16 patients). It is important to note that local relapse did not affect disease-specific survival. These results seem to suggest that a 2-cm margin may not be necessary for small tumors of lower grade in the presence of a negative frozen section. However, patients managed with limited excision techniques should be considered to be at a higher risk for local recurrence until longer-term follow-up and additional surgical series are available.

Another recent technique used in the surgical management of carcinoma in situ of the glans penis is *glans resurfacing*, also known as *glans stripping*. In this technique, subdermal dissection of the skin and subepithelial connective tissue off the underlying corpora spongiosa is performed. Shabbir and colleagues (2011a) described this procedure in 25 patients with clinical carcinoma in situ of the glans; they performed either a total or partial removal of all the glans surface tissue. Positive surgical margins were noted in 48% of patients overall but in only 20% of those having total removal. At a mean of 29 months, 5 patients underwent re-excision for unexpected invasive disease at the margin. One of 25 patients exhibited a clinical recurrence. Topical therapy was used for isolated positive margins with carcinoma in situ. Important considerations for this procedure are to document the absence of invasive cancer, to use topical therapy as an adjunct in the case of residual carcinoma in situ at a margin, and to perform careful follow-up.

Mohs Micrographic Surgery

Mohs microsurgery has historically had a positive impact on the management of penile carcinoma in situ and small superficially invasive tumors. As originally described by Mohs and colleagues (1985), it involves layer-by-layer complete excision of the penile lesion in multiple sessions (fixed tissue technique), with microscopic examination of the undersurface of each layer. Its sequential microscopic guidance offers improved precision and control of the negative margin while maximizing organ preservation. In a series of 29 consecutive cases of penile squamous cell carcinoma, the primary tumor was eradicated in 23 (92%) of 25 patients available for follow-up. Local recurrences were highly associated with tumor size (3 cm), advanced stage, and failure of previous definitive therapy (Mohs et al, 1992). These excellent results using a fixed tissue technique have not been reproduced with the currently used frozen-section methodology. Shindel and associates (2007) treated 33 patients with stage Tis (26 patients), T1 (4 patients), T2 (7 patients), and T3 (4 patients) penile cancer. Five procedures were terminated with positive margins. Of 25 patients with mean follow-up of 58 months, 8 (32%) developed recurrence. However, 7 of 8 were re-treated successfully with Mohs surgery. One patient who had progression of his disease died from it. Thus Mohs microsurgery, as currently performed, may offer no additional benefit over surgical excision with intraoperative frozen-section assessment of margin status.

Laser Ablation

The four most widely used laser energy sources are the CO₂, argon, Nd:YAG, and KTP lasers (Carpiniello et al, 1987; Malloy et al, 1988; von Eschenbach et al, 1991). Although the CO₂ laser has been widely used previously, the superficial depth of penetration (limited to 0.1 mm) makes it less than optimal for the treatment of penile carcinoma in situ or small T1 tumors. When the CO₂ laser is used, local recurrence rates have been shown to be as high as 50% (Bandieramonte et al, 1988; van Bezooijen et al, 2001). Conversely, the Nd:YAG laser results in protein denaturation at a depth of up to 6 mm by emitting at a wavelength of 1060 nm. Overall recurrence rates after laser ablation have been reported to be 7.7% for penile carcinoma in situ and have ranged from 10% to 25% for T1 lesions (Malloy et al, 1988; Windahl and Hellsten, 1995; Tietjen and Malek, 1998), but results from more contemporary series using the Nd:YAG laser exclusively have been more encouraging. Frimberger

and colleagues (2002a) treated 29 men with carcinoma in situ and stage T1 tumors, combining Nd:YAG laser ablation with tumor base biopsies to ensure negative surgical margins. Only two recurrences (6.9%) were reported at a mean follow-up of 46.7 months, which is comparable to recurrence rates after partial penectomy. In an effort to reduce the incidence of positive surgical margins, Frimberger and associates (2002b) have proposed the use of autofluorescence and 5-aminolevulinic acid–induced fluorescence for targeting of frozen-section biopsy specimens.

Laser ablation is feasible and may achieve results equivalent to those of extirpative surgery, especially when it is performed in well-selected patients in conjunction with frozen-section biopsies. In addition, laser ablation has been associated with high rates of resumption of sexual activity (75%) and overall satisfaction (78%) (Windahl et al, 2004). However, until additional long-term studies become available, laser ablation should be performed with the understanding that local recurrences may develop and that close surveillance and patient self-examination are necessary for early detection. Although well-selected patients who develop small recurrent lesions may be candidates for repeated laser ablation, recurrences are best treated with wide local excision or partial amputation.

Contemporary Penile Amputation

Penile amputation remains the standard therapy for patients with deeply invasive or high-grade cancers. **Partial or total penectomy should be considered in patients exhibiting adverse features for cure by organ preservation strategies.** These are consistently associated with tumors of size 4 cm or more, grade 3 lesions, and those invading deeply into the glans urethra or corpora cavernosa (Mohs et al, 1992; Gotsadze et al, 2000; Kiltie et al, 2000). Because recurrence rates are higher with organ-preserving strategies, compliance with follow-up is also a consideration in recommending organ preservation versus amputation. Fortunately, most patients with recurrences that are detected and treated early are not adversely affected with respect to survival (Lont et al, 2006).

On the basis of contemporary results, organ preservation strategies should be discussed with patients exhibiting optimal tumor characteristics (stages Tis, Ta, T1; grade 1 and grade 2 tumors) to assist them in making informed decisions about therapy. (See Table 37-2 for treatment modalities for the primary penile tumor.)

KEY POINTS: SURGICAL TREATMENT OF THE PRIMARY TUMOR

- Patients with small lesions of low grade and stage (Tis, Ta, T1; grade 1 and grade 2) are the optimal candidates for organ preservation to maintain sexual quality of life.
- The goals of organ preservation are to maintain glanular tissue for sensory purposes when possible and/or to maintain penile length when glans penis preservation is not possible.
- Surgical modalities include limited excision strategies, Mohs surgery, and laser ablation.
- Local recurrence rates overall after organ preservation are higher than with traditional amputation; however, when local recurrences are detected and treated, early survival does not appear to be adversely affected.
- Amputation remains the standard for large or deeply invasive lesions, to gain rapid tumor control.

TREATMENT OF THE INGUINAL NODES

The presence and the extent of metastasis to the inguinal region are the most important prognostic factors for survival in patients with squamous penile cancer. These findings affect the prognosis

TABLE 37-2 Treatment of the Primary Penile Tumor

STAGE	TREATMENT
Tis (glans)	Laser therapy, glans resurfacing; alternative: topical therapy
Ta, Tis (foreskin, shaft skin)	Surgical excision to achieve negative margin; alternatives: laser therapy, topical therapy (Tis only)
Ta, T1 grade 1-3 (glans)	Therapy based on size and position of lesion as well as potential side effects, excision, glans resurfacing procedures, glansectomy, radiotherapy (not indicated for Ta)
Ta, T1 grade 1-3 (foreskin, shaft)	Complete surgical excision to achieve negative margin
T2 (glans) without gross cavernosum involvement	Total glansectomy with or without corpora cavernosa transection to achieve negative surgical margins, partial penectomy, radiotherapy
T2 (corporeal invasion), T3	Partial or total penectomy
T4 (adjacent structures)	Consider neoadjuvant chemotherapy with surgical consolidation for responding patients if baseline resectability is a concern
Local disease recurrence after conservative therapy	Complete surgical excision to achieve negative surgical margins; may require partial or total penectomy; select patients with superficial low-grade recurrences may be candidates for repeat penile-conserving procedure
Radiotherapy	Select patients with T1-T2 tumors involving glans, coronal sulcus <4 cm

of the disease more than do tumor grade, gross appearance, and morphologic or microscopic patterns of the primary tumor.

Unlike with many other genitourinary tumors, which mandate systemic therapeutic strategies once metastasis has occurred, lymphadenectomy alone can be curative and should be performed. The biology of squamous penile cancer is such that it exhibits a prolonged locoregional phase before distant dissemination, providing a rationale for the therapeutic value of lymphadenectomy.

However, owing to the morbidity of traditional lymphadenectomy especially among patients with clinically negative groins, contemporary controversial issues include (1) the selection of patients for lymphadenectomy versus careful observation; (2) the types of procedures to correctly stage the inguinal region with low morbidity; and (3) multimodal strategies to improve survival among patients with bulky inguinal metastases.

In this rare disease, prospective randomized trials have not been performed to answer many of these questions. However, with the use of retrospective and prospective clinicopathologic data from several centers, treatment strategies are presented using the available data.

Contemporary Indications for Inguinal Lymphadenectomy

Prognostic Significance of the Presence and Extent of Metastatic Disease

Table 37-3 reveals data collected from 24 surgical series during a 37-year period. Patients proved to have no evidence of inguinal

TABLE 37-3 Carcinoma of the Penis: Prognostic Indicators for Survival

SERIES	NO. OF PATIENTS	CLINICAL AND PATHOLOGIC CHARACTERISTICS OF INGUINAL ADENOPATHY			5-YEAR SURVIVAL RATES (%)	
		PERCENTAGE WITH PALPABLE NODES	PERCENTAGE CLINICALLY FALSE POSITIVE (NODES PALPABLE, HISTOLOGIC FINDINGS NORMAL)	PERCENTAGE CLINICALLY FALSE NEGATIVE (NODES NONPALPABLE, HISTOLOGIC FINDINGS ABNORMAL)	INGUINAL NODES NEGATIVE*	INGUINAL NODES RESECTED AND POSITIVE†
Ekstrom and Edsmyer, 1958	229	33	48	—	80 ^a	42
Beggs and Spratt, 1964	88	35	36	20	72.5	45
Thomas and Small, 1968	190	—	64	20	—	26
Edwards and Sawyers, 1968	77	—	—	0	68	25
Hanash et al, 1970	169	—	58 ^b	2 ^b	77 ^c	—
Kuruvilla et al, 1971	153	39	63	10	69	33
Hardner et al, 1972	100	42	41 ^b	16 ^b	—	—
Gursel et al, 1973	64	53	60 ^b	—	58	—
Skinner et al, 1972	34	29	40	—	75	20
					87 ^d	50 ^d
de Kernion et al, 1973	48	54	38 ^b	—	84 ^e	55 ^e
Derrick et al, 1973	87	29	52	—	53	22
					76 ^d	55 ^d
Johnson et al, 1973	153	—	—	—	64.4	21.8
Kossow et al, 1973	100	51	49	25	—	— ^f
Puras et al, 1978	576	82	47	38 ^b	89	67 ^g
						29 ^h
Cabanas, 1977	80	96	65	100	90	70 ⁱ
						50 ^j
						20 ^k
Fossa et al, 1987	79	—	—	13	90	80 ^l
						20 ^m
Srinivas et al, 1987	199	63	14 ⁿ	18	74	82 ^o
						54 ^p
						40 ^q
						12 ^r

Continued

TABLE 37-3 Carcinoma of the Penis: Prognostic Indicators for Survival—cont'd

SERIES	NO. OF PATIENTS	CLINICAL AND PATHOLOGIC CHARACTERISTICS OF INGUINAL ADENOPATHY			5-YEAR SURVIVAL RATES (%)	
		PERCENTAGE WITH PALPABLE NODES	PERCENTAGE CLINICALLY FALSE POSITIVE (NODES PALPABLE, HISTOLOGIC FINDINGS NORMAL)	PERCENTAGE CLINICALLY FALSE NEGATIVE (NODES NONPALPABLE, HISTOLOGIC FINDINGS ABNORMAL)	INGUINAL NODES NEGATIVE*	INGUINAL NODES RESECTED AND POSITIVE†
McDougal et al, 1986	65	—	—	66	100	83 ^s 66 ^t 38 ^u
Young et al, 1991	34	24	27	42	77	0
Horenblas et al, 1993	110	36	26	40	100	38
Ravi, 1993a	201	53	8	16	95	81 ^v 50 ^w 86 ^x 60 ^y
Ornellas et al, 1994	414	50	51 ^y	39	87	29
Theodorescu et al, 1996	40	70	35	—	46	45
Puras-Baez et al, 1995	272	—	—	—	89	38

*On histologic or repeated physical examination.

†On histologic examination of adenectomy specimen.

^aMajority of patients received prophylactic or preoperative radiation therapy to inguinal area.^bHistologic classification based on node biopsy, not node dissection.^cCorrected 5-year survival (i.e., patients dying before 5 years without evidence of disease are excluded).^dPatients dying free of cancer before 5 years are considered surgical cures.^eThree-year survival.^fOmitted.^gPositive findings in inguinofemoral nodes.^hPositive findings in inguinofemoral and pelvic nodes.ⁱSingle inguinal node with positive findings.^jMore than one inguinal node with positive findings.^kThree-year survival with positive findings in inguinal and pelvic nodes.^lN1-2.^mN3.ⁿAfter antibiotic therapy.^oOne node positive.^pOne to six nodes positive.^qMore than six nodes positive.^rBilateral nodes positive.^sAdjunctive adenectomy.^tImmediate therapeutic adenectomy.^uDelayed therapeutic adenectomy.^vOne to three positive nodes.^wMore than three positive nodes.^xUnilateral.^ySome lymph node dissection done without antibiotic pretreatment.

metastases on the basis of histologic examination of the inguinal nodes or repeated normal examination findings over time; the average 5-year survival rate was 73% (46% to 100%). In patients with resected inguinal metastases the 5-year survival averaged 60% (0% to 86%), but this varied widely and was directly attributable to the extent of nodal metastasis (see Table 37-3). This point is illustrated in several series shown in Tables 37-3 and 37-4. Patients with minimal nodal metastases (usually two or less) exhibited 5-year survivals that ranged from 72% to 88% compared with 0% to 50% when a greater degree of nodal involvement was present (see Table 37-4).

The extent of cancer in a lymph node was also of prognostic significance. Ravi (1993a) noted ENE of cancer in lymph nodes 4 cm in size, and only 1 of 17 patients (6%) undergoing lymphadenectomy survived 5 years. Finally, pelvic lymph node involvement has been a particularly ominous finding with respect to long-term survival; the combined results of several small series reveal an average 5-year survival of 14% when pelvic nodal

metastases are present (Table 37-5). Taken together, these data suggest that the pathologic criteria associated with long-term survival after attempted curative surgical resection of inguinal metastases (i.e., 80% 5-year survival) include minimal nodal disease (up to two involved nodes in most series), unilateral involvement, no evidence of ENE of cancer, and absence of pelvic nodal metastases.

Presence of Palpable Adenopathy as a Selection Factor for Inguinal Dissection

One can conclude from these data that it is advantageous to find and to treat nodal metastasis at the earliest possible opportunity. Data in Table 37-3 suggest that the presence of palpable adenopathy is associated with proven nodal metastasis in about 43% of cases on average (range 8% to 64%). In the remainder, lymph node enlargement is secondary to inflammation. Persistent adenopathy

TABLE 37-4 Five-Year Survival (%) Related to Extent of Nodal Metastasis

SERIES	NO. OF PATIENTS	NO. OF POSITIVE NODES	
		≤2	>2
Fraley et al, 1989	31	88%	7%
Johnson and Lo, 1984a	22	85% ^a	13%
Srinivas et al, 1987	119	82%	20% ^b
Graafland et al, 2010	152	73%	27%
Ravi, 1993b	21	81% ^c	50% ^d
Pandey et al, 2006	102	76% ^c	8% ^e 0% ^f

^aApproximate.^bA subset with one to six positive nodes.^cOne to three positive nodes.^dMore than three positive nodes.^eFour to five positive lymph nodes.^fMore than five positive lymph nodes.**TABLE 37-5** Five-Year Survival Related to Pelvic Node Metastases

AUTHOR	NO. OF PATIENTS WITH POSITIVE NODES	5-YEAR SURVIVAL NO. (%)
de Kernion et al, 1973	2	1 (50)
Horenblas et al, 1993	2	0 (0)
Srinivas et al, 1987	11	0 (0)
Pow-Sang et al, 1990	3	2 (66)
Kamat et al, 1993	6	2 (33)
Ravi, 1993a	30	0 (0)
Lopes et al, 2000	13	5 (38)
Lont et al, 2007	25	4 (16)
Zhu et al, 2008	16	1 (6)
TOTAL	108	15 (14)

after treatment of the primary lesion and 4 to 6 weeks of antibiotic therapy is most often the consequence of metastatic disease. Similarly, the development of new adenopathy during follow-up is much more likely to be caused by tumor than inflammatory response. Thus historically a course of antibiotics was recommended for patients with suspicious nodes to potentially discern metastasis from cancer (Srinivas et al, 1987). However, several authors have raised the issue that this causes a significant delay and could affect survival, especially among patients who are likely to be truly positive by virtue of the stage or grade of the primary tumor (Kroon et al, 2005b; Pettaway et al, 2007). An alternative approach for such patients is to perform fine-needle aspiration cytology of palpable nodes either at the time of or immediately after treatment of the primary tumor. In the case of a positive result, definite therapy can be planned without a 4- to 6-week delay. Saisorn and associates (2006) reported a 93% sensitivity and a 91% specificity in 16 patients with palpable adenopathy (mean size 1.47 cm) undergoing fine-needle aspiration before lymphadenectomy. The recommendation for this procedure among patients with palpable nodes

was also incorporated in the European Association of Urology (EAU) Penile Cancer Guidelines. Thus, although treatment of the primary tumor and a period of antibiotics are useful to help sterilize the inguinal region, this practice is no longer advocated as a tool to select patients who either should or should not undergo lymphadenectomy. Should the fine-needle aspiration result be negative, depending on clinical suspicion, close observation, repeat aspiration, or excisional biopsy is performed because the false-negative rate of fine-needle aspiration cytology was 20% to 30% in two other older series (Scappini et al, 1986; Horenblas et al, 1991).

Evolving Indications for Lymphadenectomy in Patients without Palpable Adenopathy

Immediate versus Delayed Surgery

Considering the value of early detection and treatment of metastasis, should inguinal lymphadenectomy (ILND) be routinely performed in patients with clinically normal groin examination findings at the time of presentation of the primary lesion? This was the most controversial issue in the management of patients with squamous penile cancer previously; however, the pendulum has moved toward earlier lymphadenectomy in selected patients with penile cancer. As noted, the cure rate with ILND when nodes are positive for malignancy may be as high as 80%. A cure rate of this magnitude with surgery in the face of regional nodal metastases parallels the urologist's experience with testicular cancer, in which retroperitoneal lymphadenectomy provides cure in many patients with minimal nodal metastasis. In contrast, for other common genitourinary malignant neoplasms—bladder, prostate, and kidney—surgical cure in the presence of regional nodal metastases is rare. Given that node dissection can cure metastatic penile cancer, why is there debate about whether the procedure should be performed, especially given that regional node dissections are often advocated in other malignant neoplasms when evidence of their efficacy is marginal at best?

Morbidity versus Benefit

The reluctance to advocate automatic ilioinguinal lymphadenectomy (IILND) in all patients with penile cancer stems from the substantial morbidity the procedure can produce, as opposed to the relatively limited postoperative morbidity of pelvic or retroperitoneal lymphadenectomies. Early complications of phlebitis, pulmonary embolism, wound infection, flap necrosis, and permanent and disabling lymphedema of the scrotum and lower limbs were frequent after both inguinal and ilioinguinal node dissections (Skinner et al, 1972; Johnson and Lo, 1984a; McDougal et al, 1986; Fraley et al, 1989). Postoperative complications have been reduced by improved preoperative and postoperative care; advances in surgical technique; plastic surgical consultation for myocutaneous flap coverage; and preservation of the dermis, Scarpa fascia, and saphenous vein, as well as modification of the extent of the dissection (Catalona, 1988; Colberg et al, 1997; Bevan-Thomas et al, 2002; Coblenz and Theodorescu, 2002; Nelson et al, 2004). In the University of Texas MD Anderson Cancer Center experience, both the incidence and severity of lymphedema and skin edge necrosis were significantly decreased (Table 37-6, Fig. 37-3) (Bevan-Thomas et al, 2002).

Furthermore, experience has suggested that lymphadenectomy in the setting of microscopic disease may be less likely to produce complications than node dissection in the presence of bulky nodal metastases (Fraley et al, 1989; Ornellas et al, 1994; Coblenz and Theodorescu, 2002). This is presumably because of the reduced amount of lymphatic tissue removed, preservation of venous drainage, and less blood supply compromised. Together these factors affect the viability of skin flaps and lymphatic flow.

Mortality after ILND has been reported in association with surgery performed concomitantly with penectomy and after

TABLE 37-6 Lymphadenectomy Complications in Four Surgical Series

	JOHNSON AND LO (1984b)	RAVI (1993b)	ORNELLAS ET AL (1994)	BEVAN-THOMAS ET AL (2002)
No. of dissections	101	405	200	106
Period	1948-1983	1962-1990	1972-1987	1989-1998
COMPLICATIONS (%)				
Skin edge necrosis	50	62	45	8*
Lymphedema	50	27	23	23†
Wound infection	14	17	15‡	10
Seroma formation	16	7	6	10
Death	0	1.3	Not stated	1.8

*Significantly lower than in the three other reported series (all $P = .0001$).
†Significantly lower than in the series of Johnson and Lo ($P = .0001$).
‡Incidence among 85 lymphadenectomies performed by Gibson-type incision.
From Bevan-Thomas R, Slaton JW, Pettaway CA. Contemporary morbidity from lymphadenectomy for penile squamous cell carcinoma: the MD Anderson Cancer Center experience. J Urol 2002;167:1638–42.



Figure 37-3. Postoperative appearance after contemporary lymphadenectomy. The patient's status is post right ilioinguinal lymphadenectomy and left superficial inguinal dissection for stage T2N1M0 squamous penile cancer. Mild edema is visible on the left 10 months after surgery. Patient remains without disease at 9 years.

Clearly, lymphadenectomy is not a trivial concern, even though morbidity appears to be decreasing. If a policy of routine lymphadenectomy were adopted in all patients with clinically negative lymph nodes, the average risk of false-negative examination findings (metastasis is actually present) would be approximately 29%, with wide-ranging variation (see Table 37-3). Stated another way, an average of 70% of patients could be subjected to the morbidity of ILND with no benefit. Potential reasons for false-negative examination findings include obesity, preexisting edema, and changes from prior therapy (radiation, inguinal surgery).

One alternative to immediate lymphadenectomy for all patients has been to observe patients with normal findings on inguinal examination. Lymphadenectomy is subsequently reserved for those patients who develop palpable lymph nodes. The relevant question then becomes, can a delayed therapeutic dissection effectively salvage patients who have inguinal recurrence?

Several studies have analyzed the survival of men undergoing early versus delayed lymphadenectomy according to pathologic evaluation of nodal status. McDougal and coworkers (1986) reported a series of 23 patients with invasive primary lesions and nonpalpable nodes; 9 patients were treated with immediate adjunctive lymph node dissection (6 had positive findings), and 14 were treated with surveillance and delayed lymph node dissection. The 5-year survival in the node-positive immediate adjunctive lymphadenectomy group was 83% (5 of 6 patients), whereas in the surveillance group the 5-year survival was 36% (5 of 14 patients). However, only 1 patient in the surveillance group had a node dissection. Presumably, the other 9 patients had progressed to inoperable local tumor or distant disease before presentation, emphasizing the role of careful, frequent follow-up and the difficulty of enforcing it. A third subset in this series had palpable nodes at presentation and had immediate therapeutic lymph node dissection, with 10 of 15 patients (66%) surviving 5 years (McDougal et al, 1986). The best results were from immediate adjunctive lymph node dissection (83%), with the next best from immediate therapeutic lymphadenectomy (66%). The worst results were from the surveillance and delayed lymphadenectomy group (36%), in whom dissection was delayed until palpable nodes developed. The interval of opportunity for cure in this third group appears to have been lost.

Similarly, Fraley and associates (1989) reported that immediate adjunctive lymphadenectomy resulted in a 5-year disease-free survival in 6 of 8 node-positive patients (75%) compared with 1 of 12 patients (8%) who had been observed and then treated with delayed lymphadenectomy when nodal enlargement occurred. Six other patients in that series also had unresectable adenopathy after initial surveillance, and all died of their disease. Although only 2 of 6 patients who had immediate lymphadenectomy had more than two

palliative inguinal dissection. In both scenarios it was related to sepsis (Bevan-Thomas et al, 2002). An operative mortality of 3.3% was reported in earlier series (Beggs and Spratt, 1964). However, Johnson and Lo (1984a) and others (Ravi, 1993b; Ornellas et al, 1994; Coblenz and Theodorescu, 2002; Nelson et al, 2004) have reported no mortality in more recent series. Appropriate selection of patients along with routine preoperative antibiotic therapy and wound care to avoid septic complications has minimized this event.

positive nodes, all the patients treated by delayed lymph node dissection had three or more positive nodes.

Three other series suggest that early lymphadenectomy for varying degrees of “suspicious” or clinically positive nodes improves survival compared with the “surveillance” or delayed intervention approach in patients with clinically negative nodes (Johnson and Lo, 1984b; Ornellas et al, 1994; Kroon et al, 2005b). A series from the University of Texas MD Anderson Cancer Center compared 5-year disease-free survival of 14 patients undergoing early lymphadenectomy for clinically suspicious and histologically node-positive disease with that of 8 patients who were observed and later underwent lymphadenectomy when clinical nodal enlargement was undisputed (Johnson and Lo, 1984b). The primary tumors were of similar stage. The 5-year disease-free survival was 57% for early lymphadenectomy compared with 13% for delayed node dissection. Of note, the number of involved nodes in the immediate lymphadenectomy group (median, two) was half that of the delayed lymphadenectomy group (median, four), and no patient with more than two positive nodes survived more than 5 years.

Kroon and associates (2005b) from the Netherlands Cancer Institute compared survival of 20 patients found to have positive lymph nodes subsequent to prophylactic DSNB with that of 20 patients who underwent delayed inguinal dissection after proven nodal metastasis. The 3-year survival for patients detected during close surveillance was only 35% compared with 84% ($P = .0017$) for those undergoing early dissection. Pathologic evaluation of involved lymph nodes revealed ENE of cancer among 19 of 20 patients in the delayed group versus only 4 of 20 patients ($P = .001$) in the early group. Thus, despite careful follow-up, survival was adversely affected by the extent of cancer in involved lymph nodes.

A single large study from India disputes the magnitude of the value of early prophylactic dissection. Ravi (1993b) performed early prophylactic dissection in 113 patients with invasive penile cancer and compared the 5-year survival with that of 258 similarly staged patients who were initially observed. In the “early” group, 20 patients (18%) were found to have metastases, and all patients survived 5 years. The recurrence rate in the observed group was only 8% (21 patients). However, the 5-year survival in the patients who experienced recurrence was only 76% (compared with 100% in the early lymphadenectomy group). The enhanced survival of patients undergoing surveillance in India compared with other countries is probably attributable to patient selection factors, strict adherence to follow-up schedules, and aggressive treatment approach for recurrent disease (a combination of radiation and surgical resection) (Ravi, 1993a).

Thus, six series reveal an improvement in survival for patients undergoing early therapeutic versus delayed therapeutic dissection. Furthermore, five of the six series show that delayed therapeutic dissection can rarely salvage patients who experience recurrence. Taken together, these data suggest that a policy of immediate adjunctive or early lymphadenectomy gives greater assurance that surgical intervention will occur when tumor volume is small (see Table 37-4) (Johnson and Lo, 1984a; Fossa et al, 1987; Srinivas et al, 1987; Fraley et al, 1989; Ravi, 1993b; Kroon et al, 2005b).

Impact of Primary Tumor Histologic Features on Predicting Occult Nodal Metastasis

Although early lymphadenectomy improves survival in patients with inguinal metastases, the challenge remains to identify those patients who are truly lymph node negative to avoid the morbidity of traditional lymphadenectomy. Data gained from analysis of a variety of histopathologic variables within the primary penile tumor allow the classification of patients into higher and lower risk groups for lymph node metastasis (McDougal, 1995; Lopes et al, 1996; Theodorescu et al, 1996; Solsona et al, 2001; Ficarra et al, 2006).

Patients with primary tumors exhibiting carcinoma in situ or verrucous carcinoma have little or no risk for metastasis. Only two cases of metastasis in association with carcinoma in situ have been

TABLE 37-7 Penile Carcinoma: Corporeal Invasion and Incidence of Lymph Node Metastasis

STUDY	NO. OF PATIENTS	NO. OF POSITIVE NODES (%)	CLINICAL N STAGE
McDougal et al, 1986	23	11 (48)	N0
Fraley et al, 1989	29	26 (90)	N0
Theodorescu et al, 1996	18	12 (67)	N0
Villavicencio et al, 1997	37	14 (38)	N0
Lopes et al, 1996	44	28 (64)	NS
Heyns et al, 1997	32	15 (47)	NS
Solsona et al, 1992	42	27 (64)	NS

N, node; NS, not specified.

reported, and none of 47 cases of penile verrucous carcinoma has been shown to metastasize (Avrach and Christensen, 1976; Johnson et al, 1985; Seixas et al, 1994; Eng et al, 1995). Thus, patients with both Tis and Ta penile cancer are included in the low-risk group for inguinal metastases (Solsona et al, 2001, 2004).

In contrast, patients with corporeal invasion (stage pT2) in the penile tumor exhibit a high risk for metastasis. The average risk for inguinal metastasis among 225 patients in seven different series was 59% (Table 37-7). The risk for metastasis among patients exhibiting corporeal invasion was similar irrespective of whether palpable adenopathy was present.

Stage T1 penile cancers exhibit involvement of the subepithelial connective tissue only and lack involvement of the corpus spongiosum, corpora cavernosa, or urethra (Edge et al, 2010). Similarly staged tumors historically have been associated with a 4% to 14% incidence of nodal metastasis (Solsona et al, 1992; Villavicencio et al, 1997; Hall et al, 1998). Theodorescu and colleagues (1996) noted one exception to this relatively low rate of metastatic disease; 58% of patients (14 of 24) with pT1 primary tumors and initially negative nodes on clinical assessment subsequently developed inguinal nodal metastases. These data suggest that other variables present within the penile cancers of the cohort of patients studied (i.e., tumor grade and presence of vascular invasion) may have modified the effect of tumor stage on metastasis.

Several authors have evaluated the risk of nodal metastasis for stage T1 lesions according to tumor grade (Table 37-8). Among 73 patients with T1 grade 1 or grade 2 primary tumors, metastasis occurred in only 5 patients (7%). Recent data from Naumann and coworkers (2008), however, suggested that among T1 grade 2 tumors specifically, the risk of metastases could be higher than previously described. Among four series reporting specifically on the T1 grade 2 subset, in 129 initially node-negative patients, metastases occurred in 18 (14%) (see Table 37-8). However, 5 patients in this subset also exhibited either lymphatic or venous invasion (an adverse prognostic feature, see later). Ficarra and colleagues (2006) developed the first penile cancer nomogram using data from 175 patients. Based on tumor thickness and growth pattern, patients with T1 grade 2 tumors exhibited metastatic rates of 5% to 20%. Thus grade 2 tumors represent a heterogeneous group in which the histologic criteria used to describe grade 2 and the presence or absence of other poor prognostic features ultimately determine prognosis (Cubilla, 2009). In this regard the EAU guidelines assigned patients with T1 grade 2 tumors to the intermediate-risk category in which the risk of lymph node metastasis is greater than 16% (low risk) and less than 68% (high risk) (Solsona et al, 2004; Pizzocaro et al, 2010).

The presence of vascular invasion as a prognostic indicator of inguinal lymph node metastasis in squamous penile cancer is

now evident (Fraley et al, 1989; Lopes et al, 1996; Heyns et al, 1997; Slaton et al, 2001; Ficarra et al, 2005). Lopes and colleagues (1996) studied the prognostic value of lymphatic invasion in 146 patients with penile cancer. In a univariate analysis, clinical nodal stage, tumor thickness, lymphatic and venous embolization, and urethral infiltration were all associated with lymph node metastasis. However, subsequent to multivariate analysis, only venous and lym-

phatic invasion remained significant predictors for positive lymph nodes. Data from the University of Texas MD Anderson Cancer Center revealed that vascular invasion was absent in all patients with T1 tumors (Slaton et al, 2001). These patients were also lymph node negative at surgery. In contrast, patients with stage pT2 primary tumors exhibited nodal metastasis in 75% of cases (15 of 20) when vascular invasion was present but in only 25% of cases (3 of 12) when it was absent.

Ficarra and colleagues (2005) described prognostic factors for lymph node metastasis in 175 patients undergoing surgery for penile cancer in a multicenter study from the Northeast Uro-Oncological Group from Italy. Subsequent to multivariate statistical analysis, the presence of venous or lymphatic invasion and pathologic invasion of the corpus spongiosum or urethra were the only independent risk factors for lymph node metastasis among patients who were clinically lymph node negative. Taking this a step further and including the variables of tumor thickness, growth pattern, grade, venous or lymphatic invasion, corpus spongiosum or cavernosum involvement, urethral involvement, and palpable lymph nodes, Ficarra and colleagues (2006) developed a nomogram predicting inguinal lymph node involvement. The most important variables were venous or lymphatic invasion and the presence of palpable nodes in multivariate analysis. The concordance index of the nomogram was very good at 0.876. However, because of the complexity of the nomogram variables included, external validation of the nomogram has to date not been accomplished.

The presence of perineural invasion (Velazquez et al, 2008) and the microscopic front pattern of invasion (Guimares et al, 2006) have also been shown in recent studies to provide independent information with which to stratify a patient's risk of lymph node metastasis.

Molecular Prognostic Markers

Analysis of gene expression in penile cancer may have future implications with respect to the prediction of lymph node metastasis or survival. A review by Muneer and colleagues (2009) describes the status of several genes evaluated in tissue or serum that could have future prognostic implications with respect to predicting lymph node status or survival (Table 37-9). Zhu et al (2010) incorporated p53 expression into a nomogram that included T stage, grade, and the presence or absence of lymphovascular invasion. When compared with the EAU risk classification, the nomogram incorporating p53 would have resulted in 13 fewer lymph node dissections per

TABLE 37-8 Penile Carcinoma: Incidence of Nodal Metastasis for Stage T1, Grade 1 and Grade 2 Primary Tumors

AUTHOR	STAGE AND GRADE	NO. OF PATIENTS	NO. OF PATIENTS WITH METASTASIS (%)
Theodorescu et al, 1996	T1, G1	8	2 (25)
Solsona et al, 1992	T1, G1	19	0 (0)
McDougal, 1995	T1, G1-2	24	1 (4)
Heyns et al, 1997	T1, G1-2	9	1 (11)
Hungerhuber et al, 2006	T1, G1-2	13	1 (8)
TOTAL		73	5 (7)
Solsona et al, 1992	T1, G2	4	1 (25)
Solsona et al, 2001	T1, G2	4	1 (25)
Naumann et al, 2008*	T1, G2	16	7 (44)
Hughes et al, 2010	T1, G2	105	9 (9)
TOTAL		129	18 (14)

*Five tumors in node-positive group had lymphatic or venous invasion.

TABLE 37-9 Prognostic Molecular Markers of Lymph Node Status and Survival in Penile Cancer: Current Status

MARKER	ROLE	LYMPH NODE STATUS	SURVIVAL
Human papillomavirus (HPV)	High-risk types affect TP53 and RB function	Contradictory studies	Most studies show no correlation
TP53	Altered or mutated expression, increased proliferation, altered apoptosis, dedifferentiation	Preliminary data correlated with increased metastasis	Correlated with survival in T1 penile cancers only
CDKN2A	Inhibits RB function, enhancing proliferation	Not established	Not established
Squamous cell carcinoma antigen (TA-4)	Serum marker function unknown	Correlates with grossly evident metastases	No role
Ki-67	Nuclear protein associated with cycling cells	Predicts increased risk	No role
E-cadherin	Epithelial cell adhesion molecule lost in progression	Low expression associated with nodal metastasis	Low expression predicts worse survival
MMP-9	Matrix metalloproteinase family facilitates invasion	No role	High expression predicts recurrence

RB, retinoblastoma protein.

Modified from Muneer A, Kayes O, Ahmed HU, et al. Molecular prognostic factors in penile cancer. World J Urol 2009;27:161-7.

100 patients, thus decreasing morbidity. These data suggest the potential value of incorporating molecular features into models to enhance prognostication. Presently, however, standardization of methodologies for assessment of gene expression and the lack of large tissue banks with well-annotated clinical data for validation studies hamper efforts to rigorously evaluate the potential usefulness of such biomarkers. Prospective multi-institutional studies analyzing both pathologic and molecular features are needed to further validate which pathologic and molecular variables best stratify a patient's risk for metastasis and survival.

Contemporary Evolving Indications for Expectant Management of the Inguinal Region

Data reviewed in the preceding paragraphs along with consensus guidelines demonstrate that patients with primary tumors exhibiting carcinoma in situ (Tis), verrucous carcinoma (Ta), and stage T1, grade 1 tumors exhibit a relatively low incidence of positive lymph nodes overall (0% to 16%) and are optimal candidates for watchful waiting strategies (Pompeo et al, 2009; Pizzocaro et al, 2010). Recommendations for the management of T1 grade 2 tumors vary based on quoted rates of subsequent metastases. The former EAU guideline (Solsona et al, 2004), although classifying such cases in the intermediate-risk group, recommended observation for T1 grade 2 tumors that lacked vascular invasion and exhibited a superficial growth pattern (i.e., absence of any other adverse features). This guideline was recently modified to recommend an inguinal staging procedure for this group of patients (Pizzocaro et al, 2010). Given the low rate of metastases of 9% overall in a recent study, we agree with the Société Internationale d'Urologie/International Consultation on Urological Diseases (ICUD) recommendation that these patients may also be considered for observation (Pompeo et al, 2009; Hughes et al, 2010; see Table 37-9). This grouping of T1 grade 2 patients corresponds to the current AJCC TNM T1a classification (Edge et al, 2010). All other cases should be considered for surgical staging.

Patients with AJCC stage T1b or greater (see Table 37-1) as a group exhibit at least a 50% incidence of inguinal metastasis, so an inguinal staging procedure appears warranted. In addition, non-compliant patients with invasive primary tumors should be offered an inguinal staging procedure versus observation. Table 37-10 provides a guideline for more intensive follow-up of high-risk patients, especially within the first 2 years. It is imperative for both the patient and the physician to adhere to such follow-up agreements and to be willing to intervene immediately if initial inguinal parameters change. Leijte and colleagues (2008) have documented that only a third of patients who were initially node negative but who subsequently develop an inguinal recurrence survive 5 years.

TABLE 37-10 Penile Carcinoma: Suggested Follow-up for Patients with No Evidence of Inguinal Adenopathy Who Do Not Undergo Initial Lymphadenectomy

YEAR	INTERVAL	
	LOW-RISK GROUP*	HIGH-RISK GROUP†
1-2	3 months	2 months
3	4 months	3 months
4	6 months	6 months
5+	Annually	Annually

*Primary tumor stage Tis, Ta, and T1a.

†Primary tumor stage T1b or greater.

Indications for Modified and Traditional Inguinal Procedures

Modified Procedures

In patients with no evidence of palpable adenopathy who are selected to undergo inguinal procedures by virtue of adverse prognostic factors within the primary tumor, the goal is to define whether metastases exist with minimal morbidity for the patient. A variety of treatment options for this purpose have been reported and include fine-needle aspiration cytology, node biopsy, sentinel lymph node biopsy, extended sentinel lymph node dissection, dynamic sentinel lymph node biopsy, superficial dissection, and modified complete dissection. The technical aspects of many of these procedures are beyond the scope of this chapter but may be found in Chapter 39 and in the references by Horenblas and colleagues (2000) and Spiess and coworkers (2009).

Fine-Needle Aspiration Cytology. The experience with aspiration of clinically negative inguinal nodes guided by either lymphangiography or ultrasonography is limited. Scappini and associates (1986) performed fine-needle aspiration cytology under pedal or penile lymphangiography for nodal localization in 29 patients. Of 20 patients who had lymphadenectomy for histologic confirmation, there was complete agreement between aspiration cytology and histologic results. However, 2 of 9 patients whose cytologic analysis was negative subsequently died of metastatic disease, a presumptive 20% false-negative result. A series from Horenblas and colleagues (1991) also found that the sensitivity of fine-needle aspiration cytology was approximately 71% in 18 patients with clinically negative lymph nodes. This finding and the technical difficulty with lymphangiography make aspiration less practical as a staging technique for patients with no palpable lymph nodes. Kroon et al (2005a) described fine-needle aspiration cytology guided by ultrasonography as a preliminary study to surgical staging with DSNB. Thirty-four groins in 27 patients with clinically negative groins were found to have suspicious nodes by ultrasound examination and were aspirated. However, the sensitivity of the technique was only 39% subsequent to surgical staging. Thus, at present, fine-needle aspiration cytology of clinically negative groins does not exhibit the sensitivity for it to be relied on as a staging modality. However, direct aspiration of palpable inguinal nodes is easily performed, exhibited a sensitivity of 93% in a recent study, and, if positive, provides immediate information with which to advise patients about further treatment (Saisorn et al, 2006).

Sentinel Lymph Node Biopsy, Extended Sentinel Lymph Node Dissection, and Node Biopsy. The concept of sentinel lymph node biopsy as described by Cabanas (1977) is predicated on detailed penile lymphangiographic studies that have demonstrated consistent drainage of the penile lymphatics into a sentinel node or group of nodes located superomedial to the junction of the saphenous and femoral veins in the area of the superficial epigastric vein. In this series, when this sentinel node was negative for tumor, metastases to other ilioinguinal lymph nodes did not occur. Metastases to this node indicated the need for a complete superficial and deep inguinal dissection.

The accuracy of the sentinel node histology to identify inguinal node metastases was, however, questioned by a number of reports (Perinetti et al, 1980; Fowler, 1984; Wespes et al, 1986). Because nodal metastases became palpable within 1 year of sentinel node biopsy with normal findings in some patients in these series, a false-negative biopsy result must be presumed. In one large series, 5 of 41 patients (12%) with normal findings on sentinel node biopsy subsequently developed inguinal node metastases (Fossa et al, 1987). In Cabanas's series (1992), 3 of 31 patients with negative sentinel nodes died of disease, suggesting a false-negative rate for identifying metastases of 10%. McDougal and associates (1986) reported a 50% false-negative rate with inguinal node biopsy. A report by Pettaway and colleagues (1995), in which additional nodes around the sentinel node area were also removed, revealed that even this extended dissection was associated with a

false-negative rate of 25%. The authors hypothesized that false-negative inguinal node biopsies were the result of anatomic variation in the position of the sentinel node within the inguinal field. **Thus, biopsies directed to a specific anatomic area can be unreliable in identifying microscopic metastasis and are no longer recommended.**

Dynamic Sentinel Node Biopsy. DSNB offers the potential for precise localization of the sentinel node with the lowest morbidity of any surgical staging technique (Kroon et al, 2005c). The goal of DSNB is to define where in the inguinal lymph node field the sentinel lymph node resides through use of a combination of visual (vital blue dyes) or gamma emission (hand-held gamma probe) techniques at the time of surgery.

The technique has been studied in patients with malignant melanoma and breast and vulvar carcinomas who required evaluation of the regional lymph nodes (Morton et al, 1992; Levenback et al, 1994; Albertini et al, 1996; Gershenwald et al, 1999). The technique involves intradermal injection of a vital blue dye (isosulfan blue or patent blue dyes) or technetium-labeled colloid adjacent to the lesion. The dye (or radioactive tracer) is transported by the afferent lymphatics to a specific node in the regional nodal basin. This node is designated the sentinel lymph node. In Morton's series of 237 patients with melanoma, the sentinel lymph node was identified in 194 patients. These patients then underwent full regional lymphadenectomy, with a false-negative sentinel node in only 1% of cases.

Several studies evaluating the results of DSNB as a staging tool in penile cancer are now available. Kroon and associates (2004) updated the Netherlands Cancer Institute experience, describing their experience using the combination of preoperative lymphoscintigraphy and intraoperative intradermally injected blue dye in 123 patients with penile cancer. They identified a sentinel node in 98% of patients, for a sensitivity rate of 82% and a false-negative rate of 18% (6 patients). Four of the 6 patients subsequently died of disease progression. Spiess and associates (2007) also noted a false-negative rate of 25% among 31 patients undergoing DSNB. The Netherlands Cancer Institute group subsequently instituted several changes, including (1) routine serial sectioning of the involved lymph nodes along with cytokeratin immunohistochemistry, (2) routine exploration of groins with low or no signal subsequent to preoperative or intraoperative studies, and (3) inguinal ultrasonography with fine-needle aspiration to detect subtle architectural changes (nonpalpable) in positive lymph nodes that could result in the redistribution of lymphatic flow (Kroon et al, 2005a).

In a multicenter update that included patients assessed with the modified DSNB protocol from two high-volume centers (the Netherlands Cancer Institute and St. George's Hospital in London) the false-negative rate was 7% (6 patients) among 323 patients (Leijte et al, 2009b). Three of 6 patients with recurrence (50%) either died or developed distant metastases. **Thus DSNB, when performed at high-volume centers using a standardized protocol, has an acceptable sensitivity, but deaths from penile cancer among initially node-negative patients still occurred.** This limits the applicability of this strategy to larger centers with experienced surgeons and nuclear medicine specialists.

Superficial and Modified Complete Inguinal Dissection. Both superficial inguinal and modified complete dissections have been proposed as staging tools for the patient without palpable inguinal lymphadenopathy. Superficial node dissection involves removal of those nodes superficial to the fascia lata. A complete IILND (removal of those nodes deep to the fascia lata contained within the femoral triangle as well as the pelvic nodes) is then performed if the superficial nodes are positive at surgery by frozen-section analysis. The rationale for superficial dissection is that two series have shown no positive nodes deep to the fascia lata unless superficial nodes were also positive (Pompeo et al, 1995; Puras-Baez et al, 1995). Furthermore, Spiess and colleagues (2007) showed that among the lymph node-negative cohort of patients undergoing DSNB followed by completion superficial dissection, no patient with a negative superficial dissection experienced recurrence, with more than 3 years of follow-up. A complete modified inguinal dissection was originally

proposed by Catalona (1988) and involves smaller skin incision, limited field of inguinal dissection, preservation of the saphenous vein, and thicker skin flaps. This technique also avoids having to transpose the sartorius muscle to cover exposed femoral vessels. Unlike in superficial dissection, deep nodes within the fossa ovalis are also removed. Two reports involving 21 patients have confirmed the value of this technique, when it is properly performed, for identifying microscopic metastases with minimal morbidity (Parra, 1996; Colberg et al, 1997).

Thus, either superficial or complete modified inguinal dissection should adequately identify microscopic metastases in patients with clinically normal inguinal examination findings, without the need for a pelvic dissection if the inguinal nodes are negative. The disadvantage of the modified dissections is the higher overall complication rate (12% to 35%) when compared with DSNB (5% to 7%) (Kroon et al, 2005c; Spiess et al, 2009).

Limited dissections have the following advantages: More information is provided than by biopsy of a single node or group of nodes; the possibility of not identifying the sentinel node is limited by removal of all potential first-echelon nodes; and the dissection is readily performed by any surgeon experienced in inguinal surgery without the need for specialized equipment.

Minimally Invasive Inguinal Lymphadenectomy Using Laparoscopy or Robotic Techniques. Both the laparoscopic and robotic approaches to the inguinal region offer the potential for removing all of the inguinal lymph nodes at risk for disease while minimizing complications. The technical details of the contemporary procedure and early results have been described (Sotelo et al, 2007; Tobias-Machado et al, 2007; Matin et al, 2013). To date, the results of laparoscopic and robotic ILND have been comparable to those of open inguinal lymph dissection with comparable node counts achieved in both. A single case of inguinal recurrence reported at 12 to 33 months of follow-up and minor complications in about 20% of patients have been reported (Sotelo et al, 2009). However, in one study using a laparoscopic approach with over 600 days of follow-up, Master and colleagues (2012) noted minor complications in 27% of patients, with major complications noted in 14.6%. These were mainly infectious in nature and were managed with intravenous antibiotics or incision and drainage. Of note, among 41 dissections there was only a single case of skin edge necrosis. Matin and colleagues (2013), using a robotic-assisted approach, noted in a phase 1 pilot study that inguinal dissection appeared equivalent to an open approach in 18 of 19 (94.7%) patients when verified by a second surgeon using an open incision to inspect the same groin. Minimally invasive approaches, although promising as an inguinal staging tool, will require further validation with larger patient numbers and longer follow-up to better determine efficacy and complication rates compared with traditional approaches or DSNB.

Traditional Inguinal and Ilioinguinal Lymphadenectomy

In patients with resectable metastatic adenopathy, the potential therapeutic value of lymphadenectomy justifies the morbidity of treatment. The goals are to eradicate all obvious cancer, to provide coverage for exposed vasculature, and to provide rapid wound healing (primary closure or myocutaneous flap coverage). Several issues remain with respect to surgical decision making.

Should ILND be bilateral rather than unilateral for patients with unilateral adenopathy at initial presentation of the primary tumor? The answer to this question is yes. The anatomic crossover of penile lymphatics is well established, and bilateral drainage is the rule. In 43 of 54 patients (79%) undergoing intraoperative lymph node mapping at the Netherlands Cancer Institute, lymphatic drainage from the penis was bilateral (Horenblas et al, 2000). The contralateral node dissection may be limited to the area superficial to the fascia lata if no histologic evidence of positive superficial nodes is found at surgery by frozen-section analysis. Clinical support for a bilateral procedure is based on the finding of contralateral metastases in more than 50% of patients so treated,

even if the contralateral nodal region was normal on palpation (Ekstrom and Edsmyr, 1958).

Should bilateral ILND be performed in patients with unilateral lymphadenopathy some time after the initial presentation and treatment of the primary tumor? It is generally believed that bilateral node dissection in this setting is not necessary. The recommendation of unilateral rather than bilateral node dissection with delayed presentation of unilateral lymphadenopathy is supported by the elapsed disease-free interval of observation on the normal side. If one assumes that nodal metastases will enlarge at the same rate, the clinical palpation of nodal metastases, if present in both groins, should appear at approximately the same time. The absence of clinical adenopathy on one side despite prolonged observation suggests freedom from disease on that side (Ekstrom and Edsmyr, 1958). However, this concept may not apply to all patients with delayed recurrence. Horenblas and colleagues (2000) noted that in patients with two or more unilateral metastases, contralateral occult metastases were noted in 30% of cases. Thus, in patients with a bulky unilateral recurrence, a contralateral inguinal staging procedure should be considered. Considering the current treatment recommendations for bilateral inguinal staging procedures in men at high risk for metastasis and the definition of low-risk groups for metastasis by use of available prognostic markers, this scenario should rarely occur.

Should pelvic lymphadenectomy (PLND) be performed in all patients with inguinal metastases, considering its potential for added morbidity and relatively low therapeutic value? This issue remains controversial, but recent data suggest that PLND may be omitted in select patients with limited inguinal metastases (Lont et al, 2007; Zhu et al, 2008; Pizzocaro et al, 2010). Patients with inguinal nodal metastases are at increased risk for spread to the pelvic nodes. Ravi (1993b) found no pelvic nodal metastases when inguinal nodes were negative but found positive pelvic nodes in 17 of 75 patients (22%) with one to three positive inguinal nodes and in 13 of 23 patients (57%) with more than three positive inguinal nodes. Srinivas and associates (1987) also found a similar correlation. Horenblas and colleagues (1993) showed that among patients with a single inguinal lymph node involved without extracapsular extension, the incidence of pelvic metastases was rare; they recommended avoiding pelvic dissection in such patients. Zhu and coworkers (2008) found that the sensitivity of CT for pelvic lymph node metastasis was only 37.5%. Use of the Cloquet node in predicting a positive pelvic node was only about 30% sensitive, as well. Important predictors were the number of positive nodes and lymph node size. Two contemporary studies addressing this issue have found a 0% to 12% incidence of pelvic lymph node metastasis when patients exhibited only one or two positive inguinal nodes, especially when extracapsular extension was absent and/or size was less than 3.5 cm (Lont et al, 2007; Zhu et al, 2008). Additional factors noted in these studies included the grade of the nodal metastasis and its TP53 status. Thus, patients with only a single small lymph node metastasis discovered at the time of inguinal dissection (i.e., no extracapsular extension, not high grade) may be at very low risk for pelvic metastasis and are potentially the optimal candidates in whom PLND can be avoided.

With respect to efficacy, the 5-year survival for patients with positive pelvic nodes averages around 14% (see Table 37-4). However, data from some of the smaller series suggest that in selected instances 5-year survival can occur in patients treated with surgery alone. In the series reported by Ravi (1993b), however, patients with even a single positive pelvic node did not survive 5 years (0 of 8 patients). The difficulty in determining the potential independent value of PLND as a therapeutic procedure is related to the small numbers of patients reported, the coexisting extensive inguinal adenopathy in patients with resectable pelvic nodes, and the failure to specify sites of relapse in patients undergoing IILND (i.e., inguinal versus pelvic versus distant site).

Thus, for patients undergoing ILND for curative intent (i.e., in whom preoperative studies reveal no pelvic adenopathy), PLND should routinely be considered in patients with two or more positive inguinal lymph nodes or when extracapsular nodal

extension is present. PLND in this setting serves as an effective staging tool for identifying those patients at increased risk for pelvic metastases in whom adjunctive therapy should be considered (Lont et al, 2007; Pizzocaro et al, 2010). Given the aforementioned indications, PLND can be performed simultaneously with ILND in the setting of higher volume inguinal metastases or as a secondary procedure after inguinal pathology is available. Alternatively, if pelvic nodal metastases are proven before lymphadenectomy (based on clinical findings), consideration should be given to neoadjuvant chemotherapeutic strategies followed by surgery (Leijte et al, 2007; Pagliaro et al, 2010; National Comprehensive Cancer Network [NCCN], 2012).

KEY POINTS: TREATMENT OF THE INGUINAL NODES

- The presence and extent of inguinal metastases determine survival in penile cancer.
- Patients with persistent palpable inguinal adenopathy should undergo an inguinal staging procedure.
- On the basis of the histologic features of the primary tumor, risk of lymph node metastases can be assessed in patients with no palpable adenopathy. DSNB, superficial ILND, or close follow-up can be recommended.
- Factors associated with a high cure in surgically treated patients include no more than two inguinal metastases, unilateral involvement, no ENE of cancer, and the absence of pelvic metastases. Patients with higher volumes of disease should be considered for adjuvant or neoadjuvant therapy.
- Morbidity of lymphadenectomy is decreasing in contemporary series.
- Superficial ILND reliably determines the presence of microscopic inguinal metastases without the need for specialized facilities but can have significant morbidity.
- Modified DSNB techniques to determine microscopic inguinal disease exhibit low morbidity, have been validated externally in higher-volume centers, and are now a recommended procedure in such centers.
- Laparoscopic and robotic ILND obtains lymph node yields that are comparable to those of open techniques when used in selected patients. Additional studies with larger patient numbers and longer follow-up are required before routine adoption into clinical practice.
- PLND is now recommended when more than one inguinal lymph node exhibits metastasis or when ENE of cancer is present.

Risk-Based Management of the Inguinal Region

A contemporary schema for management of the inguinal region is presented in Figure 37-4. Assumptions for these guidelines are that the primary tumor has been adequately controlled, that the pathologic stage of the primary tumor is available, and that an inguinal examination has been performed. CT of the abdomen and pelvis as well as chest radiography or other imaging studies should also be performed as clinically indicated.

Very Low-Risk Patients

Because the incidence of inguinal metastasis is anecdotal at best for patients with stage Tis or Ta primary tumors, observation is reasonable for those patients with normal inguinal examination findings (see Fig. 37-4A, left). For patients with palpable adenopathy, a course of antibiotics should reveal those whose adenopathy is related to infection versus metastasis. A persistently palpable node should undergo fine-needle aspiration cytology; if the result is negative, an excisional biopsy is recommended. If the biopsy finding is abnormal, ipsilateral inguinal dissection with contralateral

superficial or modified complete dissection is performed. DSNB is an option in experienced centers.

Low- to Intermediate-Risk Patients (American Joint Committee on Cancer Stage T1a)

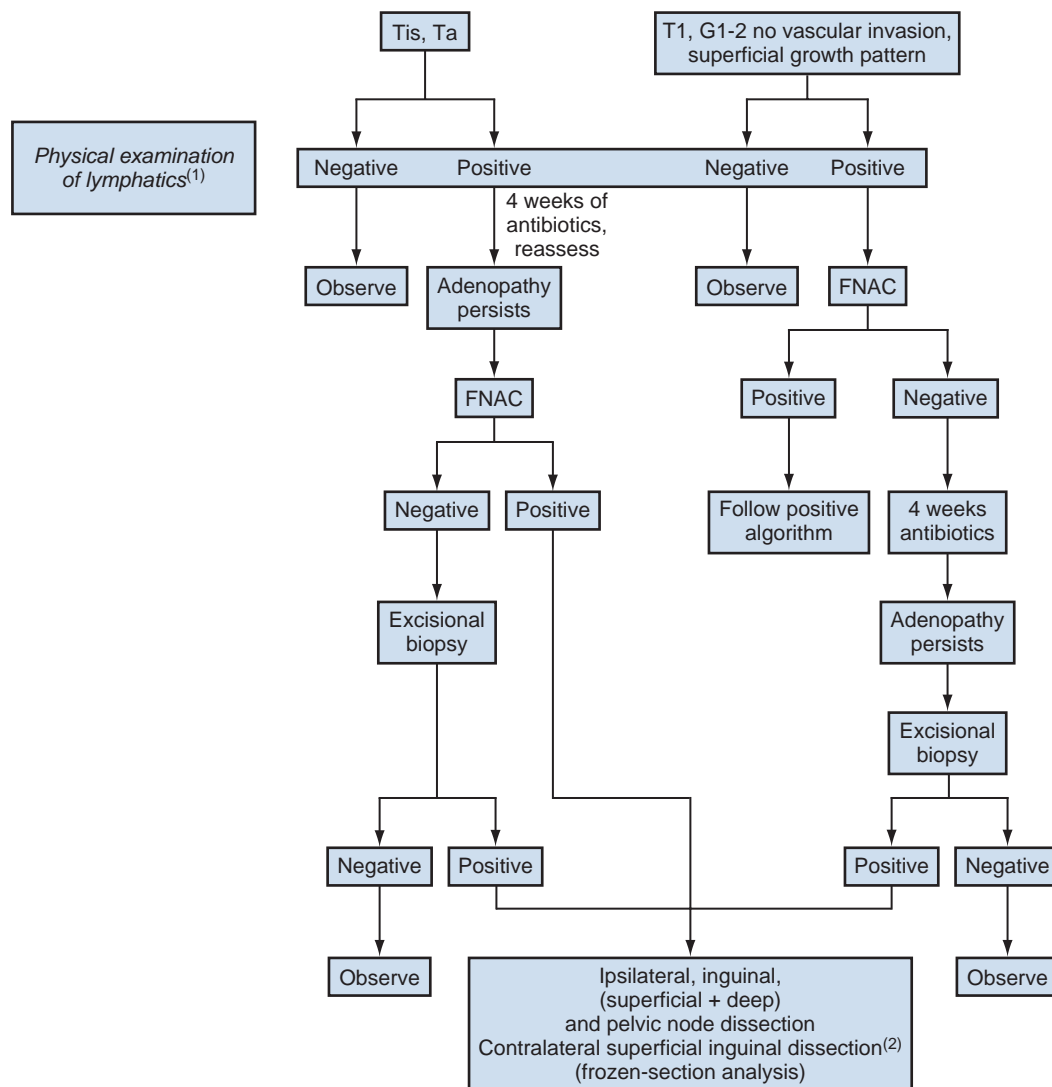
Several series have combined patients with stage T1 grade 1 and grade 2 tumors and have found them to exhibit less than a 10% incidence of inguinal metastasis (see Fig. 37-4A, right; see also Table 37-7). However, the incidence of metastasis among strictly T1 grade 2 tumors (25% to 44%) may be higher, and variable recommendations have been made. The recent EAU guidelines recommend inguinal staging for T1 grade 2 tumors (also stage T1a) among patients with clinically negative lymph nodes (Pizzocaro et al, 2010). However, observation is also an option for compliant patients in this setting (ICUD penile cancer guidelines found in Pompeo et al, 2009; NCCN penile cancer guidelines, 2012). Similar patients with palpable nodes on initial presentation should undergo fine-needle aspiration cytology. If the nodes are positive, the patients then undergo lymphadenectomy, as in Figure 37-4A. If they are negative, then a 4-week period of antibiotic therapy is reasonable. If adenopathy does not resolve, then either excisional biopsy and/or planned lymphadenectomy are reasonable options. Close

follow-up is indicated for patients whose nodes resolve after antibiotic therapy, although the overall risk in this group remains low.

High-Risk Patients (American Joint Committee on Cancer Stage T1b or Higher)

For the high-risk cohort, the incidence of inguinal metastasis ranges from 50% to 70% (see Fig. 37-4B). According to the recent guidelines, there is consensus that patients with poorly differentiated tumors, lymphovascular invasion, or pT2 or greater tumors should undergo an inguinal staging procedure (Pompeo et al, 2009; Pizzocaro et al, 2010; NCCN penile cancer guidelines, 2012). The surgical approach depicted in Figure 37-4B is designed to maximize detection and treatment for those with proven nodal metastasis while limiting the morbidity of those with negative lymph nodes at surgery. Thus surgical staging is indicated even in those patients with clinically normal inguinal examination findings. In this setting, antibiotic use minimizes the risk of inguinal wound infections or septic complications after control of an infected primary tumor, rather than influencing the decision for surgical staging.

Patients with normal inguinal examination findings are offered bilateral superficial dissection, complete modified dissection, or



(1) Includes physical examination and/or imaging studies.

A (2) Complete modified dissection and dynamic sentinel node biopsy (experienced centers) acceptable.

Figure 37-4. Management of regional disease. A, Low-risk patients.

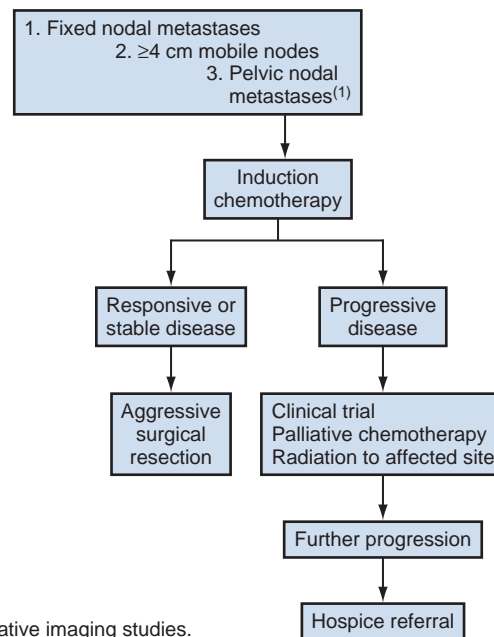
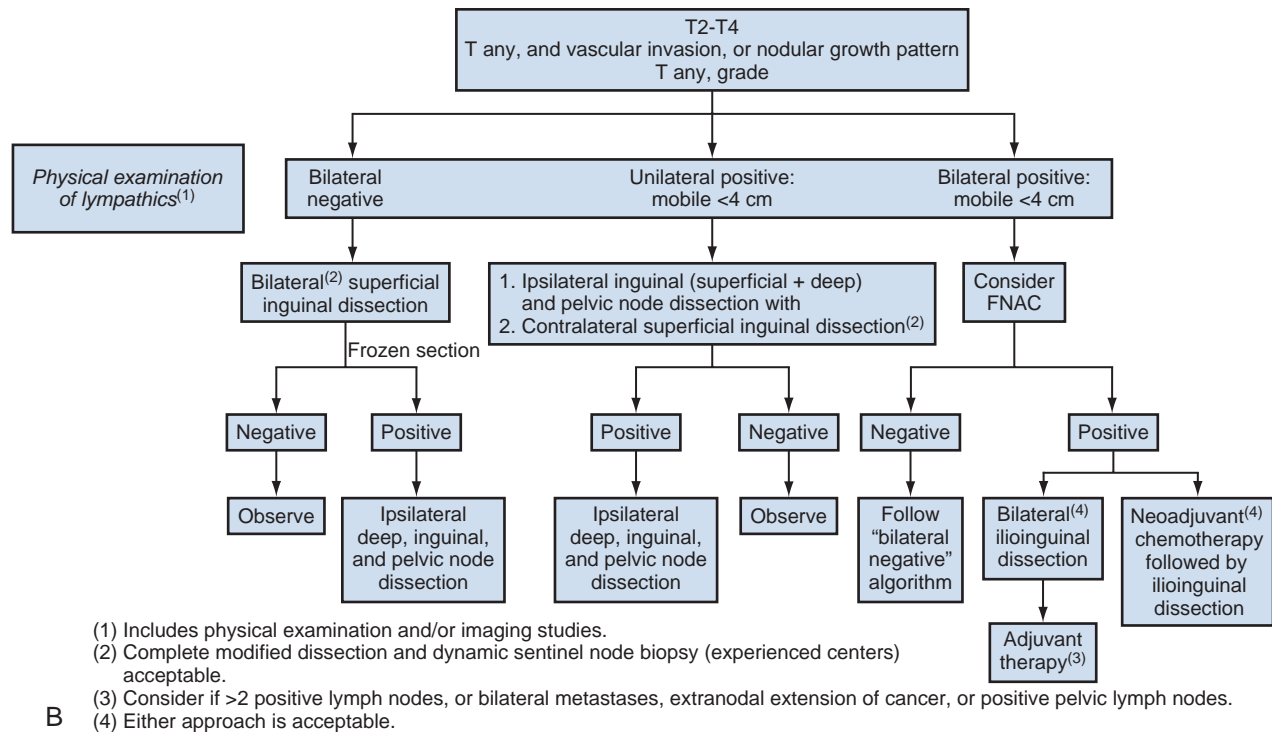


Figure 37-4, cont'd B, High-risk patients. C, Metastatic disease. FNAC, fine-needle aspiration cytology.

DSNB (with the last offered in experienced centers). If frozen-section results reveal no metastasis, the procedure is concluded. For DSNB the results are based on permanent sections; thus further therapy is planned at a second setting if needed. If either side is positive, an ipsilateral inguinal dissection is performed. Pelvic dissection in the setting of a patient with no palpable adenopathy who is discovered to have positive inguinal metastasis at frozen section is optional and based on pathologic findings (Lont et al, 2007; Zhu et al, 2008). Patients with unilateral resectable adenopathy that is strongly suggestive of metastasis should undergo an ipsilateral ilioinguinal dissection and a contralateral superficial or complete modified dissection. Frozen-section analysis then determines if deep inguinal or pelvic nodes should be excised. DSNB is another option

in managing the contralateral node-negative side. Palpable adenopathy of less than 4 cm was arbitrarily selected as a cutoff point for surgery as monotherapy because nodal metastases larger than 4 cm are associated with ENE of cancer (Ravi, 1993a).

For patients with bilateral palpable nodes that are strongly suggestive of metastasis, preoperative fine-needle aspiration cytology can be helpful for counseling of the patient as to the likelihood of the extent of surgery. For patients with negative results of fine-needle aspiration cytology, a staged surgical approach starting with superficial dissection is performed. Subsequent procedures in this setting depend on the results of frozen-section analysis. For patients requiring IILND because of metastases, adjuvant chemotherapy should be considered for those exhibiting more than two positive

lymph nodes, ENE of cancer, or pelvic nodal metastasis (Pizzocaro et al, 2010). An alternative approach to consider among patients with bilateral metastases is neoadjuvant chemotherapy followed by surgical resection as described by Pagliaro and colleagues (2010).

Bulky Adenopathy and Fixed Nodal Metastasis

Survival in patients with bulky adenopathy and fixed nodal metastasis is related to complete eradication of extensive disease (see Fig. 37-4C). This task is difficult to achieve with surgery, chemotherapy, or radiation therapy alone. The combination of surgery and chemotherapy has shown some benefit in advanced penile carcinoma (Pizzocaro et al, 1997; Corral et al, 1998; Bermejo et al, 2007; Leijte et al, 2007; Pagliaro et al, 2010). The optimal integration and timing of such therapy are unknown. A reasonable approach in this cohort of patients is to use neoadjuvant chemotherapy followed by an aggressive surgical resection for patients demonstrating either response to therapy or stable disease. The neoadjuvant approach could improve surgical resectability and avoid long delays in the administration of chemotherapy resulting from delays in postoperative healing. The prognosis is poor in patients exhibiting progression while they are receiving chemotherapy. Palliative groin dissection is a consideration but rarely provides significant palliation (Leijte et al, 2007). Hemipelvectomy in patients without distant metastases has been reported (Block et al, 1973). Endoluminal vascular stents have also been reported to have transient success in preventing vascular erosion by tumor (Link et al, 2004). Clinical trials of novel systemic strategies and radiation therapy to affected areas provide the next level of care. With further progression, supportive care provided by hospice services can provide valuable support to patients with end-stage disease.

RADIATION THERAPY

Radiation Therapy for the Primary Lesion

Primary radiation therapy has significant curative potential and may permit relative preservation of penile form and function. If local control is not achieved, salvage surgery may still be curative, and therefore in a subset of men with penile cancer radiation as an initial strategy represents a reasonable treatment strategy. Both external-beam radiotherapy and interstitial brachytherapy are currently used in treating the primary penile tumor. Before radiation therapy, circumcision is necessary to expose the lesion, to allow resolution of any surface infection, and to prevent preputial edema and subsequent phimosis.

External-Beam Radiotherapy

External-beam radiotherapy has several advantages: It is widely available, delivers a homogeneous dose, and does not require the same expertise with respect to technical skills required for delivery of effective brachytherapy. In a review, Crook and coworkers (2009) described contemporary doses and fractions as ranging from 60 Gy in 25 fractions delivered over 5 weeks to 74 Gy in 37 fractions over 7.5 weeks. This contrasts with lower doses of 50 to 55 Gy cited in older series (McLean et al, 1993; Neave et al, 1993). One of the challenges of external-beam radiotherapy is to consistently position the penis in such a way as to be accessible by the radiation beam while not implicating adjacent normal tissues and structures. This is achieved by positioning the patient supine on the treatment couch and encasing the penis in a vertical position in a block of wax or Perspex with a central cylindric chamber. The block is bivalved for ease of application, which admittedly becomes more difficult as the course of radiotherapy progresses. The second consideration involves the physical nature of megavoltage radiation beams, which spare the skin surface and deliver the radiation dose at a depth in tissue. Penile cancer is of cutaneous origin and requires full treatment of the skin surface. Wax and Perspex are both tissue-equivalent materials, so the choice of these in fabricating an immobilization device effectively boluses the penis and brings the full

dose to the skin surface. An alternative has been described, which is to treat the patient in the prone position with the penis suspended in a small waterbath container (Vujovic et al, 2001), but this is not suitable for obese patients and can be technically difficult because the penis tends to float and position itself too close to the patient's body and adjacent normal tissue.

Table 37-11 is adapted from Crook and colleagues (2009), and describes the efficacy of both external-beam radiotherapy and interstitial brachytherapy with respect to local control, cause-specific survival, complications, and penile preservation. The data represent retrospective reviews of single institution series collected over many years, during which time staging systems and treatment techniques evolved. The data thus often represent a range of doses and fractionation schemes, which permits only limited conclusions regarding optimal dose and fractionation. **Five-year local control rates among patients treated using a variety of techniques ranged from 44% to 69.7% with penile preservation rates of 50% to 65%. Thus, the ability of primary external-beam radiotherapy to control the primary tumor appears inferior to traditional surgical techniques of amputation.** However, further local control in most cases was achieved by partial or total amputation and, **more than 50% of patients treated with primary external-beam radiotherapy avoided penile amputation.** Cause-specific survival ranged from 58% to 86% depending on primary tumor stage and lymph node status.

Prognostic factors for response among patients treated with external-beam radiotherapy include dose below 60 Gy, protracted treatment time exceeding 45 days or daily fraction less than 2 Gy in addition to stage T3, size exceeding 4 cm, and high-grade tumors (Sarin et al, 1997; Gotsadze et al, 2000; Crook et al, 2009). This suggests a minimum tumor dose of approximately 66 Gy in 2-Gy fractions over a period of 6½ weeks (45 days). Hypofractionated courses (fraction size >2 Gy) may be associated with worse toxicity.

Brachytherapy

As an alternative to external-beam radiotherapy, interstitial brachytherapy using a variety of radioisotopes but most commonly iridium-192 has been reported. Gerbaulet and Lambin (1992), using percutaneously placed interstitial iridium-192 implants, reported successful local control in 82% of 109 patients, with long-term survival rates of 75% to 80% in patients with tumor-free regional lymph nodes. Rozan and associates (1995) reviewed 259 patients from multiple centers, with 5- and 10-year disease-free survival rates of 78% and 67%, respectively. Twenty-two percent of patients also had surgery ranging from circumcision or local excision (75% of procedures) to total penectomy (4%). Late side effects occurred in 53% of the group. For noninvasive or very superficial tumors, a surface mold containing iridium-192 wires can be constructed. The plastic mold is worn in close apposition to the penile shaft for 12 hours or so daily for a period of 7 to 10 days for a total tumor dose of 60 Gy (El-Demiry et al, 1984; Akimoto et al, 1997). Because the depth of tumor invasion can be difficult to ascertain by clinical examination or imaging, and because a margin of full dose (comparable to the required surgical margin) is required beyond the macroscopic disease, the mold technique is rarely appropriate. Such superficial disease may now be treated more appropriately with laser or organ-sparing surgical techniques.

Crook and associates (2009) initially reported a cohort (1989-2000) of 30 men with cT1 to cT3 squamous cell carcinoma treated with iridium-192 delivered by 17- to 19.5-gauge steel needles held in a three-dimensional parallel array by predrilled acrylic plastic templates. With a median six needles (range 2 to 9), a prescribed dose of 60 Gy (range 55 to 65 Gy) was delivered during an average of 93 hours. With a median 34 months of follow-up, there were four local failures and four regional failures, and 1 patient required partial penectomy for radionecrosis. The 2-year actuarial local failure-free rate was 85%, and successful penile conservation was 83%. Obviously, tumors could only be clinically staged, and the

TABLE 37-11 Selected Series of Studies Reporting Local Control (LC) of Disease, Cancer-Specific Survival (CSS), Complications, and Penile Preservation for Men Treated with External-Beam Radiation Therapy (XRT) or Brachytherapy (BT) as Primary Treatment for Penile Cancer

STUDY	NO. OF PATIENTS	TYPE OF RT	DOSE (Gy)	F/U (mo) MEDIAN (RANGE)	LC BY RT AT 5 YEARS	CSS AT 5 YEARS	COMPLICATIONS	PENILE PRESERVATION
EXTERNAL BEAM								
McLean et al, 1993	26	XRT	35/10-60/25	116 (84-168)	61.5%	69%	7/26 unspecified	66% crude
Neave et al, 1993	20	XRT	50-55	36 mo minimum	69.7%	58%	10% stenosis	60%
Sarin et al, 1997	59	XRT	60/30	62 (2-264)	55%	66%	3% necrosis 15% stenosis	50% crude
Gotsadze et al, 2000	155	XRT	40-60	40	65%	86%	1 necrosis 5 stenoses	65%
Munro et al, 2001	13	XRT						
Zouhair et al, 2001	23	XRT						43%
Ozsahin et al, 2006	33	XRT/BT	52	62 (2-454)	44%	—	10% stenosis	52%
Mistry et al, 2007	18	XRT	55/16-50/20	62	63%	75%	2 necroses 1 stenosis	66% crude
BRACHYTHERAPY								
Mazon et al, 1984	50	BT	60-70	(36-96)	78% crude		3 necroses 19% stenosis	74%
Delannes et al, 1992	51	BT	50-65	65 (12-144)	86% crude	85%	23% necrosis 45% stenosis	75%
Rozan et al, 1995	184	BT	63	139	86%	88%	21% necrosis 45% stenosis	78%
Soria et al, 1997	102	BT	61-70	111	77%	72%		72% (6 years)
Chaudhary et al, 1999	23	BT	50	21 (4-117)	70% (8 years)		0 necrosis 9% stenosis	70% (8 years)
Kiltie et al, 2000	31	BT	63.5	61.5	81%	85%	8 necroses 44% stenosis	75%
Crook et al, 2009	67	BT	60	48 (4-194)	87.5%	83.6%	12% necrosis 9% stenosis	88% 5 years 67% 10 years

F/U, follow-up; RT, radiation therapy.

authors stated that clinical distinction between cT1 and cT2 is subjective. Nodal failure related to tumor grade, but not tumor size. Kiltie and associates (2000), however, found local failures in 60% of tumors larger than 4 cm compared with 14% of tumors smaller than 4 cm. Mazon and colleagues (1984) and Soria and coworkers (1997) both demonstrated more local failure as the tumor invaded the corpora and with tumor size larger than 4 cm. In the initial Crook series, prophylactic lymph node dissections were not routinely performed, and as one would expect, 50% of moderately or poorly differentiated tumors recurred regionally or distally (Crook et al, 2002). Therefore, selection of patients for prophylactic lymph node dissection is recommended to be the same as selection of patients undergoing surgical removal of the primary tumor.

The Crook series was updated in 2009 to 67 patients with a median follow-up of 4 years (range 0.2 to 16.2). At 10 years the

actuarial cause-specific survival was 83.6%, and three late failures were observed (42, 64, 90 months). Penectomy was performed for 8 recurrences and 2 necroses for 5- and 10-year penile preservation rates of 88% and 67%, respectively. Inguinal lymph nodes in the most recent patients were managed with the same indications as for patients undergoing primary surgery, but with use of only biopsy information for determining high-grade disease and the presence of lymphovascular invasion. One predictor of local failure in this series was needle spacing—an increase in spacing (range 12 to 18 mm) decreased recurrences because of the wider lateral margin achieved. Overall, local control (see Table 37-11) provided by interstitial brachytherapy appeared superior to that provided by external-beam radiotherapy, with 5-year local control rates of 70% to 87%. Penile preservation rates are highest at 5 years (74% to 88%), with some decrease at 8 to 10 years (67% to 70%) (Crook et al, 2009).

Adverse Effects Associated with Radiotherapy

Acutely, after radiotherapy or brachytherapy one can expect moist desquamation at the treated site. This will be more extensive after external-beam radiotherapy because of the larger treatment volume. Re-epithelialization occurs in 4 to 8 weeks. Saline soaks and hygiene are important. Intercourse can be resumed when the patient is comfortable, but the use of additional water-based lubrication is recommended.

The two most common late side effects associated with radiotherapy are **meatal stenosis and soft-tissue ulceration**. Earlier series (from the 1960s to early 1970s) reported urethral fistula, stricture, or stenosis, with or without penile necrosis, pain, and edema (Kelley et al, 1974), in some instances necessitating secondary penectomy (Duncan and Jackson, 1972). Soft-tissue ulceration overall is reported in 0% to 23% of patients treated with external-beam or interstitial radiotherapy, with the higher rates associated with brachytherapy (see Table 37-11). In the case of persistent ulceration, a diagnostic dilemma exists in determining whether recurrent cancer is present; biopsy may be indicated. In general, ulceration is flat and superficial, with no raised or exophytic component. Close follow-up and treatment with antibiotics, vitamin E, and steroid creams are recommended. For cases resistant to these measures, a course of hyperbaric oxygen is often effective (Crook et al, 2009; Gomez-Iturriaga et al, 2011). The majority will heal with conservative management, but healing may take several weeks, and longer in diabetic patients. The more deeply invasive the original tumor, the longer healing can take. Meatal stenosis is reported in 10% to 45% of patients and may be related to increased dose per fraction in those treated with external-beam radiotherapy or needle spacing among those treated with brachytherapy. Meatal stenosis occurs later in follow-up (18 to 24 months) and may often be preceded by report of a weak, deviated or divided urinary stream. Intervention at this time using a meatal dilator will help to prevent subsequent unyielding fibrotic stenosis. Patients can be taught to do this themselves as required. If not appropriately managed, urethral strictures may occur late and may require a more formal dilation or, in very rare cases, urethroplasty.

The benefits of avoiding a mutilating surgical procedure are obvious, and although sexual function is typically reported to be preserved, the side effects of radiation on sexual quality of life have not been studied with validated instruments (Crook et al, 2009). Because brachytherapy irradiates much less of the penile shaft and erectile tissue, erectile function is more likely to be preserved than after external-beam radiotherapy. Patients and physicians must carefully consider the unique acute and long-term side effects of radiation therapy. For the elderly in whom sexual function is not an issue, partial penectomy may be quite acceptable, offering a prompt and effective treatment with relatively few side effects limiting activity in the postoperative period.

The organ-sparing benefits of radiation now must be compared with surgical choices such as laser therapy, Mohs micrographic surgery, and reconstructive surgery, all of which can provide organ sparing while minimizing functional loss. This emphasizes the need for multidisciplinary assessment and tertiary referral to centers where all options are available. Radiation may be the only solution for a patient with significant comorbidities who is not a surgical candidate.

Finally, as with any organ-sparing approach, extended follow up is essential. This must be emphasized to the patient at the time of the original treatment decision. Teaching self-examination and prompt reporting of concerns is also important. Local recurrence can be salvaged surgically without jeopardizing survival. Careful long-term follow-up is essential to detect recurrence promptly, and it must be recognized that recurrence may develop relatively late. In one series, 7 of 11 recurrences were detected after 2 years (63%) and 2 (18%) after 5 years (Mazon et al, 1984). In terms of salvage surgery, Crook et al (2009) noted that external-beam radiotherapy typically treats much more of the penile shaft, whereas brachytherapy is more focal, leading to salvage options that are more likely to result in a partial penectomy than a total penectomy.

In summary, T1 and T2 tumors smaller than 4 cm with no or minimal extension beyond the coronal sulcus respond well to radiotherapy, and with careful planning, complications can be minimized (de Crevoisier et al, 2009). Brachytherapy can provide good local control and penile preservation with faster dose delivery (4 to 5 days rather than 6 to 7 weeks) compared with external-beam radiotherapy. For the patient who is an appropriate candidate for a radiation-based approach, the selection of external-beam radiotherapy versus brachytherapy may depend on the skill and experience of the radiation oncologist involved; external-beam radiotherapy may be more widely available. Crook and colleagues' series and review (2009) would suggest that the brachytherapy technique should be expanded and studied further in a multi-institutional fashion.

The treatment of locally advanced disease is clearly associated with a higher failure rate (local, regional, and distant), and the treatment approach must take into consideration regional nodes. For these patients, brachytherapy is not an option. Combined chemoradiotherapy radio sensitizers like cisplatin weekly—standard management in squamous carcinoma of the cervix—is well tolerated, is associated with excellent response rates, and may convert a patient with inoperable disease into a surgical candidate or alternatively may be used as definitive management (Rose, 2002). This approach will be studied in a cooperative international trial run through the International Rare Cancers Initiative (Nicholson et al, 2014).

Radiation Therapy for the Inguinal Areas

The presence and extent of lymph node involvement is such a key prognostic factor in the management of penile cancer that surgical evaluation of the inguinal regions is widely accepted. Surgical evaluation of high-risk, clinically node-negative patients is recommended so that additional treatment can be tailored to the actual pathology, rather than just offering "prophylactic" radiation to the inguinal nodes. A surgical approach to resectable adenopathy is also preferable because a dose that is sufficient to sterilize macroscopic disease in the groins is poorly tolerated (Murrell and Williams, 1965; Jensen, 1977; Kulkarni and Kamat, 1994). Furthermore, assessment of the treatment of the inguinal area by primary radiation therapy is hampered by the uncertainty arising from the inaccuracy of clinical staging and the frequent lack of histologic confirmation of nodal metastases. Table 37-3 summarizes the incidence of node positivity in clinically negative groins and suggests that radiation can be avoided in the majority of cases.

One of the largest series demonstrating a benefit of radiation therapy for lymph node metastases and/or distant metastases from penile cancer was published by Ravi and associates in 1994. One hundred and twenty patients with lymph node metastases and 9 with distant metastases were managed by radiation therapy alone (palliative) or in the preoperative or postoperative setting. Pertinent to the advanced disease presentation setting, 33 patients were treated with preoperative radiation therapy at 40 Gy over 4 weeks and subsequently had ILND. Of note, after radiation therapy and surgery, only 8% had evidence of ENE, and 3% recurred within the groin. This is relevant because in a prior report within a contemporary time frame (Ravi, 1993a), the incidence of ENE was 33% among patients treated with surgery alone, and groin recurrence was noted in 19%. The differences for both ENE and local recurrence were statistically lower ($P < .01$ and $P < .03$, respectively). The data are suggestive but not definitive that preoperative radiation therapy for nodes 4 cm or larger without skin fixation improved local control. The 5-year survival among the latter group was 70% (Ravi et al, 1994). These data are consistent with the beneficial effects seen when radiotherapy is used together with surgery or chemotherapy in other squamous malignancies such as vulvar, cervical, or anal carcinomas (Epidermoid anal cancer, 1996; Montana et al, 2000; Green et al, 2001). Such approaches should be further explored in the treatment of locally advanced penile cancer.

In the series by Ravi and colleagues (1994), palliative radiation therapy ameliorated symptoms in 56% of patients with fixed groin

nodes, in 5 of 5 patients with painful bony metastases, and in 1 of 2 patients with spinal cord compression and paraplegia. However, pelvic and/or para-aortic radiation therapy was ineffective in patients with pelvic node metastases. Thus radiation therapy may be considered in patients with inoperable fixed and ulcerative inguinal lymph nodes who are not candidates for chemotherapy. On occasion, radiation to these areas is well tolerated, may result in significant palliation, and may postpone local complications for prolonged periods (Furlong and Uhle, 1953; Staubitz et al, 1955; Vaeth et al, 1970). Combined chemoradiotherapy is a promising approach, as previously mentioned, using weekly cisplatin as is successful in squamous carcinoma of the cervix (Rose, 2002).

Radiation has an important role to play as adjuvant therapy for surgically treated, pN+ patients. In a small retrospective study from Taiwan, Chen and colleagues (2004) reported regional failure rates after positive inguinal lymph node dissections in 11% (1 of 9) versus 60% (3 of 5) with and without adjuvant inguinal radiotherapy. Extrapolating from the published literature on vulvar cancer (Hyde et al, 2007), adjuvant radiotherapy 4500 cGy in 25 fractions over 5 weeks to the ipsilateral groin should be considered for patients with more than two positive nodes and for those with ENE. If the pelvic nodes are known to be clear, then the pelvis need not be included; but if pelvic node dissection has not been performed, then the radiation volume should extend to include the pelvis.

In summary, radiation therapy to the inguinal area is not recommended as prophylaxis for patients at high risk for inguinal node metastases. It is less effective therapeutically than a lymph node dissection for clinically involved nodes but should be considered as adjuvant treatment for those with more than two nodes positive or ENE. It may be useful for palliation in the situation of inoperable nodes and in a chemoradiotherapy approach may render inoperable disease resectable. Based on studies in other squamous malignancies, radiation as a part of a multimodal approach with chemotherapy and surgery among patients with advanced penile cancer should be further evaluated.

KEY POINTS: RADIATION THERAPY

- Primary radiation therapy for penile cancer may be successfully applied to select patients with T1 and T2 squamous cell carcinomas smaller than 4 cm with either external-beam radiotherapy or brachytherapy techniques.
- Salvage penectomy may be required after external-beam radiation or brachytherapy for persistent or recurrent disease or radiation necrosis. Lifelong careful follow-up is required.
- For patients selected for radiation therapy for the primary tumor, surgical management of inguinal lymph nodes should be recommended by the same criteria as for patients selected for surgical management of the primary tumor.
- Radiation to the inguinal area is not as effective as surgery for treatment of the inguinal nodes.
- Prophylactic radiotherapy has not been shown to alter the natural history of inguinal metastases and is not recommended.
- Integration of radiotherapy with surgery and chemotherapy in advanced disease requires further study.
- Palliative radiotherapy among patients with inoperable inguinal nodes may provide some benefit.

CHEMOTHERAPY

Advanced penile cancer manifesting as either bulky or unresectable regional disease or visceral metastases at initial presentation or disease recurrence is highly lethal because it is incurable in most cases with either surgery or radiotherapy alone (Ornellas et al, 1994; Ravi et al, 1994; Hegarty et al, 2006). Experience with single-agent or multiagent chemotherapy in this setting is limited because there are few phase 2 clinical trials and no randomized clinical trials. Several regimens have produced clinically meaningful

responses that have occasionally resulted in clearance of disease or facilitated surgical resection.

Single-Agent Chemotherapy

Gagliano and associates (1989) from the Southwest Oncology Group treated 26 patients, 12 of whom had received prior radiation, with low-dose (50 mg/m²) cisplatin, and observed a 15% response rate of 1 to 3 months' duration and a median overall survival of 4.7 months. In a study from Memorial Sloan Kettering Cancer Center, 13 patients with extensive disease and either prior radiotherapy or chemotherapy were treated with cisplatin 70 to 120 mg/m² every 21 days. Three of 12 evaluable patients (25%) demonstrated responses (1 complete and 2 partial; duration 2 to 8 months; Ahmed et al, 1984).

Initial favorable reports from Japan suggested that bleomycin appeared to be effective in the treatment of penile and scrotal cancer. Ichikawa and associates reported a 50% response in 24 previously untreated patients with squamous carcinoma of the penis (Ichikawa et al, 1969; Ichikawa, 1977). A similar report from Uganda documented partial or complete tumor regression in 45% of treated patients (Kyalwazi et al, 1974). A review of 90 patients from the world literature demonstrated similar responses (Eisenberger, 1992). In a study by Ahmed and colleagues (1984), 14 patients were evaluable for response to single-agent bleomycin. There was one complete response, but the patient died from bleomycin pulmonary toxicity. There were also two partial responses, for an objective response rate of 21%. The median response duration was only 3 months (range 2 to 4).

Methotrexate produced responses in 8 of 13 patients (61%) treated at Memorial Sloan Kettering Cancer Center (Ahmed et al, 1984) with one complete response. However, median response duration even with the high response rate was 3 months (2 to 31 months), and one patient died from treatment-related sepsis. Methotrexate had been shown to be active in other reports (Mills, 1972; Garnick et al, 1979). Based on the Ahmed study, in which cisplatin, bleomycin, and methotrexate were given sequentially, there did not appear to be any obvious cross-resistance to the three agents. Subsequently a three-drug trial using cisplatin, bleomycin, and methotrexate was developed.

Combination Chemotherapy

The Southwest Oncology Group reported a phase 2 study using a modified regimen that reduced the total dose of cisplatin, bleomycin, and methotrexate. Haas and associates (1999) employed combination cisplatin, methotrexate, and bleomycin in 45 patients with locally advanced or metastatic penile cancer accrued from 31 different institutions. There were five complete and eight partial responses among 40 evaluable patients (32.5% response rate). The median duration of response was 16 weeks with an overall survival of 28 weeks (Haas et al, 1999). Although the response rate appeared encouraging, it was still within the 95% confidence interval (CI) for single-agent cisplatin, and there were five treatment-related deaths in the study (one from infection and four from pulmonary complications) (Ahmed et al, 1984; Gagliano et al, 1989; Haas et al, 1999). Thus this study failed to confirm the initial high response rate of single-agent methotrexate; the response rate was not significantly higher than that of single-agent cisplatin, and bleomycin pulmonary toxicity was significant (Haas et al, 1999).

Three additional contemporary trials, all including cisplatin, revealed significant activity while omitting the bleomycin and methotrexate. Theodore and colleagues (2008) reported the results of a European Organisation for Research and Treatment of Cancer (EORTC) phase 2 study in which 28 patients with locally advanced or metastatic disease (T3, T4, N1 to N3, or M1) received combination cisplatin and irinotecan. Patients were treated in either the neoadjuvant setting for four cycles before surgery (T3, N1 or N2) or up to eight cycles (T4, N3, M1 disease). Toxicity was acceptable, with no treatment-related deaths. Eight responses were noted (two complete, six partial) for an objective response rate of 30.8% (80%

CI 18.8% to 45%). Of note, three patients taken to surgery in the neoadjuvant setting were found to have no evidence of residual disease. The authors reported the trial as negative, however, because it was powered to show an objective response rate not less than 30% by CI.

A phase 2 clinical trial of neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy (TIP) was conducted at the University of Texas MD Anderson Cancer Center (Pagliaro et al, 2010). Eligible patients had stage Tx, N2 or N3 lymph node metastases, no evidence of distant metastases (M0), and no prior chemotherapy. Treatment consisted of four courses of TIP followed by bilateral inguinal lymph node dissections, unilateral or bilateral pelvic lymph node dissections, and surgical control of the primary tumor when appropriate. The objective response rate was 50% (15 of 30 patients), and the pathologic complete response rate was 10% (3 patients). Twenty-three patients completed four courses of TIP, and 22 of those underwent surgery. Nine patients (30% for the trial, 40.9% of those completing treatment) were alive and disease free at a median follow-up of 34 months. Nineteen deaths occurred as a result of progressive disease, and 2 from unrelated causes. Toxicity was acceptable and no treatment-related deaths occurred (Pagliaro et al, 2010). Thus the data for use of the TIP regimen suggest a response rate that may be significantly higher than that of single-agent cisplatin and better tolerance than with prior bleomycin- or methotrexate-containing regimens. Table 37-12 provides safety and efficacy data for cisplatin-containing chemotherapy regimens reported thus far. Treatment-related pulmonary toxicity and death were avoided with the absence of bleomycin.

A third prospective trial evaluated the combination of docetaxel, cisplatin, and 5-fluorouracil (TPF) in patients with locally advanced or metastatic penile cancer (Nicholson et al, 2013). The objective response rate was 38.5% (10 of 26 evaluable patients), and 65.5% of patients experienced at least one grade 3 or grade 4 event. The predetermined target response rate of 60% was not reached, and the authors concluded that similar results could be achieved with 5-fluorouracil and cisplatin and that the addition of docetaxel resulted in toxicity. The objective response rate to 5-fluorouracil and cisplatin in one retrospective series was 32% (8 of 25 patients) (Di Lorenzo et al, 2012).

Data from the aforementioned three prospective trials and one retrospective series suggest that patients with advanced, unresectable primary tumors or metastatic disease can benefit from cisplatin-based chemotherapy, and selected patients with bulky regional lymph node metastases appeared to benefit from post-chemotherapy lymphadenectomy. Negative pathology in lymph nodes was seen after neoadjuvant treatment with TIP (3 of 30 patients) and irinotecan and cisplatin (3 of 7 patients). For patients

with unresectable primary tumors or bulky regional lymph node metastases, neoadjuvant treatment with a cisplatin-containing regimen may be effective and may allow curative resection. The optimal chemotherapy regimen has yet to be determined.

Adjuvant Chemotherapy

Historically, combination vincristine, bleomycin, and methotrexate therapy was administered in 12 weekly courses to 17 patients in the postoperative setting (12) or neoadjuvant setting (5) at the Milan National Tumor Institute. The patients treated were at high risk for recurrence with surgery alone; 9 showed extranodal tumor growth, 5 had pelvic nodal involvement, and 5 had bilateral metastases. At follow-up ranging from 18 and 102 months, only 1 relapse had occurred (Pizzocaro and Piva, 1988). Later, reports from this center further confirmed the value of adjuvant chemotherapy. Of 56 node-positive patients, 82% of the 25 patients receiving adjuvant vincristine, bleomycin, and methotrexate therapy survived 5 years, compared with 37% of 31 patients treated with surgery alone (Pizzocaro et al, 1995, 1997). In the neoadjuvant treatment group, partial responses were noted in 3 of 5 patients with extremely large (6 to 11 cm) nodal metastases. These three patients subsequently were completely resected and were free of tumor at intervals ranging from 20 to 72 months. These data have yet to be confirmed and will probably not be further studied, given the potential toxicities of bleomycin and methotrexate.

Postchemotherapy Surgical Consolidation

Shammas and colleagues (1992) reported on eight patients treated with the combination of cisplatin and 5-fluorouracil. Seven of the eight patients had Jackson stage III or IV disease, and two in this group had either pleural or lung metastases. One of 7 (14%) had a partial response with disappearance of lung metastases and post-surgical consolidation and lived for longer than 32 months. He received five cycles of therapy. Three patients with stable disease received only one or two cycles and survived for 2 or more to 11 months. Of note, two of three patients who ultimately had disease progression received three or four cycles of therapy and underwent surgical consolidation with survival times of 12 and 28 months from chemotherapy.

Thus, 2 of 7 patients (28%) who survived 28 and more than 32 months received significant palliation or cure from the combination. Corral and coworkers (1998) reported on the long-term follow-up of a prospective group of patients treated with bleomycin, methotrexate, and cisplatin. Among the cohort, 21 patients had penile carcinoma, with 10 of 21 (48%) having either N3 or M1

TABLE 37-12 Safety and Efficacy of Multidrug Penile Cancer Regimens without Bleomycin

	CHEMOTHERAPY	RESPONSE RATE	TREATMENT-RELATED DEATH	MEDIAN OVERALL SURVIVAL (mo)
Di Lorenzo et al, 2012*	Fluorouracil, 800-1000 mg/m ² /day, days 1-4 Continuous infusion cisplatin, 70-80 mg/m ² , day 1; cycle q3wk	32%	0/25	8
Pagliaro et al, 2010	Paclitaxel, 175 mg/m ² , day 1 Ifosfamide, 1200 mg/m ² , days 1-3 Cisplatin, 25 mg/m ² , days 1-3; cycle q3wk	50%	0/30	17.1†
Theodore et al, 2008	Irinotecan, 60 mg/m ² , days 1, 8, 15 Cisplatin, 80 mg/m ² , day 1; cycle q4wk	30.8%	0/28	4.7
Nicholson et al, 2013	Docetaxel, 75 mg/m ² , day 1 Cisplatin, 60 mg/m ² , day 1 Fluorouracil, 750 mg/m ² /day, days 1-5; cycle q3wk	38.5%	0/28	13.9

*Retrospective study.

†Neoadjuvant setting (N2-3, M0).

disease. The remainder had either N1 or N2 nodal metastases. Objective responses were noted in 12 (57%), including 2 of 5 with distant metastases. Six patients in the group (28.5%) achieved disease-free status with either chemotherapy alone (2) or surgery (3) or radiation therapy (1) with a median survival of 27.8 months. This was significantly longer than in those not achieving disease-free status (6.7 months, $P = .004$). Thus, this prospective study showed that a multidisciplinary approach to achieve disease-free status could prolong survival. Subsequently [Leijte et al \(2007\)](#) from the Netherlands Cancer Institute reviewed their experience with neoadjuvant chemotherapy in patients with initially “unresectable” penile cancer. The series included 20 patients treated with five different regimens including (1) single-agent bleomycin; (2) bleomycin, vincristine, and methotrexate; (3) cisplatin and 5-fluorouracil; (4) bleomycin, cisplatin, and methotrexate; and (5) cisplatin and irinotecan. The objective responses were evaluable in 19 (1 patient died because of bleomycin toxicity after 2 weeks), with 12 responses (63%, 2 complete, 10 partial). Surgical procedures included treatment of the primary tumor as well as inguinal and pelvic dissections. Additional soft-tissue resection including bone was sometimes required. Vascularized tissue flaps were used for inguinal reconstruction. Among 12 responders, only 9 went to surgery because 2 died of bleomycin-related complications and a third was deemed unfit for surgery. Eight of 9 responding patients taken to surgery (2 were pT0) were free of disease with a median follow-up of 20.4 months. This is in contrast to 3 nonresponders who went to surgery for palliative intent. All 3 died within 4 to 8 months as a result of locoregional recurrence. The implications of this study are that response to chemotherapy together with an aggressive surgical procedure provides the optimal scenario for significant palliation or potentially cure.

In a separate study [Bermejo et al \(2007\)](#) described the surgical considerations and complications among 10 patients who had either a response or stable disease after combination chemotherapy. The regimens included (1) bleomycin, methotrexate, and cisplatin; and (2) paclitaxel, ifosfamide, and cisplatin (TIP), or (3) paclitaxel and carboplatin. This cohort of patients exhibited bulky inguinal or pelvic metastases, with the only exclusions being patients with fixed pelvic masses or complete encasement of the femoral vessels. In addition to IILND, resection of the inguinal ligament, the inferior aspect of the rectus abdominis or external and internal oblique muscles, the spermatic cord and ipsilateral testicle, and segments of the femoral artery and vein (with subsequent patch or bypass grafting) was performed to achieve negative margins. Plastic surgery consultation was obtained for wound coverage, including the insertion of monofilament polypropylene mesh for abdominal wall defects and myocutaneous flaps of the sartorius, rectus abdominis, serratus anterior, and latissimus dorsi muscles. Among 5 patients exhibiting an objective response, 3 were alive and disease free at 48, 50, and 73 months. Two other patients died (1 of disease at 30 months, another of unknown causes at 21 months). Among the 5 remaining patients with stable disease, 3 were dead of disease within 7 months and 1 patient treated with bleomycin died of “failure to thrive” at 8 months. However, another patient treated with paclitaxel and carboplatin who achieved only stable disease was alive and disease free at 84 months. These data appear to reinforce the concept that response to systemic chemotherapy before surgery enhances the chance for long-term survival among those undergoing surgical resection. Related to systemic therapy, the authors reported that the TIP regimen was well tolerated and all three pT0 responses at surgery were among patients treated with TIP. This provided the rationale for the prospective phase 2 study discussed previously ([Pagliaro et al, 2010](#)). In that study, the patients with response to neoadjuvant TIP had significantly better overall survival ($P = .001$) and time to progression ($P < .001$) compared with those who did not.

Taken together, these data provide evidence that response to chemotherapy improves resectability and survival. Surgery among patients who do not respond to therapy may occasionally be associated with long-term survival but is more often associated with death because of either rapidly occurring locoregional recurrence or

distant metastases ([Bermejo et al, 2007](#); [Leijte et al, 2007](#); [Pagliaro et al, 2010](#)).

KEY POINTS: CHEMOTHERAPY

- Treatment with a cisplatin-containing regimen in advanced metastatic penile cancer should be considered because responses do occur and this may facilitate curative resection. The optimal chemotherapy regimen has yet to be determined.
- The use of bleomycin in the treatment of men with penile cancer was associated with an unacceptable level of toxicity and is discouraged as first-line therapy.
- Surgical consolidation to achieve disease-free status or palliation should be considered in fit patients with a proven objective response to systemic chemotherapy.
- Among patients whose tumor progresses through chemotherapy, surgery is not recommended.

NONSQUAMOUS PENILE MALIGNANT NEOPLASMS

Nonsquamous penile malignant neoplasms are extremely rare. Pathologic descriptions and local and regional treatment options are available; however, outcomes and comparisons are limited to case reports and small retrospective series. Most reports establish the following features: (1) incidence of disease, (2) distinguishing pathologic features, (3) treatment recommendations, and (4) parallels (or lack thereof) to the same carcinoma in nongenital locations.

Basal Cell Carcinoma

Although basal cell carcinoma is frequently encountered on other sun-exposed cutaneous surfaces, it is rare on the penis ([Fig. 37-5A](#)). Fewer than 30 cases have been well documented ([Goldminz et al, 1989](#); [Ladocsi et al, 1998](#); [Nguyen et al, 2006](#)). The lesion can be seen anywhere on the penis but is commonly on the penile shaft. It is slow growing, and delay in diagnosis in one series ranged from 2 months to 50 years ([Kim et al, 1994](#)). Treatment is by local excision, which is virtually always curative ([Hall et al, 1968](#); [Goldminz et al, 1989](#)). Only one case report describes what the authors believe to be the only reported case of metastatic penile basal cell carcinoma ([Jones et al, 2000](#)). [Nguyen and colleagues \(2006\)](#) reported two cases of basal cell carcinoma treated by Mohs surgery.

A benign variant of basal cell carcinoma, the premalignant fibroepithelioma of Pinkus, has been reported to occur on the penile shaft ([Heymann et al, 1983](#)). Diagnosis is made at excisional biopsy. Excision has been uniformly curative.

Melanoma and basal cell carcinoma rarely occur on the penis, presumably because the organ's skin is protected from exposure to the sun. Malignant neoplasms arising from the supporting structures of the penis are also rare and include any combination of tumors of smooth or striated muscle or of fibrous, fatty, or vascular tissue. Information about appropriate treatment of these malignant neoplasms is derived from the review of single case reports and small series ([Belville and Cohen, 1992](#)).

Melanoma

More than 150 cases of melanoma of the penis have been reported ([Fig. 37-5B](#)). Of 1200 melanomas treated at Memorial Sloan Kettering Cancer Center, only 2 were of penile origin ([Das Gupta and Grabstald, 1965](#)). At the University of Texas MD Anderson Cancer Center, less than 1% of all primary penile cancers were malignant melanomas ([Johnson and Ayala, 1973](#); [de Bree et al, 1997](#)).

Melanoma manifests as a blue-black or reddish brown pigmented papule, plaque, or ulceration on the glans penis. It occurs on the prepuce less frequently. Diagnosis is made by

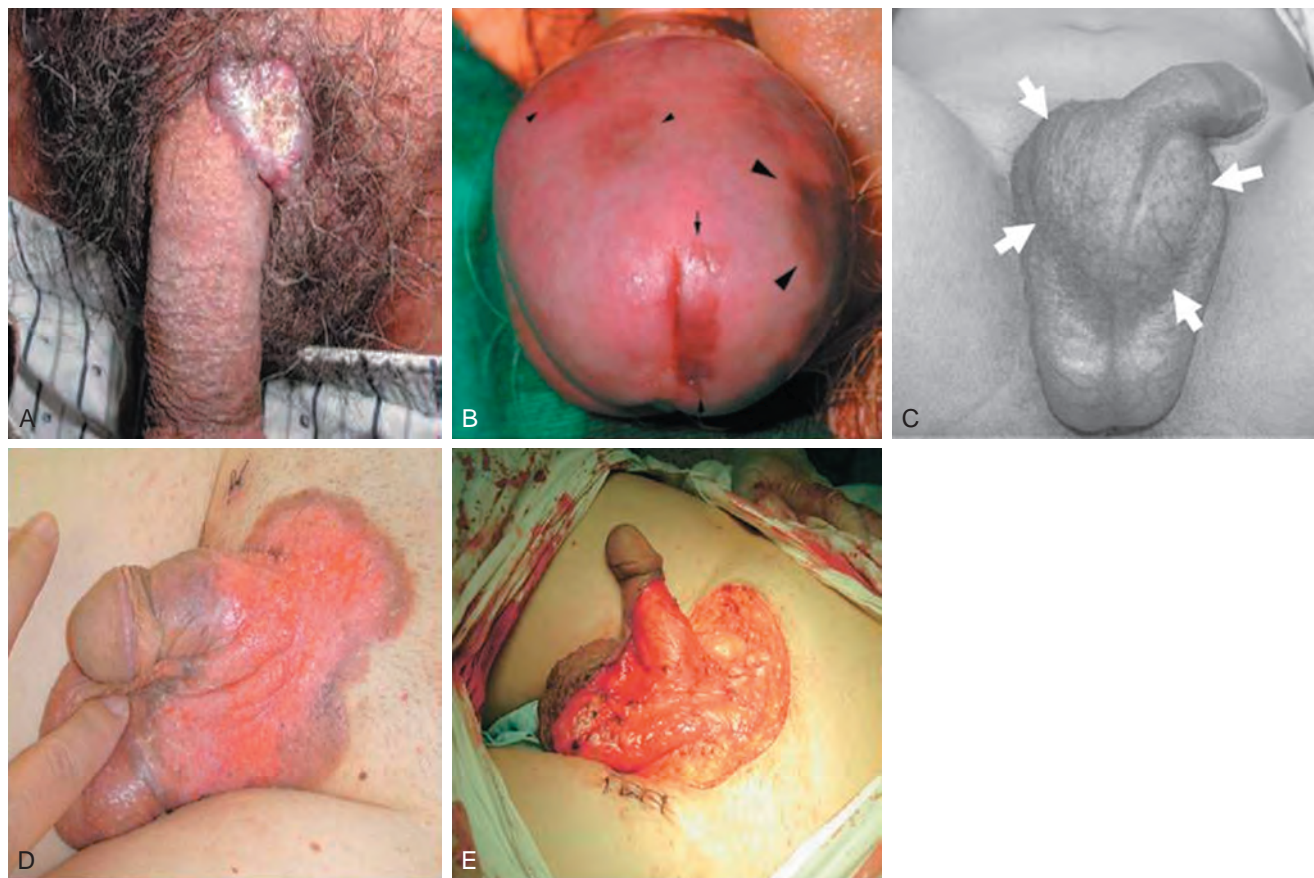


Figure 37-5. Clinical examination findings from non-squamous cell carcinomas involving the penis. **A**, Basal cell carcinoma. **B**, Melanoma. Note superficial spreading melanoma (*large arrowheads*), melanoma in situ (*arrow*), and two areas of possible melanosis (*small arrowheads*). **C**, Leiomyosarcoma (*arrows*). **D**, Paget disease. **E**, Paget disease after resection.

histologic examination of biopsy specimens, which demonstrate atypical junctional cell activity with displacement of pigmented cells into the dermis.

Prognostic characteristics that have been found significant for melanoma in other sites, such as depth of invasion (Clark staging) and thickness of the tumor (Breslow classification), have not been prospectively applied to penile lesions because experience with these lesions is limited. [Sanchez-Ortiz and colleagues \(2005\)](#) used the AJCC system for classifying cutaneous melanomas ([Fleming, 1997](#)) in the largest report to date on melanomas of the penis. This system incorporates elements of the Clark and Breslow staging systems. When this information is favorable, local excision is feasible. Distant metastatic spread has been found in 60% of patients studied ([Abeshouse, 1958](#); [Johnson et al, 1973](#); [de Bree et al, 1997](#)) in older series. However, Sanchez-Ortiz found that patients with early-stage melanomas had excellent outcomes if primary tumors were of low stage and regional lymph nodes were negative. Hematogenous metastases occur by means of the vascular structures of the corporeal bodies; lymphatic spread to the regional inguinal and pelvic nodes occurs by lymphatic permeation.

Surgery is the primary mode of treatment; radiation therapy and chemotherapy are of only adjunctive or palliative benefit. For stage I melanoma (localized lesion without metastases) and stage II melanoma (metastases confined to one regional area), adequate excision of the primary tumor by partial or total penile amputation together with en bloc bilateral ilioinguinal node dissection has historically been advocated ([Johnson et al, 1973](#); [Bracken and Diokno, 1974](#); [Manivel and Fraley, 1988](#)). In reviewing the University of Texas MD Anderson Cancer Center experience plus the literature to date, [Sanchez-Ortiz and colleagues \(2005\)](#) proposed a treatment algorithm for management of the primary tumor and

inguinal lymph nodes. For tumors of the foreskin, circumcision may be adequate. For glans tumors, a partial penectomy was recommended; and for glans-shaft tumors, a partial or total penectomy can be performed. The authors recommend bilateral modified inguinal lymph node dissections in all patients with lesions that are Breslow depth 1 mm or greater, with ulceration, or with Clark level IV or V involvement. Although dynamic sentinel lymph node biopsy techniques are increasingly used in more common sites of melanoma, their use in penile melanoma is unproven as yet. This is likely because of the rarity of the disease ([Sanchez-Ortiz et al, 2006](#)).

The prognosis for patients with penile melanoma is clearly dependent on stage of the primary tumor and the presence or absence of inguinal metastases. Contemporary staging and prognostic factors were reviewed by [Sanchez-Ortiz and coworkers \(2005\)](#). A report from the Netherlands ([van Geel et al, 2007](#)) focused on the concept of mucosal site penile melanomas—glans, meatus, fossa navicularis, and distal urethral. These lesions may appear more aggressive than cutaneous lesions, but greater delay in diagnosis may be a factor. In a pooled, retrospective analysis of 66 cases, the recurrence outcomes were similar for cutaneous melanomas of comparable tumor thickness.

Sarcomas

Primary mesenchymal tumors of the penis are rare. A thorough review of 46 such tumors from the Armed Forces Institute of Pathology revealed an equal number of benign and malignant lesions ([Dehner and Smith, 1970](#)). The patients ranged in age from newborn to the eighth decade of life. The presenting signs and symptoms of subcutaneous mass, penile pain and enlargement, priapism, and

urinary obstruction were the same for both benign and malignant lesions. A sarcoma has been reported to masquerade as a Peyronie plaque (Moore et al, 1975).

Malignant lesions were found more frequently on the proximal shaft (Fig. 37-5C); benign lesions were more often located distally. The most common malignant lesions were those of vascular origin (hemangioepithelioma), followed in frequency by those of neural, myogenic, and fibrous origin (Ashley and Edwards, 1957). Single case reports of sarcomatous lesions have been published—for example, malignant fibrous histiocytoma (Parsons and Fox, 1988), angiosarcoma (Rasbridge and Parry, 1989), leiomyosarcoma (Planz et al, 1998), epithelioid sarcoma (Leviav et al, 1988), hemangioendothelioma (Kamat et al, 2004), and osteosarcoma (Sacker et al, 1994).

Sarcomas have been classified as superficial when they arise from the integumentary supporting structures and as deep when they develop from the corporeal body supporting structures (Pratt and Ross, 1969). Wide, local surface excision and partial penile amputation for the superficial tumors have been suggested and used successfully in isolated case reports (Pak et al, 1986; Dalkin and Zaontz, 1989). Total penile amputation has been reserved for tumors of deep corporeal origin. However, local recurrences are characteristic of sarcomas (Dehner and Smith, 1970). Fetsch and colleagues (2004), from the Armed Forces Institute of Pathology, have updated their series of 14 cases of leiomyosarcoma with review of the literature. They concluded that small lesions (smaller than 2 cm) were best managed with local resection, whereas deeper-seated tumor often necessitates partial or total amputation. Deep lesions at the base of the penis have the worst prognosis.

Regional metastases are rare. Unless adenopathy is palpable, node dissections are not recommended (Hutcheson et al, 1969). Distant metastases have also been unusual (Dehner and Smith, 1970). This supports aggressive local treatment in anticipation of cure. Radiation therapy and chemotherapy have not been used extensively enough for comment on their efficacy (Fetsch et al, 2004).

Kaposi sarcoma, which is usually a cutaneous manifestation of a generalized lymphoreticular disorder, may produce genital lesions but is now most frequently associated with HIV infection.

Extramammary Paget Disease

Extramammary Paget disease (EMPD) of the penis is rare, with fewer than 30 cases reported (Mitsudo et al, 1981; Macedo et al, 1997) up to the late 1990s. However, more recently several larger series have been reported from China and Korea (Yang et al, 2005; Wang et al, 2008). It appears grossly as an erythematous, eczematoid, well-demarcated area that cannot be clinically distinguished from erythroplasia of Queyrat, Bowen disease, or carcinoma in situ of the penis. Clinical presentation includes local discomfort, pruritus, and occasionally a serosanguineous discharge involving the penis, the scrotum, or even the perianal area (Fig. 37-5D and E). On microscopic examination, identification is clearly made by the presence of large, round or oval, clear-staining hydropic cells with hypochromatic nuclei (i.e., Paget cells). The cells often stain positively for cytokeratin 7 in addition to carcinoembryonic antigen and show gross cystic fluid protein but are S-100 protein negative (O'Connor et al, 2003). The tumor behaves as a slow-growing intraepithelial adenocarcinoma with cells derived from apocrine glands. With time the cells may become invasive with dermal tumor deposits metastasizing to regional lymph nodes via dermal lymphatics (Park et al, 2001; Hegarty et al, 2011). Of note, penoscrotal EMPD may be associated with other malignancies of the genitourinary tract, such as prostate, bladder, and renal malignancies (Chanda, 1985; Ojeda et al, 1987; Koh, 1995; Allan et al, 1998), and should be evaluated for their presence. In a recent series from MD Anderson Cancer Center among 20 reported patients, 9 (45%) had at least one other malignancy including prostate, bladder, renal, skin, esophageal, and rectal sites. Of note, 8 of the 9 patients were diagnosed with the other cancer before their diagnosis of EMPD.

Two reports from the Far East have added to the case series in the literature: 130 cases of penoscrotal Paget disease from China (Wang et al, 2008) and 36 from South Korea (Yang et al, 2005). In most cases only the skin and dermis must be resected with a gross margin of up to 3 cm. Positive margins may still occur, and frozen sections are recommended to guide the extent of resection. Local skin or scrotal flaps (Wang et al, 2008) can be used to cover the defects. Patients with a positive surgical margin are at a higher risk for recurrence, and additional resection is advised. In the series from Hegarty et al (2011), no recurrences were noted among patients with intraepidermal EMPD with negative surgical margins.

In a minority of cases the tumor may invade deeper structures, necessitating more extensive resection and reconstruction, as reported in case series (Hatoko et al, 2002; Fujisawa et al, 2008). If inguinal adenopathy is present, radical node dissection is advised (Hagan et al, 1975) but prognosis is poor (Yang et al, 2005). Hegarty and colleagues (2011) described the use of neoadjuvant docetaxel and carboplatin chemotherapy and surgical resection in two patients. One patient was alive with disease at 40 months, and the other had no evidence of disease at 13 months.

Adenosquamous Carcinoma

Adenosquamous carcinoma is a rare tumor characterized by both glandular and squamous histologic elements that are independent of the urethral glands. It manifests as a large (5 to 9 cm), firm, and grayish white granular exophytic mass involving the distal shaft or glans. On microscopic examination the glands contain mucin and are positive for carcinoembryonic antigen. In one reported case, the tumor was metastatic to a single inguinal node. This patient was managed with local excision of the primary tumor and a limited inguinal node dissection and lived 9 years after treatment. Other tumors were managed with local excision and surveillance (Cubilla et al, 1996). In only the seventh reported case (Romero et al, 2006), a patient with a bulky primary mass and inguinal lymph nodes underwent total penectomy and delayed ILND and PLND with a final pathologic stage of pT2N3M0 and was free of disease at 5-year follow-up.

Lymphoreticular Malignant Neoplasm

Primary lymphoreticular malignant neoplasm rarely occurs on the penis (Dehner and Smith, 1970). Leukemia may infiltrate the corpora, resulting in priapism (Pochedly et al, 1974). A thorough search for systemic disease is necessary when lymphomatous infiltration of the penis is diagnosed. If the penile lesion is indeed a primary tumor, systemic chemotherapy may be administered. It is the most effective therapy for local disease, for potential occult deposits that may exist elsewhere, and for preservation of form and function (Marks et al, 1988). Local low-dose radiation therapy has also been reported to be successful (Stewart et al, 1985).

Metastases

Metastatic lesions to the penis are unusual, with fewer than 300 cases reported in the literature (Belville and Cohen, 1992) until the early 1990s. Their infrequency is somewhat puzzling when one considers the rich blood and lymphatic supply to the organ and its proximity to the bladder, prostate, and rectal areas frequently involved with neoplasm. It is from these three organs that the majority of metastatic penile lesions originate (Abeshouse and Abeshouse, 1961). The most likely routes of spread are by direct extension, retrograde venous and lymphatic transport, and arterial embolism. Other sources of penile metastases emanate from the gastrointestinal tract, testis, and kidney (Belville and Cohen, 1992).

The most frequent sign of penile metastasis is priapism; penile swelling, nodularity, and ulceration have also been reported (McCrea and Tobias, 1958; Abeshouse and Abeshouse, 1961; Weitzner, 1971). Urinary obstruction and hematuria may occur. The most common histologic feature of penile invasion by metastatic lesions is the replacement of one or both corpora

cavernosa, which explains the frequent occurrence of priapism. Solitary cutaneous, preputial, and glandular deposits are less common.

The differential diagnosis includes idiopathic priapism; venereal or other infectious ulcerations; tuberculosis; Peyronie plaque; and primary, benign, or malignant tumors.

Penile metastases represent an advanced form of virulent disease and usually appear rather rapidly after recognition and treatment of the primary lesion (Abeshouse and Abeshouse, 1961; Hayes and Young, 1967; Mukamel et al, 1987). On rare occasions a long period may elapse between the treatment of the primary lesion and the appearance of penile metastases (Abeshouse and Abeshouse, 1961) or the penile lesion may occur as the initial and only site of metastasis. In one report of 17 patients with penile metastases, 14 patients died of disseminated disease, with a median survival of 5 months after the diagnosis of penile metastases (Chaux et al, 2011).

Because of the association of a penile metastatic lesion with advanced disease, survival after its presentation is limited, and the majority of patients die within 1 year (Robey and Schellhammer, 1984; Mukamel et al, 1987; Fischer and Patrick, 1999). Successful palliative treatment may occasionally be possible in the case of solitary nodules or localized distal penile involvement if complete excision by partial amputation succeeds in removing the entire area of malignant infiltration (Spaulding and Whitmore, 1978). The prospect for surgical cure is minimal if proximal corporeal invasion is present. Penectomy is occasionally indicated after failure of other modalities to palliate intractable pain (Mukamel et al, 1987). Pain can also be managed by dorsal nerve section (Hill and Khalid, 1988). In general, radiation therapy has been unsuccessful, and chemotherapy has not been employed in a sufficient number of cases to warrant definitive recommendations.

KEY POINTS: NONSQUAMOUS MALIGNANT NEOPLASMS

- Basal cell carcinoma represents a highly curable variant with a relatively low metastatic potential.
- Sarcomas are prone to local recurrence; regional and distant metastases are rare. Superficial lesions can be treated with less radical procedures.
- Melanoma is an aggressive form of cancer but can be cured if diagnosed and treated with the appropriate surgical procedure at an early stage.
- EMPD disseminates by intraepidermal spread initially. Wide local excision to achieve negative margins is the therapy of choice. Invasive EMPD can be lethal.
- Penile metastases most often represent spread from a clinically obvious existing primary tumor. Prognosis is poor, and therapy should be directed toward the primary tumor site histology and local palliation.

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The complete reference list is available online at www.expertconsult.com.

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Benign Urethral Tumors

Male Urethral Cancer

BENIGN URETHRAL TUMORS

Benign tumors of the urethra are quite rare, with only a few small series and case reports available in the literature. Leiomyoma, hemangioma, and fibroepithelial polyp are most frequently reported.

Leiomyoma

Leiomyomas of the urethra occur primarily in women, most commonly in the third and fourth decade of life. As of 1995, 36 cases had been reported in the English language literature (Leidinger and Das, 1995). Leiomyomas may be urethral or paraurethral in location, and tumor may protrude from the urethral meatus (Lee et al, 1995; Goldman et al, 2007). The most common clinical presentations include palpable anterior vaginal mass, irritative voiding symptoms, urinary tract infection, and hematuria. Obstructive urinary symptoms occur less frequently (Fry et al, 1988; Leidinger and Das, 1995). Leiomyomas also may be discovered incidentally during routine pelvic examination or an unrelated surgical procedure (Cornella et al, 1997). A percentage of these tumors have been reported to be hormonally sensitive based on changes in size during pregnancy and after delivery (Fry et al, 1988; Leidinger and Das, 1995). In many cases, diagnosis is aided by ultrasonography or magnetic resonance imaging (MRI). Paraurethral leiomyoma may be excised via a transvaginal approach, whereas intraurethral lesions are treated with transurethral resection (Cornella et al, 1997). Tumor recurrence is rare, and all reported urethral leiomyomas to date have followed a benign course (Goldman et al, 2007).

Hemangioma

Urethral hemangiomas are more common in males, and the majority of tumors initially described in the literature were located within the anterior urethra (Manuel et al, 1977). Most patients present within the second or third decade of life, although it is not uncommon for symptoms to have been present for years (Roberts and Devine, 1983). Urinary tract hemangiomas may be associated with the presence of cutaneous hemangiomas or congenital disorders such as Klippel-Trenaunay syndrome (Klein and Kaplan, 1975; Jahn and Nissen, 1991). The most common symptom of a urethral hemangioma is intermittent hematuria, which can be massive at times (Parshad et al, 2001). Bloody urethral discharge or hematospermia also may be noted. Diagnosis is made by cystoscopy, but this modality may underestimate the overall extent of the hemangioma (Manuel et al, 1977; Hayashi et al, 1997). MRI may be helpful in select cases to better delineate the extent of the lesion as with other tumors of the penis (Stewart et al, 2010). Smaller hemangiomas are generally treated with transurethral fulguration or laser; however, recurrent bleeding as a result of inadequate ablation may occur. In this setting, or when the hemangioma is more extensive, open excision with one- or two-stage urethral reconstruction may be required for cure (Roberts and Devine, 1983; Parshad et al, 2001).

Female Urethral Cancer

Posterior urethral hemangioma has more recently been recognized as a cause of hematospermia and/or hematuria after ejaculation or erection in older men (Hayashi et al, 1997; Saito, 2008). The lesions typically occur between the verumontanum and the external urethral sphincter. The most common appearance is that of a small sessile lesion with associated varicosities, with pathology demonstrating cavernous hemangioma in most cases. Symptomatic posterior urethral hemangiomas respond well to transurethral resection and fulguration (Saito, 2008).

Fibroepithelial Polyp

Fibroepithelial polyps (FEPs) are benign tumors of mesodermal origin that can occur in the upper or lower urinary tract (Kumar et al, 2008). Urethral FEPs are rare and usually are diagnosed in males during the first decade of life (Aita et al, 2005). The most common clinical presentation in adults is restriction of the urinary stream, frequency, and dysuria (Kumar et al, 2008). Urinary retention is less common but has been reported (Salehi et al, 2009). Diagnosis is made by a combination of cystoscopy, retrograde urethrography, and voiding cystourethrography. FEPs are most commonly located in the posterior urethra in males (Tsuzuki and Epstein, 2005), but have been reported in the bulbar urethra (Kumar et al, 2008). They may arise from the urethra and protrude from the meatus in women (Yamashita et al, 2004; Aita et al, 2005). Transurethral resection is the treatment of choice and is usually curative. Pathologic examination is required to confirm the diagnosis and rule out a more aggressive lesion such as urothelial papilloma or inverted papilloma (Tsuzuki and Epstein, 2005).

MALE URETHRAL CANCER

General Considerations

Carcinoma of the male urethra is rare and usually manifests in the fifth decade of life (Dalbagni et al, 1999). A recent analysis of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database identified 2065 men diagnosed with primary urethral cancer in the United States between 1988 and 2006. Approximately 88% of the patients were white, and 8% African-American (Rabbani, 2011). Etiologic factors include chronic inflammation resulting from a history of frequent sexually transmitted diseases, urethritis, and urethral stricture, and there is likely to be a causal role for human papillomavirus 16 in squamous cell carcinoma of the urethra (Weiner et al, 1992; Cupp et al, 1996). The onset of malignant change in a patient with chronic urethral stricture disease may be insidious, and a high index of clinical suspicion is required to diagnose these tumors expeditiously. More than 50% of patients have a history of urethral stricture disease, almost 25% have a history of sexually transmitted disease, and 96% are symptomatic at presentation (Dalbagni et al, 1999). The most common manifesting symptoms are urethral bleeding, a palpable urethral mass, and obstructive voiding symptoms.

Pathology

Tumors of the male urethra are categorized according to location and histologic features of the cells lining the urethra (Mostofi et al, 1992) (Fig. 38-1). The bulbomembranous urethra is involved most frequently, accounting for 60% of tumors, followed by the penile urethra (30%) and prostatic urethra (10%). Although traditionally it has been held that the majority of primary urethral cancers were squamous cell carcinomas, the SEER study by Rabbani revealed transitional cell carcinoma in 77.6%, squamous cell carcinoma in 11.9%, adenocarcinoma in 5%, and other histologies in 5.5% (Rabbani, 2011). The histologic subtype of urethral cancer varies by anatomic location. Carcinomas of the prostatic urethra are of transitional cell origin in 90% and of squamous cell origin in 10%; carcinomas of the penile urethra are of squamous cell origin in 90% and of transitional cell origin in 10%; and carcinomas of the bulbomembranous urethra are of squamous cell origin in 80%, transitional cell origin in 10%, and adenocarcinoma or undifferentiated in 10% (Grigsby and Herr, 2000).

Urethral carcinoma in males can spread by direct extension to adjacent structures, usually involving the vascular spaces of the corpus spongiosum and the periurethral tissues, or it can metastasize through lymphatic embolization to regional lymph nodes. The lymphatics from the anterior urethra drain into the superficial and deep inguinal lymph nodes and occasionally into the external iliac lymph nodes. Tumors of the posterior urethra most commonly spread to the pelvic lymph nodes. Palpable inguinal lymph nodes occur in approximately 20% of cases and almost always represent metastatic disease, in contrast to penile cancer, in which a large percentage of palpable nodes may be inflammatory. Hematogenous dissemination is uncommon except in advanced disease.

Evaluation and Staging

The tumor, node, metastasis (TNM) staging classification is based on depth of invasion of the primary tumor and presence or absence

of regional lymph node involvement and distant metastasis (Table 38-1). Examination under anesthesia, consisting of cystoscopy and bimanual palpation of the external genitalia, urethra, rectum, and perineum, aids in evaluating the extent of local involvement by tumor. Transurethral or needle biopsy of the lesion is also performed. Cytologic studies of voided urine do not seem to be a reliable method for diagnosis of primary urethral carcinoma. In one study, sensitivity was greatest in men with transitional cell carcinoma (80%) and in those with tumors involving the pendulous urethra (73%) (Touijer and Dalbagni, 2004). If rectal involvement is suspected on bimanual examination or by the patient's symptoms, an evaluation of the lower colon by barium enema study and flexible sigmoidoscopy is recommended to assist with surgical planning. Local soft tissue involvement, lymph node involvement, bone extension, and the presence of distant metastatic disease are best evaluated by a computed tomography (CT) scan of the chest, abdomen, and pelvis or in some cases by MRI. MRI may be particularly helpful for detecting invasion of the corpora cavernosa and is the most sensitive staging modality for the assessment of local tumor extent (Fig. 38-2) (Vapnek et al, 1992; Stewart et al, 2010).

TABLE 38-1 Urethral Cancer Tumor, Node, Metastasis Staging System

PRIMARY TUMOR (T) (MALE AND FEMALE)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
T4	Tumor invades other adjacent organs
TRANSITIONAL CELL CARCINOMA OF THE PROSTATE	
Tis-pd	Carcinoma in situ, involvement of the prostatic ducts
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumor invades other adjacent organs (invasion of the bladder)
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, more than 2 cm but less than 5 cm in greatest dimension; or in multiple nodes, none greater than 5 cm
N3	Metastasis in a lymph node greater than 5 cm in greatest dimension
DISTANT METASTASIS (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

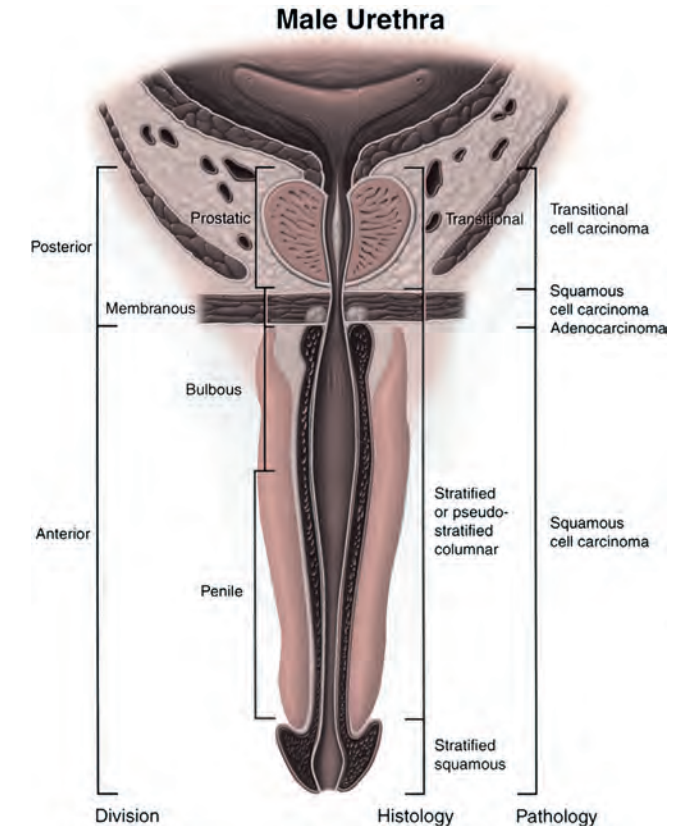


Figure 38-1. Anatomic regions of the male urethra and corresponding histology and histopathology.



Figure 38-2. Magnetic resonance image demonstrating large bulbospongiosus urethral cancer (arrow). P, penis; R, rectum.

Treatment

As in penile carcinoma, the primary form of treatment for men with urethral carcinoma is surgical excision. In general, anterior urethral carcinoma is more amenable to surgical control, and the prognosis is better than that of posterior urethral carcinoma, which is often associated with extensive local invasion and distant metastasis (Zeidman et al, 1992). A large series reported overall survival rates of 83% for low-stage tumors, 36% for high-stage tumors, 69% for anterior tumors, and 26% for those in the posterior urethra (Dalbagni et al, 1999). Similarly, a more recent study of 29 patients, 26 of whom underwent initial surgical excision, demonstrated 5-year overall survival rates of 67% for low-stage disease, 33% for high stage, 72% for anterior tumors, and 36% for posterior tumors. The majority of patients received some form of adjuvant radiation therapy or chemotherapy (Thyavichally et al, 2006).

Carcinoma of the Penile Urethra

Transurethral resection, local excision, or distal urethrectomy and perineal urethrostomy may be acceptable treatment in selected patients with superficial, papillary, or low-grade tumors. Long-term disease-free survival has been reported in this setting (Mandler and Pool, 1966; Konnak, 1980; Gheiler et al, 1998; Hakenberg et al, 2001; Karnes et al, 2010). Squamous cell carcinoma in situ of the penile urethra may extend into the distal urethra (Fig. 38-3) and has been successfully treated with partial glansectomy and distal urethrectomy with simultaneous urethral reconstruction (Nash et al, 1996) or penile urethrostomy (Fig. 38-4). In 2007, Smith and colleagues (2007) published results following penile-preserving surgery in 18 patients with squamous cell carcinoma of the penile urethra, 11 of whom had T2 and T3 disease. All underwent surgical excision with reconstruction and penile preservation, with no local recurrences. The authors therefore concluded that this was a feasible approach, and overall survival was not affected by the surgical procedure.

Partial penectomy with a 2-cm negative margin remains the traditional treatment for tumors infiltrating the corpus spongiosum and localized to the distal half of the penis. Excellent local control after this procedure has been documented (Kaplan et al, 1967; Ray et al, 1977; Anderson and McAninch, 1984; Hopkins et al, 1984; Dinney et al, 1994; Gheiler et al, 1998). If invasive



Figure 38-3. Squamous cell carcinoma in situ (erythroplasia of Queyrat) of the glans penis surrounding the urethral meatus. The patient also had significant extension of disease into the distal urethra.



Figure 38-4. Partial glansectomy and distal urethrectomy (same patient as in Figure 38-3). After negative margins were ensured, penile urethrostomy completed the procedure.

disease extends to or involves the proximal penile urethra, total penectomy is required to obtain an adequate margin of excision (Fig. 38-5). A local recurrence rate of 13% has been reported after this procedure (Kaplan et al, 1967). It is important to emphasize that accurate staging is critical to avoid underestimation of the proximal extent of the tumor. Review of previous data would suggest that radical penectomy is an insufficient operation for bulbous urethral tumors (Zeidman et al, 1992).

Although some instances of tumor control by irradiation have been reported, in general, primary radiation therapy has been reserved for patients with early-stage lesions of the anterior urethra



Figure 38-5. Large penile mass in a patient with transitional cell carcinoma of the penile urethra.

who refuse surgery. A commonly used technique consists of parallel opposed fields with the penis suspended vertically by a urethral catheter (Heysek et al, 1985). Radiation therapy has the advantage of potentially preserving the penis, but it may result in skin ulceration or necrosis, urethral stricture, or chronic edema. The long-term results of radiotherapy are difficult to evaluate because few reports are available of male patients treated with this modality (Raghavaiah, 1978; Forman and Lichter, 1992; Koontz and Lee, 2010).

Chemoradiation has been reported as a treatment modality for patients with invasive anterior urethral cancer with the intent of genital preservation (Cohen et al, 2008). The study group included nine patients with disease in the penile urethra who received a defined protocol of mitomycin-C (MMC) and 5-fluorouracil (5-FU) along with concurrent external beam radiation therapy. Five patients demonstrated a durable complete response and required no further therapy except for treatment of urethral stricture. One patient underwent subsequent salvage surgery for local recurrence and remained with no evidence of disease at last follow-up examination. Although the number of patients is limited, this may represent a reasonable consideration for effective tumor treatment with the potential for genital preservation; further study is needed. The outcome of the entire patient cohort is discussed further in the following section.

As opposed to patients with penile cancer, survival benefit from prophylactic inguinal lymph node dissection in patients without palpable inguinal nodes has not been demonstrated with urethral cancer. However, cases of cure with limited nodal disease have been reported and therefore inguinal lymphadenectomy should be considered in the presence of palpable inguinal lymph nodes. This also serves to prevent local problems such as skin breakdown, wound drainage, and vascular erosion.

Carcinoma of the Bulbomembranous Urethra

Early lesions of the bulbomembranous urethra have been treated successfully by transurethral resection or by segmental excision of the involved urethral segment with an end-to-end anastomosis. Unfortunately, cases appropriate for limited resection are rare. Poor survival figures have been recorded for all forms of treatment, but radical excision continues to be an important component of treatment in some patients. Radical cystoprostatectomy, pelvic lymphadenectomy, and total penectomy often are required. Extending the operation to include in-continuity resection of the pubic rami and the adjacent urogenital diaphragm may improve the margin of resection and local control (Mackenzie and Whitmore, 1968; Shuttleworth and Lloyd-Davies, 1969; Bracken, 1982; Klein et al, 1983; Dinney et al, 1994). Limited cases of urethrectomy alone with perineal urethrostomy for infiltrating tumors confined to the corpus spongiosum have been reported (Hakenberg et al,

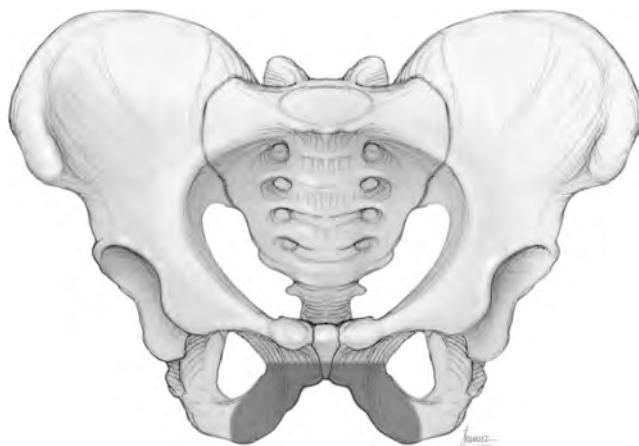


Figure 38-6. Shaded area outlines the portions of the ischiopubic rami excised at the time of inferior pubectomy during radical excision of bulbomembranous urethral cancer. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

2001). Total urethrectomy with bladder preservation, bladder neck closure, and creation of a continent catheterizable stoma may be an alternative in select cases (Grivas et al, 2012). The benefit of these more conservative approaches needs to be weighed against the probability of local relapse or dissemination of disease.

Radical extirpation is performed with the patient in the low lithotomy position to allow perineal access. Standard abdominal mobilization of the bladder is completed, except for preservation of the endopelvic fascia and the anterior pubic attachments. A modified λ or inverted U-shaped perineal incision is performed, based just medial to the ischial tuberosities, with the apex in the mid-perineum. The ischiorectal fossae are developed as in perineal prostatectomy, and a tunnel is bluntly dissected just anterior to the rectum, extending from one fossa to the other. The inferior skin flap is mobilized by sharply dividing the intervening subcutaneous tissue and rectourethral muscle. The superior flap is mobilized by sharply incising the subcutaneous tissue to the superficial Colles fascia and then continuing bilaterally to the adductor musculature at the inferior pubic rami. Circumferential incision of the skin and dartos fascia at the penoscrotal junction is performed, and the corporeal bodies are mobilized for a short distance proximally from the superior aspect of the symphysis pubis to allow subsequent inferior pubectomy. Care must be taken not to carry this dissection too far proximally to avoid breaching the anterior aspect of a locally advanced tumor. The penis is passed downward through the perineal incision. Wider exposure may be gained by dividing the scrotum in the midline if necessary. The scrotum usually can be preserved; however, bulky tumors may necessitate sacrifice of portions of the scrotum or perineal skin. In this setting, the testicles may be preserved in thigh pouches.

To complete the pubic arch resection, the adductor musculature is sharply divided bilaterally from the length of the inferior pubic ramus along the medial margin of the obturator foramen. A Gigli saw is passed along the inferior ramus just posterior to the origins of the transverse perineal musculature. An inferiorly beveled transection is made bilaterally to simplify perineal delivery of the specimen. Alternatively, an osteotome may be used for this purpose. The entire symphysis may be resected for bulky urethral lesions involving the presymphyseal tissues. This is accomplished by division of the superior rami at their junction with the symphysis. For most lesions, however, the bulk of the symphysis can be preserved with resection of the subsymphyseal arch. This procedure is preferred, when possible, to preserve stability of the pelvic girdle, and it results in a much smaller pelvic floor defect. A Gigli saw passed through the obturator foramina, or an osteotome is used to incise the symphysis transversely, joining the foramina (Fig. 38-6). The specimen



Figure 38-7. Surgical specimen after radical cystoprostatectomy, urethrectomy, penectomy, and inferior pubectomy for a large bulbomembranous squamous cell carcinoma.

is delivered en bloc (Fig. 38-7). After hemostasis is secure, the omentum is mobilized to cover the bowel. Large pelvic floor defects, such as occurring after total pubectomy, may be managed with a rectus abdominis muscle flap placed as a pelvic sling. Myocutaneous flaps can be fashioned to close large full-thickness perineal defects (Larson and Bracken, 1982).

Because of the relatively poor outcomes after surgery alone for advanced tumors of the posterior urethra, interest in multimodal therapy in this setting is increasing. Previous studies have evaluated the role of neoadjuvant chemotherapy in patients with advanced stage or metastatic disease. A regimen including methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) has been noted to have activity against transitional cell carcinoma but was ineffective against other tumor histologic types (Scher et al, 1988). Dinney and colleagues (1994) reported long-term survival in four of eight patients who presented with metastatic urethral carcinoma and were treated with cisplatin-based chemotherapy and surgical excision. On the basis of this experience, their favored regimen consisted of cisplatin, bleomycin, and methotrexate for squamous cell carcinoma and M-VAC for transitional cell carcinoma.

In 2012 the group from MD Anderson conducted a retrospective study of 44 patients with urethral carcinoma to evaluate the role of cisplatin-based chemotherapy (Dayyani et al, 2013). The study included 28 females and 16 males, and all patients but one had T3 or T4 disease. Forty-three percent had N1 and 16% M1 disease. Histologic subtypes were mixed, with the majority being squamous cell carcinoma, adenocarcinoma, and urothelial carcinoma. Thirty-six patients received one of four platinum-based chemotherapy regimens. Five were complete responders (14%), and 72% of patients achieved a complete response or a partial response. The presented results were not stratified as to gender or histology. Surgical consolidation was then performed in 21 patients, and their mean overall survival was 25.6 months. Of the 9 patients, 4 (44%) with lymph node–positive disease at diagnosis were alive, with a minimum follow-up of more than 3 years. Based on this experience, the authors concluded that it is reasonable to consider neoadjuvant chemotherapy for T3b and T4 tumors, as well as high-risk T2 and T3a lesions.

The combination of chemotherapy and radiation therapy has shown some success in a small number of patients with localized and metastatic urethral cancer (Licht et al, 1995; Oberfield et al, 1996). More commonly, these forms of treatment are combined with surgery in a multimodal approach in patients with advanced stage or metastatic disease (Johnson et al, 1989; Gheiler et al, 1998; Grigsby and Herr, 2000). A more recent study reported 18 patients with invasive urethral carcinoma who were treated initially with chemoradiation consisting of MMC and 5-FU and concurrent external beam radiation therapy to the genitalia, perineum, and inguinal and iliac lymph nodes (Cohen et al, 2008). The number of anterior

and posterior cancers was equal, and 33% were N1 or N2. Fifteen patients demonstrated a complete response. Three nonresponders underwent salvage surgery and eventually died of their disease. Of the 15 patients who experienced complete response, 10 remained with no evidence of disease at last follow-up. In the other 5 patients, local recurrence only developed in 4, who underwent salvage surgery, and 2 remained with no evidence of disease. Mean 5-year disease-free survival after chemoradiation and salvage surgery was 72%. It is interesting to note that the previously identified risk factors of tumor grade, T stage, and presence of nodal metastasis were not predictive in this series (Rabbani, 2011). Although instrumentation or surgery for urethral stricture was required in all complete response patients without local disease recurrence, 11 of 18 overall were spared radical surgery after treatment. Although this report is one of the few with a consistent patient population and treatment regimen, further study of this approach is needed to confirm the findings of this single-institution series.

Management of the Urethra after Cystectomy

General Considerations

Contemporary series have demonstrated the incidence of urethral cancer recurrence that follows cystoprostatectomy to range from 2.1% to 11.1% after cutaneous diversion (Freeman et al, 1996; Hassan et al, 2004; Nieder et al, 2004) and 0.5% to 4% after construction of an orthotopic neobladder (Freeman et al, 1996; Hassan et al, 2004; Nieder et al, 2004; Varol et al, 2004). Early studies indicated that transitional cell carcinoma involving the prostatic urethra, particularly with stromal invasion, significantly increased the probability of postoperative urethral recurrence (Hardeman and Soloway, 1990; Freeman et al, 1996). A large number of patients undergoing radical cystectomy with urinary diversion was more recently analyzed, and demonstrated urethral tumor recurrence in 5% and 7% after 5 and 10 years, respectively (Stein et al, 2005). Involvement of the prostate with tumor (either superficial or invasive) and the form of urinary diversion were independent risk factors. Estimated 10-year incidence of urethral recurrence ranged from 4% in patients with no prostatic involvement and orthotopic diversion (lowest risk group) to 24% in those with invasive prostate disease and cutaneous diversion (highest risk group). The low incidence of urethral recurrence after orthotopic bladder replacement has led most surgeons to feel comfortable proceeding with this form of diversion, as long as the findings on frozen-section biopsy of the distal prostatic urethral margin are normal at the time of cystoprostatectomy (Freeman et al, 1996; Hassan et al, 2004; Nieder et al, 2004; Stein et al, 2005). Preoperative transurethral biopsy of the prostate to assess suitability for continent diversion does not correlate with final urethral margin when the preoperative biopsy is positive and has largely been abandoned in favor of intraoperative frozen section (Kassouf et al, 2008).

Approximately 40% of urethral recurrences are diagnosed within 1 year after cystoprostatectomy, with a median time to diagnosis of 18 months (Clark et al, 2004). However, cases of late urethral recurrence have been reported, indicating the need for prolonged surveillance in these patients (Schellhammer and Whitmore, 1976; Freeman et al, 1996). Urethral wash cytology has traditionally been recommended for urethral monitoring after cutaneous diversion and leads to earlier diagnosis of urethral recurrence than when evaluation is delayed until symptoms occur. However, the presumed survival benefit afforded by surveillance with urethral wash cytology over symptomatic presentation has been called into question (Lin et al, 2003). Voided urine cytology is part of standard surveillance in patients who have undergone orthotopic diversion. Patients with positive results for urine or urethral wash cytology or symptoms of urethral bleeding, discharge, or palpable mass are evaluated with cystoscopy and biopsy. Pelvic CT or MRI may be necessary to aid in assessment of the local extent of larger invasive tumors and to assess for metastatic disease. Patients who develop urethral carcinoma in situ after orthotopic diversion may respond to urethral perfusion

with bacillus Calmette-Guérin, but this treatment is ineffective for those with papillary or invasive disease (Varol et al, 2004).

Total Urethrectomy after Cutaneous Diversion

The high or exaggerated lithotomy position provides optimal exposure for total urethrectomy, with the hips and knees gently flexed and the lower limbs abducted in boot-type stirrups. A modified λ or midline perineal incision (Fig. 38-8) is made, and the subcutaneous tissue and bulbospongiosus muscle are then divided in the midline and retracted to expose the corpus spongiosum. The corpus spongiosum is mobilized circumferentially near the level of the mid-bulbous urethra, and traction is applied to facilitate sharp dissection of the urethra distally, thus separating the corpus spongiosum from the adjacent corpora cavernosa. As dissection proceeds distally, the penis becomes inverted, the corpora cavernosa become bowed, and the glans recedes into the phallus. The penis is essentially turned inside out onto the perineum, and the dissection is completed to the base of the glans. To excise the meatus and glandular urethra, the penis is replaced in its anatomic position, and an

incision is made around the meatus and extended on each side down the ventral aspect of the glans. The distal urethra is then freed from its investments within the glans, and the isolated pendulous urethra is delivered onto the perineum. The deep spongiosum of the glans penis is reapproximated with 4-0 polydioxanone sutures in a horizontal mattress fashion; the surface layer is closed with interrupted 4-0 chromic sutures.

Proximal sharp dissection of the urethral bulb is carried out posteriorly and laterally, staying close to the bulb but avoiding entry, if possible, because bothersome bleeding will result. The urethra is detached from the corporeal bodies anteriorly to the level of the departure of the urethra from the bulb, leaving the specimen attached only by the membranous urethra itself. The bulbar arteries are usually identified at the 4-o'clock and 8-o'clock positions just inferior to the perineal membrane after they are transected during the posterior bulb dissection. They are controlled with electrocautery or suture ligation, or they can be ligated if they are identified before transection. **Care must be exercised in completing the proximal dissection, in view of the possible postcystectomy adherence of intestine to the superior surface of the urogenital**

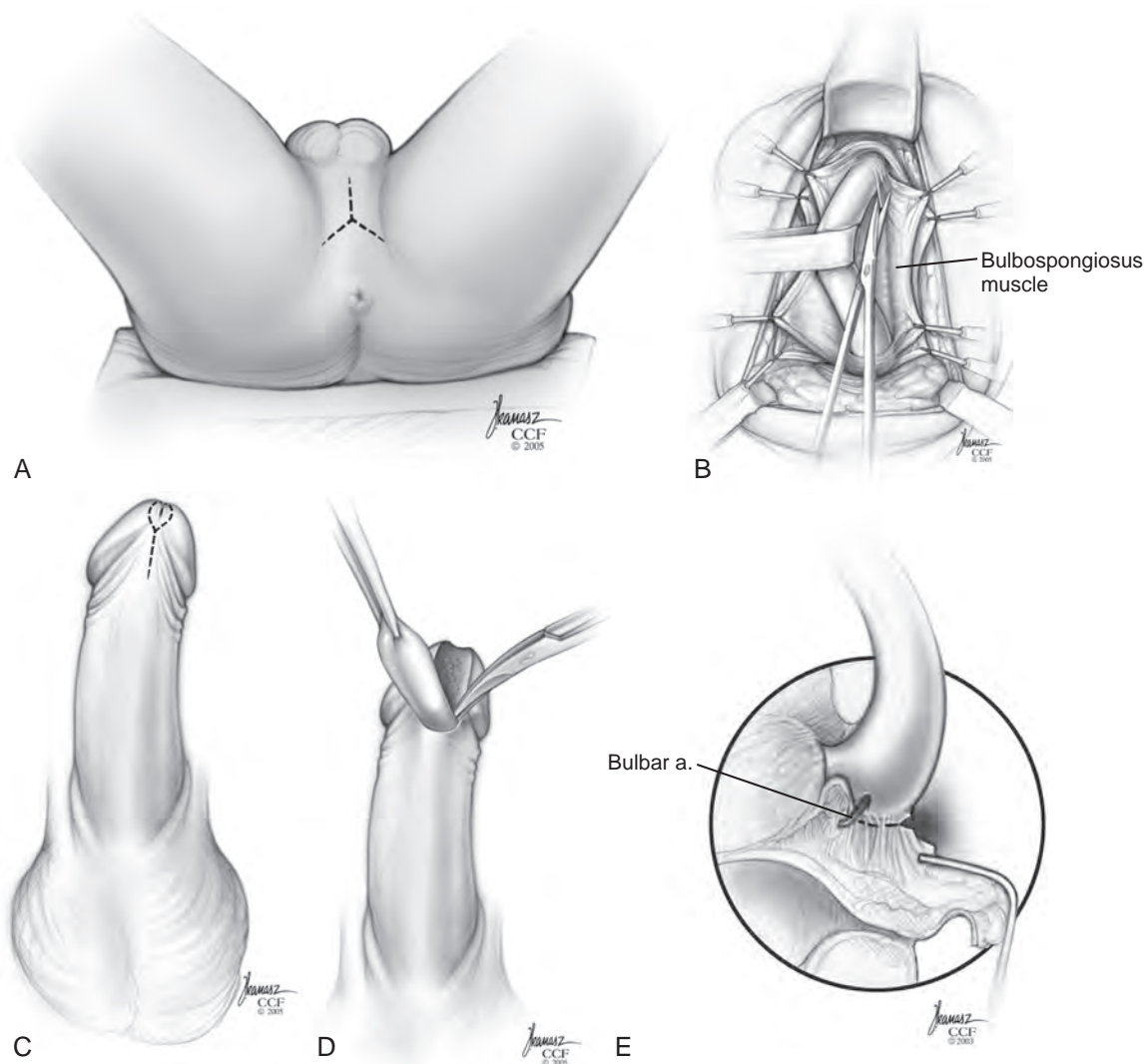


Figure 38-8. Secondary urethrectomy after previous cystoprostatectomy. A, Perineal incision. B, Division of bulbospongiosus muscle to expose the bulb of the corpus spongiosum and initial dissection of the urethra off of the corporeal bodies. C, Distal incision circumscribing the urethral meatus. D, Distal urethral dissection, which then connects to the proximal dissection at the level of the distal shaft. E, Sagittal view demonstrating posterior bulb dissection and location of the bulbar artery. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

diaphragm. This should be done under direct vision, and exposure can be aided by separating the crura of the corporeal bodies in the midline to open the intracural space. All that remains of the membranous urethra proximally is an ill-defined fibrotic band, and it should be completely excised. Frozen-section analysis of this region adds some assurance that a negative proximal margin has been attained. A small suction drain is placed in the urethral bed and brought out through the perineum. Closure of the bulbospongiosus muscle, subcutaneous tissue, and skin with interrupted absorbable sutures completes the procedure, and a light pressure dressing is applied. Superficial hematoma, edema along the penile shaft, and infection are uncommon complications.

Total Urethrectomy after Orthotopic Diversion

Total urethrectomy after orthotopic urinary diversion is performed through an abdominoperineal approach. The patient is placed in lithotomy position with boot-type stirrups that can be adjusted during the procedure. Urethrectomy is carried out to the level of the membranous urethra. Abdominal exploration with lysis of adhesions and mobilization of the orthotopic neobladder is done to the level of the urethral anastomosis. Working with careful palpation from above and below, the area of the membranous urethra and the anastomosis are dissected free in their entirety. A circular area of the pouch adjacent to the anastomosis is excised to ensure an adequate surgical margin, and the specimen is delivered through the perineum. Bleeding from the musculature within the tunnel developed during excision of the membranous urethra can be bothersome and is best controlled with suture ligatures.

In most situations, urinary diversion is accomplished with an ileal conduit. **This often can be carried out with use of bowel from the orthotopic neobladder, which may be reconfigured when necessary, with care taken to incise the bowel along visible lines of previous closure with preservation of the mesenteric blood supply.** The remaining portions of the pouch are excised. If the existing diversion has an afferent limb (e.g., Studer pouch), this segment can be used to construct the conduit without the need for manipulation of the ureters (Bissada et al, 2004). Conversion to a continent cutaneous diversion also may be possible in selected patients, depending on intra-abdominal anatomy and the motivation of the patient (Bartoletti et al, 1999; Taylor et al, 2009).

KEY POINTS: MALE URETHRAL CANCER

- In general, anterior urethral carcinoma is more amenable to surgical control, and the prognosis is better than that of posterior urethral carcinoma, which is often associated with extensive local invasion and distant metastasis.
- As opposed to penile carcinoma, benefit from prophylactic inguinal lymph node dissection has not been demonstrated in urethral cancer.
- Because of the relatively poor outcomes after surgery alone for advanced tumors of the posterior urethra, multimodal therapy should be considered
- The low incidence of urethral recurrence after orthotopic bladder replacement has led most authors to feel comfortable proceeding with this form of diversion, as long as the findings on frozen-section biopsy of the distal prostatic urethral margin are normal at the time of cystoprostatectomy.
- In converting a patient to cutaneous conduit urinary diversion, bowel from the existing orthotopic neobladder often can be reconfigured with its blood supply intact and used for this purpose.

FEMALE URETHRAL CANCER

Epidemiology, Etiology, and Clinical Presentation

A primary malignant neoplasm arising from the female urethra is rare. The literature has reported that despite the female urethra

being much shorter than its male counterpart, primary cancers of the urethra were more common in women than men (Narayan and Konety, 1992). However, more recent study has called this into question. Swartz and colleagues (2006) studied the incidence of primary urethral carcinoma in the United States and found that based on data from the SEER database, between 1973 and 2002, 1615 cases were identified, including 1075 men and 540 women. The ratio of female-to-male predominance had previously been reported as 4:1 (Narayan and Konety, 1992), but based on SEER data there is a 2:1 male-to-female predominance.

Female urethral carcinoma accounts for approximately 0.02% of female cancers (Fagan and Hertig, 1955) and less than 1% of cancers in the female genitourinary tract (Srinivas and Khan, 1987). More than 1200 cases are reported in the literature, most diagnosed in the fifth and sixth decades of life (Srinivas and Khan, 1987). Previously it was noted that approximately 85% of urethral carcinoma cases occur in white women (Terry et al, 1997); however, Swartz and colleagues (2006) reported a greater incidence of primary urethral cancers in African-American women than in white women. They found an overall annual incidence of 1.5 cases per million women, including 4.3 cases per million African-American women and 1.3 per million white women. In the Netherlands, overall crude annual incidence was 0.7 per million women, with peak incidence in the 80- to 84-year-old age group (Derksen et al, 2013).

Incidence appears to increase with age regardless of histologic subtype. The suggestion has been made that the disease is becoming even rarer, because the incidence appears to be decreasing over the time of the SEER study. Although it is likely that misclassification of the site of origin of tumors within the SEER database has led to some inaccuracy in the findings as reported by Swartz, other previous reports are likely biased by the tertiary referral center populations from which these reports originate.

Although the cause of urethral carcinoma in women has not been identified, several factors have been implicated. **Etiologic factors associated with the development of urethral carcinoma include leukoplakia, chronic irritation, caruncles, polyps, parturition, and human papillomavirus infection or other viral infections** (Mevorach et al, 1990; Grigsby and Herr, 2000). Female urethral diverticula also may predispose the patient to malignant change, with perhaps 5% of female urethral carcinomas arising within a diverticulum (Rajan et al, 1993). In a series of 90 women undergoing diverticulectomy, 5 (6%) were found to have invasive adenocarcinoma. Additionally, there was evidence of intestinal metaplasia and dysplasia in some patients (Thomas et al, 2008). Based on immunohistochemical analysis, adenocarcinomas appear to originate from different tissue origins, including (1) Skene glands as a prostatic homologue with resultant prostate-specific antigen positivity in some cases, (2) glandular metaplasia leading to columnar/mucinous adenocarcinoma, and (3) other sources leading to clear cell adenocarcinoma (Dodson et al, 1994; Murphy et al, 1999; Pongtippan et al, 2004; Reis et al, 2011; Papes and Altarac, 2013).

Anatomy and Pathology

Knowledge of urethral anatomy is essential for surgical excision and reconstruction. The female urethra has been divided into an anterior segment (distal third) and a posterior segment (proximal two thirds). **The distal third may be excised while urinary continence is maintained.** The proximal third of the urethra is lined by typical transitional urothelium and the distal two thirds by stratified squamous epithelium (Fig. 38-9). Along its length are submucosal glands composed of columnar epithelium. Lymphatic drainage differs along the course of the female urethra, as in men. Although crossover and communications are possible, lymphatics from the posterior urethra drain to the external and internal iliac and obturator lymph node chains. The anterior urethra and labia drain to the superficial and then to the deep inguinal lymph nodes (Carroll and Dixon, 1992).

The histology of the malignant neoplasm depends primarily on the site of origin within the urethra (see Fig. 38-9). Because of low numbers and varying patient populations, the most predominant

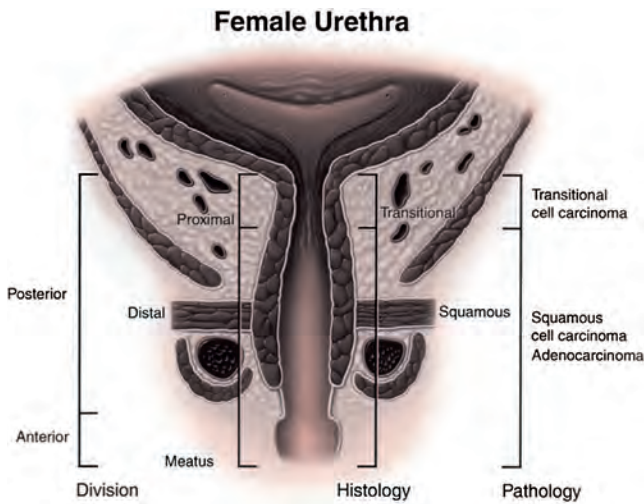


Figure 38-9. Anatomic regions of the female urethra and corresponding histology and histopathology.

cell type varies in different reported series. It is commonly believed that squamous cell carcinoma appears to be the most common histologic type, accounting for 30% to 70% of all cases. Urothelial carcinoma and adenocarcinomas are thought to be the next most common cell types (10% to 25% each). Swartz's review of SEER data found a small majority of cases were urothelial carcinomas and that among women, urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma were noted in 30%, 28%, and 29% of cases, respectively.

A study from Netherlands National Cancer Registry corroborated the SEER data and revealed that even in women, urothelial carcinoma remains the predominant cell type (Derksen et al, 2013). This study of 91 females with primary urethral carcinoma revealed urothelial carcinoma in 45%, squamous cell carcinoma in 19%, and adenocarcinoma in 29% of cases.

Other rarer cell types include lymphoma, neuroendocrine carcinoma, sarcomas, paragangliomas, melanoma, and metastasis (Johnson and O'Connell, 1983; Grabstald et al, 1966; Foens et al, 1991; Forman and Lichter, 1992; Grigsby and Herr, 2000; Swartz et al, 2006). Within urethral diverticula, an increased incidence of adenocarcinomas seems to exist, substantiating the theory that urethral diverticula in some women may arise from a glandular origin, such as the Skene glands (Spencer et al, 1990; Rajan et al, 1993; Gheiler et al, 1998; Thomas et al, 2008; Reis et al, 2011).

Diagnosis and Staging

The evaluation of women with suspected urethral carcinoma includes a thorough pelvic examination, evaluating for a palpable anterior vaginal mass for which the differential should include urethral diverticulum, urethral cancer, urethral polyp, or other benign neoplasm, such as a leiomyoma. Speculum examination should visualize the urethral meatus directly and evaluate for potential involvement of the vaginal wall and vulva. Diagnostic studies include cystourethroscopy and examination under anesthesia. MRI has been used to evaluate pelvic lesions because soft tissue contrast is superior to that with CT and it gives the best anatomic detail in this area. Additionally, MRI can assess local extension and lymph node involvement. Additional staging studies with chest radiograph or chest CT are appropriate. Bone scan may be performed if clinical suspicion exists of bony involvement as a result of bony symptoms or laboratory abnormalities such as elevated alkaline phosphatase or serum calcium. CT with positron emission tomography (CT/PET) may be useful in patients with metastatic disease although its utility is not accurately defined in urethral carcinoma. Serum prostate-specific antigen has been found to be elevated in a small number of case reports of females with adenocarcinoma, and it appears only

a minority of female patients with primary adenocarcinoma of the urethra have this elevated tumor marker (Dodson et al, 1994; Pongtippan et al, 2004). TNM staging for female urethral cancer is identical to that for male urethral cancer (see Table 38-1). Clinically palpable inguinal nodes are found in up to 30% of patients overall, and these are confirmed to be malignant in approximately 90% of cases. Up to 50% of patients with proximal or advanced urethral cancers may have palpable nodes. Pelvic nodal metastases are not uncommon, affecting 20% of cases. Metastasis outside of the pelvis at presentation is rare, however. During follow-up, another 15% of patients will develop metastatic nodal disease (Grigsby and Herr, 2000).

Treatment and Prognosis

Because of the rarity of this tumor and heterogeneity of disease, insufficient experience at any single institution within a reasonable period has precluded attempts to effectively define the natural history of the disease, recommendations for therapy, and follow-up of these patients (Grigsby and Herr, 2000). Although it is conceivable that different histologic subtypes may affect prognosis and the propensity for route of disease spread, most studies have failed to detect any differences in survival based on histologic subtype (Foens et al, 1991; Dimarco et al, 2004). Consequently, lesions of varying histologic type are often treated in a similar fashion. A recent survival analysis of SEER data in 359 women found that squamous cell carcinoma had a longer cancer-specific survival than urothelial or adenocarcinoma histologies (hazard ratio of 2.03 and 1.90, respectively) (Champ et al, 2012).

Treatment recommendations depend primarily on tumor location and clinical stage. Local excision, which should lead to excellent functional results, may be sufficient for the relatively uncommon small, superficial, distal urethral tumors. For more proximal and advanced urethral tumors, a more aggressive approach is warranted. Compared with proximal urethral cancers, distal lesions are associated with improved survival. Five-year disease-specific survival is reported at 71% for distal lesions, 48% for proximal lesions, and 24% for lesions that involve the majority of the urethra (Dalbagni et al, 1998). Surgical and radiotherapy series reflect overall 5-year survival rates of 30% to 40%. Unfortunately, little improvement has been made in treatment of this disease and survival rates have remained statistically unchanged for the last 50 years (Bracken et al, 1976; Prempre et al, 1984; Foens et al, 1991; Dalbagni et al, 1998; Dimarco et al, 2004).

In a study of SEER data encompassing 722 women with primary urethral cancer between 1983 and 2008, 359 women with non-metastatic disease were found to have enough data for cancer survival outcomes to be evaluated (Champ et al, 2012). They found that 5-year and 10-year overall survival was 43% and 32%, respectively. Cancer-specific survival at 5 and 10 years was estimated at 53% and 46%, respectively. Multivariate analysis revealed race (African-American), advanced stage, node-positive disease at time of surgery; nonsquamous histology; and advanced age as being associated with worse cancer-specific survival. Surgery was associated with improved survival, which was not seen for radiation therapy. These data do not indicate that radiation therapy lacks benefit, because selection bias and other confounding factors significantly affect interpretation of this result.

Data from the National Cancer Registry of the Netherlands evaluating 91 females with primary urethral carcinoma reported 46% of patients presenting with advanced disease (stage III or IV). Five-year survival rates of stage 0 to II, stage III, and stage IV were 67%, 53%, and 17%, respectively (Derksen et al, 2013).

Options for treatment of female urethral carcinoma include surgery, radiation therapy, and chemotherapy, alone or in combination. Treatment has trended toward a multimodality approach in recent years based on previously reported outcomes. Use of radiation therapy has increased compared to men treated for urethral carcinoma. In the study of SEER data by Champ and associates (2012), 72% had undergone some cancer-directed surgical procedure and 42% had undergone radiation. Data from the National

Cancer Registry of the Netherlands detailed treatment of 43% of patients with surgery, 16% with radiation, or radiation plus surgery in 22% (Derksen et al, 2013). Although representative of a heterogeneous group of studies, with varying treatment techniques and follow-up, reported results in case series with more than two patients based on primary treatment modalities are summarized in Tables 38-2 and 38-3 for early and advanced disease, respectively.

Distal Female Urethral Carcinoma

Small, exophytic, superficial tumors arising from the urethral meatus or distal third of the urethra may be surgically treated with circumferential excision of the distal urethra and inclusion of a portion of the anterior vaginal wall via a transvaginal approach. Frozen-section specimens of the proximal urethra should be obtained to ensure an adequate margin (Narayan and Konety, 1992). Laser coagulation of small distal tumors has been described (Stahler et al, 1985; Dann et al, 1989). In select patients with T2 or T3 cancer, bladder-sparing strategies also have been employed, if the tumor is more anterior, while an attempt is made to maintain a thorough resection. Dimarco and colleagues (2004) describe radical urethrectomy in the female patient, including excision up to the level of the bladder neck with wide resection of periurethral tissues and anterior vaginal wall. Urinary diversion is then accomplished with a catheterizable stoma (ileovesicostomy or appendicovesicostomy) to the native bladder. Tumors in the distal (anterior) urethra tend to be low stage, and cure rates of 70% to 90% have been achieved with local excision alone. However, in a study by Dimarco and colleagues (2004), 21% of patients with stage T2 or less tumors treated with partial urethrectomy had local recurrence. Other studies of partial urethrectomy, with or without

radiation therapy, for lower stage lesions have recurrence rates of 0% to 50% (Hahn et al, 1991; Gheiler et al, 1998). Meatal stenosis is a common complication, and incidence may be decreased by spatulation of the urethra. Approximation of the anterior vaginal wall and labia may help prevent urinary incontinence, although a sling procedure or other procedure to treat urinary incontinence may need to be subsequently performed. Many authors report minimal complications and rare incontinence from partial urethrectomy, but one series noted de novo or worsening stress urinary incontinence in 42% of patients (Dimarco et al, 2004).

Radiation therapy, as well as surgery, has proved effective for the treatment of low-stage distal urethral carcinomas. An overall 5-year actuarial survival rate of 41% was reported in a series of 84 patients by Garden and colleagues (1993). This was subdivided into 5-year survival of 74% if only part of the urethra was involved and 55% if the entire urethra was involved. Survival appeared to be associated with clinical stage of the tumor (Garden et al, 1993). Radiation may be delivered as external beam, brachytherapy, or combined therapy. In a series of 42 patients treated at the University of Iowa, radiotherapy delivered with combined interstitial and external beam radiation provided fewer local failures (14%) than all radiation-treated patients (36%) or those treated by surgery alone (60%). However, 5-year survival rates for irradiated and surgically treated groups are similar (Foens et al, 1991). Although doses may vary widely, a dose between 55 and 70 Gy is reported in most series. Complication rates, now decreasing, have ranged from 20% to 40%, including urinary incontinence, urethral strictures, necrosis, fistula formation, cystitis, vulvar abscess, and cellulitis (Forman and Lichter, 1992). Radiation may represent an alternative in women when surgical resection would negatively affect functional outcomes. Significant morbidity has been noted with ilioinguinal lymphadenectomy. In addition, female urethral carcinoma often spreads systemically without regional lymph node involvement. Although studies are small, no evidence for improved survival after pelvic or inguinal lymphadenectomy has been found (Grabstald et al, 1966; Levine, 1980; Dimarco et al, 2004). These findings, as well as the inability to prognosticate likelihood for micrometastatic lymph node involvement, led to the recommendation against prophylactic or diagnostic lymphadenectomy. Acknowledging that few objective data exist for making definitive decisions, recommendations for performing groin dissection have been made only for patients who present with positive inguinal or pelvic lymphadenopathy without distant metastasis or patients who develop regional adenopathy during surveillance. Late inguinal lymph node recurrences up to 7 years have been noted. The technique of ilioinguinal lymphadenectomy is identical to the dissection performed in men for penile cancer (Narayan and Konety, 1992; Grigsby and Herr, 2000).

In patients with recurrent or radioresistant tumors, neoadjuvant irradiation followed by local excision resulted in a survival advantage over radiotherapy alone (Grabstald et al, 1966; Peterson et al, 1973; Allen and Nelson, 1978). Despite early and aggressive therapy for anterior lesions, local recurrence rates and mortality remain high. Further studies are necessary to evaluate the potential role of multimodality therapy in these patients.

Proximal Female Urethral Carcinoma

Proximal female urethral carcinomas are more likely to be high stage and may extend into the bladder and vagina. Results with anterior exenteration alone resulted in a 10% to 17% 5-year survival rate and a local recurrence rate of 67% (Bracken et al, 1976; Klein et al, 1983). The poor disease-specific survival and high local recurrence rates observed with single-modality treatment of advanced female urethral carcinoma have led to the recommendation of combination therapy (Dalbagni et al, 1998, 2001; Gheiler et al, 1998). Advanced female urethral carcinoma includes tumors in a proximal location, a lesion that encompasses the entire urethra, or a locally invasive lesion that involves external genitalia, vagina, or bladder. Anterior exenteration (cystourethrectomy), pelvic lymph node dissection, and wide vaginal or complete vaginal excision are often

TABLE 38-2 Results of Various Treatment Modalities for Early Urethral Carcinoma in Women

TREATMENT	STUDY	NO. OF PATIENTS	SURVIVAL* NO. (%)
Radiotherapy	Weghaupt et al, 1984	42	30 (71)
	Pointon and Poole-Wilson, 1968	26	20 (77)†
	Taggart et al, 1972	15	8 (53)‡
	Grabstald et al, 1966	11	3 (27)
	Delclos et al, 1980	11	6 (55)
	Chu, 1973	11	7 (64)
	Antoniades, 1969	8	8 (100)§
	Prempre et al, 1984	6	6 (100)
	Johnson and O'Connell, 1983	5	3 (60)
	Klein et al, 1987	3	2 (66)¶
	TOTAL	138	93 (67)
Surgery	Grabstald et al, 1966	14	10 (71)
	Bracken et al, 1976	3	1 (33)
	Eng et al, 2003	4	4 (100)
	TOTAL	21	15 (71)
Radiotherapy plus surgery	Grabstald et al, 1966	3	2 (67)
	TOTAL	3	2 (67)

*Survival 5 to 6 years unless otherwise noted.

†Three-year survival.

‡Two-year survival with no evidence of disease.

§One patient dead of disease at 64 months.

||Patients had no evidence of disease at 4 years.

¶Patients alive at 27 and 37 months.

TABLE 38-3 Results of Various Treatment Modalities for Advanced-Stage Urethral Carcinoma in Women

TREATMENT	STUDY	NO. OF PATIENTS	SURVIVAL* NO. (%)
Radiotherapy	Pointon and Poole-Wilson, 1968	52	21 (40) [†]
	Delclos et al, 1980	25	7 (28)
	Weghaupt et al, 1984	20	10 (50)
	Grabstald et al, 1966	19	1 (5)
	Antoniades, 1969	11	4 (36) [‡]
	Prempre et al, 1984	7	4 (57)
	Hahn et al, 1991	8	3 (38)
	Chu, 1973	8	0 (0)
	Johnson and O'Connell, 1983	7	4 (57) [§]
	TOTAL	157	54 (34)
Surgery	Grabstald et al, 1966	13	2 (15)
	Bracken et al, 1976	7	3 (43)
	Moinuddin Ali et al, 1988	3	0 (0)
	TOTAL	23	5 (22)
Radiotherapy + surgery	Grabstald et al, 1966	20	5 (25)
	Johnson and O'Connell, 1983	7	3 (43)
	Hahn et al, 1991	3	9 (0)
	Moinuddin Ali et al, 1988	4	2 (50) [¶]
	TOTAL	34	19 (55)
Radiotherapy + chemotherapy ± surgery	Gheiler et al, 1998	6	3 (50) ^{**}
	Dalbagni et al, 2001	4	2 (50) ^{††}
	TOTAL	10	5 (50)

*Survival 5 to 6 years unless otherwise noted.

[†]Three-year survival.

[‡]Two patients dead of disease at 8 and 21 years.

[§]No evidence of disease at 1, 1, 3, and 6 years.

^{||}No evidence of disease at 2 months and 3, 8, and 12 years.

[¶]Alive at 48 months.

^{**}No evidence of disease at 6 months and 4 years.

^{††}No evidence of disease at 1.5 and 4 years.

required to obtain negative surgical margins. If the lesion extends into the external genitalia, partial vulvectomy or labial excision may be necessary. Anterior exenteration is performed as for bladder cancer in a female patient, with a more extensive perineal portion of the procedure to provide wide margins around the urethra. The margins of the lymphadenectomy should include the Cloquet node distally and otherwise retain limits identical to the dissection encouraged for lymphadenectomy in bladder cancer. Anterior exenteration includes the en bloc removal of the entire urethra and bladder, the uterus and adnexa, and the anterior and lateral vaginal walls. On occasion, the entire vagina may need to be resected. The perineal portion is initiated by completing an inverted U-shaped incision to encircle widely around the urethral meatus. It has been suggested that this incision be extended onto the posterior vaginal wall to the labia minora and continued anteriorly to beyond and including the clitoris (Narayan and Konety, 1992). En bloc resection of the pubic symphysis and inferior pubic rami may be necessary if the lesion encroaches anteriorly at the pubis, although the necessity of bone resection has been questioned in ensuring durable local control when intraoperative irradiation is added in suspect cases (Dalbagni et al, 2001).

Radiotherapy alone for proximal invasive urethral carcinoma has yielded poor local control, and 5-year survival rates of 0% to 57% are reported (Grabstald et al, 1966; Johnson and O'Connell, 1983; Prempre et al, 1984; Narayan and Konety, 1992). An improved mean survival rate of 54% at 5 years resulted from the combination of radiation therapy and surgery for high-stage disease (Moinuddin Ali et al, 1988; Terry et al, 1997).

A combination of chemotherapy, radiation therapy, and surgery has been recommended for optimal local and distant disease

control in advanced female urethral cancer. Patients whose treatment fails are thought likely to harbor micrometastatic disease at the time of primary treatment. For patients with squamous cell carcinoma, 5-FU plus MMC has been the most common empirically chosen regimen, in part because of its effectiveness against anal cancers (Kalra et al, 1985). For transitional cell cancers, either M-VAC or a gemcitabine regimen is recommended (Grigsby and Herr, 2000). Chemotherapy given concomitantly with radiation therapy has been shown to interfere with cell repair and thus act as a radiosensitizer. It is hoped that therapy based on this rationale may decrease local recurrence and improve survival by eliminating micrometastatic disease and preventing progression of local failures to systemic failures. The group at Memorial Sloan-Kettering has shown early results based on six patients with advanced proximal urethral tumors treated with a multimodality approach. The authors suggest that anterior exenteration with high-dose intraoperative brachytherapy followed by external beam radiation seems to improve local control. Studies must evaluate whether combined modality therapy proves to decrease distant metastasis and improve survival (Dalbagni et al, 1998, 2001).

For advanced female urethral cancer, we recommend primary chemotherapy and/or radiation therapy for locally advanced tumors. If a radiographic and endoscopic response is realized, consolidative surgery can be considered. Systemic chemotherapy should be considered for metastatic disease.

Urethral Recurrence after Cystectomy in Women


Orthotopic neobladder construction in women is now an established form of urinary diversion after radical cystectomy for

transitional cell carcinoma. The incidence of carcinoma involving the urethra in female patients undergoing cystectomy for bladder cancer ranges from 1% to 13% (Coloby et al, 1994; Stein et al, 1995, 1998; Stenzl et al, 1995). Debate still exists as to whether involvement of the bladder neck is a contraindication to orthotopic diversion; a prospective study revealed that although all patients with urethral transitional cell carcinoma on final pathologic analysis of the cystectomy specimen had involvement of the bladder neck, more than 60% of women with bladder neck involvement had no evidence of urethral transitional cell carcinoma (Stein et al, 1998). Intraoperative frozen-section analysis of the urethral stump has been subsequently espoused by some authors to determine the feasibility of urethra-sparing cystectomy and orthotopic diversion (Stein et al, 1998).


Despite the reported incidence of urethral involvement in patients who have undergone cystectomy and the increased use of orthotopic diversion in women, few cases have been reported of subsequent urethral malignant neoplasms in patients who have undergone this procedure. A review of 1054 patients undergoing radical cystectomy at a single center with a median follow-up of 10 years included 211 women, 44 of whom had an orthotopic urinary diversion. None of the 44 women developed a urethral recurrence (Clark et al, 2004). Subsequently, this group from the University of Southern California reported their first case of primary urethral recurrence in female patients selected for orthotopic urinary diversion. The patient remained without evidence of disease at 4 years of follow-up after total urethrectomy, resection of neobladder neck, and conversion of the orthotopic reservoir to a continent cutaneous urinary diversion (Stein et al, 2008). A report by Taylor and colleagues from MD Anderson (2009) reported on 260 patients after radical cystectomy and orthotopic neobladder, 10 of whom were women. There were six urethral recurrences, all in male patients. In a study by Ali-el-Dein and colleagues (2004), 145 women underwent orthotopic urinary diversion, 61% for squamous cell carcinoma, and 21% for transitional cell carcinoma. At a median follow-up of 56 months, 2 patients (1.4%) developed an isolated urethral recurrence. One patient was reportedly not a surgical candidate, and the other patient underwent urethrectomy and conversion to a continent cutaneous reservoir but died 8 months later (Ali-el-Dein et al, 2004). One additional report described urethral transitional cell carcinoma in a woman after orthotopic diversion. This patient had a high-grade lesion of the bladder base with evidence of nodal metastasis. The patient was treated initially with chemotherapy, followed by urethral resection and conversion to a continent cutaneous diversion. The patient died 5 months later with visceral metastases (Jones et al, 2000). Limited experience to date precludes the ability to make definitive treatment recommendations for women with urethral cancer recurrence after orthotopic diversion. Urethrectomy and surgical resection of the area of the urethra-pouch anastomosis with conversion to a continent cutaneous urinary diversion seem feasible and reasonable in the absence of metastatic disease. Conversion to a cutaneous urinary conduit with use of reconfigured bowel from the existing orthotopic diversion is another option (Bissada et al, 2004).

KEY POINTS: FEMALE URETHRAL CANCER

- The three most common histologies for cancer of the female urethra are urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma—each accounting for approximately 30% of cases.
- Compared with proximal urethral cancers, distal (anterior) lesions are associated with improved survival.
- Tumors in the distal urethra may be low stage, and cure rates of 70% to 90% have been achieved with local excision alone via a transvaginal approach. Radiation may represent an alternative when surgical resection would negatively affect functional outcome.
- Proximal female urethral carcinomas are more likely to be high stage and may extend into the bladder and vagina.
- Optimal treatment for advanced female urethral cancer is not well defined. Multimodal therapy is advocated. A combination of chemotherapy, radiation therapy, and surgery has been recommended for local and distant disease control.
- In appropriately selected women undergoing radical cystectomy and orthotopic diversion for bladder cancer, recurrence of cancer in the retained urethra is a rare event.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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Anatomic Considerations

Despite ongoing clinical experience, treatment of squamous cell carcinoma of the penis remains primarily surgical. Early meticulous surgical management with close follow-up typically provides the best opportunity for cure. The most important factor determining survival in patients with penile cancer is the extent of lymph node metastases (Johnson and Lo, 1984; Srinivas et al, 1987; Ravi, 1993; Horenblas and van Tinteren 1994). The management of the inguinal lymph nodes therefore is a major component of the overall treatment strategy, and appropriate decision making with regard to lymph node assessment and excision is critical.

ANATOMIC CONSIDERATIONS

Penile Lymphatics

Squamous cell carcinoma of the penis spreads initially to regional lymph nodes before the occurrence of distant metastatic disease. Lymphatic spread occurs in a systematic fashion along the normal route of penile lymphatic drainage. The superficial lymphatic system consists of vessels draining the prepuce and skin of the penile shaft that converge dorsally and then divide at the base of the penis to drain into the right and left superficial inguinal nodes. The deep lymphatic system consists of drainage from the glans penis toward the frenulum, where large trunks are formed and encircle the corona to unite with those from the other side on the dorsum. They traverse the penis to the base within the Buck fascia, draining through presymphyseal lymphatics into the superficial inguinal nodes and the deep inguinal nodes of the femoral triangle. It is not uncommon for penile cancer to metastasize to the contralateral inguinal nodes because of crossover in the symphyseal region, and this needs to be taken into account in developing a treatment strategy. Drainage subsequently proceeds from the inguinal nodes to the ipsilateral pelvic lymph nodes. It is generally accepted that penile lymphatics drain to the inguinal nodes before proceeding into the iliac nodes (Riveros et al, 1967), although some anecdotal observations have suggested that penile lymphatics may at times drain directly to the external iliac nodes (Lopes et al, 2000). This observation is most likely related to undersampling of the inguinal nodes at the time of lymphadenectomy or at the time of pathologic review. Although penile carcinoma metastatic to the inguinal lymph nodes confers a poorer prognosis overall, aggressive lymphadenectomy is associated with improved long-term survival and potential cure (McDougall et al, 1986; Horenblas and van Tinteren, 1994). In addition, immediate resection of clinically occult lymph node metastases is associated with improved survival when compared with delayed resection of involved nodes at the time of clinical detection (Kroon et al, 2005). If the tumor has spread to the pelvic nodes, long-term survival is less than 10%.

Urethral Lymphatics

Urethral lymphatic drainage runs parallel to the urethra and is located within the mucous membrane and submucosa (Spirin, 1963). This network is most dense in the area of the fossa

Penile Cancer: Surgical Management of Regional Lymph Nodes

navicularis, and these branches join the lymphatics of the glans at the prepuce. The lymphatics of the penile urethra course laterally around the corpora cavernosa to join the vessels proceeding from the glans penis. Bulbar urethral drainage is more variable and may occur along the bulbar artery toward the medial retrofemoral node or may course under the pubis toward the anterior bladder wall, terminating in the retrofemoral and medial external iliac nodes (Wood and Angermeier, 2010).

Inguinal Anatomy

The inguinal lymph nodes are divided into superficial and deep groups, which are anatomically separated by the fascia lata of the thigh. The superficial group is composed of 4 to 25 lymph nodes that are situated in the deep membranous layer of the superficial fascia of the thigh (Camper fascia). The superficial inguinal nodes have been divided into five anatomic groups (Daseler et al, 1948): (1) central nodes around the saphenofemoral junction, (2) superolateral nodes around the superficial circumflex vein, (3) inferolateral nodes around the lateral femoral cutaneous and superficial circumflex veins, (4) superomedial nodes around the superficial external pudendal and superficial epigastric veins, and (5) inferomedial nodes around the greater saphenous vein (Fig. 39-1). The deep inguinal nodes are fewer and lie primarily medial to the femoral vein in the femoral canal. The node of Cloquet is the most cephalad of this deep group and is situated between the femoral vein and the lacunar ligament (Fig. 39-2). The external iliac lymph nodes receive drainage from the deep inguinal, obturator, and hypogastric groups. In turn, drainage progresses to the common iliac and para-aortic nodes.

The blood supply to the skin of the inguinal region derives from branches of the common femoral artery—the superficial external pudendal, superficial circumflex iliac, and superficial epigastric arteries. Complete inguinal dissection necessitates ligation of these branches. Viability of the skin flaps raised during the dissection depends on anastomotic vessels in the superficial fatty layer of the Camper fascia that course lateral to medial along the natural skin lines. Because lymphatic drainage of the penis to the groin runs beneath the Camper fascia, this layer can be preserved and left attached to the overlying skin when the superior and inferior skin flaps are fashioned. On the basis of this anatomy, a transverse skin incision least compromises this blood supply. In this fashion, serious skin slough is prevented in the majority of patients. The femoral nerve lies deep to the iliacus fascia and supplies motor function to the pectineus, quadriceps femoris, and sartorius muscles. In addition, this nerve provides cutaneous sensation to the anterior thigh and should be preserved. Some of the sensory branches, however, are commonly sacrificed in the regional node dissection.

The femoral triangle is bounded by the inguinal ligament superiorly, the sartorius muscle laterally, and the adductor longus medially. The floor of the triangle is composed of the pectineus muscle medially and the iliopsoas laterally. The location of the saphenofemoral junction is estimated to be at a point two fingerbreadths lateral and two fingerbreadths inferior to the pubic tubercle.

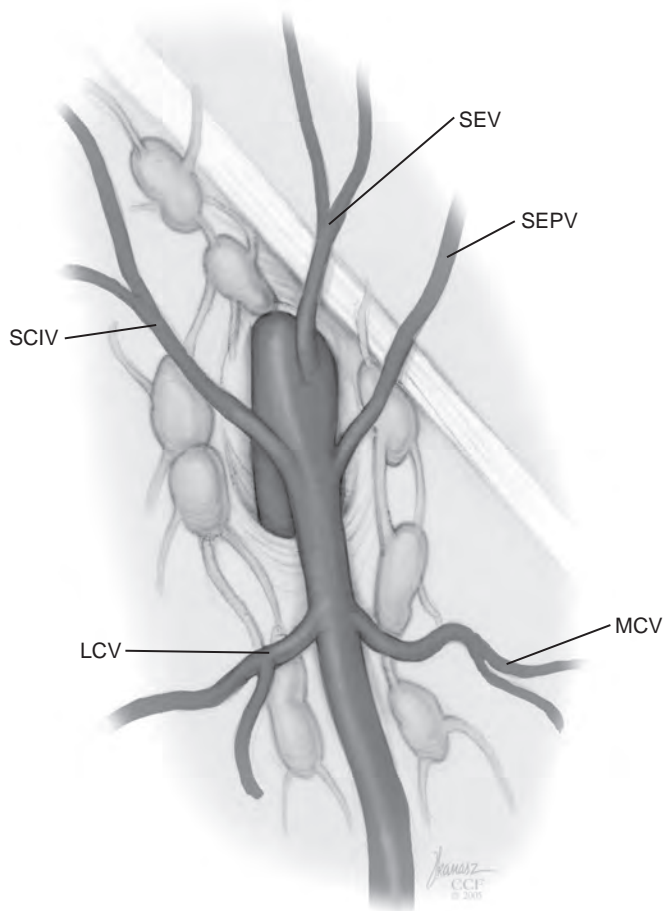


Figure 39-1. Superficial inguinal lymph nodes and the branches of the saphenous vein. LCV, lateral cutaneous; MCV, medial cutaneous; SCIV, superficial circumflex iliac; SEPV, superficial external pudendal; SEV, superficial epigastric. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All rights reserved.)

PENILE CANCER: SURGICAL MANAGEMENT OF REGIONAL LYMPH NODES

Clinically Negative Groins

Approximately 20% of patients with clinically nonpalpable inguinal nodes harbor occult metastases (Hegarty et al, 2006). Routine bilateral inguinofemoral lymph node dissection (IFLND) in these patients would overtreat 80% of them, subjecting them to potential increased morbidity. The optimal form of management would provide the ability to identify patients with metastatic penile cancer in this cohort who are potentially curable with surgical lymphadenectomy while at the same time avoiding unnecessary surgery in patients with pathologically negative inguinal nodes. Strategies to accomplish this include (1) improved prognostic algorithms and risk assessment based on the primary tumor's pathologic and clinical characteristics, (2) improved radiographic techniques, and (3) pathologic sampling of first-echelon nodes.

The indications for surgical assessment of inguinal lymph nodes when there is no palpable adenopathy are covered in Chapter 37. This section will focus on the techniques used for this purpose. The primary goal of these procedures is to accurately determine whether inguinal nodal metastases are present while minimizing patient morbidity.

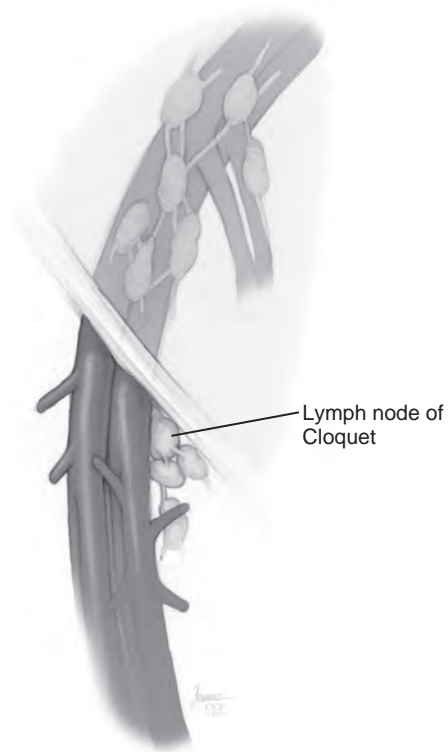


Figure 39-2. Deep inguinal lymph nodes. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All rights reserved.)

Sentinel Node Biopsy

Sentinel lymph node biopsy is the technique to remove nodes that are first affected by the spread of metastatic disease. The theory is that certain cancers typically do not spread to other lymph nodes without the necessary and stepwise involvement of the sentinel node first. Based on anatomic studies, the concept of orderly lymphatic progression of metastatic cells from the primary tumor to the sentinel node does seem to be likely with regard to squamous cell carcinoma of the penis. This approach has gained acceptance as this concept has become more widely accepted, and has also proven effective for both breast cancer and melanoma.

The technique of sentinel node biopsy in patients with invasive squamous cell carcinoma of the penis and clinically negative inguinal regions was proposed by Cabanas (1977) after extensive study of lymphangiograms and anatomic dissections. A 5-cm incision is made parallel to the inguinal crease and centered two fingerbreadths lateral and inferior to the pubic tubercle. By insertion of the finger under the upper flap toward the pubic tubercle, the sentinel lymph node is encountered and excised (Fig. 39-3). Cabanas demonstrated that the sentinel node was always positive in patients with positive metastatic inguinal nodes at time of IFLND. In the absence of tumor in the sentinel node, no metastases were found in the other inguinal lymph nodes in 31 patients. In addition, he reported that this node (subsequently termed the *Cabanas node*) was positive in 4% of patients in whom the lymph nodes were not deemed clinically suspicious. It was concluded that routine excision of this sentinel node could identify patients with micrometastatic disease earlier than waiting for clinically palpable nodes, which was standard at the time.

Although Cabanas reported 90% survival in patients with normal findings on sentinel node biopsy, subsequent authors found the results to be less satisfactory, with false-negative rates of 18% to 25% (Perinetti et al, 1980; Wespes et al, 1986;

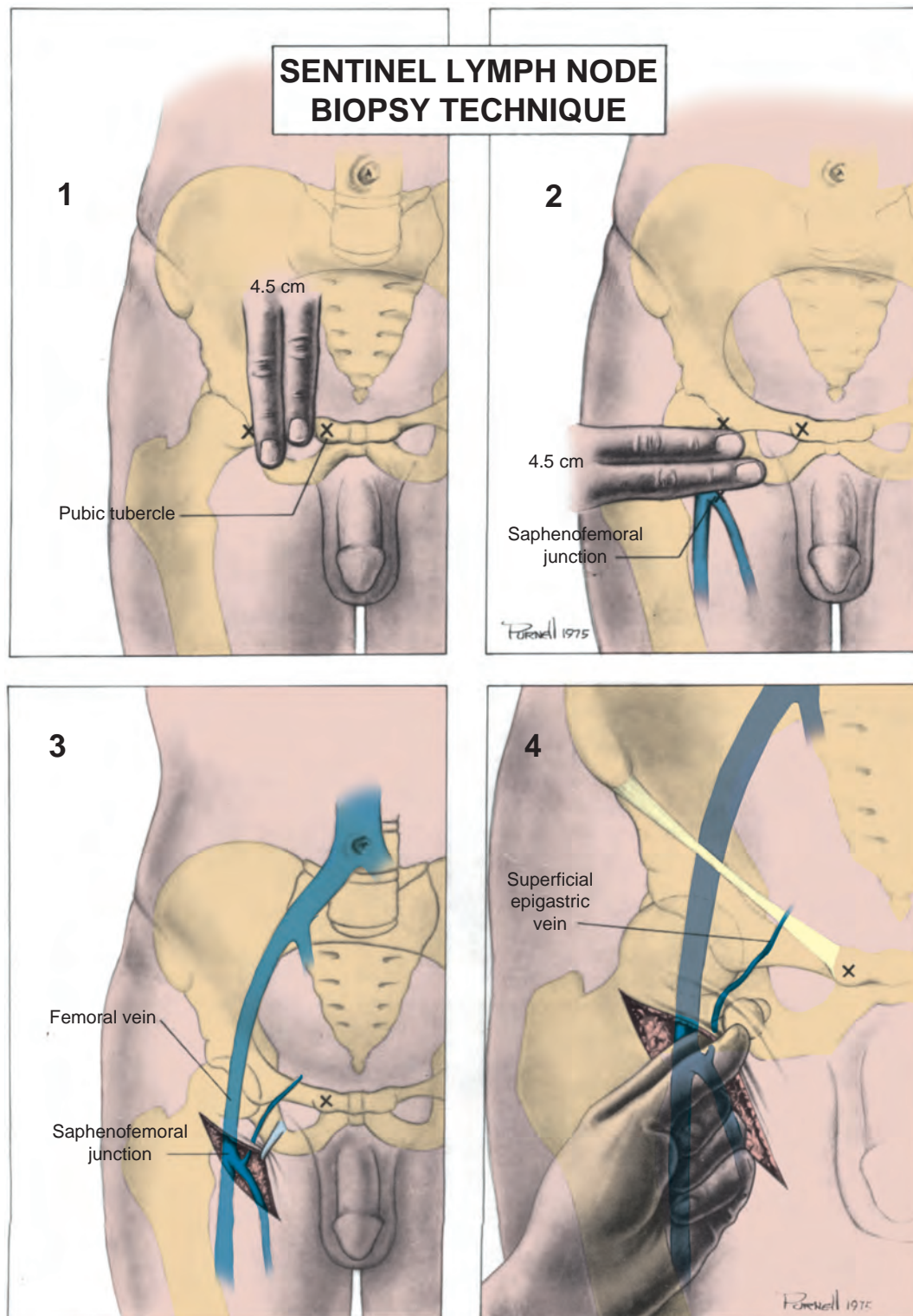


Figure 39-3. Sentinel lymph node biopsy technique as described by Cabanas in 1977. A 5-cm incision is made parallel to the inguinal crease and centered two fingerbreadths lateral and inferior to the pubic tubercle. By insertion of the finger under the upper flap toward the pubic tubercle, the sentinel lymph node is encountered and excised. (From Cabanas RM. An approach for the treatment of penile carcinoma. *Cancer* 1977;39:456–66.)

Srinivas et al, 1991). In large part, this is likely because this initial concept is based on a static location of the sentinel lymph node. As a result, this procedure is no longer recommended. In an attempt to improve sampling of the superficial nodal basin, Pettaway and colleagues (1995) evaluated extended sentinel node

biopsy, during which all of the lymph nodes between the inguinal ligament and the superficial external pudendal vein were removed. This approach has also been abandoned because it resulted in a false-negative rate of 15% to 25% (Ravi, 1993; Pettaway et al, 1995).

Dynamic Sentinel Node Biopsy

Background

Renewed interest in sentinel lymph node biopsy for penile cancer returned as breast and melanoma treatments incorporated this approach successfully. Sentinel lymph node biopsy is now the preferred method of lymph node staging in breast cancer and melanoma (Warycha et al, 2009). The group at the Netherlands Cancer Institute (NKI) pioneered dynamic sentinel lymph node biopsy (DSNB) for staging in penile cancer beginning in 1994. Since then, several groups have reported on the accuracy of DSNB in penile cancer as an alternative or adjunct to IFLND, and this procedure was included in the 2009 European Association of Urology (EAU) guidelines on penile cancer (Pizzocaro et al, 2010). This method includes preoperative lymphoscintigraphy using technetium-99m nanocolloid, preoperative patent blue dye injection, and intraoperative guidance with a gamma ray detection probe to visualize the individual drainage pattern and accurately identify the sentinel node.

DSNB has undergone modifications to reduce false-negative rates. Initial reports out of the NKI revealed a relatively high false-negative rate of 22% (Tanis et al, 2002). Leijte and colleagues reported having found that patients staged by DSNB between 1994 and 2001 had an unsatisfactory false-negative rate of 19%. Further experience and refinement in their technique resulted in a reduction to a reported 5% in patients treated between 2001 and 2004 (Leijte et al, 2007). By combining the data from the NKI in Amsterdam (297 patients) and St. George's Hospital (SGH) in London (134 patients), a false-negative rate of 7% was subsequently achieved (Leijte et al, 2009). They reported a complication rate of 4.7% (28 of 592 explored groins), primarily infection, seroma or lymphocele, or delayed bleeding. A DSNB was classified as a false-negative procedure if a regional nodal recurrence was noted on follow-up after a negative DSNB. Of 323 patients in this study with 611 clinically negative groins, six such recurrences were noted, all within 15 months. The median follow-up for the paper was 17.9 months (range, 1 to 69 months) (Leijte et al, 2009). Subsequent data out of SGH reported on 500 inguinal basins in 264 consecutive men over a 6-year period (2004 to 2010). All patients had T1G2 or higher-stage disease of the primary tumor and nonpalpable nodes in one or both inguinal basins. Minimum follow-up was 21 months (median 57 months). Seventy-three positive inguinal basins (14.6%) in 59 patients (22.3%) were identified. The authors reported a false-negative DSNB rate of 5%. Twenty patients (7.6%) were identified with postoperative complications, half of which were lymphoceles.

Further outcomes of patients treated at NKI were reported based on time period of presentation. Of 1000 patients treated since 1956, 5-year cancer-specific survival increased for each cohort subsequently treated. In patients with cN0 disease, 5-year cancer-specific survival was 91% for patients treated between 1994 and 2012 versus 82% for patients treated between 1956 and 1993. Cancer-specific survival was better in patients treated during the DSNB era than those treated during the prophylactic bilateral IFLND era (Djajadiningrat et al, 2014).

Although the goal of treatment is to find all patients with potentially curable disease, false-negative rates of 5% to 10% are believed by many to be reasonably acceptable given the substantial reduction in morbidity. The ability of other centers to obtain results seen at NKI and SGH and generalize this method has been explored. A retrospective review of DSNB in a tertiary center in Sweden between 1999 and 2011 has been reported (Kirrander et al, 2012). Of 58 patients, 115 cN0 groins were analyzed with DSNB protocol. Two patients with a negative DSNB were noted to have a clinical recurrence, consistent with a false-negative rate of 15%. This study reported an evolving procedure at this institution; for instance, ultrasound was not used preoperatively in 45% of patients in the early time period. Nonetheless, the study confirms that this methodology and technique necessitate dedicated experience to gain optimal results. The false-negative rate of 15% is comparable with

early reports from other series and is expected to fall with increased use and overall experience. In comparison, in the breast cancer literature, recommendations exist that DSNB should be performed by surgeons with at least 20 procedures per year, with the first 20 including assistance from an experienced surgeon. Before routine adoption of the procedure, a false-negative rate below 5% is suggested (Kuehn et al, 2005). The learning curve has not been well established in penile cancer, although in the study of pooled data from NKI and SGH, none of the six recurrences consistent with false negatives occurred in the initial 30 procedures (Leijte et al, 2009). Because of the rarity of penile cancer, these expectations are challenging and provide support for a referral network approach to specialized centers.

Based on the aforementioned information, DSNB should be performed with the goal of a false-negative rate at 5% or lower. Reasons postulated for the false-negative rates seen in penile cancer include (1) selection or identification of the wrong node, (2) poor pathologic sectioning or sampling such that small cancer foci are missed, and (3) tumor occupying and obstructing lymphatic channels that allows for new lymphatics or arborization to occur, leading to unorthodox drainage (Srinivas et al, 1991; Kroon et al, 2004).

Technique

Figure 39-4 outlines the technique and methodology for DSNB as espoused by groups at SGH in London and NKI in Amsterdam (Hadway et al, 2007; Leijte et al, 2007; Lam et al, 2013). Variations in the initial technique have been used to reduce false-negative rates (Kroon et al, 2004). Currently, inguinal ultrasound and fine-needle aspiration (FNA) cytology of suspect lymph nodes has been added as a preliminary step before lymphoscintigraphy. Patients with abnormal nodes on ultrasound undergo FNA, and only patients with negative FNA findings proceed to scintigraphy and DSNB. Patients with positive FNA findings undergo IFLND. The abnormal ultrasound findings used by the group at SGH to direct patients to FNA are outlined in Box 39-1. Ultrasound-guided FNA was added to the DSNB procedure in an attempt to circumvent false-negative results caused by tumor blocking and rerouting of lymphatics. Combined use of a radiotracer and blue dye is then performed to improve the identification of the sentinel node (Fig. 39-5). A meta-analysis performed by Sadeghi and colleagues revealed a pooled detection rate of 88.3%, which was improved to 90.1% if both blue dye and radiotracer were used (Sadeghi et al, 2012). Another change made to the initial DSNB protocol is that an inguinal exploration is performed after removal of the sentinel node. The groin is carefully palpated for suspicious nodes that failed to pick up any radioactive or dye tracer. Finally, a more accurate pathologic analysis of the resected node has also proven essential. A single section through a center of a node may miss micrometastatic disease. All nodes are submitted whole and embedded in paraffin. They are then serially sectioned in 2-mm increments and are evaluated with immunohistochemistry in addition to standard staining to avoid pathologic false negatives.

DSNB can be performed at the time of initial definitive primary tumor resection (after a biopsy of the penile lesion only), or after the primary tumor has been treated (with glans-preserving resection, partial or total penectomy). The group from Amsterdam has reported that postresection DSNB can be done with the technetium-99m nanocolloid injected around the resection wound or scar instead of around the tumor. They found comparable rates of sentinel node visualization (93%), sentinel node identification (100%), and detection of occult metastases (12%) when done after referral following primary tumor resection as when performed synchronously with the penile surgery (Graafland et al, 2010).

Follow-up

Strict follow-up is necessary to identify recurrences that can be managed surgically and potentially salvaged. For patients with a negative ultrasound and negative DSNB, clinical evaluation of the inguinal nodes is recommended. Examination in the office every 3

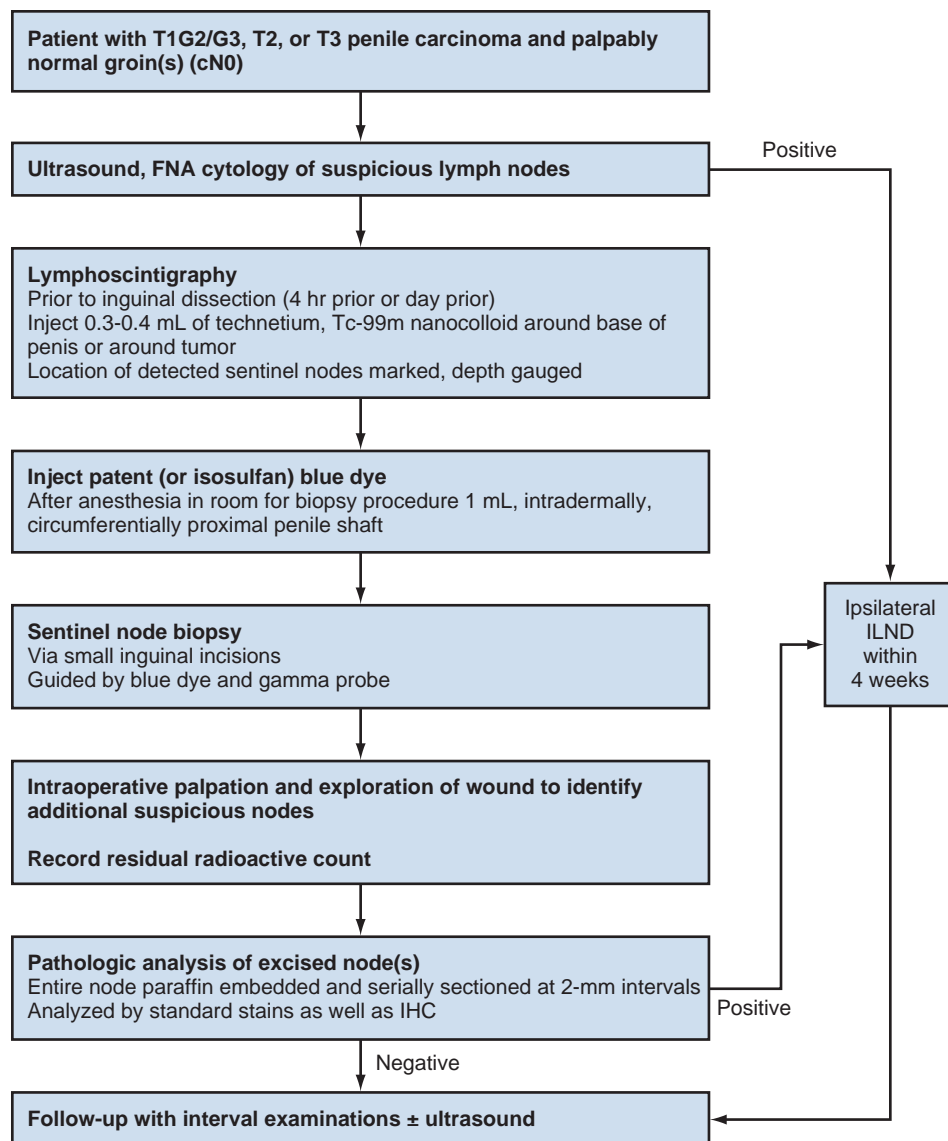


Figure 39-4. Flow diagram of technique and protocol for dynamic sentinel node biopsy. FNA, fine-needle aspiration; IHC, immunohistochemical markers; ILND, inguinal lymph node dissection. (Modified from Lam W, Alnajjar HM, La-Touche S, et al. Dynamic sentinel lymph node biopsy in patients with invasive squamous cell carcinoma of the penis: a prospective study of the long-term outcome of 500 inguinal basins assessed at a single institution. *Eur Urol* 2013; 63:657–63; and Leijte JA, Kroon BK, Olmos RA, et al. Reliability and safety of current dynamic sentinel node biopsy for penile carcinoma. *Eur Urol* 2007; 52:170–7.)

months for the first year, every 4 months for the second year, and every 6 months thereafter is recommended. Some patients may have a challenging inguinal nodal examination because of body habitus or lymphedema from prior procedures. In these patients ultrasound can be used. The role of computed tomography (CT), positron emission tomography (PET)-CT, or magnetic resonance imaging (MRI) is not well defined and sensitivity is suboptimal for low-volume metastatic disease. Finally, patients should be instructed on self-examination to be done at regular intervals (i.e., monthly) as an adjunct to their follow-up.

It is important to stress that DSNB remains a diagnostic procedure, allowing some men to avoid a therapeutic IFLND. Those with a positive DSNB should proceed to a full therapeutic lymphadenectomy. It is not appropriate for palpable lymphadenopathy and applies only to clinically negative nodes. In patients with palpable lymphadenopathy, inguinal lymphadenectomy is still recommended, as approximately one half of these patients will harbor pathologically positive lymph node metastases. Finally,

those centers employing DSNB need the experience and dedication of a multidisciplinary team of surgeons, nuclear medicine physicians, radiologists, and pathologists. The occurrence of a false negative is very serious, and salvage is usually difficult. The EAU and the International Consultation on Penile Cancer agree that DSNB is an acceptable staging procedure in the hands of experienced centers. Selection of patients is also dependent on acceptance and commitment of patients for regular follow-ups, as well as self-examination because of the possibility of false-negative findings (Hegarty et al, 2010). Whether the outcomes achieved by experienced centers can be reproduced at other small- or large-volume centers remains to be seen.

Superficial Inguinal Node Dissection

Superficial inguinal node dissection has been proposed as another method to surgically stage penile cancer patients without palpable lymphadenopathy. The procedure consists of removal of the nodal

BOX 39-1 Criteria for Identifying Suspicious Inguinal Lymph Nodes on Ultrasound

Fine-needle aspiration for cytology is performed if one or more of the following are detected:

- Increased size
- Abnormal shape
 - Rounded, with a short-long axis ratio less than 2
 - Eccentric cortical hypertrophy
- Absence of an echogenic hilum
- Hypoechogenicity of the node compared with adjacent muscle
- Lymph node necrosis
- Abnormal vascularity on power Doppler

From Lam W, Alnajjar HM, La-Touche S, et al. Dynamic sentinel lymph node biopsy in patients with invasive squamous cell carcinoma of the penis: a prospective study of the long-term outcome of 500 inguinal basins assessed at a single institution. *Eur Urol* 2013; 63:657–63.



Figure 39-5. Lymphoscintigraphy: Dynamic images are obtained in multiple projections to provide location of the nodes with radiotracer uptake and their depth. Permanent marker is used to mark the location of each “hot” node. Here, there are two identified right sentinel inguinal lymph nodes and one left sentinel inguinal lymph node.

packet superficial to the fascia lata and centered about the fossa ovalis and saphenofemoral junction. The peripheral boundaries of the dissection are similar to those described later for modified complete inguinal node dissection; however, the fascia lata is not opened. Previous studies have demonstrated no positive nodes deep to the fascia lata unless superficial nodes were also positive (Pompeo et al, 1995; Puras-Baez et al, 1995), which supports the efficacy of this procedure in surgical staging. In addition, a previous study of DSNB included a cohort of patients who underwent complete superficial node dissection. If the superficial nodes were negative, there were no recurrences with follow-up longer than 3 years (Spiess et al, 2007).

Modified Complete Inguinal Lymphadenectomy

In 1988, Catalona proposed a technique of modified inguinofemoral lymphadenectomy designed to provide staging information and therapeutic benefit similar to standard extended lymphadenectomy with less morbidity (Catalona, 1988) (Fig. 39-6). Key aspects of the procedure are (1) shorter skin incision, (2) limitation of the dissection by excluding the area lateral to the femoral artery and caudal to the fossa ovalis, (3) preservation of the saphenous vein, and (4) elimination of the need to transpose the sartorius muscle.

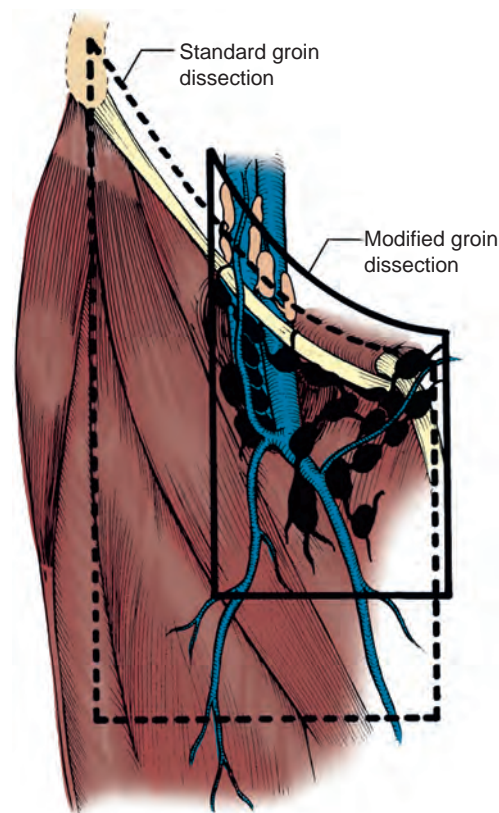


Figure 39-6. Limits of standard and modified groin dissection. (From Colberg JW, Andriole GL, Catalona WJ. Long-term follow-up of men undergoing modified inguinal lymphadenectomy for carcinoma of the penis. *Br J Urol* 1997;79:54–7.)

All of the superficial lymph nodes within the described area are removed, as are the deep inguinal nodes that are located primarily medial to the femoral vein to the level of the inguinal ligament.

The procedure begins by placing the patient into a frog-leg position. A 10-cm skin incision is made approximately 1.5 to 2 cm below the inguinal crease. Skin flaps are developed in the plane just beneath the Scarpa fascia for a distance of 8 cm superiorly and 6 cm inferiorly. The superior dissection is carried to the level of the external oblique fascia with exposure of the spermatic cord. A funiculus of lymphofatty tissue, extending from the base of the penis to the superomedial portion of the lymph node packet, is ligated and divided. Dissection commences in a caudad direction with removal of the superficial and deep inguinal nodes, with the boundaries consisting of the adductor longus muscle medially and the femoral artery laterally. The saphenous vein is identified and preserved, although a number of branches draining into it will need to be sacrificed. The nodal packet is dissected caudad to the level of the skin flap dissection (Fig. 39-7), at which point the lymphatics are carefully ligated and the specimen is delivered from the operative field (Fig. 39-8). A closed-suction drain is placed, and the incision is closed in standard fashion.

The false-negative rate for this procedure, in terms of detecting inguinal metastatic disease, ranges from 0% to 5.5% in the majority of published reports (Parra, 1996; Colberg et al, 1997; Coblenz and Theodoreescu, 2002; Bouchot et al, 2004; d’Ancona et al, 2004).

Morbidity after modified complete inguinal lymphadenectomy consists primarily of minor complications including seroma or lymphocele (0% to 26%), lymphorrhea (9% to 10%), and wound infection or skin necrosis (0% to 15%). These have been self-limited in the majority of patients (Parra, 1996; Coblenz and Theodoreescu, 2002; Jacobellis, 2003; Bouchot et al, 2004; d’Ancona et al, 2004; Spiess et al, 2009). Lower extremity edema has been reported in 0%

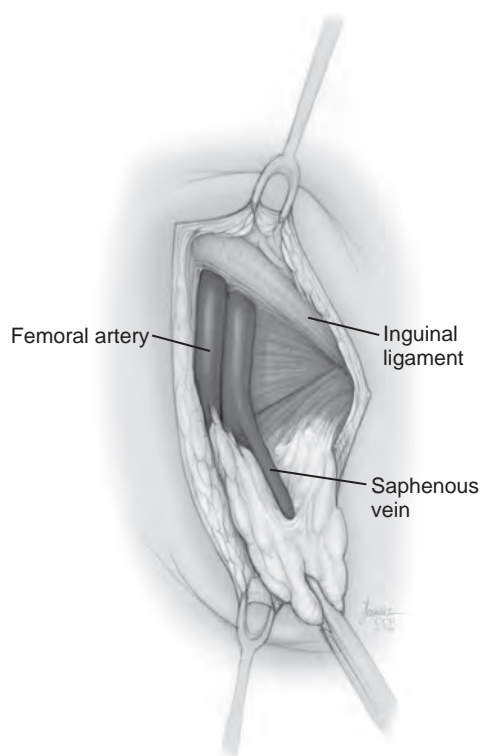


Figure 39-7. Modified inguinal lymphadenectomy. Lymph node packet is medial to the femoral artery and includes superficial and deep inguinal nodes. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All rights reserved.)

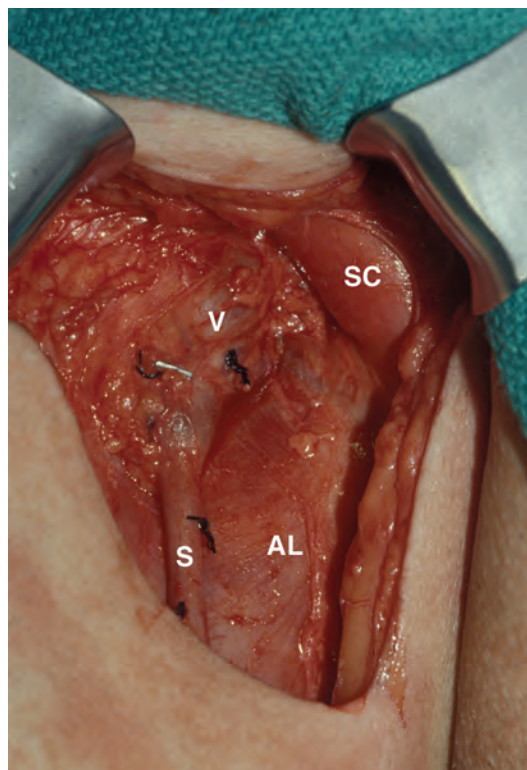


Figure 39-8. Intraoperative photograph of right inguinal region after modified lymphadenectomy. AL, adductor longus; S, saphenous vein; SC, spermatic cord; V, femoral vein.

to 36% of patients, and persistent clinically significant edema is uncommon.

The primary use of both superficial and modified complete inguinal lymphadenectomy currently is in patients with a primary tumor that places them at increased risk for inguinal metastasis and clinically negative groins on examination (stage T2 or greater, presence of vascular or lymphatic invasion, or high grade). These procedures allow for a more thorough assessment of the superficial inguinal nodal basin, do not require specialized equipment, and are associated with less morbidity than standard inguinal lymphadenectomy. If nodal metastasis is detected on frozen-section examination of the specimen, the procedure is converted to a standard radical IFLND.

Endoscopic and Robotic Inguinal Lymphadenectomy

Background

Endoscopic inguinal lymphadenectomy is a more recent technique with the potential for thorough excision of inguinal nodes with decreased morbidity. Bishoff and colleagues were first to report the use of endoscopic inguinal node dissection, in two cadavers and one patient with penile cancer (Bishoff et al, 2003). The patient required conversion to an open procedure because of inability to adequately mobilize the nodal mass superiorly. In 2006 Tobias-Machado and coworkers reported 10 patients who underwent bilateral lymphadenectomy for nonpalpable inguinal nodes. Standard open lymphadenectomy was performed on one side, and endoscopic on the other. Nodal counts were similar, with 20% complications on the endoscopic side, compared with 70% with open surgery (Tobias-Machado et al, 2006). Sotelo and colleagues reported the outcomes after 14 inguinal endoscopic lymphadenectomies in eight patients with clinical stage T2 squamous cell carcinoma of the penis, with a median operative time of 91 minutes and an average node yield of nine. No wound-related complications occurred (Sotelo et al, 2007). A detailed analysis of immediate and long-term complications using the Clavien classification system in 29 patients undergoing 41 endoscopic inguinal lymphadenectomy procedures revealed minor complications in 27%, and major complications in 14.6% (Master et al, 2012). There were no perioperative deaths. Similar experience has been reported in two recent smaller studies, demonstrating a yield of approximately 7 to 15 lymph nodes per groin and a 20% rate of seroma or lymphocele managed conservatively (Pahwa et al, 2013; Zhou et al, 2013).

In 2009, the first staged bilateral endoscopic operation performed robotically was reported (Josephson et al, 2009). Pathologic examination revealed no metastatic involvement in six superficial and four deep lymph nodes. The contralateral dissection occurred weeks later, and pathologic examination revealed five superficial and four deep negative nodes. There were no wound problems or lower extremity edema. Sotelo and colleagues reported performance of a bilateral procedure without repositioning the robot. Metastatic nodes were present bilaterally, with a yield of 19 lymph nodes on the right and 14 on the left (Sotelo et al, 2013). Matin and colleagues performed a thorough evaluation of the adequacy of a robotic inguinal lymph node dissection by subsequently opening the incision and having a second surgical oncologist look for unretrieved residual nodal tissue in 10 patients. The verifying surgeon's role was to inspect the surgical field to ensure that no additional superficial inguinal lymph nodes (e.g., above the fascia lata of the thigh) remained within the operative field. If additional tissue was removed at that time, it was sent for pathologic analysis to define whether it was nodal in origin and whether it contained metastasis. In one of these groins, two residual lymph nodes were recovered from below the Scarpa fascia along the superficial aspect of the inguinal field near the spermatic cord. No metastases were detected in these additional nodes. Among all patients undergoing robotic dissection, 18 of 19 fields (94.7%) were adequately dissected (Matin et al, 2013).

In summary, there is evidence to suggest that the morbidity of an endoscopic inguinal lymph node dissection is lower than

previously reported for open contemporary series with a similar number of nodes being harvested. The applicability of the robot is a more recent development and will need continued prospective evaluation in comparison with standard laparoscopic endoscopic procedures.

Surgical Technique

The patient is positioned on a split-leg table or in low lithotomy position to allow bilateral groin dissection without repositioning the robot. The assistant stands lateral to the right leg for a right-sided dissection and between the legs for the left side (Figs. 39-9 and 39-10). A Foley catheter is inserted in sterile fashion, after the inguinal and groin areas have been prepared and draped. Bony and soft tissue landmarks are marked on the skin surface, creating an inverted triangle in which the base is a line connecting the anterior superior iliac spine to the pubic tubercle, along the course of the inguinal ligament. The lateral boundary is the sartorius muscle angling toward the apex. The medial boundary is the adductor longus muscle, again extending toward the apex. These marks aid in correct trocar placement as well as in delineating the extent of dissection (Figs. 39-11 and 39-12).

A 2-cm incision is made 3 cm below the inferior aspect of the femoral triangle, approximately 25 cm below the inguinal ligament. A white subcutaneous layer is identified, which corresponds to the Scarpa fascia. Sweeping finger dissection is used to dissect the potential space beneath the Scarpa fascia to develop the skin flaps at the apex of the triangle out in both directions to two additional 8-mm ports (Fig. 39-13). These two primary robotic 8-mm ports are placed with finger-guided techniques laterally and medially. A

subcutaneous workspace is extended with the endoscope by sweeping with the lens itself (Fig. 39-14). The aim of this step is to create a superficial subcutaneous flap under the Scarpa fascia (Fig. 39-15). Alternatively, after the initial finger dissection, a 12-mm Origin balloon port trocar may be used (Origin Medsystems, Menlo Park, CA), set at 25 mm Hg for 10 minutes to create the space (Master et al, 2009). The workspace is then expanded with CO₂ insufflation at a pressure of 15 mm Hg. A 0-degree 10-mm lens is inserted, and one additional intervening 10-mm assistant port is placed between the camera and primary 8-mm working port on the assistant side. The robotic docking is performed as shown in Figures 39-9 and 39-10. The robot is located at 45 degrees contralateral to the first procedure (right side) and lateral to the patient in the second procedure (left side).

Our instrument preference is bipolar Maryland, or PK forceps in the left robotic arm, and monopolar scissors in the right arm to dissect the membranous and lymphatic tissue just deep to the Camper fascia. Every effort is made to completely develop the anterior working space to the inguinal ligament. The inguinal ligament is usually identified at the end of this dissection as being a transverse structure with white fibers, marking the superior limit of the dissection (Fig. 39-16). The boundaries of the dissection extend from the inguinal ligament superiorly, the sartorius muscle laterally, and the adductor longus muscle medially. One will be able to spare the saphenous vein in most patients, and the small branches of the femoral artery and vein may be clipped and divided (see Fig. 39-16). Identification of the adductor longus and sartorius muscles is facilitated by identifying the fascia of the respective muscles and correlating this to the previously made skin markings. The medial spermatic cord is seen medially. Inadvertent dissection

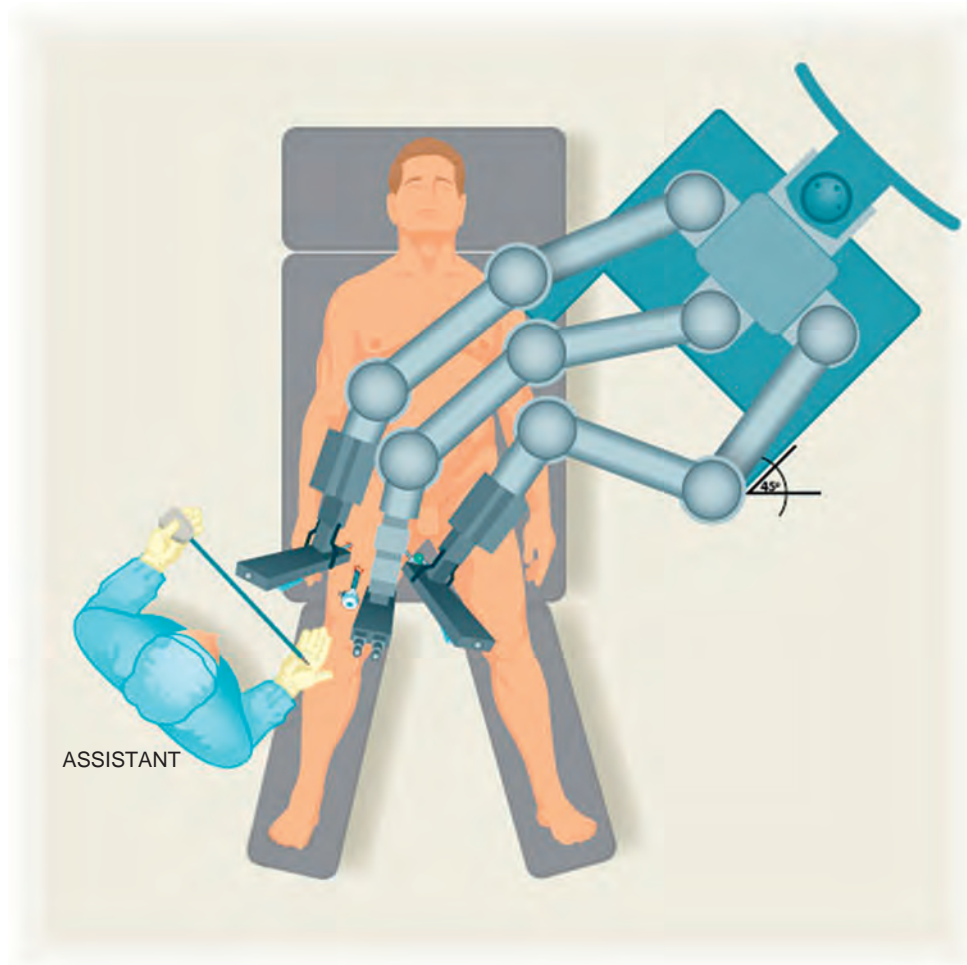


Figure 39-9. Assistant position and robotic docking for right inguinal node dissection.

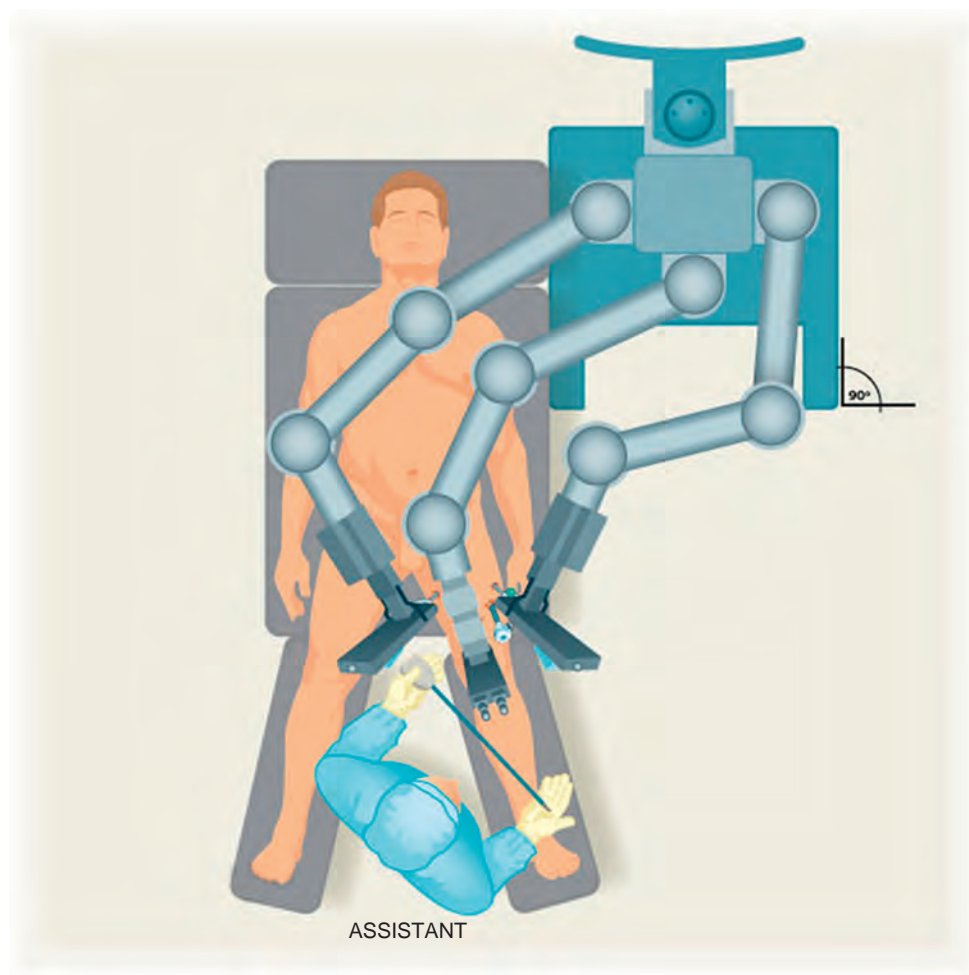


Figure 39-10. Left inguinal node dissection.

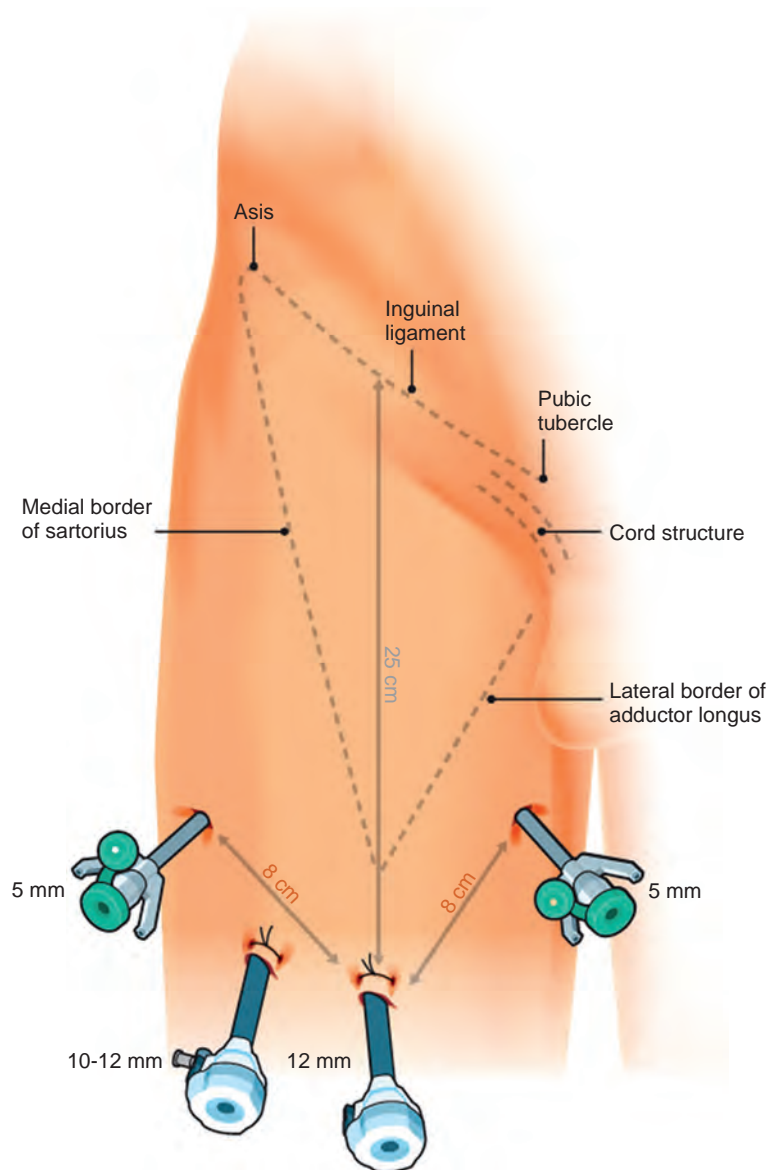


Figure 39-11. Landmarks and trocar placement for right inguinal node dissection.

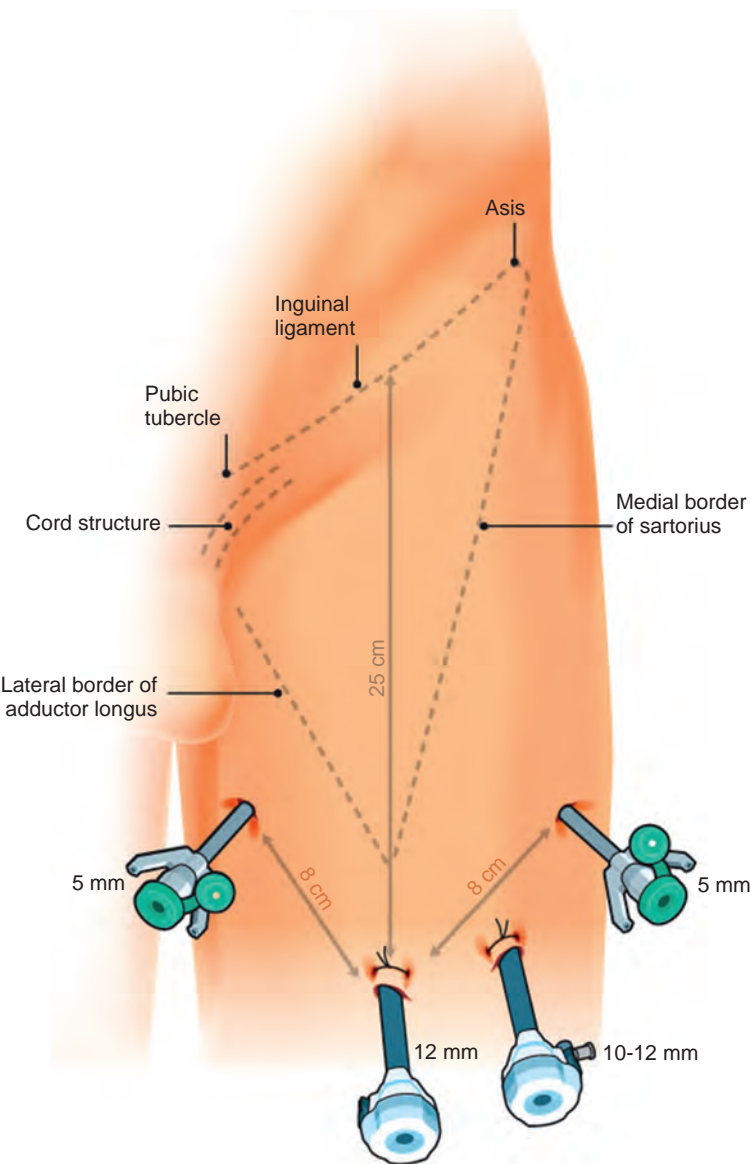


Figure 39-12. Left inguinal node dissection.

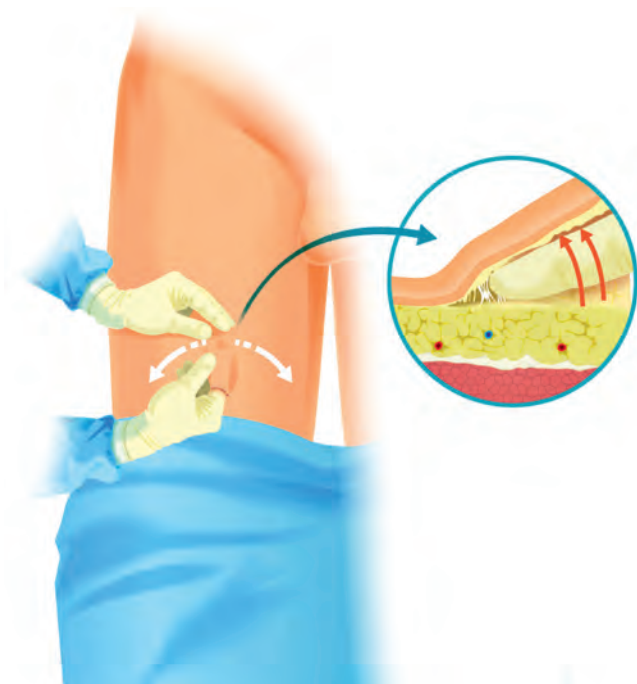


Figure 39-13. Sweeping finger dissection dissects the potential space beneath Scarpa fascia to develop the skin flaps at the apex of the triangle.

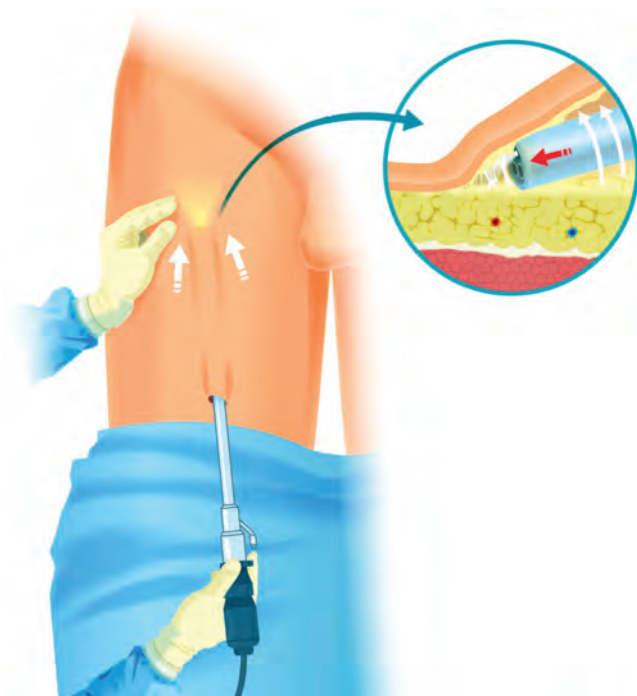


Figure 39-14. The subcutaneous workspace is extended with the endoscope by sweeping with the lens.

deep to the fascia lata is apparent when reddish muscular fibers are seen.

With blunt dissection, the nodal tissue can be rolled inward on both sides. This maneuver is continued inferiorly as much as possible from both sides to define the inferior apex of the nodal packet. The saphenous vein will be identified as it crosses the internal border of the dissection near the apex of the femoral triangle, and

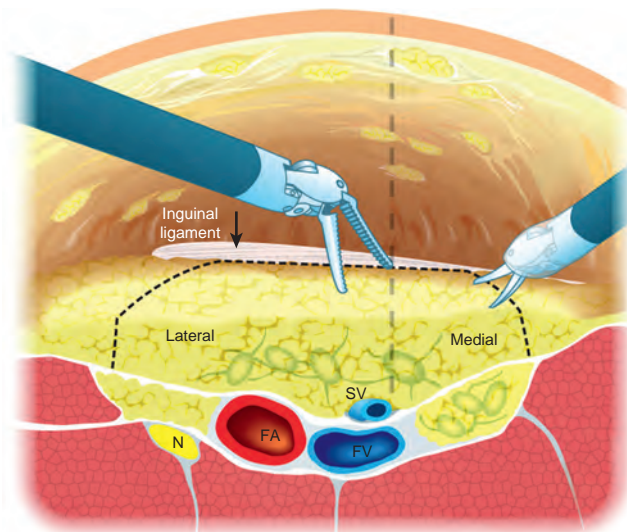


Figure 39-15. A superficial subcutaneous space is created under Scarpa fascia. FA, femoral artery; FV, femoral vein; N, femoral nerve; SV, saphenous vein.

following the vein leads the surgeon to the saphenous arch until its junction with the superficial femoral vein at the fossa ovalis. The dissection continues superiorly, where the packet is dissected off the fascia lata with a combination of sharp and blunt dissection. Typically the nondominant hand lifts the packet, and the monopolar scissors in the dominant hand advance the dissection. After the fossa ovalis is encountered, the packet is dissected away at its superolateral and superomedial limits, thereby narrowing the packet and pulling it away from the inguinal ligament. At this point the superficial and deep plane of dissection join and separate the package from the inguinal ligament (Fig. 39-17).

With the nodal packet circumferentially dissected except for its attachments to the saphenous arch, venous tributaries are clipped. Characteristic pulsations of the femoral artery serve as a nearby landmark. If possible, the packet will be released from the saphenous vein. If not, the vein can be ligated in the saphenous arch with Weck clips or an endovascular stapler. One must always attempt to preserve the saphenous vein whenever possible, however, to reduce the risk of postoperative lymphedema (Zhang et al, 2007).

The specimen is removed in an Endo Catch bag after extension of the camera trocar incision. Frozen section results determine whether a deep ipsilateral dissection will be required. We typically begin to create the working space in the other leg while waiting for results.

For the deep inguinal node dissection, the pneumoperitoneum is reestablished. The fascia lata medial to the saphenous arch is opened to expose the saphenofemoral junction. Inferomedial dissection around the femoral vein enables resection of the deep inguinal nodes (Master et al, 2009). This should be continued to the level of the femoral canal until the pectineus muscle is seen to ensure complete nodal retrieval (Fig. 39-18).

Insufflation pressure is then decreased to 5 mm Hg to confirm hemostasis. It is of great importance that meticulous control of lymphatics and excellent hemostasis be established to further reduce the risk of formation of lymphocele and/or hematoma, which could potentially become infected. A closed suction drain is positioned in the most dependent (caudal) portion of the lymphadenectomy field such that fluid tends to find the drain when the patient is upright. Trocar incisions are closed in standard fashion. The patient is allowed to ambulate the day of surgery and given a regular diet. Discharge is planned for the first postoperative day. A compressive elastic girdle, used for liposuction patients, is used to provide bilateral compression of the groins. In addition, elastic compression stockings are worn simultaneously and are used for 3

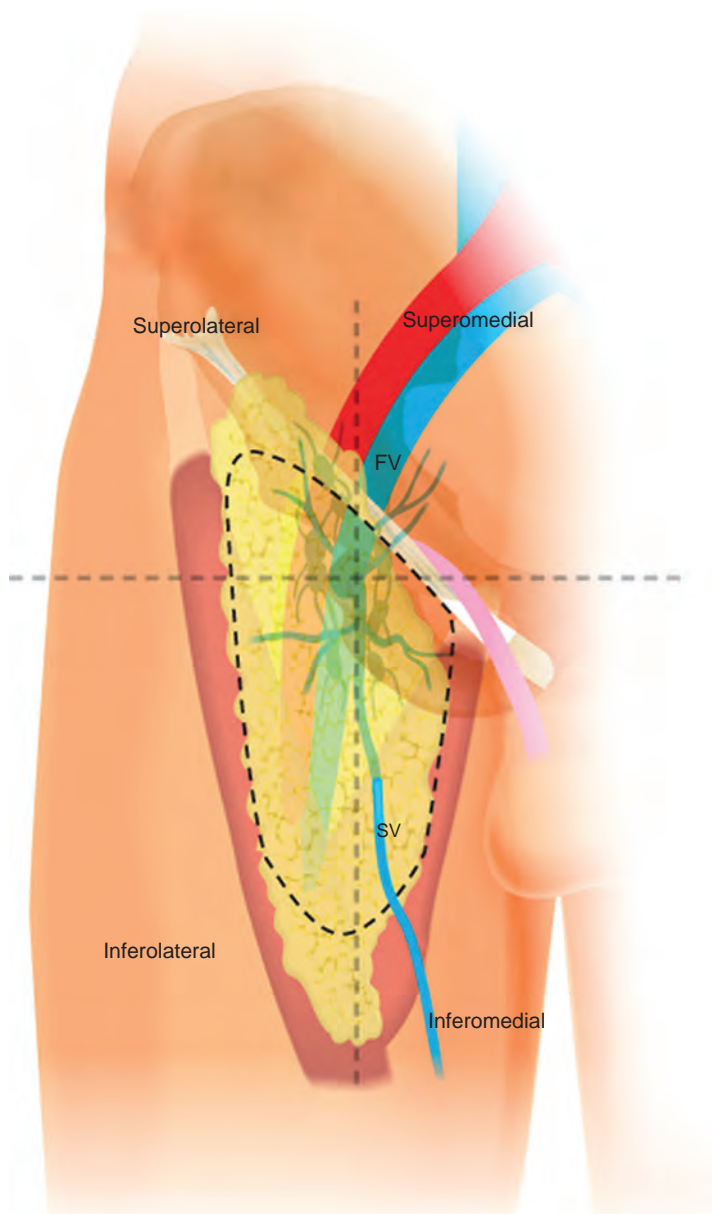


Figure 39-16. Boundaries of the inguinal node dissection. FV, femoral vein; SV, saphenous vein.

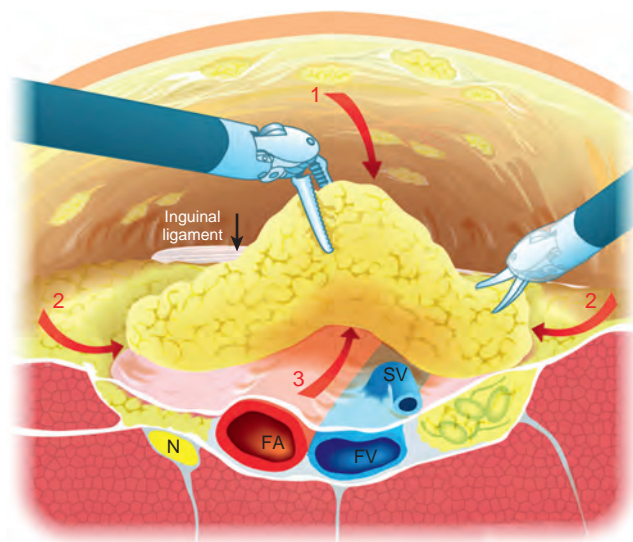


Figure 39-17. Steps in dissection of the nodal tissue; see corresponding text. FA, femoral artery; FV, femoral vein; N, femoral nerve; SV, saphenous vein.

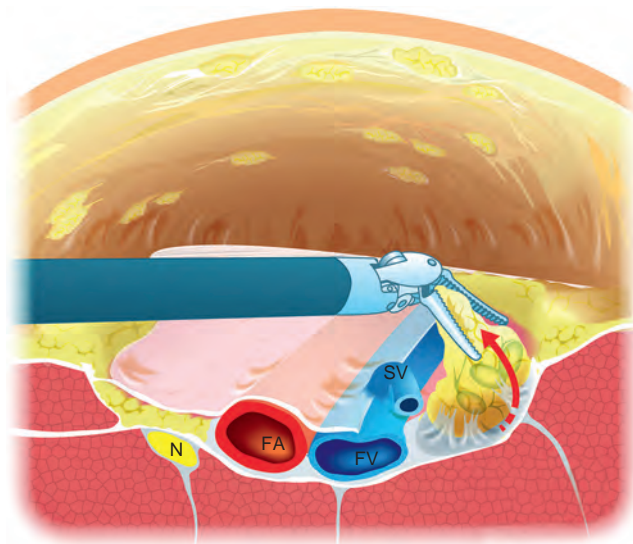


Figure 39-18. Resection of the deep inguinal nodes. FA, femoral artery; FV, femoral vein; N, femoral nerve; SV, saphenous vein.

months after surgery (Fig. 39-19). Broad-spectrum antibiotics are continued until after drains have been removed. Drains typically stay in place until the output is less than 50 mL per 24-hour period. All patients receive venous thromboembolism prophylaxis using fractionated or low-molecular-weight heparin.

Palpable Inguinal Adenopathy or Positive Inguinal Nodes

Radical Inguinofemoral Lymph Node Dissection

Radical IFLND is indicated in patients with resectable metastatic adenopathy and may be curative when the disease is limited to the inguinal nodes. We have also favored its use as a palliative procedure in patients with documented inguinal metastasis who are fit for surgery. If left unchecked, cancer-bearing inguinal nodes may lead to significant complications, such as infection or abscess with chronic foul-smelling drainage or life-threatening femoral hemor-

rhage (Fig. 39-20). Antibiotics are often administered preoperatively to reduce the inflammatory component of the regional adenopathy. The patient is positioned with the involved thigh slightly abducted and externally rotated with cushioned support under the flexed knee.

The inguinofemoral dissection is designed to cover an area outlined superiorly by a line drawn from the superior margin of the external ring to the anterior superior iliac spine, laterally by a line drawn from the anterior superior iliac spine extending 20 cm inferiorly, and medially by a line drawn from the pubic tubercle 15 cm down the medial thigh. In most situations the procedure is carried out through an oblique incision approximately 3 cm below and parallel to the inguinal ligament and extending from the lateral to the medial limit of the dissection (Fig. 39-21). If an area of the skin overlying the cancer-bearing nodes is invaded or adherent and requires excision, an elliptical incision is made around the involved skin and then extended medially and laterally. In this setting, the

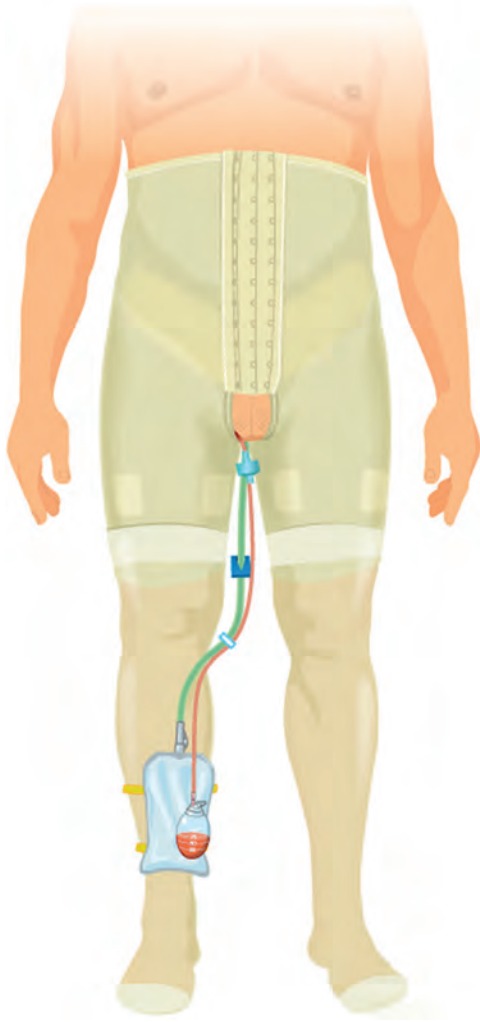


Figure 39-19. A compressive elastic girdle and elastic compression stockings are placed postoperatively.



Figure 39-20. Pelvic computed tomographic scan of patient with penile carcinoma demonstrating large left inguinal metastasis overlying the femoral vessels.

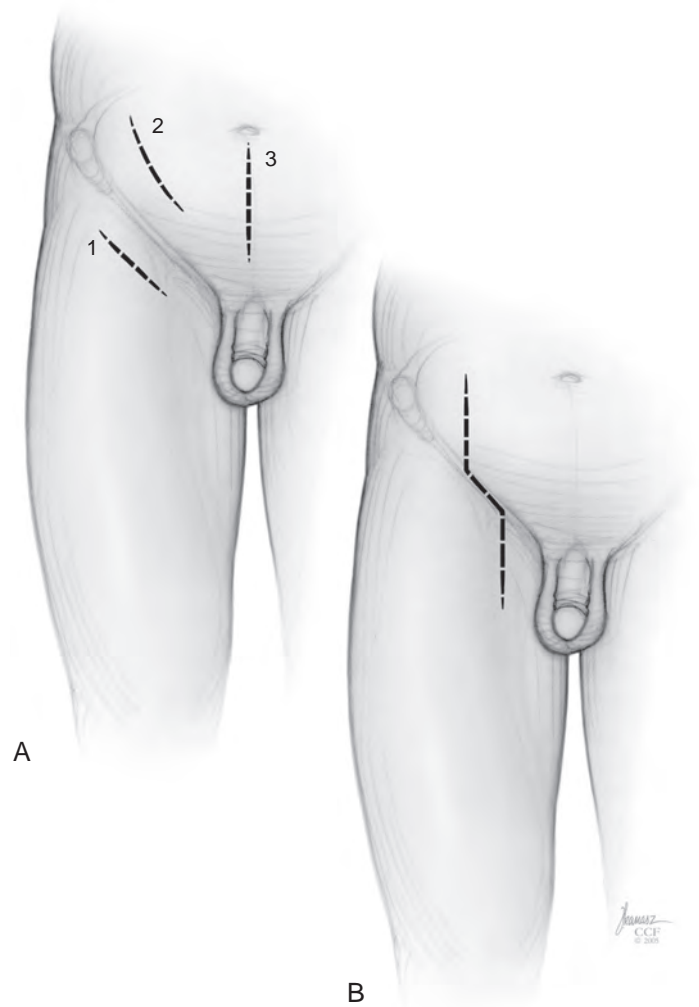


Figure 39-21. Ilioinguinal lymph node dissection. **A**, Incisions for inguofemoral lymph node dissection (1), unilateral pelvic lymph node dissection (2), and bilateral pelvic lymph node dissection (3). **B**, Single-incision approach for ilioinguinal lymph node dissection. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All rights reserved.)

incision may alternatively be extended superiorly from the lateral border of the ellipse and inferiorly from the medial border to make a single S-shaped incision for the iliac and inguofemoral dissections (Fig. 39-22).

Superior and inferior skin flaps are developed in the plane just below the Scarpa fascia. The superior flap is elevated cephalad to a point 4 cm above the inguinal ligament, and the inferior flap to the limit of the dissection. The fat and areolar tissues are dissected from the external oblique aponeurosis and the spermatic cord to the inferior border of the inguinal ligament, forming the superior boundary of the lymph node packet (Fig. 39-23). The inferior angle of the inguofemoral exposure is at the apex of the femoral triangle, where the long saphenous vein is identified and divided. In patients with minimal metastatic disease, it may be feasible and beneficial to spare the saphenous vein, and this should be considered (Fig. 39-24). Dissection is deepened through the fascia lata overlying the sartorius muscle laterally and the thinner fascia covering the adductor longus muscle medially. At the apex of the femoral triangle, the femoral artery and vein are identified, and dissection is continued superiorly along the femoral vessels. Superficial cutaneous perforating arteries are ligated as they are encountered on the

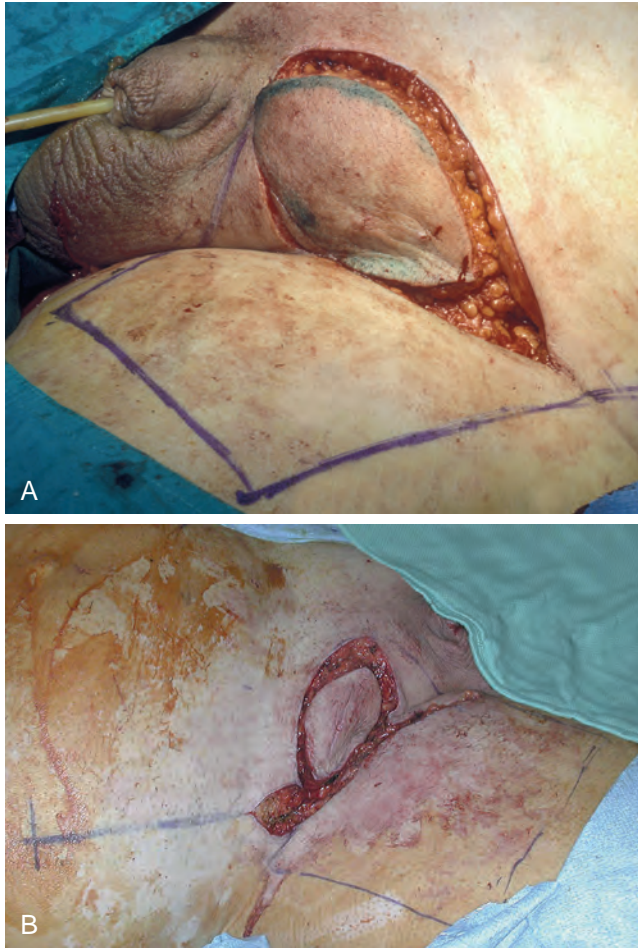


Figure 39-22. A, Incision and area of dissection for left inguinofemoral lymph node dissection with excision of adherent skin overlying nodal mass. B, Single-incision approach and area of dissection for right ilioinguinal lymph node dissection with excision of overlying skin.

surface of the femoral artery. The saphenous vein is divided at the saphenofemoral junction, and the dissection is continued superiorly to include the deep inguinal nodes medial and lateral to the femoral vein until continuity with the pelvic dissection is attained at the femoral canal (Fig. 39-25). The anterior aspects of the femoral vessels are dissected, but the femoral vessels are not skeletonized, and the lateral surface of the femoral artery is not exposed. This avoids injury to the femoral nerve and the profunda femoris artery, and the femoral nerve is usually not visible as it runs beneath the iliacus fascia.

After the femoral triangle is dissected (Fig. 39-26), the sartorius muscle is mobilized from its origin at the anterior superior iliac spine and either transposed or rolled 180 degrees medially to cover the femoral vessels. The muscle is sutured to the inguinal ligament superiorly, and its margins are sutured to the muscles of the thigh immediately adjacent to the femoral vessels (Fig. 39-27). The femoral canal is closed, if necessary, by suturing the shelving edge of the Poupart ligament to the Cooper ligament, being careful not to compromise the lumen of the external iliac vein or to injure the inferior epigastric vessels in the process. Primary closure of the inguinofemoral dissection is usually possible with minimal or no further mobilization of the excision margins. When circumstances demand a large area of inguinal soft tissue sacrifice, primary closure may be obtained by scrotal skin rotation flaps (Skinner, 1974), an abdominal wall advancement flap (Tabatabaei and McDougal,

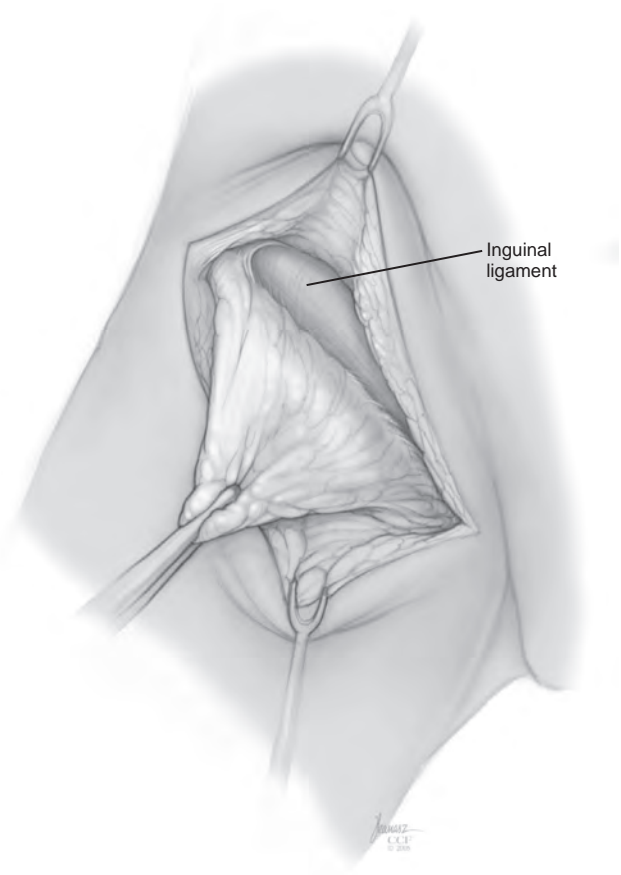


Figure 39-23. Initial dissection for radical inguinofemoral lymph node dissection with exposure of superior border defined by the external oblique fascia. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All rights reserved.)

2003), or a myocutaneous flap based on the rectus abdominis or tensor fasciae latae (Airhart et al, 1982) for more extensive defects.

Closed-suction drains are placed under the subcutaneous tissue and brought out inferiorly. During closure, the skin flaps are sutured to the surface of the exposed musculature to decrease dead space. The skin is closed with absorbable subcutaneous sutures and staples. The patient is maintained on bed rest for 2 or 3 days, and pneumatic compression stockings are used. The drains are removed after 5 to 7 days, when drainage is less than 30 to 40 mL/day. Compression stockings are recommended postoperatively. We maintain the patient on a suppressive dose of a cephalosporin for 1 to 2 months until healed to decrease the incidence of erythema and cellulitis, and this seems to improve overall wound healing.

In the past, complications related to radical ilioinguinal lymphadenectomy have been significant. In contemporary series, early minor complications have been reported in 40% to 56% of dissections (Bevan-Thomas et al, 2002; Bouchot et al, 2004; Nelson et al, 2004; Spiess et al, 2009). These consist primarily of lymphocele, wound infection or necrosis, and lymphedema. Major complications, such as debilitating lymphedema, flap necrosis, and lymphocele requiring intervention, occur in 5% to 21% of patients (Bevan-Thomas et al, 2002; Nelson et al, 2004). Deep venous thrombosis (DVT) or pulmonary embolism (PE) has been reported in 4% to 7% of patients (Johnson and Lo, 1984; Ravi, 1993; Spiess et al, 2009). Efforts to minimize lower extremity lymphedema include early use of compression stockings and saphenous vein preservation when feasible. With regard to DVT and PE, sequential

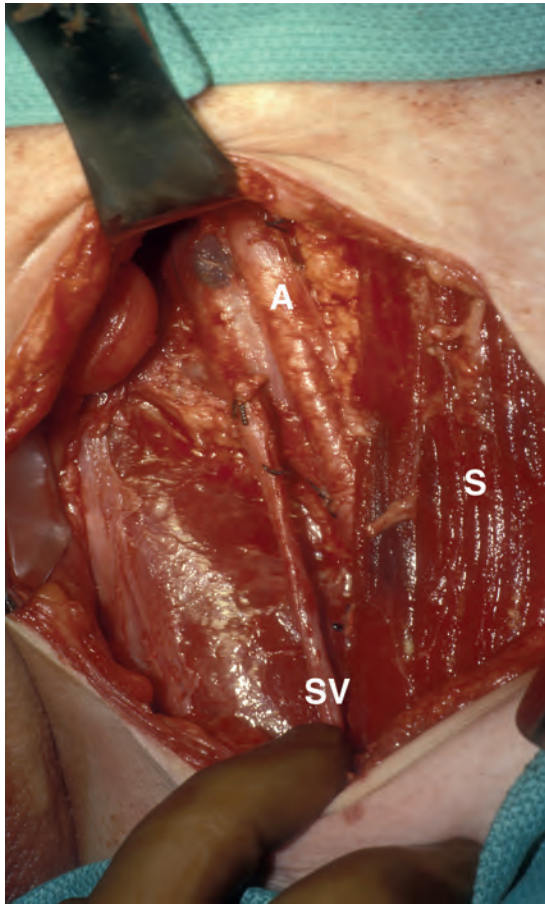


Figure 39-24. Intraoperative photograph after saphenous-sparing, radical, left inguofemoral lymph node dissection. A, femoral artery; S, sartorius muscle; SV, saphenous vein.

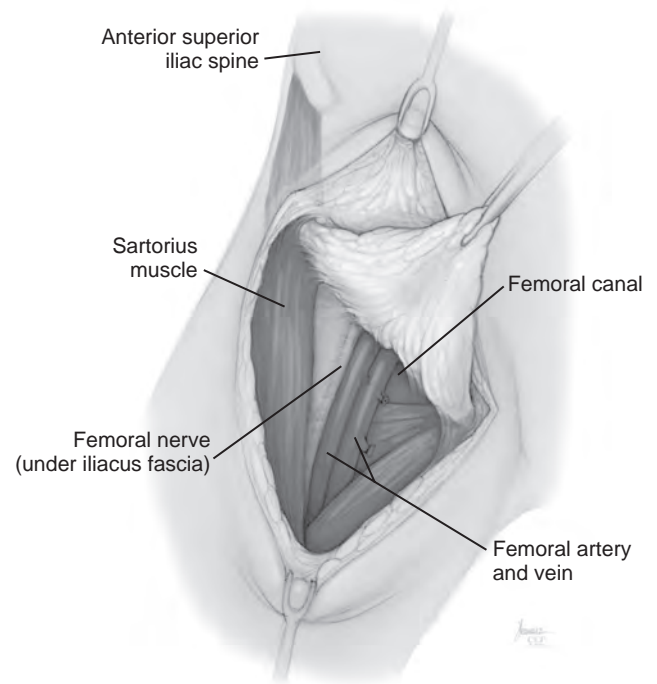


Figure 39-25. Inferior dissection during radical inguofemoral lymph node dissection with removal of lymph node packet from the inferior border of the femoral triangle. After further lateral and medial dissection, the packet will remain in continuity with the pelvic dissection in the area of the femoral canal. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All rights reserved.)

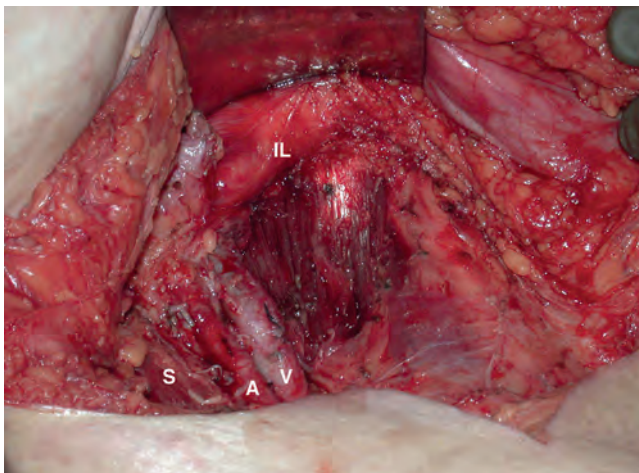


Figure 39-26. Intraoperative photograph after right radical inguofemoral lymph node dissection in an obese patient. A, femoral artery; IL, inguinal ligament; S, sartorius muscle; V, femoral vein.

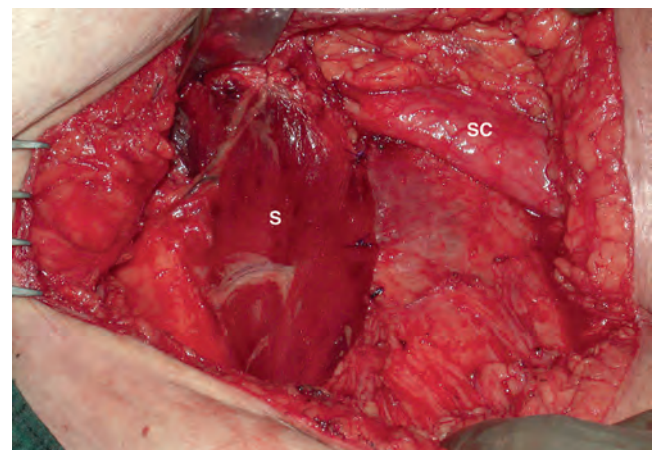


Figure 39-27. Sartorius muscle after detachment from the anterior superior iliac spine and 180-degree rotation medially, with suture fixation to the fascia of the inguinal ligament and the adductor longus. S, sartorius muscle; SC, spermatic cord.

lower extremity compression devices are placed before surgery. Use of prophylactic fractionated subcutaneous heparin or low-molecular-weight heparin is recommended while the patient is on bed rest, and the current trend is toward earlier ambulation when appropriate (Spiess et al, 2009).

KEY POINTS

- The most important factor determining survival in patients with penile cancer is the extent of lymph node metastases.
- Approximately 20% of patients with clinically nonpalpable inguinal nodes harbor occult metastases.
- Immediate resection of clinically occult lymph node metastases is associated with improved survival when compared with delayed resection of involved nodes at the time of clinical detection.
- In experienced hands, DSNB is an effective minimally invasive technique for assessment of clinically negative groins and should be performed with the goal of a false-negative rate of 5% or less.
- Superficial and modified complete inguinal lymph node dissections allow for a thorough assessment of the superficial inguinal nodal basin, do not require specialized equipment, and are associated with less morbidity than radical inguinal lymphadenectomy.
- There is early evidence to suggest that the morbidity of an endoscopic inguinal lymph node dissection may be lower than previously reported for open contemporary series with a similar number of nodes being harvested.
- Radical IFLND is indicated in patients with resectable metastatic adenopathy and may be curative when the disease is limited to the inguinal nodes.
- Penile cancer metastases to the pelvic lymph nodes do not occur in the setting of negative ipsilateral inguinal nodes.

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The complete reference list is available online at www.expertconsult.com.



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Principles of Reconstructive Surgery

Selected Processes

Trauma to the Genitalia

Urethral Stricture Disease

Pelvic Fracture Urethral Injuries

Vesicourethral Distraction Defects

Complex Fistulae of the Posterior Urethra

Curvatures of the Penis

Total Penile Reconstruction

Female-to-Male Transsexualism

Improvements in microsurgery, tissue transfer techniques, and tissue handling have expanded the repertoire of the urologic surgeon and the genitourinary reconstructive surgeon in particular. Urologists are now able to reconstruct congenital and acquired genitourinary abnormalities with greater facility. Microvascular and microneurosurgical techniques have made it possible to construct a phallus that allows a patient to void while standing and to enjoy erotic sensibility. Because the phallus has erotic sensibility and protective sensation, the patient can eventually have a prosthetic implantation that allows an acceptable sexual life. This chapter discusses the general principles of male genital reconstructive surgery; specifics include male urethral surgery, surgery for congenital and traumatic penile lesions, and complex fistula and obliterative issues associated with the posterior urethra.

PRINCIPLES OF RECONSTRUCTIVE SURGERY

Many techniques in reconstructive surgery require the transfer of tissue. Skin is one of those tissues, and its properties vary from individual to individual and from place to place on the same individual. Variable characteristics such as color, texture, thickness, extensibility, innate skin tension, and blood supply can be useful in various situations.

The term *tissue transfer* implies the movement of tissue for purposes of reconstruction. In contrast to extirpative surgery, the transfer of tissue for reconstruction requires an intimate knowledge of the anatomy of the donor and the recipient sites as well as of the principles that allow the tissue to survive after it is transferred.

The skin can be used as a model. The superficial layer of the skin is termed the *epidermis* (thickness, 0.8 to 1 mm). The deep layer of the skin is termed the *dermis*. The dermis has two layers: a superficial layer, the *adventitial dermis* (also called the *papillary* or *periadnexal dermis*, depending on the anatomy), and a deep layer, the *reticular dermis*. For genitourinary reconstruction, skin without adnexal structures is often used; the *papillary dermis* is synonymous with the *adventitial dermis*. Other tissues commonly transferred for genitourinary reconstruction include bladder and oral mucosa. The bladder epithelium is the superficial layer of the bladder; the deep layer of the bladder is termed the *lamina propria*, with superficial and deep layers. The oral mucosa is the superficial layer of much of the oral cavity, which also has a deeper layer termed the *lamina propria*, again with superficial and deep layers.

All tissue has physical characteristics: extensibility, inherent tension, and the viscoelastic properties of stress relaxation and creep. The physical characteristics of a transferred unit are primarily a function of the helical arrangement of collagen along with the elastin cross-linkages. The collagen-elastin structure is suspended in a mucopolysaccharide matrix that influences the viscoelastic properties.

Tissue can be transferred as a graft (Fig. 40-1). The term *graft* implies that tissue has been excised and transferred to a graft host bed, where a new blood supply develops by a process termed *take*. Take requires approximately 96 hours and occurs in two phases. The initial phase, *imbibition*, requires about 48 hours. During that phase, the graft survives by “drinking” nutrients from the adjacent graft host bed, and the temperature of the graft is less than the core body temperature. The second phase, *inosculation*, also requires about 48 hours and is the phase in which true microcirculation is reestablished in the graft. During that phase, the temperature of the graft increases to core body temperature. The process of take is influenced by the nature of the grafted tissue and the conditions of the graft host bed. Processes that interfere with the vascularity of the graft host bed interfere with graft take.

The *epidermal*, or *epithelial layer*, is a covering, the barrier to the “outside,” and is adjacent to the superficial dermis, or superficial lamina. At approximately this interface is the superficial plexus. In the case of skin, the plexus is the *intradermal plexus*. There are some lymphatics in the superficial dermal or tunica layer. On the under-surface of the deep dermal layer or deep lamina is the *deep plexus*. In the case of skin, this is the *subdermal plexus*. The deep dermis contains most of the lymphatics and greater collagen content than found in the superficial dermal layer. The deep or reticular dermis is generally thought to account for the physical characteristics of the tissue.

If a graft is a *split-thickness unit*, it carries the epidermis or the covering. The graft also exposes the superficial dermal (intra-dermal or intralaminar) plexus. In most grafts, the superficial plexus comprises small but numerous vessels, which conveys favorable vascular characteristics to a split-thickness unit. The unit has few lymphatics, and the physical characteristics are not carried, which accounts for the tendency of split-thickness units to be brittle and less durable. The reticular dermis is not carried with the split-thickness unit (Jordan, 1993).

A mesh graft is usually an application of the split-thickness graft. After the harvest of a sheet graft, the sheet is placed on a carrier that cuts systematically placed slits in the graft. These slits can expand the graft by various ratios (i.e., 1.5:1, 2:1, 3:1). For

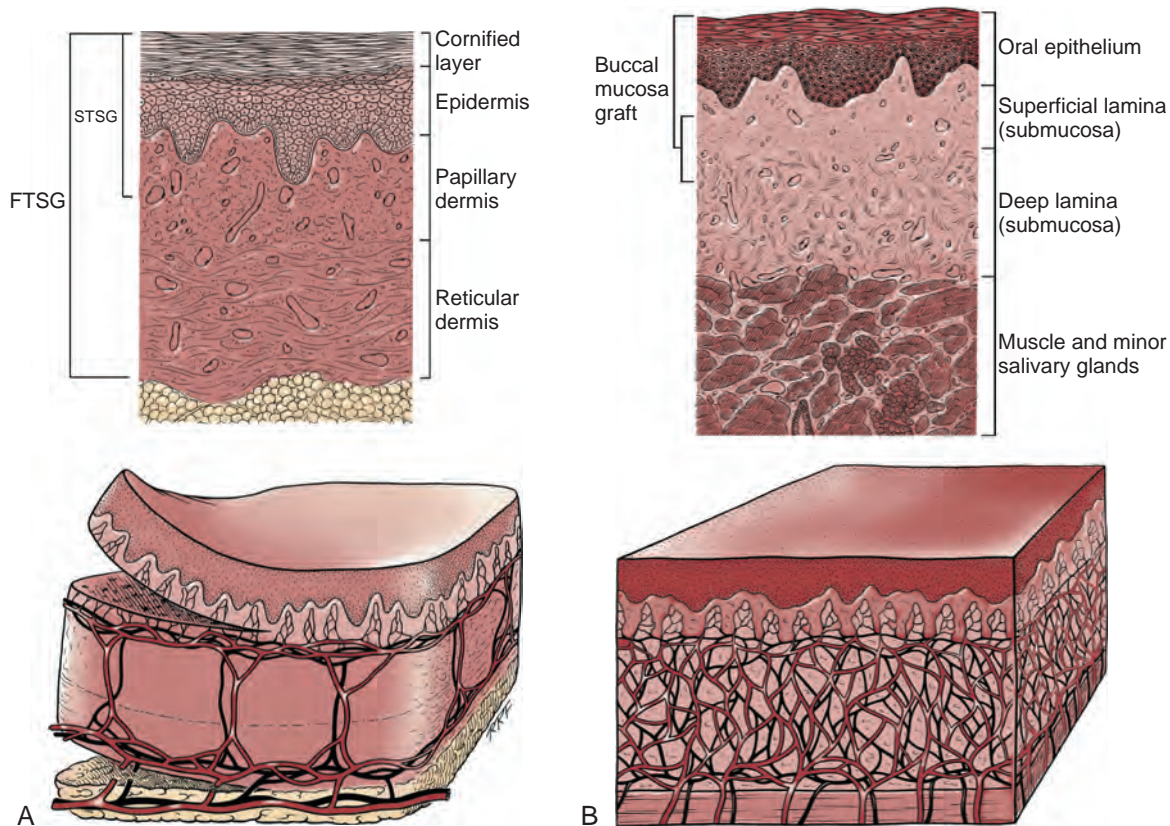


Figure 40-1. Cross-sectional diagrams (histologic appearance above, microvasculature below) of the skin. **A,** Cross-sectional diagrams of skin. **B,** Cross-sectional diagrams of oral mucosa. FTSG, full-thickness skin graft; STSG, split-thickness skin graft. (From Jordan GH, Schlossberg SM. Using tissue transfer for urethral reconstruction. *Contemp Urol* 1993;13:23.)

most genital reconstructive surgery, the slits are not for expansion but rather to allow subgraft collections to escape; in some cases, the slits allow the graft to conform better to irregular graft host beds (e.g., the testes in split-thickness skin graft scrotal construction). It has also been proposed that mesh grafts take readily because of increased levels of growth factors, possibly as a function of the slits. In general, full-thickness skin grafts are not meshed (Schreiter and Koncz, 1983; Jordan, 1993).

If a graft is a full-thickness unit, it carries the covering and the superficial dermis or lamina with all the characteristics attributable to that layer. However, it also carries the deep dermis or deep lamina. In skin, the subdermal plexus is exposed. In most cases, the plexus is composed of larger vessels that are more sparsely distributed. The graft is fastidious in its vascular characteristics. A full-thickness unit carries most of the lymphatics, and the physical characteristics are likewise carried with the transferred tissue (Devine et al, 1976; Jordan, 1993; Wessels and McAninch, 1996). Comparing the grafts that are most commonly used in genitourinary reconstructive surgery, the split-thickness skin graft has favorable vascular characteristics but tends to contract and be brittle when mature. The full-thickness skin graft tends to have more fastidious vascular characteristics, but it does not contract as much and is more durable when mature (see Fig. 40-1A). There is a difference between genital full-thickness skin (penile and preputial skin grafts) and extragenital full-thickness skin. This is probably a reflection of the increased mass of the graft in extragenital skin grafts. This increased mass makes the graft more fastidious, and the poor results reported with urethral reconstruction with extragenital full-thickness skin grafts are probably due to poor or ischemic take (Webster et al, 1984; Webster, 1987; Jordan, 1993). The posterior auricular graft (Wolfe graft) is an exception to the rule concerning extragenital skin. The postauricular skin is thin and

overlies the temporalis fascia and is thought to be carried on numerous perforators. The subdermal plexus of this graft mimics the characteristics of the intradermal plexus, and the total mass of the graft is more like that of the split-thickness unit. In the bladder epithelial graft, there is a superficial and a deep plexus; however, the plexuses are connected by many more perforators. Bladder epithelial grafts tend to have more favorable vascular characteristics. In the case of oral mucosal grafts, there is a panlamellar plexus. The oral mucosal graft can be thinned, provided that a sufficient amount of deep lamina is carried to preserve the physical characteristics (see Fig. 40-1B). Oral mucosal grafts are thought to have optimal vascular characteristics (Humby, 1941; Memmelaar, 1947). The thinned graft diminishes the total graft mass, while preserving the physical characteristics and not adversely affecting the vascular characteristics. The enthusiasm for the buccal mucosal graft seems well founded. The fact that the graft has a "wet epithelial" surface is likewise thought to be a favorable characteristic for many cases of urethral reconstructive surgery. The lingual, labial, and buccal grafts all vary in thickness and in substance. Because the labial mucosal grafts are thin, many surgeons prefer that donor site for reconstruction of the fossa navicularis (Jordan, 1993).

A series by Fichtner and colleagues (2004) reporting the use of "buccal mucosal" onlay grafts with mid-term and long-term results seems to suggest durability for these grafts. In that series, 67 patients were described, all with follow-up exceeding 5 years and some with 10 years of follow-up. All failures occurred within 12 months of the original procedure. More recent studies showed equal results with buccal and lingual grafts (Sharma et al, 2013). The dermal graft has been used for years to augment the tunica albuginea of the corpora cavernosa. When it is harvested, the graft exposes the intradermal plexus and the deep dermal plexus. The dermal

graft takes readily (is not fastidious) and has the physical characteristics normal to skin. When it is properly prepared, the tunica vaginalis graft is essentially peritoneum. The tendency of peritoneum to take readily is well documented in the literature that examines adhesion formation and in the urology literature concerning the application of peritoneal grafts for reconstruction of the urinary tract. The literature fails to define accurately what the surgeon can expect regarding physical characteristics (Jordan, 1993). Tunica vaginalis grafts have proved useful for small defects of the tunica albuginea of the corpora cavernosa, but aneurysmal dilation tends to develop when they are used for larger defects. Tunica vaginalis grafts have been tried for urethral reconstruction with uniformly poor results.

As described in the urologic literature, vein grafts are perhaps not true grafts according to the terminology used in this chapter. Vein patches are widely used in vascular surgery. The premise is that the vein survives by endothelial direct perfusion and reestablishment of vein wall blood flow by perfusion of the vasa vasorum. The vascular literature is at odds with this concept. The intima is the endothelial layer; it is thin and easily injured during the process of vein harvest and preparation, with areas of endothelial sloughing noted. Inflammatory cells and fibrin adhere to the exposed basement membrane. However, the endothelium regenerates in the first 6 weeks. The media is a combination of smooth muscle and interlaced collagen. After graft harvest, smooth muscle injury is prominently noted and is thought to be related to warm ischemia. In more mature grafts, much of the smooth muscle is replaced by a process of fibrous transformation with collagen deposition. The adventitia is a loose collagenous network interspersed with vasa vasorum. Mature vein grafts show evidence of take to the vasa vasorum. However, the adventitia becomes incorporated by periaxial connective tissues. Thrombosis in the vasa vasorum, early in the process of take, is not an unusual phenomenon. When vein grafts are exposed to arterial pressure and shear stress forces, the process colloquially described as "arterialization" occurs and is associated with changes of the vessel wall elastic properties, and the graft becomes rigid with low compliance. When these changes are noted, at least when veins are used for vessel replacement, the graft remains noncompliant throughout the remaining life of the graft (Szilagyi et al, 1973; Fuchs et al, 1978; Tolhurst and Haeseker, 1982). At the present time, vein "grafts" are being widely used for replacement of defects of the tunica albuginea of the corpora cavernosa. The pertinent points with regard to the transfer of vein patches to the corpora cavernosa and their long-term behavior have been inferred from the current vascular literature. Dermal grafts have been tried for urethral reconstruction, also with generally poor results. Rectal mucosal grafts also have been proposed for urethral reconstruction, but little is known about their graft take. In general, the vascularity of the bowel mucosa is based on the vascularity of the underlying muscle, with the mucosa carried on perforators. Little is found in the literature regarding the process of take of these grafts.

Tissue can be transferred as a flap. The term *flap* implies that the tissue is excised and transferred with the blood supply either preserved or surgically reestablished at the recipient site. Flaps can be classified by numerous criteria. Flaps can be classified on the basis of their vascularity and characterized as either random flaps (Fig. 40-2) or axial flaps (Fig. 40-3). A *random flap* is a flap without a defined cuticular vascular territory. The flap is carried on the dermal or laminar plexuses; the dimensions of random flaps can vary widely from individual to individual and from body site to body site. The term *axial flap* means that there is a defined vessel in the base of the flap. There are three types of axial flaps. The *direct cuticular axial flap* is a flap based on a vessel superficial to the superficial layer of the deep body wall fascia (see Fig. 40-3A). The classic example of a direct cuticular flap is the groin flap. A *musculocutaneous flap* (Fig. 40-4A) is based on the vascularity to the muscle. The *overlying skin paddle* is carried on perforators. If the muscle alone is carried as a flap, the overlying skin survives as a random unit. The *fasciocutaneous system* of vascularity (Fig. 40-4B) is similar to the musculocutaneous system.

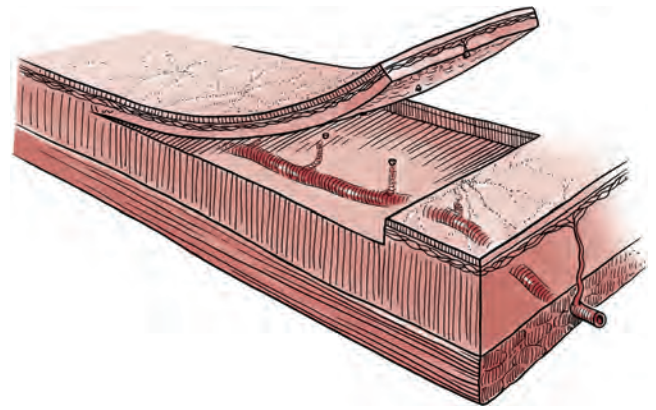


Figure 40-2. Random flap. The arterial perforators have been interrupted, and flap survival depends on the intradermal and subdermal plexuses.

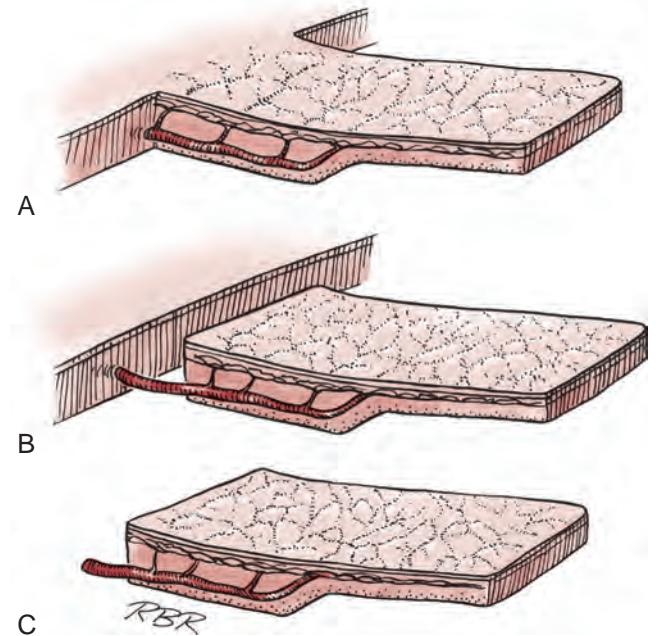


Figure 40-3. Axial flaps. Large vessels enter the base of the flaps. Survival depends on these vessels and on the random distal vascularity. A, Peninsula flap. The vascular continuity and the cutaneous continuity in the flap base are intact. B, Island flap. The vascular pedicle is intact; the cuticular continuity has been divided. These axial vessels are unsupported (dangling). C, Microvascular free-transfer flap. The free-flap cuticular and vascular connections are interrupted at the base of the flap. Vascular continuity is reconstituted in the recipient area by a microsurgical anastomosis. (From Jordan GH, McCraw JB. Tissue transfer techniques for genitourinary reconstructive surgery. AUA Update Series 1988;7:lesson 10.)

However, the deep blood supply is carried on the fascia (deep and superficial layers), and the overlying skin paddle is based again on perforators. One can transfer a fascial flap based on the deep blood supply associated with the flap; the overlying skin, if it is not carried with the flap, remains as a random unit (Ponten, 1981; Tolhurst and Haeseker, 1982; Cormack and Lamberty, 1984). It has been argued that fascia is relatively avascular and cannot serve as the "blood supply" to the fasciocutaneous unit. Actually, the fascial layer acts as a trellis—the vessels are carried much like the limbs of a vine (Jordan, 1993).

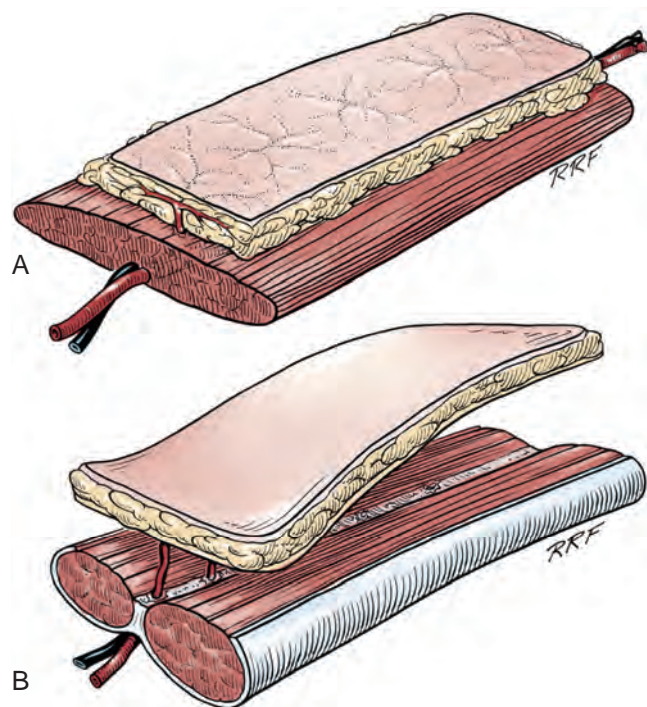


Figure 40-4. A, Musculocutaneous flap. Musculocutaneous perforators from the artery to a muscle vascularize the skin and overlying subcutaneous fat. They may be transferred as free flaps but are usually transferred locally, left attached to the vascular pedicle. B, Fasciocutaneous flap. Perforating blood vessels from rich plexuses on the superficial and deep aspects of the fascia connect to perforator vessels that communicate with the microvasculature of the overlying paddle. In genital reconstruction, these flaps are based on the dartos fascia of the penis or are free flaps from the forearm. (From Jordan GH, McCraw JB. Tissue transfer techniques for genitourinary reconstructive surgery. AUA Update Series 1988;7:lesson 10.)

A flap also can be classified by the elevation technique. A peninsular flap is a flap in which the vascular continuity and the cutaneous continuity of the flap base are left intact (see Figs. 40-2 and 40-3A). An island flap (see Fig. 40-3B) is a flap in which the vascular continuity is maintained; however, the cuticular continuity is divided. A true island flap is elevated on dangling vessels. The microvascular free-transfer flap (free flap) (see Fig. 40-3C) has the vascular continuity and the cuticular continuity interrupted. The vascular continuity is then reestablished at the recipient site.

The terminology is confusing. In genitourinary reconstructive surgical procedures, we tend to use the term *island flap*. As already mentioned, a true island flap is elevated on dangling vessels. However, the usual case is that a skin island or paddle is elevated either on the muscle, as in the gracilis musculocutaneous flap, or on the fascia, as in local genital skin flaps. The term *island flap* is not synonymous with the terms *skin island* and *skin paddle*. The usefulness of these flaps and grafts is illustrated in the discussion of surgical techniques later in this chapter. There is continued interest in the use of tissue-cultured grafts or “manufactured” grafts. The likelihood of someday being able to use off-the-shelf grafts or sheets of cultured material successfully is not far in the future (Chen et al, 1999; Atala, 2002; Rotariu et al, 2002; El-Kassaby et al, 2003; Bhargava et al, 2004).

Anatomy of the Penis and Male Perineum



Please see the Expert Consult website for this section, including Figures 40-5 to 40-13.

KEY POINTS: PRINCIPLES OF RECONSTRUCTIVE SURGERY

- Many of the techniques in reconstructive surgery require the transfer of tissue. Tissue transfer implies the movement of tissue for purposes of reconstruction. All tissue has extensibility, inherent tension, and the viscoelastic properties of stress relaxation and creep. These physical characteristics are important in predicting the behavior of transferred tissue.
- A graft is tissue that has been excised and transferred to a graft host bed, where a new blood supply develops by a process termed *take*. A flap is tissue that has been excised and transferred with the blood supply preserved or surgically reestablished at the recipient site. Grafts that have been successfully used for primary urethral reconstruction are the full-thickness skin graft, the bladder epithelial graft, the oral mucosal graft, and the rectal mucosal graft. Little is known about the characteristics of the rectal mucosal graft. The bladder epithelial graft and the oral mucosal graft have numerous vascular properties that make them desirable for urethral reconstruction. The issue of desiccation and hypertrophic growth, in the case of the bladder epithelial graft, has limited its use in the distal urethra.
- Full-thickness and split-thickness skin grafts have been used for penile reconstruction. The results with split-thickness skin grafts are so good that full-thickness grafts are rarely used for coverage of the penis. In complex cases, microvascular free-transfer technology has become a mainstay. For urethral reconstruction, skin islands based on the dartos fascia or tunica dartos have been effectively used. The dermal graft has been used for years to augment the tunica albuginea of the corpora cavernosa.
- The behavior of almost all forms of transfer can be predicted by examining histologic features and recognizing which layers provide which characteristics to the tissue.

Generalities of Reconstructive Surgical Techniques

With any surgical procedure, including reconstructive procedures of the external genitalia, there are basic rules and surgeons' biases regarding the best way to perform a certain operation. In this section, the differences are highlighted.

Reconstructive surgery is performed with all efforts aimed at minimizing tissue injury and promoting healing. Adequate visualization is essential. Surgical loupes are used by almost all surgeons performing adult and pediatric reconstructive genital surgery. A headlight or suction with attached light often adds to visualization, especially in deep perineal surgery. In penile cases, such as reconstruction of the fossa navicularis or correction of penile curvature, bipolar cautery is used exclusively. With cautery, the electrical charge is grounded either to a pad (monopolar) or to the opposite tong of the forceps (bipolar). In most instances, the field effects of the electricity are more confined with bipolar cautery. Because electricity is dissipated by conductors (in the case of human tissue, vessels, and nerves), there is a possibility of damage to these delicate structures. In other cases, monopolar cautery can be used in the superficial structures, but bipolar cautery is better during dissection around the corpus spongiosum, elevation of penile and scrotal flaps, division of the perineal intracorporeal space, and dissection of the dorsal neurovascular structures.

Appropriate instruments for genitourinary reconstructive surgery can commonly be found in a plastic surgery tray or on the peripheral vascular tray in the typical operating room. Some examples are fine tenotomy scissors, fine forceps, various skin hooks, and delicate needle holders. Sharp scissors that cut with minimal collateral trauma are essential. These instruments minimize tissue

Discussion of the anatomic relationships of the male genitourinary structures in the penis and male perineum must precede discussion of specific reconstructive surgical techniques; for a complete anatomic description please see Chapters 21 and 68.

The penile shaft (Fig. 40-5) comprises three erectile bodies, the two corpora cavernosa and the corpus spongiosum containing the urethra, along with their enveloping fascial layers, nerves, and vessels, all covered by skin. All of these structures continue into the perineum. The corpora cavernosa contain erectile tissue within a dense elastic sheath of connective tissue called the tunica albuginea. The corpora cavernosa are not separate structures but constitute a single space with free communication through an incompetent midline septum that becomes more complete toward the base of the penis. This erectile tissue contains arteries, nerves, muscle fibers, and venous sinuses lined with flat endothelial cells, and these features fill the corpora cavernosa, making its cut surface look like a sponge. This tissue is separated from the tunica albuginea by a thin layer of areolar connective tissue.

The third erectile body, the corpus spongiosum, lies in the ventral groove between the two corpora cavernosa. The tunica albuginea (adventitia) of the corpus spongiosum is thinner than the tunica albuginea of the corpora cavernosa, and the corpus spongiosum contains less erectile tissue than the corpora cavernosa. The urethra traverses the length of the penis within the corpus spongiosum. At its distal end, the corpus spongiosum expands to form the glans penis. The urethral meatus is slitlike, lying slightly on the ventral aspect of the tip of the glans, with its long axis oriented vertically. At its base, the penis is supported by two ligaments, composed primarily of elastic fibers that are continuous with the fascia of the penis. Posterior to this attachment, the right and left corpora cavernosa diverge, and the corpus spongiosum

broadens between the two crura to form the bulbospongiosus (bulb) (Fig. 40-6).

Figure 40-5 also illustrates the relationship of the erectile bodies and the urethra to the structures in the perineum. When discussing trauma and reconstruction, it is the consensus opinion of a World Health Organization conference convened in Stockholm in 2002 that the common use of the terms *anterior urethra* and *posterior urethra* be put aside and that the urethra be subdivided into six separate areas. These portions of the urethra are illustrated in Figure 40-7 and described as follows:

1. The **fossa navicularis** is contained within the spongy erectile tissue of the glans penis and terminates at the junction of the urethral epithelium with the skin of the glans. This portion of the urethra is lined with stratified squamous epithelium.
2. The **penile or pendulous urethra** lies distal to the investment of the ischiocavernosus musculature but is invested by the corpus spongiosum and maintains a constant lumen size roughly centered in the corpus spongiosum. The pendulous urethra is lined with simple squamous epithelium.
3. The **bulbous urethra** is covered by the midline fusion of the ischiocavernosus musculature and is invested by the bulbospongiosus of the corpus spongiosum. It becomes larger and lies closer to the dorsal aspect of the corpus spongiosum, exiting from its dorsal surface before the posterior attachment of the bulbospongiosus to the perineal body. The bulbous urethra is lined distally with squamous epithelium that gradually changes to the transitional epithelium found in the membranous urethra as it swings upward (Devine and Horton, 1977).
4. The **membranous urethra** is the portion that traverses the perineal pouch and is surrounded by the external urethral sphincter. This segment of the urethra is unattached to fixed structures, has

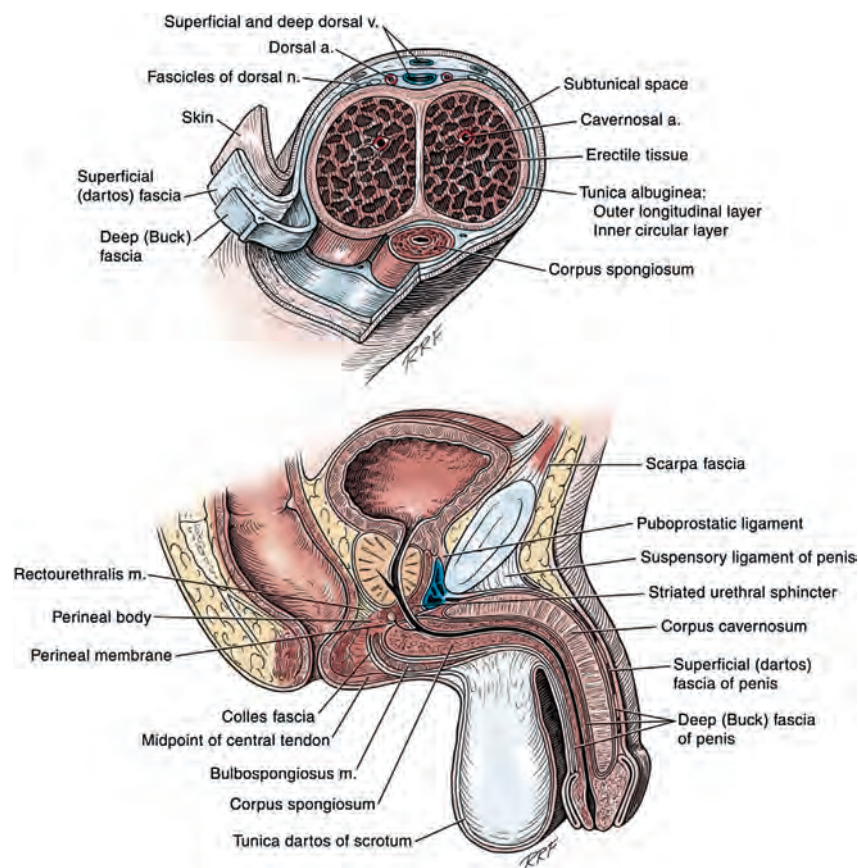


Figure 40-5. *Top*, Cross section of the penis at the junction of its middle and distal thirds. The septum is correctly illustrated as strands that interweave with the tunica albuginea ventrally and dorsally. *Bottom*, Diagram of a sagittal section of the penis and perineum illustrating the fascial layers. a., artery; m., muscle; n., nerve; v., vein.

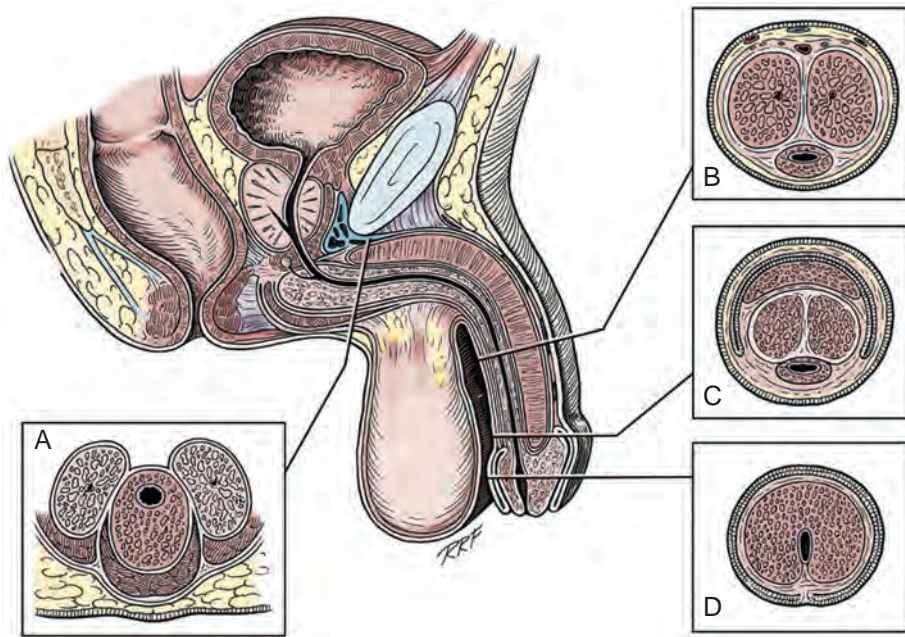


Figure 40-6. Diagrammatic cross sections of the anterior urethra. A, The bulbous urethra. The urethra is eccentrically placed in the corpus spongiosum. Proximally, the corpora cavernosa have split into individual crura, with the urethra lying against the triangular ligament. B, In the shaft of the penis, the urethra is more centrally placed in relation to the corpus spongiosum, and the corpora cavernosa are intimately fused, separated only by septal fibers. C, At the coronal margin, the urethra remains relatively centrally placed, and the corpora cavernosa are fused, again separated by septal fibers. The spongy tissue of the corpus spongiosum has become incorporated as the deep tissues of the glans. D, The fossa navicularis widens in caliber and is totally surrounded by the spongy erectile tissue of the glans penis. The urethra here is relatively ventrally placed in relation to the body of the corpus spongiosum. (From Jordan GH. Complications of interventional techniques of urethral stricture disease: direct visual internal urethrotomy, stents and laser. In: Carson C, editor. Topics in clinical urology: complications of interventional techniques. New York: Igaku-Shoin; 1996. p. 86–94.)

the distinction of being the only portion of the male urethra that is not invested by another structure, and is lined with a delicate transitional epithelium.

5. The **prostatic urethra** is the portion of the urethra that is proximal to the membranous urethra and is mostly surrounded by the prostatic stromal and glandular tissue. Its epithelium is continuous with the epithelium of the trigone and bladder.
6. The **bladder neck** is the location of the bladder neck musculature, variably surrounded by intravesical protrusion of the prostate. Its epithelium is contiguous with the epithelium of the trigone and bladder.

A submucosal layer is noted throughout the length of the urethra.

Five “sphincters” are recognized (Fig. 40-8):

1. If one begins proximally, the bladder neck is first.
2. The prostate itself is composed of a muscular stroma.
3. The prostate muscle continues into the membranous urethra as the external smooth muscle sphincter.
4. The external rhabdosphincter is often referred to as the external sphincter.
5. In the area of the membranous urethra are the muscles of recruitment, which are not true sphincters but provide aid with volitional continence.

In the penis, the erectile bodies are surrounded by Buck fascia, dartos fascia, and skin. Buck fascia is the tough, elastic layer immediately adjacent to the tunica albuginea (see Fig. 40-5). On the superior aspect of the corpora cavernosa, the deep dorsal vein, paired dorsal arteries, and multiple branches of the dorsal nerves are contained within the envelope of Buck fascia. In the midline groove on the underside of the corpora cavernosa, Buck fascia splits to surround the corpus spongiosum. Consolidation of the fascial layers (Fig. 40-9), lateral to the corpus spongiosum, attaches it to the tunica albuginea of the corpora cavernosa. Attached distally to

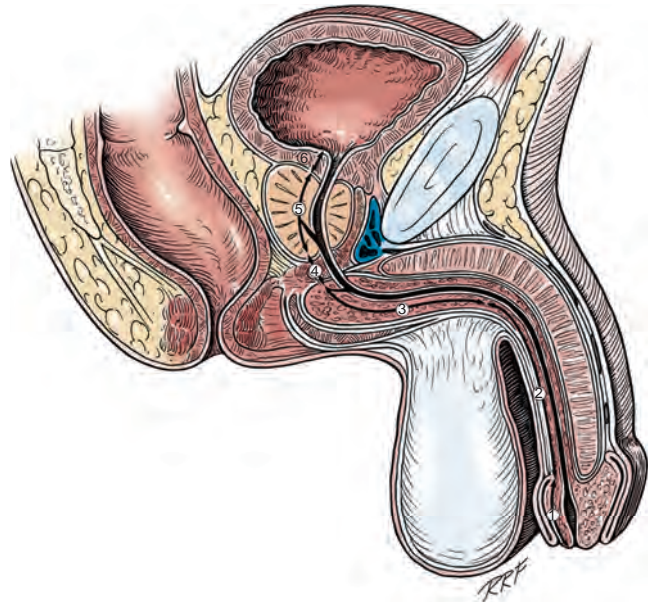


Figure 40-7. Sagittal section of the pelvis. The urethra is subdivided into the following sections: 1, fossa navicularis; 2, pendulous or penile urethra; 3, bulbous urethra; 4, membranous urethra; 5, prostatic urethra; and 6, bladder neck. By common usage, the divisions of the fossa navicularis, pendulous urethra, and bulbous urethra compose the anterior urethra, and the divisions of the membranous urethra, prostatic urethra, and bladder neck compose the posterior urethra. (Modified from Devine CJ Jr, Angermeier KW. Anatomy of the penis and male perineum. AUA Update Series 1994;8:11.)

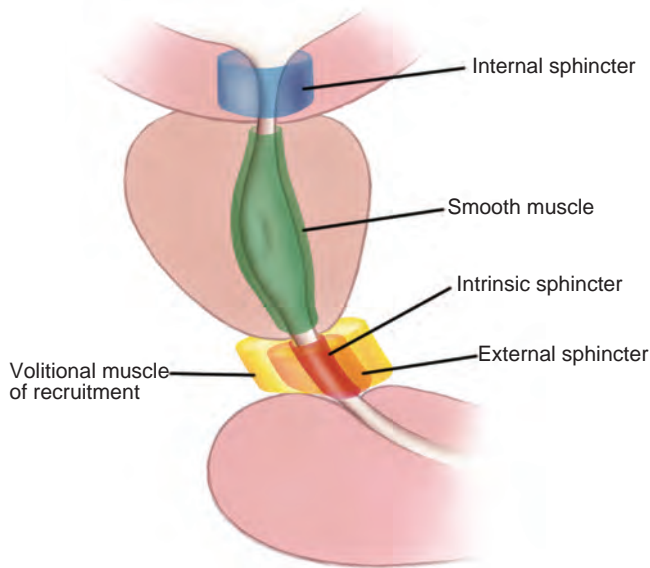


Figure 40-8. Diagrammatic representation of the sphincters surrounding the male posterior urethra.

the undersurface of the glans penis at the corona, Buck fascia extends into the perineum, enclosing each crus of the corpora cavernosa and the bulb of the corpus spongiosum, and firmly fixing these structures to the pubis, ischium, and inferior fascia of the perineal membrane (urogenital diaphragm).

Distally, the skin of the penis is confluent with the glabrous skin covering the glans. At the corona, it is folded on itself to form the foreskin (prepuce) that overlies the glans. The dartos fascia, a layer of areolar tissue remarkable for its lack of fat, separates these two layers of skin and continues into the perineum, where it fuses with the layers of the superficial perineal (Colles) fascia. In the penis, the dartos fascia is loosely attached to the skin and the deeper layer of Buck fascia and contains the superficial arteries, veins, and nerves of the penis.

Blood is supplied to the skin of the penis by the left and right superficial external pudendal vessels (Fig. 40-10A), which arise from the first portion of the femoral artery, cross the upper medial portion of the femoral triangle, and divide into two main branches, running dorsolaterally and ventrolaterally in the shaft of the penis, with collateralization across the midline. At intervals, fine branches split off to the skin, forming a rich subdermal vascular plexus that can sustain the skin after its underlying dartos fascia has been mobilized. The arteries are accompanied by venous tributaries that are more prominent and more easily seen than the arteries. Because of its remarkable thinness and mobility and the character of its vascular supply, the skin covering the penis is an ideal substitute—in some cases, for urethral reconstruction. The blood supply to the scrotal wall and ventral penile skin is based on the posterior scrotal artery, a superficial vessel from the deep internal pudendal artery (Fig. 40-10B). As with the superficial external pudendal tributaries, the posterior scrotal system provides a series of tributaries carried within the tunica dartos.

Venous Drainage

The penis is drained by three venous systems: superficial, intermediate, and deep (Fig. 40-11) (Aboseif et al, 1989). The superficial veins contained in the dartos fascia on the dorsolateral aspects of the penis unite at its base to form a single superficial dorsal vein. The superficial dorsal vein usually drains into the left saphenous vein (rarely into the right) and occasionally forms two trunks that drain into both. Veins from more superficial tissue may drain into the external superficial pudendal veins.

The intermediate system contains the deep dorsal and circumflex veins, lying within and beneath Buck fascia. Emissary veins begin within the erectile space of the corpora cavernosa and, following a perpendicular or oblique course through the tunica albuginea, emerge from the lateral and dorsal surfaces of the corpora cavernosa to empty into the circumflex veins or the deep dorsal vein. The circumflex veins are channels, usually more prominently present in the distal two thirds of the penile shaft. They arise from the corpus spongiosum, on the ventrum of the penis, and often receive the emissary veins as they travel around the lateral aspect of the corpora cavernosa, passing beneath the dorsal arteries and nerves to empty into the deep dorsal vein. The circumflex veins can also become confluent ventrally, forming periurethral veins on each side. These may become important in the treatment of impotence caused by veno-occlusive incompetence.

The deep dorsal vein is formed by five to eight small veins emerging from the glans penis to form the retrocoronal plexus, which drains into the deep dorsal vein that may consist of more than one vein lying in the midline groove between the corporeal bodies. In many patients, there is a connection between the superficial and deep dorsal veins. The vein gathers blood from the emissary and circumflex veins, and passing beneath the pubis at the level of the suspensory ligament, it leaves the shaft of the penis at the crus and drains into the periprostatic plexus.

The deep drainage system consists of the crural and cavernosal veins. The crural veins arise in the midline, in the space between the crura. Normally, they are small and almost indiscernible, joining the deep dorsal vein or the periprostatic plexus. If the deep dorsal vein has been ligated or obliterated after trauma, striking development of these veins can be noted as the intracanal space is entered during the perineal dissection for urethral repair. Emissary veins in the proximal third of the crura, near their attachment to the ischial tuberosities, join to form several thin-walled trunks on the dorso-medial surface of each corpus cavernosum. Some pass medially, joining the dorsal or crural veins, or, extending proximally, enter the periprostatic plexus. Most consolidate into one or two cavernosal veins on each side. Running in the penile hilum, deep and medial to the cavernosal arteries and nerves, they join to form a large venous channel that drains into the internal pudendal vein. Three or four small cavernosal veins emerge from the dorsolateral surface of each crus and course laterally between the bulbospongiosus and the crus of the penis for 2 to 3 cm before draining into the internal pudendal veins. These usually insignificant vessels become larger and can be noted more readily in patients with veno-occlusive erectile dysfunction. The internal pudendal veins (usually two) run together with the internal pudendal artery and nerve in the Alcock canal to empty into the internal iliac vein.

Arterial System

The blood supply to the deep structures of the penis is derived from the common penile artery, which is a continuation of the internal pudendal artery after it gives off the perineal branch (Fig. 40-12). From that point, the artery is termed the *common penile artery* and travels along the medial margin of the inferior pubic ramus. As it nears the urethral bulb, the artery divides into its three terminal branches, the bulbourethral artery, dorsal artery, and cavernosal artery.

The bulbourethral artery is a short artery or arteries of relatively large caliber that pierce the Buck fascia to enter the bulbospongiosus. These arteries are oriented almost parallel to the path of the membranous urethra.

The dorsal artery generally travels along the dorsum of the penis between the deep dorsal vein medially and the dorsal nerves laterally, with a coiled rather than a straight configuration. The artery uncoils as the penis elongates with erection, allowing flow to be maintained. Along its course, it gives off 3 to 10 circumflex branches (the circumflex cavernosal arteries) that accompany the circumflex veins around the lateral surface of the corpora cavernosa and provide vascularity to the corpus spongiosum. Its terminal branches arborize in the glans penis. In many patients, branches

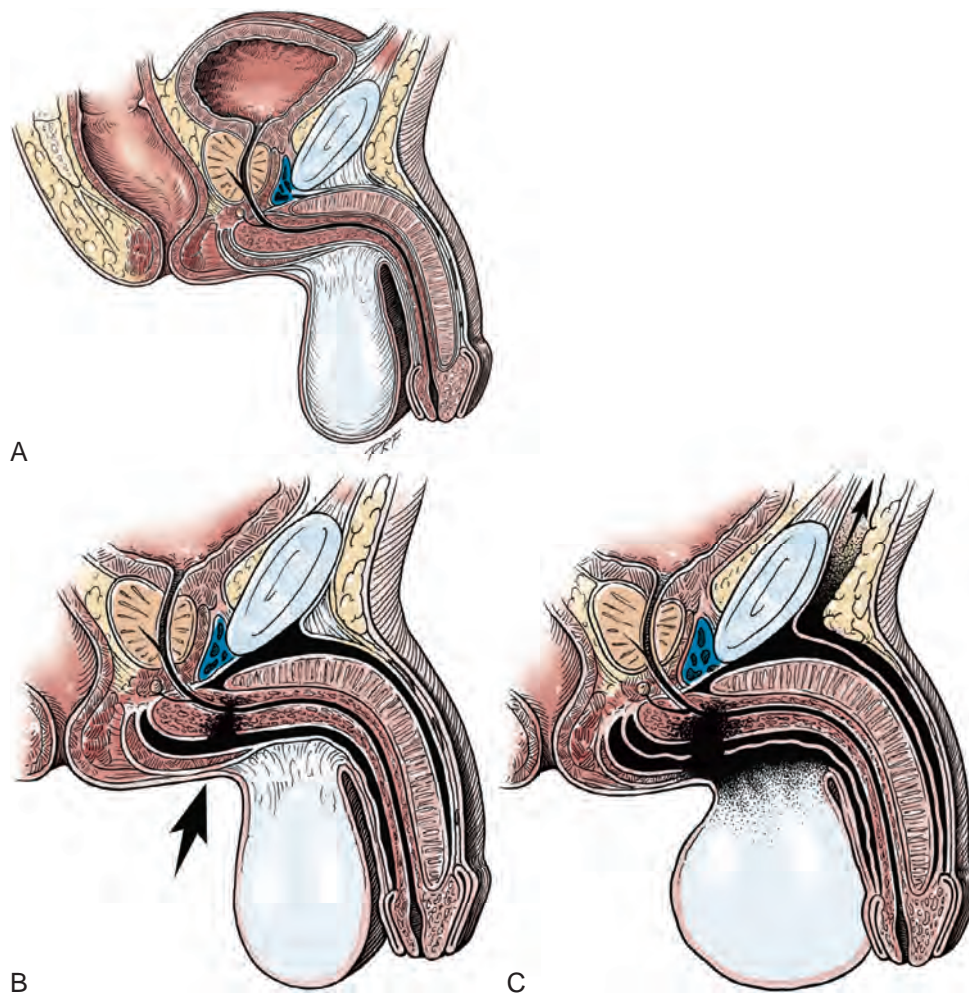


Figure 40-9. Cross sections of the pelvis. A, The normal attachment of the fasciae enveloping the penile structures. The dartos fascia is contiguous with the Scarpa fascia onto the abdomen, with the tunica dartos of the scrotum, with the Colles fascia on the perineum, and over the thigh—eventually to insert at the fascia lata. B, With trauma to the pelvis or perineum, the corpus spongiosum is injured; however, the hematoma is confined by the attachment of the Buck fascia. C, With trauma to the perineum or pelvis, the corpus spongiosum is injured, and the Buck fascia is violated; the hematoma can spread throughout the confines of the extended dartos fascia–tunica dartos system.

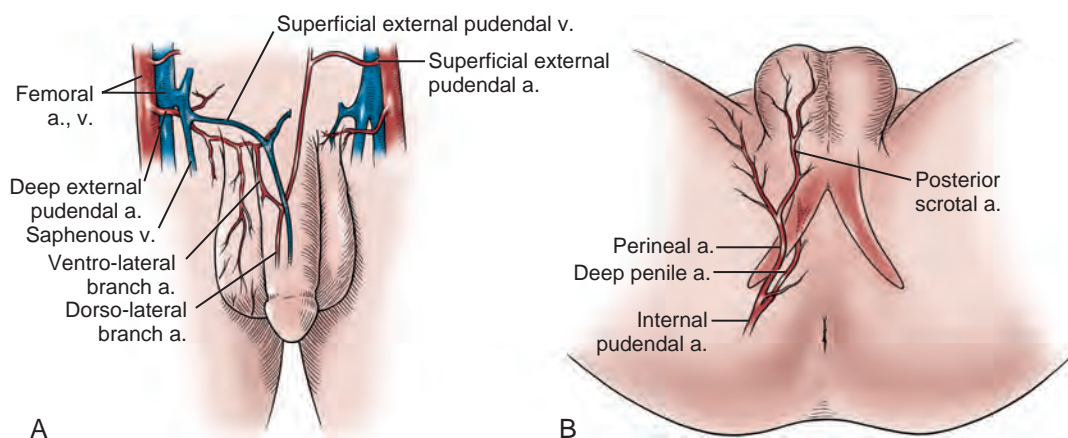


Figure 40-10. The vasculature to the genital skin. A, The superficial external pudendal vessels arborize to become the fascial blood supply contained in the dartos fascia of the penis. B, The scrotal artery is a terminal branch of the deep internal pudendal artery. This artery is thought to arborize in the tunica dartos of the scrotum and Colles fascia of the perineum. The perineal artery continues lateral to the groin crease onto the thigh and extends toward the groin. a., artery; v., vein.

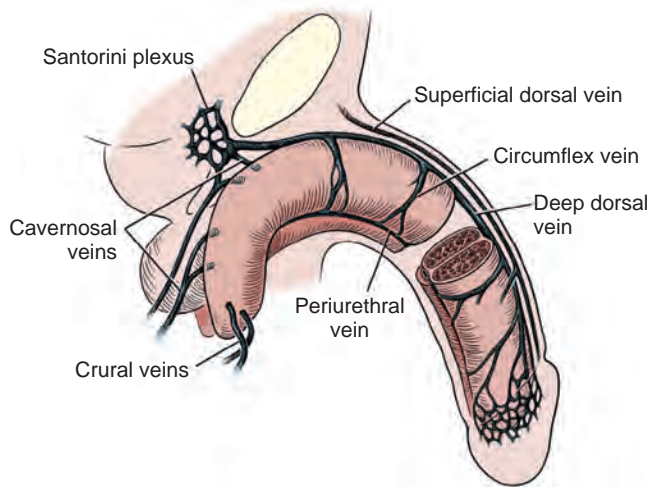


Figure 40-11. The venous drainage of the deep structures of the penis. (From Horton CE, Stecker JF, Jordan GH. Management of erectile dysfunction, genital reconstruction following trauma and transsexualism. In: McCarthy JG, editor. Plastic surgery, vol 6. Philadelphia: Saunders; 1990. p. 4213–45.)

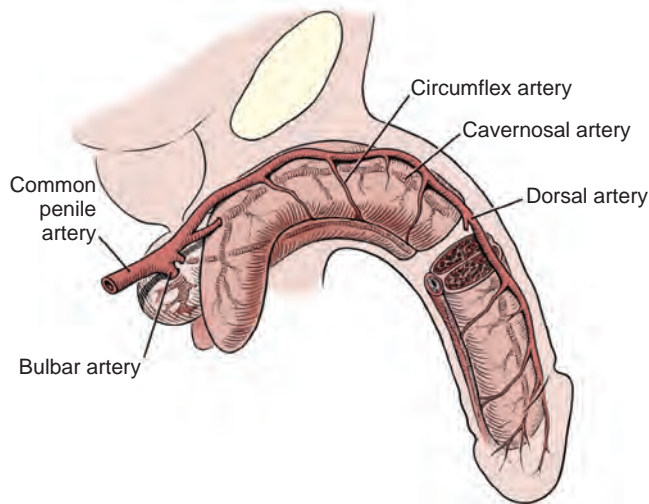


Figure 40-12. The arterial supply to the deep structures of the penis. (From Horton CE, Stecker JF, Jordan GH. Management of erectile dysfunction, genital reconstruction following trauma and transsexualism. In: McCarthy JG, editor. Plastic surgery, vol 6. Philadelphia: Saunders; 1990. p. 4213–45.)

penetrate the tunica and connect to the cavernosal arteries. The functional significance of these perforators varies from individual to individual.

The cavernosal artery, usually a single artery, arises on each side as the terminal branch of the penile artery. It enters the corpus cavernosum at the hilum and runs the length of the penile shaft, splitting off the many helicine arteries that constitute the arterial portion of the erectile apparatus. The arteries frequently branch before entering the corporeal body. Sometimes a branch enters the opposite corpus cavernosum, and occasionally a single artery branches in the penile shaft to supply both sides.

Lymphatics

Lymph drainage from the glans penis collects in large trunks in the area of the frenulum. The lymph vessels circle to the dorsal aspect of the corona, where they unite with vessels from

the other side. The vessels traverse the penis beneath Buck fascia, terminating mostly in the deep inguinal lymph nodes of the femoral triangle. Some drainage is to the presymphyseal lymph nodes and by way of these to the lateral lymph nodes of the external iliac group.

Nerve Supply

The nerves of the penis are derived from the pudendal and cavernosal nerves. The pudendal nerves supply somatic motor and sensory innervation to the penis. The cavernosal nerves are a combination of the parasympathetic and visceral afferent fibers and constitute the autonomic nerves of the penis. These provide the nerve supply to the erectile apparatus.

The pudendal nerves enter the perineum with the internal pudendal vessels through the lesser sciatic notch at the posterior border of the ischiorectal fossa. They run in the fibrofascial pudendal Alcock canal to the edge of the urogenital diaphragm. Each dorsal nerve of the penis arises in the Alcock canal as the first branch of the pudendal nerve. Traveling ventral to the main pudendal trunk above the internal obturator and under the levator ani, the dorsal nerves perforate the transverse perinei muscles to arrive on the dorsum of the penis and continue distally along the respective dorsolateral penile surface lateral to the dorsal artery. On the shaft, their fascicles fan out to supply proprioceptive and sensory nerve terminals in the tunica of the corpora cavernosa and sensory terminals in the skin. These nerves terminate in the glans penis.

Perineum

The perineum is the diamond-shaped outlet bounded anteriorly by the pubic arch and the arcuate ligaments of the pubis, posteriorly by the tip of the coccyx, and laterally by the inferior rami of the pubis and ischium. A transverse line between the ischial tuberosities divides the perineum into an anterior triangle containing the external urogenital organs and a posterior anal triangle (Fig. 40-13A and B).

Colles Fascia. In the anterior triangle, Colles fascia (see Fig. 40-13A) attaches at its posterior margin to the perineal body at the posteroinferior margin of the urogenital diaphragm. The fascia curves below the superficial transverse perinei muscles and projects forward as two layers attached laterally to the ischium and the inferior ramus of the pelvis. The loose superficial layer is fatty and is continuous with the more substantial dartos fascia (tunica dartos) of the scrotum. In the scrotum, the dartos fascial layer contains muscle fibers that cause the rugose appearance of the scrotum. The fascia also projects (but without muscle fibers) into the midline to form the septum between the halves of the scrotum. The median raphe in the skin delineates the separation of the halves of the scrotum and is continued anteriorly as a darkly colored streak in the ventral midline of the penis and posteriorly as the median raphe of the perineum terminating at the anus.

The deep membranous layer of Colles fascia is a more substantial layer that forms a roof over the scrotal cavity, separating it from the superficial perineal pouch. At the anterior aspect of the scrotum, Colles fascia joins with the dartos fascia (tunica dartos) of the scrotum, and a fold of this fascia projects backward beneath the fibers of the midline fusion of the ischiocavernosus muscle (bulbospongiosus muscle). At the base of the penis, it is continuous with the dartos fascia of the penis. Thickenings of the fascia at this level form the two suspensory ligaments of the penis. First, the outer fundiform ligament, which is continuous with the lower end of the linea alba, splits into laminae that surround the body of the penis and unite beneath it. Second, the inner triangle-shaped suspensory ligament is attached to the anterior aspect of the symphysis pubis and blends with the dartos fascia of the penis below it.

Anteriorly, Colles fascia fuses and becomes continuous with the membranous layer of the subcutaneous connective tissue of the anterior abdominal wall (Scarpa fascia). Laterally, Colles fascia

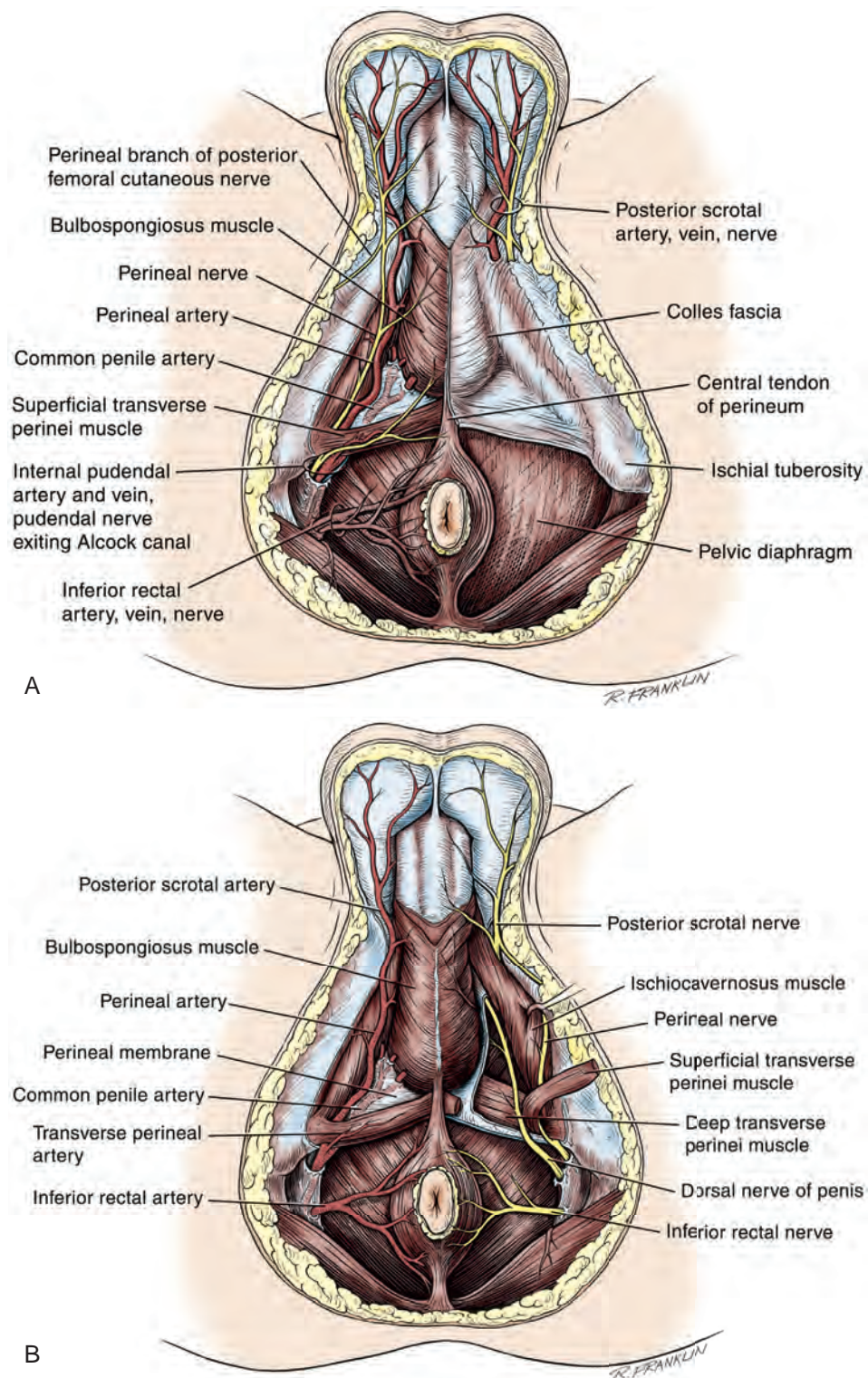


Figure 40-13. “Peel-away” diagrams of the anatomy of the perineum. **A**, The skin and subcutaneous tissues have been removed. **B**, In the anterior perineal triangle, Colles fascia has been removed. In the posterior anal triangle, the pelvic diaphragm has been removed. Note the division of the superficial transverse perineal muscle, exposing the deep transverse perineal muscle.

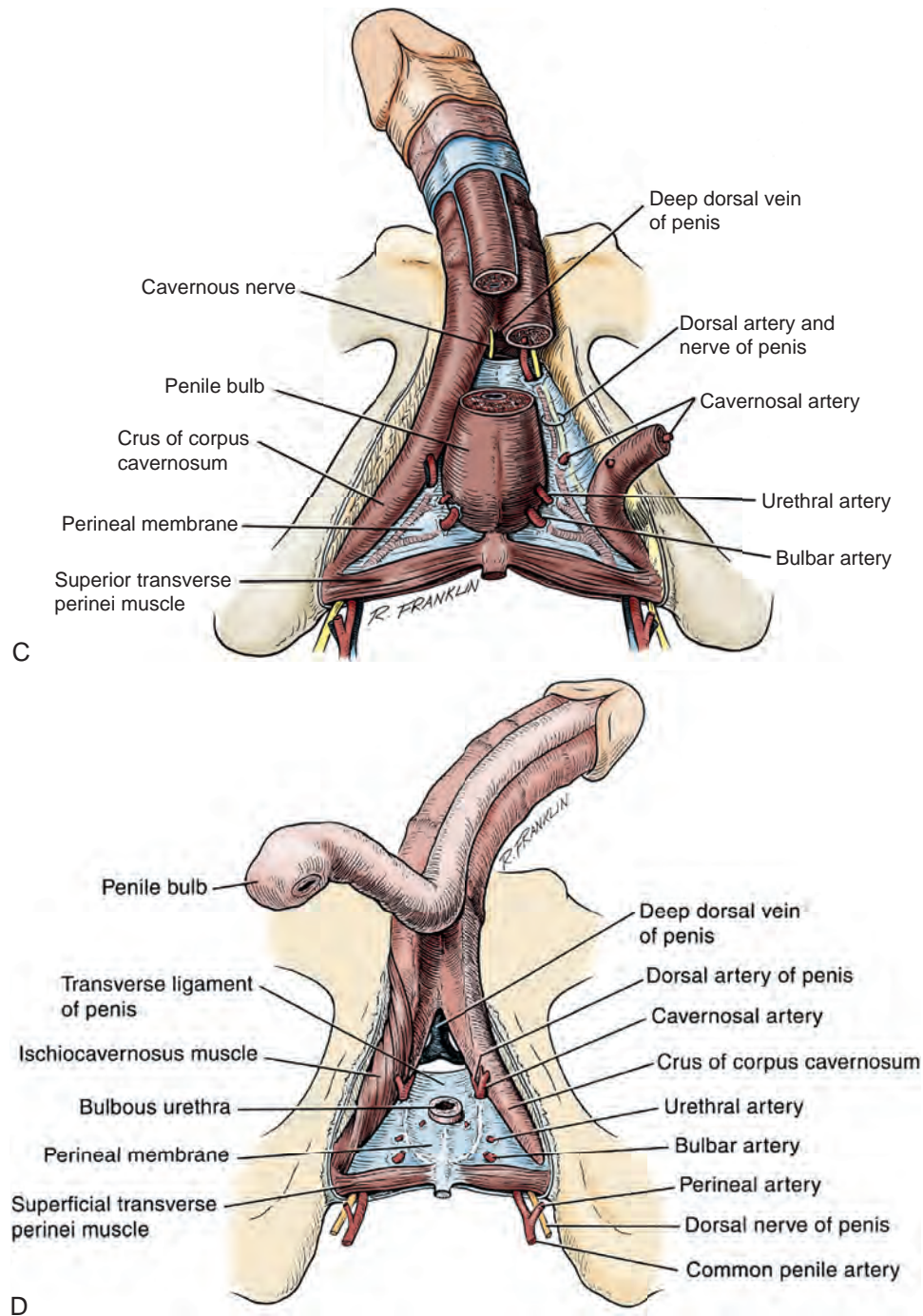


Figure 40-13, cont'd C, The anterior perineal triangle has been dissected to expose the erectile bodies. **D,** The corpus spongiosum has been divided at the departure of the urethra from the penile bulb. The intracanal space is exposed. (From Devine CJ Jr, Angermeier KW. *Anatomy of the pelvis and male perineum*. AUA Update Series 1994;13:1015.)

fuses to the pubic arch and with the fascia lata. Posteriorly, Colles fascia sweeps beneath the transverse perineal muscles, fusing with the posterior aspect of the perineal membrane. The space beneath the continuous plane formed by these fascial attachments is the superficial perineal pouch, in which infections or extravasation of urine and collections of blood (after trauma to the urethra) may be confined (see Fig. 40-9).

Superficial Perineal Space. In males, the superficial perineal space contains the continuation of the corpora cavernosa, the proximal part of the corpus spongiosum and urethra, the muscles associated with them, and the branches of the internal pudendal vessels and pudendal nerves (see Fig. 40-13B). The

ischiocavernosus muscles cover the crura of the corpora cavernosa. They attach to the inner surfaces of the ischium and ischial tuberosities on each side and insert at the midline into Buck fascia, surrounding the crura at their junction below the arcuate ligament of the penis. **The midline fusion of the ischiocavernosus muscles and bulbospongiosus muscles is in the midline of the perineum.** They are attached to the perineal body posteriorly and to each other in the midline, as they encompass the bulbospongiosus and crura of the corpora cavernosa at the base of the penis. These muscles are confluent with the ischiocavernosus muscles laterally and at their insertion into Buck fascia, covering the dorsal vessels and nerves at the base of the penis.

Central Perineal Tendon (Perineal Body). Lying just anterior to the anus, as a part of the plane separating the anterior and posterior perineal triangles, the **perineal body** is formed by the interconnection of eight muscles of the perineum (see Fig. 40-13A and B). The perineal body receives fibers from the anterior portion of the anal sphincter and is the central point of insertion of the superficial transverse perineal muscles that arise at the ischial tuberosities. The bulbospongiosus muscle (midline fusion of the ischiocavernosus muscle) is fixed to the perineal body by its most posterior fibers. The deep transverse perineal muscles and fibers from the anterior portions of the levator ani muscles attach to the deep aspect of the perineal body.

Deep Perineal Space. The urogenital diaphragm constitutes the deep perineal space (see Fig. 40-13C and D). It is contained within two layers of fascia and incompletely covers the outlet of the pelvis anterior to the deep layer of the perineal body. The deep layer of fascia is an indistinct structure—the continuation of the endopelvic obturator fascia. The superficial fascia attaches laterally to the ischial rami and the inferior ramus of the pubis. This fascia blends with the deep layer behind the perineal body and anteriorly, where it terminates with a thickened edge, the transverse perineal ligament. A space between this ligament and the arcuate ligament of the pubis accommodates the deep dorsal vein of the penis.

The deep perineal pouch (see Fig. 40-13D) contains the deep transverse perineal muscles, the external sphincter of the urethra, the bulbourethral (Cowper) glands, and the blood vessels and nerves associated with the structures within it. The sphincter urethral muscle fibers arise from the medial surface of the inferior pubic rami and pass medially toward the urethra, where they meet the fibers from the opposite side. In males, the muscle encircles the membranous urethra to function as the somatic sphincter of the urethra (Haertsch, 1981).

KEY POINTS: ANATOMY OF THE PENIS AND MALE PERINEUM

- An understanding of the anatomy is of utmost importance to the surgeon. The penile shaft is composed of three erectile bodies: the paired corpora cavernosa and the corpus spongiosum. The corpus spongiosum invests the anterior urethra.
- By consensus, the urethra has been subdivided into six separate areas: the fossa navicularis, the penile or pendulous urethra, the bulbous urethra, the membranous urethra, the prostatic urethra, and the bladder neck.
- In the male, five urethral “sphincters” are recognized. If one begins proximally, there is the bladder neck. The prostate itself is composed of a muscular stroma. The prostatic muscle continues into the membranous urethra as the external smooth muscle sphincter. The external rhabdosphincter is often referred to as the external sphincter, and in the area of the membranous urethra are the muscles of recruitment that are not true sphincters.
- The Buck fascia is devoted to the deep structures of the penis. The more areolar and superficial fascia, the dartos fascia, is related more to the skin and its vasculature.
- The blood supply to the deep structures of the penis is based on the common penile artery, which is the extension of the deep internal pudendal artery. The blood supply to the skin of the genitalia is based on the perineal branch—scrotal branch of the deep internal pudendal artery and the superficial external pudendal vessels, branches of the femoral arteries. The penis is drained by three systems: the superficial, intermediate, and deep venous systems.
- The nerves to the penis are derived from the pudendal and the cavernosal nerves. The pudendal nerve supplies somatic motor and sensory innervation to the penis. The cavernosal nerves are a combination of the parasympathetic and the visceral afferent fibers and constitute the autonomic nerves to the penis.
- The perineum is a diamond-shaped outlet bounded anteriorly by the pubic arch and the circuate ligaments of the pubis, posteriorly by the tip of the coccyx, and laterally by the inferior rami of the pubis and ischium. A transverse line between the ischial tuberosities divides the perineum into an anterior triangle containing the external urogenital organs and a posterior anal triangle.

injury from manipulation and permit more precise dissection. For urethral surgery, a set of bougie à boule sizers is essential to check the caliber of the urethral lumen. McCrea urethral sounds are a good addition to the typical van Buren sounds available in the usual operating room. For calibration, sounds do not replace the need for bougie à boule calibrators. For posterior urethral reconstruction, a sound to pass through the cystostomy tract and prostate to find the proximal end for the reconstruction is often helpful. We find that a Haygrove staff serves this role nicely. Some centers use the cystoscope for this purpose, and often it suffices well, whereas at other times it is not as effective as the Haygrove-style sound.

The choice of suture material evolves on the basis of the surgeon's experience and bias. However, there are some common principles with which most surgeons would agree. First, in urethral surgery, absorbable suture is the rule. Typical choices for most surgeons are braided absorbable sutures or the family of monofilament absorbable sutures. Chromic suture is rarely used now because the choices of other absorbable sutures seem superior in virtually all cases. In the case of tension-free closures, very small sutures can be used. In some cases, tying the suture can be awkward, and a larger suture may be warranted, even though the anastomosis is tension free. The caliber of suture should be the smallest possible to line up the tissue, which is typically not under tension. There is no reason to use suture that is stronger than the tissues that are being sutured. Fine suture such as 5-0 and 6-0 chromic or polyglactin can be used to suture the epithelium to the adventitia of the corpus spongiosum to control bleeding. For a flap or graft repair, 4-0 to 6-0 suture is usually adequate. For primary anastomosis of the corpus spongiosum or for a posterior urethral reconstruction, 3-0 suture may be appropriate because of tying concerns. The needle should be tapered if possible except when, as in urethroplasty, for example, severe spongiofibrosis or scarring is present. Some typical choices are taper needles, such as RB-1, TF, and SH-1, and cutting needles, such as P-3 and PC-3. The UR-6 half-circle taper needle that is often used in radical prostatectomy can be helpful for deep perineal anastomosis of the urethra.

Surgical position and retraction are critical to attaining good results. If possible, procedures are done with the patient supine or prone. Many procedures that previously were done with the patient in the lithotomy position can be done with the patient in the frog-leg or split-leg position. For penile surgery, a Scott retractor with stay hooks (Lone Star Medical Products, Houston, TX, the Jordan-Bookwalter perineal retractor set (C. S. Surgical, Slidell, LA; J. Hugh Knight Instrument Company, New Orleans, LA), or the Omni-Tract perineal retractor (Omni-Tract Surgical, Division of Minnesota Scientific, St. Paul, MN) is helpful. Lithotomy or exaggerated lithotomy positions are used only for the minimal time necessary. With appropriate padding for the foot and positioning without pressure on the back of the leg, complications in the low-lithotomy position are minimal. When the patient is in the supine, split-leg, and low-lithotomy positions, venous compression stockings can be used. The controversy in positioning revolves around the use of the exaggerated lithotomy position. We prefer to use this position for all bulbar and posterior urethral reconstructions. Other surgeons use a lower lithotomy position. We find the more exaggerated position to be safe and believe that it provides unequalled access to the deep perineal structures (Angermeier and Jordan, 1994). Details of positioning, as we do it, are described later. To minimize the patient's time in the exaggerated position, all graft harvesting or flap elevation is done with the patient in the flat supine position.

In addition to proper diagnosis and planning, the surgical technique is important for the overall success of reconstructive surgery. In contrast to the results of extirpative surgery, the results of reconstructive surgery depend on methods that minimize tissue damage and maximize wound healing. The key ingredients are adequate visualization, appropriate choice of suture, delicate tissue handling, appropriate positioning, and adequate retraction.

KEY POINTS: RECONSTRUCTIVE SURGICAL TECHNIQUES

- Reconstructive surgery is performed with all efforts aimed at minimizing tissue injury and promoting healing. Loupe magnification is used by almost all surgeons performing adult and pediatric reconstructive surgery. For deep exposure, a headlight or lighted suction is advantageous. Instruments must be delicate because reconstructive surgery employs small sutures and small needles.
- The choice of suture material evolves on the basis of the surgeon's experience. However, the caliber of sutures should be the smallest possible to align the tissue, which is not typically under tension. There is no reason to use suture that is stronger than the tissues being sutured.
- The choice of surgical positioning is left to the surgeon's preference.
- Proper diagnosis and planning of the surgical technique are important for the success of reconstructive surgery.

SELECTED PROCESSES

Urethral Hemangioma

Although **urethral hemangioma** is a rare condition, it is usually **persistent** and offers a challenge to the surgeon when excision is deemed necessary. Patients typically present with hematuria or a bloody urethral discharge and occasionally with obstructive symptoms. The lesions may be single or multiple, and the urethral meatus is a common location. Although the diagnosis is often made with cystoscopy, which readily visualizes the dilated blood vessels, the lesion often extends beyond the point at which it is seen with cystoscopy.

Because all reported cases of urethral hemangioma have been benign, management depends on the size and location of the lesion. Asymptomatic lesions do not require treatment and should be observed because hemangiomas can regress spontaneously. Symptomatic lesions that require treatment must be completely excised to prevent recurrence.

Although electrofulguration has been reported as a possible treatment of urethral hemangioma, it should be used only to control an acute episode. For smaller lesions, laser treatment has been successful and produces less scarring. Lasers that are used for this purpose include argon, potassium titanyl phosphate (KTP) (532 nm), and neodymium:yttrium-aluminum-garnet (Nd:YAG). The preferred treatment of larger lesions is open excision and urethral reconstruction; in some cases, this means circumferential reconstruction. Tubed graft reconstruction should be avoided; tubed flap reconstruction or tubed construction with mixed tissue transfer could be considered, although staged reconstruction is probably preferable. In addition, good initial success has been reported with polidocanol as a sclerosing agent for extensive urethral hemangiomas.

Reactive Arthritis

Reactive arthritis is characterized by a classic triad of arthritis, conjunctivitis, and urethritis. In addition, some patients have had an episode of diarrhea that preceded the development of arthritis. However, the classic triad is not present in most cases, and patients present with only arthritis affecting the knees, ankles, and feet in an asymmetrical distribution. The history of urethritis is obtained on detailed questioning.

Urethral involvement is usually mild and self-limited and constitutes a minor portion of the disease. In approximately 10% to 20% of patients, a glanular lesion is present. Referred to as **circinate balanitis**, this lesion is **diagnostic of reactive arthritis** and typically appears as a shallow, painless ulcer with gray borders. Occasionally, the lesion appears as small, red macules, 1 to 2 mm

in diameter. When the urethritis is mild and self-limited, no treatment is necessary.

In rare cases, urethritis causes severe inflammation with necrosis of the mucosa, producing uncompromising stricture disease. We have been unsuccessful in excision and replacement of the urethra in these cases. Alternatively, we perform a perineal urethrostomy and excise the entire distal urethra. This approach may decrease the rheumatic manifestations associated with reactive arthritis.

Lichen Sclerosus

Lichen sclerosus (LS) was previously known as balanitis xerotica obliterans. LS is a chronic inflammatory hypomelanotic, lymphocyte-mediated skin disorder that in men involves the prepuce and glans and frequently leads to meatal stenosis and possible urethral involvement.

The reported incidence of LS in the Western population is 1 per 300 persons; however, the worldwide prevalence may be substantially different (Wallace, 1971; Dogliotti et al, 1974; Jacyk and Isaac, 1979; Datta et al, 1993). The peak ages of recognition in women are bimodal, with many cases noted before puberty and with another peak occurring in postmenopausal women (Tasker and Wojnarowska, 2003). In men, LS seems to peak between ages 30 and 50; however, LS has been described in people of all ages, from infants to elderly adults (Tasker and Wojnarowska, 2003). LS is commonly found at the time of circumcision when performed after the neonatal period (McKay et al, 1975; Rickwood et al, 1980; Garat et al, 1986; Ledwig and Weigand, 1989; Meuli et al, 1994). **LS is the most common cause of meatal stenosis and appears as a whitish plaque that may involve the prepuce, glans penis, urethral meatus, and fossa navicularis. If only the foreskin is involved, circumcision may be curative (Akpioraye et al, 1997).** In our experience, LS usually begins as a meatal or perimeatal process in a circumcised patient, but it may involve other areas of the preputial space in uncircumcised patients. In uncircumcised men, the prepuce becomes edematous and thickened and often may be adherent to the glans (Bainbridge et al, 1971). Diagnosis is made with biopsy. Several reports have suggested an association with chronic infection by a spirochete, *Borrelia burgdorferi* (Tuffanelli, 1987; Dillon and Ghassan, 1995; Shelley et al, 1999).

The first report of what was probably LS was published by Weir in 1875. He described a case of vulvar and oral "ichthyosis" (Weir, 1875). The term *balanitis xerotica obliterans* was first applied by Stühmer in 1928. Freeman and Laymon showed that balanitis xerotica obliterans and LS were probably the same process (Freeman and Laymon, 1941; Laymon and Freeman, 1944). In 1976, the International Society for the Study of Vulvar Disease devised a new classification system unifying the nomenclature and proposed the term *lichen sclerosus* (Friedrich, 1976).

The cause of LS has not been defined. Many mechanisms have been proposed. Koebner phenomenon relates the development of LS to trauma to an affected area (Lee and Phillips, 1994). A proposed mechanism is an autoimmune event. Autoantibodies to extracellular matrix protein 1 (ECM1) were detected in the serum of 67% of patients with LS and only 7% of control subjects, which would imply an autoimmune process (Oyama et al, 2003). Reports of LS associated with vitiligo, alopecia areata, thyroid disease, and diabetes mellitus also suggest a possible autoimmune basis. Reported oxidative damage of lipids, DNA, and protein in patients with LS may explain the mechanism of sclerosis, autoimmunity and carcinogenesis of LS (Sander et al, 2004).

An infectious cause was previously implicated (Tuffanelli, 1987; Ross et al, 1990), but a more recent case-control series found no association (Edmonds and Bunker, 2010). It has also been proposed that LS has a genetic origin, based on the observation of a familial distribution of cases (Marren et al, 1995). There have been reports of concomitant existence of the disease in identical twins (Thomas and Kennedy, 1986; Fallic et al, 1997) and nonidentical twins (Cox et al, 1986), with coexistence of dermatosis. The disease also has been seen in mothers and daughters (Shirer and Ray, 1987). Studies

on the human leukocyte antigen (HLA) have suggested a genetic component in patients with LS (Marren et al, 1995).

The combination of topical steroids and antibiotics may help stabilize the inflammatory process. Conservative therapy may be warranted in patients whose meatus can easily be maintained at 14 to 16 French (Staff, 1970). In these cases, intermittent catheterization with lubrication of the catheter and meatal dilator with 0.05% clobetasol (Temovate) may be adequate treatment. Long-term antibiotic therapy may also be helpful to improve inflammation because secondary infection of the inflamed tissue may occur. We have typically used tetracycline, but a trial of long-term penicillin or advanced-generation erythromycin therapy may be warranted (Shelley et al, 1999). This nonsurgical approach to treatment is used in patients who are not good surgical candidates for other medical reasons or in older patients and in younger patients who demonstrate stable disease. Secrest and colleagues (2008) proposed a link between hypogonadism and LS in male patients. These authors consistently showed diminished testosterone levels in patients with LS and analyzed whether replacement androgen therapy would be helpful.

Surgery is indicated in young patients with severe meatal stenosis. Because patients with long-standing meatal stenosis often have severe proximal urethral stricture disease, retrograde urethrography should be performed before therapy is initiated. A simple meatotomy is generally ineffective in patients with LS. Morey and colleagues (2007) showed that an extended meatotomy in patients with refractory stenosis was successful in 14 of 16 patients (87%). Malone (2004) described a ventral/dorsal meatotomy with an inverted V-shaped relaxing incision with the apex of the V close to the proximal limit of the dorsal meatotomy.

The etiology of stricture disease associated with LS is unclear. Possible causes include iatrogenic stricture resulting from repeated instrumentation and pressure voiding associated with meatal stenosis causing secondary intravasation of urine into the glans Littre (Fig. 40-14). In cases of early LS with only meatal involvement resulting in stenosis of the fossa navicularis, prompt reconstruction seems to be successful in the long-term and seems to avoid the sequelae of panurethral stricture disease. Most surgeons believe that because LS is a disease of genital skin, better tissue for reconstruction is the oral mucosa; techniques are discussed later (Mundy, 1994; Bracka, 1999). Long-standing cases with a long length of urethral stricture are amenable to techniques of reconstruction but are very challenging. It seems that except in the case of urethral stricture disease confined only to the meatus and fossa navicularis, staged oral graft reconstruction, at least in the short-term to mid-term, seems to provide superior durable results. This may also be true in cases confined to the meatus and fossa navicularis because an analysis of patients reconstructed with the ventral transverse skin island technique showed a 50% recurrence rate even in those patients; the weakness of this analysis is that the data did not include biopsy proof that all patients had LS (Virasoro et al, 2007). We also see patients who present with a buried penis. This phenomenon occurs when the skin of the penile shaft has been lost because of severe inflammation, and the penis is trapped in the penopubic and scrotal area. These patients are often profoundly overweight, and many are diabetic; they have often had prior surgical procedures. Management of these patients is complex and ultimately determined by their desire and need for functional reconstruction. In some patients with severe urethral stricture disease, we have completely reconstructed the urethra; in others, we have simply performed a perineal urethrostomy. Perineal urethrostomy is usually technically straightforward because the rule in most patients with LS is to spare the proximal anterior urethra. We have proposed that, in many cases, the sparing of the proximal anterior urethra demonstrates the distribution of the glands of Littre for a given patient. Younger patients have requested mobilization and release of the penis with placement of a split-thickness skin graft. However, because the inflammation involves the glans penis (which is not removed), the secondary inflammation may also involve the skin graft. Lifelong monitoring of these patients for the secondary effects of inflammation is necessary.

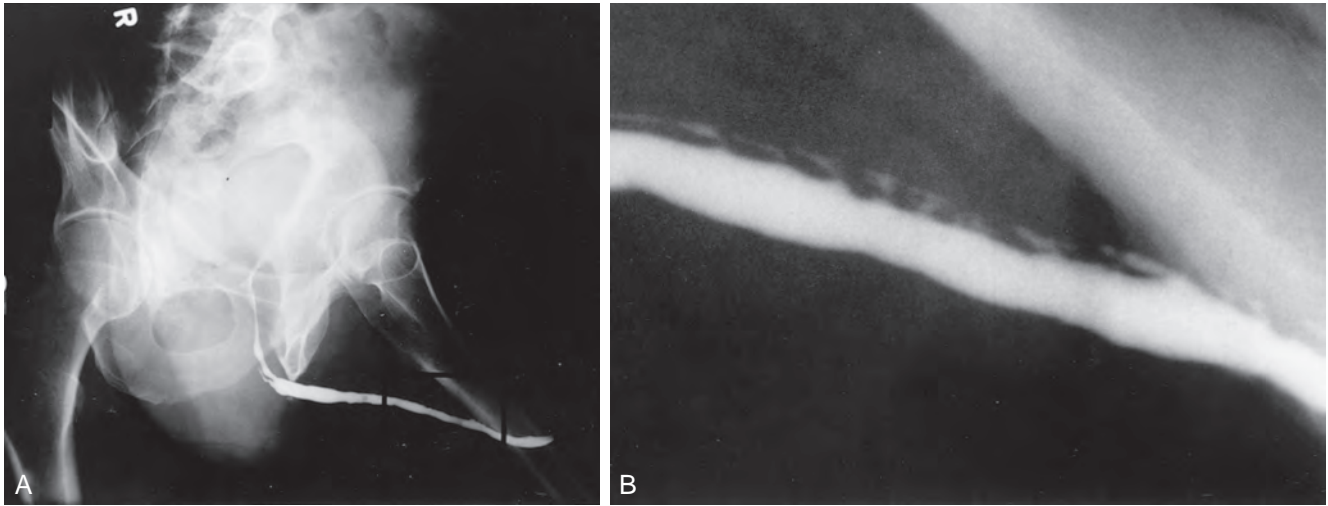


Figure 40-14. A and B, Urethrography in a patient with urethral stricture disease associated with lichen sclerosus. The intravasation of contrast material into the dilated glands of Littre during voiding is illustrated. (From Jordan GH. Management of membranous urethral strictures via the perineal approach. In: McAninch J, Carroll P, Jordan GH, editors. Traumatic and reconstructive urology. Philadelphia: Saunders; 1996.)

Finally, several reports have suggested the development of squamous cell carcinoma in patients with a long history of LS (Doré et al, 1990; Pride et al, 1993).

Amyloidosis

Amyloidosis of the urethra, although a rare disease, should be considered in the evaluation of any patient with a urethral mass. Patients may present with hematuria, dysuria, or urethral obstruction. Because the differential diagnosis includes urethral neoplasm, cystoscopy with transurethral biopsy is indicated. When the diagnosis is made, treatment should be based only on symptoms. Most patients can be observed expectantly and do not require aggressive treatment. Some patients require treatment for urethral stricture. Progression and recurrence are rare (Walzer et al, 1983; Dounis et al, 1985; Crook et al, 2002).

Urethrocutaneous Fistula

A urethrocutaneous fistula is a tract lined with epithelium that leads from the urethra to the skin. The size of a fistula can vary from pinpoint to large. Urethral fistulae may be a complication of urethral surgery or develop secondary to periurethral infection associated with inflammatory strictures or treatment of a urethral growth (condyloma or papillary tumor). Treatment of a urethral fistula must be directed not only to the defect but also to the underlying process that led to its development. Treatment varies according to the cause of the fistula. In cases of urethral reconstruction, especially reconstruction for hypospadias, fistula often occurs or recurs because of distal obstruction and high-pressure voiding. Additionally, in some cases in which multiple attempts at fistula closure have been attempted and failed, the tissues adjacent to the fistula are so scarred that staged reconstruction is needed to import "better tissue."

After urethral surgery, fistulae can develop immediately or as delayed complications. An early fistula is the result of poor local healing, possibly secondary to hematoma, infection, or tension with closure. In addition, breakdown of the urethra or overlying skin closure, or both, could occur. Very occasionally, with aggressive local care and continued urinary diversion, the fistula closes spontaneously.

Several techniques are used for fistula closure. Endoscopic and radiographic evaluation of the urethra must be performed before

the repair in all cases. If the fistula is small and closure of the hole does not decrease the lumen of the urethra, a button of skin is removed from around the fistula, and its edges are cut flush with the urethral wall. The urethra is closed with small (6-0 or 7-0) absorbable sutures, inverting the epithelial edge, and the repair is tested to ensure that it is watertight. We prefer either polyglycolic acid (Vicryl) or polydioxanone suture. Subsequent layers are designed and closed to avoid superimposed suture lines. Without question, the safest diversion is a suprapubic catheter. However, in many cases, a silicone stent that reduces pressure during voiding for 7 to 14 days suffices. The operating microscope can be useful for the closure of small fistulae, allowing the use of 8-0 polyglycolic acid suture and limiting the size of the associated skin incision.

If the fistula is so large that simple closure would compromise the lumen of the urethra, local flaps often are required. However, if the adjacent tissues are thin and poorly visualized, closure of the fistula may become a staged urethral reconstruction as mentioned earlier. For larger fistulae, a suprapubic tube for diversion is probably prudent. Mobilization of flaps, such as the tunica dartos flap, may be necessary to secure adequate tissue interposition and avoidance of superimposed suture lines.

Fistulae associated with inflammatory strictures occur as periurethral tracts and develop secondary to high-pressure voiding of infected urine. As multiple tracts develop, this problem becomes what is known as a "watering pot perineum." Repair requires suprapubic drainage, and treatment of the infection requires incision and drainage of any abscesses present. We widely excise the fistula tracts and associated inflammatory tissue and wait 4 to 6 months before repairing the underlying stricture. Flap reconstruction, if donor tissues are available, may be used. However, a staged graft procedure (discussed later) is also an excellent choice. One must be cautious in a patient with urethral fistulae but without a history of chronic obstructive voiding symptoms. In many cases, fistula or periurethral abscess may be the hallmark symptom of urethral carcinoma.

Urethral Diverticulum

A congenital diverticulum is a transitional cell epithelium-lined pouch that is the result of either a distention of a segment of the urethra or the attachment of a structure to the urethra by a narrow neck (i.e., a müllerian remnant). In male patients, a congenital anterior urethral diverticulum may result from incomplete development of the urethra, with a defect in only the ventral

wall and subsequent distention of this segment by the hydraulic force of the voiding stream (Valdivia et al, 1986; Bedos and Cibert, 1989; Ozgok et al, 1994). The downstream lip of the defect may serve as a valvular obstruction, increasing the pressure in the lumen, and subsequently the diverticulum enlarges. **Another possible etiology is injury of the urethra, which may cause an intraspongiosal hematoma.** This hematoma could create a paraurethral space and subsequent diverticulum or fistula. These defects can also be associated with urethral strictures (Bryden and Gough, 1999). It has also been suggested that congenital diverticula may represent giant cystic dilation of Cowper ducts (Gil-Vernet, 1977; Jiminez Cruz and Rioja Sanz, 1993). We do not favor this proposed suggested etiology because the diverticula seem to be slightly more distal than the expected location of Cowper ducts, and in our experience with reconstruction of a considerable number of these diverticula, no proximal limb of the ducts seems to exist in them. In many cases, endoscopic unroofing of the diverticulum remedies the voiding symptoms; although after unroofing, the patient commonly may note postvoid dribbling. Open repair essentially excises the redundancy of the urethra associated with the diverticulum. If the lumen is compromised, dorsal onlay by either graft or flap can be useful.

A congenital diverticulum in the prostatic urethra may be a large remnant of the müllerian duct associated with defects of diminished virilization. However, it often occurs in proximal hypospadias and represents an enlarged utricle (Devine et al, 1980). These diverticula may not be demonstrated with voiding urethrography but are demonstrated with cystoscopy or retrograde urethrography. The tip of a urethral catheter tends to catch in this opening, necessitating the use of something to direct the catheter tip toward the true lumen. Other than necessitating caution during evaluation, these diverticula do not usually cause problems or require treatment unless they are very large.

Large utricles can accumulate urine with voiding and then decompress after voiding. If they are large enough, the stasis of urine can be associated with recurrent urinary tract infection or difficult-to-manage "incontinence." A surgical approach to small lesions can be through a suprapubic incision, possibly opening the bladder to go through the center of the trigone. However, large diverticula can be approached trans-sacally (Peña and Devries, 1982). Although this is a complex procedure, it seems to be associated with much less morbidity than an abdominal or a perineal approach and provides superior exposure. We excise the diverticulum after exposing and dissecting its communication with the urethra. After ensuring that there is no distal obstruction to interfere with healing, we close the urethra.

Diverticula of the female urethra are covered in Chapter 90.

Paraphimosis, Balanitis, and Phimosis

Paraphimosis, or painful swelling of the foreskin distal to a phimotic ring, occurs if the foreskin remains retracted for a prolonged time. Swelling is sufficient to make reduction of the foreskin over the glans difficult. **In a very young child, paraphimosis is often seen after the foreskin has been traumatically reduced during an examination or sometimes by overzealous parental attempts at hygiene.** Traumatic, sudden reduction of a tight foreskin should be avoided in all ages and circumstances. To reduce a paraphimosis, gentle steady pressure must be applied to the foreskin to decrease the swelling; with a child, this is best accomplished in a quiet room by a parent squeezing it in the hand. Elastic wrap may be helpful in some cases. Putting an ice pack on the area for a short time before gentle compression is helpful as an analgesic. When the swelling has been reduced, the surgeon can push against the glans with the thumbs, pulling on the foreskin with the fingers. Because paraphimosis tends to recur, a dorsal slit at a minimum or a circumcision should be carried out as an elective procedure at a later date. An occasional patient presents with acute paraphimosis that has been present for many hours to days; this is typically seen in an adolescent who is reluctant to reveal the problem to his parents. In these cases, reduction may be impossible, and paraphi-

mosis should be dealt with by emergency dorsal slit or circumcision. Considerable postoperative edema is the rule in these cases.

Balanitis, or inflammation of the glans, can occur as a result of poor hygiene, from failure to retract and clean under the foreskin. The subsequent swelling makes cleaning more difficult, but the inflammation usually responds to local care and antibiotic ointment. Oral antibiotic therapy occasionally may be necessary. Balanoposthitis is a severe form of balanitis and occurs when the phimotic band is tight enough to retain inflammatory secretions, creating what amounts to a preputial cavity abscess. Occasionally, an emergent dorsal slit is required.

Phimosis, or the inability to retract the foreskin, can result from repeated episodes of balanitis. In older patients, balanitis may be a presenting sign of diabetes. In these cases, circumcision may be warranted.

Urethral Meatal Stenosis

A small urethral meatus in a newborn probably would not be called to a urologist's attention unless the stenosis is associated with other congenital deformities (e.g., hypospadias) or causes voiding difficulties or urinary tract infection (Allen and Summers, 1974). If the urethral meatus of a boy appears exceptionally narrow and there are associated symptoms, a meatotomy should be considered. For this decision to be made, voiding should be observed to note that the meatus opens as a full, forceful stream is passed. If the stream is narrow and excessively forceful, stenosis is probably present. The occluding skin is generally a thin layer that sometimes can be seen to pouch out, with the meatus opening at the dorsal lip as the child voids. **Meatal stenosis in a boy appears to be a consequence of circumcision that then allows subsequent ammoniacal meatitis.** If the child is seen with ammoniacal meatitis, we usually start meatal dilation with 0.05% clobetasol cream. Within a week, the process seems to abate. Anecdotally, the fusion of the ventral-meatal skin that causes meatal stenosis can be avoided. Parents must be counseled about the cause—that is, a wet diaper pressing for prolonged periods against the tip of the glans.

A ventral urethral meatotomy sometimes can be accomplished with the use of local anesthesia. In a young child, general anesthesia is the preferred approach, avoiding trauma to the child, the parents, and the urologist. It is important to insert the anesthetic needle into the skin fold from the underside so that the tip of the needle can be observed and controlled. If insertion is done from the outside, the needle passes through both layers of the fold, and a wheal cannot be raised because of leakage of the anesthetic solution. After the meatotomy, the edges of the cut seal together unless they are kept open. The tip of a meatal dilator is the best instrument for this purpose. The child's parents are instructed to separate the edges gently with the tip of the dilator three times a day for 7 to 10 days. The surgeon should observe the parents carry out this procedure. Pediatric meatal dilators (see later product reference) are available; however, the tip of an ophthalmic antibiotic tube also works well, and the antibiotic ointment can be used as the lubricant.

Meatal stenosis occurs in adults after inflammation, specific or nonspecific urethral infection, and trauma (especially in association with indwelling catheters, urethral instrumentation, or radical prostatectomy in some cases). It also may be the result of the failure of a previous hypospadias repair. To perform a ventral meatotomy in a normally developed penis in adolescents and adults, it is often necessary to place sutures to approximate the urethral mucosal edge to control bleeding. This step usually requires three sutures: one at the apex and one on either side. We have found a dilator made by Cook Urological (Spencer, IN; Catalog No. 073406, adult 6 to 34 French; No. 073403, pediatric 6 to 10 French) to be helpful in keeping the meatus open. In some cases, it may be necessary to perform a dorsal rather than a ventral meatotomy. This procedure can be accomplished as a Y-V-plasty after the excision of any scarred ridge of neourethra. Dorsal meatotomy, although effective in opening the meatus, often creates a cosmetically suboptimal shape of the meatus. In an adult, it is unusual for the meatal stenosis to

be an isolated finding. The stricture process usually involves the fossa navicularis to some extent as well.

Circumcision

Controversy continues regarding whether neonatal circumcision should or should not be performed (Poland, 1990; Schoen, 1990). Much attention has been focused on this issue, but despite this, many boys in the United States are circumcised. Ritual circumcision will continue; however, in ritual circumcision, it is not necessary to remove the skin but only to draw blood. **It is important not to circumcise any boy with a penile abnormality (e.g., hypospadias, chordee) that may require the foreskin during repair. Circumcision is indicated in a young boy who has had recurrent urinary tract infections thought to be associated with the redundant preputial skin.**

Most circumcisions performed just after birth are done with the Gomco clamp or one of the plastic disposable devices made for this purpose. Care should be taken to free the foreskin from the glans completely and to apply appropriate tension when the foreskin is pulled into the clamp. To prevent either a too generous or an inadequate circumcision, we find it useful to mark the foreskin carefully so that the correct level is ascertained. At our center, we perform neonatal circumcision with a penile block for anesthesia.

The most common complication is bleeding as a result of inadequate control with vascular compression. Application of an epinephrine-soaked sponge may help in controlling minimal venous bleeding. Infection can also occur and responds to local care. Any resulting skin separation should be repaired after the inflammation resolves. Minimal separation may be amenable to healing by secondary intention. Sometimes too much skin is removed, or the urethra is included in the clamp, resulting in a fistula. In many, if not most, cases in which excess skin is removed, closure can still be accomplished with aggressive frenuloplasty along with remaining skin closure by transposition of the remaining skin. If the entire penis is "scalped," it may be best managed with a split-thickness skin graft or with reapplication of the excised foreskin, after it is prepared properly as a graft. In complicated cases, burying the penis in the scrotum and repairing it at a later date may be prudent. **Monopolar electrocautery should be avoided in a neonatal circumcision because penile loss from the field distribution of the current can occur. The use of monopolar cautery with a Gomco or similar clamping device must be avoided because devastating loss of tissue can occur.**

A newborn who lost his penis because of a circumcision mishap should not be gender reassigned. Our experience with phallic construction includes many children and youths who had been converted to a female after a circumcision accident. As they passed through puberty, they realized that this sexual assignment was wrong. Most of these boys could undergo reconstruction in such a manner as to preserve reproductive function.

In adults, circumcision can be done with local anesthesia, by blocking the dorsal nerves at the base of the penis and circumferentially infiltrating the superficial layers of the penile base. In men and older boys, we favor a sleeve circumcision. With the foreskin in its retracted position, a marking pen outlines an incision, leaving a small preputial cuff. This mark should go straight across the base of the frenulum. This incision is made and carried through the dartos fascia to the superficial lamina of the Buck fascia. The foreskin is reduced, and a second incision is marked, following the outlines of the coronal margin and the V of the frenulum on the ventral side. The frenulum usually retracts into a V. In some cases, the frenulum can be lengthened by closing the edges of the V in a longitudinal orientation for a short length (frenuloplasty). If frenuloplasty is done, the proximal incision does not need to follow the V of the retracted frenulum because the ventral skin is straight. We make the skin incision and fulgurate bleeding vessels with bipolar cautery as the incision is deepened and the skin edge is mobilized. In older boys and men, the vessels are more substantial and not easily sealed by compression, no matter how vigorous. Circumcision clamps can be ineffective and are not recommended even

though larger sizes are available. After the sleeve of preputial skin has been removed, hemostasis is obtained, and the skin edges are reapproximated.

In younger boys, some surgeons may consider this sleeve procedure to be tedious and difficult. If this is the case, after the skin is marked, a dorsal slit is made through both layers of the prepuce back to the level of the corona. Following the marks, the two layers of the preputial skin are incised. Bleeders are controlled, and the skin edges are reapproximated.

Complications should be uncommon. Most patients develop some hyperesthesia of the glans, which resolves. A hematoma is probably the most common immediate complication. Some patients notice minor cosmetic imperfections that are functionally insignificant. One of the most distressing problems we see is a patient who complains that the surgeon has removed too much skin. To avoid this occurrence, a circumcision should be done precisely, and, whatever the procedure to be carried out, the incisions should first be marked with the skin lying undistorted on the shaft. Adults requesting circumcision must be carefully evaluated from a psychosexual standpoint because many of these patients who are the most persistent in requesting circumcision become the most dissatisfied after the surgery.

Circumcision has been shown in numerous studies to provide protection for men in areas where human immunodeficiency virus (HIV) is very prevalent (Auvert et al, 2005; Bailey et al, 2007; Gray et al, 2007). Circumcision has consistently been shown in well-conducted randomized controlled trials to reduce the risk of HIV acquisition in heterosexual African men by 50% to 60%. Similar prospective trials have not been performed in developed countries; however, retrospective data among heterosexual men in the United States showed a similar approximately 50% reduction in HIV prevalence among men with known exposure, suggesting the data may be extrapolated to this population. Additionally, male circumcision has been shown to reduce the risk for acquisition of herpes simplex virus type 2, human papillomavirus, genital ulcer disease, and some sexually transmitted bacterial infections (Tobian et al, 2014).

There is a biologic rationale for reduction in the spread of sexually transmitted infections, particularly HIV, with circumcision. Superficial Langerhans cells, CD4⁺ T cells, and CD8⁺ T cells are rich and less well protected by keratin on the inner aspect of the male foreskin and frenulum. When the foreskin is retracted during intercourse, this large and susceptible surface area is exposed allowing contact with HIV-infected secretions and subsequent risk for infection. Uncircumcised men have also been shown to have an increased frequency of genital ulcers and increased frequency of microtears during intercourse, both of which increase HIV transmission.

Despite the well-demonstrated benefit of circumcision in heterosexual men, the same benefit has not been shown for men who have sex with men (MSM). A large meta-analysis of more than 53,000 MSM did not demonstrate a statistically significant protection against HIV (Millett et al, 2008). Subgroup analysis demonstrated a trend toward reduced prevalence of HIV among MSM performing predominantly insertive rather than receptive anal intercourse, and others have corroborated these findings.

Failed Hypospadias Repair

In treating a patient in whom hypospadias repair has failed, it is important to obtain all available records to help determine what may have contributed to his complications. **A hypospadias repair may fail because of an inadequate correction of chordee or an inadequate urethra, with a stricture, fistula, or diverticulum (Winslow et al, 1986). It is often readily apparent from the records that not all aspects of the hypospadias deformity (i.e., ventrally displaced meatus, ventral chordee, and some expression of inadequacy of ventral tissue fusion) were addressed in the previous repairs.** Adults with urethral strictures are often seen who have had hypospadias surgery as children. Depending on the age of the patient and the preference of the treating urologist, a variety of different techniques may have been used to repair the original hypospadias. Many of these patients have persistent chordee and a

subcoronal meatus. Adults also have been seen who have had long-standing evidence of urethral fistula. In addition, some patients may have clinical findings not related to hypospadias that should have been recognized previously, especially when hypospadias is part of an overlying intersex problem. In the past, problems associated with previous failures were caused by errors in design, technique, or postoperative care (Devine et al, 1978). With more modern techniques available and with most hypospadias treated by surgeons with considerable experience, failures seem to be associated with perioperative infections or other factors that adversely affect wound healing. At the present time, complex hypospadias repair failures are encountered with much less frequency, and most that are encountered are in patients who had previous procedures more than 15 to 20 years ago. Complications in these patients resulted not from poorly designed surgery at the time but rather from the “state of the art” at the time.

Evaluation of a failed hypospadias repair includes retrograde urethrography, voiding cystourethrography, and cystoscopy. In an older patient, a reliable preoperative assessment of residual chordee can be made on the basis of the history and photographs taken at home. In younger patients, complete evaluation of more complex situations with use of anesthesia may be necessary.

In an adult patient, a detailed discussion must occur regarding the positive and negative aspects of the various approaches. Patients who were initially operated on before the late 1970s probably underwent either a graft or some form of repair using almost exclusively ventral tissue. Some of these patients still have the remnants of a dorsal hood or enough dorsal skin for a dorsal transverse penile skin island type of reconstruction to be performed.

We believe that surgical correction of complex cases requires an aggressive approach by the surgeon (Secrest et al, 1993). However, with the advent and very common usage of the tubed incised plate repair, initially described by Snodgrass (1999), the nature of failures is different, and the approaches also are remarkably different. Based on our observations, the number of failed surgeries is less, the nature of graft salvage techniques is remarkably different, and the method of addressing residual curvature is different. It is possible to reincise the “urethral plate” and tubularize it if the plate is not scarred and possible to graft the plate dorsally if it is; if the tissues are badly scarred, many surgeons revert to staged reconstruction (Snodgrass et al, 2009). The use of flaps has a place in corrective procedures, and the excision of scarred tissues causing residual curvature likewise has its place. However, plication or corporoplasty techniques for correction of residual curvature have, for the most part, become the standard of care. Graft techniques for correction of curvature are used but with far less frequency than in years past.

Residual Genital Abnormality in Patients with Closed or Diverted Exstrophy

Residual genital defects in men who have had exstrophy repaired as children can cause functional, aesthetic, and psychologic problems. The effects of these problems are compounded in men who have undergone urinary diversion and who must wear stomal appliances, although with the improvement of continent diversions, this is less of a factor. Successful reconstruction is possible except in the most severe forms of bladder exstrophy or cloacal exstrophy—when the penis or the halves of the bifid penis are truly inadequate. Even then, if normal testes are present, the success of newer techniques of phallic construction (see subsequent discussion) should lend support to considering the option of raising such a child as a boy, possibly preserving his reproductive potential through puberty. In these very difficult cases, we think that the parents must be presented with both options, gender reassignment versus eventual phalloplasty. Remarkable progress has been made in the treatment of difficult cases (Johnston, 1975; Hendren, 1979; Jeffs, 1979; Snyder, 1990; Perovic et al, 1992; Gearhart et al, 1994; Mitchell and Bagli, 1996) and in techniques of primary closure. However, many patients need further genital surgery because they

experience the hypertrophic growth spurt of the penis associated with puberty.

The goals of reconstructive surgery in male patients with exstrophy or epispadias are to produce a dangling penis with erectile bodies of satisfactory length and shape to allow sexual function and to construct a urethra that serves as a conduit for the passage of urine and ejaculate. However, experience has shown that in a patient with a diverted exstrophy and only a bladder remnant, construction of a urethra that is essentially defunctionalized is difficult. These urethras all eventually seem to fibrose and stenose. The bladder neck remnant becomes a cyst that is often colonized. Bouts of virulent epididymitis or the formation of what is really a bladder neck remnant abscess begin to occur. We have seen two patients who developed carcinoma of the prostate in a bladder neck remnant. The diagnosis in these patients was difficult, and the resultant surgery was even more difficult. Neither patient did well from the standpoint of treatment of the carcinoma. Both were seen before the aggressive use and better understanding of prostate-specific antigen.

Many patients who have undergone surgery as children do not present for correction of inadequacies of the external genitalia until after they have completed puberty and realize that their situation has not improved and is not likely to improve. Some have been in sexual situations and have encountered problems. We employ a systematic approach to accomplishing the reconstruction necessary to correct the anatomic defects in these patients (Devine et al, 1980; Winslow et al, 1988). Surgery is undertaken in a sequential fashion beginning with the simplest procedure that would achieve the desired functional result.

Lower abdominal wall scarring can be corrected or defects can be closed by fashioning peripenile flaps that are shaped like a W. In many patients, there may be wide diastasis recti that is really a ventral hernia. Anchoring of meshes or Gore-Tex can be difficult, and we have resorted to a fibular bone microvascular free transfer in several cases to reconstruct the continuity of the pubis, allowing effective closure of the abdominal hernia.

With more effective contemporary primary closure techniques, the adult reconstructive surgeon's place is primarily in the correction of hernia, or in the patient who has an inadequate penis either due to deformity, scarring, or improper gender reassignment.

TRAUMA TO THE GENITALIA

This topic is primarily covered in Chapter 101, but an additional description is included in the electronic version of this chapter. Please see the Expert Consult website for this section and Figure 40-15.

URETHRAL STRICTURE DISEASE

The term *urethral stricture* refers to anterior urethral disease, or a scarring process involving the urethral epithelium or spongy erectile tissue of the corpus spongiosum (spongiofibrosis) (Fig. 40-16). The spongy erectile tissue of the corpus spongiosum underlies the urethral epithelium, and the scarring process extends through the tissues of the corpus spongiosum in some cases and into adjacent tissues. **Contraction of this scar reduces the urethral lumen.** For example, if a normal urethra measures 30 Fr, its diameter is 10 mm, and the area of the lumen is approximately 78 mm². If scarring has resulted in a urethra that measures 15 Fr, the lumen is only 55 mm², or 29% reduced. It is evident that scar contraction caused by anterior urethral stricture disease can be asymptomatic for a while, but because the lumen is further reduced, it can be associated with marked voiding symptoms.

In contrast, posterior urethral “strictures” are not included in the common definition of urethral stricture. Posterior urethral stricture is an obliterative process in the posterior urethra that has resulted in fibrosis and is generally the effect of distraction in that area caused by either trauma or radical prostatectomy. Although the distraction defect can be lengthy in some cases, the

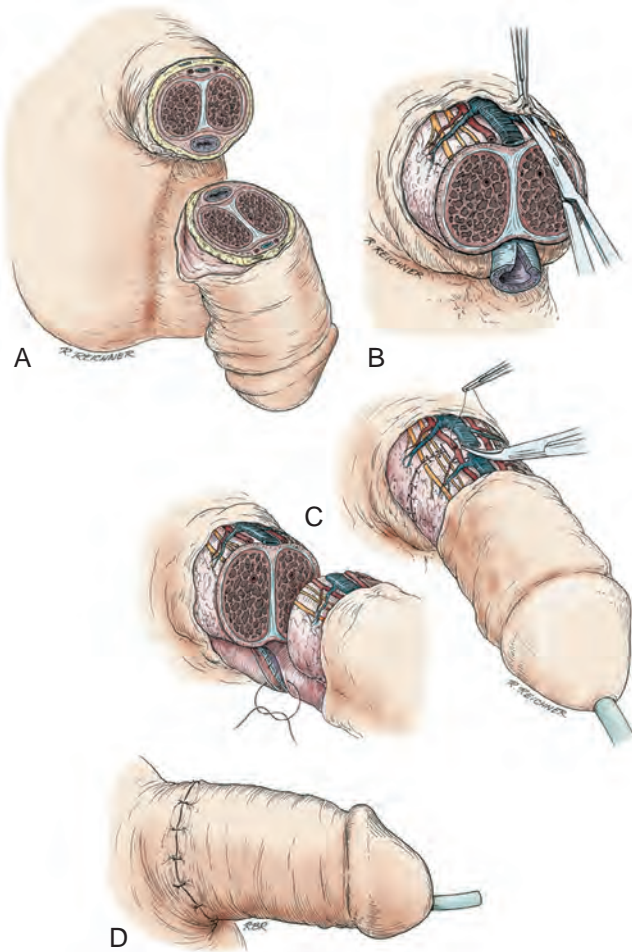


Figure 40-15. Technique of microscopic replantation after amputation of the penis. **A**, The typical appearance of a penile amputation injury. **B**, The urethra, corpora cavernosa, and dorsal neurovascular structures are exposed and minimally debrided. **C**, A two-layer spatulated urethral anastomosis is completed. Microvascular coaptation of the dorsal vein, dorsal artery, and dorsal nerves is accomplished. **D**, Coverage is accomplished with the native skin. If the patient is circumcised, the sleeve of skin between the amputation injury and the old circumcision scar should not be discarded. Should chronic edema develop, revision can be accomplished at a later date. Diversion is by way of a suprapubic cystostomy tube. A stent is inserted in the reconstructed urethra. (From Jordan GH, Gilbert DA. Management of amputation injuries of the male genitalia. *Urol Clin North Am* 1989;16:359–67.)

Penetrating Trauma to the Penis

Penetrating injuries of the penis can involve the urethra, the corporeal bodies, or both. Our choice in managing the acute injury is exploration and attempted immediate anatomic repair, perhaps placing a suprapubic tube should extensive urethral reconstruction be required. With bullet trauma, the velocity and the construction of the projectile are important factors. Small, “slow”-bullet injuries of the urethra can be successfully reconstructed primarily; however, larger, high-velocity wounds may require diversion and delayed reconstruction. Some projectiles are designed to fragment and, even if “low velocity,” can cause considerable adjacent tissue damage. Later reconstruction is directed at urethral stricture (if it occurs after the initial injury), or there is curvature of the penis secondary to damage of the corporeal bodies, or both are present. Fistulae that result from penetrating trauma to the penis are usually treatable by primary closure with interposition of superficial tissue layers between the urethra and the skin. Large fistulae may require more

complex tissue transfer and, in many ways, become more of a problem of urethral reconstruction as for stricture. The principles are discussed elsewhere in the chapter. Because of recent military actions, in which injury is due to blasts with shrapnel and high-velocity nonfragmenting projectiles, thinking on mechanisms surrounding penetrating trauma has been redefined. For example, high-velocity projectiles can truly penetrate peripheral structures with little cavitation effect, not the effect previously noted with wounds to the abdomen and chest.

Amputation of the Penis

Amputation is the ultimate penetrating penile injury. If the patient presents acutely with the amputated distal part of his penis, microvascular replantation is the favored approach (Fig. 40-15). If there is no microvascular surgeon at the center where the patient presents, he should be transferred. The amputated portion of the penis should be cleaned, wrapped in a sponge soaked in sterile saline, and placed in a sterile zipper-sealed plastic bag. The amputated penis is kept in ice slush, and replantation can be accomplished 18 to 24 hours after amputation. Often, the amputation is self-inflicted, usually during an acute psychotic break. This situation should not preclude replantation unless the patient adamantly refuses such treatment. Even then, with a court order or the agreement of two or more surgeons, replantation may be undertaken. Current legal opinion regarding a patient’s right of refusal is unhelpful in clarifying circumstances in which a patient refuses treatment but may not really be capable of true informed consent. Applying for a court order may be the safest method for obtaining consent. The patient’s condition or other circumstances may prevent his transfer for microvascular replantation. If so, replantation by the technique described by McRoberts and colleagues (1968) should be carried out. This and other series show that a high degree of success can be expected after replantation without microvascular reanastomosis (Chapple et al, 2004; Morey et al, 2004).

If the patient presents with the distal part having been disposed, or otherwise unavailable, the wound should be closed. The penis has often been stretched out during the amputation, and an excess of skin has been removed, leaving a length of intact but denuded shaft structures proximal to the amputation wound. We close the corporeal bodies with 4-0 or 5-0 polydioxanone suture, widely spatulate the urethral meatus, and immediately cover the penile shaft with a split-thickness skin graft. Other surgeons bury the shaft beneath the skin of the scrotum. In some of these patients, primary grafting of the stump allows a functional penis. However, many patients require phallic construction or penile reconstruction later.

Many sophisticated techniques for reconstruction of the traumatized penis are available. Forearm flaps have become the mainstay of penile reconstructive procedures (see subsequent discussion). The initial stage of reconstruction of the amputated penis consists of mobilization of the penile and urethral stumps.

Degloving Injuries of the Penis

Degloving injuries occur when the skin of the penis or scrotum is trapped and stripped from the deeper structures, exposing the uninjured corpora cavernosa and the testes. The tear is deep to the elastic dartos fascia. Bleeding is usually not a problem because there are not many large vessels in this space. However, the appearance of the “bare” testes and penile shaft is impressive.

When the patient presents, the wounds should be dressed in sterile saline-soaked bandages. A delay of approximately 24 hours is sufficient to define the extent of the damage. Most degloving injuries can be managed acutely with immediate reconstruction by the application of split-thickness skin grafts. The shaft is covered with a sheet graft of split-thickness skin. The testes are sutured together in the midline, fixed in their anatomic correct position, and covered with a meshed split-thickness skin graft. In the acute trauma situation, we have had good success with acute grafting and have not required temporary skin substitutes to prepare the graft bed. The parietal tunica vaginalis is opened, and the graft is placed

directly on the testes. After take of this graft, the meshing gives the appearance of rugae. With time, the effect of gravity on the testes causes the reconstructed scrotum to become pendulous and sometimes even redundant. In this repair, split-thickness skin grafts are more successful than full-thickness skin grafts because the host bed is suboptimal after a degloving injury. Although split-thickness grafts cannot be employed for single-stage urethroplasty because of contraction, contraction has not been a problem with such grafts applied to the penile shaft or testes. Adequate shaft sensation is achieved by means of the deep structures beneath the graft. Should the testis be avulsed as part of the injury, replantation is usually not an option because the process of stretching of the vessels before breaking leads to an unpredictable intimal injury.

Some surgeons bury the shaft of the penis in a subcutaneous tunnel on the abdomen and bury the testes in subcutaneous thigh pouches. McDougal (1983) described a technique to mobilize the buried testes with the overlying thigh skin, combining scrotal reconstruction with testicular replacement; this is a good way of transposing the testes and overlying tissues to an anatomically correct location. When we have managed patients who have been previously treated acutely with the placement of the testes and penis in subcutaneous tunnels, we have mobilized the testes and the penile shaft from their tunnels and immediately applied grafts of split-thickness skin, as already discussed (Morey et al, 2004).

Genital Burns

The ability to reconstruct the damage caused by genital burns often depends on how well the normal structures have been maintained after the acute injury. Careful debridement is the rule in acute management of genital burns. Corporeal tissue cannot be replaced with transferred tissue. The physiologic functions of genital tissues cannot be accurately duplicated. The unique vascularity of genital tissue allows less aggressive rather than more aggressive debridement.

Devastating urethral injuries occur with many burns. Reconstruction of the urethra depends on the nature of the injuries. When the urethra has been nearly obliterated, there usually is insufficient uninvolved, nonhirsute local genital tissue that can be transferred for urethral reconstruction. Vascularized tissue must be imported to support reconstruction of the urethra with graft techniques. In many patients, the penis has become incarcerated in contracted scar tissue after the acute injury is healed. Successful transposition of a gracilis musculocutaneous flap introduces compliant vascular tissue and skin into the area, allowing release of the penile shaft. Subsequently, the penile shaft can be covered with a split-thickness skin graft. In some patients, the genital scarring is so severe that microvascular transfer of a free flap is necessary to replace the penile shaft.

For many patients, reconstruction requires numerous stages. In several of our patients, the urethra was obliterated literally from the entry of the membranous urethra into the bulbospongiosus to the tip of the penis. A perineal urethrostomy was required while transfer of vascular tissues to the area of the perineum and penis was accomplished. When these tissues are in place, subsequent reconstruction of the urethra can be undertaken with meshed split-thickness skin grafts or buccal mucosal grafts. For coverage of large perineal or groin defects, the posterior thigh flap offers excellent bulky, sensate tissue.

Radiation Trauma

Radiation trauma to the penis occurs in two subsets of patients: patients in whom radiation has been used therapeutically for a

lesion on the penis and patients in whom radiation to the pelvis has caused chronic lymphedema. Therapeutic radiation can produce chronic suppurative gangrene. In most cases, these lesions are not amenable to reconstruction and are best managed by partial penectomy and later reconstruction, when the patient is proved to be cancer free. Also, we have treated several patients who developed tissue atrophy and further fibrosis after radiation therapy for Peyronie disease. Delivered at near-tumoricidal doses, this radiation made dermal graft repair much more difficult.

In patients who have had pelvic irradiation, the genitalia usually have one or more of the following: lymphedema, cellulitis, weeping of fluid, or lymphangiectasia. If cellulitis is part of the problem, prolonged treatment (i.e., for months) should be considered before reconstruction. We have had several patients with recurrent cellulitis who had prolonged antibiotic therapy (we use ciprofloxacin); not only did their cellulitis become quiescent, but also the lymphedema resolved significantly.

The genitalia of patients with lymphedema can be readily reconstructed. Lymphedema of the penis involves the tissues of the dartos fascia and the dermal layer of the skin. In the penis, the lymphedematous tissue can be excised by removing the dartos fascia and skin, dissecting in the layer immediately superficial to Buck fascia. In the scrotum, Colles fascia–tunica dartos and skin of the scrotum must be removed. When the lymphedematous tissue has been excised, the testes are free, and, as in a degloving injury, they must be fixed in the midline in an anatomically correct position. The scrotal skin peripheral to the edema is often normal and can be advanced to cover the testes. The shaft of the penis should be covered with a split-thickness skin graft. If the scrotum cannot be closed, a meshed split-thickness skin graft is used to cover the testes, as described previously. Grafts provide optimal reconstruction in these patients. These patients commonly have hydroceles; the parietal tunica vaginalis must be excised, and grafting can be done directly onto the visceral tunica vaginalis of the testes. If there are hydroceles, the process often is “systemic” and not local. In these cases, reconstruction using the lateral scrotal skin is seldom effective. In contrast to a full-thickness skin graft, split-thickness skin carries little of the reticular dermis and few of the lymphatic channels. Reaccumulation of lymphedema occurs within a full-thickness skin graft and can recur in a thick split-thickness graft. Local skin flaps should be avoided as previously mentioned. They often reaccumulate lymphedema when they have been transposed to the area of the genitalia. As previously noted, grafts do not develop sensation. However, good sensation usually develops, derived from the deep structures. The glans almost never accumulates disabling edema, and the sensation of the glans remains intact because the lymphedematous tissue has been excised in the plane superficial to Buck fascia, sparing the dorsal nerves of the penis. In many cases of genital lymphedema, the posterior scrotum and the lateral scrotal wall are spared from the edematous process; in these cases, the bulk of the scrotum is excised, and closure is accomplished with use of the posterior and lateral scrotum. If the edematous process also involves the lower extremities, it is best to reconstruct the scrotum with a graft as opposed to the local tissues.

Direct radiation to the penis can cause urethral injury. However, it is unusual for the urethra to be injured without damage to adjacent structures. Often, because of the vascularity of the corpus spongiosum, minimal debridement can be accomplished, leaving the patient with a fistula that can be reconstructed at a later date. The success of such reconstruction depends on the damage that the radiation has done to the adjacent structures.

KEY POINTS: TRAUMA TO THE GENITALIA

- Penetrating injuries to the penis can involve the urethra, the corporeal bodies, or both.
- With regard to bullet injuries of the urethra, the velocity of the projectile must be considered. However, recent military actions have shown that high-speed projectiles can pass through superficial structures with relatively little cavitation effect and less propagation of energy to the adjacent tissues.
- If the patient presents acutely with the amputated distal part of his penis, microvascular replantation is the favored approach. If the patient's condition or other circumstances prevent his transfer for microvascular replantation, replantation by the technique described by McRoberts should be carried out and can yield excellent results.
- Degloving injuries to the penis occur when the penis or scrotal skin is trapped and stripped from the deeper structures. Bleeding is usually not a problem. The tissues must be allowed to demarcate; acute reconstruction with grafts can be done.
- The damage caused by genital burns depends on how well the normal structures have been maintained after the acute injury. The unique vascular qualities of the penis allow careful repeated debridement as opposed to aggressive debridement.
- Radiation trauma to the penis occurs in two potential subsets: patients in whom radiation has been used therapeutically for a lesion on the penis and patients in whom radiation to the pelvis has caused chronic lymphedema. A patient with genital lymphedema can readily undergo reconstruction with either a split-thickness skin graft or, in select cases, the lateral margins and the posterior margins of the scrotum.

KEY POINTS: SELECTED PROCESSES

- Urethral hemangioma is a rare condition that is usually persistent. It can present a significant challenge to the surgeon. All reported cases of urethral hemangioma have been benign, and management depends on the size and location of the lesion.
- Reactive arthritis is characterized by a classic triad of arthritis, conjunctivitis, and urethritis. Urethral involvement is usually mild, self-limited, and a minor portion of the disease.
- LS previously was referred to as balanitis xerotica obliterans. Diagnosis is made through biopsy. LS is thought to be possibly premalignant for the development of squamous cell carcinoma of the glans. It is the most common cause of meatal stenosis. Management of patients with LS-related stricture is complex, and results to date are suboptimal. The management is determined by the desire of the patient and the need for functional reconstruction.
- Amyloidosis is a rare disease of the urethra and should be considered in the evaluation of any patient with a urethral mass. Patients present with hematuria, dysuria, or urethral obstruction.
- A urethrocutaneous fistula is a tract lined with epithelium that leads from the urethra to the skin. It may be a complication of urethral surgery or develop secondary to periurethral infection associated with inflammatory strictures or treatment of a urethral growth. Treatment of the urethral fistula must be directed not only to the defect but also to the underlying process that led to its development.
- A congenital urethral diverticulum is a transitional cell epithelium-lined pouch that is the result of either a distention of a segment of the urethra or the attachment of a structure to the urethra by a narrow neck. In male patients, "congenital" anterior urethral diverticulum may result from incomplete development of the urethra or possibly may be the result of straddle trauma that led to an intracorporeal spongiosal hematoma. Congenital diverticulum in the prostatic urethra is a remnant of the müllerian duct.
- Paraphimosis is a painful swelling of the foreskin distal to a phimotic ring. It occurs when the foreskin has been retracted and not reduced. Edema forms in the distal skin.
- Urethral meatal stenosis in a young boy appears to be a consequence of circumcision. The circumcision allows the development of ammoniacal meatitis, which can heal with a membrane across the ventral portion of the meatus. Controversy continues regarding whether neonatal circumcision should or should not be performed. If it is going to be performed, the circumcision needs to be adequate. The most common complication of neonatal circumcision, in our opinion, is when it is inadequately done.
- A patient with failed hypospadias repair can be complex. Many are victims of the technology of the time when they had their initial reconstruction. All patients with urethral involvement should be evaluated as if they have urethral stricture disease.
- Advanced techniques for the reconstruction of the exstrophy-epispadias complex have led to much better functional results and less need for secondary exstrophy reconstruction. Secondary exstrophy reconstruction is aimed at the area of the escutcheon, the dorsal base of the penis, the penile shaft, the urethra, and the penoscrotal junction.

actual process involving the tissues of the urethra is usually confined. By consensus of the World Health Organization conference, the term *stricture* is limited to the anterior urethra. Distraction defects are processes of the membranous urethra associated with pelvic fracture. Other narrowings of the posterior urethra are termed *urethral contractures* or *stenoses* (Bhargava et al, 2004).

Urethral Anatomy

Although urethral anatomy is described in the earlier section on anatomy, it is useful to re-emphasize key anatomic points. The **bulbous urethra is eccentrically placed in relation to the corpus spongiosum and is much closer to the dorsum of the penile structures** (see Fig. 40-6). As one moves distally, the pendulous or penile urethra becomes more centrally placed within the corpus spongiosum.

The genital skin has a dual (proximal and distal) and bilateral blood supply, forming a fasciocutaneous system (see Fig. 40-10). The corpus spongiosum receives blood from the common penile artery, the terminal branch of the internal pudendal artery (see Fig. 40-12). The corpus spongiosum also has a dual blood supply—a proximal blood supply and a retrograde blood supply through the dorsal arteries as they arborize in the glans penis.

Etiology

Any process that injures the urethral epithelium or the underlying corpus spongiosum to the point that healing results in a scar can cause an anterior urethral stricture. Most urethral strictures are the result of trauma (usually straddle trauma). This trauma to the urethra often goes unrecognized until the patient presents with voiding symptoms resulting from the obstruction of the stricture or scar. In most cases of straddle trauma, reconstruction of the bulbar urethral injury is possible (Park and McAninch, 2004). Iatrogenic trauma to the urethra still exists, but with the development of small endoscopes and the limitation of indications for cystoscopy in boys, we see fewer iatrogenic strictures today than in the past. The place of idiopathic urethrorrhagia with regard to strictures in children is unclear; some question whether it may be a cause of strictures in young boys regardless of whether the child underwent an endoscopic procedure (Rourke et al, 2003). No specific inciting factor has been identified as causing idiopathic urethrorrhagia. Histologic results from a patient of ours with resolving urethrorrhagia showed portions of tissues covered in part by squamous epithelium; other parts were covered by transitional epithelium; there were several areas of denuded epithelium with acute hemorrhage and neutrophilic infiltration; a few foci of microcalcification were shown; several mucus glands were found within the submucosal connective tissue as well as a few collections of amorphous material, likely mucin. These areas stained negatively with a special stain for amyloid. There was no evidence of viral cytopathic effect or malignancy. We did not see evidence of bacterial infection or viral inclusions. However, we have seen an increase in strictures associated with LS, and those strictures clearly behave much more like inflammatory strictures than traumatically induced isolated scars. Finally, posterior urethral injuries, traumatic by definition, result in obliterative or near-obliterative defects that are associated with extensive fibrosis interposed between the distracted ends of the urethra.

Inflammatory strictures associated with gonorrhea were the most commonly seen in the past and are less common now. With the advent of prompt and effective antibiotic treatment, gonococcal urethritis progresses less often to gonococcal urethral strictures. The place of *Chlamydia* and *Ureaplasma urealyticum* (i.e., nonspecific urethritis) in the development of anterior urethral strictures is unclear. No clear association between nonspecific urethritis and the development of anterior urethral stricture has been established.

As mentioned earlier, there is a definite association between the development of an inflammatory stricture and LS. LS usually begins with inflammation of the glans and inevitably causes meatal stenosis, if not a true stricture of the fossa navicularis. The cause of this distal penile skin and urethral inflammation is unknown. Some evidence suggests that the progression of the stricture eventually to involve the anterior urethra extensively may be due to high-pressure voiding that causes intravasation of urine into the glands of Littre, inflammation of these glands, and, perhaps, microabscesses and deep spongiobiosis. Whether the urethral changes and eventual fibrosis are also related to bacterial injury has not been well defined. Although the use of antibiotics seems to limit obstructive voiding

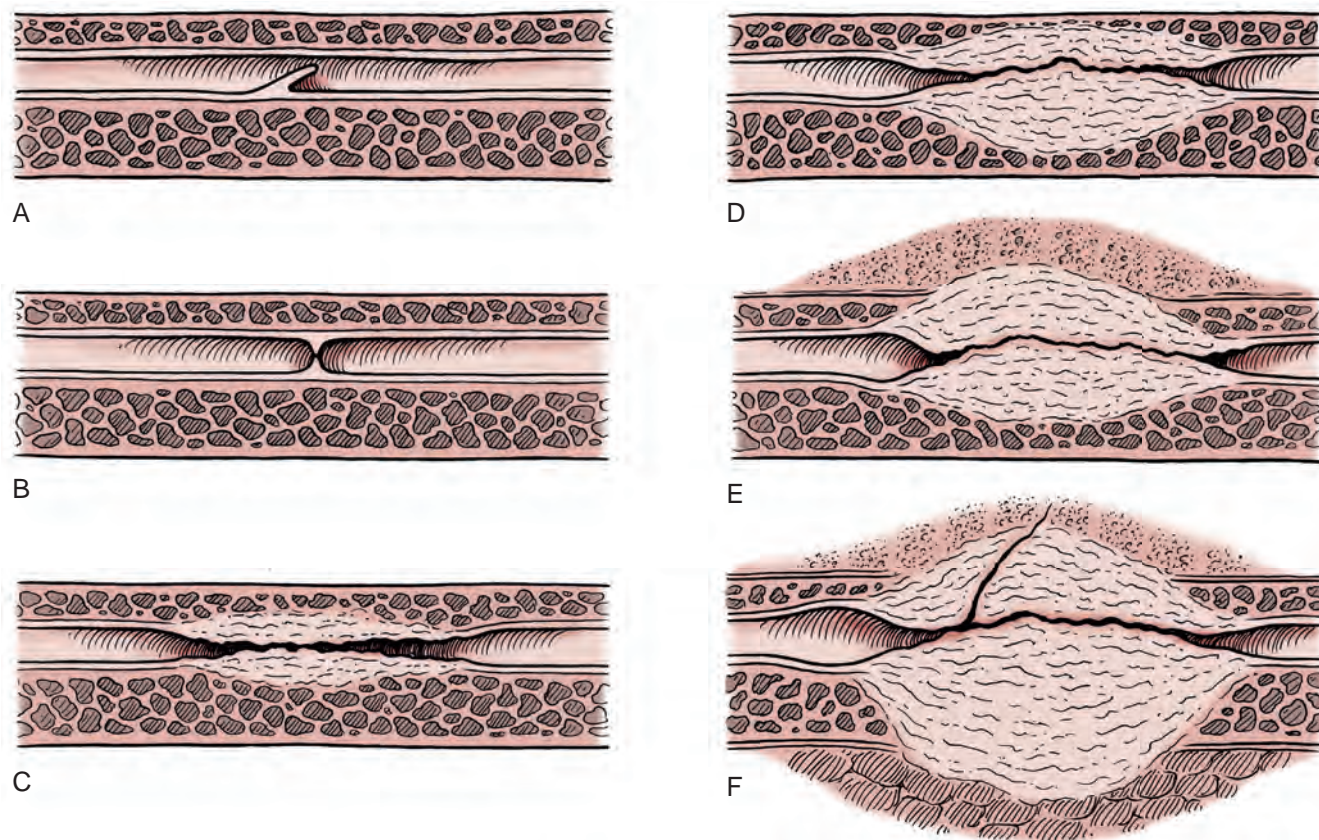


Figure 40-16. The anatomy of anterior urethral strictures includes, in most cases, underlying spongiofibrosis. A, Mucosal fold. B, Iris constriction. C, Full-thickness involvement with minimal fibrosis in the spongy tissue. D, Full-thickness spongiofibrosis. E, Inflammation and fibrosis involving tissues outside the corpus spongiosum. F, Complex stricture complicated by a fistula. This can proceed to the formation of an abscess, or the fistula may open to the skin or the rectum. (From Jordan GH. Management of anterior urethral stricture disease. *Probl Urol* 1987;1:199–225.)

symptoms in these patients, to our knowledge the literature does not show resolution of the stricture process with the use of antibiotics.

The entity known as a congenital stricture is difficult to understand. In embryologic development, if a stricture is found at a natural place where a fusion of structures occurs (i.e., the posterior and anterior urethra), a congenital stricture might be a reasonable assumption. However, the term *congenital stricture* is used by some authors to define a stricture for which there is no identifiable cause. We propose that it is reasonable to define a stricture as congenital only if it is not an inflammatory stricture, it is a short-length stricture, and it is not associated with a history of or potential for urethral trauma. These criteria limit the term *congenital stricture* to strictures of the anterior urethra found in infants before they attempt erect ambulation. So defined, congenital strictures are the rarest encountered.

Diagnosis and Evaluation

Patients who have urethral strictures most often present with obstructive voiding symptoms or urinary tract infections such as prostatitis and epididymitis. Some patients also present with urinary retention. However, on close inquiry, most of these patients are found to have tolerated notable voiding obstructive symptoms for a long time before progressing to complete obstruction.

When a patient cannot void, an attempt commonly is made to pass a urethral catheter. If the catheter does not pass, the nature of

the obstruction is determined by dynamic retrograde urethrography. Most cases are managed with acute dilation, and there are many instances in which this is not the best course for the patient. When there is doubt, we determine the nature of the stricture when possible, and selectively place a suprapubic cystostomy catheter to treat the acute situation and allow time for a more appropriate treatment plan to be devised. The practice of blind passage of filiforms and blind dilation without knowledge of the anatomy of the urethral stricture is condemned. Although detailed imaging is not always available, flexible endoscopy is almost universally available in the United States. The stricture can be visualized, and guidewire placement under direct vision can be attempted.

For an appropriate treatment plan to be devised, it is important to determine the location, length, depth, and density of the stricture (spongiofibrosis). The length and location of the stricture can be determined with radiography, urethroscopy, and ultrasonography. The depth and density of the scar in the spongy tissue can be deduced from the physical examination, the appearance of the urethra in contrast-enhanced studies, and the amount of elasticity noted on urethroscopy. The depth and density of fibrosis are difficult to determine objectively. The absolute length of spongiofibrosis may not be evident on ultrasound evaluation. Ultrasound examination can augment contrast-enhanced studies and is accurate in determining the length of narrow-caliber annularity (Morey and McAninch, 1996b). Contrast studies of the urethra are best carried out by or under the direct supervision of the surgeon responsible for treatment of the patient.

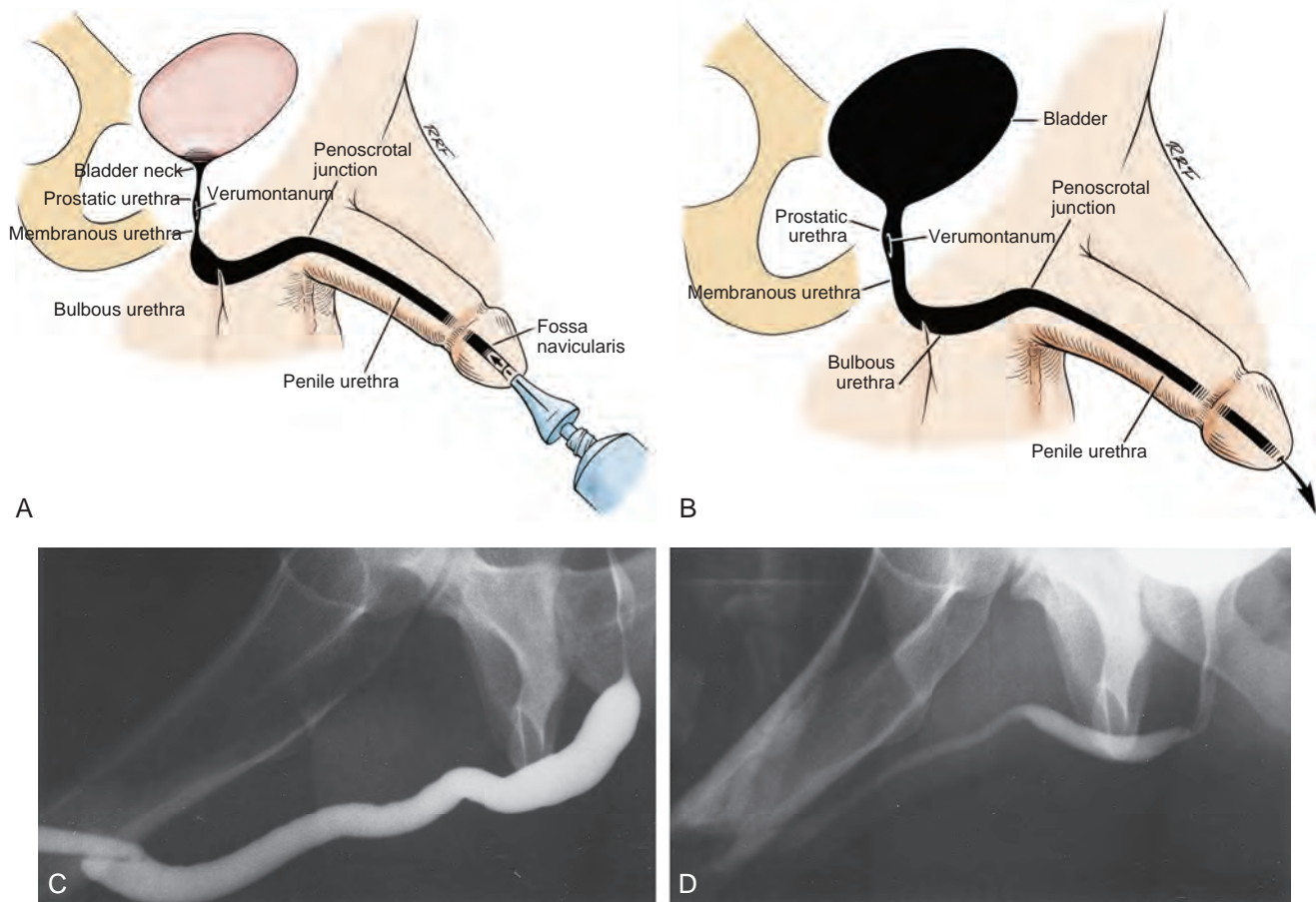


Figure 40-17. A, Representation of a dynamic retrograde urethrogram with the criteria of McCallum illustrated. B, Representation of a dynamic voiding urethrogram with the criteria of McCallum illustrated. C, Normal retrograde urethrogram. D, Normal voiding urethrogram. (A and B, Modified from McCallum RW. The adult male urethra. *Radiol Clin North Am* 1979;17:227-44.)

McCallum and Colapinto (1979a, 1979b) described the use of dynamic radiographic studies and emphasized the need for these studies to be dynamic as opposed to static (Fig. 40-17). At our center, imaging includes dynamic studies that are performed during retrograde injection of contrast material and while the patient is voiding. Even with gentle technique, extravasation during retrograde urethrography is possible in patients in whom the urethra is markedly inflamed. For this reason, contrast studies should be carried out with contrast material that is suitable for intravenous injection and used either directly from the bottle or diluted according to the manufacturer's guidelines. Contrast materials that have been thickened with lubricating jelly or anesthetic gels can be a source of problems and offer little with regard to enhancement of radiographic studies, and they do not make the studies more comfortable. Real-time ultrasound evaluation of the urethra after it has been filled with a lubricating jelly or saline has been described by Morey and McAninch (1996a, 1996b). However, it is a misconception that ultrasonography always directly visualizes the spongiositis. Morey and McAninch (1996a, 1996b) believed that ultrasonography of the bulbous urethra possibly more accurately determines the length of the stricture, which could be important in considering an anastomotic repair. If the patient is not in steep lateral oblique position for retrograde urethrography, the length of the stricture will be underestimated. Finally, during contrast-enhanced urethrography, more than one projection may be necessary to visualize the stricture. Magnetic resonance imaging (MRI) is also being explored as an adjunct to the evaluation of urethral stricture and pelvic fracture urethral injuries (PFUIs). In

our experience, the use of MRI for routine strictures or pelvic fracture urethral distraction defects is not routinely beneficial. In the case of urethral tumors, we have found MRI to be invaluable. The experience of others is commensurate with ours (Pavlica et al, 2003). In a pelvic fracture urethral distraction defect, the alignment of the two urethral ends can be defined clearly.

Endoscopic examination may be necessary after contrast studies. The flexible cystoscope has simplified this evaluation, and when local anesthesia is used, there is little discomfort associated with it. The scope can be passed to the stricture, and it often is unnecessary to pass it beyond that level. In addition, it is not always necessary, and usually not beneficial, to dilate the stricture at the time of the initial endoscopic evaluation. Pediatric endoscopic equipment has proved to be extremely valuable for examination of the urethra proximal to a narrow-caliber area without the need to dilate the narrowest area. In a patient who cannot void and has a suprapubic tube, combined contrast studies with endoscopy are helpful in defining the stricture anatomy (Fig. 40-18).

It is imperative to evaluate the urethra completely proximal and distal to the stricture with endoscopy and bougienage during surgery to ensure that all the involved urethra is included in the reconstruction. Although hydraulic pressure generated by voiding may keep segments proximal to the stricture patent, unless these segments are included in the repair, they are at risk for contraction after obstruction of the narrow-caliber segment is relieved with reconstruction. For this reason, any abnormal areas of the urethra that are proximal to a narrow-caliber segment of the stricture must be treated with suspicion. If the lumen does not appear to

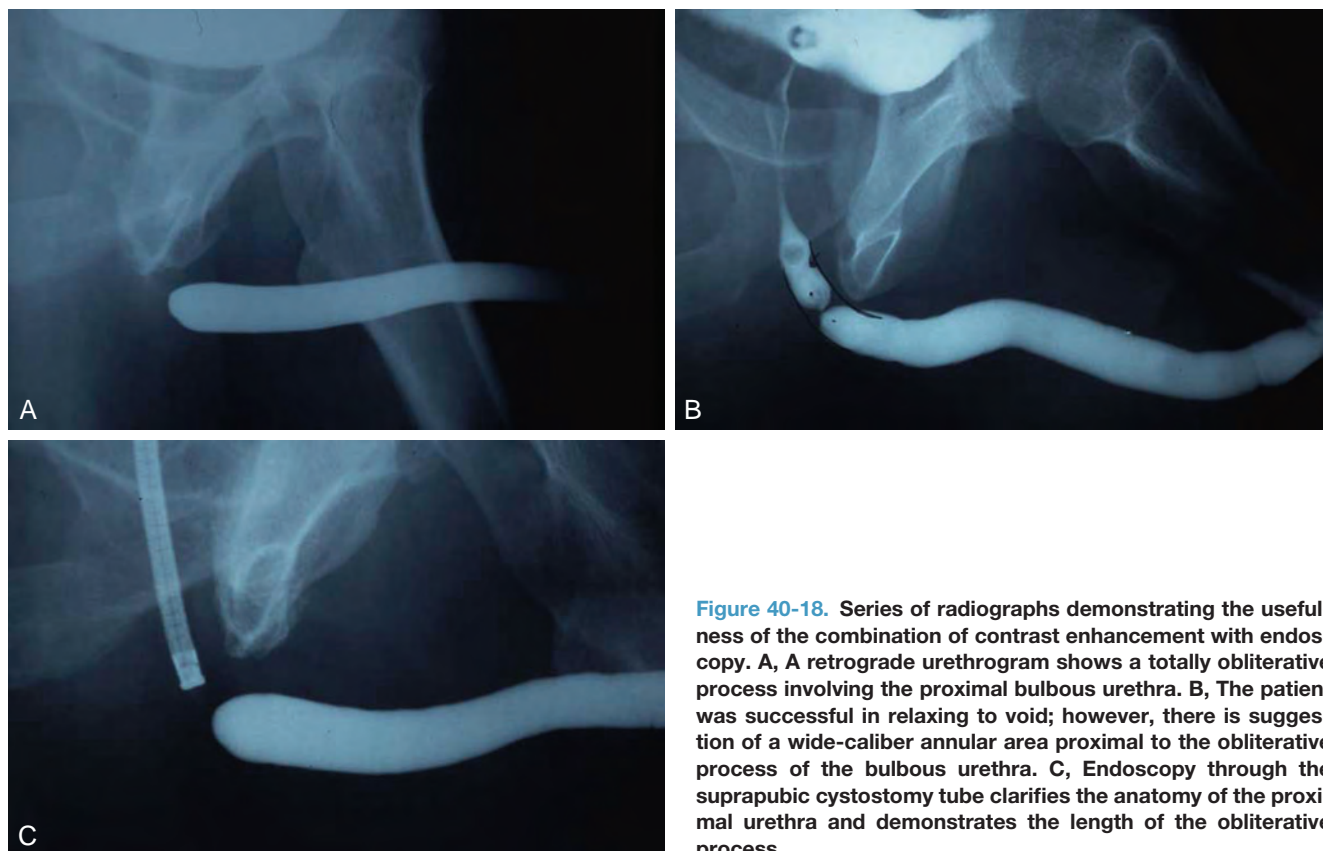


Figure 40-18. Series of radiographs demonstrating the usefulness of the combination of contrast enhancement with endoscopy. **A**, A retrograde urethrogram shows a totally obliterative process involving the proximal bulbous urethra. **B**, The patient was successful in relaxing to void; however, there is suggestion of a wide-caliber annular area proximal to the obliterative process of the bulbous urethra. **C**, Endoscopy through the suprapubic cystostomy tube clarifies the anatomy of the proximal urethra and demonstrates the length of the obliterative process.

demonstrate evidence of diminished compliance, we presume that area to be uninvolved in active stricture disease. However, coning down of the urethra suggests its involvement in the scar.

In some patients, the urethra proximal to a narrow area may remain confusing with regard to its potential for continued constriction after reconstruction. In select patients, we have found it useful to place a suprapubic tube to defunctionalize the urethra. After 6 to 8 weeks, if there is to be constriction of an area that was hydrodilated with voiding, the tendency for that constriction to occur should become apparent.

Treatment

Although the treatment of urethral stricture disease dates to the foundations of urology, significant progress made during the last 50 years allows many of the most complex strictures to be reliably reconstructed in one stage. In the past, a concept known as the reconstructive ladder was used as a treatment guideline for urethral strictures. That concept was based on the principle that the simplest procedure should always be attempted first, and sometimes repeated after failure, before moving on to more complex approaches. This approach is considered archaic in modern urethral reconstruction.

The patient and the physician must have a good understanding of the goal of treatment before the treatment choice is made. Treatment options should be discussed with the patient, with care taken to emphasize the anticipated outcome with regard to potential cure. Some patients may prefer stricture management and choose to have periodic dilations in the office, at home, or in the hospital rather than undergo technically detailed open surgery. Others may have cure as a goal and choose surgical management. Many surgical procedures today have short-term and mid-term results approaching long-term success rates of more than 90% to 95% for many strictures.

KEY POINTS: URETHRAL STRICTURE

- The term *urethral stricture* refers to anterior urethral disease and is a scarring process that involves the epithelium and the spongy erectile tissue of the corpus spongiosum. Contraction of the scar reduces the urethral lumen. Posterior urethral strictures are more correctly referred to as PFUIs; strictures of the prostatic urethra or bladder neck are properly referred to as contractures or stenoses.
- The anterior urethra is invested by the corpus spongiosum, and as it proceeds proximally it is eccentrically placed in relation to the corpus spongiosum. The genital skin has a dual and bilateral blood supply, forming a fasciocutaneous vascular system. The vascularity of the corpus spongiosum is based on the common penile artery.
- In general, most anterior urethral strictures are the result of trauma. Inflammatory strictures associated with gonorrhea are rarely seen; however, strictures associated with LS have behavior similar to inflammatory strictures.
- Patients who have urethral strictures most often present with obstructive voiding symptoms or urinary tract infections such as prostatitis and epididymitis. Patients who present with urinary retention, on close inquiry, have tolerated notable voiding obstructive symptoms for a long time.
- For an appropriate treatment plan to be devised, it is important to determine the length, location, depth, and density of the spongiofibrosis. This determination can be done with a combination of contrast-enhanced studies, endoscopy, and selective ultrasonography. It is imperative to evaluate the urethra completely proximal and distal to the stricture with endoscopy. A pediatric cystoscope is useful.

Dilation

Urethral dilation is the oldest and simplest treatment of urethral stricture disease, and for a patient with an epithelial stricture without spongiofibrosis, it may be curative. **The goal of this treatment, a concept that is frequently forgotten, is to stretch the scar without producing more scarring.** If bleeding occurs during dilation, the stricture has been torn rather than stretched, possibly further injuring the involved area.

The least traumatic method to stretch the urethra is to use soft techniques over multiple treatment sessions. We believe that the safest method of urethral dilation currently available involves the use of urethral balloon-dilating catheters. These catheters may be attached to a filiform tip or passed over a guidewire or may come with an integral coudé tip. For initial dilation, we favor the use of balloons placed over wires that have been passed through the stricture under endoscopic control.

Dilation can be curative and, in the literature, in correctly selected patients, has short-term and mid-term efficacy rates equal to internal urethrotomy. Selection criteria are discussed in the following section on internal urethrotomy. The literature does not compare internal urethrotomy and dilation in randomized selection, and we do not have a true comparison but rather comparison by retrospective analysis (Steenkamp et al, 1997).

Internal Urethrotomy

Internal urethrotomy refers to any procedure that opens the stricture by incising it transurethrally. The urethrotomy procedure involves incision through the scar to healthy tissue to allow the scar to expand (release of scar contracture) and the lumen to heal enlarged. The goal is for the resultant larger luminal caliber to be maintained after healing.

With epithelial apposition, wound healing occurs by primary intention. Internal urethrotomy does not provide an epithelial approximation but rather aims to separate the scarred epithelium so that healing occurs by secondary intention. In healing by secondary intention, epithelialization progresses from the wound edges. As it progresses from the wound edge, epithelialization slows. In an effort to aid epithelialization, nature invokes the forces of wound contraction, not to be confused with scar contraction. Wound contraction closes the wound defect and limits the size of the area that requires epithelialization, hastening the healing of the surface defect. However, in the case of internal urethrotomy, wound contraction merely tries to reapproximate the edges of the scar, putting a race into effect. If epithelialization progresses completely before wound contraction significantly narrows the lumen, the internal urethrotomy may be a success. If wound contraction significantly narrows the lumen before completion of epithelialization, the stricture has recurred. [Dubey and colleagues \(2005\)](#) showed the extent of luminal narrowing to be a predictor of success with internal urethrotomy: The narrower the percent of narrowing, the worse the outcome, with a cutoff of 74% narrowing.

Many surgeons have learned to perform internal urethrotomy by making a single incision at the 12 o'clock position. However, this location might be questioned on the basis of the location of the urethra within the corpus spongiosum. On examination of a cross section of the corpus spongiosum, it can be seen that the thinnest portion of the anterior aspect is from 10 o'clock to 2 o'clock. The distance between the anterior wall of the urethra and the corpora cavernosa is likewise short in the bulbous urethra, and a single incision at 12 o'clock could rapidly penetrate the corpus spongiosum and extend into the triangular ligament; although it might not enter the corpora cavernosa, a deep cut could enter the intracrusal space. Distally, although the anterior aspect of the corpus spongiosum is thicker, a deep incision in the more distal aspects of the anterior urethra would enter the corpora cavernosa, and these incisions have been associated with erectile dysfunction thought to be due to local cavernosal veno-occlusive dysfunction. Vigorous incisions at 10 o'clock and 2 o'clock in the bulbous urethra risk the same problem. If deep spongiofibrosis is present, stricture cure is

impossible by internal urethrotomy, and these deep incisions are unnecessary.

The most common complication of internal urethrotomy is recurrence of stricture. Less commonly noted complications of internal urethrotomy include bleeding (almost always associated with erections immediately after the procedure) and extravasation of irrigation fluid into the perispongiosal tissues. These complications are rare today because of the less frequent use of aggressive internal urethrotomy as a treatment modality for urethral strictures. Normal saline should be used as the irrigant when direct visual internal urethrotomy is performed. Additionally, with the use of deep urethrotomy incisions, another complication can be creation of a fistula between the corpus spongiosum and the corpora cavernosa and cavernosal veno-occlusive dysfunction.

A major problem with assessing the success rates of internal urethrotomy is that the nature of the strictures that have been treated with internal urethrotomy has been poorly reported. In addition, the literature is unclear regarding the goal of internal urethrotomy. For many, an internal urethrotomy is successful if it offers temporary relief. In many cases, internal urethrotomy has been reported as successful despite the fact that it has been associated with eventual stricture recurrence. A report by [Santucci and McAninch \(2001\)](#) using actuarial techniques showed the curative success rate of internal urethrotomy to be approximately 20% ([Rosen et al, 1994](#)). Evaluations by [Pansadoro and Emiliozzi \(1996\)](#) and others showed the curative success rate of direct visual internal urethrotomy to be approximately 30% to 35%. Their analysis also showed that there is virtually no increase in success rate with a second internal urethrotomy. **The data show that strictures at the bulbous urethra that are less than 1.5 cm in length and not associated with dense, deep spongiofibrosis (i.e., straddle injuries) can be managed with internal urethrotomy, with a 74% moderately long-term success rate.** The study by Pansadoro and Emiliozzi (1996) did not have any long-term successes for treated strictures outside the bulbous urethra. The variables associated with success of internal urethrotomy have been verified by other studies ([Heyns et al, 1998](#)). Many studies have shown that the success of reconstruction is diminished by multiple prior urethral dilations and internal urethrotomy ([Stone et al, 1983](#); [Albers et al, 1996](#); [Heyns et al, 1998](#)) ([Boccon-Gibod, personal communication, 2005](#)). Success rates with internal urethrotomy are not equal to success rates of open urethral reconstruction ([Mandhani et al, 2005](#)). Numerous analyses have sought to compare the cost-effectiveness of the practice of internal urethrotomy initially before consideration of open reconstruction. The analyses all differ in method and differ in findings ([Rourke and Jordan, 2005](#); [Wright et al, 2006](#); [Wessells, 2009](#)).

Several techniques have been employed to oppose the process of wound contraction and to prevent stricture recurrence. One method is to leave an indwelling Foley catheter for 6 weeks after urethrotomy, in the hope that the urethra will mold around the catheter as it heals. However, studies have shown that the failure rate of long-term catheterization after internal urethrotomy is similar to that seen with 3 to 7 days of catheterization, and even 6 weeks is insufficient time to oppose the forces of wound contraction.

Another technique used to oppose the forces of wound contraction after internal urethrotomy is home self-catheterization or home urethral obturation. After internal urethrotomy, patients generally have an indwelling catheter placed for 3 to 5 days. When the catheter is removed, the patient is started on a urethral obturation regimen. Most regimens require more frequent catheterizations early in the recovery period, with a tapering schedule during the next 3 to 6 months. Anecdotally, many surgeons have reported an improved cure rate with self-catheterization combined with internal urethrotomy. However, it has been our experience that the stricture inevitably recurs when the patient stops self-obturation, regardless of how long it has been used. That being understood, this approach can effectively manage the problems when it is combined with a urethral dilating regimen in a properly motivated patient. Colchicine, because it binds tubulin, has been used along with internal

urethrotomy (Carney et al, 2007). Initial findings in a nonrandomized study also suggest that, perhaps by pharmacologically blocking tubulin and possibly wound contracture, the results of internal urethrotomy may be better. Mitomycin C with its antifibroblast and anticollagen activity when injected submucosally has been shown to decrease the risk of recurrence after a urethrotomy (Mazdak et al, 2007).

Urethral stents (removable or permanently implantable) are another modality used in opposing the forces of wound contraction after internal urethrotomy or dilation. Removable urethral stents are designed to prevent the process of epithelialization from incorporating the stent into the urethral wall and are left in place for 6 months to 1 year before they are removed. The greatest experience with these removable stents comes from Israel (Yachia and Beyar, 1991), and centers there report good success in small series. The Memokath stent is not currently available in the United States. It is a removable stent made of nitinol with varying success rates.

Most experience with permanently implantable stents comes from Europe and the United Kingdom. Milroy (1993) reported a success rate of 84% at 4.5 years with use of the permanently implantable UroLume (Rousseau et al, 1987; Sigwart et al, 1987; Milroy et al, 1988, 1989; Sarramon et al, 1990; Ashken et al, 1991; Krah et al, 1992; Sneller and Bosch, 1992; Verhamme et al, 1993; Badlani et al, 1995; Milroy and Allen, 1996; Jordan, 1997; Tillem et al, 1997; Brandes and McAninch, 1998; Shah et al, 2003). The UroLume, made of an alloy, is designed to be incorporated into the wall of the urethra and corpus spongiosum. Available data show that the stent is best employed for relatively short strictures of the bulbous urethra associated with minimal spongiofibrosis. However, these are the strictures that are most successfully reconstructed with open techniques that offer better long-term success rates. The North American Study Group 11-year data showed that of 179 patients originally enrolled in the North American Study, 24 patients completed 11 years of follow-up. The overall success rate for all patients enrolled at 11 years is less than 30% (Shah et al, 2003). A 10-year follow-up study from The Netherlands (De Vocht et al, 2003) reported results thought to "weaken the optimistic early results"; of 15 patients implanted, only 2 were satisfied with their stent at 10 years.

Permanently implantable stents are associated with unique complications. The stents must be placed only in the bulbous urethra, and when placed beyond the area of the scrotal urethra, placement has been associated with pain on sitting and intercourse. Some patients (particularly young patients) complain of perineal pain, often with vigorous activity, even after implantation of the stent in the deep bulbous urethra. In addition, longer bulbous strictures require two stents that are overlapped. These stents can migrate away from each other, leaving a gap between them where recurrence of stricture is inevitable. When this occurs, the stricture recurrence is excised, and a third stent is placed to span the gap.

There are also specific contraindications to the use of the UroLume. Patients who have undergone prior substitution urethral reconstruction, particularly where skin has been incorporated into the urethra, have been shown to be poor candidates for implantation with the UroLume stent because contact of the stent with the skin is associated with a virulent hypertrophic reaction. These patients experience postvoid dribbling, and the hypertrophic reaction can be so severe in some cases that functional recurrence of the stricture results. Another subset of patients shown to be poor candidates for the UroLume includes patients with strictures associated with deep spongiofibrosis. Patients who fall into this category have had urethral distraction injuries and straddle injuries associated with deep fibrosis. UroLume has been taken off the market and is currently not available for implantation. However, there are still many patients who will present with UroLume stents, and many will need treatment.

To date, the results of laser urethrotomy are mixed. However, with the advent of new lasers and experience with them, future data may show better results.

Open Reconstruction: Excision and Reanastomosis

It has been demonstrated with certainty that the most dependable technique of anterior urethral reconstruction is the complete excision of the area of fibrosis, with a primary reanastomosis of the normal ends of the anterior urethra (Fig. 40-19) (Russell, 1914). The best results are achieved when the following technical points are observed: The area of fibrosis is totally excised; the urethral anastomosis is widely spatulated, creating a large ovoid anastomosis; and the anastomosis is tension free.

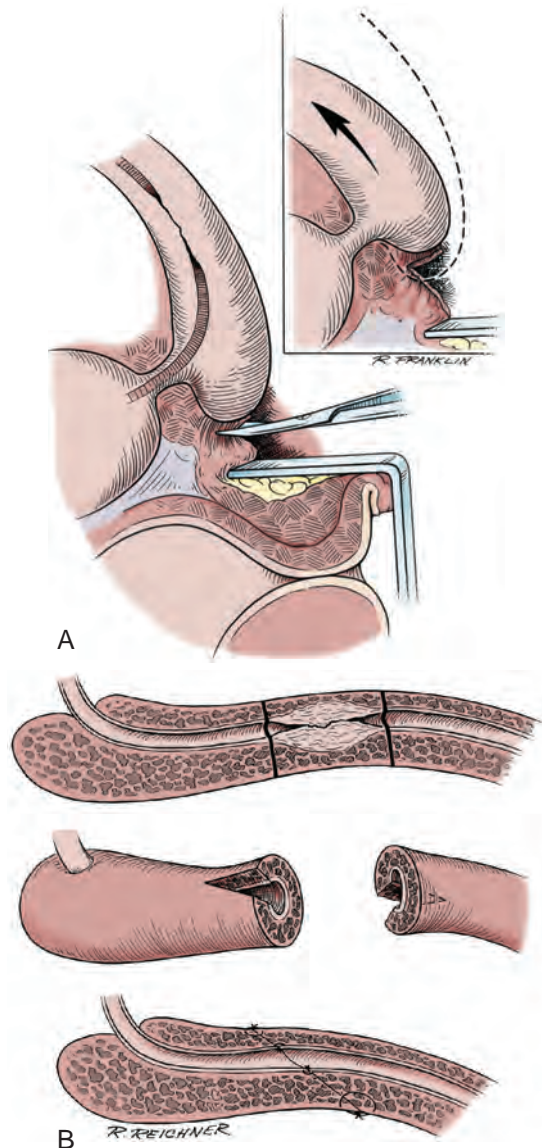


Figure 40-19. Techniques for excision and primary reanastomosis of anterior urethral stricture. A, The bulbospongiosus is released from its attachment to the perineal body. The arteries to the bulb are not divided. This technique allows the urethra to be mobilized distally. This technique combined with development of the intracru-ral space can shorten the path of the urethra by approximately 1 to 1.5 cm. B, Technique of a primary spatulated anastomosis after excision of an anterior urethral stricture. (From Jordan GH. Principles of plastic surgery. In: Droller MJ, editor. Surgical management of urologic disease: an anatomic approach. Philadelphia: Mosby; 1992. p. 1218–37.)

Lasers



Please see the Expert Consult website for this section.

Types of lasers that have been used for the treatment of urethral stricture disease include carbon dioxide (CO₂), argon, KTP, Nd:YAG, holmium:YAG, and excimer lasers. The ideal laser for use in the treatment of urethral stricture disease is one that totally vaporizes tissue, exhibits negligible peripheral tissue destruction, is not absorbed by water, and is easily propagated along a fiber. Although the CO₂ laser appears to be ideally suited, it must be used with a gas cystoscope, which carries the potential threat of a CO₂ embolus.

For the argon and the Nd:YAG lasers, the predominant mode of action is thermal necrosis, which leads to a significant potential for peripheral tissue injury rather than vaporization. The Nd:YAG laser has also been used with a bare fiber in the contact mode. A bare fiber carries with it a risk of forward scatter. When it is used in the contact mode, the YAG energy is transferred to a sapphire tip. Advocates of the use of a contact laser suggest that it obliterates the scar by vaporization; however, results with use

of these fibers are no better than results with direct cold-knife visual internal urethrotomy.

A KTP laser is essentially an Nd:YAG laser that has passed through a KTP crystal, resulting in a reduced depth of penetration. A KTP laser urethrotomy is accomplished by passing the fiber over the scar tissue to make urethrotomy cuts. The holmium:YAG laser has properties similar to the KTP laser, and, similar to the KTP laser, it provides direct contact cutting and vaporization with minimal forward scatter. Experience with the holmium:YAG laser is accumulating; anecdotally, it may have a place in the management of some strictures, in particular, strictures that are relatively isolated and short.

The excimer laser is a true vaporizing laser that has little forward scatter or peripheral tissue necrosis associated with it. Little experience with this laser has been reported, but future investigation is warranted.

The success of this procedure relies on vigorous mobilization of the corpus spongiosum. With vigorous mobilization, dissection of Buck fascia to improve compliance, development of the intracanal space, and detachment of the bulbospongiosus from the perineal body, significant lengths of stricture can be excised and reanastomosed. Strictures of 1 to 2 cm are generally easily excised with reanastomosis. In some cases, strictures 3 to 5 cm can be totally excised, and a primary reanastomosis of the anterior urethra can be performed. For very proximal short-length bulbous strictures, tension-free anastomosis can be facilitated by the dissection of the membranous urethra (Fig. 40-20). As a rule, the closer the stricture is to the membranous urethra, the longer it can be and still be reconstructed with anastomotic techniques. For many proximal strictures, a single-layer anastomosis is preferable. When the length of stricture precludes total excision of fibrosis with primary anastomosis, tissue transfer is required. Morey and Kizer (2006) published a series of patients who had stricture excision with anastomosis for strictures up to 5 cm and pointed out that younger patients have more compliant tissue, allowing the limits to be stretched.

DeCastro and associates (2002) reported an interesting variant of excision with anastomosis for anterior stricture. In that case report, a patient had two independent areas of stricture apparently separated by totally normal urethra and corpus spongiosum. The authors excised both areas of stricture independently with respective anastomosis of each site. Although this case was successful, we think that the authors' considerable experience allowed them to achieve a successful result, and a safer reconstruction with use of onlay or augmented onlay might have been better.

Jordan and colleagues (2007) first reported the use of a vessel-sparing excision and reanastomosis of the bulbar urethra. The dissection is similar to the standard excision and reanastomosis

(Fig. 40-21): The triangular ligament is divided, and the intracanal space is developed, the space between the membranous urethra and the proximal vasculature is developed, and these vessels are preserved (Fig. 40-22). The urethra is divided with the stenotic segment excised, the ends are spatulated, and the reanastomosis is performed. Andrich and Mundy (2012) described an alternative vessel-sparing technique for proximal strictures in which a longitudinal dorsal stricturotomy is performed and the stricture is excised from within the urethra without disrupting the spongiosum. After stricture excision, the ventral urethra is reapproximated primarily, and the longitudinal dorsal stricturotomy is closed horizontally, preserving the vasculature. Preserving the proximal blood supply to the bulbar urethra is advantageous in patients whose distal blood supply is compromised by trauma, previous surgery, or hypospadias. Another theoretical advantage would be a decrease in the risk of erectile dysfunction and potential decreased risk for erosion if subsequent artificial sphincter implantation were probable. Further studies need to be done to confirm the initial excellent results with the vessel-sparing technique and prove the theoretical advantages (Jordan, et al 2007; Gur and Jordan, 2008; Andrich and Mundy, 2012).

Four grafts that have been successfully used for primary urethral reconstruction are the full-thickness skin graft, bladder epithelial graft, oral mucosal graft, and rectal mucosal graft. Oral mucosal grafts, as mentioned earlier, can be taken from the cheek (buccal), the lip (labial), and the undersurface of the tongue (lingual). Split-thickness skin grafts have been used for staged anterior urethral reconstruction (Humby, 1941; Memmelaar, 1947; Pressman and Greenfield, 1953; Devine et al, 1976; Hendren and Crooks, 1980; Schreiter and Koncz, 1983; Webster et al, 1984; Hendren and Reda, 1986; Ransley et al, 1987; Burger et al, 1992; Jordan, 1993; El-Kassaby et al, 1996; Wessels and McAninch, 1996). The characteristics and microvasculature of some

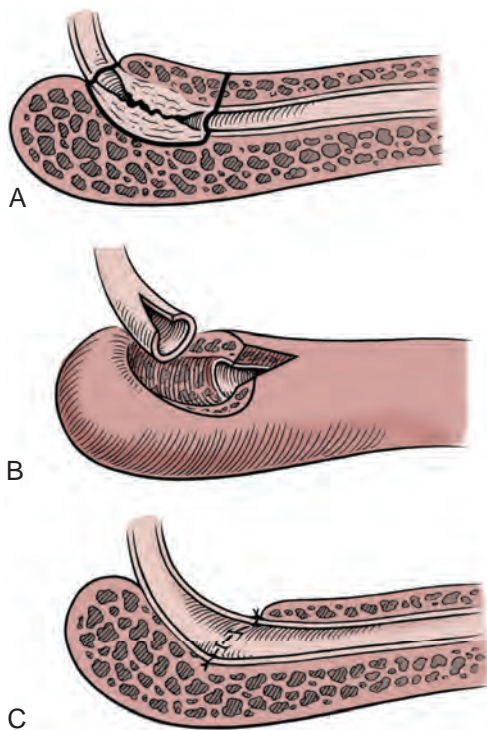


Figure 40-20. Technique of excision of very proximal bulbous urethral stricture with reanastomosis. This technique is facilitated by dissection of the membranous urethra. A, The area of the stricture is defined for excision. B, The stricture is excised, and both ends of the urethra are spatulated on the dorsal aspect. C, The anastomosis is complete.

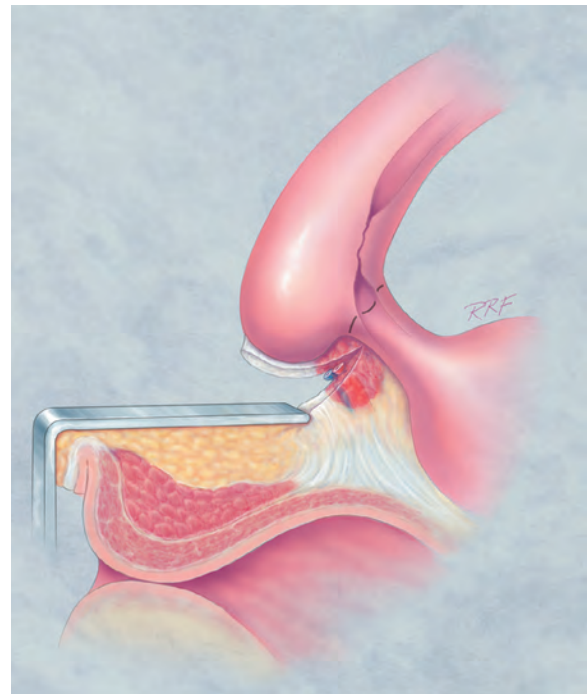


Figure 40-21. Diagrammatic representation of the dissection of the proximal corpus spongiosum, bulbospongiosum, and membranous urethra. The customary technique for dividing the urethra through the juncture of the membranous urethra with the proximal bulbous urethra—to perform an excision of stricture with a primary anastomosis. In this illustration, the proximal vasculature has been ligated and divided. The urethra can then be divided at the distal-most limits of the membranous urethra.

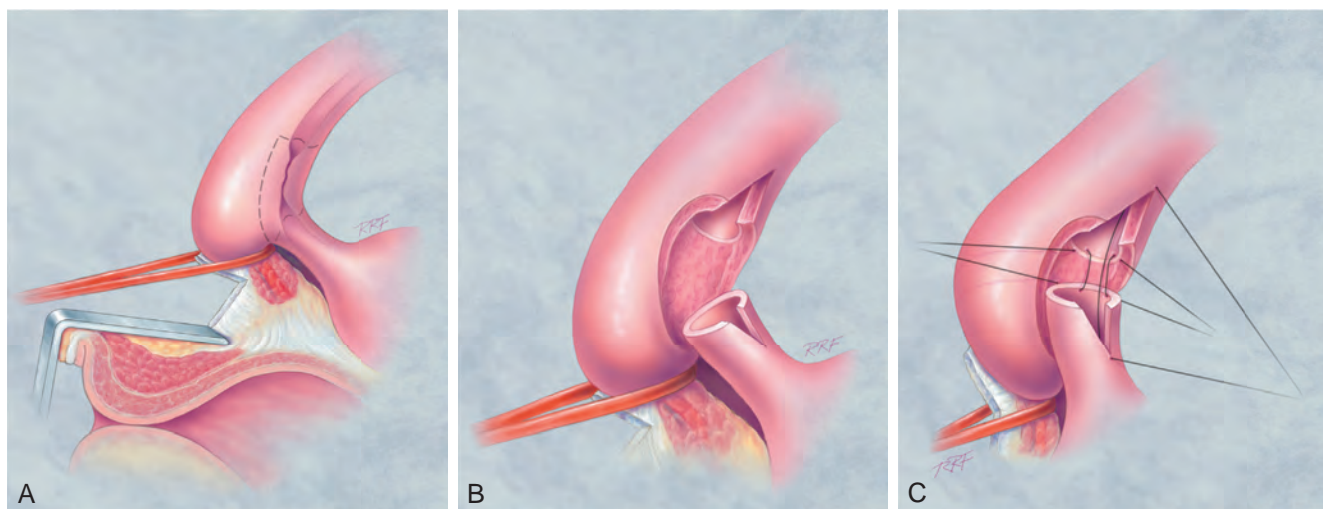


Figure 40-22. Technique of vessel-sparing excision with primary anastomosis. The proximal corpus spongiosum, bulbospongiosum, and area of the proximal vessels and membranous urethra have been dissected. **A**, Dissection of the space between the proximal vasculature and the membranous urethra is illustrated. In this technique, the arteries to the bulb can be preserved, and the membranous urethra can be divided at its juncture with the bulbous urethra. The area of proximal stricture can be excised. **B**, The stricture has been excised before placement of the anastomotic sutures. **C**, Anastomotic sutures are placed to effect the spatulated anastomosis. At this center, customarily we alternate polydioxanone sutures with Monocryl; however, any acceptable absorbable suture can be used. The membranous urethra is spatulated on the dorsum as is the proximal bulbous urethra.

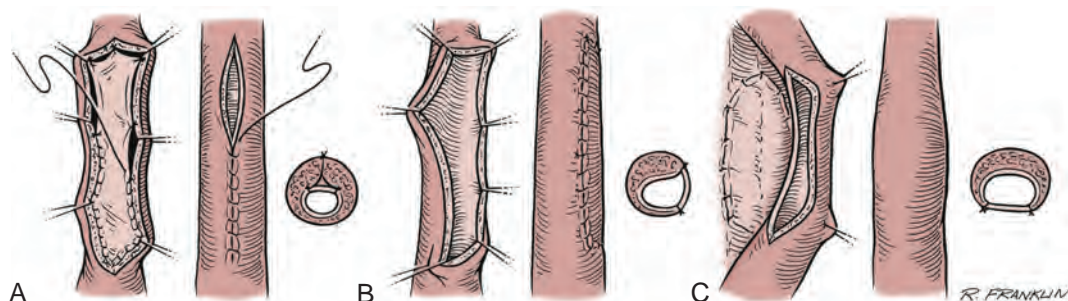


Figure 40-23. Various techniques of graft onlay. **A**, Ventral onlay with spongioplasty. **B**, Lateral onlay with quilting to the ischiocavernosus muscle. **C**, Dorsal onlay with spread fixation of the graft.

of the grafts were discussed earlier in Principles of Reconstructive Surgery.

Graft reconstruction of the urethra was almost abandoned in favor of flap reconstruction techniques. However, since the late 1990s, there has been a resurgence of interest in the use of grafts (Wessells and McAninch, 1996) and, specifically, the use of buccal mucosal grafts (Hellstrom et al, 1996; Weinberg et al, 2002; Barbagli et al, 2003; Elliott et al, 2003; Bhargava and Chapple, 2004; Kellner et al, 2004; Xu et al, 2004; Dubey et al, 2005). Grafts have been employed most successfully in the area of the bulbous urethra, where the urethra is invested by the bulk of the ischio-cavernosus muscles. However, the use of grafts other than in the area of the bulbous urethra and, in some cases, the use of tubed reconstruction are reported in increasing numbers. The grafts can be applied to the ventrum of the urethra; however, a ventral urethrotomy seems to be advantageous only if use of the spongioplasty maneuver is contemplated (Fig. 40-23). The spongioplasty procedure requires that the corpus spongiosum adjacent to the area of the stricture be relatively normal and free of fibrosis. There are data to support the superiority of results with the dorsal onlay technique and other reports showing no difference in success.

In the past, we preferred to use lateral graft onlay (see Fig. 40-23B) or dorsal graft onlay (see Fig. 40-23C). Placement of the urethrostomy laterally allows exposure of the urethra while cutting through the corpus spongiosum, where it is relatively thinner, limiting bleeding and maximizing exposure. In addition, in the bulbous urethra, the graft can be sutured to the underlying muscle bed in the hope of improving graft–host bed immobilization and approximation.

The Monseur urethral reconstruction was applied in only a few select centers (Monseur, 1980). In this technique, the urethrostomy was made through the stricture on the dorsal wall. The edges of the stricture were sutured open to the underlying triangular ligament or corpora cavernosa, or both. Barbagli and associates (1995) subsequently modified the Monseur technique (Fig. 40-24). In their modification, the urethrostomy is performed through the stricture on the dorsal wall. In the area of the urethrostomy, a graft is applied and spread fixed to the triangular ligament or corpora cavernosa, or to both. The edges of the stricturotomy are sutured to the edges of the graft and to the adjacent structures. The results of this technique are excellent. The ventral and dorsal graft onlay techniques can be used with stricture excision and strip anastomosis (augmented

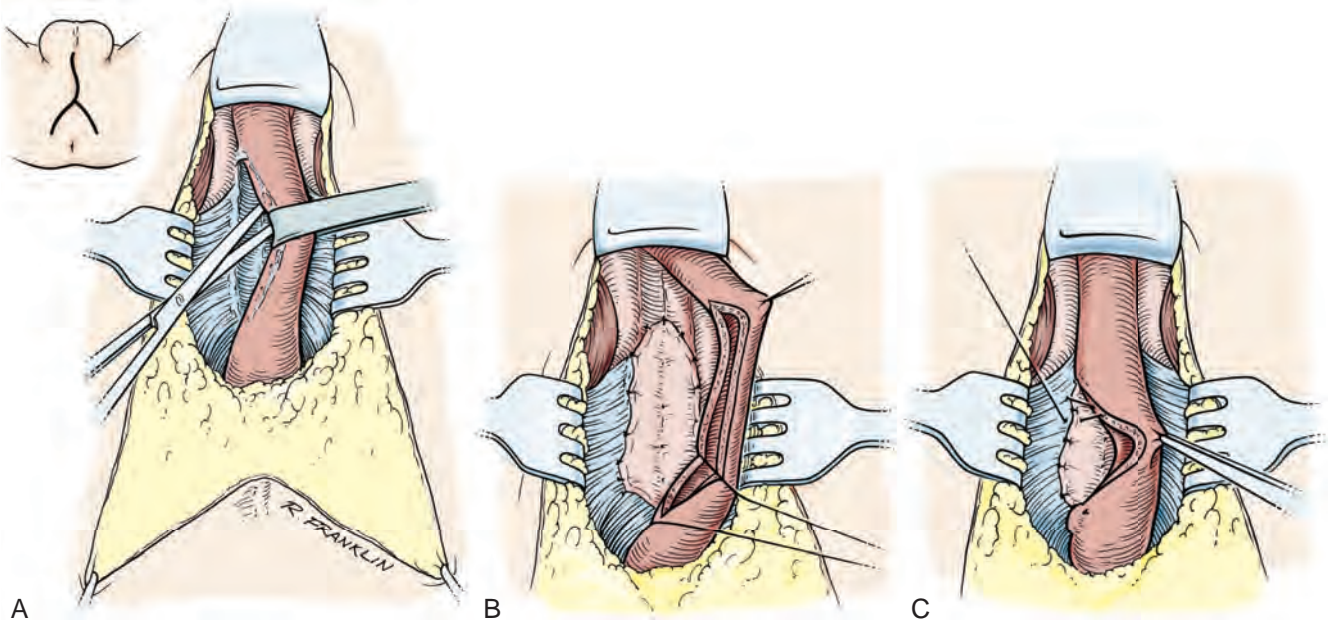


Figure 40-24. Technique of dorsal graft onlay popularized by Barbagli. A, The corpus spongiosum is detached from the triangular ligament and corpora cavernosa. B, A dorsal urethrostomy is performed. The graft is spread fixed to the corpora cavernosa. Note the pie-crusting incision. C, The edges of the stricturotomy are sutured to the graft and to the corpora cavernosa.

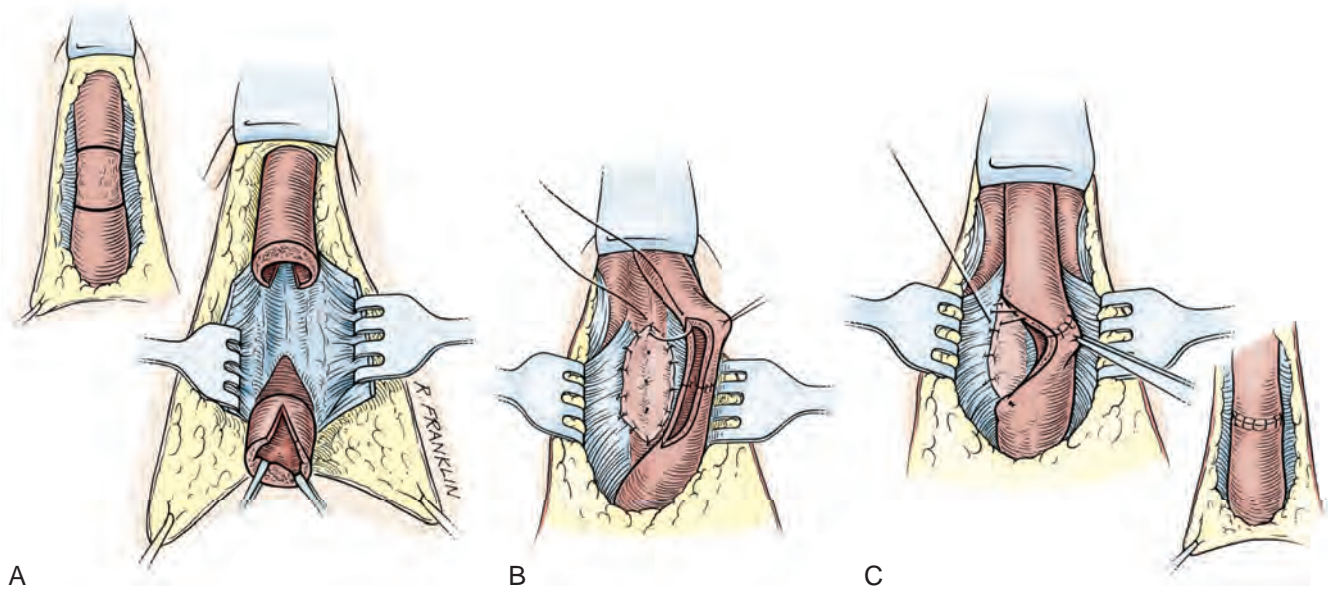


Figure 40-25. Technique of augmented anastomosis with graft onlay. A, The corpus spongiosum is detached from the triangular ligament and the corpora cavernosa. The area of spongiofibrosis is identified and marked, and the area of the narrowest caliber stricture is excised. The urethral ends are spatulated on the dorsum. B, A two-layer floor strip anastomosis is performed, and the graft is spread fixed to the corpora cavernosa. Note the pie-crusting incisions and the mattress sutures. C, The edges of the stricturotomy are sutured to the graft and to the corpora cavernosa.

anastomotic procedure) (Fig. 40-25). For proximal strictures, the vessel-sparing technique of augmented anastomosis depends on the surgeon's ability to excise the scarred epithelium and underlying corpus spongiosum tissue without the need to divide the corpus spongiosum completely.

Another option is the two-staged application of a mesh split-thickness skin graft, buccal mucosal graft, or posterior auricular

full-thickness skin graft. In the first stage of the staged graft procedure, a medium-thickness split-thickness skin graft, a buccal mucosal graft, or a Wolfe graft is placed over the dartos fascia. If the graft is placed immediately onto the tunica albuginea or corpora cavernosa, the inability to mobilize the graft makes second-stage tubularization difficult. However, there is an advantage to having at least a midline strip of the graft adherent to the corpora

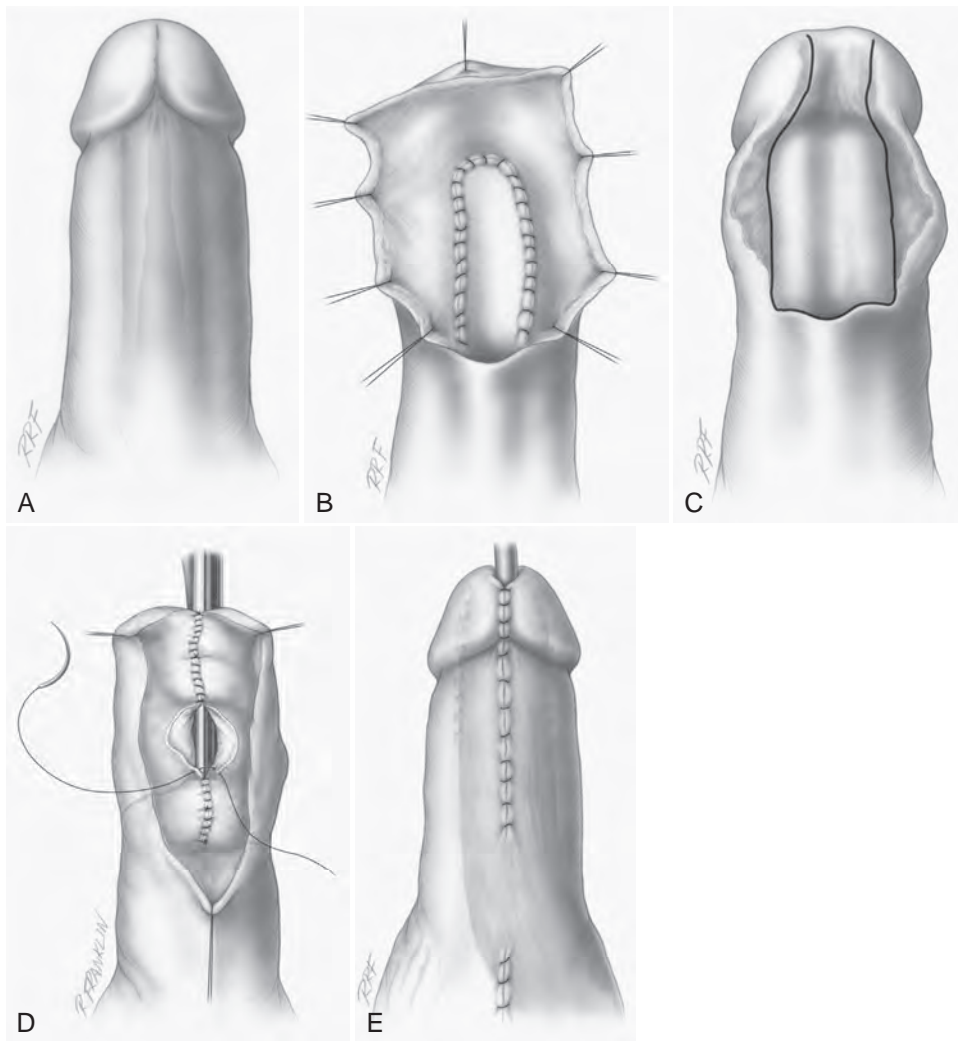


Figure 40-26. Staged reconstruction of a distal anterior urethral stricture. **A**, The appearance of the penis with the urethra (shaded area shows the location of a tight stenosis of the fossa navicularis that extends into the distal pendulous urethra). **B**, The distal narrow stricture of the fossa navicularis has been excised, and stricturotomy into the normal urethra proximal to the excised tissue has been performed. A buccal graft has been applied to the defect, but the bolster dressing has not yet been applied. **C**, After 6 months, the graft is mature. The illustration shows a Tiersch tube ready for closure. **D**, The Tiersch tube is closed with a watertight suture line. The distal urethra is usually calibrated to create a urethral lumen of approximately 28 Fr. **E**, Glans reconstruction and closure of the distal shaft has been performed (shaded area shows the tunica dartos flap that carries a parietal tunica vaginalis island). The flap is mobilized in this case from left hemiscrotum and transposed to cover the entire area of the urethral reconstruction.

cavernosa. At a later date, second-stage surgery is performed to tubularize the graft. Although Schreiter and Noll (1989), who first described the procedure of mesh split-thickness skin graft, often proceeded to the second stage within 3 to 4 months, we wait 12 months between the first-stage and second-stage surgeries if a split-thickness skin graft is used. This procedure has been found to be useful for select cases in the United States and Europe. In the United States, its use has mostly been confined to the most difficult cases, with single-stage reconstruction still applied to most cases. As already mentioned, staged graft techniques have been used effectively in complicated patients with hypospadias. Staged buccal graft operations have been successful in patients with LS with mid-term follow-up. In addition, in complicated patients with hypospadias, staged buccal grafts and posterior auricular skin grafts have been successfully employed (Fig. 40-26).

Numerous applications of genital skin islands, mobilized on either the dartos fascia of the penis or the tunica dartos of the scrotum, have been proposed for the repair of urethral stricture disease. In the past, these “flap operations” were considered separate procedures. We suggest that all these procedures are different applications of a single concept, as proposed by the microinjection studies of Quartey (1983). Skin islands can be viewed as passengers on fascial flaps, and the design of flaps for urethral reconstruction can be paralleled to the design of flaps for reconstruction in general.

There are three important considerations for the use of flaps in urethral reconstruction: the nature of the flap tissue, the vasculature of the flap, and the mechanics of flap transfer. The skin must be nonhirsute for urethral reconstruction. In addition, for

donor site consideration, it is most convenient to use the areas of redundant nonhirsute genital skin.

If the redundancy is dorsal, the skin island can be oriented transversely and mobilized on the dorsal dartos fascia after the techniques described by Duckett and Standoli in 1984 (Fig. 40-27) (Duckett, 1986; El-Kassaby et al, 1986; Duckett, 1992; Duckett et al, 1993). If there is redundancy of the ventral skin, the skin island can be mobilized as a ventral longitudinal island. These islands can be either vigorously mobilized on a ventrolaterally oriented dartos fascial flap for transposition to the perineum or less vigorously mobilized and transposed and inverted into a pendulous urethral stricture defect (Fig. 40-28) (Orandi, 1972). Ventral islands can be oriented transversely (Fig. 40-29) and longitudinally. Longer skin islands can be mobilized by orienting the island ventrally and transversely at the distal extent. This “hockey stick” orientation allows islands 7 to 9 cm (Fig. 40-30). For distal strictures of the anterior urethra, including the fossa and meatus and the pendulous urethra, the islands can be advanced to reconstruct to the level of the meatus by either developing glans wings or elevating the ventral glans.

Where there is general redundancy to the penile skin, the islands can be oriented circumferentially. These “circular skin islands” are mobilized on the entire penile dartos fascia, and the mechanics of transposition suggest that they are most efficient when they are ventrally based, with the pedicle split dorsally. In some cases, circular skin islands 15 cm can be obtained (El-Kassaby et al, 1986; McAninch, 1993; Miller and McAninch, 1993). The so-called Q flap circular island design can provide even longer islands, sometimes necessary for complex long-length anterior urethral reconstruction (Morey et al, 2000).

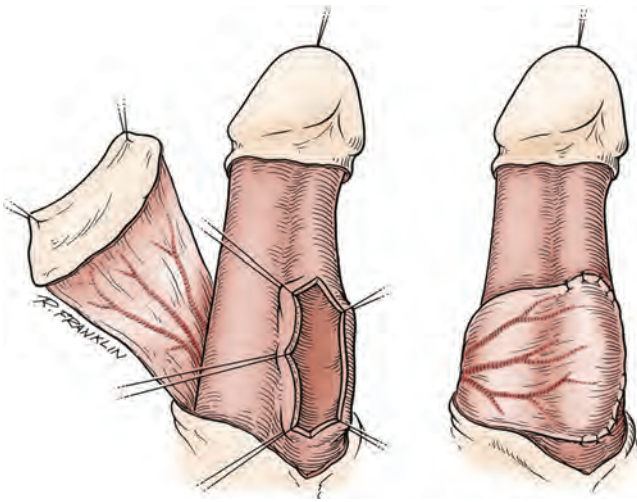


Figure 40-27. A dorsal transverse island of penile skin applied to a stricture of the urethra. The flap has been elevated on the dartos fascia, and a lateral incision into the urethra has been made. The flap is secured in place (*right*). (From Jordan GH. Management of anterior urethral stricture disease. In: Webster GD, editor. Problems in urology. Philadelphia: Lippincott; 1987. p. 217.)

It is often beneficial to combine the excision of the stricture with a skin island onlay (Fig. 40-31) or a graft onlay in an augmented anastomosis (see Fig. 40-25). We have found that segments of very narrow caliber (nearly or totally obliterating) are difficult. These segments can often be completely excised; a roof or floor strip anastomosis of the urethra is performed, and the remaining urethrotomy defect is filled with either a graft or a skin island onlay. In some patients, there are relatively large nonhirsute areas of the scrotal skin that can be elevated on the tunica dartos of the scrotum. This flap has been maligned in the literature in the past. However, we and others have extensive experience with these flaps and, in select cases, have had very good results. The fascial flap must be based laterally, and so oriented, these flaps have been shown to be extremely reliable. Because the tunica dartos has a significant muscle component, the skin island must be carefully tailored. If these skin islands are correctly tailored at the outset, they are not attended with diverticular development as some have believed they were in the past. Scrotal skin islands are not our first choice; however, for difficult cases, they remain a reasonable option.

These procedures using skin islands oriented on the penile dartos fascia have also been useful for reconstruction of the fossa navicularis (Cohney, 1963; Blandy and Tresidder, 1967; Brannen, 1976; De Sy, 1984; Jordan, 1987; Armenakas et al, 1998). In the past, meatal strictures and strictures of the fossa navicularis were managed with repeated dilations or sequential meatotomies. Because these meatotomies were seldom successful in the long-term, techniques were developed that allowed the spatulation of random penile skin flaps into the meatotomy defects. These procedures functionally improved the results; however, the cosmetic appearance of the penis was suboptimal. With the use of skin islands elevated on the dartos fascia, excellent functional and cosmetic results became the norm. The design of these islands must take into consideration the location of hair on the shaft of the penis and the mechanics of flap transfer (i.e., transposition vs. advancement) (Figs. 40-32 and 40-33). In addition, full-thickness skin has been used to reconstruct the fossa navicularis, but when they can be avoided, skin grafts are not considered appropriate for reconstruction in cases of LS. As already mentioned, there is question about the use of skin islands in general in patients with LS.

The literature is clear that onlay procedures (graft or flap) are associated with a higher success rate than tubularized grafts or tubularized skin islands (Hendren and Crooks, 1980). Tubularized grafts and skin islands should be avoided, if possible. When

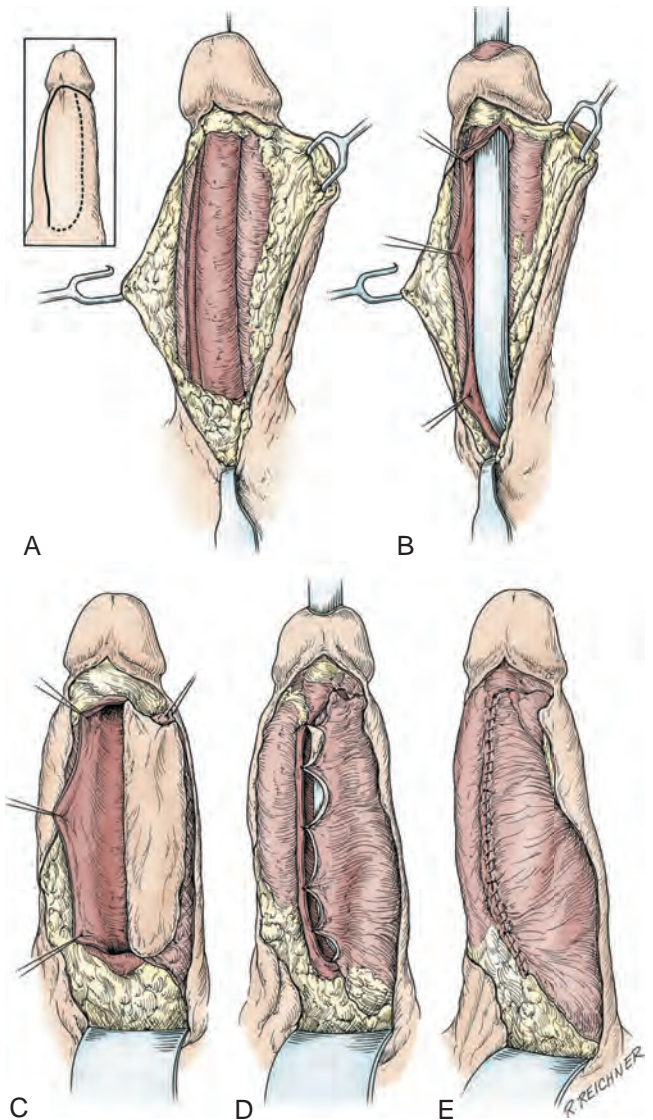


Figure 40-28. Penile longitudinal skin island. The incisions to be made to mobilize the flap are demonstrated in the *inset*. The heavy line is the primary incision made full thickness through the dartos fascia and superficial Buck fascia lateral to the corpus spongiosum. A, Dissection elevates the dartos fascial flap well past the corpus spongiosum in the midline. B, A lateral urethrostomy placed to face the flap has opened the entire length of the stricture. C, The skin paddle of the flap has been developed by making the incision outlined by the dotted line (*inset*) and undermining the skin lateral to it. The medial edge of the flap has been fixed to the edge of the stricturotomy. D, The flap is inverted into the defect. E, A watertight subepithelial suture line has been completed with a running absorbable monofilament suture. The skin will be closed with subcutaneous sutures and interrupted cutaneous sutures. (From Jordan GH. Management of anterior urethral stricture disease. In: Webster GD, editor. Problems in urology. Philadelphia: Lippincott; 1987. p. 214.)

tubularized segments cannot be avoided, the length of these segments can be limited by combining aggressive mobilization and excision. Without question, tubularized flaps provide better results than tubularized grafts. Where extremely long segments of the anterior urethra require reconstruction, a flap can be used distally and augmented by graft onlay proximally (Wessells et al, 1997). Where tubed reconstruction is required, in a small series with only short follow-up, the combination of a graft spread fixed to reestablish the "urethral plate" with flap onlay seems perhaps to

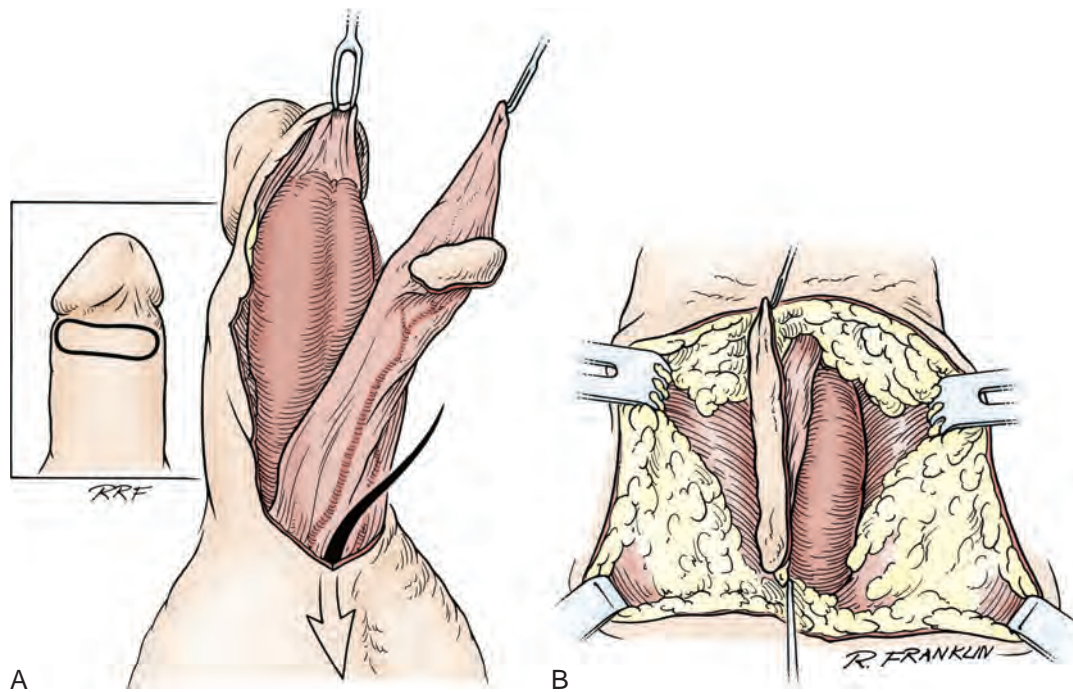


Figure 40-29. A ventral transverse skin island is elevated on the penile dartos fascia, inverted to the area of the perineum where flap onlay is accomplished. A, The skin island is elevated on the dartos fascia. B, The appearance of the flap transposed to the area of the perineum for onlay in a proximal bulbous urethral stricture.

be better than tubed flap reconstruction, even when it is employed in the onlay-tube-onlay configuration (Morey, 2001).

More recently, Kulkarni and colleagues (2012) published their approach to a single-stage panurethral reconstruction. Through a perineal incision and invaginating the penis, they described using a dorsal graft from the proximal bulbar urethra to the meatus. The mean stricture length was 14 cm, and mean follow-up was 59 months. The overall success rate was 83.7%; for primary repairs, the success rate was 86.5% compared with 61.5% in patients who failed a previous urethroplasty. Most of the recurrences the authors described were proximal.

A flap procedure that can be used as an alternative to split-thickness skin grafts when nonhirsute skin is unavailable is the epilated midline genital skin island. Similar to a split-thickness skin graft, this procedure must be viewed as a staged procedure, with the epilations being the initial stage or stages. Epilation can be accomplished with either a narrow-gauge needle and monopolar cautery or epilation needles and machines. The interval between the epilations must be 6 to 8 weeks, and urethral reconstruction cannot be accomplished until 10 to 12 weeks after the last epilation. The actual stricture repair involves elevation of the midline skin island, based on the dartos fascia of the penis and the tunica dartos of the scrotum. As with nonhirsute scrotal skin islands in general, the importance of meticulous tailoring of the scrotal portion of the island cannot be overemphasized.

Mundy (1994) analyzed a large series of urethral reconstructions. His data showed that when follow-up is limited to 1 year, the success rate with tissue transfer clusters is about 95%. However, with longer follow-up, there is deterioration over time. With excision and primary anastomosis, the success seen at 1 year seems to be more durable and does not appear to deteriorate at the same rate with time. We have reported our long-term data for excision and primary anastomosis with anterior urethral stenosis in 220 patients with a mean follow-up of 44 months; three recurrences were noted, two within the first 6 months and a third at 4 years. The rate of postoperative erectile dysfunction is 2%, with patients with severe straddle injuries being at

increased risk. In a meta-analysis of graft onlay procedures compared with flap procedures, Wessells and McAninch (1998) showed equivalent results for graft operations and flap procedures, and graft onlay procedures are technically far easier to perform. There are some cases where flap reconstruction would be expected to provide superior results (i.e., radiation strictures, patients with multiple operations, pendulous strictures). However, with the increased knowledge gained by the enthusiastic application of graft reconstruction, a paradigm for anterior reconstruction has been redefined. Although grafts have been used successfully for all segments of the anterior urethra, many authors think that, all other variables being equivalent, flaps are best suited for distal reconstruction, and grafts are best for proximal reconstruction (Greenwell et al, 1999).

Postoperative erectile dysfunction is an important issue. Our rates for anterior urethral anastomotic reconstruction were quoted earlier. In an analysis by Coursey and colleagues (2001), 200 patients who underwent urethroplasty were studied. Overall, the rate of erectile dysfunction after urethroplasty was approximately equal to the rate after circumcision. Longer-segment reconstructions were associated with a higher risk of postoperative erectile dysfunction, although the patient's erectile function improved over time in many cases.

Special mention is needed regarding reconstruction for strictures associated with LS. With the advent of flap techniques, many centers embraced these techniques for these strictures. However, analysis of results from patients with LS treated at several large centers showed a very high recurrence rate. Consequently, these centers adjusted the techniques by applying staged graft techniques (see Fig. 40-26). Staged graft techniques using skin grafts also had a very high recurrence rate in many analyses. Theoretically, because LS is a skin condition, the use of skin as a flap, single-stage graft, or staged graft does not preclude involvement of the skin with the inflammatory process (Lee and Phillips, 1994; Akporiaye et al, 1997). Surgeons at numerous centers believe that staged oral graft techniques should be employed for reconstruction of strictures associated with LS. Short-term follow-up results suggest better success

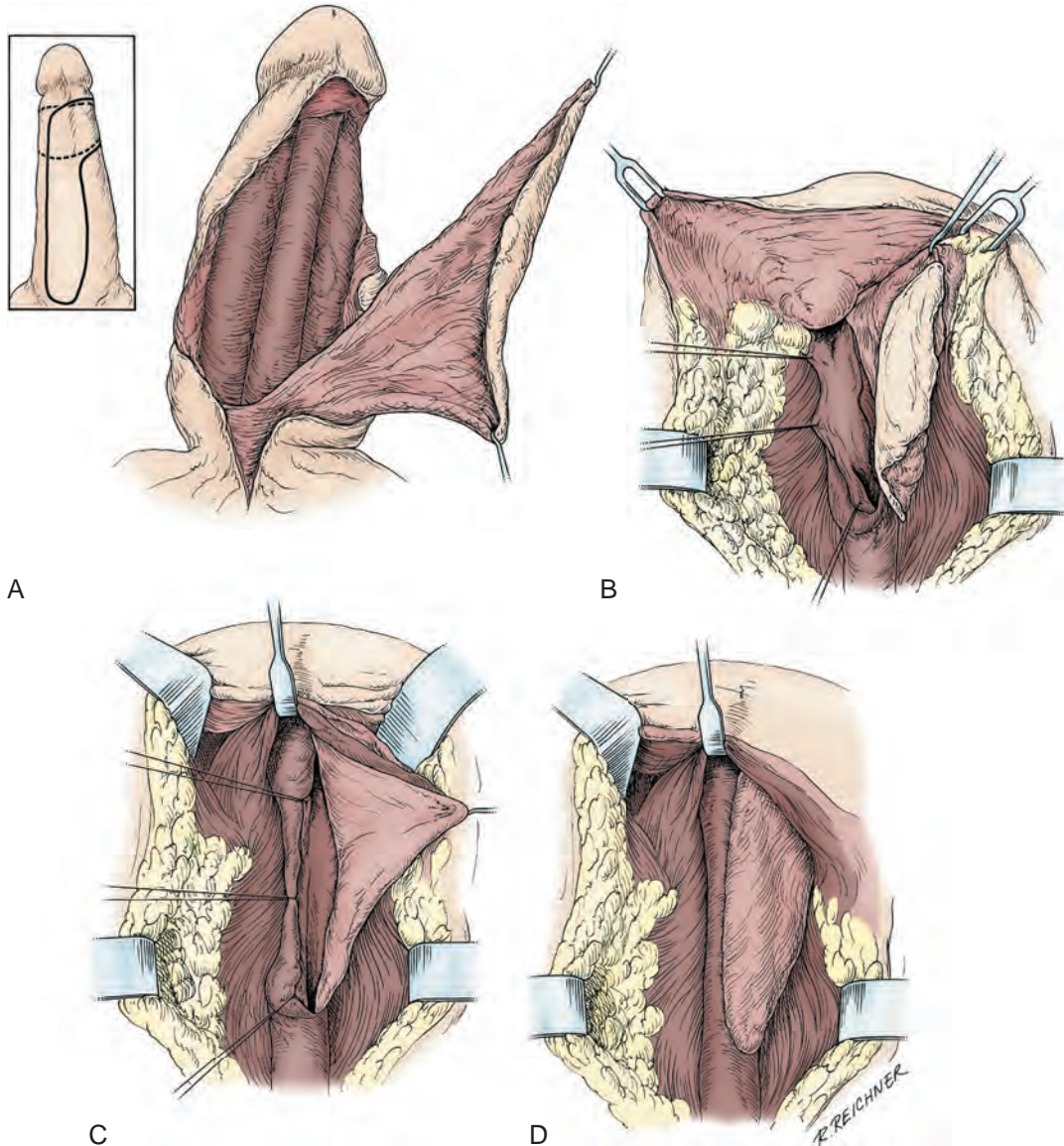


Figure 40-30. Ventral skin island for long bulbous stricture. The skin paddle of the flap is developed on the ventral midline of the penis and can be extended around the penile shaft at its distal end. A, The paddle of the flap has been incised, and its pedicle has been elevated. This pedicle includes Buck fascia and dartos fascia, denuding the tunica of the corpus spongiosum and the corpora cavernosa. The pedicle (the dartos fascia bilaterally) is based on the superficial external pudendal vessels and the internal pudendal vessels in the scrotum. Development of this pedicle allows the flap to be moved to any area of the urethra. B, The flap has been passed through a tunnel beneath the scrotum developed by dissection along the corpus spongiosum. A laterally placed urethrostomy has opened the urethral stricture. C, The deep edge of the flap is secured by the suture techniques previously described. D, Anastomosis of the flap has been completed. The pedicle can be seen extending beneath the scrotum. (From Jordan GH, McCraw JB. Tissue transfer techniques for genitourinary surgery, part III. AUA Update Series 1988;7:lesson 11.)

with this approach. Long-term follow-up results are unavailable. In a review of our experience in patients with a fossa navicularis stricture and LS, we noted a 50% recurrence in the stricture with a ventral transverse skin island (Virasoro et al, 2007).

PELVIC FRACTURE URETHRAL INJURIES

PFUIs are the result of blunt pelvic trauma and accompany about 10% of pelvic fracture injuries. Although total disruption of the urethra is possible with a straddle injury, these injuries most

commonly involve only the bulbous urethra. However, the ensuing spongiofibrosis can be associated with complete obliteration of the urethra. Distraction injuries are unique to the membranous urethra. Pelvic fracture distraction injuries of the membranous urethra have been compared with plucking an apple (prostate) off its stem (the membranous urethra). This analogy implies that the injury most frequently occurs at the apex of the prostate. However, experience shows that this is not the case, and the most frequent point of distraction is at the departure of the bulbous urethra from the membranous urethra (Andrich and Mundy, 2001; Mouraviev and Santucci, 2005). The distraction can

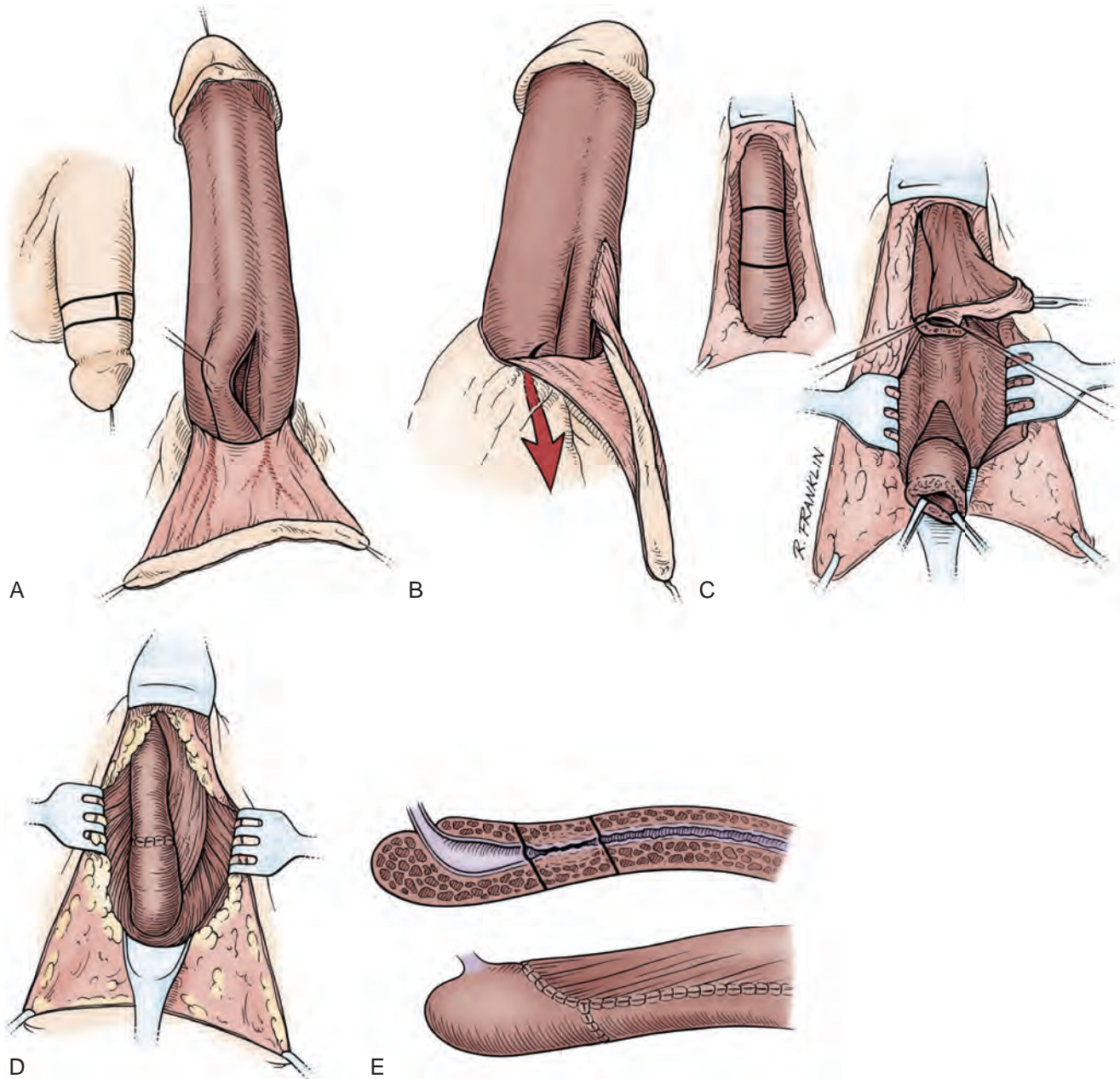


Figure 40-31. Reconstruction in a patient with a long anterior urethral stricture with a relatively short narrow-caliber section (technique of augmented anastomosis with circular skin island). **A**, A circular skin island is elevated on the dartos fascia. The patient is positioned flat on the table. **B**, The skin island onlay is begun, the rest of the flap is placed into the perineal dissection, and the penis is closed; the patient is then repositioned in the lithotomy position. **C**, The flap is retrieved through the perineal dissection. The narrow-caliber section is excised, and the urethra is spatulated on the dorsum. **D**, The onlay is completed, and the floor strip anastomosis is closed. **E**, Schematic of the surgery. (From Stack RS, Schlossberg SM, Jordan GH. Reconstruction of anterior urethral strictures by the technique of excision and primary anastomosis. *Atlas Urol Clin North Am* 1997;5:11–21.)

involve all or any portion of the membranous urethra between the departure of the bulbous urethra and the apex of the prostate. In postpubescent male patients, the injury seldom involves the prostatic urethra. In prepubescent male patients, in whom the prostatic urethra is more fragile, the injury can extend into that area.

Total distraction of the entire circumference of the urethra appears not to occur with many injuries. Instead, a strip of epithelium is left intact. In these patients, the placement of an aligning catheter may allow the urethra to heal virtually unscarred or with an easily managed stenosis. Because of flexible

endoscopy equipment, the placement of an aligning catheter is straightforward. If distraction is complete, the catheter serves to align the obliterated urethral ends, and reconstruction is facilitated. Because of the ready availability of flexible cystoscopes, some centers acutely evaluate these injuries only with endoscopy. Clinicians who are enthusiastic for this approach believe that not only can the injury be completely evaluated, but also the entire process, including the placement of an aligning catheter, is expedited (Kielbaso et al, 2001). Aligning catheters are just what the name implies—a guide, not a mechanism for placing traction on the bladder and

KEY POINTS: TREATMENT OF URETHRAL STRICTURE

- In the treatment of urethral stricture disease, the patient and the physician must have a good understanding of the goals of treatment before the treatment choice is made.
- Urethral dilation is the oldest and simplest treatment of urethral stricture disease. However, the goal of dilation is to stretch the scar atraumatically. Dilation is seldom used curatively.
- Internal urethrotomy refers to any procedure that opens the stricture by incising it transurethrally. The factors that contribute to success of internal urethrotomy have been defined as follows: internal urethrotomy should be reserved for strictures of the bulbous urethra; the stricture should be less than 1.5 cm in length; and the stricture should not be associated with dense deep spongiofibrosis. Many studies have shown that repeated dilation and internal urethrotomies diminish the success rate of eventual open urethral reconstruction.
- Numerous lasers have been used for anterior urethral strictures. To date, the results of laser urethrotomy are mixed.
- Excision with primary anastomosis has proved to be the gold standard for repair of anterior urethral strictures. Previously, excision with primary anastomosis was thought to be a relatively limited procedure and applicable only for strictures less than 1.5 to 2 cm. However, with better understanding of the anatomy, longer strictures have been successfully addressed with excision and primary anastomosis.
- Some strictures require tissue transfer, and grafts and flaps have been successfully employed. A meta-analysis by [Wessells and McAninch](#) (1998) showed that the results of graft reconstruction and flap reconstruction are equivalent. The complexity of flap procedures is greater than that of graft procedures. The concept of augmented anastomosis can be used with graft and flap onlay and is thought to provide better results than just pure onlay in many cases. When flaps are employed for urethral reconstruction, conceptually all become one operation with multidimensional application.

prostate. Aligning catheters also seem to act as a drain as the pelvic hematoma liquefies, and perhaps the presence of the catheter may allow more rapid and complete resolution of the process ([Cohen et al, 1991](#); [Herschorn et al, 1992](#); [Rehman et al, 1998](#); [Mouraviev et al, 2005](#)). Close follow-up after a voiding trial is essential because many of these patients experience stricture formation after removal of the aligning catheter and require definitive repair ([Leddy et al, 2012](#)).

Evaluation

As with the repair of any stricture or stenosis, it is important to define the precise anatomy of the pelvic fracture injury before treatment is undertaken ([McCallum and Colapinto, 1979a, 1979b](#)); this includes the depth, density, length, and location. In pelvic fracture urethral distraction defects, the depth and density of fibrosis are predictable. Although the location of the distraction injury has been shown to be an important factor in continence after reconstruction, this information should be a factor only in counseling of patients before the reconstruction and not in the treatment approach. The length of the defect is an important consideration and must be determined as precisely as possible.

Contrast studies are a first-line tool for the evaluation of PFUI. A cystogram outlines the bladder and provides information about rostral displacement of the proximal urethra. A lack of contrast material in the posterior urethra gives some information, albeit inconclusive, about the integrity of the bladder neck.

When the patient is successful in relaxing to void and the cystogram outlines the posterior urethra, a simultaneous retrograde urethrogram outlines the length of the injury defect.

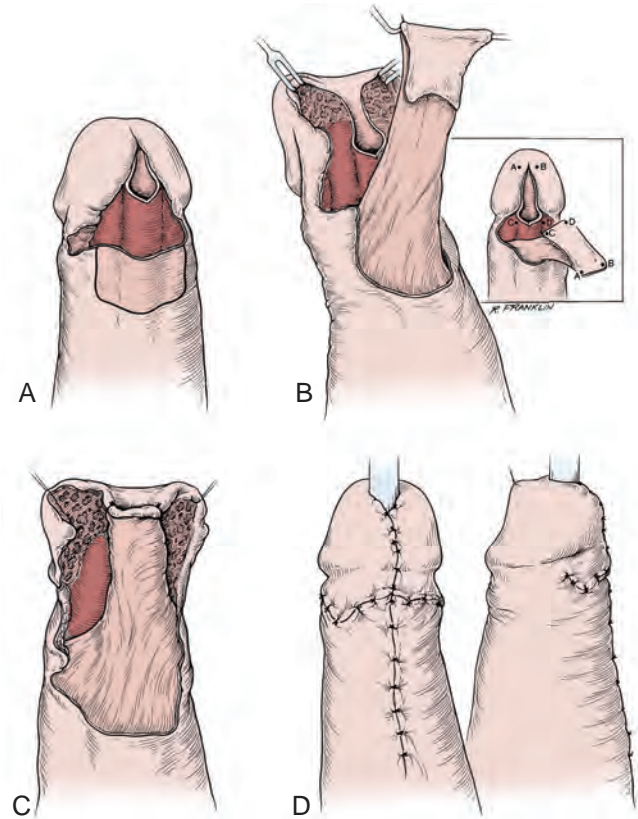


Figure 40-32. Technique of reconstruction of the fossa navicularis after Jordan. **A**, The ventral corpus spongiosum is exposed, and the urethra is opened ventrally through the area of stenosis. A transverse ventral skin island is outlined on the distal penile skin. **B**, The skin island is elevated on the ventral dartos fascia. **C**, The skin island is transposed and inverted into the meatotomy defect (*inset, B*). **D**, Appearance of the penis closed after the procedure. (**A** to **C**, From Jordan GH. Reconstruction of the fossa navicularis. *J Urol* 1987;138:1210; **D**, from Jordan GH. Reconstruction of the meatus-fossa navicularis using flap techniques. In: Schreiter F, editor. *Plastic-reconstructive surgery in urology*. Stuttgart: Georg Thieme; 1999. p. 338–44.)

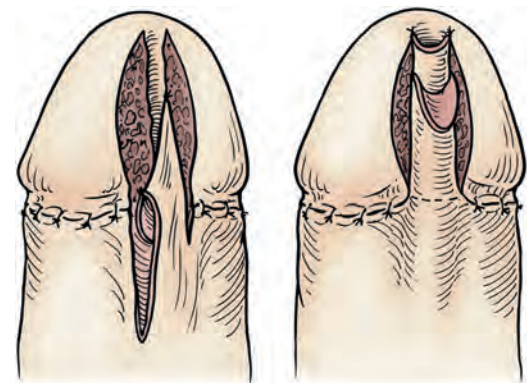


Figure 40-33. Technique after De Sy, in which a ventral longitudinal skin island is advanced into the meatotomy defect. The skin island is developed by de-epithelialization of a portion of the longitudinal flap. (From Jordan GH. Management of anterior urethral stricture disease. *Probl Urol* 1987;1:199–225.)

However, this situation is the exception rather than the rule, and retrograde urethrography is most useful for determining whether the anterior urethra is normal. If the anterior urethra is normal, it has been our experience and the experience of others that a successful anastomotic repair is ensured. A primary anastomosis has

been shown to be possible even with some involvement of the anterior urethra. Even in cases of prior failed posterior urethral reconstruction, primary anastomotic repair is often feasible, although the failure rate is slightly higher in these cases (Chapple and Pang, 1999; Flynn et al, 2003; Koraitim, 2003; Shenfeld et al, 2004). **Primary anastomosis is unquestionably the goal in all patients until it is proved impossible to perform.**

When the proximal urethra is not visualized on a simultaneous cystogram with urethrogram, endoscopy through the suprapubic tract in combination with retrograde urethrography can be used to outline the defect. After the endoscopic appearance of the bladder neck is assessed, the flexible endoscope can be advanced through the bladder neck and into the posterior urethra to the level of the obstruction. **The appearance of the bladder neck on contrast studies or on antegrade endoscopy does not accurately predict the ultimate function of the bladder neck after urethral reconstruction (Iselin and Webster, 1999).** A simultaneous retrograde urethrogram outlines the anterior urethra, with the space not visualized representing the injury defect.

Some authors have advocated MRI for the evaluation of patients with PFUIs. We have had little experience with MRI for that purpose; however, we have found the information obtained on the few studies that we have done to be useful. In these cases, there was the question of bone interposition into the injury defect, and MRI outlined this. We evaluated a case in which the prostatic urethra appeared obliterated. On MRI, one could easily see that the prostate was not only distracted from the membranous urethra but also distracted from the bladder. This information was essential to planning of subsequent reconstruction in this case. It would seem intuitively obvious that knowing the length of distraction would be helpful in determining the precise approach and steps necessary for reconstruction. However, the literature is unclear on this matter (Andrich et al, 2003; Koraitim, 2004), and it is our experience that the surgeon must be prepared to exercise all options of reconstruction in virtually all such cases (McCallum and Colapinto, 1979a, 1979b).

Repair

The timetable for the reconstruction of PFUIs is determined by the type and extent of associated injuries. If possible, it is desirable to proceed within 4 to 6 months after trauma. However, orthopedic injuries of the lower extremities often necessitate a delay in proceeding with urethral reconstruction (Mundy, 1991; Follis et al, 1992; Brandes and Borrelli, 2001).

In most cases, PFUIs are not long, and the resultant obliteration is amenable to a technically straightforward mobilization of the corpus spongiosum with a primary anastomotic technique. The classic reconstruction consists of a spatulated anastomosis of the proximal anterior urethra to the apical prostatic urethra. However, experience has demonstrated that anastomosis of the proximal anterior urethra to any segment of the posterior urethra (apical, prostatic, or below) can be successfully accomplished by a widely spatulated anastomosis in which optimal epithelial apposition is achieved. About 10% of PFUIs are associated with more complex injuries and can be associated with fistulae (most commonly urethral rectal fistulae). Reconstruction of these injuries is technically more demanding.

Several series support the concept that the bulk of PFUIs, even the most difficult cases, can be managed by the perineal approach (Webster et al, 1983; Koraitim, 1985; Webster and Sihelnik, 1985; Webster et al, 1990; Morey et al, 1996; Koraitim, 1997; Flynn et al, 2003). A transpubic or an abdominal-perineal approach, as pioneered by Waterhouse and colleagues (1973), in our experience, is unnecessary for the reconstruction of distraction injuries. In addition, pubectomy can be associated with long-term sequelae, including shortening of the penis, destabilization of erection, and destabilization of the pelvis, resulting in a chronic pain syndrome with exercise. However, some surgeons continue to rely heavily on the transpubic approach (Koraitim, 1997; Das et al, 2004).

Alternatively, the above-and-below approach has merit when concomitant surgery is planned in the region of the bladder neck. We have found and Iselin and Webster (1999) reported that the competence of the bladder neck is difficult to assess accurately before the reestablishment of urethral continuity. In the past, great reliance was placed on whether the bladder neck was closed or open on cystography. However, contrast material may opacify the prostatic urethra when the bladder neck is more than adequately competent for continence. Similarly, confidence has been placed in the appearance of the bladder neck on endoscopic examination through the suprapubic tube. Again, even when an obvious scar is noted to involve the bladder neck, follow-up of these patients after urethral reconstruction establishes continuity of the urethra and finds many patients with more than adequate continence. Other patients are believed to have incontinence secondary to scar incarceration of the bladder neck, caused by the extensive fibrosis left behind by resolution of the hematoma. However, in our experience, this is an infrequent occurrence, and the appearance of the bladder neck by any modality available is not predictive of continence. It is currently our practice to reestablish the continuity of the urethra and, when there are concerns about continence, to forewarn the patient before the urethral reconstruction. If these patients find that they experience inadequate continence postoperatively, the problem is addressed in a subsequent procedure (Bhargava et al, 2004).

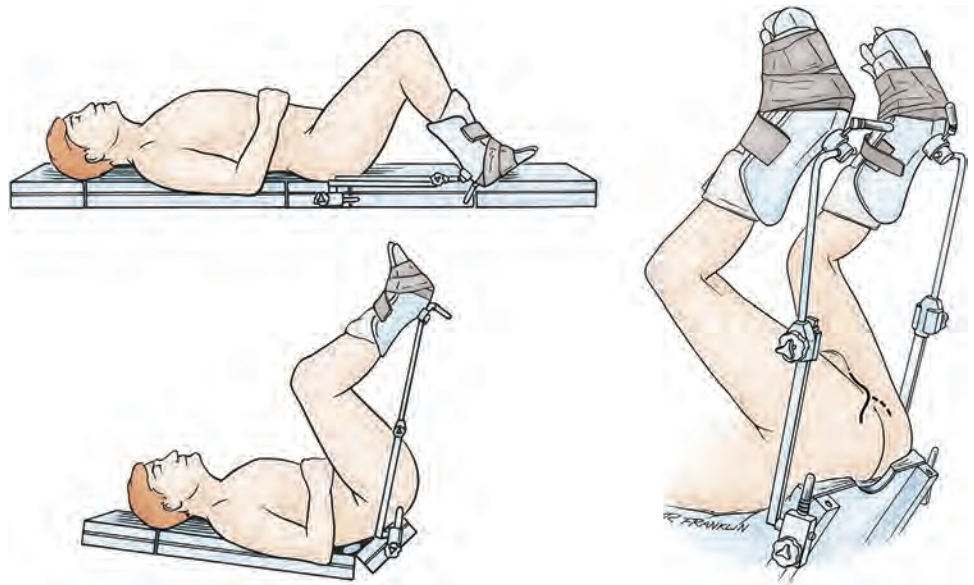
At the time of reconstruction, before the patient is placed in the lithotomy position, endoscopy is performed through the meatus and again through the suprapubic tube sinus. Endoscopy on the table is designed to ensure that there is no concomitant vesicolithiasis. The endoscopy is performed with a rigid endoscope, which is manipulated through the suprapubic tube sinus and the bladder neck and positioned against the area of total obliteration. On gentle manipulation of the endoscope, if the impulse of the endoscope tip is felt on the patient's perineum, the impulse is palpable when the perineum is opened, and an instrument is manipulated through the bladder neck during reconstruction. If the impulse is not palpable perineally at this time, it may not be palpable during dissection. We create a temporary vesicostomy in these cases, which allows us to position an instrument reliably through the bladder neck because the vesicostomy allows the surgeon to identify the bladder neck palpably before instrumentation of the posterior urethra. This maneuver has eliminated the occurrence of false passages with use of a sound such as the Haygrove staff through the suprapubic site and has eliminated the occurrence of misanastomosis of the anterior urethra to sites other than the apical proximal urethra.

We prefer the use of the exaggerated lithotomy position for the perineal approach (Fig. 40-34). This position is safe and provides optimal exposure to the area of the membranous and apical prostatic urethra (Angermeier and Jordan, 1994). A custom Skytron table, modified to allow the exaggerated lithotomy position, and a Stille-Scandia table, designed to place patients in the lithotomy position, are our preferences. The legs are carefully positioned in Allen-style or Guardian-style stirrups. Care is taken to avoid pressure on the lateral aspects of the lower extremities and calf muscles. The patient's hips are elevated into position by raising the buttocks portion of the operating table. The boots are positioned to avoid stretch injuries of the common peroneal nerves (see Fig. 40-34).

After the patient is correctly positioned, the perineal approach to reconstruction begins with an incision and dissection anterior to the transverse perinei musculature (anterior perineal triangle). This is in contrast to the approach posterior to the transverse perinei musculature (posterior anal triangle), which is useful for perineal prostatectomy. We use a λ -shaped incision (Fig. 40-35) that is carried sharply down to the midline fusion of the ischiocavernosus musculature (see Fig. 40-35A), then beneath the scrotum, to expose the uninvested portion of the corpus spongiosum. We then place a self-retaining ring retractor.

The fusion of the ischiocavernosus musculature is divided, and the musculature is cleanly dissected from the corpus spongiosum and bulbospongiosum (see Fig. 40-35B to D). The corpus spongiosum is detached from the triangular ligament and corpora cavernosa (see Fig. 40-35E), the bulbospongiosum is detached from the

Figure 40-34. Patient placed in an exaggerated lithotomy position. The hips have been rotated into position by elevation of the buttocks portion of a specially modified table. The legs are suspended from boot-style stirrups with as little flexion of the hips and knees as allowed by the design of the stirrups. (From Angermeier KW, Jordan GH. Complications of the exaggerated lithotomy position: a review of 177 cases. *J Urol* 1994;151:866–8.)



perineal body, and the dissection is carried farther down to the infrapubic space. Posterior detachment of the bulbospongiosum is carried anteriorly, and the dissection is eventually carried through the area of fibrosis (see Fig. 40-35F).

In some cases, the proximal blood supply is encountered and must be controlled. We have found that these arteries are easily controlled with a sharp-tipped hemostat and monopolar cautery. Suture ligation should be avoided in the arteries to the bulbospongiosum because of their proximity to the nerves as they are coursing into the corpora cavernosa.

We divide the triangular ligament and vigorously develop the intracural space down to the pubis (Fig. 40-36). If the dorsal vein is encountered, it is ligated and divided. It is important to ensure that the arteries were not rolled into the intracural space if the tissues were dislocated during trauma. The penetration of the cavernosal arteries or the dorsal arteries, or both, into this space is commonly seen. If there is doubt about the nature of the vessels encountered, Doppler sonography should be performed. When the pubis is exposed, the periosteal elevator can be gently introduced onto the retropubic surface, releasing and allowing the descent of the tissues from beneath the pubis.

We introduce a Haygrove staff into the suprapubic sinus and through the bladder neck to the distal limits of the posterior urethra (see Fig. 40-35G and H). The impulse is palpated, and the fibrosis is resected until normal tissue is encountered. The tissue is submitted for histologic examination. The tip of the Haygrove staff is eventually concealed only by the normal urethral epithelium, at which point we open the epithelium and control it with either a skin hook or a stitch. We perform endoscopy to ensure that the urethrotomy is at the distal limits of the posterior urethra. If a tension-free anastomosis is thought to be impossible, we mobilize the corpus spongiosum beneath the scrotum from its attachment to the corpora cavernosa. Aggressive mobilization of the corpus spongiosum is the last maneuver undertaken because it is thought to have possible ill effects on the retrograde blood supply, which in a patient with pelvic fracture may be tenuous. Meticulous detachment of the investment of Buck fascia from the corpus spongiosum increases the compliance of the corpus and limits the need for aggressive mobilization.

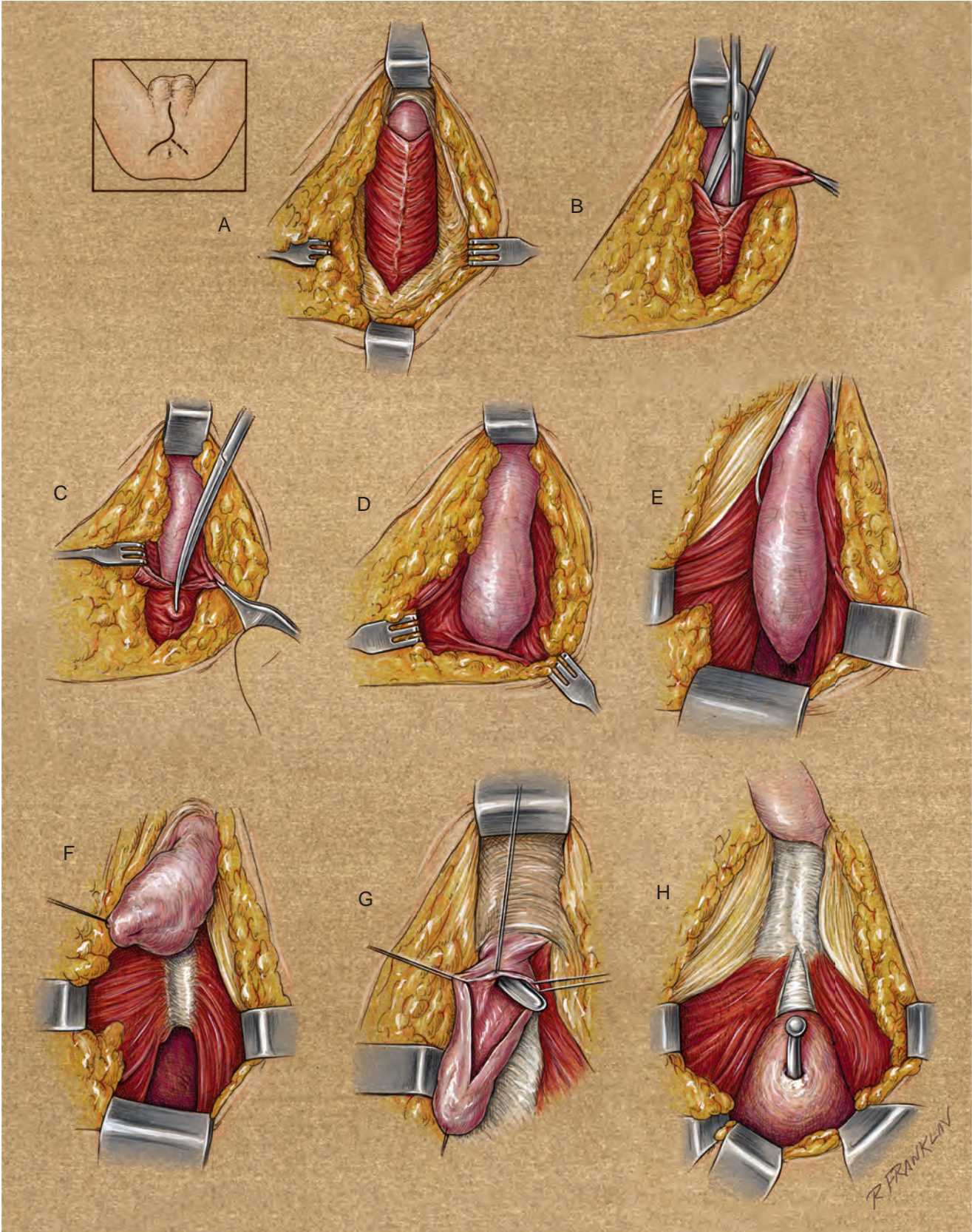
It is important to try to avoid the creation of chordee during the repair of a distraction injury. To prevent chordee, the attachment cannot be carried beyond the area of the penoscrotal attachment. However, it is warranted in some cases to counsel patients preoperatively that they may have some chordee after aggressive mobilization that results in a primary anastomotic repair. Primary anastomotic repairs have success rates in the high 90% range. If a

technique of tissue transfer is needed, the long-term cure rates may eventually be only in the mid-80% range. Most of these patients are young. Successful, durable reconstruction is of paramount importance. If chordee results, it is most often mild and not disabling sexually; in our and other surgeons' minds, it is probably a fair trade for optimizing the urethral reconstruction. Development of the intracural space—mobilization of the corpus spongiosum, infrapubectomy, and, if needed, rerouting of the corpus spongiosum—shortens the course that the corpus spongiosum must traverse and allows reconstruction without attendant chordee.

The proximal urethrotomy is spatulated so that it accepts at least a 32-Fr bougie à boule, and 10 to 12 anastomotic sutures are placed and tagged to allow identification of their position in the proximal anastomosis. We have used a combination of 3-0 Monocryl and 3-0 polydioxanone sutures for this purpose. No special needles are required for the placement of these sutures. However, a Heaney needle driver and a Ravitch needle driver can be useful in difficult cases. After spatulation of the proximal urethrotomy and placement of the sutures, we spatulate the proximal portion of the anterior urethra. The spatulation is continued until the urethrotomy accepts a 30-Fr to 32-Fr bougie à boule, and the anastomotic sutures are placed in their respective locations. Before seating the anastomosis, we introduce a soft silicone (Silastic) ribbed urethral stenting catheter through the anastomosis under direct vision. The wound is copiously irrigated to reduce the clot around the area of the anastomosis, and the anastomosis is seated.

Next, we reattach the corpus spongiosum to the corpora cavernosa and the bulbospongiosum to the perineal body. We place a small suction drain deep to the closure of the ischiocavernosus musculature and Colles fascia and a second one superficial to that closure and beneath the subcutaneous closure.

In cases in which the proximal urethra is significantly distracted in a rostral direction, the surgeon must be prepared to perform infrapubectomy (Fig. 40-37) or corporeal rerouting, or both (Fig. 40-38). Performance of the infrapubectomy, along with the development of the intercrural space, allows exposure of the apical prostatic urethra. When the prostatic urethra remains rostrally displaced, the impulse of the sound or instrument placed through the cystostomy tract into the bladder neck is often not readily apparent. In these situations, it is comforting to be able to palpate the bladder neck and the properly placed sound before embarking on a dissection beneath the pubis. In addition, if the rostral distraction is significant, the path of the anterior urethra over the hilum of the penis into the infrapubectomy often does not allow a tension-free anastomosis, and the infrapubectomy can be continued beneath



one side of the corpora cavernosa, allowing rerouting of the corpus spongiosum (see Fig. 40-38).

Postoperative Management

We use a small soft silicone (Silastic) stenting catheter. Urine is diverted via the suprapubic cystostomy, and the urethral catheter is plugged and serves as a stent only. After the reconstruction, patients are initially kept at bed rest for 24 to 48 hours and then ambulated and discharged with the suprapubic catheter and stenting urethral catheter in place. Patients are discharged on a regimen of oxybutynin and a suppressive antibiotic only if the preoperative urine culture was positive. The drains are removed as drainage allows.

A voiding trial with contrast material is performed between 21 and 28 days postoperatively. Patients are directed to stop taking oxybutynin 24 hours before the voiding trial. In anastomoses that are technically straightforward, the trial is performed at 21 days, and

in cases with more rostral distraction of the proximal urethra, the trial is delayed for 3 to 5 days longer. The trial involves removing the urethral catheter, filling the patient's bladder with contrast material, and instructing him to void. We do not use pericatheter retrograde urethrography to evaluate patients who have undergone urethral reconstruction. The voiding film is examined to ensure that there is no extravasation and that the reanastomosis appears widely patent. A urine culture specimen is also obtained, and the suprapubic catheter is plugged. The patient is allowed to void through the urethra for 5 to 7 days, and the suprapubic catheter is then removed. Approximately 6 months postoperatively and again 1 year later, patients are evaluated with flexible endoscopy. At that time, we consider the reconstruction to be mature, and it should be widely patent. If no symptoms have reappeared, we refer further follow-up examinations to the referring urologist.

We have almost completely replaced postoperative retrograde studies with flexible endoscopy. We have not found flow studies

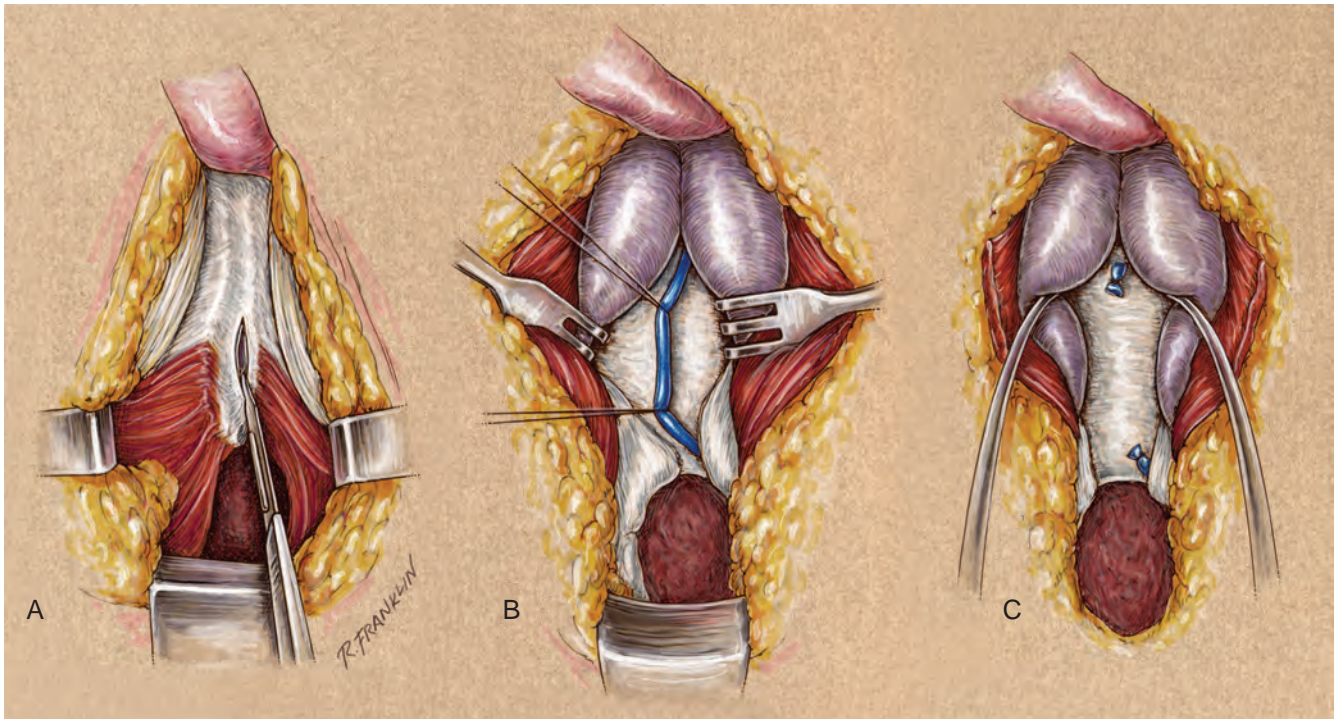


Figure 40-36. Division of the triangular ligament and development of the intracanal space. A, When the prostatic urethra is displaced, and the arc that the urethra must traverse needs to be shortened, that length can be shortened by incision of the triangular ligament. B, Incision and mobilization of the perichondrium and periosteum of the symphysis pubis to allow placement of retractors without trauma to the erectile bodies. Lateral displacement of the crura exposes the dorsal vein of the penis; after careful identification, the vein can be ligated and divided. C, Completion of the dissection affords additional exposure for resection of the fibrosis that surrounds the apex of the prostate and the proximal end of the disrupted urethra. (From Jordan GH. Reconstruction of the meatus-fossa navicularis using flap techniques. In: Schreiter F, editor. Plastic-reconstructive surgery in urology. Stuttgart: Georg Thieme; 1999. p. 338–44.)

Figure 40-35. Perineal repair of a membranous urethral stricture. A λ -shaped incision extends from the midline of the scrotum to the ischial tuberosities. A, Colles fascia has been opened to expose the midline fusion of the ischiocavernosus muscles and the tunica of the corpus spongiosum distal to the edge of the muscles. B, The scissors are introduced to develop the space between the muscle and the bulb of the urethra. C, An incision is made in the midline with the scissors, exposing the length of the bulb. D, The ischiocavernosus muscle is retracted to expose the full length of the bulb. E, The self-retaining retractor is placed to expose the inferior fascia of the genitourinary diaphragm. The bulb of the corpus spongiosum (bulbospongiosum) can be mobilized to gain access to the fibrosed area of the urethra. F, The fibrosed urethra is incised, freeing the bulb. G, The anterior urethra is opened to make an adequate lumen. H, The Haygrove staff has been passed through the suprapubic cystostomy. Resection of the fibrotic distraction defect has allowed it to pass into the perineum.

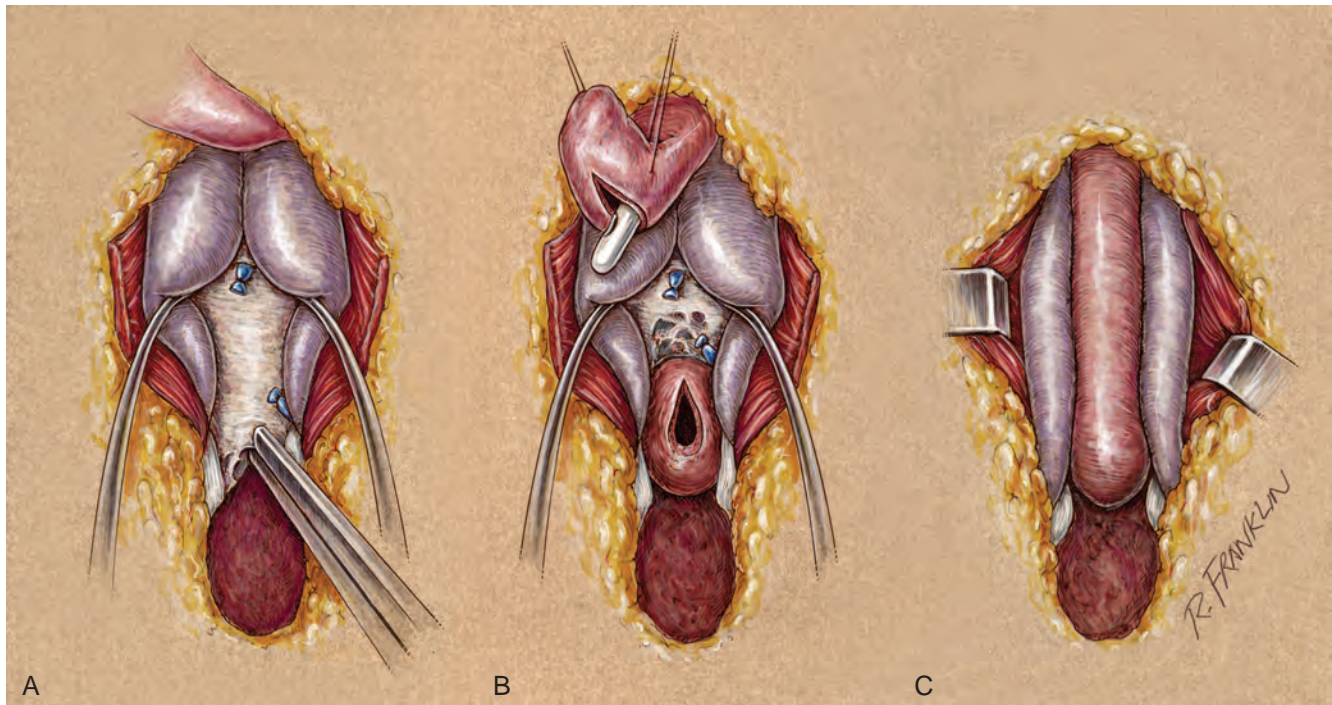


Figure 40-37. Infrapubectomy. If the prostate is elevated behind the symphysis pubis (A), the inferior aspect of the symphysis is resected with a Kerrison rongeur. As much of the bone can be removed as necessary (B) to afford a simple approximation of the ends of the urethra (C).

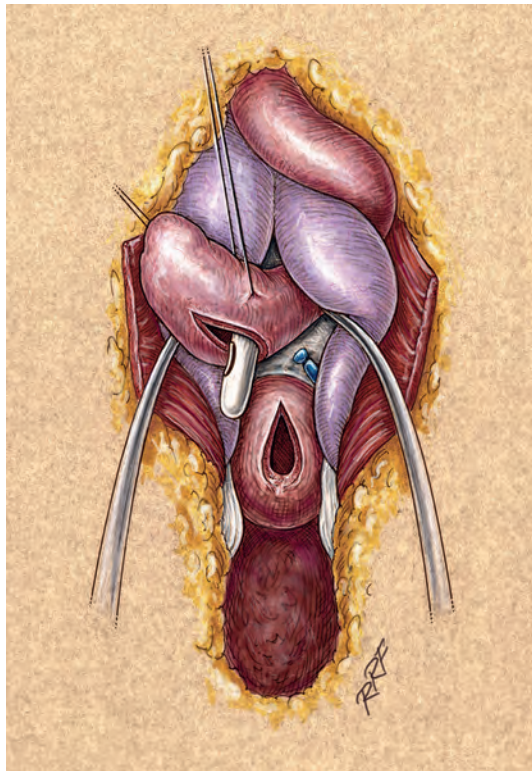


Figure 40-38. Resection of the pubis and rerouting of the urethra around the crus. When the prostate is markedly displaced, it may be necessary to expand the infrapubectomy. Sometimes, despite separation of the crura to the full extent possible, the two ends of the urethra do not meet when they are brought directly through the crus. It is necessary to bring the urethra lateral to one of the crura to make up this length.

to be valuable in observing these patients. In many cases (anterior urethral reconstruction), we have found that retrograde urethrography is more confusing than helpful.

With the use of the techniques discussed or similar techniques, curative rates for reconstruction of posterior PFUIs are in the high 90% range. In large centers, failures are not due to technical problems (i.e., anastomotic restenosis). In general, failures are indicative of ischemia of the proximal corpus spongiosum with ensuing stenosis of the mobilized corpus spongiosum. This occurs because, with mobilization, the corpus spongiosum, in essence, becomes a flap with the vascular pedicle being the retrograde vascularity from the arborization of the dorsal arteries through the glans (Fig. 40-39).

We have studied this phenomenon in trauma patients and have arrived at conclusions that we believe allow us to predict the patients at risk for this ischemic atrophy phenomenon. Initially, we used pudendal angiography to study all trauma patients who seemed to be at risk for bilateral deep internal pudendal artery injury at the time of trauma. These were patients who had evidence of injury to the dorsal penile nerves, patients in whom reconstruction had failed at other centers, patients with lateral impact pelvic fractures, and patients whose pelvic fractures were of the “wind-swept” variety (Brandes and Borrelli, 2001). We found that many patients had evidence of either unilateral or bilateral pudendal artery lesions, but that most had evidence of vascular reconstitution. Patients with an intact pudendal artery on one side often were potent and were reliably cured with reconstruction. Patients with only reconstituted vessels, either unilateral or bilateral, never were potent but were reliably reconstructed. We found that these patients were optimal candidates for penile arterial revascularization to improve potency. Because we noted this relationship to potency, we began evaluating patients with duplex ultrasonography. We found that patients with normal unilateral or bilateral pudendal arteries demonstrated normal arterial parameters on duplex evaluation. Patients with only reconstituted bilateral or unilateral arteries never had normal arterial parameters on duplex ultrasonography.

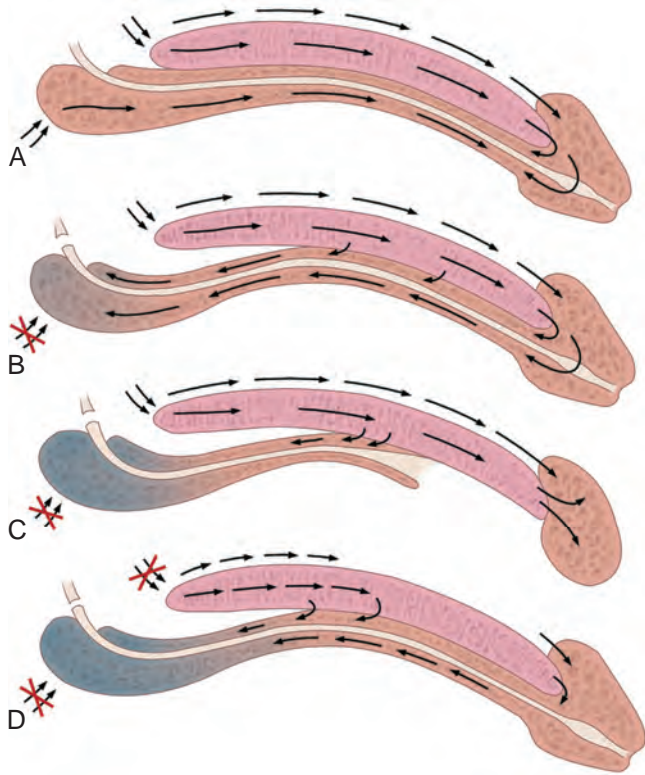


Figure 40-39. Diagrammatic representation of the deep vasculature of the penis. **A**, In the normal situation, through the common penile artery, flow is directed to the tip of the penis with arborization into the spongy erectile tissue of the glans penis. This provides retrograde flow into the corpus spongiosum. If the arteries of the bulb are intact, there is also antegrade arterial flow to the corpus spongiosum. **B**, With interruption of the arteries to the bulb and mobilization of the corpus spongiosum, all flow to the corpus spongiosum is retrograde through the common penile arterial system. **C**, In hypospadias, the distal corpus spongiosum may have been interrupted, with proximal mobilization of the corpus spongiosum and division of the arteries to the bulb. Even if the common penile circulation is intact to the tip of the penis, it may not adequately provide retrograde vascularity to the corpus spongiosum; ischemic stenosis can ensue. **D**, In the case of injury to the common penile artery, with elevation of the proximal corpus spongiosum and division of the arteries to the bulb, blood flow to the proximal corpus spongiosum may be inadequate, leading to ischemic necrosis or ischemic stenosis.

This information allows us to proceed to pudendal angiography only in patients with abnormal arterial parameters on duplex ultrasonography; patients with normal findings on ultrasonography predictably do well with reconstruction. Our data also show that patients do well with reconstruction if they have at least one side that is reconstituted, and the only patients at risk for ischemic stenosis are patients with bilateral complete obstruction of the internal pudendal vessels. In such patients, we perform penile arterial revascularization to augment the vascularity and, with that accomplished, proceed to urethral reconstruction (Jordan, 2005; Davies et al, 2009; Zuckerman et al, 2012). In many cases of pelvic fracture urethral distraction defects, erectile dysfunction is a consequence of the injury, although erectile dysfunction clearly results from the reconstructive surgery in some patients. We think that the incidence of injury to the pudendal arteries is drastically underreported and under-recognized. We and others believe that in many of these cases, the cause of erectile dysfunction is vascular (Brandes and Borrelli, 2001). However, there are at least a portion of patients

with neurogenic erectile dysfunction following PFUI, as some men experiencing ED following PFUI will have normal arterial inflow (Shenfeld et al, 2003; Metze et al, 2007).

Summary

Using the maneuvers outlined, we have found that virtually all distraction injuries can be reconstructed through a perineal approach with an anastomotic technique. Although the above-and-below approach is used when concomitant bladder neck surgery is performed, the inability to identify these patients accurately has led us to perform bladder neck surgery at a second setting. We have abandoned a transpubic approach as applied to posterior urethral distraction injuries.

Although we favor primary reconstruction of posterior urethral distraction injuries, other authors choose to manage these injuries endoscopically (Barry, 1989). We have found that the endoscopic management of PFUIs is not a simple procedure and must be undertaken only by a skilled and experienced surgeon. Many of these procedures can be categorized as a “cut-for-light” procedure. Although some surgeons report success, most cut-for-light procedures are not done with sufficient precision to allow adequate realignment of the urethra. We have seen many disasters that have resulted from these procedures and in most cases condemn the use of these modalities. In addition, no cut-for-light series compares favorably, with regard to long-term success rates, with series from large centers that use primary anastomotic techniques (Levine and Wessells, 2001).

In 1989, Marshall described his method of using stereotactic techniques for endoscopic alignment of the ends of the urethra. He emphasized the length of time it takes to obtain precise alignment before undertaking the endoscopic portion of the procedure. In his procedure, he passed a wire through the aligned ends of the urethra, minimally dilating the channel and widening it with transurethral resection. The scar is stabilized by a period of self-catheterization. While technically feasible, this approach has limited applicability for most patients. Patients whose medical condition, age, or concomitant orthopedic injury prevents them from being placed in the exaggerated lithotomy position or reconstructed using a transpubic approach may be managed with this technique.

In children, the goals of surgery are the same as in adults. In our experience, most children can undergo reconstruction by the same perineal exposure as used in adults. Exposure is more difficult, but nonetheless perineal anastomosis can be done (Hafez et al, 2005). However, the posterior, sagittal transsphincteric approach has been proposed as a better approach in children (Mathews et al, 1998; Peña and Hong, 2004). We agree that the posterior approach is an elegant method of exposure; however, with this approach, we have observed that surgeons tend to resort to techniques of substitution reconstruction where primary anastomosis could be done and, in our opinion, is superior. With our experience accumulating using the vessel-sparing approach to anterior urethral reconstruction—primary anastomosis and augmented anastomosis—we have extended the technique to select patients with pelvic fracture urethral reconstruction and have found the approach feasible with good results in a small number of patients. However, the advantage has not been proven.

VESICourethRAL DISTRACTION DEFECTS

Enthusiastic use of radical prostatectomy has led to increasing experience with patients who have had total obliteration of vesicourethral anastomosis. In some patients, there is distraction of the vesicourethral anastomosis with either a totally obliterating distraction defect or severe anastomotic stenosis. With increased use of robotic-assisted laparoscopic techniques we have seen a decrease in the number of significant anastomotic stenoses, and other authors have shown this as well (Breyer et al, 2010). This improvement may be secondary to reduction in anastomotic urine leaks, better mucosal

KEY POINTS: DISTRACTION INJURIES OF THE URETHRA

- Urethral distraction injuries are the result of blunt pelvic trauma and accompany about 10% of pelvic fracture injuries. In many injuries, there does not appear to be total distraction of the entire circumference of the urethra; instead, a strip of epithelium may be left behind.
- The use of aligning catheters acutely is controversial, but most clinicians would agree that the aligning catheter, at the very worst, facilitates subsequent reconstruction and, at best, often leaves the patient with an endoscopically manageable stenosis.
- As with any stricture, it is important to define the precise anatomy. The combination of contrast-enhanced studies with endoscopy and selective MRI is useful. The appearance of the bladder neck on contrast-enhanced studies or on antegrade endoscopy is not predictive of ultimate function of the bladder neck. Simultaneous reconstruction of the bladder neck and the posterior urethra is usually not undertaken at the present time.

apposition, and the running anastomosis allowed with the magnification and dexterity using the robotic approach.

As with other defects, it is important to determine the length of the defect accurately. This can be accomplished by simultaneous cystography with retrograde urethrography, simultaneous retrograde urethrography and antegrade endoscopy through the suprapubic tube, or both.

Numerous options are available for the management of these complex patients. Many of these patients have other medical problems, and it has been our observation that many have thick and small bladders, possibly contributing to the difficulty with the initial surgery. The ever-present issue of body habitus also must be considered and, in our opinion, contributes to problems with the initial anastomosis. An indwelling suprapubic tube must always be considered an option. In a patient who is significantly overweight, the results of aggressive reconstruction have not been good. The place for endoscopic techniques is covered later in this section; however, in the case of short-length distractions, we have had good success with aggressive incisions at the 3 o'clock and 9 o'clock positions followed in approximately 3 weeks with repeated incisions. Whether the holmium laser is better than the cold knife can be debated; the hot knife is unnecessary. If one must "core through" to establish continuity, endoscopic procedures have no place in our opinion except as discussed later. [Vanni and colleagues \(2011\)](#) published their experience with radial urethrotomy and intravesical injection of mitomycin C. They had an initial success rate of 72% in patients with recalcitrant strictures.

In some cases, a continent catheterizable bladder augmentation may be a better operation than aggressive functional reconstruction; in an obese patient, construction of a functional catheter channel can be difficult. Diversion must also be entertained, and in patients in whom functional reconstruction is not an obvious choice, it becomes a primary option.

If functional reconstruction is deemed possible, we think it is a reasonable choice, and our technique is as follows. We place the patient in a low-lithotomy position and use an abdominal-perineal combined approach. We make a lower midline incision, exposing the bladder and dissecting it from the lateral sidewall and further mobilizing the anterior bladder from beneath the pubis as aggressively as can be safely undertaken from above. We then open the peritoneum and develop the retrovesical space, again taking care to complete the dissection as safely as can be accomplished from above.

A second surgeon begins the perineal dissection by a curvilinear perineal incision similar to that used for a radical perineal prostatectomy. The dissection is posterior to the transverse perineal musculature (posterior anal triangle) and carried along the anterior rectal wall to the area where fibrosis is encountered from the prior

radical prostatectomy dissection. The impulse of the perineal surgeon's finger can usually be felt adjacent and lateral to the area of fibrosis and distraction at this point. In addition, the abdominal surgeon places a finger at the limits of the retrovesical dissection from above to provide another palpable landmark and to ensure a safe dissection anterior to the rectal wall and posterior to the bladder and trigone. The perineal dissection is joined to the abdominal dissection, and the rectal wall is completely peeled off the area of fibrosis associated with the distraction defect. We place drains between the rectum and the distraction defect, encircling the area of fibrosis.

The dissection beneath the pubis is made easier by the excision of an ellipse of the rim of the superior pubic ramus. Total pubectomy is not required. Partial pubectomy can be performed with the reciprocating attachment of the Aesculap surgical drilling device (Aesculap, Tuttlingen, Germany); this makes placement of the sutures technically straightforward and improves the exposure for the dissection and resection of the distraction fibrosis.

At this point, the bladder is opened, and the area of the bladder neck is determined. A sound is placed and advanced to the area of obliteration; this allows us to resect the well-defined area of fibrosis completely. The urethral stump is exposed and opened, and the site of the neobladder neck, having been identified, is opened. We marsupialize the bladder epithelium as described by [Eggleston and Walsh \(1985\)](#), place anastomotic sutures in the urethral stump, and pass a stenting catheter.

Before the vesicourethral anastomosis is seated, the omentum is mobilized and placed between the posterior wall of the anastomosis and the anterior rectal wall. We seat the anastomosis and wrap the omentum around the area of anastomosis, tagging it into place. The lateral vesical spaces are drained with closed suction drains, and a suprapubic tube is left in place when the vesicostomy is closed. We have been doing this procedure perineally with similar outcomes.

Postoperative care is the same as for a radical prostatectomy. Patients are discharged when their drainage and ambulation allow and their diet has been resumed. We evaluate patients 4 to 6 weeks postoperatively, with the stenting urethral catheter removed and the bladder filled by way of the suprapubic tube.

Because one attempt has failed in these patients, we generally are conservative with the timing of a voiding trial. In some cases, voiding trials are done at 2 to 3 weeks.

Our series continues to grow, and we continue to have excellent success in reconstruction. We have some patients who deem their continence adequate for their lifestyle; in the others, we have been successful with the placement of an artificial sphincter.

Other authors have proposed a different approach to these very difficult cases. In patients for whom multiple attempts at dilation or incision of these vesicourethral anastomotic stenoses have failed, [Elliott and Boone \(2001\)](#) proposed making an incision with placement of the UroLume endoprosthesis, followed at an interval by the placement of an artificial sphincter. They initially described nine men treated with this approach; seven of the men were satisfied with the results of their treatment at a mean follow-up of 17.5 months. Other authors ([Mark et al, 1993](#); [Kaplan, 2004](#); [Anger et al, 2005](#)) have proposed slight modifications of this approach and also report adequate patency and continence in these patients. With the removal of UroLume from the market, this approach is impossible.

COMPLEX FISTULAE OF THE POSTERIOR URETHRA

The increase in the performance of radical prostatectomy has also led to an increased incidence of vesicorectal or vesicourethrectal fistulae. In most cases, these are small and managed by a transperineal, transanal-transsphincteric, or posterior approach. However, some cases are complex, with the fistulae associated with large granulated cavities. The problem is magnified when radiation (brachytherapy, external beam therapy, or both) is part of the equation. With radiation fistulae, many centers

have gone to diversion with ileal conduit or bowel pouch as opposed to functional reconstruction. These cases have also been managed with the approach described earlier for vesicourethral distraction problems. However, the omentum serves an even more important purpose in these cases. In addition, with the increasing application of “minimally invasive” modalities for carcinoma of the prostate (i.e., brachytherapy, combined brachytherapy with external beam irradiation, higher dose external beam irradiation, and cryotherapy), the magnitude of complexity of these problems of prostatic urethral fistulae, granulated cavities, and severe rectal injury continues to increase. We have tried to approach these problems aggressively, with preservation of function where possible.

In many of these cases, salvage prostatectomy can be combined with rectosigmoid resection. In some cases, we have successfully reanastomosed the bladder to the membranous urethra. Preservation of continence has been mixed. In cases in which vesicourethral anastomosis is impossible, a urachal-peritoneal flap combined with a rectus abdominis muscle flap is used to bolster the closed bladder neck and to keep the closed bladder neck from sticking to the back of the pubis. The bladder is augmented, and a continent catheterizable channel is developed. In some cases, the continuity of the colon cannot be reestablished, and a colostomy is performed as distally on the descending portion of the colon as possible. Whenever continuity of the colon can be reestablished, a J-pouch coloanal anastomosis is done. Omentum is used to envelop the rectal closure or to separate the rectal closure from the vesicourethral anastomosis. The combined abdominal-perineal approach that was previously described provides excellent safe exposure for management of these complex situations. The morbidity of this approach has been acceptable.

One must be careful in addressing the irradiated bowel. We had a patient who did well with his surgery for continent catheterizable augmentation and bowel closure, but when his colostomy was reversed, he developed an overwhelming colitis and a re-fistula, with an eventual septic death. Another patient had a breakdown of his bladder neck closure and to date remains with a large vesicoabdominal fistula. These cases must be individualized. When they go well, they go wonderfully well; when they do not, they become a disaster for the patient, the patient's family, and the surgeons involved.

Zinman reported a 10-year experience with the management of rectourethral fistulae (Vanni et al, 2009). The series comprised 33 patients who had fistulae and who had not undergone irradiation and 33 patients who had undergone irradiation. Mean follow-up for the entire series was about 20 months. The review was a retrospective review taken from office records and hospital records. All fistulae were repaired by an anterior transperineal approach using gracilis muscle interposition flaps and in some cases with a buccal graft. In this series, 100% of the nonirradiated fistulae were successfully closed with a mean follow-up of 20 months, 85% of the irradiated fistulae were closed in a single stage, and 12% required an additional procedure, with an ultimate closure rate of about 97%. In the nonirradiated group, there were no urethral strictures noted with long-term follow-up; five recurrent strictures were noted in the irradiated group. In the nonirradiated group, 91% of the patients had their bowel undiverted. In the irradiated group, 39% had long-term bowel diversion. Zinman believes that the use of muscle interposition flaps are integral to achieving good results, and the use of buccal mucosal grafts, where needed to augment the closure of the urinary tract, was also believed to be invaluable (Vanni et al, 2009). An estimation of ultimate urinary and bowel function is integral to the determination of the plan for reconstruction or diversion, or both. Also, the surgical approach chosen facilitates and limits options (i.e., of the bowel, the urethra, or tissue interposition) (Lane et al, 2006).

CURVATURES OF THE PENIS

Normal elasticity and compliance of all tissue layers of the penis are critical for erectile function, tumescence, and rigidity. Tissues

KEY POINTS: VESICourethRAL DISTRACTION DEFECTS AND COMPLEX FISTULAE OF THE POSTERIOR URETHRA

- Vesicourethral distraction defects are a complication of radical prostatectomy.
- There are many options for management of these complex patients. An indwelling suprapubic tube must always be considered a long-term option. Likewise, in some cases, a continent catheterizable bladder augmentation may be a better operation than aggressive functional reconstruction. If functional reconstruction is deemed reasonable, we have employed an above-and-below technique, in which laparotomy is combined with a posterior perineal triangle dissection.
- The interposition of omentum has been used for distraction defects and for complex fistulae. This approach allows safe mobilization of the rectum from the area of the distraction scar or from the fistula site.
- When radiation is added, the complexity of reconstruction is magnified. The effects of radiation must be allowed to settle; tissue interposition is the rule, and functional reconstruction is impossible in many cases. Some think that diversion, in the case of patients who have received radiation, is the safest and best option.
- Careful consideration of ultimate urinary and bowel function is integral to proper planning of surgery.

must expand in all dimensions as the penis engorges with blood; eventually, the tissues of the tunica albuginea and the septal fibers of the corpora cavernosa are stretched to the limits of their compliance, and tumescence is converted to rigidity. In the normal penis, the tissues are symmetrically elastic, and the erection is straight. In curvature of the penis, there is relative asymmetry of one aspect of the erect penis. In some cases, this condition arises from diminished compliance of one aspect of the tunica albuginea or outright foreshortening of one aspect of the erectile bodies.

The term *chordee* means curvature, but it is commonly used as if it refers to the tissues causing the curvature. This misuse of the term is seen in the statement “the chordee was resected”; properly phrased, the statement should be “the chordee can be corrected by resecting the inelastic tissues that are causing the chordee.”

Curvatures of the penis can be congenital or acquired. Some confusion also exists in common usage of the term *congenital curvature of the penis*. The terms *congenital curvature of the penis* and *chordee without hypospadias* have often been used interchangeably. We prefer to reserve the term *chordee without hypospadias* for patients in whom the meatus is properly located on the tip of the glans penis; a ventral curvature is associated with abnormalities of the ventral fascial tissues or corpus spongiosum, or both. It has long been recognized that hypospadias is a condition that is associated in some patients with either a diminutive penis or a micropenis. Although a small penis is not diagnostic of hypospadias, it is highly unusual for a patient with hypospadias to have an exceptionally large erect penis. In contrast, other congenital curvatures of the penis (ventral, lateral, or dorsal) are inevitably associated with the finding of a large erect penis. Because the trauma that results in acquired curvature is virtually always associated with intercourse, the occurrence of acquired curvature is nil before the onset of puberty. We have seen some patients in whom there was a history of trauma during vigorous masturbation, but these patients are the exception. Similar to congenital curvatures of the penis, acquired curvatures may be dorsal, lateral, ventral, or complex.

Types of Congenital Curvature of the Penis

Please see the Expert Consult website for this section.



The urethra begins as an epithelial groove in the midline of the ventral surface of the developing penis. As the groove extends, it deepens, with the edges eventually meeting to fuse into a tube. Fusion begins proximally and progresses distally. During normal development, the fusion of the urethral tube eventually reaches the tip of the glans penis. Proliferating mesenchyma surrounds the tube, separating it from the skin, and differentiates to form the corpus spongiosum, Buck fascia, dartos fascia, and overlying ventral skin of the penis. Fetal development of the penis is regulated by testosterone, produced by the fetal testis, which is converted by 5 α -reductase to dihydrotestosterone. Dihydrotestosterone acts directly on cells with androgen receptors and on all layers of the male external genitalia. This embryologic process explains the development of the anterior urethra that is unique to males.

Maturation of these tissues into normal structures depends on the same growth factors that control the formation of the urethra. Although urethral development has progressed normally, mesenchymal tissue development in the penis may be deficient or abnormal and result in dysgenetic and inelastic fascial layers. In 1973, Devine and Horton proposed a typing classification for the various congenital curvatures. In type I congenital curvature, the urethral meatus is at the tip of the glans. However, none of the surrounding layers are normally formed, and the epithelial urethra is associated with maldevelopment of the corpus spongiosum and all the tissues superficial to the urethra. Skin coverage of the epithelial tube is present. In type II, a dysgenetic band of fibrous tissue thought to be derived from the mesenchyma, which would have produced the Buck fascia and the dartos fascia, lies beneath and lateral to the urethra. However, the urethra is contained within a normally developed and fused corpus spongiosum.

In type III, the urethra, corpus spongiosum, and Buck fascia all are normally developed and ventrally fused. However, there is a short area of inelastic tissue in the dartos layer of the penis that causes a relatively sharp bend. Abnormal development of the dartos fascia is frequently associated with complex curvatures. With extensive involvement, the inelastic dartos can be sufficient to restrain the penis and conceal the penile shaft. In many of these cases, there appears to be abnormal prominence of the mons fat pad. These stigmata are thought to be associated with an abnormality in the proper progression of virilization during fetal development.

In type IV, although the urethra, corpus spongiosum, and fascial layers are normally developed, there is relative shortness or inelasticity of one aspect of the tunica albuginea of the corpora cavernosa.

Experience has shown that most patients whose congenital curvature is type IV seem to demonstrate evidence of a hypercompliance of the tunica albuginea. In these patients, the flaccid penis is normal in size and not impressively large, whereas the erect penis is large. The tunica albuginea of the corpora cavernosa is required to expand through a wide range, and if there is asymmetry in the compliance of the tunica, curvature occurs. Patients with type IV curvature commonly notice curvature before puberty; as puberty progresses, an increase in the curvature is noted because of the penile hypertrophic growth spurt that occurs during this time.

Type V congenital curvature is also known as congenital short urethra. This term implies that there has been correct fusion of all elements of the penis (i.e., tunica albuginea, urethral epithelium, corpus spongiosum, Buck fascia, dartos fascia, and ventral skin). However, during erection, the correctly fused urethra and corpus spongiosum are not long or compliant enough to match the compliance of the other ventral tissue layers.

If type V congenital curvature exists at all, it occurs so rarely that when it is encountered, one should doubt the findings. Although discussion of the condition in the past has centered on the best location to "cut the urethra" during the repair, on the rare occasions when this condition is encountered, it is our belief that it should be diagnosed and treated only by the most experienced surgeons. In general, if the urethral meatus has developed to the tip of the glans, the urethra should not be divided to correct ventral curvature of the penis. Although there will be extremely rare exceptions to this bold statement, if those exceptions are encountered, their existence should still be questioned.

Congenital curvature types I, II, and III represent forms of the hypospadias anomaly, and we prefer to refer to them collectively under the term *chordee without hypospadias*. This term implies that although the meatus is not improperly placed, curvature is due to inappropriate fetal development of the ventral penile structures. We prefer to refer to the type IV anomaly as **congenital curvature of the penis**. If a patient has findings of hypercompliance of the corpora cavernosa and a ventral curvature, the diagnosis is congenital ventral curvature of the penis; if the hypercompliance causes a lateral curvature, it is referred to as congenital lateral curvature of the penis (left or right). Although, as mentioned, the type V anomaly is so rarely encountered that it deserves its own diagnosis, we believe its correction is best discussed with types I, II, and III, under the category of *chordee without hypospadias*.

Chordee without Hypospadias in Young Men



Please see the Expert Consult website for this section.

Congenital Curvatures of the Penis

Patients with congenital curvature of the penis can have ventral, lateral (which is most often to the left), or, unusually, dorsal curvature. Photographs of the erect penis demonstrate a smooth curvature that generally involves the entire pendulous portion of the penile shaft.

Patients are usually otherwise healthy young men between the ages of 18 and 30 years. Many of these patients have noticed curvature before passing through puberty but have presumed it to be normal. However, with puberty, they discover that the curvature is not normal; or they become sexually active and discover that the curvature impedes their efforts; or they notice increasing curvature as they pass through puberty, and this, in their minds, clearly would preclude sexual intercourse. Occasionally, a patient waits until he is older than 30 years to deal with the anomaly; even less often, a younger adolescent may discuss his genitalia with his parents.

In circumcised patients, we make an incision through the circumcision scar, which in many cases is displaced well down on the penile shaft. However, even with relatively significant displacement of the circumcision scar on the shaft of the penis, the reincision should be through the circumcision scar. The penis is degloved by dissection of the layer immediately superficial to the superficial lamina of Buck fascia.

An artificial erection is obtained with normal saline infusion or pharmacologic agents. We do not routinely recommend a tourniquet device because constricting devices can conceal the proximal limits of the curvature; this is of most significance in cases of ventral curvatures, which frequently extend proximally. Occasionally, some element of perineal pressure is initially required, but these are patients with normal erectile function, and venous occlusive function is normal. The artificial erection demonstrates the character of the curvature and the location of maximal curvature. In patients with ventral curvature, there may be some illusion of thickening of the dartos and Buck fascia, and in these patients, the fibrous tissue is mobilized and completely excised. The corpus spongiosum is detached from the corpora cavernosa and mobilized from the glans to the penoscrotal junction.

After these tissues are excised, the artificial erection is repeated, and an occasional patient is found to have complete straightening. However, most patients experience a differential elasticity between the dorsal and the ventral aspects of the corporeal bodies, and although the curvature may have been lessened, it persists unless further procedures are done to straighten the penis.

In an adult patient with persistent curvature, there are two options for surgical correction: (1) to lengthen the ventral aspect of the penis by making transverse incisions in the ventral tunica and placing an autologous tissue graft (we currently use the small intestinal submucosal graft at our institution), and (2) to shorten the dorsal aspect of the penis by elevating the neurovascular bundle, excising an ellipse or ellipses from the dorsum of the tunica albuginea, and closing the defects in watertight fashion ([Nesbit procedure \[Nesbit, 1965\]](#)). **Because the size of the erect penis is usually not a problem in these cases of congenital curvature, we have chosen the second option and strenuously discourage ventral grafting in these patients.** The recovery period after this procedure is much shorter, and the variabilities of graft take do not have to be considered. In addition, when a graft is used, there is always the possibility, although uncommon, of the development of graft-induced veno-occlusive dysfunction. **In a 2000 consensus conference sanctioned by the World Health Organization, the committee on Peyronie disease and congenital curvature of the penis agreed that most, if not all, cases in men with the classic finding of congenital curvature of the penis were best managed with plication or corporoplasty techniques but not grafting techniques ([Jardin et al, 2000; Lue, 2004](#)).** This consensus was reiterated at the next World Health Organization conference. It is preferable to

shorten the longer aspect of the penis in patients with congenital curvature. However, **if the patient falls into the category of chordee without hypospadias and shortness of the penis is an issue, we selectively use incisions with grafts to correct the curvature ([Devine and Horton, 1975](#)).**

After the decision has been made to proceed with excisions of ellipses of dorsal tunica, Buck fascia can be elevated, in concert with the dorsal neurovascular structures, by beginning just lateral to the corpus spongiosum and carrying the dissection dorsally across the midline. Alternatively, the tunica can be exposed by excising the deep dorsal vein of the penis and opening the inner lamina of Buck fascia. Elevation of the neurovascular structures is done by dissecting from the dorsal midline laterally around to the corpus spongiosum and from the coronal margin to the penopubic junction, limiting the effects of stretching the dorsal structures with exposure of the dorsum of the penis.

An artificial erection is obtained to plan the proposed ellipse excisions. We prefer to use several small ellipses rather than try to correct the curvature with one large ellipse. The first ellipse is usually positioned at the point of maximal concavity. The edges of the planned ellipse are apposed with a Prolene suture. The artificial erection is repeated to assess the effects of that excision. If there is good straightening in that area of the shaft, the incisions are again well marked, the plicating sutures are removed, and the ellipses of tunica are made with a sharp scalpel blade. By dissection in the space of Smith and removal of only an ellipse of tunica, the ellipses are carefully excised to avoid damage to the underlying erectile tissue or can be merely closed under the reapproximated edge of the defect in the tunica albuginea. The edge of the ellipse is reapproximated with a combination of interrupted 4-0 polydioxanone sutures and a watertight running 4-0 polydioxanone suture.

After closure, we repeat the artificial erection to assess the results of the first ellipse with the others. A final artificial erection should demonstrate the penis to be perfectly straight. In cases of ventral curvature or when complex curvatures are associated with an element of ventral curvature, a minimal degree of dorsal curvature after correction is acceptable. In most cases, as the sutures dissolve, the penis either remains minimally dorsiflexed or becomes perfectly straight.

The Buck fascia is closed. Two small suction drains are placed superficial to the Buck fascia but deep to the dartos fascia. We replace the skin sleeve, with its edges apposed with interrupted small Vicryl or Monocryl sutures. In all patients, we place a small Foley catheter and a small suction drain, and both are removed on the first postoperative day. Depending on the amount of edema and drainage, patients are discharged from the hospital on the evening of the first postoperative day or early the second postoperative day.

A congenital lateral curvature of the penis is often associated with some complexity of curvature; patients frequently notice lateral curvature in association with a ventral or, less commonly, a dorsal curvature. However, some patients present with only lateral curvature, with the right side larger than the left, and curvature to the left.

In some cases, a repair of the lateral curvature can be approached through a small incision at the point of maximal curvature. Laterally placed incisions on the penile shaft are not cosmetically optimal. We prefer a degloving incision after exposure of the deep penile structures; the point of maximal concavity is then marked. Prolene sutures are placed, and an artificial erection is performed again. The size of the ellipse is assessed, and the ellipse is excised and closed as discussed earlier.

As mentioned, most cases of lateral curvature are associated with complex curvatures. In these patients, the correction of the curvature is similar to that described for patients with ventral curvature, with incision through the circumcision scar with the skin reflected. In contrast to a ventral curvature, with a lateral curvature, the entire dorsal neurovascular bundle does not need to be reflected; it is seldom required and it is not considered beneficial to excise the deep dorsal vein in approaching the dorsum of the penis. The postoperative care is the same as described for a ventral curvature. For the uncommon patient with a congenital dorsal curvature of the

Patients with chordee without hypospadias usually present with either ventral curvature or ventral curvature associated with torsion (complex curvature). These young men do not typically have a greater than average stretched penile length (13.1 cm) (Schonfeld and Beebe, 1942) and will have noted curvature throughout life. If prepubescent, they have obvious curvature with erection; if postpubescent, they may offer a history of increasing curvature as they pass through puberty.

In many cases, there are abnormalities of the ventral penile skin. These abnormalities might consist of either an element of hooded preputial skin or a high insertion of the penoscrotal junction. Although patients have fusion of the preputial skin, there is also often a wrinkled appearance dorsally that we now recognize to be a form of the classic hooded preputial skin. In addition, in many cases, the tissues on the ventrum of the penis seem inelastic as the patient's penis is examined on stretch. This palpable inelasticity on the ventral penis consists of dysgenetic tissue, which can replace the Buck and dartos fascia layers; in some cases, there is an element of inelasticity of the tunica itself.

During surgical exploration, Devine and Pepe (unpublished data) obtained tissue from patients for evaluation of 5 α -reductase levels. Their data suggested a deficiency of the enzyme in the ventral dysgenetic tissue. Similarly, Silva and coworkers (2013) found reduced levels of androgen receptors in the urethral mucosa in patients with hypospadias compared with control subjects. El-Galley and colleagues (1997) also looked for growth factor deficiency in tissues of male patients with hypospadias and found a correlation. However, to our knowledge, a growth factor analysis has not been undertaken in patients with chordee without hypospadias.

An important part of the preoperative evaluation is the submission of instant or digital photographs of the erect penis, taken by the patient, documenting the curvature. The photographs are especially helpful in differentiating between the patients we refer to as having chordee without hypospadias and patients with congenital curvatures of the penis. In a patient who has chordee without hypospadias, the photograph reveals an erect penis commensurate with the size of the detumesced penis, whereas in a patient with congenital curvature, the erect penis is noticeably large. It is important to address the psychologic aspects of the condition as an integral part of the treatment; many of our patients see a psychologist preoperatively. Corrective surgery for chordee without hypospadias is highly successful, and an effective correction can be accomplished

in almost all cases with a single operation (Devine et al, 1991). In some cases, the penis has been straightened by excision of all the dysgenetic tissues from the ventral side of the penis and wide mobilization of the corpus spongiosum from the glans penis into the perineum.

Even in patients with obvious abnormalities of the corpus spongiosum (i.e., poor ventral fusion or frank bifid corpus spongiosum), wide mobilization usually reveals that it is not the corpus spongiosum that remains as the ventral limiting factor. In most patients, the penis remains curved because of the inelasticity of the ventral aspect of the corpora cavernosa themselves. In an occasional patient, the corpus spongiosum becomes atretic distal on the shaft, and the urethra itself is only an epithelium-lined tube. Even in these patients, with wide mobilization of the epithelial distal portion and elevation of the proximal corpus spongiosum, it is unusual to find the corpus spongiosum or the epithelial tube limiting the ventral erection. If the epithelial tube has served as an adequate urethra (i.e., it is not stenotic), the morbidity of urethral division and subsequent need for urethral reconstruction must be considered before such a procedure is undertaken. Because the evolution of hypospadias repairs accomplished by wide mobilization of the corpus spongiosum and epithelial and corpus spongiosal elements distal to the meatus has allowed onlay procedures, the morbidities of urethral division must be strongly considered and, we believe, usually avoided.

In children, after mobilization and excision of the dysgenetic tissues, the residual chordee can usually be corrected by making a longitudinal incision, with a sharp blade, in the ventral midline of the corpora cavernosa while an artificial erection is maintained. The incision (midline ventral septotomy) often can be extended between the corporeal bodies for a significant distance, allowing the edges of the ventral tunica to move laterally. The penis noticeably straightens with erection.

If this maneuver is insufficient, the dorsal neurovascular structures can be mobilized in concert with Buck fascia, and a small ellipse or ellipses of dorsal tunica albuginea can be excised and closed with watertight plicating sutures. Caution is important when the dorsal neurovascular structures are mobilized; with poor development of the ventral structures, which occurs in some patients, the arborization of the dorsal arteries provides the dominant vascularity to the glans.

penis, the repair is best accomplished by mobilizing the lateral aspect of the corpus spongiosum to allow small ellipses lateral to the midline to be positioned on the ventrum of the penis, by the technique described before.

Although described as a method for plication for curvature associated with Peyronie disease, corporoplasty, a procedure described by Yachia (1993), is also useful for the correction of congenital curvatures. The procedure consists of longitudinal incisions in the tunica albuginea with transverse closure. The “long side” is pliated without the need for excision; however, the plication is durable in that the tunica is opened and closed with a resulting scar, rather than reliance only on the strength of sutures as originally described by Nesbit (1965). With this technique, closure is done with absorbable monofilament suture.

Acquired Curvatures of the Penis

Acquired curvatures of the penis inevitably follow trauma to the penis. Many of these cases are associated with Peyronie disease, also believed to be associated with trauma to the penis during intercourse (Bella et al, 2007). Patients occasionally present who have had vigorous internal urethrotomy, with the incision extended outside the urethra and corpus spongiosum and involving the tunica of the corporeal bodies, causing scarring that is significant enough to be associated with curvature.

Acquired Curvatures of the Penis That Are Not Peyronie Disease

When a young man presents with an acquired curvature of the penis, one must always consider Peyronie disease. However, many men do not have true Peyronie disease. These patients, on close questioning, reveal a history of minimal lateral curvature of the penis and a clear memory of a lateral buckling injury that occurred during intercourse. In some cases, the patient remembers hearing a “snap” and notices immediate detumescence and significant ecchymosis of the penis. These patients are often referred with a diagnosis of Peyronie disease, but a diagnosis of curvature secondary to penile fracture is more accurate. Because of the noticeable events associated with fracture of the penis, many patients present acutely, and reconstruction can be accomplished at that time.

Occasionally, a patient or his primary care physician ignores the stigmata of the trauma (often described as “minimal” by patients), and the patient presents with a noticeable lateral scar that causes indentation of the lateral aspect of the penis and, in some cases, curvature. Patients who had preexisting lateral curvature may notice that their penis has been straightened by the trauma, but they are disturbed by the concavity caused by the scar. In others, the small linear scar causes a significant lateral curvature.

Another group of patients presents after a similar buckling trauma to the penis but without associated detumescence or ecchymosis. These patients report noticing that their erections were painful for a period after the trauma, and then a nodule developed in the lateral aspect of the penis. Eventually, they present with a lateral linear scar that has led to curvature and indentation at the site. We refer to this injury as a subclinical fracture of the penis.

The lesion of a subclinical fracture of the penis is believed to be due to the disruption of the outer longitudinal layer of the tunica albuginea during the buckling trauma. The inner, circular layer is not disrupted and maintains the blood-tight continuity of the corpus spongiosum. Another possible scenario is that both layers of the tunica albuginea are disrupted, but the overlying Buck fascia maintains its integrity. Some patients notice a pop with intercourse and a period of pain with erections, followed by curvature of the penis—usually dorsal. These patients probably tear the septal insertion completely. These patients have a similar presentation to patients with Peyronie disease.

Patients usually have normal erectile function after subclinical or clinical fracture of the penis; there does not appear to be an association with concomitant global cavernosal veno-occlusive

dysfunction. However, the association of cavernosal veno-occlusive dysfunction and trauma of the penis continues to be seen, and some patients have significant problems with erectile dysfunction after fracture-type injuries of the penis. These injuries are not associated with shortening of the penis. In most cases, the lack of erectile dysfunction and penile shortening help distinguish these patients from patients with Peyronie disease. If a detailed history leads one to suspect blighted erectile function, erectile function should be evaluated before proceeding with surgery. At our institution, we evaluate these patients with duplex ultrasonography and selectively with dynamic infusion cavernosometry and cavernosography.

Although foreshortening of the penis is not a characteristic of either the injury itself or the resulting scar in either of these injuries, these patients are not ideal candidates for contralateral plication procedures. This treatment would result in bilateral scars, which would cause bilateral indentations of the penis, and although the penis would have been straightened by the correction, most patients are upset by the cosmetic and functional result of a near-circumferential indentation of the penis. Instead, we excise the scar and place a graft to replace the corporotomy defect caused by the scar excision. Because these scars are on the lateral aspect of the penis, minimal mobilization of Buck fascia, associated dorsal neurovascular structures, and corpus spongiosum is required at the site.

The results of the surgical correction described have been extremely effective. Successful correction with a single operation has been achieved in all patients treated at our institution.

KEY POINTS: CURVATURES OF THE PENIS

- Curvatures of the penis can be acquired or congenital. Congenital curvatures of the penis can be categorized as chordee without hypospadias or congenital curvature of the penis.
- In general, chordee without hypospadias is a forme fruste of hypospadias. Although the meatus may not be abnormally placed, these patients usually have findings suggestive of hypospadias (i.e., malformation of the ventral structures of the penis). These patients are not characterized by large erect penises. In contrast, patients with congenital curvature of the penis seem to have exceptionally large erect penises.
- The entity of congenital curvature of the penis seems to be related to nonsymmetrical expansion of the erectile bodies, which must expand significantly during tumescence. Reconstruction in these patients generally is best accomplished by excision with plicating closure or pure plication techniques. The use of grafts is not recommended because of the unusual but real occurrence of graft-induced veno-occlusive dysfunction in certain patients.

TOTAL PENILE RECONSTRUCTION

General

The principal techniques of penile reconstruction were originally developed for treatment of trauma patients, and these patients were victims of war injuries in many injuries. In 1936, Bogaraz described a technique for phallic construction in a series of war-injured patients, and in 1944, Frumkin followed with a series from the Soviet Union. Aware of the work in the Soviet Union, Gillies and Harrison (1948) reported on a series of patients in whom they had accomplished penile reconstruction while stationed at a major hospital in the outskirts of London during World War II. In this series, numerous patients had a complete absence of the penis.

Initially, all procedures for phallic construction involved delayed formation and transfer of tubed abdominal flaps. These tubes were produced from random flaps of skin and because of their size were based on a tenuous blood supply. To allow new vascular patterns to become established in the transferred tissue, they were

formed in stages, with a “delay” between the stages. In the “tube-within-a-tube” design, the inner tube allowed the placement of a baculum during intercourse, and the outer tube provided skin coverage. Patients voided through a proximal urethrostomy. This approach continued to be the “state-of-the-art” phallic construction and penile reconstruction until 1972, when [Orticochea](#) described total reconstruction of the penis using the gracilis musculocutaneous flap. In 1978, Puckett and Montie reported a series in which they constructed the penis with a tubed groin flap. In the early cases in this series, the flap was transferred in delayed fashion to the area of the penile stump. Later in the series, a microvascular free-transfer technique was employed.

In 1984, Chang and Hwang popularized the forearm flap, based on the radial artery, for phallic construction. [Biemer \(1988\)](#) reported a modification of the forearm flap, which was also based on the radial artery; in 1990, [Farrow and colleagues](#) reported their “cricket bat” modification of the radial forearm flap. **At the present time, forearm flaps are the most commonly employed method for total phallic construction and penile reconstruction.**

The forearm flap is usually harvested from the nondominant forearm. Preoperatively, the Allen test is used to screen patients carefully for arterial insufficiency. This test involves palpation of the radial and ulnar arteries in the wrist, with the patient making a tight fist to express blood from his hand. As he opens his hand, the fingers are pale, but if palmar circulation is normal and both arteries are patent, the fingers turn pink when one of the arteries is released. On the basis of either the Allen test or the patient’s history, if there is any doubt about the integrity of the radial and ulnar arteries or the palmar arch, upper extremity angiography is performed.

As described, the forearm flap is a fasciocutaneous flap vascularized by the radial artery; however, the ulnar artery also vascularizes the forearm fascia and most of the forearm skin. The radial artery arises as a continuation of the brachial artery and proximally lies beneath the belly of the brachioradialis muscle, becoming more superficial at the wrist. The ulnar artery is also a continuation of the brachial artery and vascularizes a similar area of skin and underlying adipose tissue. The vascularity of the overlying skin is achieved by way of the underlying (antebrachial) fascia, which is the superficial fascia investing the musculature of the forearm.

The forearm flap can be elevated and transferred on the superficial fascia. The lateral and medial antebrachial cutaneous nerves appear proximally beneath the fascia. The cephalic, basilic, and medial antebrachial veins are also included in the flap and constitute a portion of the venous drainage. In some patients, the vena comitans is the dominant venous drainage system. At the time of flap transfer, it is imperative to assess the vena comitans and the superficial veins to determine which is the dominant system in the individual patient.

The various modifications of the forearm flap do not represent changes in the technique of flap elevation; rather, they are modifications in the design of the skin island and the relative position of the urethral paddle in relation to the skin that eventually becomes shaft coverage. Each of these modifications has advantages in different situations.

In the forearm flap as described by [Chang and Hwang \(1984\)](#), the shaft is covered with the radial aspect of the skin paddle. A de-epithelialized strip is made, and a second skin island, on the ulnar aspect of the skin paddle, is tubed to form the urethra. The urethral tube is rolled within the tube of skin to form a tube-within-a-tube design. In the white population, this flap has demonstrated a tendency to lead to ischemic stenosis of the lateral paddle, where the urethra is constructed.

In the cricket bat modification, the urethral tube extends distally, closely overlying either the radial or the ulnar artery. We have experience with elevation of the cricket bat modification on both arteries. Proximal to the urethral strip, a broader portion of the skin paddle provides coverage of the shaft. The urethral portion is tubed and transposed by inverting it into the center of the shaft portion of the skin paddle. The advantage of this modification lies in centering the urethral portion over the respective artery, in contrast to the Chinese design, in which the ulnar aspect is far distal from the radial artery,

with the potential for ischemic stenosis or loss of that portion. The cricket bat modification has been useful in trauma patients, particularly in patients who have a significant stump of erectile bodies and urethra left after the injury.

The modification by [Biemer \(1988\)](#) also centers the urethral portion of the flap over the artery. As described by Biemer, the flap is elevated on the radial artery and includes a vascularized piece of the radial bone intended to provide rigidity to the new penis. However, the inclusion of cartilage and bone has not been universally successful, and rigidity in these flaps is obtainable by the use of either an externally applied or an internally implanted prosthesis. If the bone is not elevated, the Biemer flap design can be elevated on either the radial or the ulnar artery. At our center, we most often elevate the flap on the ulnar artery, in a modification of the Biemer design.

Modifications of the Biemer design also include the glans construction technique that was originally described by [Puckett and Montie \(1978\)](#). In the original Biemer design, a central strip becomes the urethra, and lateral to that strip, two de-epithelialized portions and two lateral islands (lateral aspects of that skin paddle) are fused dorsally and ventrally to cover the shaft. With the modification of [Puckett and colleagues \(1982\)](#), a large island is left distally and flared back over the tip of the tubed flaps, creating the illusion of a glans penis. The Biemer design, especially when it is combined with Puckett’s design for glanular construction, offers the best cosmetic results ([Fig. 40-40](#)).

There are several disadvantages to the use of a forearm flap for phallic construction. The major disadvantage of forearm flaps is the obvious donor site deformity. We have reconstructed the donor site with full-thickness skin grafts taken from the area of the inguinal crease or buttock, and the cosmetic result is far superior to that obtained when the donor site is reconstructed with split-thickness skin graft (even thick split-thickness skin). Additionally, morbidity can be reduced with mobilization of the intact forearm skin to reduce the grafting requirement and attempts to minimize the step between the skin and muscle bed. A second disadvantage lies in the **possibility of the development of cold intolerance in the hand of the donor side.** Early in our experience with the forearm flap, we reconstructed the radial artery with an interposition vein graft. We have since abandoned this procedure in most of our series and have not seen cold intolerance in our patients. Another disadvantage occurs in male and virilized transgender patients **when the forearm skin is hirsute because the hair can be problematic** if it is included in the portion of the flap used for urethral construction. In such patients, we try to identify the potential for the problem and refer them for epilation before surgery.

[McRoberts and Sadove \(2002\)](#) proposed the use of the fibular osteocutaneous flap for phallic construction. The fibula is elevated on the periosteal vessel along with the overlying skin paddle. As they described, urethral reconstruction is by tubed graft techniques, and their procedure had a 100% urethral complication rate. [Kim and colleagues \(2009\)](#) used a radial forearm osteocutaneous flap in 40 patients with reasonable results, although for many patients the incorporation of bone did not provide sufficient rigidity for sexual function over time. For patients who need vascularized tissue only to cover the shaft of the penis, we have used the upper lateral arm flap. This is a fasciocutaneous flap, and its cutaneous vascular territory is centered on the radial collateral artery. The skin of the lateral upper arm is thin, with little subcutaneous adiposity. To mark the location of the lateral intramuscular septum and the course of the superior radial collateral artery, we draw a line joining the insertion of the deltoid with the lateral epicondyle. We begin the dissection posteriorly, elevating the superficial fascia until the posterior lateral portion of the intramuscular septum has been identified. A potential disadvantage of this flap lies in the fact that the entire venous drainage depends on the vena comitans, and although superficial veins do traverse the flap, none of them seems to provide significant venous drainage. We have found the flap to be completely reliable so far, with no losses secondary to venous insufficiency.

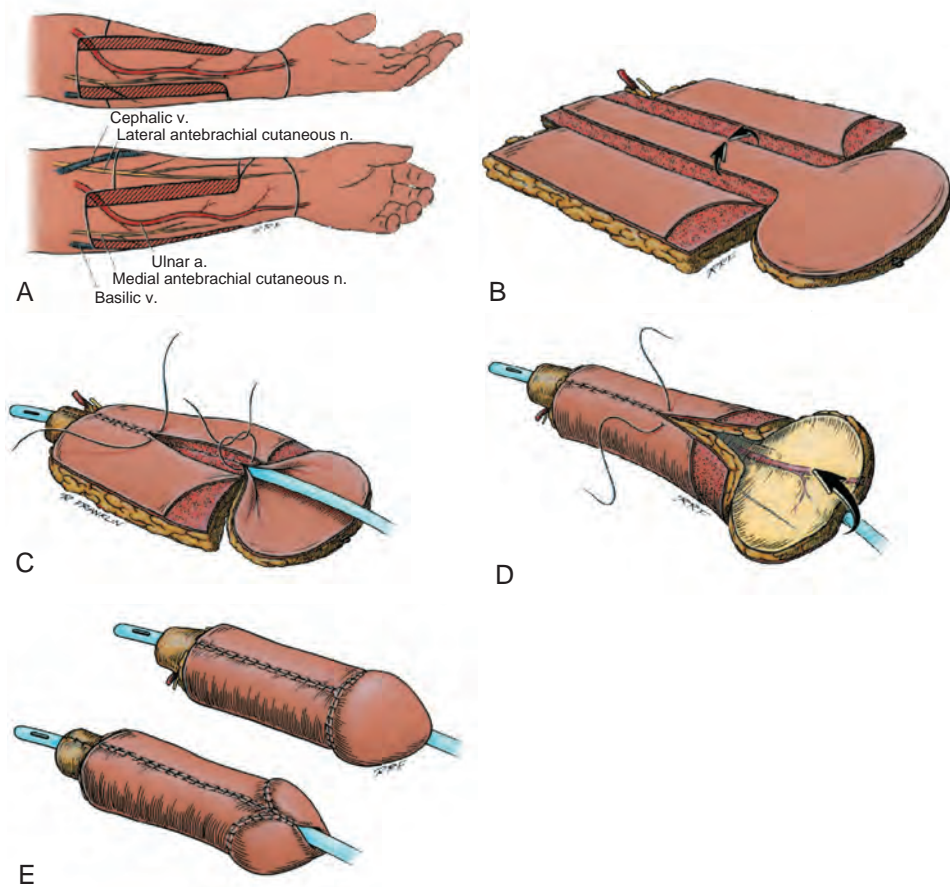


Figure 40-40. A, Schematic diagram of an ulnar forearm flap, modified Biemer design, on the patient's left (usually nondominant) forearm. B, Schematic of the elevated flap. The flap has been divided into skin islands by de-epithelializing the strips. Laterally are the shaft skin islands, medially is the urethral skin island, and distally is the integral glans, after the design of Puckett. C, Schematic of the configuration of the flap. Notice the urethral skin island has been tubularized to the level of the neomeatus. The lateral shaft skin islands are now in the process of being tubularized over the tubularized urethra. D, Schematic of the phallic flap as it is further configured. This view is of the dorsum. The ventral skin island has been closed over the urethra, and the dorsal skin islands are being collected. The integral glans will then be reflected over the dorsum of the flap. E, The appearance of the phallus after it is totally configured and transposed to the area of the "penis."

This flap has also been used for total phallic construction. For this purpose, the flap is expanded by tissue expander and elevated across the elbow, and the distal flap is elevated on the recurrent radial artery. As with the forearm flap, the donor site of an upper lateral arm flap can be disfiguring. However, because the scar is on the upper arm, it is more easily concealed beneath a shirtsleeve than a scar in the forearm. All the flaps described allow microneurosurgical coaptation of the flap cutaneous nerves with recipient nerves. With total phallic construction, the cutaneous nerves can be attached either to the dorsal nerves of the penis or to the dorsal nerves of the clitoris in a transsexual patient. When these nerves are unavailable, the nerves can be coapted to the pudendal nerve, which in most patients requires an interposition graft. These nerves are thought to provide the best restoration of erogenous cutaneous sensibility. We have also coapted the flap's cutaneous nerves to the ilioinguinal nerves, which provides sensation to the inner aspect of the thigh and the lateral aspect of the scrotum, and have achieved a reasonable degree of erogenous sensibility. The ilioinguinal nerve is also thought to provide a better degree of protective sensation (albeit less erogenous sensation) compared with the dorsal nerves (Monstrey et al, 2009).

In most patients, the deep inferior epigastric vessels are the recipient vasculature for flap transfer. These vessels are medial branches of the iliac system and lie on the dorsal (deep) aspect of the rectus abdominis muscle. The artery usually remains deep to the muscle, although an early penetration of the artery into the muscle can be observed in some patients. The artery classically bifurcates at the level of the umbilicus and is generally accompanied by two or more venae comitantes. These vessels have been elevated by several methods, and Lund and colleagues (1995) described their elevation for penile revascularization with laparoscopic techniques. When the deep inferior epigastric vessels are used, it is often necessary to include a saphenous vein for further venous runoff.

In some patients, these vessels are unavailable, and we have used a saphenous interposition graft to the superficial femoral artery. With use of this technique, we mobilize the saphenous vein well down the upper aspect of the thigh and then attach the vein to the femoral artery, making a temporary arteriovenous fistula. The fistula is divided, with the saphenous vein becoming the venous runoff and the interposition graft providing the arterial inflow. This system of recipient vessels is greatly inferior to a direct arterial anastomosis; because of this, in a few patients we have divided the profunda

femoris vessel and vigorously dissected it from its other branches. We have then performed an end-to-end (artery-to-artery) anastomosis of the ulnar artery to the profunda femoris. However, the long-term consequences to the patient of dividing the profunda femoris are unclear. Immediate reconstruction of the profunda does not appear to be advantageous because the dissection required to mobilize the profunda femoris to become a recipient vessel requires the division of numerous proximal branches, and these would not be reconstructed with an immediate reconstruction of the profunda femoris. Mention of this as a potential means of “creating” recipient vessels is not to recommend the procedure because the procedure may yet have unacceptable long-term consequences. Another option in extreme cases is to use the superficial femoral vein, which could be reconstructed with a vein interposition. When the “classic” recipient vessels are unavailable, these other methods may be acceptable. However, we strenuously caution concerning their use because the long-term consequences are unknown. We believe that division of the superficial femoral artery with immediate reconstruction is the preferable choice.

In the latter part of our series, we included the routine transfer of gracilis muscle to cover the area of the urethral anastomosis, increasing the vascularity to that area and significantly altering the incidence of anastomotic fistula and stricture formation. We also elevated a bipedicle flap from the area of the penile shaft base, which is transposed beneath the phallic flap. This flap provides increased bulk and some modicum of scrotal construction, and when it is combined with the gracilis muscle, its thickness provides excellent coverage for the juncture of the flap with the base of the neoscrotum. Mobilization of a tunica dartos flap with tunica vaginalis pedicle, or a Martius flap in a transgender patient, may obviate the necessity to elevate and transpose a gracilis muscle flap.

During the phallic construction procedure, urine is diverted by means of a suprapubic cystostomy tube, and the urethra is stented with a No. 14 soft silicone (Silastic) catheter. A voiding study is usually performed between the third and fourth postoperative week.

Outcomes after forearm free-flap phalloplasty have now been reported from several centers. Even in centers of excellence for phallic construction, complications and reoperations seem to be the rule rather than the exception. [Monstrey and colleagues \(2009\)](#) reported the largest single-stage radial forearm phalloplasty series with 289 patients over 15 years. Urologic complications were seen in 41% of patients, the most common being fistula in 25%, stricture in 8.7%, and both in 9% of patients. Stricture treatment in this series required a multitude of procedures to achieve a patent urethra; however, fistulae healed spontaneously in most cases. Tactile sensation was achieved in all patients, and many were sexually active.

Similarly, [Garaffa and coworkers \(2010\)](#) published a series from the United Kingdom on 112 patients undergoing total phallic construction with a radial forearm free flap. Reconstructions at this center are performed in stages rather than a single stage. The urethral anastomosis is deferred until several months after the flap has demonstrated stability. At a median 26 months of follow-up, 99% of patients who had achieved urethral continuity were voiding anatomically through the phallus. Despite staging the procedure, strictures still developed in 10% and fistulae in 24% of patients. Most patients (71.5%) developed phallus sensation.

Vascular complications and graft loss are the most feared morbidities associated with free-flap phalloplasty. These are rare events with rates of total flap loss ranging from 0.6% to 5% and higher rate of partial loss or limited skin necrosis ([Leriche et al, 2008](#); [Monstrey et al, 2009](#); [Garaffa et al, 2010](#)). Occasionally, minimal loss of the phallus is amenable to local wound care, but more often these cases require debridement and split-thickness skin grafting for coverage.

Rigidity for intercourse in a patient with phallic construction is usually achieved by either an externally applied or a permanently implanted prosthesis. Prosthetic implantation is never undertaken until 1 year after phallic construction because

protective sensibility must be demonstrated in the flap. When the flap is transferred, it is, by definition, rendered insensate. At about 3 to 4 months after reconstruction, as nerve regeneration occurs, sensation becomes noticeable. In addition, the urethra must be patent and proved to be durable before prosthetic implantation is undertaken.

At our center, we have a large series of patients with internally implanted devices. We have implanted hydraulic and articulated prostheses encased in Gore-Tex neocorpora. These devices are anchored to the ischial tuberosity and the pubis by anchoring the neocorpora to these bone structures. In most patients, we implant two cylinders or rods. Early in our series, we had problems with hematoma and seroma formation and subsequent infection. However, since modifying our antibiotic regimen and including the routine use of suction drains with the implant procedure, we have had excellent success with implantation. At the present time, we place the antibiotic-coated (Inhibizone) AMS 700CXR (American Medical Systems, Minnetonka, MN). The Titan prosthesis with hydrophilic coating and narrow base has also been used.

The largest published series describing the use of a mechanical prosthesis in a neophallus is from Belgium where a variety of prostheses have been put in 129 patients from 1996 through 2007 ([Hoebeker et al, 2010](#)). The proximal prosthesis was fixed to the pubic rami using either a Dacron sheath or permanent stitches through a rear tip extender. At a mean 30 months of follow-up, 41.1% of patients needed revision or explant for infection (11.9%), malfunction (13%), erosion/malposition (22.7%), or leak (9.2%). Complications are higher than seen for implants into normal corpora, which would be expected given that the neophallus has had extensive prior surgery, is not as well vascularized, and the device may be used more frequently in this traditionally young patient population.

We also have implanted testicular prostheses in many patients. In patients in whom we have used a hydraulic device, we have implanted the pump in one neohemiscrotum and a testicular prosthesis in the opposite one.

Reconstruction after Trauma

In many ways, the problems of trauma patients are more challenging to solve than the problems of patients who require total phallic construction. We have treated a large number of patients who have had devastating injuries to the penis after complicated prosthetic surgery or surgery to correct penile curvatures of Peyronie disease. The goal in these patients is to preserve the penile structures and function as much as possible and correct the deficiencies that are imposed on the patient by the trauma.

Acutely, urine must be diverted, necrotic tissue must be carefully debrided, and any foreign bodies that may have been implanted must be removed. Vigorous acute wound management stabilizes the wounds and allows active granulation to progress. In all trauma patients, an attempt should be made to save as many of the penile structures as possible.

Approximately 3 to 6 weeks after trauma, primary reconstruction can be undertaken, although we have elected to wait 4 to 6 months in some patients, depending on the situation. When significant adjacent tissue loss has occurred, the adjacent areas must be well reconstructed before proceeding with either phallic construction or penile reconstruction.

In a trauma patient, it is imperative that well-vascularized tissues be eventually transposed to the adjacent area, and reconstruction of these areas can be accomplished with numerous flaps. For groin reconstruction, the tensor fascia lata flap has been useful. The rectus femoris flap, characteristically long and large, can be transposed to the area of the lower abdomen and has been an extremely useful flap for inguinal and lower abdominal reconstruction. The gracilis muscle is an excellent flap for reconstruction of the perineum and the groin. Alternatively, the posterior thigh flap can be used for reconstruction of the groin and perineum and, in some cases, transposed to the lowermost portion of the lower

abdomen. The rectus abdominis flap is a useful flap and can be elevated with a vertical or transverse skin paddle. In addition, the flap can be transposed to either the ipsilateral or the contralateral side. Care must be taken in a patient who has had lower abdominal external beam irradiation.

Variations of the flap designs described for complete phallic construction have been successfully applied in select patients for penile reconstruction. An example is one patient who sustained an injury to his penis from a shotgun blast. The blast injured a large portion of the patient's right corpus cavernosum, and most of the penile skin was either destroyed or used for urethral reconstruction. In this patient, a flap based on the Chinese design was elevated. However, because the urethral reconstruction was accomplished with a penile skin island, the ulnar portion of the flap was not needed for that purpose. The ulnar portion was de-epithelialized and tubularized to form bulk and a new right corporeal body. This patient is now sexually active, and the bulk of the tube's dermal section gives adequate support to his penis for intercourse.

Another patient required only distal urethral construction and glans reconstruction. For this patient, we based a flap on the Biemer design to construct a glans. The proximal portions of the flap were de-epithelialized, allowing fixation of the neoglans on the tips of the corporeal bodies, and an excellent functional and cosmetic result was achieved for this patient. The versatility of free-flap technology allows the solution of complex issues with reasonably acceptable functional and cosmetic results.

FEMALE-TO-MALE TRANSSEXUALISM

Female-to-male transsexual patients present a unique challenge, and no patient should be considered for definitive reassignment surgery without having undergone complex screening and evaluation by a team consisting of mental health professionals as well as surgeons who are skilled in undertaking transgender surgery. It is imperative that an ongoing, stable, therapeutic relationship be established between the patient and a mental health professional at the time of definitive gender reassignment surgery. At our institution, the Harry Benjamin criteria (Ramsey, 1996) are strictly adhered to, and surgery is accomplished by a team of urologists, plastic surgeons, and gynecologists.

In most patients, the first stage of female-to-male transsexual surgery consists of bilateral salpingo-oophorectomy, hysterectomy, vaginectomy, and urethral lengthening with colpocleisis. Even in virginal patients, our surgeons have become skilled at accomplishing a hysterectomy and bilateral salpingo-oophorectomy by way of transvaginal surgery. We perform a vaginectomy at the same operation, leaving the anterior vaginal wall to be transposed as a random flap to lengthen the female urethra and allow colpocleisis. Lengthening of the female urethra brings the base of the native urethra up to what will be the base of the phallic flap; along with the transfer of gracilis muscle, it has significantly altered our surgical results with regard to urethral anastomotic fistula and stricture. Urine is diverted with a suprapubic tube, and a voiding trial is performed in approximately 21 days. Patients are generally in the hospital for 2 to 3 days and return 3 to 4 months later for phallic construction.

For phallic construction in a transsexual patient, we elevate a bipedicle flap of skin, as already described, from the area where the phallic structure will be implanted and transpose it to the undersurface of the neopenis. The patient is generally in the hospital for 10 to 14 days after total phallic construction, and a voiding trial with contrast material is done at about 28 days postoperatively. After 1 year, when erogenous sensibility is demonstrated and the urethra is proved to be durable, prosthetic implantation is considered.

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The complete reference list is available online at www.expertconsult.com.

KEY POINTS: TOTAL PENILE RECONSTRUCTION AND FEMALE-TO-MALE TRANSSEXUALISM

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- We prefer to use an ulnar forearm flap with a combined Puckett modification of the flap and Biemer modification of the glans. These flaps allow sensible phallic construction that lets the patient stand to void and permits eventual prosthetic implantation because the phallus has both protective and erogenous sensibility.
- The techniques employed in transsexual patients are not different from techniques employed in trauma patients. The shapes of the skin paddles often must be tailored to the individual patient.

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Surgical Anatomy of the Scrotum

Preoperative Preparation

Surgery of the Scrotal Wall

Vasectomy

Spermatocectomy and Surgery of the Epididymis

Hydrocelectomy

Surgical Treatment of Orchitis and Chronic Scrotal Pain

Surgery of the Seminal Vesicles

Management of Nonpalpable Testicular Lesions

The scrotum and its contents are unique body components because of their superficial anatomic location, which facilitates physical examination, imaging, and surgical access. Clinically, the external genitalia are one of the few organ systems in medicine that can have a significant psychosocial impact on a patient's well-being as well as their fertility potential. A significant reason that urologists must be thoroughly competent in dealing with conditions of the scrotum and scrotal contents is that physicians in other medical specialties are limited in their knowledge of scrotal anatomy, examination, disease entities, and treatment options. This unfamiliarity may seem perfunctory to most physicians, but it is of the utmost importance that urologists have a strong understanding of the anatomy, pathology, and surgical treatment of diseases that affect the external genitalia because of their significance in fertility potential and male endocrine function and impact on patient self-image.

SURGICAL ANATOMY OF THE SCROTUM

It is crucial to understand the blood supply to the organs within the scrotum when surgical intervention is indicated (Box 41-1). The availability of multiple blood supplies to the testis allows continued testicular viability when one or two of the arteries are compromised by injury or ligation. An understanding of scrotal anatomy readily permits accessibility for surgical procedures, including surgery of the scrotal wall, vasectomy, spermatocectomy, surgery of the epididymis, hydrocelectomy, and surgical treatment of orchitis and orchialgia.

Spread of Scrotal Infections and Postoperative Fluids Based on Scrotal Anatomy

There is a predictable pathway for the spread of scrotal infections including Fournier gangrene and necrotizing fasciitis of the scrotum and postoperative fluids based on scrotal anatomy. Anatomic barriers to the spread of necrotizing fasciitis include the dartos fascia of the penis and scrotum, Colles fascia of the perineum, and Scarpa fascia of the anterior abdominal wall. The testicles and epididymes are frequently spared in cases of necrotizing fasciitis of the scrotum (Figs. 41-1 and 41-2) (Gupta et al, 2007).

PREOPERATIVE PREPARATION

Anesthetic Technique for Scrotal Surgery

Effective anesthetic techniques for scrotal surgery range from local injection with or without sedation to spinal to general anesthesia. The use of a spermatic cord block with local infiltration of 0.5% lidocaine without epinephrine is a simple, cost-effective anesthetic technique that can be implemented by the surgeon for outpatient scrotal surgical procedures. Regional cord block typically can be performed without premedication with satisfactory patient analgesia (Wakefield and Elewa, 1994; Magoha, 1998). Spermatic cord block can be used in patients with large hydroceles for anesthesia by initially percutaneously draining the hydrocele, performing the block, and then performing hydrocelectomy (Reale et al, 1998). Outpatient scrotal surgery performed with midazolam sedation and a local block with sedation reversal at the end of the procedure has a very high patient satisfaction rate (Birch and Miller, 1994).

Preoperative Preparation and the Use of Antibiotics in Scrotal Surgery

The overall infection rate with scrotal surgery is relatively low, ranging from zero to 10%. There is no difference in the incidence of postoperative wound infections or complications in patients undergoing hydrocelectomy or spermatocectomy when comparing iodine-based versus chlorhexidine antiseptic preparations. Scrotal cases are considered as class II (clean-contaminated surgeries), which makes it reasonable to use preoperative antibiotics (Kiddoo et al, 2004). The American Urological Association (AUA) best practice policy statement on urologic surgery antimicrobial prophylaxis recommends a single dose of preoperative antibiotics if the patient has risk factors for infection, including advanced age, anatomic anomalies of the urinary tract, poor nutritional status, smoking, long-term corticosteroid use, immunodeficiency, externalized catheters, colonized endogenous or exogenous material, a distant coexistent infection, or prolonged hospitalization. The recommended antibiotic prophylaxis is a dose of a first-generation cephalosporin or clindamycin as an alternative antimicrobial (Wolf et al, 2008). Patients who underwent preoperative clipping for hair removal the morning of surgery had a significantly lower

BOX 41-1 Blood Supply to Testis, Epididymis, and Vas Deferens

TESTIS

Testicular (internal spermatic) artery from aorta
Deferential artery from internal iliac/superior vesical artery
Cremasteric (external spermatic) artery from inferior epigastric artery

EPIDIDYMIS

Superior epididymal artery from testicular artery
Inferior epididymal artery from deferential artery

VAS DEFERENS

Seminal vesicle region: deferential artery from internal iliac/superior vesical artery
Testicular region: deferential artery and inferior epididymal artery

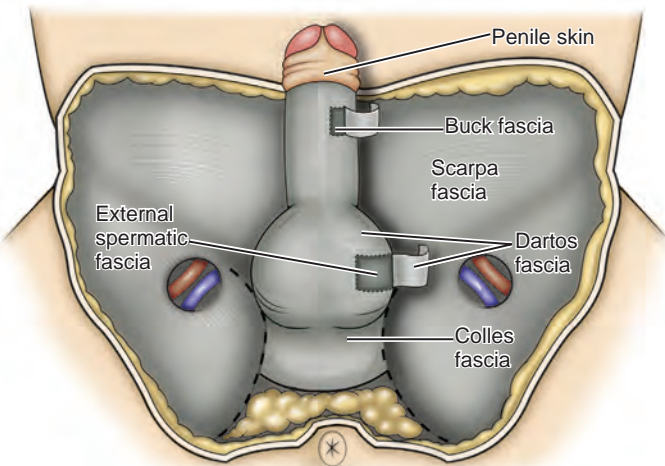


Figure 41-1. Anatomic barriers to the spread of infection. (Modified from Kavoussi PK, Costabile RA. Disorders of scrotal contents: orchitis, epididymitis, testicular torsion, torsion of the appendages, and Fournier's gangrene. In: Chapple CR, Steers WD, editors. Practical urology: essential principles and practice. London: Springer-Verlag; 2011.)

wound infection rate than patients who underwent shaving or clipping the night before surgery (Alexander et al, 1983).

SURGERY OF THE SCROTAL WALL

Cyst Excision

Patients with multiple scrotal cysts can be managed with surgical excision with excellent cosmetic results and low recurrence rates (Noël et al, 2006). The classic management of scrotal sebaceous cysts is surgical excision with excellent outcomes and minimal morbidity with good cosmetic results. Less invasive techniques, such as neodymium:yttrium-aluminum-garnet photocoagulation, have been performed successfully but are not considered standard management (Franco de Castro et al, 2002).

Partial and Total Scrotoectomy

Partial scrotoectomy is an uncommon procedure. Partial scrotoectomy is most commonly performed with infectious processes such as Fournier gangrene. Partial scrotoectomy has been advocated after

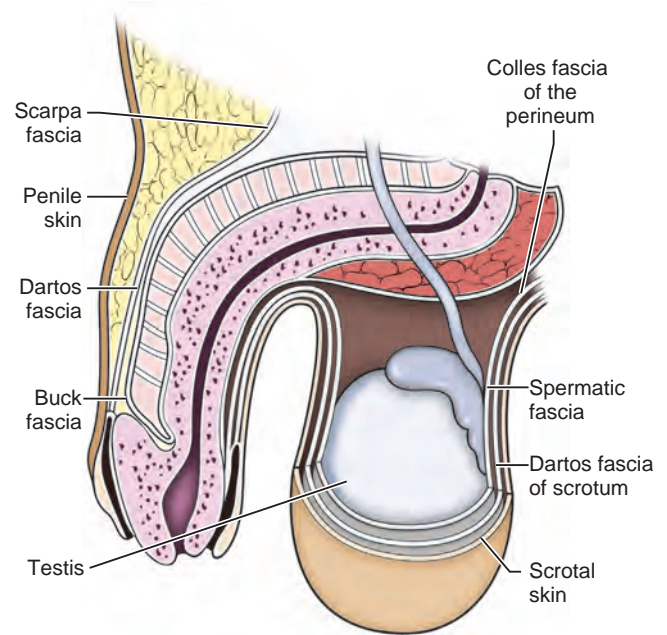


Figure 41-2. Sagittal view of anatomic barriers to the spread of infection. (Modified from Kavoussi PK, Costabile RA. Disorders of scrotal contents: orchitis, epididymitis, testicular torsion, torsion of the appendages, and Fournier's gangrene. In: Chapple CR, Steers WD, editors. Practical urology: essential principles and practice. London: Springer-Verlag; 2011.)

trans-scrotal exploration, orchiectomy, or biopsy or when aspiration has been performed for a scrotal mass and the pathology has revealed a nonseminomatous germ cell tumor of the testis. Prompt and aggressive management has resulted in no local recurrences secondary to scrotal tumor contamination, even when a tumor was found in the scrotoectomy specimen (Johnson and Babaian, 1980; Boileau and Steers, 1984; Leibovitch et al, 1995). There was no increase in local or distant recurrence in a small group that underwent aggressive local surgical resection and did not receive adjuvant chemotherapy (Giguere et al, 1988).

Total scrotoectomy is less commonly performed than partial scrotoectomy. Total scrotoectomy is often necessary when there is extensive involvement of the scrotum with Fournier gangrene. Total scrotoectomy also has been described for radical oncologic procedures, concomitantly with cystoprostatectomy, penectomy, or pelvic exenteration with aggressive cases of squamous cell carcinoma of the prostate (Sarma et al, 1991).

Debridement of the Scrotal Wall in Fournier Gangrene

Treatment of Fournier gangrene should include emergent radical surgical debridement and intravenous broad-spectrum antibiotics. When culture results are available, the antibiotics can be tailored to the organisms based on sensitivities. Treatment should be performed expeditiously and aggressively because Fournier gangrene is a life-threatening process. All nonviable and necrotic tissue must be aggressively excised (Fig. 41-3). An empirical broad-spectrum antibiotic regimen for the initial treatment of Fournier gangrene includes a third-generation cephalosporin, an aminoglycoside (if creatinine clearance is acceptable), and metronidazole (Hejase et al, 1996; Löfmark et al, 2010). Aggressive fluid resuscitation is required including the use of blood and blood products when needed. After debridement, adequate nutrition with early enteral feeding, when possible, is crucial for wound healing. Repeat debridement should be performed 2 days after the initial exploration to excise any remaining nonviable tissue. Multiple resections may be necessary. If the source of the infection is anorectal or the wound is contaminated, a colostomy may need to be



Figure 41-3. Aggressive debridement of Fournier gangrene. (From Kavoussi PK, Costabile RA. Disorders of scrotal contents: orchitis, epididymitis, testicular torsion, torsion of the appendages, and Fournier's gangrene. In: Chapple CR, Steers WD, editors. *Practical urology: essential principles and practice*. London: Springer-Verlag; 2011.)

performed to divert fecal flow (Ghnnam, 2008). Similarly, patients may require cystostomies for urinary diversion when there is a urinary source exacerbating the necrotizing fasciitis.

After the patient has been initially treated and resuscitated and all necrotic tissue has been excised, most wounds can be closed secondarily. Large wounds often require skin grafts for coverage. Fasciocutaneous rotational thigh flaps may be used for coverage with good cosmetic results (Bhatnagar et al, 2008). Wound closure is performed as soon as there is no evidence of infection or remaining necrotic tissue and there is a viable bed that will allow reapproximation or grafting (Ghnnam, 2008). In patients with less than 50% scrotal skin loss, primary closure most often can be performed without major difficulty. Rarely the testes may need to be placed in thigh pouches until the time of definitive reconstruction in cases with major scrotal skin loss (Gudaviciene and Milonas, 2008). Vacuum-assisted closure devices (Wound V.A.C.) have been used to help these complex wounds heal after wide excision and debridement. This technique has been shown to be as effective as conventional wound care in healing wounds. These patients require fewer dressing changes and have less pain, fewer skipped meals, and greater mobility (Ozturk et al, 2009). The use of a small intestinal submucosa graft and fibrin sealant is an option for closure of scrotal defects after excision for Fournier gangrene when standard grafting is impossible (Kavoussi and Bird, 2007).

A severity index was created and validated to identify prognostic factors in patients with Fournier gangrene. Parameters associated with mortality include abnormalities in heart rate, respiratory rate, serum creatinine, serum bicarbonate, serum lactate, and serum calcium. There is a 46% mortality rate in patients with a severity index score of 9 or greater and a 96% survival rate in patients with a severity index score of less than 9. Necrotizing fasciitis involving the abdominal wall or the lower extremities is associated with increased mortality (Corcoran et al, 2008).

Scrotoplasty for Other Benign Scrotal Conditions

Other nonmalignant conditions of the scrotum including hidradenitis suppurativa, postradiation lymphedema, and primary lymphangitis of the scrotum may require surgical excision. Depending on the extent and severity of the wound, different options exist for wound closure or coverage. Small lesions typically are excised and closed primarily, whereas larger wounds require split-thickness skin grafts or tissue flaps (Fig. 41-4) (Eswara and McDougal, 2013). In patients with hidradenitis suppurativa, disease recurrence has been shown to be related to disease severity and not to surgical method of reconstruction (Rompel and Petres, 2000). In patients with systemic disease (i.e., hidradenitis suppurativa, postradiation lymphedema), the surgeon and patient should be aware of potential recurrence; however, in this setting, recurrence is usually tolerated better than the initial lymphedema (Eswara and McDougal, 2013).

VASECTOMY

Vasectomy is a highly effective and safe form of contraception (Schwingl and Guess, 2000). Vasectomy was first described by Sir Ashley Cooper in the United Kingdom when he did experiments to vasectomize dogs (Cooper, 1827). Approximately 526,501 men undergo vasectomy annually in the United States, which makes vasectomy the most commonly performed urologic surgical procedure. Vasectomy is chosen as the method of contraception by 11% of married couples, and 0.01% of men between the ages of 25 and 49 undergo vasectomy annually (Barone et al, 2006).

Anesthetic Techniques for Vasectomy

Vasectomy can be performed under sedation, spinal, or general anesthesia, although most surgeons perform vasectomy under local anesthesia because most patients tolerate this method well, and it minimizes cost, anesthetic complications, and morbidity. The choice of local anesthetic is based on surgeon preference. Options for local anesthesia include 1% or 2% lidocaine without epinephrine or a 50/50 mixture of lidocaine and bupivacaine. The vas deferens is isolated through the scrotal skin and grasped tightly between the thumb and the middle finger of the nondominant hand in a superficial position just beneath the scrotal skin. A 25-gauge to 32-gauge needle is used to inject the local anesthetic subcutaneously to raise a small wheal over the vas deferens. After superficial anesthesia is achieved, the needle is carefully advanced into the vasal sheath, and a small amount of anesthetic is injected. Great care should be taken to use as few punctures as possible and as little needle movement as possible to minimize the risk of hematoma formation. EMLA (emulsion of lidocaine and prilocaine) cream applied as topical anesthesia on the scrotal skin 1 hour before injection of 1% lidocaine followed by vasectomy does not decrease the pain associated with vasectomy compared with the use of injectable anesthesia alone (Thomas et al, 2008).

The no-needle jet anesthetic technique has been described to eliminate the needle for anesthetic injection. This technique uses the MadaJet medical injector (Mada Medical Products, Carlstadt, NJ) to deliver lidocaine without epinephrine by means of a high-pressure injector through a tiny head to beneath the skin to diffuse a mist of anesthetic around the vas (Weiss and Li, 2005).

Conventional Technique

Vasectomy should be performed in a warm room with warm preparation solution to allow scrotal relaxation, regardless of the technique employed. Shaving should be done before the procedure to minimize the risk of infection. There is no difference in the rate of postvasectomy infection in men randomly assigned to prophylactic antibiotics versus no antibiotics; antibiotic prophylaxis is not recommended (Khan, 1978). In any chosen technique, the use of a single incision or bilateral scrotal incisions is based on surgeon preference. Many surgeons advocate bilateral scrotal



Figure 41-4. Wide excision of hidradenitis suppurativa of the perineum. **A, Before. B, After.** Use of excision and split-thickness skin graft for lymphedema of the penis and scrotum. **C, Before. D, After.**

incisions to minimize the risk of dividing the same side twice and to allow performing the vasectomy at a position in the midportion of the vas deferens. After induction of adequate local anesthesia, an incision is made over the isolated vas deferens, which is grasped tightly between the thumb and middle fingers. The vaginal sheath is sharply divided down to the vas. The vas is delivered through the incision; the deferential artery, nerves, veins, and adjacent tissue are separated from the vas, and the vas is divided. Some surgeons remove a small segment of vas deferens, although most urologists who perform vasectomy reversals prefer not to, which allows easier future reversal. The AUA Guideline ([American Urological Association, 2012](#)) states that removal of a segment of vas deferens for histologic confirmation is neither required nor recommended. Most surgeons occlude the testicular and abdominal ends of the vas with suture ligation, hemoclips, intraluminal fulguration with electrocautery, or fascial interposition. These techniques are discussed further later on. The same procedure is repeated on the contralateral vas deferens.

“No-Scalpel” Technique

No-scalpel vasectomy was initially described in China in 1974 ([Li, 1976](#)). Routine antibiotics are not needed for patients undergoing no-scalpel vasectomy with sterile technique ([Seenu and Hafiz, 2005](#)). **The no-scalpel technique significantly decreases the rate of hematomas, infections, and pain during the procedure.** Patients who undergo the no-scalpel technique also resume sexual activity sooner after surgery and have a shorter operative time than

occurs with the conventional technique ([Sokal et al, 1999](#); [Cook et al, 2007a](#)).

The vas and perivascular tissue are firmly secured through the skin with a ring-tipped vas deferens fixation clamp ([Fig. 41-5](#)) after local anesthesia has been administered as described earlier ([Fig. 41-6](#)). A modified, sharpened tipped curved hemostat ([Fig. 41-7](#)) is used to puncture the skin and the vas sheath, and the hemostat is spread to stretch the hole that is made. The vas is pierced with one tip of the hemostat and lifted through the skin opening. The vas is regripped with the ring clamp, and the hemostat is used to dissect the posterior perivascular tissue. The vas deferens is divided, the occlusion technique of choice is employed, inspection is done for hemostasis, and the vas deferens is replaced in the scrotum. The same procedure is performed on the contralateral vas deferens ([Huber, 1988](#)). The perforation in the skin can be closed with an absorbable suture, but it can also be left open and heals well without closure.

Minimally Invasive Vasectomy

There are several variations to the technique of the no-scalpel vasectomy; however, if there is any variation in the steps or specific instruments, the vasectomy should be called minimally invasive vasectomy rather than no-scalpel vasectomy technique. One variation of this technique employs local anesthesia; fixes the vas through the scrotal skin with the ring-tipped vas deferens fixation clamp; and pierces the scrotal skin, vas sheath, and vas deferens in the midline with a sharpened tipped curved hemostat held at 45 degrees from horizontal ([Fig. 41-8](#)). To prepare the vas deferens for division,

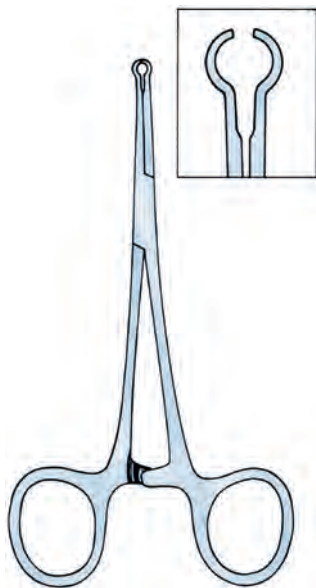


Figure 41-5. Ring-tipped vas deferens fixation clamp. The cantilevered design prevents injury. (From Li S, Goldstein M, Zhu J, et al. The no-scalpel vasectomy. *J Urol* 1991;145:341–4.)

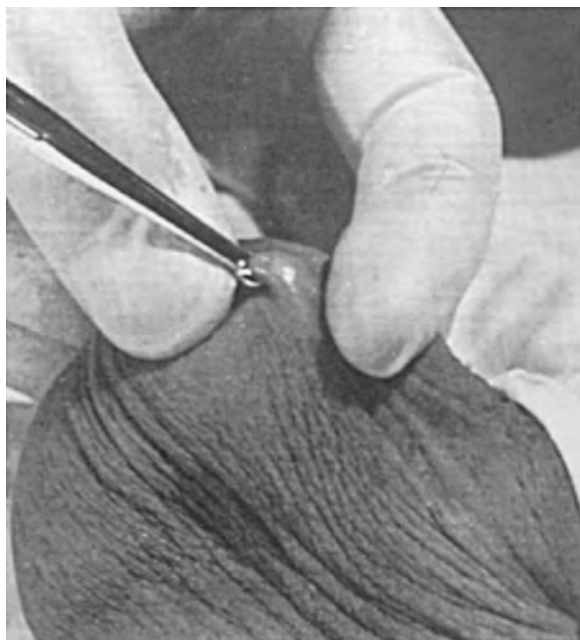


Figure 41-6. Vas fixed in the ring clamp. The scrotal skin is tightly stretched over the most prominent portion of the vas. (From Li S, Goldstein M, Zhu J, et al. The no-scalpel vasectomy. *J Urol* 1991;145:341–4.)

the clamp is rotated 180 degrees relative to the pierced vas deferens. The remainder of the procedure is performed in the same manner as described earlier, and this is done bilaterally (Schlegel and Goldstein, 1992).

Another technique for performing minimally invasive vasectomy is to isolate the vas deferens after induction of adequate local anesthesia, grasp it tightly between the thumb and middle finger, and puncture the skin overlying the vas deferens with a sharpened tipped curved hemostat. The curved hemostat is used to spread the skin to enlarge the vertical slit in the skin just large enough to allow the ring-tipped vas deferens fixation clamp to fit through to grasp the vas deferens. The vas deferens is grasped and brought up through

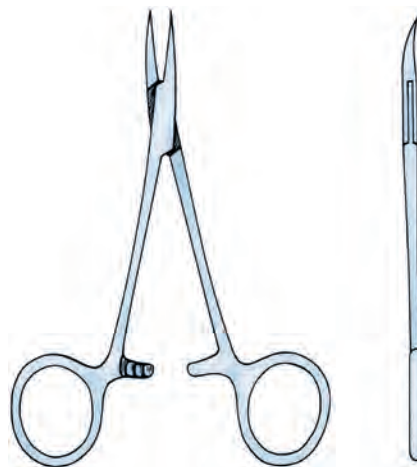


Figure 41-7. Sharp, curved mosquito hemostat. (From Li S, Goldstein M, Zhu J, et al. The no-scalpel vasectomy. *J Urol* 1991;145:341–4.)

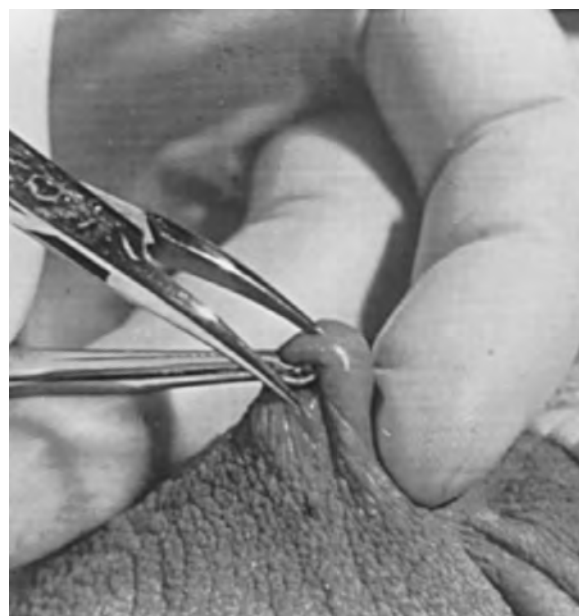


Figure 41-8. Puncture of the skin, vas sheath, and wall into the lumen. (From Li S, Goldstein M, Zhu J, et al. The no-scalpel vasectomy. *J Urol* 1991;145:341–4.)

the puncture, and the vaginal fascia and vessels can be spread off the vas deferens to expose the bare vas deferens by spreading the sharp-tipped curved hemostat onto the vaginal fascia to open the vaginal fascia (Figs. 41-9 and 41-10). The remainder of the vasectomy is performed as described earlier for bilateral procedure (Li et al, 1991). This modification of making the puncture before grasping the vas deferens with the ring-tipped vas deferens fixation clamp was found to decrease the operative time significantly and showed no difference in incision length, postoperative pain, or time to return to work in a randomized prospective evaluation (Chen et al, 2005).

Methods of Vasa Obstruction and Male Sterilization

Numerous vasectomy occlusion techniques are employed, including excision and ligation, thermal occlusion with intraluminal electrocautery, mechanical occlusion with hemoclips, fascial interposition, and chemical occlusion with percutaneous techniques. There have been concerns about the risk of vasa necrosis

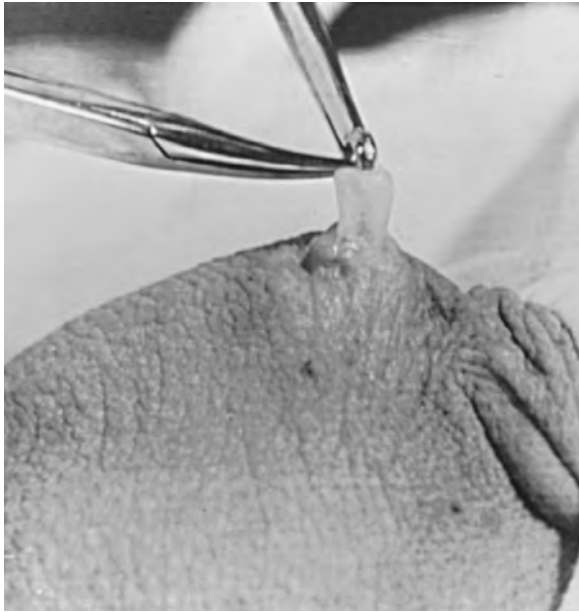


Figure 41-9. Delivery of the clean vas. (From Li S, Goldstein M, Zhu J, et al. The no-scalpel vasectomy. *J Urol* 1991;145:341–4.)

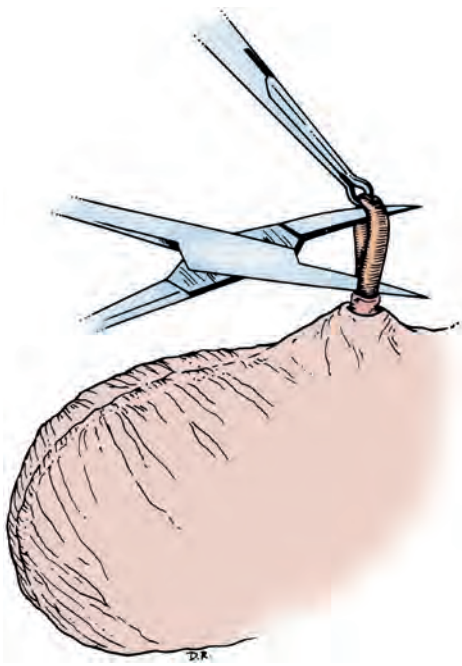


Figure 41-10. Segment cleaned. (From Li S, Goldstein M, Zhu J, et al. The no-scalpel vasectomy. *J Urol* 1991;145:341–4.)

and sloughing distal to the ligated end when suture ligation is performed, theoretically increasing the risk of recanalization. Low-voltage thermal occlusion with intraluminal electrocautery in the abdominal and testicular ends of the divided vas deferens reduces recanalization rates to less than 0.5% (Schmidt, 1987; Barone et al, 2004). Vasectomy failure rates have been reported to be less than 1% when the testicular and abdominal ends of the divided vas deferens are occluded with hemoclips (Moss, 1974; Bennett, 1976). Interposition of dartos fascia between the divided ends of the vas deferens is another technique for occlusion. This method has been reported to reduce the recanalization rate even further, to nearly zero (Esho and Cass, 1978; Sokal et al, 2004).

Percutaneous vasectomy has been performed on more than 500,000 men in China. This technique employs chemical occlusion

by fixing the vas deferens up to the scrotal skin tightly, puncturing the lumen of the vas deferens with a 22-gauge needle, and cannulating the lumen of the vas deferens with a 24-gauge blunt needle. For confirmation of vas deferens cannulation, Congo red is injected into the lumen of the abdominal end of the right vas deferens, and methylene blue is injected into the lumen of the left vas deferens before chemical occlusion by injection of 20 μ L of 2 parts phenol to 1 part *N*-butylcyanoacrylate mixture. Following chemical occlusion, the patient should void. If the urine is red, the left side was not cannulated, if it is blue, the right side was not cannulated, and if it is brown, that indicates bilateral successful cannulation (Ban, 1980; Li, 1980). Although these chemicals are not approved for use in the United States by the Food and Drug Administration, they appear to be safe based on toxicologic testing and experience in China.

Fascial interposition has been found to decrease vasectomy recanalization rates the most significantly. Randomized controlled trials examining the other techniques are unavailable. Several trials have been performed using irrigation of the abdominal ends of the vas deferens with saline, but there was no difference in time to azoospermia (Cook et al, 2007b).

Open-ended vasectomy, in which the testicular portion of the vas deferens remains patent, is another technique that has been evaluated with the aim of decreasing epididymal pressure by performing intraluminal cautery or another method of occlusion on the abdominal end, while leaving the testicular end unoccluded. Sperm granulomas develop in 97% of patients undergoing open-ended vasectomy. The granulomas are thought to reduce pressure-induced damage to the epididymis, but they increase the vasectomy failure rate to 7% to 50% (Shapiro and Silber, 1979; Goldstein, 1983). There is a significant decrease in the failure rate with open-ended vasectomy when fascial interposition is performed (decreasing the failure rate by approximately 7%) (Li et al, 1994).

Performing Vasectomy to Make Microscopic Vasectomy Reversal Easier

Technical aspects of performing vasectomy can affect the ease of microsurgical vasectomy reversal in the future if needed (Mammen et al, 2008). One procedural aspect is that excising a lengthy (>1 cm) segment of vas deferens is associated with the need for a higher scrotal incision, possibly up to the lower inguinal region, with the potential for anastomotic tension with microscopic vasectomy reversal. Vasectomy reversal can be far more difficult when a lengthy portion of the vas deferens has been excised, with concomitant increases in operative time, length of incision, and postoperative pain (Practice Committee of the American Society for Reproductive Medicine, 2006).

Another procedural aspect is the location along the length of the vas deferens where the vasectomy is performed. Experts in microsurgery agree that the anastomosis is least problematic when the lumen of the vas deferens is largest and most concentric, as opposed to the lumen in the epididymis or the convoluted vas (Mammen et al, 2008). Prospective studies show that the length of the testicular vas deferens present at the time of reversal has a direct correlation with the presence of seminal fluid containing intact sperm at the time of microscopic vasectomy reversal. A testicular length of vas deferens less than 2.7 cm correlates with seminal fluid without intact sperm 85% of the time, and testicular length more than 2.7 cm is associated with intact sperm in seminal fluid 94% of the time. For each 1-cm increase in testicular remnant length, the probability of whole sperm being present increases fourfold (Witt et al, 1994). Division of the vas deferens should be performed approximately 3 cm distal to the cauda of the epididymis in the straight portion of the vas deferens at the time of vasectomy.

The other technical aspect to consider is the occlusion technique employed. All occlusive modalities for vasectomy carry a similarly high efficacy in terms of postprocedure azoospermia. To date, no specific studies on occlusion technique as a predictor of reversal success have been performed. A simple transection of the vas

deferens followed by low-voltage intraluminal cautery occlusion and then fascial interposition provides successful vasectomy and may result in minimal inflammatory reaction. Minimizing inflammation near the vas deferens would provide the optimum condition for microscopic vasectomy reversal in the future (Mammen et al, 2008).

Postoperative Care and Follow-Up Semen Analysis

Routine postoperative care practices vary but typically include the use of ice packs on the scrotum intermittently for the first 48 hours, limited heavy or strenuous activity for 1 week, and the use of nonsteroidal anti-inflammatory drugs as needed for pain if the patient does not have any contraindications to these medications. There is no vasectomy technique that is 100% effective. Time to reach azoospermia is variable, although greater than 80% of patients achieve azoospermia by 3 months and after 20 ejaculations. The AUA Vasectomy Guideline (American Urological Association, 2012) recommends checking the first postvasectomy semen analysis 8 to 16 weeks after vasectomy. Persistent nonmotile sperm are present in 1.4% of patients after vasectomy. These data point to obtaining a semen analysis at 3 months and 20 ejaculations after vasectomy to reveal azoospermia. If the semen analysis does not show azoospermia, periodic semen analyses can be obtained every 6 to 12 weeks until azoospermia is achieved. Additional samples should be submitted if the initial semen analysis has motile sperm or greater than 100,000 nonmotile sperm/mL. Patients who have small numbers of persistent nonmotile sperm can be advised cautiously to discontinue contraception (Griffin et al, 2005). There is evidence that these men ultimately reach azoospermia. Vasectomy should be repeated if any motile sperm are seen in the ejaculate 6 months after the initial vasectomy (American Urological Association, 2012).

An immunodiagnostic test, the SpermCheck Vasectomy (ContraVac, Charlottesville, VA), has been developed to allow patients to test themselves for severe oligospermia or azoospermia at home after vasectomy. This test was developed to increase compliance with postvasectomy evaluation of semen parameters. The SpermCheck Vasectomy test was 96% accurate at predicting whether sperm counts were greater or less than a threshold of 250,000 sperm/mL (Klotz et al, 2008).

Local and Postoperative Complications

The rates of surgical complications after vasectomy are approximately 1% to 2%. Local complications of vasectomy include hematoma, infection, Fournier gangrene, chronic scrotal pain, and traumatic fistula/scrotal sinus (Awsare et al, 2005). The most important predictor of postoperative complications is surgeon volume and experience (Kendrick et al, 1987).

Hematoma is the most common complication of vasectomy. The rate of hematoma formation after vasectomy ranges from 0.09% to 29%, with a mean incidence of 2% (Kendrick et al, 1987). The no-scalpel technique has decreased the hematoma rate to a 0.5% incidence (Pant et al, 2007).

The rate of infection from vasectomy with the conventional technique was reported to be between 12% and 38% but decreased to 0.4% with the no-scalpel technique (Appell and Evans, 1980; Pant et al, 2007). Although exceedingly rare, Fournier gangrene has been reported as a complication in men undergoing vasectomy (de Diego Rodríguez et al, 2000; Romero Pérez et al, 2004).

Short-term scrotal pain lasting a few weeks can occur in 30% of men. The medical literature on postvasectomy pain syndrome, or long-term scrotal pain after surgery, consists of studies with small sample sizes, nonvalidated pain measures, high nonresponse rates, and variable outcome measures. The most robust study identified the incidence of chronic scrotal pain severe enough to seek medical attention to be 0.9% (Leslie et al, 2007), although it has been reported to be as high as 15% (McConaghy et al, 1996). Postvasectomy pain syndrome has no association with immediate postoperative complications such as hematoma or infec-

tion. There are several theories about the cause of postvasectomy pain syndrome. One is that dilation of the epididymal duct with obstruction of the testicular end of the vas deferens produces interstitial fibrosis. Another theory is that extravasation of spermatozoa, with epididymal duct rupture forming a sperm granuloma at the site where the vas deferens is transected, results in perineural fibrosis and inflammation because sperm are highly antigenic (McMahon et al, 1992). This theory contradicts the previous belief that sperm granulomas are protective against postvasectomy pain syndrome by relieving pressure, although most sperm granulomas are asymptomatic (Tandon and Sabanegh, 2008). There are markedly increased pressures in the epididymis and the testicular end of the vas deferens after vasectomy, but these pressures were not found to be transmitted to the seminiferous tubules in human micropuncture studies (Johnson and Howards, 1975). It is unclear why some patients develop long-term symptoms and others develop transient symptoms. Factors such as age, socioeconomic status, race, environment, and vasectomy technique have not identified patients at risk for postvasectomy pain syndrome (Tandon and Sabanegh, 2008).

Conservative therapy should be the first-line therapy and includes scrotal elevation and support, heat or ice (as needed for comfort), and nonsteroidal anti-inflammatory drugs. Empirical antibiotic therapy is not recommended without evidence of infection (Selikowitz and Schned, 1985). Conservative therapy should be employed for at least 3 months for postvasectomy pain. Spermatic cord blocks and pain management techniques should be considered after failure of conservative therapy.

Surgical therapy might be considered on an individualized basis if the aforementioned methods fail. When pain is clearly localized to a sperm granuloma, excision of the granuloma and intraluminal cautery occlusion of the vas deferens may relieve the pain and prevent recurrence (Schmidt, 1979). Epididymectomy has been performed in patients who had point tenderness to the epididymis and epididymal dilation after vasectomy and failed conservative therapy. Predictors of poor outcomes with epididymectomy are atypical symptoms, concomitant erectile dysfunction, and a normal-appearing epididymis on scrotal ultrasonography (West et al, 2000). Of patients who were properly selected for epididymectomy, 50% were cured of postvasectomy pain syndrome (Chen and Ball, 1991). The patient must consider that vasectomy reversal will no longer be feasible after epididymectomy. Vasectomy reversal rendered 69% of patients with postvasectomy pain syndrome pain-free (Nangia et al, 2000). Although it has been evaluated in only a small number of patients, microscopic denervation of the spermatic cord in patients who failed conservative treatment resulted in complete pain relief in 76% of these men (Ahmed et al, 1997). The last resort consideration after failure of conservative and more invasive interventions have failed is orchiectomy for severe intractable pain after vasectomy. Pain relief was reported in 73% of men who underwent inguinal orchiectomy versus 55% of men who underwent scrotal orchiectomy for postvasectomy pain syndrome (Davis et al, 1990). There is a report of 0.3% rate of scrotal sinus/vasocutaneous fistula after no-scalpel vasectomy (Pant et al, 2007).

Association of Vasectomy with Long-Term Systemic Disease

Previous studies found an increased risk of prostate cancer in men who underwent vasectomy (Giovannucci et al, 1993). Detection bias is thought to be the source of this association of prostate cancer with vasectomy (Millard, 1999). More recent investigations have found that there is no association between vasectomy and prostate cancer (Schuman et al, 1993; Holt et al, 2008). There is no association between vasectomy and prostate cancer in developing countries in which there are low incidences of prostate cancer in the general population as well (Schwingl et al, 2009). Screening recommendations for prostate cancer should be no different in men who have undergone vasectomy than in men who have not undergone vasectomy (Healy, 1993).

Vasectomy does not place the patient at an increased long-term risk for cardiovascular disease or atherosclerosis (Coady et al, 2002; Goldacre et al, 2005). Previous studies suggested that vasectomy may be a risk factor for patients with primary progressive aphasia, a dementia syndrome with aphasia as the presenting symptom (Weintraub et al, 2006). There are no longitudinal studies confirming this association, and there have been many large, epidemiologic studies comparing men with and without vasectomy that have not shown any increased risk of dementia. There is no evidence that vasectomy adversely affects psychological health status (Thonneau and D'Isle, 1990).

Antisperm Antibodies

There is a disruption of the blood-testis barrier when vasectomy is performed. Of men who undergo vasectomy, 60% to 80% have detectable levels of antisperm antibodies in the serum (Fuchs and Alexander, 1983). After vasectomy, 50% to 60% of men develop sperm agglutinating antibodies, and 20% to 30% develop sperm immobilizing antibodies (Kovacs and Frances, 1983). Although some studies suggest that antisperm antibodies persist, others suggest that they diminish 2 or more years after vasectomy, but neither immune complex deposition nor circulation is increased in men who have undergone vasectomy (Witkin et al, 1982).

KEY POINTS: VASECTOMY

- No vasectomy technique is 100% effective.
- Patients can be advised to initiate unprotected intercourse following a semen analysis obtained 8 to 16 weeks after vasectomy that demonstrates azoospermia or rare nonmotile sperm.
- The no-scalpel technique significantly decreases the rate of hematomas, infections, and pain during the procedure.
- Fascial interposition is the occlusion technique that has been found to decrease vasectomy failure rates the most significantly.
- Technical aspects of performing vasectomy can affect the ease of microsurgical vasectomy reversal in the future if needed.
- There is no association between vasectomy and prostate cancer or cardiovascular disease.

SPERMATOCECTOMY AND SURGERY OF THE EPIDIDYMIS

Surgical Indications

A spermatocele or epididymal cyst is a cystic dilation of an epididymal tubule that is benign in nature. Spermatoceles are common and are found incidentally on high-resolution ultrasonography in 30% of men. They are typically asymptomatic and do not cause epididymal obstruction, and they rarely require intervention. Men typically seek surgical treatment when the spermatocele has reached the approximate size of the testis and is causing pain with point tenderness (Walsh et al, 2007).

Surgical treatment for chronic epididymitis is poorly studied in clinical trials with no level 1 evidence to support the use of a specific surgical procedure. In one study, 10 patients with chronic epididymitis (defined as epididymal pain lasting >3 months) underwent epididymectomy for intractable symptoms. Only one of these patients had significant improvement in pain (Davis et al, 1990). Other authors reported much higher success rates, such as six out of seven patients (86%) having significant improvement in pain after epididymectomy (Chen and Ball, 1991). Chronic or recurrent epididymitis and persistent epididymalgia with point tenderness to the epididymis may be reasonable indications for epididymectomy (Padmore et al, 1996).

Surgical treatment for chronic epididymitis should be considered only after failure of extensive conservative therapy and after appropriate counseling, with the understanding that the symptoms may not improve after surgery or may worsen. A retrospective review of men who underwent epididymectomy for chronic epididymitis showed that outcomes were best when the patient had a palpable epididymal abnormality on physical examination. Men in this study without a palpable abnormality but with ultrasound changes had slightly worse outcomes, and men with neither a palpable abnormality nor a demonstrable abnormality on ultrasonography did not improve with epididymectomy (Calleary et al, 2009).

Purulent epididymitis diagnosed by a combination of physical examination, ultrasound evaluation, and occasionally needle aspiration of the epididymis is an absolute indication for epididymectomy (Arbuliev et al, 2008). Epididymectomy is also the treatment of choice for epididymal abscesses and chronic infectious epididymitis that is unresponsive to antibiotic treatment. Diagnostic epididymal puncture and aspiration should not be performed in men with interest in future fertility because this procedure would result in epididymal obstruction. Total epididymectomy may relieve chronic persistent pain localized to the epididymis after vasectomy.

Epididymal malignancies are extremely rare, and 73% of nontransilluminating, solid epididymal masses are benign adenomatoid tumors (Beccia et al, 1976). Surgical extirpation should be considered for adenomatoid tumors, especially if there is any suspicion for malignancy (Alvarez Maestro et al, 2009).

Partial and Total Epididymectomy

Any patient undergoing epididymal surgery should be counseled extensively that the surgery may impair his fertility or cause sterility if bilateral epididymal surgery is required because the distal epididymis consists of a single tubule. Partial or total epididymectomy can be approached scrotally through a median raphe or a unilateral transverse scrotal incision to deliver the testis. The vas deferens is identified, isolated, ligated, and divided. The testicular end of the vas deferens is followed to the vasoepididymal junction. The tunica vaginalis is opened, and the plane of dissection between the epididymis and the testis is found to divide the epididymis from the testis. Great care should be taken to avoid injury to the spermatic cord and testicular artery. The efferent ducts superior to the testicular vasculature are ligated with an absorbable suture to complete the epididymectomy. The edges of the tunica vaginalis where the epididymis was excised are approximated with a running absorbable suture, which helps with hemostasis. The dartos fascia and skin are closed in layers with absorbable suture. In the case of partial epididymectomy, ligations are performed between the testis and epididymis with absorbable suture to excise the affected portion of the epididymis, while leaving the remainder attached to the testis with its vascular supply intact (Figs. 41-11 and 41-12).

Spermatocelectomy and Excision of Epididymal Cysts

Spermatocelectomy can be approached scrotally through a median raphe or a unilateral transverse scrotal incision to deliver the testis. The tunica vaginalis is opened, and the spermatocele is identified and dissected free from the epididymis. The epididymal-spermatocele attachment is ligated and divided to complete the spermatocelectomy. The tunica vaginalis is closed, and the dartos fascia and scrotal skin are reapproximated in layers.

Excision of Epididymal Tumors

As discussed earlier, most epididymal nontransilluminating masses are benign adenomatoid tumors. Fine-needle aspiration of solid epididymal masses has been evaluated and found to be very accurate compared with surgical pathology (Gupta et al, 2006). When malignancy is suspected, an inguinal approach should be used with clamping of the spermatic cord and delivery of the testis. The addition of testicular hypothermia by adding ice slush to the

Chevassu maneuver (of clamping the vessels) was employed and found to salvage three of five testicles with benign processes after clamping and parenchymal biopsy (Goldstein and Waterhouse, 1983). When malignancy is ruled out, the epididymal mass may be excised as for a spermatocelectomy.

Complications

Complications of epididymectomy, spermatocelectomy, and excision of epididymal masses are rare. Complications include bleeding, infection, damage to the testicular artery with resultant testicular atrophy, and recurrence in cases of spermatocelectomy (Kiddoo et al, 2004; Zahalsky et al, 2004). Complications also include impairment of fertility with obstruction of the epididymal tubules and possible sterility in bilateral cases, necessitating counseling and recommending sperm cryopreservation in men who undergo bilateral procedures and have an interest in fertility. Approximately 17% of patients undergoing spermatocelectomy have resultant epididymal injury (Zahalsky et al, 2004). The overall complication rate has been reported to be 20%, with the most common complications being persistent scrotal pain and infection. Leaving a scrotal drain did not decrease complication rates (Kiddoo et al, 2004).

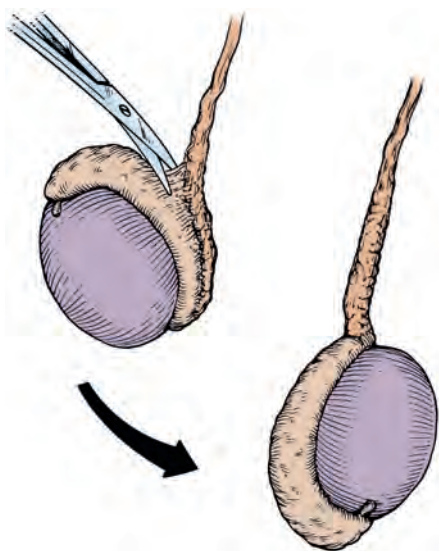
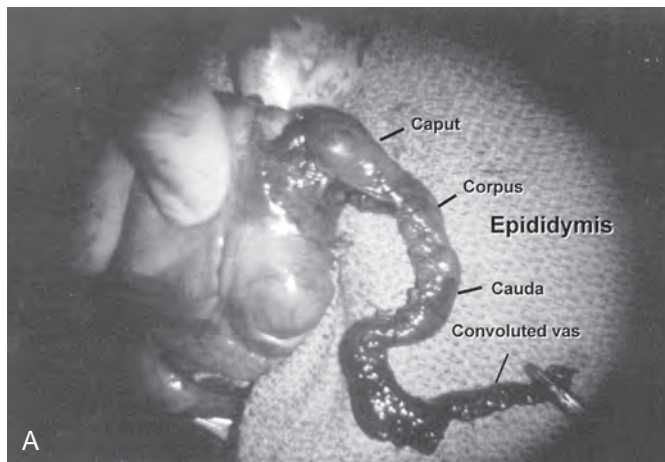


Figure 41-11. Convoluted vas dissected off the epididymal tunica.



HYDROCELECTOMY

Hydrocele in an adult is caused by excessive fluid secretion by the visceral tunica albuginea without adequate reabsorption of this fluid by the parietal peritoneum around the testis.

Inguinal Surgical Approach

Men in whom hydroceles have been diagnosed, in which there is suspicion for concomitant malignancy, should undergo high-resolution scrotal ultrasonography. If malignancy is suspected, an inguinal approach should be used to allow control of the spermatic cord in preparation for radical orchiectomy. If this approach is taken and no malignancy is encountered, the testis can be spared and the hydrocele can be repaired by one of the techniques described subsequently.

Scrotal Surgical Approaches

When there is no evidence of malignancy on physical examination and high-resolution ultrasonography, hydroceles may be approached scrotally through a median raphe or a transverse unilateral incision. In all techniques, the hydrocele is dissected and delivered intact to allow the easiest dissection. After the hydrocele is delivered, an opening in the sac is made away from the testis, epididymis, and cord structures, and the fluid is suctioned out. The hydrocele sac is opened further to expose the sac for the elected repair. The overall single-treatment success rates for surgical hydrocelectomy are between 90% and 100% (Rodriguez et al, 1981).

Excisional techniques are the least likely to result in recurrence of a hydrocele. Excising the hydrocele is recommended for large, long-standing, thick-walled, loculated hydroceles. The hydrocele sac is opened, taking great care not to injure the spermatic cord, and the sac is simply excised, leaving room to oversew the edge of the excised sac without endangering the cord or the epididymis. A 3-0 chromic suture can be used in a baseball-stitch manner to oversew the edge of the sac (Fig. 41-13).

The Jaboulay bottleneck technique (1902) is a useful method for large, floppy, thin hydrocele sacs. This technique is performed by excising the sac as described previously, but a larger margin of excision should be left between the edge of the sac and the testis and epididymis to allow for sewing the edges of the sac together behind the cord, without compressing the cord (Fig. 41-14).

If there appears to be a risk for hematoma after excision and oversewing with either technique, a Penrose drain can be left in the dependent portion of the scrotum and fixed in place to the scrotum. The dartos fascia and skin are then closed in layers. Fluffs and a scrotal support are used for the dressing.

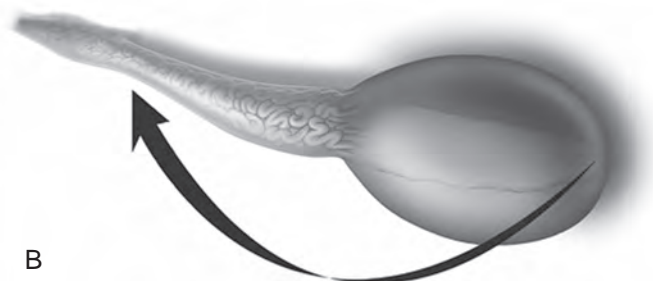


Figure 41-12. A and B, Entire vasoepididymal complex is dissected to the caput.

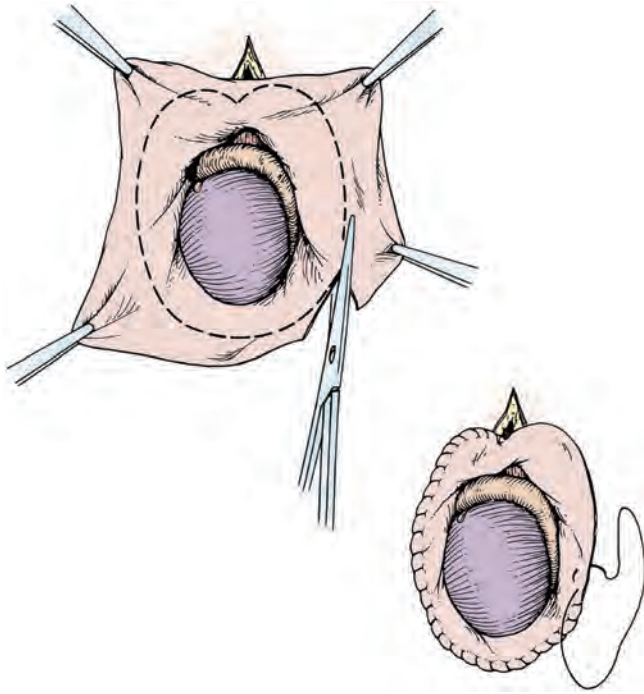


Figure 41-13. Simple excision of the thick-walled hydrocele sac and oversewn edges.

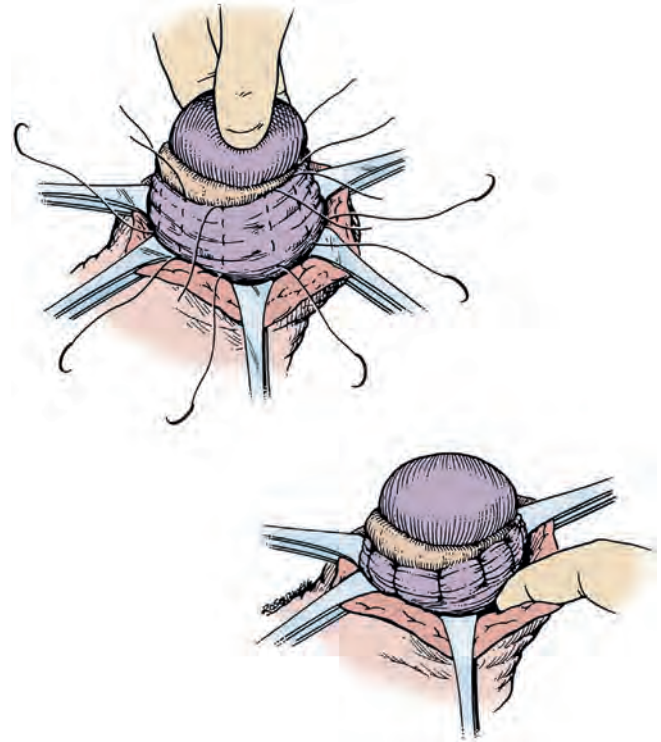


Figure 41-15. Lord plication technique.

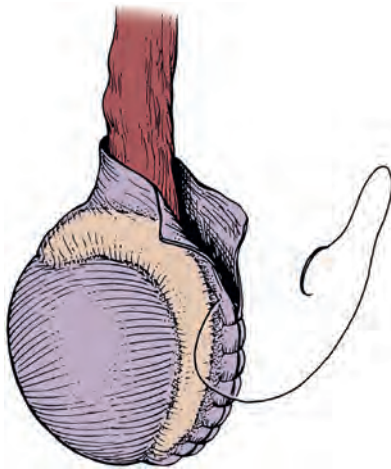


Figure 41-14. Jaboulay bottleneck technique for excision of thin, floppy sacs.

Plication techniques are suitable for smaller, thin-walled hydroceles but should not be used in large, long-standing, thick-walled, multiloculated hydroceles because this leaves a large bundle of plicated tissue in the scrotum. The **Lord plication technique** (1964) is performed by opening the hydrocele as described earlier, delivering the testis, cauterizing or oversewing the cut edges of the sac, and using interrupted, radially placed chromic sutures to plicate the sac. Closure is performed as described earlier. Drains are unnecessary with plications (Fig. 41-15).

A minimally invasive technique can be used by making a 2-cm incision in the scrotum. The hydrocele is drained, followed by excision of a portion of parietal tunica vaginalis. The tunica vaginalis is everted, sutured to the subcutaneous tissue, and a surgical drain is placed (Saber, 2011).

Sclerotherapy

Sclerotherapy is another treatment option with a single-treatment success rate ranging from 33% to 75% (Levine and Dewolf, 1988).

TABLE 41-1 Hydrocelectomy Techniques and Risks

	RECURRENCE	HEMATOMA
Excision	Decreased	Increased
Plication	Increased	Decreased

This option may be a good choice for patients who cannot tolerate anesthesia or who refuse surgical treatment. The common steps of the procedure include needle aspiration of the hydrocele fluid, followed by injection of local anesthesia, and ultimately instillation of the sclerosing agent. The most commonly used sclerosing agent is tetracycline, although 2.5% phenol solutions, 95% alcohol, and ethanolamine oleate also have been used effectively (Nash, 1984; Hellström et al, 1986; Miskowiak and Christensen, 1988). One study showed no statistically significant improvement in patients who underwent aspiration of hydrocele fluid alone versus aspiration plus instillation of tetracycline as a sclerosing agent, with a higher complication rate in the sclerotherapy group (Breda et al, 1992). When sclerotherapy was compared with hydrocelectomy, the success rate was higher in hydrocelectomy, although the hydrocelectomy group had a higher complication rate. Nonetheless, the patients who underwent hydrocelectomy had higher satisfaction rates (Beiko et al, 2003).

Complications

The most common complication after hydrocelectomy is hematoma (Table 41-1). The overall complication rate in hydrocelectomy is approximately 19%, including hematoma, infection, persistent swelling, recurrence, injury to spermatic vessels, and chronic pain. Although the use of a drain in selected patients is recommended, it has not been proven so far to decrease complication rates (Kiddoo et al, 2004). When repairing large hydroceles, great care must be taken not to injure the epididymis and spermatic vessels because they may be splayed within the hydrocele layers.

Injury to the epididymis or vas deferens can put the patient's future fertility at risk (Zahalsky et al, 2004).

Sclerotherapy complications include scrotal pain in 29% to 55% of patients (Rencken et al, 1990; Ovrebø and Vaage, 1991), recurrence, hematoma, and infection; febrile chemical epididymo-orchitis has also been reported with sclerotherapy (López Laur and Parisi, 1989; Beiko et al, 2003). Sclerotherapy can have an adverse effect on fertility and should be avoided in patients interested in maintaining fertility (Sigurdsson et al, 1994).

SURGICAL TREATMENT OF ORCHITIS AND CHRONIC SCROTAL PAIN

Orchitis is defined as inflammation of the testicle (Delavierre, 2003). Typical symptoms of orchitis include scrotal pain, swelling, tenderness, and skin fixation over the testicle. The Prehn sign has been described in orchitis and epididymitis when there is relief of pain with elevation of the testicle over the symphysis pubis (Noske et al, 1998). The Prehn sign is nonspecific and nondiagnostic and does not distinguish epididymo-orchitis from spermatic cord torsion. Orchitis can cause an irreversible effect on spermatogenesis, affecting the quality and number of spermatozoa. Lymphocytic infiltration and seminiferous tubule damage are seen on testicular biopsy specimens of subfertile men with a history of chronic orchitis (Schuppe et al, 2008).

Chronic orchialgia is defined as constant or intermittent scrotal pain lasting at least 3 months or longer and with an unclear cause (Costabile et al, 1991). In patients with clinical orchialgia, a scrotal ultrasound scan should be obtained because testicular malignancy has been reported to masquerade as orchialgia (Vaidyanathan et al, 2008). At least 10% of men with testicular malignancy initially receive an incorrect diagnosis of an acute inflammatory process or spermatic cord torsion (Cook and Dewbury, 2000). High-frequency transducer ultrasonography (7.5 to 10 MHz) is considered the best modality for evaluation of scrotal pathology including orchitis (Lee et al, 2008).

Although there is no level 1 evidence for the optimal treatment of chronic orchialgia or epididymitis, local supportive therapy, including heat, nerve blocks, analgesics, tricyclic antidepressants, anticonvulsants (e.g., gabapentin), and anti-inflammatory drugs, is commonly applied and may offer some relief (Davis and Noble, 1992). Other treatment options implemented for chronic epididymitis include phytotherapy, anxiolytics, narcotics, acupuncture, and steroid injection therapy (Nickel et al, 2002). Despite evidence that 75% of patients do not have an identifiable bacterial urinary tract infection concomitantly with clinical epididymitis, antibiotics are routinely given. Empirical antibiotic administration in the absence of positive urine cultures has been steadily increasing, from 75% to 95% between the years of 1965 and 2005. Antibiotic administration does not decrease the length of symptoms or the return to full activity in men without an identifiable bacterial pathogen (Mittmeier et al, 1966).

Orchiectomy

Surgical treatment for chronic orchialgia is poorly studied in clinical trials, with no level 1 evidence to support the use of a specific surgical procedure. In the available literature, fewer than 250 patients with chronic scrotal pain have been treated with differing surgical therapies despite the common nature of chronic scrotal pain. There is no level 1 evidence that orchiectomy is effective for the treatment of chronic orchialgia. If orchiectomy is recommended, the patient should have failed previous conservative therapy and must be apprised of the risks, benefits, and options of orchiectomy. Because many patients continue to have pain or have pain recur after orchiectomy, the surgeon should be aware of the medicolegal aspects of this action. If orchiectomy is performed, it should be performed through an inguinal incision because this approach has been shown to have a better outcome than the scrotal approach for orchialgia (Davis and Noble, 1992).

Microsurgical Denervation of the Spermatic Cord

Some surgeons have attempted microsurgical denervation of the spermatic cord for symptomatic relief of chronic scrotal pain. Microsurgical denervation of the spermatic cord was performed in 79 men on 95 testicular units for chronic orchialgia over a mean duration of 62 months. There was complete relief of pain in 71% of the patients, partial relief of pain in 17%, and no change from the preoperative status in 12%, with no patients experiencing worsened postoperative pain. The mean follow-up time was 20.3 months (Strom and Levine, 2008). Microscopic denervation has been shown to be beneficial if the patient has temporary relief of orchialgia with a spermatic cord block (Levine et al, 1996; Benson et al, 2013). Spermatic cord denervation has been shown to be successful in men who underwent alternative surgical procedures to treat chronic orchialgia (i.e., epididymectomy, varicocelectomy) (Larsen et al, 2013).

To mobilize the spermatic cord, microsurgical denervation is performed by the same approach as microscopic subinguinal ligation of the spermatic veins for varicocele repair. Microscopic transection of all branches of the genitofemoral nerve along the spermatic cord is performed, while preserving the testicular artery, the vas deferens, the vasal vessels, and some of the lymphatics (Fig. 41-16). This procedure also can be performed laparoscopically (Cadeddu et al, 1999). If fertility is not a concern, it is recommended to divide the vas deferens as well to eliminate sympathetic innervation, which may contribute to orchialgia by a sympathetic dystrophy component (Levine et al, 1996).

Large, clinically palpable varicoceles can cause orchialgia. The pain typically improves with the patient in the supine position because the varicocele decompresses. In a small series of men who underwent microscopic varicocelectomy for clinically palpable varicoceles with concomitant orchialgia, slightly more than 50% had resolution of pain, and 90% had improvement (Chawla et al, 2005). Higher success rates were reported in a previous, larger powered, retrospective study (Peterson et al, 1998). Smaller, non-clinical varicoceles are unlikely to cause orchialgia and should be managed conservatively.

Retractile testes are another source of scrotal pain in men. A careful history must be elicited to make this diagnosis because the patient may not demonstrate a retractile testis on examination. The history is consistent with orchialgia only when the testis retracts up toward the external inguinal ring. This is typically seen in younger men with hyperactive cremasteric reflexes. Orchiopexy can be performed in these patients as it would in patients with intermittent torsion (Forte et al, 2003). When orchiopexy is offered, it should be performed by a dartos pouch technique to prevent

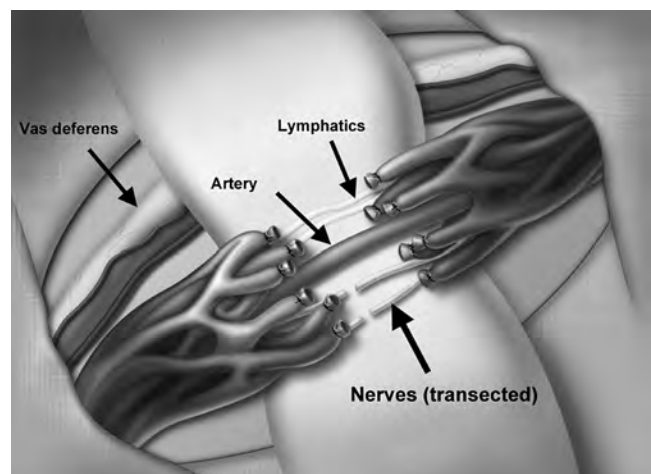


Figure 41-16. Microsurgical denervation. The goal is to transect all branches of the genitofemoral nerve while preserving the vas deferens, vasal vessels, testicular artery, and lymphatics.

retraction, as is recommended for testicular torsion (Redman and Barthold, 1995).

The other surgical treatment for orchialgia secondary to the retractile testis is to perform microscopic release of the cremasteric muscle. This technique is performed in a similar manner to microscopic subinguinal varicocelectomy. The spermatic cord is mobilized and isolated, and the cremasteric muscle is divided circumferentially, while preserving the vasculature of the spermatic cord and the vas deferens. This technique effectively releases the spermatic cord, not allowing retraction of the testis with hypercontraction of the cremasteric muscles.

KEY POINTS: SURGERY OF THE SCROTAL CONTENTS

- Patients undergoing epididymal surgery should be counseled that the surgery may impair their fertility or cause sterility if bilateral epididymal surgery is required.
- Sclerotherapy as treatment for a hydrocele can have an adverse effect on fertility and should be avoided in patients interested in maintaining fertility.
- Antibiotics should not be given for epididymitis or orchitis without evidence of infection.
- Patients with chronic orchialgia should receive a scrotal ultrasound scan.
- When a clinically palpable varicocele is encountered in a patient with orchialgia, varicocelectomy resolves the pain 50% of the time.

SURGERY OF THE SEMINAL VESICLES

In 1561, Gabriele Fallopius, a renowned Italian anatomist and physician, first described the seminal vesicles as paired male organs. He was considered an authority in the field of sexuality and advocated the use of condoms to decrease the transmission of syphilis. There was a great deal of interest in the seminal vesicles in the late 19th century because of their discovered involvement with inflammatory diseases (Brewster, 1985).

Seminal vesicle secretions contribute 50% to 80% of the volume of the ejaculate. The pH of the secreted fluid is neutral to slightly alkaline, and the mean volume is approximately 2.5 mL. The secreted fluid contains fructose and other carbohydrates necessary for sperm motility. It also contains a coagulation factor and prostaglandins A, B, E, and F (Tauber et al, 1975).

Primary disease processes of the seminal vesicles are very rare, although secondary processes are seen more commonly. Diagnosis of such entities has improved over the years with advanced imaging, particularly magnetic resonance imaging (MRI) (Kim et al, 2009; Chiang et al, 2013). Because of the anatomic location, surgical access and management of seminal vesicle pathology can be difficult for the urologist.

Anatomy

The seminal vesicles are paired male organs with no equivalent in the female. It is useful to understand the developmental anatomy of the seminal vesicles to gain a full understanding of the anatomy in adult patients. The seminal vesicles begin as bilateral dorsolateral bulbous dilations of the distal mesonephric ducts between 12 and 12½ weeks of gestation. By 13 weeks, these dilations have enlarged, and the ejaculatory ducts are beginning to form in the developing prostate (Brewster, 1985). The seminal vesicle and the ampulla of the vas deferens join posterior and superior to the prostate to form the ejaculatory duct (Nguyen et al, 1996). By the early portion of the seventh month, the seminal vesicle has multiple outpouchings and a widened main central lumen (Fig. 41-17) (Brewster, 1985).

The adult seminal vesicle measures 5 to 6 cm in length and 3 to 5 cm in diameter with a volume capacity of 13 cm, although seminal vesicles decrease in size as men age (Redman, 1987). At

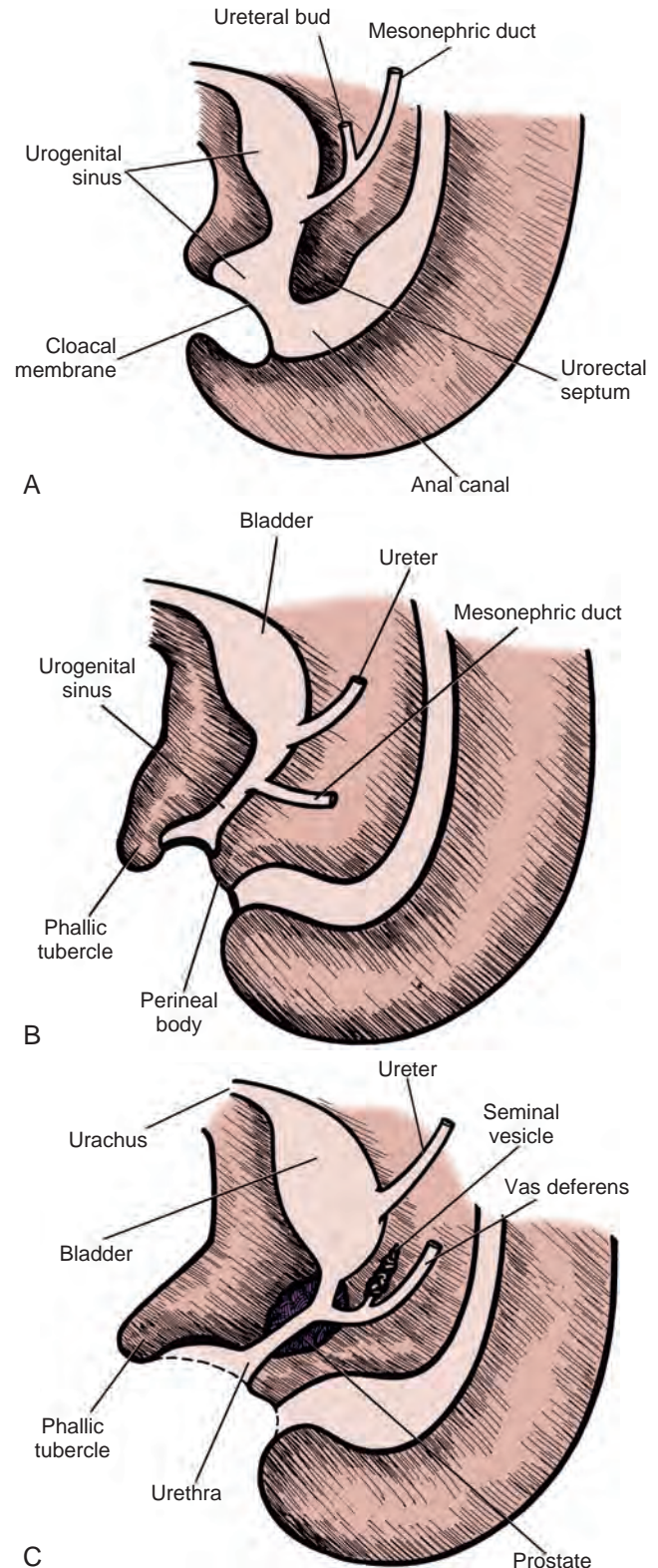


Figure 41-17. Intrauterine (fetal) development of the seminal vesicles. A, Week 5. B, Week 8. C, Week 13. (Redrawn from Langman J. *Medical embryology*. 4th ed. Baltimore: Williams & Wilkins; 1981. p. 242–3.)

the terminal portion of the vas deferens within the prostate, the major lumen of the seminal vesicle empties into the ejaculatory duct. The ejaculatory duct is in continuity with the seminal vesicle but does not share the thick muscular wall of the seminal vesicle (Fig. 41-18) (Nguyen et al, 1996). The arterial supply to the

seminal vesicle is from the vesiculodeferential artery, branching off from the umbilical artery (Braithwaite, 1952). Venous drainage of the seminal vesicle follows the arterial supply draining through the vesiculodeferential veins and the inferior vesicle plexus. Innervation of the seminal vesicles is by the hypogastric nerve (adrenergic and cholinergic) and the pelvic nerve. Lymphatic drainage of the seminal vesicles is through the internal iliac nodes (Mawhinney and Tarry, 1991).

Congenital Anatomic Anomalies of the Seminal Vesicles

The incidence of unilateral seminal vesicle agenesis is 0.6% to 1%. Unilateral seminal vesicle agenesis may be associated with ipsilateral renal anomalies and unilateral absence of the vas deferens. This anomaly is thought to be secondary to an embryologic insult at week 7 of gestation before the separation of the ureteral bud from the mesonephric duct. If this insult occurs after week 7, it is unlikely that renal agenesis would be associated with the seminal vesicle agenesis (Hall and Oates, 1993). It is common to find bilateral absence of the seminal vesicles along with congenital

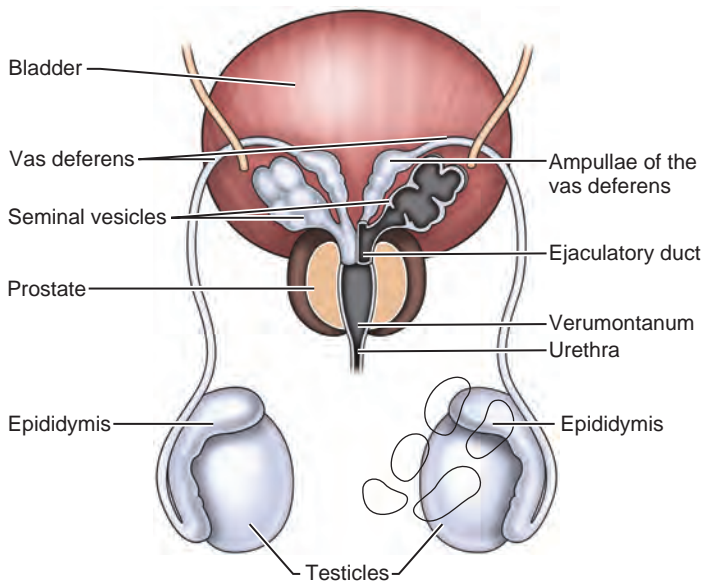


Figure 41-18. Posterior view of seminal vesicle anatomy in relation to the lower genitourinary tract (bivalved areas in dark gray).

bilateral absence of the vas deferens, which is typically associated with a cystic fibrosis transmembrane receptor mutation; 70% to 80% of affected men carry the genetic mutation associated with cystic fibrosis (Anguiano et al, 1994; Chillon et al, 1995). Treatment is necessary only when fertility becomes an issue.

Infectious Processes of the Seminal Vesicles

Infection of the seminal vesicles is seen in underdeveloped countries more frequently than in the United States. The causative agents are *Mycobacterium tuberculosis* and *Schistosoma haematobium*. The diagnosis of bacterial seminal vesiculitis can be made by transrectal or perineal needle aspiration. Surgery is not usually indicated, and culture-specific systemic antibiotics are the treatment of choice (Gutierrez et al, 1994). Very rarely, seminal vesiculectomy is necessary to prevent recurrent bacteremia or to eliminate persistent symptoms (Indudhara et al, 1991). Seminal vesicle abscesses are rare but have been associated with diabetes mellitus, long-term indwelling catheters, and endoscopic instrumentation (Gutierrez et al, 1994). Management of seminal vesicle abscesses is discussed subsequently with management of seminal vesicle cysts. Infection, obstruction, or the combination of the two can result in formation of calculi in the seminal vesicles. Patients with seminal vesicle calculi present with hematospermia, perineal pain, painful ejaculation, and infertility. These stones can be managed through an open or laparoscopic vesiculectomy, or the stone can be retrieved endoscopically using a small-caliber ureterscope (Ozgök et al, 2005; Cuda et al, 2006; Han et al, 2008).

Evaluation of Abnormalities of the Seminal Vesicles

Normal seminal vesicles are not palpable on digital rectal examination. When a seminal vesicle cyst is present, the area immediately above the prostate may be compressible on digital rectal examination. This same area may feel firm or solid when a seminal vesicle tumor is present. Semen analysis revealing a low seminal volume (<1.0 mL) and a lack of liquefaction and fructose may indicate ejaculatory duct obstruction or the absence of seminal vesicles (Goldstein and Schlossberg, 1988).

High-resolution transrectal ultrasonography (TRUS) has become the mainstay of imaging for the diagnostic evaluation of seminal vesicle pathology because it is a reliable and inexpensive imaging modality. On TRUS, the seminal vesicles can be found just superior to the prostate, between the bladder and the rectum, and can be well visualized in the anteroposterior and sagittal views. The normal seminal vesicles should appear as flat, elongated, paired structures in the above-described positions (Fig. 41-19). Along

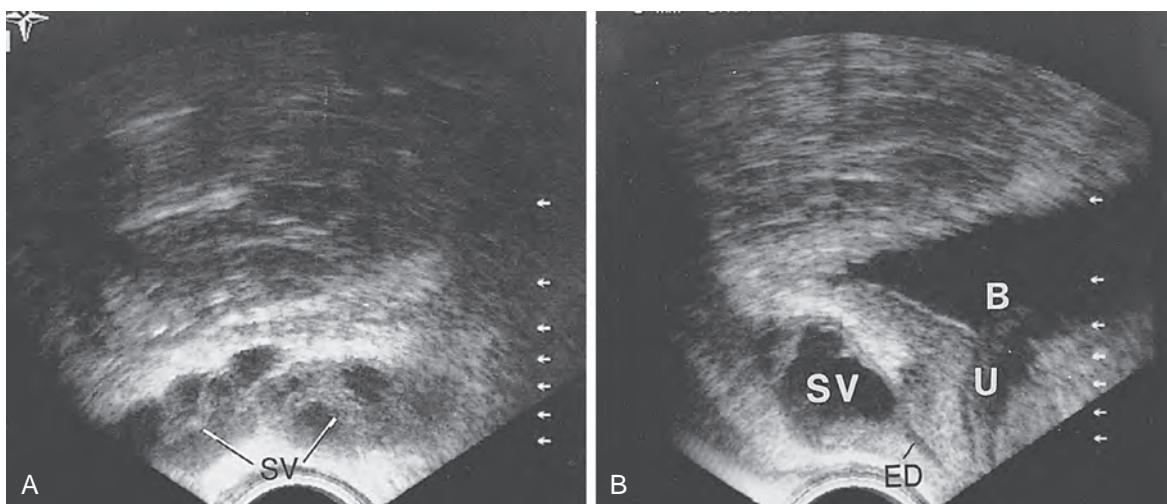


Figure 41-19. Transrectal ultrasound examination of normal seminal vesicles. A, Transverse view. B, Sagittal view. B, bladder; ED, ejaculatory duct; SV, seminal vesicle; U, urethra.

with the seminal vesicles, the ampullae of the vas deferens, the ejaculatory ducts within the prostate, and the verumontanum can be imaged and evaluated by TRUS. Abnormalities such as seminal vesicle obstruction, aplasia, atrophy, and cyst formation can be identified by TRUS (Carter et al, 1989).

Seminal vesicle obstruction may result in seminal vesicle dilation that can be identified on TRUS with the following characteristics: anteroposterior diameter of greater than 15 mm, length greater than 35 mm, and large anechoic areas that contain sperm when aspirated (Jarow, 1996; Colpi et al, 1997). Asymptomatic cystic dilation of the seminal vesicle was incidentally found in 5% of men undergoing TRUS for prostate cancer screening (Wessels et al, 1992).

Hyperechoic solid masses in the seminal vesicles (isoechoic to the prostate) revealed on TRUS are concerning for tumor. If there is a unilateral solid mass in the seminal vesicle, it is more likely to be a primary tumor, whereas if it is present in bilateral seminal vesicles, it is more likely to be a secondary tumor from a primary prostate, rectal, or bladder malignancy. TRUS-guided biopsy or aspiration is necessary to assist in the diagnosis.

Computed tomography (CT) also has been used to evaluate the seminal vesicles. The normal appearance of the seminal vesicles on CT scan is that of paired structures just below the bladder with medium contrast similar to muscle (Goldstein and Schlossberg, 1988). A seminal vesicle cyst appears on CT scan as a well-defined retrovesicular fluid density with the attenuation of water, from 0 to 10 Hounsfield units, cephalad to the prostate gland (Fig. 41-20). CT accurately images seminal vesicle anomalies and is a good modality for imaging of the ipsilateral kidney concomitantly (Arora et al, 2007).

In cases of primary seminal vesicle malignancy, CT scan may be useful to characterize the lesion further before intervention. A tumor within the seminal vesicle on CT scan has a higher attenuation than the normal seminal vesicle, but the tumor may appear cystic secondary to tumor necrosis (King et al, 1989). It is impossible to differentiate malignant tumors from benign tumors on CT scan alone, although secondary tumors from the bladder, rectum, or prostate may have a more contiguous appearance (Sussman et al, 1986). The CT findings of a leiomyosarcoma of the seminal vesicle are described as an irregular mass, resulting in enlargement of the seminal vesicle with displacement of the prostate gland (Upreti et al, 2003). CT as well as MRI allows metastatic evaluation when seminal vesicle neoplasms are characterized further (Dahms et al, 1999).

MRI demonstrates more anatomic detail than CT and is an extremely useful imaging modality for the seminal vesicles. On

T2-weighted images, the ampulla of the vas deferens is visible approximately 71% of the time and exhibits low signal intensity. The seminal vesicles exhibit high signal intensity 79% of the time, low signal intensity 19% of the time, and a heterogeneous signal intensity 2% of the time on T2-weighted images (Roy et al, 1993). On T2-weighted images, the seminal vesicles generally have similar or higher intensity than fat in patients younger than 70 years old and typically have signal intensity lower than that of fat in patients older than 70. The convolutions of the seminal vesicles can be seen on T1-weighted imaging with contrast material (Fig. 41-21) (Secaf et al, 1991).

On MRI, seminal vesicle agenesis is best exemplified on T1-weighted axial images (Fig. 41-22). Care must be taken not to mistake the vesicoprostatic venous plexus for small glands. Arterio-venous malformations appear as large ectatic vessels adjacent to the lateral edge of the seminal vesicle. After androgen ablation, seminal vesicles demonstrate low signal intensity on T2-weighted images and appear small in size (Secaf et al, 1991). After pelvic radiation, seminal vesicles appear to be decreased in size in one third of patients. In patients after pelvic radiation, 63% of seminal vesicles had a normal MRI appearance, 21% had normal signal intensity but had fewer tubules, 8% had diffuse loss of signal intensity appearing hypointense to fat, and 8% were hypointense to fat on T2-weighted images (Chan and Kressel, 1991). A seminal vesicle cyst may have variable signal intensities on T1-weighted images but typically

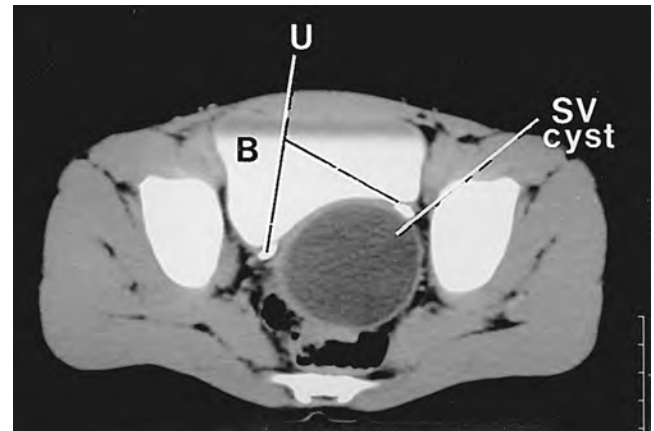


Figure 41-20. Computed tomography scan of seminal vesicle (SV) cyst. B, bladder; U, ureters.

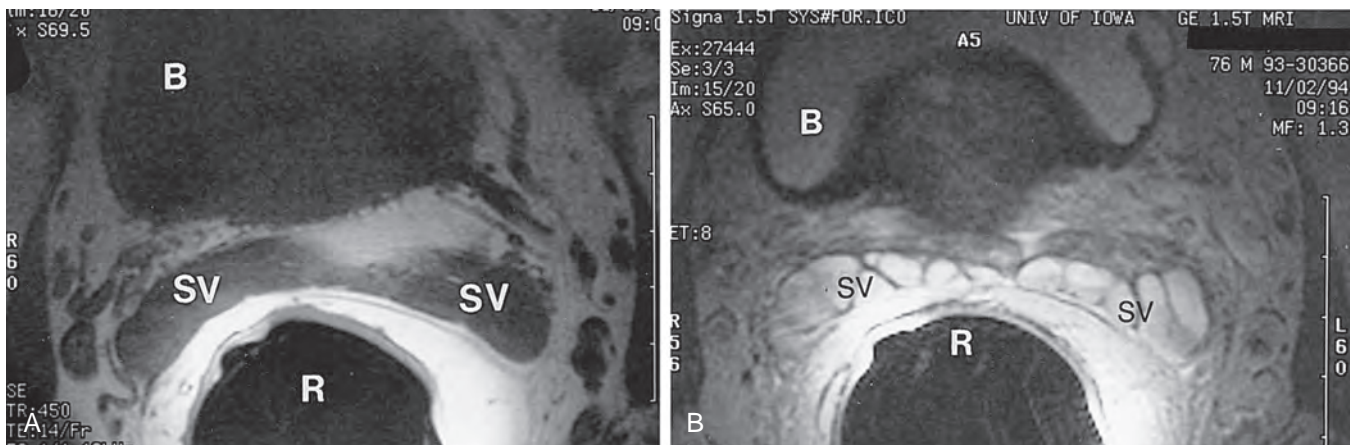


Figure 41-21. Transaxial magnetic resonance imaging of normal seminal vesicles (SV) with endorectal coli. A, T1-weighted image. B, T2-weighted image. B, bladder; R, rectum.

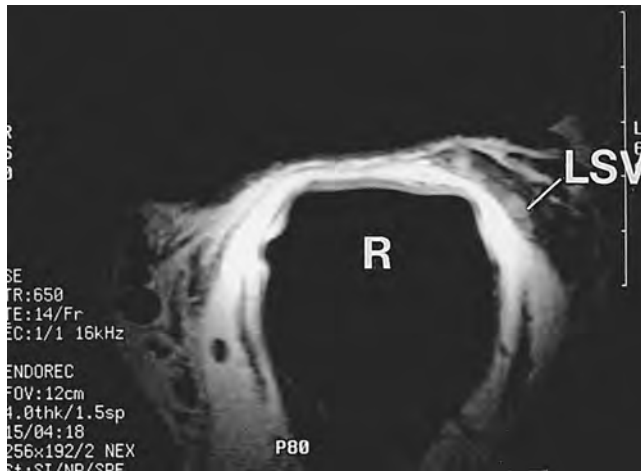


Figure 41-22. Transaxial T1-weighted endorectal magnetic resonance image of absent right seminal vesicle. LSV, left seminal vesicle; R, rectum.

demonstrates fluid signal intensities on T2-weighted images and does not enhance with administration of intravenous gadolinium. Increased T1-weighted intensity represents increased proteinaceous concentration within the cyst or hemorrhage (Arora et al, 2007). Hemorrhagic seminal vesicle cysts have high signal intensity on T1-weighted and T2-weighted images (Sue et al, 1989). A benign primary mass of the seminal vesicle appears as a sharply margined mass arising from the seminal vesicle. The most common form of malignancy affecting the seminal vesicle is invasion of prostate cancer directly into the seminal vesicle. This invasion can make the seminal vesicle appear large but does not always do so, and the seminal vesicle has low signal intensity on T2-weighted images (Secaf et al, 1991). If there is a palpable seminal vesicle abnormality, TRUS should be performed, and biopsy should be performed if there is suspicion for malignancy. MRI of the prostate and seminal vesicles may provide significantly greater detail in determination of the difference between a primary seminal vesicle mass and local extension from a prostate, bladder, or rectal malignancy.

Surgical Approaches to the Seminal Vesicles

The surgical approach to the seminal vesicles depends mainly on the expertise and comfort of the surgeon, although the characteristics of the lesion may have an impact on the decision regarding the approach. The robotic-assisted laparoscopic approach is increasingly being used for the rare seminal vesicle lesion requiring excision.

Preoperative preparation for seminal vesicle surgery should include a bowel preparation the evening before surgery, in case of the uncommon occurrence of a bowel injury; GoLYTELY is recommended. A prophylactic systemic antibiotic is administered preoperatively, and two doses are given postoperatively. The use of intermittent compression stockings to prevent deep vein thrombosis during surgery is recommended.

Anterior Surgical Approaches to the Seminal Vesicles

The anterior surgical approach to the seminal vesicles has been well established and is a good open approach for patients with large benign masses or cysts and for patients with an ectopic ureter draining into a seminal vesicle cyst, so the kidney, ureter, and seminal vesicle all can be approached concomitantly. The transvesical approach has been well described (Walker and Bowles, 1968; Politano et al, 1975). A lower midline infraumbilical incision is made sharply, and the rectus muscles are divided in the midline. The space of Retzius is developed. The anterior bladder is exposed,

and a self-retaining retractor is placed. A longitudinal incision about 7 to 10 cm long is made in the anterior bladder wall, taking care to stay at least 3 to 4 cm proximal to the bladder neck. Moist sponges are placed in the bladder dome, and a bladder blade for the retractor is used to offer exposure gently. The ureteral orifices should be identified, and 8-Fr feeding tubes can be passed gently up the ureters to help with identification of the intramural ureters. A 5-cm longitudinal incision is made in the midline of the trigone with electrocautery on cutting current. When the incision goes through the posterior bladder muscle, the ampullae of the vas deferens should be visible just below the bladder neck. The seminal vesicles should be identified just lateral to the ampullae of the vas deferens on the prostatic base. The seminal vesicle is resected and removed. Care must be taken not to dissect too deep through Denonvilliers fascia posteriorly so as not to endanger the rectum. The posterior bladder wall is closed in two layers with 2-0 absorbable suture in the muscle and 4-0 absorbable suture in the mucosa. After closure of the bladder wall, a suction drain is placed in the perivesical space, not overlying the suture line, and is brought out through a separate stab incision (Fig. 41-23). This approach has a lower rectal injury rate, although it places the ureters at a higher risk for injury and is more prone to blood loss.

The perivesical approach is useful in pediatric patients with a large seminal vesicle cyst so that nephroureterectomy can be performed along with seminal vesiculectomy. A midline or Pfannenstiel incision offers adequate exposure for this approach. Finger dissection is used to dissect the bladder from the lateral pelvic sidewall on the side with the cyst. The seminal vesicle cyst should be readily identifiable, the seminal vesicle should be dissected free in its entirety, and a 1-0 chromic suture can be placed through the cyst as a traction suture to assist with dissection. The ureter must be identified crossing the vas deferens to prevent ureteral injury. The superior, and possibly the inferior, vesicle arteries may be sacrificed to offer exposure to the base of the seminal vesicle. The cyst should be dissected away from the bladder, and any seminal vesicle vessels can be clipped and divided. When the base of the seminal vesicle is accessed at the prostate–seminal vesicle junction, it can be ligated with 2-0 absorbable suture. Dissection of the proximal portion of the seminal vesicle must be done carefully by hugging the cyst so as not to injure the neurovascular bundle, which is directly lateral to the seminal vesicle. A clip is placed just distal to the previously placed suture, and the seminal vesicle is resected. A suction drain is placed adjacent to the seminal vesicle bed and is brought out through a separate stab incision. The drain and urethral catheter may be removed in 24 hours as long as there is not excessive drainage through the drain.

A third anterior approach to the seminal vesicles that can be performed in an open or laparoscopic manner is the retrovesical approach; this is useful for bilateral seminal vesiculectomies for bilateral small cysts or benign masses (de Assis, 1952). A urethral catheter is placed, a midline incision is made or standard pelvic ports are placed, and the peritoneum is entered. A transverse incision is made in the peritoneal reflection over the rectum at the posterior bladder wall, taking great care not to enter the rectum. The posterior bladder is sharply dissected off the anterior rectal wall until the ampullae of the vas deferens and the tips of the seminal vesicles are visible. The seminal vesicles are dissected free to the base at the prostate–seminal vesicle junctions and are ligated and resected. A suction drain is placed at the posterior bladder and brought out through a separate stab incision. The incision is closed (Fig. 41-24).

Posterior Surgical Approach to the Seminal Vesicles

Although the transcoccygeal approach is the least familiar to most urologists, it may be useful for patients who have had previous suprapubic or perineal surgeries. The patient is positioned in a prone, jackknife position (Kreager and Jordan, 1965). An L-shaped hockey-stick incision is made from midway on the sacrum, 10 cm from the tip of the coccyx, and angled at the tip of the coccyx down

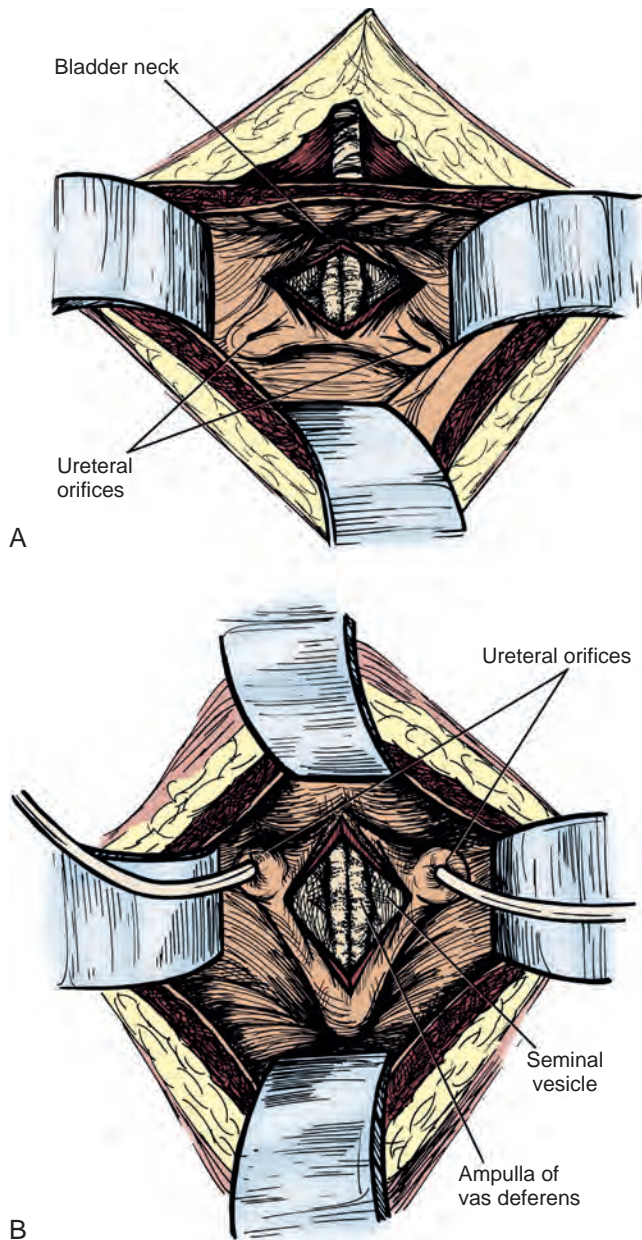


Figure 41-23. Transvesical approach to seminal vesiculectomy. A, Vertical incision between the ureteral orifices. B, Transverse incision 2 cm superior to the bladder neck below the ureteral orifices. (Redrawn from Hinman F Jr. *Atlas of urologic surgery*. Philadelphia: Saunders; 1989.)

the gluteal cleft stopping 3 cm from the anus. The lateral side of the coccyx is carefully divided free from the rectum and removed. The layers of the gluteus maximus are swept aside until the rectosigmoid is reached, and then it is carefully dissected from the underside of the sacrum. The lateral rectal wall is divided free medially from the levator ani muscle until the prostate is encountered on the side of the seminal vesicle pathology. Dissection is carried superior to the base of the prostate in the midline until the ampulla of the vas deferens is identified with the seminal vesicle just lateral to the ampulla. The seminal vesicle should be dissected and resected as previously described. A Penrose drain should be placed at the bed of the seminal vesicle and brought out through a separate stab incision from the closure. The drain can be removed in 2 to 3 days if there is no drainage (Fig. 41-25).

Laparoscopic and Robotic-Assisted Surgical Approach to the Seminal Vesicles

Laparoscopic surgery on the seminal vesicles is most commonly performed concomitantly with prostate surgery. The technique for the laparoscopic approach to the seminal vesicles was first described in 1993 (Kavoussi et al, 1993). Laparoscopy also has been applied to seminal vesiculectomy without prostatectomy and has been reported in a case of amyloidosis of the seminal vesicle (Vandwalle et al, 2007). Robotic-assisted laparoscopy also has been used to excise seminal vesicle cysts (Moore et al, 2007; Selli et al, 2008). Patients are positioned in the supine position with careful padding of all pressure points, and the arms are tucked and padded. A split-leg table is necessary for the robotic-assisted technique. Wide cloth tape is applied across the chest and hips to secure the patient to the table, and the table is placed in steep Trendelenburg position. Before gaining access, a urethral catheter and an orogastric tube should be placed to decompress the bladder and stomach for subsequent trocar placement. To gain access, a Veress needle is placed periumbilically, and a pneumoperitoneum is achieved, not exceeding pressures of 15 mm Hg. After an adequate pneumoperitoneum is achieved, the laparoscopic ports can be placed, placing the first one with an optical trocar for the camera port and the following ones under direct laparoscopic visualization. The ports can be placed in either a horseshoe or a diamond arrangement for pure laparoscopy and can be placed in the same position as would be used for prostatectomy for robotic assistance (Fig. 41-26) (Menon et al, 2003; Lee et al, 2004). The peritoneum is incised between the two obliterated umbilical ligaments just anterior to the rectum in the pouch of Douglas. The seminal vesicles can be visualized and should be dissected carefully to avoid injury to the neurovascular bundles or the surrounding viscera. Monopolar energy should not be used to minimize injury to surrounding structures, and much of this dissection can safely be performed sharply. The seminal vesicle arterial pedicle can be managed with a clip or with bipolar cautery. The seminal vesicle should be dissected toward its junction with the ampulla of the vas deferens, and both can be clipped together at the base. The specimen can be placed in an extraction bag and can be removed through one of the laparoscopic ports. The ports are closed under visualization.

The extraperitoneal laparoscopic approach to the seminal vesicles was first described in 1997 and was performed concomitantly with radical prostatectomy (Raboy et al, 1997). In the following years, this approach gained more popularity (Bollens et al, 2001; Stolzenburg et al, 2003). A 1.5-cm periumbilical incision is made, and the preperitoneal space is entered. A balloon trocar is introduced into the preperitoneal space, and insufflation is performed under direct vision. The details of the technique are described further in Chapter 115.

Surgical Treatment of Seminal Vesicle Cysts

Seminal vesicle cysts are thought to be secondary to ejaculatory duct obstruction and can be congenital or acquired (Heaney et al, 1987; King et al, 1991; Conn et al, 1992). Seminal vesicle cysts are associated with ipsilateral renal agenesis or dysplasia in two thirds of patients; the cysts are secondary to maldevelopment of the distal mesonephric duct and are an error in ureteral budding (Beeby, 1974). Seminal vesicle cysts also have been associated with polycystic kidney disease. In one report, seminal vesicle cysts were identified in 60% of patients with polycystic kidney disease, and some authors recommend that all patients with seminal vesicle cysts undergo renal imaging (Alpern et al, 1991; Hihara et al, 1993; Danaci et al, 1998). Seminal vesicle cysts should be treated only if they are symptomatic or result in ejaculatory duct obstruction and affect fertility (Surya et al, 1988).

Seminal vesicle cysts can be drained by many techniques. TRUS-guided aspiration or transperineal aspiration can be performed on small seminal vesicle cysts that are symptomatic or obstructing the ejaculatory ducts. If the cyst reaccumulates fluid, resulting in recurrent symptoms or obstruction, it may be aspirated again

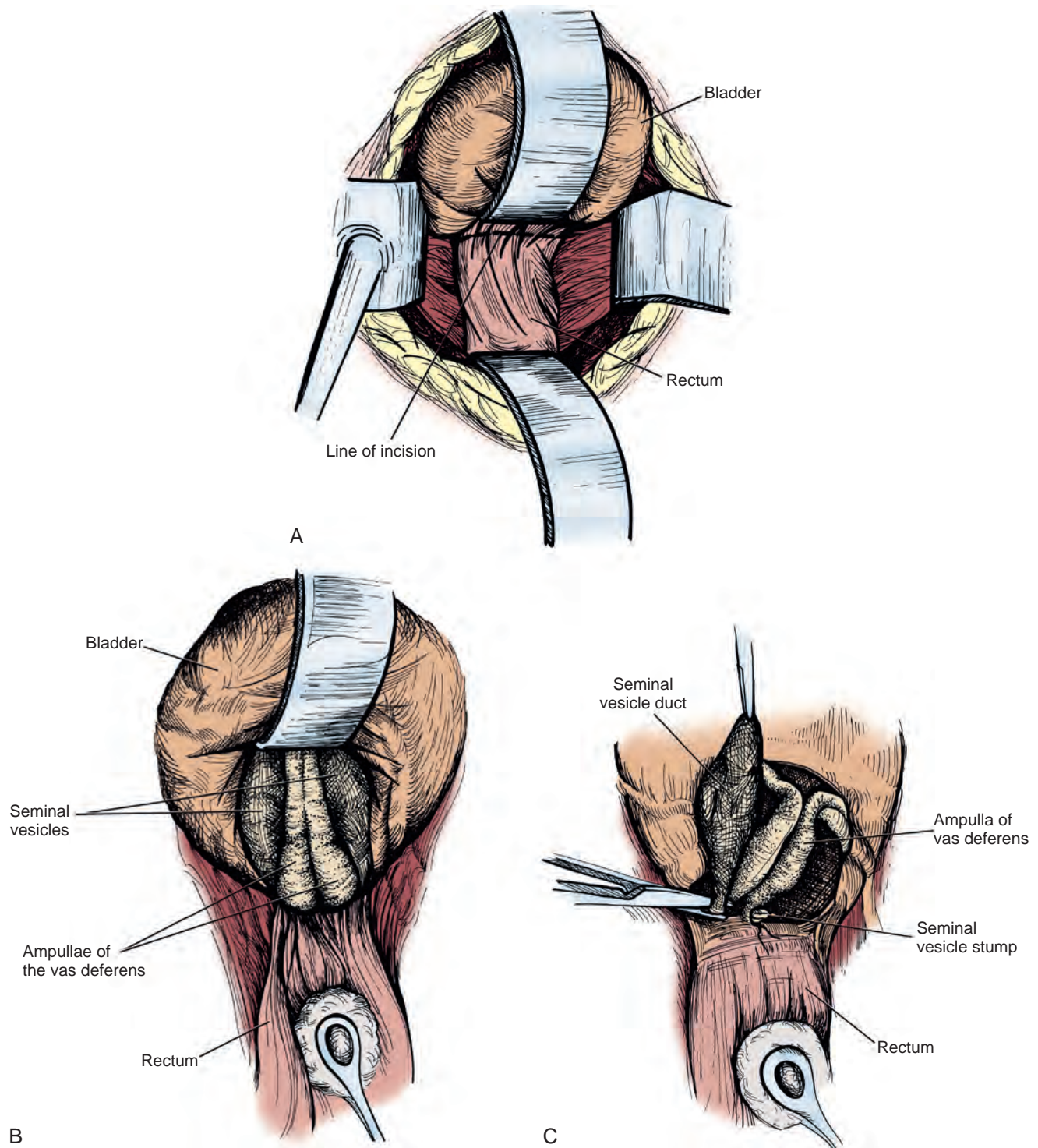


Figure 41-24. Retrovesical approach to seminal vesiculectomy. A, Incision line between base of bladder and peritoneal reflection over the rectum. B, Caudal dissection reveals the ampullae of the vas deferens on the midline and seminal vesicles immediately lateral to them. C, The duct of the seminal vesicle is ligated and transected. (Redrawn from Hinman F Jr. *Atlas of urologic surgery*. Philadelphia: Saunders; 1989.)

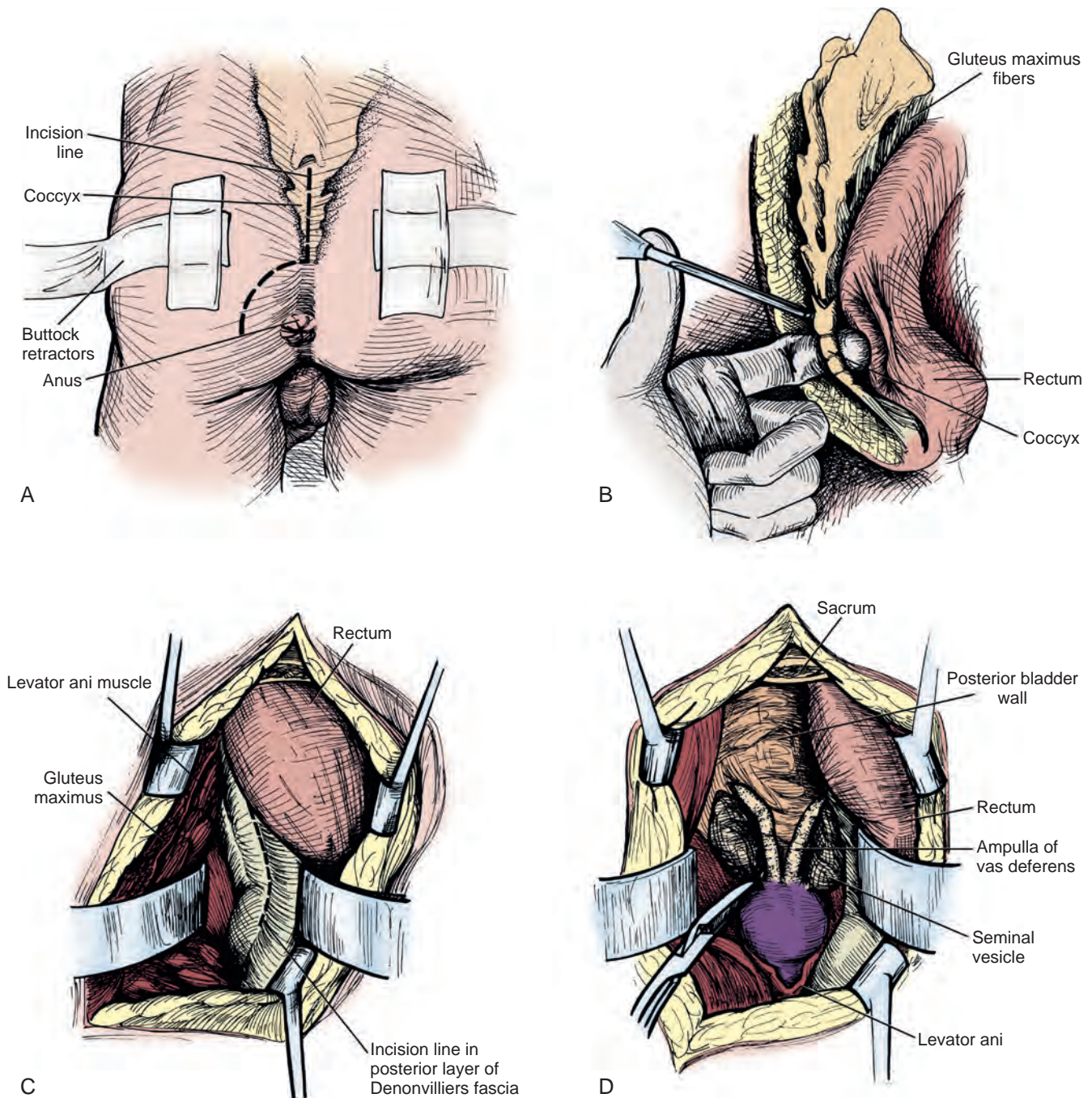


Figure 41-25. Transcoccygeal seminal vesiculectomy. **A**, Incision line over the lower sacrum on coccyx surrounding the anus. **B**, Dissection of the coccyx. **C**, Incision of Denonvilliers fascia after the rectum has been displaced. **D**, Exposure of the prostate and seminal vesicles. (Redrawn from Hinman F Jr. *Atlas of urologic surgery*. Philadelphia: Saunders; 1989.)

with the injection of a sclerosing agent such as tetracycline. A small abscess in the seminal vesicle can be managed similarly with drainage (Frye and Loughlin, 1988; Shabsigh et al, 1989; Gutierrez et al, 1994). If the seminal vesicle cyst is proximal, adjacent to the prostate, transurethral resection can be performed to unroof the cyst at the 5 o'clock and 7 o'clock positions just distal to the bladder neck (Frye and Loughlin, 1988; de Lichtenberg and Hvidt, 1989). The same outcome has been reported by incising the seminal vesicle cyst to drain it cystoscopically with the use of a Collings knife (Gonzalez and Dalton, 1998). Seminal vesicle abscesses can be managed in a similar fashion. Some groups reported using semirigid ureteroscopes to treat seminal vesicle cysts and abscesses (Razvi and Denstedt, 1995; Shimada and Yoshida, 1996; Okubo et al, 1998). If the

above-described techniques for drainage of seminal vesicle cysts are unsuccessful, open or laparoscopic excision can be performed (Moudouni et al, 2006). Seminal vesiculectomy along with nephroureterectomy should be performed in cases with an ectopic ureter. If these techniques for seminal vesicle abscess fail, open drainage is required (Kore et al, 1994).

Surgical Treatment of Tumors of the Seminal Vesicles

Benign tumors of the seminal vesicle that occur more commonly than malignant tumors include fibromas, leiomyomas, cystadenomas, schwannomas, and papillary adenomas (Mostofi and Price, 1973; Lundhus et al, 1984; Narayana, 1985; Mazur et al,

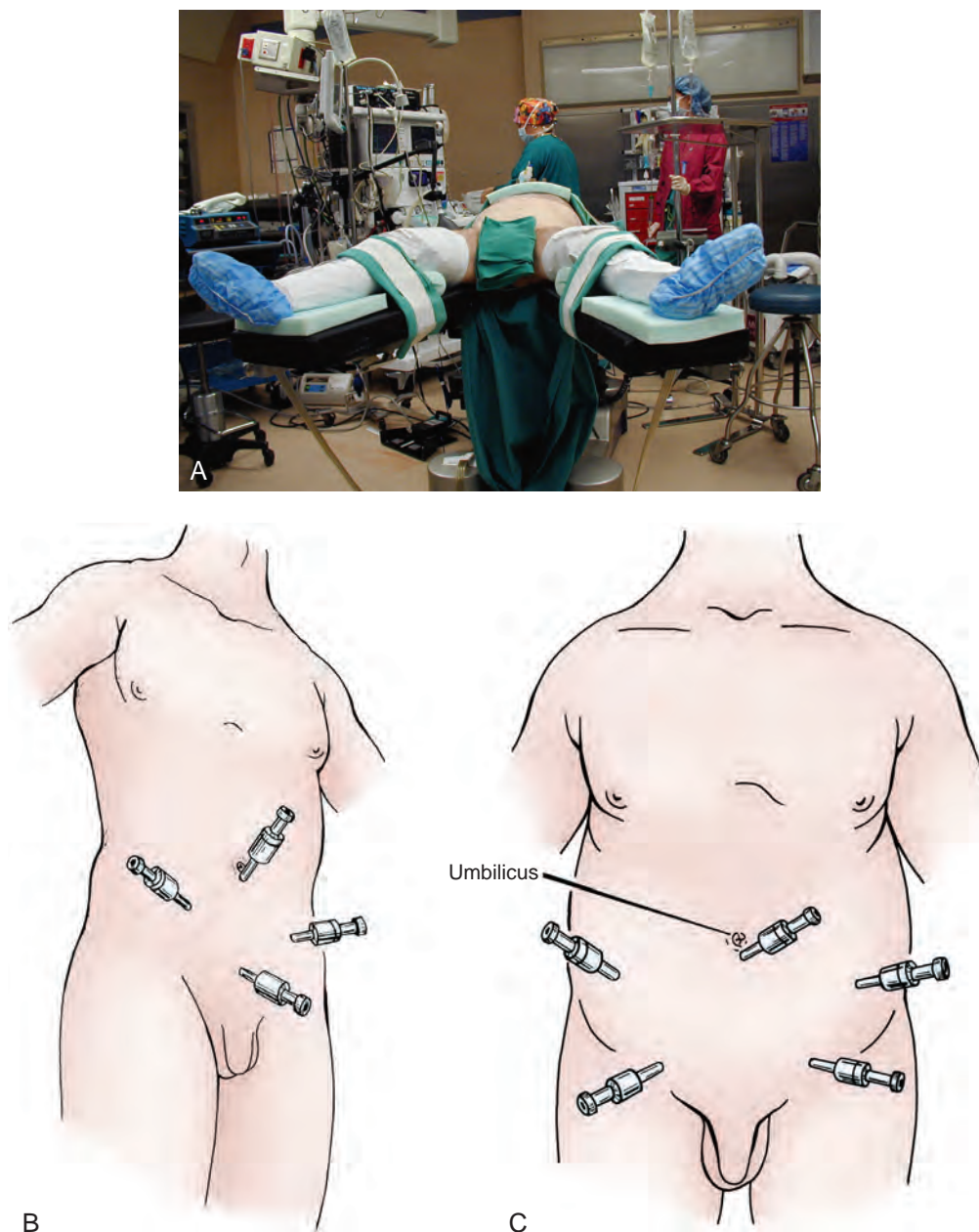


Figure 41-26. A, Positioning of the patient for laparoscopic seminal vesicle dissection. B, Diamond configuration of laparoscopic ports. C, Inverted U-shaped configuration of laparoscopic ports in obese patients. (From Winfield HN. Laparoscopic pelvic lymph node dissection for urological pelvic malignancies. *Atlas Urol Clin North Am* 1993;1:33–47.)

1987; Bullock, 1988; Gentile et al, 1994; Latchamsetty et al, 2002; Lee et al, 2006). Primary papillary adenomas and cystadenomas of the seminal vesicle typically occur in middle-aged men and are almost never bilateral, and they appear as simple cysts on imaging; the diagnosis is typically made on final pathology after excision (Mazur et al, 1987). Amyloid localized to the seminal vesicles also has been reported (Jun et al, 2003). Of men older than age 76 years, 20% have subepithelial deposits of amyloid in the seminal vesicles, and the reported incidence in male autopsies is 4% to 17% (Pitkanen et al, 1983; Ramchandani et al, 1993). Patients should be treated only if they are symptomatic and the diagnosis of amyloid of the seminal vesicle is made. Hydatid cysts of the seminal vesicle also have been reported (Kuyumcuoglu et al, 1991; Papathanasiou et al, 2006).

Seminal vesicle malignancies are extremely rare and are difficult to diagnose because patients are typically asymptomatic

until late in the course of the disease process. Primary malignancies of the seminal vesicles are extremely rare, and serum prostate-specific antigen and tissue biopsy can help differentiate primary malignancies from extension or metastasis of lymphoma, prostate, bladder, or rectal cancer. The low proliferative activity of the seminal vesicles is thought to account for the low incidence of primary malignancies of the seminal vesicle (Meyer et al, 1982). Primary adenocarcinoma of the seminal vesicle occurs in patients older than 50 years. Serum prostate-specific antigen is normal, and serum carcinoembryonic antigen is elevated (Mostofi and Price, 1973; Benson et al, 1984; Tanaka et al, 1987; Chinoy and Kulkarni, 1993; Thiel and Effert, 2002). Primary sarcoma of the seminal vesicle is an extremely rare malignancy, which is usually discovered late in the disease process and is diagnosed by biopsy (Benson et al, 1984; Chiou et al, 1985; Schned et al, 1986; Tanaka et al, 1987; Davis et al, 1988; Kawahara et al, 1988). All sarcoma

types of the seminal vesicle, including leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, and müllerian adenosarcoma-like tumor, behave very aggressively, and radical extirpation has varying outcomes (Lamont et al, 1991; Laurila et al, 1992; Amirkhan et al, 1994; Berger et al, 2002). Cystosarcoma phylloides and seminoma also have been reported as primary malignancies of the seminal vesicles (Adachi et al, 1991; Fain et al, 1993). Primary squamous cell carcinoma of the seminal vesicle has been reported and treated with surgical extirpation followed by adjuvant radiation therapy with success with short-term follow-up (Tabata et al, 2002).

Solid seminal vesicle masses that are benign on biopsy and show no evidence of local spread should be treated with seminal vesiculectomy only if they are symptomatic, which is a very rare occurrence. Solid masses of the seminal vesicles that are proven to be malignant by biopsy or with a high suspicion for malignancy should be surgically treated, although the optimal treatment is still debated because there have been so few primary seminal vesicle malignancies treated at any institution. Large primary malignancies of the seminal vesicles have been treated with radical pelvic surgery: cystoprostatectomy with pelvic lymphadenectomy or pelvic exenteration. Adjuvant therapy has not proven to be effective, although the only survivors in the literature underwent radical surgery followed by pelvic radiation and/or androgen ablation.

Complications of Seminal Vesicle Surgery

Complications of seminal vesicle surgery are minimized by the surgeon selecting the approach that he or she is most comfortable and facile performing. The surgeon must be aware of the following complications that are specific to seminal vesiculectomy. Rectal or bladder injury may occur with any surgery on the seminal vesicle. If a preoperative bowel preparation was administered, and there is no gross fecal contamination, a two-layer closure of the rectum may be performed closing the mucosal layer with a running 3-0 absorbable suture and the submucosal layer with interrupted 4-0 silk sutures. The anus also should be dilated before the end of the case. A temporary colostomy should be considered with a large rectal injury or gross fecal contamination. The bladder should be closed in two layers, leaving a urethral catheter in place for 7 to 10 days postoperatively.

Complications of the laparoscopic approach include general laparoscopic complications, such as trocar injury to the bowel or great vessels, extraperitoneal insufflation, abdominal wall bleeding, and gas embolism. Bladder and rectal injuries may be repaired laparoscopically as long as there is not gross fecal contamination with rectal injuries. The distal ureter is close to the tip of the seminal vesicle, and if the ureter is injured, it may be repaired laparoscopically, although a ureteral replant may be necessary and performed open or laparoscopically, depending on the experience of the surgeon. It is recommended that a ureteral stent and a pelvic drain be left in such cases. The neurovascular bundle runs just lateral to the tips of the seminal vesicles; injury to the neurovascular bundle can result in erectile dysfunction, regardless of the surgical approach. Potential complications of endoscopic management of the seminal vesicles include postvoid dribbling secondary to urinary reflux and infection (Goluboff et al, 1995).

MANAGEMENT OF NONPALPABLE TESTICULAR LESIONS

Data in the literature regarding the management of incidentally found testicular lesions are limited. A testicular lesion is defined as incidental when it is asymptomatic and nonpalpable and in the presence of negative tumor markers (Carmignani et al, 2003). With the increased use and availability of ultrasonography, there has been an increase in detection of these lesions; however, the overall incidence of asymptomatic, incidental testicular lesions found with scrotal ultrasonography is low. In a large series of 3000 men who underwent scrotal ultrasonography for indications of scrotal pain,

KEY POINTS: SURGERY OF THE SEMINAL VESICLES

- Seminal vesicle secretions contribute 50% to 80% of the volume of the ejaculate.
- Unilateral seminal vesicle agenesis may be associated with ipsilateral renal anomalies and unilateral absence of the vas deferens.
- Normal seminal vesicles are not palpable on digital rectal examination.
- If there is a palpable seminal vesicle abnormality, TRUS and MRI should be performed, and biopsy should be performed if there is suspicion for malignancy.
- The surgical approach to the seminal vesicles depends mainly on the expertise and comfort of the surgeon, although the characteristics of the lesion may affect the decision regarding the approach.
- Benign and malignant tumors of the seminal vesicles are very rare.

flank pain, neck mass, and retroperitoneal mass, 15 (0.5%) were discovered to have incidental testicular lesions (Comiter et al, 1995). Another large series of 1300 scrotal ultrasound scans found 27 (2%) incidental testicular lesions (Carmignani et al, 2003).

Previous studies showed an increased incidence of testicular malignancies in infertile men (Jacobsen et al, 2000). Other risk factors for the presence of malignancy include palpable testicular lesions, history of cryptorchidism, testicular atrophy, and contralateral germ cell tumor. Histologically benign lesions are more common than malignant lesions for incidentally discovered nonpalpable testicular lesions (Sheynkin et al, 2004).

Some advocate for early surgical intervention for nonpalpable testicular masses (Müller et al, 2006) with 20% of these lesions being malignant. The testicle is delivered through an inguinal incision, and the lesion is localized using intraoperative ultrasonography (Horstman et al, 1994). Hopps and Goldstein expanded on this technique by using ultrasound-guided needle localization and microsurgical exploration to assist in tumor identification (Hopps and Goldstein, 2002).

Other authors support a more conservative approach. Eifler and colleagues (2008) reported that only 6% of incidentally found testicular lesions less than 1 cm were malignant based on tissue diagnosis. These authors stated that intratesticular, hypoechoic lesions less than 5 mm in patients with negative markers are likely benign and can be followed with serial imaging. Connolly and associates (2006) identified a highly select group of patients with incidental testicular lesions less than 1 cm to follow with serial ultrasound scans. In eight patients who met criteria, only one lesion (13%) progressed on serial imaging and was a seminoma. These authors concluded that although most patients with small lesions require surgical exploration, carefully selected patients who are highly compliant can be managed safely with serial imaging. The pathologic findings from these studies are summarized in Table 41-2.

Although these lesions are rare, they present a management dilemma for urologists. In this setting, the clinician must decide whether to pursue a more aggressive approach such as inguinal orchiectomy, inguinal exploration, and excision with frozen section or a more conservative, nonoperative approach with surveillance with serial ultrasound scans. A treatment algorithm for management of nonpalpable intratesticular lesions is shown in Fig. 41-27. Malignancy should be considered when any of the following are present: mass greater than 1 cm, severe oligospermia or azoospermia, atrophy, history of cryptorchidism, prior testicular malignancy, or elevated tumor markers. If the patient is at low risk for malignancy, it is reasonable to follow the patient with serial ultrasound scans. Patients must understand that changes in size or architecture of the lesion require surgical exploration.

TABLE 41-2 Summary of Pathologic Findings from Nonpalpable Intratesticular Lesions

INSTITUTION AND REFERENCE	NO. BENIGN	NO. MALIGNANT	NO. WITHOUT TISSUE DIAGNOSIS	TOTAL NUMBER
Mt. Sinai Hospital (Buckspan et al, 1989)	4	0	0	4
Walson Army Hospital (Corrie et al, 1991)	3	0	2	5
Naval Medical Center (Horstman et al, 1994)	7	2	0	9
Brigham and Women's Hospital (Comiter et al, 1995)	2	13	0	15
Weill-Cornell (Hopps and Goldstein, 2002)	2	2	0	4
University of Milan (Carmignani et al, 2003)	10	0	0	10
SUNY Stonybrook (Sheynkin et al, 2004)	6	2	1	9
Rabin Medical Center (Tal et al, 2004)	3	6	2	11
Southern Illinois (Powell and Tarter, 2006)	2	2	0	4
Weill-Cornell (Eifler et al, 2008)	19	1	0	20
Total No. (%)	58 (64)	28 (31)	5 (5)	91

From Mammen T, Costabile RA. Management of incidentally discovered non-palpable testicular lesions. AUA Update Series 2009;28:14–9.

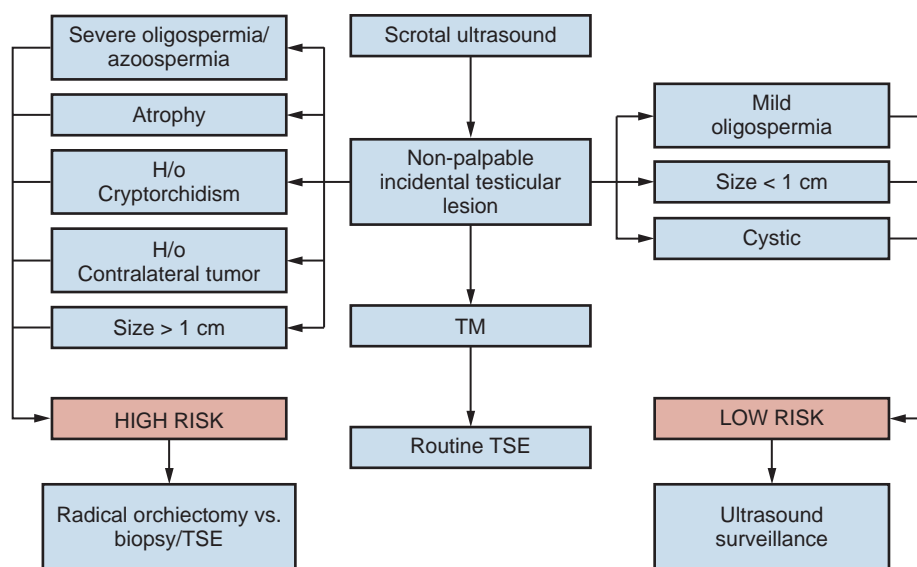


Figure 41-27. Treatment algorithm for nonpalpable testicular lesions. H/o, history of; TM, testicular microlithiasis; TSE, testis-sparing excision. (Modified from Mammen T, Costabile RA. Management of incidentally discovered non-palpable testicular lesions. AUA Update Series 2009;28:14–9.)

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The complete reference list is available online at www.expertconsult.com.

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42

Surgical, Radiologic, and Endoscopic Anatomy of the Kidney and Ureter

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Kidneys

Pelvicalyceal System

Anatomy of course does not change, but our understanding of anatomy and its clinical significance does change.

– Frank H. Netter, MD

Anatomy provides a roadmap for surgical procedures. This chapter presents the normal anatomy of the kidney and ureter. To make it more interesting for urologists, we provide clinical, radiologic, surgical, and endoscopic correlations. Of course, the human body never ceases to amaze explorers with its variations from the “normal.” With modern imaging technology, it has become possible to create three-dimensional (3D) virtual reality of each patient before surgical procedures. However, the surgeon is still advised to be cautious of the minute anomalies not appreciated on perioperative imaging studies.

KIDNEYS

Surface Anatomy and Relationships

The kidneys are paired ovoid, reddish-brown retroperitoneal organs situated in the posterior part of the abdomen on each side of the vertebral column. The kidneys lie on the psoas muscles; thus the **longitudinal axes** of the kidneys are oblique (arrows, Fig. 42-1 on the Expert Consult website), with the upper poles more medial and posterior than the inferior poles. Therefore, during percutaneous renal access, it should be noted that the lower pole of the kidney lies laterally and anteriorly relative to the upper pole. In addition, the medial aspect of each kidney is rotated anteriorly at an angle of approximately 30 degrees. The exact **position** of the kidney within the retroperitoneum varies during different phases of respiration, body position, and presence of anatomic anomalies. For example, the kidneys move inferiorly approximately 3 cm (one vertebral body) during inspiration and during changing body position from supine to the erect position. The position of the kidneys in the supine end-expiration is described here. Because of the inferior displacement of the right kidney by the liver, the right kidney sits 1 to 2 cm lower than the left kidney. Therefore the right kidney resides in the space between the top of the 1st lumbar vertebra to the bottom of the 3rd lumbar vertebra, whereas the left kidney occupies a space between the 12th thoracic vertebra and the 3rd lumbar vertebra.

Each kidney measures 10 to 12 cm in length, 5.0 to 7.5 cm in width, and 2.5 to 3.0 cm in thickness. Each adult male kidney

Ureters

weighs approximately 125 to 170 g; the kidney is 10 to 15 g smaller in females. The right kidney is slightly shorter and wider because of downward compression by the liver. The kidneys are relatively larger in children and have more prominent fetal lobulations, which generally disappear by the first year of life. In addition, the adult kidney's lateral contour might have a focal renal parenchymal bulge known as a **dromedary hump**, which is more common on the left side and has no pathologic significance. These dromedary humps are thought to be caused by the downward pressure from the liver or the spleen.

The **posterior relationships** of the kidneys are detailed in Figure 42-2 (on the Expert Consult website). Superiorly, the kidneys are related to the inferior edge of the diaphragm and the ribs. The right kidney is related to the 12th rib, and the left kidney is related to the 11th and 12th ribs. When the lower ribs are fractured during trauma, associated renal lacerations could occur. The upper poles of the kidneys come close to the diaphragm and underlying pleural cavity containing the lungs; thus any violations of the diaphragm during excision of large renal masses could lead to pleural tears and pneumothorax. Furthermore, **percutaneous access** to the upper pole of the kidneys above the 11th rib (10th intercostal space) is associated with increased risk for injuring pleura and even lungs. Therefore, when possible, subcostal (below the 12th rib) or 11th intercostal space (between the 11th and 12th ribs) access should be achieved (Fig. 42-3 on the Expert Consult website). More inferiorly, the kidneys are related to the psoas major muscle medially and both the quadratus lumborum and aponeurosis of the transversus abdominis muscles laterally. The subcostal nerve and vessels and the iliohypogastric and ilioinguinal nerves descend obliquely across the posterior surfaces of the kidneys (Fig. 42-4).

Because the kidneys are retroperitoneal organs, they are related **anteriorly** to other retroperitoneal and intraperitoneal organs (Fig. 42-5 on the Expert Consult website). The right kidney is related superiorly to the liver (both intraperitoneal and retroperitoneal bare portions) and superomedially to the adrenal gland. Inferiorly, the right kidney is related to the small intestine and hepatic flexure of the colon, and medially it is related to the second stage of the duodenum and head of the pancreas. The parietal peritoneum bridging the upper pole of the right kidney to the liver forms the **hepatorenal ligament**. Therefore excessive downward traction of the right kidney may cause capsular tear of the liver and may lead to excessive intraoperative bleeding. The left kidney is related to the stomach and spleen superiorly, adrenal gland superomedially, jejunum and splenic flexure of the colon inferiorly, and tail of the pancreas with splenic vessels medially. The parietal peritoneum bridging the upper pole of the left kidney to the spleen forms the

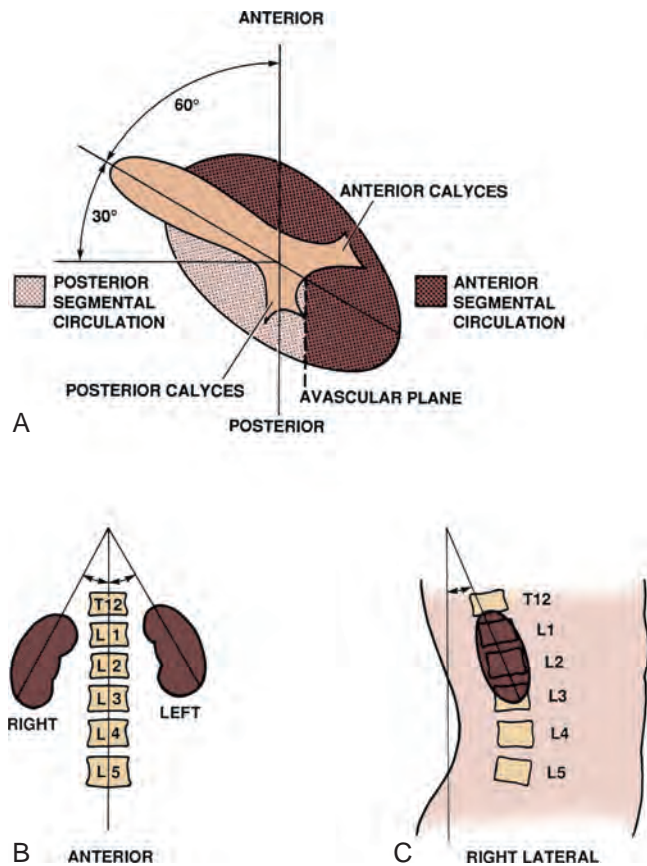


Figure 42-1. Normal rotational axes of the kidneys. **A**, Transverse view showing approximate 30-degree anterior rotation of the left kidney from the coronal plane, relative positions of the anterior and posterior rows of calyces, and location of the relatively avascular plane separating the anterior and posterior renal circulations. **B**, Coronal section demonstrating slight inward tilt of the upper poles of the kidneys. **C**, Sagittal view showing anterior displacement of the lower pole of the right kidney.

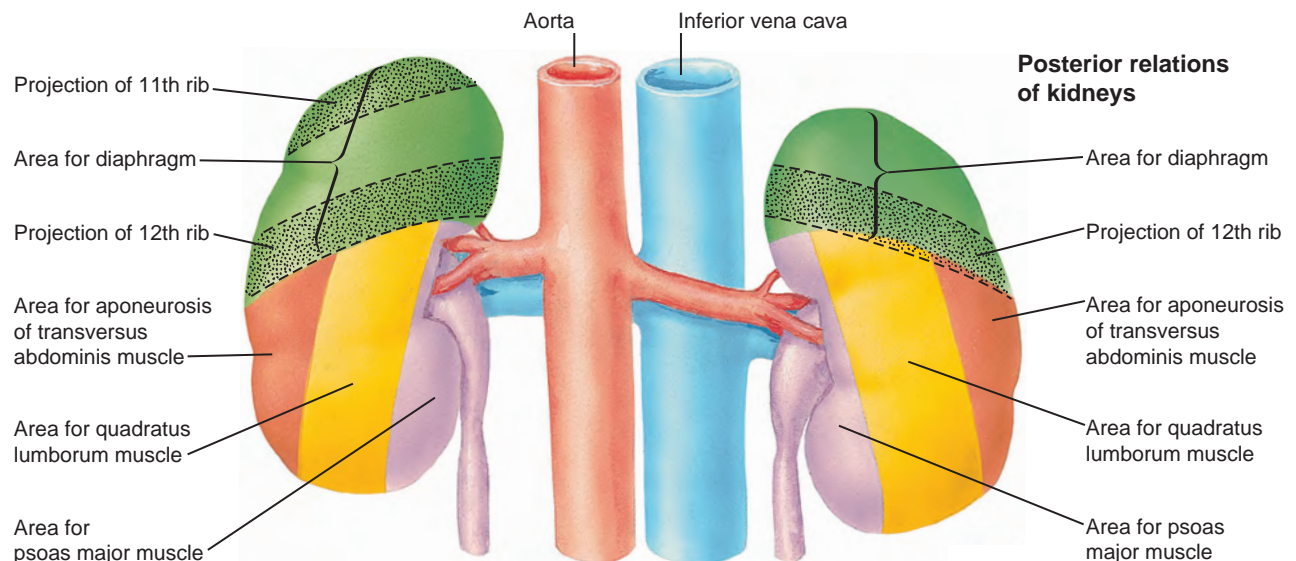


Figure 42-2. Posterior relationships of the kidneys. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

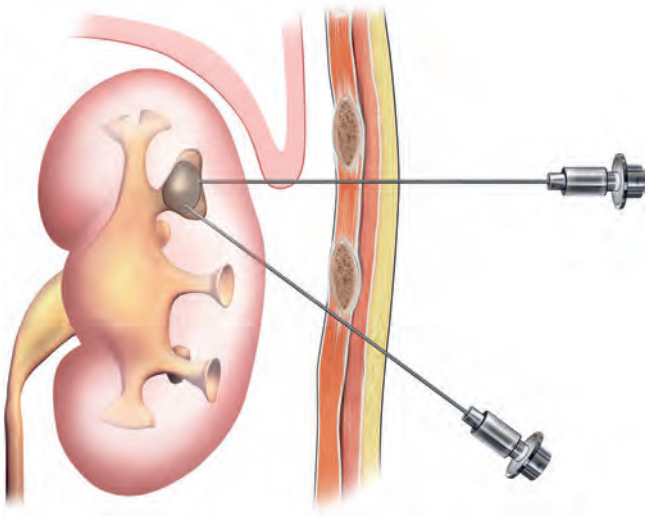


Figure 42-3. Subcostal and supracostal percutaneous access to an upper pole calyx. The supracostal approach provides more direct access and provides a better angle for endoscopy of the rest of the kidney. However, there is increased risk for pleural injury.

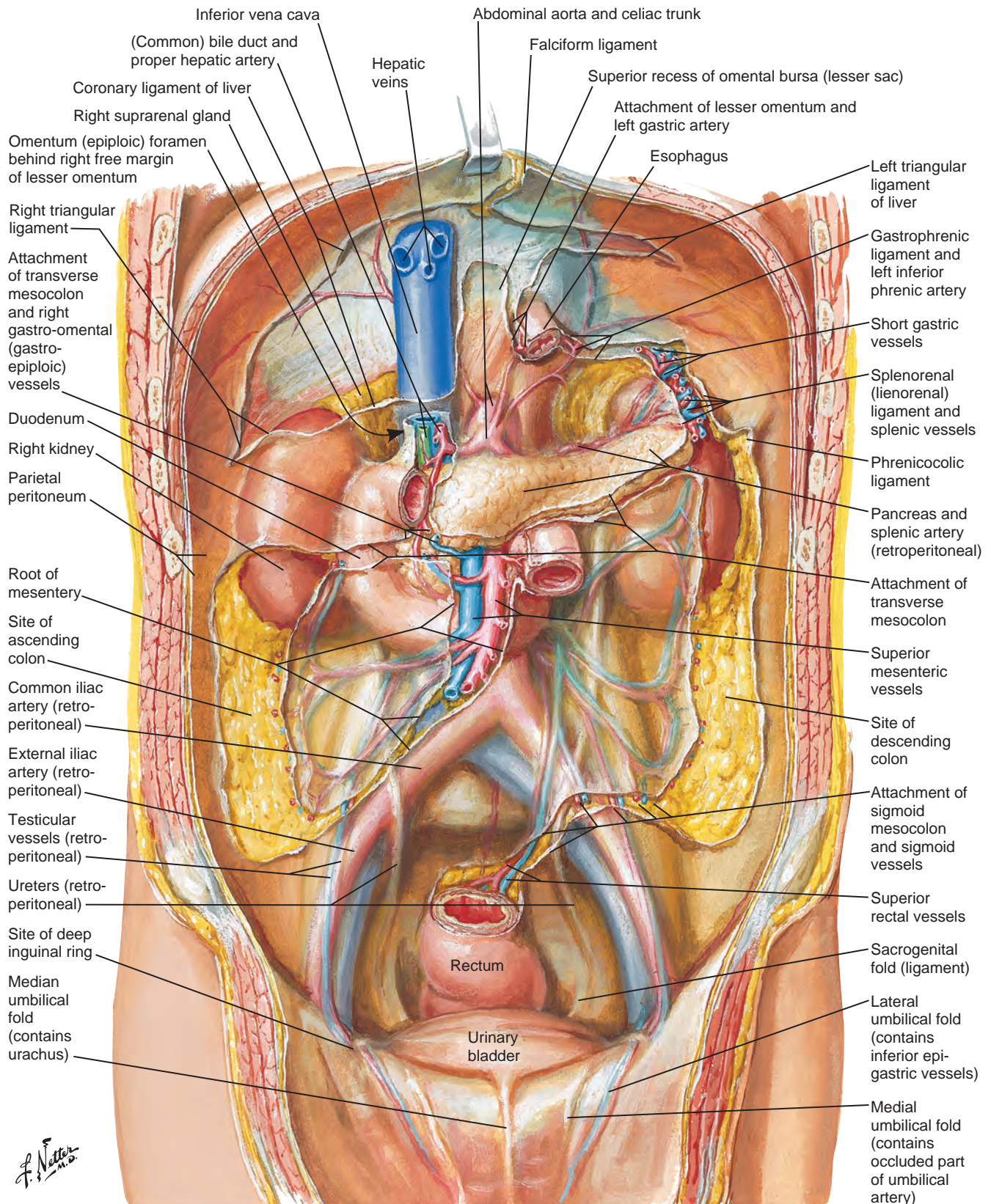


Figure 42-5. Anterior relationships of the kidneys and ureters. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

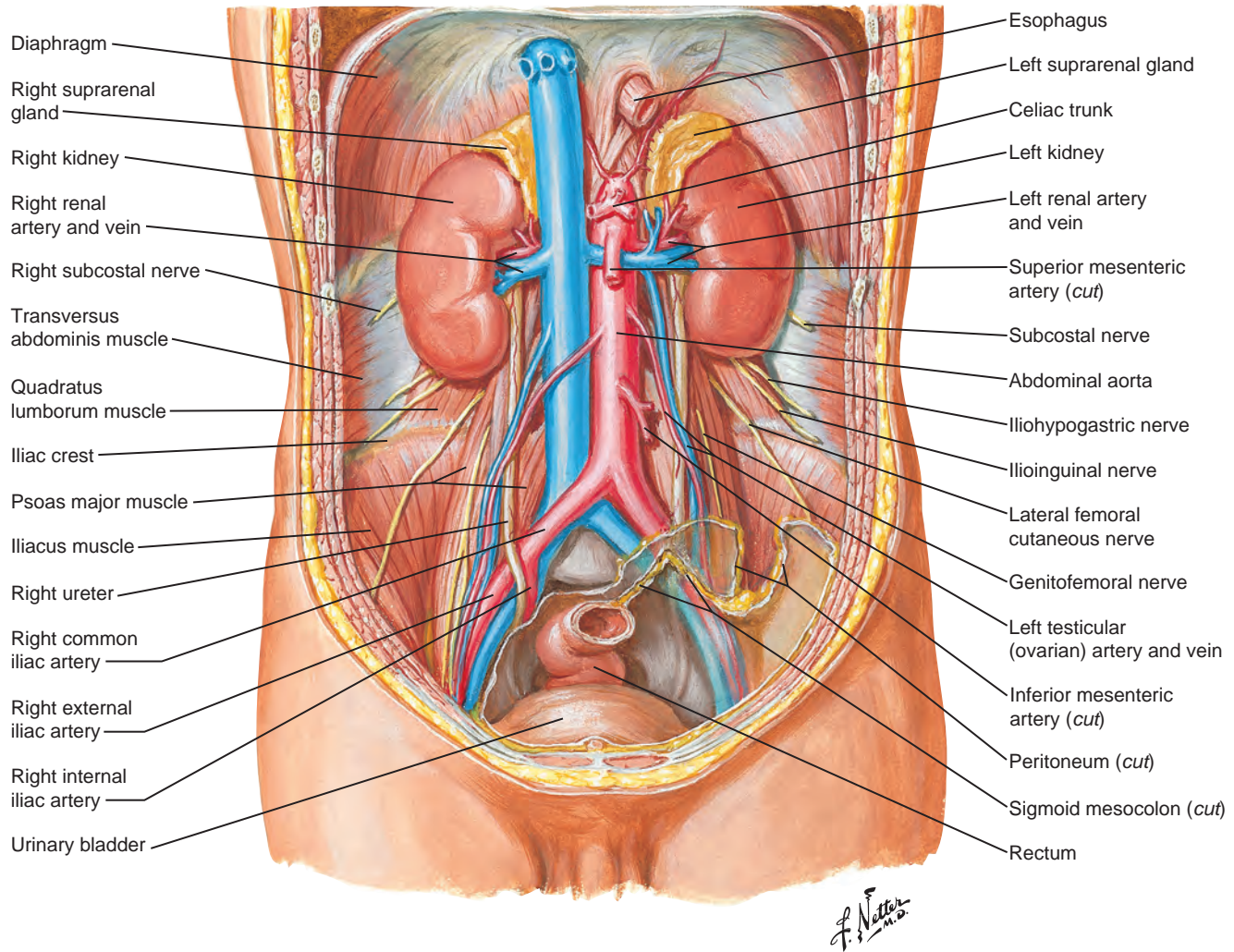


Figure 42-4. Posterior abdominal wall showing great vessels, kidneys, and adrenal glands. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

splenoarenal ligament. If excessive downward pressure is applied to the left kidney, splenic capsular tears may occur, leading to hemorrhage from the spleen.

The kidneys are surrounded by a smooth, tough fibrous capsule, which is easily removed under normal conditions. Each kidney and its vessels are surrounded by a **perinephric fat** that extends into its hollow vertical cleft, the **renal hilum**, which is the entrance to a space within the kidney called the **renal sinus**. The kidneys and adrenal glands, including the perirenal fat surrounding them, are enclosed by a condensed, membranous layer of **renal (Gerota) fascia**, which continues medially to fuse with the contralateral side (Fig. 42-6 on the Expert Consult website). This fascia extends inferomedially along the abdominal ureter as a **periureteral fascia**. The Gerota fascia encasing the kidneys, adrenal glands, and abdominal ureters is closed superiorly and laterally and serves as an anatomic barrier to the spread of malignancy and a means of containing perinephric fluid collections. Because it is open inferiorly, perinephric fluid collections can track inferiorly into the pelvis without violating the Gerota fascia.

The Gerota fascia is further surrounded by a layer of condensed fat called the **paranephric fat**, which is most obvious posteriorly and represents the extraperitoneal fat of the lumbar region. Superiorly, the Gerota fascia is continuous with the diaphragmatic fascia on the inferior surface of the diaphragm, and, inferiorly, the anterior and posterior layers of the Gerota fascia are loosely attached. The Gerota fascia is attached with the paranephric fat by collagen bundles. Therefore the kidneys are relatively kept

fixed in position by these collagen bundles, the Gerota fascia, and paranephric fat.

The relationships of the kidneys have important **surgical implications**. To access the kidneys, adrenals, or abdominal ureters, the Gerota fascia must be opened. To access the kidneys transperitoneally, the colon needs to be mobilized from the **white line of Toldt**, which is the lateral reflection of posterior parietal peritoneum over the ascending and descending colon. To access the right renal hilum, the second stage of the duodenum and head of pancreas need to be carefully mobilized using the Kocher maneuver. To access the left renal hilum, the tail of the pancreas together with the spleen and splenic vessels need to be mobilized medially.

Gross and Microscopic Anatomy

Two distinct regions can be identified on the cut surface of a bisected kidney: the cortex, which is a pale outer region, and the medulla, which is a darker inner region (Fig. 42-7 on the Expert Consult website). The renal medulla is divided into 8 to 18 striated, distinct, conically shaped areas that are frequently called renal pyramids. The apex of the pyramids forms the renal papilla, and each papilla is cupped by an individual minor calyx. The base of the pyramids is positioned at the corticomedullary boundary. The cortex and the medulla containing the renal pyramids could be differentiated on renal imaging studies (Fig. 42-8 on the Expert Consult website). Furthermore, these renal papillae could be inspected endoscopically (Fig. 42-9 on the Expert Consult website).

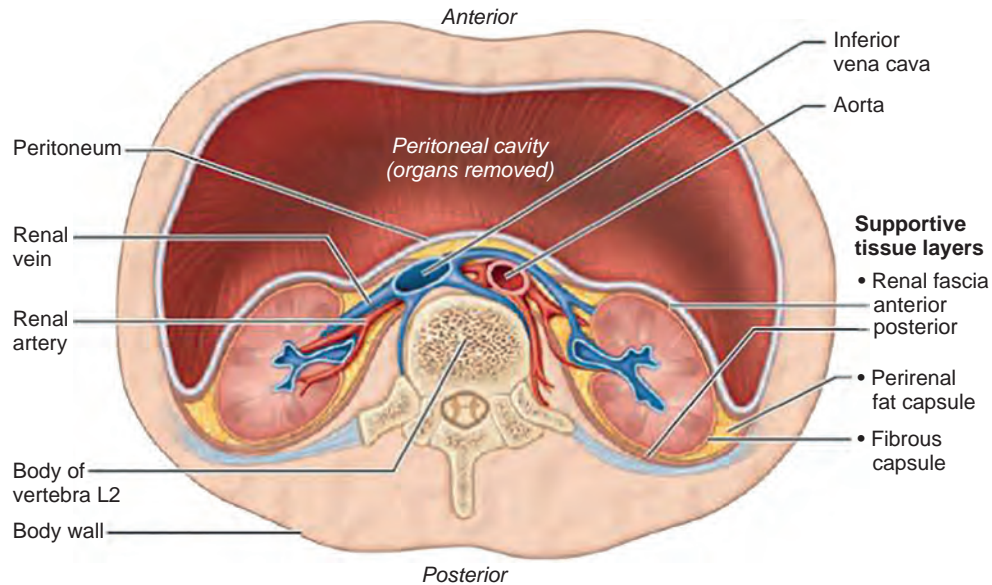


Figure 42-6. Schematic cross-sectional diagram demonstrating renal (Gerota) fascia. It shows the retroperitoneal position of the kidneys and their supportive tissues. (From Hutchinson M. *A brief atlas of the human body*. 2nd ed. Old Tappan [NJ]: Pearson Academic; 2006.)

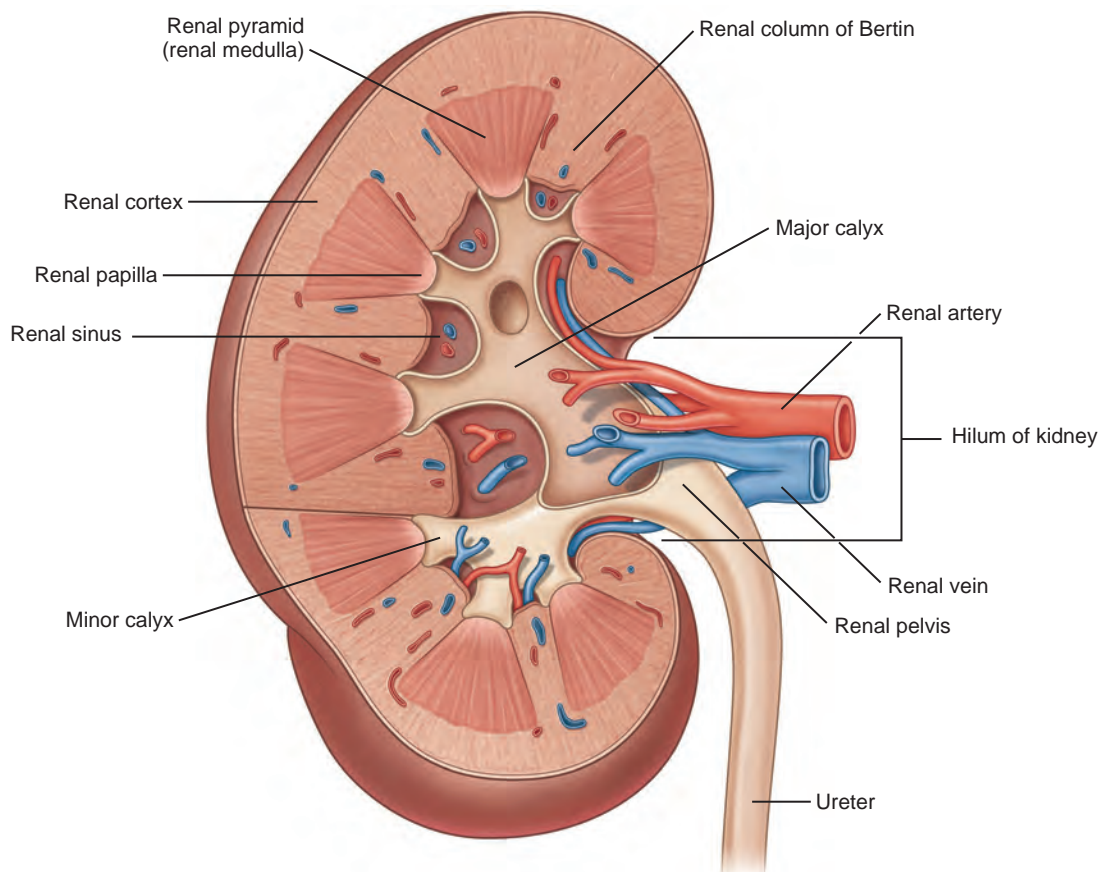


Figure 42-7. Internal structure of the right kidney. (From Drake RL, Vogl W, Mitchell AWM. *Gray's anatomy for students*. Philadelphia: Churchill Livingstone; 2005.)

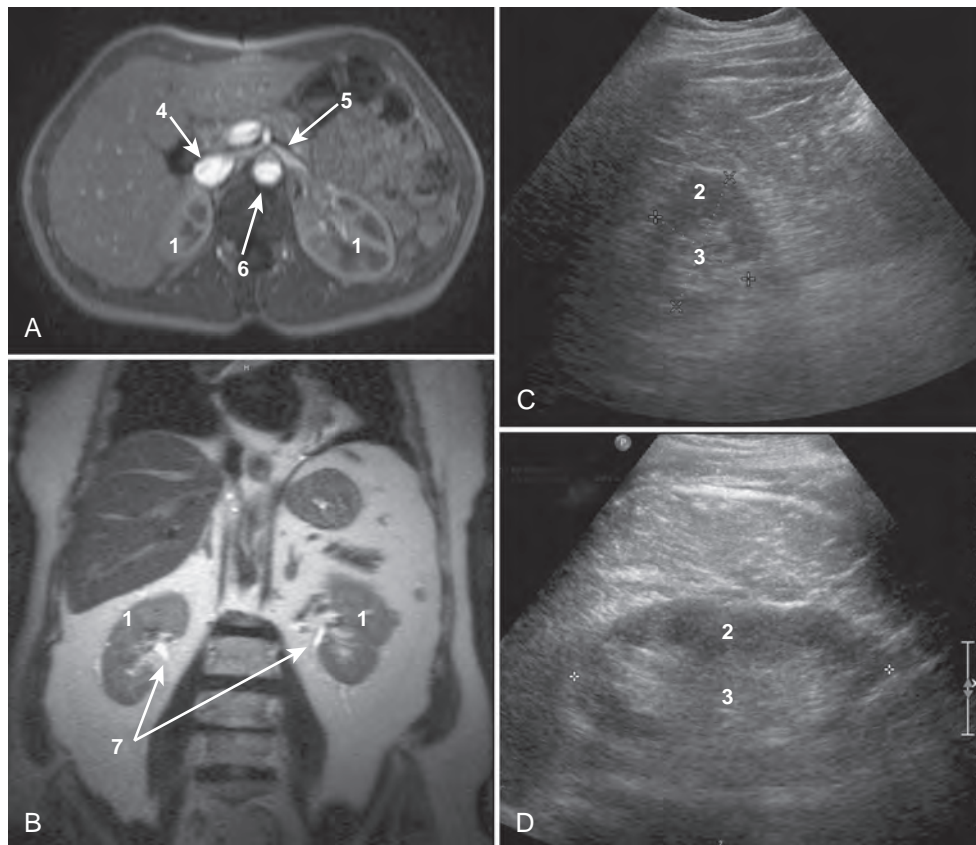


Figure 42-8. Cross-sectional imaging of the normal kidney. A, T1-weighted gadolinium-enhanced axial magnetic resonance imaging (MRI) of kidneys, including the inferior vena cava, aorta, left renal vein, and superior mesenteric artery. B, Coronal T2 MRI of the kidneys. C, Transverse ultrasound imaging of the kidney. D, Sagittal ultrasound imaging of the kidney. 1, kidney; 2, renal cortex; 3, renal medulla; 4, inferior vena cava; 5, left renal vein; 6, aorta; 7, renal collecting system.

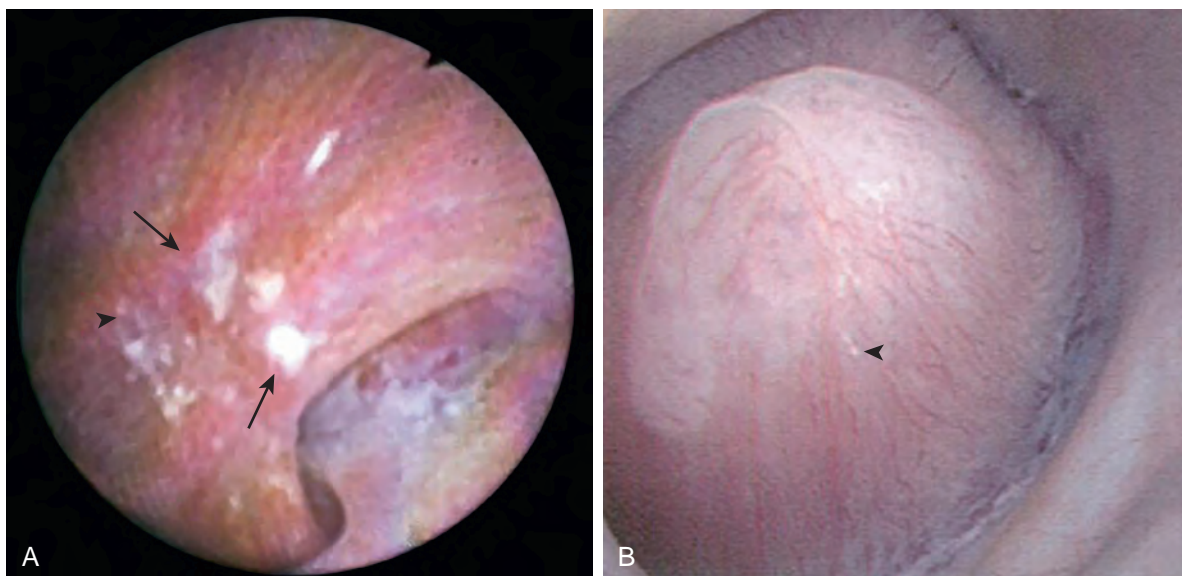


Figure 42-9. Renal papilla in a calcium oxalate stone-former (A) where several Randall plaques (arrows) appeared as irregular white areas beneath the urothelium; the plaque site lacking a urothelial layer (arrowhead) may be the site where the stone was attached to papilla. Renal papilla in a non-stone former (B) where no distinct sites of Randall plaques were noted on papilla but a nodular-appearing structure (arrowhead) was noted alongside the papilla. (From Matlaga BR, Coe FL, Evan AP, et al. The role of Randall's plaques in the pathogenesis of calcium stones. *J Urol* 2007;177:31–8.)

The renal cortex is approximately 1 cm in thickness and covers the base of each renal pyramid peripherally and extends downward between the individual pyramids to form the **columns of Bertin** (see Fig. 42-7 on the Expert Consult website). Interlobar arteries traverse these columns of Bertin from the renal sinus to the peripheral cortex and decrease in diameter as they move peripherally. Therefore percutaneous access to the collecting system is usually performed through a renal pyramid into a calyx to avoid these columns of Bertin containing larger blood vessels. The pyramids and their associated cortex form the lobes of the kidney. The lobes are visible on the external surfaces of the kidneys in fetuses, and evidence of the lobes may persist for some time after birth.

The functional unit of the kidney is the nephron (Fig. 42-10). Approximately 0.4 to 1.2 million nephrons are found in each adult kidney. The nephron consists of a glomerulus, which is composed of a capillary tuft surrounded by epithelial cells and the thin, fibrous Bowman capsule. The glomerulus filters the blood at a rate of 125 mL/min, the glomerular filtration rate, which is considered an index of renal function. The filtrate passes into the Bowman space and then into the proximal convoluted tubule, through the thin and thick limbs of the loop of Henle, to the macula densa adjacent to the glomerulus, and into the distal convoluted tubule. It then enters the collecting tubules and the ducts of Bellini. After absorption of approximately 90% of this filtrate, the remaining part constitutes the urine, which drips from the collecting ducts into the calyces, then to the renal pelvis, ureter, and bladder. Three layers separate the filtered blood from the Bowman space: a single layer of endothelial cells, a thin glomerular basement membrane, and a layer of podocytes on the other side of that basement membrane. The proximal and distal convoluted tubules and the loop of Henle are lined by a single layer of cubical epithelial cells. The cells lining the collecting ducts are cubical to columnar and are more resistant to damage than those of the renal tubules. The calyces, pelvis, ureters, bladder, and urethra are lined by transitional epithelium, the urothelium, which may change and give rise to a transitional cell carcinoma of the urinary tract or urothelial carcinoma.

KEY POINTS: THE KIDNEY

- Because the kidneys lie on the psoas muscles, the longitudinal axes of the kidneys are oblique, with the upper poles more medial and posterior than the inferior poles.
- The Gerota fascia envelops the kidney and the adrenal gland on all aspects except inferiorly, where it remains open.
- From anterior to posterior, the renal hilar structures are the renal vein (V), renal artery (A), renal pelvis (U for ureter), and posterior segmental artery (A)—making the mnemonic VAUA.
- The kidney is divided into cortex and medulla. The medullary areas are pyramidal, more centrally located, and separated by segments of cortex, the columns of Bertin.
- Each renal pyramid terminates centrally in a papilla. Each papilla is cupped by a minor calyx. A group of minor calyces join to form a major calyx. The major calyces combine to form the renal pelvis

Radiologic Anatomy of the Renal Parenchyma

In a well-prepared plain kidney-ureter-bladder (KUB) radiograph, the renal shape, margins, dimensions, and location can be identified. Both kidney shadows are clearly visible and can be assessed with regard to their position and morphology. The psoas muscle line could also be appreciated; it disappears with retroperitoneal effusions. Radiopacities, calcifications, and radiolucencies could be identified (Fig. 42-11 on the Expert Consult website). In gray-scale ultrasonography, the renal cortices of newborn kidneys are isoechoic or hyperechoic to the liver and splenic parenchyma, because of the presence of loops of Henle and proportionately greater volume of glomeruli in the cortex than in adults (Hricak et al, 1983; Kasap

et al, 2006). In adults, the normal kidneys have smooth margins and are isoechoic to the liver. However, both renal cortices and pyramids are usually hypoechoic to the liver, spleen, and renal sinus. Compared with renal parenchyma, the renal sinus appears hyperechoic because of the presence of hilar adipose tissue, blood vessels, and lymphatics (Fig. 42-12 on the Expert Consult website). On unenhanced computed tomography (CT), the renal parenchyma is homogeneous, with a density ranging from 30 to 60 Hounsfield units (HU) that increases up to 80 to 120 HU after intravenous contrast injection. After 20 to 30 seconds of contrast injection, the arterial CT phase is reached, and the corticomedullary CT phase appears after 30 to 70 seconds, when contrast accumulates in the renal cortex. The nephrographic CT phase, after 80 to 120 seconds, equally enhances renal cortex and medulla and is considered to be the optimal phase for detection of renal neoplasms. Finally, the excretory CT phase, more than 3 minutes after contrast injection, shows the opacified pelvicalyceal system, ureter, and bladder (Fig. 42-13). Magnetic resonance imaging with T1 and T2 relaxation sequences provides information regarding lipid or fat content and enhancement characteristics of tissues. T1-weighted sequences show the renal cortex much brighter than renal medulla, whereas the cortex is slightly less intense than the medulla on T2-weighted sequences. The renal pelvis containing fat appears hyperintense on both T1- and T2-weighted sequences. After injection of contrast, the nephrographic and excretory phases start after 60 to 90 and 120 seconds of contrast injection, respectively (see Fig. 42-8 on the Expert Consult website).

Of all congenital anomalies encountered in newborns, 20% to 30% affect the kidneys and ureters (Schedl, 2007). Anomalies of number, rotation, ascend, and/or fusion may be encountered. Radiologically, renal malrotation is identified because the renal pelvis appears to arise centrally instead of its medial origin from the kidney. Some calyces are located medial to the renal pelvis, a hallmark of rotational anomalies. These renal calyces appear distorted with or without obstruction (Fig. 42-14 on the Expert Consult website). Arrest or exaggeration of normal ascent of the kidneys gives rise to renal ectopia and is usually associated with malrotation. Despite the ureteral length being appropriate for the kidney position, the impaired drainage results in urinary stasis and increased chances of infection and stone formation. Moreover, blood supply to the ectopic kidney is also aberrant, originating from adjacent vessels (see Fig. 42-14 on the Expert Consult website). A kidney may cross the midline and fuse with the opposite kidney (crossed-fused ectopia). The ureter from the ectopic lower kidney crosses the midline and usually inserts into the bladder in its normal position. The two kidneys may fuse by an isthmus at their lower pole, giving rise to the horseshoe kidney (Fig. 42-15 on the Expert Consult website). It is usually positioned low in the abdomen because of its arrest by the origin of the inferior mesenteric artery. The isthmus may contain a fibrotic band or functional renal parenchyma. This kidney is usually subjected to other anomalies, especially ureteropelvic junction obstruction (UPJO), vascular anomalies, duplication anomalies, stone formation, and urinary tract infections.

KEY POINTS: RADIOLOGIC ANATOMY OF RENAL PARENCHYMA

- Although normal kidneys are isoechoic to the liver, both renal cortices and pyramids are hypoechoic to the liver, spleen, and renal sinus.
- Echogenicity correlates to the severity of pathologic changes in renal parenchyma.
- The renal parenchyma is homogeneous on unenhanced CT.
- T1-weighted sequences show the renal cortex much brighter than the renal medulla, whereas the cortex is slightly less intense than the medulla on T2-weighted sequences.
- Blood supply to an ectopic kidney originates from adjacent vessels



Figure 42-11. Plain radiograph (kidney-ureter-bladder [KUB]). This 63-year-old woman presented with recurrent urinary tract infections and was found to have a smaller left kidney with staghorn calculus on KUB.

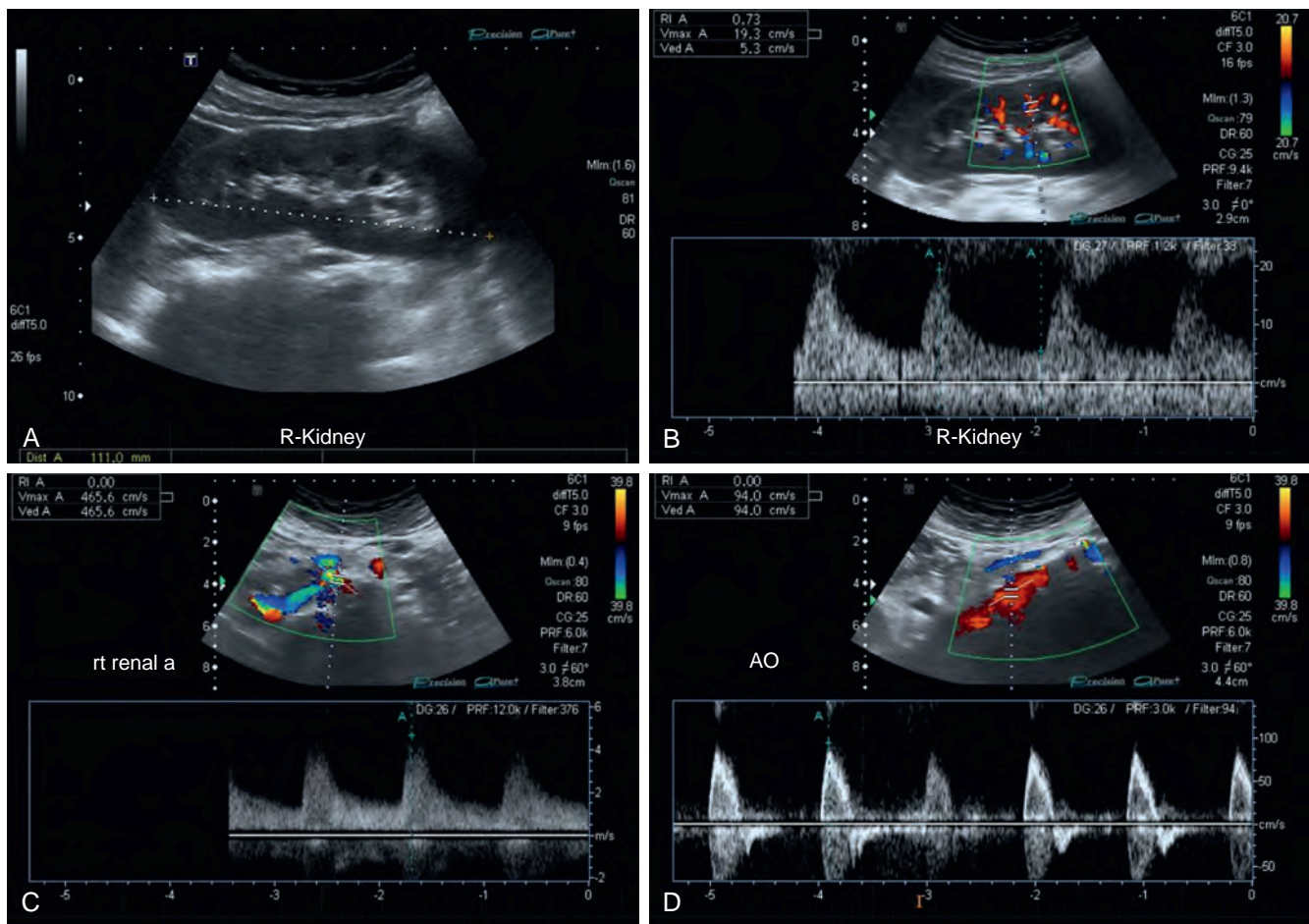


Figure 42-12. Renal ultrasonography and Doppler interrogation in a 65-year-old patient with poorly controlled hypertension. The resistive index within the renal parenchyma was 0.73. The right renal arterial peak systolic velocity reached up to 465.6 cm/sec at the ostium compared with peak systolic velocity of 94 cm/sec in the aorta (AO), suggesting severe (>50%) right renal arterial stenosis. A, Renal ultrasonography in B mode. B, Color Doppler of the renal parenchyma. C, Measurement of peak systolic velocity in right renal artery (rt renal a). D, Measurement of peak systolic velocity in the aorta. R, right.

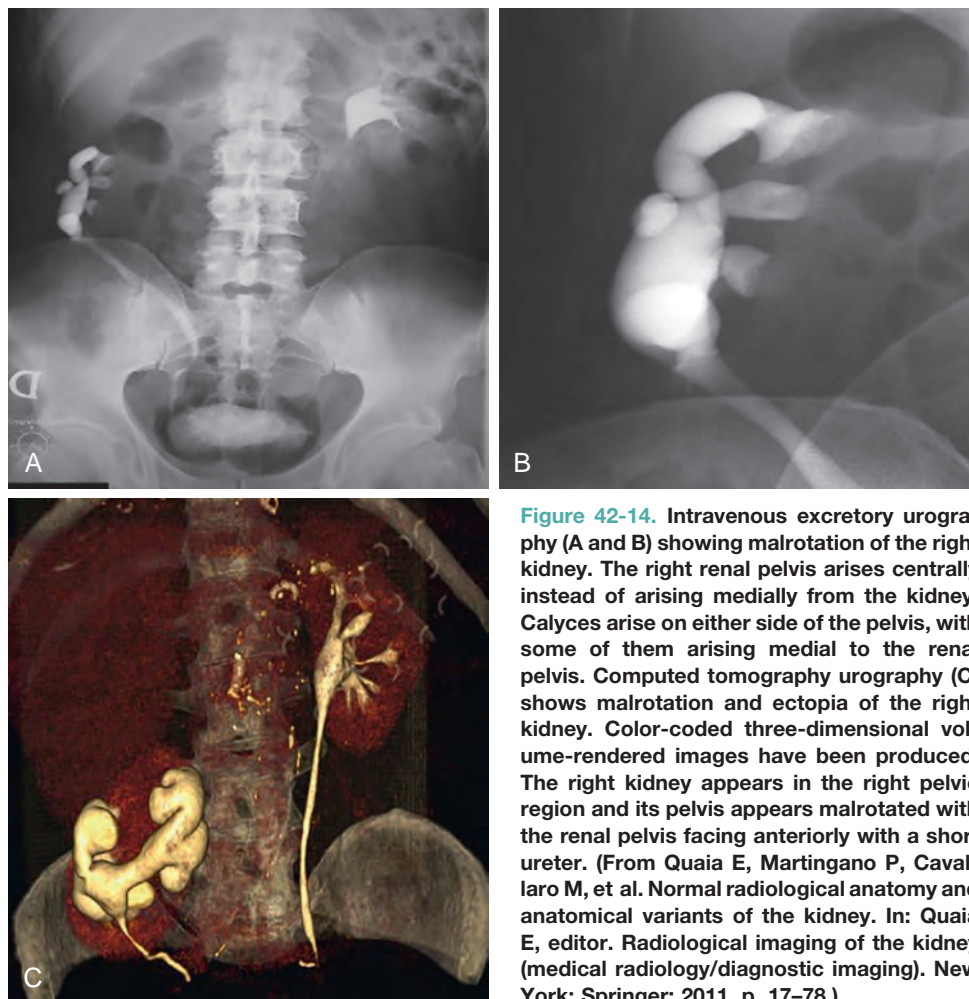


Figure 42-14. Intravenous excretory urography (A and B) showing malrotation of the right kidney. The right renal pelvis arises centrally instead of arising medially from the kidney. Calyces arise on either side of the pelvis, with some of them arising medial to the renal pelvis. Computed tomography urography (C) shows malrotation and ectopia of the right kidney. Color-coded three-dimensional volume-rendered images have been produced. The right kidney appears in the right pelvic region and its pelvis appears malrotated with the renal pelvis facing anteriorly with a short ureter. (From Quaia E, Martingano P, Cavallaro M, et al. Normal radiological anatomy and anatomical variants of the kidney. In: Quaia E, editor. Radiological imaging of the kidney (medical radiology/diagnostic imaging). New York: Springer; 2011. p. 17–78.)

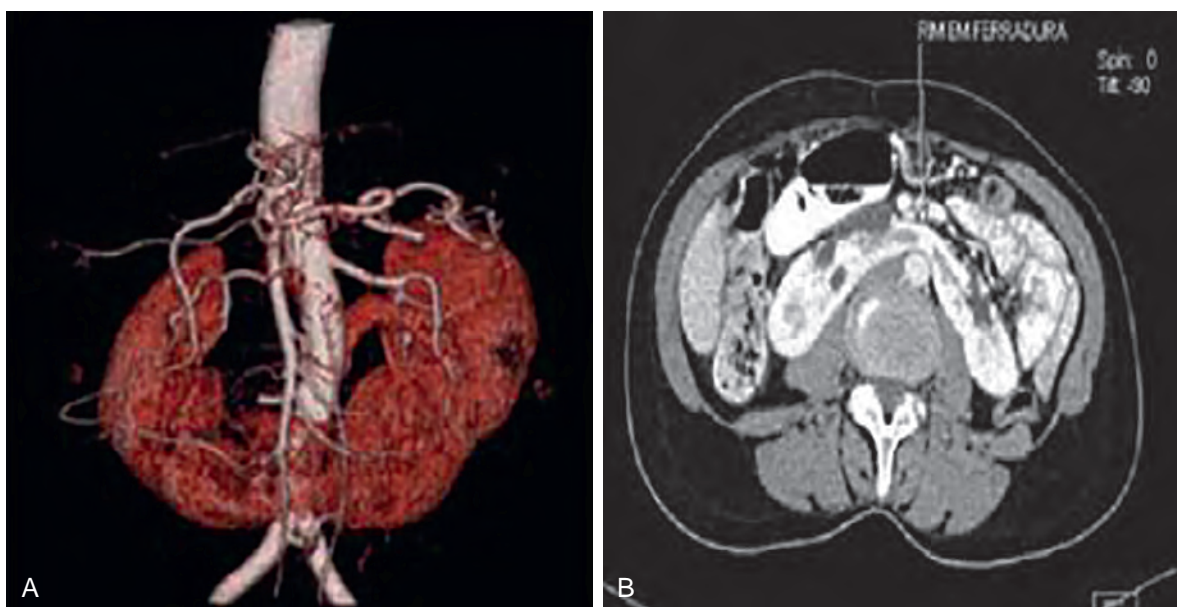


Figure 42-15. Computed tomography angiography with volume-rendered three-dimensional image (A) and axial view (B) of a horseshoe kidney showing the aberrant vasculature. (From Maranhao CP, de Miranda CM, dos Santos CJ, et al. Congenital upper urinary tract abnormalities: new images of the same diseases. Radiol Bras 2013;46:43–50.)

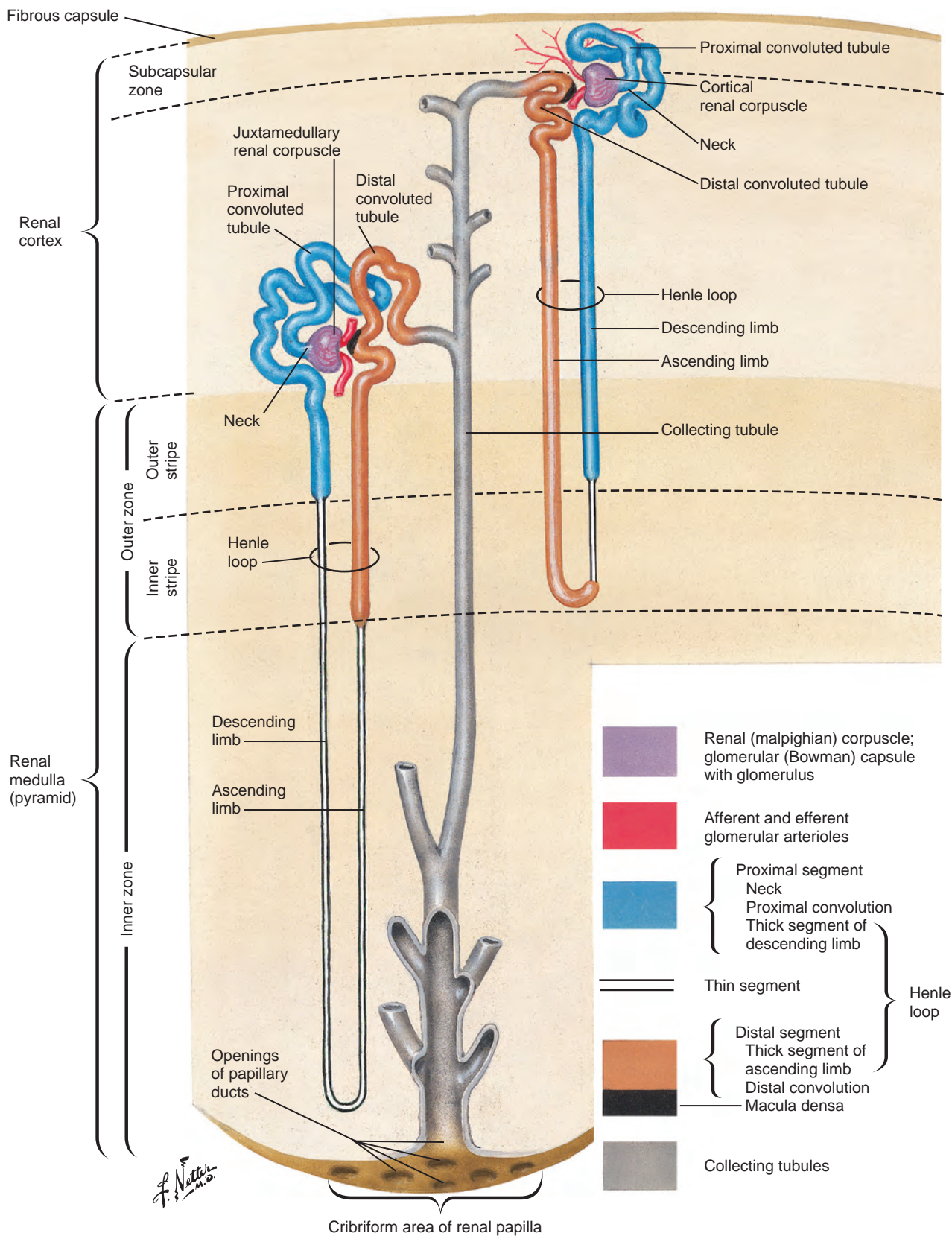


Figure 42-10. Schematic diagram of the microanatomy of the kidneys. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

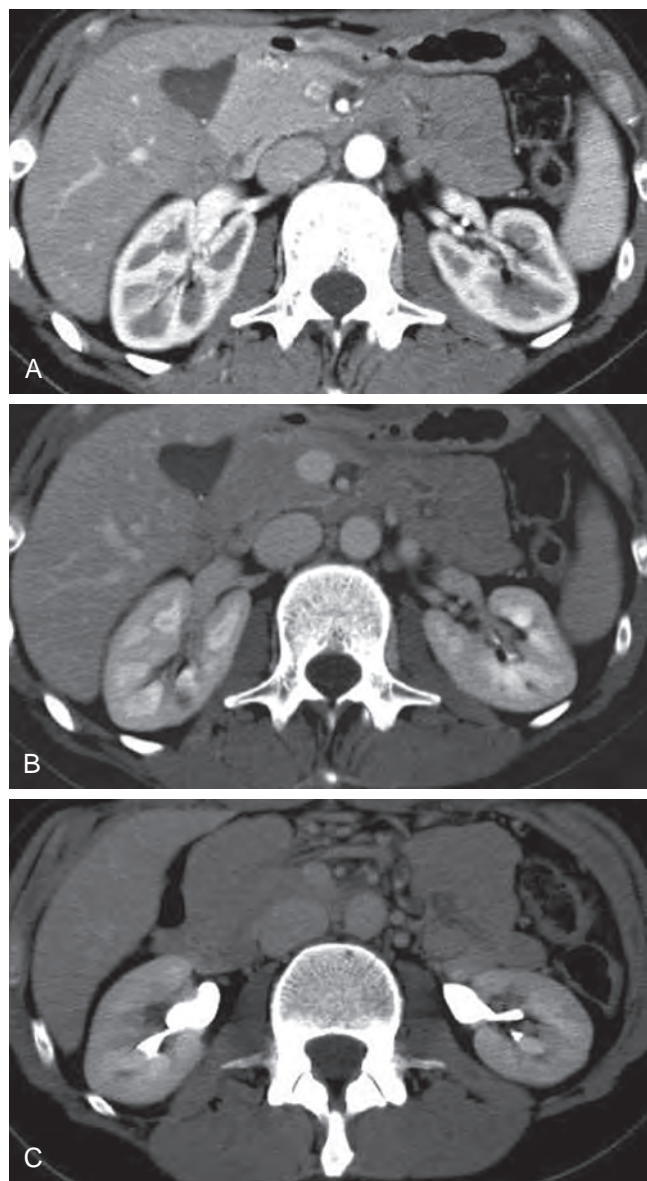


Figure 42-13. Computed tomography of normal renal parenchyma. **A**, The corticomedullary phase shows high contrast in the renal cortex after 30 to 70 seconds of contrast injection. **B**, The nephrographic phase shows renal cortex and medulla with equal enhancement after 80 to 120 seconds of contrast injection. **C**, The excretory phase shows the opacified urinary tract after more than 180 seconds. (From Quaia E, Martingano P, Cavallaro M, et al. Normal radiological anatomy and anatomical variants of the kidney. In: Quaia E, editor. Radiological imaging of the kidney (medical radiology/diagnostic imaging). New York: Springer; 2011. p. 17–78.)

Renal Vasculature

The renal pedicle classically consists of a single artery and a single vein that enter the kidney via the renal hilum (Fig. 42-16). The renal arteries arise from the aorta at the level of the intervertebral disk between the L1 and L2 vertebrae where the longer right renal artery passes posterior to the inferior vena cava (IVC). Renal arteries give branches to the adrenal glands, renal pelves, and proximal ureters. After entering the hilum, each artery divides into five segmental end arteries that do not anastomose significantly with other segmental arteries. Therefore occlusion or injury to a segmental branch will cause segmental renal infarction. Nevertheless, the area supplied by each segmental artery could be independently

surgically resected. The renal artery usually divides to form anterior and posterior divisions. The anterior division supplies roughly the anterior two thirds of the kidney, and the posterior division supplies the posterior one third of the kidney. Typically, the anterior division divides into four anterior segmental branches: apical, upper, middle, and lower. The posterior segmental artery represents the first and most constant branch, which separates from the renal artery before it enters the renal hilum. A small apical segmental branch might originate from this posterior branch, but it arises most commonly from the anterior division. The posterior segmental artery from the posterior division passes posterior to the renal pelvis while the others pass anterior to the renal pelvis. **If the posterior segmental branch passes anterior to the ureter, UPJO may occur.** In 25% to 40% of kidneys, anatomic variations in the renal vasculature have been reported. **Supernumerary renal arteries** are the most common variation, with reports of up to five arteries, especially on the left side. The main renal artery may manifest early branching after originating from the abdominal aorta and before entering the renal hilum. These prehilum arterial branches should be detected in patients undergoing evaluation for donor nephrectomy. An accessory renal artery may arise from the aorta, between T11 and L4, and terminate in the kidney. Rarely, it may also originate from the iliac arteries or superior mesenteric artery. Accessory renal arteries are seen in 25% to 28% of patients and are considered the sole arterial supply to a specific portion of the renal parenchyma, commonly the lower and occasionally the upper pole of the kidney. These accessory renal arteries may contraindicate laparoscopic donor nephrectomy and result in severe bleeding if they are injured during endopyelotomy for UPJO. Multiple renal arteries that arise from the aorta or iliac arteries are frequently seen in horseshoe and pelvic kidneys. In approximately 5% of patients, the main and accessory right renal arteries pass anterior to the IVC.

There is a longitudinal avascular plane (line of Brodel) between the posterior and anterior segmental arteries just posterior to the lateral aspect of the kidney through which incision results in significantly less blood loss. However, this plane may have various locations that necessitate its delineation before incision either by preoperative angiography or intraoperative segmental arterial injection of methylene blue. This has important surgical implications. For example, during percutaneous access into the kidney, posterior calyces along the line of Brodel are preferred. Furthermore, during anastrophic nephrolithotomy (Boyce procedure), an incision is made through this avascular plane.

At the renal sinus, each segmental artery branches into lobar arteries, which further subdivide in the renal parenchyma to form interlobar arteries (Fig. 42-17 on the Expert Consult website). These interlobar arteries progress peripherally within the cortical columns of Bertin to give the arcuate arteries at the base of the renal pyramids at the corticomedullary junction. Note the close relationship of the interlobar arteries to the infundibuli of minor calyces. Interlobular arteries branch off the arcuate arteries and move radially, where they eventually divide to form the afferent arterioles to the glomeruli. Each afferent arteriole supplies a glomerulus, one of approximately 2 million glomeruli, where urinary filtrate leaves the arterial system and is collected in the glomerular (Bowman) capsule. Blood returns from the glomerulus via the efferent arteriole and continues as either secondary capillary networks around the urinary tubules in the cortex or descends into the renal medulla as the vasa recta.

The renal venous drainage correlates closely with the arterial supply, with the exception that unlike the arterial supply, venous drainage has extensive collateral communication through the venous collars around minor calyceal infundibula (Figs. 42-18 on the Expert Consult website and 42-19). Furthermore, the interlobular veins that drain the postglomerular capillaries also communicate freely with perinephric veins through the subcapsular venous plexus of stellate veins. The interlobular veins progress through the arcuate, interlobar, lobar, and segmental veins paralleling their corresponding arteries. Three to five segmental renal veins eventually unite to form the renal vein. Because the venous drainage communicates freely forming extensive collateral venous drainage of the

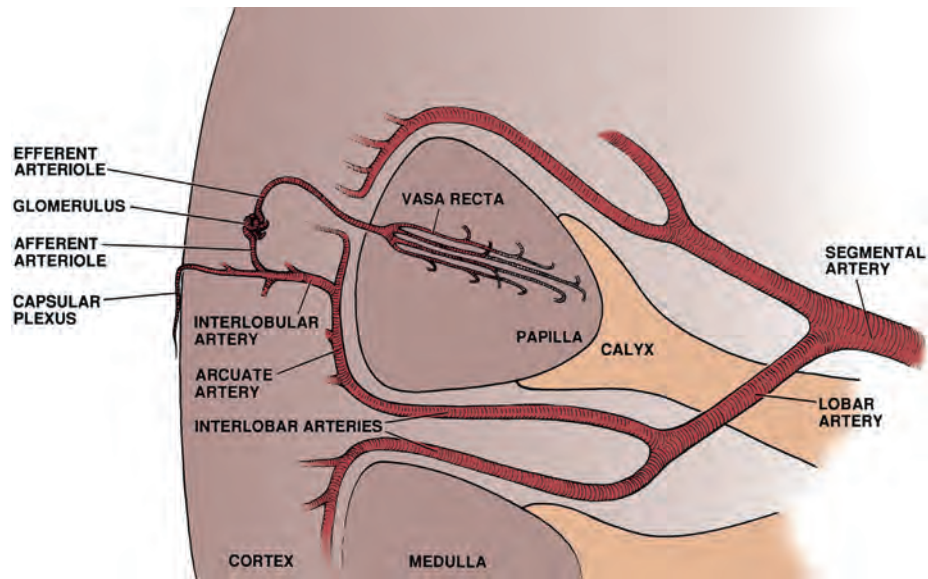


Figure 42-17. Intrarenal arterial anatomy.

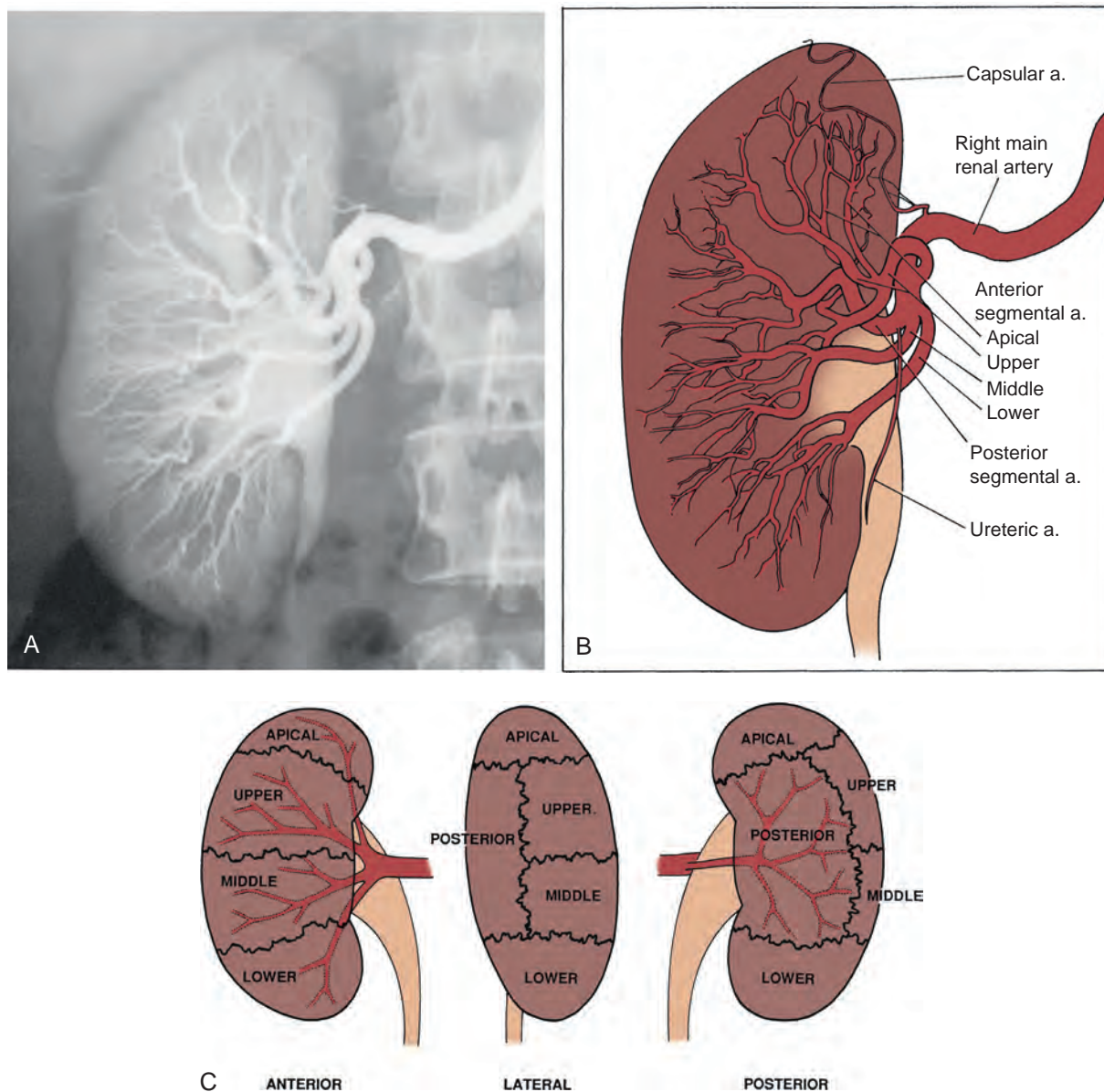


Figure 42-16. Blood supply of the kidney. **A and B,** Segmental branches of the right renal artery demonstrated by renal angiogram. **C,** Segmental circulation of the right kidney shown diagrammatically. Note that the posterior segmental artery is usually the first branch of the main renal artery and it extends behind the renal pelvis. *a*, artery.

kidney, occlusion of a segmental venous branch has little effect on venous outflow. The **right and left renal veins** lie anterior to the right and left renal arteries and drain into the IVC. Whereas the right renal vein is 2 to 4 cm long, the left renal vein is 6 to 10 cm. The longer left renal vein receives the left suprarenal (adrenal) vein and the left gonadal (testicular or ovarian) vein. The left renal vein also may receive a **lumbar vein**, which could be easily avulsed during surgical manipulation of the left renal vein. The left renal vein traverses the acute angle between the **superior mesenteric artery** anteriorly and the aorta posteriorly. In thin adolescents, the left renal vein may get compressed between the superior mesenteric artery and aorta, causing **nutcracker syndrome**. In approximately 15% of the patients, supernumerary renal veins are seen and often are retroaortic when present on the left. Accessory renal veins are more common on the right side, and the most common anomaly of the left renal venous system is the circumaortic renal vein, reported in 2% to 16% of patients. The retroaortic renal vein is less commonly seen than the circumaortic vein, in which the left renal vein

bifurcates into ventral and dorsal limbs, which encircle the abdominal aorta. In retroaortic renal vein, the single left renal vein courses posterior to the aorta and drains into the lower lumbar segment of the IVC.

In terms of imaging studies, Doppler ultrasonography clearly identifies renal arteries at their origin from the abdominal aorta (see Fig. 42-12 on the Expert Consult website). However, the main renal artery is often difficult to identify at baseline ultrasonography. Therefore computed tomography angiography (CTA) is currently considered the gold standard to assess renal arteries, with 100% sensitivity for identification of renal arteries and veins. The 3D volume-rendered CTA has emerged as a fast, reliable, and noninvasive modality that can reliably and accurately depict the number, size, course, and relationship of the renal vasculature. Arterial branches down to the segmental branches could be identified, but vessels smaller than 2 mm could be missed (see Fig. 42-15 on the Expert Consult website). Magnetic resonance arteriography uses no ionizing radiation, does not require arterial access, and includes

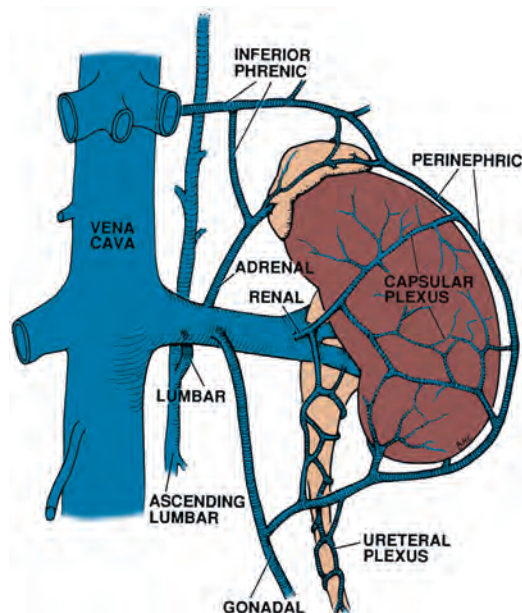


Figure 42-19. Venous drainage of the left kidney showing potentially extensive collateral circulation.

different imaging techniques to visualize renal vasculature. Contrast material can give faster, better resolution and more accurate images without artifacts.

KEY POINTS: RENAL VASCULATURE

- Each kidney is commonly supplied by a single renal artery, which arises directly from the abdominal aorta, and a single renal vein usually drains directly to the IVC.
- Each renal artery divides into five segmental branches: posterior, apical, upper, middle, and lower segmental arteries.
- The progression of arterial supply to the kidney is as follows: renal artery → segmental artery → interlobar artery → arcuate artery → interlobular artery → afferent arteriole → glomerulus → efferent arteriole.
- The veins anastomose freely throughout the kidney, whereas the arterial supply does not.
- Anatomic variations in the renal vasculature are common in 25% to 40% of kidneys.
- CTA is currently the gold standard to assess renal arteries. Accessory renal arteries are seen in 25% to 28% of patients and are considered the sole arterial supply to a specific portion of the renal parenchyma.
- Anomalies of renal veins are less common than those of the renal arteries.

Lymphatic Drainage of the Kidney

Interstitial fluid leaves the kidney by either a superficial capsular or a deeper hilar network (Fig. 42-20 on the Expert Consult website). Renal lymphatics are embedded in the periarterial loose connective tissue around the renal arteries and are distributed primarily along the interlobular and arcuate arteries in the cortex. The arcuate lymphatic vessels drain into hilar lymphatic vessels through interlobar lymphatics. As these lymphatics exit the renal hilum, they join branches from the renal capsule, perinephric tissues, renal pelvis, and upper ureter, where they empty into lymph nodes associated with the renal vein. Afterward, the lymphatic drainage varies considerably between the two kidneys. Left lymphatic drainage primarily goes into the left lateral para-aortic lymph nodes (between the

inferior mesenteric artery and diaphragm), with occasional additional drainage into the retrocrural nodes or directly into the thoracic duct above the diaphragm. Right renal lymphatic drainage primarily goes into the right interaortocaval and right paracaval lymph nodes (between common iliac vessels and diaphragm), with occasional additional drainage from the right kidney into the retrocrural nodes or the left lateral para-aortic lymph nodes.

Innervation of the Kidney

The kidney can function well without neurologic control, as evidenced by the successful function of transplanted kidneys (Fig. 42-21 on the Expert Consult website). Sympathetic preganglionic nerves originate from the 8th thoracic through 1st lumbar spinal segments, with contributions mainly from the celiac plexus and a lesser contribution from the greater splanchnic, intermesenteric, and superior hypogastric plexuses. Postganglionic sympathetic nerve fiber distribution generally follows the arterial vessels throughout the cortex and the outer medulla. These postganglionic fibers travel to the kidney via the autonomic plexus surrounding the renal artery. In addition, parasympathetic fibers from the vagus nerve travel with the sympathetic fibers to the autonomic plexus along the renal artery. The renal sympathetics cause vasoconstriction, and the parasympathetics cause vasodilatation.

PELVICALYCEAL SYSTEM

Understanding the collecting system anatomy is of utmost importance for appropriate radiologic interpretation and performance of different endourologic procedures. The upper pole of the kidney usually contains three calyces and less commonly two, whereas three or four calyces could be identified at the interpolar region and two or three calyces at the lower pole (Fig. 42-22). These calyces vary considerably not only in numbers but also in size and shape because of the different numbers of papillae they receive. A calyx may receive a single papilla, two, or even three. Compound papillae are often found in the polar regions of the kidney. The upper pole is usually drained by a single midline calyceal infundibulum, and the lower pole is drained by either a single midline calyceal infundibulum or by paired calyces. The hilar region is drained by anterior and posterior rows of paired calyces. The pelvicalyceal system may have the configuration of either a true pelvis or divided double calyceal pelvis. The true pelvis is the classic type in which the calyces drain directly through elongated necks into an elongated pelvis. This pelvis may be completely imbedded within the renal sinus (intrarenal pelvis) or mostly outside it (extrarenal pelvis). The renal pelvis is roughly pyramidal, with the base facing the parenchyma and the apex funneling down into the ureter. It usually has a capacity of 3 to 10 mL of urine.

In a divided (duplex) pelvis, it is divided at the hilum into upper and lower portions and drains a higher number of calyces than a normal pelvis. Its lower part is usually shorter but larger and often drains the hilar and the lower pole calyces. Therefore there is no direct connection between the upper and lower calyces. This usually becomes apparent during the excretory phase of a CT urogram or on retrograde pyelography. During percutaneous endoscopic evaluation of the kidney, the existence of a duplex pelvis should be considered if upper or lower pole calyces cannot be accessed through a particular calyceal access. Duplex systems are easier to recognize on retrograde nephroureteroscopy. When a duplex system is suspected during ureteroscopy, retrograde pyelography could be performed to illustrate the anomalous pelvicalyceal system.

Radiologic Anatomy of the Collecting System

After an iodinated contrast agent is injected for intravenous urography, nephrotomograms appear after 60 to 90 seconds that represent contrast material within the renal tubules. Fifteen minutes after contrast injection, a panoramic radiograph of the whole urinary tract can be obtained; the bladder finally appears 20 to 30 minutes

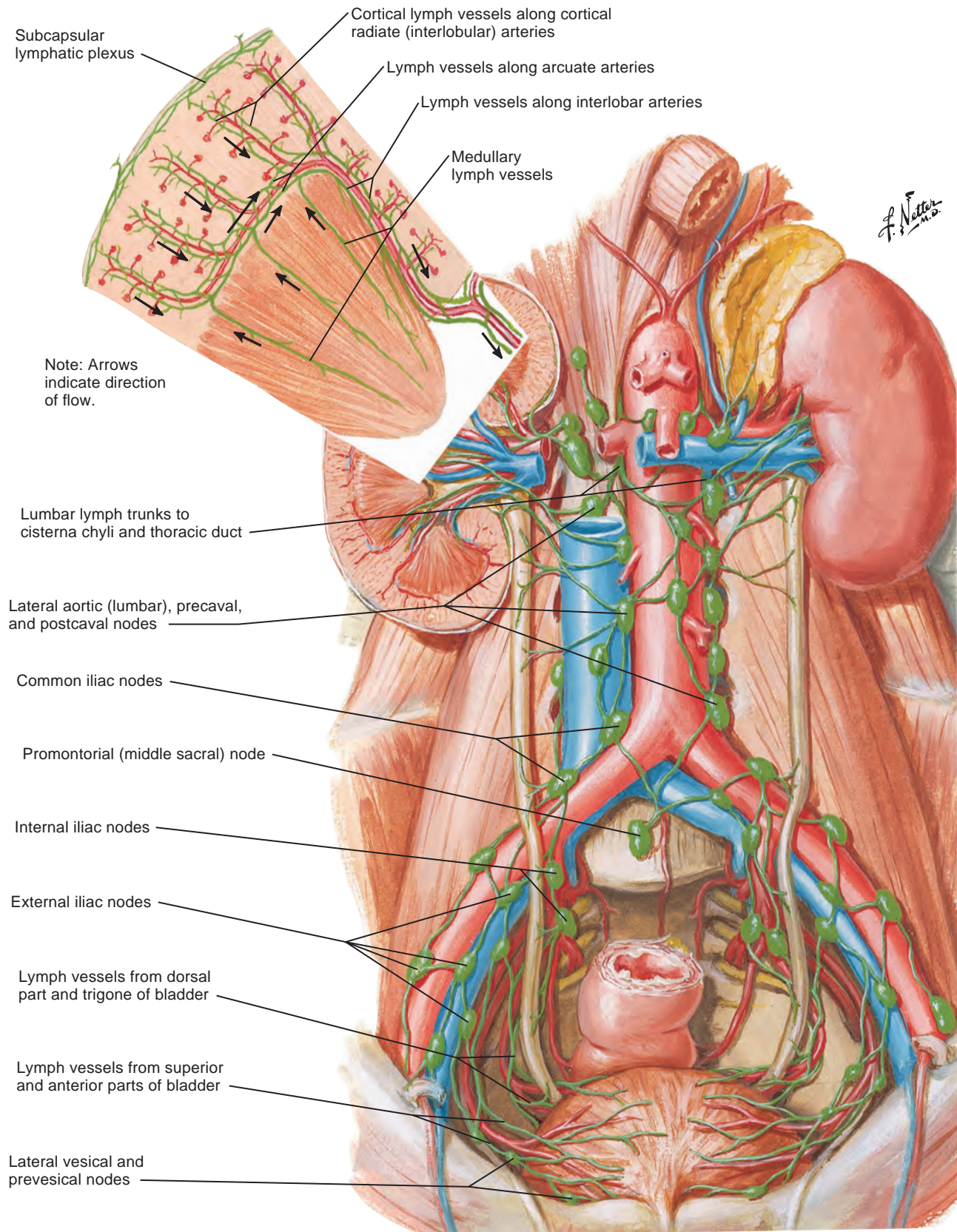


Figure 42-20. Lymphatic drainage of the kidneys and ureters. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

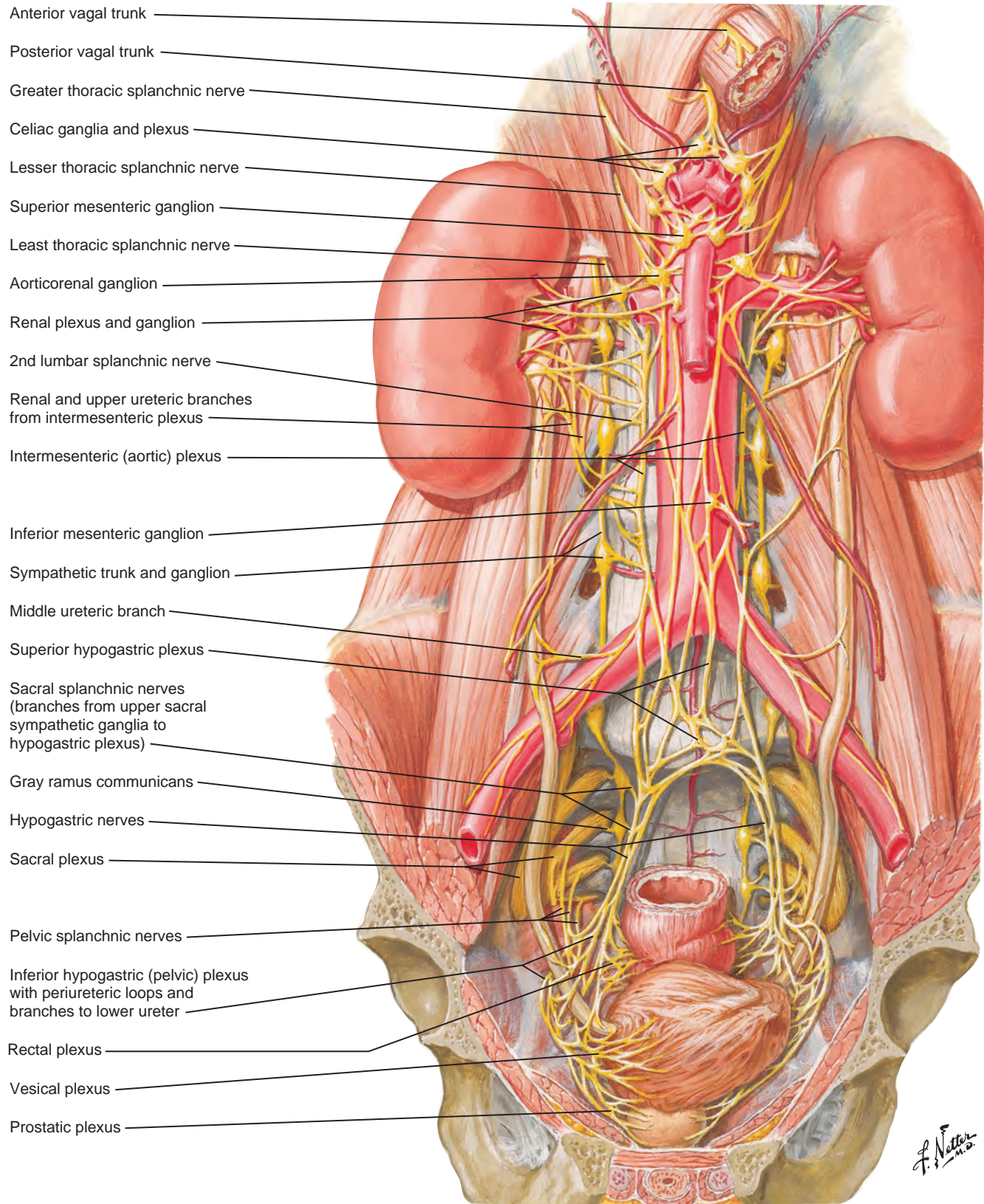


Figure 42-21. Autonomic innervations of the kidneys and ureters. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

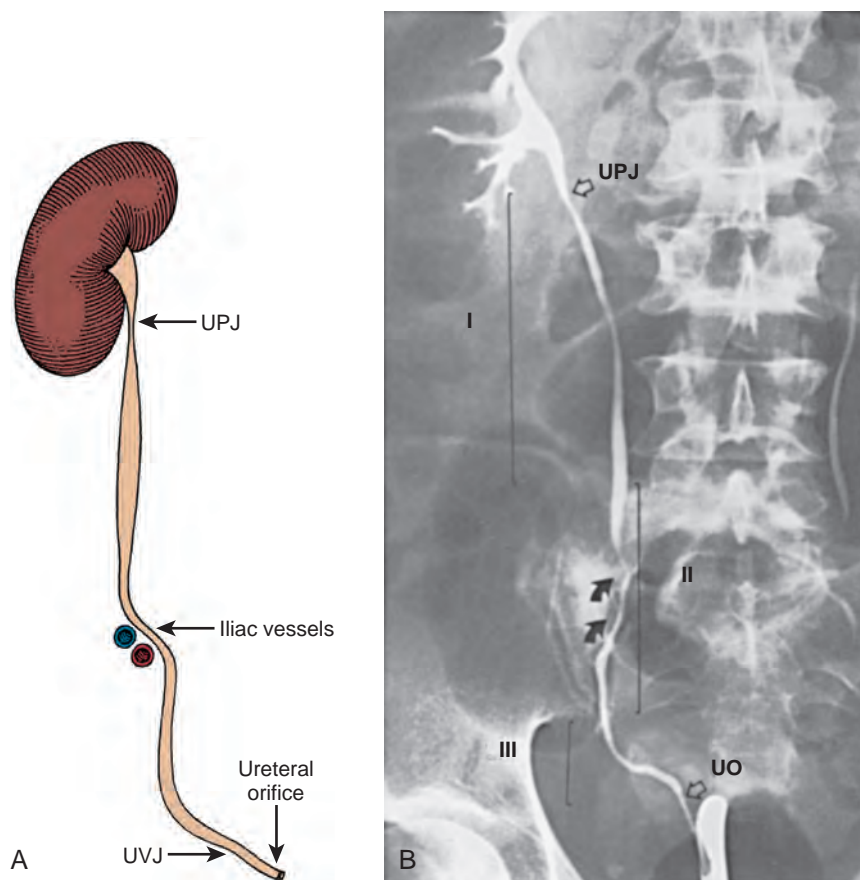


Figure 42-22. A, The ureter demonstrating sites of normal functional or anatomic narrowing at the ureteropelvic junction (UPJ), the iliac vessels, and the ureterovesical junction (UVJ). B, The right ureter, illustrated by retrograde injection of contrast material. UO, ureteric orifice in the bladder; UPJ, ureteropelvic junction; I, upper or proximal ureter, extending to the upper border of the sacrum; II, middle ureter, extending to the lower border of the sacrum; III, distal or lower ureter, traversing the pelvis to end in the bladder. Arrows indicate the course of the common iliac artery and vein.

after contrast injection. Absence of contrast excretion 24 hours after intravenous contrast injection indicates a nonfunctioning kidney. **The pelvicalyceal anatomy is variable, and no simple rule defines calyceal organization.** Currently, CT urography has replaced intravenous urography, and multidetector CT provides the ability to obtain thin (<1 mm) collimated data of the entire urinary tract during a short single breath-hold (Van Der Molen et al, 2008). Magnetic resonance urography (MRU) has two consecutive phases: a static-fluid phase and an excretory phase. The static-fluid MRU is ideally indicated for evaluation of the obstructed or dilated collecting system. The practicability of excretory MRU depends on renal function, and its quality could be improved by a low-dose furosemide diuretic. Congenital variants of the pelvicalyceal system are common, representing approximately 4% of the population. The renal pelvis may be completely intrarenal, completely extrarenal, or a combination of both (Friedenberg and Dunbar, 1990). The infundibula insert directly into the extrarenal pelvis, giving the impression of a dilated pelvis. Receiving the tip of renal papilla, the renal calyx is a concave structure with two side projections, the fornices, which surround the papilla of the renal medulla. Multiple single calyces fail to divide completely, forming a larger compound calyx that normally can be observed in the upper and lower poles of the kidneys. Each kidney contains an average of 7 to 9 calyces, although this number may vary considerably from 4 to 19 or even more. Megacalycosis represents a nonobstructive asymptomatic congenital dilatation of some or all renal calyces while the renal pelvis and ureter are normal. It involves all calyces uniformly and usually is

associated with a greater number of calyces than normal. Calyceal diverticula represent a focal extrinsic dilatation of a renal calyx that is connected to the calyceal fornix and projects into the renal cortex, not into the medulla. The renoureteral unit may show duplication anomalies, including a bifid renal pelvis and complete or incomplete ureteral duplication. Two separate pyelocalyceal collecting systems may be present in one kidney, ranging from a bifid pelvis to a bifid ureter (ureteropelvic duplication).

URETERS

The ureters are bilateral muscular retroperitoneal ducts with narrow lumens that carry urine from the kidneys to the urinary bladder (see Fig. 42-22). Each ureter runs inferiorly as a narrow continuation of its renal pelvis at the UPJ, passing over the pelvic brim at the bifurcation of the common iliac artery. They then run along the lateral wall of the pelvis to enter the urinary bladder. In adults, the ureter is 22 to 30 cm in length with a diameter of 1.5 to 6 mm; in neonates it measures 6.5 to 7.0 cm long. In the retroperitoneum, the ureter is situated just lateral to the tips of the transverse processes of the lumbar vertebrae. The ureters occupy a sagittal plane that intersects the tips of the transverse processes of these lumbar vertebrae. The ureter is arbitrarily divided into proximal (upper), middle (over the sacrum), and distal (lower) segments. However, according to international anatomic terminology the ureter consists of abdominal (from renal pelvis to iliac

vessels), pelvic (from iliac vessels to the bladder), and intramural segments.

The abdominal parts of the ureters are adherent to the retroperitoneum throughout their entire course and extend from the renal pelvis to the pelvic brim. From the back, the surface anatomy of the ureter corresponds to a line joining a point 5 cm lateral to the L1 spinous process and the posterior superior iliac spine. Normally, three constrictions could be identified radiologically in each ureter; at its junction with the renal pelvis (UPJ), where it crosses the iliac vessels, and during its passage through the wall of the urinary bladder (intramural ureter) or ureterovesical junction (see Fig. 42-22). These constricted areas are potential sites of obstruction by ureteral calculi.

Posteriorly, both ureters descend anterior to the psoas major muscle and then cross the ventral surface of transverse processes of the 3rd to 5th lumbar vertebrae and enter the pelvis at the bifurcation of the common iliac vessels (see Figs. 42-4 and 42-5 on the Expert Consult website). The bifurcation of the common iliac vessels is used intraoperatively as a landmark to look for the ureter. The genitofemoral nerve runs on top of the psoas major muscle behind the ureter. The right ureter begins behind the descending part of the duodenum, where it is crossed by the gonadal vessels (testicular or ovarian), which is called “water under the bridge.” The left ureter is covered at its origin by the initial part of the jejunum. The gonadal vessels cross the left ureter after running parallel to it for a small distance. The inferior mesenteric artery and its terminal branch, the superior rectal artery, follow a curved course close to the left ureter. Therefore, as the left ureter approaches the pelvis, it is crossed by the left colic vessels, the sigmoid colon, and its mesocolon. Just above the entry to the pelvis, the ureter is still covered by peritoneum by virtue of the ureteral fold. This location at the pelvic brim represents one of the most common areas of ureteral injury. Furthermore, the close relationship of the ureter with the terminal ileum, appendix, right and left colons, and sigmoid colon makes it susceptible for encroachment of inflammatory and malignant processes, resulting in clinical presentations ranging from microhematuria to ureteral obstruction or even fistulae.

The pelvic segment of the ureter is approximately 15 cm long—a half of its total length. At the pelvic inlet, it crosses the common iliac vessels near their bifurcation. This crossover point is usually at the bifurcation of the common iliac artery into the internal and external iliac arteries, making this a useful landmark for pelvic procedures. The ureter then runs downward and laterally toward the ischial spine on the lateral pelvic wall along the anterior border of the greater sciatic notch, dorsally accompanied by the internal iliac artery and its visceral branches and the venous plexuses as well. It is still closely related to the posterior parietal peritoneum. At the ischial spine, the ureter turns medially to descend in the endopelvic fascia with branches of the hypogastric nerves. At the lateral wall of the pelvis, this part of the ureter crosses the obturator artery, vein, and nerve. In males, the vas deferens loops medially over this part while the ureter passes the ampulla of the vas deferens and the seminal vesicles just before it enters the bladder. In females, the descending part of the pelvic segment of the ureter courses posterior to the ovary to form the posterior boundary of the ovarian fossa. The ureter then passes through the base of the broad ligament and swings in a convex curve to cross under the uterine vessels “water under the bridge” in a sagittal direction approximately 1.5 to 2 cm adjacent to the supravaginal part of the uterine cervix. The terminal ureter runs forward, accompanied by the neurovascular bundle of the bladder and passes the anterior vaginal fornix just before entering the bladder. This close proximity of the ureter to the uterine vessels is the cause of ureteral injuries during gynecologic procedures. In the case of vaginal surgery, there is a high risk for injury especially for the left ureter that crosses the anterior vaginal fornix closer than the right ureter.

Near the bladder, the terminal ureter is enveloped by a muscular layer, the Waldeyer sheath, and then pierces the bladder wall obliquely as the intramural segment (Fig. 42-23 on the Expert Consult website). The length of this intramural part of the ureter in adults is 1.2 to 2.5 cm, and in neonates it is approximately 0.5 to

0.8 cm long. The Waldeyer muscle bundles of the ureter coalesce with those of the detrusor muscle of the bladder wall. Therefore reflux of urine from the bladder to the ureter is prevented during increased intravesical pressure, such as during micturition. Another important feature of the 3D course of the ureter that is critical to appreciate and follow during rigid ureteroscopy is the angulation of the ureter as it courses through the retroperitoneum. When approaching from the retrograde direction, it is important to note that the ureter courses anterolaterally as it goes along the lateral pelvic wall. Then, as it crosses the pelvic brim, it angulates posteriorly to continue as the proximal ureter. Following the 3D course of the ureter along a safety guidewire reduces the risk for perforation, especially in patients with large impacted stones.

Radiologic Anatomy of the Ureter

The ureter could be delineated by excretory urography during expiration, because it may be kinked during inspiration as a result of downward movement of the kidney (Friedenberg and Dunbar, 1990). For radiologic purposes, radiologists describe three segments of the ureter: a proximal portion extending from its origin down to the upper border of the sacroiliac joint, a middle portion lying over the sacroiliac joint, and the remaining segment from the lower border of that joint to its entrance into the bladder, which represents the distal portion of the ureter.

The course of the ureter and its bilateral symmetry are subject to great variability. It may descend laterally away from the margin of the transverse processes or be displaced medial to the renal pedicle. A medially displaced right ureter might normally be seen in young black males (Adam et al, 1985). The right ureter may run medially behind the vein at the level of 3rd lumbar vertebra before it returns back to its lateral position. **It should be noted that the entire length of the ureter is rarely seen in a single film of the excretory urography because of its peristaltic activity.** Otherwise, ureteral atony or obstruction should be suspected (Mellins, 1986). Similarly, crossing vessels may compress the ureter and simulate areas of stricture. **Therefore the diagnosis of a ureteral stricture should not be based on a single film of excretory urography with the presence of ureteral dilatation proximal to the site of narrowing.** Ureteral duplication may be complete or incomplete (partial). Complete duplication results from the development of a second ureteric bud, and the two ureters are inserted into the bladder separately. The partial type results from redundant duplication of the single ureteric bud in which the two ureters join together above the bladder to form a single stump draining into the bladder. Complete ureteral duplication with a common or ectopic entry of the upper pole moiety, is less common than incomplete duplication. The ureter draining the upper segment of the kidney prevalently inserts in the bladder inferior and medial to the ureter draining the lower segment of the kidney (Weigert-Meyer rule). These ectopic orifices are prone to ureterocele and/or vesicoureteral reflux. The lower moiety of the completely duplicated system is generally normal. Ureteral duplication also may be bilateral. Triple moiety may be observed. In diagnosis of renal or ureteral displacement, CT scans have replaced lateral views of conventional radiography. In a standard lateral view, the normal renal collecting system should not project anterior to the spine and the ureter stays behind the anterior margin of the vertebral bodies till the level of L4. After this, the ureter lies anterior to the vertebral body by approximately one-fourth the width of the vertebral body (Friedland et al, 1983). In elderly patients with atherosclerotic vessels, ureteral narrowing at the pelvic brim at its crossing to the common iliac vessels may produce a posterior indentation that may appear as an extrinsic filling defect. Dilatation proximal to that point may be differentiated from obstruction by the absence of pelvicalyceal dilatation without delay in emptying on prone or erect films (Friedenberg and Dunbar 1990). Medial displacement of both pelvic ureteral segments might result from retroperitoneal fibrosis or pelvic lipomatosis, or it may appear after abdominoperineal surgery. However, medial displacement and concavity of a single pelvic ureter may result from enlarged hypogastric nodes, a bladder diverticulum, or

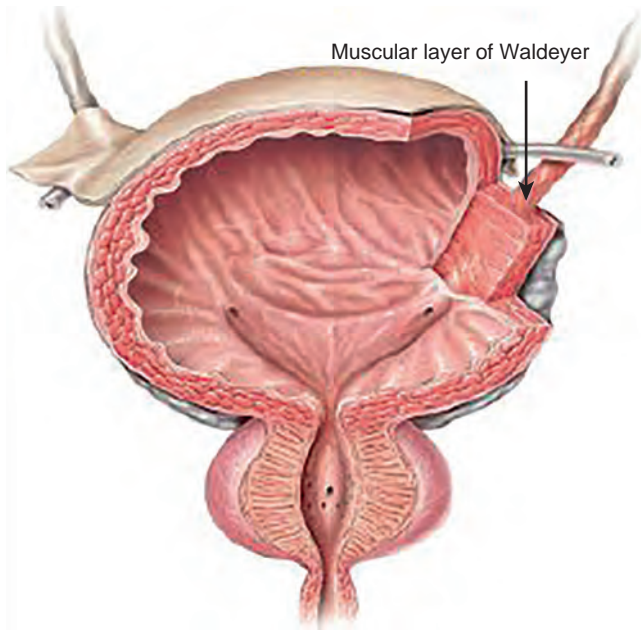


Figure 42-23. Intramural portion of the distal ureter. (From Frober R. Surgery illustrated: surgical atlas, surgical anatomy of the ureter. BJU Int 2007;100:949–65.)

aneurysmal dilatation of the hypogastric artery. Nevertheless, this may be a normal finding in adult women if only the right ureter is affected because of the uterine tilt to the left. In older men, benign prostatic hyperplasia may result in elevation of the bladder floor enough to cause the intramural segment of the ureter to curve superiorly, giving a characteristic “fish hook” or “hockey stick” appearance on excretory urography (Olsson, 1986).

KEY POINTS: RADIOLOGIC ANATOMY OF THE URETER

- It is important to have the patient empty the bladder to evaluate the distal ureter appropriately.
- Radiologically, the ureter is divided into three segments: a proximal portion from UPJ to the sacroiliac joint, a middle portion lying over the sacroiliac joint, and a distal portion from the lower border of that joint to its entrance into the bladder.
- The entire length of the ureter is rarely seen on a single film of the excretory urography because of its peristaltic activity.

Arteries, Veins, and Lymphatic Drainage of the Ureters

The abdominal portion of the ureter is supplied mainly by arterial branches medially from the main renal arteries (Fig. 42-24 on the Expert Consult website). However, this segment may be uncommonly supplied by branches arising from the abdominal aorta or gonadal arteries. These branches approach the ureters medially and divide into ascending and descending branches, forming a longitudinal anastomosis on the ureteral wall. However, despite this anastomotic plexus, ureteral ischemia is not uncommon if these small and delicate ureteral branches are disrupted. Surgeons are trained to handle ureters gently to avoid unnecessary lateral retraction and removing periureteral adventitial tissues containing the blood supply to minimize ureteral ischemia and subsequent stricture. The mid-ureter is supplied by branches arising posteriorly from the common iliac arteries. The blood supply to the distal ureter comes laterally from the superior vesical artery, a branch of the internal iliac artery. Therefore the blood supply of the ureter is medially in the proximal part, posteriorly in the mid-portion, and laterally in the distal portion. Therefore endoureterotomy should be performed laterally in the proximal ureter, anteriorly in the mid-portion, and medially in the distal ureter. Another important surgical caveat is to control the obliterated umbilical artery before mobilizing the most distal aspect of the ureter as it enters the bladder.

Veins draining the abdominal part of the ureters drain into the renal and gonadal veins. **Venous drainage of the mid- and distal ureters is into the common and internal iliac veins.** The lymphatics of the ureter form plexuses within its muscular and adventitial layers. The lymphatics from the left abdominal ureter drain into the left para-aortic lymph nodes, and the lymphatics from the right abdominal ureter drain into the right paracaval and interaortocaval lymph nodes. Lymphatic vessels from the middle part usually drain into the common iliac lymph nodes, whereas lymphatics from its intrapelvic part drain into the common, external, and internal iliac lymph nodes.

KEY POINTS: URETERS

- The course of the ureter begins posterior to the renal artery and continues along the anterior edge of the psoas muscle.
- The gonadal vessels cross anterior to the ureter in this region (*water under bridge*). The ureter next passes over the bifurcation of the common iliacs into the internal and external iliacs.
- The blood supply of the proximal ureter is medially, mid-ureter is posteriorly, and distal ureter is laterally.

Nerve Supply of the Ureter

The ureter receives a rich autonomic nerve supply that originates from the celiac, aortorenal, and mesenteric ganglia, together with the superior and inferior hypogastric (pelvic) plexuses. The sympathetic supply to the ureter arises from the preganglionic fibers of the 11th and 12th thoracic and 1st lumbar segments. Parasympathetic vagal fibers supply the upper part of the ureter via the celiac plexus, and the lower portion is supplied by the sacral segments S2 to S4. Therefore afferent nerves from the upper portion of the ureter reach the spinal cord with the sympathetic fibers between T11 and L1 and those from the lower ureter travel via the pelvic plexus between S2 and S4. These fibers conduct afferent sensory stimuli from the ureters and have a minor, if any, role in the control of ureteral motility. This is because excised portions of the ureter continue to contract without nervous control and denervation of the lower portion of the ureter does not result in reflux. As mentioned earlier, the peristalsis of the ureter originates from pacemakers in the minor calyces. Thus the exact role of autonomic input of the ureters is unclear. Distention of the renal capsule and the collecting system causes stimulation of renal pain fibers that carry signals through the sympathetic nerves, thus resulting in visceral-type referred pain in the flank, groin, or scrotal (labial) regions.

Microscopic Anatomy of the Ureter

The ureter consists of three distinct layers: the innermost is the mucosa, the middle muscular layer is the muscularis, and the outer layer is the adventitia. The mucosa consists of transitional epithelium, which has four to six layers of cells when the ureter is contracted. These cells encircle a large number of junctional complexes containing consistent level of keratin precursors that is responsible for the waterproof property of this layer. The mucosa also contains many longitudinal folds that give the empty ureter a characteristic stellar outline. The epithelium rests on a layer of connective tissue, the lamina propria, which contains the blood vessels and nerve fibers to the ureter (Fig. 42-25 on the Expert Consult website).

The muscular wall of the ureter consists of two longitudinal layers separated by a middle circular layer that may not be distinct from each other, especially in the abdominal segment of the ureter. Mostly, these muscle fibers appear to be spirally arranged by the light microscopy. However, in the distal ureter, the inner spirals are steep and the outer spirals are horizontal, thus appearing as inner longitudinal and outer circular layers in cross section. These smooth muscle layers are contiguous with the smooth muscle covering the minor renal calyces, where the pacemaker is located to initiate the rhythmic peristalsis to deliver urine.

The outermost layer, the adventitia, consists of a dense network of collagen and elastic fibers, including many blood vessels and unmyelinated nerve fibers among them. This layer is continuous proximally with the capsule at the renal pelvis while it is thickened distally by a specialized muscle fibers and fibrous tissue to form the Waldeyer sheath.

In a normal kidney, the UPJ does not differ histologically from the renal pelvis. However, in an obstructed kidney, the longitudinal muscle fibers are significantly increased with more collagen deposits around the muscle fibers in addition to attenuation of muscle bundles, leading to the physiologic obstruction known clinically as UPJO.

Endoscopic Anatomy of the Ureter and Pelvicalyceal System

Once the cystoscope is inside the bladder neck, the trigone can be seen as a raised, smooth triangle. The apex of that triangle is situated at the bladder neck, and its base is formed by the interureteral ridge or Mercier's bar, extending between the two ureteric orifices. The interureteral ridge is more prominent in males than females, and

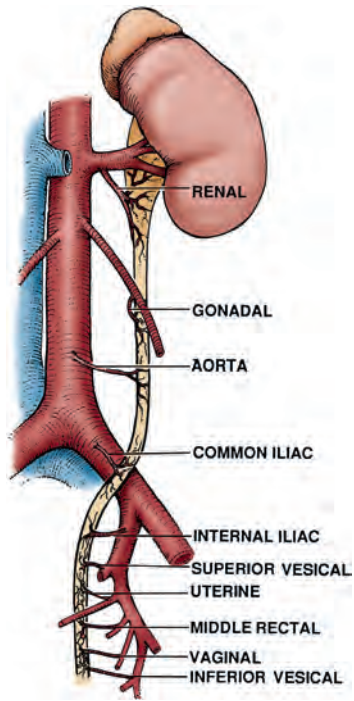


Figure 42-24. Arterial supply of the left ureter.

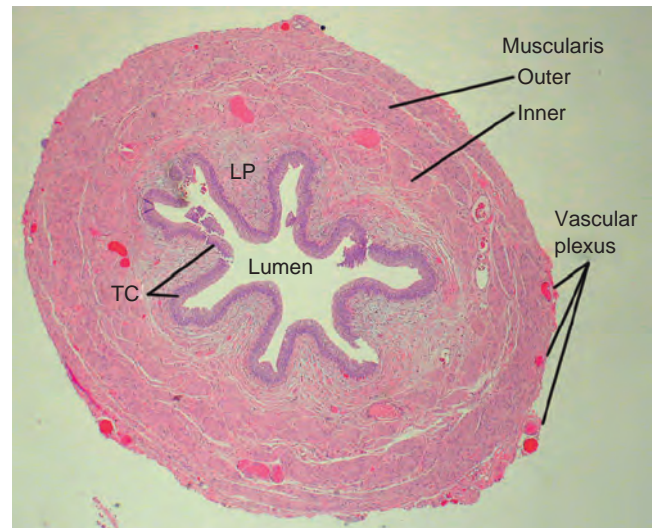


Figure 42-25. Transverse section through the ureter. Inner longitudinal layer is distinguished from outer circular and oblique muscle fibers. The rich vascular supply of the ureter is also demonstrated. LP, lamina propria; TC, transitional epithelium. (Courtesy Dr. Hossein Saboorian.)

the ureteric orifices are symmetrically located along it, approximately 1 to 2 cm from the midline. The trigone is the most vascular part of the bladder and is formed by an extension of the longitudinal muscle fibers of the ureters over the detrusor muscle. Therefore it appears cystoscopically to be more deeply colored than the rest of the bladder.

The normal ureteric orifice may appear as a volcano or a horse-shoe that is prominent and obvious on endoscopy. However, it might look like a slit that can be identified with only meticulous examination. It is pushed out laterally during bladder filling and may be quite variable in position and appearance. In normal bladder, ureteric orifices are usually surrounded by prominent mucosal vessels (Bagley et al, 1985).

The ureteric orifices are classified according to their position or configuration. They are normally located at the medial aspect of the trigone (position A). However, they may be located at the lateral wall of the bladder or at its junction with the trigone (position C) or in between positions A and C (position B) (Lyon et al, 1969). In terms of configuration, grade 0 indicates a normal ureteric orifice that looks like a cone or a volcano. Grades 1, 2, and 3 describe stadium, horseshoe, and golf-hole orifices, respectively. **The higher the grade of the orifice, the higher tendency to be laterally located and to reflux** (Fig. 42-26 on the Expert Consult website).

The intramural ureter represents the narrowest part of the ureter, with an average diameter of 3 to 4 mm. It extends from the ureteric orifice for approximately 1.5 cm, posterolaterally for 0.5 cm, and then obliquely through the detrusor hiatus for approximately 1 cm (Politano, 1972). Being the narrowest ureteral segment, the intramural ureter may need to be dilated before ureteroscopy. The other ureteral narrowing areas at the pelvic brim and UPJ are identified endoscopically by being stenotic and relatively nondistensible. However, they are relatively wider than the intramural segment. They can be easily instrumented with enough pressure from the irrigation fluid. The pulsating iliac vessels could be seen endoscopically as the ureters cross the pelvic brim and angulate posteriorly in the proximal portion.

The proximal ureter goes straight up to the UPJ; the ureter lies on the psoas major muscle, with the appearance of a typical stellate nondistended ureter. The UPJ could be identified easily endoscopically during its frequent opening and closing. The UPJ merges into the wider and more dependent part of the renal pelvis. Of interest, the respiratory movement of the kidney could be seen by endoscopy after passing the relatively fixed UPJ. The kidneys lie on the diaphragm, and thus they are affected by the respiratory movements. **Therefore, during ureteroscopy, the tidal volume could be decreased to minimize renal excursions during respiration.** Moreover, the physiologic ureteral contractions or peristalsis can be observed endoscopically. It is important to wait for the ureter to relax before pushing the ureteroscope to avoid mucosal trauma (Andonian et al, 2008b, 2010b).

The UPJ represents the apex of the funnel-shaped or conical normal renal pelvis. An extrarenal pelvis is usually larger and has longer major calyceal infundibula than an intrarenal pelvis. In the renal pelvis, the flexible ureteroscope first faces the ostia of the major calyces, which look like circular openings separated by carinae. Then the flexible ureteroscope enters a long tubular infundibulum that branches into the minor calyces. These infundibula usually connect the ostia of major calyces with their apex. For a flexible ureteroscope to pass from the axis of the upper ureteral

segment to the axis of the lower infundibulum, it should be deflected 140 (104 to 175) degrees at the ureteroinfundibular angle (Bagley and Rittenberg, 1987).

A circular muscle layer extends around the base of the papilla to help expel urine jets from papillary ducts. The renal papillae appear endoscopically as protruding discs surrounded by calyceal fornices, paler in color than the pink friable epithelium covering the papillae. Each papilla represents the apex of a renal pyramid, receiving the papillary ducts of Bellini that drain the pyramids. These ducts are minute openings that become more dilated and obvious with distal obstruction (Andonian et al, 2008a, 2010a).

KEY POINTS: ENDOSCOPIC ANATOMY

- The trigone is the most vascular part of the bladder and is formed by an extension of the longitudinal muscle fibers of the ureters over the detrusor muscle.
- Both ureteric orifices are rarely seen in a single endoscopic view.
- The interureteral ridge is more prominent in males than females, and the ureteric orifices are symmetrically located along it, approximately 1 to 2 cm from the midline.
- The intramural ureter represents the narrowest part of the ureter, with an average diameter of 3 to 4 mm.
- The extrarenal pelvis is usually larger and has longer major calyceal infundibula than the intrarenal pelvis.
- The renal papillae appear endoscopically as protruding discs surrounded by calyceal fornices, paler in color than the pink friable epithelium covering the papillae.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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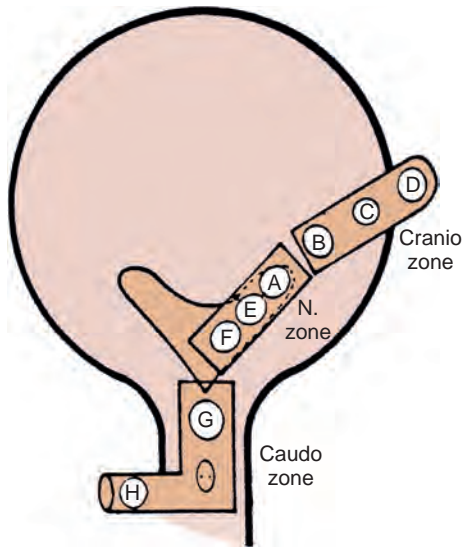


Figure 42-26. Classification of ureteric orifice position. Obstruction usually occurs in the caudo zone, and ureters positioned in the cranio zone are likely to result in reflux. Ureters positioned in the normal (N) zone are associated with normal kidneys. Because of ureteric bud abnormality, renal dysplasia occurs with ureters projecting from both abnormal positions. (From Mackie GC, Stephens FD. Duplex kidneys: a correlation of renal dysplasia with position of the ureteric orifice. *J Urol* 1975;114:274.)

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Cellular Anatomy

Development of the Ureter

Electrical Activity

Contractile Activity

Mechanical Properties

Role of the Nervous System in Ureteral Function

Urine Transport

Pathologic Processes Affecting Ureteral Function

Effect of Age on Ureteral Function

Effect of Pregnancy on Ureteral Function

Effect of Drugs on the Ureter

The function of the ureter is to transport urine from the kidney to the bladder. Under normal conditions, ureteral peristalsis originates with electrical activity at pacemaker sites located in the proximal portion of the urinary collecting system (Bozler, 1942; Weiss et al, 1967; Constantinou, 1974; Gosling and Dixon, 1974; Tsuchida and Yamaguchi, 1977; Zhang and Lang, 1994; Lammers et al, 1996; Weiss et al, 2006; Hurtado et al, 2010). The electrical activity is then propagated distally and gives rise to the mechanical event of peristalsis, ureteral contraction, which propels the bolus of urine distally. Efficient propulsion of the urinary bolus depends on the ureter's ability to completely coapt its walls (Woodburne and Lapidus, 1972). Urine passes into the bladder by way of the ureterovesical junction (UVJ), which, under normal conditions, permits urine to pass from the ureter into the bladder, but not from the bladder into the ureter.

CELLULAR ANATOMY

The primary functional anatomic unit of the ureter is the ureteral smooth muscle cell. The cell is extremely small, approximately 250 to 400 μm in length and 5 to 7 μm in diameter. The nucleus, which is separated from the remainder of the cell by a nuclear membrane, is ellipsoid and contains a darkly staining body, the nucleolus, and the genetic material of the cell. Surrounding the nucleus is the cytoplasm or sarcoplasm, which contains the structures involved in cell function. Frequently in close relation to the nucleus, mitochondria in the cytoplasm perform many of the nutritive functions of the cell. Endoplasmic reticulum or sarcoplasmic reticulum (SR) dispersed in the cytoplasm serves as Ca^{2+} storage sites.

Dispersed in the sarcoplasm are the contractile proteins, actin and myosin. Depending on the local calcium ion (Ca^{2+}) concentration, they interact to produce contraction or relaxation. Any process that leads to a significant increase in the Ca^{2+} concentration in the region of the contractile proteins results in contraction; conversely, any process that leads to a significant decrease in the Ca^{2+} concentration in the region of the contractile proteins results in relaxation. Actin is dispersed throughout the sarcoplasm in hexagonal clumps and is interspersed with the less numerous clumps of more deeply staining myosin. Dark bands along the cell surface are

referred to as *attachment plaques*. Along with dense bodies dispersed in the cytoplasm, they serve as attachment devices for the actin.

Around the periphery of the cell are numerous cavitory structures, some of which open to the outside of the cell and are referred to as *caveolae*. These caveolae contain a cytoskeletal protein, caveolin, and a variety of signal transduction molecules and receptors for growth factors and cytokines (William and Lisanti, 2004). A double-layer cell membrane surrounds the cell. The inner plasma membrane surrounds the entire cell, but the outer basement membrane is absent at areas of close cell-to-cell contact, referred to as *intermediate junctions*.

DEVELOPMENT OF THE URETER

The ureter, a 25- to 30-cm tube extending from the renal pelvis to the bladder, arises as an outpouching from the mesonephric duct. This begins on embryonic day (E) 10.5 in mice and E28 in humans. Signals from the metanephric mesenchyme, stroma, and angioblasts induce the ureteral bud to arise from the mesonephric duct, invade the metanephric mesenchyme, and undergo branching. The nephric (mesonephric or wolffian) duct cells express a number of surface receptors including RET, FGFR, AT2R, and ALK (Fig. 43-1). RET signaling is induced by glial cell line-derived neurotrophic factor (GDNF), derived from adjacent metanephrogenic mesenchyme (Pepicelli et al, 1997; Sainio et al, 1997; Shakya et al, 2005), and leads to a rearrangement of the nephric duct cells (Woolf and Davies, 2013). This movement of cells is regulated by the transcription factors ETV4 and ETV5 (Kuure et al, 2010; Yosypiv, 2014) (see Fig. 43-1). GDNF-RET signaling is a major pathway in the development of the ureter (Woolf and Davies, 2013). GDNF signals through the Ret receptor tyrosine kinase (Vega et al, 1996) and leads to activation of ERK/PI3K/PLC, which results in increased phosphatidylinositol 3-kinase (PI3K) activity and Akt/PKB phosphorylation (Tang et al, 2002). The expression of GDNF and Ret is activated by a transcription factor present in the metanephric mesenchyme, paired box 2 (Pax-2) (Brophy et al, 2001; Clarke et al, 2006), which is increased by AT2 (Zhang et al, 2004). A number of other growth factors including transforming growth factor- β (TGF- β), hepatocyte growth factor (HGF), and fibroblast growth factors (FGFs) FGF-1, FGF-2, FGF-7, and FGF-10; transcription factors including Foxd1, Wnt11, and Spry1; and matrix molecules such as heparan sulfate

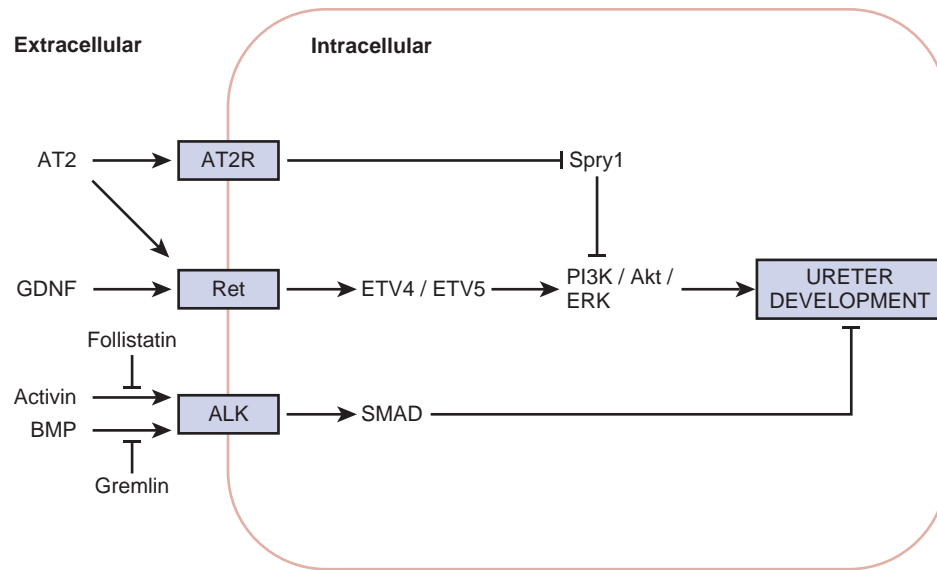


Figure 43-1. Schematic representation of selected pathways involved in ureter development.

proteoglycans, laminins, integrins, and matrix metalloproteinases (MMPs) (e.g., MMP-9) are involved in stimulation or inhibition of growth and branching of the ureteral bud (Davies et al, 1995; Mendelsohn et al, 1999; Qiao et al, 1999; Pohl et al, 2000; Davies, 2001; Qiao et al, 2001; Takemura et al, 2002; Majumdar et al, 2003; Sakurai, 2003; Bush et al, 2004; Chen et al, 2004; Basson et al, 2006).

The nephric ducts also express ALK receptors, which are activated by activins and bone morphogenetic proteins (BMPs) (TGF- β family members), leading to activation of SMADs, which inhibits ureteric bud outgrowth and ureteral development (Mae-shima et al, 2006). Activin A inhibits GDNF-induced ureteral bud formation, and this is accompanied by inhibition of cell proliferation, reduced expression of Pax-2, and decreased phosphorylation of PI3K and mitogen-activated protein (MAP) kinase in the wolffian duct. The tip of each ureteral bud is capable of inducing adjacent metanephric mesenchyme to undergo mesenchymal-to-epithelial transition (MET) with the formation of the nephron (Ekblom, 1989; Shah et al, 2004). Antagonists of the antibranching factors activin and BMP-4 are Gremlin-1 and follistatin, respectively (Woolf and Davies, 2013).

Programmed cell death, or apoptosis, is involved in branching of the ureteric bud and subsequent nephrogenesis. Inhibitors of caspases, which are involved in the apoptotic signaling pathway, inhibit ureteral bud branching (Araki et al, 1999). During development, the ureteral lumen is obliterated, and then it recanalizes (Russo-Gil et al, 1975; Alcaraz et al, 1991). It appears that angiotensin (AT2) acting through the AT2 receptor is involved in the recanalization process (Yerkes et al, 1998) and in the inhibition of aberrant ureteral budding (Oshima et al, 2001). Knockout mice for the *atr2* gene have congenital anomalies of the kidney and urinary tract, including duplicated collecting systems with a hydronephrotic upper pole moiety, multicystic dysplastic kidneys, megaureters, and ureteropelvic junction (UPJ) obstructions. Mutant mice lacking AT2 type 1 receptors fail to develop a renal pelvis and lack ureteral peristaltic activity (Miyazaki et al, 1998). AT2 acting via AT2 type 1 receptors also is involved in ureteric bud cell branching, a process that depends on phosphorylation of the EGF receptor (Iosipiv and Schroeder, 2003; Yosypiv et al, 2006) and can stimulate in vitro branching morphogenesis by directly acting on the ureteric bud (Song et al, 2011). In addition, AT2 induces the expression of the GDNF/c-Ret/Wnt11 pathway and represses Spry1 during ureteric bud branching (Yosypiv et al, 2008; Song et al, 2010). Ureteric branching also is promoted by AT2-induced signaling through PI3K/Akt and ERK (Song et al, 2011; Yosypiv, 2014). Because Spry1

inhibits ERK, this may be one mechanism to enhance c-Ret signaling and stimulate ureteric branching (Yosypiv et al, 2008; Song et al, 2010). Some GDNF targets upregulated by AT2 include transcription factors (Etv4, Etv5), signaling molecules (Vsn11), and receptors (Crlf1) (Song et al, 2011).

Another player in regulating normal ureter development is Brg1 (or SMARCA4). Brg1 is an epigenetic regulator and is part of the switch/sucrose nonfermentable (SWI/SNF) chromatin-remodeling complex. Global loss of Brg1 results in embryonic lethality (Bultman et al, 2000). Brg1 has been shown to be upstream of p63, peroxisome proliferator-activated receptor- γ (PPAR- γ), and sonic hedgehog. Ablation of Brg1 leads to ureter malformation (Weiss et al, 2013).

Calcineurin, a Ca^{2+} -dependent serine/threonine phosphatase, also appears to be an essential signaling molecule in urinary tract development. Mutant mice in which calcineurin function is removed are noted to have reduced proliferation of smooth muscle and mesenchymal cells in the developing urinary tract with abnormal development of the renal pelvis and ureter with resultant defective pyeloureteral peristalsis (Chang et al, 2004).

ELECTRICAL ACTIVITY

The electrical properties of all excitable tissues depend on the distribution of ions on both the inside and the outside of the cell membrane and on the relative permeability of the cell membrane to these ions (Hodgkin, 1958). The ionic basis for electrical activity in ureteral smooth muscle has not been fully described; however, many of its properties resemble those in other excitable tissues.

Resting Potential

When a ureteral muscle cell is in a nonexcited or resting state, the electrical potential difference across the cell membrane, the transmembrane potential, is referred to as the *resting membrane potential* (RMP). The RMP is determined primarily by the distribution of potassium ions (K^+) across the cell membrane and by the permeability of the membrane to K^+ (Hendrickx et al, 1975). In the resting state, the K^+ concentration on the inside of the cell is greater than that on the outside of the cell—that is, K^+_i is greater than K^+_o —and the membrane is preferentially permeable to K^+ . Because of the tendency for the positively charged K^+ ions to diffuse from the inside of the cell, where they are more concentrated, to

the outside of the cell, where they are less concentrated, an electrical gradient is created, with the inside of the cell membrane being more negative than the outside (Fig. 43-2A). The electrical gradient that is formed tends to oppose the further movement of K^+ outward across the cell membrane along its concentration gradient, and an equilibrium is reached.

If the membrane in the resting state were exclusively permeable to K^+ , the measured RMP of the ureteral smooth muscle cell would approximate -90 mV, the K^+ equilibrium potential, as predicted by the Nernst equation:

$$E_k = -RT/nF \ln(K^+)_i / (K^+)_o$$

where E_k is the potential difference attributable to the concentration difference of K^+ across the cell membrane, R is the molar gas constant, T is the absolute temperature, n is the number of moles of K^+ , and F is the Faraday constant (Nernst, 1908). However, in the ureter and in other smooth muscles, the RMP is considerably less than the K^+ equilibrium potential, with values of -33 to -70 mV, the inside of the cell being negative with respect to the outside (Kuriyama et al, 1967). Studies from single isolated ureteral cells show spontaneous transient hyperpolarizations with the RMP transiently becoming more negative (Imaizumi et al, 1989). This phenomenon appears to be the result of spontaneous release of

Ca^{2+} from the SR with activation of tetraethylammonium (TEA) and charybdotoxin-sensitive Ca^{2+} -dependent K^+ channels ($I_{K[Ca]}$). Although the low resting potential of ureteral cells may be explained in part by a relatively small resting K^+ conductance (Imaizumi et al, 1989), it also may be a result of the contribution of other ions.

One such ion that could account for the relatively low RMP of the ureter and other smooth muscles is the sodium ion (Na^+) (Kuriyama, 1963). In the resting state, the Na^+ concentration on the outside of the cell membrane is greater than that on the inside—that is, Na^+_o is greater than Na^+_i . If the resting membrane were somewhat permeable to Na^+ , both the concentration and the electrical gradient would support an inward movement of Na^+ across the cell membrane, with a resultant decrease in the electronegativity of the inner surface of the cell membrane (Fig. 43-2B).

If such an inward movement of Na^+ went unchecked, the RMP would be expected to decrease to a level lower than that actually observed, and the concentration gradient for Na^+ might become reversed. To maintain a steady-state ion distribution across the cell membrane with K^+_o less than K^+_i and Na^+_o greater than Na^+_i and to prevent the transmembrane potential from becoming lower than the measured ureteral RMP, an active mechanism capable of extruding Na^+ from within the cell against a concentration and electrochemical gradient is required (Fig. 43-2C). Such an outward Na^+ pump that is coupled with an inward movement of K^+ derives its energy requirements from the dephosphorylation of adenosine triphosphate (ATP) (Casteels, 1970). Na^+ - Ca^{2+} exchange also may play a role in Na^+ extrusion, especially when the Na^+ pump is inhibited (Aickin, 1987; Aickin et al, 1987; Lamont et al, 1998).

The dynamic processes illustrated in Figure 43-2 enable the ureter in its resting state to maintain a relatively low RMP. In addition to the mechanisms described, the distribution of chloride ions (Cl^-) across the cell membrane and the relative permeability of the membrane to Cl^- may affect the maintenance of the RMP in the ureter and other smooth muscles (Kuriyama, 1963; Washizu, 1966). Activation of Ca^{2+} -activated Cl^- channels ($ClCa$) also can decrease the membrane potential and therefore depolarizes the membrane (Verkman and Galietta, 2009).

Action Potential

The transmembrane potential of an inactive or resting ureteral cell remains stable until it is excited by an external stimulus (electric, mechanical, or chemical) or by conduction of electrical activity (action potential) from an already excited adjacent cell. When a ureteral cell is stimulated, depolarization occurs, with the inside of the cell membrane becoming less negative than it was before stimulation. If a sufficient area of the cell membrane is depolarized rapidly enough to reach a critical level of transmembrane potential, referred to as the **threshold potential**, a regenerative depolarization, or action potential, is initiated.

The changes that occur are diagrammatically depicted in Figure 43-3. If a stimulus is very weak, as shown by arrow *a*, the transmembrane potential may remain unchanged. A slightly stronger, yet subthreshold, stimulus may result in an abortive displacement of the transmembrane potential, but not to such a degree that an action potential is generated (arrow *b*). If the stimulus is strong enough to decrease the transmembrane potential to the threshold potential, the cell becomes excited and produces an action potential (arrow *c*). The action potential, which is the primary event in the conduction of the peristaltic impulse, has the capability to act as the stimulus for excitation of adjacent quiescent cells and through a complicated chain of events gives rise to the ureteral contraction.

When the ureteral cell is excited, its membrane loses its preferential permeability to K^+ and becomes more permeable to Ca^{2+} ions that move inward across the cell membrane primarily through fast L-type Ca^{2+} channels and give rise to the upstroke of the action potential (Fig 43-4A) (Kobayashi, 1965; Kuriyama and Tomita, 1970; Imaizumi et al, 1989; Lang, 1989, 1990; Sui and Kao, 1997a, 1997b; Smith et al, 2002). L-type Ca^{2+} channels are inhibited by the calcium channel blocker nifedipine and by

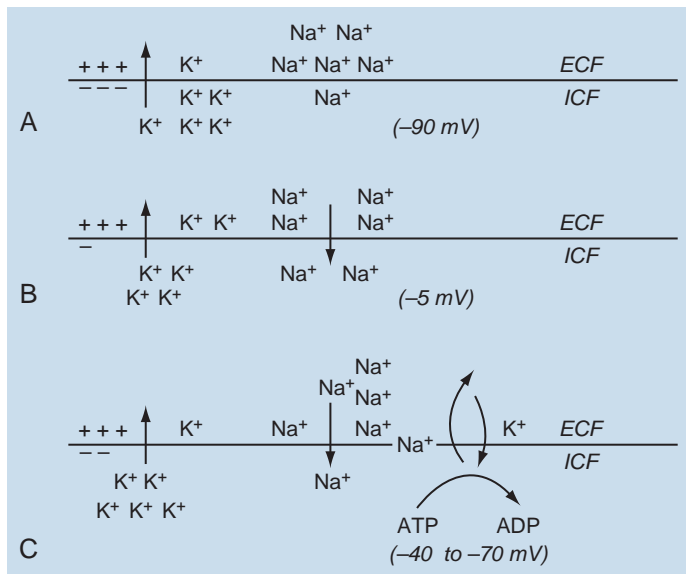


Figure 43-2. Ionic basis for the resting membrane potential (RMP) in smooth muscle. In the resting state, the K^+ concentration inside the cell is greater than the K^+ concentration outside the cell, and the Na^+ concentration outside the cell is greater than the Na^+ concentration inside the cell. A, Electrochemical changes that would occur if the membrane were solely permeable to potassium. Potassium would diffuse from the inside of the cell, where it is more concentrated, to the outside of the cell, where it is less concentrated. The outward movement of the positively charged K^+ ions would make the inside of the cell membrane negative with respect to the outside of the cell membrane. B, Electrochemical changes that would occur if the resting membrane were also permeable to sodium. An inward movement of Na^+ along its concentration gradient would make the inside of the cell membrane less negative with respect to the outside of the cell membrane than is depicted in A. C, Pump mechanism for extruding Na^+ from within the cell against concentration and electrochemical gradients. Inward movement of K^+ is coupled with outward movement of Na^+ . This mechanism helps to maintain a steady state of ion distribution across the cell membrane and a stable RMP. ECF, extracellular fluid; ICF, intracellular fluid. (From Weiss RM. Ureteral function. *Urology* 1978;12:114.)

cadmium (Cd^{2+}) and are potentiated by barium (Ba^{2+}). As the positively charged Ca^{2+} ions move inward across the cell membrane, the inside of the membrane becomes less negative with respect to the outside and may even become positive at the peak of the action potential, a state referred to as *overshoot*. Na^{+} ions also may play a role in the upstroke of the ureteral action potential (Kobayashi, 1964, 1965; Muraki et al, 1991). The rate of rise of the upstroke of the ureteral action potential is relatively slow, 1.2 ± 0.06 V/sec in the cat (Kobayashi, 1969). This compares with a 610 V/sec rate of rise in dog cardiac Purkinje fibers (Draper and Weidmann, 1951) and a 740 V/sec rate of rise in skeletal muscle (Ferroni and Bianchi,

1965). The slow rate of upstroke rise of the ureteral action potential accounts for the slow conduction velocity in the ureter.

After reaching the peak of its action potential, the ureter maintains its potential for a period of time (plateau of the action potential) before the transmembrane potential returns to its resting level (repolarization) (Kuriyama et al, 1967). The plateau phase of the guinea pig action potential is superimposed with multiple oscillations, a phenomenon not observed in the rat, rabbit, or cat (Fig. 43-5) (Bozler, 1938). The plateau phase appears to depend on the persistence of an inward Ca^{2+} current and on Na^{+} influx through a voltage-dependent Na^{+} channel (see Fig 43-4A) (Kuriyama and Tomita, 1970; Imaizumi et al, 1989; Sui and Kao, 1997a). Also involved in the plateau formation is the maintenance of depolarization by an inward calcium-dependent chloride current ($I_{\text{Cl}(\text{Ca})}$) which is countered by outward voltage-gated and Ca^{2+} -activated K^{+} currents (K_{Ca}) (Smith et al, 2002). There are species differences in the ionic currents involved in the formation of the action potential, with the Ca^{2+} -activated chloride current being present in the rat but not in the guinea pig ureter. The inward Cl^{-} current can be inhibited by niflumic acid and by Ba^{2+} (Smith et al, 2002). The oscillations on the plateau of the guinea pig action potential appear to depend on the repetitive activation of an inward Ca^{2+} current (Kuriyama and Tomita, 1970) and of a Ca^{2+} -dependent outward K^{+} current (Imaizumi et al, 1989). Prolongation of the inward calcium current and the duration of the action potential correlates with an increased force of contraction (Burdyga and Wray, 1999b).

The activation of a Ca^{2+} -dependent K^{+} current that is involved in repolarization is mainly a result of Ca^{2+} release from the endoplasmic reticulum that is triggered by the influx of extracellular Ca^{2+} through voltage-dependent Ca^{2+} channels. The increase in intracellular Ca^{2+} concentration during the upstroke and plateau of the action potential finally may activate the outward Ca^{2+} -dependent K^{+} current ($I_{\text{K}(\text{Ca})}$) to such a degree that repolarization occurs with return of the transmembrane potential to its resting level (see Fig 43-4A) (Imaizumi et al, 1989; Sui and Kao, 1997c). The $I_{\text{K}(\text{Ca})}$ is sensitive to inhibition by TEA. TEA increases the amplitude and duration of in vitro ureteral contractions (Floyd et al, 2008). A voltage-dependent, Ca^{2+} insensitive outward K^{+} current (I_{TO}) also

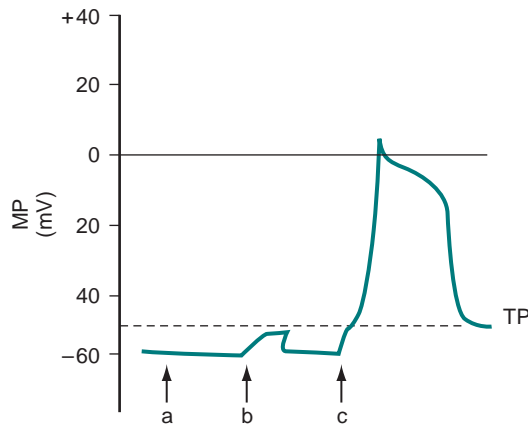


Figure 43-3. Response of ureteral transmembrane potential to stimuli. At arrow a, a weak stimulus is applied that does not alter the resting membrane potential (MP). At arrow b, a stimulus is applied that decreases the transmembrane potential but not to the level of the threshold potential (TP) (subthreshold stimulus). At arrow c, a stimulus is applied that decreases the transmembrane potential to TP, and an action potential is initiated (suprathreshold stimulus). (From Weiss RM. Ureteral function. *Urology* 1978;12:114.)

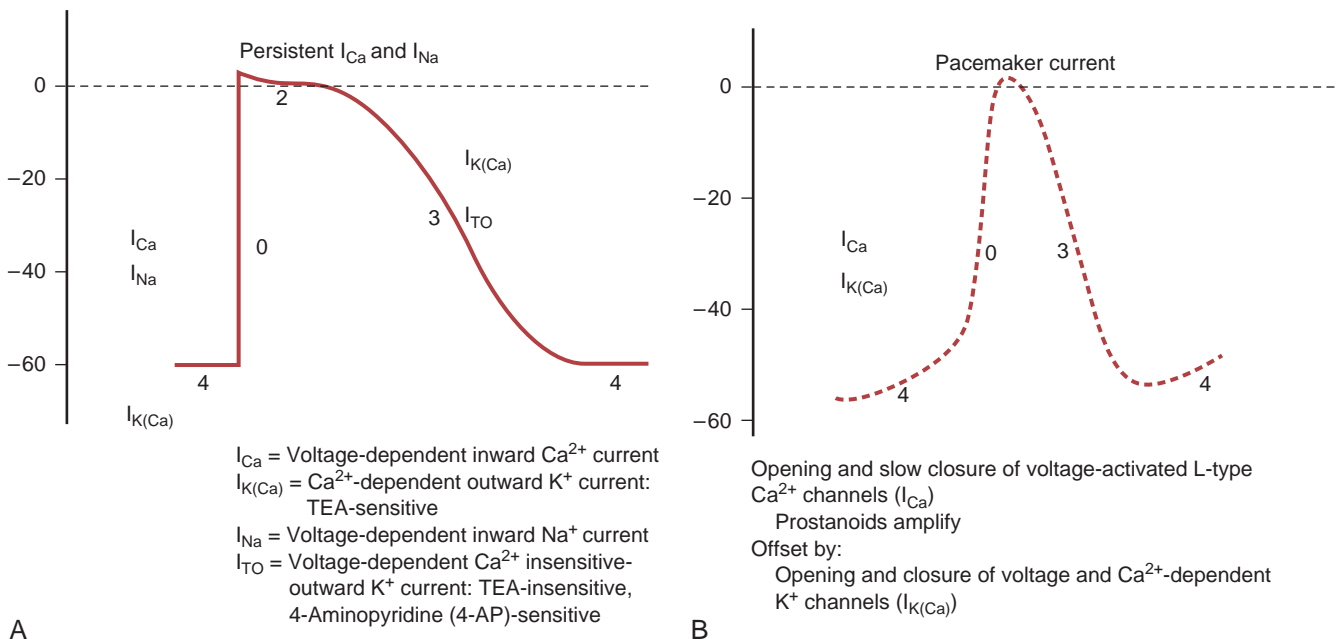


Figure 43-4. Schematic representation of ionic currents in A, nonpacemaker (solid line) and B, pacemaker (dashed line) action potentials: 0, upstroke or depolarization phase; 2, plateau phase; 3, repolarization phase; and 4, resting potential of the nonpacemaker cell and spontaneous depolarization phase of the pacemaker cell. A spontaneous decrease in the transmembrane potential of pacemaker cells accounts for their spontaneous activity. TEA, tetraethylammonium.

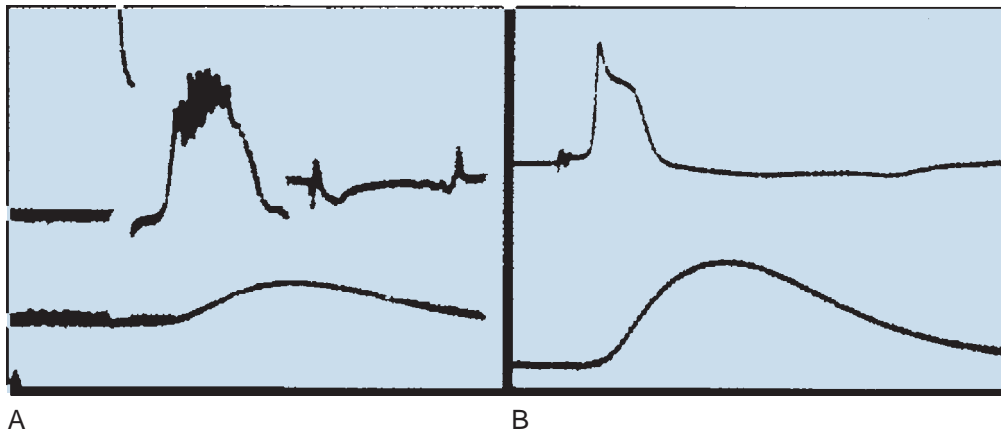


Figure 43-5. Intracellular recordings of ureteral action potentials (*upper tracings*) and isometric recordings of contractions (*lower tracings*) in response to electric stimuli. Action potentials precede contractions. **A**, Guinea pig ureter; oscillations on the plateau of the action potential. **B**, Cat ureter; no oscillations on the plateau of the action potential. (From Weiss RM. Ureteral function. *Urology* 1978;12:114.)

appears to be involved in the repolarization (Lang, 1989; Imaizumi et al, 1990). These currents are TEA insensitive and 4-aminopyridine (4-AP) sensitive. In the rat but not the guinea pig ureter there is a late TEA-, Cd^{2+} -, and Ca^{2+} -insensitive outward K^+ current that also is involved in the repolarization process. The duration of the action potential in the cat ranges from 259 to 405 msec (Kobayashi and Irisawa, 1964).

In summary, the RMP of the ureteral cell is approximately -33 to -70 mV and is determined primarily by the distribution of K^+ ions across the cell membrane and the relatively selective permeability of the resting cell membrane to K^+ . When excited by a suprathreshold stimulus, the membrane becomes less permeable to K^+ and more permeable to Ca^{2+} , which moves inward across the cell membrane and provides the ionic mechanism for the development of the upstroke of the action potential. After reaching the peak of its action potential, the membrane maintains a depolarized state—plateau of the action potential—for a period of time before the membrane potential of the activated cell returns to its resting level (repolarization). The plateau appears to be related to a persisting inward Ca^{2+} current and to an influx of Na^+ . Repolarization of the membrane is related to a renewed increase in permeability to K^+ .

Pacemaker Potentials and Pacemaker Activity

Electrical activity arises in a cell either spontaneously or in response to an external stimulus. If the activity arises spontaneously, the cell is referred to as a *pacemaker cell*. Pacemaker cells differ from nonpacemaker cells in that their transmembrane resting potential is lower (less negative) than that of nonpacemaker cells (Lang and Zhang, 1996) and does not remain constant but rather undergoes a slow spontaneous depolarization (see Fig. 43-4B). If the spontaneously changing membrane potential reaches the threshold potential, the upstroke of an action potential occurs. The ionic conduction underlying pacemaker activity in the upper urinary tract is caused by the opening and slow closure of voltage-activated L-type Ca^{2+} channels (Santicioli et al, 1995a). This is opposed by the opening and closure of voltage- and Ca^{2+} -dependent K^+ channels. It has been suggested that prostaglandins (PGs) and excitatory tachykinins released from sensory nerves help maintain autorhythmicity in the upper urinary tract through maintenance of Ca^{2+} mobilization (Lang et al, 2002a). Tetrodotoxin and blockers of the autonomic nervous system, both parasympathetic and sympathetic, have little effect on peristalsis, suggesting that autonomic neurotransmitters have little role in maintaining pyeloureteral motility (Lang et al, 2001, 2002b). Changes in the

frequency of action potential development may result from a change in the level of the threshold potential, a change in the rate of slow spontaneous depolarization of the resting potential, or a change in the level of the resting potential.

Gosling and Dixon (1971, 1974) provided morphologic evidence of specialized pacemaker tissue in the proximal portion of the urinary collecting system and described species differences. In species with a multicalyceal system, such as the pig, sheep, and human, the pacemaker cells are located near the pelvicalyceal border (Dixon and Gosling, 1973). In species with an unicalyceal system, such as the dog, cat, rat, rabbit, and guinea pig, the pacemaker cells extend from the pelvicalyceal border to the UPJ. These atypical smooth muscle cells that give rise to pacemaker activity, in contrast to typical smooth muscle cells, have less than 40% of their cellular area occupied by contractile elements and demonstrate sparse immunoreactivity for smooth muscle and actin (Klemm et al, 1999; Lang et al, 2001). These atypical smooth muscle spindle-shaped cells are 90 to 230 μm in length, and their electrical activity consists of simple waveforms of alternating depolarizing and repolarizing phases that occur at a relatively rapid frequency of 8 to 15 per minute (Fig. 43-6A) (Tsuchida and Suzuki, 1992; Klemm et al, 1999). Pacemaker potentials have a lower RMP, a slower rate of rise, and a lower amplitude than action potentials recorded from nonpacemaker cells. In the guinea pig these atypical, presumably pacemaker, cells comprise more than 80% of the cells at the pelvicalyceal junction and about 15% of the cells in the proximal renal pelvis but are not present in the distal renal pelvis or ureter (Klemm et al, 1999). Electrical recordings correlate with histologic findings in that pacemaker potentials were not observed in the distal renal pelvis or ureter (Klemm et al, 1999).

Driven action potentials that fire at lower frequency (three to five per minute) than pacemaker potentials are recorded from longer (150 to 400 μm) spindle-shaped typical smooth muscle cells (Fig. 43-6B) (Klemm et al, 1999). Most muscle cells of the ureter (100%), distal renal pelvis (97.5%), and proximal renal pelvis (83%) are typical nonpacemaker smooth muscle cells with typical action potentials. Lang and colleagues (1998) described fibroblast-like cells resembling the interstitial cells of Cajal (ICCs), which serve as pacemaker cells in the intestine, in the proximal portion of the guinea pig renal pelvis. These ICC-like cells are irregularly shaped with oval nuclei and many branching interconnecting processes and contain numerous mitochondria, caveolae, and prominent endoplasmic reticulum. The ICC-like cells in the guinea pig are not immunoreactive for α -smooth muscle actin (α -SMA), which is present in typical smooth muscle cells, or for c-KIT, a tyrosine kinase receptor that is expressed in intestinal ICC pacemaker cells (Klemm

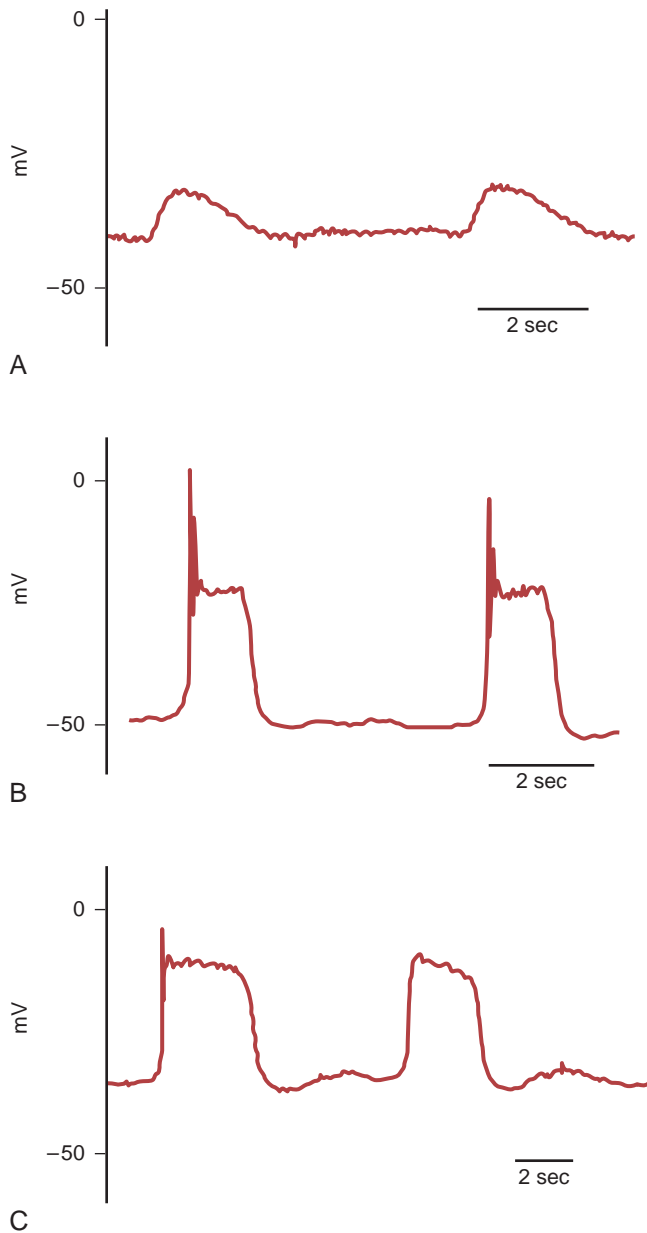


Figure 43-6. Action potentials in the upper urinary tract of the guinea pig. **A**, Pacemaker potentials. **B**, Driven action potentials. **C**, Intermediate action potentials. (Modified from Klemm MF, Exintaris B, Lang RJ. Identification of the cells underlying pacemaker activity in the guinea pig upper urinary tract. *J Physiol* 1999;519:867.)

et al, 1999). The immunoreactivity to c-KIT appears to be species specific because ICC-like cells that are immunoreactive to antibodies raised against the *c-KIT* proto-oncogene are present in the upper urinary tract of a number of mammals (Lang and Klemm, 2005; Metzger et al, 2005). Electrical recordings from these cells demonstrate action potentials with properties intermediate to pacemaker and driven action potentials. Intermediate action potentials in the guinea pig have a single spike, a plateau without the superimposed spikes seen in driven action potentials, and a rapid repolarization phase (Fig. 43-6C). Intermediate action potentials are noted in 11% to 17% of cells at the pelvicalyceal junction and the proximal and distal renal pelvis (Lang et al, 2002b). These ICC-like cells in the upper urinary tract do not appear to be primary pacemaker cells but rather may provide for preferential conduction of electrical signals from pacemaker cells to typical smooth muscle cells of

the renal pelvis and ureter (Klemm et al, 1999). In the mouse UPJ, c-KIT-positive ICC-like cells have been identified that show high-frequency spontaneous transient inward currents (STICs) that often occur in bursts and sum to produce long-lasting large inward currents (Lang et al, 2007b). It is postulated that in the absence of a proximal pacemaker, these ICC-like cells could act as pacemaker cells and trigger contractions in adjacent smooth muscle cells in the UPJ. Thus, both atypical smooth muscle cells and ICC-like cells may play a pacemaker role in the initiation and propagation of pyeloureteric peristalsis (Lang et al, 2006; Lang et al, 2007a).

c-KIT is a tyrosine kinase receptor that promotes cell migration and proliferation of melanoblasts, hematopoietic progenitors, and primordial germ cells. Mice expressing mutant inactivating c-KIT alleles lack intestinal ICCs and have abnormal intestinal peristalsis and develop bowel obstruction, showing that c-KIT is important in the development of pacemaker activity and peristalsis of the gut (Der-Silaphet et al, 1998). Pezzone and colleagues (2003) identified c-KIT-positive cells in the mouse ureter. They suggested that the difference from previous studies in the guinea pig upper urinary tract in which c-KIT positivity was not identified in ICC-like cells (Klemm et al, 1999) may have been caused by species differences, the c-KIT antibody used, and/or the fixation methods. c-KIT expression was noted to be upregulated in the embryonic murine ureter before its development of unidirectional peristaltic contractions (David et al, 2005). Incubation of isolated cultured embryonic murine ureters with antibodies that neutralize c-KIT activity altered ureteral morphology and inhibited unidirectional peristalsis. These data suggest that c-KIT-containing cells, which are most probably ICC-like cells, have an important role in pyeloureteric peristalsis. c-KIT-positive cells have been identified in the human ureter (Metzger et al, 2004; van der Aa et al, 2004) and in the human UPJ (Solari et al, 2003). In the presence of obstruction, c-KIT-positive ICC-like cells at the UPJ have been reported to be decreased (Solari et al, 2003; Yang et al, 2009) or increased (Koleda et al, 2012).

More recently, hyperpolarization-activated cation-3 (HCN3) channels were shown to be expressed at the pelvis-kidney junction and to play a role in the development of pacemaker activity. Uncoordinated peristalsis was demonstrated in renal pelvis-ureter explants that were treated with an HCN3 channel blocker (Hurtado et al, 2010). Furthermore, it has been shown that hedgehog signaling controls KIT and HCN3 expression and that the hedgehog signaling pathway is required for the development of pacemaker function and coordinated peristalsis in the mouse ureter (Cain et al, 2011). Inhibition of either c-KIT or HCN3 results in impaired ureteral peristaltic activity, suggesting that both are required for normal ureteral function.

Bolzler (1942), using small extracellular surface electrodes, demonstrated the characteristic slow spontaneous depolarization of pacemaker-type fibers in the proximal portion of the isolated ureter of a unicalyceal upper collecting system. In a multicalyceal kidney, Morita and associates (1981), using extracellular electrodes, recorded low-voltage potentials that appeared to be pacemaker potentials from the border of the pig minor calyces and the major calyx, with the contraction rhythm varying between each calyx. Multiple pacemakers fire simultaneously as coupled oscillators or individually as pacemaker activity shifts from one site to another along the renal pelvis of the unicalyceal kidney or the pelvicalyceal border of the multicalyceal pig and sheep kidney (Golenhofen and Hannappel, 1973; Constantinou et al, 1977; Constantinou and Yamaguchi, 1981; Lammers et al, 1996).

Although the primary pacemaker for ureteral peristalsis is located in the proximal portion of the collecting system, other areas of the ureter may act as latent pacemakers. Under normal conditions, the latent pacemaker regions are dominated by activity arising at the primary pacemaker sites. When the latent pacemaker site is freed of its domination by the primary pacemaker, it, in turn, may act as a pacemaker. To demonstrate latent pacemaker sites, Shiratori and Kinoshita (1961) transected the in vivo dog ureter at various levels. Before transection, peristaltic activity arose proximally from the primary pacemaker. When the ureter was transected at the

UPJ, antiperistaltic waves of lower frequency than the previous normoperistaltic waves originated from the UVJ. Division of the ureter at the UVJ did not affect the normoperistaltic waves. After division of the mid-ureter, the normoperistaltic waves in the upper segment remained unchanged, and the lower segment demonstrated antiperistaltic waves, which originated at the UVJ at a frequency less than that of the normoperistaltic waves in the upper segment. Thus, cells at the UVJ of the dog may act as pacemaker cells when freed of control from the primary proximally located pacemaker. Latent pacemaker cells are present throughout the ureter (Imaizumi et al, 1989; Meini et al, 1995).

Propagation of Electrical Activity

Excitable cells possess resistive and capacitive membrane properties similar to those of a cable or core conductor. The transverse resistance of the membrane is higher than the longitudinal resistance of the extracellular or intracellular fluid; this allows current resulting from a stimulus to propagate along the length of the fibers. The spread of current is referred to as *electrotonic spread* (Hoffman and Crane, 1960). The space constant (λ) determines the degree to which the electrotonic potential dissipates with increasing distance from an applied voltage. In a cable, this relation is expressed by

$$P = P_0 e^{-X/\lambda}$$

where X is the distance from the applied voltage, P is the displacement of the membrane potential at X , P_0 is the displacement of the membrane potential at the site of the applied voltage, e is the base of the natural logarithm, and λ is the space constant. Thus, the electrotonic potential decreases by $1/e$ in one space constant. The space constant of the guinea pig ureter as measured by extracellular stimulation is 2.5 to 3 mm (Kuriyama et al, 1967).

The time constant τ_m is expressed by

$$\tau_m = RC$$

where R is the membrane resistance and C is the membrane capacity. The time constant τ_m signifies that a small displacement of potential is decreased by $1/e$ of its value in one τ_m . The time constant of the guinea pig ureter as measured by extracellular stimulation is 200 to 300 msec (Kuriyama et al, 1967).

The ureter acts as a **functional syncytium**. Engelmann (1869, 1870) showed that stimulation of the ureter produces a contraction wave that propagates proximally and distally from the site of stimulation. Under normal conditions, electrical activity arises proximally and is conducted distally from one muscle cell to another across areas of close cellular apposition referred to as *intermediate junctions* (Uehara and Burnstock, 1970; Libertino and Weiss, 1972). The similarity of these close cellular contacts to nexuses, which have been shown to be low-resistance pathways for cell-to-cell conduction in other smooth muscles (Barr et al, 1968), suggests that a similar mechanism for conduction may be present in the ureter. Gap junctions consisting of groups of channels in the plasma membrane of adjacent smooth muscle cells enable exchange of ions and small molecules and play a role in electrical coupling between adjacent cells and in electromechanical coupling (Gabella, 1994; Santicoli and Maggi, 2000). 18 β -glycyrrhetic acid, a gap junction inhibitor, inhibits cell-to-cell electrical coupling in guinea pig renal pelvis and ureter and dissociates electrical and mechanical events (Santicoli and Maggi, 2000). Conduction velocity in the ureter is 2 to 6 cm/sec (Kobayashi, 1964; Kuriyama et al, 1967); it has been shown to vary with temperature, the time interval between stimuli (van Mastriigt et al, 1986), and the pressure within the ureter (Tsuchiya and Takei, 1990). This is in comparison to conduction velocities ranging from 1.5 to 2 m/sec in cardiac Purkinje fibers (Rosen et al, 1981) and from 10 to 100 m/sec in the dorsal and ventral roots of the spinal cord (Biscoe et al, 1977). Conduction in the ureter is similar to that in cardiac tissue, even to the extent that the Wenckebach

phenomenon (a partial conduction block) has been demonstrated in the ureter as it has been in specialized cardiac fibers (Weiss et al, 1968).

CONTRACTILE ACTIVITY

The contractile event is dependent on the concentration of free sarcoplasmic Ca^{2+} in the region of the contractile proteins, actin and myosin. Any process that results in a significant increase in Ca^{2+} in the region of the contractile proteins favors the development of a contraction; any process that results in a significant decrease in Ca^{2+} in the region of the contractile proteins favors relaxation (Fig. 43-7).

Contractile Proteins

In skeletal muscle, Ca^{2+} appears to act as a derepressor. It is thought that in the relaxed state, a regulator system, consisting of the proteins troponin and tropomyosin, prevents the interaction of actin and myosin. In the relaxed state, the troponin that is attached to the tropomyosin is inactive, and the tropomyosin prevents the interaction between actin and myosin. With activation, there is an increase in the sarcoplasmic Ca^{2+} concentration. The Ca^{2+} binds to the troponin, producing a conformational change that results in the displacement of tropomyosin, thus allowing interaction of actin and myosin and the development of a contraction.

In smooth muscle, on the other hand, Ca^{2+} appears to act as an activator. The most widely accepted theory suggests that phosphorylation of myosin is involved in the contractile process and that a troponin-like system does not constitute the primary regulatory mechanism, as it does in skeletal and cardiac muscle. With

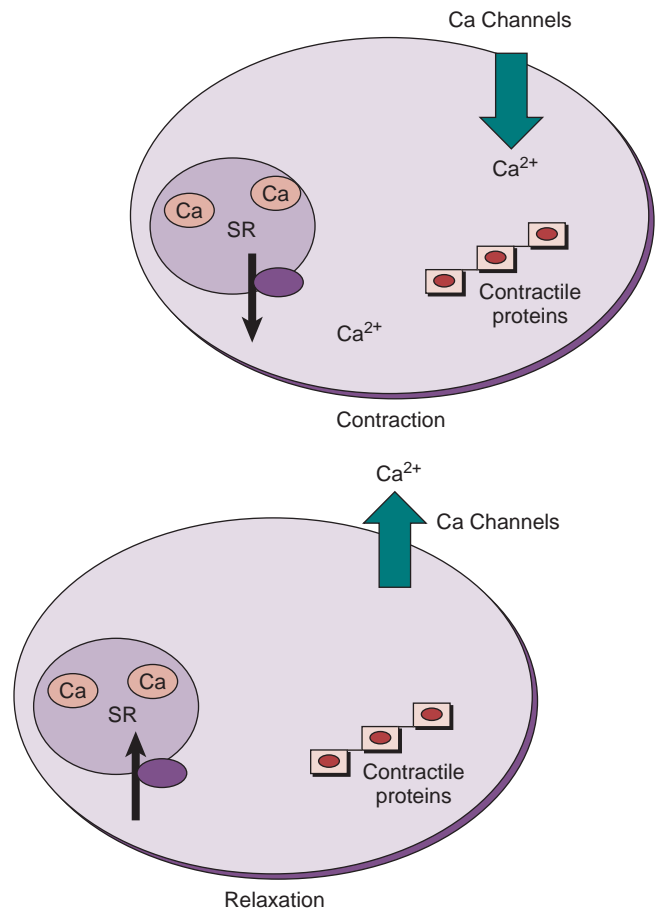


Figure 43-7. Schematic representation of calcium ion movements during contraction and relaxation. SR, sarcoplasmic reticulum.

excitation, there is a transient increase in the sarcoplasmic Ca^{2+} concentration from its steady-state concentration of 10^{-8} to 10^{-7} M to a concentration of 10^{-6} M or higher. At this higher concentration, Ca^{2+} forms an active complex with the Ca^{2+} -binding protein calmodulin (Watterson et al, 1976; Cho et al, 1988). Calmodulin without Ca^{2+} is inactive (Fig. 43-8). The Ca^{2+} -calmodulin complex activates a calmodulin-dependent enzyme, myosin light-chain kinase (see Fig. 43-8). The activated myosin light-chain kinase, in turn, catalyzes the phosphorylation of the 20,000-Da light chain of myosin (Fig. 43-9). Phosphorylation of the myosin light chain allows actin to activate myosin Mg^{2+} -ATPase activity, leading to hydrolysis of ATP and the development of smooth muscle tension or shortening (Fig. 43-10). Actin cannot activate the ATPase activity of the dephosphorylated myosin light chain.

When the Ca^{2+} concentration in the region of the contractile proteins is low, the myosin light-chain kinase is not active, because calmodulin requires Ca^{2+} to activate the enzyme. This prevents activation of the contractile apparatus, because the myosin light chain cannot be phosphorylated, a process that must precede tension development. Furthermore, a phosphatase dephosphorylates the myosin light chain, thus preventing actin activation of myosin ATPase activity, and relaxation results.

Evidence indicates that phosphorylation of the enzyme myosin light-chain kinase by a cyclic adenosine monophosphate (cAMP)-dependent protein kinase decreases myosin light-chain kinase activity by decreasing the affinity of this enzyme for calmodulin (Adelstein et al, 1981).

Although Ca^{2+} is required for most smooth muscle contractile events, there is evidence that Ca^{2+} -independent contractions can occur (Yoshimura and Yamaguchi, 1997). Carbachol, a muscarinic cholinergic agonist, and phorbol ester, which activates protein kinase C (PKC), can induce contraction in Ca^{2+} -depleted bladder strips that can be inhibited by a PKC inhibitor, H7. It is suggested that activation of PKC coupled with agonist stimulation of the muscarinic receptor can induce a Ca^{2+} -independent contraction.

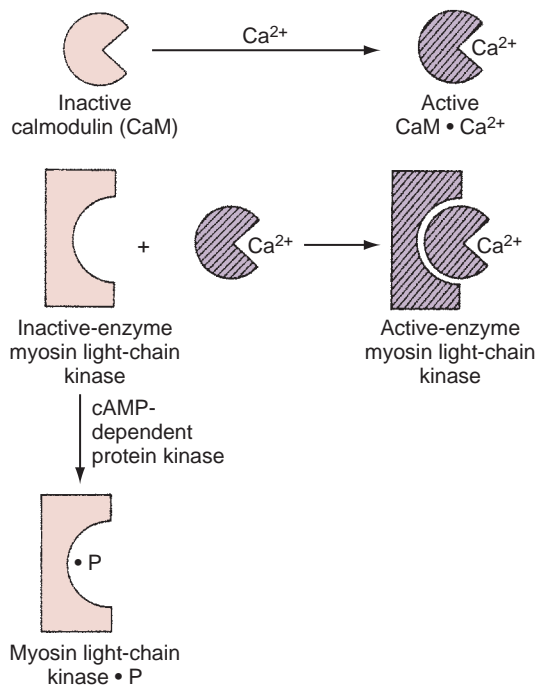


Figure 43-8. Schematic representation of the contractile process in smooth muscle. Calmodulin is activated by Ca^{2+} . The activated calcium-calmodulin complex activates the enzyme myosin light-chain kinase, which phosphorylates the light chain of myosin. Phosphorylation of myosin light-chain kinase decreases the rate of activation of the enzyme by the Ca^{2+} -calmodulin complex. cAMP, cyclic adenosine monophosphate.

Calcium and Excitation-Contraction Coupling

The mechanical event of ureteral peristalsis follows an electrical event to which it is related. The Ca^{2+} involved in the ureteral contraction is derived from two main sources. Because smooth muscle cells have a very small diameter, the inward movement of extracellular Ca^{2+} into the cell through L-type voltage-dependent Ca^{2+} channels during the upstroke of the action potential provides a significant source of sarcoplasmic Ca^{2+} (Brading et al, 1983; Hertle and Nawrath, 1989; Yoshida et al, 1992; Maggi et al, 1994a; Maggi and Giuliani, 1995; Floyd et al, 2008) (see Fig. 43-7). This inward movement of Ca^{2+} across the cell membrane is the major source of calcium used for contraction in most smooth

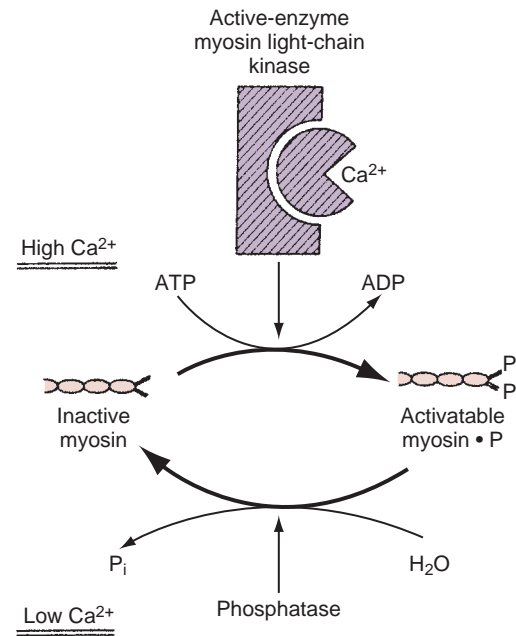


Figure 43-9. Schematic representation of the contractile process in smooth muscle. The activated enzyme myosin light-chain kinase catalyzes the phosphorylation of myosin. Myosin must be phosphorylated for actin to activate myosin adenosine triphosphatase. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

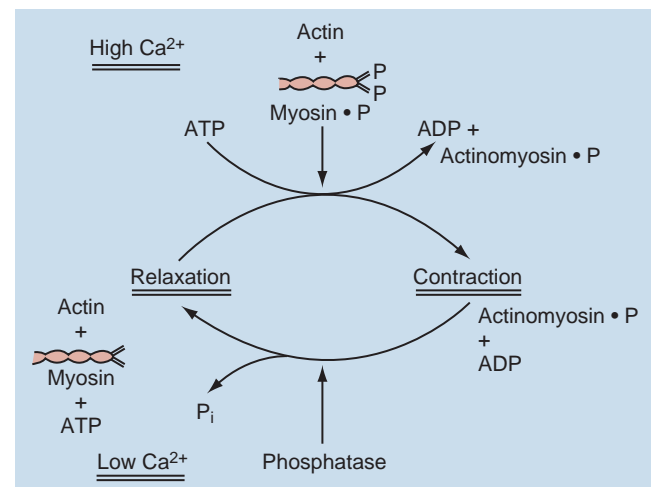


Figure 43-10. Schematic representation of the contractile process in smooth muscle. Actin activates adenosine triphosphatase activity of phosphorylated myosin. This allows interaction of actin and myosin with the development of a contraction. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

muscles. $\text{Na}^+\text{-Ca}^{2+}$ exchange, with an outward movement of Na^+ and an inward movement of Ca^{2+} , also plays a role in the ureteral contraction (Lamont et al, 1998). Furthermore, in response to an excitatory impulse, Ca^{2+} release from tightly bound storage sites (e.g., the endoplasmic reticulum or SR) also increases the Ca^{2+} concentration in the sarcoplasm (Burdyga et al, 1998, 1999a; Lang et al, 2002b). Calcium may be released from the SR of smooth muscle by an inositol 1,4,5-trisphosphate (IP_3)-induced release mechanism or by Ca^{2+} -induced Ca^{2+} release (CICR) (Somlyo and Somlyo, 1994). These processes appear to be species dependent. CICR, which involves ryanodine receptors, appears to be the sole mechanism for calcium release from the SR in the guinea pig ureter, whereas the SR store in the rat ureter appears to be exclusively under the control of IP_3 receptors (Burdyga et al, 1995). IP_3 and ryanodine receptors are expressed in the human ureter (Floyd et al, 2008). The opening of caffeine-sensitive ryanodine receptors produces small local elevations of Ca^{2+} that are termed *Ca^{2+} sparks* (Nelson et al, 1995). In addition to providing a source of calcium for contraction, Ca^{2+} released from the SR activates Ca^{2+} -sensitive surface membrane channels and modulates membrane excitability (Imaizumi et al, 1989; Carl et al, 1996). Both calcium-activated outward potassium currents (K_{Ca}) or spontaneous transient outward currents (STOCs) and calcium-activated inward chloride currents (Cl_{Ca}) or STICs have been identified in smooth muscles. These currents affect membrane potential and thus affect calcium entry through L-type Ca^{2+} channels in the membrane. The Ca^{2+} -activated chloride currents are present in rat but not guinea pig ureteral smooth muscle (Burdyga and Wray, 2002). Thus, some Ca^{2+} released from SR results in contraction, but caffeine-induced release of SR Ca^{2+} in the form of Ca^{2+} sparks increases outward potassium currents (K_{Ca}) or STOCs with an inhibitory effect on action potentials and contractility (Borisova et al, 2007). At least in the guinea pig ureter, this increase in the outward potassium current hyperpolarizes the membrane and determines the refractory period, which is important in determining the frequency of ureteral peristalsis (Burdyga and Wray, 2005).

Support for use of a dual source of Ca^{2+} in the ureter has been provided by Vereecken and coworkers (1975), who noted that it took approximately 45 minutes for spontaneous contractions of isolated guinea pig ureters to cease when the tissue was placed in a Ca^{2+} -free medium. They interpreted this to indicate that some of the Ca^{2+} involved in the contractile process is derived from tightly bound intracellular stores. They also noted that recovery of the contractile response to electric stimuli was almost immediate when the tissue was returned to a physiologic solution containing a normal concentration of Ca^{2+} . This suggests that free extracellular Ca^{2+} entering the cell during excitation also provides a source of Ca^{2+} for the contractile machinery. A similar conclusion was reached by Hong and associates (1985). There is, however, some evidence in ureteral contractions, at least in the guinea pig (Maggi et al, 1994a, 1995, 1996), and some perturbations of contractility may be related to movements of ions other than Ca^{2+} . The increase in developed force in the guinea pig ureter with intracellular acidification and decrease with intracellular alkalization appear to result from modulation of outward K^+ currents rather than effects on inward Ca^{2+} currents (Smith et al, 1998). That is, alkalization (increasing intracellular pH) enhances outward K^+ currents and this reduces excitability; acidification has the opposite effect. Relaxation results from a decrease in the concentration of free sarcoplasmic Ca^{2+} in the region of the contractile proteins. The decrease in sarcoplasmic Ca^{2+} can result from the uptake of Ca^{2+} into intracellular storage sites (Maggi et al, 1994a, 1995) or from extrusion of Ca^{2+} from the cell (Burdyga and Magura, 1988).

In addition to the Ca^{2+} -signaling cascade that affects contractility, there is a Rho/Rho-kinase signaling pathway that affects contractility by altering the Ca^{2+} sensitivity of the contractile system (Somlyo and Somlyo, 2003). The Rho-kinase pathway is involved in ureteral contractions in a number of species (Levent and Buyukafsar, 2004; Shabir et al, 2004; Hong et al, 2005). RhoA, a small GTP binding protein, binds to Rho-kinase and causes its migration to the cell

membrane, where it becomes maximally active (Leung et al, 1995; Ishizaki et al, 1996). Rho-kinase inhibits myosin phosphatase by phosphorylation of its regulatory subunit, which prevents dephosphorylation of myosin light chain, which in turn leads to Ca^{2+} sensitization of the smooth muscle with subsequent increase in contractility. Y-27632, an inhibitor of Rho-kinase, decreases both spontaneous and electric field stimulation (EFS)-induced contractile responses of in vitro rat and human ureteral segments without causing changes in calcium (Shabir et al, 2004; Hong et al, 2005). **Activation of Rho-kinase affects smooth muscle contractility without causing changes in calcium.**

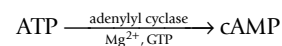
Urothelial Effects on Contractile Activity

Furchgott (1999) showed in blood vessels that the endothelium produced a factor that had a relaxing action on the smooth muscle layer of the blood vessel. This factor was originally termed *endothelium-derived relaxing factor* (EDRF) and was subsequently shown to be nitric oxide (NO). Mastrangelo and colleagues (2003) showed that the urothelium of rat ureter produced NO, which inhibited contractile responses of the rat ureter. It was shown that the urothelium inhibited spontaneous contractions of isolated rat ureteral segments and that removal of the urothelium potentiated the stimulatory effects of neurokinin A, vasopressin, carbachol, bradykinin, and AT2 (Mastrangelo and Iselin, 2007). In intact ureteral segments cyclooxygenase (COX) inhibitors potentiated the stimulatory effects of neurokinin A, vasopressin, carbachol, bradykinin, and angiotensin II. COX inhibitors had no effect on the responses to these agents in urothelium-free ureters. These data suggest that the inhibitory effects of the urothelium on ureteral contractile events may involve the participation of a urothelial COX product such as prostacyclin.

Second Messengers

The functional response to a number of hormones, neurotransmitters, and other agents is mediated by *second messengers*. The agonist, or first messenger, interacts with a specific membrane-bound receptor (Alquist, 1948; Furchgott, 1964); the agonist-receptor complex then activates or inactivates an enzyme that leads to alteration of the amount of a second messenger within the cell. These **second messengers include cAMP, cyclic guanosine monophosphate (cGMP), Ca^{2+} , IP_3 , and diacylglycerol (DG)**. They mediate the functional response to the agonist (first messenger) through a process that frequently involves protein phosphorylation.

cAMP is believed to mediate the relaxing effects of β -adrenergic agonists in a variety of smooth muscles (Triner et al, 1971; Andersson, 1972; Vesin and Harbon, 1974). According to this concept, a β -adrenergic agonist, such as isoproterenol, serves as the first messenger and combines with a receptor on the outer surface of the cell membrane (Fig. 43-11). Isoproterenol itself does not enter the cell. The **β -adrenergic agonist-receptor** complex activates the enzyme adenylyl cyclase on the inner surface of the cell membrane in close morphologic relation to the receptor. **In the presence of magnesium (Mg^{2+}) and a guanine nucleotide (GTP), adenylyl cyclase catalyzes the conversion of ATP to cAMP within the cell.**



A **stimulatory guanine nucleotide-regulatory protein, or G protein (G_s)**, acts as a functional communication between the agonist-receptor complex and the catalytic or active unit of the enzyme adenylyl cyclase. cAMP acts as a second, or “internal,” messenger of the response elicited by the β -adrenergic agonist. It has been suggested that the increase in cAMP through activation of an enzyme—that is, a protein kinase—and phosphorylation of proteins leads to the uptake of Ca^{2+} into intracellular storage sites (i.e., the endoplasmic reticulum or SR) with the resultant decrease of free sarcoplasmic Ca^{2+} in the region of the contractile proteins (Andersson and Nilsson, 1972). The decrease in sarcoplasmic Ca^{2+} in the

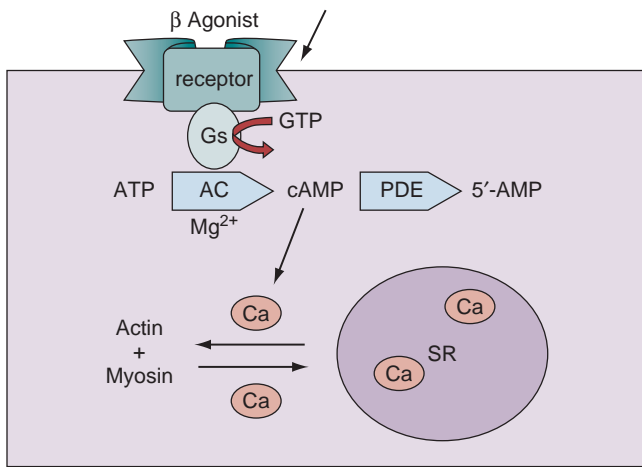
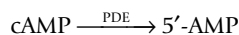


Figure 43-11. Schematic representation of the role of cyclic adenosine monophosphate (cAMP) in β -adrenergic agonist-induced relaxation of smooth muscle. Agonist combines with receptor on the outer side of the cell membrane. The receptor-agonist complex, in turn, via a stimulatory G protein, G_s , activates the enzyme adenylyl cyclase (AC) on the inner surface of the cell membrane, which in the presence of Mg^{2+} guanosine triphosphate (GTP) results in the conversion of adenosine triphosphate (ATP) to cAMP. cAMP is postulated to cause an increased uptake of Ca^{2+} into intracellular storage sites with a resultant decrease in Ca^{2+} in the region of the contractile proteins, which results in relaxation. cAMP may also have other actions (not shown) that inhibit the contractile process. The enzyme phosphodiesterase (PDE) degrades cAMP to 5'-AMP. SR, sarcoplasmic reticulum.

region of the contractile proteins leads to relaxation of the smooth muscle. β -Adrenoceptor-induced relaxation of smooth muscle also may be caused by the opening of Ca^{2+} -activated K^+ channels (Uchida et al, 2005; Ferro, 2006).

cAMP levels may be increased within the cell in two ways. One is by increasing synthesis, which involves activation of the enzyme adenylyl cyclase; the other is by decreasing degradation. The degradation of cAMP involves activation of an enzyme, phosphodiesterase (PDE):



Thus agents that either increase adenylyl cyclase activity, such as the β -adrenergic agonist isoproterenol, or decrease PDE activity, that is, phosphodiesterase inhibitors such as theophylline and papaverine, increase intracellular cAMP levels and cause smooth muscle relaxation.

Weiss and associates (1977) demonstrated the presence of both adenylyl cyclase and PDE activities in the ureter. They showed in the ureter that isoproterenol stimulates adenylyl cyclase activity and theophylline inhibits PDE activity. These two agents, which relax ureteral smooth muscle, would be expected to increase cAMP levels—*isoproterenol* by increasing synthesis and *theophylline* by decreasing degradation. Further support of a role for cAMP in smooth muscle relaxation can be derived from the findings that dibutyryl cAMP, which more readily diffuses into the intact cell and is less likely to be broken down by PDE than is cAMP, has been shown to relax a variety of smooth muscles, including the ureter (Takago et al, 1971; Wheeler et al, 1990) and that forskolin, which activates the catalytic subunit of adenylyl cyclase, relaxes the ureter (Wheeler et al, 1986; Hernández et al, 2004).

In addition to receptors and G proteins that are involved in stimulation of adenylyl cyclase and the formation of cAMP, as in the actions of β -adrenergic agonists, other receptors and G proteins inhibit adenylyl cyclase activity (Londos et al, 1981). Some actions of α_2 -adrenergic and muscarinic cholinergic agonists

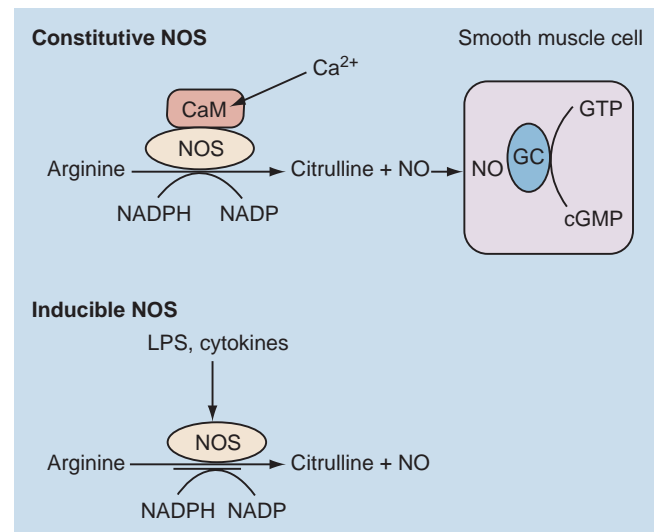


Figure 43-12. Schematic representation of inducible and constitutive nitric oxide synthase (NOS). CaM, calmodulin; cGMP, cyclic guanosine monophosphate; GC, guanylyl cyclase; GTP, guanosine triphosphate; LPS, lipopolysaccharide; NADP, nicotinamide-adenine dinucleotide phosphate, reduced; NO, nitric oxide.

involve stimulation of these inhibitory G proteins (G_i) with subsequent inhibition of adenylyl cyclase activity.

Another cyclic nucleotide, cGMP, also causes smooth muscle relaxation. cGMP is synthesized from GTP by the enzyme guanylyl cyclase and is degraded to 5'-GMP by a PDE. PDE activity that can degrade both cAMP and cGMP has been demonstrated in the canine ureter, and various inhibitors can preferentially inhibit the breakdown of one or the other cyclic nucleotide (Weiss et al, 1981; Stief et al, 1995). Insulin has been shown to activate cAMP PDE activity in the ureter (Weiss and Wheeler, 1988), and 8-bromo-cGMP has been shown to cause relaxation of a number of smooth muscles (Schultz et al, 1979), including the ureter (Cho et al, 1984).

NO stimulates soluble guanylyl cyclase activity and causes smooth muscle relaxation (Dokita et al, 1991, 1994). Nitric oxide synthase (NOS) converts L-arginine to NO and L-citrulline in a reaction that requires nicotinamide adenine dinucleotide phosphate, reduced (NADPH). There are three NOS isoforms. Neuronal NOS (nNOS) is present in neuronal tissues and is Ca^{2+} and NADPH dependent (Bredt and Snyder, 1990). It is thought that with neuronal excitation, there is an increase in Ca^{2+} concentration within nerves that leads to the synthesis of NO from L-arginine. NO released from the nerve activates the enzyme guanylyl cyclase in the smooth muscle cell with the resultant conversion of GTP to cGMP and thus smooth muscle relaxation (Fig. 43-12). Endothelial NOS (eNOS), is Ca^{2+} and NADPH dependent (Sessa, 1994). Similar to nNOS, eNOS produces small amounts of NO for prolonged periods of time. An inducible NOS isoform (iNOS) is NADPH dependent but Ca^{2+} independent and has been identified in ureteral smooth muscle (Smith et al, 1993). iNOS produces large amounts of NO for short periods of time.

NOS-containing nerves have been demonstrated in the human ureter (Stief et al, 1993; Goessl et al, 1995; Stief et al, 1996; Iselin et al, 1998), and NOS has been demonstrated in the pig UVJ (Hernández et al, 1995; Phillips et al, 1995) and in the upper ureter and calyces of pigs and humans (Iselin et al, 1998, 1999). NOS colocalizes with vasoactive polypeptide and neuropeptide Y (NPY) in nerves supplying the human ureter (Smet et al, 1994; Iselin et al, 1997). NOS localizes to parasympathetic and sensory nerves, but not to adrenergic neurons. In primary cultures of rat ureteral cells, NO production was detected in urothelial but not in smooth muscle

cells (Mastrangelo et al, 2003). These cells contain both eNOS and iNOS.

There is evidence that the NO pathway is involved in human ureteral relaxation (Stief et al, 1996; Iselin et al, 1997). The NO donor, SIN-1, relaxes human ureteral segments, an action that is inhibited by the guanylyl cyclase inhibitor methylene blue. NO donors also inhibit agonist-induced contractions of isolated pig calyceal and rat, pig, and human intravesical ureteral segments, actions that are associated with an increase in cGMP. Furthermore, NO has been shown to be involved in nonadrenergic, noncholinergic (NANC)-induced relaxation of the pig UVJ (Hernández et al, 1995). There also is evidence that adenosine relaxes the pig intravesical ureter through a process independent of NO (Hernández et al, 1999).

Some actions of α_1 -adrenergic and muscarinic cholinergic agonists and a number of other hormones, neurotransmitters, and biologic substances are associated with an increase in intracellular Ca^{2+} and are related to changes in inositol lipid metabolism. These agonists combine with a receptor on the cell membrane, and the agonist-receptor complex, via a process that involves a G protein, activates an enzyme, phospholipase C, that leads to the hydrolysis of polyphosphatidylinositol 4,5-bisphosphate with the formation of two second messengers, IP_3 and DG (Berridge, 1984) (Fig. 43-13). IP_3 mobilizes Ca^{2+} from intracellular stores (i.e., endoplasmic reticulum or SR) with an initiation of a cascade of events through the calmodulin branch of the Ca^{2+} messenger system. In smooth muscles, IP_3 is thought to be involved in brief contractile responses or in the initial phase of sustained responses (Park and Rasmussen, 1985).

The other second messenger, DG, binds to an enzyme, PKC; translocates to the cell membrane; and, by reducing the concentration of Ca^{2+} required for PKC activation, results in an increase in this enzyme's activity. The actions of PKC involve the phosphorylation of proteins (Nishizuka, 1984). The PKC branch of the Ca^{2+}

messenger system is thought to be responsible for the sustained phase of the contractile response in smooth muscle (Park and Rasmussen, 1985) and is responsive to hormonally induced changes in intracellular Ca^{2+} . PKC has been implicated in Ca^{2+} -independent smooth muscle contractions (Yoshimura and Yamaguchi, 1997). Numerous PKC isoforms have been identified. The functional activity and specificity of function of these isoforms appear to be primarily determined by the state of phosphorylation of the isoenzyme and its subcellular localization (Dempsey et al, 2000).

DG also activates the enzyme phospholipase A, which serves as a source of arachidonic acid, the substrate for PG synthesis (Mahadevappa and Holub, 1983). Arachidonic acid, in turn, may stimulate guanylyl cyclase activity with the subsequent formation of cGMP (Berridge, 1984), and this would explain the Ca^{2+} -dependent increase in cGMP levels associated with muscarinic cholinergic and α_1 -adrenergic agonist-induced contractions in smooth muscle. The observed increases in cGMP levels follow, rather than precede, the onset of contractions induced by these agonists.

Thus, a group of second messengers are involved in the transduction of the signal that is initiated when an agonist combines with a specific receptor on the cell membrane of the smooth muscle. This process of signal transduction ultimately results in the functional response to the agonist.

MECHANICAL PROPERTIES

Mechanical characteristics of muscle are commonly assessed by defining force-length and force-velocity relations. Isometric force-length measurements depend on the number of linkages between the contractile proteins, actin and myosin, that are brought into action during contraction. Force-velocity relations depend on the rate of formation and breakdown of linkages between the contractile proteins. Interventions may affect force-velocity relations, with or without affecting force-length relations. In addition to these methods of assessing mechanical properties of the ureter, the bidimensional nature of the ureter has lent itself to studies of pressure-length-diameter relations.

Force-Length Relations

Force-length relations express the relation between the force developed by muscle when it is stimulated under isometric conditions and the resting length of the muscle at the time of stimulation. With stretching of the ureter (muscle lengthening), the resting force (i.e., the tension present when the muscle is not excited) increases at a progressive rate (Weiss et al, 1972). The force developed during isometric contraction also increases with elongation until a length is reached at which the maximal contractile force is achieved. With further lengthening, the developed force decreases (Weiss et al, 1972; Thulesius et al, 1989). The ureter at this length is overstretched, or beyond the peak of its force-length curve. Ureteral resting tension is high at the length at which maximal contractile force is developed.

Because the ureter is a viscoelastic structure (Weiss et al, 1972), the resting or contractile force developed at any given length depends on the direction in which the change in length is occurring and on the rate of length change (Weiss et al, 1972; Vereecken et al, 1973). This is referred to as *hysteresis*; for the ureter, at any given length, the resting force is less and the contractile force is greater when the ureter is allowed to shorten than when the ureter is being stretched (Fig. 43-14).

When the ureter is stretched, the resting force increases. If the length is kept constant at its new longer length after a stretch, changes occur that result in a decrease in the resting force, or stress relaxation (Fig. 43-15) (Weiss et al, 1972). Within certain limits, when the ureter is stretched to a length beyond the peak of the force-length curve—that is, when the ureter is stretched to a length at which the contractile force declines in the face of increasing muscle length—the degree of stress relaxation may be such that, within a period of time, the developed force no longer declines,

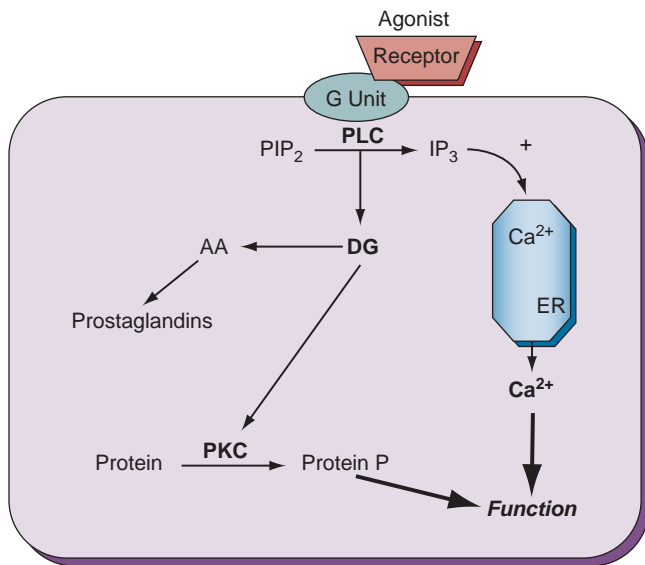


Figure 43-13. Schematic representation of the role of inositol lipid metabolism in smooth muscle function. The agonist combines with the receptor on the outer side of the cell membrane. The receptor-agonist complex in turn activates the enzyme phospholipase C (PLC), which leads to the hydrolysis of polyphosphatidylinositol 4,5-bisphosphate (PIP_2), with the formation of two second messengers, inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DG). The activation of PLC involves a G protein. IP_3 mobilizes calcium from intracellular stores (i.e., endoplasmic reticulum [ER]), and this leads to a functional response. DG binds to an enzyme, protein kinase C (PKC), which results in phosphorylation of proteins and a subsequent functional response. AA, arachidonic acid.

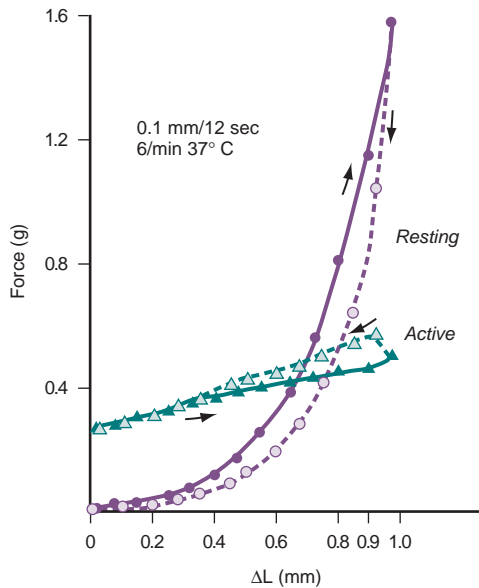


Figure 43-14. Hysteresis. Resting and contractile (active) force of cat ureter during muscle lengthening and shortening. Force is on the ordinate; change in length (ΔL) is on the abscissa. Solid symbols and solid lines show data obtained during muscle lengthening. Open symbols and dashed lines show data obtained during muscle shortening. Circles show resting force, and triangles show active or contractile force. Length and the direction of length change influence resting and contractile force. (From Weiss RM, Bassett AL, Hoffman BF. Dynamic length-tension curves of cat ureter. *Am J Physiol* 1972;222:388.)

even though the increased length is kept constant (Weiss et al, 1972). Stress relaxation can thus be considered a compensatory mechanism of a viscoelastic structure to stretch.

Force-Velocity Relations

Force-velocity curves depict the relation between the load and the velocity of shortening. A typical force-velocity curve, as predicted by Hill's equation for muscle shortening, has a hyperbolic configuration (Fig. 43-16) (Hill, 1938). From the force-velocity curve, one can extrapolate the maximal velocity of shortening (V_{max}), which represents the velocity of shortening at zero load (i.e., at isotonic conditions). V_{max} is determined by the level at which the force-velocity curve crosses the ordinate. V_{max} values in the ureter are in the range of 0.5 to 0.7 lengths per second (Biancani et al, 1984). The force-velocity curve intersects the abscissa at zero shortening, that is, at isometric conditions at which the load is great. Shortening depends on the total load lifted, with the ureter shortening to a lesser extent with heavier loads. At conditions near those of zero load, that is, conditions of free shortening (isotonic conditions), the in vitro guinea pig ureter shortens by 25% to 30% of its initial length (Biancani et al, 1984).

Pressure-Length-Diameter Relations

Because ureteral muscle fibers are arranged in a longitudinal, circumferential, and spiral configuration (Tanagho, 1971), longitudinal and diametral deformation of the ureter are interrelated. Simultaneous studies of length and diameter changes in response to an intraluminal pressure load are another means of assessing the mechanical properties of a tubular structure. After application of an intraluminal pressure, the ureter increases in both length and diameter, a process known as *creep* (Biancani et al, 1973). Deformation in response to a given intraluminal pressure load is greater in vitro than in vivo; this difference is partially negated if the in vivo preparation is pretreated with reserpine to suppress adrenergic influences

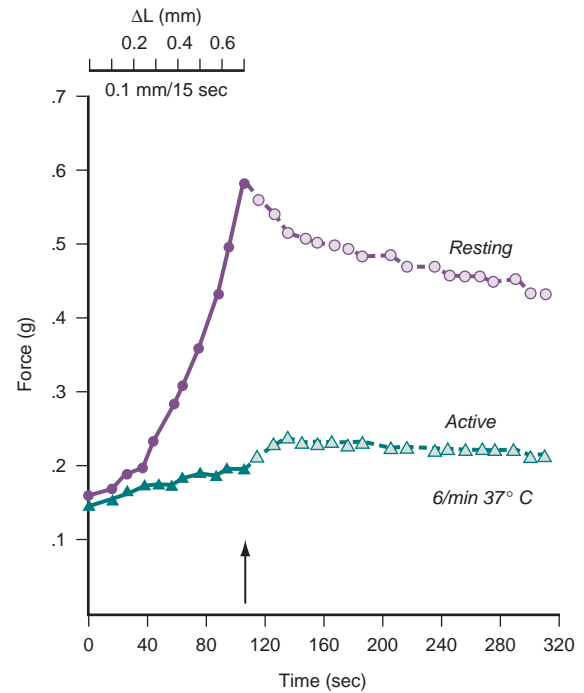


Figure 43-15. Stress relaxation. The resting and contractile (active) force of cat ureter is on the ordinate, the time from the onset of stretching is on the lower abscissa, and the change in length (ΔL) is on the left upper corner abscissa. Muscle is stretched by a given amount and then held at a fixed length. Solid symbols and solid lines show data obtained during muscle lengthening; open symbols and dashed lines show data obtained after stretching has ceased (arrow) and muscle is maintained at a constant length. Resting force decreases when muscle is held at a constant length after a stretch (stress relaxation). Contractile (active) force increases during this period of time. (From Weiss RM, Bassett AL, Hoffman BF. Dynamic length-tension curves of cat ureter. *Am J Physiol* 1972;222:388.)

(Fig. 43-17). Such data provide support for a role of the adrenergic nervous system in the control of ureteral function.

ROLE OF THE NERVOUS SYSTEM IN URETERAL FUNCTION

Some smooth muscles have a specific innervation of each smooth muscle fiber, whereas other, syncytial-type smooth muscles lack discrete neuromuscular junctions and depend on a diffuse release of transmitter from a bundle of nerves with a subsequent spread of excitation from one muscle cell to another. The ureter is a syncytial type of smooth muscle without discrete neuromuscular junctions (Burnstock, 1970).

Because peristalsis may persist after transplantation (O'Connor and Dawson-Edwards, 1959) or denervation (Wharton, 1932), because spontaneous activity may occur in isolated in vitro ureteral segments (Finberg and Peart, 1970), and because normal antegrade peristalsis continues after reversal of a segment of ureter in situ (Melick et al, 1961), it is apparent that ureteral peristalsis can occur without innervation. However, analysis of the data in the literature clearly indicates that the nervous system plays at least a modulating role in ureteral peristalsis. Morita and colleagues (1987b) have provided evidence that the autonomic nervous system may affect urine transport through the ureter by affecting both peristaltic frequency and bolus volume. Catecholamine fluorescence and acetylcholine (ACh) release studies indicate that the human ureter is supplied by sympathetic (noradrenaline-containing) and parasympathetic (ACh-containing) neurons (Duarte-Escalante et al, 1969; Del Tacca, 1978).

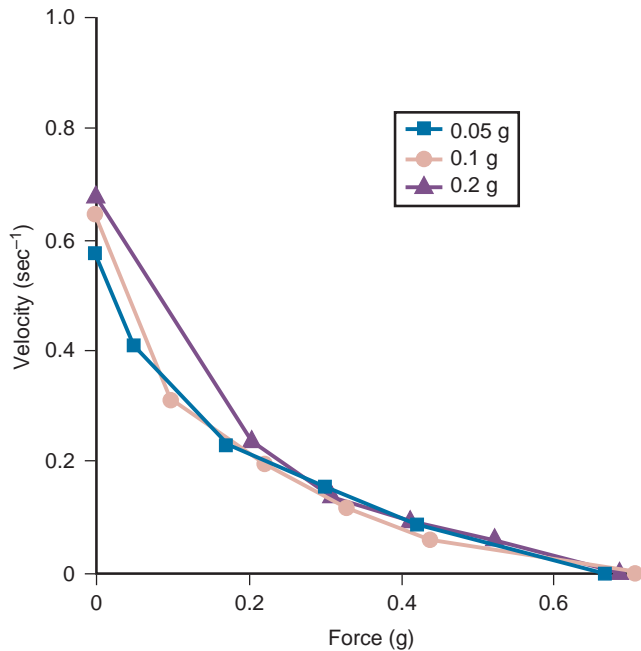


Figure 43-16. Force-velocity relation of guinea pig ureter. Specimens were stretched by three different preloads (0.05, 0.1, and 0.2 g). The velocity of shortening on the ordinate is plotted as a function of the total load lifted on the abscissa. V_{\max} is obtained by extrapolating the experimental curves to intersect the ordinate. Isometric force is given by data points where velocity equals zero. (From Biancani P, Onyski JH, Zabinski MP, et al. Force-velocity relationships of the pig ureter. *J Urol* 1984;131:988. Copyright Williams & Wilkins, 1984.)

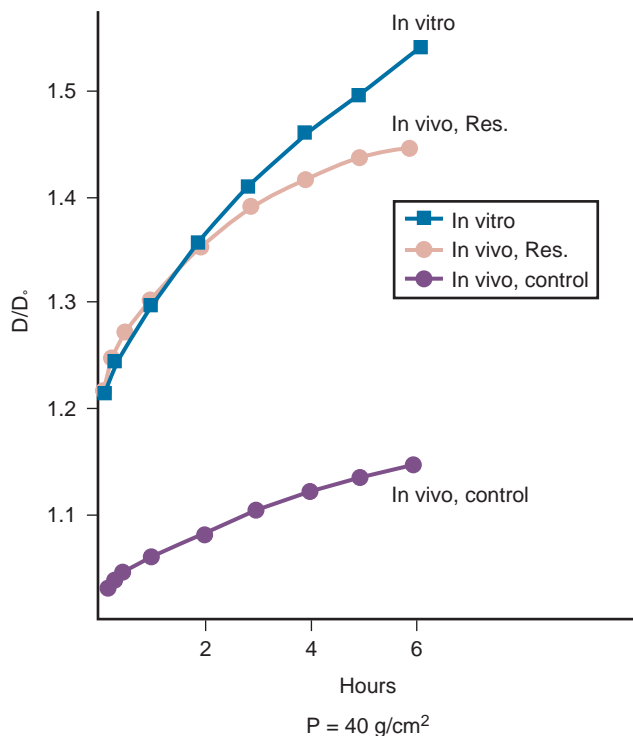


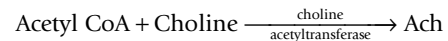
Figure 43-17. Pressure-diameter relations. An intraluminal pressure (p) load of 40 g/cm² is applied to rabbit ureters, and the change in diameter (D/D_0) is measured as a function of time. Blue squares show data obtained from in vitro ureters. Purple circles show data obtained in vivo. Pink circles show data obtained in vivo from animals previously treated with reserpine. D, diameter during deformation; D_0 , initial diameter.

Parasympathetic Nervous System

Although the role of the parasympathetic nervous system in the control of ureteral peristalsis has not been well defined, muscarinic cholinergic receptors have been demonstrated in the ureter of a number of species including the human (Latifpour et al, 1989, 1990; Hernández et al, 1993; Sakamoto et al, 2006). There are five cloned muscarinic subtypes, M_1 to M_5 . The excitatory muscarinic receptors, M_1 , M_3 , and M_5 , work through an excitatory G protein, G_q , and increase intracellular calcium by generating IP_3 and DG. The inhibitory muscarinic receptors, M_2 and M_4 , work through an inhibitory G protein, G_i , with inhibition of adenyl cyclase (Wu et al, 2000; van Koppen and Kaiser, 2003). Carbachol-induced contractile responses are primarily mediated via the M_3 receptor subtype (Tomiya et al, 2003b). It has been suggested that M_2 receptor activation may inhibit smooth muscle relaxation that results from activation of adenyl cyclase (Hegde et al, 1997). There is a higher density of M_2 than M_3 muscarinic receptors in the human ureter (Sakamoto et al, 2006).

Acetylcholinesterase-positive nerve fibers have been demonstrated in the equine ureter (Prieto et al, 1994). The cholinergic innervation is especially rich in the distal and intravesical ureter (Hernández et al, 1993). Furthermore, ACh has been shown to be released from isolated guinea pig, rabbit, and human ureters in response to EFS (Del Tacca, 1978), and this release is inhibited by the neural poison tetrodotoxin. These data suggest but do not prove that the parasympathetic nervous system has at least a modulatory role in the control of ureteral activity.

The prototypic cholinergic agonist is ACh, which serves as the neurotransmitter at (1) neuromuscular junctions of somatic motor nerves (nicotinic sites); (2) preganglionic parasympathetic and sympathetic neuroeffector junctions (nicotinic sites); and (3) postganglionic parasympathetic neuroeffector sites (muscarinic sites). ACh synthesis involves



where CoA is coenzyme A. The ACh is stored in vesicles within the synaptic terminal; its release depends on the influx of Ca^{2+} into the terminal, which presumably causes vesicle fusion with the presynaptic terminal membrane, thereby expelling ACh into the synaptic cleft. ACh subsequently is hydrolyzed by acetylcholinesterase. The muscarinic effects of cholinergic agonists can be blocked by atropine. The effects of nicotinic agonists can be blocked by nondepolarizing ganglionic blocking agents or by high concentrations of the nicotinic agonist itself, which may cause ganglionic blockade by desensitization of receptor sites after an initial period of ganglionic stimulation.

Cholinergic Agonists

Cholinergic agonists, including ACh, methacholine (Mecholyl), carbamylcholine (carbachol), and bethanechol (Urecholine), in general have been observed to have an excitatory effect on ureteral and renal pelvic function—that is, they increase the frequency and force of contractions (Verecken, 1973; Longrigg, 1974; Rose and Gillenwater, 1974; Morita et al, 1986, 1987b; Maggi and Giuliani, 1992; Hernández et al, 1993; Prieto et al, 1994). The excitatory effect of carbachol on isolated canine ureter is mediated by the excitatory M_3 -receptor subtype, and carbachol-induced inhibition of KCl-induced contractions of longitudinal canine ureteral preparations is mediated primarily via the inhibitory M_4 -receptor subtype (Tomiya et al, 2003b). ACh also has been shown to increase the duration of the guinea pig and rat ureteral action potential (Prosser et al, 1955; Ichikawa and Ikeda, 1960) and the number of oscillations on the plateau of the guinea pig ureteral action potential (Ichikawa and Ikeda, 1960).

Nicotinic agonists, such as nicotine, tetramethylammonium, and dimethylphenylpiperazine, cause an initial stimulation of nicotinic receptors followed by desensitization of the receptor sites; the receptors then become unresponsive to nicotinic agonists and also

to endogenous ACh, with a resultant transmission blockade. Nicotine, as would be expected, has been shown to have excitatory (Boyarsky et al, 1968), biphasic (Satani, 1919; Labay and Boyarsky, 1967), or inhibitory (Prosser et al, 1955; Vereecken, 1973) actions on the ureter.

Anticholinesterases

Anticholinesterases prevent the hydrolysis of ACh by cholinesterases and thus increase the duration and intensity of ACh action at both muscarinic and nicotinic receptor sites. With prolonged administration in high doses, they can result in desensitization blockade at nicotinic sites. The effects of **anticholinesterases**, such as **physostigmine** and **neostigmine**, parallel the excitatory effects of ACh and other parasympathomimetics on the ureter (Satani, 1919; Vereecken, 1973).

Parasympathetic Blocking Agents

Atropine is a competitive antagonist of the muscarinic effects of ACh. The inhibitory effects of atropine may be preceded by a transitory stimulatory effect on muscarinic receptors. Although atropine has been shown to inhibit the excitatory effects of parasympathomimetic agents (Vereecken, 1973; Longrigg, 1974) and physostigmine (Macht, 1916a) on a variety of ureteral and calyceal preparations, the majority of studies have shown that atropine itself has little direct effect on ureteral activity in a number of species (Gibbs, 1929; Gould et al, 1955; Butcher et al, 1957; Washizu, 1967; Vereecken, 1973; Reid et al, 1976), including humans (Kiil, 1957). Even when atropine has been observed to inhibit ureteral activity, its effects are frequently minimal and inconsistent (Ross et al, 1967), thus providing little rationale for its use in the treatment of ureteral colic.

Reports of the direct effects on ureteral activity of two other parasympathetic blocking agents, methantheline (Banthine) and propantheline (Pro-Banthine), also have been inconsistent (Draper and Zornigotti, 1954; Kiil, 1957; Reid et al, 1976).

Sympathetic Nervous System

The sympathetic nervous system appears to modulate ureteral activity as evidenced by the demonstration of adrenergic receptors in the ureter (Latifpour et al, 1989, 1990; Morita et al, 1994), the identification of catecholaminergic neurons in the ureter as determined by labeling tyrosine hydroxylase as a marker (Edyvane et al, 1994), and the demonstration that catecholamines are released from the ureter (Weiss et al, 1978) and renal calyx (Longrigg, 1975) in response to EFS.

The ureter contains excitatory α -adrenergic and inhibitory β -adrenergic receptors (McLeod et al, 1973; Rose and Gillenwater, 1974; Weiss et al, 1978) that have been demonstrated with receptor-binding techniques (Latifpour et al, 1989, 1990). In the human ureter, renal pelvis, and calyces, α_{1D} and α_{1A} adrenoceptor subtypes are more prevalent than the α_{1B} adrenoceptor subtype (Sigala et al, 2005; Itoh et al, 2007; Karabacak et al, 2013). The highest density of α_1 adrenoceptors is found in the distal ureter, with the relative density being α_{1D} higher than α_{1A} , which is higher than α_{1B} . This is in accord with the finding that phenylephrine, an α -adrenergic agonist, induces a greater contractile force in isolated human ureteral segments obtained from the distal than the proximal ureter (Sasaki et al, 2011). The expression of α_1 adrenoceptors is species dependent, with a higher density of α_{1A} adrenoceptors in the mouse ureter and a higher density of α_{1D} adrenoceptors in the dog and hamster ureter (Tomiya et al, 2007; Kobayashi et al, 2009a, 2009b). The α_{1A} adrenoceptor subtype is the primary receptor subtype that participates in the contraction of the mouse, hamster, and human ureter (Tomiya et al, 2007; Sasaki et al, 2008; Kobayashi et al, 2009c; Sasaki et al, 2011). It appears that α_{1A} adrenoceptors are more involved in the maintenance of baseline ureteral tonus than in the potentiation of ureteral peristaltic activity (Morita et al, 1987a; Tomiya et al, 2002).

Norepinephrine, primarily an α -adrenergic agonist (although it also can stimulate β -adrenergic receptors), increases the force of electrically induced ureteral contractions (Weiss et al, 1978). When administered in the presence of **phentolamine** (Regitine), an α -adrenergic blocking agent, norepinephrine decreases the force of ureteral contractions (Weiss et al, 1978). A similar reversal of action occurs in the in vivo ureter (McLeod et al, 1973) and can be explained by norepinephrine's primary action on inhibitory β -adrenergic receptors when the excitatory α -adrenergic receptors are blocked. Propranolol (Inderal), a β -adrenergic antagonist, potentiates the increase in contractile force induced by norepinephrine (Weiss et al, 1978). This can be explained by norepinephrine's acting more exclusively on excitatory α -adrenergic receptors when the inhibitory β -adrenergic receptors are blocked. Furthermore, **isoproterenol**, a β -adrenergic agonist, depresses contractility (Weiss et al, 1978). These data provide evidence for excitatory α -adrenergic and inhibitory β -adrenergic receptors in the ureter and are in accord with the observations of McLeod and associates (1973) and Rose and Gillenwater (1974) on in vivo ureters.

Further support for the presence of excitatory α -adrenergic and inhibitory β -adrenergic receptors in the ureter includes the demonstration of adenyl cyclase activity in the ureter (Weiss et al, 1977; Wheeler et al, 1986) and the finding that the ureters of rabbits depleted of catecholamines by the administration of reserpine undergo greater degrees of deformation when a given intraluminal pressure is applied than would result from the application of the same pressure load to the ureters of normal, non-reserpine-treated animals (see Fig. 43-17) (Weiss et al, 1974). Finally, electric stimulation with high-intensity, high-frequency, short-duration stimuli has been shown to release neurotransmitter, presumably from intrinsic neural tissue within the wall of the ureter (Weiss et al, 1978) and renal calyx (Longrigg, 1975).

Adrenergic Agonists

Norepinephrine, the chemical mediator responsible for adrenergic transmission, is synthesized in the neuron from tyrosine. After its release from the nerve terminal, some of the norepinephrine combines with receptors in the effector organ, leading to a physiologic response. The greatest percentage of the norepinephrine is actively taken up (reuptake or neuronal uptake) into the neuron. Neuronal reuptake regulates the duration that norepinephrine is in contact with the innervated tissue and thus regulates the magnitude and duration of the catecholamine-induced response. Agents such as cocaine and imipramine (Tofranil) that inhibit neuronal uptake potentiate the physiologic response to norepinephrine. The enzymes monoamine oxidase and catechol-O-methyltransferase provide degradative pathways for norepinephrine.

According to the general consensus, agents that primarily activate α -adrenergic receptors, such as norepinephrine and phenylephrine, tend to stimulate ureteral and renal pelvic activity (McLeod et al, 1973; Vereecken, 1973; Hannappel and Golenhofen, 1974; Rose and Gillenwater, 1974; Hernández et al, 1992; Rivera et al, 1992; Danuser et al, 2001), and agents that primarily activate β -adrenergic receptors, such as isoproterenol and orciprenaline, tend to inhibit ureteral and renal pelvic activity (Finberg and Peart, 1970; Ancill et al, 1972; McLeod et al, 1973; Vereecken, 1973; Hannappel and Golenhofen, 1974; Rose and Gillenwater, 1974; Weiss et al, 1978; Hernández et al, 1992; Rivera et al, 1992; Danuser et al, 2001). The β -adrenergic subtypes involved in ureteral relaxation are species specific; β_1 adrenoceptors in rat, β_2 adrenoceptors in rabbit, mainly β_3 adrenoceptors in dog, and β_2 and β_3 adrenoceptors in pig and human (Tomiya et al, 1998; Park et al, 2000; Tomiya et al, 2003a; Wanajo et al, 2004). All three β -adrenergic receptor subtypes are expressed in the human ureter (Park et al, 2000; Matsumoto et al, 2013). Immunohistochemical studies show that the β -adrenergic receptors are expressed in both the smooth muscle and the urothelium of the human ureter (Matsumoto et al, 2013). A relatively specific β_3 -adrenoceptor agonist, TRK-380, relaxes in vitro human ureteral segments, and it has been suggested that the β_3 agonist mirabegron may do the same (Matsumoto et al,

2013). A synthesized β_2/β_3 -adrenoceptor agonist, KUL-7211, was a more potent relaxant of isolated dog ureteral segments than the α -adrenergic antagonists tamsulosin and prazosin, the calcium channel blocker verapamil, and the PDE inhibitor papaverine (Wanajo et al, 2005). KUL-7211 also is a potent relaxant of the pig ureter (Wanajo et al, 2011). Intraluminal isoproterenol has been shown to lower renal pelvic pressures during ureteroscopy, with the presumption that this would decrease intrarenal backflow, which has potential harmful effects (Jung et al, 2008; Jakobsen, 2013). In rabbit renal pelvis, β_2 -adrenergic agonists inhibit contractile activity of the distal renal pelvis, and β_1 -adrenergic agonists potentiate contractile activity of the proximal renal pelvis (Kondo et al, 1989). Tyramine, whose adrenergic agonist effects are primarily the result of the release of norepinephrine from adrenergic terminals, also has a stimulatory effect on the upper urinary tract (Boyarsky and Labay, 1969; Finberg and Peart, 1970; Longrigg, 1974). The reported stimulatory effects of cocaine on ureteral activity (Boyarsky and Labay, 1969) may be explained by blockage of norepinephrine reuptake into adrenergic nerve endings, with a resultant increase in the magnitude and duration of the effect of norepinephrine.

Adrenergic Antagonists

The α -adrenergic antagonists phentolamine and phenoxybenzamine (Dibenzylamine) have been shown to inhibit the stimulatory effects of norepinephrine and other α -adrenergic agonists in a variety of preparations (Finberg and Peart, 1970; Gosling and Waas, 1971; McLeod et al, 1973; Vereecken, 1973; Hannappel and Golenhofen, 1974; Longrigg, 1974; Rose and Gillenwater, 1974; Weiss et al, 1978; Hernández et al, 1992). The α -adrenergic antagonist doxazosin has been shown to slightly reduce spontaneous contractility of in vitro pig ureter and to inhibit the contractile effects of epinephrine and phenylephrine (Nakada et al, 2007), and tamsulosin inhibited the contractility of human ureters in vitro (Rajpathy et al, 2008) and in vivo (Davenport et al, 2007). Silodosin, a selective α_{1A} receptor antagonist, was more effective in inhibiting EFS-induced contractions of human and rat isolated ureters than tamsulosin, a selective α_{1AD} receptor antagonist, or prazosin, a non-selective α -adrenergic receptor antagonist (Villa et al, 2013). The β -adrenergic antagonist propranolol has been shown to block or attenuate the inhibitory effects of β -adrenergic agonists, such as isoproterenol, in a variety of preparations (McLeod et al, 1973; Vereecken, 1973; Longrigg, 1974; Rose and Gillenwater, 1974; Weiss et al, 1978).

Sensory Innervation and Peptidergic Agents in the Control of Ureteral Function

Sensory nerves can play both a sensory afferent and motor efferent role in a given tissue. Tachykinins and calcitonin gene-related peptide (CGRP) are neurotransmitters released from peripheral endings of sensory nerves (Maggi, 1995). Tachykinins stimulate and CGRP inhibits electrical and contractile activity. Capsaicin-sensitive sensory nerves are located in the ureter (Maggi et al, 1986; Maggi and Meli, 1988; Dray et al, 1989; Ammons, 1992) and contain the tachykinins substance P, neurokinin A, and neuropeptide K (Hua et al, 1985; Sann et al, 1992), as well as CGRP (Gibbins et al, 1985; Sann et al, 1992; Tamaki et al, 1992). Immunoreactivity for tachykinins and CGRP is less in the human than in the guinea pig ureter (Su et al, 1986; Hua et al, 1987; Edyvane et al, 1992, 1994). Capsaicin in low doses inhibits ureteral activity, presumably because of the release of CGRP, but in high doses it increases ureteral activity, presumably because of release of the tachykinins neurokinin A, neuropeptide K, and substance P (Hua and Lundberg, 1986). Capsaicin administration to neonatal rats causes degeneration of CGRP-containing sensory nerves in the ureter, which is accompanied by an increase in sympathetic (noradrenergic) innervation (Sann et al, 1995). Because nerve growth factor (NGF) is responsible for both increased sensory and noradrenergic innervation, capsaicin-induced

degeneration of sensory nerves decreases NGF uptake into sensory neurons with a resultant increase in the amount of NGF available for stimulating sympathetic innervation (Schicho et al, 1998). The excitatory effects of the tachykinins are more prominent in the renal pelvis than in the ureter, and the inhibitory effects of CGRP are more prominent in the ureter than in the renal pelvis (Maggi et al, 1992b). The excitatory effects of tachykinins involve excitation of NK-2 receptors in the human, pig, and guinea pig ureter; pig intravesical ureter; and guinea pig renal pelvis (Patacchini et al, 1998; Jerde et al, 1999; Bustamante et al, 2001; Nakada et al, 2001). The inhibitory actions of the neurotransmitter CGRP appear to involve multiple mechanisms (Maggi and Giuliani, 1991; Maggi et al, 1994c). By opening ATP-sensitive K^+ channels, CGRP causes membrane hyperpolarization with a resultant blocking of voltage-sensitive Ca^{2+} channels that are involved in generation of the ureteral action potential and ureteral contraction (Maggi et al, 1994b; Santicoli and Maggi, 1994; Meini et al, 1995). CGRP-induced ureteral relaxation may also result from stimulation of adenylyl cyclase activity with a resultant increase in cAMP (Santicoli et al, 1995b). The action of CGRP on the ureter may be regulated by an endopeptidase that degrades the CGRP released from the sensory nerves (Maggi and Giuliani, 1994).

Histochemical studies show that the tachykinins and CGRP colocalize in the same nerves in the ureter (Hua et al, 1987). Peptidergic neurons containing NPY and vasoactive intestinal polypeptide (VIP) also are present in the ureter (Allen et al, 1990; Edyvane et al, 1992; Prieto et al, 1997). VIP and pituitary adenylyl cyclase-activating polypeptide (PACAP) have been shown to relax pig intravesical ureteral segments through a cAMP-dependent mechanism (Hernández et al, 2004). Edyvane and associates (1994) have provided evidence for at least four, and possibly six, different immunohistochemical populations of nerve fibers in the human ureter. The predominant types include noradrenergic nerves containing NPY, neurons containing NPY and vasoactive polypeptide, neurons containing substance P and CGRP, and neurons containing CGRP. NPY potentiates the excitatory effects of norepinephrine on the ureter (Prieto et al, 1997). Rare coexistences also were observed between CGRP and vasoactive polypeptide, CGRP and NPY, and CGRP and tyrosine hydroxylase, a marker of noradrenergic neurons. These investigators demonstrated regional differences in the innervation of the ureter, with a more extensive innervation noted in the lower than in the upper ureter.

Renal pelvic sensory nerves contain both substance P and CGRP. Increases in renal pelvic pressure result in the release of substance P and a subsequent increase in afferent renal nerve activity. CGRP potentiates the afferent renal nerve activity responses to substance P by retarding the metabolism of substance P, thus resulting in increased amounts of substance P available for potentiating afferent renal nerve activity (Contijo et al, 1999). PGs also contribute to sensory receptor activation (Kopp et al, 2000).

NANC excitatory neurotransmission is functional in the pig intravesical ureter (Bustamante et al, 2000, 2001). In the presence of agents that block adrenergic neurotransmission, muscarinic cholinergic receptors, NO synthase activity, PG synthesis, and A_1/A_2 adenosine receptors, EFS (5 Hz) induced contractions that were potentiated by the tachykinins substance P and NKA and that were inhibited by a sensory neurotoxin, capsaicin, and by an NK₂ receptor antagonist, GR94800. The EFS-induced contractions were abolished by tetrodotoxin, providing evidence that the contractions were neurogenic in origin. It has been suggested that tachykinins, especially NKA, released from capsaicin-sensitive afferent nerves and activating NK₂ receptors are involved in NANC excitatory neurotransmission.

Purinergic Nervous System

Burnstock and associates (1972) postulated that ATP could act as an excitatory transmitter in the bladder. It was subsequently shown that ATP is released along with ACh in response to nerve stimulation (Kasakov and Burnstock, 1983) and that the excitatory response

in the bladder is mediated through P2X receptors (Theobald, 1995). ATP activation of P2X purinoceptors promotes influx of extracellular Ca^{2+} into the muscle cells with resultant contraction. Although there is no evidence that ATP mediates contractions in the ureter, there is evidence to suggest that ATP is involved in nociceptive processes. P2X receptors are present in the ureter (Lee et al, 2000). ATP is released from the urothelium of human and guinea pig ureter, in response to ureteral distention (Knight et al, 2002; Calvert et al, 2008), and stimulates sensory nerves that contain purinergic receptors (Rong and Burnstock, 2004; Calvert et al, 2008).

Two classes of mechanosensitive afferent fibers have been identified in the guinea pig ureter (Cervero and Sann, 1989). It would appear that one group of fibers consists of tension receptors that respond to normal ureteral peristalsis, whereas the others are involved in the signaling of noxious events such as kidney stones and increased intraluminal pressures. Both groups are chemosensitive, being excited by K^+ , bradykinin, and capsaicin (Sann, 1998). Because both ureteral distention and exogenous ATP increase afferent nerve discharge (Rong and Burnstock, 2004), ATP may be involved in signaling visceral pain with ureteral dilatation—that is, renal colic (Burnstock, 2006, 2009). It has been proposed that ureteral distention causes release of ATP from the urothelium, which in turn activates purinoceptors on suburothelial nociceptive sensory nerves. Consistent with this postulation, ATP has been shown to be released with distention of isolated human ureteral segments; this was accompanied by staining of P2X₃ and capsaicin receptors (Calvert et al, 2008).

URINE TRANSPORT

Physiology of the Ureteropelvic Junction

At normal urine flows, the frequency of calyceal and renal pelvic contractions is greater than that in the upper ureter, and there is a relative block of electrical activity at the UPJ (Morita et al, 1981). At these flows, the renal pelvis fills; as renal pelvic pressure rises, urine is extruded into the upper ureter, which is initially in a collapsed state (Griffiths and Notschaele, 1983). Ureteral contractile pressures that move the bolus of urine are higher than renal pelvic pressures, and a closed UPJ may be protective of the kidney in dissipating backpressure from the ureter. As the flow rate increases, the block at the UPJ ceases and a 1:1 correspondence between pacemaker and ureteral contractions develops (Constantinou and Hrynczuk, 1976; Constantinou and Yamaguchi, 1981).

With UPJ obstruction, there may be areas of narrowing or valve-like processes (Maizels and Stephens, 1980) or mucosal folds (Takeyama and Sakai, 2007). In other instances, there is no gross narrowing at the UPJ, and abnormal propagation of the peristaltic impulse is a causative factor in the obstruction. In these instances, there appears to be a functional obstruction at the UPJ, because a large-caliber catheter can be passed readily through the UPJ even though urine transport is inadequate. Murnaghan (1958) related the functional abnormality to an alteration in the configuration of the muscle bundles at the UPJ, and Foote and associates (1970) observed a decrease in musculature at the UPJ. Hanna (1978), in an electron microscopic study of severe UPJ obstructions, noted abnormalities in the musculature of the renal pelvis and disruption of intercellular relations at the UPJ itself. Increased accumulation of collagen has been described in the region of the UPJ with obstruction (Murakumo et al, 1997), and it has been suggested that differences in types I and III collagen in the region of the obstructed UPJ may be age dependent (Yoon et al, 1998). Increases in smooth muscle myosin heavy chain isoforms also have been described in congenital UPJ obstruction (Hosgor et al, 2005). Studies also have shown a decrease in nerves and in NGF messenger RNA (mRNA) expression in UPJ obstruction specimens compared with controls (Wang et al, 1995; Murakumo et al, 1997). An increase in apoptosis of smooth muscle cells in the region of congenital UPJ obstruction has been reported to accompany a

decrease in smooth muscle and nerve terminals and an increase in collagen and elastin (Kajbafzadeh et al, 2006). c-KIT-positive ICC-like cells, which appear to aid in the propagation of electrical impulses from pacemaker cells to typical ureteral smooth muscle cells, have been reported to be both decreased (Solari et al, 2003; Yang et al, 2009) and increased (Koleda et al, 2012) at the obstructed UPJ. Defective contractility of UPJ segments obtained at the time of pyeloplasty has been described (Pontinca et al, 2006). A vessel or adhesive band crossing the UPJ may potentiate the degree of dilatation in any of the forms of UPJ obstruction.

The differences in the reported findings suggest a histopathologic spectrum in the group of cases referred to as *UPJ obstructions*. It appears possible that, at least in some instances, disruption of cell-to-cell propagation of peristaltic activity results in impairment of urine transport across the UPJ.

One must consider input and output when predicting whether or not dilatation will occur; the effects of diuresis and obstruction appear to be complementary and additive with respect to the development of renal pelvic and calyceal dilatation. Some UPJs can handle urine flow regardless of the magnitude of diuresis, others cause dilatation at even the lowest flows, and still others can handle low flows but cause massive dilatation at high flows (Fig. 43-18).

Propulsion of Urinary Bolus

The theoretic aspects of the mechanics of urine transport within the ureter have been described in detail by Griffiths and Notschaele (1983); these are depicted in Figure 43-19.

At normal flow rates, as the renal pelvis fills, a rise in renal pelvic pressure occurs and urine is extruded into the upper ureter, which initially is in a collapsed state. The contraction wave originates in the most proximal portion of the ureter and moves the urine in front of it in a distal direction. The urine that had previously entered the ureter is formed into a bolus. To propel the bolus of urine efficiently, the contraction wave must completely coapt the ureteral walls (Woodburne and Lapides, 1972; Griffiths and Notschaele, 1983), and the pressure generated by this contraction wave provides the primary component of what is recorded by intraluminal pressure measurements. The bolus that is pushed in front of the contraction wave lies almost entirely in a passive, noncontracting part of the ureter (Fung, 1971; Weinberg, 1974).

Baseline, or resting, ureteral pressure is approximately 0 to 5 cm H₂O, and superimposed ureteral contractions ranging from 20 to 80 cm H₂O occur two to six times per minute (Kiil, 1957; Ross et al, 1972). The urine traverses the UPJ to enter the bladder; when functioning properly, the UPJ ensures one-way transport of urine. The bolus is forced into the bladder by the advancing contraction wave, which then dissipates at the UPJ.

As with any tubular structure, the ureter can transport a set maximal amount of fluid per unit time. Under normal flows, in which bolus formation occurs, the amount of urine transported per unit time is significantly less than the maximal transport capacity of the ureter. At extremely high flows, as are used in perfusion studies (Whitaker, 1973), the ureteral walls do not coapt, and a continuous column of fluid, rather than a series of boluses, is transported.

When transport becomes inadequate, stasis of urine occurs with resultant ureteral dilatation. Inadequate transport can result either from too much fluid entering the ureter per unit time or from too little fluid exiting the ureter per unit time. Both input and output must be considered in predicting whether or not ureteral dilatation will occur. For example, a minor degree of obstruction to outflow will cause more dilatation at high flow rates than at low flow rates. Even a normal unobstructed ureter will impede urine transport if the rate of flow is great enough.

Changes in ureteral dimensions that occur in pathologic states may, per se, result in inefficient urine transport, even if the contractile force of the individual fibers is unchanged. The Laplace

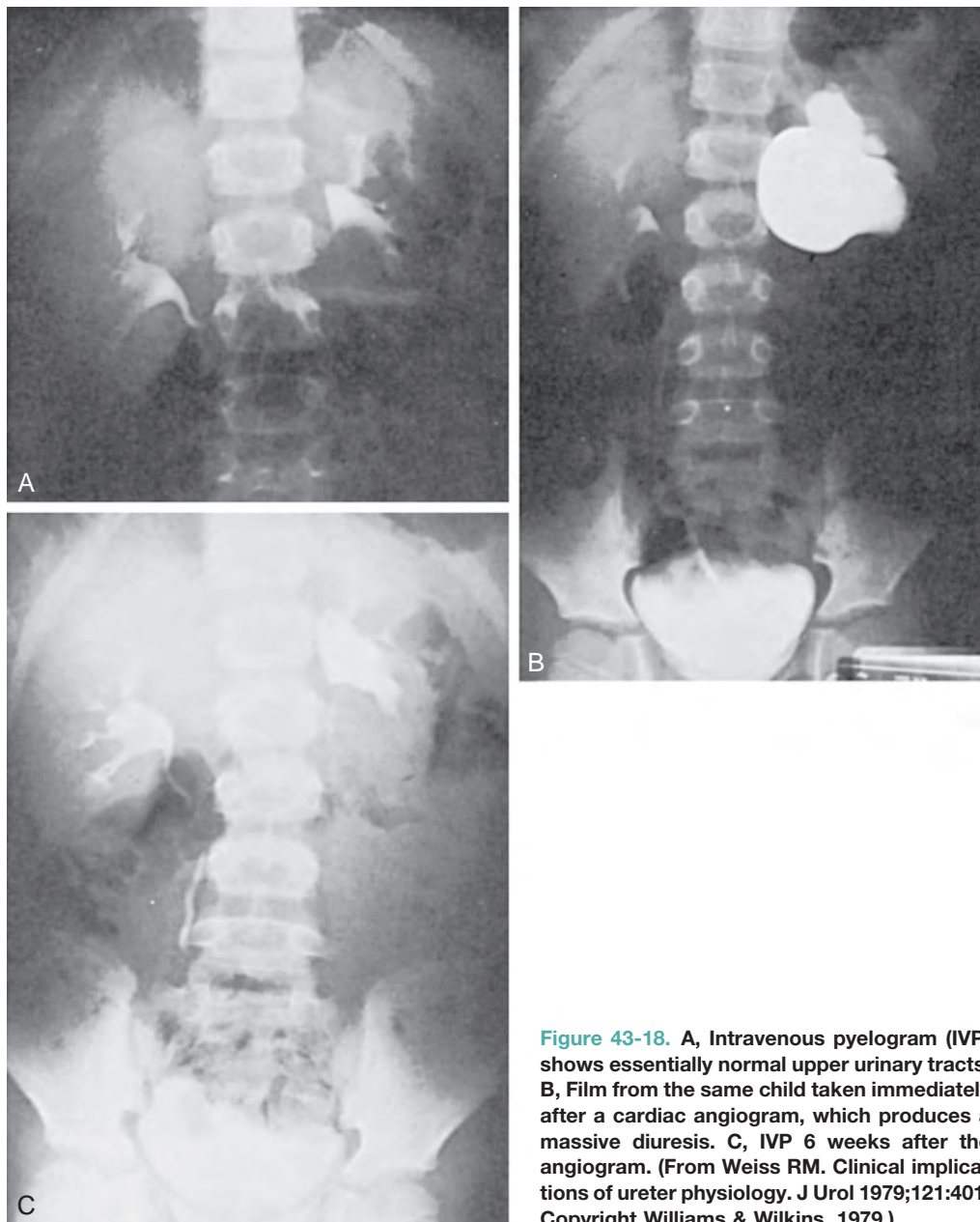


Figure 43-18. A, Intravenous pyelogram (IVP) shows essentially normal upper urinary tracts. B, Film from the same child taken immediately after a cardiac angiogram, which produces a massive diuresis. C, IVP 6 weeks after the angiogram. (From Weiss RM. Clinical implications of ureter physiology. *J Urol* 1979;121:401. Copyright Williams & Wilkins, 1979.)

equation expresses the relation between the variables that affect intraluminal pressure:

$$\text{Pressure} = \frac{\text{tension} \times \text{wall thickness}}{\text{radius}}$$

An increase in ureteral diameter in itself can decrease intraluminal pressure and result in inefficient urine transport. Such dimensional changes may, at least theoretically, be deleterious (Griffiths, 1983). Another factor may be the histologic composition of the dilated ureter, as evidenced by the description of different amounts of type I and type III collagen in primary obstructed and refluxing megaureters (Lee et al, 1998).

Effect of Diuresis on Ureteral Function

With increasing urine flow rates, the initial response of the ureter is to increase peristaltic frequency. After the maximal frequency is achieved, further increases in urine transport occur by means

of increases in bolus volume (Morales et al, 1952; Constantinou et al, 1974). At relatively low flow rates, small increases in flow result in large increases in peristaltic frequency. At higher flow rates, relatively large increases in flow result in only small increases in peristaltic frequency. As the flow rate continues to increase, several of the boluses coalesce, and finally the ureter becomes filled with a column of fluid and dilates. At these high flow rates, urine transport is through an open tube.

Effects of Bladder Filling and Neurogenic Vesical Dysfunction on Ureteral Function

Ureteral dilatation can result either from an increase in fluid input or from a decrease in fluid output from the ureter. The relation between ureteral intraluminal pressure and intravesical pressure is important in determining the efficacy of urine passage across the UVJ into the bladder. In the case of the normal ureter under normal physiologic rates of flow, ureteral contractile pressure exceeds intravesical pressure, resulting in passage of urine into the bladder. In

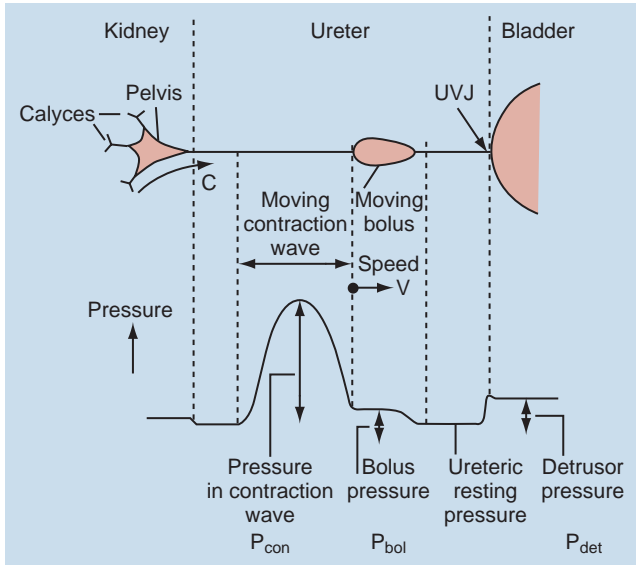


Figure 43-19. Schematic representation of a single bolus in the ureter moving away from the renal pelvis and toward the bladder. Arrow C indicates the direction of bolus transport. The corresponding distribution of pressure within the urinary tract is shown in the lower tracing. UVJ, ureterovesical junction. (From Griffiths DJ, Notschaele C. The mechanics of urine transport in the upper urinary tract. *Neurourol Urodyn* 1983;2:155.)

the dilated, poorly contracting ureter or in the normal ureter at extreme flow rates, the ureter does not coapt its walls to form boluses, and the baseline pressure in the column of urine within the ureter must exceed intravesical pressure for urine to pass into the bladder.

The pressure within the bladder during the storage phase is of paramount importance in determining the efficacy of urine transport across the UVJ. This is the pressure that the ureter needs to work against for the longest period of time. During filling of the normal bladder, sympathetic impulses and the viscoelastic properties of the bladder wall inhibit the magnitude of the intravesical pressure rise—that is, the tonus limb. With filling, the normal bladder maintains a relatively low intravesical pressure (McGuire, 1983) that facilitates the transport of urine across the UVJ and prevents ureteral dilatation. In the noncompliant fibrotic bladder and in some forms of neurogenic vesical dysfunction, the bladder is autonomous, and relatively small increases in bladder volume result in large increases in intravesical pressure with resultant impairment of ureteral emptying. The ureter initially responds to its decreased ability to empty by increasing its peristaltic frequency (Zimskind et al, 1969; Rosen et al, 1971; Fredericks et al, 1972). Ultimately, stasis occurs with the development of ureteral dilatation. The ureter has been shown to decompensate when sustained intravesical pressure approaches 40 cm H₂O (McGuire et al, 1981).

Physiology of the Ureterovesical Junction

Griffiths (1983) has analyzed the factors involved in urine transport across the UVJ. Under normal conditions and at normal flow rates, the contraction wave, which occludes the ureteral lumen, propagates distally with the urine bolus in front of it. When the bolus reaches the UVJ, the pressure within the bolus must exceed intravesical pressure for the bolus of urine to pass across the UVJ into the bladder. Under these conditions, in which the contraction wave is able to coapt the ureteral wall and move the urinary bolus distally, the pressure generated by the contraction wave exceeds the pressure within the urinary bolus. The contracted ureteral ring just proximal to the ureteral orifice at the UVJ is relevant in the antireflux

mechanism (Roshani et al, 1996). As the bolus is ejected into the bladder, the distal ureter retracts within its sheaths; this telescoping of the ureter within its sheaths aids in decreasing UVJ resistance to flow and thus facilitates urine passage into the bladder (Blok et al, 1985). The UVJ does not relax (Weiss and Biancani, 1983). Impediment of efficient bolus transfer across the UVJ into the bladder can occur when there is an obstruction at the UVJ, when intravesical pressure is excessive, or when flow rates are so high as to exceed the transport capacity of the normal UVJ. Under such conditions, in which the bolus of urine cannot pass freely into the bladder, the pressure within the bolus increases and may exceed the pressure in the contraction wave. This results in an inability of the contraction wave to completely occlude the ureter; there is retrograde flow of urine from the bolus, and only a fraction of the urinary bolus passes across the UVJ into the bladder. Griffiths (1983) has presented theoretic evidence to show that a similar situation of impaired bolus transport across the UVJ would be expected if the ureter were wide or weakly contracting, even if the UVJ were perfectly normal. The wider and more weakly contracting the ureter, the lower the UVJ resistance must be to not interfere with bolus transport. The resistance to flow at the UVJ has been variously attributed to forces in the trigone (Tanagho et al, 1968) and to detrusor pressure (Coolsaet et al, 1982).

The theoretic considerations outlined by Griffiths (1983) have direct clinical implications. If the UVJ is obstructed (i.e., has an abnormally high resistance to flow) or if the detrusor pressure is excessive, large boluses occurring at high-flow conditions would not be completely discharged into the bladder, because the contraction wave pushing the bolus would be forced open and intraureteral reflux would occur. Such obstruction at the UVJ would be detected by perfusion studies as popularized by Whitaker (1973) (i.e., the Whitaker test). On the other hand, the theory of Griffiths (1983) suggests that a similar breakdown of bolus discharge into the bladder can occur in the wide or weakly contracting ureter at high flow rates even if the UVJ is normal and that such a condition would go undetected by a Whitaker perfusion test.

There is evidence that gravity may assist urine transport and that the erect position may aid urine transport across the UVJ, especially in individuals with dilated upper tracts (Schick and Tanagho, 1973). From a practical standpoint, George and associates (1984) suggested that bed rest may be deleterious to renal function in individuals with urinary retention and wide upper urinary tracts.

PATHOLOGIC PROCESSES AFFECTING URETERAL FUNCTION

Effect of Obstruction on Ureteral Function

General

The effect of obstruction on ureteral function depends on the degree and duration of the obstruction, on the rate of urine flow, and on the presence or absence of infection. After the onset of obstruction, a backup of urine occurs within the urinary collecting system, along with an associated increase in baseline (resting) ureteral intraluminal pressure and an increase in ureteral dimensions—that is, an increase in both length and diameter (Fig. 43-20) (Rose and Gillenwater, 1973; Biancani et al, 1976). The increase in intraluminal pressure depends on the kidney's continued production of urine that cannot pass beyond the site of obstruction; the increase in ureteral dimensions results from the increased ureteral intraluminal pressure and the increased volume of urine retained within the ureter. A transient increase in the amplitude and frequency of the peristaltic contraction waves accompanies these initial dimensional and ureteral baseline (resting) pressure changes (Rose and Gillenwater, 1978; Hammad et al, 2011). There also is a decrease in the velocity of electrical impulses which correlates with decreased peristaltic activity (Hammad et al, 2011). With time, as the ureter fills with urine, the peristaltic contraction waves become smaller and are unable

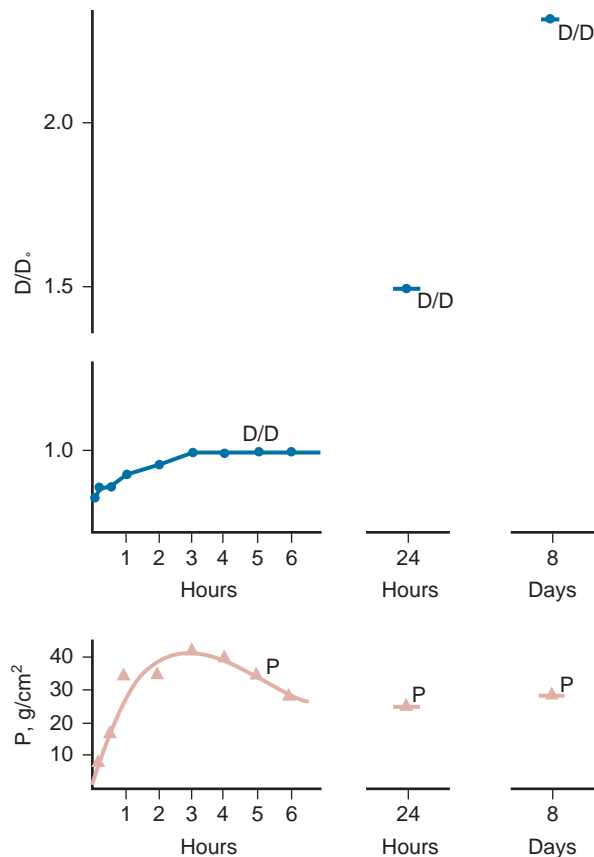


Figure 43-20. Intraluminal pressure and diameter changes after obstruction of rabbit ureter. The time from the onset of obstruction is on the abscissa. The change in diameter (D/D_0) is on the upper ordinate, and the intraluminal pressure is on the lower ordinate. During the initial 3 hours of obstruction, intraluminal pressure increased to reach a maximum and was associated with an increase in diameter. Three to 6 hours after the onset of obstruction, pressure declined, although diametral deformation persisted. After 6 hours, pressure remained essentially unchanged, although the diameter continued to increase. Each data point represents the mean \pm standard error of mean (SEM). D, diameter during deformation; D_0 , initial diameter; P, intraluminal pressure. (Modified from Biancani P, Zabinski MP, Weiss RM. Time course of ureteral changes with acute and chronic obstruction. *Am J Physiol* 1976;231:393.)

to coapt the ureteral wall. Urine transport then becomes dependent on hydrostatic forces generated by the kidney (Rose and Gillenwater, 1973). Superimposed infection may result in a complete absence of contractions in the obstructed ureter and contributes to impairment of urine transport (Rose and Gillenwater, 1973).

Within a few hours after the onset of obstruction, the intraluminal baseline ureteral pressure reaches a peak and then declines to a level only slightly higher than the normal baseline pressure. This occurs at a time in which dimensional changes remain stable (Biancani et al, 1976). The decrease in ureteral pressure can be attributed to changes in intrarenal hemodynamics, such as a reduction in renal blood flow (Vaughan et al, 1971), with resultant decreases in the glomerular filtration rate and intratubular hydrostatic pressure (Gottschalk and Mylle, 1956). Fluid reabsorption into the venous and lymphatic systems and a decrease in wall tension also may play a role in the reduction in baseline ureteral pressure (Rose and Gillenwater, 1978). The persistence of dimensional changes in the face of a decrease in intraluminal pressure depends on the hysteric properties of the viscoelastic ureteral structure (Fig. 43-21) (Weiss et al, 1972; Biancani et al, 1973; Vereecken et al, 1973; Biancani et al, 1976).

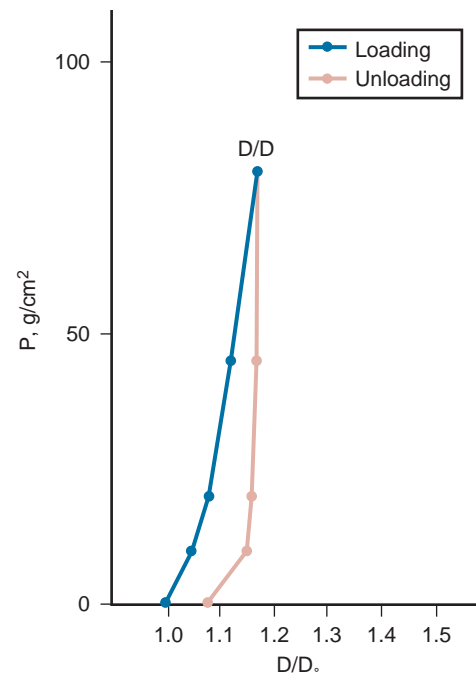


Figure 43-21. Demonstration of hysteric properties of ureter show that dimensional changes depend on intraluminal pressure and on the direction of change of that pressure. At comparable pressures, deformations are greater during ureteral emptying than during ureteral filling. The blue line shows data obtained during loading; the pink line, data obtained during unloading. D, diameter during deformation; D_0 , initial diameter; P, intraluminal pressure in grams per square centimeter. (Modified from Biancani P, Zabinski MP, Weiss RM. Time course of ureteral changes with acute and chronic obstruction. *Am J Physiol* 1976;231:393.)

As the obstruction persists, there is a gradual increase in ureteral length and diameter, which reaches considerable dimensions. This occurs even though ureteral pressure remains at a relatively low and constant level. This process, observed in viscoelastic structures, is referred to as *creep* (Biancani et al, 1973). A continued, albeit small, urine production is required for the continuing increase in intraureteral volume. Such changes account for the relatively low intrapelvic pressures clinically observed in the massively dilated, chronically obstructed upper urinary tract (Backlund et al, 1965; Struthers, 1969; Vela-Navarrete, 1971; Djurhuus and Stage, 1976) and in experimentally produced obstruction (Schweitzer, 1973; Koff and Thrall, 1981a). One could postulate that with prolonged complete obstruction, the total cessation of urine output ultimately occurs. A subsequent decrease in ureteral dimensions would depend on whether urine is reabsorbed and on the mechanical properties of the ureter at that time.

To determine the effect of obstruction on the contractile properties of the ureter, a rabbit model in which the ureter is totally obstructed for 2 weeks has been used (Hausman et al, 1979; Biancani et al, 1982). After 2 weeks of obstruction, the cross-sectional muscle area increases by 250%, ureteral length by 24%, and ureteral outer diameter by 100%. In addition to undergoing muscle hypertrophy, in vitro segments from obstructed ureters develop greater contractile forces, in both longitudinal and circumferential directions, than do segments from control ureters (Fig. 43-22). With experimental obstruction at the UPI, there also is an increase in the frequency and amplitude of spontaneous mechanical contractions of the renal pelvis and an increase in the amplitude of phenylephrine and serotonin (5-hydroxytryptamine [5-HT]) induced contractions (Ekinci et al, 2004). Determination of stress (force per unit area of muscle) provides a means of determining whether the

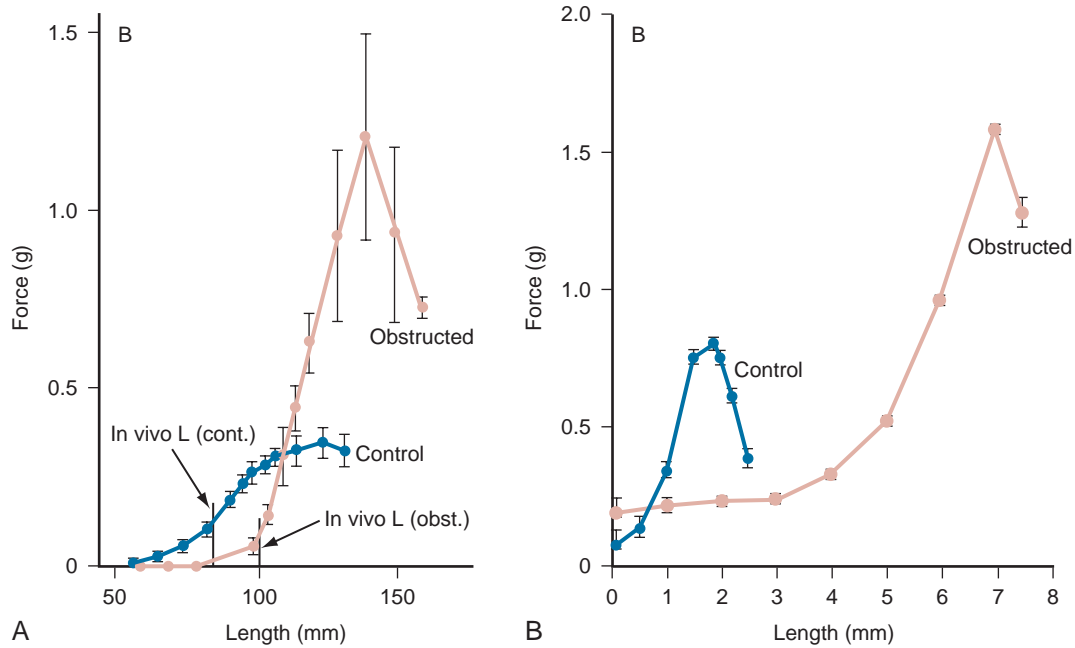


Figure 43-22. A, Active (contractile) longitudinal force-length relations of control (blue circles) and obstructed (pink circles) rabbit ureters. Each data point represents mean \pm standard error of mean (SEM). B, Active (contractile) circumferential force-length relations of obstructed (pink circles) and control (blue circles) ureteral rings. Vertical bars correspond to in vivo lengths of control and obstructed segments. (A, From Hausman M, Biancani P, Weiss RM. Obstruction induced changes in longitudinal force-length relations of rabbit ureter. *Invest Urol* 1979;17:223. Copyright Williams & Wilkins, 1979; B, from Biancani P, Hausman M, Weiss RM. Effect of obstruction on ureteral circumferential force-length relation. *Am J Physiol* 1982;243:F204.)

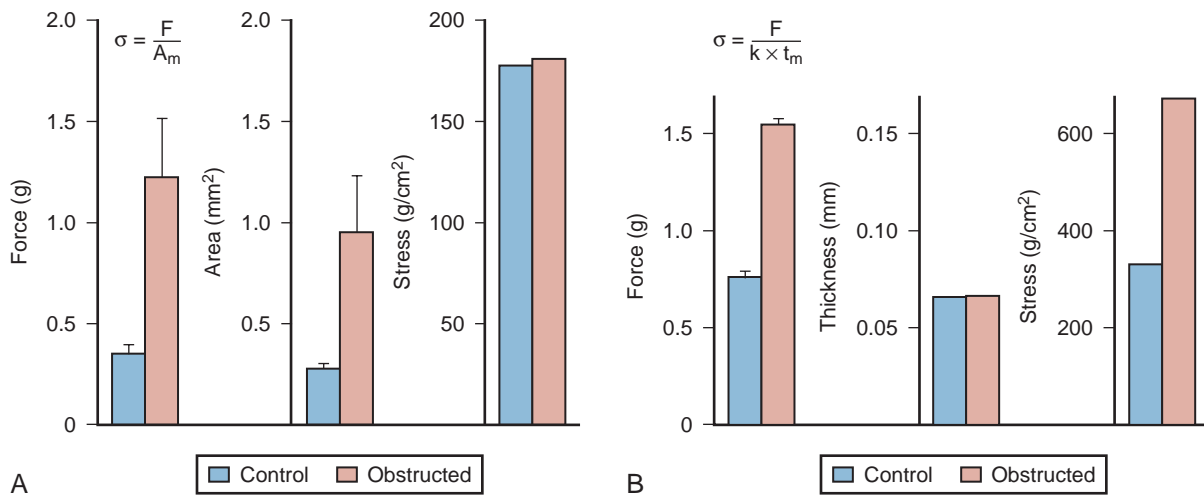


Figure 43-23. A, Longitudinal force, cross-sectional muscle area, and longitudinal stress at the length of maximal active force development. B, Circumferential force, average muscle thickness, and circumferential stress at the length of maximal active force development. σ , stress; A_m , cross-sectional muscle area; F , force; t_m , average thickness of muscle layer, a constant. (From Weiss RM, Biancani P. A rationale for ureteral tapering. *Urology* 1982;20:482.)

observed increases in developed force result from an increase in contractility or from an increase in muscle mass alone. The increases in force were associated with an increase in maximal active circumferential stress but no change in maximal active longitudinal stress (Fig. 43-23). Because there is an increase in circumferential stress and no change in longitudinal stress, the sum of the stresses (total stress) or overall contractility increases after 2 weeks of obstruction. For these differences in longitudinal and circumferential stresses to occur after obstruction, rotation of muscle bundles must occur;

otherwise, longitudinal and circumferential stresses would increase equally. The rotation could result from the greater increase in diameter than in length after obstruction, from remodeling of the muscle fibers, or from both. In addition to an increase in EFS-induced ureteral contractions with obstruction, carbachol, phenylephrine, and KCl also caused a greater increase in contractions in obstructed ureters, and the Rho-kinase inhibitor, Y-27632, has a more pronounced effect in inhibiting these contractile events in obstructed ureters (Turna et al, 2007). The expression of the two Rho-kinase

isoforms, ROCK-1 and ROCK-2, is increased in the obstructed ureter (Turna et al, 2007).

Thus, the ureter dilated after 2 weeks of obstruction is not mechanically decompensated but rather undergoes changes that result in an increase in contractility. Despite both the muscle hypertrophy and the increase in contractility, it is clinically and experimentally evident that the obstructed, dilated ureter is less able than the normal ureter to generate the contractile pressures required for urine transport (Rose and Gillenwater, 1973). The decrease in the ability to generate an intraluminal pressure despite an increase in contractility results from the increase in ureteral diameter that occurs after obstruction and can be explained by the Laplace equation:

$$\text{Pressure} = \frac{\text{stress} \times \text{wall thickness}}{\text{radius}}$$

Although contractility (stress) increases after 2 weeks of obstruction, the decrease in the wall's thickness-to-radius ratio, resulting from the marked increase in intraluminal diameter and thinning of the muscle layer, accounts for the decrease in pressure. It must be realized that a longer duration of obstruction or the presence of infection may alter these relations.

Estimates of intraluminal pressures as a function of diameter (pressure-diameter curves) can be calculated from in vitro circumferential force-length data (Fig. 43-24) (Biancani et al, 1982; Weiss and Biancani, 1982) and provide insight as to how obstruction interferes with urine transport. The validity of such calculations is supported by their correspondence to actual in vivo measurements (Rose and Gillenwater, 1973; Biancani et al, 1976). The obstructed ureter at in vivo dimensions has a higher resting (baseline) pressure and a lower contractile (active) pressure than does a control ureter. In the control ureter, the total (active plus passive or resting) pressure developed at all diameters exceeds the passive pressure marked by the horizontal dotted line, and thus the generated active or contractile pressures are able to fully coapt the ureteral lumen and propel the urine bolus. In the obstructed ureter at diameters less

than 3.3 mm, the passive pressure, as marked by the horizontal dotted line, exceeds the total pressure. The contraction ring therefore is incapable of contracting below this diameter, and the pressure in the whole ureter remains approximately uniform and equal to the passive pressure. The principal effect of the contraction wave in the obstructed dilated ureter is to slightly reduce the ureteral volume and thereby slightly raise the overall resting pressure. Thus, although the obstructed ureter is able to develop greater circumferential contractile forces than the control ureter, the expected intraluminal pressure generated by the obstructed ureter would differ little from baseline (resting) pressure, and the contraction wave occurring during propagation of peristalsis would be incapable of coapting the ureteral lumen and propelling the urine bolus in an effective manner.

It should be noted that the calculated active pressure in the obstructed ureter estimates the pressure that would develop if the whole ureter were to contract simultaneously and uniformly throughout its whole length, rather than the pressure measured in a peristaltic contraction wave, which involves contraction of only a small segment of ureter at a given time. The fact that the calculated pressures in the obstructed ureter are, if anything, a slight overestimate of expected pressures only further supports the conclusion that the obstructed ureter is incapable of coapting its lumen and efficiently propelling the urine bolus. If, however, the urine were removed from the lumen of the ureter (e.g., by relieving the obstruction), the ureter obstructed for 2 weeks would be able to immediately coapt its lumen and produce pressures comparable with those of control ureters. This can be appreciated from Figure 43-24, in which the total pressure in the obstructed ureter near zero diameter can be seen to be comparable with the total pressure in the control ureter at a similar diameter. Thus, 2 weeks of obstruction results in an increase in ureteral contractility but a decrease in contractile intraluminal pressures. This decrease in the ability to generate an active intraluminal pressure and to coapt the ureteral lumen impairs urine transport in the obstructed ureter.

Obstruction of the fetal ureter also is accompanied by an increase in ureteral weight, smooth muscle mass, extracellular matrix, and the frequency and amplitude of spontaneous ureteral contractile activity (Santis et al, 2000). Obstructed and refluxing dilated ureters have an increase in type I and type III collagen and an increased ratio of collagen to smooth muscle (Gearhart et al, 1995; Lee et al, 1998). Hydrocortisone, verapamil (a calcium channel blocker), and D-penicillamine reduce collagen III production, which is increased in a variety of obstructed ureteral states and in ureteral cell cultures (Wolf et al, 1996). Obstruction also has been shown to alter the hierarchic organization of the multiple coupled pacemakers that normally coordinate peristaltic activity (Constantinou and Djurhuus, 1981; Djurhuus and Constantinou, 1982). Such disruption causes discoordination of the pelvic contractility with resultant incomplete emptying of the renal pelvis that contributes to upper urinary tract dilatation. Retrograde propagation of electrical activity or absence of electrical activity has been observed distal to an experimental obstruction (Hammad et al, 2011).

Physiologic Methodologies for Assessing Clinical Obstruction

Various radiographic methodologies, the rationale for the use of which is based on physiologic principles, are used in the evaluation and differentiation of upper urinary tract dilatation and obstruction. Description of these examinations, which include diuretic urography, diuretic magnetic resonance urography, diuretic ultrasonography, diuretic radionuclide renography, pulsed Doppler sonographic assessment of renal vascular resistance, and ultrasonographic evaluation of ureteral peristalsis, is beyond the scope of this chapter. The best methods now available for differentiating obstructive from nonobstructive dilatation depend on assessing the efficacy of urine transport. When transport becomes inadequate, urine stagnates and dilatation occurs. Dilatation depends on the compliance of the system and can result either from too much fluid entering the

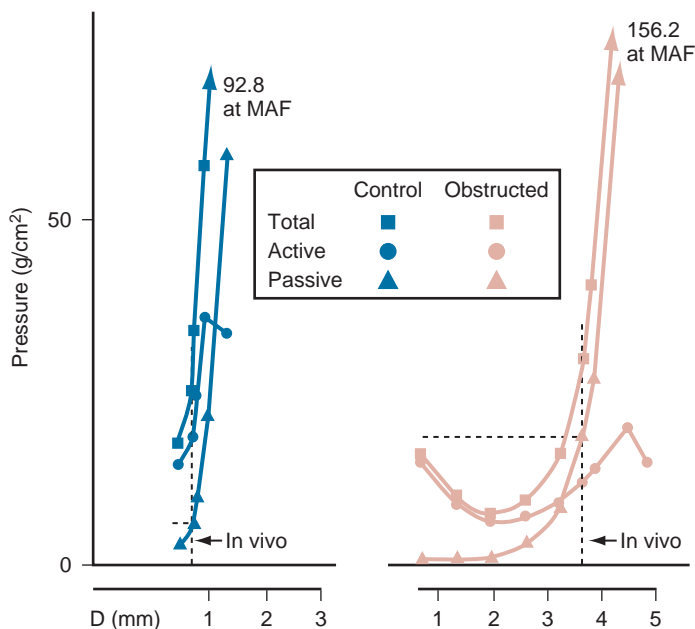


Figure 43-24. Pressure-diameter relationships of control and obstructed ureters. Calculated total, active, and passive pressures are shown as a function of intraluminal diameter (D). In vivo passive pressures are indicated by horizontal dashed lines and in vivo dimensions by vertical dashed lines. (Modified from Biancani P, Hausman M, Weiss RM. Effect of obstruction on ureteral force-length relations. *Am J Physiol* 1982;243:F204.)

system per unit time or from too little fluid exiting the system per unit time. The properly functioning upper urinary tract should transport urine over the entire range of physiologically possible flow rates without undergoing marked deformational changes or increases in intraluminal pressure of a magnitude that would be deleterious to the function of the ureter, renal pelvis, or kidney.

Measurement of basal or resting intraluminal pressures does not help in differentiating obstructive from nonobstructive dilatation, because the pressures may be low even when obstruction is present (Backlund et al, 1965; Struthers, 1969; Vela-Navarrete, 1971). The values obtained vary with the state of hydration, the degree of renal function, the severity and duration of obstruction, and the compliance of the system. Perfusion studies are used in an attempt to differentiate dilated systems that are obstructed from dilated systems that are not obstructed (Backlund and Reuterskiöld, 1969a, 1969b; Reuterskiöld, 1969, 1970; Whitaker, 1973, 1978). The technique involves cannulating the dilated upper urinary tract and perfusing the system at a rate of 10 mL/min. Pressures are measured after the achievement of steady-state conditions, which occur when an equilibrium is reached between the flow into and out of the system. Fluoroscopic monitoring aids in the interpretation of the data. The basic hypothesis in perfusion studies is that if the dilated upper urinary tract can transport 10 mL/min (a fluid load greater than it would ever be expected to handle during usual physiologic states) without an inordinate increase in pressure, any degree of obstruction that is present is not clinically significant. Whitaker (1978) and Whitaker and Flower (1981) concluded from a large clinical experience that under these flow conditions, a pressure less than 15 cm H₂O correlates with a non-obstructive state, whereas pressures greater than 22 cm H₂O invariably correlate with clinically significant obstruction (Whitaker, 1978; Witherow and Whitaker, 1981). With this definition, minor degrees of obstruction could go undetected; however, the presumption is that if at high flows the hydrostatic pressure in the system is not at a level that would produce renal deterioration, then lower, more physiologic flows surely will be tolerated. The high flows are used to stress the system and thus to detect the slightest propensity to obstruction. The interpretation of data obtained by perfusion studies is schematically shown in Figure 43-25.

For relevant information to be obtained, strict adherence to detail is required in the performance of perfusion studies. Care must be taken to ensure that an equilibrium state has been reached before pressure is measured. Extrinsic factors that affect the resistance to flow, such as the needle size, length and compliance of extrinsic tubing, viscosity of the perfusion fluid, temperature, and flow rate, must be considered when quantitative data are obtained (Toguri and Fournier, 1982). Furthermore, the bladder should be continuously drained to eliminate the bladder's effect on urine transport.

When performed and interpreted properly, perfusion studies may provide clinically relevant information in select patients. The basic problem in the interpretation of data with this and other diagnostic methods is the definition of "clinically relevant obstruction"—that is, just how much resistance to flow or increase in pressure is required to produce renal functional or anatomic deterioration as a function of time, taking into account the compliance of the system (Koff and Thrall, 1981b). Also, it is theoretically possible that the wide or weakly contracting ureter at high flow rates may interfere with bolus transport even if the UVJ is normal (Griffiths, 1983). Such an obstructive process would not be detected by perfusion studies.

These theoretic considerations provide a rationale for **ureteral tapering** (Hendren, 1970). The Laplace equation provides a possible explanation for anticipated improvement in function resulting from tapering. With ureteral tapering, muscle thickness and the ability of the ureteral fibers to contract (stress) are unchanged. The decrease in radius resulting from tapering itself, according to the Laplace equation, could account for higher intraluminal pressures, which could improve urine transport. Thus, the tapered ureter may coapt its walls more readily and generate higher intraluminal pressures even though the material itself has not changed (Weiss and Biancani, 1982). Although the possibility of deleterious effects

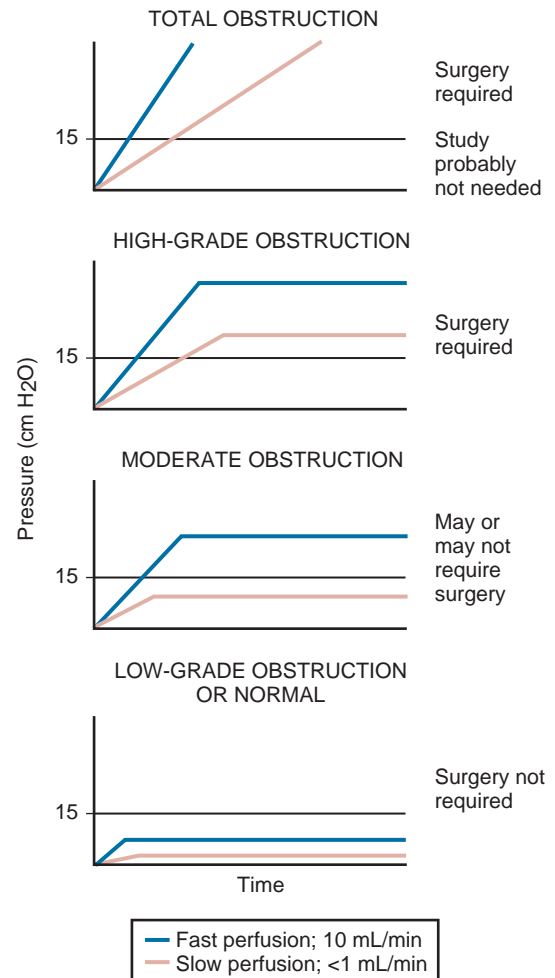


Figure 43-25. Schematic representation of data that can be obtained with perfusion studies. A fast perfusion rate, 10 mL/min, would be used in a standard Whitaker test. A slow perfusion rate, less than 1 mL/min, would be closer to more physiologic rates of flow. (From Weiss RM. Clinical implications of ureteral physiology. *J Urol* 1979;121:401. Copyright Williams & Wilkins, 1979.)

of the wide "nonobstructed" ureter remains controversial, one should consider such effects when interpreting data obtained with the present modalities for diagnosing obstruction and when determining management.

Relation between Vesicoureteral Reflux and Ureteral Function

Factors that have been implicated in the development of vesicoureteral reflux include (1) anatomic and functional abnormalities at the UVJ, (2) inordinately high intravesical pressures, and (3) impaired ureteral function. The normal intravesical ureter is approximately 1.5 cm in length and takes an oblique course through the bladder wall. It is composed of an intramural segment surrounded by detrusor muscle and a submucosal segment that lies directly under the bladder urothelium (Tanagho et al, 1968). The relation between the length and the diameter of this intravesical segment of ureter appears to be a factor in the prevention of vesicoureteral reflux. Paquin (1959) noted that the normal ratio of intravesical tunnel length to ureteral diameter was 5:1, and Tanagho and associates (1969) noted that the ratio was 1.4:1 in children with vesicoureteral reflux. The 5:1 ratio may be an overestimation, and a more recent study reported the proportion of intravesical ureteral length to intravesical ureteral diameter to be 2.23:1 (Oswald et al, 2003b).

The ratio of intravesical ureteral length to ureteral diameter is smaller in the fetus, being 0.69:1 and 1.23:1 in 11- and 20-week-old fetuses, respectively (Oswald et al, 2003a). Reflux may occur when the intravesical tunnel is destroyed. Trigonal function also may be a factor in the prevention of vesicoureteral reflux. Tanagho and associates (1965) created vesicoureteral reflux in the cat by disruption of the trigone or by sympathectomy and, conversely, increased the pressure within the intravesical ureter by electric stimulation of the trigone or by administration of IV epinephrine. The development of vesicoureteral reflux in individuals with bladder outlet obstruction and neurogenic vesical dysfunction provides evidence that increased intravesical pressures may also be a factor in certain instances of reflux.

A significant percentage of units with vesicoureteral reflux improve spontaneously with age. In a study by Jørgensen and colleagues (1984), 35% of young pigs had vesicoureteral reflux, which disappeared with age. In the pig, significant growth and organization of smooth muscle and increase in innervation occur during the postnatal period, and this might be the anatomic correlate of maturation of the UVJ during infancy and the spontaneous functional disappearance of reflux (Pirker et al, 2007).

Although an abnormality of the UVJ is the primary causative factor in most cases of reflux, there is evidence to suggest that decreased ureteral peristaltic activity can be a contributory factor. This may explain why a normal ureter may not reflux even when reimplanted into a bladder without a submucosal tunnel (Debruyne et al, 1978) or why a defunctionalized refluxing ureter may cease to reflux when a proximal diversion is taken down (Teale et al, 1976; Weiss, 1979). The observation that vesicoureteral reflux may temporarily cease after ureteral electric stimulation (Melick et al, 1966) further supports this possibility.

Even the mildest forms of vesicoureteral reflux are associated with a decreased frequency of ureteral peristalsis (Kirkland et al, 1971; Weiss and Biancani, 1983). Although this may offer further evidence that decreased peristaltic activity is a possible causative factor in the development of reflux, an alternative interpretation is that the decreased peristaltic activity reflects changes in ureteral or renal function resulting from the reflux. Finally, the success rate of antireflux procedures is lower with poorly functioning dilated ureters, and, although this may be related to technical factors, decreased peristaltic activity may be another reason for failure.

Studies in normal and mildly refluxing systems have shown that there is a high-pressure zone in the distal ureter, with a resultant pressure gradient across the UVJ (Weiss and Biancani, 1983).

Although the cause of the UVJ gradient is not known, the weight of the fluid within the bladder compressing the intravesical ureter may be a factor. Another causative factor may be bladder or trigonal tension involving myogenic or neurohumoral mechanisms. With bladder filling, there is an increase in the amplitude of the high-pressure zone that is greater in nonrefluxing than in refluxing systems. With bladder filling, the resultant UVJ-bladder pressure gradient increases in nonrefluxing systems, whereas it decreases and may disappear in refluxing systems (Fig. 43-26) (Weiss and Biancani, 1983). This decrease in pressure gradient may correspond to the time when reflux occurs and may be related to lateralization of the ureteral orifice and shortening of the intravesical tunnel. More recent studies have shown a decrease in basal and maximum pressures at the UVJ of refluxing ureters that correlated with histologic changes (Arena et al, 2007). The histologic changes included a degree of smooth muscle deterioration and atrophy, an increase in collagen deposition, and fewer c-KIT-positive ICC-like cells at the UVJ in patients with vesicoureteral reflux (Oswald et al, 2004; Schwentner et al, 2005; Arena et al, 2007). MMP-1 production and the number of CD-68+ macrophages are increased, whereas S-100 positive myelinated nerves are decreased in the distal portion of refluxing ureters (Oswald et al, 2004; Radmayr et al, 2010). MMP-1 cleaves collagen and is frequently seen in collagen-rich regions. Some MMPs can damage nerves. CD-68+ macrophages presumably phagocytize cells undergoing apoptosis. Contraction of the longitudinal muscles at the UVJ also may function as an active antireflux mechanism (Schwentner et al, 2005).

Effect of Infection on Ureteral Function

Infection within the upper urinary tract may impair urine transport. Pyelonephritis in the monkey has been associated with decreased peristaltic activity (Roberts, 1975). Furthermore, Rose and Gillenwater (1973) have shown that infection can potentiate the deleterious effects of obstruction on ureteral function. In 1913, Primbs showed that *Escherichia coli* and staphylococcal toxins inhibited contractions of in vitro guinea pig ureteral segments (Primbs, 1913). A number of studies have confirmed that bacteria and *E. coli* endotoxin can inhibit ureteral activity (Grana et al, 1965; King and Cox, 1972), although these findings have not been universal (Struthers, 1976; Thulesius and Araj, 1987). Uropathogenic *E. coli* (UPEC) decreased phasic and high K-induced contractions of isolated human and rat ureteral segments (Floyd et al, 2010). These inhibitory changes were the result of activation of K channels

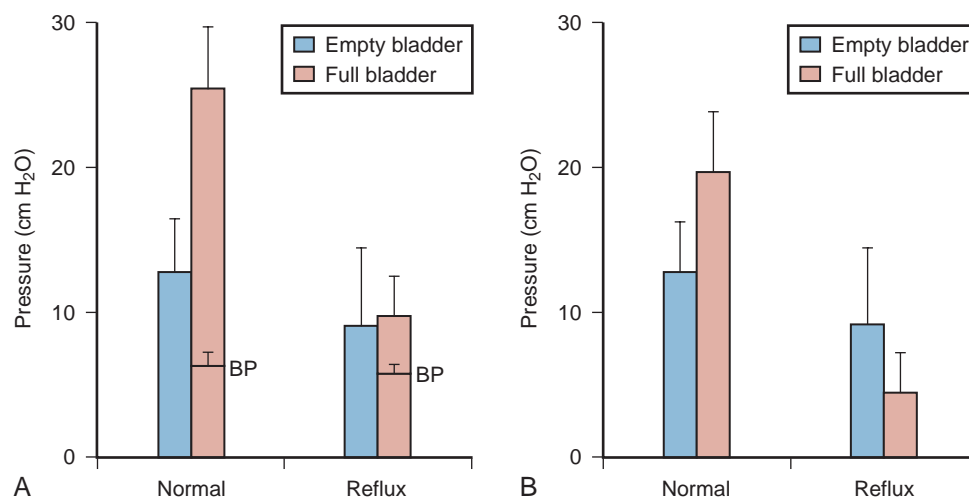


Figure 43-26. A, Ureterovesical junction pressures. Bladder pressure is approximately 0 cm H₂O with the bladder empty and is labeled "BP" with the bladder full. B, Pressure gradient across the ureterovesical junction, obtained by subtracting the bladder pressure from the ureterovesical junction pressure. (From Weiss RM, Biancani P. Characteristics of normal and refluxing ureterovesical junctions. *J Urol* 1983;129:858. Copyright Williams & Wilkins, 1983.)

with resultant inhibition of calcium entry through voltage dependent L-type calcium channels. UPEC also caused impairment of urothelial barrier function. Urothelial cells also show an increased expression of iNOS in response to bacterial invasion. Activation of iNOS leads to the formation of NO, a known smooth muscle relaxant, and this may contribute to inhibitory effects of infection on ureteral contractility (Poljakovic and Persson, 2003).

In humans, irregular peristaltic contractions with an often-decreased amplitude have been recorded with infection, and an absence of activity has been noted in the more severe cases (Ross et al, 1972). Furthermore, ureteral dilatation has been reported to result from retroperitoneal inflammatory processes secondary to appendicitis, regional enteritis, ulcerative colitis, or peritonitis (Makker et al, 1972). Infection also may reduce the compliance of the intravesical ureter and permit reflux to occur in situations in which the UVJ is intrinsically of marginal competence (Cook and King, 1979).

Effect of Calculi on Ureteral Function

Factors that affect the spontaneous passage of calculi are (1) the size and shape of the stone (Ueno et al, 1977); (2) intrinsic areas of narrowing within the ureter; (3) ureteral peristalsis; (4) hydrostatic pressure of the column of urine proximal to the calculus (Sivula and Lehtonen, 1967); and (5) edema, inflammation, and spasm of the ureter at the site at which the stone is lodged (Holmlund and Hassler, 1965).

In an attempt to understand the physiologic processes that contribute to or hinder the passage of stones through the ureter, Crowley and associates (1990) created acute ureteral obstruction in the dog with an intraluminal balloon catheter and measured intraluminal ureteral pressures and peristaltic activity above and below the acutely obstructed site. The peristaltic rate and baseline, peak, and delta (peak minus baseline) pressures increased proximal to the site of obstruction. In contrast, the peristaltic rate remained unchanged distal to the obstruction, despite decreases in the baseline, peak, and delta pressures. It was suggested that failure of transmission of effective peristalsis across the site of obstruction may hinder stone passage; however, this remains to be proved. In an experimental study, implantation of an artificial calculus in a rat ureter resulted in an increase in the amplitude of contractions, a decrease in the rate of contractions, and a decrease in baseline pressure (Laird et al, 1997). These changes persisted for a period after spontaneous passage of the calculus. It was suggested that the increased motility caused by a stone contributes to the visceral pain associated with ureteral stone passage.

Two factors that appear to be most useful in facilitating stone passage are an increase in hydrostatic pressure proximal to a calculus and relaxation of the ureter in the region of the stone. In support of the theory that hydrostatic pressure facilitates stone passage, artificial concretions with holes were shown to move more slowly in the rabbit and dog ureter than those without holes (Sivula and Lehtonen, 1967). Furthermore, ureteral ligation proximal to a concretion, which decreases hydrostatic pressure by decreasing urine output and decreases peristaltic activity proximal to a stone, hampers stone passage (Sivula and Lehtonen, 1967).

With respect to the potential facilitative effect of ureteral relaxation on stone passage, spasmolytic agents phentolamine, an α -adrenergic antagonist, and orciprenaline and isoproterenol, β -adrenergic agonists, have been shown to dilate the ureteral lumen or decrease ureteral wall tension at the level of an artificial concretion and thus permit increased fluid flow beyond the concretion (Peters and Eckstein, 1975; Miyatake et al, 2001). In a human study, renal colic was relieved by meperidine in 83% of patients, by phentolamine in 63%, and by propranolol, a β -adrenergic antagonist that presumably would interfere with the β -adrenergic inhibitory actions of catecholamines, in 0% (Kubacz and Catchpole, 1972). These data suggest that drugs with spasmolytic effects on the ureter may relieve renal colic, whereas those with spasmogenic actions do not.

Pharmacologic data can be interpreted to imply that ureteral relaxation in the region of a concretion could aid in stone passage. Agents such as theophylline (Weiss et al, 1977; Green et al, 1987), with strong relaxant effects on the ureter, have potential value in facilitating stone passage. It also has been reported that local aminophylline facilitates ureteroscopy and transureteral lithotripsy (Barzegarneshad et al, 2012) and that endoluminal administration of isoproterenol reduces renal pelvic pressures during flexible ureterorenoscopy (Jakobsen, 2013). In a rabbit in vivo model, rolipram, a cAMP-specific PDE inhibitor (PDE4 inhibitor), caused a more marked ureteral relaxation than did the nonspecific PDE inhibitors papaverine and theophylline, and without the circulatory side effects seen with the nonspecific PDE inhibitors (Becker et al, 1998). Because the relaxant effect of rolipram was similar in human and rabbit in vitro ureteral segments, it was suggested that rolipram could potentially be beneficial in the treatment of renal colic and in the facilitation of stone passage (Becker et al, 1998). Rolipram also has been shown to relax pig intravesical ureteral segments (Hernández et al, 2004). In addition to the PDE4 inhibitor rolipram, PDE5 inhibitors (cGMP-specific PDE inhibitors) relax in vitro pig and human ureteral segments (Kuhn et al, 2000; Al-Aown et al, 2011; Liatsikos et al, 2013). The relaxant effects of PDE4 and PDE5 inhibitors were paralleled by an increase in cAMP and cGMP, respectively. Gratzke and coworkers (2007) showed that PDE5 inhibitors reversed KCl-induced increases in tension of isolated human ureteral segments, with a rank order of efficacy of vardenafil (Levitra) more than sildenafil (Viagra) more than tadalafil (Cialis). Species differences in PDE subtypes may exist. Although the nonspecific PDE inhibitor papaverine decreased the frequency of ureteral peristalsis in the pig, the PDE4 inhibitor, rolipram, had no effect (Danuser et al, 2001).

A combination of the calcium channel blocker nifedipine, which causes ureteral relaxation, and the corticosteroid deflazacort, which reduces edema, was shown to facilitate spontaneous passage of 1 cm or smaller distal ureteral stones (Borghi et al, 1994; Porpiglia et al, 2000). Spontaneous expulsion of 79% of stones (average size 5.8 ± 1.8 mm) occurred in an average of 7 days in patients treated with nifedipine and deflazacort compared with spontaneous passage of 35% of stones (average size 5.5 ± 1.4 mm) within an average of 20 days in untreated patients (Porpiglia et al, 2000). In a subsequent study, the same group showed that both nifedipine and the α -adrenergic antagonist tamsulosin, when combined with deflazacort, increased the rate of spontaneous passage of lower ureteral calculi and that, in addition, tamsulosin, a selective $\alpha_{1A/1D}$ adrenergic receptor antagonist, reduced the time to spontaneous expulsion (Porpiglia et al, 2004, 2006). The researchers showed that tamsulosin alone was effective in facilitating expulsion of distal ureteral stones, and that this effect was potentiated by steroids. Steroids alone were ineffective. α_1 -Adrenergic receptors are present throughout the human ureter, with the greatest quantity of α_1 -adrenergic receptors being in the distal ureter (Sigala et al, 2004, 2005). α_{1D} mRNA was expressed throughout the human ureter, with significantly greater amounts than the α_{1A} - and α_{1B} -receptor subtypes in the proximal and distal ureter. $\alpha_{1A/1D}$ -adrenergic receptors are present in the distal ureter. A number of other studies have noted an increased spontaneous stone expulsion rate and expulsion rate after extracorporeal shock wave lithotripsy (ESWL), a decrease in renal colic, and an improved tolerance of ureteral stents with the administration of tamsulosin and other α -adrenergic antagonists (Cervenakov et al, 2002; Dellabella et al, 2003; Kupeli et al, 2004; Autorino et al, 2005; Gravina et al, 2005; Resim et al, 2005; Yilmaz et al, 2005; De Sio et al, 2006; Gravas et al, 2007; Liatsikos et al, 2007; Damiano et al, 2008; Losek and Mauro, 2008; Al-Ansari et al, 2010; Yencilek et al, 2010; Gurbuz et al, 2011; Lu et al, 2012b). Although most of the studies address the efficacy of tamsulosin in facilitating stone passage, Yilmaz and associates (2005) reported that doxazosin and terazosin were equally effective in facilitating stone passage. Dellabella and colleagues (2005) reported that tamsulosin was more effective than the calcium channel blocker nifedipine in facilitating stone expulsion. Naftopidil, an α_{1D} -adrenergic receptor antagonist, also has

been reported to be effective in facilitating the expulsion of intramural ureteral stones (Lu et al, 2012a).

Effect of Diabetes on Ureteral Function

In patients with diabetes, changes in bladder function affect the ureter. In addition, there is some evidence of a direct effect of diabetes on the ureter. The length and velocity of movement of the urinary bolus is decreased in the streptozotocin (STZ)-induced diabetic rat (Watanabe and Miyagawa, 2002). Although the frequency of contractions of in vitro segments of the renal pelvis and ureter of STZ-induced diabetic rats is unchanged, the amplitude of contractions is increased in comparison with renal pelvic and ureteral segments from control sucrose-induced diuretic rats (Davidson and Lang, 2007). Capsaicin is known to release tachykinins from sensory nerves, and it is postulated that a supersensitivity of the upper urinary tract of STZ-induced diabetic rats to the sensory neurotoxin capsaicin, and to the sensory excitatory neuropeptides substance P and neurokinin A, results from a sensory neuropathy (Davidson and Lang, 2007).

EFFECT OF AGE ON URETERAL FUNCTION

Clinically, the response of the ureter to pathologic conditions varies with age. More marked degrees of ureteral dilatation are observed in the neonate and young child than in the adult. Experimental data corroborating this clinical impression can be derived from observed age-dependent differences in the response of in vitro ureteral segments to an intraluminal pressure load. The neonatal rabbit ureter undergoes a greater degree of deformation in response to an applied intraluminal pressure than does the adult rabbit ureter (Akimoto et al, 1977). Furthermore, norepinephrine decreases the diametral deformation of the neonatal rabbit ureter in response to an applied intraluminal pressure but has little effect on the deformation of the adult rabbit ureter (Fig. 43-27). Thus, the in vitro neonatal rabbit ureter appears to be more compliant and more sensitive to norepinephrine than the adult rabbit ureter.

Age also affects the response of the ureter to β -adrenergic agonists; with aging there is a decrease in the relaxant response to the β -adrenergic agonist isoproterenol (Wheeler et al, 1990). The relaxant response to β -adrenergic agonists is related, in part, to

cAMP levels. It has been shown that with aging there is a decrease in the enzymatic activities involved in the synthesis of cAMP (Wheeler et al, 1986) but no change in the enzymatic activities involved in cAMP degradation (Cho et al, 1988). These data suggest that the decrease in the ability of isoproterenol to relax the ureter with aging is a result of a decrease in the ability of isoproterenol to activate adenylyl cyclase, the enzyme involved in cAMP synthesis. Developmental differences in the response of the ureter to metabolic inhibitors are evident, with cyanide causing a larger decrease in force in the adult than in the neonatal guinea pig ureter (Bullock and Wray, 1998a, 1998b).

A progressive increase in ureteral cross-sectional muscle area is observed in the guinea pig between 3 weeks and 3 years of age. This is in accord with the findings of Cussen (1967), who noted in a human autopsy study (subjects ranging in age from 12 weeks of gestation to 12 years of age) that there is a progressive increase in the population of smooth muscle cells and a small increase in the overall size of the individual smooth muscle cells. In addition, an irregular increase in the number of elastic fibers was observed with increasing age.

The contractility of the ureter also is affected by age. The maximal active force of isolated guinea pig ureteral segments increases between 3 weeks and 3 years of age (Fig. 43-28) (Hong et al, 1980). The increase in force developed between 3 weeks and 3 months of age seems to be attributable to an increase in contractility, because there is an associated increase in active stress (force per unit area of muscle). The increase in force developed between 3 months and 3 years of age can be explained by an increase in muscle mass alone because there is no change in active stress between these two age groups (see Fig. 43-28).

Although changes in the force-length relations of guinea pig ureter occur with age, the force-velocity relations do not change with age (Biancani et al, 1984). Thus, although ureteral contractility increases during early development, as shown by an increase in force per unit area of muscle, or stress, no significant change is apparent in the rate of the driving reactions that control the contractile process—that is, no change in shortening, velocity, work, or power.

EFFECT OF PREGNANCY ON URETERAL FUNCTION

Hydronephrosis of pregnancy begins in the second trimester of gestation and subsides within the first month after parturition. It is more severe on the right side, and the ureteral dilatation does not occur below the pelvic brim. Roberts (1976) has presented a strong case in favor of obstruction as the causative factor in the development of hydronephrosis of pregnancy, whereas other investigators have suggested a hormonal mechanism for the ureteral dilatation of pregnancy (van Wagenen and Jenkins, 1939).

Roberts (1976) emphasized the following: (1) Elevated baseline (resting) ureteral pressures consistent with obstructive changes have been recorded above the pelvic brim in pregnant women, and these pressures decrease when positional changes permit the uterus to fall away from the ureters (Sala and Rubi, 1967). (2) Normal ureteral contractile pressures recorded during pregnancy suggest that hormonally induced ureteral atony is not the prime factor in ureteral dilatation of pregnancy. (3) Women whose ureters do not cross the pelvic brim (i.e., those with pelvic kidneys or ileal conduits) do not develop hydronephrosis of pregnancy. (4) Hydronephrosis of pregnancy usually does not occur in quadrupeds, whose uterus hangs away from the ureters (Traut and Kuder, 1938). (5) Elevated ureteral pressures in the pregnant monkey return to normal when the uterus is elevated from the ureters at laparotomy or when the fetus and placenta are removed from the uterus.

Observed hormonal effects on ureteral function have been used to implicate a hormonal mechanism in the ureteral dilatation of pregnancy, although difficulties in interpretation arise from inconsistencies in the data. Several studies have shown an inhibitory

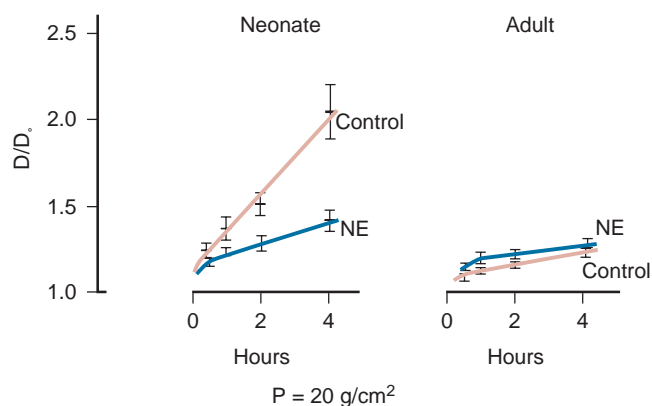


Figure 43-27. Changes in diameter of neonatal and adult rabbit ureteral segments as a function of time after the application of a constant intraluminal pressure (P) of 20 g/cm². Diametral deformation (D/D₀) of control neonatal ureters was significantly greater than that of control adult ureters. Norepinephrine (10⁻⁵ M) decreased the diametral deformation of the neonatal ureters but had no significant effect on the deformation of the adult ureteral segments. D, diameter during deformation; D₀, initial diameter; NE, norepinephrine. (From Akimoto M, Biancani P, Weiss RM. Comparative pressure = length – diameter relationships of neonatal and adult rabbit ureters. Invest Urol 1977; 14:297.)

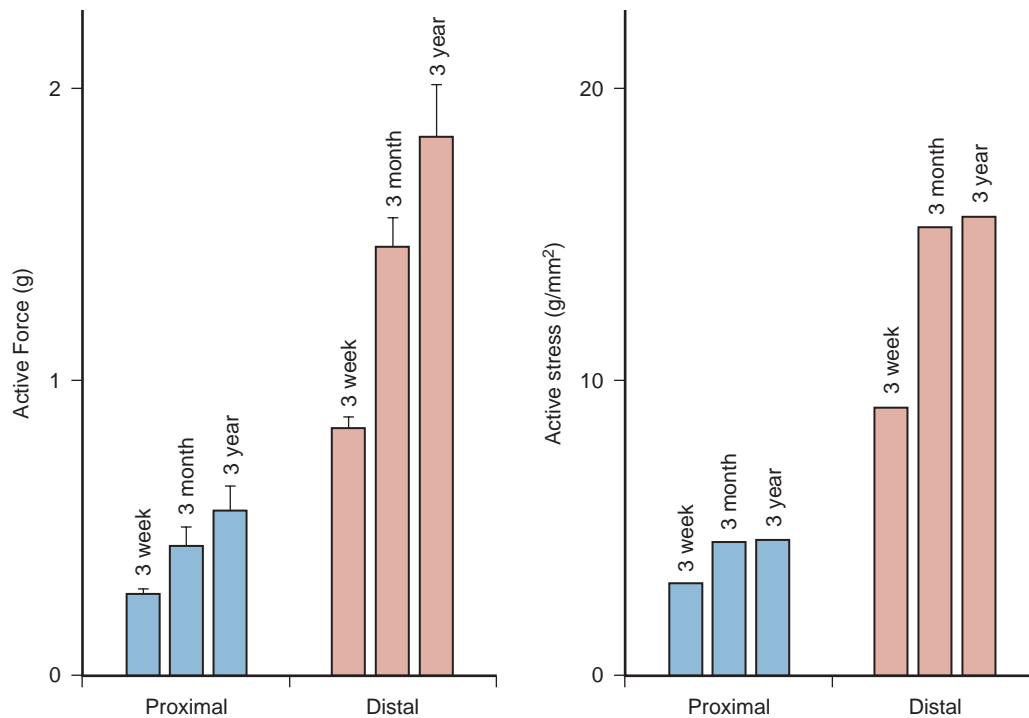


Figure 43-28. Maximal active (contractile) force and maximal active stress of proximal and distal guinea pig ureteral segments as a function of age.

effect of **progesterone** on ureteral function (Kumar, 1962). Progesterone has been noted to increase the degree of ureteral dilatation during pregnancy and to retard the rate of disappearance of hydro-ureter in postpartum women (Lubin et al, 1941). Other studies, however, have failed to demonstrate an effect of progesterone on ureteral activity in animals (McNellis and Sherline, 1967) or in humans (Lapides, 1948), and still others have failed to induce changes in ureteral activity in women through the administration of estrogens, progesterone, or a mixture of these drugs (Marchant, 1972; Clayton and Roberts, 1973). Although some workers have noted that estrogens increase ureteral activity (Hundley et al, 1942), the majority of investigators have failed to observe an effect of estrogens in animal models (Abramson et al, 1953) or in humans (Kumar, 1962). Thus, **obstruction appears to be the primary factor in the development of hydronephrosis of pregnancy**, although some evidence suggests that a combination of hormonal and obstructive factors is involved (Fainstat, 1963).

EFFECT OF DRUGS ON THE URETER

This section provides an assessment of the effects of the major classes of drugs on ureteral function. Many of the studies referred to were performed in animal models, and extrapolation of the data to the intact human ureter is often difficult. In the clinical situation, the relatively sparse blood supply to the ureter limits the distribution of drugs to the ureter, and the pharmacokinetics are quite different in the laboratory than in the clinic. In addition, many drugs with potential usefulness in the management of ureteral abnormalities have potential untoward side effects when used in concentrations required to affect the ureter.

To assess the effect of drugs on the ureter, it is necessary to understand the anatomic, physiologic, and biochemical properties of the ureter, in addition to understanding the principles of drug action. For a drug to elicit a given response, it is necessary to achieve and maintain an appropriate concentration of that drug at its site of action. Factors that can influence the achievement of an effective concentration of drug at a site of action are (1) the route of

administration and cellular distribution of the drug; (2) the dose of the drug administered; (3) the biotransformation, including metabolism and excretion, of the drug; (4) the binding of the drug to plasma and tissue proteins; and (5) the effects of age and disease on the absorption, distribution, metabolism, and elimination of the drug.

The literature contains considerable confusing and conflicting information concerning the effects of drugs on the ureter. To some extent, the discrepancies in the available data are the result of poorly controlled experimental procedures or of attempts to compare dissimilar functional responses of the ureter with a given drug. To simplify the present section, no attempt is made to analyze the validity of each pharmacologic study or to rationalize discrepancies in the literature; rather, an overview is presented with an attempt to provide a consensus that at times may be prejudiced by personal bias. Furthermore, discussion of drugs related to the nervous system, pregnancy, and a variety of pathologic states is included in earlier sections of this chapter and is not duplicated in this section.

Histamine and Its Antagonists

Histamine has a dual action on smooth muscle; it may (1) release catecholamines from sympathetic nerve endings or (2) act directly on receptors within the smooth muscle. In addition, **histamine may have excitatory or inhibitory effects on ureteral function**. The majority of studies have shown an excitatory effect of histamine on ureteral function (Borgstedt et al, 1962; Sharkey et al, 1965; Ver-ecken, 1973; Benedito et al, 1991; Smita et al, 2006), a finding that may be species dependent (Tindall, 1972). **Histamine's excitatory effect on the ureter and UVJ appears to be mediated by H_1 receptors** because they are inhibited by the H_1 -receptor antagonists mepyramine, pheniramine, and dimethindene but not by the H_2 -receptor antagonists cimetidine and ranitidine (Benedito et al, 1991; Dodel et al, 1996; Smita et al, 2006). An H_1 agonist, 2-(2-pyridyl)ethylamine, increases ureteral contractility (Dodel et al, 1996). The H_1 inhibitor pheniramine has no effect on spontaneous activity of isolated goat ureter (Smita et al, 2006). The excitatory effect of histamine on the sheep UVJ is partially blocked by

scopolamine, suggesting an indirect stimulatory action of histamine on intramural parasympathetic nerves. H₁ histamine receptors are expressed in the smooth muscle and urothelium of the human ureter (Floyd et al, 2008). The antihistamines diphenhydramine (Benadryl) and tripeleminamine have been shown to inhibit the effects of histamine on the ureter (Borgstedt et al, 1962; Sharkey et al, 1965). The H₂ receptor mediates inhibitory effects of histamine. Histamine and the H₂-receptor agonist impromidine relax precontracted ureteral segments, actions that are inhibited by the H₂-receptor antagonist cimetidine (Dodel et al, 1996).

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) has been reported to stimulate (Vereecken, 1973; Dodel et al, 1996; Hauser et al, 2002; Hernández et al, 2003), inhibit (Mazzella and Schroeder, 1960), or have no effect on (Finberg and Peart, 1970) a variety of ureteral preparations. In the pig ureter the contractile effects appear to be mediated by 5-HT₂ receptors (Hauser et al, 2002; Hernández et al, 2003). Gidener and colleagues (1999) showed that 5-HT induces concentration-dependent contractions of isolated human ureteral segments. However, their studies suggested no involvement of 5-HT₂ receptors in the contractile effects of 5-HT. Tetrodotoxin, guanethidine, and phentolamine had an inhibitory effect on 5-HT-induced contractions of pig isolated intravesical ureteral segments, suggesting that part of the contractile effects of 5-HT are indirectly mediated through release of norepinephrine from sympathetic nerves (Hernández et al, 2003).

Kinins

The kinins—kallidin, elodeisin, and bradykinin—increase the frequency of contraction and baseline intraluminal pressure of the dog ureter (Boyarsky et al, 1966a, 1966b; Labay and Boyarsky, 1966), and bradykinin decreases the contractile force of the sheep ureter (Kaygisiz et al, 1995).

Angiotensin

Angiotensin has a stimulatory effect on the ureter. AT₂ and mRNA for angiotensinogen, a principal precursor of AT₂, renin, angiotensin-converting enzyme (ACE), and the type 1 angiotensin receptor are expressed in the human ureter (Santis et al, 2003). Losartan, an AT₂ receptor antagonist, decreases the amplitude and frequency of spontaneous contractions of human ureteral segments. AT₂ induces phasic contractions of rat ureteral segments, an effect that is inhibited by losartan (Fujinaka et al, 2000). The AT₂ type 1 receptor also is expressed in the rat ureter (Paxton et al, 1993).

Narcotic Analgesics

Morphine has been reported to increase ureteral tone or the frequency and amplitude of ureteral contractions or both in a variety of experimental preparations and in humans (Macht, 1916b; Gruber, 1928; Ockerblad et al, 1935; Vereecken, 1973). Others, however, have failed to observe an effect of morphine on ureteral function (Gould et al, 1955; Kiil, 1957; Weinberg and Maletta, 1961; Ross et al, 1967).

Meperidine (Demerol) appears to have a similar excitatory effect on the activity of the intact dog ureter (Sharkey et al, 1968). Kiil (1957), however, failed to observe an effect of meperidine on ureteral peristalsis in humans. If one considers only the effects on ureteral activity, there is no basis to preferentially favor morphine or meperidine in the treatment of renal colic. Both agents may have ureteral spasmogenic effects that theoretically would detract from their value in the management of ureteral colic. They certainly do not have potentially valuable spasmolytic actions. Their efficacy in treating colic depends on their central nervous system (CNS) actions, which decrease the perception of pain.

Prostaglandins

PGs are derived from fatty acids and have a variety of biologic actions in various systems of the body. Their effects vary with the species, type of PG, endocrine status of the tissue, experimental conditions, and origin of the smooth muscle. The “primary” PGs—PGE₁, PGE₂, and PGF_{2α}—are synthesized from the fatty acid arachidonic acid by enzymatic reactions involving two COX isoforms, COX-1 and COX-2 (Vane, 1998). In most tissues COX-1 is constitutively expressed and is involved in the regulation of normal physiologic processes, whereas COX-2 is induced in response to processes such as inflammation and mitogenesis (Mitchell and Warner, 1999). These enzymatic reactions can be inhibited by indomethacin and aspirin, and by a number of COX-1 and COX-2 inhibitors. COX-1 and COX-2 receptors have been identified in the human ureter (Chaignat et al, 2008).

PGE₂ acts via four G protein-coupled receptors, PTGER₁ to PTGER₄, and PGF_{2α} acts via PTGFR. PTGER₁ and PTGER₃ induce smooth muscle contractions, PTGER₁ via activation of phosphatidylinositol hydrolysis and PTGER₃ via cAMP inhibition. PG receptors PTGER₁ and PTGFR₃ are highly expressed in human ureter urothelium and muscle (Oll et al, 2012). PTGER₂ and PTGER₄ induce smooth muscle relaxation via cAMP stimulation.

PGE₁ inhibits the activity of the dog ureter (Boyarsky et al, 1966b; Wooster, 1971; Abrams and Feneley, 1976) and guinea pig ureter (Vermue and Den Hertog, 1987). PGE₁ inhibition of ureteral activity in the guinea pig is associated with an increase in cAMP levels (Vermue and Den Hertog, 1987). In the ureter, PGE₁ activates adenylyl cyclase, and this may account for the increase in cAMP (Wheeler et al, 1986). Johns and Wooster (1975) suggested that the inhibitory effects of PGE₁ on ureteral activity depended on the sequestration of Ca²⁺ at the inner surface of the cell membrane, with a resultant increase in outward K⁺ conductance and hyperpolarization of the membrane.

Although reports have indicated that PGE₂ relaxes the ureter (Vermue and Den Hertog, 1987), other reports describe an excitatory action of PGE₂ on sheep ureter (Thulesius and Angelo-Khattar, 1985) and human ureter (Angelo-Khattar et al, 1985; Cole et al, 1988) and on renal pelvic smooth muscle (Lundstam et al, 1985). PGE₂ increases the contractility of chronically obstructed human ureters. Although it relaxes normal porcine ureter, it increases the contractility of acutely obstructed porcine ureters (Ankem et al, 2005; Lowry et al, 2005). In contrast to the inhibitory effects of PGE₁ in the dog ureter, PGE₂ increases the frequency of ureteral peristalsis in the dog (Boyarsky and Labay, 1969). In human ureteral preparations, PGE₁ and PGE₂ have been shown to decrease spontaneous contractions, whereas PGF_{2α} increased ureteral contractility (Abrams and Feneley, 1976). In human renal pelvis and ureter there is a higher concentration of PGF_{2α} than PGE₂ (Zwergel et al, 1991). PGF_{2α} increased contractility of porcine ureteral segments (Ankem et al, 2005). The prostanoid PGI₂ is synthesized in the urothelium of the ureter (Ali et al, 1998). COX inhibitors such as indomethacin have been shown to inhibit the activity of rat (Davidson and Lang, 2000), guinea pig (Davidson and Lang, 2000), sheep (Thulesius and Angelo-Khattar, 1985), and human ureters (Angelo-Khattar et al, 1985; Cole et al, 1988) and renal pelvic smooth muscle (Lundstam et al, 1985; Zhang and Lang, 1994; Santicioli et al, 1995a; Davidson and Lang, 2000).

Indomethacin has been used in the management of ureteral colic (Holmlund and Sjöden, 1978; Flannigan et al, 1983; Jönsson et al, 1987). The beneficial effects probably are the result of indomethacin's inhibition of the PG-mediated vasodilatation that occurs subsequent to obstruction (Allen et al, 1978; Sjöden et al, 1982). The vasodilatation theoretically would result in an increase in glomerular capillary pressure and a subsequent increase in pelviureteral pressure. Indomethacin, by reducing pelviureteral pressure and thus pelviureteral wall tension, might eliminate some of the pain of renal colic that is dependent on distention of the upper urinary tract. An upregulation of COX-2 mRNA and protein with obstruction supports the potential use of selective COX-2 inhibitors in the treatment of obstructive ureteral disease (Nakada et al, 2002). A

potential problem with the use of indomethacin for the treatment of renal colic is that PG-mediated vasodilatation aids in preserving renal function; thus, indomethacin may provide pain relief, but it may be potentially deleterious to renal function (Perlmutter et al, 1993; Kristova et al, 2000).

The nonspecific COX inhibitor diclofenac and the selective COX-2 inhibitors NS-398 and celecoxib have been shown to be equipotent in inhibiting agonist-induced contractions of isolated pig and human ureter (Mastrangelo et al, 2000; Nakada et al, 2000), and diclofenac also has been shown to relax human ureteral segments that were precontracted with KCl (Sivrikaya et al, 2003). NS-398 inhibition of ureteral contractility also may involve blockade of voltage-dependent calcium channels (Lee et al, 2010). The COX-2 selective inhibitor celecoxib and indomethacin inhibited porcine ureteral contractility and tumor necrosis factor- α (TNF- α)-induced prostanoid release (Jerde et al, 2005). Diclofenac, but not the COX-2 selective inhibitor valdecoxib, decreased the contractile amplitude of electrically stimulated in vitro human ureteral segments, and valdecoxib decreased the contractility of unobstructed but not obstructed ureters of the pig in vivo (Chaignat et al, 2008). Species differences may exist, with COX-2 being the primary enzyme involved in synthesizing PGs in the guinea pig upper urinary tract, and COX-1 being the primary enzyme involved in PG synthesis in the rat upper urinary tract (Davidson and Lang, 2000).

Chronic obstruction upregulates COX-2 activity in the human ureter (Nakada et al, 2002). With stretch of the porcine ureter, there is COX-2 induction in both the urothelial and smooth muscle layers, with a more significant induction in the urothelium (Jerde et al, 2006). The stretch-induced upregulation of COX-2 expression in the urothelium of the obstructed mouse ureter is mediated via PI3K (Owusu-Ofori et al, 2013). PI3K also mediates stretch-induced activation of PKC (Owusu-Ofori et al, 2013). In the normal rat ureter, COX-1 but not COX-2 mRNA was detected, and after obstruction there was an increase in COX-2 mRNA and protein expression but no change in COX-1 expression (Norregaard et al, 2006). In addition to an increased synthesis of prostanoids with obstruction, there is a decrease in prostanoid degradation contributing to the increase in prostanoids with obstruction. 15-Hydroxyprostaglandin dehydrogenase (PGDH), the enzyme responsible for PG degradation, is suppressed in the human ureter with obstruction (Jerde et al, 2004). The dilated ureter after obstruction has an increased expression of COX-2, PGE₂, TGF- β 1, α -SMA, fibrosis, apoptotic cells, and proliferation cell nuclear antigen (PCNA) (Chuang et al, 2007). The administration of the COX-2 selective inhibitor celecoxib abolished the expression of COX-2 and PGE₂, decreased the expression of TGF- β 1 and α -SMA, decreased apoptotic cells and fibrosis, but increased the expression of PCNA in the smooth muscle of the dilated obstructed ureter (Chuang et al, 2007). These investigators concluded that the COX-2 inhibitor might ameliorate, in part by inhibition of COX-2 and TGF- β 1 expression, ureteral damage resulting from obstruction.

Cardiac Glycosides

Ouabain, a cardiac glycoside, has an effect on ureteral activity that appears to be species dependent. In the isolated cat ureter, ouabain produces a marked increase in contractility, which usually is followed by a late decrease in excitability (Weiss et al, 1970). In the guinea pig ureter, ouabain inhibits activity without a preliminary potentiation of contractility (Washizu, 1968; Hendrickx et al, 1975). The inhibitory effects of ouabain are accompanied by a shortening of the action potential duration, a decrease of the number of oscillations on the plateau of the guinea pig action potential, and a decrease in the RMP.

Calcium Antagonists

Because Ca²⁺ is necessary for the development of the action potential and contraction of the ureter, agents that block the movement of Ca²⁺ into the cell would be expected to depress ureteral function. Voltage-dependent Ca²⁺ channel antagonist

binding sites (receptors) have been demonstrated in the ureter, and their density decreases with age (Yoshida et al, 1992). These dihydropyridine-sensitive, L-type, voltage-dependent Ca²⁺ channels appear to provide the main inward current for generation of the ureteral action potential and the phasic contractile response (Shuba, 1977; Brading et al, 1983; Aickin et al, 1984; Imaizumi et al, 1989; Lang, 1989). Potassium-induced ureteral contractions depend on the inward movement of Ca²⁺ through L-type voltage-dependent Ca²⁺ channels (Maggi and Giuliani, 1995). The dihydropyridine Ca²⁺ channel agonist Bay K8644 has an excitatory effect on ureteral activity (Maggi et al, 1994a; Floyd et al, 2008) and potentiates K⁺-induced contractions. The Ca²⁺ channel blockers verapamil, D-600 (a methoxy derivative of verapamil), diltiazem, and nifedipine have been shown to inhibit ureteral activity (Golenhofen and Lammel, 1972; Vereecken et al, 1975; Hertle and Nawrath, 1984; Hong et al, 1985; Sakanashi et al, 1985, 1986; Maggi et al, 1994a; Davenport et al, 2006). These inhibitory effects are accompanied by decreases in the duration of the action potential, the number of oscillations on the plateau of the guinea pig action potential, excitability, and the rate of rise and amplitude of the action potential. High concentrations of verapamil and D-600 cause a complete cessation of electrical and mechanical activity.

Potassium Channel Openers

Potassium channel openers such as cromakalim, nicorandil, BRL 38227, and PFK 217-744b hyperpolarize smooth muscle membranes and inhibit renal pelvic and ureteral activity (Kontani et al, 1993; Maggi et al, 1994b; Weiss et al, 2002; Smita et al, 2006; Floyd et al, 2008). Glibenclamide, a blocker of K⁺-ATP channels, on its own had no effect on contractility (de Moura and de Lemos Neto, 1996). The inhibitory effects of cromakalim and nicorandil are prevented by glibenclamide, providing evidence that ATP-sensitive K⁺ channels are involved in these processes (Maggi et al, 1994b; Smita et al, 2006). Activation of these K⁺ channels may reduce the probability of the opening of voltage-sensitive Ca²⁺ channels, inhibit agonist-induced increases in IP₃, or reduce Ca²⁺ sensitivity of contractile elements—processes that are important in the generation of the ureteral action potential and the contractile response (Cook and Quast, 1990; Quayle et al, 1997).

The tricyclic antidepressant amitriptyline (Elavil) has been shown to relax isolated pig and human ureteral strips by opening potassium channels (Achar et al, 2003). This relaxation response is inhibited by 4-aminopyridine (4-AP), a voltage-dependent K⁺ channel blocker. Nicorandil, a K⁺ channel opener and NO donor, stimulates guanylyl cyclase activity with formation of cGMP and hyperpolarizes the smooth muscle with resultant relaxation of rabbit, guinea pig, and human ureter (Klaus et al, 1989, 1990; Weiss et al, 2002). The relaxant effects of nicorandil can be inhibited by both the K_{ATP} antagonist glibenclamide and the guanylyl cyclase inhibitor methylene blue (Weiss et al, 2002).

Endothelins

Endothelins are potent vasoconstrictor peptides that exist in three isoforms: ET-1, ET-2, and ET-3. These peptides interact with their specific receptors: ET_A, ET_B, and ET_C. Endothelin binding sites (receptors) have been identified in the ureter and renal pelvis (Eguchi et al, 1991; Latifpour et al, 1995; Wada et al, 2001), where they are primarily of the ET_A subtype (Latifpour et al, 1995; Wada et al, 2001). Endothelins have been shown to initiate contractions in isolated guinea pig and porcine ureters (Eguchi et al, 1991; Maggi et al, 1992a) and increase the contractile force of renal pelvis smooth muscle (Wada et al, 2001). ET-1 acting on the ET_A receptor increased contractile force of rat renal pelvis smooth muscle (Grisk et al, 2010). COX-1 and Rho-kinase (ROCK) activity are required for ET-1 effects on renal pelvic contractility. ET-1, ET-2, and ET-3 increased tonic contractions and intraluminal pressures in isolated human ureteral segments. These actions were inhibited by BQ-123, an ET_A receptor antagonist, and BQ-788, an ET_B receptor antagonist. ET-1 and ET-3 inhibited spontaneous phasic activity of the isolated

human ureteral segments, an action that was not blocked by either ET_A or ET_B receptor antagonists (Jankovic et al, 2011). Diabetes upregulates the expression of ureteral endothelin receptors (Nakamura et al, 1997).

Antibiotics

Ampicillin causes relaxation of the ureter and antagonizes the stimulatory effects of barium chloride ($BaCl_2$), histamine, serotonin, and carbachol on the ureter, thus suggesting that its action is directly on the smooth muscle (Benzi et al, 1970b). Chloramphenicol, the isoxazolyl penicillins, and gentamicin also have spasmolytic effects on the ureter (Benzi et al, 1970a, 1971, 1973). The tetracyclines, on the other hand, potentiate the contractile effects of $BaCl_2$ on the ureter (Benzi et al, 1973).

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Renal Physiology

Renal physiology impacts the urologic care of patients in numerous ways. These can include the pathophysiology of surgical disease (renal tubular acidosis [RTA] and malignant paraneoplastic syndromes), the modification of surgical technique (ischemia-reperfusion injury and intrarenal surgery), or iatrogenic complications of surgery (hyponatremia and metabolic complications of urinary diversions). The purpose of this chapter is not to turn urologists into nephrologists, but rather to provide a firm fundamental knowledge of renal physiology and pathophysiology to provide the foundation for urologic-specific conditions and therapies.

RENAL PHYSIOLOGY

Vascular (Renal Blood Flow and Glomerular Flow Rate)

Renal Blood Flow

Renal blood flow (RBF) is regulated by changes in vascular resistance of all the arteries up to and including the efferent arteriole, which in turn is regulated by a variety of neurohormonal signals (see later).

Blood enters the kidney through the renal arteries and divides into progressively smaller arteries (interlobar, arcuate, and interlobular arteries) until it enters the glomerular capillary through the afferent arteriole. A portion of the plasma that enters the glomerulus is filtered across the glomerular membrane; this is called the *filtration fraction*. The rest of the blood exits the glomerular capillary through the efferent arteriole. In nephrons located in the renal cortex, these capillaries travel in close proximity to the tubules and modulate solute and water reabsorption. In juxtamedullary nephrons (located deeper in the medulla), the efferent arterioles branch out to form vasa recta, which participate in the countercurrent mechanism through which urine is highly concentrated and body water conserved (see later discussion).

Under normal resting conditions, RBF is 20% of total cardiac output. Total blood flow is different for men and women, averaging 982 ± 184 mL/min in women and 1209 ± 256 mL/min in men (Dworkin and Brenner, 2004). Renal plasma flow (RPF) is slightly less, averaging 592 mL/min in women and 659 mL/min in men, and it varies with hematocrit ($RPF = RBF \times [1 - Hct]$). RBF is not evenly distributed to all parts of the kidney. Flow to the outer cortex is two to three times greater than that to the inner cortex, which in turn is two to four times greater than that to the medulla (Dworkin and Brenner, 2004).

Determinants of Glomerular Filtration

The most important function of the kidney is the process of **glomerular filtration**. Through the passive ultrafiltration of plasma across the glomerular membrane, the kidney is able to regulate total body salt and water content, to regulate electrolyte composition, and to eliminate waste products of protein metabolism.

The process of filtration is analogous to fluid movement across any capillary wall, and is governed by Starling forces. The

Renal Pathophysiology

glomerular filtration rate (GFR) is thus determined by both hydraulic and oncotic pressure differences between the glomerular capillary and the Bowman space, as well as by the permeability of the glomerular membrane:

$$GFR = LpS \times (\Delta \text{hydrostatic pressure} - \Delta \text{oncotic pressure})$$

where Lp = glomerular permeability and S = glomerular surface area.

The rate at which filtration occurs within an individual nephron is termed the “single nephron GFR” (SN-GFR). A more relevant measurement is that of total GFR, which is the sum of all SN-GFR and is expressed in milliliters per minute. **GFR is thus a reflection of overall renal function.** Alterations in GFR can occur either with alterations in any aspect of Starling forces, or through a change in RPF.

1. *Transglomerular (hydraulic) pressure (TGP)*—the most significant determinant of GFR is the TGP. Although systemic arterial pressures impact TGP, the glomerular capillary is unique in that it is interposed between two arterioles (the afferent and efferent arterioles) and thus can regulate intraglomerular capillary pressure (IGP) independent of systemic pressures through changes in afferent and efferent arteriolar tone. In normal circumstances, the pressure within the Bowman space is essentially zero, and only in conditions of urinary obstruction does the pressure increase to clinically significant levels. Thus the $TGP = IGP$.
2. *Renal plasma flow*—increases in RPF lead to increases in GFR. Although the filtration fraction cannot exceed 20% in normal circumstances, an increase in RPF will lead to an increase in absolute GFR.
3. *Glomerular permeability*—generally, an increase in permeability does not lead to an increase in GFR, because the glomerulus is already at maximal permeability for water and other relevant solutes. It may, however, lead to increased filtration of larger molecules not normally filtered, such as albumin. Reductions in permeability, or in glomerular surface area, can lead to reductions in GFR.
4. *Oncotic pressure*—the least relevant of all the variables. Under normal circumstances, plasma proteins are not filtered across the glomerular membrane and so oncotic pressure within the Bowman space is essentially zero.

Regulation of Glomerular Filtration Rate

Under normal circumstances, GFR is tightly maintained at a relatively constant level, despite large fluctuations in systemic arterial pressures and RBF. This is accomplished through the processes of autoregulation and tubuloglomerular feedback.

1. *Autoregulation*—with increases in mean arterial pressure (MAP), afferent arteriolar tone increases to minimize increases in IGP. Similarly, with reductions in MAP, afferent arteriolar tone decreases to allow increased flow into the glomerulus to maintain IGP, thus maintaining GFR. Autoregulation of IGP is effective to a MAP of about 70 mm Hg; below that, reductions in MAP lead to similar reductions in GFR, and below a MAP of

40 mm Hg, filtration ceases. The mechanism(s) by which autoregulation is achieved is not well understood. It is likely mediated through myogenic stretch receptors in the afferent arteriole wall, possibly mediated by adenosine triphosphate (ATP) (Schnermann and Levine, 2003), but angiotensin II is also involved with more severe fluctuations.

2. **Tubuloglomerular feedback (TGF)**—cells in the macula densa monitor tubular ultrafiltrate flow rates. If SN-GFR increases, delivery of sodium cations (Na^+) and chloride anions (Cl^-) to the distal tubule also increases. This increased Cl^- delivery triggers a response by the macula densa, which ultimately leads to an increase in afferent arteriolar tone and subsequent decrease in RPF, thus returning SN-GFR (and tubular flow) back to baseline (Schnermann et al, 1998). Thus TGF can be thought of as a mechanism to minimize salt and water losses through the regulation of GFR. The mediators of this response are not well understood, but it seems that angiotensin II plays a permissive role in TGF. Both adenosine and thromboxane can cause afferent arteriolar vasoconstriction and have been implicated in TGF. Nitric oxide (NO) (Schnermann and Levine, 2003) is also believed to be important, particularly in minimizing TGF in the setting of increased NaCl intake.

Under abnormal conditions, however, neurohumoral responses become more important. With significant reductions in effective circulating volume (ECV), both norepinephrine and angiotensin II play important roles in maintaining GFR through arteriolar vasoconstriction, often at the expense of reduced RPF. Notably, renal prostaglandins (PGs) and NO offset afferent arteriolar vasoconstriction; so arteriolar tone is a balance between the vasoconstrictive and the vasodilatory effects of the previously mentioned hormones. Inhibition of PG synthesis (because of the administration of non-steroidal anti-inflammatory drugs [NSAIDs]), particularly in states of high angiotensin II production, can lead to severe vasoconstriction and acute reduction in GFR. In contrast, norepinephrine and angiotensin II levels are diminished in states of volume expansion, whereas dopamine and atrial natriuretic peptide (ANP) levels are increased to facilitate an increase in RPF (dopamine) and natriuresis (ANP), thus returning volume status back to normal.

Clinical Assessment of Glomerular Filtration Rate

Unfortunately, GFR cannot be measured directly. It can, however, be estimated by a variety of methods, some more accurate (but usually more cumbersome) than others.

Renal Clearance. The best estimate of GFR can be obtained by measuring the rate of clearance of a given substance from the plasma. However, to be accurate, the substance to be measured must meet certain criteria. It must:

- Be able to achieve a stable plasma concentration,
- Be freely filtered across the glomerulus,
- Not be secreted, reabsorbed, synthesized, or otherwise metabolized by the renal tubules, and
- Not be impacted by any other means of removal from the plasma.

If all these criteria are met, then:

$$\text{Filtered X} = \text{excreted X}$$

and since

$$\text{Filtered X} = \text{GFR} \times \text{plasma [X]}$$

and since

$$\text{Excreted X} = \text{urine [X]} \times \text{urine volume (in mL/unit time)}$$

we can now see that

$$\text{GFR} \times \text{plasma [X]} = \text{urine [X]} \times \text{urine volume}$$

$$\text{GFR} = \text{urine [X]} \times \text{urine volume} / \text{plasma [X]}$$

This is called the *clearance* of a substance and reflects the amount of plasma that is completely cleared of the substance per unit time. There are a number of substances that have been used clinically to estimate GFR.

1. **Inulin**—is a fructose polysaccharide that meets the necessary requirements, and inulin clearance is believed to be the best measure of GFR. However, it is not clinically useful because it is difficult to administer (requires an intravenous [IV] infusion of inulin) and is difficult to measure.
2. **Radiolabeled compounds**—such as iothalamate or diethylenetriaminepentaacetic acid (DTPA). These clearances are also very accurate, but are again limited in clinical use by their cost and availability (Perrone et al, 1990).
3. **Creatinine**—the most widely used estimate of GFR is the 24-hour creatinine clearance (CrCl) (Levey, 1990). It uses endogenous creatinine, which is produced at a constant rate. The rate of production varies from individual to individual, but for a single individual, daily variability is less than 10%. It has advantages in that it is easy to perform (no IV infusion), is relatively cheap, and is readily available. However, it is less accurate than inulin clearance, because some creatinine is cleared from plasma through proximal tubular secretion; thus a CrCl overestimates true GFR by an average of 10% to 20%. This becomes even more important as GFR declines, because tubular secretion increases in response to increasing serum creatinine levels and may contribute up to 35% of all creatinine removal at GFR levels of 40 to 80 mL/min (Shemesh et al, 1985). Thus at best the CrCl should be considered the “upper limit” of the true GFR.

Plasma Markers. An even simpler method to estimate GFR is with the use of plasma levels of substances that can be used as surrogate markers of GFR. To be useful, the substance must fulfill the criteria outlined previously. Three such substances have been used:

1. **Plasma creatinine (PCr)**—the most widely used plasma marker of GFR. Although creatinine production is constant within an individual from day to day, there is marked variation in production rates between individuals. The absolute rate depends on muscle mass, which in turn is influenced by age, sex, and body mass. Thus there is no single “normal” PCr that reflects a “normal” GFR; it must be individualized for every person. This can be accomplished through mathematical manipulation (see later). However, the relationship of PCr to GFR is relatively constant (Fig. 44-1), and thus changes in PCr can be used to predict corresponding changes in GFR. As a general rule, every 50% reduction in GFR results in a doubling of PCr. There are limitations to the use of the PCr, which should be noted:
 - As GFR falls, tubular secretion of creatinine increases; so PCr may not change noticeably until there has been a significant drop in GFR (Shemesh et al, 1985).
 - Creatinine production may increase in states of increased muscle breakdown (e.g., rhabdomyolysis) or with increased dietary protein intake or supplementation, leading to an underestimation of true GFR.

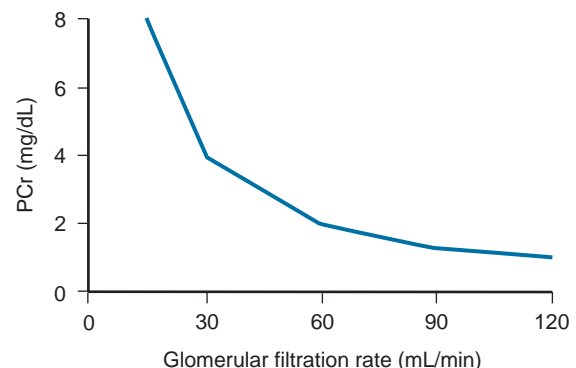


Figure 44-1. Relationship between serum creatinine and creatinine clearance. PCr, plasma creatinine.

- Creatinine production may decrease with liver cirrhosis, leading to an overestimation of true GFR.
2. *Plasma urea*—another widely used plasma marker. Urea production and excretion are highly variable, influenced, for instance, by dehydration, high-protein diets, and increased tissue breakdown. As a result, it is a much less reliable marker of GFR than is the PCr and should not be used as the sole determinant.
 3. *Plasma cystatin C*—an endogenous protein found in all nucleated cells. It has a constant rate of production unaffected by diet, and clearance is not influenced by tubular functions (Filler et al, 2005). This test is not widely available at present.

Mathematical Correction. There are a number of mathematical formulas that have been developed to improve the accuracy of the PCr estimation of GFR (National Kidney Foundation, 2002). The three most widely used are the Cockcroft-Gault, “modification of diet in renal disease” (MDRD), and CKD-EPI formulas.

1. *Cockcroft-Gault*: originally developed from data collected from individuals with normal renal function; it is a simple formula to estimate CrCl (not GFR) that corrects for age, sex, and body mass (ideal body weight [IBW]) (Cockcroft and Gault, 1976). The formula is

$$\text{CrCl} = \frac{\{(140 - \text{age}) \times (\text{IBW in kg})\}}{[\text{PCr (mg/dL)} \times 72]} \times 0.85 (\text{women})$$

It has the advantage of being very simple, but it is not as accurate as other methods when renal function is impaired.

2. *MDRD formulas*: a series of formulas derived from data collected in patients with severe renal impairment; these formulas are more complex but more accurate than the Cockcroft-Gault. The simplest estimate of GFR is the four-variable equation (PCr, age, sex, and ethnicity) (Manjunath et al, 2001):

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 186 \times (\text{PCr [mg/dL]})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

3. *Chronic kidney disease epidemiology collaboration (CKD-EPI) formula*: derived from data collected in patients with a wide range of renal function; it is a more accurate estimate of GFR in patients with normal or only mildly reduced kidney function. It has largely replaced the MDRD formula in clinical practice (Levey et al, 2009):

$$\text{GFR} = 141 \times \min(\text{SerumCreat/kappa}, 1)^{\alpha} \times \max(\text{SerumCreat/kappa}, 1)^{-1.209} \times 0.993^{\text{Age}} \times \text{Sex} \times \text{Race}$$

For females, the following values are used: Sex = 1.018; alpha = -0.329; kappa = 0.7

For males, the following values are used: Sex = 1; alpha = -0.411; kappa = 0.9

For race, black = 1.159; all others = 1

In summary, the GFR is analogous to renal function. Total GFR is a summation of all SN-GFR, which in turn are determined primarily by TGP and glomerular permeability of the individual nephrons, and it is usually tightly regulated. A GFR estimate should be obtained in all patients with renal impairment (rather than a PCr alone), and the recommended method is through the use of the CKD-EPI formula, the four-variable MDRD formula, or the Cockcroft-Gault formula.

Hormonal

Control of Renal Vascular Tone

Vascular tone of the renal vessels, the net balance of vasoconstrictive and vasodilatory forces, is crucial to the maintenance of RBF, GFR, tubular renal function, and systemic blood pressure. **There is**

BOX 44-1 Vasoactive Substances That Control Renal Artery Tone

VASOCONSTRICTION

Angiotensin II
Norepinephrine
Vasopressin
Endothelin
Atrial natriuretic peptide

VASODILATION

Nitric oxide
Carbon monoxide
Prostaglandin E₂
Acetylcholine
Serotonin/bradykinin
Glucocorticoids

KEY POINTS: RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

- GFR reflects total renal function.
- CrCl can approximate GFR.
- Formulas based on patient's age, weight, and serum creatinine can best estimate GFR.

a complex network of hormones and vasoactive substances with both direct and indirect effects, resulting in a system that is pleiotropic and redundant. Although much has been learned from animal models about the function of individual molecules, the complexity of the total system can lead to unexpected outcomes when individual pathways are manipulated pharmacologically. A summary of substances known to impact vascular tone is provided in Box 44-1.

Vasoconstrictors

Angiotensin II. Angiotensin II is a potent vasoconstrictor. In the kidney, there is a more pronounced constrictive effect on the efferent than the afferent arteriole, because of the inhibition of angiotensin II actions in the afferent arteriole by NO and PG (Arima, 2003). Elevated levels of angiotensin II are important for maintaining GFR in pathologic conditions that reduce RBF (e.g., renal artery stenosis, dietary sodium restriction). The classic effects of angiotensin II (vasoconstriction, aldosterone release, sodium retention) are mediated by the AT₁ receptor (Kaschima and Unger, 2003). The AT₂ receptor, however, may cause intrarenal dilation and be protective against renal ischemic injury (Carey, 2005).

Norepinephrine. Norepinephrine vasoconstricts all the major vascular beds in the kidney, mediated through the α₁ receptor. In patients who receive norepinephrine as a pressor agent in the face of systemic vasodilation, renal function is preserved and may actually improve (Albanese et al, 2004).

Endothelin. Endothelin is the most potent vasoconstrictor yet identified. There are three isoforms, with ET-1 being the most fully described. An endothelin precursor (big ET-1; 39 amino acids) is cleaved to ET-1 (21 amino acids) by an endothelin-converting enzyme found on the endothelial cell membrane. The endothelin receptors are subclassified into ET (A), which are purely vasoconstrictive, and ET (B). The ET (B) receptors may cause either vasodilation by stimulating the release of NO from endothelial cells, or vasoconstriction of vascular smooth muscle cells (Fellner and Arendshorst, 2004). ET-1 release is stimulated by angiotensin II, antidiuretic hormone, thrombin, cytokines, reactive oxygen species, and shearing forces acting on the vascular endothelium. ET-1 release is inhibited by NO, as well as by prostacyclin and ANP. Blockade of the ET (A) receptor can reduce renal vasoconstriction

seen in such ischemic conditions as ureteral obstruction (Bhangdia et al, 2003).

ET-1 has a number of other actions besides vasoconstriction. ET-1 stimulates aldosterone secretion, produces positive inotropy and chronotropy in the heart, decreases RBF and GFR, and releases ANP. Despite reduction in RBF, sodium excretion is increased, suggesting that ET may be responsible for maintaining sodium balance when the renin-angiotensin system is depressed (Perez del Villar et al, 2005). Medullary blood flow is preserved in the face of endothelin-induced vasoconstriction, which may explain the relative stimulation of tubular functions (Evans et al, 2004).

Vasopressin. Vasopressin acts directly on blood vessels through the vasopressin V1 receptor but does not directly change RBF at low doses (Malay et al, 2004). Vasopressin does potentiate the vasoconstrictive effects of norepinephrine (Segarra et al, 2002) and can induce renal ischemia at high doses. At the low doses typically used in the management of septic shock, renal function is preserved (Holmes et al, 2001).

Atrial Natriuretic Peptide. Atrial natriuretic peptide (ANP) is a vasoactive hormone synthesized primarily by the atria in response to stretching, as occurs during physiologic levels of volume expansion (Fig. 44-2). The primary actions of ANP on the kidney are increased GFR and natriuresis. ANP can increase GFR without a change in RBF (Sward et al, 2005) by the combination of afferent arteriolar vasodilation and efferent arteriolar vasoconstriction. In addition, ANP dilates vessels that have been precontracted by norepinephrine, angiotensin II, or vasopressin. ANP production increases during bilateral obstructive uropathy, which may be one mechanism of preserving GFR (Kim et al, 2002).

ANP increases natriuresis mainly through the inhibition of sodium reabsorption in the medullary-collecting duct (Zeidel et al, 1988); decreased renin and decreased aldosterone production may also play a role (Laragh, 1985). Clinically, however, infusion of low-dose ANP during surgery increases water and electrolyte excretion without measured systemic changes in cortisol, angiotensin II, or aldosterone (Koda et al, 2005). This approach has also been used to prevent ischemic renal damage in high-risk cardiac surgery (Sward et al, 2004).

Vasodilators

Nitric Oxide. NO is a highly reactive gas that participates in multiple physiologic and pathophysiologic reactions in the body. NO is synthesized from the reaction between arginine, reduced nicotinamide adenine dinucleotide phosphate (NADPH), and oxygen to produce citrulline, NADP, water, and NO. A family of enzymes called *nitric oxide synthase* (NOS) catalyzes this reaction. Although all NOS enzymes catalyze the same reaction, they differ in distribution, expression, and stimuli. Neuronal (nNOS, NOS-1) and endothelial (eNOS, NOS-3) are constitutively expressed, and iNOS

(NOS-2) is inducible. eNOS is found in the vascular endothelium, and the NO produced there plays a key role in vasodilation and vascular remodeling (Rudic et al, 1998). eNOS expression is stimulated by shear stress by activation of the tyrosine kinase c-SRC (Davis et al, 2004), by heat shock protein 90 (Harris et al, 2003), by oxidant stress (Cai et al, 2001), and by vascular mediators such as bradykinin, serotonin, adenosine, adenosine diphosphate/adenosine triphosphate, histamine, and thrombin (Arnal et al, 1999).

After its formation by vascular endothelial cells, NO diffuses to vascular smooth muscle cells where it activates soluble guanylyl cyclase (sGC), producing 3',5'-cyclic guanosine monophosphate (cGMP). Subsequently, cGMP activates both cGMP- and 3',5'-cyclic adenosine monophosphate (cAMP)-dependent protein kinases (PKG and PKA, respectively) leading to smooth muscle relaxation. eNOS blockade increases renal vascular resistance and decreases the glomerular ultrafiltration coefficient (Gabbai, 2001). NO also helps maintain vascular integrity, with increased expression being linked to decreased neointimal formation and medial thickening (Kawashima et al, 2001). Indeed, the degenerative changes seen in chronic allograft nephropathy related to cyclosporine use can be mitigated by increased NO expression (Chander et al, 2005). Increased eNOS activity is also associated with protection from renal ischemia-reperfusion injury (Shoskes et al, 1997).

Although raised local levels of NO from eNOS can be beneficial to renal function, induction of iNOS and overproduction of NO from inflammatory cells can be deleterious. In the face of free oxygen radicals at the site of inflammation, NO can interact with reactive oxygen species to form peroxynitrite, which induces protein damage by formation of nitrotyrosine. Increased iNOS has been related to damage from nitrotyrosine in glomerular disease (Trachtman, 2004), lupus nephritis (Takeda et al, 2004), and transplant rejection (Albrecht et al, 2002). Increased iNOS activity has direct renal effects as well, including upregulation of sodium and bicarbonate tubular transport (Wang, 2002).

Carbon Monoxide. Carbon monoxide (CO) gas is another reactive diffusible mediator with multiple effects throughout the body, especially in the kidney. Heme oxygenase (HO), an essential enzyme in heme catabolism, catalyzes the rate-limiting step in heme degradation, resulting in the formation of iron, CO, and biliverdin (Hill-Kapturczak et al, 2002). Biliverdin is subsequently converted to bilirubin by biliverdin reductase. HO is expressed in two forms, constitutive HO-2 and inducible HO-1. Increased CO production produces vasodilation in the kidney and can counteract catecholamine-induced vasoconstriction (Mustafa and Johns, 2001). In particular, both HO-1 and HO-2 are highly expressed in the medulla and help maintain renal medullary blood flow (Zou et al, 2000). In cirrhosis, decreased renal expression of HO-1 is

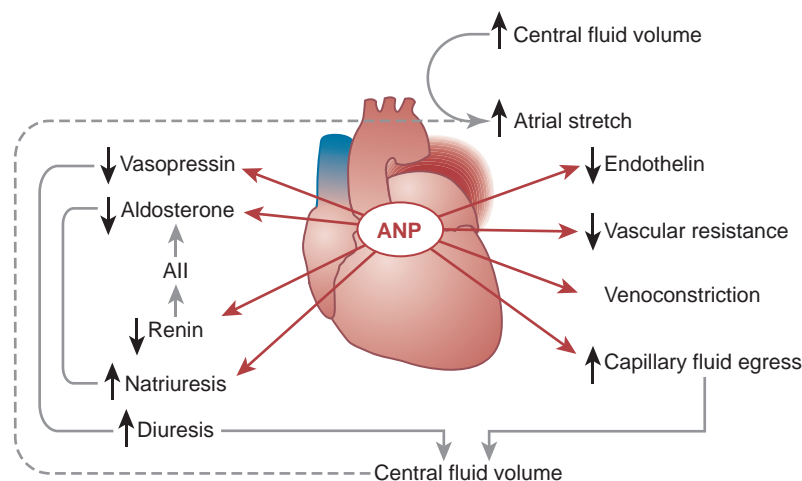


Figure 44-2. The fundamental biologic processes of atrial natriuretic peptide (ANP). AII, angiotensin II.

linked to renal dysfunction (Miyazono et al, 2002). CO also regulates sodium transport in the loop of Henle, with HO-2 blockade inhibiting sodium excretion (Wang et al, 2003) and stimulation increasing natriuresis and diuresis (Rodriguez et al, 2003).

The other primary effect of CO in the kidney is renoprotection from oxidant injury. CO includes documented anti-inflammatory, antioxidant, and cytoprotective actions (Sikorski et al, 2004). Indeed, a patient with a genetic HO-1 deficiency exhibited significant tubular and vascular endothelial injury (Ohta et al, 2000). Increased CO is protective against ischemia-reperfusion injury in native and transplant kidneys (Nakao et al, 2005). Induction of HO-1 through agents such as bioflavonoids protects against tubular damage and improves renal transplant function (Shoskes et al, 2003).

KEY POINTS: HORMONAL

- Multiple chemical mediators act on renal vascular tone, which controls RBF.
- Endothelin is the most potent vasoconstrictor.
- NO and CO are potent vasodilators.

Erythropoiesis

Red blood cell (RBC) production is a tightly regulated process. Basal RBC production is roughly 10 RBCs/hr, but this rate can be greatly increased during times of anemia or hypoxia. The kidney is the major organ involved in this process, and it is responsible for monitoring RBC levels and increasing RBC output through the production of the hormone erythropoietin.

Erythroid Progenitor Cells. Mature RBCs are produced from a small pool of multipotent progenitor cells (Suda et al, 1984), which in turn are derived from the fetal liver. The earliest committed cell is the erythroid burst-forming unit (BFU-E), which, under appropriate stimulation, divides to produce erythroid colony-forming units (CFU-E). Further differentiation leads to the production of proerythroblasts, reticulocytes, and, ultimately (after extrusion of the nucleus), mature RBCs. The entire process requires about 2 weeks.

Erythropoietin. Maturation of the BFU-E and CFU-E depends on the appropriate growth factors. The most important of these factors is erythropoietin (EPO). The kidney is responsible for the majority of EPO production (90%), whereas the liver may contribute a smaller amount (10%). Kidney-derived EPO is produced by a subpopulation of interstitial fibroblasts, and possibly proximal tubular cells, in response to decreased O_2 tension.

EPO-deficient mice die in utero with a marked reduction in erythropoiesis (Munugalavada and Kapur, 2005). Additional growth factors such as interleukin-3, GM-CSF, stem cell factor, activin, insulin-like growth factor (IGF-I), and, possibly, hepatic growth factor act synergistically with EPO to reduce apoptosis and thus promote proliferation of erythroid cells (Muta and Krantz, 1993).

EPO has also been shown to have effects outside of the bone marrow. EPO receptors have been demonstrated in kidney, brain, retina, heart, skeletal muscle, and endothelial cells (Juul et al, 1998). In the kidney, pretreatment with high-dose EPO has been shown to reduce ischemia-reperfusion injury in animal models, because of decreased apoptosis (Patel et al, 2004).

Regulation of Erythropoietin Production and Erythropoiesis. Production of EPO, and hence erythropoiesis, is closely associated with circulating O_2 tension. Under hypoxic conditions, the alpha subunit of the regulatory protein hypoxia-inducible factor-1 (HIF-1) is exposed (Wang et al, 1995). Binding of HIF-1 alpha with HIF-1 beta, hepatic nuclear factor-4 (HNF-4), and p300 turns on EPO transcription (Arany et al, 1996). After the hypoxia has been corrected, HIF-1 alpha is ubiquitinated and rapidly degraded by proteosomes, thus shutting down EPO production. There is also in vitro evidence that hypoxia itself might directly increase erythropoiesis through HIF-1-mediated increases in autocrine motility factor (AMF) production and subsequent decrease in apoptosis (Mikami et al, 2005).

In states of chronic inflammation, erythropoiesis is decreased. Apoptosis of erythroid progenitor cells occurs in the presence of the tumor-associated antigen RCAS1, which is also produced by macrophages under inflammatory conditions (Suehiro et al, 2005).

In certain malignancies, such as renal cell carcinoma, erythropoiesis is enhanced because of a mutation in the von Hippel-Lindau (VHL) gene. As a result, there are constitutively increased levels of HIF-1 and polycythemia (Wiesener et al, 2002).

Erythropoiesis is also decreased in most forms of chronic renal failure, and subsequently anemia is common in the later stages of the disease. This is because of decreased EPO levels as a result of a reduction in the number of functional EPO-producing cells within the kidney. Recombinant human erythropoietin (rHuEPO) has been shown as an effective treatment for this type of anemia.

rHuEPO has also been used to treat anemia associated with malignancy, but it must be used with caution in these conditions because its use may be associated with an increased risk of venous thromboembolism and higher mortality (Bennett et al, 2008).

Bone Mineral Regulation

Normal regulation of bone mineralization, through maintenance of serum calcium and phosphorus levels, is achieved through the actions of vitamin D, parathyroid hormone (PTH), and fibroblast growth factor-23 (FGF-23). The actions of these hormones are exerted largely through the kidney (Fig. 44-3).

Vitamin D Regulation. The kidney plays an important role in the regulation of vitamin D activity. The major source of vitamin D is through dermal synthesis of the precursor compound cholecalciferol (vitamin D_3), or through dietary intake of vitamin D_3 -fortified foods. Vitamin D_3 has minimal biological activity and requires two hydroxylations to become active. The first

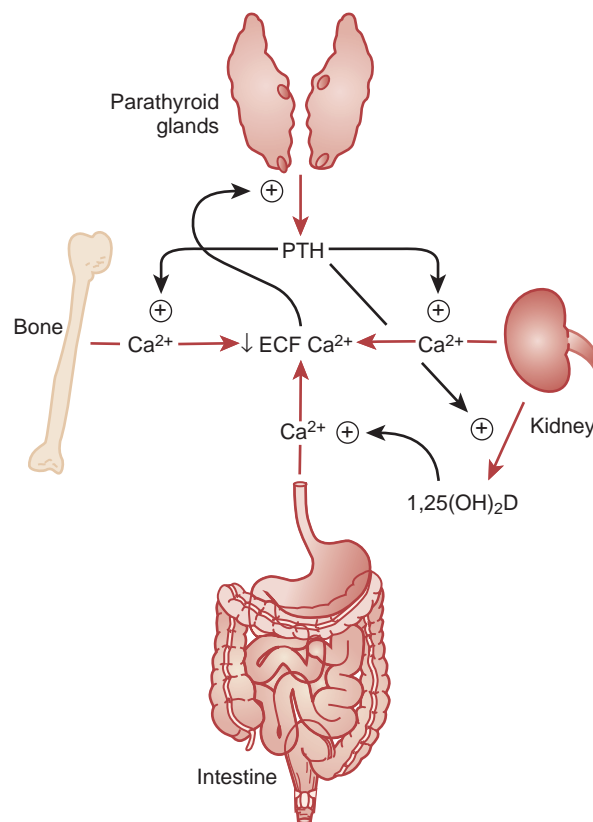


Figure 44-3. Effects of vitamin D and parathyroid hormone (PTH) on calcium homeostasis. ECF, extracellular fluid. (From Yu SLY. Renal transport of calcium, magnesium, and phosphate. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 536.)

occurs in the liver through the action of 25-hydroxylase to form 25-hydroxycholecalciferol (calcidiol). The calcidiol molecule is bound to vitamin D-binding protein and transported to the kidney, where it is filtered and reabsorbed by renal tubular cells. A second hydroxylation occurs within the tubular cell. Because these cells contain both 1α -hydroxylase and 24α -hydroxylase, hydroxylation will produce either inactive 24,25-dihydroxycholecalciferol or 1,25-dihydroxycholecalciferol (calcitriol), the biologically active form that is 100 times more potent than calcidiol. Calcitriol production is regulated by calcidiol levels as well as the 1α -hydroxylase levels. In turn, PTH and plasma phosphate levels (increased enzyme activity) and serum calcitriol levels (decreased enzyme activity) determine these (Portale et al, 1989). However, unregulated calcitriol synthesis can occur in macrophages in granulomatous conditions such as sarcoidosis and tuberculosis, and in prostate epithelial and cancer cells (Young et al, 2004).

Vitamin D Activity. Calcitriol functions through a single intracellular vitamin D receptor (VDR) to regulate gene transcription (Lowe et al, 1992). Its primary function is the maintenance of serum calcium and phosphorus levels. The four main target organs are the intestine (increases intestinal absorption of calcium, and, to a lesser extent, phosphorus), the bones (regulates osteoblast activity, and, in combination with PTH, allows for osteoclast activation and bone resorption), the kidney (increases reabsorption of calcium), and the parathyroid gland (suppresses PTH release). Evidence suggests that both calcidiol and calcitriol may also function as antiproliferative agents. Prostate epithelial and cancer cells demonstrate VDR, and vitamin D may suppress the growth of these cells, especially in combination with androgens (Tuohimaa et al, 2005).

In summary, vitamin D contributes to normal bone mineralization by maintaining normal serum calcium and phosphorus levels through increased intestinal absorption of calcium and phosphorus and increased renal reabsorption of calcium.

Parathyroid Hormone Regulation. Synthesis, secretion, and degradation of PTH are influenced directly by serum calcium levels through calcium-sensing receptors located on parathyroid cells. During periods of hypocalcemia, PTH synthesis and secretion are increased while degradation is decreased. The opposite occurs during hypercalcemia. In addition, calcitriol has a suppressive effect on PTH synthesis and parathyroid cell proliferation, mediated through vitamin D receptors located on the surface of parathyroid cells. Hyperphosphatemia also directly stimulates PTH release, primarily in advanced renal insufficiency. Finally, other cations such as magnesium and aluminum have slight stimulatory effects, likely mediated through the calcium-sensing receptors.

Parathyroid Hormone Activity. PTH exerts its activity through PTH/PTHrP receptors, which are localized primarily in the kidneys and bone.

Bone. The effect of PTH on bone metabolism depends on its administration; if given continuously, it stimulates bone resorption and increases serum calcium and phosphorus levels. Administered intermittently, it leads to increased bone formation and mineral density.

Kidney. The renal effects of PTH are threefold. First, it increases active calcium reabsorption at the level of the distal tubule (Friedman and Gesek, 1993). Second, it decreases phosphate reabsorption in the proximal convoluted tubule (PCT) (and the distal tubule, to a lesser degree) through its action on the sodium-phosphorus cotransporter (Pfister et al, 1997). Third, it stimulates calcitriol production by increasing 1α -hydroxylase levels while decreasing 24α -hydroxylase levels (Broadus et al, 1980).

In summary, PTH functions to maintain normal serum calcium and phosphorus levels by increasing bone resorption, by increasing renal reabsorption of calcium and excretion of phosphorus, and by stimulating production of calcitriol.

Fibroblast Growth Factor-23 Regulation. FGF-23 is a peptide secreted primarily by bone osteoclasts. It plays a key role in regulating serum phosphate levels through its actions on the kidney and parathyroid gland. High plasma phosphate levels and increased circulation calcitriol levels stimulate FGF-23 production. It exerts its activity through its receptor protein Klotho (Urakawa et al, 2006).

Fibroblast Growth Factor-23 Activity. FGF-23 increases phosphate excretion in the kidney by reducing the number of Na-Pi cotransporters in the PCT (Miyamoto et al, 2007). It also suppresses the activity of 1α -hydroxylase, thus decreasing calcitriol production (Saito et al, 2003). FGF-23 also acts on the parathyroid gland, reducing PTH production (Ben-Dov et al, 2007).

In summary, FGF-23 functions to maintain plasma phosphate levels through the regulation of renal phosphate excretion and both calcitriol and PTH production.

Antidiuretic Hormone

Antidiuretic hormone (ADH), or arginine vasopressin as it is called in humans, is a polypeptide secreted by the posterior pituitary gland. It functions to maintain serum osmolality and volume through the regulation of free-water excretion in the kidney.

Antidiuretic Hormone Actions

ADH increases the passive reabsorption of water at the level of the collecting duct. Through interaction with the V2 receptor, it facilitates the insertion of preformed water channels, known as aquaporin-2 (AQP-2), into the luminal membrane of the principal cells (Agre et al, 2002). This allows luminal water to enter the cell and then diffuse back into the systemic circulation through the basolateral membrane of the cell (Fig. 44-4). ADH increases urea reabsorption in the medullary collecting tubule through specific urea transporters, which helps maintain the high interstitial osmolality required for water reabsorption. ADH also increases systemic vascular resistance through interaction with the V1 receptor; this is of minor physiologic importance. Other effects of ADH include increased sodium reabsorption and potassium excretion, increased PG synthesis, increased adrenocorticotrophic hormone secretion (through V3 receptors), and release of both factor VIII and von Willebrand factor from vascular endothelium.

Control of Antidiuretic Hormone Secretion. There are two major stimuli for ADH release; these are hyperosmolality and decreased ECV, as well as a number of less common factors (Table 44-1).

Hyperosmolality. The major extracellular osmole is sodium; so for practical purposes, ADH release is governed by changes in serum sodium concentrations. Serum osmolality is monitored by osmoreceptors in the hypothalamus, and changes as little as 1% are enough to affect ADH release (Robertson, 1987).

Decreased Effective Circulating Volume. Circulating volume is monitored by pressure (baro-) receptors in the carotid sinus, which stimulate ADH release in response to reductions in ECV. These receptors are much less sensitive than the osmoreceptors, and as such, ADH release is not affected until there is a noticeable drop in MAPs (usually around 10% to 15% blood volume loss) and after other vasoconstrictive hormones, such as renin and norepinephrine, have been activated.

Other Stimuli. There are a number of other factors that can increase ADH secretion (see Table 44-1). Nausea and pain are probably the most clinically relevant, and as a result, postsurgical hyponatremia resulting from excessive ADH release is a potentially life-threatening problem.

When both decreased ECV and hyponatremia coexist, the pressure receptors usually override the osmoreceptors and prevent the inhibition of the ADH secretion that is usually seen with hyponatremia (Baylis, 1987). This is clinically relevant in conditions of decreased ECV and hyponatremia, such as congestive heart failure where ADH secretion persists despite significant hyponatremia.

Renal Tubular Function

Basic Functions

The renal tubule has two basic functions: *reabsorption* (transport of substances from lumen to blood) and *secretion* (transport of

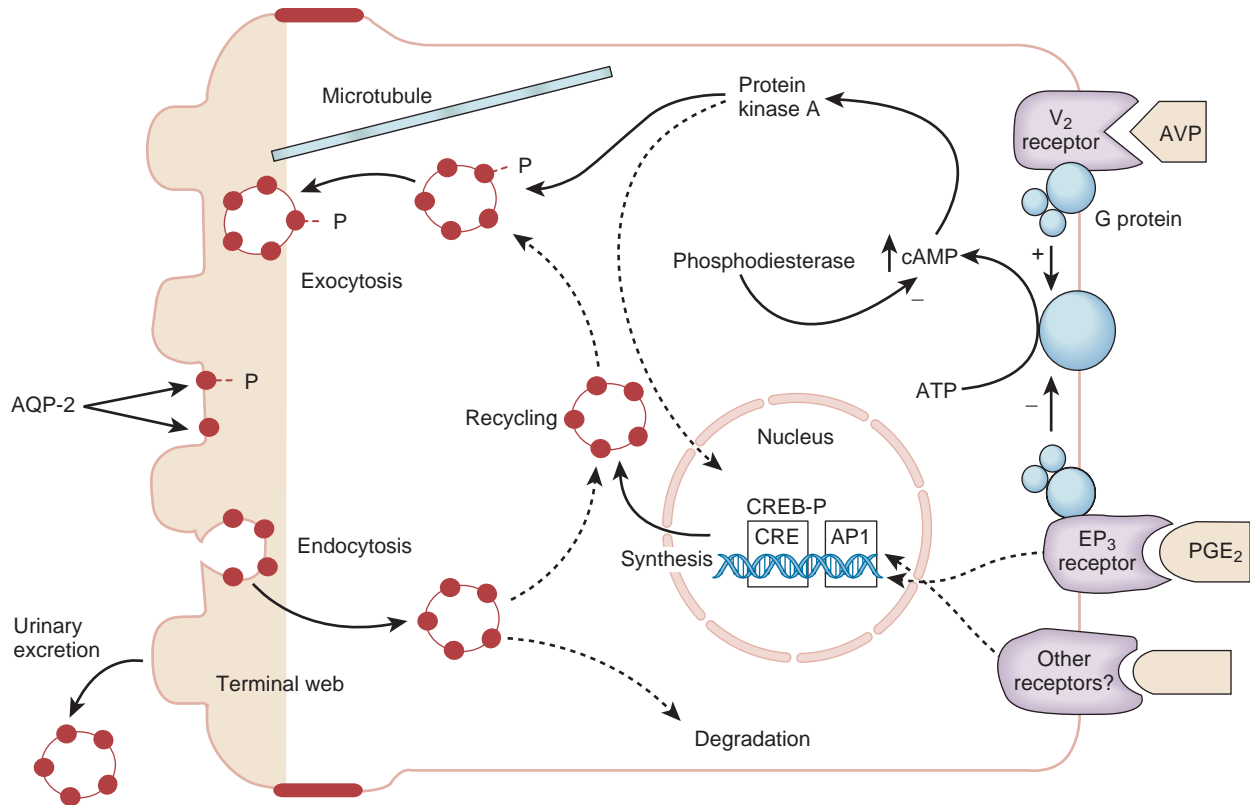


Figure 44-4. Action of antidiuretic hormone on aquaporin (AQP) transport. AP1, transcription factor; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; CRE, cAMP response element; CREB-P, CRE-binding protein; EP₃, prostaglandin receptor; PGE₂, prostaglandin E₂. (From Brown D, Nielsen S. The cell biology of vasopressin action. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 574.)

TABLE 44-1 Physiologic and Pathologic Factors Affecting the Release of Antidiuretic Hormone

STIMULI	INHIBITORS
Hyperosmolality	Hypo-osmolality
Hypovolemia	Hypervolemia
Stress (e.g., pain)	Ethanol
Nausea	Phenytoin
Pregnancy	
Hypoglycemia	
Nicotine	
Morphine	
Other drugs	

substances from blood to lumen). Transport can involve one of two pathways: either *transcellular* (across the luminal and basolateral membrane) or *paracellular* (between cells) (Fig. 44-5). Each section of the tubule (Fig. 44-6) is specialized to facilitate absorption and secretion of certain substances through a variety of transport mechanisms.

Proximal Convoluted Tubule

The PCT is responsible for reabsorption of 60% of the glomerular filtrate. In normal circumstances, it reabsorbs 65% of the filtered sodium, potassium, and calcium; 80% of filtered phosphate, water, and bicarbonate; and 100% of the filtered glucose and amino acids (Moe et al, 2004). The PCT is able to increase or decrease

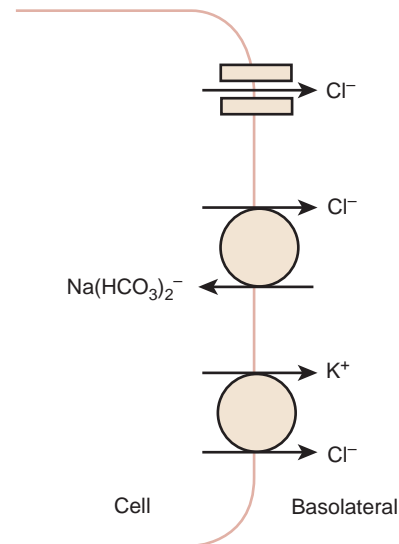


Figure 44-5. Example of transcellular transport between the tubule cell and the basolateral membrane. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 425.)

reabsorption in response to changes in GFR to maintain constant reabsorptive fractions through the process of *glomerulotubular balance*. The early (S1 and S2) segments of the PCT mainly accomplish this. The later (S3) segment is responsible for secretion of numerous drugs and toxins that are too large, or protein bound,

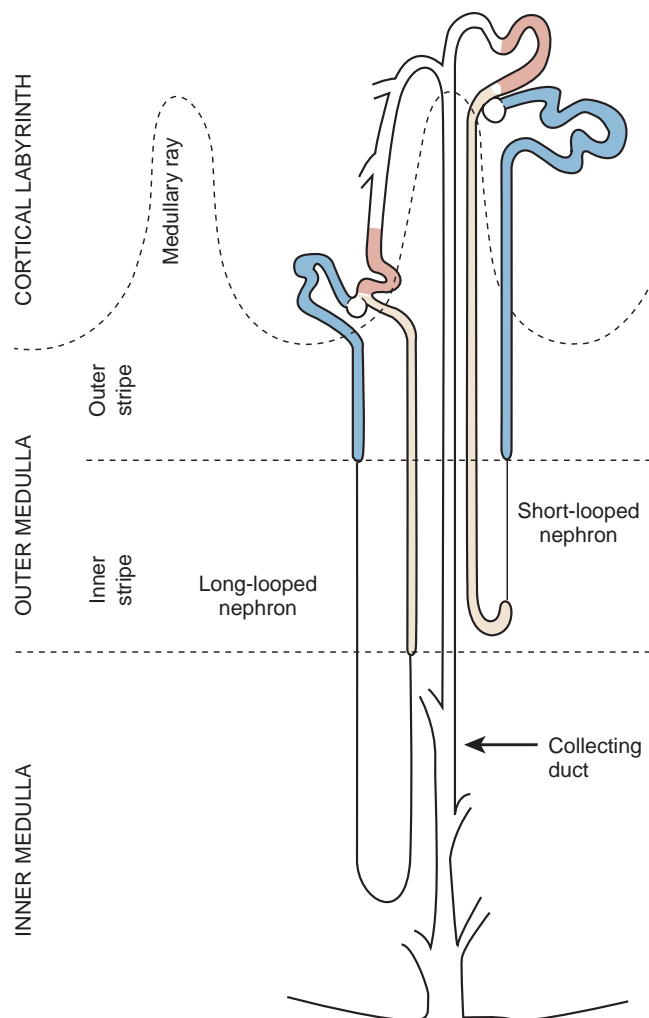


Figure 44-6. Organization of the renal tubule. (From Knepper MA, Gamba F. Urine concentration and dilution. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 601.)

to be filtered. As well, the PCT is responsible for the generation of ammonia from glutamine, which is necessary for urinary acidification.

Sodium. The majority of sodium reabsorption occurs in the PCT, and it occurs through both secondary active and passive mechanisms (Fig. 44-7).

1. *Secondary active reabsorption*—luminal Na^+ moves passively into tubular cells; this movement, however, is driven by osmotic and electrochemical gradients between the luminal and intracellular environments established by the energy-requiring Na^+ - K^+ -ATPase located in the basolateral cell membrane. There is an active exchange of three intracellular Na^+ for two extracellular K^+ ions, which keeps the intracellular sodium concentration low and the cell interior negative with respect to the lumen. This is called *secondary passive reabsorption*. Na^+ then enters the cell through coupled transport with other solutes (see later) or in exchange for H^+ through a Na^+ - H^+ antiporter. The activity of this transporter is under neurohormonal regulation and can be influenced by angiotensin II, norepinephrine, and dopamine to either increase or decrease Na^+ reabsorption in response to changes in ECV.
2. *Passive reabsorption*—this occurs when Na^+ moves paracellularly into the intercellular space. It is mediated through Cl^- transport across the paracellular pathway, which creates an electrochemical gradient favoring Na^+ movement out of the lumen into the intercellular space.

In summary, sodium is the most significant solute for the PCT for three reasons:

- It is the only solute that is actively reabsorbed (through the basolaterally located $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump).
- All other solutes are passively reabsorbed through Na^+ -coupled transport.
- Early reabsorption of Na^+ (as well as other solutes) creates an osmotic gradient that facilitates passive reabsorption of water.

Potassium. The majority of potassium reabsorption occurs by the paracellular route. It is largely dependent on sodium and fluid movement, as potassium reabsorption parallels that of water and sodium.

Bicarbonate. The majority of filtered bicarbonate (90%) is reclaimed in the PCT. There is no upper limit to bicarbonate reabsorption; in states of volume depletion and increased proximal reabsorption of Na^+ , bicarbonate reabsorption continues even in

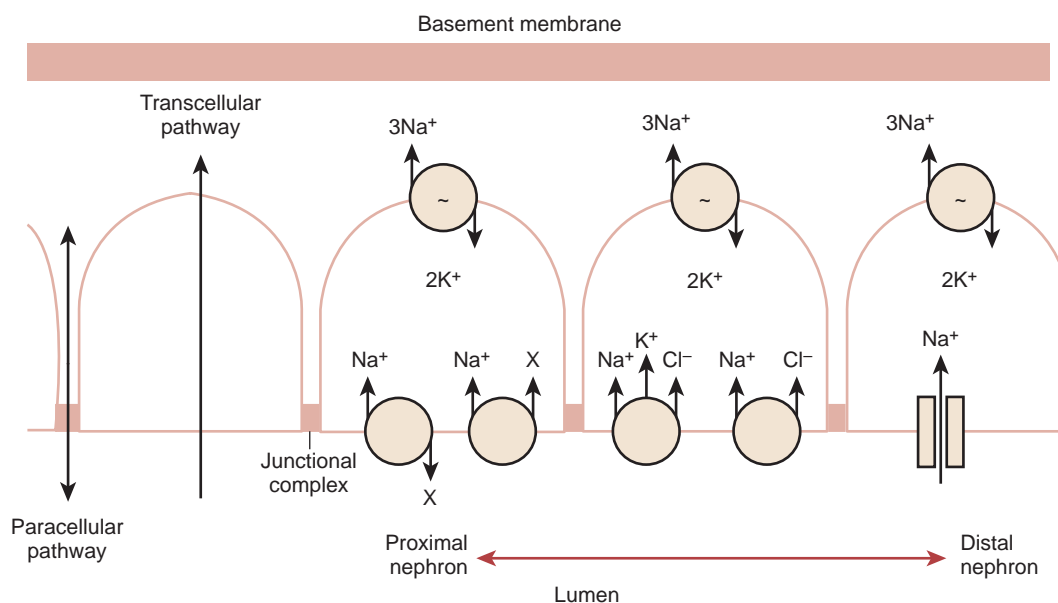


Figure 44-7. Mechanisms of sodium reabsorption in the proximal tubule. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 414.)

the presence of significant alkalemia (Moe et al, 2004). Bicarbonate is not transported across PCT cells; its reabsorption is dependent on H^+ secretion by the Na^+/H^+ antiporter. Within the lumen, bicarbonate combines with H^+ to form H_2O and CO_2 , which can diffuse intracellularly and be converted back to H^+ and bicarbonate and can subsequently be secreted through the basolateral membrane by a Na^+ -coupled transporter and returned to the circulation. Both of these reactions are catalyzed by carbonic anhydrase (Fig. 44-8).

Water. Water reabsorption in the PCT is a passive process, driven by the reabsorption of other solutes and the subsequent osmotic gradient that develops between the lumen and intercellular space. The majority of water reabsorption occurs in the late PCT. As with Na^+ movement, water can also move either transcellularly or paracellularly. Transcellular movement accounts for 80% of water reabsorption, and it occurs through the specialized water channel aquaporin-1 (AQP-1) (Agre et al, 2002). Paracellular movement accounts for only 20% of water reabsorption and occurs across the tight junctions between cells.

Glucose. Glucose reabsorption is driven by passive Na^+ reabsorption. In the early (S1 and S2) PCT, this occurs through a high-capacity, low-affinity Na^+ /glucose transporter called SGLT-2 (Moe et al, 2004). In the later (S3) segment of the PCT, reabsorption occurs through a low-capacity, high-affinity $2Na^+$ /glucose transporter (also found in intestine) called SGLT-1. Intracellular glucose is then transported out of the cell through the basolateral membrane by the facilitative transporter GLUT-2. Under normal plasma glucose levels, all filtered glucose is reabsorbed. However, if plasma levels exceed 200 mg%, then the filtered load will exceed the reabsorptive threshold and urinary glucose will be detected (Fig. 44-9).

Proteins and Amino Acids. Amino acid transport is complex. Generally, there are separate transporters for the basic, acidic, and neutral amino acids, and most are Na^+ dependent. There are a few amino acids that have specialized transporters, and some are Na^+ independent. Larger proteins are usually catabolized by brush border peptidases and reabsorbed as amino acids; some, however, enter the cell through carrier-mediated endocytosis.

Phosphate. About 85% to 90% of filtered phosphate is reabsorbed, primarily in the PCT. Phosphate reabsorption occurs through a Na^+ -phosphate cotransporter. Plasma phosphate levels, parathyroid hormone, and FGF-23 regulate the activity of this transporter (Fig. 44-10).

Calcium. Most calcium reabsorption occurs in the late S2 segment and in the early S3 segment of the PCT. It is a passive process, driven by the lumen (+) potential difference (PD). Calcium movement occurs by the paracellular route, through the specific calcium

channel claudin-2 (Amasheh et al, 2002), located in the tight junctions. It is also possible that there is a small amount of active calcium reabsorption in the late S3 segment, but this is poorly characterized (Fig. 44-11).

Magnesium. About 15% of filtered magnesium is reabsorbed in the PCT, but the mechanism is poorly understood (Konrad et al, 2004).

Loop of Henle

The loop of Henle consists of four segments; the thin descending limb (DLH), the thin ascending limb (ALH), the medullary thick

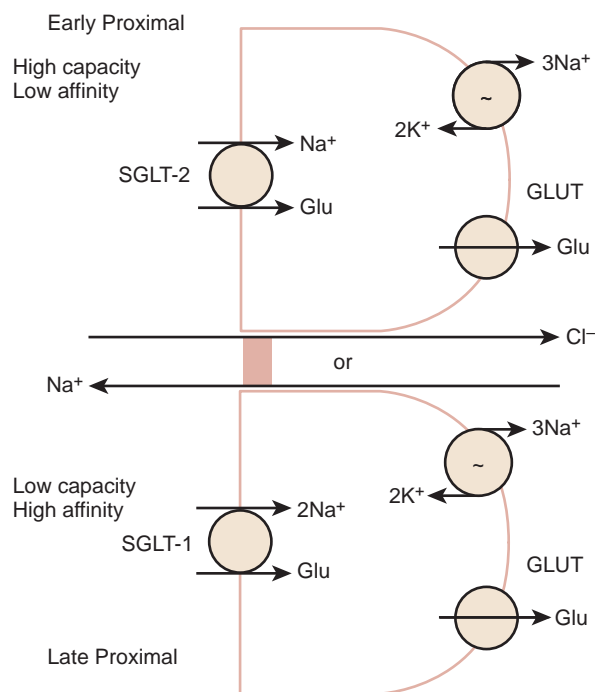


Figure 44-9. Absorption of glucose by the renal tubule. GLUT, glucose transporter; SGLT, sodium glucose-linked transporter. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 417.)

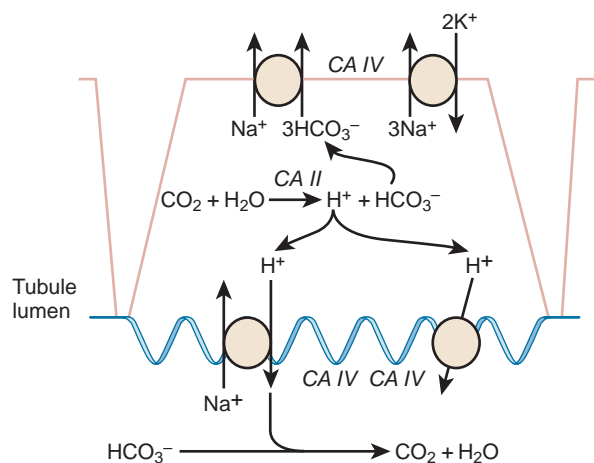


Figure 44-8. Reabsorption of bicarbonate in the renal tubule. CA, carbonic anhydrase. (From Hamm LL. Renal acidification mechanisms. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 500.)

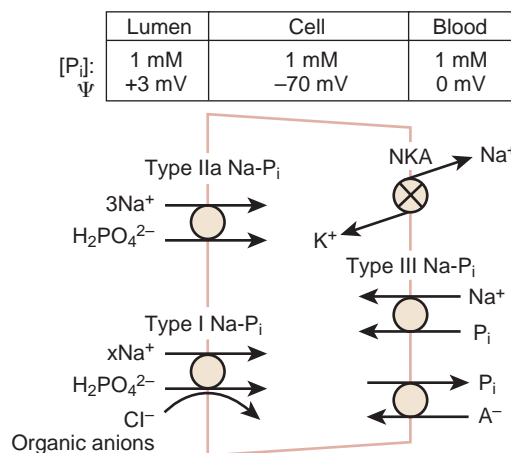


Figure 44-10. Absorption of phosphate by the renal tubule. (From Yu SL. Renal transport of calcium, magnesium, and phosphate. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 555.)

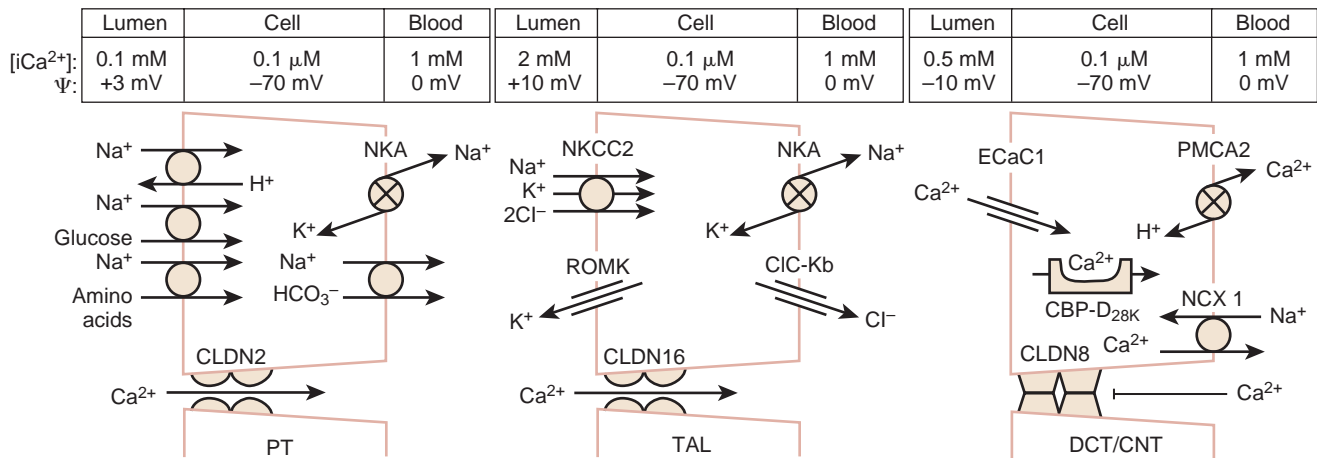


Figure 44-11. Absorption of calcium by the renal tubule. CNT, connecting tubule; DCT, distal convoluted tubule; PT, proximal tubule; TAL, thick ascending limb. (From Yu SLY. Renal transport of calcium, magnesium, and phosphate. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 538.)

ascending limb (mTALH), and the cortical thick ascending limb (cTALH). It receives the 40% of ultrafiltrate not reabsorbed by the PCT. Each segment of the loop of Henle has specific functions related to fluid, electrolyte, and acid-base balance, but the major function of the loop, as a whole, is to reabsorb 25% to 30% of the filtered Na⁺ and to reabsorb NaCl in excess of water to establish an extremely concentrated medullary interstitium, which is necessary for the excretion of a concentrated final urine. The loop of Henle, like the PCT, is also controlled by glomerulotubular balance, which maintains a consistent ultrafiltrate delivered to the collecting ducts (Fig. 44-12).

Thin Descending Limb. The DLH consists of the segment of the nephron between the end of the PCT (S3 segment) and the bottom of the loop. Cortical nephrons, in general, have short DLHs, whereas juxtamedullary nephrons have longer DLHs. There is very little active transport of any kind within the DLH, but it has very high water permeability because of abundant expression of AQP-1 (Agre et al, 2002).

Thin Ascending Limb. The ALH begins at the loop and continues up to the thick ascending limb. The ALH is of variable length; cortical nephrons may have little ALH. Similar to the DLH, there is no active transport of solutes. However, unlike the DLH, the AHL is water impermeable. There is high permeability for NaCl as well as urea; so reabsorption of these solutes occurs passively along an osmotic gradient, because the luminal concentrations of these solutes is high because of water removal during transit through the DLH.

Thick Ascending Limb. The TALH is far more active in terms of solute reabsorption than either of the thin limbs. Water reabsorption, however, is negligible because this segment of the loop is entirely impermeable to water because of the lack of aquaporins.

Sodium, Potassium, and Chloride. The TALH reabsorbs 25% to 30% of the sodium filtered across the glomerulus. This is primarily through the secondary active process driven by basolateral Na⁺-K⁺-ATPase pumps that keep intracellular sodium concentration low. Na⁺ is transported transcellularly by a Na⁺/K⁺/2Cl⁻ (NKCC2) transporter located in the apical membrane. After transportation to the inside of the cell, Cl⁻ is pumped out across the basolateral membrane by a Cl⁻/K⁺ cotransporter, which helps keep intracellular chloride concentration low. K⁺, however, preferentially exits the cell back through the apical membrane K channel ROMK and reenters the tubular lumen, where it can interact again with the NKCC2 transporter. **This K⁺ recycling is important; without it, sodium reabsorption would be limited by the luminal potassium concentration, which is much lower**

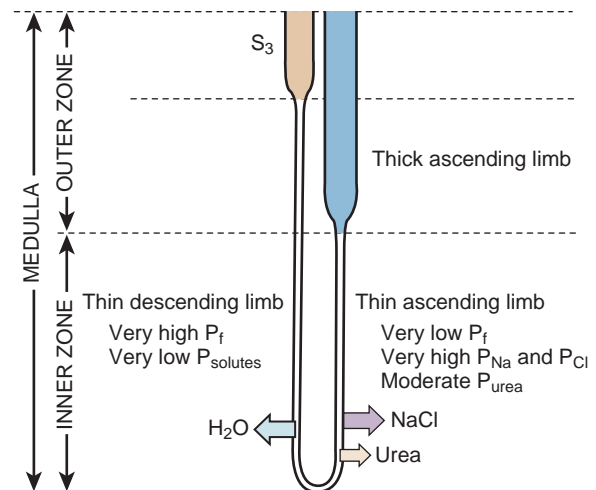


Figure 44-12. Anatomy of the loop of Henle. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 431.)

than either sodium or chloride concentrations. By recycling K⁺, the tubule is able to reabsorb sodium independent of potassium. A secondary benefit of this process is to help establish a lumen (+) PD, which helps facilitate paracellular transport of a variety of cations, including sodium (Fig. 44-13).

The NKCC2 transporter is the site of the action of loop diuretics. These drugs bind to the Cl⁻ receptor and interfere with normal transporter action, resulting in decreased NaCl reabsorption and subsequent diuresis.

Sodium reabsorption along the TALH, in the absence of water reabsorption, is critical to the formation of the interstitial concentration gradient. This gradient is essential to subsequent urinary concentrating ability in the collecting duct. It also creates a progressively more hypotonic ultrafiltrate, which is important for water diuresis to occur (see later).

Calcium and Magnesium. About 15% of the filtered calcium is reabsorbed in the TALH. Reabsorption is passively driven by the lumen (+) PD by the paracellular route, facilitated by the calcium channel paracellin-1 (also known as claudin-16). Magnesium reabsorption (60% to 70%) also occurs in the TALH in a similar manner

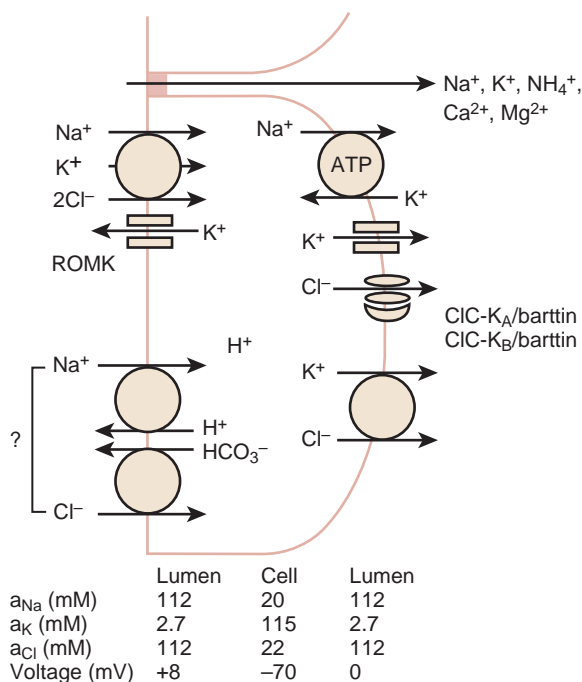


Figure 44-13. Paracellular transport of cations in the thick ascending limb. ATP, adenosine triphosphate; ROMK, renal outer medullary potassium channel. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 433.)

(Konrad et al, 2004). Inhibition of the NKCC2 transporter with loop diuretics induces renal calcium and magnesium wasting because of dissipation of the lumen (+) PD.

Bicarbonate. The TALH also reabsorbs 10% to 20% of the filtered bicarbonate, mainly through H^+ secretion by using the Na^+/H^+ exchanger. Water reabsorption occurring in the DLH increases bicarbonate reabsorption by increasing luminal bicarbonate concentrations.

Countercurrent Mechanism. A critical function of the kidney is the preservation of body water; this is accomplished through the osmotic reabsorption of solute-free water in the collecting tubule (see later) and the excretion of urine that is hyperosmolar with respect to plasma. Human kidneys can produce a urine concentration of up to 1200 mOsm/kg. To achieve this degree of urinary concentration, the kidney must be able to generate an interstitial osmotic gradient of similar degree. Through the process of *countercurrent multiplication*, the loop of Henle is able to produce an interstitial osmotic gradient ranging from 285 mOsm/kg (isosmotic with plasma) in the outer medulla to 1200 mOsm/kg in the inner medulla. The basic steps of countercurrent multiplication are as follows:

1. Medullary interstitium is made hyperosmolar by the reabsorption of NaCl (in the absence of water reabsorption) in the ascending limbs of the loop of Henle.
2. Because of the hairpin (*countercurrent*) configuration of the loop, the concentration of the luminal fluid can be progressively increased (*multiplied*) to as much as 1200 mOsm/kg (Fig. 44-14). This allows the interstitial osmolality to increase to similar levels.
3. In the presence of ADH, urea diffuses from the medullary collecting tubule into the interstitium, increasing the interstitial osmolality even further (Yang and Bankir, 2005). This includes a secondary benefit of increasing water reabsorption in the DLH, thus increasing luminal sodium and chloride concentrations in the ascending limbs and making step 1 even more efficient (Fig. 44-15).

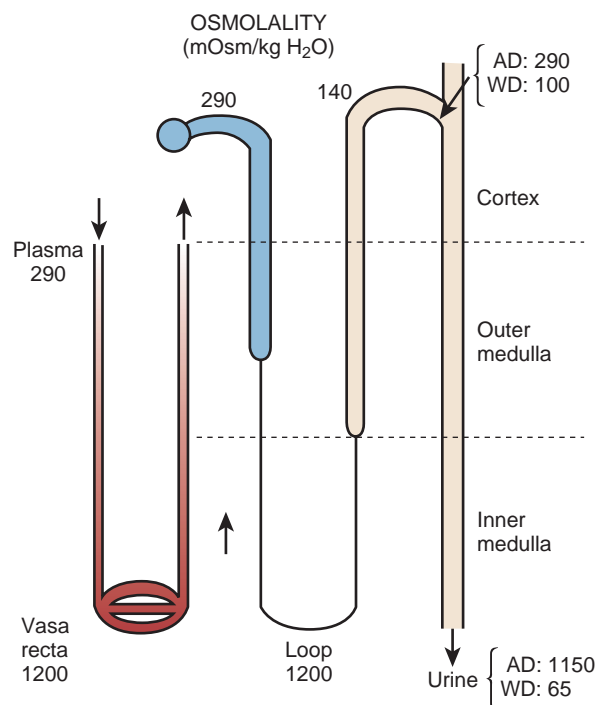


Figure 44-14. Countercurrent mechanism in the renal tubule. AD, antidiuresis; WD, water diuresis. (From Knepper MA, Gamba F. Urine concentration and dilution. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 604.)

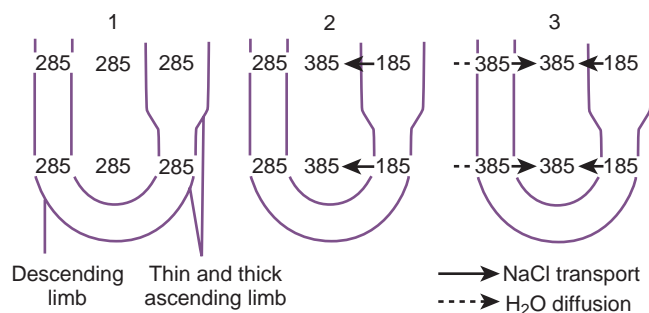


Figure 44-15. Role of active NaCl transport in initiating countercurrent multiplication. In step 1, at time zero, the fluid in the descending and ascending limbs and the interstitium is isosmotic to plasma. In step 2, NaCl is transported out of the ascending limb into the interstitium to a gradient of 200 mOsm/kg. In step 3, the fluid in the descending limb equilibrates osmotically with the hyperosmotic interstitium, primarily by water movement out of the tubule. Dilution of the interstitium by this water movement is prevented by continued NaCl transport out of the ascending limb. The result is the creation of an osmotic gradient between the ascending limb and the relatively hyperosmotic descending limb and interstitium.

4. Because of the high interstitial osmolality, water is passively reabsorbed in the medullary collecting tubule (in the presence of ADH). This could potentially lead to dilution of the interstitium. To minimize this effect, the volume of ultrafiltrate is minimized through water reabsorption in the cortical collecting tubule. Also, the vasa recta are arranged in a similar hairpin loop that allows water removal but minimizes removal of interstitial solutes (Pallone et al, 2003).

The osmotic gradient can be disturbed in certain clinical conditions. Increased medullary blood flow (as seen with osmotic diuresis) increases removal of interstitial solutes through the vasa recta

and leads to a lower interstitial osmolality. In addition, prolonged use of loop diuretics will prevent the transport of NaCl in the ascending limb of the loop of Henle, necessary for the ongoing maintenance of the interstitial hyperosmolality; hence, prolonged water diuresis may be seen after discontinuation of the drug, until the gradient can be reestablished.

Tamm-Horsfall Mucoprotein. The TALH is also the site of secretion of Tamm-Horsfall mucoprotein, or uromodulin. It is clinically important, because it forms the matrix of all urinary casts. It has been shown to be important in the prevention of urinary tract infections (Bates et al, 2004). It has also been implicated in the pathogenesis of cast nephropathy, medullary cystic renal disease, and familial juvenile hyperuricemic nephropathy.

Distal Tubule

The distal tubule is primarily involved in sodium and calcium reabsorption. There may be some capacity for H^+ and K^+ secretion, but the importance of this is unknown. The distal tubule can be subdivided into two sections, the distal convoluted tubule (DCT), and the connecting tubule (CNT).

Sodium and Chloride. The DCT reabsorbs another 5% to 10% of the sodium filtered through the glomerulus. As in the TALH, it is a secondary active process, driven by basolateral Na-K ATPase pumps, that occurs in the absence of water reabsorption. Na^+ is reabsorbed electroneutrally with Cl^- by a Na^+/Cl^- (NCC) cotransporter that can be inhibited with the thiazide diuretics. Additionally, there may be some Na^+ reabsorption by the Na^+/H^+ exchange transporter in the luminal membrane. Notably, Na^+ reabsorption in the DCT is regulated by luminal sodium concentration but not by hormonal influences. Hence, anything that increases delivery of Na^+ to the DCT will lead to increased Na^+ reabsorption in this section of the tubule. One clinical example would be the use of loop diuretics. By inhibiting the NKCC2 transporter in the TALH, Na^+ delivery increases to the DCT. In response, there is usually a marked increase in Na^+ reabsorption, which may significantly diminish the diuretic response achieved with the loop diuretic. Such a response may be minimized by concomitant use of a thiazide diuretic.

The connecting segment can also reabsorb sodium, but it does so under the influence of aldosterone, which is similar to what occurs in the principal cells of the cortical collecting tubule.

Calcium. The DCT accounts for 10% to 15% of calcium reabsorption. Unlike either the PCT or loop of Henle, calcium reabsorption in the DCT is independent of Na^+ reabsorption. Calcium enters the cell through the luminal calcium channel TRPV5 and binds to the intracellular binding protein calbindin D_{28} (Loffing and Kaissling, 2003). By doing so, free intracellular calcium concentration is kept low, thus facilitating inward movement of calcium. Extrusion from the cell occurs through the basolateral membrane using either a Ca^{2+}/H^+ (PMCA) or Na^+/Ca^{2+} (NCX) exchanger (Loffing and Kaissling, 2003). In contrast to the PCT or loop of Henle, movement of calcium by the paracellular route is inhibited because of the presence of the protein claudin-8, which markedly decreases calcium permeability through tight junctions.

Calcium reabsorption is regulated in this region by the actions of PTH and, to a lesser degree, calcitriol (vitamin D). PTH increases calcium reabsorption, possibly through alterations in intracellular voltage as a result of increased Cl^- flux through the basolateral membrane. Calcitriol is thought to increase the number of TRPV5 channels and increase calbindin production, both of which would increase calcium reabsorption (Chamoux et al, 2010; Haussler et al, 2013).

Magnesium. A total of 5% to 10% of filtered magnesium is actively reabsorbed in the DCT by the transcellular route. This likely occurs through the luminal magnesium channel TRPM6 (Voets et al, 2004) and is driven by a basolateral Na^+-Mg^{2+} pump that generates a Mg gradient favoring inward flow of Mg.

Collecting Tubule

The collecting tubule consists of two parts, the cortical collecting tubule (CCT) and the medullary collecting tubule (MCT). Whereas

the more proximal portions of the nephron are designed for bulk reabsorption of ultrafiltrate, the collecting tubules are responsible for the final qualitative changes in ultrafiltrate composition in response to dietary intake.

Cortical Collecting Tubule

The CCT consists of two distinct cell types, each with distinct functions. Principal cells (65%) are generally involved in NaCl reabsorption, whereas intercalated cells (35%) are mostly involved with acid secretion. Both are also involved in K regulation.

Principal Cells

Sodium, Potassium, and Chloride. Sodium reabsorption occurs passively through the luminal Na channel ENaC rather than through a cotransporter system (Loffing and Kaissling, 2003). Basolateral Na^+-K^+ -ATPase pumps keep intracellular sodium concentration low, facilitating inward movement of sodium. Movement of sodium intracellularly, without an accompanying anion, creates a lumen (-) PD that results in either passive paracellular movement of Cl^- out of the lumen, or secretion of intracellular K into the lumen to restore electroneutrality. Sodium reabsorption is regulated in the CCT primarily by aldosterone, which increases the number of open ENaC. Blockade of the Na channel by the diuretic amiloride leads to reduced Na reabsorption as well as K secretion, as the electrochemical gradient is eliminated, and thus the driving force for K secretion is abolished (Fig. 44-16). Prostaglandin E_2 (PGE_2) also seems to inhibit Na reabsorption, and reduction of PGE_2 by NSAIDs leads to sodium retention.

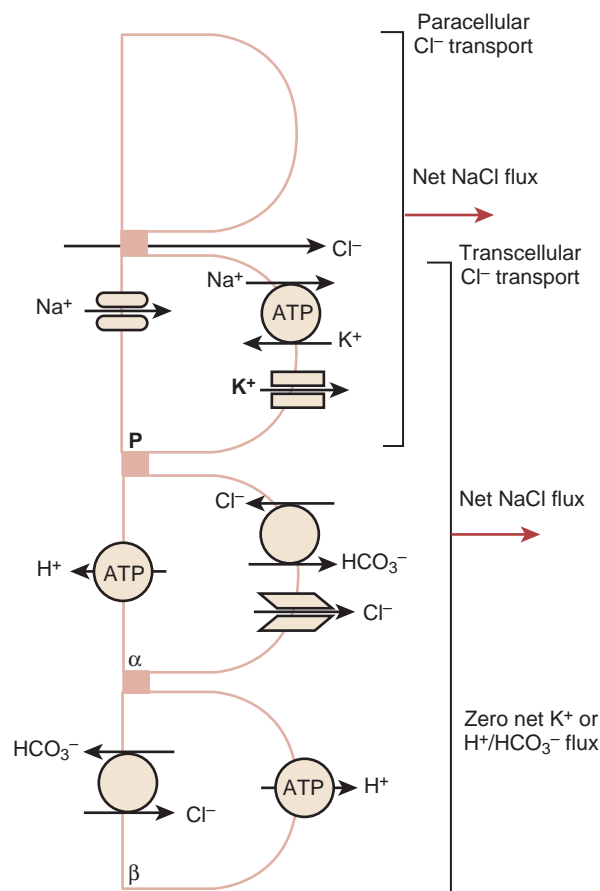


Figure 44-16. Effect of blockade of the Na channel by the diuretic amiloride. ATP, adenosine triphosphate. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: Saunders; 2004. p. 439.)

K secretion in the CCT depends not only on aldosterone-sensitive inward Na movement, but also on luminal flow rates. When flow decreases in the tubular lumen, local intraluminal potassium concentration increases and minimizes the favorable potassium gradient, thus minimizing secretion. This can be partially offset by the actions of ADH, which increase potassium secretion, possibly by the insertion of new K channels in the luminal membrane or by increased Na reabsorption (Wang, 1995). Thus any condition that leads to decreased luminal flow rates, or increased aldosterone production, can lead to reduced potassium excretion.

Water. The water permeability of the CCT is low in the basal state. However, it can be greatly increased in the presence of ADH. This is a result of the insertion of preformed AQP-2 water channels into the luminal membrane (Agre et al, 2002), which allows water to be passively reabsorbed and to equilibrate with the cortical interstitium through basolateral AQP-3 and AQP-4 channels. This is important for the development of highly concentrated final urine, because it decreases the volume of ultrafiltrate delivered to the MCT, where most of the final concentration of urine occurs (Knepper et al, 1994) (Fig. 44-17).

Intercalated Cells. There are two different types of intercalated cells, with different functions: type A intercalated cells, involved mostly with H⁺ secretion; and type B intercalated cells, involved mostly with bicarbonate secretion.

Hydrogen and Bicarbonate. In both cell types, intracellular H₂O, under the influence of carbonic anhydrase, is combined with CO₂ to produce H⁺ and HCO₃⁻. Also, in both cell types, H⁺ and HCO₃⁻ are secreted from the cell by similar transporters. However, the location of the transporters differs.

Type A intercalated cells include both H⁺-ATPase and H⁺-K⁺-ATPase pumps located on the luminal membrane, which facilitate H⁺ secretion into the tubular lumen. Bicarbonate is transported back to the systemic circulation by a HCO₃⁻/Cl⁻ transporter on the basolateral side of the cell. The net effect is the acidification of the urine and the subsequent increase in extracellular pH. As expected, this process is stimulated with the conditions of acidemia. Aldosterone seems to have a permissive effect on this, probably through actions on the H⁺-ATPase pump, because increased urine H⁺ loss and subsequent systemic alkalosis is seen in conditions of hyperaldosteronism.

Type B intercalated cells have similar transporters, but their polarity is reversed. That is, the H⁺-ATPase pumps are located on the basolateral side of the cell, whereas the HCO₃⁻/Cl⁻ transporters are localized to the luminal membrane. The result is a net loss of bicarbonate and a decrease in systemic pH. This result is necessary in states of alkalemia and it thus functions to lower systemic bicarbonate.

Potassium. Although there is normally a net secretion of potassium in the CCT, there is the potential for potassium reabsorption through the H⁺-K⁺-ATPase. This becomes more relevant in states of potassium depletion, when the activity of these pumps is increased. Although this may serve to help correct systemic hypokalemia, it is often at the expense of increased H⁺ secretion and resultant systemic alkalosis.

Medullary Collecting Tubule

The MCT is divided into the outer MCT (oMCT) and inner MCT (iMCT). Both segments contain cells similar to the principal cells and intercalated cells found in the CCT; hence, the handling of sodium, potassium, hydrogen ion, and bicarbonate is similar. The main functional difference lies with the MCT's water and urea permeabilities and thus its ability to concentrate the urine to levels far greater than that of plasma.

Water and Urea. The MCT is relatively impermeable to water in the basal state, but under the influence of ADH, permeability increases in both the iMCT and oMCT by the insertion of AQP-2 water channels. This allows water to move out of the tubule into the hyperosmolar interstitium, and urine concentration occurs. Equally important to this process is urea. The oMCT is relatively impermeable to urea, both in the basal state and under ADH stimulation. In contrast, the iMCT has a high basal permeability for urea, resulting largely from specific urea transporters (UT-A1 and UT-A3) located on the basolateral cell membrane, and also, to a lesser extent, the luminal membrane. Short-term regulation is under the influence of ADH, which can increase urea permeability as much as fourfold through an increased number of urea transporters. Longer-term regulation can be affected by protein intake. This allows a high concentration of urea to develop in the interstitium, thus sustaining the osmotic gradient that is responsible for water reabsorption and ultimately urinary concentration (Yang and Bankir, 2005).

KEY POINTS: RENAL TUBULAR FUNCTION

- The nephron has different functional segments that control homeostasis.
- Most resorption of bicarbonate and ions occurs in the proximal tubule.
- The architecture of the loop of Henle allows a highly hypertonic interstitium to develop, which is crucial to maximal urinary concentration.

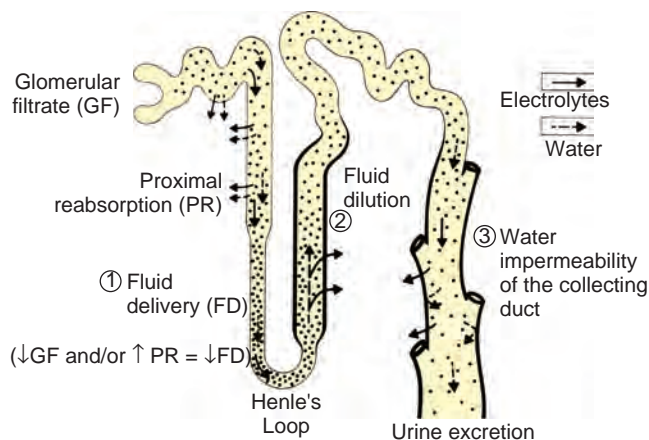


Figure 44-17. The components of the normal urine dilution mechanisms. (Redrawn from Berl T, Schrier RW. *Water metabolism and the hypo-osmolar syndrome*. In: Brenner BM, Stein JH, editors. *Sodium and water homeostasis*. New York: Churchill Livingstone; 1978. p. 1-23.)

Sodium. As mentioned earlier, Na reabsorption in the MCT is similar to that occurring within principal cells in the CCT. However, it has been shown that Na reabsorption is diminished in the MCT under conditions of volume expansion. This in part is because of the actions of ANP, which decreases Na reabsorption in the iMCT but not the oMCT. This effect seems to be a result of a reduction in the number of open Na channels in the luminal membrane.

RENAL PATHOPHYSIOLOGY

Sodium and Water Imbalances

Imbalances of sodium and water are often poorly managed and are misunderstood by clinicians, despite well-documented mechanisms and appropriate therapy. The most consistent clinical misconception is that sodium concentration reflects total body sodium content. Because sodium is primarily extracellular, the serum concentration reflects water balance. Therefore hyponatremia can occur in the face of total body sodium excess, and hypernatremia can occur with sodium deficits. For an imbalance to occur, there must be an imbalance between sodium and water that is not handled by

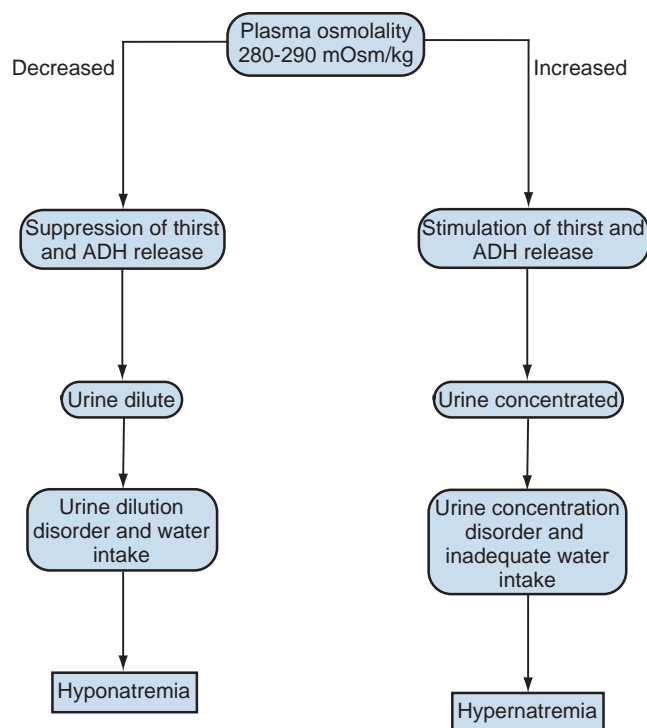


Figure 44-18. Flowchart illustrating the development of disorders of water metabolism. ADH, antidiuretic hormone.

the normal mechanisms of response. Therefore the way to approach serum sodium abnormalities is to determine the water status of the patient and then to determine why the normal compensatory mechanisms have failed (Fig. 44-18).

Hyponatremia

By definition, hyponatremia exists if there is a water excess relative to extracellular sodium that has not been handled by the normal compensatory mechanisms of thirst suppression and decreased ADH release, leading to a serum sodium less than 135 mEq/L. Hyponatremia is seldom symptomatic unless severe (<120 mEq/L), but when it is severe and/or of sudden onset, it can produce seizures, altered mental state, coma, and death. Most commonly, hyponatremia occurs because the kidney is unable to excrete solute-free urine (Mallie et al, 1997). To calculate the amount of water excreted or retained by the kidney, it is useful to consider that urine has two components: one that contains all of the solute in an isotonic solution (termed C_{osm} or osmolar clearance) and another that contains only solute-free water (termed $C_{\text{H}_2\text{O}}$ or free-water clearance). The total urine volume (V) (e.g., liters per day) is the sum of C_{osm} and $C_{\text{H}_2\text{O}}$:

$$V = C_{\text{osm}} + C_{\text{H}_2\text{O}}$$

When the urine is hypo-osmotic to plasma, $C_{\text{H}_2\text{O}}$ is a positive value. Hyponatremia occurs when one or more of these requirements are not fulfilled, such as when GFR is reduced, when diuretics impair NaCl reabsorption, or when vasopressin is in excess (e.g., SIADH). If water intake exceeds the kidney's capacity to form solute-free water (>10 to 20 L/day), hyponatremia also occurs. This abnormality in solute-free water clearance in hyponatremic patients is reflected by the failure to excrete maximally dilute urine ($U_{\text{osm}} = 100$ mOsm/kg).

The diagnosis of hyponatremia is made by measurement of serum electrolytes. There are, however, several conditions in which a low serum sodium level is misleading. The reported lab value is

usually in terms of sodium per volume of plasma, rather than water. If large molecules, such as lipids or protein, are present in large quantities, they decrease the amount of water in a given volume of plasma, but these molecules contribute little to plasma osmolality. What is truly important is the amount of osmotically active solute per volume of water. Pseudohyponatremia is most commonly seen with abnormal elevations of serum lipids or glucose. For every 1 g/dL-increase in triglycerides, measured sodium is decreased by 2 mEq/L, and for every 100 mg/dL of glucose, measured sodium is decreased by 1.6 mEq/L.

Therefore the approach to a patient with true hyponatremia begins with an assessment of volume status (Fig. 44-19). Clinical features such as skin turgor, orthostatic hypotension, jugular venous distension, ascites, and respiratory crackles can all be helpful in this decision. Patients who are clinically hypovolemic by definition will experience a sodium deficit greater than their water deficit. The appropriate renal response would be to excrete urine that is hypo-osmotic with a high $C_{\text{H}_2\text{O}}$. Therefore, if the urine is not hypo-osmotic, then the etiology is related to the kidney. Measuring the urinary sodium (U_{Na}) is a useful surrogate for urinary osmolality. Therefore a hypovolemic patient with an appropriately low U_{Na} (<20 mEq/L) has extrarenal sodium losses, such as from trauma, vomiting, diarrhea, burns, or third spacing. In a hypovolemic patient with an inappropriately high U_{Na} (>20 mEq/L), a renal source should be suspected, such as diuretic excess, osmotic diuresis, RTA, or mineralocorticoid deficiency. If the hyponatremic patient is hypervolemic, total body sodium can be low, normal, or high. A high U_{Na} that is greater than 20 mEq/L would point to renal failure. A low U_{Na} that is less than 20 mEq/L would suggest heart failure, cirrhosis, or nephrotic syndrome.

A patient who is euvolemic would exhibit low or normal total body sodium. The differential diagnosis would include glucocorticoid deficiency, hypothyroidism, stress, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH is a syndrome triggered by the release of ADH by a mechanism other than low blood volume or high plasma osmolality, one associated with increased aquaporin expression in the kidney (Kwon et al, 2001). The most common causes of SIADH are brain infections, surgery, neoplasm, and drug side effects (Box 44-2). Pharmacologic antagonists that can be used to treat patients with SIADH include lithium and demeclocycline. Lithium inhibits vasopressin action both proximal and distal to cAMP formation in the collecting duct (Miller, 1994). Demeclocycline, in doses ranging from 600 to 1200 mg/day, induces vasopressin-resistant diabetes insipidus that corrects the serum sodium within 1 to 2 weeks (Goh, 2004).

Therapy of hyponatremia is directed both at the cause of the condition and the water imbalance itself (Fig. 44-20). Patients with acute severe hyponatremia symptomatic with confusion, convulsions, or coma should undergo fluid restriction plus the administration of hypertonic (3%) saline (about 1 mL/kg/hr). Fluid overload is unlikely as long as fluid intake is restricted, but fluid may be further reduced by simultaneous administration of a loop diuretic such as furosemide, which causes excretion of hypotonic fluid equivalent to half-normal saline. The serum sodium concentration should be raised to no more than 25 mEq/L in the first 48 hours, at a rate of no more than 2 mEq/L per hour, and the target goal should be 120 to 125 mEq/L. Total sodium deficit to reach this point can be calculated as

$$(\text{Volume of distribution}) \times \text{body weight (kg)} \times (125 - \text{plasma [Na]})$$

where volume of distribution is 0.5 for men and 0.6 for women. If the hyponatremia is severe but chronic, the rate of correction should not exceed 8 to 12 mmol/L/day, otherwise a cerebral demyelination syndrome may occur (Martin, 2004). Therefore the rate of correction should be slower (0.5 to 1 mEq/L/hr). During acute intervention for severe hyponatremia, frequent electrolyte measurements and patient reassessment are required. Aggressive therapy should be discontinued when the serum sodium concentration is raised 10%

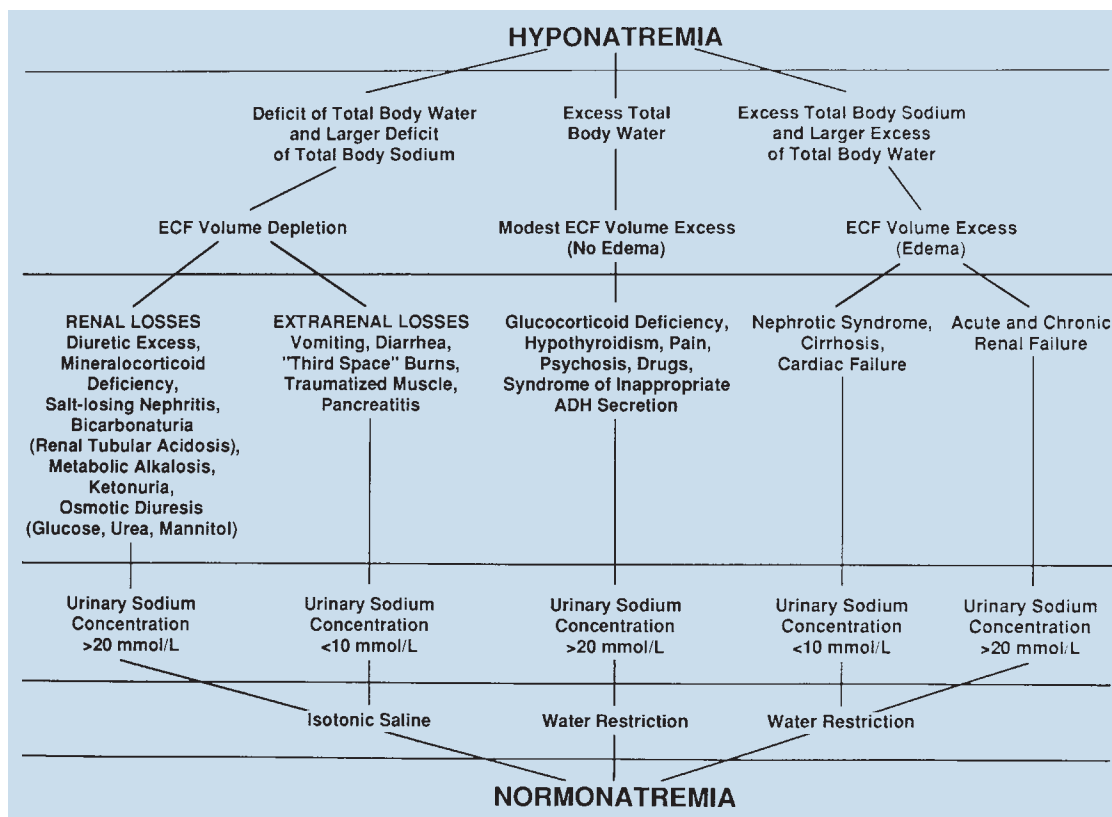


Figure 44-19. Clinical approach to patient with hyponatremia. ADH, antidiuretic hormone; ECF, extracellular fluid. (From Berl T, Anderson RJ, McDonald KM, Schrier RW. Clinical disorders of water metabolism. *Kidney Int* 1976;10:117–32.)

BOX 44-2 Disorders Associated with the Syndrome of Inappropriate Antidiuretic Hormone Secretion

CARCINOMAS

Bronchogenic
Duodenum
Pancreas
Thymoma
Ureter
Lymphomas
Ewing sarcoma
Mesothelioma
Bladder
Prostatic

PULMONARY DISORDERS

Pneumonia (viral, bacterial)
Pulmonary abscess
Tuberculosis
Aspergillosis
Positive-pressure breathing
Asthma
Pneumothorax
Cystic fibrosis

CENTRAL NERVOUS SYSTEM DISORDERS

Encephalitis (bacterial, viral)
Meningitis (viral, bacterial, tubercular, fungal)
Head trauma
Guillain-Barré syndrome
Subarachnoid hemorrhage
Subdural hematoma
Cerebellar or cerebral atrophy
Cavernous sinus thrombosis
Hydrocephalus
Shy-Drager syndrome
Rocky Mountain spotted fever
Delirium tremens
Olfactory neuroblastoma
Hypothalamic sarcoidosis
Multiple sclerosis

Modified from Levi M, Berl T. Water metabolism. In: Gonick HC, editor. *Current nephrology* (1983–1984), vol. 9. Chicago: Year Book Medical; 1986.

or symptoms subside. At that point, water restriction and reversal of underlying causes should suffice. This is also the best approach for therapy of asymptomatic hyponatremia. Obviously, patients with associated hypovolemia should have this corrected with the appropriate volume of normal saline.

Hypertatremia

The underlying problem of hypertatremia is a disorder of urine concentration with inadequate water intake (Adroque and Madias, 2000). Again, in hypertatremia it is the water balance that

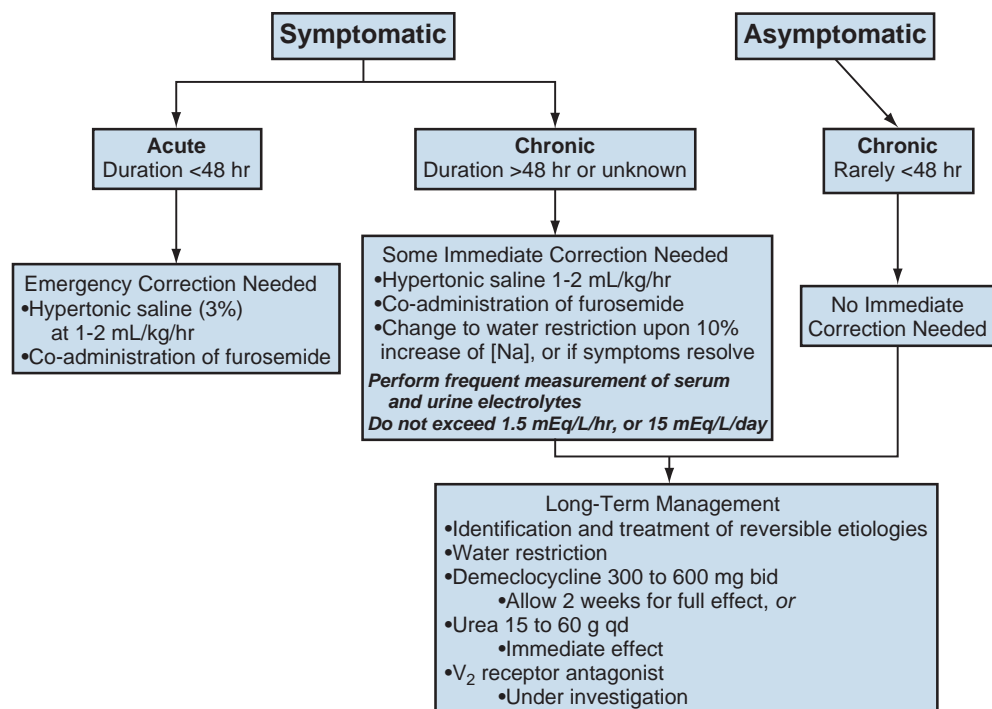


Figure 44-20. Therapy of hyponatremia. (From Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady H, Wilcox C, editors. Therapy in nephrology and hypertension. Philadelphia: Saunders; 1999. p. 261.)

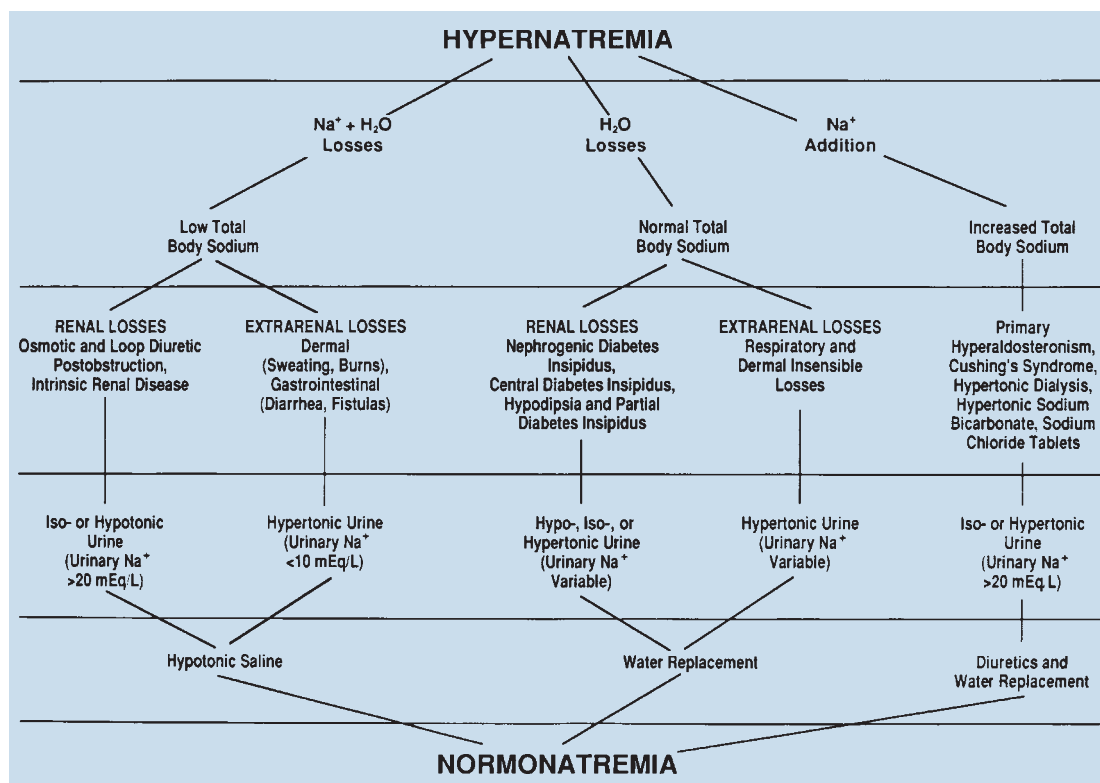


Figure 44-21. Clinical approach to patient with hypernatremia. (From Berl T, Anderson RJ, McDonald KM, Schrier RW. Clinical disorders of water metabolism. Kidney Int 1976;10:117–32.)

matters, and total body sodium can be high, normal, or even low. Symptoms are nonspecific and overlap with those seen in hyponatremia, with the early occurrence of restlessness, nausea, and vomiting, which can progress to tremor, lethargy, and coma. Indeed, mortality is higher with hypernatremia than with most

other electrolyte disorders. Most patients with an intact thirst mechanism and free access to water can prevent hypernatremia and, as such, the condition is more common at the extremes of age.

Again, the approach to a patient with hypernatremia begins with an assessment of fluid status (Fig. 44-21). Hypovolemia is

common and may be due to renal conditions that fail to adequately concentrate the urine (loop diuretics, postobstructive diuresis), or to conditions of extrarenal water loss, such as seen with burns, diarrhea, or fistulae. Patients with hypervolemia will have a metabolic or iatrogenic reason for high sodium in excess of the elevated total body water. Causes include Cushing syndrome, primary hyperaldosteronism, and excessive exogenous sodium (orally or IV). Patients who are euvoletic may have renal or extrarenal losses that may be caused by diabetes insipidus, an impairment in renal concentrating ability due to lack of central production (neurogenic), or impaired renal response (nephrogenic).

In neurogenic diabetes insipidus, vasopressin deficiency is most commonly caused by destruction of the neurohypophysis. To produce symptomatic polyuria, 80% to 90% of the neurosecretory neurons must be destroyed at or above the level of the infundibulum. Because of the reduced vasopressin level, the kidney excretes a high volume of dilute urine. This leads to a reduction in total body water, a rise in total body osmolality, and thus hypernatremia. The related cellular dehydration stimulates thirst. Compensatory water intake decreases plasma osmolality (and Na^+ concentration) toward normal, but they stabilize at the threshold level for thirst, which is slightly above normal. **As in all forms of diabetes insipidus, the ability of the kidney to maximally concentrate the urine in response to vasopressin is also impaired in neurogenic diabetes insipidus. This abnormality occurs because the medullary osmotic gradient is reduced by the high urine flow.** In nephrogenic diabetes insipidus, secretion of vasopressin by the neurohypophysis is normal, but renal responsiveness to the hormone is attenuated or absent, and urinary concentrating ability is impaired (Sasaki, 2004). Several different mutations of the aquaporin gene have been identified, which contribute to the pathogenesis of this disorder (Leung et al, 2005).

Therapy of hypernatremia is directed at fluid deficit, water replacement, and reversal of underlying causes. Hypovolemia should be initially corrected with half-normal saline. If the patient is awake and not symptomatic, oral hydration with water is sufficient. Otherwise, IV therapy should be started with the goal of slowly lowering plasma osmolality to no more than 2 mOsm/L/hr to avoid cerebral edema. The water deficit can be calculated as

$$(\text{Volume of distribution}) \times \text{body weight (kg)} \times (\text{plasma [Na]}/140 - 1)$$

where, again, volume of distribution is 0.5 for men and 0.6 for women. For patients with central diabetes insipidus, desmopressin (a synthetic exogenous vasopressin) can be administered intranasally. For nephrogenic diabetes insipidus, the underlying cause (lithium, hypercalcemia) should be treated. If polyuria persists while the kidney recovers, therapy includes modest sodium restriction, thiazide diuretics, and NSAIDs (Pattaragarn and Alon, 2003).

KEY POINTS: SODIUM AND WATER IMBALANCES

- Serum sodium represents sodium concentration and *not* total body sodium.
- The best tools to determine the cause of a sodium disorder are the history, volume status, and urinary sodium.
- Severe sodium deficit or excess must be corrected slowly.

Potassium Imbalances

Potassium is primarily an intracellular ion, and serum levels do not represent total body content in disease states. Because neuromuscular excitability is closely linked to serum potassium levels, extremes of low or high values can lead to cardiac arrhythmias and death. The body responds to changes in potassium intake and levels

by controlling urinary excretion and by changing the balance between intracellular and extracellular stores. **Urinary excretion can be increased in the kidney through increased aldosterone, a high sodium load in the distal tubule, and by acidosis. Potassium is driven into the cells by insulin, bicarbonate, and β agonists.**

Hypokalemia

The most common causes of hypokalemia are increased losses through the gastrointestinal (GI) tract or urine, and increased intracellular shift of potassium in response to alkalosis (mnemonic: aLKalosis = low K^+). The most common iatrogenic causes are diuretics, laxatives, amphotericin, theophylline, and postobstructive diuresis. Metabolic causes include conditions associated with elevated aldosterone, such as adrenal adenoma, Cushing syndrome, and adrenal carcinoma. The patient may have no symptoms or might present with signs and symptoms of his or her underlying condition (e.g., hypertension). Severe hypokalemia may produce tachycardia, heart block, and ST depression. Therapy is directed toward correction of the underlying cause and oral or parenteral potassium supplementation. In general, IV potassium replacement should not exceed 40 mEq/hr.

Hyperkalemia

Hyperkalemia usually reflects decreased renal excretion of potassium or a shift out of cells into the extracellular space (usually by acidosis). A compromised excretory capacity can be further exacerbated by a GI bleed or hemolysis. The most common causes of this condition (Box 44-3) are renal failure, drugs (potassium-sparing diuretics, lithium, digoxin, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), chronic acidosis (e.g., RTA type 4), and hypoaldosteronism. Hemolysis of the drawn blood sample can falsely elevate serum potassium. Therefore when a patient exhibits no symptoms, risk factors, or electrocardiogram (ECG) changes, but has an unexpectedly high value, the sample should be redrawn pending aggressive therapy. The classical ECG changes include a short QT interval, peaked T waves, and ultimately ventricular arrhythmias. Need for therapy is driven by the degree of elevation of potassium, the acuteness of elevation, and the presence of ECG changes. Mild hyperkalemia without ECG changes only requires dietary restriction and reversal of underlying causes. ECG changes require emergency therapy: IV calcium gluconate (to protect the heart) and a cocktail of drugs to drive the potassium into the cell, including sodium bicarbonate, insulin (administered with glucose to avoid hypoglycemia), and nebulized albuterol (especially if there is a delay in gaining IV access). Therapy to increase intracellular potassium must be coupled with a therapy to remove potassium stores, or the hyperkalemia will recur after infusions stop. Potassium-binding exchange resins (kayexalate, calcium resonium) can be used for this purpose orally or by enema. Finally, hemodialysis can most quickly and completely remove extracellular potassium.

KEY POINTS: POTASSIUM IMBALANCES

- Potassium is primarily intracellular.
- Serum potassium levels reflect total body potassium, as well as the equilibrium between intracellular and extracellular potassium.
- Alkalosis produces low serum potassium.

Acid-Base Metabolism

Although the hydrogen ion (H^+) is present in miniscule concentrations in the extracellular fluid, compared with other common

BOX 44-3 Etiology of Hyperkalemia**FACTITIOUS**

Laboratory error

Pseudohyperkalemia: in vitro hemolysis, thrombocytosis, leukocytosis

INCREASED INPUT

Exogenous: diet, salt substitutes

Endogenous: hemolysis, gastrointestinal bleeding, catabolic states, crush injury, tumor lysis

RENAL FAILURE

Acute: especially tubulointerstitial disease

Chronic: glomerular filtration rate <15 to 20 mL/min

IMPAIRED RENIN-ALDOSTERONE AXIS

Addison disease

Congenital adrenal enzyme deficiencies (e.g., corticosterone methyl oxidase deficiency)

Drug induced: heparin, prostaglandin inhibitors, angiotensin-converting enzyme inhibitors, pentamidine, β -blockers

Hyporeninemic hypoaldosteronism

Primary hypoaldosteronism (normal renin)

PRIMARY RENAL TUBULAR POTASSIUM SECRETORY DEFECT

Sickle cell disease

Systemic lupus erythematosus

Postrenal transplantation

Obstructive uropathy

Tubulointerstitial renal disease

Pseudohypoaldosteronism

Hyperkalemic distal renal tubular acidosis

INHIBITORS OF TUBULAR SECRETION

Diuretics: amiloride, spironolactone, triamterene

Cyclosporine

Lithium

Digitalis

ABNORMAL POTASSIUM DISTRIBUTION

Metabolic acidosis

Insulin deficiency

Hypertonicity (e.g., hyperglycemia)

Aldosterone deficiency

 β -Adrenergic receptor blockade α -Adrenergic receptor agonist

Exercise

Periodic paralysis

Digitalis

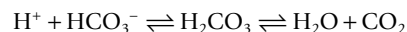
Succinylcholine

Modified from Rastegar A, DeFronzo RA. Disorders of potassium metabolism associated with renal disease. In: Schrier RW, Gottschalk CW, editors. *Diseases of the kidney*. 5th ed. Boston: Little, Brown; 1992. p. 1645–2661.

ions in the body, its primary importance is reflected by the multiple mechanisms that exist to control its concentration within a tight range. The reason for this is that small alterations in H^+ concentration have large effects on the relative concentrations of every other conjugate base and acid of all the weak electrolytes. At neutral body pH, most biologically active molecules are in

their charged state and can be more effectively trapped within cells to perform their functions. Furthermore, pH determines the net charge of proteins, which influences protein conformation and enzyme-binding characteristics. Outside normal blood pH (7.35 to 7.46), severe metabolic problems occur.

To maintain pH, the body has to handle the daily production of acid. There is a large production of acid by the metabolism of carbohydrates and fats, largely in the form of carbon dioxide, at approximately 15,000 mmol per day. CO_2 is not an acid in the classical sense of the Brønsted-Lowry theory (Kildeberg, 1983), because it is not capable of donating a H^+ to a base. CO_2 can be considered a “volatile acid” because it is easily converted into H_2CO_3 , carbonic acid:



Each molecule of CO_2 excreted by the lungs is a result of the reaction of one molecule of bicarbonate with one molecule of H^+ . The H^+ remains in the body as H_2O . The catabolism of ingested proteins to amino acids is another source of acid production, estimated at between 50 and 100 mEq of H^+ per day (sulfate from the three sulfur-containing amino acids; phosphate from phosphoproteins). Because the lungs cannot excrete these acids, they are considered “fixed” and must be excreted by the kidneys.

Therefore the body has three primary mechanisms to handle physiologic and pathophysiologic acid loads: buffers in the blood, CO_2 excretion by the lungs, and H^+ excretion by HCO_3^- metabolism in the kidneys (Vasuvattakul et al, 1992). The immediate response to an acid load is buffering. A buffer is simply a mixture of a weak acid and its conjugate base, or a weak base and its conjugate acid, that resists changes in pH when another acid or base is added. The key buffers in the blood are HCO_3^- for metabolic acids and hemoglobin for CO_2 . Within the cell, proteins and phosphates, which are found in higher concentrations than in the blood, become important as well. In the extracellular fluid, HCO_3^- is responsible for about 80% of buffering. Changes in pH are governed by the Henderson-Hasselbalch equation, which generally is

$$pH = pK_a + \log \text{base/acid}$$

When specifically formulated for the bicarbonate system it becomes

$$pH = 6.1 + \log HCO_3^- / 0.03 \times pCO_2$$

In general, optimal buffering occurs within 1.0 pH unit of the pK_a . Therefore the $pK_a = 6.1$ of bicarbonate buffer does not appear to be the most efficient for maintaining the pH 7.4 that is required for normal homeostasis. **The bicarbonate buffer system is effective despite having a low pK_a , because the body also controls pCO_2 .**

Excretion of CO_2 by the lungs can occur rapidly and can change both blood and intracellular pH. Elevated pCO_2 is detected by central and peripheral chemoreceptors that increase respiratory rate leading to increased alveolar ventilation. Respiratory compensation in response to a pure metabolic acidosis cannot reduce CO_2 to below 10 mm Hg and is therefore unable to maintain pH in the setting of a large acid load.

Although most of the daily acid production is volatile, and is therefore excreted by the lungs, the kidneys must excrete the fixed acid, and in doing so must also reabsorb most of the filtered bicarbonate so that efficient extracellular buffering can be maintained. A normal individual, with a GFR of 180 L/day and plasma $[HCO_3^-]$ of 24 mEq/L, filters 4300 mEq of HCO_3^- daily from the glomerulus into the proximal tubule. Of this filtered load, less than 0.1% normally appears in the urine. **The bulk of the filtered bicarbonate is reclaimed in the proximal nephron, with approximately 80% of the filtered HCO_3^- reabsorbed within the PCT.** In the tubular urine, H^+ and HCO_3^- are formed from CO_2 and H_2O in a reaction catalyzed by carbonic anhydrase (Kaunisto et al, 2002). The H^+ is returned to the tubular urine by two mechanisms: a Na^+-H^+ pump (“antiporter”) and a direct $H^+-ATPase$ proton pump. The net result

is the reabsorption of NaHCO_3 into the interstitial fluid and the secretion of H^+ into the proximal collecting duct urine. Note that the use of a carbonic anhydrase inhibitor, such as acetazolamide, reduces HCO_3^- reabsorption and increases excretion of Na^+ and water, resulting in a weak diuretic effect (Puscas et al, 1999). The reabsorption of HCO_3^- does not result in a net excretion of H^+ from the body; however, the proximal tubular reabsorption of HCO_3^- is essential to preserving acid-base balance. The primary factors that increase HCO_3^- reabsorption are arterial pCO_2 , HCO_3^- concentration in the lumen, luminal flow rate, and angiotensin II (de Mello-Aires and Malnic, 2002).

The remainder of the filtered bicarbonate is reabsorbed in the distal nephron by a mechanism independent of carbonic anhydrase. In the distal tubule, further H^+ is secreted through the production of "titratable acid," usually by buffering with phosphate. The term *titratable acidity* refers to the quantity of NaOH required to titrate urine back to a pH of 7.40, which is similar to that of blood. Other buffers, such as uric acid (pK_a 5.75) and creatinine (pK_a 4.97) contribute to the titratable acidity, but only to a minor extent. H^+ is also secreted through the production of ammonium ion (NH_4^+). NH_4 is produced from glutamine, primarily by proximal tubular cells (Michoudet et al, 1994). Because of its high pK_a (about 9.2), it is present almost exclusively as the NH_4^+ ion. Ammonium excretion can increase significantly during systemic acidosis (Nagami, 2004), which is the key mechanism for secreting excess H^+ , because at very low urinary pH, titratable acid cannot increase much (unless other ions, such as keto-anions, are being produced).

Regulation of H^+ secretion occurs through multiple biochemical and hormonal actions on the aforementioned system. **Volume depletion** leads to Na retention and enhanced HCO_3^- absorption, with a net loss of H^+ . **Elevated pCO_2** , as seen in chronic respiratory acidosis (see later), will lead to a renal response of increased H^+ secretion. **Reduced GFR** will reduce the amount of filtered HCO_3^- , leading to increased H^+ excretion. **High aldosterone levels** indirectly increase H^+ excretion by increasing Na^+ absorption. **Low potassium and low chloride** increase HCO_3^- reabsorption and can maintain chronic metabolic alkalosis.

Acid-Base Disorders

Those of us outside the fields of nephrology and anesthesia encounter acid-base disorders less commonly and are often intimidated by the process of working through the appropriate diagnosis. Nevertheless, after the terminology and basic equations are understood, the process is simple and, in many ways, mechanical (Corey, 2005). Common misconceptions begin with definitions of terms. **The actual pH disturbance is an "emia," and the disease causing it is an "osis."** Acidemia refers strictly to a low arterial blood pH of less than 7.36. **Alkalemia** is a blood pH of greater than 7.44. **Acidosis** is an abnormal condition or process that would lower arterial pH if no other condition existed, and **alkalosis** is a condition that would raise pH. **The basic information required to diagnose an acid-base disturbance is a history, physical examination, serum electrolytes, and arterial blood gas.** If the acid-base disorder is caused by a respiratory problem, the pCO_2 will move in a direction opposite to the pH (Madias and Adrogué, 2003). If caused by a metabolic (renal) disorder, the HCO_3^- will move in the same direction as the pH. In every disorder, there should be an attempt by the other acid-handling mechanism to compensate for the change. For instance, chronic loss of bicarbonate from the kidney causing a metabolic acidosis (low pH and low HCO_3^-) should lead to increased ventilation to try to excrete the excess acid by the lung, leading to a lower pCO_2 (respiratory compensation). In **simple** acid-base disorders, there is one mechanism causing the acid disturbance with an appropriate compensation. In **mixed** disorders, the clue to multiple mechanisms comes from significant undercompensation or overcompensation. Although formulas have been developed to predict appropriate compensation for each disorder, visual nomograms are more practically used at the bedside.

Metabolic Acidosis

In metabolic acidosis, loss of bicarbonate leads to systemic acidemia, which produces a low arterial pH and low serum HCO_3^- . The appropriate compensation is increased respiration leading to a reduced pCO_2 . In general, the expected degree of pCO_2 reduction is calculated as

$$\text{Expected } \text{pCO}_2 = 1.5 \times [\text{HCO}_3^-] + 8 \pm 2$$

This bicarbonate loss can be direct, or it can result from secondary effects of other ions. The presence of active ions that are not measured in routine blood chemistry can be detected by the anion gap. The anion gap is defined as the difference between the levels of routinely measured cations (Na^+) and anions (Cl^- and CO_2) in blood:

$$\text{Anion gap} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-) = 140 - (105 + 24) = 11$$

The normal range of the anion gap is 9 to 14 mEq/L. The predominant unmeasured anions include albumin and phosphate. The major unmeasured cations include calcium, magnesium, and gamma globulins. If the anion gap is elevated in a patient with metabolic acidosis, the condition occurs because acids that do not contain chloride are present in the blood. The most common of these are ketones (diabetic ketoacidosis), lactate (lactic acidosis), and drug intoxication (methanol, aspirin) (Levrault and Grimaud, 2003).

Metabolic acidosis with a normal anion gap is caused by direct bicarbonate loss through the gut or kidney, or by the addition of exogenous acid that is buffered by bicarbonate (Box 44-4). The patient history can provide major clues to the diagnosis, either because of GI loss (vomiting, diarrhea, fistula), drug use (acetazolamide), or previous surgery (ileal conduit). Serum potassium can be a further clue to etiology. Low potassium is associated with loss through the GI tract or RTA because renin is stimulated from the volume contraction. In acidosis

BOX 44-4 Hyperchloremic Metabolic Acidosis (Normal Anion Gap)

Acid loads

- Ammonium chloride
- Hyperalimentation
- Ketoacidosis with renal ketone loss

Bicarbonate losses

- Diarrhea
- Pancreatic, biliary, or small bowel drainage
- Ureterosigmoidostomy

Drugs

- Cholestyramine
- Calcium chloride
- Magnesium sulfate
- Posthypocapnia

Defects in renal acidification

- Proximal: decreased HCO_3^- reclamation
- Distal: decreased net acid excretion
 - Primary mineralocorticoid deficiency
 - Hyper-reninemic hypoaldosteronism
 - Mineralocorticoid-resistant hyperkalemia

Dilutional

Modified from Cogan MG, Rector FC Jr. Acid-base disorders. In: Brenner BM, Rector FC, editors. The kidney. 4th ed. Philadelphia: Saunders; 1991. p. 737–804.

associated with severe renal dysfunction, potassium will often be elevated.

Renal Tubular Acidosis

RTA is a family of syndromes of metabolic acidosis from defects in tubular H⁺ secretion and urinary acidification. They are classified according to the mechanism of defect, and each type includes different clinical manifestations.

RTA type 1 is the most common form and is the most clinically significant to the urologist. It has also been called “classic” RTA and distal RTA. The old classification of RTA type 3 is now recognized as a type 1 variant. The underlying problem is failure of H⁺ secretion in the distal nephron, which can be congenital or acquired. Associated disorders include autoimmune diseases (thyroiditis), toxic nephropathy, and chronic ureteral obstruction. The hallmark is a hyperchloremic metabolic acidosis with a high urinary pH (>5.5) in the face of persistently low serum HCO₃⁻. If no metabolic acidosis is present but the condition is still suspected, then acid loading with ammonium chloride will drop the serum HCO₃⁻ while maintaining a high urine pH. Volume contraction from sodium loss is common, which leads to secondary hyperaldosteronism and hypokalemia. These patients often develop recurrent renal stones that are composed of calcium phosphate. The most likely contributing factor is low urinary citrate, coupled with a high urinary pH and hypercalciuria. Treatment with sodium bicarbonate can alkalinize the urine, correct the sodium defect, lower aldosterone, and raise the potassium. Potassium citrate can augment the urinary citrate levels and can inhibit stone formation (Domrongkitchaiporn et al, 2002).

Type 2 RTA, also called proximal, is caused by failure of bicarbonate reabsorption in the proximal tubule (Igarashi et al, 2002). The mechanisms of H⁺ secretion in the distal tubular are overwhelmed, resulting in HCO₃⁻ loss in the urine. Cl⁻ resulting in hyperchloremia is replaced in the circulation by bicarbonate. Increased sodium delivery to the distal tubule increases aldosterone secretion resulting in hypokalemia. Ultimately, a new steady state is reached, in which serum HCO₃⁻ is decreased, and hence the filtered load, distal delivery, and urinary excretion of HCO₃⁻ are all reduced. The acidosis is self-limited, because acid production and excretion are equivalent at this reduced pH; the plasma HCO₃⁻ remains at 15 to 20 mEq/L. Because urinary citrate levels are not reduced, stone formation does not occur, despite increased urinary calcium. Because this condition is more common in children, it can lead to growth retardation and metabolic bone disease (Roth and Chan, 2001). Oral supplementation with NaHCO₃ can correct the condition but can lead to further hypokalemia, so potassium supplements may also be required. As an interesting aside (and possible memory aid), it was suggested that Dickens’ Tiny Tim character was based on a child with type 2 RTA (growth retardation, osteomalacia) that was reversed when Mr. Scrooge paid for his therapy (sodium bicarbonate).

Type 4 RTA is a result of impairment of cation exchange in the distal tubule, with reduced secretion of both H⁺ and K⁺. It is due to

aldosterone deficiency or resistance. The unique feature compared with other RTAs is hyperkalemia. Patients often have associated azotemia and hypertension. The distal tubule H⁺ pump functions normally, so patients are able to decrease urine pH to less than 5.5 in response to the acidosis. Urinary citrate may be normal or low, but renal dysfunction reduces secretion of calcium and uric acid, so stones do not form (Uribarri et al, 1994). Type 4 RTA is occasionally seen in obstructive uropathy. Therapy is typically directed at controlling the hyperkalemia.

Metabolic Alkalosis

In metabolic alkalosis, the pH will be high (alkalemia) and the HCO₃⁻ high (mirrors pH in primary metabolic disorder) (Khanna and Kurtzman, 2001). The appropriate respiratory compensation is reduced ventilation with increased pCO₂. The expected degree of respiratory compensation can be estimated by

Expected pCO₂ = 6 mm Hg per 10 mEq/L increase in HCO₃⁻

An exogenous alkali load is usually rapidly excreted into the urine by the kidney, so other mechanisms are required to maintain the disorder. Maintenance of the alkalosis requires a process that greatly impairs the kidney’s ability to excrete bicarbonate and prevent the return of the elevated plasma level to normal. Chloride deficiency leads to the kidney reabsorbing more bicarbonate anion than usual because there is not sufficient chloride anion present to maintain electroneutrality. This condition is reversed with fluid and chloride. Consequently, metabolic alkalosis is most conveniently classified as chloride responsive and chloride resistant.

The most common chloride-responsive conditions are GI loss (vomiting, nasogastric drainage, laxative abuse) and kidney loss (diuretics). These make up more than 90% of clinical cases of metabolic alkalosis (Table 44-2). Volume contraction in these conditions stimulates aldosterone production and distal secretion of H⁺ and K⁺. Thus there may be a paradoxical aciduria that will persist until volume is replaced. Chloride-resistant metabolic alkalosis is associated with potassium loss from mineralocorticoid excess. The disorders are associated with volume expansion and high urinary chloride levels, which can aid in the diagnosis. Common causes are hyperaldosteronism (primary or secondary), Cushing syndrome, diuretics, and congenital conditions such as Bartter syndrome (hyperplasia of the juxtaglomerular apparatus).

Respiratory Acidosis

In respiratory acidosis, pH is low (acidemia) and pCO₂ is high because of inadequate respiration (Epstein and Singh, 2001). The anticipated compensatory response is increased HCO₃⁻:

Acute: Expected HCO₃⁻ = 1 mEq/L for each 10 mmHg pCO₂

Chronic: Expected HCO₃⁻ = 3.5 mEq/L for each 10 mmHg pCO₂

Elevated pCO₂ can be caused by increased production of CO₂, decreased ventilation, and increased CO₂ in the inspired air.

TABLE 44-2 Differential Diagnosis of Metabolic Alkalosis

MEASUREMENT	SALINE RESPONSIVE	NORMOTENSIVE: SALINE UNRESPONSIVE	HYPERTENSIVE: SALINE UNRESPONSIVE
Urinary [Cl ⁻]	<15 mEq/L	>15 mEq/L	>15 mEq/L
Blood pressure	Normal	Normal	Increased
Differential diagnosis	Vomiting Nasogastric suction	Diuretics Bartter magnesium deficiency	Primary mineralocorticoid excess

Modified from Alpern RJ, Emmett M, Seldin DW. Metabolic alkalosis. In: Seldin DW, Giebisch G, editors. The kidney: physiology and pathophysiology. 2nd ed. New York: Raven; 1992. p. 2733–58.

Because increased production is usually handled quickly by increased respiration, and CO_2 does not vary except in ventilated patients, the most common cause is decreased ventilation. This can be a result of central depression of respiration (e.g., opiates, trauma, cervical cord trauma), chest cavity problems (e.g., pneumothorax, pulmonary edema), upper airway obstruction, or iatrogenic causes (insufficient ventilation). Because CO_2 readily diffuses across all cellular membranes, marked elevation can severely interfere with intracellular metabolism. Clinical effects of elevated pCO_2 , which are separate from acidosis per se, include elevated intracranial pressure, tachycardia, central depression, and eventually coma and death.

Respiratory Alkalosis

In respiratory alkalosis, pH is high (alkalemia) because of a low pCO_2 . This is due to hyperventilation (Foster et al, 2001). The appropriate compensatory response is a lowering of HCO_3^- by the following expected amounts:

Acute: Expected $\text{HCO}_3^- = 2 \text{ mEq/L}$ for each 10 mmHg pCO_2

Chronic: Expected $\text{HCO}_3^- = 5 \text{ mEq/L}$ for each 10 mmHg pCO_2

Common causes of hyperventilation that can lead to respiratory alkalosis are fever, pain, anxiety, septicemia, head trauma, pulmonary embolism, and iatrogenic causes (excessive mechanical ventilation). Neurologic symptoms such as paresthesia and tetany may occur. Therapy is directed toward improving oxygenation and ventilation.

KEY POINTS: ACID-BASE METABOLISM/DISORDERS

- Physiologic chemical reactions require a narrow range of serum pH.
- Acid is excreted through the lungs and the kidney.
- Type 1 RTA (distal) is the only type associated with renal stones.
- In acid-base disorders, first determine whether the kidney (HCO_3^-) or lungs (pCO_2) are responsible for the primary disorder; then determine whether the compensatory response is appropriate.

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Incidence and Etiology

Pathophysiology of Renovascular Hypertension

Pathophysiology of Ischemic Nephropathy

Screening Tests

Pathology of Renovascular Hypertension

Physiologic Significance

Management of Renovascular Hypertension

Partial or complete occlusion of one or both renal arteries may result in renal ischemia and as a consequence may result in “renovascular” hypertension, the most common form of secondary and potentially curable hypertension (Spitalewitz and Reiser, 2000; Safian and Textor, 2001). Furthermore, a substantial number of affected patients may develop ischemic nephropathy and ultimately progress to end-stage renal disease (ESRD) (Plath, 1995; Ram et al, 1995; Spitalewitz and Reiser, 2000; Safian and Textor, 2001). Although affecting only 5% of hypertensives, renal artery disease has been estimated to be the cause of renal failure in 5% to 15% of those older than 50 years of age and may account for as many as 10% to 20% of the ESRD population (Jacobson, 1988; Rimmer and Gennari, 1993; Mailloux et al, 1994; Greco and Breyer, 1997; Middleton, 1998; van Ampting et al, 2003). As a result, renovascular disease poses a major health problem and its therapy remains a challenge for physicians caring for these patients.

INCIDENCE AND ETIOLOGY

Most patients with renovascular hypertension present with moderate to severe hypertension, with only a small percentage presenting with mild hypertension or presenting as normotensive. In 10% to 45% of the cases, renovascular disease may lead to accelerated or malignant hypertension (Davis et al, 1979; Svetkey et al, 1991). Although the diagnosis of renovascular hypertension is more commonly made in Caucasians than African-Americans, the finding of a similar prevalence in both racial groups in one carefully conducted study suggests that this difference may in part be a result of racial bias in performing diagnostic studies (Svetkey et al, 1991).

The most common forms of renovascular hypertension are due to atherosclerotic disease and fibromuscular dysplasia, with the former accounting for more than two thirds of the cases. Atherosclerotic renal artery disease is most frequently seen in those older than 40 years of age, is more often seen in men than women, and generally involves the ostium and/or proximal third of the renal artery (Wollenweber et al, 1968; Plath, 1995). Fibromuscular disease is more often seen in younger Caucasian women, is usually bilateral, and unlike atherosclerotic disease it involves the more distal segments of the renal arteries (Pohl, 1993).

The following signs and symptoms should raise suspicion of the possibility of underlying renovascular disease and the need for further evaluation if warranted:

1. Severe or refractory hypertension with evidence of grade III or IV hypertensive retinopathy (particularly in Caucasians)
2. Abrupt onset of moderate to severe hypertension, particularly in a normotensive or previously well-controlled hypertensive

3. Onset of hypertension before age 20 (early onset) or after age 50 (late onset), particularly in those without a family history of hypertension
4. Unexplained worsening of renal function with or without hypertension or in association with the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) or with a reduction of blood pressure (BP) to the current accepted norm with the use of other antihypertensive agents
5. Paradoxical worsening of hypertension with the use of diuretics
6. Unexplained recurrent episodes of heart failure—“flash” pulmonary edema
7. The presence of a systolic-diastolic abdominal bruit that radiates to both flanks
8. The presence of diffuse vascular disease and/or evidence of cholesterol embolization (Rose, 1987; Plath, 1995)

Because effective BP control may be achieved in most patients with renovascular hypertension, and it remains uncertain whether the correction of an underlying vascular lesion results in long-term BP control or preservation of renal function, testing for renovascular hypertension should be pursued only if revascularization is being seriously considered. Some screening techniques (see later) pose risks to those with compromised renal function and may be associated with significant morbidity (White et al, 2006).

KEY POINTS: INCIDENCE AND ETIOLOGY

- Although renal artery disease affects only a small proportion of hypertensives, it may be the cause of renal failure in as many as 10% to 20% of patients with ESRD. Therefore renal vascular disease is a major health problem and its therapy remains a significant challenge.
- Most patients with renal vascular hypertension present with moderate to severe hypertension.
- This disease appears similarly prevalent in Caucasians and African-Americans.
- The most common form of renal vascular hypertension is atherosclerotic involvement of the renal arteries.
- It remains uncertain whether the correction of an underlying vascular lesion results in long-term BP control or preservation of renal function.

PATHOPHYSIOLOGY OF RENOVASCULAR HYPERTENSION

In 1934, Goldblatt and colleagues performed the now classic experiment on dogs to test the hypothesis of whether or not renal ischemia is the inciting event in the pathogenesis of hypertensive

nephrosclerosis (Goldblatt et al, 1934). With the use of a clamp that allowed them to control the degree of renal artery stenosis (RAS), Goldblatt was able to monitor the BP in the dogs after clamping the renal artery to one or both kidneys and to one kidney after the removal of the contralateral kidney. Because BP remained elevated in all three models, this study confirmed the hypothesis, “renal ischemia in dogs is a sufficient condition for the production of persistently elevated systolic blood pressure.” However, the mechanism by which the hypertension was induced remained to be elucidated.

Subsequently, two animal models of renal hypertension have become the hallmark for all studies on experimental renovascular hypertension. They are (1) the two-kidney hypertension model, where one renal artery is clipped and the other renal artery is left unaltered (2K1C), and (2) the one-kidney hypertension model, where one renal artery is clipped and the contralateral kidney is removed (1K1C).

These two models have clarified the vasoconstriction-volume interactions that regulate renal hypertension.

Two-Kidney, One-Clip Model

The two-kidney, one-clip model is the one most similar to human renovascular hypertension. Because of the ischemia induced by the stenosis, renin secretion is increased from the juxtaglomerular apparatus of the ischemic kidney and suppressed in the normal contralateral kidney. As a consequence of the activation of the renin-angiotensin-aldosterone system (RAAS) and an increased production of angiotensin II (AII), there is peripheral vasoconstriction and hypertension (Vaughan and Laragh, 1975). The key finding is that the hypertension that ensues is mediated by a vasoconstrictor, AII, and is therefore referred to as the **vasoconstrictor hypertensive model** (Fig. 45-1) (Vaughan and Laragh, 1975). AII stimulates aldosterone secretion and in turn sodium retention. However, the normal contralateral kidney with its renin secretion suppressed and under a higher perfusion pressure is able to excrete

most of the excess salt and water. Because there is limited sodium retention, there is no significant feedback inhibition of renin secretion in the stenotic kidney. Thus it continues to secrete AII and the vasoconstriction and hypertension is maintained. The renin dependency of hypertension in the 2K1C model has been further supported by studies using inhibitors or blockers of the RAAS such as AII antagonists (Bumpus et al, 1976; Caravaggi et al, 1976), renin antibodies (Romero et al, 1973), and ACE inhibitors (Romero et al, 1974).

This form of hypertension may be managed with reversal of the RAS (or unclipping of the “clipped kidney”), with ACE inhibition, or with angiotensin receptor blockade.

One-Kidney, One-Clip Model

In the 1K1C model there is activation of the RAAS similar to that seen in the 2K1C model. However, in contrast to the 2K1C kidney, the absence of a normal contralateral kidney prevents an ensuing natriuresis and diuresis. Thus there is volume expansion, and renin secretion is suppressed in the clipped kidney because of feedback inhibition. Volume expansion remains, and there is sustained hypertension in spite of the decreased vasoconstriction associated with the now suppressed RAAS. Despite the similarity in the initiating events in both experimental models of renal hypertension, the 1K1C model is driven by volume expansion and sodium retention with normal circulating levels of AII. This is therefore called the **volume hypertensive model** (Fig. 45-2) (Vaughan and Laragh, 1975).

PATHOPHYSIOLOGY OF ISCHEMIC NEPHROPATHY

In addition to hypertension, RAS, when hemodynamically significant, affects the entire renal functioning parenchyma and causes ischemic nephropathy, which is defined as a decrease in the glomerular filtration rate (GFR) with several histologic changes that

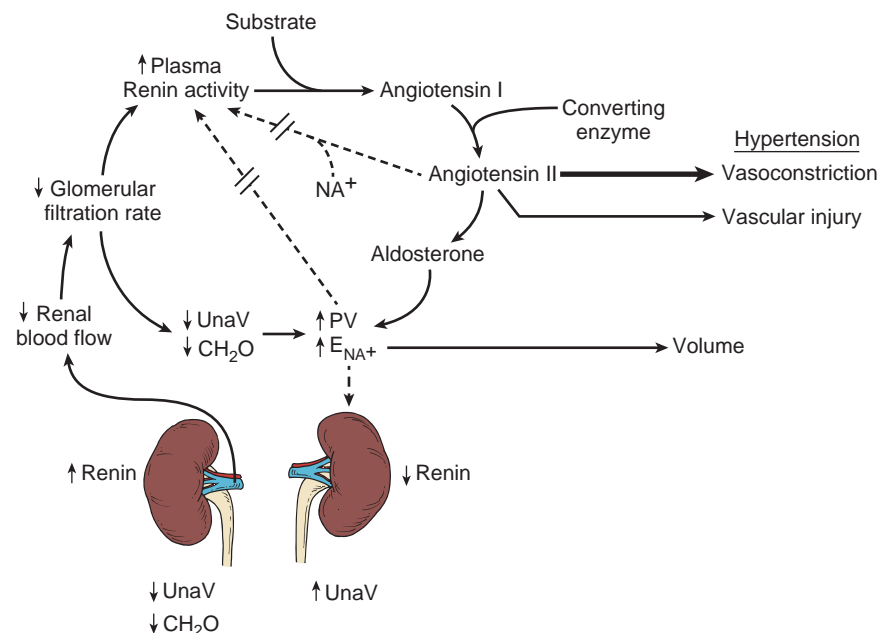


Figure 45-1. The renin system in the setting of unilateral renal artery stenosis with a normal contralateral kidney characterized by (1) high peripheral plasma renin activity, (2) contralateral suppression of renin release, and (3) a decrease in ipsilateral renal blood flow (RBF). The resultant hypertension is mediated by angiotensin II induced vasoconstriction. (From Vaughan E, Laragh J. New concepts of the renin system and vasoconstriction-volume mechanisms: diagnosis and treatment of renovascular and renal hypertension. *Urol Clin North Am* 1975;2:240–1, figure 2.)

direct stimulation of proinflammatory cytokines. In addition, RAS leads to the production of AII, which is a powerful vasoconstrictor, but in this context it is more important that AII is a profibrogenic peptide. AII has been shown to increase the production of transforming growth factor- β (TGF- β) by various cells including renal tubular cells and fibroblasts (Klahr and Morrissey, 2002). TGF- β activation stimulates fibrosis through the production of inhibitors of matrix-degrading enzymes, the transformation of fibroblasts into myofibroblasts, and the transdifferentiation of tubular epithelial cells into myofibroblasts (Eddy, 2000). AII also stimulates the production of nuclear factor- κ B (NF- κ B), a family of transcription factors that is central to controlling two autocrine-reinforcing loops that continue to amplify the production of AII and tumor necrosis factor- α (TNF- α) (Fig. 45-4) (Klahr and Morrissey, 2002). The oxidative stress of RAS fueled by AII also increases the production of adhesion molecules, chemoattractant compounds, and cytokines, further stimulating the fibrotic process (Klahr and Morrissey, 2002). These processes result in tubulointerstitial inflammation, the accumulation of extracellular proteins within the interstitial space, peritubular capillary obliteration, tubular atrophy, renal fibrosis, and ultimately loss of renal function. The previous hypotheses are supported by the fact that the administration of AII receptor antagonists or ACE inhibitors in experimental renal disease models have both been shown to reduce the production of TGF- β and to mitigate renal interstitial fibrosis (Ishidoya et al, 1995; Pimentel et al, 1995).

In summary, although the initiating event in RAS is a decrease in RBF and a measurable increase in a powerful vasoconstrictor (AII), it is likely other molecular and fibrogenic effects of this peptide are more damaging to the renal parenchyma than the decrement of RBF and the elevation in BP.

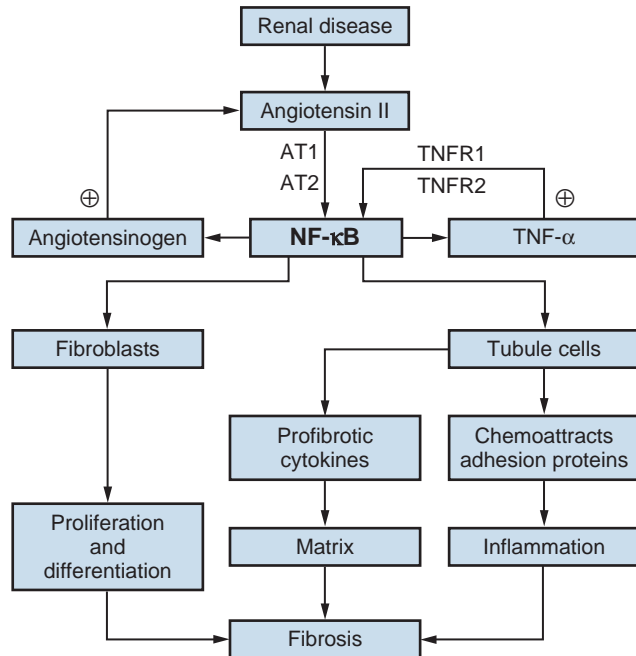


Figure 45-4. The regulation of gene expression by angiotensin II occurs through specific receptors that are ultimately linked to changes in the activity of transcription factors within the nucleus of target cells. In particular, members of the nuclear factor- κ B (NF- κ B) family of transcription factors are activated, which, in turn, fuels at least two autocrine reinforcing loops that amplify angiotensin II and tumor necrosis factor (TNF) formation. TNFR1 and TNFR2, TNF receptors. (From Novick A, Fergany A. Pathophysiology of ischemic nephropathy. In: Walsh PC, Retik AB, Vaughan ED Jr, et al, editors. *Campbell's Urology*. 8th ed. Philadelphia: Saunders; 2002. p. 239.)

KEY POINTS: PATHOPHYSIOLOGY OF ISCHEMIC NEPHROPATHY

- A stenosis of at least 70% to 80% is considered to be hemodynamically significant.
- It is unlikely that the renal damage observed in RAS is secondary to the decrement in RBF alone.
- Multiple molecular and fibrogenic factors contribute to the damage of the renal parenchyma observed after there is a decrement in RBF and an elevation in BP.

SCREENING TESTS

Several noninvasive screening tests are used for diagnosing renovascular disease. Both intravenous pyelography (IVP) and plasma renin activity were used in the past, but they have been replaced by more sensitive and specific techniques. Although renal scintigraphy with ACE inhibition is easy to perform, does not require the discontinuation of antihypertensive medications (except for ACE inhibitors and ARBs at least 48 hours before the study), and may predict the BP response to intervention, its use as an initial screening test has been questioned because of the variability of its sensitivity and its specificity in different studies. In addition, the finding of asymmetric RBF in those with moderate to severe hypertension in the absence of renovascular disease, and the test's poor diagnostic accuracy in those with advanced renal failure (particularly those with creatinine clearances <20 mL/min) or bilateral disease, further limit its utility (Setaro et al, 1991; Mann and Pickering, 1992; Pedersen, 1994; van Jaarsveld et al, 1997; van Onna et al, 2003; Krijnen et al, 2004). As a result, renal scintigraphy is no longer recommended as a screening test to establish the diagnosis of RAS. The screening tests that provide the highest sensitivity and specificity are magnetic resonance angiography (MRA), spiral (helical) computed tomography (CT), and duplex Doppler ultrasonography.

KEY POINTS: SCREENING TESTS

- Renal scintigraphy is no longer recommended as a screening test to establish the diagnosis of RAS.
- The screening tests that provide a higher sensitivity and specificity are MRA, spiral CT, and duplex Doppler ultrasonography.

Magnetic Resonance Angiography

MRA with gadolinium provides a sensitive noninvasive screening test for detecting renovascular disease. In addition to visualizing the renal artery, it can provide an assessment of the functional significance of the renovascular lesion, because both the RBF and the GFR can be determined by the study. Two prospective studies compared MRA with digital subtraction angiography (DSA) or renal angiography and demonstrated that MRA had a sensitivity of 100% for detecting a renovascular lesion of the main renal artery and a specificity of 71% to 96% (Postma et al, 1997; Rieumont et al, 1997). Three-dimensional MRA when combined with cardiac synchronization can visualize the entire length of the major renal arteries. However, lesions involving the distal, intrarenal, and accessory arteries, which may be of hemodynamic significance, may be missed because of poor visualization (Sommer et al, 1992; Klatzburg et al, 1994; de Haan et al, 1996; Schoenberg et al, 1998). Although initially thought to be safe in those with underlying renal insufficiency, concerns regarding the possibility of gadolinium-induced nephrogenic systemic fibrosis have diminished its utility in those with unstable or reduced

renal function (GFR <30 mL/min). In these patients, a noncontrast MRA study may be performed, but this shows far less sensitivity and positive predictive value than a gadolinium-enhanced study (Tan et al, 2002).

Computed Tomography

Spiral (helical) CT angiography with intravenous radiocontrast has shown in some studies a sensitivity of 98% and a specificity of 94% for detecting renovascular lesions (Olbricht et al, 1995). When compared with intra-arterial DSA in potential renal donors with normal renal function suspected of having underlying renovascular disease, CT angiography identified all lesions of the main renal artery greater than 50% and 27 of 28 accessory arteries (Kim et al, 1998). Because both the sensitivity and specificity of CT angiography decline (93% and 81%, respectively) in the presence of renal insufficiency (serum creatinine >1.7 mg/dL, and the risk of dye-induced nephrotoxicity increases, the usefulness of this screening technique is limited in those with renal insufficiency.

Duplex Doppler Ultrasonography

Similar to MRA, duplex Doppler ultrasonography provides both anatomic and functional information. Via B-mode ultrasonography, the main renal arteries may be visualized, and when combined with Doppler measurements of various hemodynamic parameters, particularly peak systolic velocity, one can accurately identify renal artery lesions (Hoffman et al, 1991; Klierer et al, 1994; Stavros and Harshfield 1994; Olin et al, 1995; Marana et al, 1998; Williams et al, 2007). The sensitivity of this technique may be further increased when ACE inhibition is used to enhance the waveforms distal to the arterial lesion (Rene et al, 1995). When the resistive index $[1 - (\text{end diastolic velocity} \div \text{peak systolic velocity})] \times 100$ is calculated during duplex Doppler scanning, a measure of the structural alterations in the smaller distal renal arteries and arterioles is obtained and may help predict the patients who will have an improvement in their BP and/or renal function following revascularization of their lesion(s) (Stavros and Harshfield, 1994; Kaplan-Pavlovic and Nadja, 1998; Marana et al, 1998; Radermacher et al, 2001). However, the accuracy is not sufficient to allow this parameter alone to determine whether one should or should not proceed with revascularization (Zeller et al, 2003; Crutchley et al, 2009).

As a screening test, duplex Doppler ultrasonography provides many advantages. It can demonstrate bilateral disease, does not require the discontinuation of antihypertensive therapy or the exposure to potentially nephrotoxic contrast, and is accurate for those with renal failure. Despite these advantages, the use of duplex Doppler ultrasonography is limited by the fact that it is time consuming, is highly operator dependent, and is a technically difficult test to perform. Further, intrarenal vascular lesions and multiple (and even main) renal arteries might not be adequately visualized in obese patients and in those with overlying intestinal gas (Hoffman et al, 1991; Olin et al, 1995; Kaplan-Pavlovic and Nadja, 1998).

Angiography

Despite a negative screening test, renovascular disease may still be present, particularly if the lesion is in the distal or intrarenal portion of the artery. Both conventional renal angiography and intra-arterial DSA remain the gold standard for diagnosing renovascular disease and are indicated if the clinical index of suspicion is high and intervention is contemplated, regardless of the outcome of the screening tests and in lieu of contrast CT angiography and MRA with gadolinium in the high-risk patient (Mann and Pickering, 1992; Canzanella and Textor, 1994). Intra-arterial DSA allows less radiocontrast to be administered (25 to 50 mL vs. 100 mL) than with a conventional renal angiogram and is thus particularly advantageous in those with underlying renal insufficiency. Although intravenous DSA is less invasive than an arterial study and does not pose a risk for cholesterol embolization, it is

less desirable because the amount of required radiocontrast is higher (150 to 200 mL) and the visualization of the renal vasculature is poorer, thus resulting in both a lower sensitivity and a lower specificity (<90%) (Working Group on Renovascular Hypertension, 1987; Dunnick et al, 1989). Digital angiography using carbon dioxide in place of radiocontrast material may provide imaging similar to that with radiocontrast studies (although the distal vasculature may not always be adequately visualized) and also might avoid the potential for radiocontrast-induced nephrotoxicity; however, this procedure is not universally available (Hawkins et al, 1994).

KEY POINTS: ANGIOGRAPHY

- MRA with gadolinium may be used as a noninvasive test to assess the functional significance of a renal vascular lesion.
- It is highly sensitive and specific.
- Its usefulness in a patient with unstable renal function or a creatinine clearance of less than 30 mL/min is limited because of concerns regarding nephrogenic systemic fibrosis.
- Spiral CT angiography is considered to be a sensitive and specific test, but it is limited in its usefulness as a screening technique in patients with renal insufficiency.
- Duplex Doppler ultrasonography, although it provides many advantages, is time-consuming, highly operator dependent, and a technically difficult test to perform, which limits its use.
- Conventional renal angiography and intra-arterial DSA remain the gold standard for diagnosing renal vascular disease.

PATHOLOGY OF RENOVASCULAR HYPERTENSION

The two main causes of renovascular hypertension are atherosclerosis and fibrous dysplasia. Atherosclerosis accounts for 70% of all renal arterial lesions (Novick et al, 1996). The remaining lesions are caused by fibromuscular dysplasia, with women being most commonly affected (Table 45-1) (Pohl, 1999; Olin et al, 2012).

Atherosclerotic renal artery disease predominantly affects men and women aged 40 to 70 years. The proximal third of the renal artery is usually involved, and in 70% to 80% of the patients there is an aortic plaque that is impinging on the renal ostium, whereas the remaining 30% exhibit nonostial narrowing usually 1 to 3 cm distal to the renal artery ostium (Pohl, 1999). It has been observed that renal arteries with greater degrees of stenosis will more likely and more quickly progress to complete occlusion. Schreiber and colleagues (1984) noted that of 18 patients presenting with RAS, of 75% to 99% on an initial angiogram, 39% progressed to complete occlusion in 13 months. This contrasts with patients who had less than 50% stenosis and 50% to 75% stenosis that progressed to complete occlusion in 59 and 23 months, respectively (Table 45-2) (Schreiber et al, 1984).

Olin and associates (2012) enrolled 447 patients from 9 different sites in the United States Registry for Fibromuscular Dysplasia and reported their results. Ninety-one percent of their patients were female with a mean age at diagnosis of 51.9 years (range 5 to 83 years). Various arteries were involved, with the renal artery being the most common in 294 (66%) of the patients; next was the extracranial carotids in 251 (56%) of the patients; and least common was the vertebral arteries in 82 (18%) of the patients. The most common presenting symptoms were hypertension, headache, and pulsatile tinnitus. There was often a past or present history of vascular events: 19.2% with a transient ischemic attack or stroke, 19.7% with arterial dissections, and 17% with aneurysms.

Hypertension, aneurysm, and arterial dissection were the most common indications for intervention in these patients (Olin et al, 2012).

There are four types of fibrous dysplasia: medial fibroplasia, perimedial fibroplasia, intimal fibroplasia, and medial hyperplasia. Medial, perimedial, and intimal fibroplastic lesions may affect the renal artery with an incidence of 30%, 5%, and 5%, respectively, and they represent 70% to 85%, 10% to 25%, and 10%, respectively, of all fibrous renal artery diseases (Table 45-3) (Pohl, 1999). Medial hyperplasia, the fourth type of fibrous dysplasia, constitutes only 2% to 3% of all fibrous dysplastic lesions.

Medial fibroplasia occurs almost exclusively in women between 25 and 50 years of age. This lesion has the characteristic “string of beads” appearance on angiography and usually will involve both renal arteries. The lesions involve the distal half of the main renal artery and may extend into the branches. Histologically, the lesions are characterized by the growth of fibroblasts in the media covered by fibrous connective tissue in the stenotic areas and thinned-out medial tissue in the aneurysmal areas, thus creating the string-of-beads appearance on angiography (Fig. 45-5) (Pohl, 1999). These patients are not likely to progress to complete occlusion, nor are they likely to experience a decrease in their overall renal function (Novick and Fergany, 2002).

TABLE 45-1 Classification of Renal Artery Disease

DISEASE	INCIDENCE (%)*
Atherosclerosis	60-80
Fibrous dysplasia	20-40
Medial	30
Perimedial	5
Intimal	5

*Percent of renal artery lesions.

From Pohl M. Renovascular hypertension and ischemic nephropathy. In: Schrier RW, editor. Atlas of diseases of the kidney: hypertension and the kidney, vol. 3. Hoboken (NJ): Wiley-Blackwell; 1999 [chapter 3, figure 3-7].

Perimedial fibroplasia also occurs almost exclusively in women, but they are younger (between 5 and 15 years of age) (Olin, 2007). The stenosis occurs classically in the midrenal artery, although it may extend into the distal renal artery and its branches. Similar to medial fibroplasia, angiography may demonstrate a string of beads. However, unlike medial fibroplasia, the aneurysmal “beads” in perimedial fibroplasia never exceed the diameter of the main renal artery. Histologically, there is widespread collagen deposition in the outer half of the media. If left untreated, perimedial fibroplasia often progresses to renal occlusion and loss of renal function (Fig. 45-6) (Pohl, 1999; Olin 2007).

Intimal fibroplasia accounts for 10% of the cases of fibromuscular dysplasia and occurs predominantly in children and younger adults (Pohl, 1999; Novick and Fergany, 2002). Histologically, there is collagen deposition within the intimal arterial layer (Olin and Sealove, 2011). This form of fibroplasia may be complicated by disruptions of the internal elastic lamina and hence may result in dissection, arterial wall hematoma, and renal infarction (Olin, 2007). The lesions are usually in the proximal renal artery; however, they may also occur in the mid- or distal renal artery and without intervention are likely to progress and result in loss of renal function (Fig. 45-7) (Pohl, 1999).

Medial hyperplasia is a rare disease, often angiographically indistinguishable from intimal fibroplasia. Histologically, there is smooth muscle cell hyperplasia with no associated fibrosis (Olin, 2007).

PHYSIOLOGIC SIGNIFICANCE

Because not all renal artery lesions will result in hypertension, the physiologic significance of a lesion should be made before undertaking any therapeutic intervention to eliminate or control hypertension (Ploth, 1995). Renovascular hypertension is more likely to be observed when the lesion is greater than or equal to 70% in one or both renal arteries or when a 50% stenosis with poststenotic dilatation is demonstrated. The clinical significance of a lesion may be determined by ACE-inhibitor scans (see previous description), the pressure gradient across the renal

TABLE 45-2 Progression of Atherosclerotic Renal Artery Disease (126 Renal Arteries*)

STENOSIS ON INITIAL ANGIOGRAM (%)	STENOSIS ON SEQUENTIAL ANGIOGRAM (%)			
	<50	50-75	75-99	100
<50% (n = 78)	54	12	8	4
(Mean angiographic interval, mo)	(41 ± .58)	(36 ± 1.8)	(51 ± 3.0)	(59 ± 5.4)
50%-75% (n = 30)		16	11	3
(Mean angiographic interval, mo)		(29 ± 1.2)	(34 ± 1.7)	(23 ± 7.1)
>75%-99% (n = 18)			11	7
(Mean angiographic interval, mo)			(21 ± 1.5)	(13 ± .8)

*Total diseased renal arteries, excluding 5 with 100% initial occlusion, 25 persistently normal, 13 with de novo stenosis (10 >50%, 3 <50%), and one congenitally absent kidney.

n, number of diseased renal arteries in each category.

From Schreiber M, Pohl M, Novick A. The natural history of atherosclerotic and fibrous renal artery disease. Urol Clin North Am 1984;11:383-92.

TABLE 45-3 Frequency and Natural History of Fibrous Renal Artery Diseases

LESION	FREQUENCY, %*	RISK OF PROGRESSION	THREAT TO RENAL FUNCTION
Intimal fibroplasia and medial hyperplasia	10	++++	++++
Perimedial fibroplasia	10-25	++++	++++
Medial fibroplasia	70-85	++	—

*Frequency relates to frequency of only the fibrous renal artery diseases.

From Pohl M. Renovascular hypertension and ischemic nephropathy. In: Schrier RW, editor. Atlas of diseases of the kidney: hypertension and the kidney, vol. 3. Hoboken (NJ): Wiley-Blackwell; 1999 [chapter 3, figure 3-4].

KEY POINTS: PATHOLOGY OF RENOVASCULAR HYPERTENSION

- There are four types of fibrous dysplasia: medial fibroplasia, perimedial fibroplasia, intimal fibroplasia, and medial hyperplasia.
- Medial fibroplasia is the most common lesion and typically presents with a characteristic “string-of-beads” appearance.
- These patients are not likely to show progression of the occlusion or to experience a decrease in overall renal function.
- Perimedial fibroplasia and intimal fibroplasia, however, are likely to progress if left untreated, resulting in loss of renal function.

artery, and by renal vein renin (RVR) measurements (Working Group on Renovascular Hypertension, 1987; Setaro et al, 1991; Mann and Pickering, 1992; Canzanello and Textor, 1994; Derkx and Schalekamp, 1994).

A significant pressure gradient (>10 to 15 mm Hg) across a renal artery lesion, which can be ascertained during intra-arterial renal angiography, may predict a reduction in BP with revascularization, whereas those without a significant gradient do not.

An RVR ratio of greater than or equal to 1.5 (affected/nonaffected side) may be observed when the lesion is the cause of “renin-dependent” hypertension. Unfortunately, the clinical utility of the RVR ratio is limited because in as many as 60% of patients, an improvement in BP may be seen following revascularization even in the absence of RVR lateralization; the RVR ratio is of poor predictive value in those with bilateral disease, it requires renal vein

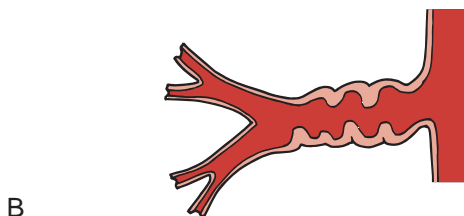
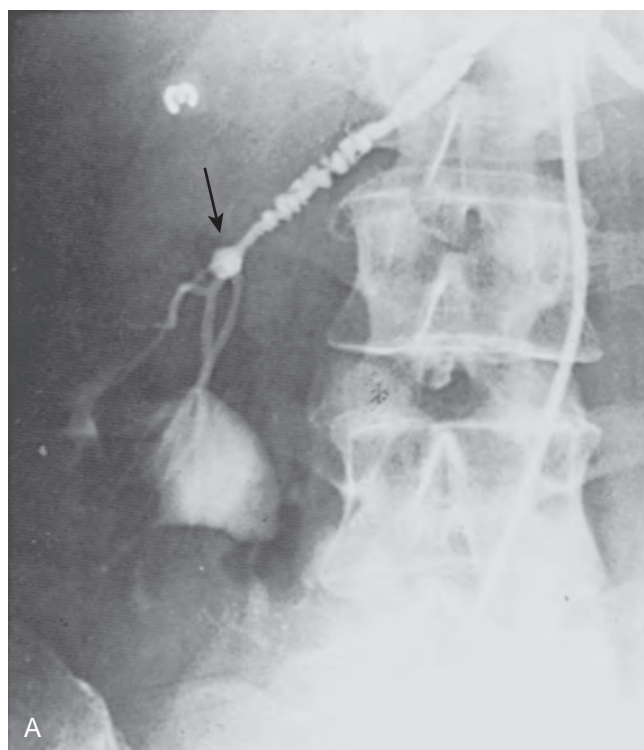


Figure 45-5. Arteriogram and schematic diagrams of medial fibroplasia. A, Right renal arteriogram demonstrating weblike stenosis with interposed segments of dilatation (large beads) typical of medial fibroplasia (“string-of-beads” lesion) (arrow). B, Schematic diagram of perimedial fibroplasia. (A, from Novick AC. Renal vascular hypertension in children. In: Kelalis PP, King LR, Belman AB, editors. Clinical pediatric urology. Philadelphia: Saunders; 1984; B, from Pohl M. Renovascular hypertension and ischemic nephropathy. In: Schrier RW, editor. Atlas of diseases of the kidney: hypertension and the kidney, vol. 3. Hoboken (NJ): Wiley-Blackwell; 1999 [chapter 3, figure 3-5].)

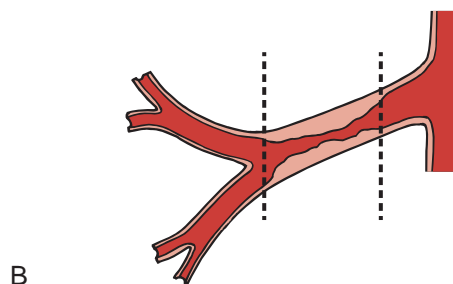
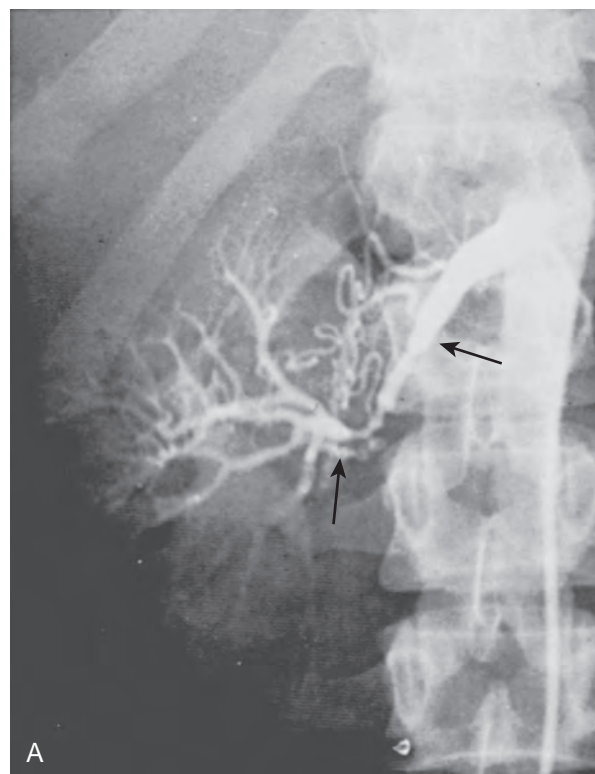


Figure 45-6. Arteriogram and schematic diagram of perimedial fibroplasia. A, Selective right renal arteriogram shows a tight stenosis in the midportion of the renal artery (arrows) with a small string-of-beads appearance, typical of perimedial fibroplasia. B, Schematic diagram of perimedial fibroplasia. (A, from Novick AC. Renal vascular hypertension in children. In: Kelalis PP, King LR, Belman AB, editors. Clinical pediatric urology. Philadelphia: Saunders; 1984; B, from Pohl M. Renovascular hypertension and ischemic nephropathy. In: Schrier RW, editor. Atlas of diseases of the kidney: hypertension and the kidney, vol. 3. Hoboken (NJ): Wiley-Blackwell; 1999 [chapter 3, figure 3-6].)

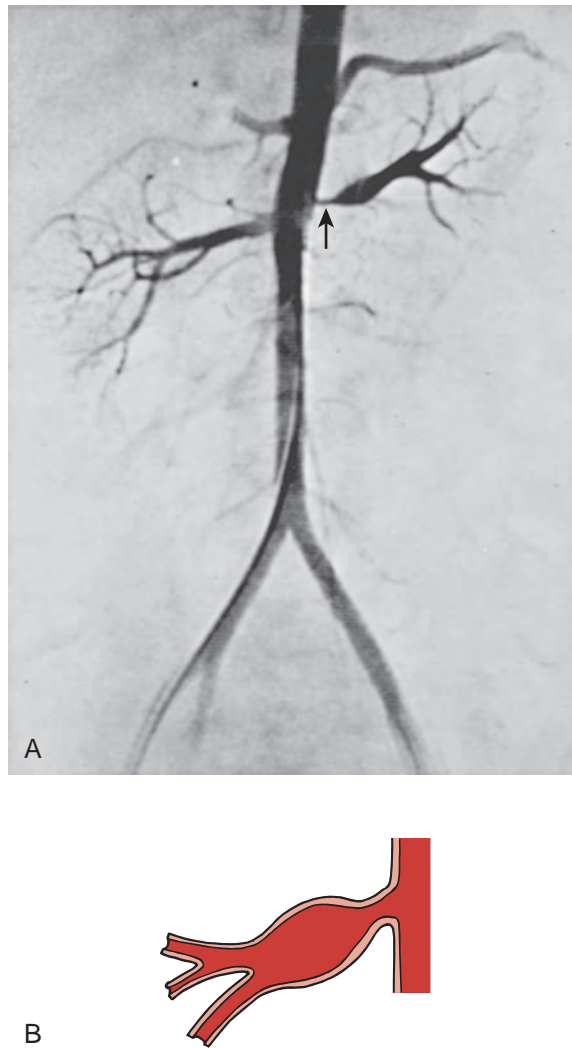


Figure 45-7. Arteriogram and schematic diagram of intimal fibroplasia. **A**, Selective right renal arteriogram demonstrates a localized, highly stenotic, smooth lesion involving the distal renal artery, from intimal fibroplasia. **B**, Schematic diagram of intimal fibroplasia. Arteriogram of a 6-year-old boy in **A** demonstrates proximal left renal artery stenosis (arrow) from intimal fibroplasia. (**A**, From Novick AC. Renal vascular hypertension in children. In: Kelalis PP, King LR, Belman AB, editors. *Clinical pediatric urology*. Philadelphia: Saunders; 1984; **B**, from Pohl M. Renovascular hypertension and ischemic nephropathy. In: Schrier RW, editor. *Atlas of diseases of the kidney: hypertension and the kidney*, vol. 3. Hoboken (NJ): Wiley-Blackwell; 1999 [chapter 3, figure 3-7].)

catheterization with the administration of radiocontrast, and it necessitates the discontinuation of antihypertensives that may alter renin secretion.

Therefore, because the physiologic significance of a renal artery lesion may not always be reliably assessed, the clinician may often need to assume a causal relationship between the lesion and hypertension when one or more of the clinical features are present, as previously outlined.

KEY POINTS: PHYSIOLOGIC SIGNIFICANCE

- One may not always be able to assess reliably the significance of a renal arterial lesion before intervention.
- The clinician therefore may need to assume a causal relationship between the lesion and the presence of hypertension.

MANAGEMENT OF RENOVASCULAR HYPERTENSION

When a diagnosis of renovascular hypertension is made, BP control may be attempted with medical therapy alone, and/or with percutaneous transluminal renal angioplasty (PTRA) (with or without stenting), or with surgery. The type of lesion (atherosclerotic or fibromuscular), its site and the extent of the renal artery involvement, the overall medical status of the patient, and the inherent risks, as well as the skill of those performing the interventional procedures, determine the best therapeutic approach.

Medical Therapy

Control of BP in those with renovascular hypertension may be achieved in more than 90% of patients with medical therapy alone. Because of the severity of the hypertension, however, therapy generally requires multiple antihypertensive medications. Although all classes of antihypertensives may be used, drugs that inhibit AII production (ACE inhibitors) or block its receptor site (ARBs) have been shown to be particularly efficacious because the hypertension is often the result of activation of the renin-angiotensin system (Franklin and Smith, 1985; Hollenberg, 1987; Imamura et al, 1995; Tullis et al, 1999; Dworkin and Cooper, 2009). When used as monotherapy, ACE inhibitors may control BP in 80% of patients, and when combined with a diuretic, control may be increased to almost 90% (Franklin and Smith, 1985; Hollenberg, 1987).

Despite BP control with medical therapy, several studies have shown that atherosclerotic renal artery lesions may progress with time. It has been noted in studies that 40% to 60% of patients have progression of their atherosclerotic renal artery lesions throughout 7 years, with half of these progressing within 2 years (Schreiber et al, 1984; Pohl and Novick, 1985; Rimmer and Gennari, 1993). Those patients with an initial stenosis greater than or equal to 75% had the fastest rate of progression, with total occlusion occurring in 40% of the lesions (Pohl and Novick, 1985). In a prospective study using serial duplex ultrasonography, 295 arteries in 170 patients were examined throughout a mean of 33 months follow-up (Caps et al, 1998a). In 91 (31%) of the 295 renal arteries, the atherosclerotic lesions progressed with time at a rate directly proportional to the severity of the lesion at baseline. Twenty-eight percent of those with less than or equal to 60% stenosis and 49% of those with greater than or equal to 60% stenosis at baseline progressed, and total occlusion was observed in 9 with "severe" stenosis ($\geq 60\%$) at baseline.

Medical therapy may reduce BP below a critical level and induce ongoing renal ischemia distal to the arterial lesion, resulting in tubular atrophy, interstitial fibrosis, glomerulosclerosis, and progressive loss of function in the affected kidney(s) (see *Angioplasty and Stenting for Preservation of Renal Function*) (Michel et al, 1986; Hricik and Dunn, 1990). These changes are more likely to be observed with antihypertensives that inhibit angiotensin or block its receptors than with others; however, this has not been uniformly seen in clinical practice (Michel et al, 1986; Hricik and Dunn, 1990; Strandness, 1994; Caps et al, 1998b; van de Ven et al, 1998). Nevertheless, renal function should be closely monitored whenever such antihypertensive agents are used in patients with renovascular hypertension, particularly when they are combined with a diuretic. In addition to monitoring the serum creatinine concentration and estimated GFR or creatinine clearance, renal sizes and cortical blood flow velocity by duplex scanning should be assessed, because they may more quickly provide evidence of irreversible nephron loss (Caps et al, 1998b). Both ACE inhibitors and ARBs, particularly in the setting of volume contraction, may also result in acute (usually reversible) renal failure in 10% to 20% of those with either bilateral RAS or RAS affecting a solitary kidney (van de Ven et al, 1998).

The lesions of medial fibroplasia, the most common form of fibromuscular dysplasia, unlike atherosclerotic disease, rarely progress. However, the less common forms of fibromuscular dysplasia

(perimedial fibroplasia, medial hyperplasia, and intimal fibroplasia) may progress and result in loss of renal function (Schreiber et al, 1984; Pohl and Novick, 1985). Thus patients with these lesions must also be monitored closely (Pohl and Novick, 1985).

KEY POINTS: MEDICAL THERAPY

- Control of BP in those with renal vascular hypertension may be achieved in the vast majority of patients with medical therapy alone.
- Despite BP control with medical therapy, studies have shown that atherosclerotic renal artery lesions may progress with time.
- Careful monitoring of renal function, particularly when using ACE inhibitors and ARBs, must be maintained.

Angioplasty and Stenting for Hypertension

Percutaneous transluminal renal artery angioplasty (PTRA) is an angiographic technique by which stenotic renal arteries are dilated with a balloon-tipped catheter. Lesions that are most amenable to PTRA include those that are less than 10 mm in length, are partially occluded, and do not involve the ostium (Geyskes, 1988; Marshall et al, 1990). Following successful PTRA, an improvement in BP may be seen as quickly as 4 to 6 hours after the procedure but is more commonly seen after 48 hours, although the maximal antihypertensive effect may not be observed for several weeks (Bonelli et al, 1995; Ram et al, 1995). In general, the absence of an early antihypertensive response suggests that a long-term improvement of hypertension is unlikely (Bonelli et al, 1995).

PTRA without stenting has proved successful for patients with underlying fibromuscular dysplasia. Previously, surgical revascularization was the only option. It has primarily been used in those with recent onset of hypertension, those with poorly controlled hypertension despite medical therapy or who are unable to tolerate medical therapy, and in those with evidence of ischemic nephropathy (Slovut and Olin, 2004). Compared with surgery, it is less costly, less invasive, may be performed in the outpatient setting, has a lower morbidity rate, and does not preclude surgical revascularization if unsuccessful. The technical success rate of PTRA in experienced hands ranges from 87% to 100%, and improvement or cure of the hypertension has been reported to occur in close to 90% in many of the larger studies (Geyskes, 1988; Canzanella et al, 1989; Ramsay and Waller, 1990; Libertino and Beckmann, 1994; Aurell and Jensen, 1997; Slovut and Olin, 2004; Mousa et al, 2012). Although successful, a restenosis rate of up to 27% may be seen and periodic surveillance with duplex Doppler sonography should be performed to monitor for disease progression, restenosis, or loss of renal mass (Slovut and Olin, 2004).

Successful PTRA in patients with unilateral atherosclerotic RAS is technically more difficult to achieve (technical success rates may be as low as 70%), and rates of cure or long-term improvement of hypertension have not been consistent (Geyskes, 1988; Canzanella et al, 1989; Ramsay and Waller, 1990; Libertino and Beckmann, 1994; Aurell and Jensen, 1997; Nordmann et al, 2003). Although cure or long-term improvement of hypertension has been reported to be as high as 60% to 70% by some, these were observed in uncontrolled trials and the site of the renal artery lesion, which is of critical importance in determining the clinical outcome, varied. This was demonstrated by Canzanella and colleagues, in which an improvement of hypertension was seen in 86% of patients with unilateral nonostial lesions as compared with 46% with unilateral ostial lesions (Canzanella et al, 1989). Further, three prospective studies comparing PTRA with medical therapy for unilateral RAS demonstrated limited benefit regarding BP control and rates of renal or cardiovascular morbidity and mortality (Plouin et al, 1998; Webster et al, 1998; van Jaarsveld et al, 2000). The

potential benefit of PTRA is further diminished by the development of reversible acute renal failure in approximately 20% of patients and with thrombosis, perforation, or dissection of the renal arteries and/or diffuse atheroembolism occurring in 15% undergoing the procedure.

The effects on BP following PTRA in patients with bilateral RAS have been disappointing as well, in part, because of the frequent presence of ostial or completely occluded lesions (Canzanella et al, 1989; Marshall et al, 1990; Ramsay and Waller, 1990). These lesions are difficult to dilate, and attempts are associated frequently with high complication rates. In general, the selection criteria for patients and the type of lesions in which PTRA has been performed are poorly delineated in most studies. When performed for bilateral RAS, PTRA may be technically unsuccessful in as many as 60%, and, when successful, cure rates of hypertension may be as low as 8% and improvement in BP seen in only 43% (Ramsay and Waller, 1990). Further, because total occlusion of the renal artery in an atrophic kidney may be seen 50% of the time, few are cured of their hypertension, and only 14% experience long-term improvement of their BP when PTRA is attempted in patients with bilateral RAS associated with an atrophic kidney (Geyskes, 1988).

Even when technically successful, the restenosis rate following PTRA is significant (30% for nonostial and 50% for ostial lesions) and may occur shortly after the procedure (15% to 30% within 2 years) with recurrence of uncontrolled or accelerated hypertension.

Intravascular stenting of atheromatous RAS has been performed at the time of angioplasty in an effort to reduce the incidence of restenosis and to improve BP control. With increasing experience throughout the years, successful stent placement can be achieved in close to 100% of patients (Rees et al, 1991; van de Ven et al, 1995; Iannone et al, 1996; Tuttle et al, 1998). Despite this high rate of technical success, the restenosis rate remains at about 15% to 25%, and this condition might occur as early as 5 months after placement of the stent (Kidney and Deutsch, 1996; Rocha-Singh et al, 2005). When comparing PTRA with stenting and PTRA alone, van de Ven and coworkers demonstrated an 88% success rate in achieving renal artery patency (defined as a residual stenosis <50%) with PTRA with stenting as compared with a 57% patency rate in those who underwent PTRA alone for their ostial RAS (defined as a stenosis >50% within the first 10 mm of the aortic lumen) (van de Ven et al, 1999). At 6 months, the primary patency rate, as determined by angiography, remained significantly greater (75% vs. 29%) and the observed rate of restenosis was also less (14% vs. 48%) in the group assigned to PTRA with stenting. Despite the fact that a better revascularization was achieved with PTRA with stenting, there was no statistically significant difference in the BP between the two groups. However, many of the patients (29%) assigned to PTRA without stenting subsequently underwent stenting for either primary or late failure of their initial procedure. These patients were included in the analysis of the PTRA group, and thus the actual BP may have been more favorable for the stented group.

Improvement of BP has also been observed by some in those who are stented after unsuccessful PTRA as well as in those in whom primary endovascular stenting (without concomitant PTRA) has been performed for atherosclerotic RAS (Dorros et al, 1995, 1998a, 1998b; Blum et al, 1997; Rocha-Singh et al, 2005). Blum and colleagues (1997) noted a cure or improvement of hypertension in 78% of 68 patients in whom stents were placed for ostial lesions after unsuccessful PTRA. However, only 64% were followed for 12 months and only 9% for 60 months in this study. In the nonrandomized study by Rocha-Singh and associates, 208 patients with de novo or restenotic aorto-ostial renal lesions that were greater than or equal to 70% underwent stenting after unsuccessful PTRA, and an improvement of hypertension was noted at both 9 and 24 months. In those who underwent primary stenting for either unilateral or bilateral disease, Dorros and colleagues (1998a, 1998b) observed a cure or improvement of hypertension in 60% of their patients at 6 months; however, the number of patients with nonostial lesions was not specified in their study, and by 1 and 4 years follow-up, overall improvement in BP control declined to 42% and

only 1% remained cured. A more recent retrospective review by Corriere and coworkers, however, demonstrated only 1.1% of their 99 patients to be cured of their hypertension, and only 20.5% to demonstrate an improvement in their BP following primary stenting of 110 atherosclerotic renal artery lesions with a mean stenosis of $79.2 \pm 12.9\%$ during their short-term follow-up (Corriere et al, 2008). Further, other studies have noted no significant improvement in BP control after either primary or secondary stenting (Harden et al, 1997; Tuttle et al, 1998).

Although the results of many earlier studies suggest that PTRa with stenting may cure or improve control of hypertension, three more recent randomized studies raise questions about the effectiveness of revascularization with stenting for BP control. The Stent Placement and Blood Pressure and Lipid-lowering for Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) trial enrolled 140 patients with BP controlled to less than 140/90 mm Hg, and with a renal ostial lesion greater than 50%, and prospectively randomized the patients to either renal artery stenting and medical therapy or medical therapy alone. At the end of follow-up, **there was no difference in the degree of BP control** (Bax et al, 2009). It should be noted, however, that 12 of the 64 patients who were randomized to stenting were found to have an ostial lesion less than 50% and were not stented, but they were included in the analysis of the stented group and thus may have negatively impacted the findings of the study (Bax et al, 2009). In the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial, 806 patients with atherosclerotic RAS were randomized to undergo revascularization and medical therapy or to undergo medical therapy alone (ASTRAL Investigators et al, 2009). As in the STAR trial, this study has also been criticized for including patients who did not have clinically significant RAS and who did not have their findings confirmed by core laboratories. After a median follow-up of 34 months, **there was no difference in BP control between the two groups**, although the number of antihypertensive medications required was slightly higher in the medically managed group.

The Cardiovascular Outcomes and Renal Atherosclerotic Lesions (CORAL) study was designed to overcome, and for the most part did overcome, the shortcomings of previous studies (Cooper et al, 2014). In short, this was a multicentered, open-label, randomized controlled trial that compared medical therapy alone with medical therapy plus renal artery stenting in patients with atherosclerotic RAS and elevated BP, chronic kidney disease, or both. **Medical therapy consisted of an ARB, a calcium channel blocker, a statin, a diuretic, and other medications as necessary.** The study sponsors supplied drugs. (Other specific details regarding the protocol and its limitations are discussed under Angioplasty and Stenting for Preservation of Renal Function.) Severe RAS was defined angiographically as a stenosis of at least 80% but less than 100% of the diameter, or stenosis of at least 60% to less than 80% of the diameter, of an artery with a systolic pressure gradient of at least 20 mm Hg. Because of enrollment constraints, the actual average percent stenosis was 73%. The primary end points of the study were occurrences of major cardiovascular or renal events. The study was not specifically designed to determine whether or not stenting would confer an additional benefit on BP control. The average systolic BP was 150 mm Hg at enrollment, and participants, on average, were taking a mean of 2.1 antihypertensive medications. Overall, a reduction of systolic BP of a mean of 15 to 16 mm Hg was achieved in both groups with an average of 3.4 medications, **not different in either group.** However, a modest, but statistically significant, reduction of 2 mm Hg in systolic BP with stenting was noted. However, **this reduction did not translate into a significant decrement in clinical events.** Therefore the risk of stenting in the group of patients studied does not seem worth the potential benefit regarding BP control.

It is important to note, however, that **patients with accelerated hypertension, flash pulmonary edema, and malignant hypertension were not included in this trial.** Therefore conclusions regarding these groups of patients cannot be drawn from this study. The approach to these patients must be individualized, and

the clinician must decide which patients may benefit from intervention.

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines were published before the publication of the results of the CORAL trial. They are as follows: PTRa is a reasonable option for (1) patients with a hemodynamically significant RAS and accelerated hypertension or malignant hypertension, (2) hypertension with an unexplained unilateral small kidney, (3) hypertension with intolerance to medication, and (4) renal stent placement that is indicated for ostial lesions that meet the clinical criteria for intervention (Hirsch et al, 2006).

Given the results of the CORAL trial, this panel may reconsider recommendation numbers 2 and 4 because these patients may have an “equivalent” response to medical therapy without the attendant risks that occur with stenting.

Previous unblinded studies have suggested that catheter-based renal artery denervation reduces BP in patients with resistant hypertension. This approach until recently would have been an alternative to medical therapy in patients with renal vascular hypertension who did not respond adequately to medical therapy and were facing transluminal angioplasty as an alternative. However, the results of the Simplicity trial have been published (Bhatt et al, 2014). A total of 535 patients underwent randomization. The patients were divided into two separate groups. They were randomly assigned in a 2 to 1 ratio to undergo renal denervation or a sham procedure. This prospective, blinded study did not show a significant reduction in systolic BP in patients with resistant hypertension who underwent the actual denervation procedure versus those who had a sham operation. Unfortunately, this option regarding the treatment of resistant hypertension is no longer tenable based on this well designed, randomized controlled trial (Bhatt et al, 2014).

KEY POINTS: ANGIOPLASTY AND STENTING FOR HYPERTENSION

- In general the effect on BP control following PTRa has been disappointing.
- Three recent trials have shown no significant difference between medically treated patients and those treated with transluminal angioplasty.
- The most recent and best-performed trial is the CORAL study that showed only a 2 mm Hg difference in BP between groups. This, however, did not translate into a significant decrement in clinical events, and it exposed the patients to the potential risks of angiography.
- Patients with accelerated hypertension flash pulmonary edema and malignant hypertension were not included in this trial. Therefore conclusions regarding these patients cannot be drawn from this or other studies.
- Renal denervation for resistant hypertension has been recently shown to be unsuccessful (SIMPLICITY trial).

Although generally safe, a 5% to 15% complication rate may be seen with PTRa or stenting. The majority of these are of minor significance and are the results of hematoma formation at the puncture site or renal spasm. However, when severe, renal artery spasm may result in local thrombosis and renal infarction, but this can usually be reversed or prevented by intra-arterial infusion of nitroglycerin. Major complications, such as reversible acute renal failure associated with radiocontrast, have been observed in approximately 20% of cases; renal artery perforation, occlusion, dissection, and irreversible acute renal failure resulting from atheroembolization are less frequent (<5%). The deployment of endovascular stents may also be complicated by malpositioning or dislocation.

Angioplasty and Stenting for Preservation of Renal Function

The lesions of atherosclerotic RAS progress with time, but it is unclear how many patients ultimately develop ischemic nephropathy or ESRD as a consequence of their vascular lesions. The rate at which these renal complications occur is also unknown.

In a retrospective study by Baboolal and colleagues (1998), the clinical course of 51 patients with significant bilateral RAS (defined as total occlusion or $\geq 90\%$ stenosis in one renal artery and $\geq 50\%$ stenosis in the contralateral artery) who were receiving medical therapy alone was examined. These patients were treated medically because of physician or patient preferences, because the lesions were thought not to be amenable to PTRAs, because the kidneys were thought to be too small and nonsalvageable, or because the operative risks were deemed too great. As a whole, the GFR fell 4 mL/min/yr (range 1 to 16 mL/min/yr), and at 5 years of follow-up ESRD developed in only 12%. ESRD occurred in those who had the most significant renal impairment (mean GFR 25 mL/min, range 15 to 56 mL/min) at the time of angiography and in whom the decline in GFR was most rapid (mean 8 mL/min/yr, range 3 to 13 mL/min/yr). Thus, despite the presence of significant RAS in all of the patients, a significant number showed either little or no change in their renal function throughout time, and 88% did not require renal replacement therapy. These findings suggest that even in the presence of significant renal artery disease, sufficient renal collateral circulation may develop to maintain adequate RBF and renal viability (Meyrier et al, 1998).

Progressive deterioration in renal function does occur, however, in a subset of patients with atherosclerotic RAS and is an increasing cause of potentially reversible renal insufficiency in the elderly as well as the primary cause of renal failure in 10% to 20% of the ESRD population (Jacobson, 1988; Rimmer and Gennari, 1993; Mailloux et al, 1994; Greco and Breyer, 1997; Middleton, 1998; Textor, 1998; van Ampting et al, 2003).

Despite renal replacement therapy, mortality rates in these individuals are greater than 50% throughout 3 years, and the 5- and 10-year survival rates are only 18% and 5%, respectively. Given the increasing number of these patients and their poor prognosis with renal replacement therapy, it is imperative that revascularization and restoration of renal function be pursued whenever there is clinically significant worsening of renal function. However, avoiding renal replacement therapy per se does not guarantee a longer survival in these patients who usually present with diffuse vascular disease.

PTRA without stenting has been shown to improve renal function in 40% and to stabilize renal function in another 30% to 40% of those with ischemic nephropathy (Canzanella et al, 1989; Sos, 1991; O'Donovan et al, 1992; Rimmer and Gennari, 1993; Greco and Breyer, 1997). These results were primarily obtained in those with nonostial lesions, and although the restenosis rate may be as high as 10% to 30%, many are amenable to repeat PTRAs (Greco and Breyer, 1997). PTRA in patients with nonostial lesions shows a success rate similar to that of surgical revascularization and poses a lower risk of morbidity and mortality. In the presence of ostial lesions, which comprise the vast majority (80% to 85%) of atherosclerotic RAS, PTRA without stenting is far less successful and effective; thus most PTRAs for atherosclerotic RAS are performed with endovascular stent placement. Endovascular stents have been placed at the time of PTRA or "primarily" (without previous PTRA) (Dorros et al, 1995, 1998a, 1998b; Boisclair et al, 1997; Harden et al, 1997; Rundback et al, 1998; Isles et al, 1999; Rees, 1999; Ives et al, 2003; Korsakas et al, 2004; Corriere et al, 2008). In these earlier studies, stenting resulted in improved renal function in 30% to 40% and stabilization of renal function in another 30% to 50%. Long-term outcomes of stenting in those with ischemic nephropathy suggested that the clinical benefit was inversely related to the level of renal function at the time of the procedure, with the greatest overall benefit observed in those with a baseline serum creatinine concentration of 1.5 to 2.0 mg/dL. Most of these studies, however,

included patients with both ostial and nonostial atherosclerotic lesions, and, in some, the stenoses were greater than or equal to 50% and may not have necessarily been of hemodynamic significance.

Several investigators have studied the effect of stenting on renal function in patients with only ostial lesions (Rees et al, 1991; van de Ven et al, 1995; Blum et al, 1997; Tuttle et al, 1998; Rocha-Singh et al, 2005). In the earlier studies by Rees and van de Ven, approximately one third of patients demonstrated improved renal function following stenting, whereas stabilization of renal function was noted in 36% in the former study and 58% in the latter (Rees et al, 1991; van de Ven et al, 1995). Both studies, however, had only short-term follow-up (mean follow-up 6.5 and 9 months, respectively) (Rees et al, 1991; van de Ven et al, 1995). Researchers of three studies have examined the long-term effects of stenting on preservation of renal function in patients with ostial lesions (Blum et al, 1997; Tuttle et al, 1998; Rocha-Singh et al, 2005). In their study, Blum and coworkers (1997) found no deterioration in renal function in their 68 patients with ostial lesions with a mean serum creatinine concentration of 1.23 ± 0.6 mg/dL (range 0.5 to 3.9 mg/dL) during a mean follow-up of 27 months after stenting following unsuccessful angioplasty. Further, 30% of patients who exhibited significant renal insufficiency at baseline remained stable. Tuttle and colleagues (1998) followed 129 patients for a mean of 24 months after undergoing either primary or secondary stenting. No significant change was observed in the patients' creatinine clearances (as determined by the Cockcroft-Gault formula) despite the low level of renal function at baseline (range 23 ± 3 to 53 ± 3 mL/min); an improvement was noted in 15%, another 81% showed stabilization of their renal function, and, of the 8 patients initially dialysis dependent, 4 recovered significant renal function and had a serum creatinine of 2.3 ± 0.5 mg/dL at 15 ± 6 months (range 9 to 24 months) (Tuttle et al, 1998). In the nonrandomized study by Rocha-Singh and coworkers (2005), 208 patients with de novo or restenotic aorto-ostial RAS greater than or equal to 70% underwent stenting after unsuccessful PTRA. At 9 and 24 months follow-up, the serum creatinine concentration remained unchanged from baseline values.

Although suggestive of benefit, all of the aforementioned studies were limited by the absence of a control group that was treated with medical therapy alone and by the fact that it was not clear if endovascular stenting was performed for the worsening of renal function. To date, three randomized studies have been performed to help clarify this issue. In the STAR trial, 140 patients with BP controlled to less than 140/90 mm Hg and with a renal ostial lesion greater than 50% were assigned to either renal artery stenting and medical therapy or to medical therapy alone. At 2 years, there was no statistical difference in the primary end point defined as a decline in creatinine clearance of greater than or equal to 20% between the two groups (Bax et al, 2009). One of the limitations of this study, however, was that 12 of the 64 patients who were randomized to stenting were found to have an ostial lesion less than 50% and were not stented, but they were included in the analysis of the stented group and thus they may have negatively impacted the findings of the study (Bax et al, 2009). Of the 806 patients with atherosclerotic RAS randomized to undergo revascularization and medical therapy or to medical therapy alone in the ASTRAL trial, no difference between the two groups was noted in the decline of renal function at 1 year (median follow-up of 34 months) (ASTRAL Investigators et al, 2009). Further, there were no differences in the outcomes based on the severity of stenosis at baseline, renal sizes, baseline-estimated GFR, the baseline serum creatinine concentration, or the rate of renal deterioration before randomization (ASTRAL Investigators et al, 2009). Similar to the findings of the STAR trial, the findings of the ASTRAL trial may have been unlikely to show a benefit from endovascular revascularization because 25% of those enrolled in the study experienced normal renal function, a significant number of patients exhibited only unilateral disease, and a significant percentage of the stenotic lesions were less than 70% and possibly of little hemodynamic significance.

As mentioned earlier, in the text regarding BP control, the findings of the CORAL trial have been published (Cooper et al, 2014). This was a multicenter, prospective, randomized, controlled study in which patients with difficult-to-control hypertension (defined as systolic BP greater than or equal to 155 mm Hg on two or more antihypertensives) or renal impairment less than 60 mL/min/1.73 m² by the Modification of Diet in Renal Disease (MDRD) formula, and RAS greater than 60% but less than 100%, were randomized to either optimal medical therapy alone or to optimal medical therapy and renal artery stenting. The participants in the CORAL trial were followed for the occurrence of adverse cardiovascular and renal events (a composite end point of death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal replacement therapy). Throughout a median follow-up of 43 months, no significant difference between the treatment groups in the rate of the individual components of the primary end point or in all-cause mortality was noted. Therefore renal artery stenting did not confer a clinically significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic RAS and hypertension or chronic kidney disease. Although the average percent stenosis was 73% overall, the investigators were unable to demonstrate a benefit among participants with RAS of more than 80% (Cooper et al, 2014).

The CORAL trial includes several strengths. Among these is the fact that the investigators created a protocol that maximized adherence to medical therapy by supplying medication and minimizing crossovers, and the fact that investigators demonstrated a 20% reduction of the primary end point at 2 years, which was half of the expected rate of 40%. They clearly demonstrated that high-quality medical therapy is of paramount importance in managing this disease. However, limitations of the study must be noted:

1. Patients with a serum creatinine of greater than 4 mg/dL were excluded.
2. Patients with a renal artery lesion that could not be treated with the use of a single stent were excluded.
3. The median percent stenosis was 73%. All patients with RAS of greater than 60% were treated, although some of these may not have been hemodynamically significant.
4. No data are provided regarding the rate of decline of renal function before enrollment into the trial.
5. The population may represent a group of patients in whom medical therapy was superior to that seen in general practice because medications were supplied to the patients.
6. A subgroup of patients may well have been excluded from the study by their physicians and sent for stenting based on their own individual practice guidelines. These patients may have had “uncontrollable” or malignant hypertension in spite of medications, or intolerance to medications, or rapidly deteriorating renal function.

As stated in an accompanying editorial, the CORAL trial struck a balance between the practical constraints of patient recruitment and the most appropriate target population for renal artery stenting. To succeed in recruiting a sufficient number of patients to achieve statistical power, patients with stenoses of at least 60% were allowed into the trial. Again, it is important to note that when patients with greater than 80% stenosis were analyzed as a subgroup, there was no difference when compared to those patients in whom less severe stenosis was observed. A more restrictive trial in patients with critical bilateral disease or a severe stenosis involving a single functioning kidney will likely never be completed. **Therefore it remains important to identify a target population with severe renal insufficiency that may benefit from intervention.** Patients who in fact have a serum creatinine of greater than 4 mg/dL, but had rapid deterioration of renal function before the time of presentation, may respond to intervention with stenting to preserve renal function. There are reports of patients who have been able to discontinue hemodialysis after renal artery stenting is performed for ischemic nephropathy. Thus salvaging renal function and control of BP

remains an issue in a proportion of patients with renal artery occlusive disease. In the majority of these patients, in general, stenting is the least invasive and most appropriate therapy. However, depending on the location of the lesion and/or its size and whether or not it is associated with lesions in the abdominal aorta or is a subtype of fibromuscular dysplasia, surgery may be the more appropriate treatment choice. (See Surgical Treatment of Renal Artery Stenosis).

Given the results of the CORAL trial, in which patients may or may not have had stable renal function, the indications for PTR for preservation of renal function outlined by the ACC/AHA remain reasonable. As per their guidelines, PTR is to be considered in patients with RAS and progressive chronic kidney disease with bilateral RAS or RAS to a solitary functioning kidney, particularly in those in whom there has been a rapid decline in renal function, without another clear cause, for the preceding 3 to 6 months (Hirsch et al, 2006).

There appears to be a “window of opportunity” defined by a serum creatinine level between 1.5 mg/dL and 3 mg/dL for most interventions to be successful. Waiting for advanced renal failure to develop diminishes the likelihood that renal function will improve after revascularization. Conversely, patients with near-normal renal function and well-controlled hypertension gain relatively little from intervention. As summarized by the authors of the CORAL trial, renal artery stenting appears not to confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in individuals with atherosclerotic RAS and hypertension or chronic kidney disease (Cooper et al, 2014).

Before undertaking revascularization for the preservation of renal function, an assessment of the likelihood of significant functional renal recovery should be assessed. In general, **improvement or stabilization of renal function is more likely to occur when the following guidelines are present (Novick et al, 1987):**

1. Visualization of the collecting system on an IVP or during the pyelogram phase of the angiogram
2. Kidney length greater than 9 cm
3. Evidence of collateral circulation filling the distal vasculature on the side of total renal artery occlusion during angiography
4. Demonstration of viable glomeruli on renal biopsy with minimal arteriolar glomerulosclerosis

Our approach to the treatment of hypertension and/or ischemic nephropathy is outlined in Figures 45-8 and 45-9.

KEY POINTS: ANGIOPLASTY AND STENTING FOR PRESERVATION OF RENAL FUNCTION

- Before the CORAL trial, most data in patients with ischemic nephropathy regarding improvement of renal function after angioplasty were limited by the absence of control groups and prospective randomization.
- The CORAL trial was a definitive, prospective, randomized control trial comparing medical therapy alone versus medical therapy with transluminal angioplasty with stenting, and it did not show any significant difference between the treatment groups in the rate of deterioration of renal function.
- There remains a subgroup of patients that may benefit from percutaneous transluminal angioplasty in addition to medical therapy (rather than medical therapy alone), because the CORAL trial did include some limitations.

Surgical Treatment of Renal Artery Stenosis

With the advent of ACE inhibitors, angiotensin receptor blockade, statins, and PTR, the need for surgical revascularization and reconstruction of the renal artery has diminished. As discussed previously in this chapter, the CORAL trial is likely to alter the need

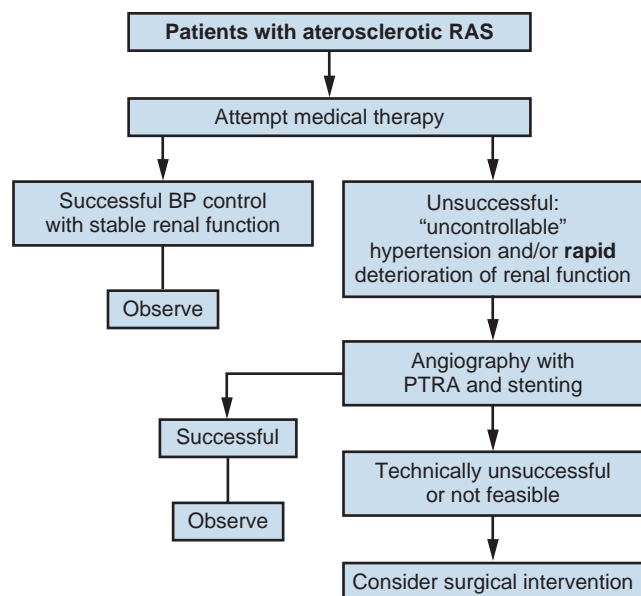


Figure 45-8. Algorithm for the management of patients with arteriosclerotic renal artery stenosis (RAS). BP, blood pressure; PTRA, percutaneous transluminal renal angioplasty.

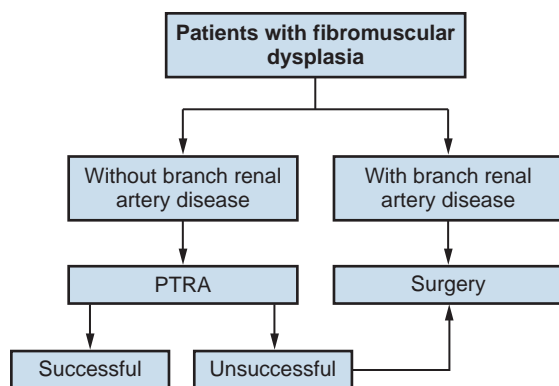


Figure 45-9. Algorithm for the management of patients with fibromuscular dysplasia. PTRA, percutaneous transluminal renal angioplasty.

for interventional treatment even further. However, an indication for surgical intervention in a select group of patients remains. Patients with RAS with concomitant aneurysmal or occlusive aortic disease, where surgery is indicated, would benefit from surgical intervention to correct both lesions if the aortic disease cannot be repaired without correcting the renal occlusive disease as well. Some surgeons may approach this by repairing the aortic disease with surgery and subsequently correct the renal artery lesion by PTRA when an indication for this intervention presents itself (Safian and Textor, 2001). Surgery is also indicated in patients who present with macroaneurysms of the renal artery associated with the stenosis because rupture of these lesions might occur if they are larger than 4 cm (Olin, 2007).

Because the CORAL trial recruited patients from primary physicians, it likely did not include patients who exhibited malignant/accelerated or uncontrollable hypertension, patients who did not tolerate medical therapy, or patients who showed rapid deterioration of renal function (1 to 6 months before presentation) with serum creatinines remaining between 1.5 and 3.0 mg/dL. These patients may well have been referred directly for an intervention. The intervention would have varied depending on the location of the lesion. PTRA would have been performed under most circumstances. However, if there was an ostial lesion greater than 10 mm,

the patient would likely have been referred for surgical revascularization. Therefore there remains a group of patients that will require surgical intervention.

KEY POINTS: SURGICAL TREATMENT OF RENAL ARTERY STENOSIS

- Although diminished, for specific patients the need for surgical revascularization of the renal artery remains.
- These patients include those with concomitant aneurysmal or occlusive aortic disease, those with macroaneurysms of the renal artery associated with stenosis, those with malignant or accelerated hypertension (with or without acute renal failure) who did not respond or cannot tolerate medical therapy, and those in whom transluminal angioplasty is technically impossible to accomplish.

The traditional criteria that will ensure the best outcome of surgical revascularization of a renal artery are (1) a kidney greater than 8 cm in length; (2) retrograde filling of the distal renal artery by collateral vessels on radiographic or scintigraphic imaging studies; (3) patency of the distal renal artery; (4) viability of the involved kidney on isotopic renography; and (5) minimal glomerular sclerosis and well-preserved tubules on renal biopsy (Garcia-Donaire and Alcazar, 2005).

Patients who require renovascular surgery often have comorbidities that make them a higher surgical risk. These comorbidities include angina (29.9%), previous myocardial infarction (27%), congestive heart failure (23.7%), cerebrovascular disease (24.8%), diabetes mellitus (18.1%), and claudication (56.4%) (Pohl, 1999). The morbidity of surgery can be diminished by the preoperative screening and correction of coronary and carotid arterial disease, excluding patients with severely diseased aortas. Aortorenal bypass is the preferred surgical technique in patients with atherosclerotic RVH when the abdominal aorta is not diseased. However, when the abdominal aorta has atherosclerotic plaques, alternative techniques for renal arterial bypass include splenorenal bypass for left renal arterial lesions, hepatorenal bypass for right arterial lesions, ileorenal bypass, bench surgery with autotransplantation of the involved renal unit, and the use of the supraceliac or lower thoracic aorta for the bypass as these are usually less involved by atherosclerotic disease. Some surgeons advocate performing unilateral revascularization in patients with bilateral disease to minimize patient operative morbidity (Pohl, 1999).

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The complete reference list is available online at www.expertconsult.com.

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Acute Kidney Injury

Acute Tubular Necrosis

Clinical Approach to the Differential Diagnosis of Acute Kidney Injury

Management of Acute Kidney Injury

Chronic Kidney Disease

Disorders of renal function are ubiquitous in the contemporary practice of medicine. Current estimates suggest that kidney disease affects approximately 10% to 13% of the adult American population (Coresh et al, 2007), and thus awareness of the diagnosis and management of this disease has been the focus of the National Kidney Foundation (NKF) and other health care organizations (www.kidney.org). In 2002 the NKF published the Kidney Disease Outcomes Quality Initiatives (K/DOQI) Guidelines setting up the framework for the definition, diagnosis, classification, and management of kidney disease (National Kidney Foundation, 2002). Although these guidelines have been recently updated (Khwaja, 2012; KDIGO Committee, 2013; Levin and Stevens, 2014), the 2002 K/DOQI guidelines broadly grouped kidney disease into two major categories: acute kidney injury (AKI) and chronic kidney disease (CKD). These conditions are common in clinical practice, so urologists are likely to encounter issues related to renal function and its aberration on a daily basis. This chapter is designed to give a contemporary insight into the nature of kidney disease and its treatment.

ACUTE KIDNEY INJURY

Definition

AKI is defined as a rapid reduction in renal function characterized by progressive azotemia (best measured clinically by serum creatinine and blood urea nitrogen [BUN]), which may or may not be accompanied by oliguria. This abrupt decline in renal function occurs during the course of hours to days and results in the accumulation of byproducts of metabolism and the dysregulation of volume, acid/base, and electrolyte homeostasis. AKI can be diagnosed with certainty when the patient's previous renal function is known and the reduction in renal function is documented. Practice guidelines proposed by Kidney Disease: Improving Global Outcomes (KDIGO) (Khwaja, 2012) defined AKI when one of the following criteria was met:

1. An increase in serum creatinine greater than or equal to 0.3 mg/dL within 48 hours
2. An increase in serum creatinine greater than or equal to 1.5 times baseline within the previous 7 days
3. Urine volume less than or equal to 0.5 mL/kg/hr for 6 hours

A new system has been proposed for the staging of AKI according to severity (Table 46-1).

The cardinal feature of AKI is a decline in glomerular filtration rate (GFR). Although ideally determined by inulin or radioisotopic clearance techniques, it is usually identified in routine clinical practice by a rise in BUN or creatinine. **It is important to understand the limitations of these common clinical chemistries so that they can be properly interpreted. The correlation among BUN, creatinine, and GFR assumes they are delivered into the serum at a constant rate. Therefore conditions such as hypercatabolic state**

and massive trauma, which may be seen in surgical patients, can affect renal functional assessment. BUN may be disproportionately elevated in states of marked volume contraction, hypercatabolic states, and with marked increases in protein loads seen with gastrointestinal bleeding or total parenteral nutrition (TPN). Serum creatinine (SCr) is a normal metabolite of muscle that is produced at a constant rate and is an endogenous marker that is used as a surrogate of GFR. In certain situations, serum creatinine may overestimate kidney function. This is explained by the fact that serum creatinine is not only filtered by the glomeruli but also secreted by the renal tubule. Moreover, in nonsteady-state circumstances, such as in patients with AKI, increases in serum creatinine levels may lag behind the actual event of renal injury. A normal or slightly low serum creatinine level in a small or malnourished patient may result in an underestimation of the level of renal impairment. Because of this, creatinine-based estimation equations in the setting of AKI may not perform well. Methods based on timed urine collections such as urinary creatinine clearance (CrCl) or measured tracers (inulin, iothalamate, and so forth) are cumbersome to perform, and they result in average values that span the test duration (Hoste et al, 2005; Levey et al, 2007). Some have advocated the use of "real-time" estimates of GFR using infused radioisotopic plasma disappearance techniques for patients with AKI in the intensive care unit (ICU), but this use has not achieved wide clinical acceptance. In clinical practice the experienced clinician infers that the patient's true GFR is significantly impaired based on a rapidly rising SCr and the clinical picture.

AKI is a common problem in the contemporary practice of medicine and urology. Prospective studies have demonstrated that 2% to 5% of all patients admitted to a general medical/surgical hospital unit will develop AKI (Nolan and Anderson, 1998). In selected patients in the ICU following cardiovascular or abdominal vascular surgery, the incidence may exceed 20%. AKI is associated with significant morbidity (which prolongs hospitalization and increases costs) and mortality (Dimick et al, 2003). The high occurrence and substantial morbidity and mortality of AKI demand a logical approach to its early recognition and prevention, as well as prompt diagnosis and management of its complications.

Epidemiology and Classification of Acute Kidney Injury

It is clinically useful to separate the causes of AKI into three major categories: prerenal, intrarenal, and postrenal. Distinguishing among the three basic categories of AKI is a challenging clinical exercise. Assigning a patient to one of the three categories usually requires a combination of clinical and laboratory evaluations and may require invasive monitoring of central hemodynamics or imaging studies of the genitourinary tract. The importance of differentiating the major causes of AKI must be stressed because the initial evaluation and management are tailored to the particular cause. Because the greatest proportion of hospital-acquired AKI is

TABLE 46-1 Proposed KDIGO Staging of Acute Kidney Injury

STAGE	SERUM CREATININE	URINE OUTPUT
1	1.5–1.9 × baseline or ≥0.3 mg/dL (≥26.5 μmol/L) increase	<0.5 mL/kg/hr for 6–12 hr
2	2.0–2.9 × baseline	<0.5 mL/kg/hr for ≥12 hr
3	3 × baseline or ≥4.0 mg/dL (≥353.6 μmol/L) increase or initiation of RRT or in patients <18 yr a decrease in eGFR <35 mL/min/1.73 m ²	<0.3 mL/kg/hr for ≥24 hr or Anuria ≥12 hr

eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy.

From Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. *Nephron Clin Pract* 2012;120(4):c179–84.

secondary to acute tubular necrosis (ATN), this chapter places special emphasis on the diagnosis, pathophysiology, and management of ATN. For example, an evaluation in Madrid reported 748 cases of AKI at 13 tertiary care hospital centers (Liano and Pascual, 1996). The causes of AKI were: 45% ATN, 21% prerenal, 13% acute or chronic kidney failure, 10% urinary tract obstruction, 4% glomerulonephritis/vasculitis, 2% acute interstitial nephritis (AIN), and 1% atheroembolic renal disease. AKI occurs more commonly in the surgical/trauma ICUs, medical ICUs, and postoperative units. A study by the American College of Surgeons National Surgical Quality Improvement Program has identified 11 independent preoperative predictors for the development of AKI including age 56 years or older, male gender, emergency surgery, intraperitoneal surgery, diabetes mellitus necessitating oral therapy, diabetes mellitus necessitating insulin therapy, active congestive heart failure, ascites, hypertension, mild preoperative renal insufficiency, and moderate preoperative renal insufficiency (Kheterpal et al, 2009).

Prerenal Azotemia

Prerenal azotemia is caused by transient renal hypoperfusion that may induce a fall in GFR and produce urinary sodium avidity. The hallmark of prerenal azotemia is its reversibility with treatment of the underlying cause and the lack of structural damage to the kidney. The “gold standard” is the response to appropriate fluid repletion or rapid reestablishment of normal renal hemodynamics, which will lead to the return of renal function to the previous baseline within 24 to 72 hours.

In normal circumstances, the kidney can maintain normal renal blood flow (RBF) and GFR down to systemic perfusion pressures of approximately 55 to 60 mm Hg (Walsh et al, 2013). The phenomenon of autoregulation consists of the intricate interplay of glomerulotubular feedback and myogenic response in afferent arterioles. In patients with CKD, hypertension, diabetes, and/or AKI, autoregulation is often compromised. In these circumstances, a reduction in GFR may occur with modest decrease in systemic pressure within what is otherwise considered normal range. In the setting of decreased renal perfusion, angiotensin II and vasodilatory prostaglandins play an important role in maintaining glomerular hydrostatic pressure and GFR. The three major determinants of GFR are renal plasma flow, glomerular hydrostatic pressure, and

BOX 46-1 Prerenal Causes of Acute Kidney Injury

VOLUME DEPLETION

Surgical: hemorrhage, shock
Gastrointestinal losses: vomiting, diarrhea, fistulae
Renal: overdiuresis, salt-wasting disorders

CARDIAC CAUSES: PRIMARY DECREASE IN CARDIAC OUTPUT

Acute disorders: myocardial infarction, arrhythmias, malignant hypertension, tamponade, endocarditis
Chronic disorders: valvular diseases, chronic cardiomyopathy (ischemic heart disease, hypertensive heart disease)

REDISTRIBUTION OF EXTRACELLULAR FLUID

Hypoalbuminemic states: nephrotic syndrome, advanced liver disease, malnutrition
Physical causes: peritonitis, burns, crush injury
Peripheral vasodilatation: sepsis, antihypertensive agents
Renal artery stenosis (bilateral)

glomerular permeability. Angiotensin II has selectively greater vasoconstrictor effects on the efferent than the afferent arteriole, whereas vasodilatory prostaglandins can cause afferent arteriolar vasodilation. **Drugs that selectively block angiotensin II synthesis, angiotensin-converting enzyme inhibitors (ACE inhibitors), and angiotensin receptor blockers (ARBs), or that inhibit vasodilatory prostaglandin synthesis such as nonsteroidal anti-inflammatory drugs (NSAIDs) (Whelton, 1999), may cause AKI.** This is prone to occur in clinical settings when GFR is already compromised (Toto et al, 1991; Whelton, 1999).

Prerenal azotemia may be encountered in both the volume-depleted and volume-overloaded patient (Box 46-1). True volume depletion may result from renal or extrarenal losses that result in systemic hypotension and renal hypoperfusion. In the volume-overloaded patient, with edematous states such as cirrhosis and congestive heart failure, prerenal azotemia may occur because the kidney perceives that the vascular system is underfilled (i.e., “ineffective arterial blood volume”). This results in renal hypoperfusion. Prerenal azotemia may also occur because of high-grade bilateral renal artery stenosis (RAS) or in states of renal hypoperfusion resulting from redistribution of extracellular fluid with peripheral vasodilation as seen with sepsis. As noted earlier, ACE inhibitors, ARBs, and NSAIDs may alter the vasoconstrictor effects of angiotensin II and the vasodilatory effects of prostaglandins to produce prerenal azotemia. This is especially the case in elderly patients with impaired GFR, subtle volume depletion, or occult RAS.

The pathophysiology of prerenal azotemia relates to the reduction in RBF. Renal hypoperfusion stimulates both the sympathetic nervous system (SNS) and renin-angiotensin system to cause renal vasoconstriction and sodium avidity. Furthermore, hypotension is a powerful stimulus to the release of an antidiuretic hormone, which mediates water reabsorption. Hence urine production is characterized by low volume, decreased concentration of urinary sodium, increased urinary excretion of creatinine, and a high urine osmolality. Microscopy of the urinary sediment is usually bland. In this setting, there is usually minimal, if any, evidence of parenchymal injury. **Therapy for prerenal azotemia is directed at optimizing volume status with isotonic fluids. In patients with the edematous disorders who have prerenal azotemia, special efforts are directed toward treating the underlying disease states (i.e., heart failure, cirrhosis) and optimizing systemic hemodynamics and renal perfusion.**

The hepatorenal syndrome (HRS) represents a unique, severe form of prerenal azotemia. HRS refers to the development of AKI in the patient with advanced hepatic disease, often resulting from

cirrhosis but also seen with metastatic tumor or alcoholic hepatitis. The reduction in renal perfusion appears to relate to a relative splanchnic vasodilatation that may be mediated via nitric oxide (NO), which is the endothelium-derived relaxing factor (Martin et al, 1998; Gines and Arroyo, 1999). HRS is characterized by oliguria, a benign urinalysis, urinary sodium avidity, and a progressive rise in serum creatinine (Cardenas, 2005). HRS is a prerenal disease because the kidneys are normal histologically and have been successfully used in renal transplantation (Koppel et al, 1969). The diagnosis is one of exclusion; after ATN, acute glomerulonephritis (AGN), vasculitis, or correctable forms of reduced renal perfusion have been excluded. Thus the diagnosis of HRS requires a lack of improvement in renal function following discontinuation of potential nephrotoxins and a trial of fluid repletion. The best hope for reversal of HRS is an improvement in hepatic function or a successful liver transplantation (Gonwa et al, 1991; Cardenas, 2005); however, not all cases of HRS will resolve with this approach (Pham et al, 2005). The use of simultaneous liver-kidney transplantation is evolving (Nadim et al, 2012). It is difficult to predict the cases of HRS that will regain renal function spontaneously with liver transplant alone versus those that exhibit irreversible renal injury and would also benefit from a kidney transplant. Protracted HRS may lead to irreversible loss of kidney function. Combination therapy with midodrine (a selective α_1 -adrenergic agonist) and octreotide (a somatostatin analogue) has been shown in a few small clinical trials to improve renal function and short-term survival (Angeli et al, 1999; Esrailian et al, 2007; Skagen et al, 2009). Terlipressin, a vasopressin analogue available in Europe, improves renal function in HRS; however, evidence regarding mortality is equivocal (Gluud et al, 2012). Nevertheless, the overall impact of medical therapy for HRS has been minimal and the outlook for HRS without liver transplantation appears bleak. The role of hemodialysis (HD) support appears to be limited to those HRS patients awaiting liver transplantation or resolution of their primary hepatic disease, because survival is generally limited by the severity of liver failure. HD is often difficult in HRS because of hemodynamic instability.

Postrenal Azotemia

Obstruction of the urinary tract may cause AKI. To be the cause of AKI, urinary tract obstruction must involve the outflow tract of both kidneys, unless preexisting renal dysfunction is present, in which case the obstruction may involve only a single kidney. Patients with acute urinary tract obstruction may present with hematuria, flank or abdominal pain, or signs of uremia. A high index of suspicion for urinary tract obstruction should exist for patients with previous abdominal or pelvic surgery, neoplasia, or radiation therapy. Although oligoanuria suggests complete obstruction, partial obstruction may exist in the presence of adequate urinary output. Oligoanuria is a powerful diagnostic clue that suggests a differential diagnosis of urinary tract obstruction, severe ATN with cortical necrosis, or bilateral vascular occlusion. Lesions that may cause obstruction can be either intrinsic or extrinsic to the genitourinary tract. If urinary tract obstruction is a diagnostic consideration, renal ultrasonography is sensitive and specific (90% to 95%) in confirming the diagnosis of hydronephrosis. This test may be operator dependent, so the experience of the radiologist is crucial. False-negative tests may be seen with periureteral metastatic disease or retroperitoneal fibrosis (Somerville et al, 1992). Renal radionuclide studies or retrograde pyelography may be helpful in this circumstance. If urinary tract obstruction is a diagnostic consideration, renal ultrasonography should be performed because obstruction represents a potentially reversible cause of AKI.

Although urologists are familiar with the various primary pathologies responsible for obstruction, iatrogenic causes should additionally be considered. Any drainage device such as a urethral catheter or ureteral stent should be assessed for patency. Hemorrhage and lymphocele are uncommon sequelae of surgery, but they can result in AKI by causing extrinsic compression. Urinary extravasation or fistula formation is a complication of urinary tract reconstruction or injury. This can cause a rise in the

BUN and serum creatinine as a result of reabsorption but preservation of actual GFR. Diagnosis of urinary extravasation requires analysis of fluid from the area near the reconstructed site. The drain creatinine is compared with the serum creatinine levels. Ratios of 10:1 are virtually diagnostic for extravasation; however, smaller ratios may be observed when the urine has been diluted by other serous fluids. Other ways to confirm urinary extravasation are by intravenous administration of a vital dye excreted by the kidneys (such as indigo carmine or methylene blue) or radiographic demonstration of a fistula (isotope renography, retrograde pyelogram, cystogram, computed tomography [CT]). This type of AKI resolves with drainage of the urinoma and definitive treatment of the urinary fistula. The reader is referred to other chapters in this text for more in-depth review of obstructive uropathy.

Intrinsic Renal Disease

The major causes of AKI resulting from intrinsic renal disease include AGN, AIN, and ATN. Because ATN is the most common cause of AKI in the hospitalized patient, special emphasis will be given to ATN.

Acute Glomerulonephritis

The presence of proteinuria, hematuria, and red blood cell (RBC) casts is highly suggestive of glomerulonephritis. The importance of the urinalysis in the evaluation of patients with AKI cannot be overemphasized, and the physician must develop skill and expertise in interpreting the microscopic findings. Such skills are critical in the recognition of AGN as the cause of AKI, because the diagnosis of AGN has a tremendous impact on disease management.

The combination of AGN (based on urinalysis findings) and a rapid loss of kidney function define the clinical syndrome of rapidly progressive glomerulonephritis (RPGN). The differential diagnosis and management of RPGN are beyond the scope of this chapter (Little and Pusey, 2004). A simplified differential diagnosis of RPGN is summarized in Box 46-2. It is crucial to appreciate the impact that urinary microscopic findings of AGN have on the aggressive evaluation and management of patients with this type of AKI. This usually includes a renal biopsy and detailed serologic evaluation for the presence of systemic vasculitis, collagen vascular disease, and an infectious process. RPGN comprises a group of glomerulonephritides that progress to renal failure in a matter of days to months in the presence of extensive extracapillary proliferation (i.e., crescent formation in a large percent of glomeruli). Patients with RPGN have been divided into three patterns defined by their immunologic pathogenesis: (1) type I: anti-glomerular basement membrane (anti-GBM) (e.g., Goodpasture); (2) type II: immune complex deposition disease (e.g., systemic lupus erythematosus [SLE], poststreptococcal glomerulonephritis); and (3) type III: pauci-immune (e.g., antineutrophil cytoplasmic autoantibody [ANCA]-positive disease such as granulomatosis with polyangiitis disease, formerly known as Wegener granulomatosis). Patients are categorized based on the results of the immunofluorescence of the renal biopsies and results of serologic testing for anti-GBM titer, ANCA, lupus serologies, and so on. Specific therapies (including parenteral steroids, cyclophosphamide or other cytotoxics, and possibly plasma exchange) tailored to the disease entity diagnosed may be lifesaving. Hence early recognition of RPGN based on urinalysis findings is critical.

Acute Interstitial Nephritis

The diagnosis of AKI secondary to AIN may be suggested by the urinalysis findings of sterile pyuria, white blood cell casts, and eosinophiluria (using Hansel stain) (Michel and Kelly, 1998). AIN is most often induced by drug therapy, although sarcoidosis, streptococcal, viral, or *Legionella* infections may also be responsible. The list of offending drugs associated with AIN is extensive, but the most

BOX 46-2 Differential Diagnosis of Rapidly Progressive Glomerulonephritis**MULTISYSTEM DISEASES**

Systemic lupus erythematosus
 Goodpasture disease
 Henoch-Schönlein purpura
 Necrotizing vasculitis (including Wegener granulomatosis)
 Cryoglobulinemia (hepatitis B or C related)
 Neoplasia (colon, lung)
 Relapsing polychondritis
 Behçet syndrome

SUPERIMPOSED ON PRIMARY GLOMERULAR DISEASE

Membranoproliferative glomerulonephritis (type I, II)
 Membranous glomerulonephritis
 IgA nephropathy

INFECTIOUS DISEASES

Poststreptococcal glomerulonephritis
 Infectious endocarditis
 Visceral sepsis
 Hepatitis B or hepatitis C infection

DRUGS AND TOXIC AGENTS

Allopurinol
 D-Penicillamine
 Hydralazine
 Rifampin

IDIOPATHIC

Type I: antiglomerular basement membrane antibody disease
 Type II: immune complex-mediated disease
 Type III: pauci-immune (ANCA positive)

ANCA, antineutrophil cytoplasmic antibody.

BOX 46-3 Drugs That Most Commonly Cause Acute Interstitial Nephritis

Nonsteroidal anti-inflammatory drugs (particularly fenoprofen)
 Penicillins and cephalosporins
 Rifampin
 Sulfonamides (furosemide, bumetanide, thiazide-type diuretics, and trimethoprim-sulfamethoxazole)
 Cimetidine, omeprazole
 Allopurinol
 Ciprofloxacin and perhaps other quinolones
 5-Aminosaliculates

common causes of AIN include those identified in [Box 46-3](#). The major histologic changes are interstitial edema and marked interstitial infiltrate of T lymphocytes and monocytes ([Laberke and Bohle, 1980](#)). Eosinophilic plasma cells and polymorphonuclear cells may also be detected. Granulomata formation, in the past thought to be particular to the renal disease of sarcoidosis, can occur in any form of AIN.

The clinical presentation, although variable, usually involves abnormal urine sediment (described earlier), fever, and a rising serum creatinine associated with the administration of the offending drug ([Nolan et al, 1986](#)). Skin rash is seen in about 25% of

cases. Eosinophilia and eosinophiluria is present in more than 75% of cases, with the exception of AIN resulting from NSAIDs, where fever, rash, and eosinophilia are typically absent. Proteinuria with most drugs is usually modest with less than 0.5 to 1 g/day. Proteinuria in the nephrotic range has been frequently seen with AIN of NSAIDs (especially fenoprofen) and in selected cases with ampicillin, rifampin, ranitidine, and interferon. It is speculated that increased glomerular capillary permeability is related to cytokine release of the infiltrating T cells ([Neilson, 1989](#)). The development of AIN is not dose dependent, and recurrence can occur with second exposures to the same or a related drug. The onset of AIN might occur from 3 to 5 days (especially second exposures) to several weeks after drug therapy.

The diagnosis is usually suspected in the AKI patient with characteristic urinary sediment abnormalities and a history of an offending drug therapy. Although the clinical picture may be highly suggestive of AIN, the diagnosis is confirmed only by renal biopsy. In a case series of patients with clinical diagnosis of AIN who had native kidney biopsies performed, urine eosinophils did not distinguish AIN from other causes of kidney disease such as ATN ([Muriithi et al, 2013](#)). When suspected, most clinicians will observe the response to withdrawing the offending agent with the expectation that renal function will begin to improve within 3 to 7 days ([Baker and Pusey, 2004](#)). No further evaluation or therapy is required if renal function improves. Lack of response, severe AKI, or uncertainty of diagnosis may be indications to proceed with a renal biopsy. There are no controlled clinical trials evaluating the efficacy of immunosuppressive therapy. There is some experimental and suggestive clinical evidence that steroid and/or cytotoxic therapy may be beneficial to hasten recovery of renal function and to reduce interstitial fibrosis.

ACUTE TUBULAR NECROSIS**Incidence and Etiology**

Overall, AKI may affect 2% to 7% of patients in a tertiary care hospital, and the incidence of AKI in the surgical or medical ICU may exceed 25% to 35%. The majority of all hospital-acquired AKI is secondary to ATN ([Myers and Moran, 1986](#); [Uchino et al, 2005](#)). Renal hypoperfusion and renal ischemia are the most common causes of ATN, although nephrotoxic insults from various agents are being recognized with increasing frequency. A detailed listing of both exogenous and endogenous nephrotoxic compounds is summarized in [Boxes 46-4](#) and [46-5](#).

Pigment Nephropathy/Rhabdomyolysis

Pigment nephropathy resulting from hemoglobin or myoglobin may be suspected in the appropriate clinical situation (post-traumatic or atraumatic after intoxications). In hemoglobinuria, there is a discrepancy between the finding of hematuria by dipstick and the absence of RBCs on urinary microscopy. In muscle breakdown caused by toxicity, trauma, surgical injury, or surgical positioning, the creatine phosphokinase (CPK) in blood is usually elevated and can be diagnostic for rhabdomyolysis. The combination of renal hypoperfusion and the nephrotoxic insult of myoglobin or hemoglobin within the proximal tubule can result in ATN.

In urology, two specific clinical circumstances have been identified in association with rhabdomyolysis. The first is protracted exaggerated lithotomy positioning, as used in urethral stricture surgery ([Anema et al, 2000](#); [Vijay et al, 2011](#)). Muscle groups of the buttocks (gluteals) are often affected. Significant rhabdomyolysis requiring gluteal fasciotomies has also been reported with robotic-assisted radical prostatectomy using lithotomy positioning ([Keene et al, 2010](#)). Long exposure to lithotomy positioning, greater than 5 hours, is the greatest risk factor. Attention to padding, positioning, and any maneuver that can reduce the duration of exaggerated positioning will help prevent this complication. The second situation is following laparoscopic donor

BOX 46-4 Causes of Exogenous Toxic Acute Kidney Injury**ANTIBIOTICS**

Aminoglycosides
Cephalosporins
Sulfonamide, cotrimoxazole
Tetracyclines
Amphotericin B
Polymyxin, colistin
Bacitracin
Pentamidine
Vancomycin
Acyclovir
Foscarnet

ANESTHETIC AGENTS

Methoxyflurane
Enflurane

CONTRAST MEDIA

Diatrizoate
Iothalamate
Bunamiodyl
Iopanoic acid

ANTIULCER REGIMENS

Cimetidine
Excess of milk-alkali

DIURETICS

Mercurials
Ticrynafen

CHEMOTHERAPEUTIC AND IMMUNOSUPPRESSIVE AGENTS

Cisplatin
Carboplatin
Ifosfamide
Methotrexate
Nitrosourea
Plicamycin
Cyclosporine A
Tacrolimus
D-Penicillamine
Recombinant IL-2
Interferon

ANALGESICS

Nonsteroidal anti-inflammatory drugs

HIV PROTEASE INHIBITORS

Indinavir
Ritonavir

ORGANIC SOLVENTS

Glycols (ethylene glycol, diethylene glycol)
Halogenated hydrocarbons (CCl₄, tetra- and trichloroethylene)
Aromatic hydrocarbons (toluene)
Aliphatic-aromatic hydrocarbons
5-Azacytidine (petroleum jelly, kerosene, turpentine, paraphenylene diamine)

HEAVY METALS AND POISONS

Insecticides (chlordane)
Herbicides (paraquat, diquat)
Rodenticide (elemental P)
Mushroom
Snake bites*
Stings*
Bacterial toxins*

CHEMICALS*

Aniline
Hexol
Cresol
Chlorates
Potassium bromate

RECREATIONAL DRUGS†

Heroin
Amphetamine

MISCELLANEOUS

Dextrans
Ethylenediaminetetraacetic acid (EDTA)
Radiation
Silicone
Epsilon-aminocaproic acid*
Angiotensin-converting enzyme inhibitors
Oral sodium phosphate bowel purgative
Hydroxyethyl starch solutions

*Direct toxicity or indirect systemic effects (shock, intravascular hemolysis, or coagulation).

†Slow onset of renal failure unless associated with rhabdomyolysis.

HIV, human immunodeficiency virus.

From Nally JV. Acute renal failure. In: Stoller JK, Ahmed M, Longworth DL, editors. The Cleveland Clinic intensive review of internal medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 568.

nephrectomy (Kuang et al, 2002; Troppmann and Perez, 2003; Reisiger et al, 2005; Deane et al, 2008) or laparoscopic nephrectomy (Glassman et al, 2007). The etiology in this circumstance has been ascribed to ischemia in the downside iliopsoas from prolonged lateral decubitus positioning. Identified risk factors include prolonged surgical time and high body mass index (Glassman et al, 2007). The clinical clues to rhabdomyolysis in the urologic setting relate to unusually severe muscle pain early in the postoperative setting combined with tea-colored urine. Patients may report downside low back pain for nephrectomy and buttock pain for lithotomy cases. Clinical suspicion is the most important feature for recognizing the diagnosis because the

condition is very uncommon. Rhabdomyolysis can be confirmed by an extremely elevated blood CPK. Early recognition of this disorder is crucial because a forced alkaline diuresis is indicated to minimize nephrotoxicity. Nonetheless, patients may require dialysis support and there is a possibility of nonrecovery of renal function.

Intrinsic/Extrinsic Toxic-Related Acute Tubular Necrosis

Similarly, the tumor lysis syndrome might be suspected in the appropriate clinical setting, when marked hyperuricemia/hyperuricosuria and crystalluria are recognized. A forced alkaline

BOX 46-5 Acute Kidney Injury Related to Endogenous Nephrotoxic Products**PIGMENT NEPHROPATHY**

Myoglobin
Hemoglobin*
Methemoglobin*

INTRARENAL CRYSTAL DEPOSITION

Uric acid
Calcium
Oxalate

TUMOR-SPECIFIC SYNDROMES

Tumor lysis syndrome
Plasma cell dyscrasias (e.g., myeloma kidney)

*Questionable direct nephrotoxic effect.

From Nally JV. Acute renal failure. In: Stoller JK, Ahmed M, Longworth DL, editors. *The Cleveland Clinic intensive review of internal medicine*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 567.

diuresis may limit nephrotoxicity and is usually recommended prophylactically before an aggressive chemotherapy regimen.

The list of potential exogenous nephrotoxic agents is exhaustive (see Box 46-4). Simply stated, for a patient who develops ATN while receiving medications, each medication should be reviewed for the possibility of nephrotoxicity. The most commonly seen nephrotoxins in the hospitalized patient include radiographic contrast material, antibiotics (especially aminoglycosides and amphotericin B), chemotherapeutic agents, NSAIDs, and ACE-inhibitor drugs.

In the contemporary practice of hospital-based medicine, recognition of AKI in human immunodeficiency virus (HIV) patients deserves special comment. Patients with HIV infection may develop AKI as a result of the same causes as uninfected patients, but protease inhibitors have been associated with the development of AKI (Izzedine et al, 2009). Ritonavir and indinavir (as well as acyclovir, foscarnet, and sulfadiazine) have been associated with reversible AKI previously thought secondary to crystalluria and intrarenal obstruction (Olyaei et al, 2000). Historically, patients treated with indinavir developed renal colic because indinavir renal stones can be associated with urinary tract obstruction (Kohan et al, 1999). This drug is now infrequently used in contemporary practice. Newer antiretroviral agents may be toxic to the kidney, and newer forms of AKI related to AIN have been described (Izzedine et al, 2009).

Natural History

The oliguric phase usually begins less than 24 hours after the inciting incident and may last for 1 to 3 weeks. Urine volume averages 150 to 300 mL/day. The oliguric phase may be prolonged in the elderly. During this phase, the clinician must be alert for the expected complications, with special emphasis on metabolic consequences, gastrointestinal bleeding, and infection.

The diuretic phase is characterized by a progressive increase in urine volume, which is a harbinger of renal recovery. However, the SCr may continue to rise for another 24 to 48 hours before it reaches a plateau and falls. Severe polyuria during this phase is currently seen less frequently. Careful management during this phase is crucial because up to 25% of deaths with AKI may occur during this phase, usually related to fluid and electrolyte abnormalities as well as infection. Finally, the recovery phase ensues. Renal function returns to near baseline, but abnormalities of urinary concentration and dilution may persist for weeks or months.

Pathophysiology

Knowledge of the basic processes involved in the development of ATN is important to understanding contemporary therapies directed at limiting renal damage and promoting more rapid renal recovery (Fig. 46-1). In hospital practice, ischemic ATN is the most commonly encountered form of the disease. Therefore the following discussion focuses on ischemic renal injury.

A variety of biochemical changes occur during ischemia and reperfusion, and these changes are responsible for the cell dysfunction observed in ATN (Myers et al, 1984; Myers and Moran, 1986). Deranged microcirculation and amplified vasoconstriction are early manifestations following hemodynamic alterations, which are shortly followed by inflammatory response (Bonventre and Yang, 2011). The sentinel biochemical event in renal ischemia, however, is the depletion of adenosine triphosphate (ATP), which is the major energy currency for cellular work. ATP is metabolized to adenosine monophosphate (AMP). During prolonged oxygen deprivation, AMP is further metabolized to the nucleosides adenosine, inosine, and hypoxanthine. These compounds diffuse from the cell, resulting in the loss of the substrate reservoir for ATP synthesis after reperfusion (Sharfuddin and Molitoris, 2011). Furthermore, hypoxanthine becomes an important substrate in the development of oxygen free radicals during the reperfusion period. Provision of exogenous adenine and inosine decreases cellular injury in experimental renal ischemia (Siegel et al, 1980).

ATP depletion results in impaired function of the plasma membrane and intracellular ATPases that are vital to normal cell function. As a consequence of impairment of the Na⁺/K⁺-ATPase, cytosolic concentrations of Na⁺ and K⁺ are altered and cell swelling results (Alejandro et al, 1995). Dysfunction of the plasma membrane Na⁺/Ca²⁺-ATPase and intracellular Ca²⁺-ATPase leads to high intracellular levels of Ca²⁺. The increase in intracellular Ca²⁺ has been associated with multiple aspects of renal cell injury including disruption of the cytoskeleton, activation of Ca²⁺-dependent phospholipases, acceleration of the conversion of xanthine dehydrogenase to xanthine oxidase (potentiating reperfusion injury), and uncoupling oxidative phosphorylation. The activation of phospholipases results in damage to the lipid bilayer, which is critical to the normal function of the plasma membrane and intracellular organelles such as mitochondria. Phospholipase activation leads to an accumulation of free fatty acids and lysophospholipids, which are detrimental to vital cellular function, although the mechanism of such action is not clear.

Oxidative stress during reperfusion after ischemia is associated with cellular damage. Recall that ATP is metabolized to hypoxanthine. High levels of intracellular Ca²⁺ activate a calmodulin-dependent protease that converts xanthine dehydrogenase to xanthine oxidase. The conversion of hypoxanthine to xanthine during reperfusion is the major source of superoxide. This is ultimately metabolized to OH⁻, which causes cell damage. Finally, the protease calpain is activated and contributes to ischemic renal injury (Edelstein et al, 1997). Calpain regulates membrane channels, kinase activation, and interactions between cytoskeletal proteins.

As the name suggests, ischemic ATN is characterized by renal tubular cell injury. This may be sublethal or lethal. Because obvious necrosis is not a cardinal histopathologic finding in ATN (Racusen et al, 1991), sublethal injury is important. During normal function of the kidney, the medulla operates at the brink of hypoxia because of the countercurrent diffusion of oxygen from the descending to ascending vasa rectae. During prolonged ischemia, medullary hypoxia intensifies and the high metabolic requirement of the nephron structures located in the outer medulla is most sensitive to injury. The S3 portion of the proximal tubule sustains the most severe injury (Witzgall et al, 1994). Other structures that sustain injury in this region include the medullary thick ascending limb (mTAL), which is metabolically active and rich in the energy that requires Na⁺/K⁺-ATPase.

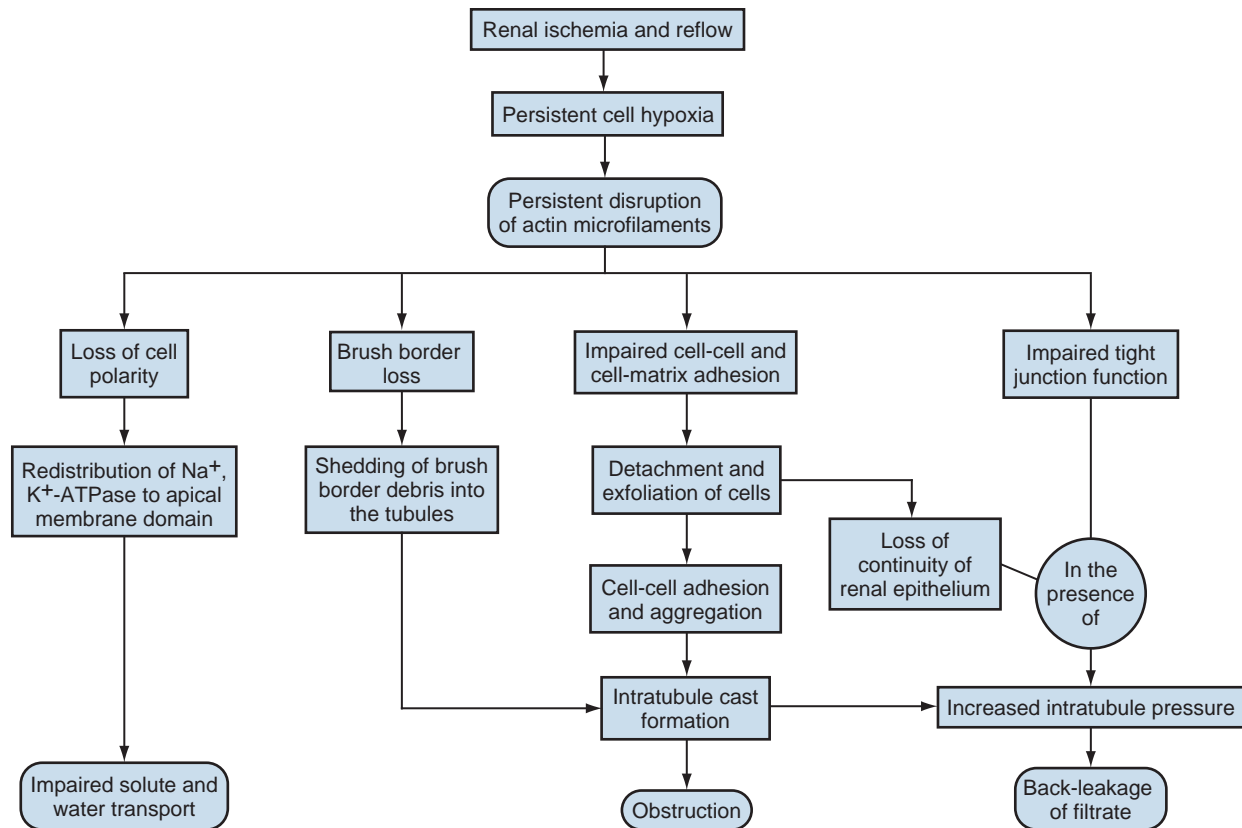


Figure 46-1. Pathophysiology of ischemic acute renal failure. The profound reduction in glomerular filtration rate associated with renal ischemia is a result of a combination of intrarenal hemodynamic alterations and tubular epithelial injury leading to tubular obstruction and back-leakage of glomerular ultrafiltrate. ATPase, adenosine triphosphatase. (From Brady HR, Brenner BM, Lieberthal W. Acute renal failure. In: Brenner BM, editor. *Brenner & Rector's the kidney*. Philadelphia: Saunders; 1996. p. 1200–52.)

Sublethal injury to tubular cells leads to aberrations in the cytoskeletal organization of the tubule cells (Molitoris, 1991; Sharfuddin and Molitoris, 2011). This is manifested as a loss in the cell polarity. The brush border disappears, and there is redistribution of the basolateral Na^+/K^+ -ATPase and integrins (Lieberthal, 1998). As a result, the normal unidirectional transport of salt and water across tubular cells is disrupted, and the ability of the renal epithelium to act as a barrier to the free movement of solute and water is lost. The loss of the tight junctions permits backleak of glomerular filtrate, which has been one of the well-established pathophysiologic features of ATN (see Fig. 46-1). In addition to the loss of tight junctions, there is a loss in cell-matrix adhesion (Gailit and Clark, 1993). The redistribution of the integrins disrupts the normal cell adherence to the tubular basement membrane. As a result, abnormal cell-cell adherence develops and contributes to tubular obstruction.

Following sublethal injury, the kidney has a remarkable capacity for repair of normal structure and function. The study of renal recovery from ATN is a relatively new concept with great potential for clinical application. Increased mitotic activity and epithelial regeneration are notable features of ATN (Thadhani et al, 1996). Certain aspects of renal recovery duplicate events in renal development (Witzgall et al, 1994). A number of growth factors play a role in recovery. Epidermal growth factor, insulin-like growth factor-1 (IGF-1), and hepatocyte growth factor have been demonstrated to limit renal injury and accelerate renal recovery in experimental ischemic ATN (Thadhani et al, 1996).

In ischemic ATN, RBF is reduced by 50% or more, and the perfusion defect is most marked in the outer medulla. The two predominant reasons for this include vasoconstriction and congestion of the medullary vasculature by leukocytes, red cells, and platelets.

Ischemic renal injury is marked by intrarenal vasoconstriction as a result of endothelial cell injury. Vasoconstriction results from the imbalance between endothelin (ET) and endothelial-derived nitric oxide (EDNO) (Lieberthal, 1998). ET receptor blockers have been shown to ameliorate ischemic renal damage and improve renal function (Lieberthal, 1998). The endothelial injury sustained in ATN also leads to decreased production of EDNO by constitutive NO synthase. The decreased EDNO leads directly to vasoconstriction but also permits increased ET production (Lieberthal, 1998).

The persistent hemodynamic abnormalities in ATN are also maintained by congestion of the medullary vasculature. Current evidence suggests that ischemic injury results in the release of inflammatory mediators that activate adhesion molecules on leukocytes and upregulates their receptors on the endothelium (Sharfuddin and Molitoris, 2011). Antibodies directed at leukocyte adhesion molecules or their endothelial ligands (i.e., intercellular adhesion molecule-1 [ICAM-1]) ameliorate ischemic renal injury (Kelly et al, 1996; Dragun and Haller, 1999). Neutrophils play an important part in the injury cascade. In models where the effects of neutrophils are eliminated by delivering antibodies to certain chemokines, injury is ameliorated (Miura et al, 2001). Interestingly, the tubular epithelium plays an active role in this inflammatory response by generating chemokines that potentiate recruitment of inflammatory cells (Bonventre and Zuk, 2004). These include monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), RANTES (regulated-on activation, normal T cells expressed and secreted), and epithelial neutrophil-activating protein 78. In addition to the role of neutrophils, there is evolving evidence that lymphocytes are important in the ischemia/reperfusion injury paradigm. Knockout mice lacking $\text{CD4}^+/\text{CD8}^+$ cell adhesion receptors

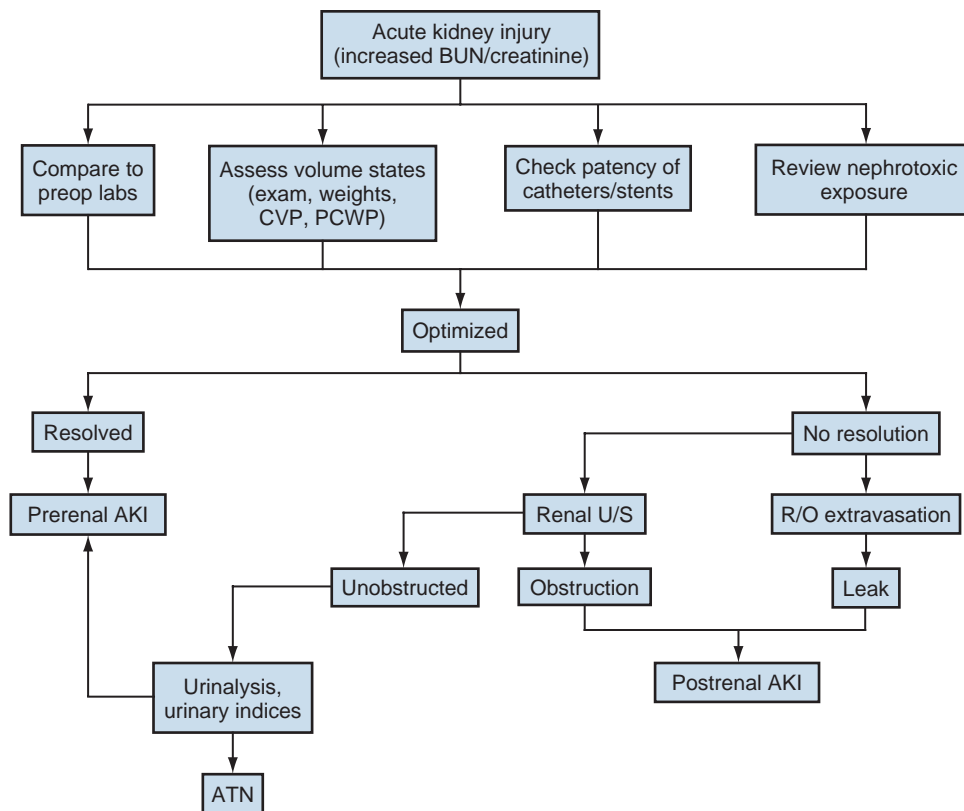


Figure 46-2. Algorithm for the differential diagnosis of acute renal failure. See text for details. AKI, acute kidney injury; ATN, acute tubular necrosis; BUN, blood urea nitrogen; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; R/O, rule out; U/S, ultrasonography. (Modified from Goldfarb DA, O'Hara JF. Etiology, pathogenesis, and management of preoperative acute renal failure. AUA Update Series. 2001;20:lesson 4. p. 26–31.)

on T lymphocytes are protected from ischemic injury (Rabb et al, 2000). Also, costimulatory blockade can ameliorate ischemic injury (Takada et al, 1997). Newer agents are being developed to handle the early inflammatory events in renal ischemia, which may bear practical application, particularly in the setting of renal transplantation.

CLINICAL APPROACH TO THE DIFFERENTIAL DIAGNOSIS OF ACUTE KIDNEY INJURY

General

Distinguishing among prerenal, intrinsic renal, and postrenal causes of AKI may prove to be a challenging clinical exercise (Fig. 46-2). A thorough history and physical examination to assess volume status, cardiovascular hemodynamics, potential nephrotoxic insults, and evidence of systemic disease should be undertaken in AKI patients. All interventions and drug therapies surrounding an AKI event should be outlined against the timeline of changes in renal function. Electronic medical records can now help facilitate this task (Goldstein et al, 2013). It is also critical to know the level of preexisting renal function. One should identify the presence of risk factors known to be associated with AKI such as advanced age; comorbid conditions (heart failure, liver failure, renal insufficiency, diabetes); radiocontrast exposure; therapy with aminoglycoside antibiotics, NSAIDs, or ACE inhibitors; and atheroembolism. In perioperative AKI, the nature and magnitude of the procedure (open vs. endoscopic), blood loss, hemodynamic stability, integrity of the urinary tract, and intraoperative drug treatment are critical intraoperative issues to identify.

On examination, the vital signs and hemodynamic parameters should be critically assessed. Hypotension, particularly orthostatic hypotension, suggests volume depletion and prerenal AKI. Hypertension with advanced renal insufficiency can be an indicator of volume overload, suggesting the need for diuretics or dialysis. A patient's weight is helpful information, and its daily measurement is important in the diagnosis and management of AKI. After major urologic procedures (e.g., cystectomy, nephrectomy, transplantation), measurement of the central venous pressure or pulmonary artery wedge pressure may provide an estimate of volume status.

Examination of the urinalysis results is fundamental to the evaluation of the patient with AKI (Perazella and Parikh, 2009). The simple urinalysis may distinguish the cause of AKI among the various possibilities. Table 46-2 highlights the various urinary abnormalities associated with the clinical diagnoses. For example, proteinuria, hematuria, and RBC casts are pathognomonic of glomerulonephritis. The classic sediment of ATN includes pigmented (muddy brown) granular casts and renal tubular epithelial cells, which may be seen in nearly 80% of cases of oliguric AKI.

Determination of urinary chemistry may be helpful in determining the cause of the AKI. The urine sodium, creatinine, and osmolality should be measured. The fractional excretion of sodium or the renal failure index should be calculated (Fig. 46-3). Note that a low fractional excretion of sodium (or renal failure index) may be associated with either prerenal azotemia or AGN (Table 46-3). These entities can be separated clinically by examination of the urinalysis results. Conditions associated with prerenal azotemia have bland urinalysis results, whereas proteinuria, RBCs, and RBC casts are seen with AGN. Other causes of AKI associated with a low fractional excretion of sodium include HRS and selected types of ATN such as that resulting from iodinated contrast material, rhabdomyolysis, sepsis, and multisystem organ failure. Both ATN and

TABLE 46-2 Urine Sediment in Acute Kidney Injury

SEDIMENT FINDINGS	DIAGNOSIS
Normal	Prerenal/obstruction
RBC casts, RBCs	AGN/vasculitis
Eosinophils	AIN
Pigmented granular casts	ATN

AGN, acute glomerulonephritis; AIN, acute interstitial nephritis; ATN, acute tubular necrosis; RBC, red blood cell.

TABLE 46-3 Patterns of Urinary Indices in Acute Kidney Injury

	PRERENAL/AGN	ATN/OBSTRUCTION
Urinary [Na ⁺] mEq/L	<20	>40
Urine: plasma creatinine	>30	<20
Renal failure index	<1	>1
FE _{Na}	<1	>1
Urinary osmolality	>500	<400

AGN, acute glomerulonephritis; ATN, acute tubular necrosis; FE_{Na}, fractional excretion of sodium.

$$\text{Fractional Excretion of Sodium (FE}_{\text{Na}}) = \left(\frac{U_{\text{Na}} \times V}{P_{\text{creat}} \times U_{\text{creat}}} \right) \times \text{PNa} \times 100\%$$

$$\text{Renal Failure Index (RFI)} = \frac{U_{\text{Na}} \times P_{\text{creat}}}{U_{\text{creat}}}$$

Figure 46-3. Urinary indices.

obstruction may have an increased fractional excretion of sodium. Here again, the urinalysis is crucial in sorting out the differential diagnosis. ATN includes classic sediment with pigmented, coarsely granular casts, but the urinalysis results seen in obstruction are often bland with or without microhematuria.

The urine output might be a clue to the diagnosis of AKI. The presence of marked oligoanuria suggests urinary tract obstruction, renovascular occlusion, or cortical necrosis. In contrast, nonoliguric AKI is being recognized with increasing frequency, and careful monitoring of serum creatinine in at-risk patients is of paramount importance.

Renal Vein Thrombosis

Renal vein thrombosis represents an uncommon cause for AKI. Certain renal diseases are associated with increased thrombosis. These include a variety of the proteinuric glomerulonephritides, especially with nephrotic range proteinuria (Barbano et al, 2013). A common disease in this category is membranous glomerulonephritis (MGN). Other causes for renal vein thrombosis that urologists would see in practice include renal cell cancer-related tumor thrombus, postoperative thrombosis related to manipulation of the renal circulation (partial nephrectomy), and renal transplantation. There are no systematic reviews of treatment for renal vein thrombosis. In medical renal disease, anticoagulation is usually prudent when thrombosis is discovered, followed by an evaluation for other thrombophilic conditions. When renal vein thrombosis threatens renal function, thrombolytic therapy has been used (Barbano et al, 2013). This technique has been extended to the renal transplant circumstance as well (Fulton

et al, 2011). For renal cancer, nephrectomy with removal of the tumor thrombus is usually the therapy of choice.

Imaging

A variety of imaging modalities show clinical usefulness in the evaluation of AKI. The most widely used is renal ultrasonography. This noninvasive and readily available study is fairly sensitive for the identification of hydronephrosis. Duplex ultrasonography of the renal artery is useful for the identification of RAS or thrombosis (Carman et al, 2001). The absence of a Doppler signal from the artery is a noninvasive examination to confirm renal artery thrombosis.

Another useful imaging study in AKI is the abdominal plain radiograph to identify the presence of renal calculi, the location of renal calculi, or both. Additionally, the abdominal plain radiograph is particularly helpful to discern the proper position of the stents and drains. The radionuclide renal scan is a useful imaging study in selected clinical circumstances. Tc99m-mercaptoacetyltriglycine (MAG3) is a more useful imaging study in renal insufficiency than Tc99m-diethylenetriaminepentaacetic acid (DTPA) and is able to evaluate both renal flow and function (Taylor, 1999). The renal scan is a simple means for evaluation of renal flow in situations where renal artery thrombosis is a serious consideration such as after partial nephrectomy or renal transplantation. It is especially useful when there is renal insufficiency that prohibits the use of iodinated contrast (Jafri et al, 1988). Urinary extravasation can also be assessed by isotope renography.

Radiocontrast studies (intravenous pyelography [IVP], CT, angiography) are of limited value during AKI because of their ability to worsen renal insufficiency. Angiography is used to confirm renal artery thrombosis, stenosis, or dissection. Contrast studies such as CT urography or IVP yield poor-quality images in azotemic patients because of the inability to excrete contrast adequately. Notwithstanding, radiocontrast studies are frequently performed just proximal to surgery and may contribute in this manner to perioperative AKI.

MANAGEMENT OF ACUTE KIDNEY INJURY

Management of AKI is based on its cause (Alkhunaizi and Schrier, 1996; DuBose et al, 1997). When AKI is identified as prerenal, correction of the precipitating factors and restoration of renal perfusion usually lead to its resolution. Nephrotoxic drugs should be eliminated when clinically appropriate. Maintaining normal volume status is essential. In the postoperative setting, this implies judicious replacement of crystalloid, colloid, and blood, with close monitoring of the central venous pressure. The management of postrenal AKI will depend on its etiology. Any obstruction needs appropriate drainage, and urinary extravasation needs to be controlled.

The management of ATN focuses on the prevention of complications and providing an environment that is conducive to renal recovery (Box 46-6). Early consultation with a nephrologist improves the outcome of patients with AKI. Delay in consultation was associated with higher mortality, longer ICU length of stay, and increased number of systems failing at the time of consultation (Mehta et al, 2002a). During the initial evaluation, it is imperative to search for reversible causes such as volume depletion, obstruction, and vascular occlusion. During the initial stages, a trial of parenteral hydration with isotonic fluids may correct AKI secondary to prerenal causes (Prowle et al, 2014). Thereafter, fluid status should be monitored vigilantly to maintain euvolemia. In a patient with oliguria, special attention must be provided to avoid excessive hydration and volume overload, which might precipitate the need for dialysis (Godin et al, 2013; Nadeau-Fredette and Bouchard, 2013). Certain volume expanders such as hydroxyethyl starch have been associated with adverse renal effects (Mutter et al, 2013).

Consideration may be given to using pharmacologic intervention to convert the patient from an oliguric to nonoliguric state. In

BOX 46-6 Complications of Acute Kidney Injury**FLUID OVERLOAD**

Hypertension
Edema
Acute pulmonary edema

ELECTROLYTE DISTURBANCES

Hyponatremia
Hyperkalemia
Hypermagnesemia
Hyperphosphatemia
Hypocalcemia
Hypercalcemia (post-rhabdomyolysis)
Hyperuricemia
Metabolic acidosis

UREMIC SIGNS AND SYMPTOMS: GASTROINTESTINAL

Nausea
Vomiting
Upper gastrointestinal bleeding

NEUROLOGIC

Mental status changes
Encephalopathy
Coma
Seizures
Peripheral neuropathy

CARDIAC

Pericarditis
Uremic cardiomyopathy

PULMONARY

Pleuritis
Uremic cardiomyopathy

HEMATOLOGIC

Bleeding
Anemia

IMMUNOLOGIC

Impaired granulocyte function
Impaired lymphocyte function

general, increases in urinary volume make it easier to address problems of volume overload, hyperkalemia, and metabolic acidosis. Increases in urine volume may also provide room for supplemental TPN in the critically ill patient. Historically, the morbidity, need for dialysis, and mortality was considered lower in the de novo nonoliguric form of ATN; however, more recent data challenge this notion (Liangos et al, 2005).

Pharmacologic Intervention

Pharmacologic intervention to convert oliguric ATN to nonoliguric ATN is a salutary goal for the reasons noted earlier (Townsend and Bagshaw, 2008). Experimental studies on the use of diuretics, dopamine, atrial natriuretic peptide (ANP), and calcium channel blockers (CCBs) that attempt to convert oliguria to nonoliguric AKI have been performed. The applicability of these experimental studies to patients with AKI remains unproved.

Uncontrolled studies suggest that patients who respond to mannitol, furosemide, or dopamine with an increased urine output have better outcomes than nonresponders (Cosentino, 1995). The responders may simply have had less severe disease from the outset. Although de novo nonoliguric AKI has been associated with a lower mortality rate, there is little evidence that conversion from an oliguric to a nonoliguric state decreased the mortality rate. For the patients with established ATN, therapy with loop diuretics may increase urine output but has little effect on the severity or duration of the AKI (Cosentino et al, 1994).

Both loop diuretics and mannitol administration were proved to minimize the degree of renal injury if given at the time of the ischemic insult (Hanley and Davidson, 1981; Schrier et al, 1984; Cosentino, 1995). This is not the same as using these diuretics for the treatment of established ATN. Both diuretics are capable of inducing a diuresis to wash out obstructive debris and casts. Loop diuretics (e.g., ethacrynic acid, furosemide, and bumetanide) exert their pharmacologic effect in the loop of Henle, causing a large solute diuresis. Additionally, they decrease active NaCl transport in the thick ascending limb of Henle and thereby limit energy requirements in the metabolically active segment, which often bears significant ischemic insult. There are several theoretic reasons that loop diuretics may be of benefit in AKI. Loop diuretics might protect cells of the ascending limb of Henle from hypoxic damage, might increase tubular flow to prevent intratubular obstruction, might inhibit tubuloglomerular feedback to maintain a favorable GFR, and might increase RBF by decreasing renal vascular resistance. The available clinical data do not support an improved outcome in patients who respond to loop diuretics (Shilliday and Allison, 1994; Shilliday et al, 1997). A prospective, randomized placebo-controlled study examining the effect of loop diuretics on renal recovery, dialysis, and death in patients with AKI showed no effect (Shilliday et al, 1997). Observational data suggested that diuretic use in critically ill patients with AKI is associated with an increased mortality rate using multivariate analysis and propensity scores (Mehta et al, 2002b). A prospective, multicenter, epidemiologic study showed that the use of loop diuretics was not associated with higher mortality (Uchino et al, 2004). Given these mixed results, it is reasonable to administer a trial of a loop diuretic in escalating doses, and if the patient does not respond, the drug should not be readministered because large doses of loop diuretics may be ototoxic and the large infusion volume may cause pulmonary edema (Nadeau-Fredette and Bouchard, 2013).

Mannitol, an osmotic diuretic, theoretically ameliorates AKI by flushing intratubular casts, increasing RBF, increasing urine flow, reducing hypoxic cell swelling, protecting mitochondrial function, and scavenging free radicals. Mannitol use continues to be promoted prophylactically in certain high-risk patient groups because of its demonstrated benefit in animal models of AKI (Burke et al, 1983; Schrier et al, 1984). Mannitol has shown some benefit in the clinical setting of AKI (Novick, 1983; Weimar et al, 1983; Simmons et al, 2008), particularly when administered prophylactically or within a short time after an ischemic or nephrotoxic insult. The best clinical example of this is its administration before renal artery clamping during partial nephrectomy or during renal transplant (Yang et al, 2014). However, other studies in humans failed to demonstrate the effectiveness of mannitol in the prevention or treatment of ischemic or toxic AKI (Burke et al, 1983; Shilliday and Allison, 1994; Yang et al, 2014).

Dopamine includes selective renal vasodilator properties that cause natriuresis and increased urine output. Low-dose "renal-dose" dopamine (0.4 to 2.0 µg/kg/min) activates dopamine-1 receptors, which induce renal vasodilation and increased RBF. An objective review of controlled studies demonstrates that these benefits remain speculative (Denton et al, 1996; Lassnigg et al, 2000). In a randomized trial of 328 critically ill patients with AKI assigned to continuous infusion of placebo or low-dose dopamine (2 µg/kg/min), peak serum creatinine concentration, requirement for dialysis, length of hospital stay, and mortality rate did not differ between the two groups (Bellomo et al, 2000). Also, prophylactic

use of low-dose dopamine in patients undergoing coronary artery bypass surgery has not proved effective in preventing the development of renal impairment in these patients (Woo et al, 2002). It is also important to note that the use of dopamine has been associated with serious cardiac, vascular, and metabolic complications in the critically ill, and therefore dopamine should be used cautiously.

Fenoldopam is a selective dopamine-1 receptor agonist (DA-1) that causes DA-1 receptor-mediated vasodilation and does not stimulate DA-2 or α - or β -adrenergic receptors. Fenoldopam reduces renal vascular resistance and increases RBF and fractional excretion of sodium and free water clearance in studies of normal volunteers and hypertensive patients (Mathur et al, 1999). A few studies in animal models (Singer and Epstein, 1998; Halpenny et al, 2001) are consistent with the notion that DA-1 agonists may be useful in preventing or treating AKI. A multicenter trial, however, did not show any protective benefit of the selective dopamine-1 agonist (fenoldopam mesylate) in the prevention of contrast-induced renal dysfunction in an at-risk population (Landoni et al, 2007). A randomized prospective study of fenoldopam in patients undergoing partial nephrectomy in a solitary kidney also failed to show a renal functional benefit (O'Hara et al, 2013).

In some animal studies, the effects of ischemic AKI could be reversed with the use of an intrarenal arterial infusion of atrial natriuretic peptide (ANP) (Nakamoto et al, 1987; Shaw et al, 1987), but other experimental studies have been contradictory. The proposed mechanism by which this occurs is the vasodilatory action of ANP. In experimental models of established ATN, the combination of ANP with dopamine to prevent systemic hypotension resulted in a rise in GFR induced by arteriolar vasodilatation. The treated animals also exhibited less tubular necrosis and fewer casts, suggesting tubular recovery was promoted. The efficacy of ANP in established ATN in humans has been evaluated in two trials (Rahman et al, 1994; Stevens et al, 2007). The first was a small, randomized trial suggesting a benefit of ANP therapy. A larger prospective, multicenter, randomized study with ANP in patients with ATN (oliguric and nonoliguric) showed no benefit on morbidity or mortality with ANP (Lewis et al, 2000). However, in a subset of patients with oliguric ATN, clinical improvement was seen with ANP infusion. Another study in a select population did not demonstrate benefit (Lewis et al, 2000).

CCBs inhibit voltage-gated calcium entry into cells and are reported to reverse vascular constriction, to increase GFR, and to improve renal plasma flow (Epstein, 1993). A few limited animal studies in experimental AKI generally support a protective benefit of CCBs. The clinical benefit of CCBs most widely studied has been the effect on graft function in renal transplant recipients (Alkhunaizi and Schrier, 1996).

In summary, review of the data regarding pharmacologic intervention for established ATN supports a trial of isotonic fluid repletion (Prowle et al, 2014). Judicious use of intravenous loop diuretics may increase urine output, but their ability to have an impact on improved patient survival in AKI is still unproven. Similarly, the clinical data on "renal-dose" dopamine are scant and do not support its widespread use in established ATN. If a trial of dopamine is considered, it should be limited to a 24- to 48-hour infusion.

Conservative Management

After the clinical diagnosis of ATN is made, conservative medical management is in order (Box 46-7). This would include attempts to minimize further renal parenchymal injury, to ensure provision of nutrition, to maintain the metabolic balance, and to promote recovery of renal function.

Optimizing the patient's volume status is imperative, particularly in patients with oliguric AKI (DiBona, 1994; Godin et al, 2013; Prowle et al, 2014). If such patients are provided with large volumes of intravenous (IV) fluid or are allowed free access to oral fluids, they are at risk for developing fluid overload or hyponatremia. In the oliguric patient, fluids should be restricted to total

BOX 46-7 Conservative Medical Management of Acute Kidney Injury

FLUID BALANCE

Careful monitoring of intake/output and weights
Maintaining euvolemia

ELECTROLYTES AND ACID-BASE BALANCE

Prevent and treat hyperkalemia
Avoid hyponatremia
Keep serum bicarbonate >15 mEq/L
Minimize hyperphosphatemia
Treat hypocalcemia only if symptomatic or if intravenous bicarbonate is required

UREMIA AND NUTRITION

Protein (1.0-1.8 g/kg/day) and maintain caloric intake; consider forms of nutritional support
Carbohydrate intake at least 100 g/day to minimize ketosis and endogenous protein
Catabolism

DRUGS

Review all medications
Stop magnesium-containing medications
Adjust dosage for renal failure; readjust with improvement of glomerular filtration rate

output plus insensible losses. If required, pharmacologic intervention with loop diuretics may promote increases in urinary volume.

Providing adequate nutrition is important for the recovery of the critically ill patient with AKI (Fiaccadori et al, 2008). Preexisting or hospital-acquired malnutrition is an important factor contributing to the high mortality seen in patients with AKI (Druml, 1992). AKI not only affects water, electrolyte, and acid-base metabolism but also induces specific alterations in protein and amino acid, carbohydrate, and lipid metabolism (Druml, 1998). The metabolic alterations in AKI patients are determined not only by acute loss of renal function but also by the underlying disease process (i.e., sepsis, trauma, or multiple organ failure) and by the type and intensity of renal replacement therapy (RRT) (Druml, 2005).

The hallmark of metabolic alterations in AKI is activation of protein catabolism with excessive release of amino acids from skeletal muscle and sustained negative nitrogen balance (Druml, 1998; Price et al, 1998). Hepatic extraction of amino acids from the circulation, gluconeogenesis, and ureagenesis are all increased. Several additional catabolic factors (secretion of catabolic hormones, hyperparathyroidism, suppression and decreased sensitivities to growth factors, and release of inflammatory mediators) are operative in AKI. All of these factors mediate protein breakdown (Cianciaruso et al, 1991).

Frequently, AKI is associated with hyperglycemia caused by insulin resistance (Klouché and Beraud, 1998). When plasma insulin concentration is elevated, maximal insulin-stimulating glucose uptake by skeletal muscle is decreased by 50%. AKI is also associated with accelerated hepatic gluconeogenesis, mainly from conversion of amino acids released during protein catabolism, which cannot be suppressed by exogenous glucose infusions (Druml, 1992). The triglyceride content of plasma lipoprotein is increased in AKI, whereas total cholesterol and high-density lipoprotein (HDL) cholesterol are decreased (Schneeweiss et al, 1990). The major cause of lipid abnormalities in AKI is impairment of lipolysis. Renal replacement therapies themselves may present significant metabolic and nutritional consequences.

Appropriate nutritional therapy in patients with AKI may be beneficial in promoting recovery (Fiacadori et al, 2008). Caloric intake should be maintained, and carbohydrate intake should be at least 100 g/day to minimize ketosis and endogenous protein catabolism. A moderate protein intake of about 1 to 1.8 g/kg by weight per day may be required to maintain positive nitrogen balance. Higher protein intakes of up to 2.5 g/kg/day have been necessary to improve nitrogen balance in critically ill AKI patients on continuous dialysis, although no survival advantage was noted. Hence it should be stressed that a low-protein intake (<0.5 g/kg/day) may be unnecessary, and protein intake should not be severely restricted in AKI to limit the need for dialysis. In terms of types of amino acids used, diet or solutions including both essential and nonessential amino acids in standard proportions are recommended. Dietary phosphorus, potassium, and sodium chloride may be restricted. In the critically ill patient, nutritional support via TPN or enteral feedings should be considered. Previous studies demonstrate that the provision of adequate nutrition to the AKI population might improve survival (Chertow et al, 2000). Patients with AKI are candidates for the development of significant electrolyte abnormalities such as hyperkalemia, metabolic acidosis, hyperphosphatemia, and hypocalcemia. The prophylactic institution of a low-potassium diet accompanied by fluid restriction and oral phosphate binders may minimize these problems.

Hyperkalemia is the most common and most dangerous electrolyte abnormality in the AKI setting (Hoorn et al, 2013; Fordjour et al, 2014). If serum potassium exceeds 6 mEq/L, an electrocardiogram (ECG) should be performed with subsequent therapy based on the ECG findings. With hyperkalemia, the earliest changes demonstrate peaked T waves with subsequent broadening of the PR interval and eventual QRS broadening, which may mature into a sine wave form. The stages of therapy for acute hyperkalemia with ECG changes include (1) stabilizing the electrical membrane of the cardiac conduction system, (2) shifting potassium back intracellularly, and (3) eventual elimination of potassium from the body. Stabilizing the membrane of the cardiac conduction system may be accomplished with IV calcium salts, which have an immediate effect and a rather short duration of action. Shifting potassium into cells may be accomplished by a combination of IV glucose and insulin or IV sodium bicarbonate. Elimination of potassium from the body in a patient with AKI may be accomplished via the gastrointestinal tract with a cationic-binding resin. One study questions the efficacy of sodium polystyrene sulfate (commonly known as Kayexalate) and identifies an underappreciated risk associated with its use, which is colonic necrosis (Sterns et al, 2010). If severe hyperkalemia exists, dialysis may be required.

Dialytic Interventions

General

Despite adequate medical therapy, dialysis may be required for patients with severe AKI. The indications for the initiation of dialysis include volume overload, severe hyperkalemia, severe metabolic acidosis, pericarditis, selected poisonings, certain drug overdoses, and uremic symptomatology.

One or more of the specific indications usually precipitates the initiation of dialysis for patients with AKI. There is still debate on whether patient morbidity and mortality might be improved by early initiation of RRT; well-conducted randomized trials are lacking. Intensive dialysis, on the other hand, compared to standard dialysis intensity did not improve survival in patients with AKI in two well-performed multicenter randomized trials (Network et al, 2008; ASTRAL Investigators et al, 2009). Nevertheless, patients with AKI should begin dialysis on detection of severe fluid or electrolyte abnormalities or uremic symptomatology that cannot be controlled with conservative or medical therapies. A theoretical concern exists that the dialysis treatment itself may present a detrimental impact on the course of AKI from ATN. Three potential mechanisms have been postulated: a fall in urine volume, dialysis-induced

hypotension, and complement activation resulting from the blood-dialysis membrane interaction. Removal of excess volume and urea may each contribute to the fall in urine volume. Whether this reduction includes an impact on the clinical recovery of ATN is speculative. Hypotension is a common complication of HD in patients with AKI. Because autoregulation is impaired in ATN, such patients may be particularly sensitive to renal hypoperfusion, perhaps because of vascular injury of the endothelium and its vasodilatory products such as prostacyclin and NO. As a result, recurrent ischemic injury is more likely to occur and possibly might delay the restoration of renal function. Complement activation during the blood-dialyzer interaction is a third possible mechanism for dialysis-induced renal injury. Animal models suggest that blood interaction with cuprophane membranes (but not more biocompatible membranes) can lead to neutrophilic infiltration into the kidney and can prolong the course of AKI.

Dialysis Prescription and Modality

The contribution of the type of RRTs to clinical outcomes in AKI remains unresolved. Several factors that are operative during RRT for AKI may affect clinical outcome. These include dialysis modality and dialyzer membrane characteristics. HD is the standard dialytic modality for hemodynamically stable patients with AKI. HD treatments may be stressful hemodynamically and may possibly be complicated by hypotension, hypoxia, bleeding related to anticoagulant administered (usually heparin), and dialysis dysequilibrium with its manifestations ranging from cramps and headaches to seizures and coma.

In the hemodynamically unstable patient, slow fluid and solute removal can be achieved with continuous renal replacement therapy (CRRT). In addition to being better tolerated hemodynamically, CRRT is also as efficient as conventional HD at removing solutes throughout the course of 24 to 48 hours. Although the clearance rates of some small solutes such as urea are slower, the rates are closer at 24 hours and more urea is removed during 48 hours with CRRT than with a single, intermittent run of standard HD.

Peritoneal dialysis (PD) permits the removal of solutes and fluid by use of the peritoneal membrane as the dialyzer. This process does not require access to the circulation and is generally less stressful hemodynamically than standard HD. For this procedure, the dialysate is instilled into the peritoneal space via a catheter that is percutaneously placed. Fluid is allowed to dwell for a time and is then removed, taking with it uremic solutes by diffusion, as well as accomplishing ultrafiltration of fluid from an osmotic pressure gradient induced by high concentrations of glucose in the dialysate. Small randomized clinical trials suggest that PD may be comparable to daily HD with regard to efficacy and clinical outcomes (Gabriel et al, 2008). Although it is not popular in the United States, this method remains an option in noncatabolic patients in which use of PD can maintain fluid and electrolyte homeostasis while preventing uremic symptomatology (Chionh et al, 2013).

Nephrologists caring for AKI patients may select a continuous or intermittent dialysis method. An analysis of nine published studies comparing CRRT to intermittent HD (IHD) in patients with AKI showed no significant difference in clinical outcomes between the two groups (Tonelli et al, 2002). A meta-analysis of 13 clinical trials, totaling 1400 patients, also observed no mortality difference between CRRT and IHD. However, after adjusting for severity of illness and study quality, mortality seemed to be lower in the CRRT group (Kellum et al, 2002). Similarly, a well-designed study of 80 critically ill patients with AKI showed no difference in survival or renal recovery between continuous venovenous hemodialysis and IHD groups (Augustine et al, 2004).

Dialysis membranes may be classified as cellulose-derived or non-cellulose-derived membranes. The non-cellulose-derived membranes are synthetic polymers and are generally more biocompatible but more expensive. A meta-analysis of clinical trials comparing biocompatible versus nonbiocompatible membranes

showed no difference in mortality between groups (Jaber et al, 2002). Given the profound morbidity of patients with AKI, if a survival advantage attributable to biocompatible membranes exists, at best it is small. Similarly, high-flux membranes have not demonstrated a survival benefit, recovery of renal function, or duration of dialysis (Ponikvar et al, 2001).

Prognosis of Acute Tubular Necrosis

The prognosis of ATN is dependent on the underlying primary disease that resulted in the AKI, as well as any complications that arise (e.g., infection, cardiovascular, gastrointestinal bleeding, central nervous system). The mortality rate for patients with ATN is consistently around 50% regardless of the study population (Biesenbach et al, 1992; Network et al, 2008). This pessimistic outlook has changed little in the past 4 decades, despite the advent of effective dialysis (Lewers et al, 1970; Di Tullio et al, 1996; Liano and Pascual, 1996; Uchino et al, 2005). Mortality rates remain high today despite effective control of uremia because of an older, sicker population with severe concomitant illnesses. Mortality rates have been quantified as high as 75% in several series in the ICU population. Higher mortality rates are seen in elderly patients, in patients with respiratory failure, with multiorgan failure, with preexisting chronic diseases, and with systemic hypotension (Obialo et al, 1999). In a prospective multicenter study of mortality with critically ill patients with ATN, the factors predictive of early mortality were male gender, oliguria, mechanical ventilation, acute myocardial infarction, cerebrovascular accident/seizure, and chronic immunosuppression (Parker et al, 1998). Leading causes of death include bronchopulmonary infections, sepsis, cardiovascular disease, and bleeding disorders. Of patients who survive ATN, nearly half will experience a complete recovery of renal function and a majority of the remainder has an incomplete recovery (Fig. 46-4) (Spurney et al, 1991). Only about 5% of all AKI patients require chronic maintenance dialysis.

A separate question is whether the development of AKI itself directly contributes to mortality. In a prospective study of 183 patients who developed AKI after IV contrast exposure, the in-hospital mortality rate was substantially higher in the AKI group (34% vs. 7%) than in a matched control (Levy et al, 1996). This effect persisted after the adjustment of other comorbid diseases. The development of AKI is also known to increase the morbidity of patients, to prolong hospitalizations, and to increase hospital costs.

Prevention of Acute Tubular Necrosis

Special attention should be focused on the prevention of AKI, because the management of ATN is primarily one of conservative care and support. Patients at high risk (i.e., patients with preexisting azotemia, the elderly, volume-depleted individuals, diabetic patients) warrant careful clinical consideration of the relative risks and benefits of diagnostic or therapeutic interventions that have potential for nephrotoxicity. This is especially true for at-risk patients

who might undergo cardiac catheterization or other diagnostic studies requiring iodinated contrast material. Several classic studies deserve comment.

A study by Solomon and colleagues (1994) confirmed that intravenous hydration with saline was critical in diminishing the nephrotoxic effects of coronary arteriography for patients with preexisting azotemia (Solomon et al, 1994). The addition of either a loop diuretic or mannitol did not improve outcome. Rudnick and colleagues (1995) published a prospective, randomized trial of nearly 1200 well-hydrated patients undergoing cardiac catheterization to examine the effects of the newer nonionic contrast material (Rudnick et al, 1995). Patients were stratified for the presence or absence of azotemia ($\text{SCr} \geq 1.5 \text{ mg/dL}$) or diabetes mellitus. In patients without azotemia (with or without diabetes mellitus), the incidence of contrast-induced renal dysfunction was low (i.e., <1% to 2%) with either the ionic or nonionic contrast material. Those with preexisting azotemia experienced a 50% reduction in contrast-associated renal dysfunction with the nonionic material. These data suggest that in azotemic patients who require cardiac angiography, a protocol of intravenous hydration and the use of a nonionic contrast material appear warranted. Moreover, a meta-analysis also demonstrated that the use of the newer iso-osmolar non-ionic agents would be of benefit when compared with hypo-osmolar agents, especially in subjects with preexisting kidney disease and diabetes (McCullough et al, 2006).

In addition to these maneuvers in high-risk patients, pretreatment with *N*-acetylcysteine (600 mg orally twice daily for 48 hours) has been shown to reduce the incidence of radiocontrast-induced nephropathy (Tepel et al, 2000). A meta-analysis of randomized clinical trials using *N*-acetylcysteine in patients with reduced renal function clearly showed risk reduction for acute radiocontrast injury (Alonso et al, 2004). Nonetheless, meta-analysis conducted separately of randomized controlled trials using *N*-acetylcysteine for the prevention of radiocontrast-induced nephropathy did not warrant a strong recommendation for its clinical use (Kshirsagar et al, 2004; O'Sullivan et al, 2013).

Several trials have compared the benefits of two hydration protocols in reducing radiocontrast-induced nephropathy. A trial involving 1620 patients undergoing coronary angioplasty demonstrated a benefit of isotonic hydration as superior to half-isotonic hydration in prevention of nephropathy (Mueller et al, 2002). A smaller, single-center prospective randomized trial showed the benefit of IV hydration with sodium bicarbonate rather than sodium chloride administered 1 hour before contrast exposure in the prophylaxis of contrast-induced renal dysfunction (Merten et al, 2004). The latter protocol includes the advantage of timing because it was initiated 1 hour before the anticipated contrast study, rather than requiring 48 hours of pretreatment with *N*-acetylcysteine. A multicenter trial did not show any protective benefit of the selective dopamine-1 agonist (fenoldopam mesylate) in the prevention of contrast-induced renal dysfunction in an at-risk population (Stone et al, 2003). Similarly, a meta-analysis did not report any compelling benefit for the use of theophylline, an adenosine antagonist, in the prevention of contrast-induced nephropathy (Bagshaw and Ghali, 2005). In the aggregate, the aforementioned recommendations for the azotemic patients who require radiocontrast procedures warrant a protocol of IV hydration with isotonic fluids (Weisbord et al, 2008) and the use of nonionic contrast material in the lowest dose possible (Perazella and Reilly, 2011). The use of sodium bicarbonate as an isotonic fluid may be beneficial. Treatment with *N*-acetylcysteine before the procedure carries little risk but it may not be an effective preventive strategy (O'Sullivan et al, 2013).

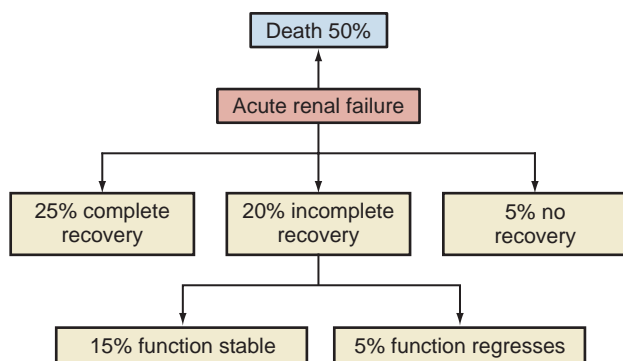


Figure 46-4. Prognosis of acute tubular necrosis.

CHRONIC KIDNEY DISEASE

The diagnosis of CKD implies a persistent abnormality in GFR with a wide spectrum of causes. The Workgroup of the U.S. National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI) Advisory Board, recommended in 2002 that “chronic

KEY POINTS: ACUTE KIDNEY INJURY

- Creatinine as an assessment of renal function needs to be interpreted in the context of clinical events that are occurring in the patient.
- AKI is categorized based on pathophysiology as prerenal, postrenal, or intrinsic renal. The etiology and pathogenesis determine management. A new definition has recently been defined.
- Prerenal azotemia is transient renal hypoperfusion and responds well to isotonic fluid replacement.
- In considering postrenal causes of AKI, do not forget fistula and other iatrogenic causes.
- The inflammatory response is important in the pathogenesis of ATN and may become a future target for therapeutic intervention.
- Conservative management predominates for ATN. This entails careful fluid management and dialysis support as needed with prevention of complications.
- Review of the data regarding pharmacologic intervention for established ATN supports a trial of isotonic fluid repletion. Judicious use of intravenous loop diuretics may increase urine output, but their ability to have an impact on improved patient survival in AKI is still unproven. Similarly, the clinical data on “renal-dose” dopamine do not support its widespread use in established ATN.
- Recommendations for the azotemic patients who require radiocontrast procedures warrant a protocol of IV hydration and the use of nonionic iso-osmolar contrast material in the lowest dose possible. Treatment with *N*-acetylcysteine and/or special hydration with prestudy sodium bicarbonate may be considered as well.

kidney disease” should be defined as sustained kidney injury longer than 3 months resulting in a GFR of less than 60 mL/min/1.73 m² (National Kidney Foundation, 2002). These guidelines were updated in 2012 by KDIGO (KDIGO Committee, 2013; Levin and Stevens, 2014). A new classification system now includes the cause of kidney disease (if known), the estimated GFR (eGFR), and the level of albuminuria (Tables 46-4 and 46-5). The CKD category 3 has been further divided into category 3a (GFR 45 to 59 mL/min/1.73 m²) and 3b (30 to 44 mL/min/1.73 m²) based on data suggesting that outcomes differ between these two ranges of GFR. This new system (Fig. 46-5) better reflects the health implications for guiding prognosis and management (KDIGO Committee, 2013). For example, if a nephrectomy is performed and the remaining kidney is perfectly normal, the resulting eGFR may be 68 mL/min/m² but, in the absence of a cause for ongoing renal injury or albuminuria, the prognosis for

CKD progression is favorable (see Fig. 46-5). Alternatively, in a patient with diabetes, and an eGFR of 68 mL/min/1.73 m² and an albumin/creatinine ratio (ACR) >300 mg/g, there is a much higher chance of renal disease progression (see Fig. 46-5). This is because the level of albuminuria indicates that diabetes is a cause for ongoing chronic kidney injury. The 2002 classification system does not distinguish a difference. The 2012 guidelines based on the cause for reduced renal function (C), eGFR (G), and level of albuminuria (A), or CGA system, are much more useful for identifying risks and implementing referral/treatment strategies.

This distinction has now been incorporated into the reporting of the prevalence for CKD. In the 2013 USRDS report (U.S. Renal Data System, 2013), the prevalence of eGFR less than 60 mL/min/m² between 2005 and 2010 was 6.1%. Defined by ACR greater than 30 mg/g, the prevalence of CKD is 9.1%, which is similar to diabetes and higher than cardiovascular disease. When the combined prevalence of low eGFR and abnormal ACR are used, the prevalence of CKD is 13.1%. This is higher than the prevalence for diabetes or cardiovascular disease. This identifies CKD as an important health issue with a significant population burden.

After an initial kidney insult, if the acute injury does not completely resolve, a continuing attrition of functional nephrons occurs with time. Figure 46-6 depicts the renal failure continuum consisting of several stages of functional deterioration associated with specific clinical and biochemical abnormalities. Small changes

TABLE 46-4 Glomerular Filtration Rate Categories in Chronic Kidney Disease

GFR CATEGORY	GFR (mL/min/1.73 m ²)	TERMS
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

*Relative to young adult level.

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for chronic kidney disease.

GFR, glomerular filtration rate.

From KDIGO Committee. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013;3(1).

TABLE 46-5 Albuminuria Categories in Chronic Kidney Disease

CATEGORY	AER (mg/24 hr)	ACR (APPROXIMATE EQUIVALENT)		TERMS
		(mg/mmol)	(mg/g)	
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased†

*Relative to young adult level.

†Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hr [ACR >2220 mg/g; >220 mg/mmol]).

AER, albumin excretion rate; ACR, albumin/creatinine ratio.

From KDIGO Committee. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013;3(1).

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is **defined** as abnormalities of kidney structure or function, present for more than 3 months, with implications for health, and CKD is **classified** based on cause, GFR category, and albuminuria category (CGA).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (mL/min/1.73 m ²) description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

Figure 46-5. Chronic kidney disease (CKD) risk for progression based on Kidney Disease: Improving Global Outcomes (KDIGO) 2013 classification of glomerular filtration rate (GFR) and albuminuria. (From KDIGO Committee. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2012;3(1).)

in the serum creatinine levels correlate with significant alterations in the GFR when renal function is greater than 60 mL/min/1.73 m². This concept is illustrated by the serum creatinine ordinate on the left side of Figure 46-6, matched to the GFR line of identity crossing through the four different phases of progressive renal disease. However, the relationship between the serum creatinine level and the GFR changes as the renal function deteriorates below 60 mL/min/1.73 m². As noted on the right side of Figure 46-6, changes in the GFR (dashed, curved line) are represented by significantly larger increases in serum creatinine level depicted on the right ordinate. This is especially true in CKD as the GFR decreases to levels below 30 mL/min/1.73 m². Although an initial insult may decrease an individual's renal reserve, biochemical abnormalities are uncommon before the "renal-insufficiency" stage. After severe renal failure occurs, clinical symptoms become more common.

The degree of adaptation taking place at each stage determines the extent of clinical and biochemical abnormalities. When kidney function is minimally impaired (≤60% of normal), physiologic adaptation is complete. When the GFR falls below 20% of normal, progressive anorexia with nausea, salt retention, acidosis, insomnia, anemia, muscle fatigue, and worsening blood pressure (BP) control may occur. Structurally, after the GFR in humans falls below 50% of normal, a relentless progressive loss of function ensues even when the initial disease becomes inactive (Mitch et al, 1976). There is significant interest in those clinical and public health initiatives that can potentially identify and prevent progressive kidney failure. Clinical practice guidelines for CKD were developed and published by the NKF in 2002 to diagnose and treat CKD and its comorbidities more consistently (National Kidney Foundation,

2002; Patel et al, 2002; Eknoyan, 2003). These guidelines have been updated to incorporate more granularity to the original classification of CKD and to provide better prognostic information (KDIGO Committee, 2013; Levin and Stevens, 2014).

Although the clinical course of progressive renal disease as illustrated in Figure 46-6 moves through several different phases, which include decreased renal reserve, renal insufficiency, renal failure, and uremia, the K/DOQI (2002) guidelines, and now the KDIGO (2012) guidelines, have developed a more uniform classification of the stages of CKD with more relevant application for management (see Fig. 46-5). These guidelines will have an impact on education between patients and providers, will enhance the public's understanding of the different levels of kidney disease, and will promote the dissemination of specific research results for each stage.

Renal Mass Reduction and Chronic Kidney Disease

Deficits in nephron number predispose to progressive renal disease and hypertension (Chertow et al, 1996). Nephron number averages approximately 600,000 per kidney in the normal kidney with a standard deviation greater than 200,000 (Nyengaard and Bendtsen, 1992). Conceptually, a significant partial ablation of renal mass through renal insult or surgical partial nephrectomy initiates a cycle of progressive glomerular injury in the remnant kidney. In this setting, the injury is associated with hyperfiltration, glomerular hypertrophy, and systemic hypertension (Brenner and Mackenzie, 1997). In human studies, Novick and colleagues demonstrated that with a greater than 50% reduction in total renal mass, the extent of proteinuria correlated directly with the

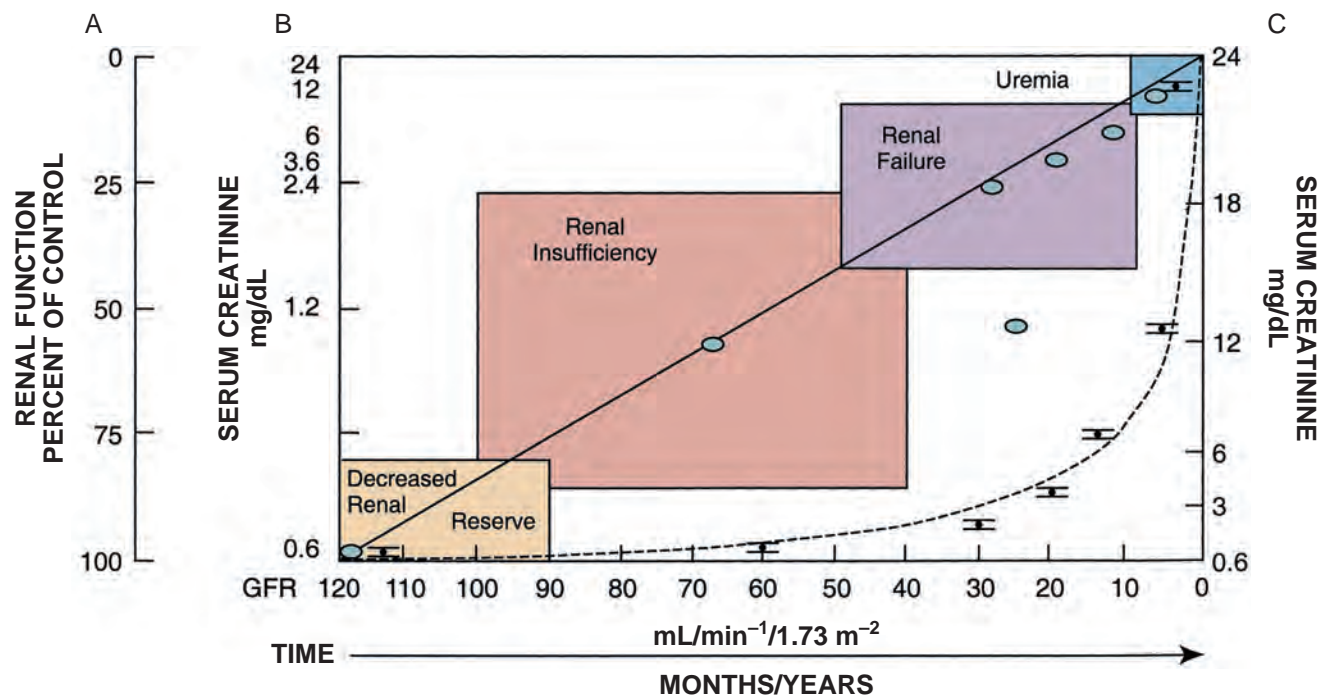


Figure 46-6. The course of progressive renal disease. The course of a patient who began with normal renal function corresponding to a serum creatinine concentration of 0.6 mg/dL and a glomerular filtration rate (GFR) of 120 mL/min/1.73 m² is shown. **Y-axes.** The geometric serum creatinine ordinate at the left (B) applies to the solid line of identity (*open circles*), and the rectangles depict the various stages of progressive renal disease. The serum creatinine ordinate at the right side of the figure (C) should be used with the *dashed curve (ax-heads)* only. The ordinate at the extreme left (A), which describes the percentage of renal function remaining, applies generally. **Line of identity.** This line shows a decrease in function from 100% to 9% of normal corresponding to the diminution in GFR from 120 to 0 mL/min/1.73 m². The matching creatinine scale (A) is geometric. **Dashed curve.** Because GFR equals daily creatinine excretion/serum creatinine concentration and because the creatinine excretion is equal to daily production, which is constant, this equation is of the form $y = k/x$, which defines a hyperbola. This relationship remains valid during the course of chronic renal disease unless the creatinine production changes. The curve emphasizes that large changes in GFR may produce small and clinically imperceptible changes in serum creatinine concentration when overall renal function is near normal. Conversely, trivial changes in GFR produce large changes in serum creatinine concentration when the GFR is low. The rate of progression throughout the delineated stages depends on the nature of the underlying renal disease, host factors, treatment, and compliance with the medical regimen. (From Kimmel PL. Management of the patient with chronic renal disease. In: Greenberg A, editor. *Primer on kidney disease*. 2nd ed. San Diego [CA]: Academic; 1998. p. 434.)

duration of follow-up and inversely with the amount of renal tissue remaining (Novick et al, 1991). This observation suggests that ongoing renal injury occurs when a specific “set point” reduction in nephron number occurs. In certain population groups, birth weight may be a risk factor for progressive renal failure if associated with intrauterine growth retardation. Low birth weight can lead to a 20% decrease in overall nephron number (Lopes and Port, 1995; Hughson et al, 2003; Keller et al, 2003). Glomerular size in African-Americans is larger than in whites, possibly reflecting smaller nephron number (Pesce, 1998) and perhaps attributable to lower birth weight (Garrett et al, 1994). Theoretically, the increased risk for African-Americans to develop “nephrosclerosis” could be linked to this low-birth-weight risk concept. Allograft nephron number (donor kidney size compared with recipient body size) may be relevant in the development of chronic rejection and failure in human transplantation setting (Brenner and Mackenzie, 1997; Poggio et al, 2006). When the body mass of the donor is small, the functional demands on the allograft will be strained and may contribute with time to ongoing injury leading to allograft failure.

Interestingly, the age at loss of renal mass influences the kidney’s response in humans. In patients undergoing unilateral

nephrectomy for Wilms tumors, renal growth was most marked in those individuals who had surgery at a younger age (Di Tullio et al, 1996). This finding can be applied to the contrasting observations comparing outcomes in congenital solitary kidney versus surgical unilateral nephrectomy. The volume of glomeruli in a congenital solitary kidney is five to six times that observed in a normal kidney (Bhathena et al, 1985). This increase in volume is associated with a decreased nephron number and could explain the higher risk for ongoing parenchymal injury compared with surgical nephrectomy cases. In contrast, postdonation GFR seems to stabilize after an initial decrease from predonation values following nephrectomy in former kidney donors (Goldfarb et al, 2001; Ibrahim et al, 2009). These reports support the concept that the true response to decreased renal mass in humans varies according to age at time of reduction, underlying conditions (causative agent, etiology), and the actual degree of reduction.

Mechanisms of Progression

Apoptosis (programmed cell death) triggered by ischemia, toxins, or endogenous mediators of damage can be the initial insult that

causes renal damage. Apoptotic cell death is an active process under molecular control of regulatory proteins and is characterized by both morphologic and functional changes. These changes usually occur as a response to the cell and microenvironment in which the presence of certain “lethal factors” (e.g., tumor necrosis factor, Fas-ligand) or the absence of “survivor factors” (e.g., EGF, IGF-1, IGF-2, basic fibroblast growth factor [bFGF]) promote apoptosis. Lethal factors can either activate specific cell death receptors or damage the cells in the absence of receptor activation (Ortiz, 2000). Although growth factors regulate hypertrophy and cell proliferation, they may also mediate apoptosis as a healing response.

Cell death follows a reduction in nephron mass. The array of events that occur with progressive nephron mass loss include SNS activation, renal structural remodeling, and altered gene expression/regulation. Renal protective interventions are designed to counter those events that adversely affect the cortex and interstitium of the kidney. Both hemodynamic and nonhemodynamic factors are involved in the sustained renal injury after an initial insult. The hemodynamic events causing an increase in single nephron glomerular filtration rate (SNGFR) include increased glomerular plasma flow rates and capillary hydrostatic pressures in the remaining glomeruli. Elevated glomerular hydrostatic pressure is a major factor in renal injury after renal mass reduction (Meyer and Rennke, 1988). However, hyperfiltration alone in response to decreased nephron mass is not sufficient to induce pathologic glomerulosclerosis and interstitial fibrosis. Neurogenic factors and hypertension also play a significant role in ongoing renal injury. Increases in angiotensin II and NO activate the SNS, which plays a dominant role in the pathogenesis of hypertension in CKD (Myers et al, 1975). The rise in central SNS activity is generated by increased local expression of nitric oxide synthase (NOS)-mRNA and NO production coupled to an upregulation of NO production by interleukin-1 (IL-1) in the brain (Campese, 2000).

Nonhemodynamic mechanisms for renal injury involve a number of complex interactions for remodeling, including structural changes, growth factors, and cytokines. Abnormal glomerular growth is associated with, and may be a marker for, the activation of these specific mechanisms leading to sclerosis during the remodeling phase after renal injury (Fogo, 2000). Injury remodeling involving both glomerular hyperplasia (increase in cell number) and glomerular hypertrophy (increase in cell size) can occur within 2 days of a significant decrease in overall renal mass (5% nephrectomy). Glomerular growth can occur because of increases in any of the cellular components. Structural changes in the glomeruli during remodeling include increased extracellular matrix (ECM) production; glomerular hypertrophy; glomerular proliferation (increase in cell number: epithelial, endothelial, mesangial cells); and glomerular basement (GBM) modification (Ma and Fogo, 2009).

Foam cells are frequently located in segments of the glomerulus that are undergoing sclerosis and in the interstitium of diseased kidneys. Oxidized low-density lipoprotein (LDL) stimulates inflammation and fibrogenic cytokine production and can cause an increase in cell apoptosis and the production of ET and thromboxane. It also causes an increase in the release of renin from juxtaglomerular cells, thus enhancing vasoconstriction (Keane, 2000).

Many diseases have been associated with an imbalance of ECM synthesis and degradation (Ma and Fogo, 2009). The glomerular mesangial cell responds to various growth factors by proliferation and increased ECM production. An increase in collagen deposition and a decrease in the degradation of ECM components lead to interstitial fibrosis. The degree of tubular interstitial fibrosis has been closely correlated with the reduction in GFR in many different animal and human studies. Angiotensin II upregulates transforming growth factor- β 1 (TGF- β 1), which is a potent fibrogenic factor playing a key role in the pathogenesis of interstitial fibrosis. The major physiologic regulators of ECM degradation in the glomerulus are matrix metalloproteinases (MMPs) (Lenz et al, 2000). MMPs are distinct, matrix-degrading enzymes such as stromelysins, gelatinases, elastases, and interstitial collagenases. Changes in MMP expression or activity can alter ECM turnover, which in turn may

lead to glomerular scarring and a decline in renal function (Zhao et al, 2013). MMPs may also indirectly affect regulation of certain growth factors that play a role in ECM turnover. Conceptually, progressive glomerular sclerosis may result from this shift in ECM turnover toward increased matrix accumulation, a decreased filtration area, and progressive renal failure.

A wide range of conditions or substances can promote intrarenal growth and glomerular sclerosis in experimental models. These include a loss of renal mass, high-protein or high-salt diet, growth hormone, IGF-1, androgens, glucocorticoids, angiotensin, aldosterone, and ET. Aldosterone may promote fibrosis by means of several mechanisms including plasminogen activator inhibitor-1 expression with consequent alterations of vascular fibrinolysis through stimulation of TGF- β 1 and reactive oxygen species. Although significant evidence has accumulated to implicate angiotensin II in mediating renal disease, aldosterone is also an important factor in causing progressive renal disease through both hemodynamic and direct cellular actions. Circulating aldosterone may mediate vascular fibrosis by a direct interaction with high-affinity, low-capacity corticoid receptors located in the cytosol of vascular fibroblasts (Lea et al, 2009).

Angiotensin II upregulates the expression of multiple growth factors and cytokines. Angiotensin II actions, which are separate from the blood pressure effect, may contribute to progressive renal disease and this helps to explain the rationale for using ACE inhibitors and ARBs in patients with CKD. A number of cell-specific growth responses (glomerular cells, endothelial cells, glomerular visceral epithelial cells, mesangial cells) regulate glomerular growth. Endothelial cells inhibit smooth muscle cell migration and proliferation and produce vascular endothelial growth factors, NO, ET, and platelet-derived growth factor (Fogo, 1999; Ma and Fogo, 2009). Vascular endothelial growth factors stimulate angiogenesis, whereas ET promotes hypertrophy and increased mesangial cell matrix.

Genetic Factors

Family members of patients with kidney disease are disproportionately affected with progressive renal failure. The familial clustering of nephropathy has been reported in diabetes, hypertension, SLE, and HIV-associated nephropathy. Interestingly, an individual's family history of end-stage renal disease (ESRD) is a better predictor of the future risk for renal failure than is blood pressure or blood glucose (Freedman et al, 1997; Satko and Freedman, 2004; Gunzler et al, 2013). A study sponsored by the National Kidney Foundation of Singapore, which screened more than 210,000 adults with renal disease, demonstrated a significant relationship between a family history and proteinuria with the potential for future renal failure (Ramirez et al, 2002). An observation of ESRD in those who have donated previously and who are still living underscores the potential role of genetics in the development of renal disease. Although the absolute rate of ESRD following living donation is extremely low, one study identified that all 9 donors developing renal failure in long-term follow-up were family members (Mjoen et al, 2014), suggesting a genetic contribution.

Our understanding of those mechanisms involved in progression to sclerosis has expanded since the early 1990s. It is now clear that genetic traits may contribute to the structural and functional adaptations to a reduction in renal mass. In diabetes, genetic signaling in response to a metabolic injury may explain why only approximately 40% of those with type 1 diabetes mellitus develop diabetic nephropathy. In the Appropriate Blood Pressure Control and Diabetic (ABCD) study, the ACE DD genotype was the strongest predictor for the presence of nephropathy (14.2% of DD homozygotes exhibit nephropathy vs. 7.8% of non-DD homozygotes) (Jeffers et al, 1997). The Genetique de la Nephropathie Diabetique study demonstrated a significant association between the D-allele frequency and progressive nephropathy in type 2 diabetic patients (Marre et al, 1997). Even in nondiabetic glomerular injury (IgA nephropathy) there was a greater reduction in GFR and worse biopsies in patients carrying the D-allele. Not only does the

DD genotype impart increased risk of progression, but this genotype is also associated with an earlier need for dialysis. More recently, APOL1 has been identified as a genetic cause of kidney disease, especially on those of African-American background (Parsa et al, 2013).

It is hoped that large, collaborative genetic analyses will identify the genes underlying diabetic nephropathy and determine if the loci identified in previous smaller studies can be duplicated (Satko and Freedman, 2004; Satko and Freedman, 2005). The NKF sponsored the Kidney Early Evaluation Program (KEEP) and the Southeastern Kidney Council/ESRD Network. These programs are screening high-risk American populations to assess the link between family history and kidney disease (Brown et al, 2003).

Etiologies for Chronic Kidney Disease

The causes of progressive CKD parallel the most common causes of ESRD. Table 46-6 lists the incident causes of ESRD of varied causes by diagnosis from the U.S. Renal Data System (U.S. Renal Data System, 2013). Diabetes mellitus and hypertension account for the largest percentage of cases (63%) followed by glomerular diseases (14%). Urologic diseases account for only 2% of overall ESRD.

In patients younger than 40 years, CKD is most commonly caused by focal segmental glomerulosclerosis (FSGS), SLE, and then congenital abnormalities of the urinary tract or MGN. Membranoproliferative glomerulonephritis (MPGN), scleroderma, and autosomal dominant polycystic kidney disease (ADPKD) account for the many cases of CKD developing in patients between the ages of 40 and 55 years. In the cohort of patients older than 55 years, atheroembolic disease, paraproteinemia (multiple myeloma, amyloid), nephrosclerosis, and analgesic nephropathy are causes of CKD. The number of individuals older than age 70 who are developing CKD is growing exponentially. Note that in patients older than 40 years there is a significant burden of CKD as a consequence of diabetes and hypertension.

The primary parenchymal renal diseases that present the greatest propensity for progress are FSGS, RPGN, and MPGN. The development of CKD in patients with minimal change disease is rare in children and is also rare in adults undergoing a steroid-responsive clinical course. Patients at highest risk are those who do not respond to steroid therapy or who become late steroid nonresponders. The course of untreated FSGS is usually progressive to ESRD. Both children and adults usually develop ESRD 5 to 20 years from presentation. Malignant FSGS on biopsy exhibits a more rapid course to ESRD in 2 to 3 years. Those features associated with a more accelerated course are proteinuria greater than 10 to 15 g/day, SCr greater than 1.5 mg/dL at presentation, significant interstitial fibrosis, and glomerular sclerosis on biopsy.

TABLE 46-6 Incidence of Reported End-Stage Renal Disease by Detailed Primary Renal Diagnosis

DIAGNOSIS	PERCENT
Diabetes mellitus	38
Hypertension	25
Glomerulonephritis	14
Cystic kidney disease	5
Urologic	2
Unknown/Missing/Other	15

The data reported here have been supplied by the U.S. Renal Data System. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

From U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda (MD): National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013.

Although MPGN type 1 is a slowly progressive disease, type 2 is more aggressive with a higher percentage of sclerotic glomeruli, crescent number, and greater degree of interstitial fibrosis. These features portend a poor outcome. Progressive renal insufficiency can occur in 20% to 25% of patients with MPGN progressing to ESRD during the course of 20 years. At presentation, it is difficult to predict the renal outcome in most patients with membranous GN compared to those with MPGN.

Forty percent of individuals with IgA nephropathy progress to ESRD after approximately 20 years of clinical disease. Markers of poor outcomes are persistent hypertension, proteinuria greater than 2 g/24 hr, initial abnormal SCr at time of biopsy, and severe sclerotic changes and interstitial fibrosis on biopsy.

A number of systemic diseases involve the kidney and can lead to progressive renal insufficiency (Box 46-8). Progressive deterioration in renal function can occur in systemic vasculitis because of Goodpasture syndrome, granulomatosis with polyangiitis (formerly Wegener granulomatosis), Henoch-Schönlein purpura, and cryoglobulinemia with or without hepatitis C. Serologic tests (cryoglobulins, ANCA analysis, immune complex

BOX 46-8 Causes of Progressive Chronic Kidney Disease

TUBULOINTERSTITIAL

Hematopoietic: sickle cell disease, lymphoproliferative, dysproteinemia, neoplastic

Urologic: ureteral obstructions, reflux, prune-belly syndrome, prostatic hypertrophy

Vascular: radiation, hypertension, atheroemboli

Metabolic: cystinosis, oxalosis, uric acid nephropathy, hypercalcemia

Immunologic: renal allograft rejection, Sjögren syndrome

Toxic: analgesic, NSAIDs, chemotherapy

Immunosuppression: tacrolimus, cyclosporine

Heavy metals: lead, lithium

HEREDITARY

Sickle cell disease

Cystic disease: ADPKD, medullary cystic disease

Alport syndrome

Karyomegalic interstitial nephritis

PRIMARY RENAL DISEASE

Glomerular: idiopathic glomerulonephritis

Minimal change disease

Focal segmental glomerulosclerosis

Membranous glomerulonephritis

IgA nephropathy

SYSTEMIC DISEASES

Diabetes mellitus

Infection-related glomerulonephritis

SLE, HSP, systemic sclerosis

Dysproteinemias/amyloid

Thrombotic microangiopathies

Vasculitis: crescentic glomerulonephritis, acute diffuse glomerulonephritis, ANCA glomerulonephritis (microscopic polyangiitis), Granulomatosis with polyangiitis, Churg-Strauss syndrome, Goodpasture syndrome, granular cell arteritis

ADPKD, autosomal dominant polycystic kidney disease; ANCA, antineutrophil cytoplasmic antibody; HSP, Henoch-Schönlein purpura; IgA, immunoglobulin A; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

markers, antibodies to hepatitis B or C, antistreptolysin O, hemolytic complement levels CH50 and C3), and biopsy of temporal artery or kidney are useful in classifying the clinical presentation into the correct vasculitis category. A significant glomerular insult on biopsy coupled with a poor response to therapy signifies patients at risk for developing worsening renal dysfunction and eventual ESRD.

In type 1 diabetic patients, 40% to 50% of patients will reach ESRD between 7 and 10 years after the onset of proteinuria. In most patients with type 2 diabetes mellitus, the time of onset is unknown, thus complicating the ability to predict the course of renal failure. Moreover, a significant percentage of patients have concomitant risk factors (smoking, hypertension, hyperlipidemia) along with the proteinuria and nephrosclerosis, and these factors may accelerate time to ESRD.

Monoclonal immunoglobulins or light chains in both the serum and urine are observed in dysproteinemic states of light-chain nephropathy, amyloid, and cryoglobulinemia. Patients usually present with undiagnosed increases in SCr and proteinuria and are usually older than 40 years. Treatment of light-chain deposition disease is suboptimal, with a significant percentage of patients progressing to ESRD if their presenting SCr values are greater than 4 mg/dL.

Malignancies of the gastrointestinal tract, breast, renal cell, prostate, or skin can mediate an immune complex nephropathy potentially leading to CKD. Urologic, gynecologic, and lymphoproliferative malignancies can also result in renal injury and progressive chronic renal insufficiency. Non-Hodgkin lymphoma is associated with MGN, and retroperitoneal tumors can cause ureteral obstruction and parenchymal infiltration, or both.

Certain hereditary diseases (sickle cell nephropathy, ADPKD, medullary cystic, aplastic, dysplastic, or hypoplastic kidneys) can also lead to CKD. ADPKD is the most common hereditary renal disorder leading to ESRD. Gene linkage may be helpful in identifying the ADPKD gene loci on the short arm of chromosome 16. This test can be performed in utero in children and in adults before cyst development. Only about 50% of ADPKD patients progress to renal failure. Risk factors for progression include male gender, African origin, early age of presentation, ADPKD 1 gene, hypertension, and gross hematuria (Grantham, 1997). Diverticular disease, cardiac valvular disease, and intracranial aneurysms are more common in ADPKD patients than in the general population and need to be considered in their care. Patients with ADPKD should be differentiated from those with acquired renal cystic disease (ARCD). ARCD develops in the setting of CKD and end-stage kidney disease and is a consequence of renal disease rather than a cause. The important correlation associated with ARCD is the increased incidence of renal cell cancer (Denton et al, 2002). Historically there has been no established correlation of ADPKD with renal cancer, although it may occur in this setting. This concept has been questioned in several pathologic studies identifying a higher incidence of tumors in ADPKD (Hajj et al, 2009; Jilg et al, 2013). It is unclear whether ADPKD itself contributes to cancer development or whether it is related to CKD/ESRD, similar to ARCD.

Medullary cystic disease sometimes can be confused with the benign condition of medullary sponge kidney. Medullary cystic disease presents in childhood with tubular cystic lesions at the cortical medullary junction and can be most accurately detected by kidney biopsy. The kidneys are usually small, and the disease progresses to ESRD at a variable rate.

Tubular interstitial disease is an uncommon cause of CKD. Clinical manifestations depend on the degree of involvement, the tubular sites involved, and the level of compensation that the uninvolved areas provide. The diagnosis of chronic interstitial nephritis depends on the urinalysis and clinical history. The urine findings are variable, and white blood cells may be present. Obtaining an accurate medication history is essential, considering the broad range of etiologies. Three percent to 20% of patients treated with lithium with the passage of time develop CKD (Boton et al, 1987). Chronic lead nephropathy may demonstrate a protracted course

that is gradually irreversible as evidenced by small contracted kidneys. Lead nephropathy can be associated with renal adenocarcinoma. Another form of chronic interstitial nephritis that progresses to ESRD is analgesic nephropathy. The course in analgesic nephropathy is variable depending on the number of pills consumed (Kuo et al, 2010).

Obstructive uropathy involving the ureter, bladder, or urethra can lead to progressive renal insufficiency. Undetected ureteropelvic junction obstruction and posterior urethral valves are the most common types of congenital causes for progressive renal failure. Newer spiral CT methods may prove helpful in identifying the obstructing lesion. Regaining renal function post-obstruction is dependent on both the degree and duration of obstruction (<2 weeks) and preservation of specific tubular acidifying abilities.

The percentage of the ESRD population whose condition is attributable to reflux nephropathy and nonreflux nephropathy has changed with time (Craig et al, 2000). In a study of pediatric renal failure trends in Australia and New Zealand, reflux represented a much larger proportion of the population in the 1970s than it did between 2002 and 2006 (Orr et al, 2009). Correspondingly, the incidence of hypoplasia/dysplasia increased during the same time period. There are debates regarding whether this may be attributed to changing disease categorization or more aggressive therapy of reflux. Finally, when stratified by age, reflux is more common in older children than hypoplasia/dysplasia, making it important for adult urologists to recognize. Women with reflux nephropathy demonstrate an increased risk of accelerated progression during pregnancy if the SCr is greater than or equal to 2.49 mg/dL. Vesicoureteral reflux may result in CKD from renal scarring. Vesicoureteral reflux may be either unilateral or bilateral, and progression to renal failure is related to the severity of reflux. Congenital reflux, particularly the higher grades, may be associated with renal dysmorphism where scarring is a nonpreventable consequence of maldevelopment. By contrast, acquired scarring is a consequence of pyelonephritis. It is this latter acquired group where aggressive management of reflux may prevent renal loss. Renal biopsy can be diagnostic, as well as prognostic, in obstructive nephropathy when relief of obstruction is not followed by restoration of renal function to baseline. A review of North American Pediatric Renal Trials Collaborative (NAPRTC) data showed that patients with reflux and CKD progressed to ESRD at a lower rate than those with aplasia, hypoplasia, or dysplasia (Novak et al, 2009). Furthermore a history of urinary tract infection on entry to the registry was a risk factor for progression to ESRD.

Through time, untreated urolithiasis can result in CKD (Saucier et al, 2010). Gupta and colleagues reviewed the natural history of 33 urinary stone patients with a presenting SCr greater than 2.0 mg/dL before surgical intervention and after placement of ureteral stent or percutaneous nephrostomy tube (Gupta et al, 1994). The mean decrease in SCr with treatment was 1.2 mg/dL. There was no statistical difference in the rate of decrease between patients with pretreatment SCr levels of 2 to 2.9 mg/dL versus those with greater than 3 mg/dL. Furthermore, in an epidemiologic study by Rule and colleagues (2009), residents from Olmsted County with a history of a documented kidney stone (n = 4774) were more likely to develop CKD after the initial diagnosis than controls (Rule et al, 2009).

RAS can result in progressive azotemia (Piecha et al, 2012; Textor et al, 2013). "Flash" pulmonary edema with oliguria and azotemia may suggest the presence of bilateral RAS, warranting further evaluation. Usually, when the SCr is greater than 3 mg/dL, there is an underlying parenchymal abnormality contributing to kidney failure, in addition to the RAS. Several large multicenter trials have demonstrated that intervention for RAS may not necessarily lead to renal functional improvement (RENAL Replacement Therapy Study Investigators et al, 2009; Cooper et al, 2014).

Accurately monitoring the rate of decline in residual renal function (RRF) is important to determine whether the observed change in RRF is consistent with the natural history of the underlying disease or the result of an acute insult. If the RRF decline is inconsistent, an evaluation to uncover an alternate cause is

warranted. Patients with CKD are at risk for acute renal failure from a broad range of causes. Nephrotoxic agents, infection, volume depletion, hypotension, progressive RAS, hypercalcemia, and hyperuricemia may all lead to worsening of underlying stable CKD as delineated in [Box 46-9](#).

BOX 46-9 Factors Associated with Acute Deteriorations in Chronic Kidney Disease

NEPHROTOXIC

Contrast-induced
Pharmacologic agents
Aminoglycoside antibiotics
Nonsteroidal anti-inflammatory drugs
Cyclooxygenase-2 inhibitors
Chemotherapeutic agents
Antirejection agents (cyclosporine, tacrolimus)
Anesthetic agents

AUTOREGULATORY DYSFUNCTION

ACE inhibitors
Angiotensin receptor blocker

ANATOMIC/STRUCTURAL

ADPKD and ACE inhibitors
Obstruction
Progressive renal artery stenosis
Renal vein thrombosis
Nephrolithiasis

HEMODYNAMIC/PERFUSION DISORDERS

Congestive heart failure
Perioperative hypotension
Volume depletion
Gastrointestinal: bleeding, diarrhea, vomiting
Excessive diuresis
Sepsis with vasodilation

PARENCHYMAL INJURY

Acute myocardial infarction
Valvular dysfunction
Superimposed “new” glomerulonephritis

INTERSTITIAL

Hypercalcemia
Hyperuricosuria
Atheroemboli

DRUG-INDUCED

Penicillin analogues
Cephalosporins
Sulfonamides
Rifampin
Diuretics
Thiazides
Furosemide

MISCELLANEOUS

Phenytoin
Allopurinol
Cimetidine

Clinical Assessment of Chronic Kidney Disease (Function, Proteinuria, Radiology, and Biopsy)

In practice, after the GFR decreases to less than 60 mL/min/1.73 m² for 3 months or more, patients are classified as having CKD ([Levin and Stevens, 2014](#)). The adjusted relative risk from a population survey adjusted for age, proteinuria, hematuria, and hypertension showed that changes in GFR occurred at a cutoff SCr value of 1.2 mg/dL (105 μm/L for women) and 1.4 mg/dL (125 μm/L for men) ([Couchoud et al, 1999](#)). However, in extrapolating SCr values to the actual GFR, the relationship was not linear (see [Fig. 46-6](#)). Furthermore, factors such as gender, race, and age affect serum creatinine levels independent of GFR.

Other measurements that complement the SCr value may provide a better index to the underlying predicted GFR. CrCl, CrCl plus urea clearance divided by 2, GFR measurements (inulin or iohalamate), and cystatin C all provide information on the level of renal function. Although the iohalamate GFR is the “gold standard” for measuring renal function, this test is not widely available. The Modification of Diet in Renal Disease (MDRD) (<http://www.mdcalc.com/mdrd-gfr-equation/>) and CKD-EPI (<http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr>) equations are widely used throughout the world to estimate CrCl ([Levey et al, 2014](#)). Cystatin C, a 13-kilodalton nonglycosylated basic protein produced by all tissues, might include an advantage in detecting minor alterations in GFR ([Levey et al, 2014](#)). Cystatin C–based estimates for GFR do not require specification of race and may work better for patients with low muscle mass.

Most forms of CKD gradually and inevitably progress to ESRD throughout a 2- to 10-year time course, depending on the underlying renal lesion responsible for the CKD, combined with patient-specific factors. The KDIGO staging and approach to treatment of CKD currently depends on the cause of CKD, the assessment of GFR (function assessment), the level of proteinuria, and the clinical comorbidities. The National Institutes of Health Consensus Conference of 1993 recommended that patients with CKD be referred to a nephrologist when the SCr has increased to 1.5 mg/dL in females and 2 mg/dL in males ([Consensus Development Conference Panel, 1994](#)).

Renal Function Assessment

Although the SCr level is widely used as an index of renal function, SCr is affected by factors other than the GFR. At any given GFR, the SCr concentration is significantly higher in men than in women, and in blacks than in whites. Total CrCl usually exceeds the GFR because of tubular secretion, whereas the urea clearance is usually lower than the GFR because of tubular reabsorption. Some advocate that the mean of the creatinine and the urea clearance might provide an improved estimate of the GFR than either of these provide separately. Factors associated with creatinine excretion (age, gender, ethnicity, tubular creatinine secretion, and inhibition) might affect the accuracy of standard SCr measurements. Two notable drugs commonly used in clinical practice that interfere with tubular excretion of creatinine are trimethoprim and cimetidine. These can alter serum creatinine–based eGFR by inhibiting tubular creatinine excretion. The MDRD study equation to predict the GFR incorporates SCr concentration and demographic characteristics (age, gender, and ethnicity). It is more accurate than other more widely used predictive equations or parameters; however, it tends to underestimate GFR at higher GFR ranges. Although the MDRD study equation has gained popularity, a newer equation to estimate GFR has been published. This new model, the Chronic Kidney Disease Epidemiology (CKD-EPI) study equation, is expected to replace the MDRD study equation because it was developed using a combination of several studies in which kidney function was measured, including the MDRD Study ([Levey et al, 2014](#)). Although this equation retains the very good performance observed with the MDRD equation in subjects with eGFR below 60 mL/min/1.73 m², it further provides a lower bias in subjects

with better preserved GFR levels (Levey et al, 2009). More recently, an equation that incorporates not only serum creatinine but also cystatin C has been proposed. Using this equation, the estimation of GFR was found to be more precise and accurate, but also, importantly, the addition of cystatin C appeared to strengthen the association between low eGFR with the risk of ESRD and mortality (<http://mdrd.com>).

Although these equations are better than other standard measures for GFR, they are still inaccurate for patients not in a steady state for creatinine balance or those with a medical condition interfering with creatinine excretion or creatinine assay, or both (diabetic ketoacidosis or therapy with certain cephalosporins). These equations are still of doubtful application in subjects with no kidney disease and normal kidney function such as potential living donors. In donors, the remaining kidney is normal and there is no underlying cause of chronic renal injury. The KDIGO cause, GFR, albuminuria represents an improved method for classifying kidney disease and more accurately portraying disease progression risk (KDIGO Committee, 2013; Levin and Stevens, 2014).

Considering the K/DOQI and the new KDIGO staging of renal function linked to the level of GFR, a number of medical centers and commercial laboratories are using eGFR from SCr as a primary method for reporting kidney function because of inadequacies in SCr alone. The MDRD study equation is used most commonly to estimate GFR; however, it is expected that most laboratories eventually incorporate the CKD-EPI equation as the main method for estimating GFR. The estimation of GFR by any equation is not appropriate for patients who experience rapidly changing kidney function, are at the extremes of age and body size, exhibit malnutrition or obesity, are paraplegic or quadriplegic, consume a vegetarian diet, or have diseases that impact skeletal muscle status. Moreover, in sick, hospitalized patients with moderate to advanced renal failure, the MDRD equations and eGFR perform poorly when estimating GFR and are not reliable measurements of RRF (Poggio et al, 2005).

Proteinuria

Proteinuria is a marker for glomerular injury. Increased excretion of albumin is a sensitive marker for CKD attributable to diabetes mellitus, glomerular disease, interstitial disease, and hypertension. The American Diabetes Association and the NKF have historically recommended screening assessment using proteinuria measurement to detect CKD (Levey et al, 1998; American Diabetes Association, 2001). More recently, the revised KDIGO classification of CKD proposed to add the presence or absence of albuminuria to the stages of CKD, especially CKD stage 3. Studies suggest that this marker is as important as GFR in predicting mortality and ESRD (Astor et al, 2011). In adults, albuminuria can be identified by the use of albumin dipstick, urinary albumin concentration, ACR measured in a spot morning urine sample, or 24-hour urinary albumin excretion (Gansevoort et al, 2005). The standard urine protein dipstick is insensitive for low concentrations of albumin (<10 mg/dL) and for some immunoglobulin light-chains. Dehydration, hematuria, exercise, infection, and extremely alkaline urine (pH >8) can cause false-positive dipstick readings. Alternatively, a random urine protein/creatinine ratio can also be used for the assessment and management of patients with established CKD (see Table 46-5). This approach provides an assessment of proteinuria comparable to a 24-hour urine collection. Exceptions are in subjects with large variations in muscle mass (either low or high) in which the ratio could be distorted.

Radiographic Assessment

The radiographic assessment of CKD patients should take into account the impact of iodinated contrast on the RRF. Imaging techniques in CKD are usually used for the investigation of new AKI or for the investigation of potential problems in nonrenal sites (e.g., cardiac catheterization, peripheral vascular concerns, abdominal

investigations). Contrast material can induce the worsening of underlying renal disease to the point of requiring RRT. The diagnostic importance of the contrast study must be weighed against the risk of contrast-induced injury so that the significance of the potential findings justify any downside risks. All patients with an eGFR less than 30 mL/min/1.73 m² should be considered for alternative diagnostic testing. For an eGFR between 30 and 60 mL/min/1.73 m², prophylactic preventive strategies to avoid worsening renal function should be implemented. Specific measures may help lower the risk for AKI in patients with CKD who are undergoing radiographic assessment. These include volume expansion, hydration with IV administration of normal saline solution (sodium chloride 0.9%), using low-osmolar contrast or iso-osmolar contrast media, and using minimal doses of contrast. Alternatively, noncontrast imaging techniques such as CO₂ angiography should be used. Avoiding short intervals between contrast studies might also be of help (Thomsen, 2003; Liss et al, 2005). See Prevention of Acute Tubular Necrosis for recommendations. The use of gadolinium instead of iodinated contrast material should be considered for those subjects with more preserved kidney function (>30 mL/min/1.73 m²), always keeping in mind the risk for nephrogenic systemic fibrosis (NSF) (Manjunath and Perazella, 2011; Perazella and Reilly, 2011).

The value of normal saline solution hydration in patients with CKD and diabetes mellitus to decrease the risk for contrast-induced nephropathy is established (Solomon et al, 1994). Although no additional benefit to mannitol has been shown in the diabetic patient undergoing radiocontrast procedures, sodium bicarbonate solution infusion along with *N*-acetylcysteine may potentially be of help. The antioxidant *N*-acetylcysteine (600 mg orally twice a day on the day before and on the day of administration of the contrast agent) along with hydration using a 0.45% saline solution intravenously may decrease the risk of AKI from radiographic contrast agents in this patient group, although debate exists regarding the value of this intervention (O'Sullivan et al, 2013).

Although not a cause of AKI or a trigger to progression of CKD, the use of gadolinium for imaging techniques such as magnetic resonance imaging (MRI) has become a matter of significant concern for subjects with moderate to advanced CKD. The association between the use of gadolinium-based agent contrast and NSF is established (Perazella, 2008; Reiter et al, 2012). NSF is a systemic condition characterized by fibrosis in several organ sites. NSF in patients with ESRD who have received gadolinium has been universally described with fibrosis of the skin. Symmetrical, bilateral fibrotic indurated plaques or subcutaneous nodules characterize this condition. The feet, ankles, shins, and hands are common initial sites of involvement followed by extension to more proximal areas of the extremities, trunk, and buttocks. Skin involvement occurs in all cases, with systemic organ involvement being more variable. Connective tissues and muscles can be involved, which limits range of motion in these patients. Other visceral organs can also be involved. The diagnosis is clinical and histopathologic. The natural history of NSF is characterized as progressive, leading to a high mortality rate, although the disease may stabilize in a small percentage of subjects.

Gadolinium is a nonionic, hyperosmolar contrast agent excreted unchanged by the kidney, so its half-life (about 1 to 1.5 hours in subjects with normal kidney function) is prolonged with decreasing kidney function. Several types of gadolinium formulations are available, and NSF has been described with all of them, although the risk may vary depending on the formulation. In contrast to iodinated contrast agents, gadolinium does not seem to have a direct nephrotoxic effect, but its toxicity to other tissues when not renally excreted is of concern.

Avoidance of gadolinium in patients with advanced kidney disease (<30 mL/min/1.73 m²) or on dialysis treatment is the main preventive strategy because no effective treatment exists after the disease has initiated (Perazella, 2008; Perazella and Reilly, 2011; Reiter et al, 2012). If the use of gadolinium is absolutely required (benefit of study outweighs risks), then HD treatment

should immediately follow the administration of gadolinium in those patients already on dialysis. PD seems not to be efficient in removing the agent, and thus a few HD sessions should be considered if gadolinium administration is unavoidable.

Urinalysis and Kidney Biopsy

The urine sediment examination is helpful in detecting CKD and in identifying the type of kidney disease. All patients with CKD should undergo a urinary sediment examination. Cells can originate from the kidney or from other sites within the urinary tract. The presence of a RBC cast strongly suggests glomerulonephritis, especially if the patient is dysmorphic. Urinary eosinophils are usually associated with allergic tubular interstitial nephritis although a study challenges that notion (Muriithi et al, 2013). If the urinalysis is negative, despite the patient's having apparent CKD, a second specimen should be examined at another time. The urine sediment should be examined because urinary dipsticks cannot detect tubular epithelial cells (that are casts in the urine), crystals, fungus, or parasites.

A renal biopsy is not usually performed to evaluate asymptomatic hematuria but is warranted if the GFR is less than 60 mL/min/1.73 m² and the urinalysis is abnormal. The approach to performing kidney biopsy, whether closed (CT-guided, ultrasonography-guided) or open (standard or laparoscopic), depends on the overall clinical status, body habitus, patient's clotting parameters, and cumulative experience of the physician. The structural severity of glomerular injury and the immunopathologic category of disease are helpful in predicting renal outcome.

Renal Protective Strategies

Regardless of the nature of the initial insult, after a critical number of nephrons are destroyed, a steady decline in GFR occurs as the progressive loss in viable nephrons occurs. Strategies for delaying the relentless loss in nephron mass (Brenner, 2003) are inconsistently used across a population with CKD. Yet, it is becoming increasingly clear that well-designed renal assessment and management programs are feasible and can be applied systematically to large numbers of CKD patients to decrease the rate of progression.

A report of the International Society of Nephrology 2004 Consensus Workshop on Prevention of Progression of Renal Disease (Zandi-Nejad and Brenner, 2005) identified a number of therapeutic measures to prevent the progression of CKD, including lifestyle modifications, blood pressure control, glycemic control, reduction of proteinuria, protein restriction, lipid control, avoidance of nephrotoxic agents, early referral to a nephrologist, correction of anemia, optimization of calcium-phosphorus product, correction of acidosis, and maintenance of fluid balance.

Various pharmacologic trials comparing different medications have shown that patients with better blood pressure control have significantly slower rates of deteriorating kidney function. New guidelines are available for treatment of hypertension in CKD (James et al, 2014). For patients with CKD, drug therapy should target blood pressure lower than 140/90 mm Hg. Drugs that block the renin-angiotensin system such as ACE inhibitors or ARBs are now first-line antihypertensive medications for patients with CKD. Conceptually, angiotensin II is critical in causing progressive renal disease by both hemodynamic and non-hemodynamic mechanisms. Blockade of the renin-angiotensin system contributes to the preservation of renal function by decreasing intraglomerular pressure and proteinuria. Because proteinuria plays a sentinel role in renal scarring, a reduction in proteinuria correlates with slowing of disease progression. A meta-analysis of randomized clinical trials confirmed the predictive value of proteinuria and the renal protective effect of proteinuria reduction by ACE inhibitor therapy in large patient series (Chiurchiu et al, 2005). Clinical research findings support the view that preservation of renal function through angiotensin blockade can be achieved in

patients with either diabetes mellitus or nondiabetic nephropathy (Kshirsagar et al, 2000b). Reductions in proteinuria are greater with ACE inhibitors than with any other antihypertensive agent at the same level of blood pressure control. Multiple ACE inhibitors have been evaluated in CKD. In the Microalbuminuria Cardiovascular and Renal Outcomes—Heart Outcome Prevention Evaluation (MICRO-HOPE) a subset of 35,077 patients with diabetes mellitus and microalbuminuria were treated with ramipril (Mann et al, 2001). Ramipril reduced the progression from microalbuminuria to overt nephropathy by 24% ($P = .027$). In the ACE Inhibitor in Progression of Renal Insufficiency (AIPRI) study, only part of the risk reduction in the ACE inhibitor group could be explained by the antihypertensive or antiproteinuric effect (Maschio et al, 1996). The AIPRI group performed a meta-analysis of 11 randomized clinical trials consisting of 17,060 patients with nondiabetic renal disease. This study included the conclusion that antihypertensive regimens containing ACE inhibitors are more effective in slowing progression than regimens without ACE inhibitors. This finding was also observed in the Ramipril Efficacy in Nephropathy (REIN) Study (GISEN Group, 1997). Jafar and colleagues (1999) proposed that ACE inhibitors act by mechanisms in addition to their blood pressure-lowering and antiproteinuric effects (Jafar et al, 1999).

ARBs inhibit the type I angiotensin II receptor. Two large prospective, randomized trials have demonstrated that ARBs delay the progression of CKD in type 2 diabetic patients with overt nephropathy (Lewis et al, 2001; Parving et al, 2001). The Irbesartan Diabetic Nephropathy Trial (IDNT) examined the effect of ARBs (irbesartan) versus conventional therapy or the CCB amlodipine in 1715 patients with type 2 diabetes. The doubling of serum creatinine was 29% ($P = .009$) and 39% ($P < .001$) less than the risk in placebo and amlodipine-treated groups, respectively. Moreover, the Microalbuminuria Reduction with Valsartan (MARVEL) trial (Parving et al, 2001) supported the view that ARBs can potentially retard the progression of CKD in patients with type 2 diabetes.

Combining ACE inhibitors and ARBs may lead to further reductions in CKD progression, along with blood pressure, proteinuria, and microalbuminuria; however, a study has questioned this approach because of safety (Fried et al, 2013). Patients in this study received an ARB and were then randomized for the additional receipt of an ACE or a placebo. The study confirmed modest benefit for progression of renal failure in the dual therapy group, but this attenuated with time. There was no mortality or cardiovascular benefit for dual therapy. The study was stopped because of safety concerns related to hyperkalemia and AKI in the dual-treated group (Fried et al, 2013). Some CKD patients on ACE inhibitors might experience an acute decrease in reserve renal function with low renal perfusion states because of dehydration, congestive heart failure, and hypotension. Individuals with bilateral RAS and ADPKD patients with cyst size larger than 10 cm may also experience a decrease in reserve renal function while on ACE inhibitor therapy. A rise in serum creatinine of more than 1 mg/dL after beginning ACE inhibitor therapy should prompt a clinical evaluation to explain the change in baseline function.

An intricate relationship exists between hemodynamic factors that regulate vascular tone and metabolic factors that govern circulating lipids. It is now apparent that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors reduce production of molecules involved in fibrogenesis, reduce mesangial and smooth muscle cell proliferation, and decrease production of integrin adhesion molecules (Keane, 2000). Although HMG-CoA reductase drugs can be part of the CKD treatment regimen, they are associated with a reduction in proteinuria and did not lead to GFR improvements (Navaneethan et al, 2009b). Their main advantage remains cardiovascular protection (Navaneethan et al, 2009b).

For more than 25 years it has been known that protein restriction can ameliorate many symptoms of renal insufficiency and prevent its progression (Fouque and Laville, 2009). However, without regular dietary consultation, patients on a low-protein diet may experience a decrease in protein intake and deterioration of several nutritional parameters. A number of different diets have been used to help slow the progression of CKD. These dietary formulations

include low-protein (0.6 g protein/kg ideal body weight) diets, very-low-protein diet (0.3 g protein/kg/day predominately vegetable protein) supplemented with essential amino acids, or very-low-protein diet supplemented with both essential amino acids and nitrogen-free analogues of amino acids (ketoacids). The overall dietary requirement in CKD is approximately 0.6 to 0.8 g of protein/kg/day (Fouque et al, 2011). An in-depth analysis of the MDRD study results did note that each 0.2-g/kg/day reduction in protein intake was associated with a 29% slower rate of loss of GFR and a 51% prolongation in the time to dialysis for nondiabetic patients (Mitch, 2000). Several additional studies have demonstrated the beneficial effect of dietary protein restriction on retarding the progression of CKD in both diabetic and nondiabetic patients (Pedrini et al, 1996; Kasiske et al, 1998; Fouque and Laville, 2009).

Table 46-7 summarizes a comprehensive strategy to achieve renal protection in patients with CKD (Jafar et al, 1999; Zandi-Nejad and Brenner, 2005; James et al, 2014). The comprehensive

strategy illustrates specific interventions, treatment approaches, monitoring, and target benchmarks of treatment.

Preoperative Evaluation of Patients with Chronic Kidney Disease and End-Stage Renal Disease

In CKD/ESRD patients scheduled for an elective surgical procedure, a thorough preoperative assessment to define risk is warranted (Trainor et al, 2011). Preoperative risk falls into three categories: patient-specific, procedure-specific, and anesthesia-specific risks (Bronson, 2000). CKD patients should be closely evaluated because they may exhibit multiple comorbidities that would affect outcome. The risk of a specific procedure is proportional to the physiologic stress associated with the procedure. The American Society of Anesthesiologists physical status scale defines five classes, each with a specific 7-day mortality from 0.07% (no organic or psychiatric disease) to 33.58% (moribund with little chance of survival). However, this scale does not consider procedure-related risks. There is no set risk profile specific for CKD. In general, procedures associated with a higher level of risk include major joint replacement, craniotomy, cardiac procedures, large bowel procedure, and exploratory laparotomies. The anesthesia-specific risk takes into account the effects of anesthetic agents and physiologic responses to a host of possible operative events such as hypotension, hypertension, blood loss, tachycardia, hypoxia, myocardial depression, and the acute worsening of renal function. **In the CKD/ESRD population the major predictors of cardiac events are the presence of active ischemia, poor left ventricular function, and baseline ventricular arrhythmia.**

Formal cardiac testing may be warranted preoperatively for patients with established ischemia, ventricular arrhythmias, and abnormal left ventricular ejection fraction. Although it is preferable to obtain an exercise imaging study rather than pharmacologic imaging study, a significant percent of CKD/ESRD patients will not achieve maximal predicted heart rate secondary to limited exercise capacity and medications. Pharmacologic testing with dobutamine stress echocardiography may be the best screening test for coronary disease in CKD (Marwick et al, 1998). A negative study showed a low frequency of events during the short term (Chertow et al, 1997).

Hypertension also plays a role in determining operative risk. A blood pressure of 180/110 mm Hg or more is associated with a greater risk for preoperative ischemic events. When possible, surgery should be delayed to bring blood pressure down to an acceptable level in patients with hypertension and CKD (James et al, 2014).

CKD patients with chronic obstructive pulmonary disease, active asthma, or a current infection are at high risk for pulmonary complications. Upper abdominal and thoracic surgeries carry the greatest risk of compromising pulmonary function. If the forced expiratory volume vital capacity in 1 second (FEV₁) is greater than 2 L, the risk of a complication is low. An FEV₁ less than 1 L is associated with a significantly greater risk. Discontinuing smoking at least 3 months before surgery can significantly decrease the risk of pulmonary complications.

CKD patients with diabetes mellitus should achieve optimal control (<200 mg/dL) before surgery. The risk for infectious complications increases with blood sugars greater than 300 mg/dL. CKD patients with diabetes mellitus on oral hypoglycemic agents should be carefully monitored because hypoglycemia with sepsis and/or malnutrition can markedly increase morbidity and mortality.

Elective surgery should be avoided in CKD/ESRD patients in a malnourished state. Serum albumin less than 3.5 g/dL, prealbumin less than 30 mg/dL, protein-nitrogen appearance or protein catabolic rate less than 0.8 g/kg/day, and subjective global nutritional assessment score of less than 5 signify malnutrition. Nutritional (protein/calorie) supplements should be used preoperatively to improve the baseline nutritional status. In the setting of anorexia, all offending drugs should be eliminated and consideration given for using pharmacologic appetite-stimulating agents (megestrol acetate).

TABLE 46-7 Comprehensive Renoprotection Strategy for Chronic Kidney Disease

FOCUS AREA	GOAL	TREATMENT
Blood pressure control	<140/90 mm Hg	ACE inhibitor ARB Salt restriction Diuresis
Reduction in proteinuria	<0.5 g/day	ACE inhibitor ARB ? Aldosterone blockade
Glycemic control	Hb _{A1C} <7%	Oral hypoglycemic agents Diet Insulin
Dietary protein restriction	0.6-0.8 g/kg/day*	Dietary consult
Lipid lowering	LDL ≤70 mg/dL†	Statin‡ Triglyceride-lowering agent
Anemia management	Hb at 11-12 g/dL	Erythropoietin Iron
Lifestyle modifications	Ideal body weight* Smoking cessation Exercise 3x/wk Depression modification	Weight-loss program (dietary counseling, surgery) Antidepressants
Calcium × phosphorous product	Ca × phos. product <55 Phosphorus <5.5 mg/dL Intact PTH 70-110 pg/mL (CKD stage 4) 30-70 pg/mL (CKD stage 3) 25 (OH) vitamin D >30 ng/mL	Vitamin D supplementation Use dietary phosphorus restriction Phosphate binders

*Avoid malnutrition.

†Consider measuring nontraditional risk factors: homocysteine, lipoprotein A, C-reactive protein, fibrinogen.

‡Treat hyperhomocysteinemia with folic acid.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; Hb, hemoglobin; LDL, low-density lipoprotein; PTH, parathyroid hormone.

Drug dosing in CKD/ESRD should be closely monitored to avoid both reversible and irreversible toxicities. Avoiding drugs that have the potential to accelerate loss of renal reserve function is of paramount importance. The risk of adverse events may be linked to the patient's degree of residual renal dysfunction. Uremic toxins might modulate cytochrome P450 enzyme activity, decrease glomerular filtration of drugs, and alter tubular secretion. High-risk therapies in the setting of CKD-ESRD include ACE inhibitors, radiographic contrast, volume depletion, NSAIDs, cyclooxygenase-2 inhibitors, and aminoglycosides.

Conservative Management: Prevention of Uremic Complications

A comprehensive approach to achieving optimal renal care begins with the early detection of renal failure followed by the initiation of interventions that delay progression, prevent uremic complications, modify comorbidities, and when necessary prepare patients for RRT to optimize patient survival (Pereira, 2000).

Decreased GFR is associated with complications in most organ systems. The most important CKD-related complications include hypertension, anemia, malnutrition, bone disease, neuropathy, and alterations in quality of life. As the patient moves from a stage 2 to higher stages of CKD, they are more likely to develop additional comorbidities. The level of scrutiny and the search for comorbidities increases as the stage of kidney disease advances. A number of factors increase cardiovascular risk. These include diabetes mellitus, hypertension, dyslipidemia, smoking, physical activity, psychological factors, anemia, arterial stiffness, vascular/valvular calcifications, and calcium and metabolic bone disease status.

Attention to risk factors is critical to extend survival because a large percentage of patients with CKD die of cardiovascular events before reaching dialysis (Chronic Kidney Disease Prognosis et al, 2010). The Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC8) has updated their guidelines (James et al, 2014). In patients with CKD who are older than 18 years, initial therapy should include an ACE inhibitor or an ARB for blood pressure control that targets blood pressure less than 140/90 (James et al, 2014). These agents provide for renal protection in addition to blood pressure control.

Traditional atherosclerotic risk factors are frequently present in CKD. Low HDL, elevated homocysteine, elevated LDL, and elevated lipoprotein A all define patients at high risk for cardiovascular events warranting lipid-lowering therapy and close cardiovascular screening. The Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) in 2001 suggested that based on results from the Heart Protection study and the PROVE-IT study, additional benefit may be achieved by reducing LDL cholesterol levels to substantially below 100 mg/L, especially in high-risk patients (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Not only should patients use medications before stage 5 of CKD, but these medications should be maintained after the patient is transplanted. A meta-analysis comparing the efficacy of various antilipidemic therapies for PD, HD, and transplant recipients demonstrated the effectiveness of HMG-CoA reductase inhibitors (Massy and Kasiske, 1996). This has been confirmed with an updated report (Navaneethan et al, 2009b). Both statin and fibric acid derivatives have proven effective, although individual differences mandate periodic monitoring of fasting lipid levels and liver function tests. Updated information suggests statin treatment in established dialysis patients should be different. Two large multicenter randomized controlled trials in which two different statins were compared with placebo in HD patients showed no difference in preventing all-cause and cardiovascular mortality despite their efficacy in lowering LDL cholesterol (Wanner et al, 2005; Fellstrom et al, 2009). Based on these studies, the use of statins to prevent mortality in dialysis patients is not warranted (Navaneethan et al, 2009a).

Cigarette smoking is universally recognized as an independent risk factor for cardiovascular disease and should be discouraged with this disease. There is a significant association between current

smoking and cardiovascular outcomes, which further emphasizes the importance of smoking cessation.

Both vascular calcification and valvular calcifications have been found to be more common in CKD patients and these present an impact on survival (Blacher et al, 1999). Although there are no randomized trials that have evaluated whether treatment of calcium-phosphorus abnormalities or the use of calcium-based phosphate binders reduces the risk of CVD outcomes, the recommendation from K/DOQI clinical practice guidelines for bone metabolism and disease in CKD is that noncalcium-based binders be used if there is evidence of severe vascular calcification (Malberti, 2013). The stage of CKD in which bone disease begins to develop has not been well documented, nor has a consensus been reached regarding the optimal screening methods for identifying early abnormalities of calcium-phosphorus metabolism and bone disease in CKD patients. Below a GFR of approximately 60 mL/min/1.73 m², there is a higher prevalence of abnormalities of bone metabolism.

Overweight and obesity are associated with increasing risks for a variety of cardiovascular complications and with higher all-cause mortality. Weight reduction is an important lifestyle modification for overweight patients. Although protein-energy malnutrition and wasting are common among CKD patients, no single nutritional marker is helpful in defining malnutrition. Changes in lean body mass throughout time in CKD may signal not only worsening uremia but also an increased risk for CVD. Specific methods for evaluating a rise in nutritional status include multifrequency bioimpedance, dual x-ray absorptiometry, subjective global assessment, and hand-grip strength.

All diabetic patients with CKD should follow the American Diabetes Association's guidelines for blood glucose control. The target for diabetes control should be a hemoglobin A_{1c} level of less than 7%, a preprandial glucose level of 80 to 100 mg/dL, and a bedtime glucose level of 100 to 140 mg/dL.

Observational studies have shown an association between anemia and adverse cardiovascular outcomes in CKD patients. It is unclear whether treatment of anemia prevents cardiovascular events in CKD patients, but one study showed that targeting higher hemoglobin levels closer to normal ranges was associated with worse cardiovascular outcomes (Singh et al, 2006). Recombinant human erythropoietin (rHu-EPO) is most likely to benefit the CKD patient who is symptomatic with a hematocrit value less than 30%. As recommended by the KDIGO 2012 guidelines, the treatment goal should be to achieve hemoglobin between 10 and 11 g/dL (KDIGO Committee, 2013). Hypertension can be more difficult to control as the hemoglobin is increased with EPO therapy.

Cardiovascular disease begins early in the course of CKD. Among patients with CrCl of less than 25 to 30 mL/min, left ventricular hypertrophy is present in 38% to 45% of patients compared with a prevalence rate of 16% to 31% among patients with higher levels of RRF. Noninvasive testing of patients with kidney failure for cardiovascular disease is helpful, especially in high-risk patients. The diagnostic accuracy of perfusion imaging is lower than in patients not in renal failure. Dobutamine echocardiography has been reported to have a sensitivity of 96% and a specificity of 86% and is the preferred screening instrument for coronary artery disease in CKD/ESRD patients (Marwick et al, 1998). Aggressively addressing comorbidities in CKD that may shorten survival is critical to extending life years for these patients.

Initiation of Renal Replacement Therapy

The 2012 KDIGO guidelines recommend the initiation of dialytic therapy when one of the following are present: symptoms or signs of uremia, inability to control blood pressure or volume, progressive deterioration of nutritional status, or cognitive impairment (KDIGO Committee, 2013). Late complications of renal failure will likely manifest after the GFR is lower than 10 mL/min/1.73 m². It is ideal, however, that patients are evaluated for initiation of RRT and, importantly, for possible preemptive renal transplantation when GFR is below 20 mL/min/1.73 m². Despite

these recommendations, a significant percentage of patients have renal reserve capacity less than 10 mL/min/1.73 m² at the start of dialysis. Obrador and colleagues examined data on 90,897 patients who began dialysis in the United States from April 1995 to September 1997 (Obrador et al, 1999). The mean \pm standard deviation SCr level at initiation was 8.5 \pm 3.8 mg/dL. The mean predicted GFR was 7.1 \pm 3.1 mL/min/1.73 m². Historically, mortality among late referrals is consistently higher than among those with more timely initiated RRT patterns. Predictors of delayed referral among a retrospective cohort of 362 predialysis patients included age 65 years or older, female gender, and congestive heart failure (Holland and Lam, 2000). For HD, mortality is highest early after its initiation (Robinson et al, 2014).

The rationale for timely initiation of RRT is based on several different, independent lines of evidence. As renal function declines, spontaneous dietary protein restriction occurs. Declining renal function is associated with abnormal protein metabolism, malnutrition, and poor clinical outcomes. A lower serum albumin level correlates with an increased mortality risk for both HD and PD patients.

End-Stage Renal Disease Demographics and Treatment Options

There is a steady growth of ESRD patients (CKD stage 5) on RRT throughout the world. The incident rate for ESRD in the United States in 2011 was 357 new cases per million of population (U.S. Renal Data System, 2013). The incidence of ESRD has minimally declined from 2005 to 2011; however, the number of prevalent cases continues to increase (U.S. Renal Data System, 2013). The number of patients with ESRD in the United States is approximately 600,000. The number of transplants has remained relatively unchanged at between 16,000 to 17,000/year, with 9500 to 10,500 deceased donor transplants and 6000 to 7000 living donors each year. There has been a 13% decline in living donation since 2004 and a change in the demographics of the donors (Rodrigue et al, 2013).

Critically important to all ESRD patients is a thorough understanding of dialysis practices that yield improved outcomes. The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a prospective, longitudinal study of HD practices from seven countries with large populations of dialysis patients (France, Germany, Italy, Japan, Spain, United Kingdom, and United States) (Young, 2000). Linking the DOPPS scope of work with the K/DOQI and now KDIGO goals will help to develop continuous quality improvement programs and provide direct feedback to participating dialysis centers worldwide (Augustine et al, 2004). The DOPPS has collected information that will affect issues that relate to anemia management, modifiable HD practices to optimize outcome, vascular access, mortality and hospitalization, nutritional indicators, depression assessment, prescription use, acidosis, and vitamin prescriptions (Pisoni et al, 2012).

The mortality rate of RRT patients is strongly influenced by the percentage of enrolled diabetic patients, the dialysis dose, the type of HD membrane, erythropoietin therapy, and the nutritional status. Adjusted mortality rates of prevalent dialysis patients in the United States are now falling (www.USRDS.org).

Poor long-term survival of ESRD patients is illustrated by comparing the expected remaining lifetime on dialysis or transplant with the general U.S. population (U.S. Renal Data System, 2013). The expected remaining lifetimes for dialysis patients were only one fourth to one sixth of those of the general population. By modality, the expected lifetimes for transplant patients were 2 to 3 times those of dialysis patients. Expected remaining lifetimes in transplant patients are now 70% to 80% of those of the general population. For the ESRD population, females have poorer outcomes as compared with males in terms of more frequent hospitalizations, frequency of anemia, vascular access problems, malnutrition, poorer quality of life, and access to transplantation (Sehgal, 2000).

Multiple RRTs are available for treatment of ESRD patients. The most commonly used RRTs are HD, PD, and renal transplantation. Other treatment options include hemodiafiltration (combination of intermittent hemofiltration with simultaneous HD) and nocturnal home HD (slow-flow HD for an extended period overnight). Outcome comparison suggests that renal transplantation is still the best overall treatment for ESRD patients, despite advances in dialytic options. The time on dialysis may have an impact on the success of replacement therapy. Patients on HD for more than 10 years have a poorer outcome when transplanted as compared with individuals receiving transplants with less time on dialysis (Meier-Kriesche et al, 2000). This finding is probably related to fixed vascular defects that occur in patients on chronic dialysis therapy. Reports confirm that longer waiting time on dialysis negatively affects post-transplant graft and patient survival (Meier-Kriesche et al, 2000). This effect was independent of age, race, donor characteristics, and original disease. Therefore patients who reach ESRD should undergo preemptive transplantation or transplantation as soon as possible after they are on dialysis.

In comparing outcomes between different RRTs for nondiabetic patients, it is essential to consider the type of statistical model used to evaluate mortality (Cox proportional hazards regression vs. Poisson regression), the type of analysis used (intent to treat vs. as treated), and the type of study patient (prevalent vs. incident) (Vonesh et al, 2000). Vonesh and colleagues reported that specific results are closely linked to stratification by age and modality (Vonesh et al, 2004). Appropriate patient selection is critical to optimizing the life years per patient with ESRD. PD provides an early survival advantage compared with HD, whereas patients older than 45 with diabetes may have a survival advantage (in months) if started on HD.

Not all patients will benefit from RRT. Recommendations for withholding or withdrawing dialysis from suboptimal adult ESRD patients have been published. These were based on feedback from the U.S. Renal Physicians Association (RPA) and American Society of Nephrology (ASN) in conjunction with broad representation from ESRD patients, family, and non-nephrologists (Galla, 2000; Fissell et al, 2005).

Currently in the United States 93% of dialysis patients are treated with HD and 7% with PD (U.S. Renal Data System, 2013). The renal disease continuum (Fig. 46-7) demonstrates the critical junctures in renal disease care extending from the early diagnosis to management of the patient on dialysis. Processes of care for each stage should be developed from evidence-based recommendations and linked to auditing tools that can provide organizations and health care teams ongoing feedback for optimizing results. The concept of RRT assignment in an integrated fashion is a key to prolonging ESRD survival. An integrated approach combining HD, PD, and renal transplant during the life of an ESRD patient may provide the best approach to optimizing survival. An integrated care approach whereby patients are started on PD and are transferred in a timely fashion to HD, when PD- or patient-related problems occur, demonstrates an increase in survival compared with those remaining on HD for their entire life span (Van Biesen et al, 2000). Box 46-10 indicates transition points that may stimulate transfer from one modality to another. RRT is preserved longer on PD than on HD. BP is better controlled, and ventricular arrhythmias are observed less often on PD than on HD. Weight gain and inadequate dialysis after 3 years are more common on PD than with HD. Although vascular access problems and hemodynamic instability are the most common reasons for transfer to PD from HD, other reasons include infection (peritonitis, catheter, tunnel infections), inadequate dialysis, and catheter malfunction. Quality guidelines are established for HD adequacy, PD adequacy, vascular access, anemia management, bone metabolism, and nutrition.

Hospitalization Risk in Chronic Kidney Disease/End-Stage Renal Disease

CKD patients are 10 times more likely to be hospitalized, and on average, hospitalization lasts 1 day longer compared with

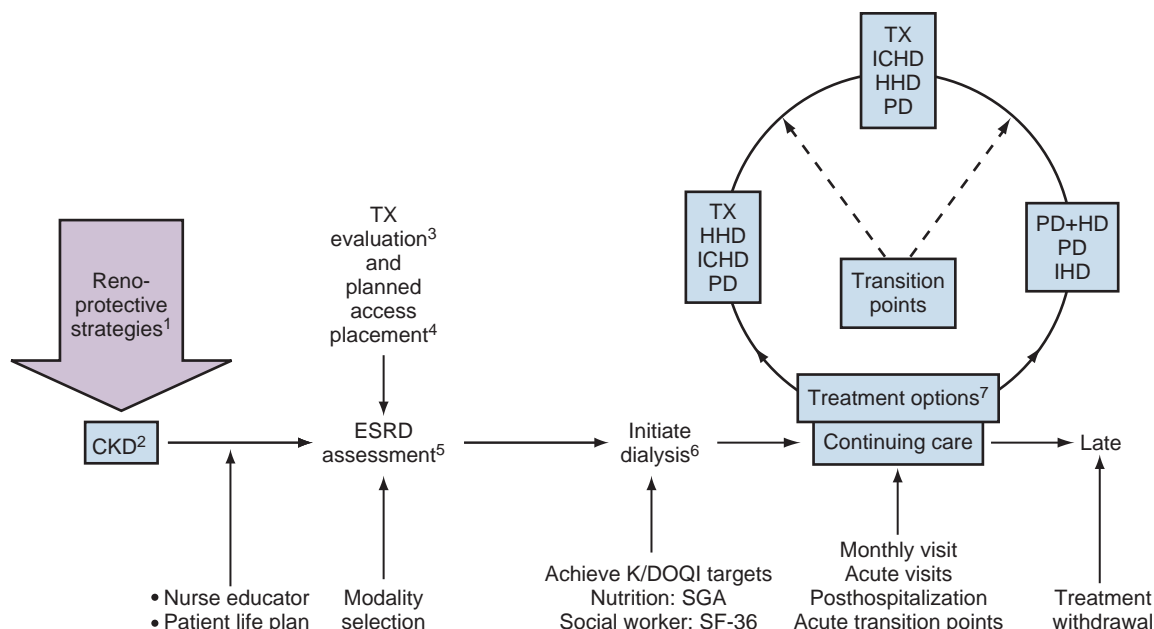


Figure 46-7. Kidney disease continuum. 1, Population screening (serum creatinine >1.2 mg/dL), delay progression (stages 1 and 2). 2, Preserve residual renal function (RRF), educate, and assess comorbidities (glomerular filtration rate [GFR] stages 3 and 4, and higher risk based on albuminuria score as well). 3, Preemptive transplant. 4, Peritoneal dialysis (PD)/hemodialysis modalities. 5, Evaluate complication/risk; RRF 15 to 29 mL/min/1.73 m²: prepare for renal replacement therapy. 6, Initiate dialysis, avoid uremic complications, define physician problem-based care (GFR stage 5: <15 mL/min/1.73 m²). 7, Integrate different therapies throughout time dependent on critical junctures to extend survival years and control comorbidities: malnutrition, uncontrolled blood pressure, inadequate solute/water removal, access failure, RRF preservation. CKD, chronic kidney disease; ESRD, end-stage renal disease; HHD, home hemodialysis; ICHD, in-center hemodialysis; IHD, intermittent hemodialysis; PD, peritoneal dialysis; SF-36, Short Form-36; SGA, subjective global assessment; TX, treatment.

BOX 46-10 Transition Points for Modality Transfers

PERITONEAL DIALYSIS TRANSFER TO HEMODIALYSIS

Recurrent infection
Catheter malfunction
Ultrafiltration failure
Adequacy (solute) failure
Psychological/cognitive burnout
Hospitalization/surgery
Uncontrolled diabetes
Hypotension

HEMODIALYSIS TRANSFER TO PERITONEAL DIALYSIS

Recurrent congestive heart failure
Vascular access failure
Hypercoagulability
Malnutrition
Intradialysis hypotension
Nursing home care

non-renal failure patients (Thamer et al, 1996). Hospital admissions for ESRD patients in the United States have remained relatively stable since 1993, and the number of hospital days has fallen 12% for HD patients, 16% for transplant, and 19% for PD patients. ESRD patients secondary to diabetes are admitted most frequently (U.S. Renal Data System, 2013). Inpatient hospital care

accounts for 41% of the total ESRD costs (Bruns et al, 1998). The most common causes of hospital admission in ESRD include infection and cardiovascular disease (U.S. Renal Data System, 2013). The total hospital discharges by general diagnostic-related group (DRG) charges from 1996 to 1998 for ESRD patients in the United States showed that the four most common causes for admission were circulatory (36.4%), renal system (15.6%), respiratory system (7.4%), and infection (5.7%) (Foley and Collins, 2007; Collins et al, 2009). The hospitalization rates for HD patients have increased 43% since 1993 with the major cause being infection (U.S. Renal Data System, 2013). Vascular catheter access remains an important source of risk. In the PD population, hospitalization rates and infection have remained stable. Patients undergoing RRT are often hospitalized with general medical problems, most often stemming from comorbid conditions. The length of stay for HD patients differed by the medical service to which they were admitted. Overall costs for hospitalization tended to be less on the nephrology service than on internal medicine service (6.3 days vs. 8.1 days) (Kshirsagar et al, 2000a). Total cost per admission was \$2848 more for an HD admit to internal medicine service versus nephrology service, and yet the risk of readmission was not significantly higher.

Rocco and colleagues identified specific risk factors for hospital use in chronic dialysis patients from a cohort of 1572 patients in Network VI (North Carolina, South Carolina, and Georgia). The strongest predictors of the number of hospitalizations per year of patients at risk included low serum albumin, decreased activity level, diabetes mellitus as a primary cause of ESRD, peripheral vascular disease, white race, increasing age, and congestive heart failure (Rocco et al, 1996). Both nutritional status (serum albumin, creatinine, transferrin, prealbumin, and lean body mass [bioelectric

TABLE 46-8 Defining Therapies for Acute Renal Failure in Patients with Chronic Kidney Disease

THERAPY	DEFINITION	INDICATION	MODALITY OPTION
Hemodialysis	Convective-based process across semipermeable membrane	Solute/H ₂ O removal Hyperkalemia	IHD, DHD, CAVHD, CVVHD
Hemofiltration	Convective-based solute removal with plasma water filtered across highly permeable membrane	Volume control, acid-base disorders, azotemia, congestive heart failure, multiorgan failure	IHD, CVVHD, CAVH
Hemodiafiltration	Convective and diffusive process across semipermeable membrane, increased small and large molecule removal	Acidosis, possible multiorgan failure, ARDS, dialysis instability	IHDF, CAVHDF, CVWHDF
Ultrafiltration	Plasma water removal, 2-5 L/24 hr	Fluid removal, congestive heart failure, total body anasarca, intubation or reintubation risk	SCUF, CVVUF, IUF
Sustained low-efficiency dialysis	Slow, convective-based process across semipermeable membrane	IHD treatment failure resulting from hypotension or inadequate clearance	SLED
Peritoneal dialysis	Diffusive and convective transport across peritoneal membrane	Azotemia, volume control, hypotension, without access to continuous hemodialysis treatments	CAPD, CCPD (APD)

APD, automated peritoneal dialysis; ARDS, acute respiratory distress syndrome; CAPD, continuous ambulatory peritoneal dialysis; CAVH, continuous arteriovenous hemofiltration; CAVHD, continuous arteriovenous hemodialysis; CAVHDF, continuous arteriovenous hemodiafiltration; CCPD, continuous cyclic peritoneal dialysis; CVVHD, continuous venovenous hemodialysis; CVWHDF, continuous venovenous hemodiafiltration; CVVUF, continuous venovenous ultrafiltration; DHD, daily hemodialysis; IHD, intermittent hemodialysis; IHDF, intermittent hemodiafiltration; IUF, intermittent ultrafiltration; SCUF, slow continuous ultrafiltration; SLED, sustained low-efficiency dialysis.

BOX 46-11 Proposed Criteria for Initiation of Renal Replacement Therapy

Oliguria (urine output <200 mL/12 hr)
 Anuria or extreme oliguria (urine output <50 mL/12 hr)
 Hyperkalemia ($[K^+]$ >6.5 mmol/L)
 Severe acidemia (pH <7.1)
 Azotemia ($[urea]$ >30 mmol/L)
 Clinically significant organ (especially lung) edema
 Uremic encephalopathy
 Uremic pericarditis
 Uremic neuropathy/myopathy
 Severe dysnatremia ($[Na]$ >160 or <115 mmol/L)
 Drug overdose with dialyzable toxin

From Bellomo R, Ronco C. Indications and criteria for initiating renal replacement therapy in the intensive care unit. *Kidney Int Suppl* 1998;66: S106-9.

impedance)] and inflammatory response (i.e., C-reactive protein [CRP]), are independent predictors of hospitalization in chronic HD patients (Ikizler et al, 1999).

Sarnak and Jaber demonstrated that mortality rates secondary to sepsis are onefold to several hundredfold higher in dialysis patterns (HD and PD) compared with the general population (Sarnak and Jaber, 2000). Renal transplant recipients have sepsis-associated mortality rates higher than the general population but lower than dialysis patients. Infection is the second leading cause of death in patients with ESRD. Acquired immune deficiencies with uremia, advanced age, and a broad array of comorbid conditions contribute to the observed infection risk and admission rate for kidney disease patients.

Acute worsening of renal function may occur in hospitalized CKD patients. The proposed criteria for initiation of RRT in this setting are listed in Box 46-11 (Bellomo and Ronco, 1998). For

ESRD patients undergoing high-risk surgery, sequential daily dialysis for 3 days preoperatively should be entertained to optimize fluid and to ensure stable serum potassium and solute levels.

In patients requiring RRT, aggressive volume and solute control are essential to achieve optimal postoperative recovery. Outpatient dialysis schedules may not meet the needs of in-hospital patients. Some individuals may require more intensive therapy either daily or continuously if they are hemodynamically unstable. A number of different therapies can be used to treat critically ill patients requiring RRT (Table 46-8). Hemodynamically unstable patients might not tolerate intermittent HD and require continuous venovenous hemodialysis.

Patients with serum albumin less than 3 g/dL with correspondingly low prealbumin values less than 25 g/dL should undergo enteral feedings or aggressive oral supplementation. TPN may be used if the gastrointestinal tract is nonfunctional. Aggressive ultrafiltration either alone or in conjunction with regular HD should be implemented to control edema and to decrease the risk for intubation or reintubation, congestive heart failure, and infectious-related complications.

CKD patients have a poorly responsive ventilator control system that impedes timely ventilator weaning (Seki et al, 1993). Therefore reintubation has a significantly higher morbidity and mortality in CKD and should be avoided. Other preventive strategies involve vaccinations (pneumococcus, influenza, hepatitis), hypertension control, identification of high-risk patients for congestive heart failure, early treatment of upper respiratory infection/bronchitis, and optimization of functional status (vision assessment, exercise, cognitive stability). Identifying patients with risk characteristics that lead to hospitalization and designing a management plan to modify risk are essential and deserving of further study.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

KEY POINTS: CHRONIC RENAL FAILURE

- The NKF developed and published clinical practice guidelines for CKD in 2002 to diagnose and treat CKD and its comorbidities more consistently. These guidelines were updated by the KDIGO ([KDIGO Committee, 2013](#)). The classification of CKD now incorporates assessment of albuminuria besides GFR estimation. This better reflects the health implications of kidney diseases.
- At a set point (usually $\geq 50\%$ reduction in GFR), a relentless progressive loss of renal function ensues even when the initial insult becomes inactive—the hyperfiltration hypothesis.
- Progression of renal insufficiency involves hemodynamic and nonhemodynamic mechanisms.
- ACE inhibitors and ARBs are the most effective agents in slowing the progression of renal disease by both hemodynamic and nonhemodynamic mechanisms.
- The most common etiologies of CKD are diabetes and hypertension.
- Comorbidities associated with CKD need treatment to optimize survival and to diminish morbidity. This includes managing hypertension, blood lipids, smoking cessation, target weight, anemia, and glycemic control.
- A serious adverse advent, NSF, has been linked to gadolinium-based contrast agents.
- Major surgical interventions mandate thorough medical evaluation, particularly cardiovascular health.

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Role of the Urologist in Renal Transplantation

End-Stage Renal Disease

Selection of Kidney Transplant Recipients

Selection of Kidney Transplant Donors

Kidney Transplant Operation

Post-transplant Care

Autotransplantation

ROLE OF THE UROLOGIST IN RENAL TRANSPLANTATION

The invention of renal replacement therapy is one of the major advances in 20th-century medicine. Dialysis treatments were initially indicated only for patients with acute kidney injury. In the first half of the century there were only short-term success and many technical failures with kidney transplantation. Through transplantation experiments in animal models many of the fundamentals of immunology were elucidated. During the Second World War the treatment of burns stimulated intense interest in skin grafting. A series of papers starting in 1944 by Peter Medawar clearly demonstrated the process of graft rejection, as well as the acceptance of tissue from the same individual or an identical twin. Moreover, elegant experiments demonstrated that rejection could be prevented by transfer of cells from the donor to the recipient during the neonatal period (Billingham et al, 1953). Advances in vascular surgical technique and tolerance induction renewed interest in organ transplantation. Urologists in France provided solutions to many of the technical barriers. A team of experts in basic science and clinical medicine led by John P. Merrill (nephrology), Joseph E. Murray (plastic surgery), and J. Hartwell Harrison (urology) at the Peter Bent Brigham Hospital performed the first successful kidney transplant between identical twins in December 1954 (Terasaki, 1991; Starzl, 1992).

Transplantation has evolved from an experimental procedure to the standard of care for many types of organ failure. The best outcomes are achieved with an integrated multidisciplinary team. Urologists will therefore continue to be called on to manage patients with organ transplants.

END-STAGE RENAL DISEASE

Incidence and Prevalence

In the 1960s dialysis was available in only a few centers and considered experimental by commercial insurance companies, but in the decades that followed, treatment options for patients with kidney failure improved dramatically. Passage of Medicare legislation in 1972 provided payment for renal replacement therapy (RRT), including maintenance dialysis and renal transplantation. In 2011 the number of patients receiving treatment for end-stage renal disease (ESRD) reached 615,899—a new high. The number of incident dialysis patients was 112,788, and 2855 patients received a preemptive transplant as their first ESRD treatment modality; thus a total of 115,643 patients began ESRD therapy in 2011—a level below that of the two prior years. The incidence of patients starting therapy on hemodialysis declined for the first time in more than three decades. The ESRD population initiated on peritoneal dialysis

now accounts for 6.6% of patients. The prevalence of ESRD included 430,273 patients on dialysis and 185,626 patients with a functioning kidney transplant, and the 1-year growth of 3.4 percent—to 615,899—was the smallest in 30 years (United States Renal Data System, 2013).

Treatment Options

Hemodialysis is usually performed in a center for 2.5 to 5 hours and three times per week. Blood is removed using a catheter in a central vein or large-bore needles inserted into an arteriovenous fistula/graft. Solutes are removed by diffusion across a semipermeable membrane. Fluid removal, also known as ultrafiltration, is controlled by regulating the hydrostatic pressure across the membrane. Patients often complain of nausea, muscle cramps, hypotension, and fatigue. Increasing the number of treatments per week and decreasing the rate of fluid removal may decrease symptoms, but is generally limited to those patients with a dedicated caregiver who can administer the treatment in the home. Permanent dialysis access using an arteriovenous fistula has the best patency rate and reduces the risk for hematogenous infection. Venous stenosis and eventual lack of vascular access is an increasingly recognized complication of prolonged dialysis using central venous catheters. If possible, a fistula should be created at least 6 months before the anticipated start of hemodialysis treatment. Peritoneal dialysis uses the fluid and solute transport characteristics of the peritoneum as an endogenous dialysis membrane. A Silastic catheter is surgically placed in the abdominal cavity, and the exit site is protected by a cuff embedded under the skin. After several weeks, 1500 to 3000 mL of sterile hypertonic solution flows into the abdomen and is allowed to dwell for a specified period to achieve the appropriate solute removal and ultrafiltration. The fluid is then discarded. The hypertonicity of the fluid is commonly obtained with glucose concentrations of 1.5% to 4.25%. This can deliver a significant caloric load and increase the risk for infection. To reduce this problem, solutions containing glucose polymers (e.g., icodextrin) have been introduced to decrease absorption of solute and increase ultrafiltration for a longer period. **Unfortunately, both icodextrin and maltose can cause falsely elevated glucose results with point-of-care devices, possibly leading to inappropriate therapy (Floré and Delanghe, 2009).** This procedure is typically done in the home by a machine that regulates the fluid flow while the patient sleeps (continuous cycling peritoneal dialysis) or periodic exchanges during the day (continuous ambulatory peritoneal dialysis). The advantages over hemodialysis include more stable blood pressure, solute removal, and promotion of patient independence. The major complications of peritoneal dialysis are bacterial peritonitis and peritoneal fibrosis.

Long-Term Complications of Dialysis

Patients with a chronic glomerular filtration rate (GFR) of less than 15 mL/min are classified as having stage 5 chronic kidney disease as defined by the National Kidney Foundation guidelines (see Chapter 46). Most patients with a GFR less than 10 mL/min are symptomatic and benefit from RRT. The decision to initiate therapy must be individualized based on patient preferences to provide the most quality-adjusted life years. As the waiting time for deceased-donor renal transplant increases, the long-term complications of dialysis may have a significant impact on the choice of renal transplantation as an appropriate treatment modality. A prolonged time on dialysis increases the risk for post-transplant morbidity and mortality.

Cardiovascular disease is prevalent in this population because hypertension and diabetes are the two most common causes of ESRD in adults. At the time of dialysis initiation, 50% to 80% of patients will have left ventricular hypertrophy, and the presence of coronary artery disease is 10- to 20-fold greater than in the general population. Patients over the age of 50 years have a 20% mortality rate during their first year of dialysis, and approximately half of the patients of this age with diabetes will die on dialysis after 5 years ([United States Renal Data System, 2013](#)). Blood pressure can be difficult to control in patients with limited kidney function. Oliguric patients are advised to limit fluid intake, leading to chronic thirst. The administration of erythropoiesis-stimulating agents has significantly reduced the need for blood transfusions, but anemia remains a common problem. Poor elimination of phosphorus by dialysis can lead to severe itching, conjunctival irritation, and alterations in bone metabolism. Hyperphosphatemia must therefore be regulated by dietary restriction and phosphate binders. Secondary hyperparathyroidism can lead to hypercalcemia. A syndrome characterized by vascular calcification, thrombosis, and necrosis known as calciphylaxis may occur if the serum calcium \times phosphorus product is greater than 60 mg²/dL². Phosphate enemas should not be administered to patients with ESRD to avoid this complication.

Hyperkalemia is also more common in ESRD and may require dietary restriction. If rapid correction is necessary, dialysis is the best option. Sodium polystyrene sulfonate in sorbitol administered either orally or per rectum may cause intestinal necrosis. The risk for this complication may be increased with impaired bowel function resulting from postoperative opioids or ileus ([Gerstman et al, 1992](#)).

Kidney transplantation is generally considered the optimal form of renal replacement therapy. Selecting the most appropriate therapy, however, must be individualized based on patient priorities and assessment of risks. Kidney transplantation should be viewed as another treatment for ESRD and not a cure. A detailed overview of the outcomes with kidney transplant in the United States is updated annually ([Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients, 2012](#)).

When compared to adults with ESRD, children are more likely to receive chronic peritoneal dialysis, and they are more likely to undergo renal transplantation ([United States Renal Data System, 2013](#)). There is a relatively greater availability of parental kidney donors, and children receive preferential priority when they are listed for deceased kidney transplantation. **Special problems in children with ESRD include limited dialysis access, growth failure, poor nutrition, and psychiatric problems.**

Results of Treatment

Data from the [U.S. Renal Data System \(2013\)](#) indicate that survival after renal transplantation is significantly better than that of patients treated with dialysis. Although this simply may mean that healthier patients are more likely to undergo transplantation, more controlled analyses have indicated a significantly reduced mortality risk for renal transplant recipients compared with acceptable transplantation candidates waiting on dialysis ([Meier-Kriesche et al, 2001](#)). Regardless of whether the treatment

modality is dialysis or transplantation, the major causes of death are, in order, heart disease, sepsis, and stroke ([United States Renal Data System, 2013](#)).

SELECTION OF KIDNEY TRANSPLANT RECIPIENTS

The goal of kidney transplantation is to improve patient survival and quality of life. The evaluation process is designed to estimate the risks and benefits of the various therapeutic options. The patient must be educated regarding the risks associated with their cause of renal failure and existing comorbidities, as well as the risk of the operative procedure and required immunosuppression. Individual estimates of patient and graft survival with various donor options should be discussed to maintain hope for a better future with realistic expectations.

Preliminary Screening

All dialysis centers in the United States are mandated to be associated with a transplant center, and all Medicare patients are legally entitled to a transplant evaluation. A preliminary screening process should identify absolute contraindications to transplantation and modifiable risk factors ([Fig. 47-1](#)). **Any patient with a GFR less than 20 mL/min should have the opportunity to meet with a transplant team to assess barriers to transplantation and potential donor options.** The transplant evaluation can be an opportunity to counsel patients and advocate for changes in lifestyle to promote health. Morbid obesity, defined as a body mass index greater than 35, is more prevalent in the dialysis population and is a significant overall risk factor ([Srinivas and Meier-Kriesche, 2013](#)). When increasing exercise and reducing caloric intake alone are not successful, surgical weight-loss treatment options should be considered. Adherence to medications, dietary recommendations, and physician appointments is critical to the success of transplantation. Missing dialysis treatments, serum phosphorus or potassium levels greater than 6 mg/dL, drug or tobacco use, and weight gain of over 3 kg between dialysis sessions should initiate appropriate consultations with physicians, social workers, and dietitians. Depression and other psychiatric illnesses can improve with proper treatment and are not absolute contraindications to transplantation. A person who can serve as a caregiver after transplantation must be identified and be included in the entire transplant process.

Cause of Kidney Disease

When kidney function is deteriorating, a biopsy provides the most definitive diagnosis. However, if patients present with small kidneys on renal ultrasound, then a biopsy will most likely show advanced fibrosis of unknown cause. A history of childhood enuresis or urinary tract infections (UTIs) may suggest unrecognized congenital disease. Patients with primary focal segmental glomerulosclerosis, hemolytic-uremic syndrome, membranoproliferative glomerulonephritis, and primary oxalosis should be informed of the significant risk for disease recurrence in the allograft. Before transplant, the rate of progression of the serum creatinine and proteinuria may help predict the risk for recurrence. Patients with primary oxalosis and other metabolic diseases may benefit from combined kidney and liver transplant. Patients with sickle cell disease, amyloidosis, and Fabry disease are also at increased risk for disease recurrence but still may benefit from transplantation compared to dialysis. Immunoglobulin A (IgA) nephropathy is a disease that commonly recurs in the transplant kidney yet rarely leads to graft failure. Hypertension and diabetes are the most common causes of renal failure in adults but generally take many years to show evidence of disease in the transplant. Autosomal dominant polycystic kidney disease (ADPKD), cystinosis, renal dysplasia, and Alport syndrome without anti-glomerular basement membrane antibodies are examples of renal diseases that do not recur in the transplanted kidneys.

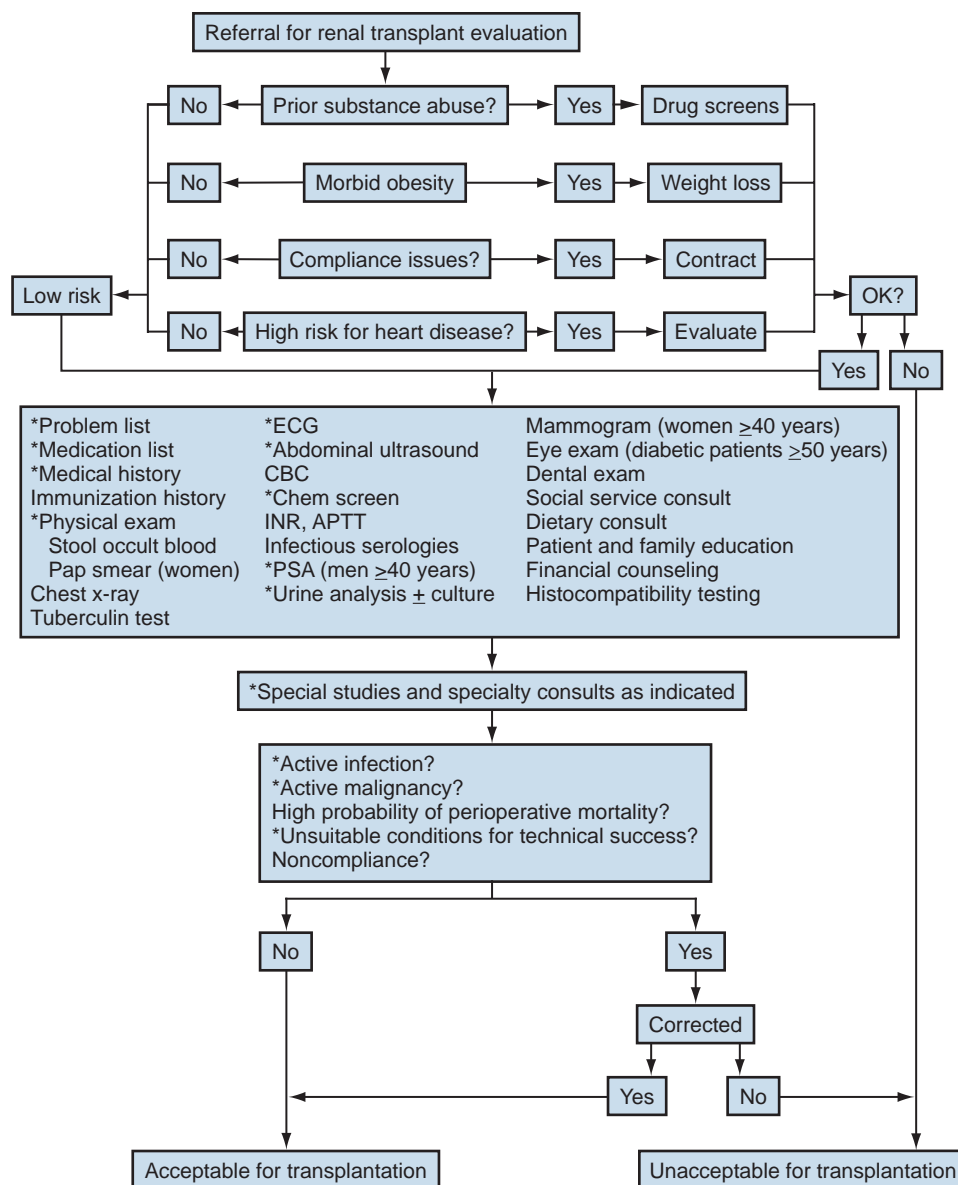


Figure 47-1. Algorithm for the evaluation of renal transplantation candidates. Circumstances may change the order in which data are obtained. APTT, activated partial thromboplastin time; CBC, complete blood cell count; ECG, electrocardiogram; INR, international normalized ratio; PSA, prostate-specific antigen. Asterisks indicate items of special significance for the urologist. (Modified from Barry JM. Current status of renal transplantation: patient evaluations and outcomes. *Urol Clin North Am* 2001;28:788.)

High Probability of Perioperative Morbidity or Mortality

Coronary artery disease is present in over 50% of patients with ESRD and may not manifest with typical symptoms. Periodic reevaluation for progression of disease is important because of the prolonged waiting time to receive a deceased-donor kidney (Lentine et al, 2012). Patients over the age of 50 years with coronary artery disease, cerebrovascular disease, congestive heart failure, diabetes, and renal failure have approximately a 25% risk for complications (Hoftman et al, 2013). Lack of mobility is a major risk factor, and simply walking with a patient for 100 yards can provide as much insight as other cardiac stress tests (McAdams-DeMarco et al, 2015). Most patients are screened with pharmacologic nuclear medicine cardiac imaging or echocardiograms to evaluate myocardial perfusion, ejection fraction, and valvular function. Abnormal cardiac testing should prompt referral to a cardiologist for further evaluation. Tobacco use is clearly linked with poor outcomes and

must be stopped. Any respiratory disease that requires home oxygen is a relative contraindication to transplantation. Patients with ADPKD who have a history of stroke or recurrent headaches, or a family history of stroke or cerebral aneurysm, should be screened for berry aneurysm of the cerebral arteries. Any history of prior severe infection should be investigated. Patients are screened for prior exposure to human immunodeficiency virus (HIV), hepatitis B and C, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) in addition to syphilis and tuberculosis. The screening for endemic infections varies across countries and local regions. Infections should be treated or prevented with immunizations, but in most cases do not preclude transplantation.

Since the development of combination antiretroviral therapy, HIV infection has evolved into a chronic condition. Selected HIV-infected patients with ESRD are kidney transplant candidates if they do not have signs of opportunistic infection, the viral load is low, and adequate T lymphocyte counts are maintained (Stock et al, 2010).

Nonadherence

The success of any complex surgical procedure is highly dependent on the patient's motivation. Resolving barriers that impede a patient's understanding of and ability to follow postoperative instructions is crucial to the long-term success of transplantation. Interpreters, financial counselors, social workers, dietitians, pharmacists, and psychiatrists are critical team members. The patient and family members must actively be engaged in working toward a better state of health. Patients with chronic illnesses may develop abnormal coping mechanisms, including overeating, lack of exercise, depression, and chemical dependence. These conditions should be identified and corrected if possible. Like many of the other diseases associated with renal failure they should be viewed as risk factors and not absolute contraindications to transplantation.

Malignancy in Transplant Candidates

Patients with renal failure have a relative risk for cancer of approximately 1.18 compared to the general population (Maisonneuve et al, 1999). The highest cancer incidence was in patients younger than 35 years of age, with a decreasing incidence with increasing age. This may be due to genetic influences, environmental exposure, inability to remove certain toxins, virus infections, or reduced immune function. Patients with invasive or metastatic malignancy have the greatest risk for recurrence, and a 5-year disease free waiting period is generally recommended before the initiation of the immunosuppression required for transplantation. Melanoma has a very high risk for recurrence, and at least a 5-year wait is advised, whereas most other skin cancers are not a contraindication. The prognosis for the treatment of many cancers continues to improve as better diagnostic tests and therapies are developed. An oncology consultation should be obtained to determine the risk for recurrence, recommended surveillance, and long-term prognosis based on pathologic grade and stage of tumor. Molecular markers continue to improve the classification of many cancers to optimize therapy.

The screening tests for malignancy in transplant candidates are the same as the general population except for an ultrasound. Abdominal ultrasonography is indicated for the evaluation of renal failure, and the results should be reviewed during the transplant evaluation to assess for conditions that may be indicative of urologic disease. The incidence of acquired cystic disease increases progressively with duration of dialysis, and up to 80% are affected after 10 years on dialysis (Ishikawa et al, 2010). Cholecystectomy is recommended for patients with gallbladder polyps greater than 1 cm in diameter, and also in patients with diabetes and gallstones because of the increased morbidity associated with acute cholecystitis after transplantation (Benjamin et al, 2009). If the risk for elective cholecystectomy is high, we do not require this procedure for listing the candidate.

Urologic Malignancy in Transplant Candidates

The best treatment of prostate cancer is determined by grade, stage, estimated longevity, and patient preference. Low-risk prostate cancer should not be considered a contraindication to transplantation because in most cases the morbidity and mortality of having ESRD is greater. Patients who have low-risk disease felt to be amenable to active surveillance should be considered candidates for transplantation as long as they adhere to their surveillance regimen. Transplant candidates with a diagnosis of intermediate- or high-risk prostate cancer need to undergo definitive treatment to be considered a kidney transplant candidate. Those patients who have undergone treatment, typically radical prostatectomy or radiation, can be evaluated for transplantation as soon as they have recovered from their treatment. Waiting time after prostate cancer treatment should be dictated by the expected survival and probability of prostate cancer recurrence after treatment. Nomograms, such as those developed by Kattan and colleagues, are useful for predicting such parameters and

are easily accessible online (<http://nomograms.mskcc.org/Prostate/index.aspx>). It is important to remember that even patients with fairly high-risk features have a low chance for disease recurrence or death from prostate cancer after treatment. For example, a 55-year-old with Gleason 4 + 4 disease with a preoperative prostate-specific antigen (PSA) of 20, can expect an 82% chance for progression-free survival at 10 years if the PSA is not detectable 2 years after treatment. We therefore find it reasonable in most intermediate- to high-risk cases to wait 1 to 2 years before transplantation. Patients who have adverse pathologic features such as positive lymph nodes or seminal vesicle involvement have lower expected survival and demand longer follow-up, usually 5 years.

Asymptomatic microscopic hematuria should be evaluated in patients with renal failure according to the American Urological Association (AUA) guidelines (Davis et al, 2012). The risk for both kidney (standardized incidence ratio [SIR] 3.6; confidence interval [CI] 3.5 to 3.8) and bladder (SIR 1.5, CI 1.4 to 1.6) cancer is increased with renal failure (Stewart et al, 2003). Renal cysts in patients with chronic kidney disease may become infected, bleed, or undergo malignant transformation. Complex cysts should be monitored with serial imaging and may be an indication for pre-transplant nephrectomy if the urine output is limited. Small, low-grade superficial (Ta) transitional cell cancer has a low risk for progression and is not a contraindication to transplantation with appropriate surveillance. Aristolochic acid, a Chinese herb used to treat labor pains and found in some weight loss remedies, has been associated with ESRD and upper tract transitional cell carcinoma. This also may be the agent responsible for Balkan nephropathy (Olivier et al, 2012). Patients with a history of exposure to solvents, tobacco, cyclophosphamide, chronic infection, or irritative voiding symptoms should have bladder wash cytology because of the increased risk for urothelial carcinoma. Patients with positive cytologic findings or high-grade or invasive tumors should have a 5-year cancer-free interval before initiation of immunosuppression to reduce the risk for tumor recurrence and progression. In situ and all noninvasive papillary tumors of the bladder do not require a waiting period (Penn, 1993). Asymptomatic renal masses are frequently detected by imaging to evaluate renal insufficiency. Approximately 20% of renal masses less than 3 cm in diameter are benign and the risk for metastasis is very low. These tumors should not limit access to transplantation. The treatment of clinical stage 1 renal tumors should be individualized as recommended by the AUA guidelines. **Active surveillance or localized therapy for urologic malignancy, with appropriate indications and patient compliance, should be considered as adequate treatment before transplantation.**

Surgical Evaluation

Preparation of a patient for kidney transplantation requires a careful assessment of the peripheral vascular system. Symptoms of claudication or rest pain should be elicited, as well as the risk factors for vascular disease. Any prior vascular surgery must be documented, particularly endovascular procedures, which are becoming more common. The character of pulses, particularly in the femoral area, should be documented. Unless evidence exists of extensive calcification or bruit, additional vascular studies are rarely necessary. However, Doppler flow ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), or angiography may be necessary to evaluate flow-limiting lesions or extensive calcification. Iodinated contrast can be nephrotoxic and must be used with caution in patients with marginal renal function. Hydration and diuresis appear to be the most effective ways to minimize the risk for renal injury. Gadolinium contrast agents have been associated with nephrogenic systemic fibrosis in some patients with marginal renal function (Chang et al, 2013). The risk is greatest for patients on dialysis. Selective angiography with carbon dioxide gas or MRI with intravenous (IV) iron contrast may be indicated in some cases to avoid nephrotoxicity.

Nephrotic syndrome can lead to a hypercoagulable state with loss of natural anticoagulants antithrombin III, protein C, and

protein S. Renal transplant recipients have an elevated risk for deep vein thrombosis and graft thrombosis when there is a history of previous dialysis access failure, miscarriage, antiphospholipid antibody syndrome, or hyperhomocysteinemia. Homozygous mutations of the methylenetetrahydrofolate reductase (*MTHFR*) gene can lead to impaired folate metabolism and hyperhomocysteinemia, which has been associated with accelerated atherosclerosis. Patients can be screened for thrombophilia by checking clotting factors, including the platelet count, prothrombin time, partial thromboplastin time, and activated protein C resistance ratio (factor V Leiden mutation).

Urologic Procedures in Renal Transplant Candidates

During the renal transplant evaluation process, potential recipients may be diagnosed with a number of urologic conditions that require intervention. Many patients with ESRD have minimal urine output that can mask abnormal bladder function. The preoperative history should review prior episodes of UTI, hematuria, urolithiasis, enuresis, incontinence, retention, and voiding dysfunction. The details of previous abdominal or pelvic surgery could have a significant impact on the optimal placement of a renal allograft. Prior pelvic radiation can inhibit bladder function and wound healing. The physical examination should include descriptions of scars, catheters, and stomas. Additional urologic studies may be indicated to evaluate the anatomy of the urinary tract, bladder function, and risk for malignancy (Table 47-1). In patients on peritoneal dialysis, fluid in the pelvis can be misinterpreted as residual urine. If patients have an inflatable penile prosthesis with an abdominal reservoir, it can be mistaken for the urinary bladder or make exposure of the bladder more challenging.

Indications and Timing of Native Nephrectomy

Preservation of residual renal function for patients on dialysis can limit the need for fluid and dietary restrictions. It also may improve the management of hypertension and reduce the risk for cardiac complications (Shemin et al, 2001). Therefore the indication for native nephrectomy must be balanced by the risk of observation. The most common indications for native nephrectomy are outlined in Box 47-1.

If the potential recipient has a living donor, it is ideal to perform nephrectomy at least 6 weeks before the scheduled transplant. However, if the patient is not on dialysis, it exposes the patient to the infectious risks and complications of dialysis. Some surgeons prefer to do the nephrectomy at the time of transplant, but this may increase the risk for complications with the transplant kidney. For patients who do not have a living donor, the timing of pretransplant nephrectomy should be based on the indication, residual urine output, and accumulated wait list time. Patients who have adult polycystic kidney disease (PKD) may require unilateral or bilateral native nephrectomy before transplantation if there is concern for malignancy, recurrent infection, intractable gross hematuria, or continued discomfort because of size. Patients who may undergo transplantation before the start of dialysis may benefit from post-transplant nephrectomy. Asymptomatic patients with severely enlarged kidneys may require native nephrectomy to make room for the renal allograft. Adequate space in the iliac fossa can generally be assessed by a combination of physical examination and abdominal imaging. If the enlarged kidney is not palpable inferior to the anterior superior iliac spine, there usually is room for a renal allograft, but this decision is ultimately made by the transplant surgeon. Nephrectomy can be performed concurrently with the renal transplant, but this may increase perioperative complications and morbidity (Fuller et al, 2005). Chronically infected kidneys should be removed, but uninfected asymptomatic urinary stones do not require treatment. Transplant candidates with a history of vesicoureteral reflux (VUR) require native nephrectomy only if the VUR is associated with recurrent urinary infections.

TABLE 47-1 Recommendations for Additional Urologic Studies in Renal Transplant Candidates

STUDIES	INDICATIONS
Voiding cystourethrogram ± urodynamics	Voiding dysfunction, history of pyelonephritis or reflux, inconclusive ultrasonography
Cystoscopy	Suspected lower urinary tract cancer or planned invasive prostate therapy
Retrograde pyelography	Planned orthotopic renal transplantation or inconclusive ultrasonography
Abdominal computed tomography scan	Inconclusive ultrasonography for stone or mass, autosomal dominant polycystic kidney disease to accurately size kidneys
Urine or bladder wash cytology	Prior cyclophosphamide therapy or significant irritative voiding symptoms
Bladder biopsy	Suspected bladder fibrosis or cancer
Retrograde loopogram	Intestinal conduit
Retrograde pouchogram	Intestinal or gastric reservoir

Modified from Barry JM. Current status of renal transplantation: patient evaluations and outcomes. *Urol Clin North Am* 2001;28:677.

BOX 47-1 Recommendations for Pretransplant Nephrectomy

Symptomatic renal stones not cleared by minimally invasive techniques or lithotripsy
 High-grade solid renal tumors with or without acquired renal cystic disease
 Polycystic kidneys that are symptomatic, extend below the iliac crest, have been infected, or have solid tumors
 Persistent anti-glomerular basement membrane antibody levels
 Significant proteinuria not controlled with medical nephrectomy or angioablation
 Recurrent pyelonephritis
 Grade 4 or 5 vesicoureteral reflux with urinary tract infections

Treatment of Bladder Outlet Obstruction

Medical management of prostate hypertrophy in potential recipients with α -adrenergic blocking agents and 5 α -reductase inhibitors is preferred. In some cases a less selective α -blocker also will be beneficial in the treatment of hypertension. Patients with residual urine output who fail conservative treatment may be treated with modalities such as transurethral resection of the prostate (TURP) or laser vaporization (Volpe et al, 2013). Caution is advised in performing transurethral resection in anuric patients because of the high risk for bladder neck contracture or prostatic fossa strictures.

Urinary Diversion and Bladder Augmentation

Renal transplant recipients should have an established urinary drainage system because cutaneous ureterostomy has a high risk for stenosis and infection. Prolonged percutaneous drainage is prone

to repeated infection with increasingly resistant organisms. Ideally the urinary reservoir should have a capacity of at least 200 mL, low storage pressure, an antirefluxing ureteral anastomosis, and the ability to empty completely.

Patients with prolonged anuria may lose bladder capacity, but even small defunctionalized bladders will frequently regain normal volume within weeks of transplantation (Wu et al, 2008). The timing of bladder surgery must be coordinated with the transplant operation. In general, reconstructive procedures involving bowel are not performed simultaneously because of the increased risk for infection and poor wound healing associated with maximal immunosuppression. However, experience with simultaneous kidney and pancreas transplant using enteric drainage demonstrates that bowel surgery is not absolutely contraindicated. Lower urinary tract reconstruction is best done with adequate urine production to reduce the risk for stricture, stones, infection, and loss of compliance. A urothelium-lined augmentation is preferred because mucus does not need to be rinsed from the reservoir on a regular basis. If the reservoir does not empty completely, patients must be taught the technique of clean intermittent catheterization. It is critical that patients and their caregivers understand that renal transplantation will not improve bladder function. They must be aware of potential complications associated with abnormal bladder function but should not be discouraged from transplantation, because longevity and quality of life can be significantly improved (Sager et al, 2011).

SELECTION OF KIDNEY TRANSPLANT DONORS

As soon as a patient is deemed to be an acceptable kidney transplant candidate, the search for a suitable kidney donor is initiated. The recipient is encouraged to bring potential living kidney donors to educational seminars. Renal transplant outcomes are significantly improved with a living compared to a deceased donor. The ultimate pairing of a kidney donor with a recipient is a complex process that involves both immunologic and nonimmunologic factors.

Deceased Donor Allocation and Selection

While potential living kidney donors are evaluated, suitable candidates are consented for kidneys from deceased donors. The Organ Procurement and Transplantation Network (OPTN) was established by the United States Congress under the *National Organ Transplant Act* of 1984. The Act called for the network to be operated by a private, nonprofit organization under federal contract. All U.S. transplant centers and organ procurement organizations (OPOs) must be members of the OPTN to receive funds through Medicare. Other members of the OPTN include independent histocompatibility laboratories and relevant medical, scientific, and professional organizations. Members of the OPTN must report data to the Scientific Registry of Transplant Recipients (SRTR). The primary goals of the OPTN are to (1) increase the effectiveness and efficiency of organ sharing and equity in the national system of organ allocation and (2) increase the supply of donated organs available for transplantation. The United Network for Organ Sharing (UNOS) administers the OPTN under contract with the Health Resources and Services Administration of the U.S. Department of Health and Human Services.

Declaration of Donor Death

As a requirement for participation in Medicare, all hospitals must report potential deaths to the local OPO. Organ procurement personnel screen all eligible donors and assign a staff member to discuss organ donation with the next of kin. Many states now have electronic donor registries and the option to give consent for organ donation with a driver's license. An extensive questionnaire, clinical history, physical examination, and laboratory tests, including assays for syphilis, hepatitis, HIV, and human T-lymphoproliferative virus, are obtained to evaluate the risk for transmissible infection and malignancy. The declaration of donor death must be made by two

BOX 47-2 Guidelines for the Determination of Death by Neurologic Criteria

- I. Complete cessation of all brain and brain stem function
 - A. Coma as evidenced by no eye opening and no response to pain other than spinal cord reflexes
 - B. Absent brain stem reflexes
 1. Pupillary reflex
 2. Oculocephalic reflex ("doll's eyes")
 3. Oculovestibular reflex
 4. Corneal reflex
 5. Oropharyngeal reflex (gag and cough)
 6. Respiratory (apnea) challenge
- II. Apnea challenge
 - A. Preoxygenate patient with 100% oxygen for roughly 10 minutes and allow PaCO_2 to normalize to 40 mm Hg
 - B. Disconnect ventilator and place large-bore catheter down the endotracheal tube to deliver 100% O_2 or place on continuous positive airway pressure with 100% O_2
 - C. Observe patient for spontaneous breaths for approximately 10 minutes
 1. Obtain arterial blood gas (ABG) sample at that time and continue the test
 2. If no spontaneous breaths and a PaCO_2 below 60 mm Hg or 20 mm Hg above the patient's baseline, repeat ABG tests until PaCO_2 meets criteria
 - D. Positive test: No spontaneous breaths with an arterial PaCO_2 60 mm Hg or greater or 20 mm Hg above the patient's baseline confirms diagnosis of brain death
- III. Complete loss of brain and brain stem function must be irreversible
 - A. Establish cause of coma
 - B. Exclude complicating conditions
 1. Pharmacologic and metabolic intoxication
 2. Hypothermia
 3. Shock
 - C. Appropriate period of observation before second clinical examination
 1. 48 hours in infants up to 2 months of age
 2. 24 hours in those between 2 months and 1 year of age
 3. 6 to 12 hours in children older than 1 year of age
 4. 6 hours in adults older than the age of 18 years
- IV. Confirmatory tests (electroencephalogram, cerebral angiography, nuclear medicine brain scan)
 - A. Mandatory if unable to satisfy criteria or if any doubt exists
 - B. May shorten the period of observation, particularly in children and young adults
 - C. May help family members understand and accept the diagnosis

From Morenski JD, Oro JJ, Tobias JD, et al. Neurologic criteria for death. *J Intensive Care Med* 2003;18:211.

physicians who are not part of the organ recovery or transplantation team, to avoid any conflict of interest. Donors may be declared dead by neurologic criteria or cardiorespiratory criteria. Neurologic criteria for brain death include coma, irreversibility, known brain damage, and absence of brain stem reflexes (Box 47-2). Electroencephalography or brain blood flow imaging is not required but may be used to confirm the diagnosis at the clinician's discretion. In donors who are declared brain dead, cardiopulmonary function can be supported through the organ recovery process to minimize warm ischemia to the potential allografts.

Donation after circulatory death (DCD) typically occurs when a potential donor does not meet brain death criteria despite being comatose and ventilator dependent. In this situation, an individual or family may consent for donation only when death is determined by cessation of cardiopulmonary function. When the decision to withdraw care is made, ventilator support is discontinued in the intensive care unit or operating room. Death is declared by absence of spontaneous respiration and sustained asystole for 5 minutes before organ recovery begins. All DCD donor organs are subject to a variable period of warm ischemia depending on the specifics of the organ recovery.

Most deceased donors are suitable for multiple organ donation. To optimize the recovery of both thoracic and abdominal organs, a median sternotomy and midline incision are used for wide exposure. The organs are quickly inspected for signs of disease. Vascular control is established above and below the organs to be removed. Cannulas for the administration of preservation solution are inserted into the aorta, clamps are applied, venous effluent is vented, and the organs are flushed, immediately cooled with ice cold saline slush, carefully separated, inspected, and packaged for transportation. Spleen and lymph nodes are removed for histocompatibility testing, and iliac vessels are removed for vascular reconstruction of pancreas and liver grafts.

Kidney Preservation

The renal tubular sodium-potassium pump is required to maintain a high intracellular concentration of potassium. This pump depends on adenosine triphosphate (ATP) and uses oxidative phosphorylation to prevent passive diffusion of water into the cells. Ischemia leads to a depletion of ATP, loss of cellular potassium and magnesium, increased calcium, anaerobic glycolysis with acidosis, and activation of lysosomal enzymes. This leads to cell swelling and acute tubular necrosis.

After kidney transplant reperfusion, oxygen delivery recovers. Hypoxanthine, a product of ATP metabolism, is oxidized to xanthine with the formation of free radicals that cause further cell damage. Cellular swelling reduces perfusion, which leads to delayed function of the allograft and increased immunogenicity.

The goal of organ preservation is to maintain intracellular physiology. Tissues more than a few millimeters in thickness cannot be safely frozen because of the expansion of intracellular water. Hypothermia (4° C) reduces cellular energy requirements and preservation solutions are designed to maintain intracellular electrolyte composition (Table 47-2). Simple cold storage is inexpensive and facilitates the transportation of the donor kidney. Pulsatile preservation pumps may reduce vascular spasm, extend the preservation

time, and reduce the need for dialysis after transplant (Opelz and Döhler, 2007). In general, both the warm and cold ischemia times should be minimized to promote recovery of the allograft.

Allocation

The number of patients listed for kidney transplantation continues to expand disproportionately to the number of kidney transplantations performed annually. There are currently more than 99,000 patients waiting for deceased-donor kidney transplants, and with about 11,000 deceased-donor kidney transplantations performed annually, there are nine times as many patients with ESRD waiting as there will be deceased donor kidneys available in the coming year (United Network for Organ Sharing, 2014a). The inadequate supply of deceased-donor kidneys is one of the factors that have increased the use of “marginal” deceased-donor organs and the number of living donor kidneys in the past decade. The increase in living renal donation has been further facilitated by the widespread adoption of minimally invasive donor nephrectomy techniques; acceptance of living, biologically unrelated renal donors; and the development of protocols for transplantation across alloantibody barriers, including ABO blood group incompatibility.

The organ allocation policies continue to be revised based on analysis of data collected by the SRTR and approval of the UNOS Board of Directors. A schematic of the current UNOS allocation policy is available at the SRTR website (United Network for Organ Sharing, 2014c). In 2013 the allocation system had four categories of kidney donors: (1) standard criteria donor (SCD) younger than 35 years of age, (2) SCD older than 35 years, (3) expanded criteria donor (ECD), and (4) donation after circulatory death (DCD). Multiorgan transplant recipients, pediatric candidates, and former living kidney donors receive priority. For most kidney transplant candidates, however, the most important factor in receiving an organ offer is time spent on the waiting list. Additional factors that may give a potential recipient more points include the quality of the human leukocyte antigen (HLA)-DR match, and high levels of HLA antibodies (>80% panel reactive antibody [PRA]).

Because there is a wide range of potential kidney donors in terms of age, state of health, determination of death, and social history, there are different categories of deceased-donor kidneys that need to be discussed with potential recipients at the time of being added to the waiting list. The category of donor organs any recipient is willing to accept must be decided by the patient and transplant physician.

SCDs are younger than 60 years of age and do not meet any of the criteria for being an ECD. ECD donors are those who are over the age of 60 or those who are between the ages of 50 and 59 with two or more risk factors such as death from a stroke, hypertension, or elevated creatinine just before organ recovery (1.5 mg/dL). ECD organs have a 2-year graft survival of 80% versus 88% for an SCD organ (Pascual et al, 2008). DCD kidneys are subject to varying lengths of warm ischemia time and are thus susceptible to delayed graft function, but long-term graft survival is comparable to that of SCD kidneys (Snoeijs et al, 2010). Depending on size, pediatric donor kidneys may be transplanted en bloc, or, if large enough, split and allocated to two recipients. Recipients of pediatric donor kidneys should ideally be less than 80 kg, and some programs prefer not to use small kidneys in highly sensitized patients, but strategies vary across programs. If a particular donor's kidneys are felt to be suboptimal for transplantation into two recipients, they may be offered as dual adult donor kidneys. Patients who are deemed appropriate for ECD organs may be good candidates for dual adult kidney transplantation. UNOS implemented a new policy for deceased donor kidneys in December 2014. The goal is to allocate kidneys with the longest expected graft survival, estimated by the kidney donor profile index (KDPI), to patients with the longest estimated post-transplant survival, and increase the access to transplantation in patients with increased levels of anti-HLA antibodies (United Network for Organ Sharing, 2014b). A

TABLE 47-2 University of Wisconsin Preservation Solution Contents

K ⁺ lactobionate	100 mM
KH ₂ PO ₄	25 mM
MgSO ₄	5 mM
Raffinose	30 mM
Adenosine	5 mM
Glutathione	3 mM
Insulin	100 U/L
Dexamethasone	8 mg/L
Allopurinol	1 mM
Hydroxyethyl starch	50 g/L
Penicillin	200,000 U/L
pH	7.45
Potassium concentration	120 ± 5 mM
Sodium concentration	30 ± 5 mM
Osmolarity	320 ± 5 mOsm/L

KDPI of more than 85% is roughly equivalent to the previous ECD kidney.

Patients with ESRD who have hepatitis C virus (HCV) infection can be transplanted with kidneys from donors who are also HCV positive. Such recipients should have detectable HCV viral load and no evidence of cirrhosis. The Centers for Disease Control and Prevention reviewed the risk for transmission of viral diseases with organ transplantation ([Centers for Disease Control and Prevention, 1994](#)). It is important to note that all donor organs, even those not considered higher risk by the Centers for Disease Control and Prevention, have the potential to transmit disease. The Public Health Service (PHS) developed guidelines to educate patients about these risks. Patients must provide written permission to receive organs from donors considered higher risk (e.g., men who have had sex with another man in the preceding 5 years, users of nonmedical IV drugs, individuals who have received money for sex or have paid for sex in the preceding 5 years, and inmates of correctional facilities) ([Public Health Reports, 2013](#)). In most cases the risk for ESRD is far greater than the risk for infection.

ABO Blood Groups

The ABO blood group system describes antigens, which are carbohydrates expressed on the surface of red blood cells. Within the first 2 years of life, most individuals have been exposed to the noninherited antigen (probably via the digestive tract) ([Auf der Maur et al, 1993](#)). An individual who is blood type B, for instance, has developed anti-A antibody and thus will react to blood type A. Patients who are blood type O have both anti-A and anti-B antibodies and generally can receive only blood and/or allografts from blood type O donors. If a kidney is transplanted between ABO-incompatible individuals, antibodies will bind to the noninherited carbohydrate antigens expressed on endothelial cells, leading to activation of the complement cascade, coagulation, thrombosis, and rapid graft loss. However, if these antibodies have a low titer at the time of transplantation and production of antibody can be limited with immunosuppressive medications, then ABO incompatible renal transplants have been achieved ([Toki et al, 2009](#)). Most of these recipients develop “accommodation” to the donor antigen, despite persistent donor-specific blood type antibody. The graft endothelial antigen expression appears to be downregulated, and chronic complement activation is minimal.

Histocompatibility

The human major histocompatibility complex (MHC) is a cluster of more than 200 genes on chromosome 6p21.31 and is responsible for HLAs that are expressed as cell surface proteins on the renal allograft. It is these glycoprotein HLA molecules that are recognized by the recipient's leukocytes, which in turn trigger the immune response. Although the MHC is a major immunologic barrier to transplantation, it serves the important function of protecting the host from pathogens. A series of international workshops led to the nomenclature of the highly polymorphic HLA antigens. They are subdivided into class I (HLA-A, HLA-B, and HLA-C), class II (HLA-DR, HLA-DQ, and HLA-DP), and HLA class III, but only class I and II are currently used in the allocation of kidneys to recipients. **HLA class I genes are expressed by all nucleated cells. HLA class II genes are expressed by antigen-presenting cells (dendritic cells, monocytes, macrophages, and B-lymphocytes) and inflamed tissues, including endothelial cells.**

A recipient with mismatched (unshared) HLA antigens in the donor is at risk for development of antibody and cellular rejection. HLA antibodies may be formed by the recipient before transplantation as a result of pregnancies, previous transplants, blood transfusions, and possibly some infections. Individuals with antibodies directed at 20% of the population are said to be sensitized; those with antibodies to 80% of the population are considered highly sensitized. Sensitized transplant candidates, particularly those who are highly sensitized, may face extreme difficulty in finding a donor to whom they will have a negative crossmatch.

Crossmatch Techniques

Organs transplanted between genetically different individuals will be rejected without immunosuppression. Predicting the risk for a particular recipient rejecting a kidney from a given donor is very important. The ability to determine a positive crossmatch traces back to the work of Terasaki in the 1960s ([Terasaki and McClelland, 1964](#), [Patel and Terasaki, 1969](#)). The least sensitive test is the complement-dependent lymphocytotoxicity (CDC) assay in which donor T (class I antigens) or B lymphocytes (class I and II antigens) are combined with recipient serum, complement is added, and cell lysis is detected by dye exclusion after a period of incubation. The CDC crossmatch detects only high levels of HLA antibodies, so a positive CDC crossmatch is generally considered a contraindication to transplantation with that particular donor.

More sensitive crossmatch techniques that are able to detect lower levels of HLA antibodies also are employed, including the flow cytometry crossmatch (FCXM) and solid-phase single-antigen bead test (SAB). The FCXM is performed separately for both T and B cells, and each histocompatibility laboratory sets channel shift levels they consider being positive. Because the FCXM detects low levels of circulating antibodies, a positive crossmatch is not typically associated with hyperacute rejection, as seen with a positive CDC, but may be associated with higher rates of early rejection and lower graft survival. Some centers will proceed with transplantation using higher levels of immunosuppression despite a positive FCXM, particularly in broadly sensitized patients. A FCXM can detect non-HLA antibodies that are common in patients with autoimmune diseases. These antibodies are not associated with allograft rejection, and the false-positive test result can be eliminated by briefly incubating the donor cells with pronase (a proteolytic enzyme that removes non-HLA surface peptides).

The assays described can be used preoperatively to determine the percentage of donors with whom the recipient is likely to have a positive crossmatch. For the CDC or FCXM, the potential recipient's serum is tested with a panel of target cells comprising representative donor lymphocytes. The percentage of donors that cause a positive crossmatch is known as the PRA. For example, a potential recipient with a PRA of 80% is likely to have a positive crossmatch with 80% of the donor population.

Solid-phase assays that use purified HLA SABs allow for specific identification of circulating HLA antibodies. The recipient serum is incubated with the antigen beads and anti-human IgG is added, allowing for the bound antibody to be measured, usually by flow cytometry. The strength of a specific antibody is then reported as fluorescence intensity. The information from SAB testing can be used to perform what is known as a virtual crossmatch. Because a given donor's HLA typing will be known, the recipient's SAB testing may be employed to identify any donor-specific antibodies (DSAs) without having the donor cells. For example, if a potential recipient is found to have strong DSA to HLA-A2 and HLA-DR17, a center may choose to consider A2 and DR17 “unacceptable” in the UNOS database and kidneys from donors with this HLA phenotype will not be offered to the patient. The frequency and ethnic distribution of the HLA antigens in the donor population are monitored. Based on the results of specific HLA antibodies, a PRA can be calculated (cPRA) ([Cecka et al, 2011](#); [Health Resources and Services Administration, 2014](#)). Antibodies reactive to common antigens can significantly prolong the waiting time to find a suitable donor. The virtual crossmatch also has become important in living-donor kidney transplantation accomplished through kidney paired donation (KPD) when donors and recipients are frequently at different transplant centers.

Living Donor Evaluation

Individuals who would like to donate a kidney must undergo an intensive evaluation by a multidisciplinary team before being deemed a suitable donor ([Delmonico, 2005](#)) ([Fig. 47-2](#)). It is preferable that a physician who is independent of the transplant team act as an advocate for the potential donor. The medical evaluation

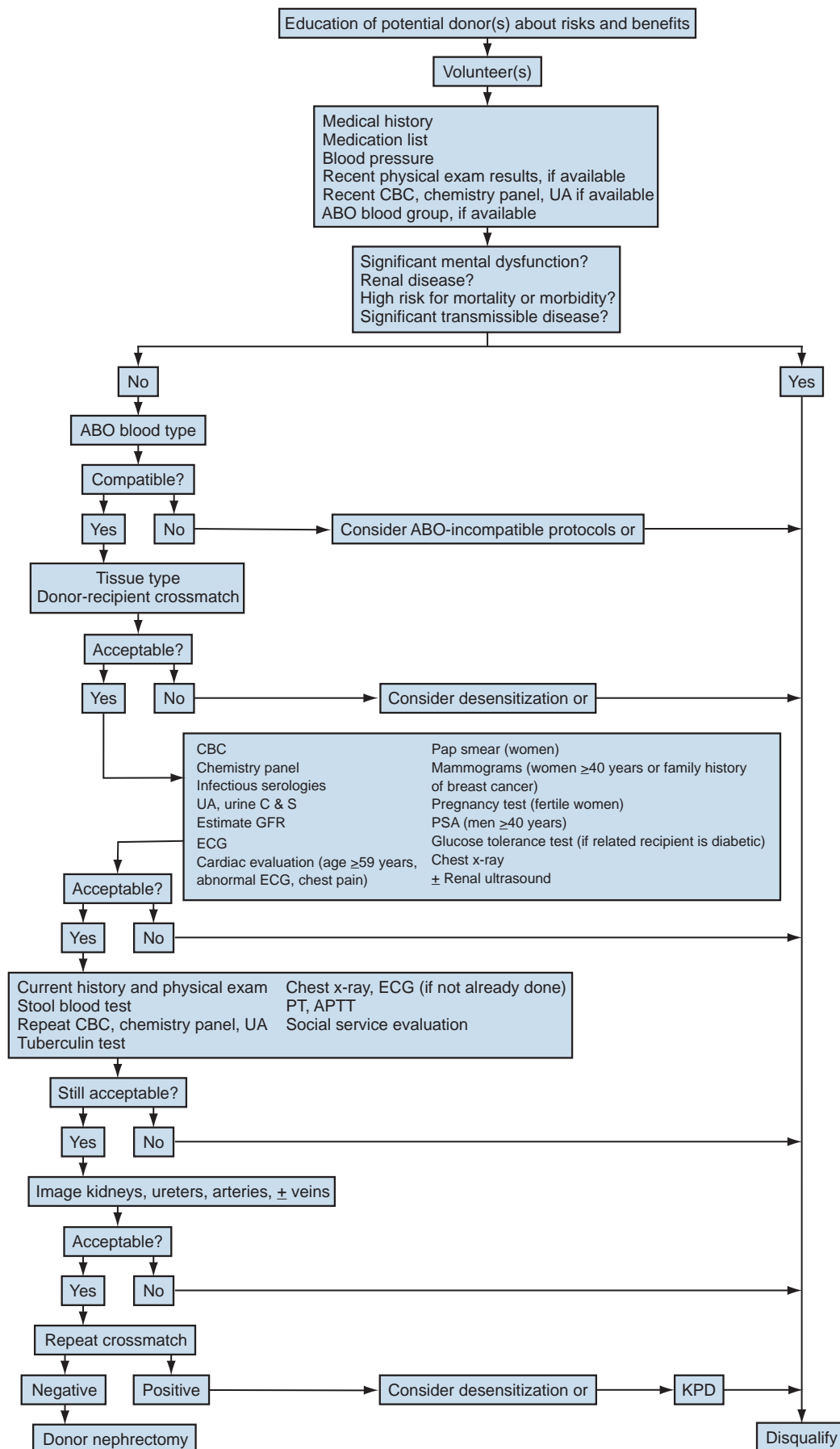


Figure 47-2. Algorithm for the evaluation of living renal donors. APTT, activated partial thromboplastin time; CBC, complete blood cell count; C&S, culture and sensitivity; ECG, electrocardiogram; GFR, glomerular filtration rate; KPD, kidney paired donation; PSA, prostate-specific antigen; PT, prothrombin time; UA, urinalysis.

includes an assessment of patient history, including medical, surgical, family, and social history. There is no upper limit for donor age, but caution is advised in donors who are quite young (younger than 25 years). Particular attention to family history of diabetes, hypertension, and renal disease is critical for younger donors because they will have more years after donation to develop such diseases themselves. Potential donors should be in excellent health with no evidence of active malignancy or infection. In recent years, some transplant centers have accepted donors who have hypertension that is well controlled with a single antihypertensive medication (Karpinski et al, 2006). Ideally, living donors should have a body mass index (BMI) that is less than 30, but some transplant centers do accept individuals with BMI above 30. It is critical to counsel all donors to maintain a healthy weight as a preventive measure for developing diseases such as diabetes mellitus and/or hypertension that may subsequently contribute to renal damage. Testing should confirm normal cardiopulmonary function, absence of diabetes, and normal renal function.

Hyperfiltration injury has not been a significant problem for living renal donors. Endogenous creatinine clearance rapidly approaches 70% to 80% of the preoperative level, and this has been shown to be sustained for more than 10 years (Najarian et al, 1992; Ibrahim et al, 2009b). The development of late hypertension is nearly the same as for the general population, and the development of proteinuria is negligible (Steckler et al, 1990; Kasiske et al, 1995). Older donor age and increased BMI have been associated with the development of hypertension and GFR under 60 mL/min/1.73 m² (Ibrahim et al, 2009b). The mortality of kidney donation has been estimated to be 0.03% (Matas et al, 2003), the risk for a potentially life-threatening or permanently debilitating complication has been estimated to be 0.23%, and there are isolated reports of ESRD developing in renal donors (Rosenblatt et al, 2008; Tong et al, 2013; Schold et al, 2014). The short- and long-term risks of living-donor nephrectomy are generally considered to be low enough and the probability of successful graft outcome high enough to make the risks acceptable for fully informed donors.

The urologic evaluation begins with a thorough history that focuses on recurrent UTIs, nephrolithiasis, genitourinary malignancy, congenital issues such as vesicoureteral reflux, and hematuria. The renal anatomy is evaluated with CT angiography of the abdomen and pelvis and should include an excretory phase to evaluate the renal collecting system and ureters. Potential recipients with a history of urolithiasis should undergo a complete metabolic stone workup. Multiple stone episodes, or the presence of multiple stones at the time of the donor evaluation, are generally considered a contraindication to donation. Patients with a single, small stone can be considered for donation if their metabolic evaluation is normal.

Women of childbearing age should be informed that pregnancy outcomes after kidney donation were similar to those reported in the general population, but inferior to predonation pregnancy outcomes (Ibrahim et al, 2009a). It is recommended that pregnancy should be delayed for at least 2 months after donation to assess renal compensation before conception (Delmonico, 2005). Hydro-nephrosis during pregnancy is more common on the right side, but to date there are no reports to demonstrate more complications with left donor nephrectomy. We advise women to be closely monitored by an obstetrician during pregnancy after kidney donation.

Managing Incompatible Living Donor and Recipient Pairs

Approximately 35% of medically suitable donors are found to be incompatible with their intended recipient because of blood-type incompatibility, and 30% of the recipients have HLA antibodies as a result of prior blood transfusions, transplants, or pregnancy (Segev et al, 2005). Traditionally, to avoid rejection, incompatible patients in this situation were told not to proceed with living-donor transplantation, but rather to wait for a compatible deceased-donor organ. With over 100,000 patients on the deceased donor wait list, patients in many parts of the country must wait for nearly 10 or more years before they are transplanted. Approximately 4000

patients on the wait list will die per year. For these reasons, multiple strategies are now employed to facilitate living-donor renal transplantation for incompatible pairs.

ABO blood-type incompatible transplantation has been performed with acceptable graft and patient survival, but longer term results are not equivalent to blood-type compatible living-donor transplants (Montgomery et al, 2012). Protocols for such transplants vary widely across different programs but may include plasmapheresis, IV immunoglobulin (IVIG), rituximab, and/or splenectomy to bring anti-ABO titers to acceptable levels. In general, ABO-incompatible recipients also require more intensive immunosuppressive regimens.

Kidney transplantation with known HLA DSAs also may be performed despite a higher risk for antibody-mediated rejection. Depending on the strength of crossmatch positivity being caused by HLA antibodies, patients may require treatments such as IVIG and/or plasmapheresis before proceeding with transplantation. As with ABO-incompatible transplantation, protocols vary widely across different centers. Donor-specific antibodies that are considered weak may not cause a positive flow cytometric or cytotoxic crossmatch, and some centers choose to proceed with no pretransplant therapy. Patients who undergo renal transplantation with known DSA require periodic monitoring to ascertain the return of strong antibodies that were previously known, or de novo DSA, both of which put the patient at risk for antibody-mediated rejection.

KPD, which encompasses chains and exchanges, has emerged as a third modality to facilitate living-donor kidney transplantation for incompatible donor and recipient pairs. Incompatible pairs are placed into a pool of other incompatible donor and recipient pairs, and compatible matches are then found by matching algorithms built into software programs. Large multicenter databases of incompatible pairs maximize the chances of finding compatible matches for participants (e.g., Alliance for Paired Donation, 2009; National Kidney Registry, 2014; United Network for Organ Sharing, 2014a). Initially, KPD comprised simple, one-way swaps between two incompatible donor and recipient pairs (Fig. 47-3). Paired donation chains can be started by "Good Samaritan"

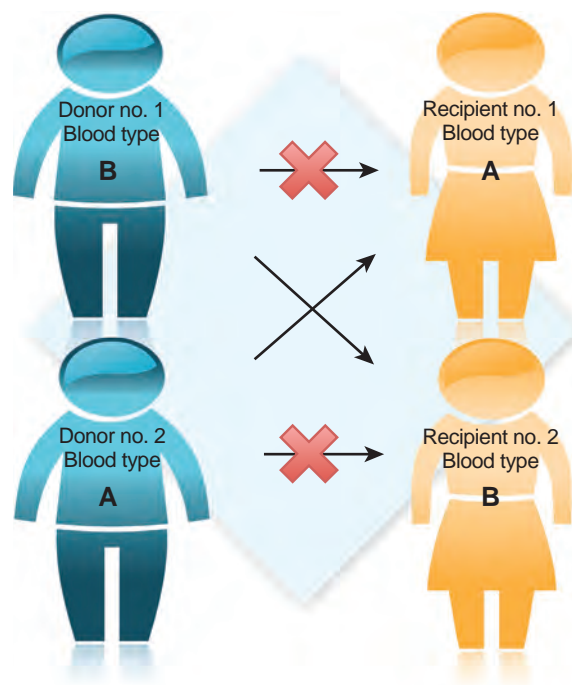


Figure 47-3. Kidney paired donation (KPD) simple two-way swap. An example of KPD between two ABO-incompatible donor and recipient pairs. KPD is employed in this situation as a simple swap that results in two blood-type compatible, living-donor transplants.

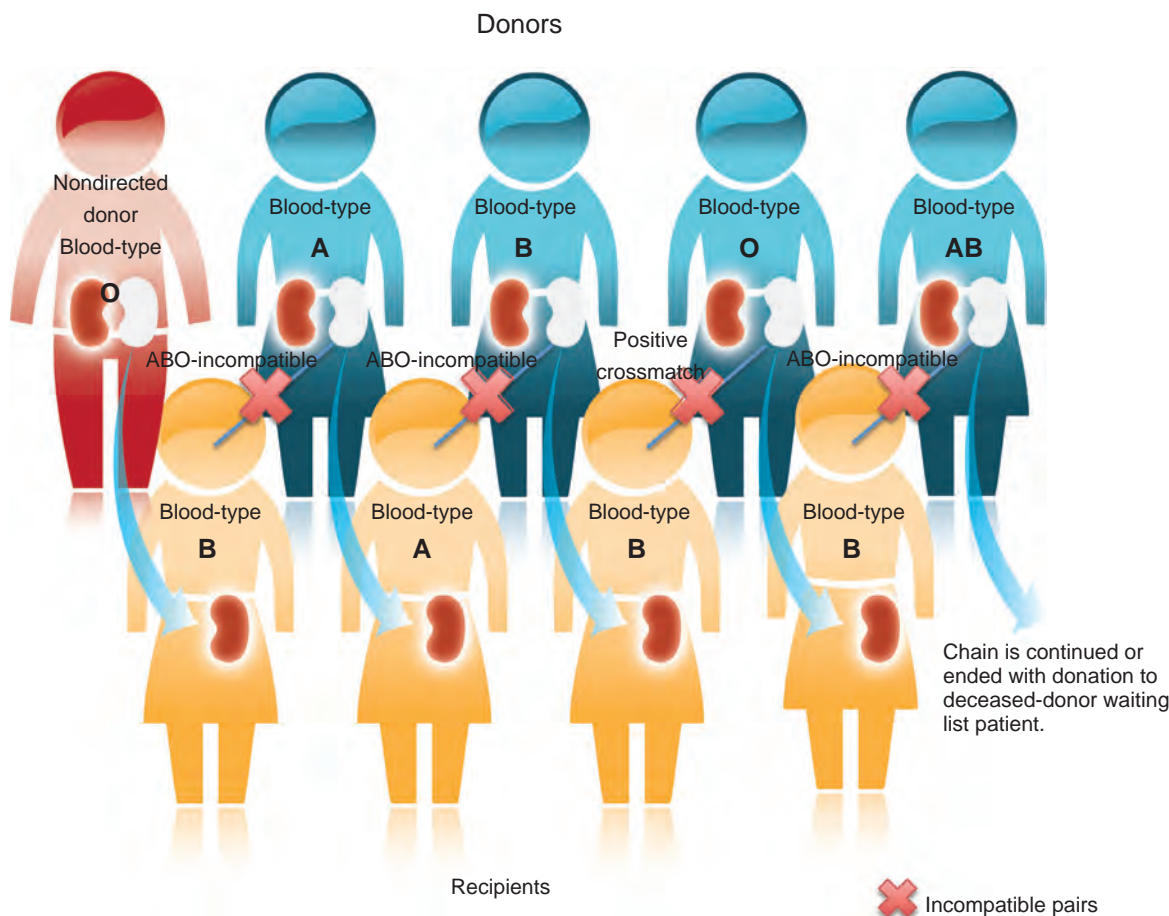


Figure 47-4. Kidney paired donation (KPD) chain. A nondirected donor is able to start a KPD “chain” that is theoretically never ending. In the chain depicted, both blood-type incompatibility and incompatibility because of a positive crossmatch are overcome by KPD, thereby allowing for multiple living-donor transplants to occur. Donors and recipients are often at different transplant centers, and transcontinental shipping of living-donor kidneys via commercial airlines has become widely accepted with excellent results.

donations, also known as nondirected donors (NDDs), who are remarkable individuals who seek to donate a kidney to a complete stranger in need. When a KPD chain is started by an NDD the number of living-donor transplants that result are theoretically unlimited; chains are often ended by offering a living-donor kidney to an individual on the deceased-donor waiting list (Fig. 47-4). The most successful KPD programs involve transplant centers all across the United States, and the transcontinental shipping of living-donor kidneys via commercial airline has greatly facilitated more KPD transplants without compromising results (Melcher et al, 2012). UNOS has recognized the importance of KPD as a method for increasing the number of living-donor transplants that can be performed and is currently evaluating the best way to maximize the potential of paired exchange (Organ Procurement and Transplantation Network, 2013).

If compatible living-donor pairs participate in a kidney exchange program, a recipient might benefit from a younger donor or a better histocompatibility match. Innovative computer software and the ability to perform virtual crossmatch testing continue to improve the efficiency of KPD.

Living Kidney Donor Operation

The laparoscopic donor nephrectomy (LDN) has become standard of care for the recovery of kidneys from living donors. The LDN has a low complication rate (6% minor, <2% major) and very low mortality rate of 0.03% (Harper et al, 2010; Segev et al, 2010). The

technique of LDN is nearly identical to that of a standard laparoscopic nephrectomy. Many centers have adopted a laparoscopic (Fig. 47-5A), hand-assisted laparoscopic (Fig. 47-5B), or robot-assisted technique. Open donor nephrectomy is rarely performed at this point but is typically accomplished through an extraperitoneal flank approach. Conversion to an open nephrectomy is not considered a complication of laparoscopic surgery, and donors should be counseled and consent received for this possibility before donation.

Special attention is paid to preserving adequate renal vessel and ureteral length for the recipient operation. Although most LDNs are left sided (because of the longer left renal vein), right-sided LDN is performed as well when indicated to preserve the “better” kidney for the donor. It is not necessary to administer IV heparin to the donor (Perry et al, 2002). The ureter is mobilized to the point at which it crosses the iliac vessels. It is unnecessary to include the gonadal vein with the ureter, and the gonadal artery should also be left intact for the donor when possible (Breda et al, 2006). The safest method for ligating the renal vessels is to employ a surgical stapling device with a vascular staple load. Stapling does not compromise vessel length for the recipient operation. Hem-o-lock clips are contraindicated in LDN because they have been associated with living-donor deaths when used to seal the aortic side of the donor renal artery. Once the kidney is removed, the renal arteries are immediately cannulated and the kidney is flushed with ice-cold heparinized (5000 U/L) lactated Ringer solution or an organ preservation fluid (if shipped).

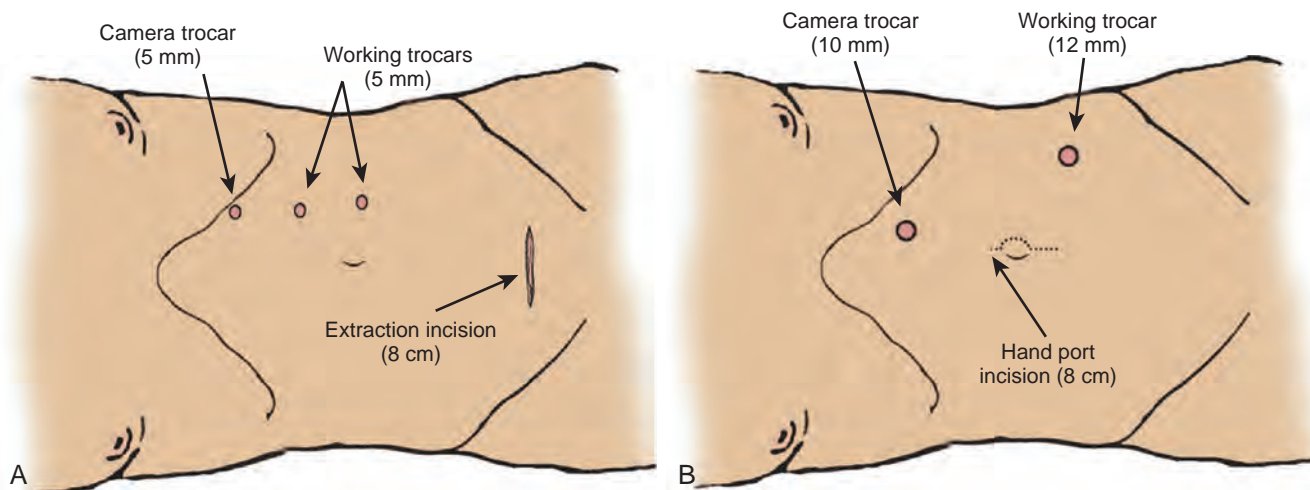


Figure 47-5. Pure laparoscopic and hand-assisted laparoscopic left donor nephrectomy. **A,** Diagram showing the location of the incision and trocar placement for left laparoscopic donor nephrectomy. **B,** Hand-assisted left laparoscopic donor nephrectomy. For a laparoscopic single-site procedure all trocars are inserted via the perumbilical incision.

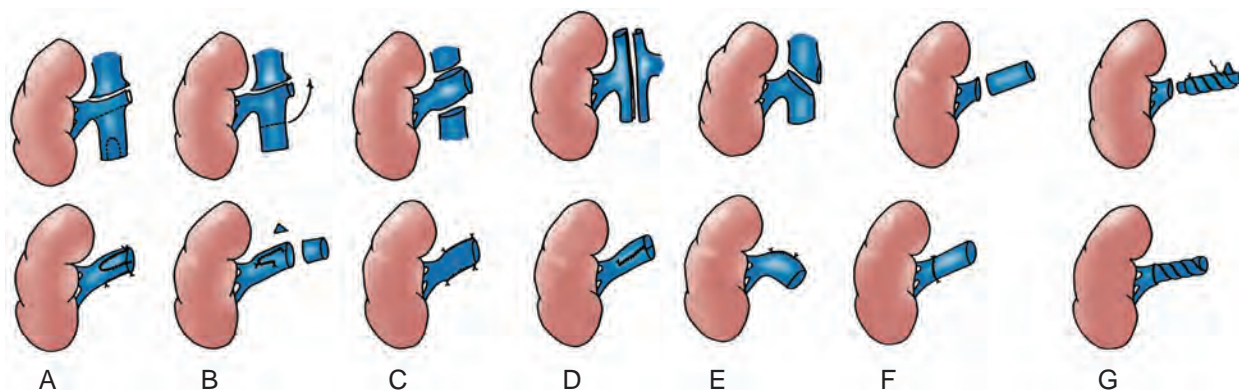


Figure 47-6. A to G, Methods of extending the right renal vein include modifications of the inferior vena cava and a free graft of donor external iliac vein. The first two methods are valuable when the cephalad portion of the right renal vein has been compromised by the separation of the liver graft from the kidney grafts. (A and B, From Barry JM, Lemmers MJ. Patch and flap techniques to repair right renal vein defects caused by cadaver liver retrieval for transplantation. *J Urol* 1995;153:1803; C, from Barry JM, Fuchs EF. Right renal vein extension in deceased kidney transplantation. *Arch Surg* 1978;113:300; D and F, from Barry JM, Hefty TR, Sasaki T. Clam-shell technique for right renal vein extension in cadaver kidney transplantation. *J Urol* 1988;140:1479; E, from Corry RJ, Kelley SE. Technic for lengthening the right renal vein of cadaver donor kidneys. *Am J Surg* 1978;135:867; G, from Nghiem DD. Spiral gonadal vein graft extension of right renal vein in living renal transplantation. *J Urol* 1989;142:1525.)

KIDNEY TRANSPLANT OPERATION

Allograft Preparation

Meticulous preparation of the renal allograft is essential. The renal vessels and ureter should be identified. The adipose tissue surrounding the kidney parenchyma is then carefully dissected off the vessels. Branches that drain into the renal vein, such as the left adrenal vein, should be ligated. Small accessory renal veins may be ligated and divided to increase the length of the main renal vein. Caution is advised in ligating large, or even medium-size accessory veins, because venous congestion has been observed. A number of techniques have been described to extend the renal vein if necessary (Fig. 47-6). Arterial branches greater than 0.5 mm in diameter should be preserved if possible (Shapiro, 1997). Fatty tissue close to the renal hilum should be ligated, because this tissue

often contains lymphatic channels that may otherwise contribute to a postoperative lymphocele.

Recipient Operation

The recipient is placed supine on the operating table and appropriately padded, and general inhalational anesthesia is induced. Prophylactic IV antibiotics are given, and a central venous catheter is placed. A urethral catheter is placed and attached to a three-way tubing system that allows for bladder filling and drainage during the operation, which can be helpful during the ureteroneocystostomy (Fig. 47-7). The bladder irrigant is preferably a broad-spectrum antimicrobial solution such as bacitracin or neomycin-polymyxin B. The bladder should be rinsed with this solution before start of the operation. If bowel has been used for urinary reconstruction, all mucus should be completely irrigated. To ensure proper blood

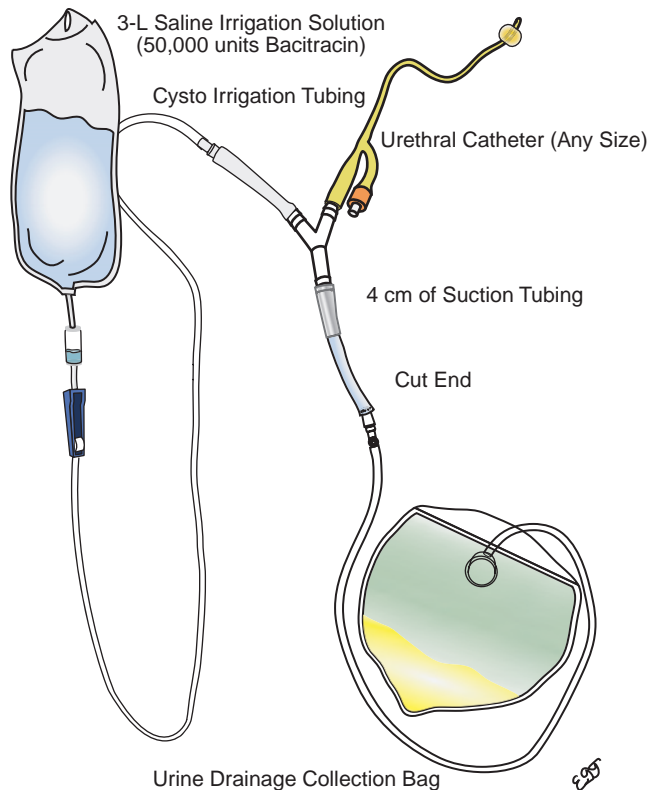


Figure 47-7. Bladder irrigation setup. This tubing system is compatible with any urinary catheter. The bladder can be filled and emptied many times without having the perineum in the operative field.

pressure once the kidney transplant is reperfused, the central venous pressure should be maintained between 10 and 15 cm H₂O with IV crystalloid and colloid solutions to achieve a mean arterial pressure that is ideally greater than 80 mm Hg. In patients who do not achieve these pressures with IV fluids only, judicious use of a dopamine drip can be considered. The perioperative induction immunosuppression should be reviewed and communicated to the anesthesia team.

A variety of incisions can be used for the recipient operation, but adequate surgical exposure that allows for vascular control is paramount. It is desirable to place the kidney extraperitoneally with the vascular anastomosis to the iliac vessels. The extraperitoneal approach is advantageous in minimizing potential complications and postoperative ileus. A Gibson incision over the right or left iliac fossa offers excellent exposure of the iliac vessels and the urinary bladder. A midline incision can be used and may be particularly useful in cases in which the vascular target includes the aorta and inferior vena cava. On rare occasions the vascular targets also may include the splenic and/or portal systems.

When a Gibson incision is used, the peritoneum is retracted medially and the retroperitoneal space overlying the iliac vessels is developed using a combination of blunt dissection and electrocautery. The inferior epigastric vessels can usually be gently retracted, but they may be divided if surgical exposure is compromised. Similarly, the round ligament may be preserved in females. The spermatic cord is identified in men as it travels inferiorly exiting the peritoneum and is carefully preserved. A self-retaining retractor is placed, without compression of the femoral canal, and the iliac vessels are exposed using the electrocautery. Lymphatic tissue overlying the vessels should be ligated or sealed with electrocautery. Care is taken to avoid injury of the genitofemoral nerve that lies anterior to the psoas muscle just lateral to the external iliac artery. Before anastomosis the kidney can be wrapped with sterile saline ice in a laparotomy sponge to keep the graft cool until reperfusion.

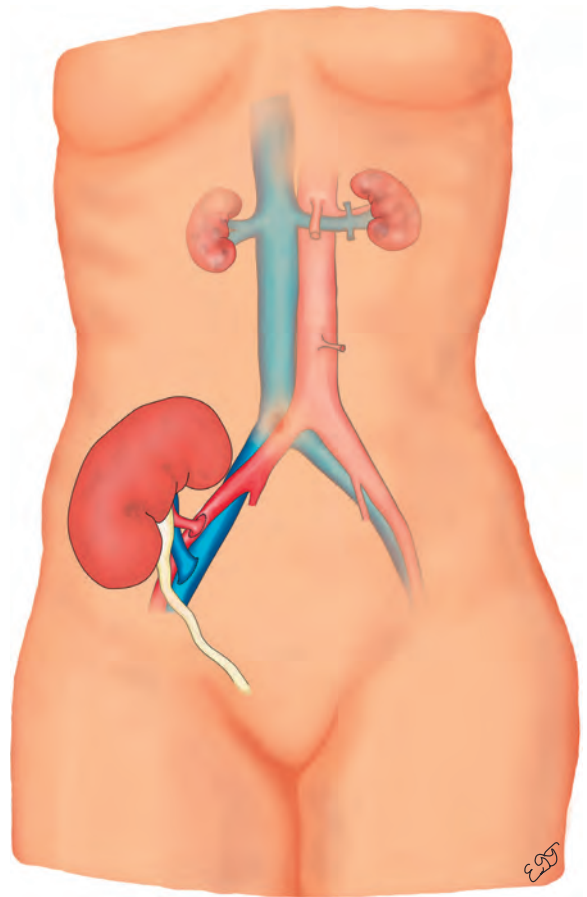


Figure 47-8. Typical anatomy of a kidney transplant. The renal vein is anastomosed to the external iliac vein, usually medial to the external iliac artery. When the recipient has a tortuous iliac artery, the venous anastomosis is best performed lateral to the bowed external iliac artery. In the absence of significant recipient arteriosclerosis, the renal artery is commonly anastomosed to the external iliac artery with 5-0 or 6-0 monofilament, nonabsorbable sutures. If significant iliac arteriosclerosis is present or the vessels are short, the common iliac artery or aorta becomes the target vessel for renal artery anastomosis.

For the vascular anastomosis, the preferred target sites are the external iliac artery and vein. In a living-donor transplant in which the donor vessels are shorter, the common iliac artery is often used. The venous anastomosis is generally performed first to limit ischemia to the leg. The venous target is occluded using vascular clamps or Rummel tourniquets according to surgeon preference. A venotomy is performed with a curved-blade scalpel, and heparinized saline solution is injected directly into the venotomy site to clear any blood or clots. A running end-to-side anastomosis is then performed with nonabsorbable monofilament polypropylene suture. The arterial anastomosis is then performed in a similar fashion. Patients with ESRD, and those with long-standing diabetes, in particular, are commonly found to have significant arteriosclerosis, and great care should be taken to recognize and avoid intimal disruptions that may lead to arterial dissection. A 2.7- to 6-mm punch facilitates the recipient arteriotomy if a donor arterial patch is not available. Before reperfusion an IV bolus of furosemide and mannitol may be administered to facilitate diuresis and act as a free-radical scavenger. Once the vascular anastomoses have been completed, the occluding clamps are removed—venous followed by arterial—and the kidney reperfused. Hemostasis is achieved, and the kidney is rewarmed with copious amounts of warm sterile saline. The allograft is then positioned in the iliac fossa such that there is no kinking of the transplant vessels (Fig. 47-8).

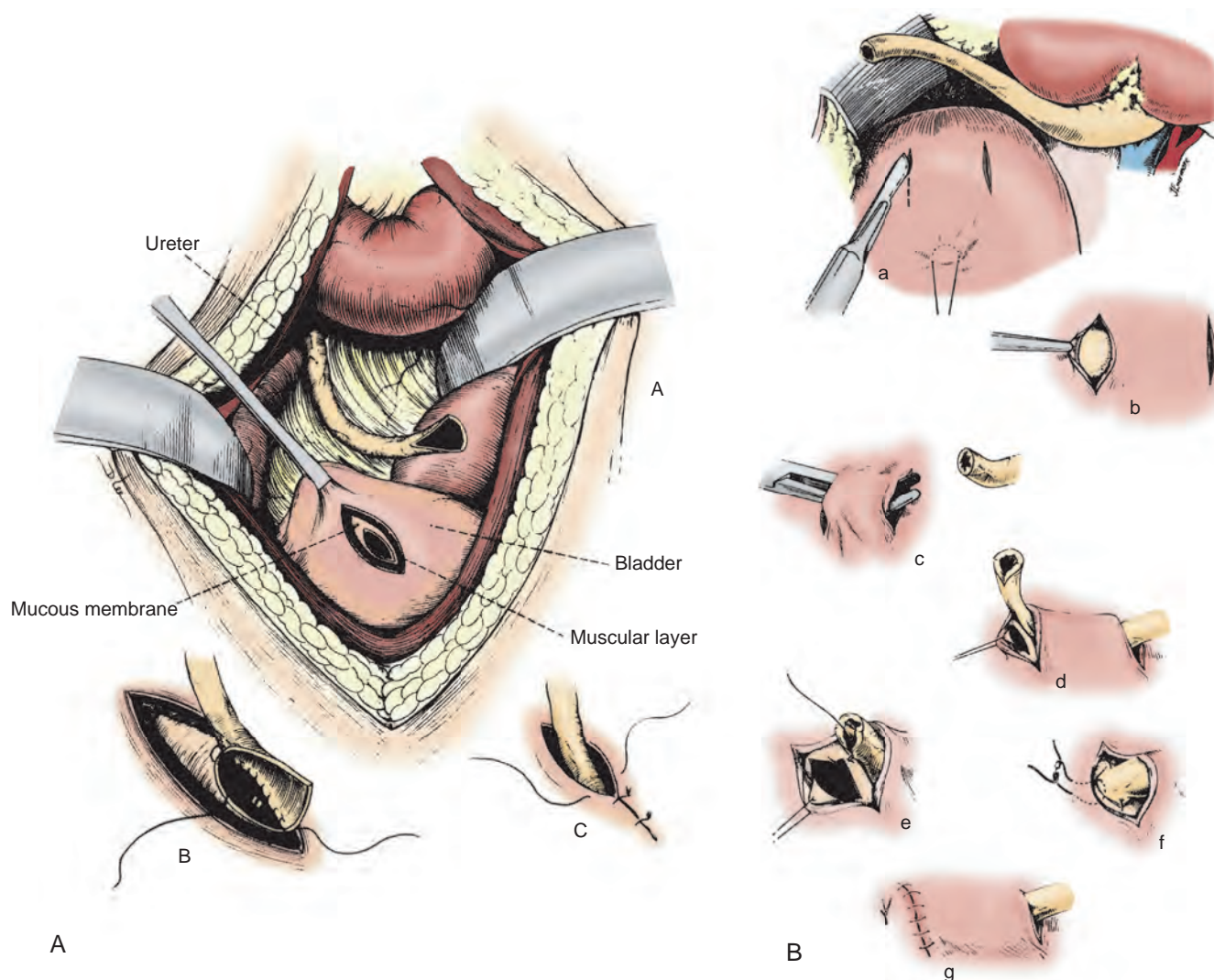


Figure 47-9. Two examples of extravesicular ureteroneocystostomy. **A**, Lich-Gregoir. An anterolateral seromuscular incision is made down to the bulging bladder mucosa. The bladder is drained, the mucosa incised, and the ureter anastomosed to the bladder (as shown) with fine absorbable sutures. A distal anchoring stitch to hold the ureter to the bladder is used to prevent proximal migration in the tunnel (not shown). The seromuscular layer is then loosely closed over the ureter. **B**, Barry. Steps a through c are completed with the bladder full of an antibiotic solution. The anesthesiologist unclamps the catheter before mucosal incision, and steps d through g are completed with fine absorbable sutures. (A, From Konnak JW, Herwig KR, Finkbeiner A, et al. Extravesicular ureteroneocystostomy in 170 renal transplant patients. *J Urol* 1975;113:299–301; B, from Barry JM. Unstenated extravesicular ureteroneocystostomy in kidney transplantation. *J Urol* 1983;129:918–9.)

The preferred technique for restoring continuity of the urinary tract with the transplant ureter is to create an antirefluxing, extravesicular, stented ureteroneocystostomy (Lich et al, 1961; Gregoir, 1962). This technique is easily reproducible in both normal and small contracted bladders, requires less ureteral length, and is generally faster than intravesicular techniques. Effort to create an antirefluxing tunnel is important to help prevent reflux of infected urine into the allograft, which may cause transplant pyelonephritis. Other extravesicular techniques have been employed, including the Barry and single-stitch techniques. It is useful to be familiar with all of them, and they should be used according to surgeon preference (Gibbons et al, 1992; Veale et al, 2007) (Fig. 47-9). The ureter should be passed below the spermatic cord, cut to allow for a tension-free anastomosis, and the periureteral tissue preserved to maximize the distal blood supply. If the allograft ureter appears compromised, options include a psoas hitch, a Boari flap, or using the ipsilateral native ureter. A double-pigtail ureteral stent should

be used in the majority of cases, because this has been shown to significantly decrease urologic complication rates (Wilson et al, 2013). Additionally, a closed suction drain is placed such that it lies in the area of the ureteral anastomosis and the vascular anastomosis. Ureteral anastomosis into a urinary diversion also should be performed with a ureteral stent, and a urinary catheter should drain the diversion as it would the native bladder.

Although indwelling urinary catheters and ureteral stents can reduce urologic complication rates, prolonged use places transplant recipients at higher risk for UTIs that may predispose them to rejection episodes. For this reason, it is recommended that the urinary catheter, closed suction drain, and ureteral stent be removed as soon as possible. In patients with reasonable bladder capacity, the urinary catheter may be removed on postoperative day 3 and the closed suction drain removed later in the day if drain output remains low.

Kidneys from small pediatric donors can be transplanted en bloc, or if deemed large enough, as single kidneys. When the

kidneys are transplanted en bloc, the entire donor aorta and inferior vena cava is typically anastomosed end to side to the iliac vessels. Because of the small size and tenuous blood supply of the ureters in such small donors, urologic complications such as urine leaks and ureteral anastomotic strictures are more common (Hobart et al, 1998). Pediatric-size ureteral stents should be employed, and consideration should be given to implanting the ureters separately such that a complication does not automatically affect both of the small allografts. Dual adult donor kidneys from marginal donors are generally not transplanted en bloc and may be placed together in the same iliac fossa or in both iliac fossae (Gill et al, 2008).

Robotic-assisted kidney and pancreas transplants have been reported (Giulianotti et al, 2010; Abaza et al, 2014). The potential advantages include a smaller incision, less pain, and a more rapid recovery. As robotic technology and operator skills improve, these small benefits may justify the added complexity, operative time, and cost associated with the procedures.

POST-TRANSPLANT CARE

Anticoagulation

Uremia can inhibit platelet aggregation and promote a bleeding tendency. Patients with coronary artery disease, particularly those with coronary stents, may take aspirin and other antiplatelet agents. Liver disease and prolonged exposure to antibiotics can lead to clotting factor deficiency. Anticoagulants such as warfarin may be prescribed to prevent fistula thrombosis or in patients with atrial fibrillation.

If a vascular anastomosis is difficult because of atherosclerosis, friable intima, small vessels, or pediatric recipient, intraoperative anticoagulation with 500 to 2000 U of IV heparin is indicated.

Perioperative anticoagulation must be individualized to take all of these factors into consideration. If the graft does not function immediately, percutaneous biopsy may be needed. Therefore long-acting anticoagulants are generally initiated once kidney function has stabilized. Low-molecular-weight heparin is eliminated by the kidney and must be used cautiously in the setting of unpredictable metabolism to minimize bleeding complications. A very low dose of IV heparin (100 U/hr) is used in the immediate postoperative period when the risk for coagulation is increased. The dose can be increased if bleeding is minimal or transitioned to antiplatelet therapy.

Surgical Complications

The most common early complications of renal transplantation include infection, bleeding, vascular thrombosis, urinary leak, and lymphatic leak. It should be noted that the signs and symptoms of surgical complications are similar to those of graft dysfunction in this population of patients. It is therefore important to consider immunologic causes as well.

Postoperative bleeding is usually discovered by abnormal vital signs and decreasing hematocrit values. Coagulation parameters should be checked. A large hematoma may compress the transplant kidney, negatively affecting renal function (Fig. 47-10). Patients who require multiple transfusions over a short period should be taken back to the operating room to evacuate any hematoma and to evaluate for a source of the ongoing bleeding. Transplant renal artery thrombosis is usually associated with delayed graft function or a hypercoagulable state, and patients with a known propensity for thrombosis should be given anticoagulation therapy. Renal artery thrombosis generally occurs within 3 days of the transplant and is associated with sudden cessation of urine output. Doppler ultrasound reveals no blood flow to the graft, and such grafts are rarely salvaged. Transplant renal vein thrombosis is also associated with a hypercoagulable state, kinking or stenosis of the vein, acute rejection, and hypotension. Doppler ultrasound may reveal a clot in the vein and decreased blood flow to the graft. As with renal artery thrombosis, emergent thrombectomy and antithrombotics should be attempted, but is rarely successful.

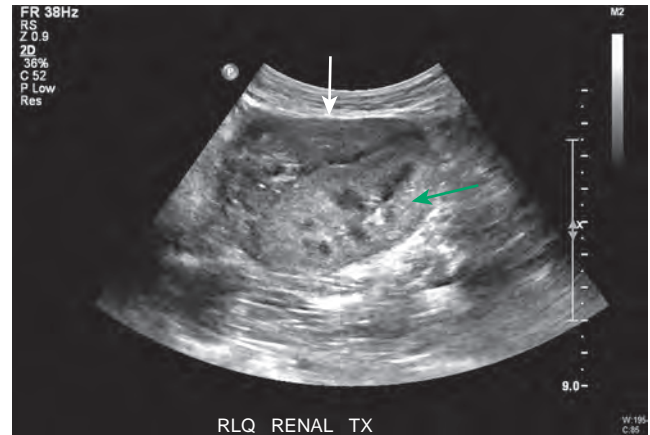


Figure 47-10. Subcapsular hematoma. Bleeding under the capsule of the kidney forms a hematoma (white arrow) which compresses the renal parenchyma (green arrow) resulting in reversal of diastolic flow on Doppler ultrasound.

Urinary leaks usually occur at the ureterovesical anastomosis and are associated with ischemic necrosis of the distal transplant ureter. Leaks manifest in the early postoperative period with decreased urine output from the urinary catheter and increased output from the closed suction drain. A urine leak is confirmed if the drain fluid creatinine is more than twice the serum creatinine or by nuclear medicine renal scan. In the case that the leak occurs after the urethral catheter has been removed, it should be replaced immediately. Many anastomotic leaks will heal with the ureteral stent in place and catheter drainage. Leaks that do not heal with conservative measures may require placement of a percutaneous nephrostomy tube or open repair.

Lymphoceles can originate from the transplant kidney or the lymphatic channels that surround the iliac vessels. Many lymphoceles are small and inconsequential, but large lymphoceles may cause pain, become infected, or compress the allograft, leading to dysfunction. Typically, lymphoceles are well visualized on ultrasound and can be initially treated with image-guided aspiration. Lymphoceles that reaccumulate require insertion of a closed suction drain. Rarely, a recurrent lymphatic leak may require use of sclerosing agents or even creation of a peritoneal window to aid in reabsorption (Chin et al, 2003). The incidence of lymphoceles can be reduced by routine placement of a closed suction drain that is removed when the daily output is less than 50 mL.

Rejection

The main function of the immune system is to protect against infection. Fundamental properties of the host defense include the ability to discriminate between self and nonself antigens and the ability to amplify the response on repeat exposure to foreign antigens. Investigating the cellular and molecular mechanisms involved in rejection of transplanted tissue has made a significant contribution to our understanding of the immune system.

Tissue that is moved from one place to another on the same individual, known as an **autologous** graft, is accepted as long as the appropriate blood supply and microenvironment exist. Similarly, tissue from genetically identical individuals, **syngeneic**, is accepted, whereas tissue from genetically different members of the same species, **allogeneic**, is usually rejected within a few weeks. Tissue from a different species, **xenogeneic**, is typically rejected very quickly.

Kidney transplant rejection can be classified by temporal occurrence of graft loss. **Hyperacute** rejection occurs shortly after the reperfusion of kidney transplants. Recipient cytotoxic antibodies and complement react with donor vascular endothelial antigens, leading to a rapid activation of the coagulation cascade and graft

thrombosis. This type of “humoral” rejection is rarely seen clinically today because of sensitive crossmatch tests to detect DSA.

Acute rejection classically occurs approximately 5 days after an allogeneic organ transplant without immunosuppression. Current immunosuppression protocols have reduced the rate of biopsy-proved acute cellular rejection to 10% to 15% in the first year. The most common manifesting sign is an increasing serum creatinine and decreasing urine output. Symptoms may include pain, swelling over the graft, malaise, and fever; but these are rare. Urinalysis may show proteinuria, hematuria, or pyuria. Imaging studies may demonstrate decreased cortical blood flow and tubular function. However, none of these findings is specific, so needle biopsy of the kidney graft is the current standard diagnostic test. The criteria for histologic classification of renal rejection were standardized at a series of meetings in Banff (Solez, 2010). The typical findings in acute cellular rejection are mononuclear infiltration of tubules and vessels. The deposition of complement fragments (C4d) in peritubular capillaries is now recognized as diagnostic of rejection frequently associated with donor-specific antibodies.

Chronic rejection is characterized by a gradual deterioration of kidney function. The histologic features of interstitial fibrosis, arteriolar sclerosis, and tubular atrophy rarely improve with augmented immunosuppression, and are in some cases the result of drug toxicity.

Immunosuppression Protocols for Kidney Transplantation

The success of organ transplantation requires a modulation of the immune response to nonself antigens expressed by the graft. The induction of donor-specific immune tolerance is the holy grail of transplantation. Tolerance would allow the immune system to accept donor organs, without compromising the normal response to infectious and malignant antigens. The fact that tolerance has been achieved in many animal studies but rarely in humans underscores the difficulty in moving this goal from the animal model to actual patients (Sykes, 2009). In successful hematopoietic cell transplantation, a balance between the host versus graft and graft versus host response allows cells from the donor and recipient to coexist. This symbiosis between donor and recipient usually requires matching of the MHC antigens, but this chimerism was recognized to also occur in some patients with poor matching and long-term function of solid-organ transplants (Starzl, 2004). Advances in immunosuppressive drugs have improved early graft survival rates, but these improvements have had little impact on late graft loss, largely because of chronic rejection. The induction of donor-specific immune tolerance would avoid these complications while also preventing chronic rejection.

Antibodies produced by B lymphocytes can recognize foreign antigens directly and are a principal component of the humoral immune response. The MHC plays an important role in the recognition of foreign proteins by the cellular immune response (Fig. 47-11). The class I antigens present peptide from endogenous proteins to CD8+ lymphocytes. Class II molecules present peptides from exogenous proteins to CD4+ lymphocytes.

The molecular mechanisms that are involved in the activation and proliferation of lymphocytes are the principal targets for blockade by pharmacologic immunosuppression. Three signals have been identified in T lymphocytes. Signal 1 is interaction between the MHC bound to antigenic peptide on an antigen-presenting cell (APC) with a specific T-cell receptor. Signal 2 is antigen-independent costimulatory interaction between molecules on the APC and T cell that lead to intracellular pathways, which stimulates interleukin-2 (IL-2) and other cytokines, as well as cytokine receptor expression. Signal 3 is stimulation of the IL-2 receptor, which leads to activation of the mammalian target of rapamycin (mTOR), which triggers cell proliferation.

Immunosuppression Protocols

Immunosuppressive protocols in kidney transplantation continue to evolve as our understanding of the biology of the immune response expands and pharmacologic agents to block the response

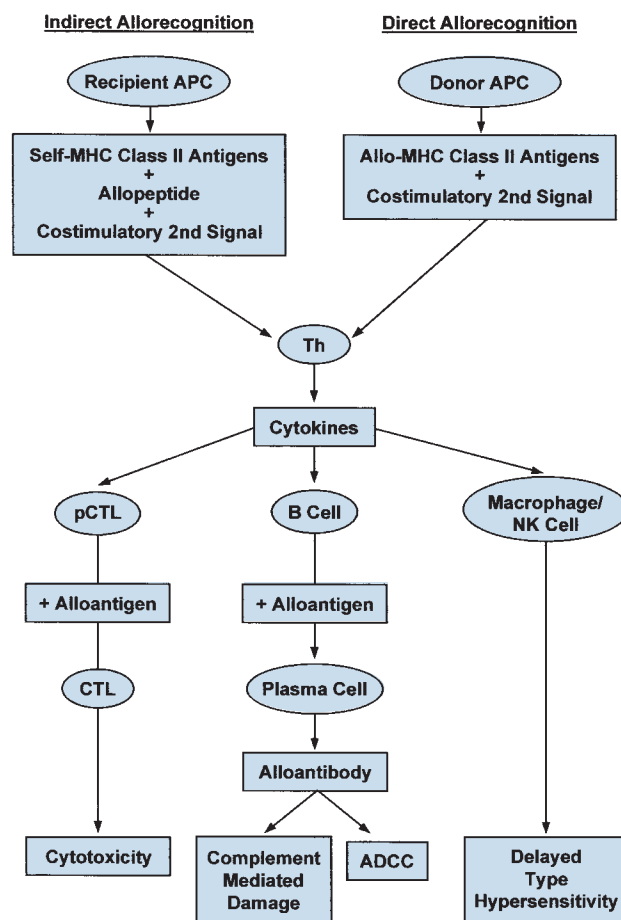


Figure 47-11. Cellular interactions in renal transplant rejection. CD4+ helper T cells (Th) are activated by antigen-presenting cells (APCs) that express incompatible major histocompatibility complex (MHC) class II antigens and provide a costimulatory second signal. The Th cells produce lymphokines that promote proliferation of B cells, maturation of CD8+ cytotoxic T lymphocytes (CTLs), activation of macrophages and natural killer (NK) cells, and induction of MHC class II antigens on renal cells. ADCC, antibody-dependent cell-mediated cytotoxicity; pCTL, precursor cytotoxic T cell.

are discovered. Antibiotics, including antifungal and antiviral drugs, also have permitted more intensive immunosuppression. Nearly all immunosuppression protocols were tested in animal models of solid-organ transplantation and then tested in humans. Some of the protocols have been developed through carefully designed clinical trials, but many have been introduced in off-label application by pioneering physicians and patients. In the 1950s the first protocols included *total-body irradiation* and *corticosteroids*. Shortly after the first successful identical twin transplant, *azathioprine* permitted graft survival with some living related donors. Most experimental models achieved superior outcomes if the T-lymphocyte population could be reduced and allowed to slowly recover. The administration of heterologous polyclonal serum from animals exposed to human immune tissue (*antithymocyte globulin*) and (*antilymphocyte globulin*) led to the concept of induction immunosuppression. It was also recognized that high doses of corticosteroids and lymphocyte depletion could reverse acute cellular rejection. Unfortunately, the 1-year graft survival was approximately 50%, with up to 20% mortality from infectious complications in this era.

In the early 1980s, *cyclosporine*, a calcineurin inhibitor, was introduced and maintenance immunosuppression in combination with azathioprine and prednisolone (triple therapy) improved 1-year graft survival rates to greater than 80%, including deceased and living-donor kidneys. The first monoclonal antibody in clinical medicine, *OKT3-antimurine CD3*, was approved in 1985 for the

treatment of steroid-resistant rejection. The success of solid-organ transplantation and the side effects of these drugs stimulated the pharmaceutical industry to develop more selective agents to target the transplant-specific immune response. Immunosuppression protocols are based on the risk for rejection (including donor and recipient factors), minimization of long-term side effects, and cost. The mechanism of action and toxicity of immunosuppressants are listed in Tables 47-3 and 47-4. Currently, the most common

protocols include a form of IV induction with antithymocyte globulin or *basiliximab*, and maintenance with *tacrolimus*, *mycophenolate*, and low-dose steroid (United States Renal Data System, 2013). Using these agents, biopsy-proved graft rejection rates are approximately 10% in the first year and mortality rates continue to improve, but approximately 40% of adult recipients become diabetic. Many of these drugs require continued monitoring of blood levels because metabolism can be affected by drug interactions (Box 47-3).

TABLE 47-3 Mechanisms of Action of Immunosuppressants

IMMUNOSUPPRESSANT	MECHANISM OF ACTION	INTERFERES WITH
Glucocorticoids	Reduce transcription of cytokine genes	Intercellular signaling
Azathioprine	Inhibits purine synthesis	Lymphocyte proliferation
Mycophenolate mofetil	Inhibits purine synthesis	Lymphocyte proliferation
Sirolimus	Inhibits cell cycle progression	Lymphocyte proliferation
Everolimus	Inhibits cell cycle progression	Lymphocyte proliferation
Tacrolimus	Inhibits calcineurin and IL-2 production	Intracellular signaling
Cyclosporine	Inhibits calcineurin and IL-2 production	Intracellular signaling
Rabbit antithymocyte globulin	Depletes T lymphocytes	Antigen recognition
Alemtuzumab (off label)	Depletes T and B lymphocytes	Antigen recognition and antibody production
Rituximab (off label)	Depletes B lymphocytes	Antibody production
Bortezomib (off label)	Proteasome inhibitor	Antibody production
Basiliximab	Blocks IL-2 receptor	Intercellular signaling
Belatacept	Costimulation blockade	Lymphocyte activation
Eculizumab (off label)	Complement inhibitor	Antibody-mediated rejection

IL-2, interleukin-2.

TABLE 47-4 Common Organ System Targets for Toxicities of Immunosuppressant Therapy

ORGAN SYSTEM	PREDNISONE	CYCLOSPORINE	TACROLIMUS	SIROLIMUS	AZATHIOPRINE	MYCOPHENOLATE
Central nervous system	+	+	+	—	—	—
Gastrointestinal system	+	+	+	—	+	+
Kidney	—	+	+	—	—	—
Hematopoietic	—	—	—	+	+	+
Skin	+	+	—	—	—	—
Endocrine	+	+	+	+	—	—
Dyslipidemia	+	+	—	+	—	—
Wound healing	+	—	—	+	—	—

BOX 47-3 Potential Drug Interactions with Cyclosporine and Tacrolimus

DRUGS THAT AFFECT PLASMA OR WHOLE BLOOD CONCENTRATES

Decrease

Rifampin
Rifabutin
Isoniazid
Phenobarbital
Phenytoin
Carbamazepine

Increase

Diltiazem
Verapamil
Nicardipine
Erythromycin
Clarithromycin
Ketoconazole
Fluconazole
Itraconazole

Increase—cont'd

Clotrimazole
Bromocriptine
Danazol
Cimetidine
Methylprednisolone
Metoclopramide

DRUGS WITH NEPHROTOXIC SYNERGY

Gentamicin
Tobramycin
Vancomycin
Azapropazone
Amphotericin B
Cisplatin
Melphalan
Cimetidine
Ranitidine
Diclofenac

TABLE 47-5 Cytomegalovirus (CMV) Serologic Examination Determines Risk for Infection and Disease

CMV SEROLOGIC FINDINGS					
DONOR	RECIPIENT		INFECTION %	DISEASE %	PNEUMONITIS %
+	–	Primary infection	70–88	56–80	30
–	+	Reactivation	0–20	0–27	Rare
+	+	Reactivation or superinfection	70	27–39	3–14
–	–		Rare		
±	+	Antithymocyte globulin induction or high-dose steroids		65	

Data from Davis CL. The prevention of cytomegalovirus disease in renal transplantation. *Am J Kidney Dis* 1990;16:175–88; and Hartmann A et al. The natural course of cytomegalovirus infection and disease in renal transplant recipients. *Transplantation* 2006;82:S15–7.

TABLE 47-6 Postoperative Infection and Peptic Ulcer Prophylaxis

PROBLEM	COMMONLY USED DRUG PROPHYLAXIS	ALTERNATE(S)
Urinary tract infection	Trimethoprim-sulfamethoxazole × 3 mo	Nitrofurantoin
<i>Pneumocystis</i> pneumonia	Trimethoprim-sulfamethoxazole × 3 mo	Pentamidine inhalant
Oral candidiasis	Nystatin suspension × 1–3 mo	Clotrimazole lozenges
Vaginal candidiasis	Clotrimazole vaginal inserts as needed	Nystatin inserts
Herpes simplex virus	Acyclovir × 3 mo if valacyclovir is not indicated	Ganciclovir, valacyclovir, famciclovir
Primary CMV disease	Valacyclovir	Ganciclovir
Recurrent CMV disease	Valacyclovir × 3 mo or during rejection therapy	Ganciclovir
Peptic ulcer disease	H ₂ -Receptor antagonist + antacid if symptomatic	

CMV, cytomegalovirus.

The development of new drugs in transplantation continues to focus on reducing nephrotoxicity, diabetes, and the gradual loss of renal function as a result of fibrosis. Despite the absence of cellular rejection, many patients will develop antibodies to antigens on the allograft, which is recognized as a significant risk factor for chronic transplant rejection. Many young patients will require more than one transplant procedure when their first transplant ultimately fails. New methods of monitoring the transplant immune response, preventing DSA, and treatments for humoral rejection are being investigated.

Infection

The timing of an infection after transplantation is critical to the appropriate diagnosis and management. Within the *first month* the organisms tend to be those causing infections at an institution in other patients with major urologic operations. The most common infections are related to technical complications of surgery and invasive medical devices and most commonly involve the genitourinary tract. The medical conditions of the patient, such as diabetes, malnutrition, obesity, abnormal urinary tract, and previous infections, increase the risk. Careful preparation of the donor graft, minimal blood loss, short ischemia time, mobilization of the patient, and prompt removal of catheters and drains reduces the risks for infection. One exception is a donor-derived infection of the graft or preservation solution. All infections should be treated with empirical antibiotics and adjusted based on the sensitivity of cultured organisms.

During months 1 to 6 after surgery, infections that are controlled by the cellular immune system are more prevalent. These opportunistic infections include fungi such as *Candida*, *Pneumocystis*, *Aspergillus*, and *Cryptococcus*; bacteria, including *Listeria monocytogenes*, *Nocardia*, and *Toxoplasmosis*; and viruses such as CMV, EBV, polyomavirus, hepatitis virus, and herpesviruses. The incidence of these infections is influenced by the recipient and donor history of preoperative exposure and augmented immunosuppression (Table 47-5).

Prophylactic treatment has significantly reduced the morbidity of immunosuppression (Table 47-6).

The infections that occur more than 6 months after transplant are influenced by graft function, risk for rejection, and previous infections. UTIs account for more than 15% of hospital readmissions in the first 2 years after kidney transplantation. Therapy should be based on a complete urologic physical examination and urine culture and sensitivity results. Recurrent UTIs should be evaluated for anatomic risk factors such as fistulas, incontinence, retention, reflux, and foreign bodies. Some patients with minimal pretransplant urine output need to be encouraged to increase fluid intake and void frequently. A voiding diary and assessment of postvoid residual facilitates patient education. If infections are infrequent, antibiotics should be provided to be initiated by the patient when symptoms occur. Some patients may benefit from continuous antibiotic suppression, but the risk for antimicrobial resistance and side effects should be minimized. Transplant vesicoureteral reflux with recurrent pyelonephritis may require ureteroneocystostomy.

Most UTIs do not improve with a reduction in immunosuppression. However, some viral infections such as adenovirus, which may manifest with hemorrhagic cystitis, and polyomavirus are exceptions. Adenovirus infection is usually self-limited and resolves with forced hydration. BK polyoma viral nephropathy can be detected by urine cytology, but is more commonly detected by polymerase chain reaction analysis of blood or urine samples. Treatment consists of reduction of immunosuppression and close monitoring of renal function.

Allograft Nephrectomy

Indications for removal of a failed kidney transplant are based mainly on signs and symptoms that happen as a result of immunosuppression withdrawal, including tenderness, graft enlargement, gross hematuria, and generalized flulike symptoms such as fever and malaise. If a patient is likely to be a candidate for

retransplantation, continued low-level maintenance immunosuppression may avoid the necessity of the allograft nephrectomy and reduce the production of HLA antibodies. Kidneys that fail within the first year of transplantation generally require removal. Those that fail as a result of chronic rejection are less likely to require removal and may be left in situ. Symptomatic patients may be treated with high-dose steroids to see if their symptoms resolve, obviating the need for allograft removal.

Allograft nephrectomy can be technically challenging, and referral to a surgeon who has experience with such procedures is advised. Within the first 6 weeks, removal of all transplanted tissue is generally a straightforward procedure. Symptomatic chronically rejected kidney transplants are generally removed in a subcapsular fashion because the capsule is likely to be adherent to the surrounding structures. The procedure carries the risk for significant perioperative morbidity, including acute hemorrhage, lymphatic leak, bowel injury, and abscess formation. The iliac vessels in the area of the allograft may become secondarily infected, leading to sepsis and/or vessel rupture.

Post-transplant Malignancy

Chronic immunosuppression increases the risk for malignancy. Skin cancer is the most common after solid-organ transplant. Malignancies associated with viral infection, including Kaposi sarcoma (human herpesvirus 8), non-Hodgkin lymphoma (EBV), and vulvar (human papillomavirus) and hepatocellular (HCV) carcinoma have a standardized incidence ratio (SIR) of greater than 5 compared to that of the general population. The incidence of kidney (SIR 4.7), bladder, and penile cancers are also increased, whereas the incidence of breast cancer was significantly decreased (SIR 0.85).

Surprisingly, the risk for prostate cancer is actually decreased in transplant recipients (SIR 0.92) (Engels et al, 2011). Therefore transplantation has little bearing on prostate cancer and the best treatment should be determined by grade, stage, estimated longevity, and patient preference. Given the increased mortality of many patients with ESRD, the risks and benefits of PSA screening should be discussed. If the native kidneys have acquired renal cysts as a result of prolonged dialysis, they should be monitored with annual renal ultrasound (Moudouni et al, 2006). Native nephrectomy is indicated for kidney transplant recipients with solid renal masses.

The interaction of urine with bowel segments may increase the risk for malignancy with immunosuppression. A history of enterocystoplasty or ureterosigmoidostomy should initiate a cancer surveillance program. The first-line adjuvant for superficial transitional cell carcinoma should be mitomycin, because thiopeta may have additive myelosuppressive effects. Bacillus Calmette-Guérin, a live attenuated bacterium, has been used in transplant recipients but may have a greater risk for systemic infection (Sun and Singh, 2010). A biopsy sample should be obtained of tumors within the kidney transplant. Lymphoma may respond to reduction of immunosuppression and has been described as post-transplant lymphoproliferative disorder. Partial nephrectomy has been curative in some donor-derived tumors.

Pregnancy and Childbearing

After successful kidney transplantation, levels of follicle-stimulating hormone, luteinizing hormone, and testosterone usually become normal and spermatogenesis improves (Akbari et al, 2003; Kheradmand and Javadneia, 2003). **Among male recipients who have fathered children, there has been no increase in congenital abnormalities in the offspring.** It is recommended, however, that impregnation be delayed for at least 1 year after transplantation (Armenti et al, 1998).

Successful renal transplantation usually restores fertility in premenopausal women. In a report based on thousands of pregnancies in renal transplant recipients, Davison and Milne (1997) reported the following: 94% of the conceptions that continued beyond the first trimester ended successfully; 50% of the deliveries were

TABLE 47-7 Pregnancy Safety and Immunosuppressants

IMMUNOSUPPRESSANT	PREGNANCY CATEGORY
Glucocorticoids	C
Azathioprine	D
Mycophenolate mofetil	D
Sirolimus	C
Cyclosporine	C
Tacrolimus	C
Monomurab CD3	C
Antithymocyte globulin	C
Rituximab	C
Bortezomib	D
Alemtuzumab	C
Daclizumab	C
Basiliximab	C

B, no fetal risk in animals, no controlled studies; C, fetal risk cannot be ruled out; D, evidence of fetal risk.

Data from Physician's Desk Reference. 63rd ed. Montvale (NJ): Thomson PDR; 2009. p. 439, 625, 762, 1226, 2313, 2389, 2625, 3264; and U.S. Food and Drug Administration. <www.fda.gov> [accessed 03.09.09].


preterm; 30% of the women developed hypertension, preeclampsia, or both; intrauterine growth restriction occurred in approximately 20%; and rejection crises occurred in 10%. **There were no frequent or predominant abnormalities in the children, the transplanted kidney rarely caused dystocia, and the transplanted kidney was not injured during vaginal delivery.** An observational study of 16,195 female kidney transplant recipients documented a markedly lower pregnancy rate and higher fetal loss rate than reported in the general U.S. population during the same time (Gill et al, 2009). Pregnancy safety information for immunosuppressive drugs is listed in Table 47-7. Guidelines for successful pregnancy are good general health for 2 years after transplantation, minimal proteinuria, no hypertension, no rejection, no urinary tract obstruction, nearly normal renal function, and low doses of maintenance immunosuppressants.

AUTOTRANSPLANTATION

Renal autotransplantation was first described for the treatment of proximal ureteral injury (Hardy et al, 1967). The advantage of this technique over reconstruction with bowel includes the possibility of creating an antireflux anastomosis without mucous drainage and fewer bowel complications. However, it is a more complex operation with a greater risk for bleeding, vascular complication, and ureteral ischemia. Previously the technique was used for complex partial nephrectomy operations or extensive vascular reconstruction, but these operations now can be done either robotically or endoscopically in most cases. If a renal vascular injury is diagnosed, it may be possible to salvage the kidney if less than 90 minutes of warm ischemia have accrued and the patient is hemodynamically stable. The kidney and ureter should be removed and immediately placed in ice cold saline. The arteries should be flushed with heparinized saline. Occluded arteries may respond to thrombolytic therapy with urokinase, streptokinase, or tissue plasminogen activator (Nakayama et al, 2006). One of the advantages of this technique is complete denervation of the kidney. This has been useful as a last resort when other forms of pain management have failed. Relocation of the kidney into the pelvis with anastomosis of the renal pelvis to the bladder has been described for patients who are severe recurrent stone formers; autotransplantation in such cases promotes stone passage and allows for easy inspection with a flexible cystoscope (Flechner et al, 2011).

KEY POINTS

- The incidence of ESRD is greater than any urologic malignancy except prostate cancer.
- More patients die annually of ESRD than of any urologic malignancy.
- The first long-term success with human kidney transplantation occurred in 1954.
- Medicare coinsurance has been one of the most significant advances for the treatment of patients with ESRD.
- Evaluation of ESRD patients for renal transplantation is important to prevent wastage of kidney grafts because of transplantation into unsuitable recipients.
- New options are available to allow transplantation with ABO incompatibility and positive crossmatches between donors and recipients.
- Laparoscopic donor nephrectomy has reduced disincentives for living renal donors.
- Urologists must be aware of the urologic problems that may prevent or impair renal transplant technical success.
- Urologists must be aware of the potential genitourinary problems of transplant recipients.

 Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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48

Pathophysiology of Urinary Tract Obstruction

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Prevalence

Diagnosis and Imaging

Hemodynamic Changes with Obstruction

Egress of Urine from the Kidney

Effects of Obstruction on Tubular Function

Pathologic Changes of Obstruction

Molecular Mechanisms of Tubulointerstitial Fibrosis

Clinical Impact of Renal Obstruction

Treatment of Renal Obstruction

Urinary tract obstruction is a major clinical problem that affects both children and adults and can result in permanent renal damage. The degree of injury to the kidney and the effect on overall renal function depends on the severity of the obstruction (partial or complete, unilateral or bilateral), the chronicity of the obstruction (acute vs. chronic), the baseline condition of the kidneys, and the presence of other mitigating factors such as urinary tract infection (UTI). The cause of urinary tract obstruction can be congenital or acquired and benign or malignant, and a list of possible etiologic factors is provided in [Box 48-1](#).

The histologic derangements associated with obstruction are localized primarily to the interstitial compartment of the kidney and include massive tubular dilation, progressive interstitial fibrosis, and a loss in renal mass secondary to apoptotic cell death ([Misseri et al, 2004](#)). These changes and any resulting impact on renal function are collectively referred to as *obstructive nephropathy*. Although urinary tract obstruction often results in *hydronephrosis*, or dilation of the renal pelvis and/or calyces, hydronephrosis can be present in the absence of obstruction. The diagnosis of urinary tract obstruction therefore requires other clinical and radiographic findings, rather than the presence of hydronephrosis alone.

PREVALENCE

Obstructive uropathy accounts for approximately 10% of all cases of renal failure. In an autopsy series of 59,064 individuals ranging from neonates to geriatric subjects, the prevalence of hydronephrosis was originally estimated to be 3.1% ([Bell, 1950](#)). Hydronephrosis was found to be more prevalent in women between the ages of 20 and 60 years, which was attributed to pregnancy and the development of gynecologic malignancies. In contrast, hydronephrosis was more prevalent in men after age 60 because of the presence of prostatic disease.

In consecutive autopsy series of 3172 stillbirths, infants, and children performed over a 12-year period, urinary tract malformations were found in 78 (2.5%) cases. Hydronephrosis and/or hydro-ureter accounted for 35.9% of urinary tract abnormalities ([Tan et al, 1994](#)). A slightly higher autopsy incidence of hydronephrosis in children (2%) was reported by [Campbell \(1970\)](#). Among children, hydronephrosis appears to be somewhat more prevalent in boys and the majority of cases occur in subjects younger than 1 year.

DIAGNOSIS AND IMAGING

Clinical Presentation

The clinical presentation of urinary tract obstruction can be quite variable depending on the site, degree, and chronicity of the obstruction. Flank pain secondary to stretching of the collecting system is the most common symptom in patients with acute obstruction; is typically an unrelenting, excruciating pain that can radiate to the lower abdomen and testicles or labia on the affected side; and is often associated with nausea or vomiting. In contrast, chronic obstruction of the urinary tract is usually a relatively painless phenomenon and patients may be entirely asymptomatic. Obstruction of the bladder outlet is most often associated with voiding symptoms of frequency, urgency, hesitancy, nocturia, poor urinary stream, and the sensation of incomplete emptying. Anuria is a rare but dramatic and fairly specific presenting sign of urinary tract obstruction.

Obstructive uropathy always should be considered in patients with new-onset hypertension and in patients with renal failure without a history of renal disease, diabetes, or hypertension. In addition, urinary tract obstruction always should be investigated as a possible contributing factor in patients with recurrent UTIs. Because the clinical signs and symptoms of obstructive uropathy are so variable, the diagnosis depends on prompt and appropriate imaging.

Laboratory Studies

The initial workup of a patient suspected of having urinary tract obstruction should begin with a urinalysis and microscopic analysis. An assessment of renal function and measurement of serum electrolytes should be performed, and in the patient with acute renal failure, an assessment of urinary diagnostic indices including the fractional excretion of sodium (FE_{Na}) should be performed.

Urinalysis

The urinalysis and microscopic analysis is necessary in the complete evaluation of a patient suspected of having urinary tract obstruction and/or renal failure. The urinalysis can provide an estimation of osmolality, evidence of UTI, insight into stone formation based

BOX 48-1 Possible Causes of Obstructive Nephropathy**RENAL****Congenital**

Polycystic kidney
Renal cyst
Peripelvic cyst
Ureteropelvic junction obstruction

Neoplastic

Wilms tumor
Renal cell carcinoma
Transitional cell carcinoma of the collecting system
Multiple myeloma

Inflammatory

Tuberculosis
Echinococcus infection

Metabolic

Calculi

Miscellaneous

Sloughed papillae
Trauma
Renal artery aneurysm

URETER**Congenital**

Stricture
Ureterocele
Obstructing megaureter
Retrocaval ureter
Prune belly syndrome

Neoplastic

Primary carcinoma of ureter
Metastatic carcinoma

URETER—CONT'D**Inflammatory**

Tuberculosis
Amyloidosis
Schistosomiasis
Abscess
Ureteritis cystica
Endometriosis

Miscellaneous

Retroperitoneal fibrosis
Pelvic lipomatosis
Aortic aneurysm
Radiation therapy
Lymphocele
Trauma
Urinoma
Pregnancy
Radiofrequency ablation

BLADDER AND URETHRA**Congenital**

Posterior urethral valve
Phimosis
Hydrocolpos

Neoplastic

Bladder carcinoma
Prostate carcinoma
Carcinoma of urethra
Carcinoma of penis

Inflammatory

Prostatitis
Paraurethral abscess

Miscellaneous

Benign prostatic hypertrophy
Neurogenic bladder
Urethral stricture

on crystals that may be present in the urine, and the possible presence of medical renal disease with the presence of protein and/or cellular casts.

Fractional Excretion of Sodium

The FE_{Na} test often is used to differentiate among the three types of acute renal injury: prerenal, intrinsic, and postrenal.

$$FE_{Na} = (P_{Cr} \times U_{Na}) / (P_{Na} \times U_{Cr})$$

where P_{Cr} is defined as the serum creatinine level, U_{Na} is urine sodium level, P_{Na} is serum sodium level, and U_{Cr} is the urine creatinine level. An FE_{Na} less than 1% suggests a prerenal cause of acute renal failure (i.e., hypovolemia, congestive heart failure, renal artery stenosis, sepsis). An FE_{Na} greater than 1% will indicate intrinsic causes of acute renal failure (i.e., acute tubular necrosis, glomerulonephritis, acute interstitial nephritis), and an FE_{Na} greater than 4% indicates postrenal causes of acute renal failure (i.e., benign prostatic hyperplasia [BPH], bladder stones, bilateral ureteral obstruction [BUO]).

Assessment of Renal Function

Measurement of glomerular filtration rate (GFR) is considered the gold standard in identifying patients with renal insufficiency or renal failure. Normal GFR varies and generally decreases with age. The measurement of true GFR can be tedious and impractical; therefore a variety of tests are used to estimate GFR, with the most common being serum creatinine. Creatinine remains imprecise, however, because of variability with age, gender, race, and relationship with muscle mass. A number of formulas have been developed to estimate GFR using serum creatinine, age, and gender, including the Cockcroft-Gault formula (see below), the modification of diet in renal disease equation, and the newer Chronic Kidney Disease Epidemiology Collaboration equation.

$$\text{Estimated GFR (eGFR)} = (140 - \text{Age}) \times \text{Wt (kg)} \times (0.85 \text{ if female})$$

$$72 \times \text{Serum creatinine (in milligrams per deciliter)}$$

In general, a GFR greater than 90 mL/min/1.73 m² is considered normal, between 60 and 90 mL/min/1.73 m² is considered a mild

decline in renal function, between 30 and 60 mL/min/1.73 m² is a moderate decline in renal function, between 15 and 30 mL/min/1.73 m² is a severe decline in renal function, and less than 15 mL/min/1.73 m² is considered renal failure (Siddiqui and McDougal, 2011).

Diagnostic Imaging

Because the clinical presentation of the patient with urinary tract obstruction can be so variable, prompt and accurate diagnosis of obstruction depends on appropriate imaging. A review of the imaging modalities currently available and their advantages and limitations is presented in the following section.

Ultrasonography

Renal ultrasonography remains a first-line imaging modality in the evaluation of a patient suspected of having urinary tract obstruction because of its availability, low cost, and lack of ionizing radiation. It does not require the administration of iodinated contrast and can therefore safely be performed in patients with renal insufficiency or a contrast allergy. The renal ultrasound primarily provides anatomic information about the kidney, including renal size, cortical thickness, corticomedullary differentiation, and grade of collecting system dilation. Although the presence of hydronephrosis is suggestive of underlying obstruction, it is important to recognize that hydronephrosis is an anatomic finding, not a functional diagnosis, and that hydronephrosis alone does not indicate urinary tract obstruction. Significant hydronephrosis can be present in the absence of obstruction (e.g., in the patient with vesicoureteral reflux), and significant obstruction can be present in the absence of severe hydronephrosis, as is often the case very early in the course of acute renal obstruction. Parenchymal thinning and small renal size can be evidence of chronic renal obstruction, and bladder distention in association with hydronephrosis can be suggestive of bladder outlet obstruction. Standard renal sonography may appear normal in 50% of patients with acute urinary obstruction, and distinguishing obstructive from nonobstructive collecting system dilation can be difficult, especially when the obstructing agent is not visualized (Platt et al, 1989; Mostbeck et al, 2001).

The introduction of duplex Doppler sonography was subsequently suggested as a means to improve the ability of ultrasonography to diagnose renal obstruction in patients. In the early 1990s, changes in intrarenal arterial waveforms were shown to be associated with urinary obstruction, and the resistive index (RI) (defined as the peak systolic velocity–end diastolic velocity/peak systolic velocity) was advanced as a technique to improve detection of urinary obstruction during ultrasonography. It has been shown that after a short period of prostaglandin-mediated vasodilation, renal blood flow decreases and renal vascular resistance increases in response to obstruction. In general, an RI of 0.70 is considered to be the upper limits of normal in adults (Tublin et al, 2003), although important exceptions to this value have been reported. It is common for the mean RI to exceed 0.70 in children in the first year of life, and it can exceed 0.70 for at least the first 4 years. The RI also can exceed 0.70 in elderly patients without renal insufficiency. Initial clinical studies evaluating the RI threshold of 0.70 in the diagnosis of obstruction were encouraging, with a 92% sensitivity and 88% specificity. The diagnosis of obstruction increased further when the difference in RI (δ RI) between the affected kidney and contralateral kidney was found to be greater than 0.1 (Platt et al, 1989).

Although encouraging studies evaluating RI have been reported, subsequent clinical trials and animal studies investigating RI in the detection of renal obstruction have been discouraging. Chen and associates (1993) demonstrated that the RI is normal in most patients with partial or mild obstruction. Similarly, when discriminatory thresholds for obstruction (mean RI \geq 0.7, δ RI \geq 0.1) were used in the detection of patients with acute renal colic, the sensitivity and specificity of the Doppler examination was found to be only

44% and 82%, respectively (Tublin et al, 1994). It has subsequently been demonstrated that radiocontrast can induce vasoconstriction and increase RI during Doppler sonography (Hetzel et al, 2001) and that nonsteroidal anti-inflammatory drugs (NSAIDs) can significantly decrease the RI of acutely obstructed kidneys (Shokeir et al, 1999), both of which may have been factors confounding the results of clinical studies investigating RI in the diagnosis of renal obstruction. Despite these observations, however, skepticism over the utility of RI to detect renal obstruction has increased, and with widespread acceptance of noncontrast computed tomography (CT) scanning as the gold standard in the detection of renal calculi, the routine use of RI analysis in the evaluation of possible renal obstruction has declined.

Color Doppler ultrasonography has been shown to reliably identify ureteric jet dynamics in the bladder, and this has evolved as another diagnostic tool to distinguish obstructive from non-obstructive hydronephrosis. Burge and colleagues (1991) demonstrated that there was a significant decrease in the frequency of ureteral jets in patients with obstructing ureteral stones compared to the normal ureter. More recently, Jandaghi and associates (2013) demonstrated that there is a significant decrease in the frequency, duration, and peak velocity of urine jets emanating from the obstructed ureterovesical junction when compared to the contralateral side, and differences of 1.5 jets/min, 2.5 seconds, and 19.5 cm/sec in ureteral jet frequency, duration, and peak velocity, respectively, were proposed as cutoff points between obstructed and normal ureters. de Bessa and colleagues (2008) evaluated the frequency of urine jets in children who had obstructive versus nonobstructive hydronephrosis and demonstrated that a relative jet frequency (RJF = jet frequency of the hydronephrotic side divided by the sum of both ureteral jets over 5 minutes) of less than 25% had a sensitivity of 87% and a specificity of 96% in detecting obstruction. Although the analysis of ureteral jets is easily applied during routine ultrasonography and may offer some valuable insight into the presence of obstruction, it does require good hydration of the patient and is limited by the requirement of a normal contralateral collecting system for comparison.

One of the most common causes of urinary tract obstruction is the presence of renal or ureteral calculi. Although ultrasonography does not have the sensitivity of CT in detecting stones, it avoids the cumulative radiation dose from CT and can reveal secondary effects of urolithiasis, including hydronephrosis, infection, or abscess formation. It also has the advantage of detecting radiolucent stones. Ultrasound may detect calculi as small as 0.5 mm under optimal conditions, and stones typically manifest on ultrasound as echogenic foci in the collecting system associated with acoustic shadowing. In a recent pooled analysis, however, ultrasound was demonstrated to have only a 45% sensitivity and 94% specificity in detecting ureteral stones and 45% sensitivity and 88% specificity in detecting renal calculi compared to non-contrast CT (Ray et al, 2010). It has also been shown that ultrasound overestimates renal stone size compared to CT, particularly for stones 5 mm or less. Direct visualization of stones can be difficult on ultrasound, because of the presence of overlying bowel gas and the relative depth of the ureter within the pelvis, and can be further complicated in obese patients with large amounts of intervening fat (Cheng et al, 2012). Because of these limitations, ultrasound is primarily used as a first-line investigative tool only in pediatric and pregnant patients, but it can be used for routine follow-up in all patients with urolithiasis.

Nuclear Renography

Nuclear medicine plays a critical role in the evaluation of the patient with possible urinary tract obstruction because it is the only imaging modality that can provide noninvasive information about dynamic renal function. The nuclear study of choice in the evaluation of the obstructed collecting system is diuretic renography, most commonly performed using the radiopharmaceutical technetium-99m–mercaptoacetyl triglycine (^{99m}Tc-MAG3). ^{99m}Tc-MAG3 is preferred for diuretic renography because it has high

extraction by the kidneys, rapid clearance, low radiation dose, and tubular secretion. Renal uptake is 55% compared with 20% uptake by ^{99m}Tc -diethylenetriaminepentaacetic acid (^{99m}Tc -DTPA), the other radiopharmaceutical used for diuretic renography, resulting in better cortical imaging for both qualitative and quantitative analysis (He and Fischman, 2008). As opposed to ^{99m}Tc -MAG3, which is actively secreted by the tubules, ^{99m}Tc -DTPA is removed almost exclusively by glomerular filtration and is therefore the agent most suited to measurement of GFR. Adequate imaging of the collecting system, however, is GFR-dependent with DTPA and is quite limited in patients with renal insufficiency and those younger than 6 months of age because of the immaturity of renal function.

The normal renogram curve has three distinct phases. The initial phase is characterized by rapid uptake of the radiopharmaceutical by the kidneys, reflecting renal perfusion. The second phase is characterized by a more gradual rise in uptake over time, usually peaking after 2 to 5 minutes, and it is during the second phase that renal function is primarily evaluated. Urinary obstruction can diminish the rate of uptake of the radiotracer during the second phase and can therefore alter the assessment of differential renal function. The third phase is the excretory phase and is characterized by a gradual decrease in renal counts over time. The third phase is often augmented by the administration of a diuretic (diuretic renogram) to induce high urine flow and prevent the false positive results that can be caused by urine stasis in a dilated collecting system. By convention, a kidney is considered unobstructed if the time for half of the tracer to leave the collecting system ($T_{1/2}$) is less than 10 minutes, is equivocal if the $T_{1/2}$ is 10 to 20 minutes, and is considered obstructed if the $T_{1/2}$ is greater than 20 minutes. False-positive results can be seen in the presence of dehydration because of the suboptimal response to a diuretic agent, poor renal function, high-grade reflux, and in the presence of massive collecting system dilation with urinary stasis (Goldfarb et al, 2006). Renal immaturity in neonates also may generate false-positive results (Karam et al, 2003).

To improve the accuracy of diuretic renography and limit false-positive results, patients should be well hydrated for the study. The well-tempered renogram was originally described for children in 1992 as a means to ensure a standardized level of hydration with the administration of intravenous (IV) fluids before and during the course of the study (Conway and Maizels, 1992). Bladder distention and elevated bladder pressures can limit the ability of the upper urinary tract to drain and may artificially prolong the excretory phase of the study. Routine catheter placement is therefore recommended for any patient who is unable to urinate voluntarily and also should be considered for any patient with significant reflux, bladder pathology (i.e., neurogenic bladder), or a low-lying pelvic kidney from which the signal might be obscured by bladder filling. Patient position during the study also appears to affect results, and urine flow may be slow and resemble obstruction when the patient is supine. It is therefore suggested that a later static image be obtained in any patients with prolonged $T_{1/2}$ after they have assumed an upright gravity-assisted posture (Wong et al, 2000).

Timing of diuretic administration is somewhat controversial, and multiple different protocols have been established. Traditionally, furosemide is injected 20 minutes after the radiopharmaceutical is administered (F+20), although the diuretic can be administered 15 minutes before tracer injection (F-15) or at the time of tracer injection (F+0). The advantages of the F+20 technique are that the modifications to the drainage curve caused by furosemide can be observed, and if adequate kidney washout has occurred during the basic renogram, one can potentially avoid the administration of furosemide (Piepsz, 2011). With earlier administration of furosemide (F-15, F+0), urine flow is increased dramatically throughout the entire study, and Turkolmez and colleagues (2004) found that these protocols allowed clarification of obstruction in cases of equivocal F+20 studies. The disadvantage of the F+0 protocol is that early furosemide injection can result in acceleration of renal transit and an underestimation of renal function on the side with a short transit time (Donoso et al, 2003). A recent study suggested

improved results when patients were placed in a seated position and furosemide was administered 10 minutes after the radiopharmaceutical (F+10) (Tartaglione et al, 2013). It is important to keep in mind that measurement of differential renal function and tracer washout will vary depending on the protocol and radiopharmaceutical used, and care should be taken when interpreting results if comparative studies have been performed using different protocols or radiopharmaceuticals.

Computed Tomography

Cross-sectional imaging provided by CT generates greater anatomic definition than ultrasonography, and because of its speed, safety, and accuracy, noncontrast helical CT (NHCT) has become the imaging modality of choice for patients suspected of having ureteral obstruction. In a landmark study, Smith and colleagues (1995) demonstrated the superiority of unenhanced helical CT in the evaluation of possible ureteral obstruction compared to excretory urography. Unenhanced helical CT gives information about obstructing and nonobstructing stones, and it can reveal signs associated with ureteral obstruction even after stone passage, including hydronephrosis, perinephric stranding, and the "tissue rim sign." These secondary signs have been reported to have a positive predictive value of greater than 90% for the presence of acute ureteral obstruction (Smith et al, 1996; Heneghan et al, 1997). CT has a reported sensitivity of 96% for stone detection with a specificity and positive predictive value of 100% (Worster et al, 2002) and can detect most radiolucent stones with the exception of protease inhibitor stones (i.e., indinavir sulfate) and mucoid matrix stones. In addition, NHCT has been demonstrated to diagnose a wide spectrum of significant and alternative diagnoses in 10% of patients being evaluated for renal colic (Katz et al, 2000).

Although the unenhanced helical CT is the modality of choice in the evaluation of patients with acute renal colic, it has a limited ability to evaluate chronic obstruction of the urinary tract and various causes of obstruction other than calculi. Over the past decade, multidetector CT urography (CTU) has emerged as the imaging modality of choice for a comprehensive evaluation of the urinary tract (Washburn et al, 2009). The traditional CTU technique involves three imaging phases using a single IV bolus injection of contrast. An unenhanced phase is initially performed, followed by a nephrogenic phase obtained approximately 100 to 120 seconds after contrast injection, and an excretory phase is performed after a greater time delay to evaluate the urothelium. With the advent of improved software and high-resolution thin-slice CT scanning, three-dimensional reconstruction of the urinary tract can be performed and has been helpful in characterizing many obstructive lesions of the urinary tract. In addition to stones, calyceal diverticulum, crossing vessels causing ureteropelvic junction obstruction, duplication anomalies in nonfunctioning systems, ureteroceles, and ectopic ureteral insertions can all be visualized with good accuracy.

The primary concern regarding widespread use of CT is its high associated radiation exposure. The average mean effective dose for a single unenhanced CT has been reported to be 8.5 millisieverts (mSv) (Poletti et al, 2007) for a multidetector CT compared to 6.5 mSv for a single-detector CT and 1.5 mSv for an excretory urogram series (Katz et al, 2006). This dose can rapidly accumulate if there are multiple phases to the CT or the patient presents repeatedly. It has been estimated that the risk for fatal cancer is 0.05%, or 1 in 2000, for 10 mSv of ionizing radiation (Brenner et al, 2001). The risks are more concerning in children, because they are more sensitive to radiation-induced carcinogenesis and have a longer period for cancer to develop. A recent study demonstrated that children receiving a cumulative brain dose of 50 milligrays (mGy) or more from CT had a 2.8 times higher risk for developing brain cancer and those receiving a cumulative bone marrow dose of 30 mGy or more from CT had a 3.2 times greater risk for developing leukemia (Pearce et al, 2012; Miglioretti et al, 2013). Because of these risks, low-dose protocols have emerged with very little loss in diagnostic accuracy (Poletti et al, 2007). Stones

smaller than 3 mm, impaction at the ureterovesical junction, and patient obesity, however, have been shown to impair the diagnostic accuracy of low-dose techniques (Kennish et al, 2010).

Magnetic Resonance Urography

Magnetic resonance urography (MRU) is an imaging modality that integrates excellent anatomic information with functional data and avoids ionizing radiation. Because of its significant cost and restricted availability, it is not a first-line imaging modality in the evaluation of a urinary obstruction at this time, but because of its major advantages to conventional imaging, MRU has the potential to become the imaging study of choice for the evaluation of urinary tract abnormalities in the future. The MRU protocol begins with standard T1- and T2-weighted imaging through the abdomen and pelvis without contrast. Gadolinium-diethylenetriaminepentaacetate dimeglumine (Gd-DTPA) is then administered in conjunction with furosemide, and T1-weighted imaging is performed, allowing visualization of both the concentrating and excretory functions of the kidney. MRU measurements of differential renal function and contrast excretion have been shown to correlate well with DTPA nuclear scintigraphy (Perez-Brayfield et al, 2003), but MRU has the advantage of providing excellent anatomic visualization of even nonfunctioning renal moieties. The MRU measurement of contrast excretion is the renal transit time, which is defined as the time it takes for contrast to pass from the renal cortex to the proximal ureters, and is classified as normal if it is 4 minutes or less, equivocal if longer than 4 and less than 8 minutes, and obstructed if 8 minutes or longer (Jones et al, 2004). El-Nahas and colleagues (2007) reported that MRU has 100% sensitivity in diagnosing upper urinary tract obstruction, and MRU has been demonstrated to be valuable in diagnosing urinary tract abnormalities when traditional imaging is inconclusive (Payabvash et al, 2008). Unfortunately, MRU detection of renal and ureteral stones is poor in comparison to CT because stones appear as signal voids on T1- and T2-weighted images. MRU sensitivity for detecting stones has been reported to be 68.9% to 81% (Blandino et al, 2001; Shokeir et al, 2004), but accuracy is greatly improved with gadolinium-enhanced excretory MRU, with sensitivities approaching 90% to 100% (Cerwinka and Kirsch, 2010). The biggest risk of MRI is the development of nephrogenic systemic fibrosis, which was linked to gadolinium-based contrast agents in 2006 and appears to occur only in patients with severe renal impairment (Thomsen, 2006). The incidence of nephrogenic systemic fibrosis in patients with risk factors has been demonstrated to be 3%, and new recommendations now limit the use of gadolinium in patients with renal impairment (Cerwinka and Kirsch, 2010).

Excretory Urography

Excretory urography was previously considered the imaging modality of choice in the evaluation of patients suspected of having urolithiasis and/or urinary tract obstruction. Although it largely has been replaced with CTU, it does provide both anatomic and functional information and can be useful in certain clinical situations. Imaging during excretory urography depends on glomerular filtration and renal excretion of iodinated contrast medium; therefore the utility of excretory urography is limited in patients with renal insufficiency. The risk for contrast nephropathy also increases with worsening renal function. Excretory urography should not be performed in patients with a history of contrast allergy or those in whom radiation exposure is a concern (i.e., pregnancy).

A delay in contrast uptake and excretion by the kidney (delayed nephrogram) can be indicative of urinary tract obstruction, and the subsequent opacification of the collecting system with contrast can be helpful in identifying the level and potentially the source of obstruction. In addition, small renal size, parenchymal thinning, calyceal clubbing, and significant ureteral dilation and tortuosity can be signs of chronic urinary tract obstruction.

Whitaker Test

The Whitaker test, first described in 1973, is a urodynamic evaluation of the upper urinary tract that is helpful in differentiating an obstructed collecting system from an unobstructed hydronephrotic collecting system. Renal scintigraphy can give false-positive results in the face of massive collecting system dilation or poor renal function, because continued filling, rather than drainage, of the collecting system occurs in response to furosemide, leading to an apparent prolongation in the calculated washout time. The Whitaker test involves placement of a percutaneous needle in the collecting system of the kidney and the infusion of contrast at a rate of 10 mL/min. A urodynamic catheter is also placed in the bladder, and intravesical pressures are monitored and subtracted from measured intrapelvic pressures during the infusion. Intrapelvic pressures are noted at the time that contrast is first seen extending past the ureteropelvic junction and past the ureterovesical junction. Pressures less than 15 cm H₂O are considered normal, greater than 22 cm H₂O are indicative of obstruction, and between 15 and 22 cm H₂O are considered indeterminate. Although the reproducibility and clinical utility of the Whitaker test have been questioned (Djurhuus et al, 1985), the test recently has been shown to determine or contribute to therapeutic management in 84% of cases of suspected obstruction and to accurately predict both obstruction and nonobstruction in 77% of cases (Lupton and George, 2010). A study by Veenboer and de Jong in 2011 demonstrated a 100% negative predictive value in the ability of the Whitaker test to diagnose the absence of obstruction. Although the Whitaker test has limited applicability in clinical practice, it continues to have a valuable role in the evaluation of equivocal upper urinary tract obstruction, especially when noninvasive investigations are inconclusive.

Retrograde Pyelography

Retrograde pyelography refers to the injection of contrast into the upper collecting system through a cystoscopic approach. The technique accurately defines ureteral and upper collecting system anatomy and can determine the location of an obstructive lesion. It is most often used to define the anatomy of the collecting system when it has not been adequately defined by other imaging modalities or when a patient has risk factors for receiving iodinated contrast material. Because retrograde pyelography involves intubation of the ureter with a catheter, bacteria may be introduced into the upper urinary tract during the procedure. The technique is therefore associated with an increased risk for UTI/sepsis in the setting of obstruction if the collecting system is not subsequently drained.

Antegrade Pyelography

Antegrade pyelography is most often used when retrograde pyelography is not technically feasible or when other imaging studies do not adequately define the collecting system.

HEMODYNAMIC CHANGES WITH OBSTRUCTION

Glomerular Filtration and Renal Blood Flow

Many functional changes occur in the kidney associated with obstructive nephropathy that affect renal hemodynamics. To understand the relationship between changes in renal hemodynamics and the alterations in GFR that occur during and after obstruction, it is important to understand the factors that influence GFR. GFR is defined by the equation:

$$\text{GFR} = K_f(P_{GC} - P_T - \pi_{GC})$$

where K_f is a glomerular ultrafiltration coefficient related to the surface area and permeability of the capillary membrane. P_{GC} refers to glomerular capillary pressure, which is influenced by both renal plasma flow (RPF) and the resistance of the afferent and efferent

arterioles. The hydraulic pressure driving fluid into Bowman space is resisted by the hydraulic pressure of fluid within the renal tubules (P_T) and π_{GC} , which is the oncotic pressure of proteins in the glomerular capillary and efferent arteriole. In addition to tubular hydraulic pressure and the oncotic pressure of proteins in the capillary, glomerular capillary pressure is also influenced by RPF:

$$RPF = \frac{(\text{Aortic pressure} - \text{Renal venous pressure})}{\text{Renal vascular resistance}}$$

Renal Vascular Resistance

Renal vascular resistance is primarily mediated by changes in the resistance of the afferent and efferent arterioles; therefore constriction of the afferent arteriole will result in a decrease in P_{GC} and GFR, whereas constriction of the efferent arteriole will increase P_{GC} . Renal obstruction can transiently or permanently affect some or all of the determinants of GFR, depending on the length and degree of obstruction.

Unilateral Ureteral Obstruction

Differences exist in the hemodynamic changes that occur in response to unilateral ureteral obstruction (UUO) as compared to BUO. Animal experiments have demonstrated a triphasic pattern of renal blood flow (RBF) and ureteral pressure changes during UUO (Fig. 48-1). Initially, there is an increase in pressure within the renal tubules of the affected kidney secondary to obstruction and a subsequent decrease in GFR. The vasculature of the kidney attempts to compensate for the decreased GFR with an increase in RBF mediated by the release of vasodilators, such as prostaglandin E_2 (PGE_2) (Allen et al, 1978) and nitric oxide (NO) (Lanzone et al, 1995). This phase lasts 1 to 2 hours. During the

second phase, lasting 3 to 4 hours, ureteral pressure remains elevated but RBF begins to decline, and, in the final phase, both ureteral pressure and RBF flow progressively decline, resulting in a gradual loss in renal function (Vaughan et al, 1970; Moody et al, 1975). The late-phase decline in RBF and ureteral pressure appears to be mediated by an increase in afferent arteriolar resistance. In addition to impeding RBF, it has been shown that increased afferent arteriolar resistance causes a decrease in effective glomerular capillary pressure and a resulting decrease in renal tubular pressure (Arendshorst et al, 1974). During the late phase of obstruction, there is also a shift in RBF from the outer cortex to the juxtamedullary region of the kidney and large portions of the cortical vascular bed become unperfused or underperfused (Yarger and Griffith, 1974). Reduced GFR at this stage is therefore not only the result of a reduction in P_{GC} in individual glomeruli because of increased afferent arteriolar resistance but also occurs because of a global lack of perfusion of many glomeruli.

The mechanism of obstruction-induced increased afferent arteriolar resistance was initially thought to be due to upregulation of the renin-angiotensin system or increased thromboxane A_2 expression, but subsequent studies have not revealed a significant effect of these mediators on the renal hemodynamic response to obstruction (Vaughan et al, 2004). More recently, NO has been implicated in the late renal hemodynamic changes observed during UUO. NO is a vasodilator formed by the conversion of arginine to NO by nitric oxide synthase (NOS). NOS is present in the kidney, and the inducible form of NOS (iNOS) is upregulated in the kidney in response to obstruction (Miyajima et al, 2001b). A study by Felsen and associates in 2003 demonstrated that animals administered L-arginine demonstrated an increase in RBF and ureteral pressure in response to obstruction that was not observed in controls, suggesting that a lack of availability of substrate for NO production may be the mechanism of late-phase decreases in RBF and tubular pressure (Felsen et al, 2003).

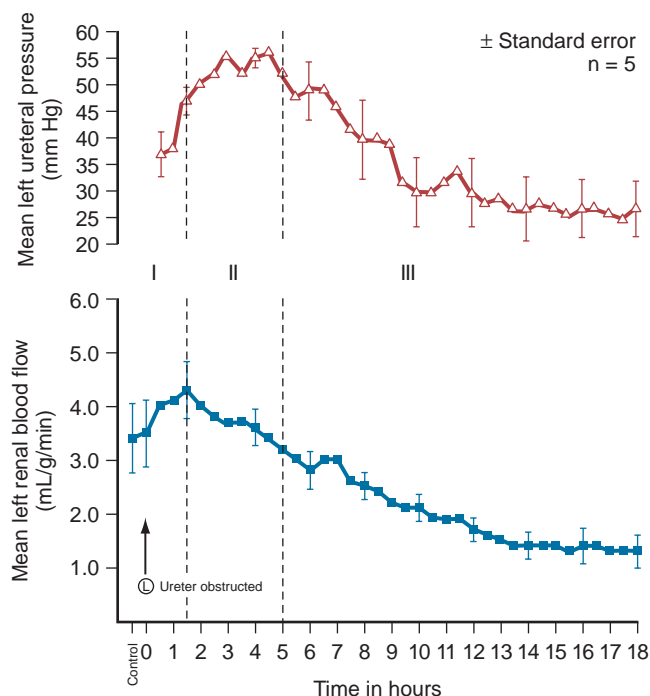


Figure 48-1. Triphasic relationship between ipsilateral renal blood flow (RBF) and left ureteral pressure during 18 hours of left ureteral obstruction. The three phases are designated by Roman numerals and separated by vertical dashed lines. In phase I, RBF and ureteral pressure rise together. In phase II, the RBF begins to decline and ureteral pressure remains elevated. In phase III, the blood flow and ureteral pressure decline together. (From Moody TE, Vaughan ED Jr, Gillenwater JY. Relationship between RBF and ureteral pressure during 18 hours of total ureteral occlusion: implications for changing sites of increased renal resistance. *Invest Urol* 1975;13:246-51.)

Bilateral Ureteral Obstruction or Obstruction of a Solitary Kidney

BUO (or obstruction of a solitary kidney) is characterized by only a modest initial increase in RBF lasting about 90 minutes, followed by a decrease in bilateral RBF (Gulmi et al, 1995). Unlike UUO, in which the ureteral pressure is initially elevated but quickly decreases to preocclusion pressures by 24 hours, ureteral pressure remains elevated for at least 24 hours with BUO. This prolonged elevation in intratubular pressure contributes to the decrease in GFR observed with BUO. It has been shown, however, that the decrease in GFR and RBF is more pronounced in animals with UUO compared to BUO (Siegel et al, 1977). The mechanism of these hemodynamic differences appears to be related to the site of vasoconstriction in the glomerulus. During UUO, preglomerular vasodilation is followed by a more prolonged preglomerular vasoconstriction, and this increase in afferent arteriolar resistance causes a reduction in glomerular capillary pressure that in turn results in decreased intratubular pressure. In contrast, during BUO preglomerular vasodilation is followed by a prolonged postglomerular vasoconstriction. This increase in efferent arteriolar resistance results in increased P_{GC} and intratubular pressure despite a decrease in RBF. The positive effect of increased P_{GC} on GFR is offset by the persistent elevation in tubular pressure. As with UUO, it appears that NO has an important role in early vasodilation of the afferent arteriole (Reyes and Klahr, 1992). A number of other vasoactive mediators have been implicated in the hemodynamic changes observed during BUO. Inhibition of platelet-activating factor, a potent vasodilator, has been shown to significantly decrease GFR and effective RPF in animals with BUO (Reyes and Klahr, 1991), and inhibition of endothelin (a vasoconstrictor) in animals with BUO has been shown to attenuate the observed decreases in GFR and effective RPF (Reyes and Klahr, 1992). Although a number of different vasoactive mediators likely contribute to the hemodynamic response during BUO, atrial

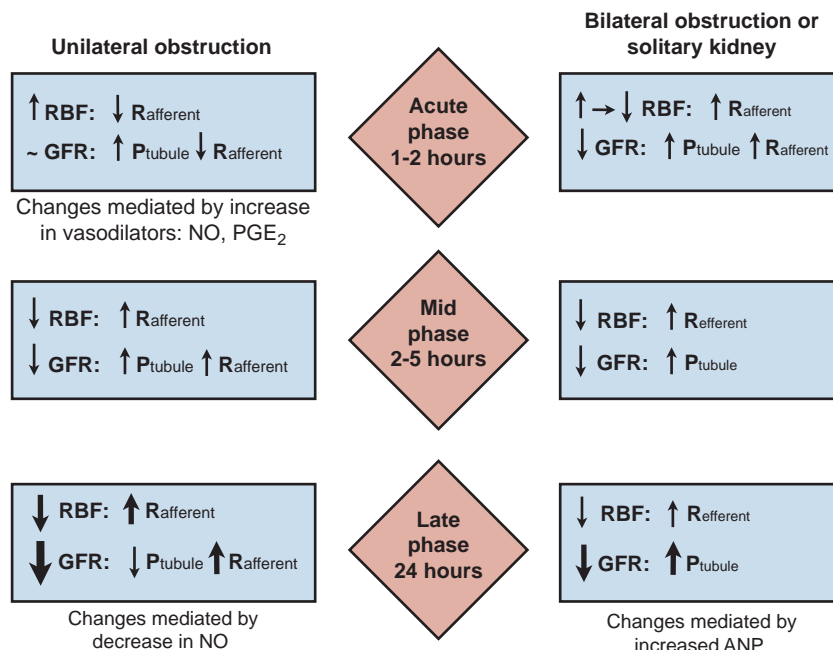


Figure 48-2. Summary of the functional changes during ureteral obstruction. ~, little change; ANP, atrial natriuretic peptide; GFR, glomerular filtration rate; NO, nitric oxide; PGE₂, prostaglandin E₂; P_{tubule}, tubular hydraulic pressure; RBF, renal blood flow; R_{afferent}, afferent arteriolar resistance; R_{efferent}, efferent arteriolar resistance.

natriuretic peptide (ANP) appears to have a unique role in BUO and may be largely responsible for the different hemodynamic response observed with BUO as compared to UUO. Because there is no second renal unit to compensate for the ureteral obstruction, intravascular volume increases in response to BUO and serves as a stimulus for secretion of ANP. ANP in turn increases afferent arteriolar dilation and efferent arteriolar vasoconstriction, leading to an increase in P_{GC} and intratubular pressure (Maack et al, 1996). It also decreases the sensitivity of tubuloglomerular feedback, inhibits release of renin, and increases the glomerular ultrafiltration coefficient K_f, which is related to the surface area and permeability of the capillary membrane. Indeed, high plasma levels of ANP have been demonstrated in animals with BUO as compared to control animals or those with UUO (Purkerson et al, 1989; Kim et al, 2001b), and it has been postulated that increased levels of ANP may exert a protective effect on GFR during BUO that is not seen with UUO.

The intrarenal distribution of blood flow is also quite different with BUO as compared to UUO. Animal studies have demonstrated that there is a shift of blood flow from the juxtamedullary region of the kidney to the outer cortex in response to BUO, which is the opposite of that seen with UUO (Jaenike, 1972; Solez et al, 1976). These alterations in the distribution of renal cortical blood flow also may contribute to the differences in GFR observed between BUO and UUO.

In summary, the hemodynamic changes observed with both UUO and BUO involve increases in renal vascular resistance and ureteral pressure. The timing and regulation of these changes, however, are different (Fig. 48-2). During UUO, early renal vasodilation is followed by prolonged preglomerular vasoconstriction that results in normalization of intratubular pressure. In contrast, during BUO there is little early vasodilation and the later postglomerular vasoconstriction is associated with increased intratubular pressures.

Partial Ureteral Obstruction

Although most models of urinary tract obstruction study complete obstruction over variable times, many clinical situations involve partial ureteral obstruction (PUO). The effects of PUO on renal

hemodynamics and GFR are variable, depending on the severity and the duration of obstruction. In general, PUO results in decreased RBF and GFR in the ipsilateral kidney (Wen et al, 1999; Wen, 2002). Chronic PUO has been reported to decrease RBF to 25% of normal (Stecker and Gillenwater, 1971), and a shift in renal cortical blood flow from the outer cortex to the inner cortex has been documented (Yarger et al, 1980). It appears that the degree of RBF decline depends on the severity of obstruction (Chevalier, 1984; Chevalier and Kaiser, 1984). Although PUO has not been studied as extensively as UUO, a similar array of vascular mediators have been implicated in the increased afferent arteriolar resistance that occurs in response to PUO, including prostaglandins (Ichikawa and Brenner, 1979) and the renin-angiotensin system (Beharrie et al, 2004). A major problem with studies involving partial obstruction is the ability to accurately reproduce the degree of obstruction in each animal. Thornhill and associates (2005) describe a method of ligating the ureter over a wire of calibrated diameter, which then can be removed to create a partial obstruction. The authors found that when the ureter was reduced by 70% to 75%, GFR was reduced by 80% after 28 days of partial UUO.

EGRESS OF URINE FROM THE KIDNEY

Although normal flow of urine from the kidney through the urinary tract is compromised with obstruction, urine may still egress from the kidney. A rupture of the calyceal fornix and subsequent extravasation of urine can occur during acute obstruction, typically in response to ureteral stones (Stenberg et al, 1988), although it also can be seen with congenital abnormalities such as posterior urethral valves. Extravasation of urine into the venous and lymphatic system also may occur in the setting of urinary obstruction. During chronic obstruction, fluid is thought to exit primarily into the renal venous system.

EFFECTS OF OBSTRUCTION ON TUBULAR FUNCTION

Obstruction of one or both kidneys can have profound effects on the concentrating ability of the kidney and on sodium, potassium,

and hydrogen excretion. The ability of the kidney to recover normal excretory function after relief of obstruction depends on the degree and severity of obstruction. Postobstructive diuresis often will accompany relief of BUO but is not typically observed with relief of UUO, secondary to the presence of a functional contralateral kidney that can maintain fluid balance. The eventual correction of abnormal renal tubular function depends on the degree and duration of obstruction.

Urinary Concentrating Ability

Normal urine concentrating ability depends on a hypertonic medullary interstitial gradient, which is established by active sodium transport out of the tubule and the countercurrent exchange mechanism. It also depends on the variable permeability of the tubules to water, mediated by aquaporin (AQP) water channels. Obstructive nephropathy can disrupt all or some of these mechanisms and lead to a defect in urine concentrating ability.

AQPs are protein channels that form pores in the membrane of renal tubular cells. AQPs selectively conduct water into and out of the cell and are essential for the urine concentrating ability of the kidney. Aquaporin 2 (AQP2) is exclusively expressed in the principal cells of the collecting tubule and collecting duct and is the predominant vasopressin-regulated water channel. Vasopressin is secreted into the bloodstream from the posterior pituitary gland in response to increased serum osmolality or a reduction in circulating volume. After vasopressin binds to cell surface receptors in the collecting tubule, cytoplasmic vesicles containing AQP2 channels fuse with the apical membrane of tubular cells to facilitate water movement out of the collecting duct and its subsequent reabsorption.

After 24 hours of BUO there is a marked reduction in AQP2 expression in the kidney (Frøkiaer et al, 1996; Stodkilde et al 2011), which results in an impaired ability of the kidney to reabsorb water once the obstruction has been relieved. It has been demonstrated that AQP2 expression remains 50% of normal levels 7 days after relief of obstruction. AQP1, 3, and 4 expression levels also have been shown to be downregulated in response to BUO (Li et al, 2001; Nielsen et al, 2007), and although AQP2 and AQP3 expression will normalize within 30 days of release of BUO, AQP1 remains downregulated and may contribute to the long-term polyuria and impaired concentrating ability of obstructive nephropathy. Downregulation of AQP channels is also observed in response to UUO, but the clinical manifestations are not as evident because the contralateral kidney is able to regulate fluid balance. A significant decrease in AQP2 levels is observed in the obstructed kidney (23% normal), and a moderate decrease in AQP2 levels is observed in the nonobstructed kidney (75% normal) after 24 hours of UUO (Frøkiaer et al, 1997), suggesting both local and systemic effects on AQP expression. Angiotensin has been implicated in obstruction-induced AQP2 downregulation, because blockade of the angiotensin I receptor has been shown to prevent the decreased expression of AQP2 (Jensen et al, 2006), and antioxidants, such as *N*-acetylcysteine, appear to upregulate AQP2 expression and protect against the urinary concentrating defect caused by obstructive injury (Shimizu et al, 2008).

Sodium Transport

A decrease in sodium transport in the nephron is observed after release of obstruction, and this salt wasting also contributes to the concentrating defect observed in response to obstruction. Previous studies have indicated that the major defects in renal tubular sodium reabsorption localize to the distal segments of the nephron (Li et al, 2003; Jensen et al 2006). A significant downregulation in major sodium transporters occurs within the nephron 24 hours after the onset of UUO and occurs in both the obstructed and unobstructed kidneys. Similarly, a significant downregulation in major sodium transporters occurs in response to BUO, and in both models of injury the downregulation in sodium transporters has

been shown to contribute to the observed natriuresis (Li et al, 2003; Jensen et al, 2006). The natriuresis following relief of BUO is typically greater than that after UUO because BUO causes retention of sodium, water, urea nitrogen, and increased production of ANP, all of which stimulate sodium wasting after relief of obstruction.

PGE₂ has an important role in tubular water and salt transport and the regulation of renal hemodynamics (Harris and Breyer, 2001). It has been demonstrated that PGE₂ inhibits NaCl reabsorption in the thick ascending limb of the loop of Henle and vasopressin-induced increases in water permeability in collecting ducts (Torikai and Kurokawa, 1983; Aarab et al, 1999). Cyclooxygenase (COX) is the rate-limiting enzyme in the synthesis of prostaglandin from arachidonic acid, and Norregaard and associates (2005) demonstrated that COX-2 and PGE₂ synthesis are upregulated in the kidney in response to 24 hours of BUO and that COX-2 inhibition prevents PGE₂ release and the observed downregulation in AQP2 and major sodium channel expression in response to obstruction.

Hydrogen Ion Transport and Urinary Acidification

Obstruction causes a deficit in urinary acidification that has been demonstrated in human subjects and animal models. The defect is characterized by the inability of the kidney to lower urinary pH maximally (<5.5) under the stimulus of systemic acidemia. Evidence suggests that the major acidification defect is in the distal nephron, most likely related to defective H⁺ secretion in the distal tubule and collecting duct and/or decreased bicarbonate reabsorption in the juxtamedullary nephron. Obstruction has been demonstrated to significantly decrease the expression of multiple acid-base transporters in the kidney, including the type 3 Na⁺/H⁺ exchanger, the electrogenic Na⁺/HCO₃⁻ cotransporter, the Na⁺-K⁺ (NH₄⁺)-2Cl⁻ cotransporter, and the electroneutral Na⁺/HCO₃⁻ cotransporter, in addition to decreasing the expression of H⁺-ATPase in the kidney (Wang et al, 2009). Valles and Manucha (2000) demonstrated that the decrease in H⁺-ATPase observed during UUO is mediated by an increase in iNOS, which in turn appears to be regulated by angiotensin II.

In the proximal tubule, glutamine uptake and ammonia generation are diminished after release of obstruction, resulting in a greater proportion of H⁺ that will be buffered as a titratable acid in combination with phosphate, creatinine, and other bases. The largest component of titratable acid is phosphate, and because phosphate excretion may be compromised in response to obstruction, the net result may be a lower urinary pH related to unbuffered protons in spite of a net decrease in total H⁺ secretion.

Other Cation Transport

Obstruction has an effect on other cation transport as well. In UUO, potassium secretion is decreased in proportion to the decrease in GFR after release of a 24-hour period of UUO (Harris and Yarger, 1975). This may be due to reduced delivery of sodium to the distal nephron and a low flow state, although other investigations also indicate an intrinsic defect in potassium secretion (Thirakomen et al, 1976). In contrast, potassium excretion increases in parallel with sodium excretion after relief of BUO, and it appears that proximal reabsorption of potassium remains unchanged whereas its secretion in the collecting duct is increased after relief of obstruction. This may be related to increased water and sodium delivery to the collecting duct and to the presence of high levels of ANP that can stimulate potassium secretion in the distal nephron (Sonnenberg and Wilson, 1976). Magnesium excretion is also markedly increased after release of either UUO or BUO. This most likely results from compromised transport in the thick limb of Henle. The effects on phosphate reabsorption after the release of obstruction vary depending on whether it was bilateral or unilateral. When BUO is released, accumulated phosphate is rapidly excreted in proportion to sodium (Beck, 1979). Conversely, a decrease in phosphate excretion and a net retention occur with release of UUO.

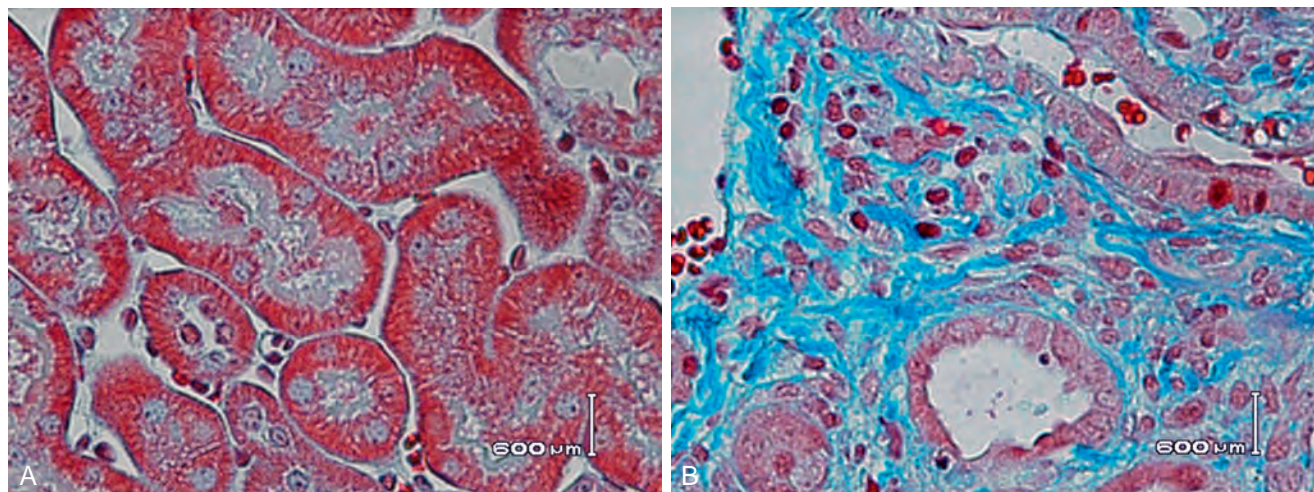


Figure 48-3. Masson trichrome stained tissue sections from a mouse kidney exposed to sham operation (A) or 2 weeks of unilateral ureteral obstruction B. Staining depicts significant collagen deposition (blue) and expansion of the interstitial space in response to obstruction.

PATHOLOGIC CHANGES OF OBSTRUCTION

Gross Pathologic Findings

The gross pathologic changes that occur in the kidney in response to obstruction have been well described in animal models and parallel findings in humans. After 42 hours of obstruction, there is dilation of the collecting system and blunting of the papillary tips associated with an increased weight of the kidney. Collecting system dilation and renal weight further increase, and the parenchyma becomes edematous after 7 days of obstruction. Further collecting system dilation develops after 12 days of obstruction, but after 21 to 28 days the cortex and medullary tissue in the obstructed kidney become diffusely thinned. [Ladefoged and Djurhuus \(1976\)](#) demonstrated that obstructed kidneys are enlarged, with a cystic appearance but lower weight, compared to the normal contralateral kidneys 6 weeks after obstruction.

Microscopic Pathologic Findings

Urinary tract obstruction results in a progressive and eventually permanent loss in renal function. The histologic derangements associated with early obstruction are localized primarily to the tubulointerstitial compartment of the kidney and include massive tubular dilation, progressive tubulointerstitial fibrosis, inflammatory cell infiltration, and apoptotic renal tubular cell death. Although the glomeruli of the kidney are relatively spared, damage to the tubulointerstitial compartment of the kidney is quite severe ([Nagle et al, 1973](#); [Sharma et al, 1993](#); [Misseri et al, 2004](#)). Inflammatory cell infiltration occurs early in the course of obstruction ([Diamond et al, 1994, 1998](#)) and results in the release of a variety of cytokines and growth factors that stimulate fibroblast proliferation and activation and an imbalance in extracellular matrix (ECM) synthesis, deposition, and degradation. This results in an expansion of the interstitial space and a disruption in normal cellular communication ([Fig. 48-3](#)). Increasing tubular cell death accompanies progressive interstitial fibrosis ([Docherty et al, 2006](#)), and long-standing obstruction ultimately results in glomerulosclerosis ([Figs. 48-4 and 48-5](#)) most likely as a result of chronic inflammation ([Steinhardt et al, 1988](#)) and/or hyperfiltration injury ([Pascual et al, 1998](#)). Although extensive glomerulosclerosis has been shown to correlate well with a decrease in renal function in patients with obstruction, milder degrees of fibrosis and glomerulosclerosis can be seen in up to 25% of patients with obstruction and normal differential function on radionuclide imaging ([Elder et al, 1995](#)).

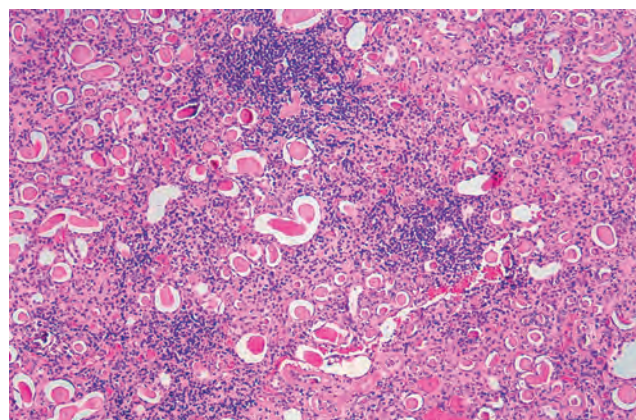


Figure 48-4. Sections of deep cortex and outer medulla from a patient with chronic obstructive uropathy. Tubules demonstrate thyroidization-type atrophy interspersed with a mononuclear inflammatory infiltrate. (Hematoxylin and eosin staining; original magnification, $\times 25$.) (Courtesy Dr. Sami Iskandar.)

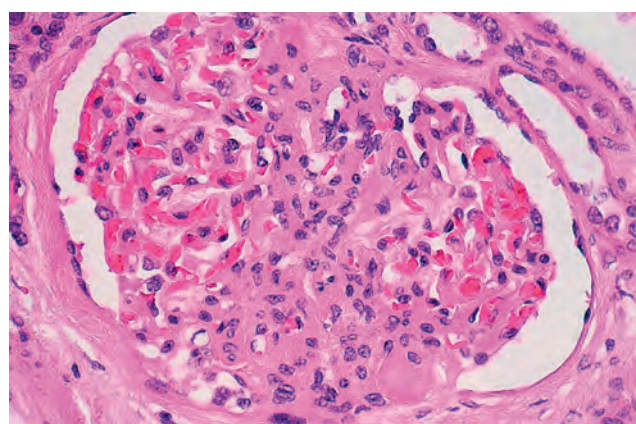


Figure 48-5. Sections of deep cortex and outer medulla from a patient with chronic obstructive uropathy. Glomerulus with segmental tuft sclerosis (center) and hyalinosis is seen. (Hematoxylin and eosin stain; original magnification, $\times 100$.) (Courtesy Dr. Sami Iskandar.)

MOLECULAR MECHANISMS OF TUBULOINTERSTITIAL FIBROSIS

Inflammatory Cell Infiltration

Tubulointerstitial fibrosis is a major pathologic component of obstructive renal injury, and its presence contributes to obstruction-induced renal dysfunction. In fact, progressive tubulointerstitial fibrosis is the final common pathway for all kidney diseases that lead to chronic renal failure (Zeisberg and Neilsen, 2010). One of the earliest histologic changes in the obstructed kidney is an increase in inflammatory cell infiltration into the interstitial compartment of the kidney. Macrophage infiltration has been documented as early as 4 hours after the onset of renal obstruction (Schreiner et al, 1988), and the recruitment of macrophages, as well as other inflammatory cells, into the interstitial space appears to be mediated by chemokine production. All types of renal cells can express chemokines in response to immunologic, toxic, ischemic, or mechanical injury, and the interaction of chemokines with specific receptors expressed on immune cells (chemokine receptors) facilitates the migration of leukocytes and macrophages across the endothelium (Anders et al, 2003). Once these inflammatory cells populate the interstitium, they begin to elaborate a wide array of proinflammatory cytokines and growth factors that contribute to renal injury, including tumor necrosis factor- α (TNF- α) and transforming growth factor- β 1 (TGF- β 1) (Klahr and Morrissey, 2002; Misseri et al, 2004). Increased expression of chemokines has been demonstrated in response to obstruction, including monocyte chemoattractant protein-1 (MCP-1 or chemokine ligand 2 [CCL2]), macrophage inflammatory protein-1 α (MIP-1 α or CCL3), macrophage inflammatory protein-1 β (MIP-1 β or CCL4), and CCL7, and blockade of CCL2 and CCL7 has further been shown to ameliorate obstruction-induced tubulointerstitial fibrosis (Wada et al, 2004; Bani-Hani et al, 2009; Gonzalez et al, 2013). Indeed, MCP-1 has recently been identified as a potential urinary biomarker of obstruction in children with hydronephrosis (Madsen et al, 2013). Although this inflammatory cell infiltrate is certainly critical to the pathophysiology of urinary tract obstruction, cytokines and proinflammatory mediators can also be produced by renal tubular epithelial cells independent of macrophage infiltration (Kaneto et al, 1996; Misseri et al, 2004; Franke et al, 2012).

Fibroblasts and Extracellular Matrix Production

Fibroblasts in the renal interstitium are considered the primary source of ECM, and tubulointerstitial fibrosis is associated with a significant accumulation of matrix-producing fibroblasts. In response to stimulation from cytokines and growth factors, fibroblasts will secrete collagen, elastin, proteoglycans, and fibronectin into the interstitial space (Fig. 48-6). This process is normally tightly regulated by matrix metalloproteinases (MMPs), a family of enzymes responsible for tissue remodeling and the degradation of both collagenous and noncollagenous components of ECM. MMPs are excreted by a variety of cells, including fibroblasts, endothelial cells, macrophages, and lymphocytes, in an inactive form that requires further processing to become active. Control of MMP activity occurs both in the activation of the latent enzyme and with direct inhibition of the active enzyme (Ronco et al, 2007). Tissue inhibitors of MMPs (TIMPs) are produced by both tubular cells and interstitial cells in the kidney, and they function to inhibit the activity of MMPs. Dramatic increases in TIMP expression have been demonstrated in response to obstruction (Engelmyer et al, 1995; Kim et al, 2001a), and it has been postulated that increased ECM deposition during obstructive injury is due to increased TIMP inhibition of MMPs. The role of MMPs in renal fibrosis, however, appears to be much more complex than originally theorized. MMP-2 and MMP-9 have been the focus of most studies in the kidney. Although some studies demonstrate an acceleration of renal fibrosis with pharmacologic inhibition of MMP-2 and MMP-9 (Zeisberg et al, 2006), studies using MMP-9 knockout mice have

demonstrated a dramatic reduction in tubulointerstitial fibrosis in response to renal obstruction (Wang et al, 2010), and mice transgenic for MMP-2 expression (i.e., overexpression) demonstrate interstitial fibrosis, glomerulosclerosis, tubular atrophy, and renal failure in the absence of superimposed injury (Cheng et al, 2006). It appears that in addition to their degradative effect on ECM, MMPs can disrupt tubular basement membrane integrity and trigger epithelial-to-mesenchymal transition, a process that contributes to fibrosis by expanding the number of matrix-producing fibroblasts in the interstitium.

Epithelial-to-Mesenchymal Transition

Although the role of fibroblasts in renal fibrosis is well accepted, their origin and process of activation remain controversial. Resident interstitial fibroblasts, bone marrow fibroblasts, migrating leukocytes, and vascular endothelial cells are all potential sources of renal interstitial fibroblasts. Growing evidence suggests that under pathologic conditions, renal tubular epithelial cells can also undergo a phenotypic transformation into matrix-producing myofibroblasts by a process termed epithelial-mesenchymal transition (EMT) (Strutz et al, 1995; Healy and Brady, 1998; Bani-Hani et al, 2008). These activated fibroblasts acquire mesenchymal markers, migrate into the interstitial space across damaged tubular basement membranes, and become capable of producing ECM. EMT appears to be a major contributing factor to tubulointerstitial fibrosis in the obstructed kidney, and Iwano and coworkers (2002) have demonstrated that a substantial number of interstitial fibroblasts originate from tubular epithelium during renal obstruction. In fact, selective blockade of EMT in animal models impressively reduces fibrosis after obstructive injury, underscoring the importance of EMT in renal fibrogenesis (Iwano et al, 2002; Yang and Liu, 2002). A number of growth factors, cytokines, and ECM compounds regulate EMT, of which TGF- β 1 is the chief and most studied mediator. Interleukin (IL)-18 has been found to initiate and complete the entire EMT process in renal tubular epithelial cells independent of TGF- β 1 activity (Bani-Hani et al, 2009). Because EMT is a gene-directed process, it is uniquely suited to pharmacologic manipulation, which may be of great therapeutic potential in the management of patients with fibrotic renal disease.

Cytokines and Vasoactive Mediators of Fibrosis

Transforming Growth Factor- β

TGF- β 1 has long been regarded as one of the most critical mediators of obstruction-induced renal injury. Renal TGF- β 1 expression increases progressively after the onset of obstruction (Kaneto et al, 1993), and evidence indicates that TGF- β 1 is a major regulator of fibrosis via stimulation of EMT and fibroblast proliferation (Postlethwaite et al, 1987; Fan et al, 1999; Zeisberg et al, 2003), ECM synthesis (Roberts et al, 1992), and the simultaneous inhibition of collagenase and degradative MMPs (Chandrasekhar and Harvey, 1988; Border and Noble, 1994). TGF- β 1 is expressed both by macrophage and resident tubular cells, and, upon activation, TGF- β 1 will bind to its receptor and stimulate the Smad family of proteins to multimerize into a transcription-regulating complex that translocates into the nucleus and exerts TGF- β 1's biologic effects (Massague and Chen, 2000).

Bone morphogenic protein-7 (BMP-7) is a member of the TGF- β superfamily that inhibits TGF- β -dependent biologic functions (Meng et al, 2013), but the mechanism by which BMP-7 counteracts TGF- β activity remains unclear. Several studies have demonstrated that exogenous BMP-7 can not only inhibit TGF- β 1-induced EMT and renal fibrosis but actually induce mesenchymal-to-epithelial transition in adult fibroblasts and facilitate regeneration of the injured kidney (Patel and Dressler, 2005; Zeisberg et al, 2005). The BMP-7 pathway is activated after correction of renal obstruction, and activation of BMP-7 during renal recovery promotes the resolution of fibrosis and the restoration of normal renal architecture (Manson et al, 2011). Although the downstream

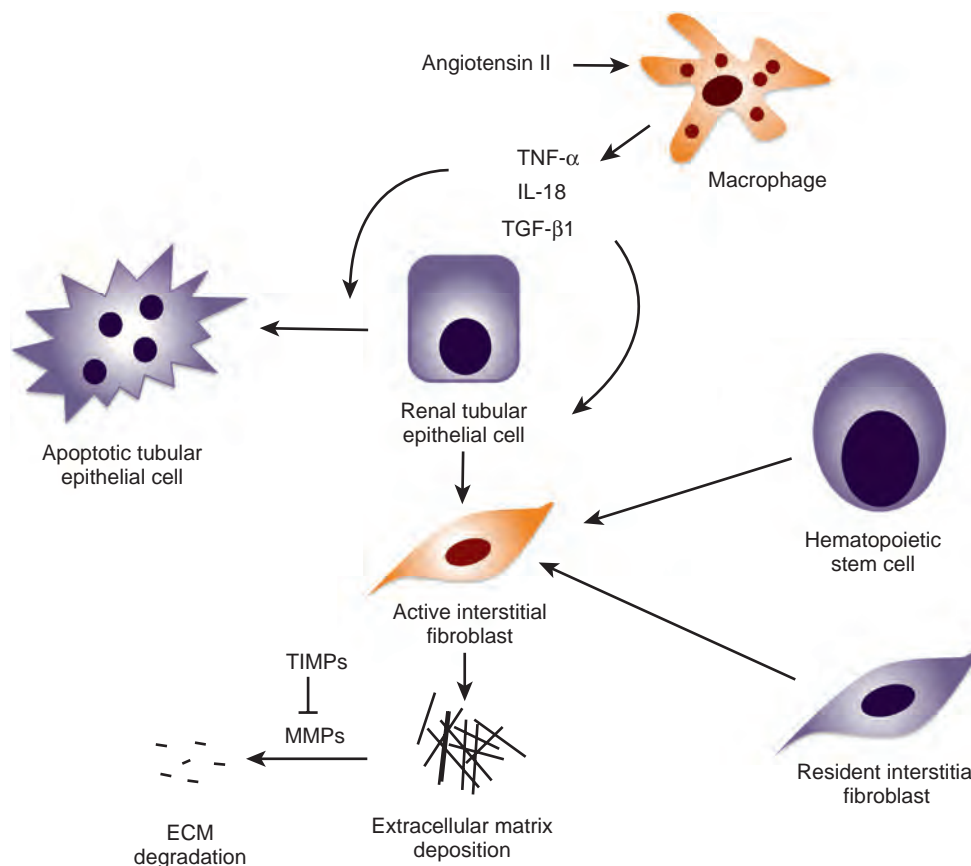


Figure 48-6. Mechanisms of tubulointerstitial fibrosis during renal obstruction. After infiltration of the interstitial space by activated macrophages, inflammatory mediators are released, including transforming growth factor- β 1 (TGF- β 1), tumor necrosis factor- α (TNF- α), and interleukin-18 (IL-18) that trigger renal tubular cell apoptosis, the transformation of renal tubular cells into matrix-producing fibroblasts, and further inflammatory cell infiltration. Additional fibroblasts are recruited from the bone marrow, and resident fibroblasts in the interstitial space are stimulated to secrete extracellular matrix. Angiotensin II is produced in response to the decreased renal blood flow associated with obstruction, and it further stimulates macrophage infiltration and cytokine production (TNF- α and TGF- β 1). The resulting imbalance in extracellular matrix deposition results in expansion of the interstitial space and increasing tubulointerstitial fibrosis. ECM, extracellular matrix; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of MMPs.

mechanisms that contribute to BMP-7-mediated kidney repair remain unclear, BMP-7 has promising therapeutic potential for obstructive renal injury.

Tumor Necrosis Factor- α

TNF- α is a potent proinflammatory cytokine implicated in the pathophysiology of a wide range of renal diseases (Klahr and Morrissey, 1998; Donnahoo et al, 1999; Guo et al, 2001). TNF- α is capable of upregulating its own expression as well as the expression of other inflammatory mediators (i.e., IL-1, NO, cell adhesion molecules, eicosanoids) and can recruit and stimulate various cells in the immune system. TNF- α is produced both by resident renal tubular cells and infiltrating macrophage, and its production is increased significantly in the kidney in response to obstruction (Kaneto et al, 1996; Misseri et al 2004). TNF- α has a role in fibrotic renal injury, stimulating ECM accumulation, inhibition of ECM degradation, and upregulation of a number of cytokines and transcription factors involved in tubulointerstitial fibrosis, including TGF- β 1. Genetic deletion of the TNF- α receptor and inhibition of TNF- α pharmacologically both cause a dramatic reduction in obstruction-induced renal fibrosis (Guo et al, 1999, 2001; Meldrum

et al, 2007), and inhibition of TNF- α has been shown to reduce tubulointerstitial fibrosis even when administered late in the course of renal injury (Khan et al, 2005).

Interleukin-18

IL-18 is a recently discovered proinflammatory cytokine that has been found to be a sensitive and early marker of renal tubular damage, with urinary IL-18 levels predictive of acute tubular injury before creatinine levels and urine output become altered (Parikh et al, 2005). Liang and associates (2007) have also shown that circulating IL-18 levels and renal tubular IL-18 receptor expression is significantly increased in patients with chronic kidney disease. IL-18 expression is dramatically increased in response to obstruction, and IL-18 has been shown to directly stimulate EMT in renal tubular cells in vitro and inflammatory cell infiltration and fibrotic injury in vivo. Inhibition of IL-18 activity prevents obstruction-induced EMT, fibroblast proliferation, and fibrosis independent of TGF- β 1 and TNF- α activity, indicating that IL-18 is an important mediator of obstruction-induced renal injury through an alternative signaling mechanism (Bani-Hani et al, 2009).

Angiotensin II

The renin-angiotensin system has been implicated in the pathophysiology of obstructive uropathy because of the substantial vasoconstriction of the renal vascular bed observed during renal obstruction. Angiotensin II (AT2), a potent vasoconstrictor, is produced after conversion of AT1 to AT2 by the angiotensin-converting enzyme (ACE). AT2 production is rapidly stimulated after onset of renal obstruction and has been linked to many of the pathophysiologic processes involved in obstruction, including altered hemodynamics and renal fibrosis. AT2 upregulates TGF- β 1 and TNF- α expression during renal obstruction (Ishidoya et al, 1995; Guo et al, 2001), and ACE inhibition and inhibition of the AT2 receptor have been shown to decrease TGF- β 1 expression, ECM deposition, macrophage recruitment, and the extent of obstruction-induced renal fibrosis (Klahr and Morrissey, 1997; Morrissey and Klahr, 1998; Guo et al, 2001). AT2 also has been implicated in the perturbation of interstitial capillary circulation that occurs in fibrotic renal disease, resulting in chronic renal hypoxia and further stimulation of EMT and cytokine production (Norman et al, 2003; Zeisberg and Neilson, 2010). Indeed, angiotensin inhibition currently represents the principal clinical therapeutic approach to slowing or preventing the progression of most forms of renal disease (Chevalier et al, 2009).

Apoptosis

Apoptosis, or programmed cell death, is the major mechanism by which renal tubular cell death and a reduction in renal mass occur after renal obstruction (Gobe and Axelsen, 1987; Truong et al, 1998). Apoptosis is present in both normal and disease states and can be triggered by either a death receptor signaling pathway (i.e., TNF- α binding to its receptor) or an intrinsic pathway involving disturbances in the mitochondrial membrane and release of cytochrome *c*. After stimulation of either of these signaling pathways, caspases (cysteiny l aspartate-specific proteinases), which are a family of 12 enzymes that act as the effector molecules for apoptosis, become activated. Caspases function to cleave various nuclear and cytoplasmic substrates, resulting in nuclear fragmentation and condensation. The cell is then broken down into multiple membrane-bound spherical bodies, called apoptotic bodies, which are phagocytized by adjacent healthy cells. Compared to necrosis, this unique mechanism of cell death maintains cell membrane integrity and thereby minimizes the involvement of inflammatory scavenger cells and the overall inflammatory response (Wyllie et al, 1980). Renal tubular and interstitial cells are most susceptible to apoptotic cell death during renal obstruction (Truong et al, 1998). Choi and colleagues (2000) demonstrated renal tubular cell apoptosis beginning after 4 days and peaking after 15 days of renal obstruction, whereas interstitial cell apoptosis increased progressively over the duration of renal obstruction. Glomerular cells, on the other hand, appear to be very resistant to obstruction-induced apoptosis, with no evidence of glomerular cell apoptosis occurring after 90 days of renal obstruction (Truong et al, 1998).

Many of the cytokines and vasoactive factors implicated in EMT and tubulointerstitial fibrosis also appear to mediate apoptotic cell death in response to renal obstruction, in part by increasing caspase expression and activation. TGF- β 1 directly stimulates renal tubular cell apoptosis in vitro (Schuster and Kriegelstein, 2002; Yang et al, 2006), and TGF- β 1 inhibition has been shown to prevent obstruction-induced and stretch-induced renal tubular cell apoptosis (Miyajima et al, 2000, 2001a). TNF- α is a directly cytotoxic cytokine that induces apoptosis in many cells, including renal tubular cells, through interactions with its membrane-bound receptors, TNFR1 and Fas. The expression of TNF-related apoptotic molecules (i.e., TNFR1 and Fas) increases in parallel to observed increases in obstruction-induced tubular cell apoptosis (Choi et al, 2000), and TNF- α neutralization has been shown to ameliorate obstruction-induced apoptosis and pro-apoptotic signaling (Misseri et al, 2005). IL-18 has similarly been demonstrated to be an important mediator

of renal tubular cell apoptosis both in vitro and in response to UUO (Zhang et al, 2011). The effect of AT2 on obstruction-induced apoptosis is less clear. Morrissey and Klahr (1999) demonstrated that an AT2 type 2 receptor antagonist inhibits obstruction-induced apoptosis, but other investigators have found no benefit of either ACE inhibitors or AT2 type 2 receptor antagonists in preventing obstruction-induced apoptosis (Chevalier et al, 1999a; Radovic et al, 2008). These diverging cellular responses to a single stimulus suggest that renal tubular epithelial cells may undergo an adaptive (EMT) versus death (apoptosis) response depending on the degree or duration of stimulation.

CLINICAL IMPACT OF RENAL OBSTRUCTION

Hypertension

Hypertension can develop in response to urinary tract obstruction and is more common in the presence of BUO than in the presence of UUO. Vaughan and Gillenwater (1973) noted hypertension in 17 of 22 patients with BUO that was reversible on relief of obstruction in all but 2 patients. Increased ANP levels and intravascular volume have been documented in patients with BUO and suggest a volume-mediated mechanism for hypertension in these patients. Hypertension is less common in patients with UUO (Vaughan and Sosa, 1990) and does not appear to be related to volume overload because the normal contralateral kidney is able to eliminate excess volume and solutes. The renin-angiotensin system is upregulated in response to UUO and has been implicated as the mechanism of hypertension in these patients. Previous studies have demonstrated that blockade of the AT2 type 2 receptor with losartan prevents the rise in systolic blood pressure associated with UUO and normalizes systolic blood pressure in chronically hypertensive UUO rats (el-Dahr et al, 1993). Hypertension is therefore more likely to occur in response to BUO and more likely to be reversed after relief of obstruction in patients with BUO compared to UUO.

Compensatory Renal Growth

First described by Hinman in 1943, compensatory renal growth refers to the development of increased volume of the contralateral kidney in response to UUO or renal agenesis (Taki et al, 1983; Peters et al, 1993). The development of contralateral renal growth is influenced by age and the degree and duration of obstruction. Studies in human patients who underwent nephrectomy demonstrated that a reduction in renal compensatory growth occurs with increasing age (Edgren et al, 1976). Compensatory renal growth appears to be directly proportional to the duration of obstruction and is less prominent with partial rather than complete UUO (Chevalier and Kaiser, 1984; Chevalier et al, 1987, 1999b; Eskild-Jensen et al, 2001). Interestingly, a recent study also demonstrated that compensatory renal growth, renal hypertrophy, and GFR are increased in response to unilateral nephrectomy in male rats as compared to female rats or gonadectomized groups (Azurmendi et al, 2013), suggesting that sex hormones have a role in this adaptive response as well. While the kidney enlarges, an increase in the number of nephrons or glomeruli does not occur, indicating that the increase in renal volume is primarily a consequence of cellular hypertrophy rather than hyperplasia (Peters et al, 1993). A recent study in fetal sheep, however, demonstrated that animals subjected to $\frac{3}{4}$ nephrectomy had increased cortical thickness, tubular hypertrophy, and a lower glomerular density but a striking increase in glomerular number compared to animals subjected to $\frac{1}{2}$ nephrectomy. Furthermore, the magnitude of the regenerative process appeared to be more dependent on the severity of renal reduction than on the timing of renal reduction (Sammur et al, 2013). This adaptive response allows the remaining kidney to ensure homeostasis and compensate for the lack of functioning contralateral renal tissue; however, the mechanisms behind compensatory renal growth remain poorly understood.

Insulin-like growth factor (IGF-1) appears to be an important mediator of compensatory renal hypertrophy (Cleper, 2012). IGF-1

is a growth factor that has a critical role in renal development, growth, and function (Kamenicky et al, 2014). Exogenous IGF-1 has been shown to increase GFR in normal humans (Guler et al, 1989) and attenuate renal injury resulting from obstruction in animals (Chevalier et al, 2000). IGF-1 levels are significantly elevated in the contralateral kidney after unilateral nephrectomy or UUO (Serel et al, 2000), and evidence suggests that IGF-1 expression may be increased in immature kidneys compared to mature kidneys after unilateral nephrectomy (Mulroney et al, 1992). Significant increases in serum IGF-1 levels have also been demonstrated in humans after donor nephrectomy, and IGF-1 levels have been positively correlated with the increased renal volume demonstrated on postoperative imaging after donor nephrectomy (Nam et al, 1999). Other growth factors have been implicated as effectors of this process (i.e., TGF- β 1, hepatocyte growth factor); however, the sensors of reduced renal mass that stimulate compensatory renal hypertrophy remain unknown.

TREATMENT OF RENAL OBSTRUCTION

Pain Management

The first-line approach for the patient presenting with renal colic is the administration of analgesics. Opioids have a rapid onset of analgesia but may promote nausea and emesis, cause excessive sedation, and have the potential to be abused. NSAIDs are nonopioid analgesics that—unlike opioids—target the inflammatory basis of pain. Renal colic is thought to arise from increased collecting system pressure and an acute distention of the collecting system (Holmlund, 1983), and NSAIDs have been demonstrated to reduce collecting system pressure. Indomethacin and other NSAIDs cause a decrease in renal pelvic pressure in response to obstruction (Sjodin et al, 1982; Gasparich and Mayo, 1986; Frøkiaer et al, 1993) that is thought to be mediated by a reduction in RBF. Perlmutter and associates (1993) demonstrated that ketorolac induces a prompt reduction in both RBF and intrapelvic pressure in canines with UUO. COX-2 inhibitors are a form of NSAID that block the synthesis of prostaglandins from arachidonic acid. It has previously been shown that COX-2 inhibitors can prevent PGE-mediated downregulation of AQP channels and major sodium channels in response to obstruction (Norregaard et al, 2005), and the resulting decrease in hydrostatic pressure within the tubules may provide an additional mechanism for the NSAID-mediated reduction in intrapelvic pressures.

In clinical trials, NSAIDs have proved to be superior to opioids in managing renal colic and are associated with a greater reduction in pain scores, less need for “rescue” analgesia, and less emesis than with opioids (Holdgate and Pollock, 2004). NSAIDs should not be used in patients with renal insufficiency, however, because renal dysfunction can be exacerbated by the decrease in RBF induced by NSAIDs. COX-1 inhibitors also should not be used in patients at risk for gastrointestinal bleeding or when optimal platelet function is needed, and COX-2 inhibitors have been linked to an increased risk for myocardial infarction and stroke as a result of an adverse effect on blood vessels (Cannon and Cannon, 2012). Although opioids have untoward side effects, they still provide excellent analgesia and remain an important tool in the management of the patient with renal colic. The α_1 -blocker Flomax has been used for medical expulsive therapy, and studies have demonstrated the ability of α_1 -blockers to facilitate stone passage and reduce the requirement for analgesics (Wang et al, 2008).

Renal Drainage

Prompt drainage of the obstructed kidney is important to relieve pain and prevent functional decline. Minimally invasive endourologic and interventional radiologic techniques allow for temporary drainage until a definitive procedure can be performed, and in some circumstances it may be a permanent management option. Urine cultures should be obtained from the obstructed renal unit at the

time of relief of obstruction when infection is suspected, and antibiotic therapy should be instituted. Ureteral obstruction that is symptomatic, accompanied by fever, complicated by undrained infection, or determined to be high grade, bilateral, or inducing renal failure warrants immediate drainage.

Both percutaneous nephrostomy tubes and internal stents have been shown to be equally effective in relieving an obstructed collecting system with similar complication rates (Regalado, 2006). Percutaneous nephrostomy tubes are larger caliber and offer the advantage of providing superior drainage, especially if the fluid is more purulent. The catheters can be irrigated to prevent clogging, the urine output of the kidney can be measured, and excessive ureteral manipulation can be avoided, decreasing the risk for sepsis or rupture. The procedure can also be done using ultrasound guidance with local anesthesia and conscious sedation, eliminating the need for an anesthesiologist and ionizing radiation exposure. Internal stents offer the advantage of increased patient comfort with no catheter extending out of the flank, and a lower potential risk for bleeding complications. Therefore internal stent placement should be considered first for patients that are coagulopathic. If thick purulent fluid is obtained from the kidney at the time of ureteral stenting, placement of a large-diameter stent is recommended and/or placement of a diversion stent that can be irrigated and monitored. Internal stent placement typically requires greater x-ray exposure than percutaneous nephrostomy placement, which may be of concern in pregnant patients (Mokhmali et al, 2001; McAleer and Loughlin, 2004), and accelerated stent encrustation in this patient population resulting from increased calcium excretion may increase the risk for stent failure (Goldfarb et al, 1989).

Historically, ureteral stenting has not been very effective for treating patients with extrinsic ureteral obstruction. Docimo and Dewolf (1989) reported a 43% failure rate in stents placed for extrinsic obstruction, the majority related to malignancy, and Chung and colleagues (2004) similarly identified a 42% rate of stent failure in these patients, with a diagnosis of cancer, metastatic disease requiring chemotherapy or radiation, and renal insufficiency predictors of stent failure. New metallic stents composed of a unique continuous unfenestrated coil of nonmagnetic alloy have proved to be safe and effective for patients with extrinsic compression of the ureter and offer longer indwelling times (3.5 to 11 months). Age and preoperative serum creatinine levels have been identified as independent risk factors for metallic stent failure, and lower gastrointestinal tract cancers have been associated with longer metallic stent duration times than genitourinary cancers (Chow et al, 2014).

Renal Recovery after Obstruction

The duration and severity of obstruction has a significant influence on renal functional recovery. When acute complete ureteral obstruction is promptly relieved, full recovery of global GFR can occur, but longer periods of complete ureteral obstruction are associated with diminished return of GFR. The persistent decrease in GFR and RBF after relief of obstruction is due to persistent vasoconstriction of the afferent arteriole. Vaughan and Gillenwater (1971) performed some of the initial studies on recovery of renal function after obstruction. In a canine model of UUO, they noted that full recovery of renal function occurred after 7 days of UUO whereas only 70% recovery of GFR occurred after 14 days of UUO, 30% after 4 weeks of UUO, and none after 6 weeks of UUO. More recent studies demonstrated that renal damage can persist despite recovery of renal function. After 3 days of UUO in a rat model of obstruction, GFR and RBF returned to baseline levels within 14 days in the previously obstructed kidney (Ito et al, 2004), but interstitial fibrosis and tubular apoptosis continued to increase after relief of obstruction. Mouse studies suggest that after 7 days of obstruction, normal renal function is not restored in the previously obstructed kidney even after 30 days of recovery, with GFR and RBF reduced by 40% and the urine albumin-to-protein ratio increased by 2.8-fold. The remaining intact nephrons are hypertrophied, and there

is evidence of substantial glomerular injury (Chaabane et al, 2013). In humans, delayed relief of obstruction (>2 weeks) has been demonstrated to decrease long-term renal function and increase the risk for hypertension (Lucarelli et al, 2013).

Other factors that influence the return of renal function after relief of obstruction include a lesser degree of obstruction, greater compliance of the collecting system, and the presence of pyelolymphatic backflow (Shokeir et al, 2002). Conversely, older age and decreased cortical thickness are predictors of diminished recovery of renal function after relief of obstruction (Lutaif et al, 2003). The presence of increased collagen deposition in renal parenchyma at the time of pyeloplasty has been shown to have a negative impact on recovery of renal function, because it demonstrates a more advanced state of renal fibrosis (Kim et al, 2005; Kiratli et al, 2008). Relief of obstruction is also different with BUO than with UUUO. As a result of the increased volume expansion, accumulation of urea and other osmolytes, and increased levels of ANP, a profound diuresis and natriuresis accompanies relief of BUO as opposed to UUUO. In addition, patients with BUO or obstruction of a solitary kidney are at risk for chronic urinary acidification and concentrating defects (Berlyne, 1961).

Thompson and Gough (2001) demonstrated that dimercaptosuccinic acid (DMSA) is superior to Mag3 and DTPA in measuring function of the obstructed kidney and predicting the ultimate outcome of surgical intervention. Mag3 was found to underestimate the potential of the kidney for recovery and was associated with a large variation in accuracy. The superiority of DMSA in assessing function under these circumstances appears to be related to its fixation to the renal cortex and delayed clearance. In cases in which renal function is significantly depressed on diuresis renography and nephrectomy is being considered, a preoperative DMSA scan may be of additional value in surgical planning.

Choice of Surgical Intervention

Definitive management of urinary tract obstruction is based on the cause of obstruction, status of the contralateral kidney, function of the affected kidney, and patient's age and overall medical status. A number of different endoscopic, open, laparoscopic, and robotically assisted ablative and reconstructive options are available and are discussed elsewhere in this text. In general, a nephrectomy should be considered for an obstructed kidney that contributes less than 10% to the patient's overall renal function. The decision to remove a kidney, however, should be made only after the kidney has been adequately drained for a sufficient period to allow maximal recovery and an accurate assessment of renal function (Kerr, 1954). In the setting of global renal insufficiency, the decision is more complicated and patients may elect management with a chronic indwelling stent or nephrostomy tube to prevent more rapid progression to dialysis.

Postobstructive Diuresis

Mechanism of Postobstructive Diuresis

Postobstructive diuresis, defined as a period of significant polyuria, may develop after the relief of urinary tract obstruction. Urine outputs of 200 mL/hr or greater may be encountered. Although this primarily occurs after relief of BUO, it can occur rarely in the presence of a normal contralateral kidney (Schlossberg and Vaughan, 1984). The diuresis is generally a physiologic response to the accumulated solutes and volume expansion that have occurred during obstruction. Sodium, urea, and free water are eliminated, and the diuresis subsides after homeostasis is achieved (Loo and Vaughan, 1985).

Pathologic postobstructive diuresis may ensue, characterized by inappropriate renal handling of water and/or solutes. Downregulation of sodium transport channels (Li et al, 2003), downregulation of AQP channels (Li et al, 2001), poor responsiveness of the collecting duct to vasopressin, and altered regulation

of ANP (Kim et al, 2001b) can result in a disruption of the medullary interstitial solute gradient and profound diuresis and natriuresis.

Clinical Management of Postobstructive Diuresis

The majority of patients do not demonstrate a clinically significant postobstructive diuresis after relief of urinary tract obstruction, and those who are susceptible typically exhibit signs of fluid overload, including edema, congestive heart failure, and hypertension (Loo and Vaughan, 1985). Most commonly, postobstructive diuresis develops after relief of urinary retention, and the speed at which the bladder is drained has not been shown to have any effect on the development of postobstructive diuresis or hematuria (Nyman et al, 1997).

After relief of obstruction, patients with BUO or an obstructed solitary kidney should be monitored for the development of postobstructive diuresis. Patients with normal renal function, normal electrolytes, no evidence of fluid overload, and a normal mental status should have their vital signs and urine output monitored regularly, and they should be given free access to oral fluids. If evidence of a postobstructive diuresis develops, vital signs, urine output, and electrolytes should be monitored more frequently, and patients should continue to have free access to oral fluids. Generally, patients with a normal mental status should not be given IV fluids because this may prolong the period of diuresis. This is a physiologic diuresis that, in the majority of cases, resolves when free water and excess solutes are eliminated. In patients with impaired renal function, altered mental status, and signs of fluid overload, more intense monitoring is indicated. A urine osmolality should be checked, and vital signs and urine output should be checked frequently. Electrolytes should be monitored every 12 hours or more often if necessary. Patients with poor cognitive function should be given IV fluids, although at a rate below maintenance. If pathologic diuresis ensues, the patient can become hypovolemic as a result of excess water loss, and electrolyte abnormalities may develop as result of salt or potassium wasting. Very intense monitoring and careful fluid and electrolyte replacement are indicated in these patients. The urine is usually isosthenuric initially, and IV fluid replacement with 0.45% saline administration at a rate lower than the urine output is recommended (Frøkiaer and Zeidel, 2007). Changes in the type and amount of IV fluid administration are based on the patient's clinical status, serum, and urinary electrolytes.

Experimental Modulation of Postobstructive Diuresis

Experimental data suggest the potential for pharmacologic manipulation of postobstructive diuresis. It remains unclear, however, what role pharmacologic manipulation might play in clinical practice. As discussed previously, BUO is associated with increased COX-2 expression, and selective COX-2 inhibition prevents the downregulation of AQP2 channels in response to obstruction (Norregaard et al, 2005). Norregaard and colleagues (2007) demonstrated that COX-2 activity increases in the postobstructive phase and that this contributes to polyuria and an impaired urine-concentrating ability. After administration of a selective COX-2 inhibitor, the authors demonstrated that urine output was reduced but sodium excretion and GFR remained unchanged 24 hours after release of BUO. Evidence also exists that sildenafil citrate (Viagra) can induce accumulation of AQP2 channels in collecting duct cells in vitro, independent of vasopressin stimulation, by activating a parallel pathway mediated by cyclic guanosine monophosphate (Bouley et al, 2005). Clearly, further research is required to identify effective management strategies for postobstructive diuresis and to determine which patients would benefit from pharmacologic manipulation.

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The complete reference list is available online at www.expertconsult.com.



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Evaluation of Upper Tract Obstruction

Ureteropelvic Junction Obstruction

Retrocaval Ureter

Ureteral Stricture Disease

Ureteroenteric Anastomotic Stricture

Retroperitoneal Fibrosis

Technologic advances continue to evolve both the diagnostic and therapeutic alternatives available in the contemporary management of upper urinary tract obstruction. The obstructive processes may be intrinsic, extrinsic, congenital, or iatrogenic, and in many patients the cause of obstruction may not be immediately evident. Furthermore, making an accurate diagnosis of obstruction can be challenging.

The treatments for upper tract obstruction range from ureteral stent placement to complex procedures involving ileal interposition or autotransplantation. Myriad skills are required for total surgical management of upper urinary tract obstruction. Not surprisingly, endourology, laparoscopy, and robotics continue to be more prominent in the surgical management of upper urinary tract obstruction. As a result of the wide array of available treatments, the urologist must have an understanding of the indications and risks of all the alternatives.

This chapter provides a state-of-the-art presentation of the diagnostic and therapeutic management strategies for patients with upper urinary tract obstruction. The chapter is organized by the anatomic location of obstruction. The etiology, diagnosis, indications for intervention, risks, and therapeutic options (including endoscopic, laparoscopic, robotic, and open approaches) are thoroughly reviewed.

EVALUATION OF UPPER TRACT OBSTRUCTION

The increasing use of computed tomography (CT) scanning in emergency departments and for various screening purposes has led to frequent suspicion of upper tract obstruction (Davis, 2012). Moreover, the widespread use of low-dose CT scans, which are often of lower resolution, may necessitate follow-up imaging (Zagoria and Dixon, 2009). After low-dose CT, the urologist can use ultrasound, excretory urography, diuretic renography, CT urography, retrograde pyelography, Whitaker tests, and ureteroscopy to delineate the precise cause and subsequent treatment strategy of upper tract obstruction. For each specific disorder presented here, we will discuss the recommended approach to the upper tract evaluation.

URETEROPELVIC JUNCTION OBSTRUCTION

The diagnosis of ureteropelvic junction (UPJ) obstruction (UPJO) describes a functionally significant impairment of urinary transport from the renal pelvis to the ureter. Although most cases are congenital, the problem may not become clinically apparent until much later in life (Jacobs et al, 1979). Acquired conditions such as stone disease, postoperative or inflammatory stricture, or urothelial neoplasm may also manifest clinically with symptoms and signs of obstruction at the level of the UPJ. Similarly, extrinsic obstruction can occur at this level as well. This section focuses primarily on the

diagnosis and treatment of “congenital” UPJO, although these techniques may be applied to the management of certain acquired conditions, in particular urinary stones.

Pathogenesis

Congenital UPJO typically results from intrinsic disease. A frequently found defect is the presence of an aperistaltic segment of the ureter, perhaps similar to that found in primary obstructive megaureter. In these cases, histopathologic studies reveal that the spiral musculature normally present has been replaced by abnormal longitudinal muscle bundles or fibrous tissue (Allen, 1970; Foote et al, 1970; Hanna et al, 1976; Gosling and Dixon, 1978) (Fig. 49-1). This results in failure to develop a normal peristaltic wave for propagation of urine from the renal pelvis to the ureter. Recognition that this type of segmental defect is often responsible for UPJO is of utmost importance clinically because such ureters may appear grossly normal at the time of surgery and, in fact, may often be calibrated to 14 Fr or greater. Further investigations in the cause of UPJO have shown decreased density of interstitial cells of Cajal at the UPJ in children, but less so in cases involving solely intrinsic UPJO (Solari et al, 2003; Koleda et al, 2012). In addition, the cytokine produced in the urothelium has also been proposed to exacerbate UPJO (Chiou et al, 2005). Other experimental studies have implicated transforming growth factor- β , epidermal growth factor expression, nitric oxide, and neuropeptide Y in UPJ stenosis (Knerer et al, 2001; Yang et al, 2003). A less frequent intrinsic cause of congenital UPJO is true ureteral stricture. Such congenital ureteral strictures are most frequently found at the UPJ, although they may be located at sites anywhere along the lumbar ureter. Abnormalities of ureteral musculature have been implicated as electron microscopy has demonstrated excessive collagen deposition at the site of the stricture (Hanna et al, 1976).

Intrinsic obstruction at the UPJ may also result from kinks or valves produced by infoldings of the ureteral mucosa and musculature (Maizels and Stephens, 1980). In these patients the obstruction may actually be at the level of the proximal ureter. This phenomenon appears to result from retention or exaggeration of congenital folds normally found in the ureter of developing fetuses. In some of these patients the defects are bridged by ureteral adventitia. Grossly, this can manifest as external bands or adhesions that appear to be causing the obstruction. In fact, Johnston and colleagues in 1977 reported that lysis of external adhesions can at times reestablish flow without pyeloplasty (Johnston et al, 1977). In the majority of patients, however, these bands or adhesions are likely to be a secondary phenomenon associated with intrinsic obstruction, so operative pyeloplasty would usually be most effective. The presence of these kinks, valves, bands, or adhesions may also produce angulation of the ureter at the lower margin of the renal pelvis in such a manner that as the pelvis dilates anteriorly and inferiorly, the ureteral insertion is carried further proximally. In these patients the

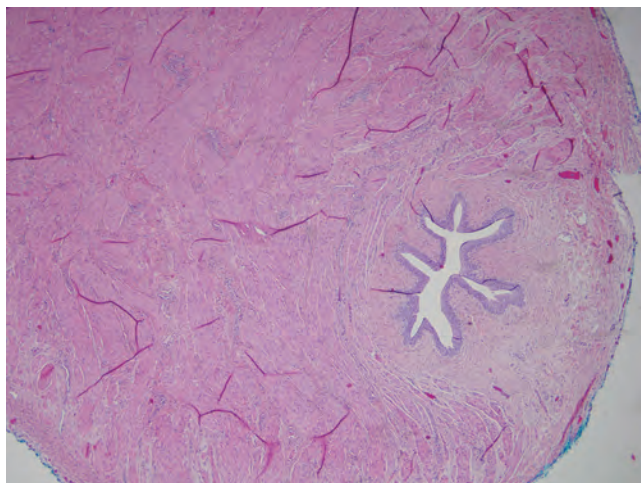


Figure 49-1. The microphotograph is taken through the ureteropelvic junction. There is marked attenuation of smooth muscles and smooth muscle in disarray and hypertrophy surrounding the urothelial lining.

most dependent portion of the pelvis is inadequately drained and the apparent high insertion of the ureteral ostium is actually a secondary phenomenon (Kelalis, 1976). In at least some patients, however, the high insertion itself is likely the primary obstructing lesion because this phenomenon is found more frequently in the presence of renal ectopia or fusion anomalies (Zincke et al, 1974; Das and Amar, 1984). Thus a high insertion can have implications in the subsequent surgical management, particularly endourologic approaches.

Controversy persists regarding the potential role of “aberrant” vessels in the etiology of UPJO. Significant crossing vessels have been noted in up to 63% of patients with UPJO but in as little as 20% of individuals with normal kidneys (Quillin et al, 1996; Zeltser et al, 2004; Richstone et al, 2009). Although these lower pole vessels have often been referred to as aberrant, these segmental vessels, which may be branches from the main renal artery or arise directly from the aorta, are usually normal variants (Stephens, 1982). In some patients, these lower pole vessels cross the ureter posteriorly and truly have an aberrant course. Historically, it has been believed that the associated vessel alone does not cause the primary obstruction (Hanna, 1978). In fact, the true cause is an intrinsic lesion at the UPJ or proximal ureter that causes dilation and ballooning of the renal pelvis over the polar or aberrant vessel. Recent studies using three-dimensional (3D) multidetector row CT demonstrated that the precise location of crossing vessels did not correspond to the obstructive transition point in patients with UPJO (Lawler et al, 2005). In contrast, one group found improvement in patients undergoing only ligation of crossing vessels (Keeley et al, 1996). Richstone and colleagues reviewed histopathology from 95 patients with UPJO and found that 43% of 65 patients with a crossing vessel had no intrinsic abnormality (Richstone et al, 2009). Regardless, the presence of crossing vessels most certainly has a detrimental effect on the success rates of endopyelotomy (Van Cangh et al, 1994; Nakada et al, 1998). UPJO with concomitant anatomic anomalies such as horseshoe kidney and pelvic kidney also present surgical challenges. Notably, the emphasis on laparoscopic and robotic pyeloplasty has quelled the interest in the relevance of preoperative assessment of crossing vessels because this can be addressed at the time of reconstruction.

UPJO may also result from acquired lesions. In children, vesico-ureteral reflux can lead to upper tract dilation with subsequent elongation, tortuosity, and kinking of the ureter. In some patients these changes may only mimic the radiographic findings of true UPJO. However, true UPJO can definitely coexist with vesicoureteral reflux, although it may be difficult to determine whether the anomalies are merely coincident or whether the upper tract ureteral obstruction has resulted from the reflux (Lebowitz and Johan,

1982). Diuretic renography is the first-line modality for differentiating between UPJO and reflux. Other acquired causes of obstruction at the UPJ include benign lesions such as fibroepithelial polyps (Berger et al, 1982; Macksood et al, 1985), urothelial malignancy, stone disease, and postinflammatory or postoperative scarring or ischemia. For these acquired diseases, the techniques discussed in this section may be useful adjuncts for management of the obstruction as long as the primary problem is also addressed where appropriate. For instance, fibroepithelial polyps can be managed using retrograde ureteroscopy and holmium laser excision (Lam et al, 2003a).

Patient Presentation and Diagnostic Studies

UPJO, although most often a congenital problem, can manifest clinically at any time of life. Historically, the most common presentation in neonates and infants was the finding of a palpable flank mass. However, the current widespread use of maternal prenatal ultrasonography has led to a dramatic increase in the number of asymptomatic newborns being diagnosed with hydronephrosis, many of whom are subsequently found to have UPJO (Bernstein et al, 1988; Wolpert et al, 1989). A fraction of cases may also be found during evaluation of azotemia, which may result from bilateral obstruction in a functionally or anatomically solitary kidney. UPJO may also be incidentally found during studies performed to evaluate unrelated anomalies such as congenital heart disease (Roth and Gonzales, 1983). In older children or adults, intermittent abdominal or flank pain, at times associated with nausea or vomiting, is a frequent presenting symptom. Hematuria, either spontaneous or associated with otherwise relatively minor trauma, may also be an initial symptom. Laboratory findings of microhematuria, pyuria, or frank urinary tract infection might also bring an otherwise asymptomatic patient to the urologist. Rarely, hypertension may be a presenting finding (Riehle and Vaughan, 1981).

Radiographic studies should be performed with a goal of determining both the anatomic site and the functional significance of an apparent obstruction. Although excretory urography remains a reasonable option for radiographic diagnosis, this study is rarely used today. Classically, excretory urographic findings include delay in function associated with a dilated pelvicalyceal system. If the ureter is visualized, it should be of normal caliber. In some patients, symptoms may be intermittent and urography findings between painful episodes may be normal. In such cases the study should be repeated during an acute episode when the patient is symptomatic (Nesbit, 1956). Provocative testing with diuretic urography may allow accurate diagnosis in select patients. The patient should be well hydrated and the study then performed after injection of furosemide, 0.3 to 0.5 mg/kg (Malek, 1983) (Fig. 49-2).

CT scan is usually obtained for any patient with acute flank pain (Fielding et al, 1997; Dalrymple et al, 1998; Vieweg et al, 1998) (Fig. 49-3). Moreover, contrast-enhanced CT scans provide detailed anatomic and functional information to aid in diagnosis of UPJO (Fig. 49-4). Both ultrasonography and CT scanning also have a role in differentiating acquired causes of obstruction such as radiolucent calculi or urothelial tumors. In neonates and infants, the diagnosis of UPJO has usually been suggested either by routine performance of maternal ultrasonography or by the finding of a flank mass. In either setting, renal ultrasonography is usually the first radiographic study performed. Ideally, ultrasonography should be able to visualize dilation of the collecting system to help differentiate UPJO from multicystic kidney and determine the level of obstruction. UPJO and multicystic kidneys are distinguishable in the majority of patients by ultrasound alone. With UPJO, the pelvis is visualized as a large, medial sonolucent area surrounded by smaller, rounded sonolucent structures representing dilated calyces. At times, dilated calyces will be seen connecting to the pelvis via dilated infundibula (Fig. 49-5). More recently, Dias and colleagues have shown that prenatal renal pelvis dilation can predict the need for surgical repair of the UPJ (Dias et al, 2013).

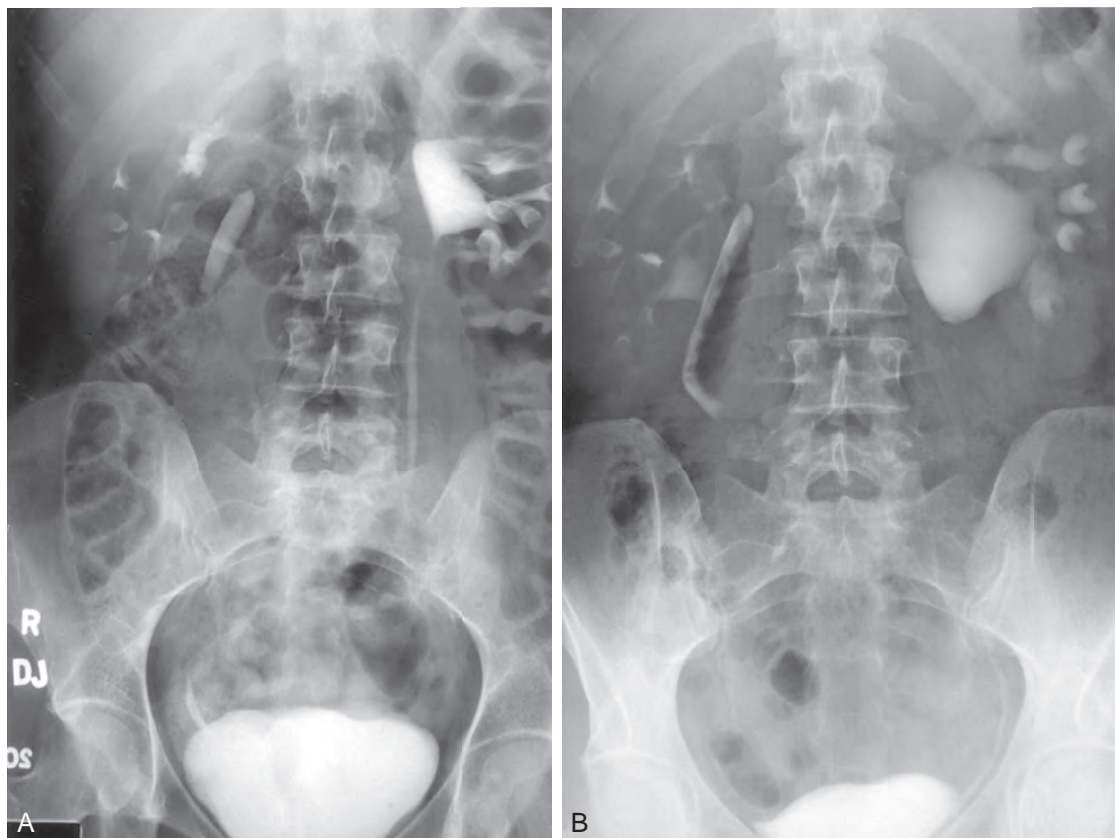


Figure 49-2. A, This patient with intermittent left flank pain underwent intravenous urography. The calyces are sharp bilaterally without evidence of obstruction. However, there is a “box-shaped” pelvis on the left side, which may be associated with intermittent obstruction. B, This intravenous urogram in the same patient was performed along with injection of intravenous furosemide, which brought out the obvious left-sided ureteropelvic junction obstruction. The patient’s symptoms were subsequently relieved with a left pyeloplasty.



Figure 49-3. Noncontrast computed tomography scan performed as the initial radiographic study in a patient with left flank pain revealed hydronephrosis to the level of the ureteropelvic junction (UPJ). No calculus was visualized, and a presumed diagnosis of UPJ obstruction was considered. This proved correct on subsequent radiographic studies.

Occasionally, a solid-appearing renal cortex can be seen surrounding the sonolucent areas or separating the dilated calyces. In contrast, the cysts of multicystic kidneys are visualized as various-sized sonolucent areas in random distribution. Although the cysts may be connected, this is rarely visualized sonographically.

Furthermore, little solid tissue is seen, and what is present has a random distribution among the cysts. Rarely a large, centrally located cyst may cause confusion in the diagnosis (King et al, 1984a). In this setting, a renal scan should be performed. Specifically, a technetium Tc99m-diethylenetriaminedipentaacetic acid (^{99m}Tc -DTPA) scan allows differentiation of these two entities. Multicystic kidneys rarely reveal concentration of this isotope. When uptake is seen, the areas of functioning tissue are initially discrete and are usually medial to the bulk of the mass, which itself remains a “cold” area. In contrast, neonatal kidneys with UPJO usually exhibit good concentration of the isotope. Furthermore, even with severe obstruction in which only a cortical rim remains, uptake of the isotope will be seen peripherally in the cortex, again helping to differentiate this from multicystic kidney (King et al, 1984a).

Diuretic renography is effective in predicting recovery of function in cases in which intravenous urography has revealed nonvisualization. Diuretic renography allows quantification of the degree of obstruction and can help differentiate the level of obstruction. Today, ^{99m}Tc -mercaptoacetyl triglycine (^{99m}Tc -MAG3, or MAG3) is the preferred isotope over ^{99m}Tc -DTPA or radioiodinated Hippuran because of favorable imaging and dosimetry considerations (Roarke and Sandler, 1998). Diuretic renography remains a commonly used study for diagnosing both UPJ and ureteral obstruction because it provides quantitative data regarding differential renal function and obstruction, even in hydronephrotic renal units. Diuretic renography is noninvasive and readily available in most medical centers. Ideally, diuretic renography can be used to follow patients for functional loss, most effectively when a standard protocol is used. The diuretic is given 20 minutes into the study to allow time for filling of the collecting system. One study found

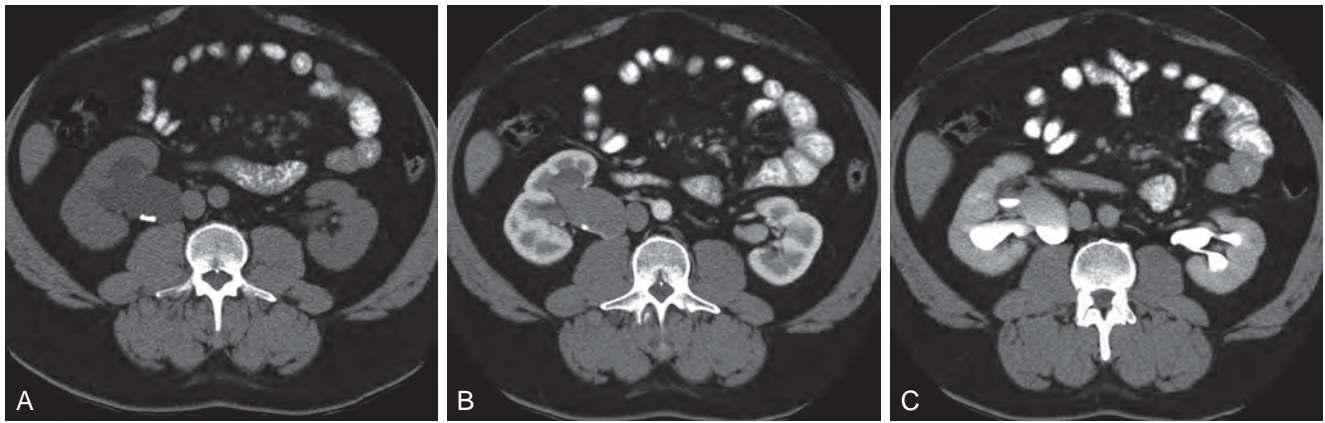


Figure 49-4. A, Contrast-enhanced computed tomography scan identifies a classic ureteropelvic junction (UPJ) appearance in early-phase imaging. B, Early images reveal normal nephrogram and delayed filling of the obstructed, dilated UPJ. C, Delayed images demonstrate holdup of contrast drainage on the right compared with the normal left side.

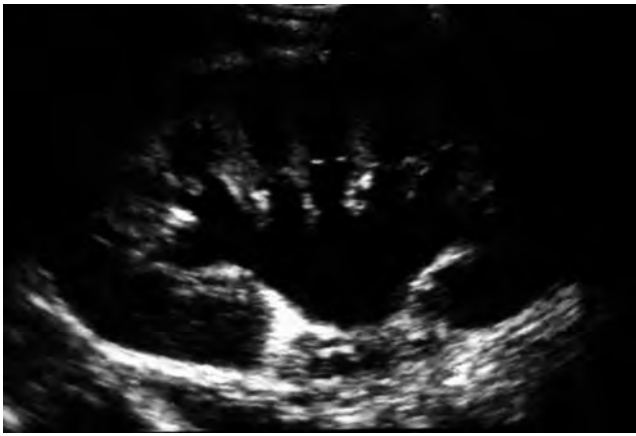


Figure 49-5. Classic ultrasound image of ureteropelvic junction obstruction, with dilated renal pelvis and infundibula and calyces. The ureter is not visualized in this image.

diuretic renography to be useful in children to rule out concomitant UPJO with associated high-grade reflux (Stauss et al, 2003). There is evidence that diuretic renography using MAG3 is a most accurate study for patients with UPJO after therapeutic intervention (Niemczyk et al, 1999) (Fig. 49-6).

The diagnosis of UPJO can generally be made with a high degree of certainty on the basis of the clinical presentation and the results of any one or more of the imaging studies already cited. It is preferable to have a combination of anatomic and functional studies, such as retrograde pyelogram and diuretic renography, to best plan therapy. Retrograde pyelography thus retains a role for confirmation of the diagnosis and for demonstration of the exact site and nature of obstruction before repair. In most cases, this study is performed at the time of the planned operative intervention to avoid the risk of introducing infection in the face of obstruction. However, retrograde pyelography is indicated emergently whenever the UPJO requires acute decompression, such as in the setting of infection or compromised renal function. If cystoscopic retrograde manipulation has been unsuccessful or may be hazardous, particularly in neonates or infants, placement of a percutaneous nephrostomy is preferred. This allows the performance of antegrade studies that will help define the nature and exact anatomic site of obstruction. It also allows decompression of the system in patients with associated infection or compromised renal function and allows assessment of recoverability of renal function after decompression. When there remains some

doubt as to the clinical significance of a dilated collecting system, placement of a percutaneous nephrostomy tube allows access for dynamic pressure perfusion studies. First described by Whitaker in 1973, the renal pelvis is continuously perfused at 10 mL/min with normal saline solution or dilute radiographic contrast solution under fluoroscopic control. Renal pelvic pressure is monitored during the infusion, and the pressure gradient across the UPJ is determined. During the infusion, the bladder is continuously drained with an indwelling catheter to prevent transmission of intravesical pressures. Renal pelvic pressure ranging up to 12 to 15 cm H₂O during this infusion suggests a nonobstructed system. In contrast, pressures in excess of 15 to 22 cm H₂O are highly suggestive of a functional obstruction. Pressures between these extremes may be nondiagnostic (O'Reilly, 1986).

Although pressure perfusion studies can often provide valuable information regarding the functional significance of an apparent obstruction, these studies can at times be inaccurate. This inaccuracy may be a result of variations in renal pelvic anatomy and compliance (Koff et al, 1986) or positional variations (Ellis et al, 1995). The urologist must collate the clinical presentation and results of all diagnostic studies performed to identify the best clinical intervention.

Indications and Options for Intervention

Contemporary indications for intervention for UPJO include the presence of symptoms associated with the obstruction, impairment of overall renal function or progressive impairment of ipsilateral function, development of stones or infection, or, rarely, causal hypertension. The primary goal of intervention is relief of symptoms and preservation or improvement of renal function. Traditionally, such intervention should be a reconstructive procedure aimed at restoring nonobstructed urinary flow. This is especially true for neonates, infants, or children in whom early repair is desirable because these patients will have the best chance for improvement in renal function after relief of obstruction (Bejjani and Belman, 1982; Roth and Gonzales, 1983; Wolpert et al, 1989). However, timing of the repair in neonates remains controversial (DiSandro and Kogan, 1998; Koff, 1998; Hanna, 2000; Koff, 2000; Shokeir and Nijman, 2000), mostly because of difficulty in defining those kidneys truly at risk for functional obstruction. In a prospective study of 104 neonates with primary unilateral hydronephrosis suspected of being caused by UPJO, after a mean follow-up of 21 months, only 7 (7%) required pyeloplasty for functional obstruction, defined as a progression of hydronephrosis or a 10% reduction in differential glomerular filtration rate on serial ultrasonography and diuretic renography (Koff and Campbell, 1994). All treated patients had a return of

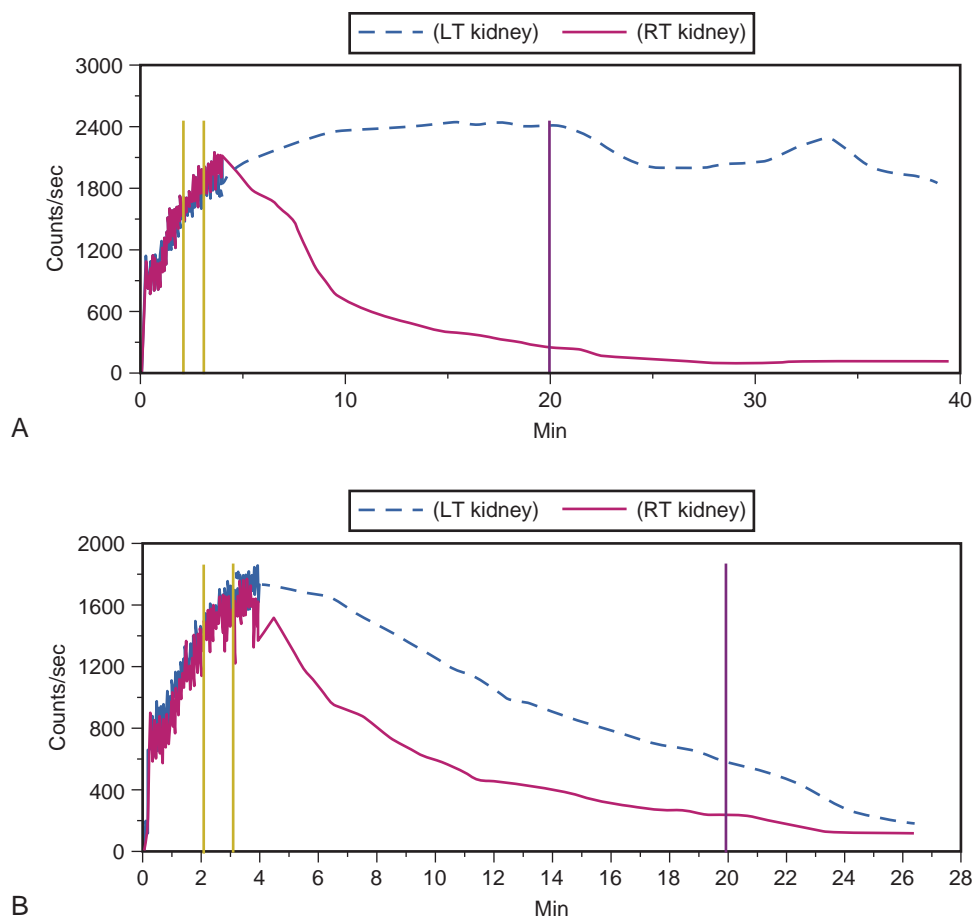


Figure 49-6. A, ^{99m}Tc -mercaptoacetyltri-glycine (MAG3) diuretic renography revealing functional ureteropelvic junction obstruction of the left kidney, with a $T_{1/2}$ greater than 40 minutes. Furosemide was administered 20 minutes into the study (vertical purple line). B, Follow-up study reveals normal renal drainage after robotic pyeloplasty with spontaneous drainage before furosemide administration.

renal function to predetermination levels, supporting selective nonoperative management of neonatal hydronephrosis.

UPJO may not become apparent until middle age or later (Jacobs et al, 1979). Occasionally, if the patient is asymptomatic and the physiologic significance of the obstruction seems indeterminate, careful observation with serial follow-up renal scans is appropriate. Gurbuz and colleagues observed minimally symptomatic UPJO and found 29% required surgery over a 4-year period (Gurbuz et al, 2011). Gulur and colleagues noted that 3 of 14 patients with UPJO lost less than 10% renal function over a mean of 44 months of observation (Gulur et al, 2009). However, the majority of affected patients ultimately benefit from reconstructive intervention (Jacobs et al, 1979; Clark and Malek, 1987; O'Reilly, 1989). When intervention is indicated, the procedure of choice has historically been dismembered pyeloplasty; however, less invasive endourologic approaches have a role as an alternative (Brannen et al, 1988; Motola et al, 1993a; Kletscher et al, 1995; Cohen et al, 1996; Nadler et al, 1996; Thomas et al, 1996; Tawfik et al, 1998; Lechevallier et al, 1999; Gerber and Kim, 2000; Nakada, 2000; Conlin, 2002). Moreover, laparoscopic and robotic pyeloplasty has gained acceptance as primary therapy at centers with appropriate experience (DiMarco et al, 2006; Rassweiler et al, 2007).

Although success rates with most endourologic techniques have not proven to be comparable with those of pyeloplasty, it has been suggested that the success rates may be improved with careful patient selection. In an important prospective study, Van Cangh and colleagues (1994) achieved an overall success rate for endopyelotomy of 73%. However, these investigators found the presence of

crossing vessels to be a major determinant of outcome (42% success rate in the setting of a crossing vessel vs. 86% success without a crossing vessel). Furthermore, when endopyelotomy was applied to patients with "a high degree of obstruction," the success rate was only 60% compared with an 81% success rate for those patients with "low-grade" obstruction. When patients with both a crossing vessel and a high degree of obstruction were excluded from analysis, the success rate improved to 95%, which is comparable with that of open pyeloplasty. However, other studies have suggested a less important role for these factors with regard to their impact on a successful outcome (Gupta et al, 1997; Danuser et al, 1998; Nakada et al, 1998). The use of color Doppler imaging has proven effective in diagnosing crossing vessels, as have magnetic resonance imaging (MRI) and CT (Mitterberger et al, 2008). Moreover, an incisional approach may be favored in patients who are poor surgical candidates or in patients poorly suited to an abdominal approach (Elabd et al, 2009).

Although the indications for intervention for UPJO are similar regardless of technique, it is critical to discuss the risks and benefits of all available options with patients. Accordingly, each patient should be advised individually on the basis of all the anatomic and functional information available preoperatively. In this setting, many patients will opt for a minimally invasive approach, even with the understanding that success rates may be lower or that secondary intervention may become necessary. As a result of studies linking crossing vessels to hindered endourologic successes, there is increased interest in intraoperative management of the UPJ and crossing vessel by either an open or a laparoscopic approach (Conlin, 2002). Therefore, for secondary UPJO, it remains

reasonable to recommend an open or laparoscopic approach to any patient in whom primary endourologic management has failed and an endourologic approach to those in whom open or laparoscopic repair has failed. Of note, the results of endourologic management after failed pyeloplasty remain excellent (Jabbour et al, 1998; Canes et al, 2008; Patel et al, 2011).

Rarely, nephrectomy may be the procedure of choice. Indications for nephrectomy as primary therapy include diminished function or nonfunction of the involved renal moiety and a normal contralateral kidney on the basis of radiographic and nuclear studies. These patients may be symptomatic with urinary tract infections or pain. In such cases, ultrasonography or CT scanning is typically performed and will reveal only a thin shell of parenchyma remaining. Renography can provide quantitative measures of renal function, and, in general, kidneys with less than 15% differential function are nonsalvageable in adults. If the potential for salvageability of function is still unclear, an internal stent or percutaneous nephrostomy may be placed for temporary relief of obstruction and renal function studies subsequently repeated. Nephrectomy may also be considered for patients in whom the obstruction has led to extensive stone disease with chronic infection and significant loss of function in the face of a normal contralateral kidney. Removal of the kidney may also be chosen over reconstruction for patients in whom repeated attempts at repair have already failed and in whom further intervention would therefore be extremely complicated. This option should be considered only when the contralateral kidney is essentially normal.

Options for Intervention

Endourologic Management. Operative intervention for UPJO has historically provided a widely patent, dependently positioned, well-funneled UPJ. In addition, the option to reduce the size of the renal pelvis is readily available with this approach. Although formal pyeloplasty has stood the test of time with a published success rate of nearly 95%, endourologic alternatives to standard operative reconstruction are still used (Clark et al, 1987; Elabd et al, 2009). The advantages of endourologic approaches include reduced hospital stays and postoperative recovery. However, the success rate does not approach that of open, laparoscopic, or robotic pyeloplasty. Furthermore, whereas open, laparoscopic, or robotic pyeloplasty can be applied to almost any anatomic variation of UPJO, consideration of any of the less invasive alternatives requires that the surgeon take into account the degree of hydronephrosis, ipsilateral renal function, concomitant calculi, and possibly the presence of crossing vessels. Of note, Albani and colleagues (2004) reported contemporary long-term results with various endopyelotomy approaches to have a success rate of 67%, with the majority of failures in the first 32 months. More recently, DiMarco and colleagues (2006) reported long-term follow-up of more than 400 patients undergoing either percutaneous antegrade endopyelotomy or pyeloplasty. The 3-, 5-, and 10-year success rates were superior for pyeloplasty, 85% versus 63%, 80% versus 55%, and 75% versus 41%. Moreover, Rassweiler and colleagues (2007) compared retrograde laser endopyelotomy with laparoscopic retroperitoneal pyeloplasty in 256 patients in a 10-year single-surgeon experience and found success rates were 73% for laser endopyelotomy compared with 94% for pyeloplasty.

Endourologic management of UPJO was introduced by Ramsay and colleagues in 1984 as a “percutaneous pyelolysis” and then popularized in the United States by Badlani and colleagues (1986), who coined the term *endopyelotomy*. Although various nuances in the technique have been described (Korth et al, 1988; Van Cangh et al, 1989; Ono et al, 1992), the basic concept of the endopyelotomy is a full-thickness lateral incision through the obstructing proximal ureter, from the ureteral lumen out to the peripelvic and periureteral fat. A stent is placed across the incision and is left to heal, in keeping with the original work of Davis in 1943, who performed an “intubated ureterotomy” to repair UPJO. Subsequently, alternative techniques using a retrograde approach to the UPJ were developed. The retrograde approach most used today is

the ureteroscopic approach, typically using the holmium laser to incise the UPJ under direct visual control. Alternatively, a cautery wire balloon endopyelotomy, which incises the UPJ under fluoroscopic control, or percutaneous endopyeloplasty may be used (Gill et al, 2002; Elabd et al, 2009). Recently, Vaarala and colleagues reported a small series of 64 patients who underwent either antegrade or retrograde cold knife or cautery wire balloon endopyelotomy. In this study, success rates ranged from 79% to 83%, without statistically significant differences among the three treatments (Vaarala et al, 2008). Of note, transplantation complications are particularly suited to endoscopic management, either antegrade or retrograde (Schumacher et al, 2006; Gdor et al, 2008b). As far as efficacy is concerned, there continues to be little evidence for significant differences among endopyelotomy techniques. The differences lie in technical considerations and complications.

Percutaneous Antegrade Endopyelotomy

Indications and Contraindications. The indications to intervene for any patient with UPJO include the presence of symptoms, progressive or overall impairment of renal function, development of upper tract stones or infection, or, rarely, causal hypertension. Historically, a percutaneous approach for definitive management of UPJO was offered only to those patients undergoing percutaneous removal of associated stones or to those in whom open pyeloplasty had previously failed. However, encouraging results ultimately led many centers to offer percutaneous endopyelotomy as primary therapy for almost any patient with UPJO. Even with the acceptance of laparoscopic and robotic pyeloplasty, percutaneous endopyelotomy remains appropriate for patients with UPJO and concomitant pyelocalyceal stones, which can then be managed simultaneously. Contraindications to a percutaneous endopyelotomy are similar to the contraindications to any endourologic approach and include a long segment (>2 cm) of obstruction, active infection, and untreated coagulopathy. Whereas the impact of crossing vessels is controversial, the mere presence of crossing vessels is not a contraindication to an endopyelotomy (Motola et al, 1993b; Nakada et al, 1998; Lam et al, 2003b). However, significant entanglement of the UPJ by crossing vessels can occasionally be identified, and this may render any endourologic approach unsuccessful. When such entanglement is suggested by intravenous or retrograde pyelography, it can be reliably verified with 3D helical CT (Kumon et al, 1997) (Fig. 49-7).



Figure 49-7. A, Contrast-enhanced computed tomography scan reveals apparent right ureteropelvic junction obstruction in this patient with right flank pain. A crossing lower pole artery is visible on this coronal section.

Patient Preparation. Patients undergoing a percutaneous endopyelotomy undergo preoperative evaluation and preparation as if they were undergoing any percutaneous, laparoscopic, or open renal intervention. The evaluation includes an assessment for any comorbidity that may increase the risk of anesthesia. Sterile urine should be ensured at the time of definitive intervention. If upper tract infection cannot be cleared because of obstruction, temporization should be accomplished through use of internal stenting or percutaneous nephrostomy drainage alone. The patient should be counseled as to the risks and benefits of the procedure, and in particular the fact that the success rate of any endourologic approach, including percutaneous endopyelotomy, may be less than that of formal reconstruction. Patients should also be counseled of the risk of bleeding requiring transfusion, urinary leak, drainage-related complications, and hydropneumothorax, particularly if upper pole access is used.

Technique. An endopyelotomy cannot be performed safely by any route until access across the UPJ is established. This can be accomplished in a retrograde fashion cystoscopically or in an antegrade manner percutaneously. For retrograde access, the UPJ can almost always be traversed using a hydrophilic wire passed through an open-end catheter. Once the hydrophilic wire is successfully positioned in the pyelocalyceal system, the open-end catheter is advanced over it into the renal pelvis. The wire can then be withdrawn so that contrast material can be injected through the open-end catheter to guide subsequent percutaneous access.

With the patient in the prone position, the site for percutaneous access is chosen to allow straightforward access to the UPJ. In general, a midposterior or superolateral calyx is chosen, although occasionally an inferolateral calyx may be used. Typically, the UPJ can be intubated in an antegrade fashion when the tract is initially established with fluoroscopic control. Alternatively, once the tract has been dilated and nephroscopy has been performed, a wire can again be passed in a retrograde fashion through the open-end catheter and grasped from above so that through-and-through access is reestablished. In either case, as soon as access is obtained with one wire, an introducing catheter is used to pass a second wire as a safety wire, so a working and a safety wire are now both in place. At this point, percutaneous access is complete and the endopyelotomy may be performed.

In the original descriptions of the technique both from the Institute of Urology in London (Ramsay et al, 1984) and from Long Island Jewish Hospital in New York (Badlani et al, 1986),

the endopyelotomy was performed using a cold knife technique under direct vision. With one or two wires in place across the UPJ, a direct vision “endopyelotome” is used. This hook-shaped cold knife may be used to completely incise the UPJ in a full-thickness manner, from the ureteral lumen to periureteral and peripelvic fat. **Rigorous anatomic studies have shown the incision should usually be made laterally because this is the location devoid of crossing vessels** (Sampaio and Favorito, 1993; Sampaio, 1998). However, in cases of high insertion, the incision should instead “marsupialize” the proximal ureter into the renal pelvis, such that an anterior or posterior incision may be required. When such incisions are done under direct vision, any crossing vessel can be directly visualized and avoided. In addition to the endopyelotome, the holmium laser or the cutting balloon catheter may also be used to perform an antegrade endopyelotomy.

Once the incision is complete, stenting is accomplished. There remains no consensus as to the optimal stent size or duration for endopyelotomy. A No. 14/7-Fr endopyelotomy stent may be used, passed in an antegrade fashion with the larger-diameter end of the stent positioned across the UPJ. In some cases, especially when the patient has not been pre-stented, passage of this large-caliber stent may be difficult. In those instances, a No. 10/7-Fr endopyelotomy stent or even a standard No. 8-Fr internal stent may be used without compromising the ultimate outcome. Once proper positioning of the stent has been determined fluoroscopically, any remaining safety wires are withdrawn. One group showed no difference between larger and standard stents in a porcine study of endopyelotomies (Moon et al, 1995). Alternatively, Danuser and colleagues (2001) demonstrated improved success rates using a modified 27-Fr stent after percutaneous endopyelotomy at nearly 2 years of follow-up.

In the setting of a high insertion, the incision can often be extended to the dependent portion of the renal pelvis under direct vision, bridging the gap between the lateral wall of the ureter and the medial wall of the pelvis, across the periureteral and peripelvic fat (Fig. 49-8). Once the incision is complete, the stent is already in place and nephrostomy drainage is instituted for 24 to 48 hours.

Postoperative Care. Avoidance of strenuous activity for 8 to 10 days after the procedure is recommended. The ideal stent size, duration of stent placement, and radiographic follow-up after endopyelotomy remain unclear (Canes et al, 2008). One study did report a benefit to larger stents in patients undergoing antegrade endopyelotomy (71% vs. 93%); however, a large-bore (27-Fr) catheter was

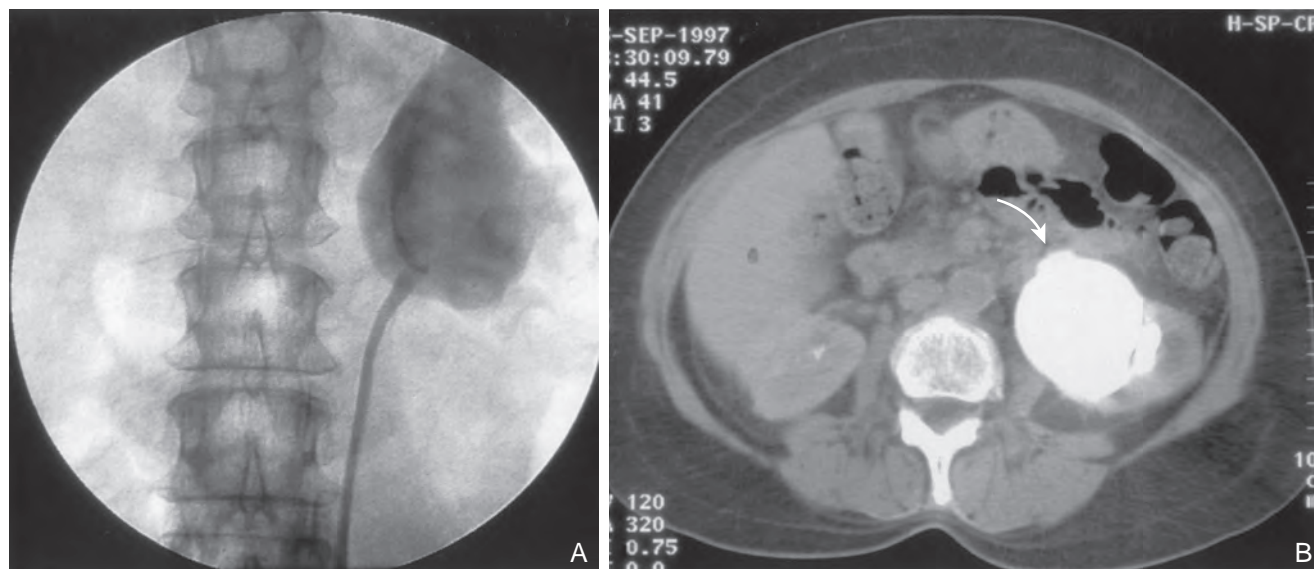


Figure 49-8. A, Retrograde study in this patient with left ureteropelvic junction obstruction reveals a “high insertion” of the left ureter. B, Computed tomography scan in the same patient reveals the ureter inserting on the anatomically anterior aspect of the renal pelvis. A marsupializing incision must be made in a true posterior direction from the ureter into the renal pelvis.

used for the initial 3 weeks postoperatively (Danuser et al, 2001). On the other hand, Kletscher and colleagues (1995) reported no benefit to larger stents, as did Hwang and colleagues (1996). Wolf and colleagues (1997) reported improved success using larger stents (12 Fr) in endouretotomy patients in a retrospective review. Regarding stent duration, less is known. The original report and recommendation of 6 weeks by Davis (1943) is still often used, although Mandhani and colleagues (2003) identified no difference in results when comparing 57 patients stented for 2 weeks versus 4 weeks. Although the need for prophylactic antibiotics while the stent is indwelling is not literature based, many use a daily suppressive dose.

Once the stent is removed, the patient returns 1 month later for clinical follow-up and radiographic evaluation. In general, this includes a history, physical examination, urinalysis, and diuretic renography. If the patient remains asymptomatic and the diuretic renography reveals normal drainage (normal $T_{1/2}$), reevaluation is performed at 6 months and then at 12-month intervals. Most literature indicates that the majority of endopyelotomy failures occur within the first year of the procedure; however, longer-term studies demonstrate failures well beyond that timeframe (Nadler et al, 1996; Albani et al, 2004; DiMarco et al, 2006; Doo et al, 2007). For most adults, 2- to 3-year follow-up is justified because studies indicate that even at 36 months some late failures are identified, but relatively few are identified at 60 months (Doo et al, 2007).

Results. The immediate and long-term results of percutaneous endopyelotomy are well established. Although percutaneous endopyelotomy compares favorably with open operative pyeloplasty in terms of postoperative pain, length of hospital stay, and return to prehospitalization activities (Karlin et al, 1988; Brooks et al, 1995), retrograde endopyelotomy and laparoscopic and robotic pyeloplasty also offer favorable convalescence.

Gerber and Lyon in 1994 reviewed the outcome of percutaneous endopyelotomy in 672 patients reported from 12 centers and found a success rate ranging from 57% to 100% (mean, 73.5%) at follow-up ranging from 2 to 96 months. Currently, success rates approaching 85% to 90% are being reported at experienced centers, with little difference in outcome noted in those patients undergoing the procedure for primary versus secondary UPJO (Motola et al, 1993a; Kletscher et al, 1995; Shalhav et al, 1998). Of note, Knudsen and colleagues (2004) reported long-term results in 80 patients after use of the cold knife and holmium laser for antegrade endopyelotomy, with 55-month follow-up. This series had a success rate of 67%, slightly lower than otherwise reported. It is interesting to note that DiMarco and colleagues (2006) reported on 182 antegrade endopyelotomies with a recurrence-free survival over 10 years at a single center as low as 41%. Of note, Schumacher and colleagues (2006) reported on three successful antegrade endopyelotomies in transplanted kidneys in 2006.

When percutaneous endopyelotomy does fail, several options exist including a retrograde endopyelotomy; repeat percutaneous endopyelotomy; and laparoscopic, robotic, or open operative intervention. There remains a role for spiral CT angiography in failed endopyelotomy, to rule out a crossing vessel. If a significant vessel is found, repeat endopyelotomy is usually not recommended (Nakada et al, 1998; Sampaio, 1998; Nakada, 2000). Alternatively, operative intervention is typically offered to any patient in whom an endourologic approach has failed. Some studies suggest that the results of laparoscopic pyeloplasty will not be compromised, whereas Sundaram and colleagues reported longer operative times in these circumstances (Motola et al, 1993b; Gupta et al, 1997; Conlin, 2002; Sundaram et al, 2003).

Complications. The complications associated with percutaneous endopyelotomy are analogous to those associated with percutaneous nephrolithotomy (Badlani et al, 1988; Weiss et al, 1988; Cassis et al, 1991; Malden et al, 1992; Bellman, 1996), and hemorrhage is a risk of any percutaneous upper tract procedure including endopyelotomy. However, because in patients with UPJO the renal parenchyma is usually thinner than that associated with a normal kidney, and because the collecting system is dilated, this risk may be different than that in the general population of stone

patients undergoing percutaneous manipulation. Acute management in this setting is usually conservative to start: bed rest, hydration, and transfusion if necessary. The nephrostomy tube should not be irrigated acutely. Rather, it is preferable to allow the pyelocoliceal system to tamponade the bleeding. When continued bleeding does not respond to these conservative measures, the next step is selective angiographic embolization. **In general, the urologist should have a low threshold to proceeding to angiography, to minimize the need for transfusion and potential exploration. Successful angiographic embolization often obviates the need for operative intervention.**

Infection is a risk of any urinary tract manipulation including percutaneous endopyelotomy, and all attempts should be made to sterilize the urinary tract before the procedure. Whereas the role of prophylactic antibiotics at the outset of the procedure in the setting of a sterile urine is unproven, most urologists give a second-generation cephalosporin "on call" to the procedure. Consideration should be given to the use of prophylactic antibiotics while the endopyelotomy stent is indwelling for the month after the procedure, especially in women who are more prone to bacteriuria.

Persistent obstruction is rare in the early postoperative period because of the internal stent. Occasionally the stent can be obstructed from blood clots, and continued nephrostomy drainage for a few days typically allows the problem to resolve spontaneously.

Percutaneous Endopyeloplasty. Percutaneous endopyeloplasty is a hybrid technique described as an endoscopic Heineke-Mikulicz repair performed through a percutaneous tract. In other words, endopyeloplasty combines percutaneous endopyelotomy and an endoscopic Fenger plasty. Stein and colleagues reported 55 patients with short-term follow-up with more than 90% success (Stein et al, 2007). Endopyeloplasty may not be effective for secondary UPJO because tissue scarring may inhibit the endoscopic reconstruction. More recently a technique modification was reported requiring no specialized equipment (laparoscopic needle holders and a nephroscope) in 10 patients (Lezrek et al, 2012). Regardless, this procedure is less mainstream at this time.

Simultaneous Percutaneous Endopyelotomy and Nephrolithotomy. Percutaneous endopyelotomy is appropriate when the UPJO is associated with upper tract stone disease because the stones can be managed concomitantly. In such cases, percutaneous access is again established with a wire across the UPJ. The stone should be removed before the endopyelotomy so that stone fragments do not migrate into the peripelouretal tissue, as can happen if the endopyelotomy is performed first. Otherwise, localized obstruction may result from fibrosis or granuloma formation (Giddens et al, 2000; Streem, 2000). The urologist must take care to ensure that the UPJO is not a result of edema from the concomitant stone disease, in particular with stone disease in the renal pelvis. In this circumstance, initial management of the stone percutaneously and subsequent radiographic assessment of the UPJ once the stone has been removed are most prudent. In addition, if a nephrostomy tube is retained, a Whitaker test is straightforward and definitive to assess for persistent obstruction. Conversely, UPJO and solitary lower pole calculi do not represent a dilemma regarding UPJ edema, and combined percutaneous management remains most efficient. Alternatively, laparoscopic or robotic pyeloplasty with concomitant stone removal is also effective for these patients. Often the deciding factor between percutaneous and laparoscopic approaches relates to the stone burden present and the experience of the surgeon (Sutherland and Jarrett, 2009).

Retrograde Ureteroscopic Endopyelotomy. A ureteroscopic approach to endopyelotomy was first suggested in 1985 when Bagley and colleagues reported a combined percutaneous and flexible ureteroscopic procedure approach for management of an "obliterated" UPJ (Bagley et al, 1985). Subsequently, Inglis and Tolley (1986) reported a ureteroscopic "pyelolysis" for UPJO. Shortly thereafter, Clayman and colleagues (1990) reported an initial experience in a small number of patients with ureteroscopic endopyelotomy with a 3-Fr or 5-Fr cutting electrode passed under direct vision using large, rigid or flexible ureteroscopes. In that series, however, an 8-Fr nephrostomy tube was placed at the outset

of the procedure and left indwelling for at least 48 hours. Therefore, that series still represented a “combined” endourologic approach to endopyelotomy. Stents were routinely left in place for 6 to 8 weeks, after which diagnostic studies were performed. With a mean follow-up approaching 1 year, a success rate of 81% was achieved in 16 patients. However, two patients developed distal ureteral strictures, probably resulting from the larger-diameter rigid instrumentation. Cold knife ureteroscopic endopyelotomies are still reported. [Butani and Eschghi \(2008\)](#) identified 96% success rates in primary procedures with an average 5-year follow-up, although rigid ureteroscopy and preprocedure stents were necessary.

Advances in instrumentation and technique now allow a ureteroscopic approach to be performed reliably at a single setting ([Conlin and Bagley, 1998](#)), and this is now considered the standard. The main advantage of a ureteroscopic approach is that it allows direct visualization of the UPJ and assurance of a properly situated, full-thickness endopyelotomy incision without the need for percutaneous access. Another advantage of the ureteroscopic approach is a decrease in cost compared with the use of the cautery wire balloon, assuming ureteroscopic equipment and electroincision or holmium laser are already available. Moreover, the risks and morbidity of percutaneous access are avoided with the ureteroscopic procedure. [Gettman and colleagues](#) found that the retrograde ureteroscopic endopyelotomy was more cost effective than hot-wire cutting balloon endopyelotomy, antegrade endopyelotomy, and pyeloplasty for treating UPJO when taking into account treatment failures ([Gettman et al, 2003](#)).

Indications and Contraindications. The indications for a ureteroscopic endopyelotomy include functionally significant obstruction, as defined earlier. Contraindications include long areas of obstruction and upper tract stones, which are best managed simultaneously with alternative approaches, usually percutaneously or laparoscopically. Another consideration is that in patients with significant hydronephrosis, the evidence indicates an antegrade endopyelotomy may be more efficacious ([Lam et al, 2003b](#)).

Technique. The instrument that allows the most straightforward retrograde access to the UPJ, as well as providing an effective working channel, is a small caliber (≤ 7 -Fr) semirigid ureteroscope. In women, the UPJ can often be reached with a 6.9-Fr semirigid ureteroscope. In men, small-caliber (≤ 7.5 -Fr) actively deflecting flexible ureteroscopes are typically used, and today with availability of improved ureteral access sheaths and improved flexible ureteroscopes, many retrograde endopyelotomies are done using the flexible ureteroscope.

General anesthesia is used to minimize patient movement during ureteroscopy and the subsequent incision of the UPJ. In preparation for the endopyelotomy, a retrograde pyelogram is performed under fluoroscopic control at the outset of the procedure. A hydrophilic guidewire is passed cystoscopically under fluoroscopic control and coiled in the pyelocalyceal system. The cystoscope is then withdrawn and exchanged for the semirigid ureteroscope. The ureteroscope is passed alongside the guidewire to the level of the UPJ. If the distal ureter is too narrow to allow easy passage of the ureteroscope, the intramural ureter can be dilated using a 5-mm balloon or a 9- or 10-Fr “introducing” catheter. If the ureter is still too narrow at any point to easily accommodate the ureteroscope, then an internal stent is placed and the procedure postponed for 5 to 10 days to allow passive ureteral dilation. Alternatively, an actively deflecting flexible ureteroscope may be used, and in most cases a ureteral access sheath is quite useful. The sheath allows for rapid transfer of the ureteroscope for assessment of the UPJ. Once the flexible ureteroscope is passed to the UPJ, a 200- μ m holmium fiber is placed through the working channel and the UPJ is incised in the appropriate location, as suggested by the radiographic studies ([Figs. 49-9 and 49-10](#)).

Once the UPJ is reached with the ureteroscope, the renal pelvis is drained to assist movement across the UPJ during the incision. When using a semirigid ureteroscope, the 200- or 365- μ m holmium laser fiber is inserted through the working channel as the ureteroscope is positioned at the proximal extent of the UPJ or in the renal

pelvis itself. At a setting of 0.8 to 1.2 J and a frequency of 10 to 15 Hz, the UPJ is incised, usually in a posterolateral direction, while the ureteroscope is withdrawn back down across the UPJ. This procedure is repeated, and the incision gradually deepened to extend into the peripelvic and periureteral retroperitoneal space. Because this is done gradually and under direct vision, any visualized vessels, and thus potentially significant bleeding, are usually avoided.

The incision is carried caudally into normal ureteral tissue, until the UPJ is widely patent. Injection of contrast material through the ureteroscope can demonstrate extravasation and confirm an adequate depth of incision, although this is usually not necessary because the entire procedure has been performed under direct vision. Balloon dilation up to 24 Fr can also be performed to complete the incision. If any small bleeding points are visualized ureteroscopically, they can be treated by defocusing the holmium laser. Similarly, the balloon can be reinflated to allow tamponade for 10 minutes to see if the bleeding will subside. The ureteroscope is then withdrawn from the ureter while the safety wire is left in place in the renal pelvis for subsequent passage of a stent. Experimental studies have shown that 36-Fr balloon dilation alone can create linear incisions in the UPJ ([Pearle et al, 1994](#)). Although retrograde balloon dilation alone has been reported for treatment of UPJO, long-term follow-up studies have shown a diminishing success rate over time, as low as 42% ([McClinton et al, 1993; Webber et al, 1997](#)).

Once the ureteroscope has been removed, a stent is advanced over the remaining wire using fluoroscopic guidance. A Foley catheter is left indwelling, again to obviate the risk of reflux and extravasation at the site of the endopyelotomy incision and to rapidly identify any significant bleeding. Diuretic renography is performed 4 weeks after stent removal to assess results. Clinical and radiographic follow-up is then continued at 6- to 12-month intervals for 24 to 32 months.

Results. [Biyani and colleagues \(1997\)](#) described their initial experience with a ureteroscopic approach using holmium laser energy. With a mean follow-up of slightly more than 12 months, they achieved a success rate of 87.5% in a small group of patients. One patient developed a urinoma, which was managed conservatively. In 1998, [Renner and colleagues](#) reported a larger series of patients undergoing ureteroscopic laser endopyelotomy. With a semirigid ureteroscope, the UPJ was incised at a posterolateral location unless vessels were visualized in that area, in which case a contralateral incision was made. [Tawfik and colleagues \(1998\)](#) reported the Jefferson Medical College experience with ureteroscopic endopyelotomy. These investigators combined endoluminal ultrasound with their ureteroscopic approach to definitively identify crossing vessels or a ureteropelvic septum, which is present in patients with high-inserting ureters. The authors believed this helped them definitively site their endopyelotomy incision. Different modalities were used for the endopyelotomy itself including electrocautery and holmium laser. An 87.5% success rate was achieved in 32 patients. There were no significant bleeding complications, and all patients were discharged within 24 hours of the procedure.

Several investigators have reported success rates of 70% to 80% with follow-up out to 5 years using ureteroscopic holmium laser endopyelotomy ([Gerber and Kim, 2000; Matin et al, 2003; Elabd et al, 2009](#)). [Yanke](#) reported on 128 retrograde ureteroscopic endopyelotomies with a 60% success rate at 20 months; [Rassweiler and colleagues](#) reported 73% success in 113 patients at 63 months ([Rassweiler et al, 2007; Yanke et al, 2008](#)). Improved results were reported by [Conlin](#) (91% success rates) with retrograde endopyelotomy in patients when culling patients with crossing vessels greater than 4 mm using preoperative ultrasonography ([Conlin, 2002](#)). [Giddens and colleagues](#) also published excellent results after culling patients with anterior and posterior crossing vessels from retrograde endopyelotomy using endoluminal ultrasound ([Giddens et al, 2000](#)). Today, endoluminal ultrasound is rarely used to identify crossing vessels because similar data can be obtained using less invasive studies ([Mitterberger et al, 2008](#)). Regardless, the best endopyelotomy success rates still lag behind those of open or laparoscopic pyeloplasty.

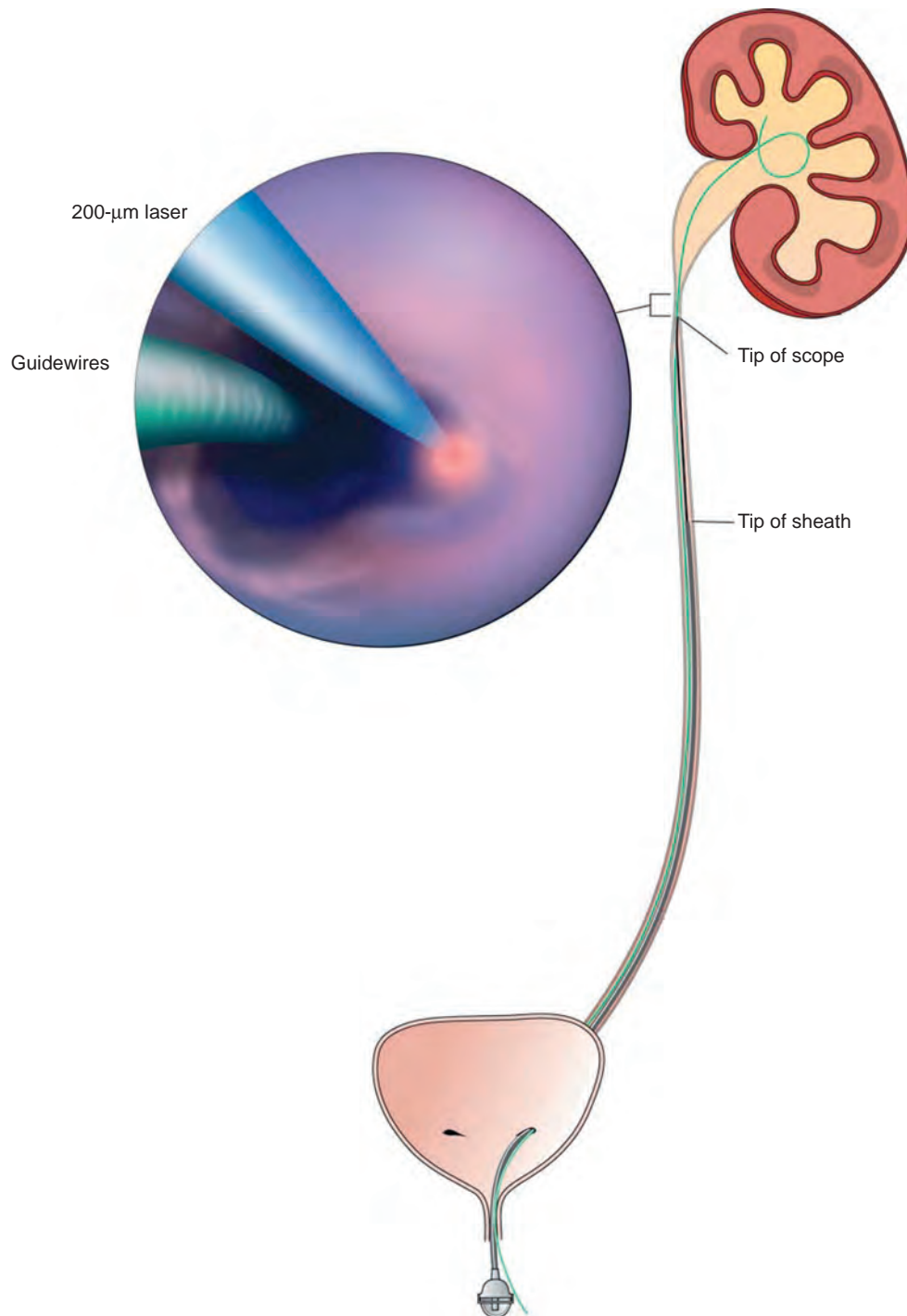


Figure 49-9. Flexible ureteroscopic endopyelotomy using holmium laser, demonstrating endoscopic view of the ureteropelvic junction (*inset*). A safety wire is in place, and the ureterscope is passed through a ureteral access sheath as a lateral incision is being made under endoscopic view, using holmium laser fiber. A properly sited, complete incision is straightforward with this direct visualization technique.

Complications. Complications of this approach have diminished in frequency and severity with the refinement of ureteroscopic instrumentation and the introduction of small-caliber holmium laser fibers. Postprocedural ureteral strictures are rare in contemporary series, and angiographic embolization and nephrectomy are rare when the retrograde approach is used. Most complications are minor and relate primarily to urinary leak, stent migration, and infection (Tawfik et al, 1998; Gerber and Kim, 2000). Castle and colleagues reported on ureteroarterial fistula 2 weeks

after retrograde laser endopyelotomy, which could be fulgurated ureteroscopically (Castle et al, 2009).

Retrograde Cautery Wire Balloon Endopyelotomy. Use of a cautery wire balloon for management of UPJO was first reported in a clinical series by Chandhoke and colleagues in 1993. Because the procedure is guided fluoroscopically, such vessels may increase the risk of hemorrhage after activation of the cautery wire balloon (Wagner et al, 1996). Some authors recommended preoperative imaging for such vessels with relatively noninvasive techniques such

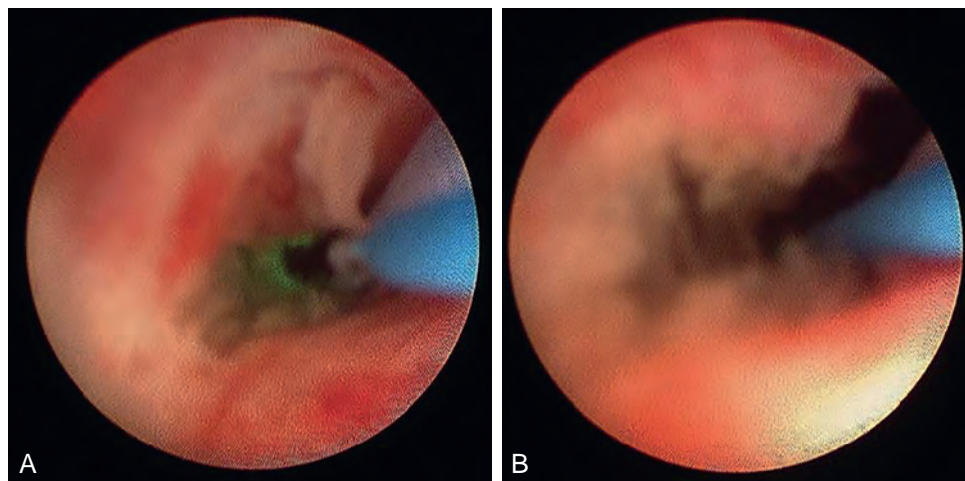


Figure 49-10. A, Endoscopic view of ureteropelvic junction (UPJ) stenosis with safety wire and laser fiber during incision. B, After incision, note full-thickness incision and minimal bleeding with capacious UPJ.

as CT or 3D CT angiography (Stroom and Geisinger, 1995; Quillin et al, 1996; Nakada et al, 1998; Herts et al, 1999; Nakada, 2000). Nadler and colleagues (1996) reported on 28 patients 2 or more years after cautery wire balloon endopyelotomy. With a mean follow-up of 32.5 months, subjective improvement was noted in 61% of patients, and 81% had a patent UPJ on the basis of diuretic renography or Whitaker testing. More recent studies have demonstrated lower success rates than these initial series (32% to 63%) and perhaps that high-grade hydronephrosis has a negative impact on success (Albani et al, 2004; Sofras et al, 2004). El-Nahas and colleagues (2006) reported a small prospective randomized trial comparing retrograde ureteroscopic endopyelotomy to the hot-wire balloon endopyelotomy in 40 patients. Although the results were not statistically significant, they found superior success rates (85% compared with 65%) and lower complication rates with the ureteroscopic endopyelotomy. Ponsky and Stroom (2006) reported on 64 patients undergoing either ureteroscopic endopyelotomy or hot-wire balloon endopyelotomy and found equivalent success rates with both procedures yet higher major complication rates in the cautery wire balloon endopyelotomy, specifically transfusion and selective embolization. Elabd and colleagues (2009) reported a higher rate of hemorrhage using this technique compared with a laser incisional approach. In summary, improved ureteroscopic instrumentation, laser technology, and the benefits of direct endoscopic visualization make ureteroscopic endopyelotomy the pervasive retrograde approach.

Operative Interventions

Historical Notes. The historical aspects of UPJ repair were previously examined by Kay (1989) and by Schaeffer and Grayhack (1986). The first reconstructive procedure was performed by Trendelenburg in 1886; however, the patient died of postoperative complications. In 1891 Kuster divided the ureter and reanastomosed it to the renal pelvis, thus apparently performing the first successful dismembered pyeloplasty (Kuster, 1892). Kuster's technique, however, was prone to recurrent stricture. In 1892 Fenzer applied the Heineke-Mikulicz principle to UPJ repair. This surgical technique involves transverse closure of a longitudinal incision. However, this technique can cause shortening of the suture line on one side, thus resulting in buckling or kinking of the UPJ with recurrent obstruction. In 1916 Schwyzer introduced the Y-V pyeloplasty, which was subsequently modified by Foley in 1937 (Foley, 1937). However, this technique was best applied to high ureteral insertions and was essentially unsuitable when the UPJ itself was already in a dependent position. Later, flap techniques were

KEY POINTS: ENDOUROLOGIC MANAGEMENT OF URETEROPELVIC JUNCTION OBSTRUCTION

- Contemporary indications for intervention for UPJO include the presence of symptoms associated with the obstruction, impairment of overall renal function or progressive impairment of ipsilateral function, development of stones or infection, or, rarely, causal hypertension.
- The advantage of endoscopic management is the avoidance of the intra-abdominal approach; however, the success rates do not approach that of laparoscopic or robotic pyeloplasty.
- Whereas open, laparoscopic, or robotic operative intervention can be applied to almost any anatomic variation of UPJO, consideration of any of the less invasive alternatives requires that the surgeon take into account the degree of hydronephrosis, ipsilateral renal function, concomitant calculi, and, possibly, the presence of crossing vessels.
- In general, the urologist should have a low threshold to proceeding to angiography in patients with bleeding after endopyelotomy to minimize the need for transfusion and potential exploration. Successful angiographic embolization often obviates the need for operative exploration, which can lead to nephrectomy.

developed that were more universally applicable including the spiral flap of Culp and DeWeerd (1951) and the vertical flap of Scardino and Prince (1953). Thompson and colleagues (1969) reported the use of a renal capsular flap for complex cases in which an adequate amount of renal pelvis is not available for repair.

In 1949 Nesbit followed the principle of Kuster's dismembered procedure and further modified it by creating an elliptical anastomosis to decrease the likelihood of stricture formation at the site of repair. Also in 1949, Anderson and Hynes described their modifications of this dismembered technique that involved anastomosis of the spatulated ureter to a projection of the lower aspect of the pelvis after a redundant portion was excised (Anderson and Hynes, 1949). Use of healing by secondary intention was also investigated in the similar time period. The techniques of intubated ureterotomy were popularized by Davis in 1943, but they had been previously described by Fiori in 1905, Albarran in 1909, and Keyes in 1915.

Developments in minimally invasive surgery have led to a dramatic rise in the use of laparoscopic and robotic techniques in the reconstruction of the UPJ (Jacobs et al, 2013). Irrespective of

surgical approach, several basic principles must always be applied to maximize the success of surgical repair. **For any procedure, the resultant anastomosis should be widely patent and completed in a watertight fashion without tension. In addition, the reconstructed UPJ should allow a funnel-shaped transition between the pelvis and the ureter that is in a position of dependent drainage.** Because the goal of minimally invasive surgery is to mimic open surgery, the operative principles are reviewed here together with specific technical nuances for each approach.

Before the definitive surgical management, drainage of a kidney with UPJO is recommended only in select circumstances including infection associated with the obstruction or azotemia resulting from obstruction in a solitary kidney or bilateral disease. Procedural drainage may be of value in the uncommon scenario of severe, unrelenting pain requiring emergent relief of obstruction. For any of these situations, such drainage can be achieved by placement of an internal ureteral stent or a percutaneous nephrostomy tube. **The clinical indications for placement of stents or nephrostomy tubes intraoperatively remain controversial and vary among urologists.** For adults, our preference is for routine placement of a soft, inert, self-retaining internal ureteral stent, which is removed 4 to 6 weeks postoperatively. Such stents in adults can be easily removed in an outpatient office setting using local anesthesia. Routine use of internal ureteral stents offers several advantages, especially in the early postoperative period. Such practice appears to decrease the amount and length of time of urinary extravasation at the surgical repair site, thereby decreasing the risk of secondary fibrosis. Decreased urinary extravasation also allows earlier removal of external drains. For uncomplicated pyeloplasty in adult patients, there appears to be no advantage to using both a nephrostomy tube and a stent because this may result in a prolonged hospital stay and an increased incidence of infection (Wollin et al, 1989). Instead, nephrostomy tubes may be reserved for complicated procedures such as those required for secondary UPJO or those associated with active inflammation. However, if a percutaneous nephrostomy tube was placed preoperatively, it is usually left in place to allow proximal diversion and access for antegrade radiographic studies during the postoperative period.

Although the use of internal stents and nephrostomy tubes remains somewhat controversial, provision of external drainage from the site of surgical repair is absolutely necessary. Such external drainage may be achieved with a Penrose or closed suction drain placed near, but not on, the suture line and brought out through a separate stab incision. This practice helps to minimize the risk of urinoma formation leading to possible disruption of the suture line, scarring, or sepsis.

Dismembered Pyeloplasty

Indications. At present, a dismembered pyeloplasty is preferred by most urologists in the surgical repair of UPJO because this procedure is almost universally applicable to the different clinical scenarios. This approach can be used regardless of whether the ureteral insertion is high on the pelvis or already dependent. It also permits reduction of a redundant pelvis or straightening of a tortuous proximal ureter. Furthermore, **anterior or posterior transposition of the UPJ can be achieved when the obstruction is the result of accessory or aberrant lower pole vessels (Boylu et al, 2009).** In addition, unlike the flap techniques, **only a dismembered pyeloplasty allows complete excision of the anatomically or functionally abnormal UPJ itself.** It is important to note that a dismembered pyeloplasty is not well suited to UPJO associated with lengthy or multiple proximal ureteral strictures or to patients in whom the UPJO is associated with a small, relatively inaccessible intrarenal pelvis. This surgical repair can be accomplished by either open or minimally invasive techniques, with the reconstruction of the UPJ being essentially the same.

Technique. Surgical exposure to the UPJ is achieved by first identifying the proximal ureter in the retroperitoneum. The proximal ureter is then dissected cephalad to the renal pelvis, leaving a large amount of periureteral tissue to preserve the ureteral blood supply. A marking stitch of fine suture can be placed on the lateral aspect of the proximal ureter, below the level of the obstruction, to assist

proper orientation for the subsequent repair. The UPJ tissue is typically excised, and the proximal ureter is then spatulated on its lateral aspect. The apex of this lateral, spatulated aspect of the proximal ureter is brought to the inferior border of the renal pelvis, and the medial side of the ureter is brought to the superior aspect (Fig. 49-11B). The anastomosis is then performed with fine interrupted or running absorbable sutures, placed full thickness through the ureteral and renal pelvic walls, in a watertight manner (Fig. 49-11C). As discussed earlier, our preference for adult patients is to routinely perform the anastomosis over an internal ureteral stent, which is left indwelling.

If the renal pelvis is exceptionally redundant, a “reduction” pyeloplasty can be performed by excising the redundant portion of the pelvis, but this is often unnecessary (Stein et al, 1996; Morsi et al, 2013) (Fig. 49-12). The cephalad aspect of the pelvis is then closed with running absorbable sutures down to the dependent portion, which will subsequently be anastomosed to the ureter. In the event that aberrant or accessory lower pole vessels are found in association with the UPJO, a dismembered pyeloplasty allows transposition of the UPJ in relation to these vessels (Fig. 49-13).

Surgical Approaches for Pyeloplasty

Open Surgery. Several types of open surgical incisions have been used for pyeloplasty in the management of UPJO. An anterior extraperitoneal approach is chosen by some because it allows surgical repair with minimal mobilization of the pelvis and proximal ureter. Alternatively, a posterior lumbotomy provides direct exposure to the UPJ and again allows repair with minimal mobilization of the surrounding structures. Like the anterior extraperitoneal approach, posterior lumbotomy is best suited to relatively thin patients without previous ipsilateral surgery. Our personal preference for most patients undergoing primary surgical repair of UPJO is an extraperitoneal flank approach. This incision may be subcostal but is usually performed through the bed of the 12th rib or carried anteriorly off its tip. The extraperitoneal flank approach is advantageous in that it is familiar to all urologists and provides excellent exposure without regard to body habitus. In the presence of other renal anomalies associated with the UPJ, such as horseshoe or pelvic kidney, anterior extraperitoneal approaches are often preferable, although laparoscopic management may be considered in this setting.

Laparoscopic and Robotic Intervention. Laparoscopic approach to pyeloplasty was first introduced in 1993 by Schuessler and colleagues (1993) and has been developed worldwide as a viable minimally invasive alternative to open pyeloplasty and endopyelotomy. Relative to both open pyeloplasty and endopyelotomy, laparoscopic pyeloplasty is associated with greater technical complexity and a steeper learning curve (Calvert et al, 2008). **In the hands of experienced laparoscopic surgeons, it has been shown to provide lower patient morbidity, shorter hospitalization, and faster convalescence, with the reported success rates matching those of open pyeloplasty (≥90%).** Autorino and colleagues conducted a meta-analysis of studies comparing open and minimally invasive pyeloplasty techniques and found both to have similar success and complication rates with a weighted mean difference in hospital stay of 2.68 days favoring minimally invasive surgery (Autorino et al, 2014). Following the similar surgical principles of anatomic dissection and repair used in open pyeloplasty, laparoscopic pyeloplasty has been shown to provide the success rates surpassing those of endopyelotomy by approximately 10% to 30% (Simforoosh et al, 2004).

The introduction of the surgical robotic platform, with its shorter learning curve and wristed instrumentation that facilitates the ergonomics of intracorporeal suturing, has led to widespread use of minimally invasive pyeloplasty. Gettman and colleagues reported the first patient experience with robotic-assisted laparoscopic pyeloplasty in 2002 (Gettman et al, 2002). Jacobs and colleagues (2013) reported a 360% increase in the use of minimally invasive pyeloplasty between 2001 and 2009, an increase that was felt to be at least in part related to adoption of robotic pyeloplasty at many

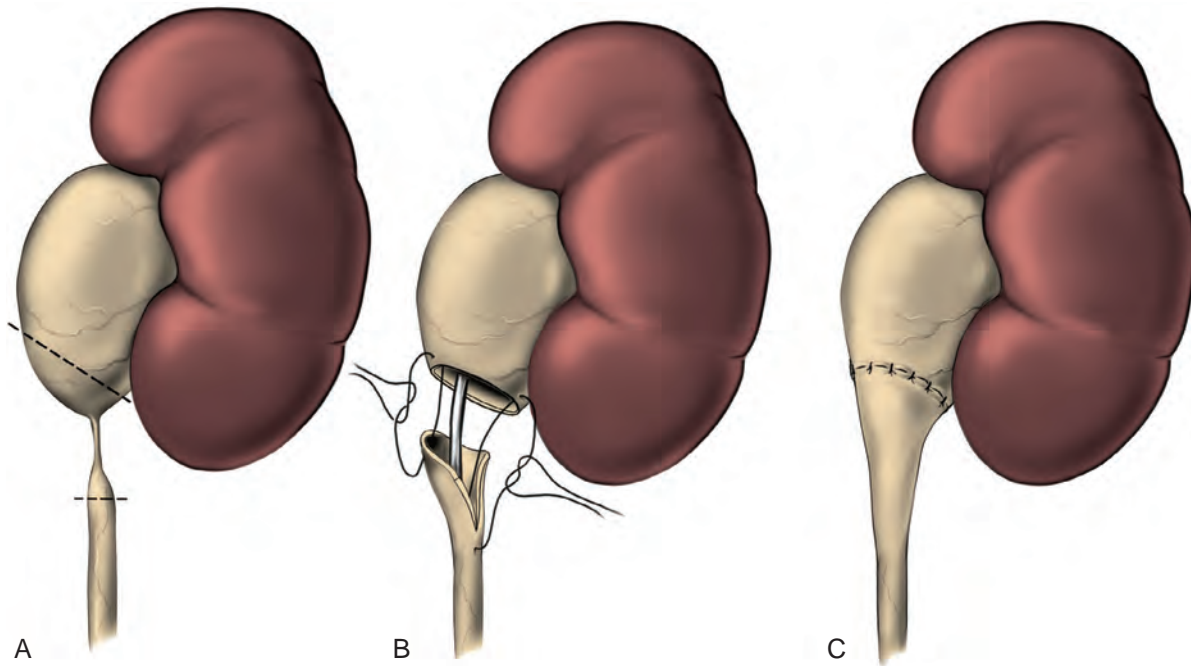


Figure 49-11. A, Traction sutures are placed on the medial and lateral aspects of the dependent portion of the renal pelvis in preparation for dismembered pyeloplasty. A traction suture is also placed on the lateral aspect of the proximal ureter, below the level of obstruction. This will help maintain proper orientation for the subsequent repair. B, Ureteropelvic junction is excised. The proximal ureter is spatulated on its lateral aspect. The apex of this lateral, spatulated aspect of the ureter is then brought to the inferior border of the pelvis while the medial side of the ureter is brought to the superior edge of the pelvis. C, Anastomosis is then performed with fine interrupted or running absorbable sutures placed full thickness through the ureteral and renal pelvis walls in a watertight fashion. In general, we prefer to leave an indwelling internal stent for adult patients. The stent is removed 4 to 6 weeks later.

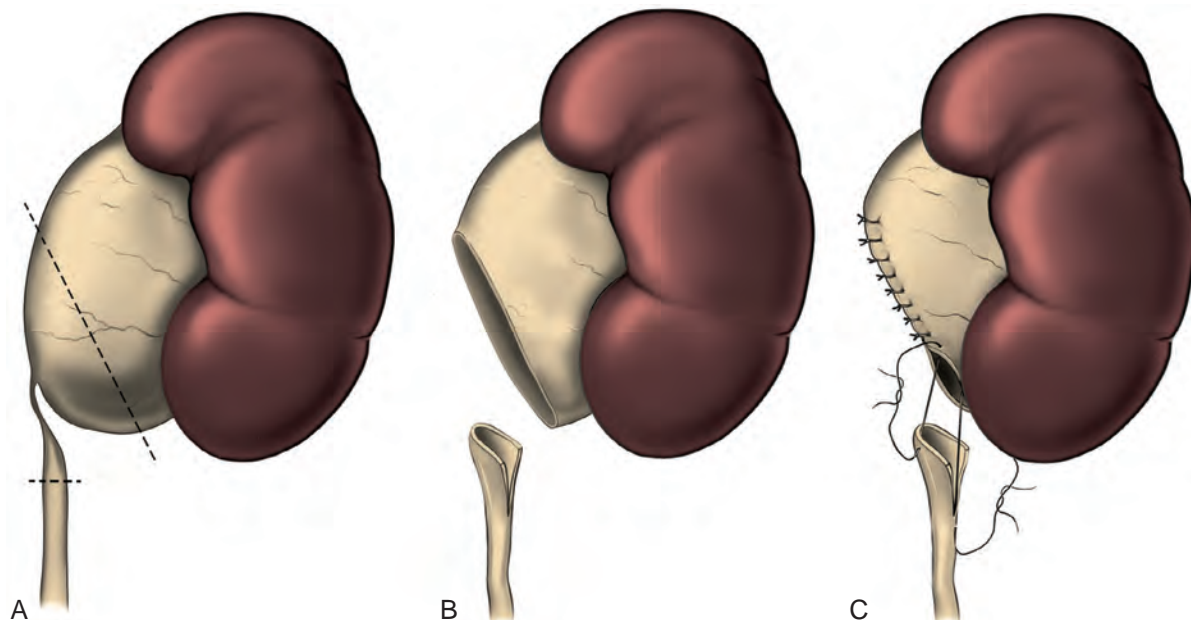


Figure 49-12. A, For large or redundant renal pelvises, a reduction pyeloplasty is performed by excising the redundant portion between traction sutures. B, The cephalad aspect of the pelvis is then closed with running absorbable suture down to the dependent portion. C, The dependent aspect of the pelvis is then anastomosed to the proximal ureter.

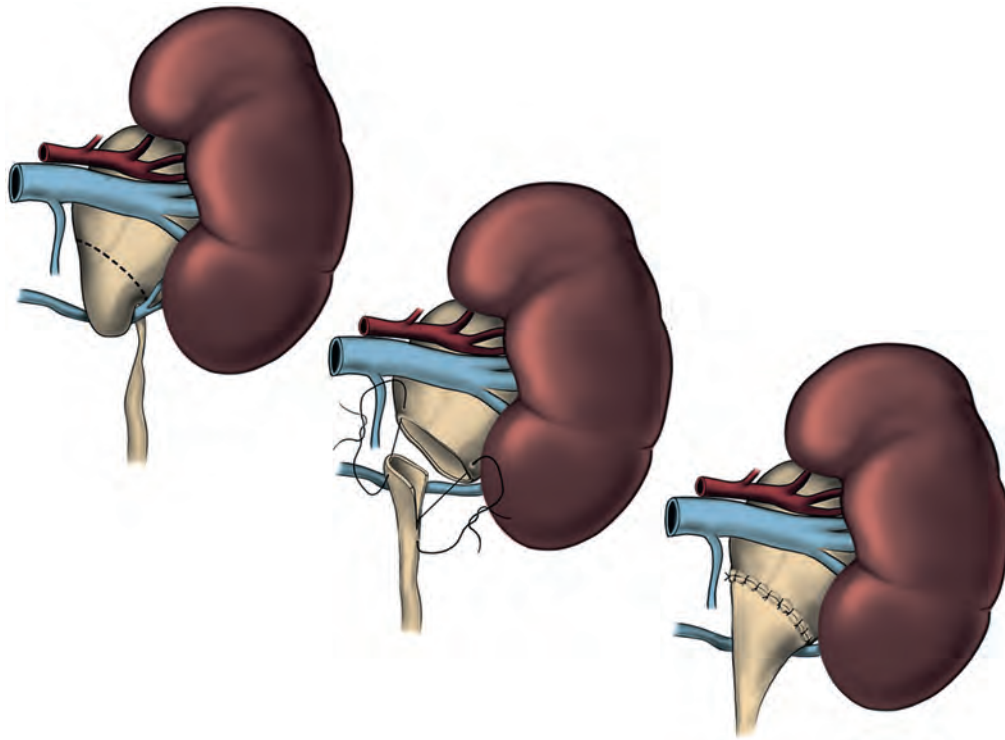


Figure 49-13. When aberrant or accessory lower pole vessels are found in association with the ureteropelvic junction (UPJ) obstruction, a dismembered pyeloplasty allows transposition of the UPJ in relation to the vessels.

centers. Similarly, [Sukumar and coauthors \(2012\)](#) found that the use of minimally invasive pyeloplasty in the United States increased from 2.4% to 55.3% from 1998 to 2009, driven by robotics, which accounted for 45.1% of pyeloplasties performed in 2009. Preoperative, intraoperative, and postoperative techniques are analogous in these approaches, and therefore the next section refers to both laparoscopic and robotic pyeloplasty.

Indications and Contraindications. The indications and contraindications for a laparoscopic repair are similar to those for either an endourologic or an open operative procedure. Indications to intervene include the presence of clinical symptoms of UPJO, the progressive impairment of renal function, and the development of ipsilateral upper tract calculi or infection. Cases requiring the transposition of crossing vessels obstructing the UPJ or the size reduction for massively dilated renal pelvis are suitable for the laparoscopic approach. Absolute contraindications to intervention include the presence of uncorrected coagulopathy, the absence of adequate treatment of active urinary tract infection, and the presence of cardiopulmonary compromise unsuitable for surgery. The objective of the laparoscopic surgery is to provide a tension-free, watertight repair with a funnel-shaped drainage product to relieve clinical symptoms and to preserve renal function.

Techniques. Several laparoscopic techniques for pyeloplasty have been described in the literature including the standard transperitoneal approach (including transmesenteric), retroperitoneal approach, anterior extraperitoneal approach, laparoendoscopic single-site surgery (LESS) approach, and robotic-assisted approach. For each approach, a dismembered Anderson-Hynes pyeloplasty, which is preferred by most surgeons, or one of the nondismembered methods such as Y-V plasty and flap pyeloplasty (Culp) analogous to those described for the open pyeloplasty can be used.

Transperitoneal Laparoscopic Approach. The initial transperitoneal approach to laparoscopic pyeloplasty was first described by [Schuessler and colleagues \(1993\)](#) and [Kavoussi and Peters \(1993\)](#), and this approach has been the most widely used laparoscopic

method owing to its associated large working space and familiar anatomy. Before the laparoscopic portion of the procedure, cystoscopy with retrograde pyelography may be first performed to define the anatomy and confirm the diagnosis, followed by placement of a ureteral stent and a urethral Foley catheter. Alternatively, the surgeon may place a stent laparoscopically in an antegrade fashion after incising the UPJ. The patient is placed in a 45-degree lateral decubitus position, and access to the peritoneal cavity is obtained via either the Veress needle or the Hasson access technique. Three to five laparoscopic ports are placed after the creation of CO₂ pneumoperitoneum. Typically the umbilical port is for laparoscope use. Colonic mobilization to expose the retroperitoneal structures is the initial step of the laparoscopic procedure, although the transmesenteric approach without bowel mobilization has been reported if the renal pelvis or ureter can be readily recognized through the descending colonic mesentery ([Romero et al, 2006](#)). In a nontransmesenteric approach, after medial mobilization of the colon, the ureter is identified and dissected in the cephalad direction to achieve mobilization of the ipsilateral proximal ureter, UPJ, and renal pelvis ([Fig. 49-14A](#)). Extensive dissection of the ureter and excessive electrocautery use in close proximity to the ureter should be avoided to minimize injury to its vascular supply. At this time, the anatomy of the proximal ureter, renal pelvis, and nearby vasculature are carefully examined to determine the cause of the UPJO and the appropriate type of surgical repair. The general methods and principles of various types of surgical repair for laparoscopic pyeloplasty are identical to those described for open pyeloplasty. If dismembered pyeloplasty is to be performed, which is suitable for the presence of crossing vessels, the renal pelvis is first transected circumferentially above the UPJ and the lateral aspect of the proximal ureter is spatulated ([Fig. 49-14B](#)). The renal pelvis and proximal ureter are then transposed to the opposite side of the crossing vessel, if such vessel is present, and the ureteropelvic anastomosis is then completed with intracorporeal suturing techniques ([Fig. 49-14C and D](#)). If the surgeon opted for antegrade laparoscopic stent placement, this can be accomplished by passing a wire down

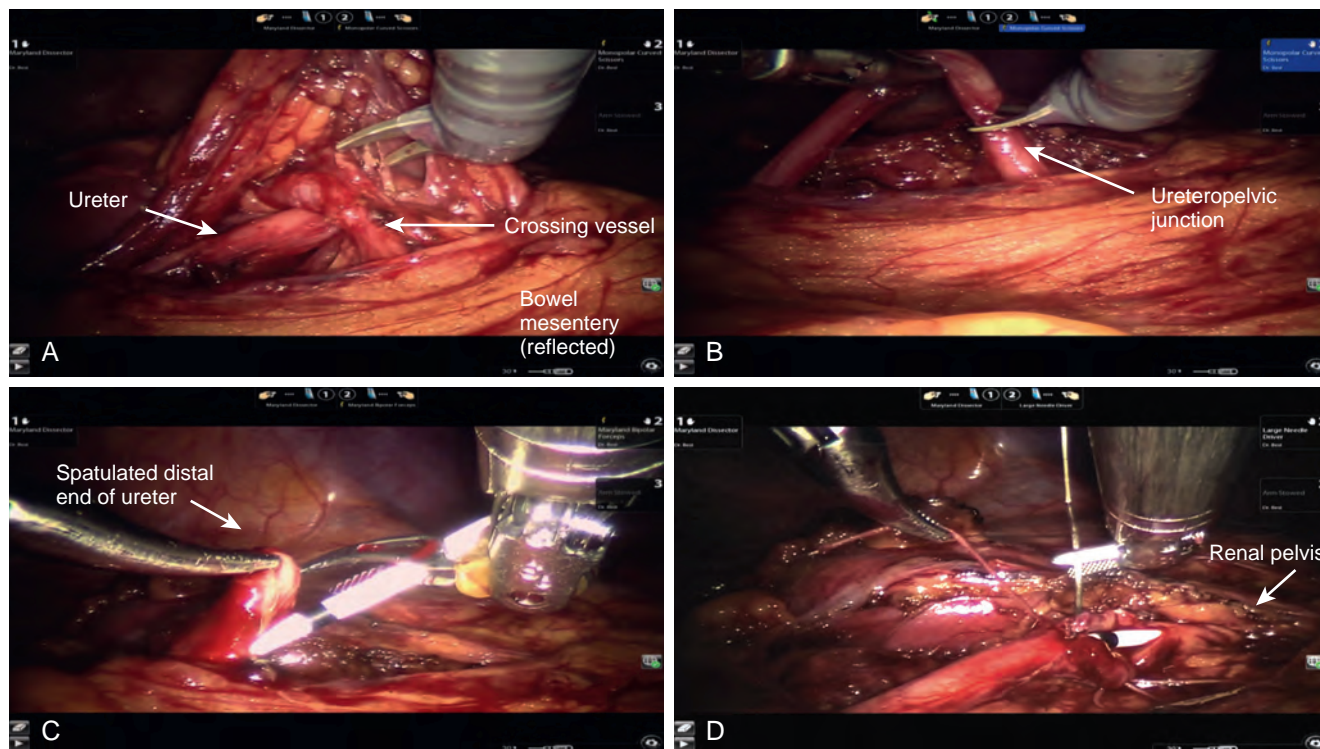


Figure 49-14. Transperitoneoscopic view of a patient undergoing a right robotic laparoendoscopic single-site pyeloplasty. Patient's head is to the right of the images. A, A lower pole crossing vessel is being mobilized off the anterior surface of the ureteropelvic junction (UPJ). B, The right proximal ureter being transected sharply after complete mobilization of the proximal ureter and UPJ. C, Percutaneous antegrade placement of a double-J ureteral stent through a small puncture in the subcostal region (not shown). D, Completion of the anterior portion of the ureteropelvic anastomosis.

the ureter through either the upper quadrant port or a 14-gauge angiocatheter passed through the subcostal region. Clamping the Foley catheter and allowing the bladder to fill before wire passage can facilitate this process. After the wire has been placed, a stent can be inserted over the wire using the pusher. Watching for drainage of urine through the stent perforations can be a helpful sign that the distal end of the stent is well-positioned in the bladder and is another reason to consider clamping the catheter until the stent is in place. In the presence of redundant renal pelvis, reduction pyeloplasty may be performed by excising redundant renal pelvic tissue and closing the pyelotomy. The actual laparoscopic suturing maneuver can be accomplished either freehand or with a semiautomated device (Endo Stitch, Covidien, Norwalk, CT). Either continuous running or simple interrupted sutures may be used in the dismembered laparoscopic pyeloplasty, typically with 4-0 absorbable suture. A surgical drain is placed after the completion of the anastomosis, and one of the trocar sites is typically used as the drain exit site.

Transmesenteric Modification of the Transperitoneal Approach.

In select cases, it may be possible to forgo the initial step of colonic mobilization to reveal the UPJ by instead carefully opening the mesocolonic mesentery directly over the UPJ, being careful not to damage any mesenteric or crossing vessels. After incision of the mesentery, the UPJ is mobilized and reconstructed in the same fashion as the standard retrocolic approach described earlier. To use the transmesenteric approach, the dilated renal pelvis must be well visualized, and this is more often possible in thinner, younger patients with less adipose in their mesenteries. Also, preoperative stent placement typically deflates the renal pelvis and may obscure its visualization in this approach. Because the colon is not reflected, operative times using the transmesenteric approach may be shorter (Romero et al, 2006; Castillo et al, 2007; Shadpour et al, 2012). Some authors have reported a shorter

hospital stay in transmesenteric approach patients, theorizing an earlier return of bowel function owing to minimal bowel manipulation during surgery (Romero et al, 2006; Porpiglia et al, 2008; Shadpour et al, 2012).

Vascular Transposition. An alternative approach has been described to treat an obstruction related to lower pole crossing vessels, also known as the *vascular hitch*, in which the lower pole vessels are mobilized and moved to a more cranial position overlying the renal pelvis rather than the UPJ without dismembering the UPJ itself (Meng and Stoller, 2003; Simforoosh et al, 2005; Masood et al, 2009; Sakoda et al, 2011). The majority of the reports on this approach describe its use in the pediatric population, although a series of 42 patients ranging in age from 7 to 69 years reported a 90% success rate (Nouralizadeh et al, 2010). Gundeti and colleagues (2008) performed vascular transposition procedures in 20 children with a 95% success rate at a mean of 22 months' follow-up. However, Nerli and coauthors (2009) noted the uncertainty as to whether the crossing vessels are the sole cause of obstruction as a possible reason for the failure they noted in a 9-year-old on whom they performed a vascular hitch.

Retroperitoneal Laparoscopic Approach. The initial retroperitoneoscopic approach to pyeloplasty was first reported by Janetschek and colleagues (1996). Cystoscopy with retrograde pyelography and ureteral stent placement are first performed as described earlier. For the retroperitoneal approach, the patient is usually positioned in the flank position with the use of flexion and elevation of the kidney rest. Following Hasson access technique to enter the retroperitoneum, a retroperitoneal working space can be created with balloon dilation. After CO₂ pneumoretroperitoneum, three or four laparoscopic ports are used to perform the laparoscopic pyeloplasty. The ureter is usually identified early in the procedure, and the dissection, mobilization, and UPJ repair steps are identical to those described for the transperitoneal approach.

Anterior Extraperitoneal Laparoscopic Approach. The anterior extraperitoneal laparoscopic approach to pyeloplasty was first described by Hsu and colleagues (2003). Cystoscopy with retrograde pyelography and ureteral stent placement are first performed as described earlier. For the anterior extraperitoneal approach, medial mobilization of the peritoneal sac containing the bowel contents en bloc is performed. Subsequently, full exposure of the anterior aspects of the retroperitoneal structures including the ipsilateral ureter and kidney comes into view. The proximal ureter, UPJ, and renal pelvis are identified, dissected, mobilized, and repaired as in the transperitoneal laparoscopic pyeloplasty. The entire procedure is completed in an extraperitoneal manner. A surgical drain is similarly placed at the end of the procedure.

Robotic-Assisted Laparoscopic Approach. The robotic-assisted laparoscopic pyeloplasty in the experimental setting was first reported by Sung and colleagues (1999). Its feasibility was subsequently confirmed with worldwide clinical application in recent years (Gettman et al, 2002; Palese et al, 2005; Mufarrij et al, 2007; Schwentner et al, 2007; Yanke et al, 2008). The most widely used robotic system in the clinical setting today is the da Vinci Robotic System (Intuitive Surgical, Sunnyvale, CA), and the reported benefits of the robotic system include enhanced 3D vision, motion scaling, tremor reduction, improved dexterity, and increased range of motion. Typically the procedure is performed in a transperitoneal manner providing a larger working space for the robotic arms, although the feasibility of the retroperitoneal approach has been demonstrated (Kaouk et al, 2008; Cestari et al, 2010). A ureteral stent may be placed in a cystoscopic retrograde or laparoscopic antegrade manner. In both transperitoneal and retroperitoneal approaches, at least four trocars are used in a robotic-assisted procedure, including three for the robotic arms (including one for the camera) and one for the surgical assistant to perform suction, irrigation, retraction, and suture introduction. After the initial laparoscopic access and trocar placement, the robotic system is placed in close proximity to the operating table and the robotic arms are attached to the laparoscope and specifically designed laparoscopic instruments. The surgeon at the console operates via the control of the robotic arms, while the assistant remains at the bedside

and performs suction, retraction, exchange of laparoscopic instruments, suture needle introduction, and removal. The general surgical steps are identical to those described for non-robotic-assisted laparoscopic pyeloplasty.

Laparoendoscopic Single-Site Surgery Approach. Since the adoption of laparoscopic and robotic techniques, LESS has been developed in an effort to further decrease surgical invasiveness and improve morbidity (Kaouk et al, 2011). Proponents of the LESS approach suggest it may offer patients improved cosmetic outcomes by decreasing the number of ports from three, four, or five to a single periumbilical incision that is often hidden (Fig. 49-15). In LESS, all the instruments are inserted through a single location. This approach abandons the common laparoscopic principle of triangulation of the ports and results in ergonomic challenges and the clashing of instruments as they compete for space in a limited working envelope. Although this approach increases the level of complexity in performing the procedure, in experienced hands, complication rates of LESS pyeloplasty are similar to those with other minimally invasive approaches (Rais-Bahrami et al, 2013; Tugcu et al, 2013). Pyeloplasty is particularly appealing for LESS because there is no sizeable specimen to be extracted and the incisions can be kept small. However, laparoscopic suturing can be quite challenging in LESS, and some authors report using an accessory subcostal needlescopic instrument and port to facilitate anastomotic suturing.

Typically, a 2.5- to 3-cm intraumbilical or periumbilical incision is made using the Hasson technique. A variety of purpose-built LESS port devices are commercially available. Alternatively, three separate 5-mm ports can be placed in individual incisions inside the umbilicus. A 5-mm laparoscope is commonly used in LESS to reduce instrument conflict, and a right-angle adapter for the light cord can also be helpful to reduce external conflicts with other operating instruments. Various bent and articulating instruments are available to help reduce instrument conflicts ("sword fighting") inside the abdomen. Some surgeons have found a deflecting laparoscope to be helpful as well.

The technical challenges of LESS suturing have led some urologists to apply the robotic platform to LESS pyeloplasty. Just as the

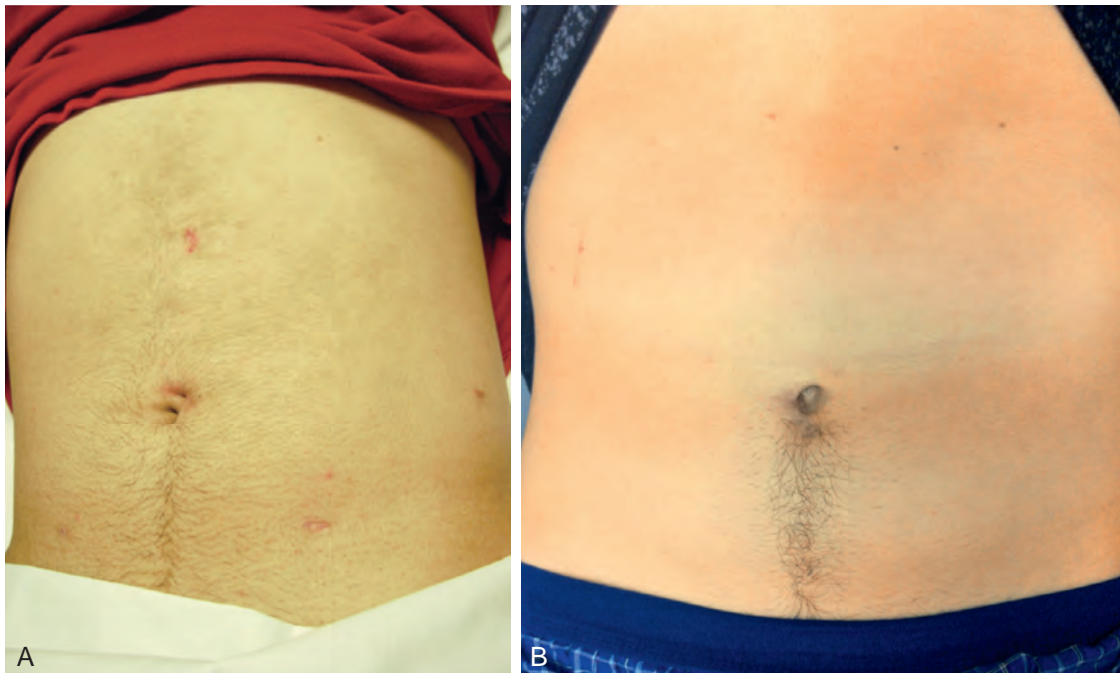


Figure 49-15. A, Postoperative photograph of the abdomen of a patient with left-sided laparoscopic dismembered pyeloplasty. Note the four small scars from the laparoscopic procedure. B, Postoperative appearance of the scar from a right-sided robotic laparoendoscopic single-site pyeloplasty, performed through a single incision at the umbilicus.

articulating instrumentation can shorten the learning curve and facilitate anastomotic reconstruction in standard robotic pyeloplasties, robotic LESS has been reported by several authors as having ergonomic advantages over standard LESS (Desai et al, 2009; Stein et al, 2010; Cestari et al, 2012; Olweny et al, 2012; Tobis et al, 2013). Purpose-designed equipment for robotic LESS remains limited at this time, but future technologic advances may further adoption of these advanced techniques. Renal functional outcomes of both LESS and robotic LESS pyeloplasty have been reportedly excellent, with symptomatic and radiographic success seen in 93% of patients in a recent study by Harrow and colleagues (2013).

Postoperative Care and Complications. Typically, a clear liquid diet is initiated on postoperative day 1 and advanced rapidly after minimally invasive pyeloplasty. Perioperative prophylactic antibiotic coverage is maintained. The Foley catheter is usually removed 24 to 36 hours postoperatively, and the surgical drain is removed before hospital discharge if the drain output remains negligible. If the drain output increases after the Foley catheter removal, the Foley catheter should be replaced for 7 days to eliminate urinary reflux along the stent in the treated ureter and decrease urinary extravasation at the ureteropelvic anastomosis. The ureteral stent is typically removed 4 to 6 weeks later in an outpatient setting, and follow-up including the use of imaging studies such as diuretic renal scan is performed as for an open pyeloplasty. Most of the complications of laparoscopic pyeloplasty are similar to those of general laparoscopic procedures including colonic injury, hemorrhage, ileus, pneumonia, congestive heart failure, thrombophlebitis, and urinoma formation. In the first 100 cases of laparoscopic pyeloplasty performed at Johns Hopkins (Jarrett et al, 2002), such complications occurred in 12% of the patients. Another large-scale review involving 189 cases of laparoscopic pyeloplasty identified an approximately 2% to 2.3% intraoperative complication rate and a 12.9% to 15.8% postoperative complication rate (Rassweiler et al, 2008).

Results

Open Approach. The overall success of open dismembered pyeloplasty has been favorable in the literature. In a retrospective review, Persky and colleagues (1977) noted that none of their 109 dismembered pyeloplasties for UPJO required subsequent nephrectomy. In another retrospective review involving 111 patients with UPJO undergoing open surgical repair over a 15-year-period, Clark and Malek (1987) found 95% success in resolution of clinical symptoms and 91% success in decompression of pelvicalyceal system on urography after one surgical repair. Of the 111 patients with open pyeloplasty, 95 patients (86%) underwent dismembered pyeloplasty. Examining the functional outcomes on the basis of split-function analysis from preoperative and postoperative renal scans, O'Reilly (1989) found that open Anderson-Hynes dismembered pyeloplasty arrested functional deterioration in almost every case and improved function significantly in the majority in 26 consecutive patients with UPJO.

Minimally Invasive Approaches. Most of the published laparoscopic pyeloplasty reports have used the classic Anderson-Hynes dismembered technique because most laparoscopic surgeons attempt to duplicate the well-established principles of open surgery (Bauer et al, 1999; Janetschek et al, 2000; Eden et al, 2001; Soulie et al, 2001; Jarrett et al, 2002; Turk et al, 2002; Inagaki et al, 2005; Bachmann et al, 2006; Rassweiler et al, 2008). The overwhelming majority of patients in these recent series had primary laparoscopic pyeloplasties, and the mean operative times were in the range of 119 to 252 minutes. In the experienced hands, the entire procedure can be consistently performed in less than 3.5 hours (Jarrett et al, 2002), reflecting greater confidence in intracorporeal suturing and knot tying. Perioperative complication rates are low, ranging from 2% to 15.8%, demonstrating the safety of the laparoscopic procedure. Open conversion rates are also low, in the range of 0% to 5.5%. Furthermore, blood transfusion risks are low, being limited to anecdotal reports. Postoperative analgesic use is usually minimal. Mean length of hospital stay ranges from 2.6 to 4.5 days, and the average has decreased to 3.8 days in the series reported since 2000. With mean follow-up times of 14 to 26 months, the rates of surgical

success (defined as durable clinical and/or radiographic success) reach the range of 87% to 99%, with the majority of contemporary series reporting success rates of greater than 95%. The safety and efficacy of laparoscopic pyeloplasty have also been demonstrated in the pediatric population, including patients younger than 1 year (Metzelder et al, 2006).

Most failures from laparoscopic pyeloplasty occur in the first 2 years, although up to 30% of failed cases may occur after 2 years postoperatively (Madi et al, 2008). For the patients in whom laparoscopic pyeloplasty fails, open surgery has been used as a salvage procedure, with success rates of approximately 86% (Thomas et al, 2005). However, most patients can be well managed with endoscopic intervention such as endopyelotomy, with success rates of approximately 70% (Varkarakis et al, 2004).

More data on robotic-assisted laparoscopic pyeloplasty have emerged recently (Table 49-1) (Palese et al, 2005; Mufarrij et al, 2007; Schwentner et al, 2007; Yanke et al, 2008). As in the conventional laparoscopic studies, the overwhelming majority of the patients in these recent series had primary robotic-assisted laparoscopic pyeloplasties. The mean operative times are in the range of 100 to 299 minutes. Perioperative complication rates are low (3% to 24%). Open conversion rates are also relatively low (0% to 6.8%). Postoperative analgesic use is typically minimal. Mean length of hospital stay is in the range of 2.2 to 2.8 days. With mean follow-up times of 11 to 39.1 months, the rates of surgical success (defined as durable clinical and/or radiographic success) are in the range of 94.7% to 100%. These results were similar to those from the historic laparoscopic series in the literature. The feasibility of the robotic approach has also been demonstrated in pediatric patients (Atug et al, 2005b; Lee et al, 2006). The additional reported benefits provided by the robot include better 3D magnification, increased range of motion, and ease of dissection and suturing. However, the value of the robot in the setting of clinical pyeloplasty remains controversial and has been addressed by one recent study (Link et al, 2006). In this study comparing robotic and laparoscopic pyeloplasty in a prospective manner, the mean operative time and total room time for robotic cases were found to be significantly longer than for laparoscopic cases by 19.5 and 39 minutes, respectively. Robotic cases were also found to be more costly than laparoscopic cases (2.7 times) owing to longer operative time, increased consumables costs, and depreciation of the robot system. In the hands of experienced laparoscopic surgeons, the use of the robot does not seem to provide significant clinical or cost advantage compared with the conventional laparoscopic approach. In addition to cost, other concerns related to robotic-assisted laparoscopic pyeloplasty include limited instrumentation and need for experienced bedside laparoscopic assistance (Peschel et al, 2004).

To date, no prospective randomized trial has been performed comparing laparoscopic and open pyeloplasty. The unwillingness of the patients to undergo randomization because of the different levels of perceived invasiveness appears to be the most significant barrier to completing such studies. Although the success rates of pyeloplasty are, in general, high, late failures can occur and long-term follow-up may be helpful in identifying these patients. DiMarco and colleagues (2006) reported that success rates of pyeloplasty in their series of 175 patients dropped from 85% at 3 years to 75% at 10 years, lower than they anticipated.

Primary UPJO associated with renal anomalies such as horseshoe kidneys and pelvic kidneys has also been managed with laparoscopic pyeloplasty safely and successfully (Janetschek et al 1996; Hsu et al 2003; Bovie et al 2004). Furthermore, secondary UPJO has similarly been managed with success. In a retrospective review, Sundaram and colleagues (2003) identified 36 cases of laparoscopic transperitoneal pyeloplasty for secondary UPJO, mostly following failed retrograde or antegrade endopyelotomies. Mean operative time was 6.2 hours, longer than the reported times associated with primary UPJO. Open conversion was necessary in 1 patient, and postoperative complication occurred in 8 patients. With a mean follow-up of 21.8 months, the overall success rate involving a greater than 50% decrease in pain, a patent UPJ, and stable or improved function of the affected renal unit was 83% (30 of 36 patients).

TABLE 49-1 Comparative Series of Robotic versus Laparoscopic Pyeloplasty

AUTHOR, YEAR		n	MEAN AGE (yr)	EBL (mL)	OR TIME (min)	DURATION OF FOLLOW-UP			HOSPITAL STAY (DAYS)	COMPLICATIONS	SUCCESS RATES
						(MONTHS)	(MONTHS)	(MONTHS)			
Link et al, 2006	LP	10	38.0	NSD	80.7 ± 21.9*	5.6				None	100% (authors note short follow-up limits meaning of success)
	RAP	10	46.5	NSD	100.2 ± 9.1*	5.6				10% (1 delayed urine leak)	100%
Weise and Winfield, 2006	LP	14	24.5		271	10		2		0	100% (64% "strict" success; no pain and no obstruction on nuclear scan)
	RAP	31	26		299	6		2		0	97% (66% "strict" success)
Kim et al, 2008	LP	58	Peds		196 ± 38			0.9 ± 0.23		3.4%	97%
	RAP	84	Peds		188 ± 45.8			1.5 ± 0.55		0	99%
Hemal et al, 2010	LP	30	28.1	100	145 ± 44	18		5.5 ± 3.8		10%	97%
	RAP	30	24.9	40	99 ± 29	18		2.5 ± 0.8		3.3%	93%
García-Galisteo et al, 2011	LP	33	NR	NR	152.1 ± 23.3	42.5		4.5 ± 1.5		51.5%	93.9%
	RAP	17	NR	NR	121.6 ± 13.3	20.6		2.4 ± 0.5		23.5%	94.1%
Olweny et al, 2012†	LP (LESS)	10	35.8	42	188	10		2.6		20	88%
	RAP (LESS)	10	40.3	56	226	3		2.6		10	100%
Kumar and Nayak, 2013	LP	11	25	46	150 (11-200)	NR		2.9		None	100%
	RAP	19	21	54	129 (70-180)	NR		2.8		None	100%

*Significant difference, $P = .018$.

†LESS LP versus LESS RAP.

EBL, estimated blood loss; LESS, laparoendoscopic single-site surgery; LP, laparoscopic pyeloplasty; NR, not reported; NSD, no significant difference; OR, operating room; Peds, pediatric cases only; RAP, robotic assisted pyeloplasty.

Shapiro and colleagues (2009) identified 9 cases of laparoscopic transperitoneal pyeloplasty for secondary UPJO after a failed open procedure. Mean operative time was 204 minutes. At a median follow-up of 66 months, 89% (8 of 9) patients had clinical and radiologic resolution of UPJO, with stable renal function, pain-free status, and patent UPJ.

Special Situations of Laparoscopic and Robotic-Assisted Laparoscopic Management of Ureteropelvic Junction Obstruction

Laparoscopic and Robotic-Assisted Laparoscopic Ureterocalicostomy. Ureterocalicostomy has been completed successfully via both laparoscopic and robotic-assisted laparoscopic approaches. Gill and colleagues (2004) performed laparoscopic ureterocalicostomy in two patients with UPJO associated with small renal pelvis and dilated lower pole calix. In both patients a double-J ureteral stent was first placed into the ipsilateral ureter cystoscopically. With the patient in a 45- to 60-degree flank position, a transperitoneal approach using three or four ports was used to gain access to the ipsilateral renal unit laparoscopically. A circular rim of the tip of the thin lower pole renal parenchyma was identified and excised. The UPJ was transected, followed by ligation of the renal pelvic opening. The ureter was spatulated laterally, and end-to-end ureterocalyceal anastomosis with mucosa-to-mucosa apposition over the preplaced double-J stent was performed with freehand intracorporeal suturing and knot-tying techniques. The general reconstructive principles are identical to those of open ureterocalicostomy described previously, including the need to achieve tension-free, watertight, dependent drainage.

The largest series of laparoscopic ureterocalicostomies reports outcomes in six procedures. All six remain successful radiographically at a mean of 30 months' follow-up, and there were no major complications (Arap et al, 2014).

Casale and colleagues (2008) reported successful robotic-assisted laparoscopic ureterocalicostomy in nine pediatric patients, following the identical reconstructive principles described earlier. Mean operative time was 168 minutes, and feasibility of the use of the robot was well demonstrated. All patients were found to have no evidence of obstruction on diuretic radionuclide imaging at 12 months postoperatively.

Laparoscopic and Robotic-Assisted Pyeloplasty with Concomitant Pyelolithotomy. Presence of calculi in the setting of UPJO can be managed laparoscopically with success. In a retrospective review, Ramakumar and colleagues (2002) reported 20 cases of laparoscopic pyeloplasty with concomitant extraction of renal stones through the pyelotomy site under laparoscopic guidance. In the series, extraction of the calyceal stones was assisted by the use of a flexible cystoscope introduced through a 10- to 12-mm port site. At a mean follow-up of 3 months, 90% of patients were stone free, and 90% patients had patent UPJ radiographically. In another retrospective review, Stein and colleagues (2008) reported 15 cases of laparoscopic pyeloplasty with concomitant pyelolithotomy, involving the use of laparoscopic graspers, flexible cystoscopes, and/or laparoscopic irrigation. The overall stone-free rate was 80%. Robotic-assisted laparoscopic pyeloplasty with concomitant pyelolithotomy, using similar instruments including laparoscopic graspers, has also been demonstrated in 8 patients (Atug et al, 2005a). To complete the pyelolithotomy, one of the robotic arms was temporarily undocked to allow passage of a flexible nephroscope into the renal pelvis to gain visualization of the stones in the collecting system. In this small series, all patients were rendered stone free.

Laparoscopic Dismembered Tubularized Flap Pyeloplasty. Presence of a significant upper ureteral defect after the excision of UPJ stricture may also be managed laparoscopically with success. Kaouk and colleagues (2002) described a case of laparoscopic pyeloplasty for secondary UPJO, in which a 3-cm upper ureteral defect was found after excision of the long stricture. Using a four-port transperitoneal approach, a wide-base renal pelvic flap was created and tubularized to bridge the defect, using intracorporeal freehand

suturing techniques. At a 2-month follow-up, excretory urography and diuretic renal scan confirmed a widely patent upper ureter.

Laparoscopic Calicovesicostomy. Presence of a large-capacity bladder in the setting of UPJO associated with a low-lying obstructed renal unit can be managed successfully using an unconventional laparoscopic reconstructive strategy. Hsu and colleagues (2006) described a case of laparoscopic management of UPJO involving a horseshoe kidney with a unilateral hydronephrotic yet functioning lower pole moiety, ipsilateral ureteral duplication with high bifurcation, and complex anomalous renal vasculature. Rather than performing tedious anatomic dissection and complex ureteral reconstruction in such a scenario as required in conventional laparoscopic pyeloplasty, a nephrotomy was created at the most dependent portion of the hydronephrotic lower pole moiety and then laparoscopically anastomosed to the bladder dome vesicostomy using intracorporeal freehand suturing and knot-tying techniques. At the 4-month follow-up, patent calicovesicostomy was confirmed endoscopically and clinically.

KEY POINTS: LAPAROSCOPIC AND ROBOTIC INTERVENTION

- Transperitoneal laparoscopic approach is the most widely used method owing to its associated large working space and familiar anatomy.
- Retroperitoneal laparoscopic approach and anterior extraperitoneal approach rely on creation of a working space using manual or balloon dilation.
- Laparoscopic management of UPJO has been shown to provide a low perioperative complication rate, a short hospital stay, and success rates greater than 95% in experienced hands.

Other Reconstructive Procedures Involving the Ureteropelvic Junction (Non-Anderson-Hynes)

Although the Anderson-Hynes dismembered pyeloplasty is the most commonly performed technique for reconstruction of the UPJ, other techniques or modifications may be useful in particular situations as dictated by patient anatomy. These variations can in many cases be performed through either open or minimally invasive approaches, depending on the skill level of the surgeon.

Flap Procedures

Foley Y-V Plasty

Indications. The Foley Y-V plasty was originally designed for repair of an UPJO. Secondary to a high ureteral insertion. Like other flap techniques, however, its use has in general been replaced by the more versatile dismembered pyeloplasty. As with other flap techniques, the Foley Y-V plasty is specifically contraindicated when transposition of lower pole vessels is necessary. In situations requiring concomitant reduction of redundant renal pelvis, this technique is also of little value.

Technique. In Foley Y-V plasty, the renal pelvis and proximal ureter are first exposed, and a widely based triangular or V-shaped flap is outlined with methylene blue or fine stay sutures. The base of the V is positioned on the dependent, medial aspect of the ipsilateral renal pelvis and the apex at the UPJ. The incision from the apex of the flap (the stem of the Y) is then performed along the lateral aspect of the proximal ureter. The surgical incision in the ureter should be long enough to completely traverse the area of stenosis and extend for several millimeters into the normal-caliber ureter (Fig. 49-16A). The renal pelvic flap and ureterotomy are then created. A fine scalpel blade is used for the initial pelvic incision, after which Potts or fine Metzenbaum scissors are used to complete the flap and ureterotomy (Fig. 49-16B). An internal ureteral stent is placed and the repair performed over it. First, the apex of the pelvic flap is approximated to the apex (inferior aspect) of the

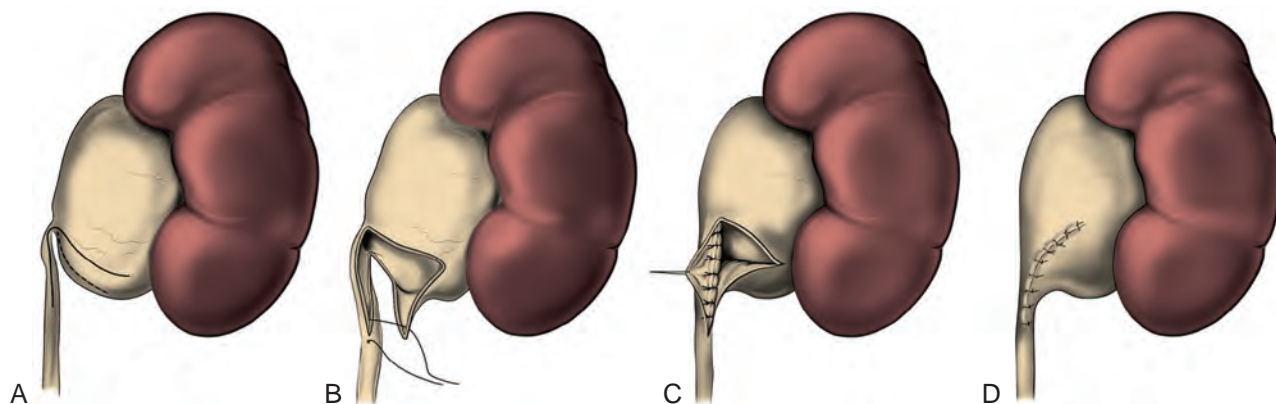


Figure 49-16. A, Foley Y-V plasty is best applied to a ureteropelvic junction (UPJ) obstruction associated with a high insertion of the ureter. The flap is outlined with tissue marker or stay sutures. The base of the V is positioned on the dependent, medial aspect of the renal pelvis and the apex at the UPJ. The incision from the apex of the flap, which represents the stem of the Y, is then carried along the lateral aspect of the proximal ureter well into an area of normal caliber. B, The flap is developed with fine scissors. The apex of the pelvic flap is then brought to the most inferior aspect of the ureterotomy incision. C, The posterior walls are then approximated using interrupted or running fine absorbable suture. D, The anastomosis is completed with approximation of the anterior walls of the pelvic flap and ureterotomy.

ureterotomy incision using fine absorbable suture. The posterior walls are then approximated using fine interrupted or running suture (Fig. 49-16C). Interrupted technique is likely to minimize pursing or buckling of the suture line, as well as local tissue ischemia. Anastomosis of the anterior walls is then performed, thereby completing the surgical repair (Fig. 49-16D).

Culp-DeWeerd Spiral Flap

Indications. In general, the Culp-DeWeerd spiral flap is best suited for large, readily accessible extrarenal pelves in which the ureteral insertion is already in a dependent, oblique position. Although most of these patients are also good candidates for a standard or reduction dismembered pyeloplasty, the spiral flap may be of significant value when both UPJO and a relatively long segment of proximal ureteral narrowing or stricture occur in the same setting.

Technique. The spiral flap is first outlined with a broad base positioned obliquely on the dependent aspect of the renal pelvis. To maximize preservation of the flap blood supply, the base is placed in a position anatomically lateral to the UPJ, that is, between the ureteral insertion and the renal parenchyma. The pelvic flap itself may be spiraled posteriorly to anteriorly or vice versa. In either case, the anatomically medial line of incision (farthest from the parenchyma) is carried down the proximal ureter, completely traversing through the obstructed segment (Fig. 49-17A). Appropriate placement of the apex of the flap is determined by the length of flap needed. This, in turn, depends on the length of proximal ureter to be bridged. The longer the flap required, the farther away the apex will be from the base. However, to preserve vascular integrity of the flap, the ratio of flap length to width should not be greater than 3:1. In general, the outline of the flap should be made longer than what may initially be perceived as necessary, because the flap will shrink once the pelvis is incised. If the flap is found to be too long, excess length can be reduced by trimming back the apex, thereby preserving its blood supply. Once the flap has been created, the apex is rotated down to the most inferior aspect of the ureterotomy (Fig. 49-17B). The anastomosis with fine absorbable sutures is subsequently performed over an internal stent (Fig. 49-17C).

Scardino-Prince Vertical Flap

Indications. In general, the Scardino-Prince vertical flap technique has limited clinical application. It may be appropriately used only when a dependent UPJ is situated at the medial margin of a large, square ("box-shaped") extrarenal pelvis (Fig. 49-18A). Its use in most instances has been replaced by a standard dismembered

pyeloplasty, although the vertical flap may be preferable for relatively long areas of proximal ureteral narrowing. It is important to note that the vertical flap technique typically cannot produce as long a flap as the spiral flap.

Technique. The Scardino-Prince vertical flap is similar to the spiral flap technique except that the base of the flap is positioned more horizontally on the dependent aspect of the renal pelvis, between the UPJ and the renal parenchyma. The flap itself is created by straight incisions converging from the base vertically to the apex on either the anterior or the posterior aspects of the renal pelvis. The site of the apex and the length of the flap are determined by the length of proximal ureter to be bridged. The medial incision is carried down the proximal ureter, completely traversing through the stenotic area and into normal-caliber ureter, using fine scissors (Fig. 49-18B). The apex of the flap is then rotated down and approximated to the most inferior aspect of the ureterotomy. Finally, the flap is closed with interrupted or running fine absorbable sutures (Fig. 49-18C).

Intubated Ureterotomy

Indications. The Davis intubated ureterotomy, which is rarely used today, was developed for surgical repair of lengthy or multiple ureteral strictures. If these strictures are found in association with UPJO, the intubated ureterotomy may be combined with any of the standard pyeloplasty procedures. However, in such situations the intubated ureterotomy would be best combined with a spiral flap procedure. Compared with the vertical flap, the spiral flap can be made longer, which allows more of the strictured area to be bridged by a pelvic flap, thereby leaving a shorter area to rely on healing by secondary intention. In fact, in this specific clinical setting, any flap technique would be preferable to a dismembered repair, at least with regard to blood supply preservation and subsequent healing.

Technique. A flap is outlined as described previously, with the ureterotomy to be made completely through the long, strictured area (Fig. 49-19A). The flap is then created, with minimal dissection of the ureter to preserve its blood supply. Unlike uncomplicated pyeloplasties, these cases require routine nephrostomy tube drainage to prevent postoperative urinoma formation. Nephrostomy drainage in these cases also allows access for subsequent antegrade radiographic studies during the postoperative period.

On the basis of the original description, the ureteral intubation is achieved with a stenting catheter that is placed across the stenotic area to the distal ureter or bladder. Proximally, it is brought out through the renal cortex alongside a nephrostomy tube. Currently,

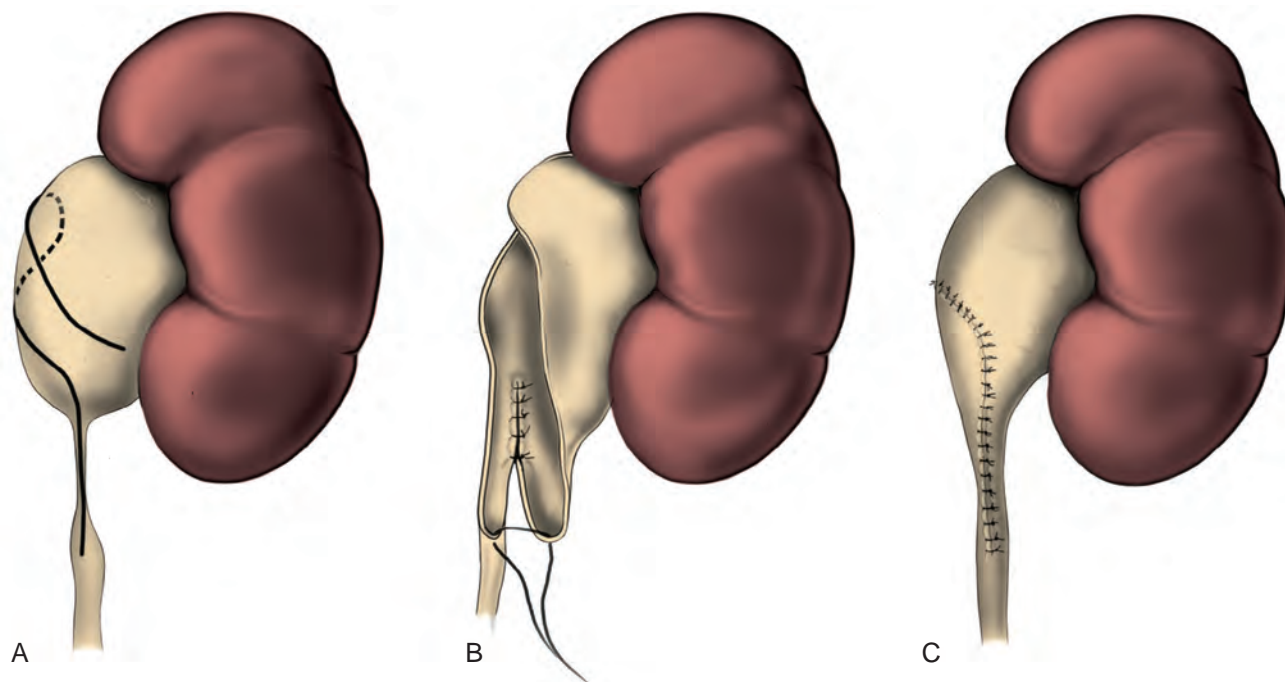


Figure 49-17. A, A spiral flap may be indicated for relatively long areas of proximal ureteral obstruction when the ureteropelvic junction (UPJ) is already in a dependent position. The spiral flap is outlined with the base situated obliquely on the dependent aspect of the renal pelvis. The base of the flap is positioned anatomically lateral to the UPJ, between the ureteral insertion and the renal parenchyma. The flap is spiraled posteriorly to anteriorly or vice versa. The anatomically medial line of incision is carried down completely through the obstructed proximal ureteral segment into normal-caliber ureter. The site of the apex for the flap is determined by the length of flap required to bridge the obstruction. The longer the segment of proximal ureteral obstruction, the farther away is the apex because this will make the flap longer. However, to preserve vascular integrity of the flap, the ratio of flap length to width should not exceed 3:1. B, Once the flap is developed, the apex is rotated down to the most inferior aspect of the ureterotomy. C, The anastomosis is then completed, usually over an internal stent, again using fine absorbable sutures.

most urologists use a self-retaining, soft, inert, internal ureteral stent instead. The apex of the flap is brought over the stent as far down as possible on the ureterotomy, and the flap is closed with either interrupted or running absorbable suture (Fig. 49-19B). The distal aspect of the ureterotomy is then left open for secondary healing via ureteral regeneration (Fig. 49-19C).

An antegrade nephrostogram is usually obtained 6 weeks after the surgery. If there is no extravasation, the ureteral stent is removed cystoscopically and an antegrade radiographic study is repeated. When ureteral patency without extravasation is ensured with such study, the nephrostomy tube is clamped and subsequently removed.

Ureterocalicostomy

Indications. Ureterocalicostomy may be used as a primary reconstructive procedure whenever an UPJO or proximal ureteral stricture is associated with a relatively small intrarenal pelvis (Fig. 49-20A).

When the UPJ is associated with rotational anomalies such as horseshoe kidney (Levitt et al, 1981), ureterocalicostomy may be useful to provide completely dependent drainage. Furthermore, ureterocalicostomy is a well-accepted salvage technique for the failed pyeloplasty (Ross et al, 1990).

Technique. The ureter is first identified in the retroperitoneum and dissected proximally with a generous amount of periureteral tissue. For secondary procedures, however, extensive scarring may preclude adequate identification and dissection of the renal pelvis itself (Fig. 49-20B). The kidney is then mobilized to gain access to the lower pole. An important technical point in ureterocalicostomy is that the parenchyma overlying the lower pole calyx must be resected rather than simply incised because a simple nephrotomy may lead to a secondary stricture (Couvelaire et al, 1964).

The proximal ureter is first spatulated laterally, and the ureterocalyceal anastomosis is completed over an internal stent. Leaving an indwelling nephrostomy tube should also be considered in these patients. The first suture is placed at the apex of the ureteral spatulation and lateral wall of the calyx, and the second suture is placed 180 degrees away. The remainder of the anastomosis is then performed using an interrupted open suture technique—that is, each suture placed is left untied until the final one is in place (Fig. 49-20C). This method seems to provide a more accurate anastomosis under direct vision. When the full set of circumferential sutures has been placed, the sutures are secured down together (Fig. 49-20D). The renal capsule is closed over the cut surface of the parenchyma if possible. However, such closure should not be close enough to the anastomosis itself to cause extrinsic compression on the anastomosis. Instead, the anastomosis should be covered with perinephric fat or a peritoneal or omental flap (Fig. 49-20E). A follow-up urogram is usually obtained 1 month after the ureteral stent extraction (Fig. 49-20F).

Reports exist of laparoscopic and robotic ureterocalicostomy (Gill et al, 2004; Korets et al, 2007; Casale et al, 2008). Arap and colleagues (2014) reported 100% success at a mean of 30 months after laparoscopic ureterocalicostomy in six patients.

Salvage Procedures. Failed open pyeloplasty is a challenging problem that is usually best managed initially with an endourologic approach. In some patients, such an approach may not be applicable. In these cases, successful reconstruction can at times be achieved using one of the flap or dismembered techniques already described. The secondary open operative reconstruction may be significantly aided by the placement of a ureteral catheter

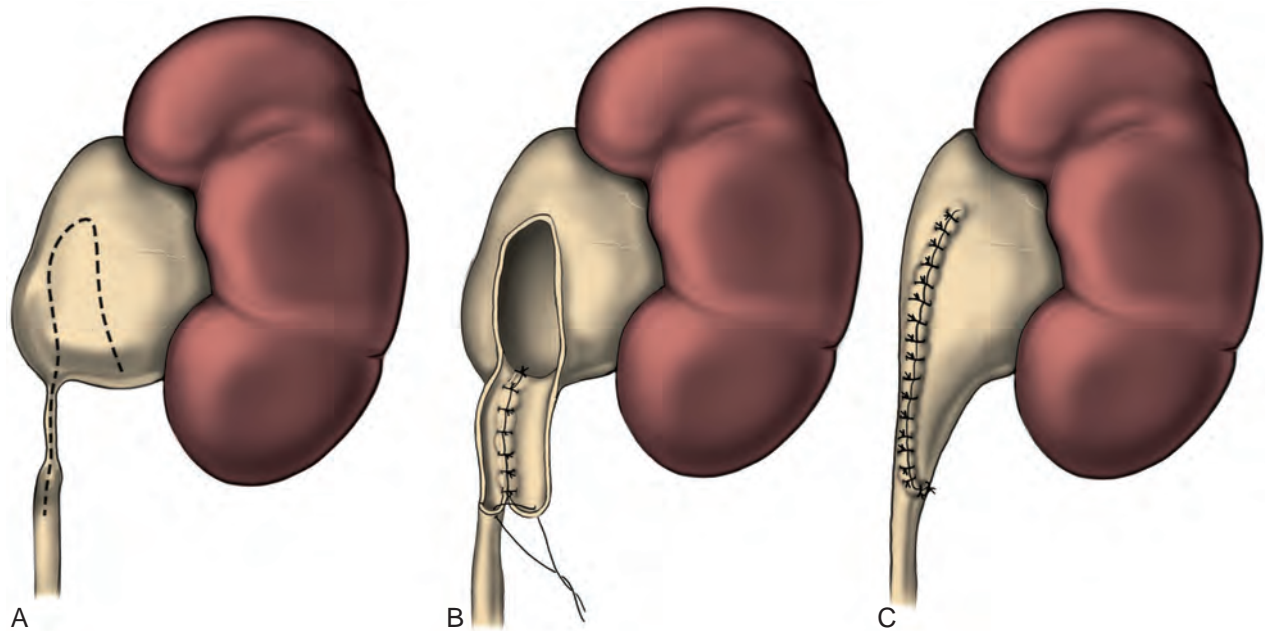


Figure 49-18. A, A vertical flap technique may be used when a dependent ureteropelvic junction (UPJ) is situated at the medial margin of a large, box-shaped extrarenal pelvis. In contrast to the spiral flap, the base of the vertical flap is situated more horizontally on the dependent aspect of the renal pelvis, between the UPJ and the renal parenchyma. The flap itself is formed by two straight incisions converging from the base vertically up to the apex on either the anterior or the posterior aspect of the renal pelvis. As for the spiral flap, the position of the apex determines the length of the flap, which should be a function of the length of proximal ureter to be bridged. The medial incision of the flap is carried down the proximal ureter completely through the strictured area into normal-caliber ureter. B, The apex of the flap is rotated down to the most inferior aspect of the ureterotomy. C, The flap is then closed by approximating the edges with interrupted or running fine absorbable sutures.

to aid intraoperative identification and dissection of the ureter and renal pelvis. In these situations, there is often a relatively long length of proximal ureteral stenosis to repair, and wide mobilization of the kidney and ureter is usually a necessity. This helps to bridge the area of stenosis and allows a tension-free secondary pyeloplasty.

Several other options are available for these secondary and often complex repairs. These surgical alternatives include those generally available for any extensive ureteral problem such as ileoureteral replacement and autotransplantation with a Boari flap pyelovesicostomy. For cases in which function of the involved kidney is already significantly compromised and the contralateral kidney is normal, nephrectomy can be considered.

Postoperative Care and Management of Complications. In general, external drains are removed 24 to 48 hours after cessation of urinary drainage, and internal ureteral stents, if placed, are removed on an outpatient basis approximately 4 to 6 weeks after the surgery. If a nephrostomy tube is used, a nephrostogram is obtained no sooner than 7 to 10 days postoperatively, or even later for particularly complicated repairs. If nephrostogram demonstrates a patent anastomosis without obstruction or extravasation, the tube is clamped for 12 to 24 hours and removed if there is no flank pain, fever, or leakage around the tube.

RETROCAVAL URETER

Etiology and Diagnosis

Retrocaval ureter is a rare congenital urologic anomaly. It occurs as a consequence of the persistence of the posterior cardinal veins during embryologic development (Considine, 1966). Its presence should be suspected with the finding of a

characteristic S-shaped deformity on intravenous or retrograde pyelography (Fig. 49-21A). Today, a definitive diagnosis can be made noninvasively using 3D CT imaging (Fig. 49-21B) (Pienkny et al, 1999). Procedural intervention is indicated in the presence of functionally significant obstruction leading to pain or renal function deterioration.

Operative Intervention

Open Surgical Management

The standard repair of retrocaval ureter is open surgical pyelopyelostomy. In this procedure, the ureter, dilated renal pelvis, and inferior vena cava are identified and dissected using the standard open surgical techniques. The dilated renal pelvis is then transected, then the ureter is transposed to its normal anatomic position anterior to the vena cava (Fig. 49-22). Pyelopyelostomy is then performed circumferentially with absorbable sutures in a tension-free, watertight manner. A surgical drain and internal ureteral stent are typically used.

Laparoscopic Surgical Management

Retrocaval ureter has been managed successfully with the laparoscopic approach in the clinical setting as shown by a series of sporadic case reports (Baba et al, 1994; Matsuda et al, 1996; Polascik and Chen, 1998; Salomon et al, 1999; Gupta et al, 2001; Ramalingam and Selvarajan, 2003). Either a transperitoneal or a retroperitoneal approach may be used laparoscopically. A double-J ureteral stent is first placed into the ipsilateral ureter cystoscopically. After transperitoneal or retroperitoneal laparoscopic access has been achieved, the ipsilateral ureter is identified and mobilized off the

inferior vena cava. The ureter is then divided at the most distal segment of the dilated ureter. A redundant segment of dilated proximal ureter and stenotic segment of ureter are excised if present. The ureteral ends are positioned anterolateral to the vena cava, spatulated for 1.5 to 2 cm on opposite ends, and then anastomosed with absorbable sutures applied with intracorporeal suturing techniques over the stent. Tension-free, watertight anastomosis is the objective. A surgical drain is then left in place before formal laparoscopic exit. The surgical drain is typically removed within a few days postoperatively, and the ureteral stent is typically removed 4 to 6 weeks postoperatively.

More recently, retrocaval ureter has been managed successfully with the robotic-assisted laparoscopic approach (Mufarrij et al, 2007; Hemal et al, 2008; Smith et al, 2009). A transperitoneal approach providing a large working space is typically used. The general principles of laparoscopic ureteral dissection, division, transposition, and anastomosis are identical to those described in conventional laparoscopic approach. At least four different ports are involved, including three for the robot and one for the surgical assistant providing suction, irrigation, suture introduction, and retraction.

The overall clinical results of the laparoscopic repair with or without the use of robots in the literature have been favorable,

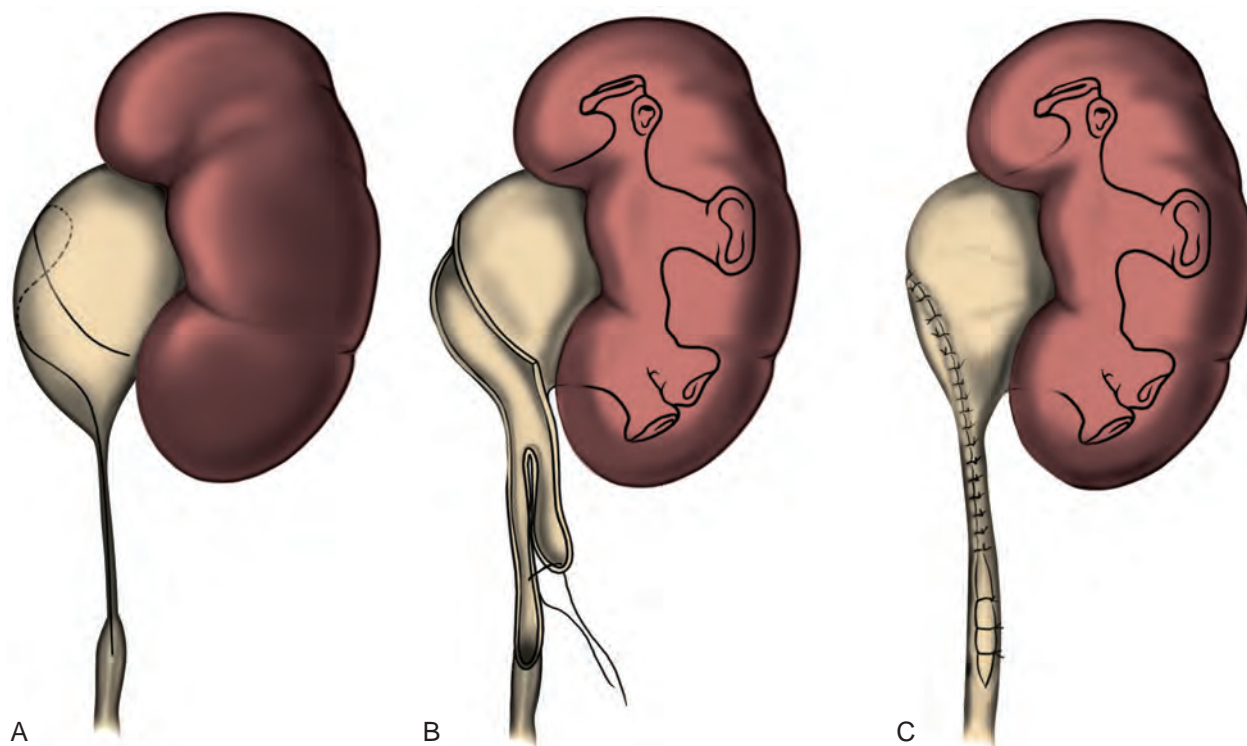
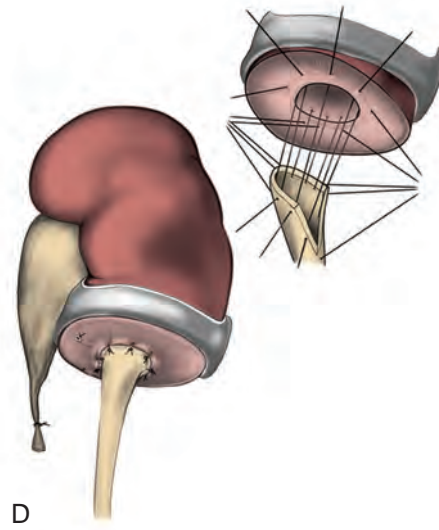
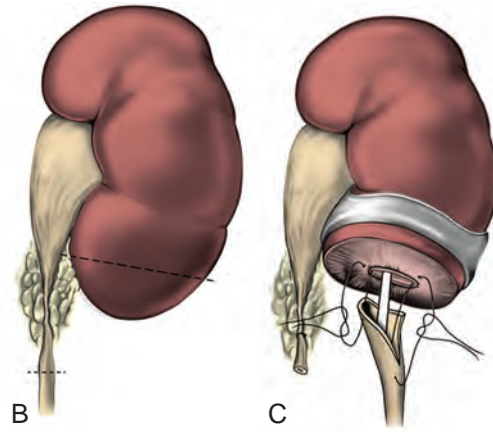
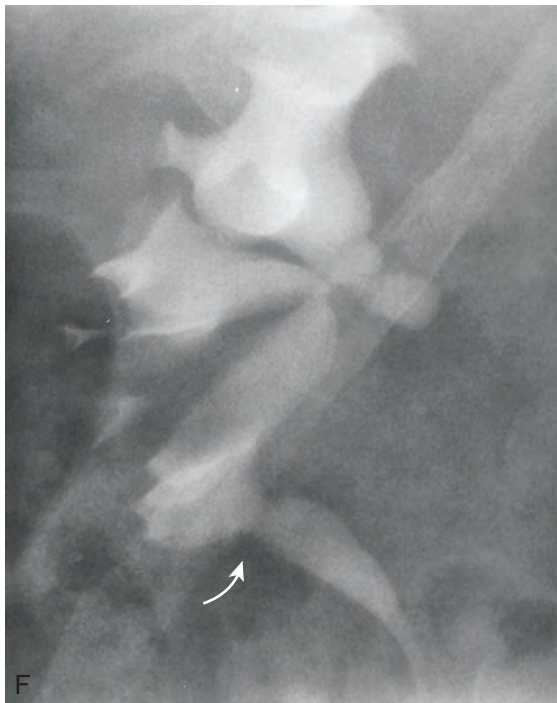


Figure 49-19. A, Intubated ureterotomy may be of value when a ureteropelvic junction obstruction is associated with extremely long or multiple ureteral strictures. A spiral flap is outlined and developed as described in Figure 49-20. The ureterotomy incision will be carried completely through the long strictured areas or through each of the multiple areas of stricture. B, The flap is developed, taking care to use minimal dissection of the ureter to preserve its blood supply. In contrast to uncomplicated repairs, nephrostomy tube drainage is used routinely. A self-retaining, soft, inert internal ureteral stent is then placed and positioned proximally in the renal pelvis or lower infundibulum and distally in the bladder. The apex of the flap is then brought as far down as possible over the stent on the ureterotomy, and the flap is closed with interrupted or running absorbable suture. C, The distal aspect of the ureterotomy is left open to heal secondarily by ureteral regeneration. A few fine absorbable sutures may be loosely placed to keep the sides of the ureter in apposition to the stent.

Figure 49-20. A, This patient reported progressive right flank pain and was found on this retrograde study to have a ureteropelvic junction obstruction (arrow) associated with a small intrarenal pelvis. This situation may be best managed with a ureterocalicostomy. B, The ureter is identified in the retroperitoneum and dissected proximally as far as possible. The kidney is mobilized as much as necessary to gain access to the lower pole and to subsequently perform the anastomosis without tension. A lower pole nephrectomy is performed, removing as much parenchyma as necessary to widely expose a dilated lower pole calyx. C, The proximal ureter is spatulated laterally. The anastomosis should subsequently be performed over an internal stent, and consideration should also be given to leaving a nephrostomy tube. The initial sutures are placed at the apex of the ureteral spatulation, and the lateral wall of the calyx with a second suture is placed 180 degrees from that. D, Anastomosis is then completed in an open fashion, placing each suture circumferentially (inset) but not securing them down until the anastomosis has been completed. E, Renal capsule is closed over the cut surface of the parenchyma whenever possible. However, the capsule should not be closed near the anastomosis itself because that may compromise the lumen by extrinsic compression. Instead, the anastomosis should be protected with a graft of perinephric fat or a peritoneal or omental flap. F, Intravenous urogram 2 months after right ureterocalicostomy reveals a widely patent ureterocalyceal anastomosis at the lower pole (arrow).



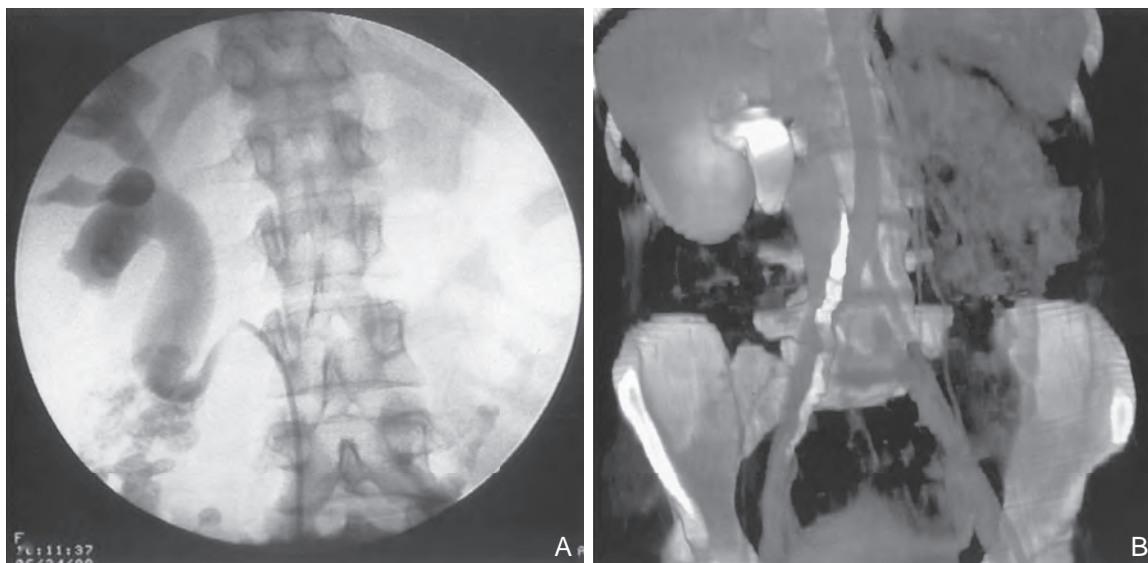


Figure 49-21. A, Retrograde pyelography in a patient with right-sided hydronephrosis. This study reveals a typical S-shaped deformity secondary to the ureter coursing laterally to medially posterior to the inferior vena cava. B, Three-dimensional spiral computed tomography demonstrates the presence of a retrocaval ureter.

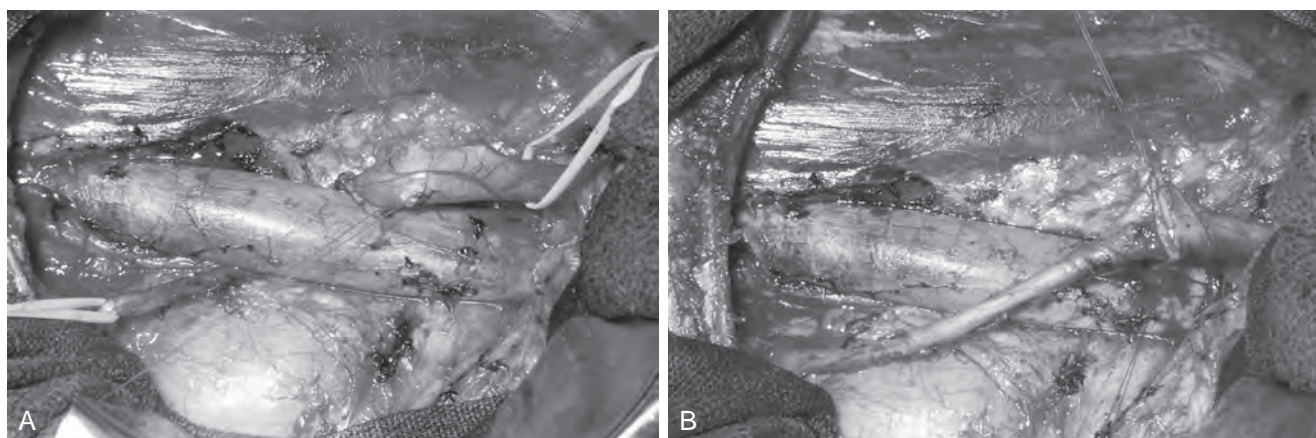


Figure 49-22. A, Intraoperative photograph of a patient with retrocaval ureter undergoing surgical repair via a retroperitoneal flank approach. Right side of the photo represents the cephalad direction. Note the dilated proximal right ureter passing behind the inferior vena cava. B, Right ureteropelvic anastomosis has been completed after transection of the right renal pelvis and transposition of the ureter anterior to the inferior vena cava.

indicating minimal postoperative patient morbidity, short convalescence, and anastomotic patency on short-term radiographic follow-up.

KEY POINTS: RETROCAVAL URETER

- Retrocaval ureter results from the persistence of the posterior cardinal veins.
- Retrocaval ureter can be diagnosed using intravenous or retrograde pyelography or 3D CT.
- Procedural intervention is indicated in the presence of functionally significant obstruction, and both open and laparoscopic approaches can be successfully applied.

URETERAL STRICTURE DISEASE

Etiology

Common causes of ureteral stricture formation include ischemia, surgical and nonsurgical trauma, periureteral fibrosis, malignancy, and congenital factors ([Box 49-1](#)). Proper evaluation and treatment of a ureteral stricture is essential to preserve renal function and rule out the presence of malignancy. Although the classic radiographic presentation of a transitional cell carcinoma of the ureter is a radiolucent filling defect within the lumen with the characteristic goblet sign, it may have the same appearance as a benign stricture. In addition, metastatic tumors such as cervical, prostate, ovarian, breast, and colon cancer may appear as a ureteral stricture ([Lau et al, 1998](#)). Although the incidence of ureteral

BOX 49-1 Etiology of Ureteral Stricture

Malignancy (e.g., transitional cell carcinoma, cervical cancer)
 Ureteral calculus
 Radiation
 Ischemia or trauma caused by surgical dissection
 Periureteral fibrosis caused by abdominal aortic aneurysm or endometriosis
 Endoscopic instrumentation
 Renal ablation injury
 Infection (tuberculosis)
 Idiopathic condition

strictures in the general population is unknown, it is clear that the presence of ureteral calculi and associated treatment of stones are risk factors. Roberts and colleagues (1998) evaluated 21 patients with impacted ureteral stones and found that impaction for more than 2 months' duration was associated with a 24% incidence of stricture formation. Any ureteral instrumentation can lead to the development of a ureteral stricture. As advances in ureteroscopic technology have provided smaller, more actively deflecting instruments with digital optics, ureteroscopic procedures have become less traumatic and are now associated with a long-term complication rate of less than 5% (Harmon et al, 1997; Delvecchio et al, 2003; Ambani et al, 2013). Moreover, more urologists are comfortable with endoscopic incisions as a result. Other causes of benign ureteral strictures include radiation; abdominal aortic aneurysm; infections such as tuberculosis and schistosomiasis; endometriosis; and trauma including iatrogenic injury from previous abdominal or pelvic surgery or post-renal ablation injury (ElAbd et al, 1996; Lacquet et al, 1997; Ramanathan et al, 1998; Oh et al, 2000; Johnson et al, 2004). Patients with presumed idiopathic ureteral strictures should be evaluated with CT scan to rule out the presence of an intrinsic ureteral malignancy or a lesion causing extrinsic compression.

Diagnostic Studies and Indications for Intervention

The presence of obstruction on standard CT can identify ureteral stricture disease, but antegrade or retrograde pyelogram, CT urography, or diagnostic ureteroscopy is necessary to define the location and length of the ureteral stricture. Subsequent ureteroscopy with biopsy or barbotage should be performed in any patient in whom the cause of the stricture is not certain. Diuretic renography will provide differential renal function and evaluate the renal unit for functional obstruction. It is important to assess the renal unit for function before starting treatment because endourologic therapies, in general, require 25% function of the ipsilateral moiety to have reasonable success rates (Wolf et al, 1997). Once a ureteral stricture is diagnosed, indications for intervention include the need to rule out malignancy, ongoing renal obstruction, recurrent pyelonephritis, and pain associated with functional obstruction.

Endourologic Options for Intervention**Ureteral Stent Placement**

Ureteral stent placement is effective acutely in treating most ureteral strictures, in particular intrinsic ureteral strictures. Wenzler and colleagues reported good success rates in treating intrinsic ureteral obstruction, with 88% success rates at 26 months (Wenzler et al, 2008). Although intrinsic ureteral strictures can be managed or temporized with ureteral stents, patients with extrinsic ureteral compression eventually require percutaneous drainage or surgical management (Docimo and Dewolf, 1989; Chung et al, 2004).

If the patient is not a candidate for definitive repair or has a poor prognosis, chronic stent placement with periodic stent changes can be considered. In addition, patients undergoing systemic treatments for malignancies can be managed with periodic stent changes. The use of chronic stent placement must be guarded, particularly when treating ureteral obstruction from extrinsic compression because adequate drainage may be short-lived (Docimo and Dewolf, 1989; Chung et al, 2004). Careful monitoring of the upper tracts and patient symptoms is warranted in this subgroup of patients. Rosevear and colleagues (2007) reported an 84% success rate at 16 months in their series using ureteral stents, with 68% of the patients having malignancy. The remainder included patients with retroperitoneal fibrosis (RPF) and other benign extrinsic diseases. The use of tandem ureteral stent placement (two parallel stents) has been shown to be effective in benign and malignant extrinsic ureteral obstruction (Yohannes and Smith, 2001; Elsamra et al, 2013). Elsamra and colleagues reported on 66 patients managed with tandem ureteral stent placement, with stent failure in 12% of patients with malignant obstruction and none with benign ureteral obstruction. Alternatively, tandem ureteral stent placement may be an excellent option in patients in whom single-stent drainage fails.

After initial reports in 2006, the use of metallic stents in patients with malignant ureteral obstruction has gained popularity (Borin et al, 2006). Liatsikos and coauthors reported on 50 patients treated with the full metallic stent, and although concerns arose regarding stent exchange and encrustation, overall the study supported use of the stent at 12-month intervals (Liatsikos et al, 2010). Kadlec and colleagues reported 5-year data showing good results for use of full-length metal stents with up to a 3-year duration of stent drainage of long-term benign and malignant obstruction in select patients (Kadlec et al, 2013). Expandable metallic mesh stents that allow tissue ingrowth have proven to have problems with encrustation, hyperplastic reactions, and tumor ingrowth (Liatsikos et al, 2009).

Alternatively, Papatsoris reported using nonmesh thermoexpandable metallic stents with both drainage and therapeutic benefits, although urinary tract infections, stent migration, encrustation, and obstruction were similarly identified (Papatsoris et al, 2010). Goldsmith and associates found a 35% failure rate of metallic stents in 25 patients undergoing stent placement for malignant obstruction. Persistent obstruction, distal stent migration, and subcapsular hematoma were noted, and at the present time there is no clear consensus regarding the benefits of metallic stents (Goldsmith et al, 2012).

Balloon Dilation

Retrograde Balloon Dilation. Retrograde dilation of ureteral strictures has historically been part of the urologic armamentarium. The technique was rarely definitive and usually required repeated dilations on a regular basis. In the early 1980s angiographic and vascular balloons were introduced into urologic practice, and the technique of balloon dilation with temporary internal stenting became an accepted mode of treatment (Banner et al, 1983; Finnerty et al, 1984).

As for any patient with a ureteral stricture, the indications to intervene include functionally significant obstruction. Contraindications to this approach include active infection or a stricture longer than 2 cm because dilation alone will rarely be successful in this setting. Moreover, any endoscopic technique is likely to fail with strictures greater than 2 cm (Fig. 49-23).

A retrograde approach is indicated whenever access across the strictured area is easily accomplished using transurethral techniques. In general, the procedure begins with a retrograde pyelogram performed under fluoroscopic control to precisely delineate the site and length of stricture. A floppy-tipped guidewire is passed in a retrograde fashion across the strictured area and coiled proximally in the pyelocalyceal system. This is most easily accomplished by passing an open-end catheter up to the level of the stricture to use as a guide for the hydrophilic or floppy-tipped wire. Passage of the open-end catheter through the strictured area over the wire will then aid subsequent passage of a balloon catheter. Techniques for

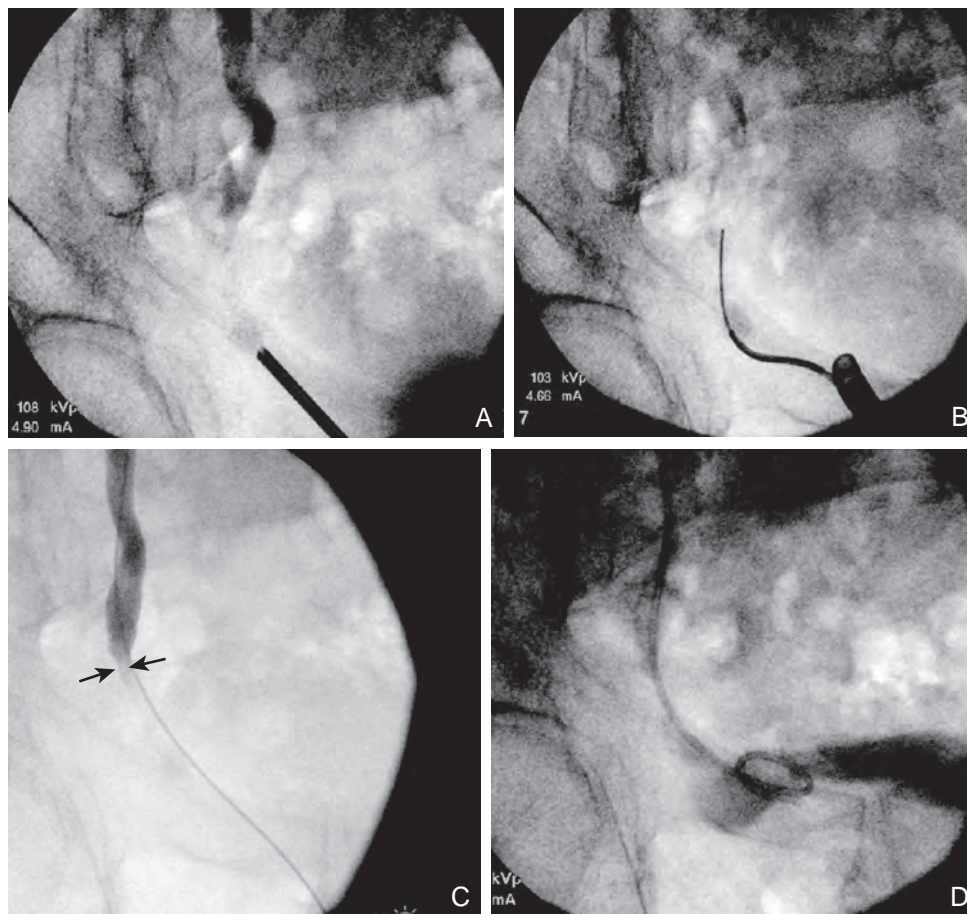


Figure 49-23. A, Antegrade and retrograde contrast demonstrating a distal ureteral stricture following prior traumatic ureteroscopic stone procedure. B, Image demonstrating complex guidewire access across this long and narrow stricture with retained proximal stones. C, The stricture is greater than 2 cm, and minimal contrast would pass through antegrade. D, Image after ureteral stent placement. This patient required ureteral reimplantation and stone removal.

bypassing difficult areas of obstruction have been described in detail (Mata et al, 1994).

At this point, the open-end catheter is withdrawn and replaced with a high-pressure, 4-cm-long, 5- to 8-mm balloon. Under fluoroscopic control, the balloon catheter is positioned across the strictured area, with proper position ensured by visualization of radiopaque markers at the tips of the balloon. Balloon inflation is then begun, and a waist will be visualized at the strictured area, which will disappear with progressive balloon inflation (Fig. 49-24). After 10 minutes of tamponade, the balloon is deflated and withdrawn. A guidewire is still in place, and this is used to pass an internal stent, which is left indwelling for 2 to 4 weeks. Follow-up diuretic renography is usually performed approximately 1 month after stent extraction and at 6- to 12-month intervals thereafter.

Occasionally, access across the involved area cannot be obtained using fluoroscopic control alone. In such cases direct ureteroscopic visualization can aid initial passage of the guidewire, and the procedure can be continued as described. Alternatively, a low-profile balloon can be passed through the ureteroscope and the stricture dilated under direct vision.

Antegrade Balloon Dilation. At times, retrograde access across a strictured area is impossible. In such cases, access can be obtained using an antegrade approach and fluoroscopic control (Mitty et al, 1983; Banner and Pollack, 1984), with or without direct antegrade ureteroscopic visualization (de Jonge et al, 1986). Percutaneous nephrostomy drainage is established; in cases associated with infection or compromised renal function, percutaneous drainage alone is instituted to allow resolution of infection and return to

baseline renal function. Once that is accomplished, the percutaneous tract is used for access for a fluoroscopically or ureteroscopically guided approach. The procedure is then analogous to a retrograde approach. Under fluoroscopic guidance, an antegrade contrast agent study is used to definitively define the site and length of the stricture. A floppy-tipped guidewire or glidewire is passed antegrade across the level of obstruction; then a balloon catheter is passed, and the balloon is progressively inflated until the waist disappears. The balloon catheter is withdrawn over a wire and replaced with an internal stent, and a nephrostomy tube is also left indwelling. A follow-up nephrostogram is obtained within 24 to 48 hours to ensure proper positioning of a functional internal stent, and at that time the nephrostomy tube can be removed. Alternatively, access can be maintained by the use of an internal-external stent, which can be capped to allow internal drainage.

Results. Initial reports of retrograde and antegrade balloon dilation of ureteral strictures suggested that results were better when the stricture was anastomotic and of relatively short duration and length (King et al, 1984b; Chang et al, 1987; Netto et al, 1990). Goldfischer and Gerber (1997) reviewed the literature regarding results of balloon dilation of ureteral strictures and found reported success rates ranging from 50% to 76%. In that review, the best results were obtained in patients with iatrogenic, non-anastomotic strictures such as those who had undergone ureteroscopic instrumentation. In that setting, a success rate of 85% was achieved compared with a rate of 50% for anastomotic strictures. Alternatively, Ravary and colleagues found a 40% success rate using retrograde balloon dilation in treating inflammatory

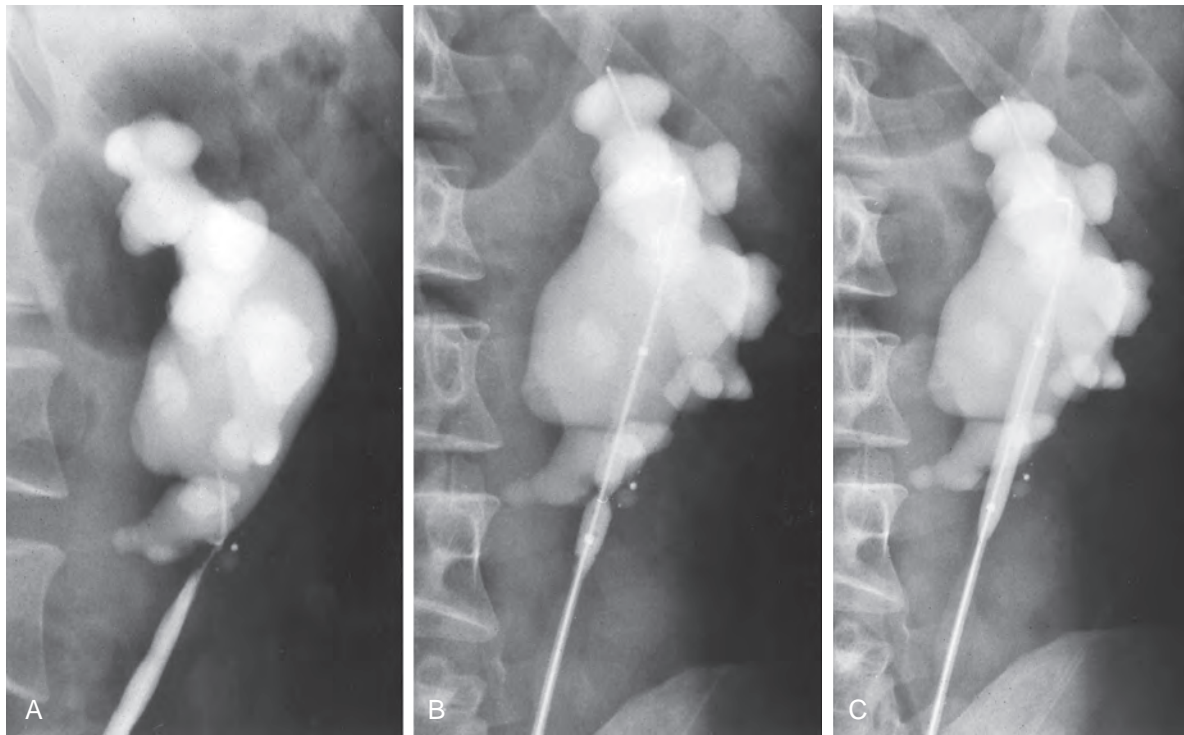


Figure 49-24. A, Retrograde study confirms a short stricture at the level of the ureteropelvic junction in this patient with a horseshoe kidney referred after failed ureteroscopic management of a ureteral calculus impacted at that level. B, The stricture has been traversed with a guidewire, over which a high-pressure balloon has been passed. A waist is evident at the level of the stricture during initial balloon inflation. C, Balloon inflation and stricture dilation are complete with disappearance of the waist.

ureteral strictures at 16 months' follow-up (Ravery et al, 1998). Richter and colleagues (2000) reviewed their results with balloon dilation in 114 patients with a minimum 2-year follow-up. As in other series, balloon dilation was more successful for patients with relatively short strictures. In addition, these authors noted the significance of an intact vascular supply on the success of this procedure. Koukouras reported antegrade percutaneous balloon treatment of iatrogenic ureteral strictures with 72% success at 1-year follow-up (Koukouras et al, 2010). One series of transplant ureteral strictures in which percutaneous balloon dilation was used in 14 transplant patients demonstrated 79% success at 29 months. Notably, these were short, anastomotic strictures in patients on immunosuppression (Voegeli et al, 1988). Others report endoureterotomy as the primary treatment option in such cases (Duty et al, 2013). Of note, in experimental models, balloon dilation created longitudinal incisions similar to endoureterotomy, explaining some of the success seen with use of balloon dilation in ureteral strictures (Nakada et al, 1996).

Endoureterotomy

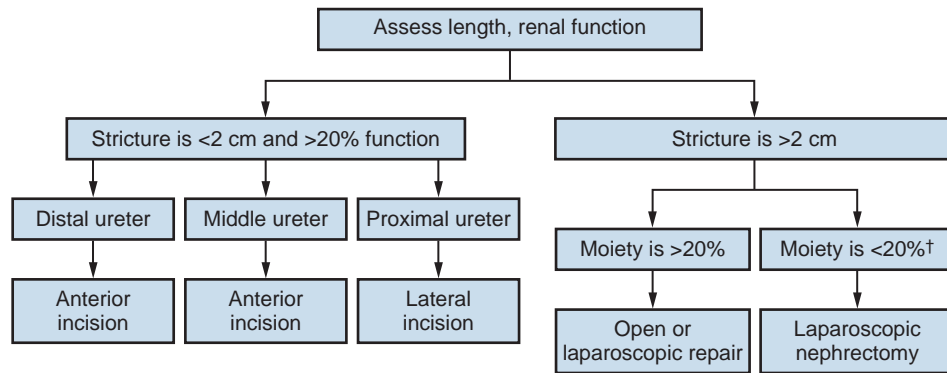
Endoluminal ureteral incision is a logical extension of balloon dilation for "minimally invasive" management of ureteral strictures. As for balloon dilation, access to and across the strictured area can be obtained in a retrograde or antegrade fashion, although a retrograde approach is preferred because it is less invasive. The antegrade approach is indicated when percutaneous access is already present. The procedure is performed under direct vision using ureteroscopic control or it can be guided fluoroscopically using the hot-wire cutting balloon catheter. In general, radiographic follow-up using diuretic renography is recommended for up to 2 years to detect most late failures (Wolf et al, 1997).

Retrograde Ureteroscopic Approach. A retrograde study is performed under fluoroscopic control at the outset of the procedure.

Whenever possible, a floppy-tipped guidewire or hydrophilic glide-wire is passed across the level of obstruction as outlined earlier. If a wire cannot be passed across the strictured area using fluoroscopic control alone, the flexible ureteroscope is passed to the level of obstruction, and the guidewire is advanced through the ureteroscope across the involved area under direct vision. The ureteroscope is then withdrawn, but a safety wire is always left in place across the stricture. The ureteroscope is then reintroduced and passed alongside the guidewire to the level of obstruction.

The position for the endoureterotomy incision is chosen as a function of the level of the ureter involved. In general, lower ureteral strictures are incised in an anteromedial direction, taking care to stay away from the ilioc vessels. In contrast, upper ureteral strictures are incised laterally or posterolaterally, again away from the great vessels (Meretyk et al, 1992) (Fig. 49-25).

The ureterotomy incision itself can be performed using a cold knife (Schneider et al, 1991; Yamada et al, 1995), a cutting electrode (Conlin et al, 1996), or a holmium laser. Today, the holmium laser represents the dominant approach to endoscopic incisions. In all cases the incision is made from the ureteral lumen out to peri-ureteral fat in a full-thickness fashion. Proximally and distally, the endoureterotomy should encompass 2 to 3 mm of normal ureteral tissue. In certain instances the stricture must be balloon dilated to gain access across the stricture (Fig. 49-26). Similarly, the strictures may be balloon dilated after endoincision, to enlarge the incision. Once the endoureterotomy incision is complete, the remaining guidewire is used to pass an internal stent. In general, the larger-diameter stents should be considered because larger stents (8 to 12 Fr) have been associated with improved results (Hwang et al, 1996; Wolf et al, 1997). Similarly, Wolf and colleagues (1997) found benefit in the injection of triamcinolone ureteroscopically after endoureterotomy. Steroids and other biologic response modifiers may eventually have a role in the future in managing select strictures.

OPTIMAL THERAPY FOR BENIGN URETERAL STRICTURES*

*Consider balloon if transplant on immunosuppression.

†Pediatric patients and select patients with renal insufficiency may warrant repair.

Figure 49-25. Algorithm for management of benign ureteral stricture disease.

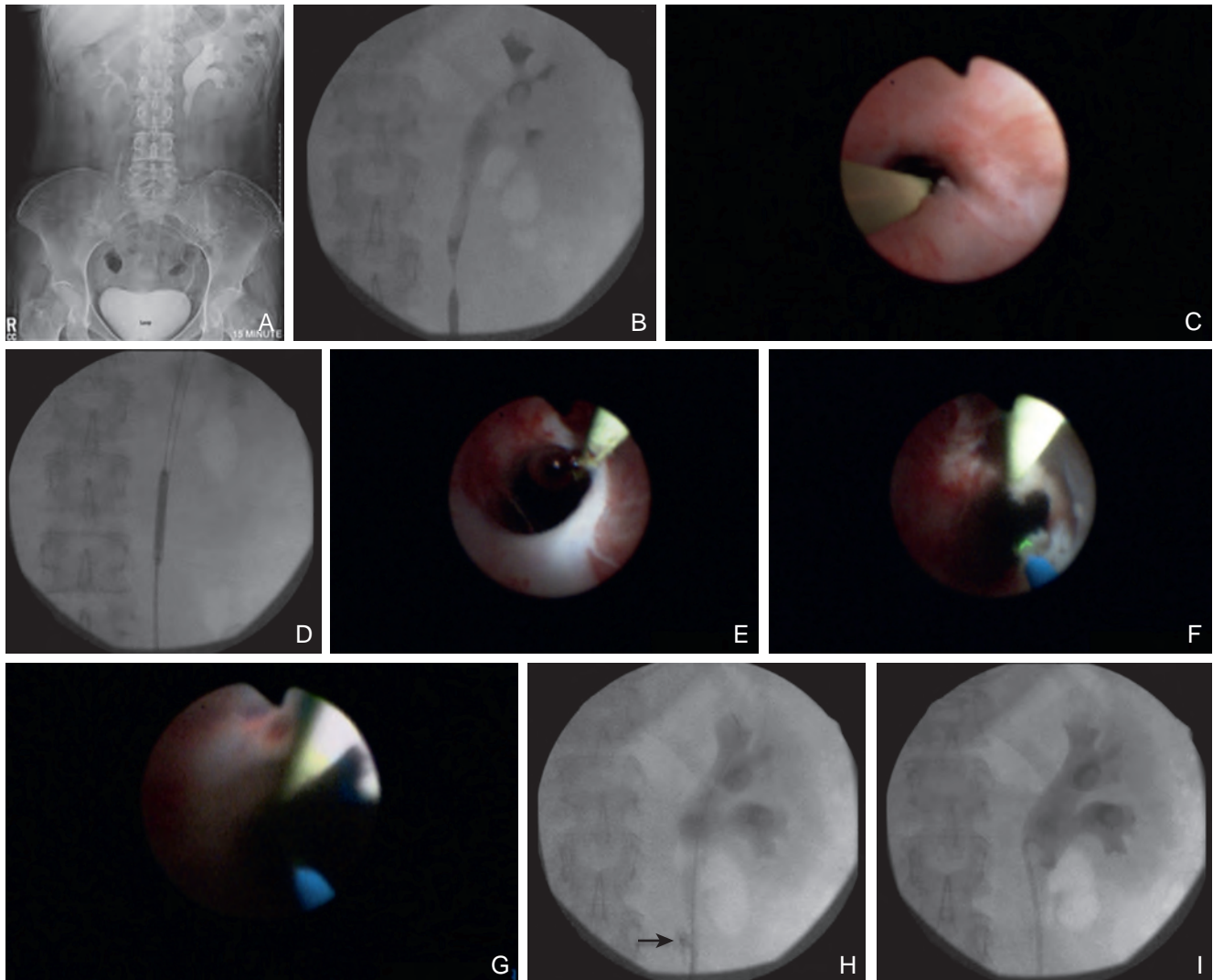


Figure 49-26. A, Preoperative excretory urogram showing proximal ureteral stricture after ureteral injury. B, Fluoroscopic image of flexible ureterscope at stricture. C, Corresponding endoscopic image of stricture. D, Fluoroscopic image of balloon dilation to enable incision of ureteral stricture. E, Endoscopic image of strictured area after balloon dilation (note resultant full-thickness, lateral incision). F, Endoscopic view completing laser incision of stricture. G, Endoscopic view of full-thickness incision. H, Fluoroscopic image demonstrating extravasation (arrow). I, Fluoroscopic image after stent placement.

Results. The success of holmium laser endoureterotomy ranges from 66% to 83% in series of more than 10 patients with longer than 12 months' follow-up (Lane et al, 2006; Hibi et al, 2007; Gdor et al, 2008b). There is early evidence that strictures related to stone impaction and prior stone treatment may have lower success rates (56% in one series) than typical benign strictures (Gdor et al, 2008a). Of note, as ureteroscopy and laser lithotripsy continue to grow, more strictures involving impacted stones may be encountered, and this may become a growing clinical problem. Gdor and colleagues reported 67% success in treating transplant ureteral strictures using the holmium laser at 58 months' follow-up, and more recently Mano and coauthors reported an 83% success rate in 26 transplant patients at 44 months' follow-up, with 67% of the patients having undergone initial percutaneous balloon dilation (Gdor et al, 2008b; Mano et al, 2012). **The familiarity of ureteroscopy, coupled with relative availability of the holmium laser, makes retrograde laser endoureterotomy an attractive initial management strategy for ureteral strictures less than 2 cm in length.** Meretyk and Razdan both reported poor results using the retrograde approach in patients with strictures longer than 2 cm (Meretyk et al, 1992; Razdan et al, 2005).

Antegrade Approach. When direct visual ureteroscopic access to the strictured area cannot be accomplished in a retrograde fashion, an antegrade approach may be used. Nephrostomy tube drainage is instituted, and any associated infection or compromised renal function is allowed to resolve before definitive incision. The percutaneous tract is dilated to a size large enough to allow a working sheath through which a flexible ureteroscope is passed. The procedure is then performed in a fashion analogous to a retrograde approach. A safety wire should be in place at all times alongside the ureteroscope, across the obstructed area and coiled distally in the bladder.

Combined Retrograde and Antegrade Approach. Rarely, a ureteral stricture is associated with an area of complete ureteral obliteration across which a wire cannot be passed to allow subsequent balloon dilation or ureteroscopic endoureterotomy. In such cases a combined retrograde and antegrade approach has been described (Cardella et al, 1985; Conlin et al, 1996; Beaghtler et al, 1997; Knowles et al, 2001). The obstructed area is defined radiographically with a simultaneous antegrade and retrograde pyelogram. Endoscopes are passed simultaneously in both a retrograde and an antegrade manner, and the two opposing ureteral ends are localized under fluoroscopic guidance. A working guidewire is then passed from one end of the ureter, through and through to the other lumen, using a combination of fluoroscopic and direct visual control. For completely obliterated ureteral segments, this is most easily accomplished using the stiff end of a guidewire passed through a semirigid ureteroscope via the retrograde approach, although when a semirigid ureteroscope cannot be placed, a flexible ureteroscope or even an open-end ureteral catheter can be used to stabilize the wire from above or below. A "cut to the light" technique can be helpful in this setting. The ureteral segments are aligned as closely as possible under endoscopic and fluoroscopic guidance, and the light source to one of the ureteroscopes is turned off. The light from the opposite ureteroscope is then used to aid incisional restoration of urinary continuity. The strictured area is then recannulated using the stiff end of a guidewire, a small electrocautery electrode, or holmium laser. Once through-and-through control is obtained with a guidewire, a stent is passed and left in place for 8 to 10 weeks. As with other endourologic approaches to ureteral strictures, success rates are inversely related to the length of the strictured area. **Although success rates may be uncertain, internalization of urinary flow, even when dependent on long-term stent placement, can be a quality-of-life advantage for certain high-risk patients.** Knowles and colleagues reported a 90% patency rate at 36 months' follow-up for use of cautery wire balloon incision to treat 10 patients with obliterated distal ureteral segments, 3 of whom required the combined approach (Knowles et al, 2001). Bach and colleagues reported a retrograde blind (fluoroscopically guided) endoureterotomy with a 61% success rate in patients with subtotal ureteral strictures (Bach et al, 2008).

KEY POINTS: ENDOUROLOGIC MANAGEMENT OF URETERAL STRICTURES

- Proper evaluation and treatment of a ureteral stricture are essential to preserve renal function and rule out the presence of malignancy. It is critical to assess the renal unit for function before starting treatment because endourologic therapies typically require 25% function of the ipsilateral moiety.
- The use of chronic stent placement for extrinsic ureteral obstruction must be guarded, because the drainage is often limited. Innovations in stents and stent techniques have led to long-term success in select patients with malignant ureteral obstruction.
- The indications to intervene for ureteral stricture disease include clinical symptoms and functionally significant obstruction. Contraindications to this approach include active infection or a stricture longer than 2 cm.
- Current available reports and the familiarity of ureteroscopy, coupled with relative availability of the holmium laser, make retrograde laser endoureterotomy an attractive initial management strategy for short ureteral strictures.
- The position for the endoureterotomy incision is chosen as a function of the level of the ureter involved. In general, lower ureteral strictures are incised in an anteromedial direction, taking care to stay away from the iliac vessels. In contrast, upper ureteral strictures are incised laterally or posterolaterally, away from the great vessels.

Surgical Repair

Before any surgical repair, it is essential to conduct careful evaluation of the nature, location, and length of the ureteral stricture. Preoperative assessment typically includes an intravenous pyelogram (or antegrade nephrostogram) and a retrograde pyelogram if indicated, because the location and length of the stricture heavily influence the options for repair. Other studies such as a nuclear medicine renogram to assess renal function and ureteroscopy, ureteral barbotage, and/or brushing to rule out carcinoma should be individualized. On the basis of such information, the appropriate surgical procedure can then be planned for the patient (Table 49-2).

Ureteroureterostomy

A short defect involving the upper ureter or mid-ureter, either in the form of stricture or as a consequence of recent injury, is most appropriate for ureteroureterostomy. On the other hand, a lower ureteral stricture is usually best managed by ureteroneocystostomy with or without a psoas hitch or Boari flap. In the transplant setting, a donor ureteral stricture may be managed by a ureteroureterostomy to a healthy, native ureter. Because tension on the anastomosis almost always leads to stricture formation, only short defects should be managed by end-to-end ureteroureterostomy. Determination of whether or not enough ureteral mobility can be achieved to allow tension-free ureteroureterostomy usually cannot be made until the

TABLE 49-2 Bridging Various Ureteral Defect Lengths with Different Reconstructive Surgical Techniques

TECHNIQUE	URETERAL DEFECT LENGTH (cm)
Ureteroureterostomy	2-3
Ureteroneocystostomy	4-5
Psoas hitch	6-10
Boari flap	12-15
Renal descensus	5-8

time of surgery, and thus the urologist must be prepared to pursue other options.

Open Approach. The choice of surgical incision depends on the level of the ureteral stricture. A flank incision is appropriate for the upper ureter. A Gibson or a lower midline incision is suitable for the middle and lower ureter. If the patient has sustained an iatrogenic ureteral injury from a previous surgery performed through a Pfannenstiel incision, the same incision may be used for the ureteral reconstruction. In such a situation, proximal ureteral dissection may be difficult through the Pfannenstiel incision, requiring cephalad extension of the lateral portion of the incision in a “hockey stick” fashion. Extraperitoneal dissection is usually performed except in cases of transperitoneal surgical ureteral injury.

After surgical incision, the retroperitoneal space is developed as the peritoneum is mobilized and retracted medially. Frequently, the ureter can be easily identified as it crosses the iliac vessels. A Penrose drain or vessel loop may be placed around the ureter to assist its atraumatic handling. Direct handling of the ureter with forceps should be minimized. Care should be taken to preserve its adventitia, which loosely attaches the blood supply to the ureter.

During ureteral dissection and mobilization, enough mobility must be achieved to avoid tension after the excision of the diseased ureter. With a gunshot injury, devitalized tissue and an adjacent segment of normal-appearing ureter should be excised to eliminate late ischemia and stricture formation from the blast effect. Once both ends of the ureter have been adequately trimmed to healthy areas, mobilized, and correctly oriented, they are spatulated for approximately 5 to 6 mm. Spatulation is performed for both ureteral segments at 180 degrees apart. If a grossly dilated ureter is involved, it may be transected obliquely and not spatulated to match the circumference of the nondilated segment. A fine,

absorbable suture is placed in the corner of one ureteral segment and the apex of the other, and the two ends of the suture are tied outside the ureteral lumen. The opposite corner and apex are similarly sutured and approximated. The anastomosis may then be completed by running these two sutures continuously and tying them to each other or in an interrupted fashion (Fig. 49-27). A double-J ureteral stent should be placed before completion of the anastomotic closure. Stent placement can be facilitated by passing the wire through one of the side holes in the middle of the stent to straighten and stiffen the stent enough to permit it to pass. Observation of reflux of methylene blue irrigant from the bladder to the ureterotomy can be used to verify the appropriate placement of the distal stent in the bladder. Retroperitoneal fat or omentum may be used to cover the anastomosis.

Laparoscopic or Robotic Approach. A laparoscopic or robotic approach may be offered to patients with ureteral stricture disease. [Nezhat and colleagues \(1992\)](#) first reported laparoscopic management of an obstructed ureter resulting from endometriosis. In this case, ureteroureterostomy was performed laparoscopically over a ureteral stent after resection of the obstructed ureteral site. Most of the studies since that time consist of single case reports or small series. Several reports of laparoscopic ureteroureterostomy to unobstruct a duplicated system in the pediatric population have appeared ([Piaggio and Gonzalez, 2007](#); [Smith et al, 2009](#)). More recently, the robotic-assisted approach has been applied to laparoscopic ureteroureterostomy in a small number of patients ([Mufarrij et al, 2007](#); [Passerotti et al, 2008](#); [Lee et al, 2010](#)). Lee and colleagues reported a series of three robotic ureteroureterostomies, all successful by symptom and nuclear renal scan criteria at an average of 24 months. The overall clinical experience in minimally invasive ureteroureterostomy is limited worldwide. However, in the hands of the

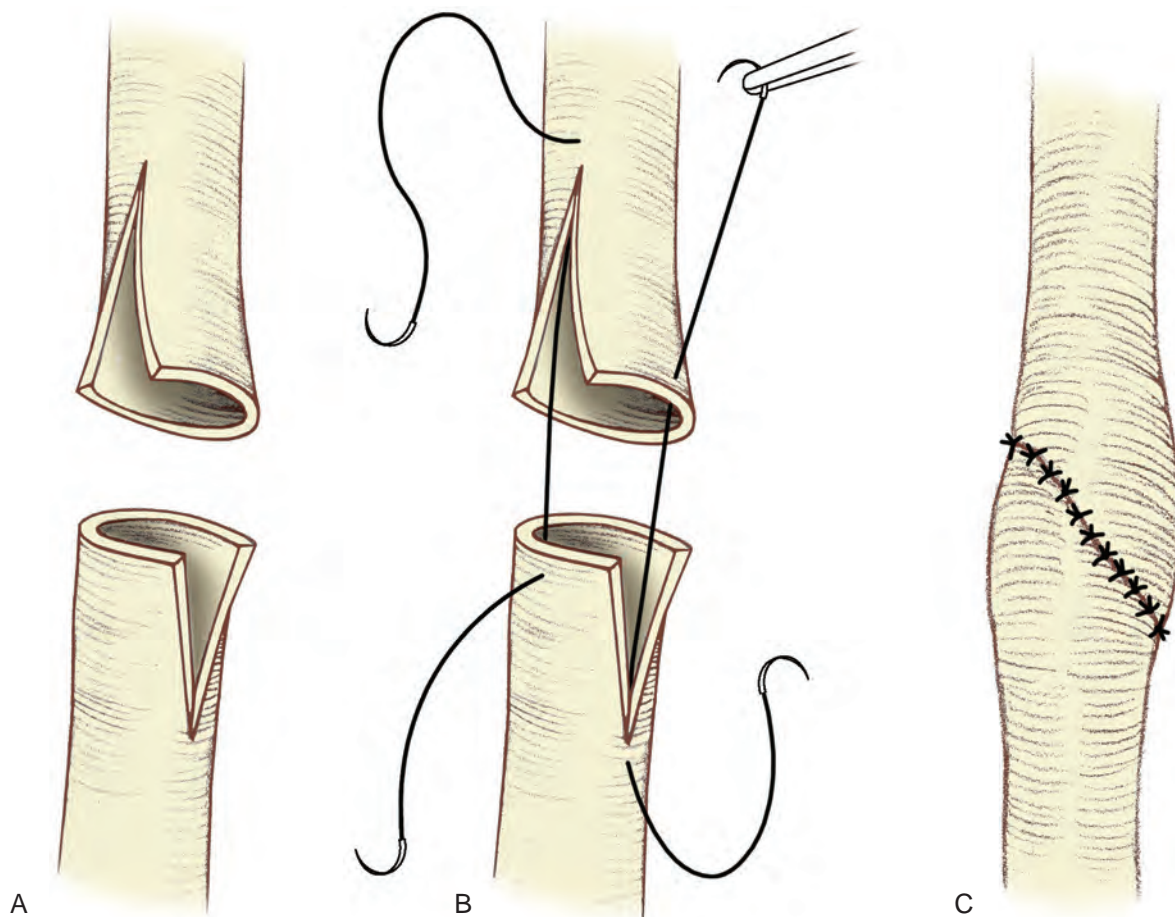


Figure 49-27. A, Spatulated ureteral ends. B, Placement of sutures. C, End-to-end ureteroureterostomy.

experienced surgeon, it appears to be a viable minimally invasive approach applicable to almost any patient with a relatively short area of obstruction.

Postoperative Care. The postoperative care of ureteroureterostomy patients is similar, regardless of surgical approach. A surgical drain is placed, and a Foley catheter is usually left indwelling for 1 to 2 days. The surgical drain may be removed if there is minimal output for 24 to 48 hours. If the surgical procedure is not performed entirely in a retroperitoneal manner, it is important to determine the nature of the fluid from the surgical drain, which can be achieved by checking the creatinine level of the fluid. If there is no urinary extravasation, the drain can then be removed. The double-J ureteral stent is removed endoscopically, usually 4 to 6 weeks postoperatively.

The success rate for a tension-free, watertight ureteroureterostomy is high—greater than 90% (Carlton et al, 1969; Guiter et al, 1985). If a urinary fistula is suspected, a plain abdominal radiograph should first be obtained to verify the position of the double-J stent. The proximity of a drain to the anastomosis should also be checked because it may exacerbate a leak. Suction should be stopped if a suction drain device is used because straight drainage may assist closure of the ureteral leakage site. Reflux from voiding or bladder spasms may also contribute to prolonged urinary extravasation, a problem that can be managed by Foley catheter drainage and anticholinergics. Prolonged urinary leakage from the anastomosis may require the placement of a nephrostomy tube for proximal urinary diversion.

Ureteroneocystostomy

Ureteroneocystostomy to manage vesicoureteral reflux is covered elsewhere in the text. Ureteroneocystostomy without a psoas hitch or Boari flap in an adult is appropriate for injury or obstruction affecting the distal 3 to 4 cm of the ureter. For open ureteroneocystostomy, a lower midline, Pfannenstiel, or Gibson incision may be used, and in general the extraperitoneal approach is preferable. After surgical incision, the ureter is usually identified as it crosses the iliac vessels, dissected distally, and transected at the level of the obstruction. After adequate proximal ureteral mobilization, direct ureteroneocystostomy is performed only if a tension-free anastomosis is possible. Otherwise, a psoas hitch or Boari flap should be used as an adjunct. A direct, nontunneled anastomosis may be performed if postoperative reflux is acceptable. Otherwise, a submucosal tunnel is created for antireflux anastomosis. A double-J stent and surgical drain are used as described earlier for ureteroureterostomy.

The issue of refluxing versus antirefluxing anastomosis in ureteroneocystostomy in adults has been examined previously. In a retrospective review of adult patients with ureteroneocystostomy, no significant difference in the preservation of renal function or risk of stenosis was identified in the refluxing versus antirefluxing procedures (Stefanovic et al, 1991). However, it is unclear if a nonrefluxing anastomosis decreases the risk of pyelonephritis in an adult patient.

Minimally Invasive Ureteroneocystostomy. Successful laparoscopic application to ureteroneocystostomy has been reported by a variety of investigators (Ehrlich et al, 1993; Reddy and Evans, 1994; Yohannes and Smith, 2001; Gözen et al, 2010). In the management of distal ureteral stricture, laparoscopic ureteroneocystostomy is usually performed transperitoneally, incorporating intracorporeal suturing techniques, because it provides a large working space. Ureteral stenting is typically used postoperatively as in open surgery. Although this procedure requires intracorporeal laparoscopic suturing, the overall clinical experience for laparoscopic management of distal ureteral strictures has been increasing over time. Abraham and colleagues reported their experience performing laparoscopic ureteral reimplantation in 36 patients and reported success in all patients at a mean of 16 months' follow-up (Abraham et al, 2011). Overall, the clinical outcomes have been reported to be favorable to and comparable with those of open surgical procedures while providing minimal postoperative morbidity, as in many other laparoscopic urologic procedures. LESS neocystostomy has been reported as well (Khanna et al, 2012).

As is the case for many reconstructive urologic procedures, urologists have reported finding the robotic platform useful in neocystostomy (Fig. 49-28) (Mufarrij et al, 2007; Laungani et al, 2008; Williams and Levillie, 2009). This procedure can typically be performed using a four-arm robotic approach with port placement similar to that of a robotic prostatectomy or with ports shifted slightly cephalad. Isac and colleagues reported similar success rates for robotic and open neocystostomy, with the robotic approach being associated with a significantly shorter hospital stay (3 vs. 5 days, $P = .0004$) and less narcotic use (morphine equivalent, 104.6 vs. 290 mg, $P = .0001$) (Isac et al, 2013). Musch and colleagues reported a robotic approach to be effective even in cases requiring a psoas hitch or Boari flap (Musch et al, 2013).

Open Psoas Hitch

The psoas hitch is an effective method to bridge a defect of the lower third of the ureter. However, a ureteral defect extending proximal to the pelvic brim usually requires more than a psoas hitch alone. Indications include distal ureteral stricture, injury, and failed ureteroneocystostomy (Prout and Koontz, 1970; Ehrlich et al, 1978; Rodo Salas et al, 1991). A psoas hitch may also be used in conjunction with other maneuvers such as a transureteroureterostomy (TUU) in more complicated urinary tract reconstruction. In general, a small, contracted bladder with limited mobility is considered a contraindication. In addition to the preoperative radiographic and endoscopic evaluation described previously, urodynamic studies may provide information regarding detrusor capacity and compliance before the surgery. Bladder outlet obstruction or neurogenic dysfunction, if present, needs to be treated preoperatively.

To gain access to the distal ureter, a Pfannenstiel or lower midline incision is usually used. An extraperitoneal approach is preferred, if possible. In such a scenario, the space of Retzius is developed and the bladder mobilized by freeing its peritoneal attachments and

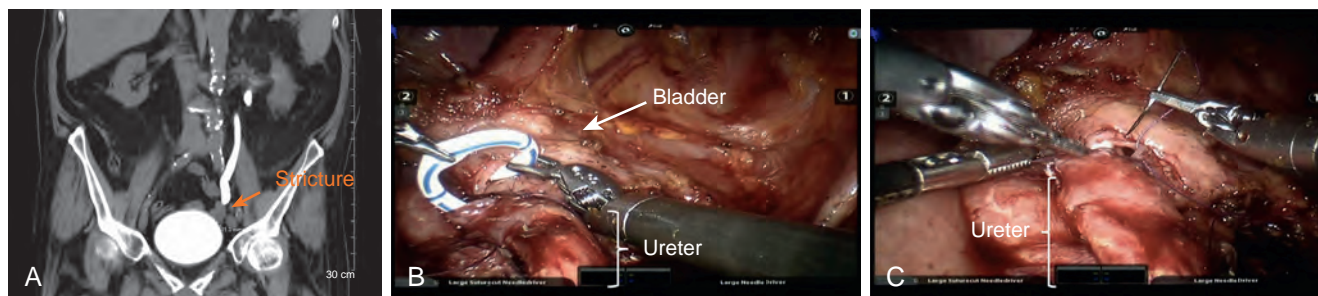


Figure 49-28. Intraoperative photograph of a patient undergoing a robotic right ureteral neocystostomy for distal ureteral stricture seen in CT urography (A). B, The distal coil of the ureteral stent being placed through the opening in the bladder after completion of half the ureteral anastomosis. C, Completing the ureteral anastomosis.

dividing the vas deferens or round ligament. With traction, the ipsilateral dome of the bladder should be able to reach the level proximal to the iliac vessels. **Additional mobility can be achieved by dividing the contralateral superior vesical artery.** The ipsilateral ureter is identified as it crosses the iliac vessels, is mobilized, and is divided just above the diseased segment. An anterior cystotomy, usually created in a vertical or oblique fashion, is frequently made to assist manual displacement of the bladder toward the ipsilateral ureter. The ureter is delivered into the lumen of the bladder at the ipsilateral superolateral aspect of the dome, followed by the tension-free anastomosis with or without a submucosal tunnel. **The ipsilateral bladder dome is secured to the psoas minor tendon or the psoas major muscle using several absorbable sutures.** Care should be taken to avoid injury to the genitofemoral nerve and the femoral nerve in the vicinity when placing these sutures. Alternatively, psoas fixation may be performed before ureteroneocystostomy. A double-J stent is used usually, followed by closure of cystotomy with absorbable sutures (Fig. 49-29).

Relative to simple ureteroneocystostomy, the psoas hitch can provide an additional 5 cm of length. Relative to the Boari flap, the advantages of psoas hitch include increased technical simplicity and decreased risk of vascular compromise and voiding difficulties. The success rate of ureteroneocystostomy with a psoas hitch is greater than 85% in both adults and children on the basis of reports (Mathews and Marshall, 1997; Ahn and Loughlin, 2001). Complications occur uncommonly but have included urinary fistula, ureteral obstruction, nerve injury, bowel injury, iliac vein injury, and urosepsis (Fig. 49-30).

Laparoscopic Psoas Hitch

Ureteroneocystostomy with psoas hitch has been performed laparoscopically with success (Nezhat et al, 2004). Successful robotic-assisted application has also been reported (Mufarrij et al, 2007; Patil et al, 2008; Schimpf and Wagner, 2009). In general, preoperative ureteral stenting is performed, and the procedure is typically

completed via the transperitoneal approach. Overall, the clinical experience with such procedures is quite limited in the literature. However, on the basis of short-term and intermediate-term follow-up data to date, the clinical outcomes appear to be satisfactory and equivalent in experienced hands.

Open Boari Flap

When the diseased ureteral segment is too long or when ureteral mobility is too limited for a tension-free ureteroureterostomy to be performed, a Boari flap may be a useful alternative. Boari first described the use of this technique in the canine model in 1894. A Boari flap can be constructed to bridge a 10- to 15-cm ureteral defect, and a spiraled bladder flap can reach the renal pelvis in some circumstances, especially on the right side. As with a psoas hitch, evaluation of bladder function and capacity should be performed preoperatively in addition to the ureteral evaluation. Bladder outlet obstruction and neurogenic dysfunction, if present, should be addressed preoperatively. **A small bladder capacity is likely to be associated with difficult or inadequate Boari flap creation, warranting consideration of alternative methods in the preoperative surgical planning.**

In Boari flap procedure, a Pfannenstiel incision may be used at the time of surgery, although a midline incision is preferable and allows easier access to the upper ureter. The bladder is mobilized from its peritoneal attachments, and the umbilical ligaments are divided. The contralateral bladder pedicle is divided and ligated, allowing greater mobility toward the ipsilateral ureter, and the ipsilateral bladder pedicle including the superior vesical artery is preserved. The affected ureter is carefully mobilized, with care being taken to preserve its blood supply. The diseased segment is then excised. After identification of the ipsilateral superior vesical artery or one of its branches, a posterolateral bladder flap is outlined on the basis of this vascular supply. The flap continues obliquely across the anterior bladder wall, with the base of the flap being at least 4 cm in width and the tip of the flap being at least 3 cm in width.

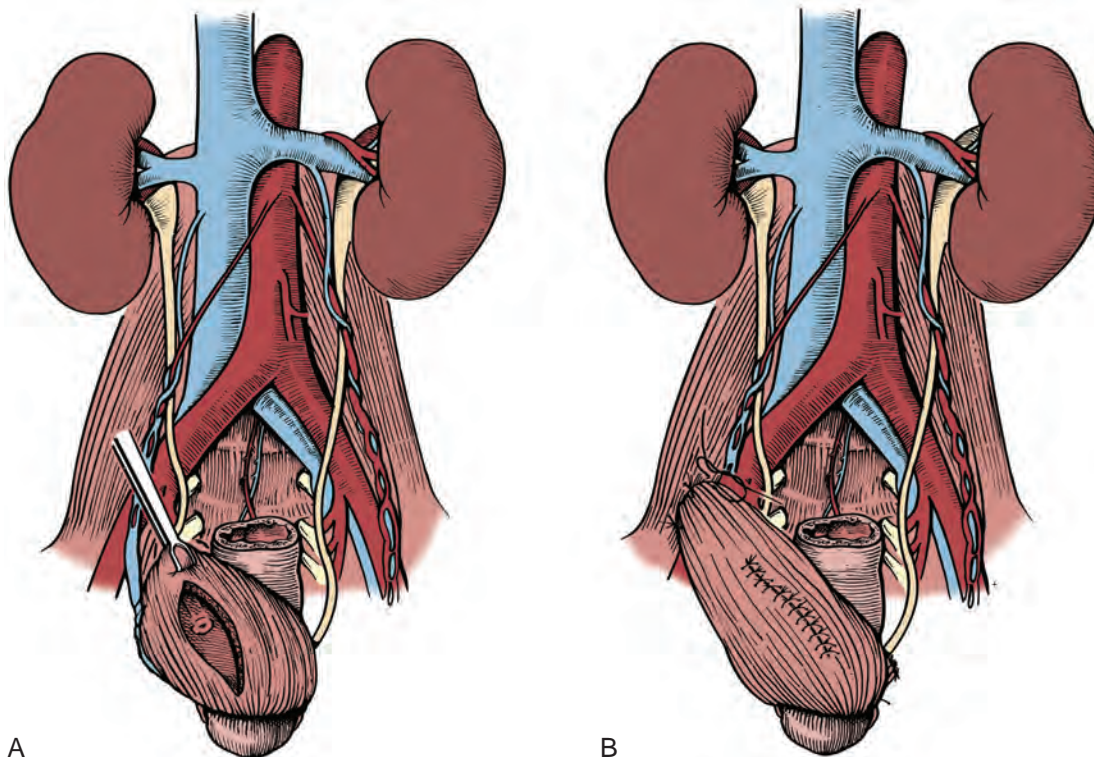


Figure 49-29. A, For a psoas hitch, an anterior cystotomy is performed after bladder mobilization. B, The bladder dome is fixed to the ipsilateral psoas tendon, and the ureteral reimplantation is completed in a tension-free manner.

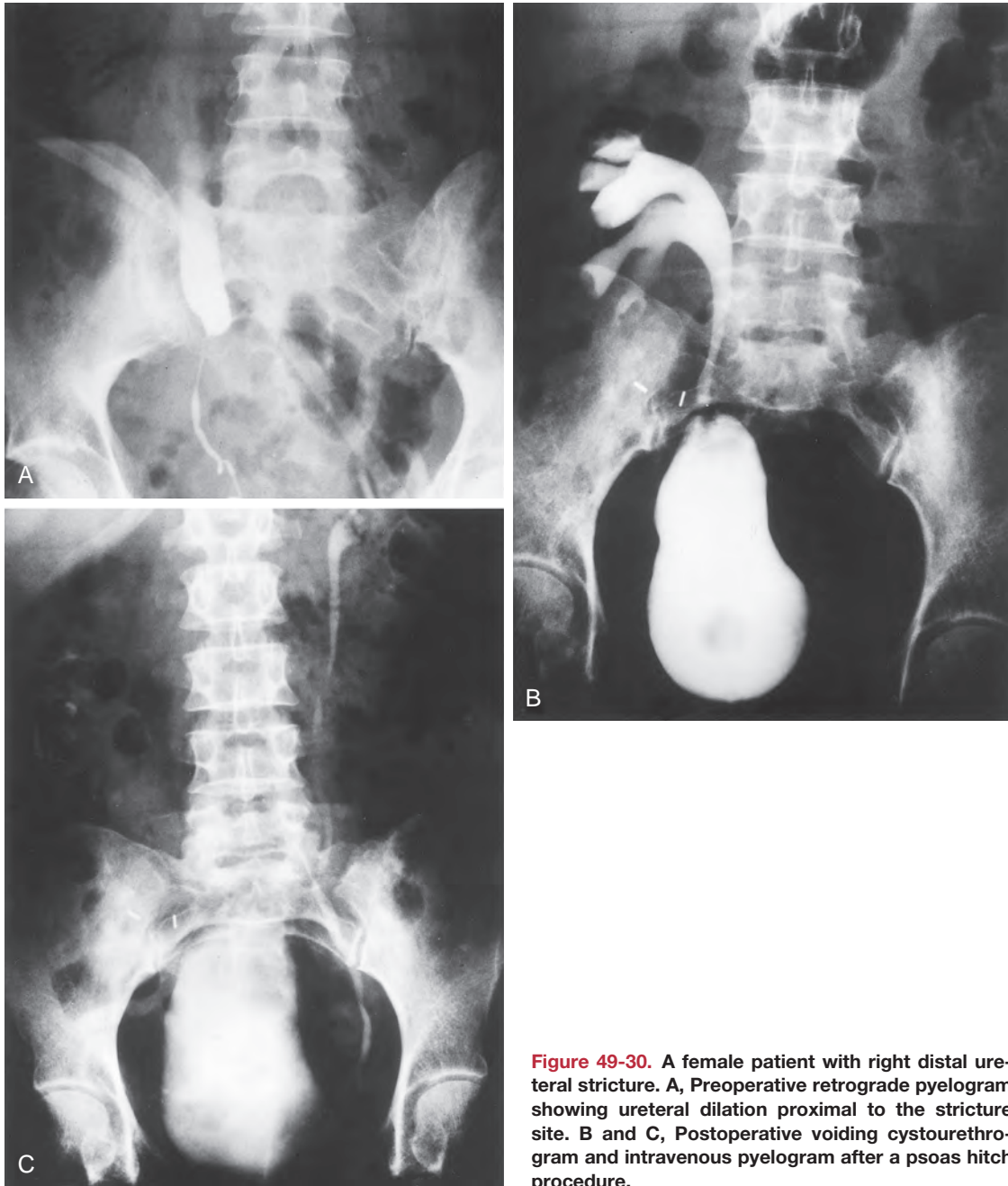


Figure 49-30. A female patient with right distal ureteral stricture. A, Preoperative retrograde pyelogram showing ureteral dilation proximal to the stricture site. B and C, Postoperative voiding cystourethrogram and intravenous pyelogram after a Boari flap procedure.

The flap length should equal the estimated ureteral defect plus an additional 3 to 4 cm if a nonrefluxing anastomosis is planned. Furthermore, the ratio of flap length to base width should not be greater than 3:1 to help minimize flap ischemia.

After bladder flap creation, the distal end of the flap is pexed to the psoas minor tendon or psoas major muscle with several absorbable sutures. The ureter is delivered through a small opening created in the posterior flap, and a tension-free mucosa-to-mucosa refluxing anastomosis is performed after spatulation of the distal ureteral end. Alternatively, a nonrefluxing tunneled anastomosis can be used. The flap is then tubularized anteriorly and closed using absorbable suture. Furthermore, the ureteral adventitia may be secured to the distal aspect of the flap, and the base of the flap may be secured to the psoas (Fig. 49-31).

The number of reported patients treated with a Boari flap is small, yet the results are good if a well-vascularized flap is used (Ockerblad, 1947; Scott and Greenberg, 1972; Thompson and Ross, 1974; Middleton, 1980; Benson et al, 1990; Motiwala et al,

1990) (Fig. 49-32). Clearly, the most common complication is stricture formation, resulting from either ischemia or excessive tension on the anastomosis. Rare pseudodiverticulum has also been reported (Berzeg et al, 2003). Mauck and colleagues reported success in 9 of 10 patients with proximal ureteral strictures treated with a Boari flap (with or without simultaneous downward nephropexy) at 12.8 months' mean follow-up (Mauck et al, 2011).

Laparoscopic Boari Flap

The laparoscopic Boari flap procedure has been uncommonly yet successfully performed in the clinical setting. Kavoussi and colleagues reported three successful cases for distal ureteral obstruction, in which a transperitoneal approach was used (Fugita et al, 2001). Following the same principles as in open surgery, the bladder flap was created and anastomosed to the ureteral end over a stent in a tension-free, watertight manner. Operative time ranged from 120 to 330 minutes, and blood loss ranged from 400 to 600 mL.

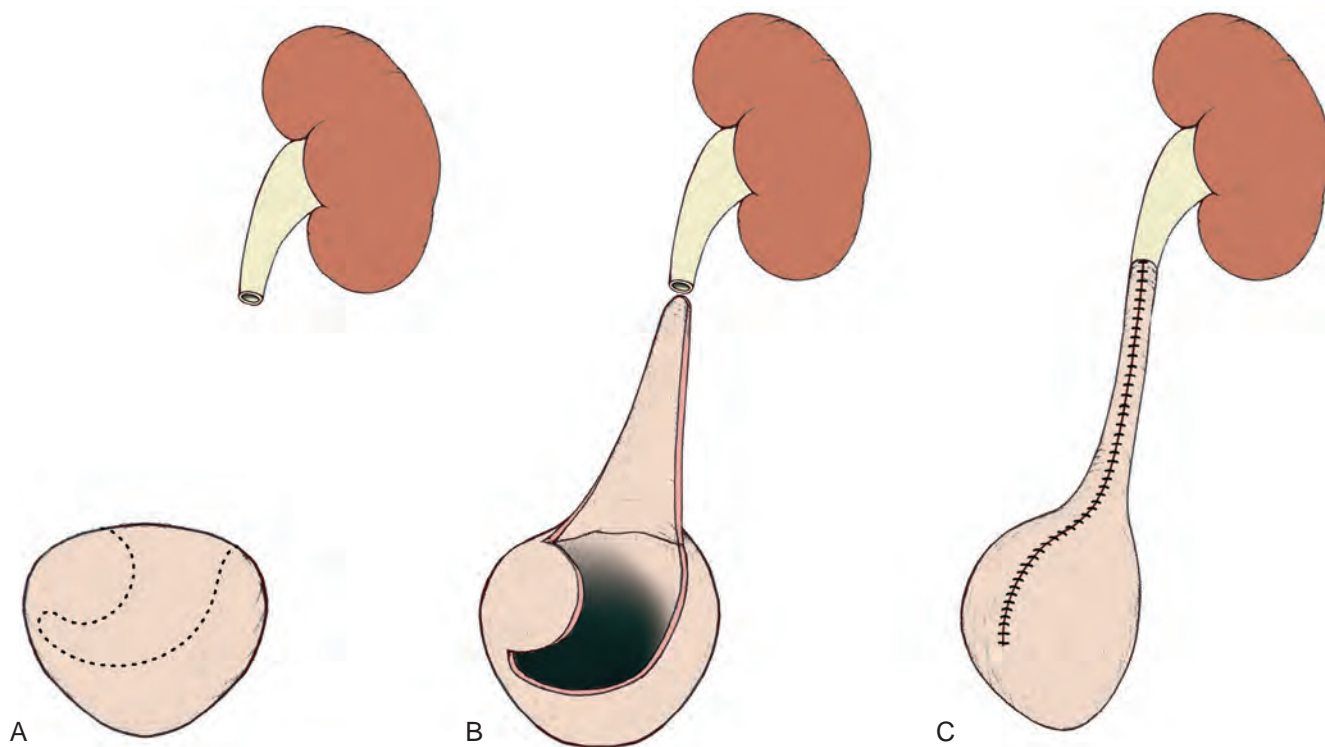


Figure 49-31. A, For a Boari flap, the intended flap is first marked on the anterior and lateral aspects of the mobilized bladder. B, The flap is created, ensuring good vascular supply. C, Ureteroneocystostomy is completed, with the longitudinal bladder tube closure.

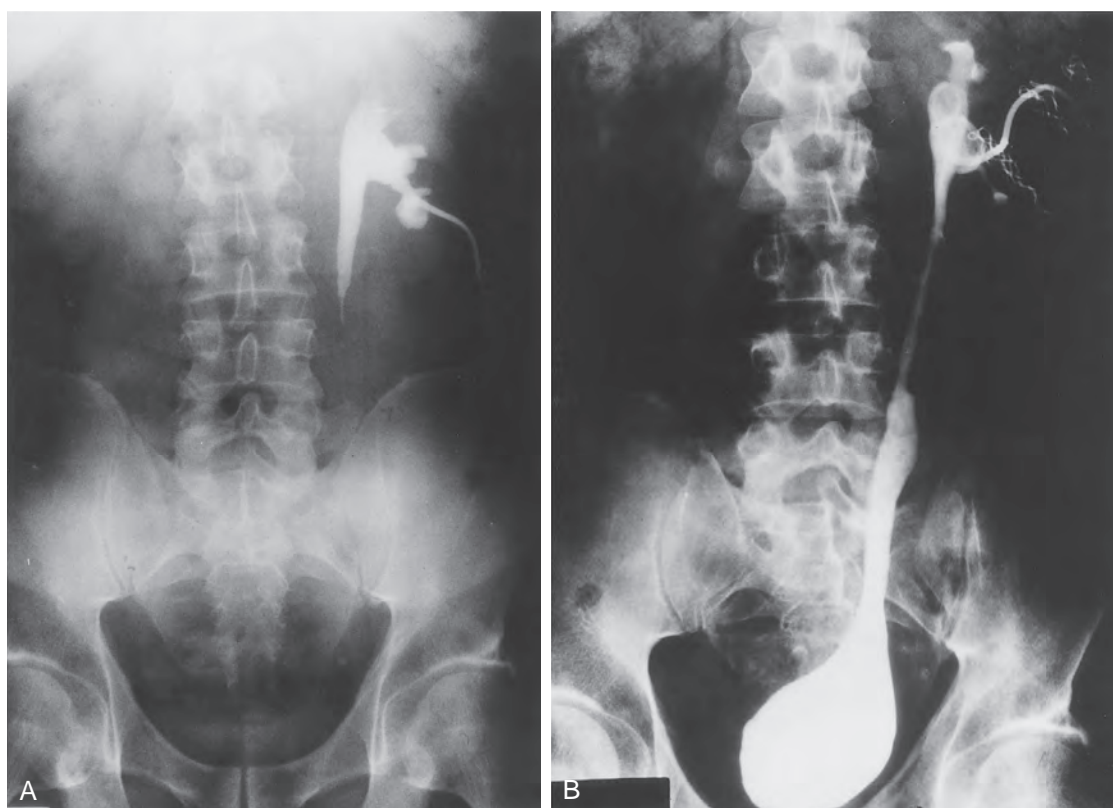


Figure 49-32. A, Preoperative nephrostogram of a patient with left proximal ureteral injury after aortobifemoral bypass surgery. B, Postoperative voiding cystourethrogram after a Boari flap procedure.

Two patients were discharged home within 3 days postoperatively, and 1 patient was hospitalized for 13 days for *Clostridium difficile* colitis. With a follow-up of more than 6 months, there was radiographically demonstrated patency of the anastomosis. In this report, the information regarding the length of distal ureteral stricture was not available. More recently, a laparoscopic Boari flap procedure assisted by the robot has been successfully performed (Schimpf and Wagner, 2009; Allaparthi et al, 2010; Yang et al, 2011; Kozinn et al, 2012; Musch et al, 2013). The transperitoneal approach has been used in all cases reported thus far.

Renal Descensus

Renal mobilization, which was originally described by Popescu in 1964, can provide additional length to bridge a defect in the upper ureter or decrease tension on a ureteral repair (Harada et al, 1964; Popescu, 1964; Passerini-Glazel et al, 1994). A transperitoneal, subcostal, midline, or paramedian incision may be used to gain access to the kidney and the appropriate level of the ureter. After entry to the Gerota fascia, the kidney is completely mobilized and rotated inferiorly and medially on its vascular pedicle. The lower pole of the kidney is then secured to the retroperitoneal muscle using several absorbable sutures. Up to 8 cm of additional length may be gained using this technique. In such cases the renal vessels—especially the renal vein—limit the extent to which the kidney can be mobilized. As a solution, the technique for division of the renal vein with reanastomosis more inferiorly to the inferior vena cava may be performed but is rarely applied clinically. Renal descensus may also be combined with other reconstructive techniques such as a Boari flap to repair pan-ureteral strictures. In addition, laparoscopic techniques have been reported (Sutherland et al, 2011).

Intubated Ureterotomy

The Davis intubated ureterotomy has been described previously in this chapter. Because of the development of the more effective surgical treatment alternatives, this procedure is described primarily for historical interest. In general, an intubated ureterotomy is used for a ureteral stricture too long for conventional ureteroureterostomy or ureteroneocystostomy and has been performed to treat strictures up to 10 to 12 cm in length. An innovative modification to this procedure has incorporated a buccal mucosal patch graft in a small number of patients with good results (Naude, 1999).

Open Transureteroureterostomy

The initial clinical application of TUU was described by Higgins (1934). In the management of ureteral stricture, a TUU may be used when ureteral length is insufficient for anastomosis to the bladder (Brannan, 1975). The only absolute contraindication is insufficient length of the donor ureter to reach the contralateral recipient ureter in a tension-free manner. However, any disease process that may affect both ureters represents a relative contraindication. Absolute contraindications include the presence of a diseased recipient ureter or a donor ureter of inadequate length. Relative contraindications include history of nephrolithiasis, RPE, urothelial malignancy, chronic pyelonephritis, and abdominopelvic radiation. Reflux to the recipient ureter, if present, needs to be identified and corrected simultaneously. Therefore a voiding cystogram should be performed preoperatively, in addition to the other imaging and endoscopic studies previously described for thorough evaluation of both ureters.

In performing a TUU, a midline, transperitoneal approach is used to gain access to both ureters. After medial colonic mobilization, the affected ureter is mobilized, preserving the adventitia with the ureteral blood supply, and divided just proximal to the level of obstruction. The contralateral colon is medially mobilized. Only the portion of recipient ureter needed for the anastomosis is exposed, which is typically 5 cm proximal to the level of division of the affected ureter. A tunnel under the sigmoid colon mesentery

is created proximal to the inferior mesenteric artery to avoid ureteral tethering by this vessel, after which the donor ureter is brought through the tunnel to the recipient side. Mobilization of the recipient ureter should be minimized to help preserve the integrity of its vascular supply. An anteromedial ureterotomy is made in the recipient ureter, which is then anastomosed to the spatulated donor ureteral end in a tension-free, watertight manner using either interrupted or running absorbable sutures. A double-J ureteral stent is usually passed from the donor renal pelvis through the anastomosis and into the bladder. A second ureteral stent may also be placed throughout the length of the recipient ureter if the ureter is found to be adequately large in diameter.

The clinical success of TUU has been demonstrated by multiple investigators. Hendren and Hensle (1980) reported 75 cases of pediatric TUU without compromising a single recipient kidney. Hodges and colleagues (1980) reported similar success in a large group of children and adults. However, two patients required revision because of ureteral kinking by the inferior mesenteric artery. The successful application of TUU was further confirmed more recently by Pesce and colleagues (2001). In two other recent studies, nephrectomy for ureteral stenosis was found to be rarely necessary (Mure et al, 2000; Sugarbaker et al, 2003).

Laparoscopic Transureteroureterostomy

A few reports of successful laparoscopic TUU exist, and this may be a viable option in skilled hands, although long-term clinical data to support this technique do not yet exist (Piaggio and Gonzalez, 2007; Kaiho et al, 2011).

Open Ileal Ureteral Substitution

Surgical management of long length of ureteral defect or loss, especially the proximal ureter, is particularly challenging (Benson et al, 1990). Reconstruction of the ureter with tissue lined with urothelium is most preferable because urothelium is not absorptive and is resistant to the inflammatory and potentially carcinogenic effects of urine (Harzmann et al, 1986). Incorporation of other tissue in ureteral repair is, therefore, reserved for situations in which a defect cannot be bridged by other methods or the bladder is unsuitable for reconstruction. In this scenario, ileal interposition has been demonstrated to be a satisfactory option for complicated ureteral reconstruction. On the other hand, the appendix and fallopian tube have been found to be unreliable ureteral substitutes.

Shoemaker reported the first ileal ureter in a woman with tuberculous involvement of the urinary tract in 1909 (Moore et al, 1956). Later, the metabolic and physiologic effects of the ileal ureter were investigated in the canine model (Hinman and Oppenheimer, 1958; Martinez et al, 1965). When an isoperistaltic segment of ileum is directly anastomosed to the bladder, reflux and renal pelvic pressure increase are usually seen only during voiding. The retrograde transmission of intravesical pressure is dependent on the length of ileum segment used in interposition and the voiding pressure. In patients with ileal segments longer than 15 cm, Waldner and colleagues (1999) found no reflux into the renal pelvis in a report involving 19 patients with ileal ureter with refluxing ileovesical anastomosis. Comparing dogs with tapered versus nontapered ileal segments, Waters and colleagues (1981) found no difference in renal perfusion pressure or metabolic derangements.

A large clinical experience in ileal ureter involving 89 patients was reported by Boxer and colleagues (1979). Only 12% of patients with normal preoperative renal function developed significant metabolic problems postoperatively, and preoperative renal function was identified to be an important prognostic factor. In a separate study, nearly half of those with a serum creatinine of greater than 2 mg/dL developed hyperchloremic metabolic acidosis, requiring conversion to a conduit (Koch and McDougal, 1985). In the same study, patients with bladder dysfunction also experienced more complications. No sufficient clinical data exist to establish the superiority of a tapered segment, a nonrefluxing anastomosis, or a shorter, segmental replacement over a standard ileal substitution

(Waters et al, 1981). Therefore, the contraindications to an ileal ureteral substitution are baseline renal insufficiency with a serum creatinine of greater than 2 mg/dL, bladder dysfunction or outlet obstruction, inflammatory bowel disease, and radiation enteritis.

Before the surgical procedure, a full mechanical and antibiotic bowel preparation is often used. A long midline incision is made. The ipsilateral colon is mobilized medially, and the affected ureter is dissected proximally to the level of healthy tissue. The proximal anastomosis may be performed at the level of the renal pelvis if the entire upper ureter is unhealthy. The length of the ureteral defect is measured, and an appropriate segment of distal ileum is chosen. The segment should be at least 15 cm away from the ileocecal valve, and adequate blood supply should be confirmed before harvesting. The mesentery is usually divided more extensively than with a standard ileal conduit to provide greater mobility. Occasionally, a segment of colon may be more accessible than ileum and is harvested using similar surgical principles. In the presence of a scarred or intrarenal pelvis, ileocalicostomy may be performed (McQuitty et al, 1995). In this circumstance, excision of a piece of lower pole renal parenchymal tissue is helpful in preventing stenosis at the anastomosis, as in a typical ureterocalicostomy. After bowel division, the distal end of the ileal segment is marked for orientation, and bowel-to-bowel continuity is reestablished. A small window is made in the colonic mesentery, through which the segment of ileum is delivered laterally. Alternatively, the cecum and ascending colon can be reflected superiorly to avoid mesenteric window creation in performing right ureteral reconstruction. The orientation of the ileal segment is checked to ensure isoperistalsis, and the anastomoses are performed at the level of the renal pelvis or lower pole calyx and at the bladder (Fig. 49-33). Bilateral ileal ureteral substitution may be achieved by using a longer segment that travels intraperitoneally from one kidney to the other and then to the

bladder. An alternative to such is to use two separate bowel segments.

Perioperative complications associated with ileal ureter include early urinary extravasation or urinoma formation and obstruction from edema, a mucous plug, or a kink in the segment. Ischemic necrosis of the ileal segment may occur and should be considered if signs of an acute abdomen are present. Significant electrolyte abnormalities and renal insufficiency are unusual if preoperative renal function is normal. Patients with worsening metabolic abnormalities associated with a progressively dilating ileal ureter should be evaluated for vesicourethral dysfunction. Furthermore, malignancy arising from an ileal ureter segment has been reported in four cases in the literature (Austen and Kalble, 2004), and it is recommended that regular endoscopic examination be performed starting at postoperative year 3 for early detection of such malignancy. However, Bonfig and colleagues (2004) confirmed the safety and reliability of ileal ureter creation for complex ureteral stricture and loss in 43 patients with a mean follow-up of 40.8 months. A more recent study from Wolff and coauthors (2011) reported long-term follow-up in 17 patients undergoing ileal ureteral substitution (median 174 months) and found that 15 patients still had ileal ureters at the end of the study interval, although 3 patients were on dialysis by that time. The mean creatinine value at last follow-up was 1.8 ± 0.6 mg/dL.

Laparoscopic Ileal Ureteral Substitution

The clinical experience in laparoscopic ileal ureteral substitution is limited worldwide, yet this procedure appears to hold significant promise. Gill and colleagues (2000a) reported successful laparoscopic ileal ureter replacement using a transperitoneal, three-port approach. The entire procedure including freehand suturing and knot tying was performed using intracorporeal laparoscopic

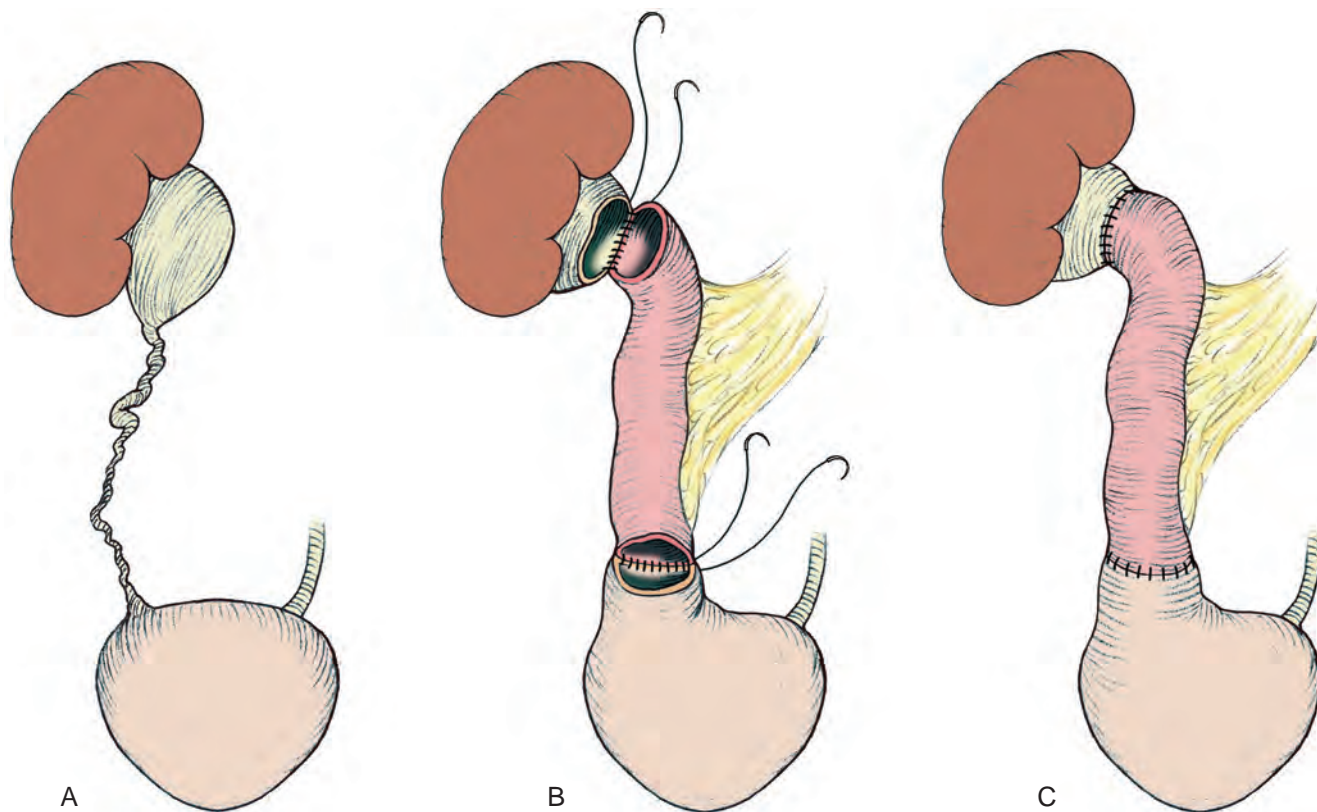


Figure 49-33. A, In ileal ureteral substitution, the affected ureter is first identified and dissected; this is followed by removal of the diseased portion. B, A piece of ileum is brought through the colonic mesentery to bridge the renal pelvis and the bladder. C, Both proximal and distal anastomoses are completed in a full-thickness, watertight, tension-free manner.

techniques. The feasibility of the laparoscopic approach was affirmed in a more recent publication from [Stein and colleagues \(2009\)](#), which compared seven laparoscopic ileal ureters created during the same time period as seven open procedures. This retrospective comparison found analgesic use and time to convalescence to favor the laparoscopic approach (median morphine equivalents 38.9 vs. 322.2 mg, $P = .035$, and 4 vs. 5.5 weeks, $P = .03$, respectively). Although median follow-up was short, particularly in the laparoscopic cohort (13 months, range 2 to 79), the authors reported that all procedures were successful by both imaging and symptomatic measurements.

In addition, robotic-assisted laparoscopic ileal ureter has also been performed via a transperitoneal, four-port approach successfully ([Wagner et al, 2008](#)). Total operative time was 9 hours, with an acceptable hospital stay of 5 days.

Autotransplantation

In 1963 Hardy performed the first autotransplantation for a patient with proximal ureteral injury. Since then, clinical autotransplantation has been performed for a variety of problems including extensive ureteral loss or stricture ([Hardy, 1963](#); [Novick and Stewart, 1981](#); [Chuang et al, 1999](#); [Wotkowicz and Libertino, 2004](#)). In general, autotransplant is considered when the contralateral kidney is absent or poorly functioning or when other methods for ureteral substitution or repair are not feasible. The kidney is harvested with maximal vessel length as in a typical live donor nephrectomy for allotransplantation, and the renal vessels are anastomosed to the iliac vessels to reestablish renal perfusion. A healthy segment of the proximal ureter is anastomosed to the bladder ([Bodie et al, 1986](#)). Alternatively, the ipsilateral renal pelvis may be anastomosed directly to the bladder ([Kennelly et al, 1993](#)).

Not surprisingly, laparoscopy has been successfully incorporated in autotransplantation for severe ureteral loss. Nephrectomy can be performed laparoscopically as in any typical laparoscopic donor nephrectomy, followed by renal graft retrieval, bench preparation, and autotransplantation in the ipsilateral iliac fossa via a Gibson incision using the standard open surgical techniques ([Fabrizio et al, 2000](#); [Meng et al, 2003](#); [Blueblond-Langner et al, 2004](#)). The use of laparoscopy in autotransplantation has been shown to provide reduced postoperative analgesic need and faster recovery because a large open upper abdominal or flank incision for renal harvest is avoided. Laparoscopic nephrectomy in autotransplantation is most commonly performed transperitoneally. However, retroperitoneal approach for such purpose has been applied successfully by [Gill and colleagues \(2000b\)](#).

URETEROENTERIC ANASTOMOTIC STRICTURE

Incidence and Etiology

Several factors determine the incidence of stricture formation at the anastomosis of the ureter and intestine at the time of urinary diversion. The longest follow-up data available are for urinary conduits, in which the stricture rate is 4% to 8% and strictures are more common on the left ([Schmidt et al, 1973](#); [Skinner et al, 1980](#); [Mattei et al, 2008](#)). Factors potentially influencing outcome in this population include the technique used for ureteral dissection, the segment of bowel used for the diversion, and the type of anastomosis performed. Because ureteral ischemia is central to the cause of ureteroenteric strictures, careful attention to dissection is necessary to prevent complications.

The ureteral blood supply runs parallel to the ureter in the adventitia, and although ureteral mobilization is necessary to approximate the ureter and bowel and prevent tension on the anastomosis, stripping the ureter of its surrounding adventitia can lead to ureteral ischemia and stricture formation. The ileotomy technique is also a consideration. Cheng and associates reported using a shield-shaped ileotomy rather than a slit-shaped incision and found a 4.3% stricture rate compared with 8.3% in a retrospective assessment ([Cheng et al, 2011](#)). Barbieri and colleagues reported

KEY POINTS: SURGICAL REPAIR OF URETERAL STRICTURE

- Only short ureteral defects may be managed by end-to-end ureteroureterostomy.
- Distal ureteral stricture may be managed with ureteroneocystostomy with a psoas hitch or Boari flap.
- A Boari flap may be used to bridge a 10- to 15-cm ureteral defect. Small bladder capacity is a contraindication to such flap creation. Care should be taken to ensure adequate vascular supply to the flap.
- TUU is contraindicated in the presence of any disease process that may affect both ureters. It is also contraindicated if there is insufficient length of the donor ureter to reach the contralateral recipient ureter in a tension-free manner.
- Ileal ureter is useful in the presence of extensive ureteral loss. It is contraindicated in patients with baseline renal insufficiency with a serum creatinine of greater than 2 mg/dL, bladder dysfunction or outlet obstruction, inflammatory bowel disease, or radiation cystitis.
- Autotransplantation is considered when the contralateral kidney is absent or poorly functioning or when other methods for ureteral substitution or repair are not feasible.
- Laparoscopic or robotic reconstructive techniques in the hands of urologists skilled in these approaches may provide quicker recovery for patients.

ureteroileal anastomosis with intraluminal visualization in 118 patients with a 4.2% stricture rate at 15 months, all on the left side ([Barbieri et al, 2010](#)). With this approach the conduit is opened on the antimesenteric border to allow for direct visualization of the anastomosis. Moreover, Mattei and colleagues reported numerous advantages to routine stenting of ureteroileal anastomosis ([Mattei et al, 2008](#)). When performing an ileal conduit, the left ureter is brought underneath the sigmoid mesentery just overlying the aorta. The additional length and dissection needed on the left and the possibility of angulation around the inferior mesenteric artery may lead to a higher incidence of stricture formation on the left ([Mansson et al, 1989](#); [Barbieri et al, 2010](#)).

Controversy exists over the choice of bowel segment used for conduit diversion. One theoretic advantage to the use of colon is the feasibility of performing a nonrefluxing anastomosis. However, the reported incidence of renal deterioration with a nonrefluxing versus a refluxing ureterocolonic anastomosis has been mixed, and there does not appear to be a clear advantage with respect to renal function and colonization with a nonrefluxing anastomosis. The issues influencing stricture formation in continent urinary diversions become even more complex owing to the variety of bowel segments, reservoir configurations, and types of anastomoses available for reconstruction. The reported rate of ureteroenteric anastomotic stricture after continent diversion is 3% to 25%, with the majority occurring within the first 2 years ([Lugagne et al, 1997](#); [Weijerman et al, 1998](#); [Kouba et al, 2007](#)). Despite the paucity of randomized studies, there remains evidence in the literature that the risk of obstruction with a nonrefluxing anastomosis is significantly higher than that of a refluxing anastomosis. [Pantuck and colleagues \(2000\)](#) compared 60 nonrefluxing ureteroenteric anastomoses with 56 direct, refluxing anastomoses and found the long-term stricture rates to be 13% and 1.7%, respectively. With a mean follow-up of 41 months, there was no significant difference in the two groups with respect to hydronephrosis, pyelonephritis, nephrolithiasis, or renal insufficiency. Similarly, Roth and colleagues found a greater than fivefold increase in ureteral strictures in the group undergoing a nonrefluxing anastomosis ([Roth et al, 1996](#)). Their data also indicated that the risk of obstruction was unrelated to surgical expertise.

[Studer and colleagues \(1995\)](#) have reported a randomized study evaluating a nonrefluxing versus a refluxing anastomosis into an

isoperistaltic afferent ileal limb. Thirteen percent of nonrefluxing anastomoses resulted in stricture formation, as compared with 3% of refluxing anastomoses. Although there is no clear evidence that reflux into an adult kidney is detrimental, it is clear that obstruction is quite harmful to renal function. These studies and others support the use of a refluxing anastomosis in low-pressure continent reservoirs.

Kouba and colleagues compared the Wallace and Bricker techniques of ureteroileal anastomosis for continent and incontinent diversions and found low rates of stricture (0% to 3%) using both techniques in 186 patients with 34-month follow-up. Notably, with use of the Wallace technique (joined ureters) no strictures were identified, compared with 3.7% in patients undergoing the Bricker technique (separate ureters). Of note, the group undergoing the Bricker anastomosis had a higher BMI than the Wallace group (Kouba et al, 2007).

Evaluation

Screening of the upper tracts in patients who have undergone any type of urinary diversion may include renal ultrasound, CT, or MRI. If a stone or recurrent tumor is suggested, a CT scan or MRI is necessary for a more detailed assessment. In addition, patients with renal colic, recurrent urinary tract infection, or loss of renal function will require evaluation. In patients with hydronephrosis, CT urography, excretory urography, loopogram, or antegrade nephrostogram can provide information on the length and location of a stricture. Diuretic renography is indicated in patients with hydronephrosis to assess differential renal function and confirm the presence of functional obstruction. If hydronephrosis is present but renal function is insufficient for intravenous urogram or renography, placement of a nephrostomy tube and performance of an antegrade nephrostogram are both diagnostic and therapeutic. This approach is also useful before endoscopic intervention because it clarifies stricture length, which aids in surgical planning.

Indications for Intervention

Not all patients with urinary diversion and hydronephrosis require intervention. **Most patients with a long-term urinary conduit will have an element of chronic hydronephrosis that is not secondary to obstruction. In this population, a decrease in renal function or loss of reflux on a routine loopogram should prompt diuretic renography to quantitatively assess for functional obstruction.** Indications for intervention in patients with diversions and hydronephrosis include pain, infection, and renal insufficiency associated with functional obstruction. Although recurrence of transitional cell carcinoma at the level of the anastomosis is uncommon, the radiographic picture of an irregular mass at the level of the stricture and the rapid progression of obstruction and loss of renal function should prompt further evaluation and intervention (Tsuji et al, 1996).

A particularly challenging subset of patients is those undergoing urinary diversion as part of a pelvic exenteration for gynecologic malignancy. Penalver and colleagues (1998) reported on 66 patients, 95% of whom had undergone previous pelvic irradiation. Early and late complications at the ureteroenteric anastomosis were 22% and 10%, respectively. Eighty-five percent of the postoperative complications were managed successfully by conservative measures such as percutaneous nephrostomy.

Endourologic Management

Endourologic management of ureteroenteric strictures has evolved in a manner analogous to that for ureteral stricture disease. Although the initial procedures involved simple balloon dilation and stent placement, unsatisfactory results led to incisional techniques using electrocautery; more recently, the laser was applied using both fluoroscopic and direct endoscopic control. The current state-of-the-art incisional technique for endoureterotomy includes small-caliber flexible ureteroscopic instrumentation along with

holmium laser incision (Siegel et al, 1982; Muench et al, 1987; Cornud et al, 1992; Delvecchio et al, 2000; Laven et al, 2001, 2003; Schöndorf et al, 2013).

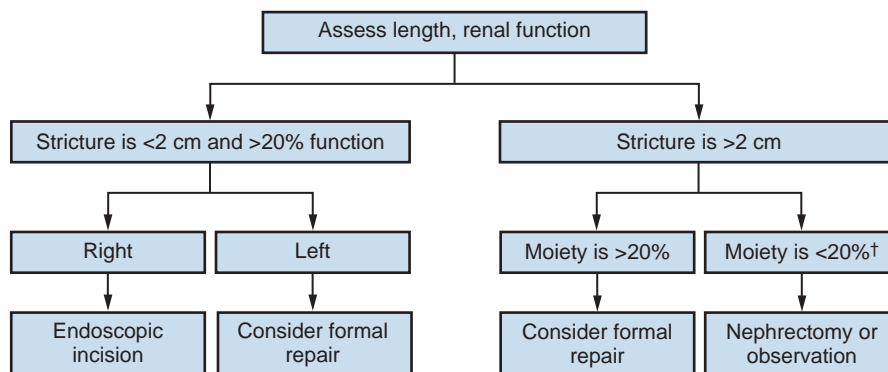
Endourologic management of ureteroenteric or ureterocolic strictures, unlike the management of ureteral strictures, still favors antegrade management. Accordingly, endourologic procedures typically begin with antegrade percutaneous access. Simple percutaneous drainage is continued to allow relief of any associated infection or obstruction-related renal dysfunction. Once the patient's condition is clinically stable, fluoroscopic control is used to pass a guidewire in an antegrade fashion across the anastomotic stricture, over which a balloon catheter can be positioned and inflated until the waist disappears. Stents are a routine part of endourologic management, and these are typically inserted in this same antegrade fashion. However, because of difficulty with mucous plugging of stents in this setting, many centers routinely use an internal-external stent, which can be easily flushed or changed over a wire. In addition, retrograde looposcopic access can be combined with percutaneous access and antegrade passage of a wire. With through-and-through control, the anastomosis can be visualized fluoroscopically or, preferably, with direct ureteroscopic, looposcopic, or trans-stomascopic visualization. Any number of procedures can then be used for the dilation itself including balloon dilation alone, electroincision with an electrode or hot-wire cutting balloon, or holmium laser incision. In all cases, a stent is placed, usually for 4 to 8 weeks.

Balloon dilation of ureteroenteric strictures was one of the first endourologic forms of management used, and fortunately long-term results are available. Notably, short-term reports of use of high-pressure balloon dilation have demonstrated success rates as high as 61% (Ravery et al, 1998). Alternatively, Shapiro and colleagues (1988) reported balloon dilation for 37 benign ureteroenteric strictures in 29 patients. Only 6 dilations (16%) were considered to have a successful result at least 1 year after interventional treatment, and repeat dilations were often required to maintain ureteral patency. Similarly, Kwak and colleagues (1995) achieved an overall success rate of less than 30% at 9 months for patients undergoing antegrade balloon dilation of ureteroenteric strictures. More recently, DiMarco and colleagues (2001) reported a 5% 3-year success rate in 52 balloon dilations of ureteroenteric anastomotic strictures. Recently Schöndorf and associates reported on 74 patients with ureteroenteric anastomotic strictures with a 26% success rate with endourologic intervention compared with a 91% success rate with open intervention at 29 months. **For strictures greater than 1 cm, the endourologic success rate was 6%, compared with a 50% success rate in strictures less than 1 cm. Endourologic intervention was successful 19% on the left compared with 41% on the right, whereas no difference was noted in sidedness with open repair (Schöndorf et al, 2013).**

Metallic stents have also been used for ureteroenteric anastomotic strictures, with acceptable short-term results. Overall, of 30 patients in the published literature, the reported patency rate is greater than 80% with 6- to 22-month follow-up (Kurzer and Leveillee, 2005). **There is a higher incidence of encrustation and stone formation with use of metallic stents for ureteroenteric anastomotic strictures, in addition to the risks of tissue ingrowth, recurrent obstruction, and stent migration (Kurzer and Leveillee, 2005; Gorin et al, 2011; Ng et al, 2013).** This may explain the limited published data regarding use of this approach.

Cautery wire balloon incision has also been reported in patients treated for ureteroenteric strictures (Lin et al, 1999; Schöndorf et al, 2013). For benign strictures, stent-free long-term patency was achieved in only 30% of patients. Meretyk and colleagues reviewed the long-term results of endourologic management of ureteroenteric anastomotic strictures at Washington University. In that study, 15 patients with 19 ureteroenteric strictures were followed for an average of 2.5 years. An antegrade approach was used most frequently and was usually combined with electroincision. A 57% long-term stent-free patency rate was achieved, even with follow-up longer than 2 years (Meretyk et al, 1991). **Whereas long-term patency of most endoscopic procedures approaches only 50%,**

OPTIMAL THERAPY FOR URETEROENTERIC ANASTOMOTIC STRICTURES*



*Consider balloon if transplant on immunosuppression.

†Pediatric patients and select patients with renal insufficiency may warrant repair.

Figure 49-34. Algorithm for management of ureteroenteric anastomotic stricture disease.

such approaches may be used preferentially as the initial intervention in select patients. Definitive operative management is reserved for patients in whom endourologic intervention fails and for patients with strictures longer than 1 cm (Kramolowsky et al, 1987, 1988; Schöndorf et al, 2013).

Cornud and associates (1996) reported their long-term results with percutaneous electroincision of ureterointestinal anastomotic strictures and specifically compared the results of fluoroscopic and endoscopic guidance. Twenty-seven patients were followed for longer than 1 year after stent removal, and an overall patency rate of 71% was reported. These investigators found better results when direct endoscopic control was combined with fluoroscopic guidance, compared with fluoroscopic guidance alone. In that report, right common iliac artery damage was reported during electroincision in 1 patient who had the procedure performed under fluoroscopic guidance alone. As a result, direct visual approaches have been favored for the management of ureteroenteric or ureterocolic anastomotic strictures, and the holmium laser has proven to be an excellent incisional tool. Endoureterotomy is typically performed in an antegrade manner, and success rates ranging from 50% to 80% have been reported (Singal et al, 1997; Laven et al, 2001; Watterson et al, 2002). These reports suggest the left side is more resistant to management because the majority of the failures occurred on the left side (Laven et al, 2003; Schöndorf et al, 2013). When considering endoscopic incision of a left ureteroenteric stricture, the risk of hemorrhage is a consideration because the sigmoid mesentery can be in close proximity. This, taken with the lower success rates of all endoscopic approaches on the left side, supports serious consideration for primary repair when treating left ureteroenteric anastomotic strictures (Fig. 49-34). In spite of this, Lovaco and colleagues reported good success treating 25 ureteroenteric strictures with endoureterotomy by an intraluminal invagination technique, with 80% success at more than 50 months' follow-up. Of note, this approach increases the distance between the incision site and surrounding vessels and viscera and does not favor left or right strictures (Lovaco et al, 2005).

RETROPERITONEAL FIBROSIS

Presentation and Etiology

RPF is typically characterized by the presence of an inflammatory, fibrotic process in the retroperitoneum causing compression of the retroperitoneal structures including the ureters. RPF most commonly affects patients who are 40 to 60 years of age. However, more than 30 cases of RPF have been reported in patients younger than 18 years of age (van Bommel, 2002). RPF cases have a male predominance, with a male-to-female ratio of 2:1 to 3:1. The true

KEY POINTS: URETEROENTERIC STRICTURES

- Although long-term patency of minimally invasive procedures for ureteroenteric strictures is in the range of 50%, such approaches are still used as the initial intervention, reserving operative management for those patients in whom endourologic intervention fails.
- When considering endoscopic incision of a left ureteroenteric anastomotic stricture in an ileal conduit, hemorrhage is a concern because the sigmoid mesentery can be in close proximity. Considering the low success rates of endoscopic approaches in this scenario, these patients may be best treated with definitive repair.
- Acceptable long-term success rates have been reported with open or robotic repair of ureteroenteric anastomotic strictures. As expected, strictures longer than 1 cm were more likely to recur and procedures on the left side had lower success rates.

incidence is unknown but has been estimated to be 1 per 200,000 to 500,000 per year.

In general, the retroperitoneal fibrotic mass centers around the distal aorta at L4 to L5 and wraps around the ureters, leading to hydronephrosis via extrinsic compression on the ureters or interference with ureteral peristalsis (Lepor and Walsh, 1979; Koep and Zuidema, 1987). In most patients, the presenting symptom is pain in the lower back and/or flank. The pain, which is typically dull, noncolicky, and unchanged with posture, may radiate to the lower abdomen or groin. Furthermore, the pain is often relieved by aspirin rather than narcotics. Other symptoms include weight loss, anorexia, nausea, generalized malaise, fever, hypertension, and oliguria or anuria. The mass may compress the inferior vena cava, resulting in deep venous thrombosis and lower extremity edema (Rhee et al, 1994). The mass may extend proximally to the renal hilum and encase the renal vein, resulting in renal vein hypertension and subsequent gross hematuria (Powell et al, 2000). Aortic obstruction and involvement of the mediastinum, the biliary system, the mesentery, and the kidney itself are rare (Tripodi et al, 1998; Azuma et al, 1999; Dejaco et al, 1999; Klisnick et al, 1999). Distal extension to the bifurcation of the iliac vessels may occur, and extension to the spermatic cord with scrotal involvement has been reported (Palmer and Rosenthal, 1999; Schulte-Baukloh et al, 1999). Duration of symptoms before diagnosis is usually 4 to 6 months, and approximately half of the patients have fibrosis that has caused significant ureteral obstruction and symptoms secondary to uremia.

In approximately 70% of patients, the disease is idiopathic. Currently, idiopathic RPF is considered part of the spectrum of chronic periaortitis, a large vessel vasculitis (Pipitone et al, 2012). Ceroid, a complex polymer of oxidized lipids and protein found in atherosclerotic plaques, has been suggested as the antigen initiating the inflammatory response (Parums et al, 1991). Indeed, a higher incidence of aortic aneurysms has been identified in patients with RPF (Breems et al, 2000). RPF usually occurs as an isolated disease entity, but it may occur as part of multifocal fibrosclerosis, a rare syndrome characterized by fibrosis involving multiple organ systems. In such a scenario, the clinical presentation may include RPF, sclerosing mediastinitis, sclerosing cholangitis, orbital pseudotumor, and Riedel thyroiditis (Dehner and Coffin, 1998; Özgen and Cila, 2000). The pathogenesis of these disorders is unknown but appears to be autoimmune in nature.

Among the 30% of RPF patients who have an identifiable cause, drugs such as methysergide (Sansert) and other ergot alkyls are most commonly associated with RPF. β -Blockers and phenacetin have also been implicated. The exact pathophysiology of drug-induced RPF remains unknown. Other causes of RPF include malignancies such as lymphoma, the most common malignancy in RPF cases, and multiple myeloma, carcinoid, pancreatic cancer, prostate cancer, and sarcoma (Webb and Dawson-Edwards, 1967; Usher et al, 1977). Radiotherapy for retroperitoneal malignancy is also known to produce a residual fibrotic mass leading to secondary ureteral obstruction. Asbestos exposure has also been associated with RPF in exposed workers in Finland, via gastrointestinal and pulmonary lymphatic drainage (Scheel and Feeley, 2013). In addition, infectious causes such as tuberculosis, *Actinomyces*, gonorrhea, and schistosomiasis have been suggested in the pathogenesis of RPF.

Association of RPF with membranous glomerulonephritis has also been documented in the literature (Mercadal et al, 2000; Shirota et al, 2002). The exact cause remains unclear, although the association has been speculated to be secondary to an unknown antigen triggering systemic immune response that leads to RPF. Association of RPF with ankylosing spondylitis and Wegener granulomatosis has also been reported, further suggesting an underlying immune cause in some patients (Izzedine et al, 2002; LeBlanc et al, 2002).

Pathologically, the typical gross appearance of RPF is that of a smooth, flat, tan-colored, dense mass enveloping the surrounding retroperitoneal structures. It is also known to invade the ureter or psoas muscle. Histologically, the appearance of RPF is that of a nonspecific inflammatory process that varies with the stage of the disease. Early in the disease, affected tissue consists mainly of collagen bundles with capillary proliferation and inflammatory cells including lymphocytes, plasma cells, and fibroblasts. In the later stage, the mass becomes relatively acellular and avascular, consisting of sheets of hypocellular collagen. RPF secondary to malignancy is often histologically indistinguishable from idiopathic RPF, and it can be identified only on the basis of the demonstration of small islands of tumor cells within the fibrotic mass.

Evaluation

In most RPF patients, the clinical symptoms are generally nonspecific, and physical examination is usually unrevealing. Laboratory evaluation may reveal an elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), moderate leukocytosis, anemia, and variable renal insufficiency with associated electrolyte abnormalities. The ESR and CRP are elevated in one half to two thirds of patients with idiopathic RPF (Pipitone et al, 2012). If the overall renal function is normal, an excretory urogram or more commonly CT urography may be performed. Typical findings include hydronephrosis with medial deviation of the proximal ureter and mid-ureter and a smoothly tapered ureter at the level of obstruction. Urinary obstruction is usually bilateral, but unilateral cases have been described. Uncommonly, there are patients with symptoms of urinary obstruction but little hydronephrosis on imaging.



Figure 49-35. Typical computed tomographic findings of retroperitoneal fibrosis. The study demonstrates the presence of a homogeneous mass obliterating the outline of the great vessels at the lumbar area.

CT scan typically reveals hydronephrosis associated with a well-delineated retroperitoneal soft tissue mass enveloping the great vessels and the ureters (Fig. 49-35). If the patient has significant renal impairment, a retrograde pyelogram may be performed. In the radiographic evaluation of RPF, MRI can also be helpful because the mass itself has characteristic T1- and T2-weighted images. RPF is characterized as a diffusely low signal intensity on T1-weighted imaging, although the T2 signal may vary considerably, with high signal intensity consistent with active disease (Fig. 49-36). With treatment, T2 signal often diminishes and thus provides a measure of therapeutic efficacy. Moreover, gadolinium enhancement may also prove valuable in assessing the response to treatment because associated decreases in gadolinium contrast enhancement should also be expected after appropriate therapy (Cronin et al, 2008). Similarly, contrast enhancement on CT can also be used to monitor therapy, as can positron emission tomography (PET). In fact, PET appears to be the most sensitive imaging study for disease activity (Pipitone et al, 2012).

If a kidney is suspected to be nonfunctioning, differential renography should be considered to determine renal function because it may affect surgical planning. Representative biopsy samples of the mass should be obtained percutaneously or at the time of open or laparoscopic ureterolysis to rule out malignancy and allow one to proceed with treatment for RPF.

Management

Initial Management

The initial management of RPF depends on the patient's clinical status. Patients with hydronephrosis and uremia should be emergently decompressed by either percutaneous nephrostomy or indwelling ureteral stents. The advantages to placing ureteral stents include the opportunity to perform retrograde pyelograms to evaluate the anatomy and the convenience of internal drainage. It is interesting to note that ureteral stent placement is usually not difficult to perform in the setting of ureteral obstruction caused by RPF. In a critically ill patient with electrolyte abnormalities and little or no urine output, nephrostomy tube placement is favored. After renal decompression, the patient should be monitored closely for postobstructive diuresis, renal function status, and appropriate replacement of fluids and electrolytes.

After the initial management, an attempt to identify the cause of RPF should be made. Methysergide or any other potentially

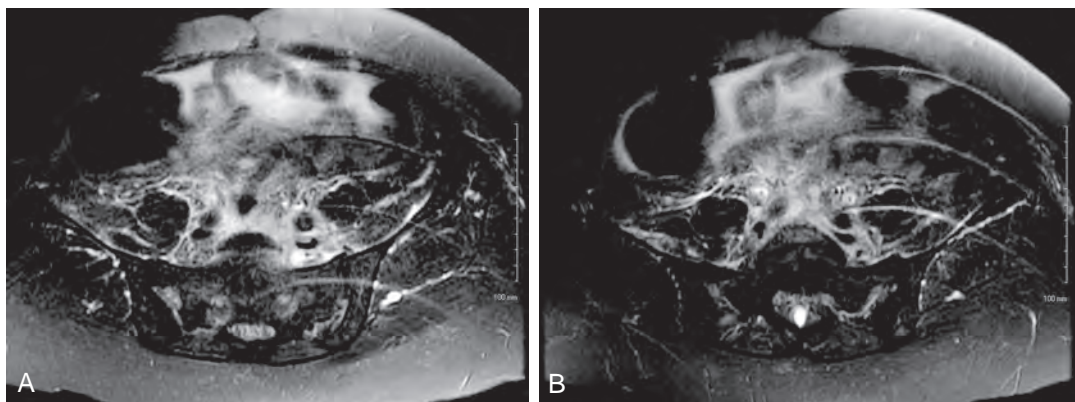


Figure 49-36. A, T2-weighted magnetic resonance image of a symptomatic patient demonstrating retroperitoneal fibrosis with enhancement and thus active disease. B, Same patient after 1 month of medical therapy; note the decrease in enhancement on this corroborative T2-weighted image.

inciting drug, if identified, should be discontinued. Although most patients with malignant RPF have a prior history of malignancy, a thorough evaluation for occult malignancy with careful application of imaging studies is necessary. Biopsy to rule out malignancy, performed percutaneously or at the time of ureterolysis to provide long-term relief of obstruction, should be considered. However, some believe that in patients with no history of prior malignancy, no classic radiographic features on MRI or CT, and no lymphadenopathy, a biopsy is not essential before medical therapy.

Medical Management

Once the diagnosis of idiopathic RPF is made, the common primary medical management has been steroid therapy. In the medical literature there are approximately 170 cases of idiopathic RPF treated with steroids that resulted in about an 80% clinical response, including a decrease in size of the mass and improvement in ureteral obstruction or inferior vena cava compression (Kearney et al, 1976; Baker et al, 1987; Adam et al, 1998; Higgins et al, 1998; van Bommel, 2002; Fry et al, 2008). The characteristic clinical response to steroid therapy includes resolution of pain and constitutional symptoms within days after treatment, a rapid fall of ESR, and diuresis. Dose and duration of steroid therapy vary considerably in the literature, but most regimens start with initial doses of 60 mg daily tapered to 5 mg daily. Chronic steroid therapy up to 2 years has been shown to provide significant improvement in clinical symptoms and regression of retroperitoneal mass (Kardar et al, 2002), although relapse during tapering occurs in 25% to 50% of patients (Pipitone et al, 2012). Patients who have evidence of active inflammation—manifested by increased ESR, CRP, leukocytosis, or active inflammation on a biopsy—are more likely to respond to steroid therapy.

In addition to steroids, immunosuppressive agents including azathioprine, cyclophosphamide, cyclosporine, colchicine, and mycophenolate mofetil have been described to provide benefit in idiopathic RPF in isolated reports (Wagenknecht et al, 1981; McDougal et al, 1991; Grotz et al, 1998; Marzano et al, 2001; Vega et al, 2009). Medroxyprogesterone acetate, progesterone, and particularly tamoxifen have also been found to be beneficial in idiopathic RPF (Clark et al, 1991; Benson and Baum, 1993; Al-Musawi et al, 1998; Dedeoglu et al, 2000; Puce et al, 2000; Pipitone et al, 2012). The exact mechanisms of action of these medications are unclear, but they are believed to inhibit fibroblastic proliferation leading to clinical response. Use of immunosuppressive agents is reserved for patients in whom steroid therapy fails, because relapses are as high as 50% during steroid tapering (Pipitone et al, 2012).

Surgical Management: Open Ureterolysis

Ureterolysis may be performed open surgically or laparoscopically, although open surgery has been considered the standard (Lindell and Lehtonen, 1988; Elashry et al, 1996). It is performed with concomitant biopsy of the mass in patients with an unclear diagnosis as the definitive initial treatment or in those in whom medical therapy has failed. When open surgery is performed, a midline, transperitoneal abdominal incision is made to allow access to both ureters. Placement of ureteral catheters or stents before the abdominal incision is advisable to assist identification and dissection of the ureters. Although hydronephrosis may be unilateral on preoperative assessment, the process in general is bilateral, requiring bilateral ureterolysis. After medial mobilization of the ascending and descending colon, deep biopsies of the mass should be performed for frozen and permanent section to rule out malignancy. Dissection should begin at the distal, nondilated ureteral segment to avoid injury to the thin, dilated proximal segment. A right-angle clamp can be placed between the ureter and the retroperitoneal mass along the course of the ureter, and the fibrotic tissue is then incised above the clamp. This is repeated throughout the length of the entrapped ureter, using both blunt and sharp dissection techniques to free the affected ureter from its fibrous bed. The ureteral wall may become quite thin at times following the dissection. An inadvertent ureterotomy should be closed with absorbable suture. Ureteral excision with ureteroureterostomy is usually unnecessary.

After bilateral ureterolysis, the ureters should be repositioned and protected from further fibrous entrapment. Several surgical options are available. One option is to retract the ureters laterally and secure the overlying peritoneum medially to the psoas muscle to maintain the ureters in this location. Another option is to close the peritoneum behind the ureters so that the ureters may be displaced anteriorly into the peritoneal cavity (Tresidder et al, 1972). It is important not to obstruct the ureter in the closure of the peritoneum at the ureteral hiatus. In a report on a group of patients with idiopathic RPF undergoing intraperitoneal placement of the ureters or lateral retroperitoneal placement of the ureters, no difference in the radiologic or clinical outcome was found (Barbalias and Liatsikos, 1999). In the setting of extensive RPF, a more definitive approach is to surround the ureters with omentum and reposition them within the peritoneal cavity (Carini et al, 1982). For the omental wrap to be performed, the omentum is first mobilized from its attachment to the transverse colon, followed by its division along its midline with ligation of the small omental vessels up to the gastric attachment. The short gastric vessels are then divided and ligated at the level of the stomach wall, after which the two halves of the omentum can be retracted

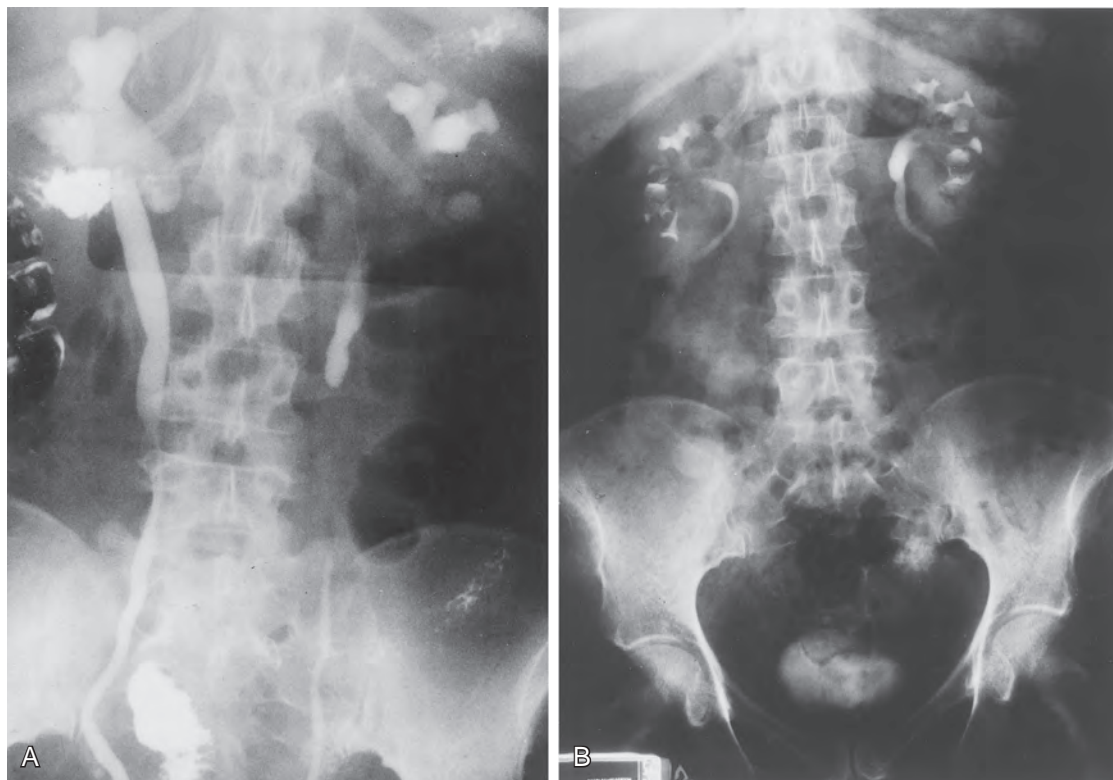


Figure 49-37. A, Preoperative intravenous contrast-enhanced radiograph of a patient with idiopathic retroperitoneal fibrosis, showing bilateral hydronephrosis with medial deviation of the ureters. B, Postoperative radiograph of the same patient after surgical ureterolysis with intraperitoneal omental wrapping.

laterally on the basis of the right and left gastroepiploic arteries. The entire length of the ureter can be surrounded by omental tissue, which is tacked in place with absorbable sutures (Fig. 49-37). The omentum provides protection of the ureter against recurrent extrinsic compression and vascularity to a potentially ischemic ureter. Steroid therapy may be used postoperatively in an attempt to prevent recurrent upper tract and venous compression. If no ureterotomy occurs during ureterolysis, the previously placed stents may be removed shortly after surgery.

If ureterolysis is impossible to perform owing to extensive periureteral fibrosis, renal autotransplantation may be performed if the ipsilateral renal unit demonstrates satisfactory function (Penalver et al, 2001). If no significant renal function can be recovered after an adequate time period of decompression in the presence of the satisfactory contralateral renal function, nephrectomy may be considered.

Surgical Management: Laparoscopic Ureterolysis

The first laparoscopic ureterolysis was reported by Kavoussi and Clayman in 1992 (Kavoussi et al, 1992). Subsequent success with such technique was confirmed by others (Puppo et al, 1994). Another report described experience with laparoscopic ureterolysis in 13 patients including bilateral procedures in 7 and unilateral procedures in 6 (Fugita et al, 2001). Preoperative stent placement was performed in all patients before laparoscopy. For each ureter, the laparoscopic procedure was performed using a transperitoneal four-port approach. After incision of the posterior peritoneum and mobilization of the colon, the affected ureter was dissected free from the retroperitoneal fibrotic tissue. Multiple frozen-section biopsy specimens of the periureteral tissue were obtained to rule out malignancy. The edge of the posterior peritoneum was reapproximated to the sidewall underneath the ureter to intraperitonealize the ureter. Laparoscopic ureterolysis was completed successfully

in 85% (11) of the cases, with 2 (15%) open conversions because of iliac vein injury (in one patient) and marked fibrosis (in one patient). Mean operative time was 381 minutes for bilateral procedures and 192 minutes for unilateral procedures. Mean use of parenteral analgesics was 59 mg of morphine sulfate equivalent. Mean hospital stay was 4 days. Postoperative complications occurred in 30% (4) of the patients and included epididymitis, umbilical port erythema, prolonged ileus, and urinary retention. Pathology showed fibrous tissue with lymphocytes, plasma cells, macrophages, and fibroblast proliferation in all patients. At a mean follow-up of 30 months, upper tract imaging such as intravenous urography or renal scan showed lack of obstruction in 92% (12) of the patients. A multi-institutional survey that included 17 academic centers identified that centers with a fellowship-trained laparoscopist performed laparoscopic ureterolysis, and in 59% of centers urologists performed the medical management. Notably in this survey, the reported laparoscopic success rates were 83% (Duchene et al, 2007).

A more recent retrospective comparison of laparoscopic and open ureterolysis (16 ureters in each group) concluded that the minimally invasive approach was associated with a shorter hospital stay (mean 2.1 vs. 5.9 days, $P = .004$) but that success and complication rates were similar with both approaches (Styn et al, 2011).

Robotic ureterolysis for RPF has also been reported. Keehn and colleagues (2011) treated a total of 21 renal units in 17 patients with robotic ureterolysis and omental wrapping. Fourteen percent recurred and required a secondary surgical intervention, whereas 86% remain patent at a mean follow-up of 20.5 months. The researchers reported one perioperative complication, an enterocutaneous fistula from an unrecognized thermal bowel injury that required bowel resection.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

KEY POINTS: RETROPERITONEAL FIBROSIS

- In general, the retroperitoneal fibrotic mass centers around the distal aorta at L4 to L5 and wraps around the ureters, leading to hydronephrosis via extrinsic compression on the ureters or interference with ureteral peristalsis. In most cases the disease is idiopathic, associated with chronic aortitis.
- RPF symptoms and signs are usually nonspecific. Laboratory evaluation may show an elevated ESR, CRP, moderate leukocytosis, anemia, and variable renal insufficiency associated with electrolyte abnormalities.
- Initial management of RPF in the presence of hydronephrosis and uremia includes emergent decompression by percutaneous nephrostomy or indwelling ureteral stents. After decompression, the patient should be monitored closely for postobstructive diuresis.
- The most common primary medical management of idiopathic RPF has been steroid therapy, with immunosuppressive agents as second line.
- In surgical bilateral ureterolysis, the ureters need to be protected by intraperitonealization or omental wrapping. Both open and laparoscopic techniques may be applied successfully. If ureterolysis is impossible to perform, renal autotransplantation may be performed.

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Renal Injuries

RENAL INJURIES

The kidneys are the most commonly injured genitourinary organs from external trauma. Advances in radiographic staging, improvements in hemodynamic monitoring, and wider use of angioembolization have improved the rates of renal preservation and decreased unnecessary surgery. **The majority of blunt and many penetrating injuries to the kidneys no longer require open surgical intervention.** Close follow-up of these patients and timely treatment of nonoperative failures or complications are still mandatory.

Presentation and History

Motor vehicle accidents, falls from heights, and assaults contribute to the majority of blunt renal trauma. Direct transmission of kinetic energy and rapid deceleration forces place the kidneys at risk. **Perhaps the most important information to obtain in the history of blunt renal injury is the extent of deceleration involved in high-velocity impact trauma.** Significant acceleration/deceleration can cause rare but lethal renovascular injuries. These occur when the kidney tears at retroperitoneal points of fixation such as the renal hilum or ureteropelvic junction, resulting in renal artery thrombosis, renal vein disruption, and renal pedicle avulsion. A more specific history of injury mechanism can be helpful. For example, the majority of the renal injuries after automobile accidents were caused by unrestrained drivers with direct impact on the steering wheel or side impact with the lateral door, often with 30 cm or more of door incursion (Kuan et al, 2007). Understanding details of the accident from first responders at the scene can increase the level of suspicion for renal injury.

Penetrating renal injuries most often come from gunshot and stab wounds. Gunshot wounds comprise the great majority of the penetrating trauma, with stab wounds a distant second (86% vs. 14%). Penetrating mechanisms lead to higher rates of significant and persistent renal bleeding, need for renorrhaphy/nephrectomy, and complications when managed nonoperatively. Of all patients sustaining renal trauma in a large urban series, renal gunshot wounds occurred in approximately 4% (McAninch et al, 1993).

Stab wounds from assault or self-inflicted injuries can cause both renovascular and parenchymal injuries. Common entry sites including the upper abdomen, flank, and lower chest should alert the clinician to possible renal involvement. **Trauma to the anterior axillary line is more prone to damage important renal structures such as the renal hilum and pedicle compared to the posterior axillary line, which more commonly results in parenchymal injury.** Should the weapon be recovered, its dimensions should be noted because the length and width give valuable information on its penetrating and destructive characteristics.

Physical examination of all body systems must be detailed and complete. In a conscious patient, a thorough history can be taken during the examination. Rapid resuscitation according to American Association for the Surgery of Trauma (AAST) guidelines should be followed for polytrauma. With a blunt mechanism, cervical spine

Ureteral Injuries

immobilization is mandated until confirmed intact by radiography. Examination of the abdomen, chest, and back must be performed. The presence of a flank hematoma, abdominal or flank tenderness, rib fractures, and penetrating injuries to the low thorax or flank indicate possible renal injury. **Ipsilateral rib fracture can increase the incidence of significant renal trauma threefold.**

Gunshot injuries can be misleading in that small entrance wounds may underestimate larger tissue destruction within the body. Exit wounds are frequently, but not necessarily, much larger. Soft tissue and bone can alter the bullet's trajectory; thus the projectile may not take a direct path from entrance to exit. Bullet fragments can create secondary missiles, resulting in multiple injury tracts. When radiographs of the chest and abdomen are taken, it is useful to place a small metallic object at entrance and exit sites to help define these locations on the films.

Hematuria

The best indicators of significant urinary system injury include gross and microscopic hematuria (>5 red blood cells/high-power field [RBCs/HPF] or positive dipstick finding), especially when associated with acceleration/deceleration injury, penetrating trauma, or hypotension in the field or emergency room (systolic blood pressure <90 mm Hg).

The degree of hematuria and the severity of the renal injury do not consistently correlate. Gross hematuria has been observed in minor renal contusions, and microscopic hematuria has been seen in some with severe renal injuries. Hematuria was absent in 7% of 420 grade IV renal injuries in a recent analysis (Shariat et al, 2008a), and 36% of renal vascular injuries from blunt trauma demonstrated no blood in the urine (Cass, 1989). Also, approximately 50% of injuries to the ureteropelvic junction have no microscopic or gross hematuria. In patients with blunt trauma, microscopic hematuria associated with shock significantly increases the incidence of severe renal injuries (Nicolaisen et al, 1985; Mee and McAninch, 1989; Mee et al, 1989; Miller and McAninch, 1995).

The first aliquot of urine obtained by catheterization or voiding is used to determine the presence of hematuria. Later urine samples may be diluted by diuresis from resuscitation fluids, resulting in an underestimation or absence of hematuria. Any degree of visible blood in the urine is regarded as gross hematuria. Microscopic hematuria can be detected by dipstick analysis or microanalysis. The dipstick method is rapid and has a sensitivity and specificity for detection of microhematuria of more than 97%, even though a poor correlation with actual urinalysis was noted in a single study (Chandhoke and McAninch, 1988). **Although critical to the initial evaluation of traumatic urinary tract injury, the presence or absence of hematuria should not be the sole determinant in the assessment of a patient with suspected renal trauma.** Because the significance of hematuria varies with blunt and penetrating mechanisms, the importance of proper detection and staging of renal injuries, usually by computed tomography (CT), must be emphasized.

Classification

The AAST Organ Injury Scaling Committee (Moore et al, 1989) provides the most widely used and accepted classification of renal injury (Table 50-1, Fig. 50-1). Based on accurate grading made possible by contrast-enhanced CT, the AAST injury severity scale is a powerful and valid predictive tool for clinical outcomes in patients with renal trauma (Santucci et al, 2001).

Indications for Renal Imaging

The criteria for radiographic imaging include the following:

1. All penetrating trauma with a likelihood of renal injury (abdomen, flank, or low chest entry/exit wound) who are hemodynamically stable enough to have a CT (instead of going right to the operating room or angiography suite)

2. All blunt trauma with significant acceleration/deceleration mechanism of injury, specifically rapid deceleration as would occur in a high-speed motor vehicle accident or a fall from heights
3. All blunt trauma with gross hematuria
4. All blunt trauma with microhematuria and hypotension (defined as a systolic pressure of less than 90 mm Hg at any time during evaluation and resuscitation)
5. All pediatric patients with greater than 5 RBCs/HPF

An extensive prospective study based at San Francisco General Hospital evaluating indications for radiographic imaging was ongoing for more than 25 years. The findings have been updated on three reports (Nicolaisen et al, 1985; Mee and McAninch, 1989; Miller and McAninch, 1995) (Fig. 50-2). Based on information from this study, all patients with blunt trauma with gross hematuria and patients with microscopic hematuria and shock (systolic

TABLE 50-1 American Association for the Surgery of Trauma Organ Injury Severity Scale for the Kidney

GRADE*	TYPE	DESCRIPTION
I	Contusion Hematoma	Microscopic or gross hematuria, urologic studies normal Subcapsular, nonexpanding without parenchymal laceration
II	Hematoma Laceration	Nonexpanding perirenal hematoma confined to renal retroperitoneum <1 cm parenchymal depth of renal cortex without urinary extravasation
III	Laceration	>1 cm parenchymal depth of renal cortex without collecting system rupture or urinary extravasation
IV	Laceration Vascular	Parenchymal laceration extending through renal cortex, medulla, and collecting system Main renal artery or vein injury with contained hemorrhage
V	Laceration Vascular	Completely shattered kidney Avulsion of renal hilum, devascularizing the kidney

*Advance one grade for bilateral injuries up to grade III.

Data from Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: spleen, liver, and kidney. J Trauma 1989;29:1664-6.

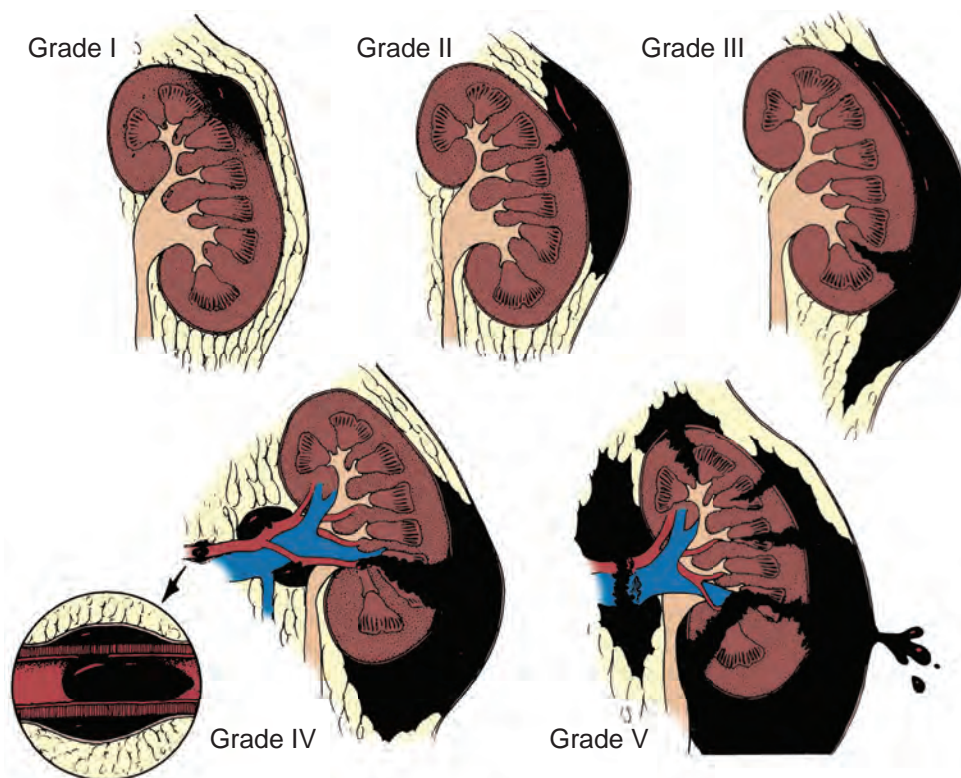


Figure 50-1. Classification of renal injuries by grade (based on the organ injury scale of the American Association for the Surgery of Trauma [based on Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: spleen, liver, and kidney. J Trauma 1989;29:1664-6.]).

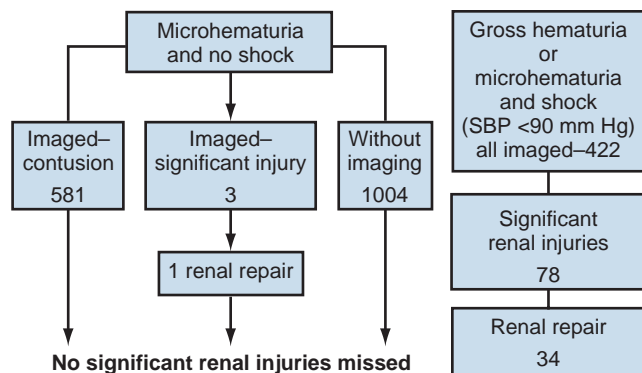


Figure 50-2. Algorithm demonstrating the results of the authors' study on radiographic assessment of renal injuries. In adults with blunt trauma, imaging studies may be performed selectively. SBP, systolic blood pressure. (From Miller KS, McAninch JW. Radiographic assessment of renal trauma: our 15-year experience. *J Urol* 1995;154:352–5.)

blood pressure < 90 mm Hg any time during evaluation and resuscitation) should undergo renal imaging, usually with CT using intravenous (IV) contrast and with delayed films to evaluate urinary extravasation.

Patients with microscopic hematuria without hypotension or acceleration/deceleration injury can be observed clinically without imaging. First noted by Miller and McAninch (1995) but confirmed by several subsequent findings, these patients rarely have a significant injury (<0.0016%). However, if renal injury is suspected on the basis of history, examination, or the patient's subsequent clinical course, imaging should be performed. It is important to remember that blunt rapid deceleration injuries, such as high-speed motor vehicle accidents or falls from great heights, pose a higher risk for vascular pedicle or ureteral injury.

Penetrating injuries with any degree of hematuria should be imaged. In a report by Carroll and McAninch (1985), 27 of 50 patients with penetrating renal trauma had only microscopic hematuria. Three of these had practically undetectable amounts of microhematuria—0 to 3 RBCs/HPF. Despite this, one of the three had a renal pedicle injury.

Pediatric patients (younger than 18 years) sustaining blunt renal trauma generally can be evaluated like adults (Santucci et al, 2004a), with a few caveats:

1. Children are known to be at a greater risk for renal trauma than adults after blunt abdominal injury (Brown et al, 1998a) perhaps because of larger comparative kidney size and less relative rib coverage over the kidneys (Buckley and McAninch, 2004).
2. Importantly, children often do not become hypotensive with major blood loss, and in the absence of this sign can still have significant exsanguinating renal injury. Liberal use of renal imaging is probably warranted. Children have a high catecholamine output after trauma, which maintains blood pressure until approximately 50% of blood volume has been lost.
3. Children have a higher proportion of renal abnormalities such as severe hydronephrosis or Wilms tumor, which may result in significant renal injury with seemingly insignificant renal trauma.

Imaging Studies

Contrast-enhanced CT is the gold standard for genitourinary imaging in renal trauma (Bretan et al, 1986; Federle et al, 1987). Quick, highly sensitive, and specific, CT provides the most definitive staging information—parenchymal lacerations are clearly defined; extravasation of contrast-enhanced urine can easily be detected (Fig. 50-3); associated injuries to the bowel, pancreas, liver, spleen, and other organs can be identified; and the degree of retroperitoneal bleeding can be assessed by the size of the retroperitoneal hematoma. Lack of uptake of contrast material in the parenchyma

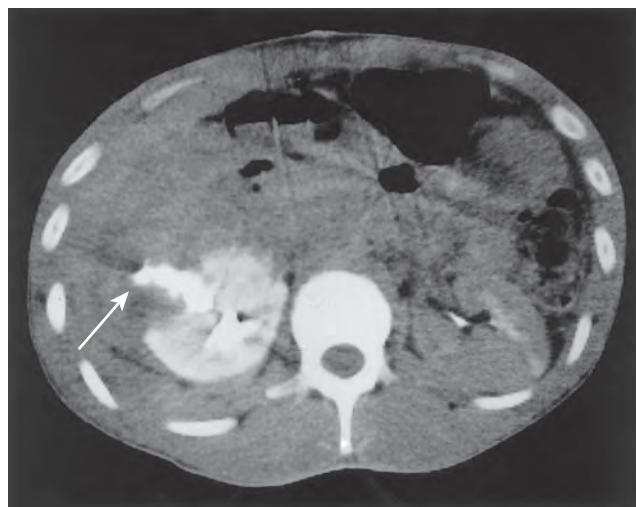


Figure 50-3. Computed tomography scan of a right renal stab wound (grade IV) (arrow), demonstrating extensive urinary extravasation and large retroperitoneal hematoma.

suggests arterial thrombosis (Fig. 50-4) or transection. Detection of fine anatomic detail of the most serious injuries (urinary extravasation, active arterial bleeding, and severe parenchymal/vascular injuries) has translated into improved confidence in our ability to understand which injuries can be managed nonoperatively.

Currently, spiral CT is being used in many centers to evaluate renal injuries (Brown et al, 1998b). Arteriovenous scanning (typically 80 seconds after contrast administration) provides visualization of the kidneys in the nephrogenic phase of contrast excretion and is necessary to detect arterial extravasation. Injury to the renal collecting system may be missed if contrast material has not had time to be excreted into the parenchyma and collecting system adequately. Repeated/delayed scanning of the kidneys 10 minutes after injection of contrast identifies parenchymal lacerations and urinary extravasation accurately and reliably. Expert opinion holds that delayed films may be omitted when the kidneys are deemed normal, and no perinephric, retroperitoneal, pelvic, or perivesical fluid is present (Santucci et al, 2004b). Findings on CT that raise suspicion for major injury are (1) medial hematoma, suggesting vascular injury; (2) medial urinary extravasation, suggesting renal pelvis or ureteropelvic junction avulsion injury; (3) global lack of contrast enhancement of the parenchyma, suggesting renal artery occlusion; and (4) the combination of two or more of the following: large hematoma greater than 3.5 cm, medial renal laceration, and vascular contrast extravasation (suggesting brisk active bleeding).

Patients with two or three of these last features (no. 4 in the previous list) require open surgery or angioembolization nine times more frequently than those with none or one of these features (Dugi et al, 2010). Also, active extravasation of intravascular contrast seen on CT (i.e., the patients are bleeding so briskly as to be detectable on the vascular phase CT scan) is highly associated with the need for subsequent angioembolization (Nuss et al, 2009) (Fig. 50-5). The widespread use and anatomic detail provided by CT imaging has now supplanted the much less sensitive and less specific excretory urography (IV pyelography [IVP]) for grading purposes.

One major limitation of CT is the inability to define a renal venous injury adequately. With normal arterial perfusion, the parenchyma appears normal and the collecting system may contain contrast material. A medial hematoma accompanying the preceding findings suggests a venous injury. Most venous injuries will either bleed so much they will have to go to the operating room or tamponade and stop bleeding and thus require no further treatment. The true clinical significance of the insensitivity of CT to renal vein injury is currently unknown.

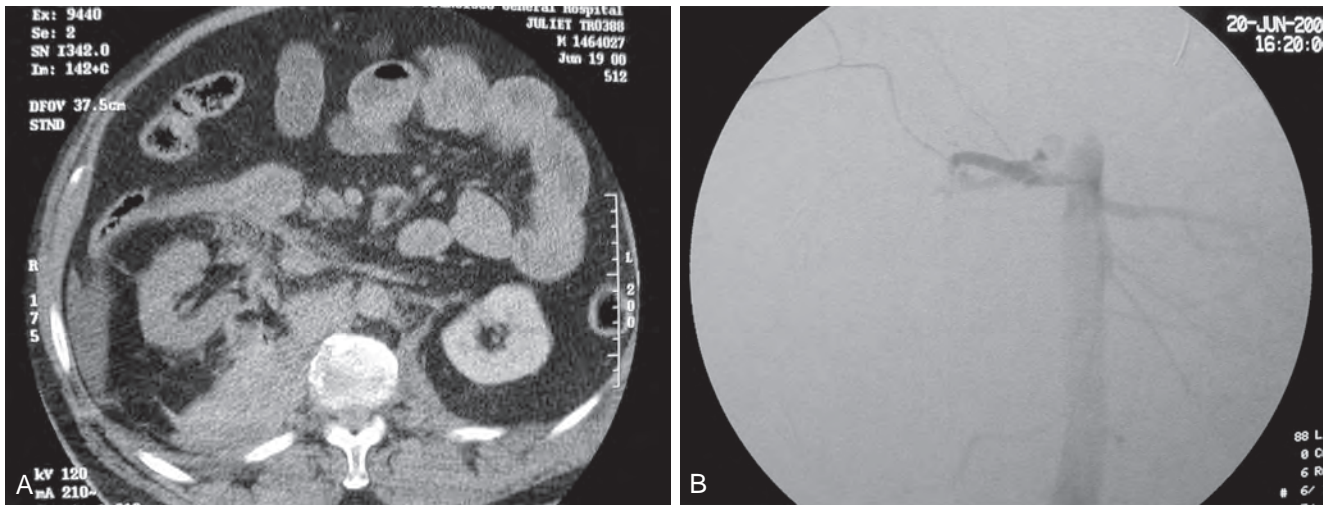


Figure 50-4. A, Computed tomography showing right renal artery thrombosis after crush injury. Note poor contrast uptake in right kidney compared to left and diffuse soft tissue injury medial to right kidney in the area of the renal artery. B, Angiogram showing right renal artery thrombosis after crush injury.



Figure 50-5. Computed tomography showing left renal fossa hematoma after blunt renal trauma, with bright jet of active extravasation of intravascular contrast indicating brisk active bleeding.

There is a limited continuing role for intraoperative “one-shot” IVP. The indications are uncommon, but when the surgeon encounters an unexpected retroperitoneal hematoma surrounding a kidney during abdominal exploration in a patient without a previous CT scan, the study can provide essential information. The main purpose of the one-shot IVP is to assess the presence of a functioning contralateral kidney and help radiographically stage the injured side. It is crucially important to know if a patient has only one kidney, because any unnecessary attempts at repair that might endanger that remaining kidney must be avoided. The IVP technique is key to gaining important information and minimizing the time involved; only a single film is taken 10 minutes after IV injection (IV push) of 2 mL/kg of contrast material. The study is particularly helpful in determining whether urinary extravasation is present. If the study is normal, exploration of the injured side may be avoided. If findings are not normal or near normal, the kidney should be explored to complete the staging of the injury and reconstruct any abnormality found.

Morey and coworkers (1999) reported their experience with one-shot intraoperative IVP for the immediate management of renal injuries; in 50 patients the film quality was adequate to avoid renal

exploration in 32%. This report supports the value of this intraoperative imaging technique when done properly.

Sonography is used in the immediate evaluation of abdominal injuries (focused assessment with sonography for trauma [FAST] examination), but the study has poor specificity in the adult renal patient for renal injuries. If necessary, sonography can confirm the presence of two kidneys and can detect a retroperitoneal hematoma.

Angioembolization

Renal arteriography and embolization is an increasingly used modality in renal trauma. In the right setting, it can be used to stop significant renal bleeding without the need for laparotomy. Most angiography literature consists of case reports and a single report of patients found in an administrative database; however, it appears to be commonly used clinically. It is critically important that if angioembolization is used, the local angiography team is experienced, the procedure can be done without delay, and that the patient can be monitored and even resuscitated during transport to and in the angiography suite. Superselective embolization therapy for renal trauma may provide an effective and less invasive technique to avoid unnecessary exploration that could otherwise result in a nephrectomy. Initial failure is common, between 13% and 88% (Breyer et al, 2008; Sugihara et al, 2012), but subsequent embolization was highly successful in at least one series (Hotelling et al, 2011).

Traumatic pseudoaneurysms and arteriovenous fistulas are often treated by angiographic embolization with a high expected success rate (Fig. 50-6). In special clinical circumstances, endovascular stents have been used with reported success during angiography in patients with renal artery thrombosis occurring from intimal flaps (Goodman et al, 1998). Longer term follow-up and more cases are needed to determine whether this will be a successful management approach, especially considering that most stents require anticoagulation after placement, which may not be possible in a trauma patient.

Nonoperative Management

Significant renal injuries (grades II to V) are found in only 5% of renal trauma cases (Miller and McAninch, 1995). Nonoperative management has become the standard of care in hemodynamically stable, well-staged patients with AAST grade I to III renal injuries, regardless of mechanism (Santucci et al, 2004b). Most

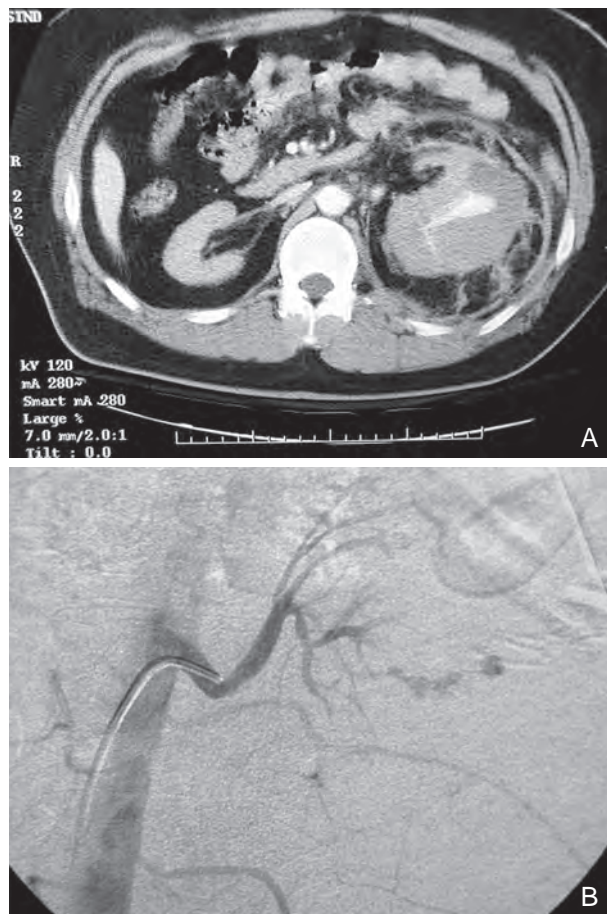
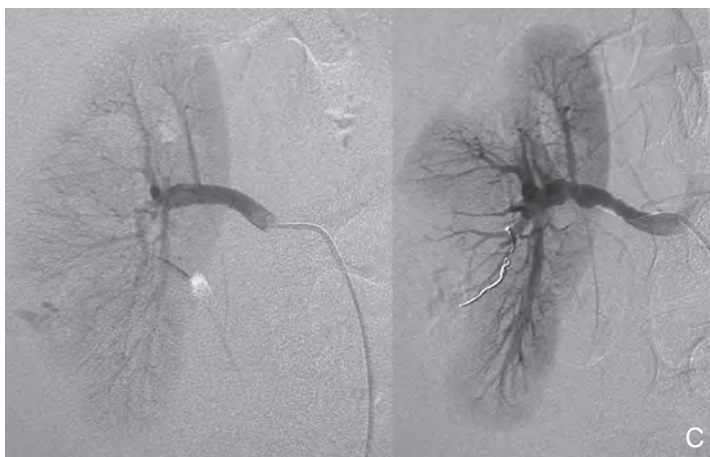


Figure 50-6. A, Computed tomography showing left post-traumatic arteriovenous fistula. B, Angiogram showing left post-traumatic arteriovenous fistula. C, Angioembolization of right renal laceration: arteriography demonstrating active arterial bleeding. Coil embolization was used to control bleeding. Note the presence of the coil and large, triangular area of infarct.



experts agree that patients with grade IV and V injuries more often require surgical exploration, but even these high-grade injuries can be managed without renal operation if carefully staged and selected (Fig. 50-7) (Santucci and McAninch, 2000; Santucci et al, 2004b; Buckley and McAninch 2006; Umbreit et al, 2009; Van der Wilden et al, 2013).

A trial of expectant management has been advocated for most adult blunt renal parenchymal injuries, many renal stab wounds, and selected renal gunshot wounds. Bluntly injured kidneys often heal well when managed conservatively, even in the setting of urinary extravasation and nonviable tissue. Overall, 98% can be successfully managed without exploration. Even very high-grade injuries can sometimes be treated nonoperatively. In a series of six hemodynamically stable, grade V blunt injuries, all were treated successfully without surgery (Altman et al, 2000). Patients who are exsanguinating from the kidney may still require exploration and subsequent nephrectomy/renorrhaphy, but those who are hemodynamically stable are often successfully treated without surgery (Moolman et al, 2012). Delayed bleeding, usually amenable to angioembolization, occurs in 9%.

Penetrating trauma from gunshot or stab wounds to the kidney also can be managed nonoperatively in stable patients. In one large series, 55% of renal stab wounds and 24% of gunshot wounds were appropriately managed nonoperatively in carefully selected patients with well-staged injuries (McAninch et al, 1991). Contrary to past teaching, obligatory exploration is no longer mandated for renal gunshot wounds. Serafetinides and associates (2004) treated 40 patients (54%) with low-velocity gunshot wounds expectantly with few complications.

Stab injuries have even more evidence to support conservative management. Nonoperative management was successful and resulted in no delayed nephrectomies in a cohort of 108 hemodynamically stable patients with stab wound (Armenakas et al, 1999).

Some blunt and penetrating abdominal trauma may require laparotomy because of associated nonurologic injury, but even in these cases it is not necessary to explore the kidney additionally (Shariat et al, 2008b). The only absolute indication for kidney exploration is a pulsatile and expanding retroperitoneal hematoma that suggests renal artery laceration. This is a vanishingly rare clinical entity.

All patients with high-grade injuries selected for nonoperative management should be closely observed with serial hematocrit readings and vital signs. Supporting data are lacking, but we empirically prescribe bed rest until gross hematuria resolves. **No routine CT imaging is required in patients without symptoms (fever, flank pain, dropping hematocrit, increasing hematuria, etc.)** (Davis et al, 2010). Although most grade II to IV injuries resolve uneventfully, delayed renal bleeding sometimes can occur (Wessells et al, 1997). Should bleeding persist or delayed bleeding occur, angiography with selective embolization of bleeding vessels can obviate surgical intervention. The patient should be watched and warned about the possibility of acute or delayed renovascular hypertension. Delayed bleeding after discharge to home is rare but does occur.

The failure rate of nonoperative management is as high as 20% (average ~ 10%), but most patients require only a stent or angioembolization. The complication rate of nonoperative treatment is much lower than that of aggressive surgical exploration and results in shorter intensive care unit (ICU) stays, shorter hospital stays, lower mortality, and fewer transfusions (Bjurlin et al, 2011). However, it cannot be overemphasized that patients who are exsanguinating from the kidney require rapid open surgical or in some cases quick expert angioembolization to avoid death.

In severe renal injuries with continued urinary extravasation, placement of an internal ureteral stent for drainage may prevent prolonged urinary extravasation and decrease the chance of perirenal urinoma formation. On occasion, retrograde placement of

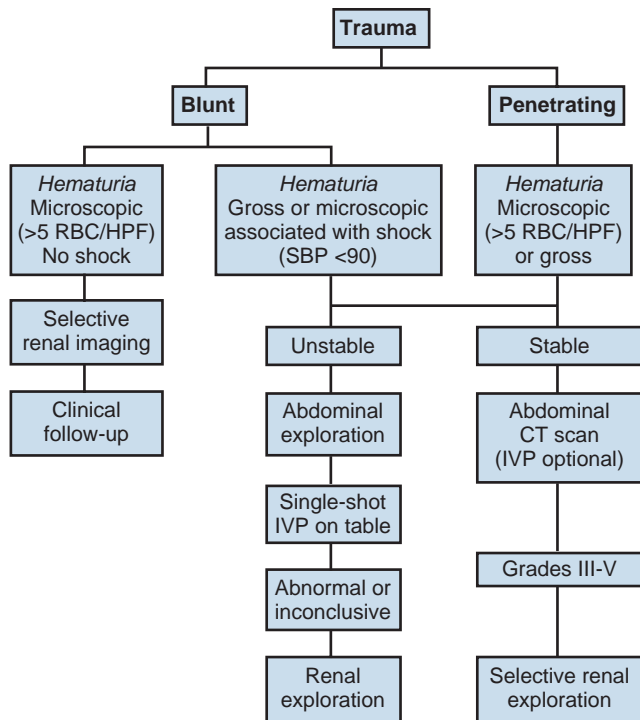


Figure 50-7. Flow chart for adult renal injuries to serve as a guide for decision making. CT, computed tomography; IVP, intravenous pyelography; RBC/HPF, red blood cells per high-power field; SBP, systolic blood pressure.

ureteral stents is not possible. Examples include concomitant pelvic fracture urethral distraction defects, severe genital trauma prohibiting urethral access, complete ureteral transection, and fractures prohibiting the dorsal lithotomy position. Percutaneous nephrostomy drainage with consideration for antegrade ureteral stent placement is a viable option in these situations. Stenting and draining will facilitate renal healing.

Fluid collections seen on serial imaging for renal trauma are hematomas, urinomas, or abscesses. Urinomas can be distinguished from hematomas by their radiographic characteristics. Urinoma density in Hounsfield units (HU) ranges from 0 to 20; hematoma density is almost always greater than 30 (Federle and Jeffrey, 1983). Also, urinomas enhance with contrast pooling dependently during delayed phase imaging (5 to 20 minutes after IV injection of contrast). Abscesses have rim enhancement and high attenuation fluid (HU > 20) on contrasted films (Allen et al, 2012). When the perinephric fluid collection persists despite ureteral stenting or percutaneous nephrostomy drainage, placement of a percutaneous drain can facilitate healing and prevent or treat abscesses.

Operative Management

Indications for renal exploration or speedy angioembolization after trauma can be separated into absolute and relative (Voelzke and McAninch, 2008). Absolute indications include (1) hemodynamic instability with shock, (2) expanding/pulsatile renal hematoma (usually indicating renal artery laceration), (3) suspected renal vascular pedicle avulsion (grade 5), and (4) ureteropelvic junction disruption. Relative indications are (1) urinary extravasation with significant renal parenchymal devascularization (older data suggest higher complication rate than average if watched, but these also can be closely observed), (2) renal injury together with colon/pancreatic injury (these patients have a higher complication rate if their renal injury is not repaired at the time of colon/pancreatic injury, but the renal injury may be closely observed after repair of the enteric injury), and (3) a delayed diagnosis of arterial injury (which will most likely need delayed nephrec-

tomy). More recent data suggest that patients with renal devascularization and urine leak actually have excellent outcomes, with only 1 of 18 (6%) patients requiring subsequent intervention during conservative management of segmental renal artery injuries (Elliott et al, 2007).

Urinary extravasation alone from a grade IV parenchymal laceration or fornical rupture can be managed nonoperatively with an expectation of spontaneous resolution of more than 90%. Should nonviable tissue constitute more than 25% in association with a parenchymal laceration, urinary extravasation, or both, the potential for complications greatly increases and operative management may be considered (Alsikafi et al, 2006).

Renal Exploration

Surgical exploration of the acutely injured kidney is best done by a transabdominal approach, which allows complete inspection of intra-abdominal organs and bowel. In some reported series of penetrating injuries, nonrenal organ injury has been noted to be as high as 94% (McAninch et al, 1993). Injuries to the great vessels, liver, spleen, pancreas, and bowel can be identified and stabilized, if necessary, before renal exploration.

The surgical approach to renal exploration is shown in Figure 50-8 (McAninch and Carroll, 1989). The renal vessels are isolated before exploration to provide the immediate capability to occlude them if massive bleeding should ensue when the Gerota fascia is opened (Scott and Selzman, 1966). The small bowel is eviscerated and lifted out of the surgical field. This exposes the mid-retroperitoneum. An incision is made over the aorta in the retroperitoneum just superior to the inferior mesenteric artery. The incision is extended superiorly to the ligament of Treitz. Exposure of the anterior surface of the aorta is accomplished and followed superiorly to the left renal vein, which crosses the aorta anteriorly. A vessel loop is placed on the right or left renal vein as necessary. The vein usually must be retracted cephalad, perhaps with a Deaver retractor, and the left and right renal arteries will be found underneath. The artery is secured with vessel loops. The right renal vein also can be secured through this incision; but if this proves difficult, reflecting the second portion of the duodenum provides excellent exposure to the vein.

Large hematomas may extend over the aorta and obscure the landmarks for the planned initial retroperitoneal incision. In such instances, the inferior mesenteric vein can be used as an anatomic guide for an appropriate incision. By making the retroperitoneal incision just medial to the inferior mesenteric vein and dissecting through the hematoma, the anterior surface of the aorta can be identified and followed superiorly to the crossing left renal vein.

The kidney is then exposed by incising the peritoneum lateral to the colon, followed by mobilization off the Gerota fascia. This maneuver often requires release of the splenic (left) or hepatic (right) attachments of the colon. The Gerota fascia is then opened, and the kidney with injury is completely dissected from the surrounding hematoma. Should troublesome bleeding develop, the previously isolated vessels can be temporarily occluded with a vascular clamp or a vessel loop tourniquet.

Is Early Vessel Isolation Necessary? Renal bleeding is a major cause of nephrectomy in renal trauma. Obtaining early vascular control before opening the Gerota fascia can decrease renal loss; in a comparative series, the total nephrectomy rate was reduced from 56% to 18% when vascular control was obtained (McAninch and Carroll, 1982). Carroll and coworkers (1989) reported that the looped vessels only needed to be temporarily clamped in approximately 2% of renal explorations. In a series of 133 renal units in which early vessel isolation and control were achieved before opening the Gerota fascia, McAninch and associates (1991) found that a renal salvage rate of 89% was possible.

Corriere and colleagues (1991) reported a series of renal units in which vascular control was obtained only if needed after opening the Gerota fascia. In this group, the total nephrectomy rate was 37%. Atala and coworkers (1991) reported a similar group of patients with a total nephrectomy rate of 36%. On the whole, the

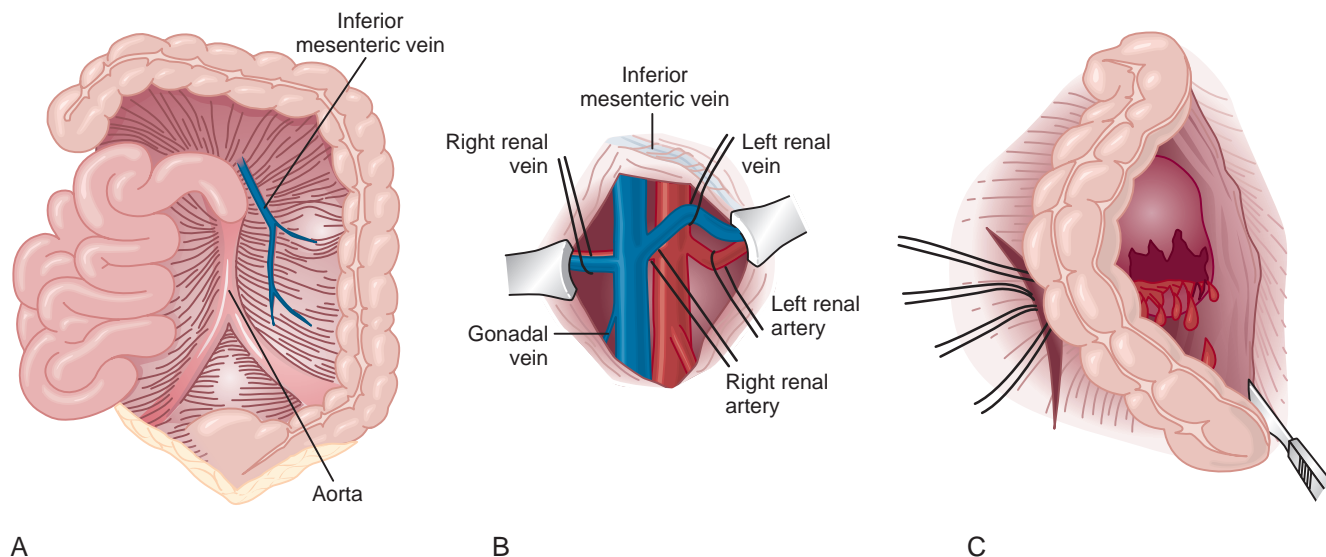


Figure 50-8. The surgical approach to the renal vessels and kidney. **A,** Retroperitoneal incision over the aorta medial to the inferior mesenteric vein. **B,** Anatomic relationships of the renal vessels. **C,** Retroperitoneal incision lateral to the colon, exposing the kidney.

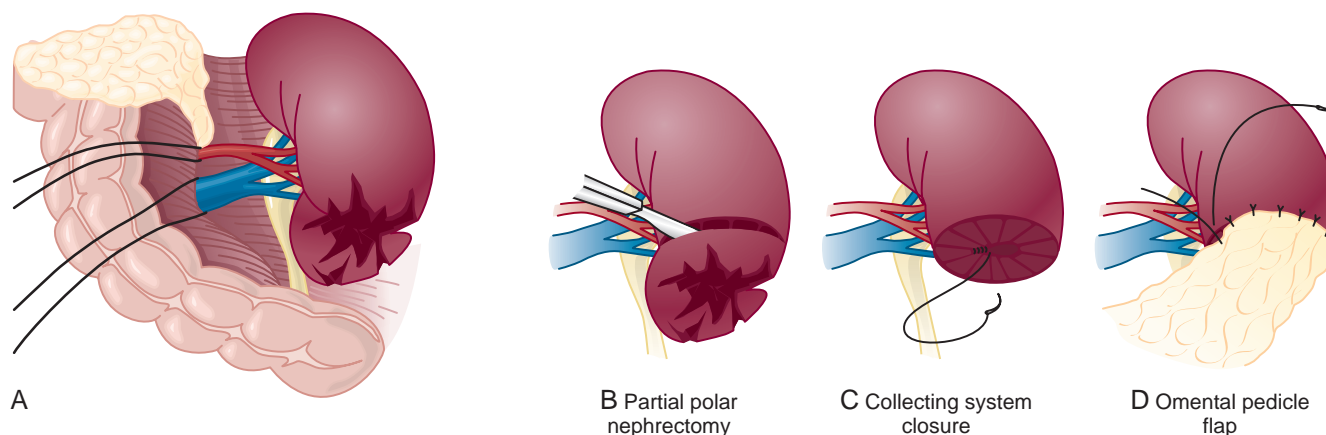


Figure 50-9. Technique for partial nephrectomy. **A,** Total renal exposure. **B,** Sharp removal of nonviable tissue. **C,** Hemostasis obtained and collecting system closed. **D,** Defect covered.

currently available data support an improved renal salvage rate with early vascular control because patients who require temporary vascular occlusion cannot be reliably identified before renal inspection. The studies that claim vascular control is unnecessary have an almost threefold higher rate of renal loss than those that always get control.

Renal Reconstruction

The principles of renal reconstruction after trauma include complete renal exposure, measures for temporary vascular control, limited debridement of nonviable tissue, hemostasis by individual suture ligation of bleeding vessels, watertight closure of the collecting system if necessary/possible, reapproximation of the parenchymal defect, coverage with nearby fascioadipose flaps (Gerota fascia or omentum) if feasible, and liberal use of drains (Fig. 50-9).

Renorrhaphy is illustrated in Figure 50-10. Note the approximation of the margins of the laceration (3-0 Vicryl or similar suture) with the use of renal capsule over an absorbable hemostatic agent bolster such as Gelfoam (Pfizer, New York, NY).

When polar injuries cannot be reconstructed, a partial nephrectomy can be performed. The open parenchyma should be covered

when possible by a pedicle flap of omentum (see Fig. 50-9). With its rich vascular and lymphatic supply, omentum promotes wound healing and decreases the risk for delayed bleeding and urinary extravasation. Should it not be available, the use of absorbable mesh, peritoneal graft, or retroperitoneal fat also has been successful.

Hemostatic agents such as Floseal (Baxter, Deerfield, IL) are potent and have an increasing role in the management of genitourinary trauma (Fig. 50-11). Based on experience from nephron-sparing surgery, gelatin matrix was applied to a porcine model of complex renal trauma and demonstrated less mean blood loss than conventional suture treatment (Hick et al, 2005).

In a high percentage of major renal injuries, intra-abdominal structures are also injured, with the liver and spleen being the most common. Injuries to the colon, pancreas, and stomach also occur frequently, and in previous years total nephrectomy was suggested because of the high complication rate with attempted renal salvage. However, renal repair in these injuries has been successful with minimal complications (Rosen and McAninch, 1994; Wessells and McAninch, 1996; Master and McAninch, 2006). Drains should be used liberally after these repairs.

Renovascular Injuries. Renovascular injuries after trauma are uncommon and often have associated injuries requiring operative

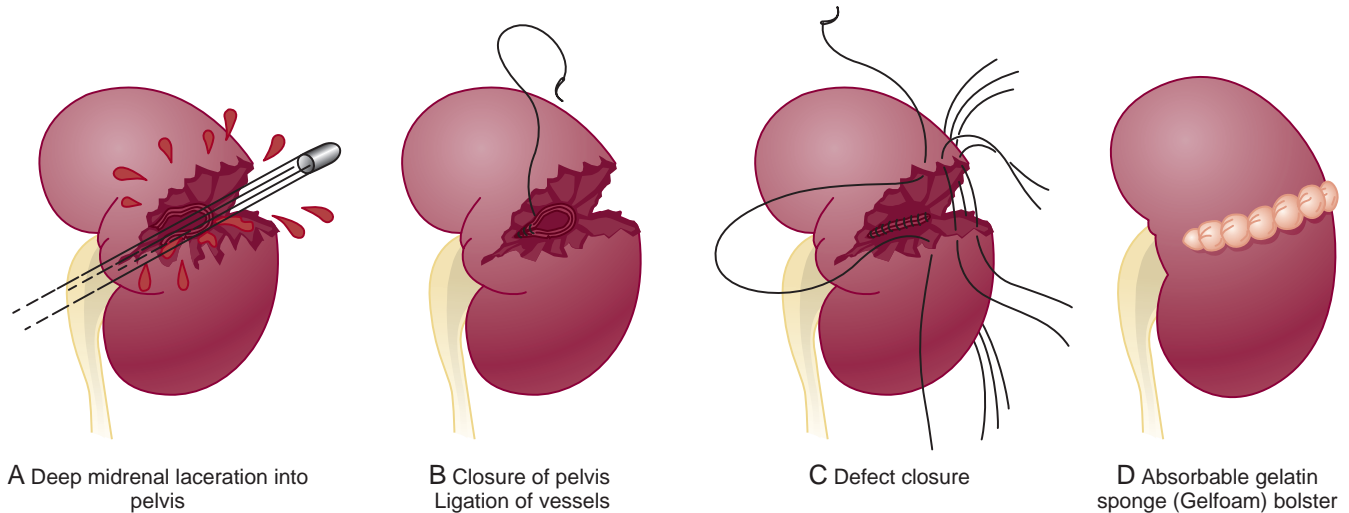


Figure 50-10. Technique for renorrhaphy. **A**, Typical injury in midportion of kidney. **B**, Debridement, hemostasis, and collecting system closure. **C**, Approximation of parenchymal margins. **D**, Sutures tied over gelatin sponge bolster.

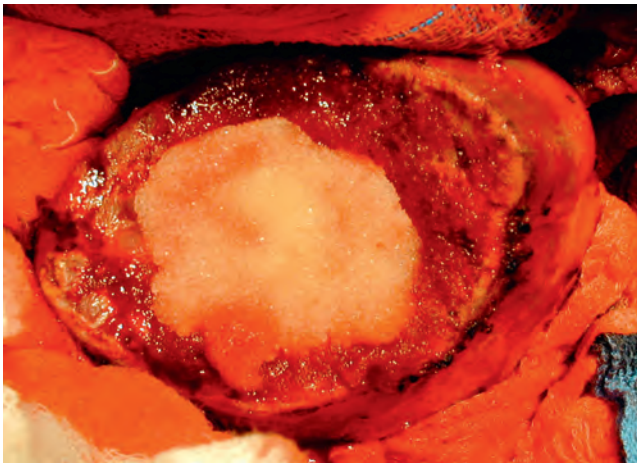


Figure 50-11. Partial nephrectomy showing excellent hemostasis with use of Floseal only.

intervention. For major renovascular injuries in patients with two kidneys, speedy nephrectomy is advocated. In rare instances in which vascular repair is technically feasible, renal salvage rates are disappointingly low, exemplified by a 33% renal salvage rate for main renal artery reconstruction even in the most expert of hands (Elliott et al, 2007). Vascular repair requires occlusion of the involved vessel with vascular clamps. The lacerated main renal vessels can be repaired with 5-0 nonabsorbable vascular suture (Fig. 50-12).

Main renal artery thrombosis from blunt trauma occurs most often secondary to deceleration injuries. The mobility of the kidney results in stretch on the renal artery, which in turn causes the arterial intima, low in elastic fibers, to disrupt. The consequent thrombus occludes the vessel, rendering the kidney ischemic (Fig. 50-13). Prompt diagnosis by CT or angiography may lead to immediate renal exploration in the appropriate candidate in an attempt to salvage the kidney, but outcomes for salvage remain dismally low, and nephrectomy is almost always required (Knudson et al, 2000).

Case reports of successful renal revascularization through the use of endovascular stents during angiography offer a new and perhaps promising approach to the problem of blunt trauma renal artery thrombosis caused by the intimal flap (Inoue et al, 2004; Memon and Cheung, 2005). The great disadvantage of this approach has

been the inability to safely institute post-stent anticoagulation in the patient with polytrauma.

Surgical revascularization is seldom successful in renal artery thrombosis, and at least 43% of patients with repairs developed hypertension (Haas et al, 1998). Many patients with renal vascular injury are critically injured, with numerous associated organ injuries; time constraints thus limit attempts at vascular repair, and a nephrectomy must be done. Hypertension also was possible in those observed nonoperatively, and subsequent nephrectomy whether immediate, early, or late is almost always required (Knudson et al, 2000).

Injuries to the main renal vein may require repair with fine vascular suture (5-0) (see Fig. 50-12). Partial occlusion of the vein is ideal during repair, but in some instances total temporary occlusion with vascular clamps is necessary.

Damage Control

Coburn (2002) and Pursifull and colleagues (2006) noted the benefit of damage control to improve renal salvage after polytrauma. The area around the injured kidney is packed with laparotomy pads to control bleeding, with a planned return in approximately 24 hours to explore and evaluate the extent of injury. This allows the cold, acidotic, and coagulopathic patient to be stabilized in the ICU before any attempt at potentially lengthy renal reconstruction is attempted. Damage control may allow patients with complex renal injuries to avoid unneeded nephrectomy. This approach is commonly used by trauma surgeons in patients with nonrenal injuries.

Indications for Nephrectomy

The ability to reconstruct an injured kidney depends on numerous factors. In an unstable patient, if damage control is not an option, total nephrectomy would be indicated immediately when the patient's life would be threatened by attempted renal repair. When Nash and colleagues (1995) examined the reasons for nephrectomy in patients with renal injuries, 77% required removal because of the extent of parenchymal, vascular, or combined injury. The remaining 23% required nephrectomy in otherwise reconstructable kidneys because of hemodynamic instability; this should be avoided.

Complications

Persistent urinary extravasation can result in urinoma, perinephric infection, and, rarely, renal loss. These patients are initially

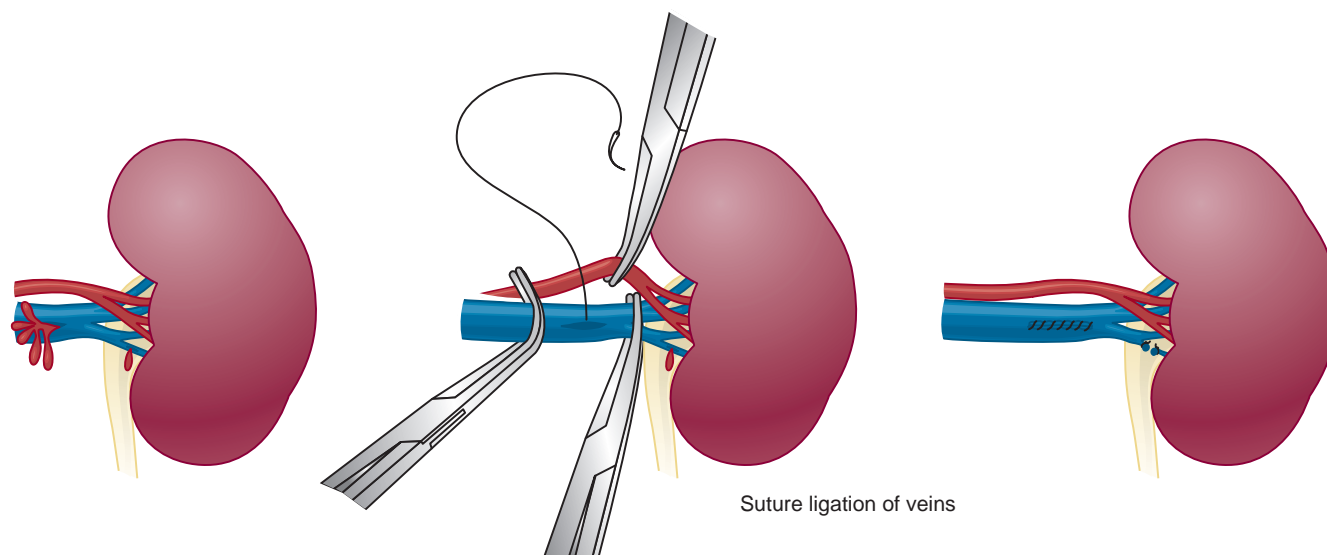


Figure 50-12. Vascular injuries. *Left*, Venous injuries may occur in the main renal vein or the segmental branches. *Middle*, Repair of main renal vein. *Right*, Ligation of segmental branch can be done safely.

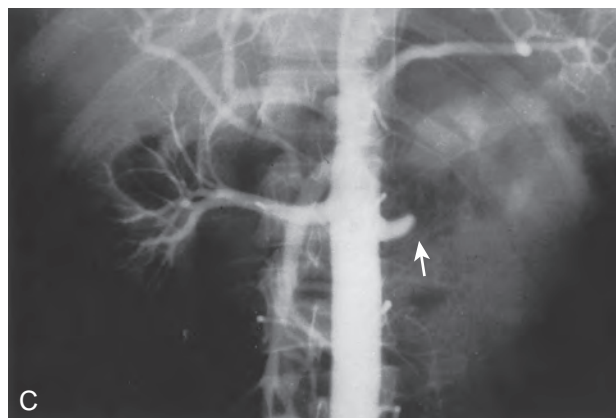
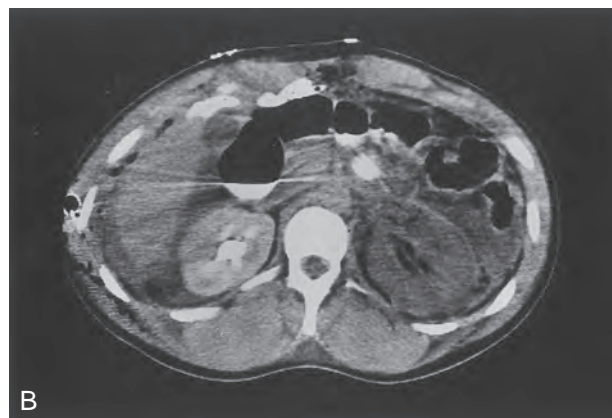
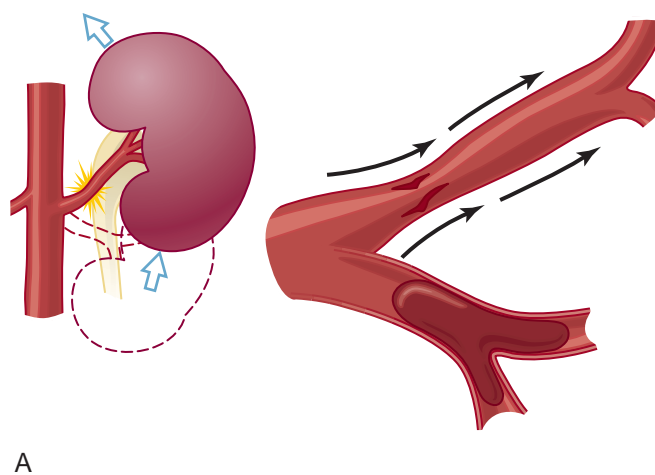


Figure 50-13. A, Movement of the kidney from blunt trauma (deceleration injury) causes stretch on the renal artery, resulting in rupture of the arterial intima and formation of a thrombus. B, Computed tomography of a left kidney with renal artery thrombosis, demonstrating lack of contrast material perfusion to the kidney. C, Arteriography demonstrating complete occlusion of the left renal artery (arrow) secondary to thrombus formation.

administered systemic antibiotics, although data supporting their use does not exist. In a high percentage, the extravasation resolves spontaneously (Matthews et al, 1997). Should it persist, placement of an internal ureteral stent often corrects the problem. The addition of a percutaneous nephrostomy or transcutaneously placed urinoma drain may be required in patients not cured by ureteral stent placement.

Delayed renal bleeding can occur up to several weeks after injury but usually occurs within 21 days. The initial management is bed rest and hydration. Should the bleeding persist, angiography frequently can localize the bleeding vessel and embolization often can gain control.

Perinephric abscess rarely occurs after renal injury; persistent urinary extravasation and urinoma are the typical precursors. Urinary drainage with a ureteral stent with or without percutaneous nephrostomy followed by percutaneous abscess drainage offers a good initial method of management, followed by surgical drainage (rarely) if necessary.

Hypertension is seldom noted in the early postinjury period (Monstrey et al, 1989) but can occur later. The basic mechanisms for arterial hypertension as a complication of trauma are (1) renal vascular injury, leading to stenosis or occlusion of the main renal artery or one of its branches (Goldblatt kidney); (2) compression of the renal parenchyma with extravasated blood or urine (Page kidney); and (3) post-trauma arteriovenous fistula. In these instances, the renin-angiotensin axis is stimulated by partial renal ischemia, resulting in hypertension (Goldblatt et al, 1934; Cosgrove et al, 1973).

KEY POINTS: RENAL TRAUMA

- Expectant management strategies of renal trauma allow for maximal renal preservation.
- The degree of hematuria and the severity of renal injury do not consistently correlate.
- Contrast-enhanced CT is the gold standard for genitourinary imaging in renal trauma.
- Patients with microscopic hematuria without shock can be observed clinically without imaging studies.
- Hemodynamically stable, well-staged renal injuries can be conservatively managed (even with high-grade injuries).
- Selective embolization provides an effective and minimally invasive means to stop active bleeding from parenchymal lacerations and segmental arterial injury.
- CT findings suspicious for significant renal injury include (1) medial hematoma (vascular pedicle injury), (2) medial urinary extravasation (renal pelvis or ureteropelvic junction injury), (3) lack of contrast enhancement of the parenchyma (main renal arterial injury), and (4) active intravascular contrast extravasation (arterial injury with brisk bleeding).
- Intraoperative one-shot IVP confirms the presence of a contralateral functioning kidney and may be helpful to define urinary extravasation.
- During renorrhaphy, early vascular control before opening the Gerota fascia can decrease renal loss.

URETERAL INJURIES

Cause

Acute ureteral injury results from external trauma, open surgery, laparoscopy, and endoscopic procedures. Intraoperative suture ligation, sharp incision and transection, avulsion, devascularization, and heat (e.g., microwave, electrocautery, or vibratory energy) or freezing (cryoablation) energies can produce ureteral damage. Additionally, external violence from high-speed blunt mechanisms and penetrating stab and gunshot wounds contributes to the overall incidence. An unrecognized or mismanaged ureteral injury can lead to significant complications, including urinoma, abscess, ureteral stricture, urinary fistula, and potential loss of an ipsilateral renal

TABLE 50-2 American Association for the Surgery of Trauma Organ Injury Severity Scale for the Ureter

GRADE*	TYPE	DESCRIPTION
I	Hematoma	Contusion or hematoma without devascularization
II	Laceration	<50% transection
III	Laceration	≥50% transection
IV	Laceration	Complete transection with <2 cm devascularization
V	Laceration	Avulsion with >2 cm devascularization

*Advance one grade for bilateral up to grade III.

From Moore EE, Cogbill TH, Jurkovich GJ, et al: Organ injury scaling. III. Chest wall, abdominal vascular, ureter, bladder, and urethra. *J Trauma* 1992;33:337–9.

unit. Increased nephrectomy rates and a prolonged hospital stay are associated with a delayed or missed diagnosis from penetrating ureteral trauma (Kunkle et al, 2006). Ureteral injuries are often subtle, and clinicians must maintain a high index of suspicion to prevent comorbidity.

External Trauma

Damage to the ureter after external violence is quite rare, occurring in less than 4% of all penetrating and less than 1% of all cases of blunt trauma (Table 50-2). During wartime in the past century, 3% to 15% of urologic injuries have ureteral involvement, with an average of 5% over reports from World War II up to modern conflicts (Busch et al, 1967; Selikowitz, 1977; Marekovic et al, 1997). In the nonmilitary setting, a similar 2% to 3% of ureteral injuries are caused by civilian gunshot wounds. **These patients often have significant concomitant injuries and a devastating degree of mortality that approaches one third** (Medina et al, 1998). Associated visceral injury is common—predominantly small (39% to 65%) and large (28% to 33%) bowel perforation (Presti et al, 1989; Campbell et al, 1992; Medina et al, 1998). A significant percentage (10% to 28%) of patients with ureteral injuries also has associated renal injuries (Presti et al, 1989; Medina et al, 1998). A smaller percentage (5%) has associated bladder injuries (Medina et al, 1998).

The mechanism by which bullets injure the ureter is thought to be similar to the mechanism by which they injure analogous structures such as blood vessels—that is, not only by direct transection but by disruption of the delicate intramural blood supply. In experimental models, such microvascular damage has been found as far away as 2 cm from the point of transection (Amato et al, 1970), although ureters seldom need massive debridement and can generally be minimally debrided back to a bleeding edge. Some authors have even advocated injection of IV fluorescein and examination of the ureter by Wood lamp to ensure viability (Gill and McRoberts, 1992); however, we have not found published evidence to support this technique.

Whereas penetrating trauma imparts a large degree of energy over a small area (as in the course of a bullet), patients with blunt trauma with ureteral injuries are subject to extreme force applied over the entire body, like a fall from heights or a high-speed motor vehicle accident. The great degree of energy imparted to the victim is associated with such uncommon injuries as fractured lumbar processes (Evans and Smith, 1976) and thoracolumbar spinal dislocation (Campbell et al, 1992). The presence of massive force injuries in the patient with blunt trauma should always increase the level of suspicion for ureteral injury.

Patients with penetrating trauma with any degree of hematuria or a wound pattern that suggests the possibility of genitourinary injury should be imaged. Patients with blunt trauma with gross

hematuria or microhematuria plus hypotension, a history of significant deceleration, or significant associated injuries also should be imaged (Mee and McAninch, 1989). Mechanism of injury and physical examination findings must be taken into account. For example, a history of rapid deceleration was found in 100% of patients with ureteropelvic junction (UPJ) injury in one small series (Boone et al, 1993).

Surgical Injury

Any abdominopelvic surgical procedure, whether gynecologic, obstetric, general surgical, or urologic can potentially injure the ureter. The overall incidence of ureteral injury varies between 0.5% and 10% (Al-Awadi et al, 2005). Analysis of 13 published studies concluded that the following procedures contribute to iatrogenic ureteral injuries: hysterectomy (54%), colorectal surgery (14%), pelvic procedures such as ovarian tumor removal (8%), transabdominal urethropyexy (8%), and abdominal vascular surgery (6%) (St. Lezin and Stoller, 1991). One series reported that repeat cesarean section also can result in a large proportion of ureteral injuries, in this case up to 23% of the reported ureteral injuries at one hospital (Ghali et al, 1999). The total incidence of ureteral injury after gynecologic surgery is reported to be 0.5% to 1.5%, and after abdominoperineal colon resection it ranges from 0.3% to 5.7% (St. Lezin and Stoller, 1991). Historically, open urologic procedures, because they often occur in proximity to the ureters, were also responsible for a significant number (21%) of reported ureteral injuries (Selzman and Spirnak, 1996), but they are now extremely rare owing to improved ureteroscopic techniques and equipment.

Vascular Surgery. Intraoperative ureteral manipulation resulting in subsequent hydronephrosis is common after aortoiliac and aortofemoral bypass surgery (12% to 20%), but the course is benign in most (St. Lezin and Stoller, 1991). Surgical devascularization or inflammation can result in symptomatic ureteral stenosis, often delayed in manifestation by months, occurring in only 1% to 2% of these patients (St. Lezin and Stoller, 1991; Adams et al, 1992).

In patients undergoing intra-abdominal vascular surgery, risk factors for surgical injury of the ureter include reoperation; placement of a vascular graft anterior to the ureter (Adams et al, 1992); and large, dilated arterial aneurysms that cause retroperitoneal inflammation that can involve the ureter. The majority (up to 85%) of surgical injuries to the ureter after vascular procedures are not recognized immediately (Adams et al, 1992). Postoperative symptoms of missed ureteral injury include flank pain (36% to 90%), fever, ileus, abdominal distention, and urinary fistula (St. Lezin and Stoller, 1991; Adams et al, 1992).

Ureteroarterial fistulas deserve special mention. This rare and potentially catastrophic condition should be diagnosed and treated immediately because it can cause life-threatening hematuria. The fistula, mostly between the ureter and ipsilateral iliac artery, can be associated with previous pelvic surgery, radiation therapy, long-term indwelling ureteral stents, infection, primary vascular disease, and pregnancy. The experience using endovascular stent grafts for the acute treatment of this devastating event has increased since Kerns and colleagues (1996) first reported success with the technique (Araki et al, 2008). Many will need to be repaired primarily.

Robotic and Laparoscopic Surgery. Since the inception of laparoscopic surgery in the 1960s and robotic surgery in the 1990s, ureteral injuries have occurred (Grainger et al, 1990). The explosion of laparoscopic and robotic surgery into other surgical specialties has meant that the incidence of ureteral injury during and after minimally invasive surgery has likewise skyrocketed. At one center, the incidence of ureteral injuries from laparoscopy went from 0% of all reported ureteral injuries in the early 1980s to 25% of all the reported ureteral injuries only 5 years later (Assimos et al, 1994). As laparoscopic experience grew, that high incidence of injury fell to a baseline of 0.8% on a subsequent review of 1300 laparoscopic urologic procedures (Vallancien et al, 2002). Currently, the reported rate of ureteral injury varies between 0.5% (experienced surgeons) and 14% (inexperienced surgeons) after laparoscopic hysterectomy

(Harkki-Siren et al, 1999; Cosson et al, 2001; Leonard et al, 2007). The rate of urologic injury after robot-assisted surgery is not known yet, but rates of robotic surgery increased more than 1000% over the last decade. Currently, there are early media and legal allegations of increased complications from robotic surgery that are being attributed to the learning curve of the procedure.

A large percentage of ureteral injuries after gynecologic laparoscopy occur during electrosurgical or laser-assisted lysis of endometriosis (Grainger et al, 1990). There are probably three reasons for this: (1) endometrioma can involve the ureter either extrinsically or intrinsically; (2) long-standing endometriosis can cause intraperitoneal adhesion, making ureteral visualization difficult (Ribeiro et al, 1999); and (3) the disease can deviate the ureters medially away from their normal anatomic position (Nackley and Yeko, 2000). A significant number of ureteral injuries also occur during tubal ligation, even when bipolar cautery is used (Grainger et al, 1990).

In 1999 a series of 118 patients reported a 3.4% incidence of ureteral injury after laparoscopic hysterectomy severe enough to cause obstruction (Ribeiro et al, 1999). However, a recent combined series of six larger groups with a much greater number of patients and presumably more experienced surgeons demonstrated a more reasonable 1% rate (Leonard et al, 2007). Of ureteral injuries during hysterectomy, 50% have no identifiable risk factors. The other 50% are associated with malignancy, endometriosis, prior surgery, and surgery for prolapse (Vakili et al, 2005).

Technologic advances have allowed for thermoablative treatment of renal tumors that can result in ureteral damage. There may be a potentially higher risk for ureteral stricturing associated with ablation of medial or lower pole masses. In a porcine model, deliberate targeting of vital renal structures demonstrated an association of ureteropelvic fistula and injury with radiofrequency ablation (Brashears et al, 2005). With experience, the real clinical risks have decreased. A recent multi-institutional review of 271 thermoablative procedures for small renal tumors reported only one ureteral injury (Johnson et al, 2004).

In contradistinction to open operation, in which at least one third of ureteral injuries are recognized immediately (Rodriguez and Payne, 2001), fewer injuries to the ureter are immediately identified after laparoscopy (Grainger et al, 1990; Parpala-Sparman et al, 2008). Therefore, during laparoscopy and robotic surgery, a high index of suspicion for ureteral injury is required. The symptoms may develop acutely or insidiously, depending on the mechanism. Postoperatively, patients must be monitored for fever, peritonitis, and leukocytosis (Grainger et al, 1990; Parpala-Sparman et al, 2008), which herald the potential for missed ureteral injury. A smaller number of patients with missed ureteral injury present with hematuria or a pelvic mass representing urinoma (Grainger et al, 1990). A low threshold for postoperative imaging is required, especially in those with these symptoms.

Avoiding and Detecting Ureteral Injury. Avoidance of ureteral injury is predicated on intimate knowledge of its location, especially its relation to the uterine and ovarian arteries, if those structures are going to be ligated, as in a hysterectomy (Fig. 50-14). Visualization of the ureter in the area of the uterosacral ligaments is thought to be especially difficult, and special care must be taken in this area (Grainger et al, 1990). It is axiomatic that ureteral injury is more likely in cases of uncontrolled bleeding, and adequate intraoperative hemostasis and surgical exposure should further decrease these injuries, even in high-risk cases (Cosson et al, 2001; Liapis et al, 2001). Intraoperative hydration or diuretic administration has been suggested to enhance ureteral visualization and potentially decrease the risk for injury, although data to support this claim do not exist. Preoperative ureteral stenting can be used to ease identification of the ureter in high-risk cases; however, published data in the gynecologic and colectomy population show that, although it may increase intraoperative recognition of ureteral injury, it may not actually decrease ureteral injuries (Leff et al, 1982; Bothwell et al, 1994; Kuno et al, 1998). Ureteral stents are not without complications; the rate of anuria after bilateral prophylactic ureteral stent placement has been reported between 1% and 5%

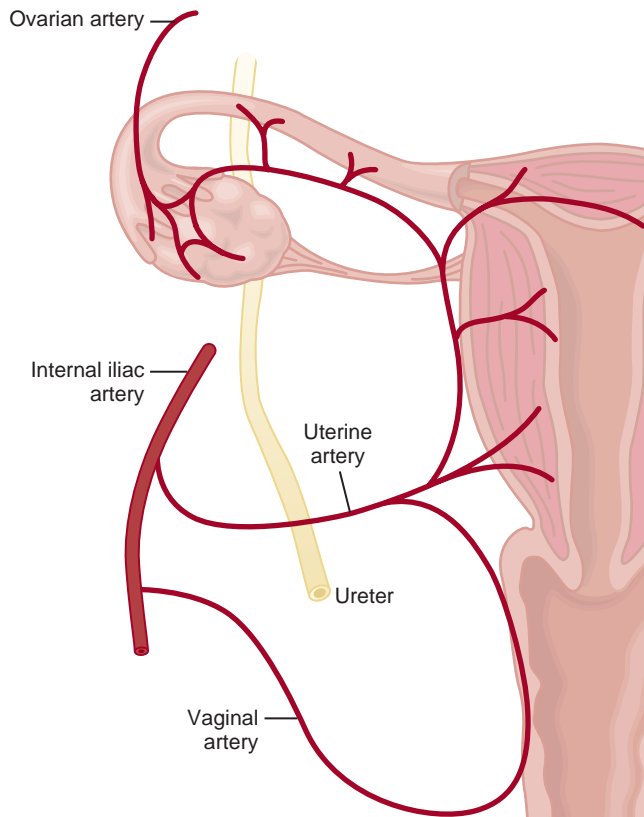


Figure 50-14. Ureteral anatomy showing relationship to fallopian tube and uterine artery.

(Leff et al, 1982; Sheikh and Khubchandani, 1990; Kyzer and Gordon, 1994), and the rate of iatrogenic ureteral injury during stent placement 1% (Bothwell et al, 1994). One study showed that stents might even increase rather than reduce the chance for intraoperative injury (Dowling et al, 1986). Ureteral stent placement is not always successful; stents cannot be placed on one side in 13% of cases, and total failure to place either catheter can occur in 2% (Bothwell et al, 1994). Lighted fiberoptic ureteral catheters have been used with good effect (Ben-Hur and Phipps, 2000), and newer, smaller 5-Fr models may avoid the complications of ureteral edema and obstruction, which have been reported after the use of larger, older-model lighted stents (Chahin et al, 2002).

Some authors have advocated maneuvers to check the patency of the ureter after all surgeries in which ureter injury is commonly reported (e.g., hysterectomy). Cystoscopy without indigo carmine/methylene blue administration, used to document the absence of hematuria and the presence of bilateral ureteral jets, is a poor predictor of injury. In one decade-long study, it missed more injuries than it detected (Dandolu et al, 2003). In another, it increased the detection rate from 30% to 96% (Vakili et al 2005), showing a benefit. Purposefully opening the retroperitoneum before or after hysterectomy has been advocated to avoid ureteral injury or at least allow intraoperative detection. A majority of authors on the subject advocate this approach (Cruikshank, 1986; Neuman et al, 1991; Cosson et al, 2001; Liapis et al, 2001); one author suggests it may contribute to ureteral devascularization by inadvertent disruption of the delicate distal ureteral blood supply (Nezhat et al, 1995). Mere digital palpation of the ureter, perhaps through the unopened retroperitoneum, appears to be ineffective (Symmonds, 1976). Some nonurologists have advocated grasping the ureter with forceps to evoke ureteral peristalsis as a measure of an uninjured ureter, but this is highly ineffective and should never be relied upon. Finally, some authors recommend injection of 5 to 10 mL of IV indigo carmine dye followed by cystoscopy to ensure patency of the ureters after laparoscopic hysterectomy. When this technique was used in

118 patients undergoing laparoscopic hysterectomy, 4 of 4 cases of ureteral occlusion were identified immediately (mostly caused by suture ligation) and repaired immediately without complications (Ribeiro et al, 1999).

Note that IV methylene blue and indigo carmine are generally considered by most urologists to be benign drugs, but their use has resulted in patient deaths and fetal deaths when used in pregnant women. It always must be avoided in pregnant women and in patients who are taking selective (e.g., paroxetine, sertraline, fluoxetine, fluvoxamine, citalopram) or nonselective (e.g., imipramine) serotonin reuptake inhibitors. Methylene blue is a potent monoamine oxidase inhibitor and has caused deaths from serotonin toxicity in patients taking medications that increase serotonin levels. IV methylene blue also should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency because it can cause methemoglobinemia and hemolysis. IV indigo carmine is implicated in rare but serious cases of bronchospasm, bradycardia, hypotension, hypotension (most common), and anaphylactoid reactions (Jeon et al, 2012).

The Tenuous Ureteral Blood Supply. The distal ureteral blood supply is variable (Daniel and Shackman, 1952). It is estimated by cadaver studies that 10% of females carry a disproportionate amount of their distal ureteral blood supply via uterine artery branches. These branches are necessarily severed when the uterine artery is ligated during the course of a normal hysterectomy. It has been experimentally proved on cadavers that 40% of females have decreased ureteral perfusion after ligating the uterine artery. The resultant hypothesis is that distal ureteral devascularization may be an unavoidable consequence in a small percentage of women after hysterectomy (Michaels, 1948). Ureteral devascularization tends to manifest differently from other ureteral injuries. Patients tend to present late (more than a week after surgery, but as late as 1 to 2 months), usually with ureteral stenosis, urinoma, or even uretero-vaginal fistula that was not seemingly present at the time of surgery or the early days after surgery.

Ureteroscopic Injury

Since Kaufman (1984) first reported ureteral injury after rigid ureteroscopy in 1984, countless ureteral misadventures have resulted from this procedure. In fact, ureteroscopic injury was the most common cause of iatrogenic ureteral trauma in some modern series (Johnson et al, 2004). In the late 1980s, an explosion of ureteral injuries coincided with the widespread use of ureteroscopy (Huffman, 1989). Improvements in equipment and operator experience subsequently decreased the rate of ureteral perforation, to a stable average of 7% in the 1990s (range 0% to 28%) (Huffman, 1989). More recent expert series have a perforation rate of 1% to 5% (Schuster et al, 2001), of which 0.2% requires open surgery (Butler et al, 2004) with an additional 5% incidence of delayed stricture occurrence (Schuster et al, 2001).

One factor cited as a cause of ureteral injury during ureteroscopy was the persistence of stone basket attempts after recognition of a ureteral tear. Current recommendations are to stop the procedure and place a ureteral stent when ureteral perforations are identified (Chang and Marshall, 1987). The wide use of the holmium:yttrium-aluminum-garnet (Ho:YAG) laser to fragment larger stones before basket manipulation is attempted should further decrease the potential for this complication (Bagley et al, 2004). Extraureteric extrusion of calculi during laser fragmentation or basket retrieval has shown to be a minor complication and only rarely leads to stricture formation (Kriegmair and Schmeller, 1995).

It is also recommended to perform ureteroscopy alongside or over a wire placed up into the renal pelvis (Chang and Marshall, 1987; Flam et al, 1988), although some experts no longer use a safety wire during routine flexible ureteroscopy (Bratslavsky and Moran, 2004). This wire facilitates not only safe ureteroscopy but also placement of a ureteral stent later in the case if necessary. Factors associated with higher complication rates during ureteroscopy were longer surgery times, treatment of renal calculi, surgeon inexperience, and previous irradiation (Huffman, 1989;

Schuster et al, 2001; Fuganti et al, 2008). During stone fragmentation attempts, electrohydraulic lithotripsy (now hardly used) is associated with the highest risk for ureteral injury, followed by the neodymium:YAG (Nd:YAG) laser and finally by the Ho:YAG laser (Johnson and Pearle, 2004). Factors that are thought to protect against ureteral injury are smaller (Flam et al, 1988; Huffman, 1989) and flexible ureteroscopes (Huffman, 1989). Ureteral access sheaths also protect the ureter, but the sheaths themselves can cause ureteral wall injury, especially if the patient did not receive a ureteral stent preoperatively (Traxer and Thomas, 2013). Smaller diameter (≤ 14 -Fr) sheaths are preferred for nonstented ureters.

Diagnosis

Gunshot and Stab Wounds

Hematuria. Hematuria is a nonspecific indicator of urologic injury. Significant ureteral injury can occur in the absence of hematuria (Elliott and McAninch, 2006). Because many (25% to 45%) cases of ureteral injury after violence do not demonstrate even microscopic hematuria (Presti et al, 1989; Campbell et al, 1992; Brandes et al, 1994; Palmer et al, 1999), a high index of suspicion is required in cases of potential ureteral injury after penetrating trauma.

Intraoperative Recognition. In an analysis of previously published reports concerning ureteral injury from external violence, Armenakas and associates (1999) noted that 93% of injuries were recognized promptly, including 57% that were identified intraoperatively. We and others (Brandes et al, 1994; Medina et al, 1998) make every attempt to diagnose these injuries during exploration. Intraoperative detection requires a high degree of suspicion, but there is evidence that specific vigilance for ureteral injuries may decrease the incidence of missed injuries (McGinty and Mendez, 1977). The trajectory of the knife or missile must be carefully examined during laparotomy and ureteral exploration undertaken in all cases of potential injury. With a 75% sensitivity for traumatic ureteral injury, wound location may be the only indicator for identifying ureteral injury in the acute setting (Elliott and McAninch, 2003). Liberal use of preoperative diagnostic tools (urinalysis, IVP, CT), even if imperfect, is helpful. Intraoperative recognition of ureteral or renal pelvis injury may be aided by using a small needle to inject 1 to 2 mL of methylene blue (10 mg/mL) directly into the renal pelvis. Care must be taken not to inject excessive dye, because it can spill and stain local tissues, making dye determination of the source of leak impossible.

Inadequate exploration or a low index of suspicion in the presence of multiple injuries is often responsible for missed ureteral injury. In the largest meta-analysis to date, analyzing 16 busy trauma centers with 429 ureteral injuries with laparotomy, a collective 11% miss rate of ureteral injury was noted (Kunkle et al, 2006). Delayed diagnosis in that series was associated with a prolonged hospital stay and increased rates of nephrectomy. An unrecognized or undertreated ureteral injury can lead to other significant complications, including urinoma, abscess, ureteral stricture, and urinary fistula.

Vigilance for delayed presentation of ureteral injuries allows detection of initially missed injuries. Fever, leukocytosis, and local peritoneal irritation are the most common signs and symptoms of missed ureteral injury and always should prompt CT examination. In contrast to acute injuries, “missed” injuries that are discovered more than 48 hours after injury may be best diagnosed with retrograde ureterography if possible. This procedure has the added benefit of allowing immediate attempts at ureteral stent passage to aid urinary drainage, avoid or treat urinoma, and allow healing without further surgery in rare cases.

Imaging Studies

Excretory Urography. Ureteral injuries after external violence, unlike renal injuries, are difficult to detect with the usual array of diagnostic tools: preoperative urinalysis, CT scan, and intraoperative one-shot IVP. IVP is often unhelpful, proving nondiagnostic 33% to 100% of the time (Palmer et al, 1983; Presti et al, 1989; Campbell et al, 1992; Brandes et al, 1994; Azimuddin et al, 1998; Elliott and McAninch, 2003). However, in the absence of a better



Figure 50-15. Excretory urography demonstrating extravasation in the upper right ureter consequent to stab wound. Note lack of contrast (arrow) in the ureter below the site of injury, indicating complete ureteral transection.

test, we still recommend intraoperative one-shot pyelography together with intraoperative inspection to detect ureteral injuries and assess the functional status of the contralateral system. When intraoperative one-shot IVP abnormalities are found, obvious contrast extravasation can sometimes be seen (Fig. 50-15). However, IVP findings are often subtle and nonspecific (e.g., delayed function, ureteral dilation, and ureteral deviation). Insensitivity of these usual diagnostic tools and high false-negative rates are some of the reasons why delay of detection occurs in 8% to 20% of cases (Presti et al, 1989; Brandes et al, 1994; Palmer et al, 1999).

Computed Tomography. CT is used increasingly in the evaluation of the trauma patient, and although it appears promising in detecting ureteral injuries (Kawashima et al, 2001), there are only a handful of published reports (Kenney et al, 1987; Townsend and DeFalco, 1995). Ureteral injuries can be difficult to diagnose on CT. If the urinary extravasation from upper ureteral injury is contained by the Gerota fascia, the extent of medial leakage can be small, obscuring the diagnosis (Kenney et al, 1987). It is also known that ureteral injuries often manifest with absence of contrast in the ureter on delayed images. This underscores the absolute necessity of tracing both ureters throughout their entire course on CT scans obtained to evaluate urogenital injuries (Townsend and DeFalco, 1995). Because modern helical CT scanners can obtain images rapidly, before IV contrast dye is excreted in the urine, delayed images must be obtained (5 to 20 minutes after contrast injection) to allow contrast material to extravasate from the injured collecting system, renal pelvis, or ureter (Brown et al, 1998b; Mulligan et al, 1998; Kawashima et al, 2001). Because ureteral injuries are often detected late, periureteral urinoma seen on delayed CT scans may be diagnostic (Gayer et al, 2002).

In reported series, all patients with significant ureteropelvic laceration, for instance, had either medial extravasation of contrast material or nonopacification of the ipsilateral ureter on CT (Kenney



Figure 50-16. Computed tomography showing right medial extravasation of contrast material in a patient with a renal pelvis laceration.

et al, 1987; Kawashima et al, 2001) (Fig. 50-16) or a “circumrenal” contrast extravasation (Kawashima et al, 1997).

Retrograde Ureterography. Retrograde ureterograms, the most sensitive radiographic test for ureteral injury, are used in some centers as a primary diagnostic technique to detect acute ureteral injuries (Campbell et al, 1992); however, we tend to use noninvasive methods such as one-shot IVP and CT scan to make the diagnosis intraoperatively when feasible. Retrograde ureterography is used, however, to delineate the extent of ureteral injury seen on CT scan or IVP if further clinical information is needed. Retrograde ureterography is most commonly used to diagnose initially missed ureteral injuries, because it allows the simultaneous placement of a ureteral stent if possible.

Antegrade Ureterography. Antegrade ureterography is seldom used in our practice. In cases in which ureteral injury is discovered, we most often plan retrograde ureterography and stent placement or open repair. If retrograde stent placement is not possible (usually secondary to a large gap in the two ends of the transected ureter), we attempt antegrade ureterography and stent placement at the time of percutaneous nephrostomy placement (Toporoff et al, 1992).

Management

See Figure 50-17.

General Principles

Following certain general principles of ureteral surgery increases the success rate of this delicate surgery. Repair of the ureter must be meticulous (Fig. 50-18). Ureteral blood supply is tenuous, and a sequela of imperfect repair can be urine leakage that can result in patient debility, nephrectomy, and, in rare cases, even death. Principles of management of the injured ureter are as follows:

1. Mobilize the injured ureter carefully, sparing the adventitia widely, so as not to devascularize the ureter further.
2. Debride the ureter minimally but judiciously until edges bleed, especially in high-velocity gunshot wounds.
3. Repair ureters with spatulated, tension-free, stented (Palmer et al, 1983), watertight anastomosis, using fine absorbable monofilament such as 5-0 polydioxanone and retroperitoneal drainage afterward. Use optical magnification if necessary.
4. Retroperitonealize the ureteral repair by closing peritoneum over it if possible.
5. Do not tunnel ureteroneocystostomies but rather create a widely spatulated nontunneled anastomosis.

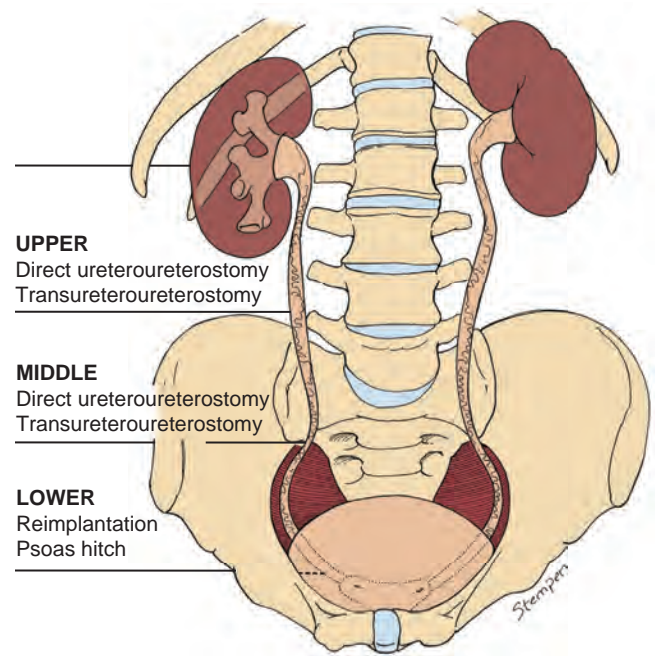


Figure 50-17. Suggested management options for ureteral injuries at different levels.

6. With severely injured ureters, blast effect, concomitant vascular surgery, and other complex cases, consider omental interposition to isolate the repair when possible.
7. If immediate repair is not possible, tie off the ureter with long silk sutures and plan to repair it later (damage control). Ipsilateral drainage can be achieved by placing a single J stent brought out cutaneously or a percutaneous nephrostomy tube placed later.

External Trauma

Contusion. Ureteral contusions, although the most minor of ureteral injuries, can heal with stricture or breakdown later if microvascular injury results in ureteral necrosis, with an incidence that is not currently known. **Severe or large areas of contusion should be treated with excision of the damaged area and ureteroureterostomy/ureteroneocystostomy.** The safest approach in ureteral contusions that do not appear to require excision/anastomosis is to place a ureteral stent. Only truly minor injuries can go untreated, but the patients should be watched for signs of delayed urine leak.

Management of ureteral leak is by percutaneous nephrostomy placement and ureteral catheter placement for at least 6 weeks, which provides surprisingly good success rates (83% [Toporoff et al, 1992] to 88% [Lang, 1984]). Other authors have recommended stenting for a longer period—up to 8 weeks (Steers et al, 1985).

Upper Ureteral Injuries

Ureteroureterostomy. Ureteral avulsion from the renal pelvis, or even very proximal ureteral injury, can be managed by reimplantation of the ureter directly into the renal pelvis (Fig. 50-19). These can be done open, laparoscopically, or robotically (Mufarrij et al, 2007). Ureteroureterostomy, or so-called end-to-end repair, is used in injuries to the upper two thirds of the ureter. It is required commonly—up to 32% of the time in large series (Presti et al, 1989; Elliott and McAninch, 2003)—and has a reported success rate as high as 90% (Carlton et al, 1971). Complications after ureteroureterostomy, usually urine leakage, occur 10% to 24% of the time (Bright and Peters, 1977a; Pitts and Peterson, 1981; Presti et al, 1989; Campbell et al, 1992; Velmahos et al, 1996; Medina et al, 1998). Other acute complications include abscess and fistula. Chronic complications, usually ureteral stenosis, are less common, involving approximately 5% (Palmer et al, 1999) to 12%

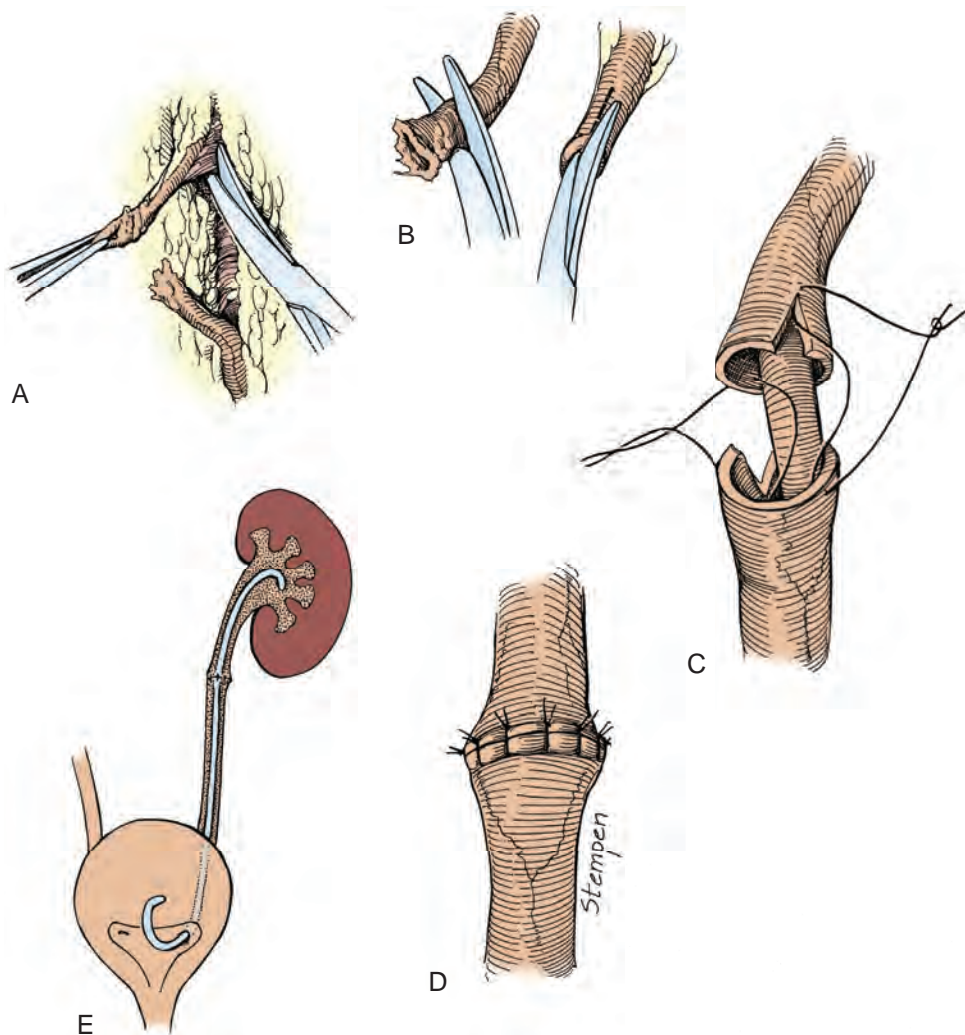


Figure 50-18. Technique of ureteroureterostomy after traumatic disruption. A, Injury site definition by ureteral mobilization. B, Debridement of margins and spatulation. C, Stent placement. D, Approximation with 5-0 absorbable suture. E, Final result.

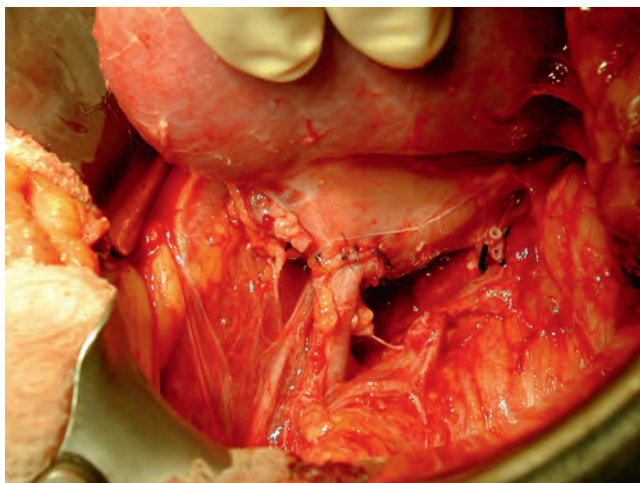


Figure 50-19. Proximal ureter is spatulated and sutured to the renal pelvis.

(Velmahos et al, 1996) of patients. Interestingly, some authors report prolonged leakage of urine from the drain in patients with ureteral injury after external violence who underwent repair but otherwise did well. Steers and colleagues (1985) reported that most of their patients had persistent drainage (averaging 12 days) from the retroperitoneal Penrose drain after repair. This has not been our experience, but this observation might prompt watchful waiting in such patients who leak persistently after repair. Routine retroperitonealization of the repair may decrease the time or severity of postoperative urine leakage.

Rarely, ureterocalycostomy, in which the ureteral stump is sewn end-to-side into an exposed renal calyx, also can be used where there is profound damage to the renal pelvis and UPJ (Matlaga et al, 2005). This is a technically challenging case. It can be difficult to find an inferior calyx; it requires renal surgery equivalent to a partial nephrectomy; and sewing the small, medially located ureter to a large laterally located renal calyx can be difficult or even impossible. With technologic advances, robotics can be successfully and safely used for a wide variety of delayed upper urinary tract reconstructions, including dismembered pyeloplasty, ureteroureterostomy, and ureterocalycostomy.

Autotransplantation. Autotransplantation of the kidney has been used after profound ureteral loss or after multiple attempts at ureteral repair have failed. This maneuver remains the final option before nephrectomy. Despite great efforts, renal units are sometimes lost after autotransplantation, occurring in 4 of 39 kidneys in two

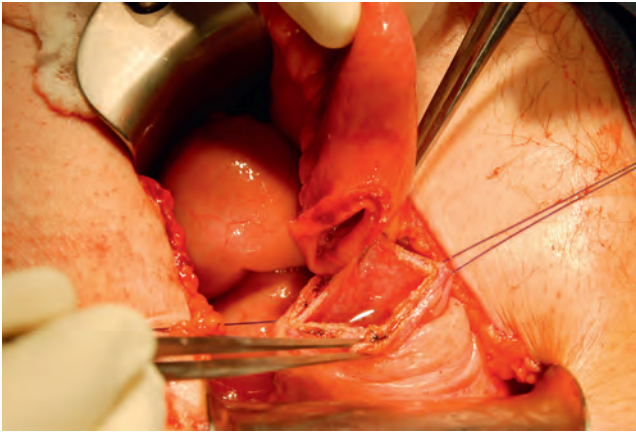


Figure 50-20. Nontapered distal ileal segment is anastomosed to the bladder in a wide open fashion.

combined series (Bodie et al, 1986; Eisenberg et al, 2008), although centers with significant transplant experience have reported good results.

Bowel Interposition. Delayed ureteral repairs, especially when a very long segment of ureter is destroyed, also can be performed by creation of a ureteral conduit out of ileum in much the same way that an ileal conduit is constructed to drain the urine after cystectomy. Success rates for ileal replacement of the ureter have been reported to be 81% (Boxer et al, 1979; Verduyck et al, 2002) to 100% (Matlaga et al, 2003; Bonfig et al, 2004). A recent review of long-term complications of 99 renal units reported a 3% anastomotic stricture and 6% fistula rate (Armatys et al, 2009). Some have used the Monti procedure, in which short segments of small or large bowel are formed into a long, thin tube successfully in ureteral reconstruction (Ubrig et al, 2001; Ali-el-Dein and Ghoneim, 2003). Laparoscopic-assisted ureteral interposition by ileum has been described in two patients (Castillo et al, 2008). The use of appendix in open (Jang et al, 2002) and laparoscopic (Reggio et al, 2008) ureteral substitution has also been reported. Although most practitioners create a wide-open, refluxing, ileal replacement of the ureter (Fig. 50-20), it appears that significant clinical reflux is not a problem (Waldner et al, 1999). We often prefer a standard ileal ureter technique instead of tapered bowel or appendix because patients place a premium on the reliability of the repair, and in our experience the ileal ureter operation is very reliable. Ileal interposition is not suggested for acute repair of ureteral injury but rather would be used in delayed or staged repairs.

Monitoring after Ureteral Repair. Monitoring after ureteral repair is a matter of personal preference. We tend to leave the stent in for 6 weeks. At the time of stent removal, we usually perform a retrograde ureterogram to document healing without leakage or stenosis. One month postoperatively, we perform a furosemide (Lasix) renogram to document that the system continues to be unobstructed. Four months postoperatively we perform a renal ultrasound to document lack of hydronephrosis, which itself might indicate late obstruction. Ureteral injury repairs often happen in the setting of ureteral devascularization; late stenosis can occur.

Nephrectomy. Rarely, acute nephrectomy is required to treat ureteral injury after external violence. Reasons for nephrectomy include associated severe visceral injuries (although damage control without nephrectomy is nearly always preferable) or severe associated injury to the ipsilateral kidney when renal repair is not possible (McGinty and Mendez, 1977; Gill and McRoberts, 1992). Delayed nephrectomy may be required because of poor renal function (which can sometimes be seen after delayed recognition of an obstructing ureteral injury), severe panureteral injury when ileal ureter or other reconstruction is impossible, or persistent ureteral fistula (especially vascular fistula) despite previous intervention (Ghali et al, 1999). In general, nephrectomy must be avoided if at all possible.

Midureteral Injuries

Transureteroureterostomy. A rarely used (Presti et al, 1989) but often (90% to 97%) successful (Rainwater et al, 1991; Sugarbaker et al, 2003) technique in adults is transureteroureterostomy. Pediatric series show a lower success rate of 70% (Mure et al, 2000). This form of repair involves bringing the injured ureter across the midline and anastomosing it end-to-side into the uninjured ureter and is most often performed as a secondary or delayed procedure. It also might be mandated in some cases of middle or distal ureteral injury in which ureteroureterostomy or bladder flap/hitch repair is impossible (usually because of severe bladder scarring, a congenitally small bladder, or a very long segment of missing ureter). Laparoscopic transureteroureterostomy has been performed in the pediatric population (Piaggio and González, 2007).

However, transureteroureterostomy leaves the patient and urologist with some vexing problems postoperatively. The injured ureter becomes difficult to intubate or image with ureteroscopy through the bladder; ureteral access needs to be provided by a nephrostomy placed on the injured side. Some authors feel this operation is contraindicated in patients with a history of urothelial cancer or calculi, although this information is seldom available to the operating trauma surgeon. Caution is required while performing this procedure because it involves surgery on the uninjured, contralateral ureter with the theoretical risk for converting unilateral ureteral injury into (iatrogenic) bilateral ureteral injury. Instead of transureteroureterostomy, we prefer either ileal interposition or ureteroureterostomy with renal mobilization if necessary.

Lower Ureteral Injuries

Ureteroneocystostomy. Ureteroneocystostomy is used to repair distal ureteral injuries that occur so close to the bladder that the bladder does not need to be brought up to the ureteral stump with a psoas hitch or Boari procedure. Standard principles of ureteroneocystostomy include a long, nontunneled, spatulated, stented anastomosis. Refluxing ureteroneobladder (Minervini et al, 2005) and uretero-ileal loop (Wiesner and Thuroff, 2004) anastomoses show no increase in complications related to urine reflux, although these populations of patients are different from the average trauma population and reports do not address whether ureteral implantation into the native bladder is equally safe. Further study is needed to resolve this issue, but we favor nontunneled anastomoses because we prefer the low risk for clinically significant reflux to the higher risk for ureteral obstruction using a tunneled approach.

Psoas Bladder Hitch. The psoas hitch procedure (Fig. 50-21) is a mainstay in the treatment of injuries to the lower third of the ureter and has a high success rate, from 95% to 100% (Middleton, 1980; Riedmiller et al, 1984; Ahn and Loughlin, 2001). We prefer it over ureteroureterostomy in lower ureteral injuries because the tenuous ureteral blood supply might not survive transection. Some authors prefer end-to-end repair in lower ureteral injuries when the distal stump is preserved (Paick et al, 2006).

Boari Flap. Injuries to the lower two thirds of the ureter with long ureteral defects (too long to be bridged by bringing the bladder up in the psoas hitch procedure) can be managed with a Boari flap or a transureteroureterostomy (Fig. 50-22). In this case, a pedicle of bladder is swung cephalad and tubularized to bridge the gap to the injured ureter. The procedure is time-consuming, however, and is not appropriate for most acute injuries. It is not commonly performed, but authors report a high success rate (Benson et al, 1990).

Minimally Invasive. More recently, laparoscopic and robotic repair of distal ureteral injuries has emerged as a viable alternative to open surgery (Mufarrij et al, 2007). Laparoscopic direct ureteroneocystostomy, psoas bladder hitch, and Boari flap reconstructions have been described (Fugita et al, 2001; Schimpf and Wagner, 2008). A review of early results demonstrates laparoscopic ureteral reimplantation as effective as open techniques (Ogan et al, 2008). In a recent study of 45 patients undergoing laparoscopic ureteroneocystostomy, overall success, defined as radiographic evidence of no residual obstruction, symptoms, renal deterioration, or need for subsequent procedures was 96% (Seideman et al, 2009). Although limited data exist and longer term outcomes are needed, many centers now use

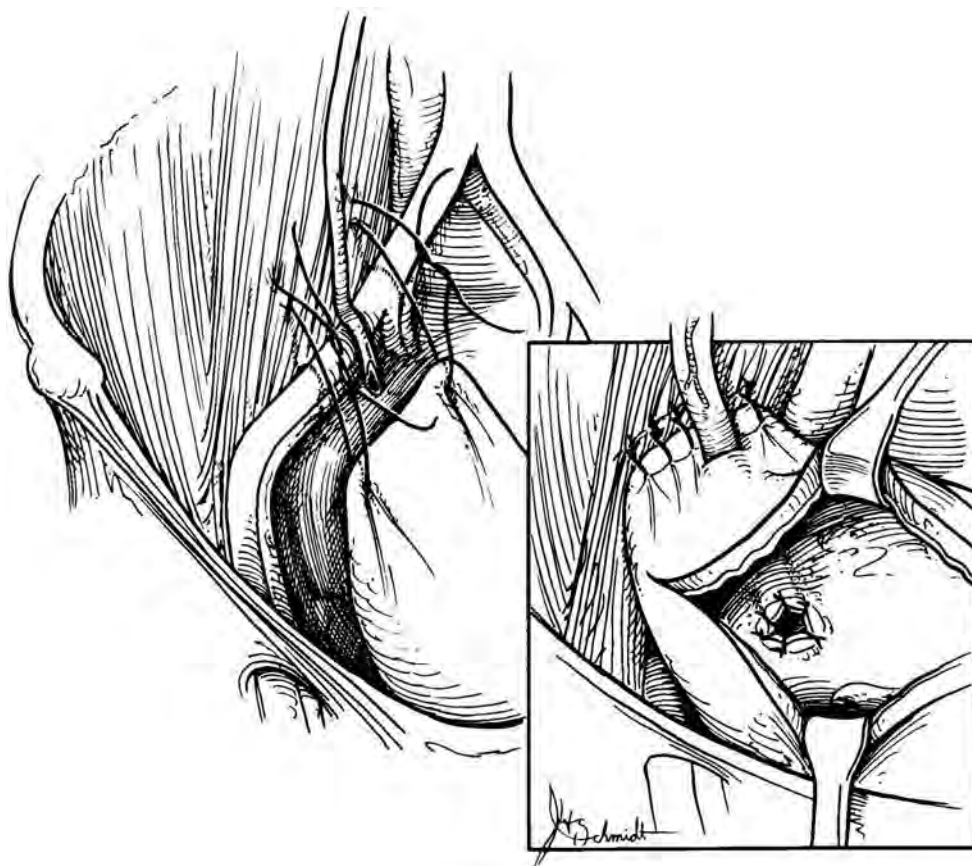


Figure 50-21. Psoas hitch. Bladder is opened and secured to the psoas muscle to facilitate ureteral anastomosis. (From Hohenfellner M, Santucci RA. *Emergencies in urology*. Heidelberg (Germany): Springer; 2007. © Copyright, 2007 Dr. Markus Hohenfellner, with permission.)

laparoscopic and even robotic management as primary treatment. Laparoscopic or robotic repair of ureteral injuries may indeed be the standard of care.

Partial Transection. Primary repair of a partial transection is used in the majority of ureteral injuries, up to 58% of the time in one large series (Presti et al, 1989). Principles of primary repair involve spatulated, watertight closure, with interrupted or running 5-0 or 6-0 absorbable monofilament such as Maxon (polyglyconate) or Dexon (polyglycolic acid). The ureteral injury is closed by converting a longitudinal laceration into a transverse one so as not to narrow the ureteral lumen (Heineke-Mikulicz procedure) and repeat retroperitonealized if possible. An internal stent and retroperitoneal drain are always placed.

Damage Control. In cases of ureteral injury after external violence, it is sometimes necessary to treat the injured ureter by deferring definitive treatment until later. This is usually because the patient is too unstable to tolerate the operative time required to complete the repair (Cass, 1983). Some have suggested that in cases of severe hemorrhagic shock, uncontrollable intraoperative bleeding, or severe colon injury (especially those requiring colectomy), ureteral repair should be avoided in favor of nephrectomy or staged repair (Velmahos et al, 1996).

The four options for damage control in ureteral injuries are (1) do nothing, but plan a reoperation when the patient is more stable, usually within 24 hours; (2) place an internal or exteriorized ureteral stent and do nothing else; (3) exteriorize the ureter; or (4) tie off the ureter and plan percutaneous nephrostomy (Hirshberg et al, 1994). In most cases of planned staged repair, we tie off the damaged ureter, using long silk ties to aid the dissection of the ureteral stump during the second-stage repair. The kidney is then drained percutaneously. We advocate percutaneous (not intraoperative or intra-abdominal) placement of a nephrostomy tube, either by the surgeon just postoperatively or later by interventional radiologists. We have

found that intraoperative open nephrostomy placement can be too time-consuming in these unstable patients. Alternatively, a single J stent can be placed into the ureter, the distal ureteral injury tied off over the stent, and the stent end externalized through the abdominal wall (Gill and McRoberts, 1992; Ball et al, 2005). If possible, appropriate planned ureteric reconstruction should be done after functional and anatomic imaging is performed.

Surgical Injury

Timing of Repair. The ideal timing of curative surgery is controversial. Experts suggest fixing intraoperatively discovered injuries immediately. Even with immediate recognition, success is not ensured. In small series, patients with immediately repaired ureteral injuries still suffered urine leak, fistula, and even nephrectomy (Grainger et al, 1990; Mandal et al, 1990). Experts suggest that postoperatively discovered injuries be immediately repaired when detected within 72 hours. Injuries discovered after this 3-day period are drained with stent, percutaneous nephrostomy, or both, and definitive repair is delayed until 6 weeks after injury. This putatively avoids an inflammatory phase, when ureteral repairs are thought to be less reliable. Others recommend immediate repair whenever injuries are discovered, even in the 3- to 42-day window that some avoid surgery. These authors cite low complication rates, similar to injuries that are recognized immediately (Witters et al, 1986; Ghali et al, 1999). However, delayed diagnosis of ureteral injury may increase the complication rate of the repair significantly (Selzman and Spirnak, 1996), from 10% to 40% in one series (Campbell et al, 1992). Some have suggested that delaying the repair (6 weeks) avoids this risk (Cangiano and deKernion, 1988).

In the period between 3 and 42 days after injury, discovering the injury “early” (say, in the first week) versus late (say, after a month) does not seem to affect outcomes. Most injuries, in fact, are

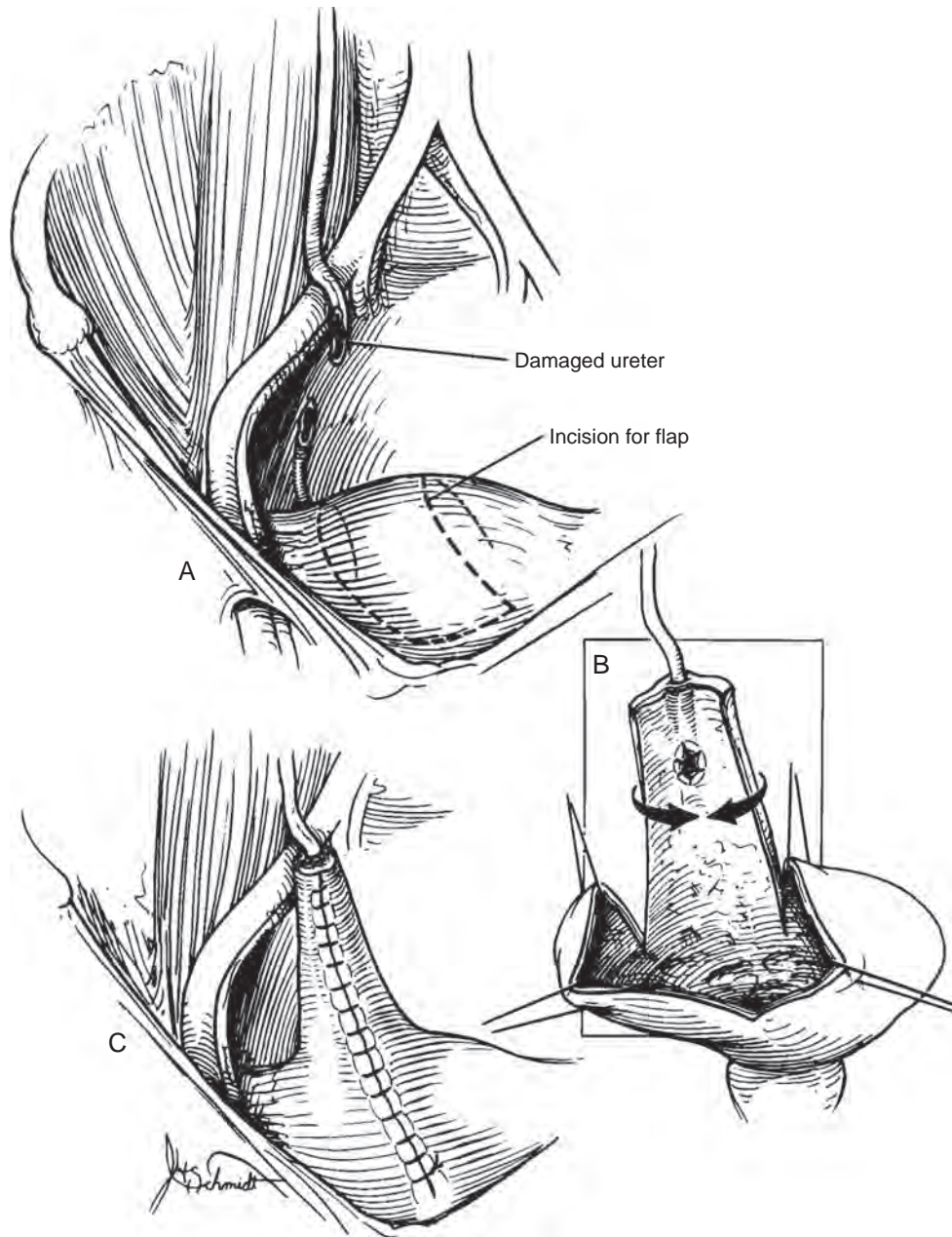


Figure 50-22. Boari flap. Bladder flap is marked (A), mobilized free (B), tubularized (C). (From Hohenfellner M, Santucci RA. *Emergencies in urology*. Heidelberg (Germany): Springer; 2007. © Copyright, 2007 Dr. Markus Hohenfellner, with permission.)

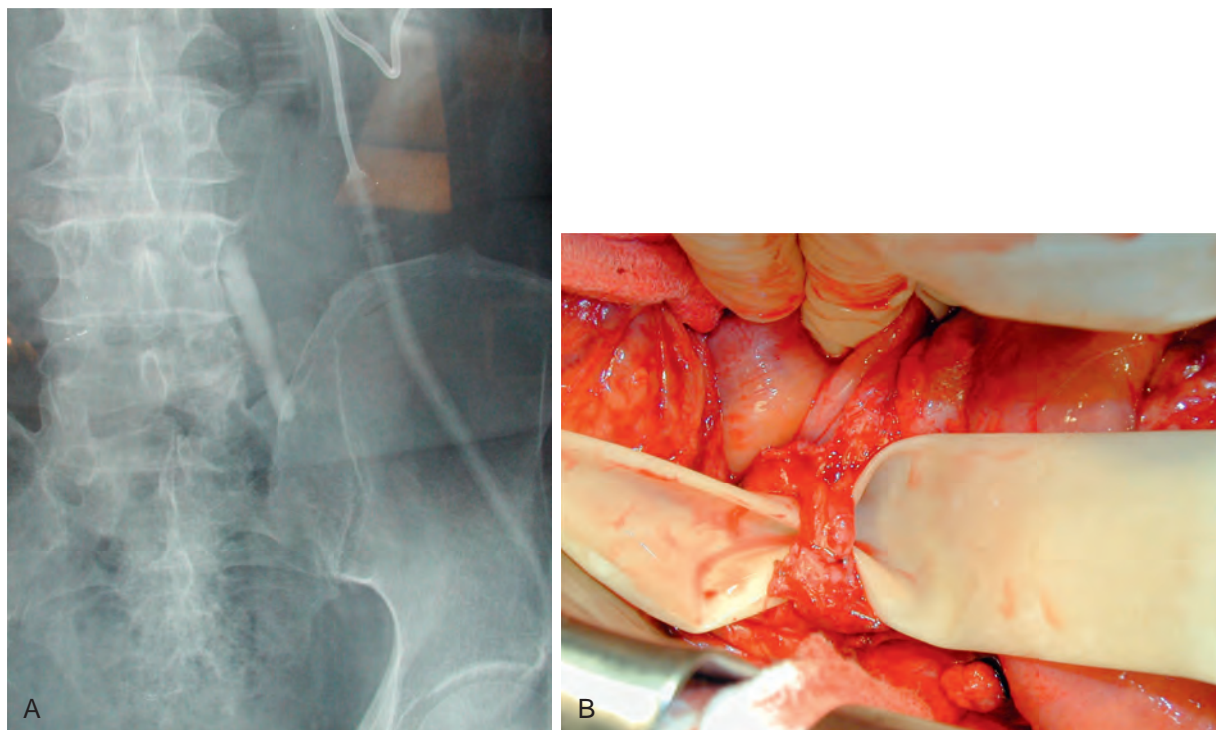


Figure 50-23. A, Left nephrostogram showing abrupt mid-ureteral cutoff consistent with (inadvertent) suture ligation of the ureter. B, Intraoperative view of left mid-ureteral suture ligation.

discovered in this period (Oh et al, 2000; Hatch et al, 1984), and in one series almost half were discovered more than 6 weeks after the initial surgery (Badenoch et al, 1987). Cure rates appear equal in the early and late discovery groups (Brandt et al, 2001; Liapis et al, 2001).

Ligation. Ligation of the ureter should be treated by removal of the ligature and observation of the ureter for viability. If viability is in question, ureteroureterostomy or ureteral reimplantation should be performed (Assimos et al, 1994; Brandes et al, 2004) (Fig. 50-23). Placement of a ureteral stent, by opening the bladder or by immediate cystoscopic placement, is highly advised.

Transection

Immediate Recognition. Injuries discovered immediately after nonaortic surgery are largely treated in the same way as ureteral injury after external violence. Most lacerations can be treated with ureteroureterostomy, although additional maneuvers such as omental wrapping of the repair or placement of an ipsilateral nephrostomy tube have been advocated to decrease the potential for urine leakage or breakdown of the repair (Adams et al, 1992). With increasing laparoscopic and robotic popularity, many of these injuries are now being treated without the need for open conversion (Dinlenc et al, 2004; Ou et al, 2005). Ureteroscopic (Tsai et al, 2000) ureteroureterostomies for operative ureteral injuries also have been reported, although we have no direct experience with them.

Ureteral injuries that occur during vascular graft surgery are a special case. Intraoperative management of these should be primary ureteroureterostomy with isolation of the repair with omentum (Adams et al, 1992). Nephrectomy in cases of ureteral injury should be avoided. Although nephrectomy avoids the potential for postoperative urine leakage around an aortic or iliac vascular graft (Schapira et al, 1981), it increased the mortality rate. In patients with a ruptured aneurysm, it can increase the fatality rate fourfold, from 3% to 12% (Schapira et al, 1981). We recommend careful repair of the ureteral injury, reserving nephrectomy for patients who develop urine leakage postoperatively.

Delayed Recognition. Intraoperative recognition of ureteral injuries occurs in as few as 34% of patients undergoing open operation

(Ghali et al, 1999) and as few as 0% of those undergoing laparoscopy (Grainger et al, 1990). Delayed diagnosis of ureteral injury is most often (66% [Ghali et al, 1999] to 76% [Grainger et al, 1990]) achieved by CT pyelography, IVP, or retrograde ureterography (Grainger et al, 1990). In a series of 35 ureteral injuries, patients present with a variety of signs and symptoms: anuria (14%, most with bilateral injury), urogenital fistula (11%), persistent pain or fever (9%), urinary leakage from the wound (9%), hydronephrosis (3%), and hematuria (3%) (Ghali et al, 1999). Some authors cite a triad of fever, leukocytosis, and generalized peritoneal signs as being most diagnostic for missed ureteral injury (Medina et al, 1998). Repair of these delayed-recognition injuries is controversial. Some advocate immediate attempt at placement of a double-J ureteral stent (Bright and Peters, 1977b), but this is not always possible. Reported success varies widely: 5% to 10% (Dowling et al, 1986; Hoch et al, 1975), 20% (Ghali et al, 1999; Oh et al, 2000), and 50% (Cormio et al, 1993). When stent placement is possible, some authors have reported a spontaneous healing rate as high as 73% (Dowling et al, 1986) or as low as 0% (Oh et al, 2000). Usually, failure to place a stent is due to complete obstruction of the ureter or to too long a gap (Cormio et al, 1993). Some authors have suggested that stenting alone has the highest failure rate in those with multiple previous pelvic operations, radiation therapy, or significant previous ureteral surgery (Chang and Marshall, 1987). The ideal length of time to leave the stent has never been studied in a randomized, prospective, double-blind fashion, but some authors recommend at least 6 weeks (Selzman and Spirnak, 1996). Some authors had increased healing rates when stents are left in for 3 months (Cormio et al, 1993), although this has not been observed in our practice. Most authors report low rates of spontaneous healing with stenting alone; in a series of ureteral injuries after laparoscopies that were recognized late (3 to 33 days after surgery), all ultimately required open repair (Oh et al, 2000). The literature and our experience seem to indicate that a majority of patients will require definitive repair of significant ureteral injuries, whether stent placement is possible or not. If stents cannot be placed, the urine must still be drained and percutaneous nephrostomy should be placed.

We first attempt retrograde placement of a ureteral stent in most cases of delayed recognition of ureteral injury. If stent placement is achieved, open repair is planned only in patients with persistent leakage or significant ureteral stricture (Dowling et al, 1986; Cormio et al, 1993). In cases in which we cannot place a retrograde ureteral stent, we usually place a nephrostomy tube and make an immediate or delayed attempt at antegrade stenting of the injury. If this initially fails, we place a nephrostomy tube and wait 7 to 14 days to reattempt antegrade ureteral stenting. We and our patients highly prefer internalized double-J stents over percutaneous nephrostomies whenever possible. Ureteral balloon catheters, which are designed to stop urine from traveling down the ureter, have been advocated if simple stenting does not eliminate associated urine leakage or urinoma, although we often have found them to be ineffective. If the ureter ultimately cannot be stented, a percutaneous nephrostomy is placed. We think the safest approach is to allow at least 6 weeks for complete healing of the wounds, then attempt open repair. Some have reported the requirement for even longer ureteral drainage in certain special cases, such as in the presence of ureteroenteric fistula (Bright and Peters, 1977b). We recognize that some experts in the field repair these injuries whenever they are discovered, with seemingly good results (Bright and Peters, 1977b; Flynn et al, 1979; Blandy et al, 1991; Oh et al, 2000).

Some authors have advocated treating postinjury ureteral stenosis endoscopically with either balloon dilation (Richter et al, 2000) or laser incision (Singal et al, 1997; Patel and Newman, 2004). Others have used endoluminal stents for ureteral obstruction after injury with good results in limited numbers of patients (Yohannes et al, 2001; Wenzler et al, 2008). We personally have had poor results after endoscopic dilation and incision techniques in the long, devascularized, postinjury or postoperative ureteral strictures that seem to dominate our practice, although we may try them in short, uncomplicated strictures before open repair is contemplated. Metal endoluminal stents must be considered experimental until large series validate their use.

Ureteroscopy Injury

Avulsion. Ureteral avulsion during ureteroscopy is treated in the same manner as ureteral injuries after open or laparoscopic surgery, as detailed in the section on ureteral transection.

Perforation. Ureteral perforation during ureteroscopy can be treated by ureteral stenting, usually with no subsequent complications (Flam et al, 1988; Huffman, 1989). The safest approach is to avoid injury by always performing ureteroscopy over a ureteral guidewire and by placing a second ureteral safety wire that is always in place during ureteroscopy and facilitates ureteral stent placement in the presence of problems. We recognize that some expert centers do not use a ureteral guidewire during ureteroscopy and that some no longer use a safety wire (Bratslavsky and Moran, 2004), but we think that at least a safety wire is most prudent for the majority of practitioners.

KEY POINTS: URETERAL TRAUMA

- Ureteral injuries must be carefully sought, or they will be missed.
- After penetrating injury, use CT scan and intraoperative one-shot IVP liberally.
- After penetrating injury, determine the course of the knife or bullet tract to ensure that the ureter is not at risk.
- If delayed recognition is suspected, use CT and retrograde pyelography aggressively.
- Safe ureteroscopy practices should be followed, including using sound technique, limiting ureteroscopy times, using safety wires, scoping over guidewires, and halting ureteroscopy immediately in the face of any ureteral injury.
- Retroperitoneal surgery should be undertaken only with constant attention to the location of the ureter. Intraoperatively, expose and inspect the ureter when necessary.
- See Figure 50-24.

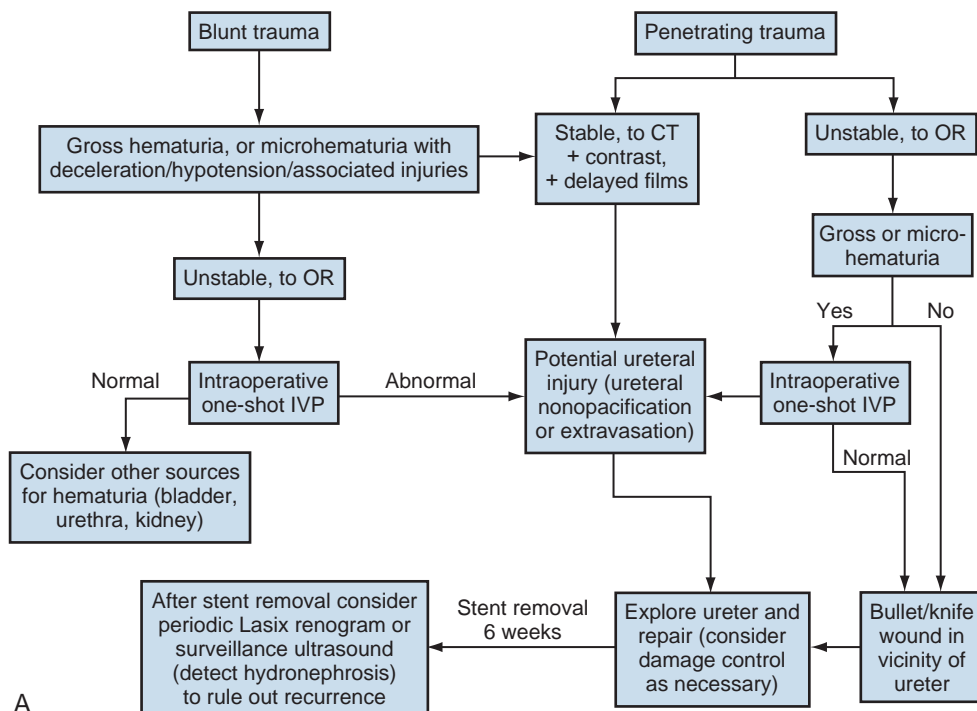


Figure 50-24. Algorithms for the diagnosis and treatment of ureteral injuries. **A, From external violence.** *Continued*

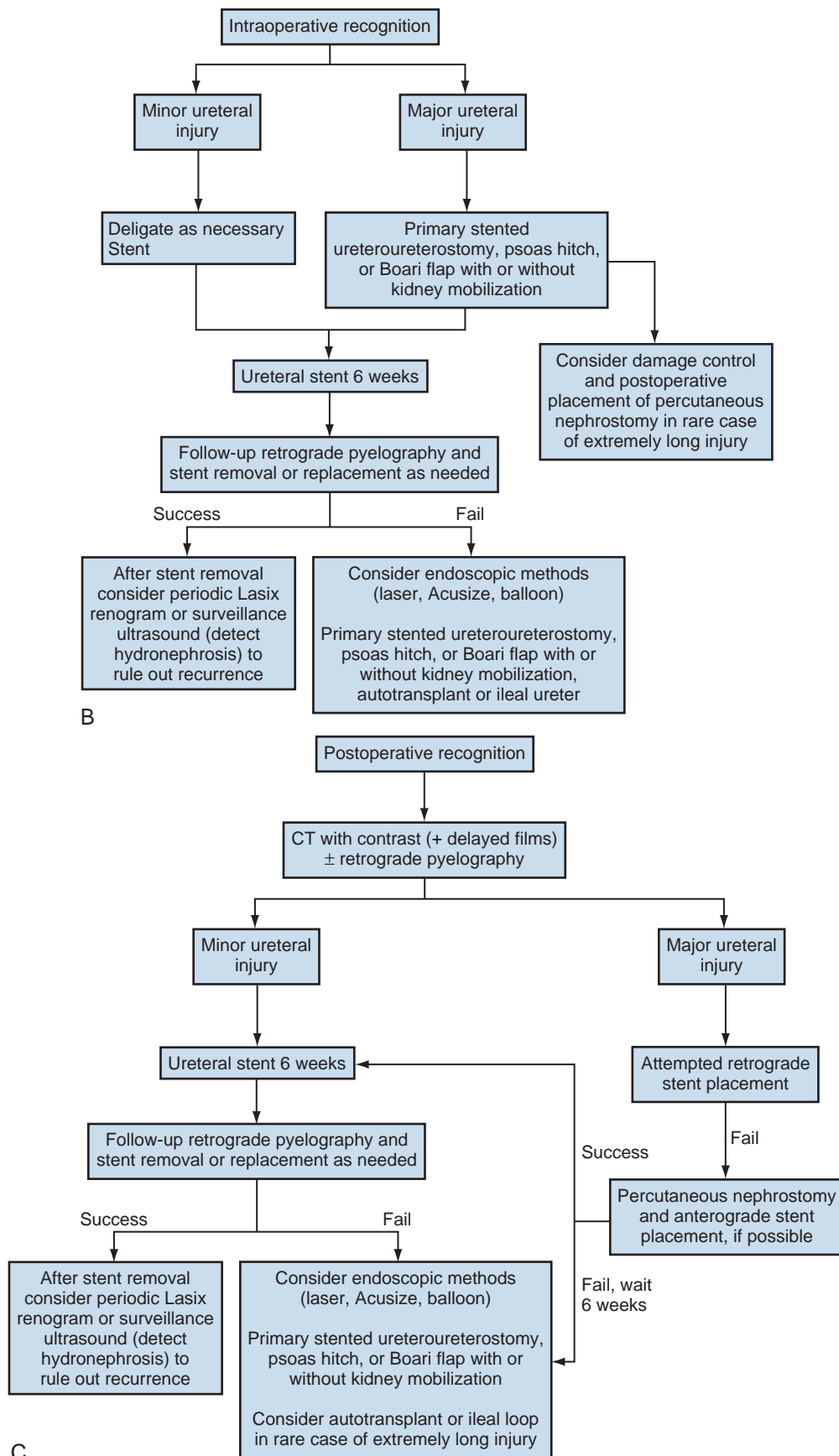


Figure 50-24, cont'd B, Discovered intraoperatively. C, Discovered postoperatively. CT, computed tomography; IVP, intravenous pyelography; OR, operating room.

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The complete reference list is available online at www.expertconsult.com.

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51

Urinary Lithiasis: Etiology, Epidemiology, and Pathogenesis

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Epidemiology of Renal Calculi

Physicochemistry and Pathogenesis

Mineral Metabolism

Pathophysiology of Upper Urinary Tract Calculi

Although stone disease is one of the most common afflictions of modern society, it has been described since antiquity. With Westernization of global culture, however, the site of stone formation has migrated from the lower to the upper urinary tract and the disease once limited to men is increasingly gender blind. Revolutionary advances in the minimally invasive and noninvasive management of stone disease over the past two decades have greatly facilitated the ease with which stones are removed. However, surgical treatments, although they remove the offending stone, do little to alter the course of the disease. Indeed the overall estimated annual expenditure for individuals with insurance claims corresponding to a diagnosis of nephrolithiasis was nearly \$2.1 billion in 2000, reflecting a 50% increase since 1994 (Pearle et al, 2005). Given the frequency with which stones recur, the development of a medical prophylactic program to prevent stone recurrences is desirable. To this end, a thorough understanding of the etiology, epidemiology, and pathogenesis of urinary tract stone disease is necessary.

EPIDEMIOLOGY OF RENAL CALCULI

The lifetime prevalence of kidney stone disease is estimated at 1% to 15%, varying according to age, gender, race, and geographic location. Data from the National Health and Nutrition Examination Survey (NHANES) data sets have demonstrated a linear increase in the prevalence of kidney stones for U.S. adults over the last several decades (Stamatelou et al, 2003), with the most recent prevalence estimate of 8.8% for the period 2007-2010 (Scales et al, 2012).

The rise in kidney stone prevalence is a global phenomenon. Data from five European countries, Japan, and the United States showed that the incidence and prevalence of stone disease has been increasing over time around the world (Romero et al, 2010). In a unique data set derived from a series of nationwide surveys conducted by the Japanese Society on Urolithiasis Research, Yasui and colleagues (2008) found an increase in the age-adjusted annual incidence of first-time stone events from 54.2 per 100,000 in 1965 to 114.3 per 100,000 in 2005. Although the incidence increased in all age groups and in both men and women, the age of peak incidence shifted in men from 20 to 49 years in 1965 to 30 to 69 years in 2005 and in women from 20 to 29 years in 1965 to 50 to 79 years in 2005.

It has been suggested that the rise in stone incidence and prevalence seen in the United States and worldwide can be attributed in part to a rise in the detection of asymptomatic calculi through

increased utilization of radiographic imaging, particularly computed tomography (Boyce et al, 2010; Edvardsson et al, 2013). Edvardsson and colleagues (2013) identified 5945 incident stone formers in the Icelandic population from 1985 to 2008 and found that the annual incidence of stones increased significantly from 108 per 100,000 in the first 5 years of the study to 138 per 100,000 through the remainder of the study interval ($P < .001$). However, they found that the annual incidence of symptomatic stones did not increase significantly, despite significant increases in the incidence of asymptomatic stones in both genders (from 7 to 24 per 100,000 in men, $P < .001$, and from 7 to 21 per 100,000 in women, $P < .001$).

Gender

Historically, stone disease affected adult men more commonly than adult women. By a variety of indicators, including inpatient admissions, outpatient office visits, and emergency department visits, men were affected two to three times more often than women (Soucie et al, 1994; Pearle et al, 2005). However, recent evidence suggests that the difference in incidence between men and women is narrowing. Using the National Inpatient Sample data set representing hospital discharges, Scales and colleagues (2007) found that, although overall population-adjusted discharges for a diagnosis of renal or ureteral calculus increased by only 1.6% from 1997 to 2002, discharges for women increased by 17% while discharges for men decreased by 8.1%. This trend reflects a change in the ratio of male-to-female discharges from 1.7 in 1997 to 1.3 in 2002. Lieske and colleagues (2006) utilized the Rochester Epidemiology Project data (including office, emergency department, and nursing home visits and inpatient and outpatient admissions) to compare the age-adjusted incidence of new symptomatic stone disease from 1970 to 2000 and found similar trends with regard to gender. Although the total rate of symptomatic stone disease for each decade in this time period remained relatively flat ($P = .33$), the rate of symptomatic stones in men declined by 1.7% per year (age-adjusted $P = .019$) but increased in women by 1.9% per year (age-adjusted $P = .064$), resulting in an overall decrease in the male-to-female ratio of symptomatic stones from 3.2 to 1.3 ($P = .006$) during this time period. Another, more contemporary geographic epidemiologic database, the Marshfield Epidemiologic Study Area Database, showed a decline in the male-to-female ratio for urolithiasis from 1.4 in 1992 to 1.0 in 2008 (Penniston et al, 2011).

Using NHANES data, Stamatelou and colleagues (2003) reported a slight decrease in the male-to-female ratio of stone disease, from 1.75 (between 1976 and 1980) to 1.54 (between 1988 and

1994), with the most recent data (2007-2010) revealing a stone prevalence of 10.6% in men and 7.1% in women for a ratio of 1.49, which is only slightly lower than that reported for 1988-1994 (Scales et al, 2012).

Race/Ethnicity

Racial/ethnic differences in the incidence of stone disease have been observed. Among U.S. men, Soucie and colleagues (1994) found the highest prevalence of stone disease in whites, followed by Hispanics, Asians, and African-Americans, who had prevalences of 70%, 63%, and 44% of whites, respectively. Among U.S. women, the prevalence was highest among whites but lowest among Asian women (about half that of whites). According to the most recent NHANES data set, Hispanics (odds ratio [OR] 0.60, 95% confidence interval [CI] 0.49 to 0.73, $P < .001$) and black non-Hispanics (OR 0.37, 95% CI 0.28 to 0.49, $P < .001$) were significantly less likely to report a history of stone disease compared to white non-Hispanics (Scales et al, 2012).

Mente and colleagues (2007) attempted to identify genetic influences on stone disease by comparing stone prevalence among different ethnic groups residing in the same geographic region. Using Europeans (Caucasians) as the reference group, the relative risk of calcium stones was higher in individuals of Arabic (OR 3.8, 95% CI 2.7 to 5.2), West Indian (OR 2.5, 95% CI 1.8 to 3.4), West Asian (OR 2.4, 95% CI 1.7 to 3.4), and Latin American (OR 1.7, 95% CI 1.2 to 2.4) origin and significantly lower in those of East Asian (OR 0.4, 95% CI 0.3 to 0.5) and African (OR 0.7, 95% CI 0.5 to 0.9) descent. Interestingly, despite differences in prevalence of stone disease according to ethnicity, Maloney and colleagues (2005) observed a remarkably similar incidence of metabolic abnormalities between white and nonwhite stone formers from the same geographic region, although the distribution of abnormalities differed, suggesting that dietary and other environmental factors may outweigh the contribution of ethnicity in determining stone risk.

The gender distribution of stone disease varies according to race. Sarmina and colleagues (1987) noted a male-to-female ratio among whites of 2.3 and among African-Americans of 0.65. Michaels and colleagues (1994) also noted a reversal of the male predisposition to stone disease in Hispanics and African-Americans, reporting a male-to-female ratio of 1.8 among Asians, 1.6 among whites, 0.7 among Hispanics, and 0.5 among African-Americans, among a group of patients undergoing shockwave lithotripsy. Dall'era and colleagues (2005) reviewed emergency department records to identify patients presenting with symptomatic renal or ureteral calculi and found a male-to-female ratio of 1.17 among Hispanic patients compared with 2.05 for white patients.

Age

Stone occurrence is relatively uncommon before age 20 but peaks in incidence in the fourth to sixth decades of life (Marshall et al, 1975; Johnson et al, 1979). Lieske and colleagues (2006) found a peak incidence from ages 60 to 69 years in men, but relatively little change in incidence between ages 20 and 70 years for women, with a slightly higher incidence in women 30 to 39 years and 60 to 69 years.

It has been observed that women show a bimodal distribution of stone disease, demonstrating a second peak in incidence in the sixth decade of life corresponding to the onset of menopause and a fall in estrogen levels (Marshall et al, 1975; Johnson et al, 1979). This finding and the lower incidence of stone disease in women compared with men have been attributed to the protective effect of estrogen against stone formation in premenopausal women, owing to enhanced renal calcium absorption and reduced bone resorption (McKane et al, 1995; Nordin et al, 1999). Indeed, Heller and colleagues (2002) identified lower urinary saturation of calcium oxalate and brushite in women compared with men. Moreover, urinary calcium was lower in women than in men until beyond age 50, when it reached equivalence in the two groups. Estrogen-treated

postmenopausal women had lower urinary calcium and saturation of calcium oxalate than untreated women.

Fan and colleagues (1999) found that androgens increased and estrogens decreased urinary and serum oxalate in an experimental rat model, perhaps accounting for the reduced risk of stone formation in women. However, van Aswegen and colleagues (1989) found lower levels of urinary testosterone in stone formers compared with non-stone-forming control subjects, further confounding the issue.

Geography

The geographic distribution of stone disease tends to roughly follow environmental risk factors; a higher prevalence of stone disease is found in hot, arid, or dry climates such as the mountains, desert, or tropical areas. However, genetic factors and dietary influences may outweigh the effects of geography. Finlayson (1974) reviewed several worldwide geographic surveys and found that areas of high stone prevalence included the United States, the British Isles, Scandinavian and Mediterranean countries, northern India and Pakistan, northern Australia, Central Europe, portions of the Malay peninsula, and China. Within the United States, Mandel and Mandel (1989a, 1989b) identified the highest rates of hospital discharges for patients with calcium oxalate stones in the Southeast and for uric acid stones in the East, among the veteran patient population (Fig. 51-1). Soucie and colleagues (1994) found increasing age-adjusted prevalence rates in both men and women going from north to south and west to east, with the highest prevalence observed in the Southeast. After controlling for other risk factors, the authors determined that ambient temperature and sunlight were independently associated with stone prevalence (Soucie et al, 1996).

Climate

Seasonal variation in stone disease is likely related to temperature by way of fluid losses from perspiration and perhaps by sunlight-induced increases in vitamin D. Prince and Scardino (1960) noted the highest incidence of stone disease in the summer months, July through September, with the peak occurring within 1 to 2 months of maximal mean temperatures (Prince et al, 1956). Using data obtained from the Taiwan National Health Insurance Research Database (1999-2003), Chen and colleagues (2008) analyzed

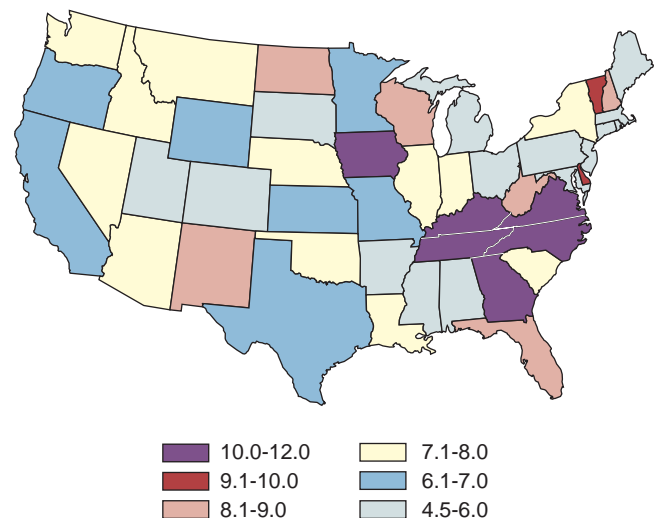


Figure 51-1. Geographic distribution of urinary tract stone disease in the U.S. veteran population from 1983 to 1986. Data are expressed as urinary tract stone patients per 1000 hospital discharges. (From Mandel NS, Mandel GS. Urinary tract stone disease in the United States veteran population: II. Geographical analysis of variations in composition. *J Urol* 1989;142:1516.)

monthly inpatient and outpatient medical benefit claims for a primary diagnosis of renal or ureteral calculi or renal colic and found that the peak incidence of stone-related claims occurred in July through September, with a sharp decline in claims in October. Ambient temperature, atmospheric pressure, and hours of sunshine all correlated with monthly stone-related claims, but after adjusting for seasonality, month, and trend, ambient temperature was found to be the most important determinant of stone-related events.

The study of military personnel translocated to desert locations has provided a unique opportunity to study the effect of climate on a defined population. [Pierce and Bloom \(1945\)](#) reported that American soldiers in an undisclosed desert location had an increase in symptomatic episodes of renal colic during the summer season. Another study of military personnel who developed symptomatic stones after arrival in Kuwait and Iraq revealed a mean time interval to stone formation of 93 days ([Evans and Costabile, 2005](#)). Finally, [Parry and Lister \(1975\)](#) measured urinary calcium and magnesium levels in soldiers before and 10 days after transfer to the Persian Gulf and noted increased urinary calcium levels from baseline in those soldiers transferred during the summer months but not among those transferred during the “cold season,” which was attributed to sunlight-induced increased production of 1,25-dihydroxyvitamin D₃ (1,25[OH]₂D₃). Thus it is likely that climate and geography influence the prevalence of stone disease indirectly, through effects on temperature and possibly sunlight.

[Brikowski and colleagues \(2008\)](#) constructed two alternate models describing the temperature dependence of stone disease on the basis of reported regional stone prevalence rates and corresponding mean annual temperatures in order to predict the anticipated change in stone prevalence resulting from global warming. Prevalence rates obtained from the Second Cancer Prevention Survey of 1982 ([Soucie et al, 1996](#)) were consistent with a nonlinear, or peaked, relationship between temperature and stone prevalence, while a data set from the Veterans Administration that was analyzed by the Urologic Diseases in America project ([Pearle et al, 2005](#)) more closely approximated a linear fit. Using a moderate-severity warming model to predict temperature change resulting from global warming in the United States, the authors estimated an increase of 1 to 1.5 million lifetime cases of climate-related nephrolithiasis by 2050. According to the linear model of temperature dependence, the net effect of warming will be a northward expansion of the current-day “stone belt” (which occupies primarily the Southeast part of the United States) into the Midwest, such that by 2050 it will occupy the entire southeastern portion of the country and all of California. The nonlinear model predicts that the zone of elevated stone risk currently located in the Southeast will expand northward to include a band of states from Kansas to Virginia and Northern California, but with the increase in prevalence primarily concentrated south of the temperature threshold.

[Fakheri and Goldfarb \(2009\)](#) later revisited the analysis correlating mean annual temperature and stone prevalence and confirmed that temperature positively correlated with rate of stone prevalence. However, they further established that the temperature dependence of stone disease could be attributed primarily to an effect on men. For every unit degree Fahrenheit increase in temperature, the percent prevalence rate increased by 0.15 ($R^2 = 0.37$) in men and 0.04 ($R^2 = 0.51$) in women. The pathophysiology responsible for these gender-based differences in response to temperature has not been elucidated to date but is likely affected by confounders such as differential sunlight exposure, occupation, and hydration status.

Occupation

Heat exposure and dehydration constitute occupational risk factors for stone disease as well. Cooks and engineering room personnel, both of whom are exposed to high temperatures, were found to have the highest rates of stone formation among personnel of the Royal Navy ([Blacklock, 1969](#)). Likewise, [Atan and colleagues \(2005\)](#) found a significantly higher incidence of stones among steelworkers exposed to high temperatures (8%) compared with those working in normal temperatures (0.9%). Metabolic evaluation of these two

groups of workers showed a higher incidence of low urine volume and hypocitraturia among the workers in the hot area. [Borghi and colleagues \(1993\)](#) also noted differences in the incidence of stone disease and urinary stone risk factors between workers at a glass plant who were or were not chronically exposed to high temperatures causing massive perspiration. Those exposed to high temperatures exhibited lower urine volumes and pH, higher uric acid levels, and higher urine specific gravity, leading to higher urinary saturation of uric acid. Accordingly, those workers who formed stones had a remarkably high incidence of uric acid stones (38%).

Individuals with sedentary occupations such as those in managerial or professional positions have been found to carry an increased risk of stone formation for unclear reasons ([Blacklock, 1969](#)). This finding is consistent with the work of [Robertson and colleagues \(1980\)](#), who reported an increased risk of stone disease in affluent individuals, countries, and societies, which may be reflective of a more indulgent diet and lifestyle.

Obesity, Diabetes, and Metabolic Syndrome

The association of body size and incidence of stone disease has been extensively investigated. In two large prospective cohort studies of men and women, the prevalence and incident risk of stone disease were directly correlated with weight and body mass index (BMI) in both sexes, although the magnitude of the association was greater in women than in men ([Curhan et al, 1998](#); [Taylor et al, 2005b](#)). Although these investigators identified a reduced risk of incident stone formation with high fluid intake (men and women) and low protein intake (men) ([Curhan et al, 1993, 1997](#)), they found that obesity and weight gain were independent risk factors for incident stone formation that could not be accounted for by diet alone ([Taylor et al, 2005b](#)). [Nowfar and colleagues \(2011\)](#) utilized a large all-payer inpatient care database and likewise found an increased risk of stones with obesity that was more pronounced in women than men. Finally, [Semins and coworkers \(2010\)](#), using claims data, found an increasing risk of kidney stones with increasing BMI, up to a BMI of 30 kg/m², at which point the risk stabilized.

The constellation of visceral obesity along with hyperlipidemia, hypertriglyceridemia, hyperglycemia, and/or hypertension, known as metabolic syndrome, has also been linked to an increased risk for kidney stones. Utilizing the NHANES III (1988-1994) data set, [West and colleagues \(2008\)](#) found that those with a diagnosis of metabolic syndrome were significantly more likely to report a history of kidney stones compared to healthy subjects (8.8% vs. 4.3%, respectively, $P < .001$). Furthermore, they found that the prevalence of a self-reported history of kidney stones increased with the number of metabolic syndrome traits, with the prevalence of kidney stones estimated at 3% for no traits, 7.5% for three traits, and 9.8% for five traits. Multivariate analysis revealed that the presence of four or five metabolic syndrome traits was associated with a more than twofold increase in the odds of a self-reported stone history (OR 2.42, 95% CI 1.57 to 3.73). [Jeong and colleagues \(2011\)](#) corroborated these findings in a large, healthy screened population in Asia.

Metabolic syndrome has been implicated as a potential precursor of type 2 diabetes mellitus. [Taylor and colleagues \(2005a\)](#) prospectively studied the association between diabetes and incident kidney stones in three large cohorts (Nurses' Health Study I [NHS I], composed of older women; Nurses' Health Study II [NHS II], composed of younger women; and the Health Professionals Follow-Up Study [HPFS], composed of men) and found that, after adjusting for BMI, diet, and thiazide use, a history of diabetes was associated with an increase in incident kidney stones in women but not men. Conversely, a history of kidney stones was associated with an increase in the incidence of self-reported diabetes for both women and men (OR 1.33, 95% CI 1.18 to 1.50 for older women; OR 1.48, 95% CI 1.14 to 1.91 for younger women; and OR 1.49, 95% CI 1.29 to 1.72 for men). In addition, in a prospective study from Taiwan, [Chung and coworkers \(2011\)](#) observed a 1.3-fold higher likelihood of being diagnosed with diabetes in a group of

individuals within 5 years of a diagnosis of kidney stones than in a comparison cohort of individuals who did not form stones (95% CI 1.26 to 1.39, $P < .001$). Stone formers with type 2 diabetes have been shown to have higher urinary oxalate and lower urine pH than nondiabetic stone formers (Eisner et al, 2010a).

While the association between obesity, diabetes, and metabolic syndrome has been explored in the epidemiologic literature, the exact pathophysiologic mechanism responsible for this association has yet to be completely defined; however, a central theme of these comorbidities is a metabolic state of insulin resistance. Evidence linking obesity and insulin resistance with low urine pH and uric acid stones (Maalouf et al, 2004a, 2004b), as well as an association between hyperinsulinemia and hypercalciuria (Kerstetter et al, 1991; Shimamoto et al, 1995; Nowicki et al, 1998), could account for an increased risk of uric acid and/or calcium stones in obese patients. A study of stone-forming and non-stone-forming participants in the HPFS (599 stone-forming and 404 non-stone-forming men), NHS I (888 stone-forming and 398 non-stone-forming older women), and NHS II (689 stone-forming and 295 non-stone-forming younger women) for whom 24-hour urine studies were collected correlated urinary stone risk profiles with BMI (Taylor and Curhan, 2006). Subjects with higher BMI excreted more urinary oxalate, uric acid, sodium, and phosphorus than those with lower BMI. Furthermore, similar to other studies, urinary supersaturation of uric acid increased with BMI.

It has been suggested that the association of obesity with calcium oxalate stone formation is primarily due to increased excretion of promoters of stone formation (Siener et al, 2004; Negri et al, 2007). In contrast, the association of obesity and uric acid stone formation is primarily influenced by urinary pH.

Cardiovascular Disease

A number of investigators have explored the association between hypertension and kidney stones. Analysis of data from the HPFS and NHS I found that a history of nephrolithiasis was associated with an increased risk of developing hypertension (Madore et al, 1998a, 1998b), an association that was shown to be strongest among overweight female stone formers (Gillen et al, 2005). Increased dietary intake of substances associated with both hypertension and stone disease, including calcium, sodium, and potassium, has been proposed as a possible explanation for this finding. Borghi and colleagues (1999) observed higher urinary calcium, uric acid, and oxalate and supersaturation of calcium oxalate in men and women with hypertension compared to normotensive individuals. In another study, hypertensive stone formers were found to excrete about 25 mg/day more calcium than normotensive stone formers (Eisner et al, 2010b).

Stone disease has also been linked to heart disease. One longitudinal study found a 31% higher incidence of myocardial infarction among those with a history of kidney stones compared to those without stones, even after adjusting for comorbidities, including chronic kidney disease (Rule et al, 2010). In addition, Reiner and coworkers (2011) documented an association between history of kidney stones and subclinical carotid atherosclerosis in young men and women. Finally, Ferraro and colleagues (2013b) explored the association between kidney stones and risk of heart disease in three large cohort studies, NHS I, NHS II, and HPFS, and found that a history of kidney stones was associated with a modest but significant increase in heart disease in both female cohorts but not in the male cohort. The etiology of this gender difference has not been elucidated.

Water

The beneficial effect of a high fluid intake on stone prevention has long been recognized. In two large observational studies, fluid intake was found to be inversely related to the risk of incident kidney stone formation (Curhan et al, 1993, 1997). Furthermore, in a prospective, randomized trial assessing the effect of fluid intake on stone recurrence among first-time idiopathic calcium stone

formers, urine volume was significantly higher in the group assigned to a high fluid intake compared with the control group receiving no recommendations, and, accordingly, stone recurrence rates were significantly lower (12% vs. 27%, respectively) (Borghi et al, 1996).

Geographic differences in the incidence of stone disease have been ascribed in some cases to differences in the mineral and electrolyte content of water in different areas. Although several investigators reported a lower incidence of stone disease in geographic regions with a “hard” water supply compared with a “soft” water supply, where water “hardness” is determined by content of calcium carbonate (Churchill et al, 1978; Sierakowski et al, 1979), others found no difference. Schwartz and colleagues (2002) found no association between water hardness and incidence of stone episodes, although they did observe a correlation between water hardness and urinary magnesium, calcium, and citrate levels.

KEY POINTS: EPIDEMIOLOGY

- Upper urinary tract stones occur more commonly in men than women, but there is evidence that the gender gap is narrowing.
- Whites have the highest incidence of upper tract stones compared with Asians, Hispanics, and African-Americans.
- Prevalence of stone disease shows geographic variability, with the highest prevalence of stone disease in the Southeast.
- The risk of stone disease correlates with weight and BMI.
- Stone disease has been correlated with a number of systemic disorders, including diabetes, metabolic syndrome, and cardiovascular disease.

PHYSICOCHEMISTRY AND PATHOGENESIS

The physical process of stone formation comprises a complex cascade of events that occurs as the glomerular filtrate traverses the nephron. It begins with urine that becomes supersaturated with respect to stone-forming salts, such that dissolved ions or molecules precipitate out of solution and form crystals or nuclei. Once formed, crystals may flow out with the urine or become retained in the kidney at anchoring sites that promote growth and aggregation, ultimately leading to stone formation. The discussion that follows describes the process of stone formation from a physicochemical standpoint.

State of Saturation

A solution containing ions or molecules of a sparingly soluble salt is described by the *concentration product*, which is a mathematic expression of the product of the concentrations of the pure chemical components (ions or molecules) of the salt. For example, the concentration product (CP) expression for sodium chloride is $CP = [Na^+][Cl^-]$. A pure aqueous solution of a salt is considered *saturated* when it reaches the point at which no further added salt crystals will dissolve. The concentration product at the point of saturation is called the *thermodynamic solubility product* (K_{sp}), which is the point at which the dissolved and crystalline components are in equilibrium for a specific set of conditions. At this point, addition of further crystals to the saturated solution will cause the crystals to precipitate unless the conditions of the solution, such as pH or temperature, are changed.

In urine, despite concentration products of stone-forming salt components such as calcium oxalate that exceed the solubility product, crystallization does not necessarily occur because of the presence of inhibitors and other molecules that allow higher concentrations of calcium oxalate to be held in solution before precipitation or crystallization occurs. In this state of saturation, urine is considered to be *metastable* with respect to the salt. As concentrations of the salt increase further, the point at which it can no

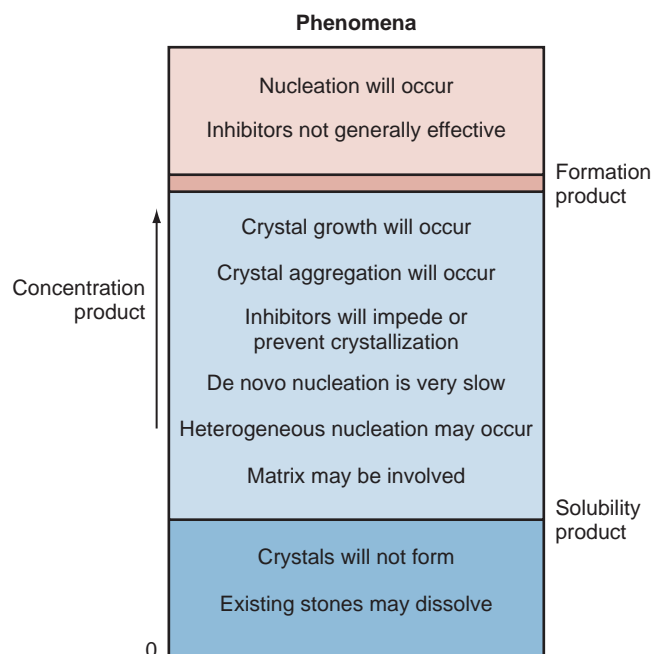


Figure 51-2. States of saturation. Listed are solid-solution phenomena that are likely to occur at a given range of concentration products. Three general situations are considered: (1) concentrations less than the solubility product (undersaturation), (2) concentrations that are metastable with respect to de novo precipitation (between the solubility product and the formation product), and (3) concentrations that are greater than the formation product (unstable). (From Meyer JL. *Physicochemistry of stone formation*. In: Resnick MI, Pak CYC, editors. *Urolithiasis: a medical and surgical reference*. Philadelphia: Saunders; 1990. p. 11–34.)

longer be held in solution is reached and crystals form. The concentration product at this point is called the *formation product* (K_f).

The solubility product and the formation product differentiate the three major states of saturation in urine: undersaturated, metastable, and unstable (Fig. 51-2). Below the solubility product, crystals will not form under any circumstances and dissolution of crystals is theoretically possible. At concentrations above the formation product, the solution is unstable and crystals will form. In the metastable range between the solubility product and the formation product, in which the concentration products of most common stone components reside, spontaneous nucleation or precipitation does not occur despite urine that is supersaturated. It is in this area that modulation of factors controlling stone formation can take place and therapeutic intervention is directed.

In the metastable range of concentration products, although crystal growth can occur on existing crystals, de novo formation of crystals cannot occur in the length of time it normally takes for the filtered urine to reach the bladder. However, crystal formation can occur in this range under certain circumstances. First, in parts of the nephron local concentration products may exceed the formation product for long enough time periods to allow nucleation to occur. Second, local areas of obstruction or stasis in the upper urinary tract may prolong urinary transit time and allow crystal formation to occur in metastable urine. Finally, microscopic impurities or other constituents in the urine can facilitate the nucleation process by adsorption of the crystal components in a geometric way that resembles the native crystal. The energy required for this “heterogeneous nucleation” process is much less than that required for “homogeneous nucleation.”

To estimate the state of saturation for any given crystal system such as calcium oxalate or calcium phosphate, Pak and Chu (1973) developed a mathematic formula, the *activity product ratio*, that takes into account urine pH and the ionic activities of all major ion

species directly involved in the stone-forming process or those that affect the overall ionic strength of the urine. Finlayson subsequently developed a computer program, EQUIL 2, to measure the state of saturation, which is commonly used today (Werness et al, 1985). The *relative saturation ratio* (RSR) or *concentration product ratio* (CPR) is defined as the ratio of the concentration product of the urine to the solubility product of the specified stone-forming salt. A reduction in the numerator will lead to undersaturation of the urine with respect to the stone-forming salt and consequently reduce the likelihood of precipitation. Thus, at RSR values less than 1, crystals will dissolve; at RSR values greater than 1, crystals will form and grow. Reducing the RSR can be accomplished by reducing the urinary concentrations of the stone components (e.g., calcium or oxalate) by reducing the filtered load or by increasing urinary reabsorption. In addition, complexation with substances such as citrate reduce available free ionic calcium and decrease the RSR. On the other hand, manipulation of factors such as pH can significantly impact the concentration of ions such as phosphate, the generation of which is highly pH dependent. Manipulation of pH has little effect on oxalate concentration, however, because oxalic acid is a strong acid ($pK = 4$) and pH changes within the physiologic range will have little effect on oxalate concentration.

Rodgers and colleagues (2006) introduced another computer program, JESS (Joint Expert Speciation System), to calculate urinary saturation of stone-forming salts as an estimate of the propensity for stone formation, thereby challenging the accuracy of the widely accepted EQUIL 2 computer program. The JESS program recognizes several soluble complexes not taken into account by EQUIL 2, including dicalcium-dihydrogen phosphate and calcium phosphocitrate, whose formation depends on pH and citrate. Consequently, the fraction of ionized calcium, phosphate, and oxalate estimated by JESS will be lower than that estimated by EQUIL 2. In order to resolve the discrepancy between the two programs, the supersaturation index (SI) according to JESS and the RSR according to EQUIL 2 were compared with experimentally determined urinary saturation of brushite (Pak et al, 2009b) and calcium oxalate (Pak et al, 2009a). The experimentally determined method measures the CPR without using computer-derived ionic activities. By determining the concentration product before and after incubation with a synthetic stone-forming salt, this method directly estimates saturation by measuring the extent of stone growth (in a supersaturated solution) or dissolution (in an undersaturated solution). No significant difference was found between experimentally determined CPR and JESS-derived SI, for either brushite or calcium oxalate. However, EQUIL 2–derived RSR was consistently and significantly higher than both CPR and SI, overestimating CPR by about 80% for brushite and 50% for calcium oxalate. **Because CPR is too labor intensive for routine use, SI according to JESS probably provides a more reliable estimation of urinary saturation than RSR derived from EQUIL 2.**

Historically, urinary oxalate has been considered a more important contributor to calcium oxalate stone formation than urinary calcium, because a rise in urinary calcium concentration impacted urinary saturation of calcium oxalate less than a rise in oxalate concentration (Nordin et al, 1972; Robertson and Peacock, 1980). Furthermore, at high urinary calcium concentrations the saturation of calcium oxalate reached a plateau that did not exceed the theoretic formation product of calcium oxalate, whereas high oxalate concentrations did, thereby increasing the risk of calcium oxalate crystal formation. Pak and colleagues (2004), however, challenged the notion that urinary oxalate exerts a greater pathogenetic effect than calcium in calcium oxalate stone formation. They demonstrated that the choice of stability constant used for calculating the RSR determines the relative effects of urinary calcium and oxalate concentration. Using the commonly accepted stability constant of 2.746×10^3 (used in the EQUIL 2 program), the effect of urinary calcium and oxalate proved to be equivalent. Thus they concluded that **urinary calcium and oxalate are both important and equal contributors to calcium oxalate stone formation**. As such, reduction in both calcium and oxalate will be effective in reducing the RSR, and intervention to prevent stone formation can be directed

at either. When these studies were repeated using JESS, the same finding of an equivalent effect of calcium and oxalate on urinary SI of calcium oxalate was found, although the dependence of SI on calcium and oxalate was less marked than was demonstrated for RSR (Pak et al, 2009a).

Nucleation and Crystal Growth, Aggregation, and Retention

In normal human urine, the concentration of calcium oxalate is four times higher than its solubility in water. Urinary factors favoring stone formation include low volume and citrate, while increased calcium, oxalate, phosphate, and uric acid all increase calcium oxalate supersaturation. Once the concentration product of calcium oxalate exceeds the solubility product, crystallization can potentially occur. However, in the presence of urinary inhibitors and other substances, calcium oxalate precipitation occurs only when supersaturation exceeds solubility by 7 to 11 times.

Homogeneous nucleation is the process by which nuclei form in pure solution. Nuclei are the earliest crystal structures that will not dissolve. Small nuclei are unstable; below a critical size threshold, dissolution of the crystal is favored over crystal growth. If the driving force (supersaturation level) and the stability of the nuclei are adequate and the lag time to nucleation is sufficiently short compared with the transit time of urine through the nephron, the nuclei will persist. Inhibitors, such as citrate, destabilize nuclei, whereas promoters stabilize nuclei by providing a surface with a binding site that accommodates the crystal structure of the nucleus. In urine, crystal nuclei usually form through heterogeneous nucleation by adsorption onto existing surfaces of epithelial cells (Umekawa et al, 2001), cell debris (Fasano and Khan, 2001), or other crystals (Kok, 1997).

Within the timeframe of transit of urine through the nephron, estimated at 5 to 7 minutes, crystals cannot grow to reach a size sufficient to occlude the tubular lumen. However, if enough nuclei form and grow, aggregation of the crystals will form larger particles within minutes that can occlude the tubular lumen. Inhibitors can prevent the process of crystal growth or aggregation. Magnesium and citrate inhibit crystal aggregation. Nephrocalcin, an acidic glycoprotein made in the kidney, inhibits calcium oxalate nucleation, growth, and aggregation (Nakagawa et al, 1987; Asplin et al, 1991). Tamm-Horsfall mucoprotein, the most abundant protein in urine, inhibits aggregation (Hess et al, 1991), and uropontin inhibits crystal growth (Shiraga et al, 1992). Bikunin, the light chain of inter- α -trypsin, has been shown to be an efficient inhibitor of crystal nucleation and aggregation.

Opposing views regarding the formation and growth of crystal particles have led to controversy over the concept of free crystal particle growth versus fixed particle growth. Although it was initially concluded that free particle stone formation was impossible within the normal transit time through the nephron (Finlayson and Reid, 1978), later recalculation using current nephron dimensions, supersaturation, and crystal growth rates determined that crystalline particles can be formed that are large enough to be retained during normal transit time through the kidney (Kok and Khan, 1994).

Fixed particle growth theory presupposes an anchoring site to which crystals bind, thereby prolonging the time the crystals are exposed to supersaturated urine and facilitating crystal growth and aggregation. A number of mechanisms have been proposed to account for crystal fixation. One favored theory proposes that oxalate-induced injury to renal tubular epithelial cells promotes adherence of calcium oxalate crystals (Miller et al, 2000). In animal models of stone formation in which administration of high oxalate loads leads to calcium oxalate crystal formation, elevated urinary levels of enzyme markers of cell injury, including *N*-acetyl- β -glucosidase and alkaline phosphatase, provide evidence of damage to renal tubular epithelial cells (Khan et al, 1992; Thamilselvan and Khan, 1998). Oxalate-induced cell injury is thought to be mediated by way of reactive oxygen species (Thamilselvan and Khan, 1998; Thamilselvan et al, 1999). Not only are high concentrations of oxalate toxic to renal tubular cells, but calcium oxalate crystals themselves have also been shown to promote damage to cells (Khan

et al, 1993, 1999; Thamilselvan and Khan, 1998; Thamilselvan et al, 1999). Davalos and colleagues (2010) demonstrated in cell culture that calcium oxalate monohydrate crystals induced oxidative stress to renal tubular epithelial cells, leading to eventual apoptosis through pathways that have yet to be defined. Furthermore, they showed that *N*-acetylcysteine, a potent antioxidant, effectively neutralized this cytotoxicity and allowed for retention of renal cell integrity. Asselman and coworkers (2003) used ethylene glycol to induce hyperoxaluria in rats and showed that calcium oxalate adherence occurred only to injured renal cells. Additionally, they showed that markers of kidney injury and inflammation, including hyaluronan, osteopontin, and cell surface receptor CD44, were preferentially expressed at times of crystal adherence.

In addition to these findings in animal models and in vitro systems, Holoch and Tracy (2011) demonstrated an association between antioxidants and stone disease in human patients. Significantly lower levels of serum antioxidants (α -carotene, β -carotene, and β -cryptoxanthin) were found in those who reported a history of stones than in non-stone-forming controls, suggesting that higher levels of antioxidants may confer protection from stone formation. Of note, in vivo evidence for oxalate-induced tubular damage in humans has been lacking. Indeed, no increase in markers of oxidative stress or renal cell injury has been observed in normal individuals or stone formers after ingestion of a large oxalate load (Knight et al, 2007).

Oxidative stress has been implicated as a pathophysiologic mechanism to explain the epidemiologic associations that have been demonstrated between diabetes, metabolic syndrome, and coronary heart disease (Khan, 2012). Furthermore, Yoshioka and colleagues (2010) suggested that the gender disparity historically seen in stone disease may be attributed to differential antioxidant production associated with testosterone and estradiol. They found in a rat model that increased testosterone was associated with increased oxidative stress and stones, while increased levels of estradiol suppressed both of these parameters.

How oxalate-induced renal tubular cell damage potentially promotes crystal retention is not known. Randall (1937) first observed areas of damage associated with subepithelial plaques on the renal papillae. Later, structural analyses in hyperoxaluric rats demonstrated crystals attached to the injured epithelium lining the collecting ducts (Khan, 1991). In vitro studies confirmed increased binding of calcium oxalate crystals to injured renal epithelial cells in culture (Verkoelen et al, 1998). Whether the renal tubular cells or the interstitium constitutes the primary site of stone formation is unclear. Evidence of endocytosis of calcium oxalate crystals into renal tubular cells has been demonstrated in patients with disorders of oxalate metabolism (Saxon et al, 1974; Mandell et al, 1980; Lieske et al, 1992). Intracellular incorporation of these crystals could potentially lead to cell death and deposition of crystals in the interstitium, or transport of the crystals from the lumen to the basement membrane side could promote cell damage and subsequent erosion through to the papillary surface. Knoll and colleagues (2004) demonstrated in cell culture that oxalate-induced damage was more pronounced in renal nontubular compared with tubular cell lines and, further, that renal epithelial cells were more vulnerable to the toxic effects of oxalate on their basolateral side compared with their apical (luminal) side, implicating the interstitium as a possible site of primary stone formation.

In light of these findings, a number of investigators have revisited the role of Randall plaques in the pathogenesis of stone formation. Low and Stoller (1997) mapped the papillae of patients undergoing endoscopic stone removal, as well as control subjects undergoing endoscopy for unrelated reasons, and found that papillary plaques occurred in 74% of stone formers compared with only 43% of control subjects. Stoller and colleagues (2004) hypothesized that the inciting event in the pathogenesis of stones may be vascular injury to the vasa recta near the renal papilla. Repair of damaged vessel walls could involve an atherosclerotic-like reaction that results in calcification of the endothelial wall, followed by erosion into the papillary interstitium and then into the collecting ducts, where it could serve as a nidus for stone formation.

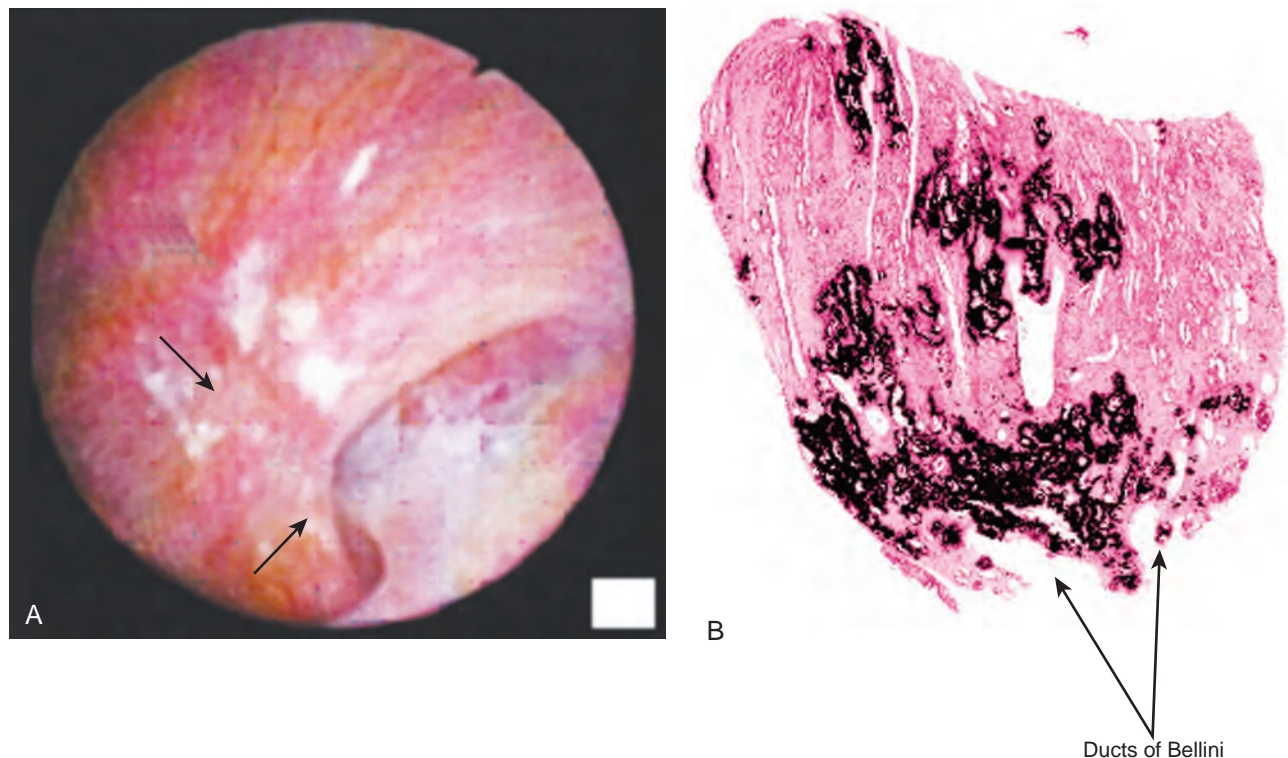


Figure 51-3. Endoscopic (A) and histologic (B) images of Randall plaques in calcium oxalate patients. A, Sites of Randall plaques (arrows) appear as irregular white areas beneath the urothelium. B, A low-magnification light-microscopic image of a papillary biopsy specimen. Sites of calcium deposits were stained black by the Yasue metal substitution method for calcium histochemistry. (From Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. *J Clin Invest* 2003;111:607–16.)

Evan and colleagues (2003) presented an alternative view of the pathogenesis of stone formation on the basis of extensive analysis of papillary plaques derived from biopsies obtained during percutaneous nephrolithotomy in idiopathic calcium oxalate stone formers. They localized the origin of the plaque to the basement membrane of the thin limbs of the loops of Henle and demonstrated that the plaque subsequently extends through the medullary interstitium to a subepithelial location (Fig. 51-3). Once the plaque erodes through the urothelium, it is thought to constitute a stable, anchored surface on which calcium oxalate crystals can nucleate and grow as attached stones. The origin of the crystals that initiate the plaque at the basement membrane of the thin loop of Henle is unclear; however, they do not appear to come from the renal tubular cells or lumen (Evan et al, 2003). One theory suggests that these crystals arise *de novo* by high concentrations of calcium oxalate inducing local inflammation that triggers phenotypic differentiation of tubular epithelial cells into mesenchymal cells with osteogenic activity (Gambaro et al, 2008). Support for this hypothesis comes from the fact that bone osteoid proteins, including osteopontin and osteocalcin, have been found in the plaques.

Among idiopathic calcium oxalate stone formers, the volume of papillary surface covered by plaque was shown to correlate negatively with urine volume and positively with hypercalciuria (Kuo et al, 2003a, 2003b) and the number of stones formed (Kim et al, 2005), providing further corroborating clinical evidence for this sequence of events. Furthermore, Matlaga and colleagues (2006) observed that in approximately half of a studied cohort of calcium oxalate stone formers the stones were observed to be attached to the renal papillae, suggesting that formation of attached stones is an early step in the process of stone formation. Miller and coworkers (2009) further substantiated this hypothesis by endoscopically imaging and recording the details of stone location for nine idiopathic hypercalciuric stone formers undergoing percutaneous neph-

rolithotomy or ureteroscopy. They observed that 90 of 115 stones were attached to papillae and 81 of the 90 attached stones were visually confirmed to be attached specifically to plaque. Furthermore, among 25 stones that were not attached to papillae, evidence from micro-computed tomographic analysis suggested that they originated on interstitial plaques (Miller et al, 2010). These findings support the hypothesis that growth on plaque is the primary mechanism of stone growth for idiopathic calcium stone formers.

Using high-resolution Fourier transform infrared microspectroscopy and electron diffraction, the crystal component of plaque was determined to be calcium apatite (Evan et al, 2003). Further analysis revealed that the deposits consisted of individual laminated particles with mineral and organic layers. All crystals were coated with organic material, and osteopontin was identified on the outer surface of the crystal at the junction of the overlying organic molecular layer, potentially implicating osteopontin in plaque biology (Evan et al, 2005). Daudon and colleagues (2007) analyzed more than 5000 stones associated with plaque and found that carbapatite constituted the main component of the plaque in nearly all cases.

One intriguing but unproven hypothesis for the origin of the calcium phosphate particles described earlier involves nanobacteria, or calcifying nanoparticles (CNPs), which are self-propagating entities that precipitate calcium apatite on their exterior membrane but for which to date no genomic material has been identified (Kajander and Ciftcioglu, 1998). Although the existence of these particles has been questioned (Cisar et al, 2000), several lines of evidence support a role of CNPs in stone formation (Kajander et al, 2001). CNPs have been detected in blood, blood products, and kidney stones, as well as in other pathologic calcifications (Ciftcioglu et al, 1999, 2006). They have been shown to promote rapid precipitation of calcium phosphate from blood under physiologically unfavorable conditions (Kajander and Ciftcioglu, 1998), and in an

animal model intrarenal injection of CNP was shown to induce renal calcification (García Cuerpo et al, 2000). In a recent study in which renal papillary and blood samples were obtained from human patients undergoing nephrectomy, immunohistochemical staining using anti-CNP antibodies was positive in 8 of 11 papillary samples in which Randall plaques were visualized and in only one of those in which they were not (Ciftçioğlu et al, 2008). In addition, 12 of 14 samples positive for CNP-like spheres on scanning electron microscopy demonstrated CNP growth in culture, compared with only one of three scanning electron microscopy-negative samples. Although not necessarily causative, these findings loosely suggest an association between CNP and Randall plaque. CNPs have also been associated with cardiovascular calcification and atherosclerotic disease (Shiekh et al, 2009) and have been implicated in endothelial damage of blood vessels causing subsequent calcification, perhaps providing a common pathogenetic link for CNP involvement in stone formation.

The pathogenesis of stone formation in other calcium stone formers and in noncalcium stone formers may differ from that of typical idiopathic calcium oxalate stone formers. Indeed, distinct morphologic subtypes characterizing particular patient phenotypes have been found, consistent with divergent underlying pathophysiologic abnormalities. Unlike idiopathic calcium oxalate stone formers, patients with enteric hyperoxaluria resulting from intestinal bypass for obesity demonstrate no plaque but instead show apatite crystal deposits plugging the inner medullary collecting duct lumens, along with associated epithelial cell damage with interstitial inflammation and fibrosis (Fig. 51-4) (Evan et al, 2003). Interestingly, despite the acidic urine typically found in these patients, the crystal deposits are composed of apatite, which is generally unstable at low urine pH, suggesting discordance between local tubular pH and final urinary pH (Evan et al, 2006a).

Brushite stone formers have been found to have pathology intermediate between idiopathic calcium oxalate stone formers and intestinal bypass patients, demonstrating interstitial apatite plaque and apatite plugging of the inner medullary and terminal collecting ducts, along with associated collecting duct injury and

interstitial fibrosis (Fig. 51-5) (Evan et al, 2005). The pathogenesis of brushite stones has been postulated by Evan and colleagues (2005) to occur by way of crystallization of apatite in the collecting ducts leading to collecting duct injury, cell death, and enlargement of collecting ducts. Interstitial inflammation in response to the injured cells may lead finally to progressive involvement of adjacent renal tissue. Observing a recent increase in the incidence of brushite stones, Krambeck and colleagues (2010) hypothesized that some brushite stones may begin as calcium oxalate stones after an initial insult incites plaque formation. Further insult, perhaps caused by infection or shockwave lithotripsy, then leads to tubular dysfunction causing an alkaline environment, inflammation, and intraductal hyaluronic acid deposition, ultimately promoting a transition to brushite stones.

With distal renal tubular acidosis (RTA), patients typically exhibit extensive renal calcifications. In a subgroup of patients with distal RTA in whom most of the calcifications were surgically removable, endoscopic inspection of the renal papillae demonstrated a variety of findings (Evan et al, 2007). In some patients minimal papillary changes were observed, whereas in others the papillae were pitted and contained calcium phosphate plugs protruding from dilated collecting ducts with extensive surrounding fibrosis. Randall plaques were rarely encountered. In contrast, patients with primary hyperparathyroidism display histologic features of brushite stone formers, including plugging of ducts of Bellini and inner medullary collecting ducts, but also display interstitial deposits of plaque and associated stone overgrowth traditionally seen with idiopathic calcium oxalate stone formers (Evan et al, 2008).

Finally, although patients with cystinuria were found to have plugging of the terminal collecting ducts of Bellini with masses of cystine crystals, surprisingly apatite deposits were also identified in the inner medullary collecting ducts and in the thin ascending limbs of the loops of Henle. It was speculated that perhaps the alkali load associated with treatment of cystine stone formers or obstruction of the inner medullary collecting ducts by the cystine plugs resulting in an acidification defect could promote apatite crystallization (Evan et al, 2006b).

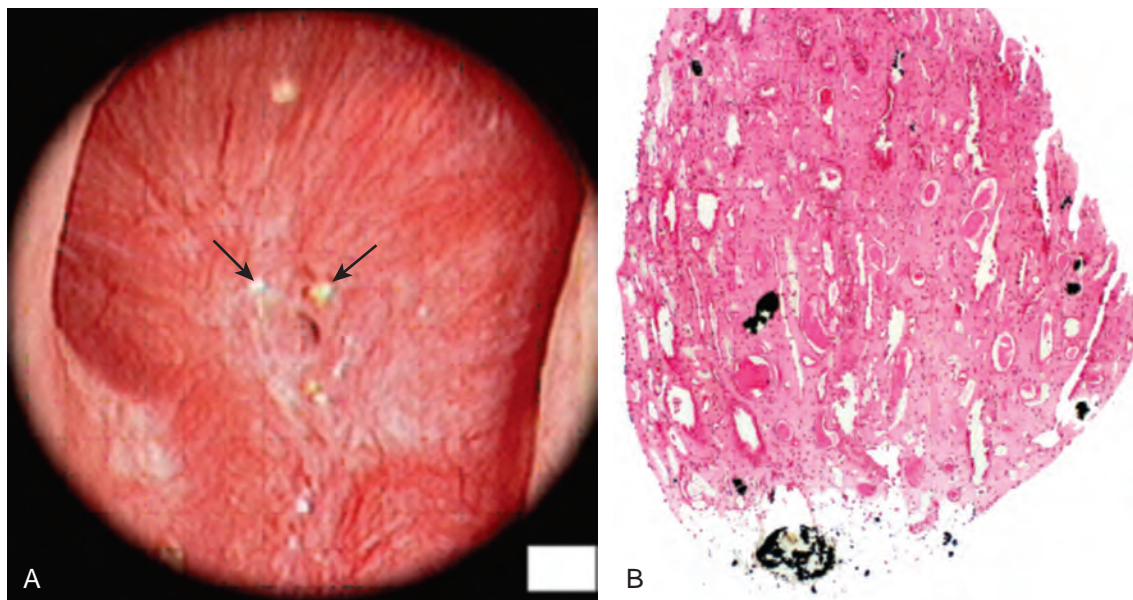


Figure 51-4. Endoscopic (A) and histologic (B) images of Randall plaques in intestinal bypass patients. A, Sites of Randall plaques (arrows) appear as irregular white areas beneath the urothelium. B, A low-magnification light-microscopic image of a papillary biopsy specimen. Sites of calcium deposits were stained black by the Yasue metal substitution method for calcium histochemistry. (From Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. *J Clin Invest* 2003;111:607–16.)

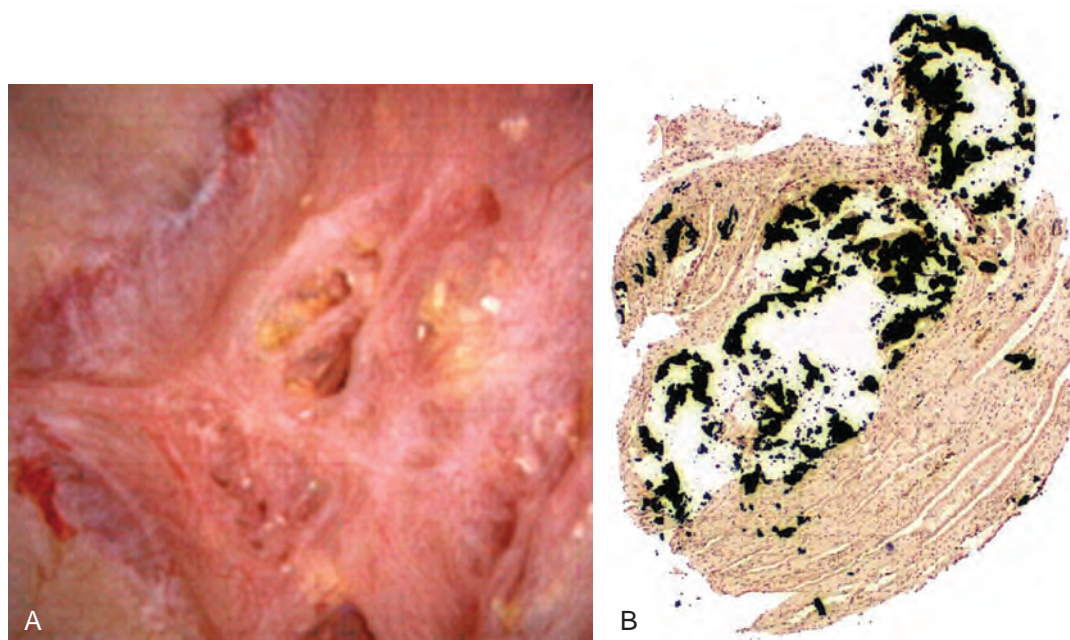


Figure 51-5. Endoscopic (A) and histologic (B) images of Randall plaques in brushite patients. A, Sites of Randall plaque appear as irregular white areas of crystalline deposit beneath the urothelium. In addition, a yellowish crystalline deposit is apparent at the opening of the ducts of Bellini. B, A low-magnification light-microscopic image of a papillary biopsy specimen. Sites of calcium deposits were stained black by the Yasue metal substitution method for calcium histochemistry. A large amount of Yasue-positive material is seen in the ducts of Bellini. (From Evan AP, Lingeman JE, Coe FL, et al. Crystal-associated nephropathy in patients with brushite nephrolithiasis. *Kidney Int* 2005;67:576–91.)

Whether tubular or interstitial calcifications are primarily responsible for renal stone formation is not entirely clear, and it is likely that both mechanisms play a role in particular clinical scenarios. Retention of crystals in the tubular lumen may lead to nephrocalcinosis, which may or may not be associated with renal stone formation. However, these crystals may lead to obstruction-induced tubulopathy and ultimately renal failure. Experimental evidence suggests that crystals bind preferentially to regenerating/redifferentiating renal tubular cells (Verkoelen and Verhulst, 2007). Crystal binding to the surface of these cells is thought to be mediated by a number of luminal membrane molecules, including hyaluronic acid, osteopontin, annexin-II, and nucleolin-related protein. Clinical observation of nephrocalcinosis in 60% of preterm infants may be related to exposure of differentiating renal tubular epithelial cells to crystalluria caused by furosemide treatment (Ezzedeen et al, 1988; Downing et al, 1992). Indeed, the kidneys of these infants have been shown to strongly express hyaluronic acid and osteopontin at the luminal membrane (Verhulst et al, 2005).

Inhibitors and Promoters of Crystal Formation

At the concentrations at which most stone-forming salt components (including calcium, oxalate, and phosphate) are present in urine, urine is supersaturated, thereby favoring crystal formation. However, the presence of molecules that raise the level of supersaturation needed to initiate crystal nucleation or reduce the rate of crystal growth or aggregation prevents stone formation from occurring on a routine basis. Although inhibitors have been identified that prevent calcium oxalate and calcium phosphate crystallization, no specific inhibitors are known that affect uric acid crystallization. Additionally, interference with the site of adhesion of crystals to the renal epithelium can prevent calculus retention and growth (Kumar et al, 2005).

Whole urine, when added to a solution of calcium phosphate, raises the supersaturation level required to initiate calcium phosphate crystallization (formation product) (Fleisch and Bisaz, 1962). Inorganic pyrophosphate was found to be responsible for 25% to 50% of the inhibitory activity of whole urine against calcium phosphate crystallization. Using different methodology, citrate, magnesium, and pyrophosphate together were noted to account for approximately 20% of the inhibitory activity of whole urine, with citrate the most important factor (Bisaz et al, 1978).

Citrate acts as an inhibitor of calcium oxalate and calcium phosphate stone formation by a variety of actions. First, it complexes with calcium, thereby reducing the availability of ionic calcium to interact with oxalate or phosphate (Meyer and Smith, 1975; Pak et al, 1982). Second, it directly inhibits the spontaneous precipitation of calcium oxalate (Nicar et al, 1987) and prevents the agglomeration of calcium oxalate crystals (Kok et al, 1986). Although it has limited inhibitory effect on calcium oxalate crystal growth, it has potent activity in reducing calcium phosphate crystal growth (Meyer and Smith, 1975). Lastly, citrate prevents heterogeneous nucleation of calcium oxalate by monosodium urate (Pak and Peterson, 1986).

The inhibitory activity of magnesium is derived from its complexation with oxalate, which reduces ionic oxalate concentration and calcium oxalate supersaturation (Meyer and Smith, 1975). A recent study showed that magnesium reduced the contact time between calcium and oxalate molecules in vitro, an effect that showed synergism with citrate and was negated by the presence of uric acid (Riley et al, 2013). Pyrophosphate, phosphate, and magnesium have all been shown to inhibit crystal growth, but only high concentrations of magnesium and pyrophosphate have been shown to inhibit aggregation (Kok et al, 1988).

Polyanion macromolecules, including glycosaminoglycans, acid mucopolysaccharides, and RNA, have been shown to inhibit crystal

nucleation and growth by bonding with surface calcium ions. The most prominent glycosaminoglycan in human urine is chondroitin sulfate (Angell and Resnick, 1989). However, among the glycosaminoglycans, heparin sulfate interacts most strongly with calcium oxalate monohydrate crystals (Yamaguchi et al, 1993). Erturk and colleagues (2002) utilized a dye-binding assay to measure urinary glycosaminoglycan concentration and found a significantly lower concentration in stone formers than in controls. Furthermore, recurrent stone formers demonstrated lower levels of glycosaminoglycans than those who had experienced a single stone episode. While these macromolecular proteins have been shown to inhibit stone aggregation, Reid and colleagues (2011) demonstrated through nuclear magnetic resonance spectroscopy that glycosaminoglycans and proteins are strongly integrated into the mineral lattice of apatite-predominant phosphate stones. Furthermore, they found that nonphosphate crystals such as calcium oxalate and uric acid did not exhibit composite lattices containing these proteins. These findings are consistent with plaque formation as apatitic foci that develop in a basement membrane environment rich in extracellular matrix proteins and glycosaminoglycans.

Two urinary glycoproteins, nephrocalcin and Tamm-Horsfall glycoprotein, are potent inhibitors of calcium oxalate monohydrate crystal aggregation (Nakagawa et al, 1987). Nephrocalcin is an acidic glycoprotein containing predominantly acidic amino acids that is synthesized in the proximal renal tubules and the thick ascending limb. In simple solution, nephrocalcin strongly inhibits the growth of calcium oxalate monohydrate crystals (Nakagawa et al, 1987), and it has also been shown to inhibit nucleation and aggregation of calcium oxalate crystals (Coe et al, 1994). Nephrocalcin has been identified in four isoforms: non-stone formers excrete greater quantities of two isoforms associated with the most inhibitory activity, whereas stone formers excrete urine enriched for the two isoforms lacking inhibitory activity (Nakagawa, 1997). The isoforms with inhibitory activity were found to contain γ -carboxyglutamic acid residues that were lacking in the isoforms isolated from stone formers.

Tamm-Horsfall protein is expressed by renal epithelial cells in the thick ascending limb and the distal convoluted tubule as a membrane-anchored protein that is released into the urine after cleavage of the anchoring site by phospholipases or proteases. Tamm-Horsfall is the most abundant protein found in the urine and a potent inhibitor of calcium oxalate monohydrate crystal aggregation, but not growth. The role of Tamm-Horsfall protein in stone formation is controversial and may depend on the state of the molecule itself, which determines whether it functions as an inhibitor or a promoter of crystal formation. In alkaline urine it is a strong inhibitor of calcium oxalate monohydrate crystal aggregation, while in acidic urine it polymerizes into a configuration that promotes crystal aggregation (Hess, 1992). A study using a Tamm-Horsfall knockout (*Thp*^{-/-}) mouse model demonstrated spontaneous formation of calcium oxalate crystals in the kidneys of mice fed ethylene glycol and vitamin D, suggesting a protective role of Tamm-Horsfall protein against crystallization of calcium salts (Mo et al, 2004). A subsequent study on more than 250 Tamm-Horsfall protein-null mice demonstrated a consistent phenotype of progressive renal calcification that consisted of hydroxyapatite in the interstitial space of renal papillae resembling the plaques seen in idiopathic calcium oxalate stone formers (Liu et al, 2010).

Osteopontin, or uropontin, is an acidic phosphorylated glycoprotein expressed in bone matrix and renal epithelial cells of the ascending limb of the loop of Henle and the distal tubule. Osteopontin has been shown to inhibit nucleation, growth, and aggregation of calcium oxalate crystals, as well as to reduce binding of crystals to renal epithelial cells in vitro (Asplin et al, 1998; Wesson et al, 1998). In an osteopontin knockout mouse model, intratubular calcium oxalate crystals could be induced in mice exposed to high levels of oxalate by ethylene glycol feeding (Wesson et al, 2003). Interestingly, in a *Thp*^{-/-} mouse model, mice fed ethylene glycol and vitamin D exhibited a dramatic increase in osteopontin levels over baseline but still formed calcium oxalate crystals (Mo et al, 2004). The authors concluded that osteopontin may

constitute an inducible inhibitor of calcium oxalate crystallization that works in conjunction with constitutively expressed Tamm-Horsfall protein to prevent crystallization.

Urinary prothrombin fragment 1 (F1) is a crystal matrix protein named for its resemblance to the F1 degradation product of prothrombin. Ryall and colleagues (1995) purified urinary prothrombin F1 from human urine and utilized an artificial crystallization system to determine that it was associated with a reduction in crystal aggregation and deposition.

Lastly, inter- α -trypsin is a glycoprotein synthesized in the liver that is composed of three polypeptides (two heavy chains and one light chain), of which bikunin comprises the light chain. Bikunin is a strong inhibitor of calcium oxalate crystallization, aggregation, and growth in vitro (Hochstrasser et al, 1984; Atmani and Khan, 1999), and its expression has been shown to be upregulated in a rat model when exposed to oxalate.

Matrix

Renal calculi consist of both crystalline and noncrystalline components. The noncrystalline component is termed *matrix*, which typically accounts for about 2.5% of the weight of the stone (Boyce and Garvey, 1956). In some cases, matrix comprises the majority of the stone (up to 65%), usually in association with chronic urinary tract infection (Boyce and Garvey, 1956; Allen and Spence, 1966). The exact composition of matrix is difficult to ascertain because only 25% of it is soluble (Ryall, 1993); however, chemical analysis reveals a heterogeneous mixture consisting of approximately 65% protein, 9% nonamino sugars, 5% glucosamine, 10% bound water, and 12% organic ash (Boyce, 1968). Among the proteins incorporated into the matrix substance are Tamm-Horsfall protein, nephrocalcin, a γ -carboxyglutamic acid-rich protein, renal lithostathine, albumin, glycosaminoglycans, free carbohydrates, and a mucoprotein called matrix substance A (Hess and Kok, 1996). Boyce and colleagues (1962) found that substance A is immunologically unique and present in the matrix component of all stone formers. Moore and Gowland (1975) determined that substance A is composed of three or four distinct antigens unique to stones that were detected in the urine of 85% of stone formers but in no normal individuals. A study using reverse-phase, high-performance liquid chromatography and tandem mass spectrometry to evaluate calcium oxalate stones identified 68 distinct proteins with 95% confidence, including a significant number of inflammatory proteins (immunoglobulins, defensin-3, clusterin, complement C3a, kininogen, and fibrinogen) (Canales et al, 2008). Comparing the matrix component of 13 calcium oxalate and 12 calcium phosphate stones, these investigators found that inflammatory proteins comprised the predominant proteins in both stone types, with many proteins in common, suggesting a shared pathogenesis for the two stone types that involves inflammation (Canales et al, 2010). The exact role of matrix in stone formation, whether as promoter, inhibitor, or passive bystander, has yet to be elucidated.

KEY POINTS: PHYSICOCHEMISTRY AND PATHOGENESIS

- Urine must be supersaturated for stones to form.
- Supersaturation alone is not sufficient for crystallization to occur in urine, owing to the presence of urinary inhibitors.
- Nephrocalcin, uropontin, and Tamm-Horsfall protein are important inhibitors of crystal nucleation, growth, or aggregation.
- Urinary calcium and oxalate contribute equally to urinary saturation of calcium oxalate.
- Common calcium stones may originate from subepithelial plaques composed of calcium apatite that serve as an anchor on which calcium oxalate stones can grow.
- The noncrystalline component of stones is matrix, which is composed of a combination of mucoproteins, proteins, carbohydrates, and urinary inhibitors.

MINERAL METABOLISM

Calcium

Thirty to 40 percent of dietary calcium is absorbed from the intestine, with most being absorbed in the small intestine and only approximately 10% absorbed in the colon (Bronner and Pansu, 1999). By a process of intestinal adaptation, absorption of calcium varies with calcium intake. At times of low calcium intake, fractional calcium absorption is enhanced; during high calcium intake, fractional calcium absorption is reduced. With a calcium-rich diet, a nonsaturable, paracellular pathway for calcium absorption predominates. A saturable, vitamin D-dependent transcellular pathway constitutes the major pathway for intestinal calcium absorption when calcium intake is limited; this pathway is downregulated by a diet replete in calcium (Buckley and Bronner, 1980; Bronner et al, 1986). Because of the saturable component of calcium transport, a larger portion of calcium is absorbed when it is divided into several doses taken hours apart than with a large single dose (Phang et al, 1968). A small amount of calcium is secreted into the lumen of the intestine, thereby reducing net calcium absorption such that, overall, 100 to 300 mg of a total average calcium intake of 600 to 1200 mg daily will be absorbed.

Calcium is absorbed in the ionic state, and incomplete calcium absorption is due in part to formation of soluble calcium complexes in the intestinal lumen. **Therefore substances that complex with calcium, such as phosphate, citrate, oxalate, sulfate, and fatty acids, reduce the availability of ionic calcium for absorption (Allen, 1982).** Calcium readily complexes with phosphate in the intestinal lumen, but because calcium phosphate formation is dependent on pH ($pK = 6.1$), high luminal pH favors calcium phosphate complexation, thereby reducing calcium availability. On the other hand, calcium oxalate complex formation displays less pH dependence and complex formation is less reversible. Consequently, an oxalate-rich diet reduces calcium absorption. Transcellular calcium absorption is mediated by $1,25(\text{OH})_2\text{D}_3$ (calcitriol), which is reported to enhance calcium permeability at the brush border of the intestinal epithelial cells (Fontaine et al, 1981).

The active form of vitamin D, $1,25(\text{OH})_2\text{D}_3$, is the most potent stimulator of intestinal calcium absorption. After conversion of 7-dehydrocholesterol in the skin to previtamin D_3 promoted by sunlight, previtamin D_3 is hydroxylated in the liver to 25-hydroxyvitamin D_3 , which is further hydroxylated in the proximal renal tubule to $1,25(\text{OH})_2\text{D}_3$. The conversion of 25-hydroxyvitamin D_3 to $1,25(\text{OH})_2\text{D}_3$ is stimulated by parathyroid hormone (PTH) and by hypophosphatemia. **A decrease in serum calcium increases secretion of PTH, which in turn directly stimulates the enzyme 1α -hydroxylase, which is located in the mitochondria of the proximal renal tubule.** After transport via the bloodstream to the intestine, $1,25(\text{OH})_2\text{D}_3$ binds to the vitamin D receptor in the brush border membrane epithelial cells to enhance calcium absorption.

Calcitriol acts on the bone and kidney in addition to its action in increasing intestinal calcium absorption. In the bone, $1,25(\text{OH})_2\text{D}_3$, along with PTH, promotes the recruitment and differentiation of osteoclasts that subsequently mobilize calcium from the bone. Consequently, the filtered load of calcium and phosphate increases. However, PTH increases renal calcium reabsorption and enhances phosphate excretion, leading to a further net increase in serum calcium, which suppresses further PTH secretion and synthesis of $1,25(\text{OH})_2\text{D}_3$. Calcitriol modulates parathyroid function by inhibiting synthesis of PTH through enhanced vitamin D receptor and calcium-sensing receptor (CaSR) expression in the parathyroid glands (Dusso et al, 2005).

PTH is critical in maintaining normal calcium concentration in the extracellular fluid. PTH is an 84-amino acid protein that is the cleavage product of the precursor protein prepro-PTH. **Only mature PTH is secreted from the parathyroid gland, and the most potent stimulus for its secretion is a decrease in serum calcium (Sherwood et al, 1968).** In response to serum calcium levels, the G-protein-coupled extracellular CaSR regulates PTH secretion and

renal tubular calcium reabsorption (Devuyst and Pirson, 2007). PTH stimulates mobilization of calcium from bone through the action of osteoclasts, further raising serum calcium and phosphorus. The action of PTH is mediated through changes in cyclic adenosine monophosphate and phospholipase C (Dunlay and Hruska, 1990; Muff et al, 1992). **At the kidney, PTH enhances renal calcium reabsorption and reduces renal tubular reabsorption of phosphate.** It also stimulates synthesis of $1,25(\text{OH})_2\text{D}_3$, which leads to enhanced intestinal calcium and phosphate absorption. PTH has no direct effect on intestinal calcium absorption.

Calcium absorption in the kidney is complex, but recent work has begun to elucidate the proteins and mechanisms involved. On average, only 1% to 3% of filtered calcium is excreted in the urine, with most being reabsorbed paracellularly in the renal proximal tubule (60% to 65%) and thick ascending limb of the loop of Henle (25% to 30%). The remaining 8% to 10% of filtered calcium is reabsorbed transcellularly in the distal convoluted tubule (Friedman, 2007).

The paracellular absorption of calcium in the proximal tubule and thick ascending limb of the loop of Henle occurs by several mechanisms. First, calcium travels through paracellular channels found at the tight junctions of epithelial cells in the proximal tubule. The integral membrane proteins of the tight junction include occludin, junctional adhesion molecules, and claudins (Furuse et al, 1993; Ebnet et al, 2004; Hou, 2013). Claudins are a family of proteins with four transmembrane domains (Lal-Nag and Morin, 2009; Hou, 2013), including claudin-2, which has been implicated in paracellular reabsorption of calcium and other cations in the proximal tubule (Muto et al, 2010), and claudin-16 and claudin-19, which form a paracellular channel complex that allows selective cation permeation in the thick ascending limb (Hou et al, 2008, 2009).

Calcium is passively reabsorbed from the lumen of the thick ascending limb of the loop of Henle into the interstitial space through a paracellular pathway driven by a lumen-positive transepithelial voltage gradient (Hou, 2013). The positive luminal voltage occurs as a result of apical potassium secretion and basolateral chloride secretion, as well as by way of a transepithelial NaCl concentration gradient over the cation-selective paracellular channel in the thick ascending limb.

The CaSR plays a role in renal handling of calcium, and its expression predominates in the thick ascending limb. Serum calcium stimulates the CaSR to increase expression of claudin-14, which blocks the calcium channels formed by the claudin-16/19 complex, thereby reducing paracellular calcium reabsorption (Gong et al, 2012; Toka et al, 2012).

Transcellular calcium absorption in the distal convoluted tubule occurs via several mechanisms (Mensenkamp et al, 2006, 2007). Calcium enters the epithelial cells of the distal tubule through a transcellular channel (transient receptor potential vanilloid 5, or TRPV5), which is unique among other channels in the TRP family because of its high calcium selectivity. Calcium flux through TRPV5 into the distal tubule cells is controlled at several levels, including TRPV5 gene expression, feedback inhibition, and trafficking across the plasma membrane. Inactivation of TRPV5 in mice leads to severe hypercalciuria, which is compensated for by increased intestinal calcium absorption resulting from enhanced calcitriol synthesis. Calcium is bound in the cell to a chaperone protein (calbindin-D28k), which facilitates diffusion across the cell from the apical to the basolateral space where calcium can then exit.

Phosphorus

Like calcium, inorganic phosphate absorption is dependent on both saturable transcellular and nonsaturable paracellular transport. At low phosphorus concentrations (1 to 3 mmol/L), saturable absorptive transport occurs. At higher phosphorus levels, absorption increases without saturation (Walton and Gray, 1979). Approximately 60% of dietary phosphate is absorbed in the intestine. Active absorption of phosphate from the intestine involves a $1,25(\text{OH})_2\text{D}_3$ -regulated, sodium-dependent transport process (Danisi and Straub,

1980; Lee et al, 1986). Phosphate absorption is highly pH dependent; low luminal pH reduces while high pH enhances phosphate transport.

Approximately 65% of absorbed phosphate is excreted by the kidney and the remainder by the intestine. In normal healthy adults, 80% to 90% of the filtered load of phosphate is reabsorbed in the renal tubule and 10% to 20% is excreted in the urine. **Regulation of renal phosphate handling is primarily by way of PTH, which inhibits renal tubular reabsorption of filtered phosphate.**

Magnesium

Magnesium is absorbed from the intestine by passive diffusion or active transport, although passive diffusion accounts for most of the net magnesium absorption. Magnesium is absorbed in both the large and small intestine, with the majority absorbed from the distal small intestine. Hormonal regulation of magnesium is primarily through vitamin D.

Oxalate

Oxalate metabolism differs markedly from calcium metabolism. Although 30% to 40% of ingested calcium is absorbed from the intestine, only 6% to 14% of ingested oxalate is absorbed (Holmes et al, 1995; Hesse et al, 1999). Oxalate absorption occurs throughout the intestinal tract, with about half or more occurring in the small intestine and half in the colon (Holmes et al, 1995). Although oxalate absorption is difficult to measure directly, it has historically been estimated by urinary oxalate excretion, a relationship that is valid only if there is a linear relationship between ingested and excreted oxalate and if absorbed oxalate is not significantly taken up in the tissues, metabolized, or secreted back into the intestine. Holmes and colleagues (2001) in fact demonstrated that the relationship between ingested oxalate and absorbed oxalate is curvilinear, owing to higher absorption of oxalate at low intake than at high intake. Moreover, they showed that oxalate absorption varies widely among individuals, ranging from 10% to 72% of ingested oxalate. A recent study suggested that hyperoxaluric stone formers absorb more oxalate in response to an oral oxalate load than stone formers with normal oxalate excretion (Krishnamurthy et al, 2003). Knight and colleagues (2007), however, found no difference between normal subjects and stone formers in intestinal absorption or renal handling of oxalate. In patients with small bowel disease or history of intestinal resection and an intact colon, oxalate absorption is markedly increased (Barilla et al, 1978).

Oxalate transport occurs via both transcellular and paracellular pathways. Although transport by way of paracellular pathways and some nonmediated transcellular pathways is primarily passive, driven by electrochemical or concentration gradients, transcellular transport is largely actively mediated by membrane carriers. The transport protein responsible for oxalate secretion has been suspected to belong to the SLC26 family of solute-linked carrier (SLC) anion exchangers. A putative anion exchange transporter, SLC26A6, that is expressed in the apical membrane of small intestinal and perhaps colonic epithelial cells has been implicated in intestinal oxalate transport (Hatch and Freel, 2005). Evidence suggests that oxalate may be secreted, as well as absorbed, in the intestine (Jiang et al, 2006). In vitro flux studies using intestinal segments of mutant mice lacking SLC26A6 showed enhanced net absorption of oxalate as a result of defective oxalate secretion. Furthermore, in vivo *Slc26a6*-null mice were found to have elevated plasma and urinary oxalate levels, reduced fecal oxalate excretion, and a high incidence of calcium oxalate bladder stones compared with wild-type mice. These findings provide compelling evidence for a possible role of SLC26A6 in oxalate secretion and suggest a potential target for therapeutic agents that modify urinary oxalate absorption.

A number of other factors can influence oxalate absorption, including the presence of oxalate-binding cations such as calcium or magnesium and oxalate-degrading bacteria. Coingestion of calcium- and oxalate-containing foods leads to formation of calcium oxalate complexes, which limits the availability of free

oxalate ion for absorption (Liebman and Chai, 1997; Hess et al, 1998; Penniston and Nakada, 2009). Oxalate-degrading bacteria, notably *Oxalobacter formigenes*, use oxalate as an energy source and consequently reduce intestinal oxalate absorption. The mechanism of action of *O. formigenes* in reducing urinary oxalate excretion may not be entirely accounted for by degradation of intestinal oxalate. In vivo and ex vivo studies in *O. formigenes*-colonized rats demonstrated reduced urinary oxalate excretion and net colonic oxalate secretion, suggesting that *O. formigenes* may interact directly with intestinal mucosal cells to stimulate secretion of endogenously derived oxalate (Hatch et al, 2006).

The potential for therapeutic use of probiotics or oxalate-degrading enzyme preparations has been explored in mice models and in several short-term clinical trials. In two knockout mice models, one of which resembles primary hyperoxaluria, administration of an oxalate-degrading enzyme reduced urinary oxalate and prevented nephrocalcinosis (Grujic et al, 2009). Likewise, in a small study of patients with primary hyperoxaluria and normal renal function or varying degrees of renal failure, administration of *O. formigenes* was associated with a reduction in serum and/or urinary oxalate (Hoppe et al, 2006). However, a subsequent randomized trial in 43 patients with primary hyperoxaluria administered oral *O. formigenes* versus placebo failed to show a treatment effect in reducing urinary oxalate (Hoppe et al, 2011). Similarly, although one uncontrolled study (Campieri et al, 2001) of calcium oxalate stone formers with mild hyperoxaluria showed a 24% to 40% reduction in urinary oxalate with the administration of a preparation of mixed lactic acid bacterium species, a randomized, controlled trial (Goldfarb et al, 2007) failed to demonstrate an effect of the same probiotic. At this time, the contribution of *O. formigenes* to the overall risk of stone formation is not fully understood.

Absorbed oxalate is nearly completely excreted in the urine (Hodgkinson and Wilkinson, 1974; Prenan et al, 1982). Urinary oxalate is derived from both endogenous production in the liver (from ascorbic acid and glycine) and dietary sources. Recent evidence suggests that, on average, half of urinary oxalate is derived from the diet, with the precise amount depending on the relative amount of ingested calcium and oxalate (Holmes et al, 2001).

It is estimated that between 86% and 98% of oxalate is ultrafilterable. However, renal tubular handling of oxalate has not been clearly defined, although both secretion and reabsorption have been suspected. There is evidence from a number of animal models of a secretory pathway for oxalate that likely resides in the renal proximal tubule (Holmes and Assimos, 2004). The SLC26 transport proteins responsible for oxalate secretion include one implicated in intestinal oxalate secretion, SLC26A6. However, to date, no specific transporter has been definitively linked to renal oxalate secretion, and a recent study in a rat model investigating the role of a likely candidate, the basolateral anion exchanger sulfate anion transporter-1 (SAT1, or SLC26A1), found no correlation between changes in renal expression of SAT1 messenger RNA or protein and hyperoxaluria (Freel and Hatch, 2012).

Clinical evidence also supports renal oxalate secretion, although it is not clear if renal handling of oxalate differs between stone formers and non-stone formers (Schwille et al, 1989; Holmes et al, 2005; Knight et al, 2007). Holmes and coworkers (2005) studied six normal subjects administered increasing oral oxalate loads and found oxalate clearance ratios consistent with renal oxalate secretion, with up to 50% of urinary oxalate accounted for by oxalate secretion at the highest oxalate load. These investigators subsequently compared plasma and urine oxalate levels in idiopathic hypercalciuric stone formers versus normal subjects both while fasting and after consuming three low-oxalate meals (Bergsland et al, 2011). Despite no difference in plasma oxalate between the two groups in either the fasting or fed states, urinary oxalate and fractional excretion was higher in patients than normal subjects. Of note, fractional excretion of oxalate exceeded 1, indicating oxalate secretion, in almost a third of patients and no controls, suggesting that renal oxalate secretion may play a role in regulating plasma oxalate levels.

KEY POINTS: MINERAL METABOLISM

- Calcium absorption occurs primarily in the small intestine at a rate that is dependent on calcium intake.
- 1,25-Dihydroxyvitamin D₃ is the most potent stimulator of intestinal calcium absorption.
- PTH stimulates 1 α -hydroxylase in the proximal tubule of the kidney to convert 25-hydroxyvitamin D₃ to 1,25(OH)₂D₃.
- PTH enhances proximal tubular reabsorption of calcium and renal phosphate excretion.
- Intestinal oxalate absorption is influenced by luminal calcium, magnesium, and oxalate-degrading bacteria.

PATHOPHYSIOLOGY OF UPPER URINARY TRACT CALCULI

Classification of Nephrolithiasis

The most common component of urinary calculi is calcium, which is a major constituent of nearly 80% of stones. Calcium oxalate comprises about 60% of all stones; mixed calcium oxalate and hydroxyapatite make up 20% and brushite stones make up 2%. Uric acid and struvite (magnesium ammonium phosphate) each comprise approximately 7% of stones, and cystine stones represent only about 1% (Table 51-1) (Wilson, 1989). Stones associated with medications and their byproducts, such as triamterene, silica, indinavir, and ephedrine, are uncommon and usually preventable.

Most classification systems for nephrolithiasis differentiate stones on the basis of the underlying metabolic or environmental abnormalities with which they are associated (Table 51-2). A number of pathophysiologic derangements contribute to calcium stone formation, either alone or in combination, including hypercalciuria, hypocitraturia, hyperuricosuria, and hyperoxaluria (Coe et al, 2005). Uric acid, cystine, and struvite stones form in relatively unique settings; uric acid stones form only in an acid urine, cystine stones are the result of impaired renal reabsorption of cystine, and infection stones occur in alkaline urine produced by urease-producing bacteria. For some stones such as cystine, knowledge of the chemical composition of the stone may provide sufficient infor-

mation to initiate appropriate therapy. However, because of the multiple causes associated with calcium-based stones, an understanding of the underlying metabolic disorders and environmental factors that predispose to stone formation is required in order to implement a rational treatment plan. Recent investigation into the molecular and genetic causes of stone formation may ultimately translate into newer treatment strategies (Frick and Bushinsky, 2003; Langman, 2004; Devuyst and Pirson, 2007).

Calcium Stones

Hypercalciuria

Hypercalciuria is the most common abnormality identified in calcium stone formers (Pak et al, 1982; Coe et al, 1992; Bushinsky,

TABLE 51-1 Stone Composition and Relative Occurrence

STONE COMPOSITION	OCCURRENCE (%)
CALCIUM-CONTAINING STONES	
Calcium oxalate	60
Hydroxyapatite	20
Brushite	2
NON-CALCIUM-CONTAINING STONES	
Uric acid	7
Struvite	7
Cystine	1-3
Triamterene	<1
Silica	<1
2,8-Dihydroxyadenine	<1

From Pearle MS, Pak YC. Renal calculi: a practical approach to medical evaluation and management. In: Andreucci VE, Fine LG, editors. International yearbook of nephrology. New York: Oxford University Press; 1996. p. 69–80.

TABLE 51-2 Diagnostic Classification of Nephrolithiasis

CONDITION	METABOLIC/ENVIRONMENTAL DEFECT	PREVALENCE (%)
Absorptive hypercalciuria	Increased gastrointestinal calcium absorption	20-40
Renal phosphate leak	Impaired renal phosphorus absorption	
Renal hypercalciuria	Impaired renal calcium reabsorption	5-8
Resorptive hypercalciuria	Primary hyperparathyroidism	3-5
Hyperuricosuric calcium nephrolithiasis	Dietary purine excess, uric acid overproduction	10-40
Hypocitraturic calcium nephrolithiasis		10-50
Isolated	Idiopathic	
Chronic diarrheal syndrome	Gastrointestinal alkali loss	
Distal renal tubular acidosis	Impaired renal acid excretion	
Thiazide-induced	Hypokalemia	
Hyperoxaluric calcium nephrolithiasis		2-15
Primary hyperoxaluria	Oxalate overproduction	
Dietary hyperoxaluria	Increased dietary oxalate	
Enteric hyperoxaluria	Increased intestinal oxalate absorption	
Hypomagnesiuric calcium nephrolithiasis	Decreased intestinal magnesium absorption	5-10
Gouty diathesis	Low urinary pH	15-30
Cystinuria	Impaired renal cystine reabsorption	<1
Infection stones	Infection with urease-producing bacteria	1-5
Low urine volume	Inadequate fluid intake	10-50
Miscellaneous or no abnormality	NA	<3

Modified from Pearle MS, Pak CY. Renal calculi: a practical approach to medical evaluation and management. In: Andreucci VE, Fine LG, editors. International yearbook of nephrology. New York: Oxford University Press; 1996. p. 69–80.

1998). However, the role of hypercalciuria in stone formation is controversial, because of the overlap in urine calcium levels between stone formers and non-stone formers (Robertson and Morgan, 1972; Coe et al, 1992). There are several lines of evidence that support a pathogenetic role for hypercalciuria in stone formation. First, hypercalciuria is common in stone-forming patients, occurring in 35% to 65% of patients (Levy et al, 1995). Indeed, treatment strategies aimed at reducing urinary calcium levels are associated with a reduction in stone recurrence rates (Pearle et al, 1999), and medical therapy often fails in patients with persistent hypercalciuria (Strauss et al, 1982). In addition, multivariate analysis of a subset of men and women from three large epidemiologic studies in whom 24-hour urine studies were available revealed that, after adjusting for other factors, the risk of incident stone formation increased with increasing urinary calcium (Curhan et al, 2001). Lastly, recent investigations of Randall plaques as potential precursors to calcium stone formation have shown that plaques occur more commonly in stone formers and their number directly correlates with urine calcium levels and number of stone episodes (Kuo et al, 2003b; Kim et al, 2005).

High urinary calcium concentrations lead to increased urinary saturation of calcium salts (Pak and Holt, 1976) and reduced urinary inhibitory activity by way of complexation with negatively charged inhibitors such as citrate and chondroitin sulfate (Zerwekh et al, 1988). The normal kidney filters approximately 270 mmol of calcium daily and reabsorbs all but 4 mmol (Bushinsky, 1998). However, a variety of conditions lead to elevated urinary calcium levels and increased urinary saturation of calcium salts. Criteria defining hypercalciuria are variable, but the strictest definition classifies hypercalciuria as greater than 200 mg of urinary calcium/day after adherence to a 400-mg calcium, 100-mg sodium diet for 1 week (Menon, 1986). Parks and Coe (1986) defined hypercalciuria as excretion of greater than 4 mg/kg/day or greater than 7 mmol/day in men and 6 mmol/day in women. However, arguably a threshold level of calcium that separates hypercalciuria from normocalciuria is artificial, and urinary calcium demonstrates a spectrum of effects over its range by which higher or lower calcium levels are associated with a greater or lesser effect.

Historically, the term *idiopathic hypercalciuria* was applied to stone formers for whom classification of their metabolic abnormality was difficult. Calcium transport is regulated at three sites: intestine, bone, and kidney. Dysregulation at any of these sites can lead to hypercalciuria. In 1974, Pak and colleagues divided hypercalciuria into three distinct subtypes on the basis of unique pathophysiologic abnormalities: absorptive hypercalciuria due to increased intestinal absorption of calcium, renal hypercalciuria due to primary renal leak of calcium, and resorptive hypercalciuria due to increased bone demineralization.

Although historically this classification system has been used because of its utility in simplifying the understanding and treatment of specific metabolic derangements, many have argued that hypercalciuria is associated with multiple, interrelated disturbances that cannot be readily separated into a specific organ system (Coe et al, 1992). Furthermore, studies into the molecular mechanisms of stone formation have identified gene mutations that can affect several organ systems, culminating in hypercalciuria (Frick and Bushinsky, 2003; Langman, 2004). Indeed, utilization of a classification system for hypercalciuria has not been associated with superior therapeutic efficacy and is therefore not routinely implemented in clinical practice. Although improved understanding of the molecular and genetic causes of stone disease may well change the categorization and management of stones in the future, for the purposes of this chapter, the standard classification system will be utilized.

Absorptive Hypercalciuria. Absorptive hypercalciuria (AH) is defined as increased urinary calcium excretion (>0.2 mg/mg creatinine) after an oral calcium load. Although fasting urinary calcium is usually normal in AH (<0.11 mg/dL glomerular filtration), severe forms of AH may occasionally be associated with fasting hypercalciuria as well. The underlying pathophysiologic abnormality in AH is increased intestinal absorption of calcium, which occurs in

approximately 30% of stone formers. Dietary calcium restriction may normalize urinary calcium in some patients with AH (type II) but not in others (type I). The added systemic load of calcium caused by intestinal calcium hyperabsorption results in a transient increase in serum calcium, which suppresses serum PTH and results in increased renal filtration of calcium, ultimately leading to hypercalciuria. Because the increase in intestinal absorption of calcium is matched by enhanced renal calcium excretion, serum calcium level remains normal.

The cause of increased intestinal absorption of calcium has been variously ascribed to vitamin D-independent and dependent processes, as well as to upregulation of the vitamin D receptor (Breslau et al, 1992). However, no proposed mechanism completely accounts for all the findings associated with absorptive hypercalciuria, and there is no clear evidence that upregulation of intestinal calcium absorption is the primary cause. There are several genetic abnormalities that can potentially impact vitamin D activity. The active form of vitamin D, $1,25(\text{OH})_2\text{D}_3$, is generated by way of 1-hydroxylation of $25(\text{OH})\text{D}_3$ by the gene product of cytochrome P450 (CYP) 27B1 (CYP27B1), which is present in a variety of tissues. The mitochondrial enzyme $1,25(\text{OH})_2\text{D}$ -24-hydroxylase (CYP24A1), which is present in the intestine and kidney, inactivates both major vitamin D metabolites, $25(\text{OH})\text{D}_3$ and $1,25(\text{OH})_2\text{D}_3$. Bi-allelic mutations in CYP24A1 have been shown to reduce activity of the enzyme, resulting in elevated levels of $1,25(\text{OH})_2\text{D}_3$, particularly in individuals taking large amounts of vitamin D (Schlingmann et al, 2011). Mutations in this gene are responsible for increased sensitivity to vitamin D supplementation in the autosomal recessive disorder idiopathic infantile hyperkalemia. In adults, recessive mutations in CYP24A1 have been associated with a syndrome characterized by hypercalcemia, hypercalciuria, nephrocalcinosis, and nephrolithiasis (Dinour et al, 2013; Nesterova et al, 2013). Genome-wide association studies revealed an association between CYP24A1 variants and serum vitamin D concentrations (Wang et al, 2010). The frequency of $1,25(\text{OH})_2\text{D}$ -24-hydroxylase deficiency is estimated at 4% to 20% in the general population (Nesterova et al, 2013). However, while these mutations may be common, not all affected individuals will demonstrate clinically significant abnormalities.

Hypersensitivity to vitamin D has also been shown to increase intestinal calcium absorption and cause hypercalciuria (Bushinsky and Monk, 1998). Moreover, several studies have linked hypercalciuria and the vitamin D receptor (VDR) gene. Jackman and colleagues (1999) identified a polymorphism in VDR in 19 patients with a family history of nephrolithiasis and hypercalciuria, thereby establishing a potential link. Likewise, Scott and colleagues (1999) identified linkage between a microsatellite marker and the VDR locus on chromosome 12q12-q14 in a cohort of 47 French-Canadian pedigrees with idiopathic hypercalciuria and calcium nephrolithiasis.

Other studies, however, failed to confirm the association of VDR abnormalities with hypercalciuria (Zerwekh et al, 1995, 1998). Indeed, other genetic loci have been identified in association with AH. Reed and colleagues (1999, 2002) mapped the locus for an inherited form of AH to chromosome 1q23.3-q24 and found a putative gene (subsequently shown by others to be homologous with the rat soluble adenylate cyclase gene) in this region in 12 unrelated white AH patients.

Another proposed etiology of AH is renal phosphate wasting leading to a subsequent increase in active vitamin D. Patients with hereditary hypophosphatemic rickets with hypercalciuria (HHRH) manifest this abnormality, which is characterized by decreased renal reabsorption of phosphate, hypophosphatemia, and a subsequent compensatory increase in vitamin D levels, leading to enhanced absorption of calcium and phosphate from the intestine and hypercalciuria (Tieder et al, 1987). The mutations associated with HHRH are thought to be inherited in an autosomal recessive pattern. Candidate genes for HHRH include *SLC34A1* and *SLC34A3*, which encode sodium-coupled phosphate transporters located in the apical membrane of the renal proximal tubule (NaPi-IIa and NaPi-IIc, respectively) (Devuyst and Pirson, 2007). Renal phosphate leak,

however, is a rare cause of nephrolithiasis, affecting at most 2% to 4% of patients (Levy et al, 1995).

Renal Hypercalciuria. The kidney filters approximately 270 mmol of calcium and must reabsorb more than 98% of it to maintain calcium homeostasis (Bushinsky, 1998). Approximately 70% of calcium reabsorption occurs in the proximal tubule, with paracellular pathways predominating (Frick and Bushinsky, 2003). In renal hypercalciuria, impaired renal tubular reabsorption of calcium results in elevated urinary calcium levels leading to secondary hyperparathyroidism (Coe et al, 1973). Serum calcium levels remain normal because the renal loss of calcium is compensated by enhanced intestinal absorption of calcium and bone resorption as a result of increased secretion of PTH and enhanced synthesis of $1,25(\text{OH})_2\text{D}_3$. **High fasting urinary calcium levels (>0.11 mg/dL glomerular filtration) with normal serum calcium values are characteristic of renal hypercalciuria.** The elevated fasting urinary calcium and serum PTH levels differentiate renal from absorptive hypercalciuria.

The actual cause of renal calcium leak is not known. However, insight into the abnormalities associated with renal hypercalciuria comes from studies of several monogenetic disorders associated with hypercalciuria and nephrolithiasis (Gambero et al, 2004; Langman, 2004; Devuyt and Pirson, 2007; Ferraro et al, 2013a). Dent disease (X-linked recessive nephrolithiasis) is linked to defects in chloride channel-5 (ClC-5), which is located in the proximal renal tubule, the thick ascending limb of the loop of Henle, and the α -type intercalated cells of the collecting ducts. Dent disease is characterized by hypercalciuria, proteinuria, nephrolithiasis, nephrocalcinosis, and progressive renal failure. Although the exact mechanism by which loss of ClC-5 results in hypercalciuria is not well understood, it may involve loss of PTH as part of the low-molecular-weight proteinuria, leading to elevated calcitriol levels (Reinhart et al, 1995; Nakazato et al, 1997).

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is caused by mutations in claudin-16 (also known as paracellin-1) and claudin-19, members of the claudin gene family of tight junction proteins that are involved in the voltage-driven paracellular reabsorption of magnesium and calcium in the thick ascending limb and distal convoluted tubule (Simon et al, 1999; Konrad et al, 2006). FHHNC patients develop a characteristic triad of hypomagnesemia, hypercalciuria, and nephrocalcinosis as a result of progressive magnesium and calcium wasting. Other claudin abnormalities have also been associated with nephrolithiasis. A genome-wide association study conducted in 3773 hypercalciuric kidney stone patients and 42,510 control subjects from Iceland and the Netherlands identified four common, synonymous variants in the claudin-14 gene locus that were found to be significantly associated with kidney stones and reduced bone mineral density (Thorleifsson et al, 2009). Claudin-14 deregulation blocks the claudin-16 channel and phenocopies FHHNC to a variable degree.

Bartter syndrome encompasses a group of autosomal recessive disorders involving dysfunction in the thick ascending limb of the loop of Henle that is characterized by salt wasting and hypokalemic metabolic acidosis, with variable occurrence of hypercalciuria and nephrolithiasis (Devuyt and Pirson, 2007). This disorder arises from a mutation in any of the genes encoding membrane proteins involved in transepithelial sodium chloride transport across the thick limb of the loop of Henle: *SLC12A1*, which encodes the $\text{Na}^+, \text{K}^+, 2\text{Cl}^-$ cotransporter, NKCC2; *KCNJ*, which encodes the apical renal outer medullary potassium channel, ROMK; *CLCNKB*, which encodes the basolateral chloride channel, ClC-Kb; and *BSND*, which encodes a subunit (Barttin) for the chloride channel proteins ClC-Ka and ClC-Kb.

Activating mutations in the gene encoding the CaSR have been associated with an autosomal dominant form of hypocalcemia by which low serum PTH levels lead to reduced renal calcium reabsorption and subsequent hypocalcemia and hypercalciuria (Devuyt and Pirson, 2007). A potent activating mutation in the CaSR has been associated with salt-losing nephropathy and secondary hyperaldosteronism (Bartter syndrome type V), which is likely related to

dysfunction of ROMK as a result of constitutive activation of the abnormal CaSR (Vargas-Poussou et al, 2002). The CaSR regulates calcium reabsorption in the thick ascending limb through changes in paracellular permeability (Loupy et al, 2012).

Loss-of-function polymorphisms in the CaSR gene have also been associated with idiopathic nephrolithiasis. Two synonymous single nucleotide polymorphisms (rs6776158 and rs1501899) that significantly reduce renal CaSR messenger RNA levels have been shown to be highly associated with normocitraturic nephrolithiasis (Vezzoli et al, 2010, 2011). Reduced CaSR expression can increase paracellular calcium reabsorption in the thick ascending limb of the loop of Henle, leading to interstitial calcium precipitation and hypocalciuria. Diminished calcium delivery to the collecting duct may impact the cellular mechanism for urinary acidification and concentration, leading to calcium oxalate stone formation. Other mutations in the genes for the $\text{Na}^+, \text{K}^+, 2\text{Cl}^-$ cotransporter NKCC2 and the potassium channel ROMK have been associated with autosomal recessive disorders characterized by fasting hypercalciuria and nephrocalcinosis.

Understanding these genetic disorders has the potential to further elucidate the tubular handling of calcium and the pathophysiology of renal hypercalciuria.

Resorptive Hypercalciuria. Resorptive hypercalciuria is an infrequent abnormality most commonly associated with primary hyperparathyroidism. Primary hyperparathyroidism is the cause of nephrolithiasis in about 5% of cases (Broadus, 1989). Excessive PTH secretion from a parathyroid adenoma leads to excessive bone resorption and increased renal synthesis of $1,25(\text{OH})_2\text{D}_3$, which in turn enhances intestinal absorption of calcium. The net effect is elevated serum and urine calcium levels and reduced serum phosphorus levels. Although most patients with primary hyperparathyroidism demonstrate hypercalcemia and hypercalciuria, a normal serum calcium level in the presence of an inappropriately high serum PTH value may be seen in some cases, making the diagnosis more difficult. Administration of a thiazide diuretic will enhance renal calcium reabsorption and exacerbate the hypercalcemia, thereby facilitating the diagnosis ("thiazide challenge") (Eisner et al, 2009).

Primary hyperparathyroidism is associated with nephrolithiasis in less than 5% of affected individuals (Heath et al, 1980; Parks et al, 1980). However, the diagnosis should be suspected in patients with nephrolithiasis and serum calcium levels greater than 10.1 mg/dL (Broadus et al, 1980; Menon, 1986). Serum calcium levels can vary by up to 5%, and patients with mild hyperparathyroidism may exhibit relatively small increases of serum calcium (Yendt and Gagne, 1968). Therefore repeated measurements of serum calcium, along with serum intact PTH, may be necessary to make the diagnosis. Measurement of serum ionized calcium may help in equivocal cases because ionized calcium may be elevated in the setting of normal serum calcium (Yendt and Gagne, 1968). PTH also increases excretion of bicarbonate and phosphorus from the proximal renal tubule, resulting in phosphaturia and mild hyperchloremic acidosis.

Sarcoid and Granulomatous Disease. Additional, rare causes of resorptive hypercalciuria include hypercalcemia of malignancy, sarcoidosis, thyrotoxicosis, and vitamin D toxicity. Many granulomatous diseases, including tuberculosis, sarcoidosis, histoplasmosis, leprosy, and silicosis, have been reported to produce hypercalcemia. Among these, sarcoidosis is most commonly associated with urolithiasis. The hypercalcemia in sarcoidosis is due to the production of $1,25(\text{OH})_2\text{D}_3$ from 1α -hydroxylase present in macrophages of the sarcoid granuloma, causing increased intestinal absorption of calcium, hypercalcemia, and hypercalciuria (Hendrix, 1966; Bell et al, 1979). Pulmonary alveolar cells and lymph node homogenates in patients with sarcoidosis are capable of synthesizing vitamin D, a function usually limited to the kidney. Most patients with sarcoidosis have a suppressed level of PTH secondary to hypercalcemia (Cushard et al, 1972). Sarcoidosis can also be differentiated from other diagnoses by the rapid resolution of hypercalcemia with initiation of corticosteroid therapy (Breslau et al, 1982).

Malignancy-Associated Hypercalcemia. While primary hyperparathyroidism is the most common cause of hypercalcemia in an outpatient setting, malignancy is the main cause of hypercalcemia in hospitalized patients (Rizzoli and Bonjour, 1992). An assay for intact PTH can help distinguish patients with hyperparathyroidism from those with other causes of hypercalcemia (Burtis et al, 1990). Tumors in patients with humoral hypercalcemia produce a PTH-related protein (PTHrP) whose production is regulated by CaSRs on the cell surface (Chattopadhyay, 2006). Lung and breast cancers account for about 60% of malignancy-associated hypercalcemia, whereas renal cell (10% to 15%), head and neck (10%), and hematologic cancers such as lymphoma and myeloma (10%) account for the rest. Although direct mechanical destruction of bone constitutes one cause of hypercalcemia, many tumors secrete humoral factors, including PTHrP, transforming growth factor- α , and cytokines such as interleukin-1 and tumor necrosis factor, which activate osteoclasts and result in bone lysis and hypercalcemia (Burtis et al, 1990; Mundy, 1990; Edelson and Kleerekoper, 1995).

Glucocorticoid-Induced Hypercalcemia. Glucocorticoids can significantly alter calcium metabolism through their actions on bone, intestine, and parathyroid glands. Their most potent effect is related to calcium metabolism in bones, where glucocorticoids promote bone resorption and reduce bone formation, ultimately leading to osteopenia with chronic use (Manelli and Giustina, 2000). Additionally, they stimulate release of PTH (Fucik et al, 1975). On the other hand, glucocorticoids inhibit intestinal absorption of calcium, which accounts for their effectiveness in preventing hypercalciuria induced by sarcoidosis (Manelli and Giustina, 2000). The net effect probably favors promotion of stone formation because nephrolithiasis is common in patients with Cushing syndrome (Faggiano et al, 2003). In one study, stones were found in 50% of patients with active Cushing syndrome, 27% of cured patients, and 6.5% of controls. Compared to controls, patients with active disease had a significantly higher prevalence of hypercalciuria, hypocitraturia, and hyperuricosuria, but these patients were also at greater risk of obesity and diabetes, which have been linked to stone formation (Faggiano et al, 2003).

Hyperoxaluria

Hyperoxaluria, defined as urinary oxalate greater than 40 mg/day, leads to increased urinary saturation of calcium oxalate and subsequent promotion of calcium oxalate stones. Additionally, oxalate

has been implicated in crystal growth and retention by means of renal tubular cell injury mediated by lipid peroxidation and the generation of oxygen free radicals (Ravichandran and Selvam, 1990). Membrane injury facilitates the fixation of calcium oxalate crystals and subsequent crystal growth. Antioxidant therapy has been shown to prevent calcium oxalate precipitation in the rat kidney and to reduce oxalate excretion in stone patients (Selvam, 2002). Similarly, calcium oxalate crystal deposition on urothelium in vitro was prevented by free radical scavengers such as phytic acid and mannitol, purportedly by protecting the membrane from free radical-mediated damage (Thamilselvan and Selvam, 1997; Selvam, 2002). Recent human studies, however, failed to demonstrate increases in markers of oxidative stress or renal injury in normal subjects and stone formers ingesting large doses of oxalate (up to 8 mmol), thus calling into question the importance of oxalate-induced cell membrane damage in calcium oxalate stone formation (Knight et al, 2007).

Causes of hyperoxaluria include disorders in biosynthetic pathways (primary hyperoxaluria); intestinal malabsorptive states associated with inflammatory bowel disease, celiac sprue, or intestinal resection (enteric hyperoxaluria); and excessive dietary intake or high substrate levels (vitamin C) (dietary hyperoxaluria).

Primary Hyperoxaluria. The primary hyperoxalurias (PHs) are the result of rare autosomal recessive inherited disorders in glyoxylate metabolism by which the normal conversion of glyoxylate to glycine is prevented, leading to preferential oxidative conversion of glyoxylate to oxalate, an end product of metabolism (Fig. 51-6). The markedly high levels of urinary oxalate that ensue (>100 mg/day) lead to increased saturation of calcium oxalate and formation of calcium oxalate complexes and crystals in the renal tubular lumen. Some crystals attach to the surface of renal tubular epithelial cells and further aggregate into stones, whereas others are internalized into tubular cells and then extruded into the renal interstitium, leading to marked nephrocalcinosis (Hoppe et al, 2009). Renal injury may be a consequence of direct cell toxicity from either high oxalate concentration or calcium oxalate crystals, mediated through reactive oxygen species. Renal impairment occurs from recurrent obstructing calcium oxalate stones and as a result of renal parenchymal inflammation and interstitial fibrosis from severe nephrocalcinosis (Mulay et al, 2013). With progressive renal damage, renal elimination of oxalate is impaired, leading to systemic deposition of calcium oxalate crystals, or systemic oxalosis.

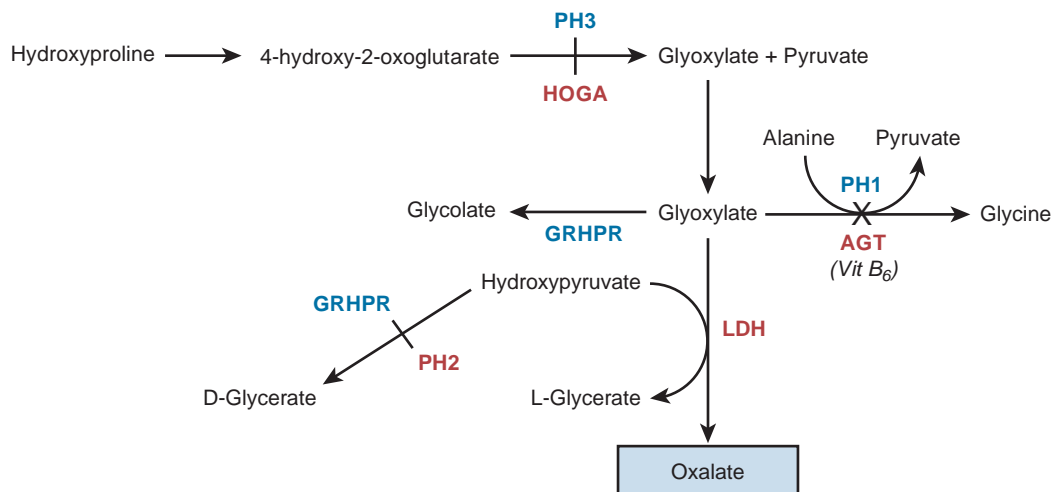


Figure 51-6. Pathway of oxalate metabolism in the liver. Defects in alanine:glyoxylate amino-transferase (AGT) are associated with primary hyperoxaluria type 1 (PH1), defects in glyoxylate reductase/hydroxypyruvate reductase (GRHPR) are associated with primary hyperoxaluria type 2 (PH2), and defects in 4-hydroxy-2-oxoglutarate aldolase (HOGA) are associated with primary hyperoxaluria type 3 (PH3). LDH, lactate dehydrogenase.

Three forms of PH have been identified (types 1, 2, and 3) that differ in the enzyme and intracellular organelle affected. The primary enzyme catalyzing glyoxylate conversion to glycine is the pyridoxal phosphate-dependent alanine-glyoxylate aminotransferase (AGT), which is synthesized in the liver peroxisome. Mutations in this gene (AGXT) result in primary hyperoxaluria type 1 (PH1), and patients with this disorder have elevated levels of oxalate and frequently glycolate. End-stage renal disease (ESRD) occurs during the second to third decade of life in most patients with PH1, making it the most aggressive form of the disease (Hoppe et al, 2009). Elucidation of the crystal structure of AGT to 2.5 Å has improved the understanding of mutations in the gene for this protein (Zhang et al, 2003). The most common mutation of AGXT results in a substitution of glycine by arginine at position 170; in the setting of a proline-to-leucine substitution at position 11 present in a polymorphic minor allele, this causes the enzyme to inappropriately target the liver mitochondria, where it is metabolically inactive, rather than the liver peroxisomes (Fargue et al, 2013a). Patients with this mutation are responsive to pyridoxine therapy because pyridoxine is metabolized to pyridoxal phosphate, an essential cofactor for AGT, which results in an increased enzyme catalytic activity and enhanced peroxisome targeting (Fargue et al, 2013b). To date, at least 178 mutations have been identified in the AGXT gene.

Primary hyperoxaluria type 2 (PH2) is associated with a defect in glyoxylate reductase/hydroxypyruvate reductase (GRHPR) in the liver, resulting in hyperoxaluric nephrolithiasis, but with a less aggressive course with regard to renal failure than PH1 (Johnson et al, 2002). Patients with PH2 have elevated urinary levels of L-glyceric acid and oxalate because reduced GRHPR enzyme activity leads to increased hydroxypyruvate and glyoxylate, which are converted by lactate dehydrogenase to L-glyceric acid and oxalate, respectively. A total of 30 mutations have been identified in the GRHPR gene (Cochat and Rumsby, 2013).

A third type of primary hyperoxaluria has recently been recognized. Primary hyperoxaluria type 3 (PH3) is caused by a defective mitochondrial enzyme, 4-hydroxy-2-oxoglutarate aldolase (HOGA), which is thought to play a role in hydroxyproline metabolism (Belostotsky et al, 2010). 4-Hydroxy-2-oxoglutarate derived from hydroxyproline is converted to pyruvate and glyoxylate in a reaction catalyzed by HOGA. However, the mechanism by which this defect leads to hyperoxaluria has not been established. Although PH3 is associated with hyperoxaluria and severe hypercalciuria, the recurrent calcium oxalate stone formation seen in early childhood may become clinically silent later in life, and there are no reports to date of progression to ESRD in these patients (Hoppe, 2012).

If untreated, PH1 inevitably leads to end-stage renal failure, which occurs by age 15 in 50% of affected patients and is associated with an overall death rate of approximately 30% (Cochat et al, 1999). Because the liver is the only organ responsible for detoxification of glyoxylate, combined liver-kidney transplantation is accepted treatment for most patients with severe PH. Reported 5-year patient survival and liver allograft survival after combined liver-kidney transplantation are 80% and 72%, respectively (Jamieson, 2005). Furthermore, the renal function of survivors reportedly remains stable over time (Cochat et al, 1999; Hoppe and Langman, 2003). Isolated kidney transplantation is the treatment of choice for patients with PH2 and ESRD, because hypoxanthine-guanine phosphoribosyl transferase (HGPRT) is not liver-specific. PH3 has not been associated with ESRD and transplantation in this setting has not been reported.

Enteric Hyperoxaluria. The most common cause of acquired hyperoxaluria is enteric hyperoxaluria. This abnormality is associated with chronic diarrheal states, by which fat malabsorption results in saponification of fatty acids with divalent cations such as calcium and magnesium, thereby reducing calcium oxalate complexation and increasing the pool of available oxalate for reabsorption (Earnest et al, 1975). The poorly absorbed fatty acids and bile salts may increase colonic permeability to oxalate, further enhancing intestinal oxalate absorption (Dobbins and Binder, 1976; Hatch and Freel, 2008). A strong relationship between fecal fat and urinary oxalate excretion has been demonstrated in patients

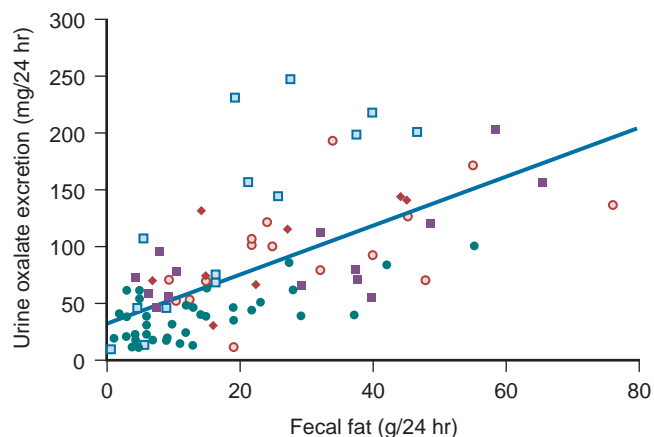


Figure 51-7. The relationship between fecal fat and urinary oxalate excretion in patients with steatorrhea. Diet oxalate was 300 to 500 mg/day in all but one study, in which it was 55 to 90 mg/day. Diet calcium was 500 to 900 mg/day in all studies when reported. Normal urine citrate was less than 50 mg/day in all studies, except one in which it was less than 34 mg/day. Oxalate = $2.1 \times \text{fecal fat} + 30.7$ ($r^2 = 0.4$, $n = 96$, $P < .001$). (From Worcester EM. Stones due to bowel disease. In Coe F, Favus M, Pak C, et al, editors. *Kidney stones: medical and surgical management*. New York: Lippincott-Raven; 1996. p. 883–903.)

with steatorrhea (Fig. 51-7) (Worcester, 1996). Dehydration, hypokalemia, hypomagnesiuria, hypocitraturia, and low urine pH also increase the risk of calcium oxalate stone formation in patients with chronic diarrheal syndrome. Malabsorption of any cause can lead to increased intestinal absorption of oxalate. Therefore small bowel resection, intrinsic disease, and jejunioileal bypass (Cryer et al, 1975) have all been associated with hyperoxaluria.

As the prevalence of obesity in the population has increased, bariatric surgery has become more popular and pervasive. Although jejunioileal bypass for obesity was discontinued in the past in part due to renal failure and nephrolithiasis induced by severe hyperoxaluria, modern bariatric surgery was thought to provide a safer alternative for weight loss. However, a 2005 report from the Mayo Clinic revealed two patients with oxalate nephropathy and renal failure who required dialysis and/or renal transplantation among 23 patients with enteric hyperoxaluria and calcium oxalate stones after Roux-en-Y gastric bypass surgery (Nelson et al, 2005). Since then, a number of retrospective (Asplin and Coe, 2007; Patel et al, 2009), cross-sectional (Maalouf et al, 2010), and prospective (Park et al, 2009; Duffey et al, 2010) studies have shown increased urinary oxalate excretion in non-stone-forming individuals after Roux-en-Y gastric bypass and other malabsorptive bariatric procedures. The rise in urinary oxalate was shown to develop at least 6 months after bypass surgery (Sinha et al, 2007). To varying degrees, the increase in urinary oxalate was offset by a decline in urinary calcium and uric acid, leading to conflicting effects on urinary saturation of calcium oxalate.

Despite some variation in the observed effect on urinary analytes, an increased rate of stone formation has been reported after gastric bypass surgery. Using a claims database, Matlaga and associates (2009) found that 7.65% of 4639 patients after Roux-en-Y gastric bypass surgery versus 4.63% of 4639 obese controls were diagnosed with kidney stones ($P < .0001$) after a median observation period of 4.6 years and 4.1 years, respectively. The risk appears to be limited to patients undergoing gastric bypass surgery, as a similar claims study demonstrated a higher rate of stone formation in a control group compared to a group of patients undergoing gastric banding (5.97% vs. 1.49%, respectively) (Semins et al, 2009). Indeed, a comparison of 27 patients after Roux-en-Y gastric bypass surgery with 12 patients after gastric banding revealed higher urinary oxalate, lower urinary calcium, and marginally lower urinary citrate in the bypass group compared to the banding group, suggesting that

gastric banding is not associated with malabsorption and enteric hyperoxaluria (Penniston et al, 2009).

The etiology of the hyperoxaluria observed after gastric bypass surgery has not been fully elucidated. Although loss of *O. formigenes*, an oxalate-degrading bacterium that resides in the intestinal tract, has been suggested as a possible source, the presence of low *O. formigenes* colonization levels in morbidly obese patients prior to Roux-en-Y gastric bypass surgery argues against this hypothesis (Duffey et al, 2011). Moreover, no significant difference in *O. formigenes* colonization was found between 10 post-bariatric surgery patients and 13 morbidly obese controls (40% vs. 15%, respectively) (Froeder et al, 2012). However, the urinary oxalate response to an oral oxalate load was more pronounced in patients after bariatric surgery than before and greater than the response in morbidly obese controls, suggesting that hyperoxaluria observed after bariatric surgery is due to increased intestinal absorption of dietary oxalate. Indeed, Kumar and colleagues (2011) prospectively studied 11 morbidly obese subjects before and 6 and 12 months after bariatric surgery (Roux-en-Y gastric bypass or biliopancreatic diversion-duodenal switch) and found significant increases in plasma oxalate, urine calcium oxalate supersaturation, and fecal fat excretion at both time points after surgery. Unlike previous studies, no significant increase in urinary oxalate or decline in urinary calcium was observed, likely as a result of aggressive calcium supplementation postsurgery. However, urinary oxalate was elevated in a 24-hour urine collection obtained after an oral oxalate load at both 6 and 12 months. These findings suggest that the etiology of the hyperoxaluria and increased stone risk associated with bariatric surgery is at least in part due to malabsorption and enteric hyperoxaluria.

Dietary Hyperoxaluria. Overindulgence in oxalate-rich foods such as nuts, chocolate, brewed tea, spinach, potatoes, beets, and rhubarb can result in hyperoxaluria in otherwise normal individuals. The contribution of dietary oxalate to urinary oxalate excretion can range from 24% to 42% (Holmes et al, 2001). In addition, severe calcium restriction may result in reduced intestinal binding of oxalate and increased intestinal oxalate absorption. Ascorbic acid supplementation has been shown to increase urinary oxalate levels by in vivo conversion to oxalate (Traxer et al, 2003), although increased clinical rates of stone formation have not been unequivocally linked to ascorbic acid use (Curhan et al, 1996, 1999).

Recent studies have also implicated *O. formigenes*, an oxalate-degrading intestinal bacterium, as a potential modulator of intestinal oxalate levels (Duncan et al, 2002). Stone formers were found to have reduced levels or absent colonization of *O. formigenes* compared with non-stone-forming control subjects, and individuals lacking the bacteria have been shown to have higher urinary oxalate levels (Sidhu et al, 1999; Mikami et al, 2003; Troxel et al, 2003). In a recent large case-control study of age- and gender-matched recurrent calcium oxalate stone formers ($n = 274$) and normal subjects ($n = 259$), 17% of stone formers and 38% of normal subjects tested positive for *O. formigenes* (Kaufman et al, 2008). Controlling for confounding factors, the OR for colonization (case vs. control) was 0.3 (95% CI 0.2 to 0.5). Interestingly, median urinary oxalate levels did not differ between those with or without *O. formigenes* colonization. Cystic fibrosis patients, many of whom are exposed to prolonged antibiotic use, have also been shown to have absence of *O. formigenes* from the intestinal tract and corresponding elevated urinary oxalate levels (Sidhu et al, 1998). Likewise, *O. formigenes* colonization was compared between a group of patients with *Helicobacter pylori* treated with antibiotics and a group of patients without *H. pylori*. Among 12 patients positive for *O. formigenes* not treated with antibiotics, 92% of patients remained *O. formigenes*-positive at 1 and 6 months. In contrast, among 19 subjects with *H. pylori* who received antibiotics, only 36.8% remained colonized with *O. formigenes* 1 and 6 months after treatment (Kharlam et al, 2011). These findings highlight the potential prolonged effect of antibiotic therapy on intestinal colonization of *O. formigenes* and a potential role in modulating stone risk.

Idiopathic Hyperoxaluria. Several studies have suggested that mild hyperoxaluria is as important a factor as hypercalciuria in the pathogenesis of idiopathic calcium oxalate stones (Menon, 1986;

Robertson and Hughes, 1993). In some populations, such as those inhabiting the Arabian Peninsula, the prevalence of calcium-containing stones is considerably higher than in the West despite the almost complete absence of hypercalciuria (Robertson and Hughes, 1993). Hyperoxaluria is implicated as the predominant risk factor in this population.

Abnormalities in the metabolism and transport of oxalate may contribute to calcium oxalate nephrolithiasis. Baggio and colleagues (1986) detected a higher rate of oxalate flux across the red blood cell membrane at steady state in 114 patients with a history of calcium oxalate kidney stones compared with control subjects. Treatment with oral hydrochlorothiazide (50 mg/day), amiloride (5 mg/day), or both restored normal or nearly normal red blood cell oxalate exchange in all of the patients who initially demonstrated increased rates. Up to 50% of the time, however, the abnormality in red blood cell oxalate transport is not associated with hyperoxaluria. Furthermore, Motola and colleagues (1992) found high rates of oxalate flux in non-calcium oxalate stone formers as well, thus leading some to question the importance of this mechanism in calcium oxalate stone formation.

Hyperuricosuria

Hyperuricosuria is defined as urinary uric acid exceeding 600 mg/day. Up to 10% of calcium stone formers have high urinary uric acid levels as an isolated abnormality, but it is found in combination with other metabolic abnormalities in up to 40% of calcium stone formers (Preminger, 1992). The mechanism by which hyperuricosuria induces calcium oxalate stones is not completely elucidated. Hyperuricosuria has been postulated to increase urinary levels of monosodium urate, which in turn promotes calcium oxalate crystallization through heterogeneous nucleation, or epitaxial crystal growth (Pak and Arnold, 1975). In addition, uric acid has been shown to reduce the effectiveness of naturally occurring macromolecular inhibitors of crystallization (Robertson et al, 1976; Zerwekh et al, 1983). However, some investigators dispute the effect of monosodium urate and attribute the effect of uric acid on calcium oxalate stone formation to the simple process of "salting out," whereby the solubility of calcium oxalate in solution is decreased (Ryall et al, 1991; Grover and Ryall, 1994).

The most common cause of hyperuricosuria is increased dietary purine intake. However, acquired and hereditary diseases may also be accompanied by hyperuricosuria, including gout, myeloproliferative and lymphoproliferative disorders, multiple myeloma, secondary polycythemia, pernicious anemia, hemolytic disorders, hemoglobinopathies and thalassemia, complete or partial HGPRT deficiency, overactivity of phosphoribosylpyrophosphate synthetase, and hereditary renal hypouricemia (Halabe and Sperling, 1994). The identification of a urate transporter, the anion exchanger URAT1, in the proximal renal tubule may provide new insight into the causes of hyperuricosuria (Enomoto et al, 2002; Ichida et al, 2004). Mutations in SLC22A12, the gene encoding URAT1, have been shown to cause hyperuricosuric hypouricemia (renal uric acid leak) along with exercise-induced acute renal failure and a high risk of kidney stones (Enomoto et al, 2002; Tanaka et al, 2003; Ichida et al, 2004; Iwai et al, 2004).

Not all evidence supports a role for uric acid in calcium oxalate stone formation. Among 3350 male and female participants (2237 stone formers and 1113 non-stone formers) from three large cohort studies who collected 24-hour urine specimens for stone risk analysis, after adjusting for other urinary parameters, urinary uric acid excretion was significantly inversely associated with incident kidney stone formation in men, marginally inversely associated in younger women, and not associated in older women (Curhan and Taylor, 2008). On the other hand, a randomized trial among hyperuricosuric, normocalciuric calcium oxalate stone formers demonstrated a greater than twofold reduction in stone recurrence rates among patients randomized to allopurinol versus those taking placebo (Ettinger et al, 1986). However, the mechanism of action of allopurinol in reducing stone recurrence rates cannot be definitively attributed to its effect in reducing urinary uric acid.

Hypocitraturia

Hypocitraturia is an important and correctable abnormality associated with nephrolithiasis that exists as an isolated abnormality in up to 10% of calcium stone formers and is associated with other abnormalities in 20% to 60% of stone formers (Pak, 1994; Levy et al, 1995). Citrate is an important inhibitor that can reduce calcium stone formation by several mechanisms. First, citrate reduces urinary saturation of calcium salts by complexing with calcium (Pak et al, 1982). Second, citrate directly prevents spontaneous nucleation of calcium oxalate (Sakhaee et al, 1987). Third, citrate inhibits agglomeration and sedimentation of calcium oxalate crystals (Kok et al, 1986; Tiselius et al, 1993a, 1993b), as well as the growth of calcium oxalate and calcium phosphate crystals (Meyer and Smith, 1975). Finally, normal urinary citrate levels can enhance the inhibitory effect of Tamm-Horsfall glycoprotein (Hess et al, 1993).

Hypocitraturia is defined as a urinary citrate level less than 320 mg/day. Acid-base state is the primary determinant of urinary citrate excretion. Metabolic acidosis reduces urinary citrate levels secondary to enhanced renal tubular reabsorption and decreased synthesis of citrate in peritubular cells (Hamm, 1990). A study comparing normal subjects and stone formers noted comparable mean serum citrate levels and filtered citrate loads in the two groups; however, 24-hour urinary citrate and the fasting citrate-to-creatinine ratio were significantly reduced and mean tubular reabsorption of citrate was significantly increased in the stone formers compared with control subjects (Minisola et al, 1989).

Indirect evidence for a primarily renal etiology of hypocitraturia comes from a study comparing intestinal absorption of citrate in idiopathic hypocitraturic stone formers and normal subjects (Fegan et al, 1992). Oral ingestion of citrate was followed by rapid and efficient absorption in both groups, with 96% to 98% absorbed within 3 hours. As such, hypocitraturia is unlikely to arise from impaired gastrointestinal absorption of citrate in stone formers without overt bowel disease.

Low urinary citrate results from a variety of pathologic states associated with acidosis. Distal RTA is characterized by high urine pH (>6.8), high serum chloride, and low serum bicarbonate and potassium (Preminger et al, 1985). The inability to acidify urine in response to an oral acid (ammonium chloride) load confirms the diagnosis of RTA. Chronic diarrheal states cause intestinal alkali loss in the stool with subsequent systemic acidosis and hypocitraturia (Rudman et al, 1980). Excessive animal protein can provide an acid load, reducing citrate levels (Breslau et al, 1988). Indeed, a metabolic study evaluating the effect of a high-protein, low-carbohydrate diet demonstrated a significant reduction in urinary citrate and pH, likely as a result of low citrus and high animal protein intake (Reddy et al, 2002). Diuretics such as thiazides induce hypokalemia and intracellular acidosis (Nicar et al, 1984). Angiotensin-converting enzymes can cause hypocitraturia independently of systemic acidosis or hypokalemia, perhaps as a result of intracellular acidosis (Melnick et al, 1998). Finally, strenuous exercise may induce lactic acidosis (Sakhaee et al, 1987). However, hypocitraturia may also represent an isolated abnormality unrelated to an acidotic state.

Citrate levels in the urine increase in alkalotic states, as well as with elevated levels of PTH, estrogen, magnesium, calcitonin, and vitamin D (Hamm and Hering-Smith, 2002).

Low Urine pH

At low urine pH (<5.5), the undissociated form of uric acid predominates, leading to uric acid and/or calcium stone formation. Calcium oxalate stones form as a result of heterogeneous nucleation with uric acid crystals (Coe and Kavalach, 1974; Pak et al, 1976). Any disorder leading to low urine pH may predispose to stone formation. Chronic metabolic acidosis can lead to low urine pH, hypercalciuria, and hypocitraturia. Acidosis increases bone resorption and produces renal calcium leak (Lemann, 1999; Lemann et al, 2003). "Gouty diathesis," or idiopathic low urine pH, refers to a stone-forming propensity characterized by low urine pH of

unknown etiology with or without associated gouty arthritis (Levy et al, 1995).

Renal Tubular Acidosis

RTA is a clinical syndrome characterized by metabolic acidosis resulting from defects in renal tubular hydrogen ion secretion or bicarbonate reabsorption. There are three types of RTA: 1, 2, and 4. Type 1 (distal) RTA is of particular significance to urologists not only because it is the most common form of RTA but also because it is the form of RTA most frequently associated with stone formation, which occurs in up to 70% of affected individuals (Van den Berg et al, 1983). Indeed, symptoms associated with nephrolithiasis led to the initial diagnosis of RTA in upward of 50% of cases (Van den Berg et al, 1983).

Acid-base balance is maintained by the kidney through several mechanisms involving both the proximal and distal nephron. Because bicarbonate is freely filtered at the glomerulus, the kidney must reabsorb or regenerate nearly all of the filtered bicarbonate each day (≈ 4500 mmol) to maintain its buffering capacity, a process that takes place primarily in the proximal renal tubule (Pohlman et al, 1984). Furthermore, the kidney must excrete excess acid, which accumulates from the breakdown of carbohydrates, fats, and proteins and as a result of bicarbonate loss in the stool. Net acid excretion occurs in the distal renal tubule. A defect in either bicarbonate reabsorption or acid excretion will lead to metabolic acidosis.

Filtered bicarbonate (HCO_3^-) is almost completely reabsorbed in the proximal renal tubule through an indirect mechanism involving hydrogen (H^+) secretion (Laing et al, 2005). Carbonic anhydrase in the tubular cells generates H^+ and HCO_3^- , thereby providing H^+ ions that are secreted into the tubular lumen by way of a Na^+/H^+ exchanger in the apical membrane. Sodium (Na^+) pumped out of the proximal tubule cell by the sodium-potassium adenosine triphosphatase (Na^+/K^+ -ATPase) exchanger located in the basolateral membrane drives the Na^+/H^+ exchanger in the apical membrane by reducing intracellular sodium. At the same time, HCO_3^- is transferred via a basolateral $\text{Na}^+/\text{HCO}_3^-$ cotransporter into the plasma. Additional active H^+ secretion into the tubular lumen is accomplished by an apical H^+ -ATPase. Luminal H^+ ion combines with filtered HCO_3^- to form H_2CO_3 , which is rapidly converted by another form of carbonic anhydrase to H_2O and CO_2 , which diffuses back in to the cell. The net effect is transepithelial HCO_3^- absorption without causing net H^+ secretion or a significant change in urinary pH.

The distal nephron is the site of net elimination of H^+ , although 5% to 10% of filtered bicarbonate is also reabsorbed there in a manner similar to the proximal nephron. Hydrogen binds with urinary buffers such as titratable acid (mainly phosphate) and ammonia, allowing net elimination of hydrogen in the form of NH_4^+ . H^+ excretion occurs through active secretion from α -intercalated cells. These cells secrete H^+ into the distal tubule using H^+ -ATPase and a H^+/K^+ -ATPase exchanger (Laing et al, 2005). The intercalated cells also have a $\text{Cl}^-/\text{HCO}_3^-$ anion exchanger that transports HCO_3^- into the blood. These active pumps generate a 1000:1 hydrogen ion gradient between the cell and the tubular lumen, allowing reduction of urine pH to as low as 4.5 (Kinkead and Menon, 1995). Another contributing factor is the lack of luminal carbonic anhydrase that prevents the rapid dissociation of carbonic acid catalyzed by the enzyme.

Distal and proximal RTA occur as a result of impairment of net excretion of acid into the urine (distal or type 1) or of reabsorption of bicarbonate (proximal or type 2). Distinction between these abnormalities provides the basis for classification of RTA into proximal or distal, although both share the characteristic findings of hyperchloremic metabolic acidosis associated with inappropriately high urinary pH.

Type 1 (Distal) Renal Tubular Acidosis. Type 1 RTA comprises a syndrome of abnormal collecting duct function characterized by inability to acidify the urine in the presence of systemic acidosis. The classic findings include hypokalemic, hyperchloremic,

non-anion gap metabolic acidosis along with nephrolithiasis, nephrocalcinosis, and elevated urine pH (>6.0). Patients with incomplete RTA also demonstrate defective renal acid excretion manifested as failure to lower urine pH below 5.5 after an acid load, but they do not manifest metabolic acidosis and consequently have normal serum electrolytes (Osther et al, 1989).

Patients with distal RTA commonly present as adults with symptoms of nephrolithiasis (Caruana and Buckalew, 1988). However, children comprise a third of affected individuals, and they often present with vomiting or diarrhea, failure to thrive, or growth retardation. The most common stone composition associated with distal RTA is calcium phosphate as a result of hypercalciuria, hypocitraturia, and increased urinary pH (Van den Berg et al, 1983; Pohlman et al, 1984). The metabolic acidosis promotes bone demineralization, which leads to secondary hyperparathyroidism and hypercalciuria. Profound hypocitraturia, perhaps the most important factor in stone formation in this setting, is due to impaired citrate excretion as a result of metabolic acidosis but may also be related to abnormal renal tubular citrate transport or migration of citrate into the mitochondria as a result of intracellular acidosis (Osther et al, 1989; Kinkead and Menon, 1995).

Distal RTA occurs as a consequence of dysfunction of the α -type intercalated cells, which secrete protons into the urine via an apical H^+ -ATPase that is coupled to an anion exchanger (AE1) located at the basolateral membrane (Fig. 51-8) (Karet, 2002). Mutations in three genes in the α -type intercalated cells have been implicated in hereditary distal RTA; *SLC4A1* encodes the AE1 Cl^-/HCO_3^- anion exchanger, and *ATP6V1B1* and *ATP6V0A4* encode the B1 and A4 subunits, respectively, of H^+ -ATPase. A fourth gene, *CA2*, encodes carbonic anhydrase II, which is found in the proximal tubule, the loop of Henle, and the α -intercalated cells of the collecting duct. Because carbonic anhydrase II affects bicarbonate reabsorption as well as H^+ secretion, mutations in *CA2* present a mixed pattern of proximal and distal RTA (Batlle and Haque, 2012).

Distal RTA is a heterogeneous disorder that may be hereditary, idiopathic, or acquired (Laing et al, 2005). Although most cases of distal RTA are sporadic, both autosomal dominant and autosomal recessive patterns of inheritance have been identified. The inherited forms of distal RTA are associated with growth retardation, nephrocalcinosis, renal calculi, and hypokalemic metabolic acidosis, but the phenotype is usually more severe in the autosomal recessive form of the disease. Autosomal recessive distal RTA also tends to occur earlier in life and is additionally associated with mental retardation and sensorineural hearing loss or deafness.

Mutations in the *SLC4A1* gene are most commonly associated with the autosomal dominant form of distal RTA, which can present in the complete or incomplete form, although an autosomal recessive form associated with a mutation in this gene is endemic in

Southeast Asia. This form of distal RTA, which is always complete, is commonly associated with hemolytic anemia and severe hypokalemia (Batlle and Haque, 2012). Hearing loss is not usually a feature of mutations in the *SLC4A1* gene.

Mutations in the *ATP6V1B1* and *ATP6V0A4* genes encoding H^+ -ATPase have been primarily associated with autosomal recessive distal RTA (Batlle et al, 2006). Although mutations in *ATP6V1B1* have been implicated in RTA and severe childhood deafness, mutations in *ATP6V0A4* have been associated with a milder form of hearing loss that occurs later, in early adulthood (Karet et al, 1999; Batlle et al, 2006).

Most mutations in the *CA2* gene have been identified in patients of Arabian origin. *CA2* mutations are recessive and lead to a mixed proximal-distal RTA picture characterized by bicarbonate wasting, inability to acidify the urine below pH 5.5, and reduced NH_4^+ excretion (Batlle and Haque, 2012). Carbonic anhydrase II catalyzes the hydration of CO_2 to H^+ and HCO_3^- .

Secondary distal RTA in sporadic cases is commonly associated with autoimmune diseases such as Sjögren syndrome and systemic lupus erythematosus, and it occurs more frequently in women than men (Buckalew, 1989). Secondary RTA is also associated with obstructive uropathy, pyelonephritis, acute tubular necrosis, hyperparathyroidism, and idiopathic hypercalciuria.

Type 2 (Proximal) Renal Tubular Acidosis. Proximal RTA is characterized by a defect in HCO_3^- reabsorption associated with initial high urine pH that normalizes as plasma HCO_3^- decreases and the amount of filtered HCO_3^- falls (Laing et al, 2005). With reduced capacity of the proximal tubule to reclaim filtered HCO_3^- , more HCO_3^- is delivered to the distal tubule, which has a limited capacity for bicarbonate reabsorption. Consequently, bicarbonaturia ensues, resulting in reduced net acid excretion and metabolic acidosis. As the filtered HCO_3^- load declines with progressive metabolic acidosis, less bicarbonate reaches the distal tubule until eventually the capacity of the distal tubule is sufficient to handle the load and no further bicarbonate is lost. At steady state, serum HCO_3^- is low (15 to 18 mEq/L) and urine pH is acidic (<5.5).

This syndrome is usually associated with generalized defects in proximal tubule function similar to Fanconi syndrome, with loss of glycogen, protein, uric acid, and phosphate (Rocher and Tannen, 1986). Nephrolithiasis is uncommon in this disorder owing to relatively normal urinary citrate excretion (Laing et al, 2005). The clinical manifestations of proximal RTA include growth retardation and hypokalemia in children resulting from metabolic acidosis. Metabolic bone disease is seen more frequently with proximal RTA because of associated abnormalities in vitamin D metabolism and hypophosphatemia (Kinkead and Menon, 1995).

Most cases of proximal RTA are sporadic, but inherited diseases associated with proximal RTA have been described. In humans and terrestrial vertebrates, the kidneys control systemic pH in part by absorbing filtered HCO_3^- in the proximal tubule via an electrogenic Na^+/HCO_3^- cotransporter (NBCe1/SLC4A4) located in the basolateral membrane of the proximal tubule. Homozygous point mutations in *NBCe1* cause proximal RTA, glaucoma, and cataracts (Igarashi et al, 1999). Other mutations in this gene have been identified that cause voltage- and Na^+ -dependent transport abnormalities, thereby causing both insufficient HCO_3^- reabsorption by the kidney (proximal RTA) and inappropriate anterior chamber fluid transport (glaucoma) (Dinour et al, 2004).

Carbonic anhydrase II catalyzes the hydration/dehydration of CO_2 and H_2CO_3 and is expressed in the renal proximal tubule, loop of Henle, and intercalating cells of the collecting duct, as well as in brain glial cells and bone osteoclasts (Laing et al, 2005). Deficiency of carbonic anhydrase II (carbonate hydrolyase, EC 4.2.1.1) is the primary defect in the syndrome of osteopetrosis, proximal RTA, and cerebral calcification. Fortunately, this is a rare abnormality (Sly et al, 1985; Roth et al, 1992).

Type 4 (Distal) Renal Tubular Acidosis. Type 4 RTA is associated with chronic renal damage, usually seen in patients with interstitial renal disease and diabetic nephropathy. Reduction in glomerular filtration results in hyperkalemic, hyperchloremic metabolic acidosis caused by loss of HCO_3^- in the urine and decreased

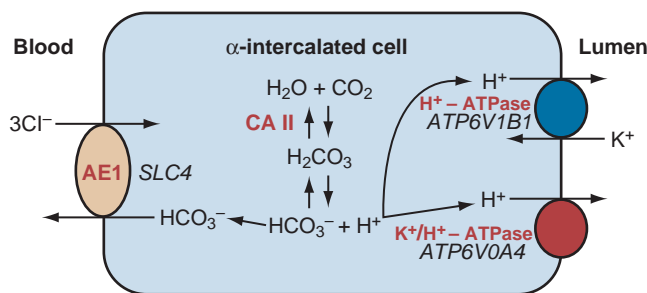


Figure 51-8. Mechanism of acidification in the collecting duct α -intercalated cell. Enzymes are shown in red and their corresponding genes in italics. The α -intercalated cells secrete H^+ into the lumen of the distal tubule and collecting duct by way of an apical H^+ -ATPase and possibly an H^+, K^+ -ATPase exchanger. Bicarbonate is transported into the blood via a Cl^-, HCO_3^- anion exchanger (AE1) on the basolateral membrane. Defects in the AE1 Cl^-, HCO_3^- anion exchanger or in H^+ -ATPase result in failure to acidify the urine in distal RTA. CA II, carbonic anhydrase II.

excretion of ammonium (Pohlman et al, 1984). Aldosterone resistance is commonly associated with type 4 RTA (Davidman and Schmitz, 1988). Because aldosterone contributes to stimulation of distal acidification and H^+ , K^+ exchange, aldosterone resistance results in decreased ammonia generation and further exacerbates hyperkalemia (Davidman and Schmitz, 1988). Patients with type 4 RTA can still generate acidic urine in response to an acid challenge.

Renal stone formation is uncommon in patients with type 4 RTA. A study comparing patients with type 4 RTA and matched subjects with a similar degree of renal impairment found that patients with type 4 RTA had significantly lower urinary pH and decreased urinary calcium excretion compared to controls (Uribarri et al, 1994). The protection against renal stone formation in these patients may be attributed to reduced renal excretion of stone-forming substances such as calcium and uric acid owing to impaired renal function.

Hypomagnesiuria

Hypomagnesiuria is a rare cause of nephrolithiasis, affecting less than 1% of stone formers as an isolated abnormality, although it can be found in conjunction with other abnormalities in 6% to 11% of cases (Levy et al, 1995; Schwartz et al, 2001). Magnesium complexes with oxalate and calcium salts, and therefore low magnesium levels result in reduced inhibitory activity. Low urinary magnesium is also associated with decreased urinary citrate levels, which may further contribute to stone formation (Preminger et al, 1989; Schwartz et al, 2001). Whether low magnesium is the cause or effect of low citrate is not clear. Low magnesium levels occur with poor dietary intake or as a result of reduced intestinal absorption associated with intestinal abnormalities producing chronic diarrheal syndrome.

Although a number of studies in rats have implicated hypomagnesiuria as a factor in stone formation (Rushton and Spector, 1982), others (Faragalla and Gershoff, 1963; Borden and Lyon, 1969; Rattan et al, 1993) have questioned the impact of magnesium (Su et al, 1991). Clinical studies regarding the role of magnesium are contradictory. Schwartz and colleagues (2001) found that hypomagnesiuric patients had higher stone recurrence rates than patients with normal urinary magnesium. However, other studies found no difference in magnesium excretion between stone patients and controls (Johansson et al, 1980; Esen et al, 1991). Of note, the lack of difference in mean magnesium levels may be a result of the small fraction of stone formers with low urinary magnesium levels.

Although magnesium has been shown to increase urinary pH, citrate, and magnesium levels and therefore to decrease urinary saturation of calcium oxalate in vitro (Khan et al, 1993) and in vivo (Curhan et al, 2001), two randomized trials comparing magnesium oxide with placebo or no treatment in stone formers failed to demonstrate clinical benefit (Wilson et al, 1984; Ettinger et al, 1988).

Uric Acid Stones

Most mammals, except humans and Dalmatians, synthesize the hepatic enzyme uricase, which catalyzes the conversion of uric acid to allantoin, the end product of purine metabolism (Yu, 1981; Bannasch et al, 2004). Consequently, humans accumulate significantly higher levels of uric acid in their blood and urine (Watts, 1976; Yu, 1981). Because allantoin is 10 to 100 times more soluble in urine than uric acid, humans are prone to uric acid stone formation. Uric acid comprises 8% to 10% of all kidney stones in the United States and up to 25% in certain regions in Germany (Maalouf et al, 2004a).

Uric acid is a weak acid with a pK_a of 5.35 at 37° C. At that pH, half of the uric acid is present as the urate salt and half as free uric acid. Because sodium urate is approximately 20 times more soluble than the free acid, the relative proportion present as free uric acid strongly determines the risk of stone formation. **Urine pH is a critical factor in determining uric acid solubility;** at pH 5, even modest amounts of uric acid exceed uric acid solubility, whereas at pH 6.5,

concentrations of uric acid exceeding 1200 mg/L remain soluble (Fig. 51-9) (Asplin, 1996). Under normal conditions, the limit of uric acid solubility is approximately 96 mg/L, a level readily exceeded by normal daily uric acid excretion, which averages 500 to 600 mg/L. Consequently, urine may reach supersaturation, particularly at pH less than 6. Low urine pH increases concentrations of sparingly soluble undissociated uric acid, which leads to direct precipitation of uric acid. Of note, uric acid and sodium urate have been implicated as nuclei for calcium oxalate stones through heterogeneous nucleation and epitaxial crystal growth, and thus low urine pH is thought to be a risk factor for uric acid, calcium oxalate, and mixed calcium and uric acid stones (Maalouf, 2011).

The process of uric acid stone formation once uric acid crystals precipitate has not been fully elucidated. Although some investigators have suggested that uric acid crystal adhesion to kidney epithelial cells (Koka et al, 2000) and inhibitors such as glycosaminoglycans (Ombra et al, 2003) may play a role in uric acid stone formation, the involvement or importance of these factors in uric acid stone formation is unclear.

The three main determinants of uric acid stone formation are low pH, low urine volume, and hyperuricosuria (Fig. 51-10). The most important pathogenetic factor is low urine pH because most patients with uric acid stones have normal uric acid excretion but invariably demonstrate persistent low urine pH (Pak et al, 2001; Sakhaee et al, 2002). Uric acid stones can develop as a result of congenital, acquired, or idiopathic causes. Congenital disorders associated with uric acid stones involve renal tubular urate transport or uric acid metabolism, leading to hyperuricosuria. Acquired causes of uric acid stones such as chronic diarrhea, volume depletion, myeloproliferative disorders, high animal protein intake, and uricosuric drugs may affect any of the three factors determining uric acid stone formation. Patients with "gouty diathesis" or idiopathic uric acid nephrolithiasis typically demonstrate decreased fractional excretion of urate and do not have gout (Maalouf et al, 2004a). Patients with idiopathic uric acid nephrolithiasis differ from those with hyperuricosuric calcium nephrolithiasis in that the former generally have normal urinary uric acid levels and acidic urine, whereas the latter have hyperuricosuria and normal urine pH (Pak et al, 2002). Patients with hyperuricosuria frequently have high urinary sodium and calcium levels leading to increased urinary saturation of sodium urate and calcium oxalate, placing them at risk for calcium oxalate stones (Sorensen and Chandhoke, 2002).

Pathogenesis of Low Urine pH

Although the pathogenesis of low urine pH in idiopathic uric acid stone formers is not known with certainty and may be multifactorial, several potential mechanisms have been proposed. Sakhaee and colleagues (2002) first observed that normouricosuric individuals with pure uric acid stones were more likely to have diabetes mellitus or to demonstrate glucose intolerance than normal individuals or those with mixed uric acid–calcium oxalate or pure calcium oxalate stones. Furthermore, when a group of normouricosuric uric acid stone formers was placed on a controlled metabolic diet, the urinary pH was lower than that of either normal volunteers or other stone formers (mixed uric acid–calcium oxalate or calcium oxalate). Further investigation revealed that the uric acid stone formers excreted less acid into the urine as ammonium and proportionately more titratable acid and less citrate in order to maintain normal overall acid-base balance. **This apparent impairment in ammonium excretion in uric acid stone formers has been putatively linked to an insulin-resistant state.**

Supporting this hypothesis, Pak and colleagues (2003) noted a higher prevalence of uric acid stones and low urinary pH among patients with non–insulin-dependent diabetes mellitus (34%) than among nondiabetic stone formers. Daudon and colleagues (2006) analyzed 2464 calculi and also found that uric acid stones comprised 36% of stones among 272 patients with type 2 diabetes mellitus but only 11% among 2192 patients without type 2 diabetes. Furthermore, uric acid stone formers have been found to share many of the characteristic features of the metabolic syndrome (a

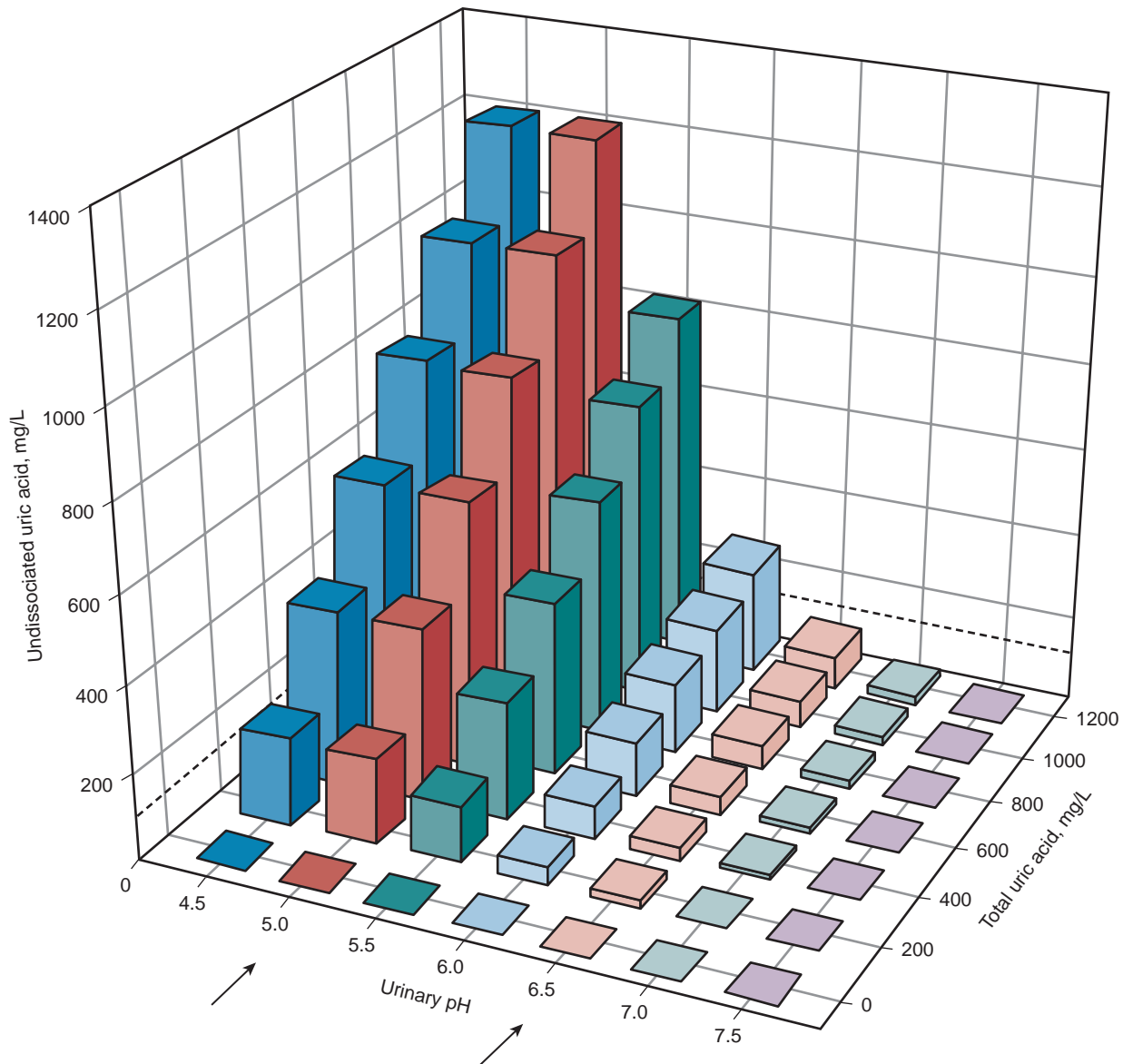


Figure 51-9. Relationship among undissociated uric acid, total uric acid, and urinary pH. The limit of solubility of undissociated uric acid is depicted by the dotted line (≈ 100 mg/L). Two hypothetical urine pH values are considered (arrows). At low pH (e.g., 5.0), even a modest amount of total urinary uric acid will exceed its solubility. At high pH (e.g., 6.5), even massive hyperuricosuria is well tolerated. (From Maalouf NM, Cameron MA, Moe OW, et al. Novel insights into the pathogenesis of uric acid nephrolithiasis. *Curr Opin Nephrol Hypertens* 2004;13:181–9.)

condition defined by insulin resistance and high-risk atherosclerotic cardiovascular disease), including hypertriglyceridemia, hyperglycemia, obesity, and hypertension (Sakhaee et al, 2002; Pak et al, 2003). In an elegant series of experiments, Abate and colleagues (2004) performed hyperinsulinemic euglycemic clamps to measure insulin sensitivity in a diverse group of non-stone-forming normal volunteers and a group of uric acid stone formers and determined that, among normal subjects, low urine pH correlated with low rates of glucose disposal (indicating insulin resistance) in both groups, but uric acid stone formers displayed the most severe levels of insulin resistance. This association of insulin resistance with low urinary pH was further corroborated by the finding of a strong inverse association of body weight (known to be associated with peripheral insulin resistance) and urinary pH, even after adjusting for urinary sulfate (a marker of animal protein intake) (Maalouf et al, 2004b).

The mechanism by which insulin resistance leads to low urine pH has not been completely elucidated. However, insulin has been shown in vitro to promote renal ammoniogenesis from the substrate glutamine (Chobanian and Hammerman, 1987; Nissim et al, 1995) and also to stimulate the Na^+/H^+ exchanger (NHE3) in the proximal tubule, which is responsible for either the direct transport or trapping of ammonium in the urine (Kliscic et al, 2002). Impaired ammonium production or excretion as a result of insulin resistance could leave hydrogen ions unbuffered in the urine, thereby leading to reduction in urine pH (Fig. 51-11).

Acidic urine pH may also be promoted by increased endogenous uric acid production or by dietary influences. When idiopathic uric acid stone formers and normal subjects were maintained on a fixed, low acid-ash diet, net acid excretion was higher in the former group compared with the latter, implicating higher endogenous acid production (Sakhaee et al, 2002). Furthermore, when

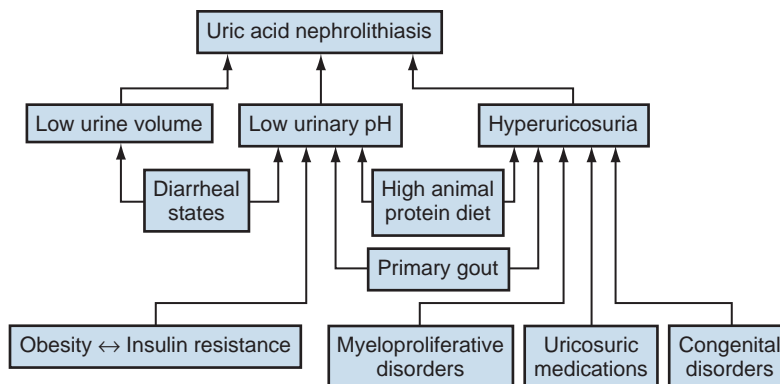


Figure 51-10. Pathophysiology and etiology of uric acid nephrolithiasis. The three major pathophysiologic mechanisms that contribute to uric acid nephrolithiasis are low urine volume, low urinary pH, and hyperuricosuria. Each of these mechanisms can result from diverse etiologies. The most important pathogenetic factor is low urinary pH. (From Maalouf NM, Cameron MA, Moe OW, et al. Novel insights into the pathogenesis of uric acid nephrolithiasis. *Curr Opin Nephrol Hypertens* 2004;13:181–9.)

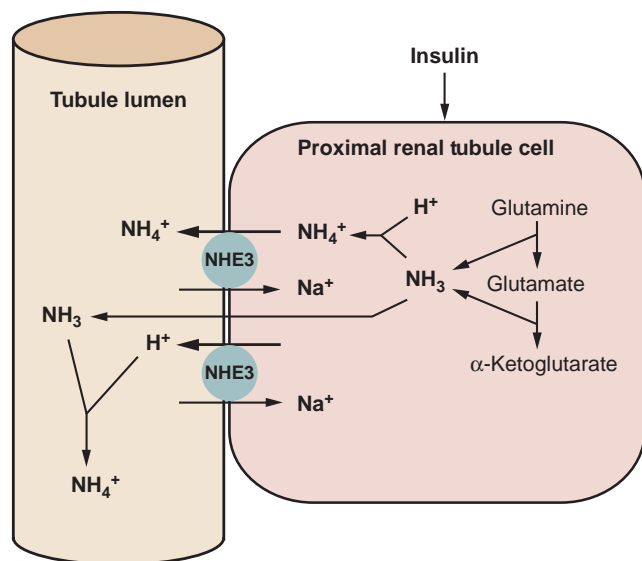


Figure 51-11. Potential effects of the insulin-resistant state on the generation and secretion of ammonium in the proximal tubule. The deamination of glutamine and glutamate provides ammonia. Insulin stimulates glutamine metabolism, as well as the sodium-hydrogen exchanger NHE3. NHE3 mediates ammonium transport by either directly carrying the ammonium ion or providing the luminal hydrogen ion to trap ammonia. The end product of glutamine metabolism is α -ketoglutarate. (Modified from Maalouf NM, Cameron MA, Moe OW, et al. Novel insights into the pathogenesis of uric acid nephrolithiasis. *Curr Opin Nephrol Hypertens* 2004;13:181–9.)

controlled for urinary sulfate (a marker of acid intake), net acid excretion was higher in uric acid stone formers and in non-stone formers with type 2 diabetes compared with normal controls (Cameron et al, 2006). These studies suggest that, in the setting of impaired ammonium excretion and increased endogenous acid production resulting from obesity and/or insulin resistance, titratable acids comprise the primary urinary buffer, and while acid-base equilibrium can be maintained, it occurs at a lower pH than is typically maintained by ammonium, which has a higher pK_a .

Lipotoxicity, a process whereby fat is redistributed into nonadipocyte tissues such as the heart, liver, skeletal muscle, and pancreatic beta cells, resulting in cellular injury, has been implicated in

impaired insulin sensitivity, cardiac dysfunction, and hepatic steatohepatitis and has recently been postulated to play a role in the pathogenesis of chronic renal disease (Bagby, 2004; Weinberg, 2006; Wahba and Mak, 2007). Whether or not lipotoxicity plays a role in impaired ammonium excretion or increased endogenous acid production leading to low urine pH in uric acid stone formers is unknown (Sakhaee, 2009). However, studies in a rodent model of metabolic syndrome (Zucker diabetic fatty rat) and a proximal tubular cell line demonstrated that renal steatosis may be responsible for the reduced expression and activity of NHE3, the primary mediator of ammonium excretion (Bobulescu et al, 2008, 2009). Interestingly, recent proteomic analysis of the matrix component of uric acid stones identified 242 unique proteins among five stones, with the largest proportion of proteins involved in the inflammation and complement pathways; the most commonly involved metabolic pathways associated with these proteins were the phospholipid and fatty acid pathways (Jou et al, 2012).

Dietary content also plays a role in determining urine acidity. Breslau and colleagues (1988) evaluated 15 normal subjects in a three-way randomized, crossover study involving three 12-day phases of study in which subjects were maintained on a controlled metabolic diet containing vegetable protein, vegetable and egg protein, or animal protein, with increasing sulfate content, respectively, in the three diets. As the fixed acid content of the diets increased, urinary calcium excretion increased from 103 mg/day on the vegetarian diet to 150 mg/day on the animal protein diet ($P < .02$). Moreover, the animal protein-rich diet was associated with the highest excretion of undissociated uric acid and lowest excretion of citrate because of the reduction in urinary pH. Urinary crystallization studies revealed that the animal protein diet, when matched for electrolyte composition and quantity of protein with the vegetarian diet, conferred an increased risk of uric acid stones, but because of opposing factors, not of calcium oxalate or calcium phosphate stones.

Hyperuricosuria

Hyperuricosuria is defined as urinary uric acid exceeding 600 mg/day. Hyperuricosuria predisposes to uric acid stone formation by causing supersaturation of the urine with respect to sparingly soluble undissociated uric acid. Patients with gout and urinary uric acid levels less than 600 mg/day had significantly fewer stones than those with uric acid levels greater than 1000 mg/day (Hall et al, 1967; Yu and Gutman, 1967). The causes of hyperuricosuria have been discussed previously but include dietary factors, as well as acquired and hereditary diseases and defects in the urate transporter.

Low Urinary Volume

All conditions that contribute to low urinary volume increase the risk of uric acid supersaturation. [Borghi and colleagues \(1993\)](#) noted high uric acid relative supersaturation in workers exposed to hot temperatures compared with those working in normal temperatures. Likewise, high rates of uric acid stone formation have been found in populations living in warmer climates such as Israel ([Shekarriz and Stoller, 2002](#)).

Cystine Stones

Cystinuria is an inherited autosomal recessive disorder (or rarely autosomal dominant with incomplete penetrance) characterized by a defect in intestinal and renal tubular transport of dibasic amino acids, resulting in excessive urinary excretion of cystine ([Ng and Stroom, 1999, 2001](#)). Although the defect also results in high urinary concentrations of lysine, ornithine, and arginine, the poor solubility of cystine leads to stone formation. Cystine is a dimer, composed of two cysteine molecules linked via a disulfide bond. Cystine is much less soluble than cysteine and is responsible for cystine stone formation. Cystine stones are rare, occurring in the United States and Europe with an incidence of only 1 in 1000 to 1 in 17,000 ([Caballo-Tomas et al, 1999; Knoll et al, 2005](#)). In children, cystinuria is the cause of up to 10% of all stones ([Faerber, 2001; Erbağci et al, 2003; Knoll et al, 2005](#)).

Under normal conditions amino acids are freely filtered by the glomerulus and almost completely reabsorbed in the renal proximal tubule. Cystine and the other dibasic amino acids are transported across the apical membrane of the renal proximal tubule by a sodium-independent heteromeric amino acid transporter in exchange for neutral amino acids. Cystine is reduced intracellularly to cysteine, thereby providing a favorable gradient for continued cystine reabsorption ([Broer, 2008](#)). In cystinuria, the defect in cystine transport results in high urinary levels. Several factors determine the solubility of cystine, including cystine concentration, pH, ionic strength, and urinary macromolecules. The main contributor to cystine crystallization is supersaturation because there is no specific inhibitor of cystine crystallization in the urine ([Pak and Fuller, 1983](#)). Because of the poor solubility of cystine in urine, precipitation of cystine and subsequent stone formation occur at physiologic urine conditions ([Joly et al, 1999](#)). The solubility of cystine is highly pH dependent, with solubilities of 300 mg/L, 400 mg/L, and 1000 mg/L at pH levels of 5, 7, and 9, respectively ([Dent and Senior, 1955](#)). Ionic strength also influences solubility, and as much as 70 mg of additional cystine can be dissolved in each liter of solution as ionic strength increases from 0.005 to 0.3 ([Pak and Fuller, 1983](#)). Macromolecules such as colloid also increase cystine solubility, although the mechanism is unclear ([Pak and Fuller, 1983](#)). Therefore cystine is more soluble in urine than in synthetic solution ([Fig. 51-12](#)).

Other factors may contribute to stone formation in cystinuric patients as well. [Sakhae and colleagues \(1989\)](#) evaluated 27 patients with documented cystine nephrolithiasis and identified hypercalciuria in 19%, hyperuricosuria in 22%, and hypocitraturia in 44%, which could contribute to formation of not only cystine stones but also calcium or mixed calcium-cystine stones.

The genetics of cystinuria have been studied extensively. Two genes involved in the disease have been identified: *SLC3A1* ([Pras et al, 1994](#)), which resides on the short arm of chromosome 2 and codes for a 663-amino acid heavy subunit (rBAT) of the cystine transporter, and *SLC7A9* ([Feliubadaló et al, 1999](#)), which is located on the long arm of chromosome 19 and codes for a 487-amino acid light subunit (b⁰+AT) of the cystine transporter. The two subunits form a heterodimer that resides in the apical membrane of the proximal tubule cells. As of 2010, a total of 133 and 95 mutations had been reported in the *SLC3A1* and the *SLC7A9* genes, respectively ([Chillaron et al, 2010](#)).

Historically, three types of cystinuria have been recognized in humans—type I, type II, and type III—on the basis of levels of urinary cystine in obligate heterozygote parents of the proband

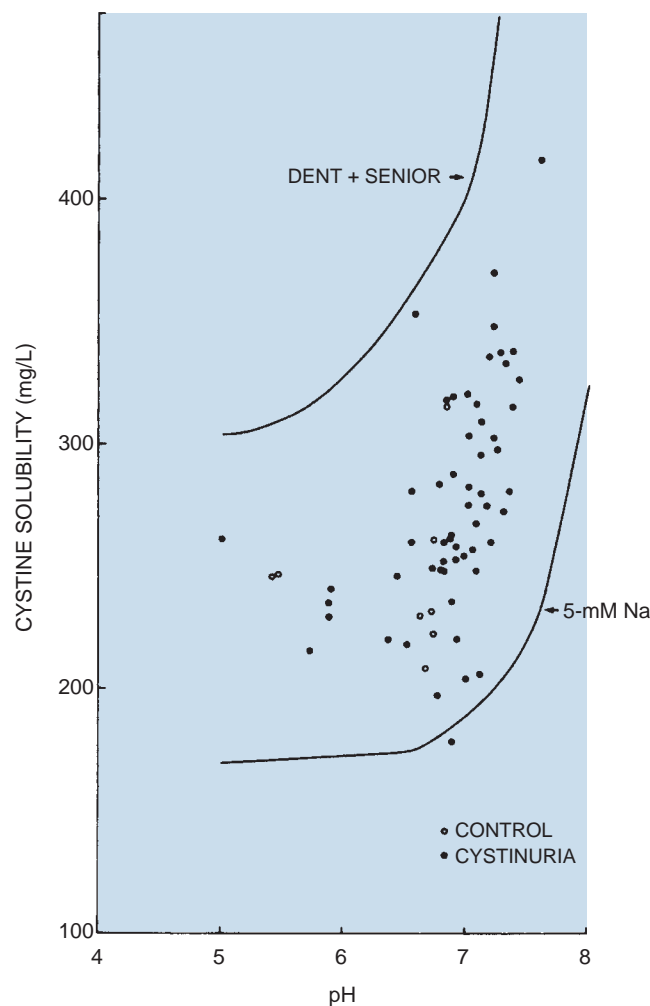


Figure 51-12. Cystine solubility in urine. Each point represents solubility of cystine determined in a separate urine sample by incubation with an excess of solid cystine. The solubility curve of [Dent and Senior \(1955\)](#) and that obtained in a 5-mM sodium cacodylate solution are plotted for comparison. (From [Pak CY, Fuller CJ. Assessment of cystine solubility in urine and of heterogeneous nucleation. J Urol 1983;129:1066–70.](#))

([Rosenberg et al, 1966](#)). However, this classification correlated poorly with molecular findings, and therefore it has been revised by the International Cystinuria Consortium (ICC) to take into account the chromosomal localization of the mutation: type A (chromosome 2), type B (chromosome 19), and type AB (both chromosomes) ([Dello Strologo et al, 2002](#)). Homozygotes with the condition exhibit urinary cystine levels as high as 2000 $\mu\text{mol/g}$ of creatinine. Review by the ICC revealed that the average age at first stone diagnosis was 12.2 years, with a mean number of stone episodes of 0.42 and 0.21 per year occurring in men and women, respectively ([Dello Strologo et al, 2002](#)). Although mean urinary cystine levels are significantly higher in heterozygotes with type B abnormalities (475 $\mu\text{mol/g}$ creatinine) compared with those with type A abnormalities (70 $\mu\text{mol/g}$ creatinine), there is no difference in stone formation between the two groups, and, in fact, stone formation is uncommon ([Dello Strologo et al, 2002](#)).

Although stone formers in general have been found to have a higher likelihood of developing chronic kidney disease ([Worcester et al, 2006b](#)), cystine stone formers have been shown to have lower creatinine clearances than other stone formers ([Worcester et al, 2006a](#)). A potential explanation for this finding is the observation

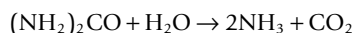
that cystinurics undergo more open surgical procedures, including nephrectomy, than their calcium oxalate stone-forming counterparts (Assimos et al, 2002). Histologically, these patients have been observed to have dilated ducts of Bellini plugged by cystine crystals as well as evidence of cortical glomerulosclerosis and interstitial fibrosis (Evan et al, 2006b).

Infection Stones

Infection stones are composed primarily of magnesium ammonium phosphate hexahydrate ($\text{MgNH}_4\text{PO}_4 \cdot 6\text{H}_2\text{O}$) but may in addition contain calcium phosphate in the form of carbonate apatite ($\text{Ca}_{10}[\text{PO}_4]_6 \cdot \text{CO}_3$). A Swedish geologist discovered magnesium ammonium phosphate in guano and named it "struvite" after his mentor, naturalist H.C.G. von Struve (Griffith and Osborne, 1987). Brown (1901) first theorized that bacteria split urea, thereby setting up the condition for stone formation, and he later isolated *Proteus vulgaris* from a stone. Hager and Magath (1925) postulated that a bacterial enzyme hydrolyzed urea, and Sumner (1926) isolated urease from *Canavalia ensiformis*. It is now well established that struvite stones (magnesium ammonium phosphate) occur only in association with urinary infection by urea-splitting bacteria (Griffith and Musher, 1973).

Pathogenesis

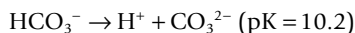
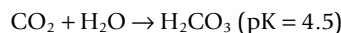
The process of urealys provides an alkaline urinary environment and sufficient concentrations of carbonate and ammonia to induce the formation of infection stones. Because urease is not present in sterile human urine, infection with urease-producing bacteria is a prerequisite for the formation of infection stones. A cascade of chemical reactions generates the conditions conducive to the formation of infection stones. Urinary urea, a constituent of normal urine, is first hydrolyzed to ammonia and carbon dioxide in the presence of bacterial urease:



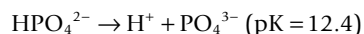
The alkaline urine that results from this reaction (pH 7.2 to 8.0) favors the formation of ammonium:



Under physiologic conditions, the alkaline urine would prevent further generation of ammonium. However, in the presence of urease, ammonia continues to be produced, further increasing urinary pH. The alkaline environment also promotes the hydration of carbon dioxide to carbonic acid, which then dissociates into HCO_3^- and H^+ . Further dissociation of HCO_3^- yields carbonate and another hydrogen ion:



The dissociation of hydrogen phosphate under alkaline conditions provides phosphate, thereby completing the generation of constituent ions for infection stone formation:



This chemical cascade, along with physiologic concentrations of magnesium, provides the constituents necessary for precipitation of struvite. In addition, the concentrations of calcium, phosphate, and carbonate allow precipitation of carbonate apatite and hydroxyapatite, thereby comprising the components of infection stones (Fig. 51-13).

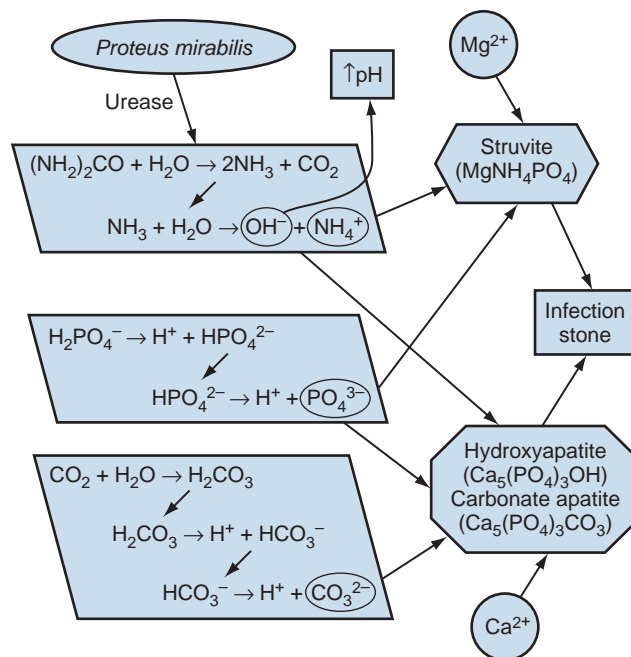


Figure 51-13. Schematic depicting concurrent events leading to struvite stone formation. (From Johnson DB, Pearle MS. Struvite stones. In: Stoller ML, Meng MV, editors. Urinary stone disease: the practical guide to medical and surgical management. Totowa [NJ]: Humana Press; 2007.)

Although infection stones are a direct result of persistent or recurrent infection with urease-producing bacteria, they may also be associated with or exacerbated by urinary obstruction or stasis (Bichler et al, 2002). Therefore growth of infection stones can progress at a rapid rate.

Bacteriology

Although the family Enterobacteriaceae comprises the majority of urease-producing pathogens, a variety of gram-positive and gram-negative bacteria and some yeasts and *Mycoplasma* species have the capacity to synthesize urease (Table 51-3). The most common urease-producing pathogens are *Proteus*, *Klebsiella*, *Pseudomonas*, and *Staphylococcus* species, with *Proteus mirabilis* the most common organism associated with infection stones. Although *Escherichia coli* is a common cause of urinary tract infections, only rare species of *E. coli* produce urease (Bichler et al, 2002).

Bacteria may be involved in stone formation by damaging the mucosal layer of the urinary tract, resulting in both increased bacterial colonization and crystal adherence (Parsons et al, 1984; Grenabo et al, 1988; Djojodimedjo et al, 2013). It has been proposed that ammonium, generated as a result of urealys, may alter the glycosaminoglycan layer present on the surface of the transitional cell layer and significantly increase bacterial adherence to normal bladder mucosa, further exacerbating infection risk (Parsons et al, 1984). In addition, a study in rats found that injury to the bladder mucosa increased crystal adherence to the bladder wall, a process that was potentiated by the presence of common bacteria such as *Proteus*, *E. coli*, *Enterococcus*, and *Ureaplasma urealyticum* (Grenabo et al, 1988). Another potential mechanism for increased stone formation in the presence of bacteria is the finding that particular bacteria, such as *E. coli* and *Proteus*, may alter the activity of urokinase and sialidase, whereas organisms not typically associated with infection stones do not (du Toit et al, 1992). This altered enzymatic activity may explain the frequent association of *E. coli* with stone formation despite lacking urease activity (Holmgren et al, 1989).

TABLE 51-3 Organisms That May Produce Urease

ORGANISMS	USUALLY (>90% OF ISOLATES)	OCCASIONALLY (5%-30% OF ISOLATES)
Gram-negative	<i>Proteus rettgeri</i> <i>Proteus vulgaris</i> <i>Proteus mirabilis</i> <i>Proteus morgani</i> <i>Providencia stuartii</i> <i>Haemophilus influenzae</i> <i>Bordetella pertussis</i> <i>Bacteroides corrodens</i> <i>Yersinia enterocolitica</i> <i>Brucella</i> species	<i>Klebsiella pneumoniae</i> <i>Klebsiella oxytoca</i> <i>Serratia marcescens</i> <i>Haemophilus parainfluenzae</i> <i>Bordetella bronchiseptica</i> <i>Aeromonas hydrophila</i> <i>Pseudomonas aeruginosa</i> <i>Pasteurella</i> species
Gram-positive	<i>Flavobacterium</i> species <i>Staphylococcus aureus</i> <i>Micrococcus</i> <i>Corynebacterium ulcerans</i> <i>Corynebacterium renale</i> <i>Corynebacterium ovis</i> <i>Corynebacterium hofmannii</i>	<i>Staphylococcus epidermidis</i> <i>Bacillus</i> species <i>Corynebacterium murium</i> <i>Corynebacterium equi</i> <i>Peptococcus asaccharolyticus</i> <i>Clostridium tetani</i> <i>Mycobacterium rhodochrous</i> group
Mycoplasma	T-strain <i>Mycoplasma</i> <i>Ureaplasma urealyticum</i>	
Yeasts	<i>Cryptococcus</i> <i>Rhodotorula</i> <i>Sporobolomyces</i> <i>Candida humicola</i> <i>Trichosporon cutaneum</i>	

From Gleeson MJ, Griffith DP. Infection stones. In: Resnick MI, Pak CYC, editors. Urolithiasis: a medical and surgical reference. Philadelphia: Saunders; 1990. p. 115.

Epidemiology

Although infection stones comprise only 5% to 15% of all stones (Levy et al, 1995), they have been thought to be the most common component of staghorn calculi. However, a recent analysis of the composition of 52 staghorn calculi demonstrated that only 44% of stones were infection stones, while 56% of stones were metabolic, with calcium phosphate the most common (Viprakasit et al, 2011). Moreover, struvite-carbonate apatite was the most common stone composition among a population of African-American stone formers in Ohio, accounting for a third of stones in males and nearly half of stones in females in this population (Sarmina et al, 1987). **Because infection stones occur most commonly in those prone to frequent urinary tract infections, struvite stones occur more often in women than men by a ratio of 2:1 (Resnick, 1981).** Other populations at risk of recurrent infection include the elderly (Kohri et al, 1991), premature infants or infants born with congenital urinary tract malformation, diabetics, and those with urinary stasis as a result of urinary tract obstruction, urinary diversion, or neurologic disorders. Spinal cord-injured patients are at particular risk for both infection and metabolic stones owing to neurogenic urinary tract dysfunction and hypercalciuria related to immobility. Patients with a functionally complete cord transection are at highest risk of developing a staghorn calculus (DeVivo et al, 1984).

Miscellaneous Stones

Xanthine and Dihydroxyadenine Stones

Xanthine stones comprise a rare stone type that is often confused with uric acid stones because both are radiolucent. They form as a result of an inherited disorder in the catabolic enzyme xanthine dehydrogenase (XDH) or xanthine oxidase, which catalyzes the

conversion of xanthine to uric acid. Because xanthine is poorly soluble in urine, the high levels of xanthine that accumulate in XDH deficiency lead to xanthine stones (Cameron et al, 1993).

Allopurinol, which inhibits XDH and is consequently used to treat hyperuricemia and hyperuricosuria, can, at high levels, predispose to xanthine stones. This side effect is distinctly uncommon because the drug causes only partial inhibition of the enzyme and rarely reduces serum uric acid to levels lower than 3 mg/dL. Patients with Lesch-Nyhan syndrome who suffer from an inherited deficiency of the purine salvage enzyme HGPRT are occasionally treated with high enough doses of allopurinol to place them at risk for xanthine stones (Cameron et al, 1993).

Children with inherited deficiencies of adenine phosphoribosyltransferase can also present in infancy with renal complications and stones (Cameron et al, 1993). Children with adenine phosphoribosyltransferase deficiency may be difficult to distinguish from those with HGPRT deficiency because the insoluble product excreted, 2,8-dihydroxyadenine, is chemically similar to uric acid. Like xanthine stones, 2,8-dihydroxyadenine stones are extremely insoluble at any pH, but stone formation can be averted by the administration of allopurinol.

Ammonium Acid Urate Stones

Ammonium acid urate stones represent less than 1% of all stones (Herring, 1962; Kohn et al, 1986). In developing countries, however, endemic ammonium acid urate urolithiasis is still observed because it comprises bladder calculi in children (Minon Cifuentes and Pourmand, 1983; Vanwaeyenbergh et al, 1995). Conditions associated with ammonium acid urate crystallization include laxative abuse, recurrent urinary tract infection, recurrent uric acid stone formation, and inflammatory bowel disease (Dick et al, 1990; Pichette et al, 1997; Soble et al, 1999). Soble and

colleagues (1999) reviewed their experience with 44 patients identified as having stones composed of ammonium acid urate, although the ammonium acid urate contribution varied from 2% to 60%. Among these patients, 25% had a history of inflammatory bowel disease, 14% had a history of significant laxative abuse, 41% were morbidly obese, 36% had a history of recurrent urinary tract infections, and 21% had a history of recurrent uric acid stones. The subgroup of patients with inflammatory bowel disease and ileostomy as the sole clinical risk factor had the highest mean ammonium acid urate content (39%), and ammonium acid urate constituted the predominant stone type in seven of eight such patients.

Patients with ileostomy after colectomy have markedly reduced urinary volume, pH, and sodium and are not prone to hyperoxaluria as are other individuals with bowel disease because the colon is the main site of dietary oxalate absorption (Kennedy et al, 1982). Therefore these patients are prone to ammonium acid urate and uric acid stones rather than calcium oxalate stones. The underlying pathophysiologic mechanism of ammonium acid urate stone formation attributable to laxative abuse has been postulated to be dehydration resulting from gastrointestinal fluid loss, causing intracellular acidosis and enhanced ammonia excretion. Because urinary sodium is low in the setting of laxative use, urate complexes with abundant ammonia, thereby leading to urinary supersaturation of ammonium acid urate.

Bowyer and colleagues (1979) demonstrated that ammonium acid urate precipitation is favored at pH 6.2 to 6.3. The association of recurrent uric acid stones with ammonium acid urate stones is likely related to the shared risk factors of low urine volume and pH. Soble and colleagues (1999) identified nine patients with stones of mixed composition, containing both uric acid and ammonium acid urate (mean ammonium acid urate content 27%), although eight of the nine patients had uric acid as the predominant constituent (range 40% to 95%). They theorized that transient fluctuations in urinary acidity and ammonium and sodium levels may shift the balance between uric acid and sodium- or ammonium-bound urate excretion.

Among the ammonium acid urate stone producers in Soble and colleagues' (1999) study, obesity (BMI >30) was the most prevalent characteristic in 41% of patients, after excluding patients with inflammatory bowel disease and ileostomy (none of whom was obese). Indeed, a statistically significant correlation was found between BMI and ammonium acid urate content. This is consistent with recent evidence suggesting a correlation between stone risk and obesity (Powell et al, 2000) and between obesity and low urine pH (Maalouf et al, 2004b).

Matrix Stones

The association between urinary proteins and stone formation has long been recognized. Early experiments demonstrated that protein suspensions could promote calcium stone formation (Kimura et al, 1976). Both osteopontin and calprotectin have been shown to play a role in forming the matrix structure of urinary calcium stones (Tawada et al, 1999; Kleinman et al, 2004). However, stones composed predominantly of matrix are rare; these "stones" are typically radiolucent and may be mistaken for tumor or uric acid stones depending on the imaging study obtained (Bani-Hani et al, 2005).

The literature regarding matrix stones is sparse, consisting mostly of anecdotal case reports (Boyce and King, 1963; Allen and Spence, 1966; Bani-Hani et al, 2005). The matrix component of calcium-based stones comprises only 2.5% of the dry weight of the stone, whereas pure matrix stones may contain upwards of 65% protein (Allen and Spence, 1966). Boyce and Garvey (1956) determined that the composition of matrix stones was approximately two-thirds mucoprotein and one-third mucopolysaccharide by weight. Furthermore, they found that the matrix substance in crystalline calculi is closely related to the matrix substance found in matrix calculi. However, it is unclear why some matrix calculi fail to fully calcify.

Although some have theorized that reduced urinary calcium levels may account for the preferential formation of matrix stones (Boyce and King, 1959; Allen and Spence, 1966), a recent metabolic evaluation of five patients with matrix stones revealed normal urinary calcium excretion (Bani-Hani et al, 2005). In renal failure patients undergoing dialysis, proteinuria may contribute to an increased risk of matrix stone formation. In these patients, matrix stones have been shown to include both microfibrillar protein (Bommer et al, 1979) and β_2 -microglobulin (Linke et al, 1986). Recent analysis of the matrix stone from a single patient with *Proteus* urinary tract infection by scanning electron microscopy revealed fibrous netlike laminations containing bacterial, cellular, and crystalline material (Canales et al, 2009). Proteomic analysis identified 33 unique proteins, of which 90% had not been previously reported as components of matrix stones and 70% are considered inflammatory or defensive in nature.

Medication-Related Stones

Drug-induced stones form either directly as a result of precipitation and crystallization of a drug or its metabolite or indirectly by altering the urinary environment, making it favorable for metabolic stone formation (Daudon, 1999). Drugs such as loop diuretics (furosemide, bumetanide) and carbonic anhydrase inhibitors (acetazolamide, topiramate, and zonisamide) contribute to calcium stone formation (Matlaga et al, 2003). Ephedrine (Powell et al, 1998; Assimos et al, 1999), triamterene (Ettinger et al, 1980; Carr et al, 1990), guaifenesin (Assimos et al, 1999), silicate (Farrer and Rajfer, 1984), indinavir (Bruce et al, 1997; Gentle et al, 1997), and ciprofloxacin (Matlaga et al, 2003) have all been associated with stones composed of the drug itself in patients who consumed excessive amounts.

Medications That Directly Promote Stone Formation

Antiretroviral Agents. Indinavir sulfate is a protease inhibitor that has been shown to be effective in increasing CD4+ cell counts and decreasing HIV-RNA titers in patients infected with human immunodeficiency virus (HIV) or who have acquired immunodeficiency syndrome (Wu and Stoller, 2000). However, indinavir poses a risk for indinavir stone formation in treated patients, leading to an estimated incidence of 4% to 13% (Wu and Stoller, 2000). Indinavir is rapidly absorbed from the intestine, achieving peak plasma concentrations in less than 1 hour. The drug is metabolized in the liver and eliminated primarily in the stool, but about half of the ingested dose of indinavir is excreted essentially unchanged in the urine (Sutherland et al, 1997). In pure form, indinavir is relatively insoluble in aqueous solution, although the solubility is pH dependent. With a pK_a of 5.5, indinavir has a solubility of 0.300 mg/mL at pH 5, 0.035 mg/mL at pH 6.0, and 0.020 mg/mL at pH 7.0 (Daudon et al, 1997; Hermieu et al, 1999). Although indinavir solubility increases significantly at pH levels below 5.5, the standard dose of indinavir in an individual with an average urine volume and pH would produce a urinary concentration of indinavir near the limit of solubility 3 hours after ingestion (Daudon et al, 1997). As such, individuals taking indinavir on a regular basis are at high risk of producing indinavir stones because of the high urinary excretion and poor solubility of the drug at physiologic urinary pH. Initiation of indinavir in 54 asymptomatic, indinavir-naïve, HIV-positive individuals led to indinavir crystalluria in 67% of subjects (Gagnon et al, 2000). After the first 2 weeks, indinavir crystalluria remained constant at a frequency of approximately 25% of urine sediments examined at each test point.

Indinavir is now an infrequently used antiretroviral agent, replaced with newer generation agents. Kidney stone formation has been associated with a number of newer antiretroviral agents, including lopinavir-ritonavir (Doco-Lecompte et al, 2004), ritonavir-boosted atazanavir (Rockwood et al, 2011; Hamada et al, 2012), nelfinavir (Engeler et al, 2002), and amprenavir (Feicke et al, 2008). Ritonavir-boosted atazanavir, currently one of the more widely used agents, has been shown to have a nearly 7% incidence of stone formation, higher than most of the other new agents

(Rockwood et al, 2011; Hamada et al, 2012). Because stone formation associated with these agents is thought to be the result of high urinary excretion and low solubility of the drug in urine, agents with higher excretion rates are associated with higher rates of stone formation; 7% of ritonavir-boosted atazanavir is excreted in the urine unmetabolized versus less than 3% for nelfinavir and amprenavir, which have lower rates of stone formation.

Triamterene. Triamterene is a potassium-sparing diuretic commonly used for the treatment of hypertension. It is an uncommon stone composition, accounting for only 0.4% of 50,000 calculi in one report, with only one third of the stones composed largely or entirely of triamterene (Ettinger et al, 1980). An evaluation of triamterene stone formers revealed no significant differences between patients and matched control subjects with respect to total recovery of the drug, hourly excretion patterns, and urinary concentrations of triamterene and its sulfate metabolite (Ettinger, 1985). Approximately half of all subjects tested demonstrated urine concentrations of the sulfate metabolite that exceeded the observed solubility limit. One investigation determined that triamterene is more likely to become incorporated into existing stones or stone nuclei than to promote stone formation independently (Werness et al, 1982). This may account for the rarity of this stone in nonrecurrent stone formers, as well as the finding that hospitalization rates for urinary stones did not differ between patients prescribed triamterene and hydrochlorothiazide (Jick et al, 1982).

Guaifenesin and Ephedrine. Consumption of large quantities of guaifenesin and ephedrine can lead to stones composed of their metabolites (Powell et al, 1998; Assimios et al, 1999). Most of the patients reported to have these stones are found to have consumed large quantities of over-the-counter preparations of cold medicine for the stimulatory properties of the ephedrine component, and a history of drug abuse is not uncommon (Assimios et al, 1999). Herbal ecstasy and ma huang are also popular ephedrine-containing preparations that are abused for stimulatory properties (Mack, 1997). Unfortunately, chronic ephedrine use leads to tachyphylaxis and prompts the use of increasing doses to achieve a comparable effect. Serious toxicity may result from ephedrine abuse, including death, cardiomyopathy, stroke, hypertension, and seizures.

Silicate Stones. Silica is a common element seen in vegetables, whole grains, seafood, and even drinking water that is easily excreted in the urine (Matlaga et al, 2003). Silicate stones are extremely rare and have been associated with consumption of large amounts of silicate-containing antacids such as magnesium trisilicate (Haddad and Kouyoumdjian, 1986; Daudon, 1999).

Medications That Indirectly Promote Stone Formation. Other medications indirectly promote stone formation by increasing urinary stone risk factors. Corticosteroids, vitamin D, and phosphate-binding antacids can induce hypercalciuria. **Thiazides cause intracellular acidosis and subsequent hypocitraturia** (Nicar et al, 1984). Loop diuretics such as furosemide and bumetanide inhibit sodium and calcium resorption in the thick ascending loop of Henle, which in addition to a diuretic effect results in hypercalciuria (Matlaga et al, 2003). Renal calculi have been identified in up to 64% of low-birth-weight infants receiving furosemide therapy, and stones are consistently composed of calcium oxalate (Hufnagle et al, 1982; Shukla et al, 2001).

Carbonic anhydrase inhibitors such as acetazolamide block resorption of sodium bicarbonate at multiple segments in the nephron, thereby inducing a metabolic acidosis and leading to urinary alkalinization (Parfitt, 1969). Chronic use results in hypocitraturia, hypercalciuria, and increased risk for calcium phosphate stones (Matlaga et al, 2003). Topiramate is a widely used drug approved for the treatment of seizures and prophylaxis of migraine headaches but is additionally increasingly used for the treatment of a variety of other disorders, such as obesity, neuropathic pain, alcoholism, type 2 diabetes, cigarette smoking, and cocaine dependence. Topiramate inhibits several isoenzymes of carbonic anhydrase with subsequent stone-potentiating effects (Vega et al, 2007). Although the incidence of calcium stones with topiramate use in adults based on short-term clinical trials was reported

as 1.2% to 1.5% in the package insert, this number is thought to be an underestimate. Indeed, a recent retrospective study identified 150 individuals who were treated with topiramate out of 1500 adults in an electronic database from an epilepsy monitoring unit, among whom 75 were successfully contacted and queried regarding their kidney stone history (Maalouf et al, 2011). A total of eight subjects reported a diagnosis of kidney stones since the start of topiramate use, resulting in 10.7% prevalence. Furthermore, 15 patients among the 67 patients without a history of stones from the same study group were evaluated with computed tomographic imaging at an average of 43 months of topiramate use, revealing a 20% prevalence of asymptomatic stones, suggesting the problem is much more prevalent than previously suspected.

The risk of stone formation with topiramate use is related to its action as a carbonic anhydrase inhibitor. A recent cross-sectional study comparing 32 topiramate-treated patients with 50 normal controls revealed systemic metabolic acidosis, increased fractional excretion of bicarbonate, higher urine pH, and lower urinary citrate excretion in the topiramate-treated group (Welch et al, 2006). Likewise, in a short-term longitudinal study of seven patients before and 3 months after initiation of topiramate, significant metabolic acidosis and increased urine pH, bicarbonate excretion, and saturation of calcium phosphate were seen with initiation of the drug (Welch et al, 2006). Furthermore, topiramate-induced hypocitraturia demonstrates a dose-dependent response that additionally correlates inversely with duration of treatment (Kaplon et al, 2011). Zonisamide, a sulfonamide agent that also exerts an antiepileptic effect and has a weak carbonic anhydrase activity, has also been associated with increased risk of kidney stone formation (Zaccara et al, 2011).

Laxative abuse has also been associated with stone formation because persistent diarrhea increases the risk of ammonium acid urate stones. Patients abusing laxatives excrete large amounts of ammonia in the urine to eliminate excess acid, resulting in low urine pH. In the setting of low urine volume resulting from dehydration and low urinary sodium from laxative use, the urine of these patients can be highly supersaturated with respect to ammonium urate (Soble et al, 1999; Matlaga et al, 2003). Lastly, cytotoxic agents promote a high cell turnover, resulting in urinary excretion of large amounts of uric acid.

Anatomic Predisposition to Stones

Patients with anatomic anomalies associated with urinary obstruction and/or stasis have been noted to have a high incidence of associated stones. It has long been debated whether the predisposition to stone disease is a result of urinary stasis and delayed transit time through the nephron, leading to higher likelihood of crystal formation and retention, or if these patients form stones as a result of the same or unique metabolic abnormalities associated with stone formation.

Ureteropelvic Junction Obstruction

The incidence of renal calculi in patients with ureteropelvic junction obstruction (UPJO) is nearly 20% (David and Lavengood, 1975; Lowe and Marshall, 1984; Clark and Malek, 1987). However, Husmann and colleagues (1995) provided several lines of evidence to suggest that patients with UPJO and concurrent renal calculi carry the same metabolic risks as other stone formers in the general population. First, among 111 adult patients with UPJO and stones for whom long-term follow-up was available, 62% developed recurrent stones after treatment of the UPJO and 43% of the recurrences occurred in the contralateral kidney. These findings suggest that a metabolic predisposition persisted despite correction of the obstruction. Second, 76% of 42 patients with noninfectious stones who underwent a metabolic evaluation demonstrated an underlying metabolic abnormality that could account for the stones, a rate comparable to that of other stone formers (Pak, 1982; Yagisawa et al, 1999). Finally, the type and distribution of metabolic

abnormalities identified in these patients were similar to those of the general stone-forming population: hypercalciuria in 46% of patients, hyperuricosuria in 11%, hypocitraturia in 13%, primary hyperparathyroidism in 13%, and RTA in 3% (Pak et al, 1980). Treatment of patients with identifiable abnormalities significantly reduced their rate of recurrence, from 55% in patients managed conservatively to 17% in treated patients.

Matin and Stroom (2000) also performed metabolic evaluations before definitive repair in 47 patients with UPJO with or without associated stones. An identifiable abnormality was found in 67% of the stone patients compared with only 33% of the control group; urinary calcium and the incidence of hypercalciuria and hyperuricosuria were significantly higher in the patients with stones compared with the controls, further underscoring the contribution of pathophysiologic background to stone-forming risk in patients with anatomic abnormalities.

Similar findings in two series of children with UPJO and concurrent renal calculi further support a metabolic contribution to stone formation in the presence of renal obstruction. Tekin and colleagues (2001) prospectively compared children with UPJO with and without stones to a control group of calcium stone formers without UPJO. Both groups of stone formers, those with and without UPJO, exhibited significantly higher urinary levels of citrate and lower levels of oxalate compared with the non-stone-forming children with UPJO. Husmann and colleagues (1996) reported a 70-fold increased risk of stone formation in the pediatric population with UPJO compared with normal children. Among 22 children who underwent treatment of their stones and UPJO, 68% of patients with nonstruvite stones developed a recurrence after surgical treatment, and a metabolic abnormality was identified in 68%. Among the seven patients with nonstruvite renal calculi who did not experience a recurrence, only 29% had an identifiable metabolic abnormality. Thus correction of the UPJO did not prevent recurrent stones in most patients, further emphasizing the role of underlying metabolic abnormalities in the etiology of renal calculi in patients with UPJO.

Horseshoe Kidneys

Horseshoe kidneys occur with a prevalence of 0.25% but have an associated rate of renal calculi of 20% (Janetschek and Kunzel, 1988; Cussenot et al, 1992). Because of the high insertion of the ureter into the renal pelvis, there is a relative impairment of renal drainage, predisposing to UPJO. Therefore the risk of stone formation has been attributed to urinary stasis rather than to metabolic derangements. Raj and colleagues (2004) reviewed 37 patients with horseshoe kidneys and stones and identified at least one metabolic abnormality in all 11 patients in whom 24-hour urine collections were available. Compared with a group of stone formers with normal renal anatomy, the patients with horseshoe kidneys exhibited a similar distribution of metabolic derangements, with the exception that hypocitraturia was over-represented (55% in the patients with horseshoe kidneys vs. 31% in controls). It seems clear that although urinary stasis likely contributes to a propensity toward stone formation in patients with horseshoe kidneys, an underlying metabolic abnormality is required for stone formation to occur.

Caliceal Diverticula

Caliceal diverticula are associated with stones in up to 40% of patients (Middleton and Pfister, 1974). Like stones in horseshoe kidneys, it is unclear whether the stones are caused by local anatomic obstruction and urinary stasis or are due to underlying metabolic factors. Two groups of investigators have addressed this issue. Hsu and Stroom (1998) identified metabolic abnormalities, including hypercalciuria, hyperoxaluria, and hyperuricosuria, in 50% of 14 patients with stone-bearing caliceal diverticula. Notably, 64% of patients reported a history of synchronous or metachronous stones at a site distinct from the diverticulum, supporting the idea of underlying metabolic risk as a contributing cause of the stones. In

contrast, Liatsikos and colleagues (2000) compared 49 patients with caliceal diverticula and stones with 44 stone formers without diverticula and found a low rate of metabolic abnormalities in both groups (25% in patients with diverticula and 23% in the control patients). Of note, however, the metabolic evaluation in this study involved measurement of only urinary volume, creatinine, calcium, phosphorus, oxalate, and uric acid. Because low urinary pH and hypocitraturia are identified in approximately 10% and 28% of recurrent stone formers, respectively (Levy et al, 1995), the number of metabolic abnormalities reported in this series is likely under-represented. Finally, a study by Matlaga and colleagues (2007) evaluated 29 patients who underwent percutaneous treatment of stone-bearing calyceal diverticuli and compared their 24-hour urine collections with those of 245 calcium oxalate stone formers and 162 normal controls. The urinary stone risk parameters of the patients with calyceal diverticular stones were similar to those of calcium oxalate stone formers, who demonstrated significantly greater hypercalciuria and higher calcium oxalate supersaturation compared with normal controls. Interestingly, urine aspirated directly from the diverticulum had lower calcium oxalate supersaturation than that of urine obtained from the ipsilateral and contralateral renal pelvis. These findings imply that calyceal diverticular calculi arise from a combination of metabolic abnormalities and urinary stasis.

Stones formed in caliceal diverticula are mainly composed of calcium oxalate monohydrate, but they can also contain struvite-carbonate apatite owing to an infectious component. Concomitant urinary tract infection is found in up to 40% of cases, with *E. coli*, *Proteus*, and *Pseudomonas* being the most frequent pathogens (Monreal et al, 1998; Daudon et al, 2003).

Medullary Sponge Kidney

Medullary sponge kidney (MSK) is a disorder characterized by ectasia of the renal collecting ducts. Nephrocalcinosis and renal calculi are frequent complications of MSK (Lavan et al, 1971; Parks et al, 1982; Sage et al, 1982; Ginalska et al, 1990), but the exact risk factors for stone formation are not clearly understood. Although recurrent infection and urinary stasis within the ectatic tubules pose a risk for stone formation (Ginalska et al, 1990), renal tubular defects, including hypercalciuria, impaired renal concentrating ability, and defective urinary acidification after an ammonium chloride load, have been detected in some MSK patients (Granberg et al, 1971), further potentiating the risk of stone formation. Osther and colleagues (1988) performed ammonium chloride load tests in 13 patients with MSK and found renal acidification defects in 9 patients: 8 with distal RTA and 1 with proximal RTA. Likewise, Higashihara and colleagues (1984) reported renal acidification defects in 80% of 11 MSK patients (36% with distal RTA) and impaired concentrating ability in 90% of these 11 patients. The identification of mutations in the hydrogen proton pump genes *ATP6V1B1* and *ATP6V0A4* in two patients with MSK lends further support to an association between MSK and distal RTA (Carboni et al, 2009).

Despite these findings, three studies performed specifically on MSK patients with nephrolithiasis revealed no case of associated RTA (O'Neill et al, 1981; Parks et al, 1982; Yagisawa et al, 2001). O'Neill and colleagues (1981) identified hypercalciuria as the most common metabolic abnormality in 17 patients with MSK and nephrolithiasis, occurring in 88% of patients and attributed to absorptive hypercalciuria in most cases (59%). The spectrum of abnormalities in these patients was judged to be comparable with that of the general stone-forming population. Other investigators identified hypercalciuria less frequently, in only 9% to 44% of MSK patients with nephrolithiasis. In some cases, the cause of the hypercalciuria was attributed to renal calcium leak by which renal calcium reabsorption was presumed to be impaired by damaged renal tubules (Yendt, 1981; Parks et al, 1982; Yagisawa et al, 2001). Yagisawa and coworkers (2001) identified hypocitraturia as the most common metabolic abnormality, occurring in 77% of 22 MSK patients. Kinoshita (1990) likewise reported hypocitraturia in

58% of MSK patients. Thus it appears that although renal acidification defects may be associated with MSK, hypercalciuria and hypocitraturia are likely contributing factors even in the absence of RTA.

Stones in Pregnancy

Symptomatic stones during pregnancy occur at a rate of 1 in 250 (Lewis et al, 2003) to 1 in 3000 (Butler et al, 2000) pregnant women. Like stones in nonpregnant women, they occur more commonly in white than African-American women (Lewis et al, 2003). The majority of symptomatic stones occur in the second and third trimesters of pregnancy, heralded by symptoms of flank pain or hematuria (Stothers and Lee, 1992; Butler et al, 2000; Biyani and Joyce, 2002; Lewis et al, 2003). The diagnosis can be difficult in this patient population; up to 28% of women are misdiagnosed with appendicitis, diverticulitis, or placental abruption (Stothers and Lee, 1992).

A number of physiologic changes occur during pregnancy. Physiologic hydronephrosis occurs in up to 90% of pregnant women and persists up to 4 to 6 weeks postpartum (Swanson et al, 1995). Although hydronephrosis may be in part due to the effects of progesterone, compression of the ureters by the gravid uterus is at least a contributory, if not the primary, factor (Gorton and Whitfield, 1997; McAleer and Loughlin, 2004). Dilation is typically greater in the right ureter as a result of the engorged uterine vein and derotation of the enlarged uterus (Biyani and Joyce, 2002). The physiologic dilation may promote crystallization as a result of urinary stasis (Swanson et al, 1995), and the increased renal pelvic pressure has been suggested to increase the likelihood of stone movement and symptoms.

Important physiologic changes in the kidney occur during pregnancy and modulate urinary stone risk factors. Renal blood flow increases, leading to a 30% to 50% rise in glomerular filtration rate, which subsequently increases the filtered loads of calcium, sodium, and uric acid (McAleer and Loughlin, 2004). Hypercalciuria is further enhanced by placental production of $1,25(\text{OH})_2\text{D}_3$, which increases intestinal calcium absorption and secondarily suppresses PTH (Gertner et al, 1986; Biyani and Joyce, 2002). Hyperuricosuria has also been reported as a result of increased filtered load of uric acid (Swanson et al, 1995).

Despite increases in a number of stone-inducing analytes, pregnant women have been shown to excrete increased amounts of inhibitors such as citrate, magnesium, and glycoproteins (Mairkranz et al, 1987; Smith et al, 2001). Therefore the overall risk of stone formation has been reported to be similar in gravid and non-gravid women (Coe et al, 1978; Drago et al, 1982). Although some studies found that the stone composition is similar between gravid and nongravid women, one multi-institutional study found that 74% of stones from pregnant women were composed predominantly of calcium phosphate and 26% were predominantly calcium oxalate (Coe et al, 1978; Drago et al, 1982; Ross et al, 2008).

KEY POINTS: PATHOGENESIS

- Absorptive hypercalciuria is characterized by normal serum calcium, normal or suppressed PTH, normal fasting urinary calcium, and elevated urinary calcium.
- Renal hypercalciuria is due to impaired renal calcium reabsorption, which stimulates PTH secretion and leads to fasting hypercalciuria.
- Resorptive hypercalciuria is primarily due to primary hyperparathyroidism but may be seen with granulomatous diseases that elaborate $1,25(\text{OH})_2\text{D}_3$.
- The most important determinant of uric acid stone formation is low urinary pH.
- Low urine pH seen in uric acid stone formers is likely due to impaired ammoniogenesis as a result of insulin resistance and excess acid production.
- In distal RTA, a defective H^+ -ATPase accounts for excretion of excess acid into the distal tubule.
- Formation of infection stones requires alkaline urine that can be achieved only with infection with urease-producing bacteria.

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The complete reference list is available online at www.expertconsult.com.



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Diagnostic Evaluation of Nephrolithiasis

Use of Stone Analysis to Determine Metabolic Abnormalities

Role of Imaging in Determining Stone Composition

Economics of Metabolic Evaluation

Classification of Nephrolithiasis and Diagnostic Criteria

Conservative Medical Management

Selective Medical Therapy of Nephrolithiasis

Miscellaneous Scenarios

Summary

DIAGNOSTIC EVALUATION OF NEPHROLITHIASIS

Symptomatic urinary calculi are undoubtedly associated with significant patient discomfort. Despite the ability of many stones to pass spontaneously, the surgical treatments for calculi may themselves be morbid. Patients may suffer financial pain because of the expense of emergency department visits, office visits, surgical procedures, or time lost from work, in addition to the physical sequelae. Logically, most patients are interested in learning how to prevent a recurrence of such an episode. Through even a rudimentary understanding of the physiologic causes of urinary calculus formation, physicians may offer a straightforward approach to elucidating the metabolic basis of nephrolithiasis for any given patient. This evaluation should be simple to perform, it must be economically viable, and it should provide information that can be applied toward a selective, rational therapy of stone disease (Pak et al, 1980a).

Any evaluation should be able to identify associated metabolic disorders responsible for recurrent stone disease. These metabolic problems include distal renal tubular acidosis (RTA), primary hyperparathyroidism, enteric hyperoxaluria, cystinuria, and gouty diathesis. In many of these relatively uncommon conditions, it is generally agreed that selective medical therapy is indicated not only to prevent further stone formation but also to correct underlying physiologic disturbances that may lead to nonrenal complications (Pak et al, 2002a, 2003a).

Selection of Patients for Metabolic Evaluation

Debate continues regarding which patients require an extensive metabolic evaluation. First-time stone formers often have been estimated to have a 50% risk for recurrence within the subsequent 10 years (Uribarri et al, 1989). In two separate studies, Ljunghall and Danielson attempted to measure the incidence of a stone recurrence in a Northern European population (Ljunghall and Danielson, 1984; Ljunghall, 1987). A retrospective review estimated the chance of recurrence at nearly 50% at 5 years, whereas a prospective evaluation noted a lower overall rate of 53% within 8 years. Males had both a higher incidence of calculi overall and a higher recurrence rate. Patients had a higher risk for repeat stones in the years immediately after their first episode. It is not completely apparent whether these were preexisting stones that passed later or whether they represent the formation of new calculi.

In fact, recent evidence suggests that the prevalence of kidney stones has nearly doubled in the United States between 1994 and 2010 (Scales et al, 2012). Along with the overall increase in preva-

lence of kidney stones, there is an increasingly higher percentage of female stone formers (Scales et al, 2007). Other investigators have confirmed this finding with the reported ratio of male to female stone formers consistent between reports at 1.3:1 and 1.2:1 (Scales et al, 2007; Nowfar et al, 2011). In fact, the largest epidemiologic study to date suggests the male-to-female ratio of stone formers has now decreased to 1.45:1, not as a result of a decrease in male stone formation but as a significant increase in female stone formation (Pearle et al, 2005). This finding is thought to be due to changes in diet and lifestyle.

First-Time Stone Formers

Considering that dietary and fluid manipulation alone can reduce rates of stone recurrence, some suggest that first-time stone formers should be provided empirical fluid and dietary recommendations until they suffer a recurrence (Borghi et al, 1996). Indeed, studies of single-stone formers placed on a conservative program of high fluid intake alone or combined with avoidance of dietary excess, revealed a low incidence of recurrent stone disease (Hosking et al, 1983). Calling this finding the *stone clinic effect*, Hosking and colleagues noted metabolic inactivity in nearly 60% of all patients followed for over 5 years.

In comparison, Pak (1982) found that single-stone formers have an equally high incidence of metabolic abnormalities as recurrent stone formers. Furthermore, these derangements are just as severe, leading the authors to conclude that single-stone formers should undergo the same evaluation as recurrent stone formers. Similar findings were reported in a series of 182 patients, in which half of the patients had hypercalciuria or hyperuricosuria and roughly 20% had a systemic disorder that predisposed the patients to the formation of calculi (Strauss et al, 1982b). The remainder, 29.1%, had no metabolic disorder. Patients with single stones tended to be older when they passed their stones and required a greater rate of intervention to treat the calculus. The recurrence for both groups of patients was very similar (~10% at 3 years). Because the authors did not note substantial differences between solitary and recurrent stone disease, they recommended that first-time stone formers be evaluated similar to patients with recurrent stone disease. A more recent study comparing the frequencies of metabolic abnormalities between first-time stone formers and recurrent stone formers found no difference between the two groups (Eisner et al, 2012). Approximately 40% of both first-time and recurrent stone formers had hypercalciuria, 45% of both groups had hypocitraturia, and approximately 30% had hyperoxaluria. The authors suggest it is reasonable to perform a full metabolic evaluation in first-time stone formers.

This approach has been partially refuted by [Yagisawa and colleagues \(1998\)](#), who noted that men with recurrent calculi had a higher rate of metabolic derangements than first-time stone formers. Although women had a trend toward the same pattern, this achieved statistical significance only with regard to decreased levels of urinary citrate (hypocitraturia). A more complete discussion of the economic aspects surrounding the decision to perform a metabolic evaluation is found later in this chapter.

Importantly, the formation of a first stone may be the harbinger of a more severe underlying systemic disorder such as RTA, bone disease, or hypercalcemia resulting from hyperparathyroidism. In such patients, metabolic evaluation is justified solely to make the correct diagnosis to prevent extrarenal complications. With the development of reliable parathyroid hormone assays, it is unacceptable to wait for bone loss before embarking on curative therapy. Although the clinical significance of normocalcemic hyperparathyroidism has been questioned and is frequently simply observed, current practice favors the treatment of patients with at least 1 mg per deciliter above the upper limit of normal, marked hypercalciuria (urinary calcium excretion of more than 400 mg/day), reduced bone density, and an age of less than 50 years ([Bilezikian and Silverberg, 2004](#)).

The decision to thoroughly investigate a first-time stone former should ideally be shared by the physician and the patient. Whereas some first-time stone formers will readily accept and follow conservative therapy, others may elect to undergo a thorough evaluation. It is quite reasonable to determine the extent of evaluation according to the estimation of potential/risk for recurrent stone formation ([Smith, 1984](#)). Patients at higher risk for repeat episodes are those with a family history of stones and those with intestinal disease (particularly when causing chronic diarrheal states), pathologic skeletal fractures, osteoporosis, urinary tract infection (UTI), or gout. In these patients, an extensive evaluation is recommended. In addition, obese patients with stones, particularly obese women, have significantly elevated risk for recurrence and should be given consideration for metabolic evaluation ([Taylor et al, 2005](#)). Diabetes has been correlated with an increased risk for stone disease, and patients with diabetes and stones, particularly those with poorly controlled diabetes, should be considered for a full metabolic evaluation ([Weinberg et al, 2014](#)). Any patients with stones composed of cystine, uric acid, or struvite should undergo a complete metabolic workup.

All children should be required to undergo a complete investigation because they have been found to have a significant risk for underlying metabolic disturbances ([Polito et al, 2000](#); [Tekin et al, 2001](#); [Pietrow et al, 2002](#); [Coward et al, 2003](#); [Bartosh, 2004](#)). Pediatric patients with stones have a high rate of underlying metabolic abnormalities. Moreover, pediatric patients with metabolic abnormalities have been shown to have recurrence at a higher rate than those without metabolic risk factors ([Abhishek et al, 2013](#)). Additionally, these young patients have more at stake, because early, repeated episodes of urinary obstruction, UTI, and repeated radiographic imaging all have associated morbidities.

African-Americans previously have been observed to have a significantly lower incidence of nephrolithiasis than their white counterparts. Indeed, in a study by [Sarmina and colleagues \(1987\)](#), white patients had urinary calculi three to four times as often as black subjects. In contrast to findings of male predominance of stones in whites, [Michaels and associates \(1994\)](#) reported that women made up roughly 60% of the African-American patients with stones. [Sarmina and colleagues \(1987\)](#) found a higher incidence of infection calculi in the African-American population, whereas these stone types were excluded from analysis in the study by [Michaels and associates \(1994\)](#).

Additional support that race and ethnicity play a role in stone disease is provided by [Mente and coworkers \(2007\)](#). Compared to Europeans, East Asian and African patients had a decreased relative risk for calcium nephrolithiasis, and Arabic, West Indian, West Asian, and Latin American patients had an increased relative risk. The authors found differing urinary profiles for a variety of the ethnicities reported when compared to those of Europeans.

BOX 52-1 Indications for a Metabolic Stone Evaluation

Recurrent stone formers
Strong family history of stones
Intestinal disease (particularly chronic diarrhea)
Pathologic skeletal fractures
Osteoporosis
History of urinary tract infection with calculi
Personal history of gout
Infirm health (unable to tolerate repeat stone episodes)
Solitary kidney
Anatomic abnormalities
Renal insufficiency
Stones composed of cystine, uric acid, struvite

However, despite the decreased risk for calcium stone formation, patients of African ancestry demonstrated no significant differences in urinary metabolic derangements. A more recent study looking at the prevalence of stones in the United States between 2007 and 2010 found a significantly lower rate of stones for African-Americans, Hispanics, and multiracial persons compared to that in whites ([Scales et al, 2012](#)). Although the prevalence of stones in African-Americans remained lower than in whites, the increase in stone prevalence from the previous report (1988 to 1994) to the current report (2007 to 2010) was over 150%.

Following the assumption that a lower incidence of calculi might imply a significant risk for a metabolic or anatomic abnormality in patients who still manage to make calculi, it seems reasonable to advocate for the performance of a metabolic evaluation for all patients of African-American descent. This suggestion is supported by recent studies that assessed the underlying metabolic abnormalities of nonwhite stone formers. African-Americans, Asians, and Hispanics appear to have a surprisingly similar incidence of underlying metabolic disturbances when compared with white stone formers. These results suggest that dietary and environmental factors may be as important as ethnicity in the cause of stone disease ([Beukes et al, 1987](#); [Maloney et al, 2005](#)).

Regardless of whether a particular patient requires a full metabolic evaluation, it is prudent to perform at least a screening evaluation combined with a thorough history and physical examination to assess for underlying systemic syndromes that may cause recurrent calculi and extrarenal complications. This assessment also should screen for patients at an increased risk for stone recurrence, as outlined in the previous paragraphs ([Box 52-1](#)).

KEY POINTS: SELECTION OF PATIENTS FOR METABOLIC EVALUATION

- The incidence of nephrolithiasis is increasing.
- The historic male predominance of stone formers is disappearing.
- Racial “protection” may be overcome by dietary indiscretions.
- Children should generally be evaluated because of concerns about renal damage and long-term sequelae of stone recurrence.

Abbreviated Protocol for Low-Risk Single-Stone Formers

In single-stone formers without increased risk for recurrence, the following abbreviated protocol may be applied ([Box 52-2](#)). A thorough medical history should be obtained for any underlying conditions that may have contributed to the stone disease. Because of the association between bowel disease and calcium oxalate nephrolithiasis (enteric hyperoxaluria), a careful history of bowel habits

BOX 52-2 Abbreviated Evaluation of Single-Stone Formers**History**Underlying predisposing conditions (as per [Box 52-1](#))

Medications (calcium, vitamin C, vitamin D, acetazolamide, steroids)

Dietary excesses, inadequate fluid intake, excessive fluid loss

Multichannel blood screen

Basic metabolic panel (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine)

Calcium

Intact parathyroid hormone

Uric acid

Urine**Urinalysis**

pH > 7.5: infection lithiasis

pH < 5.5: uric acid lithiasis

Sediment for crystalluria

Urine culture

Urea-splitting organisms: suggestive of infection lithiasis

Qualitative cystine**Radiography**

Radiopaque stones: calcium oxalate, calcium phosphate, magnesium ammonium phosphate (struvite), cystine.

Radiolucent stones: uric acid, xanthine, triamterene

Intravenous pyelogram: radiolucent stones, anatomic abnormalities

Stone analysis

and bowel disease should be sought ([Smith et al, 1972](#); [Bohles et al, 1988](#); [Lindsjo et al, 1989](#); [McConnell et al, 2002](#); [Worcester, 2002](#); [Parks et al, 2003b](#)). This includes questions regarding chronic diarrhea that could be caused by inflammatory bowel disease (Crohn disease, ulcerative colitis) or irritable bowel syndrome. A history of gout should be sought, because this finding may predispose the patient to hyperuricosuria or gouty diathesis with either uric acid calculi or calcium oxalate stone formation ([Grover and Ryall, 1994](#); [Khatchadourian et al, 1995](#); [Kramer and Curhan, 2002](#)). As described by [Pak and colleagues \(2003c\)](#), patients with a history of diabetes mellitus may be at an increased risk for developing a gouty diathesis, with altered ammonium management, acidic urine, and a predisposition for a mixture of calcium oxalate and/or uric acid stones.

A thorough surgical history should be obtained focusing particularly on bariatric surgery and surgeries on the intestinal tract. Roux-en-Y gastric bypass surgery has been shown to significantly increase the risk for kidney stones ([Matlaga et al, 2009](#)). This study demonstrated a significantly higher rate of stones in obese patients who underwent gastric bypass surgery compared to obese patients who had not (7.65% vs. 4.63%). In contrast to gastric bypass surgery, restrictive bariatric surgeries such as gastric sleeve or gastric band do not seem to increase the risk for kidney stone formation ([Chen et al, 2013](#)). Bowel resection, particularly of the small intestines, can lead to malabsorption with an increased risk for kidney stone formation, and patients with prior bowel surgery should be considered for a metabolic evaluation.

In addition, information should be obtained concerning the patient's dietary habits, including fluid consumption and excessive intake of certain foods, as well as a list of all medications taken. A social history may provide obvious clues regarding a patient's hydration status. Does the patient have access to fluids on a regular basis? Does the patient perform daily tasks that would increase the insensible losses of fluids? Patients on prolonged bed-rest demonstrate alterations in urinary chemistry such that urinary calcium and phosphorus excretion increase significantly, leading to

significant increases in urinary saturation of calcium phosphate, calcium oxalate, and monosodium urate, particularly during bed-rest ([Hwang et al, 1988](#)). A family history may reveal a genetic predisposition to urinary calculi if there is a history of close relatives affected by nephrolithiasis. Age of onset of the patient or of affected relatives may give clues regarding genetic disorders such as autosomal recessive cystinuria.

A multichannel blood screen is helpful in identifying certain systemic problems. These include primary hyperparathyroidism (high serum calcium and low serum phosphorus), renal phosphate leak (hypophosphatemia), uric acid lithiasis (hyperuricemia), and distal RTA (hypokalemia, decreased serum carbon dioxide).

Voided urine specimens should be obtained for comprehensive urinalysis and culture. The urinalysis should include pH determination (preferably with an electrode), because a pH greater than 7.0 is suggestive of infection lithiasis or RTA, whereas a pH less than 5.5 suggests uric acid lithiasis secondary to gouty diathesis.

The urine sediment should be examined for crystalluria, because particular crystal types may give a clue as to the composition of stones the patient is forming. Tetrahedral "envelopes" are seen in calcium oxalate lithiasis ([Fig. 52-1](#)), and rectangular, "coffin-lid" crystals are often seen in patients with struvite calculi (see [Fig. 52-1](#)). Hexagonal crystals confirm cystinuria (see [Fig. 52-1](#)); uric acid crystals may be seen as amorphous fibers or as irregular plates. The microscopic appearances of common calculi are summarized in [Table 52-1](#).

Urine cultures are performed if there is a suspicion of infection-related calculi or if there are signs or symptoms of a UTI. A culture that is positive for urea-splitting organisms such as *Proteus*, *Pseudomonas*, *Klebsiella*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* would help explain the formation of a struvite calculus. A positive culture also will warrant therapy with appropriate antibiotics before initiation of any surgical procedure to remove the stone. The surgical management of a calculus during an active infection will place the patient in great risk for bacteremia or sepsis. **Unfortunately, many infected calculi will harbor bacteria even after treatment with broad-spectrum antibiotics.** [Korets and colleagues \(2011\)](#) evaluated the concordance between preoperative bladder urine cultures with renal pelvic urine cultures and stone cultures in patients undergoing percutaneous nephrolithotomy. They found that despite treatment with culture-specific antibiotics, stone culture was positive in 17 patients (8.6%) who had a positive preoperative bladder urine culture. Another 16 patients had a positive stone culture associated with a negative preoperative bladder culture. Furthermore, [McAleer and associates \(2003\)](#) demonstrated that infection calculi contain large quantities of endotoxin after disintegration. In a comparison of infected versus noninfected calculi, infected stones contained 36 times more endotoxin. Half of the infected calculi grew bacterial cultures that were different from the preoperative urine specimens. The same investigators described how endotoxin can cause a vascular collapse because it induces physiologic changes consistent with those of septic shock ([McAleer et al, 2002](#)).

Abdominal x-ray films (kidney-ureter-bladder [KUB]) should be obtained to document the existence of any current stones within the urinary tract. The radiopacity of any existing stones may suggest the type of stones present. Although magnesium ammonium phosphate and cystine stones are often radiopaque, they are not as dense as calcium oxalate or calcium phosphate stones. A plain abdominal film is also useful in identifying nephrocalcinosis (suggestive of RTA). A noncontrast computed tomography (NCCT) scan may be obtained to confirm the presence of radiolucent stones and also identify any anatomic abnormalities that may predispose the patient to stone formation. It is important to realize that the radiographic evaluation of a patient during a metabolic workup of stone disease will differ from an approach taken during an episode of acute renal colic. In an acute stone episode, the majority of patients will be examined with NCCT, which is able to quickly image the entire collecting system in a rapid sequence ([Fig. 52-2](#)) ([Smith et al, 1995](#); [Sommer et al, 1995](#); [Katz et al, 1996](#); [Fielding et al, 1997](#); [Freed et al, 1998](#)).

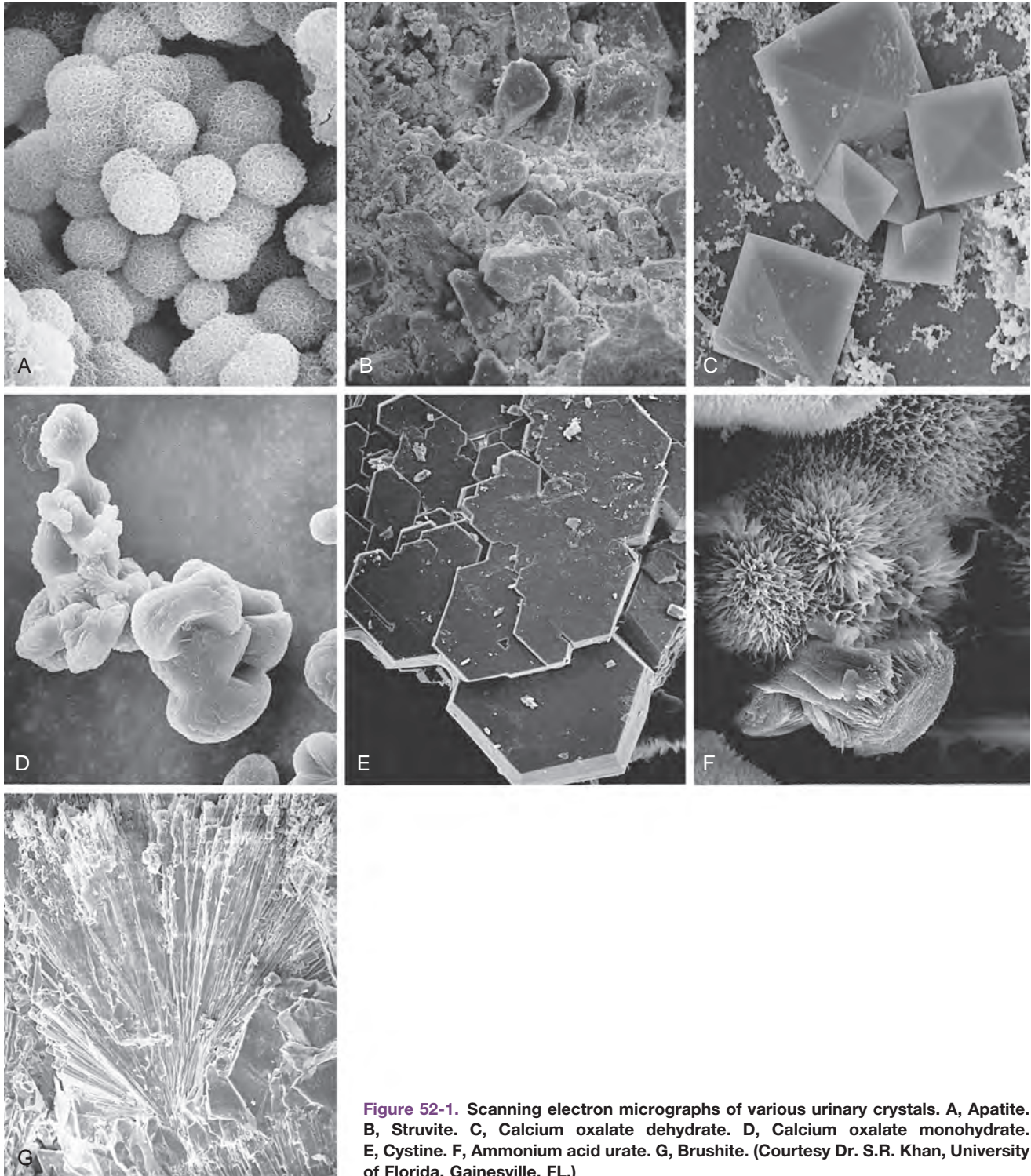


Figure 52-1. Scanning electron micrographs of various urinary crystals. A, Apatite. B, Struvite. C, Calcium oxalate dehydrate. D, Calcium oxalate monohydrate. E, Cystine. F, Ammonium acid urate. G, Brushite. (Courtesy Dr. S.R. Khan, University of Florida, Gainesville, FL.)

In patients who are seen for metabolic evaluation, an NCCT may not be justified because of concerns regarding cost and radiation exposure. Digital tomosynthesis is a promising new imaging technology that may be useful for the evaluation and follow-up of patients with recurrent stones. It is performed with a plain abdominal radiograph and a single tomographic sweep of the x-ray emitter. Multiple coronal slice images are then reconstructed by digital software. Digital tomosynthesis has been shown to have improved sensitivity over that of plain KUB for the detection of renal stones

and significantly less radiation than an NCCT (Mermuys et al, 2010; Neisius et al, 2014).

Finally, available stones should be analyzed to determine their crystalline composition. The presence of uric acid or cystine would suggest the presence of a gouty diathesis or cystinuria, respectively. The finding of struvite, carbonate apatite, and magnesium ammonium phosphate would suggest infection lithiasis. A predominance of a hydroxyapatite component suggests the presence of RTA or primary hyperparathyroidism and warrants an assessment of basic

electrolytes. Stones composed of pure calcium oxalate or mixed calcium oxalate and hydroxyapatite are less useful diagnostically because they may occur in several entities, including absorptive and renal hypercalciuria, hyperuricosuric calcium nephrolithiasis, enteric hyperoxaluria, hypocitraturic calcium nephrolithiasis, and low urine volume (Kourambas et al, 2001; Pak et al, 2004).

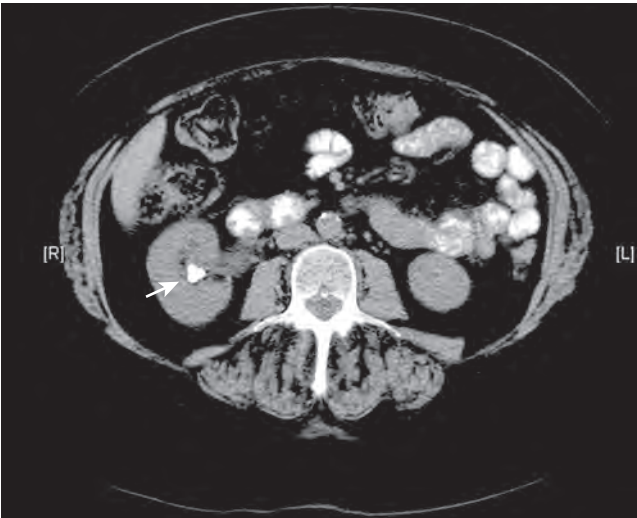


Figure 52-2. Computed tomography image of a urinary calculus. All stones (with the exception of some medication calculi) appear as dense, white objects (arrow) within the urinary collecting system.

KEY POINTS: ABBREVIATED PROTOCOL FOR LOW-RISK SINGLE-STONE FORMERS

- A complete medical history should be obtained from all stone formers.
- Patients should be screened for medical diseases that predispose to calculi.
- Serum metabolic panel and urinalysis tests should be performed.
- Urine microscopy for crystals may provide clues to diagnosis.
- Stone analysis may improve the accuracy of further evaluation.
- Basic radiography (plain films) should screen for existing calculi.

Extensive Diagnostic Evaluation

A more extensive evaluation, directed at the identification of underlying physiologic derangements, should be performed in patients with recurrent nephrolithiasis as well as in stone formers at increased risk for further stone formation.

Pak and colleagues (1980a) initially described an extensive outpatient (ambulatory) evaluation in 1980 and subsequently made minor revisions to help simplify the process (Levy et al, 1995). The basic strategy involves two outpatient visits, and most of the required laboratory analyses can be performed in a routine clinical laboratory, with only a few of the specialized techniques being performed in a more sophisticated laboratory. The entire schedule of visits and tests is outlined in Table 52-2.

Before and throughout the period of evaluation, the patient is instructed to discontinue any medication known to interfere with the metabolism of calcium, uric acid, or oxalate. These medications include vitamin D, calcium supplements, antacids, diuretics, acetazolamide, and vitamin C. Any current medication for stone treatment (thiazides, phosphate, allopurinol, or magnesium) should be discontinued as well, to better determine the patient’s baseline physiology (and pathophysiology). Two random 24-hour urine samples are collected. These 24-hour specimens are obtained with the patient on a random diet, which is reflective of their usual dietary intake. It is important to stress to the patient to maintain their normal diet and fluid intake during urine collections. An attempt on the patient’s part to suddenly eat well or to increase fluid consumption for the sake of the test will only mask the underlying causes of the stone disease.

Most patients will require detailed instructions on the proper collection of a complete 24-hour urine specimen. The patient

TABLE 52-1 Microscopic Appearance of Common Urinary Calculi

CHEMICAL TYPE	APPEARANCE
Calcium oxalate monohydrate	Hourglass
Calcium oxalate dihydrate	Envelope, tetrahedral
Calcium phosphate-apatite	Amorphous
Brushite	Needle shaped
Magnesium ammonium phosphate (struvite)	Rectangular, coffin-lid
Cystine	Hexagonal
Uric acid	Amorphous shards, plates

TABLE 52-2 Outline of Extensive Ambulatory Protocol

		BLOOD				URINE					
		COMPLETE BLOOD COUNT			URIC CREATININE	SODIUM	pH	TOTAL VOLUME	OXALATE	CITRATE	QUALITATIVE CYSTINE
		CMP	PTH	CALCIUM							
Visit 1*	X	X		X	X	X	X	X	X	X	X
Visit 2†		X	X	X	X	X	X	X	X	X	X
Fast				X		X			X		
Load				X		X		X			

*History and physical examination, diet history, radiologic evaluation, two 24-hour urines on random diet and dietary instruction for restricted diet.
†Twenty-four-hour urine on restricted diet (400 mg calcium and 100 mEq sodium/day, fast and load test).
CMP, comprehensive metabolic panel; PTH, parathyroid hormone.
Modified from Pak CY, Britton F, Peterson R et al. Ambulatory evaluation of nephrolithiasis: classification, clinical presentation and diagnostic criteria. Am J Med 1980;69:19–30.

should choose a day when all voids can be completely captured and when the specimen will represent a typical day. The first morning void is discarded, because this represents urine from the previous night and may not have had a predictable starting point. From that point on, all urine must be collected in the appropriate, laboratory-provided container. The canister may need to be kept on ice and/or preservatives should have been added according to the requirements of the specific laboratory. When the patient awakens the next morning, the first morning void is collected with the rest of the specimen, thereby completing a full 24 hours. Total urinary creatinine should be measured to provide an internal check. Males will be expected to have produced roughly 20 to 25 mg of creatinine for every kilogram of body weight during the 24-hour period. Females generally have less muscle mass and therefore will typically produce 15 to 20 mg of creatinine for every kilogram of body weight in 24 hours. Significant aberrations in total creatinine excretion from these estimated values imply incomplete collection, overcollection, greater than expected muscle mass, or less than expected muscle mass.

In the past, a third 24-hour sample was collected after 1 week with the patient on a diet restricting calcium, sodium, and oxalate. This dietary restriction was imposed to standardize the diagnostic tests, to better assess the cause of hypercalciuria (i.e., absorptive hypercalciuria I vs. absorptive hypercalciuria II), and to prepare for the “fast and calcium load” test, which was performed on the second visit. Blood samples are obtained as outlined in Table 52-2.

Fast and Calcium Load Test

Because of the similar treatment of patients with absorptive hypercalciuria and renal leak, the performance of fast and calcium load testing is no longer performed by most clinicians. With very little therapeutic distinction, there is not much of an incentive to discriminate between the two types of hypercalciuria. However, differentiation between absorptive hypercalciuria and renal hypercalciuria is mainly of historical interest because the treatment for both is the same (see Selective Medical Therapy of Nephrolithiasis, later in this chapter). When new, more targeted medications are developed, this distinction will be clinically applicable. A description of the fast and calcium load study is included here primarily for completeness and historical purposes.

A fast and calcium load study may be performed on the morning of the second visit (Pak et al, 1975). The purpose of this exercise is to help delineate between various causes of hypercalciuria. As explained in Chapter 51 in greater detail, some patients are too efficient at absorbing calcium from the intestinal tract (absorptive hypercalciuria I and II), whereas others suffer from a constant loss of calcium from the renal tubules (renal calcium leak). A third subset of patients has an overabundance of circulating parathyroid hormone, usually from a single parathyroid adenoma, and has a constant loss of calcium and phosphate (resorptive hypercalciuria or primary hyperthyroidism, respectively).

To differentiate among these three hypercalciuric subtypes, it is essential that the patients have adhered to the restricted diet for at least 7 days before this testing so as to eliminate the effects of absorbed calcium on fasting calcium excretion. To ensure adequate hydration, distilled water (300 mL each) is taken 12 hours and 9 hours before the calcium loading. Other than water ingestion at these time periods, the patients are to be fasting. Two hours before the scheduled calcium loading, patients empty their bladder completely, discard this urine, and drink an additional 600 mL of distilled water. All urine produced over the next 2 hours is collected as a pooled sample before taking an oral calcium load (fasting urine). After the 2-hour fasting urine collection has been completed, a 1-g oral calcium load is administered using 250 mL of a liquid synthetic diet (Calcitest) as a carrier solution. This synthetic “meal” is prepared by adding 500 mL of water to a can of Calcitest. Because 250 mL of the synthetic meal contains only 100 mg of calcium, 39 mL of Neo-Calglucon (900 mg of calcium) must be added to bring the total calcium up to 1 g. The final mixture should be taken slowly over a 5- to 10-minute period.

For the next 4 hours, urine is again collected as a pooled sample (postload urine). Both fasting and postload samples are then assayed for calcium and creatinine. Fasting urinary calcium is expressed as milligrams per deciliter glomerular filtrate (GF) because it is reflective of renal function. To obtain this unit of measurement, the urinary calcium in milligram per milligram creatinine is multiplied by the serum creatinine in milligram per deciliter. Normal fasting urinary calcium is less than 0.11 mg/dL GF. The postload urinary calcium is best expressed as milligram per milligram creatinine because it is a function of a fixed oral calcium load. The normal value for this measurement is less than 0.2 mg calcium/mg creatinine.

KEY POINTS: EXTENSIVE DIAGNOSTIC EVALUATION

- A complete metabolic evaluation may be obtained as an outpatient.
- Calcium fast and load tests can discriminate between the various forms of hypercalciuria.
- Routine performance of calcium fast and load tests is not required to complete a metabolic evaluation.

Simplified Metabolic Evaluation

The previously described extensive ambulatory protocol affords the physician a high diagnostic yield and is quite reliable. Unfortunately, many practicing physicians have found this protocol to be time-consuming and difficult to perform because of the inability to find a reliable local laboratory or perceived complexities of the evaluation protocol. Indeed, the full evaluation does entail several office visits and requires strict adherence to fluid protocols during the calcium fast and load tests.

Several authors have suggested a more simplified approach that uses the same standard principles and procedures as the full outpatient evaluation. These simplified protocols do not include the calcium fast and loading tests and may not require adherence to a restricted diet, permitting them to be performed in a single office visit. Rivers and colleagues (2000) recommend the collection of two separate 24-hour urine specimens. One is collected while on a restricted diet, and the other allows a random (typical) diet. Such manipulation is well tolerated by the patient and may allow for identification of the various types of hypercalciuria with reasonable certainty.

Pak (1997) recognized the cumbersome nature of an extensive evaluation and made similar recommendations. Based on the findings of a single 24-hour urine collection, patients are evaluated and treated without all steps of fasting and loading calcium challenges. Patients are separated into complicated and uncomplicated calcium stone disease, based on the presence or absence of normocalcemia, normouricemia, and calcium stones and the absence of UTI, bowel disease, or marked hyperoxaluria. Comprising the majority of all patients, uncomplicated calcium stone disease is further separated into a hypercalciuric group and a normocalciuric group. Medical therapy is then based on this distinction.

Lifshitz and colleagues (1999) advocated for a less complex approach. All patients undergo a basic metabolic screening, searching for systemic disorders that could pose a long-term health risk. They suggest that all patients should be advised about conservative nonspecific preventive measures. Patients at high risk for forming stones should have a more extensive metabolic evaluation based on two 24-hour urine samples.

The cornerstone of these simplified protocols has been the development of a urine preservation method that allows collection of urine without refrigeration. The patient is then able to submit an aliquot to a central laboratory for the analysis of various stone-forming substances (Nicar et al, 1987). The urinary constituents most commonly assayed include calcium, oxalate, citrate, total volume, sodium, magnesium, potassium, pH, uric acid, and sulfate. Although most of these parameters are self-evident, sulfate is added to the list to assess the volume of protein loading from animal meat.

From such determinations, the urinary saturation with respect to stone-forming salts can be calculated.

At present, multiple laboratories offer services focused on simplified, accurate 24-hour urine assessment for stone-forming risk factors. These laboratories provide collection containers with chemical preservatives (obviating iced storage and transport) and extrapolate 24-hour cumulative data from the submission of a small aliquot of the entire collection. After the values of all urinary constituents and saturations have been determined, the physician receives a computer printout that provides a numeric display of the test results (Fig. 52-3). A graphic display of this information also may be generated, highlighting the increased or reduced risk for each environmental, metabolic, or physicochemical factor (Fig. 52-4). These results should aid the physician in formulating a metabolic/physiologic diagnosis. It may be difficult to make a definitive diagnosis on a single 24-hour urinalysis; therefore repeated evaluation is often warranted. For example, it is desirable to confirm the presence of hypocitraturia or hyperuricosuria by repeat measurements.

Controversy exists regarding the necessity of collecting two separate 24-hour urine specimens. As noted earlier, Rivers and colleagues (2000) advocated for the collection of two samples while the patient is on differing diets (random and restricted). Assuming that the patient complies, these data may be used to discern between

absorptive hypercalciuria II and renal leak (hypercalciuria disappears while the patient is on the restricted diet in absorptive hypercalciuria II). Researchers from Dallas suggest that only a single 24-hour collection is required (Pak et al, 2001). Their study retrospectively reviewed and compared the results of two 24-hour urine samples that were collected on random diets. They noted no significant difference in the excretion of urinary calcium, oxalate, uric acid, citrate, pH, total volume, sodium, potassium, sulfate, or phosphorus. They concluded that the reproducibility of urinary stone risk factors was adequate in repeat samples, enough so that therapy would not have been altered.

Conversely, Parks and colleagues (2002) noted significant disparities between two separate collections. Over 1000 patients were examined from both private practice and academic settings. They noted that within nearly 70% of the comparisons, there were large enough differences that the standard deviation would contain clinically relevant disparities. The authors therefore conclude that relying on one specimen alone could easily lead to misdiagnosis and, consequently, mismanagement.

Finally, it is important to note that the "normal limits" cited on commercially available urine analysis packages may not be the same as normal values quoted previously. Therefore close attention should be paid to patients who may fall in the gray zone when using a commercially available urine analysis package.

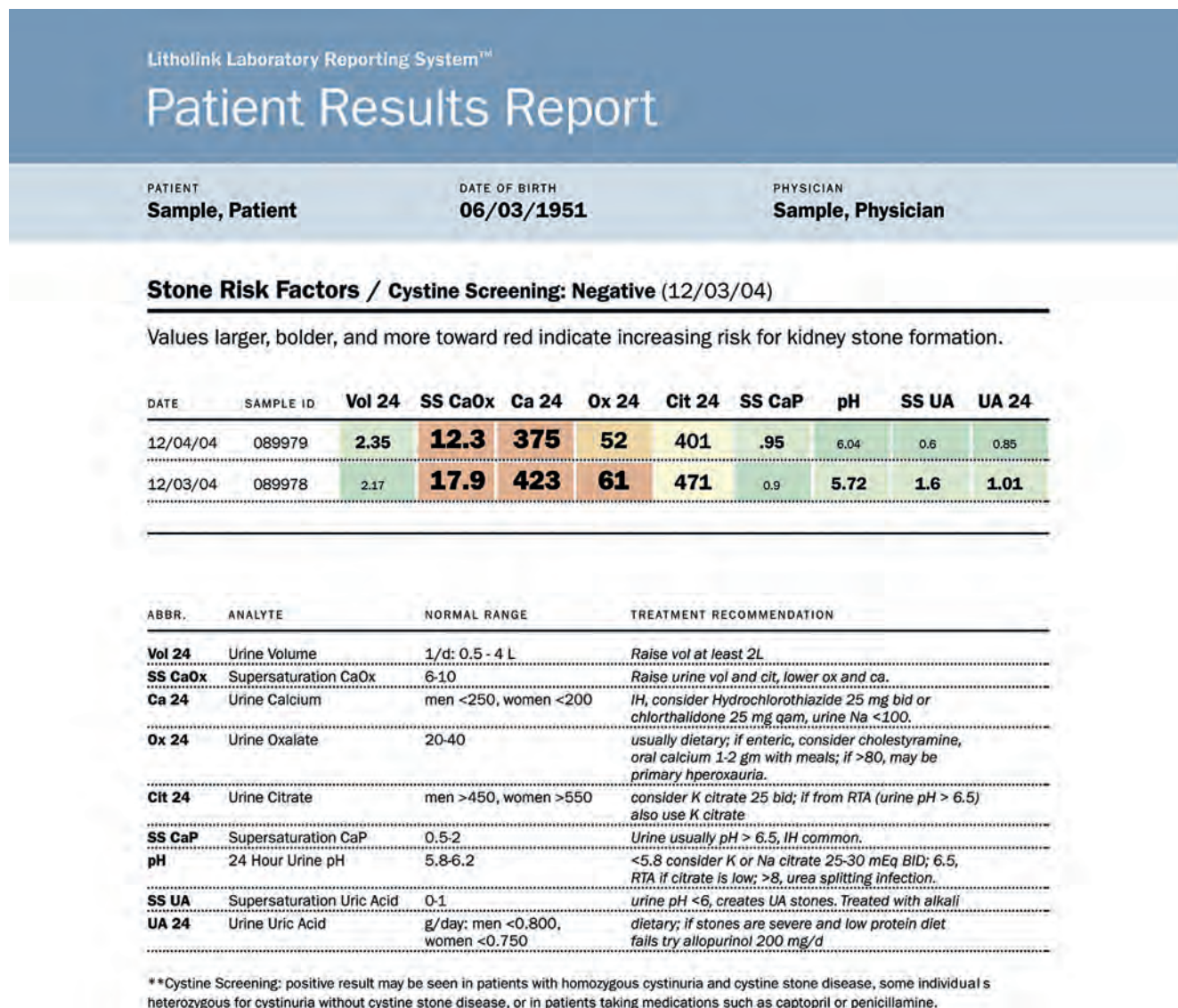


Figure 52-3. Commercial 24-hour urine results are available and simplify the collection and reporting process. (Courtesy Litholink, Chicago, IL.)

PATIENT INFORMATION	
SSN	111-11-1111
Patient Name	
Physician Name	
Laboratory	Mission Pharmacal Reference

Stone Risk Diagnostic Profile

LAB INFORMATION	
No.	81324
Control Number	11A22456
Date Sample Collected	01/01/2005
Date Sample Received	01/03/2005

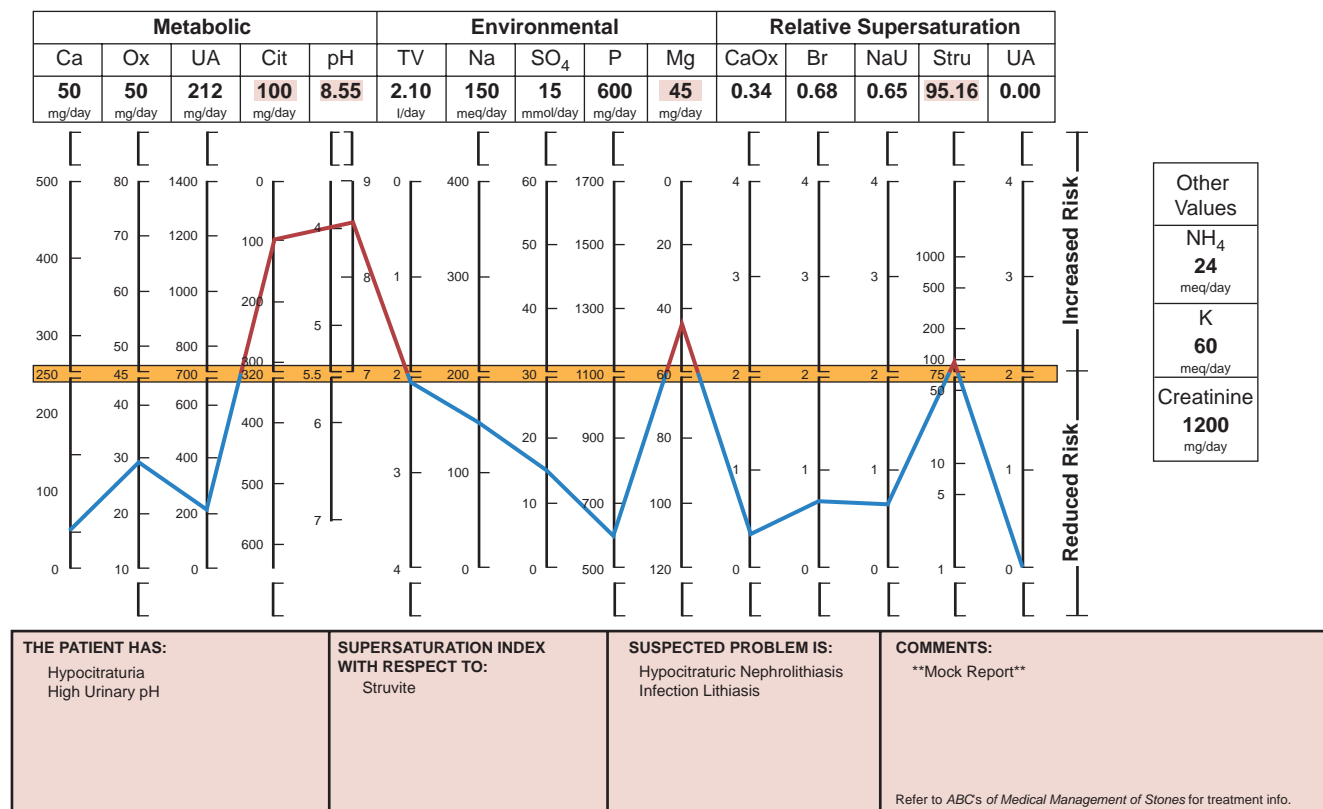


Figure 52-4. Results of 24-hour urine tests may be presented graphically to assist with interpretation and planning. (Courtesy Mission Pharmacal, San Antonio, TX.)

KEY POINTS: SIMPLIFIED METABOLIC EVALUATION

- A simplified metabolic evaluation of nephrolithiasis has been established.
- Commercial laboratories may facilitate the collection of 24-hour urine studies.
- There is no consensus regarding the need for one versus two 24-hour urine collections during an initial evaluation (although we prefer two random collections).

USE OF STONE ANALYSIS TO DETERMINE METABOLIC ABNORMALITIES

Questions have arisen regarding the necessity of both chemical stone analysis and metabolic evaluation for patients with nephrolithiasis. **Although stone composition analysis is neither always feasible nor desirable, there is helpful information from such an investigation that can aid with preventive therapy.** Unfortunately, chemical and mineralogic names of common calculi are sometimes used interchangeably, causing significant confusion for the clinician. A list of these names is provided in [Table 52-3](#).

[Parks and colleagues \(1997\)](#) demonstrated that a given patient's supersaturation of urinary crystals coincides with the stones produced by the patient. Indeed, in their study, treatments that reduced stone rates also reduced the supersaturation values of the

TABLE 52-3 Mineralogic Names of Renal Calculi

RENAL CALCULI	MINERAL NAME
Calcium oxalate monohydrate	Whewellite
Calcium oxalate dihydrate	Weddellite
Calcium hydrogen phosphate dihydrate	Brushite
Tricalcium phosphate	Whitlockite
Carbonite-apatite	Carbonite-apatite
Magnesium ammonium phosphate	Struvite
Cystine	None
Uric acid	None

historical stone composition for that patient. If calculi develop as a result of prolonged supersaturation of various crystals (e.g., calcium oxalate, urate), it is further reassuring that "snapshot," pooled urine supersaturation measurements accurately track stone admixtures and are a reliable index of long-term, "average" renal and urine supersaturations.

Assessment of stone composition, not just urinary crystal supersaturation, can be a helpful adjunct to a metabolic evaluation. **Because most stones are a mixture of more than one component, the relative ratios or predominance of any particular molecule may have predictive value.** In an analysis of almost 1400 patients who had both stone analysis and a complete metabolic evaluation,

[Pak and colleagues \(2003b\)](#) noted that calcium apatite and mixed calcium oxalate–calcium apatite stones were associated with the diagnoses of RTA and primary hyperparathyroidism (odds ratios [OR], ≥ 2), but not with chronic diarrheal syndromes. As the phosphate content of the stone increased from calcium oxalate to mixed calcium oxalate–calcium apatite, and finally to calcium apatite, the percentage of patients with RTA increased from 5% to 39%, and those with primary hyperparathyroidism increased from 2% to 10%. Not surprisingly, pure and mixed uric acid stones were strongly associated with a gouty diathesis and brushite stones were associated with RTA. As expected, a very strong association was found between infection stones and infection and between cystine stones and cystinuria.

These findings were further supported by [Kourambas and colleagues \(2001\)](#). Stone composition correlated with metabolic findings in a series of 100 consecutive patients. A significant risk for RTA was documented in patients producing predominantly calcium phosphate calculi. Kourambas and colleagues maintain that the finding of a noncalcareous stone simplifies the evaluation by focusing the ensuing workup on the most obvious cause. Pure uric calculi are primarily a result of gouty diathesis, and these patients may not require further testing.

Finally, [Lingeman and associates \(1995\)](#) noted that the finding of pure struvite/calcium apatite in a staghorn calculus predicted a low likelihood of finding other metabolic abnormalities during a workup. In their series, only 2 of 14 with pure infection stones had additional abnormalities compared to 7 of 7 patients with mixed chemical compositions. They therefore suggest that patients with pure infection stones will not benefit from additional evaluation. In a more recent report, metabolic abnormalities were found in 3 of 5 patients with pure struvite stones and 17 of 22 with mixed struvite stones ([Iqbal et al, 2013](#)). This suggests that in patients with pure struvite stones, a metabolic evaluation should be considered to aid in stone prevention.

KEY POINTS: USE OF STONE ANALYSIS TO DETERMINE METABOLIC ABNORMALITIES

- Stone analysis may obviate the need for a complete metabolic evaluation.
- Stone composition can direct metabolic investigation.

ROLE OF IMAGING IN DETERMINING STONE COMPOSITION

Radiologic imaging is mainly used for determination of the presence or absence of calculi, renal anatomy, and associated findings (i.e., hydronephrosis). Thus diagnostic imaging plays a crucial role in the surgical planning and follow-up of patients with nephrolithiasis. Aside from the inability to identify pure uric acid stones on plain radiography compared to computed tomography (CT), diagnostic imaging has not historically proved to be beneficial in the medical evaluation and management of stone disease.

Accompanying the ubiquity and increased utility of CT imaging, a number of authors have sought to identify characteristics by stone composition that could be determined from this diagnostic modality ([Mitcheson et al, 1983](#); [Newhouse et al, 1984](#); [Mostafavi et al, 1998](#); [Nakada et al, 2000](#); [Saw et al, 2000](#); [Motley et al, 2001](#); [Bellin et al, 2004](#); [Deveci et al, 2004](#); [Sheir et al, 2005](#)). These investigations focused on Hounsfield unit (HU) measurements to determine stone composition. Both in vitro and in vivo work demonstrated significant differences in HU between pure uric acid stones and other stone types. However, it has been more difficult to differentiate pure struvite from cystine, calcium oxalate from brushite, and stones of mixed composition. Because of the significant variance in the readings obtained for different stone types, even with optimization of standard CT variables (collimation, pitch), this information has been of little clinical value.

More recently, the application of dual-energy CT (DECT) technology is demonstrating the potential to better characterize stone type. In vitro studies using ratios of HU during DECT have been able to distinguish among uric acid, calcium phosphate, and calcium oxalate calculi ([Matlaga et al, 2008](#)). Further discrimination of stone composition has been reported by two other sets of investigators. [Boll and associates \(2009\)](#), using an alternative calculation method, showed graphical separation of relatively pure cystine, struvite, calcium oxalate, calcium phosphate, and brushite stones. This group's "DECTslope" algorithm identified stone compositions unambiguously; however, separation of calcium oxalate and calcium phosphate calculi was not obtained. In an in vivo study, this same group was able to successfully identify stone composition and differentiate calcium oxalate from brushite stones ([Zilberman et al, 2010](#)). [Grosjean and colleagues \(2008\)](#) further characterized uric acid, cystine, struvite, calcium oxalate dihydrate, brushite, and calcium oxalate monohydrate into distinct groups with the use of DECT attenuation values. The ability to differentiate stone composition was noted to be lost when the image was subjected to respiratory motion artifact. [Primak and coworkers \(2007\)](#) used commercially available software to differentiate uric acid stones from non-uric acid stones. They were able to demonstrate 100% accuracy in differentiating between uric acid and non-uric acid stones. The exception was in an obese model, in which accuracy decreased to 92%. Early work with DECT is promising but must be confirmed in vivo before incorporation into clinical decision making for the metabolic evaluation and medical management of nephrolithiasis.

ECONOMICS OF METABOLIC EVALUATION

There is no doubt that the costs associated with the treatment of nephrolithiasis are substantial. In 1984, [Shuster and Scheaffer](#) estimated that the average stone episode cost approximately \$2000, exclusive of recurrences. At the time, this finding was based on a predominance of open surgical approaches with an average hospital stay lasting 4 to 5 days. The average annual cost of recurrence for a current stone case was conservatively estimated to be in the range of \$300 to \$400. Based on these conservative projections, they estimated that the entire national population of white males in the age range of 18 to 60 years yielded an annual cost because of kidney stones approaching \$315,000,000 ([Shuster and Scheaffer, 1984](#)).

By 1993 the estimated costs continued to climb, despite advances in technology and decreases in inpatient care. Indeed, [Clark and associates \(1995\)](#) performed a review of prevalence data for urolithiasis and the relative frequency of surgical treatments from Civilian Health and Medical Program of the Uniformed Services claims data. They found that the total annual cost for the evaluation and management of nephrolithiasis to be \$1.83 billion in the United States alone.

At the onset of the new millennium, the economic burden of urolithiasis continued to rise. Estimations of the annual medical expenditures for stone disease in the United States for 2000 were \$2.1 billion, inclusive of \$971 million for inpatient services, \$607 million for physician office and hospital-based outpatient services, and \$490 million for emergency room charges ([Pearle et al, 2005](#)). These calculations are based on a range of nationally available datasets and do not necessarily reflect the additional societal costs of lost productivity and social service support. These costs are clearly not negligible because the peak incidence of urolithiasis occurs in patients between 20 and 60 years of age (the years of highest workers' productivity) and an analysis of more than 300,000 beneficiaries from 25 large U.S. employers identified that 30% of patients with urolithiasis missed an average of 19 hours of work and had an additional \$3500 in annual medical costs ([Saigal et al, 2005](#)).

With the increasing incidence of stone disease, it only can be concluded that the national health care expenditure for urolithiasis will continue to rise. Particularly worrisome is the increasing evidence that obesity confers an increased risk for nephrolithiasis,

which is quite sobering considering the epidemic of obesity that is enveloping the United States (Curhan et al, 1998a; Ekeruo et al, 2004; Morrill and Chinn, 2004; Rigby et al, 2004; Strumpf, 2004; Taylor et al, 2005; Scales et al, 2012).

With these figures in mind, prudence would dictate that medical prevention could help curb runaway costs and prevent long-term sequelae of recurrent nephrolithiasis. The emergence and instant appeal of shock wave lithotripsy and improved endoscopy in the mid-1980s prompted some authors to remind the urologic community that medical assessment was still a viable option (Resnick and Pak, 1987; Preminger, 1994). However, office visits, serum studies, and 24-hour urine studies have their own costs. Is there a break-even point at which the costs of a metabolic evaluation, pharmacologic prophylaxis, and continued office visits are less than the expense of surgical management?

Chandhoke (2002) compared the cost of medical prophylaxis with the cost of clinically managing recurrent stone episodes. Additionally, he determined the stone recurrence rate without prophylaxis (stone frequency) at which these two treatment approaches became cost equivalent. This review conducted a cost survey in 10 countries to compare costs of medical prophylaxis and managing recurrent acute stone episodes. Costs of an acute stone episode included an emergency department visit, associated radiographic imaging to confirm diagnosis of a symptomatic stone, and outpatient treatment of upper urinary tract stones that did not pass spontaneously. Costs of medical management included an initial limited metabolic evaluation, drug therapy, a follow-up office visit every 6 months that included a 24-hour urinalysis, and yearly radiographic KUB imaging. Not surprisingly, the costs of medical prophylaxis and managing an acute stone episode varied significantly from country to country. The stone frequency at which costs of these management options became equivalent ranged from 0.3 to 4 stone episodes per year. This study concluded that medical management of a first stone episode is not cost-effective and that individual decisions should be determined by local costs.

Researchers at the University of Texas, Southwestern Medical Center have created a decision tree model to evaluate the cost-effectiveness and stone recurrence rates of common management strategies in stone formers (Lotan et al, 2004). They evaluated four common medical strategies: dietary measures alone (conservative), empirical drug treatment, or directed drug therapy based on simple or comprehensive metabolic evaluation. The model made reasonable assumptions regarding costs for evaluation, medications, emergency treatment, and surgery for stone recurrence. A review of the literature guided estimations of stone recurrence and risk reduction from various medical therapies. They found that first-time stone formers were best treated with a conservative approach because it was the least costly and it yielded a stone formation rate of 0.07 stone per patient yearly. For recurrent stone formers, conservative treatment was less costly than drug treatments but it was associated with a higher stone recurrence rate (0.3 stone per patient yearly). Directed medical therapies were more costly than conservative treatment (\$885 to \$1187 vs. \$258 yearly), but they provided the obvious advantage of decreasing recurrence rates by 60% to 86%.

The authors went on to compare the expense of the simple medical evaluation and associated management as described earlier in this chapter and noted it to be more costly than empirical treatment but also more effective. Importantly, a complete evaluation with attendant treatment offered no advantage in cost or efficacy over empirical treatment or modified simple metabolic evaluation and management. The authors also recommended that first-time stone formers be treated with conservative therapy because it is both cost-effective and efficacious. In contrast, however, recurrent stone formers should be treated medically after a simplified evaluation, because of the high recurrence rate of stone formation. Despite the recommendation for recurrent stone formers to undergo a simplified evaluation, Milose and colleagues found that in 2006 only 7.9% of high-risk stone formers were evaluated with 24-hour urine collections (Milose et al, 2013).

KEY POINTS: ECONOMICS OF METABOLIC EVALUATION

- Routine performance of a comprehensive metabolic evaluation may not be economically sound if applied to all stone patients.
- Many first-time stone formers may not benefit economically from a metabolic evaluation unless initial screening puts them in a high-risk category.
- Recurrent stone formers are best treated with a metabolic evaluation and directed medical therapy.

CLASSIFICATION OF NEPHROLITHIASIS AND DIAGNOSTIC CRITERIA

Using an ambulatory protocol, the cause of nephrolithiasis can be classified into 12 separate categories reflecting specific physiologic derangements. The details regarding the physiology and pathophysiology of these distinct entities are included in Chapter 51. These categories are listed in Table 52-4, along with the relative frequency of their occurrence as noted by Pak and colleagues at a dedicated Stone Clinic in an academic medical center (Levy et al, 1995). An argument can be made that these relative incidences may not be representative of the general population for two reasons. First, referral to an academic center may imply a more serious version of stone disease and may therefore represent a selection bias. Second, recognizing that there are at least some regional variations of stone incidence (Harvey et al, 1990), this particular patient population may be distinctly different from those in a different region of the United States or other regions of the world.

Calcium-Based Calculi

Hypercalciuria (>200 mg/day)

Absorptive Hypercalciuria. The classification of nephrolithiasis recognizes three broad categories of hypercalciuria. Absorptive hypercalciuria involves an increase in the amount of calcium absorbed by the intestinal tract. In absorptive hypercalciuria I, this increased absorption will occur regardless of the amount of calcium in the patient's diet. Therefore these subjects will demonstrate an increased urinary excretion of calcium on both the fasting and the loading specimens. In contrast, patients with absorptive hypercalciuria II will have a normal amount of urinary calcium excretion during calcium restriction, but will show elevations during their regular diet. Patients with both subtypes of absorptive hypercalciuria will have normal serum calcium and a normal level of circulating intact parathyroid hormone (iPTH). In fact, these patients often demonstrate a low iPTH because of suppression from a constant abundance of available serum calcium.

Renal Hypercalciuria. Renal hypercalciuria (also known as renal leak hypercalciuria) is thought to be due to a wasting of calcium by the functioning nephron. The details of this process and various hypotheses are outlined in Chapter 51. As a result of constant loss of calcium from the distal tubules, these patients will demonstrate hypercalciuria during all phases of fasting, loading, or restricting of dietary calcium. Most patients with renal hypercalciuria will have a normal serum calcium, but may exhibit a mild elevation of iPTH as the regulatory systems attempt to keep up with the constant loss of calcium.

Resorptive Hypercalciuria (Primary Hyperparathyroidism). Patients with resorptive hypercalciuria suffer from an overproduction of parathyroid hormone from either one dominant adenoma or diffuse hyperplasia of all four glands. The hallmark of this disorder is the persistence of increased urinary calcium during all parts of the dietary calcium manipulations. In addition, these patients frequently demonstrate hypercalcemia and elevations of the parathyroid hormone. The measurement of only the iPTH

TABLE 52-4 Classification of Nephrolithiasis

	PERCENT	
	SOLE OCCURRENCE	COMBINED OCCURRENCE
Absorptive hypercalciuria	20	40
Type I		
Type II		
Renal hypercalciuria	5	8
Primary hyperparathyroidism	3	8
Unclassified calcium nephrolithiasis	15	25
Hyperoxaluric calcium Nephrolithiasis	2	15
Enteric hyperoxaluria		
Primary hyperoxaluria		
Dietary hyperoxaluria		
Hypocitraturic calcium Nephrolithiasis	10	50
Distal renal tubular acidosis		
Chronic diarrheal syndrome		
Thiazide-induced Idiopathic		
Hypomagnesuric calcium nephrolithiasis	5	10
Gouty diathesis	15	30
Cystinuria	<1	
Infection stones	1	5
Low urine volume	10	50
No disturbance and miscellaneous	<3	
TOTAL	100	

Modified from Levy FL, Adams-Huet B, Pak CY. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. *Am J Med* 1995;98: 50–9.

has avoided confusion from the measurement of fragments of the same molecule (Kao et al, 1982; Nussbaum et al, 1987) and has greatly enhanced the ability to make this diagnosis.

Unfortunately, some patients may have normocalcemic hyperparathyroidism. These patients may be hard to distinguish from those with renal leak hypercalciuria, during which serum calcium will be normal but a mild elevation of the iPTH can occur, creating a secondary hyperparathyroidism. In these instances the patients can be treated with a 2-week course of a thiazide diuretic, such as chlorthalidone 25 mg daily. If the patient actually has renal leak, the calcium loss should be suppressed and the iPTH should return to normal (Aroldi et al, 1979; Barilla and Pak, 1979; Zechner et al, 1981). Those with true primary hyperparathyroidism will continue to circulate elevated levels of iPTH and may become mildly hypercalcemic, although this latter feature has been debated in the literature (Klimiuk et al, 1981; Farquhar et al, 1990; Strong et al, 1991).

Idiopathic Hypercalciuria. Idiopathic hypercalciuria can be found in both normal people and stone formers (Coe et al, 1979). These patients may demonstrate elevated amounts of urine calcium in all phases of the dietary calcium manipulation, but will not demonstrate serum abnormalities. **On a cautionary note, this term does not always enjoy a strict definition and is sometimes sub-**

TABLE 52-5 Differential Diagnosis of Hypercalciuria

	ABSORPTIVE	RENAL	RESORPTIVE
Serum calcium	Normal	Normal	Elevated
Parathyroid function	Suppressed	Stimulated (secondarily)	Stimulated (primarily)
Fasting urinary calcium	Normal	Elevated	Elevated
Intestinal calcium absorption	Elevated (primarily)	Elevated (secondarily)	Elevated (secondarily)

stituted to describe patients with hypercalciuria who have not undergone further evaluation to discriminate among the various subcategories. Although this diagnosis is not as “clean” as possible, it represents a more pragmatic approach to hypercalciuria, because the treatment for absorptive and renal hypercalciuria is often the same (as outlined later in this chapter). Table 52-5 summarizes the laboratory parameters that help delineate the various types of hypercalciuria.

KEY POINTS: HYPERCALCIURIA

- Hypercalciuria can be divided into three causes: excessive gastrointestinal (GI) absorption, renal tubular leak, hyperparathyroidism.
- Idiopathic hypercalciuria refers to unevaluated or unknown cause.

Hyperuricosuric Calcium Oxalate Nephrolithiasis

Patients with hyperuricosuria may be prone to the formation of calcium oxalate calculi through the process of heterogeneous nucleation (also referred to as epitaxy) (Coe and Kavalach, 1974; Pak and Arnold, 1975; Coe, 1980). The details of this process are outlined in Chapter 51. These patients give a history of calcium oxalate nephrolithiasis and may have a history of hyperuricemia with symptomatic gout. During metabolic evaluation, these patients will demonstrate hyperuricosuria (>800 mg/day).

Hyperoxaluria (>40 mg/day)

Enteric Hyperoxaluria. This entity is often one of the most striking findings during a metabolic evaluation because it involves multiple factors, all caused as a result of chronic diarrhea with its attendant dehydration and bicarbonate losses (Worcester 2002). The main hallmark is, of course, hyperoxaluria with values that can be quite high (i.e., > 50 mg/day). As a result of intestinal fluid loss, patients will often exhibit low urine volumes. The bicarbonate loss (and the consumption of citrate as an acid/base buffer) also can cause a low urine pH and hypocitraturia (Rudman et al, 1980). Urine calcium excretion is often low because of the saponification of oral calcium with poorly absorbed fats in the intestinal tract.

Primary Hyperoxaluria. Primary hyperoxaluria is an extremely rare disorder caused by an inborn error of metabolism. The more common variant, type 1, is due to a defect of the enzyme alanine glyoxylate aminotransferase (AGT) via an autosomal recessive inheritance. Type 2 is a less common variant thought secondary to a defect in D-glycerate dehydrogenase, which has both glyoxylate and hydroxypyruvate reductase. Primary hyperoxaluria usually manifests during childhood with early stone formation, tissue

deposition of oxalate (oxalosis), and renal failure resulting from nephrocalcinosis. Death often occurs before age 20 in untreated patients (Williams and Smith, 1968; Leumann and Hoppe 1999). Metabolic evaluation will reveal high urine oxalate excretion and high serum levels of this molecule.

Mild Metabolic Hyperoxaluria (Dietary). The importance of dietary oxalate and the possibility of an inheritable sensitivity to oral oxalate loads are debated and are discussed in Chapter 51. It appears increasingly evident that a deficiency of a bacterium found within intestinal flora (*Oxalobacter formigenes*) is a factor in the formation of calcium oxalate calculi (Allison et al, 1986; Sidhu et al, 1999; Troxel et al, 2003; Siener et al, 2013). In some patients, the cause of *Oxalobacter* deficiency may be iatrogenic because it is sensitive to a number of commonly prescribed antibiotics, including ciprofloxacin and levofloxacin (Lange et al, 2012). Regardless of the underlying cause, some patients without primary hyperoxaluria or without a history of bowel disorders will demonstrate an elevation of oxalate in 24-hour urine collection. A review of the patient's dietary habits may reveal a predisposition for foods that are particularly high in oxalate. **Although this molecule is ubiquitous and cannot be avoided, certain foods can deliver substantial amounts of oxalate in one serving.** Box 52-3 presents an abbreviated list of foodstuff that are particularly high in oxalate (Assimos and Holmes, 2000; Holmes and Assimos, 2004). A recent pilot study suggests that compliance with dietary modifications to reduce oxalate intake can be improved with an interactive Internet program (Lange et al, 2013).

Hypocitraturic Calcium Nephrolithiasis (<550 mg, Female; <450 mg, Male)

There is some controversy regarding the definition of normal urinary citrate excretion. Women tend to have higher urinary citrate measurements than men, particularly before menopause (Pak, 1990). Despite noting gender differences, Pak (1990) and colleagues define normal urine citrate as greater than 320 mg for both genders. In some of the earlier studies from Dallas, hypocitraturia was found in up to 50% of all patients evaluated, frequently in association with other abnormalities (Nicar et al, 1983). Parks and Coe (1986) also noted the importance of urinary citrate for the prevention of calcareous stones and have set the limits of normal at higher values, with men being more than 450 mg and women at more than 550 mg daily. Nevertheless, hypocitraturia is considered one of the more common metabolic diagnoses, probably second only to hypercalciuria. There are four causes of hypocitraturia, as described in the following section.

Distal Renal Tubular Acidosis (Type 1). Patients may have either an acquired or an inheritable version of RTA, with the incomplete version representing a less serious clinical pattern. Regardless of the actual cause, the laboratory hallmark of this disease is a low urine citrate (hypocitraturia) with an inappropriately high urine pH (Wang and Preminger, 2011). Often, the measured 24-hour urine citrate will be quite diminished, with values less than 100 mg/day. The urine pH will be elevated to 6.5 or above. Hypokalemia is often evident on the serum studies, as is hyperchloremia. A non-anion gap acidosis may be present as well

with carbon dioxide values in the mid-teens (Preminger et al, 1985). First void urine samples can be evaluated to assess the urine pH and screen for RTA. Patients with RTA will be unable to acidify urine overnight and should have a urine pH no lower than 5.5.

Distal RTA may manifest as an isolated entity, or it may be the secondary manifestation of a variety of systemic and renal disorders. More than two thirds of patients with distal RTA are adults, but occasionally children will be identified with this disorder. Infants generally present with vomiting or diarrhea, failure to thrive, and growth retardation; children often present with metabolic bone disease and renal stones; and adults frequently present with symptoms attributable to nephrolithiasis and nephrocalcinosis.

Up to 70% of adults with distal RTA have kidney stones (Caruana and Buckalew, 1988). Those patients with onset at an early age or with severe forms of the disorder may develop nephrocalcinosis and eventual renal insufficiency (Fig. 52-5). RTA is more common in women, accounting for nearly 80% of all cases. It is very important to note that secondary RTA can be induced by many common urologic disorders that also may be sought after a diagnosis of acquired RTA. These include obstructive uropathy, pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, idiopathic hypercalciuria, and primary hyperparathyroidism and can lead to secondary RTA (Buckalew, 1989) (Box 52-4).

Some patients will have an incomplete variant of the disease with less marked hypocitraturia and a more normal urine pH level.

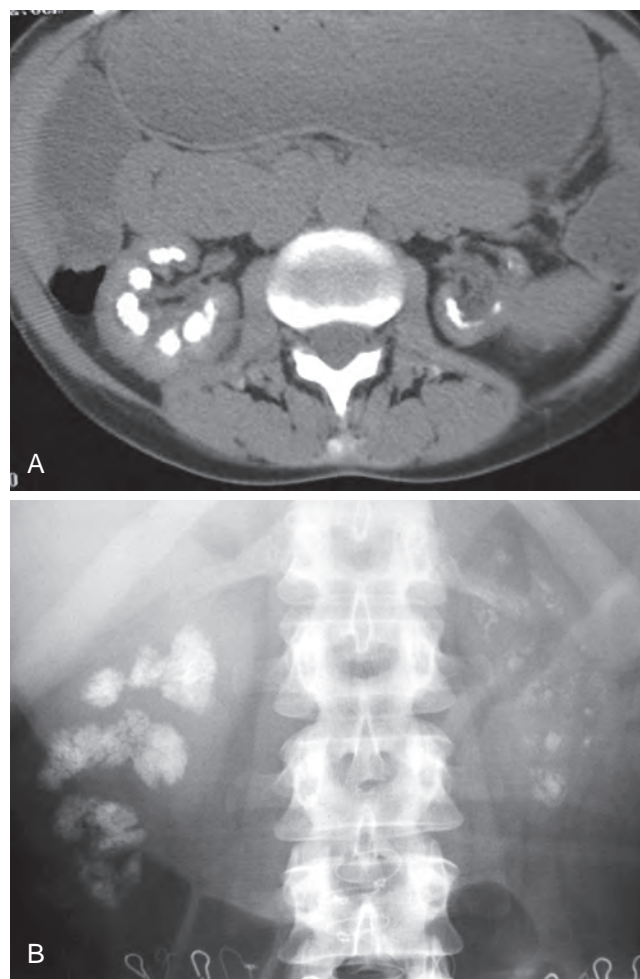


Figure 52-5. Computed tomography (CT) (A) and plain film (B) of a patient with renal tubular acidosis and renal failure. Both kidneys demonstrate severe calcification of the medullary pyramids consistent with nephrocalcinosis. Note the atrophic left kidney on the CT image (A).

BOX 52-3 Foods Containing High Levels of Oxalate

Tea (black)	Okra
Cocoa	Berries (some)
Spinach	Chocolate
Mustard greens	Nuts
Pokeweed	Wheat germ
Swiss chard	Soy crackers
Beets	Pepper
Rhubarb	

BOX 52-4 Causes of Acquired Renal Tubular Acidosis

Obstructive uropathy
 Recurrent pyelonephritis
 Acute tubular necrosis
 Renal transplantation
 Analgesic nephropathy
 Sarcoidosis
 Idiopathic hypercalciuria
 Primary hyperparathyroidism

Incomplete variants can be diagnosed with the use of an ammonium chloride loading challenge. In this evaluation, the fasting patient is given 0.1 g of ammonium chloride per kilogram of body weight in crushed granules mixed with a soft drink. Subsequently, hourly measurements of urinary pH and bi-hourly measurements of serum pH or bicarbonate are taken over 4 to 6 hours (Pohlman et al, 1984). If the serum pH falls below 7.32, or the bicarbonate falls below 16 mmol/L but urinary pH remains at or above 5.5, the diagnosis of incomplete distal RTA is confirmed. If at any time the urinary pH falls below 5.5, the diagnosis of incomplete distal RTA is excluded (Preminger et al, 1985, 1987, 1988).

Chronic Diarrheal States. The laboratory findings in a patient with a chronic diarrheal disorder are similar to those in patients with enteric hyperoxaluria. However, these patients do not tend to suffer from the bowel inflammation and subsequent heightened permeability to oxalate. Therefore urinary oxalate may be mildly elevated, but usually not to the extent as found in patients with bowel resection or inflammatory disorders. These patients likely will demonstrate moderate decreases in urinary citrate excretion with associated low urine volumes (Fegan et al, 1992; Caudarella et al, 1993; Worcester, 2002; Parks et al, 2003b).

Thiazide-Induced Hypocitraturia. One of the side effects of thiazide therapy is the development of hypocitraturia. This defect is presumably secondary to the hypokalemia and resultant intracellular acidosis that may develop after prolonged therapy with thiazides (Pak et al, 1985b). Because thiazides are still widely used as a diuretic and for the management of hypertension, some patients may present with a stone episode after prolonged therapy with this medication. Stone patients who are treated with thiazides for the control of hypercalciuria should be screened for hypocitraturia (Pak et al, 1985b).

Idiopathic Hypocitraturia. Patients with idiopathic hypocitraturia include all those with 24-hour urine citrate less than 550 mg (males) or 450 mg (female) in the absence of any of the previously noted disease states. It is important to consider unrecognized incomplete RTA as a potential diagnosis, because this disorder carries with it a significant risk for long-term morbidity. Additionally, a careful history should be taken to screen for bowel dysfunction.

KEY POINTS: HYPOCITRATURIA

- The definition of hypocitraturia may vary greatly.
- Severe hypocitraturia should immediately raise suspicions for RTA.
- Hypocitraturia frequently accompanies other diagnostic categories.

Hypomagnesuric Calcium Nephrolithiasis (<80 mg)

Hypomagnesuric calcium nephrolithiasis is characterized by low urinary magnesium, hypocitraturia, and low urine volume. It is frequently associated with chronic thiazide therapy (Ljunghall et al, 1981; Preminger et al, 1989). More commonly, inflammatory bowel disorders, particularly those that cause malabsorption, have

been implicated in this process (Preminger et al, 1989). Excessive dependence on laxatives may induce a pattern similar to chronic diarrheal states (Dick et al, 1990; Soble et al, 1999). The importance of this disorder has been questioned, however, with the suggestion that the stone-risk association of hypomagnesuria may actually be due to its effect on urinary citrate (Schwartz et al, 2001).

Uric Acid–Based Calculi**Gouty Diathesis**

The pathophysiology of uric acid nephrolithiasis is explained in detail in Chapter 51 but does deserve some mention to better understand its diagnosis. Because there are no known inhibitors of uric acid crystallization, undissociated uric acid will precipitate when the urine becomes supersaturated. The sigmoidal-shaped solubility curve will predict that at a pH of 6.5 more than 90% of all uric acid is ionized and therefore soluble. Fifty percent of uric acid will be soluble at a pH of roughly 5.5 (pK_a) (Gutman and Yu, 1968). By definition, patients with gouty diathesis have a urine pH of less than 5.5.

It follows, then, that patients with gouty diathesis and uric acid calculi tend to have lower urine pH than normal subjects (Gutman and Yu 1968). Measurements of this molecule at 24 hours often will be greater than 800 mg. Up to 20% of patients with gout will develop uric acid calculi, prompting examination of serum for hyperuricemia. Often, 24-hour urine collections can underestimate the total amount of uric acid if the specimen pH drops lower than 5.5. In this scenario, the uric acid forms precipitates and settles to the bottom of the collection container.

It should not be difficult to distinguish between patients with hyperuricosuric calcium nephrolithiasis (HUCN), who form calcium oxalate stones, and those with gouty diathesis, who can form either uric acid or calcium oxalate calculi. Patients with HUCN present with normal urinary pH and hyperuricosuria, accompanied sometimes by hypercalciuria. In contrast, those with gouty diathesis have a low fractional excretion of urate (that contributes to hyperuricemia) and low urinary pH (that leads to increased amount of undissociated uric acid) (Khatchadourian et al, 1995; Pak et al, 2003c). The varying biochemical and physicochemical presentations of the two conditions can be ascribed to overindulgence with purine-rich foods in those with HUCN and underlying primary gout in those with gouty diathesis (Pak et al, 2002b).

A dietary history should be obtained from all patients with uric acid calculi, because they may have a tendency to purine gluttony (high intake of animal protein). An astute clinician will at least give a brief consideration to the possibility of a neoplastic or myeloproliferative disorder. Patients with diabetes mellitus also may form uric acid calculi as a result of disorders in ammonium handling with subsequent low urine pH (Pak et al, 2003c; Eisner et al, 2010b).

Uric acid calculi can be notoriously radiolucent. Tomography may overcome this difficulty (Fig. 52-6), as can the acquisition of an NCCT scan. DECT can be used to distinguish uric acid calculi from calcium stones with a high degree of accuracy (Primak et al, 2007). These stones frequently have an orange appearance, especially when viewed endoscopically. Uric acid–stone formers can have a propensity to produce large volumes of very small calculi that may cause obstruction as they pass down the ureter.

KEY POINTS: URIC ACID–BASED CALCULI

- Hyperuricosuria may be associated with pure uric acid calculi or calcium oxalate calculi.
- Patients with gout may be predisposed to uric acid stones.
- Dietary indiscretion (purine gluttony) should always be suspected.

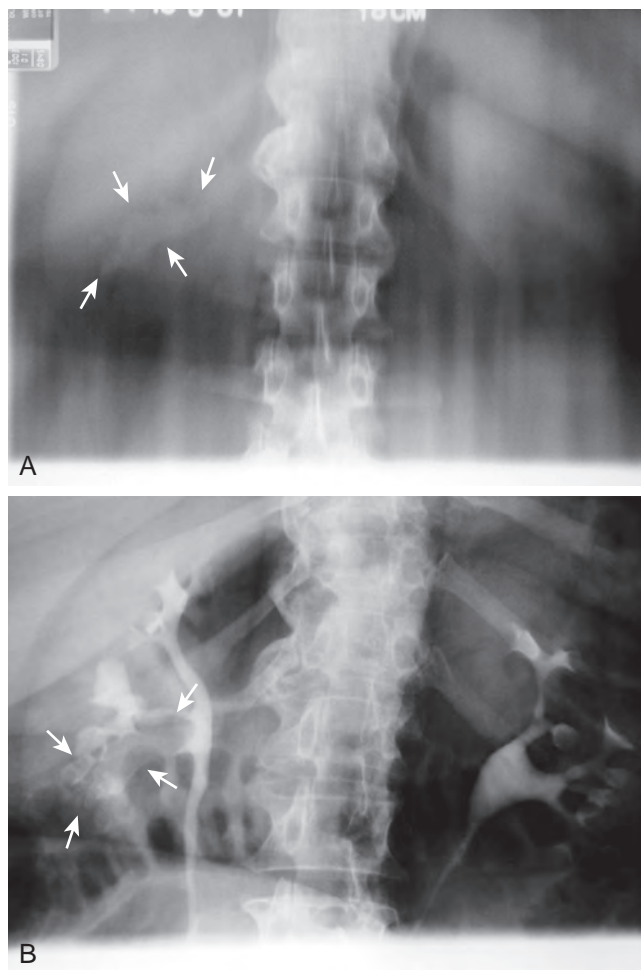


Figure 52-6. A, Plain film tomographic appearance of a lower pole partial staghorn uric acid calculus (arrows). B, The addition of intravenous contrast demonstrates the stone as a “filling defect” (arrows) during the excretory portion of the intravenous pyelogram.

Cystinuria

Cystinuria is caused by an autosomal recessive error of transepithelial transport involving the intestine and kidneys (Thier et al, 1965; Pak and Fuller, 1983). In this disease, patients are unable to reabsorb the dibasic amino acids: cystine, ornithine, lysine, and arginine. The resultant accumulation of cystine causes crystallization when concentrations rise above the saturation point (~ 250 mg cystine per liter of urine) (Pak and Fuller, 1983).

Patients with this disorder may present at a young age and may have affected first-degree relatives. The stones are often yellow and waxy and are relatively faint on plain radiography. Staghorn calculi or multiple, filled calyces are common (Fig. 52-7).

Historically, a diagnosis of cystinuria was made with the use of a sodium nitroprusside spot test that turned purple in the presence of cystine (Smith, 1977). Although this test is a helpful screening adjunct, quantitative measurements of cystine can be difficult to perform because of interference from other sulfhydryl-containing compounds (such as medications used to treat this disorder) or from significant variances with minor changes in urine pH or creatinine content (Pak and Fuller, 1983). Coe and colleagues (2001) developed a more reliable method of cystine supersaturation measurement that may greatly aid in the diagnosis and especially the management of cystinuria (Nakagawa et al, 2000).

Patients with cystinuria may demonstrate additional metabolic anomalies on 24-hour urine studies (Sakhaee et al, 1989). In controlled dietary assessment of 27 patients with cystinuria, hypercalciuria was noted in 18.5% of patients and hyperuricosuria in 22.2%. Hypocitraturia was identified in 44.4% and was associated with

defective renal acidification in 80% of the patients in whom it was tested. The authors noted that hypercalciuria, hyperuricosuria, and hypocitraturia frequently accompany cystinuria and speculated that these conditions might be renal in origin, rather than a result of dietary or environmental aberrations. They further concluded that these unrelated anomalies may contribute to the formation of calcium and uric acid stones, which sometimes complicate cystine nephrolithiasis.

KEY POINTS: CYSTINURIA

- Cystinuria manifests when concentrations exceed 250 mg/L.
- Cystinuria may be accompanied by other metabolic abnormalities.
- Cystine stone formation is based solely on urinary cystine concentration.

Infection Calculi (Struvite)

Struvite calculi form in the presence of alkaline urine ($\text{pH} > 7.2$) and in an environment rich in ammonia (Nemoy and Staney, 1971). The ammonia is thought to be produced by the splitting of urea by colonization with bacteria that produce urease. The details of this process are presented in Chapter 51. Many bacterial organisms are able to produce this enzyme (Table 52-6), the most notorious of which is *Proteus mirabilis*. Although *Escherichia coli* is not able to split urea, it may be associated with struvite calculi in up to 13% of infections (perhaps through a metachronous infection).

Patients with these calculi may present with the symptoms of acute pyelonephritis, including fevers, chills, flank pain, dysuria, frequency, urgency, and malodorous, cloudy urine. Some patients may exhibit more chronic symptoms of malaise, fatigue, loss of appetite, and generalized weakness. Rarely, infections and obstruction have been long-standing enough to produce xanthogranulomatous pyelonephritis, which may cause the failure of an entire kidney or may just affect a portion. Spontaneous fistulae may develop to external surfaces or to peritoneal contents (Fig. 52-8).

Women are more often affected with struvite calculi than men, likely because of an increased susceptibility to urinary tract colonization. A history of a foreign body (e.g., forgotten stent, suture material, staple) or neurogenic bladder may be noted. Struvite calculi can be quite large and often fill multiple calyces or even the entire collecting system (Fig. 52-9). Urine cultures often will reveal a bacterial pathogen, although, as noted previously, the presence of a sterile urine culture does not preclude the sequestration of bacteria within the calculus itself.

There is debate concerning the incidence of associated metabolic anomalies in patients with struvite calculi. Resnick (1981) advocates the performance of a metabolic evaluation for all patients with infection calculi, because of a high incidence of positive findings. Conversely, Lingeman and colleagues (1995) studied 22 patients with infection calculi and noted that patients with pure struvite calculi were significantly less likely to have metabolic anomalies on 24-hour urine evaluation than those patients with mixed compositions of struvite and calcium oxalate. More recently, Iqbal and colleagues (2013) reviewed their experience with struvite stones. They reported that 60% of pure struvite-stone formers and 77% of mixed struvite-stone formers had metabolic abnormalities on 24-hour urine collections. The most common abnormalities were hypercalciuria and hypocitraturia.

KEY POINTS: INFECTION CALCULI (STRUVITE)

- Women produce more infection calculi than men.
- The urine pH is usually greater than 6.5 to 7.0.
- Urea-splitting organisms are frequent.
- Infection calculi commonly produce staghorn stones.

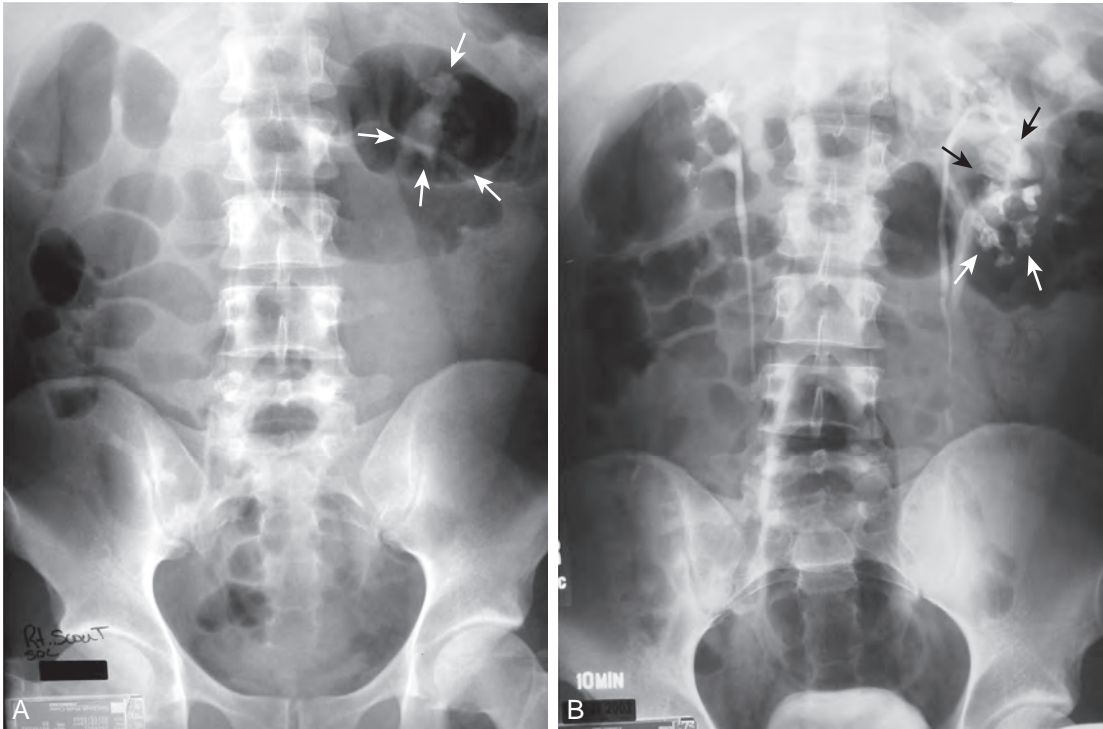


Figure 52-7. Cystine calculi are radiopaque on plain film, but are less dense than other calcium-based calculi. **A,** Note the stone (arrows) within the lower pole of this duplicated system. **B,** Similar to uric acid stones, the cystine calculus (arrows) is more clearly distinguished during the excretory phase of the intravenous pyelogram.

TABLE 52-6 Urea-Splitting Organisms

ORGANISMS	USUALLY (>90% OF ISOLATES)	OCCASIONALLY (5%-30% OF ISOLATES)
Gram positive	<i>Proteus rettgeri</i> <i>Proteus vulgaris</i> <i>Proteus mirabilis</i> <i>Proteus morganii</i> <i>Providencia stuartii</i> <i>Haemophilus influenzae</i> <i>Bordetella pertussis</i> <i>Bacteroides corrodens</i> <i>Yersinia enterocolitica</i> <i>Brucella</i> spp.	<i>Klebsiella pneumoniae</i> <i>Klebsiella oxytoca</i> <i>Serratia marcescens</i> <i>Haemophilus parainfluenzae</i> <i>Bordetella bronchiseptica</i> <i>Aeromonas hydrophila</i> <i>Pseudomonas aeruginosa</i> <i>Pasteurella</i> spp.
Gram positive	<i>Flavobacterium</i> spp. <i>Staphylococcus aureus</i> <i>Micrococcus</i> <i>Corynebacterium ulcerans</i> <i>Corynebacterium renale</i> <i>Corynebacterium ovis</i> <i>Corynebacterium hofmannii</i>	<i>Staphylococcus epidermidis</i> <i>Bacillus</i> spp. <i>Corynebacterium murium</i> <i>Corynebacterium equi</i> <i>Peptococcus asaccharolyticus</i> <i>Clostridium tetani</i> <i>Mycobacterium rhodochrous</i> group
<i>Mycoplasma</i>	T-strain <i>Mycoplasma</i> <i>Ureaplasma urealyticum</i>	
Yeasts	<i>Cryptococcus</i> <i>Rhodotorula</i> <i>Sporobolomyces</i> <i>Candida humicola</i> <i>Trichosporon cutaneum</i>	

From Gleeson MJ, Griffith DP. Infection stones. In: Resnick MI, Pak CYC, editors. Urolithiasis: a medical and surgical reference. Philadelphia: Saunders; 1990. p. 115.

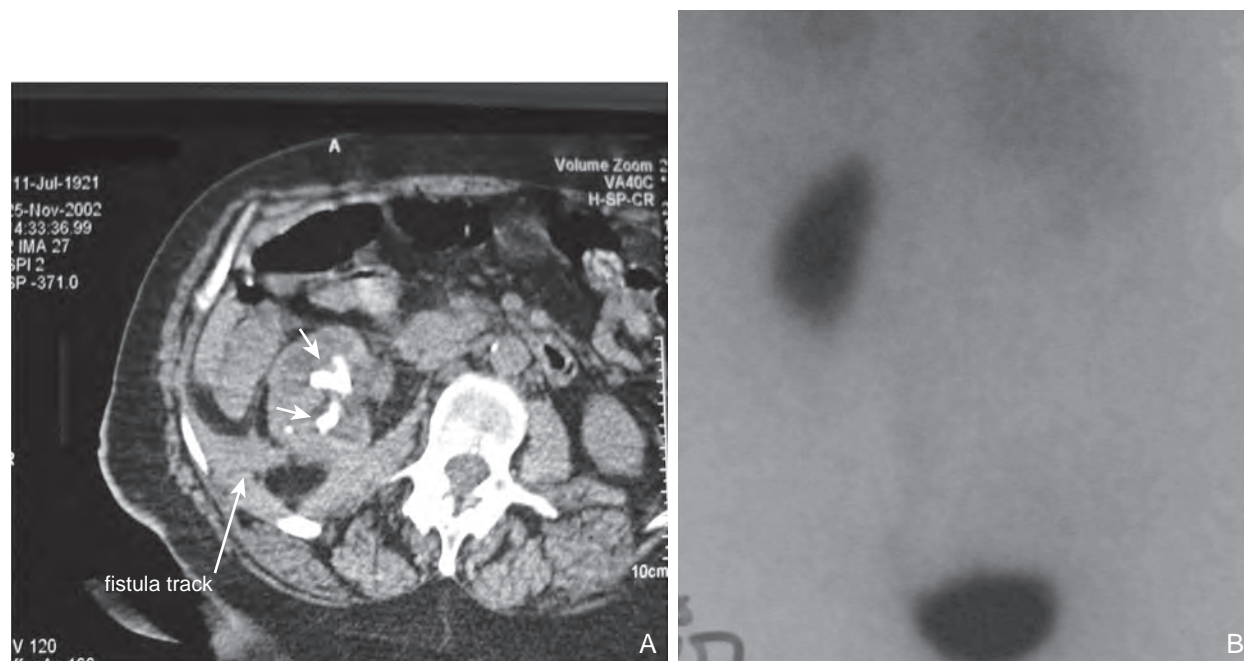


Figure 52-8. A, Computed tomography image of a staghorn calculus within the right kidney. Arrow points to a fistula that spontaneously eroded through the triangle of Petit. This patient denied a history of recurrent urinary tract infections. B, Nuclear renogram of the same patient as in A. Note the complete lack of function of the affected kidney. This organ was removed laparoscopically.



Figure 52-9. Plain film of a patient with bilateral staghorn calculi composed entirely of struvite. This patient had a history of recurrent urinary tract infections dating back 15 years.

Low Urine Volumes (<2000 mL)

Some patients will exhibit very few abnormalities other than low urine volumes on a complete evaluation. From a simplistic view, a low volume of urine output will concentrate the molecular components of crystal formation and raise the supersaturation risk. Intuitively, a patient with a relative state of dehydration will trend toward acidic urine, lowering the urine pH toward the pKa of uric acid (5.5) and potentially consuming titratable buffers such as citrate.

Many patients with low urine volumes work in professions that induce high insensible losses of fluid (e.g., manual labor, outdoor exposure) (Sakhaee et al, 1987; Borghi et al, 1990, 1993a). Many

BOX 52-5 Potential Causes of Erroneous 24-Hour Urine Collection Results

- Error in collection technique (e.g., improper use of preservatives, ice)
- Failure to collect a full 24 hours' worth of urine
- Changes in the patient's diet for the sake of the study
- Intermittent indiscretions in diet
- Failure of specimen to accurately represent typical day
- Bacterial contamination

work in environs that do not allow easy access to fluids and work breaks (assembly line, surgeons). A focused social history should elucidate these factors and allow for proper identification and subsequent counseling.

No Disturbances

Pak and associates (1980a) estimated that 3% of all patients undergoing a full metabolic evaluation will demonstrate no abnormalities. Although on the surface, these patients may present less of a diagnostic challenge, there is always a concern that the collections are not representative of the patient's true metabolic state (Box 52-5). This could be secondary to an error in collection technique, failure to collect a full 24 hours' worth of urine, changes in the patient's diet for the sake of the study, or intermittent indiscretions in diet. Furthermore, it is important to remember that a 24-hour urine collection represents a pooled sample. Heavy oxalate loading at one particular meal or bolus replacement of fluids at the end of a work day may produce average values that look normal, but actually hide periods of extreme urine parameters that promote stone formation. Finally, most patients will collect their requested 24-hour specimens on days when they are home and able to stay close to the collection container. For most, this occurs on a weekend or nonworking day. It is very possible (and quite likely)

TABLE 52-7 Diagnostic Criteria

	SERUM			URINARY							
	Ca	P	PTH	Ca FASTING	Ca LOAD	Ca RESTRICTED	UA	Ox	Cit	pH	Mg
Absorptive hypercalciuria type I	N	N	N	N	↑	↑	N	N	N	N	N
Absorptive hypercalciuria type II	N	N	N	↑	N	N	N	N	N	N	N
Renal hypercalciuria	N	N	↑	↑	↑	↑	N	N	N	N	N
Primary hyperparathyroidism	↑	↓	↑	↑	↑	↑	N	N	N	N	N
Unclassified hypercalciuria	N	N/↓	N	↑	↑	↑	N	N	N	N	N
Hyperuricosuria	N	N	N	N	N	N	↑	N	N	N	N
Enteric hyperoxaluria	N/↓	N/↓	N/↓	↓	↓	↓	↓	↑	↓	N	N
Hypocitraturia	N	N	N	N	N	N	N	N	↓	N	N
Renal tubular acidosis	N	N	N/↑	↑	N	N/↑	N	N	↓	N/↑	N
Hypomagnesuria	N	N	N	N	N	N	N/↓	N	↓	N	↓
Gouty diathesis	N	N	N	N	N	N	N/↑	N	N/↓	↓	N
Infection lithiasis	N	N	N	N	N	N	N	N	↓	↑	N

Fasting samples represent 2-hour collections obtained in morning after an overnight fast. Calcium load samples were obtained over a 4-hour period subsequent to oral ingestion of 1 g calcium.

↑, high; ↓, low; Cit, citrate; Mg, magnesium; N, normal; Ox, oxalate; PTH, immunoreactive parathyroid hormone; UA, uric acid.

that collections on these days do not represent the patient's typical metabolic milieu that exists during the rest of the week (Rodgers et al, 1994, 1995; Norman, 1996; Hess et al, 1997).

The diagnostic criteria for the 12 principal classifications described in this section are summarized in Table 52-7.

CONSERVATIVE MEDICAL MANAGEMENT

Certain conservative recommendations should be made for all patients regardless of the underlying cause of their stone disease. Unfortunately, it can be difficult to reach consensus regarding specific details from the available literature.

Fluid Recommendations

Volume

One mainstay of conservative management is the forced increase in fluid intake to achieve a daily urine output of at least 2 liters (Borghi et al, 1999). Increased urine output may have two effects. First, the mechanical diuresis that ensues may prevent urinary stagnation and the formation of symptomatic calculi. It is more likely that the creation of dilute urine alters the supersaturation of stone components. Indeed, Pak and colleagues (1980b) measured in vitro and in vivo effects of urinary dilution and discovered that both significantly reduced the urinary activity product ratio (state of saturation) of calcium phosphate, calcium oxalate, and monosodium urate. Moreover, the formation product ratio—that is, the minimum supersaturation needed to elicit spontaneous nucleation—of calcium oxalate significantly increased.

Researchers at the University of Chicago demonstrated that failure to increase urine output was one of three very strong predictors of relapse for patients followed in a dedicated stone clinic (Strauss et al, 1982a). The previously described stone clinic effect has been primarily attributed to increases in fluid intake and attendant increases in urinary output (Hosking et al, 1983).

However, although the concept of increased fluid intake is quite simple, it can be quite difficult to achieve patient compliance. Anecdotally, most physicians with an interest in kidney stone disease have seen that many patients are unable to maintain increased urinary output over the long term. This general impression has been borne out in an analysis of urine output changes from a large series

of 2877 patients (Parks et al, 2003a). In this amalgam of university and private practice patients, the average increase in urinary volume was only 0.3 L/day. In addition, intermittent compliance may not be effective, because small, early stones may develop during periods of intense dehydration. At least one author suggested that if a patient is able to voluntarily force fluid intake long enough to dilute renal concentrating abilities, then thirst mechanisms will take over and help maintain a high fluid intake and high urine output (Burns and Finlayson, 1981). Unfortunately, the more recent data from Parks and colleagues (2003a) has not proved this finding to be reliable.

Water Hardness

If water intake is so important, is there a difference between levels of water hardness that might ameliorate or augment its benefit? This concept has been the topic of conflicting articles within the general urologic and epidemiologic literature. In one study, patients with a known history of calcium nephrolithiasis were divided according to postal zip codes. Twenty-four-hour urine measurements were compared, as was the history of stone episodes (Schwartz et al, 2002). Although the 24-hour urine calcium, magnesium, and citrate levels increased directly with drinking water hardness, no significant change was found in urinary oxalate, uric acid, pH, or volume. Most importantly, the number of total lifetime stone episodes was similar between patients residing in areas with soft public water and hard public water. Patients consuming the softest water formed 3.4 lifetime stones, and those who consumed the hardest water developed 3.0 lifetime stones. The authors noted that although water hardness can alter urinary parameters, this factor ultimately appears to have little effect on clinical outcome.

These findings are further supported by earlier work from Shuster and associates (1982). They examined 2295 patients from two regions: the Carolinas, which had soft water and high stone incidence, and the Rockies, which had hard water and low stone incidence. Home tap water samples from urinary stone patient hospitalizations were compared with controls. After adjusting for environmental factors, no significant difference between the two groups was obtained in tap water calcium, magnesium, and sodium concentrations. An incidental but potentially important finding was that those consuming water from a private well had an estimated relative risk for stone formation of 1.5 compared to those using public water. They ultimately concluded that water hardness should be a minor concern with respect to stone formation.

Unfortunately, this issue has not been completely put to rest, because there is still evidence that hard water may confer some excess risk for stone formation. In a well-controlled study involving fixed diets and a crossover design, 18 subjects with a history of calcium nephrolithiasis drank only hard water, soft water, or tap water (Bellizzi et al, 1999). The urinary levels of calcium demonstrated a significant 50% increase in the absence of changes of oxalate excretion. Although these changes are concerning, it is important to note that stone events were not used as a primary outcome. Another recent controlled diet study also demonstrated an increase in urinary calcium-to-creatinine ratio in stone formers who consumed hard water versus water that was less hard (Mirzazadeh et al, 2012).

Carbonated Beverages

A number of studies suggest that carbonated water offers increased protection against recurrent stone formation as compared to still water (Rodgers 1997, 1998; Bren et al, 1998; Caudarella et al, 1998; Coen et al, 2001). It should be noted that these studies focused primarily on carbonated water, which has been demonstrated to increase urinary citrate levels.

Other types of carbonated beverages have been examined. One study demonstrated that increased intake of soda can confer an increased risk for subsequent stone recurrence (Shuster et al, 1992). The study sample consisted of 1009 male subjects, who reported consuming at least 160 mL/day of soft drinks. Half of the subjects were randomized to refrain from consuming soft drinks, and the remaining subjects served as controls. The intervention group had an observed 6.4% advantage in actuarial 3-year freedom from recurrence over the control group. One important secondary finding was that those who reported that their most consumed drink was acidified by phosphoric acid but not citric acid had a 15% higher 3-year recurrence-free rate than the controls. Meanwhile, those who consumed drinks acidified by citric acid had no increase in stone episodes when compared to controls. A number of citrus-flavored sodas (orange flavored, lemon/lime flavored) have been shown to have high citrate content, which may aid in stone prevention (Haleblian et al, 2008; Eisner et al, 2010a).

Recently, a comparison of self-selected diets to standardized diets combined with regulated fluid intake with still water, or two sugar-free, caffeine-free carbonated beverages (one with high citrate content) documented no difference in urinary parameters among the standardized diets with regulated fluid intake, but a significant increase in urinary volume and a decrease in calcium oxalate saturation when these were compared to the self-selected diets (Passman et al, 2009).

Additional epidemiologic studies have demonstrated the effects of particular fluids on the risk for stone recurrence (Curhan et al, 1996a, 1998b). For both men and women, there was a decrease in the risk for nephrolithiasis for those who consumed increased volumes of water, caffeinated or decaffeinated coffee, tea, beer, and wine. Conversely, daily servings of apple or grapefruit juice increased the risk for stone events. Despite the epidemiologic evidence, the supersaturation risks associated with grapefruit juice have largely been discredited by subsequent evaluations (Goldfarb and Asplin, 2001; Trinchieri et al, 2002; Honow et al, 2003).

In contrast to these epidemiologic findings, recent evidence suggests that caffeine intake may increase the risk for stone recurrence in calcium-stone formers by increasing the excretion of calcium. Caffeine increased urinary calcium/creatinine, magnesium/creatinine, citrate/creatinine, and sodium/creatinine, but not oxalate/creatinine in stone formers and controls. Furthermore, supersaturation calculations increased, despite the noted increases in the inhibitors citrate and magnesium (Massey and Sutton, 2004).

Citrus Juices

Lemonade and orange juice have long been used as an adjunct to water to provide increased urinary volume as well as increased urinary citrate excretion. In a study of 12 hypocitraturic patients,

lemonade made from reconstituted lemon juice provided enough citrate to correct the hypocitraturia in 7 subjects (Seltzer et al, 1996). Urinary calcium excretion decreased an average of 39 mg daily, whereas oxalate excretion was unchanged. The lemonade mixture was well tolerated, with only two patients reporting mild indigestion that did not require cessation of therapy. Wabner and Pak (1993) similarly evaluated the effects of orange juice on the urinary parameters of normal subjects and found that compared to potassium citrate, orange juice delivered an equivalent alkali load and caused a similar increase in urinary pH (6.48 vs. 6.75 from 5.71) and urinary citrate (952 vs. 944 from 571 mg/day). Therefore orange juice, like potassium citrate, decreased urinary undissociated uric acid levels and increased the inhibitor activity (formation product) of brushite (calcium phosphate). However, orange juice increased urinary oxalate and did not alter calcium excretion, whereas potassium citrate decreased urinary calcium without altering urinary oxalate. They concluded that orange juice could be beneficial in the control of calcareous and uric acid nephrolithiasis. Further work evaluating the effects of distilled water, orange juice, and lemonade are provided by Odvina (2006). In a randomized, crossover study under controlled metabolic conditions, 13 patients were evaluated. The author found that orange juice intake, and not lemonade or water, led to a higher urinary pH and increased urinary citrate level. Urinary calcium was not different between the groups but oxalate was elevated in the orange juice arm. Finally, the supersaturation of calcium oxalate and undissociated uric acid were lowest during the orange juice phase, but the brushite supersaturation was significantly higher during this phase.

In comparison, a recent evaluation of reconstituted lemonade (1 oz RealLemon in $\frac{3}{4}$ cup of water) compared to 60 mEq of potassium citrate did not identify an increase in the urinary citrate excretion for the lemonade arm (Koff et al, 2007). Additionally, patients on lemonade therapy did not significantly alter their urinary pH, but a slight, though nonsignificant, increase in urinary volume was noted. However, 48% of the patients in this study did not demonstrate hypocitraturia before treatment, potentially confounding the results.

Using nuclear magnetic resonance spectroscopy, the citrate concentrations of a number of commercially available citrus and citrus-based beverages was assessed (Haleblian et al, 2008). This finding confirmed that natural juices are highest in citrate and potassium content, with grapefruit juice containing the greatest amount of citrate (197.5 mEq/L), followed closely by lemon and orange juice (145.48 and 144.57 mEq/L, respectively). Of the commercially available citrus-based beverages, Crystal Light (Kraft Foods, Northfield, IL) exhibited the highest concentration of citrate (117.2 mEq/L). The clinical effects of citrus-based beverages in patients with hypocitraturia have yet to be studied but may offer alternatives to patients who are not agreeable to citrus juices.

Overall, most evidence suggests that it is not the type of fluid ingested that is important for stone prevention but rather the absolute amount of fluid volume taken in per day. We therefore encourage all of our stone formers to drink at least 3000 mL/day to maintain a urine output greater than 2500 mL/day.

KEY POINTS: FLUID RECOMMENDATIONS

- Patients should be strongly encouraged to consume enough fluids to produce 2 L/day.
- Water hardness is unlikely to play a significant role in recurrence risk.
- Carbonated water may confer some protective benefit.
- Soda flavored with phosphoric acid may increase stone risk, whereas those with citric acid may decrease risk.
- Citrus juices (particularly lemon and orange juices) may be a useful adjunct to stone prevention.

Dietary Recommendations

Although metabolic abnormalities probably contribute to the majority of risk factors for recurrent nephrolithiasis, increasing evidence suggests that dietary changes are having an important impact on renal stone disease. Indeed, recent studies have documented an increasing incidence of nephrolithiasis, along with a greater propensity of female stone disease, than previously reported. A more complete discussion of these trends can be found in the previous chapter on the epidemiology and pathophysiology of nephrolithiasis (Pak et al, 1997; Ramello et al, 2000; Trinchieri et al, 2000; Coward et al, 2003; Hesse et al, 2003; Stamatelou et al, 2003; Amato et al, 2004). Therefore alterations in diet and physical activity may significantly reduce the incidence of recurrent nephrolithiasis.

Protein Restriction

Epidemiologic studies from a number of countries have shown that the incidence of renal stones is higher in populations in which there is an increased animal protein intake. For example, in the northern and western regions of India, animal protein intake is approximately 100% greater than in the southern and eastern regions and the rate of kidney stones is four times greater. In the United Kingdom, the frequency of upper tract stone disease correlates with the per capita expenditure on foodstuffs (Robertson et al, 1979, 1982). This effect may be partly because protein intake is higher in affluent people, and stone formation, for some reason, seems to be higher in the economically advantaged. When populations are matched for economic status, the intake of protein and other dietary constituents does not differ in patients with recurrent stones and controls. Even in subjects thus matched, however, patients with stones secrete greater quantities of calcium in the urine than do controls for a given intake of protein (Wasserstein et al, 1987). Thus patients with stones may be more sensitive to dietary protein loading than normal subjects.

Protein intake increases urinary calcium, oxalate, and uric acid excretion and the mathematically calculated probability of stone formation even in normal subjects. Indeed, according to Burns and Finlayson (1981), ingestion of protein is second only to ingestion of vitamin D in enhancing intestinal absorption of calcium. Early investigations of purine loading in controlled clinical laboratory settings confirmed the risk for hypercalciuria and hyperuricosuria with a diet high in animal protein (Pak et al, 1978; Fellstrom et al, 1983; Breslau et al, 1988). Patients with stones also exhibit inappropriate hypercalciuria in response to carbohydrate, sodium, and oxalate intake. In one acute study, dietary protein restriction resulted in a decrease in calcium, phosphate, and oxalate (Liatsikos and Barbalias, 1999). In another study in hypercalciuric patients, protein restriction resulted in decreased urinary uric acid and increased urinary citrate as well (Giannini et al, 1999).

Borghesi and colleagues (2002) provide further support to the importance of dietary protein in stone formation. In a prospective fashion, patients were randomized to either a low-protein, low-salt, moderate-calcium diet or to a low-calcium diet. Although acknowledging that it is difficult to separate the potential effects of the three facets of the first diet, there was a convincing 50% reduction in stone events compared to those patients on the low-calcium diet (Borghesi et al, 2002). In another dietary study, the same group of investigators suggests that diets high in fruits and vegetables impart a significantly reduced risk for stone formation than do those diets high in animal protein (Meschi et al, 2004). Twelve normal subjects had fruits and vegetables eliminated from their diets, and 26 hypocitraturic calcium-stone formers (with low fruit and vegetable intake) had their diet supplemented with low-oxalate-containing fruits and vegetables. The normal subjects (without fruit and vegetable intake) demonstrated significant decreases in urinary potassium (−62%), magnesium (−26%), citrate (−44%), and oxalate (−31%) while increasing their urinary excretion of calcium (+49%) and ammonium (+12%). In contrast, the hypocitraturic calcium-stone formers (with increased fruit and vegetable intake) significantly increased

their urinary volume (+64%), pH (5.84 → 6.19), potassium (+68%), magnesium (+23%), and citrate (+68%) while decreasing excretion of ammonium (−18%). Finally, the relative supersaturation of calcium oxalate and calcium phosphate rose significantly for the normal subjects without fruit and vegetable intake while the supersaturation of calcium oxalate and uric acid fell in the stone formers with fruit and vegetable intake.

More recently, the Dietary Approaches to Stop Hypertension (DASH) style diet has been evaluated for its effect on kidney stone formation. The DASH diet is rich in fruit and vegetables, moderate in low-fat dairy products, and low in animal protein. In a prospective population-based study, higher DASH scores were associated with a lower risk for kidney stone formation (Taylor et al, 2009). The inhibitory effect of the DASH diet is likely related to increase in urinary citrate and urine volume. A higher DASH score was associated with a higher urinary citrate and an increased volume on 24-hour urine collection (Taylor et al, 2010).

Not all investigators have noticed the relationship between intake of meat and hypercalciuria. Brockis and colleagues (1982) demonstrated that mean urinary excretion of calcium and oxalate were similar in matched groups of vegetarians and nonvegetarians. A large study at the University of Pennsylvania found that patients with recurrent nephrolithiasis consumed a diet similar in composition to that of case controls (Goldfarb, 1994). Most studies, however, suggest that an increased intake of meat may exacerbate calcium oxalate stone disease.

Sodium Restriction

Sodium restriction has been widely recommended as an important element of dietary prevention of recurrent nephrolithiasis (Massey and Whiting, 1995). Indeed, the evidence implicating excess sodium ingestion as a cause of calcium stone disease comes from several authors in different countries. Ito and colleagues (1993) from Japan have noticed that calcium-stone formers had increased levels of sodium ingestion compared to the daily recommended allowances for the Japanese nation. They also found that stone formers consumed larger amounts of animal protein. They did not comment on whether the increased sodium ingestion was caused by the protein excess or whether it acted as an independent risk factor.

Researchers in Dallas, Texas have confirmed the effects of salt-loading in a controlled crossover study involving normal volunteers. In their study, 14 normal subjects participated in two phases of study of 10 days' duration each, comprising a low-sodium phase (basal metabolic diet containing 50 mmol/day of sodium) and a high-sodium phase (basal diet plus 250 mmol/day of sodium chloride). The high sodium intake significantly increased urinary sodium (34 to 267 mmol/day), calcium (2.73 to 3.93 mmol/day), and pH (5.79 to 6.15) and significantly decreased urinary citrate (3.14 to 2.52 mmol/day). They noted that a high sodium intake not only increased calcium excretion but also increased urinary pH and decreased citrate excretion. The net effect of a high-sodium diet was an increased propensity for the crystallization of calcium salts in urine (Sakhaee et al, 1993).

Additionally, the previously quoted investigation by Borghesi involving dietary manipulation included a low-salt diet, limited to 50 mmol/day of sodium chloride (Borghesi et al, 2002). When combined with animal protein restriction and moderate calcium ingestion, a reduced-sodium diet will decrease stone episodes by roughly 50%. Further work from Italy has demonstrated that calcium-stone formers who ingest large quantities of daily salt are more likely to suffer from decreased bone mineral density (Martini et al, 2000). In this study of 85 patients, all females were premenopausal, underscoring the risks for further osteopenia that they might develop later in life. After adjustment for calcium and protein intakes, age, weight, body mass index (BMI), urinary calcium, citrate and uric acid excretion, and duration of stone disease, multiple-regression analysis showed that a high sodium chloride intake (≥ 16 g/day) was the single variable that was predictive of risk for low bone density in calcium stone-forming patients (OR = 3.8).

Conversely, patients with hypocitraturic calcium oxalate stone formation may benefit from sodium supplementation (Stoller et al, 2009). Eight patients with isolated hypocitraturia, based on 24-hour urinalysis were managed with regular diet and potassium citrate for 7 days, followed by the addition of 3 g of daily sodium supplementation for 7 days. The cohort had significant increases in total urinary volume and sodium excretion over 24 hours but did not demonstrate significant increases in calcium, oxalate, and uric acid, which led to significant decreases in the urinary supersaturation relative risk ratio for calcium oxalate stones.

KEY POINTS: DIETARY RECOMMENDATIONS

- Randomized studies have confirmed the advantage of a diet with reduced animal protein (meat) intake.
- A diet high in fruits and vegetables imparts a reduced risk for stone formation over diets high in animal protein.
- Randomized trials have demonstrated a benefit of dietary sodium restriction in both normal volunteers and stone formers.

Obesity

Obesity has been associated with impaired carbohydrate tolerance and an inappropriate calcium response to glucose ingestion. Thus the hypercalciuria seen in meat eaters may be a function of increased body weight (Menon and Krishnan, 1983). Trinchieri and colleagues (1998b) found that daily urinary oxalate excretion was related to BMI in a group of stone formers. The association between body size and risk for stone formation was studied formally by the Curhan group (Curhan et al, 1998a). In two large cohorts—the Health Professionals Follow-Up Study (HPFS) and the Nurses Health Study (NHS)—the prevalence of stone disease history and the incidence of new stone formation were directly associated with weight and BMI. The magnitude of the association was greater in women than in men. Subsequently, Taylor and Curhan (2006) performed a subset analysis on the HPFS and NHS cohorts with evaluation of 24-hour urinalyses. Higher BMI was found to be associated with increased urinary excretion of oxalate, sodium, uric acid, calcium, and phosphorus, as well as lower pH. It is noted, however, that calcium excretion was no longer associated with BMI once corrected for phosphorus and sodium excretion, thereby suggesting calcium excretion is more closely related to composition of diet and not obesity.

These same cohorts of patients have been continuously followed, and the group from Boston has provided a recent update on the role of obesity and nephrolithiasis. **They demonstrated that increased BMI, larger waist size, and weight gain correlated with an increased risk for stone episodes. This increased stone risk was still more pronounced for women than men (Taylor et al, 2005).**

In a review of a large national database, Powell and colleagues (2000) examined the serum and 24-hour urine parameters from nearly 6000 patients with a history of nephrolithiasis. Within this cohort, obese patients had increased urinary excretion of sodium, calcium, magnesium, citrate, sulfate, phosphate, oxalate, uric acid, and cystine combined with a decrease in urinary pH. Furthermore, obesity was associated with increased urinary volumes and urine osmolality compared with the nonobese patients. Sodium and sulfate excretion is related to daily intake of salt and protein; thus these findings support the theory that excessive food consumption is linked to risk for nephrolithiasis in obesity. Despite the global changes in urinary metabolites, only obese women (compared to nonobese women) had an increase in the stone episodes. Similar findings from Siener and associates (2004) support the association of obesity with the risk for stone formation. In an analysis of urine chemistries from 527 calcium oxalate–stone formers, the authors identified positive correlations between BMI and sodium, phosphorus, and uric acid excretion and negative correlations between BMI

and urinary pH. Citrate and urinary volume did not correlate with BMI, unlike in Powell's report.

One component of the American diet that appears to be related to obesity and metabolic syndrome is fructose. Fructose adds a caloric load to the American diet and may additionally directly affect the risk for stone formation. Taylor and Curhan's (2008b) analysis of the HPFS and NHS (I and II) documented that increasing fructose intake correlated with an increasing relative risk for incident stone formation, regardless of BMI, caloric intake, or other risk factors. This simple sugar has been shown to increase urinary calcium excretion in both rats and humans in limited studies, as well as the production and excretion of uric acid in humans (Koh et al, 1989; Milne and Nielsen 2000; Taylor and Curhan, 2008b). A more recent study evaluating the impact of fructose consumption on stone risk found that there was no change in 24-hour urine calcium, oxalate, or uric acid excretion with increasing fructose consumption (Knight et al, 2010).

One study has specifically evaluated the metabolic disturbances of obese patients, defined as a BMI greater than 30 (Ekeruo et al, 2004). It was determined that the most common manifesting metabolic abnormalities among obese patients included gouty diathesis (54%), hypocitraturia (54%), and hyperuricosuria (43%), which manifested at levels that were significantly higher than those found in nonobese stone formers. When present, chemical stone analysis showed a predominance of uric acid calculi, implicating excessively acid urine in these subjects. Directed medical therapy and dietary recommendations were able to dramatically reduce stone episodes for these patients.

Metabolic Syndrome

Metabolic syndrome consists of a cluster of disease states—glucose intolerance, elevated blood pressure, dyslipidemia, and central obesity—that increase the risk for developing type 2 diabetes and coronary vascular disease. All of these issues are frequently found in the obese population. Assessment of the overall rise of type 2 diabetes, obesity, metabolic syndrome, and stone disease suggests potential correlation among these states. A number of investigations have shown an increased risk for stone disease in patients with metabolic syndrome (Kadlec et al, 2012; Sakhaee et al, 2012; Cho et al, 2013). Cho and colleagues (2013) reported on the stone composition of patients with metabolic syndrome. Although the most common stone composition was calcium oxalate, these patients had a significantly higher risk for having a uric acid stone compared to patients without metabolic syndrome.

A number of studies have identified an increased risk for stone disease in diabetics (Pak et al, 2003c; Taylor et al, 2005; Lieske et al, 2006; Weinberg et al, 2014). Lieske and colleagues (2006) identified an OR of 1.22 for diabetes among stone formers, whereas Taylor and associates (2005) found a relative risk of 1.31 to 1.38 of stone formation in patients with diabetes, depending on age and sex. These studies confirm the earlier work by Pak and coworkers, in which uric acid stones were identified in a statistically significant predominance for patients with diabetes, indicating innate metabolic abnormalities specific to patients with diabetes.

Recent studies suggest that the increased incidence of uric acid stone formation in obese stone formers may be secondary to the production of more acidic urine than in nonobese patients. Combined data from the two largest stone centers in the United States found that urine pH appears to be directly correlated with body size (Maalouf et al, 2004). Furthermore, patients with type 2 diabetes have been found to have lower urinary pH than nondiabetics independent of the formation of uric acid stones (Cameron et al, 2006). When evaluating patients who form uric acid stones, Sakhaee and associates (2002) identified a much higher incidence of diabetes (both types 1 and 2) compared to other groups. Because individuals with diabetes have impaired ammonium excretion, they have been shown to have an increased incidence of uric acid stone formation (Pak et al, 2003c; Abate et al, 2004). Finally, low urine pH has been shown to directly correlate with the number of metabolic syndrome features (Maalouf et al, 2007). From evaluation of

24-hour urinalyses in 148 non-stone forming patients, a statistically significant linear relationship was identified in which each additional characteristic of metabolic syndrome portended a decrease in urine pH. Additionally, the degree of insulin resistance was also inversely related to urinary pH.

Impact of Weight-Loss Diets

As the epidemic of obesity has increased in Western society, so too has the popularity of weight-reducing diets. Current dietary fads include the use of low-carbohydrate, high-protein, high-fat diets (Atkin's Diet, South Beach Diet, and Sugar Busters Diet). A number of studies have documented an increase in the urinary calcium load from increased protein intake (Licata et al, 1979; Breslau et al, 1988). In a study of the impact of a high-protein, low-carbohydrate diet (Atkins Diet), 10 healthy subjects engaged in a low-carbohydrate, high-protein diet for 6 weeks under the care of a clinical dietitian (Reddy et al, 2002). After 6 weeks, urine pH decreased from 6.09 to 5.67, net acid excretion increased by 51 mEq/day, urinary citrate levels decreased from 763 mg/day to 449 mg/day. In addition, urinary saturation of undissociated uric acid increased more than two-fold, urinary calcium levels increased from 160 mg/day to 248 mg/day, causing an estimated calcium balance decrease of 90 mg/day. **Therefore the consumption of a low-carbohydrate, high-protein diet delivers a marked acid load to the kidney, increases the risk for stone formation, and may increase the risk for bone loss.** Although changes in urinary parameters are recognized, there has yet to be a study investigating the incidence of stone disease in a population conforming to this diet. Potentially, addition of alkali therapy may reduce the acidosis and hypercalciuria, while normalizing citrate metabolism without increase in caloric intake. **As mentioned earlier, a diet high in fruits and vegetables and low in animal protein, specifically the DASH diet, is associated with a reduced risk for stone formation (Taylor et al, 2009).**

Impact of Bariatric Surgery

Bariatric surgery continues to increase in popularity and administration as rates of obesity rise. Historically, the initial weight-loss operation was jejunioileal bypass. As a result of the significant complications associated with this procedure—liver disease, malnutrition, bone disease, arthritis, kidney failure, and renal calculi—the Food and Drug Administration banned its application in 1979 (Clayman et al, 1978).

In 2005 the most common bariatric procedure was Roux-en-Y gastric bypass (RYGB), accounting for 70% to 90% of weight-loss surgeries in the United States (Santry et al, 2005). A worldwide survey study performed in 2011 demonstrated that RYGB made up 46.6% of weight-loss procedures, followed by sleeve gastrectomy (27.8%) and adjustable gastric banding (17.8%) (Buchwald and Oien, 2013). Though initially thought to have a significantly lower risk for stone disease, a number of studies have reported a risk for oxalate nephropathy and nephrolithiasis in the RYGB population (Nelson et al, 2005; Asplin and Coe, 2007; Nasr et al, 2008). Nelson and associates (2005) identified 14 of 23 patients presenting with an incident stone event at a mean of 29 months. More sobering is that 2 patients in this study and 11 patients in a report from the Columbia group developed oxalate nephropathy and progressed to end-stage renal disease requiring dialysis. Twenty-four-hour urinary assessment in stone formers after RYGB identified an elevated mean oxalate excretion (83 mg/day vs. 34 mg/day, $P < .001$) compared to normal non-stone formers. These studies evaluated patients with nephrolithiasis after RYGB; therefore the incidence of new-onset stone formation and prevalence of hyperoxaluria in this population cannot be determined.

Prospective data are emerging that evaluate this population before and after bariatric surgery (Sinha et al, 2007; Duffey et al, 2008). Urinary oxalate excretion was noted to increase significantly in both investigations, but with varying time courses. Duffey and associates (2008) found an increase from 31 mg/day to 41 mg/day ($P < .05$) at 3 months after surgery; Sinha and colleagues (2007)

identified a significant increase in urinary oxalate excretion at 12 months postoperatively. In an attempt to quantify the prevalence of hyperoxaluria, a multi-institutional study evaluated 58 non-stone forming patients 6 months after bariatric surgery (RYGB and biliopancreatic diversion) (Patel et al, 2009). The authors found a 74% and 26% prevalence of hyperoxaluria (>45 mg/day) and profound hyperoxaluria (>100 mg/day), respectively, on a single 24-hour urine collection, which decreased to 52% and 9%, respectively, when two 24-hour urinalyses were evaluated.

Adjustable gastric banding has been gaining in popularity as a means of weight-loss surgery. Penniston and colleagues (2009b) evaluated 24-hour urine collections after bariatric surgery in 27 patients who underwent RYGB and 12 patients who underwent gastric banding. The patients who underwent RYGB were found to have low urine volumes, hypocitraturia, and hyperoxaluria. However, the patients who underwent adjustable gastric banding were found only to have low urine volume, suggesting they may not be at as high a risk for stone formation. Another study comparing 24-hour urine parameters in patients who underwent RYGB, adjustable gastric banding, and sleeve gastrectomy found significantly lower 24-hour urine oxalate in those who underwent either adjustable gastric banding or sleeve gastrectomy compared to RYGB (Semins et al, 2010). In a retrospective review of patients who underwent either adjustable gastric banding or sleeve gastrectomy, Chen and colleagues (2013) found a very low incidence of kidney stones in either cohort. These studies suggest that restrictive bariatric surgery incurs a lower risk for subsequent stone development than RYGB.

Currently, the pathophysiology of bariatric surgery-induced hyperoxaluria remains unclear. Potential causes include alteration in intestinal flora (i.e., *Oxalobacter formigenes*), fat malabsorption, or a reduced amount of oxalate secretion. However, as the rate of bariatric surgery increases lockstep with the rising tide of obesity, identification of the mechanisms and treatment strategies will become increasingly important to minimize the risk for increased stone formation.

KEY POINTS: OBESITY

- Obesity is an independent risk factor for nephrolithiasis, particularly for women.
- Metabolic syndrome is associated with lower urinary pH.
- Obese patients have a higher propensity for uric acid calculi.
- High-protein, low-carbohydrate diets alter urinary parameters and may increase the risk for stone formation.
- Roux-en-Y-gastric bypass surgery may significantly increase the overall risk for stone formation.

Role of Dietary Calcium

The preponderance of evidence now supports the maintenance of a moderate calcium intake in the face of calcareous nephrolithiasis (Curhan et al, 1993; Curhan, 1997; Takei et al, 1998; Trinchieri et al, 1998a; Martini and Wood, 2000; Lewandowski et al, 2001; Borghi et al, 2002; Heller et al, 2003; Taylor et al, 2004). Older recommendations to significantly restrict calcium intake likely led to an increase in available intestinal oxalate. As a result, this limitation in dietary calcium may subsequently increase oxalate absorption, thereby raising the supersaturation of calcium oxalate. As noted earlier, a prospective, randomized study has shown that patients on a moderate-calcium diet, combined with salt restriction and moderation of animal protein had half as many stone episodes as those who attempted to follow a calcium-restricted diet (Borghi et al, 2002). Review of a large cohort of middle-aged nurses revealed that there was a decreased incidence of nephrolithiasis in subjects who had increased levels of dietary calcium (Curhan, 1997; Curhan et al, 1997). Interestingly, this protection did not remain for those who received increased calcium intake from supplements instead of from dietary sources (i.e., dairy products).

There is further evidence to suggest that calcium supplementation can be safe if attention is paid to preparation and especially to timing. In a review of postmenopausal women, authors have demonstrated that initiation of calcium supplementation does not have deleterious effects on urinary calcium, oxalate, or citrate levels. Furthermore, calcium supplement with a meal or combined calcium supplement and estrogen therapy was not associated with a significant increased risk for calcium oxalate stone formation in the majority of postmenopausal osteoporotic patients (Domrongkitchaiporn et al, 2002b). Additional work from the same group determined that the timing of calcium supplementation may have positive or negative effects (Domrongkitchaiporn et al, 2004). In a study of healthy male recruits, the authors compared the urinary effects of calcium carbonate supplementation taken with meals versus at bedtime. In both instances, urinary calcium excretion increased equal amounts. However, for those taking the calcium supplement with meals, this increase was offset by an equally significant decrease in urinary oxalate. As a result, there was no increase in urinary supersaturation of calcium oxalate when calcium supplementation was taken with meals, a protection that did not remain for the nighttime bolus ingestion.

Evidence also suggests that the type of calcium supplementation may have an impact on the potential of stone formation. Two long-term studies from researchers in Dallas document that supplementation with calcium citrate does not have a significant impact on stone formation. Calcium citrate is an over-the-counter calcium preparation that provides 950 mg of calcium citrate and 200 mg of elemental calcium in each tablet. As with other available calcium supplements, calcium citrate will significantly increase urinary calcium excretion. Yet, this preparation offers the benefit of also increasing urinary citrate excretion. The concomitant increase in citruria potentially offsets the lithogenic potential of calcium supplement-induced hypercalciuria and therefore provides a more stone-friendly calcium supplement (Sakhaee et al, 2004).

One clinical trial further studied the effects of long-term calcium citrate supplementation in premenopausal women. This investigation demonstrated that the urinary saturation of calcium oxalate and calcium phosphate (brushite) did not significantly change during calcium citrate therapy. It appears that the lack of calcium supplement-induced hypercalciuria was secondary to the down-regulation of intestinal calcium absorption, because of prolonged calcium supplementation and the inhibitory effects of citrate included in the calcium citrate preparation. The results of this long-term calcium citrate trial suggest that calcium supplementation using calcium citrate does not increase the propensity for crystallization of calcium salts within the urine. This protective effect is most likely due to an attenuated increase in urinary calcium excretion (from a decrease in fractional intestinal calcium absorption), a decrease in urinary phosphorus, and an increased citruric response (Sakhaee et al, 1994).

Role of Vitamin D and Bisphosphonates

Controversy exists over the role of vitamin D supplementation and kidney stone formation. The Women's Health Initiative randomized clinical trial comparing calcium plus vitamin D supplementation versus placebo in postmenopausal women found a 17% increased incidence of self-reported stones in the group receiving calcium plus vitamin D. The increased risk was not associated with any other demographic factors (Wallace et al, 2011). In this study, vitamin D was used as a supplement and not for repletion of low vitamin D levels.

Two studies have evaluated the effects of vitamin D repletion on 24-hour urine calcium. Leaf and associates (2012) enrolled 29 calcium-stone formers with low serum vitamin D. Participants were given vitamin D 50,000 international units once per week for 8 weeks. The mean serum vitamin D levels increased significantly during the study from 17 ± 6 ng/mL to 35 ± 10 ng/mL; however, the mean 24-hour urine calcium did not increase (257 ± 54 mg/day to 255 ± 88 mg/day) (Leaf et al, 2012). Despite the fact that there was no overall change in urinary calcium for the entire

cohort, 11 of the participants did have an increase in their 24-hour urine calcium. The authors recommend monitoring of 24-hour urine calcium in patients who undergo vitamin D repletion. Penniston and colleagues (2009a) evaluated 24-hour urine calcium excretion in postmenopausal women with no history of stones undergoing vitamin D repletion. They also found no overall difference in calcium excretion.

Bisphosphonates are common treatment for osteoporosis. A recent prospective study compared the effects of alendronate alone to alendronate combined with hydrochlorothiazide in patients with calcium stones, hypercalciuria, and decreased bone density. Both groups showed a significant decrease in urinary calcium and increase in bone density. The combination of alendronate and hydrochlorothiazide had a significantly greater effect on urinary calcium and bone density than alendronate alone (Arrabal-Polo et al, 2013). It appears that bisphosphonates are safe and possibly preventive for patients with calcium nephrolithiasis.

KEY POINTS: ROLE OF DIETARY CALCIUM, VITAMIN D, AND BISPHOSPHONATES

- Dietary calcium restriction actually increases stone recurrence risk.
- Calcium supplementation is likely safest when taken with meals.
- Calcium citrate appears to be a more stone-friendly calcium supplement because of the additional inhibitory action of citrate.
- Vitamin D repletion is likely safe for stone formers; however, 24-hour urine calcium should be monitored during vitamin D therapy.
- Bisphosphonates combined with thiazide diuretics appear to reduce hypercalciuria while protecting the bone.

Oxalate Avoidance

The contribution of dietary oxalate consumption to urinary oxalate can vary. Some have estimated that only 10% to 20% of urinary oxalate is usually derived from dietary sources (Williams and Wandzilak, 1989). More recently, Holmes and associates (2001) found that the contribution of dietary oxalate to urinary oxalate ranged from $24.4\% \pm 1.5\%$ on a diet of 10 mg/day of oxalate to $41.5\% \pm 9.1\%$ on a diet of 250 mg/day of oxalate. They also demonstrated that the mean contribution of dietary oxalate increased when calcium consumption decreased (Holmes et al, 2001). Although dietary oxalate clearly plays a role in increased urinary oxalate, it is difficult to restrict its intake because oxalate is ubiquitous and found in most vegetable matter. However, it is important to avoid large portions of foodstuffs that are rich in oxalate, such as spinach, beets, chocolate, nuts, and tea. Whereas general advice on a restricted-oxalate intake might be given to patients with recurrent nephrolithiasis, a low-oxalate diet would be most useful in patients with enteric hyperoxaluria, those with underlying bowel abnormalities, or patients who have undergone gastric bypass surgery (Holmes and Assimos, 2004). Box 52-3 presents an extensive list of foods containing a high level of oxalate. It is notable that recent work has illustrated similar relationships of dietary intake and urinary excretion of oxalate in a cross-sectional analysis of HPFS and NHS (I and II) for both stone formers and non-stone formers, thereby further adding to the question of the impact that dietary oxalate has on urinary oxalate excretion (Taylor and Curhan, 2008a).

Repeated concerns have been raised regarding the risk of vitamin C (ascorbic acid) ingestion and the possibility of its conversion to oxalate with subsequent urinary excretion. Unfortunately, conflicting evidence has been presented by multiple authors (Weaver, 1983; Trinchieri et al, 1991, 1998b; Urivetzky et al, 1992; Curhan et al, 1996b, 1999; Baxmann et al, 2003; Traxer et al, 2003). In fact, conflicting conclusions have been reported even from the same

TABLE 52-8 Physicochemical and Physiologic Effects of Pharmacologic Therapy

	SODIUM CELLULOSE PHOSPHATE	ORTHOPHOSPHATE	THIAZIDE	ALLOPURINOL	POTASSIUM CITRATE
Urinary calcium	Marked decrease	Mild decrease	Moderate decrease	No change	Mild decrease
Urinary phosphorus	Mild increase	Marked increase	Mild increase/no change	No change	No change
Urinary uric acid	No change	No change	Mild increase/no change	Marked decrease	No change
Urinary oxalate	Mild increase	Mild increase/no change	Mild increase/mild decrease	No change	No change
Urinary citrate	No change	Mild increase	Mild decrease	No change	Marked increase
Calcium oxalate saturation	Mild decrease/no change	Mild decrease	Mild decrease	No change	Moderate decrease
Brushite saturation	Moderate decrease	Mild increase	Mild decrease	No change	No change

group of authors, underscoring the need for close scrutiny of presented data. Some of the confusion stems from differences in study end points. Although ingestion of large amounts of vitamin C may demonstrate increases in 24-hour oxalate excretion and therefore calcium oxalate supersaturation, this does not guarantee an eventual increase in the formation of symptomatic calculi. A recent large, prospective cohort of men found that increased ascorbic acid intake was associated with two-fold increased risk for kidney stone formation (Thomas et al, 2013).

In the end, it seems reasonable to avoid heavy dosing of vitamin C. Limiting one's intake to a maximum daily dose of less than 2 g is an easy recommendation to follow (Traxer et al, 2003).

KEY POINTS: OXALATE AVOIDANCE

- Avoidance of excess dietary oxalate loading is reasonable and intuitive.
- Vitamin C in large doses may increase the risk for stone recurrence. Doses should probably be limited to 2 g/day.

Conservative Management Summary

It is anticipated that with these conservative measures alone, a significant number of patients may be able to normalize their urinary risk factors for stone formation. Thus only these conservative measures may be necessary to keep their stone disease under control. After 3 to 4 months on conservative management, patients should be re-evaluated using either standard laboratory assays or an automated urinalysis package. If the patient's metabolic or environmental abnormalities have been corrected, the conservative therapy can be continued and the patient followed every 6 to 12 months with repeat 24-hour urine testing as indicated. It is believed that follow-up is essential not only to monitor the efficiency of treatment but also to encourage patient compliance. If, however, a metabolic defect persists, a more selective medical therapy may be instituted. For example, if significant hyperuricosuria (urinary uric acid > 800 mg/day) persists even after dietary restriction of meat products, medical therapy with allopurinol may be instituted.

SELECTIVE MEDICAL THERAPY OF NEPHROLITHIASIS

Improved elucidation of the pathophysiology and the formulation of diagnostic criteria for different causes of nephrolithiasis have made feasible the adoption of selective treatment programs (Pak et al, 1981; Preminger and Pak, 1985). Such programs should (1) reverse the underlying physicochemical and physiologic derangements, (2) inhibit new stone formation, (3) overcome nonrenal complications of the disease process, and (4) be free of serious side effects. The rationale for the selection of certain treatments is the

TABLE 52-9 Dosages of Common Medications Used to Prevent Urinary Calculi

MEDICATION	DOSAGE
Thiazide diuretics	
Hydrochlorothiazide	25 mg PO bid
Chlorthalidone	25-50 mg PO daily
Indapamide	2.5 mg PO daily
Sodium cellulose phosphate	10-15 g/day divided with meals
Orthophosphate	0.5 g PO tid
Potassium citrate	20 mEq PO bid-tid
Allopurinol	300 mg PO daily
Magnesium gluconate	0.5-1 g tid
Pyridoxine (B ₆)	100 mg PO daily
D-Penicillamine	250 mg PO daily (titrated to effect)
α-Mercaptopropionyl glycine	100 mg PO bid (titrated to effect)
Captopril	25 mg PO tid
Acetohydroxamic acid	250 mg PO bid-tid

assumption that the particular physicochemical and physiologic aberrations identified with the given disorder are etiologically important in the formation of renal stones (as previously discussed) and that the correction of these disturbances would prevent stone formation. Moreover, it is assumed that such a selective treatment program would be more effective and safe than "random" therapy. Despite a lack of conclusive experimental verification, these hypotheses appear reasonable and logical. Common medications used to treat urinary stone disease and their expected actions are summarized in Table 52-8. Medication dosages are noted in Table 52-9, and side effects are outlined in Table 52-10. A simplified treatment algorithm outlining basic evaluation and management is illustrated in Figure 52-10.

Efficacy Outside of an Academic Center

One potential criticism of the "selective" metabolic management of nephrolithiasis is that the collection of multiple urine and serum studies can be too time-consuming to be feasible outside of an academic medical center with its dedicated research staff. Although a commitment to follow-up can be tedious, it should be no worse for patients with kidney stones than it is for those followed for urologic cancer or voiding dysfunction.

Indeed, Lingeman and colleagues (1998) compared the results of patient management from seven private practices to that achieved by a dedicated university clinic. Of note, the specialized stone

TABLE 52-10 Potential Side Effects of Medications Used to Prevent Urinary Lithiasis

MEDICATION	SIDE EFFECT
Thiazide diuretics Hydrochlorothiazide Chlorthalidone Indapamide	Potassium wasting, muscle cramps, hyperuricosuria, intracellular acidosis, hypocitraturia
Sodium cellulose phosphate (SCP)	GI distress, hypomagnesemia, hyperoxaluria, PTH stimulation
Orthophosphate	Similar to SCP, soft tissue calcification
Potassium citrate	GI upset, hyperkalemia
Allopurinol	Rash, myalgia
Magnesium gluconate pyridoxine (B ₆)	Diarrhea
D-Penicillamine	Nephrotic syndrome, dermatitis pancytopenia
α -Mercaptopropionyl glycine	Rash, asthenia, rheumatologic complaints, GI distress, mental status changes
Captopril	Rash, cough, hypotension
Acetohydroxamic acid	Thromboembolic phenomena, tremor, headache, palpitations, edema, GI distress, loss of taste, rash, alopecia, anemia, abdominal pain

GI, gastrointestinal; PTH, parathyroid hormone.

management software and laboratory resources of the university clinic supported the private centers. They found that supersaturation values were effectively reduced in the network and stone clinic and that the reduction was proportional to the initial supersaturation value and increase in urine volume. The stone clinic achieved a greater supersaturation reduction, higher fraction of patient follow-up, and greater increase in urine volume, but the treatment effects in the network were, nevertheless, substantial and significant.

This finding is supported by a further study demonstrating the efficacy of medical prophylaxis when administered in a private practice setting (Mardis et al, 2004). When compared to conservative measures of dietary recommendations and fluid management, active pharmacologic treatment achieved a significantly greater reduction in stone episodes. These findings prompted Mardis and coworkers (2004) to conclude that medications validated in trials and guided by metabolic evaluation lower stone recurrence when used in a private practice setting, as they do in clinical trials from academic medical centers.

Absorptive Hypercalciuria

Thiazides

Currently no treatment program is capable of correcting the basic abnormality of absorptive hypercalciuria I and thiazide diuretics are not considered a selective therapy for absorptive hypercalciuria, because they do not decrease intestinal calcium absorption in this condition (Pak, 1979). However, this class of medication has been widely used to treat absorptive hypercalciuria, because of its hypocalciuric action and the high cost and inconvenience of alternative therapy (sodium cellulose phosphate, which is no longer available in the United States). The use of thiazides was first described by Yendt and colleagues (1966) for the treatment of undifferentiated hypercalciuria.

Thiazides directly stimulate calcium resorption in the distal nephron while promoting excretion of sodium. Long-term thia-

zide therapy results in volume depletion, extracellular volume contraction, and proximal tubular resorption of sodium and calcium. Thiazides may increase urinary excretion of magnesium and zinc, but these responses are not consistent. Potassium losses from thiazide therapy can cause hypocitraturia, as a result of hypokalemia with intracellular acidosis.

Studies indicate that thiazide may have a limited long-term effectiveness in absorptive hypercalciuria type I (Zerwekh and Pak, 1980; Preminger and Pak, 1987). Despite an initial reduction in urinary excretion, the intestinal calcium absorption remains persistently elevated. These studies suggest that the retained calcium may be accreted in bone at least during the first few years of therapy. Bone density, determined in the distal third of the radius by photon absorptiometry, increases significantly during thiazide treatment in absorptive hypercalciuria, with an annual increment of 1.34%. With continued treatment, however, the rise in bone density stabilizes and the hypocalciuric effect of thiazide becomes attenuated. These results suggest that thiazide treatment may cause a low turnover state of bone that interferes with a continued calcium accretion in the skeleton. The "rejected" calcium would then be excreted in urine. In contrast, bone density is not significantly altered in renal hypercalciuria, in which thiazide has been shown to cause a decline in intestinal calcium absorption commensurate with a reduction in urinary calcium.

Further work on this topic has been reported (Pak et al, 2003a). In this study, 28 patients with absorptive hypercalciuria type 1 were managed with thiazide (20) or indapamide (8) and potassium citrate for 1 to 11 years while maintained on low-calcium oxalate diet. Serum and urinary chemistry studies and bone mineral density were measured at baseline and at the end of treatment. During treatment, urinary calcium significantly decreased but urinary oxalate did not change. Urinary pH and citrate significantly increased, and urinary saturation of calcium oxalate significantly decreased by 46%. Stone formation rate decreased significantly from 2.94 to 0.05 per year. Notably, L2 to L4 bone mineral density increased significantly by 5.7% compared to normal peak value and by 7.1% compared with normal age-matched and gender-matched values. The authors concluded that dietary moderation of calcium and oxalate, combined with thiazide and potassium citrate, satisfactorily controlled hypercalciuria, while preventing the complication of osteopenia commonly associated with absorptive hypercalciuria.

Although side effects are generally mild, they occur in approximately 30% to 35% of patients treated with thiazides. Side effects are usually seen on initiation of treatment but disappear with continued therapy. Lassitude and sleepiness are the most common symptoms and can occur in the absence of hypokalemia. Potassium supplementation always should be considered, particularly in patients with evident potassium deficiency, patients on digitalis therapy, and those individuals who develop hypocitraturia. Addition of potassium citrate has been documented to prevent occurrence of hypokalemia and hypochloremic metabolic acidosis in patients undergoing long-term thiazide therapy (Odvina et al, 2003). Thiazides also may cause impaired carbohydrate tolerance and hyperuricemia. A more distressing complication is decreased libido or sexual dysfunction, which is seen in a small percentage of patients. It is reasonable to check a basic metabolic panel 1 to 2 weeks after initiating thiazides to monitor for hypokalemia, particularly if the patient is not started on potassium citrate concurrently.

Occasionally, thiazides unmask primary hyperparathyroidism (i.e., "thiazide challenge"). Patients with normal serum calcium may develop elevated serum calcium on thiazides (Wermers et al, 2007). Wermers and colleagues (2007) reported this occurs an average of 6 years after initiation of thiazide. In this heterogeneous population (3% of which were known stone formers), hyperparathyroidism was diagnosed in 64% of patients who had persistently elevated serum calcium after the thiazide was stopped. Another way a thiazide challenge can be used is to differentiate primary and secondary hyperparathyroidism (Eisner et al, 2009). In patients with nephrolithiasis, hypercalciuria, and elevated serum parathyroid hormone, hydrochlorothiazide 25 mg orally twice daily was

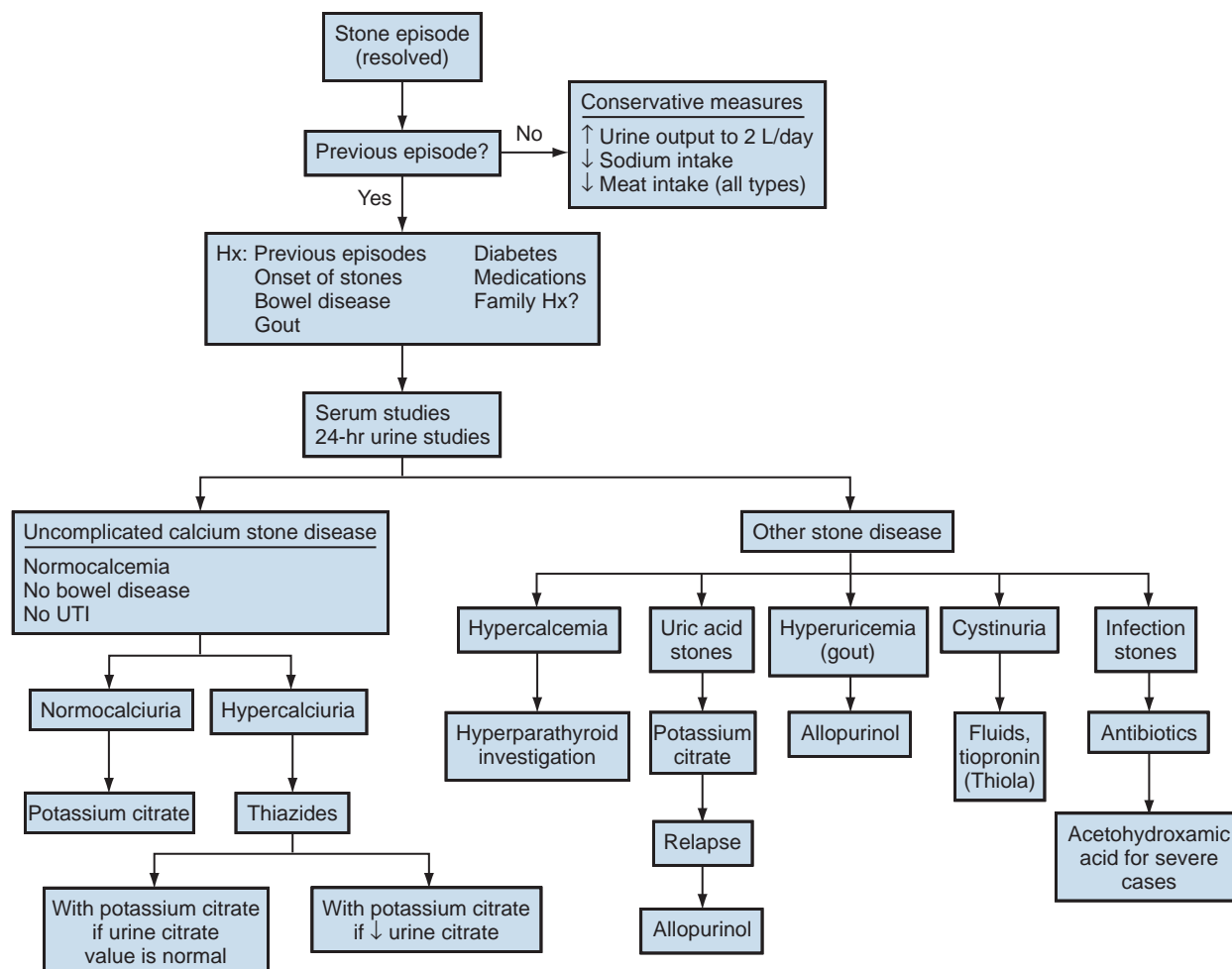


Figure 52-10. Simplified treatment algorithm for the evaluation and medical management of urinary lithiasis. Hx, history; UTI, urinary tract infection. (Modified from C. Y. Pak.)

administered for 2 weeks. If the parathyroid hormone remains elevated, the diagnosis of primary hyperparathyroidism is confirmed. If it returns to normal, the diagnosis is secondary hyperparathyroidism from renal leak hypercalciuria.

Sodium Cellulose Phosphate

Sodium cellulose phosphate, given orally, is a nonabsorbable ion exchange resin that binds calcium and inhibits calcium absorption (Pak et al, 1974). Unfortunately, despite early enthusiasm, the use of sodium cellulose phosphate has largely fallen out of favor and this medication is no longer available in the United States.

Guidelines for the Use of Thiazides in Absorptive Hypercalciuria

Thiazides do not correct the basic, underlying physiologic defect in absorptive hypercalciuria. Some guidelines are offered until more selective therapy can be developed.

In patients with absorptive hypercalciuria type I, thiazide is the first choice and should be combined with potassium citrate and dietary moderation of dairy products (2 or 3 servings per day) and restriction in dietary sodium and oxalate. If thiazides lose their hypocalciuric action (after long-term treatment), a drug holiday may be instituted and then thiazide therapy may be resumed. It is recommended that potassium citrate and dietary alterations continue during this period. Further research is warranted to identify a medication that will selectively reduce increased intestinal calcium absorption, thereby decreasing the calcium load available for urinary excretion and stone formation.

Other Hypocalciuric Agents

Other long-acting agents are preferred in place of hydrochlorothiazide for the treatment of hypercalciuria. These medications include chlorthalidone (25 to 50 mg/day) or indapamide (2.5 mg/day). Indapamide is technically not a thiazide but does share a successful hypocalciuric effect with the other agents. Both of these agents have been shown to be equally efficacious, yet may improve patient compliance with more convenient once-daily dosing (Jaeger et al, 1986; Lemieux, 1986; Coe et al, 1988; Ettinger et al, 1988; Ohkawa et al, 1992; Borghi et al, 1993b; Martins et al, 1996).

Amiloride in combination with thiazide (Moduretic) may be more effective than thiazide alone in reducing calcium excretion (Maschio et al, 1981; Leppla et al, 1983). However, this medication does not augment citrate excretion. Because amiloride is a potassium-sparing agent, potassium replacement is not necessary and could, in fact, be problematic. It is not advisable to provide potassium supplementation to patients receiving a potassium-sparing diuretic. Although the potassium-sparing effects of amiloride may be beneficial, the use of triamterene, another potassium-sparing agent, should be undertaken with caution because of reports of triamterene stone formation (Watson et al, 1981; Werness et al, 1982; Ettinger, 1985; Sorgel et al, 1985).

Absorptive Hypercalciuria Type II

In absorptive hypercalciuria II, no specific drug treatment may be necessary because the physiologic defect is not as severe as in absorptive hypercalciuria I. In addition, many patients show disdain for drinking fluids and therefore excrete concentrated urine. A moderate calcium intake (400 to 600 mg/day) and high fluid intake

(sufficient to achieve a minimum urine output > 2 L/day) would seem ideally indicated, because normocalciuria could be restored by dietary calcium restriction alone, and increased urine volume has been shown to reduce urinary saturation of calcium oxalate. Moreover, avoidance of excessive sodium intake might further decrease hypercalciuria and potential stone formation in patients with absorptive hypercalciuria II.

Orthophosphate

Orthophosphate (neutral or alkaline salt of sodium and/or potassium, 0.5 g phosphorus three or four times per day) has been shown to inhibit 1,25-(OH)₂D synthesis (Van Den Berg et al, 1980; Insogna et al, 1989). However, there is as yet no convincing evidence from randomized trials that this treatment restores normal intestinal calcium absorption. Orthophosphate reduces urinary calcium probably by directly impairing the renal tubular reabsorption of calcium and by binding calcium in the intestinal tract. Urinary phosphorus is markedly increased during therapy, a finding reflecting the absorbability of soluble phosphate. Physicochemically, orthophosphate reduces the urinary saturation of calcium oxalate but increases that of brushite. Moreover, the urinary inhibitor activity is increased, probably owing to the stimulated renal excretion of pyrophosphate and citrate. Although contrary reports have appeared, this treatment program has been reported to cause soft tissue calcification and parathyroid stimulation (Dudley and Blackburn, 1970). Orthophosphate is contraindicated in nephrolithiasis complicated by UTI because of the increased phosphorus load.

KEY POINTS: ABSORPTIVE HYPERCALCIURIA

- Sodium cellulose phosphate effectively decreases the absorption of intestinal calcium but has been abandoned because of GI intolerance and side effects.
- Thiazides do not treat the underlying cause of absorptive hypercalciuria, but do reduce urinary calcium and manage its symptoms.
- Care should be taken when using diuretics to prevent hypokalemia with subsequent hypocitraturia.
- Orthophosphates may have a role for the treatment of absorptive hypercalciuria when other methods are ineffective.

Renal Hypercalciuria

Thiazides are ideally indicated for the treatment of renal hypercalciuria. This diuretic has been shown to correct the renal leak of calcium by augmenting calcium reabsorption in the distal tubule and by causing extracellular volume depletion and stimulating proximal tubular reabsorption of calcium. The ensuing correction of secondary hyperparathyroidism restores normal serum 1,25-dihydroxyvitamin D (1,25-[OH]₂D) and intestinal calcium absorption. Thiazides have been shown to provide a sustained correction of hypercalciuria commensurate with a restoration of normal serum 1,25-(OH)₂D and intestinal calcium absorption for up to 10 years of therapy (Preminger and Pak, 1987).

Physicochemically, the urinary environment becomes less saturated with respect to calcium oxalate and brushite during thiazide treatment, largely because of the reduced calcium excretion. Moreover, urinary inhibitor activity, as reflected in the limit of metastability, is increased by an unknown mechanism. These effects are shared by hydrochlorothiazide 25 mg twice per day, chlorthalidone 25 to 50 mg/day, or indapamide 2.5 mg/day. Potassium citrate supplementation (40 to 60 mEq/day) is advised, because this medication has been shown to be effective in averting hypokalemia and increasing urinary citrate, when administered to patients with

calcium nephrolithiasis taking thiazide (Nicar et al, 1984; Pak et al, 1985a).

A more complete discussion of the mechanism of action, efficacy, and side effects of thiazides for the treatment of hypercalciuria is presented in the preceding section. Furthermore, Table 52-11 provides a summary of the results of randomized trials involving the use of thiazides for the treatment of hypercalciuria. Of note, a recent meta-analysis of medical therapies for calculus prevention demonstrated that only thiazides have shown strong evidence for efficacy in randomized trials (Pearle et al, 1999).

KEY POINT: RENAL HYPERCALCIURIA

- Thiazides are first-line therapy for the treatment of renal leak hypercalciuria.

Primary Hyperparathyroidism

Parathyroidectomy is the optimum treatment for nephrolithiasis in patients with primary hyperparathyroidism (Parks et al, 1980; Fraker, 2000). This therapy may include the resection of a dominant adenoma or a removal of all four hyperplastic glands. After removal of abnormal parathyroid tissue, urinary calcium is expected to return to normal, commensurate with a decline in serum calcium and intestinal calcium absorption. However, these findings are not always dependable, because some patients may suffer from changes in tubular and glomerular functions as a result of long-standing hypercalcemia/hypercalciuria (Farias et al, 1996). Moreover, it is imperative to repeat a 24-hour urinary calcium determination to make sure the hypercalciuria has resolved.

There is no established medical treatment for the nephrolithiasis of primary hyperparathyroidism. Although orthophosphates have been recommended for the disease of mild-to-moderate severity, their safety or efficacy has not yet been proved. These medications should be used only when parathyroid surgery cannot be undertaken. Estrogen has been reported to be useful in reducing serum and urinary calcium in postmenopausal women with primary hyperparathyroidism (Herbai and Ljunghall, 1983; Marcus et al, 1984; Coe et al, 1986; Selby and Peacock, 1986; Boucher et al, 1989; Diamond et al, 1996; Orr-Walker et al, 2000).

KEY POINT: PRIMARY HYPERPARATHYROIDISM

- Hyperparathyroidism complicated by stone disease is best treated with surgical excision of the adenoma(s).

Hyperuricosuric Calcium Oxalate Nephrolithiasis

There are two pharmacologic approaches to the management of hyperuricosuric calcium nephrolithiasis. The first involves decreasing the production of uric acid. Allopurinol (300 mg/day) may be used to block the ability of xanthine oxidase to convert xanthine to uric acid (Coe, 1978). The resultant decrease in serum uric acid will ultimately lead to a decrease in urinary uric acid as well. Allopurinol's use in hyperuricosuria associated with dietary purine overindulgence also may be reasonable if patients are unable or unwilling to comply with dietary purine restriction. Physicochemical changes ensuing from restoration of normal urinary uric acid include an increase in the urinary limit of metastability of calcium oxalate (Pak et al, 1978). Thus the spontaneous nucleation of calcium oxalate is slowed by allopurinol treatment, probably via inhibition of monosodium urate-induced stimulation of calcium oxalate crystallization (Pak et al, 1979; Coe et al, 1980). Because of the potential exaggeration of monosodium urate-induced calcium oxalate crystallization, a moderate sodium restriction (150 mEq/day) is also advisable.

TABLE 52-11 Randomized Trials Using Thiazides for the Management of Nephrolithiasis

YEAR	AUTHOR	DIAGNOSIS	AGENT	NO. PATIENTS	NO. CONTROLS	EFFICACY	FOLLOW-UP	COMMENTS
1981	Brocks et al	Recurrent calcium stones	Bendroflumethiazide, 2.5 mg tid	29	33	83% remission in controls, 85% in treated: not significant	1.6 yr	Not all patients were hypercalciuric. Only 16% of expected stones formed in controls, 24% in treated
1982	Scholz et al	Recurrent calcium stones	Hydrochlorothiazide, 25 mg bid	25	26	77% remission in controls, 76% in treated: not significant	1 yr	Fasting urinary calcium increased before treatment, decreased with thiazides, but not in controls. Urine output increased in both groups, indicating that hydration was sufficient
1984	Laerum and Larsen	Recurrent stone formers	Hydrochlorothiazide, 25 mg bid	25	25	45% remission in controls, 75% in treated: significant difference. Controls formed 21 stones, treated formed 230 stones: not significant	3 yr	General practice study. 75% of patients did not have hypercalciuria. Differences seen only after 18 mo
1988	Ettinger et al	Recurrent calcium stones	Chlorthalidone, 25 or 50 mg/day	42	31	55% remission in controls, 86% in treated: significant	3 yr	Only 15% of patients had hypercalciuria. Compliance to diet not encouraged or assessed; to drugs, assessed. Urine output not measured. 16% dropout rate in controls, 35%-40% dropout rate with chlorthalidone
1984	Wilson et al	Recurrent calcium stone	Hydrochlorothiazide, 100 mg/day	21	23	65% remission in controls, 70% in treated: not significant. 0.32 stone/yr in controls; 0.15 stone/yr in treated: significant	<3 yr	Not all patients had hypercalciuric stones. Other treatments—phosphates, magnesium, allopurinol—were ineffective
1992	Ohkawa et al	Idiopathic hypercalciuria	Trichlormethiazide, 4 mg/day	82	93	86% remission in controls, 92% in treated: not significant. Stone formation rate significantly lowered in treated patients	3 yr	This was a multi-institutional study. All patients had hypercalciuria. Many were single-stone formers
1993b	Borghi et al	Idiopathic hypercalciuria	Indapamide, 2.5 mg/day, or indapamide plus allopurinol, 300 mg/day	25	25	65% remission in controls, 95% in treated: significant		Urinary output did not rise in either group; thus hydration may not have been effective
TOTAL				249	256	73% remission in controls, 85% in treated patients		Beneficial effects with treatment seen only in trials with follow-up of ≥ 2 yr

There are few convincing randomized trials demonstrating the efficacy of allopurinol for the treatment of hyperuricosuria. However, one study by [Ettinger and colleagues \(1986\)](#) does stand out. In this double-blind, prospective, randomized trial, allopurinol was given to 60 patients with hyperuricosuria, normocalciuria, and recurrent calcium oxalate stones. A 6-month grace period was established, during which any new calculus that was passed was not considered to represent failure of therapy. With a follow-up of up to 39 months, new stone events (stone growth or recurrence) occurred in 58% of the patients on placebo and 31% of the patients on allopurinol. The placebo group had 63.4% fewer calculi, whereas the allopurinol group had 81.2% fewer calculi. The mean rate of calculus events was 0.26 per patient per year in the placebo group and 0.12 in the allopurinol group. The allopurinol group had a significantly longer time before the recurrence of stones.

Alternatively, management of hyperuricosuria may be approached by altering the urinary milieu such that uric acid remains in a dissolved state ([Pak and Peterson, 1986](#)). Central to this approach would be the obvious advantage of copious amounts of dilute urine to maintain uric acid at a low concentration. Attempts to maintain the urine at a pH above the pKa also may be successful by promoting dissolution of this molecule ([Pak et al, 1986b](#)). This effect is usually achieved by the use of an alkalinizing agent such as potassium citrate (at a dose of 30 to 60 mEq/day in divided doses). In the study by Pak and colleagues, the treatment produced a sustained rise in urinary pH by 0.55 to 0.85 to the high normal range. Urinary citrate levels rose by 249 to 402 mg/day. Commensurate with these changes, urinary saturation of calcium oxalate (relative saturation ratio) and the amount of undissociated uric acid declined significantly. Stone formation declined from 1.55 per patient-year to 0.38 per patient-year during the mean treatment period of 2.35 years. Stones ceased to form in 16 of 19 patients during treatment.

There is some evidence that changes in urinary pH alone are inadequate for the management of hyperuricosuria ([Pak et al, 2002b](#)). If this is the case, the efficacy of citrate for the management of hyperuricosuria calcium nephrolithiasis may stem from the inhibitory activity of citrate with respect to calcium and oxalate crystallization.

Potassium citrate may be particularly useful in patients with mild-to-moderate hyperuricosuria (<800 mg/day), especially in whom hypocitraturia is also present.

KEY POINTS: HYPERURICOSURIC CALCIUM OXALATE NEPHROLITHIASIS

- Patients with hyperuricosuria should be instructed to decrease dietary purine intake.
- Allopurinol can decrease uric acid production and may be ideal for those patients with a history of gout.
- Potassium citrate can effectively alter the urinary milieu in patients with hyperuricosuria by decreasing the supersaturation of uric acid and calcium oxalate.

Enteric Hyperoxaluria

The management of patients with enteric hyperoxaluria usually involves directed therapy that addresses several abnormalities or abnormal physiology. Oral administration of over-the-counter calcium preparations (0.25 to 1 g four times per day) or magnesium has been recommended for the control of calcium nephrolithiasis of ileal disease ([Worcester, 2002](#)). Although urinary oxalate may decrease (probably from binding of oxalate by divalent cations), the concurrent rise in urinary calcium may obviate the beneficial effect of this therapy, at least in some patients ([Barilla et al, 1978](#)).

Cholestyramine has also been suggested for the management of calculi in this disorder ([Stauffer, 1977](#)). This medication may be

useful by binding bile salts in the bowel lumen, thereby decreasing the irritation of the colonic mucosa and the subsequent hyperabsorption of oxalate ([Caspary et al, 1977](#)). The replacement of dietary fat with medium-chain triglycerides may be helpful in patients who also have malabsorption.

Patients may exhibit hypomagnesiuria as a result of impaired intestinal absorption of magnesium. Because magnesium has been shown to complex oxalate, hypomagnesiuria may increase the urinary saturation of calcium oxalate ([Caudarella et al, 1993](#)). Although oral magnesium supplements may correct hypomagnesiuria, they also may provoke further diarrhea. Magnesium gluconate (0.5 to 1 g three times per day) appears to be better tolerated than magnesium oxide or hydroxide. **Treatment with potassium citrate (60 to 120 mEq/day) may correct the hypokalemia and metabolic acidosis in patients with enteric hyperoxaluria and, in some individuals, increase urinary citrate toward normal.** Consideration should be given to providing the liquid form of potassium citrate in patients with rapid GI transit times, because the liquid form of this medication may be better absorbed than the slow-release, wax matrix pills.

A high fluid intake is recommended to ensure adequate urine volume. Excessive fluid loss may be present, and an antidiarrheal agent may be necessary before sufficient urine output can be achieved. Calcium citrate may theoretically have a role in management of enteric hyperoxaluria. This treatment may lower urinary oxalate by binding oxalate in the intestinal tract. Calcium citrate also may raise the urinary citrate and pH by providing an alkali load ([Harvey et al, 1985](#)). Finally, calcium citrate may correct the malabsorption of calcium and adverse effects on the skeleton by providing an efficiently absorbed formulation of calcium.

Recently, the use of probiotics and the alteration of gut flora have been investigated ([Hoppe et al, 2005](#); [Lieske et al, 2005](#)). The goal of these strategies is to increase the degradation of oxalate, thereby preventing intestinal absorption. The use of lactic acid bacteria and *O. formigenes* has preliminarily demonstrated reduction in urinary excretion of oxalate. Larger, long-term assessment is needed, but further investigation into this relatively novel treatment approach is clearly warranted.

Pyridoxine has been used to treat patients with elevated oxalate in primary hyperoxaluria. It is converted to pyridoxal phosphate, which is a cofactor for AGT. Deficiency of AGT is the cause of primary hyperoxaluria type 1. Pyridoxine has been shown to increase the expression, catalytic activity, and peroxisomal import of AGT ([Fargue et al, 2013](#)). It also has been reported for patients with idiopathic hyperoxaluria. In a retrospective study, [Ortiz-Alvarado and colleagues \(2011\)](#) found that a combination of dietary counseling (low-oxalate diet) and pyridoxine significantly reduced urinary oxalate in patients with idiopathic hyperoxaluria. The authors did not note any side effects from pyridoxine treatment. This may be an alternative treatment for patients with refractory hyperoxaluria.

KEY POINTS: ENTERIC HYPEROXALURIA

- Fluid intake should be strongly encouraged to correct the relative state of dehydration.
- Dietary calcium may help bind intestinal oxalate and decrease its absorption.
- Slow-release formulations of citrate should be avoided.

Hypocitraturic Calcium Oxalate Nephrolithiasis

In patients with hypocitraturic calcium oxalate nephrolithiasis, potassium citrate treatment is capable of restoring normal urinary citrate, lowering the urinary saturation, and inhibiting crystallization of calcium salts. Because hypocitraturia is found in a number of different conditions, each will be addressed individually.

Distal Renal Tubular Acidosis

Potassium citrate therapy is able to correct the metabolic acidosis and hypokalemia found in patients with distal RTA (Preminger et al, 1985; Wang and Preminger, 2011). In addition, this medication is capable of restoring normal urinary citrate, although large doses (up to 120 mEq/day) may be required in severe acidotic states. With correction of the acidosis, urinary calcium should decline into the normal range. Because urinary pH is generally high to begin with in patients with RTA, the overall rise in urinary pH is small.

Potassium citrate therapy typically produces a sustained decline in the urinary saturation of calcium oxalate (from reduction in urinary calcium and in citrate complexation of calcium). The urinary saturation of calcium phosphate does not increase because the rise in phosphate dissociation is relatively small and is adequately compensated by a decline in ionic calcium concentration. In addition, the inhibitory activity against the crystallization of calcium oxalate and calcium phosphate is augmented because of the direct action of citrate.

Investigators from Thailand suggest that the target dose of potassium citrate for children with distal RTA should be 3 to 4 mEq/kg per day in divided doses (Domrongkitchaiporn et al, 2002c; Tapaneay-Olarn et al, 2002).

Chronic Diarrheal States

The full management of enteric stone disease has been discussed previously in this chapter. Part of the entire management should involve the use of citrate to correct the acidosis that accompanies the chronic bicarbonate losses with diarrhea. The amount of potassium citrate will depend on the severity of hypocitraturia in these patients, with dosages ranging from 60 to 120 mEq in three or four divided doses.

It is recommended that a liquid preparation of potassium citrate be used rather than the slow-release tablet preparation; the slow-release medication may be poorly absorbed because of rapid intestinal transit time. In addition, frequent dose schedules (3 or 4 times per day) for the liquid preparation is necessary because this form of the medication has a relatively short duration of biologic action.

Thiazide-Induced Hypocitraturia

As noted previously, thiazide therapy may cause hypocitraturia as a result of thiazide-induced hypokalemia with resultant intracellular acidosis (Nícar et al, 1984). Therefore it should be a common practice to administer potassium supplementation, preferably in the form of potassium citrate, to patients receiving thiazides for treatment of hypercalciuria. Potassium citrate has been shown to be equally effective as potassium chloride in correcting thiazide-induced hypokalemia. Moreover, the addition of potassium citrate not only prevents a fall in urinary citrate during thiazide therapy, but may raise citrate excretion (Pak et al, 1985b).

Idiopathic Hypocitraturic Calcium Oxalate Nephrolithiasis

This entity includes hypocitraturia occurring alone, as well as in conjunction with other abnormalities (e.g., hypercalciuria or hyperuricosuria). Stones formed in this condition are predominantly composed of calcium oxalate. Potassium citrate therapy may produce a sustained increase in urinary citrate and a decline in the urinary saturation of calcium oxalate (Pak and Fuller, 1986). Two agents have been used for the treatment of hypocitraturia: sodium potassium citrate, commonly used in Europe, and potassium citrate—in liquid form or as a wax matrix tablet—used in the United States. The usual therapeutic dose is 30 to 60 mEq/day given in divided doses or as a single evening dose (Berg et al, 1992). Sodium citrate does not lower urinary calcium excretion, perhaps as a result of the increased sodium load associated with this therapy (Sakhaee et al, 1983; Preminger et al, 1988).

In general, citrate is well tolerated, although the potential for gastric upset is real. The current formulation of potassium citrate embedded within a wax matrix may help alleviate the risk for gastric irritation. Patients are strongly encouraged to take this medication with meals to act as a further buffer.

Long-term therapy with this medication has been shown to provide a favorable durable response in alteration of urinary parameters and stone formation rate (Robinson et al, 2009). In a retrospective cohort of 503 patients on potassium citrate therapy for a mean of 41 months (range 6 to 168), urinary pH and citrate demonstrated significant increases (pH, 5.9 to 6.46; citrate, 470 to 700 mg/day), with substantial improvement in urinary parameters in as little as 6 months of therapy. In addition potassium citrate decreased the stone formation rate from 1.89 stones per patient per year to 0.46.

Concern has been raised, however, regarding the overalkalinization of urine and an increase in the formation rate of calcium phosphate stones. Researchers analyzed a large stone database of over 1200 patients and identified a three-fold increase in calcium phosphate content of stones over the last three decades (Parks et al, 2004). As would be expected, rising urinary pH was directly associated with this finding, therefore raising the question of the role of potassium citrate in this finding of increasing calcium phosphate content. The same group of researchers then analyzed patients who transformed their stone content to increased calcium phosphate and found that those patients who transformed did receive more potassium citrate compared to those who did not transform (Parks et al, 2009). The authors point out that the effect on urinary pH is possibly offset by the rise in urinary citrate.

Further work on this issue has shown that although the urinary pH does increase while patients are taking long-term potassium citrate, the stone formation rate in patients with a urine pH greater than 6.5 is as significantly decreased as in patients with a potassium citrate-treated pH less than 6.5. Although stone composition was not evaluated in this particular study, the lack of difference in the stone formation rate in patients with a high urine pH strongly suggests that citrate administration does not increase the risk for calcium phosphate stone formation (Robinson et al, 2009).

KEY POINTS: HYPOCITRATURIC CALCIUM OXALATE NEPHROLITHIASIS

- Citrates are generally well tolerated, with only a small risk for GI upset.
- Citrates are first-line therapy for the management of RTA, thiazide-induced hypocitraturia, and idiopathic hypocitraturia.
- There is conflicting evidence of an increased risk of calcium phosphate stone formation with the long-term use of potassium citrate therapy.

Hypomagnesuric Calcium Nephrolithiasis

Hypomagnesuric calcium nephrolithiasis is characterized by low urinary magnesium, hypocitraturia, and low urine volume. Therefore management should include restoration of urinary magnesium levels with either magnesium oxide or magnesium hydroxide, as well as correction of the hypocitraturia with potassium citrate. The administration of magnesium salts was first advocated on the theory that it reduced urinary excretion of oxalate. Some magnesium salts increase urinary magnesium excretion and thus produce a more favorable magnesium-to-calcium ratio in the urine, a condition that offers relative protection against stone formation. Magnesium decreases renal tubular citrate resorption through the chelation of citrate and thus increases urinary citrate excretion. Melnick and coworkers (1971) found that stone recurrence dropped from 6 stones per year to 0.073 stone per year in a group of 149 recurrent calcium oxalate-stone formers treated with magnesium oxide. Prien and Gershoff (1974) reported that

approximately 70% of patients administered 300 mg of magnesium oxide and 100 mg of pyridoxine demonstrated complete cessation of stone formation. [Johansson and associates \(1980\)](#) treated 56 patients with 400 to 500 mg of magnesium hydroxide. Of the treated patients, 80% were free of stones, in comparison to 50% who did not receive magnesium supplementation. The rate of stone formation dropped from 0.8 stone per year to 0.03 stone per year in the treated patients and from 0.5 stone per year to 0.22 stone per year in the control subjects. At least one randomized trial showed no difference in recurrence rates between treated and untreated patients ([Ettinger et al, 1988](#)).

Several magnesium salts have been used for the treatment of stone disease. Magnesium oxide and magnesium hydroxide are poorly absorbed and produce only a slight decrease in urinary oxalate and a modest increase in urinary magnesium ([Barilla et al, 1978](#); [Johansson et al, 1980](#)). Urinary calcium levels are increased during magnesium oxide supplementation ([Melnick et al, 1971](#); [Fetner et al, 1978](#); [Tiselius et al, 1980](#)), and thus urinary saturation of calcium oxalate is not significantly lowered with magnesium oxide. [Lindberg and colleagues \(1990\)](#) found that either magnesium citrate or magnesium oxide induced only modest beneficial changes in urinary biochemistry when administered on an empty stomach. When the magnesium salts were provided with meals, however, they caused more prominent changes in urinary biochemistry and lowered the relative saturation of urine with calcium oxalate or brushite.

GI intolerance is the major side effect of magnesium therapy. At this time, magnesium supplementation is not widely used. Magnesium supplementation had been used in patients with sodium cellulose phosphate for the treatment of patients with absorptive hypercalciuria type I and currently may be used with potassium citrate in patients with chronic diarrheal syndromes.

A new magnesium preparation (potassium-magnesium citrate) has been developed, but not yet approved for use, that provides both magnesium and citrate in the same tablet. This formulation of potassium-magnesium citrate has been shown to provide as much bioavailable potassium as other preparations ([Koenig et al, 1991](#)). In addition, magnesium excretion was significantly increased, as was the excretion of urinary citrate. The ability to deliver potassium has been further studied as it relates to thiazide-induced hypokalemia. This medication was demonstrated to provide just as much bioavailable potassium as other, standard, agents ([Wuermser et al, 2000](#)).

[Ettinger and colleagues \(1997\)](#) reported on a randomized, double-blind trial of potassium-magnesium citrate versus placebo. In their study, new calculi formed in 63.6% of subjects receiving placebo and in 12.9% of subjects receiving potassium-magnesium citrate. When compared with placebo, the relative risk for treatment failure for potassium-magnesium citrate was 0.16. The authors concluded that potassium-magnesium citrate effectively prevents recurrent calcium oxalate stones and could be depended on to provide up to 85% protection over 3 years. Similar to work performed with potassium citrate, [Odvin and colleagues \(2006\)](#) demonstrated the ability of potassium-magnesium citrate in preventing hypokalemia and hypomagnesemia in patients on thiazide therapy.

KEY POINTS: HYPOMAGNESURIC CALCIUM NEPHROLITHIASIS

- Magnesium supplementation can provide benefits in stone reduction.
- The use of magnesium has been limited by the risk for diarrhea.
- Potassium-magnesium may restore urinary magnesium and citrate levels with minimal GI side effects.

Gouty Diathesis

The major goal in the management of gouty diathesis is to increase the urinary pH above pH 5.5, preferably between 6.0

and 6.5 ([Khatchadourian et al, 1995](#)). In the past, urine alkalinization has been accomplished with either sodium bicarbonate or various combinations of sodium and potassium alkali therapy. Although sodium alkali may enhance dissociation of uric acid and inhibit uric stone acid formation by raising urinary pH, this medication may be complicated by the development of calcium-containing stones (calcium phosphate and/or calcium oxalate). Potassium citrate is advantageous because it is not only a good alkalinizing agent, but it appears to be devoid of the complication of calcium stones. Potassium citrate should be given at doses sufficient to maintain urinary pH at approximately 6.5 (30 to 60 mEq/day in two or three divided doses). **Attempts at alkalinizing the urine to a pH of greater than 7.0 should be avoided. At a higher pH, there is a danger of increasing the risk for calcium phosphate stone formation.** If the urinary uric acid excretion is elevated or hyperuricemia exists, allopurinol (300 mg/day) should be added.

Cystinuria

The object of treatment for cystinuria is to reduce the urinary concentration of cystine to below its solubility limit (200 to 300 mg/L) ([Pak and Fuller, 1983](#)). The initial treatment program includes a high fluid intake to attempt to produce 2½ to 3 liters of urine per day. This amount of urine output will dramatically raise the denominator of the concentration fraction and help reduce the supersaturation of urine with respect to cystine. Others have recommended the oral administration of soluble alkali (potassium citrate) at a dose sufficient to raise the urinary pH to 6.5 to 7.0 ([Chow and Streem, 1998](#); [Joly et al, 1999](#)). This treatment strategy attempts to increase the solubility of the filtered cystine to prevent crystal formation. Although alkali therapy may help, it is important to remember that the pKa of cystine is 8.3, which creates two problems. First, it is quite difficult to achieve a urine pH this high, making excessive alkalinization an unrealistic target. Second, raising the urine pH to these levels will put the patient at risk for the formation of calcium phosphate calculi.

There is good evidence that excess dietary sodium can lead to increases in cystine excretion ([Norman and Manette 1990](#); [Lindell et al, 1995](#); [Rodriguez et al, 1995](#); [Fjellstedt et al, 2001](#)). Indeed, these authors have demonstrated that the restriction of dietary sodium should be an integral aspect of the global management of cystinuric patients. [Fjellstedt and colleagues \(2001\)](#) demonstrated that the use of sodium citrate rather than potassium citrate may diminish the efficacy of other medical interventions, such as the sulfhydryl-containing compound α -mercaptopyrionylglycine (Thiola).

When this conservative program is ineffective, the next line of therapy involves the use of agents that increase cystine solubility in urine by formation of a more soluble mixed-disulfide bond (i.e., cystine to drug, rather than cystine to cystine). These agents include α -mercaptopyrionylglycine (tiopronin [Thiola]), D-penicillamine (Cuprimine), and captopril.

The first agent studied was D-penicillamine. Interestingly, very little has been written specifically about this agent and its use in the treatment of cystinuria since the 1960s to 1970s ([Crawhall and Thompson, 1965](#); [McDonald and Henneman, 1965](#); [Lotz et al, 1966](#); [Combe et al, 1993](#)). Although moderately effective, D-penicillamine quickly became associated with frequent side effects, including nephrotic syndrome, dermatitis, and pancytopenia. One recent study documented 9 of 11 patients without toxicity for an average of 109 months of follow-up after an initial dose escalation ([DeBerardinis et al, 2008](#)). Typical doses start at 250 mg/day and are titrated to effect.

The next medication to be introduced for the treatment of cystinuria was α -mercaptopyrionylglycine (tiopronin [Thiola]) ([Remien et al, 1975](#); [Hautmann et al, 1977](#); [Johansen et al, 1980](#)). This agent also contains a sulfhydryl group that forms a disulfide bond with cystine. Although it has been shown to be slightly less effective at capturing cystine molecules in vivo ([Harbar et al, 1986](#)), α -mercaptopyrionylglycine is better tolerated than D-penicillamine and therefore enjoys clinical superiority ([Pak](#)

et al, 1986a). However, side effects are still possible with tiopronin. Indeed, Pak and colleagues (1986a) demonstrated that overall side effects to α -mercaptopropionylglycine were relatively common, and occurred in 64.7% without a history of D-penicillamine treatment, compared to 83.7% who suffered toxicity to D-penicillamine. Moreover, serious adverse reactions requiring cessation of therapy were less common with α -mercaptopropionylglycine. Among the patients who took both drugs, 30.6% had to stop taking α -mercaptopropionylglycine, whereas 69.4% could not tolerate D-penicillamine. Common side effects include asthenia, GI distress, rash, joint aches, and mental status changes. Dosages start at 100 mg, taken orally two times per day and are titrated to achieve urinary concentrations of cystine less than 250 mg/L urine. Pak has reported total daily doses as high as 1200 mg (Pak et al, 1986a).

As described earlier in this chapter, Coe and colleagues have presented an assessment of cystine prophylaxis based upon the supersaturation of cystine in the presence of thiol-based medications (Coe et al, 2001). In essence, this assay measures how much “room” there is in the patient’s urine for more cystine to be dissolved. Demonstration that the urine is not yet fully saturated implies a lower risk for spontaneous stone formation.

Finally, the angiotensin-converting enzyme inhibitor captopril has been used to treat cystinuria because of its available sulfhydryl group. Although this agent enjoyed early enthusiasm (Sloand and Izzo, 1987; Streem and Hall, 1989; Cohen et al, 1995), its popularity seems to have waned (Michelakakis et al, 1993). Side effects are less severe than the other agents and include fatigue, hypotension, and chronic cough. Yet, there have been no long-term clinical trials demonstrating the effectiveness of captopril in preventing recurrent cystine stone formation.

The medical management of cystinuria can be quite challenging. Although the array of medication choices is not particularly complicated, it is often difficult to achieve patient compliance (Barbey et al, 2000). Indeed, because of the genetic nature of the disease process, these patients frequently begin their stone formation at a young age, thereby exposing their kidneys to the risk for chronic stone passage and potential parenchymal loss (Lindell et al, 1997). Assimos and colleagues (2002) examined the clinical status of 40 cystinuric patients followed at two medical centers and compared their kidney health to that of 3964 calcium oxalate–stone formers enrolled in a database. The mean serum creatinine for stone-forming cystinuric patients was significantly higher than that of the calcium oxalate cohort. Male gender, increasing number of open surgical stone removal procedures, and nephrectomy were significant variables associated with an increased serum creatinine. An alarming number of cystinuric patients had undergone nephrectomy for any reason (14%) versus the patients in the calcium oxalate cohort (3%).

Unfortunately, despite the obvious consequences of poor medical compliance, a recent study suggests that few patients are able to achieve and maintain targeted goals of medical intervention (Pietrow et al, 2003). Of the 26 patients followed at a dedicated stone center, only 15% achieved and maintained therapeutic success, as defined by urine cystine concentration less than 300 mg/L. An additional 42% achieved therapeutic success but subsequently had failure at an average of 16 months (range 6 to 27). Of these patients, two thirds were able to regain therapeutic success at an average of 9.4 months (range 4 to 20). However, 19% never achieved therapeutic success and an additional 23% failed to present to follow-up appointments or provide subsequent 24-hour urine studies, despite their having been referred to a tertiary care center. It is very important to note that patient self-assessment of medical compliance was uniformly high regardless of physician perceptions or treatment results.

Infection Lithiasis

The preferred management of struvite calculi involves aggressive surgical approaches. The American Urological Association Nephrolithiasis Guidelines Committee has strongly recommended

KEY POINTS: CYSTINURIA

- The medical compliance of patients with cystinuria can be poor.
- Treatment consists of aggressive fluid intake, urinary alkalization, salt avoidance, and the use of a cystine-binding agent.
- α -Mercaptopropionylglycine (Thiola) is the most frequently used cystine-binding agent.

endoscopic-based therapy (i.e., percutaneous nephrolithotomy) as the first-line therapy for managing complex renal staghorn calculi (Preminger et al, 2005). This report noted that complete elimination of all infected stone material is essential for the prevention of recurrent struvite stone formation. A complete discussion of surgical therapy for large calculi is beyond the scope of this chapter and can be found elsewhere within this text.

The medical management of infection calculi centers on the prevention of recurrence, rather than medical dissolution. Thus long-standing effective control of infection with urea-splitting organisms should be achieved if at all possible with improved bladder health, adequate urinary drainage, and suppressive antibiotics (Hess, 1990; Bichler et al, 2002). Unfortunately, such control is difficult to obtain in the face of residual calculi because stones often harbor organisms and endotoxin within their interstices (Rocha and Santos, 1969; McAleer et al, 2002, 2003). Antibiotics should be tailored to the predominant organism found on culture and sensitivity screening (Hugosson et al, 1990). Notably, cultures do not always correlate well between a patient’s urine and a resuspension of stone material (Fowler, 1984). Therefore strong clinical suspicion is always indicated, and all patients undergoing removal of presumed struvite calculi should be covered with broad-spectrum antibiotics that account for local resistance patterns. Although cultures may become negative during treatment, it is important to remember that recurrence of colonization is likely if residual fragments remain within the collecting system.

After surgical stone removal, residual fragments may be dissolved with hemiacidrin irrigation (Renacidin) under very careful observation. Historically, use of this agent was associated with significant toxicity and even death. Closer scrutiny revealed that many, if not most, of these cases involved the use of irrigation in infected urine and/or sepsis. Therefore this agent should be employed only after UTI and/or colonization has been brought under control. Chemolysis with various agents is no longer routinely used for the management of struvite calculi.

Acetohydroxamic acid, a urease inhibitor, may reduce the urinary saturation of struvite and therefore retard stone formation (Griffith et al, 1978). When given at a dose of 250 mg three times per day, acetohydroxamic acid has been shown to prevent recurrence of new stones and inhibit the growth of stones in patients with chronic urea-splitting infections. At least two studies have demonstrated significant efficacy in randomized, placebo controlled trials (Williams et al, 1984; Griffith et al, 1991). In these investigations, patients were treated with acetohydroxamic acid and antibiotics. Recurrence rates and subsequent stone growth were significantly less for patients treated with drug therapy compared to placebo. In addition, in a limited number of patients, this agent has caused dissolution of existing struvite calculi (Rodman et al, 1983). However, a significant percentage of patients receiving chronic acetohydroxamic acid therapy have experienced minor side effects and 15% developed deep venous thrombosis. Indeed, Rodman and colleagues (1987) demonstrated that patients receiving acetohydroxamic acid enter into a state of low-grade intravascular coagulation requiring careful follow-up for signs of thrombosis. Several authors reported high rates of medication cessation because of intolerable side effects. In the previously noted randomized studies, 22% to 68% of treated patients had to stop therapy and withdraw from the investigation. Reported side effects have been varied and include thromboembolic phenomena, tremor,

headache, palpitations, edema, GI distress, loss of taste, rash, alopecia, anemia, and abdominal pain. Because of these concerns, this agent is frequently reserved for patients deemed too ill for surgical management. Other acidifying agents have been reported by [Wall and Tiselius \(1990\)](#) but do not appear to have been widely used. These include ammonium chloride, methenamine hippurate, and ascorbic acid.

Controversy exists as to whether patients with infection stones warrant metabolic evaluation with 24-hour urine collections. In one study, only 14% of patients with a pure struvite stone had a metabolic abnormality on 24-hour urine collection. Of the patients who had a mixed struvite stone, 100% had a metabolic abnormality ([Lingeman et al, 1995](#)). A more recent retrospective review found that three in five patients with a pure struvite stone had a metabolic abnormality on 24-hour urine collection. Two of the patients were found to have hypercalciuria, one patient had hypocitraturia, and one patient had hyperoxaluria. Of the patients with mixed struvite stones, 77% had a metabolic abnormality. The authors found that with appropriate medical management of both the metabolic abnormalities and the UTI with either acetohydroxamic acid and/or suppressive antibiotics, 60% of patients with residual stone demonstrated no stone growth at a median follow-up of 22 months ([Iqbal et al, 2013](#)). Therefore there may be some value in performing 24-hour urine collections in patients with struvite stones and appropriately managing their metabolic abnormalities.

KEY POINTS: INFECTION LITHIASIS

- Struvite calculi are best managed with surgical removal rather than chemical dissolution.
- Recurrent infections (and therefore recurrent calculi) may be avoided with the use of antibiotic prophylaxis.
- Acetohydroxamic acid (Lithostat) can effectively inhibit urease, but its widespread use is precluded by significant side effects.

Ammonium Acid Urate Stones

Ammonium acid urate calculi are infrequently seen in industrialized nations and are often associated with laxative abuse ([Dick et al, 1990](#); [Kato et al, 2004](#)). The largest described series was reported in 1999 ([Soble et al, 1999](#)). In this series, 23 women and 21 men ranging in age from 20 to 81 years (mean 48.7 years) were treated for stones partly composed of ammonium acid urate. Stone composition ranged from 2% to 60% ammonium acid urate (mean 24.1%) of the total stone mass. No patient had a pure ammonium acid urate stone, although 11 (25%) had stones with ammonium acid urate as the predominant crystal. The authors identified one or more potential risk factors for ammonium acid urate for most patients. Of the patients, 25% had a history of inflammatory bowel disease, with 22.7% having undergone ileostomy diversion, 13.6% admitted to a history of significant laxative use or abuse, 40.9% were morbidly obese, 36.4% had a history of recurrent UTIs, and 20.5% had a history of recurrent uric acid stones. Based on these findings, the authors suggested that laxative abuse should not be assumed for all patients with ammonia acid urate calculi, but rather conditions resulting in metabolic acidosis, the prime risk factor for urate stones. Therefore a full history and metabolic evaluation should be sought for each patient.

Medical treatment for these calculi is determined by the underlying cause of the stone. Those with laxative abuse are strongly encouraged to develop a healthier bowel regimen. Those with chronic infections are treated much like those with struvite calculi. Bowel disease is treated, if possible, while standard recommendations of fluid intake, oral calcium, alkalization, and oxalate reduction are made. Those with a history of uric acid calculi are also treated in a similar manner with increased fluid intake, protein and salt restriction, alkalization with potassium citrate, and the possible use of allopurinol.

Miscellaneous and Drug-Induced Stones

Some stones are formed from supersaturation of the medications themselves or may be due to the effects of a particular agent. Several medications have been associated with stone disease and are listed in [Box 52-6](#).

Calculi formed from antiretroviral medications used to treat human immunodeficiency virus (HIV) have been described, particularly with indinavir (Crixivan) ([Bach and Godofsky, 1997](#); [Hug et al, 1999](#); [Sundaram and Saltzman, 1999](#); [Saltel et al, 2000](#)). These calculi can be quite soft and often dissipate rapidly during endoscopy or shock wave lithotripsy. Difficulties may arise during diagnosis—indinavir stones may not be visible on plain film radiography and even may be undetectable on a stone protocol CT ([Gentle et al, 1997](#); [Sundaram and Saltzman, 1999](#)). Treatment entails aggressive hydration and endoscopy for stones that do not pass spontaneously. The radiolucency of the calculi often precludes successful treatment with shock wave lithotripsy. In the short term, patients may be temporarily taken off of indinavir until an aggressive fluid habit can be established. Some patients require cessation of this antiretroviral drug and the initiation of a different agent.

As described earlier, triamterene, a potassium-sparing antihypertensive agent may crystallize in the urinary tract, requiring cessation of this medication ([Werness et al, 1982](#); [Sorgel et al, 1985](#)). For this reason, triamterene is not recommended as an adjunct to thiazides during the treatment of hypercalciuric states.

Carbonic anhydrase inhibitors may be associated with the formation of calcium-based calculi, particularly calcium phosphate ([Kondo et al, 1968](#); [Parfitt, 1969](#)). In this scenario, the use of the medication creates a chronic intracellular acidosis. This effect in turn creates a urinary milieu reminiscent of a distal tubular acidosis with hyperchloremic acidosis, high urine pH, extremely low urinary citrate, and hypercalciuria. Treatment may be accomplished with potassium citrate replacement or, more logically, cessation of the medication.

Topiramate is prescribed for the treatment of refractory epilepsy and recurrent migraine headaches and was recently approved for weight loss. Unfortunately, it may mimic the effect of a carbonic anhydrase inhibitor with resultant metabolic acidosis, hypocitraturia, hypercalciuria, and elevated urine pH ([Kossoff et al, 2002](#); [Kuo et al, 2002](#); [Lamb et al, 2004](#)). Potassium citrate has been shown to restore urinary citrate and prevent recurrent stone disease ([Vega et al, 2007](#); [Warner et al, 2008](#); [McNally et al, 2009](#); [Kaplan et al, 2011](#)).

Finally, multiple authors have described calculi that have formed in patients taking over-the-counter supplements containing ephedrine ([Blau, 1998](#); [Powell et al, 1998](#); [Assimos et al, 1999](#);

BOX 52-6 Medications Associated with Renal Calculus Formation

CALCULI FORMED FROM DRUG

Indinavir
Ephedrine
Triamterene
Magnesium trisilicate antacids (silicates)
Trimethoprim-sulfamethoxazole

CALCULI PROVOKED BY DRUG

Carbonic anhydrase inhibitors
Topiramate
Furosemide
Vitamin C (excess)
Vitamin D (excess)
Laxatives

Hoffman et al, 2003; Bennett et al, 2004; Smith et al, 2004; Whelan and Schwartz, 2004). These calculi are likely radiolucent, but have been reported to be “visible” on noncontrast CT. Ephedrine stones have been treated with a variety of methods, including shockwave lithotripsy, endoscopy, and even alkalization therapy. Because this supplement has a risk for abuse, it may be difficult to effectively interfere with the formation of future stone events.

MISCELLANEOUS SCENARIOS

Medical Management of Bladder Calculi

In the United States, bladder calculi usually occur in men older than 50 years of age and are usually associated with bladder outlet obstruction. The diagnosis of a bladder stone should result in a complete urologic evaluation for factors that cause urinary stasis, such as urethral stricture, benign prostatic hyperplasia, bladder diverticulum, and/or a neurogenic bladder. Occasionally, bladder stones may result as a consequence of a retained foreign body.

In contrast to renal stones, bladder stones are usually composed of uric acid (in noninfected urine) or struvite (in infected urine). Reports from the United States revealed uric acid stones in nearly 50% of patients with bladder stones (Douenias et al, 1991). Such patients often have bladder outlet obstruction, causing them to decrease fluid intake with the resultant production of concentrated acidic urine. The occurrence of calcium oxalate or cystine stones in the bladder suggests the presence of calculi in the kidney with subsequent ureteral passage and entrapment in the bladder.

Bladder calculi are usually solitary, but may develop in large numbers in the presence of urinary stasis (Sarica et al, 1994). The typical symptoms of a vesical stone are intermittent, painful voiding and terminal hematuria. Discomfort may be dull, aching, or sharp suprapubic pain, which is aggravated by exercise and sudden movement. Severe pain usually occurs near the end of micturition, when the stone becomes impacted at the bladder neck. Relief may be afforded by assuming a recumbent position. The pain may be referred to the tip of the penis, the scrotum, or the perineum and on occasion to the back or the hip. Besides pain, there may be an interruption of the urinary stream from impaction of the stone at the bladder neck or urethra.

Bladder calculi are frequently missed on plain film because of a high component of uric acid and because of overlying prostatic tissue. Such stones form negative shadows in the cystogram phase of intravenous urography. Ultrasonography is useful for detecting radiolucent calculi. Cystoscopic examination is the surest method for detecting vesical calculi.

The vast majority of bladder calculi can be removed via endoscopic techniques. Various lithotripters have been used, including ultrasonic handpieces, lasers, pneumatic devices, and electrohydraulic probes. Transurethral and percutaneous approaches have been described with good success (Dhabalia et al, 2011; Philippou et al, 2011). Renacidin may prove beneficial in irrigating indwelling suprapubic or urethral catheters to decrease and prevent encrustation and occlusion (Kennedy et al, 1992; Getliffe et al, 2000). Twice-daily or thrice-daily irrigation with 0.25% or 0.5% acetic acid solution also serve as beneficial prophylaxis against recurrent struvite calculi when catheters must be left indwelling for long periods. Uric acid calculi may be dissolved by irrigation with alkaline solutions.

The mainstay of therapy for the prevention of recurrent bladder calculi involves relief of the bladder outlet obstruction. This treatment may include the performance of a transurethral resection of the prostate or an open prostatectomy if the gland is quite large.

Medical Management of Pediatric Calculi

Children may develop urinary calculi because of several underlying causes, as outlined in Chapter 51. Evaluation and management depend on the causative process.

Neonatal Nephrolithiasis

Neonates with furosemide-induced nephrolithiasis present with hematuria, worsening renal function, and calcific densities on ultrasonography or plain film radiography. Nephrocalcinosis is often present on imaging studies. This same process has been seen in other infants with severe low birth weight and/or prematurity and no history of loop diuretic usage.

Management of neonatal nephrolithiasis entails the obvious optimization of the infant's overall health. Cessation of furosemide diuresis is considered helpful and standard therapy. There has been previous suggestion that treatment with thiazide diuretics may actually promote the resolution of this process and reverse the likely parenchymal injury (Noe et al, 1984). This observation has not been supported by other investigators, however. Pope and colleagues (1996) noted a 50% resolution rate of the nephrocalcinosis after cessation of loop diuretics, but this finding was unrelated to any other factor, including the use of thiazides. Instead, a low calcium-to-creatinine ratio at the time of diagnosis was the best predictor of resolution. Further research by Knoll and Alon (2000) using an animal model of the disease did not demonstrate a therapeutic effect of the use of thiazides on furosemide-induced nephrocalcinosis.

At the very least, this evidence suggests that neonates treated with loop diuretics should be screened for the development of nephrocalcinosis. Although switching to a thiazide diuretic may not actively cause the dissolution of calculi, it at least removes the causative agent and allows the kidney an opportunity to heal and clear the calcium deposits.

Children and Adolescents

As children reach physical maturity at a younger age, it is not surprising that the incidence of urinary calculi in adolescence appears to be increasing. Within the United States this finding is likely further related to the increasing prevalence of obesity within this same age group. Nevertheless, the appearance of urinary calculi during childhood should raise the distinct possibility of an inherited genetic disorder, such as cystinuria, distal RTA, or primary hyperoxaluria.

The evaluation of pediatric nephrolithiasis has been hampered in the past by a lack of consensus regarding normal laboratory values during 24-hour urine collections in children. Clinicians have therefore relied on calculated ratios to correct for the wide variation in weight within this diverse patient population. The most important of these has been the urinary calcium-to-creatinine ratio. A calculated urinary calcium-to-creatinine ratio above 0.2 has been considered abnormal and frequently prompts intervention.

Several investigators have explored the use of urinary supersaturation calculations to assess for stone risk factors in children (Battino et al, 2002; Lande et al, 2005). These calculations may miss abnormalities otherwise overlooked by traditional cumulative measurements. At least one of these authors, however, notes that the importance of supersaturation wanes considerably in the face of low urine volumes (Lande et al, 2005).

Evidence strongly supports close and aggressive follow-up of pediatric stone formers. Pietrow and associates (2002) found that 50% of children 10 years or younger with urinary calculi have an identifiable metabolic derangement. Additionally, those with abnormal urinary metabolites are five times more likely to have recurrent stones. However, the identification of these abnormalities is more challenging in the pediatric population. Reference values for this population are not as well defined and may require adjustments based on body weight and urinary creatinine level to best delineate abnormalities (Borawski et al, 2008).

The medical management of nephrolithiasis and the prevention of subsequent recurrences in children do not differ that dramatically from the approaches undertaken for adults. All patients (and their parents) are counseled to improve fluid intake. Dietary recommendations are similar to those made for

adults. It is important to emphasize that dietary calcium is not to be avoided in this age group. Rather, calcium should be sought through the ingestion of dairy and other natural sources rather than with the use of supplements. Such sources will also bind dietary oxalate during meals and may decrease calcium oxalate supersaturation in the urine.

Children with cystinuria or hyperoxaluria are managed as outlined in the previous section within this chapter. The exception to this would be a general reticence to begin sulfur-binding agents in cystinuric children, without first maximizing fluid intake and the use of citrates to alkalinize the urine.

Children with documented hypocitraturia and/or distal RTA are usually treated with citrates at a dose of 4 mg/kg/day (Domrongkitchaiporn et al, 2002a). Hypercalciuria may respond to increased fluid intake and decreased sodium (salt) ingestion, much like the adult population. Thiazides may be employed for recalcitrant hypercalciuria. The long-term efficacy and safety of thiazides in the pediatric population has not been well studied and established.

Medical Management of Calculi during Pregnancy

The management of calculi during pregnancy is currently undergoing a transformation. These changes, however, are developing mainly within the realm of surgical intervention, not medical therapy. As noted in Chapter 51, pregnant women create a unique urinary environment that is prone to stone formation. Although the amount of urinary calcium rises quite notably (Gertner et al, 1986), this effect is offset by an accompanying increase in urinary citrate. As a result, it is widely assumed that there is no net increase or decrease in the risk for calculi formation during pregnancy (Coe et al, 1978; Maikranz et al, 1987). As a result of these temporary physiologic changes, a metabolic evaluation is not generally undertaken to determine the cause of the stone disease until after the woman has delivered and returned to her baseline state of health.

Patients with a history of stones should be strongly encouraged to maintain high fluid intake. Dietary recommendations should be reinforced. Patients who have previously undergone metabolic evaluation and are on medical therapy should be informed about the compatibility of their medications with pregnancy.

The acute evaluation of a pregnant woman with suspected renal colic begins with a thorough history and physical examination. A urinalysis is obtained and examined for signs of active UTI. Patients may present with vague abdominal pain, unexplained fevers, recurrent UTIs, persistent bacteriuria, or microscopic hematuria. A previous history of nephrolithiasis should be sought because the increased dilation of the ureters during pregnancy may increase the risk that a preformed stone will break loose and attempt to pass.

Radiation exposure to the fetus should be avidly avoided. Therefore ultrasonography has become the first-line imaging study to search for calculi during pregnancy. Although this modality provides adequate images of the kidneys, it can be difficult to fully discern the ureters and their contents. Additionally, hydronephrosis of pregnancy may be confused for hydronephrosis from an obstructing calculus. A limited intravenous pyelogram (IVP) may be obtained that consists of one scout image followed by one plate taken approximately 30 minutes after the injection of contrast. Each plain film exposes the fetus to 0.1 to 0.2 rads, well below the threshold of 1.2 rads, at which the risk begins to increase. Radiation exposure should be particularly avoided during the first trimester during the time of organogenesis and the greatest fetal risk.

In keeping with the concern of fetal radiation exposure, assessment of a low-dose CT protocol was performed (White et al, 2007). The average radiation exposure was 0.7 rads (0.2 to 1.3 rads). Of the 20 patients evaluated for flank pain, 13 were identified as having urinary stones ranging from 1 to 12 mm. Magnetic resonance imaging (MRI) has also been reported for stone diagnosis in pregnant patients (Mullins et al, 2012). A report comparing the effectiveness of different imaging modalities during pregnancy found a 23% rate of negative ureteroscopy for a presumed stone when

ultrasound alone was used for diagnosis (White et al, 2013). This is compared to a 4.2% negative ureteroscopy rate when CT was used and a 20% negative ureteroscopy rate when MRI was used.

Approximately 66% to 85% of pregnant women with ureteral colic spontaneously pass the calculi when treated conservatively with hydration, analgesics, and, if infected, antibiotics (Jones et al, 1979; Stothers and Lee 1992). The goal of therapy for the remaining patients is to do the least required to keep the kidney functioning, the patient free from symptoms, and the urine uninfected. Stents should be placed cystoscopically with minimal radiographic or sonographic monitoring (Loughlin and Bailey, 1986; Jarrard et al, 1993). Because many expectant mothers take calcium supplementation, a more stone-friendly form of this mineral has been developed (Citracal Prenatal Rx; Mission Pharmaceutical, San Antonio, TX). In this formulation, calcium is bound to citrate, which delivers extra stone inhibitor into the urine and thereby offsets the effects of worsening absorptive hypercalciuria. Iron and folate are also added to complete the elements commonly found in prenatal multivitamin supplements. Although there are no randomized data to support the use of this supplement in pregnant women, its use does make intuitive sense for patients at risk for recurrent calculi during pregnancy.

KEY POINTS: MEDICAL MANAGEMENT OF CALCULI

- Bladder calculi are best managed with endoscopic techniques. Subsequent recurrence is prevented by relief of the bladder outlet obstruction.
- Neonatal nephrocalcinosis is frequently caused by loop diuretics. Cessation of this medication is essential.
- Neonatal nephrocalcinosis may be reversed by the use of thiazides.
- The majority of ureteral calculi during pregnancy pass spontaneously.
- There is a growing trend toward endoscopic relief of symptomatic calculi during pregnancy.

SUMMARY

Appropriate metabolic evaluation and selective medical therapy of nephrolithiasis is highly effective in preventing new stone formation. A remission rate of greater than 80% and overall reduction in individual stone formation rate of greater than 90% can be obtained in patients with nephrolithiasis. In patients with mild-to-moderate severity of stone disease, virtually total control of stone disease can be achieved, with a remission rate of greater than 95%.

Selective pharmacologic therapy of nephrolithiasis also encompasses the advantages of overcoming nonrenal complications, as well as averting certain side effects that may be caused by nonselective medical therapy. Despite these advantages, it is clear that selective medical therapy cannot provide total control of stone disease. A satisfactory response requires continued, dedicated compliance by patients to the recommended program and a commitment of the physician to provide long-term follow-up and care.

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The complete reference list is available online at www.expertconsult.com.

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Historical Overview

Renal Calculi

Ureteral Calculi

HISTORICAL OVERVIEW



Please see the Expert Consult website for details.

RENAL CALCULI

One of the core tenets of renal stone surgery is to maximize stone removal while minimizing attendant morbidity to the patient. Before the era of endourology, stones were removed via open stone surgery, which provided high stone-free rates but came with a high rate of complications. In the early 1980s, SWL was developed and proved to have an excellent safety profile while achieving acceptable stone-free rates. During the same time period, PCNL was developed and refined such that it is now considered the gold standard for large and complex kidney stone disease for most patients. Over the last two decades as the technology has improved and the surgical technique diffused, URS has been used with increasing frequency in the treatment of renal stones. More recently, in experienced hands, it has been demonstrated that laparoscopic and robotic-assisted renal stone surgery can be safely used in selected patients with good outcomes. In areas where endourologic technology is widely available, open stone surgery is pursued only 1% of the time or less, and even in developing countries open stone surgery rates have dropped dramatically from 26% to 3.5% (Paik and Resnick, 2000; Honeck et al, 2009).

Thus, for most urologists the armamentarium to surgically treat kidney stones consists of four minimally invasive modalities including SWL, URS, PCNL, and laparoscopic or robotic-assisted stone surgery. Staged procedures of a given modality and combinations of different modalities (i.e., “sandwich technique” using SWL and PCNL, and SWL and URS) have been described as well. There appears to be an evolving paradigm shift in the surgical treatment of upper tract stones, with an increasing use of URS and a reciprocal decreasing use of SWL (Lee and Bariol, 2011; Ordon et al, 2014).

Deciding on the optimal treatment for a given patient is not always clear and depends on many variables, which can be broadly lumped into stone-related factors, renal anatomic factors, and clinical factors (Box 53-1). The combination of these factors, availability of technology and equipment, and familiarity of the urologist with the different surgical techniques ultimately determines which treatment is preferred for a given patient. The purpose of this section is to provide a framework to help guide the urologist in matching a given patient's unique clinical situation and renal stone disease characteristics to the most effective and least morbid surgical therapy (Fig. 53-1).

Natural History

The incidence of asymptomatic renal stones has been reported in approximately 10% of screened populations. In one evaluation of just over 5000 patients undergoing screening computed tomography (CT) colonography, asymptomatic urinary stones were found in 7.8% of patients, with a mean size of 3 mm and an average of two stones per patient (Boyce et al, 2010). In another study evaluating almost 2000 potential kidney donors, asymptomatic renal stones were found in 9.7% of patients (Lorenz et al, 2011). It is interesting to note that the true natural history of renal calculi, in particular asymptomatic renal calculi, has not been well characterized. Treatment is generally recommended for symptomatic stones, including those associated with pain, infection, obstruction, active stone growth, and significant hematuria. However, the available evidence is less clear on how to approach minimally symptomatic or asymptomatic renal calculi.

Before the era of minimally invasive stone treatments, asymptomatic and minimally symptomatic stones were not actively removed, given the high morbidity associated with treatment. Currently, with the expanding availability of SWL and URS, treatment of small stones can be offered with low surgical morbidity. Although some small, asymptomatic renal stones may never require treatment, a review of the known behavior of such stones suggests that many will grow over time, become symptomatic, and ultimately require treatment.

Nonstaghorn Renal Calculi

A number of studies have reviewed the fate of asymptomatic renal stones while under observation; however, the longest follow-up for any of these series is approximately 10 years, with the majority of them following patients for less than 5 years. Thus the true natural history of asymptomatic renal stones over an extended time period is unknown. Most studies evaluating this type of stone presentation report the rate of spontaneous passage, the rate of intervention, and the rate of stone progression, often defined as stone growth, development of symptoms, or need for intervention.

Hubner and Porpacz (1990) reviewed the natural history of renal stones in 62 patients managed before the advent of SWL or widespread URS. Of this cohort, spontaneous passage was seen in 16%, whereas 40% required surgical intervention. Stone growth was noted in 45% of patients, urinary tract infection (UTI) occurred in 68%, and pain developed in 51%. Similar results were found by Glowacki and colleagues (1992), with 32% of initially asymptomatic renal stones becoming symptomatic. Of these patients, half (15%) spontaneously passed their stones, and the calculated 5-year

Kidney Calculi

Although calculi in the kidney were rare before the Industrial Revolution (Shah and Whitfield, 2002), the existence of nephrolithiasis was known to Hippocrates, who described the symptoms of renal colic: "An acute pain is felt in the kidney, the loins, the flank and the testis of the affected side; the patient passes urine frequently; gradually the urine is suppressed. With the urine, sand is passed." It is not certain whether Hippocrates actually performed surgery on patients with renal calculi, but he did describe the following operations: the drainage of tuberculous and nontuberculous pyelonephritic abscesses, the incision of swelling in the loin caused by renal tumefaction resulting from stone, and the drainage of kidneys with acute congestion caused by pyelonephritis (Wershub, 1970). In the centuries that followed Hippocrates, there was little scientific progress in the surgical therapy for patients with renal calculi. The alleged first account of a surgical attempt to remove a stone from a patient's kidney is the case of the French archer of Bagnolet. Little is known of the authenticity of this tale of a condemned man with a renal calculus who agreed to allow surgery on the affected kidney with the condition that if he survived he would be freed. According to the anecdote, the man survived the open surgical stone removal and was freed in 1474 (Herman, 1973). Unfortunately, there are no first-hand records of this event. The first verifiable account of renal stone surgery was in 1550, when Cardan of Milan opened a lumbar abscess on a young girl and removed 18 calculi (Desnos, 1972). For the next two centuries, most surgeons were in agreement that the only indication for open renal surgery was the infected calculus kidney, distended by the accumulation of purulent matter, or those kidneys in which the calculus could be palpated in the organ itself.

In 1734 Lafite incised a swelling in a patient's loin and drained considerable purulence. Twenty-two days later the pus reaccumulated; he probed the incision and found a stone in the region of the kidney. Lafite widened the prior incision and removed two calculi; the patient recovered well. Four years later Lafite again removed stones from a man who had undergone drainage of a lumbar swelling 11 years before and who had a persistent urinary fistula. Lafite concluded that it was possible to remove the stones at the time of the first surgical intervention rather than subject the patient to multiple procedures (Ballenger et al, 1933). In 1872, William Ingalls of Boston City Hospital removed a large calculus from the right kidney of a 31-year-old woman with a persistent pyelocutaneous fistula (Spirnak and Resnick, 1983). Ingalls incised the sinus tract of the fistula and extracted the stone with forceps, thus performing the first recorded nephrolithotomy in America. In 1880, Henry Morris of England was the first to remove a stone from an otherwise healthy kidney by nephrolithotomy, extracting a 31-g mulberry calculus from the kidney of a young woman (Dudley, 1973).

As the surgical techniques of nephrolithotomy evolved, renal parenchymal incisions were made in a variety of different ways in an effort to reduce hemorrhagic morbidity. Heineke in 1879 first described a pyelotomy incision for the extraction of calculi. The operation rapidly found favor and was used by many surgeons, although it was not possible to extend the incision to permit extraction of large renal calculi without damaging the retropelvic renal artery (Wershub, 1970). Josef Hyrtl in 1882 and Max Brödel in 1902 described a relatively avascular plane near the midline (5 mm posterior) of the convex border of the kidney through which the collecting system of the kidney could be entered. In continental Europe, credit for the plane was given to Hyrtl; but in England and the United States it was called the *Brödel bloodless line* or the *Brödel white line* (Schultheiss et al, 2000). Although the existence of this avascular plane was an important discovery, surgeons continued to find that bleeding during nephrolithotomy was a considerable problem. Zuckerkandl described an inferior pyelonephrolithotomy in which a pyelotomy incision was extended into the lower pole of the kidney. Partner recommended a V-shaped incision with two limbs radiating toward the poles of the kidney. Other attempts were made to control the persistent problem of bleeding, including compres-

sion of the hilar vessels and various methods of suturing. In 1887, Czerny was the first to approximate the cut edges of the incised kidney with suture to control hemorrhage and to prevent fistula formation. In the same year, Guyon reported that nephrectomy, although efficacious in curing patients with calculus pyonephrosis, was more dangerous than nephrolithotomy because lithiasis was often bilateral (Wershub, 1970). In 1889 Kümmell was the first surgeon to perform a partial nephrectomy for calculus pyonephrosis (Redman, 1983). Lower, in 1913, revived interest in pyelolithotomy when he suggested that this technique might be a safer and easier method of removing renal calculi than nephrolithotomy. Although several small series of cases indicated that there might be a higher incidence of stone recurrence after pyelolithotomy, other studies showed that recurrence was no more common than it was after nephrolithotomy (Murphy, 1972). These findings, in conjunction with rapid advancements in the field of radiography, brought about a decided preference for pyelolithotomy (Gil-Vernet and Culla, 1981). In 1943 Dees and Fox reported the first use of coagulum to remove small stones and stone fragments from the renal pelvis and calyces (Marshall, 1983). Fibrinogen and thrombin were used to make a coagulum that was injected into the renal pelvis and produced a flexible cast of the pelvis and calyces. The use of this technique was limited initially owing to the scarcity of materials and the risk of blood-borne disease transmission. However, interest in coagulum pyelolithotomy was renewed when cryoprecipitate was found to be a safe and readily available source of concentrated fibrinogen (Fischer et al, 1980).

An important advance in the open surgical approach to the kidney was the intrasinusally extended pyelolithotomy, pioneered by Gil-Vernet in 1965. Because of its wide applicability and minimal morbidity, this approach to the renal collecting system became the procedure of choice for treatment of the majority of renal pelvic calculi. Patients harboring large or complex calculi could be effectively treated with extended pyelolithotomy combined with multiple radial nephrotomies (Wickham et al, 1974). In 1968 Smith and Boyce described *anatomic nephrolithotomy*, a procedure that derived its name from the technique of incising the renal parenchyma along the avascular plane between the anterior and posterior vascular distributions. Because an incision in this plane does not interrupt the blood supply to the renal parenchyma, it does not result in atrophy, hence the term *anatomic*. This procedure permits a relatively bloodless operation that encompasses stone removal, reconstruction of the calyceal system, and closure of the renal capsule with preservation of renal function. Although stone-free rates of these modern surgical techniques were excellent, morbidity was significant, and the search for new techniques and technologies continued.

Ureteral Calculi

Ambroise Paré is credited with the first account of a ureteral calculus, when, in 1564, he described "the cruel pain [that] tormented the patient in that place where the stone lodged." Paré also stated that death was the consequence of having calculi impacted in both ureters (Murphy, 1972). Morris recounted that surgical intervention was an option in the treatment of ureteral stones when he reported in 1898 that "operations on the ureter are an advance of the last few years, but not many have been recorded up to the present time" (Ballenger et al, 1933). Thomas Emmet of New York published an account in 1879 of three female patients with stones impacted at the distal aspect of the ureter. In one patient Emmet opened the bladder and removed the stone with forceps; in a second patient he removed a stone by cutting down on it through the vaginal wall. These procedures were the first records of a surgeon making a definite diagnosis of ureteral calculus and deliberately and successfully performing a ureterolithotomy. In the years that followed, intraperitoneal, perineal, sacral, transrectal, and transvaginal approaches were used. In 1910, Gibson of New York described an incision parallel to and just above the Poupart ligament, wholly extraperitoneal, by which the lower ureter, even down to its entrance into the bladder, could be readily exposed. This safe and comparatively

easy approach to the ureter gave open ureterolithotomy a solid basis for success.

The Rise of Endourology

Before the development of endoscopy, attempts to blindly extract calculi were not uncommon. In 1889, Gustav Kolisher performed the first successful stone manipulation, reporting that he “located the stone with a metal-tipped catheter several inches above the ureteric orifice and through it injected 30 cc of sterile oil,” displacing the stone (Murphy, 1972).

The development of minimally invasive surgical techniques for the treatment of patients with urinary lithiasis has been greatly dependent on technologic advances in the fields of **fiberoptics**, **radiographic imaging**, and **lithotripsy** (shock wave, ultrasonic, electrohydraulic, and laser). These advancements have accelerated the evolution of modern techniques of calculus removal, including **ureterorenoscopy** (URS), **percutaneous nephrolithotomy** (PCNL), and **extracorporeal shock wave lithotripsy** (SWL). In 1979, Arthur Smith defined the term *endourology* as closed controlled manipulation within the genitourinary tract (Smith et al, 1979).

Ureterorenoscopy

The practice of URS began by happenstance when in 1912 Hugh Hampton Young introduced a pediatric cystoscope into the massively dilated ureter of a child with posterior urethral valves (Young and McKay, 1929). Aided by the child's secondary ureteral dilation, Young was able to advance the cystoscope to the level of the renal pelvis, thus becoming the first urologist to view the intrarenal collecting system endoscopically. Unfortunately the following three decades held few significant advances in ureteroscopic technology until knowledge of fiberoptics could be put to clinical use. By 1957, Curtiss and Hirschowitz combined a large number of glass fibers into a coherent bundle and fused the fibers at their ends to allow them to move individually along their length, thus creating the first flexible endoscope (Hirschowitz et al, 1957). In 1964, Marshall reported the first urologic use of this new type of flexible endoscope when he passed the scope through an open ureterotomy to the level of the renal pelvis, thereby performing the first flexible URS. Subsequently, two of his associates, McGovern and Walzak, performed the first transurethral flexible URS when they passed the same 9-Fr flexible endoscope to inspect a ureteral calculus. Since then, developments in optics and mechanics have greatly improved the design of flexible ureteroscopes.

Currently available ureteroscopes range from 54 to 70 cm in length and have a tapered shaft diameter that increases proximally. As the tip of the ureteroscope is inserted into the ureter and passed retrograde, the ureter is slowly dilated. Initial ureteroscopes had neither a working nor an irrigating channel. Most modern ureteroscopes have a single working channel, and some have a second irrigation channel that serves to distend the ureter and maintain visualization.

Early flexible ureteroscopes were passive, and the subsequent incorporation of active tip deflection has greatly increased their usefulness. *Active deflection* refers to deflection of the tip of the endoscope, which is controlled by the surgeon through a lever mechanism on the handle of the endoscope. Flexible ureteroscopes have been introduced with two segments of active deflection, with the active primary site of deflection providing 170 to 180 degrees of up-and-down movement; the secondary active deflection, located several centimeters proximal to the primary deflection, is a 130-degree one-way downward deflection. This design greatly facilitates entry into the lower pole infundibulum. Other manufacturers have designed flexible ureteroscopes with 270 degrees of deflection, which also facilitates entry into the lower pole infundibulum.

More recently, efforts have been devoted to advancing the imaging capability of the flexible ureteroscope. Digital endoscopes, which incorporate an optical chip (complementary metal-oxide semiconductor [CMOS] or charge-coupled device [CCD]) at the tip have been introduced. Although the initial generation of these chips

were quite large, further refinements have reduced their size so that they can be applied to flexible ureteroscopes. Advantages associated with this technology include improved optical characteristics, obviating focus and white-balancing issues, and decreased surgeon fatigue, because cumbersome proximal camera and light cord attachments are not required. Image-processing software permits digital zoom capability as well. In comparing digital flexible URS with conventional fiberoptic flexible URS, investigators have noted that the digital devices are associated with superior imaging characteristics (Humphreys et al, 2008). Disadvantages of the digital device must be recognized, however: Digital ureteroscopes are larger in diameter than their fiberoptic counterparts, and the technology also is more costly.

It is interesting to note that the first reports of rigid URS trailed those of flexible URS by almost 10 years. In 1977 Goodman reported on three cases in which a pediatric cystoscope was used to treat patients with ureteral malades. These initial rigid ureteroscopes used a rod-lens system that was large (10 to 13 Fr) and inflexible. Most rigid ureteroscope designs have replaced this rod-lens system of image transmission with fiberoptics, which allows significant reduction in the size of the endoscope. In addition, the flexibility of the fiberoptic bundles allows the shaft of the endoscope to become somewhat bendable along its vertical axis, hence the term *semirigid ureteroscope*.

Parallel to improvements in rigid and flexible ureteroscopes were advances in intracorporeal lithotripters, including ultrasonic, electrohydraulic, pneumatic, and laser probes, allowing efficient stone fragmentation through the miniaturized modern ureteroscopic equipment. Many new stone-retrieval devices, designed to pass through the working channel of a ureteroscope, have been introduced with the capability for manipulation and deflection.

Percutaneous Stone Removal

The first description of percutaneous stone removal was that of Rupel and Brown (1941) of Indianapolis, who removed a stone through a previously established surgical nephrostomy. It was not until 1955, however, that Goodwin and associates described the first placement of a percutaneous nephrostomy tube to drain a grossly hydronephrotic kidney. These researchers did not have the benefit of radiographic guidance, and so the drainage tube was placed without imaging. In 1976, Fernstrom and Johansson first reported the establishment of percutaneous access with the specific intention of removing a renal stone. Subsequent advances in endoscopes, imaging equipment, and intracorporeal lithotripters allowed urologists and radiologists to refine these percutaneous techniques through the late 1970s and early 1980s into well-established methods for removal of upper urinary tract calculi.

Extracorporeal Shock Wave Lithotripsy

The phenomenon that sound waves can be focused has been known since antiquity. The ancient Greeks, as taught by Dionysius, used this knowledge to construct vaults that allowed them to overhear the conversations of their imprisoned enemies. In the 18th and 19th centuries, cabinets constructed with echo or sound mirrors were capable of transmitting the ticking of a pocket watch over a distance exceeding 60 feet.

High-energy shock waves, too, have been recognized for many years. Examples of high-energy shock waves include the blast effect associated with explosions, as well as the potentially window-shattering sonic boom created when aircraft pass beyond the speed of sound. Engineers at Dornier Medical Systems in what was then West Germany, during research on the effects of shock waves on military hardware, demonstrated that these shock waves are reflectable and therefore focusable. The possibility of applying shock wave energy to human tissue was discovered when, by chance, a test engineer touched a target body at the very moment of impact of a high-velocity projectile. The engineer felt a sensation similar to an electric shock, although the contact point at the skin showed no damage at all (Hepp, 1984). This observation and its potential

military applications led Dornier to pursue a method of generating a reproducible shock wave.

Beginning in 1969 and funded by the German Ministry of Defense, Dornier began a study of the effects of shock waves on tissue. Specifically, the study was to determine if the shock waves generated by a projectile striking the wall of a military tank would damage the lungs of a crew member leaning against the same wall. During the study, Dornier engineers developed techniques to reproducibly generate shock waves. In the course of this effort the engineers discovered that shock waves generated in water could pass through living tissue (except for the lung) without discernible damage to the tissue but that brittle materials in the path of the shock waves would be fragmented.

At some point a possible medical application of shock waves became apparent: If shock waves could safely pass through tissue but fragment brittle materials, perhaps they could be used to break up kidney stones. Dornier engineers found that lower-energy shock waves, which would be appropriate for medical applications, could be generated in a predictable and reproducible manner by an underwater electrical spark discharge.

In 1972, on the basis of preliminary studies performed by Dornier Medical Systems, an agreement was reached with Egbert Schmiedt, director of the urologic clinic at the University of Munich, to proceed with further investigation of the therapeutic potential of this technology ([Chaussy and Fuchs, 1986, 1989](#)). This research was supported by the West German Federal Ministry of Research and Technology, and the development of the Dornier lithotripter progressed through several prototypes, ultimately culminating in February 1980 with the first treatment of a human by SWL. The production and distribution of the Dornier HM3 lithotripter began in late 1983, and SWL was approved by the U.S. Food and Drug Administration in 1984. Since Dornier's pioneering work, numerous other companies have demonstrated that shock waves capable of stone fragmentation may be generated by electromagnetic induction, microexplosions, focused lasers, and piezoelectric crystals. To date, more than 3000 lithotripters of all types have been placed worldwide, and more than 1 million patients are treated annually with SWL.

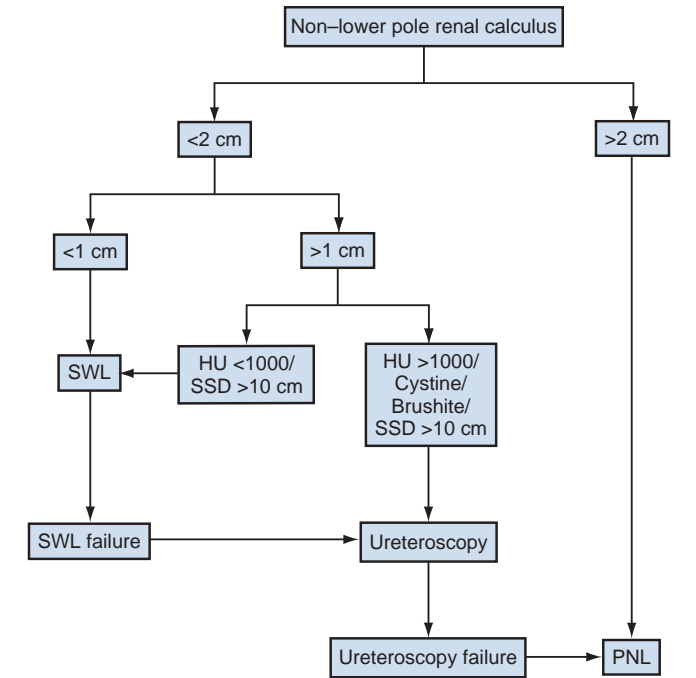


Figure 53-1. Treatment algorithm. HU, Hounsfield unit; PNL, percutaneous nephrolithotomy; SSD, skin-to-stone distance; SWL, shock wave lithotripsy. (Modified from Wen CC, Nakada SI. Treatment selection and outcomes: renal calculi. *Urol Clin North Am* 2007;34[3]: 409–19.)

BOX 53-1 Factors Affecting Management of Renal Stones	
STONE-RELATED FACTORS	CLINICAL (PATIENT) FACTORS
Size	Infection
Number	Obesity
Location	Body habitus deformity
Composition	Coagulopathy
RENAL ANATOMIC FACTORS	Juvenile
Obstruction or stasis	Elderly
Hydronephrosis	Hypertension
Ureteropelvic junction obstruction	Renal failure or transplant
Calyceal diverticulum	Solitary kidney
Horseshoe kidney	Urinary diversion
Renal ectopia or fusion	Pregnancy
Lower pole	

probability of developing symptoms from initially asymptomatic renal stones was 48.5%. [Keeley and colleagues \(2001\)](#) randomized 228 patients with asymptomatic renal stones to SWL or observation. Spontaneous passage was noted in 17% of the observation group and 28% of the SWL group ($P = .06$). There was no difference in the need for additional interventions (analgesics, antibiotics, SWL, stent insertion, URS) between the observation and SWL groups (15% vs. 21%, $P = .27$); however, invasive interventions were required only in the observation group. Despite this, there was no appreciable difference in renal function, quality of life, or stone-related symptoms between the two groups, leading the authors to conclude that SWL was not advantageous for small, asymptomatic renal stones.

[Burgher and colleagues \(2004\)](#) retrospectively reviewed 300 male patients with asymptomatic renal stones with a mean follow-up of 3.26 years. Disease progression, defined as the need for interven-

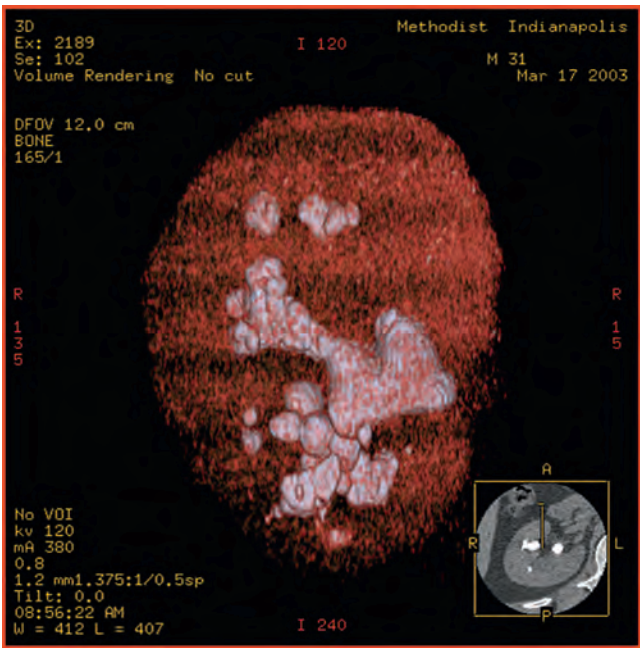


Figure 53-2. Three-dimensional computed tomography reconstructed image of a staghorn calculus.

tion, stone growth, or the development of stone-related pain, was seen in 77% of patients, with 26% of patients requiring surgery. Larger stone size and renal pelvis location were associated with disease progression. All renal pelvis stones and those larger than 15 mm experienced disease progression. The extrapolated risk of intervention at 7 years was 50%. In a similar study by [Boyce and colleagues \(2010\)](#), 20.5% of initially asymptomatic patients with renal stones became symptomatic over a 10-year period. [Koh and colleagues \(2012\)](#) found a 20% rate of spontaneous passage, 46% rate of stone progression, and 7.1% rate of intervention.

[Inci and associates \(2007\)](#) showed that approximately one third of lower pole calculi enlarge, 21% pass spontaneously, and 11% eventually require intervention. Mean stone size was 8.8 mm, and average follow-up was 52 months. No intervention was required in any patient during the first 2 years of observation. In a similar prospective, randomized study, [Yuruk and colleagues \(2010\)](#) demonstrated an 18.7% intervention rate for asymptomatic lower pole renal stones, with a median time to intervention of 22.5 months. [Kang and colleagues \(2013\)](#) reported a 29% spontaneous passage rate, 24.5% intervention rate, and 53.6% stone-related-events rate in 347 patients with mean follow-up of 31 months.

Taken together, these studies imply a number of findings about asymptomatic renal stones that can be used to advise patients as to their ideal care. First, overall stone disease progression, as defined by the development of stone-related symptoms or stone growth, occurs in as many as 50% to 80% of cases, with a calculated risk of approximately 50% at 5 years. Second, spontaneous stone passage occurs about 15% of the time and is more likely in stones 5 mm in size or smaller. Third, larger stones and those located in the renal pelvis are more likely to become symptomatic. Finally, the risk of eventual surgical intervention for initially asymptomatic renal stones is approximately 10% to 20% at 3 to 4 years after the stones are initially discovered.

Staghorn Calculi

Staghorn calculi are large renal stones that occupy most or all of the renal collecting system. The name arises from the fact that these stones look like the antlers of a deer or stag on imaging ([Fig. 53-2](#)). The stones frequently involve the renal pelvis and branch into the surrounding infundibula and calyces. No standardized definitions exist for complete and partial staghorn stones, although most

consider complete staghorn stones to occupy the entire renal collecting system, whereas partial staghorn stones occupy less. Struvite composes the majority of staghorn stones, although this configuration of collecting system involvement can include any type of stone (Segura et al, 1994). Before the era of endourology, staghorn stones were not always treated, because the surgical morbidity was high and achieving stone-free status was challenging (Segura, 1997). More recent data have improved our understanding of the natural history of staghorn stones, and the contemporary consensus is that staghorn stones should be treated. **Untreated, staghorn stones are associated with recurrent UTIs, urosepsis events, renal functional deterioration, and a higher likelihood of death (Blandy and Singh, 1976; Koga et al, 1991; Segura et al, 1994; Teichman et al, 1995).** Complete renal function loss in 50% of affected kidneys can occur after 2 years without treatment. Indeed, the American Urological Association (AUA) guideline on the management of staghorn calculi (2005) advocates for the surgical treatment of newly diagnosed struvite staghorn stones in otherwise healthy individuals, with complete stone removal as the therapeutic goal (Preminger et al, 2005).

Pretreatment Assessment

Before the surgical treatment of renal and ureteral stones, a thorough medical history and physical examination, proper imaging studies, and appropriate laboratory tests are necessary in all patients. In some instances, more elaborate laboratory analysis and upper urinary tract anatomic and functional studies may provide important additional information that is useful in surgical decision making.

Medical History

A number of medical and surgical conditions affect urinary calculi formation and have an impact on treatment planning. Medical conditions that predispose to nephrolithiasis formation should be considered in all stone formers (Strauss et al, 1982). Hyperparathyroidism, renal tubular acidosis (type 1), inflammatory bowel disease and chronic diarrhea, prior intestinal resection and gastric bypass surgery, sarcoidosis, cystinuria, metabolic syndrome and diabetes, gout, recurrent UTIs, spinal cord injury, prior urinary tract surgery, anatomic abnormalities, and medullary sponge kidney, among others, are all associated with urinary stone formation. In addition to treating symptomatic stones in these patients, medical treatment is often required for the underlying disorder and usually assists in preventing further stone formation.

An understanding of a patient's prior stone surgeries and stone composition is also important. Patients with particularly dense stones (i.e., cystine, calcium oxalate monohydrate, brushite) and obese patients are less well suited for SWL, and complete stone clearance is essential with infectious stones. Failed prior approaches may certainly suggest the need for a more invasive or comprehensive approach for the new presentation, as well as a correction of any anatomic factors that may be associated.

Certainly, all patients, and in particular those with a history of cardiovascular and cerebrovascular disease, need to be risk stratified and medically optimized before any stone therapy. Patients on anticoagulation, those with high cardiovascular risk, and those with recent coronary artery stents may need to remain on anticoagulative or antiplatelet agents perioperatively, which must be considered when selecting the best surgical approach. Consultation with the patient's cardiologist or hematologist is recommended.

Imaging

Preoperative urinary tract imaging is required in all patients before surgical intervention, to assess stone size and anatomic considerations (stone location, obstruction, stone radiologic characteristics). In the past, plain abdominal radiography and intravenous urography and tomography were routinely used; however, plain abdominal radiography (kidney-ureter-bladder [KUB] study) has

limited sensitivity and specificity, and its ability to easily demonstrate a stone is subject to multiple stone and patient anatomic factors. Approximately 10% to 20% of stones are uric acid and hence radiolucent, and roughly a third of ureteral stones occur in the mid-ureter and hence are screened by the sacroiliac bone structure. In addition, body habitus can influence film quality, as will the presence of bowel contents, which can screen a stone from view (Levine et al, 1997; Jackman et al, 2000).

More recently, noncontrast helical CT has gained widespread acceptance as the imaging modality of choice for urinary stones (Heidenreich et al, 2002). CT visualizes almost all renal stone types and has sensitivities and specificities of greater than 95%, which is considerably better than any other imaging modality, even at low dose protocols and across all body habitus (Chen et al, 1999; Hamm et al, 2001; Pfister et al, 2003; White et al, 2007; White, 2012). In addition, CT has the advantage of providing three-dimensional anatomic information about the kidney and adjacent organs, relevant treatment strategy considerations such as skin-to-stone distance, and stone density characteristics to help guide therapeutic choices (White, 2012).

Routine CT scanning may expose patients to cumulative radiation risks; accordingly, modern low-dose imaging protocols are widely used to adhere to the ALARA ("as low as reasonably achievable") principle and thus reduce the radiation exposure while retaining sufficient anatomic and stone details (Lipkin and Preminger, 2013). Only on occasion are more detailed anatomic and functional studies necessary, such as contrast-enhanced studies or renal scintigraphy.

Renal ultrasound has become a more widely used modality for initial evaluation in recent years. Greater experience in its use among both urologists and emergency medicine physicians has led to its greater availability as a screening tool to determine whether a CT scan is necessary (Dalziel and Noble, 2013). Kocher and colleagues reported that use of CT for suspected renal colic had increased from 4% to 42% between 1996 and 2007, although there was no overall increase in stone diagnosis or hospital admissions during the same period of time (Kocher et al, 2011). Recognition of this overuse of CT scanning has led to the implementation of urinalysis- and renal ultrasound-based algorithms to try to decrease it (Edmonds et al, 2010; Riddell et al, 2014).

Chronic kidney stone formers can also be monitored over time with serial ultrasound examinations as a means to reduce radiation exposure to these patients. The limitations of renal ultrasound include the inability to visualize most ureteral stones and a well-recognized poor correlation between measured and actual stone size and location.

More recently, high-Tesla magnetic resonance imaging (MRI) and magnetic resonance urography are being explored as possible alternatives to CT. Preliminary studies have reported sensitivities, specificities, and diagnostic accuracies of 80% or higher for renal and ureteral stones (Semins et al, 2013).

Laboratory Tests

Preoperative urinalysis and culture are mandatory before any stone surgery, and positive cultures should prompt appropriate treatment before the day of surgery. Administration of preoperative antibiotics for 1 week preceding surgery may reduce associated complications (Mariappan et al, 2006; Bag et al, 2011). Despite appropriate antibiotic therapy, sepsis is still a risk; both stone culture and renal pelvis culture are better predictors of postoperative sepsis and infectious complications than bladder urine culture results (Mariappan et al, 2005). Therefore, patients with radiographic or clinical histories suspicious for infectious or struvite stones should receive culture-directed or broad-spectrum antibiotics before surgery.

Urinalysis may reveal clues to underlying stone composition based on the presence of crystals, and urinary pH may add useful information when one is considering uric acid stones or the presence of urease-producing bacteria.

Assessment of underlying renal function is necessary, and serum creatinine often serves as an adequate evaluation, although it reflects

total function only. As stated earlier, prolonged presence of untreated staghorn stones, or a long-term, chronically obstructed kidney can significantly affect function of the affected kidney, and in patients with severe, unrecoverable compromise, nephrectomy rather than stone removal may be the most prudent treatment.

Preoperative serum chemistries are important because they may provide clues to underlying systemic diseases such as renal tubular acidosis or hyperparathyroidism or other metabolic derangements. When PCNL or laparoscopic or open stone removal is contemplated, preoperative complete blood counts should be obtained. Routine assessment of coagulation status using prothrombin time (PT) and activated partial thromboplastin time (APTT) is imperative in patients on anticoagulation therapy, but recent reviews have suggested that routine testing may not be necessary. This has been slow to be adopted in clinical practice owing to a lack of prospective, randomized controlled trials (Dzik, 2004).

Stone Factors

When treatment for any patient with a renal stone is being contemplated, the main stone-related factors include stone burden (total number and size of stones), stone location, and stone composition. Unless prior stone composition is known, absolute stone type is difficult to determine preoperatively. Certain predictions regarding stone composition can be made based on CT scan data, with increasing resistance to fragmentation associated with higher Hounsfield unit (HU) measurements. In addition to stone density, stone burden and location play important roles in the selection of the optimal surgical approach.

Treatment Decision by Stone Burden

The total kidney stone burden, or total volume of stone(s) requiring treatment, is arguably the most important factor influencing treatment decisions. Problematically, however, there is no standard for reporting kidney stone burden. Accordingly, the following decision analysis is based on the largest single-dimensional stone diameter measured on plain radiography or CT. Based on the available evidence, it is convenient to stratify stone burdens as those up to 1 cm, those between 1 cm and 2 cm, and those greater than 2 cm.

Because staghorn stones reflect additional complexity with respect to treatment owing to both the volume and the branched nature of the stone, and because there is ample literature specifically regarding staghorn stones, these are discussed separately.

Kidney Stone Burden up to 1 cm. The majority (50% to 60%) of solitary kidney stones are 1 cm or less in diameter, and many of them are asymptomatic (Cass, 1995; Renner and Rassweiler, 1999; Logarakis et al, 2000). Given enough time, however, many will enlarge or become associated with clinical factors that warrant treatment. Almost all renal stones 1 cm or smaller may be treated with SWL, URS, or PCNL. Laparoscopic or open stone removal is necessary in exceedingly rare cases, most often when there is underlying aberrant anatomy.

SWL has been considered first-line treatment for these smaller kidney stones without complicating clinical or renal anatomic considerations because it is the least invasive modality, achieves reasonably high stone-free rates, and requires the least technical skill. More recently, flexible URS use, instrumentation, and familiarity are growing within the urologic community, and in experienced hands, flexible URS should now be considered an alternative first-line therapy for kidney stone burden 1 cm or less in size. Stones with high attenuation on CT (≥ 900 HU) and those located in lower pole calyces represent special situations for which SWL clearance rates are poor. In these instances, URS or PCNL may be the preferred first-line treatment options or become necessary if SWL fails.

The European Association of Urology (EAU), in its urolithiasis guidelines, recommends SWL as the preferred first-line therapy for all kidney stones smaller than 10 mm, with URS as an alternative for selected cases and PCNL reserved for when SWL and URS have

failed (Turk et al, 2013). The AUA has not published guidelines for renal stones smaller than 10 mm.

For kidney stones 1 cm or less in diameter, SWL achieves stone-free rates of approximately 50% to 90% and effectiveness quotients of approximately 50% to 70% (Ackermann et al, 1994; Abdel-Khalek et al, 2004; Albala et al, 2005; Galvin and Pearle, 2006; Tailly et al, 2008; Micali et al, 2009). It should be recognized that most of these studies have assessed stone-free outcomes using renal ultrasound or plain radiography. Successful clearance is highest for stones in the renal pelvis and ureteropelvic junction (UPJ); 80% to 88%), favorable for stones in the upper and middle calyces (approximately 70%), and consistently less for lower pole stones (35% to 69%) (Fialkov et al, 2000; Albala et al, 2001; Pearle et al, 2005; Danuser et al, 2007). Stone-free rates with the newer second- and third-generation SWL machines have been somewhat disappointing and have yet to match those seen with Dornier HM3, which is considered the gold standard treatment in SWL. This has been the consequence of downsizing the newer generation lithotripters in an attempt to make them more portable and decrease anesthetic requirements.

Even for kidney stones smaller than 1 cm, myriad circumstances exist for which SWL is contraindicated or less effective than other modalities. Box 53-2 lists the contraindications for SWL; Box 53-3 describes clinical and renal anatomic factors that make SWL less favorable than URS or PCNL for treating kidney stones.

Over the last decade, technologic advances in flexible endoscope design and instrumentation have facilitated the use of URS, also referred to as *retrograde intrarenal surgery*, for the treatment of kidney stones. Multiple reports have now clearly established URS as a reasonable alternative for the treatment of most kidney stones, especially those smaller than 1 cm. Flexible, rather than semirigid, URS is usually necessary to access most middle and lower calyces. Compared with SWL, URS has the advantage of actively removing stones and thereby expediting stone clearance.

Contemporary URS for renal stones 1 cm or smaller offers stone-free rates of approximately 80% to 90%, with recent series reporting even better outcomes. Note that many of these reports are from high-volume stone centers. Thus, URS for small renal stones in experienced hands consistently provides stone-free rates superior to those of SWL and requires fewer ancillary procedures to do so.

BOX 53-2 Contraindications to Shock Wave Lithotripsy

- Pregnancy
- Uncorrected coagulopathy or bleeding diathesis
- Untreated urinary tract infection
- Arterial aneurysm near stone (renal or abdominal aortic aneurysms)
- Obstruction of urinary tract distal to stone
- Inability to target stone (skeletal malformation)

BOX 53-3 Factors Negatively Affecting Shock Wave Lithotripsy Success

- Stone composition (cystine, brushite, calcium oxalate monohydrate, matrix)
- Stone attenuation ≥ 1000 HU
- Skin-to-stone distance >10 cm (morbid obesity)
- Renal anatomic anomalies (horseshoe kidney, calyceal diverticulum)
- Unfavorable lower pole anatomy (narrow infundibulopelvic angler, narrow infundibulum, long lower pole calyx)

Sabnis and associates (2013) randomized 70 patients with renal stones smaller than 1.5 cm to either micro-PCNL or URS and found a 94% clearance rate for URS and 97% clearance rate for micro-PCNL. Sener and colleagues (2014) prospectively randomized patients with lower pole calculi to SWL or flexible URS and found a significantly better stone-free rate with URS (100% vs. 91.5%), whereas the SWL cohort required an average of 2.7 treatment sessions. The Global Ureteroscopy Study, which included an international, multi-institutional cohort of 11,885 patients, reported an 85.6% stone-free rate, although this study included both ureteral and renal stones (de la Rosette et al, 2014).

These excellent results contrast sharply to those from the well designed, multicenter, prospective, randomized Lower Pole II study, which reported only a 50% stone-free rate for URS of lower pole stones 1 cm or smaller (Pearle et al, 2005). This difference is believed to be secondary to the use of CT to evaluate stone-free status and the fact that this study accrued patients more than a decade ago, closing in 2003. Since that time, URS has experienced marked technologic advances, which are believed to have made URS safer and better.

The increased stone clearance of URS compared with SWL comes at the cost of a traditionally higher, albeit low, complication rate. Contemporary ureteroscopic series have shown a noticeably lower rate of complications than in prior years. In the Global Ureteroscopy Study, the overall complication rate was 3.5%, with sepsis (0.3%), ureteral stricture (0.3%), and death (0.02%) occurring rarely (de la Rosette et al, 2014). Similarly low complication rates have been reported by others, with rates of ureteral perforation, avulsion, and stricture rates all below 1%, and often below 0.5% (Butler et al, 2004; Geavlete et al, 2006). Taken together, the recent literature suggests that URS in experienced hands has an excellent safety profile, with stone-free rates and treatment efficiency superior to SWL for small renal stones.

PCNL is reserved for failures of SWL and URS or for patients with anatomic considerations making PCNL vastly superior, such as lower pole stones with acute infundibulopelvic angles or calyceal diverticula. So-called “mini” and “micro” PCNL procedures appear to offer similar stone-free rates as traditional PCNL, but with an overall lower complication rate thought to be secondary to the smaller tract dilation. Such techniques may be ideally suited for stones smaller than 1 cm that require PCNL.

Kidney Stone Burden between 1 and 2 cm. For renal stones between 1 cm and 2 cm, SWL, URS, and PCNL are the most frequently used treatments, with laparoscopic and open stone removal seldom necessary. Stone location, composition, and density and patient anatomic factors become increasingly relevant as stone burden enlarges and have an important impact on treatment outcomes. Larger stone burdens located in lower pole calyces, increasing skin-to-stone distance, and unfavorable lower renal pole anatomy all decrease the success rates of SWL and URS but have limited influence on PCNL outcomes. Thus, for renal calculi between 1 cm and 2 cm, stone-specific and anatomic factors must be carefully considered when weighing the relative outcomes and invasiveness of each procedure (see Fig. 53-1).

As a general principle, the efficacy of SWL decreases while the need for ancillary procedures and re-treatment increases as stone burden enlarges (Drach et al, 1986; Lingeman et al, 1986; El-Assmy et al, 2006; Wiesenthal et al, 2011). The same holds true for URS, although to a lesser degree. Although clearance of residual fragments has been observed up to 2 years after SWL, larger initial stone burdens are associated with larger postoperative residual fragments and higher re-treatment rates (Fig. 53-3).

For stones between 1 cm and 2 cm that are *not* located in the lower pole, SWL has traditionally been recommended as first-line therapy, and remains so in the most updated urolithiasis guidelines from the EAU (Turk et al, 2013). In general, SWL is favored when stones are not located in the lower pole, stone attenuation is less than approximately 900 HU, skin-to-stone distance is less than 10 cm, and the patient has no history of SWL-resistant minerals (cysteine, calcium oxalate monohydrate, brushite). When these factors are present, URS or PCNL should be considered

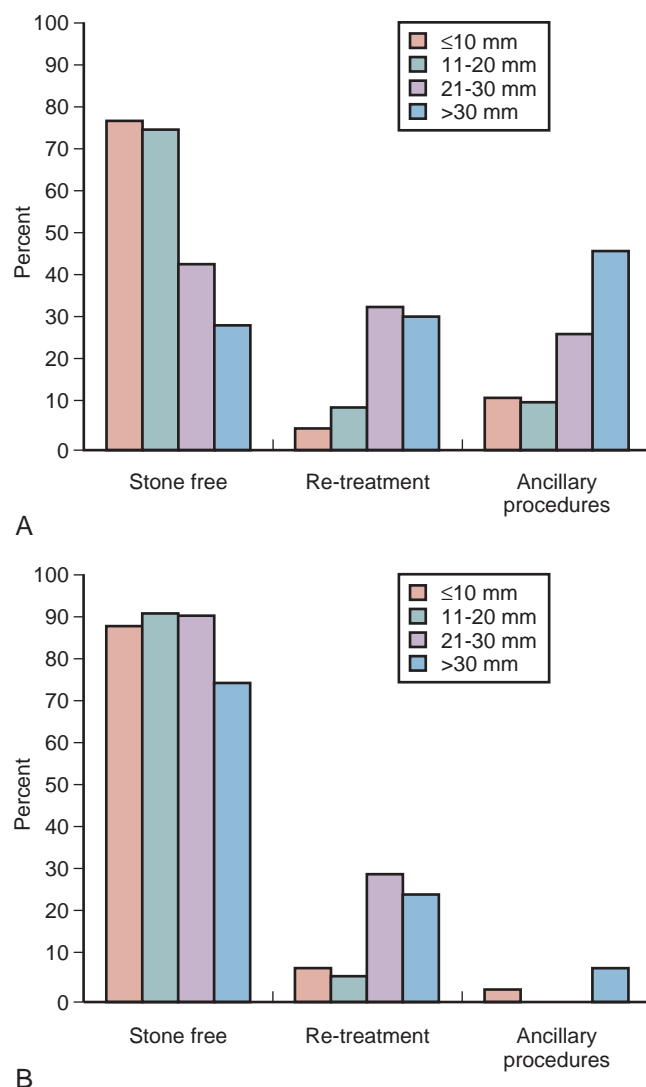


Figure 53-3. A, Solitary nonstaghorn calculi treated by shock wave lithotripsy, stratified by size. B, Solitary nonstaghorn calculi treated by percutaneous nephrolithotomy, stratified by size.

a more desirable initial treatment because SWL is more likely to fail.

Shock wave lithotripsy treatment success rates exceeding 70% have been reported for stones in the upper (71.8%) and middle (76.5%) calyces (Saw and Lingeman, 1999). Lower pole stone clearance rates range lower, between 37% and 61% (Saw and Lingeman, 1999; Albala et al, 2001; Riedler et al, 2003). Nomograms have been developed to predict SWL treatment success and reflect worse outcomes with increasing stone burden and skin-to-stone distance (Kanao et al, 2006; Wiesenthal et al, 2011). The nomogram by Kanao and colleagues (2006) predicts stone-free rates after a single SWL session of 56.8% (11 to 15 mm) and 35.1% (16 to 20 mm) for solitary calyceal stones and 64.4% (11 to 15 mm) and 42.7% (16 to 20 mm) for renal pelvis stones.

URS is a reasonable treatment approach for many kidney stones between 1 cm and 2 cm. In general, URS provides stone-free outcomes that are at least comparable, and often superior, to SWL for such renal stones. Moreover, fewer treatment sessions are usually necessary. The tradeoff, again, is a historically higher rate of complications for URS inherent in its more invasive nature. Grasso (2000) reviewed the outcomes of URS at a single, high-volume stone center and found an overall success rate of 81% after one procedure and 90% after two procedures. Single-procedure treatment success was highest for stones in upper and middle calyces

(90%) and lower for stones in the renal pelvis and lower pole calyces (approximately 80%).

URS is also useful as a salvage therapy for failed SWL, rendering 58% of these patients stone free after a single treatment session and up to 76% of patients stone free after two URS sessions (Jung et al, 2006). Unlike SWL, which becomes less effective with increasing skin-to-stone distance, similar URS results have been found in patients with normal, overweight, and obese body mass indexes (BMIs) (Caskurlu et al, 2013).

PCNL accomplishes higher stone-free rates and requires fewer auxiliary procedures than SWL or URS for renal stones between 1 cm and 2 cm. The greater invasiveness and higher rate of significant complications of PCNL limit its widespread adoption to the treatment of all renal stones larger than 1 cm. Several series have emerged comparing outcomes among SWL, URS, and PCNL for kidney stones 1 to 2 cm in size (Resorlu et al, 2013; Bas et al, 2014). Success rates were highest for PCNL (91% to 98%), quite respectable for URS (87% to 91%), and significantly lower for SWL (66% to 86%). As expected, the PCNL groups experienced more overall and serious complications, but they also had the lowest need for additional procedures. The difference in treatment success is even more apparent when comparing SWL (37%) with PCNL (95%) for lower pole stones as demonstrated in the prospective, randomized Lower Pole I study (Albala et al, 2001).

In the last few years, smaller PCNL access sheaths have been used in an attempt to reduce PCNL-related morbidity, and out of this experience have come the terms “mini-perc” and “micro-perc.” No precise definitions have been coined, but mini-perc in general refers to PCNL performed through sheaths from 12 Fr to 20 Fr, whereas micro-perc is performed through a 16-gauge needle (Helal et al, 1997; Sabnis et al, 2012).

A few prospective reports with small sample sizes have surfaced evaluating mini-perc and micro-perc (Mishra et al, 2011; Sabnis et al, 2012, 2013). In general, mini-perc has showed equivalent stone clearance to standard PCNL (96% vs. 100%) with a smaller hemoglobin drop, shorter hospital stay, and decreased analgesic requirement. Mini-perc and URS were also found to be essentially the same in terms of stone clearance (100% vs. 97%), whereas URS was associated with a lower hemoglobin drop and less analgesic medication. Similarly, micro-perc and URS showed similar stone clearance (97% vs. 94%) and essentially equivalent blood loss, postoperative pain, and length of stay. Notably, mini-perc and micro-perc techniques are mainly performed in highly specialized, high-volume stone centers. These procedures are of significant interest, although the techniques have not yet been widely adopted by the urologic community at large. Certainly, additional studies with larger sample sizes are necessary to better evaluate these techniques and their learning curves.

Kidney Stone Burden Greater than 2 cm. PCNL should be considered first-line therapy for kidney stone burdens 2 cm and greater. Unlike URS and SWL, the success of PCNL is relatively independent of stone location and stone composition. Stone clearance was once considered independent of stone burden as well, although more recent studies suggest that stone-free rates decrease as stone burdens increase (Lingeman et al, 1987; Desai et al, 2011). Nonetheless, modern-day PCNL is the most efficient means to remove stone burdens 2 cm and greater in a single surgical setting. It is also routinely associated with shorter operative times and a lower likelihood of requiring a staged procedure, which is usually the norm when URS, SWL, or both are used to tackle larger stones. Meanwhile, the complication and re-treatment rates rise noticeably when SWL monotherapy is used to approach these larger stones.

As the most efficient means to remove large stones from the kidney, PCNL has consistently achieved stone clearance rates of at least 75%, and often much higher, when used by many different groups across the world (Segura et al, 1985; Albala, 2001; Osman et al, 2005a; de la Rosette et al, 2011). Clearance of lower pole stones is also excellent with PCNL, with a rate that has been reported as high as 95% in the Lower Pole I study (Albala et al, 2001). The superior stone-free rates come as a tradeoff for more frequent and more serious complications after PCNL compared with either URS

or SWL. Overall complication rates between 20% and 30% have been reported, with most contemporary series showing rates of transfusion of 5% to 10%, severe sepsis of 1% or less, and delayed bleeding requiring angioembolization of 1% or less (Michel et al, 2007; de la Rosette et al, 2011). Stone-free rates can be improved and blood loss decreased when flexible nephroscopy is used to augment standard PCNL (Gucuk et al, 2013).

Early after its introduction, SWL was recognized as a suboptimal modality to efficiently clear renal stones 2 cm or greater, as was reported at a National Institutes of Health (NIH) consensus conference (Consensus conference, 1988). Subsequent studies confirmed overall success rates below 30% for stones 3 cm and greater treated with SWL monotherapy (Murray et al, 1995). More recently, stone-free rates of 59% were demonstrated after SWL monotherapy for larger renal stones; however, steinstrasse (23%) and the need for secondary procedures (20%) occurred frequently (El-Assmy et al, 2006). The previously described SWL nomograms predict a stone clearance of 30% or less for renal stones 2 cm or greater (Kanao et al, 2006). When SWL is combined with URS under a single anesthesia, stone clearance rates of nearly 77% can be achieved, but require multiple stages (Hafron et al, 2005).

In the late 1990s, URS surfaced as a viable, low-morbidity alternative to SWL for large renal stones. One of the first series was reported by Grasso and colleagues (1998), with a stone-free rate of 76% after a single URS procedure and improving to 91% after a second stage. Unfortunately, at 6 months of follow-up only 60% of patients were completely clear of stones. Since this report, however, many others have followed, which describe similarly encouraging outcomes, including a mean stone-free rate of 93.7% (77% to 96.7%), an average minor complication rate of 5%, an average major complication rate of 5%, and an average of 1.6 procedures to accomplish such success (Breda et al, 2008; Mariani, 2008; Breda et al, 2009; Bader et al, 2010; Aboumarzouk et al, 2012a). More recently, a few studies have directly compared PCNL with URS for stones 2 cm and larger (Akman et al, 2012a, 2012c; Bryniarski et al, 2012). Overall, stone clearance rates remain consistently higher for PCNL (91% to 96%) than for URS (71% to 93%), and URS cohorts required staged procedures 20% to 30% of the time. Thus PCNL remains the first-line treatment for kidney stone burdens 2 cm and greater, unless significant comorbidities or contraindications to PCNL are present (frailty, coagulopathy, refusal of transfusion). In such patients, though less efficient and potentially requiring multiple stages, less invasive alternatives such as URS should be considered.

Staghorn Stones. PCNL is the method of choice for treating partial and complete staghorn kidney stones, with the caveat that poorly or nonfunctioning kidneys and those associated with xanthogranulomatous pyelonephritis may be best managed with nephrectomy. Both the AUA Nephrolithiasis Guideline Panel and the EAU urolithiasis guidelines recommend PCNL as the first-line therapy for staghorn stones in most patients (Preminger et al, 2005; Turk et al, 2013). Stone-free rates are higher with PCNL (78%) than with SWL (22% to 54%) or open surgery (71%). When staghorn stones are discovered, active stone removal should be pursued unless the patient cannot safely tolerate the surgery. Observation and nonoperative management should be discouraged, because the natural history of untreated staghorn stones has shown that they may eventually cause complete loss of function in the affected kidney, can be the cause of recurrent UTIs and sepsis episodes, and are associated with an increased overall mortality (Blandy and Singh, 1976; Rous and Turner, 1977; Koga et al, 1991; Segura et al, 1994; Teichman et al, 1995; Preminger et al, 2005). PCNL has proven itself safe and effective in both the adult and pediatric populations (Kumar et al, 2011).

No standardized classification system exists for staghorn kidney stones; however, in general they are defined as branched stones that occupy much of the intrarenal collecting system. Most staghorn stones occupy the renal pelvis and extend into one or more of the surrounding calyces. Historically, staghorn stones have been described as either partial or complete, depending on how fully they occupy the intrarenal collecting system. Multiple other staghorn

classification schemes have been developed but have not been widely adopted because they are cumbersome to use and have not yet made a meaningful impact on clinical decision making (Rocco et al, 1984; Griffith and Valiquette, 1987; Ackermann et al, 1989; Di Silverio et al, 1990; Mishra et al, 2012). CT with sagittal and coronal reformatting can provide excellent anatomic and stone dimension details and is valuable in preoperative treatment planning (Nadler et al, 2004; Thiruchelvam et al, 2005).

Infectious stones, those composed of magnesium-ammonium-phosphate (or “struvite”), alone or in combination with calcium carbonate apatite, have long been considered the most frequently occurring composition of staghorn calculi, with cystine, uric acid, and calcium oxalate also exhibiting the ability to form staghorn configurations. A more recent report has challenged this understanding, describing a single-center experience with 52 complete staghorns of which 56% were metabolic in nature and 44% were infectious (Gettman and Segura, 1999; Viprakasit et al, 2011). Complete stone clearance is paramount in patients with infectious stones. Incomplete stone removal in these patients can predispose to further UTIs and rapid stone recurrence, because the urease-producing bacteria can persist within the residual stone fragments (Nemoy and Staney, 1971).

Staghorn stones are challenging to treat, frequently require multiple percutaneous access tracts and/or multiple stages, and have high treatment-related morbidity. Surgical strategy should focus on selecting the procedure, or combination of procedures, most likely to render the patient stone free while minimizing morbidity. For most patients, SWL monotherapy should be avoided because it is highly unlikely to be successful and frequently is complicated by steinstrasse. In the only prospective, randomized trial comparing SWL with PCNL for staghorn stones, PCNL provided superior stone-free rates (74% vs. 22%), shorter overall treatment duration, and fewer septic complications (Meretyk et al, 1997).

Combination therapy with multiple endourologic modalities has been used as an alternative to PCNL monotherapy. In one such approach, referred to as sandwich therapy and popularized in the 1990s, staghorn stones were treated first with PCNL, then with SWL for residual or inaccessible stones, and finally with another percutaneous procedure to clear any remaining fragments (Streem et al, 1997). However, outcomes for combination therapy were comparable to those attained with PCNL monotherapy or open nephrolithotomy (Lam et al, 1992b). Because PCNL allows rapid and effective treatment of large stone burdens, as well as efficient stone clearance rather than requiring spontaneous passage, combined approaches should be based around PCNL as the principal procedure. The use of flexible nephroscopy during PCNL can improve stone clearance and also reduce the number of access tracts necessary by allowing access to calyces unreachable with rigid instruments (Wong and Leveillee, 2002). Retrograde flexible URS can be of similar benefit (Marguet et al, 2005).

URS as the sole modality to treat complete staghorn stones is highly unlikely to be successful and has not been reported. URS may be considered an alternative to PCNL for simple partial staghorn stones in patients with favorable anatomy or with contraindications to PCNL, although it often requires multiple stages (Cohen et al, 2013).

Laparoscopic and robotic-assisted techniques have been described in small series for the treatment of complete, or nearly complete, staghorn stones (Giedelman et al, 2012; King et al, 2014). Although these techniques have been shown to be feasible, actual stone-free rates were relatively low (29% to 67%) and the techniques provide no obvious advantage over PCNL for routine staghorn stones in anatomically straightforward situations. In extenuating circumstances, such as ectopic kidneys, laparoscopic or robotic assistance may prove helpful in allowing safe access into the collecting system.

Open nephrolithotomy, once the preferred approach to staghorn stones, is now reserved for rare instances where complicating factors make PCNL impossible or unlikely to achieve reasonable stone clearance within an acceptable number or combination of procedures. Stone-free rates for open surgery have been reported to be as

high as 85%; however, since the rise of endourology and PCNL, superior stone-free rates are routinely achievable with PCNL (Lingeman et al, 1987; Al-Kohlany et al, 2005). In addition, length of hospital stay, the risks for blood transfusions and of renal function loss, and postoperative pain and convalescence all favor PCNL over open nephrolithotomy.

Treatment Decision by Stone Localization

Although total stone burden is arguably the most important consideration when deciding how to approach a given patient's stone disease, the location and distribution of stones within the kidney are often the next most important considerations; this is particularly true for stones between 1 cm and 2 cm in size. The location of stones within the kidney can be simplified to two groups: lower pole stones and non-lower pole stones. Lower pole stones tend to prove the most difficult to treat, especially when the lower pole anatomy is unfavorable (acute infundibulopelvic angle, long infundibular length, narrow infundibular width), because it becomes challenging to reach this location ureteroscopically or to ensure stone clearance with SWL. Because stones within the lower pole are dependently positioned, they are less likely to pass spontaneously after fragmentation by SWL or URS without adjunctive positioning or the use of percussion techniques to assist passage. In addition, the unfavorable anatomic factors may limit passage of fragments even with those adjunctive treatments.

Many studies have evaluated the impact of lower pole stone location on treatment success and complications for a variety of stone treatment modalities. Further discussion of lower pole stones and the influence of lower pole anatomy on treatment outcomes is covered in the section on lower pole calculi. Suffice it to say, **stones situated in the lower pole prove more difficult to clear with URS or SWL, and therefore stones 1 cm or larger within the lower pole may be most efficiently treated with PCNL.** Stones in a non-lower pole location tend to respond more readily to SWL and URS, making those techniques more competitive with PCNL.

For non-lower pole renal stones treated with SWL, firm conclusions about treatment outcomes based on differences in non-lower pole renal stone location are difficult to make because the available studies use a variety of different lithotripters and include nonuniform stone burdens and wide variation in both the assessment and definition of successful stone clearance. Nevertheless, some patterns emerge when the available data are pooled (Graff et al, 1988; Kosar et al, 1998; Coz et al, 2000; Obek et al, 2001; Egilmez et al, 2007; Turna et al, 2007; Seitz et al, 2008; Khalil, 2012; Neisius et al, 2013). In general, **non-lower pole kidney stone treatment success by SWL tends to be similar for any given stone size regardless of the precise intrarenal location.** That is, stone clearance rates and effectiveness quotients are reported as statistically similar for stones in the renal pelvis, upper pole calyces, and middle calyces within a given study, despite differences in absolute numbers among studies. Thus, stone size and composition, rather than stone location, should dictate SWL treatment decisions.

Few recent studies have evaluated URS outcomes based on stone location. With the vast advancements in endourology over the past decade, flexible ureteroscopes can often access all locations within the intrarenal collecting system.

Before the newer-generation flexible ureteroscopes with improved deflection capabilities, lower pole calculi often proved more challenging to access and completely clear. With modern flexible ureteroscopes, however, lower pole stones can be reached in most instances, and small or partially fragmented stones can often be repositioned into more favorable intrarenal locations (e.g., renal pelvis or upper pole). **Excellent stone clearance with URS has been reported for all renal stone locations (>80% to 90%), suggesting that stone size and density, along with patient anatomy, are more important factors than intrarenal stone location when considering URS treatment decisions** (Portis et al, 2006; Perlmutter et al, 2008; Hussain et al, 2011).

Similar to URS, data are sparse with regard to PCNL outcomes based on specific stone location. With the addition of flexible

nephroscopy at the time of initial PCNL, much of the kidney and hence stones in many intrarenal locations are accessible through the initial percutaneous tract. There is, however, **some evidence to suggest that upper pole calyceal stone location in patients undergoing PCNL is an independent predictor of incomplete stone clearance**, although this study concentrated on single-tract PCNL only (Shahrour et al, 2012). In developing a nomogram to predict stone-free status after PCNL, Smith and colleagues found that stones within the middle calyx and renal pelvis were more likely to be cleared than stones in an upper or lower calyceal location (Smith et al, 2013). It is interesting to note that, other than for staghorn stones, upper calyx location was associated with the lowest stone clearance, inferior even to stones within the lower pole.

Results from the PCNL global study demonstrated a higher rate of postoperative complications for large calyceal stones compared with large renal pelvis stones. However, those in the large calyceal stone group had more overall comorbidities and higher American Society of Anesthesiologist scores, which may be significant confounding variables (Xue et al, 2012).

Anterior versus posterior calyceal stone location may also affect PCNL outcomes. When targeting directly into the stone-bearing calyx, anteriorly located calyces require longer tract lengths and traverse more renal parenchyma than posteriorly located calyces. Tepeler and colleagues explored this hypothesis in a series in which patients were divided and found no difference in overall success and complication rates, but did note a trend toward increased severe hemorrhagic events in the cohort with anterior calyceal stones (Tepeler et al, 2013).

Treatment by Stone Composition

Stone composition has significant implications with respect to treatment outcomes primarily with SWL, whereas URS, PCNL, and laparoscopic and open stone surgery appear to be only minimally affected. When composition is known, a prior stone analysis can be used to better decide on therapy.

In general, cystine, calcium phosphate (specifically “brushite”), and calcium oxalate monohydrate stones are the most resistant to SWL. The remainder of the common stone types by order of increasing fragility are struvite, calcium oxalate dihydrate, and finally uric acid stones (Pittomvils et al, 1994; Zhong and Preminger, 1994; Saw and Lingeman, 1999).

Zhong and Preminger (1994) showed that brushite and calcium oxalate monohydrate stones’ resistance to SWL can be explained by their inherent mechanical properties (higher Young’s modulus, greater hardness and fracture toughness). The resistance of cystine stones to SWL lies in their ductile structure, which conveys a higher resilience to internal crack propagation and a higher deformation capability. In addition, SWL fragmentation of cystine, brushite, and calcium oxalate monohydrate results in relatively larger stone fragments than other stone compositions, which may negatively affect subsequent stone clearance (Dretler, 1988; Pittomvils et al, 1994; Rutchik and Resnick, 1998).

In vitro studies have shown that holmium laser lithotripsy fragmentation efficiency is also dependent on stone composition, with the poorest fragmentation seen for calcium oxalate monohydrate stones and moderate fragmentation seen for uric acid and cystine stones (Teichman et al, 1998a). However, this may have little clinical practicality, as a separate study by Teichman and associates (1998b) demonstrated that holmium laser lithotripsy was able to successfully fragment all stone types tested and resulted in no fragments larger than 4 mm (Teichman et al, 1998b). Moreover, when stone basket extraction was added to holmium laser lithotripsy, Wiener and colleagues showed that operative time was independent of stone composition (Wiener et al, 2012).

Stone attenuation values (in Hounsfield units) on CT have been correlated to stone composition, although overlap exists across many stone types. Numerous investigators have shown that uric acid stones consistently have lower Hounsfield unit values than calcium oxalate monohydrate stones and can be readily discerned from them on helical CT (Mitcheson et al, 1983; Mostafavi

et al, 1998; Nakada et al, 2000; Kulkarni et al, 2013; Marchini et al, 2013). Moreover, uric acid stones tend to display more homogeneous attenuation throughout a given stone than calcium oxalate stones (Marchini et al, 2013). Discriminating between struvite- and calcium-containing stones is usually not possible based on stone attenuation alone, as considerable overlap exists between them.

Even though stone attenuation values are far from perfect in accurately determining stone composition, stone attenuation can be helpful in predicting treatment success with SWL. Multiple studies now show that attenuation values higher than 900 to 1000 HU are associated with poorer outcomes with SWL (Joseph et al, 2002; Gupta et al, 2005; Wang et al, 2005; El-Nahas et al, 2007). Indeed, Gupta and colleagues (2005) have shown a linear relationship between SWL fragmentation success and stone attenuation, with decreasing fragmentation as stone attenuation increases. Joseph and colleagues (2002) reported that stone clearance with SWL occurred in just 54.5% of patients with stone attenuation levels above 1000 HU, whereas success was seen in 85.7% of patients when stone attenuation was between 500 and 1000 HU and in all patients with stone attenuation below 500 HU. Ouzaid and associates (2012) showed that a threshold of 970 HU was the most sensitive and specific cutoff value to predict treatment success with SWL. Stones below 970 HU were associated with an SWL treatment success rate of 96%, whereas stones above 970 HU were successfully treated only 38% of the time. Similar to the study by Gupta and coworkers (2005), this study found a linear association between SWL success and stone attenuation.

Matrix. Matrix renal stones are rare, and unlike most other renal stones in that they are predominantly (approximately 65%, range 42% to 84%) composed of organic proteins, sugars, and glucosamines, whereas other crystalline calculi have only minimal organic material (2.5%) (Boyce and King, 1959). In addition, these stones are soft, gelatinous, and relatively amorphous (Fig. 53-4). Matrix stones can be challenging to diagnose preoperatively, as they can mimic upper tract collecting system soft-tissue masses and require a high index of suspicion. Traditionally described as radiolucent, these stones often exhibit either a radiodense calcific center or faint peripheral rim of radiodensity, and both of these signs are frequently visible on preoperative imaging (Fig. 53-5) (Bani-Hani et al, 2005; Shah et al, 2009). These stones tend to be large and can assume partial staghorn configurations, and therefore PCNL is the preferred treatment approach for most matrix renal stones owing to its high success rates and low recurrence rates. It should be noted that descriptions of successful treatment with URS have been reported (Stoller et al, 1994b; Rowley et al, 2008; Shah et al, 2009; Chan et al, 2010), but SWL is ineffective in these stones, given their soft composition and relative paucity of brittle mineral content.

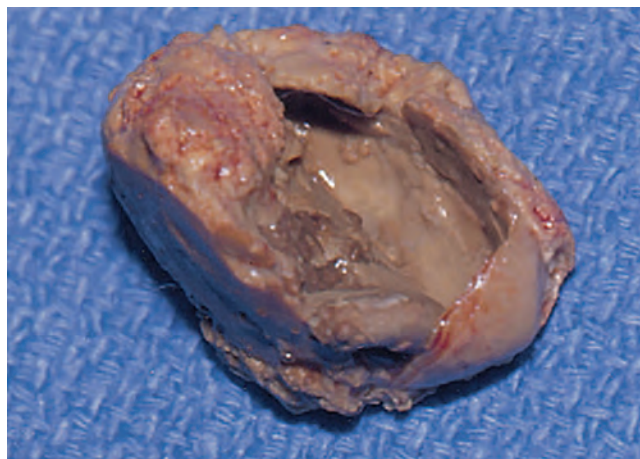


Figure 53-4. Matrix stone with soft, gelatinous, amorphous consistency and air pocket. (From Bani-Hani AH, Segura JW, Leroy AJ. Urinary matrix calculi: our experience at a single institution. *J Urol* 2005;173:120-3.)



Figure 53-5. Computed tomography imaging of matrix stone showing radiodense rim and radiolucent center. (From Bani-Hani AH, Segura JW, Leroy AJ. Urinary matrix calculi: our experience at a single institution. *J Urol* 2005;173:120–3.)



Please see the Expert Consult website for additional details related to treatment by stone composition.

Renal Anatomic Factors

Ureteral Pelvic Junction Obstruction

Ureteropelvic junction obstruction (UPJO) is associated with kidney stones up to 20% to 30% of the time (Rutchik and Resnick, 1998; Berkman et al, 2009). Before undertaking any surgical correction, it is vitally important to try to distinguish if the UPJO is the underlying disorder with subsequent renal stone formation, or if a renal pelvis or UPJ stone provoked edema at the UPJ, giving the misleading appearance of UPJO when none actually exists. Although this is not always straightforward, review of CT cross-sectional imaging can provide some insights. For example, when smaller stones are found in calyceal locations with a significantly hydronephrotic renal pelvis and tight UPJ or proximal ureter, UPJO is likely the primary pathology with resulting stone formation. On the contrary, a stone lodged at the UPJ or a renal pelvis stone in close proximity to the UPJ may be the primary pathology causing the obstruction, with no UPJO actually existing.

If there is any question about primary UPJO or a mimic from a UPJ or renal pelvis stone, then the kidney stones should be treated and no specific therapy should be directed at the UPJ. Rather, 4 to 6 weeks after the stone has been treated, follow-up renal imaging (sonogram, CT, or MRI) can be performed to ascertain if hydronephrosis persists, and if so, further renal functional imaging may be indicated (diuretic renogram). Alternatively, if a nephrostomy tube is in place and the presence of UPJO remains equivocal, then a Whitaker test can be performed. If UPJO is confirmed at that time, only then is UPJ repair recommended.

Similarly, it is important to determine the overall renal function of the affected kidney if it appears atrophic or with thinned parenchyma. If a nonfunctioning or poorly functioning kidney is confirmed, then the simplest option may be nephrectomy rather than simply treating the stone. It is also important to determine if the UPJ has been operated on in the past. Reports have shown that UPJO that recurs after previous endopyelotomy responds favorably to minimally invasive or open pyeloplasty and that UPJO that recurs after previous pyeloplasty responds well to endopyelotomy (Canes et al, 2008; Patel et al, 2011).

A variety of strategies can be used to treat UPJO with concomitant kidney stones, with the ultimate goal of repairing the UPJO and restoring normal renal drainage while simultaneously rendering the patient stone free. PCNL with antegrade endopyelotomy, laparoscopic or robotic pyeloplasty with pyelolithotomy or neph-

rolithotomy, and retrograde endopyelotomy with URS stone removal have all been described. Endopyelotomy should be discouraged when long strictures (>2 cm) are encountered or prior endopyelotomy has been performed and failed.

As a general rule, it is prudent to clear the stone burden before incising the UPJO during endopyelotomy and before completing the UPJ repair with pyeloplasty. This is particularly important for PCNL with antegrade endopyelotomy, so that stone fragments do not extrude or settle near the area of the UPJ incision. Stone incorporated in or near the endopyelotomy site can lead to restricting through granuloma and fibrosis formation (Giddens et al, 2000). Retrograde endopyelotomy with URS stone treatment is also susceptible to this problem, as endopyelotomy is necessary as an initial step to allow the ureterorenoscope access to the kidney, and any subsequent attempts at stone fragmentation or retrieval may result in residual fragments lodging in close proximity to the UPJ.

Over the last decade an increasing number of reports have surfaced describing laparoscopic and robotic pyeloplasty with simultaneous kidney stone removal, and when combined with the available literature on minimally invasive UPJO repair, a number of patterns emerge. There appears to be no difference in operative outcomes, success, or complications of UPJO repair between laparoscopic and robotic pyeloplasty (Braga et al, 2009). Short-term success for laparoscopic and robotic pyeloplasty is excellent at over 90% and appears superior to that of antegrade endopyelotomy, which is closer to 70% to 80% (Knudsen et al, 2004; Rassweiler et al, 2007; Berkman et al, 2009). Berkman and colleagues (2009) found PCNL at the time of percutaneous antegrade endopyelotomy to have no effect on success rates of relieving obstruction. Long-term outcomes with endopyelotomy or pyeloplasty are worse than short-term results, with recurrence seen in 25% of pyeloplasties and approximately 60% of endopyelotomies after 10 years (DiMarco et al, 2006).

Laparoscopic, and more recently robotic, pyeloplasty with concurrent renal calculi removal through a pyelolithotomy achieves a stone-free rate of 75% to 100%, and with a pyeloplasty a success rate exceeding 90% (Ramakumar et al, 2002; Atug et al, 2005; Mufarrij et al, 2008; Srivastava et al, 2008; Stein et al, 2008; Stravodimos et al, 2014). Laparoscopic graspers, flexible nephroscopes and wire baskets passed through laparoscopic or robotic trocars, laparoscopic irrigation, and robotic graspers have all been used to remove renal stones through the pyelotomy incision. Operative times are approximately 3.5 to 4 hours. In one small series, combined robotic nephrolithotomy and UPJO repair was undertaken and the use of intraoperative ultrasound aided in stone identification within the kidney to direct small nephrolithotomy incisions (Ghani et al, 2014).

In very select cases in which patients have larger, highly complex stone burdens and calyceal anatomy unlikely to permit adequate stone clearance through the standard pyeloplasty incisions, performing standard PCNL first and then performing laparoscopic pyeloplasty under the same anesthetic has been described with encouraging results (Agarwal et al, 2008). However, this approach is associated with longer operative time of almost 4 hours. All patients were stone free by renal sonography at 6 months and demonstrated adequate renal drainage on renogram.

Calyceal Diverticula

Calyceal diverticula are urothelium-lined, nonsecretory, cystic dilations of the intrarenal collecting system that are thought to arise embryonically. They were first described by Rayer in 1841 and were first given the name *calyceal diverticula* in 1941 by Prather (Rayer, 1841; Prather, 1941). They have a narrow connection to the normal pelvicalyceal system, which is thought to allow for preferential urine filling and poor urine drainage from the diverticulum. Calyceal diverticula are rare, with a reported incidence of 0.2% to 0.6% in patients undergoing intravenous urography (IVU) (Middleton and Pfister, 1974; Timmons et al, 1975; Wulfsohn, 1980; Michel et al, 1985). They may arise from any portion of the pelvicalyceal system, with (approximately) 50% or more originating from the upper pole calyces, 30% from the middle pole calyces or renal pelvis, and 20%

Stone composition has the largest impact on SWL results, whereas URS, PCNL, and laparoscopic and open stone surgery are less affected by stone composition, if at all. Therefore, factoring stone composition into treatment decision analysis is most relevant for stones 2 cm or less in size, for which SWL is often considered first-line therapy or as a first-line therapeutic option. In general, cystine, calcium phosphate (specifically “brushite”), and calcium oxalate monohydrate stones are the most resistant to SWL. When patients are known to harbor such stones, in particular when combined with lower pole stone location, long skin-to-stone distances, or increasing stone burdens above 1 cm, SWL success rates decrease substantially. In such patients, recognition of this limitation should prompt consideration of another modality (e.g., URS or PCNL).

In 1988, Dretler introduced the concept of stone fragility, describing it as “the ease with which a stone fragments during SWL.” He demonstrated in vitro that calculi of various compositions fragment differently under a given set of SWL parameters (Dretler, 1988). Thereafter, additional investigations revealed that cystine, brushite, and calcium oxalate monohydrate stones were the most refractory to SWL fragmentation, with cystine and brushite being most resistant. The remainder of the common stone types by order of increasing fragility are struvite, calcium oxalate dihydrate, and finally uric acid stones (Pittomvils et al, 1994; Zhong and Preminger, 1994; Saw and Lingeman, 1999).

Zhong and Preminger (1994) showed that brushite and calcium oxalate monohydrate stones’ resistance to SWL can be explained by their inherent mechanical properties (higher Young’s modulus, greater hardness and fracture toughness). The resistance of cystine stones to SWL lies in their ductile structure, which conveys a higher resilience to internal crack propagation and a higher deformation capability. In addition, SWL fragmentation of cystine, brushite, and calcium oxalate monohydrate results in relatively larger stone fragments than other stone compositions, which may negatively affect subsequent stone clearance (Dretler, 1988; Pittomvils et al, 1994; Rutchik and Resnick, 1998). Williams and associates evaluated the number of shock waves necessary to completely fragment stones of different compositions and demonstrated a considerably higher mean number of shocks necessary for cystine (5937 shocks) and brushite (1681 shocks) stones compared with other stone types, with uric acid stones (400 shocks) requiring the least (Williams et al, 2003).

The internal structure of a stone, not just its composition, influences stone fragility, and it has been demonstrated that stones of a given mineral type can exhibit a wide range of fragility (Williams et al, 2003). This is particularly relevant for cystine stones, wherein the prevailing belief is that these stones are all resistant to SWL. In actuality, early work by Bhatta and associates showed that cystine calculi come in two predominant substructures: those with a rough external surface and those that are smooth (Bhatta et al, 1989). The rough cystine stones had well-formed, repeating internal hexagonal crystals, whereas the smooth cystine stones had irregular crystals that did not interlace well. Kim and associates took this one step further, showing that cystine stones with mixed internal low- and high-attenuation regions on CT were more readily fragmented by SWL than those with a homogeneous appearance (Kim et al, 2007). In fact, the homogeneous cystine stones required approximately 60% more shocks for comminution. This same phenomenon has been seen in calcium oxalate monohydrate stones as well with more homogeneous stones relatively more resistant to SWL than those with a heterogeneous appearance on CT (Fig. 53-6) (Zarse et al, 2007). Viewing the CT scan with bone windows can facilitate the identification of the internal structure of renal stones (Williams et al, 2002).

In vitro studies have shown that holmium laser lithotripsy fragmentation efficiency is also dependent on stone composition, with the poorest fragmentation seen for calcium oxalate monohydrate stones and moderate fragmentation seen for uric acid and cystine stones (Teichman et al, 1998a). However, this may have little clinical practicality, as a separate study by Teichman and associates (1998b) demonstrated that holmium laser lithotripsy was able to successfully fragment all stone types tested and resulted in no fragments larger than 4 mm (Teichman et al, 1998b). Moreover, when stone basket extraction was added to holmium laser lithotripsy, Wiener and colleagues (2012) showed that operative time was independent of stone composition. This study included cystine, calcium oxalate monohydrate, brushite, and uric acid stone types, among others (Wiener et al, 2012).

Unfortunately for the vast majority of patients requiring surgical treatment for kidney stones, the stone composition is unknown before surgery, and treatment decisions must be made according to information available preoperatively. Considerable information may be gleaned from preoperative imaging that can inform treatment decisions. Details about stone size, shape, and density are

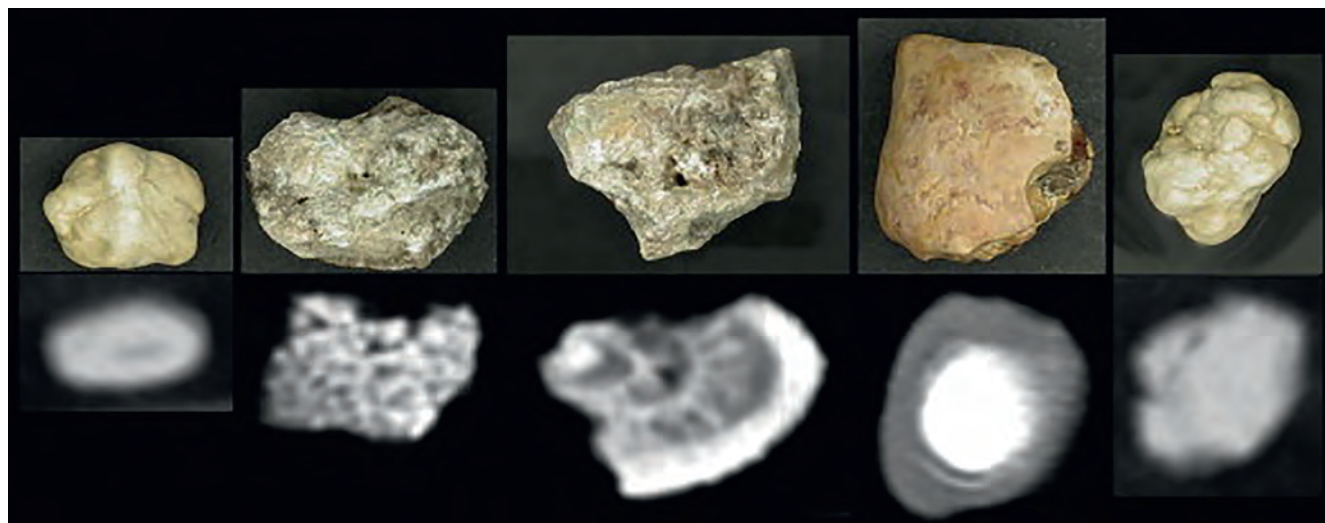


Figure 53-6. Photographic and helical computed tomography images show structural variability in stones of the same type. Note that although all stones depicted are calcium oxalate in type, some have a mottled structure and others have a lamellar structure.

readily obtainable from modern CT imaging software, and noncontrast helical CT is both the most sensitive and the most widely used initial imaging study in the evaluation of suspected urolithiasis. Anatomic detail and skin-to-stone distance can also be easily determined on axial CT slices. **The combination of anatomic and stone characteristics becomes most important when deciding if a given stone is amenable to SWL or if another treatment modality should be chosen.**

Before the widespread use of CT, the imaging nuances of plain radiography were used in an attempt to predict stone fragility by SWL. Uric acid stones are radiolucent on plain radiography but readily visible on CT and respond well to SWL if they can be appropriately targeted. Stones with irregular contour and reticulated, spiculated structure tended to fragment more easily than stones with homogeneous architecture and smooth edges (Dretler, 1988; Dretler and Polykoff, 1996). Assessments of relative stone radiodensity suggested that stones more dense than nearby bony structures (transverse process or 12th rib) were more resistant to SWL than less dense stones. In addition, cystine stones have been noted to appear as ground glass on plain radiography, and when this is seen preoperatively, treatments other than SWL should be sought.

Stone attenuation values (in HU) on CT have been correlated to stone composition, although overlap exists across many stone types. Numerous investigators have shown that **uric acid stones consistently have lower Hounsfield unit values than calcium oxalate monohydrate stones and can be readily discerned from them on helical CT** (Mitcheson et al, 1983; Mostafavi et al, 1998; Nakada et al, 2000; Kulkarni et al, 2013; Marchini et al, 2013). Moreover, uric acid stones tend to display more homogeneous attenuation throughout a given stone than calcium oxalate stones (Marchini et al, 2013). Discriminating between struvite- and calcium-containing stones is usually not possible based on stone attenuation alone, because considerable overlap exists between them.

Differentiation among the various calcium-containing stones remains difficult, but in vitro evaluation using dual-source CT has shown promise in distinguishing between calcium oxalate and calcium phosphate stones (Matlaga et al, 2008; Boll et al, 2009). More recently, single-source dual-energy CT has been shown to accurately predict stone composition in stone formers with uric acid stones (6 patients), cystine stones (1 patient), and 79% of patients with calcium stones (15 of 19 patients) (Hidas et al, 2010). In the same study, the sole patient with a struvite stone was incorrectly predicted.

Even though stone attenuation values are far from perfect in accurately determining stone composition, stone attenuation can be helpful in predicting treatment success with SWL. **Multiple studies now show that attenuation values higher than 900 to 1000 HU are associated with poorer outcomes with SWL** (Joseph et al, 2002; Gupta et al, 2005; Wang et al, 2005; El-Nahas et al, 2007). Indeed, Gupta and colleagues (2005) have shown a linear relationship between SWL fragmentation success and stone attenuation, with decreasing fragmentation as stone attenuation increases. Joseph and colleagues (2002) reported that stone clearance with SWL occurred in just 54.5% of patients with stone attenuation levels exceeding 1000 HU, whereas success was seen in 85.7% of patients when stone attenuation was between 500 and 1000 HU and in all patients with stone attenuation below 500 HU. Ouzaid and associates (2012) showed a threshold of 970 HU to be the most sensitive and specific cutoff value to predict treatment success with SWL. Stones below 970 HU were associated with an SWL treatment success rate of 96%, whereas stones above 970 HU were successfully treated only 38% of the time. Similar to the study by Gupta and coworkers (2005), this study found a linear association between SWL success and stone attenuation.

Cystine. As previously described, cystine stones prove more resistant to SWL than other stone types based on their inherent chemical structure, which gives them a ductile nature, or ability to deform instead of crack, rather than any underlying hardness or density. The natural history for most cystinuric patients is recurrent stone formation over their lifetime, and although medical management

can prove useful in prevention, compliance with it is difficult and overall poor (Pietrow et al, 2003; Ahmed et al, 2008). Recurrence rates as high as 73% are seen at 5 years, and patients with residual fragments undergo more frequent re-treatments than those rendered stone free (Knoll et al, 1988; Chow and Streem, 1998). Furthermore, cystinurics have relatively worse renal function compared with calcium oxalate stone formers, and the greatest decline in renal function is found in those cystinurics who have required more stone surgeries (Barbey et al, 2000; Assimos et al, 2002). The goal, then, is to minimize surgery in these patients and, when possible, treat them in a minimally invasive manner.

Of the currently available treatment modalities, URS should assume a prominent role in the surgical management of cystinurics. Although PCNL may be necessary to treat excessively large stone burdens or complete staghorn stones, repeated PCNL, and in particular open stone removal, can contribute to renal functional decline. Therefore, URS for stone burdens in excess of 2 cm may still be the preferred surgical approach if stone clearance can be reasonably expected within one or two stages. For smaller cystine stones in non-lower pole locations and in patients with favorable anatomy (i.e., skin-to-stone distance <10 cm), SWL may be considered as a treatment option if flexible URS equipment or the technical familiarity to perform flexible URS proficiently is unavailable. However, poorer stone clearance rates than for noncystine stones should be expected, and the patient counseled appropriately.

Ureterorenoscopic management of cystine stone formers has shown favorable results with minimal morbidity (Rudnick et al, 1999; Trinchieri et al, 2007; Ahmed et al, 2008; Ruggera et al, 2011). Unfortunately, no contemporary studies using present-day flexible ureteroscopic technology have been reported, but given the limited clinical effect of stone composition on holmium laser lithotripsy, similarly excellent results should be expected for cystinurics undergoing URS. Despite this, the results of Rudnick and colleagues (1999) more than a decade ago demonstrating that encouraging treatment success (83%) with URS was achievable in cystinurics with stones up to 3 cm challenged the prevailing treatment algorithm at the time proposed by Kachel and colleagues (1991). Based on their work, Kachel and colleagues (1991) recommended that cystine stones smaller than 1.5 cm in diameter be treated with SWL and cystine stones larger than 1.5 cm in diameter be approached with PCNL. Stone-free rates with PCNL for cystine stones routinely offer stone-free rates exceeding 90%, whereas SWL outcomes are lower, with a 70.5% stone-free rate for stones smaller than 20 mm and a 41% stone-free rate for stones 20 mm or larger (Hockley et al, 1989).

Brushite. From a treatment decision perspective, brushite stones should be approached like cystine stones, and minimally invasive therapies should assume a primary role. The main reason for this is that brushite stones are relatively refractory to SWL, surpassed only by cystine stones (Dretler, 1988; Ringden and Tiselius, 2007). With contemporary URS achieving stone-free rates in excess of 90%, even for stones larger than 2 cm, URS in skilled hands should be at the top of the minimally invasive treatment options for brushite stone formers (Aboumarzouk et al, 2012a). With an average of 1.5 treatment sessions necessary, SWL monotherapy has been shown to achieve treatment success in only 65% of patients and complete stone-free status in only a meager 11% of patients (Klee et al, 1991).

A retrospective review of 82 brushite stone formers showed that stone-free status was attainable in 92% of patients with one or two procedures, with most of these being PCNL (Krambeck et al, 2010). In this analysis, recurrent stone events were seen in 38% of patients at an average of 33 months after last treatment, and all had some underlying metabolic derangement found on 24-hour urine analysis, underscoring the importance of metabolic stone evaluation and long-term management in this population. It is interesting to note that up until a decade ago, SWL appears to have been used more frequently in brushite stone formers than in calcium oxalate stone formers (Parks et al, 2004). It is unclear if this is a result of the lower fragility of brushite stones, thereby subjecting brushite stone formers to more SWL treatments per stone burden, on average.

Medication-Precipitated Stones. Renal calculi composed predominantly of a medication or one of its metabolites have been described, albeit rarely. Ephedrine and guaifenesin are both radiolucent but respond well to minimally invasive therapy such as SWL and URS (Blau, 1998; Powell et al, 1998; Assimios et al, 1999). Indinavir is a protease inhibitor used to treat patients with human immunodeficiency virus and has been shown to precipitate and form stones in 4% to 13% of patients who use this medication (Wu and Stoller, 2000). Average time between medication initiation and stone event has been reported as 21.5 weeks (Reiter et al, 1999). The stones are often small and are radiolucent on plain radiography and CT. Smaller stones pass spontaneously in more than 60% of reported cases, so a trial of nonoperative management with analge-

sics, α -blockers, and hydration is warranted (Daudon et al, 1997; Kohan et al, 1999; Reiter et al, 1999; Nadler et al, 2003). It is recommended that indinavir be temporarily discontinued as well. Indications for surgical treatment or intervention, therefore, are no different than for other stones of similar size, and all minimally invasive modalities (URS, SWL, PCNL) have been successfully applied to protease inhibitor stones.

In addition, other medications have been known to form stones, including triamterene, magnesium trisilicate, ciprofloxacin, and sulfa drugs (Matlaga et al, 2003b). Finally, drug-induced calculi can occur because of loop diuretics or increased metabolites that precipitate, such as xanthine stones induced by allopurinol (Greene et al, 1969).

stemming from the lower pole calyces (Abeshouse and Abeshouse, 1963; Waingankar et al, 2014).

Stone formation within calyceal diverticula has been reported to occur between 10% and 50% of the time (Yow and Bunts, 1955; Williams et al, 1969; Middleton and Pfister, 1974). A combination of urinary stasis and metabolic derangements is believed to underlie stone development in these structures (Burns et al, 1984; Hsu and Streem, 1998; Liatsikos et al, 2000; Matlaga et al, 2007). Hsu and Streem (1998) reported a 50% rate of metabolic abnormalities in 14 patients with stones in calyceal diverticuli. In contrast, Liatsikos and colleagues (2000) reported that only 25% of patients with calyceal diverticular stones have metabolic abnormalities, compared with 77% of patients without urinary tract anatomic anomalies.

A large percentage of calyceal diverticula are asymptomatic and require no treatment; however, **diverticular stones associated with pain, recurrent infections, hematuria, or a decline in renal function warrant treatment.** Similar to other locations in the kidney, stones within calyceal diverticula have been managed through a variety of approaches including open surgery, SWL, URS, PCNL, and laparoscopic and robotic modalities. The preferred management approach depends on both stone and diverticular anatomic characteristics. Open surgery is primarily of historic interest except in extenuating circumstances, and when undertaken, the diverticulum is marsupialized and cavity lining fulgurated.

Shock wave lithotripsy has been used to treat calyceal diverticular stones, albeit with modest results, and should not be considered first-line therapy for most symptomatic diverticular stones. Although the underlying pathogenesis is not fully understood, ablation of the calyceal diverticular lining, dilation of the diverticular neck to improve drainage, or both are considered integral to achieving stone clearance and preventing stone recurrence (Cohen and Preminger, 1997). Neither of these is accomplished with SWL. Stone-free rates for SWL are typically poor, ranging from 4% to 58% (Renner and Rassweiler, 1999; Turna et al, 2007). In one of the largest reported series involving SWL of calyceal diverticular stones, Turna and associates (2007) showed a 21% stone-free rate, although 60% of patients did experience symptom relief. Symptom-free status has been achieved in 36% to 86% of patients after SWL across a number of series, with the average closer to 60%; all studies, however, involved relatively few patients. Streem and Yost (1992) reported the highest symptom relief (86%) and stone-free rates (58%) after SWL, and these results appear to be reliant on strict patient selection criteria including stones smaller than 1.5 cm and large, patent diverticular necks on IVU. With longer follow-up averaging about 24 months (12 to 49 months), the symptom-free rate had declined to 75% and stone recurrence was witnessed in one patient. In general, with longer follow-up, symptom-free status consistently appears to diminish (Jones et al, 1991a; Streem and Yost, 1992; Turna et al, 2007).

URS is a reasonable first-line treatment approach for patients with small (<2 cm) calyceal diverticular stones arising from an upper or middle calyx, and with a diverticular neck that is short and identifiable (Grasso et al, 1995b; Waingankar et al, 2014). Diverticular stones in these locations are usually accessible via retrograde URS, whereas lower pole diverticular stones present more of a challenge owing to angulation. The holmium laser can be used to incise the narrow diverticular neck, fragment stones within, and ablate the diverticular lining. Stone-free rates of 50% to 90% are found in most series, though Auge and colleagues (2002) found a much lower symptom-free rate of 35% (Fuchs and David, 1989; Grasso et al, 1995b; Batter and Dretler, 1997; Chong et al, 2000; Auge et al, 2002; Legraverend et al, 2013). Adequate diverticular obliteration is lower with the ureteroscopic approach (approximately 20%) than with a percutaneous approach (>70%), hence the need to ensure a patent and well-draining diverticular neck.

In general, most URS failures have occurred in lower pole diverticula, although a small number have occurred in upper pole diverticula with unfavorable acute-angle offshoots of the calyceal diverticular neck. Unfortunately, the ostium to calyceal diverticulum cannot be successfully located in up to 25% of cases, and when this occurs the diverticular stones cannot be treated ureteroscopically

(Auge et al, 2002; Canales and Monga, 2003). Legraverend and associates reported a 62% stone-free rate, which increased to 84% when residual fragments less than 3 mm were included. Symptom-free rate was 93%. Overall, stone-free rates are superior to those achievable with SWL but inferior to those of PCNL. Furthermore, staged URS procedures are not uncommon in this setting.

PCNL should be considered first-line treatment for most calyceal diverticular stones. Stone-free rates (70% to 100%) and symptom-free rates (77% to 100%) are excellent for PCNL, and the percutaneous approach has the most data supporting its efficacy (Hulbert et al, 1986; Cohen and Preminger, 1997; Shalhav et al, 1998; Al-Basam et al, 2000; Monga et al, 2000; Auge et al, 2002; Kim et al, 2005; Krambeck and Lingeman, 2009). Diverticular ablation rates are also excellent (>70%) with a percutaneous approach, and the overall success rates appear durable (Shalhav et al, 1998; Monga et al, 2000). Directly puncturing into the calyceal diverticulum is preferable and allows for stone fragmentation and removal, easy fulguration of the diverticular lining, and dilation of the diverticular neck if visible and desired. Ultrasound or CT guidance can be used in selected cases when retrograde contrast instillation does not fill the calyceal diverticulum and when diverticular stones are nonradiopaque (Matlaga et al, 2006a). Posteriorly located diverticuli are particularly well suited for a percutaneous approach because there is usually minimal renal parenchyma between the diverticulum and renal capsule. Anteriorly located calyceal diverticula can also be managed with a percutaneous approach; however, it is often difficult to incise and dilate the diverticular neck secondary to unfavorable angles between the entry vector and the neck.

Laparoscopic and robotic approaches for the treatment of symptomatic stones within calyceal diverticuli have been described and are usually reserved for anteriorly located, symptomatic diverticuli with thin overlying renal parenchyma, which are otherwise not amenable to less invasive endoscopic methods (Gluckman et al, 1993; Ruckle and Segura, 1994; Harewood et al, 1996; Hoznek et al, 1998; Curran et al, 1999; Miller et al, 2002; Terai et al, 2004; Wyler et al, 2005; Akca et al, 2014). Both retroperitoneal and transperitoneal approaches have been used, with the retroperitoneal method providing easier access to posteriorly located diverticula. Outcomes are superb, with a 100% stone-free rate in those series reporting it as an outcome, approximately a 92% cavity ablation rate, and a 75% to 87% average symptom resolution rate (Waxman and Winfield, 2009; Basiri et al, 2013; Waingankar et al, 2014). The average operative time reported in these studies is approximately 180 minutes, which is longer than for the other surgical approaches. Important common considerations for this approach include the use of intraoperative ultrasound to assist with diverticulum localization, direct cavity lining ablation using electrocautery or argon beam coagulation, and suturing of the diverticular neck when required to manage wide-mouthed diverticulum.

Horseshoe Kidneys and Renal Ectopia

Horseshoe Kidneys. Horseshoe kidneys are the most common renal fusion anomaly, with a reported incidence of 1 in 400 live births (Pitts and Muecke, 1975; Evans and Resnick, 1981). It is important to recognize that there is a 15% to 20% incidence of kidney stone disease in horseshoe kidneys. Most stones are composed of calcium oxalate, with the most common locations being the renal pelvis and posterior lower pole calyces (Evans and Resnick, 1981; Tan et al, 2013). Embryonically, the abnormal medial fusion of the left and right metanephric blastemata creates an isthmus that anchors the fused kidneys at the level of the inferior mesenteric artery, leading to incomplete renal ascent and malrotation (Hohenfellner et al, 1992) (Figs. 53-7, 53-8, and 53-9).

As a result, a number of anatomically important changes are noted. The renal pelvis becomes elongated and anteriorly located, the UPJ has a high insertion into the renal pelvis and is also anteriorly situated, and the proximal ureter courses more anteriorly than usual because it must traverse over the isthmus of the horseshoe kidney. Collectively, these changes are thought to impede normal urinary drainage and to promote urinary stasis and renal stone



Figure 53-7. Antegrade nephrostogram obtained after percutaneous nephrolithotomy of a horseshoe kidney via an upper pole access. Note the subcostal nature of the access and the unique calyceal orientation inherent in a horseshoe kidney.



Figure 53-8. Coronal computed tomographic reconstruction of horseshoe kidney with bilateral staghorn calculi. Note the medial and inferior position of the horseshoe kidney.

formation. These anatomic and functional changes have an impact on the various treatment options for renal stones, and specific horseshoe kidney anatomy, stone location, and stone size must also be considered when choosing the optimal stone treatment. The presence of impaired renal drainage or UPJO should preclude SWL

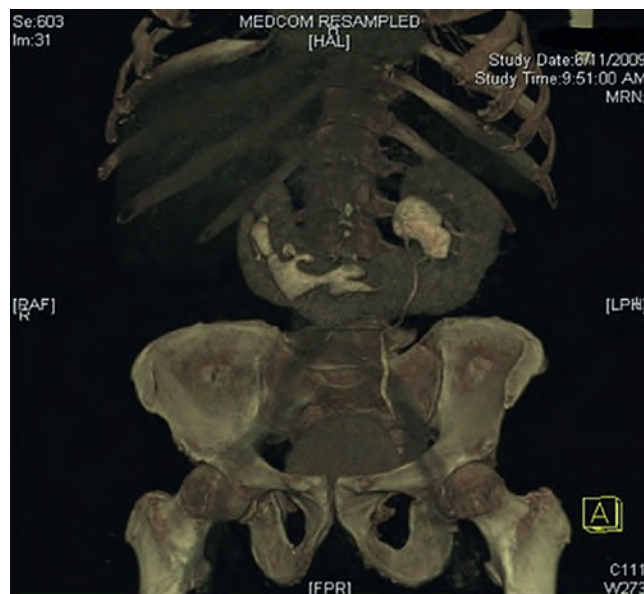


Figure 53-9. Three-dimensional computed tomographic reconstruction of horseshoe kidney with bilateral staghorn calculi. Note the medial and inferior position of the horseshoe kidney. (From Tan YK, Cha DY, Gupta M. Management of stones in abnormal situations. *Urol Clin North Am* 2013;40:79–97.)

treatment, and other modalities that can address the obstruction, such as PCNL or laparoscopic pyeloplasty, should be pursued. In general, stones smaller than 15 mm and not situated in the lower pole can be approached with SWL or URS. Stones that fail treatment with SWL or URS and stones larger than 15 mm should be considered for PCNL. Based on numerous reports, stone clearance and complications in horseshoe kidneys appear to be no different than for PCNL on orthotopic kidneys.

SWL can be considered for stones less than 1.5 cm in diameter located in the renal pelvis or nondependent upper pole and mid-pole calyces. Stone-free rates of 28% to 80% have been reported, with an average closer to 58%. Moreover, multiple treatment sessions are almost always necessary (Lampel et al, 1996; Elliott et al, 2010; Ray et al, 2011; Tan et al, 2013). On average, a higher number of shocks are necessary per treatment session, and a higher re-treatment rate is found versus similar stones in orthotopic, anatomically normal kidneys (Chaussy and Schmiedt, 1984; Drach et al, 1986; Lingeman et al, 1986).

In a series of 11 patients by Vandeursen and Baert (1992), an average of 3.8 treatment sessions per renal unit were required to achieve a 55% stone-free rate, whereas the series by Ray and colleagues (2011) showed an average of 1.7 SWL sessions for a stone-free rate of 39%. In addition, Ray and colleagues (2011) reported an abysmal 9.1% stone-free rate and 25% treatment success rate after single-session SWL at 3 months in 41 patients with horseshoe kidneys. In this series, 73% of patients required additional treatments in the form of repeat SWL, PCNL, or URS, and stone-free rate and overall success rate improved to 39.1% and 63.6%, respectively (Ray et al, 2011). The efficiency quotient was disappointing, at 10.5%. Just as SWL efficacy diminishes as stone burden increases in anatomically normal kidneys, so too it diminishes in horseshoe kidneys with increasing stone burden. Sheir and colleagues (2003) found superior stone-free rates of 79% for stones up to 15 mm, compared with 53% for stones larger than 15 mm. Kirkali and colleagues (1996) similarly found poor stone-free rates (28%) for stones larger than 10 mm.

Before SWL treatment, UPJO and poor pelvicalyceal drainage must be excluded, because these are not uncommon in horseshoe kidneys and severely curtail SWL success. The more medial and central location of the horseshoe kidney makes it more difficult to properly target calyceal and renal pelvis stones because of the

overlying vertebrae, pelvic bones, and bowel gas. Anteromedially located calyceal stones present the greatest difficulty. Positioning patients in the prone position or in the modified supine position can optimize stone targeting and is often necessary for stones situated below the pelvic brim (Jenkins and Gillenwater, 1988; Gupta and Lee, 2007). In addition, long skin-to-stone distances are frequently encountered in horseshoe kidneys, which can also hinder SWL efficacy. When SWL is chosen and skin-to-stone distances are outside of the focal zone of the lithotripter, a “blast path” technique can be used, during which the stone is targeted along the same axis but beyond F2, and relies on shock wave energy transmission past F2 to fragment the stone (Locke et al, 1990).

URS is challenging in horseshoe kidneys owing to the high ureteral insertion and tortuous course of the anteriorly displaced ureter. The need for ureteral dilation is not uncommon, and ureteral access sheaths, if able to be placed safely, can significantly expedite repeated entry to and withdrawal from the pelvicalyceal system. Flexible ureteroscopes are almost always necessary to access renal stones in a retrograde fashion, and the use of small-caliber nitinol baskets and holmium laser fibers can minimize loss of URS tip deflection. **Given the aberrant anatomy, ureteroscopy appears to be ideally limited to stone burdens 2 cm or less.** Moreover, staged procedures are common when approaching these stones ureteroscopically, and particularly so among the largest stones. Given the often compromised drainage associated with horseshoe kidneys, fragmented stones should be basket extracted rather than left in situ and left to pass spontaneously.

A number of small retrospective series report favorable surgical outcomes and low morbidity with URS for stone burdens less than 2 cm in horseshoe kidneys (Andreoni et al, 2000; Weizer et al, 2005; Symons et al, 2008). No reports focus on larger stone burdens, and none compare URS with SWL or PCNL in a direct fashion. Atis and coworkers (2013) reviewed outcomes in 20 patients with 25 stones in horseshoe kidneys. Mean stone size was 17.8 mm and stone-free rate after a single procedure was 70%. Weizer and colleagues (2005) detailed the URS outcomes in 4 patients with horseshoe kidneys and four pelvic kidneys. Mean stone size was 1.4 cm, complete stone clearance was found in 75% of patients, and 88% of patients were symptom free after the procedure. Finally, Molimard and associates (2010) reported results in 17 patients with horseshoe kidneys, 4 of whom had undergone failed previous PCNL and 8 of whom had undergone failed prior SWL. In this series, mean stone burden was 16 mm, and an average of 1.5 procedures per patient were required to achieve an 88% stone-free rate, which included residual fragments smaller than 3 mm. Thus, URS can render patients stone free more than 70% of the time when stone burdens are less than 2 cm, although a staged approach may be necessary at least half the time.

PCNL is the treatment of choice for stone burdens 2 cm and greater in horseshoe kidneys, with treatment results similar to those obtained in normal kidneys. It is also the preferred method when less invasive methods, such as SWL and URS, fail to adequately treat lesser stone burdens, or when stone density may further decrease expected successful treatment with those methods. Stone-free rates are superior to those achieved with SWL or URS. Overall, an average stone-free rate of 82% to 84% has been reported, with contemporary series describing stone-free rates of 90% or greater with the concomitant use of flexible nephroscopy (Janetschek and Kunzel, 1988; Esuvaranathan et al, 1991; Jones et al, 1991b; Al-Otaibi and Hosking, 1999; Raj et al, 2003; Shokeir et al, 2004; Gupta et al, 2009b; Elliott et al, 2010; Ozden et al, 2010).

Familiarity with the anatomy of the horseshoe kidney is key to safely performing PCNL. Percutaneous access to the horseshoe kidney is often preferentially directed at a posterior upper pole calyx, which results in an access tract situated more medially than those created in orthotopic kidneys. This is because the malrotation of the horseshoe kidney positions the renal pelvis anteriorly and angles the posterior calyces almost directly posteriorly compared with normally positioned kidneys. Percutaneous tracts through the posterior upper pole calyx provide easy access into the renal pelvis and laterally positioned calyces (Elliott et al, 2010).

However, the high insertion of the lower pole, combined with the anteromedially situated calyces, will often require a flexible nephroscope to reach all calyces in the system. In addition, the more anteriorly and centrally positioned horseshoe kidney causes the access tract to be longer, and this may necessitate use of extra-long access sheaths, nephroscopes, and instruments, especially in obese patients. A retrorenal colon may accompany horseshoe kidneys, and given the altered anatomy, preoperative CT is recommended to fully evaluate the safest percutaneous tract. Supracostal access is rarely necessary because the entire horseshoe kidney is often situated below the 12th ribs, and consequently pleural injuries are rare (Raj et al, 2003; Shokeir et al, 2004). The Clinical Research Office of the Endourological Society (CROES) PCNL study group showed that median operative time was longer and percutaneous access more likely to be unsuccessful (5% vs. 1.7%) in horseshoe kidneys than orthotopic kidneys (Osther et al, 2011).

Laparoscopic assistance is only rarely used for stone surgery on horseshoe kidneys and only a few case reports exist. In general, this adjunctive technique can be useful when particularly large renal pelvis stones exist or when concomitant UPJO exists and pyelolithotomy with or without pyeloplasty is contemplated (Stein and Desai, 2007; Symons et al, 2008; Tan et al, 2013).

Renal Ectopia. Ectopic kidneys are most commonly situated in the pelvis, with the incidence of pelvic kidneys estimated at 1 in 2200 to 1 in 3000 patients. More rarely, ectopic kidneys can be located in the abdomen, in the thoracic cavity, or in a crossed, retroperitoneal location. The approach to kidney stone treatment in these instances should be highly tailored to the specific individual, stone burden, and kidney location, along with any associated kidney drainage impediments. Similarly to horseshoe kidneys, evaluation for impaired renal drainage or UPJO is prudent before embarking down a treatment path, because pelvic kidneys are routinely malrotated and often have a high ureteral insertion or UPJO, which can further hinder stone fragment passage (Gleason et al, 1994). In the appropriate setting, SWL, URS, PCNL, and laparoscopy can all be selectively applied to achieve good stone clearance rates.

Shock wave lithotripsy achieves stone-free rates of 25% to 92%, although multiple treatment sessions are the norm (Theiss et al, 1993; Talic, 1996; Semerci et al, 1997; Gallucci et al, 2001; Sheir et al, 2003; Tunc et al, 2004). With the pelvic kidney shielded posteriorly by the bony pelvis, prone positioning is often necessary to improve shock wave delivery to the pelvic kidney stones when this technique is selected. If treatment with SWL is entertained for stones in ectopic kidneys, renal functional studies evaluating renal drainage (e.g., renography) are recommended, because the presence of impaired kidney drainage is a relative contraindication to proceeding with SWL. Ureteroscopy has also been described for pelvic and ectopic kidneys with stone-free rates of 75% after a single setting, showing that URS and SWL can achieve similar outcomes but URS is more efficient (Weizer et al, 2005). This is likely because of the active fragment removal with URS, whereas SWL requires spontaneous drainage of fragments, which can be problematic in a poorly draining ectopic kidney. Ureteral access sheaths can greatly facilitate re-entry into the ectopic kidney; however, their placement should be undertaken with caution because the associated ureters can be quite tortuous and perhaps prone to injury with sheath advancement.

Stones within pelvic kidneys present unique challenges when one is attempting to perform PCNL because clear access to the kidney is seldom encountered. Nonetheless, stone clearance rates are better for PCNL than for SWL, at least in part because of active stone extraction and the ability to perform flexible nephroscopy. Traditional posterior access is hampered by the bony pelvis, and even when it can be safely accomplished can result in debilitating femoral neuropathy (Monga et al, 1995). Patients must usually be in the supine position, and safe access into the collecting system is rarely feasible without CT or laparoscopic assistance, although it has been described ultrasonographically. Desai and Jasani (2000) report a technique exploiting transperitoneal ultrasound guidance for supine PCNL in pelvic kidneys in which the ultrasound probe is used to both target the kidney and maneuver intervening intra-abdominal contents out of the way of the proposed access tract.

(Desai, 2009). In this series of 16 patients, 1 experienced a bowel injury. Given its limitations, this method is unlikely to prove successful in overweight or obese patients. Rare case reports of transhepatic, transiliac, and trans-sciatic punctures have been described; however, such approaches should be considered only in the highly selected patient and done in conjunction with CT guidance and the interventional radiologist (Matlaga et al, 2006b).

Laparoscopic assistance has been used during PCNL to ensure a safe percutaneous access tract into the kidney by mobilizing and displacing any overlying intestines and directly observing the needle puncture into the kidney (Fig. 53-10). This was first described by Eshghi and associates (1985), and others have followed suit since then (Holman and Toth, 1998; Maheshwari et al, 2004; Gowel et al, 2006; Matlaga et al, 2006b; El-Kappany et al, 2007; Elbahnasy et al,

2011). Excellent stone-free rates are reported and overall morbidity is low. Most of these techniques use a Trendelenburg position to mobilize the intestines during a transperitoneal procedure. To minimize the risks of urinary leakage to the peritoneal cavity, appropriate postoperative drain placement is recommended. Zafar and Lingeman (1996) have described a simultaneous laparoscopic nephrostomy closure and ureteral catheter placement during pelvic kidney PCNL, thereby avoiding the need for an intra-abdominal drain. An entirely extraperitoneal approach to minimize the risk of intraperitoneal leakage has also been described (Holman and Toth, 1998).

Purely laparoscopic or robotic approaches to pelvic and ectopic kidneys provide high success with low morbidity and are particularly appealing treatment options when simultaneous repair of UPJO is planned (Chang and Dretler, 1996; Hoenig et al, 1997; Kamat and Khandelwal, 2004; Nayyar et al, 2010; El-Bahnasy et al, 2011). The concept is the same as for horseshoe kidneys: A pyelotomy is made to clear renal pelvis stones, and a flexible nephroscope and stone basket are then inserted through one of the laparoscopic trocars to access and clear calyceal stones. Stone-free rates of 80% to 100% have been reported (Ramakumar and Segura, 2000; Atug et al, 2005; Masson and Hoenig, 2008). Most authors use a transperitoneal approach, although Gaur and colleagues detail a retroperitoneal approach (Gaur et al, 1994).

For kidney stones in ectopic and horseshoe kidneys, SWL is a reasonable treatment option when stones are smaller than 1.5 cm and there is no UPJO or demonstration of poor renal drainage. URS may also be reasonable for stone burdens less than 2 cm, although they may require multiple treatment sessions. For stone burdens of 2 cm or more, PCNL or laparoscopy should be the initial treatment; a combination of the two procedures is expected for pelvic kidneys. When UPJO is confirmed, laparoscopy is the treatment of choice because it can address the stones and provides the highest success rate for UPJ repair.

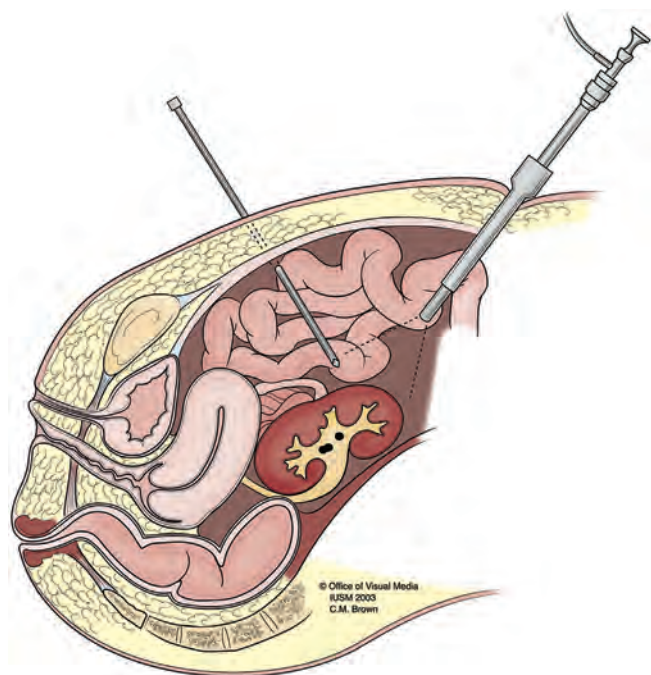


Figure 53-10. Laparoscopy-assisted percutaneous nephrolithotomy technique in which the bowel is reflected off the ectopic kidney before radiographically and laparoscopically guided percutaneous access. (© 2003, Indiana University Medical Illustration Department.)

Lower Pole Calculi

The preferred treatment of lower pole renal calculi has generated appreciable controversy over the last few decades (Tolley and Downey, 1999; Raman and Pearle, 2008; Yuruk et al, 2010). Regarding non-lower pole intrarenal calculi, stones within the lower pole tend to have worse surgical stone clearance rates compared with other locations when stratified by size and composition. The management strategy for lower pole stones continues to evolve as ureteroscopic capabilities improve and the limitations of the newer generations of shock wave lithotripters become more evident (Fig. 53-11).

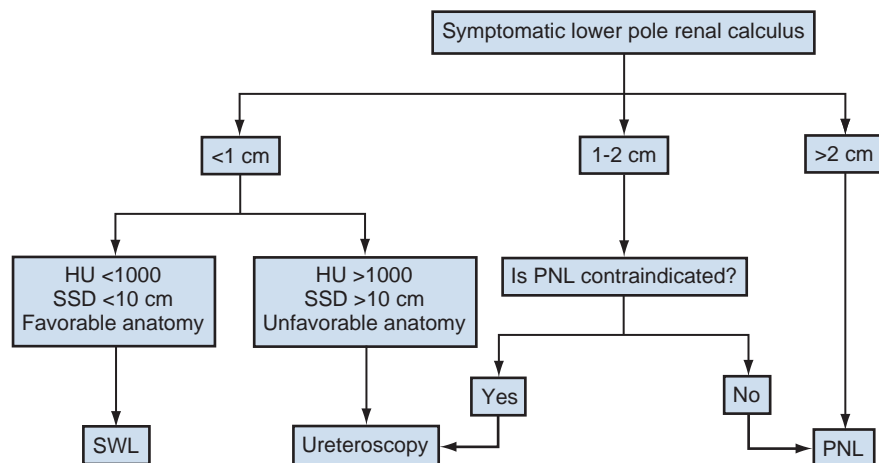


Figure 53-11. Treatment algorithm: lower pole stones. HU, Hounsfield unit; PCNL, percutaneous nephrolithotomy; SSD, skin-to-stone distance; SWL, shock wave lithotripsy. (Modified from Galvin DJ, Pearle MS. The contemporary management of renal and ureteric calculi. *BJU Int* 2006;98:1283-8.)

As discussed previously in the section on stone factors, overall stone burden is the main driver of treatment decisions for lower pole stones. Treatment decisions are most conveniently divided into stone burdens less than 1 cm, stone burdens of 1 to 2 cm, and stone burdens greater than 2 cm. Lower pole kidney stone burdens 2 cm or larger in size are best approached with PCNL because the collective evidence shows that PCNL offers a considerably higher stone-free rate in a single procedure than URS or SWL. For lower pole stone burdens of 1 cm to 2 cm, PCNL remains the most efficient treatment option, although it is more invasive, and is preferred when prior URS or SWL attempts have been unsuccessful. Ureteroscopy is the treatment modality of choice when PCNL is completely or relatively contraindicated and is a reasonable first-line option in experienced hands. In general, SWL results are disappointing for lower pole stone burdens over 1 cm, and therefore SWL should not be recommended as an initial treatment modality for such stones. For lower pole stones 1 cm or less, stone characteristics and patient factors become relatively more important than for larger stone burdens and should be incorporated into treatment recommendations. Stone burdens 1 cm or less in size may be reasonably approached with any modality including observation if completely asymptomatic, although future stone disease progression is likely. Lower-density stones that are less dense in nature and are in nonobese patients

without acute lower pole infundibulopelvic angles are among the few in the lower pole for which SWL provides a reasonable chance of success. Meanwhile, URS, with improved ureteroscope and instrumentation, has allowed improved access into the lower pole and expanded its use. Finally, PCNL should be used for stones that have failed less invasive treatment modalities or are extremely large or dense.

Historically, shortly after its clinical dissemination, it was realized that SWL provided unsatisfactory results for larger lower pole stones ([Consensus conference, 1988](#)). In fact, multiple series over the last 20 years have shown stone-free rates of approximately 50% or less for lower pole stones 1 to 2 cm, and less than approximately 30% for lower pole stones larger than 2 cm ([Table 53-1](#)). It was hypothesized that the gravity-dependent nature of the lower pole and certain lower pole anatomic characteristics may impede stone clearance ([Sampaio and Aragao, 1992, 1994](#); [Elbahnasy et al, 1998](#)). Sampaio and Aragao executed a series of elegant anatomic studies to better define the anatomy of the lower pole by creating polyester resin endocasts of the pelvicalyceal collecting system using adult cadaveric kidneys. They hypothesized that a number of different lower pole anatomic features may reduce stone passage, including a narrow lower pole infundibulum (width <4 mm), an acute lower pole infundibulopelvic angle (<90 degrees), and multiple lower pole infundibula rather than a single infundibulum ([Fig. 53-12](#)).

TABLE 53-1 Treatment Outcomes for Lower Pole Calculi

STUDY	STONE-FREE RATE (%)		
	SHOCK WAVE LITHOTRIPSY	URETEROSCOPY	PERCUTANEOUS NEPHROLITHOTOMY
LOWER POLE CALCULI <1 CM			
Lingeman et al, 1994	74		100
Elashry et al, 1996		87	
Elbahnasy et al, 1998	52	62	
Grasso and Ficazzola, 1999		82	
Gupta et al, 2000	72		
Kourambas et al, 2000		85	
Albala et al, 2001	63		100
Hollenbeck et al, 2001		82	
Schuster et al, 2002		79	
Sorensen and Chandhoke, 2002	74		
Pareek et al, 2005	47		
Pearle et al, 2005*	35	50	
LOWER POLE CALCULI 1 TO 2 CM			
Lingeman et al, 1994	56		89
Grasso and Ficazzola, 1999		71	
Saw and Lingeman, 1999	55		
Gupta et al, 2000	51		
Albala et al, 2001	23		93
Hollenbeck et al, 2001		63	
Madbouly et al, 2001	57		
Schuster et al, 2002		64	
Sorensen and Chandhoke, 2002	41		
Sumino et al, 2002	51		
Kuo et al, 2003*		31	76
LOWER POLE CALCULI >2 CM			
Lingeman et al, 1994	33		94
Grasso et al, 1998		76	
Grasso and Ficazzola, 1999		65	
Albala et al, 2001	14		86
El-Anany et al, 2001		60	

*Computed tomography-measured outcome.

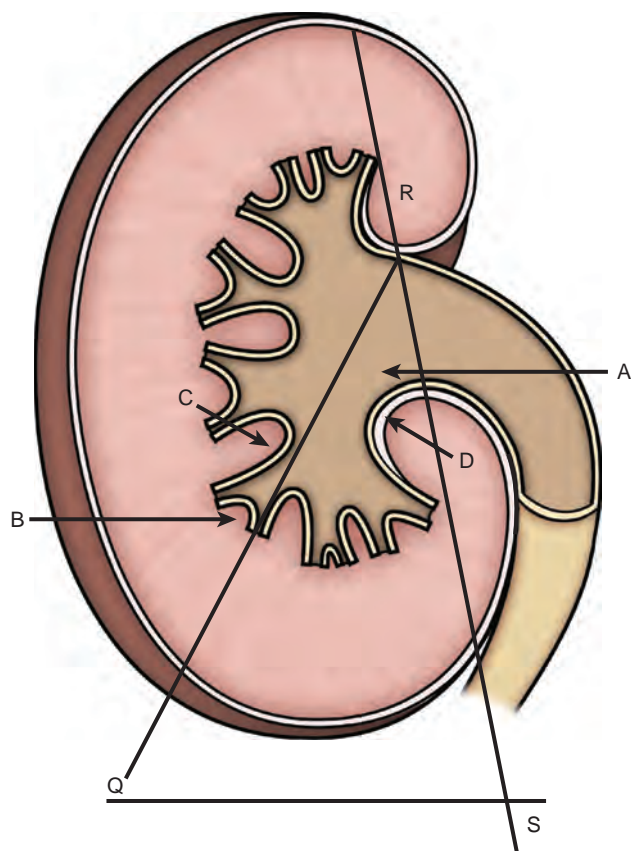


Figure 53-12. Measurement scheme for lower pole anatomy. Lower pole infundibular length: measure A to B. Lower pole infundibular width: measure C to D. Lower pole infundibulopelvic angle: measure QRS angle. (From Albala DM, Assimos DG, Clayman RV, et al. Lower pole I: a prospective randomized trial of extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy for lower pole nephrolithiasis—initial results. *J Urol* 2001;166:2072–80.)

Similar findings have been demonstrated in subsequent investigations, suggesting that lower pole infundibular length greater than 3 cm, infundibular width less than 5 mm, and infundibulopelvic angle less than 70 degrees inhibit lower pole stone clearance during SWL (Sabnis et al, 1997; Elbahnasy et al, 1998). It is interesting to note that other studies have shown no effect of lower pole anatomy on stone clearance after SWL (Albala et al, 2001; Sorensen and Chandhoke, 2002).

In an attempt to improve stone clearance rates after SWL of lower pole calculi, a number of supplemental therapies have been proposed and examined. McCullough (1989) anecdotally reported that postural drainage may assist in the elimination of retained fragments from dependent calyces. Brownlee and associates (1990) subsequently treated patients with residual lower pole fragments with controlled inversion therapy, using intravenous hydration, inversion, and percussion. D'a Honey and associates (2000) reported a pilot study to determine whether mechanical percussion with inversion therapy and furosemide-induced diuresis can move stone fragments out of the lower pole of the kidney. At a mean time of 63 days after SWL, this group reported an 83% stone passage rate. In a subsequent study, Pace and associates (2001) compared the effectiveness of mechanical percussion, inversion, and furosemide-induced diuresis with observation for elimination of lower calyceal fragments after SWL. They reported that 40% of patients with residual lower pole fragments treated with this regimen became stone free compared with 3% in the observation group; the observation group was then treated with this regimen as part of a crossover design, and 43% were rendered stone free.

Chiong and colleagues (2005) performed a similar study and showed that percussion, diuresis, and inversion therapy improved

stone-free rates after SWL for lower pole stones. A recent Cochrane review included the studies by Pace and colleagues and Chiong and colleagues and concluded that overall evidence was limited, but that percussion, diuresis, and inversion were safe, were well tolerated, and appeared to modestly aid in stone passage after SWL (Liu et al, 2013). Other authors have reported lower pole irrigation techniques as adjuncts to SWL (Nicely et al, 1992; Graham and Nelson, 1994). More recently, pharmacotherapy with potassium citrate and thiazide diuretics has been described (Soygur et al, 2002; Arrabal-Martin et al, 2006). However, at this point in time none of these techniques has gained widespread acceptance.

The superiority of PCNL over SWL in clearing lower pole stones first became widely evident in a meta-analysis performed by Lingeman and colleagues in 1994 (Lingeman et al, 1994). In this report, PCNL achieved an overall 90% stone-free rate compared with 60% for SWL. Subgroup analysis stratified by stone burden showed that stones 10 mm or smaller had a 74% clearance rate with SWL and 100% clearance rate with PCNL, whereas stones 10 to 20 mm had a 56% clearance rate with SWL and an 89% clearance rate with PCNL (see Table 53-1). An even larger difference was appreciated for lower pole stones larger than 2 cm, for which stone-free rates were 94% for PCNL and only 33% for SWL. On regression analysis, increasing stone size was associated with decreasing stone clearance for SWL but had no demonstrable effect on PCNL.

After these retrospective data, a number of prospective trials ensued confirming the dominance of PCNL over SWL for the vast majority of lower pole stones (Albala et al, 2001; Yuruk et al, 2010). In the multicenter, prospective, randomized Lower Pole I study by Albala and associates (2001), stone-free rates as evaluated by nephrotomograms at 3 months after treatment were 95% for PCNL and only 37% for SWL. Stone-free rates for SWL were particularly low for stones 10 mm and larger: 23% for stones 1 to 2 cm, and 14% for stones larger than 2 cm. Yuruk and colleagues (2010) randomized 90 patients with lower pole stones 2 cm or smaller to SWL, PCNL, or observation. PCNL achieved a 97% stone-free rate compared with a 55% stone-free rate with SWL when patients were assessed at 3 months after treatment. As an additional component of this study, dimercaptosuccinic acid (DMSA) renal scintigraphy was performed in all patients, and a higher percentage of SWL patients (16%) were found to have developed renal scarring compared with the PCNL cohort (3%). Of note, these SWL patients had received three treatment sessions with an average of 1863 shocks per session. Ozturk and colleagues retrospectively reviewed 221 SWL, 144 PCNL, and 38 URS procedures and showed a 94% success rate with PCNL, a 76% success rate with SWL, and a 73% success rate for URS (Ozturk et al, 2013).

In an analogous fashion, SWL has been compared with URS for lower pole stone treatment, and the most contemporary results favor URS, although this was not always the case. In the seminal prospective, multicenter randomized trial by Pearle and colleagues (2005) comparing URS with SWL for lower pole stones 1 cm or smaller, stone-free status was accomplished in 50% of URS cases and only 35% of SWL cases, although the difference was not found to be statistically significant. Not unexpectedly, the convalescence time was less, and the health care–related quality of life measures were better for the SWL cohort (Pearle et al, 2005). More recently, Sener and colleagues performed a single-center randomized trial comparing SWL with URS for lower pole stones 1 cm or less in diameter (Sener et al, 2014). Treatment success was defined as stone-free or residual fragments less than 3 mm, and patients with acute infundibulopelvic angles (<30 degrees) were excluded. Stone-free status was achieved in 100% of URS cases and 91.5% of SWL cases, although an average of 2.7 SWL sessions per patient were necessary.

Recent series evaluating outcomes for lower pole stone burdens of 1 to 2 cm further highlight the ascendancy of URS over SWL, especially with respect to treating increasing lower pole stone burden. Stone-free rates of 85% and higher have been reported for single-session URS compared with 54% to 68% for multisection SWL (El-Nahas et al, 2012; Resorlu et al, 2013; Singh et al, 2014). Moreover, re-treatment rates and auxiliary treatment rates are

consistently higher for SWL, whereas complication rates are commensurate between the two modalities. These studies echo the results of [Pearle and coworkers \(2005\)](#), as voiding symptoms and convalescence time are more favorable for SWL than URS.

Since the early reports of URS for lower pole calculi in the mid and late 1990s, endourology has witnessed considerable progress in instrument design and surgical technique. These, in turn, have made URS more effective than SWL in treating lower pole stones ([Elashry et al, 1996](#); [Grasso and Ficazzola, 1999](#)). Smaller ureteroscopes with improved tip deflection and better stone manipulation instruments aid in accessing and fragmenting lower pole stones. Nitinol stone baskets have been used to reposition stones from the lower pole to more optimal intrarenal positions for lithotripsy, such as the middle or upper pole calyces ([Kourambas et al, 2000](#)). Stone-free rates approaching and exceeding 90% have been reported when stones were repositioned out of the lower pole, compared with stone-free rates closer to 80% when stones were fragmented in situ within the lower pole ([Kourambas et al, 2000](#); [Schuster et al, 2002](#)). Furthermore, contemporary URS outcomes appear to depend on lower pole infundibulopelvic angle, as was shown by [Resorlu and colleagues \(2012b\)](#), who found that URS was successful in 91% of cases when the angle was greater than 45 degrees versus only 65% of the time with more acute angles. In this same study, infundibular length and width did not affect URS outcomes.

Given the advancements in ureteroscopic design and technique, a number of investigators have sought to compare URS and PCNL for lower pole stones ([Kuo et al, 2003](#); [Bozkurt et al, 2011](#); [Kirac et al, 2013](#)). The Lower Pole Study Group compared URS and PCNL for lower pole stones of 1 cm to 2.5 cm. PCNL achieved a 71% stone-free rate, whereas URS achieved a 37% stone-free rate as determined by CT. The length of hospitalization was shorter for those undergoing URS; however, overall convalescence was not statistically different and was attributed to ureteral stent-related morbidity in the URS cohort ([Kuo et al, 2003](#)). [Bozkurt and associates \(2011\)](#) retrospectively compared outcomes between PCNL and URS for lower pole stones of 1.5 cm to 2 cm. Single-stage stone-free rates of 93% (PCNL) and 89% (URS) were appreciated. The PCNL group required more blood transfusions, but otherwise complications were similar between groups. It is important to recognize that this was not a randomized study, and patients with unfavorable lower pole anatomy (acute infundibulopelvic angles, small infundibular width) were preferentially treated with PCNL.

The same group also retrospectively compared URS with mini-PCNL for stones smaller than 1.5 cm and found equivalent stone-free rates of 89% between the two modalities. Not surprisingly, operative time, mean fluoroscopy time, and length of hospital stay were longer for PCNL ([Kirac et al, 2013](#)). Taken collectively, these data suggest that URS performed by clinicians experienced with the technique can produce excellent stone-free rates approaching those of PCNL. **The key to excellent URS outcomes appears to be careful patient selection, which includes those patients with favorable lower pole anatomy (nonacute lower infundibulopelvic angle, wide lower pole infundibulum).**

Not enough data exist to determine the optimal place for mini- and micro-PCNL in the treatment of lower pole stones, although initial results are encouraging in terms of both stone clearance and overall morbidity.

URETERAL CALCULI

Just as for renal calculi, the urologists's armamentarium to surgically treat ureteral stones consists of four minimally invasive modalities including SWL, URS, PCNL, and laparoscopic or robotic-assisted stone surgery. Open ureteral stone surgery is rarely performed when access to minimally invasive modalities exists and is often reserved for instances in which less invasive options have failed. There appears to be an evolving paradigm shift in the surgical treatment of upper tract stones, with an increasing use of URS and a reciprocal decreasing use of SWL for upper urinary tract stone disease ([Lee and Bariol, 2011](#); [Ordon et al, 2014](#)). Determining the

KEY POINTS: RENAL CALCULI

- SWL success is highest in stones 1 cm or smaller, 800 to 900 HU or lower, and in a non–lower pole location.
- PCNL offers the highest successful stone treatment for stones larger than 2 cm (including staghorn configuration), across all density measurements, and in all intrarenal locations.
- URS offers excellent success for all stone locations, although it may have decreased effectiveness in the lower pole.
- URS may be safely performed in patients with active anticoagulation or antiplatelet therapy.
- The outcomes of PCNL and URS are independent of the patient's BMI, whereas SWL success falls with increasing obesity.
- Stones that are symptomatic, obstructing, or associated with infections should be treated to ensure clearance.

BOX 53-4 Factors Affecting Management of Ureteral Stones

STONE-RELATED FACTORS

Location
Size
Composition
Degree of obstruction

CLINICAL FACTORS

Symptom severity
Patient's expectations
Associated infection
Solitary kidney
Abnormal ureteral anatomy

TECHNICAL FACTORS

Available equipment
Cost

optimal treatment for a given patient is not always straightforward and depends on stone-related factors, clinical factors, and technical factors ([Box 53-4](#)). It is the interplay of these factors and the familiarity of the urologist with each surgical technique that ultimately determine the best treatment modality for a given patient. The purpose of this section is to provide a framework to help guide the urologist in matching a given patient's unique clinical situation and ureteral stone disease characteristics to the most effective and least morbid surgical therapy.

Natural History

When a renal calculus begins to pass, it moves from the kidney into the UPJ and into the ureter proper. At that point, depending on the size of the stone relative to the ureter throughout its course, the stone will begin to obstruct the kidney. The first manifestation of this is an increase in the intra-collecting system pressure, which will stretch the renal pelvis, calyces, and renal capsule. It is during this phase that the traditional colic of a stone episode will begin.

This increase in intraluminal pressure will increase the hydrostatic pressure exerted on the walls of the renal pelvis and ureter, which can cause the failure of normal peristalsis. Pressure further increases at that point, with direct transmission to the nephron tubules, with a resulting drop in the glomerular filtration rate (GFR). Pressure will subsequently decrease to the levels that were present before obstruction developed, usually within 12 to 24 hours. Accordingly, the renal colic episode caused by a stone is often limited to severe pain from the acute renal stretch, followed by gradual resolution of the pain. Further movement of the stone

down the ureter can relieve the pressure and reobstruct further distally, explaining the intermittent nature of renal colic as a stone passes.

Long-term obstruction can cause permanent damage to the kidney's function; therefore, regardless of the absence of pain or infection, a stone must either pass spontaneously or be surgically treated. Key to the passage of a stone is ureteral peristalsis, not hydrostatic pressure (Lennon et al, 1997). When the ureter is not otherwise obstructed, the chief determinant of stone passage is the diameter of the stone in its transverse orientation (Ueno et al, 1977). Next most important is the location of the stone within the ureter at presentation, with a review of the literature demonstrating a 71% chance of passage of a distal ureteral stone versus 22% for proximal stones (Morse and Resnick, 1991). Additional evidence supports the idea that the likelihood of spontaneous passage may be directly related to stone location at the time of presentation (Hubner et al, 1993; Coll et al, 2002).

With respect to size as a predictor of spontaneous passage, meta-analysis of the available literature (as described in the AUA ureteral stone guidelines) demonstrates a 68% chance of passage for stones 5 mm or smaller, and an estimated 47% chance for stones 6 to 10 mm in size (Preminger et al, 2007). These rates can be enhanced with medical expulsive therapy (MET) using either calcium channel blockers (such as nifedipine) or α -receptor blockers (such as tamsulosin). α -Blockers appeared to offer an overall greater increase of spontaneous passage, with an absolute increase in chances of passage calculated at 29% across all stones. Thus, for ureteral calculi 5 mm or smaller, MET with expectant management is a reasonable therapeutic choice (Table 53-2).

Pretreatment Assessment

The pretreatment assessment, including medical history, imaging, and laboratory testing, for ureteral stones is similar to that for renal stones, and the reader is directed to the previous section on this topic in the renal calculi section of this chapter. Particular attention should be directed toward the duration of symptoms, given the fact that long-term obstruction can result in irreversible nephron loss. Any suggestion of fever in the setting of a ureteral stone strongly suggests the presence of infection proximal to the point of obstruction, and, regardless of how the patient appears at presentation, there should be a low threshold to proceed with urgent or immediate urinary tract drainage.

Specific symptoms may give clues to the course of the episode: New-onset urgency and frequency may herald a stone at the UVJ irritating the bladder, or the sudden relief of flank pain might indicate either passage or forniceal rupture as the pressure in the collecting system dramatically decreases. Assessment of renal function is paramount because ureteral stones are often obstructing at the time of presentation, and therefore renal function may be impaired

by obstruction, dehydration, or a combination of both. The associated physiologic stress of an acutely obstructing stone can lead to white blood cell (WBC) demarginalization and an elevated serum WBC count. Thus, leukocytosis in these patients may or may not represent an actual infection. In addition, it should be kept in mind that urinary tract stones frequently lead to pyuria and leukocyte esterase positivity on urinalysis, and these findings do not always represent an active UTI. However, if there is any concern regarding an associated UTI, then the immediate focus should be on urinary tract decompression rather than definitive surgery.

Stone Factors

Treatment Decision by Localization

Proximal and Mid-Ureter. The chief determinant of the optimal treatment for calculi in these locations is size. As previously mentioned, those which are more proximal and greater in size are significantly less likely to pass spontaneously. There is a paucity of data on the effectiveness of MET use in proximal and mid-ureteral stones, although since many of these stones do migrate distally, presumptive use of MET is not contraindicated (Hollingsworth et al, 2006; Seitz et al, 2009).

For stones that do not move in a reasonable time frame, or in the setting of recurring severe pain, or if the patient prefers, surgical therapy is indicated. Primary options include SWL and URS, although PCNL and antegrade nephroscopy may be indicated for select cases. Pooled data, as evaluated in the AUA ureteral stone guidelines, have defined outcomes in proximal and mid-ureteral stones (of all sizes) in patients who underwent SWL, with overall 82% and 73% treatment success rates, respectively (Preminger et al, 2007). When considering proximal ureteral stones that are 1 cm or smaller, SWL success rises among these pooled series to 90% (85% to 93%), and 84% (65% to 95%) for mid-ureteral stones. For stones larger than 1 cm, rates of complete stone clearance drop in both groups, to 68% for proximal and 76% for mid-ureter stones.

Similarly, the guidelines pooled numerous studies to evaluate outcome success for URS for these locations and sizes, demonstrating an overall success of 81% for proximal and 86% for mid-ureteral stones (Preminger et al, 2007). Calculi 1 cm or smaller again demonstrated higher success rates in both groups than did larger stones. A further breakdown of selected studies assessing stone-free rates after ureteroscopy for proximal ureteral stones is shown in Table 53-3.

It is interesting to note that the likelihood of postoperative results requiring additional procedures was 1.5 with SWL for these larger stones, and only 1.07 for URS. Of related interest, the cost-efficiency of management of proximal ureteral stones has been shown to be superior for URS when compared with SWL, when used as the initial treatment procedure (Lotan et al, 2002).

TABLE 53-2 Likelihood of Spontaneous Stone Passage

STUDY	NO. OF PATIENTS	NO. REQUIRING INTERVENTION (%)	NO. PASSING STONE (%)
STONE SIZE <5 MM			
Miller and Kane, 1999	59	4 (7)	55 (93)
Hussain et al, 2001	9	0 (0)	9 (100)
Coll et al, 2002	114	29 (25)	85 (75)
Kupeli et al, 2004	15	12 (80)	3 (20)
Weighted average	197	23	77
STONE SIZE >5 MM			
Miller and Kane, 1999	16	8 (50)	8 (50)
Hussain et al, 2001	15	6 (40)	9 (60)
Coll et al, 2002	73	42 (58)	31 (42)
Weighted average	104	54	46

TABLE 53-3 Ureteroscopic Treatment Outcomes for Proximal Ureteral Calculi

STUDY	NO. OF PATIENTS	MEAN STONE SIZE (mm)	STONE-FREE RATE (%)
Lam et al, 2002	31	8.2	97
Sofer et al, 2002	194	12.0	97
Aghamir et al, 2003	115	>10	75
Sozen et al, 2003	36	7.4	83
Fong et al, 2004	51	9.0	90
Wu et al, 2005	39	15.1	92
Lee et al, 2006	20	18.5	35
Preminger et al, 2007	2242	<10	80
		>10	79
Perez Castro et al, 2014	2611	81 mm ²	85

For very large proximal ureteral calculi not amenable to either SWL or URS (including large or dense stones, severe inflammatory response at the site of stone impaction that prevents passage of a guidewire from below, or associated ureteral pathology), a **percutaneous and antegrade approach may be ideal** (Maheshwari et al, 1999). Depending on the exact location within the ureter and calyx for percutaneous entry, such stones may be amenable to either rigid or flexible endoscopy. The opportunity to clear stone fragments using the access tract may offer optimal success for these challenging stones.

Lastly, laparoscopic and robotic ureterolithotomy have been described for proximal and mid-ureteral calculi, with success rates for stone clearance in selected cases of 93% to 100% (Hemal et al, 2010; Yasui et al, 2013). Significant discussion regarding such an approach, in many cases significantly more invasive than SWL, URS, or PCNL with antegrade endoscopy, should be undertaken with the patient when considering this option.

It is important to note that stones in a mid-ureteral location are typically handled in much the same way as proximal calculi, although some considerations relative to the pelvic anatomy will apply. With respect to SWL, the presence of the bony structures lying posterior to the ureter at this level can interfere with fluoroscopic or plain film imaging of the stone, as well as pose challenges to positioning the patient so that shock wave energy does not pass through the bone. Oblique or prone positioning may be required for SWL at this level.

Finally, URS for the mid-ureteral stone can often be accomplished with a semirigid ureteroscope; however, limitations caused by the iliac vessels, particularly in male patients, may be encountered. In addition, proximal migration of these stones can sometimes present a challenge with semirigid instrumentation. The availability of flexible ureteroscopes and the skills to perform flexible URS will improve the overall success rates and decrease complications (Perez Castro et al, 2014).

Distal Ureter. As discussed earlier, distal stones are most likely to pass with observation or MET (Preminger et al, 2007). The most typical site for impaction in this region of the ureter is at the UVJ; stones reaching this location often cause significant irritative symptoms owing to stimulation of the bladder, a clinical sign that helps localize them. When stones fail to pass, once again surgical therapy is indicated.

SWL and URS both remain the mainstays of treatment of distal ureteral stones. Once again, the AUA ureteral stone guidelines

TABLE 53-4 Ureteroscopic Treatment Outcomes for Distal Ureteral Calculi

STUDY	NO. OF PATIENTS	MEAN STONE SIZE (mm)	STONE-FREE RATE (%)
Pearle et al, 2001	32	6.4	91
Sofer et al, 2002	348	10.3	99
Zeng et al, 2002	180	6-20	93
Aghamir et al, 2003	247	<10	96
Sozen et al, 2003	464	8.8	95
Preminger et al, 2007	5952	<10	97
		>10	93
Perez Castro et al, 2014	4446	67 mm ²	94

present a detailed review of pooled studies to identify success rates in both procedures. Among reviewed series using SWL for distal ureteral stones, the overall success rate was 74%. When considering stones 1 cm or smaller, an overall success rate of 86% was noted, whereas stones larger than 1 cm yielded a success rate of 74% (Preminger et al, 2007). In the same ureteral calculi guidelines analysis, URS for the distal ureteral calculus was shown to yield a 94% overall success rate, with stones 1 cm or smaller at 97% and over 1 cm at 93% success rate. A further breakdown of selected studies assessing stone-free rates after ureteroscopy for distal ureteral stones is shown in Table 53-4.

When comparing SWL with URS for the distal stone, reviewing the combined data for SWL in this fashion, one must consider the variation in lithotripters used that would affect overall outcomes in the multitude of series. In one randomized controlled trial comparing SWL with URS for distal ureteral calculi up to 15 mm in size, SWL was equally as effective as URS (100% in both groups), although it should be noted that this series used only the highly effective HM3 lithotripter (Pearle et al, 2001).

All Locations. Additional factors to consider in addition to stone-free success rates in the choice of therapy include the following:

- The complications of therapy such as sepsis, steinstrasse, ureteral stricture, and ureteral injury
- Anesthetic requirements
- Bleeding risk in patients with anticoagulation or antiplatelet therapy
- Recovery expectations
- Potential need for adjunctive procedures

Treatment Decision by Stone Burden

As described earlier, SWL success for ureteral stones at all locations is significantly affected by the total stone burden, just as it is for renal calculi: The larger the stone(s), the less effective the treatment (Preminger et al, 2007). As a specific example, the success rates for SWL at the distal ureter were 86% for stones 1 cm or smaller and 74% for those larger than 1 cm, and such differences held true for all locations. In contrast, URS had a much smaller degree of variation in terms of success based on stone burden: 97% success for stones 1 cm or smaller and 93% for those larger than 1 cm.

In a cost-comparison study of the management of ureteral calculi, Lotan and colleagues demonstrated that URS was associated with a lower cost than SWL for proximal stones, even before factoring in the higher adjunctive procedure rate associated with SWL (Lotan et al, 2002). The prospective comparison of SWL to URS for

distal stones by Pearle and colleagues showed that the overall complication rate was lower for SWL (9%) compared with URS (25%), though this was shown to mostly be related to urinary retention or significant colic requiring emergency evaluation or admission for pain control (and more likely to be clarified as a “minor” complication in the current literature) (Pearle et al, 2001).

Treatment by Stone Composition

As discussed earlier with respect to renal calculi, stone composition, if known or able to be predicted radiologically, can be useful in selecting the most appropriate therapy. Brushite (calcium phosphate) stones, calcium oxalate monohydrate, and cysteine stones are all more resistant to SWL therapy and can be expected to have better rates at all sizes and locations with URS (Rudnick et al, 1999; Ahmed et al, 2008). Similarly to renal calculi, assessment of ureteral stone density based on the Hounsfield units on CT scan can offer valuable predictive ability as to the stone-free rate using SWL (Joseph et al, 2002; Gupta et al, 2005; Wang et al, 2005; El-Nahas et al, 2007). In identical fashion as well, skin-to-stone distance—reflected in body habitus—can be measured on the CT scan, again allowing more informed prediction of SWL success.

Therefore, where possible to obtain prior stone composition data or prediction of composition based on radiologic studies, this should be undertaken so as to best inform the patient regarding choices of therapy.

It should be clear that it is imperative to tailor therapy choices to the individual patient, after careful discussion of outcomes of treatment: success rates, adjunctive procedures, and treatment-related morbidity. Both patient factors (body habitus, coagulation status, medical comorbidities) and stone factors (location, burden, composition) must be considered when selecting the optimal treatment for ureteral calculi.

Ureteral Anatomic Factors

Megaureter

Congenital megaureter most often is seen in children and usually represents an abnormality of the distal ureter or ureterovesical junction (UVJ) in which there is either an aperistaltic segment (causing obstruction) or incompetent UVJ (causing reflux), which yields dilation of the ureter. The first description of this condition in the literature was by Caulk in 1923 (Caulk, 1923). Subsequently a number of attempts to classify megaureter were undertaken, culminating in the consensus of a committee made up of members of the American Academy of Pediatrics, Society of Pediatric Urological Surgeons, and the Society for Pediatric Urology. These criteria have remained the most comprehensive system for classifying the megaureter (Stephens, 1977). Under this system, megaureters can be identified as refluxing, obstructed, and nonrefluxing and nonobstructed.

The majority of megaureters that are obstructed or refluxing are discovered when symptomatic during childhood and may require surgical repair. Reports of nonoperative, conservative management have been published, suggesting that some of these will resolve with the evolution of the UVJ as the child grows (Pitts and Muecke, 1974; Oliveira et al, 2000). The most typical operative repair has been ureteral reimplantation with, or without, tapering, but a recent report suggests that short-segment megaureters may be able to be successfully managed with endoureterotomy (Christman et al, 2012).

Megaureter has been associated with stones in both the pediatric population and rarely the adult population (Rosenblatt et al, 2009). Management strategies will significantly depend on the patient's surgical history, if any, and on recognition of any intrinsic ureteral obstruction that exists independent of the stone's location. Previously reimplanted ureters may be difficult to access in retrograde fashion, limiting the ability to place stents or approach stones via URS. In addition, an obstructed megaureter must be expected to lead to difficulties passing fragments after URS is performed.

Guidance as to ideal management is limited, as only case reports or small series have been reported in adults. In a nonobstructed megaureter, MET, SWL, and URS are all viable initial strategies. In the obstructed megaureter, strategies to manage both the stone and the underlying pathology have included the following:

- Retropulsion of the stones to the kidney, treatment of the stones via PCNL, and repositioning the patient to perform ureteroneocystostomy (Kumar et al, 2014)
- Ureterolithotomy with ureteroneocystostomy, open (Solinas et al, 2010; Demirtas et al, 2013) or robotic-assisted laparoscopic (Hemal et al, 2009)
- Ureteroscopy with endoureterotomy (in short-segment cases <3 cm), which would make concomitant ureteroscopic treatment of stone possible (Christman et al, 2012)

Clearly, when considering stone treatment in patients with a megaureter, one must choose a strategy that will account for both the stone and the underlying ureteral pathology.

Duplicated Collecting System

Duplication anomalies of the collecting system arise from ureteral bud abnormalities during gestation, occurring with an incidence of approximately 0.8% and following the Weigert-Meyer “rule” (Schlussel, 2007). This principle explains that in complete duplications, separate ureters enter the bladder with the more medial and inferior orifice draining the upper pole while the more lateral and superior orifice drains the lower pole. In incomplete duplications, there is only one ureteral orifice on that side within the bladder, with a variable level of bifurcation of the separate ureters which lead to the upper and lower moieties.

There are limited reports describing URS management of stones in partially or completely duplicated systems, but it is clear that ureteroscopy for these systems is little different from the more common single ureter. In the setting of a complete duplication, retrograde pyelography should be performed for each orifice to confirm which ureter contains the stone to be treated, and then treatment proceeds as usual.

In partial duplications, retrograde pyelography should be performed to locate the level of bifurcation in addition to the stone, with recognition of the fact that an intramural ureter location of the division of the two systems is most common (Rich, 1988). This can potentially inhibit visualization if the retrograde catheter is past the point of bifurcation. In this situation, ureteroscopy, following dilation of the ureteral orifice when necessary, can be used to directly inspect for the other moiety of the second ureter. In such cases, simultaneous stenting of both upper and lower pole ureteral segments may be necessary.

Ureteral Stricture or Stenosis

The presence of intrinsic ureteral obstruction will certainly affect the selection of ideal stone treatment in a number of ways. First, an untreated stricture or stenosis will preclude fragment passage and hence create an expectation of SWL failure. Second, the mechanism that is chosen to deal with the obstruction may facilitate and/or dictate how the stone will be managed. Finally, the physical properties of the stricture may mandate a particular course of action.

Most important, not every narrow point that is encountered in the ureter reflects a pathologic stricture, particularly when a stone may be impacted there. Inflammatory reaction and ureteral spasm may account for a significant portion of apparent obstructions that are encountered. In these situations, it is critical to recognize that overdilation of the ureter via endoscopic approach may cause localized ureteral injury (Eshghi, 1988). Despite this concern, balloon dilation of the ureter, when required for ureteroscopy, is safe and effective in the vast majority of patients (Huffman and Bagley, 1988). If the area of obstruction is felt to reflect spasm, placing a stent to allow passive dilation will facilitate a second-stage procedure in both pediatric and adult patients (Hubert and Palmer, 2005; Rubenstein et al, 2007).

When a definite stricture is present, underlying causes must be considered. Methods of dealing with ureteral strictures are covered elsewhere in this text and may provide the primary guidance for dealing with a ureteral stricture; a postretroscopy stricture is obviously significantly different from a radiation-induced one.

Endoureterotomy can be performed at all levels of the ureter; however, it will have a lower rate of long-term success in longer strictures (Wolf et al, 1997). Few data have been reported on the concomitant use of ureteroscopic laser lithotripsy at the time of an endoureterotomy or endopyelotomy, though there is a recognized potential for stone fragments to come to rest in the periureteral space and cause granulomatous inflammatory reaction and recurrent stricture (Dretler and Young, 1993). It is possible that, if URS is the preferred management strategy, endoureterotomy should be undertaken as a first stage, with placement of a ureteral stent to allow healing, and subsequent URS to manage the stone at a second stage.

Alternatively, consideration may lead one to proceed with open, laparoscopic, or robotic-assisted laparoscopic treatment for both the stricture and the stone in the same session. Numerous reports of laparoscopic and robotic-assisted ureterolithotomy have been reported, and the identical techniques and approaches used for management of a ureteral stricture can be used to also treat a ureteral stone in the same session (Dogra et al, 2013; Nasseh et al, 2013; Singh et al, 2013).

Technical Factors



Please see the Expert Consult website for details.

KEY POINTS: URETERAL CALCULI

- Conservative therapy, including MET, has its greatest success in stones 5 mm or smaller, but may still see fair success rates in stones up to 10 mm in size.
- Fever, or the presence of clinical or laboratory signs of UTI, may herald impending sepsis, a life-threatening condition; emergent drainage and decompression with either stent or nephrostomy should be undertaken.
- SWL and URS are both considered first-line therapies for stones at all locations within the ureter, although a higher rate of ancillary procedures should be expected with stones larger than 10 mm.
- Positioning challenges may be present for SWL in the mid-ureteral stone, requiring prone or oblique positioning for a clear blast path to the stone.

Clinical Factors for Upper Urinary Tract Calculi

Complete treatment planning for upper tract stones must incorporate the relevant clinical factors for a given patient, in addition to the stone-specific and anatomic factors (see Box 53-1). Certain patient conditions, anatomic aberrations, and underlying comorbidities assume significant importance in counseling patients on the relative risks and benefits of the different treatment options, as each can influence surgical outcomes and complications. Hence, a tailored approach to the individual patient is best.

Urinary Tract Infection

UTIs are common in the setting of upper tract calculi and should be adequately treated before any stone treatment. It is interesting to note that offending bacteria may reside deep within stones and prove impossible to eradicate without complete stone removal. Because of this, it may be difficult to completely sterilize the urine before stone surgery, in which case at least a short course of preoperative, culture-directed antibiotics is recommended. When infectious stones are suspected, every attempt at complete removal of stones should be undertaken because residual fragments commonly

harbor bacteria that can serve as a nidus for recurrent UTIs and promote rapid stone regrowth (Bichler et al, 2002). Therefore, PCNL and URS, when active stone extraction is possible, are preferred over SWL, in which stone clearance relies on physiologic stone passage and may take months to reach completion.

The rate of sepsis after PCNL or SWL is approximately 1% when preoperative urine cultures are negative. However, when preoperative bacteriuria exists or there is evidence of distal obstruction, the rate of sepsis associated with SWL for staghorn stones increases substantially (2% to 56%) and SWL should not be pursued (Zink et al, 1988; Lam et al, 1992a; Meretyk et al, 1992, 1997).

A UTI associated with an obstructing upper tract stone (ureteral or renal) represents a true urologic emergency and requires emergent urinary tract drainage. This is accomplished by either ureteral stenting or percutaneous nephrostomy. Attempts to definitively treat the obstructing stone should be postponed until the patient is stabilized and the infection is completely treated. Measures to treat the stone before patient stabilization and clearance of the infection risk worsening sepsis and death. In these instances, a urine culture from the obstructed segment is helpful to guide subsequent antibiotic therapy.

Renal Function

Assessment of underlying renal function becomes most important when there is suspicion that nephrectomy rather than stone removal is the treatment of choice. This scenario is encountered most frequently with staghorn stones, a history of recurrent pyelonephritis or renal abscess episodes, or xanthogranulomatous pyelonephritis and with chronic, relatively asymptomatic renal obstruction from ureteral stones. Renal imaging can provide clues to poor underlying renal function, including renal cortical atrophy or thinned renal parenchyma. In these instances, further functional renal studies, such as diuretic renography, can be used to quantify remaining renal function. In equivocal cases, temporary relief of obstruction with ureteral stenting or percutaneous nephrostomy is warranted, after which renal function can be reassessed. **The general consensus is that symptomatic upper tract stones located in renal units with approximately 15% or less split function should be considered for nephrectomy, and stone-specific, nephron-sparing treatments should not be pursued.**

A considerable body of evidence exists evaluating the effects of SWL and PCNL on renal function, while there is a relative paucity of data surrounding URS effects on renal function (Wood et al, 2011; Kartha et al, 2013; Sninsky et al, 2014). It is believed that URS induces minimal renal parenchymal damage, and although few studies have evaluated this directly at a histologic or biochemical level, no change in long-term renal function has been reported even after multiple URS treatments (Lee and Bagley, 2001; Sninsky et al, 2014). More robust and in-depth data exist and have consistently shown that SWL and single-access tract PCNL do not appear detrimental to total renal function over the long term (Chandhoke et al, 1992; Lee and Bagley 2001; Canes et al, 2009; El-Tabey et al, 2014; Sninsky et al, 2014). These results have been repeatedly shown in patients with renal insufficiency and with solitary kidneys for both SWL (Kulb et al, 1986; Chandhoke et al, 1992; Zanetti et al, 1992; Cass, 1994; Eassa et al, 2008; El-Assmy et al, 2008; Krambeck et al, 2008a) and PCNL (Alken, 1982; Marberger et al, 1985; Schiff et al, 1986; Agrawal et al, 1999; Singh et al, 2001; Canes et al, 2009; Kuzgunbay et al, 2010; Unsal et al, 2010). It is interesting to note that renal scintigraphy and single-photon emission computed tomography (SPECT) evaluation of kidneys after PCNL have also confirmed no changes in total renal function, although new focal cortical defects and reduced renal functional activity were seen in a minority of patients at the site of percutaneous renal access (Unsal et al, 2010; Akman et al, 2012a). The effects of multi-access tract PCNL on renal functional outcomes are mixed, with some investigators suggesting no effect on renal function (Moskovitz et al, 2006) and others showing renal deterioration (El-Tabey et al, 2014).

Considering the available evidence, as long as adequate renal function exists and nephrectomy is not being entertained, stone

The treatment of patients with ureteral calculi depends on multiple surgical technologies, and the availability of certain equipment will affect the possible options for treatment. Few operating environments will have all possible lithotripters, ureteroscopes, lithotrites, or stone-retrieval devices immediately available. In addition, the surgeon's preference and technical expertise will also affect the technique chosen. The majority of urologists and patients with stone disease in the United States do not have direct access to a fixed lithotripter on an unlimited basis. Therefore, treatment decisions may need to be modified according to lithotripter availability. Patients with symptomatic ureteral stones and no immediate lithotripter access have several options: They may be clinically observed with pain and emetic control; they can undergo placement of an internal ureteral stent to relieve the symptoms of renal colic (but then may develop stent-related morbidities); or they may have primary ureteroscopic removal of the stone, provided the requisite endoscopic equipment is available.

Because of recent pressures to decrease resource use, there is increasing emphasis in the modern medical environment on the reduction of cost. Such economic pressures have promoted the movement toward less invasive, more cost-effective therapy for patients with ureteral stones. Most studies performed in the United States have found that ureteroscopy is a more cost-effective intervention than SWL, a differential that is likely a result of the higher re-treatment rate associated with SWL. [Grasso and colleagues \(1995a\)](#) analyzed the cost of ureteroscopy and SWL for patients with ureteral calculi. When they compared outpatient ureteroscopic lithotripsy with SWL monotherapy, treatment costs were similar.

However, the addition of re-treatments and auxiliary procedures after SWL more than doubled the costs and weighed heavily against this modality's cost-effectiveness. [Kapoor and associates \(1992\)](#) compared the treatment costs of SWL and ureteroscopy: As a consequence of the significantly higher success rates (97% vs. 75%), ureteroscopy was the more cost-effective treatment approach. [Parker and associates \(2004\)](#) studied the cost associated with treating proximal ureteral stones and found that ureteroscopy was less costly, again as a consequence of its superior initial treatment success. Several investigators have approached the question of cost-effective treatment for ureteral calculi by constructing decision analysis models. [Wolf and associates \(1995\)](#) used a literature-based probability decision tree to determine the more effective and cost-efficient therapy for patients with distal ureteral calculi and found that although initial SWL was only slightly more expensive than ureteroscopy, the cost differential increased when additional complications and re-treatments were calculated. [Lotan and associates \(2002\)](#) also constructed a decision analysis model to determine the most cost-effective treatment for ureteral stones. Although observation was the least costly intervention, ureteroscopy was a less costly intervention than SWL for the treatment of stones at all locations in the ureter. A recent systematic review comparing the cost of SWL versus URS evaluated 10 different studies and found overwhelmingly that URS saved costs and achieved a higher stone-free rate for ureteral stones at all locations than SWL, though few of the studies were well designed. Thus, taken all together, **ureteroscopy is the most cost-effective treatment strategy for ureteral stones at all locations, after observation fails.**

treatment decisions should not, in general, be based on renal function. Rather, they should be based on stone-specific characteristics, renal anatomic factors, and other more relevant clinical factors.

Solitary Kidney

The main considerations in treating stones in congenitally, surgically, and functionally solitary kidneys include having a lower threshold to treat asymptomatic renal stones and ensuring sufficient renal drainage after stone treatment. By virtue of the fact that only one kidney exists or is functioning, a single, obstructing stone leads to total urinary obstruction and demands urgent attention. **It is for this reason that proactive treatment of asymptomatic stones, which might otherwise be observed when two functioning kidneys exist, is recommended in solitary kidneys.** The perils of complete ureteral obstruction, especially with concomitant UTI, can be life-threatening for patients with solitary kidneys. In the setting of clinical instability, UTI, or electrolyte abnormalities, initial urinary decompression via ureteral stenting or percutaneous nephrostomy drainage should be undertaken. Once the patient is clinically stable, and after treatment of any associated infection, definitive stone treatment may be pursued following the strategies outlined in the ureteral calculi section. Although not mandatory based on any meaningful evidence, it is highly advocated to place a ureteral stent after ureteroscopic manipulation, because temporary ureteral edema and occlusion caused by spasm or fragments can result in acute kidney injury and anuria.

Morbid Obesity

A BMI above 40 kg/m² is considered morbid obesity by the World Health Organization. Obesity, and in particular morbid obesity, can pose physiologic and technical challenges that must be accounted for when recommending stone treatment to such patients (Giblin et al, 1995; Freedman et al, 2002). Proper preoperative medical optimization and risk stratification are imperative, because obesity has been linked to a number of medical conditions that increase anesthetic risk, including cardiovascular disease, diabetes mellitus type II, and obstructive sleep apnea (among others). **Ureterorenoscopy and PCNL outcomes appear to be relatively independent of obesity status, whereas those after SWL are drastically worse.**

SWL is frequently suboptimal in morbidly obese patients, and in some cases it is actually impossible as patients may exceed the weight limitations of the lithotripter table or gantry. Many studies have shown increasing BMI to be a negative prognosticator for stone-free status after SWL (Ackermann et al, 1994; Portis et al, 2003). Moreover, the significant adipose tissue found in the morbidly obese can attenuate x-ray through-transmission, making it difficult to localize stones with fluoroscopy. If the stone is visible but located beyond the F2 focus of the lithotripter, a blast path technique may be used in which the stone is targeted along the same axis as the F2 focal point and relies on high pressures, though slightly defocused, generated beyond F2 to fragment the stone (Whelan et al, 1988; Locke et al, 1990). Given this, it is often necessary to use higher energy settings in obese patients, and lithotripters offering the highest peak pressures and longest focal length are preferred.

Skin-to-stone distance, or the distance between the SWL transducer and stone, has emerged as an important factor affecting SWL outcomes and is readily measured on axial CT slices. In general, the larger the skin-to-stone distance, the worse the fragmentation during SWL. Many studies have shown that **SWL outcomes worsen when skin-to-stone distance exceeds 10 cm** (Pareek et al, 2005; El-Nahas et al, 2007; Wiesenthal et al, 2011; Foda et al, 2013). Furthermore, Pareek and colleagues (2005) found that skin-to-stone distance was a stronger predictor of stone-free status than BMI. Perks and associates (2008) reviewed SWL in 111 patients with solitary stones 5 to 20 mm in size and found the best treatment success (91%) for skin-to-stone distances below 9 cm and stone attenuation below 900 HU, and the lowest treatment success (41%) for skin-to-

stone distances greater than 9 cm and stone attenuation exceeding 900 HU.

More recently, excessive visceral fat, as measurable on noncontrast CT, has proved to be a useful prognosticator for SWL outcomes. Indeed, increasing abdominal circumference, visceral fat, subcutaneous fat, and perirenal and pararenal fat are all associated with decreasing stone-free rates after SWL (Juan et al, 2012). Taking this one step further, Zhou and colleagues (2013) demonstrated that increasing visceral fat was an independent predictor of uric acid stones. Hence, a trial of urinary alkalinization is recommended in obese patients with radiolucent stones, a low urinary pH, and no other indications for urgent decompression.

PCNL in the morbidly obese is feasible and reportedly safe but also requires some technical modifications. Extra-long instruments (fascial dilators, access sheath, nephroscope, stone graspers) may become necessary, and mobility around the collecting system from a given access tract may be hindered by the long tract length. **Most available data confirm that stone-free rates are not affected by obesity, although there is some suggestion that stone-free rates are lower, and major complication rates are higher, in the morbidly obese** (Pearle et al, 1998; Koo et al, 2004). El-Assmy and associates (2007) and Kuntz and colleagues (2014) found no difference in stone-free rates, complications, auxiliary procedure rates, or length of stay among patients stratified by BMI, and proved that “tubeless” PCNL could be performed safely in these individuals. It is interesting to note that the CROES PCNL global study found equivalent stone-free rates for normal, overweight, and obese cohorts (approximately 80%), but significantly lower stone-free rates for the morbidly obese group (65.6%) (Fuller et al, 2012). Overall complication rates did not differ either among groups, although a greater percentage of major complications (Clavien-Dindo III to V) were found in the morbidly obese (10.5%) relative to the other groups (3.5% to 3.9%).

URS success and safety do not appear to change in the morbidly obese (Dash et al, 2002; Preminger et al, 2007; Natalin et al, 2009). Accordingly, URS may be the preferable treatment modality for obese patients without exceedingly complex or large stone burdens. Chew and colleagues (2013) performed a multicenter trial comparing URS in patients with normal BMIs with those considered overweight or obese; no significant difference was found in stone-free rates. Aboumarzouk and colleagues (2012c) performed a systematic review of URS in obese patients (mean BMI 42.2 kg/mm²) and found an excellent pooled stone-free rate (87.5%), mean operative time (97.1 minutes), and complication rate (11.4%).

Old Age and Frailty

Recently the concept of frailty has gained considerable attention in the surgical literature, although it has been somewhat slow to permeate into the field of urology. There is mounting evidence to suggest that the degree of frailty a patient exhibits, rather than his or her chronologic age, is a more robust predictor of postoperative complications (Makary et al, 2010; Revenig et al, 2014). At present, there are limited data on the effects of frailty on stone treatment outcomes; however, extrapolating from the available frailty literature in other fields, the frailest of patients may be better served with less invasive stone treatments (URS or SWL). Resorlu and associates (2012a) conducted a multicenter, retrospective review of PCNLs in elderly patients and found that a higher Charlson Comorbidity Index score was associated with a significantly higher rate of severe medical complications and hemorrhage. Similarly, many elderly patients have less physiologic reserve to handle an acute, obstructing stone event well, or to successfully tolerate a drawn-out trial of passage. In these instances, a more direct treatment strategy with early relief of urinary obstruction is prudent.

A number of groups have looked at PCNL outcomes in elderly populations and have found essentially unchanged surgical success, albeit with a higher rate of complications. Doré and colleagues (2004) reviewed PCNL outcomes in 201 patients age 70 and older and found a stone-free rate of 70.8%. Early work by Stoller

and colleagues (1994a) showed that PCNL was safe in patients older than 65 years but was associated with more frequent blood transfusions (26% vs. 14%). Akman and colleagues (2012b) compared URS and PCNL outcomes in patients older than 65 years and reported excellent stone-free rates (93% for URS, 96% for PCNL), reasonable operative times (65 minutes for URS, 41 minutes for PCNL), and acceptable complication rates (10.7% for PCNL, 7.1% for URS). In the largest published series on the topic, no difference was appreciated in stone-free rates (79% vs. 82%) or length of hospitalization in elderly (median age 74 years) versus younger (median age 49 years) cohorts, but there was a higher overall complication rate (19.9% vs. 6.6%) in the elderly (Okeke et al, 2012).

Shock wave lithotripsy in the elderly is feasible as well, but it may be associated with an increased risk of perinephric hematoma. Dhar and associates (2004) found a 1.67-times increased risk of hematoma formation after SWL with every 10-year increase in patient age, although subsequent studies have not consistently borne this out. Reports on treatment success with SWL in the elderly are mixed, showing a trend toward lesser success for renal stones and no effect on ureteral stones (Delakas et al, 2003; Abe et al, 2005; Ng et al, 2007). Furthermore, URS does not appear to confer any known additional risks to the elderly.

Spinal Deformity or Limb Contractures

Patients with spinal deformities and limb contractures present a number of challenges that can be anticipated preoperatively. Despite its minimally invasive nature, SWL is often unsuccessful, and with high re-treatment and auxiliary procedure rates, because it can be difficult or impossible to properly position these patients on the lithotripter table. Moreover, stone targeting may be fraught with difficulties, as scoliosis and abnormal pelvic anatomy can preclude an acceptable shock wave blast path. Fragment passage can also be hindered by aberrant renal location and associated poor upper tract drainage. Few contemporary reports exist, but older studies show only modest stone-free results in this population, along with a frequent need for multiple treatment sessions (Neuwirth et al, 1986; Lazare et al, 1988).

PCNL and URS are good alternatives to SWL, and both have been used with good success, although special considerations are necessary with each (Rubenstein et al, 2004; Goumas-Kartalas et al, 2010; Resorlu et al, 2012c). For URS, patient anatomy may preclude rigid instrument use (cystoscopy and ureteroscopy). The use of ureteral access sheaths is encouraged, if they can be safely placed, because they can provide rapid re-entry into the otherwise challenging-to-access upper collecting system. PCNL remains the preferred method of stone treatment in many of these patients, particularly with large and complex stone burdens. Stone clearance rates with PCNL are no different than in the general population, although there is a greater need for secondary procedures. Furthermore, PCNL in these circumstances is associated with a higher rate of infectious complications (Culkin et al, 1990; Symons et al, 2006; Goumas-Kartalas et al, 2010; Nabbout et al, 2012). Given the abnormal anatomic relationships in these patients, preoperative CT of the abdomen and pelvis is essential in planning optimal renal access and may reveal the need for CT guidance or potentially even laparoscopic guidance in selected situations to avoid bowel or solid organ injury (Matlaga et al, 2003a).

Uncorrected Coagulopathy

Uncorrected coagulopathy is a contraindication to SWL and PCNL; however, URS can be successfully undertaken in such circumstances with little to no increase in surgical morbidity. When coagulopathies have been corrected, patients should be considered candidates for SWL and PCNL, assuming no other contraindications exist. Many instances of life-threatening retroperitoneal hemorrhage have been reported after SWL use in patients on continuous anticoagulant and antiplatelet agents (Ruiz and Saltzman, 1990; Streem and Yost, 1990; Katz et al, 1997; Zanetti et al, 2001; Sare et al, 2002; Alsaikhan and Andonian, 2011).

For patients with imperative indications to remain on antiplatelet therapy (e.g., recent coronary artery stenting) or anti-coagulant agents (e.g., high-risk atrial fibrillation, venous thromboembolic disease, or mechanical cardiac valves), URS with holmium:yttrium-aluminum-garnet (Ho:YAG) laser lithotripsy is the treatment modality of choice. Since Grasso and Chaliki (1998) first reported the safe use of URS and Ho:YAG laser lithotripsy in patients with uncorrected coagulopathies, numerous other reports have followed recapitulating not only the safety, but also the high efficacy of URS in these challenging scenarios (Watterson et al, 2002; Turna et al, 2008; Aboumarzouk et al, 2012b). Of note, Ho:YAG laser lithotripsy is preferred and is considered safer than other intracorporeal lithotripters (Watterson et al, 2002).

Prior Renal Surgery

Prior renal surgery or trauma can lead to fibrosis, scarring, and deformity of the intrarenal collecting system, which in turn can complicate renal stone surgery. This situation is less frequently encountered today because fewer open stone surgeries are performed worldwide. Prior renal surgery is not a contraindication to any form of renal stone surgery and presents no new specific concerns, in and of itself. Thus, all treatment modalities may be employed as necessary, given appropriate indications (SWL, URS, PCNL). Certain precautions should be taken, however; the possibility of poor renal drainage should be entertained, as previous surgery can predispose to infundibular stenosis and iatrogenic UPJO. If obstruction is found or suspected, a treatment modality other than SWL should be chosen. URS and PCNL may be used as previously described. Of note, during URS an infundibulotomy may be necessary to adequately access a stone trapped behind an area of infundibular stenosis. Nevertheless, stone-free rates of 79% after a single URS and 92% after a secondary URS have been described (Osman et al, 2012).

PCNL after prior open kidney surgery and after prior SWL has been described by multiple investigators. For the most part, prior renal surgery (open or SWL) has no effect on PCNL complication rates (Tugcu et al, 2008; Gupta et al, 2009a; Yuruk et al, 2009; Resorlu et al, 2010; Zhong et al, 2013). A single recent retrospective study found a higher need for renal angioembolization to control postoperative bleeding in patients with previous open nephrolithotomy; however, this finding has not been corroborated by others (Yesil et al, 2013). The effect of prior open surgery on stone-free rates is less consistent, with some studies showing rates that are worse (Gupta et al, 2009a) and others showing unchanged rates (Tugcu et al, 2008; Resorlu et al, 2010).

Prior SWL therapy can make salvage PCNL more difficult, as evidenced by longer operative times and lower stone-free rates (Yuruk et al, 2009; Zhong et al, 2013). This is the presumed result of stone fragment scattering after SWL and the tendency for some of the stones to embed suburothelially within the renal parenchyma. In fact, the more ineffective the prior SWL attempt (i.e., less fragmentation), the better the expected results from the following PCNL. Bon and associates (1993) found a 92% success rate for nonfragmented stones compared with a 64% success rate in patients with numerous fragments.

Urinary Diversion

Renal and ureteral stones in patients with urinary diversions present unique obstacles. Adequate preoperative imaging is essential to provide details on the anatomy of the urinary diversion and provide clues to possible routes to access the stone. It may also suggest the presence of urinary stasis and obstruction within the diversion, which if present should also be addressed to minimize the risk of stone recurrence. In general, SWL, PCNL and antegrade URS, retrograde URS, or a combination thereof can be exploited.

As in other instances, SWL should not be used in the setting of urinary obstruction. However, without urinary obstruction, a single session of SWL can achieve success rates of 60% to 65% (Deliveliotis et al, 2002; El-Assmy et al, 2005). Retrograde URS is usually

confined to flexible instruments, and redundant ileal conduits and large-capacity urinary reservoirs with some form of nonrefluxing ureteral anastomosis often require flexible instruments to locate the ureteral "orifices." Successful access to the upper urinary tract has been reported up to 75% of the time in urinary diversions, with a much lower rate seen in Indiana pouches (Hyams et al, 2009). Loopograms or pouchograms can aid in locating ureteral insertions when upper tract reflux exists. Alternatively, intravenous indigo carmine or contrast can be used as well. For patent ureteroenteric anastomoses, the judicious use of ureteral access sheaths can both facilitate upper tract re-entry and protect the anastomotic site.

For larger stone burdens and when retrograde access is not possible, PCNL becomes the treatment modality of choice, with a reported stone-free rate of 75% to 88% (Wolf and Stoller, 1991; El-Nahas et al, 2006; Hertzog et al, 2013). In addition, percutaneous access can allow antegrade URS to achieve access to the ureter when retrograde techniques fail. Complication rates of 8% to 30% have been reported for percutaneous approaches to stones in these patients. Percutaneous access may require ultrasound guidance if retrograde or antegrade contrast filling of the pelvicalyceal system is not possible.

Renal Transplants

The general consensus is to remove upper tract stones within renal transplants, as the consequences of an obstructing stone can be devastating. Indeed, because of the lack of innervation in renal transplants, obstructing stones do not manifest with typical renal colic. Rather, vague graft site discomfort, fevers, oliguria, hematuria, or rising creatinine may be the only presenting signs.

SWL has been described for stones in transplant kidneys and is an option for stones smaller than 1.5 cm; however, high re-treatment rates and auxiliary procedure rates should be expected (Klingler et al, 2002; Challacombe et al, 2005). Given that the renal allograft is located near the bony pelvis, prone positioning is often necessary. Antegrade and retrograde URS have been used to successfully treat transplant kidney and ureteral stones. Angled catheters and guidewires are often indispensable in achieving retrograde access, and prior placement of a percutaneous nephrostomy tube can facilitate antegrade URS and obviate the need for percutaneous tract dilation (Hyams et al, 2012). Stone-free rates of 67% to 92% have been reported, although no large series exist (Del Pizzo et al, 1998; Basiri et al, 2006).

PCNL remains the preferred treatment choice for large-burden stones (>1.5 cm) or if less invasive methods have failed. Stone-free rates ranging from 77% to 100%, similar to rates in the general population, have been reported (He et al, 2007; Krambeck et al, 2008b; Rifaoglu et al, 2008). When obtaining percutaneous access to transplant kidneys, CT or ultrasound guidance is advisable because there is a risk for intervening bowel. Furthermore, some reports describe difficulty with percutaneous access secondary to a fibrous capsule that develops around certain transplanted kidneys and may require use of metal fascial dilators to overcome. Percutaneous access with a 16-Fr peel-away sheath has been illustrated; this mini-PCNL technique is thought to carry a lower risk of surgical bleeding and still be of significant usefulness for these stones (He et al, 2007).

Duration of Ureteral Stone Presence

As discussed in the natural history section on ureteral calculi, after the initially reversible physiologic changes seen with acute ureteral obstruction, chronic ureteral obstruction can ultimately lead to permanent renal damage. Patients attempting to spontaneously pass a ureteral stone should be intermittently imaged to evaluate for persistent or worsening hydronephrosis and stone location and passage. Active stone treatment of any form is indicated when obstruction has persisted for approximately 4 weeks (Singal and Denstedt, 1997). Continued renal blockage after this time may lead to irreversible kidney damage (Vaughan and Gillenwater, 1971). Holm-Nielsen and associates (1981) reported that of 134 patients

with unilateral ureteral stones, one third of the patients with obstruction lasting more than 4 weeks developed irreversible renal damage. Similarly, Kelleher and associates (1991) found that sequential renal scintigraphy performed on 76 patients with obstructive ureteral calculi demonstrated an 18% incidence of reduced renal function (defined as a decrease in relative function greater than 7%).

KEY POINTS: CLINICAL FACTORS

- Definitive stone treatment should be undertaken only in the setting of sterile urine, although a negative urinalysis may be an applicable surrogate to negative culture.
- Morbid obesity significantly affects SWL success rate.
- Kidneys with inherent drainage problems, such as those with UPJO, infundibular stenosis, or ectopic or horseshoe configuration, need to have the underlying obstruction managed in addition to treatment of the stone.
- In kidneys with poor (<15%) function, nephrectomy may be the optimal treatment.

Evaluation of Outcome

Assessment and Fate of Residual Fragments

In the era of open stone surgery, residual fragments of any size suggested a failed procedure. In the modern era with the rise of endourology and the frequent use of SWL, URS, and PCNL, postoperative residual fragments are relatively common. However, the definition and optimal management of residual fragments continue to generate controversy.

With the increasing popularity of SWL in the 1980s and the observation that many patients retained small fragments of questionable clinical relevance after such therapy, the concept of **clinically insignificant residual fragments (CIRF)** was introduced and would become incorporated into the definition of a successful treatment outcome (Newman et al, 1988). These fragments were initially, and arbitrarily, defined as residual fragments 4 mm or less in diameter that were nonobstructive, noninfectious, associated with sterile urine, and in an otherwise asymptomatic patient (Newman et al, 1988). Since then, the term has been applied to fragments of various sizes, with most studies using a cutoff between 2 mm and 4 mm.

Therefore, since the introduction of SWL, treatment outcomes for patients with renal calculi have been reported by two different terms: stone-free rate and success rate. The stone-free rate is self-explanatory, but the success rate includes patients who are stone free as well as those with CIRF. These different methods of reporting treatment results, the lack of a standard definition for CIRF, and the various modalities used for assessing postprocedural stone-free status (KUB studies, nephrotomography, ultrasonography, CT) make the comparison of endourologic stone outcomes difficult. Further complicating matters is the fact that stone fragment passage after SWL is not immediate; as many as 85% of patients have radiologic evidence of residual fragments several days after SWL (Drach et al, 1986). Although most fragments pass spontaneously during the first 3 months after SWL, continued clearance can occur for more than 24 months after treatment (Chaussy and Schmiedt, 1984; Graff et al, 1988; Kohrmann et al, 1993).

In an attempt to better characterize the clinically meaningful success of any given stone treatment, Clayman and colleagues (1989) introduced the effectiveness quotient:

$$\frac{\% \text{ stone free}}{100\% + \text{retreatment} + \% \text{ auxiliary procedures}} \times 100$$

The effectiveness quotient accounts for the re-treatment rate, stone-free rate, and number of ancillary procedures and is useful in comparing results among different treatment modalities. For

example, the study by Netto and colleagues (1991) compared PCNL and SWL for the treatment of stones in lower pole calyces. The PCNL group had a 93.6% stone-free rate with no need for re-treatment, whereas the SWL group had a 79.2% success rate with a 41.6% re-treatment rate. The relative success rates for PCNL and SWL were not significantly different; however, a significant difference was appreciated when comparing the effectiveness quotients (93.7% for PCNL vs. 55.9% for SWL).

The term *clinically insignificant residual fragments* may be a misnomer because many small residual fragments eventually become clinically significant and symptomatic by dislodging and causing obstruction, serving as niduses for further stone growth, or acting as a source for persistent infections (Streem et al, 1996; Zanetti et al, 1997; Candau et al, 2000; Delvecchio and Preminger, 2000). Streem and colleagues (1996) reported that 43% of initially deemed CIRF became symptomatic at a mean follow-up of 23 months. Moreover, complete stone removal appears to decrease the risk of stone recurrence (Singh et al, 1975; Patterson et al, 1987; Newman et al, 1988). Stone recurrence rates of 6% to 15% have been reported for patients rendered stone free after SWL, compared with rates of 17% to 80% when residual fragments remained (Graft et al, 1988; Newman et al, 1988; Nijman et al, 1989; Beck and Riehle, 1991; Fuchs et al, 1991; Zanetti et al, 1991; Nakamoto et al, 1993). Residual fragments are most likely to pass when located within the ureter, and least likely to pass when located in the lower pole.

In a large review on SWL by Rassweiler and colleagues (2001), CIRF were found to spontaneously pass in 25%, remain stable in 55%, and become clinically significant in 20% of patients, with anywhere from 4% to 25% of patients requiring a subsequent intervention to address the residual fragment. A similar spontaneous passage rate of 25% to 30% has been reported by others (Streem and associates, 1997; Candau et al, 2000). When pooling the findings from the available prospective data, the probability that CIRF after SWL later become clinically significant increases with lower pole fragments, increasing fragment burden, increasing fragment number, and longer follow-up (Streem et al, 1996; Khaitan et al, 2002; Osman et al, 2005b).

Many investigators have noted that, after SWL, residual fragments are commonly localized to lower pole calyces no matter where the stone was treated in the kidney (Drach et al, 1986; Graft et al, 1988; Liedle et al, 1988; Zanetti et al, 1991; Kohrmann et al, 1993). It is interesting to note that the incidence of stone recurrence is greater in the lower pole calyces after SWL than it is after PCNL (Zanetti et al, 1991; Kohrmann et al, 1993; Carr et al, 1996). Furthermore, at 1-year follow-up there is a significantly greater rate of new stone formation in those treated with SWL, and the recurrent stones are more likely to be in the lower calyces. A plausible explanation for these results is that fine debris, undetectable by imaging, persists after SWL and, because of gravity, settles in the most dependent calyces and serves as a nidus for new stone formation. Supporting this hypothesis are the results from Carr and colleagues (1996) showing that de novo stone formation occurs significantly more often after SWL (22%) than PCNL (4%).

Stone-free rates after PCNL vary widely from 40% to well above 90%. However, as with SWL reporting, the definition of stone free is not consistent across studies (Park et al, 2007; Skolarikos and de la Rosette, 2008). Raman and colleagues (2009) found an 8% rate of residual fragments by CT scan, with approximately half located in the lower pole. Of the patients with residual fragments, 43% developed a stone-related event at a median of 32 months after initial PCNL. Fragments larger than 2 mm in greatest diameter were more likely to undergo a secondary procedure and independently predicted a postoperative stone-related event. Similarly, fragments located in the renal pelvis and ureter were associated with a stone event on multivariate analysis but also were associated with the highest likelihood of spontaneously passing (Ganpule et al, 2009; Raman et al, 2009).

Few investigators have evaluated the destiny of residual fragments after URS. The recent meta-analysis by the AUA and EAU revealed that residual fragments occur in 6% of cases for distal

ureteral stones, 14% of cases for mid-ureteral stones, and 19% of cases for proximal ureteral stones (Preminger et al, 2007). The limited data in which CT was used to evaluate residual fragment status after URS have shown stone-free rates of only 50% to 54% (Pearle et al, 2005; Portis et al, 2006). Expanding the definition of treatment success to also include fragments 2 mm or smaller improves the success rate to 62% to 84% (Portis et al, 2006; Macejko et al, 2009; Rippel et al, 2012). Schatloff and associates (2010) found that patients with residual fragments after semirigid ureteroscopy were significantly more likely to experience unanticipated medical visits (3% vs. 30%) and exhibited a trend toward more ancillary procedures (0% vs. 7%) and more frequent rehospitalization (0% vs. 10%). Over a 19-month period after URS, Rebuck and colleagues (2011) reported a 20% rate of unplanned stone events, a 22% rate of spontaneous passage, and a 57% rate of persistent residual fragments (≤ 4 mm).

In patients with infection-related calculi, the consequence of residual fragments is particularly harmful. Residual fragments may harbor offending bacteria and thus predispose to persistent infection. Furthermore, stone regrowth has been reported in up to 75% of such patients after SWL, compared with 10% of patients who experienced complete stone removal (Beck and Riehle, 1991; Zanetti et al, 1991).

For patients with metabolic stone disease, complete stone removal does not prevent stone recurrence, but it does prolong the intervals between symptomatic events and treatment (Chow and Streem, 1998). Thus, residual stones, including small stones, may not have an immediate clinical relevance but are likely to affect the patient's well-being in the long term.

The sensitivity of the method used to detect remaining fragments has important effects on the reported incidence and size of residual fragments. As stated, plain radiography, nephrotomography, ultrasonography, intravenous urography, and CT have all been used to evaluate residual fragments. Plain radiography, ultrasonography, and CT are used most frequently in contemporary practice. In the current era with the recognition that repeated radiation exposure from CT may be harmful, the routine use of CT scan for follow-up studies should be done cautiously and only when necessary.

In early studies investigating stone clearance after SWL, plain radiography was commonly used to determine stone-free status for radiopaque calculi and could detect opaque stone fragments as small as 2 mm (Thornbury and Parker, 1982). Plain radiography has a sensitivity of approximately 60% for detecting urinary stones (Mutgi et al, 1991; Assi et al, 2000; Ege et al, 2004; Johnston et al, 2009). However, Denstedt and coworkers (1991) reported that for patients with large renal calculi treated by a combination of PCNL and SWL, plain radiography overestimated stone-free rates by 35% and 17%, respectively, compared with flexible nephroscopy. Nephrotomography, although becoming obsolete in many centers, has proved superior to plain radiography in detecting residual fragments (Hjollund Madsen, 1972; Schwartz et al, 1984; Goldwasser et al, 1989).

Traditionally, ultrasonography has been inferior to plain radiography in detecting urinary calculi, with particular deficiency in detecting ureteral stones (Yilmaz et al, 1998; Older and Jenkins, 2000). The sensitivity of ultrasonography to detect urinary calculi over the last decade has ranged from 24% to 57% (Fowler et al, 2002; Ullusan et al, 2007; Viprakasit et al, 2012), although these results were potentially confounded because CT scans and ultrasounds were rarely done on the same day and infrequently performed by a dedicated uro-ultrasonographer. Kanno and colleagues (2014) recently reported a 70% ultrasound sensitivity in detecting renal stones when the ultrasound was done the same day as the CT, average patient BMI was 23, and all ultrasounds were performed by experienced ultrasonographers. Hence, even under the most favorable circumstances, ultrasound may still miss up to 30% of renal stones.

Despite its shortcomings, in detecting ureteral stones, ultrasound is highly effective in diagnosing hydronephrosis. In fact, some advocate for ultrasonography after all ureteroscopic procedures because silent obstruction has been reported to occur in certain, albeit rare,

instances (Weizer et al, 2002). A prospective study comparing the relative efficacy of abdominal radiography and renal ultrasonography versus excretory urography for the evaluation of asymptomatic patients 1 month after SWL treatment demonstrated that the combination of ultrasonography and abdominal radiography was as good as or better than intravenous urography in identifying residual stone fragments and hydronephrosis, suggesting that **routine radiologic evaluation of asymptomatic patients after SWL could be limited to abdominal radiography and ultrasonography** (Coughlin et al, 1989).

Although flexible nephroscopy may be considered the gold standard for assessment of residual stones after PCNL, its routine use has been challenged by studies showing the high sensitivity of CT in detecting residual stones after PCNL. **Pearle and coworkers (1999)** noted that CT had 100% sensitivity for detecting residual stones after PCNL in 36 patients evaluated with both CT and flexible nephroscopy. Selective use of flexible nephroscopy based on positive CT findings would have avoided an unnecessary procedure in 20% of patients. In a retrospective study of 121 patients who underwent CT after PCNL (including 59% stone-free patients and 16% patients with fragments of 1 to 3 mm), **Waldmann and associates (1999)** reported that routine nephroscopy would not have been required in 75% of cases. Given its wide availability and high sensitivity, CT has become the primary method for evaluation of residual stone fragments after PCNL. However, this must be balanced with the need to minimize unnecessary radiation exposure in patients.

KEY POINTS: RESIDUAL FRAGMENTS

- Many small residual fragments will eventually become clinically significant and symptomatic.
- In the setting of infectious stones, residual stones portend a future of UTIs and stone recurrence; therefore, aggressive treatment with removal of fragments is usually indicated.
- Risks for stone recurrence are higher in the setting of residual stone fragments, because stone growth on an existing crystal matrix is harder to prevent than spontaneous nucleation of new stones.

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The complete reference list is available online at www.expertconsult.com.

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STONE REMOVAL: SURGICAL TECHNIQUES AND TECHNOLOGY

Intracorporeal Lithotripsy

Ureteroscopy and percutaneous nephrolithotomy (PNL) occupy an essential place in the treatment of urinary calculi as increasing technologic advancements allow easier access to stones in all parts of the kidney and ureter. In particular, improvements in ureteroscopic equipment emphasize the need for appropriate and effective miniaturized intracorporeal lithotripsy devices. Smaller ureteral stones can be extracted intact with endoscopic baskets or grasping devices after ureteral dilation, if necessary. However, larger ureteral stones require lithotripsy to permit the safe extraction of calculus fragments. The fragmentation of renal stones during PNL requires an approach different from that applied to ureteral intracorporeal lithotripsy. Although small and flexible endoscopic lithotrites are essential for the occasional difficult-to-approach kidney stone, renal stones can be visualized with a rigid nephroscope in most cases. In these situations, with a large kidney stone burden, the efficiency of the lithotrite is the most important requirement and size and flexibility are of secondary importance. The urologist who treats patients with urolithiasis thus requires an armamentarium of intracorporeal lithotripsy devices, each maximizing a different quality (e.g., size, flexibility, efficiency).

Four techniques are available for intracorporeal lithotripsy: electrohydraulic lithotripsy (EHL), laser lithotripsy, ultrasonic lithotripsy, and ballistic lithotripsy. These techniques can be divided into those lithotrites that are flexible (laser lithotripsy and EHL) and those that are rigid (ultrasonic and ballistic lithotripsy). This chapter will review the mechanisms, advantages, disadvantages, and surgical techniques of the various flexible and rigid intracorporeal lithotripters.

Flexible Lithotripters

Electrohydraulic Lithotripsy. EHL was invented in 1955 by Yutkin, an engineer at the University of Kiev, and was the first technique developed for intracorporeal lithotripsy (Grocela and Dretler, 1997). The first reported use of EHL outside the Eastern Bloc was in 1960, when a modified version of Yutkin's invention, the Urat-1, was used to fragment bladder calculi (Rouvalis, 1970). EHL was first applied to renal calculi during an open surgical lithotomy in 1975 (Raney and Handler, 1975). In 1985, Lytton reported the first experience treating patients with ureteral stones with a rigid ureteroscope and a 5-Fr EHL probe; no immediate or long-term complications were encountered (Green and Lytton, 1985). The use of smaller EHL probes through a flexible ureteroscope was first reported in 1988 (Begun et al, 1988).

The EHL probe is essentially an underwater spark plug composed of two concentric electrodes of different voltage polarities separated by insulation. When a current sufficient to overcome the insulative gap is applied, a spark is produced. The spark discharge

causes the explosive formation of a plasma channel and vaporization of the water surrounding the electrode. The rapidly expanding plasma causes a hydraulic shock wave followed by formation of a cavitation bubble (Fig. 54-1). Depending on the proximity of the probe to the stone surface, the collapse of the cavitation bubble may be symmetrical (at a distance of ~ 1 mm from the stone), resulting in a strong secondary shock wave, or asymmetrical (at a distance equivalent to a maximum bubble radius of ~ 3 mm), leading to the formation of high-speed microjets (Vorreuther et al, 1995; Zhong et al, 1997). Unlike in shock wave lithotripsy (SWL) the shock wave is not focused, so the stone must be placed where the shock wave is generated. The first EHL probes developed were of larger diameters (9 Fr) and, because of their size, had a narrow margin of safety. Later improvements in technology allowed the development of smaller probes, from 1.6 to 5 Fr, that were safer and had the ability to be passed through small-diameter, flexible ureteroscopes without occluding the irrigation or working channel. There is little difference in fragmentation ability among the different-sized probes, but the larger probes tended to be more durable (Segura, 1999). Subsequent improvements in the EHL generator allowed the surgeon more control over energy discharge, pulse, and duration. Although it was originally hypothesized to function optimally in a $\frac{1}{6}$ to $\frac{1}{2}$ normal saline solution, Denstedt and Clayman (1990) demonstrated that EHL works equally well in a normal saline solution, eliminating the hazard of irrigating the upper urinary tract with a hypotonic solution.

Advantages and Disadvantages. The major disadvantage of EHL is its propensity to damage the ureteral mucosa and its association with ureteral perforation. Raney (1978) reported that with a 9-Fr probe, 90% of ureteral stones could be successfully fragmented, but there was a 40% incidence of ureteral extravasation. Ureteral perforation remained an issue of concern with EHL in the ureter despite advancements in technology and technique. Hofbauer and coworkers (1995), in a prospective study of 72 patients, reported a perforation rate of 17.6% with EHL versus 2.6% with pneumatic lithotripsy. However, others have reported a lower rate of perforation, with a mean incidence of 8.5% recorded. Vorreuther and associates (1995) suggested that the mechanism of damage is the expansion of the cavitation bubble and thus injury may occur even when the probe is not in direct contact with the mucosa. The diameter of the cavitation bubble depends on the energy used and can expand to more than 1.5 cm when energies greater than 1300 mJ are employed. Therefore the risk for perforation is greater with higher energies, such as in treatment of a hard stone. Even with smaller probes and lower energy settings, perforation may occur if repeated pulses are applied close to the mucosa. Santa-Cruz and colleagues (1998), in a comparative in vitro study, reported that the holmium laser and EHL were associated with a higher risk for perforation compared with the coumarin pulsed-dye laser and pneumatic lithotripter. When the authors placed a 3-Fr probe 0.5 mm from the ureteral wall, perforation was induced with an average of 24 pulses. The risk for perforation may be higher for impacted stones associated with significant mucosal edema or if vision is

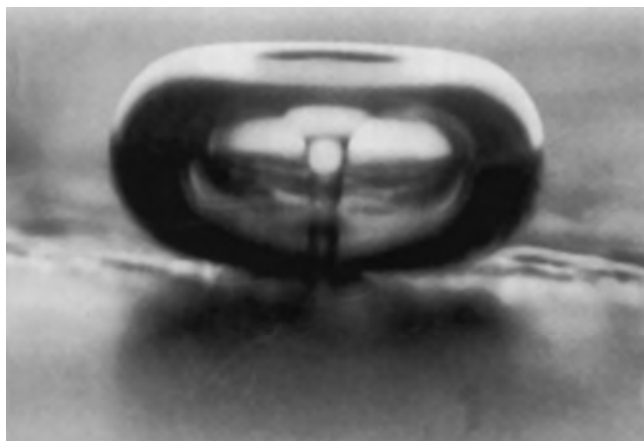


Figure 54-1. Photograph of liquid microjet produced by an asymmetrically collapsing cavitation bubble. (Courtesy Dr. Larry Crum.)

impaired by the minor hemorrhage that commonly occurs during EHL (Hofbauer et al, 1995).

As with most lithotrites, retrograde propulsion of calculi and fragments can occur during EHL and is more pronounced than with holmium:yttrium YAG lithotripsy (Teichman et al, 1997). In a series of 43 patients treated for proximal ureteral calculi, 14% required subsequent SWL for stones that migrated into the kidney (Yang and Hong, 1996). Placement of a basket or other retention device above the stone may prevent stone retropulsion. However, care should be taken not to activate the EHL device directly on the basket wires or the guidewire. Another disadvantage of EHL compared with holmium:yttrium-aluminum-garnet (YAG) lithotripsy is the larger number and size of fragments produced, especially for stones larger than 15 mm. The repeated passage of the ureteroscope to extract the multiple stone fragments produced during EHL may exacerbate mucosal irritation (Teichman et al, 1997).

EHL will successfully fragment 90% of stones. However, treatment failures may be due to a variety of stone compositions. Stone surface characteristics also may play a role in fragmentation efficiency; rough calculi have been reported to fragment more readily than smooth calculi (Basar et al, 1997). Although EHL successfully fragments most ureteral stones, the average 3-month stone-free rate is only 84% because some of the fragments created during lithotripsy and not removed may be retained in the ureter. Stone-free rates decrease with ureteral stones larger than 15 mm and are significantly lower than those reported for holmium:YAG lithotripsy (67% vs. 100%) (Teichman et al, 1997).

The advantages of EHL include probe flexibility, especially the smaller probes such as the 1.9 Fr, which allows intracorporeal lithotripsy throughout the entire upper urinary tract through rigid or flexible ureteroscopes. Only the holmium:YAG laser, configured with the 200- μ m fiber, offers comparable size and flexibility advantages (Elashry et al, 1996). The 1.6-Fr EHL probe may be even more flexible than the 200- μ m laser fiber (Poon et al, 1997).

EHL is also the least costly intracorporeal device, requiring the purchase of a comparatively inexpensive generator and probes. An average of 1 to 1.3 probes are used per case, except in instances of harder stones (e.g., calcium oxalate monohydrate stones), when two or more EHL probes may be needed (Elashry et al, 1996; Huang et al, 1998).

Technique. For intraureteral lithotripsy, the smaller 1.6- and 1.9-Fr probes should be used. The EHL fiber tip should be positioned 2 to 5 mm distal to the end of the ureteroscope to protect the lens system from being damaged when the probe is discharged. Before the EHL generator is activated the stone must be clearly visible. The probe is placed approximately 1 mm from the stone surface, a distance allowing maximum shock wave emission (Zhong et al, 1997). Initially, low voltage (50 to 60 V) and short intermittent or single pulses are used to enhance safety. The generator output is increased as needed to fragment the stone. However, it is recom-

mended that the treating physician limit the maximum output used in treating ureteral stones to minimize the risk for perforation. The goal of the treatment is to create fragments that can be removed with grasping forceps or a basket device or fragments that are likely to pass spontaneously. Attempts to reduce the stone to fragments smaller than 2 mm are not recommended because damage to the urothelium may occur (Denstedt and Clayman, 1990). After 50 to 60 seconds of firing, the insulation at the tip of the probe may peel away and at this time a new probe should be used (Segura, 1999).

Laser Lithotripsy. Laser is an acronym for light amplification by stimulated emission of radiation, which is a concise description of how a laser works. Laser energy is produced when an atom is stimulated by an external energy source, which creates a population of electrons in an excited state. These excited or higher energy electrons can release their excess energy in the form of photons or light energy. Laser light differs from natural light in that it is coherent (all photons are in phase with one another), collimated (photons travel parallel to each other), and monochromatic (all photons have the same wavelength (Floratos and de la Rosette, 1999)). These unique features of laser light allow considerable energy to be transmitted in a highly concentrated manner. Lasers are named after the medium that generates their specific wavelength of light; for example, the laser was developed in 1960 and the first medium used was the ruby. In 1968, Mulvaney and Beck reported that although the ruby laser could effectively fragment urinary calculi, it generated excessive heat and was not appropriate for clinical use. This continuous-wave laser simply heats the stone until vaporization occurs, which requires the laser to generate heat greater than the melting point of the stone. A solution for this problem came with the development of pulsed lasers: the application of pulsed energy results in high-power density at the stone's surface but little heat dissipation. The first widely available laser lithotrite was the pulsed-dye laser, which employed a coumarin green dye as the liquid laser medium. Although the coumarin pulsed-dye laser represented a major advancement in intracorporeal lithotripsy, there were a number of significant drawbacks to this technology in that stones of certain composition (calcium oxalate monohydrate, cystine) would not fragment well or even at all, coumarin dye is a toxic agent and required cumbersome disposal procedures, and the required eye protection made visualization of the stone and fiber difficult.

Continued technologic advancements eventually led to the development of the holmium:YAG laser. The holmium laser is a solid-state laser system that operates at a wavelength of 2140 nm in the pulsed mode. Pulse duration of the holmium laser ranges from 250 to 350 microseconds and is substantially longer than the pulse duration in pulsed-dye lasers. The holmium laser is highly absorbed by water; because tissues are composed mainly of water the majority of the holmium laser energy is absorbed superficially, which results in superficial cutting or ablation. The zone of thermal injury associated with laser ablation ranges from 0.5 to 1.0 mm (Wollin and Denstedt, 1998). The mechanism of stone fragmentation of the holmium:YAG laser is different from that of the pulsed-dye lasers. The long holmium:YAG pulse duration produces an elongated cavitation bubble that generates only a weak shock wave, in contrast to the strong shock wave produced by short-pulse lasers. Vassar and associates (1999) demonstrated that during holmium lithotripsy, stone fragmentation began before bubble collapse and shock wave production. Furthermore, no stone fragmentation occurred when the fiber was discharged at an incident angle of 90 degrees. Lithotripsy was more efficient for dry stones in air, indicating that the holmium laser requires direct absorption of laser energy. These data, as well as the presence of thermal products after holmium irradiation, such as glowing hot stone fragments, indicate that holmium laser lithotripsy occurs primarily through a photothermal mechanism that causes stone vaporization (Dushinski and Lingeman, 1998; Wollin and Denstedt, 1998; Vassar et al, 1999).

Advantages and Disadvantages. The holmium:YAG laser can transmit its energy through a flexible fiber, which facilitates intracorporeal lithotripsy throughout the entire collecting system. However, compared with EHL, the holmium:YAG laser is safer and

more efficient. Whereas EHL may cause injury to the ureter even when the probe is activated several millimeters away from the ureteral wall, the holmium laser may be safely activated at a distance of 0.5 to 1 mm from the ureteral wall (Santa-Cruz et al, 1998). **The ability of the holmium laser to fragment all stones regardless of composition is a clear advantage** over the coumarin pulsed-dye laser. Successful fragmentation of ureteral stones of all compositions has been reported, and mean perforation and stricture rates are generally in the range of 1% to 2%. During PNL the holmium laser is most helpful in clearing smaller stones (<2 cm) when the use of flexible instruments is required for access to stones in a calyx remote from the nephrostomy site. **The holmium laser is one of the safest, most effective, and most versatile intracorporeal lithotripters.** Further advantages of the holmium laser include its production of significantly smaller fragments compared with other lithotrites. These small fragments are easily irrigated out of the collecting system, which reduces the need for extraction of the fragments with basket or grasping devices (Teichman et al, 1998a). **The holmium laser produces a weak shock wave, which reduces the likelihood of retropulsion of the stone** or stone fragments compared with EHL or pneumatic lithotrites (Teichman et al, 1998a; Vassar et al, 1999; Sofer and Denstedt, 2000). However, the 365- and 550- μ m laser fibers will cause significantly more retropulsion than the 200- μ m fibers (White et al, 1998). Of note, Kang and associates (2006) demonstrated that not just the laser fiber size, but also laser settings, such as the pulse duration, will affect stone retropulsion. The authors found that stone retropulsion could be significantly reduced by increasing the laser pulse duration.

The holmium laser has several distinct operating advantages compared with the coumarin pulsed-dye laser. The required eye protection for the holmium laser does not compromise the ureteroscopic view of the stone or the fiber (Segura, 1999). In fact, the holmium laser properties are such that with use of energy levels applied for stone disease (i.e., less than 15 W), the operator's cornea would be damaged only if it were positioned at a distance of 10 cm or less from the fiber (Scarpa et al, 1999). The holmium laser is more compact than the coumarin laser, requires minimal maintenance, and is ready for use 1 minute after it is activated.

The major disadvantage of the holmium laser is the initial high cost of the device and the cost of the laser fibers. Elashry and coworkers (1996) noted an advantage of EHL over holmium laser lithotripsy in capital and service contract cost and lithotripter cost per case. However, **the holmium laser has multiple soft tissue applications and can be used to treat patients with benign prostatic hyperplasia, strictures, and urothelial tumors.** In addition, the laser fibers are reusable, so that the effective cost of the holmium laser device and reusable fibers may be lower than that of EHL (Teichman et al, 1998a). The most significant improvement in holmium laser lithotripsy will likely come from improved delivery fibers. At present, the smallest fiber in widespread use, the 200- μ m fiber, impedes deflection of a flexible ureteroscope by up to 20 degrees. As smaller laser fibers, such as those of 150- μ m diameter and smaller, are produced, it is likely that this effect on endoscope deflection will be further reduced. The fracture of a laser fiber inside an endoscope can result in a catastrophic failure of the scope, because when this occurs the fiberoptic bundles that transmit images and light are generally destroyed. Future efforts toward maximizing fiber durability may reduce these events.

The thulium fiber laser has emerged as a potential therapeutic alternative to the holmium laser, because it may hold several advantages over the holmium platform. Its laser fibers are smaller, which may permit improved endoscope deflection and irrigation flow (Blackmon et al, 2010). At present, though, its use in lithotripsy remains investigational.

Technique. The technique of holmium laser lithotripsy is relatively straightforward and involves placement of the fiber on the stone surface before the laser is activated. Clear vision is essential at all times to avoid mucosal perforation. After initiation of holmium laser lithotripsy, a short pause is often required because of the "snowstorm effect" created by the scattering of minute stone fragments, which can be cleared by endoscopic irrigation (Scarpa et al,

1999). Caution must be exercised in operating the holmium laser near a guidewire or a basket because **the holmium laser is capable of cutting through metal** (Freiha et al, 1997; Lane et al, 2005). Furthermore, the laser fiber should extend at least 2 mm beyond the tip of the endoscope to avoid destroying the lens system or the working channel of the endoscope. Baskets used to stabilize calculi during laser lithotripsy should be the preformed type and not the type manufactured by bending of the wire; if they are inadvertently transected by the holmium laser, they will retain the basket shape and not cause a sharp barbed effect (Grasso and Chalikh, 1998).

Holmium laser fibers are available in 200-, 365-, 550-, and 1000- μ m diameters as well as end- or side-firing fibers. However, only the 200- and 365- μ m fibers are used for flexible intracorporeal lithotripsy. Teichman and colleagues (1998b) reported that the 550- μ m side-firing fiber is more effective than the end-firing fiber during PNL, suggesting that the more nearly normal (perpendicular) laser-to-calculus incident angle provided by the side-firing fiber enhances lithotripsy. However, in treatment of ureteral stones, the end-firing fiber may produce a better angle of attack. **Lithotripsy with the holmium laser depends on the pulse energy output and the diameter of the optical delivery fiber, suggesting that lithotripsy efficiency correlates with energy density** (Vassar et al, 1998). Energy density increases with decreasing fiber diameter, although Calvano and associates (1999) demonstrated, in vitro, that peak lithotripsy occurred with 365- and 550- μ m fibers, whereas the 200- μ m fiber can act as a fine drill, which is less effective. Compared with some of the soft tissue applications of the holmium laser, the power used for stone fragmentation is considerably lower. In general, pulse energies of 0.6 to 1.2 J and pulse rates of 5 to 15 Hz are used (Wollin and Denstedt, 1998; Spore et al, 1999). Because high-pulse energy narrows the safety margin and may increase stone retropulsion as well as fiber damage, **it is recommended that treatment be begun with low-pulse energy (e.g., 0.6 J) with a pulse rate of 6 Hz and that pulse frequency be increased (in preference to increasing pulse energy) as needed to speed fragmentation** (Spore et al, 1999). To maximize lithotripsy efficiency, the treating physician should move the laser fiber over the stone surface in a "painting" fashion, vaporizing the stone rather than fragmenting it, and avoid drilling into the stone, fracturing the fiber tip, or drilling past the stone, damaging the urothelium. The laser fiber should be kept at least 1 mm from the urothelium, and lithotripsy should proceed until the stone fragments are small enough to be passed spontaneously or can be safely retrieved with a basket or grasping device.

Stone retropulsion during laser lithotripsy can be advantageous in certain settings. When a stone is positioned in a renal calyx, firing the laser at high frequency will agitate the stone material, bringing the stones or pieces of the stone into rapid close contact with the tip of the laser fiber. Stone fragmentation is enhanced by the increasing likelihood of direct laser contact or contact with other calculus material. This phenomenon has been termed the "popcorn technique," because it bears a semblance to popcorn kernels popping in a heater (Chawla et al, 2008).

Lithotripters

Ballistic Lithotripsy. Ballistic lithotripsy relies on energy generated by the movement of a projectile (Fig. 54-2). The initial movement of the projectile can be induced by a variety of stimuli, but once the projectile is in contact with another object the ballistic energy is transferred to the object. Flexible objects preserve the momentum of the energy, but inflexible objects, such as a stone, fragment on impact (a "jackhammer" effect).

Several manufacturers have introduced ballistic lithotrites. The Swiss LithoClast (Boston Scientific, Natick, MA), introduced in the early 1990s, was the first ballistic lithotrite. The metal projectile in the hand piece of the LithoClast is propelled by measured bursts of compressed air against the head of a metal probe at a frequency of 12 cycles per second. The probe tip is placed against the stone, and the LithoClast is activated by a foot pedal (Denstedt et al, 1992). Rane and associates (2008) first reported on a novel, handheld ballistic lithotripter, the StoneBreaker (Cook Medical, Bloomington,

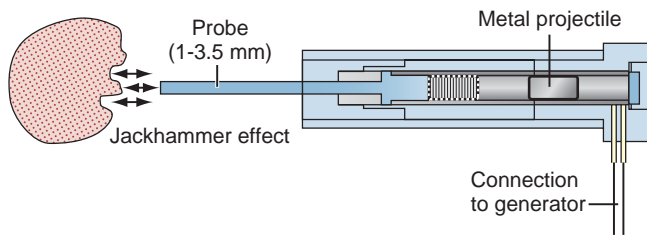


Figure 54-2. Schematic illustration of the LithoClast (Electromedical Systems, Kaufering, Germany) hand piece mechanism. An oscillating pellet provides ballistic energy to the probe, resulting in a jackhammer-like effect on calculi. (Courtesy Dr. John Denstedt.)

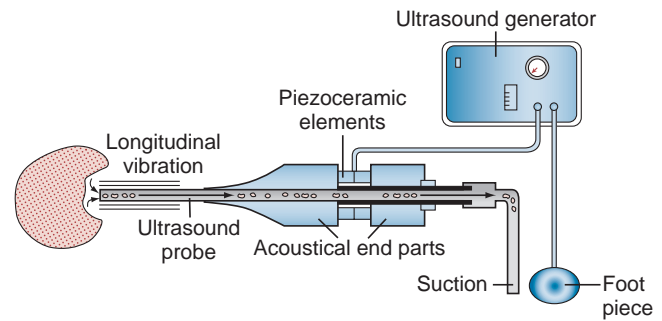


Figure 54-3. Ultrasound lithotripsy generator and hand piece.

IN). This portable device uses a small cylinder-based air supply, rather than hospital air, simplifying its ergonomic profile. Chew and associates (2011) reported a multicenter trial that compared the StoneBreaker with the Swiss LithoClast during PNL, and found that the StoneBreaker was easier to set up and use, and stone fragmentation with it was more rapid. Wang and associates (2012) investigated an alternative hand-held device, the Swiss LithoBreaker (Electro Medical Systems, Nyon, Switzerland), an electrokinetic device. In their in vitro effort, the authors found that although it was efficient in a ureteroscopic model, it performed poorly in a percutaneous model (Wang et al, 2012).

Advantages and Disadvantages. The ballistic lithotrites provide an effective means for stone fragmentation in the entire urinary tract, with a wide margin of safety. Successful fragmentation of ureteral stones of all compositions has been reported in 73% to 100% of cases, a success rate similar to that of EHL. The lower success rate of 73.7% reported by Knispel and associates (1998) suggests reduced efficiency of the LithoClast when it is applied through the deflected working channel (30 degrees) of the 6.9-Fr semirigid ureteroscope. As well, a significant decrease in the maximum tip displacement and velocity of the LithoClast 0.89-mm flexible probe occurs when it is used through a flexible ureteroscope deflected more than 24 degrees (Zhu et al, 2000). Grocela and Dretler (1997) also reported that for the current ballistic devices, bowing of the probe during lithotripsy results in significant power loss. Ballistic devices may be especially advantageous when large or hard stones are encountered during PNL or endoscopic lithotripsy of bladder calculi. In contrast to ureteral stones, kidney stones are easily "pinned down" against the urothelium during ballistic lithotripsy, allowing a rapid and more efficient fragmentation method than ultrasonic lithotripsy. Once the bulk of the calculus is fragmented, lithotripsy can be completed with the ultrasonic lithotripter, which can also aspirate minute stone fragments (Denstedt, 1993; Teh et al, 1998; Yavasoglu et al, 1999). Compared with EHL, ultrasonic lithotripsy, and laser lithotripsy, ballistic devices have a significantly lower risk for ureteral perforation (Piergiorganni et al, 1994). In an animal model, despite 6 minutes of activation in direct contact with the ureteral wall, a ballistic lithotripter was unable to cause perforation (Santa-Cruz et al, 1998). Furthermore, because no heat is produced during lithotripsy, the risk for thermal injury to the urothelium is eliminated.

One of the advantages of ballistic lithotrites is their relatively low cost and low maintenance. Although the devices are more expensive than EHL, in terms of capital equipment purchasing, there are no disposable costs and the probes have an extremely long life span (Hofbauer et al, 1995).

Disadvantages of ballistic devices include the rigid nature of the technology, which requires ureteroscopes or nephroscopes with straight working channels. In addition, ballistic lithotripsy is associated with a relatively high rate of stone retropulsion, reported in 2% to 17% of ureteral stone treatments. Often, failure to fragment a stone is related to an inability to trap a ureteral stone in a capacious ureter (Denstedt et al, 1992). The migration rate depends on the initial stone location; there is a higher chance of stone migration for proximal ureteral stones compared with distal ureteral

stones (Knispel et al, 1998). Limited data are available on the beneficial effects of suction devices, such as the LithoVac (Boston Scientific), in limiting stone migration. Delvecchio and colleagues (2003) reported the use of the 0.8-mm pneumatic lithotripsy probe placed through a 4.8-Fr hollow LithoVac suction probe in 21 patients with ureteral stones. Overall stone-free rate at 3 months was 95%, and the suction device reportedly facilitated lithotripsy by preventing stone migration and maintaining a clear endoscopic view.

Teichman and associates (1998a) reported that fragments larger than 4 mm are produced by all types of endoscopic lithotrites, with the exception of the holmium:YAG laser. Fragmenting a stone into pieces smaller than 4 mm with a ballistic lithotripter can be challenging, especially a hard stone in a dilated ureter. Fragments larger than 4 mm are associated with a higher rate of repeated ureteroscopy and therefore should be removed with baskets or stone graspers during the initial procedure (Keeley et al, 1999).

Technique. Like other lithotrites, the ballistic lithotripter should be activated only when there is a clear view of the stone and the probe position can be identified. Fixation of the stone is rarely difficult in the kidney or the bladder but may be a problem in the ureter. Fixation of ureteral stones with a basket or proximal placement of a ureteral occlusion device is sometimes necessary (Ursiny and Eisner, 2013). The goal of ballistic lithotripsy in the ureter is to generate fragments that are small enough to permit spontaneous passage (<2 mm). However, more often, larger fragments have to be removed with a basket or grasping device. The relatively atraumatic nature of ballistic lithotripsy may allow the avoidance of stent placement after ureteroscopy. Tan and colleagues (1998) reported the use of a stent in only 9 of 68 patients undergoing ballistic lithotripsy. In this series, difficult ureteral access and severe edema and trauma at the site of stone impaction were indications for stent placement.

Ultrasonic Lithotripsy. Mulvaney (1953) first reported the use of ultrasonic vibrations to break renal calculi in 1953. Since then, ultrasonic lithotripsy has become a commonly used modality for the treatment of renal calculi during PNL and for the fragmentation of bladder and ureteral stones. The ultrasound probe works by applying electrical energy to excite a piezoceramic plate in the ultrasound transducer (Fig. 54-3). The plate resonates at a specific frequency and generates ultrasonic waves at a frequency of 23,000 to 25,000 Hz. At operating frequencies there is no audible sound, although 98 dB of ultrasonic inaudible noise levels has been measured (Segura and LeRoy, 1984).

Ultrasound energy is transformed into longitudinal and transverse vibrations of the hollow steel probe, which then transmits the energy to the calculus. The probe tip causes the stone to resonate at high frequency and to break; but when the probe is placed on compliant tissue, such as urothelium, damage is minimal because the tissue does not resonate with the vibrational energy (Grocela and Dretler, 1997). Although some heat may develop at the end of the probe during lithotripsy, with an irrigation rate of 30 mL/min the temperature increase at the tip of the probe can be reduced to a maximum of 1.4°C (Marberger, 1983). Because irrigation may be limited during ureteroscopy, ultrasonic lithotripsy is more efficient during PNL, owing to the greater flow of irrigant through the larger diameter ultrasonic probes that can be used. The

ultrasonic lithotripter system is connected to suction so that debris from the stone is removed continuously with the irrigating fluid during lithotripsy. In addition, the flow of fluid through the hollow probe serves to cool the instrument. Heating of the ultrasound transducer should alert the surgeon to possible occlusion in the probe lumen, an occurrence more commonly encountered with small-diameter probes that are used in the ureter. Although many manufacturers provide an integrated power and suction foot switch for the ultrasonic unit, wall suction with intermittent clamping of the suction tubing by an assistant is a simple and inexpensive alternative. In general, suction is applied only when the ultrasonic lithotripter is activated, and suction pressures in the range of 60 to 80 cm H₂O are sufficient to maintain adequate flow of irrigant during lithotripsy. Higher suction pressures tend to draw air bubbles into the system, impeding vision. Ultrasonic probes are available at sizes ranging from 2.5 to 12 Fr. The 2.5-Fr probe is solid and contains no hollow center for suction. Therefore, when it is used in the ureter, heat dissipation is slow. Bending the probe results in energy loss at the convexity of the bend, with the energy being transformed to heat (Marberger, 1983).

Stones vary in their susceptibility to destruction with ultrasound. Although the chemical composition of the stone influences the time required for complete disintegration (cystine, calcium oxalate monohydrate, and uric acid being the most resistant to fragmentation), the size, density, and surface structure of the calculus appear to be more important. Smaller stones are more rapidly destroyed, as are rough stones. Smooth-surfaced large stones may be more difficult to fragment (Marberger, 1983; Segura and LeRoy, 1984).

Advantages and Disadvantages. The major advantage of ultrasonic lithotripsy is the efficient combination of stone fragmentation and simultaneous fragment removal. Fragments smaller than 2 mm are aspirated through the hollow lithotrite along with the irrigation fluid. Larger fragments may be removed with forceps or baskets. The efficiency of this technique coupled with the minimal risk for serious tissue damage has made this technology popular. Ultrasonic lithotripsy is often the first modality used for stone fragmentation during PNL.

However, the rigid nature of ultrasonic probes and their small diameter limit the appeal of this technology in treatment of ureteral stones. A ureteroscope with a straight working channel is required. Furthermore, a relatively large 5-Fr working channel is needed to accommodate the 4.5-Fr hollow probe. However, success rates between 69% and 100% have been reported (Denstedt, 1996; Gur et al, 2004). The technology may be particularly useful for patients with large ureteral stones as well as for those with steinstrasse because removal of stone debris is facilitated. Excellent results also have been reported for distal ureteral stones easily accessible to the rigid ureteroscope (Grocera and Dretler, 1997; Segura, 1999). Chaussy and colleagues (1987) reported a 96.6% complete fragmentation rate in 118 patients with a 2.5-Fr solid probe that can be used with smaller ureteroscopes, and Fuchs (1988) reported similar results. However, in a later report, Murthy and associates (1997) compared a group of 25 patients treated by a rigid ureteroscope and the 3-Fr ultrasonic solid probe with a group of 122 patients treated by the LithoClast ballistic device, and the overall success rate was significantly higher for the LithoClast group than for the ultrasonic group (97.3% vs. 84%, respectively).

Technique. When ultrasonic lithotripsy is applied during PNL the stone should first be trapped between the probe and the urothelium. The application of gentle pressure to the stone enhances fragmentation, but the temptation to push too hard should be avoided because calculi can easily be pushed through the urothelium. The risk for perforation increases with smaller or more rugedly surfaced stones because the force applied to the stone is transferred to a smaller surface area of the urothelium. The risk for perforation is particularly high in the thin-walled renal pelvis or ureter rather than in a calyx that is backed by renal parenchyma.

When ureteral stones are treated the ureter may need to be dilated to allow passage of the offset rigid ureteroscope. The ultrasonic probe is passed through the working channel and placed directly on the stone. If necessary, the stone can be engaged in a

stone basket to prevent proximal migration. As with other intracorporeal lithotripsy devices the goal of treatment is either to fragment the stone completely or to generate fragments that are small enough to be extracted or passed spontaneously.

Combination Ballistic and Ultrasonic Devices

Several manufacturers have introduced combined ultrasonic and pneumatic devices that aim to combine the superior fragmentation ability of the pneumatic component with the ability of the ultrasonic modality to simultaneously evacuate stone fragments. The first combination device brought to the clinical market was the LithoClast Ultra, which relied on a combination hand piece (actually, two separate hand pieces connected together) to join the ultrasonic and pneumatic components. The first portion of the combination hand piece was a traditionally designed pneumatic handle, with a smaller diameter solid probe. The ultrasonic handle, driven by a standard piezoelectric mechanism, was modified to allow the coaxial insertion of the pneumatic probe. Each modality can be activated separately or in unison; when operated in unison, the ballistic fragmentation of the stone is accomplished with the pneumatic component and the ultrasonic component then removes the resulting debris.

Given the varied types of rigid intracorporeal devices (stand-alone ballistic and ultrasonic as well as combination ballistic and ultrasonic), a rigorous and impartial evaluation of intracorporeal lithotripters is a subject of importance to urologists. Each device may have certain unique properties that make it more suitable for particular applications, and manufacturer's claims may contain elements of bias that make it difficult for the urologist to ascertain which device may be most suitable to purchase. Therefore a number of investigators have devised testing methods to compare intracorporeal lithotrites. Liatsikos and associates (2001) first reported an in vitro testing system designed to measure the efficiency of ultrasonic lithotrites in which stone phantoms were fragmented in a nephroscope-guided manner. The inherent weakness in this study design was that stone fragmentation was directed by hand, which could introduce significant operator bias. Haupt and Haupt (2003) subsequently reported an in vitro system that relied on an elaborate weight and fulcrum to bring a stone phantom into contact with the probe tip at a constant force. Although operator bias was no longer present, this system was complex and cumbersome, making replication challenging. Kuo and associates (2003b) have presented a novel and simple hands-free testing system in which the ultrasonic hand pieces were secured upright and the stone phantom placed into contact with the probe by a weight mechanism (Fig. 54-4). This design system was first used to test the efficiency of pure ultrasonic lithotrites and measured the time it took for the probe to penetrate the stone phantom. In this study the Olympus LUS-2 (Olympus, Melville, NY) produced the fastest overall stone penetration time.

After the introduction of the combination ultrasonic and pneumatic devices, the same testing apparatus previously used by Kuo and associates (2004) to evaluate the ultrasonic devices was used to evaluate the LithoClast Ultra. Because of the wide variety of ultrasonic power and pneumatic frequency settings available, the testing apparatus was used to assess the efficiency of various setting combinations. The end point was stone penetration time, and the fastest stone penetration times were achieved at settings of 100% ultrasonic power and 12-Hz pneumatic frequency. Pietrow and associates (2003) evaluated the efficiency of the LithoClast Ultra combination device in a clinical setting, performing a prospective, randomized trial comparing the combination device with standard ultrasonic lithotrites in patients undergoing PNL. The stone clearance times were significantly better for the combination device than for the conventional ultrasonic lithotripters.

The CyberWand (Gyrus ACMI, Southborough, MA) is an intracorporeal lithotripter that relies on a dual ultrasonic probe design that incorporates coaxial high-frequency and low-frequency probes. The dual probe design creates a synergistic effect, which enables efficient stone fragmentation while still allowing the suction evacuation of small fragments in the same way as other ultrasonic devices.

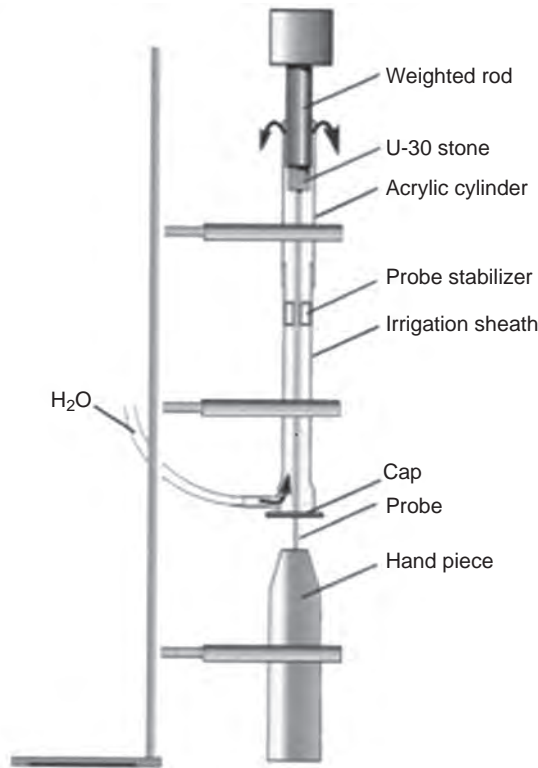


Figure 54-4. In vitro testing apparatus for a “hands-free” testing approach to the evaluation of intracorporeal lithotrites.

Kim and associates (2007) used the previously mentioned hands-free testing design previously described by Kuo and associates (2003a) to find that the stone penetration time for the CyberWand was almost twice as rapid as it was for the LithoClast Ultra.

Krambeck and associates (2011) reported a multicenter trial comparing the CyberWand with a conventional ultrasonic device (Olympus LUS-II) and found that there was no appreciable difference in stone fragmentation rates or complications between the two devices. Chu and associates (2013) also investigated whether pneumatic, ultrasonic, or combination devices had an effect on postoperative fever; in a study of over 5000 patients collated through the Clinical Research Office of the Endourological Society, they found that the lithotrite had no effect (Chu et al, 2013).

Conclusion

The current technology of intracorporeal lithotripsy provides the urologist with several effective options for stone fragmentation, depending on the type of endoscope used (rigid or flexible) and the location and accessibility of the stone. The holmium laser has become the mainstay of ureterorenoscopic lithotripsy by virtue of its ability to fragment all stones. As well, the use of small-diameter fibers allows access to all areas of the ureter and intrarenal collecting system. However, for patients with complex, large-volume calculi undergoing PNL, the combination devices will permit more efficient fragmentation of the stone. When selecting a lithotripter for purchase, the institution must take into account the number and nature of stone-related procedures performed to maximize the utility and cost-effectiveness of the device.

Extracorporeal Shock wave Lithotripsy

Methods and Physical Principles

In extracorporeal SWL a source external to the patient's body generates a shock wave. Specifically, the energy source rapidly deposits

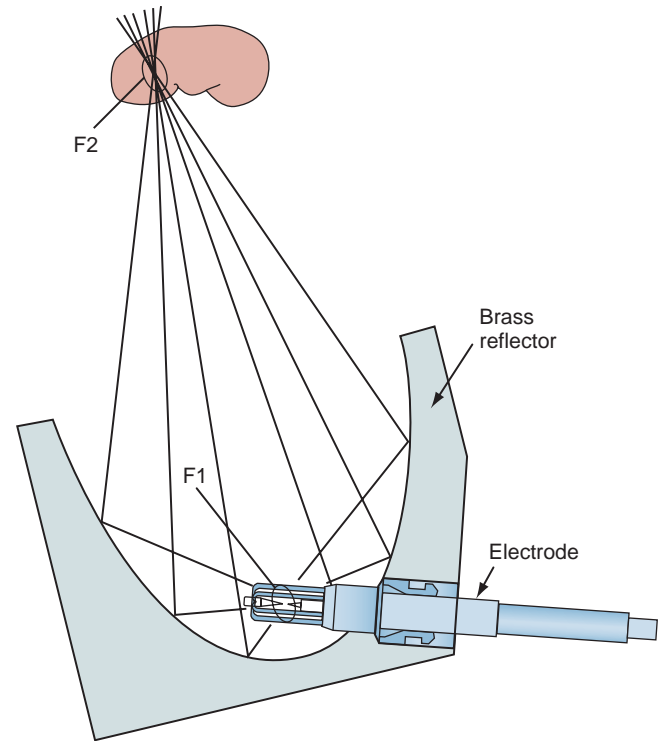


Figure 54-5. Schematic view of an electrohydraulic shock wave generator. An electrode is used to generate a shock wave. F1, focus 1; F2, focus 2.

pulses of energy into a fluid environment, which results in the generation of a shock wave. Shock waves are surfaces that divide material ahead, not yet affected by the disturbance, from that behind, which has been compressed as a consequence of energy input at the source (Sturtevant, 1996). These waves move faster than the speed of sound, and the stronger the initial shock, the faster the shock wave moves. Their behavior is characteristic of the propagation of nonlinear waves. Although the shock waves in lithotripters generate large pressures, they are relatively weak in that they induce only slight compression and deformation of a material. The uniqueness of the shock wave lithotripter is in its exploitation of shock wave focusing. Relatively weak, noninvasive waves are generated externally and transmitted through the body. The shock waves build to sufficient strength only at the target, where they generate enough force to fragment a stone.

Generator Type. The three primary types of shock wave generators are electrohydraulic (spark gap), electromagnetic, and piezoelectric.

Electrohydraulic (Spark Gap) Generator. In the electrohydraulic shock wave lithotripter, a spherically expanding shock wave is generated by an underwater spark discharge (Cleveland et al, 2000). High voltage is applied to two opposing electrodes positioned about 1 mm apart. The high-voltage spark discharge causes the explosive vaporization of water at the electrode tip. For the spherically expanding shock wave to be focused on a calculus the electrode is placed at one focus (termed F1) of an ellipsoid and the target (the kidney stone) is placed at the other focus (termed F2). Figure 54-5 shows a hemiellipsoid reflector and a spark gap typical of those used in the older electrohydraulic machines. This arrangement allows the projection of the majority of the original shock wave energy from the electrode tip to the stone, provided the electrode tip is precisely at F1. The body of the electrode varies in orientation among machines in that it is positioned within the ellipsoid to provide an easy means of replacement as it deteriorates.

The clear advantage of this generator is its effectiveness in breaking kidney stones (Lingeman, 1997). Disadvantages are the

substantial pressure fluctuations from shock to shock and a relatively short electrode life. New, longer life electrodes (like the NewTrode by HMT, Lengwil, Switzerland) have been developed to overcome these drawbacks. Another issue to consider is that as the electrode deteriorates, it wears down, and a 1-mm displacement of the electrode tip off F1 can shift F2 up to 1 cm off the initial target.

Electromagnetic Generator. Whereas the electrohydraulic lithotripter produces focused shock waves by bouncing spherically expanding shocks off an ellipsoid reflector, the electromagnetic generators produce either plane or cylindrical shock waves. The plane waves are focused by an acoustic lens (Fig. 54-6); the cylindrical waves are reflected by a parabolic reflector (Fig. 54-7) and trans-

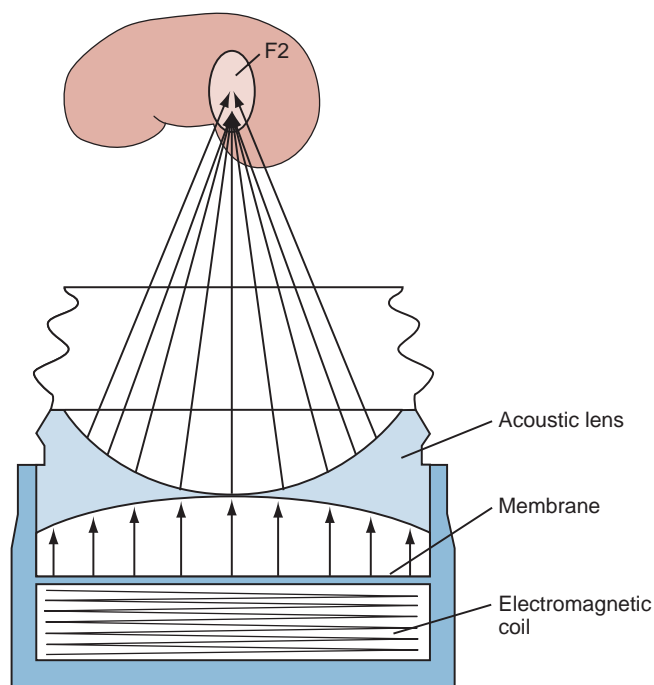


Figure 54-6. Schematic view of an electromagnetic shock wave generator that uses an acoustic lens to focus the shock wave. An electromagnetic coil is used to generate the shock wave. F2, focus 2.

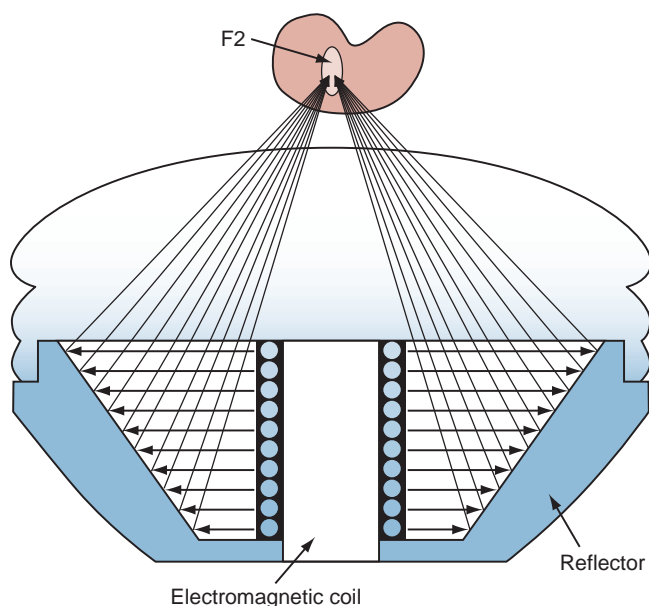


Figure 54-7. Schematic view of an electromagnetic shock wave generator that uses a parabolic reflector to focus the shock wave. An electromagnetic coil is used to generate the shock wave. F2, focus 2.

formed into a spherical wave. The basic design of an electromagnetic generator is simple. Figure 54-6 shows a system that uses a water-filled shock tube containing two conducting cylindrical plates separated by a thin insulating sheet. When an electrical current is sent through one or both of the conductors, a strong magnetic field is produced between the conductors, moving the plate against the water and thereby generating a pressure wave. The electromagnetic force that is generated, termed *magnetic pressure*, causes a corresponding pressure (shock wave) in the water. The shock front produced is a plane wave that is of the same diameter as the current-carrying plates. The energy in the shock wave is concentrated onto the target by focusing it with an acoustic lens. The electromagnetic system that uses a cylindrical source (see Fig. 54-7) also has a cylindrical coil surrounded by a cylindrical membrane that is pushed away from the coil by the induction of a magnetic field between the two components. In both systems the pressure pulse has only one focal point (F2) that is positioned on the target.

Electromagnetic generators are more controllable and reproducible than electrohydraulic generators because they do not incorporate a variable in their design such as the underwater spark discharge. Other advantages include the introduction of energy into the patient's body over a large skin area, which may cause less pain. In addition, a small focal point can be achieved with high-energy densities, which may increase its effectiveness in breaking stones. This generator will deliver several hundred thousand shock waves before servicing, thereby eliminating the need for frequent electrode replacement, which is required with most electrohydraulic machines. A disadvantage of this design may be that the small focal region of high energy results in an increased rate of subcapsular hematoma formation. The rate of subcapsular hematoma formation for the Storz Modulith (Storz Medical, Tägerwil, Switzerland) has been suggested to be 3.1% to 3.7% (Dhar et al, 2004). Piper and associates (2001) suggested that perinephric hematomas may occur in up to 12% of patients treated with a DoLi S lithotripter (Dornier Medical Systems, Kennesaw, GA). In contrast, perinephric hematomas were reported to occur in approximately 0.6% of patients undergoing SWL with the unmodified Dornier HM3 machine (Chaussy and Schmiedt, 1984; Knapp et al, 1987).

Piezoelectric Generator. The piezoelectric lithotripter also produces plane shock waves with directly converging shockfronts. These generators are made of a mosaic of small, polarized, polycrystalline, ceramic elements (barium titanate), each of which can be induced to rapidly expand by the application of a high-voltage pulse (Fig. 54-8). Owing to the limited power of a single piezoelectric element, 300 to 3000 crystals are necessary for the generation of a sufficiently large shock pressure. The piezoelectric elements are usually placed on the inside of a spherical dish to permit convergence of the shockfront. The focus of the system is at the geometric center of the spherical dish.

The advantages of this generator include the focusing accuracy, a long service life, and the possibility of an anesthetic-free treatment because of the relatively low-energy density at the skin entry point of the shock wave. For this reason, piezoelectric lithotripters in general tend to produce less discomfort than do lithotripters with other energy sources. A major disadvantage of this system is the insufficient power it delivers, which hampers its ability to effectively break renal stones. The piezoelectric energy sources produce some of the highest peak pressures of any lithotripter, but the actual energy delivered to the stone per shock wave pulse is several orders of magnitude lower than that delivered by an electrohydraulic machine because of the extremely tiny volume of F2.

Other Generators. Microexplosive generators have also been produced but have not gained widespread acceptance. The explosion of tiny lead azide pellets within a parabolic reflector generates the device's shock wave (Kuwahara et al, 1987). Despite the effectiveness of this type of generator in producing shock waves, this technology has not met with commercial success because of concerns about the storage and handling of the volatile lead azide pellets. Still other methods of shock wave generation use a laser beam or a

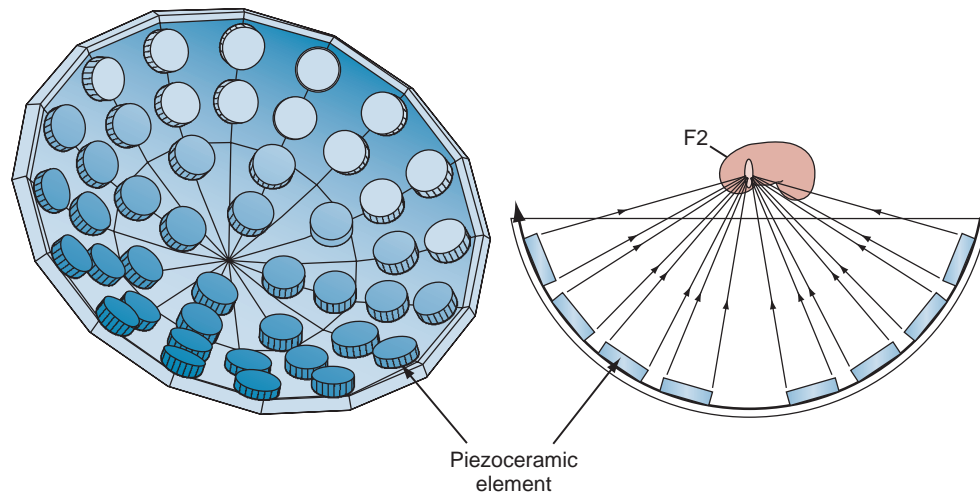


Figure 54-8. Schematic view of a piezoelectric shock wave generator. Numerous polarized polycrystalline ceramic elements are positioned on the inside of a spherical dish. F2, focus 2.

multistage light gas gun, but these too have not been well received commercially.

Focused ultrasound has emerged as a technology that can expel small stones or stone fragments from the urinary system (Sorensen et al, 2013). Harper and associates (2013) reported an in vitro study that effectively and rapidly migrated stone material through a urinary system phantom. Although the technology is not yet clinically available, it may ultimately play a role in extracorporeal stone management.

Imaging Systems. There are three basic designs used by lithotripter manufacturers for stone localization. They are fluoroscopy alone, ultrasonography alone, and the combination of ultrasonography and fluoroscopy.

Fluoroscopy Alone. The original Dornier HM3 lithotripter used two x-ray converters arranged at oblique angles to the patient and 90 degrees from each other to localize the stone effectively at F2. To reduce the cost of lithotripters, an adjustable C-arm has been subsequently introduced on many devices. There is presently a remarkable similarity in the fluoroscopic systems used among manufacturers. This appears to be primarily the result of a common theme in the industry to develop multifunctional tables around these machines. The fluoroscopic system typically consists of a high-quality digitized x-ray imaging system mounted on a rotatable C-arm with an isocentrically integrated shock wave source. Because the shock wave head can be rotated out of the field of the fluoroscopic system, the table can be used for routine urologic fluoroscopic applications.

The primary advantages of fluoroscopy still include its familiarity to most urologists, the ability to visualize radiopaque calculi throughout the urinary tract, the ability to use iodinated contrast agents to aid in stone localization, and the ability to display anatomic detail. The disadvantages include the exposure of the staff and patient to ionizing radiation, the high maintenance demands of the equipment, and the inability to visualize radiolucent calculi without the use of radiographic contrast agents.

Ultrasonography Alone. Ultrasonic localization was initially designed to aid multifunctional lithotripters for treatment of both urinary and biliary stones. It is presently used in several low-cost machines because it is inexpensive to manufacture and maintain compared with fluoroscopic systems. Another major advantage of this technology is in the treatment of children and infants when concern exists about the dose of ionizing radiation. In addition, ultrasonography can localize slightly opaque or nonopaque calculi.

Despite its advantages, ultrasound imaging has a number of significant disadvantages. Sonographic localization of a kidney stone requires a highly trained operator. Complicating the issue of stone detection is the fact that it is almost impossible to view a kidney stone in areas such as the middle third of the ureter or when there is an indwelling ureteral catheter. Once a stone is fragmented,

it is difficult to identify each individual stone piece. Unfortunately, these disadvantages tend to overshadow the advantages of ultrasound imaging.

Combination of Ultrasonography and Fluoroscopy. As the demand for interdisciplinary lithotripters has increased, the lithotripsy industry has responded, in some cases combining ultrasonography and fluoroscopy for stone localization. There are clearly advantages to these setups, but each system has a drawback that limits one of the functions of the system.

Anesthesia. The approach to anesthesia for lithotripsy has changed considerably since clinical SWL began in 1980. At that time, regional or general anesthesia was used in all instances because the unmodified HM3 device (15.6-cm ellipsoid; 80-nF generator) produced a powerful shock wave and treatment at recommended energy levels caused intolerable pain. Subsequently, urologists and lithotripter manufacturers recognized that the HM3 is considerably more powerful at the recommended energy setting than is necessary for the fragmentation of most renal calculi, an observation that spawned interest in less powerful lithotripters with lessened anesthesia requirements (Wilbert et al, 1987; Marberger et al, 1988). Several researchers have noted that the original HM3 lithotripter without modification produces excellent clinical results when it is used at lower energy settings (Pettersson et al, 1989; Tiselius, 1991; Tolley et al, 1991). In addition, such settings create a smaller lesion at F2 in experimental animals (Connors et al, 2000).

The discomfort experienced during SWL is related directly to the energy density of the shock wave as it passes through the skin and the size of the focal point. In the past decade several new and useful anesthetic techniques adaptable to SWL have been produced that were not available at the time SWL was introduced and include short-acting parenteral sedative-narcotics and topical agents.

Short-acting agents, such as the narcotic alfentanil and the sedative-hypnotics midazolam and propofol, have been used in various combinations to allow most SWL treatments with any lithotripter (including the unmodified Dornier HM3) to be accomplished comfortably for the patient without the need for general or regional anesthesia. Monk and associates (1991) compared two sedative-analgesic techniques (midazolam-alfentanil vs. fentanyl-propofol) and found that both techniques provided adequate anesthesia for SWL with use of an unmodified Dornier HM3 lithotripter. Anesthesia and recovery times were significantly shorter than those recorded for epidural anesthesia techniques. These findings have been confirmed by others (Nelson et al, 2001; Burmeister et al, 2002; Ozcan et al, 2002).

Another approach to minimize anesthesia requirements during SWL has been the use of topical agents. EMLA cream, a eutectic mixture of lidocaine and prilocaine, has been shown significantly to reduce anesthesia requirements during SWL (Basar et al, 2003).

A topical agent, EMLA cream should be applied at least 45 minutes before SWL. The combination of topical agents and short-acting intravenous agents is likely to minimize the amount of these agents required and to shorten recovery times.

Calculi composed of cystine, calcium oxalate monohydrate, or brushite are known to be resistant to fragmentation; if their presence is anticipated, delivery of higher levels of shock wave energy with attendant increased anesthesia requirements should be expected (Dretler, 1988; Klee et al, 1991). Thin patients have more pain during SWL because the converging shock wave is more concentrated at the point of skin penetration. Children and extremely anxious individuals may be served best by general anesthesia. If a lengthy treatment session is anticipated (i.e., bilateral SWL or treatment of ureteral and renal stones), the larger amount of topical and intravenous agents required lessens their appeal.

One important observation regarding the issue of general anesthesia versus intravenous sedation was reported by Sorensen and colleagues (2002) and Eichel and colleagues (2001). In a comparison of patients treated with the DoLi 50 lithotripter, the patients who received general anesthesia experienced a significantly greater stone-free rate than did the patients who underwent intravenous sedation. One possible explanation for this finding is the more controlled respiratory excursion that is conferred by the general anesthetic.

Lithotripter Comparisons

Shock wave lithotripters are considered by the U.S. Food and Drug Administration to be Class II devices. For a lithotripter to be brought to market simply requires documentation that the device has the same intended use and the same technologic characteristics as a predicate device that has already been approved and brought to market. Specific testing that evaluates, in a proscribed manner, the lithotripter's treatment efficacy and safety is not required. Largely as a consequence of this practice, few, if any, appropriately designed comparative trials of lithotripters exist in the published literature. In addition, there are no validated standards within the litho-

tripsy industry regarding a method of quantification of the power and efficiency of lithotripters, a problem further compounded by a lack of knowledge of the number of shock waves that can be safely administered to a kidney during any single SWL session with any lithotripter. Although there is general consensus that re-treatment rates are an appropriate indicator of lithotripter effectiveness, the lack of clinical agreement about the appropriate outcome of lithotripsy (i.e., stone free vs. residual fragments of various size) further hampers comparisons of lithotripters.

Only a small part of the literature published to date on the outcomes of SWL presents data that are stratified sufficiently to permit a meaningful comparative analysis. Surprisingly, despite the proliferation of lithotripters and the variety of solutions devised for stone targeting and shock wave delivery, no other lithotripter system has convincingly equaled or surpassed the results produced by the unmodified Dornier HM3 device. That the most effective lithotripter was invented first is a remarkable achievement for Dornier. In general, the less powerful lithotripters with smaller focal points result in lower stone-free rates or higher re-treatment rates. Additionally, it is now recognized that SWL inflicts a trauma similar to a renal contusion, which occasionally can result in adverse clinical sequelae. Potential concerns about the long-term effects of lithotripsy with the unmodified Dornier HM3 device may have been one motivating factor in the trend within the lithotripsy industry toward, at first, lower power but eventually higher power lithotripters with smaller focal points, with the goal that the efficacy of lithotripsy could be maintained while producing fewer deleterious effects on renal tissue (Figs. 54-9 and 54-10). Unfortunately, the newer lithotripters are less efficacious than the original Dornier device, and no published information is available to suggest that newer lithotripters produce fewer adverse effects for equivalent degrees of efficacy.

Mechanisms of Stone Comminution

Present knowledge in the field of SWL suggests that comminution of a renal stone in a lithotripter field is the consequence of

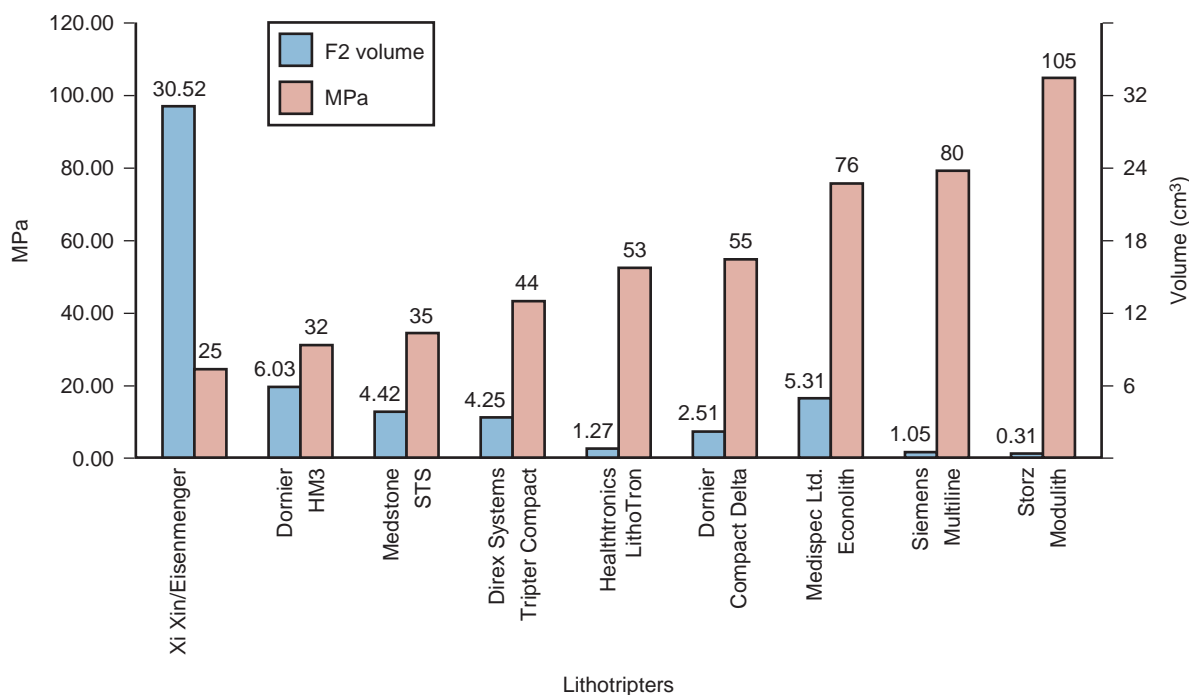


Figure 54-9. Comparison of the peak amplitude and size of the focal volume of nine different lithotripters. The general trend (from left to right) is a decrease in the device focal volume and an increase in the peak positive pressure. At the far left is the Xi Xin/Eisenmenger lithotripter, a new design that goes against the trend with a diminished peak amplitude and enlarged focal area. F2, focus 2.

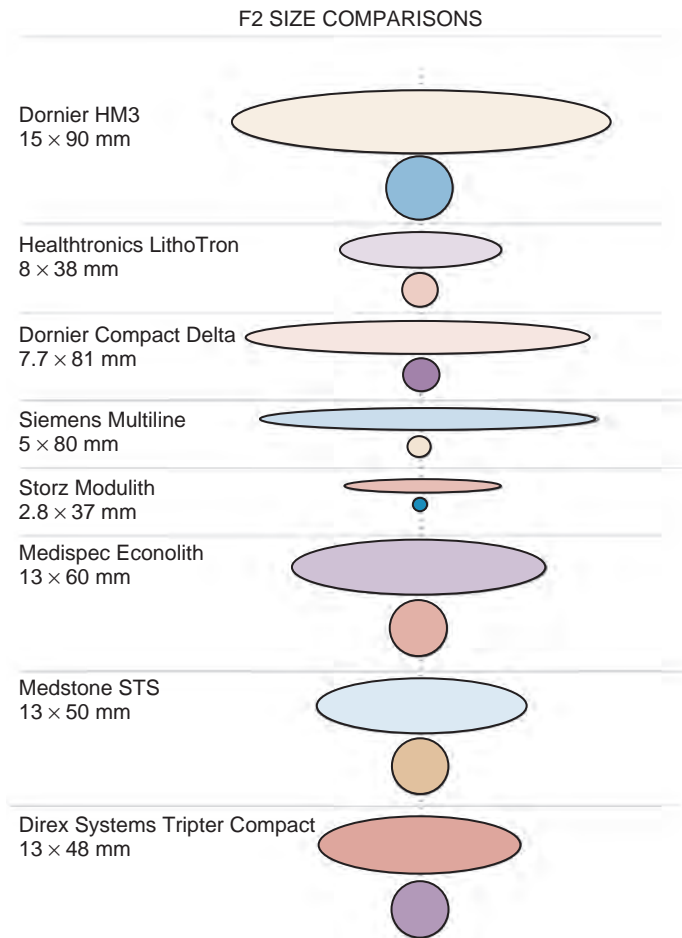


Figure 54-10. Comparison of the focal zones of selected clinical lithotripters showing their dimensions along the axis of the lithotripter (ellipses) and in the focal plane at the focus (circles). F2, focus 2.

failure of the stone material because of the mechanical stresses produced either directly by the incident shock wave or indirectly by the collapse of cavitation bubbles. These events could be occurring simultaneously or separately at the surface of the stone or within the interior of the stone (Fig. 54-11). Several potential mechanisms for SWL stone breakage have been described: spall fracture, squeezing, shear stress, superfocusing, acoustic cavitation, and dynamic fatigue.

Before each of these mechanisms is discussed, consideration of the typical shock wave profile is required. A typical pressure pulse generated by an electrohydraulic shock wave lithotripter is shown in Figure 54-12. It involves an initial short and steep compressive front with pressures of approximately 40 megapascals (MPa) that is followed by a longer, lower amplitude negative (tensile) pressure of 10 MPa, with the entire pulse lasting for a duration of 4 microseconds. Note that the ratio of the positive to negative peak pressures is approximately 5:1. Pressure measurements near the focal region of a Dornier unmodified HM3 indicate a 6-dB beam, of a width of approximately 15 mm. Because kidney stones are also generally of this dimension, the wavefront incident on the stone can be considered a plane wave (Müller, 1990; Cleveland et al, 2000).

The first mechanism by which a stone might break is through **spall fracture**. Once the shock wave enters the stone it will be reflected at sites of impedance mismatch. One such location is at the distal surface of the stone at the stone-fluid (urine) interface (although there could be other internal sites, such as cavities in the stone and interfaces of crystalline and matrix materials). As the shock wave is reflected, it is inverted in phase to a tensile (negative) wave. If the tensile wave exceeds the tensile strength of the stone,

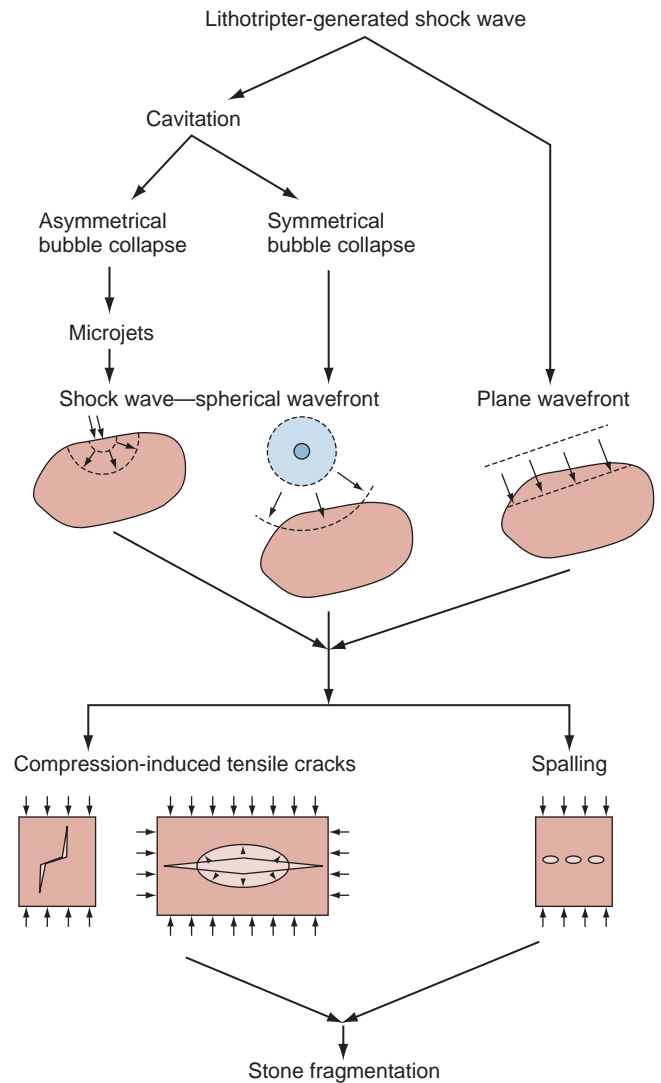


Figure 54-11. Summary of how the various mechanical forces generated by a lithotripsy shock wave might cause a kidney stone to fracture. (Reproduced with permission from Dr. Bradley Sturtevant.)

there is an induction of nucleation and growth of microcracks that eventually coalesce, resulting in stone fragmentation, which is termed **spallation**. The failure plane is located perpendicular to the applied tensile stress. This mechanism is thought to be of considerable importance in that kidney stones, like most brittle materials, will be much more likely to fail under tension rather than compression (Johrde and Cocks, 1985). Lokhandwalla and Sturtevant (2000) suggest that the trailing negative pressure of the lithotripter pulse also exerts tensile stresses of an order of magnitude similar to that of the spall mechanism. Contributing factors to the effectiveness of spallation in generating stone breakage appear to be the size and the shape of the stone as well as its physical properties (i.e., fracture toughness, acoustic speed, density, void dimensions). More spherically shaped stones may focus the tensile wave after reflection and thus further increase the tensile stress. Stones with larger diameters may allow sufficient tensile stress to be generated so that the tensile strength of the stone can be exceeded more easily. If these factors are important, then smaller, irregularly shaped stones may not fracture by spallation.

Eisenmenger (1998) first suggested that the **second mechanism for stone breakage, termed squeezing-splitting or circumferential compression**, occurs because of the difference in sound speed between the stone and the surrounding fluid. The shock wave inside the stone advances faster through the stone than the shock wave propagating in the fluid outside the stone. The shock wave

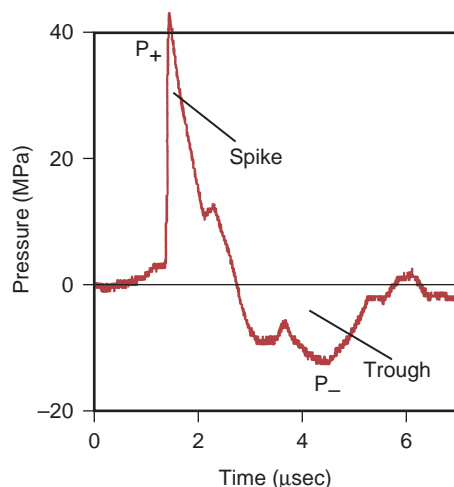


Figure 54-12. A typical pressure pulse at the lithotripter focus (F2) as measured by a polyvinylidene difluoride membrane hydrophone. First, there is a steep positive pressure front of about 40 MPa, which is followed by a negative pressure of 10 MPa, with the entire pulse lasting for a duration of 4 μ sec. (From Coleman AJ, Saunders JE, Preston RC, et al. Pressure waveforms generated by a Dornier extracorporeal shock wave lithotripter. *Ultrasound Med Biol* 1987;13: 651-7.)

that propagates in the fluid outside the stone thus produces a circumferential force on the stone, resulting in a tensile stress in the stone that is at its maximum at the proximal and distal ends of the stone. The resulting squeezing force could split the stone either in a plane parallel to the shock wave propagation direction or, depending on the elastic properties of the stone, possibly in a plane parallel to the shock wave front. It has been theorized that squeezing should be enhanced when the entire stone falls within the diameter of the focal zone. Thus current third-generation lithotripters that have very small focal zones will not make use of this mechanism, because the stone size is typically greater than the focal zone, whereas the original Dornier HM3 machine would.

The third mechanism is shear stress. Shear stress will be generated by shear waves (also termed *transverse waves*) that develop as the shock wave passes into the stone. The shear waves propagate through the stone and will result in regions of high shear stress inside the stone. In contrast to compression waves, which move the molecules in the direction of propagation, a shear wave results in translation of molecules transverse to the direction of propagation, and therefore the molecules are not compressed but are shifted sideways by the wave. Many materials are weak in shear, particularly if they consist of layers, because the bonding strength of the matrix between layers often has a low ultimate shear stress. Calcium oxalate stones commonly possess alternating layers of mineral and matrix, and the shear stress induced by the transverse wave could cause such stones to fail. Theoretical work by Sapozhnikov and colleagues (2003) suggests that the shear wave mechanism will lead to a tensile strain in cylindrical stones that is 5 to 10 times larger than that induced by spall. They also suggest that cracks will be initiated in the center of the stone and grow in a direction perpendicular to the axis of the stone.

The fourth mechanism for stone breakage, *superfocusing*, is the amplification of stresses inside the stone because of the geometry of that stone. The shock wave that is reflected at the distal surface of the stone can be focused by either refraction or diffraction from the corners of the stone. Several groups have demonstrated that these reflected waves can be focused to regions of high stress in the interior of the stone and that this can lead to failure (Gracowski et al, 1993; Xi and Zhong, 2001). The regions of high stress (both tensile and shear) depend on the geometry of the stone as well as its elastic properties.

The fifth potential mechanism for SWL stone breakage is *cavitation* (Coleman et al, 1987; Crum, 1988; Vakil and Everbach,

1993; Zhong and Chuong, 1993; Zhong et al, 1993). Cavitation is defined as the formation and subsequent dynamic behavior of bubbles. The lithotripter-generated pressure field has been found to induce cavitation in both in vitro and in vivo studies. The negative pressure in the trailing part of the pulse causes bubbles to grow at nucleation sites. A nucleation site is an inhomogeneity in the fluid, which leads to preferential formation of free gas under stress. During the negative pressure wave, the pressure inside the bubble falls below the vapor pressure of the fluid, and the bubble fills with vapor and grows rapidly in size (almost three orders of magnitude). As these bubbles grow, they oscillate in size for about 200 microseconds and then collapse violently, giving rise to high pressures and temperatures. In the absence of any boundaries, a cavitation bubble remains spherical during collapse, releasing energy primarily by sound radiation, the majority of which is in the form of a shock wave (see Fig. 54-12). This shock wave generates a positive and negative wave and therefore can induce all of the fragmentation mechanisms described in the preceding section. However, in the presence of a boundary, a liquid jet, also termed a *cavitation microjet*, forms inside the bubble during the collapse (Crum, 1979, 1988). This jet can accelerate to extremely high speeds because it converts most of its kinetic energy from the collapse of the cavity interface to the jet itself. The typical bubble radii found in SWL vary from 1 μ m to 1 mm, and bubble jet velocities range from 22 m/sec to 800 m/sec. In actual jet-impact cases the duration of the pressure pulse is only a few microseconds, and, in most instances, the peak pressure lasts for only approximately 1 microsecond. If the liquid jet is near the surface of a stone, it creates a locally compressive stress field in the stone, which propagates spherically into the stone interior.

Numerous investigators have exposed either aluminum foil or brass plates to the focused shock wave generated by a Dornier HM3 machine and observed significant microjet damage (pitting) on the surfaces of these metals. If this event occurs at the surface of a kidney stone, erosion of this surface would be expected; Averkiou and Crum (1996) reported this event for SWL-treated plaster of Paris target stones. To determine if cavitation is the primary mechanism of stone fragmentation, investigators have developed in vitro systems that would eliminate or damp cavitation events. Such systems have included a viscous medium that possesses a much lower number of nucleation sites and a chamber that allows increasing of the ambient pressure that surrounds the growing cavitation bubbles (Vakil et al, 1991; Delius, 1997; Stonehill et al, 1998). These in vitro systems have shown reduced stone damage along with a reduction in cavitation activity. Work by Bailey and associates (1998, 1999), in which the positive and negative waves were inverted with a pressure release reflector, also showed a reduction in stone comminution. All of these studies suggest that cavitation plays a significant role in damaging brittle objects.

The final mechanism of stone breakage to be considered defines stone breakage in terms of a dynamic fracture process, in which the damage induced by SWL accumulates during the course of the treatment, leading to the eventual destruction of the stone. Essential to this process are nucleation, growth, and coalescence of flaws within the stone caused by a tensile or shear stress (Fig. 54-13). Because renal calculi are not homogeneous but rather have either a lamellar crystalline structure bonded by an organic matrix material or an agglomeration of crystalline and non-crystalline material there are numerous sites of preexisting flaws (microcracks). All of the fracture mechanisms described have the potential to generate progressive damage to the interior of the stone. By use of the cohesive-zone model, a mathematical approach of predicting the qualitative features of transient microcrack damage accumulation, Lokhandwalla and Sturtevant (2000) were able to calculate the number of shock waves required for a spall-like failure to occur in a typical calcium oxalate monohydrate calculus. The values they determined had a range of two orders of magnitude (30 to 3000 shocks), which is well within the clinical dose presently used to treat patients. These investigators further suggested that mechanisms other than spall are also likely to inflict damage to stones and spall may be a factor only in a small portion of the stone.

Bioeffects: Clinical Studies

Acute Extrarenal Damage. SWL induces acute injury in a variety of extrarenal tissues (Evan et al, 1991, 1998). SWL has been associated with trauma to organs such as the liver and skeletal muscle, as evidenced by elevated levels of bilirubin, lactate dehydrogenase, serum aspartate transaminase, and creatine phosphokinase within 24 hours of treatment (Lingeman et al, 1986; Ruiz Marcellan and Ibarz Servio, 1986; Parr et al, 1988). These parameters begin to fall within 3 to 7 days of SWL treatment and are normal at 3 months. Other findings of damage outside the kidney have included reports of visceral injuries, such as perforation of the colon, hepatic hematoma, splenic rupture, pancreatitis, and abdominal wall abscess. Extrarenal vascular complications have been reported to occur as well, such as rupture of the hepatic artery, rupture of the abdominal aorta, and iliac vein thrombosis. Thoracic events, such as pneumothorax and urinothorax, have even been described. Fortunately, these events are all exceedingly rare and have generally been presented as isolated incidents.

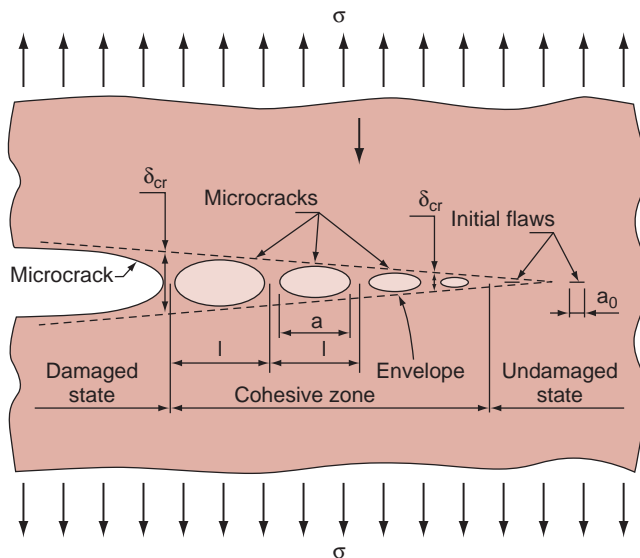


Figure 54-13. Coalescence of microcracks with a main crack. The undamaged stone has some initial flaws or microcracks of known length. These flaws occur in renal calculi either at a lamellar crystalline structure bonded by an organic matrix material or at an agglomerate of crystalline and noncrystalline material. When stressed, these microcracks grow until they coalesce with the main crack, and because this event is repeated throughout the stone, it eventually fragments. (Reproduced with permission from Dr. Bradley Sturtevant.)

In addition, early clinical studies noted that shock waves could induce cardiac arrhythmia, an observation that led to electrocardiographic synchronization with R-wave triggering on the Dornier HM3 device (Chaussy and Schmiedt, 1984). However, later clinical studies with non-water bath lithotripters have concluded that treating ungated to cardiac rhythm is safe.

Although the lithotripter is characterized by the spatial distribution of its acoustic output (the focal zone, or F2), it is known that high acoustic pressure does extend beyond this zone (Fig. 54-14). Therefore it is reasonable to expect that organs other than the kidney are exposed to stresses sufficient to cause injury. One such organ is the pancreas; a retrospective follow-up study from the Mayo Clinic suggests that patients who underwent SWL for the treatment of kidney stones in 1985 were at increased risk for developing diabetes mellitus compared with controls (Krambeck et al, 2005). The development of diabetes was related to the total number of shock waves and the power level of the lithotripter. Although these data are provocative, there were a number of limitations of the study, including that the stone disease of the SWL cohort was more severe than that of the control cohort, a family history of diabetes was not ascertained for either group, and the data for the SWL group were collected by self-report questionnaire whereas the control group was examined by chart review. Several other groups have subsequently investigated this subject; however, these findings have not been confirmed by any other study (Sato et al, 2008; Makhoul et al, 2009; Chew et al, 2012). Notably, de Cogain and associates (2012) performed a population-based study of Olmsted County, Minnesota, and did not find any association between SWL and diabetes.

Acute Renal Injury: Structural and Functional Changes. Virtually all patients who undergo SWL for renal stones demonstrate hematuria after approximately 200 shock waves. Hematuria is so common that it may be considered an incidental finding, and its severity is rarely of concern. Although hematuria was initially considered to be a consequence of irritation of the urothelium as stones were fragmented by shock waves, it is now known that such is not the case. Detailed morphologic studies have demonstrated that shock waves rupture blood vessels and can damage surrounding renal tubules (Fig. 54-15). SWL is now known to induce such structural changes in the treated kidney in the majority, if not all, of SWL patients, regardless of the type of lithotripter employed (Box 54-1).

In porcine subjects, the preferred animal model for studying acute renal injury, SWL traumatizes vessels ranging in size from the glomerular and cortical capillaries and vasa recta, to the larger arcuate and intralobular vessels. The resulting hemorrhagic lesion generally extends from cortex to medulla and comprises torn blood vessels with platelet aggregation and red blood cells in the interstitial space (Figs. 54-16 and 54-17). Affected renal corpuscles typically show breaks in the Bowman capsule, blood in the urinary space, and damage to the podocytes and mesangial cells (Fig. 54-18). Renal tubules often contain blood cell casts, and the tubular cells may show ischemic changes. In the setting of a more severe injury, complete necrosis of the endothelium and vascular smooth

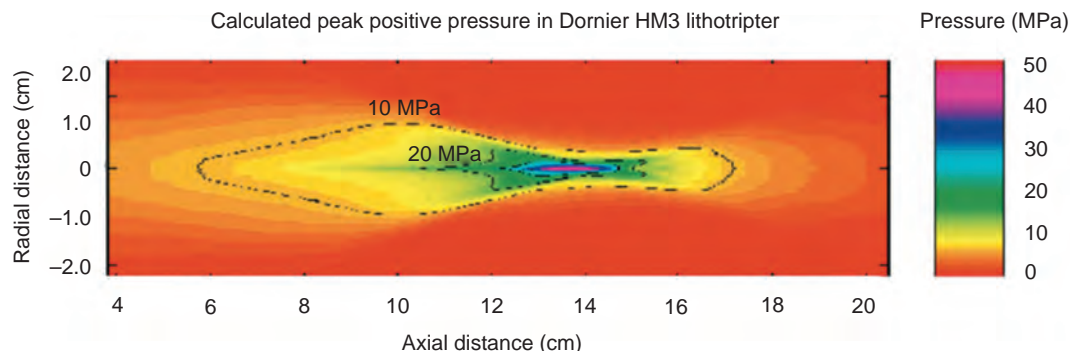


Figure 54-14. Predicted peak positive pressure in a Dornier HM3 lithotripter. The pressure is not focused to a point but extends over a finite volume.



Figure 54-15. Macroscopic photomicrograph of a coronal section through the kidney of a juvenile pig (~6 weeks old) treated with 2000 shocks at 24 kV by an unmodified Dornier HM3 lithotripter and examined 4 hours after treatment. The region of intraparenchymal hemorrhage has been colored red by an automated computer color recognition program. Note that the lesion involves multiple papillae and in some regions extends through the cortex to the renal capsule, where a subcapsular hematoma may develop.

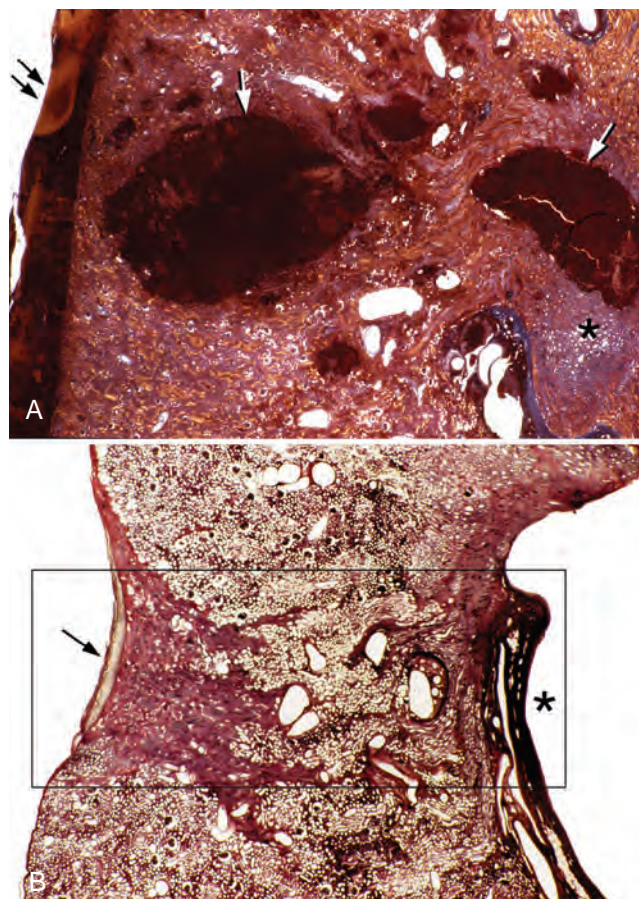


Figure 54-16. Light micrographs of an acute shock wave lithotripsy (SWL)-induced lesion at F2 (A) and subsequent chronic changes at a similar site 3 months after SWL treatment (B). Each pig kidney was treated with 2000 shock waves at 24 kV by an unmodified Dornier HM3 lithotripter. The acute lesion is characterized by numerous sites of hemorrhage (arrows) that extend from an individual renal papilla (asterisk) to the outer cortex of the kidney. Note a subcapsular hematoma (double arrows, A). The tissue section in B is similar in location to that seen in A but is shown at 3 months after SWL. A rectangle outlines the site of focus 2. Within that region there is complete loss of the renal papilla (the asterisk indicates where it should be), and only scar tissue is found in the adjacent cortical tissue (arrow).

BOX 54-1 Renal Side Effects of Shock Wave Lithotripsy in Experimental Canine and Porcine Animal Models

ACUTE HISTOLOGIC CHANGES

- Venous thrombi
- Cellular disruption and necrosis
- Mild tubular necrosis (ischemic changes)
- Intraparenchymal hemorrhage
- Tubular dilation and cast formation
- Damage and rupture of veins and small arteries
- Rupture of glomerular and peritubular capillaries

CHRONIC HISTOLOGIC CHANGES

- Nephron loss
- Dilated veins
- Streaky fibrosis
- Diffuse interstitial fibrosis
- Calcium and hemosiderin deposits
- Hyalinized and acellular scars from cortex to medulla

muscle may result. A typical clinical dose of 2000 shock waves with the Dornier HM3 lithotripter, operated at 24 kV with shock waves delivered at 2 Hz, produces a lesion measuring 5% to 6% of the functional renal volume (Fig. 54-19).

There have been reports of moderate-to-severe renal injury occurring after SWL, generally manifesting as a hemorrhagic event. Hematoma rates range from less than 1% to as high as 20%, depending on the type of lithotripter used and the treatment parameters employed, as well as the radiographic modality and timing of imaging follow-up. In addition, the later generation of lithotripters that have small focal areas and extremely high peak positive pressures are reported to produce higher clinically significant hematoma rates (3% to 12%), a trend that is worrisome (Thuroff et al, 1988; Ueda et al, 1993; Kohrmann et al, 1995; Piper et al, 2001). Several risk factors for the development of a post-SWL hematoma have been identified (Box 54-2). Dhar and associates (2004) reported that the probability of a subcapsular hematoma increased 2.2 times for every 10-year increase in the patient's age. Knapp and associates (1988) found patients with existing hypertension to be at increased risk for the development of perinephric hematomas as a consequence of SWL. In particular, those patients having unsatisfactory control of their hypertension at the time of SWL had the

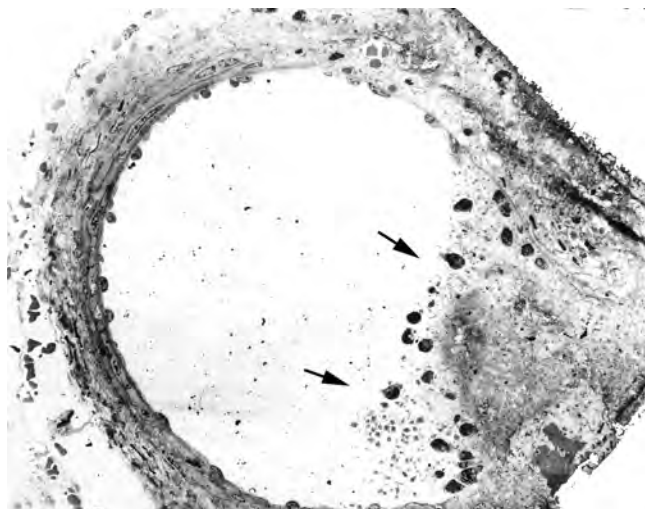


Figure 54-17. Low-magnification transmission electron micrograph demonstrating injury to a medium-sized artery located within F2 of a pig treated with 2000 shock waves at 24 kV. The shock wave-induced injury to the right side of this vessel resulted in a rupture site that permitted extravasation of blood into the nearby interstitium. The site of injury in the vessel wall is plugged with a clot (arrows).

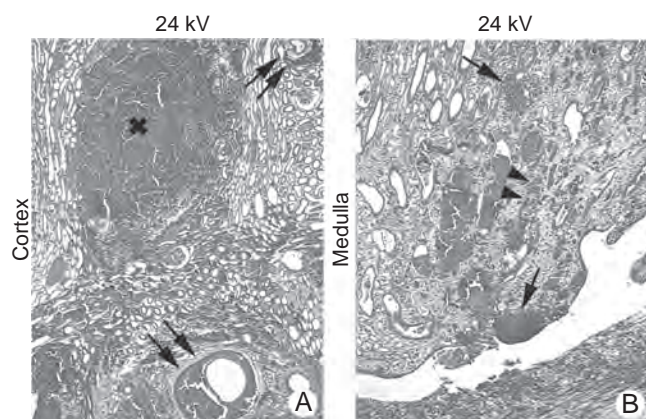


Figure 54-18. This series of light microscope panels depicts the injury seen in the cortex and medulla from an animal treated with 2000 shock waves at 24 kV by an unmodified Dornier HM3 lithotripter. A and B illustrate extensive injury in both cortex and medulla. Within the cortex, disruption of arterial walls with hemorrhage (double arrows) is noted near sites of intraparenchymal bleeding (x). The first site of injury appears to occur in the renal medulla, where damage is noted to small vessels, which causes intraparenchymal hemorrhage (arrows) adjacent to damaged collecting ducts (arrowheads).

BOX 54-2 Acute Renal Side Effects: Risk Factors for Shock Wave Lithotripsy

- Age
- Obesity
- Coagulopathies
- Thrombocytopenia
- Diabetes mellitus
- Coronary heart disease
- Preexisting hypertension

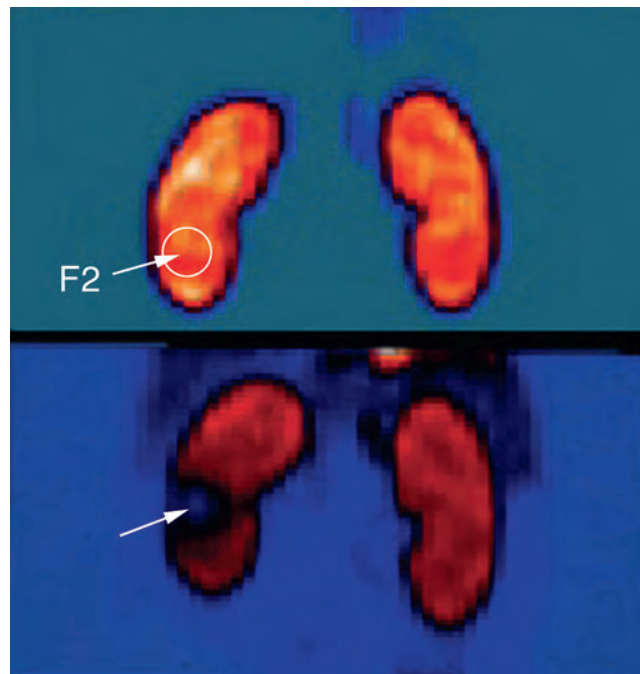


Figure 54-19. Shock wave lithotripsy-treated and control kidneys imaged by positron emission tomographic scanning before and immediately after treatment with 3500 shock waves to the lower pole, at level six, with a DoLi 50 device. The site of focus 2 (F2) (lower pole) on the shocked kidney shows a 50% reduction of renal blood flow (arrow).



Figure 54-20. Magnetic resonance image taken 24 hours after shock wave lithotripsy with 1200 shocks at 22 kV (by an unmodified Dornier HM3 lithotripter) shows a large subcapsular hematoma (arrows) in the treated (left) kidney.

highest incidence of hematoma formation. Additional risk factors for hemorrhage were diabetes mellitus, coronary artery disease, and obesity, all of which suggest a link to a vascular disorder. The appearance of renal hematomas can range in severity from a mild contusion localized within the renal parenchyma to a large hematoma (Fig. 54-20) associated with severe bleeding, possibly necessitating blood transfusion or rarely even angiographic embolization. Although some hematomas may persist for many months to years, it has been reported that most resolve within weeks and without long-term sequelae.

Chronic Renal Injury: Structural and Functional Changes. At present there is a paucity of information on the chronic injury

TABLE 54-1 Blood Pressure Changes in Patients Treated with Shock Wave Lithotripsy

STUDY	LENGTH OF STUDY (mo)	NO. SHOCKS		CHANGE IN INCIDENCE OF HYPERTENSION	CHANGE IN DIASTOLIC BLOOD PRESSURE
		RANGE	MEAN		
Liedle et al, 1988	40	Not recorded	1043	No change	Not recorded
Williams et al, 1988	21	800-2000	1400	Increased	Increased
Puppo et al, 1988	12	1100-1900	1380	No change	No change
Montgomery et al, 1989	29	110-3300	1429	Increased	No change
Lingeman et al, 1990		Not recorded	1289	No change	Increased
Yokoyama et al, 1992	19	1500-3000	Not recorded	Not recorded	Increased
Janetschek et al, 1997	26	2600-3000	2735	Increased (60-80 yr age group)	Increased (60-80 yr age group)
Jewett et al, 1998	24	Not recorded	4411	No change	No change
Strohmaier et al, 2000	24			Increased	Increased
Elves et al, 2000	26.4	Not recorded	5,281	No change*	No change*
Eterovic et al, 2005	3	1800-3200	Not recorded	No change	No change
Krambeck et al, 2006a	228	500-4500	1125	Increased	Not recorded
Eassa et al, 2008	43.6	Not recorded	Not recorded	Increased	No change
Sato et al, 2008	204	400-2300	928	No change	Not recorded

induced by SWL, the result in great part of the lack of experimental animal studies. Nonetheless, it is well accepted that shock waves damage blood vessels, and the resulting hemorrhage initiates an inflammatory response that ultimately leads to scar formation. Parenchymal fibrosis, a precursor to renal scarring, is seen as early as 1 month after SWL, and scar formation also has been reported to be a dose-dependent phenomenon. Clinically there are **four potential chronic renal changes that may be associated with SWL treatment**. They are an accelerated rise in systemic blood pressure, a decrease in renal function, an increase in the rate of stone recurrence, and the induction of brushite stone disease. All four effects appear to be linked to the observation that the acute renal injury at F2 progresses to scar formation.

The possibility that SWL might be associated with significant changes in systemic blood pressure was first suggested by [Peterson and Finlayson \(1986\)](#) and has been investigated by others ([Table 54-1](#)). [Lingeman and coworkers \(1987\)](#) reported that 8.2% of 243 patients who were normotensive at the time of SWL developed blood pressure changes requiring antihypertensive medication. Mean follow-up in this group of patients was 1.5 years, giving an annualized incidence of hypertension of 5.5%. Similar data have been reported by [Williams and Thomas \(1989\)](#). After these reports suggesting that hypertension could be a long-term complication of SWL, a large study involving almost 1000 patients was undertaken at the Methodist Hospital of Indiana ([Lingeman et al, 1990](#)). This study found a small but statistically significant change in diastolic blood pressure associated with SWL therapy. The observed effect of SWL on diastolic pressure change persisted even after controlling statistically for other variables that might be associated with variation in blood pressure, such as age, sex, pretreatment baseline blood pressure, and number of treatment sessions. [Janetschek and colleagues \(1997\)](#) performed a prospective study that demonstrated age was a significant risk factor for post-SWL hypertension, with an increase in intrarenal resistive index observed in patients 60 years of age and older. The mechanism of hypertension after SWL is not well elucidated. Although subcapsular hematomas can induce hypertension, such changes are generally transient. There has been a report, however, of mesangial proliferation in porcine models after SWL that could induce hypertensive changes.

SWL treatment may also be associated with a long-term reduction in renal function. [Williams and associates \(1988\)](#) found a **significant decrease in the percentage of effective renal plasma flow 17 to 21 months after SWL for patients with two kidneys**. [Orestano and colleagues \(1989\)](#) noted that patients receiving more

than 2500 shocks had a reduction in creatinine clearance and a prolongation of ^{131}I -Hippuran transit time 30 days after SWL in the treated kidney; in some cases, similar findings were noted in the contralateral kidney. [Lingeman and associates](#) reported that patients with a solitary kidney demonstrated elevated serum creatinine levels 5 years after SWL ([Brito et al, 1990](#)). These observations stand in contrast to the early reports by [Chaussy and Fuchs \(1986\)](#), which suggest a significant increase in renal function 3 months to 1 year after SWL. In addition, a longer follow-up study of patients treated in Munich failed to confirm this increase in renal function ([Liedle et al, 1988](#)).

An additional concern is that **stone recurrence rates may be higher after SWL because of residual stone debris** ([Pearle et al, 1999](#)). A study by [Carr and associates \(1996\)](#) documented new stone formation in 298 consecutive patients who initially were determined to be stone free after SWL and compared those findings with those of 62 patients treated by PNL. Their data showed a significant increase in the rate of new stone formation within 1 year of SWL treatment compared with PNL. The authors suggested that fine sand debris generated from SWL treatment remained in the kidney and gravity acted to position it as a nidus in the calyceal system.

A significant increase in the number of calcium phosphate stone formers has been reported during the past three decades ([Mandel et al, 2003](#); [Parks et al, 2004](#)). An intriguing finding in the work by Parks and colleagues was that when all kidney stone formers were analyzed for the number of SWL procedures, the **calcium phosphate stone formers had received a significantly higher number of procedures than did the idiopathic calcium oxalate stone formers when rates were adjusted for number of stones and duration of stone disease**. Furthermore, the brushite stone formers had received a significantly greater number of SWL treatments than had the apatite stone formers. The histopathologic examination of the brushite stone formers revealed advanced levels of tissue changes in the renal cortex and papilla that included interstitial fibrosis, tubular atrophy, glomerular obsolescence, and deposition of large amounts of biologic hydroxyapatite in the lumens of inner medullary collection ducts ([Evan et al, 2005](#)). Although these data do not establish a cause-and-effect relationship, clearly there is an association between brushite stone disease and high levels of SWL treatment sessions. Because apatite stone disease is likely to be related to higher urine pH levels in these patients, animal studies that showed the initial site of SWL injury to be localized to the microvessels and collecting duct of the renal papilla may explain the loss of control over normal urinary fluid pH.

Mechanism for Tissue Injury

The mechanism for the traumatic effects of SWL is not known, although [Delius and colleagues \(1988\)](#) have speculated that the violent collapse of cavitation bubbles generated by the shock waves is primarily responsible for the cellular changes ([Box 54-3](#)). This concept is based on data showing that cavitation bubbles are present during shock wave application and that lithotripter shock waves can cavitate water and blood in vitro ([Coleman et al, 1987](#)). [Crum \(1988\)](#) documented that SWL does produce acoustic cavitation, possibly as the result of the high intensity of the shock wave amplitude and noted that the cavitation microjets are sufficiently forceful to pit or deform metal test foils. [Zhong and coworkers \(2001\)](#) suggested that it is expansion of the bubbles in a vessel that will lead to rupture of the wall of that blood vessel, testing this in an in vitro setting.

No group had been able to positively detect and validate acoustic cavitation within the kidney during SWL treatment until [Bailey and associates \(2005\)](#) created a passive cavitation detection system using two confocal spherical bowl piezoelectric transducers. This device was used for coincidence detection of cavitation bubble emissions within a $2 \times 2 \times 2$ -mm sampling volume centered on F2 of a Dornier HM3 lithotripter. An ultrasound scan head targeted at this spot was used to image echogenicity in and around the sample volume. Signal (passive cavitation detection, hyperechoic spots) was intense in the urinary space during SWL treatment, and a signal was also seen in the renal cortex after only 1000 shocks. At that time a small fluid space was noted at the site of the parenchymal signal. These data suggest that **once blood vessels have been ruptured and blood has collected in pools there is a greater potential for cavitation to occur. The pooling of blood provides a large fluid-filled space for cavitation bubbles to grow and collapse.** In this model the accuracy of tissue targeting was confirmed by inducing a lesion with high-intensity focused ultrasound. Further evidence that cavitation plays a role in tissue injury comes from a study by [Evan and associates \(2002\)](#) in which the degree of tissue injury was compared between a standard rigid reflector and a pressure release reflector. The pressure release reflector generates a shock wave in which the negative tail precedes the positive peak, resulting in a suppression of cavitation activity. No injury was detected in the kidneys treated with the pressure release reflector; the standard rigid reflector induced the expected lesion.

Techniques to Optimize Shock wave Lithotripsy Outcome

For all lithotripters the urologist has the ability to control a number of device parameters that may affect the ultimate treatment outcome ([Box 54-4](#)). These parameters include the acoustic output and focal volume that are employed, optimal coupling, the number of shock waves administered, the rate at which they are dispensed, and the power or voltage that is used. In addition, other intraoperative

factors that may affect stone breakage can be controlled, such as anesthetic technique.

Although all lithotripters generate waveforms that are fundamentally similar, lithotripters may be distinguished from one another by the peak pressure and spatial extent of their acoustic field. The physics of acoustics dictate that the pressure field of a lithotripter is focused not at a particular point in space but rather is distributed over a volume of space. Most commonly, that focal zone is a cigar-shaped region, although the volume of that zone may differ greatly among devices. Recent in vitro studies suggest that the focal width generated by a lithotripter affects stone breakage; a wider focal width has been reported to increase the likelihood of stone breakage ([Sapozhnikov et al, 2007](#)). Because the kidney tends to move, as a consequence of respiratory motion, the stone may move in and out of a narrow focal zone. Another potential drawback of a narrow focal zone is that less energy may be deposited into the stone. When the focal zone is narrower than the stone being treated, the tensile stress inside a stone is reduced; for the stone to be subjected to the full force of shear stress, the outer surface of the stone must be subjected to high-pressure shock wave energy.

The first-generation lithotripter was a water bath design that was a large, stationary machine. The present generation of lithotripters has dry treatment heads, which make them smaller and more easily transportable. However, they require a coupling medium, such as gel or oil, to join the patient to the device. Optimal coupling permits the efficient transfer of energy from the lithotripter to the patient; poor coupling will reduce stone breakage. Most commonly, energy transfer through a coupling medium is attenuated by air pockets in the coupling interface itself. Decoupling and recoupling, which may occur during repositioning of a patient during SWL, can generate large-volume air pockets in the coupling medium. Such air pockets can have a dramatic effect on treatment efficacy; air pockets of just 2% of the coupling interface reduce breakage by 20% to 40% ([Pishchalnikov et al, 2006](#); [Neucks et al, 2008](#); [Li et al, 2012](#)). Although there is no way to monitor coupling during treatment, simple steps can minimize the likelihood of air pockets developing. Dispensing gel from a squirt bottle and rubbing the gel by hand to cover the treatment head and skin degrades the coupling interface. Improved coupling can be achieved by delivering a large volume of gel as a mound dispensed from the stock jug and allowing the gel to spread on contact between the treatment head and the skin.

During an SWL treatment session the urologist can directly control the rate at which shock waves are delivered and the number of shock waves dispensed. In a recent literature review and meta-analysis of randomized controlled trials evaluating different shock wave delivery rates, a rate of 60 shocks per minute was found to break stones more effectively than 120 shocks per minute ([Semins et al, 2008](#)). Cavitation is thought to play a role in this effect,

BOX 54-3 Reversible and Irreversible Injury

REVERSIBLE CHANGES

Mild tubular necrosis
Casts and red blood cells in tubular lumen
Vacuolar changes of tubular lumen
Mild interstitial edema and hemorrhage

IRREVERSIBLE CHANGES RESULTING IN LOSS OF RENAL TISSUE

Disruption of nephrons
Extensive interstitial edema
Large hematomas of cortex and medulla
Rupture and occlusion of veins and arteries
Fracture of glomerular and peritubular capillaries

BOX 54-4 Factors That Induce the Degree of Renal Trauma Associated with Shock Wave Lithotripsy

AGGRAVATING FACTORS

Number of shocks
Period of shock wave administration: Shorter period increases damage
Accelerating voltage: Higher voltage increases damage
Type of shock wave generator: First- versus second/third-generation devices
Kidney size: Juvenile versus adult
Preexisting renal impairment

MITIGATING FACTORS

Pretreatment with 100 to 500 shocks at low energy level to reduce lesion size
Treatment at a slow rate of shock wave delivery (≤ 60 shocks/min)

because the dynamic bubbles are given a longer time interval to dissipate with a slower rate and therefore have less of a shielding effect and energy draw from subsequent shocks. The disadvantage of a slow rate is, of course, a longer treatment time, particularly if the number of shock waves being delivered is predetermined. However, slowing the rate also has been shown to be protective of kidney vasculature (Evan et al, 2007). The lowest number of shock waves possible should be used to reduce renal injury, but this number is generally predetermined and many patients are likely to be overtreated. Risks and benefits need to be weighed regarding possible overtreatment versus need for further procedures when deciding on shock wave number.

Another parameter urologists adjust is the energy setting on the machine. Increasing the power setting on most electromagnetic lithotripters actually narrows the focal zone, which, as discussed earlier, decreases stone breakage and may also increase the risk for renal injury and renal hematoma (Connors et al, 2000). In the past several years, studies have shown that “ramping up” the energy of the lithotripter can be protective of renal injury (Fig. 54-21). Lesion size is decreased after pretreatment with low-energy shock waves (100 to 2000 at 12 kV followed by 24 kV) (Willis et al, 2006). Interestingly, Connors and coworkers (2009) showed in a pig model that the voltage that is initiated is less important than the actual ramping up, because pretreatment groups with 100 shock waves at 18 or 24 kV both had significantly smaller lesions than just treating with 2000 shock waves at 24 kV without pretreatment. The reduction in renal injury is thought to be secondary to vasoconstriction because the same beneficial effect was blocked when dopamine was administered (Willis et al, 2006). Handa and associates (2012) reported that a pause in treatment, when switching from low-energy to high-energy settings, is not necessary provided that the delivery of low-energy shock waves lasted at least 4 minutes. In addition, ramping up the voltage has been shown to result in better stone breakage when using the same total shock wave energy (Zhou et al,

2004). With regard to voltage parameters, the technique of ramping up appears to both improve stone breakage and reduce tissue injury.

The original lithotripter, the Dornier HM3, required a general anesthetic for treatment. However, later generations of lithotripters were developed for treatment to be performed without anesthesia. To minimize treatment discomfort the lithotripters were designed with wider aperture, which will spread the acoustic field across a broader area of the patient's skin, reducing skin surface pain. However, this wider aperture resulted in a narrow focal zone, which had a deleterious effect on stone breakage. Interestingly, the higher pressures used with these newer machines result in higher adverse event rates as well. The effect of respiratory motion, as described previously, further hampers stone targeting and acts to reduce stone breakage rates.

To reduce stone motion, urologists can perform SWL with general anesthesia, which will control the patient's respiratory rate and volume. Two clinical studies compared the outcome of SWL performed with intravenous sedation and SWL performed with general endotracheal anesthesia. General anesthesia yielded significantly better outcomes: 78% to 87% stone-free rates versus 51% to 55% with intravenous sedation (Eichel et al, 2001; Sorensen et al, 2002). Because general anesthesia is associated with superior outcomes, this may be the anesthesia of choice for SWL, unless contraindicated for medical reasons.

KEY POINTS: SHOCK WAVE LITHOTRIPSY

- Most patients with uncomplicated kidney stones can be successfully treated with SWL.
- Shock waves break stones via multiple different mechanisms, including both compressive and tensile forces.
- SWL is associated with both anatomic and functional injuries to the kidney.
- The effectiveness of SWL can be enhanced by ensuring optimal coupling of the patient to the lithotripter, treating at a slower rate (60 shocks/min), and treating with general anesthesia.
- The adverse effects of SWL may be reduced by initiating treatment at low power settings and slowly ramping up the power to standard treatment energy.

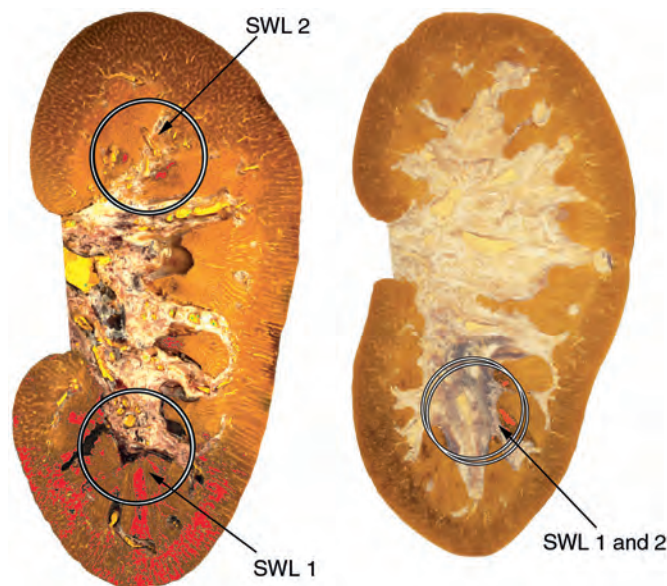


Figure 54-21. On the left is a coronal section of a kidney from an animal treated with 2000 shocks at 24 kV first to the lower pole (shock wave lithotripsy [SWL] 1) and then an additional 2000 shocks at 24 kV to the upper pole (SWL 2) of the same kidney. The typical lesion (in red) is seen at the lower pole; however, a greatly reduced lesion is seen on the upper pole. These data suggest that a pretreatment protocol might reduce the lesion induced by a clinical dose of shock waves. At right, lesion size is shown in an animal first treated at the lower pole with 500 shocks at 12 kV (SWL 1) and then treated again at the lower pole with 2000 shocks at 24 kV (SWL 2). A greatly reduced lesion is also noted for this protocol.

Percutaneous Nephrolithotomy

Fernstrom and Johansson (1976) first reported the technique of creating a percutaneous tract specifically to remove a stone. Subsequent reports have established PNL as a routinely used technique to treat patients with large or otherwise complex calculi (Alken et al, 1981; Wickham and Kellett, 1981; Segura et al, 1982; Clayman et al, 1984). Advances in surgical technique and technology have enabled the continuous evolution of PNL, allowing the urologist to remove calculi percutaneously with increasing efficiency. Because the percutaneous approach to stone removal is superior to the open approach in terms of morbidity, convalescence, and cost, PNL has replaced open surgical removal of large or complex calculi at most institutions (Matlaga and Assimos, 2002). Furthermore, the number of PNL procedures performed each year in the United States is increasing as patients with more complex health status are treated minimally invasively (Mirheydar et al, 2013). The specific aspects of percutaneous techniques as they relate to stone removal are delineated and discussed in the following section.

Preparation of the Patient

The initial evaluation of the patient who is being considered for PNL should be a complete history and physical examination. A complete medical history will identify patients with an absolute contraindication to PNL, such as uncorrected coagulopathy, as well as those with an active, untreated urinary tract infection (UTI). The placement of a percutaneous nephrostomy drain, without manipulation of the calculus, may be an appropriate

therapy if the stone is associated with obstruction of the renal unit and sepsis. If it is medically feasible, **aspirin and other antiplatelet medications should be discontinued 7 days before the date of surgery** (Mak and Amoroso, 2003). In patients with a higher risk for thrombotic complications, such as those with ball cage aortic valves or mechanical heart valves with atrial fibrillation, bridging therapy with low-molecular-weight heparin may be necessary. In such instances the heparin should be discontinued 24 hours before the procedure and resumed 24 hours postoperatively if feasible based on amount of active hematuria (Riley and Averch, 2012).

Preoperative laboratory evaluation of patients scheduled for PNL should include a complete blood cell count as well as serum electrolyte determinations and renal function tests. Martin and colleagues (2000) reported that it is unnecessary to obtain screening coagulation studies before PNL for an otherwise healthy patient. **Urine culture is mandatory for all patients who undergo PNL;** perioperative antibiotics can be appropriately tailored to culture-specific organisms. Typing and screening of the patient's blood should be performed, although preoperative crossmatching usually is not necessary.

The standard usage of helical computed tomography (CT) to evaluate the patient with urolithiasis has eliminated the need to perform preoperative intravenous urography or retrograde pyelography (Park and Pearle, 2006). **In most cases, the decision to perform PNL may be based on the stone burden displayed on the CT images.** The main advantage of CT is the ability to assess the spatial relationship of the kidney relative to the stone and that of the kidney in relation to adjacent peritoneal and retroperitoneal structures. Retrorenal colon has been reported to be present in less than 1% of all patients, but its incidence may be higher in those who have undergone jejunioileal bypass, those in a nursing home, those with spinal cord injury, or those with spinal deformities such as advanced scoliosis (Sherman et al, 1985; Onder et al, 2014). These patients will benefit from an initial CT scan. Patients with ectopic kidneys, both congenital and iatrogenic (e.g., due to renal allograft, autotransplantation), as well as patients with dysmorphic body habitus because of congenital malformations such as spinal dysraphism also may benefit from cross-sectional imaging before PNL; intra-abdominal structures, such as the bowel, may be located between the skin and the renal access point in such cases. A kidney-ureter-bladder (KUB) radiograph may be obtained immediately before the procedure to verify stone location if there is concern for stone migration. Retrograde pyelography can be performed at the time of the surgical procedure, acquiring information about calyceal anatomy that may aid in selecting the targeted puncture site. However, for certain patients, such as **those with calyceal diverticula or duplicate collecting system, for whom the surgical approach is affected by the diverticulum's relationship to the collecting system, intravenous or retrograde pyelography may be required at the time of initial evaluation.** Radionuclide scanning may be necessary in selected patients, particularly those harboring staghorn calculi, to evaluate differential renal function.

Antibiotics. Although data to support the need for antibiotic prophylaxis during PNL is limited because of the lack of randomized controlled clinical trials, it is generally accepted that antibiotic prophylaxis will reduce infectious complications. Based on the American Urological Association (AUA) Best Practice Statement, the antimicrobial of choice is a first- or second-generation cephalosporin or an aminoglycoside with metronidazole or clindamycin; ampicillin/sulbactam or a fluoroquinolone is recommended as an alternative (Wolf et al, 2008). A multi-institutional study compared patients receiving any type of preoperative antibiotics to those who received no antibiotics and found that the antibiotic group had a lower fever, a lower retreatment and complication rate, and a higher stone-free rate compared to those who did not receive antibiotics (Gravas et al, 2012). Mariappan and associates (2005) reported a prospective controlled study that also found that oral ciprofloxacin 1 week before PNL significantly reduced the risk for postoperative urosepsis. Bag and associates (2011) also found in a prospective randomized trial that 1 week of nitrofurantoin, which reaches therapeutic levels only in the urinary tract, produced similar results, with

a decrease in endotoxemia and systemic inflammatory response syndrome. Importantly, these studies highlight that **urinary calculi may harbor bacteria even though bacteriuria is only intermittently present**, which is particularly true in the patient who has been taking antibiotics in the past. For patients who do have preoperative bacteriuria, stone cultures produced bacteria in 77% of cases in a series reported by Larsen and associates (1986). The most frequently identified organisms were *Proteus mirabilis*, *Escherichia coli*, *Klebsiella* species, *Pseudomonas* species, *Enterococcus* species, and *Enterobacter* species. However, sterile urine does not preclude postoperative bacteriuria, because Charton and colleagues (1986) reported a 35% incidence of bacteriuria after PNL among patients with sterile preoperative urine culture specimens in whom prophylactic antibiotic therapy was not used. Mariappan and associates (2005) also reported that the best correlate with post-PNL sepsis or SIRS is stone culture or renal pelvic urine culture, not bladder urine culture. **The fragmentation of stones, despite sterile urine, may release preformed bacterial endotoxins and viable bacteria that place the patient at risk for septic complications** (Scherz and Parsons, 1987; McAleer et al, 2002, 2003; Paterson et al, 2003). Therefore patients who have radiographic or clinical features suggestive of struvite or in whom infection is suspected should receive broad-spectrum antibiotics before surgery to reduce the risk for sepsis. Antibiotic treatment also may reduce bleeding secondary to inflammation and friability of renal parenchyma. **Approximately one third of patients with an indwelling ureteral stent will, despite sterile urine on a preoperative analysis, be colonized with bacteria; Enterococcus and Staphylococcus epidermidis are the most frequent offending organisms** (Reid et al, 1992; Lifshitz et al, 1999). For patients with indwelling stents, then, a course of antibiotic prophylaxis, particularly for gram-positive organisms, may be beneficial before instrumentation.

Anesthesia. PNL can be performed after the administration of general, epidural, or local anesthesia. Local anesthesia, usually in combination with intravenous sedatives and analgesics, has been reported in a number of centers (Clayman et al, 1983; Hulbert et al, 1986; Preminger et al, 1986; Ohlsen and Kinn, 1993; Li et al, 2013). Local anesthesia may be an option when general anesthesia is contraindicated. A local anesthetic, such as lidocaine, can be delivered into the access tract by use of an 8.3-Fr anesthetic injection catheter with multiple side holes or with a dual-lumen ureteral access catheter (Dalela et al, 2004) or using a 23-gauge spinal needle with injection along the access tract to the renal capsule (Li et al, 2013). Regional anesthesia (e.g., epidural, spinal) can be used for percutaneous procedures, but several problems may be associated with these regional anesthetic techniques. First, a relatively high block is necessary to eliminate all renal pain. Second, distention of the renal pelvis during PNL may cause a vasovagal reaction that is not always prevented by regional anesthesia (Grasso and Taylor, 1997). However, despite these potential complications, several studies have demonstrated the success of regional anesthesia for PNL with decreased overall analgesia requirements and complication rates similar to those with general anesthesia (Karacalar et al, 2009; Singh et al, 2011; Nouralizadeh et al, 2013). Currently, general anesthesia is usually preferred when a more lengthy procedure is planned because it is the best means of protecting the airway when patients are in a prone position. **In cases in which upper pole puncture is contemplated, general anesthesia is preferred because it permits control of respiratory movements, which is essential to minimize the risk for pulmonary complications. A close relationship between the surgeon and the anesthesia team is essential to optimize the outcome of a PNL procedure.** The anesthesiologist should be aware that pulmonary injuries, including hydrothorax and pneumothorax, can occur during PNL; to that end, the anesthesiologist should monitor airway pressures, end-tidal carbon dioxide levels, and oxygen saturation and should auscultate the lungs frequently. Acute anemia from blood loss or dilution also may occur, emphasizing the need for frequent hemodynamic assessments. Because of the large amounts of fluids administered to the patient during nephroscopy there is a potential risk for hypothermia, a disorder associated with an increased risk for morbid cardiac events. Warming of

irrigation fluids as well as patient warming devices may attenuate this risk.

Postoperatively, pain is managed with opioid analgesia and anti-inflammatory medication when not contraindicated. A prospective randomized double-blind placebo controlled trial found no difference in complications but also no improvement in pain when ketorolac was administered continuously compared to placebo after PNL (Grimsby et al, 2012). D'a Honey and associates (2013) assessed the utility of intercostal nerve block in controlling immediate postoperative pain after PNL and found that nerve blockage with 0.5% bupivacaine and epinephrine significantly decreased narcotic use and improved patient-perceived quality of life.

The fundamental techniques of gaining and maintaining percutaneous access are reviewed in Chapter 8.

Stone Removal. After the nephrostomy access has been appropriately dilated and the Amplatz sheath positioned, the urologist can proceed with stone removal by endoscopic techniques. In the early days of PNL several authors reported the successful extraction of renal calculi with Randall forceps (modified to allow passage over a guidewire) or stone baskets under only fluoroscopic, not visual, guidance (Castaneda-Zuniga et al, 1982; Pollack and Banner, 1984). However, fluoroscopically guided stone removal is no longer recommended because it is not as safe or as efficient as the removal of calculi under direct vision.

Physiologic solutions should be used for irrigation during PNL to minimize the risk for dilutional hyponatremia in the event of large-volume extravasation (Carson, 1986). The height of the irrigant during rigid nephroscopy should be maintained at 80 cm or less above the patient to minimize intrapelvic pressure and to prevent fluid absorption through pyelovenous backflow (Miller and Whitfield, 1985). The use of an Amplatz working sheath also prevents elevated intrapelvic pressures. Rigid nephroscopy is performed initially, and stones up to 1 cm in diameter can be grasped with rigid graspers or stone baskets and extracted intact through the 30-Fr Amplatz sheath. Stones larger than 1 cm require fragmentation before extraction. Several intracorporeal lithotripsy techniques are available and are covered elsewhere in this chapter.

Rigid nephroscopy is the preferred method for stone removal; however, only the simplest intrarenal collecting systems can be completely inspected with a rigid nephroscope through a single access. Therefore flexible nephroscopy should be used during every PNL to survey the entire intrarenal collecting system for residual stone fragments. With an Amplatz sheath in place, pressurization of irrigation fluid (up to 300 mm Hg) during flexible nephroscopy is used to adequately distend the collecting system and improve visualization. The entire collecting system should be examined systematically, including the proximal ureter. Injection of contrast material through the flexible nephroscope and occasional fluoroscopy is helpful in maintaining orientation and verifying that each calyx has been inspected. Small stone fragments can be removed with a stone basket passed through the flexible instrument, and larger stones can be fragmented with laser or EHL. Alternatively, fragments may be flushed or manipulated into the renal pelvis, where they may be retrieved more easily with rigid instruments. The goal of PNL is complete or nearly complete clearance of stone material at the time of the primary procedure, which greatly simplifies secondary procedures, if necessary. Furosemide can be administered intravenously when the nephrostomy tube is placed at the conclusion of PNL to promote and to maintain diuresis.

Multiple different sizes and shapes of nephrostomy tubes are currently available for use at time of PNL. The role of nephrostomy tube drainage is to aid in healing of the nephrostomy tract, promote hemostasis, prevent urinary extravasation, drain infection, and allow re-entry if necessary. Recently, tubeless (ureteral stent is left instead of nephrostomy tube) and even totally tubeless (no drainage device used) PNL have been introduced and popularized. Comparison of nephrostomy tube size, shape, and tubeless and totally tubeless procedures is presented elsewhere in the textbook.

Technique Modifications. In an attempt to decrease morbidity association with PNL, modifications have been made to the size of the renal access tract, resulting in the new designations of "mini-

percutaneous nephrolithotomy," "ultra-mini-percutaneous nephrolithotomy," and "micro-percutaneous nephrolithotomy." The mini-PNL was first introduced by Jackman and colleagues in 1997 and decreased using a 13-Fr percutaneous access sheath for stone removal. Subsequent authors have reported their variations of the technique (Lahme et al, 2001; Li et al, 2010). Mini-PNL has been found to be associated with longer operative times and technical limitations on the part of the operating surgeon because of the need to fragment stones into small pieces and poor visualization in the presence of bleeding (Li et al, 2010); however, overall blood loss and transfusion rates with mini-PNL are lower compared to those with standard PNL. Further miniaturization of the access to 11-Fr inner diameter/13-Fr outer diameter ureteral access sheath has led to the ultramini-PNL, where stones are fragmented with a holmium laser and then allowed to pass spontaneously down the ureter. Desai and colleagues (2013) reported a stone-free rate of 97.2% at 1 month postoperatively, with a 16.7% overall complication rate. Most recently, percutaneous lithotripsy has been described using a 4.85-Fr all-seeing needle, termed the micro-PNL. The all seeing needle allows for visualization inside the kidney and directed laser lithotripsy using a 200-micrometer laser fiber (Desai et al, 2011). A recent comparison of micropercutaneous lithotripsy to ureteroscopy found similar stone clearance rates between the two procedures, but a higher rate of postoperative pain and greater decrease in hemoglobin in the micro-PNL patients (Sabnis et al, 2013). Although all of the recent technique modifications work to decrease overall patient morbidity, because of technical limitations with the mini-, ultramini-, and micro-PNL their exact role in the treatment of upper tract nephrolithiasis is uncertain and continues to be defined.

Special Situations

Calyceal Diverticula. Calyceal diverticula are nonsecretory, transitional cell epithelium-lined cystic cavities within the renal parenchyma. A narrow communication with the pelvicalyceal system almost always exists. The incidence of calyceal diverticula diagnosed on routine intravenous pyelography ranges from 0.21% to 0.45% (Hulbert et al, 1986). Although the incidence of calyceal diverticula is low, calculi formation within the diverticula is high as reported in 9.5% to 50% of cases (Jones et al, 1991b). Treatment of calculi within a calyceal diverticulum can be difficult and percutaneous removal has the reported highest treatment success rate of all endourologic minimally invasive treatment modalities (Krambeck and Lingeman, 2009). Percutaneous access into stone-bearing diverticula poses several unique problems. Direct puncture is often difficult because of the small size of the cavity and the frequent occurrence of calyceal diverticula in the upper pole of the kidney. After successful puncture is achieved, negotiation of a guidewire into the renal pelvis is often not possible. A similar situation can occur when a stone fills a calyx so completely that a guidewire cannot be passed through the infundibulum into the renal pelvis or in the rare case of infundibular stenosis. To overcome these difficulties, a special access technique is required.

If the calculi are visible on fluoroscopy it is often preferable to puncture directly onto the stone (Ohlson and Kinn, 1993); however, contrast media can be instilled through a ureteral catheter to help localize the diverticulum and if necessary contrast material can be injected directly into the diverticulum via CT guidance to assist with localization (Matlaga et al, 2006). Direct puncture into the diverticulum allows use of rigid instruments that provide superior visualization compared with flexible instruments that are used in an indirect approach. Optimal visualization is essential in trying to identify the communication between the diverticulum and the renal collecting system. Direct access also allows for easy fulguration of the urothelium by a resectoscope equipped with a roller-ball electrode. Jones and colleagues (1991b) reported that direct percutaneous access into the diverticulum could be established in all but 2 of 24 patients. Likewise, Shalhav and associates (1998) reported that in a group of 30 patients with calyceal diverticula, direct access was performed in 28 patients. When direct puncture fails, a

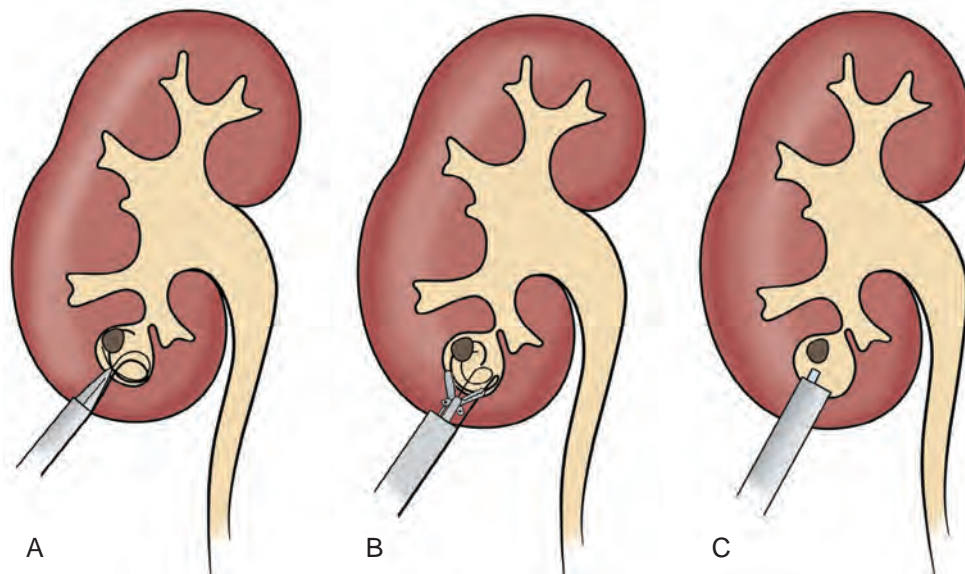


Figure 54-22. Access into small diverticula. A, Balloon dilator is advanced as far as possible without perforating the back wall of the diverticulum. The working sheath is placed just outside the diverticulum. B, Alligator forceps spread the parenchyma and allow advancement of the nephroscope under vision into the diverticulum. The working sheath is then advanced over the nephroscope and into the diverticulum (C).

neighboring calyx can be punctured and the diverticulum entered indirectly by perforating the wall of the diverticulum or by entering in a retrograde fashion through the diverticular neck (Hedelin et al, 1988). However, results with an indirect approach are inferior (Jarrett and Smith, 1986).

Kim and associates (2005a) have described a single-stage technique for the treatment of patients with calculi residing in a calyceal diverticulum (Fig. 54-22). Once the diverticulum is punctured, a 0.035-inch movable core J-wire is coiled within the diverticulum. It is important to ensure that not only the floppy tip of the wire but also the solid core is coiled within the diverticulum, so that sufficient stabilization is provided for proper placement of coaxial dilators. A second 0.035-inch movable core J-wire serving as a safety wire is then passed through the 10-Fr sheath of the coaxial dilator. With two guidewires coiled within the diverticular lumen, balloon dilation of the track can be performed safely. Care should be taken to avoid perforation of the back wall of the diverticulum. Once the balloon dilator is inflated, the working sheath is passed over the balloon as close as possible to the diverticulum without advancing the balloon. In small diverticula, this results in the placement of the sheath outside the diverticulum. An 11-Fr alligator forceps is passed through the rigid nephroscope and used to follow the wire and gently spread renal parenchyma to allow entry into the calyceal diverticulum under direct vision. Stone material is then extracted. Careful inspection of the urothelium with the rigid nephroscope, and in cases of a large diverticulum a flexible nephroscope as well, is performed in an effort to identify a flattened renal papilla, which suggests an obstructed calyx rather than a diverticulum. The neck of the diverticulum is often difficult to identify because it can be diminutive. Methylene blue injected through the ureteral catheter can facilitate visualization of the ostium. Once a guidewire is passed into the renal pelvis, the neck of the diverticulum can be balloon dilated or incised.

Because calyceal diverticula are lined by a nonsecretory endothelium, most authors advocate fulguration at the time of PNL because this will ablate 76% to 100% of diverticula (Monga et al, 2000; Kim et al, 2005b). Auge and associates (2002) and Turna and associates (2007) also have reported the results of long-term studies in which they found that PNL accompanied by ablation of the diverticulum is associated with superior stone-free rates. Alternatively, one series of 10 patients in which the nephrostomy tube was left in place for

2 weeks suggested that trauma to the wall of the diverticulum caused by the dilation process alone is sufficient to ablate the diverticular lumen (Hulbert et al, 1986). However, Donnellan and colleagues (1999) reported that treatment of 20 patients with calyceal diverticula by dilation or incision of the diverticular neck without fulguration resulted in complete ablation of the diverticulum in only 30% of patients, leading the authors to conclude that fulguration should be performed routinely to ensure diverticular ablation. Typically, after ablation of the diverticulum, a nephrostomy tube is placed for 48 to 72 hours.

Horseshoe Kidney. Horseshoe kidney is the most common congenital renal anomaly found in 1 in 474 abdominal CT scans (Glodny et al, 2009), with a male-to-female ratio of 2:1 (Jones et al, 1991a). The unique location and orientation of the horseshoe kidney are due to the incomplete cephalad migration and malrotation of the kidney, a consequence of the entrapment of the isthmus under the inferior mesenteric artery (Hohenfellner et al, 1992). The uteropelvic junction (UPJ) is commonly deformed owing to the high insertion of the ureter into a typically elongated renal pelvis. The insertion of the proximal ureter is similarly aberrant; it drapes ventrally over the renal symphysis, where it may be compressed by vessels supplying the lower pole and isthmus. Ureteral obstruction that may result from these anomalies can give rise to hydronephrosis, urinary stasis, sepsis, and calculi formation in up to 70% of patients (Jones et al, 1991a; Lampel et al, 1996).

In considering PNL in a horseshoe kidney, the characteristic lower and centrally oriented position of the kidney, the orientation of the collecting system, and the abnormal blood supply should be taken into account. Janetschek and Kunzel (1988) performed post-mortem examinations of six horseshoe kidneys, in situ, and found normal renal arteries in all specimens. However, accessory arteries entering the renal hilum, aberrant polar and isthmus arteries originating from the aorta, and hypogastric and common iliac arteries were noted as well; all blood vessels, except a select few supplying the isthmus, entered the kidney from its ventromedial aspect. Glodny and colleagues (2009) examined CT scans of 90 patients with horseshoe kidneys and found that cephalad the vasculature had little variation; however, more caudally the renal vasculature varied considerably. Therefore, a puncture of the dorsal or dorso-lateral aspect of the kidney will be well away from major renal vessels.

Skoog and associates (1985) reported an association between horseshoe kidney and retrorenal colon. A preoperative CT should be performed to assess the presence of a retrorenal colon as well as to define the stone-bearing calyces. The lower pole calyces lie within a coronal plane, angled medially, and are seldom suitable for direct puncture (Al-Otaibi and Hosking, 1999). However, the upper pole calyces are more posterior and lateral and are often subcostal, providing a convenient and relatively safe route for PNL access. The standard site for PNL (inside the posterior axillary line just caudal to the 12th rib) is punctured, but the angle of the puncture is caudad rather than cephalad. Because most of the calyces of horseshoe kidneys point either dorsomedially or dorso-laterally, they are more favorably positioned for puncture than are normal renal units (Janetschek and Kunzel, 1988). Because of the malrotation of the kidney, the renal pelvis may be more anteriorly located and the length of the nephrostomy tract often exceeds the length of the rigid nephroscope, necessitating the use of flexible nephroscopy or multiple accesses. Flexible nephroscopy also may be required to gain access to the lower medial calyces, where stones are often found.

Raj and associates (2003) reported a multicenter analysis of 24 patients with calculi in a horseshoe kidney who underwent PNL. The overall stone-free rate was greater than 90%, most accesses were upper pole, and flexible nephroscopy was performed in almost all patients. The authors noted that the rigid nephroscope was rarely sufficient to remove the whole stone burden. Miller and associates (2008) reported a similar series of patients undergoing PNL of horseshoe kidneys; upper pole access was used in all cases, as was flexible nephroscopy. A prospective multi-institution study from the Clinical Research Office of the Endourology Society noted similar stone-free results in patients with horseshoe kidneys compared to normal kidneys (76.6% vs. 76.2%) but found operative times to be significantly longer in the patients with horseshoe kidney with a higher rate of overall failed procedures in all patients with renal anomalies (Osther et al, 2011).

Transplantation and Pelvic Kidneys. Urolithiasis is uncommon in patients who have undergone renal transplantation, with a reported incidence of 0.5% to 3% (Harper et al, 1994; Shoskes et al, 1995; Del Pizzo and Sklar, 1999). Factors that may predispose transplant recipients to form calculi include metabolic abnormalities, foreign bodies (nonabsorbable suture material, forgotten stents), recurrent infection, and papillary necrosis. On occasion, calculi may have been present in the donor kidney (Pardalidis et al, 1994). Verrier and colleagues (2012) reviewed their 32-year experience and noted a significant decrease in the incidence of transplant urolithiasis after the introduction of routine ureteral stenting and early intervention for ureteral obstruction after transplantation. Typical renal colic does not occur because the transplantation kidney and ureter are denervated; the presentation may instead resemble acute rejection or acute tubular necrosis (Harper et al, 1994; Rhee et al, 1999). Benoit and colleagues (1996) reported that in a series of 1500 transplantation patients, 12 (0.8%) were diagnosed with urinary calculi. Three patients presented with obstructive anuria, one patient presented with abdominal pain, and eight patients were asymptomatic and diagnosed by ultrasonography. Krambeck and colleagues (2008) found that acute renal failure, hematuria, and UTI were the most common presenting symptoms in 13 renal transplant patients treated with PNL.

Renal allografts present a unique anatomic situation for PNL. The most common surgical anatomy is for the donor left kidney to be placed extraperitoneally into the recipient's right iliac fossa; alternatively, the right kidney is transplanted in the left iliac fossa. In either case, the renal pelvis is located medially, requiring that the kidney be rotated 180 degrees on its axis. Thus the posterior calyces point anteriorly and, consequently, an anterior approach to the kidney is similar to a posterior approach to native kidneys. In the usual percutaneous approach to a transplanted kidney the patient is placed in the lithotomy position, which allows simultaneous cystoscopic access to the bladder. A ureteral catheter is inserted for instillation of contrast material. Access is most safely established (i.e., avoiding intraperitoneal contents) into the lower pole with the

skin puncture as caudal as possible. Percutaneous access to transplanted kidneys is actually facilitated by their superficial location. However, scar formation around the graft may make the initial needle puncture and tract dilation more difficult (Rhee et al, 1999). Once access is established, PNL can be performed by standard methods (Pardalidis et al, 1994; Krambeck et al, 2008). Del Pizzo and Sklar (1999) reported the use of a mini-percutaneous technique in 14 transplantation patients in whom access was established with the aid of intraoperative ultrasonography with a 16-Fr suprapubic peel-away introducer and sheath. No data are available to show an advantage of the mini-percutaneous technique compared with the larger diameter working sheaths. Although delayed closure of the access site after catheter removal in immunosuppressed transplantation patients is a concern, most authors report that even nephrostomy tracts dilated to 30 Fr closed normally (Caldwell and Burns, 1988; Gedroyc et al, 1989; Del Pizzo and Sklar, 1999; Krambeck et al, 2008). Rifaioğlu and associates (2008) reported that not all patients will require tract dilation to 30 Fr, and in some cases acceptable outcomes may be achieved with percutaneous flexible nephroscopy alone.

Patients with ectopic pelvic kidneys necessitate a different and more complicated approach for PNL as a result of their unique anatomy. The incidence of pelvic kidney has been estimated to range from 1 in 2200 to 1 in 3000 in autopsy series (Zafar and Lingeman, 1996). The pelvic kidney is retroperitoneal, posterior to the peritoneum and anterior to the sacrum. Interposing bowel loops between the kidney and the anterior abdominal wall prevent a direct puncture through the anterior abdominal wall. Eshghi and colleagues (1985) first described a laparoscopically assisted PNL technique for pelvic kidneys, a technique that has been further characterized by others (Zafar and Lingeman, 1996; Holman and Toth, 1998; Matlaga et al, 2006). Desai and associates (2007) reported on PNL in pelvic ectopic kidneys using only ultrasound guidance. Although the stone-free rate was 100%, a bowel injury did occur in one patient. Consequently, if laparoscopy will not be used to assist guidance and reflect intervening organs away from the anticipated course of percutaneous access, percutaneous access could be obtained using CT guidance (Fig. 54-23), as described by Matlaga and associates (2003).

Staghorn Calculi/Complex Stones. Patients suffering from staghorn calculi or complex renal calculi remain a challenging problem for the practicing urologist. Most staghorn stones are composed of struvite, and factors that predispose to UTI and retained urine increase the likelihood of struvite stone formation (Gettman and Segura, 1999). However, other crystals, including cystine, calcium

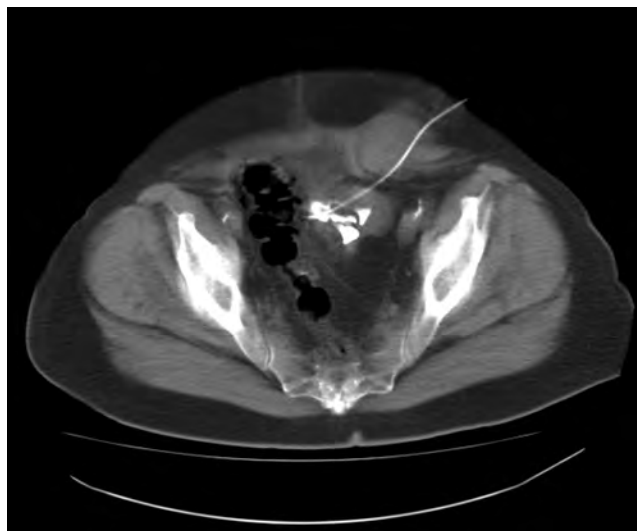


Figure 54-23. Computed tomography–guided percutaneous access of a renal transplant for subsequent percutaneous nephrolithotomy procedure.

oxalate monohydrate, and uric acid, can assume a staghorn configuration. In general, the goal for patients with staghorn calculi should be stone free, because if all of the infected stone debris is not evacuated, urea-splitting bacteriuria may persist, which can ultimately lead to eventual stone regrowth.

The management of patients with staghorn stones by a combined approach must be viewed as primarily percutaneous, with SWL being used only as an adjunct to minimize the number of access points required. Improved PNL techniques incorporating the increasing use of flexible nephroscopy and providing complete or nearly complete clearance of stone material at the time of the primary procedure may have decreased or eliminated the need for additional SWL treatment (Preminger et al, 2005).

Desai (2009) and colleagues published the largest series of staghorn calculi treated with PNL, which included 834 procedures in 773 patients. The overall stone-free rate was 86%, and the authors found that with time, experience, and advancements in technology there was a reduction in operative and hospital duration, tract numbers, reintervention and complication rates, and likelihood of residual fragments. Soucy and colleagues (2009) also published their series of 509 staghorn calculi treated percutaneously. Only 16% of patients required multiple access tracts and transfusion rate was low at 0.8%. Overall stone-free rate was 90%, with 9% of patients requiring a secondary procedure. Duvdevani and colleagues (2007) presented their series of 1585 PNL cases, which included staghorn calculi. Their results demonstrated that as stone surface area increased, stone-free results decreased, with staghorns having an 88.6% stone-free result by KUB. Only 8% of their patients overall required more than one percutaneous access tract, and 24% required a secondary procedure. However, a recent study from the Clinical Research Office of the Endourological Society compared outcomes of PNL in 1466 staghorn calculi to 3869 nonstaghorn calculi patients at 96 centers worldwide (Desai et al, 2011). Those patients with staghorns had a higher rate of multiple access tracts (16.9% vs. 5.0%), higher overall complication rate including bleeding and fever, and lower stone-free rate (56.9% vs. 82.5%).

In general, if a single access tract is to be used in treating complex branching stones, the upper pole is preferred. An upper pole access allows for treatment of the upper pole, renal pelvis, and many lower pole stones using the rigid nephroscope. Midcalyceal stones can then be treated using a flexible nephroscope and holmium laser. When pressurized irrigant is used the debris and fragments created by the holmium laser in most cases will wash out the access sheath or into the renal pelvis, where it can be retrieved with the rigid nephroscope and suction.

Morbid Obesity. Patients with morbid obesity present technical as well as anesthetic challenges during any surgical intervention (Freedman et al, 2002). Often, one or more comorbid factors complicate management of these patients. General anesthesia may be a special concern for obese patients in the prone position because of restricted respiratory capacity that may require higher ventilation pressures intraoperatively. Multiple studies have not demonstrated an increase in overall morbidity in the obese patient undergoing PNL. Pearle and coworkers (1998) were the first to examine the issue of PNL among the obese and found that performing standard prone PNL was not associated with an increased risk for morbidity; in fact, complication and transfusion rates as well as the length of hospitalization were no different compared to those in nonobese patients. Subsequent authors have observed that PNL outcomes are independent of body mass index (BMI) (Koo et al, 2004), including stone-free results (El-Assmy et al, 2006). However, a multi-institution study of 3709 PNL procedures performed across the globe found that complication rates were not associated with BMI, but patients with a higher BMI were more likely to have comorbid conditions, including chronic anticoagulation, and a lower overall stone-free rate (Fuller et al, 2012).

Positioning the morbidly obese patient for PNL can be difficult; and in particular for large patients, two surgical tables may need to be secured together (Hofmann and Stoller, 1992). Patient positioning should be closely inspected, and pressure points should be identified and padded. Hofmann and Stoller (1992) described a

morbidly obese patient who developed acute rhabdomyolysis secondary to crush injuries from placement in the lateral approach; if this technique is used, care must be taken to minimize muscle crush injury. Some authors have used awake intubation and patient self-positioning for the morbidly obese patient to decrease the likelihood of nerve or muscle damage (Wu et al, 2009). The major difficulty in performing PNL in the morbidly obese patient is the long distance from the skin to the collecting system, which may exceed the length of the working sheath or the length of the rigid nephroscope. **Extralong Amplatz working sheaths (≥ 20 cm) and extralong rigid nephroscopes are now available that can overcome this challenge.** Alternatively, the Amplatz sheath can be secured by a suture, allowing easy retrieval even when it migrates under the skin. On occasion, when the long Amplatz sheath is not sufficient to reach the kidney, an incision can be made through the subcutaneous tissue to the muscles of the flank, and the PNL tract created from the level of the muscle sheath (Curtis et al, 1997). Alternative instrumentation also can be employed; Giblin and colleagues (1995) described the successful use of a 30-Fr gynecologic laparoscope (with a working length of 27 cm) in patients in whom the skin-to-stone distance precluded the use of standard access sheaths and nephroscopes. Another possibility is to dilate the tract and place a nephrostomy tube for 1 week to let the tract mature. In some cases, maturation of the tract allows the kidney to fall back posteriorly closer to the skin, allowing the use of standard nephroscopic instrumentation. Flexible nephroscopy also can be performed through the mature tract, reducing the necessity of rigid nephroscopy (Hofmann and Stoller, 1992). Liberal use of flexible nephroscopy in obese patients improves the stone-free rate and decreases the need for additional access (Pearle et al, 1998).

After stone removal, if a nephrostomy tube is placed, consideration should be given to the type of nephrostomy tube used. **Tube displacement tends to occur more often in morbidly obese patients**, so balloon-type catheters or re-entry Malecot catheters may be preferable (Carson et al, 1988). Alternatively, if a Cope loop catheter is used, placement of a ureteral catheter should be considered to ensure that access to the kidney is not lost should the nephrostomy tube become displaced.

Bilateral Simultaneous Percutaneous Nephrolithotomy

Patients with large, bilateral stone burdens present a formidable challenge to the urologist; rendering these patients stone free can require staged procedures and multiple anesthetics. In 1987, Colon-Perez and associates (1987) first reported simultaneous bilateral PNL in a series of three patients. Since that time the procedure has evolved and several dictums have been established. It is recommended that either the side that is more symptomatic or the side that is more difficult be treated first. Patients may be positioned prone or with the treated side elevated.

Most groups have reported that there is a marked advantage in terms of hospitalization and convalescence, suggesting that a simultaneous bilateral PNL provides the patient a less morbid, more rapid method of stone resolution than does staged PNL or a sandwich technique (Dushinski and Lingeman, 1997; Nadler et al, 1998; Holman et al, 2002). Silverstein and associates (2004) also reported that stone-free rates, blood loss per operation, and transfusion rates for simultaneous and staged bilateral PNL were similar. Furthermore, the reduced total operative time, hospital stay, and total blood loss along with the requirement for only one anesthesia session makes simultaneous bilateral PNL an attractive option for selected patients. However, a recent evaluation using the Clavien scoring system for postoperative complications found that bilateral PNL was associated with a higher rate of low-grade complications compared to unilateral single access PNL (Kadlec et al, 2013). Desai and associates (2007) have issued a caveat that patients with exceptionally large stone burdens or complex intrarenal collecting system anatomy should not be selected for a simultaneous bilateral PNL. Bagrodia and associates (2009) performed an outcome cost analysis of simultaneous bilateral PNL, confirming the superior morbidity and convalescence of this approach.

Taking all of the evidence together, should a simultaneous bilateral approach be selected the second side should be pursued only if no significant bleeding is encountered on the first side, the first side did not take an undue amount of time, the patient is clinically stable, and the anesthesia team is agreeable.

Complications

Even for the most experienced urologist, major complications can still occur in up to 7% of patients undergoing PNL and minor complications may be encountered in up to 25% of patients (Preminger et al, 2005). **Hemorrhage is the most significant complication of PNL, with transfusion rates reported to be from less than 1% to 10%.** A multi-institution study of more than 5000 patients from 96 different centers reported an overall transfusion rate of 5.7% (Yamaguchi et al, 2011). Risk for hemorrhage was associated with stone burden and operative duration. Bleeding from an arteriovenous fistula or pseudoaneurysm that requires angiographic embolization occurs in less than 1% of patients (Keoghane et al, 2013). Other potential complications include sepsis (postoperative temperature $> 38.5^{\circ}\text{C}$ [101.3°F] is found in almost one fourth of patients undergoing PNL), adjacent organ injury (bowel, spleen), failed access, and perforation of renal pelvis and ureter. The need for open surgery is rare and mostly reported as part of early experience in various studies. The mortality rate of PNL is between 0.03% and 0.8% (Lang, 1987; Lee et al, 1987; Henriksson et al, 1989; Jones et al, 1991a; Lam et al, 1992; Segura et al, 1994; Dyer et al, 1997; Matlaga et al, 2004; de la Rosette et al, 2011). When supracostal puncture is performed, the risk for pneumothorax or pleural effusion requiring drainage can vary widely from 1.8% to as high as 8% in historical series (Picus et al, 1986; de la Rosette et al, 2011). Finally, failure of equipment is an often ignored but significant potential complication. Experience of the center performing the PNL procedure also can contribute to overall complication rates and stone-free results. Opondo and colleagues (2012) evaluated PNL performed at 96 centers worldwide. The results of their study found that as their institution case volume increased, so did stone-free rates. Complication rates and duration of stay diminished with increasing case volume after adjusting for stone burden and other cofactors. The highest stone-free results and lowest complication rates were observed in centers with greater than 120 cases per year.

During initial experiences with PNL, concern was expressed about the extent of renal damage caused by the creation and dilation of the transparenchymal nephrostomy tract. However, although some scarring does occur along the percutaneous tract, there is little or no significant effect on renal function (Eshghi et al, 1989).

Because the kidney is an extremely vascular organ, some degree of bleeding occurs during every PNL. Significant bleeding usually requires cessation of the procedure because of impaired visualization. In most cases the source of hemorrhage is venous and placement of a nephrostomy tube is usually sufficient to control the bleeding. If bleeding persists despite the placement of a nephrostomy tube, clamping the tube for a time may facilitate the tamponade of any bleeding points. If these measures do not control the hemorrhage, a Kaye nephrostomy tamponade balloon catheter should be placed. The Kaye nephrostomy tube incorporates a low-pressure 12-mm balloon that may be left inflated for prolonged periods to tamponade bleeding from the nephrostomy tract (Kaye and Clayman, 1986). If bleeding persists despite placement of a Kaye catheter, immediate angiography should be performed to identify a possible arteriovenous fistula or false aneurysm. Angiography is both diagnostic and therapeutic, because arteriovenous fistulas and false aneurysms are best managed by embolization. In the rare event that bleeding cannot be controlled with angiography, partial nephrectomy may be required.

PNL can lead to some absorption of irrigation fluid; therefore the use of physiologic irrigating solutions is mandatory. The amount of absorbed fluid depends mostly on the irrigant pressure and the length of the procedure; thus an access sheath should be used. Larger amounts of fluid absorption may occur with extravasation of fluid as a result of collecting system perforation. Extravasation

usually occurs into the retroperitoneal tissue and may be noted by medial displacement of the kidney during fluoroscopy. Minor perforations are common during PNL; premature termination of the procedure usually is not necessary when a low-pressure system (e.g., Amplatz sheath) is being used. However, with more significant perforations, termination of the procedure and nephrostomy drainage are advisable. Intraperitoneal extravasation is a less common but potentially more serious complication than retroperitoneal extravasation. Because the patient is prone, abdominal distention may be difficult to recognize, although the anesthesiologist will usually note a gradual rise in the patient's diastolic blood pressure with consequent narrowing of the pulse pressure and increase in central venous pressure; in advanced cases, ventilation may become difficult because of increased abdominal pressure. Early recognition of major extravasation is crucial. Before the standard use of access sheaths it was recommended that accounting of the irrigant input and output be maintained and if a discrepancy of more than 500 mL were encountered the procedure should be aborted (Lee et al, 1986; Segura, 1993). However, a strict accounting of irrigating fluid balance is not necessary when an access sheath is properly placed. Intraperitoneal extravasation may be treated by vigorous diuresis; alternatively, peritoneal drainage has been reported (Carson and Nesbitt, 1985).

When a supracostal puncture is performed, extravasation of irrigant into the pleural cavity may occur. The use of a working access sheath tends to minimize extravasation into this space because intrarenal pressure remains low. The chest should be examined at the end of PNL procedures in which a supracostal puncture is used. Fluoroscopy with use of the C-arm is usually sufficient to examine for pneumothorax or hydrothorax (Ogan et al, 2003). If the surgeon has a high index of suspicion for a thoracic complication, a chest radiograph may be obtained postoperatively. If a greater than 10% pneumothorax or hydrothorax occurs, aspiration is generally sufficient because lung injury is extremely rare. Should the pneumothorax recur, a chest tube should be placed. Ogan and Pearle (2002) described placement of a chest tube under fluoroscopic guidance at the time of the PNL.

Colonic injury is an unusual complication and is often diagnosed on postoperative nephrostogram or CT imaging, although passage of gas or feculent material through the nephrostomy tract, intraoperative diarrhea, and hematochezia or peritonitis are all signs of a possible colonic perforation. Typically, the injury is retroperitoneal; thus signs and symptoms of peritonitis are infrequent. If the perforation is extraperitoneal, management may be expectant, with placement of a ureteral catheter or double-J stent to decompress the collecting system and withdrawal of the nephrostomy tube from an intrarenal position to an intracolonic position to serve as a colostomy tube (Gerspach et al, 1997). The colostomy tube is left in place for a minimum of 7 days and removed after a nephrostogram or a retrograde pyelogram shows no communication between the colon and the kidney (LeRoy et al, 1985; Wolf, 1998).

Ureteroscopic Management of Ureteral Stones

Basic ureteroscopic techniques and intracorporeal lithotripsy techniques have been reviewed elsewhere. Herein, issues of anesthesia and specific points of technique and complications of ureteral stone management are reviewed.

The increasing miniaturization of and improvements in the technology of ureteroscopy have greatly altered the anesthetic considerations associated with this procedure. Ureteroscopy was initially performed exclusively under general or regional anesthesia as a consequence of the large-caliber ureteroscopes that were available. However, as ureteroscopes have become more diminutive, intravenous sedation, or sedoanalgesia, has provided another practical anesthetic option for patients harboring ureteral stones. The short duration of modern sedoanalgesic agents allows rapid relief of pain, efficient titration of analgesia, and rapid recovery after the procedure. Ureteroscopy can be safely and efficiently performed under local or intravenous sedation, with success rates equivalent to those of patients undergoing general or regional anesthesia (Cybulski

et al, 2004; Park et al, 2004). Because most ureteral orifices will accommodate a 6- to 7-Fr device, immediate access to ureteral calculi with a 7-Fr flexible ureteroscope is possible. Furthermore, the small-diameter fibers of the holmium:YAG laser allow the immediate treatment of ureteral calculi.

The ability to fragment and remove calculi with a ureteroscope has dramatically advanced the urologist's ability to render patients stone free with a single procedure. Early stone-free results with flexible ureteroscopy did not exceed those of in situ SWL (Drach et al, 1986; Bagley, 1990; Frang et al, 1992; Mogensen and Andersen, 1994). However, as smaller ureteroscopes were introduced and the holmium:YAG laser became available, success rates for ureteroscopy have increased (Preminger et al, 2007). Although it is a more invasive technique than SWL, ureteroscopy with small, rigid or flexible endoscopes is the most efficient technique for treatment and removal of ureteral stones. Patients desiring a single procedure with maximal efficacy should be counseled on the advantages of a ureteroscopic approach.

When the ureteral orifice is too narrow to accommodate the ureteroscope, dilation may be accomplished with serial dilators, balloons, or even the ureteroscope itself. The anatomy of male patients may not allow a rigid ureteroscope to be easily passed above the iliac vessels, but a flexible ureteroscope usually can be advanced over a guidewire. The entire ureter can be more easily accessed with a rigid ureteroscope in female patients. Once the stone is visualized, fragmentation with the lithotrite of choice is performed. Complete fragmentation to a size less than that of the safety wire diameter (0.035 inch) should allow passage of all fragments without sequelae. Alternatively, fragmentation to a size sufficient for extraction by a stone retrieval device achieves a stone-free state for the patient at the end of the procedure.

Multiple different devices exist to prevent stone retropulsion from the ureter into the kidney during lithotripsy. These antiretropulsion devices are covered extensively elsewhere in this textbook. Their overall benefit is seen with semirigid ureteroscopy when the surgeon wishes to avoid performing flexible nephroscopy of the kidney to retrieve any small fragments that may have traveled proximally at time of treatment of the ureteral stone. If ureteral edema or injury is present after stone extraction, a postureteroscopy stent should be placed to prevent colic and obstruction. Multiple meta-analyses have found that for uncomplicated ureteroscopy, a ureteral stent may be safely omitted (Nabi et al, 2007; Makarov et al, 2008; Pengfei et al, 2011). If the clinical situation does not allow primary ureteroscopy (sepsis, inability to advance the ureteroscope, ureteral injury, equipment failure), a ureteral stent is placed and the problem corrected. Secondary or post-stent ureteroscopy has the advantage of working through a dilated ureter, often allowing the use of larger rigid ureteroscopes.

Ureteral Access Sheath

The use of a ureteral access sheath as an adjunct to ureteroscopy was first reported by Takayasu and Aso in 1974 as a means to simplify access to the intrarenal collecting system. It was not until more than two decades later that the ureteral access sheath was rediscovered and refined, simplifying the deployment and safety of these devices. The present generation of ureteral access sheaths consists of a hydrophilic outer coating, as well as a tapered transition from obturator to sheath, which facilitates their retrograde placement. The walls of the sheaths are designed not only for a slim profile but also for strength and often are reinforced so as to resist kinking.

Kourambas and associates (2001) reported that the ureteral access sheath can be successfully deployed in over 90% of attempted placements. In this randomized controlled study these authors also found that the use of an access sheath decreased operating room time, simplified re-entry of the ureter, and, likely as a consequence of these two points, was associated with decreased operating room costs. In a larger, retrospective study from the same institution, L'Esperance and associates (2005) reported on a series of 173 patients undergoing ureteroscopy with an access sheath and compared these outcomes to those of 83 patients undergoing ureteros-

copy without an access sheath. They found that the stone-free rate was significantly higher when the access sheath was employed (79% vs. 67%; $P = .042$). Portis and associates (2006) also reported on a prospective series of patients undergoing ureteroscopy with a ureteral access sheath and commented that the sheath facilitated the active extraction of all stone fragments. Finally, ureteral access sheaths may have an added benefit when treating infection-related calculi, because the use of a sheath has been reported to maintain low intrapelvic pressures during ureteroscopy (Rehman et al, 2003). Additionally, as irrigating fluid drains through the access sheath external to the patient, the need for periodic emptying of the patient's bladder during a prolonged procedure is eliminated. However, potential drawbacks to the ureteral access sheath have been identified. Traxer and Thomas (2013) observed a 46.5% ureteral injury rate at time of ureteroscopy when a ureteral access sheath was used; however, in only 13.3% of cases was the injury deep enough to involve the ureteral musculature. Another study noted that not placing a stent after ureteroscopy with an access sheath was associated with a significantly higher postoperative pain score and higher likelihood of contact with a medical provider for pain (Torricelli et al, 2014).

Complications

As modern ureteroscopes have become smaller and less traumatic, as safer intracorporeal lithotripters have become widely available, and as a better understanding of the technical principles of ureteroscopy has been developed, the number of complications arising from the management of ureteral stones has been steadily decreasing.

Fortunately, most of the complications caused by ureteral stones and their management respond favorably to simple drainage of urine with ureteral catheters or stents. A study of 11,885 ureteroscopy procedures reported an overall complication rate of only 3.5%, with the most frequent complication being fever (1.8%) (de la Rosette et al, 2014).

Perforation. As is true with most ureteroscopic complications, the incidence of ureteral perforation has decreased over time, as technology and technique continue to improve. In a series of ureteroscopic procedures reported in 1992, ureteral perforation was reported in approximately 15% of cases. More recent series report a perforation rate of 0% to 4% (Preminger et al, 2007; Bader et al, 2012). A number of actions may result in a ureteral perforation; some of the more commonly encountered scenarios include the splitting of a ureter after balloon dilation, forceful placement of ureteral access sheath, or a traumatic injury from forceful and misdirected manipulation of a stone. In some cases an intracorporeal device such as a lithotrite or electrocautery can cause full-thickness damage to the ureter. The incidence of ureteral perforation varies among the different intracorporeal lithotrites, with the highest incidence of ureteral perforation occurring with EHL. Baskets and grasping devices also may cause injury, because in the process of grasping a stone or lesion it is possible to inadvertently snare part of the ureter, which may result in a perforation. Traxer and Thomas (2013) observed a 46.5% ureteral injury rate at time of ureteroscopy when a ureteral access sheath was used; however, in only 13.3% of cases was the injury deep enough to involve the ureteral musculature. Finally, the pressurized irrigation can cause perforation or calyceal rupture.

Adherence to the tenets of safe ureteroscopy will minimize the likelihood of a ureteral perforation. Nonetheless, such a complication may still occur and it is important for the urologist to be familiar with the treatment of this event. **When a ureteral perforation is recognized, the ureteroscopic procedure should be terminated and a stent placed across the injury.** The risk for perforation underscores the importance of using saline as an irrigant, to prevent electrolyte derangements due to fluid extravasation. In cases of a severe injury, with significant extravasation of fluid, a percutaneous nephrostomy drain also may be necessary. Urinoma can result from perforation as well and may need to be drained. Antibiotics should be given because of the risk for infected urine and abscess

formation. In general, a stent should be left in place for approximately 4 weeks after injury. Subsequent imaging after ureteral stent removal is mandatory, to evaluate for a proper healing and adequate drainage.

Schuster and associates (2002) found a significant association of ureteral perforation with increased operative time. This suggests that if the procedure is difficult and not progressing, it is wise for the urologist to stop, place a stent, and plan for a staged procedure. The best prevention strategies are similar to the principles discussed earlier, including controlled maneuvers without force, knowing the margin of safety of the equipment being used, and always using both a working and safety guidewire.

Stricture. The development of a postoperative ureteral stricture is one of the more serious complications that may occur after ureteroscopy. Approximately two decades ago, the reported incidence of ureteral stricture after ureteroscopy was as high as 10%. More recently, however, the incidence of a postoperative stricture is reported to be 3% to 6% (Preminger et al, 2007) and in one review as low as 0 to 0.2% (Bader et al, 2012). It is likely that the improvements in surgical technology and technique are responsible for this dramatic reduction.

Although the cause of a ureteral stricture is likely multifactorial, certain factors have been reported to increase patient risk for stricture development. Roberts and coworkers (1998) reported a 24% stricture rate for stones that had been impacted an average of 11 months. Impacted stones are defined by the inability to pass a wire or catheter beyond the stone or stones that have been present and not moved for 2 months or more. Meng and coworkers (2003) reported that a ureteral perforation also may increase the risk for stricture formation, finding that strictures occurred in 5.9% of patients who suffered a ureteral perforation during ureteroscopy. It may be that an inflammatory response that results in devascularization and ischemia promote this process, because such local changes can result in a cicatrization of the ureter. Patients with a history of ureteral surgery, pelvic radiation, and impacted stones are also at greater risk secondary to altered blood flow and poor healing. Devascularization injury can result in ureteral necrosis, which necessitates open or laparoscopic repair. However, some patients develop a ureteral stricture in the presence of no intraoperative misadventures, suggesting that there is much about this process that remains to be elucidated.

To reduce the risk for stricture, care should be taken during all parts of the procedure, because the traumas that may increase the risk for this event are many and varied. **Overly aggressive manipulation of a ureteroscope across a narrow segment of ureter, as well as trauma or perforation from injudicious manipulation of intracorporeal devices or lithotrites may increase the risk for stricture.** Because of the reported occurrence of a postoperative ureteral stricture even after an uncomplicated ureteroscopy, it is recommended that all patients undergo postoperative imaging after ureteroscopic instrumentation to ensure that such a complication is recognized. Although most patients with a stricture will be symptomatic, between 0.4% to 4% will be entirely asymptomatic (Bugg et al, 2002; Weizer et al, 2002; Karadag et al, 2008), so imaging is recommended by the AUA in all patients to exclude such cases of silent obstruction (Fulgham et al, 2013).

The management of a postureteroscopic ureteral stricture will depend primarily on its length and location, although other factors such as the time elapsed since injury, nature of trauma, and patient-specific parameters merit consideration. For many short strictures, endoscopic management may be appropriate, and incision and dilation may yield a good result. For longer strictures, however, ureteral reconstruction can be more complex, requiring either open or laparoscopic repair. The types of reconstruction available are essentially the same as those for ureteral avulsion. If a stricture is short but has failed endoureterotomy, a ureteroureterostomy may be possible after the affected portion has been resected.

Submucosal Stone and Lost Stone. The submucosal stone and the lost stone represent two points on a continuum of iatrogenic displacement of a ureteral calculus into the wall of the ureter. Extrusion of a urinary calculus may occur in up to 2% of ureteroscopic

procedures. When the stone migrates only to the submucosa, a problematic complication can develop, because removal of such stones is difficult. If submucosal stones are encountered, laser excision followed by ureteral stent placement is recommended. Submucosal stones are of concern, because they can increase the risk for ureteral stricture formation.

Complete extrusion of a calculus, also known as a lost stone, can occur in the setting of a ureteral perforation. In most cases, if the fragment is completely outside the collecting system it can be left in place. Attempts to retrieve the stone may exacerbate the injury and increase the risk for significant irrigant extravasation. When an extruded stone is recognized, the procedure should be terminated and a ureteral stent placed. Antibiotics should be administered to prevent the theoretical risk for abscess formation, although such a complication would be rare. One of the most serious sequelae of such an event is the later development of a ureteral stricture; for this reason patients who have calculus extrusion should undergo postoperative imaging, which will confirm the stone location. It is possible that, in the future, the lost stone could be confused for a ureteral stone, and it is important for the patient to be aware that such a situation exists.

Avulsion. Perhaps the most catastrophic complication that can occur during a ureteroscopic procedure is avulsion of the ureter. Fortunately, such a complication is a rare occurrence, reported in less than 0.06% to 0.5% of all cases (Bader et al, 2012); in fact, a review of over 1000 patients undergoing ureteroscopy reported no episodes at all of ureteral avulsion (Krambeck et al, 2006b). **Ureteral avulsion generally occurs as a consequence of overly forceful manipulation of a large or impacted calculus; however, a scabbard effect also can be created with resulting avulsion at time of scope withdrawal if too large a rigid ureteroscope is forcefully advanced up the ureter.** It has been reported that the proximal third of the ureter may be at greatest risk for avulsion, because it is the portion of the ureter that has the least muscular tissue support. A ureteral avulsion is usually diagnosed when a portion of the ureter is withdrawn from the patient, along with the stone and basket or grasper.

There are a number of maneuvers the urologist can undertake to avoid a ureteral avulsion. **Blind basketing, the removal of a ureteral calculus without the aid of endoscopy, may increase the risk for ureteral avulsion and should never be considered an appropriate method of stone extraction (Preminger et al, 2007).** In fact, even endoscopically guided basketing should be reserved for small stones only. In general, a safe ureteroscopic procedure relies on the placement of both safety and working guidewires. **Before engaging a stone in a basket or grasping device, it should be endoscopically evaluated to determine if it is of a size that would be likely to be extracted out of the ureter.** When the stone is engaged in the basket or grasper, the stone and device should both be kept under direct vision as they are extracted, so that the size of the stone can be continually compared with the size of the ureteral lumen. If the stone appears to be too large to be removed intact, it should be fragmented into smaller pieces that may either pass spontaneously or be extracted. If a stone too large to pass through the ureter is inadvertently engaged with a basket or grasping device, it should be released or replaced more proximally. If it is not possible to release the stone, the basket should be disassembled and the ureteroscope passed alongside the basket and the entrapped stone fragmented in situ. The use of a grasping device, rather than a basket, may simplify the release of an entrapped stone. The great benefit of having a safety wire in place is that should a stone become entrapped in the ureter a ureteral stent may be placed that will passively dilate the upper urinary tract and perhaps permit a more straightforward procedure at a later date.

Should a ureteral avulsion occur, a reasoned and considered approach to the management of the affected patient is advised. Although it may be tempting to perform an immediate primary repair at the time of injury, in general a delayed repair is recommended. The patient should undergo immediate diversion of the renal unit with the placement of a percutaneous nephrostomy drain. In some cases, a urinoma may develop as a consequence of

urinary extravasation; these collections are generally amenable to percutaneous drainage. Subsequent ureteral reconstruction techniques depend on the location of the injury and the amount of viable ureter that remains. For extensive injuries the treatment options are generally limited to ileal interposition (ileal ureter) or renal autotransplantation. Although a transureteroureterostomy may be a replacement option for some patients who have a ureteral injury, this repair technique is contraindicated in stone formers. For a more distal ureteral injury, a ureteral reimplantation with either a psoas hitch or Boari flap also may be successful. Nephrectomy has been reported to be an option for these patients as well; however, given the recurrent nature of stone disease and the fact that stone formers may be at increased risk for hypertension and diabetes, this approach is controversial.

Ureteroscopic Management of Intrarenal Calculi

Over the previous two decades, advances in fiberoptic technology have facilitated the development of practical flexible ureteroscopes; concomitant improvements in flexible intracorporeal lithotripters as well as intracorporeal grasping devices have promoted the use of flexible ureteroscopes for the treatment of renal calculi with a high degree of success. A study of 11,885 patients at 114 centers found that 25.2% of ureteroscopic procedures were performed for renal calculi (de la Rosette et al, 2014). Fuchs and Fuchs (1990) reported the first large series of patients with renal calculi who were treated by flexible ureteroscopy. In all cases, flexible ureteroscopy was performed after a 1- to 2-week period of ureteral stent placement. The overall stone-free rate was 87%, and the only complications reported were two cases of sepsis. The subsequent introduction of more miniaturized, flexible, actively deflectable ureteroscopes (7.5 Fr) has permitted the majority of ureteroscopic procedures to be performed without routine ureteral dilation. In two large series of patients with renal stones who underwent treatment with holmium laser lithotripsy, ureteral dilation was necessary in only 31% (Sofer and Denstedt, 2000) and 33% (de la Rosette et al, 2014) of patients. Numerous baskets and graspers now allow full deflection of flexible ureteroscopes, facilitating treatment of often difficult-to-access lower pole stones (Lukasewycz et al, 2004; Pearle et al, 2005).

As ureteroscopic technology has advanced, and as surgeons have gained increasing comfort with this technique, ureteroscopic lithotripsy intervention has become an increasingly common treatment for patients with renal calculi. Single session success rates, generally defined as successful fragmentation with complete stone clearance or the presence of "clinically insignificant" residual fragments, are reported to be in the 70% to 80% range (Mariani, 2007; Ricchiuti et al, 2007; Breda et al, 2008). However, when CT imaging is used to assess stone-free results range from 62% to 84% and vary based on the size of the renal stone (Portis et al, 2006; Macejko et al, 2009; Rippel et al, 2012). Success rates may be improved for larger stones if a secondary procedure is performed (Hyams et al, 2010). Even the treatment of staghorn calculi has been described, although this is not a widely used technique (Mariani, 2007). Complication rates are low, with fever and UTI being the most commonly encountered adverse events.

Technique

Proximal ureteral and intrarenal calculi can be accessed with actively deflectable, flexible ureteroscopes. Although, historically, a ureteral stent was left indwelling before ureterorenoscopy, this maneuver is currently necessary only when difficulty is encountered introducing the flexible ureteroscope into the ureter. If necessary, the stent is left for 2 to 4 weeks before the procedure (Erhard et al, 1996). The use of small-diameter ureteroscopes minimizes the necessity of ureteral dilation for stone access and may decrease associated morbidity. In cases of multiple stones or large stone burden requiring multiple passages of a basket, a ureteral access sheath may facilitate stone removal. A comparative study of ureteroscopic lithotripsy with or without access sheath showed that operative time was significantly

reduced by use of the access sheath, despite a greater mean stone burden in the access sheath group (Kourambas et al, 2001).

When a retrograde ureteroscopic approach is used to treat patients with intrarenal calculi, two wires are placed initially. The flexible ureteroscope is passed over one working wire in a monorail fashion. Saline is used for irrigation. When an implement is present within the working channel, simple gravity irrigation is inadequate and pressurized irrigation is required. The holmium:YAG laser lithotripter is used in almost all cases. Stones in lower pole calyces can be treated in situ or moved, with flexible graspers or a basket, into a position that allows better visualization. A head-down patient position with the ipsilateral flank elevated may help with stone and fragment visualization because fragments tend to migrate superiorly and are thus more easily localized during treatment. When access into the lower pole is difficult, prone positioning of the patient with the head down 20 degrees has been shown to provide the broadest angle of entry to the lower pole infundibulum (Bercowsky et al, 1999). The goal of holmium laser lithotripsy is to reduce the stone to fine dust and to small fragments 2 mm or less in diameter. If the stone is large, the collecting system often may become lined with fine dust and debris, which can obscure residual stones. Furthermore, poor visualization may lead to perforation. In such cases, either the irrigant in the intrarenal collecting system may be aspirated through the ureteroscope or a ureteral stent can be placed and the situation approached in a staged fashion.

Fragmentation of stones in situ in the lower pole can be challenging. If the lower pole infundibulum is accommodating, the most straightforward way to treat the stone is to engage it in a nitinol basket and displace it to the renal pelvis or an upper pole calyx. In this way it is generally a straight passage of the scope, with minimal deflection of the tip, which will simplify ureteroscopic laser lithotripsy. Residual fragments also should be more likely to evacuate spontaneously from the kidney.

Open Stone Surgery

Historically, most patients with symptomatic upper urinary tract calculi underwent open surgical lithotomy. Those patients with a small-to-moderate stone burden typically underwent pyelolithotomy, radial nephrolithotomy, or ureterolithotomy. For patients harboring staghorn calculi, more extensive procedures were required, including anastrophic nephrolithotomy, extended pyelolithotomy combined with radial lithotomies, and bench surgery with autotransplantation. However, the introduction of SWL and the development of endourologic techniques for stone removal have dramatically diminished the role of open stone surgery, especially for stone removal procedures, and open surgery is now one of the least common treatments of patients harboring upper urinary tract calculi. Turney and colleagues (2012) reported an 83% reduction in the number of open stone procedures performed from 2000 to 2010. Matlaga and Assimos (2002) reported that of 986 surgical procedures for stone removal performed at their institution between 1998 and 2001, 0.7% were open surgical procedures. Others have reported similar findings (Table 54-2), with an incidence of open stone surgery ranging from 0.3% to 5.4% (Assimos et al, 1989; Segura, 1990; Kane et al, 1995; Paik et al, 1998).

Renal Calculi

Minimally invasive techniques have clear advantages over open surgical techniques for patients harboring small-to-moderate burdens in otherwise normal kidneys. In 1985, Brannen and associates retrospectively compared PNL and open surgery for the treatment of patients with renal and proximal ureteral stones. Although the overall stone-free rate was similar, those patients treated by PNL experienced a shorter hospital stay, a lower narcotic requirement, and a shorter recovery period. Preminger and associates (1985) compared 88 patients undergoing PNL with 41 patients undergoing open stone surgery and found that PNL was associated with lower postoperative morbidity, more rapid convalescence, greater satisfaction of the patient, and reduced hospital costs for stones smaller

TABLE 54-2 Open Stone Surgery in the Modern Era

	ASSIMOS ET AL, 1989	KANE ET AL, 1995	PAIK ET AL, 1998	MATLAGA AND ASSIMOS, 2002
No. of open stone surgery cases (% of total stone removal procedures)	37 (4.1)	25 (3.13)	42 (5.4)	7 (0.7)
Stone-free rate (%)	100	71	93	100
INDICATIONS (%)				
Complex stone burden	3 (8.1)	3 (12)	23 (55)	0
Endoscopic treatment failure	18 (49)	51 (20)	12 (29)	1 (14)
Anatomic abnormality or concomitant open surgery	13 (35)	8 (32)	11 (46)	6 (86)
Body habitus	5 (14)	5 (19)	4 (10)	0
Other	2 (5)	6 (24)	4 (10)	0

than 2.5 cm. [Brown and associates \(1986\)](#) also demonstrated that PNL is more cost-effective than open stone surgery because of its reduced morbidity.

A more controversial issue has been the treatment of patients harboring staghorn calculi, a condition that carries a significant risk for mortality if it is untreated. [Boyce and Elkins \(1974\)](#) established anatomic nephrolithotomy as a standard treatment of patients with staghorn stones in the United States. Overall, the reported stone-free rate after open surgery for struvite calculi is approximately 85%, with a 30% stone recurrence rate over 6 years ([Griffith, 1978](#)). In comparing results for a combination of PNL and SWL with reported results of anatomic nephrolithotomy, [Kahnoski and associates \(1986\)](#) reported stone-free rates (85%) similar to those for the open surgical procedures, although convalescence and hospital stay for PNL were shorter and blood loss was less.

[Snyder and Smith \(1986\)](#) compared PNL with anatomic nephrolithotomy for patients with staghorn calculi. They reported that although the retained stone fragment rate was higher for PNL than for anatomic nephrolithotomy (13% vs. 0%), shorter procedure times, reduced need for blood transfusions and narcotics, and far more rapid return to work were achieved with PNL.

A meta-analysis undertaken by the AUA documented stone-free rates of 81.6% for open stone surgery, 80.8% for combined PNL and SWL, 73.3% for PNL, and only 50% for SWL monotherapy ([Segura et al, 1994](#); [Preminger et al, 2005](#)). The more invasive the procedure, the greater is the stone-free rate; however, morbidity was higher as well. Although SWL carried the lowest morbidity, a greater number of unplanned post-treatment interventions were necessary. The AUA concluded that for most patients, neither SWL monotherapy nor open stone surgery should be the first-line treatment of staghorn stones. As a guideline, PNL, followed by SWL or repeated PNL procedures as warranted, should be used for most patients with struvite staghorn calculi.

There are no strict guidelines that define which patient should undergo an open surgical procedure for stone removal. Some indications, such as a stone burden too large for PNL, clearly rely on the surgeon's judgment and experience and the availability of equipment. Also, those patients harboring calculi that may require multiple PNL or SWL treatments may be good candidates for an open procedure. Although a single open surgical procedure may seem to be the optimal procedure in the short term, the inevitable scar tissue that develops will compromise any future stone removal procedures. A small group of patients whose conditions are refractory to PNL, SWL, and ureteroscopy may require an open surgical procedure as a salvage technique.

Nephrectomy remains an option for patients with nonfunctioning kidneys or stone disease with a normal contralateral kidney. Partial nephrectomy is also an option for a stone in a localized area of irreversibly poor function. In addition, patients with an associated anatomic abnormality requiring open operative intervention, such as UPJ obstruction and infundibular stenosis, may be candi-

dates for an open surgical approach. Some patients requiring open surgery unrelated to their urologic problem also may benefit from a simultaneously performed open procedure.

Ureteral Calculi

Although ureterolithotomy has been a time-honored technique for many decades, it is seldom performed in the modern, endourologic era. A meta-analysis undertaken by [Segura and associates \(1997\)](#) for the AUA demonstrated median stone-free rates of 87% and 90% for stones in the distal ureter treated by open surgical removal and ureteroscopy, respectively. In the proximal ureter, the stone-free rate for ureterolithotomy was 97% compared with 83% and 72% for SWL and ureteroscopy, respectively. Although the results of open surgery in the proximal ureter in this historic analysis were somewhat better than those of minimally invasive techniques, the greater morbidity and longer hospitalization associated with open surgery favored a primary endourologic solution for ureteral stones. Further miniaturization of ureteroscopes, combined with the now widespread availability of the holmium:YAG laser, has increased the success rate for a ureteroscopic approach to proximal ureteral calculi. [Grasso and Bagley \(1998\)](#) reported a large series of patients undergoing ureteroscopy for proximal ureteral calculi, finding a 97% stone-free rate. Open surgery for patients with ureteral stones is now indicated only as a salvage procedure, when a planned abdominal operation coincides with a symptomatic ureteral stone episode, or when another ureteral abnormality requires open surgical repair.

Laparoscopic and Robotic Stone Removal

The surgical technique and outcomes of laparoscopic and robotic stone surgery are discussed in subsequent chapters; the focus of the following section is a brief overview of the role of laparoscopic and robotic procedures in the modern era of stone surgery. The advent of laparoscopic and subsequently robotic renal and ureteral stone removal procedures has provided the urologist with another means to circumvent open stone surgery. Every type of "lithotomy" procedure by use of a laparoscopic or robotic approach has been reported ([Raboy et al, 1992](#); [Winfield et al, 1993](#); [Ruckle and Segura, 1994](#); [Van Cangh et al, 1995](#); [Harmon et al, 1996](#); [Goel and Hemal, 2001](#); [Deger et al, 2004](#); [King et al, 2013](#)). However, because of higher morbidity and longer hospitalization a laparoscopic or robotic approach to stone removal should be considered only if the results with SWL or endoscopic approaches are expected to be poor ([Preminger et al, 2005, 2007](#)).

In certain cases a laparoscopic or robotic approach may be considered a reasonable therapy. Situations that may benefit from a laparoscopic approach include pyeloplasty with pyelolithotomy; patients harboring stones in poorly functioning polar areas or with nonfunctioning kidneys; pelvic kidneys containing a large stone

volume, in which laparoscopic techniques can be used to reflect overlying bowel, allowing pyelolithotomy or percutaneous stone removal; and ureterolithotomy for the extremely rare endoscopic failure or large/multiple impacted ureteral calculi. Case series of robotic and laparoscopic anastrophic nephrolithotomy have been published (Zhou et al, 2001; Simforoosh et al, 2008; Giedelman et al, 2012; King et al, 2013). Stone-free results range from 28% to 91%, and warm ischemia is used. It must be recognized that such procedures can be technically demanding and require a skilled laparoscopic/robotic surgeon to be performed with minimal morbidity. In present practice, the use of laparoscopy and robotics in the treatment of renal calculi continues to be limited; Desai and Assimos (2008) reported that only 1% of patients undergo such an approach, with the most common indication being renal stones with a concomitant UPJ obstruction.

KEY POINTS: STONE REMOVAL—SURGICAL TECHNIQUES AND TECHNOLOGY

- The holmium:YAG laser is one of the safest, most versatile, and most effective intracorporeal lithotripters and has become the standard lithotrite for the ureteroscopic approach.
- For patients undergoing PNL, a rigid lithotripter, such as a combination ultrasonic/ballistic device, will provide for more efficient stone removal than will a flexible lithotripter.
- For PNL, the preferred point of entry into the collecting system is along the axis of the calyx, through the papilla.
- The role of open, laparoscopic, and robotic stone surgery remains limited to unique cases in which the stone burden or patient anatomy precludes successful endoscopic treatment.

URINARY CALCULI DURING PREGNANCY

Incidence

Urolithiasis is an infrequent complication of pregnancy. However, pain from renal colic is the most common nonobstetric reason for hospital admission during pregnancy (Rodriguez and Klein, 1988). Furthermore, the occurrence of urinary calculi during pregnancy presents danger not only to the mother but also to the fetus because renal colic, infection, and obstruction are all associated with premature labor (Maikranz et al, 1987; Hendricks et al, 1991). The reported incidence of symptomatic urinary calculi during pregnancy ranges from 1 in 200 to 1 in 2500 pregnancies; the wide variation in reported incidence may be due to the small numbers of patients in these studies (Gorton and Whitfield, 1997). However, the incidence of symptomatic urinary calculi has been calculated to be the same for pregnant women as for nonpregnant women of childbearing age (Coe et al, 1978; Hendricks et al, 1991). Multiparous women have been reported to be affected more often than primiparous women, in some cases by a ratio of approximately 3:1 (Horowitz and Schmidt, 1985; Rodriguez and Klein, 1988). However, when it is adjusted for age, the incidence for multiparous women is no greater than that for primiparous women (Swanson et al, 1995). Calculi present with equal frequency on the left and right sides, although ureteral calculi occur almost twice as frequently as renal calculi (Stothers and Lee, 1992; Parulkar et al, 1998). The majority of patients with symptomatic calculi present during the second or third trimesters but rarely during the first trimester (Denstedt and Razvi, 1992; Stothers and Lee, 1992; Swanson et al, 1995).

Although symptomatic urolithiasis may be an uncommon complication of pregnancy, renal colic during pregnancy is a serious concern because such an event may be dangerous to both the mother and the fetus. Swartz and associates (2007) analyzed the hospital discharge data from 1987 through 2003 in the state of Washington and found that women admitted for nephrolithiasis had a significantly greater (adjusted odds ratio 1.8) risk for preterm

delivery than women without stones. Lewis and associates (2003) also reviewed a large database comprising over 21,000 deliveries and found that of the 86 patients diagnosed with a stone during pregnancy there was an increased risk for preterm premature rupture of membranes (2.9% in patients without stones vs. 7% in those with stones). Preterm premature rupture of membranes, as the authors note, carries with it an increased risk for morbidity and mortality to the newborn.

Etiology

Pregnancy induces significant physiologic alterations, some of which affect the urinary system. The most remarkable anatomic change is the dilation of the renal calyces, pelvis, and ureters, which is usually evident by the first 6 to 10 weeks of gestation. Pregnancy-induced hydronephrosis is the most common cause of dilation of the urinary tract in pregnancy and may cause flank discomfort or even mimic renal colic. Upper tract dilation is seen in up to 90% of pregnant women by the third trimester and may persist for as long as 12 weeks postpartum (Boridy et al, 1996). The right ureter tends to be more dilated than the left, and the dilation rarely is observed distal to the pelvic brim (Schulman and Herlinger, 1975). Rarely, spontaneous rupture of the kidney may occur; if it does, it more commonly happens on the right side (MacNeily et al, 1991; Loughlin, 1994). Both humoral and mechanical factors have been implicated in the cause of hydronephrosis in pregnant women. Circulating progesterone, a humoral factor that is increased in pregnancy, causes relaxation of ureteral smooth muscle, reducing ureteral peristalsis. Paller and Ferris (1996) reported that dilation of the urinary collecting system can be reproduced in an animal model by the administration of estrogen and progesterone. However, recent evidence suggests that mechanical factors, in particular the gravid uterus directly compressing the ureters, are likely to be primary in the pathogenesis of this condition; women with an altered upper urinary tract in whom the ureter does not cross the pelvic brim, such as those with ileal conduit or renal ectopia, do not experience hydronephrosis during pregnancy (Rasmussen and Nielsen, 1988; Dafnis and Sabatini, 1992; Swanson et al, 1995). Although the exact cause of hydronephrosis of pregnancy is not yet well defined, most would agree that both mechanical and humoral factors play a role in the pathogenesis of this condition.

Other important physiologic changes in pregnancy include an increase in renal plasma flow, which induces a 30% to 50% increase in glomerular filtration rate. As a result of this physiologic alteration the normal ranges of serum creatinine and blood urea nitrogen are approximately 25% lower for the pregnant patient. Importantly, then, a serum creatinine value that is in the normal range for the nonpregnant population may actually represent a decrease in renal function for the pregnant patient (Paller and Ferris, 1996). The increase in renal plasma flow and glomerular filtration rate also increases the filtered loads of sodium, calcium, and uric acid, causing a state of hypercalciuria and hyperuricosuria (Boyle et al, 1966; Howarth et al, 1977; Gertner et al, 1986). Hypercalciuria is further exacerbated by the suppression of parathyroid hormone and the increase in circulating 1,25-dihydroxycholecalciferol produced by the placenta, which increases intestinal absorption of calcium. Twenty-four-hour urine chemistries performed among pregnant women have demonstrated that urinary pH is elevated in the course of pregnancy, most dramatically during the second trimester (Resim et al, 2006). However, these potentially lithogenic physiologic changes are offset by an increase in the excretion of urinary inhibitors, such as citrate and magnesium, as well as an increase in urine output (Biyani and Joyce, 2002). It has been postulated that metabolic alterations in the urine may contribute to the accelerated encrustation of ureteral stents during pregnancy (Denstedt and Razvi, 1992; Loughlin, 1994). Ross and associates (2008) reported that stones that occur during pregnancy are most commonly calcium phosphate in composition, a finding that may be explained by the relatively elevated urinary pH and hypercalciuria that occur in the pregnant state.

Evaluation

Although renal colic is the most common nonobstetric cause of abdominal pain in hospitalized pregnant women, the diagnosis of urolithiasis in the pregnant patient can be challenging; many of the usual manifesting signs and symptoms may be masked by the patient's gravid status. As gestation progresses, the perception and localization of pain may be altered. [Stothers and Lee \(1992\)](#) reported that 28% of pregnant patients ultimately diagnosed with an obstructing stone were initially, and incorrectly, diagnosed with appendicitis, diverticulitis, or placental abruption. For most patients, however, **the most common presenting symptom is flank pain, usually accompanied by either macroscopic or microscopic hematuria** and, in some cases, UTI ([Stothers and Lee, 1992](#)). Hematuria can occasionally occur in the normal course of pregnancy; however, hematuria without discomfort is unusual in a patient with stone disease ([Swanson et al, 1995](#)). It is particularly important to obtain a urine specimen for culture from these patients because pyuria commonly may be seen in the urinalysis of a pregnant patient, which diminishes the sensitivity of this test in detecting UTI ([Hendricks et al, 1991](#); [Houshiar and Ercole, 1996](#); [Parulkar et al, 1998](#)). A diagnosis of urinary calculi should be considered in evaluation of a pregnant patient who suffers from persistent UTI or infection with a urea-splitting organism. Other symptoms that may indicate urolithiasis include irritative voiding symptoms, chills, nausea, and vomiting. However, these symptoms also may occur with other intra-abdominal conditions so the urologist must maintain a high index of suspicion when examining these patients.

An important factor in the radiographic evaluation of pregnant patients with stone disease is the risk for ionizing radiation exposure to the fetus. The principal effects of irradiation on the fetus include teratogenesis, carcinogenesis, and mutagenesis. However, the risk associated with radiation depends critically on the gestational age and the amount of radiation delivered ([Biyani and Joyce, 2002](#)). **During the first trimester, the period of early organogenesis and rapid cell division, the embryo is sensitive to the effects of radiation** ([Swartz and Reichling, 1978](#)). Although the fetus has diminished sensitivity to the teratogenic effects of radiation in the second and third trimesters, such exposure may increase the risk for development of childhood malignant neoplasia ([Harvey et al, 1985](#)).

Because the radiation dose below which no deleterious effects on the fetus may occur has not been defined with certainty, it may be presumed that exposure to any level of radiation will carry some degree of risk. For this reason **ultrasonography has become the standard initial study in evaluation of the pregnant patient thought to be experiencing renal colic**. Unfortunately, it can be difficult to adequately visualize the ureter with ultrasound examination as well as to distinguish dilation of the ureter that may be associated with a normal pregnancy from ureteral obstruction because of calculus. [Stothers and Lee \(1992\)](#) reported that renal ultrasonography for the detection of calculi had a sensitivity of 34% and a specificity of 86%. [Butler and associates \(2000\)](#) similarly reported that ultrasonography diagnosed 60% of 35 women who were later proved to have nephrolithiasis. Several techniques have been recommended to improve the diagnostic capability of this technology. Color Doppler imaging allows the sonographer to differentiate the iliac artery and vein from the dilated ureter. [MacNeily and associates \(1991\)](#) reported that the use of this technique can distinguish a dilated infrailiac ureter, which was strongly correlated with ureteral obstruction. Color Doppler imaging also can demonstrate jets of urine expelled from the ureter into the bladder. [Deyoe and associates \(1995\)](#) reported that if there are no ureteral jets on the suspected side of obstruction, ureteral obstruction can be diagnosed with a sensitivity of 100% and a specificity of 91%. However, [Burke and Washowich \(1998\)](#) reported that there is variation in ureteral jet symmetry in later pregnancy and recommended the use of this technique with caution. Renal vascular resistance increases in the presence of acute obstruction, and duplex ultrasonography allows the quantification of this alteration by calculating the kidney's resistive index ([Ulrich et al, 1995](#)). [Shokeir and Abdulma-](#)

[about \(1999\)](#) prospectively evaluated 117 nonpregnant patients with ultrasonography; they reported that resistive index measurements had 77% sensitivity and 83% specificity in diagnosis of ureteral calculi and that change in resistive index had 88% sensitivity and 98% specificity. [Horrigan and associates \(1996\)](#) reported that renal resistive index remains unchanged from the nonpregnant state throughout the course of pregnancy and also is unaffected by the physiologic hydronephrosis of pregnancy, which suggests that this imaging modality may be useful in detecting acute obstruction in this population. [Shokeir and associates \(2000\)](#) evaluated pregnant women in a manner similar to their initial study and found that resistive index had a sensitivity of 45% and a specificity of 91% in detecting an obstructing ureteral calculus; change in resistive index had a sensitivity of 95% and a specificity of 100%. If an obstructing calculus cannot be visualized by conventional renal sonography, **transvaginal ultrasonography can provide imaging of the distal ureter**. [White and associates \(2013\)](#) performed a multicenter longitudinal study of imaging modalities to detect stone in pregnant women ([White et al, 2013](#)). Importantly, they found that 14% of women undergoing intervention for a radiographically detected stone ultimately were found to harbor no such stone.

If the clinician determines that ultrasound evaluation is inadequate, other imaging studies may be considered. **If intravenous pyelography is required, a limited study is recommended**. [Stothers and Lee \(1992\)](#) were able to visualize calculi in 16 of 17 pregnant patients with a three-film study, obtaining scout, 30-second, and 20-minute films. Nuclear renography is a technique that can provide a functional assessment of pregnant patients with suspected ureteral obstruction while exposing them to a limited amount of radiation. However, the radioisotope is excreted in the urine, and the bladder reservoir can provide a significant source of radiation exposure to the fetus, necessitating high fluid intake and frequent voiding for these patients ([Biyani and Joyce, 2002](#)). This radiographic technique unfortunately does not provide good anatomic detail or visualization of calculi. Magnetic resonance imaging (MRI) does not rely on ionizing radiation or contrast medium, making it a potentially attractive tool to evaluate pregnant patients. Because MRI does not visualize calcium, stones are seen as filling defects overlying the high signal intensity of urine ([Fig. 54-24](#)). The visualization of smaller stones with this technique is difficult ([Hattery and King, 1995](#); [Roy et al, 1995](#)). [Spencer and associates \(2004\)](#)

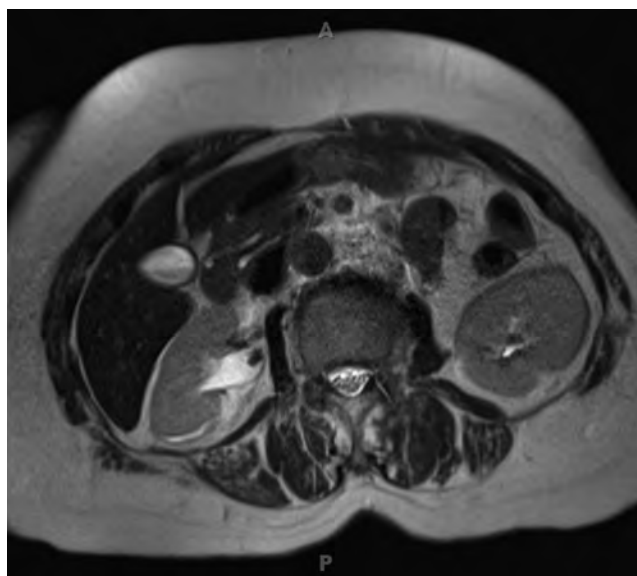


Figure 54-24. Magnetic resonance urogram from a pregnant woman with right renal colic, demonstrating a right ureteropelvic junction stone as a filling defect in the bright, T2-weighted urinary collecting system.

reported on the use of MRI to evaluate pregnant women with hydronephrosis and flank pain and found that this technique enabled the accurate distinguishing of physiologic hydronephrosis of pregnancy from hydronephrosis resulting from an obstructing ureteral calculus. Mullins and associates (2012) also described a half Fourier single-shot turbo spin-echo (HASTE) MRI protocol that increased the utility of MRI in the evaluation of pregnant women. White and associates (2007) reported on a technique of low-dose radiation exposure CT for the evaluation of pregnant women; however, at present the reliability of low-dose CT in the diagnosis of urinary calculi is unresolved. **Conventional CT should be avoided during pregnancy because the radiation dose is particularly high.**

Treatment

Of pregnant patients with symptomatic calculi, 50% to 80% will pass their stones spontaneously when treated conservatively with hydration and analgesia (Denstedt and Razvi, 1992; Stothers and Lee, 1992; Gorton and Whitfield, 1997; Parulkar et al, 1998). Intervention is required in approximately one third of patients, usually for pain uncontrolled by analgesia or signs of persistent obstruction and infection. When treatment is selected, it should be recognized that there is some controversy regarding the most appropriate method of intervention. Some have maintained that ureteral stents are the optimal treatment of such patients. Although ureteral stents do effectively drain an obstructed collecting system, they are by no means the perfect solution to this problem. The changes in urinary chemistry that occur during pregnancy, in particular the hypercalciuria and hyperuricosuria, have been implicated in the accelerated encrustation of ureteral stents that is encountered in this population. As a consequence of this phenomenon it has been recommended that ureteral stents placed in pregnant women be exchanged every 4 to 6 weeks. Ostensibly, then, for a woman in an early gestational stage, multiple stent changes will be required over the course of the pregnancy. An indwelling stent places these women at an increased risk for bacteriuria, UTI, and stent migration, all of which are serious morbidities that may have an adverse effect on the pregnancy. Ureteral stents themselves are associated with pain, which can have a negative impact on a patient's quality of life.

Percutaneous nephrostomy drains are an alternative treatment option for pregnant women with obstructing renal calculi. Just as with ureteral stents, nephrostomy tubes will effectively drain an obstructed collecting system. However, many of the same limitations that apply to ureteral stents also apply to nephrostomy drains. Khoo and associates (2004) reported that of 29 pregnant women managed with nephrostomy drainage, over half required tube exchanges, replacements, or flushings that were required because of either dislodgement or obstruction. Kavoussi and associates (1992) also reported that the majority of pregnant patients managed with nephrostomy drainage will require exchange of the tube because of occlusion from debris. One third of the patients in the series reported by Kavoussi and associates ultimately required nephrostomy removal as a result of recurrent drain obstruction, fever, or pain.

Both ureteral stent placement and nephrostomy drain placement are temporizing procedures that do not remove the obstructing symptomatic calculus. Therefore both of these interventions imply that in the postpartum period the mother will require a definitive procedure to remove the calculus. It may be hypothesized that one of the advantages of both ureteral stent and nephrostomy drain placement is that neither of these procedures requires a general anesthetic. However, many of the reports of ureteroscopy in pregnancy have described local anesthesia, regional anesthesia, or sedoanalgesia, all approaches that obviate the need for general anesthesia. It is likely that recent improvements in surgical technology may be responsible for the increased usage of ureteroscopy in the treatment of pregnant women. In recent years there have been great advances in both semirigid and flexible ureteroscopes. As recently as a decade ago, standard ureteroscope diameter ranged up to 11 Fr, in contrast to modern endoscopes that typically have a diameter of 6 to 8 Fr. Consequently, accessing all aspects of the renal collecting system in

a safe and expedient manner is now a straightforward endeavor that generally does not require ureteral dilation or other extraordinary maneuvers. The widespread use of intracorporeal lithotrites such as the holmium laser permits the safe and atraumatic fragmentation of calculi at any location. Improvements in flexible grasping devices have enhanced the efficiency of stone extraction.

Overall, complications in pregnant women undergoing ureteroscopy are uncommon. Semins and associates (2009) performed a meta-analysis of all reports of ureteroscopy of pregnant women to define the rate of complications in this population. They then compared the complication rate to the AUA/EAU Ureteral Stones Guidelines and found that there were no differences in the complication rates among pregnant and nonpregnant women undergoing ureteroscopy. Johnson and associates (2012) confirmed these findings as they reported a multicenter trial that examined ureteroscopy in pregnant women; a complication rate of 4% was found.

Other treatment modalities that are effective in the nonpregnant patient are not appropriate for this population. Although there have been reports of the inadvertent treatment of pregnant patients with SWL, with no adverse sequelae to the fetus, pregnancy remains a contraindication to this treatment modality (Chaussey and Fuchs, 1989; Frankenschmidt and Sommerkamp, 1998). PNL should be deferred until after birth because this procedure often requires prolonged anesthesia and radiation exposure.

KEY POINTS: URINARY CALCULI DURING PREGNANCY

- Ultrasonography is the standard initial imaging study in evaluation of a pregnant patient.
- Improvements in ureteroscopy technology now permit ureteroscopic access to and treatment of stones at any location in the collecting system of the pregnant patient.
- It is important to minimize ionizing radiation exposure to the pregnant patient during ureteroscopy by use of a below-table x-ray source and to shield the fetus with a lead apron placed below the patient.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Bladder Calculi

Prostatic Calculi

Urethral Calculi

Preputial Calculi

Lower urinary tract lithiasis is among the oldest of known human maladies, with an often dubious and barbaric legacy spanning the full course of recorded human history. Notable sufferers of lower urinary tract lithiasis include Isaac Newton, Benjamin Franklin, Francis Bacon, John Marshall, Peter the Great, Louis XIV, George IV, Boerhaave, Scarpa, and Napoleon Bonaparte and his descendants (Ellis, 1969; Khai-Linh and Segura, 2006).

Shattock (1905) described what might be the earliest known case of lower urinary tract stone disease, when excavation of gravesites in Egypt showed a 6.5-cm bladder calculus within the pelvis of the body of a 16-year-old boy, dating back to approximately 4800 BCE. Given that the methods of burial diverged from Egyptian tradition, little else about the background of the remains could be surmised.

Although little is known about the understanding and treatment of urinary lithiasis in ancient civilizations, it is apparent that the affliction was so commonplace by the 5th century BCE that it warranted specific mention in the works of the prolific Greek physician Hippocrates (Pardalidis et al, 2007; Herr, 2008). Perhaps the most famous instance is his proclamation within the oath bearing his name, stating “I will not cut for stone, even for patients in whom the disease is manifest; I will leave this operation to be performed by practitioners, specialists in this art” (Adams, 1938). Whether this was an early acknowledgment of the emerging field of urology or a caution for physicians to exclude themselves from the lowly butchery perpetrated by early lithotomists remains a matter of debate (Herr, 2008).

Vague descriptions of urinary stone extraction can be found in ancient texts of the Roman, Greek, Persian, and Hindu civilizations; however, the term *lithotomy* was not coined until 276 BCE by the Greek Ammonius, and the procedure was not described in detail until the writings of the Roman Cornelius Celsus nearly 300 years later in CE 20 (Pardalidis et al, 2007; Herr, 2008).

Accounts of the Celsian method of cystolithotomy conjure up terrifying images of harrowing, regularly fatal interventions in which the patient, generally a child no older than 14, would be bound or held fast to a table with his legs severely jackknifed and abducted to expose the perineum. One or two fingers would be inserted into the rectum to locate the stone and manually draw it down toward the bladder neck. The perineum was then incised widely with a chisel-like razor, rending the flesh until the bladder was entered, and the stone was then extracted using a forceps or a hook. If the patient were lucky enough to survive the operation before exsanguinating, the surgeon would leave this wound open, applying a dressing of oil-soaked wool or freshly killed and gutted fowl (Moore, 2005; Pardalidis et al, 2007; Trompoukis et al, 2007; Herr, 2008). Recovery was often as agonizing as the initial procedure, when leakage of urine through the wound proved excruciating for the young patient (Trompoukis et al, 2007). Infection, incontinence, impotence, and fistula formation were all-too-common

morbidities of the procedure, and nearly half of all patients died soon after the operation (Moore, 2005; Herr, 2008).

The grotesque and morbid nature of the procedure, however, hardly served to dissuade many sufferers of bladder stones from submitting themselves to the procedure. Galen and other notable physicians of the day began performing lithotomy, thereby legitimizing the procedure to some degree. In addition, midwives underwent instruction and education in the technique to offer treatment to female patients. By the Middle Ages the practice of lithotomy was a booming business, performed mostly by roving lithotomists of varying skill and competence who would ply their trade for a fee, performing the procedure on as many patients as possible before being driven out of town as their patients expired en masse (Herr, 2008).

Although small refinements were made to the procedure through the ensuing centuries, the practice of lithotomy remained largely unchanged for nearly 1500 years (Herr, 2008). In Paris during the early 16th century, Jacques de Beaulieu, a poorly trained and uneducated monk known more famously today as the subject of the children’s song “Frere Jacques” than as a pioneering surgeon of his time, refined the techniques of Pierre Franco using a lateralized perineal approach that proved a slightly less morbid operation. Although many surgeons of the time dismissed Frere Jacques as a quack, he became a prolific practitioner of lithotomy, providing his services to more than 5000 patients throughout Europe (Kelly, 1909; Bail, 1932; Moore, 2005; Herr, 2008). de Beaulieu’s methods were later adopted by William Cheselden, a Briton, who perfected the techniques of his forebears, introducing new instrumentation and an informed anatomic approach that reduced the mortality of lithotomy to less than 10% (Gross and Gross, 1876; Moore, 2005; Herr, 2008).

Fortunately, modern advances in surgical technology and aseptic technique have transformed this once deadly affliction into an eminently manageable and rarely fatal disease process. In addition, changing diets and the advance of industrialization have served to reduce significantly the incidence of lower urinary tract calculi, especially in the Western world.

BLADDER CALCULI

Bladder stones are the most common manifestation of lower urinary tract lithiasis, currently accounting for 5% of all urinary stone disease and approximately 1.5% of urologic hospital admissions in industrialized Western nations (Smith and O’Flynn, 1975; Schwartz and Stoller, 2000; Papatsoris et al, 2006). Bladder calculi in nonendemic areas are typically found in adults and are almost always associated with other disease processes resulting in urinary stasis or the introduction of a foreign body (Schwartz and Stoller,

2000). In endemic regions, however, bladder calculi often arise in children in whom major anatomic abnormalities do not coexist; in these regions, dietary intake and socioeconomic factors primarily influence the formation of bladder calculi (Andersen, 1962; Asper, 1984).

Primary Bladder Calculi

Formerly common in Europe and the United States, primary bladder calculi of childhood have been practically eliminated by the spread of industrialization and the modernization of the Western diet since the early 1900s (Van Reen, 1980; Schwartz and Stoller, 2000). However, childhood bladder lithiasis remains common in endemic regions, throughout a stone belt reaching from northern Africa, through the Middle East and the Balkans, and into India, Japan, Thailand, and Indonesia; it is uncommon in the southern hemisphere (Valyasevi and Van Reen, 1968; Valyasevi and Dhanamitta, 1974; Thalut et al, 1976; Asper, 1984; Teotia and Teotia, 1990; Hesse and Siener, 1997; Kamoun et al, 1999; Rizvi et al, 2003; Ali and Rifat, 2005). It is important to note that the term *primary* in this context refers to the fact that these stones develop in the absence of any known functional, anatomic, or infectious factors and the term does not necessarily imply that stones have formed de novo in the bladder (Andersen, 1962).

Primary bladder calculi are most common in children younger than the age of 10, with a peak incidence at 2 to 4 years of age (Valyasevi and Van Reen, 1968; Thalut et al, 1976; Teotia and Teotia, 1990; Ali and Rifat, 2005). The disease is much more common in boys than in girls, with ratios ranging from 9:1 to as high as 33:1 in areas of India (Andersen, 1962; Thalut et al, 1976; Van Reen, 1980; Kamoun et al, 1999; Rizvi et al, 2003). Stones are usually solitary and after removal they rarely recur (Valyasevi and Van Reen, 1968; Van Reen, 1980; Teotia and Teotia, 1990). Ammonium acid urate, calcium oxalate, uric acid, and calcium phosphate are the most common components of primary bladder calculi (Valyasevi and Van Reen, 1968; Teotia and Teotia, 1990).

Predisposition to the formation of bladder calculi appears to arise from a number of nutritional and socioeconomic factors. Children in endemic regions often consume a predominantly cereal-based diet that is poor in animal protein and low in phosphate (Thalut et al, 1976; Van Reen, 1980; Teotia and Teotia, 1990). In some regions, infant diets consist only of predigested rice that is first chewed by the mother, as well as breast milk, both of which are critically low in protein and phosphate (Andersen, 1962; Valyasevi and Van Reen, 1968; Thalut et al, 1976). Low dietary intake of phosphate not only leads to hypophosphaturia but also to hyperammonuria, promoting the precipitation of both calcium oxalate and ammonium acid urate (Teotia and Teotia, 1990). In addition, in the poor villages of Thailand, tampala and bamboo shoots, both of which are rife with bioavailable oxalate, are a frequent staple for infants (Valyasevi and Dhanamitta, 1974), which when combined with low dietary intake of vitamins B₁, B₆, and magnesium can lead to hyperoxaluria and the formation of calcium oxalate stones. Vitamin A deficiency can also lead to urothelial degeneration, which may also promote stone formation (Teotia and Teotia, 1990).

In addition, substandard living conditions and poor sanitation can lead to a paucity of adequate drinking water and to an increased prevalence of diarrhea, which in turn can lead to dehydration and supersaturation of stone-forming compounds in the urine (Valyasevi and Van Reen, 1968; Thalut et al, 1976; Van Reen, 1980; Schwartz and Stoller, 2000).

Children suffering from primary bladder calculi rarely present acutely. There is often a prodrome consisting of the passage of sandy urine or the presence of dusty crystals in dried urine that heralds the precipitation of urinary solutes. Children often complain of vague abdominal discomfort, dysuria, frequency, and hematuria. Pulling of the penis is considered by some to be pathognomonic, because it indicates the child is suffering from stranguria; frank urinary retention, however, is rare. In some cases, rectal prolapse and conjunctival hemorrhages may develop as the result of intense

straining to void (Thalut et al, 1976; Teotia and Teotia, 1990; Ali and Rifat, 2005).

Prevention consists mostly of dietary modification. In Thailand, phosphate supplementation was found to reduce oxalate crystalluria significantly, even without concomitant reduction in oxalate intake (Valyasevi and Dhanamitta, 1974). However, other authors suggest a transition to a mixed-cereal diet with milk supplementation as the most practicable solution for bladder stone prevention (Teotia and Teotia, 1990).

KEY POINTS: PRIMARY BLADDER CALCULI

- Primary bladder calculi are more common in children exposed to low-protein, low-phosphate diets.
- Primary bladder calculi rarely recur after treatment.

Secondary Bladder Calculi

Bladder calculi of the type commonly encountered throughout the Western world are typically found in men older than age 60 and are usually in concert with lower urinary tract obstruction, which prevents complete bladder emptying (Doudenias et al, 1991; Takasaki et al, 1995; Hesse and Siener, 1997; Yasui et al, 2008). Since the mid-1970s, the overall incidence of bladder calculi appears to have stabilized or decreased among males and increased slightly for females; these trends are likely caused by the increase in the size of the elderly population as life expectancies lengthen, as well as by an overall increase in the number of female genitourinary procedures performed annually (Schwartz and Stoller, 2000; Terai et al, 2008; Yasui et al, 2008).

Bladder calculi may arise de novo within the bladder or may result from the maturation of stone nidi that migrate from the upper tracts and subsequently fail to be voided spontaneously. The latter appears to be far less common than initially postulated, because only 3% to 17% of patients will report a history of renal colic to suggest the passage of a calculus from the upper tracts (Aird, 1957; Smith and O'Flynn, 1975; Doudenias et al, 1991). The frequent absence of calcium oxalate in the nucleus of most bladder stones further suggests against an upper tract origin (Doudenias et al, 1991; Vanwaeyenbergh et al, 1995). The pathogenesis and composition of bladder calculi depend largely on the inciting pathologic process and the presence or absence of infection.

Bladder Outlet Obstruction and Acquired Lower Urinary Tract Pathologic Process

Bladder outlet obstruction resulting in incomplete emptying and the retention of stone fragments is the most common predisposing factor for bladder stone formation in non-neurogenic bladders and is present in 45% to 79% of all patients diagnosed with vesical calculi (Smith and O'Flynn, 1975; Doudenias et al, 1991; Takasaki et al, 1995). In men, outlet obstruction is generally related to benign prostatic hyperplasia, whereas urethral kinking from a cystocele or pelvic organ prolapse is often the culprit in females (Smith and O'Flynn, 1975; Doudenias et al, 1991; Sarica et al, 1994; Nieder et al, 1998; Schwartz and Stoller, 2000; Papatsoris et al, 2006). Urethral stricture, bladder neck contracture, and bladder diverticula are also secondary causes that may interrupt normal voiding patterns (Smith and O'Flynn, 1975; Doudenias et al, 1991).

The composition of stones resulting from anatomic obstruction varies with geography and ethnicity. In Europe, struvite, calcium phosphate, and uric acid predominate, whereas in Japan uric acid calculi are uncommon and calcium stones are increasing in incidence, now representing 72% of all stones found in a recent series. Calcium oxalate comprises the majority of bladder stones found in the United States, although uric acid stones predominate among the American Jewish population (Smith and O'Flynn, 1975; Doudenias et al, 1991; Hesse and Siener, 1997; Papatsoris et al, 2006;

Yasui et al, 2008). Stones are usually solitary, although multiple stones may exist in 25% to 30% of patients (Sarica et al, 1994).

Intravesical Foreign Body

Foreign material within the bladder provides an ideal nidus for stone formation and is responsible for the majority of bladder calculi diagnosed in females (Smith and O'Flynn, 1975; Schwartz and Stoller, 2000; Papatsoris et al, 2006). Often a foreign body within the bladder will encrust initially with calcium oxalate as a result of the normal stasis that occurs with the storage of urine. Should infection supersede, rapid coalescence of the stone may occur as struvite is deposited on the nascent stone (Dalton et al, 1975; Khan and Wilkinson, 1990; Vanwaeyenbergh et al, 1995; Schwartz and Stoller, 2000).

The vast majority of intravesical foreign bodies result from iatrogenic interventions, although self-mutilation plays a role in a minority of patients (Dalton et al, 1975; Douenias et al, 1991; Schwartz and Stoller, 2000); complications resulting from urogynecologic interventions predominate. Inadvertent violation of the bladder with suture material during suspension or sling procedures is a common source of an intravesical foreign body. This error is often not detected intraoperatively, underscoring the importance of thorough cystoscopic inspection before the conclusion of the procedure (Zderic et al, 1988). Along with the rise in popularity of incontinence surgery involving synthetic mesh, such as tension-free vaginal tape procedures, an increase has been noted in calculi forming on portions of the mesh that have eroded into the bladder (Chamary, 1995; Koelbl et al, 2001; Irer et al, 2005; Mustafa and Wadie, 2007). In addition, erosion of wire suture used for cerclage has been reported (Ehrenpreis et al, 1986). Stone encrustation of migrated intrauterine devices, pessaries, and contraceptive diaphragms has also been reported (Staskin et al, 1985; Khan and Wilkinson, 1990; Mahazan, 1995; Chow et al, 1997; Maskey et al, 1997; Schwartz and Stoller, 2000; Demirci et al, 2003; Chae et al, 2012). In addition, unrecognized anorectal impalement, although an uncommon occurrence, has been reported to provide a foreign body nidus for bladder stone formation (Guha et al, 2012).

In men who have undergone radical retropubic prostatectomy, formation of stone on eroded silk sutures used to ligate the dorsal vein complex have been reported (Scheidler et al, 1990; Miller et al, 1992). Stones may also form on nondegradable surgical clips placed near the vesicourethral anastomosis that have migrated into the bladder; such stones have been reported with both metal and plastic clips, although the true incidence of this complication remains unclear (Banks et al, 2008; Kadekawa et al, 2009; Mora et al, 2010; Yi et al, 2010). In addition, necrotic tissue resulting from chemical ablation of the prostate for benign prostatic hyperplasia has been cited as a nidus for stone formation (Ikari et al, 2005), as has the presence of intraprostatic stents (Chiu et al, 1991; Squires and Gillatt, 1995). Migration of seeds following prostate brachytherapy is common and can be associated with bladder stone formation (Sugawara et al, 2009; Miyazawa et al, 2012; Leapman et al, 2014). Erosion of an inflatable penile prosthesis and artificial urinary sphincters resulting in stone encrustation has also been reported (Dupont and Hochman, 1988; Barroso et al, 2000; Bartolletti et al, 2000).

The development of bladder calculi is an infrequent complication of long-term urinary tract drainage. Encrustation of short-term ureteral stents is a common finding, although significant intravesical stone formation may occur in instances where the stent is left resident for an extended period (Giannakopoulos et al, 2001; Damiano et al, 2002; Hao et al, 2008; Vanderbrink et al, 2008; Waters et al, 2008). Long-term bladder drainage may also result in bladder lithiasis, with a reported incidence of 0.07% to 2.2% in patients with chronic indwelling catheters (Kohler-Ockmore and Feneley, 1996). In instances in which Foley balloons burst intravesically, retained fragments frequently lead to subsequent stone formation (Chute, 1962; Smith and O'Flynn, 1975). Even patients who perform clean intermittent catheterization may not be immune, because inadvertent introduction of hair into the bladder with the

passage of the catheter may provide a nidus for stone formation (Derry and Nuseibeh, 1997).

On rare occasions, intravesical calculi may also arise as a result of the migration and erosion of foreign bodies unrelated to genitourinary manipulation. These include orthopedic cement, surgical clips, ventriculoperitoneal shunts, and abandoned gallbladder stones resulting from spillage during cholecystectomy (Radford and Thomson, 1989; Chia and Ross, 1995; Maier and Treu, 1996; Eichel et al, 2002).

Neurogenic Bladder and Spinal Cord Injury

Neurogenic bladder resulting from spinal cord injury or myelomeningocele places patients at increased risk of bladder stone formation. For adults with spinal cord injury, the risk for bladder stone formation peaks at 3 months after the initial injury, and within 10 years 15% to 30% of patients will have formed at least one stone (Chen et al, 2001). Unfortunately, after a patient has formed one stone, the risk for subsequent stone formation quadruples (Ord et al, 2003). The level and severity of the spinal cord injury appears to be closely correlated with the risk of bladder stone formation, especially after the first year (Chen et al, 2001; Sugimura et al, 2008). This is possibly because of the inability of quadriplegics with complete cord lesions to perform intermittent catheterization themselves, relying instead on caretakers or a chronic indwelling catheter for bladder management (Sugimura et al, 2008).

Indeed the manner of bladder management in spinal cord injury appears to have a significant impact on the risk of stone formation. One large study of more than 450 patients noted that the use of clean intermittent catheterization was associated with a significant reduction in the risk of bladder stone formation, with an annual risk of 0.2%, compared with 4% in those patients managed by a chronic indwelling catheter (Ord et al, 2003). This finding has been corroborated by other reports (Mitsui et al, 2000; Chen et al, 2001). In addition, the use of clean intermittent catheterization is associated with a 40-fold decrease in the risk for hospital admissions as a result of bladder calculi (Ord et al, 2003). As such, clean intermittent catheterization is the recommended form of bladder management for all patients in whom it is feasible (Feifer and Corcos, 2008). However, for patients who must rely on chronic indwelling catheters, suprapubic cystostomy provides no benefit compared to urethral catheterization in terms of the development of bladder calculi, although patients often report greater satisfaction with the former (Ord et al, 2003; Sugimura et al, 2008).

The incidence of bladder calculi in children with neurogenic bladder is far lower than in adults, developing in only 5% to 8% of nonaugmented children performing clean intermittent catheterization. The incidence of bladder stones is slightly higher, however, in children who catheterize through a Mitrofanoff conduit than in those who catheterize per urethra (Barroso et al, 2000).

Bladder Calculi in Transplant Patients

Bladder calculi are uncommon complications of solid organ transplantation, occurring primarily in pancreatic allografts drained via the bladder. In all reported instances, nonabsorbable suture material or surgical clips have been found to serve as the nidus for stone formation (Hakim et al, 1997; Del Pizzo et al, 1998; Hahnfeld et al, 1998; Rhee et al, 1999; Schwartz and Stoller, 2000). Stone formation may be potentiated by low serum pH because of bicarbonate leak, as well by as urinary stasis and incomplete bladder emptying resulting from diabetic uropathy. When combined with an increased coincidence of bacteriuria caused by colonization of included duodenal segments and the effects of immunosuppression, the ideal milieu for calculus formation can arise (Rhee et al, 1999). The reported incidence of bladder calculi in pancreatic allograft recipients ranges from 0.5% to 10% (Hakim et al, 1997; Del Pizzo et al, 1998; Hahnfeld et al, 1998).

Bladder calculi may also occur after renal transplantation without simultaneous pancreatic transplant, with incidences ranging from 0% to 5% in the literature. In most instances, suture material serves

as the nidus for stone formation; however, although two studies identified the development of calculus material on absorbable polyglactin sutures, another large series showed that calculus formation only occurred in cases where nonabsorbable suture material had been used for the ureterovesical anastomosis (Leunissen et al, 1987; Klein and Goldman, 1997; Rhee et al, 1999; Lipke et al, 2004).

KEY POINTS: SECONDARY BLADDER CALCULI

- Secondary bladder calculi are generally associated with bladder outlet obstruction.
- Patients with spinal cord injury are at increased risk of bladder stone formation.
- Intermittent catheterization decreases the risk of bladder stone formation in comparison to an indwelling catheter.

Augmented Bladders and Urinary Diversion

Bladder and pouch stones are known complications of augmentation cystoplasty and urinary diversion. They arise from a complex interplay of functional, anatomic, metabolic, and infectious factors.

Bladder Augmentation

The reported incidence of bladder calculus after augmentation cystoplasty ranges from 10% to as high as 52.5% (Edin-Liljegren et al, 1996; Kaefer et al, 1998; Kronner et al, 1998; Bertschy et al, 2000; Mathoera et al, 2000; Madersbacher et al, 2003). Unlike traditional adult urolithiasis, females are more commonly affected than males, likely owing to the high incidence of cloacal abnormality requiring additional procedures beyond augmentation (Mathoera et al, 2000). Mean time to the formation of first stone ranges from 24.5 to 68 months, and after the first incidence the risk of recurrence is 19% to 44% (Blyth et al, 1992; Palmer et al, 1993; Kronner et al, 1998; Mathoera et al, 2000; Woodhouse and Lennon, 2001; DeFoor et al, 2004; Hensle et al, 2004).

Because bacteriuria and urinary tract infection are commonplace after augmentation cystoplasty, it is not surprising that the vast majority of associated calculi contain a significant struvite component (Blyth et al, 1992; Palmer et al, 1993; Kaefer et al, 1998; Hensle et al, 2004; Robertson and Woodhouse, 2006). Interestingly, however, struvite is not the predominant component in most infection-related stones found in augmented bladders; rather, one study showed a predominance of calcium phosphate in these stones, which is likely because of the lower pH required for precipitation of calcium phosphate as compared with struvite. In addition, up to 14% of patients were found to have noninfectious stones, consisting of calcium phosphate and calcium oxalate with no struvite component (Allison et al, 1985; Robertson and Woodhouse, 2006). Uric acid calculi are rare in augmented bladders (Blyth et al, 1992; Palmer et al, 1993; Hensle et al, 2004; Robertson and Woodhouse, 2006). The treatment of recurrent urinary tract infections with antibiotics might have the deleterious effect of eradicating *Oxalobacter formigenes* within the gut, leading to an increase in intestinal oxalate absorption and hyperoxaluria (Robertson and Woodhouse, 2006).

However, infection is just one aspect of the milieu that can lead to stone formation in augmented patients. As in nonaugmented bladders, urinary stasis and incomplete bladder emptying serve to potentiate bladder stone formation. Factors that might contribute to stasis include bladder neck reconstruction, artificial urinary sphincter placement, and urethral sling procedures, all of which are designed to provide hypercontinence (Kronner et al, 1998). In addition, catheterization through nondependent access, such as through Mitrofanoff channels, is associated with a higher risk of stone formation (Kaefer et al, 1998; Kronner et al, 1998; Barroso et al, 2000). Dehydration, hypocitraturia, hypercalciuria, as well as high urinary pH in intestinal augments may also contribute to stone formation (Woodhouse and Robertson, 2004).

The role of intestinal mucus in stone formation remains controversial. Bladder calculi are found almost exclusively in patients who have undergone augmentation cystoplasty with ileum or colon and are rarely encountered after augmentation using stomach or ureter or after autoaugmentation (Kaefer et al, 1998; Kronner et al, 1998; Bertschy et al, 2000; Mathoera et al, 2000; DeFoor et al, 2004; Woodhouse and Robertson, 2004). Although some cite the production of enteric mucus as a predisposing factor in bladder stone formation, both as a nidus for stone formation and as a promoter of bacterial biofilm formation (Bruce et al, 1984; Blyth et al, 1992; Khoury et al, 1997), others have challenged that notion. Three studies have evaluated the role of regular bladder irrigation to promote mucus washout; two found a significant reduction in the incidence of bladder calculi, suggesting that **mucus production has little effect on stone formation** (Brough et al, 1998; Mathoera et al, 2000). Another study, however, showed that the incidence of recurrent urinary tract infection could be reduced through a regular irrigation regimen, with a reduction of the incidence of bladder stones to less than 10% in augmented children (van den Heijkant et al, 2011). In addition, it has been suggested that the low urinary pH associated with gastric segments inhibits bacterial growth and the precipitation of struvite, thus explaining their decreased propensity for stone formation (Kaefer et al, 1998; Kronner et al, 1998). Indeed some of the few accounts of vesical stone formation after gastrocystoplasty have resulted in the administration of histamine blockade for patients, which raises the urinary pH (Kaefer et al, 1998).

Despite the apparent advantages of gastrocystoplasty as related to bladder stone formation, the use of the stomach includes significant comorbidity, such as hypokalemic hypochloremic alkalosis and hematuria-dysuria syndrome, and this comorbidity recommends against its routine use (Rink et al, 1995; Kronner et al, 1998).

Urinary Diversion

Similar to augmentation cystoplasty, urinary diversion using intestinal segments is associated with the formation of conduit and reservoir calculi, with incidences largely dependent on the type of diversion created. Calculi in incontinent diversions, such as ileal and colon conduits, are relatively uncommon. Despite early reports of a high rate of stone formation in ileal conduits created using stapler devices in several small series, the incidence in large modern experiences is low, ranging from 0% to 7.3% (Brenner and Johnson, 1985; Turk et al, 1999). Urinary stasis from stomal stenosis is believed to be a major predisposing risk factor in these cases, and, despite early concerns, encrustation of stone material on staple lines is not always the rule (Dunn et al, 1979; Brenner and Johnson, 1985; Madersbacher et al, 2003; L'Esperance et al, 2004).

Likewise the incidence of stone formation in both orthotopic neobladder and Indiana pouch diversion is low, ranging from 2.9% to 12.9% in modern series (Terai et al, 1996; Turk et al, 1999; Abol-Enin and Ghoneim, 2001; Deliveliotis et al, 2001; Beiko and Razvi, 2002). However, **patients who undergo continent diversion with a Kock pouch reservoir often do not fare as well, with incidences of pouch stone formation of up to 50%** (Ginsberg et al, 1991; Arai et al, 1993; Terai et al, 1996; Woodhouse and Lennon, 2001). Major contributing factors in the formation of Kock pouch calculi include exposed staple lines used to create the nipple valve, as well as the use of a nonabsorbable mesh collar. Elimination of the collar and the use of absorbable staples is associated with a significant reduction in the incidence of pouch calculi to as low as 10% (Ginsberg et al, 1991; Arai et al, 1993; Arif et al, 1999; Beiko and Razvi, 2002).

Struvite and calcium phosphate calculi predominate, indicating an infectious component in the development of most calculi in urinary diversions (Kaefer et al, 1998; Arif et al, 1999; Turk et al, 1999). In addition, patients with continent diversions were noted to have increased levels of urinary calcium, magnesium, and phosphate, as well as low levels of urinary citrate; metabolic acidosis might also occur. These metabolic derangements may further potentiate stone formation (Terai et al, 1995, 1996).

Presentation and Management

The most common presenting symptom of bladder calculi is macroscopic hematuria, which generally is terminal (Smith and O'Flynn, 1975; Papatsoris et al, 2006). Intermittency, frequency, urgency, dysuria, decreased force of the urinary stream, incontinence, and lower abdominal pain aggravated by brisk movement might also be present (Ellis et al, 1969; Smith and O'Flynn, 1975; Douenias et al, 1991; Miller et al, 1992; Sarica et al, 1994; Irer et al, 2005; Papatsoris et al, 2006). Larger stones tend to cause fewer symptoms, likely because of restricted movement within the bladder (Douenias et al, 1991). Bladder stones are rarely asymptomatic at the time of discovery (Smith and O'Flynn, 1975; Rhee et al, 1999).

The options for management of vesical calculi are varied. Any planned intervention should also aim to correct the underlying urinary tract pathologic process, when appropriate, to prevent stone recurrence.

Nonoperative Management

Chemical dissolution is rarely considered a primary form of management, because treatments are protracted and often do not address underlying functional or anatomic pathology. When administered properly, Renacidin is well tolerated and may be used to dissolve struvite and calcium phosphate calculi. This method involves the placement of a urinary catheter for continuous bladder irrigation of Renacidin solution. Alternatively, the solution can be administered intravesically 3 to 4 times daily and allowed to dwell for 30 to 45 minutes (Mulvaney, 1960; Mulvaney et al, 1960; Woodside and Crawford, 1980). Although effective for select patients, the use of Renacidin can be associated with catastrophic complications including death (Gonzalez et al, 2012). Great care must be taken to ensure that the patient remains free of any overt signs of systemic infection and that the catheter does not become obstructed. In addition, Renacidin is contraindicated in patients with renal insufficiency (Mulvaney et al, 1960; Wilson et al, 1986; Gonzalez et al, 2012). Uric acid calculi may be dissolved with oral administration of potassium citrate or intravesical administration of alkaline solutions (Asper, 1984; Rodman et al, 1984; Blyth et al, 1992; Drach, 1992; Menon and Resnick, 2002; Papatsoris et al, 2006). Irrigations with acetohydroxamic acid have proven effective in reducing the incidence of catheter encrustation in patients requiring chronic indwelling catheters (Burns and Gauthier, 1984).

Open and Percutaneous Cystolithotomy

Previously considered the gold standard for bladder stone treatment, the open approach has fallen into disfavor as newer, less invasive techniques have come to the fore. Open cystolithotomy, although successful, is associated with the need for prolonged catheterization, increased length of hospital stay, and poor cosmesis from the required incision (Bhatia and Biyani, 1994; Demirel et al, 2006). However, one group has reported on the successful implementation of drainless and catheterless open suprapubic cystolithotomy in children after meticulous two-layer closure of the cystotomy. After the procedure most patients were immediately ambulatory and most had no difficulty voiding. However, 7% of patients eventually required catheterization, including one patient who developed a leak and subsequent wound infection (Rattan et al, 2006).

Percutaneous techniques have been championed, especially in patients without serviceable urethral access, such as patients who have undergone previous bladder neck reconstruction or closure. This method generally involves the creation and dilation of a suprapubic tract after the bladder is distended. An Amplatz sheath is used in the vast majority of reported techniques, although concern regarding the inadvertent loss of access has compelled some to use a Hasson trocar instead (Ikari et al, 1993; Agrawal et al, 1999; Franzoni and Decter, 1999; Wollin et al, 1999; Segarra et al, 2002; Demirel et al, 2006; Aron et al, 2007; Hubscher and Costa, 2011).

A combination of ultrasonic and pneumatic energy is used to fragment the stone; small fragments may be suctioned whereas larger fragments are removed using stone forceps. In addition, an Ellik evacuator or similar device can be used to remove small fragments (Loeb et al, 2012). Placing the stones in an entrapment sac can reduce the risk of collateral damage, and this has been shown to reduce operative times (Tan et al, 2014). Suprapubic or transurethral catheter drainage is required for 1 to 5 days (Ikari et al, 1993; Franzoni and Decter, 1999; Wollin et al, 1999; Demirel et al, 2006; Aron et al, 2007).

Average operative times for percutaneous cystolithotomy range from 20 to 86 minutes (Wollin et al, 1999; Demirel et al, 2006; Aron et al, 2007), with successful eradication of stone in 89% to 100% of patients after a single procedure. Complications, including urine leak and persistent hematuria, are rare, occurring in approximately 1% of patients (Ikari et al, 1993; Franzoni and Decter, 1999; Wollin et al, 1999; Demirel et al, 2006).

Proponents of the percutaneous approach to cystolitholapaxy cite its safety and expedience, as well as the elimination of potential traumatic risk to the urethra from repeated instrument passage (Ikari et al, 1993; Wollin et al, 1999). For patients requiring surgical management for prostatic hyperplasia, transurethral resection of the prostate can be safely performed after percutaneous cystolithotomy (Aron et al, 2007).

Transurethral Cystolitholapaxy and Lithotripsy

The transurethral approach for bladder stone treatment is attractive because it allows the use of a natural orifice for access. A lithotrite may be used but this has fallen into disfavor owing to the high incidence of mucosal injury and bladder perforation as well as the inability to address large calculi and a high rate of stone recurrence (Barnes et al, 1963; Smith and O'Flynn, 1977; Nseyo et al, 1987; Bhatia and Biyani, 1994; Teichman et al, 1997; Schwartz and Stoller, 2000; Lipke et al, 2004; Singh and Kaur, 2011). Modern series report the use of the holmium laser, electrohydraulic lithotripter, and lithoclast technology, all with success in both adults and children (Bülow and Frohmüller, 1981; Teichman et al, 1997; Sathaye, 2003; Lipke et al, 2004; Okeke et al, 2004; Isen et al, 2008). However, in addition to the need for multiple probes, electrohydraulic energy is associated with a higher incidence of complications, including mucosal injury and hematuria (Teichman et al, 1997; Lipke et al, 2004). One earlier series reported a 1.6% incidence of bladder perforation with electrohydraulic lithotripsy, although this has not been reported in modern series (Bülow and Frohmüller, 1981).

Holmium laser lithotripsy has become the modality of choice, owing to its ability to treat large calculi while incurring a minimum of collateral damage. Most patients undergoing laser lithotripsy will be rendered stone free in one procedure with no major complications (Teichman et al, 1997; Lipke et al, 2004). Some favor the use of a side-firing laser, owing to the increased stability and maneuverability of the fiber as well as the shorter operative times (Teichman et al, 1997).

To prevent potential traumatic injury to the urethra from the repeated passage of instruments, one group advocates the use of a transurethral Amplatz sheath after gentle urethral dilation (Okeke et al, 2004). Should a sheath not be used, others advocate adequate urethral lubrication and preoperative meatotomy to reduce the incidence of postoperative stricture disease, although the long-term success of this strategy has not been reported (Sathaye, 2003). Concomitant transurethral resection of the prostate can be performed if necessary, and two surgeons may perform it concurrently (Zhao et al, 2013), although caution is advised owing to associated complication rates as high as 21% (Nseyo et al, 1987; Aron et al, 2007).

Shock Wave Lithotripsy

Extracorporeal shock wave lithotripsy has been successfully used for the treatment of bladder calculi. The patient is placed in a prone position to eliminate obfuscation by the pelvis and sacral spine on fluoroscopy. A Foley catheter is introduced to allow for filling and

drainage of the bladder, the latter of which provides for immobility of the stone during fragmentation, although this method is not used by all authors (Bhatia and Biyani, 1994). Cystoscopic evacuation of stone fragments is necessary for larger calculi (Bosco and Nieh, 1991; Bhatia and Biyani, 1994). Per session, 1000 to 4800 shocks are generally required to produce adequate fragmentation, and re-treatment is necessary in 10% to 25% of patients (Bosco and Nieh, 1991; Bhatia and Biyani, 1994; Millán-Rodríguez et al, 2005). Shock wave lithotripsy results in success in 93% to 100% of patients (Bosco and Nieh, 1991; Millán-Rodríguez et al, 2005).

Treatment of Stones in Augmented Bladders and Urinary Diversions

The treatment of calculi in augmented bladders and urinary diversion presents a unique challenge in that **intra-abdominal spillage of urine and irrigation can lead to peritonitis** (Palmer et al, 1993; Kronner et al, 1998; Khai-Linh and Segura, 2006). However, treatment principles remain largely unchanged from the treatment of calculi in intact bladders.

Calculi within conduit diversions are perhaps the most simple to manage, because the majority of calculi will pass spontaneously. For those calculi that do not readily pass, looposcopy with lithotripsy and stone extraction are easily performed (Shapiro et al, 1975; Middleton and Hendren, 1976; Brenner and Johnson, 1985; Ginsberg et al, 1991; L'Esperance et al, 2004). However, if stomal stenosis is diagnosed at the time of presentation, stoma revision is advised (L'Esperance et al, 2004).

Orthotopic diversions and augmented bladders may be safely treated through a transurethral approach (Kronner et al, 1998; DeFoor et al, 2004; L'Esperance et al, 2004). In patients who have undergone bladder neck reconstruction or anti-incontinence procedures, great care must be exercised to prevent disruption of the continence mechanism (Woodhouse and Robertson, 2004). The use of instrumentation up to 21 Fr with and without dilation in these instances has been reported, with no ill effects on continence (Palmer et al, 1993). **Endoscopic management through a Mitrofanoff catheterizable conduit is not advised**, because disruption of the continence mechanism can occur (DeFoor et al, 2004; L'Esperance et al, 2004). Visualization of stone fragments embedded in redundant folds of the augmented bladder may render complete eradication of stone through a transurethral approach difficult (Woodhouse and Robertson, 2004).

Success with percutaneous access to augmented bladders has been reported, although the risk of extravasation of irrigant material can occur if the bladder is not adherent to the abdominal wall. Inadvertent bowel injury and bladder perforation might occur, although the incidence is rare (Palmer et al, 1993; Docimo et al, 1998; Kaefer et al, 1998; Woodhouse and Lennon, 2001; Cain et al, 2002; Woodhouse and Robertson, 2004). In skilled hands, the **percutaneous approach can prove as efficacious as open cystolithotomy** (Docimo et al, 1998). Open cystolithotomy is often the preferred approach for large stone burdens or multiple calculi (Blyth et al, 1992; Palmer et al, 1993; Kaefer et al, 1998; Kronner et al, 1998; Woodhouse and Lennon, 2001; DeFoor et al, 2004; Woodhouse and Robertson, 2004).

The management of pouch calculi depends largely on the pouch type. **Trans-stomal endoscopic management of Indiana and Penn pouch stones is not recommended** owing to concerns regarding injury to the catheterizable limb or disruption of the continence mechanism (Patel and Bellman, 1995; L'Esperance et al, 2004; Lam et al, 2007). In such cases, percutaneous access is advocated (Arai et al, 1993; Hollensbe et al, 1993; Patel and Bellman, 1995; Beiko and Razvi, 2002; L'Esperance et al, 2004). However, the larger caliber and intussuscepted nipple of the Kock pouch allows for safe trans-stomal endoscopic access (Ginsberg et al, 1991; Cohen and Strem, 1994; Patel and Bellman, 1995; Woodhouse and Lennon, 2001). Extracorporeal shock wave lithotripsy has been attempted in a limited number of patients with good initial success (Boyd et al, 1988; Cohen and Strem, 1994).

One novel approach to the percutaneous management of pouch calculi consists of the introduction of a flexible cystoscope through the catheterizable stoma, followed by distention of the pouch. Percutaneous access is obtained under direct vision, and a laparoscopic entrapment sac is passed through the percutaneous tract. The stones are then loaded into the sac and the sac is then partially extruded through the access tract. An Amplatz sheath is introduced into the sac, and ultrasonic lithotripsy is performed to reduce the stones, allowing for extraction through the percutaneous site (Lam et al, 2007).

KEY POINTS: PRESENTATION AND MANAGEMENT

- Hematuria is the most common sign of bladder stones.
- Percutaneous cystolithotomy is highly successful in clearing bladder stones and might be less traumatic than transurethral approaches.

Bladder Calculi and Bladder Cancer

Bladder calculi may be associated with urothelial malignancy, certainly as a byproduct of malignancy in terms of encrustation of bladder tumor or necrotic areas of tissue after transurethral resection of bladder tumor (Smith and O'Flynn, 1975). In addition, some authors suggest that the presence of bladder stones may also promote malignant change through chronic irritation of the bladder mucosa, similar to the link previously noted between mucosal irritation and inflammation from long-term indwelling catheters and squamous cell bladder cancer (Groah et al, 2002; Papatsoris et al, 2006; Chung et al, 2013). However, of the few focused studies examining this relationship, in none were the researchers able to find a causal link between bladder stones and subsequent malignancy (La Vecchia et al, 1991; Jhamb et al, 2007).

PROSTATIC CALCULI

Prostatic calculi are overwhelmingly common, with 99% of asymptomatic adult men noted to have some degree of prostatic calcification at the time of autopsy, regardless of age (Søndergaard et al, 1987). Although small areas of microcalcification are generally noted during the second and third decades of life, a sharp increase in the size and overall calculus load occurs during the fifth decade of life, which is a trend that appears to continue with further aging (Klimas et al, 1985; Søndergaard et al, 1987; Bock et al, 1989; Geramoutsos et al, 2004). Prostate-specific antigen levels are unaffected by the presence of prostatic calculi (Lee et al, 2003).

Pathogenesis and Associated Anatomic Data

Prostatic calculi are believed to arise as a result of inspissation of prostatic secretions within the prostatic ducts. Subsequently, concentric layers of stone material, generally composed of calcium phosphate and calcium carbonate, are deposited on this inspissated core, resulting in gradual growth of the calculus (Sutor and Wooley, 1974; Torres et al, 1979; Kamai et al, 1999). These calculi typically remain asymptomatic throughout an individual's lifetime; however, rare cases of exceptionally large calculi causing urinary tract obstruction have been reported (Kamai et al, 1999; Bedir et al, 2005).

The majority of calculi, up to 93%, are found in the posterior and posterolateral zones of the prostate, along the course of large prostatic ducts (Young, 1934; Huggins and Bear, 1944; Fox, 1963; Hassler, 1968; Søndergaard et al, 1987). The second most common area of incidence appears to be centrally located within the anterior aspect of the prostate, found in approximately 23% of patients (Hassler, 1968; Søndergaard et al, 1987). Although scattered microcalcifications are noted within the central zone, the presence of large calculi abutting the urethra is rare, perhaps explaining the infrequency of associated obstructive urinary symptomatology

(Søndergaard et al, 1987; Kamai et al, 1999; Bedir et al, 2005). In the elderly, prostatic calculi are more commonly encountered in hyperplastic prostates with areas of nodularity; however, anatomic studies fail to show a correlation between areas of nodularity and areas of stone formation (Søndergaard et al, 1987). Prostatic calcification may occur as a rare complication of external-beam irradiation for prostate cancer (Jones et al, 1979).

Implications for Chronic Pelvic Pain Syndrome, Prostatitis, and Prostate Cancer

Given the high incidence of chronic pelvic pain in the male population (McNaughton Collins et al, 1998, 2002; Roberts et al, 1998; Benway and Moon, 2008), interest has been focused on evaluating the potential role of prostatic calculi in the natural history of chronic pelvic pain syndromes. It is estimated that 25% to 47% of men with chronic pelvic pain syndrome harbor significant areas of calcification within the prostate (Evans et al, 2007; Shokses et al, 2007), although the significance of these calculi remains unclear.

One study of males between the ages of 21 and 50 showed that patients with at least one symptom of prostatitis are 3.2 times more likely to harbor large, coarse prostatic calculi than asymptomatic age-matched cohorts, whereas diffuse areas of microcalcification do not appear to be correlated with prostatitis symptoms. Moreover, the authors noted that it is the size, and not the number of stones, that appears to correlate with the risk of pelvic pain syndromes (Geramoutsos et al, 2004).

Another study found that the presence of calculi does not correlate with the severity of prostatitis symptoms on validated questionnaires; however, the duration of reported symptoms is positively correlated with the presence of prostatic stones. Interestingly, patients with prostatic stones were less likely to demonstrate pelvic floor tenderness on examination than those patients whose imaging did not demonstrate significant prostatic calcification. In addition, patients with prostatic calculi were more likely to exhibit positive localized cultures for pathogens such as *Escherichia coli*, enterococci, *Klebsiella* species, and gram-positive pathogens, as well as higher white blood cell counts in expressed prostatic secretions (Shokses et al, 2007). However, other investigators have found no concrete association between prostatic inflammation and infection and the presence of calculi (Hassler, 1968; Søndergaard et al, 1987).

Although some reports have proposed an association between inflammation of the prostate and an increased risk of prostate cancer (Roberts et al, 2004; Sutcliffe and Platz, 2007, 2008), the lack of reliable association between prostatic calculi and inflammation casts doubt on the role of prostatic calculi in the pathogenesis of prostate cancer. Indeed a focused pathologic evaluation of patients with prostate cancer showed no association between areas of calcification and the location of adenocarcinoma (Muezzinoglu and Gurbuz, 2001).

Evaluation and Management

Because most prostatic calculi are asymptomatic, few patients will ever require specific evaluation for intraprostatic stone disease. However, imaging tests performed for other indications may show the presence of prostatic calcification. On plain film, prostatic calculi are noted in up to 14% of patients (Fox, 1963). Because computed tomography and magnetic resonance imaging are not advocated for the evaluation of patients with benign prostatic disease (Scheckowitz and Resnick, 1995), reports on the incidence of prostatic calculi with cross-sectional imaging have not been reliably documented. Transrectal ultrasonography is highly sensitive for the detection of large prostatic calculi, although it does not appear to resolve areas of diffuse calcification accurately, as evidenced by the more than twofold increase in the discovery of calcifications on pathologic sectioning (Søndergaard et al, 1987; Shokses et al, 2007).

For rare patients who experience significant morbidity from prostatic calculi, removal of the affected tissue through open

prostatolithotomy, transurethral resection, or fragmentation with holmium laser lithotripsy should prove curative (Kamai et al, 1999; Bedir et al, 2005; Shah et al, 2007; Goyal et al, 2013).

URETHRAL CALCULI

Urethral calculi are among the least common manifestations of lower urinary tract lithiasis, representing only 0.3% of all urinary stone disease in an endemic region (Aegukkatajit, 1999). Urethral calculi are exceedingly uncommon throughout industrialized Western societies but are more commonly encountered in underdeveloped nations, as well as in endemic regions throughout Asia and the Middle East (Amin, 1973; Koga et al, 1990; Seltzer et al, 1993; Aegukkatajit, 1999; Menon and Martin, 2002; Verit et al, 2006).

Urethral calculi present with a bimodal age distribution, with peak incidences in early childhood as well as in the fourth decade of life (Kamal et al, 2004; Verit et al, 2006). Increased urinary peak flow rates may exert a protective effect in the second and third decades of life by allowing for increased clearance of calculi that migrate into the urethra, which may in part account for the relative paucity of urethral stone disease noted in this demographic group (Jørgensen and Jensen, 1996; Kamal et al, 2004; Verit et al, 2006).

Pathogenesis and Composition

Urethral calculi may result from migration from the bladder or upper tracts or may arise de novo, generally in association with an anatomic abnormality such as a stricture or diverticulum or from condensation on a foreign body. They occur very rarely in females, owing to the comparatively shorter urethral length (Menon et al, 1998; Menon and Martin, 2002; Kamal et al, 2004; Verit et al, 2006; Rivilla et al, 2008).

Migratory Calculi

Migratory calculi account for a large proportion of urethral calculi in children and adults living in underdeveloped nations, where cereal-based diets predominate (Menon and Martin, 2002; Verit et al, 2006). A lower urinary tract pathologic process, such as benign prostatic hyperplasia, urethral stricture, or meatal stenosis, is often present and may serve as a predisposing factor that inhibits the ability to clear migratory calculi (Hegele et al, 2002; Kamal et al, 2004; Verit et al, 2006). Patients may also have a history of instrumentation or self-mutilation, which may contribute to urethral anomalies such as strictures (Subbarao et al, 1998).

Although the bladder was long believed to be the primary source of migratory urethral calculi (Shanmugam et al, 2000), recent evidence is challenging that supposition. Calcium oxalate is the predominant component in 86% to 100% of modern migratory urethral calculi, a component associated primarily with upper tract calculi and found rarely in native bladder calculi, where struvite and uric acid components predominate (Douenias et al, 1991; Menon et al, 1998; Kamal et al, 2004; Verit et al, 2006). Furthermore, one study showed that only 2% of patients with migratory urethral calculi had associated bladder stones, whereas 18% were found to have concurrent upper tract calculus disease (Kamal et al, 2004). In addition, in endemic areas where cereal-based diets have been abandoned in favor of more protein-rich foods, there has been a precipitous drop in the incidence of bladder calculi yet little decrease in that of urethral calculi (Aegukkatajit, 1999; Verit et al, 2006) or upper tract stone disease (Kamal et al, 2004).

Primary Urethral Calculi

Calculi that arise de novo in the urethra do so primarily through condensation of stone material on urethral foreign bodies or from stasis of urine in urethral diverticula. Struvite stones predominate, although calcium phosphate and uric acid calculi have also been reported (Singh and Neogi, 2006). Concomitant urinary

tract infection with *E. coli*, *Proteus*, or enterococci is often diagnosed at the time of presentation (Subbarao et al, 1998; Gokce et al, 2004; Gallo et al, 2007; Rivilla et al, 2008; Susco et al, 2008).

When incorporating hair-bearing grafts, urethroplasty and hypospadias repair can lead to urethral stone formation. Despite attempts at thorough epilation of the graft, hair-bearing follicles may persist, leading to symptomatic hairball formation in 3% to 8% of patients undergoing the procedure (Rogers et al, 1992; Singh and Hemal, 2001). Stone encrustation of the hairball may occur, leading to symptomatic urethral calculi that remain adherent to the graft (Singh and Hemal, 2001; Walker and Hamilton, 2001; Rodriguez-Villalba et al, 2003; Hayashi et al, 2007). In addition, exposed suture material from urethral reconstruction may serve as a nidus for stone formation (Frydenberg and Love, 1988).

For patients afflicted with maladies of the prostate, including benign prostatic hyperplasia and prostate cancer, minimally invasive alternatives to simple and radical prostatectomy are becoming more commonplace. However, despite the success of these techniques, unanticipated outcomes of these techniques may lead to urethral lithiasis. For patients who have undergone transurethral resection or ablation of the prostate for benign disease, devitalized and necrotic residual tissue, along with associated inflammation, may serve as a nidus for stone formation within the prostatic urethra (Gawande, 1986; Aus et al, 1997); stone composition in these rare cases often consists of brushite, as well as apatite and calcium oxalate (Magura et al, 1980; Gawande, 1986). In addition, proteinaceous secretions from the residual tissue may also serve as a nidus for stone accumulation; in such instances, apatite and calcium phosphate may comprise a larger proportion of stone material (Sutor and Wooley, 1974; Gawande, 1986).

Urethral calculi are also a rare long-term complication of patients undergoing brachytherapy and cryoablation of the prostate for carcinoma. Radioactive seeds left in situ after administration of brachytherapy may be prone to migration. Seeds that migrate into the urethra can serve as a nidus for calcification. Often these patients present with a primary complaint of intermittent gross hematuria instead of the obstructive symptoms more commonly encountered in other forms of urethral lithiasis (Steinmetz and Barrett, 2006). Urethral calculi are also reported as rare complications of prostate cryotherapy for carcinoma, again with necrotic residual tissue serving as a nidus for stone formation. Previous treatment with external-beam irradiation and inadequate urethral warming appear to contribute to an increased risk of postoperative urethral lithiasis (Aus et al, 1997).

Finally, urethral lithiasis may arise as a secondary complication from self-mutilation. For instance, one report describes encrustation of two safety pins that had been inserted by a mentally handicapped patient. The stone was discovered after an indolent course with only mild lower urinary tract symptomatology (Gokce et al, 2004).

Calculi within Urethral Diverticula

Calculi found in association with a urethral diverticulum may either represent a primary calculus resulting from stasis of urine or they may represent collection of migratory stone material (Dorairajan, 1963; Subbarao et al, 1998; Shanmugam et al, 2000; Walker and Hamilton, 2001). Stones will form in 1% to 10% of all urethral diverticula (Beatrice and Strebel, 2008); and with only one documented exception in the literature, a urethral diverticulum is present in nearly all reported cases of urethral calculi in females (Martínez-Maestre et al, 2000; Gallo et al, 2007; Beatrice and Strebel, 2008; Rivilla et al, 2008; Susco et al, 2008). Diverticula may arise from congenital malformation or from traumatic or iatrogenic injury to the urethra, including straddle injuries, vaginal delivery, periurethral gland abscess, pelvic fracture, endoscopic and open surgical misadventure, and long-term urethral catheterization (Mohan et al, 1980; Parker et al, 2007; Beatrice and Strebel, 2008; Lin et al, 2008). However, antecedent urethral injury is absent in 50% to 90% of reported cases of male urethral diverticula (Marya et al, 1977; Bazeed et al, 1981). Stone composition of these calculi

has not been reliably reported in the literature, although diverticular calculi are often associated with urinary tract infection (Subbarao et al, 1998; Gallo et al, 2007; Susco et al, 2008).

Presentation and Evaluation

The presentation of urethral calculus largely depends on pathogenesis and location of the stone within the urethra. Patients with migratory calculi often present with acute lower urinary tract symptoms from sudden impaction of the stone, including stranguria, urinary retention, gross hematuria, and dysuria, whereas those with de novo urethral calculi and those residing in diverticula often present with more insidious symptoms. Urinary tract infection is frequently diagnosed at the time of presentation (Hassan and Mahammed, 1993; Subbarao et al, 1998; Shanmugam et al, 2000; Kamal et al, 2004). In women, urethral calculi can be associated with chronic pelvic pain (Thomas and Crew, 2012).

In one large contemporary series, acute urinary retention was the presenting complaint in 78% of all patients with urethral calculi, whereas an additional 22% reported decrease of the urinary stream with dribbling of urine (Kamal et al, 2004). Older reports vary widely, however, in terms of presentation, with urinary retention rates as low as 0% and as high as 89% (Amin, 1973; Selli et al, 1984; Sharfi, 1991).

Migratory urethral calculi are typically solitary, although multiple calculi have been reported as urethral steinstrasse after shock wave lithotripsy and also in one child with a proximal urethral stricture resulting from self-mutilation (Biyani et al, 1993; Subbarao et al, 1998; Atikeler et al, 2005; Verit et al, 2006). A total of 32% to 88% reside in the posterior urethra, whereas 8% to 58% are located in the bulbous and penile urethra and 4% to 11% are found at the fossa navicularis (Shanmugam et al, 2000; Kamal et al, 2004).

Calculi within urethral diverticula may be either singular or multiple. Their natural history is often insidious, with minimal obstructive symptoms. Rather, a protracted course of increasing lower abdominal, pelvic, and perineal discomfort, as well as hematuria, dysuria, and dyspareunia, is often the norm (Subbarao et al, 1998; Koh et al, 1999; Martínez-Maestre et al, 2000; Gallo et al, 2007; Beatrice and Strebel, 2008; Susco et al, 2008). In females, urinary frequency and stress urinary continence also have been reported (Susco et al, 2008).

Patients do not often seek treatment immediately, with delays ranging from several months to up to 10 years (Koh et al, 1999; Gallo et al, 2007; Beatrice and Strebel, 2008; Rivilla et al, 2008; Susco et al, 2008). In instances of prolonged delays in diagnosis, urethrocuteaneous or urethrorectal fistulae may develop and may serve as the presenting complaint, especially in patients unable to report lower urinary tract discomfort, such as infants and patients with spinal cord injuries (Kaplan et al, 2006; Shamsa et al, 2008).

In most cases of penile and female urethral calculi, the stone is readily palpable on examination, often recognized as a hard mass along the expected course of the male urethra or as a firm mass in the anterior vaginal wall (Subbarao et al, 1998; Martínez-Maestre et al, 2000; Gokce et al, 2004; Kaplan et al, 2006; Gallo et al, 2007; Beatrice and Strebel, 2008; Susco et al, 2008). Prostatic calculi are less commonly palpable and often require imaging or cystoscopic visualization to confirm the diagnosis (Gawande, 1986; Aus et al, 1997; Steinmetz and Barrett, 2006).

Despite early reports indicating that 60% of urethral calculi were radiolucent, in the modern era 98% to 100% of urethral calculi are radiopaque and can be visualized on plain radiographs (Kamal et al, 2004; Verit et al, 2006). In addition, prostatic calculi are easily visualized on transrectal ultrasonography, as evidenced by significant shadowing around an area of increased signal density (Aus et al, 1997). However, given the potential for associated anatomic abnormality, many authors now advocate the use of urethrography or cross-sectional imaging to aid in diagnosis (Koh et al, 1999; Singh and Hemal, 2001; Hayashi et al, 2007; Rivilla et al, 2008; Susco et al, 2008).

Treatment

Treatment of urethral calculi is largely determined by their location within the urethra, as well as by the presence of an associated anatomic pathologic process such as a diverticulum. Stones located in the posterior urethra may be pushed back into the bladder for subsequent fragmentation with electrohydraulic or laser lithotripsy, a procedure that includes a success rate of 66% to 86% (Aus et al, 1997; Kamal et al, 2004; Verit et al, 2006). If subsequent fragmentation in the bladder is unsuccessful, open cystolithotomy may be required (Kamal et al, 2004). Shock wave lithotripsy after pushback into the bladder has been reported, although success rates were only reported at 60% (El-Sharif and Prasad, 1995).

For stones in the anterior urethra, retrograde relocation to the bladder is rarely feasible and should therefore not be attempted. However, extraction of the stone by “milking” may be successful, provided the stone is smooth; the risk of urethral injury related to this method of extraction is unknown, and thus caution should be exercised (Rodriguez Martinez et al, 2000; Kamal et al, 2004; Maheshwari and Shah, 2005). In addition, milking of the calculus is not advocated if the stone is large or irregular or if it has a spiked surface (Kamal et al, 2004). Some authors have noted success with spontaneous expulsion of small distal stones after the intraurethral administration of lidocaine jelly (El-Sharif and El-Hafi, 1991; Kamal et al, 2004). Success with simple cystoscopic extraction has also been reported (Atikeler et al, 2005).

For calculi not amenable to simple manipulation, urethrotomy with stone extraction has long been the norm and is still advocated when concurrent urethroplasty or urethrocuteaneous fistula repair is required (Singh and Hemal, 2001; Gokce et al, 2004). Reports suggest, however, that *in situ* lithotripsy of urethral calculi may be feasible, with reported success rates of up to 80% (Kamal et al, 2004). Electrohydraulic and Swiss lithoclast fragmentation has been reported, although concerns exist regarding the potential for collateral damage to the surrounding urethral tissue (El-Sharif and El-Hafi, 1991; Koh et al, 1999; Kamal et al, 2004; Verit et al, 2006; Hayashi et al, 2007). Holmium laser lithotripsy has therefore been advocated, citing excellent efficacy with minimal trauma to the surrounding urethral tissue (Walker and Hamilton, 2001; Maheshwari and Shah, 2005).

Stones within diverticula may be addressed with incision of the diverticulum and stone extraction, although success with *in situ* lithotripsy has been reported in a female patient (Subbarao et al, 1998; Singh and Neogi, 2006; Susco et al, 2008). Diverticulectomy and urethral repair may be performed concurrently or in a staged fashion (Subbarao et al, 1998; Martínez-Maestre et al, 2000; Karanth et al, 2003; Singh and Neogi, 2006).

PREPUTIAL CALCULI

Preputial calculi are relatively uncommon manifestations of lower tract calculus disease, with only a handful of reported cases in the literature during the past 2 centuries. Preputial calculi may occur at any age but are far more common among adults and the elderly (Sharma and Bapna, 1977).

Virtually all cases of preputial calculi are associated with severe phimosis in uncircumcised males. Additional risk factors include poor hygiene and low socioeconomic status (Ellis et al, 1986).

Preputial calculi are postulated to arise from one of three possible mechanisms, including inspissated smegma, stasis with precipitation of urinary salts, or a combination of the two, typically with a nidus of smegma acting as a condensation nucleus for the precipitation of urinary salts (Winsbury-White, 1954; Ellis et al,

1986; Mohapatra and Kumar, 1989). In addition, smegma itself may act as a direct local irritant leading to inflammation and scarring of the prepuce, which can cause further obstruction and urinary stasis (Parkash et al, 1973; Mohapatra and Kumar, 1989) and in some cases might create phimosis so severe that the prepuce may serve as an expansile urinary reservoir that collects large amounts of voided urine (Williamson, 1932). Other less common avenues of pathogenesis include the presence of a foreign body, such as suture material (Ellis et al, 1986), as well as trapping of voided bladder calculi in patients with severe phimosis (Williamson, 1932; Nagata et al, 1999).

In nearly all reported cases of preputial calculi, **progressive difficulty with voiding is the most common presenting complaint**. Other symptoms may include dysuria, gross hematuria, foul-smelling discharge, ballooning of the prepuce with voiding, and palpable calculi within the preputial sac (Williamson, 1932; Shahi and Ram, 1962; Sharma and Bapna, 1977; Ellis et al, 1986; Mohapatra and Kumar, 1989; Nagata et al, 1999). In rare cases, presentation may be delayed until urinary retention develops (Shahi and Ram, 1962).

Evaluation includes careful history, noting the duration and nature of symptoms, as well as history of calculus disease. On physical examination, tight phimosis is often encountered along with inflammation of the prepuce (Williamson, 1932; Shahi and Ram, 1962; Sharma and Bapna, 1977). The stones are often palpable on examination and may be freely mobile within the preputial sac (Williamson, 1932). Bilateral inguinal lymphadenopathy, if present, should raise the suspicion of concurrent penile carcinoma (Mohapatra and Kumar, 1989). Imaging with plain radiography may help to confirm the diagnosis of preputial calculi (Mohapatra and Kumar, 1989; Nagata et al, 1999).

Treatment involves removal of the calculi as well as the primary cause of urinary obstruction and stasis, generally by circumcision or a dorsal slit procedure (Williamson, 1932; Shahi and Ram, 1962; Sharma and Bapna, 1977; Mohapatra and Kumar, 1989; Nagata et al, 1999). All foreign objects, including suture material, should be removed in their entirety (Ellis et al, 1986). The excised preputial tissue should be sent for histopathologic evaluation to rule out carcinoma. In addition, if an underlying ulceration of the glans is noted, a biopsy of the lesion should also be submitted for pathologic evaluation (Sharma and Bapna, 1977; Mohapatra and Kumar, 1989).

Opening of the preputial sac generally shows multiple smooth, rounded calculi, which are brittle on examination (Williamson, 1932; Shahi and Ram, 1962). Stone composition varies in published reports but stones are most commonly composed of ammonium magnesium phosphate; however, other materials, including urate, calcium phosphate, and calcium oxalate, may be encountered as well (Sharma and Bapna, 1977; Ellis et al, 1986; Mohapatra and Kumar, 1989; Nagata et al, 1999). Culture may show the growth of various pathogens, including enterococci and *E. coli*, the latter of which may be carcinogenic (Hawksworth and Hill, 1971; Ellis et al, 1986; Mohapatra and Kumar, 1989). All symptoms typically completely resolve after circumcision and calculus removal.

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The complete reference list is available online at www.expertconsult.com.



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56

Benign Renal Tumors

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Renal Cysts

Papillary Adenoma of the Kidney

Metanephric Adenoma

Oncocytoma

Angiomyolipoma

Mixed Mesenchymal and Epithelial Tumors

Cystic Nephroma

Mixed Epithelial and Stromal Tumors

Leiomyoma

Other Benign Renal Tumors

Benign renal neoplasms constitute a rather large and heterogeneous group of renal lesions that can be found in the kidney. These include the simple renal cyst, selected complex renal cysts, cortical and metanephric adenomas, angiomyolipoma, oncocytoma, the rarer cystic nephroma, mixed epithelial-stromal tumor, and leiomyoma, as well as other, even more esoteric tumor types. Management approaches to these lesions can vary widely, from no management for the simple renal cyst to selective embolization for larger angiomyolipomas and surgical extirpation for solid renal masses when the differential diagnosis includes renal cell carcinoma (RCC). With the increased use of cross-sectional abdominal imaging for renal-specific as well as other nonspecific complaints, it is expected that the identification of both benign and malignant renal tumors will continue to increase in the coming years (Patard, 2009). Moreover, with the increased use of and refinements in renal mass biopsy, the management of both benign and malignant renal neoplasms is still evolving in such a way that the indications for intervention, and the type of intervention, may change significantly in the coming years (Lane et al, 2008a; Campbell et al, 2009). Now, with advanced multidimensional imaging techniques as well as minimally invasive, nephron-sparing surgical approaches, percutaneous ablative approaches, and the concept of active surveillance in the armamentarium of the practicing urologist, management of all renal lesions, including those that are presumptively benign, continues to evolve (Raj et al, 2007; Benway and Bhayani, 2009; Murphy et al, 2009).

At present, however, the urologist is left primarily with imaging studies such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) to assess whether a renal lesion is benign or malignant before therapeutic decisions are made. And unless the mass has clear radiographic features that suggest a benign cause, such as clear evidence of fat seen with most angiomyolipomas or the smooth walls and lack of enhancement of a simple or minimally complex cyst, the vast majority of benign renal lesions are diagnosed only after definitive therapy such as surgical intervention has been implemented. Several clinical features have been linked to an increased likelihood of a renal mass having a benign cause, including smaller size of mass and female sex and older age of patient, but none of these factors can be relied on to avoid intervention if a specific pretherapy diagnosis cannot be made (Kutikov et al, 2006; Snyder et al, 2006; Glassman et al, 2007; Lane et al, 2007; Beisland et al, 2009; Murphy et al, 2009).

In this chapter the most common benign renal neoplasms that occur in the kidney are identified. The discussion is then focused on the etiology and natural history, clinical presentation, histology and molecular biology, imaging characteristics, and treatment options, when treatment is indicated.

RENAL CYSTS

In much the same way as the molecular biology of RCC was elucidated through the study of familial genetic syndromes such as von Hippel-Lindau disease, the molecular basis for cyst formation has been further elucidated through the genetic analysis of familial renal cystic syndromes, such as autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). Through these studies researchers have identified that loss of specific genes, such as *PKD1* (encodes for polycystin-1 protein) or *PKD2* (encodes for polycystin-2 protein), leads to cyst formation in patients with ADPKD. Polycystin-1 and polycystin-2 form a complex that represents a critical ion channel in the kidney, the loss of which results in cyst formation through the loss of intracellular calcium dysregulation (Pei, 2003; Weimbs, 2007; Ibraghimov-Beskrovnaya and Bukanov, 2008). More recently, defects in primary cilia—nonmotile organelles present on the surface of renal tubular epithelial cells—have been implicated in renal cystic diseases, and much research is currently being conducted to further elucidate this link (Lina and Satlinb, 2004). Similarly, mutations in the *PKHD1* (polycystic kidney and hepatic disease 1) gene, which encodes the fibrocystin/polyductin protein (normally interacts with polycystin-2), were found to be the cause of ARPKD (Onuchic et al, 2002). Whether these genetic changes are common to sporadic forming “benign” renal cystic disease remains to be proven, but many of the phenotypic and genetic changes noted in the kidneys of patients with familial cystic disease syndromes have been identified in sporadic cystic disease (Qian et al, 1996; Pei, 2001).

Perhaps the best description of the natural history of sporadic renal cysts can be found in the recently updated study by Terada and associates (2008). In this study of 61 patients with simple renal cysts and a mean of 10 years of follow-up, the authors noted that the cysts increased in both size and number over time. The average increase in size of the cysts was 1.9 mm/yr, but the authors

also noted that the rate of size increase decreased with age. It is interesting to note that two cysts developed renal neoplasms during the course of the study, and no differences were noted in the clinical characteristics of the cysts that developed neoplasms and those that did not. Regarding the risk factors for the development of cysts, increasing age, male gender, presence of hypertension, and presence of renal insufficiency were all associated with the development of sporadic renal cysts (Terada et al, 2004). Renal cysts remain the most common benign renal lesions, representing more than 70% of asymptomatic renal masses. They can be solitary or multiple and unilateral or bilateral (Terada et al, 2002).

In addition to sporadic cystic disease of the kidney and the cysts that occur with familial syndromes such as ADPKD and ARPKD, cysts are also known to occur in association with end-stage renal disease in patients on dialysis (Bisceglia et al, 2006). There appears to be a higher incidence of RCC associated with the development of acquired renal cystic disease, much like that seen with von Hippel-Lindau disease and tuberous sclerosis, such that the pathogenesis of these cystic lesions may be quite different from

that seen with sporadic simple or minimally complex cysts (Truong et al, 2003).

Renal cystic lesions can be imaged through a variety of radiographic techniques, including ultrasonography, CT, and MRI. On ultrasonography, simple renal cysts have a smooth wall, are fluid filled with no internal echoes, and have evidence of posterior wall enhancement. Evidence of internal echoes, calcifications or nodularity in the wall, or internal septa on ultrasonography suggests a more complex cyst that might be worthy of further imaging that includes intravenous administration of a contrast agent (Quia et al, 2008; Eknayan, 2009).

The Bosniak classification for renal cystic lesions, as reviewed in Table 56-1, is the most useful and widely employed method for characterizing renal cystic lesions and for assessing the likelihood of the presence of a concomitant malignancy within the cyst (Bosniak, 1986; Israel and Bosniak, 2005; Warren and McFarlane, 2005). In general, Bosniak class I, II, and IIF cysts are likely to represent benign lesions, thus requiring either no therapy or just continued radiographic follow-up, in the case of class IIF lesions (Fig. 56-1). These recommendations are based on a number of

TABLE 56-1 Bosniak Classification of Renal Cysts

BOSNIAK CLASSIFICATION	IMAGING CHARACTERISTICS	INCIDENCE OF MALIGNANCY	THERAPY
I	Simple cyst with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density in Hounsfield units and does not enhance with intravenous administration of a contrast agent.	1.7%	No therapy or follow-up required
II	Cyst may contain a few hairline thin septa and fine calcifications, or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high-attenuation lesions <3 cm (so-called <i>high-density cysts</i>) are well margined and do not enhance with intravenous administration of a contrast agent.	18.5%	No therapy or follow-up required
IIF	Cysts may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Their wall or septa may contain calcifications that may be thick and nodular, but no measurable contrast enhancement is present. These lesions are typically well margined. Totally intrarenal nonenhancing high-attenuation renal lesions ≥3 cm are also included in this category.	18.5%	Repeat imaging to assess stability of size and radiographic characteristics
III	“Indeterminate” cystic masses have thickened irregular or smooth walls or septa in which measurable contrast enhancement is present.	33%	Excision or ablation
IV	Clearly malignant cystic masses can have all the criteria of category III but also contain enhancing soft-tissue components.	92.5%	Excision or ablation

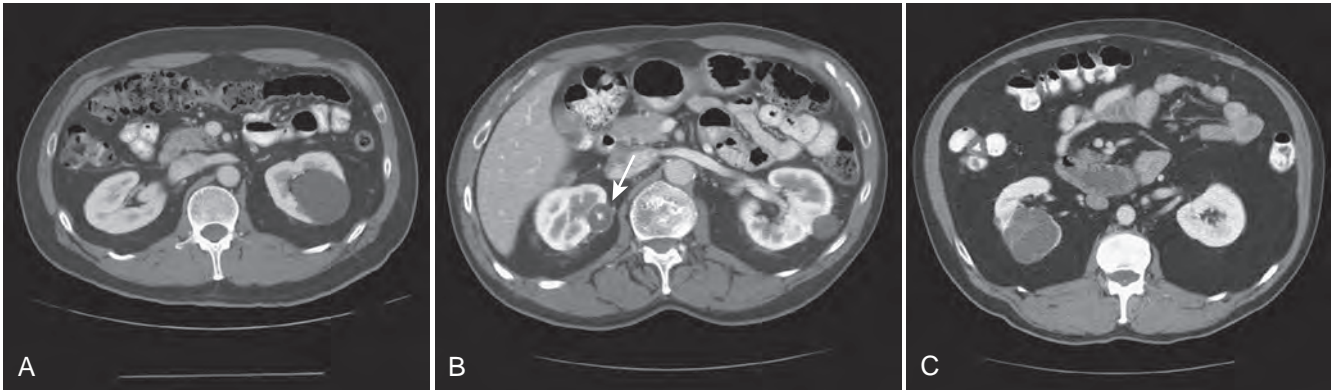


Figure 56-1. A, Computed tomography (CT) scan of a Bosniak I renal cyst. B, CT scan of a Bosniak II renal cyst. Note internal calcification. C, CT scan of a Bosniak IIF renal cyst. Several thin irregular septations are present within the cyst. (Copyright 2009, C. G. Wood.)

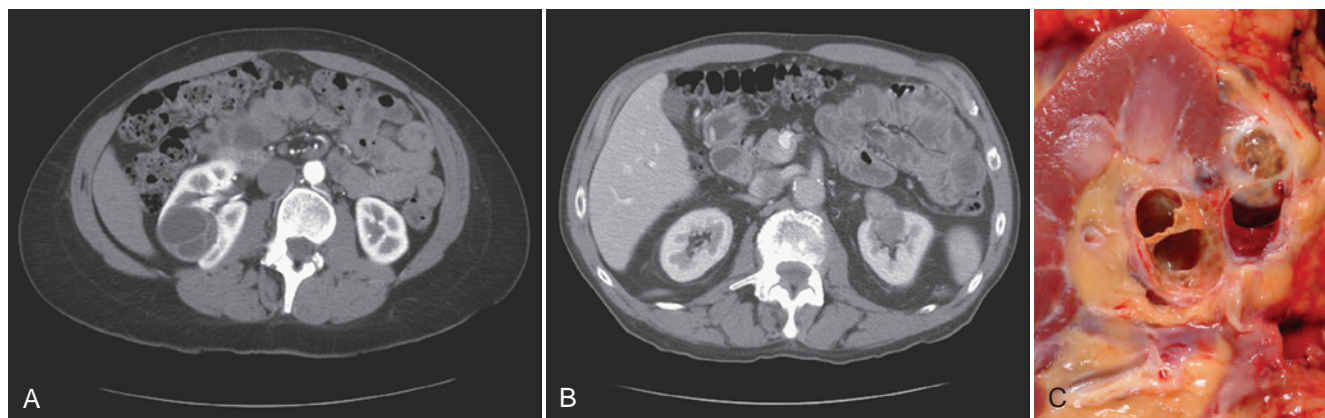


Figure 56-2. A, Computed tomography (CT) scan of a Bosniak III renal cyst. Thick, irregular septations are present within the cyst. B, CT scan of a Bosniak IV renal cyst, with a solid enhancing nodule. C, Bivalved Bosniak IV renal cyst demonstrating a solid component that proved to be conventional renal cell carcinoma. (Copyright 2009, C. G. Wood.)

series published in the literature by Bosniak and others that include both radiographic as well as pathologic follow-up (Israel and Bosniak, 2003; Warren and McFarlane, 2005; Gabr et al, 2009; O'Malley et al, 2009).

Because of the higher risk of malignancy associated with Bosniak class III and IV lesions, therapy is recommended (Fig. 56-2). The definitive therapy would be surgical excision, although ablative therapies such as cryotherapy or radiofrequency ablation of cystic masses have been reported (Raman et al, 2009) (see Chapter 57).

Although the Bosniak classification was originally devised and implemented using CT scans, it can be used with MRI as well, although caution must be exercised because MRI tends to exaggerate some findings related to cysts (Bosniak, 2012). For example, MRI can make septa appear thicker, which could make enhancement of cyst walls and septa more obvious, as a result of inferior spatial resolution and superior contrast resolution with MRI. This could make Bosniak II cysts look like IIF and IIF look like III, especially in cysts less than 2.5 cm in size. However, MRI does have an advantage in hemorrhagic lesions or other lesions that have high intensity on CT (Bosniak, 2012).

The overwhelming majority of simple or minimally complex cysts require no further follow-up or therapy once diagnosed (Eknoyan, 2009). Rarely, benign cystic lesions of the kidney can grow to such a large size that they can cause pain or other symptomatology, including hypertension (Porpiglia et al, 2009; Zerem et al, 2009). Symptoms can also occur as a consequence of hemorrhage within the cyst or spontaneous or traumatic cyst rupture (Hughes et al, 1995; Rainio et al, 2006; Ishikawa et al, 2008; Vaidyanathan et al, 2008).

A variety of therapeutic interventions have been described for benign symptomatic cystic lesions of the kidney. These include aspiration, surgical resection, cyst decortications, and sclerotherapy with a variety of different agents (Cho et al, 2008; Ham et al, 2008; Baysal and Soylu, 2009; Canguven et al, 2009; Choi et al, 2009; Porpiglia et al, 2009). Although none of these approaches seems to be better than the others described, it is noted that with aspiration and sclerotherapy there is a higher incidence of cyst recurrence and multiple treatments may be needed to satisfactorily ablate the cystic lesion. A word of caution is warranted regarding the treatment of peripelvic cysts: given their proximity to the vital structures of the kidney, including the renal vessels and collecting system, laparoscopic rather than percutaneous approaches may be associated with a higher safety margin and better efficacy (Okumura et al, 2003; Camargo et al, 2005).

KEY POINTS: RENAL CYSTS

- Renal cysts remain the most common of benign renal lesions, representing more than 70% of asymptomatic renal masses.
- The overwhelming majority of simple or minimally complex cysts require no further follow-up or therapy once diagnosed.
- The Bosniak classification for renal cystic lesions is the most useful and widely employed method for characterizing renal cystic lesions and assessing the likelihood of the presence of a concomitant malignancy within the cyst.

PAPILLARY ADENOMA OF THE KIDNEY

The designation and management of papillary adenomas remain a subject of controversy in the urologic literature. These lesions are small, solid cortical renal lesions that are thought to have a benign course (Renshaw, 2002). To be considered papillary adenomas, these lesions should histologically be 5 mm or smaller; well circumscribed; characterized by uniform basophilic or eosinophilic cells with benign-appearing nuclear and cellular features; and arranged in papillary, tubular, or tubulopapillary architecture; and they should not resemble clear cell, chromophobe, or collecting duct RCC (Grignon and Eble, 1998). The incidence of papillary adenomas increases with age (40% of patients over 70 years of age in autopsy studies) and male sex, and these tumors also have been associated with acquired renal cystic disease that results in end-stage renal failure (Xipell, 1971; Hughson et al, 1986; Reis et al, 1988; Leroy et al, 2001; Denton et al, 2002; Snyder et al, 2006; Ferda et al, 2007). The incidence of papillary adenomas in autopsy series ranges from 7% to 23%, although antemortem pathologic diagnosis of renal adenoma is much less common, in part owing to the pathologist's concern that there are no reliable histopathologic, ultrastructural, or immunohistochemical criteria to distinguish benign from malignant lesions of the kidney (Licht, 1995). In fact, in a more recent study in which immunohistochemical analyses were used to further characterize renal adenomas, it was suggested that these lesions may be linked to the development of papillary RCC and represent a biologic link and continuum as a premalignant precursor (Wang et al, 2007). In this study, researchers examined 542 nephrectomy specimens obtained over 8 years. Seven percent of these demonstrated evidence of papillary adenoma; and of these, 47% were associated with a

concomitant papillary RCC, whereas 53% were associated with other renal tumor histologies. Papillary adenomas that arose in the setting of papillary RCC tended to be multiple (61%), whereas papillary adenomas associated with other renal tumors were only one or two in number. Eighty-two percent of papillary adenomas found in the study had a similar immunohistochemistry staining profile to papillary RCC, staining positive for AMACR. In other studies, renal adenomas shared similar cytogenetic profiles to papillary RCC, such as loss of Y chromosome and trisomy of chromosomes 7 and 17, thus suggesting a biologic link between the two neoplasms, with papillary adenomas being potential precursor lesions (Kovacs et al, 1991; Kovacs, 1993; Presti et al, 1998; Brunelli et al, 2003a).

The overwhelming majority of papillary adenomas remain asymptomatic, are undetectable radiographically because of their small size (<1 cm), and require no further therapy. Size of the neoplasm has historically been used to differentiate renal adenoma from more malignant neoplasms of the kidney. Thoenes and colleagues (1986) provided a reassessment of the histologic classification of renal tumors and defined renal adenoma as a tumor with nuclear grade I and a diameter of at least 1 cm. For many years, a “3-cm rule” was pervasive in the urologic literature, dating back to the original autopsy studies by Bell (1938) in which he noted that only 1 of 38 renal cortical tumors had associated metastases whereas 70 of 106 tumors larger than 3 cm were associated with metastases.

The diagnosis of papillary adenoma remains controversial; many believe that all solid renal epithelium-derived masses are potentially malignant and therefore should undergo treatment (Renshaw, 2002).

KEY POINTS: PAPILLARY ADENOMA OF THE KIDNEY

- The diagnosis of papillary adenoma remains controversial; many believe that all solid renal epithelium-derived masses are potentially malignant and therefore should undergo treatment.
- Papillary adenomas may be linked to the development of papillary RCC and could represent a biologic link and continuum as a premalignant precursor.
- The incidence of papillary adenomas increases with age and male sex, and these tumors also have been associated with acquired renal cystic disease seen in patients on hemodialysis.

METANEPHRIC ADENOMA

In 1995, Davis and colleagues (1995) reported 50 cases of an unusual and new renal lesion with distinctive histologic features and a benign clinical course despite occasional symptomatic presentation and large tumor size. In this series, mean tumor size was 5.5 cm (up to 15 cm), and nearly half of the patients had flank pain, gross hematuria, or a palpable mass. Six additional patients had polycythemia, and hypercalcemia has also been reported in association with this tumor type, which was designated *metanephric adenoma* (Davis et al, 1995; Mahoney et al, 1997; Kuroda et al, 2003b). Metanephric adenoma was officially accepted as a primary benign renal tumor based on consensus from the Heidelberg classification (Kovacs et al, 1997). A female predominance (2:1) has been noted in several series (Davis et al, 1995; Jones et al, 1995; Snyder et al, 2006; Bastide et al, 2009). Incidental presentation is most common, and peak incidence is in the fifth decade of life (Renshaw, 2002). Polycythemia can be seen in 10% of patients and appears to be caused by the production of erythropoietin and other cytokines by the tumor (Yoshioka et al, 2007; Bastide et al, 2009). Radiographically these tumors can have peripheral or central calcifications and may be hypovascular on contrast-enhanced CT and hyperechoic on ultrasonography (Bastide et al, 2009). These tumors

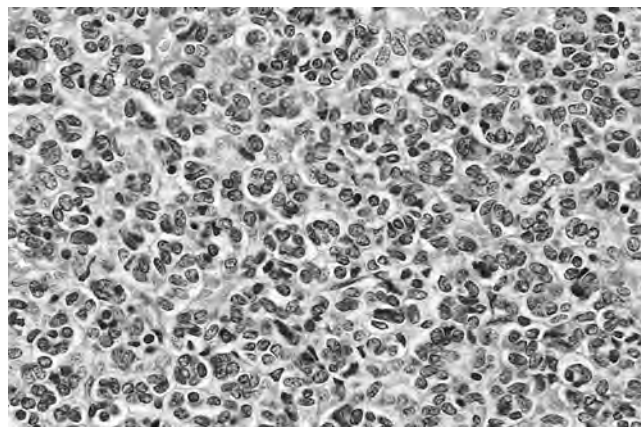


Figure 56-3. Classic metanephric adenoma with small, intensely basophilic cells arranged in an acinar pattern.

tend to be solitary, hypodense or isodense, with a poorly defined margin, with less enhancement than the medulla and cortex during all contrast-enhanced CT phases (Zhu et al, 2014).

On microscopic examination these tumors consist of very small, often highly basophilic epithelial cells that form small acini and occasionally tubular or papillary structures within a predominantly acellular stroma (Fig. 56-3). Davis and colleagues (Renshaw, 2002) argued that metanephric adenoma might be histologically related to epithelial Wilms tumor because they believed that it exhibited histologic similarities to the metanephric, hamartomatous elements of nephroblastomatosis. Along these lines, it is interesting to note that many of these tumors exhibit evidence of regression in the form of scarring or calcification. In addition, Muir and colleagues (2001) have shown positive staining for the Wilms tumor protein WT1 and an immunohistochemical staining profile that suggests a histogenetic relationship to Wilms tumor. An alternative theory for the origin of metanephric adenoma was proposed by Brown and associates (1997), who found gain of chromosomes 7 and 17 by fluorescent in situ hybridization in 8 of 11 of these tumors. These findings suggest a clonal neoplastic disorder potentially related to papillary RCC, but others have argued that this series may have been contaminated by inclusion of some cases of papillary RCC, which can be difficult to differentiate from metanephric adenoma (Brunelli et al, 2003b). Szponar and colleagues (2010) performed high-resolution array comparative genomic hybridization (array CGH) on six patients with metanephric adenoma, and none showed any DNA copy number changes. Pan and Epstein (2010) also performed array CGH on nine patients, and conversely noted only four patients with normal chromosome copy numbers. Five patients had gain of chromosome 19, confirmed using fluorescence in situ hybridization (FISH). Arroyo and colleagues (2001) showed that metanephric adenomas are part of a spectrum of related tumors, bridging metanephric stromal tumors, metanephric adenofibromas, and Wilms tumor. This potential link was also reviewed by Argani (2005). Pesti and colleagues (2001) have described a putative tumor suppressor gene for metanephric adenoma at chromosome 2p13. Various immunohistochemical stains have been evaluated to help distinguish metanephric adenoma from other renal neoplasms. The Wilms tumor marker WT1 is frequently expressed in metanephric adenoma (Muir et al, 2001; Bosco et al, 2007). α -Methylacyl-CoA racemase (AMACR) is poorly expressed in metanephric adenoma but highly expressed in papillary RCC (Olgac et al, 2006), whereas S-100 protein expression is very high in metanephric adenoma, weak in Wilms tumor, and absent in papillary RCC (Azabdaftari et al, 2008). Skinnider and colleagues (2005) demonstrated the potential utility of an expression panel to help differentiate papillary RCC and metanephric adenoma using a panel of cytokeratins 7, 8, 18, and 19 and vimentin. Use of these various markers appears to have improved the diagnostic yield of percutaneous biopsy and

fine-needle aspiration (Bosco et al, 2007; Patel et al, 2009), but the index of initial suspicion needs to be high for biopsy to be considered. Recently, Choueiri and colleagues (2012) evaluated *BRAF* V600E status in 29 patients with metanephric adenoma, and noted that 90% had *BRAF* V600E mutations. Such a mutation could be potentially studied during investigation of small renal masses with percutaneous biopsies.

Only one case of metastasis has been described in association with classic metanephric adenoma into a regional lymph node, and death related to this entity has not been reported (Drut et al, 2001). However, Picken and colleagues (2001) have described a single case of malignant stromal elements associated with a metanephric neoplasm of the kidney in a 21-year-old woman who died of progressive cancer, and they have proposed that there may be a spectrum of metanephric tumors that includes rare, aggressive variants. Atypical histologic features and multifocality in childhood have also been reported (Jain et al, 2007; Kohashi et al, 2009). Given the rarity of this tumor and the lack of highly predictive clinical or radiographic criteria, metanephric adenoma remains primarily a pathologic diagnosis. If radiographic findings raise the index of suspicion, then percutaneous core biopsy with fine-needle aspiration may prove helpful in establishing a diagnosis for nephron-sparing treatment or observation, but most patients will require surgical excision because of concern for malignancy (Fig. 56-4).

KEY POINTS: METANEPHRIC ADENOMA

- Metanephric adenoma is a recently described, rare, benign mass that radiographically may be indistinguishable from RCC.
- It is typically found incidentally, has a female predominance, and has a peak incidence in the fifth decade of life.
- The diagnosis is often made after surgical excision and can be confirmed with immunohistochemical panels for cytokeratins, WT1, S-100, and AMACR and by checking for *BRAF* V600E mutations.

ONCOCYTOMA

Renal oncocytoma is the most common benign tumor that appears as an enhancing renal mass on cross-sectional imaging and is presumed to be RCC until surgical excision, representing one of the ultimate challenges in preoperative diagnosis for the urologist. It accounts for 3% to 7% of kidney tumors (Morra and Das, 1993). Oncocytoma was initially described by Zippel in 1942 (Zippel,

1942) and then became accepted as a distinct entity after a report of 13 cases in 1976 by Klein and Valensi (Klein and Valensi, 1976). Multiple additional reports since that time, including more recent genotyping studies, confirm it to be a benign histology with a distinct cell of origin and genetic abnormalities (Lieber et al, 1987; Davis et al, 1991; Licht et al, 1993; Amin et al, 1997; Perez-Ordóñez et al, 1997; Dechet et al, 1999; Chao et al, 2002; Kuroda et al, 2003a). Cases of metastatic disease have been reported, yet these are considered exceptionally rare and may represent cases of malignant degeneration or pseudometastases (Paner et al, 2005; Oxley et al, 2007).

Recent clinical studies highlight the differing incidence of oncocytoma based on age and gender. Cao and colleagues (2005) and Skolarus and colleagues (2008) showed an increasing incidence of oncocytoma in older patients with a small incidentally discovered renal mass. Two different reports highlight that younger females are nearly twice as likely as their male counterparts to have a benign tumor, which includes oncocytoma and angiomyolipoma; these findings are probably largely driven by the higher rates of angiomyolipoma in women (Cao et al, 2005; Snyder et al, 2006).

Grossly these tumors are mahogany or tan, homogeneous, and well circumscribed with a pseudocapsule and a central stellate scar in some patients (Fig. 56-5). Microscopically the cells are round or polygonal and arranged in a nested growth pattern. The cells are large, uniform, and highly eosinophilic, owing to an abundance of mitochondria (Renshaw, 2002). In up to one third of patients, hemorrhage, extension into perinephric fat, vascular invasion, cellular atypia, prominent nucleoli, and pleomorphism may be seen, yet the clinical behavior in these cases is within what is expected with a benign course (Davis et al, 1991; Amin et al, 1997; Perez-Ordóñez et al, 1997). The most common genetic abnormality is loss of heterozygosity at chromosomes 1 and/or 14 (Presti et al,



Figure 56-4. Computed tomography scan showing a metanephric adenoma in a middle-aged woman. (Copyright 2009, S. F. Matin.)

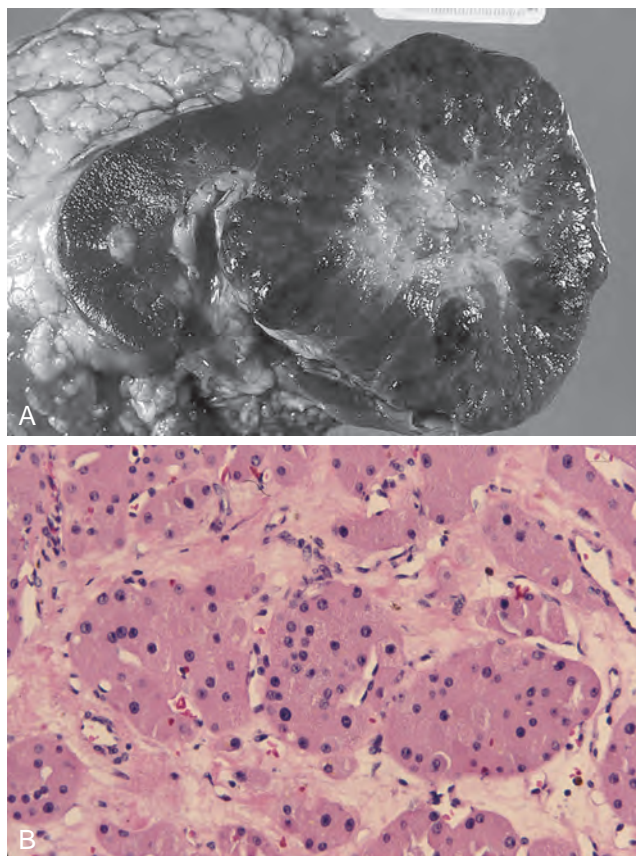


Figure 56-5. A, Bivalved renal oncocytoma demonstrating central scar. B, Oncocytoma with large eosinophilic cells arranged in distinct nests.

1996; Herbers et al, 1998; Lindgren et al, 2004; Paner et al, 2007). Other common cytogenetic findings include loss of the Y chromosome and chromosome 14q and rearrangements of 11q13 (Schwerdtle et al, 1997; Herbers et al, 1998; Chao et al, 2002; Polascik et al, 2002; Lindgren et al, 2004). The chromosomal abnormalities typically seen in RCC are not seen in renal oncocytomas, further reinforcing the concept that these tumors are genotypically distinct from RCC (Herbers et al, 1998; Minor et al, 2003). However, histologically, the greatest dilemma arises from distinguishing chromophobe and clear cell RCC with eosinophilic characteristics from oncocytoma. Hale colloidal iron staining is the classic differentiating marker for oncocytoma, but it can have nonspecific staining and be difficult to interpret (Leroy et al, 2000). Cytokeratin profiles are helpful in distinguishing these histologic findings (Skinnider et al, 2005; Adley et al, 2006). Expression of cytokeratin-7 is seen in 66% of chromophobe RCC and only 5% of oncocytomas, and parvalbumin is expressed in 100% of chromophobe RCC and 47% of oncocytomas (Leroy et al, 2000; Adley et al, 2006). Various other markers have been recently described to differentiate oncocytoma from RCC, particularly chromophobe RCC, but the clinical usefulness of most of these has not yet been fully developed. These include Pax-2, expressed in metanephric tissues and vital for renal tubule development; pattern of claudin-7 and claudin-8 expression (Osunkoya et al, 2009); tight junction proteins expressed in distal nephron epithelium; a vimentin expression pattern (Hes et al, 2007); c-KIT expression; S-100 (Pan et al, 2004; Lin et al, 2006; Hes et al, 2007; Li et al, 2007; Rocca et al, 2007; Lechpammer et al, 2008; Gupta et al, 2009; Osunkoya et al, 2009); NPM (nucleophosmin/B23) (Sari et al, 2012); and LMP2 (Zheng et al, 2013); or a combination of these markers (Kim et al, 2009). More recently, Ehsani and colleagues (2013) used immunohistochemistry to study the expression of BCA2, a RING E3 ligase, in patients with renal masses, and noted that 100% (114/114) of patients with RCC were negative for BCA2 expression, and 100% (38/38) of patients with oncocytomas were positive for BCA2 expression. An "optimal" panel for distinguishing between chromophobe and clear cell RCC and oncocytoma was recommended by Liu and colleagues in 2007, consisting of a combination of three markers (vimentin, glutathione-S-transferase- α , and epithelial cell adhesion molecule). These investigators achieved 100% sensitivity and 100% specificity for the differential diagnosis of chromophobe carcinoma, oncocytoma, and clear cell carcinoma (Liu et al, 2007). The feasibility of molecular signatures and gene profiling as potentially useful tests for the accurate diagnosis of tumors such as oncocytoma is being evaluated (Schuetz et al, 2005; Yang et al, 2006), but such studies are not yet a clinical reality.

As noted previously, there are several distinct similarities to chromophobe RCC, which also is derived from the distal renal tubules. Chromophobe RCC, particularly the eosinophilic variant, and oncocytoma are histologically similar and their distinction often requires additional pathologic testing (Weiss et al, 1995; Renshaw, 2002). The commonality of these two tumors is further evidenced in patients with Birt-Hogg-Dubé syndrome, in whom both oncocytomas and chromophobe RCC develop, in addition to cutaneous fibrofolliculomas and spontaneous pneumothoraces (Pavlovich et al, 2005; Toro et al, 2008). Some of the renal tumors display a histology between these two tumors, prompting some to speculate that chromophobe RCC and oncocytoma represent points in a spectrum of neoplasia (Chao et al, 2002; Linehan, 2003; Pavlovich et al, 2005; Toro et al, 2008).

The greatest clinical dilemma remains the inability to confidently differentiate between renal oncocytoma and RCC on clinical or radiographic testing. Both have a similar age at presentation with peak incidence in the seventh decade, have a 2:1 male-to-female predominance, and are similarly sized at presentation. Although oncocytomas traditionally were more likely to be asymptomatic at presentation, most RCC are also diagnosed incidentally in the current era, eliminating this clinical scenario as a differentiator (Davis et al, 1991; Licht et al, 1993; Lieber, 1993; Amin et al, 1997; Perez-Ordóñez et al, 1997; Dechet et al, 1999). The typical spoke-wheel pattern seen on angiography or the stellate scar on

cross-sectional imaging may bring up the question of a renal oncocytoma, but these findings have a poor predictive value by themselves (Davidson et al, 1993; Licht et al, 1993; Licht, 1995; Hilton, 2000; Choudhary et al, 2009). On CT scan, oncocytomas appear to have a high peak Hounsfield unit (HU) attenuation (similar to RCC); however, this peak has been found to occur more frequently during the nephrogenic phase (whereas in RCC it occurred more often in the corticomedullary phase) (Pierorazio et al, 2013). Conversely, other groups have found that segmental enhancement inversion on CT scan was not a reliable indicator of oncocytoma (McGahan et al, 2011; O'Malley et al, 2012). On MRI, oncocytomas may have distinct T1 and T2 signal patterns that can be suggestive, but these are not definitive findings (Harmon et al, 1996). T2-weighted images on MRI do not differentiate oncocytoma from RCC (Dann et al, 2006; Rosenkrantz et al, 2010). More recently, Cornelis and colleagues (2013) studied MRI in patients with oncocytoma or RCC and noted that complete late enhancement in the central area of the mass occurred more frequently in oncocytomas compared with RCC (74% vs. 12%, respectively), and that the absence of T2 signal intensity inversion or presence of signal drop on chemical-shift imaging could potentially rule out oncocytoma on MRI scans. For lesions undergoing surveillance, the growth rates of RCC and oncocytoma are similar, so growth kinetics also do not help differentiate these tumors (Chawla et al, 2006; Crispin and Uzzo, 2007; Siu et al, 2007; Kawaguchi et al, 2011). In 4% to 13% of patients, tumors are multicentric, are bilateral, or have a metachronous presentation (Lieber et al, 1987; Davis et al, 1991; Licht et al, 1993; Amin et al, 1997; Perez-Ordóñez et al, 1997; Dechet et al, 1999; Tickoo et al, 1999; Minor et al, 2003). The entity of renal oncocytomatosis, now referred to as *oncocytosis*, was first described by Warfel and Eble (1982) in a report of a patient with more than 200 oncocytomas in both kidneys. Familial renal oncocytomas was initially described (Weirich et al, 1998) in five families in which it presented at a young age as multicentric, bilateral, recurrent oncocytomas. Nonfamilial forms of bilateral multifocal oncocytomas resembling oncocytomatosis can also occur (Fig. 56-6). A recent cytogenetic evaluation of a patient with apparently sporadic oncocytomas and hybrid tumors showed different chromosomal losses than the Birt-Hogg-Dubé syndrome (Al-Saleem et al, 2004).

Historically, fine-needle aspiration or core biopsy was compromised by high rates of false-negative results and nondiagnostic specimens, given the difficulty in differentiating oncocytoma with RCC subtypes (Weiss et al, 1995; Campbell et al, 1997). However, the diagnostic accuracy of percutaneous biopsy has markedly improved, particularly when a core biopsy is done in addition to a fine-needle aspiration and is bolstered with the use of immunostains (Liu and Fanning, 2001; Barocas et al, 2006; Lebret et al, 2007; Volpe et al, 2007; Kummerlin et al, 2008; Schmidbauer et al, 2008), prompting some investigators to revisit the role of the biopsy in the management of some patients with an incidental renal tumor (Shah et al, 2005; Lebret et al, 2007; Volpe et al, 2007). When multiple tumors are present, one must consider the possibility of RCC coexisting with oncocytoma, the incidence of which in some series has been shown to be as high as 32% (Davis et al, 1991; Licht et al, 1993; Licht, 1995; Gudbjartsson et al, 2005). Biopsy in these patients must be thoughtfully considered to obtain a sampling of all sites of disease that are of concern.

Treatment options for a known oncocytoma range from observation to thermal ablation, laparoscopic or open partial nephrectomy, and even radical nephrectomy depending on the clinical scenario and uncertainty regarding the diagnosis (Licht, 1995; Romis et al, 2004; Gudbjartsson et al, 2005; Crispin and Uzzo, 2007). If oncocytoma is highly suspected and surgery is indicated, a nephron-sparing approach is preferred, given the benign nature of these lesions and the very low probability of recurrence (Licht, 1995; Romis et al, 2004; Gudbjartsson et al, 2005). Frozen section analysis is usually not sensitive enough to differentiate the eosinophilic appearance of oncocytomas from eosinophilic RCC and should not be used to guide surgical strategy. Thermal ablation, although sometimes reported as a treatment option, commits the

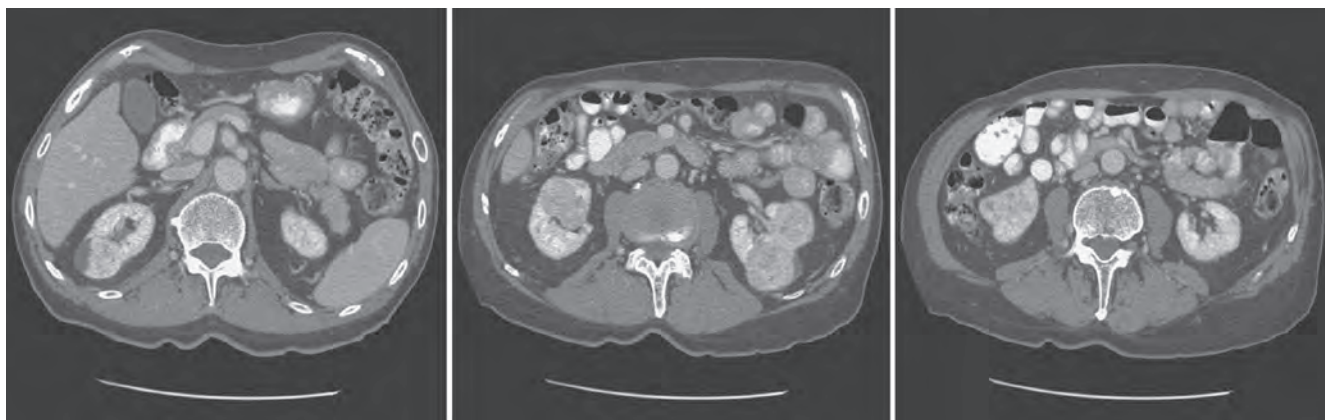


Figure 56-6. Computed tomography scan of a patient with multiple bilateral oncocytomas.
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patient to long-term radiographic surveillance, given the lower success rates of these procedures and the unknown long-term outcomes, tests that would be considered unnecessary should surgical excision be performed. In most cases the treatment options are isolated to observation, particularly for the older or sicker patient, and surgical resection, particularly for the younger healthier patient.

KEY POINTS: ONCOCYTOMA

- Renal oncocytoma is a common benign renal tumor that is clinically and radiographically indistinguishable from RCC.
- There may be a higher incidence of oncocytoma in older patients with a small renal mass as opposed to younger patients.
- Oncocytomas are derived from the distal renal tubules, similar to chromophobe RCC, and may represent a spectrum of neoplasia as evidenced in the Birt-Hogg-Dubé genetic syndrome. However, there is no evidence that oncocytomas undergo malignant transformation in sporadic cases.
- If oncocytoma is suspected preoperatively, a percutaneous core biopsy in addition to fine-needle aspiration may reliably provide a diagnosis when core tissue is available for additional immunohistochemical studies.
- Recent advancements in immunohistochemical markers have greatly improved the diagnostic accuracy of pathologic diagnosis from pathologic specimens and even core biopsy specimens.
- Frozen section analysis at the time of surgery may not reliably distinguish oncocytoma from RCC and should not be used to guide surgical strategy.

ANGIOMYOLIPOMA

Renal angiomyolipoma was originally described in 1900 by Grawitz (Grawitz, 1900). Angiomyolipoma accounts for less than 10% of renal tumors, with autopsy series and ultrasound-screened populations showing incidences of 0.3% and 0.13%, respectively, in the general population (Eble, 1998). It is a benign neoplasm; in its classic form it consists of thick-walled poorly organized blood vessels, smooth muscle, and varying levels of mature adipose tissue (Tamboli et al, 2000; Nelson and Sanda, 2002; Bissler and Kingswood, 2004). It was initially considered to be a form of hamartoma, but recent evidence suggests a neoplastic origin with evidence of a monoclonal, rather than polyclonal, source (Green et al, 1996; Sepp et al, 1996; Kattar et al, 1999). Angiomyolipoma is now considered to be derived from perivascular epithelioid cells, therefore belonging to a group of tumors referred to as *PEComas* (perivascular epithelioid cell tumors) (Bissler and Kingswood, 2004).

The tumor strongly expresses estrogen receptor β , progesterone receptor, and androgen receptor; is predominantly found in females; and is rare before puberty, suggesting a potential hormonal influence (Henske et al, 1998; L'Hostis et al, 1999; Boorjian et al, 2008).

Genetic studies in patients with tuberous sclerosis complex (TSC) resulted in discovery of two genes associated with angiomyolipomas: *TSC1* on chromosome 9q (encoding for hamartin protein) and *TSC2* on chromosome 16p (encoding for tuberlin protein) (European Chromosome 16 Tuberous Sclerosis Consortium, 1993; Henske et al, 1995; van Slegtenhorst et al, 1997). In sporadic TSC patients, 10% had *TSC1* mutations, 68% had *TSC2* mutations, and 22% had no mutations detected (Jones et al, 1999; Dabora et al, 2001).

The typical sporadic presentation is of a middle-aged woman with a single asymptomatic tumor. Sporadic angiomyolipomas appear to have a slow growth rate and are usually detected incidentally (Seyam et al, 2008). **Angiomyolipoma is the most common renal neoplasm associated with spontaneous perirenal hemorrhage, closely followed by RCC (Zhang et al, 2002).** Skolarus and colleagues (2008) suggested that there may be a decreased incidence of sporadic angiomyolipoma with increasing age. These tumors are most often sporadic but can also be associated with autosomal dominant TSC. **Twenty percent to 30% of angiomyolipomas occur in patients with TSC, and approximately 50% of patients with TSC develop angiomyolipomas (Eble, 1998; Neumann et al, 1998; Tamboli et al, 2000; Lendvay and Marshall, 2003; Minor et al, 2003).** TSC-associated angiomyolipomas typically manifest at a younger age (mean age 30 years); there is less female-to-male predominance (2:1) with multiple, bilateral, and symptomatic tumors (Eble, 1998; Neumann et al, 1998; Lendvay and Marshall, 2003). Because of the variable penetrance of the TSC mutation, the classic triad of seizures, adenoma sebaceum, and mental retardation may not be present because this mutation is seen in a minority of patients (Steiner et al, 1993). Patients with TSC also develop renal cysts and may be at higher risk of developing RCC. Lymphangioleiomyomatosis is also significantly associated with renal involvement in TSC (Rakowski et al, 2006).

Similar to RCC, most angiomyolipomas are now diagnosed incidentally during workup of unrelated complaints (Lemaitre et al, 1997; Seyam et al, 2008). The literature correlating tumor size and symptoms, however, is derived from before this era, when most angiomyolipomas were diagnosed after the development of symptoms. The Wunderlich syndrome, or massive retroperitoneal hemorrhage, representing the most significant complication of renal angiomyolipoma, was reported in up to 10% of patients and could be associated with significant morbidity and potential mortality if not promptly treated (Oesterling et al, 1986; Steiner et al, 1993; Eble, 1998). Pregnancy appears to increase the risk of hemorrhage from angiomyolipoma, a factor that can influence clinical decision making (Eble, 1998).

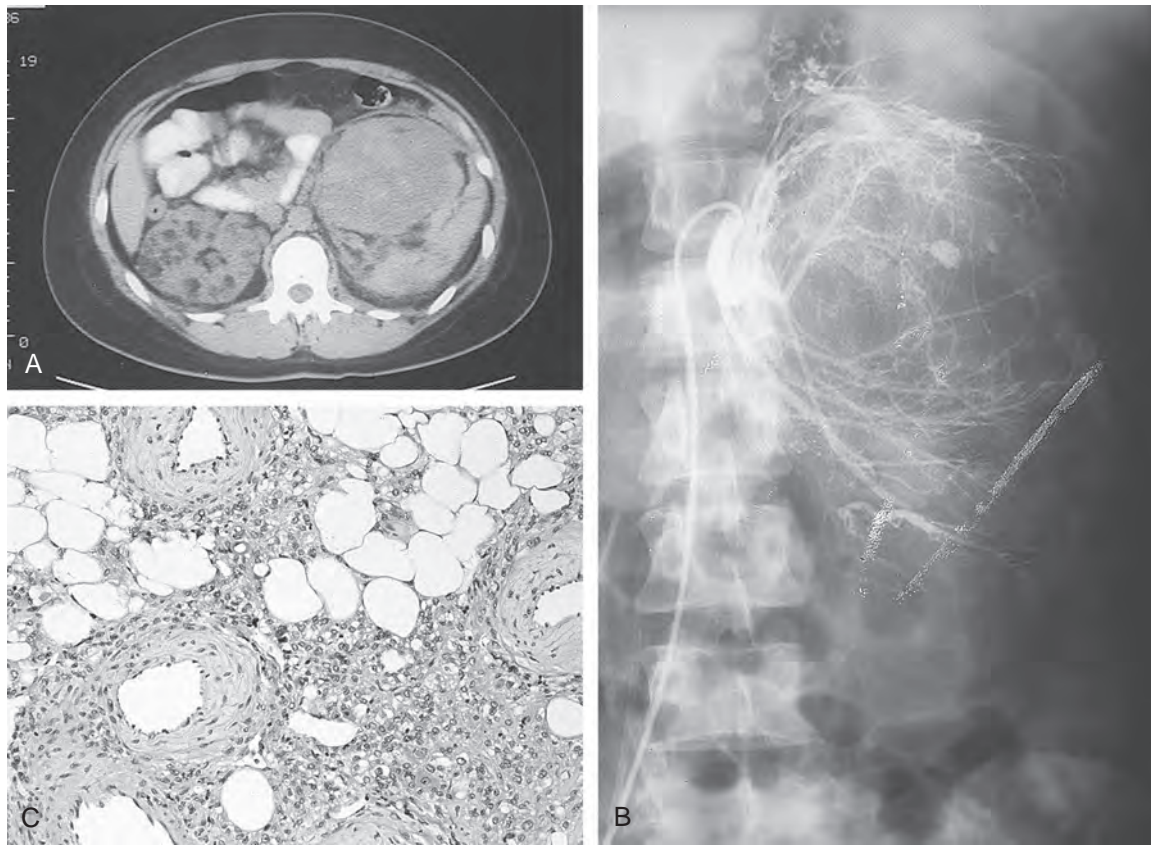


Figure 56-7. A, Computed tomography scan demonstrating large bilateral renal angiomyolipomas in a patient with tuberous sclerosis. B, Renal angiogram shows increased vascularity and aneurysmal dilation characteristic of angiomyolipoma. C, Typical microscopic appearance of angiomyolipoma with admixture of mature adipose tissue, smooth muscle, and thick-walled blood vessels.

Angiomyolipoma is the only benign renal tumor that is confidently diagnosed on cross-sectional imaging (Fig. 56-7). The presence of fat (confirmed on nonenhanced thin-cut CT by a value of -20 HU or less) within a renal lesion is considered the diagnostic hallmark (Jinzaki et al, 1997; Lemaitre et al, 1997; Bosniak et al, 1998; Simpfendorfer et al, 2009). Recently a study using a cutoff value of -10 HU showed an area under the curve of 0.83 for diagnosis of angiomyolipoma (Davenport et al, 2011). Findings of more than 20 pixels with attenuation less than -20 HU and of more than 5 pixels with attenuation less than -30 HU have been shown to have a positive predictive value of 100% (Simpfendorfer et al, 2009). Ultrasonography shows a well-circumscribed, highly echogenic lesion with shadowing (Siegel et al, 1996; Lemaitre et al, 1997). On angiography (or CT-angiography) aneurysmal dilation is found in 50% of angiomyolipomas (Lemaitre et al, 1997). The size of the aneurysms has been reported to correlate with the risk of rupture (Yamakado et al, 2002). MRI can be used in difficult cases, when the lesion has minimal fat, or in lieu of CT, with angiomyolipomas appearing hypointense on fat-suppressed T1 sequencing. In addition, angiomyolipoma appear hyperintense on T1 and T2 sequences as a result of their fat content (Kim et al, 2006; Halpenny et al, 2010).

Despite the radiographic hallmarks of angiomyolipoma, the diagnosis can be difficult to make in the three following situations: confusion with liposarcoma, possibility of fat-containing RCC, and possibility of a fat-poor angiomyolipoma resembling an RCC. Large angiomyolipomas can be confused with retroperitoneal liposarcomas, which are very rare. A good-quality, high-resolution CT, however, will invariably show several features that are characteristic of angiomyolipoma, the primary one being a small indentation of the renal parenchyma even when the tumor envelops

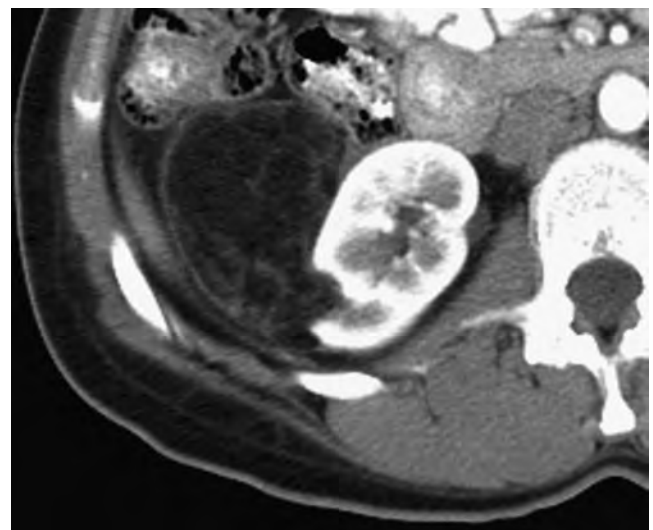


Figure 56-8. Computed tomography scan of angiomyolipoma with parenchymal indentation. (Copyright 2009, S. F. Matin.)

the kidney (Fig. 56-8), whereas liposarcomas will compress or only extrinsically push the renal parenchyma (Clark and Novick, 2001; Wang et al, 2002). Although RCC containing fat density has also been reported, these extremely rare cases also contained calcifications, a finding almost never seen with angiomyolipoma (Henderson et al 1997; Lemaitre et al, 1997; Roy et al, 1998). Most recently,

two cases of RCC with very small amounts of intratumoral fat but without calcification were reported, adding to two other reported cases in the literature (Hayn et al, 2009). Fat-poor angiomyolipoma, seen in 14% or more of patients, is much more difficult to diagnose, owing to the paucity of mature adipose tissue (Lemaitre et al, 1997; Kim et al, 2004; Milner et al, 2006). Lane and colleagues (2008a) showed that fat-poor angiomyolipoma was more commonly single, smaller, and found in older patients. Various imaging modalities have attempted to accurately identify these lesions preoperatively and differentiate them from RCC, with mixed success. On CT many appear to have hyperattenuation on noncontrast imaging and have a homogeneous and prolonged enhancement pattern (Jinzaki et al, 1997; Kim et al, 2004; Hafron et al, 2005; Milner et al, 2006; Silverman et al, 2007). Detailed pixel distribution analysis cannot differentiate between fat-poor angiomyolipoma and RCC (Catalano et al, 2008). Ultrasonography can show a hyperechoic or isoechoic lesion, suggesting a fat-poor angiomyolipoma (Jinzaki et al, 1997). Because of the nonspecific nature of these findings most patients are often treated as having a presumed RCC. However, these radiographic findings may prompt the attentive urologist to consider a percutaneous biopsy if the suspicion is raised by imaging. Percutaneous biopsy can play an important role in diagnosis in these patients because a core biopsy should be eminently accurate in the diagnosis of angiomyolipoma (Lebret et al, 2007; Silverman et al, 2007), especially when supplemented with immunohistochemical staining for HMB-45 protein (Pea et al, 1991). Epithelial markers should be negative in a typical angiomyolipoma (L'Hostis et al, 1999).

Although an invariably benign nature of angiomyolipoma is well accepted, extrarenal occurrences are occasionally seen and have been reported in the hilar lymph nodes, retroperitoneum, and liver, with direct extension into the venous system (Eble, 1998; Türker Köksal et al, 2000; Göğüş et al, 2001; Nelson and Sanda, 2002; Lin et al, 2003; Bissler and Kingswood, 2004; Akcali et al, 2006; Haritharan et al, 2006; Blick et al, 2008; Schade et al, 2008). Even in these patients a benign clinical course follows, indicating multicentric origin rather than malignancy with metastasis. Many angiomyolipomas exhibit regions of cellular atypia, and the pathologic differential diagnosis can include a number of subtypes of sarcoma, including fibrosarcoma, leiomyosarcoma, and liposarcoma, depending on the relative amounts of adipose, vascular, or smooth muscle tissue present (Wang et al, 2002). Positive immunoreactivity for HMB-45 (human melanoma black 45), a monoclonal antibody raised against a melanoma-associated antigen, is characteristic for angiomyolipoma and can be used to differentiate this tumor from sarcoma and other tumors (Eble, 1998), even on biopsy specimens. There have been two reports of high-grade and eventually lethal leiomyosarcoma arising within an angiomyolipoma. Christiano and colleagues (1999) have described a highly pleomorphic angiomyolipoma that was associated with the development of multiple pulmonary nodules, the majority of which stained positive for HMB-45 (Ferry et al, 1991). They believed that this case represented a malignant transformation of angiomyolipoma, which, if it does occur, must be exceedingly rare. However, these cases may also have represented the entity of epithelioid angiomyolipoma described by Mai and colleagues (1996). In 1997 Eble and colleagues published a report of their experience with five patients who had angiomyolipoma with a predominant epithelioid component (Eble et al, 1997); more recently, this malignant epithelioid variant of angiomyolipoma that can metastasize has been further described in patients with and without TSC, many of whom succumbed to the disease (Pea et al, 1998; L'Hostis et al, 1999; Martignoni et al, 2000; Cibas et al, 2001; Menè et al, 2001; Nelson and Sanda, 2002; Saito et al, 2002; Bissler and Kingswood, 2004; Huang et al, 2007; Limaïem et al, 2008; Matsuyama et al, 2008; Moudouni et al, 2008; Zanelli et al, 2008; Kato et al, 2009). This phenotype is characterized by epithelioid cells that are cytokeratin negative and HMB-45 positive. Whether this extremely rare variant represents malignant degeneration of a preexistent angiomyolipoma or a de novo tumor without a benign precursor remains unknown.

For optimal management of angiomyolipoma, treatment must be individualized. The management should take into account the size of the tumor, presence of symptoms, and patient factors. In particular, the risk of hemorrhage must be weighed during the evaluation. In general, most symptomatic angiomyolipomas have been relatively large and most studies in the literature have focused on a 4-cm cut point (Steiner et al, 1993; Nelson and Sanda, 2002). On the basis of an extensive literature review, Oesterling and coworkers (1986) reported that 82% of patients with angiomyolipomas larger than 4 cm in diameter were symptomatic, with 9% in hemorrhagic shock at the time of presentation; in contrast, patients with smaller tumors were symptomatic 23% of the time. Echoing these findings, Dickinson and colleagues (1998) reported that all 18 patients with angiomyolipomas smaller than 4 cm in their series were asymptomatic, whereas 7 of 13 patients with angiomyolipomas of 4 to 8 cm and 5 of 6 patients with tumors larger than 8 cm required intervention, primarily related to pain or bleeding. These observations have been confirmed and extended by a number of investigators (Blute et al, 1988; Steiner et al, 1993; Lemaitre et al, 1995; De Luca et al, 1999; Seyam et al, 2008). Steiner and colleagues (1993) reported that patients with angiomyolipomas larger than 4 cm were symptomatic 52% of the time, with 30% requiring surgical intervention, whereas patients with smaller tumors never required surgery and were asymptomatic 76% of the time. Although it was primarily retrospective, limited follow-up with a mean of 4 years was available for 24 patients with 28 tumors in this series. Interval growth was documented in 6 of 13 tumors with diameter of more than 4 cm and in 4 of 15 tumors smaller than 4 cm. A slower growth rate and a low risk of hemorrhage for smaller tumors were also supported by Kennelly and colleagues (1994), who observed 17 angiomyolipomas with tumor size of less than 4 cm for a mean of 3.8 years. Similarly, De Luca and colleagues (1999) studied 32 incidentally discovered angiomyolipomas smaller than 5 cm in diameter and found that 92% remained asymptomatic and unchanged in size. Even so, occasional larger angiomyolipomas undergoing observation, some for up to 18 years, can remain asymptomatic (Kennelly et al, 1994; Hadley et al, 2006; Danforth et al, 2007), reinforcing the concept that size represents a continuum of risk, not an absolute phenomenon, and highlighting the need for individualized tailoring of treatment recommendations. Multifocal angiomyolipomas and those in patients with tuberous sclerosis represent a special group that has demonstrated increased growth rates of approximately 20% per year, in contrast to a mean growth rate of 5% per year for solitary, sporadic angiomyolipomas (Steiner et al, 1993; Nelson and Sanda, 2002; Harabayashi et al, 2004; Seyam et al, 2008).

Although no large prospective studies evaluating the long-term outcomes of angiomyolipomas have been performed, the information reviewed here allows one to propose general guidelines for management. Asymptomatic, smaller tumors, which by convention have been those with a diameter less than 4 cm, can be observed expectantly, with repeat initial imaging at 6 to 12 months to define the growth rate and clinical significance. Repeat imaging can be lengthened once stability has been established, with follow-up performed only annually or biannually for smaller tumors (Oesterling et al, 1986; De Luca et al, 1999; Matin et al, 2008). Intervention should be considered for larger tumors, particularly if the patient is symptomatic, taking into account the patient's age, comorbidities, and other related factors. In women of childbearing age and patients with limited access to surveillance or to emergency care, a proactive approach should also be considered (Nelson and Sanda, 2002). A nephron-sparing approach, by either selective embolization or open or laparoscopic or robotic partial nephrectomy, is clearly preferred to radical nephrectomy in patients with angiomyolipomas requiring intervention. Preservation of renal tissue remains a priority in those with TSC or multicentric angiomyolipoma and particularly in patients with underlying renal insufficiency. The feasibility and efficacy of partial nephrectomy by either wedge resection or enucleation in patients with angiomyolipoma is well established, with preservation of renal function achieved even in patients with large lesions in a solitary kidney.

(Fazeli-Matin and Novick, 1998; Boorjian et al, 2007; Minervini et al, 2007). Selective embolization is reported by some to be the preferred modality, and data from 76 patients in six series have documented long-term success in most patients (Nelson and Sanda, 2002; Harabayashi et al, 2004). However, a substantial proportion of patients experienced persistent or recurrent symptoms or hemorrhage, and most of these required repeated procedures, including embolization or surgery (Hamlin et al, 1997; Han et al, 1997; Kehagias et al, 1998; Mourikis et al, 1999; Nelson and Sanda, 2002; Lenton et al, 2008). The overall complication rate with embolization in these series was 10%, similar to rates of partial nephrectomy (Boorjian et al, 2007), and included hemorrhage, abscess formation, or sterile liquefaction of the tumor requiring percutaneous drainage or surgical intervention. These data highlight the need for extended follow-up after selective embolization, which would not be required after partial nephrectomy (Nelson and Sanda, 2002). Selective embolization should be considered as first-line therapy in patients with acute or potentially life-threatening hemorrhage, because surgical exploration in this setting is often associated with total nephrectomy (Pappas et al, 2006; Chang et al, 2007). Ablative therapies such as radiofrequency ablation (Prevoo et al, 2008) and cryoablation (Bachmann et al, 2005; Byrd et al, 2006; Littrup et al, 2007; Caviezel et al, 2008) have also been used for the treatment of angiomyolipoma, but follow-up remains short, the evaluation of success remains poorly defined, and the duration for continued radiographic surveillance is unknown, thus committing the patient to multiple, long-term imaging. Ablative therapies may have their best role for the treatment of patients with TSC who have multicentric angiomyolipomas or older patients with comorbidities who require treatment and are not candidates for embolization.

Research into the molecular aspects of renal angiomyolipomas in patients with TSC showed a link between loss of TSC2 protein as a result of TSC2 mutation and activation of the mammalian target of rapamycin (mTOR) pathway (by demonstrating presence of S6K and phosphor-S6K in angiomyolipoma tissues) (El-Hashemite et al, 2003). Consequently, sirolimus was investigated in a phase 2 trial in 16 patients and showed an impressive response rate of 50% (using Response Evaluation Criteria in Solid Tumors [RECIST]) in the size of angiomyolipomas (Davies et al, 2011). Sirolimus was used in a neoadjuvant fashion in three patients with TSC with angiomyolipomas not amenable to surgical resection; after sirolimus treatment, tumor volume shrinkage of 38% to 95% was seen, and partial nephrectomy subsequently became feasible in all three patients (Staehler et al, 2012). Recently, everolimus was studied in a phase 3 trial in this patient setting and showed a response rate of 44% in angiomyolipomas (all measured at least 3 cm at study entry) (Bissler et al, 2013). This exciting research has led to a massive jumpstart of many clinical trials, several still ongoing, using mTOR inhibitors in patients with TSC and angiomyolipomas.

KEY POINTS: ANGIOMYOLIPOMA

- Angiomyolipoma is the only benign renal tumor confidently diagnosed on cross-sectional imaging by the presence of fat on nonenhanced thin-cut CT. Fat-poor angiomyolipoma may still be confused with RCC, but if it is suspected preoperatively then percutaneous biopsy is eminently capable of providing the diagnosis, with positivity for HMB-45 typically seen with angiomyolipoma.
- Angiomyolipoma is the most common renal tumor associated with spontaneous hemorrhage, followed by RCC.
- Treatment must be individualized based on the presentation, pregnancy status, tumor size, and renal function.
- The treatment of choice in patients with acute hemorrhage is selective renal angioembolization.
- Treatment options for elective management of larger angiomyolipomas include selective renal angioembolization and open or minimally invasive partial nephrectomy. Embolization is associated with a high rate of secondary procedures.

MIXED MESENCHYMAL AND EPITHELIAL TUMORS

Although considered separate entities by the 2004 World Health Organization classification of renal neoplasms, cystic nephroma and mixed epithelial and stromal tumors of the kidney (MESTs) are rare benign renal neoplasms that have overlapping clinical, morphologic, and immunohistochemical characteristics (Lopez-Beltran et al, 2006; Turbinder et al, 2007; Montironi et al, 2008). Recent demonstration of striking similarities between global gene expression profiles in cystic nephroma and MEST further strengthens the notion that these two entities represent opposite ends of the spectrum of the same biologic process (Zhou et al, 2009). Female predilection and history of hormonal ablation therapy in male patients, combined with the frequent expression of estrogen and progesterone receptors, suggest that the sex-steroid hormones might play a role in the pathogenesis of these rare lesions (Turbinder et al, 2007; Montironi et al, 2008; Stamatiou et al, 2008).

CYSTIC NEPHROMA

Cystic nephroma is a characteristic renal lesion with a bimodal age distribution and a benign clinical course (Tamboli et al, 2000). Diagnostic peaks occur primarily in the first 2 to 3 years of life, predominantly in boys, and again in the fourth and fifth decades with a significant (8:1) female prevalence (Madewell et al, 1983; Upadhyay and Neely, 1989; Castillo et al, 1991; Kuzgunbay et al, 2009; Stamatiou et al, 2008). As with other renal lesions, presenting signs can include abdominal mass, pain, and hematuria, but the majority of cystic nephromas are incidental findings (Madewell et al, 1983; Kuzgunbay et al, 2009). Several familial cases have been reported in the literature, and there have been anecdotal reports of sarcoma and clear cell carcinoma arising from cystic nephroma (Bal et al, 2005; Omar et al, 2006; Raj et al, 2006; Ashley and Reinberg, 2007).

Radiologically, most cystic nephromas are solitary, centrally located, and widely variable in size (mean size 9 cm) and commonly demonstrate curvilinear calcifications, herniation into the renal collecting system, and septal enhancement (Fig. 56-9A and B) (Madewell et al, 1983; Turbinder et al, 2007). Consequently, reliable radiologic differentiation between cystic nephroma and cystic RCC in adults or Wilms tumor in children is not possible (Vujanic et al, 2000).

Histologically, cystic nephromas are well encapsulated by a thick fibrous pseudocapsule and are composed of cysts lined by flattened, cuboidal, or hobnail epithelium (see Fig. 56-9C). The stromal component can range from dense paucicellular collagen to markedly cellular fascicles of spindle cells, closely resembling ovarian stroma (Tamboli et al, 2000). Immunohistochemical studies reveal affinity of the epithelial component for cytokeratins, whereas stromal components frequently stain positive for CD10, calretinin, inhibin, estrogen, and progesterone receptors (Turbinder et al, 2007; Montironi et al, 2008).

Because of concern for cystic Wilms tumor, most children with cystic nephromas continue to be managed by radical nephrectomy, whereas a nephron-sparing approach with partial nephrectomy, if feasible, is an attractive option in adults.

MIXED EPITHELIAL AND STROMAL TUMORS

MEST is a rare benign adult renal neoplasm with a variable admixture of epithelial and mesenchymal components (Pawade et al, 1993; Adsay et al, 2000). Previously these tumors were described as congenital mesoblastic nephroma, leiomyomatous renal hamartoma, solid and cystic biphasic tumor, cystic hamartoma, solitary multilocular cyst, and adult metanephric stromal tumor (Adsay et al, 2000; Pierson et al, 2001; Mai et al, 2007). Similar to cystic nephromas, MEST exhibits striking female predominance with a diagnostic peak in the fifth decade (mean age 46 years old). The majority of women diagnosed with MEST had

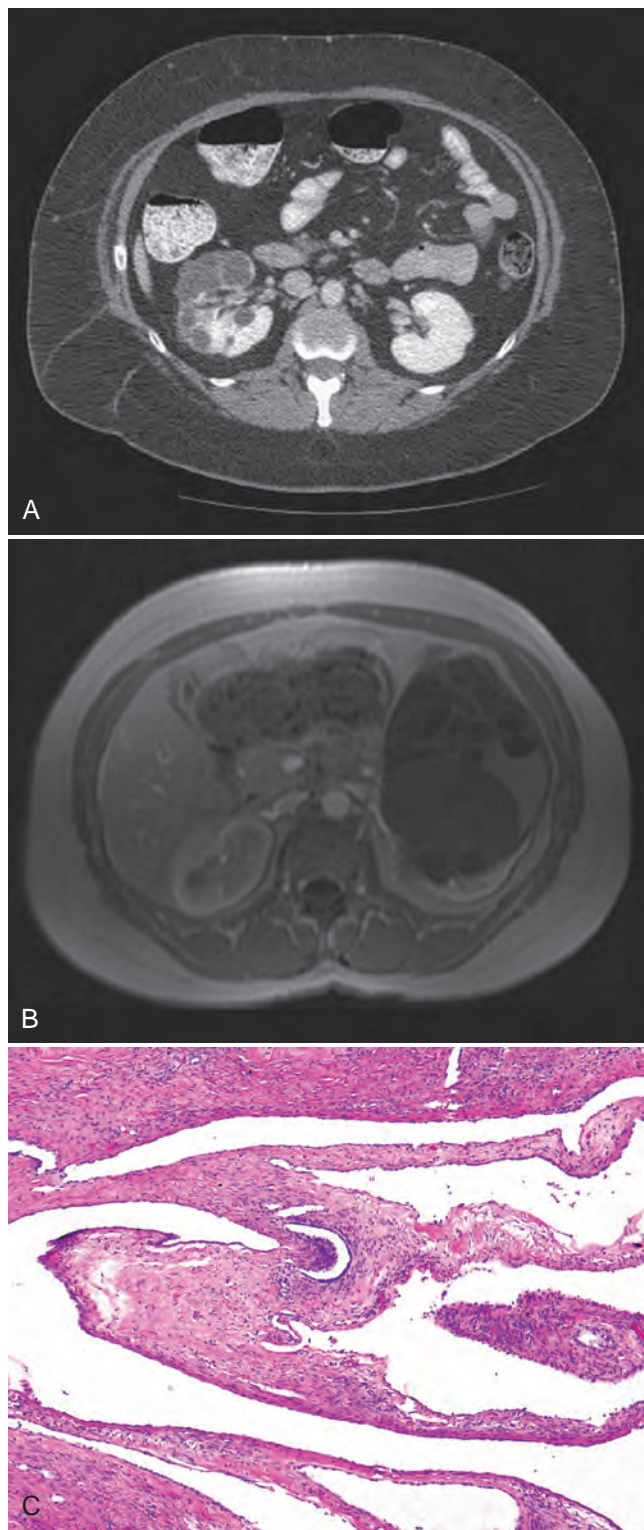


Figure 56-9. Cystic nephroma. Computed tomography (A) and magnetic resonance imaging (B) scans do not allow reliable distinction from cystic renal cell carcinoma or cystic Wilms tumor. C, The variably sized cystic spaces are lined by flattened epithelium (low magnification). (Copyright 2009, V. Margulis.)

a history of receiving estrogen replacement therapy, and the only male patient in the largest MEST series had a long history of androgen deprivation therapy for prostate cancer (Adsay et al, 2000). Presenting signs and symptoms of MEST are similar to those of cystic nephroma, with the majority detected incidentally (Adsay et al, 2000; Turbiner et al, 2007; Montironi et al, 2008).

Radiologic appearance of MEST is of a complex cystic renal mass, typically classified as Bosniak class III to IV lesions, indistinguishable from cystic RCC (Fig. 56-10A) (Adsay et al, 2000). A typical MEST has a benign clinical course, but recently a case of malignant transformation to a sarcomatoid carcinoma and several cases of local recurrence of a malignant stromal component with a dismal clinical course have been described (Adsay et al, 2000; Nakagawa et al, 2004).

Grossly, MEST appears encapsulated and ranges from 2 to 24 cm (mean 6 cm) (Adsay et al, 2000; Mai et al, 2007). Involvement of renal hilum and compression of the pelvicalyceal system is common, but gross infiltration of adjacent renal parenchyma is not seen (see Fig. 56-10B). The mesenchymal component is characterized by spindle cells showing variable degrees of smooth muscle, fibroblastic, or myofibroblastic differentiation with interspersed collagen bundles. The epithelial components vary from regular tubules to complex tubulopapillary structures with or without cystic dilatation, lined by cuboidal to flattened epithelium that may show clear cell changes and have a characteristic hobnail appearance (see Fig. 56-10C) (Adsay et al, 2000; Antic et al, 2006; Turbiner et al, 2007; Montironi et al, 2008). As in cystic nephroma, the epithelial components stain positive for cytokeratins whereas estrogen and progesterone receptor staining has been observed in the majority of the mesenchymal elements of MEST (Adsay et al, 2000).

A preoperative diagnosis of MEST should be considered in perimenopausal women receiving hormone therapy; however, because radiologic differentiation from RCC is not reliable, surgical intervention, preferably with a nephron-sparing approach, should be offered to appropriately selected patients.

KEY POINTS: CYSTIC NEPHROMA AND MIXED EPITHELIAL-STROMAL TUMOR

- These tumors are at opposite ends of the spectrum of the same biologic process with overlapping clinical, morphologic, and immunohistochemical characteristics.
- There is a female predilection, and a history of hormonal ablation therapy is noted in male patients.
- Frequent expression of estrogen and progesterone receptors in tumor tissue is reported.
- Clinical distinction from RCC or cystic Wilms tumor is not possible.
- If feasible, a nephron-sparing approach with partial nephrectomy is the preferred management strategy.

LEIOMYOMA

Leiomyomas are rare, benign tumors that may arise from smooth muscle cells anywhere along the genitourinary tract (Tamboli et al, 2000). In the kidney these tumors most commonly arise from the renal capsule, but renal pelvis and renal vein sites of origin have been reported (Wells et al, 1981; Steiner et al, 1990; O'Brien et al, 1992; Rao et al, 2001). Leiomyomas are found at autopsy with a frequency of 4.2% to 5.2%, but only a minority are discovered clinically, representing approximately 1.5% of all benign renal tumors treated surgically (Romero et al, 2005). As with other renal lesions, in the age of widespread use of CT abdominal imaging, the vast majority of leiomyomas are found incidentally (Romero et al, 2005; Derchi et al, 2008).

Renal leiomyomas have a characteristic appearance of a small exophytic renal mass with or without enhancement arising from renal capsule, but conclusive radiologic differentiation from RCC is not possible (Fig. 56-11A) (Steiner et al, 1990; Derchi et al, 2008).

Grossly, leiomyomas are firm, well encapsulated solid lesions. Histologic examination reveals intersecting fascicles of smooth muscle with no evidence of hypercellularity, pleomorphism, mitotic

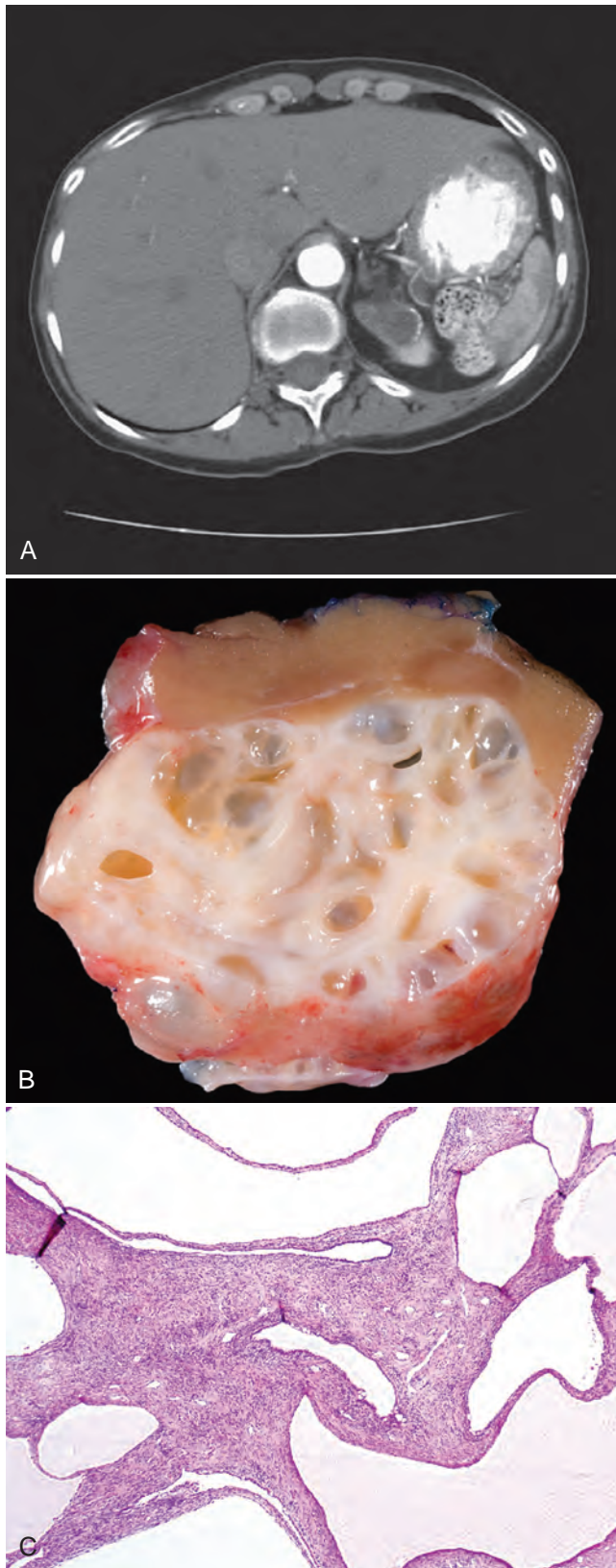


Figure 56-10. Mixed epithelial and stromal tumor. A, Computed tomography scan characteristics are not distinguishable from renal cell carcinoma. B, Gross photograph of a partial nephrectomy specimen demonstrating a well-circumscribed mass composed of variably sized cysts separated by thick white septa. C, Medium-power magnification shows cysts lined by hobnail cells and spindle cell stroma. (Copyright 2009, V. Margulis.)

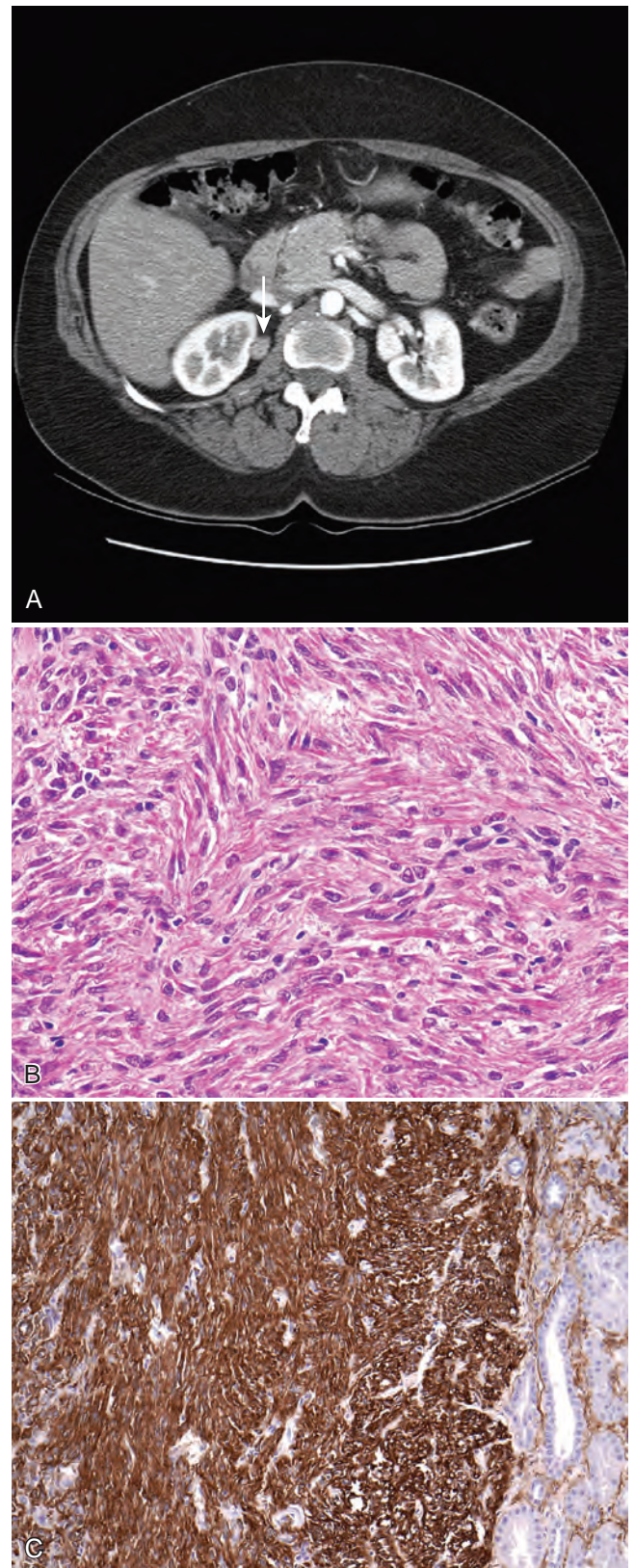


Figure 56-11. Renal leiomyoma. A, Computed tomography scan with characteristic appearance of a small renal mass arising from the renal capsule. B, Medium-power magnification shows uniform spindle cells with thin cigar-shaped nuclei, without any pleomorphism. C, Strong positive immunohistochemical staining with smooth muscle actin in the leiomyoma. Note lack of smooth-muscle actin staining in the normal renal tubules on the right. (Copyright 2009, V. Margulis.)

activity, or necrosis (see Fig. 56-11B) (Steiner et al, 1990; Tamboli et al, 2000). Immunohistochemical stains confirm the smooth muscle nature of the tumor with strong diffuse positive staining for smooth muscle markers desmin and caldesmon (see Fig. 56-11C) (Romero et al, 2005). Some leiomyomas positively stain for HMB-45, suggesting a possible link to angiomyolipoma and other PComas (Bonsib, 1996). Large lesions have traditionally been managed with radical nephrectomy, but nephron-sparing approaches should be considered for peripherally located small lesions.

KEY POINTS: LEIOMYOMA

- The characteristic appearance is of a small solid renal mass arising from the renal capsule.
- Radiologic differentiation from RCC is not possible.
- Nephron-sparing approaches are preferred when technically possible.

OTHER BENIGN RENAL TUMORS

A multitude of rare benign tumors derived from the various mesenchymal components of the kidney have been described and include multiple histiotypes, such as hemangioma, lymphangioma, juxtaglomerular cell tumor, renomedullary interstitial cell tumor, intrarenal schwannoma, and solitary fibrous tumor (Ligato et al, 1999; Tamboli et al, 2000). Current radiologic methods do not allow for conclusive differentiation of these benign tumors from malignant renal lesions, and surgical excision is often needed for pathologic confirmation.

Hemangiomas are benign vascular tumors that affect young adults with no gender predilection. These tumors are typically single and unilateral and for the most part occur close to the renal pyramids and pelvis. They do not have a capsule and they appear spongy red, with irregular vascular spaces lined by a single-cell endothelial layer (Tamboli et al, 2000). Renal hemangiomas are commonly sporadic but can also occur with syndromes such as Klippel-Trenaunay, Sturge-Weber, and systemic angiomas.

Lymphangiomas are rare benign tumors arising from the renal capsule and growing as a renal sinus mass or peripelvic mass. Some patients exhibit genetic abnormalities such as trisomy 7, monosomy X, and *VHL* abnormalities (Debiec-Rychter et al, 1990; Caduff et al, 1997). Lymphangiomas are encapsulated, diffusely cystic, with communicating cysts composed of fibrous septations lined by flat endothelium.

Juxtaglomerular cell tumor (also known as *reninoma*) is a benign tumor of the renal juxtaglomerular cell apparatus (Robertson et al, 1967; Wong et al, 2008). With fewer than 100 cases reported in the literature, women in the third and fourth decades are most commonly affected (Martin et al, 2001; Rubenstein et al, 2002; Wong et al, 2008). **Clinical presentation is dominated by hypersecretion of renin and includes hypertension and hypokalemia and associated symptoms such as polydipsia, polyuria, myalgia, and headaches** (Schonfeld et al, 1991; Rubenstein et al, 2002). Laboratory testing usually reveals elevated plasma renin activity, secondary hyperaldosteronism, hypokalemia, and a solitary renal lesion. The radiologic appearance is that of a small (<3 cm) solid hypovascular renal mass; and surgical excision, preferably sparing the remaining renal parenchyma, results in rapid decline of plasma renin levels, normalization of blood pressure, and resolution of the associated symptoms (Dunnick et al, 1983; Schonfeld et al, 1991; Tanabe et al, 2001). Histologic examination reveals sheets of polygonal to spindle-shaped cells with indistinct cell borders, abundant eosinophilic cytoplasm, and minimal atypia (Martin et al, 2001). Strong immunostaining for factor VIII and factor VIII-related antigens is characteristic and confirms derivation from endothelial cell lineage (Sanfilippo et al, 1982). Cells will also stain for renin, CD34, vimentin, and actin (Martin et al, 2001).

Although a benign clinical course is expected, one case of malignant reninoma has been documented in the literature (Duan et al, 2004).

Renomedullary interstitial cell tumors are commonly seen at autopsy (Reese and Winstanley, 1958), measure less than 5 mm in size, and are typically asymptomatic, without any effect on blood pressure. Cells are polygonal or stellate in a basophilic stroma and contain minimal collagen.

Intrarenal schwannoma is very rare, with fewer than 20 cases reported. Tumors cause nonspecific signs and symptoms, are well encapsulated, and are composed of spindle cells in a palisading format (Singer and Anders, 1996; Alvarado-Cabrero et al, 2000).

Solitary fibrous tumor is a clinically important entity, as it tends to manifest as a large mass with gross hematuria and could be mistaken for RCC or sarcoma. It is a rare tumor, reported in fewer than 50 patients to date (Khater et al, 2013). Tumors arise from the renal parenchyma, are well circumscribed, and consist of bland spindle cells and collagenous bands. Typically, staining for CD34, CD99, and BCL-2 ascertains the diagnosis of solitary fibrous tumor (Wang et al, 2001; Magro et al, 2002).

KEY POINTS: OTHER BENIGN RENAL TUMORS

- Numerous rare benign tumors derived from the various mesenchymal components of the kidney have been described.
- Radiologic differentiation from renal malignancy is not possible.
- Reninoma, a benign tumor of the renal juxtaglomerular cell apparatus, is an important but rare cause of secondary hypertension and hypokalemia.

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The complete reference list is available online at www.expertconsult.com.



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Historical Considerations

Classification

Radiographic Evaluation of Renal Masses

Renal Cell Carcinoma

Treatment of Localized Renal Cell Carcinoma

Treatment of Locally Advanced Renal Cell Carcinoma

Other Malignant Renal Tumors

HISTORICAL CONSIDERATIONS

The introduction of nephrectomy and other surgeries for renal diseases provided the clinical information and histopathologic insight that form the basis of current concepts regarding renal tumors. The first documented nephrectomy was accomplished in 1861 by Wolcott, who operated with the mistaken assumption that the tumor mass was a hepatoma. In 1867, Spiegelberg removed a kidney incidentally in the course of excising an echinococcus cyst. The first planned nephrectomy was performed by Simon in 1869 for persistent ureteral fistula, and this patient survived with cure of the fistula. One year later (1870), the first planned nephrectomy in the United States was successfully accomplished by Gilmore in Mobile, Alabama, for treatment of atrophic pyelonephritis and persistent urinary tract infection (Herr, 2008). Harris (1882) subsequently reported on 100 surgical extirpations of the kidney, a sufficient number to permit analysis of clinical, surgical, and pathologic features of renal disorders that require surgery.

With surgical intervention, tissue became available to pathologists for histologic interpretation. Unfortunately, such interpretation was not always accurate, and there were often serious professional differences of opinion. According to Carson (1928), the first accurate gross description of kidney tumors dates to 1826, with König's observations. In 1855, Robin examined solid tumors apparently arising in the kidney and concluded that renal carcinoma arose from renal tubular epithelium. This interpretation was confirmed by Waldeyer in 1867. Unfortunately, theoretical and practical considerations of renal tumors were confused by Grawitz (1883), who contended that such apparent renal tumors arose from adrenal rests within the kidney. He introduced the terminology *struma lipomatodes aberrata renis* as descriptive nomenclature for the tumors of clear cells that he believed were derived from the adrenal glands. He based his conclusions not only on the fatty content of the tumors, analogous to that seen in the adrenal glands, but also on the location of the tumors beneath the renal capsule, the approximation to the adrenal glands, the lack of similarity of the cells to uriniferous tubules, and the demonstration of amyloid similar to that seen with adrenal degeneration.

This histogenetic concept was adopted by subsequent investigators, and pathologists of the era readily embraced the idea that renal tumors truly arose from the adrenal glands. In 1894, Lubarch endorsed the idea of a suprarenal origin of renal tumors, and the term *hypernephroid tumors*, indicating origin above the kidneys, was advocated by Birch-Hirschfeld (Birch-Hirschfeld and Doederlein, 1894). This semantic and conceptual mistake led to the introduction of the term *hypernephroma*, which predominated in the literature describing parenchymal tumors of primary renal origin. Some clarification of the histopathology of renal tumors was derived from the work of Albarran and Imbert (1903), and the four-volume

contribution of Wolff (1883), written between 1883 and 1928, added further historical significance to the understanding of renal tumors (Herr, 2008).

The modern era has brought an appreciation that renal cell carcinoma (RCC) includes a number of distinct subtypes derived from the various parts of the nephron, each with a unique genetic basis and tumor biology (Rini et al, 2009; Linehan and Ricketts, 2013). Other major advances in the past several decades have included the introduction of radical nephrectomy (RN) followed by a trend toward less radical approaches, including kidney-sparing surgery and a variety of minimally invasive approaches (Robson, 1963; Novick, 2007; Volpe et al, 2011). One common theme that has persisted is that RCC remains primarily a surgical disease and, although immune-based and targeted molecular approaches can provide durable clinical responses, cure is rarely seen without complete surgical excision of RCC (Rini et al, 2009; Kroeger et al, 2014). Unfortunately, the incidence of RCC is gradually increasing and, despite a trend toward earlier detection, mortality rates remain high.

CLASSIFICATION

Renal masses can be malignant, benign, or inflammatory as classified by Barbaric (1994) (Box 57-1), or they can be classified based on radiographic appearance (simple cystic, complex cystic, solid) (Box 57-2). These classification schemes have been updated based on current knowledge about the distinct subtypes of RCC and other benign and malignant tumors of the kidney (Eble et al, 2004; Algaba et al, 2011). Malignant renal tumors include RCC, urothelium-based malignancies, sarcomas, embryonic or pediatric tumors, lymphomas, and metastases. Benign renal tumors are diverse and present unique diagnostic challenges (see Chapter 56). Inflammatory and vascular lesions must also be considered in the differential diagnosis.

RADIOGRAPHIC EVALUATION OF RENAL MASSES

Several radiographic modalities are currently available for detection and evaluation of renal masses, each with relative strengths and limitations (Kang and Chandarana, 2012). A systematic approach is necessary to ensure diligent evaluation of suspected renal masses, given the large differential diagnosis and considerable overlap between benign and malignant renal lesions (Fig. 57-1; see Box 57-2) (Simmons et al, 2007).

Although intravenous pyelography was often the first test that indicated a renal mass in the past, it has now fallen out of favor (Kang and Chandarana, 2012). The lack of sensitivity

BOX 57-1 Renal Masses Classified by Pathologic Features**MALIGNANT**

Renal cell carcinoma
 Urothelium-based cancers
 Urothelial carcinoma
 Squamous cell carcinoma
 Adenocarcinoma
 Sarcomas
 Leiomyosarcoma
 Liposarcoma
 Angiosarcoma
 Hemangiopericytoma
 Malignant fibrous histiocytoma
 Synovial sarcoma
 Osteogenic sarcoma
 Clear cell sarcoma
 Rhabdomyosarcoma
 Wilms tumor
 Primitive neuroectodermal tumor
 Carcinoid tumor
 Lymphoma/leukemia
 Metastasis
 Invasion by adjacent neoplasm

BENIGN

Cystic lesions
 Simple cyst
 Hemorrhagic cyst

BENIGN—cont'd

Solid lesions
 Angiomyolipoma
 Oncocytoma
 Renal adenoma
 Metanephric adenoma
 Cystic nephroma
 Mixed epithelial-stromal tumor
 Reninoma (juxtaglomerular cell tumor)
 Leiomyoma
 Fibroma
 Hemangioma
 Vascular lesions
 Renal artery aneurysm
 Arteriovenous malformation
 Pseudotumor

INFLAMMATORY

Abscess
 Focal pyelonephritis
 Xanthogranulomatous pyelonephritis
 Infected renal cyst
 Tuberculosis
 Rheumatic granuloma

BOX 57-2 Radiologic and Pathologic Correlates for Renal Masses**SIMPLE CYSTIC**

Benign cyst
 Parapelvic cyst
 Hydronephrosis
 Caliceal diverticulum

COMPLEX CYSTIC

Cystic RCC
 Hemorrhagic cyst
 Hyperdense cyst
 Benign complex cyst
 Cystic nephroma
 Mixed epithelial-stromal tumor
 Cystic Wilms tumor
 Infected cyst/abscess
 Hydrocalix
 Arteriovenous malformation
 Renal artery aneurysm

STRONGLY ENHANCING SOLID MASS

Clear cell RCC
 Angiomyolipoma
 Oncocytoma (occasionally)
 Papillary RCC (occasionally)
 Chromophobe RCC (occasionally)

MODERATELY ENHANCING SOLID MASS

Papillary RCC
 Chromophobe RCC
 Oncocytoma
 Other benign tumors
 Fat-poor angiomyolipoma
 Adenoma
 Metanephric adenoma
 Unifocal lymphoma
 Sarcoma
 Lobar nephronia
 Infarct

MULTIFOCAL/BILATERAL MASSES

Familial RCC
 Metastases
 Sporadic, multifocal RCC
 Angiomyolipomas (tuberous sclerosis)
 Lymphoma
 Cystic tumors (autosomal dominant polycystic kidney disease)

INFILTRATIVE MASS

Lymphoma
 High-grade urothelial carcinoma
 Sarcomatoid differentiation
 Collecting duct carcinoma
 Renal medullary carcinoma
 Xanthogranulomatous pyelonephritis
 Metastasis (occasionally)

CALCIFIED MASS

RCC
 Urothelial carcinoma
 Benign complex cyst
 Xanthogranulomatous pyelonephritis
 Renal artery aneurysm
 Concomitant nephrolithiasis

FAT-CONTAINING MASS

Angiomyolipoma
 Liposarcoma
 Lipoma

RCC, renal cell carcinoma.

Modified from Simmons MN, Herts BR, Campbell SC. Image based approaches to the diagnosis of renal masses [lesson 39]. AUA Update Series 2007;26:382–91.

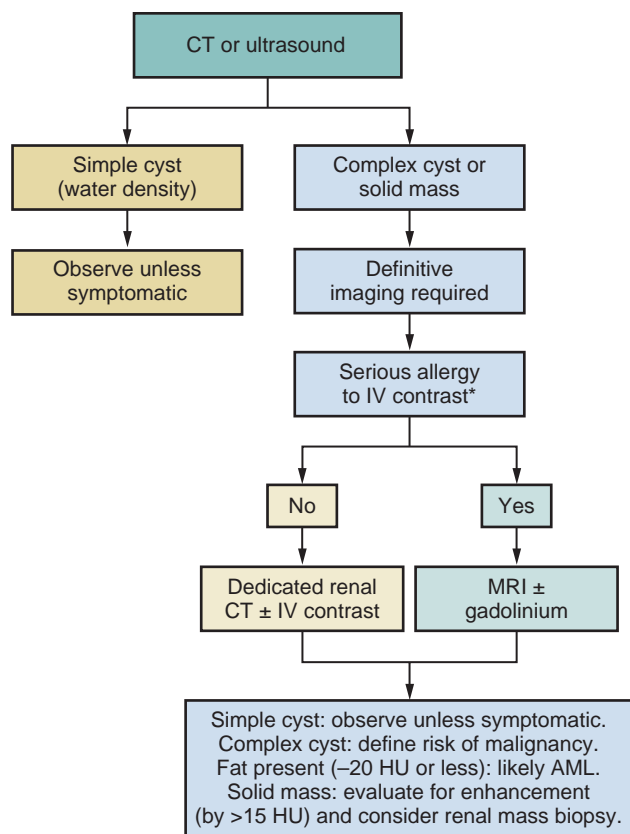


Figure 57-1. Algorithm for radiographic evaluation of renal masses. AML, angiomyolipoma; CT, computed tomography; HU, Hounsfield units; IV, intravenous; MRI, magnetic resonance imaging. *In the presence of chronic kidney disease, the risks of contrast nephropathy must also be weighed against those of nephrogenic systemic fibrosis associated with gadolinium administration.

and specificity of intravenous pyelography for the detection of parenchymal tumors is well documented. In particular, intravenous pyelography may miss small anterior or posterior lesions that do not distort the collecting system or contour of the kidney. Features suggestive of malignancy on intravenous pyelography include calcification within the mass, increased tissue density, irregularity of the margin, and distortion of the collecting system (Zagoria, 2000).

Ultrasonography is a noninvasive and relatively inexpensive modality that can differentiate cystic versus solid renal masses, and it continues to play an important role for such lesions. Strict ultrasonographic criteria for simple cysts have been defined and include a smooth cyst wall, a round or oval shape without internal echoes, and through-transmission with strong acoustic shadows posteriorly. If these criteria are met, observation is sufficient in an asymptomatic patient. In evaluating complex renal cysts, important ultrasonographic features include thickness and contour of the cyst wall, number and thickness of any septa, presence of any calcifications, density of cyst fluid, and presence of solid or nodular components. Ultrasonography is helpful in suggesting the fat content of an angiomyolipoma (AML) by its characteristic increased echogenicity (Nelson and Sanda, 2002). A renal mass that is not clearly a simple cyst by strict ultrasound criteria should be evaluated further with computed tomography (CT).

A dedicated renal CT scan remains the single most important radiographic test for delineating the nature of a renal mass. CT, with and without the administration of contrast material, is necessary to take full advantage of the contrast enhancement characteristics of highly vascular renal parenchymal tumors (Kang and Chandarana, 2012). In general, any renal mass that enhances with

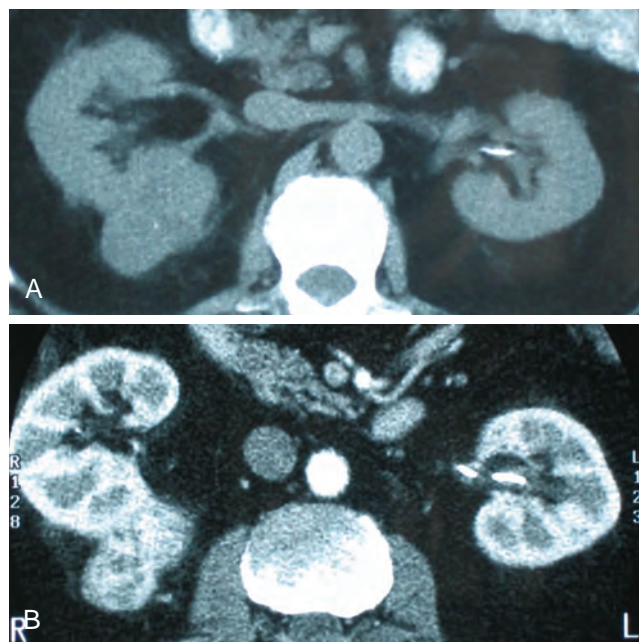


Figure 57-2. A, Computed tomography (CT) scan without administration of contrast material shows solid, right posterior renal mass. B, After administration of the contrast agent, CT scan shows that the mass enhances more than 20 HU and is thus highly suggestive of renal cell carcinoma (RCC). This mass was excised and confirmed to be a clear cell RCC. (Courtesy Dr. Terrence Demos, Maywood, IL.)

intravenous administration of contrast material on CT by more than 15 Hounsfield units (HU) should be considered an RCC until proved otherwise (Fig. 57-2). Solid masses that also have substantial areas of negative CT attenuation numbers (below -20 HU) indicative of fat are diagnostic of AML (Nelson and Sanda, 2002). In 10% to 20% of solid renal masses, CT findings are indeterminate, and additional imaging, biopsy, or surgery is needed to establish a definitive diagnosis. On occasion, CT demonstrates an enhancing renal segment that is isodense with the remainder of the kidney, suggestive of a renal pseudotumor. In the latter instance, renal mass biopsy should be considered.

Magnetic resonance imaging (MRI) is the alternate standard imaging modality for the characterization of a renal mass (Kang and Chandarana, 2012; Donat et al, 2013). Enhancement indicative of malignancy can also be assessed by MRI with intravenous gadolinium-labeled diethylenetriaminepentaacetic acid, although the assessment is qualitative rather than quantitative (Fig. 57-3). This technique is most useful in patients for whom iodinated contrast medium is contraindicated because of severe allergy. One concern with MRI with gadolinium is the uncommon but potentially serious complication of nephrogenic systemic fibrosis, which is more common in patients with chronic kidney disease (CKD) (Bach and Zhang, 2008). Current recommendations are to avoid MRI with gadolinium, particularly serial studies, in this population whenever possible, and to dialyze patients after the study if end-stage renal disease is present. MRI without contrast can be performed in patients with CKD and a renal mass, but some radiologists prefer CT with intravenous contrast and careful periprocedural hydration; in either case, decision making must be individualized. Contrast-enhanced ultrasonography using microbubbles has also shown promise for the characterization and assessment of enhancement of renal masses and may play an important role in patients with CKD in the future (Simmons et al, 2007).

Renal arteriography has a limited role in the diagnostic evaluation of renal masses and is primarily reserved for patients with concomitant renal artery disease. In equivocal cases, the presence or absence of neovascularity may help establish the diagnosis of

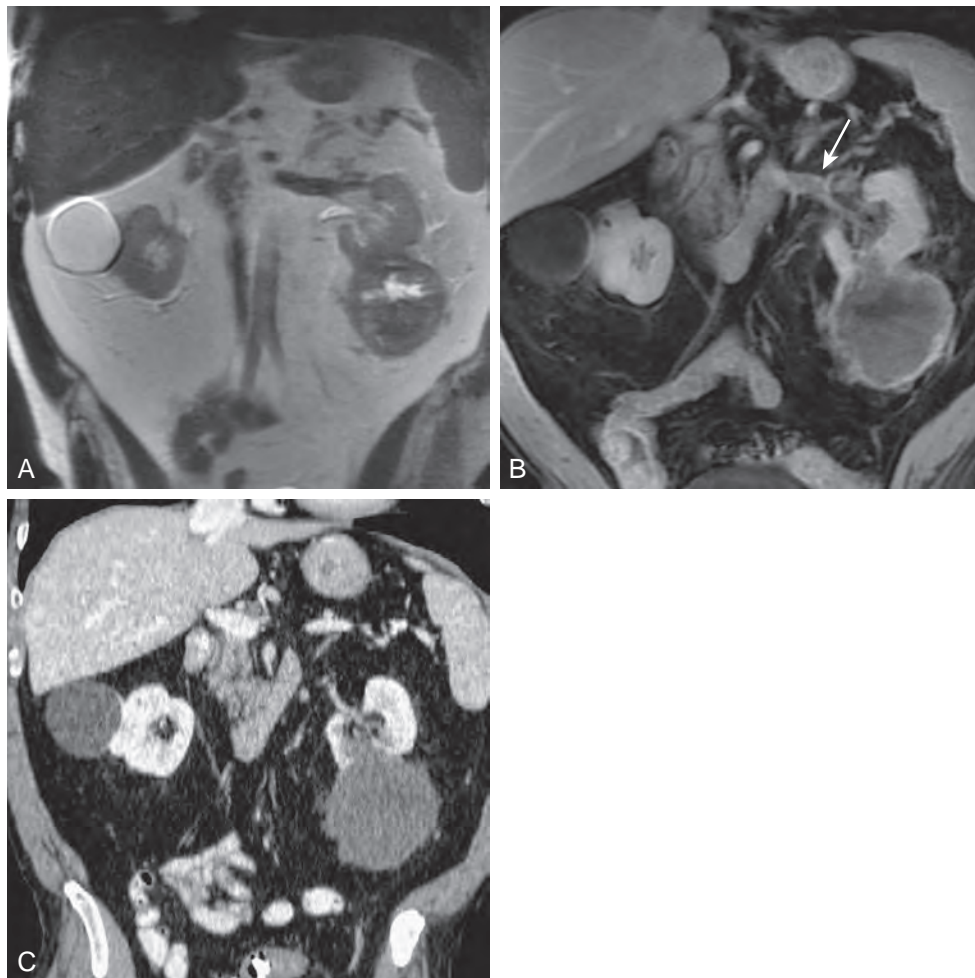


Figure 57-3. Renal cell carcinoma on pre- and postcontrast magnetic resonance image (MRI) and contrast-enhanced computed tomography (CT). **A**, Precontrast, T2-weighted MRI showing a simple cyst in the right kidney and heterogeneous 8.5 cm, lower pole tumor in the left kidney. **B**, Postcontrast, fat-saturated, T1-weighted MRI reveals further anatomic details regarding the left renal tumor, including a tumor thrombus (arrow) within the renal vein not reaching the inferior vena cava. **C**, Contrast-enhanced CT imaging (parenchymal phase) from the same patient also shows the left renal tumor. MRI was performed in this patient because of equivocal findings on the initial CT scan regarding a renal vein thrombus, which was seen clearly on both pre- and postcontrast MRI. (Courtesy Dr. Leena Mammen, Grand Rapids, MI.)

RCC. However, 20% to 25% of RCCs are angiographically indistinct, even though most of these tumors are not truly avascular and demonstrate contrast enhancement by 10 to 25 HU on CT.

For radiographically detected solid renal masses, the differential diagnosis is extensive and includes conditions such as RCC, oncocytoma, AML, urothelial carcinoma, metastasis, abscess, infarct, vascular malformation, and renal pseudotumor (see [Box 57-2](#)). The diagnosis of most of these lesions can be established on the basis of clinical presentation and characteristic radiographic features, occasionally combined with endourologic studies or renal mass biopsy ([Dyer et al, 2008](#); [Kang and Chandarana, 2012](#)). However, it is often not possible to reliably distinguish RCC from benign renal neoplasms, including oncocytoma and fat-poor AML, with current diagnostic techniques. Ten to 20 percent of small, solid, CT-enhancing renal masses with features suggestive of RCC prove to be benign after surgical excision ([Corcoran et al, 2013](#)). Although oncocytoma is a benign tumor (see Chapter 56), it can be multifocal and is occasionally associated with RCC in the same or the opposite kidney ([Licht et al, 1993](#); [Dechet et al, 1999](#); [Adamy et al, 2011](#); [Boris et al, 2011](#); [Childs et al, 2011](#)).

Renal mass biopsy is now being revisited for the evaluation of renal masses ([Lane et al, 2008](#); [Samplaski et al, 2011](#); [Volpe et al,](#)

[2012](#)). Historically the false-negative rate of renal mass biopsy was thought to be 18%, too high to justify routine use. However, most of these “false negatives” were in reality instances in which the mass could not be adequately targeted or the material obtained was insufficient for the pathologist to make a definitive determination. Review of this literature has shown that, although about 15% of renal mass biopsy specimens are nondiagnostic, the real false-negative rate is now less than 1% ([Lane et al, 2008](#)). Overall accuracy is greater than 80%. Assessment of histologic type can be facilitated by selective use of immunohistochemical stains when microscopic features are not diagnostic, but nuclear grade at biopsy does not always correlate with the final grade at nephrectomy, in part due to tumor heterogeneity ([Ficarra et al, 2011](#); [Abel et al, 2012](#)). The risks of clinically significant perinephric bleeding and pneumothorax also appear to be low (<1%), and needle track seeding is exceedingly rare when centrally located, infiltrative renal masses are excluded. Poorly differentiated urothelial carcinoma is much higher risk for needle track seeding than RCC. Given the great heterogeneity in the tumor biology of enhancing clinical T1 renal masses, renal mass biopsy is now being considered more frequently, particularly in patients who are potential candidates for a wide variety of treatment options ranging from observation to

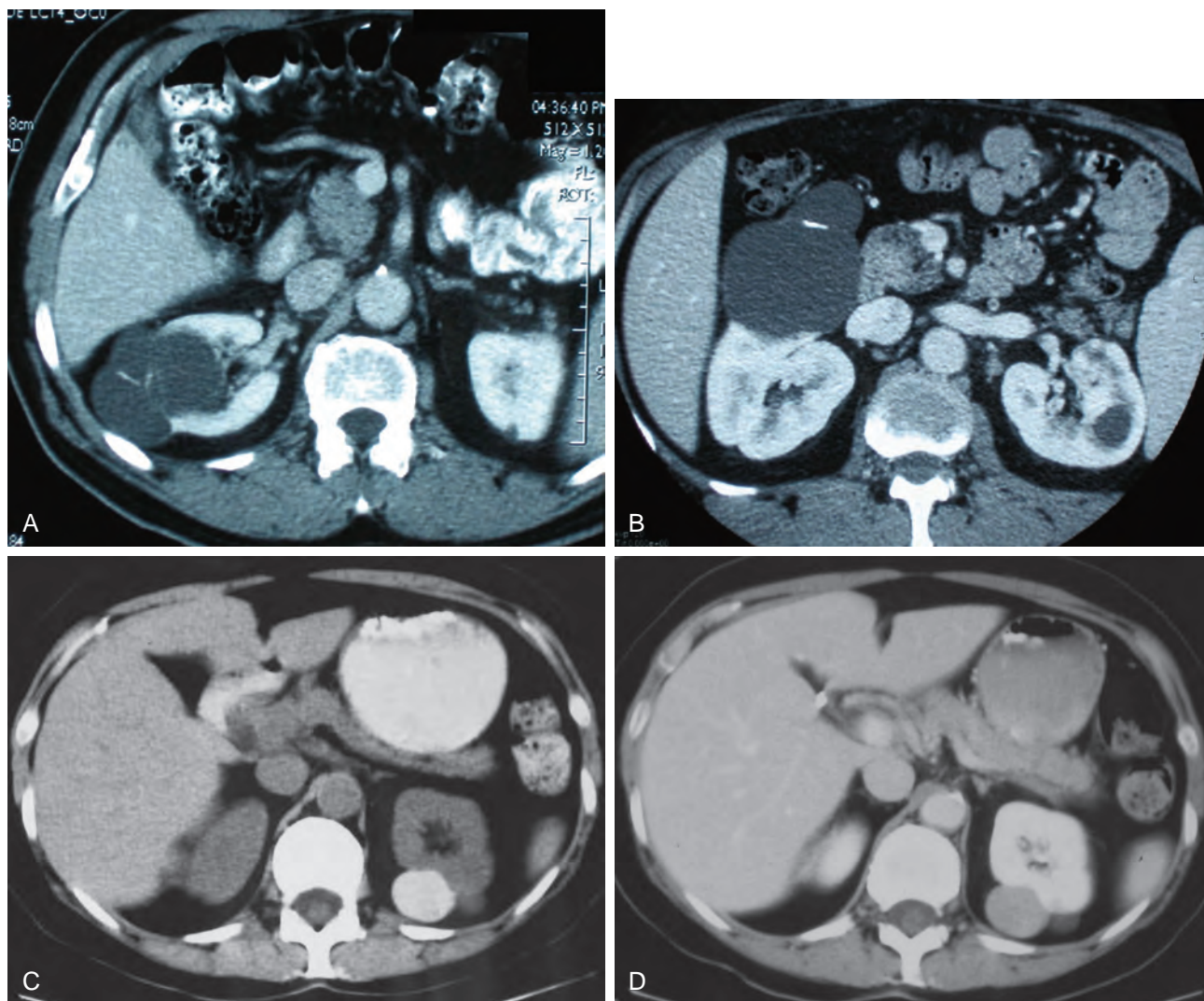


Figure 57-4. Bosniak category II renal cysts. A, Computed tomography (CT) scan shows right renal cyst with thin internal septation. B, CT scan in another patient shows relatively thin, curvilinear calcification in the septa of the wall of right renal cyst. C, CT scan without administration of contrast material shows small, smooth-walled, high-density left renal cyst. D, CT scan after administration of contrast material shows no enhancement of the cyst. This is an extreme example of a hyperdense cyst. (Courtesy Dr. Terrence Demos, Maywood, IL.)

surgical excision. Younger, healthy patients who are unwilling to accept the uncertainty associated with renal mass biopsy are still typically managed primarily based on radiographic and clinical considerations. More traditional indications for renal mass biopsy include suspicion of renal abscess or when RCC must be differentiated from metastatic malignant disease or renal lymphoma (Somani et al, 2007; Volpe et al, 2012).

Evaluation of Cystic Renal Lesions

The differentiation between benign renal cysts and cystic RCC remains one of the more common and difficult problems in renal imaging (Bosniak, 2012). When a complex renal cyst is identified, determination of its benign or malignant nature is based on evaluation of the wall of the lesion; its thickness and contour; the number, contour, and thickness of any septa; the amount, character, and location of any calcifications; the density of fluid in the lesion; the margination of the lesion; and the presence of solid components. Bosniak developed a useful classification scheme primarily based on CT imaging criteria that divides renal cystic lesions into categories that are distinct from one

another in terms of the likelihood of malignancy (Israel and Bosniak, 2005). Category I lesions are uncomplicated, simple, benign cysts of the kidney that are straightforward to diagnose on ultrasonography, CT, or MRI. These are by far the most common renal cystic lesions, and in the absence of associated symptoms, no treatment is necessary.

Category II lesions are minimally complex cysts that are generally benign but have some radiologic findings that cause concern (Fig. 57-4). These lesions include septated cysts, cysts with calcium in the wall or septum, infected cysts, and hyperdense (high-density) cysts (Israel and Bosniak, 2005). Hyperdense cysts are benign lesions that contain old, degenerated, or clotted blood; therefore, the CT attenuation of their contents is increased (>20 HU). Classic hyperdense renal cysts are small (<3 cm), round, and sharply margined and do not enhance after the administration of contrast material (see Fig. 57-4). This category has now been subdivided to differentiate category II lesions that do not require surveillance from category IIF lesions that mandate surveillance. The nuances involved in this classification are highlighted in Table 57-1. High-quality imaging, preferably CT, and considerable radiologic expertise are required to optimize the

TABLE 57-1 Classification of Complex Renal Cysts

BOSNIAK CLASSIFICATION	RADIOGRAPHIC FEATURES	RISK OF MALIGNANCY	MANAGEMENT
I	Water density Homogeneous, hairline thin wall No septa No calcification No enhancement	None	Surveillance not necessary
II	Few hairline septa in which “perceived” enhancement may be present Fine calcification or short segment of slightly thickened calcification in wall or septa No unequivocal enhancement Hyperdense lesion: ≤ 3 cm, well marginated, with no unequivocal enhancement	Minimal Minimal	Surveillance not necessary Periodic surveillance
IIF	Multiple hairline thin septa Minimal smooth wall thickening “Perceived” enhancement of wall or septae may be present Calcification may be thick or nodular, but must be without enhancement Generally well marginated No unequivocal enhancement Hyperdense lesion: >3 cm or totally intrarenal, with no enhancement	3%-5% 5%-10%	Periodic surveillance Periodic surveillance
III	“Indeterminate,” thickened irregular or smooth walls or septa in which measurable enhancement is present	50%	Surgical excision
IV	Clearly malignant lesions that can have all the criteria of category III but also contain enhancing soft-tissue components	75%-90%	Surgical excision

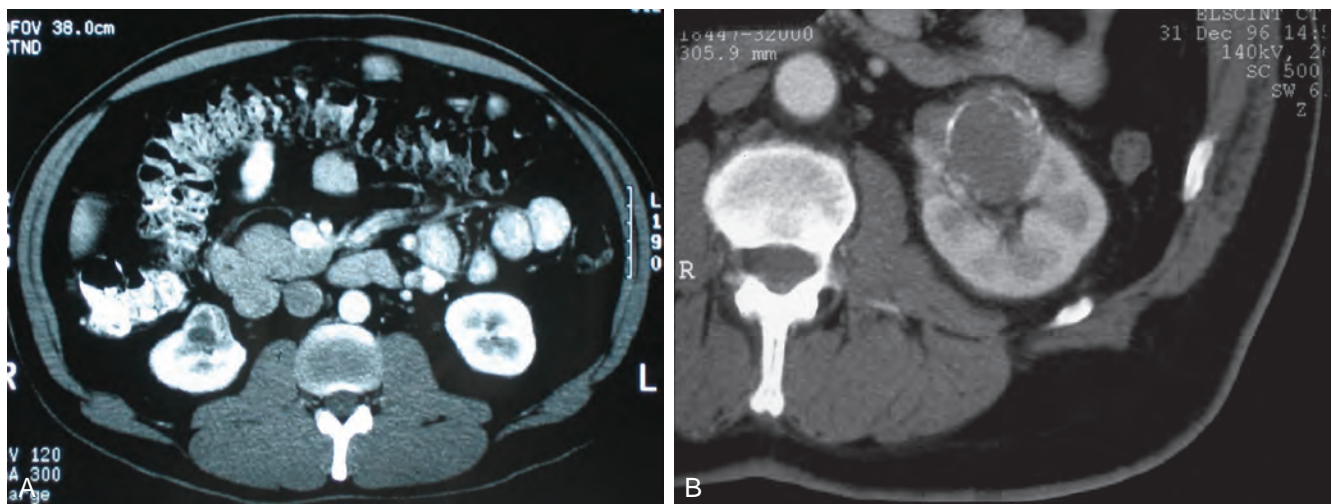


Figure 57-5. Bosniak category III cysts. A, Computed tomography (CT) scan shows complex right renal cyst with thick and irregular septa and inhomogeneous character. B, CT scan shows somewhat thick-walled, complex left renal cyst also exhibiting irregular calcification and moderate heterogeneity. (Courtesy Dr. Terrence Demos, Maywood, IL.)

characterization of complex renal cystic lesions. The risk of radiographic progression of category IIF lesions is about 15%, so these lesions should be observed with periodic renal imaging. Overall risk of malignancy in this category is 3% to 10%, although higher proportions of malignancy in surgically treated IIF lesions have been reported (O'Malley et al, 2009a; Smith et al, 2012; Graumann et al, 2013; El-Mokadem et al, 2014).

Category III lesions are more complex renal cysts that cannot be confidently distinguished from malignant neoplasms (Israel and Bosniak, 2005; Smith et al, 2012; Goenka et al, 2013). The radiographic features include thickened irregular or smooth walls or septa in which measurable enhancement can be observed (Fig. 57-5). In the absence of a mitigating factor such as renal trauma or infection, surgical exploration is usually indicated in

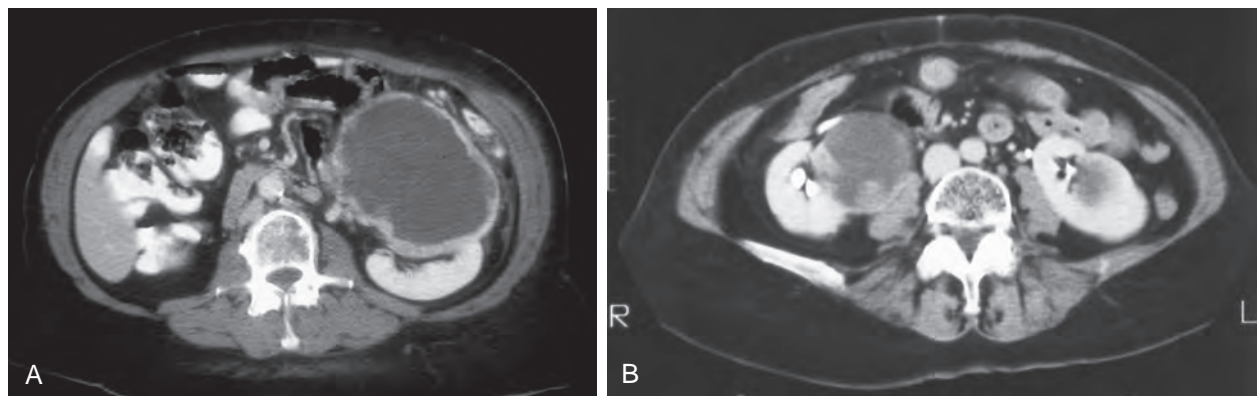


Figure 57-6. Bosniak category IV cysts. A, Computed tomography (CT) scan shows complex left renal cystic lesion with thick, enhancing walls. B, CT scan shows complex right cystic lesion with enhancing nodular areas and inhomogeneity. Both lesions proved to be renal cell carcinoma.

healthy patients. About 50% of these lesions are malignant; the remainder prove to be benign multiloculated, hemorrhagic, or densely calcified cysts (see [Box 57-2](#)). Fine-needle aspiration of complex cysts is rarely performed because of concern about sampling error and tumor cell spillage.

Category IV lesions have large cystic components; irregular, shaggy margins; and, most important, solid enhancing portions that provide a definitive diagnosis of malignancy ([Fig. 57-6](#)) ([Israel and Bosniak, 2005](#)). Category IV lesions are almost invariably cystic RCCs that, if localized, require surgical treatment.

RENAL CELL CARCINOMA

Incidence

RCC, which accounts for 2% to 3% of all adult malignant neoplasms, is the most lethal of the common urologic cancers. Five-year relative survival rates for patients diagnosed in 2002 to 2008 were 71% for kidney cancer, 78% for bladder cancer (excluding carcinoma in situ), and 99% for prostate cancer ([Siegel et al, 2013](#)). Approximately 65,000 new diagnoses of RCC are made each year in the United States, and 13,000 patients die of disease ([Siegel et al, 2013](#)). Overall, approximately 12 new cases are diagnosed per 100,000 population per year, with a male-to-female predominance of 3:2 ([Siegel et al, 2013](#)). This is primarily a disease of older adults, with typical presentation between 50 and 70 years of age ([Pantuck et al, 2001b](#); [Wallen et al, 2007](#); [Siegel et al, 2013](#)). However, diagnosis of renal cancer has increased more rapidly in those less than 40 years of age than any other age group ([Neppl et al, 2012](#)). Incidence rates are 10% to 20% higher and 5-year survival rates 5% lower in African-Americans for unknown reasons ([Lipworth et al, 2006](#); [Stafford et al, 2008](#); [Chow et al, 2013](#); [Siegel et al, 2013](#)). The majority of cases of RCC are believed to be sporadic; only 2% to 3% are proven to be familial ([Lipworth et al, 2006](#)).

The incidence of RCC has increased since the 1970s by an average of 3% to 4% per year, largely related to the more prevalent use of ultrasonography and CT for the evaluation of a variety of abdominal complaints ([Decastro and McKiernan, 2008](#); [Kümmeler et al, 2008](#)). This trend has correlated with an increased proportion of incidentally discovered and localized tumors and with improved 5-year survival rates for patients with this stage of disease ([Pantuck et al, 2001b](#); [Parsons et al, 2001](#); [Kane et al, 2008](#)). However, other factors must also be at play because a steadily increasing mortality rate from RCC per unit population has been observed in all ethnic groups and both genders since the 1980s ([Chow et al, 1999](#); [Siegel et al, 2013](#)). This rising mortality rate is particularly troubling because the proportion of advanced tumors has actually decreased ([Wallen et al, 2007](#); [Decastro and](#)

[McKiernan, 2008](#); [Siegel et al, 2013](#)). This suggests that a deleterious change in tumor biology may have occurred during the past several decades, perhaps related to tobacco use, dietary factors, or exposure to other carcinogens ([Pantuck et al, 2001b](#); [Parsons et al, 2001](#); [Hock et al, 2002](#); [Kane et al, 2008](#)).

RCC in childhood is uncommon, representing only 2.3% to 6.6% of all renal tumors in children ([Broecker, 2000](#)). Mean age at presentation in children is 8 to 9 years, and the incidence is similar in boys and in girls. Although Wilms tumor is much more common in younger children, RCC is as common as Wilms tumor during the second decade of life. RCC in children and young adults is more likely to be symptomatic, locally advanced, high grade, and of unfavorable histologic subtypes ([Sánchez-Ortiz et al, 2004b](#); [Estrada et al, 2005](#); [Cook et al, 2006](#)). TFE3 protein overexpression, which correlates with the presence of *ASPL-TFE3* and *PRCC-TFE3* gene translocation events involving the X and first chromosomes, is relatively common in children and young adults with RCC and is unique to this population ([Heimann et al, 2001](#); [Geller et al, 2008](#)). The clinical significance of TFE3 protein overexpression is not well defined, although preliminary data suggest that these tumors may show differential sensitivity to certain chemotherapeutic agents ([Heimann et al, 2001](#); [Argani et al, 2002](#); [Pérot et al, 2003](#); [Bruder et al, 2004](#)). A distinct pathologic subtype has been described in patients with TFE3 overexpression that exhibits both clear cell and papillary features ([Algaba et al, 2011](#)). Most studies suggest that stage for stage, children and young adults with RCC may respond better to surgical therapy, and a number of long-term survivors have been reported after RN and lymphadenectomy for lymph node–positive disease ([Abou El Fettouh et al, 2002](#); [Sánchez-Ortiz et al, 2004b](#); [Geller et al, 2008](#)). An aggressive surgical approach with formal lymphadenectomy has thus been recommended at the time of RN when RCC is suspected in children or young adults ([Selle et al, 2006](#); [Bosquet et al, 2008](#)).

Etiology

RCCs were traditionally thought to arise primarily from the proximal convoluted tubules, and this is probably true for the clear cell and papillary variants. However, we now know that other histologic subtypes of RCC, such as chromophobe RCC and collecting duct carcinoma, are derived from the more distal components of the nephron ([Pantuck et al, 2001a](#)). The most generally accepted environmental risk factor for RCC is tobacco exposure, although the relative associated risks have been modest, ranging from 1.4 to 2.5 compared with controls. All forms of tobacco use have been implicated, and risk increases with cumulative dose or pack-years. Relative risk is directly related to duration of smoking and begins to fall after cessation, further supporting a cause-and-effect relationship ([Parker et al, 2003b](#); [Hunt et al, 2005](#); [Ljungberg](#)

et al, 2011). Tobacco use accounts for 20% to 30% of cases of RCC in men and 10% to 20% in women.

Obesity is now accepted as another major risk factor for RCC, with an increased relative risk of 1.07 for each additional unit of body mass index (Renehan et al, 2008). The increased prevalence of obesity likely contributes to the increased incidence of RCC in Western countries, and it has been estimated that more than 40% of cases of RCC in the United States may be causally linked to obesity (Calle and Kaaks, 2004). Potential mechanisms linking obesity to RCC include increased insulin-like growth factor-1 expression, increased circulating estrogen levels, and increased arteriolar nephrosclerosis and local inflammation (Calle and Kaaks, 2004; Ljungberg et al, 2011).

Hypertension appears to be the third major etiologic factor for RCC. Diuretics and other antihypertensive medications have also been implicated, but the weight of the epidemiologic evidence suggests that it is the underlying disorder, hypertension, rather than the treatment, that increases the risk of RCC (Lipworth et al, 2006; Ljungberg et al, 2011). The proposed mechanisms are hypertension-induced renal injury and inflammation or metabolic or functional changes in the renal tubules that may increase susceptibility to carcinogens (Lipworth et al, 2006; Ljungberg et al, 2011).

Although a number of other potential etiologic factors have been identified in animal models, including viruses, lead compounds, and more than 100 chemicals such as aromatic hydrocarbons, no specific agent has been definitively established as causative in human RCC. The potential role of trichloroethylene exposure has been actively investigated; some studies showed relative risks ranging from twofold to sixfold, but others have argued that inherent biases likely account for these results (Kelsh et al, 2010). Slightly increased relative risks for RCC have been reported for workers in the metal, chemical, rubber, and printing industries and those exposed to asbestos or cadmium, but the data are not particularly convincing (Ljungberg et al, 2011).

Case-control studies have shown that RCC is more common among individuals with low socioeconomic status and urban background, although the causative factors have not been defined. The typical modern Western diet (high in fat and protein), increased intake of dairy products, and increased consumption of coffee or tea have been associated with RCC, but the relative risks have been modest, and conflicting data are available in most instances (Ljungberg et al, 2011). A family history of RCC may also be a factor; one study showed a relative risk of 2.9 for individuals with a first- or second-degree relative with RCC (Gago-Dominguez et al, 2001).

Other potential iatrogenic causes include regular usage of non-steroidal anti-inflammatory drugs, which was associated with a relative risk of 1.51, while aspirin and acetaminophen were not associated with any increased risk (Cho et al, 2011). Retroperitoneal radiation therapy, typically administered for Wilms tumor or testicular cancer, appears to be a risk factor for RCC, although the relative risks are low (Romanenko et al, 2000). An increased incidence of RCC is also observed in patients with end-stage renal disease and certain familial syndromes such as tuberous sclerosis, as discussed later (Linehan and Ricketts, 2013).

Familial Renal Cell Carcinoma and Molecular Genetics

Since the early 1990s, significant advances have been made in our understanding of the molecular genetics of RCC. Novel familial syndromes of RCC have been identified, and the tumor suppressor genes and oncogenes contributing to the development of both sporadic and familial forms of this malignancy have been characterized (Table 57-2) (Linehan and Ricketts, 2013). The impact of this new information should not be underestimated because it has fundamentally changed our perceptions about RCC. We now, more than ever, recognize the distinct nature of the various subtypes of RCC, and advances in molecular genetics have contributed to a major revision in the histologic classification of this malignant neoplasm (Zhou, 2009; Linehan and Ricketts, 2013). A direct and beneficial impact on patient management has also been achieved,

with targeted molecular agents now extending survival for patients with advanced RCC (Linehan, 2012).

Knudson and Strong recognized that familial forms of cancer might hold the key to the identification of important regulatory elements known as tumor suppressor genes (Knudson, 1971; Knudson and Strong, 1972). Their observations about the childhood tumor retinoblastoma, in which familial cases tend to be multifocal and early onset, led them to propose a two-hit theory of carcinogenesis. They hypothesized that a gene product that could suppress tumor development must be involved and that both alleles of this “tumor suppressor gene” must be mutated or inactivated for tumorigenesis to occur. Furthermore, Knudson postulated that patients with familial cancers are born with one mutant allele and that all cells in that organ or tissue are at risk, accounting for the early onset and multifocal nature of the disease. In contrast, sporadic tumors develop only if a mutation occurs in both alleles within the same cell; and because each event occurs with low frequency, most tumors develop late in life and in a unifocal manner (Knudson, 1971; Knudson and Strong, 1972). Knudson’s hypothesis has proved true for retinoblastoma and a number of other tumor types, including RCC (Linehan and Ricketts, 2013). Identification of familial cases of RCC was particularly important because it allowed linkage analysis between affected family members.

von Hippel-Lindau Disease, VHL Gene, and Genetics of Clear Cell RCC

The familial form of clear cell RCC is von Hippel-Lindau disease. This is a relatively rare autosomal dominant disorder that occurs with a frequency of 1 per 36,000 population. Major manifestations include the development of RCC, pheochromocytoma, retinal angiomas, and hemangioblastomas of the brainstem, cerebellum, or spinal cord (Table 57-3) (Kim et al, 2010; Linehan and Ricketts, 2013). All of these tumor types are highly vascular and can lead to substantial morbidity, much of which can be avoided with prompt recognition and careful, skilled management. In particular, central nervous system lesions can lead to paralysis or death and retinal lesions to blindness if they are not identified and managed in an expedient manner. Other common or important manifestations of von Hippel-Lindau disease include renal and pancreatic cysts, inner ear tumors, and papillary cystadenomas of the epididymis (Neumann and Zbar, 1997). An increased incidence of neuroendocrine tumors of the pancreas has also been reported in von Hippel-Lindau disease (Zbar et al, 1999). Penetrance for all of these traits is far from complete, and some, such as pheochromocytomas, tend to be clustered only in certain families (Table 57-4) (Neumann and Zbar, 1997). RCC develops in about 50% of patients with von Hippel-Lindau disease and is distinctive for early age at onset (often in the third, fourth, or fifth decade of life) and bilateral and multifocal involvement (Kim et al, 2010; Linehan and Ricketts, 2013). With improved management of the central nervous system manifestations of the disease, RCC has now become the most common cause of mortality in patients with von Hippel-Lindau disease. Screening for von Hippel-Lindau disease and important considerations for the management of RCC in von Hippel-Lindau disease are reviewed later in this chapter.

Early clues to the genetic elements involved in RCC development came from cytogenetics. These studies demonstrated a common loss of chromosome 3 in kidney cancer, particularly the clear cell variant, and led to intensive efforts to find a tumor suppressor gene in this region (Zbar et al, 1987; Seizinger et al, 1988). Reports by Kovacs and colleagues (1989a) and Cohen and colleagues (1979) of translocations involving chromosome 3 further implicated this chromosome as an important regulatory element. Sophisticated molecular genetic linkage studies in patients with von Hippel-Lindau disease eventually led to the identification of the VHL tumor suppressor gene (Latif et al, 1993). The role of this gene at chromosome 3p25-26 as a tumor suppressor for both sporadic and familial forms of clear cell RCC has been confirmed (Linehan

TABLE 57-2 Familial Renal Cell Carcinoma (RCC) Subtypes

SUBTYPE	GENE (CHROMOSOME)	MAJOR CLINICAL MANIFESTATIONS
von Hippel-Lindau disease	<i>VHL</i> gene (3p25-26)	Clear cell RCC Retinal angiomas Central nervous system hemangioblastomas Pheochromocytoma Other tumors
Hereditary papillary RCC	<i>c-MET</i> proto-oncogene (7q31)	Multiple, bilateral type 1 papillary RCCs
Familial leiomyomatosis and RCC	Fumarate hydratase (1q42-43)	Type 2 papillary RCC Collecting duct carcinoma Leiomyomas of skin or uterus Uterine leiomyosarcomas
Birt-Hogg-Dubé syndrome	Folliculin (17p11)	Multiple chromophobe RCC, hybrid oncocyctic tumor, oncocytomas Clear cell RCC (occasionally) Papillary RCC (occasionally) Facial fibrofolliculomas Lung cysts Spontaneous pneumothorax
Succinate dehydrogenase RCC	Succinate dehydrogenase complex subunits: <i>SDHB</i> (1p36.1-35) or <i>SDHD</i> (11q23)	Chromophobe, clear cell, type 2 papillary RCC; oncocytoma Paragangliomas (benign and malignant) Papillary thyroid carcinoma
Tuberous sclerosis	<i>TSC1</i> (9q34) or <i>TSC2</i> (16p13)	Multiple renal angiomyolipomas Clear cell RCC (occasionally) Renal cysts/polycystic kidney disease Cutaneous angiofibromas Pulmonary lymphangioleiomyomatosis
PTEN hamartoma tumor syndrome (Cowden syndrome)	<i>PTEN</i> (10q23)	Breast tumors (malignant and benign) Epithelial thyroid carcinoma Papillary RCC or other histology

Modified from Linehan WM. Molecular targeting of the *VHL* gene pathway in clear cell kidney cancer. *J Urol* 2003;170:593-4; and Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer. *Semin Cancer Biol* 2013;23:46-55.

TABLE 57-3 Manifestations of the von Hippel-Lindau Disease

ORGAN SYSTEM	LESION	INCIDENCE (%)
Eye	Retinal angiomas (benign)	49-59
Central nervous system	Hemangioblastomas (benign)	42-72
Kidney	Clear cell renal cell carcinoma Renal cysts	24-70 22-59
Adrenal gland	Pheochromocytoma	18
Pancreas	Neuroendocrine tumors (benign and malignant) Pancreatic cysts	12 benign, 2 malignant 21-72
Epididymis	Cystadenoma	10-26
Ear	Endolymphatic sac tumor	10

Modified from Neumann HP, Zbar B. Renal cysts, renal cancer and von Hippel-Lindau disease. *Kidney Int* 1997;51:16-26; Zbar B, Kaelin W, Maher E, et al. Third International Meeting on von Hippel-Lindau disease. *Cancer Res* 1999;59:2251-3; and Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer. *Semin Cancer Biol* 2013;23:46-55.

and Ricketts, 2013). The *VHL* gene consists of three exons, and it encodes a protein of 213 amino acids. A large number of common mutations or “hot spots” in the gene have been identified, and a direct correlation between genotype and phenotype has been established in some cases (McNeill et al, 2009). For instance, missense mutations (type 2 mutations) that result in a full-length but non-functional protein are commonly found in families with von

Hippel-Lindau disease that develop pheochromocytomas, whereas deletions leading to a truncated protein (type 1 mutations) are typically found in families that do not develop pheochromocytomas (see Table 57-4) (McNeill et al, 2009). The identification of this tumor suppressor gene represented a major advance in the field and required close collaboration between clinical urologic oncologists and molecular geneticists. The important historical steps in solving

TABLE 57-4 Incidence of the Major Manifestations of von Hippel-Lindau Disease by Mutation Status

DISEASE TYPE	HEMANGIOBLASTOMA	RCC	PHEOCHROMOCYTOMA	GERMLINE MUTATION TYPES
1	High	High	Low	Full gene deletions, partial gene deletions, nonsense mutations, splice acceptor mutations
2A	High	Low	High	Missense mutations (surface mutations causing only partial loss of function)
2B	High	High	High	Partial gene deletions, nonsense mutations, missense mutations (in elongin C binding area)
2C	No	No	High	Missense mutations in other specific areas

RCC, renal cell carcinoma.
Modified from Linehan WM, Ricketts CJ. The metabolic basis of kidney cancer. *Semin Cancer Biol* 2013;23:46–55.

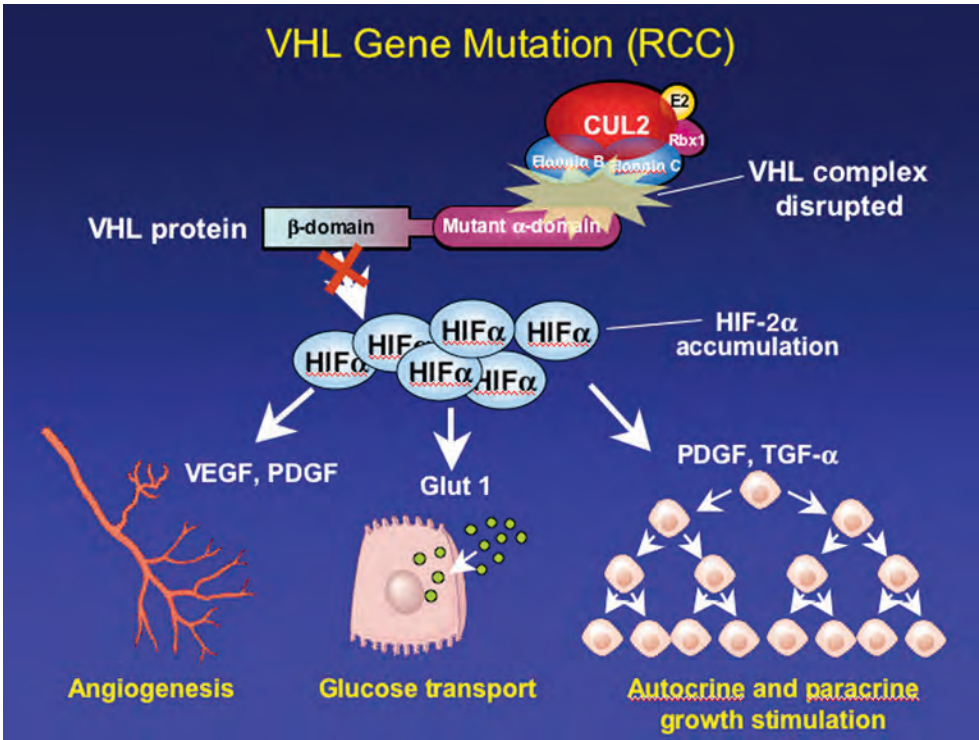


Figure 57-7. Biologic functions of the von Hippel-Lindau (VHL) protein. The wild-type VHL protein targets hypoxia-inducible factor-2α (HIF-2α) for degradation. Mutation of the VHL gene allows HIF-2α to accumulate, leading to increased expression of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), glucose transporter 1 (Glut 1), and transforming growth factor-α (TGF-α). This in turn has important implications with respect to tumor angiogenesis, metabolic activity, and autocrine and paracrine stimulation. RCC, renal cell carcinoma. (From Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol* 2003;170:2163–72.)

this challenging puzzle have been reviewed by Linehan and Zbar and their colleagues, who spearheaded this important effort (Linehan and Ricketts, 2013).

Subsequent work has focused on the function of the VHL protein and its likely mechanisms of action. The VHL protein is known to bind to elongins B and C, CUL-2, and RBX1 to form an E3 ubiquitin ligase complex, and thereby modulates the degradation of important regulatory proteins (Linehan and Ricketts, 2013; Shen and Kaelin, 2013). A critically important function of the VHL protein complex is to target the hypoxia-inducible factors 1α and 2α (HIF-1α and HIF-2α) for ubiquitin-mediated degradation, keeping the levels of HIFs low under normal conditions. The HIFs are intracellular proteins that play an important role in regulating cellular responses to hypoxia, starvation, and other stresses. Inactivation or mutation of the VHL gene leads to

accumulation of HIFs, most notably HIF-2α (Shen and Kaelin, 2013). Accumulation of HIF-2α leads to a severalfold upregulation of the expression of vascular endothelial growth factor (VEGF), the primary angiogenic growth factor in RCC, contributing to the pronounced neovascularity associated with clear cell RCC. HIF-2α also upregulates the expression of transforming growth factor-α, platelet-derived growth factor, glucose transporter 1, erythropoietin, and carbonic anhydrase IX, which also promote tumorigenesis (Fig. 57-7). Through these and other mechanisms the VHL protein appears to influence the cell cycle, cellular differentiation, tumor invasiveness, intracellular processing of important matrix molecules, and immunomodulatory status (Shen and Kaelin, 2013). VHL also upregulates HIF-1α, which to some extent counterbalances the tumorigenic effects of HIF-2α, and this remains an important area of investigation (Shen and Kaelin, 2013).

The other three most commonly mutated genes involved in the development of sporadic clear cell RCC are also located on the short arm of chromosome 3, which is affected in more than 90% of clear cell RCC cases (Cancer Genome Atlas Research Network, 2013). Unlike *VHL*, these genes, which include *PBRM1*, *BAP1*, and *SETD2*, are all involved in chromatin remodeling and histone methylation (Dalglish et al, 2010; Varela et al, 2011; Cancer Genome Atlas Research Network, 2013; Farley et al, 2013). *SETD2* mutations, for instance, have been shown to result in alterations in methylation status at multiple sites of the genome (Varela et al, 2011).

Familial Papillary Renal Cell Carcinoma and Genetics of Papillary Renal Cell Carcinoma

Several studies have documented distinct cytogenetic findings in non-clear cell histiotypes of RCC; chromosome 3 and *VHL* gene abnormalities are uncommon in these variants (Linehan and Ricketts, 2013). These observations suggested a distinct genetic basis for non-clear cell RCC. Papillary RCC, the second most common histologic subtype of RCC, is characterized by trisomy for chromosomes 7 and 17 as well as abnormalities on chromosomes 1, 12, 16, 20, and Y (Linehan and Ricketts, 2013). In 1995, Zbar and colleagues at the National Cancer Institute reported a second familial syndrome of RCC—hereditary papillary RCC (HPRCC). This followed a number of isolated case reports that suggested clustering of papillary RCCs within certain families. In Zbar and colleagues' series (1995) there were 10 families with 41 affected members (29 men and 12 women). Median age at diagnosis was 45 years, and most patients developed multifocal and bilateral papillary RCC. Type 1 papillary RCC is typically found in this syndrome rather than type 2, which is commonly seen in the hereditary leiomyomatosis and RCC syndrome. Unlike von Hippel-Lindau disease, most patients with HPRCC do not develop tumors in other organ systems (Linehan and Ricketts, 2013). Mean survival in affected individuals was only 52 years in Zbar and colleagues' series, although the number of patients dying of RCC was not defined. The development of CKD as a result of a combination of malignant replacement of the renal mass and loss of functioning nephrons secondary to various interventions is a potential contributor to morbidity and mortality in this syndrome (Ornstein et al, 2000). CT is the preferred imaging modality for patients with HPRCC because it has the greatest sensitivity for detecting the small, hypovascular lesions that are common in this syndrome.

Studies of families with HPRCC demonstrate an autosomal dominant mode of transmission, similar to all of the familial RCC syndromes, and provide insight into the molecular genetics of HPRCC as well as a subset of patients with sporadic papillary RCC (Linehan and Ricketts, 2013). Again, molecular linkage analysis in affected families played a key role in the discovery of this gene, which was localized to chromosome 7q31. However, in this case, the inciting event is activation of a proto-oncogene, rather than inactivation of a tumor suppressor gene. Missense mutations of the *c-MET* proto-oncogene at 7q31 were found to segregate with the disease, implicating it as the relevant genetic locus (Schmidt et al, 1997). The protein product of this gene is the receptor tyrosine kinase for hepatocyte growth factor, also known as scatter factor, and its activation leads to cellular proliferation and other potential tumorigenic effects (Vira et al, 2007). Most of the mutations in HPRCC have been found in the tyrosine kinase domain of *c-MET* and apparently lead to constitutive activation (Schmidt et al, 1997; Sudarshan and Linehan, 2006). Relatively early onset and multifocality in HPRCC are due to inheritance of the mutated *c-MET* gene, which places all the cells in the kidney at risk from birth, but the incomplete penetrance and variable clinical course associated with this syndrome suggest that additional genetic loci or epigenetic phenomena may modulate the phenotype (Linehan and Ricketts, 2013). Whereas tumors in HPRCC tend to be less aggressive than their sporadic counterparts, it is clear that some can metastasize and become lethal. Schmidt and colleagues reported *c-MET* mutations in 13% of

patients with sporadic papillary RCC, suggesting that this molecular defect also contributes to a subset of this disease population (Sudarshan and Linehan, 2006; Linehan and Ricketts, 2013). Small molecule inhibitors of the *c-MET* receptor are currently in development and may prove useful for the management of HPRCC and the subset of patients with sporadic RCC who harbor this mutation (Bellon et al, 2008; Pfaffenroth and Linehan, 2008; Linehan and Ricketts, 2013).

Hereditary Leiomyomatosis and Renal Cell Carcinoma

In 2001, Launonen and colleagues described a new familial renal cancer syndrome in which patients commonly develop cutaneous and uterine leiomyomas and type 2 papillary RCC (Linehan and Ricketts, 2013). Mean age at diagnosis is in the early 40s. Renal tumors in this syndrome are unusual for familial RCC in that they are often solitary and unilateral, and they are more likely to be aggressive than other forms of familial RCC. Collecting duct carcinoma, another highly malignant variant of RCC, has also been observed in this syndrome, which was named hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome.

The HLRCC locus was mapped to a region on 1q42-44, and this was later shown to be the site of the fumarate hydratase gene (Tomlinson et al, 2002; Toro et al, 2003; Alam et al, 2005; Pavlovich et al, 2005). Again, autosomal dominant inheritance was observed, and this appears to be a tumor suppressor gene rather than an oncogene. Fumarate hydratase is an essential enzyme in the Krebs cycle of oxidative metabolism. The exact mechanisms by which this leads to malignancy are still under investigation, although hypotheses about this date back to the 1920s and the proposed Warburg effect. One potential explanation is that inactivation of mitochondrial oxidative metabolism prevents the cell from efficiently creating ATP from glucose, leaving the cell with the sense that it is in an anaerobic or hypoxic environment. This in turn may lead to increased expression of growth factors and thus promote tumorigenesis.

Penetrance for RCC in HLRCC is lower than for the cutaneous and uterine manifestations, with only a minority (20%) of patients developing RCC. In contrast, almost all individuals with this syndrome will develop cutaneous leiomyomas and uterine fibroids (if female), usually manifesting at the age of 20 to 35 years. A high proportion of women have had a hysterectomy for fibroids before formal diagnosis of HLRCC (Coleman, 2008). Leiomyosarcomas of the uterus have been reported in HLRCC, although they appear to be uncommon (Sudarshan and Linehan, 2006; Pfaffenroth and Linehan, 2008). Prompt surgical management of the renal tumors is recommended in this syndrome, given their tendency toward aggressive behavior (Grubb et al, 2007; Coleman, 2008). This is in contrast to most of the other familial syndromes of RCC, for which management tends to be more conservative.

Succinate Dehydrogenase Renal Cell Carcinoma

A newly described familial RCC syndrome that shares many features with HLRCC is succinate dehydrogenase renal cell carcinoma (SDH-RCC) (Ricketts et al, 2012). Individuals with germline mutation of one of the multiple genes encoding subunits of the Krebs cycle enzyme succinate dehydrogenase, including *SDHB*, *SDHC*, and *SDHD*, are at increased risk for RCC, which can also follow an aggressive clinical course (Vanharanta et al, 2004; Ricketts et al, 2008, 2012). Another example of the Warburg effect in cancer, individuals with SDH-RCC typically present with early onset and aggressive disease, leading Linehan and colleagues to recommend wide surgical excision of these tumors when suspected (Ricketts et al, 2012).

Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé syndrome, in which patients develop cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothoraces, and

a variety of renal tumors primarily derived from the distal nephron, is named after three Canadian physicians who first described the cutaneous lesions in 1977 (Pavlovich et al, 2005; Adley et al, 2006). The renal tumors typically include chromophobe RCC, oncocytomas, and hybrid or transitional tumors that exhibit features of both of these entities (Boris et al, 2011). However, other forms of RCC, including a substantial proportion of clear cell RCC, have been observed in this syndrome (Adley et al, 2006). Overall penetrance for renal tumors is 20% to 40%, but when they occur they are often bilateral and multifocal (Pavlovich et al, 2005; Toro et al, 2008). Average age at renal tumor diagnosis is approximately 50 years. Most renal tumors in Birt-Hogg-Dubé syndrome have limited biologic aggressiveness, although metastatic behavior and lethality have been reported (Pavlovich et al, 2005).

The *BHD* gene responsible for this syndrome has been mapped to chromosome 17p12q11.2 and is now fully sequenced (Khoo et al, 2001). Recent studies have shown that the gene product is the tumor suppressor folliculin (Adley et al, 2006; Toro et al, 2008). Folliculin forms a complex of proteins that appears to interface with the mammalian target of rapamycin (mTOR) pathway, and germline mutations in this gene have been found in 88% of kindreds (Toro et al, 2008). When folliculin is inactivated, both mTOR signaling complexes 1 and 2 (mTORC1 and mTORC2) are activated, which leads to increased transcriptional activity and nuclear translocation of TFE3 (Hasumi et al, 2009; Hong et al, 2010). As with all of the other well-characterized familial RCC syndromes, an autosomal dominant pattern of inheritance is observed and genetic testing is now available (see Table 57-2).

Cowden Syndrome

Cowden syndrome is one of several syndromes that result from germline mutations of the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene, which together are termed *PTEN* hamartoma tumor syndrome. Individuals with Cowden syndrome carry a 50% lifetime risk of female breast cancer, 34% lifetime risk of RCC, and 10% lifetime risk of epithelial thyroid carcinoma (Starink et al, 1986; Mester et al, 2012). Patients with clinical features of Cowden syndrome but without *PTEN* mutations were subsequently found to have mutations in *KILLIN*, an adjacent tumor suppressor gene that was also associated with increased incidence of RCC (Bennett et al, 2010). Based on a greater than 31-fold increased risk of RCC, individuals with Cowden or Cowden-like syndrome should be screened with CT or MRI for RCC. RCC in this syndrome is most often of papillary histology, although chromophobe and clear cell histology have also been reported (Mester et al, 2012; Shuch et al, 2013b).

Tumor Biology and Clinical Implications

Resistance to Cytotoxic Therapy

RCC is a prototype of the chemorefractory tumor because it has demonstrated only limited or modest responses to traditional chemotherapeutics (Motzer and Russo, 2000; Rini et al, 2009). Study of the tumor biology of RCC provides insight into its refractory nature and, through elucidation of the VEGF and mTOR pathways, has yielded agents with clinical benefit for advanced disease (Table 57-5) (Rini et al, 2009). Expression of multidrug resistance proteins, which act as energy-dependent efflux pumps for a wide variety of hydrophobic compounds, contributes to the chemorefractory nature of advanced RCC. However, the resistance of RCC to cisplatin and other agents that are not extruded by multidrug resistance proteins suggests redundancy in resistance mechanisms. The ancillary benefit of this refractoriness has been an impetus for clinical investigations of immunomodulators and targeted molecular therapies, which have markedly altered our paradigms for the management of patients with advanced RCC (see Chapter 63).

TABLE 57-5 Tumor Biology and Clinical Implications

BIOLOGIC CHARACTERISTIC	CLINICAL IMPLICATIONS
Expression of multidrug resistance	Contributes to chemorefractory nature of RCC
Immunogenic	10%-20% response rate with interferon or IL-2 3%-5% complete response rate with high-dose IL-2 Modulation of PD-1 and other costimulatory molecules is under active investigation
Angiogenic	Vascular invasion can lead to venous tumor thrombus 20%-40% response rates with agents targeting VEGF (bevacizumab) or the VEGF receptor (sunitinib, sorafenib, pazopanib, axitinib, etc.) Prolonged recurrence-free survival and overall survival with some antiangiogenic agents
Dependence on mTOR pathway	Agents targeting mTOR prolong survival in patients with poor-risk RCC (temsirolimus) and demonstrate responses in patients failing prior targeted molecular therapies (everolimus)

IL-2, interleukin-2; mTOR, mammalian target of rapamycin; PD-1, programmed death-1; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.

Immunobiology and Immune Tolerance

Several lines of evidence demonstrate that RCC is immunogenic, and this knowledge has stimulated intensive efforts to harness the immune system to improve outcomes for patients with advanced disease (McDermott and Atkins, 2013). Tumor-infiltrating immune cells can be readily isolated from RCC, including cytotoxic T cells with specificity for antigens on tumor cells as well as dendritic cells and helper T cells, which express interleukin (IL)-1 and IL-2 and function as antigen-presenting cells. The molecular mechanisms involved in the interactions of the host immune system with the tumor have yielded insights and promising new therapies for RCC (McDermott and Atkins, 2013). New agents that activate or block downregulation of T cells, prime dendritic cells with tumor antigens, or inhibit tumor-induced immunosuppression have entered clinical trials (Brahmer et al, 2012).

Of the tumor-associated antigens for RCC, carbonic anhydrase IX (CA-IX or MN-9) has demonstrated the most specificity (Shuch et al, 2008). This antigen, which is recognized by the G250 monoclonal antibody, is expressed almost ubiquitously by clear cell RCC and only rarely by other RCC subtypes. Immunohistochemical analysis of CA-IX expression has been investigated as a diagnostic and a prognostic marker for clear cell RCC (Bui et al, 2003; Divgi et al, 2007, 2013; Leibovich et al, 2007). In normal tissues, the expression of CA-IX is restricted to the gastric mucosa, large bile ducts, and pancreas, and its expression in normal renal epithelial cells is suppressed by wild-type VHL protein. Radioactively labeled G250 has shown promise for the detection of RCC metastases by radionuclide scanning (Brouwers et al, 2003), and more recently by positron emission tomography (Divgi et al, 2007, 2013). All these potential applications of CA-IX are, at present, promising but experimental.

A second class of factors that may modulate immunotherapeutic responses in kidney cancer are factors that downregulate

effector T cells (McDermott and Atkins, 2013). Cytotoxic T-lymphocyte antigen-4 (CTLA-4) expression on the surface of activated T cells halts the immune response to the tumor. Blockade of CTLA-4, such as by the CTLA-4 antibody ipilimumab, leads to major tumor responses, but also significant potential toxicity. Similarly, the programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) pathway leads to decreased effector T-cell activity. PD-L1 (or B7-H1) is a member of a family of cell surface glycoproteins that are expressed on various immune and nonimmune cells (Thompson et al, 2007b). PD-L1 is a T-cell coregulatory molecule that is normally expressed by macrophage lineage cells, can be induced on activated T lymphocytes, and is aberrantly expressed by RCC (Thompson et al, 2007b). Tumor-associated PD-L1 impairs antigen-specific T-cell function, and blockade of this pathway has been shown to potentiate antitumoral responses in preclinical models (Thompson et al, 2004). Thompson and associates (2006) have shown that PD-L1 expression by clear cell RCC tumors correlates with aggressive pathologic features and is associated with an increased risk of disease progression, even after multivariate adjustment. PD-1 blockade has been associated with significant clinical response in phase I and II trials, and phase III testing is ongoing at present (McDermott and Atkins, 2013).

Clinical observations such as validated responses to immunotherapy, prolonged disease stabilization, and occasional spontaneous tumor regression also support the immunogenicity of RCC. The response of RCC to immunomodulators, such as IL-2, interferon- α , and tumor-infiltrating lymphocytes, argues in favor of an important role for the immune system in the tumor biology of RCC (Coppin, 2008). Indeed, high-dose IL-2 remains a treatment with curative potential for patients with metastatic RCC, with durable and complete regression of disease accomplished in a finite proportion (3% to 5%) of patients (Coppin, 2008; Amin and White, 2013). The estimated incidence of spontaneous regression of RCC is between 0.3% and 1% (Oliver et al, 1989). Most spontaneous regressions have been noted in patients with pulmonary metastases and have occurred after cytoreductive nephrectomy, but regression of primary RCC has also been reported in the absence of any form of treatment (Vogelzang et al, 1992). Remission can be durable, and this phenomenon, although rare, is thought to be real and has been assumed to be due to immune surveillance, although other possibilities cannot be excluded (Coppin, 2008).

Unfortunately, response rates of immunotherapy for RCC have been disappointing, typically ranging from 15% to 20%, despite a variety of creative treatment strategies, suggesting immune tolerance (Amin and White, 2013). A number of observations support impaired immune surveillance in RCC, and a variety of mechanisms affecting virtually all levels of regulation of the immune system have been proposed. Defects in transcriptional regulation via nuclear factor- κ B are present in the tumor-infiltrating lymphocytes and dendritic cells of 60% of RCCs (Finke et al, 2001; Thornton et al, 2004). Defective nuclear factor- κ B signaling impairs lymphocyte function, predisposes lymphocytes to apoptosis, and leads to deficient recruitment and activation of dendritic cells. Improved understanding of the mechanisms contributing to immunotolerance in RCC should suggest novel and rational strategies for improving outcomes for patients with advanced disease. For example, in addition to its anti-VEGF activity, sunitinib also appears to stimulate antitumor immunity by reversing myeloid-derived suppressor cell-mediated immunosuppression (Ko et al, 2009).

Angiogenesis and Targeted Pathways

RCC has long been recognized as one of the most vascular of cancers, as reflected by the distinctive neovascular pattern exhibited on renal angiography and robust enhancement observed on dedicated renal CT. The primary angiogenesis inducer in clear cell RCC is VEGF, which is suppressed by the wild-type VHL protein under normal conditions and is dramatically upregulated during tumor development (Gnarra et al, 1996; Iliopoulos

et al, 1996). Functional relevance of VEGF has been demonstrated by studies showing increased levels of VEGF in the serum and urine of patients with RCC. Increased expression of VEGF is also found in hypervascular tumors when compared to hypovascular tumors (Takahashi et al, 1994).

VEGF is actually a family of ligands consisting of several subtypes, most of which are regulated by HIFs and VHL and bind to one or more of the corresponding VEGF receptor (VEGFR) family members (Lane et al, 2007c). VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1) are receptor tyrosine kinases that are the target of several multi-tyrosine kinase inhibitors with activity against RCC (Carmeliet, 2005; Hicklin and Ellis, 2005). Upon binding of ligand (VEGF), key tyrosine residues along the intracellular portion of the VEGFR are phosphorylated, which leads to the binding of specific intracellular factors and activation of corresponding signal transduction pathways. Pathways known to be activated by phosphorylation of VEGFRs include the Raf-MEK-Erk and phosphatidylinositol-3-kinase/Akt/mTOR pathways that promote endothelial cell survival and proliferation (Carmeliet, 2005; Hicklin and Ellis, 2005). However, the promiscuity of the interactions between the various ligands, receptors, and downstream effectors leads to a variety of effects that may be difficult to predict in the absence of analyses investigating the complete microenvironment of the cancer or endothelial cell. This promiscuity is likely a major reason that therapeutic agents that have similar modes of action (so-called VEGF receptor tyrosine kinase inhibitors) are found to have somewhat disparate clinical or off-target effects. In contrast, bevacizumab is a monoclonal antibody that binds to VEGF and sequesters the ligand so that it cannot interact with VEGFR; its clinical activity is therefore almost certainly directly related to this activity.

Given the dependence of RCC on angiogenesis and the absence of generally effective forms of systemic therapies in the previous millennium, it is not surprising that RCC has been targeted for anti-VEGF approaches. Initial clinical trials identified several antiangiogenic compounds, such as TNP-470, roquinoximex, and thalidomide, with limited activity in patients with advanced RCC (de Wit et al, 1997; Stadler et al, 1999). More promising results were then reported for bevacizumab, a humanized anti-VEGF antibody that was associated with a significant delay in time to progression for patients with metastatic RCC compared with placebo (Yang et al, 2003). Bevacizumab therapy commonly leads to shrinkage in the total tumor burden, although in this initial experience objective partial responses were uncommon and there were no complete responses, consistent with a tumorostatic rather than a tumoricidal mechanism of action. A number of other multiple kinase inhibitors that target the VEGF pathway were subsequently tested in clinical trials and found to have substantial activity in patients with advanced RCC, culminating in approval of several such agents by the U.S. Food and Drug Administration (FDA) beginning in December 2005 and extending into the current era (see further details in Chapter 63) (Motzer et al, 2006, 2013a, 2013b; Haddad and Rini, 2012).

More recently, the Cancer Genome Atlas Research Network (2013) has provided a comprehensive molecular characterization of clear cell RCC that will serve as a solid foundation for future studies in this field. Analyses performed in this landmark study included next-generation sequencing to evaluate the whole genome of 22 tumors and whole-exome sequencing of 417 additional tumors. DNA copy number and genotype, CpG DNA methylation, messenger RNA expression, microRNA expression, and protein expression were also analyzed in these same 400-plus tumors, providing a wealth of information about the molecular features of clear cell RCC. Main findings included the identification of alterations in genes controlling cellular oxygen sensing, such as VHL, and the maintenance of chromatin states, such as PBRM1, BAP1, and SETD2. In total, 19 significantly mutated genes were identified, including the above but also genes involved in the PI3K/AKT pathway (Dalgleish et al, 2010). Mutation of the H3K36 methyltransferase SETD2 was notable in that it is associated with widespread DNA hypomethylation, and complex integrative analyses suggested that mutations involving the SWI/SNF chromatin

remodeling complex (*PBRM1*, *ARID1A*, *SMARCA4*) could have broad effects on other signaling pathways. Overall, the analyses provided strong evidence for a metabolic shift in aggressive cancers, with downregulation of genes involved in the tricarboxylic acid (TCA) cycle, upregulation of pentose phosphate and glutamine transporter genes, decreased AMPK and PTEN protein levels, and increased acetyl coenzyme A carboxylase protein. **The recurring theme of metabolic remodeling in clear cell RCC suggests multiple new windows into future targets for disease treatment.**

Other Signal Transduction and Cell Cycle Regulation Pathways

Aberrant activation of additional signal transduction pathways in RCC may also contribute to altered cell cycle kinetics, and these pathways represent excellent targets for therapeutic

intervention. One such regulatory pathway in RCC is the mTOR pathway, which interfaces with Akt (protein kinase B) and the *PTEN* tumor suppressor gene (Hudes, 2009; Barthélémy et al, 2013). Expression of mTOR is upregulated by various growth factors or by mutation or loss of *PTEN*. Through complex pathways involving a variety of intermediaries, the mTOR pathway leads to increased expression of HIF-1 and other growth-promoting and potentially tumorigenic sequelae. Inhibition of mTOR with temsirolimus (Torisel) has yielded prolonged survival in patients with poor-risk, metastatic RCC, and everolimus (Afinitor) has shown efficacy for patients who have failed tyrosine kinase inhibitors, confirming the clinical relevance of the mTOR pathway (Hudes et al, 2007; Motzer et al, 2008). Both of these mTOR inhibitors are now also approved by the FDA. Other potential factors involved in RCC pathogenesis, including the *c-MET* proto-oncogene, the insulin-like growth factor axis, telomerase, apoptotic factors, and extracellular matrix proteins, are reviewed in Box 57-3.

BOX 57-3 Tumor Biology: Other Signal Transduction and Cell Cycle Regulation Pathways

A wide array of cellular factors has been shown to be dysregulated in the serum, urine, and/or tumors of patients with RCC. None of these associations, however, has been sufficiently validated to be used in routine clinical practice. For example, increased telomerase activity, which has been found in 56% to 93% of RCCs, may affect the cell cycle by maintaining telomere length (Mehle et al, 1994; Yoshida et al, 1998). Progressive telomere loss occurs each time a normal cell divides and eventually leads to growth inhibition and cellular senescence (Mekhail et al, 2003). Dysregulation of factors involved in apoptosis, or programmed cell death, has also been reported in RCC and may contribute to tumor viability and treatment failure (Gobé et al, 2002; Rajandram et al, 2012; Sejima et al, 2012). Insulin-like growth factor receptor expression has also been correlated with decreased survival in patients with RCC (Parker et al, 2003a).

Proliferative index, as defined by proliferating cell nuclear antigen or Ki-67 staining, has correlated with pathologic parameters and clinical outcomes in RCC, suggesting that regulation of the cell cycle plays an important role in the tumor biology of RCC (Bui et al, 2004; Tollefson et al, 2007). **Increased expression of transforming growth factor- α and its receptor tyrosine kinase, the epidermal growth factor receptor (EGFR), have been reported in RCC** and may contribute to tumorigenesis by promoting cell proliferation or transformation through an autocrine mechanism. The functional relevance of EGFR in the development of RCC has also been suggested by preclinical studies testing the efficacy of the C225 monoclonal antibody, which neutralizes EGFR and blocks tumor growth and metastasis. Unfortunately, phase II clinical trials using agents that target EGFR, including erlotinib (Tarceva), gefitinib (Iressa), panitumumab (Vectibix), and lapatinib (Tykerb), demonstrated a lack of substantial activity in patients with advanced RCC (Rini, 2010). Based on these disappointing results, agents targeting the EGFR pathway have fallen out of favor, although selective treatment of patients who overexpress EGFR may still be a consideration in the future.

The hepatocyte growth factor and its receptor, the *c-MET* proto-oncogene, may also contribute to the pathogenesis of RCC (Giubellino et al, 2009; Gibney et al, 2013; Harshman and Choueiri, 2013). The role of activating mutations of the *c-MET* proto-oncogene in the etiology of hereditary papillary RCC has already been discussed, but data suggest that upregulated expression of this ligand may occur in most of the histologic subtypes of RCC (Giubellino et al, 2009; Harshman and Choueiri, 2013). Hepatocyte

growth factor is expressed by proximal tubular cells in the normal kidney, where it is involved in branching tubulogenesis of the developing kidney and regeneration after renal injury. In vitro, hepatocyte growth factor has mitogenic and morphogenic effects on renal epithelial cells. Increased serum levels of hepatocyte growth factor have also been reported in most patients with RCC, independent of histologic subtype, and activation of the receptor by phosphorylation at two sites is associated with cancer progression, making *c-Met* a potential therapeutic target for RCC (Gibney et al, 2013). Taken together, these data suggest that hepatocyte growth factor and its receptor may play an important role in the tumor biology of RCC, although constitutive activation of the receptor, which may be the most potent mechanism, appears to be primarily limited to familial papillary RCC.

PROTEASES, ADHESION, AND THE EXTRACELLULAR MATRIX

Interactions among cancer cells, adjacent cells, and the surrounding matrix can strongly influence their pathogenic potential (Jonasch et al, 2012). Altered intracellular processing and secretion of fibronectin and other matrix proteins is found in RCC, representing one consequence of *VHL* gene mutation (Ohh et al, 1998). This fundamental defect most likely has important effects on tumor biology, given the important role of the matrix in regulating cellular differentiation and tumor invasiveness and metastasis. Increased expression of proteases, such as plasmin and the matrix metalloproteinases, has correlated with reduced survival in RCC and may also contribute to the aggressive behavior of RCC (Jonasch et al, 2012). Downregulation of E-cadherin and cadherin-6, which mediate adhesion between cancer cells, is well documented in RCC and has correlated with poor outcomes in most studies (Russell and Ohh, 2007). Aberrant regulation of the catenin family, the cytoplasmic proteins that bind cadherins and mediate their effects on the cytoskeleton, has also been observed in RCC, and a correlation with compromised survival has been reported (Banumathy and Cairns, 2010).

Other studies have defined the adhesion molecules that facilitate interactions between tumor cells and endothelial cells in RCC (Banumathy and Cairns, 2010). Sialyl-Lewis^x/endothelial leukocyte adhesion molecule-1 and very late antigen-4/vascular cell adhesion molecule-1 interactions regulate this process, which presumably influences the ability of tumor cells to move into or out of the vascular system during the metastatic cascade (Steinbach et al, 1996; Ohba et al, 2005).

Pathology

Most RCCs are round to ovoid and circumscribed by a pseudo-capsule of compressed parenchyma and fibrous tissue rather than a true histologic capsule. Unlike upper tract urothelial carcinomas, most RCCs are not grossly infiltrative, with the notable exception of collecting duct carcinoma and sarcomatoid variants. Tumor size has averaged between 4 and 8 cm in most series but can vary from a few millimeters to large enough to fill the entire abdomen. Tumors smaller than 3 cm were previously classified as benign adenomas, but some small tumors have been associated with metastases (Nguyen and Gill, 2009), and most pathologists agree that, with the exception of oncocytomas and some small (<5-mm) low-grade papillary adenomas, there are no reliable histologic or ultrastructural criteria to differentiate benign from malignant renal epithelial tumors (see Chapter 56). When they are bivalved, RCCs consist of yellow, tan, or brown tumor interspersed with fibrotic, necrotic, or hemorrhagic areas; few are uniform in gross appearance. Cystic degeneration is found in 10% to 25% of RCCs and appears to be associated with a better prognosis compared with purely solid RCC (Webster et al, 2007; Jhaveri et al, 2013). Calcification can be stippled or plaquelike and is found in 10% to 20% of RCCs.

Nuclear features can be highly variable. Grading has been based primarily on nuclear size and shape and the presence or absence of prominent nucleoli. Fuhrman’s system (Table 57-6) is an independent prognostic factor for RCC generally and for clear cell RCC in particular (Fuhrman et al, 1982). Recent evidence suggests that Fuhrman grade is also a significant predictor of outcome for papillary RCC (Klatte et al, 2010a; Sukov et al, 2012), but features other than nuclear characteristics may form the basis of a preferred scheme for chromophobe RCC (Delahunt et al, 2007; Finley et al, 2011; Cheville et al, 2012).

Aggressive local behavior is not uncommon with RCC and can be expressed in a variety of ways. Frank invasion and perforation of the renal capsule, renal sinus, or collecting system are found in approximately 20% of cases, although displacement of these structures is a more common finding. Further spread to involve adjacent organs or the abdominal wall is often precluded by the Gerota fascia, although some high-grade RCCs are able to overcome this natural barrier. One unique feature of RCC is its predilection for involvement of the venous system, which is found in 10% of RCCs, more often than in any other tumor type (Skinner et al, 1972; Scheff et al, 1978). This is most commonly manifested in the form of a contiguous tumor thrombus that can extend into the inferior vena cava (IVC) as high as the right atrium. Many such tumor thrombi are highly vascularized by arterial blood flow (Novick et al, 1990), and some directly invade the wall of the renal vein or vena cava, which correlates with compromised prognosis (Skinner et al, 1972; Scheff et al, 1978; Zini et al, 2008).

Most sporadic RCCs are unilateral and unifocal. Bilateral involvement can be synchronous or asynchronous and is found in 2% to 4% of sporadic RCCs, although it is considerably more common in patients with familial forms of RCC, such as von Hippel-Lindau disease. Multicentricity, which is found in 10% to 20% of cases, is more common in association with papillary histology and familial RCC (Mukamel et al, 1988; Cheng et al, 1991; Krambeck et al, 2008). Satellite lesions are often small and

difficult to identify by preoperative imaging, intraoperative ultrasonography, or visual inspection; they appear to be the main factor contributing to local recurrence after partial nephrectomy (Mukamel et al, 1988). Microsatellite analysis suggests a clonal origin for most multifocal RCC within the same kidney (Junker et al, 2002), but tumor in the contralateral kidney is likely to be an independent growth if it is synchronous or a metastasis if it is asynchronous (Kito et al, 2002). Molecular analyses, such as gene expression profiling, may help to determine whether an asynchronous tumor is a second primary tumor or a metastasis (Lane et al, 2009a). Most recently, comprehensive sequencing of multiple biopsy specimens obtained from primary and metastatic tumors in the same patient has revealed significant intratumor heterogeneity (Gerlinger et al, 2012). These studies suggest that analysis of single biopsy samples may underestimate this inherent heterogeneity and prevent discernment of “driver” mutations from “passenger” mutations, presenting significant challenges to personalized medicine and biomarker development.

All RCCs are, by definition, adenocarcinomas, derived from renal tubular epithelial cells (Zhou, 2009) (Table 57-7). Most RCCs share ultrastructural features, such as surface microvilli and complex intracellular junctions, with normal proximal tubular cells and are believed to be derived from this region of the nephron (Kim and Kim, 2002; Axelson and Johansson, 2013). Two aggressive subtypes of RCC, renal medullary carcinoma and collecting duct carcinoma, appear to be derived from more distal elements of the nephron (Störkel et al, 1997; Zambrano et al, 1999; Abern et al, 2012).

Since the early 1990s the histologic classification of RCC has undergone several major revisions (see Table 57-7) (Zambrano et al, 1999; Zhou, 2009; Algaba et al, 2011). Traditionally, RCC was divided into four histologic subtypes: clear cell, granular cell, tubulopapillary, and sarcomatoid. On the basis of advances in the molecular genetics of RCC and a more discerning interpretation of histologic and ultrastructural features, a newer classification scheme was proposed by Kovacs (1993). This classification system was approved by an international consensus workshop of clinicians and researchers in the field (Weiss et al, 1995; Störkel et al, 1997; Zambrano et al, 1999). In this system, granular cell tumors were reclassified into other categories based on distinct histopathologic features, chromophobe RCC was recognized as a new RCC subtype, and sarcomatoid features were categorized as variants of other histologic subtypes rather than a distinct tumor type. Current practice is to identify the primary histologic subtype and comment on the presence and extent of sarcomatoid differentiation rather than to separate these tumors into a distinct category, although the prognostic implications have not changed (Cheville et al, 2004; Algaba et al, 2011). Depending on well-defined histologic and ultrastructural criteria, granular cell tumors were reclassified as papillary RCC or as eosinophilic variants of chromophobe RCC or combined with clear cell RCC. Another important development was the identification of renal medullary carcinoma that is common in young African-Americans with sickle cell trait (Davis et al, 1995; Abern et al, 2012). With additional advances in ancillary pathologic studies, including electron microscopy, immunohistochemistry, molecular genetics, and cytogenetics, several additional unique subtypes of RCC have been identified since implementation of the 1993 classification system. Based on these findings, an updated classification of malignant epithelial tumors of the kidney was

TABLE 57-6 Fuhrman’s Classification System for Nuclear Grade in Renal Cell Carcinoma

GRADE	NUCLEAR SIZE	NUCLEAR OUTLINE	NUCLEOLI
1	10 μm	Round, uniform	Absent or inconspicuous
2	15 μm	Irregular	Small (visible at 400× magnification)
3	20 μm	Irregular	Prominent
4	≥20 μm	Bizarre, often multilobed	Prominent, heavy chromatin clumps present

TABLE 57-7 Pathologic Subtypes of Renal Cell Carcinoma (RCC)

HISTOLOGY*	FAMILIAL FORM AND GENETIC FACTORS	GROSS CHARACTERISTICS	MICROSCOPIC PATHOLOGIC CHARACTERISTICS	OTHER CHARACTERISTICS
Clear cell RCC (70%-80%)	von Hippel-Lindau disease <i>VHL</i> gene (3p25-26) mutation or hypermethylation Chromosome 3p deletions Also, loss of chromosome 8p, 9p, 14q; gain of chromosome 5q	Well-circumscribed, lobulated, golden yellow tumor Necrosis and hemorrhage common Venous involvement also common Cystic degeneration	Hypervascular tumor Nests or sheets of clear cells with delicate vascular network IHC†: LMWCKs,‡ vimentin, EMA, CA-IX	Originates from proximal tubule Aggressive behavior more common Tumor shrinkage common with targeted molecular therapy May respond to immunotherapy
Multilocular cystic clear cell RCC (uncommon)	Identical to clear cell RCC	Well-circumscribed mass of small and large cysts	Cysts lined by single layer of grade 1 clear cells No expansive nodules of tumor cells	Almost uniformly benign clinical behavior
Papillary RCC (10%-15%)	Type 1: HPRCC syndrome Activation of <i>c-MET</i> oncogene (7q31-34) by mutation common in HPRCC but uncommon (~10%) in sporadic cases Trisomy of chromosome 7 and 17; loss of Y Type 2: HLRCC syndrome Fumarate hydratase gene (1q42-43) mutation in HLRCC	Fleshy tumor with fibrous pseudocapsule Necrosis and hemorrhage are common	Hypovascular tumor Papillary structures with single layer of cells around fibrovascular cores Type 1: basophilic cells with low-grade nuclei Type 2: eosinophilic cells with high-grade nuclei IHC: LMWCKs, CK7 (type 1 > type 2), AMACR	Originates from proximal tubule Commonly multicentric Common in ARCD Type 1: good prognosis Type 2: worse prognosis
Chromophobe RCC (3%-5%)	Birt-Hogg-Dubé syndrome Folliculin gene mutation (17p11) Loss of multiple chromosomes (1, 2, 6, 10, 13, 17, 21, Y)	Well-circumscribed, homogeneous Tan or light brown cut surface	“Plant cells” with pale cytoplasm, perinuclear clearing or “halo,” nuclear “raisins,” and prominent cell borders Positive Hale’s colloidal iron staining IHC: diffuse CK7	Originates from intercalated cells of collecting duct Generally good prognosis, although sarcomatoid variant associated with poor prognosis
Collecting duct carcinoma (<1%)	Unknown Multiple chromosomal losses	Firm, centrally located tumor with infiltrative borders Light gray to tan-white	Complex, highly infiltrative cords within inflamed (desmoplastic) stroma High-grade nuclei, mitoses	Originates from collecting duct Poor prognosis May respond to chemotherapy
Renal medullary carcinoma (rare)	Associated with sickle cell trait	Infiltrative, gray-white Extensive hemorrhage and necrosis	Poorly differentiated cells with lacelike appearance Inflammatory infiltrate	Originates from collecting duct Dismal prognosis
Unclassified RCC (1%-3%)	Unknown	Varied	Varied	Origin not defined Generally poor prognosis
RCC associated with Xp11.2 translocations/ <i>TFE3</i> gene fusions (rare)	Various mutations involving chromosome Xp11.2 resulting in <i>TFE3</i> gene fusion	Well-circumscribed, tan-yellow tumor	Variable; often clear cells with papillary architecture IHC: nuclear <i>TFE3</i>	Occurs in children and young adults; 40% of pediatric RCC t(X;17) presents with advanced stage and follows indolent course t(X;1) can recur with late lymph node metastases

Continued

TABLE 57-7 Pathologic Subtypes of Renal Cell Carcinoma (RCC)—cont'd

HISTOLOGY*	FAMILIAL FORM AND GENETIC FACTORS	GROSS CHARACTERISTICS	MICROSCOPIC PATHOLOGIC CHARACTERISTICS	OTHER CHARACTERISTICS
Post-neuroblastoma RCC (rare)	Unknown	Well circumscribed	Oncocytic or clear cells with solid and papillary architecture	Occurs exclusively in children with prior neuroblastoma
Mucinous tubular and spindle cell carcinoma (rare)	Unknown	Well-circumscribed, tan-white-pink tumors centered in medulla	Mixture of tubules and spindle-shaped epithelial cells; mucin background	Favorable prognosis

*Sarcomatoid variants of all of these subtypes have been described and are associated with compromised prognosis.

†Immunohistochemistry using these markers can help to differentiate between RCC subtypes.

‡Cytokeratin (CK): low-molecular-weight cytokeratins (LMWCKs).

AMACR, alpha-methylacyl-coenzyme A racemase; ARCD, acquired renal cystic disease; CA-IX, carbonic anhydrase IX; CK7, cytokeratin 7; EMA, epithelial membrane antigen; HLRCC, hereditary leiomyomatosis and RCC; HPRCC, hereditary papillary RCC; IHC, immunohistochemistry; RCC, renal cell carcinoma.

Modified from Eble JN, Sauter G, Epstein JI, et al. Pathology and genetics of tumours of the urinary system and male genital organs. 3rd ed. WHO classification of tumours, vol. 7. Lyon (France): IARC Press; 2004; and Srigley JR, Delahunt B, Eble JN, et al. ISUP Renal Tumor Panel. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am J Surg Pathol 2013;37:1469–89.

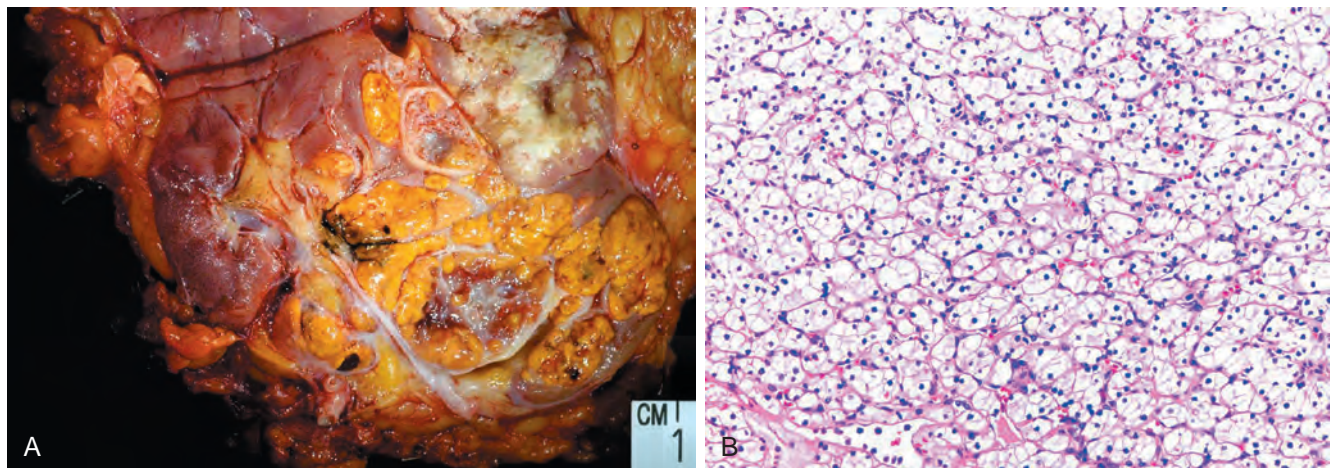


Figure 57-8. A, Clear cell renal cell carcinoma (RCC) with typical golden yellow color. B, Low-power view of typical microscopic appearance of a low-grade clear cell RCC demonstrating a delicate vascular network interspersed within homogeneous nests of cells with clear cytoplasm. (Courtesy Dr. Ming Zhou, Cleveland, OH.)

presented by the World Health Organization in 2004 and remains current at this time (see Table 57-7) (Eble et al, 2004).

The World Health Organization classification reflects current understanding of RCC not as a single malignant neoplasm but rather as a group comprising several different tumor subtypes, each with a distinct genetic basis and unique clinical features. Important changes include the addition of several RCC subtypes with distinct pathologic and clinical features that were previously grouped within “conventional” or unclassified RCC. One example of this is RCC associated with Xp11.2 translocations/*TFE3* gene fusions, which has microscopic features of both clear cell and papillary RCC and occurs primarily in children and young adults (Argani et al, 2001; Camparo et al, 2008; Geller et al, 2008). Another is mucinous tubular and spindle cell carcinoma, which is indolent in almost all instances (Hes et al, 2002; Ferlicot et al, 2005; Fine et al, 2006). Sophisticated gene expression profiling and proteomic analyses support the individuality of each of these tumor subtypes and hold great promise for differentiating additional subtypes in the future (Yang et al, 2006; Jonasch et al, 2012). This is clearly a field in evolution, with changes stimulated by basic science advances and astute clinical observation.

Clear Cell Renal Cell Carcinoma

Clear cell RCC accounts for 70% to 80% of all RCCs, representing the garden variety of RCC formerly known as “conventional” RCC (Störkel et al, 1997; Deng and Melamed, 2012). These tumors are typically yellow when they are bivalved and are highly vascular, containing a network of delicate vascular sinusoids interspersed between sheets or acini of tumor cells (Fig. 57-8). On microscopic examination, clear cell RCC can include clear cell, granular cell, or mixed types. Clear cells are typically round or polygonal with abundant cytoplasm containing glycogen, cholesterol, cholesterol esters, and phospholipids, all of which are readily extracted by the solvents used in routine histologic preparations, contributing to the clear appearance of the tumor cells (Farrow, 1997). However, granular cells, which have eosinophilic cytoplasm and abundant mitochondria, can predominate. Three to five percent of clear cell RCCs demonstrate sarcomatoid features, and clear cell RCC is more likely to exhibit venous tumor extension than any other subtype of RCC (Rabbani et al, 2004). In general, patients with clear cell RCC have a worse prognosis compared with papillary or chromophobe RCC, even after stratification for stage and grade (Cheville

et al, 2003; Deng and Melamed, 2012). Chromosome 3 alterations occur in more than 90% of clear cell RCCs, leading to mutation or inactivation of the *VHL*, *PBRM1*, *SETD2*, or *BAP1* genes, which are all present on this portion of the genome (Cancer Genome Atlas Research Network, 2013; Linehan and Ricketts, 2013). The familial form of clear cell RCC, the von Hippel-Lindau syndrome, in which the *VHL* tumor suppressor gene is inactivated, has already been reviewed.

Papillary Renal Cell Carcinoma

Papillary RCC, which was also designated chromophilic RCC in previous classification schemes, is the second most common histologic subtype (Sukov et al, 2012). It represents 10% to 15% of all RCCs, with several features that distinguish it from clear cell RCC. On microscopic examination, most tumors in this category consist of basophilic or eosinophilic cells arranged in papillary or tubular configuration (Fig. 57-9). Gross features of papillary RCC include beige to white color, spherical boundary, and frequent hemorrhage, which may mimic cystic components radiologically. One unique feature of papillary RCC is its tendency toward multicentricity, which approaches 40% in many series and occurs more commonly in patients with end-stage renal failure and acquired renal cystic disease (Deng and Melamed, 2012).

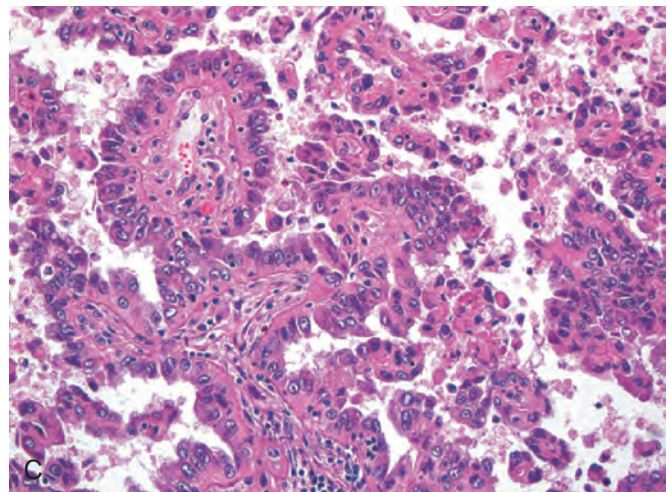
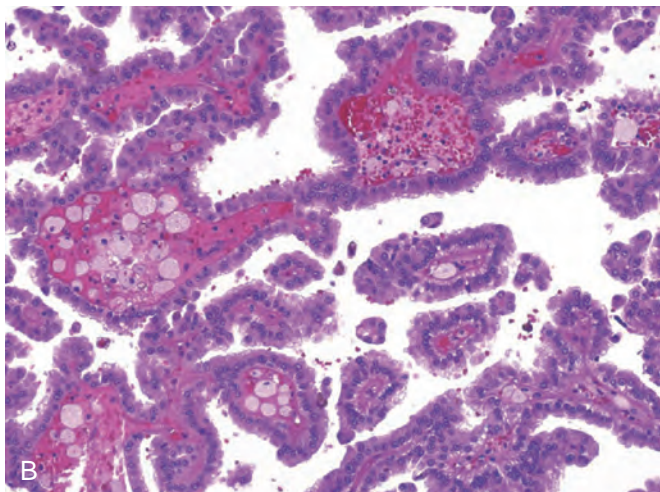
Two distinct variants of papillary RCC have been described by characteristic cytogenetics, immunostaining profiles, and gene expression profiling (see Fig. 57-9B and C) (Störkel et al, 1997; Eble et al, 2004; Yang et al, 2005). Type 1 papillary RCC, the more common form, consists of basophilic cells with scant cytoplasm; type 2 papillary RCC includes potentially more aggressive variants with eosinophilic cells and abundant granular cytoplasm (Pignot et al, 2007). The two subtypes of papillary RCC

correspond with two familial RCC syndromes: HPRCC syndrome (type 1) and HLRCC syndrome (type 2). Although mounting molecular and genetic evidence indicate that these two subtypes appear to represent distinct entities, subclassification of papillary RCC into type 1 and type 2 is not routinely practiced within the community of genitourinary pathologists at present, and grade may be of greater prognostic significance (Yang et al, 2005; Klatte et al, 2010a, 2010b). The cytogenetic abnormalities associated with the more common type 1 papillary RCC are characteristic and include trisomy of chromosomes 7 and 17 and loss of the Y chromosome (Kovacs et al, 1989b). Other common findings include gain of chromosomes 12, 16, and 20 and loss of heterozygosity on chromosome 14 (Deng and Melamed, 2012). *VHL* mutations are rare in papillary RCC, confirming distinct genetic pathways to tumorigenesis (Kenck et al, 1996). Papillary RCC is more likely to be hypovascular, perhaps owing to the lack of *VHL* mutations that regulate VEGF, the primary proangiogenic molecule in RCC (Blath et al, 1976). As discussed earlier, activating mutations of the *c-MET* proto-oncogene located on chromosome 7 appears to be common and pathogenic in hereditary papillary RCC (Schmidt et al, 1997). Indeed, this genetic defect is now being targeted for novel treatment approaches with use of small molecule inhibitors (Jonasch et al, 2012; Harshman and Choueiri, 2013).

The prognosis associated with papillary RCC remains controversial. Five-year cancer-specific survival rates for patients with papillary RCC traditionally ranged from 86% to 92%, in part because papillary RCCs often presented with low stage and grade (Mancilla-Jimenez et al, 1976; Deng and Melamed, 2012). However, more recent studies that have utilized immunohistochemistry and cytogenetics to define papillary histology contain an increased proportion of high-grade and advanced tumors that, while still in the minority, can prove to be lethal. In part this is due to the



Figure 57-9. A, Papillary renal cell carcinoma (RCC) often presents with multiple small, mildly enhancing renal tumors as demonstrated on this computed tomography image. B, Microscopic appearance of type 1 papillary RCC demonstrating basophilic cells with scant cytoplasm and low-grade nuclei. C, In contrast, type 2 papillary RCC consists of eosinophilic cells with abundant granular cytoplasm and high-grade nuclei. (Courtesy Dr. Ming Zhou, Cleveland, OH.)



ineffectiveness of current systemic therapies against papillary RCC (Lager et al, 1995; Renshaw, 2002; Margulis et al, 2008; Amin and White, 2013). At present, most authors believe that papillary RCC, and type 1 papillary RCC in particular, carries a better prognosis than clear cell RCC when compared grade for grade and stage for stage (Deng and Melamed, 2012).

Papillary adenomas are small (≤ 5 -mm) tumors that resemble papillary RCC under the microscope, are often well encapsulated and low grade, and are commonly found at autopsy (Algaba et al, 2011). These lesions, which possess many of the same genetic alterations found in larger papillary RCCs, are benign neoplasms (see Chapter 56).

Chromophobe Renal Cell Carcinoma

Chromophobe RCC, first described by Thoenes and colleagues in 1985, is a distinctive histologic subtype of RCC that represents 5% of all RCCs and appears to be derived from the cortical portion of the collecting duct (Algaba et al, 2011). The tumor cells typically exhibit a relatively transparent cytoplasm with a fine reticular pattern that has been described as a “plant cell” appearance (Fig. 57-10). Most chromophobe RCCs are resistant to the pigment used during typical hematoxylin and eosin staining, but eosinophilic variants constitute about 30% of cases (Thoenes et al, 1988;

Nagashima, 2000). In either case, a perinuclear clearing or “halo” is typically found and electron microscopic findings consist of numerous 150- to 300-nm microvesicles, which are the single most distinctive and defining feature of chromophobe cell carcinoma. These microvesicles characteristically stain positive for Hale colloidal iron, indicating the presence of a mucopolysaccharide unique to chromophobe RCC (see Fig. 57-10). Immunohistochemistry typically reveals positive staining for pan-cytokeratin, epithelial membrane antigen, and parvalbumin and negative for vimentin and CD10 (Algaba et al, 2011). Genetic analysis typically reveals massive chromosomal losses, most frequently the whole chromosomes 1, 2, 6, 10, 13, 17, 21, and Y, and flow cytometric analysis has demonstrated hypodiploid DNA content in most cases (Bugert et al, 1997). Chromophobe RCC is commonly seen in the Birt-Hogg-Dubé syndrome, but most cases are sporadic (Linehan and Ricketts, 2013).

Most studies of the clinical behavior of chromophobe RCC suggest a better prognosis for localized chromophobe RCC than for clear cell RCC but a poor outcome in the subset of patients with sarcomatoid features or metastatic disease (Renshaw et al, 1996; Klatte et al, 2008). Most early reports suggested a tendency to remain localized despite growth to large size, as well as a predominance of low-grade disease (Thoenes et al, 1988). Subsequent reports have verified that chromophobe RCC generally presents at

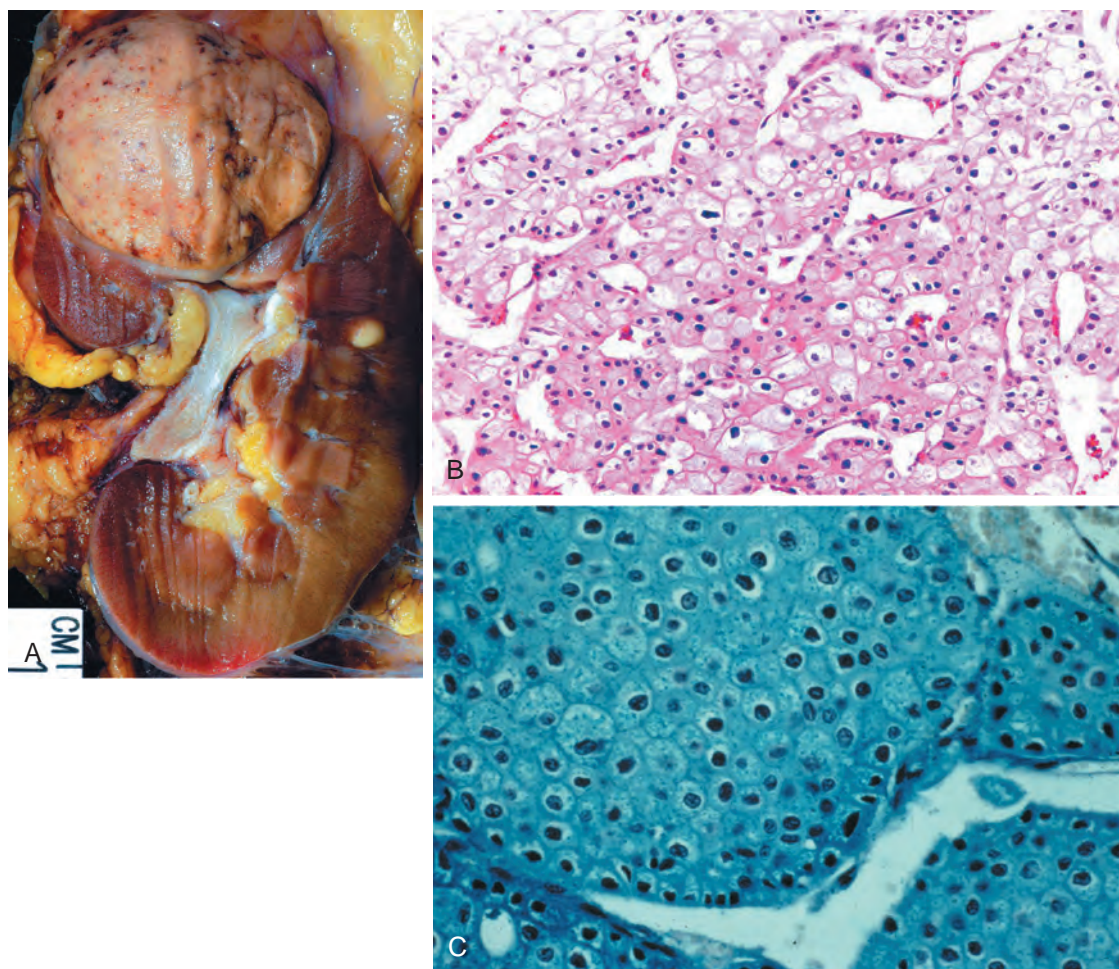


Figure 57-10. A, Chromophobe renal cell carcinoma (RCC) typically appears as a well-circumscribed, homogeneous, tan tumor. B, Chromophobe RCC with admixture of classic (chromophobic) and eosinophilic cells. Characteristic features include distinct cytoplasmic borders, perinuclear “halos,” and nuclear “raisins.” The classic variant is notable for its “plant cell” appearance. C, Chromophobe RCC stains positive for Hale colloidal iron and demonstrates multiple microvesicles on analysis by electron microscopy. (Courtesy Dr. Ming Zhou, Cleveland, OH.)

an earlier stage, with more than 90% of patients remaining cancer free for 5 or more years after treatment (Klatte et al, 2008; Deng and Melamed, 2012). Limited data exist regarding treatment of metastatic chromophobe RCC, with most evidence suggesting limited activity of tyrosine kinase inhibitors and mTOR inhibitors in this population (Tannir et al, 2012; Kroeger et al, 2013). Clearly, further clinical evaluation will be required to identify the most effective therapeutic agents for patients with metastatic, non-clear cell RCC.

Collecting Duct Carcinoma

Carcinoma of the collecting ducts of Bellini is a relatively rare subtype of RCC, accounting for less than 1% of all RCCs (Algaba et al, 2011). Collecting duct carcinoma often presents earlier in life and with advanced stage (Tokuda et al, 2006; Karakiewicz et al, 2007c; Wright et al, 2009). Small collecting duct carcinomas can arise in a medullary pyramid, but most are large, infiltrative masses and extension into the cortex is common (Pickhardt et al, 2001; Deng and Melamed, 2012). On microscopic examination, these tumors consist of an admixture of dilated tubules and papillary structures typically lined by a single layer of cuboidal cells, often creating a cobblestone appearance. Deletions on chromosome 1q and monosomy of chromosomes 6, 8, 11, 18, 21, and Y have been reported, but the number of tumors analyzed thus far has been limited (Fuzesi et al, 1992; Steiner et al, 1996; Polascik et al, 2002). The characteristic immunophenotype of these tumors is coexpression of low- and high-molecular-weight cytokeratins and *Ulex europaeus* agglutinin-1 reactivity (Rumpelt et al, 1991). Positivity for E-cadherin and c-KIT help to distinguish this entity from aggressive papillary RCC, but this staining profile can also be present in urothelial carcinoma and differential diagnosis often requires careful examination of multiple sections (Kobayashi et al, 2008). Most reported cases of collecting duct carcinoma have been high grade, advanced stage, and unresponsive to conventional therapies (Tokuda et al, 2006; Karakiewicz et al, 2007c; Wright et al, 2009). Reflecting the fact that collecting duct carcinoma may share features in common with urothelial carcinoma, some patients with advanced collecting duct carcinoma have responded to cisplatin- or gemcitabine-based chemotherapy (Milowsky et al, 2002; Peyromaure et al, 2003; Oudard et al, 2007; Kobayashi et al, 2008; Dason et al, 2013). Other centers have used sunitinib and other VEGF inhibitors for this aggressive cancer with only marginal benefit (Ansari et al, 2009; Tannir et al, 2012).

Renal Medullary Carcinoma

Renal medullary carcinoma is a subtype of RCC that occurs almost exclusively in patients with the sickle cell trait. It is typically diagnosed in young African-Americans, often in the third decade of life, and many cases are both locally advanced and metastatic at the time of diagnosis (Davis et al, 1995; Swartz et al, 2002). Most patients do not respond to therapy and succumb to their disease in a few to several months. Mean survival in Davis and coworkers' series (1995), which consisted of 34 patients, was only 15 weeks. This tumor shares many histologic features with collecting duct carcinoma, and some consider it a subtype of collecting duct carcinoma or at least a closely related tumor (Swartz et al, 2002; Algaba et al, 2011). Renal medullary carcinoma is thought to arise from the calyceal epithelium near the renal papillae but is often highly infiltrative. The site of origin (renal papillae) and association with sickle cell trait suggest that a relatively hypoxic environment may contribute to tumorigenesis.

Sarcomatoid Differentiation

Sarcomatoid differentiation is found in 1% to 5% of RCCs, most commonly in association with clear cell RCC or chromophobe RCC, but variants of most other subtypes of RCC have been described (Ro et al, 1987; Shuch et al, 2012a). Most authors now believe that sarcomatoid lesions represent poorly differentiated regions of other histologic subtypes of RCC rather than independently derived tumors (DeLong et al, 1993; Eble et al, 2004). A thorough search for epithelial-derived malignant components is almost always fruitful; it is rare to find a truly pure sarcomatoid renal mass. For this reason, this entity is no longer recognized as a distinct histologic subtype of RCC (Eble et al, 2004). Sarcomatoid differentiation is characterized by spindle cell histology, positive staining for vimentin, infiltrative growth pattern, aggressive local and metastatic behavior, and poor prognosis (Fig. 57-11). Invasion of adjacent organs is common, and median survival has been less than 1 year in most series (Ro et al, 1987; Molina et al, 2011). Multimodal approaches should be considered if performance status allows, based on the extremely poor prognosis with surgery alone and selected reports demonstrating modest response rates in patients receiving IL-2-based immunotherapy, chemotherapy, or targeted molecular therapy after surgery (Shuch et al, 2012b).

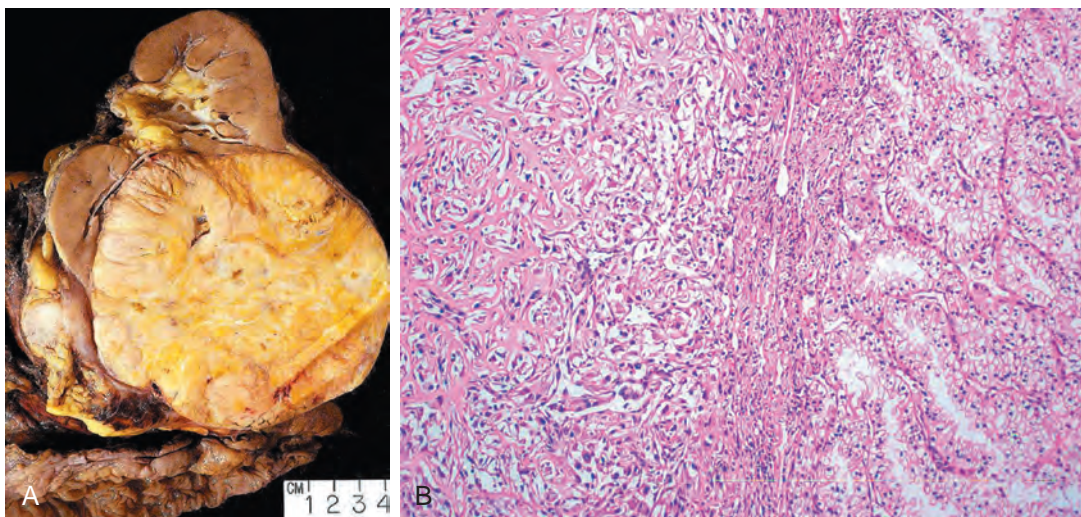


Figure 57-11. A, Clear cell renal cell carcinoma (RCC) with sarcomatoid differentiation demonstrating extension into the perinephric fat. B, High-grade RCC with typical spindle cell appearance on the left indicating a component of sarcomatoid differentiation. (Courtesy Dr. Ming Zhou, Cleveland, OH.)

Unclassified Renal Cell Carcinoma

Unclassified RCC represents a small minority of cases (1% to 5%) of presumed RCC with features that remain indeterminate even after careful analysis (Crispen et al, 2010). Most are poorly differentiated and are associated with a highly aggressive biologic behavior and a particularly poor prognosis (Amin et al, 2002; Karakiewicz et al, 2007b). Included within this “catch-all” category are RCCs with extensive sarcomatoid differentiation and no discernible epithelial component. Advances in molecular diagnostics, such as gene expression profiling, may enable further classification of unusual tumors that previously would have fallen into this category and identify candidate pathways for targeted molecular therapeutics (Yang et al, 2006; Jonasch et al, 2012). Low-grade tumors such as hybrid oncocytic tumors, which are indeterminate between chromophobe RCC and oncocytoma, should not be placed into this category, which denotes poor prognosis.

Clinical Presentation

Because of the sequestered location of the kidney within the retroperitoneum, many renal masses remain asymptomatic and nonpalpable until they are locally advanced. With the more pervasive use of noninvasive imaging for the evaluation of a variety of nonspecific symptom complexes, more than 60% of RCCs are now detected incidentally (Silverman et al, 2008). Several studies have shown that such tumors are more likely to be confined to the kidney, and a positive impact on survival has been reported, although the contributions of lead and length time biases have not been defined (Tsui et al, 2000; Decastro and McKiernan, 2008; Kane et al, 2008).

Symptoms associated with RCC can be due to local tumor growth, hemorrhage, paraneoplastic syndromes, or metastatic disease (Box 57-4). Flank pain is usually due to hemorrhage and clot obstruction, although it can also occur with locally advanced or invasive disease. The classic triad of flank pain, gross hematuria, and palpable abdominal mass is now rarely found. This is fortunate because this constellation of findings almost always denotes advanced disease, and some refer to it as the “too late triad.” Before the advent of ultrasonography and CT, most patients with RCC presented with one or more of these signs or symptoms, and many were incurable. Other indicators of advanced disease include constitutional symptoms such as weight loss, fever, and night sweats, and physical examination findings such as palpable cervical lymphadenopathy, nonreducing varicocele, and bilateral lower extremity edema resulting from venous involvement. A minority of patients present with symptoms directly related to

metastatic disease, such as bone pain or persistent cough. A less common but important presentation of RCC is that of spontaneous perirenal hemorrhage, in which the underlying mass may be obscured. Zhang and colleagues (2002) have shown that more than 50% of patients with perirenal hematoma of unclear etiology have an occult renal tumor, most often AML or RCC. Repeat CT a few months later will often provide a definitive diagnosis.

Paraneoplastic syndromes are found in 10% to 20% of patients with RCC, and few tumors are associated with the diversity of such syndromes (Table 57-8). In fact, RCC was previously referred to as the internist’s tumor because of the predominance of systemic rather than local manifestations. Now, a more appropriate name would be the radiologist’s tumor, given the frequency of incidental detection (Parsons et al, 2001; Decastro and McKiernan, 2008). Nevertheless, it is still important to evaluate for paraneoplastic phenomena because they can be a source of major morbidity and can affect clinical decision making. Under normal circumstances, the kidney produces 1,25-dihydroxycholecalciferol, renin, erythropoietin, and various prostaglandins, all of which are tightly regulated to maintain homeostasis. RCC may produce these substances in pathologic amounts, and it may also elaborate a variety of other physiologically important factors, such as parathyroid hormone–like peptides, lupus-type anticoagulant, human chorionic gonadotropin, insulin, and various cytokines and inflammatory mediators. These substances are believed to be responsible for the development of constitutional symptoms such as weight loss, anemia, and paraneoplastic syndromes.

Hypercalcemia has been reported in up to 13% of patients with RCC and can be due to either paraneoplastic phenomena or osteolytic metastatic involvement of the bone (Klatte et al, 2007c; Schwarzbarg and Michaelson, 2009). The production of parathyroid hormone–like peptides is the most common paraneoplastic etiology, although tumor-derived 1,25-dihydroxycholecalciferol and prostaglandins may contribute in a minority of cases (Klatte et al, 2007c; Pepper et al, 2007). The expression of parathyroid hormone–like peptides is suppressed by the wild-type VHL protein, and these peptides may act as potent growth factors for RCC (Massfelder et al, 2004). The signs and symptoms of hypercalcemia are often nonspecific and include nausea, anorexia, fatigue, and decreased deep tendon reflexes. Medical management predominates and includes vigorous hydration followed by diuresis with furosemide and the selective use of bisphosphonates, corticosteroids, or calcitonin. Bisphosphonate therapy is now established as a standard of care for patients with hypercalcemia of malignancy, as long as renal function is adequate (Schwarzbarg and Michaelson, 2009). Zoledronic acid, 4 mg intravenously every 4 weeks, appears to be particularly effective in patients with RCC but must be withheld in the presence of renal insufficiency (Lipton et al, 2003; Schwarzbarg and Michaelson,

BOX 57-4 Clinical Presentation of Renal Cell Carcinoma

- Incidental presentation
- Symptoms of localized disease:
 - Hematuria
 - Flank pain
 - Abdominal mass
 - Perirenal hematoma
- Obstruction of the inferior vena cava:
 - Bilateral lower extremity edema
 - Nonreducing or right-sided varicocele
- Symptoms of systemic disease:
 - Persistent cough
 - Bone pain
 - Cervical lymphadenopathy
 - Constitutional symptoms
 - Weight loss/fever/malaise
 - Paraneoplastic syndromes

TABLE 57-8 Incidence of Systemic Syndromes Associated with Renal Cell Carcinoma

SYNDROME	%
Elevated erythrocyte sedimentation rate	55.6
Hypertension	37.5
Anemia	36.3
Cachexia, weight loss	34.5
Pyrexia	17.2
Abnormal liver function	14.4
Hypercalcemia	4.9
Polycythemia	3.5
Neuromyopathy	3.2
Amyloidosis	2.0

Modified from Gold PJ, Fefer A, Thompson JA. Paraneoplastic manifestations of renal cell carcinoma. Semin Urol Oncol 1996;14:216–22.

2009). Indomethacin has also proved useful in a minority of cases (Gold et al, 1996). More definitive management includes nephrectomy and occasional metastasectomy, depending on the clinical circumstances. Hypercalcemia related to extensive osteolytic metastases is much more difficult to palliate because it is not amenable to surgical approaches, but many such patients may respond to bisphosphonate therapy (Lipton et al, 2003; Young and Coleman, 2013). Some patients with hypercalcemia related to osteolytic metastases may also benefit from focused radiation therapy if limited sites of involvement can be identified.

Hypertension and polycythemia are other important paraneoplastic syndromes commonly found in patients with RCC (Moein and Dehghani, 2000). Hypertension associated with RCC can be secondary to increased production of renin directly by the tumor; compression or encasement of the renal artery or its branches, effectively leading to renal artery stenosis; or arteriovenous fistula within the tumor. Less common causes include polycythemia, hypercalcemia, ureteral obstruction, and increased intracranial pressure associated with cerebral metastases. Polycythemia associated with RCC can be due to increased production of erythropoietin, either directly by the tumor or by the adjacent parenchyma in response to hypoxia induced by tumor growth (Wiesener et al, 2007).

One of the more fascinating paraneoplastic syndromes associated with RCC is nonmetastatic hepatic dysfunction, or Stauffer syndrome, which has been reported in 3% to 20% of cases (Giannakos et al, 2005; Kranidiotis et al, 2009). Almost all patients with Stauffer syndrome have an elevated serum alkaline phosphatase level, 67% have elevated prothrombin time or hypoalbuminemia, and 20% to 30% have elevated serum bilirubin or transaminase levels. Other common findings include thrombocytopenia and neutropenia, and typical symptoms include fever and weight loss, which is not surprising given that many patients are found to harbor discrete regions of hepatic necrosis. Hepatic metastases must be excluded. Biopsy, when indicated, often demonstrates nonspecific hepatitis associated with a prominent lymphocytic infiltrate. Elevated serum levels of IL-6 have been found in patients with Stauffer syndrome, and it is believed that this and other cytokines may play a pathogenic role. Hepatic function normalizes after nephrectomy in 60% to 70% of cases. Persistence or recurrence of hepatic dysfunction is almost always indicative of the presence of viable tumor and thus represents a poor prognostic finding.

A variety of other less common but distinct paraneoplastic syndromes associated with RCC include Cushing syndrome, hyperglycemia, galactorrhea, neuromyopathy, clotting disorders, and cerebellar ataxia (Sufrin et al, 1989). In general, treatment of paraneoplastic syndromes associated with RCC has required surgical excision or systemic therapy and, except for hypercalcemia, medical therapies have not proved helpful.

Screening and Clinical Associations

A number of factors make screening for RCC appealing (Carrizosa and Godley, 2009). Most important, RCC remains primarily a surgical disease requiring early diagnosis to optimize the opportunity for cure. Unfortunately, our ability to salvage patients with advanced disease remains limited. Consistent with these observations, several studies have demonstrated an apparent advantage to early or incidental diagnosis of RCC (Lee et al, 2002; Leslie et al, 2003).

The primary factor that limits the widespread implementation of screening for RCC is the relatively low incidence of RCC in the general population (approximately 12 cases per 100,000 population per year) (Jemal et al, 2011). In this setting a screening test must be almost 100% specific to avoid an unacceptably high false-positive rate, which would lead to unnecessary, expensive, and potentially harmful diagnostic or therapeutic procedures. In addition, even if the test were 100% sensitive and specific, the yield from screening would be so low that it would not be considered cost effective (Cohn and Campbell, 2000; Carrizosa and Godley, 2009). Even when one considers populations with established risk factors

for RCC, such as male gender, increased age, and heavy tobacco use, generalized screening would be difficult to justify because the increase in relative risk associated with each of these factors is at best twofold to threefold (Cohn and Campbell, 2000; Carrizosa and Godley, 2009). Another confounding factor is the prevalence of clinically insignificant tumors such as renal adenomas, which are found at autopsy in 10% to 20% of individuals, and other benign or slow-growing tumors (Cohn and Campbell, 2000; Pantuck et al, 2000; Parsons et al, 2001). There is clearly a risk that such clinically insignificant lesions could be detected, leading to unnecessary evaluation and treatment (Pantuck et al, 2000; Parsons et al, 2001). All these factors recommend against generalized screening efforts for the detection of RCC.

Review of the literature describing the use of dipstick analysis for hematuria and ultrasonography or CT for screening for RCC supports these conclusions (Herts and Baker, 1995; Cohn and Campbell, 2000; Carrizosa and Godley, 2009). Urinalysis is simple and inexpensive, but the yield of RCC in several screening studies has been exceedingly low. In part, this may be because small RCCs are often not associated with hematuria (gross or microscopic) because this is a parenchymal rather than a urothelium-based malignant neoplasm. The incidence of RCC in ultrasound or CT screening studies has ranged from 23 to 300 per 100,000 population, much higher than expected. In addition, an increased proportion of organ-confined tumors has been found in screened populations compared with historical controls (Turney et al, 2006; Carrizosa and Godley, 2009). However, the incidence of RCC in these studies is still relatively low, and it is unlikely that such efforts would be considered cost effective. Overall, the yield of RCC in such studies is an order of magnitude lower than the yield from prostate-specific antigen–based screening for prostate cancer, and many of the same controversies about lead and length time biases that have plagued the debate about screening for prostate cancer also apply to RCC (Carter et al, 2013). Because of these considerations, it is difficult to justify generalized screening efforts for RCC given the currently available technology.

Several investigators are now reporting novel molecular assays to detect RCC-related biomarkers in the urine or serum that may substantially alter our perspective about screening for RCC. These assays can detect microsatellite alterations in the DNA, *VHL* gene mutations or hypermethylation, upregulation of angiogenic factors (including VEGF), or expression of RCC-specific proteins such as CA-IX and aquaporin-1 (Jonasch et al, 2012).

For now, however, the focus of screening for RCC must be on well-defined target populations, such as patients with end-stage renal disease and acquired renal cystic disease, tuberous sclerosis, and familial RCC (Box 57-5). Eighty percent of patients with end-stage renal disease eventually develop acquired renal cystic disease, and 1% to 2% of this subgroup develops RCC (Ishikawa et al, 2010). Overall, the relative risk of RCC in patients with end-stage renal disease has been estimated to be 5- to 20-fold higher than that in the general population (Farivar-Mohseni et al, 2006). Fifteen percent of patients with RCC in the setting of end-stage renal disease have metastases at the time of presentation, and many such patients die of malignant progression (Ishikawa et al, 2010; Hurst et al, 2011). Given these considerations, screening for RCC is recommended in this population, which is substantial, representing almost 300,000 patients in the United States alone. Concerns about screening this population include short life expectancy, increased incidence of adenomas (20% to 40% vs. 10% to 20% in the general population), complexity of imaging given the altered architecture associated with acquired renal cystic disease, and inevitable cost-related issues. A reasonable compromise for patients with end-stage renal disease is to target those without other major comorbidities, to delay screening until the third year on dialysis, and to take into account gender and type of renal replacement therapy, although data about the last factors are admittedly controversial (Carrizosa and Godley, 2009). Interestingly, renal transplant recipients remain at high risk for RCC in the native kidneys, with detection in between 1.4% and 2.3% of patients within 3 years of transplantation, leading to a recommendation for continued

BOX 57-5 Screening for Renal Cell Carcinoma: Target Populations**PATIENTS WITH END-STAGE RENAL DISEASE**

Screen only patients with long life expectancy and minimal major comorbidities

Periodic ultrasound examination or CT scan beginning during third year on dialysis

PATIENTS WITH KNOWN VON HIPPEL-LINDAU DISEASE

Obtain biannual abdominal CT or ultrasound study beginning at the age of 15 to 20 years

Periodic clinical and radiographic screening for nonrenal manifestations

RELATIVES OF PATIENTS WITH VON HIPPEL-LINDAU DISEASE

Obtain genetic analysis

If positive, follow screening recommendations for patients with known von Hippel-Lindau disease

If negative, less stringent follow-up is required

RELATIVES OF PATIENTS WITH OTHER FAMILIAL FORMS OF RENAL CELL CARCINOMA

Obtain periodic ultrasound or CT study and consider genetic analysis

PATIENTS WITH TUBEROUS SCLEROSIS

Periodic screening with ultrasound examination or CT scan

PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Routine screening not justified

CT, computed tomography.

periodic radiologic screening even after transplantation (Ianhez et al, 2007; Hurst et al, 2010).

An increased incidence of RCC has also been debated in tuberous sclerosis, an autosomal dominant disorder in which patients can develop adenoma sebaceum (a distinctive skin lesion), epilepsy, mental retardation, and renal cysts and AMLs (Choyke et al, 2003; Lendvay and Marshall, 2003; Narayanan, 2003; Cohen and Zhou, 2005; Rakowski et al, 2006). Many cases of RCC in this syndrome have been characterized by early onset and multifocality, suggesting a genetic predisposition (Lendvay and Marshall, 2003). In addition, the Eker rat, which is mutant for the rodent homolog of the TSC2 gene responsible for the development of tuberous sclerosis in humans, develops RCC at high frequency, as do Tsc2-deficient knockout mice (McDorman and Wolf, 2002; Lendvay and Marshall, 2003). Such biologic and clinical observations argue in favor of an increased predisposition for RCC in this syndrome, which is consistent with most, although admittedly not all, relevant demographic data (Linehan and Ricketts, 2013). A reasonable conclusion is that periodic renal imaging should be pursued in patients with tuberous sclerosis; such a policy will also facilitate follow-up for the development and progression of AML.

Screening for RCC in autosomal dominant polycystic kidney disease (ADPKD) remains controversial. Imaging is extremely difficult in this population related to the altered intrarenal architecture, and several studies have found no significantly increased risk of RCC in ADPKD (Gregoire et al, 1987; Mosetti et al, 2003; Hajj et al, 2009; Jilg et al, 2013). The increased incidence of adenomas and other benign lesions in ADPKD also mitigates against a potential benefit of screening. Taken together, these

considerations suggest that routine screening for RCC in patients with ADPKD should not be pursued.

Special consideration should be given to von Hippel-Lindau disease in any discussion of the value of screening for RCC. This syndrome should be considered in any patient with early-onset or multifocal RCC or RCC in combination with any of the following: a history of visual or neurologic disorders; a family history of blindness, central nervous system tumors, or renal cancer; or coexistent pancreatic cysts, epididymal lesions, or inner ear tumors (Kim et al, 2010; Linehan and Ricketts, 2013). Patients suspected of having von Hippel-Lindau disease, or the appropriate relatives of those with documented disease, should strongly consider genetic evaluation. Patients with germline mutations of the VHL gene can be identified and offered clinical and radiographic screening that can identify the major manifestations of von Hippel-Lindau disease at a presymptomatic phase, allowing potential amelioration of the considerable morbidity associated with this syndrome (Linehan and Ricketts, 2013). Investigators at the National Institutes of Health have recommended that such patients be evaluated with (1) annual physical examination and ophthalmologic evaluation beginning in infancy; (2) estimation of urinary catecholamines at the age of 2 years and every 1 to 2 years thereafter; (3) MRI of the central nervous system biannually beginning at the age of 11 years; (4) ultrasound examination of the abdomen and pelvis annually beginning at the age of 11 years, followed by CT every 6 months if cysts or tumors develop; and (5) periodic auditory examinations (Linehan and Ricketts, 2013). Less intensive protocols have also been advocated, although all relevant organ systems should be addressed (Fraser et al, 2007). Individuals who are found to be wild type for both alleles of VHL also benefit because they can be spared much of the expense and anxiety associated with such intensive surveillance protocols.

Molecular screening is also available for patients suspected of having hereditary papillary RCC and other familial forms of RCC and should be discussed with appropriate family members (Linehan and Ricketts, 2013). Again, individuals at risk, as defined by the presence of mutations of the c-MET proto-oncogene or other relevant genetic alterations, and those with suggestive clinical or family histories should be evaluated with abdominal ultrasonography or CT at periodic intervals. Further testing may be indicated according to the syndrome involved.

Staging

Until the 1990s the most commonly used staging system for RCC was Robson's modification of the system of Flocks and Kadesky, and this schema is still embedded in the mindset of many older urologists (Fig. 57-12) (Robson, 1963; Robson et al, 1969). In retrospect, the limitations of this classification scheme are readily evident. The primary problem can be found in stage III, where tumors with lymphatic metastases, a very poor prognostic finding, were combined with those with venous involvement, many of which can be treated and potentially cured with an aggressive surgical approach (Gettman and Blute, 2002; Leibovich et al, 2003b; Nguyen and Campbell, 2006). Further imprecision resulted from the fact that the extent of venous involvement was not delineated in this system, and tumor size, an important prognostic parameter, was not incorporated. The tumor, node, and metastasis (TNM) system proposed by the Union International Contre le Cancer represents a major improvement because it defines the anatomic extent of disease more explicitly (Leung and Ghavamian, 2002; Nguyen and Campbell, 2006; Decastro and McKiernan, 2008).

In 2009 the American Joint Committee on Cancer proposed a revision of the TNM system that is now the recommended staging system for RCC (Table 57-9). The TNM classification for RCC has undergone several modifications in the past three decades in an effort to more accurately reflect tumor biology and prognosis. It is important to be cognizant of these changes when comparing studies from different eras (Nguyen and Campbell, 2006). In the 2002 version, stage T1 was subdivided to reflect data in the literature demonstrating excellent outcomes for patients with small

STAGING OF RENAL CELL CARCINOMA

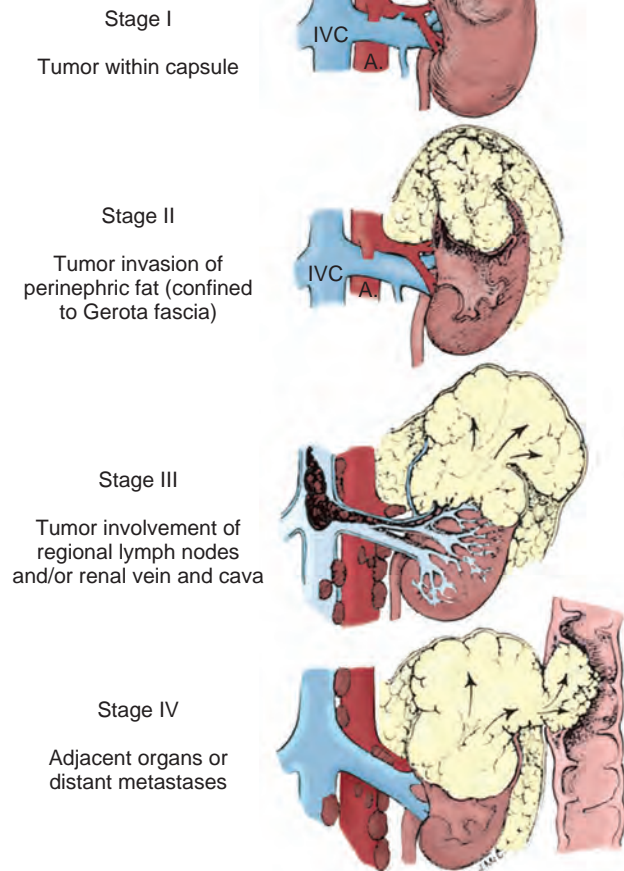


Figure 57-12. Staging of renal cell carcinoma as proposed by Holland, in accordance with classification systems developed by Robson, Murphy, and Flocks and Kadesky. A, aorta; IVC, inferior vena cava. (From Holland JM. Cancer of the kidney: natural history and staging. Cancer 1973;32:1030. Copyright © 1973 American Cancer Society.)

(≤ 4 cm), unilateral, confined tumors managed by either partial or RN (Igarashi et al, 2001; Nguyen and Campbell, 2006). The most recent change for organ-confined tumors is a subdivision of T2 tumors (see Table 57-9), supported by a number of studies demonstrating prognostic relevance at the 10-cm breakpoint (Frank et al, 2005; Klatte et al, 2007b).

Other major revisions in 2009 included a reclassification of tumors with adrenal metastasis, venous thrombi, and lymphatic involvement, representing a substantial departure from previous staging paradigms for RCC. Contiguous extension of tumor into the ipsilateral adrenal gland is now classified as T4 and metastatic involvement of either adrenal as M1, reflecting likely patterns of dissemination. The poor prognosis of adrenal involvement from RCC is well documented and supported this important change (Thompson et al, 2005b; Nguyen and Campbell, 2006; Kirkali et al, 2007; von Knobloch et al, 2009). The favorable prognosis of isolated renal venous thrombi prompted a downgrading from stage T3b to stage T3a in the 2009 version (Moinzadeh and Libertino, 2004; Leibovich et al, 2005a; Shvarts et al, 2005a; Margulis et al, 2007b). Finally, lymphatic extension, which previously was subdivided based on the number of involved nodes, has now been compressed to simplify this aspect of the staging process, because prognostic relevance of the previous version was not observed (Edge et al, 2010). Recent studies suggesting independent prognostic power related to invasion of the sinus fat or collecting system remind us that continued re-evaluation and validation of the TNM

TABLE 57-9 International TNM Staging System for Renal Cell Carcinoma

T: PRIMARY TUMOR

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor ≤ 4.0 cm and confined to the kidney
T1b	Tumor > 4.0 cm and ≤ 7.0 cm and confined to the kidney
T2a	Tumor > 7.0 cm and ≤ 10.0 cm and confined to the kidney
T2b	Tumor > 10.0 cm and confined to the kidney
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

N: REGIONAL LYMPH NODES

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis in regional lymph node(s)

M: DISTANT METASTASES

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

STAGE GROUPING

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	Any N	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Modified from Edge SB, Byrd DR, Compton CC. AJCC cancer staging manual. 7th ed. New York: Springer-Verlag; 2010.

system for RCC will be required to optimize its value moving into the future (Jeon et al, 2009; Verhoest et al, 2009; Anderson et al, 2011; Brookman-May et al, 2011). The T3 category in particular remains a matter of ongoing debate in the field (Bertini et al, 2009; Moch et al, 2009).

TNM staging classically is defined by the most advanced feature demonstrated by the tumor, yet important prognostic information can be lost in the process. Many renal tumors exhibit multiple adverse findings, such as high-level tumor thrombus along with ipsilateral adrenal involvement. Ideally all of the relevant anatomic staging information would be captured, at least parenthetically (e.g., "pT4 [ipsilateral adrenal involvement; also exhibiting IVC thrombus above the diaphragm]"). Future staging systems will need to capture all of this information, because a number of investigators have demonstrated a compromised prognosis for patients with multiple adverse factors (Leibovich et al, 2005a; Shvarts et al, 2005a; Terrone et al, 2006; Ficarra et al, 2007; Klatte et al, 2009a).

The clinical staging of renal malignant disease begins with a thorough history, physical examination, and judicious use of

laboratory tests (Nguyen and Campbell, 2006; Decastro and McKiernan, 2008). Systemic symptoms such as significant weight loss (>10% of body weight), cachexia, or poor performance status at presentation all suggest advanced disease, as do physical examination findings of a palpable mass or lymphadenopathy. A nonreducing varicocele and lower extremity edema suggest venous involvement. Significant anemia, hypercalcemia, abnormal liver function parameters or sedimentation rate, or elevated serum alkaline phosphatase or lactate dehydrogenase level all point to the probability of advanced disease (Nguyen and Campbell, 2006; Lane and Kattan, 2008).

The radiographic staging of RCC can be accomplished in most cases with a high-quality abdominal CT scan and a routine chest radiograph, with selective use of MRI and other studies as indicated (Choyke et al, 2001; Ng et al, 2008; Herts, 2009). MRI can be reserved primarily for patients with locally advanced malignant disease, equivocal venous involvement, or allergy to intravenous contrast material (Choyke et al, 2001; Zhang et al, 2007; Herts, 2009). CT findings suggestive of extension into the perinephric fat include perinephric stranding (Fig. 57-13), which is a nonspecific finding, or a distinct soft tissue density within the perinephric space, which is a more definitive but uncommon finding (Bechtold and Zagoria, 1997; Herts, 2009). Overall, the accuracy of CT or MRI for detection of involvement of the perinephric fat is low, reflecting the fact that extracapsular spread often occurs microscopically (Choyke et al, 2001; Kamel et al, 2004; Zhang et al, 2007). Ipsilateral adrenal involvement can be assessed with reasonable accuracy through a combination of preoperative CT and intraoperative inspection. Patients with an enlarged or indistinct adrenal gland on CT, extensive malignant replacement of the kidney, or a palpably abnormal adrenal gland are at risk for ipsilateral adrenal involvement and should be managed accordingly (Paul et al, 2001; Sawai et al, 2002; Zhang et al, 2007; Kobayashi et al, 2008; Ng et al, 2008; Lane et al, 2009c).

Enlarged hilar or retroperitoneal lymph nodes (2 cm or more in diameter) on CT almost always harbor malignant change, but this should be confirmed by surgical exploration or percutaneous biopsy if the patient is not a surgical candidate. Many smaller nodes prove to be inflammatory rather than neoplastic and should not preclude surgical therapy (Choyke et al, 2001; Israel and Bosniak, 2003; Ng et al, 2008; Herts, 2009). MRI can add specificity to the evaluation of retroperitoneal nodes by distinguishing vascular structures from lymphatic ones (Bassignani, 2006).



Figure 57-13. Computed tomography scan after administration of contrast agent shows right renal tumor with perinephric stranding suggesting invasion of the perinephric fat.

MRI is still the premier study for evaluation of invasion of tumor into adjacent structures and for surgical planning in these challenging cases (Pretorius et al, 2000; Choyke et al, 2001; Herts, 2009). Obliteration of the fat plane between the tumor and adjacent organs (e.g., the liver) on CT can be a misleading finding and should prompt further imaging with MRI. In reality, surgical exploration is often required to make an absolute differentiation.

The sensitivities of CT for detection of renal venous tumor thrombus and IVC involvement are 78% and 96%, respectively (Ng et al, 2008; Herts, 2009). CT findings suggestive of venous involvement include venous enlargement, abrupt change in the caliber of the vein, and filling defects. The diagnosis is strengthened by the demonstration of collateral vessels. Most false-negative findings occur in patients with right-sided tumors in whom the short length of the vein and the mass effect from the tumor combine to make detection of the tumor thrombus difficult (Herts, 2009). Fortunately, most such cases are readily identified and dealt with intraoperatively. MRI is well established as the premier study for the evaluation and staging of IVC tumor thrombus, although recent data suggest that multiplanar CT is likely equivalent (Pretorius et al, 2000; Aslam Sohaib et al, 2002; Zhang et al, 2007; Ng et al, 2008). Venacavography is now best reserved for patients with equivocal MRI or CT findings or for patients who cannot tolerate or have other contraindications to cross-sectional imaging. Transesophageal echocardiography also appears to be accurate for establishing the cephalad extent of the tumor thrombus, but it is invasive and provides no distinct advantages over MRI or CT in the preoperative setting (Glazer and Novick, 1997).

Metastatic evaluation in all cases should include a routine chest radiograph, systematic review of the abdominal and pelvic CT or MRI, and liver function tests (Griffin et al, 2007; Ng et al, 2008; Herts, 2009). Bone scintiscan can be reserved for patients with elevated serum alkaline phosphatase, bone pain, or poor performance status (Shvarts et al, 2004) and chest CT scan for patients with pulmonary symptoms or an abnormal chest radiograph (Choyke et al, 2001). Patients with locally advanced disease, enlarged retroperitoneal lymph nodes, or significant comorbid disease may mandate more thorough imaging to rule out metastatic disease and to aid in treatment planning (Choyke et al, 2001; Griffin et al, 2007). Positron emission tomography (PET) has also been investigated for patients with high risk of metastatic RCC, with most studies showing good specificity but suboptimal sensitivity. At present its best role is for patients with equivocal findings on conventional imaging. In this setting an abnormal PET scan may increase the concern about metastatic disease and could influence further evaluation and management (Griffin et al, 2007; Powles et al, 2007; Bouchelouche and Oehr, 2008). Biopsy of the primary tumor and/or potential metastatic sites is also selectively required as part of the staging process.

Prognosis

Important prognostic factors for cancer-specific survival in patients with nonmetastatic RCC include specific clinical signs or symptoms, tumor-related factors, and various laboratory findings (Box 57-6) (Lane and Kattan, 2008; Meskawi et al, 2012). Overall, tumor-related factors such as pathologic stage, tumor size, nuclear grade, and histologic subtype have the greatest utility on an independent basis. However, an integrative approach, combining a variety of factors that have proved to have independent value on multivariate analysis, appears to be most powerful (Meskawi et al, 2012). Patient-related factors such as age, CKD, and comorbidity have a significant impact on overall survival and should be a primary consideration during treatment planning for patients with localized RCC (Hollingsworth et al, 2006; Kutikov et al, 2010).

Clinical findings suggestive of a compromised prognosis in patients with presumed localized RCC include symptomatic presentation, weight loss of more than 10% of body weight, and poor performance status (Lane and Kattan, 2008). Anemia, thrombocytosis, hypercalcemia, albuminuria, and elevated serum alkaline

phosphatase, C-reactive protein, lactate dehydrogenase, or erythrocyte sedimentation rate, as well as other paraneoplastic signs or symptoms, have also correlated with poor outcomes for patients with RCC (Lane and Kattan, 2008; Magera et al, 2008b). Although abnormal values are more common in patients with advanced RCC,

some of these abnormalities, including hypercalcemia, anemia, and elevated erythrocyte sedimentation rate, were independent predictors of cancer-specific mortality in patients with localized clear cell RCC after accounting for other major prognostic factors (Magera et al, 2008b).

Pathologic stage has proved to be the single most important prognostic factor for RCC (Leibovich et al, 2005b; Lane and Kattan, 2008; Kanao et al, 2009). The RCC TNM staging system clearly distinguishes between patient groups with different predicted cancer-specific outcomes (Table 57-10), confirming that the extent of locoregional or systemic disease at diagnosis is the primary determinant of outcome for this disease (Lane and Kattan, 2008). Several studies demonstrate 5-year survival rates of 70% to 90% for organ-confined disease and document a 15% to 20% reduction in survival associated with invasion of the perinephric fat (Lane and Kattan, 2008). Renal sinus involvement is classified along with perinephric fat invasion as T3a, and several studies suggest that these patients may be at even higher risk for metastasis related to increased access to the venous system (Bonsib et al, 2000; Thompson et al, 2005a; Bertini et al, 2009; Jeon et al, 2009). Collecting system invasion has also been shown to confer poorer prognosis in otherwise organ-confined RCC (Uzzo et al, 2002; Klatte et al, 2007a; Verhoest et al, 2009; Anderson et al, 2011). Several reports have shown that most patients with direct or metastatic ipsilateral adrenal involvement, which is found in 1% to 2% of cases, eventually succumb to systemic disease progression, suggesting a hematogenous route of dissemination or a highly invasive phenotype (Sagalowsky et al, 1994; von Knobloch et al, 2009). The most recent staging system now reclassifies tumor as T4 if there is direct invasion of the adrenal gland or otherwise as M1, to reflect this poor prognosis (Thompson et al, 2005b; Edge et al, 2010).

Venous involvement was once thought to be a very poor prognostic finding for RCC, but several reports demonstrate that many patients with tumor thrombi can be salvaged with an aggressive surgical approach. These studies document 45% to 69% 5-year survival rates for patients with venous tumor thrombi as long as the tumor is otherwise confined to the kidney (Martinez-Salamanca et al, 2011). Patients with venous tumor thrombi and concomitant lymph node or systemic metastases have markedly decreased survival, and those with tumor extending into the perinephric fat have intermediate survival (Martinez-Salamanca et al, 2011). The most recent version of the TNM system advocates capturing all such adverse features during the staging process. Recent studies suggest that patients with microvascular invasion may have compromised outcomes compared to matched tumors

BOX 57-6 Prognostic Factors for Renal Cell Carcinoma

CLINICAL

Performance status
Systemic symptoms
Symptomatic vs. incidental presentation
Anemia
Hypercalcemia
Elevated lactate dehydrogenase
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Thrombocytosis
Elevated alkaline phosphatase

ANATOMIC

Tumor size
Venous involvement
Extension into contiguous organs
Adrenal involvement (direct or metastatic)
Lymph node metastases
Distant metastases
Metastatic burden of disease

HISTOLOGIC

Nuclear grade
Histologic subtype
Presence of sarcomatoid features
Presence of histologic necrosis
Vascular invasion
Invasion of perinephric or renal sinus fat
Collecting system invasion
Surgical margin status

Modified from Lane BR, Kattan MW. Prognostic models and algorithms in renal cell carcinoma. *Urol Clin North Am* 2008;35:613–25.

TABLE 57-10 Tumor, Node, Metastasis (TNM) Stage and 5-Year Survival for Renal Cell Carcinoma

FINDINGS	ROBSON STAGE	TNM (2002)	TNM (2009)	5-YEAR SURVIVAL (%)
Organ-confined (overall)	I	T1-2N0M0	T1-2N0M0	70-90
≤4.0 cm	I	T1aN0M0	T1aN0M0	90-100
>4.0 cm to 7.0 cm	I	T1bN0M0	T1bN0M0	80-90
>7.0 to 10.0 cm	I	T2N0M0	T2aN0M0	65-80
>10.0 cm	I	T2N0M0	T2bN0M0	50-70
Invasion of perinephric or renal sinus fat	II	T3aN0M0	T3aN0M0	50-70
Invasion of renal vein or branches	IIIA	T3bN0M0	T3aN0M0	40-60
Invasion of IVC below diaphragm	IIIA	T3cN0M0	T3bN0M0	30-50
Invasion of IVC above diaphragm or invasion of IVC wall	IIIA	T3cN0M0	T3cN0M0	20-40
Direct adrenal involvement	II	T3aN0M0	T4N0M0	0-30
Locally advanced (invasion beyond Gerota fascia)	IVA	T4N0M0	T4N0M0	0-20
Lymph node involvement	IIIB	(Any)TN1-2M0	(Any)TN1M0	0-20
Systemic metastases	IVB	(Any)T(Any)NM1	(Any)T(Any)NM1	0-10

IVC, inferior vena cava.

Data from Hafez et al, 1999; Leibovich et al, 2005a; Thompson et al, 2005a; Lane and Kattan, 2008; Campbell et al, 2009; Martinez-Salamanca et al, 2011; and Haddad and Rini, 2012.

without these features, indicating that even microscopic venous or lymphatic involvement may be a poor prognostic sign (Feifer et al, 2011; Kroeger et al, 2012).

The prognostic significance of the cephalad extent of tumor thrombus has been controversial, and it is difficult to compare various series because of selection biases and related covariables (Leibovich et al, 2005a; Wotkowicz et al, 2008). In several series the incidence of advanced locoregional or systemic disease increased with the cephalad extent of the tumor thrombus, accounting for the reduced survival associated with tumor thrombus extending into or above the level of the hepatic veins (Wotkowicz et al, 2008). However, other data suggest that the cephalad extent of tumor thrombus is not of prognostic significance as long as the tumor is otherwise confined (Libertino et al, 1987; Blute et al, 2007). Direct invasion of the wall of the vein appears to be a more important prognostic factor than level of tumor thrombus and is now classified as pT3c independent of the level of tumor thrombus (Hatcher et al, 1991; Zini et al, 2008).

The major drop in prognosis comes in patients whose tumor extends beyond the Gerota fascia to involve contiguous organs (stage T4) and in patients with lymph node or systemic metastases (Thompson et al, 2005b; Margulis et al, 2007a). Lymph node involvement has long been recognized as a dire prognostic sign because it is associated with 5- and 10-year survival rates of 5% to 30% and 0% to 5%, respectively (Phillips and Taneja, 2004; Crispen et al, 2011). Systemic metastases also portend a particularly poor prognosis for RCC, traditionally with 1-year survival of less than 50%, 5-year survival of 5% to 30%, and 10-year survival of 0% to 5%, although these numbers have improved modestly in the era of targeted treatments (Haddad and Rini, 2012). Patients presenting with synchronous metastases fare worse, with many patients dying of disease progression within 1 to 2 years (Leibovich et al, 2005a; Mekhail et al, 2005; Haddad and Rini, 2012; Heng et al, 2013). For patients with asynchronous metastases, the metastasis-free interval has proved to be a useful prognosticator because it reflects the tempo of disease progression (Maldazys and deKernion, 1986; Motzer et al, 2004; Mekhail et al, 2005). Other important prognostic factors for patients with systemic metastases include performance status, number and sites of metastases, anemia, hypercalcemia, elevated alkaline phosphatase or lactate dehydrogenase levels, thrombocytosis, and sarcomatoid histology (Lane and Kattan, 2008). The presence of bone, brain, and/or liver metastases and multiple metastatic sites have been associated with further compromise in prognosis (Mekhail et al, 2005; Escudier et al, 2007; McKay et al, 2014). These factors have been used to effectively categorize patients with metastatic RCC as low, intermediate, and poor risk, with corresponding differences in median survival (Motzer et al, 2004; Heng et al, 2013). These risk groups provide important information for determining the likelihood of benefit a patient may expect to receive after cytoreductive nephrectomy and/or resection of other metastatic disease.

Another significant prognostic factor for RCC is tumor size, which has proved to be an independent prognostic factor for both organ-confined and invasive RCC (Kattan et al, 2001; Kontak and Campbell, 2003; Lane and Kattan, 2008). To a large extent, this is due to a strong correlation between tumor size and pathologic tumor stage, but several studies have demonstrated that tumor size can function as an independent prognostic factor (Kattan et al, 2001; Sorbellini et al, 2005; Crispen et al, 2008a; Nguyen and Gill, 2009). Larger tumors are more likely to exhibit clear cell histology and high nuclear grade, and both of these factors correlate with a compromised prognosis (Frank et al, 2003; Lane et al, 2007a; Thompson et al, 2009). A review of 1771 patients with organ-confined RCC showed 10-year cancer-specific survival rates of 90% to 95%, 80% to 85%, and 75% for patients with pT1a, pT1b, and pT2 tumor, respectively (Patard et al, 2004a). Many other studies have also shown a particularly favorable prognosis for the unilateral pT1a tumors that are now being discovered with increased frequency. In series from the Cleveland Clinic and the Mayo Clinic, such tumors were associated with greater than 95% 5-year

cancer-specific survival rates, whether they were managed with nephron-sparing surgery or RN (Butler et al, 1995; Cheville et al, 2001; Lane et al, 2013b).

Other important prognostic factors for RCC include nuclear grade and histologic subtype. Several grading systems for RCC have been proposed on the basis of nuclear size and morphology and presence or absence of nucleoli. Unfortunately, interobserver variability is common in the assignment of nuclear grade; there is no ideal classification system that can overcome the subjectivity of this exercise. Nevertheless, almost all the proposed grading systems have provided prognostic information for RCC, and nuclear grade has proved in most cases to be an independent prognostic factor when subjected to multivariate analysis (Zisman et al, 2001; Lohse et al, 2002, 2005; True, 2002; Lang et al, 2005; Lane and Kattan, 2008; Ficarra et al, 2009).

Fuhrman's classification system has been the most generally adopted grading system for RCC. In the original report, the 5-year survival rates for grades 1 to 4 were 64%, 34%, 31%, and 10%, respectively, and nuclear grade proved to be the most significant prognostic factor for organ-confined tumors in this series (Fuhrman et al, 1982). Subsequent reports have demonstrated correlations between Fuhrman's nuclear grade and tumor stage, tumor size, venous tumor thrombi, and lymph node and systemic metastases (Ficarra et al, 2009). Although significant differences according to nuclear grade have been reported in series that have included patients with all types of RCC or clear cell RCC alone, the relevance of the Fuhrman classification system to evaluation of other subtypes of RCC is not entirely clear (see Pathology). Recent evidence suggests that Fuhrman grade has prognostic significance in papillary RCC, but that characteristics other than nuclear features may better predict the aggressiveness of chromophobe RCC and other oncocytic neoplasms (Klatte et al, 2010a; Finley et al, 2011; Delahunt et al, 2013; Meskawi et al, 2013).

Histologic subtype also carries prognostic significance, although, again, primarily at the ends of the spectrum. The presence of sarcomatoid differentiation or collecting duct, renal medullary, or unclassified histologic subtype denotes a poor prognosis (Zhou, 2009; Deng and Melamed, 2012). Several studies now suggest that clear cell RCC may have a worse prognosis on average compared with papillary or chromophobe RCC, although there are clearly poorly differentiated tumors in each of these subcategories that can be lethal (Teloken et al, 2009; Leibovich et al, 2010; Deng and Melamed, 2012). Finally, several subtypes of RCC are predictably indolent, including multiloculated cystic clear cell RCC and mucinous tubular and spindle cell carcinoma.

A variety of molecular factors have correlated with outcomes for RCC in observational studies and will likely prove to be useful in the future (Jonasch et al, 2012; Keefe et al, 2013). This includes hypoxia-inducible factors, genes controlling cellular oxygen sensing, maintenance of chromatin states, costimulatory molecules, cell cycle regulators, and adhesion molecules in addition to many others (Box 57-7) (Jonasch et al, 2012). Aggressive cancers demonstrate downregulation of genes involved in the TCA cycle and upregulation of the pentose phosphate pathway (Cancer Genome Atlas Research Network, 2013). In general, clinical validation has not yet been achieved with any of these factors and they remain primarily investigational.

Several investigators have now developed tools that integrate clinical risk factors with pathologic factors, and this has greatly improved our predictive capacity for patients with RCC. Incorporation of the strongest predictors into a nomogram is one way to provide an individual assessment of risk that clinicians can use during patient counseling (see Table 57-11 for a comprehensive list of published integrated staging systems). Kattan and colleagues (2001) developed the first of these for RCC, and several nomograms have been introduced subsequent to this. One such nomogram incorporating stage, size, grade, and symptoms at presentation has been validated using multi-institutional data sets and outperforms several of the other existing prognostic tools for localized RCC (Fig. 57-14) (Karakiewicz et al, 2007a).

BOX 57-7 Molecular Prognostic Factors for Renal Cell Carcinoma (RCC)

Dozens of genes that may have prognostic or therapeutic significance for patients with RCC have been identified using high-throughput technologies (Takahashi et al, 2006; Zhao et al, 2006; Brannon et al, 2010; Keefe et al, 2013). Gene expression profiling (cDNA microarrays) can quantify the levels of thousands of individual messenger RNA transcripts within an individual tumor sample. Alterations in gene expression can then be correlated with the amount and location of specific gene products (proteins) using immunohistochemical staining of cancer specimens (Kim et al, 2004a; Parker et al, 2009). Construction of tissue microarrays can facilitate the screening of hundreds of tumors, but interpretation of results can be challenging due to tumor heterogeneity and the selection of only a small amount of tissue for analysis. Furthermore, when evaluating the potential value of a new marker, it is important to consider its contribution after accounting for other known prognostic factors (George and Bukowski, 2007; Tunuguntia and Jorda, 2008).

Several molecular markers appear to serve as independent prognostic factors for RCC and have provided important insights into tumor biology (see *Tumor Biology and Clinical Implications*) (Bui et al, 2001; Han et al, 2003; Crispen et al, 2008a; Nogueira and Kim, 2008; Parker et al, 2009). One such factor is CA-IX, which is regulated by the *VHL* gene and overexpressed in most clear cell RCCs (Bui et al, 2003, 2004; Leibovich et al, 2007). Although initial studies indicated that decreased expression of CA-IX is independently associated with poor survival in patients with metastatic RCC (Bui et al, 2003; Kim et al, 2005), this association does not appear to apply for patients with localized disease (Kim et al, 2005; Leibovich et al, 2007). CA-IX also may serve as a marker for response to systemic therapy, making CA-IX immunostaining of particular value for patients with advanced disease (Bui et al, 2004; Atkins et al, 2005; Cho et al, 2007). B7-H1 is a T-cell coregulatory molecule that is a strong independent predictor of disease progression for RCC (Thompson et al, 2006; Parker et al, 2009). This association holds even after accounting for other molecular factors and established clinical and pathologic predictors (Krambeck et al, 2007; Parker et al, 2009). Increased proliferative index as assessed by Ki-67 has also been correlated with reduced survival in clear cell RCC (Bui et al, 2004; Klatte et al, 2009b; Parker et al, 2009). Although initial data indicated that Ki-67 expression was a surrogate for histologic necrosis, more recent studies have found Ki-67 to be an independent predictor and have incorporated it into predictive algorithms (Tollefson et al, 2007; Klatte et al, 2009b; Parker et al, 2009). Other factors that appear to be useful include cell cycle regulators, such as the tumor suppressor gene *TP53* (Kim et al, 2004a; Shvarts et al, 2005b; Klatte et al, 2009b); various growth factors and their receptors, including members of the VEGF family (Jacobsen et al, 2000; Phyoc et al, 2008; Rivet et al, 2008; Klatte et al, 2009b); adhesion molecules; and other factors, such as survivin (Parker et al, 2006, 2009; Byun et al, 2007; Krambeck et al, 2007).

Two other integrated staging systems that have been used to risk stratify patients for clinical trials are the UCLA Integrated Staging System (UISS) and the Mayo Clinic Stage, Size, Grade and Necrosis (SSIGN) score. The UISS was developed based on multivariate analysis revealing three independent prognostic factors for RCC, namely TNM stage, performance status, and tumor grade (Zisman et al, 2001). The UISS was subsequently

modified to identify patients with localized or metastatic disease at low, intermediate, and high risk of disease progression and has been validated internally and externally (Zisman et al, 2002; Patard et al, 2004b; Cindolo et al, 2005, 2008; Parker et al, 2009). Molecular factors such as *TP53*, Ki-67, VEGF family members, and CA-IX have also been incorporated into UISS-based algorithms to predict outcomes for patients with localized or metastatic RCC (Kim et al, 2005; Klatte et al, 2009a).

The SSIGN score can be used to estimate cancer-specific survival based on TNM stage, tumor size, nuclear grade, and presence of tumor necrosis (Frank et al, 2002). The SSIGN score has been validated in multiple data sets, but the inclusion of histologic necrosis as a predictor limits its clinical usefulness (Ficarra et al, 2006, 2009; Fujii et al, 2008; Zigeuner et al, 2010). The group at the Mayo Clinic has also developed a dynamic outcome prediction model that provides patients with cancer-specific survival rates that improve as the disease-free interval following surgery increases and a model in which molecular data are incorporated with the SSIGN components into a BioScore (Thompson et al, 2007c; Parker et al, 2009).

TNM staging systems and prognostic algorithms have different purposes. The TNM staging system is used to provide a universal language for communication between clinicians and patients and is based solely on the anatomic extent of cancer dissemination. A wealth of literature now supports the notion that algorithms that incorporate multiple predictive elements, such as nomograms and artificial neural networks, outperform risk assessment based on expert opinion or simpler models, such as classic staging systems (Ross et al, 2002; Isbarn and Karakiewicz, 2009; Shariat et al, 2009). The development and use of these integrated staging systems can help guide counseling and follow-up of patients with RCC and identify patients more likely to benefit from specific interventions.

TREATMENT OF LOCALIZED RENAL CELL CARCINOMA

Localized renal masses have increased in incidence related to more widespread use of cross-sectional imaging and now represent a relatively common clinical scenario (Lipworth et al, 2006; Jemal et al, 2009; Miller et al, 2010a). Our perspectives about clinical T1 renal masses have changed substantially in the past two decades. Previously, all were presumed to be malignant and managed aggressively, most often with RN. We now recognize great heterogeneity in the tumor biology of these lesions, and multiple management strategies are now available, including RN, partial nephrectomy (PN), thermal ablation (TA), and active surveillance (AS) (Kunkle et al, 2008; Campbell et al, 2009; Aron et al, 2010; Van Poppel et al, 2011a; Volpe et al, 2011; Kim and Thompson, 2012) (Fig. 57-15). Concepts that were once controversial, such as elective PN, are now accepted as standards of care (Kunkle et al, 2008; Campbell et al, 2009). A greater understanding of the tumor biology and appreciation of the deleterious functional consequences of RN has stimulated a reassessment of this field (Russo and Huang, 2008; Campbell et al, 2009). Ongoing debates about the relative merits of PN and RN and other management strategies have spawned a vibrant literature over the past few years.

Overall, about 20% of solid, enhancing, clinical T1 renal masses are benign, most often oncocytomas or atypical AMLs, although the incidence of benign pathology can vary greatly in different subpopulations (Frank et al, 2003; Russo and Huang, 2008; Campbell et al, 2009; Gill et al, 2010a). Young to middle-age women, in particular, are more likely to have benign pathology, as high as 40% in some series (Eggerer et al, 2004). One potential explanation is that some benign renal masses, such as cystic nephroma and atypical AML, may be influenced by the hormonal milieu and are thus more common in women. In contrast, the proportion of benign tumors appears to increase gradually in males as they age (Lane et al, 2007a). An even more important determinant of benign pathology is tumor size, with multiple studies confirming this (Campbell et al, 2009). Frank and colleagues

TABLE 57-11 Integrated Predictive Tools for Renal Cell Carcinoma (RCC)

STUDY	SETTING, SUBTYPE	PATIENTS, SOURCE	PROGNOSTIC INDICATORS	OUTCOME OF INTEREST	ACCURACY (%), FORMAT
PREOPERATIVE					
Lane et al (2007a)	Localized renal tumors amenable to PN	862; Single institution	Tumor size, symptoms, gender, age, smoking	Histology	56%-64% (internal) Nomogram
Kutikov et al (2011)	Localized renal tumors	1750; Single institution	Tumor anatomy (RENAL score), gender, age	Histology	73%-76% (external) Nomogram
Yaycioglu et al (2002)	Localized renal tumors	296; Single institution	Tumor size, symptoms	Recurrence	65%-66% (external) Risk groups
Cindolo et al (2003)	Localized renal tumors	660; Multi-institution	Tumor size, symptoms	Recurrence	67%-75% (external) Risk groups
Raj et al (2008)	Localized renal tumors	2517; Multi-institution	Tumor size, symptoms, gender, lymphadenopathy, necrosis on imaging	Recurrence	80% (internal) Nomogram
Kanao et al (2009)	Localized and metastatic renal tumors	545; Single institution	TNM stage	Survival	81% (internal) 69%-82% (external)
Kutikov et al (2010)	Localized renal tumors	30,801; Population based	Tumor size, race, gender, age	Survival	70%-73% (external) Nomogram
POSTOPERATIVE					
Kattan et al (2001)	Localized RCC	601; Single institution	TNM stage, tumor size, histology, symptoms	Recurrence	61%-84% (internal) 74% (external) Nomogram
Leibovich et al (2003a)	Localized clear cell RCC	1671; Single institution	TNM stage, tumor size, nuclear grade, histologic necrosis	Recurrence	70%-80% (external) 84% (internal) Risk groups
Sorbellini et al (2005)	Localized clear cell RCC	701; Single institution	TNM stage, tumor size, nuclear grade, histologic necrosis, microvascular invasion, symptoms	Recurrence	78%-79% (external) 82% (internal) Nomogram
Zisman et al (2001)	Localized RCC	661; Single institution	TNM stage, nuclear grade, performance status	Survival	64%-86% (external) Algorithm, decision boxes
Zisman et al (2002)	Localized and metastatic RCC	814; Multi-institution	TNM stage, nuclear grade, performance status, metastasis (UISS)	Survival	64%-86% (external) Algorithm, decision boxes
Frank et al (2002)	All stages clear cell RCC	1801; Single institution	TNM stage, tumor size, nuclear grade, histologic necrosis (SSIGN)	Survival	75%-88% (external) 84% (internal) Risk groups
Kim et al (2004b)	Localized and metastatic RCC	318; Single institution	TNM stage, performance status, metastasis; expression of TP53, vimentin, CA-IX in patients with metastatic disease	Survival	79% (internal) Nomogram
Karakiewicz et al (2007a)	All stages clear cell RCC	313; Multi-institution	TNM stage, tumor size, nuclear grade, histologic subtype, local symptoms, age, gender	Survival	84%-88% (internal) Nomogram
Parker et al (2009)	Localized clear cell RCC	634; Single institution	Expression of B7-H1, survivin, Ki-67 (BioScore)	Survival	75% (internal) Algorithm, risk groups
Klatte et al (2009a)	Localized clear cell RCC	282; Single institution	Expression of Ki-67, TP53, endothelial VEGFR-1, epithelial VEGFR-1, epithelial VEGF-D	Survival	89% (internal) Nomogram
Iimura et al (2009)	Localized clear cell RCC	249; Multi-institution	TNM stage, tumor necrosis, serum CRP	Survival	82% (internal) Algorithm, risk groups

CA-IX, carbonic anhydrase-IX; CRP, C-reactive protein; PN, partial nephrectomy; RENAL, Radius, Endophytic vs. exophytic, Nearness to collecting system, Anterior/posterior, and Location relative to polar lines; SSIGN, Mayo Clinic Stage, Size, Grade and Necrosis Score; TNM, tumor, node, metastasis; UISS, UCLA Integrated Staging System; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Modified from Meskawi M, Sun M, Trinh QD, et al. A review of integrated staging systems for renal cell carcinoma. Eur Urol 2012;62:303-14.

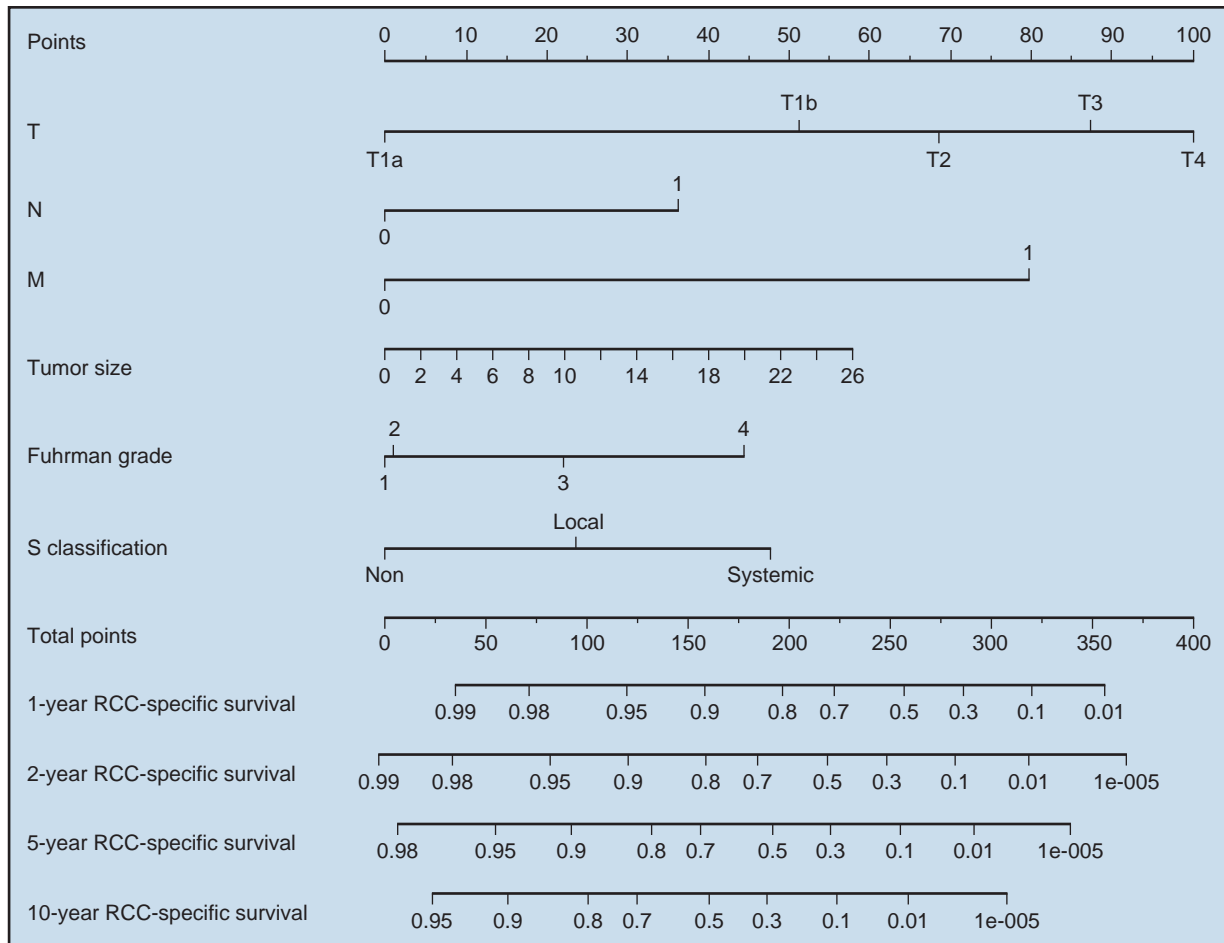


Figure 57-14. Postoperative nomogram predicting renal cell carcinoma (RCC)-specific survival at 1, 2, 5, and 10 years after nephrectomy. To use, locate the tumor stage on the T axis. Draw a line upward to the Points axis to determine how many points toward survival the patient receives for this parameter. Repeat this process for the other axes—N, M, Tumor size, Fuhrman grade, and S classification (nonsymptomatic, local symptoms, systemic symptoms)—each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate the sum on the Total points axis. Draw a straight line down to find the probability that the patient will remain free of death from RCC for 1, 2, 5, or 10 years, assuming the patient does not die of another cause first. (From Karakiewicz PI, Briganti A, Chun FK, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol* 2007;25:1316–22.)

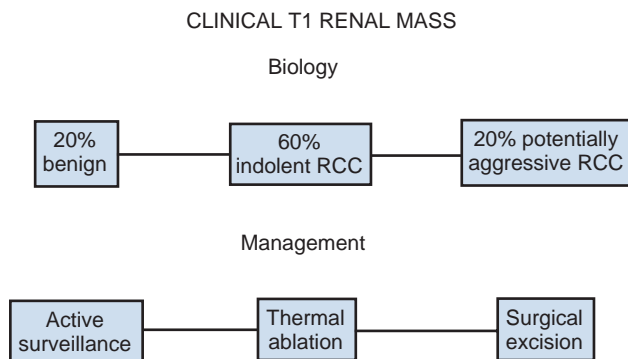


Figure 57-15. Clinical T1 renal masses are heterogeneous, with 20% benign and only about 20% exhibiting potentially aggressive features. Management options have expanded greatly, ranging from radical nephrectomy, the previous standard, to active surveillance. RCC, renal cell carcinoma.

(2003) have demonstrated a direct relationship between tumor size and the incidence of malignancy. In their series, 30% of tumors less than 2 cm were benign, compared with 21% of tumors between 2 and 4 cm. In contrast, only 9.5% of clinical T1b tumors were benign. Tumor size has also correlated with biologic aggressiveness for clinical T1 renal masses, as reflected by high tumor grade, locally invasive phenotype, or adverse histologic subtype. In the study by Frank and colleagues (2003), such adverse findings were uncommon in tumors less than 4 cm diameter. In this subset only 1.7% demonstrated invasion of the perinephric fat, 0.7% had venous involvement, 0.6% had lymph node involvement, and only 15% were high grade. Such features were more commonly observed in clinical T1b tumors in this and other series. Other studies suggest a cut point at 3 cm, with tumors larger than this much more likely to exhibit potentially aggressive histopathologic features (Remzi et al, 2006; Pahernik et al, 2007). Surveillance studies confirm a slow growth rate and low risk of metastasis for many small renal tumors (Bosniak et al, 1995; Kunkle et al, 2007, 2008; Abouassaly et al, 2008; Crispen et al, 2009).

Other clinical factors such as patient age and sex, symptomatic presentation, and smoking history have also been studied, although none of these factors can provide substantial predictive value with respect to tumor aggressiveness (Lane et al, 2007a). Current algorithms incorporating clinical and radiographic factors to predict tumor aggressiveness are very limited in their accuracy, with concordance indices less than 0.60, not much better than a coin flip (Lane et al, 2007a; Kutikov et al, 2011). Conventional renal mass biopsy can substantially improve on this, having demonstrated reasonable accuracy for assessment of tumor histology, and should be considered in patients who are candidates for a wide range of management strategies (Lane et al, 2008; Schmidbauer et al, 2008; Leveridge et al, 2011; Samplaski et al, 2011; Volpe et al, 2012). Some centers are now routinely performing renal mass biopsy in the evaluation of localized renal masses, and are reporting encouraging results regarding potential clinical utility (Halverson et al, 2013). However, younger, healthy patients who are unwilling to accept the uncertainty associated with renal mass biopsy and older, frail patients who will be managed conservatively independent of biopsy results should still be managed without a biopsy. An alternative to renal mass biopsy has recently been reported, namely PET scanning coupled with administration of radioactively labeled anti-CA-IX monoclonal antibody. Specificity for clear cell RCC and type 2 papillary RCC has been demonstrated, potentially allowing for noninvasive risk stratification for patients with localized renal masses (Divgi et al, 2013).

Renal Function after Surgery for Localized Renal Cell Carcinoma

Notwithstanding advances in our understanding of the genetics and biology of RCC, surgery remains the mainstay for curative treatment of this disease. The objective of surgical therapy is to excise all tumor with an adequate surgical margin. Simple nephrectomy was practiced for many decades but was supplanted by RN when Robson and colleagues (1969) established this procedure as the gold standard curative operation for localized RCC. RN is still a preferred option for many patients with localized RCC, such as those with very large tumors (most clinical T2 tumors) or the relatively limited subgroup of patients with clinical T1 tumors that are not amenable to nephron-sparing approaches (Nguyen et al, 2008a). RN has more recently fallen out of favor for small renal tumors because of concerns about CKD, and should only be performed when necessary in this population (Nakada, 2005; Nguyen et al, 2008a; Russo and Huang, 2008; Campbell et al, 2009).

The main concern with RN is that it predisposes to CKD, which is potentially associated with morbid cardiovascular events and increased mortality rates. Several studies have shown an increased risk of CKD on longitudinal follow-up after RN, including a landmark study from the Memorial Sloan Kettering Cancer Center that looked at 662 patients with a small solitary tumor, a normal opposite kidney, and a "normal" serum creatinine level—essentially patients who would be considered for elective PN (Huang et al, 2006; Russo and Huang, 2008). The first major finding was that 26% of this patient population had preexisting grade 3 CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²), demonstrating that this patient population is substantially different than the kidney transplant donor population that is often considered analogous. In reality, the donor population is not comparable because it is carefully screened to exclude CKD and related comorbidities. The second major finding was that the incidence of grade 3 CKD was much more common after RN than PN: 65% versus 20%, respectively ($P < .001$). More severe CKD (eGFR <45 mL/min/1.73 m²) was also much more common after RN than PN: 36% versus 5%, respectively ($P < .001$).

Several studies illustrate the potential negative implications of CKD, including a population-based study that followed more than a million subjects for 2.8 years and reported increased rates

of cardiovascular events and death as the degree of CKD worsened even after controlling for hypertension, diabetes, and other potential confounding factors (Go et al, 2004). The relative risks of cardiovascular events were 1.4, 2.0, 2.8, and 3.4 for eGFR of 45 to 60, 30 to 45, 15 to 30, and less than 15 mL/min/1.73 m², respectively. Relative death rates were 1.2, 1.8, 3.2, and 5.9 for these same subgroups, respectively. These data highlight the potential need to optimize renal function and underscore nephron sparing as an important principle in the management of clinical T1 renal masses, particularly small renal masses (Miller et al, 2008; Russo and Huang, 2008; Thompson et al, 2008; Campbell et al, 2009; Huang et al, 2009; Lane et al, 2009b).

Multiple retrospective series in the past 5 years have compared PN versus RN for the management of clinical T1 renal masses, almost uniformly concluding in favor of PN (Kim et al, 2012b; MacLennan et al, 2012). A recent meta-analysis of this literature looked at over 30 such studies and revealed the following statistically significant results in favor of PN: (1) a 61% risk reduction for the development of severe CKD, (2) a 19% risk reduction in overall mortality, and (3) a 29% risk reduction in cancer-specific mortality. The retrospective nature of these studies naturally raises concern about selection bias, and the third result listed above substantiates this concern. Clearly, PN is not a stronger oncologic intervention than RN, and the only reasonable way to explain an advantage for PN with respect to cancer-specific outcomes is selection bias. One cannot help but wonder whether selection bias may also be contributing to the overall survival advantage for PN (Campbell et al, 2013; Shuch et al, 2013a).

A prospective trial of RN versus PN was reported in 2011 that has stimulated great controversy. This trial, EORTC 30904, randomized over 500 patients with small (<5.0-cm) unifocal tumors and a normal contralateral kidney to RN versus elective PN, and showed an advantage for RN in terms of lower perioperative morbidity, while PN provided better renal functional outcomes (Van Poppel et al, 2011b). Oncologic events were uncommon, as expected for small renal masses, and similar in both groups. Based on prevailing paradigms, we would have expected better overall survival in the PN group, primarily driven by reduced cardiovascular morbidity. However, 10-year overall survival was in reality better for RN than PN (81% vs. 76%, respectively, $P < .05$), and cardiovascular deaths were less common in the RN group. This trial has some flaws and most thought leaders in the field, including the authors, do not choose to interpret it literally. However, EORTC 30904 has stimulated further research by suggesting that the functional advantage of PN in the setting of a normal contralateral kidney may not be as beneficial as previously believed.

Further studies have suggested that there may be a difference between CKD resulting from medical causes (CKD-M) and that resulting from surgery (CKD-S). Patients with CKD caused by hypertension or diabetes will continue to suffer from these comorbidities, and will likely experience progressive decline in renal function, eventually affecting survival. The medical literature confirms this, as outlined above (Go et al, 2004). However, patients with CKD primarily resulting from surgical removal of nephrons typically do not need further surgery, and might stabilize (Campbell et al, 2013). This hypothesis was recently tested in a series of over 4000 patients with localized RCC managed with PN or RN, including 1182 with CKD prior to management (CKD-M) and 927 who developed CKD only after surgery (CKD-S) (Lane et al, 2013a). The mean annual decline of renal function was 4.7% in patients with CKD-M compared to only 0.7% for the CKD-S group. In addition, the survival of patients with CKD-S was very similar to the group of patients with no CKD, and substantially better than patients with CKD-M. Further research will be required, but such studies suggest that the impact of CKD resulting from surgery may not be as great as previously thought, at least in the setting of a normal contralateral kidney.

The recent controversies discussed above have created some confusion for those at the periphery of this field, but certain fundamental principles can be supported, as illustrated in the Key Points box.

KEY POINTS: PARTIAL VERSUS RADICAL NEPHRECTOMY

- PN is preferred for small renal masses (T1a, <4.0 cm) whenever feasible, because RN represents gross overtreatment for most such lesions, which tend to have limited biologic potential.
- PN is also strongly preferred whenever preservation of renal function is potentially important, such as patients with pre-existing CKD, those with an abnormal contralateral kidney, or those with multifocal or familial RCC.
- Larger renal tumors (clinical stages T1b and T2) have increased oncologic potential and have often already replaced a substantial portion of the parenchyma, leaving less to be saved by PN. In the setting of a normal contralateral kidney, the relative merits of PN versus RN can be debated in this population.
- Well-designed randomized, prospective trials will be required to provide higher quality data and to allow for more rational management of patients with localized renal tumors.

Radical Nephrectomy

The prototypical concept of RN encompasses the basic principles of early ligation of the renal artery and vein, removal of the kidney with primary dissection external to the Gerota fascia, excision of the ipsilateral adrenal gland, and performance of an extended lymphadenectomy from the crus of the diaphragm to the aortic bifurcation (O'Malley et al, 2009b). Controversy has arisen regarding the need for many of these practices on a routine basis (Lam et al, 2004). Performance of a perifascial nephrectomy is of undoubted importance during RN for preventing postoperative local tumor recurrence because approximately 25% of clinical T1b/T2 RCCs manifest perinephric fat involvement (Lam et al, 2007; Thompson et al, 2007a). Preliminary renal arterial ligation remains an accepted practice; however, in large tumors with abundant collateral vascular supply, it is not always possible to achieve complete preliminary control of the arterial circulation (O'Malley et al, 2009b). It has been well demonstrated that removal of the ipsilateral adrenal gland is not routinely necessary in the absence of radiographic adrenal enlargement unless the malignant lesion extensively involves the kidney and/or is locally advanced (Lane et al, 2009c; Bratslavsky and Linehan, 2011; Weight et al, 2011). Location of the tumor in the upper portion of the kidney immediately adjacent to the adrenal gland is another relative indication for adrenalectomy (Siemer et al, 2004; Lane et al, 2009c).

The need for an extensive lymphadenectomy in all patients undergoing RN also remains controversial, and a randomized study of lymphadenectomy versus controls at the time of renal surgery failed to show a distinct advantage (Phillips and Taneja, 2004; Patard et al, 2005; Leibovich and Blute, 2008; Blom et al, 2009). There are several factors that mitigate against a benefit of routine lymphadenectomy (Leibovich and Blute, 2008; O'Malley et al, 2009b). RCC metastasizes through the bloodstream independent of the lymphatic system in many patients, and the lymphatic drainage of the kidney is highly variable. Even an extensive retroperitoneal dissection may not remove all possible sites of metastasis. Many believe that only a relatively small percentage of patients (<2% to 3%) are likely to benefit from routine lymphadenectomy, namely, the subset of patients with micrometastatic disease (Giuliani et al, 1990; Leibovich and Blute, 2008; O'Malley et al, 2009b). In all likelihood, the involved lymph nodes in many of these patients would be removed by conventional RN, which incorporates the renal hilar and immediately adjacent paracaval or para-aortic lymph nodes. At present, the need for routine performance of an extended lymphadenectomy in all cases of RN is not well defined and most urologists perform this selectively based on age, comorbidities, and tumor characteristics (see *Treatment of*

Locally Advanced Renal Cell Carcinoma) (Blute et al, 2004a; Daneshmand et al, 2005; Leibovich and Blute, 2008; Crispen et al, 2011).

Open surgical techniques for RN are described in detail in Chapter 60. The surgical approach for RN is determined by the size and location of the tumor as well as by the body habitus of the patient (Diblasio et al, 2006). The operation is usually performed through a transperitoneal incision to allow abdominal exploration for metastatic disease and early access to the renal vessels. The authors prefer an extended subcostal incision for most patients undergoing open RN, although a midline incision is a reasonable alternative, and the thoracoabdominal approach can be useful for very large and potentially invasive tumors involving the upper portion of the kidney. An extraperitoneal flank incision may be appropriate in elderly patients or patients of poor surgical risk, but exposure can be limiting, particularly for large tumors or those with contentious hilar anatomy (Diblasio et al, 2006; Russo, 2006). In reality, most of these patients are now managed with a laparoscopic approach in this era.

Laparoscopic RN is now established as a less morbid alternative to open surgery in the management of low- to moderate-volume (10 to 12 cm or smaller), localized RCCs with no local invasion, limited or no venous involvement, and manageable lymphadenopathy. Current minimally invasive techniques allow replication of the important tenets of RN, and oncologic and other outcome data reflect this at several centers (Wille et al, 2004; Permpongkosol et al, 2005; Berger et al, 2009a). A variety of approaches, including transperitoneal, retroperitoneal, and hand-assisted laparoscopic RN, have been popularized and are described elsewhere in this text (see Chapter 61) (Nadler et al, 2006; Chung et al, 2007; Kawauchi et al, 2007; Miyake et al, 2007). The current data suggest that elderly and morbidly obese patients, those with a history of previous abdominal surgery, and those with large tumor size may also be considered for minimally invasive renal surgery, although selection of patients must be judicious and surgical expertise and experience should also be taken into account (Viterbo et al, 2005; Feder et al, 2008; Gabr et al, 2008; Tan et al, 2011). One concern is that laparoscopic RN has become particularly appealing to patients and physicians alike, and this has likely been a major driver in the overutilization of RN for small renal masses over the past several years (Fig. 57-16).

Several studies on outcomes after RN for localized RCC have now demonstrated that the risk of postoperative recurrent malignant disease is stage dependent, and surveillance protocols should reflect this (Stephenson et al, 2004; Skolarikos et al, 2007). A recent American Urological Association (AUA) Guidelines Panel reviewed this literature and provided recommendations for the surveillance of patients after renal surgery for localized renal RCC (Donat et al, 2013). Table 57-12 outlines general surveillance considerations that apply to all patients managed for a localized renal mass, including the role of laboratory testing, longitudinal assessment of renal function, and specific indications for central nervous system or bone imaging. Table 57-13 provides stage-specific information for patients managed with surgical excision, particularly the indications for abdominal and thoracic imaging.

Partial Nephrectomy

Nephron-sparing surgery for the treatment of a renal tumor was first described by Czerny in 1890 (reviewed in Herr, 2005). However, high morbidity limited its application. In 1950, Vermooten suggested that peripheral encapsulated renal neoplasms could be excised locally while leaving a margin of normal parenchyma around the tumor. Interest in PN for RCC has subsequently been stimulated by advances in renal imaging, experience with renal vascular surgery for other conditions, improved methods of preventing ischemic renal damage, growing numbers of incidentally discovered low-stage RCCs, greater appreciation of the deleterious effects of CKD, and encouraging long-term survival in patients undergoing this form of treatment (Uzzo and Novick, 2001). Nephron-sparing surgery entails complete local resection of

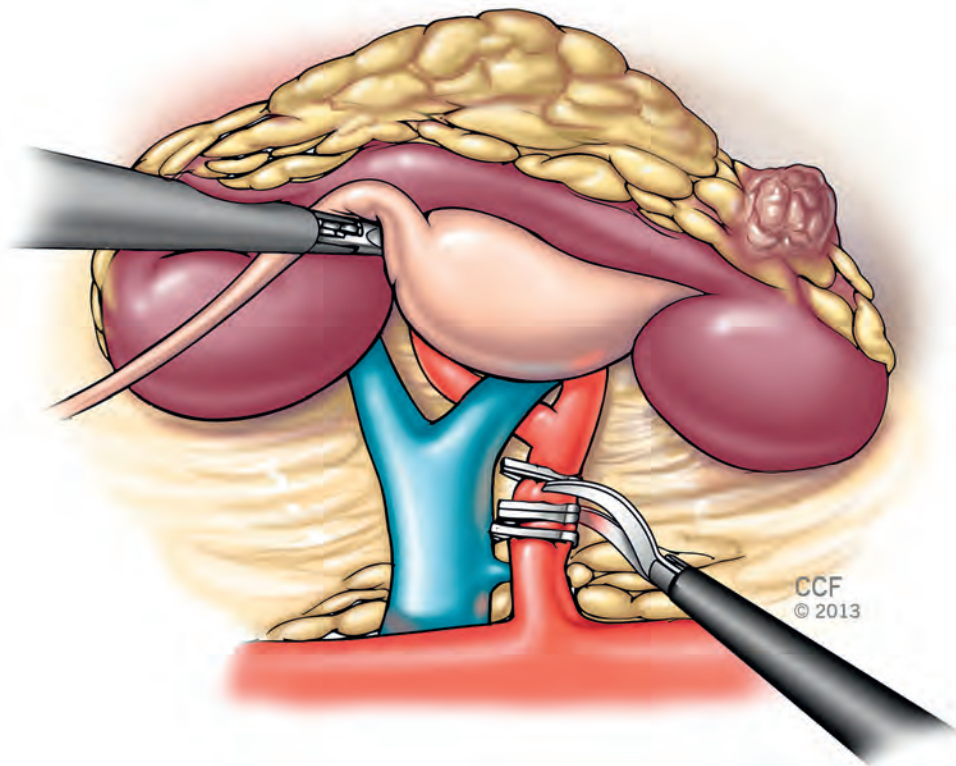


Figure 57-16. Laparoscopic radical nephrectomy (a retroperitoneal approach is illustrated) provides excellent oncologic outcomes and rapid recovery but predisposes patients to chronic kidney disease and potential cardiovascular risks and increased mortality rates. Nephron-sparing approaches should be prioritized whenever reasonable. (Reprinted with permission, Cleveland Clinic Center for Medical Art and Photography, © 2013. All Rights Reserved.)

the tumor while leaving the largest possible amount of normal functioning parenchyma in the involved kidney (Fig. 57-17).

Accepted indications for PN traditionally included situations in which RN would render the patient anephric or at high risk for ultimate need of dialysis (Licht et al, 1994; Russo et al, 2008; Campbell et al, 2009). This encompassed patients with bilateral RCC or RCC involving a solitary functioning kidney. A solitary functioning kidney may be the result of unilateral renal agenesis, prior removal of the contralateral kidney, or irreversible impairment of contralateral renal function by a benign disorder. Another traditional relative indication for PN was represented by patients with unilateral RCC and a functioning opposite kidney affected by a condition that might threaten its future function, such as renal artery stenosis (Campbell et al, 1993; Hafez et al, 2000), hydronephrosis, chronic pyelonephritis, ureteral reflux, calculus disease, or systemic diseases such as diabetes and nephrosclerosis (Uzzo and Novick, 2001; Campbell et al, 2009; Novick, 2009).

In patients with bilateral synchronous RCC, the general approach has been to preserve as much functioning renal tissue as possible. This entails performing bilateral PNs when feasible, usually as staged procedures, particularly if the tumors are relatively large. When a locally extensive tumor on one side precludes nephron-sparing surgery, an RN is performed on the more involved side along with a contralateral PN (Booth et al, 2008; Nguyen et al, 2008a; Rothman et al, 2008). Margin width appears to be immaterial as long as the final margins are negative; this is particularly relevant when the tumor is located within the hilum and preservation of renal function is at a premium (Li et al, 2008; Yossef-owitch et al, 2008; Campbell et al, 2009; Bensalah et al, 2010; Bernhard et al, 2010; Sundaram et al, 2011; Marszalek et al, 2012).

Patients with RCC involving a functionally or anatomically solitary kidney must be advised about the potential need for temporary or permanent dialysis postoperatively. In the series by

Fergany and colleagues (2006), 3.5% of patients with a solitary kidney managed with PN required temporary dialysis, and 18 of 400 patients (4.5%) eventually progressed to end-stage renal failure at a mean of 3.6 years after surgery. Many of these patients also had preexisting CKD before surgery, and in some instances only a small remnant kidney could be preserved because of large tumor size and anatomic considerations. Similarly, Ghavamian and colleagues (2002) reported a 12.7% incidence of acute renal failure when operating on a solitary kidney, with 15.9% of patients developing proteinuria and 12.7% experiencing severe CKD on a long-term basis. A functioning renal remnant of at least 20% to 30% of one kidney is necessary to avoid end-stage renal failure, although this presumes good functional status of the remaining parenchyma (Uzzo and Novick, 2001). Overall preservation of renal function is thus achieved in the great majority of patients with PN, even in patients with traditional imperative indications (Nguyen et al, 2008a). Local recurrence after PN for imperative indications traditionally ranged from 3% to 5%, because many of these cases were particularly challenging owing to hilar tumor location, the need to minimize the amount of excised functional parenchyma, tumor multifocality, or other complexities (Uzzo and Novick, 2001; Nguyen et al, 2008a).

In some patients with absolute indications, PN may not be anatomically feasible and radical surgery followed by dialysis may need to be considered. Renal transplantation may be an option for some of these patients after an appropriate cancer-free interval. An alternative approach is a trial of tyrosine kinase inhibitor therapy in an effort to downsize the tumor and enable PN, which can be successful in some instances (Thomas et al, 2009a; Gorin et al, 2012a; Kroon et al, 2013). Renal mass biopsy should be performed because clear cell histology appears to respond best to this approach (Rini et al, 2012). Meticulous surgical technique is paramount because the tyrosine kinase inhibitors can

TABLE 57-12 Surveillance for Clinically Localized Renal Neoplasms: General Considerations

FOLLOW-UP MEASURE	RECOMMENDATION
Physical examination and history	History and physical examination directed at detecting signs and symptoms of metastatic spread or local progression.
Laboratory testing	Basic laboratory testing, including BUN/creatinine, urinalysis, and eGFR, for all patients. Progressive renal insufficiency should prompt nephrology referral. CBC, LDH, LFTs, alkaline phosphatase, and serum calcium per discretion of the physician.
Central nervous system imaging	Acute neurologic signs should lead to prompt neurologic cross-sectional imaging of the head or spine based on localized symptoms.
Bone scan	Elevated alkaline phosphatase, clinical symptoms such as bone pain, and/or radiographic findings suggestive of a bony neoplasm should prompt a bone scan. Bone scan should not be performed in the absence of these signs and symptoms.

BUN, blood urea nitrogen; CBC, complete blood count; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; LFTs, liver function tests.

Modified from Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA guideline. *J Urol* 2013;190:407–16.

impair tissue healing, and these agents should be withheld for at least a few half-lives before and after PN (Thomas et al, 2009b; Hellenthal et al, 2010; Chapin et al, 2011).

PN is now standard of care for the management of small renal masses (clinical T1a) in the presence of a normal contralateral kidney, presuming that the mass is amenable to this approach (Huang et al, 2009; Lane et al, 2009b). A robust literature demonstrates equivalent oncologic outcomes with PN when compared with RN in appropriately selected patients, and the renal functional outcomes tilt the balance in favor of nephron-sparing approaches whenever feasible (Russo and Huang, 2008; Thompson et al, 2008; Huang et al, 2009; Van Poppel et al, 2011a). Prior experience with “elective” PN for T1a RCC demonstrated local recurrence rates of 1% to 2%, and overall cancer-free survival well over 90% (Campbell et al, 2009). The morbidity of PN has also decreased substantially in recent years in experienced hands (Thompson et al, 2005c; Joudi et al, 2007; Patard et al, 2007). The majority of local recurrences observed after PN are most likely a manifestation of undetected microscopic multifocal RCC in the renal remnant—most are found distant from the previous tumor bed. Concern about local recurrence after elective PN is counterbalanced by a 1% to 2% incidence of contralateral RCC on longitudinal surveillance, in which case RN would have left the patient with tumor in a solitary kidney (Nguyen et al, 2008a; Russo et al, 2008).

Evaluation of patients with RCC for PN should include preoperative testing to exclude locally extensive or metastatic disease and additional specific renal imaging to delineate the relationship of the tumor to the intrarenal vascular supply and collecting system. Three-dimensional volume-rendered CT (or MRI) is now established as a noninvasive imaging modality that can accurately depict the renal parenchymal and vascular anatomy in a format

TABLE 57-13 Surveillance after Radical or Partial Nephrectomy*

FOLLOW-UP MEASURE	RECOMMENDATION
LOW-RISK PATIENTS (pT1N0MX)	
Abdominal imaging	Partial Nephrectomy: Obtain a baseline abdominal scan (CT or MRI) within 3-12 months following surgery. If the initial postoperative scan is negative, abdominal imaging (US, CT, or MRI) may be performed yearly for 3 years based on individual risk factors. Radical Nephrectomy: Patients should undergo abdominal imaging (US, CT, or MRI) within 3-12 months following surgery. If the initial postoperative imaging is negative, abdominal imaging beyond 12 months may be performed at the discretion of the clinician.
Chest imaging	Partial and Radical Nephrectomy: Obtain a yearly CXR for 3 years and only as clinically indicated beyond that time period.
MODERATE- TO HIGH-RISK PATIENTS (pT2-4N0MX OR pT[ANY]N1MX): PARTIAL OR RADICAL NEPHRECTOMY	
Abdominal imaging	A baseline abdominal scan (CT or MRI) within 3-6 months following surgery with continued imaging (US, CT, or MRI) every 6 months for at least 3 years and annually thereafter to year 5. Imaging beyond 5 years may be performed at the discretion of the clinician. Perform site-specific imaging as symptoms warrant.
Chest imaging	Obtain a baseline chest scan (CT) within 3-6 months following surgery with continued imaging (CXR or CT) every 6 months for at least 3 years and annually thereafter to year 5. Imaging beyond 5 years is optional and should be based on individual patient characteristics and tumor risk factors.

*Please also refer to Table 57-12 for general considerations related to surveillance.

CT, computed tomography; CXR, chest x-ray; MRI, magnetic resonance imaging; US, ultrasound.

Modified from Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA guideline. *J Urol* 2013;190:407–16.

familiar to urologic surgeons (Uzzo et al, 2000; Simmons et al, 2007; Novick, 2009). This study integrates essential information from arteriography, venography, excretory urography, and conventional two-dimensional CT into a single imaging modality and obviates the need for more invasive renal imaging. The surgical techniques for performing nephron-sparing surgery in patients with RCC are reviewed in Chapters 60 and 61.

One of the largest reported studies of nephron-sparing surgery is from the Cleveland Clinic and reviewed the results of PN for the treatment of localized, sporadic RCC in 485 patients (Hafez et al, 1999). The mean postoperative follow-up was 4 years, and overall and cancer-specific 5-year survival rates

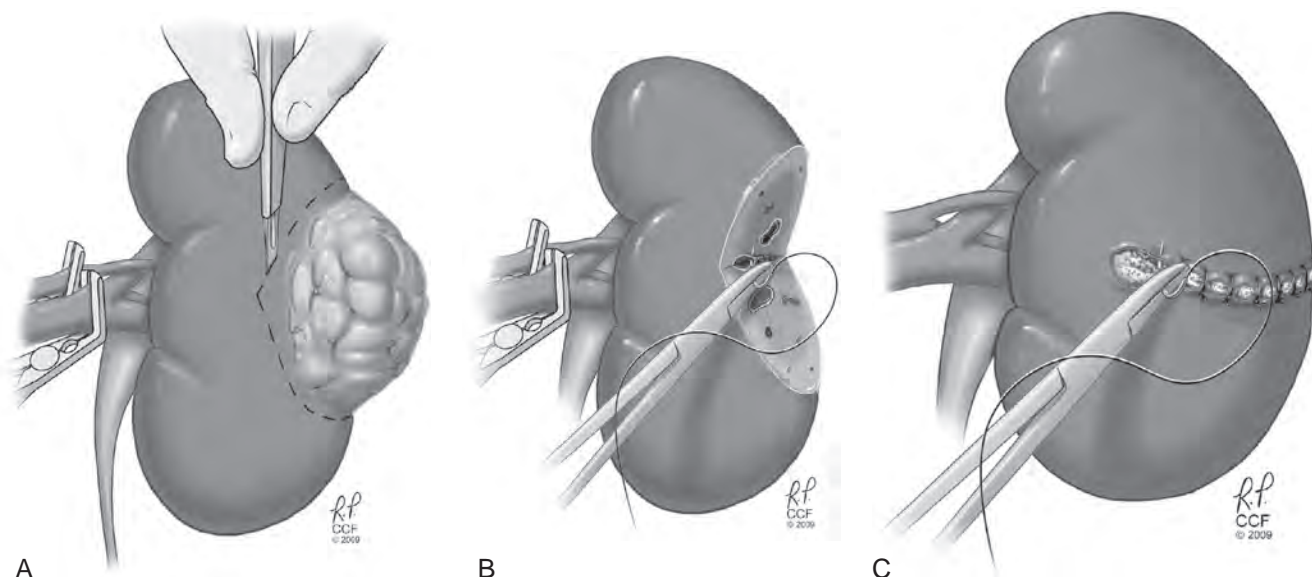


Figure 57-17. Essential steps in partial nephrectomy as illustrated with open approach. A, Temporary occlusion of the vascular pedicle and excision of the tumor with a rim of normal parenchyma. B, Closure of the collecting system and ligation of transected vessels. C, Capsular reconstruction. (Reprinted with permission, Cleveland Clinic Center for Medical Art and Photography, © 2007-9. All Rights Reserved.)

for patients in this series were 81% and 92%, respectively. Recurrent RCC developed postoperatively in 44 patients (9%), comprising 16 (3.2%) with local recurrence in the remnant kidney and 28 (5.8%) with metastatic disease. In another study from the Cleveland Clinic, long-term results of nephron-sparing surgery were reviewed in 107 patients with localized sporadic RCC treated before 1988 who were followed for a minimum of 10 years or until death (Fergany et al, 2000). Cancer-specific survival was 88% at 5 years and 73% at 10 years. Long-term renal function was preserved in 100 patients (93%). These results are particularly impressive given the patient population in that era, almost all of whom underwent PN for imperative indications. Ten-year follow-up was also provided by Herr (1999), who reported that 97% of patients remained cancer free after PN in the setting of a normal contralateral kidney, a more select population of patients. These data confirm that nephron-sparing surgery provides effective long-term therapy for patients with localized RCC and can preserve renal function in the overwhelming majority (Nguyen et al, 2008a; Ching et al, 2013).

A more recent trend has been to perform PN by minimally invasive approaches, with several series reporting encouraging results (Gill et al, 2002, 2003, 2006, 2007, 2010b; Permpongkosol et al, 2006a; Gill, 2012; Lane et al, 2013c). Whether pure laparoscopic or facilitated by robotic assistance (see Chapter 61), it is now possible to replicate the essential steps of the open surgical technique for many tumors, including occlusion of the renal vasculature, excision of the tumor with a rim of normal parenchyma, and intracorporeal suturing to close the collecting system and repair the capsular defect (Desai et al, 2003). Margin status and oncologic outcomes associated with laparoscopic or robotic PN appear to be equivalent to open PN in experienced hands, presuming sensible patient selection (Lane and Gill, 2007). The RENAL (Radius, Endophytic vs. exophytic, Nearness to collecting system, Anterior/posterior, Location relative to polar lines) and other nephrometry scoring systems allow for assessment of the complexity of the tumor and have facilitated comparison of evolving surgical techniques for PN in this era (Kutikov and Uzzo, 2009; Simmons et al, 2010, 2012). Early to intermediate experience with laparoscopic PN demonstrated increased rates of urologic complications such as postoperative hemorrhage and need for subsequent surgery despite selection for less complex tumors

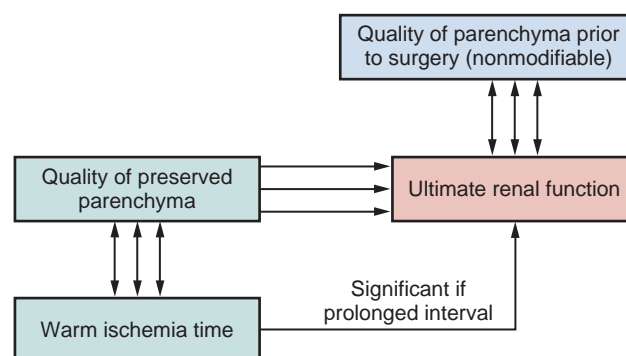


Figure 57-18. Determinants of ultimate renal function after partial nephrectomy. The quality and quantity of preserved parenchyma are the main determinants of renal function after partial nephrectomy, with ischemic injury playing a secondary role as long as limited warm ischemia or hypothermia is utilized. Prolonged warm ischemia, however, can lead to irreversible loss of nephron function.

in healthier patients (Gill et al, 2007). However, further experience and more prevalent utilization of robotic assistance have led to substantially reduced morbidity, and these minimally invasive approaches are now well established in our armamentarium for PN, presuming sensible patient selection based on tumor complexity and surgeon experience (Turna et al, 2009; Gill et al, 2010b; Dulabon et al, 2011; Kaouk et al, 2011, 2012; Mullins et al, 2012; Lane et al, 2013c).

One ongoing controversy in the field relates to the determinants of renal function after PN, which has important implications with respect to surgical technique. One of the main objectives of PN is to preserve as much renal function as possible, and the factors that can influence ultimate renal function include the quality of the parenchyma prior to surgery, the quantity of vascularized parenchyma that can be preserved, and potential deleterious effects of ischemia (Fig. 57-18). The quality of the parenchyma is for the most part nonmodifiable, essentially setting the baseline of renal function that would persist if no intervention was performed.

Most studies that have incorporated the other two, potentially modifiable, factors into multivariable analysis suggest that the number of preserved nephrons is the primary factor determining renal function after PN, while ischemic injury plays a secondary role (Song et al, 2009; Lane et al, 2011; Simmons et al, 2011; Weight and Thompson, 2012). Stated another way, as long as the warm ischemic interval is limited (<25 minutes) or hypothermia is applied, most preserved nephrons will recover their function (Campbell, 2012; Thompson et al, 2012; Mir et al, 2013). Precise excision of the tumor with a small rim of normal parenchyma along with careful reconstruction of the kidney to minimize devascularization is of paramount importance and can be facilitated by a short ischemic interval to allow for a bloodless field. Hypothermia should be considered for more complex cases or whenever a prolonged ischemic interval is anticipated, particularly for patients with a solitary kidney or preexisting CKD. However, other techniques and perspectives, such as the concept of segmental arterial clamping (Gill et al, 2011, 2012; Shao et al, 2011), have shown promise and further investigation will be required to address ongoing controversies in this field (see Chapter 61).

Surveillance of patients after PN, similar to RN, can be tailored to pathologic tumor stage; the basic recommendations are detailed in Tables 57-12 and 57-13. These protocols should help minimize costs, radiographic exposure, and patient inconvenience while still allowing for detection of most clinically relevant recurrences (Donat et al, 2013).

Patients who undergo nephron-sparing surgery for RCC may be left with a relatively small amount of renal tissue and are at risk for development of long-term renal functional impairment from hyperfiltration renal injury (Modlin and Novick, 2001; Abdi et al, 2003; Lane et al, 2009b; Novick, 2009). In a study of 14 patients observed for up to 17 years after PN in a solitary kidney, patients with more than 50% reduction in overall renal mass were found to be at increased risk for development of proteinuria, focal segmental glomerulosclerosis, and progressive renal failure (Novick et al, 1990). The development of proteinuria correlated directly with the length of follow-up and inversely with the amount of remaining renal tissue. Renal biopsy revealed focal segmental glomerulosclerosis in several patients with severe proteinuria (Fig. 57-19). These findings mirror those observed in experimental animal models of partial renal ablation (Brenner,

1983). Because proteinuria is the initial manifestation of this phenomenon, a 24-hour urinary protein measurement should be obtained yearly in patients with a solitary remnant kidney to screen for hyperfiltration nephropathy. Efforts to prevent or to ameliorate the damaging effects of renal hyperfiltration have focused on dietary and pharmacologic interventions, primarily the use of angiotensin-converting enzyme inhibitors combined with a low-protein diet (Goldfarb, 1995; Novick and Schreiber, 1995).

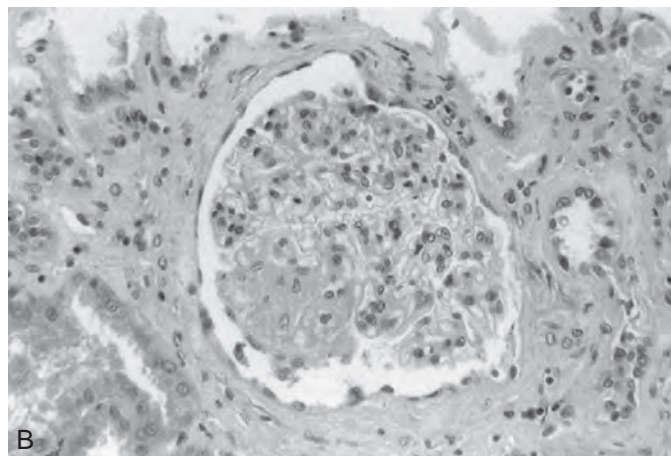
Thermal Ablative Therapies

Thermal ablative therapies, including renal cryosurgery and radiofrequency ablation (RFA), have emerged as alternative nephron-sparing treatments for patients with localized RCC (Murphy and Gill, 2001; Sterrett et al, 2008). Both can be administered percutaneously or through laparoscopic exposure and thus offer the potential for reduced morbidity and more rapid recovery (Johnson et al, 2004; Sterrett et al, 2008). Effect on renal function is typically limited, and these modalities appear to be reasonable choices for select patients with tumor in a solitary kidney, although PN remains the optimal choice in this circumstance (Weisbrod et al, 2010; Altunrende et al, 2011). In general, long-term efficacy of TA is not as well established when compared to surgical excision, and current data suggest that the local recurrence rates are somewhat higher than those reported for traditional surgical approaches (Kunkle et al, 2008; Campbell et al, 2009). Another concern has been the lack of accurate histologic and pathologic staging associated with these modalities, because the treated lesion is left in situ.

The ideal candidates for TA procedures may be patients with advanced age or significant comorbidities who prefer a proactive approach but are not optimal candidates for conventional surgery, patients with local recurrence after previous nephron-sparing surgery, and patients with hereditary renal cancer who present with multifocal lesions for which multiple PNs might be cumbersome (Kunkle et al, 2008). Patient preference must also be considered, and some patients not fitting these criteria may also select TA, a decision that can be supported as long as balanced counseling about the current status of these modalities has been provided (Matin and Ahrar, 2009; Faddegon and Cadeddu,



Figure 57-19. A, Ten years after partial nephrectomy for a large tumor in a solitary left kidney, an intravenous pyelogram shows function of small renal remnant. The patient had developed nephrotic syndrome at this time. B, Renal biopsy specimen shows focal segmental glomerulosclerosis indicative of hyperfiltration nephropathy.



2012). Finally, tumor size is also an important factor in patient selection because the current technology does not allow for reliable treatment of lesions larger than 4.0 cm in diameter, and success rates appear to be highest for tumors smaller than 2.5 to 3.0 cm (del Cura et al, 2010; Tracy et al, 2010; Tanagho et al, 2012; Atwell et al, 2013).

Experience with renal cryosurgery predates that of RFA and has been more extensive (Sterrett et al, 2008). Established prerequisites for successful cryosurgery include rapid freezing, gradual thawing, and a repetition of the freeze-thaw cycle. The mechanism underlying tissue cryodestruction is thought to involve immediate membrane and cellular damage followed by microcirculatory failure (Stein and Kaouk, 2007). Intracellular ice irreversibly disrupts cell organelles and the cell membrane, a lethal event. Delayed microcirculatory failure occurs during the slow thaw phase of the freeze-thaw cycle, leading to circulation arrest and cellular anoxia. Cells that survive the initial cryogenic assault are destroyed by this secondary insult of ischemia. Repetition of the rapid freeze-slow thaw cycle potentiates the damage (Hinshaw and Lee, 2004).

Further work defined treatment parameters required to bring this treatment into the clinical domain. Chosy and colleagues (1996) demonstrated that complete and reliable tissue necrosis could be consistently achieved only at temperatures of -19.4°C or lower. Campbell and coworkers (1998) confirmed that the target lethal temperature of -20°C was achieved at a distance of 3.1 mm inside the leading edge of the iceball as visualized by real-time ultrasonography. Thus, to ensure complete cell kill, the iceball must extend well beyond the visible margins of the targeted tumor. In practice, we routinely extend the iceball approximately 1 cm beyond the edge of the tumor, as determined by real-time imaging (Gill et al, 1998). The availability of sophisticated and reliable ultrasonography and the introduction of finer cryoprobes that allow more accurate and less traumatic probe placement have contributed to even greater interest in visceral cryosurgery (Sterrett et al, 2008).

Clinical experience and follow-up of patients after renal cryoablative therapy suggests successful local control in about 90% of patients, although many studies provide limited, and often incomplete, follow-up (Gill et al, 2005; Stein and Kaouk, 2007; Campbell and Palese, 2011; Klatte et al, 2011; Guillotreau et al, 2012). Diagnosis of local recurrence after TA can be challenging because evolving fibrosis within the tumor bed can be difficult to differentiate from residual cancer. In general, central or nodular enhancement within the tumor bed on extended follow-up has been considered diagnostic of local recurrence, and the clinical experience with cryoablation has thus far supported this (Bolte et al, 2006; Weight et al, 2008). However, only a minority of studies have incorporated routine post-therapy biopsies to provide histologic confirmation of oncologic status (Gill et al, 2000; Weight et al, 2008). Other findings that suggest local recurrence include a progressive increase in size of an ablated neoplasm, new nodularity in or around the treated zone, failure of the treated lesion to regress over time, or satellite or port site lesions (Donat et al, 2013). If these features are found, biopsy and possible retreatment should be considered. The AUA guidelines for surveillance after TA are outlined in Tables 57-12 and 57-14.

Reported rates of local recurrence in some of the TA series may represent underestimates because about 20% of small renal masses are benign rather than RCC, and a pretreatment biopsy, although strongly advocated in the field, has not been routinely performed in many series (Heilbrun et al, 2007; Sterrett et al, 2008). In general, the literature regarding TA is still notable for a variety of deficiencies, including limited follow-up in the great majority of studies and poor quality of reporting (Campbell and Palese, 2011; Kang et al, 2012). More mature data are now available in a limited number of studies, supporting encouraging outcomes for smaller tumors, particularly those less than 3.0 cm in diameter, yet the cumulative experience continues to suggest that local control after cryoablative therapy remains suboptimal

TABLE 57-14 Surveillance after Renal Ablation*

FOLLOW-UP MEASURE	RECOMMENDATION
Diagnostic biopsy	Patients should undergo a pretreatment diagnostic biopsy.
Abdominal scan	Cross-sectional scanning (CT or MRI) with and without IV contrast unless otherwise contraindicated at 3 and 6 months following ablative therapy, with continued scanning annually thereafter for 5 years. Imaging beyond 5 years is optional based on individual risk factors.
Chest imaging	Patients who have either biopsy-proven low-risk renal cell carcinoma, [†] oncocytoma, a tumor with oncocytic features, nondiagnostic biopsies, or no prior biopsy should undergo annual CXR for 5 years. Imaging (CXR or CT) beyond 5 years is optional based on individual patient risk factors and the determination of treatment success. Radiographic scanning is not recommended with pathologic confirmation of benign disease at or before treatment and post-treatment radiographic confirmation of treatment success and no evidence of treatment-related complications.
Repeat biopsy	New enhancement, a progressive increase in size of an ablated neoplasm with or without contrast enhancement, new nodularity in or around the treated zone, failure of the treated lesion to regress over time, or satellite or port site lesions should prompt a repeat lesion biopsy. Observation, repeat treatment, and surgical intervention should be discussed for recurrence.

*Please also refer to Table 57-12 for general considerations related to surveillance.

[†]Based on the definitions adopted for this guidelines process, thermal ablation should be restricted primarily to low-risk patients. In more general terms, any patient with renal cell carcinoma managed with thermal ablation should undergo annual CXR for 5 years.

CT, computed tomography; CXR, chest x-ray; IV, intravenous; MRI, magnetic resonance imaging.

Modified from Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA guideline. J Urol 2013;190:407–16.

when compared to surgical excision (Kunkle et al, 2008; Guillotreau et al, 2012). For instance, in the series from Aron and colleagues (2010), the local recurrence rate at 5 years was 9%, and in the series from Lusch and colleagues (2013) it was approximately 8%. This can be contrasted with 5-year local recurrence rates of about 1% to 2% for surgical excision for analogous small renal masses (Campbell et al, 2009).

Other concerns with cryoablation, and TA in general, relate to surgical salvage and potential morbidity. Most local recurrences can be salvaged with repeat ablation, although some patients with progressive disease eventually require conventional surgery. Nguyen and colleagues (2008b) have shown that PN and minimally invasive approaches are occasionally precluded in this

setting because of the extensive fibrotic reaction induced by TA. This reaction appears to be more significant after cryoablation than after RFA, although the precise reasons for this are unclear at present (Kowalczyk et al, 2009). Complications associated with cryoablation can include renal fracture, hemorrhage, adjacent organ injury, ileus, and wound infection, although major morbidity is decidedly uncommon (Sidana et al, 2010; Tsivian et al, 2010). As expected, the incidence of treatment failure or complications after TA correlates with tumor size and complexity, as estimated by the RENAL scoring system (Schmit et al, 2013).

The experience with RFA has been more variable, likely related to surgeon experience, the availability of different platforms that can be accessed to perform this procedure, and inability to monitor treatment progress as stringently as cryoablation (Sterrett et al, 2008). Application of high-frequency electrical current by RFA induces excitation of ions, frictional forces, and heat, which in turn cause denaturation of intracellular proteins and melting of cellular membranes, a lethal sequence of events. These effects are observed at tissue temperatures above 41°C but increase directly with increasing temperature and duration of treatment (Sterrett et al, 2008). Temperatures in excess of 100°C are typically obtained at the tips of the probes, and thermosensors can be used to monitor progress during active treatment. Temperature dissipates at points more distant from the probe tip, and multiple probes or types are typically required to achieve adequate heating of the entire region of interest (Murphy and Gill, 2001). One disadvantage of RFA is that the treatment effect is potentially more difficult to monitor in real time—there is no true “iceball equivalent” (Zelkovic and Resnick, 2003). Rather, treatment is typically based on empirical results from previous probe alignments, supplemented by data from thermoprobes, and this allows a fairly predictable target zone of up to 4.0 cm to be treated in most cases. Maximal tumor size that can be reliably treated would of necessity be smaller than this, given the need to extend the treatment zone beyond all edges of the tumor.

Local control after RFA is difficult to determine owing to a number of complexities, although most estimate that this will be 80% to 90% on a longitudinal basis using strict definitions of local recurrence (Kunkle et al, 2008; Campbell et al, 2009). Loss of enhancement on cross-sectional imaging within the lesion has generally been accepted as an indicator of success, although this has been challenged. Weight and colleagues (2008) reported 6 patients with no enhancement on MRI performed 6 months after RFA who were found to have apparently viable cancer cells on biopsy of the tumor bed. The issue of potential false-negative and false-positive imaging findings after TA remains a concern, although such events appear to be relatively uncommon (Matin, 2010). More strict definitions of local control after TA were recently advocated by an AUA guidelines panel and are reviewed in Table 57-14 (Donat et al, 2013).

The technology for RFA continues to improve, and most contemporary series report relatively low rates of local recurrence, although some patients require repeat treatments to achieve local control, which is an infrequent event with cryoablation and rarely required with conventional surgical treatments for localized RCC (Sterrett et al, 2008). In the series from Tracy and colleagues (2010) there were seven treatment failures and nine other local recurrences among 179 patients with biopsy proven RCC during median follow-up of 27 months. Using strict criteria, local control was achieved in 91% of patients in this series; however, many of the patients with local recurrence were potentially salvaged with repeat ablation or surgical excision, and overall cancer-specific survival remained high. Longer follow-up will be required to more fully evaluate outcomes in this and other series in the RFA literature. Some RFA series report even more encouraging results, particularly for tumors less than 3.0 cm diameter (Atwell et al, 2013), whereas others have reported 5-year local recurrence rates as high as 39% (Samarasekera et al, 2013).

Complications from RFA are uncommon but have included acute renal failure, stricture of the ureteropelvic junction,

necrotizing pancreatitis, and lumbar radiculopathy, so careful and judicious selection of patients is essential (Sterrett et al, 2008). Direct comparison with cryoablation is inevitable but perhaps unfair because RFA is earlier in its development and recent reports suggest great promise (Sterrett et al, 2008; Atwell et al, 2013).

Other exciting new technologies, such as high-intensity focused ultrasound (HIFU) and frameless, image-guided radio-surgical treatments (CyberKnife), are also under development and may allow extracorporeal treatment of small renal tumors in the future (Ponsky et al, 2007; Haber et al, 2010; Kroeze et al, 2012). However, at present cell kill with these modalities is not sufficiently reliable and they are best considered developmental (Castle et al, 2011).

Active Surveillance

There was once relatively little information about the growth rate of RCC because almost all renal tumors were excised shortly after detection based on prior paradigms of management (Jewett and Zuniga, 2008; Graversen et al, 2011; Lane et al, 2012). The incidental discovery of many small RCCs in asymptomatic elderly patients or those of poor surgical risk has provided the opportunity to observe the growth rate of these tumors in patients who are unable or unwilling to undergo surgery (Abouassaly et al, 2008; Chen and Uzzo, 2009; Crispen et al, 2009; Rosales et al, 2010; Mason et al, 2011). Bosniak and associates (1995) reported one of the first and largest series of AS that included 72 small (<3.5 cm) renal tumors in 68 patients who were observed with serial imaging studies for intervals ranging from 2 to 10 years (mean, 3.3 years). On CT these were well-margined, homogeneous, solid, enhancing tumors consistent with RCC. During the period of observation these tumors grew at slow and variable rates of up to 1.1 cm per year, with a median growth rate of 0.36 cm per year. In 32 patients whose tumors grew to larger than 3 cm, surgical excision was performed; all the excised tumors proved to be stage pT1a RCCs, and the majority were grade 1 tumors. Significantly, none of the patients developed metastasis during the period of surveillance.

Subsequent series from several institutions have confirmed that many small renal masses will grow relatively slowly (median growth rate 0.12 to 0.34 cm/yr) and with a relatively low rate of metastasis (1.2% to 2.0% during 2 to 4 years of follow-up), suggesting that this may be a reasonable management strategy in carefully selected patients who are not candidates for conventional surgery or thermal ablative approaches (Campbell et al, 2009; Graversen et al, 2011; Jewett et al, 2011; Smaldone et al, 2012). However, a critical review of this literature is required to recognize the potential limitations of these studies (Campbell et al, 2009). First, most AS series have included only relatively small, well-margined, and homogeneous renal masses, reflecting strong selection bias. A substantial proportion (20% or more) of these tumors may have been benign—biopsy was only performed in a minority of patients in these series. In addition, follow-up in most series is limited to 2 to 3 years, and in some cases the growth rate was calculated backward by obtaining old films for which the lesion of interest was either previously missed or dismissed, introducing a possible ascertainment bias (Jewett and Zuniga, 2008; Crispen et al, 2012). Finally, in most of these series there is a subpopulation of patients with rapidly growing tumors that appear to have more aggressive characteristics. For instance, in the series from Volpe and colleagues (2004), 25% of the masses doubled in volume in 12 months and 22% reached a diameter of 4 cm, triggering surgical intervention. Similarly, Sowers and Siemens (2004) reported 9 tumors with mean growth rate of 1.43 cm per year, representing a substantial proportion of their patients. Salvage of patients with metastatic RCC is unlikely, and in some patients the window of opportunity for nephron-sparing surgery may be lost.

Nevertheless, these studies suggest that patients with small, solid, enhancing, well-margined, homogeneous renal lesions,

who are elderly or poor surgical risks, can safely be managed with observation and serial renal imaging at 6-month or 1-year intervals (Jewett and Zuniga, 2008; Campbell et al, 2009; Chen and Uzzo, 2009; Kutikov et al, 2012). In this population, the risk of competing noncancer causes of death and the risk of intervention will most often outweigh the risk of RCC progression (Hollingsworth et al, 2007). In fact, recent data indicate that active treatment of small renal masses in elderly patients (>75 years of age) may not confer a measurable survival benefit over AS, further supporting a conservative approach in many of these patients (Lane et al, 2010). Prospective data and studies with more prolonged follow-up are now becoming available, and in general are supportive of AS in appropriately selected patients (Haramis et al, 2011; Jewett et al, 2011). The AUA guidelines provide recommendations for follow-up of patients on AS, as outlined in Tables 57-12 and 57-15, including consideration for renal mass biopsy to stratify oncologic risk.

In general, AS is not appropriate for patients with larger (>3 to 4 cm), poorly marginated, or nonhomogeneous solid renal lesions, or when biopsy indicates a potentially aggressive RCC, except in patients with limited life expectancy (Remzi et al, 2006; Kunkle et al, 2007). AS is also not advisable in younger, otherwise healthy, patients with small, solid tumors that have radiographic

characteristics consistent with RCC (Campbell et al, 2009; Lane et al, 2012). Even if these lesions are smaller than 3 cm, the current data indicate that most will grow and eventually reach a size at which metastasis becomes a possibility. Unfortunately, growth rates on observation do not allow for reliable differentiation of benign versus malignant histology (Siu et al, 2007; Crispen et al, 2008b; Kawaguchi et al, 2011). Therefore, in this setting, it is more appropriate to consider treating the tumor by surgical excision or TA when it is small, clearly localized, and still amenable to nephron-sparing approaches (Van Poppel and Joniau, 2007; Campbell et al, 2009; Chen and Uzzo, 2009).

Clinical T1 Renal Mass: Algorithm for Management

Acknowledging substantial controversy with respect to the management of small renal masses, with some current practices discordant with what the literature supports, the AUA Practice Guidelines Committee organized a panel to review this topic (Campbell et al, 2009). This process included a systematic meta-analysis of the literature, and the final document was vetted through an extensive peer review process. As expected, the database for open surgical techniques was most substantial and mature (Table 57-16). In contrast, follow-up for many of the other modalities was rather limited. Review of the data demonstrates strong selection biases, with RN procedures used to treat larger tumors, and AS and TA primarily applied to an older population of patients. There were almost no comparative studies; the overwhelming majority were retrospective and primarily observational. Other limitations of the data are detailed in the final document. The analysis revealed a small number of statistically significant comparisons of consequence for which confounding factors were unlikely to account for differences.

One such finding pertained to urologic complications, such as postoperative hemorrhage or urine leak, with PN procedures (laparoscopic and open) associated with the highest rates, likely reflecting the substantial technical challenges associated with these procedures (Table 57-17). This was thought to be a valid finding because PN procedures tended to be applied to younger patients and smaller tumors—patients who would be less likely to have such complications unless the complications were associated with procedural characteristics. A second significant result related to local recurrence, which was defined as any persistent or recurrent disease present in the treated kidney or ipsilateral renal fossa after initial treatment. This definition was adopted from standardized terminology developed by the International Working Group on Image-guided Tumor Ablation (Goldberg et al, 2005; Campbell et al, 2009). TA procedures had significantly higher rates of local recurrence when compared with all other treatment modalities (Table 57-18). This was also judged to be a valid finding, because these modalities were used to treat relatively small tumors and had short follow-up durations. In reality, it has been estimated that, when confounding factors such as length of follow-up are

TABLE 57-15 Active Surveillance: Imaging Recommendations*

FOLLOW-UP MEASURE	RECOMMENDATION
Percutaneous biopsy	Percutaneous biopsy may be considered prior to active surveillance.
Abdominal imaging	Cross-sectional scanning (CT or MRI) within 6 months of active surveillance initiation to establish a growth rate, with continued imaging (US, CT, or MRI) at least annually thereafter.
Chest imaging	Patients with biopsy-proven renal cell carcinoma or a tumor with oncocytic features on active surveillance should undergo annual CXR.

*Please also refer to Table 57-12 for general considerations related to surveillance.

CT, computed tomography; CXR, chest x-ray; MRI, magnetic resonance imaging; US, ultrasound.

Modified from Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA guideline. J Urol 2013;190:407–16.

TABLE 57-16 Patient Demographics and Study Information

	AS	RFA	CRYO	LPN	OPN	LRN	ORN
Median Patient Age, years	68	70	66	60	60	61	63
(No. studies; No. pts*)	(12; 390)	(19; 745)	(15; 644)	(26; 2245)	(28; 6418)	(17; 1581)	(16; 6235)
Median Tumor Size, cm	2.2	2.7	2.6	2.6	3.0	5.1	5.4
(No. studies; No. pts*)	(12; 390)	(19; 745)	(15; 644)	(26; 2245)	(25; 5596)	(15; 1391)	(14; 584)
Median Follow-Up, months	29	19	17	15	47	18	58
(No. studies; No. pts*)	(12; 390)	(10; 528)	(10; 463)	(17; 1639)	(22; 5057)	(8; 795)	(13; 5294)

*Numbers of studies and patients differ across variables because some studies did not report all information.

AS, active surveillance; Cryo, cryoablation; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radical nephrectomy; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RFA, radiofrequency ablation.

Modified from Campbell SC, Novick AC, Beldegrun A, et al. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1271–9.

TABLE 57-17 Major Urologic Complications

STUDY TYPE	NO. OF STUDIES	COMPLICATION RATE* (95% CONFIDENCE INTERVAL†)		MEDIAN PATIENT AGE (yr)	MEDIAN TUMOR SIZE (cm)
RFA	20	6.0	(4.4-8.2)	70	2.7
Cryo	15	4.9	(3.3-7.4)	67	2.6
LPN	22	9.0	(7.7-10.6)	60	2.6
OPN	15	6.3	(4.5-8.7)	59	3.0
LRN	13	3.4	(2.0-5.5)	61	5.1
ORN	6	1.3	(0.6-2.8)	62	5.2

*Statistically significant differences ($P < .05$): ORN rates are significantly lower than all other interventions; LPN rates are significantly higher than Cryo, RFA, LRN, and ORN rates; OPN rates are significantly higher than LRN and ORN rates; Cryo, RFA, and LRN rates are significantly higher than ORN rates; LPN and OPN rates are statistically indistinguishable; OPN, Cryo, and RFA rates are statistically indistinguishable; Cryo, RFA, and LRN rates are statistically indistinguishable.

†Calculated using a random effects model.

Cryo, cryoablation; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radical nephrectomy; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RFA, radiofrequency ablation.

Modified from Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. *J Urol* 2009;182:1271-9.

TABLE 57-18 Local Recurrence-Free Survival

STUDY TYPE	NO. OF STUDIES	SURVIVAL RATE* (95% CONFIDENCE INTERVAL†)		MEDIAN PATIENT AGE (yr)	MEDIAN TUMOR SIZE (cm)	MEDIAN FOLLOW-UP (mo)
RFA	10	87.0	(83.2-90.0)	70	2.7	19
Cryo	10	90.6	(83.8-94.7)	67	2.6	18
LPN	17	98.4	(97.1-99.1)	61	2.6	15
OPN	21	98.0	(97.4-98.5)	60	3.1	47
LRN	8	99.2	(98.2-99.7)	61	4.6	18
ORN	10	98.1	(97.3-98.6)	63	4.8	58

*Statistically significant differences ($P < .05$): LPN, OPN, LRN, and ORN rates are statistically indistinguishable and are all significantly higher than Cryo and RFA rates; Cryo and RFA rates are statistically indistinguishable.

†Calculated using a random effects model.

Cryo, cryoablation; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radical nephrectomy; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RFA, radiofrequency ablation.

Modified from Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. *J Urol* 2009;182:1271-9.

taken into consideration, the local recurrence rates for cryoablation and RFA will be substantially higher than for surgical excision (Kunkle et al, 2008). Many such recurrences can be salvaged with repeat ablation, but when this is not possible, surgical salvage can be challenging (Kunkle et al, 2008; Nguyen et al, 2008b; Kowalczyk et al, 2009). Other ongoing concerns with TA were reviewed previously. Analyses of other survival end points, such as metastasis-free, cancer-specific, and overall survival, indicated that all such survival rates were relatively high across treatments, reflecting the limited biologic aggressiveness of most clinical T1 renal tumors. Given strong selection biases and highly variable follow-up differences across treatments, comparisons related to these outcomes were not informative (Campbell et al, 2009).

Final management recommendations were framed in terms of each treatment modality's utility in the context of four index patients defined by tumor size (T1a vs. T1b) and general health (Fig. 57-20). Index patient 1, a healthy patient with a clinical T1a renal mass, is the most commonly encountered scenario. PN is a standard for this patient, with RN an alternate standard that should be applied only when PN is not feasible. One of the main concepts that is emphasized by this guideline document relates to the status of **nephron-sparing approaches as an overriding principle for the management of small renal masses, presuming that adequate oncologic control can be achieved** (Campbell et al, 2009). TA and AS are both options for index patient 1, although there are substantial concerns about these management strategies in this healthy patient. Given the complexity of counseling with such divergent

options for management, the panel believed strongly that a urologist should be involved in this process. The ongoing controversies about the management of larger renal masses in the presence of a normal contralateral kidney, and the need for better quality data, namely prospective, randomized trials, in this domain were reviewed previously. The panel also strongly advocated research priority for renal mass biopsy with molecular profiling to improve the estimation of tumor aggressiveness and facilitate more rational patient selection in this field (Fig. 57-21).

Nephron-Sparing Surgery in von Hippel-Lindau Disease and Other Forms of Familial Renal Cell Carcinoma

RCC in von Hippel-Lindau disease differs from its sporadic counterpart in that the diagnosis is made at a young age and there are usually multiple bilateral renal tumors (Kim et al, 2010; Linehan and Ricketts, 2013). Although these are generally low-stage tumors, they are capable of progression to metastasis and represent a frequent cause of death in patients with von Hippel-Lindau disease. RCC in these patients is characterized histopathologically by both solid tumors and renal cysts that contain either frank carcinoma or a lining of hyperplastic clear cells representing incipient carcinoma (Fig. 57-22).

The surgical options in patients with bilateral RCC and von Hippel-Lindau disease are bilateral nephrectomy and renal replacement therapy or nephron-sparing approaches such as PN

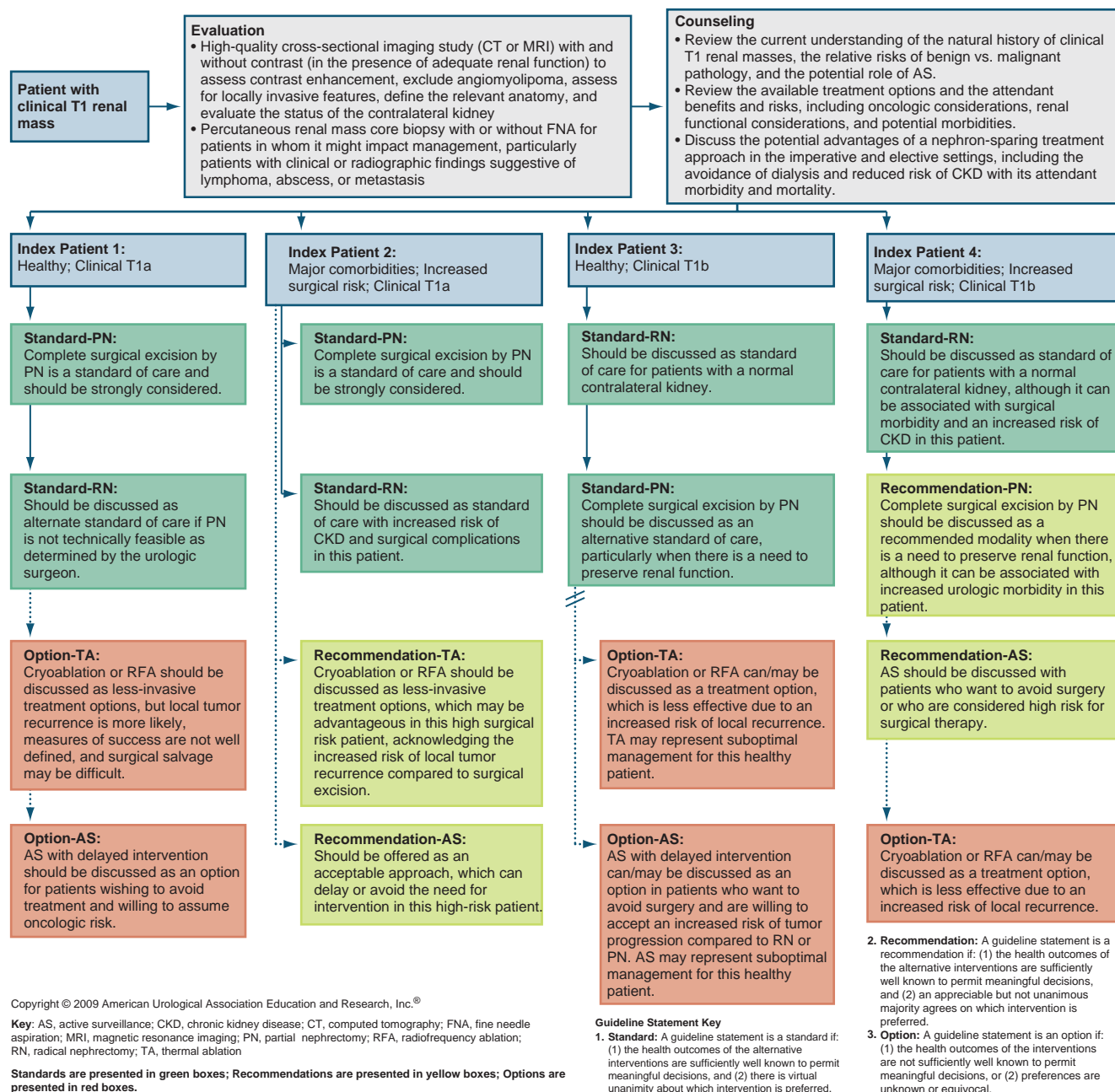


Figure 57-20. Algorithm for the evaluation, counseling, and management of the patient with a clinical T1 renal mass. (From American Urological Association Education and Research, Inc. Algorithm for management, <<https://www.auanet.org/common/pdf/education/clinical-guidance/Renal-Mass-Algorithm.pdf>>; 2009 [accessed 29.06.15].)

or TA to avoid end-stage renal disease. The general philosophy has been to pursue nephron-sparing strategies whenever possible, given the multifocal nature of the disease, even for centrally located tumors (Grubb et al, 2005; Shuch et al, 2012b; Linehan and Ricketts, 2013). For PN, an enucleative approach is often preferred rather than wide resection. Although early results of PN were promising, subsequent studies suggested a high incidence of post-operative tumor recurrence in the remaining portion of the kidney (Novick and Streem, 1992; Grubb et al, 2005). It is likely that most of these local recurrences were a manifestation of occult microscopic RCC that was not removed at the time of the original PN.

One multicenter study delineated the long-term outcomes after surgical treatment of localized RCC in 65 patients with von

Hippel-Lindau disease (Steinbach et al, 1995). RCC was present bilaterally and unilaterally in 54 and 11 patients, respectively. RN and PN were performed in 16 and 49 patients, respectively, and the mean postoperative follow-up interval was 68 months. The 5-year and 10-year cancer-specific survival rates for all patients were 95% and 77%, respectively. The corresponding rates for patients treated with PN were 100% and 81%, respectively. Survival free of local recurrence after PN was 71% at 5 years but only 15% at 10 years. Other studies confirm that patients with von Hippel-Lindau disease are at much higher risk for local recurrence than patients with sporadic RCC.

Duffy and colleagues (2004) at the National Cancer Institute have defined a 3-cm threshold for intervention in patients with

von Hippel-Lindau disease. In their series, a total of 108 patients with von Hippel-Lindau disease and solid renal tumors smaller than 3 cm were observed and none developed metastatic disease during mean follow-up of 58 months. In contrast, metastases developed in 20 of 73 patients (27.4%) with tumors larger than 3 cm and the frequency of metastases increased with increasing tumor size. A 3-cm cut point has thus been proposed to reduce the number of surgical interventions, to optimize renal function, and to minimize the risk of metastatic disease. This recommendation also applies to patients with HPRCC and Birt-Hogg-Dubé syndromes (Shuch et al, 2012b). However, HLRCC and SDH-RCC are exceptions in that tumors in these syndromes are typically more aggressive and should be managed accordingly, even when less than 3 cm (Shuch et al, 2012b).

Taken together, these studies suggest that PN can provide effective initial treatment of patients with RCC and von Hippel-Lindau disease but should be withheld until tumor size reaches or eclipses 3.0 cm. In recent years, TA has been used more frequently in this patient population as an alternative nephron-sparing approach (Matin et al, 2008; Park and Kim, 2010; Joly et al, 2011). After initial management, patients with von Hippel-Lindau disease must be observed closely because most will eventually develop locally recurrent RCC with the concomitant need for repeat renal intervention (Grubb et al, 2005; Ploussard et al, 2007). In this setting, repeat PN can be challenging because of

postoperative fibrosis, and TA may be preferred to reclaim local control (Liu et al, 2010; Agochukwu et al, 2012; Shuch et al, 2012b). Targeted agents are now being investigated in an effort to slow disease progression in patients with this syndrome (Grubb et al, 2005; Shuch et al, 2012b). When removal of all renal tissue is necessary for oncologic reasons, renal transplantation can provide satisfactory replacement therapy for end-stage renal disease and appears to be safe despite the tumor diathesis (Goldfarb et al, 1997).

Comprehensive management of patients suspected of having familial RCC should also include genetic counseling and screening for other manifestations of the disease process (as discussed in the earlier section on familial RCC and molecular genetics) (Shuch et al, 2012b). For patients with von Hippel-Lindau disease, identification of pheochromocytoma or central nervous system hemangioblastoma is particularly important before surgical intervention for RCC (Linehan and Ricketts, 2013).

TREATMENT OF LOCALLY ADVANCED RENAL CELL CARCINOMA

Inferior Vena Caval Involvement

One of the unique features of RCC is its frequent pattern of growth intraluminally into the renal venous circulation, also known as **venous tumor thrombus**. This growth may extend into the IVC with cephalad migration as far as the right atrium or beyond. The absence of metastases in many patients with vena caval extension is an intriguing aspect of this cancer's behavior (Gettman and Blute, 2002; Wotkowicz et al, 2008). Forty-five to 70 percent of patients with RCC and IVC thrombus can be cured with an aggressive surgical approach including RN and IVC thrombectomy (see **Key Points** box).

Overall, involvement of the venous system with RCC occurs in 4% to 10% of patients. IVC tumor thrombus should be suspected in patients with a renal tumor who also have lower extremity edema, isolated right-sided varicocele or one that does not collapse with recumbency, dilated superficial abdominal veins, proteinuria, pulmonary embolism, right atrial mass, or nonfunction of the involved kidney. Staging of the level of IVC thrombus is as follows: I, adjacent to the ostium of the renal vein; II, extending up to the lower aspect of the liver; III, involving the intrahepatic portion of the IVC but below the diaphragm; and IV, extending above the diaphragm. The prognostic significance of IVC thrombus level has been controversial. Most studies suggest that the incidence of locoregional or systemic progression

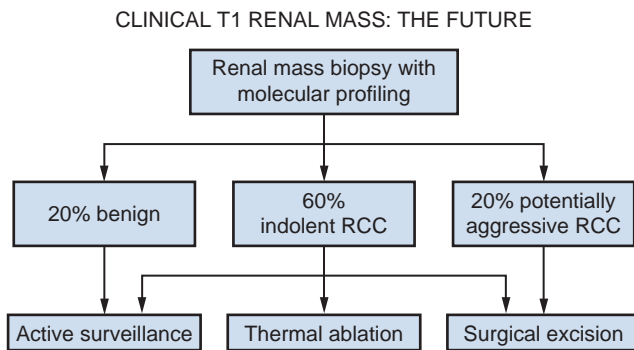


Figure 57-21. The American Urological Association guideline panel for the management of the clinical T1 renal mass strongly advocates research priority for renal mass biopsy with molecular profiling to facilitate more rational management of this patient population. RCC, renal cell carcinoma.

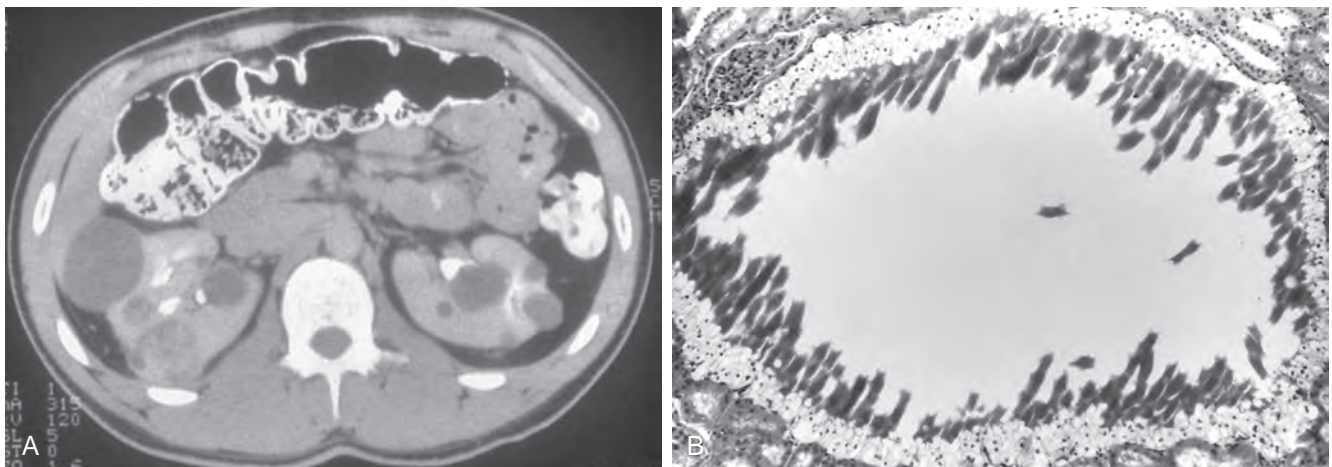


Figure 57-22. A, Computed tomography scan after administration of contrast agent shows bilateral solid and cystic renal masses in patient with von Hippel-Lindau disease. B, Histopathologic section of one of the renal cysts shows lining of clear cells representing incipient carcinoma.

KEY POINTS: TREATMENT OF LOCALLY ADVANCED RENAL CELL CARCINOMA

- Forty-five to 70 percent of patients with venous tumor thrombus can be cured with nephrectomy and thrombectomy.
- Thrombus extending into the IVC below the main hepatic veins can be readily managed with isolation of the involved vasculature and removal of the tumor thrombus.
- Thrombus extending above the main hepatic veins requires more extensive dissection, venovenous bypass, or cardiopulmonary bypass and circulatory arrest.
- For large tumors with radiographic suspicion of invasion into adjacent structures (cT4), complete excision with en bloc resection of the involved structures provides the only chance of cure.
- Bulky lymphadenopathy carries a poor prognosis similar to metastatic disease, although surgical resection should be considered if feasible and if appropriate given careful assessment of disease burden and patient age/comorbidities.
- High-quality preoperative imaging (CT or MRI) should be obtained in proximity to the anticipated surgery to plan for and achieve intraoperative success.
- Although locally advanced RCC is still primarily a surgical disease, adjuvant systemic therapy trials should be encouraged and, in select patients, neoadjuvant approaches may be considered.

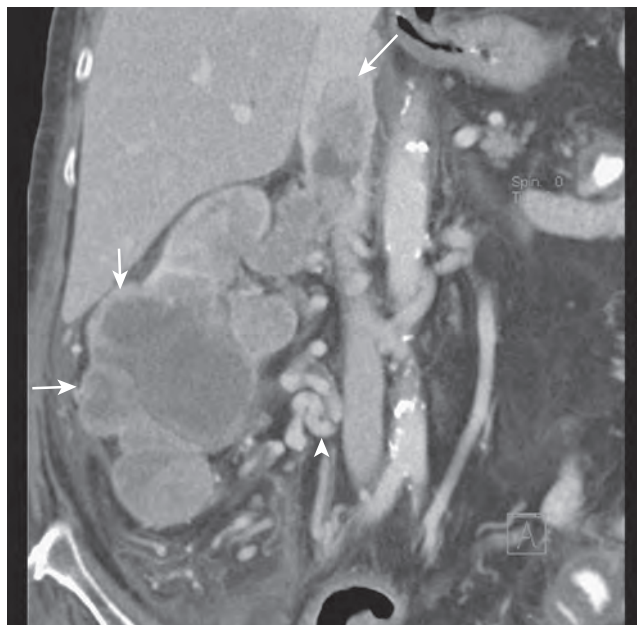


Figure 57-23. Computed tomography scan demonstrating lower pole right renal cell carcinoma (*short arrows*) with level III inferior vena cava (IVC) thrombus. The *long arrow* indicates the upper extent of the tumor thrombus within the intrahepatic portion of the IVC. The *arrowhead* indicates extensive retroperitoneal venous collateral vessels associated with restricted flow within the IVC.

is higher in patients with level III-IV IVC thrombus, and this probably accounts for the reduced survival reported in this subgroup in some series (Sosa et al, 1984; Quek et al, 2001; Zisman et al, 2003; Kim et al, 2004; Leibovich et al, 2005a). Other series have shown that any IVC involvement is worse than renal vein involvement without distinction with regard to IVC level; in these series, other factors, such as nodal or metastatic involvement and tumor grade, have more impact on overall survival (Blute et al, 2004b; Terakawa et al, 2007). However, even patients with level IV IVC thrombi can be cured with surgical resection, in the absence of metastases and other adverse features (Libertino et al, 1987; Glazer and Novick, 1996; Ciancio et al, 2007; Granberg et al, 2008). The seventh edition of the TNM staging system distinguishes tumors with thrombi above the diaphragm (stage T3c) from those with IVC thrombi below the diaphragm (stage T3b) and those with thrombi only within the renal vein or its major branches (stage T3a) (Edge et al, 2010).

MRI is a noninvasive and accurate modality for demonstrating both the presence and the cephalad extent of vena caval involvement and has been the preferred diagnostic study at many centers for the past few decades (Goldfarb et al, 1990; Pouliot et al, 2010). Administration of gadolinium during the study often allows tumor thrombus to be differentiated from bland thrombus, because the latter does not demonstrate enhancement. More recent evidence suggests that multiplanar CT can provide essentially equivalent information (Fig. 57-23) (Ng et al, 2008; Guzzo et al, 2009). The importance of high-quality preoperative imaging cannot be overemphasized, and this imaging should be obtained as close as possible to the date of surgery because progression of the tumor thrombus may mandate important changes in intraoperative management (Blute et al, 2004b; Wotkowicz et al, 2008).

Invasive contrast-enhanced imaging is reserved for patients in whom MRI and CT findings are equivocal or for whom MRI and CT are contraindicated. Although inferior venacavography remains an accurate diagnostic study, this invasive technique is generally unnecessary in the modern imaging era. Renal arteriography can also be used as an adjunctive preoperative study; vascularization of IVC tumor thrombus is observed in 35% to 40% of cases (Fig. 57-24) (Novick et al, 1990; Wotkowicz et al, 2008). When this finding is present, preoperative embolization of the renal artery can

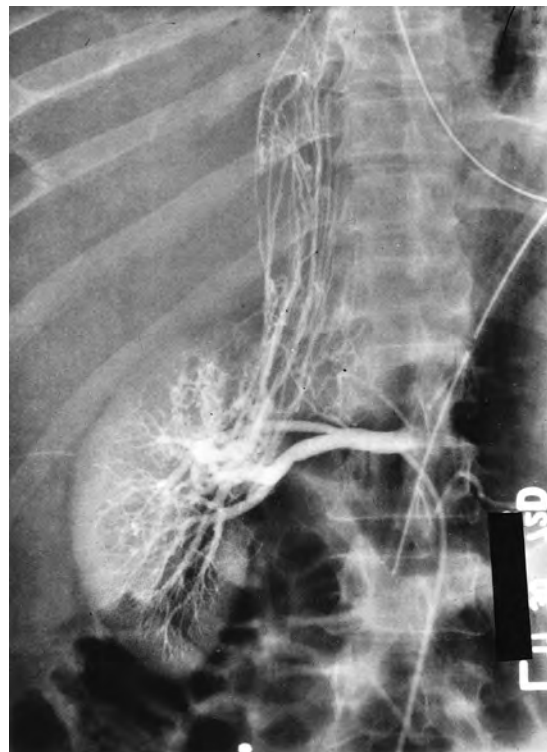


Figure 57-24. Right renal arteriogram shows arterialization of a supradiaphragmatic vena caval thrombus.

be considered in an attempt to shrink the thrombus and facilitate the surgical procedure. In patients with extensive supradiaphragmatic vena caval thrombi, when adjunctive cardiopulmonary bypass with deep hypothermic circulatory arrest is considered, coronary angiography should also be performed preoperatively (Novick et al,

1990). If significant obstructing coronary lesions are found, these can be repaired simultaneously during cardiopulmonary bypass.

Transesophageal echocardiography is an invasive study that is unnecessary before surgery, but can be an important intraoperative diagnostic modality for evaluation of thrombus extension, monitoring for embolic phenomena, recognition of residual tumor during and after resection, and assessment of preload/cardiac function during IVC clamping (Glazer and Novick, 1997; Wotkowicz et al, 2008; Cywinski and O'Hara, 2009; Shuch et al, 2009).

The surgical approach is tailored to the level of IVC thrombus, but uniformly begins with careful mobilization of the kidney and early ligation of the arterial blood supply (Blute et al, 2004b; Shuch et al, 2009; Gorin et al, 2012b). In general, level I thrombi are isolated by a Satinsky clamp and are thus readily addressed (Fig. 57-25A). Level II thrombi require sequential clamping of the caudal IVC, contralateral renal vasculature, and cephalad IVC along with mobilization of the relevant segment of the IVC and occlusion of lumbar veins. The renal ostium is then opened and the thrombus is removed, all in a bloodless field (Fig. 57-25B). When tumor thrombus invades the wall of the vena cava, aggressive resection of the involved cava and attainment of negative surgical margins are required to minimize the risk of recurrence (Blute et al, 2007; Wotkowicz et al, 2008). IVC grafting or reconstitution is required in

some instances, but patients with a completely occluded IVC do not require this because of collateral blood flow (Sarkar et al, 1998; Blute et al, 2007; Hyams et al, 2011). Distal bland thrombus within the IVC or iliac vessels may be left in situ, although the IVC should be ligated or clipped cephalad to this level to prevent pulmonary embolism.

Vascular control for level III and level IV IVC thrombi requires more extensive dissection, venovenous bypass, or cardiopulmonary bypass and hypothermic circulatory arrest. For level III thrombi, mobilization of the liver and exposure of the intrahepatic IVC will often allow the thrombus to be mobilized caudad to the hepatic veins, and venous isolation can then proceed as for a level II thrombus (Fig. 57-25C) (Gallucci et al, 2004). If this is not possible, the IVC should be clamped above the liver and a Pringle maneuver performed to temporarily occlude the portal triad (Ciancio et al, 2007, 2011). Venovenous bypass is commonly used in these cases but may not be required if adequate collateral flow is present. Level IV IVC thrombi have traditionally been managed with cardiopulmonary bypass and hypothermic circulatory arrest, and this is still the preferred approach in complex cases (Blute et al, 2007; Wotkowicz et al, 2008). However, many centers are now trying to avoid hypothermic circulatory arrest because of the hypo-coagulable state that ensues when coming off the pump and

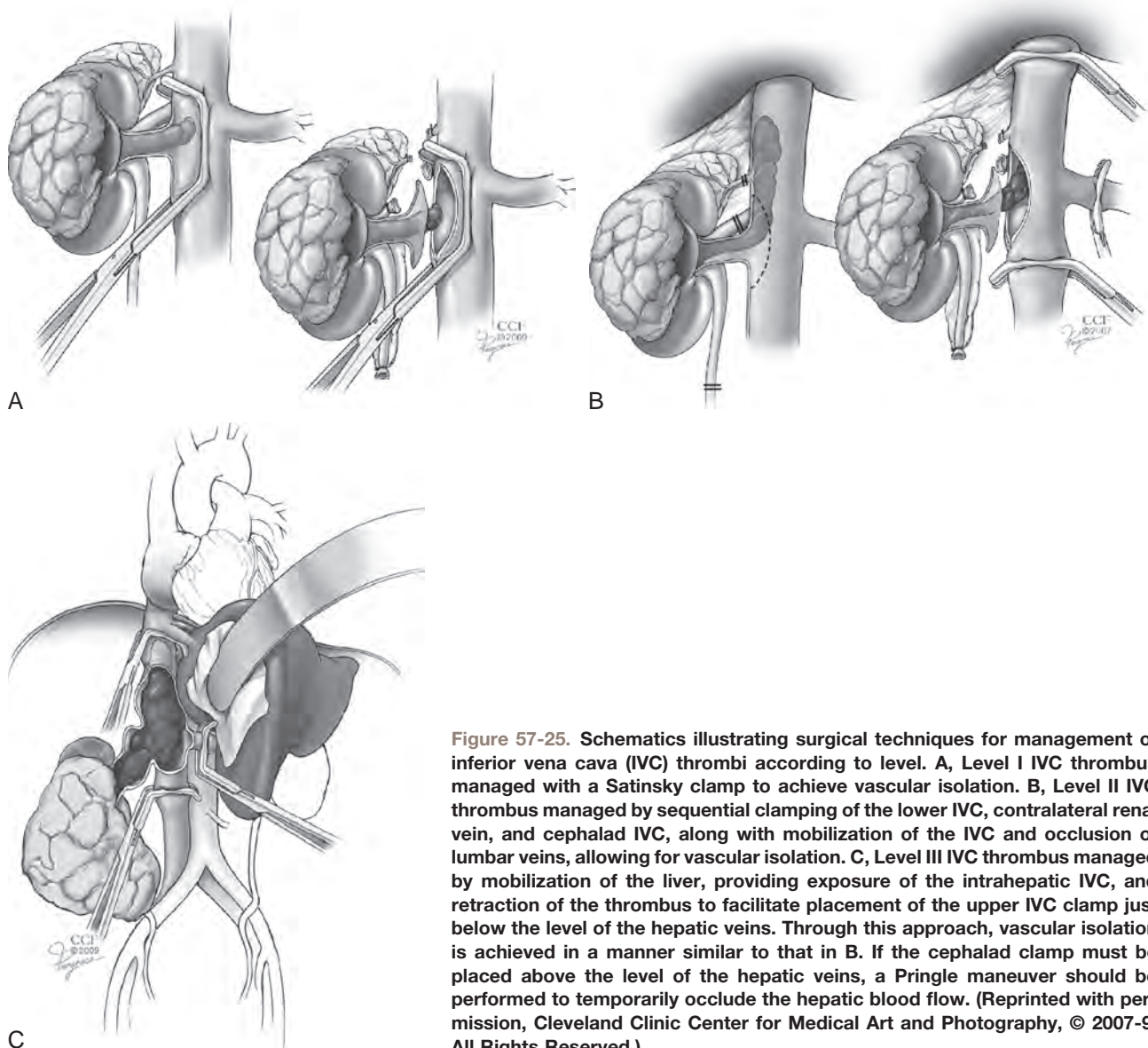


Figure 57-25. Schematics illustrating surgical techniques for management of inferior vena cava (IVC) thrombi according to level. A, Level I IVC thrombus managed with a Satinsky clamp to achieve vascular isolation. B, Level II IVC thrombus managed by sequential clamping of the lower IVC, contralateral renal vein, and cephalad IVC, along with mobilization of the IVC and occlusion of lumbar veins, allowing for vascular isolation. C, Level III IVC thrombus managed by mobilization of the liver, providing exposure of the intrahepatic IVC, and retraction of the thrombus to facilitate placement of the upper IVC clamp just below the level of the hepatic veins. Through this approach, vascular isolation is achieved in a manner similar to that in B. If the cephalad clamp must be placed above the level of the hepatic veins, a Pringle maneuver should be performed to temporarily occlude the hepatic blood flow. (Reprinted with permission, Cleveland Clinic Center for Medical Art and Photography, © 2007-9. All Rights Reserved.)

increased risk of cerebrovascular accident and myocardial infarction (Ciancio et al, 2011; Navia et al, 2012). If the thrombus is mobilized below the atrium, sequential vascular control can often be achieved without opening the heart (Ciancio et al, 2010). Further detail about these procedures can be found in Chapter 60.

The risk of morbidity can be substantial for thrombi extending above the diaphragm, and mortality rates associated with RN and IVC thrombectomy have been reported to be as high as 5% to 10% in some series, depending on patient comorbidities and tumor characteristics (Blute et al, 2004b; Ciancio et al, 2010; Navia et al, 2012). Therefore patient selection and surgical planning are of paramount importance (Ciancio et al, 2010; Pouliot et al, 2010). Although there may be a palliative role for surgery in some patients with metastasis who experience severe disability from intractable edema, ascites, cardiac dysfunction, or associated local symptoms such as abdominal pain and hematuria, most such patients will not benefit due to risk of perioperative morbidity and limited life expectancy (Slaton et al, 1997; Culp et al, 2010).

Locally Invasive Renal Cell Carcinoma

The sequestered location of RCC results in occasional patients presenting with large primary tumors that invade adjacent structures. Patients with pathologic stage T4 disease have represented less than 2% of surgical series, but this proportion will increase with the reclassification of adrenal involvement into this category (Thompson et al, 2005a; Karellas et al, 2009). Patients with locally advanced RCC usually present with pain, generally from invasion of the posterior abdominal wall, nerve roots, or paraspinal muscles. Large tumors may indent and compress adjacent liver parenchyma but seldom actually grow by direct extension into the liver, and intrahepatic metastases are more common (Yezhelyev et al, 2009). Margulis and colleagues (2007a) reported that invasion of adjacent organs was confirmed pathologically in only 40% of the patients in whom it was suspected on preoperative imaging. Duodenal and pancreatic invasion is uncommon and a poor prognostic sign. The propensity for RCC to parasitize vessels may account for extension into the colon and its mesentery. In evaluation of patients with large, invasive upper quadrant abdominal masses, a broad differential diagnosis should be considered, including adrenocortical carcinoma, urothelial carcinoma, sarcoma, and lymphoma, in addition to locally invasive RCC.

Because surgical therapy is the only potentially curative management for RCC, extended operations with en bloc resection of adjacent organs are occasionally indicated. Complete excision of the tumor, including resection of the involved bowel, spleen, or abdominal wall muscles, is the aim of therapy. However, even with an aggressive surgical approach the prognosis remains poor. In the series from Margulis and colleagues (2007a), 10 of 12 patients with pathologic T4 disease experienced disease recurrence at a median of 2 months after surgery. Similarly, although negative surgical margins were achieved in 63% of patients in another series,

34 of 38 patients (90%) ultimately died of disease at a median of 12 months after surgery (Karellas et al, 2009). For these reasons, neoadjuvant systemic therapy is a valid consideration for patients with potentially “unresectable” RCC because it can provide a “litmus test” to identify patients who are destined to progress rapidly.

Important perioperative concerns for patients with locally advanced RCC include a comprehensive preoperative consent, including the potential for increased morbidity and resection of adjacent organs, a full bowel preparation, and consideration for preoperative embolization of the renal arterial blood supply. The latter may reduce bleeding if there is a contentious renal hilum as a result of encasement of the vessels or bulky lymphadenopathy. Vaccination against *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, and *Neisseria meningitidis* should be performed preoperatively when splenectomy is likely during nephrectomy (Shatz, 2005; Habermalz et al, 2008). If not already immunized, splenectomized patients should receive these vaccines in the postsurgical setting to prevent sepsis caused by one of these encapsulated organisms (Shatz, 2005; Habermalz et al, 2008).

Incomplete excision of a large primary tumor, or debulking, is rarely indicated as survival estimates are only 10% to 20% at 12 months (Dekernion et al, 1978; Karellas et al, 2009). The role of radiation therapy in the treatment of locally extensive RCC is controversial. Several early studies suggested that preoperative radiotherapy could improve survival (Cox et al, 1970). A subsequent study by van der Werf-Messing (1973), however, compared results for preoperative therapy with controls and found no survival difference at 5 years. Routine postoperative radiotherapy has not been shown to influence overall survival and can be hazardous because of proximity of small bowel, which is highly radiosensitive.

Lymph Node Dissection for Renal Cell Carcinoma

The need for extensive lymphadenectomy in patients undergoing RN remains controversial, as a randomized trial of lymphadenectomy at nephrectomy failed to show a distinct advantage (Leibovich and Blute, 2008; Blom et al, 2009; Crispen et al, 2011). The main limitation of this trial was the inclusion of patients at low risk for nodal metastasis (81% were grade 1 or 2 and 72% were organ confined); lymph node metastases were present in only 4% of patients undergoing complete lymph node dissection (Blom et al, 2009). Based on this trial, a compelling argument for lymph node dissection in patients with clinically localized RCC cannot be supported. Of greater impact is the study from Blute and colleagues (2004a) who elucidated pathologic features associated with increased risk for nodal metastases, as detailed in Table 57-19. Based on this study and a subsequent prospective evaluation of this approach, patients with two or more of these risk factors should be considered for extensive lymph node dissection incorporating ipsilateral great vessel and interaortocaval regions and extending from

TABLE 57-19 Risk of Regional Lymph Node Metastases in Renal Cell Carcinoma Based on Pathologic Risk Factors

NO. OF RISK FACTORS*	PERCENTAGE OF PATIENTS IN THIS RISK GROUP	PERCENTAGE WITH POSITIVE LYMPH NODES IN RETROSPECTIVE SERIES†	PERCENTAGE WITH POSITIVE LYMPH NODES IN PROSPECTIVE SERIES‡
0	44% (729/1652)	0.4% (3/729)	—
1	18% (302/1652)	1.0% (3/302)	—
2	17% (276/1652)	4.4% (12/276)	20% (7/35)
3	13% (209/1652)	12% (26/209)	37% (26/71)
4	7.3% (121/1652)	13% (16/121)	49% (26/53)
5	0.9% (15/1652)	53% (8/15)	50% (5/10)

*Risk factors include grade 3 or 4, sarcomatoid component, tumor size ≥ 10 cm, pathologic stage T3 or pT4, and histologic tumor necrosis.

†Data from Blute et al, 2004a; lymph node dissection performed in 58% of 1652 patients overall.

‡Data from Crispen et al, 2011; lymph node dissection performed in 41% of 415 patients with 2+ risk factors.

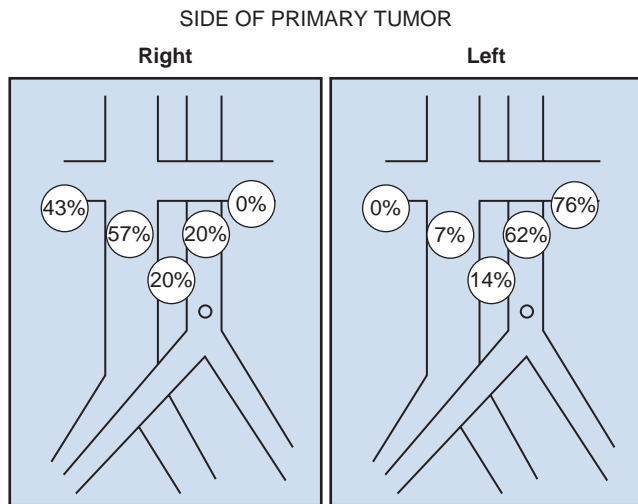


Figure 57-26. Frequency of lymph node positivity detected at extended lymphadenectomy in patients with lymph node positive renal cancer at nephrectomy. (From Crispin PL, Breau RH, Allmer C, et al. Lymph node dissection at the time of radical nephrectomy for high-risk clear cell renal cell carcinoma: indications and recommendations for surgical templates. *Eur Urol* 2011;59:18–23.)

the crus of the diaphragm to the common iliac artery. Forty-five percent of these patients had positive lymph nodes outside of the renal hilar region (Fig. 57-26) (Crispin et al, 2011).

Local Recurrence after Radical Nephrectomy or Nephron-Sparing Surgery

Local recurrence of RCC after RN, which includes recurrence in the renal fossa, ipsilateral adrenal gland, or ipsilateral retroperitoneal lymph nodes, is an uncommon event, occurring in 2% to 4% of cases (Margulis et al, 2009). Risk factors include locally advanced or node-positive disease and adverse histopathologic features (Esrig et al, 1992; Sandock et al, 1995; Levy et al, 1998). In contrast, local recurrence after RN is rare in patients with organ-confined RCC. Only about 40% of local recurrences are isolated; the majority of patients with local recurrence also have systemic disease, and a thorough metastatic evaluation should be pursued (Schrodter et al, 2002; Eggener et al, 2008).

Surgical resection of isolated local recurrence of RCC after RN should be considered, because it can provide long-term cancer-free status for 30% to 40% of patients (Master et al, 2005; Bandi et al, 2008; Margulis et al, 2009). Complete resection of abdominal recurrences is often a formidable task because the natural tissue barriers are no longer present and invasion of contiguous organs is common. En bloc resection of adjacent organs is often required, and the risk of morbidity can be substantial (Gogus et al, 2003; Eggener et al, 2008; Margulis et al, 2009). Margulis and colleagues (2009) have reported on 54 patients with local recurrence after nephrectomy managed by surgical resection, 69% of whom also received adjunctive systemic therapy. Risk factors associated with cancer-specific death after resection included recurrent tumor size, sarcomatoid features in the recurrence specimen, positive surgical margins, abnormal alkaline phosphatase, and increased lactate dehydrogenase. Patients with 0, 1, and greater than 1 adverse risk features demonstrated cancer-specific survival times of 111, 40, and 8 months, respectively. Intraoperative radiation has not been found to be of oncologic benefit (Master et al, 2005), but radiation therapy may be of value for palliation of symptomatic local recurrence in patients who are not operative candidates.

Local recurrence in the remnant kidney after PN for RCC has been reported in 1.4% to 10% of patients, and the main risk factor is advanced T stage (Campbell and Novick, 1994; Lane and

Gill, 2007; Krambeck et al, 2008). Most of these local recurrences are distant from the tumor bed and are thus probably a result of unrecognized tumor multicentricity or de novo occurrence rather than true treatment failure (Campbell and Novick, 1994; Lane and Novick, 2007; Krambeck et al, 2008). Recent data confirm that local recurrence after PN is uncommon, even with a positive surgical margin (Permpongkosol et al, 2006b; Kwon et al, 2007; Kutikov et al, 2008; Yossepowitch et al, 2008). Patients with isolated local recurrence after PN can be considered for repeat PN, completion nephrectomy, TA, or AS (Bratslavsky et al, 2008; Johnson et al, 2008; Magera et al, 2008a; Berger et al, 2009b). TA is now being used more frequently in this setting because of concern about fibrosis within the renal fossa, but conventional PN can and should be performed when anatomy and tumor characteristics are amenable (Gittes and Blute, 1982; Moll et al, 1993; Campbell and Novick, 1994; Frank et al, 2005; Bratslavsky and Linehan, 2011). Regardless, tumor characteristics, age and comorbidities, disease-free interval, and renal function status should all be considered during patient counseling, and a biopsy of the recurrent tumor may also be useful.

Local recurrence after TA often represents treatment failure; many local recurrences develop within the previous tumor bed (McDougal et al, 2005; Matin et al, 2006; Levinson et al, 2008; Nguyen et al, 2008b; Berger et al, 2009b). Reported incidences range between 3% and 10% for cryoablation and between 5% and 20% for RFA (Kunkle and Uzzo, 2008; Kunkle et al, 2008; Levinson et al, 2008; Weight et al, 2008; Berger et al, 2009b). Importantly, the true incidence of local recurrence in this population is not well defined because radiographic factors predictive of recurrence have been challenged, particularly for RFA; most studies have not incorporated routine biopsy of the tumor bed during surveillance, and length of follow-up in many series is limited (Stein and Kaouk, 2007; Weight et al, 2007). Most of these recurrences can be managed with repeat ablation, but this is not always feasible. Beyond this, management options are similar to those for recurrence after PN, with the caveat that salvage surgery in this setting is often challenging owing to the dense inflammatory reaction induced by TA (Nguyen et al, 2008b; Kowalczyk et al, 2009).

Adjuvant Therapy for Renal Cell Carcinoma

Unfortunately, recurrence develops in a significant proportion of patients thought to be rendered disease free after surgical resection, primarily due to occult micrometastatic disease. Although postsurgical recurrence is not common in patients with low-stage, organ-confined disease, locally advanced RCC and RCC with other adverse histopathologic features carry a significant risk of recurrence. Various predictive tools can assist in the assessment of the risk in individual patients (Kim et al, 2012a), although on the whole, distant metastases develop in 20% to 35% and local recurrence in 2% to 5% of patients (Lane and Kattan, 2008). In view of these findings, a strong rationale for systemic adjuvant therapy exists in high-risk patients. However, none of the adjuvant studies in this field have been convincingly positive thus far, and the standard of care remains observation if the patient will not consider an adjuvant trial (see Key Points box).

The primary clinical end point used in most adjuvant trials has been recurrence-free survival. Ideal trial design incorporates placebo-controlled and blinded protocols and independent radiographic review to confirm that all entered patients are truly disease free at study entry and to confirm and accurately time all recurrences. Intent-to-treat analysis is another strong expectation in this field (Kenney and Wood, 2012). Until recently, many adjuvant trials for patients with RCC have been underpowered to detect small differences in survival, and primary end points related to tumor recurrence have been difficult to assess in view of flaws in study design. A variety of adjuvant approaches have been investigated, including hormonal manipulation, radiotherapy, immunotherapeutics, vaccines, and, most recently, targeted molecular agents. Early adjuvant trials tested postoperative medroxyprogesterone acetate (Pizzocaro et al, 1987) or perioperative radiotherapy (van der Werf-Messing, 1973) with negative results.

KEY POINTS: TREATMENT OF LOCAL RECURRENCE AND ADJUVANT THERAPY FOR RENAL CELL CARCINOMA

- Isolated local recurrence after RN occurs in 2% to 4% of patients, and a thorough metastatic evaluation should be pursued if resection is under consideration.
- Local recurrence after PN is more common at sites distant from the tumor bed and can be managed by repeat PN, completion nephrectomy, TA, or AS.
- Local recurrence after TA often reflects incomplete tumor eradication; management options include repeat ablation, AS, or salvage surgery.
- Despite a significant likelihood of recurrence of RCC with poor-risk features, there is no established evidence of a benefit for adjuvant therapy in patients who appear to be cancer free after surgical resection, and observation remains the standard of care.
- Ongoing adjuvant clinical trials investigating targeted molecular agents and other novel systemic approaches should be supported in an effort to identify an efficacious adjuvant strategy.

Despite demonstrable antitumor effects in patients with metastatic disease, IL-2 and interferon alfa did not prove to be beneficial in the adjuvant setting. Four randomized studies were performed, three with interferon alfa and one with IL-2 (Pizzocaro et al, 2001; Clark et al, 2003; Messing et al, 2003). The studies investigating interferon used various doses, preparations (L-interferon, interferon alfa-2a, interferon alfa-2b), and duration of therapy; none demonstrated a benefit when compared with controls. Clark and colleagues (2003) randomized 69 high-risk patients after complete surgical resection to observation versus high-dose IL-2. An interim analysis prompted closure of the trial primarily because of the toxicity of high-dose IL-2; there was no clinically meaningful benefit for the population as a whole or in the subgroups that were analyzed.

A variety of autologous tumor vaccine–based approaches have been used to immunize RCC patients in the postoperative setting, again with essentially negative results (Galligioni et al, 1996;

Jocham et al, 2004; Wood et al, 2008). More recently, the results of the ARISER adjuvant trial were released, representing another negative adjuvant trial for RCC. This study investigated girentuximab, a chimeric monoclonal antibody directed against G250, a cell surface antigen expressed by the majority of clear cell RCC. In 2012, the interim analysis showed no improvement in median disease-free survival, and the trial was terminated.

Current trials using targeted molecular agents with activity in patients with metastatic RCC have enrolled a large number of patients with surgically resected RCC who are at high risk for recurrence (Table 57-20) (Jonasch and Tannir, 2008; Kenney and Wood, 2012). These agents are orally administered and thus their use is appealing in an adjuvant setting, although there are many uncertainties regarding optimal choice of agent and dose and duration of therapy. In addition, the toxicities of these agents may limit their usefulness in the adjuvant setting because patients taking a potentially preventive treatment tend to have a much lower threshold for toxicities. Some of these trials have completed accrual and final analysis can be expected in approximately 2015. Please refer to Chapter 63 for a more detailed discussion of these targeted treatments and their rationale for patients with advanced RCC.

OTHER MALIGNANT RENAL TUMORS**Sarcomas of the Kidney**

Sarcomas represent 1% to 2% of all malignant renal tumors in adults, with a peak incidence in the fifth decade of life (Vogelzang et al, 1993; Miller et al, 2010b). Renal sarcoma is less common but more lethal than sarcoma of any other genitourinary site, including the prostate, bladder, and paratesticular region (Russo et al, 1992). Differentiation of renal sarcoma from sarcomatoid RCC is often difficult on the basis of clinical presentation, radiographic findings, and, in some cases, pathologic analysis. Identification of any features of the various subtypes of RCC excludes the diagnosis of primary renal sarcoma. The common signs and symptoms associated with renal sarcoma in adults include palpable mass, abdominal or flank pain, and hematuria and are similar to those seen with large, rapidly growing RCCs (Economou et al, 1987). Specific findings suggestive of sarcoma rather than RCC

TABLE 57-20 Ongoing Clinical Trials of Adjuvant Treatment for Renal Cell Carcinoma (RCC)

TRIAL	STUDY GROUPS	TREATMENT DURATION	INCLUSION CRITERIA
Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Cell Carcinoma (ASSURE)	Sunitinib vs. sorafenib vs. placebo	1 year	Clear cell and non-clear cell RCC eligible Stage T2-T4 or stage T1b and G3-4 N1 if complete dissection performed
Sorafenib for Patients with Resected Primary Renal Cell Carcinoma (SORCE)	Sorafenib (for 1 or 3 years) vs. placebo	3 years	Clear cell and non-clear cell RCC eligible Mayo Clinic progression score 3-11
Sunitinib vs. Placebo for the Treatment of Patients at high risk for Recurrent Renal Cell Cancer (S-TRAC)	Sunitinib vs. placebo	1 year	Predominant clear cell histology eligible High-risk RCC according to UISS*
Everolimus for Renal Cancer Ensuing Surgical Therapy (EVEREST)	Everolimus vs. placebo	1 year	Clear cell and non-clear cell RCC eligible Stage T2-T4 or stage T1b and G3-4 N1 if complete dissection performed
Adjuvant Axitinib Treatment of Renal Cancer (ATLAS)	Axitinib vs. placebo	3 years	Clear cell predominant (>50%) eligible pT2 and G3-4, or pT3a and > 4 cm, or pT3b/pT3c/pT4, or N1
Pazopanib as an Adjuvant Treatment for Locally Advanced Renal Cell Carcinoma (PROTECT)	Pazopanib vs. placebo	1 year	Clear cell predominant (>50%) eligible pT2 and G3-4, pT3, pT4, or N1

*UISS: UCLA Integrated Staging System (Zisman et al, 2002).

include apparent origin from the capsule or perisinuous region, growth to large size in the absence of lymphadenopathy, presence of fat or bone suggestive of liposarcoma or osteosarcoma, and hypovascular pattern on angiography, although one notable exception is the hemangiopericytoma, which is highly vascular (Shirkhoda and Lewis, 1987). Renal sarcoma should be suspected in any of these circumstances or in any patient with a very large or rapidly growing renal mass (Table 57-21).

Sarcomas of the kidney, like sarcomas of any other site, share in common a distinct tumor biology that has important implications with respect to management (Russo et al, 1992). These tumors are derived from mesenchymal components and are thus free of many of the natural barriers to dissemination that confine other tumor types. They are typically surrounded by a pseudocapsule that is often infiltrated with cancer cells, which can extend for some distance into the surrounding tissues. In many cases this cannot be recognized macroscopically, although it is often manifested in the form of local recurrences, which are common after surgical extirpation, even when a wide excision has been performed. High-grade sarcomas often metastasize, with the lungs being a primary site of spread, and prognosis is poor; many patients die of disease progression in a matter of months. Low-grade sarcomas tend to pursue a more indolent course, although local recurrences often require repeat resection to prolong survival and minimize morbidity.

In general, the most important prognostic factors for sarcomas are margin status and tumor grade. The initial resection is the key event because this is the best chance for a long-term cure. For renal sarcomas this often mandates RN along with en bloc excision of adjacent organs (Brescia et al, 2008; Wang et al, 2011). MRI can be useful for preoperative planning by defining tissue planes and proximity to vital structures. This is primarily a surgical disease, and wide excision is the goal with intraoperative monitoring of margin status. Chemotherapeutic agents that have demonstrated activity against metastatic sarcomas include doxycycline and ifosfamide, but even in the best of circumstances response rates are disappointing (Antman et al, 1993; Miller et al, 2010b). The

combination of radiation therapy and chemotherapy, which has proved effective in an adjuvant setting for the management of sarcomas of the extremity, has not provided much benefit for renal or retroperitoneal sarcomas (Russo et al, 1992). At present, the role of such adjuvant approaches for the management of renal sarcomas is not well defined, although a multimodal approach is often pursued if performance status allows, given the poor prognosis.

The largest single-institution series of renal sarcomas include only 15 to 41 cases and represent a composite experience extending for a period of several years (Shirkhoda and Lewis, 1987; Wang et al, 2011). In all such series leiomyosarcoma has been the most common histologic subtype, and in many series liposarcoma has been the second most common. In contrast, for retroperitoneal sarcomas, the order is reversed, with liposarcoma being the most common histologic subtype (Karakousis et al, 1995). All such series report a poor prognosis; the experience of Srinivas and colleagues (1984) at Memorial Sloan Kettering Cancer Center is representative. In this series of 16 patients with renal sarcomas, 15 underwent nephrectomy, often with en bloc excision of adjacent organs; 5 received adjuvant radiation therapy and chemotherapy without apparent benefit; and 13 died within 6 months after surgery. Saitoh and colleagues (1982) defined the common sites of metastases of renal sarcomas: lung first and foremost but also lymph nodes and liver.

Leiomyosarcoma is the most common histologic subtype of renal sarcoma, accounting for 50% to 60% of such tumors (Fig. 57-27). The cell of origin is the smooth muscle cell of the capsule or other perinephric structures (Moudouni et al, 2001; Deyrup et al, 2004; Wang et al, 2011). Niceta and associates (1974) identified 66 cases of renal leiomyosarcoma in the literature and reported a female predominance; most patients presented in the fourth through sixth decades of life. Renal leiomyosarcoma, like other renal sarcomas, tends to displace rather than invade the parenchyma, and is characterized by rapid growth rate, frequent metastasis, and high local and systemic recurrence rates (Deyrup et al, 2004). In the cases reviewed by Niceta and associates (1974), most patients were treated primarily with RN and died within 2 years. In the Mayo Clinic series, 14 of 15 patients with renal leiomyosarcoma

TABLE 57-21 Characteristics of Other Malignant Renal Tumors

TUMOR TYPE	CHARACTERISTICS	MANAGEMENT
Sarcomas	Leiomyosarcoma most common Typically hypovascular Often rapidly growing and occasionally appear to be derived from the renal capsule	Wide local excision with confirmation of negative margins
Renal lymphoma and leukemia	Multiple radiographic patterns described Typically hypovascular Suspect in patients with massive retroperitoneal lymphadenopathy or lymphadenopathy in other regions of the body or atypical locations	Biopsy should be considered Extirpative surgery should be avoided Typically managed with chemotherapy and/or radiation therapy
Metastatic tumors	Most common sources include lung, breast, and gastrointestinal cancers, malignant melanoma, and hematologic malignancies Typically hypovascular and multifocal	Biopsy should be strongly considered Typically managed with systemic therapy or palliative care
Carcinoid	Typically hypovascular May present as carcinoid syndrome Derived from neuroendocrine cells	Surgical excision
Small cell carcinoma of the kidney	Neuroendocrine derivation Typically hypovascular Most locally advanced or metastatic	Multimodal therapy with surgery and platinum-based chemotherapy
Primitive neuroectodermal tumor	Derived from primitive neural crest cells Hypovascular pattern typical Poor prognosis	Multimodal therapy
Wilms tumor	Heterogeneous solid renal mass on computed tomography	Multimodal therapy analogous to treatment protocols for pediatric Wilms tumor

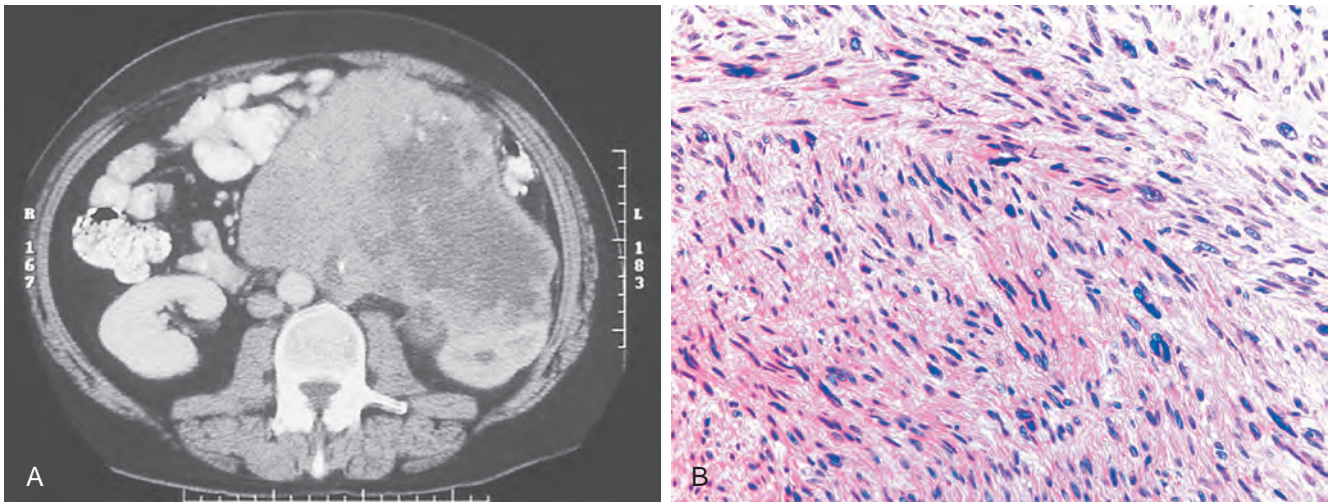


Figure 57-27. A, Computed tomography scan demonstrates a large leiomyosarcoma of the left kidney. B, Microscopic features of leiomyosarcoma include spindle cells, blunt-ended nuclei, and eosinophilic cytoplasm. (Courtesy Dr. Michael McGuire, Evanston, IL and Dr. Ming Zhou, Cleveland, OH.)

died of disease progression within 4 months to 5.5 years after surgery (Frank et al, 2000).

Other than leiomyosarcoma, a wide variety of histologic subtypes have been described because almost every conceivable type of sarcoma has been found in the kidney. **Liposarcoma** is readily distinguished from RCC because of the presence of adipose tissue, but is often confused with AMLs or large, benign renal lipomas (Frank et al, 2000). Renal liposarcoma typically develops in the fifth and sixth decades of life and often grows to extremely large size. Response to radiation therapy and cisplatin-based chemotherapy in an adjuvant setting has been reported by Beldegrun and deKernion (1987) and should be considered in patients with high-grade disease or positive margins. **Osteogenic sarcoma** is a rare but distinctive form of renal sarcoma that contains calcium and is often rock hard (Micolonghi et al, 1984; Leventis et al, 1997). Extensive calcification in a large, hypovascular tumor should suggest the diagnosis. The appearance on plain films can mimic a staghorn calculus, but the readily evident mass effect should suggest xanthogranulomatous disease or, more rarely, osteogenic sarcoma. Again, prognosis is poor; most patients die of disease progression within a few years after diagnosis. **Less common histologic subtypes include** rhabdomyosarcoma, fibrosarcoma, carcinosarcoma, malignant fibrous histiocytoma, synovial sarcoma, schwannoma, angiosarcoma, and malignant hemangiopericytoma (Srigley et al, 2013). Malignant hemangiopericytomas are notable for their extensive vascularity (Chaudhary et al, 2007; Brescia et al, 2008). Preoperative angioembolization has been described and may simplify surgical excision (Smullens et al, 1982).

Renal Lymphoma and Leukemia

Renal involvement with hematologic malignancies, which include the lymphomas and leukemias, is common—it is found at autopsy in approximately 34% of patients dying of progressive lymphoma or leukemia. However, these processes are uncommonly seen in clinical practice because they are often silent and generally occur only as a late manifestation of systemic disease (Pollack et al, 1987; McVary, 1991). The role of the urologist in the evaluation of renal lymphoma or leukemia is critically important and can include differentiation from other renal malignant neoplasms, timely provision of a pathologic diagnosis, and preservation of renal function (McVary, 1991). Renal involvement is more common with non-Hodgkin lymphoma than with Hodgkin disease, and, as with most other forms of extranodal non-Hodgkin

TABLE 57-22 Computed Tomographic Findings Associated with Lymphoma

FINDING	INCIDENCE (%)
Multiple renal masses	45
Solitary renal mass	15
Renal invasion from enlarged retroperitoneal lymph nodes	25
Diffuse renal involvement	10
Predominantly perinephric involvement	5

Data from Pollack et al, 1987, and Heiken et al, 1991.

lymphoma, histologically diffuse forms predominate over nodular forms (Pollack et al, 1987; O’Riordan et al, 2001). Primary renal lymphoma is rare, with only a few well-documented case reports in the literature (Pollack et al, 1987; Ahmad et al, 2005; Garcia et al, 2007). This is not surprising given the relative paucity of lymphoid tissue in the normal renal parenchyma. Hematogenous dissemination of lymphoma to the kidney is most common and is thought to occur in 90% of cases; direct extension from retroperitoneal lymph nodes accounts for the remainder. Hartman and colleagues (1982) have shown that the most common pattern of renal involvement consists of multiple small renal nodules that tend to develop between the individual nephrons. Eventually, these nodules become confluent, forming radiographically detectable masses. At the extreme, they can replace the entire parenchyma of the kidney, leading to renal failure.

The CT scan is the radiographic modality of choice for the diagnosis of renal lymphoma and for monitoring response to therapy (Pollack et al, 1987; Urban and Fishman, 2000). The common radiographic patterns associated with renal lymphoma have been defined by Heiken and associates (1991) and confirmed by a number of other investigators (Table 57-22). Renal lymphoma can present as multiple distinct renal masses; as a solitary renal mass, which can be difficult to differentiate from RCC; as diffuse renal infiltration; or as direct invasion of the kidney from enlarged retroperitoneal nodes (Sheth et al, 2006). A hypovascular pattern on angiography is typical for renal lymphoma (Pollack et al, 1987). Renal lymphoma should be suspected in patients with massive retroperitoneal lymphadenopathy, splenomegaly, or lymphadenopathy in other regions of the body or atypical regions within

the retroperitoneum. Relative to this, the main landing zones for RCC should be kept in mind—the interaortocaval region for right RCC and para-aortic region for left RCC—and lymphadenopathy centered outside of these areas should raise suspicion for lymphoma. Any patient with a prior history of lymphoma and a renal mass should also be evaluated for renal recurrence rather than for RCC. In general, lymphomas are more common in patients with iatrogenic immune suppression, acquired immunodeficiency syndrome, autoimmune diseases, or graft-versus-host disease and in patients with a history of radiation therapy (McVary, 1991). These clinical associations may also increase the index of suspicion about a diagnosis of systemic lymphoma.

Renal involvement related to leukemia is more common in children, paralleling the demographics of the disease, and is more commonly due to lymphocytic leukemia than the myelogenous forms (Pollack et al, 1987). Leukemia typically involves the kidney in a diffusely infiltrative pattern and most often represents a late manifestation of systemic disease.

If lymphoma or leukemic renal involvement is suspected, consideration should be given to percutaneous biopsy or aspiration to obtain a pathologic diagnosis (Herts, 2012); if exploratory surgery is necessary, intraoperative biopsy and frozen-section analysis should take priority. Extirpative surgery should be avoided if renal lymphoma and leukemia are suspected because the primary treatment of these processes is systemic chemotherapy with or without radiation therapy (McVary, 1991). The classic chemotherapy regimen for non-Hodgkin lymphoma is the CHOP protocol, which includes cyclophosphamide, doxorubicin, vincristine, and prednisolone (Colevas et al, 2000). Nephrectomy is seldom indicated except in patients with severe symptoms, such as uncontrollable hemorrhage. The other notable exception is the extremely rare patient with primary renal lymphoma in whom a combination of nephrectomy and systemic chemotherapy may represent optimal therapy (Garcia et al, 2007; Hart et al, 2012). Fourteen cases of marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue localized to the kidney have been described, with some apparently cured by surgery alone (Garcia et al, 2007).

Both renal lymphoma and leukemia are commonly silent but can be associated with hematuria, flank pain, or progressive renal failure. Fever, weight loss, and fatigue, the so-called B symptoms of lymphoma, are much more common (Zomas et al, 2004). Renal failure can be due to extensive replacement of the functioning parenchyma or bilateral ureteral obstruction associated with enlarged retroperitoneal lymph nodes (McVary, 1991). In reality, renal failure in such patients is more often related to medical causes, such as hypercalcemia or urate nephropathy, which can develop during systemic treatment of advanced disease.

Metastatic Tumors

Metastatic tumors are the most common malignant neoplasms in the kidney, outnumbering primary renal tumors by a wide margin. Autopsy studies have shown that 12% of patients dying of cancer have renal metastases, making the kidney one of the most common sites for metastatic dissemination (Pollack et al, 1987). The profuse vascularity of the kidney makes it a fertile soil for the deposition and growth of cancer cells. Almost all renal metastases develop through a hematogenous route of spread. Direct invasion of tumors derived from adjacent organs such as the pancreas, colon, and adrenal gland is much less common. The most frequent sources of renal metastases include lung, breast, and gastrointestinal cancers, malignant melanoma, and the hematologic malignant neoplasms (Choyke et al, 1987; Pollack et al, 1987; Aron et al, 2004; Stage et al, 2005). Of the solid malignant neoplasms, lung cancer is most commonly associated with renal metastases. Olsson and colleagues (1971) found that 20% of patients dying of lung cancer had renal metastases, 60% of which were bilateral. Klinger (1951) reviewed 5000 autopsies and found 17 cases of renal metastases from lung cancer, 11 from gastric cancer, 9 from breast cancer, 7 from pancreatic cancer, 4 from esophageal cancer, 6 from other gastrointestinal primary cancers, and 1 from

malignant melanoma. Most renal metastases are multifocal, and almost all are associated with widespread nonrenal metastases (Pollack et al, 1987; Choyke et al, 2003). Choyke and associates (1987) reported that renal metastases from lung, breast, and colon carcinomas are notable because they are occasionally large and solitary, making them difficult to differentiate from RCC.

The typical pattern of renal metastases consists of multiple small nodules that are often clinically silent, although they can lead to hematuria or flank pain in exceptional circumstances (Pollack et al, 1987). CT typically demonstrates isodense masses that enhance only moderately (5 to 30 HU) after administration of intravenous contrast material (Pollack et al, 1987).

Renal metastases should be suspected in any patient with multiple renal lesions and widespread systemic metastases or a history of nonrenal primary cancer. If there is any uncertainty about the diagnosis, percutaneous renal biopsy usually provides pathologic confirmation (Sánchez-Ortiz et al, 2004a). Most patients with renal metastases are managed with systemic therapy or placed on a palliative care pathway, depending on the clinical circumstances. Nephrectomy is almost never required except in extenuating circumstances, such as renal hemorrhage that is refractory to embolization. Patients with a solitary, strongly enhancing renal lesion and a history of organ-confined, nonrenal malignant disease are more likely to have RCC, particularly if the interval between the two diagnoses is substantial. In one study involving 100 consecutive patients with a renal mass and a history of nonrenal malignancy, none of the 54 patients without other evidence of disease progression had a renal metastasis (Rybicki et al, 2003; Sánchez-Ortiz et al, 2004a).

Other Malignant Tumors of the Kidney

Other malignant tumors of the kidney include adult Wilms tumor and neuroendocrine tumors such as renal carcinoid, small cell carcinoma, and primitive neuroectodermal tumor (PNET). All are relatively uncommon, but each has distinct tumor biology.

Carcinoid tumors arise from neuroendocrine cells, which are not normally present in the kidney (Romero et al, 2006). This is thus a rare renal malignant neoplasm with fewer than 60 cases reported in the English literature (Hansel et al, 2007; Lane et al, 2007b; Canacci and MacLennan, 2008). An association with horseshoe kidneys has been reported, with previous studies showing an increased relative risk of 82-fold compared with normal kidneys (Begin et al, 1998; Romero et al, 2006). Carcinoid tumors stain positive for markers of neuroendocrine tissue such as neuron-specific enolase and chromogranin (Lane et al, 2007b). Measurement of urinary or plasma serotonin or its metabolites can be diagnostic (Kulke and Mayer, 1999). Only a minority of patients will present with the carcinoid syndrome—episodic flushing, wheezing, and diarrhea (Jensen and Doherty, 2001; Romero et al, 2006; Lane et al, 2007b). Median age at diagnosis is 49 years (Romero et al, 2006). CT findings are nonspecific, and many renal carcinoids are small and nonaggressive. However, in a review of renal carcinoids, metastases were found in 46% of patients at diagnosis (Romero et al, 2006). Surgical excision is the mainstay of treatment (Kawajiri et al, 2004). Nephron-sparing surgery is preferred if the diagnosis is suspected preoperatively. Prognosis is good, particularly when associated with a horseshoe kidney (Begin et al, 1998; Lowrance et al, 2006). Significant adverse prognostic factors include age older than 40 years, tumor size greater than 4 cm, high mitotic rate, purely solid gross morphology, metastasis at initial diagnosis, and tumor extending through the renal capsule (Romero et al, 2006).

Other neuroendocrine tumors, including small cell carcinoma and large cell neuroendocrine carcinoma, can occur in the kidney but are even less common than renal carcinoids (Gonzalez-Lois et al, 2001; Majhail et al, 2003; Lane et al, 2007b). Approximately 30 cases of small cell carcinoma of the kidney have been reported for which another primary site could not be identified (Gonzalez-Lois et al, 2001; Kilicarsalan Akkaya et al, 2003; Mirza and Shahab, 2007). On pathologic examination, small cell carcinoma has

features of neuroendocrine and epithelial neoplasms and must be differentiated from Wilms tumor, PNET, lymphoma, and metastasis from pulmonary small cell carcinoma. Positive staining for neuron-specific enolase, chromogranin, and synaptophysin is characteristic (Kilicarsalan Akkaya et al, 2003). Preoperative differentiation from RCC is difficult, although a relatively hypovascular pattern may be an indication. Many small cell carcinomas of the kidney are locally advanced or metastatic at presentation, and flank pain or hematuria is common. Multimodal therapy with nephrectomy or tumor debulking combined with platinum-based chemotherapy regimens is advocated for extrapulmonary small cell carcinoma in general and may also be useful for the renal manifestation of this malignant neoplasm (Majhail et al, 2003; Mirza and Shahab, 2007). Long-term survivors are rare, and new treatment regimens are needed.

PNET is related to the Ewing sarcoma family of tumors that are more common in the pediatric population, typically manifesting in the bone or soft tissues of the extremities, trunk, and head and neck and only rarely in the viscera or kidneys (Jimenez et al, 2002; Maly et al, 2004; Bartholow and Parwani, 2012). However, all ages may be affected and several cases of PNET have been reported in the kidneys of adults (Karnes et al, 2000; Doerfler et al, 2001; Pomara et al, 2004; Thyaviahally et al, 2008). These tumors are derived from primitive neural crest cells, and positive staining for CD99 in addition to vimentin, cytokeratin, and neuron-specific enolase strongly supports the diagnosis (Conlusen et al, 2001; Ginsberg et al, 2002; Maly et al, 2004; Ellinger et al, 2006). On microscopic examination, renal PNET typically shows small round cells that may form characteristic Homer-Wright rosettes (Pomara et al, 2004; Thyaviahally et al, 2008). A characteristic t(11;22)(q24;q12) translocation is highly specific for PNET and can help differentiate it from neuroblastoma or adult Wilms tumor (Parham et al, 2001; Jimenez et al, 2002). Clinical symptoms are nonspecific; CT often demonstrates a heterogeneous ill-defined mass with areas of necrosis, and equivocal enhancement with contrast medium is typical (Doerfler et al, 2001). Renal PNET appears to behave more aggressively than similar tumors at other sites, exhibiting a strong propensity for local recurrence and early metastasis to lymph nodes, lung, liver, and bone (Conlusen et al, 2001; Parham et al, 2001; Thyaviahally et al, 2008). Multimodal treatment protocols combining tumor debulking, chemotherapy targeted to round cell or Ewing's family of tumors, and radiotherapy to the renal bed are often employed, but prognosis is poor, with overall 5-year disease-free survival of 45% to 55% (Casella et al, 2001; Ellinger et al, 2006; Thyaviahally et al, 2008).

Wilms tumor is the most common abdominal malignant neoplasm in children, but 3% of Wilms tumors are seen in adults. Of these, 20% are found between the ages of 15 and 20 years and the remaining 80% are distributed between the third and seventh decades of life (Winter et al, 1996). Adult and pediatric Wilms tumors are histologically similar with a distinctive triphasic pattern consisting of varying amounts of blastema, epithelium, and stroma (Orditura et al, 1997). Pathologic staging is the same as for pediatric Wilms tumor. Adult Wilms tumor typically presents as a heterogeneous intrarenal mass on CT with a relatively hypovascular pattern. Differentiation from RCC can be difficult if not impossible in many cases (Winter et al, 1996; Reinhard et al, 2004). Clinical presentation of adult Wilms tumor is also similar to that of RCC, and this tends to be an unsuspected pathologic diagnosis in most cases. Multimodal therapy should be considered, analogous to the treatment protocols for pediatric Wilms tumor (Neville and Ritchey, 2000; Firoozi and Kogan, 2003; Terenziani et al, 2004). Prognosis is worse for adults with Wilms tumor than for children with this malignant neoplasm because adults are more likely to present with advanced disease and a sudden drop in performance status (Winter et al, 1996).

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Basic and Clinical Biology

Epidemiology

Etiology

Natural History

Histopathology

Diagnosis

Staging and Prognosis

Treatment

Follow-Up

BASIC AND CLINICAL BIOLOGY

An upper tract urothelial cancer (UTUC) is essentially any neoplastic growth of urothelium from renal calices to distal ureter. Although these tumors share similarities with urothelial cancers of the bladder and most data have been extrapolated from the latter, there are innate differences between these two neoplastic processes that warrant consideration when counseling patients about their disease and making treatment decisions. These anatomic and molecular differences are explored further in this chapter.

EPIDEMIOLOGY

Incidence and Mortality Rates

Upper urinary tract carcinoma is a relatively rare disease, comprising 5% to 10% of all urothelial tumors (Siegel et al, 2013), with highest incidences occurring in Balkan countries, where these cancers represent 40% of all renal neoplasms (Grollman, 2013). The peak incidence occurs in individuals in their 70s and 80s, and the disease occurs in up to 2 per 100,000 per year in Western countries (Roupret et al, 2011). Most occurrences are in a single renal unit, and synchronous bilateral urothelial upper tract tumors are rare (about 1.6%) (Holmång and Johansson, 2004). Metachronous occurrences are 80% after bladder cancer and 2% to 6% after contralateral kidney UTUC (Novara et al, 2009; Li et al, 2010). Most of these occur in the renal pelvis, followed by the ureter. **The frequency of urothelial tumors of the upper tract is increasing** (McCarron et al, 1982; Richie, 1988; Williams, 1991; Herr, 1998; Munoz and Ellison, 2000; David et al, 2009). An evaluation of the data from 1973 to 2005 using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database showed increase in the annual incidence rates from 1.88 to 2.06 cases per 100,000 person-years (Raman et al, 2010). This change came mostly from ureteral neoplasms (0.69 to 0.91); the incidence of renal pelvis neoplasms had slightly decreased during the studied period (1.19 to 1.15). There was an observed trend toward earlier diagnosis of neoplasms, as the proportion of earlier-stage tumors increased from 7.2% in 1973 to 1984 to 31% in 1994 to 2005. This trend was also confirmed by data from the National Cancer Data Base (NCDB) for the United States for the years 1993 to 2005 (David et al, 2009). Although the authors reported a significant increase in high-grade tumors in both the renal pelvis and the ureter, the percentage of early-stage tumors also increased for each of the sites. Worse survival has been associated with increasing age, male gender, black non-Hispanic race, and

advanced tumor stage (Raman et al, 2010). Another series analyzing SEER data from 1973 to 1996 showed 5-year disease-specific survival rates of 75% overall and 95%, 88.9%, 62.5%, and 16.5% for in situ, localized, regional, and distant disease, respectively.

Variations by Gender, Race, and Age

Unlike the 4:1 ratio of presentation of bladder cancer in men to women, UTUC develops in men twice as frequently as in women (Greenlee et al, 2000; Lughezzani et al, 2010b). In addition, whites are about twice as likely as African-Americans to develop upper tract tumors (Greenlee et al, 2000). Even though some reports suggest that disease-specific annual mortality is greater in black men than in white men (7.4% vs. 4.9%) and greater in women than in men (6.1% vs. 4.4%) (Munoz and Ellison 2000), two recent multicenter studies (Fernández et al, 2009; Shariat et al, 2011) found lack of association between pathologic features or survival based on gender. Another study revealed no gender difference in disease-specific mortality after radical nephroureterectomy when clinicopathologic features were controlled for (hazard ratio [HR] 1.07, $P = .4$). It is interesting to note that in this study, female gender was associated with advanced stage (pT3) (odds ratio [OR] 1.15, $P = .03$) (Lughezzani et al, 2010b). In general, patients with upper tract cancer are older than patients with bladder tumors (Melamed and Reuter, 1993). Presentation in a patient younger than 60 years should raise the flag of hereditary UTUC as part of the Lynch syndrome spectrum of malignancies (Audenet et al, 2012). As discussed later in prognostic factors, advanced age may portend a worse cancer-specific prognosis. (Audenet et al, 2012).

ETIOLOGY

Genetic

Hereditary UTUC is associated with hereditary nonpolyposis colorectal carcinoma (HNPCC), or Lynch syndrome (Lynch et al, 1990). Patients with this syndrome have mutations in the DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* and may develop colonic, urothelial, gastric, pancreatic, uterine, sebaceous, and ovarian carcinomas. The associated urothelial cancers mainly arise in the upper tract, and it is unclear if carriers of these mutations may also have a higher risk of bladder malignancy (van der Post et al, 2010; Skeldon et al, 2013) or if this is a result of seeding of the bladder from the upper tract. Unlike with nonhereditary cancers, these patients are typically younger (mean age 55 years)

and are more likely to be female (Lynch et al, 1990). Besides the young age at presentation, presence of either a personal history or having two first-degree relatives with an HNPCC-associated cancer (particularly colon and endometrial) should raise suspicion for a hereditary component, and these patients are advised to undergo tissue evaluation for microsatellite instability or formal genetic testing if normal and tumor tissues are not available (Roupret et al, 2008; Acher et al, 2010; Audenet et al, 2012).

External Risk Factors

Aristolochic Acid Nephropathy

Several studies have suggested that aristolochic acid, which is found in plants *Aristolochia fangchi* and *Aristolochia clematitis*, has a mutagenic action on codon 139 of p53 gene. This mutation is predominant in patients with Balkan endemic nephropathy (BEN) and Chinese herb nephropathy. BEN is characterized by a degenerative interstitial nephropathy occurring in Balkan countries where these plants are endemic and grow as weeds in wheat fields (Grollman et al, 2007). It has a familial, but not inherited pattern, and incidence has been declining over the past 20 years (Stefanovic et al, 2008). The role of dietary exposure to aristolochic acid in BEN is supported by the fact that the family members who leave home early in life may not be affected (Radovanovic et al, 1985). Affected families display a much higher incidence of UTUC, but not bladder cancer (Petkovic, 1975). Tumors are usually of low grade and are more frequently multiple and bilateral than are UTUCs with other causes. Poorer outcomes are still seen in women (HR 2.2), with tumor size larger than 3 cm (HR 2.8), and with stage T3 or T4 disease (HR 3.1) (Dragicevic et al, 2007). The term *Chinese herb nephropathy* appeared after more than 100 patients in Belgium developed end-stage renal failure after consumption of Chinese herbal products that contained *A. fangchi*, and about half of whom developed UTUC with histologic features and genetic hallmarks identical to those of BEN (Cosyns et al, 1999; Nortier et al, 2000). The very high prevalence of UTUC in Taiwan and China is suspected to be in large part a result of the use of *Aristolochia* in various herbal remedies.

Smoking

Cigarette smoking appears to be the most important of the modifiable risk factors for UTUC and has been linked to generation of aromatic amines, which are metabolized into highly carcinogenic *N*-hydroxylamine. Individual susceptibility to effects of smoke may be linked to genetic polymorphisms in enzymes that neutralize this substance (Hung et al, 2004). This risk is dose related, ranging from OR 2.0 for a smoking history of 20 pack-years or less versus 6.2 for 60 or more. Observation suggests that smoking cessation offers the benefit of decreased risk (OR 2.3 for former vs. 4.4 current smokers). In addition, the risk from smoking seems more often to lead to ureteral rather than to renal pelvic tumors (McLaughlin et al, 1992).

Coffee

There have been reports of increased incidence of urothelial cancers with consumption of coffee (Ross et al, 1989); however, this relationship is confounded by smoking among habitual coffee drinkers (Villanueva et al, 2009). Recently, a study of 233,236 subjects in the European Prospective Investigation into Cancer and Nutrition with a mean follow-up of 9.3 years failed to establish association between risk of urothelial cancer and intake of water, coffee, tea, and dairy beverages (Ros et al, 2011).

Analgesics

Analgesic abuse is a well-documented risk factor associated with the development of UTUC (Johansson et al, 1974; Morrison, 1984; McCredie et al, 1986). In one study, 22% of patients with renal pelvic tumors and 11% of patients with ureteral tumors reported a

history of analgesic abuse with a latency period of approximately 2 years (Steffens and Nagel, 1988). Although phenacetin is the most well described causative agent in analgesic nephropathy, most patients have reported taking combination preparations that included caffeine, codeine, acetaminophen, and aspirin or other salicylates (De Broe and Elseviers, 1998). Histologic findings associated with analgesic abuse include thickening of the basement membrane (pathognomonic) and papillary scarring. Thickening of the basement membrane has been demonstrated in 15% of patients with UTUC and should alert the physician to the presence of analgesic abuse and the subsequent risk of contralateral involvement (Palvio et al, 1987). The degree of papillary scarring also appears to be closely related to tumor grade, although not with the development of squamous metaplasia or squamous cancer. Experimental evidence supports phenacetin-induced papillary necrosis as a cofactor in renal failure and carcinogenesis (Stewart et al, 1999). As phenacetin was replaced by its nontoxic metabolite paracetamol (acetaminophen), considering the long latent period of more than 20 years between the analgesic use and appearance of UTUC, the number of these cases has declined.

Arsenic

Excess inorganic arsenic in drinking water from artesian wells is a major health hazard in certain parts of the world and is associated with an increased risk of UTUC in addition to other diseases (Yang et al, 2002; Tan et al, 2008). Chronic exposure to arsenic in southwestern Taiwan has long been associated with a form of peripheral vascular disease known as *blackfoot disease* that causes dry gangrene of the extremities. This corresponds to a disproportionately increased rate of UTUC among urothelial cancers (20% to 25%) in this area. In addition to the fact that in these patients tumors in the ureter are twice as common as renal pelvic tumors, they behave in a similar fashion to other upper urinary tract tumors of similar grade and stage. There is a 1:2 male-to-female ratio of the upper tract tumors seen in Taiwan in contrast to the male predominance seen in all other areas of the world, which may be a result of higher exposure of women to arsenic fumes during cooking by steam heat over boiling water. If this is correct, it implies an inhalation risk as well as the risk of ingestion from drinking water with high arsenic content.

Occupation

A significantly increased risk for UTUC has been reported for persons with exposure to aromatic hydrocarbons, especially those used in chemical, petroleum, and plastic industries (risk ratio [RR] 4); patients with exposure to coal or coke (RR 4); and patients with exposure to asphalt or tar (RR 5.5) (Jensen et al, 1988). Aromatic amines account for carcinogenicity of β -naphthylamine and benzidine, both of which have been banned in most countries. In addition, chlorinated solvents used in metallurgy and printing have been implicated in the etiology of UTUC (OR 1.8). For these occupational hazards, both the type (contact or vapor inhalation) and duration of exposure (average 7 years) as causative agents are important, and the tumors can occur at long intervals (20 years) after exposure (Colin et al, 2009).

Chronic Inflammation, Infection, or Iatrogenesis

The development of squamous cell cancer (and less commonly adenocarcinoma) has been shown to be related to chronic bacterial infection associated with urinary stones and obstruction (Codec and Murrah, 1985; Spires et al, 1993). In addition, exposure to alkylating chemotherapy, such as cyclophosphamide and ifosfamide, also appears to confer an increased risk (RR 3.2) via production of acrolein metabolite (McDougal et al, 1981; Brenner and Schellhammer, 1987). Habitual daily use of anthranoid and chemical laxatives for more than 1 year has been associated with a ninefold risk of developing UTUC, but the carcinogenic mechanism is unclear (Pommer et al, 1999).

NATURAL HISTORY

Origins and Patterns of Recurrence

UTUCs are often associated with a poor prognosis. Up to 19% of patients with UTUC have been reported to have metastatic disease on initial presentation (Akaza et al, 1970). However, recent multicenter studies have suggested that although UTUCs are more often invasive and poorly differentiated than bladder cancers, in pathologically matched cohorts cancer-specific outcomes occur with equal frequency among patients with upper and lower tract (bladder) urothelial cancers (Catto et al, 2007; Moussa et al, 2010). In the cohort of patients with bladder and UTUC who were treated with radical cystectomy or nephroureterectomy, on direct comparison of the subset of patients with pathologic T1 or less or T4 disease, the location of neoplasm predicted survival (Rink et al, 2012a). In the cohort of patients with pT1 or less, this difference was partly attributed to aggressive features in the non-muscle-invasive bladder carcinoma, prompting radical cystectomy and technical limitations of upper tract sampling, necessitating early nephroureterectomy for patients with earlier stages of disease; and in the pT4 cohort, this may have been a result of a large proportion of patients with prostatic stromal invasion in the bladder cancer group, which still allows for complete excision of tumor with radical cystoprostatectomy (Green et al, 2013).

Ureter versus Renal Collecting System

Ureteral tumors occur more commonly in the lower than in the upper ureter. Overall, about 70% of ureteral tumors occur in the distal ureter, 25% in the mid-ureter, and 5% in the proximal ureter (Anderstrom et al, 1989; Messing and Catalona, 1998). This phenomenon may be a reflection of downstream implantation. One area of consensus is that removal of the entire ureter is mandatory when upper urinary tract cancers are removed by nephroureterectomy. Bilateral involvement (either synchronous or metachronous) occurs in 1.6% to 6.0% of sporadic UTUC (Babaian and Johnson, 1980; Murphy et al, 1981; Kang et al, 2003). There is no consensus on whether primary location of UTUC affects the cancer-specific mortality. Some studies show that even though ureteral location of cancer confers increased risk of advanced-stage at nephroureterectomy (Margulis et al, 2010), this does not translate into poor survival (Margulis et al, 2010; Raman et al, 2010). Other studies have shown that ureteral location of UTUC predicts recurrence and cancer-specific survival when compared with pelvicalyceal location (Park et al, 2004; Yafi et al, 2012). However, most of the authors agree that tumor grade and stage, along with lymphovascular invasion (LVI) and lymph node spread, trump the location in predicting cancer-related outcomes (Favaretto et al, 2010; Raman et al, 2010; Cha et al, 2012; Yafi et al, 2012). In one series, 5-year survival was 100% for Ta and Tis, 91.7% for T1, 72.6% for T2, and 40.5% for T3 tumors. Multivariate analysis in this series showed that tumor stage ($P = .0001$) and age of the patient ($P = .042$) were the only statistically significant predictors of survival (Hall et al, 1998a).

Chronology of Bladder and Upper Tract Urothelial Carcinomas

Upper Urinary Tract Tumors after Known Bladder Cancer

Particular insight into the contemporary risk for UTUC after treatment of bladder cancer is provided in several large series (Oldbring et al, 1989; Solsona et al, 1997; Herr, 1998; Rabbani et al, 2001; Mullerad et al, 2004; Sved et al, 2004; Canales et al, 2006; Tran et al, 2008; Wright et al, 2009). UTUCs have traditionally been reported to develop in 2% to 4% of patients with bladder cancer, with interval to recurrence ranging from 17 to 170 months, although higher rates up to 25% have been reported (Herr et al, 1996; Solsona et al, 1997). This discrepancy in numbers may be the result

of selection of patients, with more high-grade and dysplastic tumors reported in these series.

On the basis of SEER data from 1973 to 1996, UTUC developed in 657 of 91,245 patients with bladder cancer with a median follow-up of 4.1 years (Rabbani et al, 2001). The relative risk for white men and women was 64.2% and 75.4% at or before 2 years, 44.3% and 40.5% at 2 to 5 years, 50.8% and 42.1% at 5 to 10 years, and 43.2% and 22.2% at more than 10 years, respectively. These authors concluded that the incidence of UTUC is stable on long-term follow-up and that upper tract surveillance must remain rigorous for an extended period. The incidence of upper tract recurrence has been shown to be higher in patients with carcinoma in situ (CIS) than in patients with noninvasive papillary urothelial cancers and in patients treated with cystectomy for CIS rather than for invasive cancer (Solsona et al, 1997; Slaton et al, 1999; Canales et al, 2006). In another study of patients with bladder cancer, upper urinary tract recurrence was more likely to occur in patients with T1 versus Ta disease (HR 1.16), those with high-grade bladder cancer (HR 2.16), and patients with trigonal or periureteral presentation (HR 1.76) (Wright et al, 2009). On pathologic evaluation, recurrence was most likely to be superficial (Ta, T1, Tis) and to occur in the distal ureter only (47%). However, this finding has not been reported in all series. Earlier studies showed that in patients with Ta, T1, and Tis bladder cancers treated with bacille Calmette-Guérin (BCG), there was a 21% upper tract recurrence rate after a median interval of 7.3 years; the majority of tumors were invasive, and 38.8% of patients with recurrence died of their upper urinary tract disease (Herr et al, 1996).

In a recent meta-analysis of 27 studies with 13,185 participants who underwent cystectomy for bladder cancer, low-grade tumors, non-muscle invasive tumors, presence of CIS, multiple urothelial recurrences, multifocal tumors, history of previous UTUC, positive ureteral margin, N0 status, and involvement of male prostatic urethra or female urethra conferred increased risk of development of subsequent UTUC (Picozzi et al, 2012). Some of these factors (low grade, N0 stage, prostatic stromal vs. urethral involvement) were attributed to inferior patient survival in the presence of these adverse features. The type of urinary diversion did not show difference; however, it was assumed that the patients with continent diversion had more favorable disease features, hence introducing a selection bias in this cohort. Because there is no set protocol for UTUC surveillance after bladder cancer, follow-up schedule varied, and the majority of recurrences were diagnosed by symptoms, prevalently hematuria. Recurrences were mostly detected in the advanced or metastatic state, resulting in poor disease-specific survival (Picozzi et al, 2012). Sved and colleagues (2004) reported upper tract tumors in 2% of patients (5 of 235) observed for a mean of 42 months after radical cystectomy for bladder cancer. Upper tract tumor was diagnosed at a mean follow-up of 39.6 months, because of hematuria in four patients, and on routine intravenous urography in the remaining patient. Presence of a tumor in the prostatic urethra of the cystectomy specimen, which may be a predictor of a higher risk of multifocal disease, was the only initial tumor feature that was associated with a higher risk of subsequent upper tract tumor. Canales and coworkers (2006) found that patients with two or more stage Ta bladder cancer recurrences within 12 months were at increased risk for upper tract tumors and that surveillance of the upper tracts is indicated. In addition, presence of ureteral reflux and bladder cancers arising close to a ureteral orifice have also been shown to predispose to UTUC (Zincke et al, 1984; Herr et al, 1992; Hudson and Herr, 1995).

Delayed recurrence is more common in the ureter than in the renal pelvis and appears to occur earlier (at 40 vs. 67 months). In patients treated with BCG for CIS of the bladder, upper urinary tract cancer is even more common (about 30% of cases) and appears to occur distally (in the distal, juxtavesical, and intramural portions of the ureter), especially in patients subjected to cystectomy whose disease is refractory to BCG. Therefore, in cases of high-risk bladder cancer (high-grade T1 disease or CIS), at least imaging of the upper urinary tract should be performed annually as part of routine follow-up (Herr et al, 1996).

Bladder Recurrence after Upper Urinary Tract Tumors

Patients with upper urinary tract tumors are at risk for development of bladder cancer, with an estimated incidence that varies in multiple reports from 15% to 75% within 5 years of the development of the upper tract cancer (Kakizoe et al, 1980; Huben et al, 1988; Anderstrom et al, 1989; Hisataki et al, 2000; Miyake et al, 2000; Kang et al, 2003). This high incidence of metachronous bladder involvement suggests that routine bladder surveillance should be performed. Why do bladder cancers follow upper tract cancers more often than bladder cancers are followed by upper tract cancers? Theories include downstream seeding, longer exposure time to carcinogens in the bladder, and greater number of urothelial cells in the bladder that are subject to random carcinogenic events. Many would agree that most recurrences downstream are caused by seeding. This is supported by the monoclonal nature of the bladder tumor recurrences (Junker et al, 2005), and the pattern of recurrence especially after nephroureterectomy. Most recurrences in the bladder occur within 2 years and are usually at the sites of bladder trauma during total ureterectomy (Kang et al, 2003). It is interesting to note that renal insufficiency is associated with a higher risk of contralateral upper tract tumor.

Studies have suggested that in rapidly recurrent high-grade cancers, specific gene mutations are also demonstrated in subsequent bladder cancers (Harris and Neal, 1992; Lunec et al, 1992; Habuchi et al, 1993). Association of a higher bladder tumor incidence after upper tract tumor multifocality supports a role of distal seeding (Matsui et al, 2005). In contrast, microsatellite studies in low-grade UTUCs, which tend to recur less rapidly in the bladder, have suggested genetic discordance between these upper tract tumors and subsequent bladder cancers in 46% of cases (Takahashi et al, 2000), supporting a field effect (Takahashi et al, 2001). The paradoxical finding that the risk of subsequent bladder tumor is inversely related to upper tract tumor size and stage may reflect a higher and earlier risk of death from the primary tumor in these cases. In the reports by Hisataki and coworkers (2000), Matsui and associates (2005), and Terakawa and colleagues (2008), increased upper tract tumor stage at the time of nephroureterectomy correlated with a higher risk for subsequent bladder tumor. In a recent European multicenter study reported by Novara and coworkers (2009), prior bladder tumor before upper tract tumor was the only independent risk factor for bladder tumor after nephroureterectomy in multivariate analysis. Raman and associates (2007) reported that the grade, but not the stage, of the prior upper tract tumors correlated with the pathologic findings of the subsequent bladder tumors.

Association with Carcinoma in Situ

As would be expected, the risk of bilateral disease and multifocality increases with the presence of CIS. The risk of bilateral disease is around 3% to 5% overall but can be as high as 25% when there is associated CIS of the bladder (Herr et al, 1996). In addition, these patients are at higher risk for subsequent panurothelial disease. In such cases, management should take into account the high probability that there will be multifocal disease. This approach should include a conservative approach when feasible and frequent follow-up of bladder and extravesical sites such as prostatic urethra and upper urinary tracts.

Dissemination of Disease

Urothelial carcinoma of the upper urinary tract may spread via direct invasion into the renal parenchyma or surrounding structures, lymphatic or hematogenous invasion, and epithelial spread by seeding or direct extension. It is clear that high-grade tumors demonstrate a greater propensity to invade and that non-organ-confined disease (>pT2) is the most significant predictor of the development of metastases (95%), followed by vascular invasion (83%) and lymphatic invasion (77%) (Davis et al, 1987; Margulis et al, 2009).

Lymphatic

Depending on the location of the tumor in the renal pelvis, upper or lower two thirds of the ureter, lymphatic spread from the upper urinary tract extends to the renal hilar, para-aortic, paracaval, inter-aortocaval, and ipsilateral common iliac and pelvic lymph nodes (Batata and Grabstald, 1976; Kondo et al, 2007). This extension is directly related to the depth of invasion of the primary tumor.

Hematogenous

The most common sites of hematogenous metastases from upper tract tumors are the liver, lung, and bone (Batata et al, 1975; Brown et al, 2006). Although it is very rare, direct extension into the renal veins and vena cava may occur in renal pelvic tumors (Jitsukawa et al, 1985; Geiger et al, 1986).

Epithelial

Spatially distinct synchronous and metachronous tumors have prompted the rise of two theories of their origin. Monoclonal theory explains the epithelial spread of the tumors via urinary seeding and/or intraepithelial migration of malignant cells (Harris and Neal, 1992), and these multiple tumors are then the descendants of single genetically modified neoplastic cells. Epithelial spreading may occur in both antegrade and retrograde manners. Antegrade seeding is more common and thought to be the most likely explanation for the high incidence of recurrence in patients in whom a ureteral stump is left in situ after nephrectomy and incomplete ureterectomy (Johnson and Babaian, 1979). In contrast, the "field effect" theory assumes the propensity of urothelium to diffusely form unrelated de novo tumors as a result of exposure to a mutagenic environment. It seems that a small but significant proportion of multifocal cancers are, in fact, derived from different clones (Hafner et al, 2002). Not excluding the idea of molecular evolution of the tumors arising from a single clone, the dual pattern of molecular evidence currently supports the view that urothelial tumors can develop monoclonally through epithelial intraluminal dissemination of tumor cells and field "cancerization."

Panurothelial Disease

Panurothelial disease is defined as a disease involving the bladder as well as two extravesical sites. In males, this could include one or both upper urinary tracts and/or the prostatic urethra, and in females the bladder and both upper urinary tracts. The low frequency of panurothelial disease and the lack of prospective studies do not permit absolute conclusions about treatment impact and outcomes. Solsona and colleagues (2002) described their experience with panurothelial disease. In this cohort of 35 patients, the population most at risk was those with high-risk superficial bladder multifocal tumors and those with associated bladder CIS. The approach of these researchers was cystectomy for high-grade and any invasive disease, and management of the upper tracts was largely conservative with local resection and treatments for noninfiltrating tumors and radical excision with more aggressive tumors. These patients, however, present a large clinical dilemma, as the only curative approach would be a total removal of the genitourinary tract.

More recently, Nguyen and colleagues (2014) described their experience with panurothelial disease. They identified 35 patients with histologically proven urothelial carcinoma of the bladder and both upper urinary tracts. The average follow-up was 95 months. They identified two distinct groups: those with initial upper tract pathology in 17 and initial bladder pathology in 18 patients. They found there was no statistically significant difference between those who had bladder pathology first and those who had upper tract pathology first. Within that group there were 8 patients who originally had low-grade disease on presentation and subsequently transitioned to multifocal high-grade disease and tumor invasion and progression. Four of these patients who initially had multifocal

low-grade tumors rapidly progressed to high-grade tumors and metastatic disease and death. The demographics of this group were quite interesting: There was a similar distribution of men and women, and nearly half did not have a smoking history. Individual genetic factors may play a role in susceptibility of these patients, which is witnessed by the fact that most of these individuals had a history of another malignancy or a family history of cancer. These genetic alterations, if found, may provide a clue in identifying those patients who may benefit from total removal of urothelium.

This undoubtedly represents a very perplexing population of patients and difficult management problems. The role of systematic disease has not yet been established; however, most would agree that cystectomy is indicated for those with multifocal high-grade disease. In addition, there should be close surveillance of the upper tract for any infiltrating disease. In younger patients, it may be helpful to have early recognition of disease progression and early choice of total removal of the genitourinary system as a way of preventing progression to metastatic disease and potential death. Certainly, more studies are needed in this area.

HISTOPATHOLOGY

The majority of upper tract tumors are urothelial cancers. These are largely derived from transitional urothelium; squamous cell cancers and adenocarcinomas represent a small minority (Bennington et al, 1975; Vincente et al, 1995; Flanigan and Kim, 2004).

Normal Upper Tract Urothelium

Whereas the bladder is of endodermal origin, the ureter and renal pelvis are derived from the mesoderm. Nevertheless, the urothelial lining of the upper urinary tract closely approximates that of the bladder except for the markedly reduced thickness of the muscle layer and the abutting of the urothelium to the renal parenchyma proximally. The epithelial layer is continuous from the level of the calyces to the distal ureter. It has been postulated that the urothelial layer may even “extend” into the collecting ducts, raising the possibility that collecting duct renal cancers may be closely related to urothelial cancers and perhaps better treated by agents used for urothelial cancers (Orsola et al, 2005). This observation needs further confirmation.

Renal Pelvis and Calyces

The walls of the calyces and the pelvis contain fibrous connective tissue and two layers of smooth muscle and are lined on their inner surfaces with transitional epithelium (Dixon and Gosling, 1982) (Figs. 58-1 and 58-2). Thin muscle layers originate in the minor calyces and form a spiral, helical arrangement (Fig. 58-3).

Ureter

The ureter demonstrates two continuous thin muscle layers with a loosely spiraled internal layer and a more tightly spiraled external layer. In the lower third of the ureter, a third outer longitudinal layer is present. All three layers merge with the three layers (inner longitudinal, middle circular, and outer longitudinal) of the bladder wall, which run longitudinally, transversely, and obliquely. Beneath the outer muscle coat is the serosa, made up of loose connective tissue and containing blood vessels and lymphatics (Hanna et al, 1976; Notley, 1978) (Figs. 58-4 and 58-5).

Abnormal Urothelium

Metaplasia and Dysplasia

Several studies have suggested that UTUCs progress through histologic changes from hyperplasia to dysplasia to frank CIS in a significant proportion of patients (Heney et al, 1981; McCarron et al, 1982). CIS may be patchy and may extend proximally to the



Figure 58-1. Low-magnification view of a section through the kidney. The renal medulla ends in the pointed renal papilla. Urine empties into the Y-shaped space made up of the renal calyces (the arms of the Y) and the pelvis (the base of the Y).

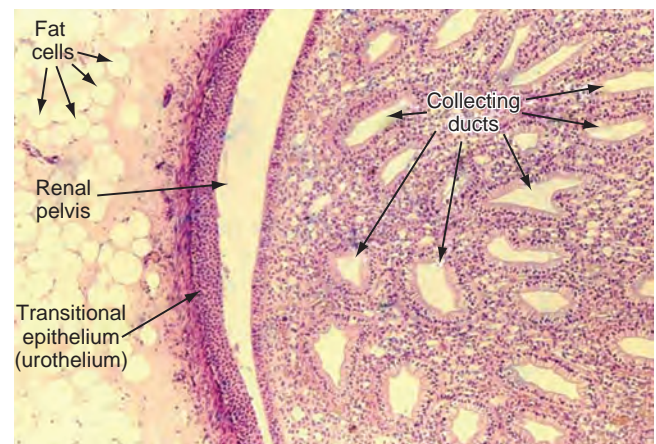


Figure 58-2. This image shows several large collecting ducts near the end of a medullary pyramid (i.e., close to their opening into the pelvis). The transitional epithelium of the renal pelvis is continuous with that of the ureters and bladder.

collecting ducts of the kidney (Mahadevia et al, 1983). More severe urothelial dysplastic changes are associated with a greater risk for tumor recurrence in the distal ureter and bladder and a reduced prognosis.

Benign Lesions: Papillomas and von Brunn Nests

Papillomas and inverted papillomas are generally considered benign lesions; however, because of their association with either synchronous or metachronous upper tract urothelial tumors (Renfer



Figure 58-3. In this specimen from the renal pelvis the connective tissue immediately beneath the epithelium is inconspicuous, obscured by a layer of smooth muscle (note elongated nuclei). Beneath the smooth muscle is loose connective tissue, including conspicuous adipocytes.

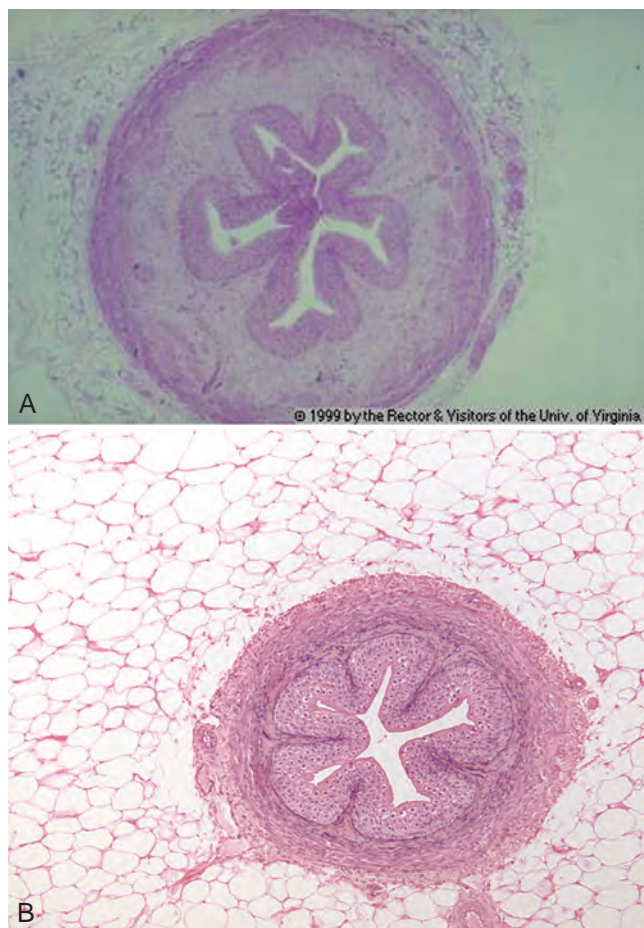


Figure 58-4. A and B, Cross section of ureter. The ureter has an irregular lumen, which is lined by transitional epithelium. Under the epithelium is a connective tissue layer and, beneath that, three layers of smooth muscle: inner longitudinal, middle circular, and outer longitudinal. (A, © 1999, Rector & Visitors of the University of Virginia.)

et al, 1988; Stower et al, 1990; Chan et al, 1996; Cheville et al, 2000), they require close surveillance. One series demonstrated an 18% incidence of malignancy associated with inverted papilloma of the ureter (Grainger et al, 1990). Other studies have suggested that there are two types of urinary inverted papilloma. The lesions of type 1 behave in a benign fashion, whereas those of type 2 may have a malignant potential. Because there is currently no way to

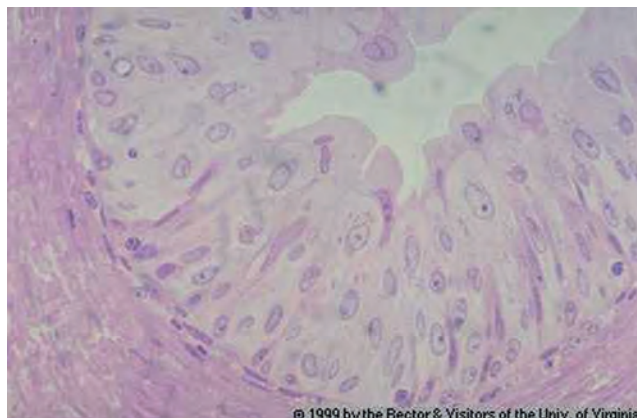


Figure 58-5. Transitional epithelium and loose connective tissue that compose the mucosa of the urinary tract. Transitional epithelium superficially resembles nonkeratinized stratified squamous epithelium, but note that the epithelial cells nearest the apical (outer) surface are not flattened but cuboidal. Transitional epithelium is a stratified epithelium characterized by the fact that the most apical cells are the roundest and largest in diameter. It is designed to be able to increase its surface area as the lumen is dilated by urine. (© 1999, Rector & Visitors of the University of Virginia.)

distinguish between these two types, it has been advised that follow-up for all cases of inverted papilloma should be continued for at least 2 years after initial diagnosis (Asano et al, 2003). Similarly, these findings suggest that close surveillance of the upper tracts for malignancy is warranted when inverted papilloma is diagnosed.

Urothelial Histology

Urothelial carcinomas make up more than 90% of upper urinary tract tumors. They may manifest as flat (CIS), papillary or sessile lesions, and may be unifocal or multifocal. On histologic examination these lesions are similar to urothelial carcinoma of the bladder, but the relative thinness of the muscle layer of the renal pelvis and ureter makes invasion through the muscle coat an earlier event. CIS, as in the bladder, can be particularly difficult to identify and can vary in appearance from a whitish plaque to epithelial hyperplasia or a velvety red patch as a result of increased submucosal vascularity (Melamed and Reuter, 1993). Progression to muscle invasion or invasion into the renal parenchyma or adventitial tissues may occur and is more likely, given the relative thinness of the muscle coat of the upper tracts. Reported variants of urothelial carcinoma are squamous cell, glandular, sarcomatoid, micropapillary, neuroendocrine, and lymphoepithelial and can be seen in as high as 25% of UTUCs. Although all of these variants are considered aggressive tumors, some data show that with adjustment for the rest of clinicopathologic characteristics, variant histology has not been shown to predict poor clinical outcome (Rink et al, 2012b).

Micropapillary Variant. A micropapillary variant of urothelial carcinoma (MPUC) in the bladder is associated with aggressive behavior. This histologic subtype is very rare in the upper urinary tract, and most patients have advanced disease at presentation. Contrary to the study by Rink and colleagues, two studies (Holmäng et al, 2006; Sung et al, 2014) independently linked the micropapillary variant to inferior progression and cancer-free survival. Holmäng described 26 patients with this entity in the upper urinary tract. Twenty-two patients had stage T3 disease at presentation, and CIS or LVI was noted in 64% and 81% of patients, respectively. Five-year survival was only 26.9%, and overall the disease-specific mortality was 77%. In the multivariable model (Sung et al, 2014), MPUC still remained a statistically significant independent predictor for progression-free survival (HR 3.85, $P = .003$). MPUC was associated with poorer cancer-specific survival than non-MPUC ($P < .001$).

Nonurothelial Histology

Nonurothelial carcinomas of the upper tracts represent a wide spectrum of lesions, from benign to highly malignant. The most common of these are squamous cell cancers and adenocarcinomas.

Squamous Cell Cancers. Pure squamous cell cancers make up 0.7% to 7.0% of upper urinary tract cancers (Babaian and Johnson, 1980; Blacker et al, 1985). They are frequently associated with a condition of chronic inflammation or infection or with analgesic abuse (Stewart et al, 1999). These tumors occur six times more frequently in the renal pelvis than in the ureter and are typically moderately to poorly differentiated and more likely to be invasive at the time of presentation.

Adenocarcinomas. Adenocarcinomas account for less than 1% of all renal pelvic tumors and are typically associated with long-term obstruction, inflammation, or urinary calculi (Stein et al, 1988; Spire et al, 1993). These tumors typically are at an advanced stage on presentation and display a poor prognosis.

Other Miscellaneous Tumors. Fibroepithelial polyps (Musselman and Kay, 1986; Blank et al, 1987) and neurofibromas (Varela-Duran et al, 1987) are uncommon benign lesions that are typically treated by simple excision. Neuroendocrine (Ouzzane et al, 2011b) and hematopoietic (Igel et al, 1991) tumors and sarcomas (Coup, 1988; Madgar et al, 1988) have also been reported to involve the upper urinary tracts. Because of the rare nature of these tumors they are typically treated by excision with adjuvant therapy that is based on the experience with tumors of similar histology occurring elsewhere in the body.

DIAGNOSIS

The most common presenting sign of upper tract urothelial tumors is hematuria, either gross or microscopic. This occurs in 56% to 98% of patients (Murphy et al, 1981; Guinan et al, 1992a; Raabe et al, 1992). Flank pain is the second most common symptom, occurring in 30% of tumors. This pain is typically dull and believed to be secondary to a gradual onset of obstruction and hydronephrotic distention. In some patients, pain can be acute and can mimic renal colic, typically ascribed to the passage of clots that acutely obstruct the collecting system. These common symptoms of localized disease (hematuria, dysuria) and of advanced upper tract tumors (weight loss, fatigue, anemia, bone pain) are similar in type and frequency to those of bladder cancer. However, flank pain caused by obstruction by tumor or clot is more prevalent in upper tract tumors, having been reported in 10% to 40% of cases (Babaian and Johnson, 1980; McCarron et al, 1983; Richie, 1988; Williams, 1991; Melamed and Reuter, 1993). About 15% of patients are asymptomatic at presentation and are diagnosed when an incidental lesion is found on radiologic evaluation. Patients may also have symptoms of advanced disease, including flank or abdominal mass, weight loss, anorexia, and bone pain. Nearly all upper tract tumors are diagnosed during the patient's life, and therefore UTUC represents a rare autopsy finding (Resseguie et al, 1978).

Radiologic Evaluation

Although intravenous pyelography has been the traditional means for diagnosis of upper tract lesions, this has been supplanted by computed tomographic urography. Computed tomography (CT) is easier to perform and less labor intensive than intravenous pyelography. It also has a higher degree of accuracy in determining the presence of renal parenchymal lesions. Alleviating the concern for missing the small urinary filling defects (<5 mm) between the "cuts" of the traditional CT scan, a three-dimensional reconstruction of image of the upper tracts appears to be equal to intravenous pyelography in imaging the ureters and renal pelvis (McTavish et al, 2002). With CT urography, the sensitivity for detecting upper tract malignant disease has been reported to approach 100%, with a specificity of 60% and a negative predictive

value of 100% (Caoili et al, 2002). CT urography does, however, expose the patient to higher doses of radiation.

Radiolucent filling defects, obstruction or incomplete filling of a part of the upper tract, and nonvisualization of the collecting system are the typical findings suggestive of an upper urinary tract tumor. Identification of filling defects, which account for 50% to 75% of cases, typically requires the intravenous administration of contrast material (Murphy et al, 1981; Fein and McClennan, 1986). The differential diagnosis of these defects includes blood clot, stones, overlying bowel gas, external compression, sloughed papilla, and fungus ball. Stones can be ruled out most easily by confirmation of calcification by renal ultrasonography or CT. Urothelial cancers have an average density of 46 Hounsfield units (HU) and a range of 10 to 70 HU (Lantz and Hattery, 1984). This is in contrast to an average of 100 HU seen in radiolucent uric acid stones (range, 80 to 250 HU). Thus CT can be useful in distinguishing between these two common causes of radiolucent filling defect on excretory urography or retrograde ureterography. The impact of hydronephrosis and nonvisualization for renal pelvis tumors versus ureteral tumors as indicators of a higher stage is uncertain. Nonvisualization is reported in 20% of renal pelvis tumors, only 33% of which are invasive (McCarron et al, 1983). Nonvisualization is reported in 37% to 45% of ureteral tumors and carried a 60% risk of invasion in one series (McCarron et al, 1983). In other reports there is no correlation of nonvisualization and stage (Batata and Grabstald, 1976; Anderstrom et al, 1989). Hydronephrosis with or without an associated filling defect is linked with invasion in 80% of ureteral tumors (McCarron et al, 1983; Cho et al, 2007).

Radiolucent, noncalcified lesions may require additional evaluation by retrograde urography or ureteroscopy, with or without biopsy and cytology. Overall, retrograde urography has an accuracy of 75% in diagnosis of an upper tract malignant neoplasm (Murphy et al, 1981). An incompletely filled or obstructed renal infundibulum or calyx, occurring in 10% to 30% of cases, again typically requires retrograde urography or ureteroscopy to confirm the diagnosis.

Evaluation of the contralateral kidney is important not only because of possible bilaterality of the disease but also because it allows a determination of the functionality of the contralateral kidney. At times, a split-function renal scan may be helpful in determining the contribution of both the "diseased" and the presumed "normal" kidney to the patient's overall renal function.

Some have suggested that ultrasonography has sensitivity equal to that of urography in evaluating patients with painless gross hematuria for upper tract malignant disease (Yip et al, 1999; Data et al, 2002). For staging purposes, CT or magnetic resonance imaging (MRI) is most useful in determining the extent of invasion, an associated mass lesion outside the collecting system, and the presence of lymph node or distant metastases (Milestone et al, 1990). CT is also more sensitive than conventional radiography in determining minimally radiopaque substances, making it useful in identifying urine excreted by poorly functioning areas of kidney (as in obstructed areas) (Kenney and Stanley, 1987). The greatest downside of CT or MRI is in the detection of small lesions that may be lost in volume averaging in addition to poor sensitivity for assessment of invasion. In one series, CT predicted TNM stage in 60% of patients; it understaged 16% and overstaged 24% (Scolieri et al, 2000).

Cystoscopy

Because upper urinary tract tumors are often associated with bladder cancers, cystoscopy is mandatory in the evaluation to exclude coexistent bladder lesions.

Ureteroscopic Evaluation and Biopsy

The technical advances achieved in the realm of endoscopic equipment have made the flexible and rigid ureteroscope a key part of the evaluation (and treatment) of upper urinary tract tumors. **Diagnostic accuracy can be improved from approximately 75% with**

excretory or retrograde urography alone to 85% to 90% when it is combined with ureteroscopy (Stroom et al, 1986; Blute et al, 1989). Although pyelovenous and pyelolymphatic migration has been reported with ureteroscopy, this phenomenon appears to be uncommon and should not preclude its use (Lim et al, 1993).

As with bladder tumors, 55% to 75% of ureteral tumors are low grade and low stage (Cummings, 1980; Richie, 1988; Williams, 1991). Also, like bladder cancers, approximately 85% of renal pelvic tumors are papillary and the remainder sessile. Invasion of the lamina propria or muscle (stage T1 or T2) occurs in 50% of papillary and in more than 80% of sessile tumors. Overall, 50% to 60% of renal pelvic tumors are invasive into either the lamina propria or muscle. In ureteral tumors, invasion is also more common than in bladder tumors (Anderstrom et al, 1989; Williams, 1991).

In addition to visualization of the tumor, ureteroscopy allows more accurate biopsy of suspected areas, with either biopsy forceps or brushing. Despite reports of changes in grade or stage from diagnostic biopsy (Smith et al, 2011) to subsequent resection, reasonable histologic correlation (78% to 92%) between the ureteroscopic biopsy specimen and the final pathologic specimen has been established (Keeley et al, 1997c; Guarnizo et al, 2000; Brown et al, 2007). It appears that fresh samples obtained ureteroscopically provide the best chance of predicting eventual pathologic findings. In one study, a cell block from biopsy specimens was prepared when a visible tumor was present, and grades of ureteroscopic biopsy specimens were compared with grades and stages of surgical specimens in 42 cases. Of 30 low- or moderate-grade specimens, 27 (90%) proved to be low- or moderate-grade urothelial carcinoma; 11 of 12 high-grade specimens (92%) proved to be high-grade urothelial cancer, and 8 (67%) were invasive (T2 or T3) (Keeley et al, 1997c). In contrast, the urologist's impression of the tumor grade based on ureteroscopic appearance is likely to be correct in only 70% of cases, suggesting that biopsy is also needed to further define this important aspect of staging (El-Hakim et al, 2004).

Because of the small size and shallow depth of ureteroscopic biopsy specimens, a precise correlation with eventual tumor stage is difficult. Therefore, in predicting the tumor stage, a combination of the radiographic studies, the visualized appearance of the tumor, and the tumor grade provides the surgeon with the best estimation for risk stratification. In general, CIS of the upper tract is a presumptive diagnosis that is made by the presence of unequivocally positive selective cytology in the absence of any radiographic or endoscopic findings. The exception is when the diagnosis is made because of a ureteral CIS finding at cystectomy. Although, as stated earlier, grading of the tumors may be fairly accurate, staging is much more problematic. Of 40 urothelial tumors staged in one series (40% in the renal pelvis, 20% in the proximal ureter, and 40% in the distal ureter), ureteroscopic grade matched surgical grade in 78% of cases and was less than surgical grade in the remaining 22%. Lamina propria was present in 68% of biopsy specimens (62% of cup biopsies and 100% of loop biopsies), but tumors thought to be Ta were upstaged to T1 to T3 in 45% of cases at the time of complete resection of the lesion (Guarnizo et al, 2000). Therefore, accurate tumor grading on ureteroscopic biopsy may help in estimating tumor stage. In one series, a biopsy specimen showing grade 3 tumor accurately predicted tumor stage in more than 90% of cases (Skolarikos et al, 2003).

Is ureteroscopy (with or without biopsy) necessary in all cases of suspected upper tract tumors? No. In fact, ureteroscopy should probably be reserved for situations in which the diagnosis remains in question after conventional radiographic studies and for those patients in whom the treatment plan may be modified on the basis of the ureteroscopic findings, for example, endoscopic resection. Although there is no evidence that ureteroscopy diminishes the prognosis of a patient destined to proceed to nephroureterectomy, and although the risks of tumor seeding, extravasation, and dissemination are low in experienced hands, these risks are real and should preclude ureteroscopy when it is unnecessary (Hendin et al, 1999).

Antegrade Endoscopy

In some cases of upper tract tumors, percutaneous access to the renal pelvis may be required for diagnosis or treatment. In such cases, antegrade urography and ureteroscopy may be useful for tumor resection, biopsy, or simple visualization. Larger-caliber scopes that can be passed into the renal pelvis in this manner may be particularly helpful in resecting or debulking larger volumes of tumor in this area (Stroom et al, 1986; Blute et al, 1989). One must remember, however, that tumor cell implantation in the retroperitoneum and along the nephrostomy tube tract has been reported after these procedures (Tomera et al, 1982; Huang et al, 1995).

Role of Cytology and Other Tumor Markers

Urine cytology is a specific tool that is useful in the diagnosis of upper tract carcinomas. On the other hand, the sensitivity of cytology remains an issue. In general, the sensitivity of voided urine (or bladder wash) cytology is directly related to tumor grade. **Overall accuracy estimates of the sensitivity of cytology have ranged from about 20% for grade 1 tumors to 45% and 75% for grade 2 and grade 3 tumors, respectively** (Murphy and Soloway, 1982; Konety and Getzenberg, 2001).

Even if a voided cytology specimen is abnormal in a patient with an upper tract filling defect, one must be cautious in determining the site of origin of the malignant cells. Ureteral catheterization for collection of urine or washings may provide more accurate cytologic results. However, even in this setting, a substantial false-negative or false-positive result (22% to 35%) can be expected (Zincke et al, 1976). It would appear that saline washing provides a better cell yield and improves cytologic results secondary to the release by hydroscopic forces of loosely adherent cells from the urothelium. Still better accuracy can be achieved by brush biopsy through a retrograde catheter or ureteroscope. Sensitivity in the 90% range with specificity approaching 90% may be possible with these techniques (Stroom et al, 1986; Blute et al, 1989). Brush biopsies have, however, also been reported to result in severe complications, including massive hemorrhage and perforation of the urinary tract with extravasation (Blute et al, 1981).

It appears that the exposure of urothelial cells to ionic, high-osmolar contrast agents as in retrograde pyelography may worsen cytologic abnormalities. Thus, it is probably prudent to obtain cytologic specimens before the use of these agents (Terris, 2004).

Early results suggest that fluorescence in situ hybridization (FISH) also may be useful in the diagnosis of upper tract urothelial tumors. In a study of 21 consecutive upper urinary tract urothelial cancer patients and 10 healthy controls in which FISH probes were used for chromosomes 3, 7, 17, and the *CDKN2A* (9p21) gene, overall sensitivity of FISH was significantly higher than that of cytology and specificity for both was 100% (Luo et al, 2009). However, this small study has not yet been validated.

STAGING AND PROGNOSIS

Staging

The staging of upper urinary tract tumors parallels the staging of bladder tumors.

TNM Staging System

The TNM classification and staging system is the most commonly used. A comparison of the American Joint Committee on Cancer (AJCC) staging system and the TNM system is presented in Table 58-1.

The histologic characteristics and biology of upper tract tumors still affect treatment decisions, technologic improvements notwithstanding. The entity of benign papilloma, which responds favorably regardless of the extent of treatment, is well described in older series of upper tract tumors (Bloom et al, 1970; Batata and Grabstald, 1976). The existence of similar low-grade papillomas of low-grade

TABLE 58-1 American Joint Committee on Cancer (AJCC) and TNM Staging and Classification Systems for Upper Urinary Tract Tumors

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Ta	Papillary noninvasive carcinoma.
Tis	Carcinoma in situ.
T1	Tumor invades subepithelial connective tissue.
T2	Tumor invades the muscularis.
T3	Tumor invades periureteral fat (for renal pelvis only).
	Tumor invades beyond muscularis into perinephric fat or the renal parenchyma.
T4	Tumor invades adjacent organ or through the kidney into the perinephric fat.
LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases
N1	Metastasis to a single lymph node, 2 cm or less in greatest dimension.
N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension.
N3	Metastasis in a lymph node, more than 5 cm in greatest dimension.
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant metastasis.
AJCC STAGING SYSTEM	TNM CLASSIFICATION SYSTEM
0	T0
I	Ta, Tis, T1, N0, M0
II	T2, N0, M0
III	T3, N0, M0
IV	T4 or any T, N+, M+

malignant potential in the bladder remains controversial (Cheng et al, 1999; Cheng and Bostwick, 2000; Oyasu, 2000). It is unclear whether the differences between upper tract papillomas and bladder papillomas are biologic or semantic. Approximately 85% of renal pelvis tumors are papillary; the remainder are sessile. This distribution is similar to that of bladder tumors. However, the stage of upper tract tumors is T1 or T2 in approximately 50% of papillary and 80% of sessile lesions, respectively (Cummings, 1980; Richie, 1988; Williams, 1991). Thus, 50% to 60% of renal pelvis tumors are invasive, in contrast to most bladder tumors, which are noninvasive; 55% to 75% of ureteral tumors are low grade and low stage, but invasion is still more common than among bladder tumors (Anderstrom et al, 1989; Williams, 1991). Patients with upper urinary tract tumors are most often in the sixth or seventh decade of life on presentation and thus are usually older than patients with bladder tumors (Melamed and Reuter, 1993).

Tumors of the renal pelvis are slightly more common than ureteral tumors (Batata and Grabstald, 1976; Richie, 1988; Maulard-Durdax et al, 1996). Ureteral tumors occur in the distal, middle, and proximal segments in 70%, 25%, and 5% of cases, respectively (Babaian and Johnson, 1980; Anderstrom et al, 1989; Williams,

TABLE 58-2 Correlation of Tumor Stage and Grade for Upper Tract Urothelial Tumors

LOCATION AND STAGE	HIGH GRADE (%)
PELVIS	
Low	5
High	91
URETER	
Low	26
High	64

Data from McCarron JP Jr, Mills C, Vaughn ED Jr. Tumors of the renal pelvis and ureter: current concepts and management. *Semin Urol* 1983;1:75–81.

1991; Messing and Catalona, 1998). After conservative treatment, ipsilateral upper tract tumor recurrence is common in a proximal-to-distal direction and is seen in 33% to 55% of patients (Mazeman, 1976; Johnson and Babaian, 1979; Babaian and Johnson, 1980; Cummings, 1980; McCarron et al, 1983). Recurrence proximal to the original lesion is rare.

This high rate of ipsilateral recurrence results in part from a multifocal field change, which is even more pronounced than in bladder cancer. Areas of atypia, dysplasia, or CIS are reported in 60% to 95% of specimens after nephroureterectomy for renal pelvis tumor (Johansson et al, 1976; Kakizoe et al, 1980; Heney et al, 1981; Nocks et al, 1982; McCarron et al, 1983; Melamed and Reuter, 1993). Molecular techniques demonstrate that downward seeding of tumor accounts for some recurrences (Harris and Neal, 1992).

Metachronous bilateral upper tract tumors are rare. In a review of all 768 cases of upper tract tumor reported in western Sweden from 1971 to 1998, the rate of metachronous bilateral tumors was 3.1% and was associated with increased age and short survival time after the event (Holmäng and Johansson, 2006).

The occurrence of bladder tumors after upper tract tumors, and vice versa, is another expression of the field change, multifocal risk that affects initial treatment decisions. CIS is present in the distal ureter at the time of cystectomy in 7% to 25% of cases (Melamed and Reuter, 1993; Solsona et al, 1997; Herr, 1998); 15% to 50% of all cases of upper tract tumor occur in patients with a history of bladder tumor (Batata and Grabstald, 1976; Babaian and Johnson, 1980). The incidence of upper tract tumor after bladder tumor is 2% to 4% with a mean time to occurrence of 70 months (Shinka et al, 1988; Oldbring et al, 1989; Melamed and Reuter, 1993; Herr et al, 1996). Upper tract tumors are reported in 3% to 9% of patients after cystectomy for bladder cancer in older series (Zincke and Neves, 1984; Mufti et al, 1988).

Three particular forms of upper tract urothelial tumors, two associated with environmental exposure (aristolochic acid nephropathy, which includes Balkan and Chinese herbal nephropathy, as well as those seen in arsenic-endemic regions), analgesic abuse, and those associated with Lynch syndrome, have an even higher tendency to multiple and bilateral recurrences than do sporadic tumors (Markovic, 1972; Petkovic, 1975; Mahoney et al, 1977; Johansson and Wahlquist, 1979; Melamed and Reuter, 1993; Stewart et al, 1999; Tan et al, 2008; Hubosky et al, 2013). The typically low-grade nature of the tumors and the frequent renal insufficiency seen in Balkan nephropathy underscore the importance of conservative treatment when possible. The degree of scarring of renal papillae seen in phenacetin abuse correlates in a dose-dependent manner with the risk of high tumor grade and progression. Calcification of renal papillae after analgesic abuse is associated with development of squamous carcinoma of the renal pelvis (Stewart et al, 1999).

There is a strong correlation of grade and stage for upper tract tumors. The single most important determinant of outcome is pathologic tumor stage (Tables 58-2 and 58-3) (Bloom et al, 1970;

TABLE 58-3 Literature Review of Overall Survival of Patients with Upper Tract Urothelial Tumors (Renal Pelvis or Ureter) by Stage and Grade

	5-YEAR SURVIVAL (%)
TUMOR GRADE	
1-2	40-87
3-4	0-33
TNM STAGE	
Ta, T1, Tc1s	60-90
T2	43-75
T3	16-33
T4	0-5
N+	0-4
M+	0

Grabstald et al, 1971; Batata et al, 1975; Wagle et al, 1975; Babaian and Johnson, 1980; Cummings, 1980; McCarron et al, 1983; Huben et al, 1988; Anderstrom et al, 1989; Guinan et al, 1992b; Terrell et al, 1995; Messing and Catalona, 1998).

Upper tract tumors spread in the same ways as bladder tumors do, through lymphatic and hematogenous routes and by direct extension into contiguous structures, and most metastatic recurrences develop in the first 2 to 3 years after surgery (Brown et al, 2006). The common metastatic sites are the lungs, liver, bones, and regional lymph nodes. Preoperative evaluation for the extent of disease includes chest radiography, abdominal CT, liver function tests, and occasional bone scintigraphy. The thin muscle layer of the renal pelvis and ureter may allow earlier penetration of invasive upper tract tumors than is seen in bladder neoplasms (Cummings, 1980; Richie, 1988). The renal parenchyma may be a barrier, slowing distant spread of stage T3 renal pelvis tumors. In contrast, periureteral tumor extension carries a high risk of early tumor dissemination along the periureteral vascular and lymphatic supply. Improved survival of patients with stage T3 renal pelvis tumors versus ureteral tumors has been reported by several investigators (Batata and Grabstald, 1976; Guinan et al, 1992a; Park et al, 2004). Guinan and colleagues (1992a) confirmed this observation among 611 patients treated at 97 hospitals and in a collection of 250 cases reported in the literature. The 5-year survival rates for patients with stage T3 tumors of the renal pelvis and ureter were 54% and 24%, respectively. In a multivariate analysis, patients with ureteral tumors had a higher local and distant failure rate than did those with renal pelvis tumors of the same stage and grade (Park et al, 2004). Some have proposed subclassification of renal pelvis tumors into pT3a for infiltration of the renal parenchyma and pT3b for invasion of peripelvic adipose tissue, because the patients with pT3b have an increased risk of recurrence (Rosigno et al, 2012). Renal pelvis and upper ureteral tumors spread initially from hilar to para-aortic and paracaval nodes, whereas distal ureteral tumors spread to pelvic nodes (Batata et al, 1975; Heney et al, 1981; Nocks et al, 1982; Mahadevia et al, 1983; McCarron et al, 1983; Jitsukawa et al, 1985; Geiger et al, 1986).

Prognostic Factors

Stage

Stage is currently the most important predictor of survival in patients with upper tract urothelial tumors (Png et al, 2008). The most commonly used staging system is the TNM system (see the section on staging). Prognosis decreases as stage increases; the most significant decrease in survival is observed in T3 tumors that have penetrated into the perirenal, renal sinus, or periureteral

fat (Grabstald et al, 1971). Extranodal extension in patients with nodal involvement appears to predict clinical outcomes (Fajkovic et al, 2012).

Grade

The traditional grading system used for bladder cancer is also applicable to upper urinary tract tumors. Broder's original system, modified by Ash, grades tumors from grade 1 to grade 4: Grade 1 tumors are primarily papillomas, and grade 4 tumors are highly anaplastic and poorly differentiated tumors (Melamed and Reuter, 1993). The World Health Organization's system, proposed by Mostofi, eliminates papillomas and grades tumors from grade 1 to grade 3. Tumor grading has also been divided into low grade and high grade (Epstein et al, 1998). Papillomas and papillary urothelial neoplasms of low malignant potential are also described. Certainly, tumors of high grade are more likely to invade into the underlying connective tissue, muscle, and surrounding tissues. Tumors of high grade are also more likely to be associated with concomitant CIS.

Location

There remains disagreement as to whether the location of an upper tract tumor affects prognosis. Some have argued that when renal pelvic and ureteral tumors are matched for stage, there is no significant difference in prognosis (Hall et al, 1998b; Isbarn et al, 2009). Other studies have suggested that renal pelvic tumors have a better prognosis than ureteral cancers, even when adjusted for stage (Park et al, 2004; Ouzzane et al, 2011a). Multifocality portends worse prognosis (Chromecki et al, 2012).

Tumor Architecture

Papillary tumors seem to have better outcomes than sessile lesions (Remzi et al, 2009; Fritsche et al, 2012). As in bladder cancer, CIS of the upper tract is associated with higher risk for disease progression and a likelihood of future development of invasive urothelial cancers. CIS of the distal ureter is most common in patients with bladder CIS treated with BCG (30% likelihood).

Hydronephrosis

The presence of hydronephrosis has been shown in various studies to be a valuable and independent predictive factor for advanced disease stage and survival in UTUC patients (Cho et al, 2007; Brien et al, 2010; Ito et al, 2011; Ng et al, 2011).

Tumor Size

Although the role of tumor size is still an evolving criterion, recent studies suggest that tumors greater than 3 to 4 cm may be associated with worse survival as well as a higher risk of bladder recurrence (Cho et al, 2007; Simone et al, 2009a).

Age

Advanced age is a predictor of recurrence-free, disease-specific, and overall survival (Shariat et al, 2010; Chromecki et al, 2011). It is unclear whether the tumor biology or difference in care of elderly patients is responsible for this observation. In the study by Chromecki and colleagues (2011), addition of Eastern Cooperative Oncology Group (ECOG) performance status to the multivariate analysis abolished this association. Nevertheless, most advanced-age patients are cured with radical surgery, so age alone should not preclude the standard of care treatment for this population.

Race

Review of SEER data showed that black non-Hispanic race is associated with increased mortality compared with white non-Hispanic

race (Raman et al, 2011). Comparison of Japanese and European patients revealed no differences in survival (Matsumoto et al, 2011).

Tumor Multifocality

Presence of tumor in two or more sites within urothelium is defined as multifocality and serves as an independent predictor of poor clinical outcome. In a study by Novara and colleagues (2007), presence of multifocality increased disease-specific mortality by a factor of 3. In another cohort of patients, presence of multifocality was associated with disease-specific survival on univariate but not on multivariate analysis (Brown et al, 2006).

Tumor Necrosis

Extensive necrosis has been shown to correlate with aggressive clinicopathologic features, including stage, grade, LVI, presence of CIS, sessile architecture, and lymph node metastases (Zigeuner et al, 2010). Presence of tumor necrosis was also reported to independently predict recurrence-free and cancer-specific survival (Simone et al, 2009a; Zigeuner et al, 2010). However, a recent multicenter study contradicted this observation; the presence of necrosis alone was not predictive of survival on multivariate analysis (Seitz et al, 2010). Further studies validating this feature are needed.

Lymph Node Involvement

Involvement of regional lymph nodes in UTUC is an independent factor predicting poor survival (Hall et al, 1998a; Brown et al, 2006; Margulis et al, 2009). Depending on the stage and grade of the tumor, up to 40% of patients appear to harbor lymphatic metastases. The current paradigms are shifting toward primary treatment with platinum-based neoadjuvant chemotherapy in the population with radiographic suspicion for lymph node involvement, with surgical consolidation offered only if a significant response is seen. Similarly to bladder carcinoma, lymph node density is an emerging factor for clinical prediction in UTUC. In a study of patients who underwent lymphadenectomy at the time of radical nephrectomy, lymph node density of 30% or more was associated with poor clinical outcomes (Bolenz et al, 2009).

Lymphovascular Invasion

LVI has been suggested to be an independent prognostic factor for disease-specific survival in UTUC and should be commented on in pathologic evaluation. Unfortunately, it is not seen on ureteroscopic biopsy specimens and serves only as a prognostic tool after surgical resection. In three single-center and two multicenter series including a total of 1841 patients with upper tract tumors, the prevalence of LVI varied from 23.7% to 37.8%. LVI correlated with increasing tumor stage and grade and with disease recurrence and disease-specific survival (Akao et al, 2008; Bolenz et al, 2008; Lin et al, 2008; Chung et al, 2009). Kikuchi and colleagues (2009) reported on a large international, 13-center collaborative series of 1453 patients who underwent radical nephroureterectomy for upper tract urothelial tumors. The overall prevalence of LVI was 24%. LVI correlated with tumor grade stage, lymph node status, and tumor necrosis. In multivariate analysis, LVI was an independent predictor of disease recurrence and survival for patients with either negative lymph nodes or unknown nodal status. However, LVI was not an independent predictor of outcome for patients with positive lymph nodes.

Molecular Biology (Chromosome Abnormalities) and Markers

The characterization of genetic pathways leading to UTUC is a work in progress. Despite similarities in the molecular basis of UTUC to bladder carcinoma, disparities on a genetic and epigenetic level make them divergent entities. Microsatellite instability and hypermethylation seem to emerge as key differences between upper and lower tract urothelial neoplasms. On the other hand, several gene

foci on chromosome 9 are mutated in 50% of the UTUC cases, and results of comparative genomic hybridization have shown concordance between tumors of renal pelvis and bladder in the losses at 2q, 8p, 9q, 11p, 13q, 17p, and 18q, and gains at 1q, 6p, 8q, and 17q chromosomes (Rigola et al, 2001). A more recent study by Zhang and colleagues (2010) found similar gene expression profiles in renal pelvic and bladder tumors, including common cytogenetic alterations +1p36, +6p22, +7, +8q22, -9p21, +11q, -13q, +17, +19q13, and +20q.

Despite multiple recent advances in the identification of molecular markers, none of them have been validated for clinical use. Future prospective studies may help provide insight into their utility as clinical prediction tools. Nevertheless, it is worth mentioning some of the markers that show promise as candidates for future development.

Cell Cycle Markers. The TP53 nuclear protein staining of cytology specimens obtained ureteroscopically appears to correlate well with the presence of UTUC. In one study, of 36 TP53-positive specimens 28 had simultaneous evidence of urothelial carcinoma; 80% of the remaining patients who were evaluated serially also had confirmed UTUC. All 14 TP53-negative studies occurred in patients with no sign of concurrent malignant disease on ureteroscopy (Keeley et al, 1997b). Zigeuner and associates (2004) reported that decreased TP53 immunoreactivity and TP53 overexpression in upper tract tumors were associated with advanced tumor stage and poor prognosis. However, the findings were not independent of stage and grade in multivariate analysis.

CDKN1B. CDKN1B (formerly p27), a cyclin-dependent kinase inhibitor, has been shown to predict the prognosis of upper tract tumors. In one study, low levels of CDKN1B staining were indicative of a worse disease-specific survival (Kamai et al, 2000).

Apoptosis. Expression of Bcl-2 and survivin correlates with advanced cancers, and levels of survivin are associated with disease-specific survival (Jeong et al, 2009).

Cell Migration and Invasion. Expression of E-cadherin and metalloproteinases (MMPs) are associated with poor prognosis. Immunohistochemistry of MMPs correlates with pT stage and disease-specific survival.

Angiogenesis. Hypoxia-inducible factor-1 α (HIF-1 α) is a transcription factor that plays an important role in cellular hypoxia adaptation. In a series of patients with upper tract UTUC, positive HIF-1 α expression was found in two thirds of patients (and was absent in normal urothelium). HIF-1 α was significantly associated with high T stage, nodal stage, and grade as well as cancer-specific survival (hazard ratio 2.23; $P = .004$) (Ke et al, 2008).

Cell Proliferation. Overexpression of Ki-67 predicts progression and disease-specific survival (Jeon et al, 2010) and development of metachronous tumors (Joung et al, 2008). Epidermal growth factor receptor (EGFR) is associated with stage, grade, and squamous differentiation of UTUC. Overexpression and immunoreactivity of nuclear factor- κ B (NF- κ B) are predictors of disease-specific survival and overall survival. HER2 overexpression, although rare in UTUC, correlates with higher stage and grade, but not survival.

Cell Differentiation. Uroplakin III expression is associated with lower stage and grade and disease-specific survival. On multivariate analysis it outperformed stage and lymph node status as a predictor of survival (Ohtsuka et al, 2006). Snail is associated with stage, grade, and LVI and is predictive of recurrence and disease-specific survival (Kosaka et al, 2010). In situ hybridization of telomerase mRNA component hTR is increased with advanced stage and may be associated with disease-free and overall survival (Nakanishi et al, 1999).

Mitosis. Aurora-A regulates spindle assembly during mitosis. Its overexpression is associated with presence of vascular invasion and recurrence (Scarpini et al, 2012).

MET and RON. Recently the roles of c-MET and RON, members of the MET proto-oncogene family of tyrosine kinases, have been studied in upper urinary tract tumors (Comperat et al, 2008). c-MET overexpression correlated with vascular invasion and a worse clinical outcome, whereas overexpression of RON did not correlate with outcome.

COX-2. Abnormal expression of cyclooxygenase-2 (COX-2) has been reported in many forms of human cancer, including bladder urothelial cancer. Kang and coworkers (2008) reported that abnormal expression of COX-2 in stromal cells of upper urinary tract cancers correlated with high tumor stage and grade and poor prognosis.

Microsatellite Instability. Patients with HNPCC, or Lynch syndrome, show genomic alterations in DNA mismatch repair genes (Amira et al, 2003). Furthermore, an inverted growth pattern of cancer has also been associated with microsatellite instability, with a sensitivity and specificity of 0.82 in one study. This finding suggests that microsatellite instability may serve as a marker for inverted growth in upper urinary tract cancers (Hartmann et al, 2003). Ho and coworkers (2008) have reported that a urine-based assay testing for a total panel of 77 markers for microsatellite instability in 30 patients detected 83.3% of cases of an upper urinary tract tumor. Testing for microsatellite instability on resected tumor and normal tissues to screen for Lynch syndrome is a well-established tool for colon cancer and could be considered particularly for those patients with UTUC meeting criteria suggestive of Lynch syndrome (Audenet et al, 2012).

Ploidy-Flow Cytometry. Tumor ploidy has been shown to correlate with survival in upper tract tumors. In one study, tumor aneuploidy was associated with poor 5- and 10-year survival rates of 25% and 0%, respectively (Blute et al, 1988).

Other Markers. Rapid urine tests for urothelial malignant neoplasms have been studied extensively for the purpose of identifying lower urinary tract tumors. Less is known about their value in upper tract cancers. Urinary levels of NMP22, a nuclear matrix protein-based marker, have been found to be elevated in patients with upper tract cancer (Carpinito et al, 1996). Although the sensitivity of this test for determining the presence of low-grade tumors is probably higher than that of cytology, the specificity is low. Urine FISH was reported to have a sensitivity of 87.5% and a specificity of 80% for detection of upper tract tumors in a small series (Akkad et al, 2007).

In one series, an analysis of fibrinogen-fibrin degradation products (AuraTek FDP) was compared with the bladder tumor antigen (BTA) test and urine cytology. In this study, the accuracy of the FDP test was 83% compared with 62% for BTA and 59% for cytology (Siemens et al, 2003). Telomerase activity has been shown to be present in most (>95%) upper tract UTUCs. It can be detected in exfoliated urinary specimens in a high percentage of patients and thus may prove to be a potentially useful marker (in addition to conventional cytology) to identify upper tract cancers (Wu et al, 2000).

Clinical Prediction Tools

Because clinical staging is difficult owing to the challenges in determining invasion on biopsy or imaging, and as the popularity of neoadjuvant approaches increases, clinical prediction tools have been developed to provide better risk stratification before definitive therapy, as well as after nephroureterectomy.

Preoperative. Various studies used clinical, radiographic, and pathologic factors to better determine the risk of invasive disease. The largest analysis of a multi-institutional patient cohort by Margulis and colleagues (2010) showed that combination of grade, tumor architecture, and location achieved 76.6% accuracy as a prognostic tool in predicting non-organ-confined disease.

Postoperative. Construction of nomograms to predict oncologic outcomes after nephroureterectomy using demographic and clinicopathologic data has attracted much interest in the past few years. Using SEER data, Jeldres and colleagues (2010b) looked at patient age, race, and sex; tumor grade, stage, and location; nodal status; and bladder cuff removal status at surgery. The nomogram with the greatest predictive value for 5-year cancer-specific mortality-free rate (75.4%) included patient age, tumor grade, pT stage, and nodal involvement. Yates and colleagues (2012) pooled data from 21 French institutions to develop a nomogram for 5-year cancer-specific survival. On multivariate analysis, T stage, N status, grade, age, and location were associated with cancer-specific survival, and

the resulting nomogram had an accuracy of 78%. In another study, pathologic characteristics of an international cohort of patients (Cha et al, 2012) were used to build predictive tools for recurrence and disease-specific survival. On multivariate analysis, T stage, presence of nodal disease, LVI, sessile architecture, and presence of CIS were associated with recurrence-free survival. For cancer-specific survival, T stage, lymph node metastasis, LVI, and sessile tumor architecture showed independent prognostic value. These nomograms predicted recurrence-free and cancer-specific survival with 76.8% and 81.5% accuracy, respectively. In a more recent study (Roupret et al, 2013), the data from French and international cohorts of patients were merged to develop an optimized nomogram for cancer-specific survival. This nomogram combined patient age, T stage, N stage, tumor architecture, and LVI with an ensuing discriminative accuracy of 0.8.

To predict intravesical recurrence after nephroureterectomy with bladder cuff excision, data from multiple European and North American centers was analyzed (Xylinas et al, 2013). Bladder recurrence at 3, 6, 12, 18, 24, and 36 months was predicted with 67.8% accuracy using the reduced-type nomogram, which was based on patient age, gender, prior bladder cancer, tumor location, stage, presence of CIS, and lymph node involvement. When surgical characteristics (laparoscopic vs. open surgery and type of distal ureter management) were added to this model, accuracy of the nomogram increased to 69%. The authors suggested using this nomogram for use of postoperative intravesical instillation of chemotherapy and optimization of cystoscopic surveillance schedule.

TREATMENT

Surgical Management

The treatment of upper tract urothelial tumors has undergone significant changes. The relatively low frequency of these lesions and the existence of only three prospective randomized trials do not permit absolute conclusions about treatment impact on outcomes. In the past, treatment recommendations were based, at least in part, on practical limitations in follow-up and detection of local disease recurrence. Technologic improvements in imaging and, most important, direct endoscopic visualization of all levels of the urinary tract allow earlier and more accurate initial diagnosis and treatment and improved follow-up. Treatment may be based primarily on the risk the tumor poses and on the efficacy of a specific treatment rather than on other considerations. The specific indications and techniques for each form of treatment (open vs. laparoscopic radical nephroureterectomy; open vs. retrograde endoscopic vs. percutaneous renal-sparing tumor ablation) are addressed later in this chapter. However, the following introductory considerations apply.

The least invasive treatment necessary for safe control of the tumor is preferred, but never at the risk of compromising oncologic control, as UTUC is unforgiving to surgical indiscretions, which also are rarely able to be salvaged by other modalities. Most upper tract urothelial tumors are not large or bulky. Thus, laparoscopic surgery is ideal, at least for the renal portion of radical nephroureterectomy when the tumor warrants removal of the entire renal unit. A variety of approaches with various combinations of laparoscopic and open techniques are used for distal ureterectomy. Select low-grade non-invasive upper tract tumors can be managed initially by ablative renal-sparing surgery. Retrograde ureteroscopy and ureteropyeloscopy are preferred when tumor size, number, and access allow complete tumor ablation. Percutaneous antegrade tumor ablation is chosen when the anatomy and the tumor do not allow complete ablation through a retrograde approach.

Radical Nephroureterectomy

Indications. Radical nephroureterectomy with excision of a bladder cuff is the gold standard for large, high-grade, suspected invasive tumors of the renal pelvis and proximal ureter (Batata and Grabstald, 1976; Skinner, 1978; Babaian and Johnson, 1980; Cummings, 1980; Murphy et al, 1981; Nocks et al, 1982; McCarron

et al, 1983; Richie, 1988; Williams, 1991; Messing and Catalona, 1998). Radical surgery also retains a role in treatment of low-grade, noninvasive tumors of the renal pelvis and upper ureter when they are large, multifocal, or rapidly recurring despite maximal efforts at conservative surgery.

Techniques

Open Radical Nephroureterectomy. There are a variety of surgical approaches to open radical nephroureterectomy, which are mostly dictated by the surgeon's experience and patient's body habitus. Nephroureterectomy is one of the few multi-quadrant operations that urologists perform; a variety of approaches are attempted. Patient may be positioned supine or in modified flank position. In male patients the genitalia are included in the surgical field so that the bladder catheter may be accessed during the procedure. Our preference is a midline approach, which gives the most optimal exposure to the retroperitoneal lymph nodes and bladder. This incision, however, may be limiting in exposure of the upper pole of the left kidney, especially in obese patients. Other incisions are flank, subcostal, and thoracoabdominal. The choice of these incisions necessitates using an additional Gibson, midline, or Pfannenstiel incision for bladder cuff removal (Fig. 58-6).

After incision of the white line of Toldt, the ipsilateral colon is mobilized to expose the Gerota fascia. Ideally, the hilum is controlled before excessive manipulation of the kidney and ureter. The renal hilum is exposed, reflecting duodenum medially on the right side. For left-sided tumors, care should be taken to avoid injury to the pancreatic tail and spleen. The renal artery and vein are secured and divided in a standard manner. Various options for ligating the vessels are used, including suture ligature, ties, a combination of ties with clips, and stapling devices using an endovascular load. The ureter is typically ligated at this time to prevent migration of tumor fragments into the bladder. The entire kidney is mobilized, taking care to stay outside of the Gerota fascia (Fig. 58-7). On the right side, attachments between the liver and kidney, and on the left side the splenorenal ligament, are incised, allowing mobility of the kidney. Traditionally, the ipsilateral adrenal gland has been removed

with the specimen, although adrenalectomy does not aid the oncologic control of UTUC, unless its direct involvement is suspected based on preoperative imaging or intraoperative examination. Thus as a routine, concomitant adrenalectomy is unnecessary.

Management of Distal Ureter and Bladder Cuff

Complete removal of the distal ureter and bladder cuff offer superior oncologic outcomes to incomplete resection. In addition, adequate cystoscopic surveillance of a residual distal ureter stump after nephroureterectomy is virtually impossible, contributing to high rates of local recurrence. **Therefore the entire distal ureter, including the intramural portion and the ureteral orifice, has to be removed.** The kidney and proximal ureter may be kept in continuity with the distal segment; however, the bulk of the attached kidney

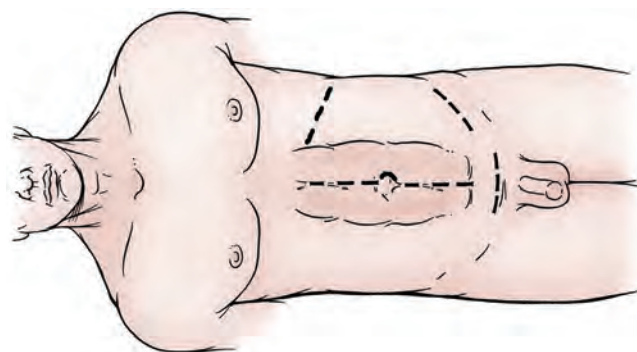


Figure 58-6. Choice of incision for radical nephroureterectomy (midline, subcostal, flank or thoracoabdominal) is dictated by surgeon's preference and experience. Unless a midline incision is used, an additional Gibson, low midline, or Pfannenstiel incision is necessary for bladder cuff removal.

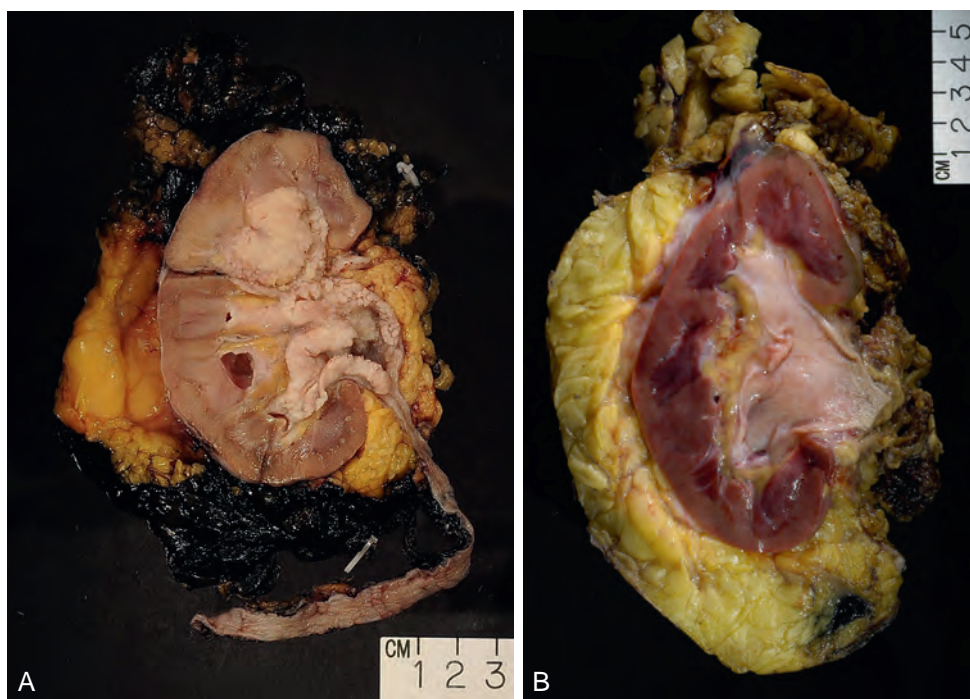


Figure 58-7. A, Radical nephroureterectomy specimen including kidney, Gerota fascia, and ureter. The adrenal gland should not be routinely removed with the specimen, unless its involvement is suspected. B, This bivalved specimen shows a normal collecting system and renal pelvis without tumor. (Courtesy Donna Hansel, MD, PhD, Department of Pathology, University of California, San Diego.)

makes its manipulation difficult, and apart from helping the pathologist with specimen orientation, this technique is not necessary as long as the distal ureter is divided in a controlled manner between ties or clips at a location that is free of gross tumor. There are at least five different techniques described for distal ureterectomy, and most of these apply to both open and laparoscopic surgery.

Traditional Open Distal Ureterectomy. With a Gibson, low midline, or Pfannenstiel incision, bladder cuff removal is performed using a transvesical (Fig. 58-8), extravesical (Fig. 58-9), or combined approach. Any of these methods is acceptable, provided that the whole ureter, including the intramural portion and mucosa of the ureteral orifice, are removed with the surgeon's visual confirmation

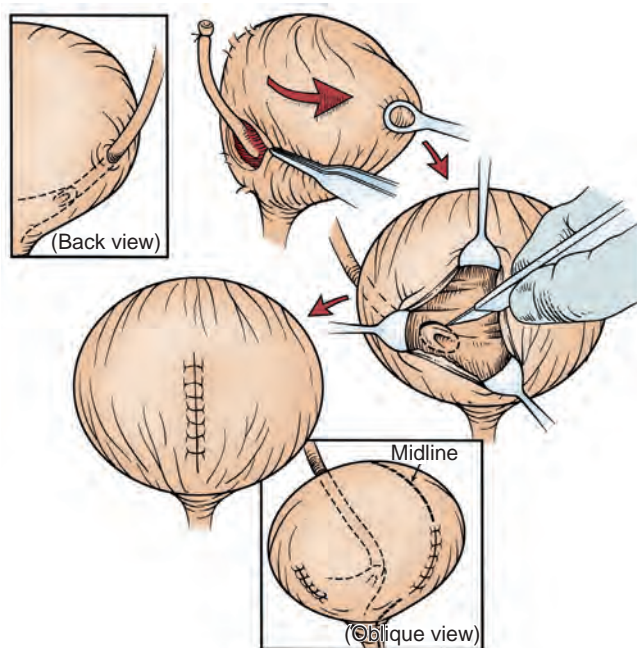


Figure 58-8. Complete distal ureterectomy with bladder cuff is performed by combined extravesical and transvesical dissection.

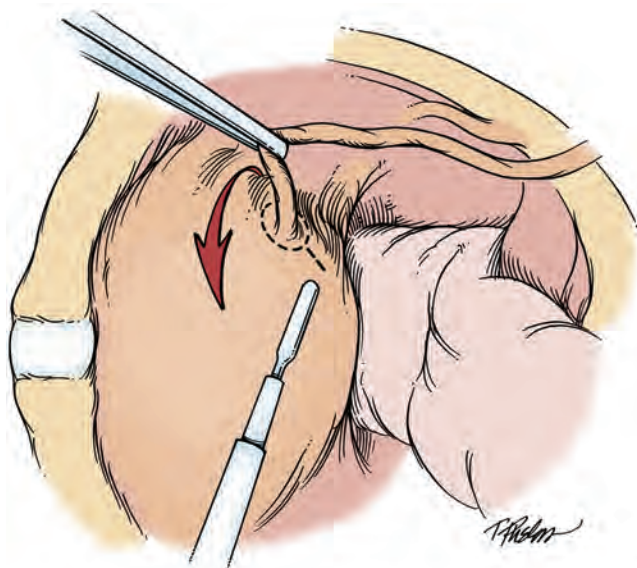


Figure 58-9. Complete distal ureterectomy by extravesical approach. Traction is placed, everting the orifice outside the bladder. Care must be taken to ensure complete removal and to avoid injury to the contralateral ureteral orifice.

of complete resection. For the extravesical approach, distal ureter is freed toward the bladder to the point of intramural ureter. Gentle traction on the ureter and full bladder may aid in this step; however, for adequate access to the entire intramural ureter, the lateral pedicle of the bladder (obliterated artery; superior, middle, and inferior vesical arteries) must be ligated and divided. Care must be taken to avoid uncontrolled entry to the urinary tract. A cuff of bladder is removed en bloc with ureter by applying a clamp to bladder wall and excising the full intramural portion of the ureter, taking care to stay away from the contralateral ureteral orifice. In the transvesical approach, an anterior cystotomy is made and intravesical dissection of the ureter is performed, including a traditional 1 cm mucosal area around the orifice. A wider margin can be taken if a gross tumor is seen protruding from the orifice; and if invasive intramural tumor is suspected, an en bloc partial cystectomy may be required to ensure negative margins. Cystotomy defects are closed in two layers with interrupted or running absorbable sutures: The first layer should incorporate mucosa, and the second layer should include detrusor muscle and adventitia. A Foley catheter is placed and maintained for 5 to 7 days, and a suction drain is left in the perivesical space.

Transvesical Ligation and Detachment Technique. The transvesical ligation and detachment technique mimics open bladder cuff removal. Before the nephrectomy portion, the patient is placed in the low lithotomy position, a cystoscope is passed into the bladder and kept in place, and the bladder is filled. One or two 5-mm trocars are placed intravesically from the suprapubic area. An Endoloop is placed around the ureteral orifice, and a ureteral catheter is advanced into the ureter through the Endoloop. With a Collins knife the bladder cuff is incised, and this incision is carried into the extravesical space (Fig. 58-10). Retraction is provided by the grasper through one of the trocars. Once the ureter is freed, the Endoloop is cinched around the ureter as the catheter is removed. This creates a "closed" urothelium with subsequent en bloc removal of specimen, and extravasation of fluid from the bladder is minimized by continuous suction from the second intravesical trocar. There has been excellent clinical success reported with this technique (Gill et al, 1999), but the learning curve is difficult, and repositioning of the patient for the nephrectomy portion is required. Patients with distal ureteral tumors, disease in the bladder, or prior pelvic radiation are not candidates for this technique.

Transurethral Resection of the Ureteral Orifice. Transurethral resection of the ureteral orifice is also referred to as a "pluck" technique and can be used in patients with proximal tumors and absence of bladder disease (Abercrombie et al, 1988; Palou et al, 1995). With the patient in the lithotomy position, the resectoscope is inserted into the bladder and aggressive resection of the ureteral orifice and intramural ureter is performed down to the perivesical fat (Fig. 58-11). This facilitates the plucking of the distal ureter during the nephrectomy portion of the procedure. Even though equivalent oncologic outcomes have been reported in limited studies (Walton et al, 2009), concerns about tumor seeding of the extravesical space and the potential for leaving incompletely resected ureter have caused this technique to be largely abandoned (Jones and Moisey, 1993; Arango et al, 1997).

Intussusception (Stripping) Technique. The intussusception technique was initially described in 1953, and several modifications have been described since then (McDonald, 1953; Clayman et al, 1983; Roth et al, 1996; Angulo et al, 1998). It is contraindicated in the presence of ureteral tumors. At the beginning of the procedure, a ureteral catheter is placed in the ureter, and nephrectomy is carried out as usual. The distal ureter is isolated extravesically, and a tie is placed around it, securing the catheter to the ureter (Fig. 58-12). After the nephrectomy portion has been completed, the ureter is transected between ties and the bladder cuff is incised cystoscopically with a Collins knife. By pulling on the ureteral catheter, the distal ureter is everted inside the bladder. The intussuscepted ureter is then removed by traction out of the urethra. The edges of the bladder mucosa can be fulgurated. The concerns with this technique include exposure of bladder urothelium to ureteral mucosa with extensive manipulation of the ureter and the potential for

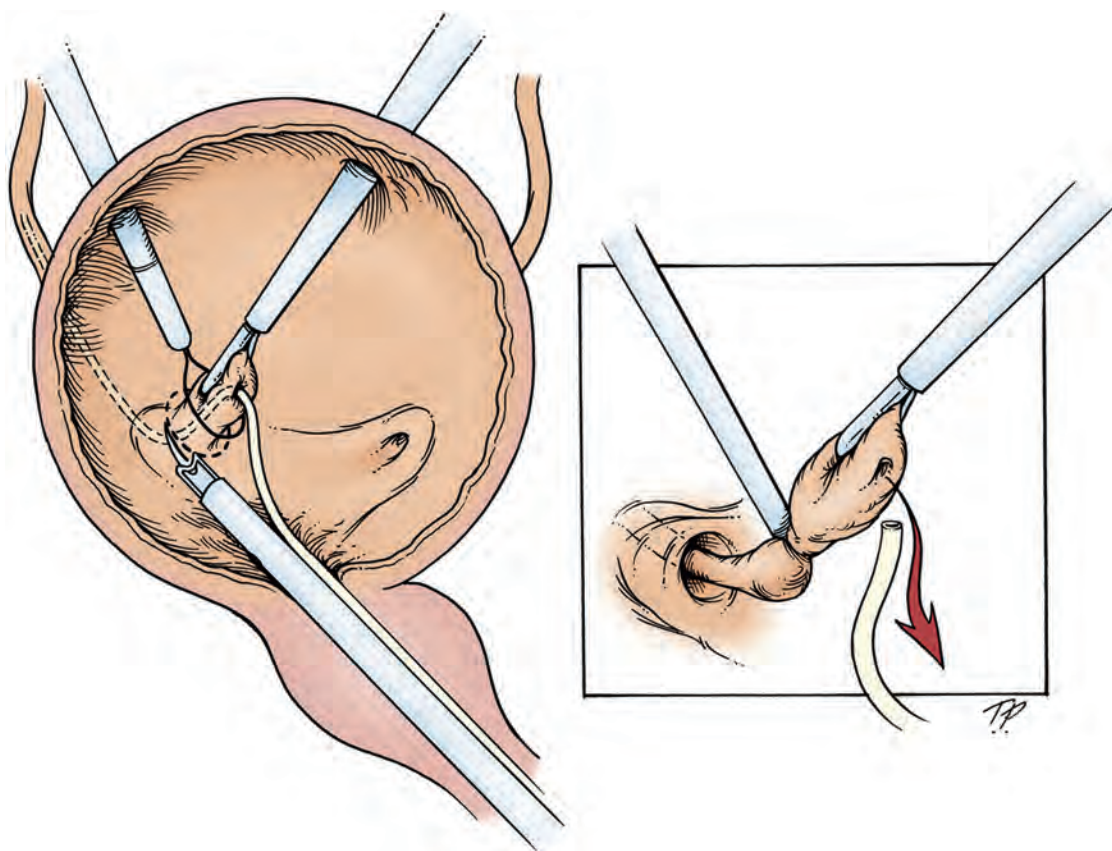


Figure 58-10. A ureteral catheter is placed, and two laparoscopic ports are placed transvesically. The ureteral orifice is tented up; a loop is placed around the orifice to occlude the opening and to place traction on the ureter. A Collins knife then facilitates the dissection to the extra-vesical space.

incomplete intramural ureter excision. In addition, a failure rate of 18.7% has been described in which there was disruption of the ureter during manipulation and the need for an additional surgical incision (Giovansili et al, 2004).

Total Laparoscopic Technique. A total laparoscopic approach is attractive to many because it avoids incision into the urinary tract, and in experienced hands the operative time is reduced. Initially, cystoscopy is performed and the ureteral orifice is cauterized, which may be preceded by placement of a ureteral catheter and incision of an intramural tunnel at the 12 o'clock position. The nephrectomy portion is performed as usual, and the distal ureter is traced to detrusor muscle. The ureteral dissection is carried down to the bladder. The detrusor muscle is split and the ureter retracted in antegrade direction. The endovascular stapler is then used to place a staple line as distally as possible. A fulguration mark helps serve as an identifier of the bladder cuff (Fig. 58-13). The concerns with this technique include the potential for leaving ureter mucosa within the staple line and the inability of the pathologist to evaluate the distal margin because of the presence of staples. Laparoscopic stapling has been associated with a higher risk of positive margins, which in this disease is associated with significantly reduced survival (Steinberg and Matin, 2004; Matin and Gill, 2005). Contraindications include the presence of distal ureteral tumors.

Adjuvant Therapy Following Distal Ureterectomy to Decrease Bladder Recurrence. Bladder tumor recurrence after nephroureterectomy is a relatively common event. Although some cases are from the field effect (Hafner et al, 2002), most researchers believe that most instances are a result of the monoclonal theory of tumor seeding, especially with downstream recurrences (Takahashi et al, 2001; Catto et al, 2006). This is also supported by the patterns of recurrence after surgical treatment, occurring more frequently at the surgical site of distal ureterectomy. In an effort to decrease this

recurrence rate, several authors have described a single postoperative dose of intravesical mitomycin. O'Brien and colleagues (2011) described a single postoperative dose of mitomycin C in a randomized prospective nonblind trial. They found that a single postoperative dose of mitomycin C was able to reduce the risk of bladder tumor within the first year after nephroureterectomy to 11% from over 50%. Another randomized prospective study by Ito and colleagues (2013) using pirarubicin showed very similar findings. Use of mitomycin after transurethral resection of bladder tumor (TURBT) had already shown efficacy in a study. This is an evolving area but should be considered as part of the treatment program after any treatment of the upper tracts in an effort to decrease the risk of bladder seeding, particularly because both studies showed very high tolerability and a low incidence of adverse events.

Lymphadenectomy

The role and extent of lymphadenectomy for UTUC has been under debate for a long time (Nakazono and Muraki, 1993; Komatsu et al, 1997). Limited or regional lymphadenectomy is included with radical nephroureterectomy. For renal pelvis and proximal or middle ureteral tumors, this includes the ipsilateral renal hilar nodes and the adjacent para-aortic or paracaval nodes, and pelvic nodes for distal ureteral tumors (Grabstald et al, 1971; Batata et al, 1975; Batata and Grabstald, 1976; Skinner, 1978; Johansson and Wahlquist, 1979; Babaian and Johnson, 1980; Cummings, 1980; Heney et al, 1981; McCarron et al, 1983; Richie, 1988; Williams, 1991; Messing and Catalona, 1998; Brausi et al, 2007; Kondo et al, 2007; Abe et al, 2008). This dissection adds little time or morbidity to the surgery. Kondo and Tanabe (2012) proposed an extended lymphadenectomy template based on the location of the tumor (Fig. 58-14). For tumors of the renal pelvis this includes ipsilateral

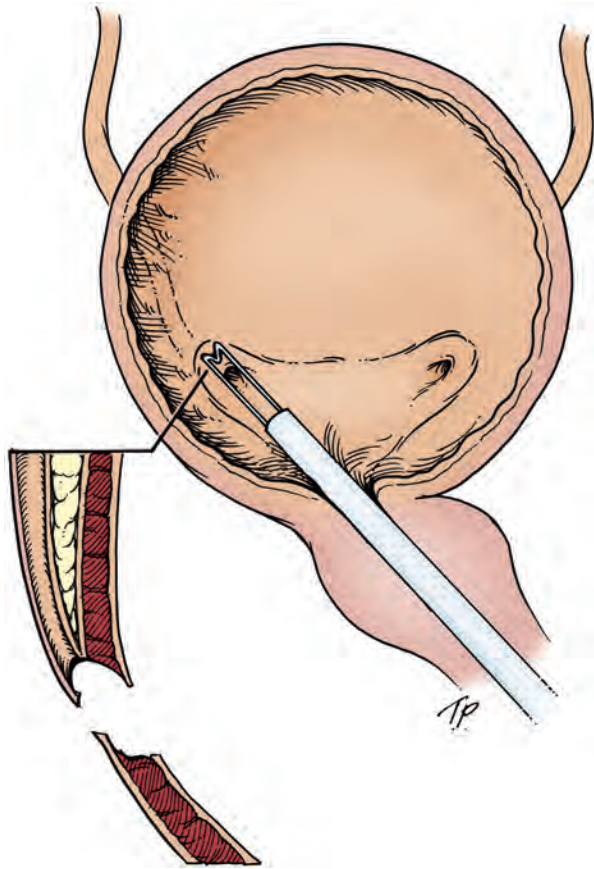


Figure 58-11. The entire orifice and intramural ureter are resected transurethrally until the extravascular fat is seen. This portion is usually done at the beginning but can be done at the end of the procedure.

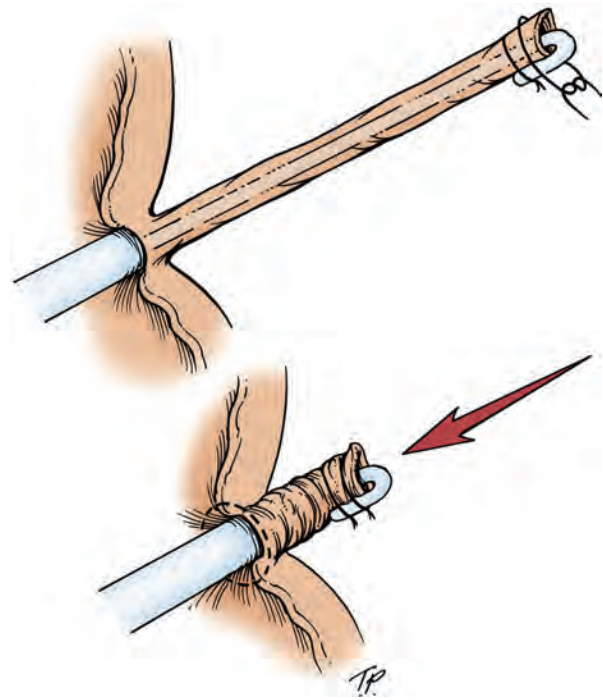


Figure 58-12. With the intussusception technique, a ureteral catheter is placed at the beginning of the case. After nephrectomy the ureter is divided and the catheter is secured to the distal portion of the ureter. The patient is moved to the lithotomy position, and the ureter is intussuscepted into the bladder with retrograde traction. A resectoscope is used to excise the attached orifice.

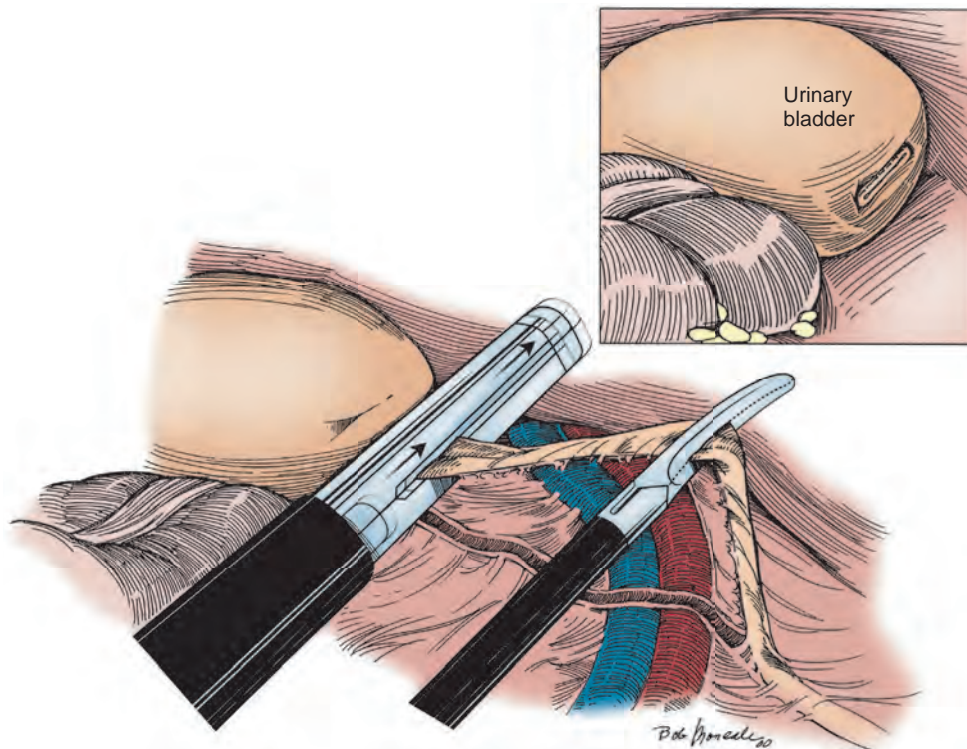


Figure 58-13. The ureter is dissected extravesically to the ureteral orifice. Lateral traction is placed on the ureter, everting the orifice, and the endovascular stapling device is placed at the distal margin, providing simultaneous ligation and division of the distal ureter at the level of the bladder. A cystoscope can be placed to ensure that the entire ureter is removed.

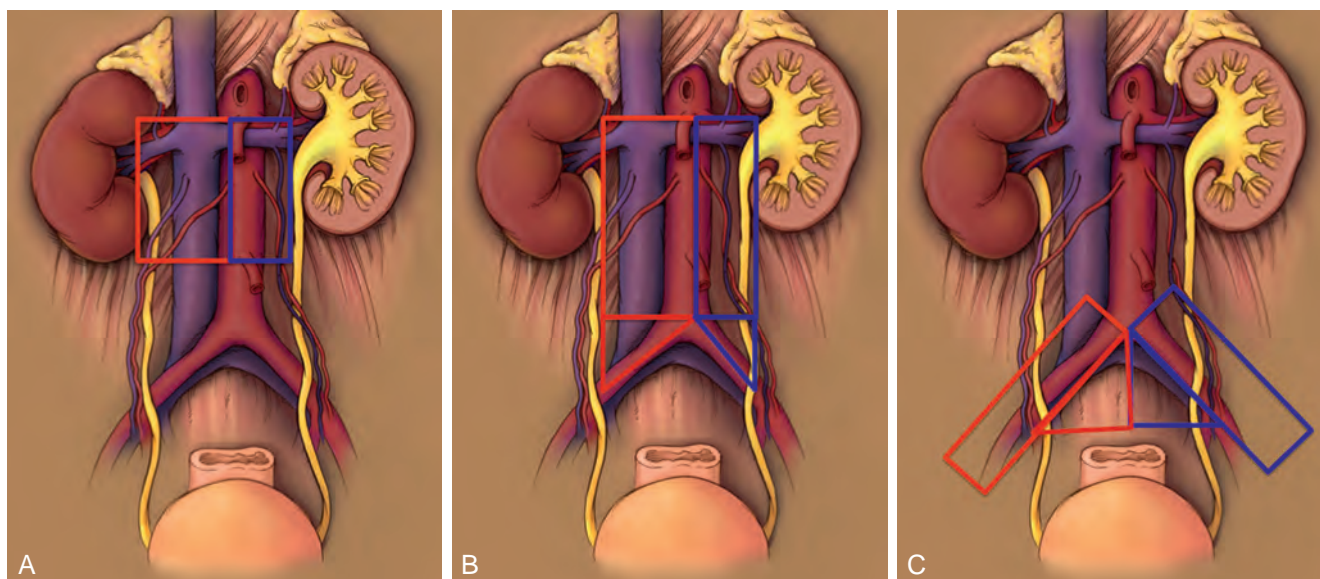


Figure 58-14. A, In addition to ipsilateral hilar nodes, the extended lymphadenectomy template for tumors of the renal pelvis includes paracaval, retrocaval, and interaortocaval lymph nodes for right-sided, and para-aortic lymph nodes for left-sided tumors. The inferior mesenteric artery marks the inferior boundary of the template. B, For tumors of the upper two thirds of the ureter, this template is extended to the level of bifurcation of aorta. C, The extended lymphadenectomy template for tumors in the distal ureter includes ipsilateral common, external and internal iliac, obturator, and presacral nodes.

hilar, paracaval, retrocaval, and interaortocaval nodes up to the level of the inferior mesenteric artery for right-sided tumors, and ipsilateral hilar and para-aortic nodes up to the level of the inferior mesenteric artery for left-sided tumors. For tumors of the upper two thirds of the ureter (above the crossing of the inferior mesenteric artery with the common iliac artery), the template is similar, but the distal border of dissection is extended to the level of aortic bifurcation. For tumors of the lower third of the ureter, these include ipsilateral obturator, internal, external, and common iliac, and presacral packets.

The analysis of the literature is complicated by lack of uniformity in templates for lymphadenectomy and the inconsistent pattern of spread compared with bladder cancers. Lymph node involvement is reported in 12% to 25% of patients with UTUC, although it increases with advanced stage and grade. The reported numbers are 0% to 3% in pTa/pTis, 0% to 6.3% in pT1, 0% to 40% in pT2, 19% to 47% in pT3, and 20% to 100% in pT4. However, the median number of lymph nodes removed and the boundaries of lymphadenectomy varied widely in these studies (Weight and Gettman, 2011). Multiple series of lymphadenectomy at the time of nephroureterectomy (Secin et al, 2007; Roscigno et al, 2008, 2009; Abe et al, 2010; Lughezzani et al, 2010a; Burger et al, 2011) confirm that oncologic outcomes for patients with pN0 are better than pNx, and worse for pN+ compared with pNx groups. The importance of number of lymph nodes removed was addressed by Roscigno and colleagues (2009), who reported that removal of eight or more nodes increased the chance of finding positive lymph nodes by 49% and improved disease-specific survival for those with pT1 or greater disease. Kondo and colleagues (2010) stressed the importance of the dissection template over the nodal counts for survival difference. Several other studies explored the effects of lymphadenectomy on survival. Brausi and colleagues (2007) reported increased overall survival for T2 to T4 patients who underwent lymphadenectomy versus those who had nephroureterectomy only, suggesting a potential therapeutic benefit. Kondo and colleagues (2007) observed a survival advantage when complete lymphadenectomy was performed in patients with pT3 or higher disease. In both of those studies, univariate analysis was performed, which may not have adjusted for presence of confounding variables.

In summary, prospective studies are needed to assess the role of lymphadenectomy in UTUC. As with bladder cancer, it appears to have prognostic and therapeutic value in patients with invasive disease (T2 to T4), and extended lymphadenectomy is beneficial for accurate staging.

Results. Multiple series reported on strong correlation of outcome with tumor stage and grade. Recently, additional prognostic factors, such as tumor architecture, presence of CIS, LVI, and lymph node positivity, were shown to correlate to oncologic outcomes (Margulis et al, 2009; Cha et al, 2012).

Complete ureterectomy with bowel cuff excision should accompany nephroureterectomy for UTUC. The risk of tumor recurrence in a remaining ureteral stump is 30% to 75% (Bloom et al, 1970; Strong et al, 1976; Johansson and Wahlquist, 1979; Babaian and Johnson, 1980; Kakizoe et al, 1980; Mullen and Kovacs, 1980; McCarron et al, 1983). Techniques such as simple extravesical dissection and tenting up of the ureter will result in an incomplete removal of the distal ureter (Strong et al, 1976). Smith and colleagues (2009) presented data on a single-center experience comparing oncologic outcomes following variations in technique of the distal ureterectomy. The techniques were divided into definitive, which included any approach that resulted in excision of the distal ureter with bladder mucosal cuff, and nondefinitive, which included detachment of the ureter at or above the level of detrusor. Nondefinitive management of the distal ureter was associated with higher rates of local and distal recurrence and inferior disease-specific and overall survival. Complete ureterectomy with a bowel cuff should also be performed in the setting of a renal unit draining into a urinary diversion. Tumor recurrence rates up to 37.5% have been reported when ureteroenteric anastomosis was not removed (Mufti et al, 1988).

Researchers in multiple series have recommended radical nephroureterectomy as a treatment that provides optimal oncologic control (Batata et al, 1975; Johansson and Wahlquist, 1979; Murphy et al, 1980; McCarron et al, 1983; Zungri et al, 1990). Margulis and colleagues (2009) conducted a retrospective review of 1363 patients from 12 tertiary care centers worldwide who underwent radical nephroureterectomy with curative intent. Although the data for open and laparoscopic cases were pooled together, most

patients (77%) underwent open nephroureterectomy. The pT stage was evenly distributed among Ta, T1, T2, and T3, but less than 5% of patients had T0, Tcis, or T4 each. Two thirds of patients had high-grade tumors, and 28% had concomitant CIS. Around 10% of patients had lymph node positivity, and 16% received perioperative chemotherapy. Disease recurrence was observed in 28% of patients at a median of 10.4 months. During a median follow-up of 37.2 months, 30% of patients died, and 61% of the deaths were attributable to the patients' disease. In summary, radical nephroureterectomy provides reasonable oncologic control, with outcomes largely dependent on clinicopathologic characteristics. It is warranted for patients with high-grade invasive organ-confined or locally advanced disease (stage T1 to T4, N0 to N2, M0). **Comparative data of extirpative versus conservative management are lacking, because the populations of patients who undergo these surgeries are very different. Treatment decisions in patients with compromised renal function must balance the potential curative effect of radical surgery with the morbidity associated with dialysis.**

Laparoscopic Radical Nephroureterectomy

Indications. The indications for laparoscopic nephroureterectomy are the same as those for open nephroureterectomy. Exceptions may include large bulky tumors with involvement of adjacent structures or those wherein extended lymph node dissections may be considered. Laparoscopic nephroureterectomy can be performed by transperitoneal, retroperitoneal, hand-assisted (Ni et al, 2012), and robotic approaches. **In general, the laparoscopic approach shows a significant decrease in morbidity compared with an open surgical approach for appropriately selected patients.** All laparoscopic techniques involve two distinct portions of the procedure: nephrectomy and proximal ureterectomy, and excision of the distal ureter with intact specimen extraction for accurate staging. Management of the distal ureter is described previously in the chapter. One should bear in mind several factors with laparoscopic nephroureterectomy, including the risk of tumor seeding from both the ureter and the bladder. For these reasons, removal of an intact specimen is desirable. The incision should be strategically placed for both extraction of the specimen and dissection of the distal ureter. Because an incision is necessary regardless of the approach chosen, some techniques for avoidance of a second incision for the distal ureter described previously are less useful.

Technique

Transperitoneal Laparoscopic Nephroureterectomy

Laparoscopic Removal of Kidney Down to Mid-Ureter. The patient is placed supine with the ipsilateral hip and shoulder rotated approximately 20 degrees (Fig. 58-15). The patient is secured to the table and can be easily moved from the flank position (nephrec-

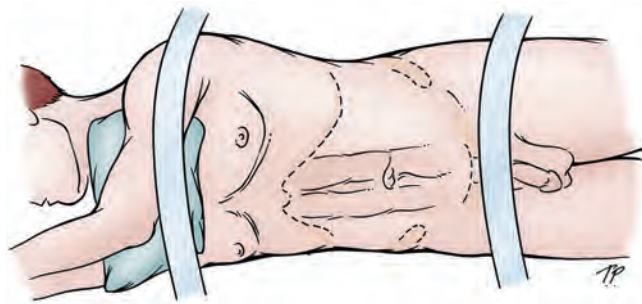


Figure 58-15. The patient is positioned on the table in a modified lateral decubitus position with the ipsilateral flank rotated up 15 degrees. The patient is secured to the table at the chest, waist, and lower extremity. This setup allows the patient to be moved to the full flank or supine position with simple rotation of the operating table. (From Jarrett TW. Laparoscopic nephroureterectomy. In: Bishoff JT, Kavoussi LR, editors. Atlas of laparoscopic retroperitoneal surgery. Philadelphia: Saunders; 2000. p. 105.)

tomy portion) to the modified supine position (open portion) by rotating the operative table. The ipsilateral flank and urethra are prepared and draped, and a Foley catheter is placed before insufflation of the abdomen.

The abdomen is insufflated, and three or four trocars are placed as outlined in Figure 58-16, with the first usually being the lateral trocar. Subsequent trocars are placed under direct vision. With this configuration, the camera is kept at the umbilicus for the entire procedure. The upper midline and lateral trocars are used by the surgeon for the dissection of the kidney and the proximal half of the ureter. The lower midline and lateral trocars are used for the dissection of the distal ureter. A 3-mm trocar just below the xiphoid can be helpful in retracting the spleen and liver for left- and right-sided lesions, respectively. The exception is with obese patients, in whom shifting of the trocars may be necessary to provide optimal visualization (Fig. 58-17). If a hand-assist approach is chosen, the hand port site should be placed so that it can be used for the dissection of the distal ureter and open bladder cuff as indicated.

The table is rotated so that the patient is in the flank position. The peritoneum is incised along the white line of Toldt from the level of the iliac vessels to the hepatic flexure on the right and to the splenic flexure on the left. The colon is moved medially by releasing the renocolic ligaments while leaving the lateral attachments of the Gerota fascia in place to prevent the kidney from

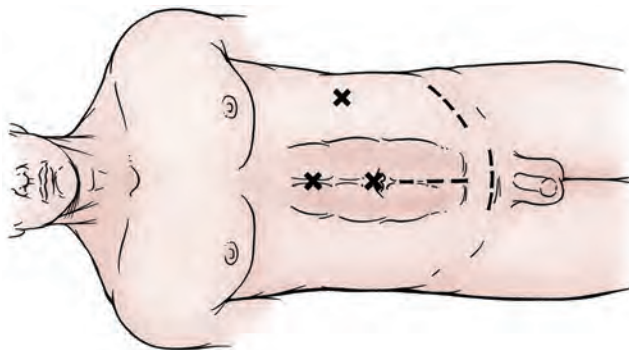


Figure 58-16. Port configuration for laparoscopic-assisted nephroureterectomy. Three ports are typically used for the kidney and upper ureteral dissection. A fourth midline port between the umbilicus and symphysis can be placed, if needed, for further ureteral dissection. The incision is then strategically placed to allow the distal ureteral dissection and specimen removal. The choice of incision largely depends on patient factors and level of dissection reached during the laparoscopic portion of the procedure. A low abdominal (midline or Pfannenstiel) incision is favored if the dissection is below the iliac vessels. A Gibson-type incision will give exposure of the more proximal ureter, if necessary.

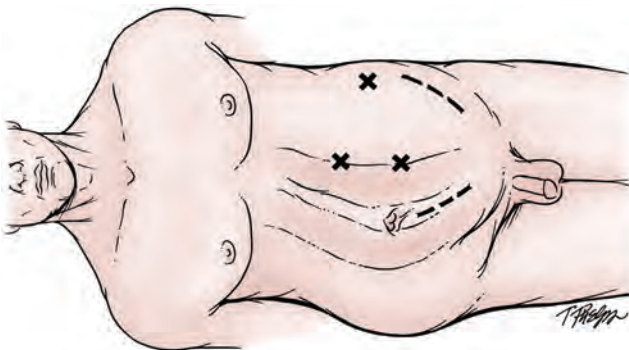


Figure 58-17. For obese patients undergoing laparoscopic-assisted nephroureterectomy, the trocars are shifted laterally to accommodate the increased distance from the kidney.

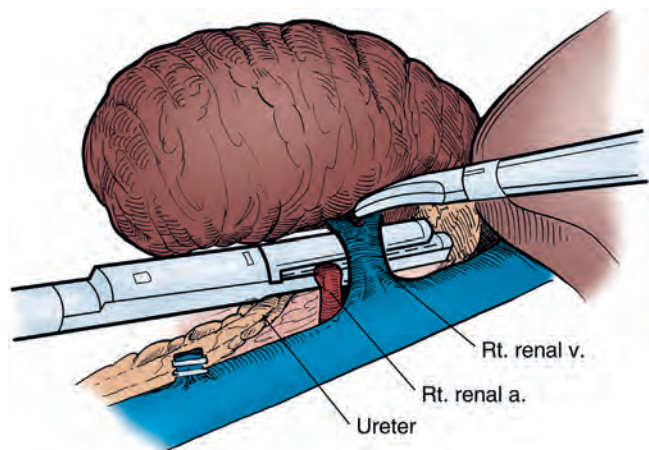


Figure 58-18. The vessels of the renal hilum are carefully dissected, and the endovascular stapling device, with a vascular load, is used to simultaneously ligate and divide the vessels in a controlled environment. (From Jarrett TW. Laparoscopic nephroureterectomy. In: Bishoff JT, Kavoussi LR, editors. *Atlas of laparoscopic retroperitoneal surgery*. Philadelphia: Saunders; 2000. p. 112.)

“flopping” medially. The colon mesentery should be mobilized medial to the great vessels to facilitate dissection of the ureter, renal hilum, and local lymph nodes as needed.

Proximal Ureteronephrectomy. The proximal ureter is identified, just medial to the lower pole of the kidney, and dissected toward the renal pelvis, avoiding skeletonization and maintaining copious periureteral fat if any tumor is located in this area. If an invasive ureteral lesion is suspected, the dissection should include a wide margin of tissue. The renal hilum is identified, and its vessels are exposed with a combination of blunt and sharp dissection. The artery is ligated and divided by use of a stapling device with a vascular load or multiple clips. The renal vein is then divided in a similar fashion (Fig. 58-18). With vascular control ensured, most prefer to ligate the ureter with a clip as previously described, and the kidney is dissected free outside the Gerota fascia. Similar to the procedure described for open nephroureterectomy, the adrenal gland does not need to be removed routinely. The ureteral dissection is continued distally, keeping in mind that the ureteral blood supply is generally anteromedially located in the proximal third, medially located in the middle third, and laterally located in the distal third. Dissection of the lower half may require placement of the fourth trocar. In the area of primary disease, surrounding tissue should be left to provide an adequate tumor margin. The ureteral dissection is continued as far as is technically feasible. If the distal limits of the dissection are below the level of the iliac vessels, the remainder of the procedure can easily be completed through a lower abdominal incision. The specimen is placed in the pelvis, and the renal bed is inspected meticulously for bleeding. At this time, the 10-mm port sites are closed before proceeding to the open portion of the case.

Open Distal Ureterectomy with Excision of Bladder Cuff. The patient is now moved to the supine position, which can usually be done without reoperation, and a low midline Pfannenstiel or Gibson incision is made. The choice of incision largely depends on the tumor location, the body habitus of the patient, and the most caudal level of ureteral dissection attained during the laparoscopic portion. The Gibson incision is preferable when the distal ureter cannot be freed laparoscopically to the level of the iliac vessels.

Dissection of the Distal Ureter. If one is to consider a total laparoscopic procedure or to minimize the open distal portion, the ureteral dissection needs to continue to the level of the bladder. The patient is placed in the Trendelenburg position to move the bowel contents out of the pelvis. The peritoneal incision is extended from the level of the iliac vessels into the pelvis lateral to the bladder and medial to the median umbilical ligament (Fig. 58-19). The vas

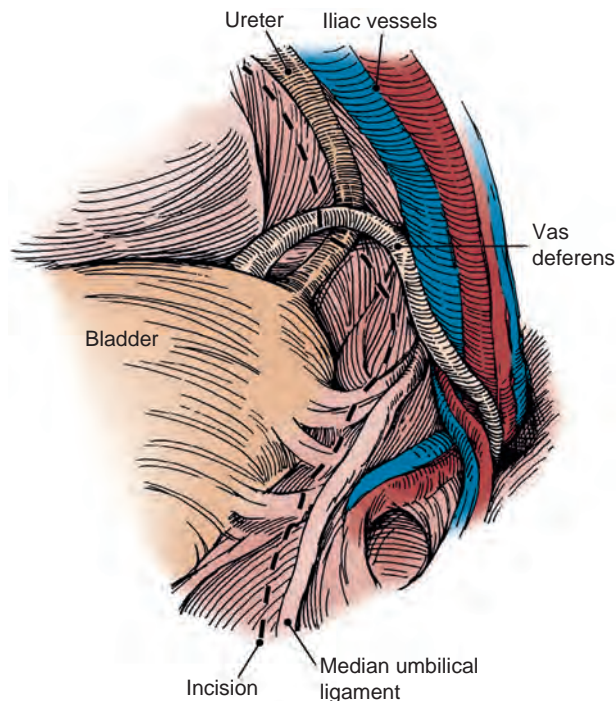


Figure 58-19. The peritoneal incision is continued below the iliac vessels medial to the median umbilical ligament and lateral to the bladder. The vas deferens is divided between clips in the male patient. In the female patient the round ligament is divided, giving full exposure of the distal ureter to the bladder.

deferens in male patients and the round ligament in female patients is clipped and divided if exposure is limited. The ureter can now be traced between the bladder and the median umbilical ligament down to its origin at the bladder. Optimal exposure of the entire intramural ureter is gained by division of the lateral pedicle of the bladder, allowing medial rotation of the bladder exposing the entire length of ureter. The bladder cuff may be dissected extravesically, freeing the ureter from the surrounding detrusor muscle; alternatively, opening the bladder immediately around the ureteral orifice allows direct visual confirmation for complete resection of the bladder cuff. Yet another alternative during a complete extravesical approach is flexible cystoscopy in confirming complete ureterectomy and patency of the contralateral ureteral orifice. The techniques for open distal ureterectomy and bladder cuff excision are described in the section on open techniques.

Robotic-Assisted Laparoscopic Nephroureterectomy. With the increased use of robotics in urologic surgery, robotic-assisted nephroureterectomy has become a feasible alternative to more traditional open or laparoscopic technique. The availability of the da Vinci S system with longer instruments and improved range of motion with less arm clashing has allowed performing the surgery without the need to re-dock the robot or reposition the patient for the distal ureterectomy portion. Proper port positioning is paramount to the success of this technique (Fig. 58-20). The 12-mm camera port is placed at the level of umbilicus, lateral to rectus sheath, followed by placement of cephalad (port 1) and caudad (port 2) 8-mm robotic ports, both of which are positioned 7 to 8 cm away from the camera port on the same line. The third robotic port (port 3) is placed about 5 cm cranial to iliac crest, close to the anterior axillary line. The assistant port is placed in the midline in or around the umbilicus. Docking the robot, the left arm is placed in port 1, the right arm is placed in port 2, and the fourth arm is placed in port 3 and is used for retraction. Once the nephrectomy portion is completed, the retraction instrument is moved to port 1 and the left arm to port 3 for distal ureter and bladder cuff dissection. For extravesical dissection of the ureter, a distended bladder is helpful in tracing the ureterovesical junction. Once the distal

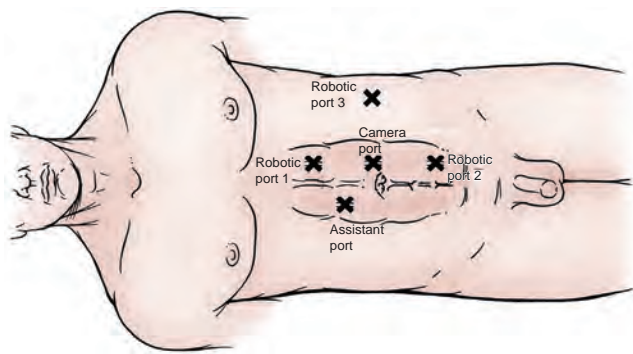


Figure 58-20. Port configuration for robot-assisted laparoscopic nephroureterectomy. For nephrectomy and upper ureterectomy portion, the retraction instrument is placed in port 3, and for distal ureterectomy with bladder cuff removal, the retraction instrument is moved to port 1 and the left arm to port 3.

ureter is dissected out of the detrusor, the bladder can be emptied. Placement of stay sutures medial and lateral to the incision site of the ureterovesical junction aids in subsequent reconstruction of the bladder. The bladder should be closed in two layers (Hemal et al, 2011).

Results. The first laparoscopic nephroureterectomy was performed in 1991 by Clayman and associates. Since that time the technical aspects and safety of laparoscopic procedures have been well established. There are multiple reviews and published series of laparoscopic nephroureterectomy with varying techniques (Jarrett et al, 2001; Stifleman et al, 2001; Bariol et al, 2004; Hsueh et al, 2004; Matin and Gill 2005; Wolf et al, 2005; Ni et al, 2012; Rai et al, 2012). Each varies with regard to approach (transperitoneal vs. retroperitoneal), management of the distal ureter by open removal, transurethral resection, and total laparoscopic management. As with other laparoscopic renal procedures, there is no clear-cut benefit of any one approach with regard to morbidity, cosmesis, or return to activity. All, however, show a benefit with regard to morbidity compared with open surgery. More recently, the robotic technique has been described (Hemal et al, 2011) with only short-term follow-up.

The efficacy of laparoscopic nephroureterectomy is being established for cancer control. With intermediate and long-term follow-up, cancer-related outcomes appear comparable to those of the open counterpart (McNeill et al, 2000). El Fettouh and colleagues (2002), in a multi-institutional study with 116 patients, showed the local and bladder recurrence rates to be 2% and 24%, respectively. The rate of distant metastasis was 9%, and positive margins were seen in 4.5% of cases. More recently, Berger and associates (2008) showed 5-year cancer-specific survival rates of 80%, 70%, 68%, 60%, and 0% for stage Ta/Tis, T1, T2, T3, and T4 lesions, respectively. Schatteman and associates (2007) similarly showed cancer-specific survival rates of 100%, 86%, 100%, 77%, and 0% for stage Ta, T1, Tis, T3, and T4 lesions. In both studies there was a worsening prognosis with increasing tumor stage. Long-term data are available from Muntener and associates (2007a), who studied 37 patients with follow-up of 60 to 148 months. In this study, 11 patients had disease progression and died 7 to 59 months after the operation. Tumor stage was the only factor significantly associated with disease recurrence. Ni and colleagues (2012) compared open with laparoscopic outcomes in a larger review of comparative studies. Although the results were not statistically significant, the study showed that laparoscopic surgery had a higher 5-year cancer-specific survival and lower bladder and overall recurrence rates compared with open techniques. With appropriate patient selection, the laparoscopic approach offers reliable safety and oncologic efficacy with the advantage of lower morbidity for well-selected patients. In the only surgical randomized controlled trial comparing laparoscopic and open extirpative surgery, Simone and colleagues (2009b) showed no difference in metastasis-free and cancer-specific survival

in patients with organ-confined disease. However, in this study, patients with high-grade disease or pT3 or higher stage benefited from open nephroureterectomy.

Local recurrence and port-site seeding are major concerns. There have been 12 reported instances of port-site seeding involving UTUC. Two of these cases were discovered after simple nephrectomy for presumed benign disease in which the principles of surgical oncology were inadvertently not followed (Ahmed et al, 1998; Otani et al, 1999). All were for high-grade disease. Muntener and associates (2007b) reported a single case of local recurrence among 166 cases. In this instance there was obvious violation of the ipsilateral urinary tract, noted perioperatively. Although the potential for seeding exists, it seems to be decreasing and the risk does not appear any higher than that for the open surgical counterpart as long as good surgical principles are followed.

In summary, there does not appear to be a significant difference between laparoscopic and open nephroureterectomy when the principles of surgical oncology are followed. Management of the bladder cuff still has shown variability and a tendency toward higher recurrences with minimally invasive approaches. Lymphadenectomy can be performed laparoscopically and should be used based on the clinical situation. Even extended lymph node dissections can be considered in those with advanced laparoscopic skills.

Open Nephron-Sparing Surgery for Renal Pelvis Tumors

Indications. Open conservative surgery may be considered in rare cases of renal pelvic tumors when nephron sparing for preservation of renal function is required (Gittes, 1966; Petkovic, 1972; Mazeman, 1976; Johnson and Babaian, 1979; Babaian and Johnson, 1980; Cummings, 1980; Wallace et al, 1981; Tomera et al, 1982; McCarron et al, 1983; Zincke and Neves, 1984; Bazeed et al, 1986; Ziegelbaum et al, 1987; Messing and Catalona, 1998; Goel et al, 2006). When choosing this approach, one needs to be aware of inferior oncologic outcomes. Patients who may benefit from this approach are those with a unifocal low or high-grade tumor in a solitary kidney, synchronous bilateral tumors, and predisposition to form multiple recurrences (Fig. 58-21) (Huffman et al, 1985). The definitive diagnosis, tumor location, and grade should be verified by direct endoscopic visualization and biopsy of the lesion (Gill et al, 1973). Preoperative determination of the stage of UTUC tumors remains difficult (Smith et al, 2011), mainly because of technical limitations of use of small biopsy instruments through the narrow channel of the flexible ureteroscope. Brush biopsy may be used if cup biopsy forceps fail to obtain adequate tissue. The documented risk of wound implantation by tumor is low after open conservative surgery if simple precautions are followed to minimize spillage (Gittes, 1980; Tomera et al, 1982; McCarron et al, 1983). Modern percutaneous antegrade renal surgery allows resection of virtually any lesion formerly treated by open pyelotomy, and the risk of tumor spillage is even lower (see following discussion).

Technique. Usually cross-sectional imaging such as CT or MRI is sufficient for preoperative preparation. In the case of rare hypervascular renal pelvis tumors, renal angiography with embolization of segmental artery may be considered for the ease of identification and tumor removal.

The patient is placed in a flank position. The full flank position with flexion of the table elevates the kidney and provides optimal exposure to the renal hilum and renal pelvis. When the patient is positioned properly on the table, elevation of the kidney rest does not provide any additional benefit with exposure and may cause ischemia to the contralateral kidney (Matin and Novick, 2001). A flank, subcostal, or rarely thoracoabdominal incision is made. An extraperitoneal approach is preferred, but if an extended lymphadenectomy is planned, consideration should be given to transperitoneal surgery. A portion of the 11th or 12th rib may be removed, although it is not usually necessary. Removal of a rib may be helpful in obese patients or in those with a high kidney, with a tradeoff of increased postoperative discomfort. After the incision is completed, similarly to radical nephroureterectomy, the kidney is mobilized to allow identification of the renal hilum. Once the renal vessels are



Figure 58-21. Patient with an invasive tumor of the upper calyx of a solitary kidney. The patient elected an upper pole partial nephrectomy.

exposed and isolated using a vessel loop, the Gerota fascia is opened and the entire kidney is mobilized within it.

To minimize the risk of tumor spillage and seeding, the wound is packed with sponges before an incision is made in urothelium. The renal pelvis is defatted to allow optimal visualization, and a curvilinear incision is made to access the tumor. After excision of the tumor, its base is fulgurated with electrocautery or argon beam. Eventually the pelvis is closed with an absorbable suture, such as 3-0 Vicryl.

The techniques of partial nephrectomy for renal pelvis tumors are essentially the same as for standard open partial nephrectomy, with notable nuances that are not intuitive. For example, the margin of resection is often not visible, as the intrarenal urinary system does not have surface landmarks. Thus, use of intraoperative ultrasound is nearly imperative to accurately determine the margins of parenchymal resection that correspond to the intrarenal urinary system. To minimize tumor seeding, the involved segment of the collecting system is clamped before tumor manipulation. After the excision of the tumor with overlying parenchyma of the kidney, the collecting system defect is closed with an absorbable suture. Parenchymal bleeders are oversewn with a 3-0 Vicryl suture. In addition, argon beam may be used to coagulate the parenchymal surface. Capsular 2-0 Vicryl interrupted or U-stitches are used to approximate the edges of the renorrhaphy bed with or without the use of Surgicel bolsters. Additional hemostatic agents may be used at the discretion of the surgeon. Edges of previously incised Gerota fascia are approximated using a 2-0 Vicryl suture line.

A suction drain is placed in the renal bed in all cases. We do not use a urinary stent routinely, unless there is a suspicion for a ureter stricture downstream.

Results. The reported overall risk of tumor recurrence in the ipsilateral renal pelvis after initial pyelotomy or partial nephrectomy varies from 7% to 60% (Mazeman, 1976; Murphy et al, 1981; Wallace et al, 1981; McCarron et al, 1983; Zincke and Neves, 1984; Ziegelbaum et al, 1987; Messing and Catalona, 1998; Goel et al,

2006). The risk of recurrence after conservative surgery increases with tumor stage from less than 10% for grade 1 to 28% to 60% for grades 2 and 3. The moderate to high risk of recurrence primarily reflects the inherent multifocal atypia and field change of the renal pelvis (Heney et al, 1981; Nocks et al, 1982; Mahadevia et al, 1983; McCarron et al, 1983). The possibility of incomplete initial treatment of the primary tumor cannot be totally excluded.

Estimates of overall and cancer-specific survival after conservative surgery of renal pelvis tumors are hampered by the lack of prospective, controlled, randomized trials and the small numbers of affected patients. The inherent bias introduced by selection of patients for conservative treatment based on medical comorbidities is another variable. Murphy and associates (1980) reported 5-year survival of 75% and 2-year survival of 46% after conservative surgery in patients with grade 1 and grade 2 renal pelvis tumors, respectively. McCarron and associates (1983) reported rates of cures, cancer-related deaths, and deaths from unrelated causes of 33% each in nine patients who underwent conservative surgery. Radical nephroureterectomy and dialysis still offer the best chance of cure and survival in patients with a large, invasive, high-grade, organ-confined renal pelvis tumor (T2N0M0) in a solitary kidney (Gittes, 1980; McCarron et al, 1983). Although the issue of morbidity on hemodialysis is always a concern, for a younger patient with a long life horizon, this risk is minimal in the face of an aggressive high-grade UTUC. Smaller and low-grade tumors may be managed with endoscopic ablation, avoiding the need for open surgery.

Open Segmental Ureterectomy

Ureteroureterostomy

Indications. Segmental ureterectomy is indicated for noninvasive tumors of the proximal ureter or mid-ureter that are not able to be removed endoscopically, or for high-grade or invasive tumors when preservation of renal unit is necessary. Achieving a clear margin and still being able to mobilize enough well-vascularized ureter to perform a tension-free anastomosis is paramount to the success of this procedure and the major limiting challenge.

Technique. The patient is positioned in full or modified flank position. A flank incision from the tip of the 12th rib provides access to the proximal ureter or mid-ureter. With use of an extraperitoneal approach, the ureter is identified, mobilized, and secured with vessel loops. The tumor is palpated, and the ureter is ligated 1 to 2 cm above and below the suspected tumor margin (Fig. 58-22). This location can be also verified by preoperative cross-sectional imaging. The diseased ureter is excised and clear margins ascertained by frozen pathology. After regional lymphadenectomy is performed, both ends of the ureter are spatulated and anastomosed with an interrupted 4-0 Vicryl suture. The success of reconstruction depends on preservation of the blood supply to the ureter and adequate mobilization of the ureteral edges to achieve a tension-free anastomosis. If a large segment of ureter is excised, mobilization and descensus of kidney may be performed to provide additional length to the proximal ureter. A ureteral stent is placed before completion of the anastomosis.

Distal Ureterectomy and Direct Neocystostomy or Ureteroneocystostomy with a Bladder Psoas Muscle Hitch or a Boari Flap

The distal ureterectomy is performed as described in the prior section. The ureter is mobilized to achieve a tension-free anastomosis and spatulated. Ureterovesical anastomosis may be performed using an extravesical or intravesical approach. Whether to perform a refluxing or nonrefluxing anastomosis remains a matter of debate. The benefits of a nonrefluxing anastomosis include limit of infection to the lower tract and the theoretic possibility of avoiding seeding of the upper tract. A refluxing anastomosis may make surveillance of the upper tracts easier. If an extravesical approach is

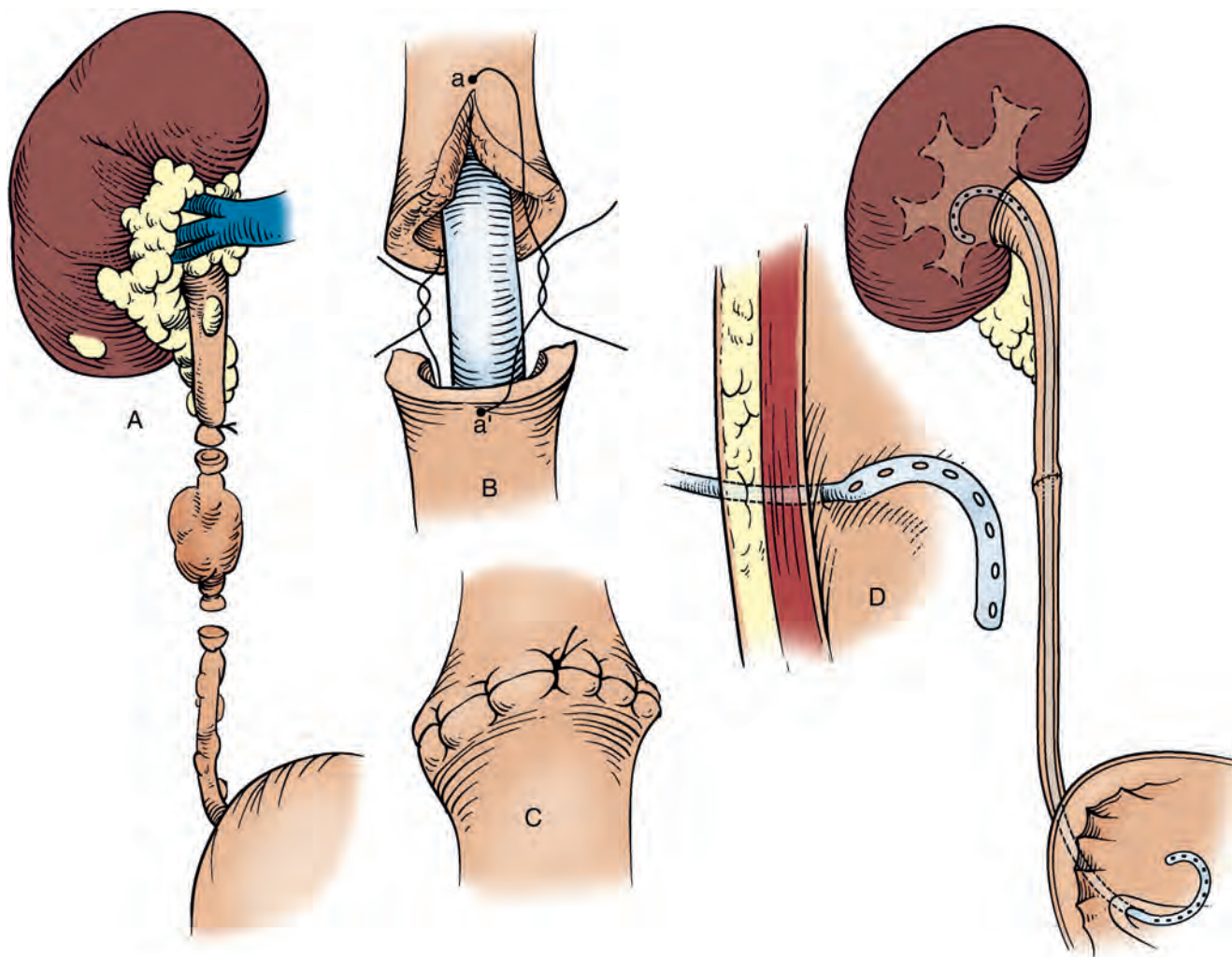


Figure 58-22. A, Segmental ureterectomy between ties for a large, invasive tumor of the mid-ureter. B and C, Ureteroureterostomy of spatulated ends of the ureter. The repair is performed over an internal stent. D, Completed repair with closed-suction drain in retroperitoneal space.

desired, bladder detrusor muscle is incised, exposing the mucosa. A mucosal slit is performed at the distal aspect of this incision. An anastomosis is performed using continuous or interrupted 3-0 Vicryl sutures through the full thickness of the ureter and bladder mucosa. At the distal portion of the anastomosis, two of these sutures are passed through the full thickness wall of the bladder to anchor the ureter and prevent sliding out of the tunnel. The bladder detrusor is then closed on the top of the ureter with interrupted absorbable sutures, such as 2-0 Vicryl, to achieve a nonrefluxing mechanism. A ureteral stent may be placed before completion of the anastomosis.

For the intravesical technique, an anterior cystotomy is made. An incision is made at the posterolateral wall of the bladder and a 2- to 3-cm submucosal tunnel is fashioned. The ureter is brought through this tunnel. After the ureter is spatulated, the anastomosis is performed with interrupted absorbable sutures.

If a long segment of distal ureter is excised and a tension-free anastomosis cannot be achieved by simple ureteroneocystostomy, an additional 5 cm in length can be gained by using a psoas hitch of the bladder. The bladder is mobilized anteriorly and laterally, and in women the round ligament is divided. The contralateral superior vesical artery can also be divided to gain further mobility. After ureterovesical anastomosis is completed, the ipsilateral dome of the bladder is sutured to the psoas tendon using several interrupted sutures. Care should be taken to avoid injury or entrapment of the genitofemoral nerve.

If additional length is desired, a Boari flap can help gain another 10 to 15 cm in length and in some cases may be able to reach all the way to renal pelvis (Fig. 58-23). If a Boari flap is planned, it is advisable to obtain a preoperative cystogram to assess bladder capacity, because a small-capacity irradiated bladder is a contraindication to this technique. A U-shaped bladder wall flap or, if a longer segment is desired, an L-shaped segment, is developed. To ensure a good blood supply to the flap, the base of the flap should be at least 2 cm greater than the apex. To achieve adequate width of tubularized segment, the width of the flap should be at least three times the diameter of the ureter. The tip of the flap is secured to the psoas muscle using interrupted absorbable suture, and the spatulated ureter is anastomosed to the flap in the end-to-end fashion. The flap is then tubularized and closed with two layers of absorbable sutures. A ureteral catheter is placed before closure of the flap. After all of these techniques, it is advisable to use a suction drain in the retroperitoneum and 7- to 10-day Foley drainage of the bladder. After extensive reconstruction, a cystogram should precede Foley removal.

Ileal Ureteral Replacement

When a long segment of ureter is diseased, a segment of ileum can be used to reconstruct the urinary system. The appendix has also been used for segmental ureteral substitution (Goldwasser et al, 1994). Through a midline intraperitoneal incision, 20 to 25 cm of

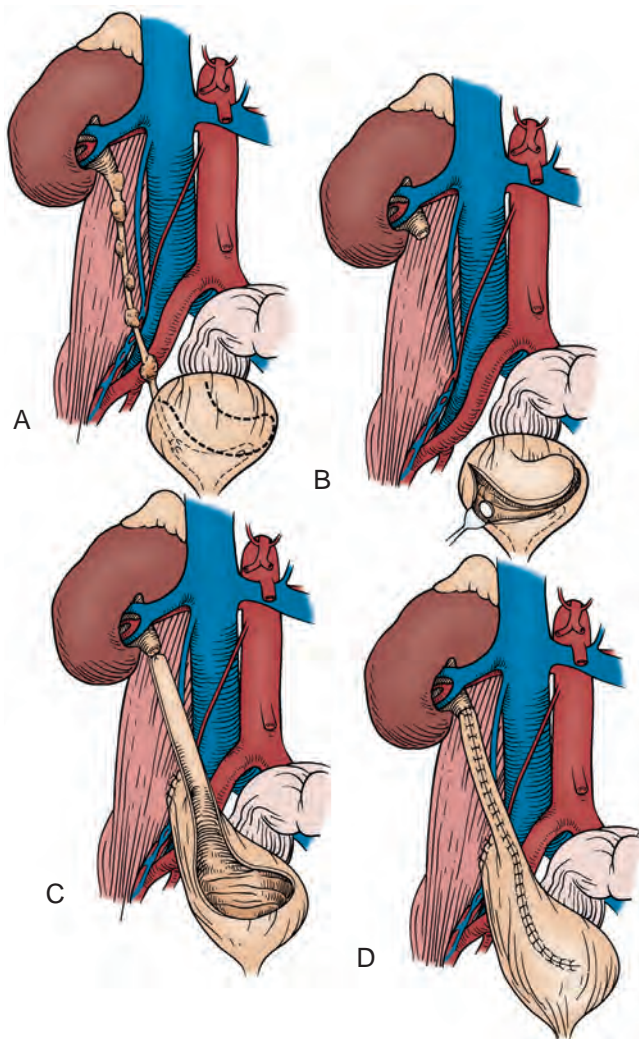


Figure 58-23. A, Subtotal ureterectomy required for nephron sparing in a patient with multiple diffuse ureteral tumors. B, A spiral flap is fashioned from the anterior bladder wall. C, The psoas hitch plus Boari flap reaches the remaining proximal ureter. D, Completed anastomosis and bladder closure.

ileum is harvested at least 15 cm away from the ileocecal valve. Bowel continuity is re-established using a stapled anastomosis. With a running absorbable suture, the ileal segment is anastomosed to the renal pelvis proximally in an end-to-end fashion and an isoperistaltic direction. If the proximal portion of the ureter is healthy, the ileal segment can be anastomosed to it in an end-to-side fashion. A ureteral catheter is placed before completion of the anastomosis. Distally, the segment is anastomosed to the posterior wall of the bladder in an end-to-side manner through an intravesical approach. This anastomosis is done in two layers. A suction drain is positioned in retroperitoneum close to anastomotic sites. Optimal drainage is important for proper healing, so a large Foley catheter is inserted in the bladder and left for at least 1 week post-operatively. It may need to be irrigated frequently. A nephrostomy tube may be used to drain the kidney. Before removal of the tubes, a cystogram and nephrostogram are obtained.

In skilled hands, renal autotransplantation is a feasible alternative to ileal replacement. Another approach that may help avoid ileal reconstruction involves mobilization of the kidney with subsequent nephropexy of Gerota fascia to the cut edge of the peritoneum, placing traction in the caudal direction (Fig. 58-24). It may add up to 8 to 10 cm of length on the left side owing to longer left renal vein. This approach has been used laparoscopically, avoiding the need for a second flank incision (Sutherland et al, 2011).

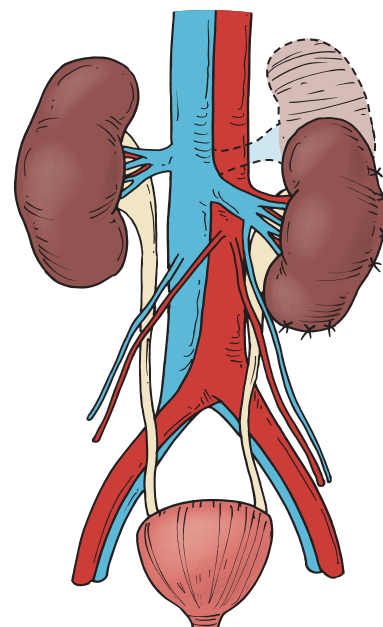


Figure 58-24. Mobilization of the kidney with subsequent nephropexy of Gerota fascia to cut edge of peritoneum, placing traction in the caudal direction, may add up to 10 cm of length on the left side.

Results

In the past, some authors recommended radical nephroureterectomy for all patients with upper tract urothelial tumors (Skinner, 1978). Others suggested segmental ureterectomy only for patients with low-grade, noninvasive tumors of the distal ureter (Babaian and Johnson, 1980). The outcome of patients with UTUC of the ureter strongly correlates with tumor stage and grade regardless of the extent of surgical treatment (Tables 58-4 and 58-5). A single-center study evaluating the prognostic factors in urothelial tumors of the ureter showed an 80% 10-year progression-free survival and 10% ipsilateral tumor recurrence (Lehmann et al, 2007), although the majority of these patients had non-muscle-invasive disease. Overall, 145 patients were evaluated, and 51 underwent segmental ureterectomy. When adjusted for clinicopathologic characteristics, the outcomes were similar for patients who underwent nephroureterectomy versus segmental ureterectomy. The mean follow-up in this study was 96 months. Leitenberger and colleagues (1996) reported their experience with organ-sparing surgery for ureter cancer. Out of 40 patients, 13 underwent extirpative nephron-sparing surgery, and recurrence was observed in 4 patients, all of whom had invasive disease. Anderstrom and colleagues (1989) reported no tumor-related deaths and only 1 recurrence among 21 patients treated with segmental ureterectomy for low-grade, noninvasive ureteral tumors who were observed for a median of 83 months. McCarron and associates (1983) reported 5-year survival of 64% for patients with stage Ta tumors treated by either segmental ureterectomy or endoscopic tumor ablation. In the same series, 5-year tumor-free survival rates were 66% and 50% for stage T1 and T2 tumors, respectively, treated with segmental or distal ureterectomy. In the series by Grabstald and coworkers (1971), disease-specific survival rates were 64% and 100% for stage Ta to T1 and stage T2 disease, respectively. All deaths were from unrelated causes. In contrast, for patients with stage T3 disease, cancer-specific survival was only 7% and the rate of death caused by tumor was 87%. A recent SEER database review of 2044 patients with a mean follow-up of 30 months showed no difference in 5-year cancer-specific mortality in segmental ureterectomy versus nephroureterectomy, adjusted for pathologic stage (Jeldres et al, 2010a).

The risk of ipsilateral recurrence after conservative treatment of ureteral tumors is 33% to 55% (Mazeman, 1976; Johnson and

TABLE 58-4 Five-Year Survival (%) for Patients with Ureteral Tumors by Stage and Grade

	BLOOM ET AL, 1970 (N = 102)	BATATA AND GRABSTALD, 1976 (N = 77)	MCCARRON ET AL, 1983	JELDRES ET AL, 2010a
TUMOR GRADE				
1-2	56-83	50-80	60-87	232
3-4	16	0-20	15	146
TNM STAGE				
Ta, T1, Tcis	62	60-90	64-81	231
T2	50	43	46	192
T3	33	16	22	124
T4	—	—	—	22
N+	0	0	4	—
M+	0	0	—	—

TABLE 58-5 Results of Segmental Resection for Localized Ureteral Tumors

STUDY	NO. OF PATIENTS	LOCAL RECURRENCE (%)	FOLLOW-UP (mo)
Johnson and Babaian, 1979	6	16.6	44
Zungri et al, 1990	35	8.5	86
Maier et al, 1990	17	17.6	41.4
Wallace et al, 1981	7	14.3	93.6
Anderstrom et al, 1989	21	4.7	83
Leitenberger et al, 1996	13	30	42
Lehmann et al, 2007	51	14	96

Babaian, 1979; Babaian and Johnson, 1980; McCarron et al, 1983; Williams, 1991). Most recurrences are distal to the original lesion, but proximal recurrences are also seen (Strong et al, 1976). The risk for recurrence and the need for follow-up are lifelong (Herr, 1998), because late recurrence can be seen (Grossman, 1978). Segmental ureterectomy is offered for low-grade, non-muscle-invasive disease of the proximal ureter or mid-ureter that is not amenable to complete ablation by endoscopic means because of tumor size or multiplicity. Distal ureterectomy and neocystostomy may be offered for low-grade, low-stage, or in select cases, high-grade, locally invasive tumors of the distal ureter when renal preservation is necessary.

Laparoscopic or Robotic Distal Ureterectomy and Reimplantation

Various laparoscopic techniques for distal ureterectomy and reimplantation have been reported (Roupret et al, 2007). The robotic approach may assist with the reconstruction portion of the procedure. The indications are the same as those for the open counterpart, and the techniques are reserved for low-risk distal tumors. The distal ureter is dissected down to the ureteral orifice, and the proximal end is anastomosed to the bladder using standard techniques. The early reports are encouraging, but strict adherence to oncologic principles must be followed.

Endoscopic Treatment

Basic Attributes

Hugh Hampton Young described the first endoscopic evaluation of the upper urinary tract in 1912. Subsequent advances in technology allow us to reach all parts of the urinary tract with minimal morbidity through antegrade and retrograde approaches. Diagnosis and treatment of UTUC have become possible with these improvements because tumor biopsy and ablation by various energy sources are

possible through even the smallest instruments. In addition, miniaturization has made follow-up surveillance of the upper tract more practical with the use of smaller ureteroscopes, which usually do not require previous stenting, or with active dilation of the distal ureter.

Tumors of the upper urinary tract can be approached in a retrograde or antegrade fashion. The approach chosen depends largely on the tumor location and size. In general, a retrograde ureteroscopic approach is used for low-volume ureteral and renal tumors. An antegrade percutaneous approach is preferred for larger tumors of the upper ureter or kidney and for those that cannot be adequately manipulated in a retrograde approach because of location (e.g., lower pole calyx) or previous urinary diversion. In cases with multifocal involvement, combined antegrade and retrograde approaches can be considered (Fig. 58-25).

The basic principles for treatment of UTUC are similar to those for the bladder counterpart (Fig. 58-26). The tumor is sampled and ablated by electrocautery or laser energy sources. A staged procedure should be considered for high-volume disease or disease that is thought to represent high pathologic grade or stage. In such cases, when subsequent nephroureterectomy most likely will be necessary for cure, only biopsy and partial ablation are performed to minimize the risks of perforation or major complications. Endoscopic management is completed only after the pathologic examination shows that the patient is an acceptable candidate for continued minimally invasive endoscopic management. If the pathologic process is unresectable, of high grade, or invasive, the patient should proceed immediately to nephroureterectomy, provided he or she is medically fit. Patients who undergo renal-sparing therapy must be committed to a lifetime of follow-up with radiographs and endoscopy.

Ureteroscopy and Ureteropyeloscopy

The ureteroscopic approach to tumors was first described by Goodman in 1984 and is generally favored for ureteral and smaller renal tumors. With the advent of small-diameter rigid and flexible

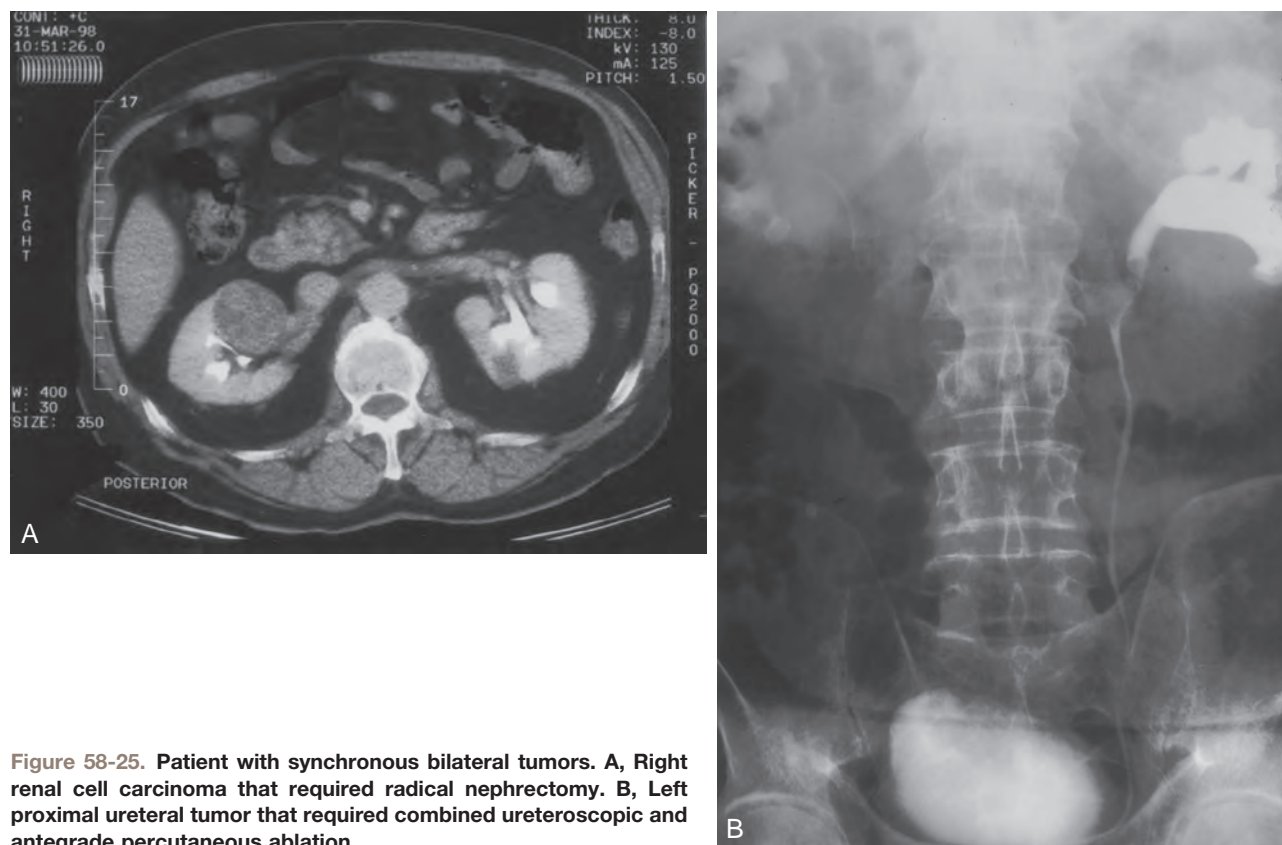


Figure 58-25. Patient with synchronous bilateral tumors. **A**, Right renal cell carcinoma that required radical nephrectomy. **B**, Left proximal ureteral tumor that required combined ureteroscopic and antegrade percutaneous ablation.

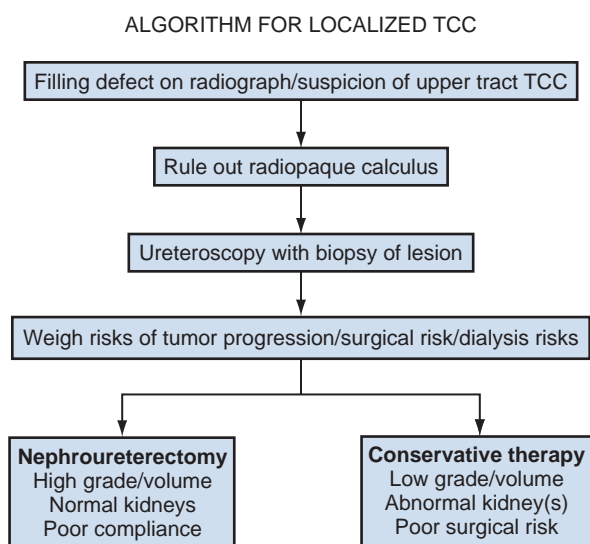


Figure 58-26. Algorithm for endoscopic approach to upper tract transitional cell carcinoma (TCC).

ureteroscopes, tumor location is less of a limiting factor than it used to be. The advantage of a ureteroscopic approach is lower morbidity than that of the percutaneous and open surgical counterparts, with the maintenance of a closed system. With a closed system, nonurothelial surfaces are not exposed to the possibility of tumor seeding.

The major disadvantages of a retrograde approach are related to the smaller instruments required. Smaller endoscopes have a smaller field of view and working channel. This limits the size of tumor that can be approached in a retrograde fashion. In addition, some portions of the upper urinary tract, such as the lower pole

calyces, cannot be reliably reached with working instruments. Smaller instruments limit the ability to remove large tumors and to obtain deep specimens for reliable staging. In addition, retrograde ureteroscopy is difficult in patients with prior urinary diversion.

Technique and Instrumentation. A wide variety of ureteroscopic instruments are available, each with its own distinct advantages and disadvantages. In general, rigid ureteroscopes are used primarily for the distal ureter and mid-ureter. Access to the upper ureter and kidney with rigid endoscopy is unreliable, especially in the male patient. Larger, rigid ureteroscopes provide better visualization because of their larger field of view and better irrigation. Smaller rigid ureteroscopes (8 Fr) usually do not require active dilation of the ureteral orifice (Fig. 58-27A). Newer-generation, flexible ureteropyeloscopes are available in sizes smaller than 8 Fr to allow simple and reliable passage to most portions of the urinary tract (Abdel-Razzak and Bagley, 1993; Grasso and Bagley 1994; Chen and Bagley 2000; Chen et al, 2000). These are generally preferred in the upper ureter and kidney, where the rigid ureteroscope cannot be reliably passed. Flexible ureteroscopes, however, have technical limitations, such as a small working channel, that limit irrigant flow and the diameter of working instruments. Further limitations of flexible ureteroscopy include reduced access to certain areas of the kidney, such as the lower pole, where the infundibulopelvic angle may limit passage of the scope, and prior urinary diversion (Fig. 58-27B).

Endoscopic Evaluation and Collection of Urine Cytology Specimens. Cystoscopy is performed and the bladder inspected for concomitant bladder disease. The ureteral orifice is identified and inspected for lateralizing hematuria. A small-diameter (6.9 or 7.5 Fr) ureteroscope is passed directly into the ureteral orifice, and the distal ureter is inspected before any trauma from a previously placed guidewire or dilation. A guidewire is then placed through the ureteroscope and up the ureter to the level of the renal pelvis under fluoroscopic guidance. The flexible ureteroscope is used to visualize the remaining urothelium. When a lesion or suspicious area is seen, a normal saline washing of the area is performed before

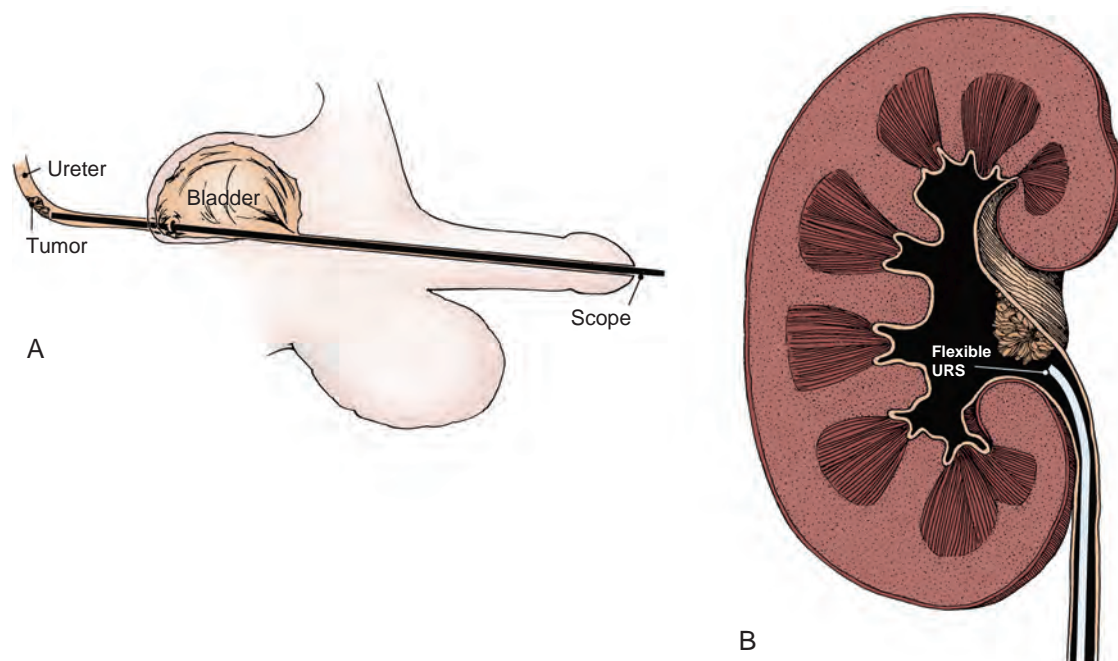


Figure 58-27. A, Rigid ureteroscopic approach. B, Flexible ureteroscopic approach. URS, ureteroscope.

biopsy or intervention (Bian et al, 1995). If the ureter does not accept the smaller ureteroscope, active dilation of the ureter is necessary.

Special circumstances include prior urinary diversion and tumor confined to the intramural ureter. With cases of prior urinary diversion, identification of the ureteroenteric anastomosis is difficult and may require antegrade percutaneous passage of a guidewire down the ureter before endoscopy. The wire can be retrieved from the diversion, and the ureteroscope can be passed in a retrograde fashion. The nephrostomy tract does not need to be fully dilated in this setting. Wagner and associates (2008) described their experience with endoscopic monitoring of patients with ureteral CIS after radical cystectomy. A second type of case is tumor in the intramural ureter. When a tumor protrudes from the ureteral orifice, complete ureteroscopic ablation of the tumor or aggressive transurethral resection of the entire most distal ureter can be done with acceptable results (Palou et al, 2000).

Biopsy and Definitive Treatment. Three general approaches can be used for tumor ablation: bulk excision with ablation of the base, resection of the tumor to its base, and diagnostic biopsy followed by ablation with electrocautery or laser energy sources. Regardless of technique used, special attention to biopsy specimens is necessary. Specimens are frequently minute and should be placed in fixative at once and specially labeled for either histologic or cytologic evaluation (Tawfik et al, 1997).

Ureteroscopic Techniques. The tumor is debulked by use of either biopsy forceps or a flat wire basket engaged adjacent to the tumor (Fig. 58-28A). Next, the tumor base is treated with either electrocautery or laser energy sources. This technique is especially useful for low-grade papillary tumor on a narrow stalk. The specimen is sent for pathology evaluation.

Alternatively, a ureteroscopic resectoscope is used to remove the tumor (Fig. 58-28B). Only the intraluminal tumor is resected, and no attempt is made to resect deep (beyond the lamina propria). Extra care is necessary in the mid-ureter and upper ureter, where the wall is thin and prone to perforation. With larger-volume disease of the distal ureter, Jarrett and associates (1995a) described extensive dilation of the ureter followed by resection with a long standard resectoscope. The tumor is adequately sampled with forceps and sent to the pathology laboratory for diagnostic evaluation. The

tumor bulk is then ablated to its base with laser or electrocautery energy (58-28C and D). Multiple biopsy specimens are often required when small, flexible 3-Fr biopsy forceps are used. Electrocautery delivered through a small Bugbee electrode (2 or 3 Fr) can be used to fulgurate tumors. However, the variable depth of penetration can make its use in the ureter dangerous, and circumferential fulguration should be avoided because of the high risk of stricture formation. More recently, laser energy with either a neodymium:yttrium-aluminum-garnet (Nd:YAG) (Smith et al, 1984; Schilling et al, 1986; Schmeller and Hofstetter, 1989; Carson, 1991) or a holmium:YAG (Ho:YAG) (Bagley and Erhard, 1995; Razvi et al, 1995; Matsuoka et al, 2003; Suoka et al, 2003) source has been popular. Each has characteristic advantages (Fig. 58-29) and can be delivered through small, flexible fibers (200 or 365 μ m) that fit through small, flexible ureteroscopes without significant alteration of irrigant flow or scope deflection. The Ho:YAG laser is well suited for use in the ureter. The tissue penetration is less than 0.5 mm, which allows tumor ablation with excellent hemostasis and minimal risk of full-thickness injury to the ureter. Its shallow penetration may, however, make its use cumbersome with larger tumors, especially in the renal pelvis. Settings most commonly used for the Ho:YAG laser are energy of 0.6 to 1 J with frequency of 10 Hz. The Nd:YAG laser has a tissue penetration of up to 5 to 6 mm, depending on laser settings and duration of treatment. In contrast to the Ho:YAG laser, which ablates tumor, the Nd:YAG laser works by coagulative necrosis with subsequent sloughing of the necrotic tumor. The safety margin is significantly lower and can limit its use in the ureter, where the ureteral wall is thin. Settings most commonly used for the Nd:YAG laser are 15 W for 2 seconds for ablation of tumor and 5 to 10 W for 2 seconds for coagulation.

A ureteral stent is placed for a variable duration to aid with the healing process. Large tumors usually require multiple treatment sessions during several months.

Results. There are no published series of randomized controlled trials comparing endoscopic therapy and nephroureterectomy, and all are case series (level 4 evidence). Multiple series have shown the safety and efficacy of ureteroscopic treatment of UTUC (Daneshmand et al, 2003; Krambeck et al, 2007; Lucas et al, 2008; Thompson et al, 2008; Gadzinski et al, 2010; Cutress et al, 2012). See Table 58-6 for a summary of the largest current series. In a literature

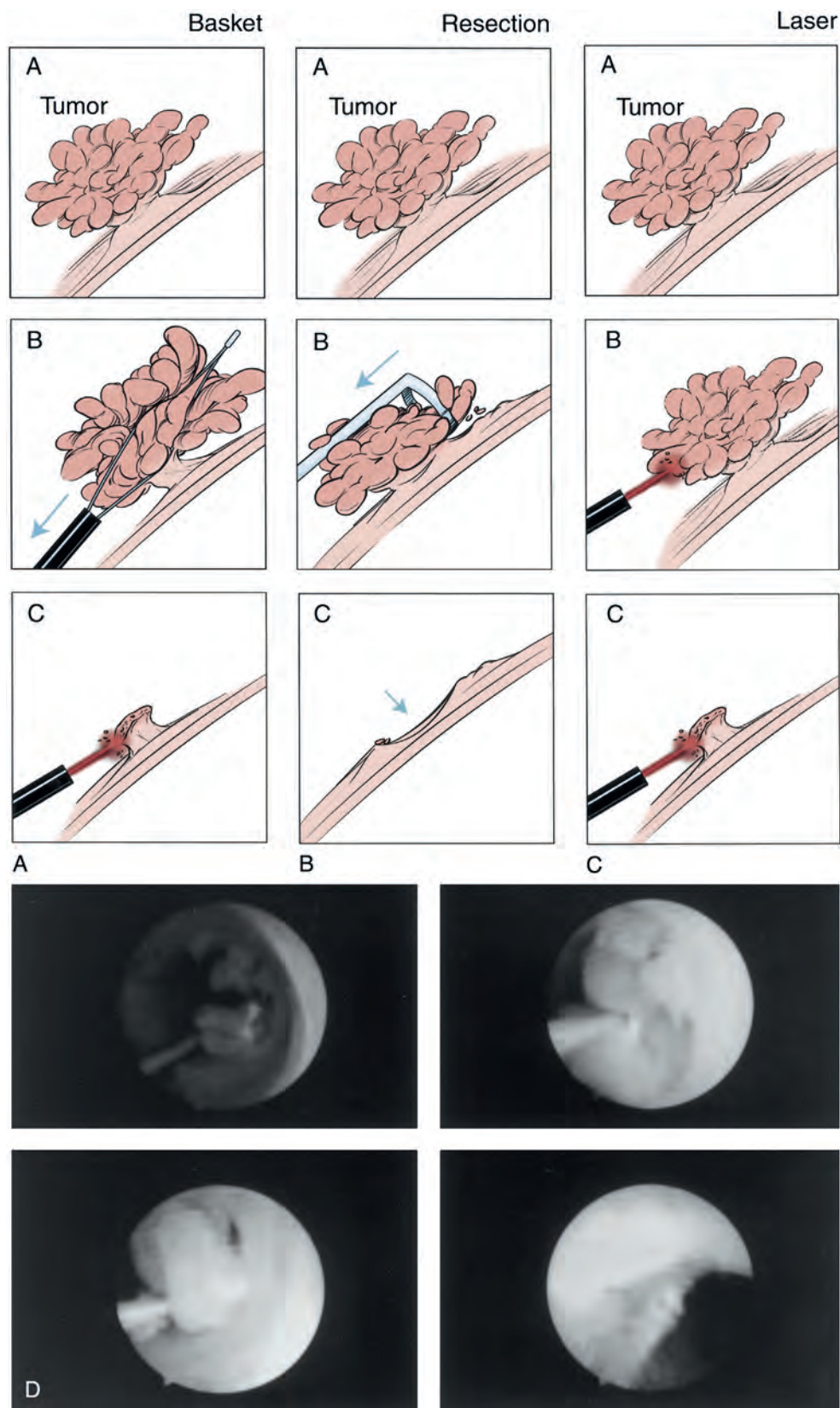


Figure 58-28. Techniques for ureteroscopic treatment of ureteral and renal tumors. **A,** The tumor is identified and removed piecemeal by grasping forceps to its base. **B,** Alternatively, a flat wire basket can be deployed alongside the tumor. The tumor is engaged and removed, with care taken not to avulse the adjacent ureter. With either of these techniques, the base is treated with electrocautery or a laser energy source. **C,** The tumor is identified and removed by a ureteroscopic resectoscope. The technique differs from the technique for bladder tumors in that only intraluminal tumor is resected. No attempt is made to resect deep, as with a bladder tumor. The scope is not arching deep into the tissue. **D,** The tumor is sampled for diagnostic purposes. The bulk of the tumor is then ablated with electrosurgical or laser energy. In general, laser energy is preferred because it has more reliable delivery of energy and depth of penetration. The two most commonly used energy sources are holmium:yttrium-aluminum-garnet and neodymium:yttrium-aluminum-garnet.

Ho:YAG	Minimal penetration (<0.5 mm) Efficient ablation of tumor Precise cutting Setting 0.6-1.2 joules/8-10 Hz
Nd:YAG	Deep penetration (5-6 mm) Excellent hemostasis Tumor ablation by coagulative necrosis Settings: 20-30 watts

Figure 58-29. Characteristics of holmium:yttrium-aluminum-garnet (Ho:YAG) and neodymium:yttrium-aluminum-garnet (Nd:YAG) laser energy sources.

review of 736 patients (Cutress et al, 2012), the overall recurrence rate for the upper tract was 53%, and the risk of bladder recurrence was 34%. Disease progression was present in 15%, with 9% recurrence with metastatic disease. The failure rate of ureteroscopic therapy was 24%, with 19% undergoing subsequent nephroureterectomy. There was, however, considerable bias for favorable tumor characteristics (unifocal, low grade, and small tumor size). As with any urothelial cancer, the most important prognostic indicator for tumor recurrence was grade. Cutress and associates (2012) showed the upper tract recurrence rates for grades 1, 2, and 3 lesions to be 52%, 54%, and 76%, respectively. The upper tract recurrence rate and disease-free survival were both worse with higher-grade tumors.

The literature shows the long-term feasibility of the ureteroscopic approach, but concerns over the high rate of ipsilateral recurrences remain. Daneshmand and colleagues (2003) reported a large number of recurrences with an overall ipsilateral recurrence rate of 90% with three to four recurrences per patient. Cutress and colleagues (2012) reported 5-year recurrence-free survival rates of 13% to 54% in the largest series. This is important in considering patients with a normal contralateral kidney. Patients must be counseled on the need for lifetime follow-up and possible treatment of ipsilateral recurrence.

Complications were uncommon and usually related to the patient's comorbidities. Complications specific to ureteroscopic therapy were 14% (Cutress et al, 2012) and included ureteral perforation, which can be managed with an indwelling ureteral stent, and ureteral stricture, which occurred in 11%. The complication rates seemed to have dropped in more contemporary series, most likely related to smaller endoscopes, improved laser energy sources, and refinements in endoscopic techniques.

Two major concerns of the ureteroscopic approach are the accuracy of ureteroscopic biopsies and the limitations of biopsies, especially with regard to staging. Retrospective reviews of patients who underwent ureteroscopic biopsy followed by nephroureterectomy found the accuracy of ureteroscopic diagnosis to be 89% to 94% and the pathologic grading to match the open surgical technique in 70% to 92% (Keeley et al, 1997a; Guarnizo et al, 2000; Smith et al, 2011). From prior studies, we know that there is a good correlation between grade of lesion and stage (Chasko et al, 1981; Heney et al, 1981). This holds true for the ureteroscopic approach (Keeley et al, 1997c) because 87% of patients with grade 1 or grade 2 tumors had noninvasive disease (stage Ta or T1), whereas 67% of patients with grade 3 tumors had invasive disease (stage T2 or T3). This information supports the notion that tumor grade is the most important prognostic factor; and although stage cannot be directly assessed, noninvasive disease can be expected in most cases of low-grade tumor.

A final concern is whether ureteroscopy promotes progression or spread of disease to other urothelial surfaces or metastatic sites. There have been reports of increased tumor appearance in refluxing ureters of patients with bladder tumors (de Torres Mateos et al, 1987) and in the ipsilateral urinary tract and bladder of patients after ureteroscopic treatment. However, Kulp and Bagley (1994)

reported on 13 patients who underwent multiple ureteroscopic treatments followed by nephroureterectomy; they found no unusual propagation of cancer in the specimens. Concerns that ureteroscopy may promote metastatic spread were raised by Lim and associates (1993), who found tumor cells in renal lymphatics after ureteroscopy. However, Hendin and colleagues (1999) reported no increased risk of metastatic disease in a group of patients who underwent ureteroscopy before nephroureterectomy compared with a group undergoing nephroureterectomy alone.

Percutaneous Approach

The percutaneous approach was first described by Tomera and coworkers in 1982 and is generally favored for larger tumors located proximally in the renal pelvis or proximal ureter. The main advantage of the percutaneous approach is the ability to use larger instruments that can remove a large volume of tumor in any portion of the renal collecting system. Because deeper biopsy specimens are obtained, tumor staging as well as grading is usually possible. In addition, a percutaneous approach may avoid the limitations of flexible ureteroscopy, especially in complicated calyceal systems or areas difficult to access, such as the lower pole calyx or the upper urinary tract of patients with urinary diversion. With a percutaneous approach, the established nephrostomy tract can be maintained for immediate postoperative nephroscopy and administration of topical adjuvant therapy.

The main disadvantages are the increased morbidity compared with ureteroscopy and the potential for tumor seeding outside the urinary tract. Establishment of the nephrostomy tract has inherent risks, and the procedure usually requires inpatient admission. Distinct risks related to a percutaneous approach are loss of urothelial integrity and exposure of nonurothelial surfaces to tumor cells. This open system provides the possibility of tumor implantation in the nephrostomy tract.

Technique and Instrumentation

Establishment of the Nephrostomy Tract. Cystoscopy is performed, and an open-ended ureteral catheter is positioned in the pelvis. Contrast material is injected to define the calyceal anatomy, and a percutaneous nephrostomy tract is established through the desired calyx (Fig. 58-30). If the patient is in the prone split leg position, a flexible ureteroscope can be passed to the desired area and renal access obtained under direct and fluoroscopic guidance. Tumors in peripheral calyces are best approached with direct puncture distal to the tumor (Fig. 58-31), avoiding trauma to or direct puncture into the tumor. Disease in the renal pelvis and upper ureter is best approached through an upper or middle pole access to allow scope maneuvering through the collecting system and down the ureteropelvic junction. The tract is dilated by either sequential (Amplatz) or balloon dilation to accommodate a 30-Fr sheath. Correct positioning of the nephrostomy tract is crucial to the success of the procedure and should be done by the urologist or by the radiologist after direct consultation with the operating surgeon. Some practitioners prefer to perform this in two stages, with establishment of a tract first and allowing this to mature over 1 to 2 weeks, followed by tract dilation and treatment. Alternatively, if only a diagnostic procedure needs to be performed, such as evaluation of positive cytology findings after cystectomy and diversion, one may also use the initial smaller nephrostomy tract to introduce a flexible ureteroscope. Otherwise, a nephroscope is inserted, and the ureteral catheter is grasped, brought out the tract, and exchanged for a stiff guidewire, thus providing both antegrade and retrograde control. Complete nephroscopy is performed with rigid and flexible endoscopes when necessary. Any suspicion of upper ureteral involvement warrants antegrade ureteroscopy.

Biopsy and Definitive Therapy. After identification, the tumors are removed by one of the following four techniques (Fig. 58-32). In the first technique, which uses cold-cup biopsy forceps through a standard nephroscope, the bulk of the tumor is grasped by forceps and removed in piecemeal fashion until the base is reached (see Fig. 58-32A). A separate biopsy of the base is performed for staging purposes, and the base is cauterized with a Bugbee electrode and

TABLE 58-6 Ureteroscopic Management

STUDY	NUMBER OF PATIENTS	FOLLOW-UP (mo)	UPPER TRACT RECURRENCE (%)	BLADDER RECURRENCE (%)	NEPHROURETERECTOMY RATE (%)	DISEASE PROGRESSION (%)	FAILED MANAGEMENT (%)	COMPLICATIONS (%)
Martínez-Piñero et al, 1996	54	31	23	ND	10	ND	28	23
Daneshmand et al, 2003	30	31	90	23	13	20	47	17
Johnson et al, 2005	35	52	68	ND	3	0	3	9
Gadzinski et al, 2010	34	18	31	15	ND	15	ND	9
Pak et al, 2009	57	53	90	ND	19	7	19	ND
Thompson et al, 2008	83	55	55	45	33	14	33	
Cutress et al, 2012	73	54	69	43	19	19	30	16

ND, not disclosed.

Modified from Cutress ML, Stewart GD, Zakikhani P, et al. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. BJU Int 2012;110:614–28.

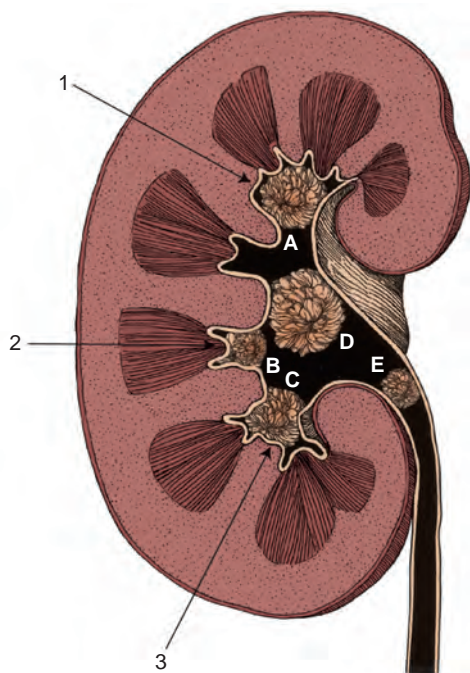


Figure 58-30. Nephrostomy tract puncture site. Position of the nephrostomy is imperative for successful percutaneous resection of transitional cell carcinoma of the renal collecting system and upper ureter and requires careful preoperative evaluation of radiographs for tumor location. Tumors in peripheral calyces (A to C) are best approached by direct puncture as far distally in the calyx as possible. Tumors in the renal pelvis (D) and upper ureter (E) are best approached by puncture to an upper (1) or middle (2) calyx, which allows the scope to be maneuvered in the renal pelvis and down the ureter. Tumors in the lower calyx are approached by lower calyx puncture (3).

cautery. Low-grade papillary lesions on a thin stalk are easily treated in this manner with minimal bleeding.

Alternatively, a cutting loop from a standard resectoscope or bipolar resectoscope is used to remove the tumor to its base (see Fig. 58-32B). A monopolar resection does carry the risk of absorption of large volumes of hypo-osmotic irrigant, and thus bipolar resection may be preferred. Once again, the base should be resected and sent separately for staging purposes. This approach is more effective for larger, broad-based tumors for which simple debulking to a stalk is not possible.

For the third technique, which uses flexible or rigid endoscopes, the tumor is sampled and treated with Ho:YAG or Nd:YAG laser at 25 to 30 W (Fig. 58-32C and D). Tissue may also be obtained with a small snare used for gastrointestinal polyps.

Regardless of approach, a nephrostomy tube is left in place. This access can be used for second-look follow-up nephroscopy to ensure complete tumor removal (Fig. 58-33). Nephroureterectomy is indicated if the pathologic examination shows high-grade or invasive disease.

Second-Look Nephroscopy. Follow-up nephroscopy is performed 4 to 14 days later to allow adequate healing. The tumor resection site is identified, and any residual tumor is removed. If no tumor is identified, the base should be sampled and treated by cautery or the Nd:YAG laser (15 to 20 W and 3-second exposures). The nephrostomy tube can be removed several days later if all tumors have been removed. If the patient is being considered for adjuvant topical therapy, a small, 8-Fr nephrostomy tube is left to provide access for instillations. Some authors advocate third-look nephroscopy before removal of the nephrostomy tube (Jarrett et al, 1995b).

Results. As with the ureteroscopic approach, there are no randomized controlled trials and only limited contemporary case series (Table 58-7) with adequate numbers and follow-up from which to draw reasonable conclusions (Goel et al, 2003; Palou et al, 2004; Roupret et al, 2007; Rastinehad et al, 2009). In a literature review of 288 patients, Cutress and colleagues (2012) found an overall rate of upper tract recurrence of 26% and a bladder recurrence rate of 31%. Failed endoscopic management occurred in 32% with a nephroureterectomy rate of 22%. Disease progression occurred in

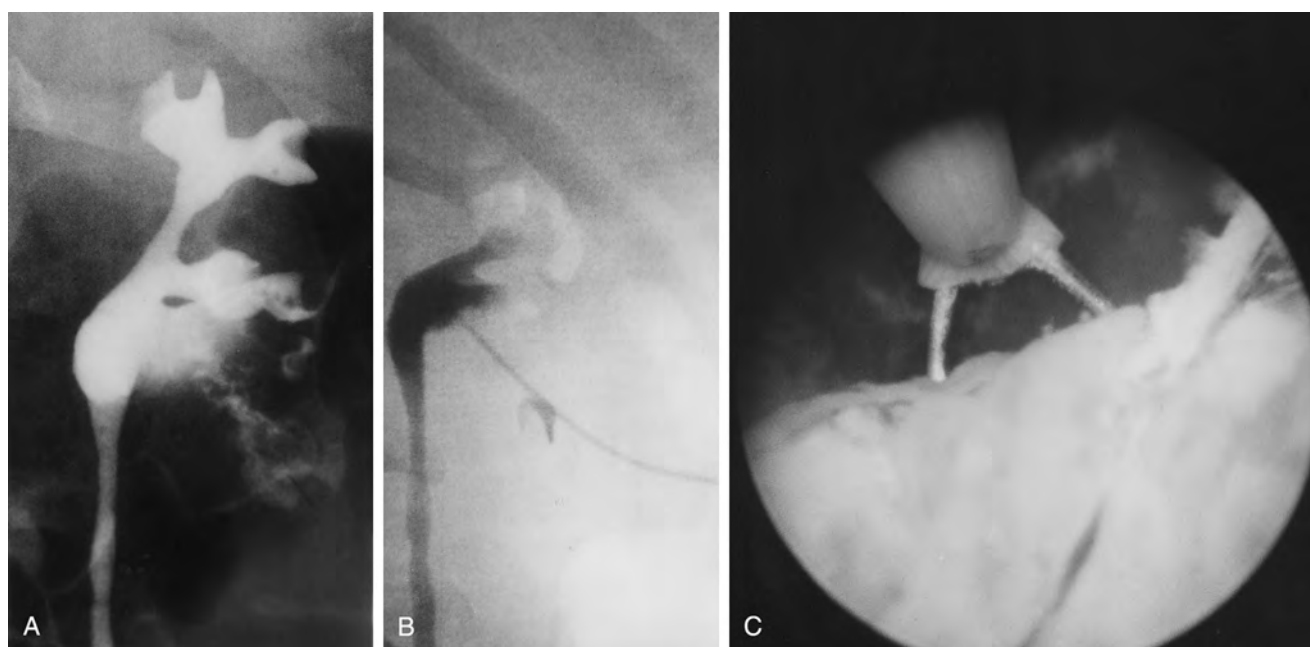


Figure 58-31. A, Retrograde pyelogram of a man with transitional cell carcinoma of the lower calyx in a solitary kidney. B, Access distal in the calyx allows a clear view of the tumor. C, Subsequent resection.

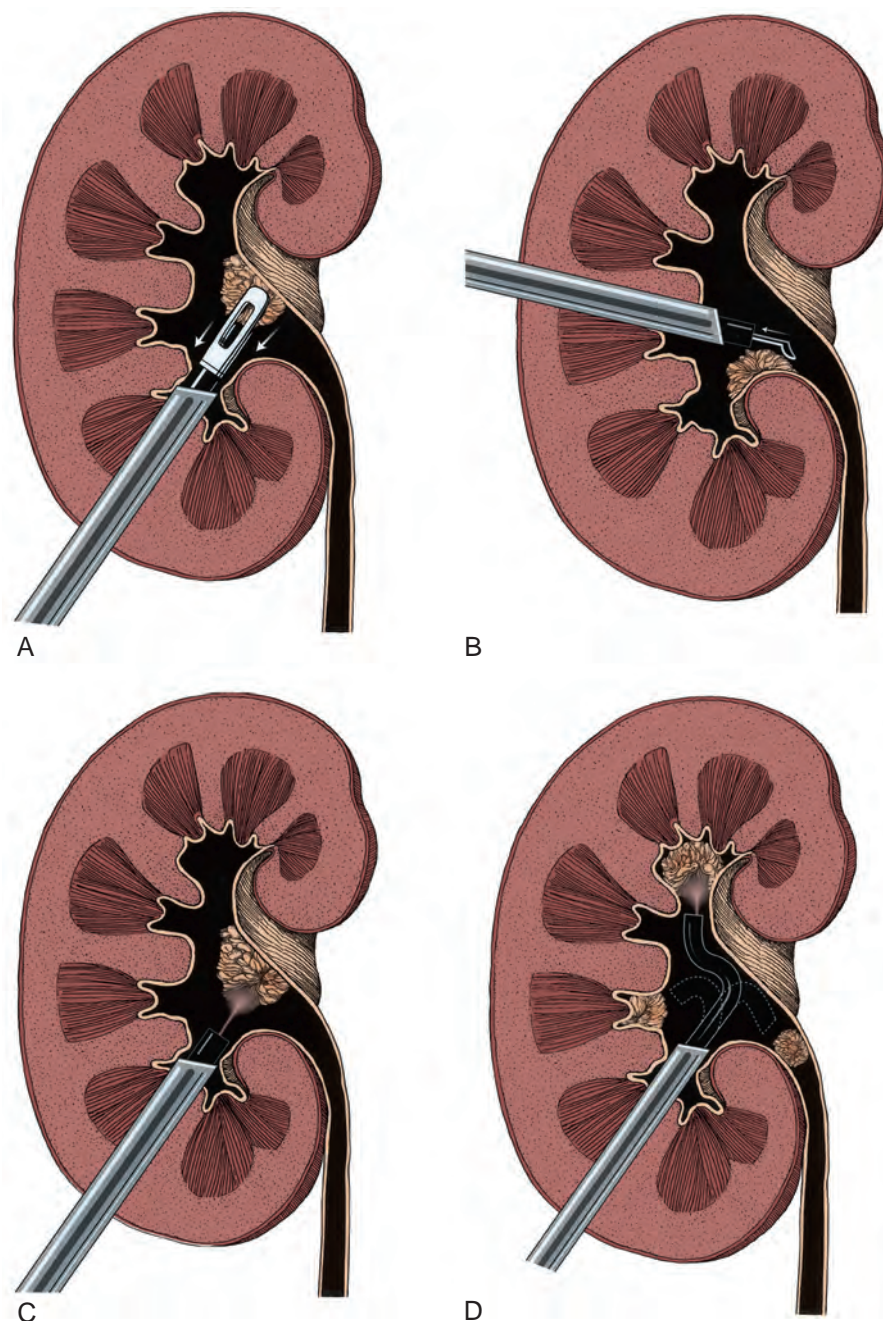


Figure 58-32. Techniques for percutaneous removal of transitional cell carcinoma of the renal collecting system. A, The tumor is identified and debulked by forceps to its base. The base is sampled and sent separately for evaluation. This technique works well for papillary tumors on a narrow stalk. Broad-based tumors may cause excessive bleeding and are best approached with resection or laser therapy. B, With use of a standard resectoscope the tumor is identified and resected to its base. Special care should be taken to avoid resection into major renal vasculature. The tumor is identified, sampled for diagnostic purposes, and treated by holmium or neodymium laser sources. This can be done through a standard nephroscope (C) or with a flexible cystoscope (D).

17%, with 6% going on to develop metastatic disease. As expected, tumor grade strongly predicted outcomes. [Cutress and associates \(2012\)](#) showed the upper tract recurrence rate for grades 1, 2, and 3 lesions to be 23%, 30%, and 40%, respectively. [Lee and colleagues \(1999\)](#) reviewed their 13-year experience with percutaneous management, comparing 50 patients who underwent percutaneous management with 60 patients who underwent nephroureterectomy, and found no significant difference in overall survival. As expected, patients with low-grade disease did well regardless of modality and

patients with high-grade disease did poorly regardless of treatment option.

Most would agree from the literature that percutaneous management is acceptable in patients with low-grade (grade 1) disease regardless of the status of the contralateral kidney, provided the patient is committed to lifelong endoscopic follow-up. Patients with high-grade or grade 3 disease do poorly regardless of modality chosen but should probably undergo nephroureterectomy to maximize cancer therapy (provided they are medically fit). The

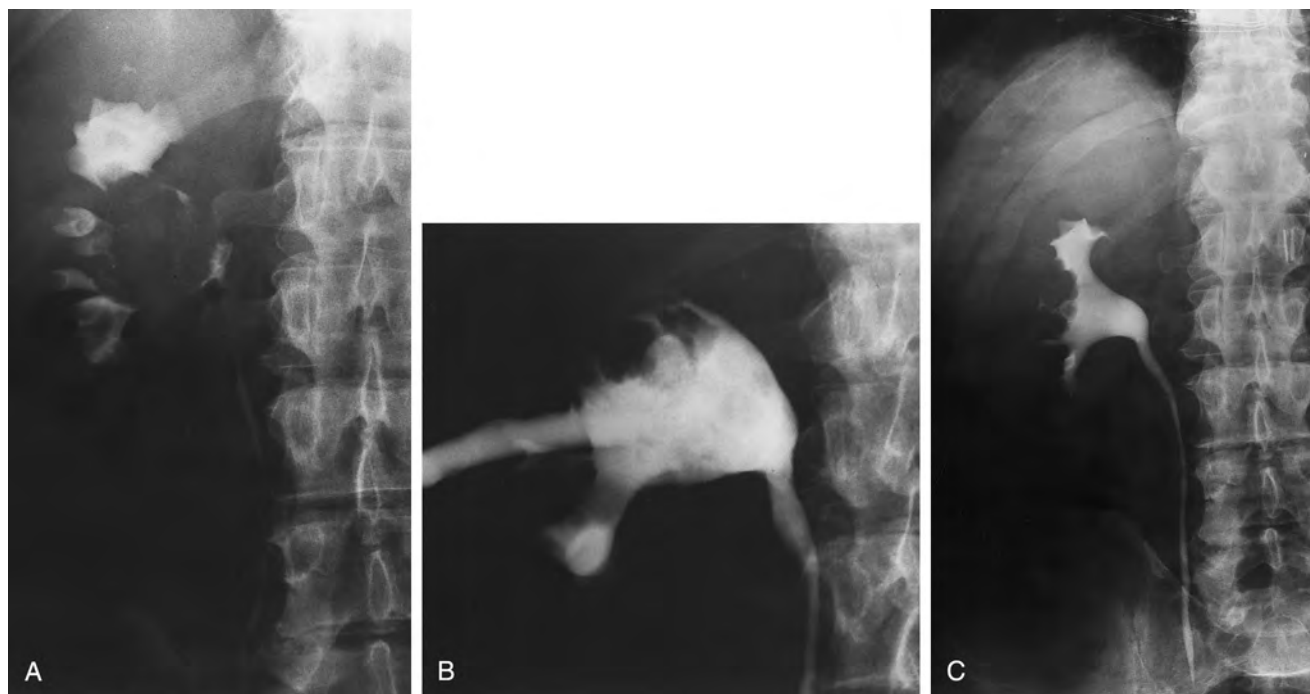


Figure 58-33. A, A 65-year-old man with a solitary kidney and a 5-cm renal pelvis tumor. B, Nephrostogram after patient underwent staged resection. C, Three-month follow-up retrograde pyelogram after completed resection. The patient showed grade 1 transitional cell carcinoma without invasion to submucosa.

largest area of controversy surrounds the use of percutaneous management for patients with grade 2 disease and a normal contralateral kidney. [Jabbour and associates \(2000\)](#) retrospectively evaluated 24 patients and found a disease-specific survival of 95% overall and 100% and 80% for stage Ta and stage T1 lesions, respectively. This study shows an acceptable result with conservative treatment of noninvasive grade 2 disease. With more invasive lesions, the potential for disease progression and metastatic disease is significant and nephroureterectomy should be considered.

Complications from percutaneous management of tumors are similar to those for benign renal processes and include bleeding, systemic absorption of hypo-osmotic irrigation (with monopolar resection), perforation of the collecting system, and secondary ureteropelvic junction obstruction. Cutress showed the overall complication rate to be 27% with transfusion, dialysis and renal failure being the most significant. Complications increase in number and severity with higher tumor grade ([Jarrett et al, 1995a](#)). This finding is probably a result of the more extensive pathologic process and treatments necessary to eradicate the tumor. Unlike ureteroscopic resection, the percutaneous method can stage tumors, and, as expected, stage increases with tumor grade.

A major concern of the percutaneous approach is the potential seeding of nonurothelial surfaces with tumor cells. There have been multiple reported cases of nephrostomy tract infiltration with high-grade tumors ([Tomera et al, 1982](#); [Slywotzky and Maya, 1994](#); [Huang et al, 1995](#); [Oefelein and MacLennan, 2003](#); [Treuthardt et al, 2004](#)). [Cutress and colleagues \(2012\)](#), however, showed only a 0.3% overall rate of tumor seeding. Tract seeding is a possibility but appears to be an uncommon event.

Management of Positive Upper Tract Urinary Cytology or Carcinoma in Situ

Evaluation

An unequivocal positive voiding urinary cytology usually indicates presence of urothelial carcinoma. Most cases are from a bladder source; however, extravesical sites may be involved, including the

upper urinary tracts and the prostatic urethra in men. Often, the diagnosis is difficult owing to the limitations of radiographic evaluation of upper tracts and the complexity of upper tract endoscopy compared with the bladder. In addition, the interpretation of minute pathologic specimens of the upper urinary tract makes precise histologic diagnosis and staging difficult. [Figure 58-34](#) outlines the algorithm for management of a positive urinary cytology as described by [Schwalb and associates \(1994\)](#). One must first repeat the cytology to confirm the findings. The next step involves radiographic evaluation of the upper tracts, usually with CT urography and a complete bladder evaluation including biopsies and tumor resection if tumor is present. If the bladder evaluation was positive for urothelial carcinoma, the initial treatment at that point is to treat the bladder with either intravesical therapy and/or tumor resection and follow the voided urinary cytologies. If these remain positive despite a negative bladder evaluation or after successful treatment of the bladder, then one should proceed to evaluating extravesical sites. If the initial bladder evaluation was negative, then one may proceed directly to evaluation of extravesical sites. Evaluation of extravesical sites should include selective cytologies from each upper urinary tract, ensuring noncontamination of the specimen from the bladder or urethra, as well as resection of a representative specimen of the prostatic urethra in men. Selective cytologies should preferably be done, along with ureteroscopy, to allow for direct visualization of the upper urinary tracts.

Carcinoma in Situ of the Upper Urinary Tracts

The diagnosis of CIS of the upper urinary tracts is a difficult one because of the inability to evaluate the urothelium of the upper tracts with adequate tissue samples. In most cases the diagnosis is one of exclusion wherein there is a persistent positive selective cytology in the absence of any ureteroscopic or radiographic findings. Treatment is not well established: Radical nephroureterectomy was performed in the past for a unilateral cytologic abnormality of the upper tract to eliminate presumed CIS. This practice is not recommended ([Gittes, 1980](#); [McCarron et al, 1983](#); [Williams, 1991](#); [Messing and Catalona, 1998](#)). Upper tract cytology suffers

TABLE 58-7 Percutaneous Management

STUDY	NUMBER OF PATIENTS (%)	FOLLOW-UP (mo)	UPPER TRACT RECURRENCE (%)	BLADDER RECURRENCE	NEPHROURETERECTOMY RATE (%)	DISEASE PROGRESSION (%)	FAILED MANAGEMENT (%)	COMPLICATIONS (%)
Jarrett et al, 1995b	36	55	33	ND	42	16	33	25
Patel et al, 1996	26	45	35	42	19	8	23	27
Goel et al, 2003	20	64	65	15	50	35	50	20
Palou et al, 2004	34	51	44	ND	26	ND	—	6
Roupret et al, 2007	24	62	13	17	21	17	—	10
Rastinehad et al, 2009	89	61	33	ND	13	20	—	ND

ND, not disclosed.

Modified from Cutress ML, Stewart GD, Zakikhani P, et al. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. BJU Int 2012;110:614–28.

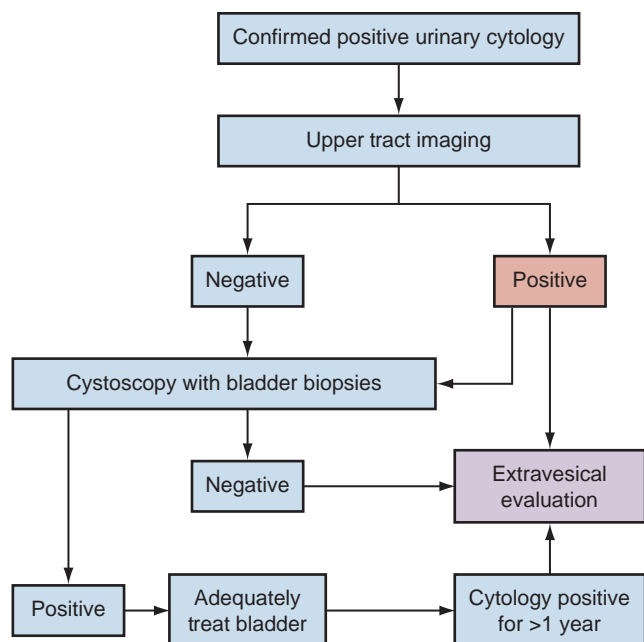


Figure 58-34. Algorithm for management of a positive urinary cytology.

from the same limitations in specificity as does bladder cytology. Furthermore, properly collected upper tract samples are of limited volume and cell count compared with bladder washings. Any source of inflammation, such as urinary infection or calculus, may produce a false-positive result. A subsequent cytologic abnormality from the contralateral side during follow-up is not rare in cases of true-positive results from early CIS (Murphy et al, 1974; Khan et al, 1979). There is one large series and many small series of topical therapy of the upper tract with immune therapy and chemotherapy via retrograde and antegrade approaches with variable response rates. Patients with CIS appear to do equally as well as their bladder counterparts in these limited, retrospective studies (Giannarini et al, 2011) (see section on topical therapy). Placement of a nephrostomy tube seems to be the more reliable delivery system. Most would not intervene initially with surgical intervention in the absence of any histologic, radiographic, or endoscopic finding owing to the limitations of cytology alone with false-positive results and the high risk for bilateral disease in the future. In addition, segmental resection is usually not effective in addressing the problem because of the multifocality of the disease. Nephroureterectomy is, however, indicated if one can confirm radiographically or endoscopically that the patient has more than just surface disease. Frequent-interval re-evaluation with urinalysis, bladder and possible selective cytology, cystoscopy every 3 months, and retrograde pyelography or ureteropyeloscopy every 6 months is indicated for 1 to 2 years.

Another scenario is CIS of ureteral margins during radical cystectomy. There is controversy over the proper management of this finding, which definitely confers a risk of disease progression. However, many do not progress, and when they do, recurrences may not be isolated to the distal ureteral margin. Wagner and colleagues (2008) studied a select group with serial endoscopy and found that recurrences were found at the site of the margin but also at other sites. Herr and colleagues (1996) showed that many did not show any tumor at the margin site but did show a high risk of overall disease progression to death from metastatic disease.

Adjuvant Therapy

After Organ-Sparing Therapy

Any procedure short of extirpative surgery has a higher local recurrence owing to the established risk of ipsilateral recurrence. Several

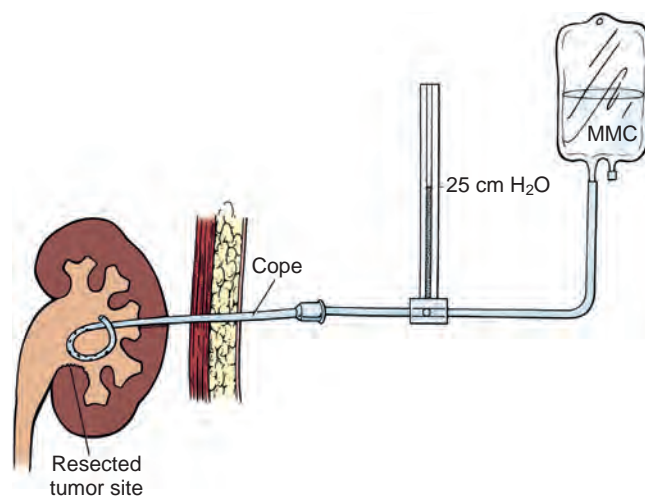


Figure 58-35. Setup for administration of topical immunotherapy or chemotherapy to the upper urinary tract through a previously placed nephrostomy tube. Therapy is instilled by gravity with a mechanism that prevents excessive intrarenal pressures. High pressures have been linked to complications of systemic absorption and bacterial sepsis. MMC, mitomycin C.

approaches are available to minimize these risks. They fall into two basic categories: instillation of immunotherapeutic or chemotherapeutic agents, and brachytherapy of the nephrostomy tract.

Instillation Therapy. Instillation therapy is used in two settings for treatment of UTUC, namely as primary treatment for CIS and as adjuvant therapy after endoscopic or organ-sparing therapy. Delivery of the agents presents an additional challenge and can be accomplished in several ways. Accepted techniques include antegrade instillation through a nephrostomy tube (Fig. 58-35) and retrograde instillation directly into a ureteral catheter. Attempting to induce reflux in a patient using an indwelling ureteral stent or by iatrogenically created vesicoureteral reflux appears to be an unreliable method of effective drug administration to the upper tracts. Patel and Fuchs (1998) described a convenient technique of outpatient instillation through a ureteral catheter placed suprapubically, but given the concern over tumor implantation, this technique is rarely used. Regardless of the technique chosen, administration to the upper urinary tract should be done under low pressure and in the absence of active infection to minimize the risk of bacterial sepsis or systemic absorption of the agent.

Results. The same agents used to treat urothelial carcinoma of the bladder are used to treat tumors of the upper urinary tract. Most historical studies have described small, retrospective, uncontrolled series of patients undergoing therapy with thiotepa (Elliott et al, 1996; Patel et al, 1996), mitomycin (Cornu et al, 2010; Cutress et al, 2012), and BCG (Palou et al, 2004). See Table 58-8 for a summary.

Gemcitabine has been used intravesically as an alternative to BCG with fewer side effects. We may see a larger role in the upper urinary tract. Although the cumulative experience appears encouraging, definitive conclusions are not easily reached. Possible reasons for this include (1) insufficient numbers to show clinical significance because of the relative rarity of the disease; (2) tumors of the upper urinary tract, which have a tumor biology different from that of their bladder counterparts; and (3) a nonstandardized and possibly inadequate delivery system that, unlike in the bladder, does not allow uniform delivery of the agent with adequate dwell time to enable a clinical response.

The largest experience is from use of BCG via a nephrostomy tube for primary treatment of CIS, and in this setting favorable responses are seen. In a recent update of this experience with 55 patients, a 57% 5-year recurrence-free survival was seen; on the

TABLE 58-8 Adjuvant Upper tract Instillation

AGENT	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	COMPLICATIONS (%)	BENEFIT SHOWN
THIOTEPA				
Elliot et al, 1996	4	60	ND	Benefit not evaluated
Patel et al, 1996	1	1	1 death from sepsis	No benefit
MMC				
Keeley et al, 1997a	19	30	10	Safety, no definite benefit
Martínez-Piñero et al, 1996	41	31	3 (death from systemic absorption)	14% recurrence compared with 25% without MMC
Cornu et al, 2010	35	24	9	Benefit not evaluated
Cutress et al, 2012	73	63	18	No benefit
BCG				
Clark et al, 1999	17	21	ND	No benefit
Palou et al, 2004	34	51	6	No benefit
Giannarini et al, 2011	22	42	20	No benefit
			1 death from sepsis	
Rastinehad et al, 2009	89	61	2 deaths from sepsis	No benefit

BCG, bacille Calmette-Guérin; MMC, mitomycin C; ND, not disclosed.

Modified from Cutress ML, Stewart GD, Zakikhani P, et al. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. *BJU Int* 2012;110:614–28.

other hand, patients treated in adjuvant fashion after endoscopic ablation had inferior results (Giannarini et al, 2011). The greatest experience with chemotherapy is with the use of mitomycin C, but because of the smaller numbers of patients and variable selection criteria, no definite conclusions can be reached, with the exception that mitomycin is very well tolerated and has a very low adverse event profile (Audenet et al, 2013).

In the study with intrarenal perfusion of BCG, despite initial return of cytology results to normal, 50% of patients (5 of 10) developed disease recurrence after a mean follow-up of 50.9 months, and all of these had cancer-specific mortality (Hayashida et al, 2004). The initial results regarding response are encouraging; however, the recurrences with possible disease progression should not give the clinician optimism for long-term cure. Although removal of a renal unit for CIS alone is not urged, patients need to be followed vigilantly for disease progression.

The most common complication of instillation therapy is bacterial sepsis. To minimize this problem, patients must be evaluated for active infection before each treatment, and only a low-pressure delivery system should be used. Agent-specific complications of the various therapies include ramifications of systemic absorption of the agent. Bellman and colleagues (1994) described upper urinary tract complications of percutaneous BCG instillation. Granulomatous involvement of the kidney in the absence of systemic signs of BCG infection was most commonly seen. Mukamel and associates (1991) saw an inordinate decrease in renal function for patients receiving BCG who had vesicoureteral reflux.

Brachytherapy. Brachytherapy to the nephrostomy tract through iridium wire or delivery system was described by Patel and coworkers (1996) and Nurse and colleagues (1989). There were no instances of tract recurrences in this series, although the authors acknowledged the rarity of the event. The only major complication attributed to the brachytherapy was cutaneous fistula formation requiring nephroureterectomy.

After Complete Excision

Radiation Therapy. The rationale for focal radiation therapy is to decrease the risk of local relapse after radical surgery for locally

advanced non-organ-confined disease (stage T3 to T4, N+). Most series concluding that postoperative irradiation is beneficial are small or even anecdotal, uncontrolled, and retrospective (Holtz, 1962; Brady et al, 1968; Leiber and Lupu, 1978). In one series with 41 patients, postoperative radiation therapy decreased local recurrence but had no effect on distant relapse or survival (Brookland and Richter, 1985). Maulard-Durdux and associates (1996) retrospectively reviewed 26 patients who received 46 Gy to the wound bed after radical surgery for upper tract tumors. Tumors were grade 2 in 40% and grade 3 in 60% of patients. Tumor stage was T2, T3, and N+ in 42%, 58%, and 35% of cases, respectively. Five-year survival is shown in Table 58-3. Overall 5-year survival was 49%, with 30% remaining disease free. All patients with local relapse also had distant relapse, leading the authors to conclude that adjuvant radiation therapy is not beneficial.

The largest experience addressing this issue is that reported by Hall and associates (1998b). A retrospective review of 252 patients with upper tract tumors who were observed for a median of 64 months was performed. Radical nephroureterectomy was performed in 77% of patients. Initial tumor stage was T3 in 19% and T4 in 10% of patients; 50% and 52%, respectively, of patients with stage T3 and stage T4 tumors received 40 Gy to the wound bed postoperatively. Disease-specific and overall 5-year survival rates were 41% and 28%, respectively, for patients with stage T3 disease. Actuarial 5-year disease-specific survival rates for stage T3 with or without adjuvant radiation therapy were 45% and 40%, respectively. Median survival was 6 months for stage T4 disease. There were no long-term survivors in this group. Local relapse occurred in only 9% of the entire series and was seen only in patients with stage T3 and stage T4 disease. Among the patients who received adjuvant radiation, isolated local relapse without distant metastases occurred in only 10% and 4% of stage T3 and stage T4 cases, respectively.

Czito and colleagues (2004) retrospectively analyzed the cohort of 31 patients with advanced disease (T3 or T4 and/or N+) disease who received adjuvant radiation with or without chemotherapy. Most of these patients had undergone nephroureterectomy, and 5 patients had residual gross disease after surgery. After administration of two to four cycles of MVC (methotrexate-vinblastine-cisplatin), 9 patients received radiation with concurrent cisplatin

administration. The other 22 patients were treated with radiotherapy only. The mean dose of radiation was 46.9 Gy, and the group that received chemotherapy had a larger proportion of patients with adverse pathologic features, such as higher stage and grade. On univariate analysis, there was an observed improved 5-year overall and disease-specific survival with the use of chemotherapy. Thus **radical nephroureterectomy alone provides a high rate of local control. Adjuvant radiation without chemotherapy for high-stage disease does not protect against a high rate of distant failure. There may be a role for combined radiation-chemotherapy regimens in patients with advanced disease with adverse features; however, the current evidence supporting this is small and retrospective in nature.**

Systemic Chemotherapy. The use of agents for UTUC has been extrapolated from chemotherapy regimens used in bladder urothelial cancer. There are no randomized trials evaluating the effects of neoadjuvant or adjuvant chemotherapy on patients with UTUC, and the small number of cases treated with adjuvant chemotherapy precludes definitive conclusions of efficacy.

The strongest current argument is for use of neoadjuvant therapy, because many patients have baseline chronic kidney disease, which worsens after nephroureterectomy, rendering them ineligible to receive the full-dose cisplatin-based chemotherapy (Lane et al, 2010). There are two reports on the use of neoadjuvant therapy. The initial data came from a small series of 15 patients who received MVAC (methotrexate, vinblastine, Adriamycin, and cisplatin), MEC (methotrexate, etoposide, and cisplatin), or MVEC (methotrexate, vinblastine, epirubicin, and cisplatin) regimens before nephroureterectomy (Igawa et al, 1995). All of the patients had advanced disease, with 6 having T2N0M0, 4 with T3N0-1M0 and 5 with T4N0-3M0. Of these patients, 13% achieved complete, and 40% partial, pathologic response. The authors reported a positive correlation between pathologic response and disease-specific survival. Another retrospective case-control study (Matin et al, 2010) of 150 high-risk UTUC patients, 43 of whom received neoadjuvant therapy with a variety of regimens (MVAC, cisplatin-gemcitabine-ifosfamide [CGI], gemcitabine-paclitaxel-doxorubicin [GTA], cisplatin-gemcitabine [GC], and others), observed a significant incidence of pathologic downstaging of tumors and a 14% complete response rate. A recent update of these patients showed significant improvement in 5-year survival in those receiving neoadjuvant chemotherapy versus a matched historical cohort (94% vs. 58%, $P < .001$) (Porten et al, 2013).

Adjuvant therapy is used infrequently in the treatment of UTUC, and most publications are based on retrospective review of institutional experience. A study of 27 patients with pT3N0M0, 16 of whom received platinum-based therapy after nephroureterectomy, reported no significant difference in recurrence-free and disease-specific survival after 40 months of follow-up (Lee et al, 2006). Another study compared the outcomes of 24 patients with pT2-3N0M0 disease who received MVAC chemotherapy after nephroureterectomy with those of a similar group of patients who did not receive adjuvant therapy. The authors did not observe a significant difference in 10-year overall survival rates. A multi-institutional retrospective review of pT3-4N0M0 and N+ patients (Hellenthal et al, 2009) who did or did not receive platinum-based chemotherapy failed to show a significant difference in the overall or disease-specific survival rates. However, in this cohort, adjuvant therapy was more commonly used in patients with higher tumor grade and stage. In contrast, Kwak and colleagues (2006) showed a twofold decrease in recurrence of cancer and a significant reduction in disease-specific mortality (28.1% vs. 81.8%) in the pT2-3N0M0 patient population who received platinum-based chemotherapy. **In summary, to date there is a lack of controlled trials that establish the efficacy of either neoadjuvant or adjuvant chemotherapy in this UTUC. However, given the significant influence of renal function on eligibility to receive effective chemotherapy, the focus is shifting toward a neoadjuvant approach, with several trials underway at the time of this writing. Further studies are needed to aid in providing recommendations in this setting.**

Treatment of Metastatic Disease

There are limited data on efficacy of chemotherapy in metastatic UTUC. Prospective randomized trials comparing chemotherapeutic regimens for UTUC are not feasible owing to the rarity of these patients. Therefore the data for chemotherapy response rates for upper tract disease are extrapolated from observations in urothelial cancer, most of which do not stratify results by original location of tumor. In a study of 184 patients accrued over three consecutive time intervals from 1986 to 2004 at MD Anderson Cancer Center, the median recurrence-free survival was 2.4 years and did not improve over time (Brown et al, 2006). The decline in renal function after nephroureterectomy in these mostly elderly patients may compromise the ability to administer effective postoperative chemotherapy and is yet another reason to consider neoadjuvant chemotherapy for patients with high-risk upper tract tumors. When there is evidence of regional lymph node metastases, initial chemotherapy should be given as the primary therapy, and surgery should be withheld until a good—ideally a complete—radiographic response is seen. At that time, consolidative surgery can be offered, similar to the paradigm for bladder urothelial carcinoma.

The MVAC regimen continues to have the highest response rate (Sternberg et al, 1989); however, its toxicity prohibits optimal dosage and duration in a large proportion of patients. In addition, complete responses are rare in the metastatic setting, and the duration of response is limited, with overall survival of 12 to 24 months. For all these reasons there is considerable ongoing investigation with newer agents, including paclitaxel, ifosfamide, carboplatin, gemcitabine, and vinflunine, used in various combinations and sequences (Roth et al, 1994; Bajorin et al, 1998; Redman et al, 1998; Vaughn et al, 1998; Kaufman et al, 2000; Lorusso et al, 2000; Bamias et al, 2006; Vaughn et al, 2009; Siefker-Radtke et al, 2013). Carboplatin is frequently substituted for cisplatin because of either limitations of renal function or concerns over toxicity with the latter, but the results with carboplatin remain inferior (Galsky et al, 2012). Many of these show initial overall response rates similar to the response rate to the MVAC regimen and lower toxicity. However, thus far, complete responses are rare, and there are no head-to-head comparison studies evaluating their durability or survival advantage compared with the MVAC regimen. A variation of standard MVAC is the dose-dense regimen, whereby all drugs are given at the same time with cell support, and this regimen has actually been shown to have a lower toxicity profile and may have better responses (Sternberg et al, 2006).

Results from a recent randomized phase III study comparing paclitaxel, cisplatin, and gemcitabine (PCG) versus gemcitabine and cisplatin (GC) in chemotherapy-naïve patients with metastatic or locally advanced urothelial cancer (Bellmunt et al, 2012) showed that after a median follow-up of 4.6 years, with addition of paclitaxel, there was improvement in median overall survival (15.8 months vs. 12.7 months). The overall response rate was 55.5% with the use of PCG and 43.6 with GC, and both of the regimens were well tolerated. Of the 626 patients in this cohort, 82 had primary carcinoma of the renal pelvis or ureter; although there was no specific breakdown of the outcomes for this group of patients, on post hoc analysis the overall survival benefit was more pronounced in the group of patients with primary bladder tumors.

There have been encouraging early results with cabozantinib, the inhibitor of MET and VEGF pathways, in patients in whom previous chemotherapy has failed (Fig. 58-36). The patient accrual portion of a phase II trial is ongoing; it is hoped that this trial will provide further insight into the effects of this drug, which has shown clinical activity in multiple solid tumors. Recently, immune modulation using a variety of checkpoint inhibitors has shown promise in the treatment of multiple malignancies, including urothelial carcinoma. Targeting the inhibitory surface receptor PD-1, activation of which by PD-L1 ligand confers inhibition of T-cell proliferation and cytokine production, has produced remarkable clinical activity in phase I trials in metastatic urothelial carcinoma (Plimack et al, 2014; Powles et al, 2014) with favorable side effect profile, and most importantly, infrequent renal impairment. Currently there are

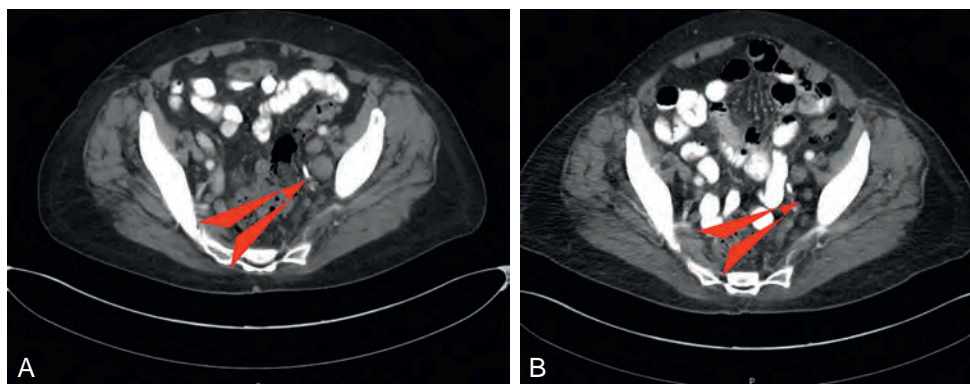


Figure 58-36. A, A patient with urothelial cell carcinoma of the kidney and left inguinal lymphadenopathy. B, The patient had a sustained almost complete response at 9 weeks and 16 weeks after treatment with cabozantinib. Red arrowhead points to resolving adenopathy.

- Physical examination, urine cytology (only for high-grade lesions), and cystoscopy
 - Every 3 months—first year
 - Every 6 months thereafter—years 2 through 3
 - Yearly—thereafter
- Contralateral imaging (IVU or retrograde pyelography)—yearly
- Ipsilateral endoscopy (patients undergoing organ-sparing therapy)—
 - Every 6 months—first several years
 - Yearly—thereafter
- Metastatic evaluation—necessary in all patients with significant risk of disease progression (i.e., high grade or invasive disease)
 - Physical examination, chest x-ray, comprehensive metabolic panel with liver enzymes
 - Every 3 months—first year
 - Every 6 months—years 2 through 3
 - Yearly—years 4 and 5
 - After 5 years—evaluation of urothelium only
 - Computed tomography or MRI of abdomen and pelvis—
 - Every 6 months—years 1 and 2
 - Yearly—years 3 through 5
 - Bone scan—only for elevated alkaline phosphatase level or symptoms of bone pain

Figure 58-37. Follow-up begins after open surgery or when the patient is rendered tumor free by endoscopic management. The commencement of follow-up may be altered according to the potential for disease progression. IVU, intravenous urography.

ongoing phase II and III trials investigating efficacy of these agents against commonly used chemotherapeutics as a second-line therapy, with the results expected to be reported by 2017 (Wu et al, 2015). Even though to date no single study has specifically addressed the effect of checkpoint inhibition in the upper tract urothelial tumors, we are hopeful that this information is forthcoming.

In summary, UTUC, like bladder cancer, is chemosensitive, but established chemotherapy regimens are toxic and lack sustained response. Unique to this population is the high rate of baseline chronic kidney disease, which worsens after nephroureterectomy. It is hoped that continuous advancement in development of novel targeted therapies and experimentation with new chemotherapeutic regimens will help optimize the treatment of metastatic UTUC.

FOLLOW-UP

Issues in Assessing for Recurrence

The propensity of upper tract tumors for multifocal recurrence and metastatic spread with more dysplastic lesions makes follow-up complicated. Postoperative evaluation must routinely include eval-

uation of the bladder, the ipsilateral (if organ-sparing therapy was chosen) and contralateral urinary tracts, and the extraurinary sites for local and metastatic spread. A follow-up regimen is thus dependent on the time from surgery, the approach chosen (organ sparing vs. radical), and the potential for metastatic spread. General recommendations for time intervals are listed in Figure 58-37.

General Procedures

All patients should be assessed at 3-month intervals the first year after they are rendered tumor free by endoscopic or open surgical approaches (Keeley et al, 1997a). After the first year, this evaluation can be spaced out. This schedule is largely based on work with bladder urothelial carcinoma, showing that most tumor recurrences after bladder resection develop in the first year (Varkarakis et al, 1974; Loening et al, 1980). The upper urinary tract is more difficult to monitor, and delayed recognition of upper tract tumor recurrence may lead to disease progression and poor results (Mazeman, 1976). Evaluation should include history, physical examination, urinalysis, and office cystoscopy because of the high risk of bladder recurrences in patients treated both conservatively and with nephroureterectomy (Mazeman, 1976). If the patient requires endoscopic evaluation of the upper urinary tract, cystoscopy can be done in conjunction with that procedure.

Urine cytology may be helpful in assessing for upper tract recurrence, especially for high-grade tumors (Murphy et al, 1981). The usefulness, however, is decreased with less dysplastic tumors (Grace et al, 1967; Sarnacki et al, 1971; Zincke et al, 1976). The same tumor markers under study for bladder urothelial carcinoma are promising for UTUC (Brown, 2000). One marker that may be preferentially more involved in UTUC than in bladder cancer is the DNA mismatch repair gene *MSH2* (Leach et al, 2000).

Specific Procedures

Bilateral disease, either synchronous or metachronous, is seen in 1% to 4% of patients (Petkovic, 1975; Babaian and Johnson, 1980; Murphy et al, 1981), and thus imaging of the contralateral kidney is required on a regular basis. Yearly CT urography is usually sufficient and also can serve for metastatic surveillance, having replaced intravenous urography. However, retrograde pyelography may be necessary if the patient is not a candidate for injection of iodinated contrast medium or if the urographic phase is not diagnostic. Magnetic resonance urography is another option for those unable to receive iodinated contrast, but patients with a creatinine clearance below 30 mg/dL may not receive gadolinium contrast because of concerns with development of nephrogenic systemic fibrosis. CT or ultrasonography is helpful in distinguishing stones from soft tissue densities. Further evaluation of filling defects on imaging studies usually requires ureteroscopic evaluation.

If an organ-sparing approach is chosen, the ipsilateral urinary tract must be assessed as well as the remainder of the urinary tract. The frequency and duration of the follow-up assessments depend largely on the grade and stage of the lesion, but they are usually every 6 months for several years and annually thereafter. Radiographic evaluation of the upper tracts alone is not adequate because [Keeley and colleagues \(1997a\)](#) showed that 75% of early tumor recurrences were visible endoscopically and not radiographically. With tumors approached in a percutaneous fashion, early follow-up nephroscopy can be performed through the established nephrostomy tract.

In the past, the burden of repeated endoscopic evaluation of the upper urinary tracts was a major deterrent to conservative therapy. The use of smaller, 7.5-Fr flexible ureteroscopes has greatly eased the burden of follow-up because ureteroscopes can be reliably passed up the ureter without the need for dilation of the ureteral orifice or prior stenting. Others have advocated resection of the ureteral orifice to facilitate subsequent surveillance ureteroscopy in the office setting ([Kerbl and Clayman, 1993](#)). Even though technology has somewhat facilitated follow-up, both physician and patient must be committed to nephron-sparing treatment.

Metastatic Restaging

Metastatic restaging is required in all patients at significant risk for disease progression to local or distant sites. This group includes those with high-grade or high-stage (>pT1) disease. Metastatic restaging is usually not necessary for low-grade disease when the risks of invasive and subsequent metastatic disease are negligible. Included in metastatic restaging is imaging of the ipsilateral renal bed for recurrence with cross-sectional imaging. Follow-up restaging includes chest radiography, liver function tests, cross-sectional body imaging, and selective use of bone scintigraphy based on an understanding of natural disease history and metastatic pathways ([Korman et al, 1996](#)). Follow-up of the upper tracts should be lifelong owing to a lifetime risk of development of upper tract tumors in patients with prior bladder cancer ([Herr et al, 1996](#)).

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Epidemiology, Etiology, and Pathogenesis

Classification and Pathology

Staging of Retroperitoneal Sarcomas

Clinical Presentation and Workup

Treatment

Conclusions

PPrimary retroperitoneal tumors (RPTs) refer to a group of rare neoplasms arising in the retroperitoneum and pelvis. Although RPTs do not necessarily arise from the urogenital tract, urologists are often involved in their diagnosis and management. Furthermore, because the urinary tract is located in the retroperitoneum and pelvis, it often becomes involved with a growing RPT, necessitating proficiency in complex reconstructive urology with the goal of organ and function preservation, or occasionally organ resection.

As a group, RPTs share some important biologic features that distinguish them from most other solid tumors. Unlike most carcinomas whose clinical manifestation, evolution, and sites of metastasis are variable depending on the organ of origin, retroperitoneal sarcomas share many common clinical features that are less influenced by tumor tissue of origin. Such features include a tendency for extensive growth before becoming clinically evident; a propensity for hematogenous dissemination typically to the lungs and liver, rather than metastasis via lymphatic pathways; and local invasion of adjacent organs. Furthermore, in most cases these tumors do not originate in a specific organ but rather grow from connective tissues normally present in the retroperitoneum and pelvis. Occasionally, heterotopic tumors occur where the tumors resemble tissues not expected within a specific anatomic area. Examples for the former tumors include liposarcoma, leiomyosarcoma, and angiosarcoma, whereas examples for the latter lesions include synovial sarcoma and osteogenic sarcoma.

RPTs represent a heterogeneous group of neoplasms comprising a majority of malignant mesenchymal cancers and a minority of benign lesions. Retroperitoneal sarcomas represent a minority of all mesenchymal cancers, most of which affect the extremities, head and neck area, and genitalia (Jemal et al, 2009).

Despite similar histologic features, retroperitoneal sarcomas may follow a more aggressive clinical course compared with their extremity counterparts. Because extremity sarcomas are more common than retroperitoneal sarcomas, much of the treatment principles germane to these tumors were gleaned from experience with extremity sarcomas; however, many differences exist with respect to the means of diagnosis, the extent of surgery, and the role of radiotherapy.

KEY POINTS: INTRODUCTION

- RPTs are a heterogeneous group of tumors.
- Malignant mesenchymal tumors are the most common type of RPTs.

EPIDEMIOLOGY, ETIOLOGY, AND PATHOGENESIS

As a group RPTs represent a combination of sarcomas and other benign and malignant lesions, and as the result the true incidence

of RPTs is unknown. However, **sarcomas are the most prevalent entity in this group.** It is estimated that in 2013 there were 12,020 cases of soft tissue sarcomas within the United States, with 4740 cancer-specific deaths among both adults and children (Siegel et al, 2014). Soft tissue sarcomas constitute roughly 1% and 15% of all adult and pediatric neoplasms, respectively. One of the many challenges imparted in the management of sarcomas pertains to the fact that there are over 50 different histologic subtypes, resulting in a highly heterogeneous cohort of tumors encompassed within this tumor type designation. The anatomic site of origin of sarcomas is an important consideration in the management and expected treatment outcome of such tumors. It is reported that 60% of sarcomas originate from the extremities, 20% from the trunk, 15% from the retroperitoneum, and 5% to 10% from the head and neck (Pisters et al, 2011). The prognosis of retroperitoneal sarcomas is generally poor (Cormier and Pollock, et al, 2004). This is probably due to their location deep in the retroperitoneal cavity, where lesions do not readily lend themselves to detection by physical examination and the potential space of the abdomen allows for their growth to a considerable size and advanced stage before becoming clinically apparent (Paryani et al, 2012). In fact, over 50% of tumors exceed 15 cm in diameter at the time of diagnosis and tumors weighing more than 30 kg have been reported (Lehnert et al, 2009). Combined, liposarcoma, leiomyosarcoma, and malignant fibrous histiocytoma account for 80% of all retroperitoneal sarcomas (Rajiah et al, 2011). Although retroperitoneal sarcomas can occur in any age group, most are found in the sixth decade of life and men are affected slightly more often than women. Two thirds of the patients are diagnosed with high-grade disease and 10% with metastasis, mainly to the lungs and liver (Lewis et al, 1998). No specific causative factor has been identified for soft tissue sarcomas; however, radiation exposure has been implicated in the development of sarcoma within the radiated field in approximately 0.1% of the patients, typically 10 or more years after radiation exposure. The most characteristic postradiation sarcoma is malignant fibrous histiocytoma. Other risk factors include genetic predisposition; exposure to certain carcinogens, particularly dioxin; viral infection; and immunodeficiency. Occasionally, sarcoma may grow within a scar or site of previous injury and inflammation. Although sarcomatous transformation of a neurofibroma into a neurofibrosarcoma has been described, benign mesenchymal tumors almost never transform into malignant counterparts, such as lipoma transforming into liposarcoma or hemangioma developing into hemangiosarcoma. Several hereditary syndromes and congenital conditions have been associated with the development of soft tissue tumors. Research on family members affected by these syndromes has led to the identification of specific gene aberrations found in some of the sarcomas. Gardner syndrome consists of colon polyposis and mesenchymal tumors, including osteomas, lipomas, and epidermal cysts. Low-grade fibrosarcoma has been associated with this syndrome, and mutations on locus 21 to 23 on chromosome 5 have

been reported. Familial retinoblastoma has been associated with osteogenic sarcoma; and deletions in the retinoblastoma (Rb) gene have been associated with leiomyosarcoma. Other hamartomatous syndromes associated with increased soft tissue sarcoma risk include neurofibromatosis, tuberous sclerosis, von Hippel-Lindau syndrome, and Peutz-Jeghers syndrome.

The origin of soft tissue sarcomas is believed to be dormant mesodermal embryonic stem cells residing within normal adult connective tissues. These cells might be affected by exogenous stimuli such as radiation exposure, inflammation, or genetic aberration induced by carcinogens or viruses, thereby initiating the process of tumor development and progression. Several observations support the stem cell origin, as discussed in the following text.

The vast majority of soft tissue sarcomas arise de novo, and malignant transformation in preexisting benign lesions rarely has been reported. Whereas carcinomas often occur from epithelial linings with rapid cellular turnover, adult mesenchymal tissues have a much slower cellular recycling process and some are devoid of it entirely; thus genetic aberrations acquired by a mature mesenchymal cell that has low or no proliferative capability may render the defective cell prone to apoptosis and less likely to evolve into cancer. In addition, the high variability of sarcoma types, including the presence of heterotopic tissues such as synovial or osteogenic sarcomas in sites that are devoid of bone or synovium, alludes to a process of tumorigenesis from a pluripotent progenitor cell—the mesenchymal stem cell.

KEY POINTS: EPIDEMIOLOGY, ETIOLOGY, AND PATHOGENESIS

- Retroperitoneal sarcomas are the most prevalent primary RPTs.
- Of retroperitoneal sarcomas, 80% consist of the combination of liposarcomas, leiomyosarcomas, and malignant fibrous histiocytomas.
- Benign mesenchymal tumors almost never transform into malignant counterparts.

CLASSIFICATION AND PATHOLOGY

Benign Lesions

Benign RPTs are much less common than retroperitoneal sarcomas. The more frequent of these are lipoma, myelolipoma, leiomyoma, schwannoma, extra-adrenal pheochromocytoma, paraganglioma, and cystadenoma. **Although subcutaneous lipoma is the most common benign mesenchymal tumor, benign retroperitoneal lipoma is very rare.** Similarly, uterine leiomyoma is very prevalent in adult women. Less frequently, leiomyomas have been reported in other organs, including the kidney, prostate, ureter, bladder, spermatic cord, and penis. However, retroperitoneal leiomyoma is very rare. These are relatively small tumors, and when larger than 6 cm in diameter they are considered malignant. On light microscopy, spindle-shaped cells with cytoplasmic vacuole and central nuclei are typically present, although areas with clear cells may also be present.

Although the distinction of benign lesions from malignant tumors is difficult, some features are more characteristic of benign lesions. Most benign RPTs are small, well-circumscribed lesions and are found incidentally in asymptomatic patients. Conversely, most malignant RPTs are large and may occasionally reach enormous size; they often have poorly defined boundaries and are frequently associated with symptoms, most of which are attributed to compression of nearby organs or inanition. In addition, calcifications in retroperitoneal lesions are more characteristic of malignancy and they are rarely found in benign tumors. Although accurate histologic diagnosis is not possible based on imaging studies, some lesions have a typical appearance that can help predict their

presence. In a multivariate analysis that included 194 patients with RPTs, the following features were independently associated with the presence of a malignancy: ill-defined margins, irregular surfaces, long diameter greater than 6.75 cm, short diameter greater than 6.25 cm, solid or mixed texture, and a sensitivity and specificity of 77% and 81%, respectively (Zheng et al, 2014).

Benign retroperitoneal lipomas are typically homogenous, hypodense well-circumscribed or encapsulated lesions; however, distinction from low-grade liposarcoma, angiomyolipoma, or myelolipoma may be difficult. Microscopic examination reveals homogenous large cells with fat-laden cytoplasm leading to a flat eccentric nucleus. Excessive blood vessels or collagen may be found in variants termed as angioliipomas or fibrolipomas, respectively. Benign hibernoma (tumor of brown fat) has been reported mainly in adults. The tumor consists of large lobulated cells with cytoplasmic fat granules that stain positively with Sudan dyes. The pattern of vascular supply of these tumors is similar to that observed in the organs of hibernating mammals.

Schwannomas, ganglioneuromas, and paragangliomas are benign myxoid tumors often located in the paravertebral area. They may be oval, small, well-circumscribed masses but occasionally may be large. Anterior displacement of the pancreas or great vessels is typical. Whereas schwannomas are benign tumors arising from nerve sheath supporting cells typically with no associated symptoms, paragangliomas are composed of adrenergic nerve cells and are capable of releasing norepinephrine, provoking a syndrome akin to a pheochromocytoma, functionally producing catecholamines.

Malignant Lesions

Besides primary retroperitoneal sarcomas, other systemic cancers may manifest with retroperitoneal masses and need consideration in the differential diagnosis. Retroperitoneal lymphoma may manifest with retroperitoneal diffuse lymph node enlargement. Occasionally the involved lymph nodes will coalesce to form irregular masses that are indistinguishable from other primary RPTs. Lymphoma may even mimic retroperitoneal fibrosis with a homogenous dense midline mass that resembles fibrosis. **Metastatic germ cell tumors may lead to retroperitoneal lymphadenopathy that may be bulky.** Typically such masses deflect the ureters laterally, but may occur in between or anterior to the great vessels. The diagnosis of germ cell tumor can be established easily by finding a testicular mass and elevated relevant serum markers. Lymphoma may be associated with splenomegaly, elevated lactate dehydrogenase, and other symptoms.

Primary mesenchymal tumors can be classified according to the mesenchymal tissue component of origin. The primitive mesenchyme in the embryo gives rise to the development of primitive connective tissue, including adipose, fibrous, synovial, and osseous/cartilage tissues; angioblastic tissues, including blood vessels and lymphatics; and muscle tissue, including smooth or striated muscles. Table 59-1 depicts the classification of benign and malignant mesenchymal tumors according to the mesenchymal tissue of origin.

Liposarcoma is by far the most common type of retroperitoneal sarcoma. Several classifications of these have been proposed. Enzinger and Winslow (1962) modified a previous classification by Stout and proposed five categories: (1) myxoid, (2) well-differentiated, (3) round cell, (4) de-differentiated, and (5) pleomorphic. The first two are considered low-grade and the last three high-grade sarcomas. **Myxoid liposarcomas** are composed of primitive lipoblasts that do not have the typical fat-laden cytoplasm but rather resemble primitive mesenchymal cells. Abundant capillary network and myxoid matrix are other typical components. The histologic appearance of **well-differentiated liposarcoma** closely resembles that of a benign lipoma, and the distinction between the two by imaging and even under the microscope is a challenge. In fact, many well-differentiated liposarcomas are misdiagnosed as deeply seated lipomas. In a recent study, experienced magnetic resonance imaging (MRI) radiologists who were blinded

TABLE 59-1 Classification of Mesenchymal Tumors

TISSUE OF ORIGIN	BENIGN TUMOR	MALIGNANT TUMOR
Adipose	Lipoma Angiolipoma/angiomyolipoma Lipoblastoma Hibernoma Lipomatosis	Well-differentiated liposarcoma De-differentiated liposarcoma Myxoid liposarcoma Round cell (poorly differentiated) Pleomorphic type
Fibrous	Fibroma Angiofibroma Myositis ossificans Elastofibroma Aggressive fibromatosis	Fibrosarcoma
Fibrous histiocytic	Fibrous histiocytoma Juvenile xanthogranuloma Xanthoma Others	Malignant fibrous histiocytoma Storiform, myxoid, giant cell, xanthomatous variants
Muscle tissue Smooth muscle Striated muscle	Leiomyoma Epithelioid leiomyoma Angiomyoma Leiomyomatosis Rhabdomyoma	Leiomyosarcoma Epithelioid leiomyosarcoma Rhabdomyosarcoma
Neural tissue Sympathochromaffin tumors	Schwannoma Neurofibroma Neurofibromatosis Ganglioneuroma Pheochromocytoma	Malignant schwannoma Malignant peripheral nerve sheath tumor Malignant granular cell tumor Malignant melanoma Neuroepithelioma Ewing sarcoma Ganglioneuroblastoma Neuroblastoma Malignant pheochromocytoma
Synovial tissue	Synovioma Giant cell tumors of the tendon sheath	Synovial sarcoma
Vascular tissue	Hemangioma	Angiosarcoma Kaposi sarcoma
Lymphatic tissue	Lymphangioma	Lymphangiosarcoma

to the histologic diagnosis failed to distinguish lipomas from well-differentiated liposarcomas in 30% of the cases. Distinction criteria included nodularity, stranding, and tumor borders (O'Donnell et al, 2013). Although well-differentiated liposarcomas seldom metastasize, local recurrence is common and long-term prognosis is influenced by the morbidity caused by such recurrences involving other organs and the morbidity of the necessary surgeries.

Round cell liposarcoma is composed of small round cells uniform in size and closely packed together. There is no specific pattern of cellular arrangement and intracellular lipid content is scarce. **De-differentiated liposarcoma** is characterized by the coexistence of well-differentiated and poorly differentiated areas within the same tumor. Occasionally, at the time of local recurrence other phenotypes may be present, including malignant fibrous histiocytoma, rhabdomyosarcoma, or leiomyosarcoma.

Characteristic features of **pleomorphic liposarcoma** include a disorderly growth pattern with cellular pleomorphism, giant cells, and anaplastic pyknotic nuclei. Because this anaplastic tumor resembles other undifferentiated sarcomas, some lipoblastic presence must be documented to confirm this diagnosis. All lipocytes and lipoblasts stain positive with the immunostaining agent S-100, rendering this a useful tool in establishing this diagnosis. Genetic aberrations, including a balanced translocation of chromosomes 12 and 16 t(12:16) (q13:p11), appear in 90% of myxoid liposarcoma cases and are pathognomonic of this sarcoma (Eneroth et al,

1990). Ring chromosome 12 is typical of well-differentiated liposarcomas but also has been demonstrated in benign lipomas (Dal Cin et al, 1993).

Malignant fibrous histiocytoma has been the subject of controversy from both an ontogenetic and diagnostic standpoint. Although its name implies that histiocytes are the building block and cell of origin, truly this is a fibroblast neoplasm. Microscopic findings include round histiocyte-like cells, spindle-shaped fibroblasts, foamy cells, giant cells, and lymphocytes. Several subtypes have been reported; whereas the myxoid subtype is associated with a somewhat more favorable prognosis, the other subtypes are aggressive and show a high tendency to metastasize. In addition, some studies have shown an association between the presence of lymphoproliferative disorders, including leukemia, and both Hodgkin and non-Hodgkin lymphoma, and the development of malignant fibrous histiocytoma. The cause of this apparent relationship between malignant fibrous histiocytoma and hematologic malignancies remains unclear.

Retroperitoneal leiomyosarcomas usually occur in women in their 7th decade. The tumors attain very large size and include cystic degeneration and necrosis. Microscopic findings include spindle-shaped cells with abundant cytoplasm and cigar-shaped nuclei. As is the case with well-differentiated liposarcoma, distinction of a leiomyoma from a leiomyosarcoma is difficult even under rigorous microscopic review. Parameters suggestive of malignancy include

tumor size, pleomorphism, cellularity, necrosis, atypia, and mitosis. Of these, mitosis is the most highly predictive feature and in RPTs 1 mitosis per 10 high-power fields (HPFs) is characteristic of malignancy, whereas more mitotic figures are tolerated in smooth muscle tumors in other anatomic locations. Tumor grade is an important prognostic factor because high-grade tumors are associated with a less favorable outcome.

KEY POINTS: CLASSIFICATION AND PATHOLOGY

- Benign retroperitoneal lipomas are very rare as opposed to subcutaneous benign lipomas, which are the most common type of benign mesenchymal tumor.
- In addition to primary retroperitoneal sarcomas, other systemic malignancies such as retroperitoneal lymphoma and metastatic germ cell tumors may manifest as retroperitoneal masses and need consideration in the differential diagnosis.
- Retroperitoneal liposarcoma is by far the most common type of retroperitoneal sarcoma.

STAGING OF RETROPERITONEAL SARCOMAS

Hematogenous spread is the principal route of metastasis for sarcomas, and the lungs are the most common metastatic site for such tumors, followed by the liver. Because cross-sectional imaging is necessary as the initial diagnostic workup, liver involvement will be picked up in the initial imaging procedure. Chest computed tomography (CT) is required for all retroperitoneal sarcomas to detect pulmonary metastasis. Other sites such as bones and brain are infrequently involved, and routine imaging of these sites using brain MRI and bone scintigraphy is not required in the absence of relevant symptoms. The exceptions may be lymphangiosarcoma, osteogenic sarcoma, and Ewing sarcoma—all of which also may involve the skeleton, and bone scans should be obtained in such patients.

The tumor, node, metastasis (TNM) staging system has been used to define the local and systemic extent of tumors as follows:

T0	No demonstrable tumor
T1	Tumor measuring <5 cm in maximal diameter
T2	Tumor measuring ≥5 cm in maximal diameter
T3	Evidence of macroscopic invasion of nearby structures by the tumor
N0	No histologic evidence of regional lymph node involvement
N1	Histologically proved regional lymph node involvement
M0	No distant metastasis
M1	Distant metastasis present

In addition, the extent of surgical resection of the primary tumor is also reported, because this has been shown to portend prognostic implication, as follows:

R0	Tumor was entirely resected with no residual tumor and negative surgical margins
R1	Microscopic residual tumor = positive surgical margins
R2	Macroscopic residual tumor
R3	Tumor spillage and dissemination during resection

With regard to retroperitoneal sarcomas, in most cases tumor stage is T2 or more; the extent of other structure invasion plays a minor prognostic role as long as the tumor may be completely resected; and lymphatic involvement is rare.

Besides this staging system, several histologic parameters have been shown to affect prognosis. Tumor grade is the most

important of those; it is determined by taking into account tumor cellularity, pleomorphism, necrosis, anaplasia, and mitosis. Of these, the mitotic index (number of mitoses per 10 HPFs) and necrosis are independent prognostic factors whose impact is variable depending on tumor type (El-Jabbour et al, 1990; Hashimoto et al, 1992; Catton et al, 1994). In addition, molecular markers, including ploidy, chromosomal aberrations, proliferative index, and tumor promoter and suppressor gene mutations have been shown to influence outcome.

KEY POINTS: STAGING OF RETROPERITONEAL SARCOMAS

- The most common site of metastatic progression of retroperitoneal soft tissue sarcomas is the lungs, followed by the liver.
- In addition to TNM clinical staging, other prognostic factors for retroperitoneal sarcomas include tumor grade, mitotic index, necrosis, and molecular markers.

CLINICAL PRESENTATION AND WORKUP

Before histologic diagnosis of an RPT is available, its presence is typically heralded by imaging findings either as part of a workup for a suggestive clinical presentation or as an incidental finding on an imaging procedure undertaken for other unrelated reasons. At present, cross-sectional imaging by CT or MRI provides accurate data on tumor size, location, relations to nearby structures, and other features, including heterogeneity, boundaries, vasculature, necrosis, and calcification. CT depicts a solid (>15 Hounsfield units) texture to the suspect lesions, but may demonstrate necrosis, calcifications, and anatomic relations to nearby blood vessels and organs. Adipose tissue tumors may show the typical hypodense attenuation; however, the distinction of various types of benign and malignant fat-containing tumors is not possible by CT. The presence of dense areas within a fatty tumor may allude to de-differentiated liposarcoma. Most RPTs have long T₁ and T₂ relaxation times and appear hypointense on T₁-weighted images and hyperintense on T₂-weighted images. MRI has been very sensitive in demonstrating fat-containing tumors. The role of positron emission tomography (PET-CT) for initial diagnosis and staging is less well established, and probably it is most useful to delineate retroperitoneal lymphoma, which is PET positive in many cases, and distinguish it from other tumors. In contrast, several reports found correlation between fluorodeoxyglucose (FDG) avidity and grade of liposarcoma, although FDG avidity of other sarcomas is less predictable and often absent (Kitajima et al, 2013). In the postsurgery follow-up phase there may be a role for PET-CT, because it showed superior specificity compared with contrast-enhanced CT for well-differentiated liposarcoma, lymph node metastasis, and pulmonary metastasis. The specificity of PET-CT remained poor for leiomyosarcoma and liver metastasis (Niccoli-Asabella et al, 2013). At the present time, the role of PET-CT in the management of RPTs remains unclear.

Due to their location deep in the retroperitoneum, which is not a confined space, many RPTs can grow to a vast size before prompting the patient's attention. Thus very large tumors (>15 cm or weighing several kilograms) may occasionally be found. In the absence of distant metastasis and local involvement of nearby organs, most tumors can remain asymptomatic for an extended duration. Eventually, however, a sensation of an abdominal mass or abdominal pain (in 80% of patients) and constitutional symptoms, such as weight loss (30% of patients), fatigue, early satiety, and inanition may ensue, as the metabolic requirements of the growing tumor deplete the host of needed resources. Neurologic symptoms also occasionally may occur. A typical complaint is of weight loss in conjunction with abdominal girth enlargement as a

result of the presence of a large abdominal tumor. Compression of nearby organs may elicit additional symptoms, including abdominal discomfort, nausea, flank or pelvic pain, and hematuria.

Physical examination may be unrevealing, or a large abdominal mass may be palpated and sometimes even be visible. Leg edema and symptoms of inferior vena cava syndrome may be found. Abdominal ultrasound is often used as a screening tool to evaluate physical findings of an abdominal mass or suspicious symptoms. However, cross-sectional imaging with CT or MRI provides a more accurate diagnosis of the primary tumor and provides local staging. Further staging with a chest CT is routine. The differential diagnosis of retroperitoneal masses includes lymphoma, retroperitoneal sarcoma, metastasis, and, rarely, benign RPTs. Nonsolid lesions such as congenital and acquired cysts, arterial aneurysms, and inflammatory lesions (i.e., psoas abscess) usually can be suspected based on previous patient history and the liquid content that is readily discerned by cross-sectional imaging.

Role of Pretreatment Biopsy

A pretreatment biopsy is important in cases in which lymphoma is suspected. Because the mainstay of lymphoma therapy is not surgery but rather systemic chemotherapy, a percutaneous imaging-guided needle biopsy may expedite the diagnosis and direct the patient toward appropriate treatment (Quinn et al, 1995). Other clinical scenarios in which a biopsy may be indispensable include patients in whom metastasis from a preexisting cancer is suspected, patients with a mass that appears surgically unresectable, or patients with a suspected sarcoma in whom metastatic disease is noted on imaging, and a biopsy may guide chemotherapy. It is also highly recommended to obtain a pretreatment biopsy sample to establish the diagnosis and grade in select patients suspected of having a surgically resectable retroperitoneal/intra-abdominal sarcoma (Von Mehren et al, 2015). It is well established within the sarcoma literature that the underlying tumor biologic status (grade) and sarcoma histologic subtype are important prognostic factors for retroperitoneal sarcomas and often both can be characterized on a diagnostic biopsy specimen, hence often enabling us to develop a personalized treatment approach to a given patient (Gronchi et al, 2004; Grobmyer et al, 2010). The pretreatment biopsy is particularly useful if the suspected soft tissue sarcoma is being considered for presurgical therapy (i.e., radiotherapy and/or systemic therapy). However, if the final common pathway is surgery, a preoperative biopsy is in fact not necessary. One such example in which preoperative imaging without a biopsy is all that is needed is in a patient with a retroperitoneal liposarcoma. If a pretreatment biopsy is felt to be beneficial, it can be performed by an interventional radiologist or surgeon using either an image (CT, MRI, or ultrasound)-guided core (14- or 16-gauge coaxial needle) or, rarely, an open/minimally invasive surgical incisional-guided technique, depending on the location of the retroperitoneal mass and amenability to a minimally invasive procedural technique. It is thought by many experts that an image-guided core biopsy is the preferred technique, avoiding the potential of cancer dissemination within the future surgical field from an open/minimally invasive surgical biopsy, which can complicate and potentially adversely affect the outcome of the subsequent definitive management. A frozen section assessment of the biopsy can at times be beneficial in ensuring that an adequate diagnostic biopsy specimen has been obtained but should not be used, for example, during surgery because it is often inaccurate for such tumors. Whenever feasible, a retroperitoneal (vs. transperitoneal) image-guided biopsy should be obtained to avoid the theoretical risk for peritoneal seeding along the needle tract. It is important to highlight at this point that although a fine-needle aspiration is a convenient way of obtaining tissue, it is often nondiagnostic and/or minimally informative in providing histopathologic details because of the small amount of tissue obtained with this technique (Domanski, 2007). At times, a biopsy guided by endoscopy (upper or lower gastrointestinal endoscopy or bronchoscopy) may be appropriate to access a thoracic, abdominal, or

pelvic situated lesions. Importantly, definitive treatment decisions often cannot be finalized until the diagnostic biopsy has been reviewed by a pathologist with expertise in soft tissue sarcomas, often necessitating the use of immunohistochemical staining and molecular testing.

KEY POINTS: CLINICAL PRESENTATION AND WORKUP

- A pretreatment biopsy is important in cases in which lymphoma is suspected. In addition, a biopsy may be indispensable in patients in whom metastasis from a preexisting cancer is suspected, patients with a mass that appears surgically unresectable, or patients with a suspected sarcoma in whom metastatic disease is noted on imaging and a biopsy may guide subsequent systemic therapy. It is also highly recommended to perform a pretreatment biopsy to establish the diagnosis and grade in select patients suspected of having a surgically resectable retroperitoneal/intra-abdominal sarcoma.
- If a pretreatment biopsy is felt to be beneficial, it can be obtained by an interventional radiologist or surgeon using either an image (CT, MRI, or ultrasound)-guided core (14- or 16-gauge coaxial needle) or, rarely, an open/minimally invasive surgical incisional-guided technique depending on the location of the retroperitoneal mass and amenability to a minimally invasive approach.

TREATMENT

Principles of Sarcoma Surgery

Definitive surgical resection remains the standard primary treatment of retroperitoneal sarcomas; however, if it is deemed a tumor cannot be surgically resected while ensuring negative surgical margins, preoperative (neoadjuvant) radiotherapy and/or systemic therapy should be considered, with such cases best managed by a multidisciplinary team (medical and surgical oncology as well as input from radiation oncology). In retroperitoneal sarcomas deemed resectable with anticipated negative final surgical margins, it cannot be emphasized enough that the quality and adequacy of the surgical resection is imperative in determining the likelihood of potential cure (Bonvalot et al, 2012). Unlike primary tumors of epithelial origin, which are typically contained within a single organ site and therefore can be surgically eradicated by the resection of that specific organ, retroperitoneal sarcomas typically extend, with direct contact to a number of abdominal/retroperitoneal structures without necessarily invading them based on preoperative imaging. In consequence, **local control remains a significant problem and furthermore is the leading cause of death, particularly for the low- to intermediate-grade tumors**, which are estimated to constitute approximately 75% of all retroperitoneal sarcomas.

Earlier retroperitoneal sarcoma surgical series had reported disappointing local recurrence-free survival (RFS) rates of 50% at 5 years (Lewis et al, 1998); however, more recent surgical series have reported significantly improved RFS rates of up to 75% to 80% at 5 years (Bonvalot et al, 2010; Gronchi et al, 2012), as shown in Table 59-2. The better surgical outcomes reported in recent years can be attributed in large part to a more aggressive approach in which all concerning organs suspected to be involved are resected en bloc with the specimen whenever feasible. This minimizes the risk for microscopically positive surgical margins. It is evident that a fine line exists between the resection of organs potentially grossly or microscopically involved with a retroperitoneal soft tissue sarcoma and the resection of important vital organs for which there is questionable involvement and potential exponentially increasing morbidity and/or mortality of the resection. It must be emphasized, however, as nicely depicted in an editorial, that the liberal resection

TABLE 59-2 Historical Series on Surgical Outcomes of Retroperitoneal Sarcoma Resection

SURGICAL SERIES	STUDY PERIOD	STUDY POPULATION	COMPLETE RESECTION (%)	OVERALL SURVIVAL (% AT 5 YR)	LOCAL RFS (% AT 5 YR)	MEDIAN FOLLOW-UP (MO)
Lewis et al (1998)	1982-1997	231	80	54	59	28
Stoeckle et al (2001)	1980-1994	145	65	49	42	47
Gronchi et al (2004)	1982-2001	167	88	54	63	66
van Dalen et al (2007)	1989-1994	143	70	39	NR	122
Strauss et al (2010)	1990-2009	200	90	68	55	29
Bonvalot et al (2010)	2000-2008	249	93	65	78	37
Gronchi et al (2012)	2002-2008	136	94	68	79	48

NR, not reported; RFS, recurrence-free survival.

of adjacent uninvolved viscera may allow a subset of patients to more consistently achieve microscopically negative resection margins, but it remains unclear whether this additional resection translates into an improvement in cancer-specific survival (Pisters, 2009). It is reasonable to recommend in patients with low-grade soft tissue retroperitoneal sarcomas that they undergo such a surgical approach because such tumors have such a low metastatic potential. It can be argued, however, that such patients may harbor indolent disease that can remain asymptomatic for months to years, thereby putting into question the ultimate benefit of surgical resection. Regardless, the objective of surgical resection in this clinical context is to achieve a wide microscopic negative surgical margin by removing easily disposable organs (e.g., kidney, spleen, tail/body of pancreas, psoas muscle) while performing only what is critical in terms of the resection of vital anatomic structures (e.g., aorta, inferior vena cava, iliac vessels, duodenum, head of pancreas, diaphragm, femoral nerve). When true extension into major vascular structures is anticipated, expertise in the surgical management of vascular resection, with the potential use of vascular bypass or grafting, should be readily available and the potential necessity for major intraoperative transfusions should be anticipated and discussed with the patient and anesthesia team preoperatively. In some cases, it is feasible to dissect major vessels under the adventitia, bone under the periosteum, and nerves under the epineurium as a means to obtain negative microscopic margins (Kawaguchi et al, 2004; Lin et al, 2007). However, if the adventitia of these respective organs is invaded, these should be resected if deemed technically feasible, taking the patient's performance status, comorbidities, and estimated prognosis into account. Surgeons embarking on such procedures must determine which anatomic sites must be resected to ensure negative microscopic surgical margins are obtained and balance this in the context of optimizing the patient's quality of life and minimizing the morbidity of the surgical procedure. Such decisions and considerations taken by the surgeon must take into account the patient's individual expectations and goals as well as whether this is a primary versus recurrent retroperitoneal sarcoma. Clearly, all of these nuances of the surgical management of a retroperitoneal sarcoma must be discussed with the patient preoperatively and counseled accordingly.

A very meticulous review of preoperative imaging by the surgeon and his team is imperative before embarking on retroperitoneal sarcoma surgical resection. A CT scan with intravenous contrast of the abdomen and pelvis is the most frequently used diagnostic imaging modality. CT imaging is excellent in diagnosing a suspected retroperitoneal liposarcoma, with typically well-differentiated fat usually indicative of a low-grade liposarcoma, although renal angiomyolipomas and adrenal myelolipomas remain in the differential diagnosis and must be considered. To distinguish these from one another, it must be remembered that angiomyolipomas frequently have smooth muscle and large vascular structures within the fatty component of the mass whereas adrenal myelolipomas are solely fat-containing tumors that originate from within the anatomic boundaries of the adrenal gland. **A principle to adopt**

is that any large lipomatous tumor originating from the retroperitoneal space be considered a well-differentiated retroperitoneal liposarcoma until proved otherwise. Importantly, if a fat-containing tumor has one or more areas of increased density, the diagnosis of a retroperitoneal liposarcoma is more significantly suspected. It can be challenging to determine if these areas of greater density in fact represent de-differentiated components of the tumor versus potential well-differentiated liposarcomatous histologic subtypes such as inflammatory, myxoid-like, or sclerosing lesions (Lahat et al, 2009). If the surgeon feels this determination may influence his treatment decision in terms of proceeding with surgical resection versus consideration of neoadjuvant radiotherapy and/or systemic therapy, a diagnostic percutaneous biopsy sample can be obtained. At this point, it is important to highlight a common mistake made by treating physicians/surgeons not intricately familiar with the radiographic appearance of retroperitoneal liposarcomas, which is to focus on the high-density component of the lipomatous tumor and assume the rest of the fat is normal, which consequently may be left behind at the time of the surgical resection at some centers not exhibiting such surgical expertise/experience. **In retroperitoneal masses exhibiting higher density without a fatty component on CT imaging (with intravenous contrast), a percutaneous biopsy should be considered absolutely necessary to differentiate a soft tissue retroperitoneal sarcoma from other tumor types, such as a germ cell neoplasm (in males), lymphoma, or a desmoid tumor. It should be considered absolutely imperative to perform a bilateral testicular physical examination in any male patient presenting with an RPT, with a bilateral testicular ultrasound with Doppler performed in any male patients with a concerning testicular examination for a solid intraparenchymal testicular mass, with the use of testicular cancer serum tumor markers (α -fetoprotein, β -human chorionic gonadotropin, and lactate dehydrogenase) encouraged as well.**

Although many surgical approaches can be employed in tackling what often can be large retroperitoneal liposarcomas, the most common incisions are typically a midline or subcostal/chevron approach. Both incision types allow for excellent exposure to abdominal/pelvic organs, which can be reflected superiorly to allow access to retroperitoneal organs and major vascular structures (van Vreeland et al, 1995). For large RPTs situated in the right upper quadrant, some surgeons prefer a thoracoabdominal incision allowing great visibility and enabling extensive mobilization of the liver, with great exposure of the intrathoracic and intra-abdominal components of the inferior vena cava as well as the right kidney and adrenal gland. Before initiating the surgical resection, it is sometimes deemed beneficial to cystoscopically place a temporary open-end ureteral stent(s) in that large retroperitoneal sarcomas often can intimately involve various segments of the ureter; hence the placement of such stents can serve as a reference point to the precise intraoperative location of the ureter(s) in their entirety, thereby potentially obviating the risk for any intraoperative ureteral injuries and need for ureteral reconstruction.

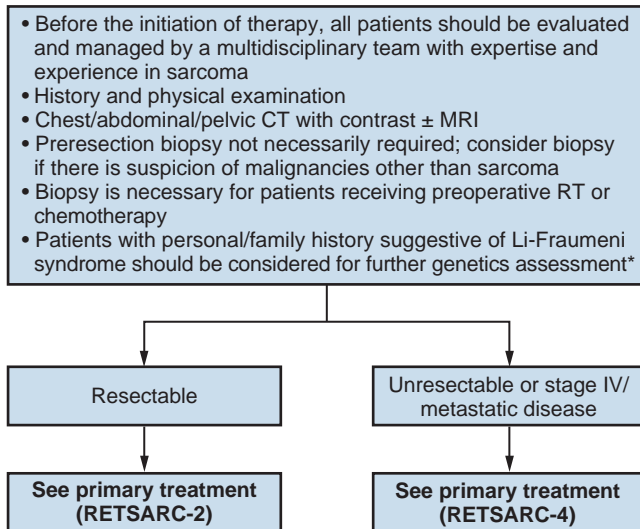
Evidence-Based Treatment Guidelines

The pivotal therapeutic consideration in the management of retroperitoneal/intra-abdominal sarcomas pertains to a determination of whether it is felt the retroperitoneal sarcoma is resectable versus unresectable (or stage IV), as shown in [Figure 59-1](#) ([Von Mehren et al, 2015](#)). This determination should be made by a multidisciplinary team with expertise in the management of sarcomas after careful review of the case using CT imaging with intravenous contrast (\pm MRI) of the chest, abdomen, and pelvis. As discussed in the prior section, a biopsy of the mass (percutaneous core needle biopsy preferably) can be helpful in confirming the histologic diagnosis of a sarcoma and/or determining if neoadjuvant radiotherapy and/or systemic chemotherapy would be beneficial for large (typically > 4 cm) or de-differentiated tumors. In this context for surgically managed retroperitoneal sarcomas in which microscopic or grossly positive margins are anticipated based on intraoperative surgical findings, surgical clips should be applied in these areas to mark the site(s) at increased risk for local recurrence. Although adjuvant radiotherapy is not generally advocated for low-grade retroperitoneal/intra-abdominal soft tissue sarcomas, some have advocated postoperative adjuvant radiotherapy for intermediate- to high-grade tumors, but it is widely believed that such therapy has a limited role because the required radiation dose for local cancer control in the adjuvant setting exceeds that tolerable by the bowel. In this regard, most experts believe adjuvant radiotherapy should be reserved to imperative indications such as grossly positive surgical margins after surgical resection in patients not amenable to repeat resection with negative gross and final

surgical margins. As discussed in earlier sections, it is imperative for surgeons conducting retroperitoneal sarcoma surgery to strictly adhere to the principle of surgical resection with negative margins with the removal of all involved organs. Surgical margins should be documented by both the surgeon and pathologist in evaluating the status of the resection margins. If a surgical margin is deemed positive on final pathologic review, surgical repeat resection should be strongly considered provided this is not deemed either excessively morbid and/or adversely affecting the subsequent quality of life these patients would be rendered ([Von Mehren et al, 2015](#)).

In retroperitoneal/intra-abdominal sarcomas deemed unresectable (or stage IV), a biopsy (preferably percutaneous image guided) to establish the diagnosis should be considered to help confirm first the diagnosis of a soft tissue sarcoma as well as the grade and histopathologic features of the underlying tumor, because these may help dictate which systemic therapies may be best suited for such patients, as shown in [Figure 59-2](#). The role of a multidisciplinary team with expertise in the management of soft tissue sarcomas is imperative in such cases, because patients often will benefit from both local (surgery or radiotherapy) and systemic therapy, as shown in the National Comprehensive Cancer Network® (NCCN®) treatment algorithm. In patients with unresectable (or stage IV) retroperitoneal/intra-abdominal sarcomas being treated with a combination of radiotherapy and systemic therapy, external beam radiotherapy typically is employed in an attempt to obtain local control, often concomitantly with systemic therapy (i.e., chemotherapy and/or small molecule targeted therapy). If the tumor is deemed to have a favorable response with downstaging such that it becomes resectable, subsequent consolidative surgery is recommended. Patients with unresectable (or stage IV) retroperitoneal/intra-abdominal sarcomas exhibiting either no evidence of downstaging after systemic therapy (\pm radiotherapy) or deemed unresectable at time of attempted consolidative surgery, should be treated with palliative therapeutic options (radiotherapy, chemotherapy, surgery), with the end point of such therapy being symptomatic control. Additional therapeutic options for such patients include resection of metastatic sites of disease if the primary tumor can be controlled as well as observation if they remain asymptomatic. If these patients are symptomatic, it is reasonable to consider a palliative surgical resection, which can provide some degree of (short-term) local cancer control with a resulting improved quality of life. Clinical trial participation should be considered for such patients, with best supportive care measures being initiated in patients with symptomatic disease progression. In this regard, it is important to highlight that observation itself is a suitable option in asymptomatic patients because it optimizes the quality of life of these patients in the context of their adverse prognosis. Similarly, in some select reports, incomplete surgical resection of retroperitoneal liposarcomas has in fact been shown to improve survival in addition to successful symptom palliation ([Shibata et al, 2001](#)). Supportive measures should be initiated early in such patients because the likelihood of rapid cancer progression and symptomatology is exceedingly high over the subsequent weeks.

WORKUP

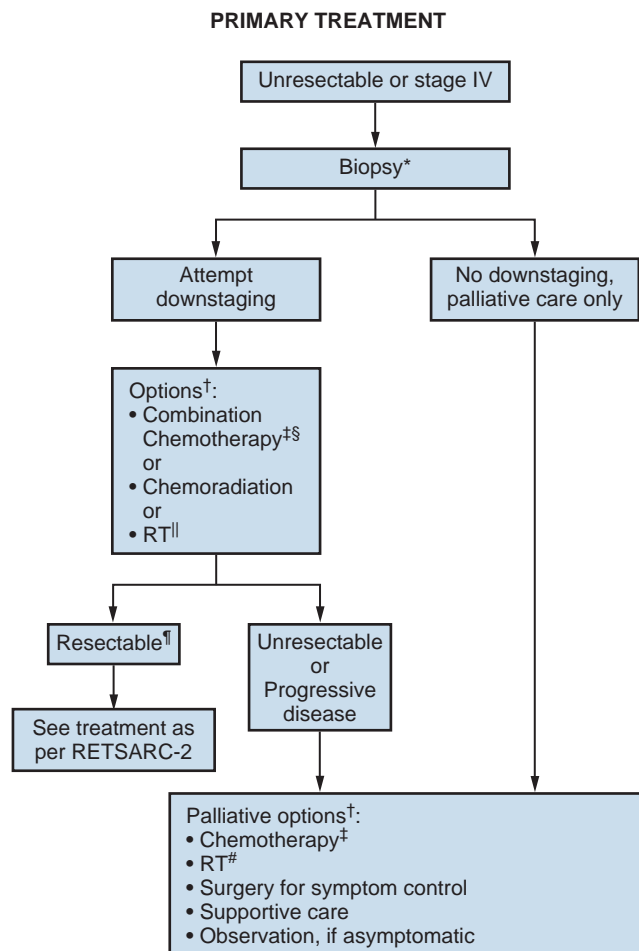


*See NCCN Guidelines for genetic/familial high-risk assessment: breast and ovarian.

Figure 59-1. Algorithm illustrating the workup of a retroperitoneal sarcoma. CT, computed tomography; MRI, magnetic resonance imaging; RT, radiotherapy. (Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.1.2015. © 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.)

Role of Perioperative Radiotherapy

Radiotherapy is an integral therapeutic tool in the management of retroperitoneal soft tissue sarcomas, with its potential role as a primary treatment modality or as part of a multimodal treatment in which it is typically delivered in the neoadjuvant (preoperative) or adjuvant (postoperative) setting. A number of pioneering studies have supported the important therapeutic role of radiotherapy in the management of soft tissue retroperitoneal sarcomas ([Suit and Russell, 1975](#); [Tepper et al, 1984](#)). Significant technologic milestones have been reached in the delivery of radiotherapy with brachytherapy, intensity-modulated radiation therapy (IMRT), and intraoperative radiation therapy (IORT), now readily available choices and offering patients potential superior treatment outcomes ([DeLaney et al, 2005](#)). As has been shown in several long-term



*See principles of pathologic assessment of sarcoma specimens (SARC-A).

†Balance risks of treatment, likelihood of rendering patient resectable, and performance status of patient with potential clinical benefits. The options listed may be used either alone, sequentially, or in combination.

‡See systemic therapy agents and regimens with activity in soft tissue sarcoma (SARC-E).

§The most active chemotherapy regimen in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna) (Judson et al, 2014).

||See radiation therapy guidelines (SARC-D).

¶Resection of resectable metastatic disease should always be considered if primary tumor can be controlled.

#Palliative RT requires balancing expedient treatment with sufficient dose expected to halt the growth of or cause tumor regression. Numerous clinical issues regarding rapidity of growth, the status of systemic disease, and the use of chemotherapy must be considered. Recommended only for patients with unresectable or progressive disease.

Figure 59-2. Treatment algorithm for an unresectable or stage IV retroperitoneal sarcoma. RT, radiotherapy. (Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.1.2015. © 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.)

studies, IORT in select patients with primary and recurrent retroperitoneal soft tissue sarcomas results in excellent local control and disease-free survival with limited treatment-related morbidity (Willett et al, 1991; Gieschen et al, 2001). IMRT similarly allows delivery of high doses of radiation to the primary tumor site while

minimizing radiation exposure to the surrounding tissues by contouring the external radiotherapy through highly precise treatment planning and simulation (Leibel et al, 2002). In contrast, IORT entails the application of radiotherapy during surgery, typically using a brachytherapy or electron beam radiotherapy technique.

Preoperative radiotherapy is frequently used in the management of large or poorly differentiated retroperitoneal sarcomas because, first, the treatment volume is typically a smaller field, being that the entire operative field does not need to be covered, and as well the risk for tumor seeding at time of surgical resection is reduced as a consequence of the preoperative radiotherapy. The sarcoma may or may not shrink, but the pseudocapsule surrounding the tumor often will thicken and be rendered avascular, which can facilitate the subsequent surgical resection. The main drawback to preoperative radiotherapy is that it can impair wound healing, typically with an interval of 3 to 6 weeks between the completion of radiotherapy and the definitive proceeding surgical resection, which may result in significant local effects of acute radiation delivery (inflammation, tissue edema, and poor tissue and wound vascularity). It is important to note, however, that some reports would suggest that preoperative radiotherapy followed by aggressive surgical resection, although well tolerated, did not result in a significant clinical improvement in treatment specific outcomes versus surgery alone (Ballo et al, 2007). A typical preoperative dose of radiotherapy of 50 Gy is employed, and if wide negative surgical margins are obtained at the time of resection, no further radiotherapy is often recommended, because reported local control rates of up to 95% have been reported when preoperative radiation at a treatment dose of 50 Gy is employed and negative surgical margins are obtained on the subsequent surgical resection. However, in cases in which a positive or close positive margin is demonstrated, a radiation boost delivered by external beam radiotherapy or IORT is often recommended. An IORT dose of 10 to 12.5 Gy is recommended for microscopically positive margins, and an IORT dose of 15 Gy is recommended for gross residual disease (Von Mehren et al, 2015).

Postoperative radiotherapy has been demonstrated to improve local cancer control for high-grade soft tissue sarcomas in patients with positive surgical margins (Alektiar et al, 2000; DeLaney et al, 2007). Recommendations pertaining to adjuvant radiotherapy, however, should be individualized and not entirely based on margin status at time of the original or subsequent repeat resection, as demonstrated by the exceedingly low 5-year local recurrence rate of 9% reported in a cohort of limb-affecting soft tissue sarcomas on their repeat resection exhibiting negative surgical margins with no subsequent adjuvant radiotherapy (Cahlon et al, 2008). Postoperative radiotherapy can be delivered in one of several ways, including external beam radiotherapy, brachytherapy, or IORT. It is important to emphasize that adjuvant radiotherapy should not be considered in any way as a compensation for incomplete or poorly conducted surgical resection because the primary end point of retroperitoneal sarcoma surgery should be complete resection with negative gross and microscopic surgical margins while attempting to preserve all nonaffected organs. A therapeutic principle often adhered to is that adjuvant radiotherapy would be the treatment of choice to control microscopic residual disease if repeat resection is not feasible or is refused by patients. When adjuvant radiotherapy is employed, typically the entire operative field is included within the treatment area, with the total dose delivered taking into account the maximal tolerable dose such tissues can be safely administered. Postoperative external beam radiotherapy for such tumors has frequently been conducted using IMRT technology (proton therapy has as well been used in recent years) requiring complex pretreatment planning, taking into account the extent of the surgical procedures and redistribution of organs after the prior resection. IORT can also be used in the postoperative adjuvant setting; however, it has never been shown to be superior to external beam radiotherapy, so definitive recommendations of IORT versus other adjuvant radiotherapy modalities are inconclusive at the present time (Tran et al, 2006). When administered to patients with positive surgical margins, IORT is

delivered at 10 to 16 Gy followed by consolidative external beam radiotherapy at a dose of 50 Gy (Von Mehren et al, 2015).

Role of Perioperative Systemic Therapy

The benefits imparted by neoadjuvant systemic chemotherapy followed by surgical resection have been for the most part inconsistent. In one prior study, the benefit of neoadjuvant chemotherapy was demonstrated only among patients with high-grade sarcomas larger than 10 cm (Grobmyer et al, 2004). The only reported prospective trial comparing surgery alone versus neoadjuvant chemotherapy and followed by surgical resection among patients with high-grade sarcomas was a negative study and did not validate the benefit of treating such patients with a multimodal approach (Gortzak et al, 2001). In this trial, the estimated 5-year disease-free survival was 52% and 56% for the surgery alone and neoadjuvant chemotherapy followed by surgery arms, respectively, which was a non-statistically significant difference. Similarly, the 5-year overall survival rates were 64% and 65%, respectively, for both these treatment arms.

Significantly more robust data exist to support the benefit imparted to adjuvant (i.e., postoperative) systemic chemotherapy in terms of recurrence-free survival among patients with soft tissue sarcomas, although most of these data pertain to extremity sarcomas. An Italian phase 3 trial randomized patients with high-grade primary or recurrent soft tissue sarcomas to undergo either surgical resection alone or surgery followed by systemic chemotherapy consisting of epirubicin and ifosfamide (Frustaci et al, 2001). The estimated overall survival benefit of systemic chemotherapy was 13% at 2 years and subsequently increased to 19% at 4 years. In a subsequent study at a median follow-up of 90 months, the authors reported a 5-year overall survival rate of 66% and 46%, respectively, for this combination treatment arm versus surgery alone (Frustaci et al, 2003). Unfortunately, this difference was not statistically different when the intention-to-treat analysis was conducted. Several meta-analyses have been conducted validating the benefit of adjuvant systemic chemotherapy after surgical resection for soft tissue sarcomas. In a meta-analysis of 14 randomized trials, 1568 patients with soft tissue sarcoma were treated with surgery and adjuvant chemotherapy employing doxorubicin-based regimens versus surgery alone. There was a demonstrated and statistically significant improvement in recurrence-free survival rates to the multimodal treatment area; however, there was no statistically significant improvement in overall survival, although this trended toward significance (Sarcoma Meta-analysis Collaboration, 1997). This benefit of adjuvant systemic chemotherapy was subsequently validated in another meta-analysis in which there was an improvement in local, distant, and overall recurrence-free survival in addition to an overall survival benefit with this multimodal approach (Pervaiz et al, 2008). In a recent study by the French Sarcoma Group, they corroborated the benefit of postoperative chemotherapy with a significant improvement in reported 5-year metastatic-free survival of 58% and 49% for surgery and adjuvant chemotherapy versus surgery alone for solely grade 3 soft tissue sarcomas, respectively, but this was not shown for grade 2 tumors using the Fédération Nationale des Centres de Lutte Contre le Cancer grading system (Italiano et al, 2010). A recent phase 3 study was completed by the European Organisation for Research and Treatment of Cancer (EORTC) (study 62931) in which 351 patients with macroscopically completely resected grade 2 to 3 tumors in the absence of metastatic disease were randomized to postoperative chemotherapy using ifosfamide and doxorubicin versus observation (Woll et al, 2007). The interim analysis of this study revealed no survival benefit to postoperative chemotherapy in patients with high-grade soft tissue sarcomas (the estimated 5-year recurrence-free survival was 52% in both arms). The finalized analysis of this EORTC collaborative trial is needed to further delineate the role of adjuvant systemic chemotherapy using conventional regimens after complete surgical resection of soft tissue sarcomas.

A number of single-agent (dacarbazine, doxorubicin, epirubicin, and ifosfamide) or combination multiagent regimens (doxorubicin

BOX 59-1 Systemic Chemotherapy Regimens Employed in the Management of Retroperitoneal Sarcomas

SINGLE-AGENT REGIMENS

Dacarbazine
Doxorubicin
Epirubicin
Eribulin
Gemcitabine
Ifosfamide
Liposomal doxorubicin
Pazopanib
Temozolomide
Vinorelbine

MULTIAGENT COMBINATION REGIMENS

AD regimen (doxorubicin, dacarbazine)
AIM regimen (doxorubicin, ifosfamide, mesna)
Gemcitabine and dacarbazine
Gemcitabine and docetaxel
Gemcitabine and vinorelbine
Ifosfamide, epirubicin, mesna
MAID (mesna, doxorubicin, ifosfamide, dacarbazine)

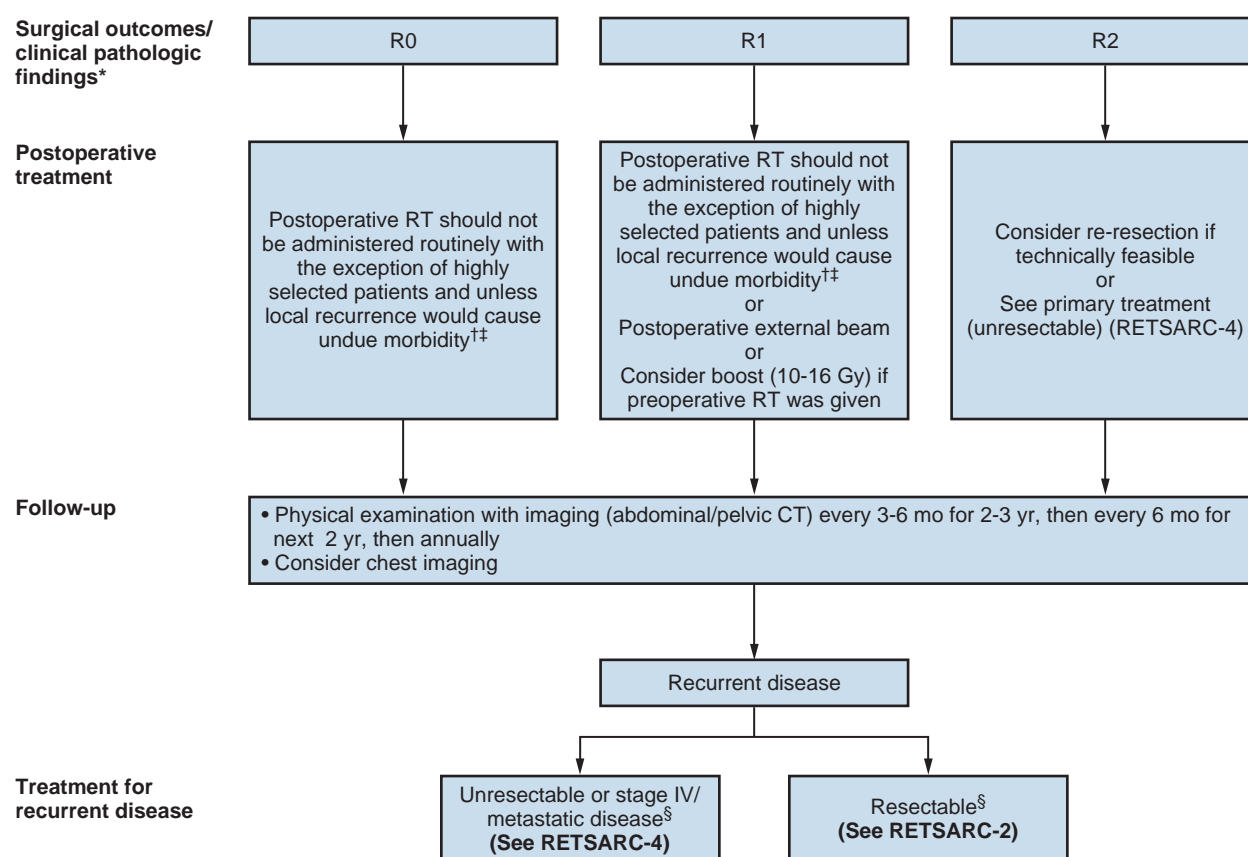
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or epirubicin with either ifosfamide and/or dacarbazine) have been employed in the management of advanced or unresectable soft tissue sarcomas, as shown in Box 59-1 (Von Mehren et al, 2015). In addition, other systemic agents and/or combinations are actively being studied in present prospective trials, including gemcitabine, docetaxel, vinorelbine, pegylated doxorubicin, and temozolomide. Single-agent gemcitabine has been shown to have only moderate efficacy in the management of advanced soft tissue sarcomas (Von Burton et al, 2006), whereas combination systemic regimens employing gemcitabine and docetaxel were more potent in the management of unresectable leiomyosarcomas after disease progression after doxorubicin-based systemic therapies (Hensley et al, 2002). In subsequent studies, this combination regimen of gemcitabine and docetaxel was determined to be effective for a host of other sarcoma subtypes (Leu et al, 2004). In a phase 2 trial, a multiagent systemic regimen of gemcitabine and docetaxel was shown to offer an improvement in both progression-free (6.2 months vs. 3.0 months) and in overall survival (17.9 months vs. 11.5 months) compared to single-agent gemcitabine systemic therapy alone (Maki et al, 2007). A number of other systemic chemotherapeutic drugs, including temozolomide, pegylated liposomal doxorubicin, and vinorelbine, have some activity as single agents in the management of soft tissue sarcomas (Von Mehren et al, 2015). Trabectedin is a newer systemic agent that interferes with DNA binding and has similarly shown some promising phase 2 clinical activity in the management of advanced soft tissue sarcomas (Le Cesne et al, 2005). In addition, trabectedin is presently being investigated in an ongoing multicenter trial as a salvage agent in patients with refractory or relapsing soft tissue sarcomas after standard initial systemic therapy. The finalized data from this trial has yet to be published.

Targeted agents are a new class of drugs that have shown great promise in the management of advanced and/or unresectable soft tissue sarcomas of various subtypes. One of the best studied targeted agents as pertains to soft tissue sarcomas is the tyrosine kinase inhibitor pazopanib (Sleijfer et al, 2009). In a prior phase 3 prospective trial (EORTC 62072), a cohort of patients with metastatic soft tissue sarcoma (N = 369) having failed at least one prior course of anthracycline-based systemic chemotherapy were randomized to either pazopanib or placebo (Van Der Graaf et al, 2011). In the present study, pazopanib was shown to significantly improve progression-free survival versus placebo (20 weeks and 7 weeks, respectively), with a trend toward improved overall survival (11.9 months and 10.4 months, respectively) although this difference did not reach statistical significance. A number of other targeted agents (including imatinib, sunitinib, crizotinib, bevacizumab, and sirolimus) are actively being studied in the management of a host of advanced soft tissue sarcoma subtypes with encouraging results; however, these results remain preliminary at the present time. These systemic agents hence may be worthwhile to consider in select cases as well as always considering active ongoing clinical trials currently available to patients with relapsing or refractory disease after conventional standard first-line therapy.

Surveillance Strategies after Definitive Therapy

After definitive surgical resection, patients must be diligently followed by the multidisciplinary team because patients are at significant risk for local and distant cancer progression. The advent of postoperative predictive tools such as nomograms to estimate the likelihood of recurrence and/or survival in patients with retroperitoneal soft tissue sarcomas after surgical resection has allowed clinicians to tailor their surveillance strategy and adjuvant therapy considerations to the individualized patient (Anaya et al, 2010). The most important determinant of the likelihood of sarcoma recurrence pertains to the surgical margin status. Patients rendered R0, with no residual microscopic disease can be considered for postoperative adjuvant radiotherapy in highly selected cases, but typically such patients are not strongly recommended adjuvant radiotherapy and are followed by physical examination and imaging of the abdomen and pelvis (CT with intravenous contrast) every 3 to 6 months for up to 2 to 3 years and thereafter every 6 months for next 2 years and then annually, as shown in the NCCN treatment algorithm shown in Figure 59-3. Such patients should as well be considered for chest imaging (chest radiograph or CT chest noncontrast). In contrast, patients with



*See principles of surgery (SARC-C).

[†]See radiation therapy guidelines (SARC-D).

[‡]For example, critical anatomic surface where recurrence would cause morbidity.

[§]If not previously administered, consider preoperative RT and/or chemotherapy.

Figure 59-3. Algorithm detailing the indications for postoperative and proposed surveillance strategy of retroperitoneal sarcoma after primary treatment. RT, radiotherapy. (Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.1.2015. © 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.)

retroperitoneal/intra-abdominal sarcomas surgically resected but exhibiting microscopic residual disease (R1) should be considered for postoperative adjuvant radiotherapy, particularly if they had not received preoperative neoadjuvant radiotherapy or a boost dose (10 to 16 Gy) if neoadjuvant radiotherapy had been delivered. Such patients should similarly be followed by physical examination and imaging of the abdomen and pelvis (CT with intravenous contrast) every 3 to 6 months for up to 2 to 3 years and thereafter every 6 months for next 2 years and then annually. Chest imaging (chest radiograph or CT chest noncontrast) should be offered as well to such patients. As discussed in the prior section, patients with gross residual (R2) disease should be strongly advocated to undergo a repeat resection if deemed feasible and thereafter be carefully followed as advocated for patients with R1 disease.

KEY POINTS: TREATMENT

- Definitive surgical resection remains the standard primary treatment of most primary retroperitoneal soft tissue sarcomas deemed resectable.
- If, after multidisciplinary team review, a retroperitoneal sarcoma is deemed not surgically resected with negative surgical margins, preoperative (neoadjuvant) radiotherapy and/or systemic therapy should be considered.
- It is essential that surgeons conducting retroperitoneal sarcoma surgery strictly adhere to the principle of surgical resection with negative margins with the removal of all involved organs.
- Recommendations pertaining to adjuvant radiotherapy should be individualized and not solely based on margin status at time of the original or subsequent repeat resection.
- It is imperative to understand that adjuvant radiotherapy should not be considered a compensation for incomplete or poorly conducted surgical resection.
- Most of the data supporting the benefits imparted to adjuvant systemic chemotherapy in terms of recurrence-free survival among patients with soft tissue sarcomas pertains to extremity soft tissue sarcomas.
- The most important determinant of the likelihood of a retroperitoneal sarcoma recurrence pertains to the surgical margin status.
- Patients with retroperitoneal/intra-abdominal sarcomas surgically resected but exhibiting microscopic residual disease (R1) should be considered for postoperative adjuvant radiotherapy.

CONCLUSIONS

The management of retroperitoneal soft tissue sarcomas has evolved dramatically in recent years, with the role of preoperative imaging (and/or surgical) biopsy often being beneficial in cases in which the diagnosis is in question or in delineating the potential merit of preoperative (neoadjuvant) radiotherapy and/or chemotherapy in either poorly differentiated tumors or in those in which resectability is in question (using a systemic regimen specifically directed to that sarcoma subtype). It is imperative for surgeons embarking in retroperitoneal sarcoma surgery to understand the prognostic importance of complete surgical resection, with negative gross and microscopic surgical margins; in this regard, the extent of surgical resection may be quite extensive at times, requiring surgeons to have a wide surgical skill set in gastrointestinal, vascular, orthopedic, and reconstructive techniques. Retroperitoneal soft tissue sarcomas are rare tumor types; therefore we encourage centers and urologists caring for such patients to discuss these cases as part of multidisciplinary treatment teams such that the proper integration of suitable therapies is adopted when appropriate to optimize treatment-specific outcomes. Finally, new systemic therapy combinations and targeted agents are redefining the treatment approach to advanced soft tissue sarcomas; hence the treatment outlook for such patients is believed to be significantly more promising in the years to come.

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The complete reference list is available online at www.expertconsult.com.



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Historical Perspective

Preoperative Evaluation and Preparation

Surgical Approaches

Surgery for Benign Diseases

Surgery for Malignancy

HISTORICAL PERSPECTIVE

Kidney-related diseases have significantly helped our understanding of the normal physiology of the kidney. As a result of better understanding of the pathophysiology and anatomic structures of the kidney, surgical approaches to management of renally related disease have evolved. From the first successful nephrectomy in 1869 for management of ureterovaginal fistula to the first radical nephrectomy, renal vasculature and caval reconstructions and advances made in retroperitoneal and transabdominal approaches for renal surgery have all stemmed from improved understanding of the surgical anatomy of the kidney and its surrounding structures. Therefore, for appropriate decision making in the perioperative period, detailed knowledge of the renal anatomy is paramount. Since renal anatomy has been discussed in detail in the anatomy chapters of this book, it will not be repeated here and the reader is referred to those chapters for review and understanding of the important surgical anatomic landmarks necessary for renal surgery.

PREOPERATIVE EVALUATION AND PREPARATION

Prior to any renal surgery, a global assessment of the patient's renal function is important. Routinely, preoperative urinalysis, urine culture, and serum creatinine (SCr) and hemoglobin should be evaluated. Patients with locally advanced or metastatic disease should be screened for hepatic dysfunction (Stauffer syndrome) and any associated coagulopathy. Patients' renal function can be evaluated by estimating the glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease Study equation (Levey et al, 1999):

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})$$

Those in good health with two normally functioning kidneys are at low risk of requiring postoperative dialysis following open renal surgery; however, patients with GFR less than 60 mL/min or significant proteinuria are at increased risk of requiring dialysis. As a result, perioperative consultation with a nephrologist can be most useful in optimizing a patient's renal function pre- and postoperatively.

Assessment of cardiac and pulmonary status is important prior to any surgery, but because of the potential for significant cardiopulmonary compromise resulting from intraoperative positioning,

potential for blood loss, and possible fluid shifts, particular care needs to be taken to maximize cardiopulmonary function preoperatively (Fleisher et al, 2007a, 2007b).

In the modern era, cross-sectional imaging is a necessary step prior to any renal surgery (Bradley et al, 2011). Computed tomography (CT) and/or magnetic resonance imaging (MRI) studies are useful for proper surgical planning and assessment of renal parenchyma, renal pelvis and ureter, and renal vasculature (Fig. 60-1) (Derweesh et al, 2003; Herts, 2005).

Renal artery embolization (RAE) has been employed for palliation of inoperable renal tumors in order to control bleeding for large locally advanced renal tumors (Fig. 60-2 on the Expert Consult website) (Klimberg et al, 1985). In addition, RAE has been utilized to aid in surgical dissection of large renal tumors (Wszolek et al, 2008). Possible benefits of RAE prior to nephrectomy include shrinkage of an arterialized tumor thrombus to ease surgical removal, reduced blood loss, facilitation of dissection as a result of tissue plane edema, and ability to ligate the renal vein before the renal artery. However, because postinfarction syndrome, which includes flank pain, nausea, and fever, occurs in approximately three fourths of patients, RAE is not utilized by all surgeons, and in some retrospective series RAE is associated with high blood loss, possibly secondary to the increased edema associated with the infarcted renal tissue (Schwartz et al, 2007).

Surgical site infection can be minimized by following the American Urological Association's guidelines (Wolf et al, 2008). A single dose of cefazolin or clindamycin for patients undergoing renal surgery with negative urine culture is prescribed. Any active urinary tract infection should be treated preoperatively.

Prophylactic Measures

Mechanical bowel preparation is not indicated for open renal surgery unless there is concern about intestinal involvement of a pathologic process or iatrogenic intestinal trauma is likely because of multiple prior abdominal surgeries, with likely requirement of extensive lysis of adhesions. When bowel preparation is utilized, potential adverse effects need to be taken into consideration, including chronic renal deficiency particularly in older adult individuals (Heher et al, 2008). For renal surgeries that may require long postoperative care and management in the intensive care unit, prophylaxis with proton pump inhibitors or sucralfate has been shown to reduce gastric stress ulcers (Bredenoord et al, 2013).

While there is little evidence to support the use of thromboembolic prophylaxis for renal surgery, extrapolation from other similar surgeries suggests that routine use of intermittent pneumatic compression devices is useful to reduce the risk of

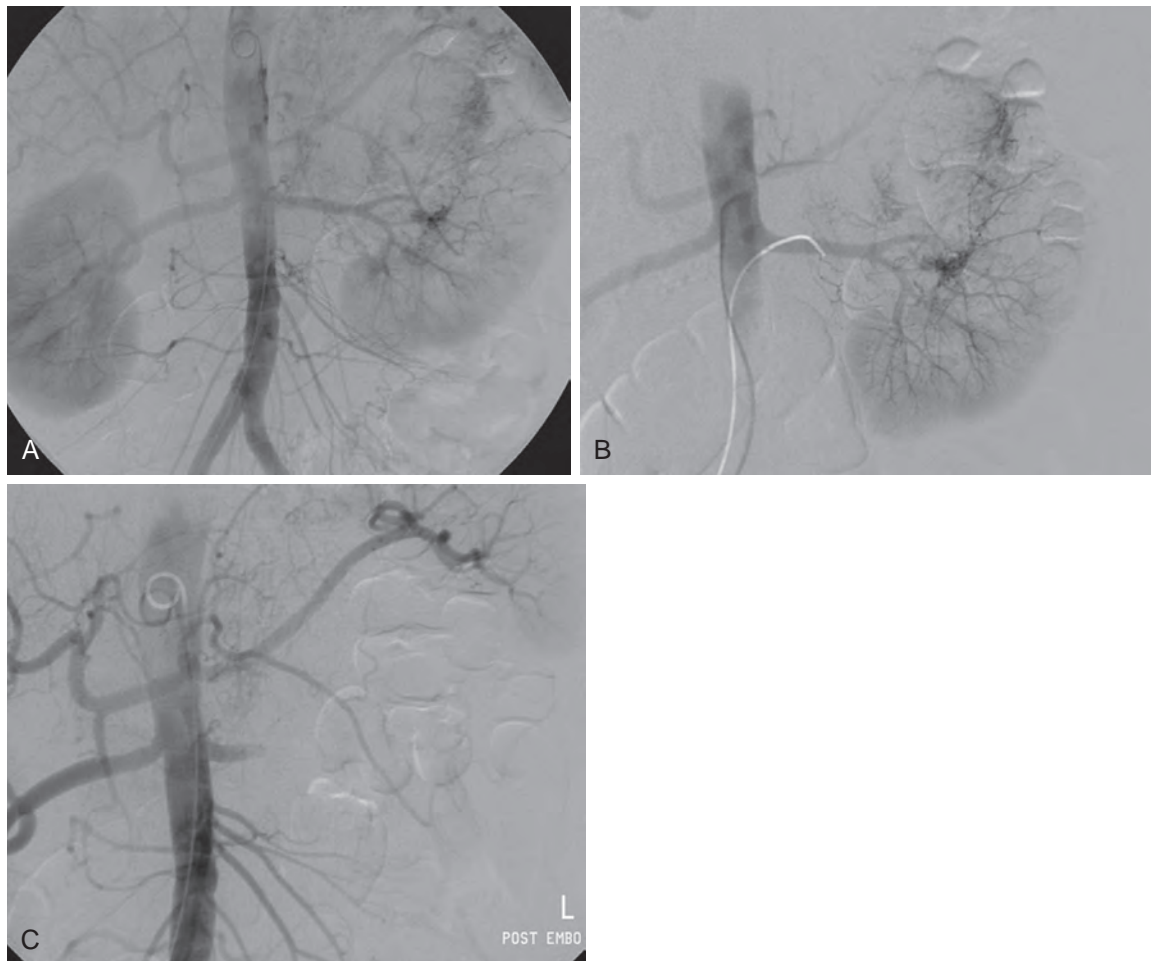


Figure 60-2. A, Aortogram in a patient with a left hypervascular renal mass. Note the pooling of contrast medium in the upper pole. B, Left selective artery angiogram before coil placement. C, Aortogram after coil placement demonstrating abrupt cutoff of flow from the left renal artery.

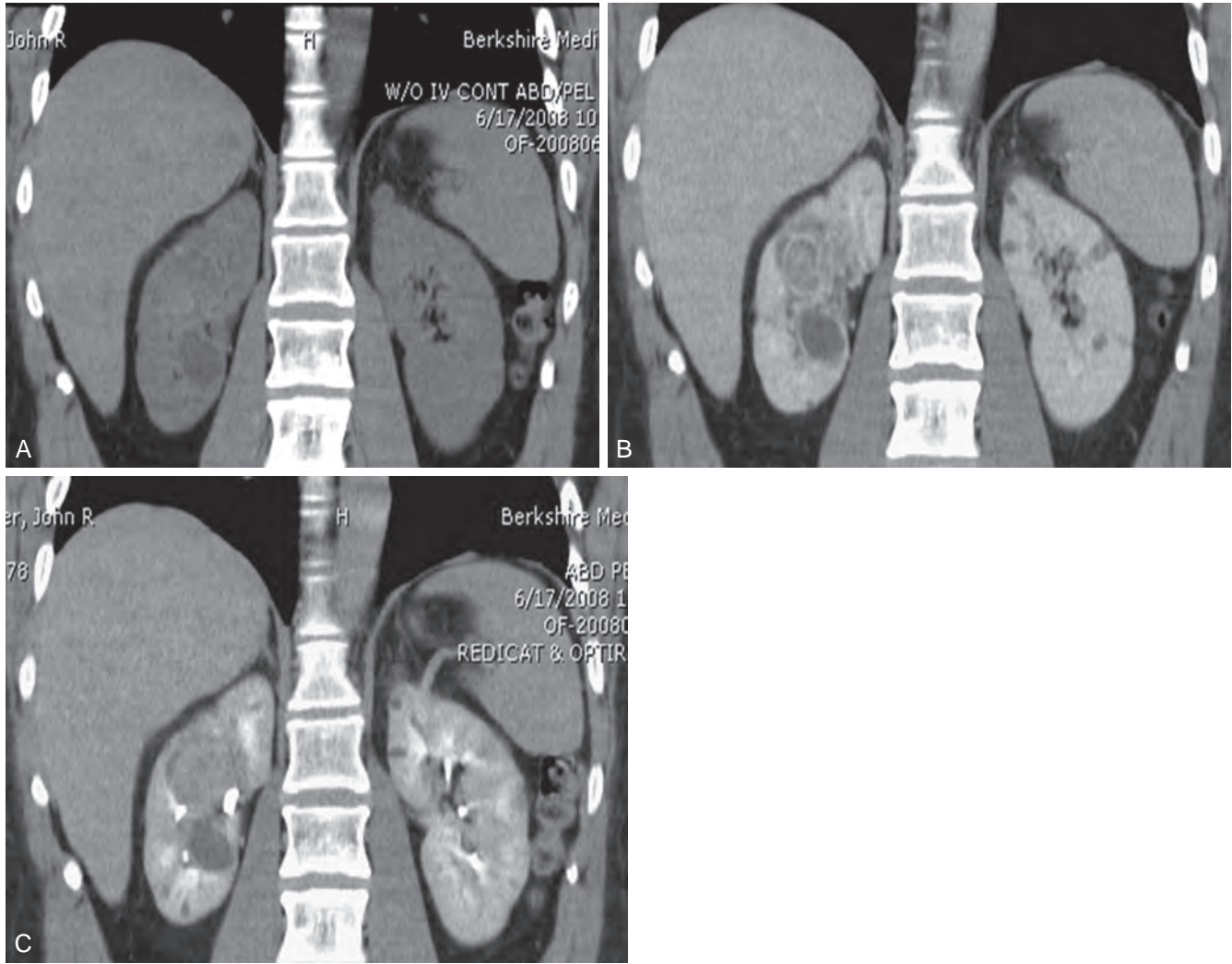


Figure 60-1. A, Preoperative computed tomography imaging demonstrates a large (4-cm) hilar lesion during a noncontrast film in a patient with a history of von Hippel-Lindau disease. B, Contrast administration demonstrates enhancement of a large intrarenal mass and nearby simple cyst. C, Delayed images depict close proximity to collecting system.

postoperative deep venous thrombosis. The American College of Chest Physicians advises pharmacologic therapy once the bleeding risk has diminished (Geerts et al, 2008). The American Urological Association recommends use of mechanical prophylaxis in all patients undergoing open surgery and consideration of pharmacologic prophylaxis in patients with elevated risk for deep venous thrombosis.

For cigarette smokers who are anticipating elective open renal surgery, if time permits, a 4- to 6-week preoperative smoking cessation program has been shown to reduce postoperative complications. Other strategies to reduce postoperative respiratory complications include the use of incentive spirometry in high-risk patients or simply deep breathing exercises in low-risk individuals (Overend et al, 2001).

Surgical Instruments

Self-retaining retractors (Omni-Tract, Omni-Tract Surgical, St. Paul, MN; Bookwalter, Codman & Shurtleff, Raynham, MA; or Balfour, Sklar Surgical Instruments, West Chester, PA), long genitourinary surgical instruments, bulldog and/or Satinsky vascular pedicle clamps, surgical clips, and a suction drain are common instruments available and used for most open renal surgeries.

SURGICAL APPROACHES

Adequate exposure is the hallmark of effective open renal surgery. Anatomic knowledge and consideration of adjacent visceral organs during the surgical approach are critical for safe surgical management. For right kidney surgery, the liver, colon, and duodenum serve as critical landmark structures, and for left kidney surgery, the spleen, tail of the pancreas, and colon need to be heeded. Proper incision and exposure minimize the amount of required retraction and minimize the likelihood of retractor-related injuries. The ideal surgical approach is one that is tailored not only to the operation being performed but also to the anatomy as defined on preoperative imaging, previous surgical history, body habitus, and presence of limiting factors such as kyphoscoliosis or pulmonary disease (Wotkowicz and Libertino, 2007).

Flank Approaches

For a flank incision, with the patient in the lateral decubitus position, the table is flexed between the iliac crest and costal margin. With the kidney bar raised, the structures of the retroperitoneum are better exposed; however, care needs to be taken to avoid injury to a previously repaired contralateral kidney.

Flank approaches may not be ideal in patients with preexisting cardiopulmonary deficits because exaggerated lateral decubitus positioning may compromise pulmonary function and venous return to the heart. In patients with severe kyphosis, the flank approach may not allow proper exposure of the retroperitoneum and may lead to unanticipated pressure on the flank and vertebral bones. Therefore, the surgeon needs to be familiar with other approaches and tailor the incision for each individual case.

Subcostal Flank Approach

The subcostal approach provides excellent exposure to the proximal ureter and renal parenchyma. It is well suited for approaches to the lower renal pole, ureteropelvic junction, and proximal ureter. However, access to the renal hilum is poor, making the subcostal approach somewhat limiting for management of large renal masses. In addition, it is not an ideal approach for partial nephrectomy, since excellent exposure and access to the renal hilum are required (Fig. 60-3).

After induction of anesthesia, insertion of an endotracheal tube, and introduction of a Foley catheter into the urinary bladder to monitor urine output, the patient is placed in the lateral decubitus position. The head is supported to avoid excess flexion at the cervical spine. A kidney bar can be employed if necessary; the tip of the 12th rib should be positioned over the kidney bar (Fig. 60-4 on the Expert Consult website). The patient's back is supported by a rolled blanket or surgical beanbag. To preserve stability and prevent forward roll, the dependent leg is flexed at the hip and knee and the top leg is kept straight. A pillow is placed between the knees. An axillary roll is deployed just caudal to the axilla to prevent compression or injury of the axillary neurovascular bundle. Other pressure points, including the upper foot, are padded with foam. The nondependent arm should be placed on a padded Mayo stand so that the arm is horizontal with slight forward rotation at the shoulder. The bed is flexed until the flank muscles are under stretch. The bed is placed in Trendelenburg position so that the flank is rendered parallel to the floor. The patient is secured to the mobile part of the operating table with 2-inch-wide adhesive tape, which fixes the patient in place while allowing adjustment of flexion.

After sterile preparation and draping, the skin incision begins at the costovertebral angle, approximately at the lateral border of the sacrospinalis muscle just inferior to the 12th rib. The incision is made a fingerbreadth below and parallel to the 12th rib and is carried onto the anterior abdominal wall. In an attempt to avoid the subcostal nerve, the incision can be curved gently downward at

the midaxillary line. If needed, the incision can be extended caudally or medially to the lateral border of the rectus abdominis.

The incision is carried sharply through the subcutaneous tissue, exposing the fascia of the latissimus dorsi and external oblique muscles. Electrocautery is used to incise the muscles in the line of the incision, starting with the latissimus dorsi posteriorly (Fig. 60-5 on the Expert Consult website). The posterior inferior serratus muscles, which insert into the lower four ribs, are also encountered in the posterior portion of the wound and transected. In the anterior aspect of the wound the external oblique muscle is divided. These maneuvers expose the fused lumbodorsal fascia, which gives rise to the internal oblique and transversus abdominis muscles. The lumbodorsal fascia and internal oblique muscle are divided (Fig. 60-6). By using two fingers inserted into an opening created in the lumbodorsal fascia at the tip of the 12th rib, the peritoneum is swept medially as the transversus abdominis is split digitally. The subcostal nerve should be identified between the internal oblique and transversus abdominis muscles and spared (Figs. 60-7 and 60-8).

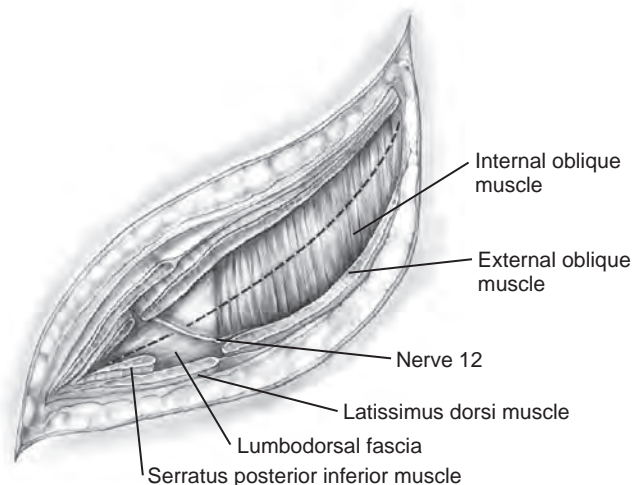


Figure 60-6. Dissection through flank muscles. (From Libertino JA, editor. *Reconstructive urologic surgery*. 3rd ed. Philadelphia: Mosby; 1998.)

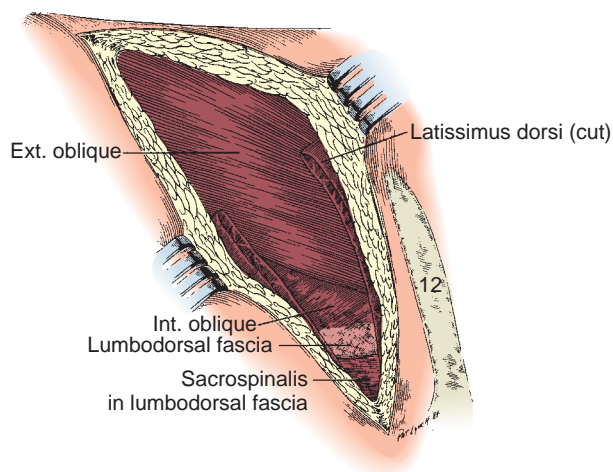


Figure 60-3. Left subcostal incision. The latissimus dorsi muscle has been divided to expose the lumbodorsal fascia and the posterior aspects of the abdominal muscles.

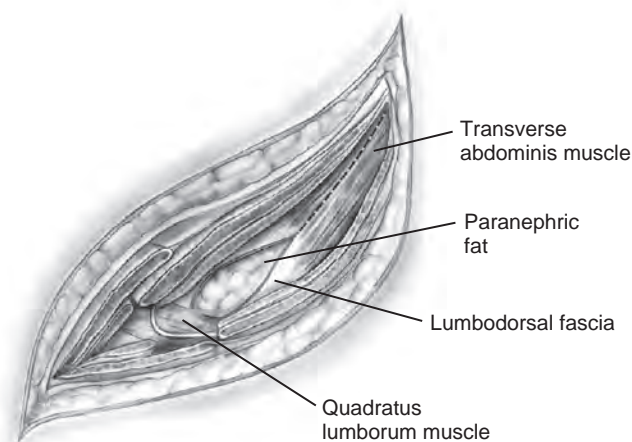


Figure 60-7. Opening lumbodorsal fascia to gain entrance to retroperitoneum. (From Libertino JA, editor. *Reconstructive urologic surgery*. 3rd ed. Philadelphia: Mosby; 1998.)

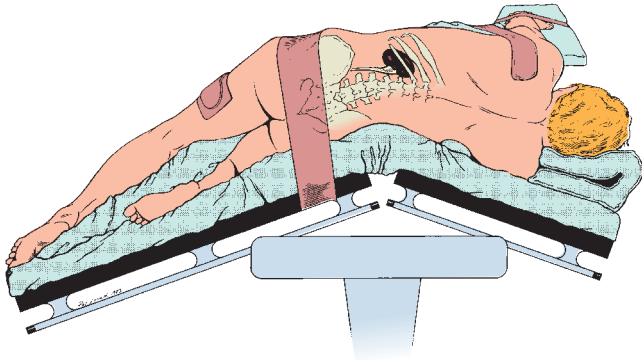


Figure 60-4. Position of the patient for the flank approach. Note the axillary pad. The kidney bar may be elevated if further lateral extension is needed.

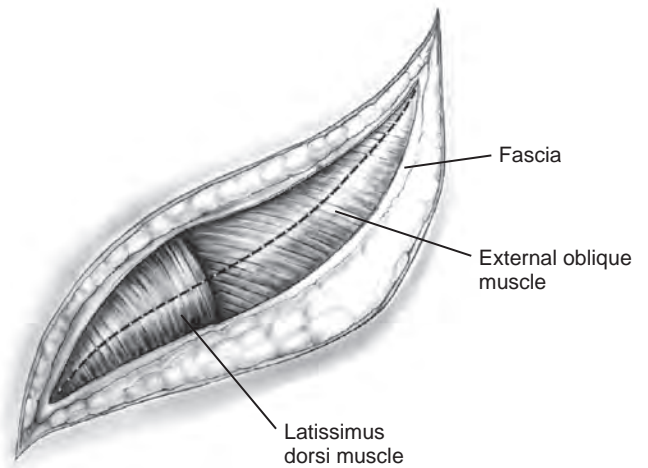


Figure 60-5. Superficial incision through flank. (From Libertino JA, editor. *Reconstructive urologic surgery*. 3rd ed. Philadelphia: Mosby; 1998.)

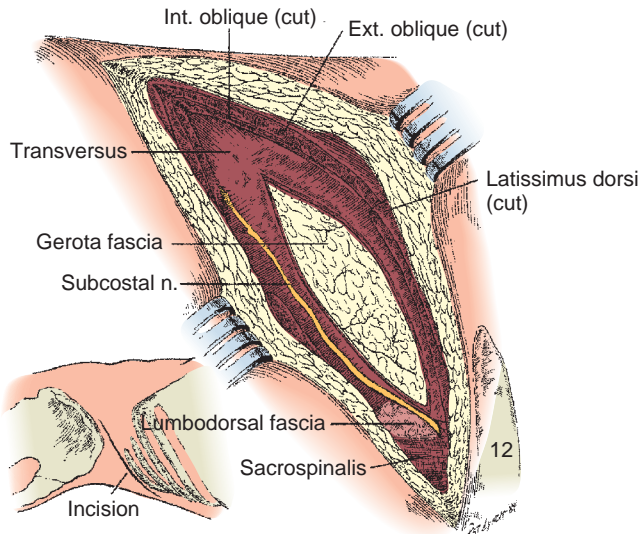


Figure 60-8. The lumbodorsal fascia and transverse abdominal muscle have been divided to expose the Gerota fascia. The subcostal nerve and vessels pierce the lumbodorsal fascia posteriorly and course forward on the transverse abdominal muscle.

To maximize exposure in the posterior aspect of the incision, one may incise the posterior angle of the lumbodorsal fascia, exposing the sacrospinalis and quadratus lumborum muscles. Dividing the costovertebral ligament permits superior retraction of the 12th rib if enhanced exposure is deemed necessary. A Bookwalter flank retractor is used for exposure.

Supracostal Flank Approach

The supracostal flank incision (above the 11th or 12th rib) is favored by many open renal surgeons. An extraperitoneal, extrapleural approach can potentially minimize postoperative complications and lead to a more rapid recovery. [Turner Warwick \(1965\)](#), who popularized the approach, believed that the supracostal approach provides maximal posterior exposure, simplifies wound closure, and is less morbid than a transcostal incision requiring rib resection. More recently, an 8-cm modified mini-flank supra-11th rib incision has been described as a safe, effective approach to radical or partial nephrectomy for renal cortical tumors ([Diblasio et al, 2006](#)).

The level of the incision is determined by the patient's anatomy, the location of the lesion, and the planned procedure. Positioning is similar to that described for the subcostal flank approach.

A skin incision at the superior aspect of the 12th or 11th rib is made, beginning at the lateral border of the sacrospinalis muscle and continuing until the lateral border of the ipsilateral rectus abdominis muscle. The incision is carried through the subcutaneous tissue. The latissimus dorsi and posterior inferior serratus muscles are transected in the posterior aspect of the wound, revealing the intercostal muscles.

The external and internal oblique muscles are divided. The lumbodorsal fascia is opened at the tip of the rib to avoid both peritoneum and pleura. Moving medially, the transversus abdominis muscle is divided carefully while sweeping the peritoneum medially and inferiorly. The diaphragm is exposed by transection of the transversalis muscle. The pleura is identified between the divided transversus abdominis muscle and the diaphragm and can be mobilized superiorly.

The lateral aspect of the sacrospinalis is identified and is either incised or retracted to permit access to the neck of the rib and its attachments. Division of the intercostal muscles should start at the most distal aspect of the rib and proceed toward the spine. The corresponding intercostal nerve is identified and spared. To avoid the neurovascular bundle, the intercostal muscles are divided in

close proximity to the superior aspect of the rib. The plane between the chest wall and pleura is developed by entering the investing fascia surrounding the intercostal nerve, which allows an extrapleural dissection ([Fig. 60-9](#) on the Expert Consult website). The slips of the diaphragm attached to the inferior ribs are transected.

Dorsal Lumbotomy Approach

This approach is typically reserved for pediatric patients and for thin adults requiring bilateral nephrectomy. The advantage to this approach is low morbidity, since no muscle is transected. The main disadvantage is lack of exposure, particularly to the renal hilum and its vessels, making this approach very challenging particularly for obese and muscular individuals and patients with high-riding enlarged kidneys ([Andaloro and Lilien, 1975](#); [Gardiner et al, 1979](#); [Novick, 1980](#)).

The patient is first anesthetized and intubated in the supine position. The patient is then rolled into the prone position (ventral decubitus/ventral recumbent position) with the help of several operating room personnel and the operating table is flexed approximately 10 degrees. The arms may be tucked inward or positioned and supported cranially in an overhead swimming position. To protect the face and endotracheal tube, a C-shaped face support or doughnut-shaped foam pad may be used. The head can be rotated sideways or face downward. Eyes and ears are appropriately padded. To avoid axillary plexus injury, the humerus should not be forced into the axilla. The elbow should be flexed approximately 90 degrees and padded to prevent ulnar nerve injury. The knees should be padded and, to avoid pressure injury to the toes, the ankles should be supported and raised so that the toes do not touch the operating table. If necessary, the breasts should be displaced medially and cranially. Women who are pregnant or lactating, have breast implants, are obese, or have enlarged breasts are at risk of trauma to their breasts. The penis and scrotum should not be compressed by the body weight. In cases in which there are bowel/urinary abdominal stomas, extreme care should be taken to avoid excess pressure on these structures. In such cases, longitudinal torso frames/rolls should be used to minimize pressure from the anterior chest/abdominal structures.

The prone position may be poorly tolerated by older adults, patients with cervical spine pathology, patients with unstable chest walls following trauma, and patients with a known thoracic outlet syndrome. From a cardiovascular standpoint, the thoracic outlet syndrome (resulting from an anomalous cervical rib or some other anatomic reason) can occur particularly when the arms are located in the swimmer's position and the head is turned to one side. Because of increased pressure on the sternum, unanticipated pressure may be generated on the mediastinum, reducing coronary blood flow. Hemodynamically, the central venous pressure may rise, resulting in venous engorgement and potentially increased bleeding. From a respiratory standpoint, an increased amount of work is required to breathe when prone, an endotracheal tube can be displaced accidentally, and the risk of venous air embolism from central lines is increased. From a neurologic standpoint, rotation of the head can modify the cerebral blood flow and place the patient at risk of cerebral ischemia.

The dorsal lumbotomy approach is an anatomic approach to the kidney, with incision of fascial planes rather than muscle ([Fig. 60-10](#)). A vertical skin incision is made from the inferior border of the 12th rib to the iliac crest, in line with the lateral border of the sacrospinalis muscle. The subcutaneous tissues are divided, exposing the latissimus dorsi muscle. The aponeurosis of the latissimus dorsi is separated from the posterior layer of the lumbodorsal fascia where it overlies the sacrospinalis muscle. The posterior layer of the lumbodorsal fascia, a strong fascial covering, is incised, which allows the sacrospinalis muscle to be retracted medially. The costovertebral ligament is divided, which permits superolateral retraction of the 12th rib, which improves access superiorly. The fused middle and anterior layers of the lumbodorsal fascia are divided, permitting the quadratus lumborum muscle to be retracted medially. The ilio-inguinal nerve should be identified and spared. Entry into the

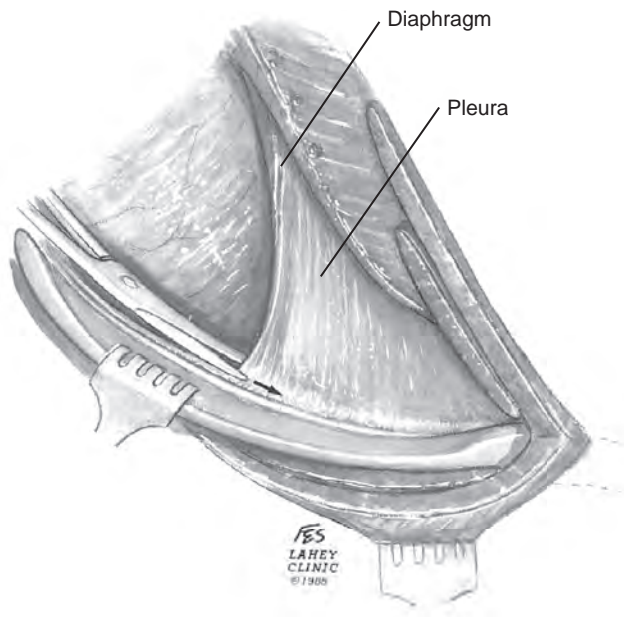


Figure 60-9. Following the intercostal nerve to remain extrapleural back to the intercostal ligament. (© The Lahey Clinic.)

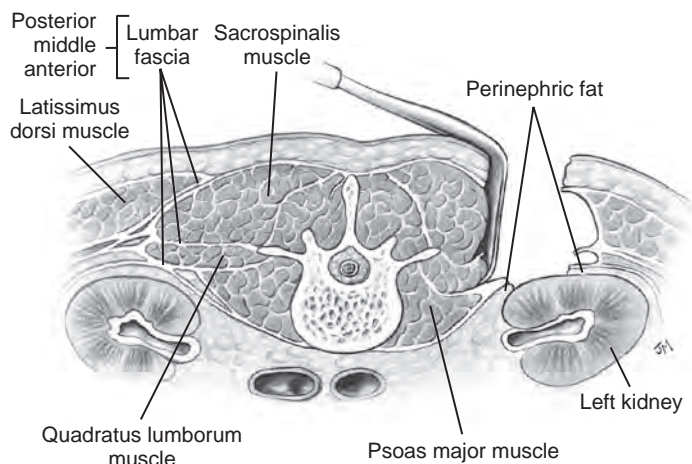


Figure 60-10. Cross-sectional view of Gil-Vernet approach. (From Libertino JA, editor. *Reconstructive urologic surgery*. 3rd ed. Philadelphia: Mosby; 1998.)



Figure 60-11. Thoracoabdominal incision at the supra-10th rib border with patient in lateral decubitus position.

paranephric space is achieved by incising the transversalis fascia. Division of the perinephric fascia reveals the kidney.

Thoracoabdominal Approach

The thoracoabdominal approach (Fig. 60-11) is ideal for the management of large renal masses, suprarenal or upper pole masses, renal tumors with venous extension, and tumors involving adjacent structures.

The patient is positioned in a semioblique manner as described above for the flank approaches, with a rolled blanket or beanbag supporting the flank. The legs are positioned similar to the traditional flank position. The pelvis is rotated to a more horizontal position than for the flank incisions, at an angle of approximately 45 degrees.

The level of the incision is determined by the nature of the tumor, including size and relationship to surrounding structures. Depending on the location of the tumor, access is gained through the 8th, 9th, 10th, or 11th intercostal spaces. The skin incision begins at the lateral aspect of the sacrospinalis muscle over the 10th or 11th rib and can travel as far as the contralateral rectus abdominis muscle or caudally toward the symphysis pubis.

The internal oblique and transversus abdominis muscles are transected. The underlying peritoneum is opened, and the peritoneal cavity and chest are entered. Staying close to the superior

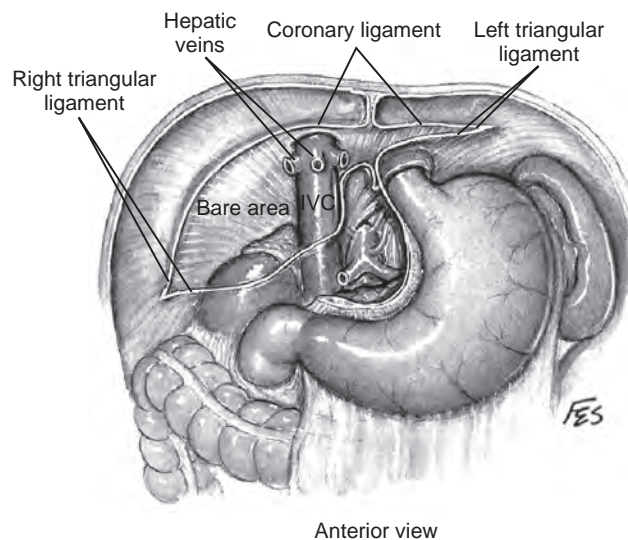


Figure 60-12. Relationship of liver and triangular and coronary ligaments to inferior vena cava (IVC). (© The Lahey Clinic.)



Figure 60-14. The white line of Toldt is incised from the hepatic flexure to the common iliac artery and the ascending colon is reflected medially. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

border of the rib, the intercostal muscles are divided, which exposes the underlying pleura and diaphragm. The pleura is opened sharply, taking care to avoid the lung. The costovertebral ligament is divided. The diaphragm is opened from its thoracic surface. Starting anteriorly and proceeding posteriorly, the diaphragm is opened in a curvilinear fashion staying about two fingerbreadths from the chest wall to avoid injuring the more central phrenic nerve.

The liver or spleen is gently retracted upward. Additional hepatic mobility can be obtained by dividing the coronary ligament and the right triangular ligament of the liver (Fig. 60-12; Fig. 60-13 on the Expert Consult website). For right-sided tumors, the kidney and great vessels are approached by mobilizing the colon medially and Kocherizing the duodenum (Figs. 60-14 and 60-15 on the Expert Consult website; Fig. 60-16). For tumors on the left, the colon and

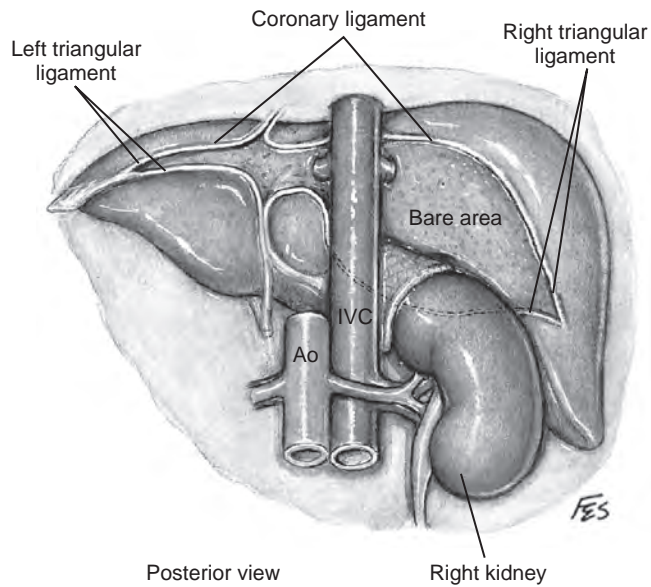


Figure 60-13. Posterior view of relationship of liver and triangular and coronary ligaments to inferior vena cava (IVC). Ao, aorta. (© The Lahey Clinic.)

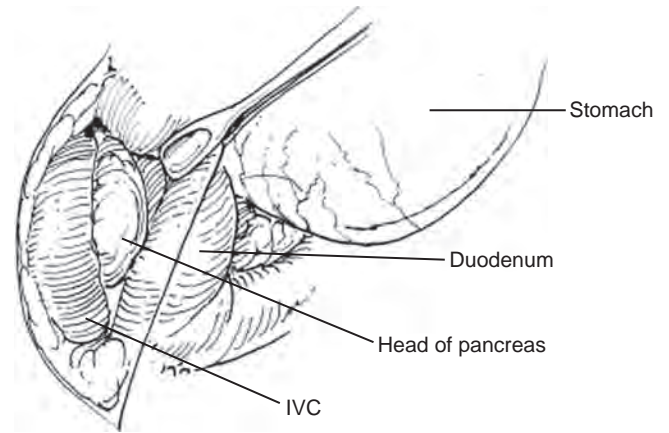


Figure 60-15. For right-sided tumors, the duodenum is exposed and then reflected medially by means of a Kocher maneuver. IVC, inferior vena cava. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

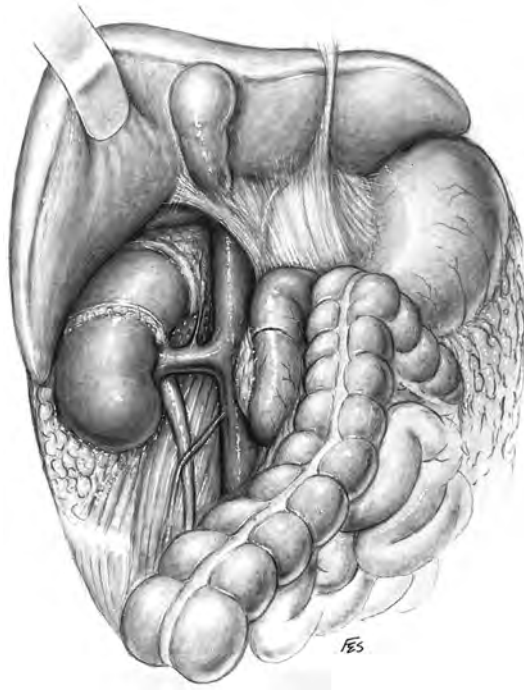


Figure 60-16. Access to the vena cava can be achieved using the Langenbeck maneuver whereby the right triangular and coronary ligaments of the liver are divided, permitting the right lobe of the liver to be rotated medially and cephalad, exposing the retrohepatic inferior vena cava up to the diaphragms. (© The Lahey Clinic.)

the tail of the pancreas are mobilized (Fig. 60-17 on the Expert Consult website; Fig. 60-18).

Anterior Approaches

Anterior Midline Approach

An anterior midline incision is the incision of choice for management of renal trauma because it permits exploration for associated intraperitoneal injuries. It can also be employed for renovascular surgery, for reconstructive procedures, including ileal ureteral replacement, and for bilateral renal procedures.

With the patient in the supine position, a midline skin incision is carried out between the xiphoid process and the symphysis pubis. After dividing the subcutaneous tissues with electrocautery, the linea alba is sharply incised to expose the underlying preperitoneal fat and peritoneum. The peritoneum is grasped with two smooth forceps and incised. The ligamentum teres should be divided and suture ligated.

Control of the renal pedicle can be obtained directly through the posterior parietal peritoneum or by medial reflection of the colon. On the left, the approach involves a vertical incision in the posterior peritoneum below the ligament of Treitz. This space contains the anterior surface of the aorta, the crossing left renal vein, and often the inferior mesenteric vein and gonadal vessels. The superior mesenteric artery should be on the anterior surface of the aorta and is usually 1 to 2 cm cephalad to the left renal vein. Gentle dissection along the hilum at this level provides good vascular control. A second approach to the left renal hilum is through the lesser sac. In this approach, the gastrocolic omentum is divided and entered. The transverse colon can then be retracted inferiorly. The peritoneum below the pancreas can be incised. The vessels are identified. This permits access to the renal pedicle both anteriorly and posteriorly. The artery can be isolated posteriorly and the venous system identified and controlled anteriorly.

Similarly, the right kidney can be reached directly by incision of the hepatic flexure and a Kocher maneuver to free the duodenum

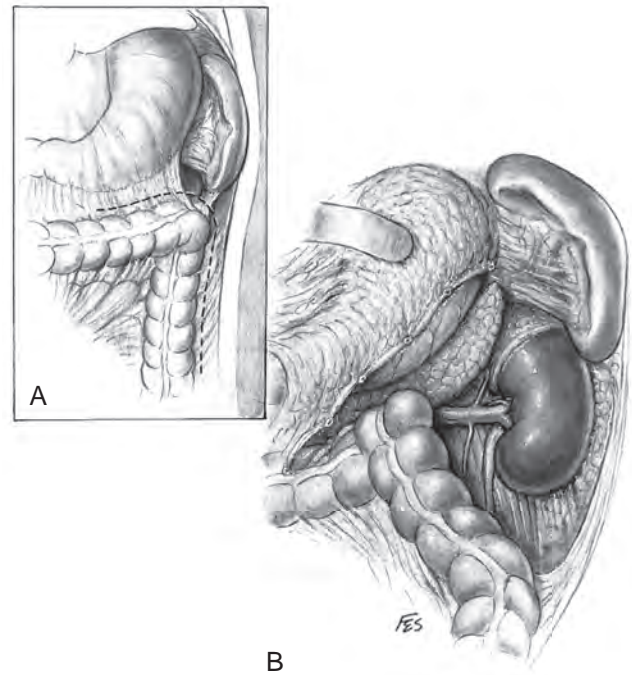


Figure 60-18. A, Left gastrocolic, phrenocolic, and lateral peritoneal attachments are divided. B, Stomach, pancreas, and spleen are gently retracted upward without mobilizing the kidney. (© The Lahey Clinic.)

and reflect it medially. Further incision along the white line of Toldt frees the colon, permitting exposure of the anterior Gerota fascia. After the duodenum is reflected, the anterior surface of the vena cava is exposed. Care is taken not to injure the pancreas, gonadal vein, adrenal vein, or accessory renal vessels. The main renal vein is mobilized. Posterior to the renal vein along its superior margin lies the renal artery (Fig. 60-19 on the Expert Consult website), which normally runs a retrocaval course. The renal artery can be isolated here or between the vena cava and aorta when greater length is required.

Anterior Subcostal Approach

For the anterior subcostal approach, the patient is placed in the supine position. Some surgeons choose to place a rolled blanket underneath the lumbar spine in order to facilitate exposure with hyperlordosis. However, **excessive hyperlordosis can lead to excessive unwanted tension on the great vessels, minimizing blood flow. Also, excessive hyperlordosis may lead to postoperative lower back pain. In patients with spinal stenosis, hyperlordosis is not recommended.** In the supine position, the arms can be tucked at the side or abducted at 90 degrees while supported on arm pads. The elbows should be well protected with adequate padding to avoid ulnar nerve injury.

The supine position can cause several important problems; therefore care should be taken to avoid complications from positioning. The pressure points (occiput, dorsal torso, sacrum, dorsal legs, and heels) should be well padded. From a cardiovascular perspective, supine positioning can result in supine hypotension (aortocaval syndrome) if excess adiposity or abdominal masses compress the great vessels. From a musculoskeletal perspective, low back pain is frequent, particularly in those patients with scoliotic and kyphotic spine deformities. Artificial hip and knee joints may also be placed under stress.

Chevron Incision (Bilateral Anterior Subcostal Approach)

The chevron incision, which is composed of bilateral anterior subcostal incisions, is ideal for renovascular surgery and radical

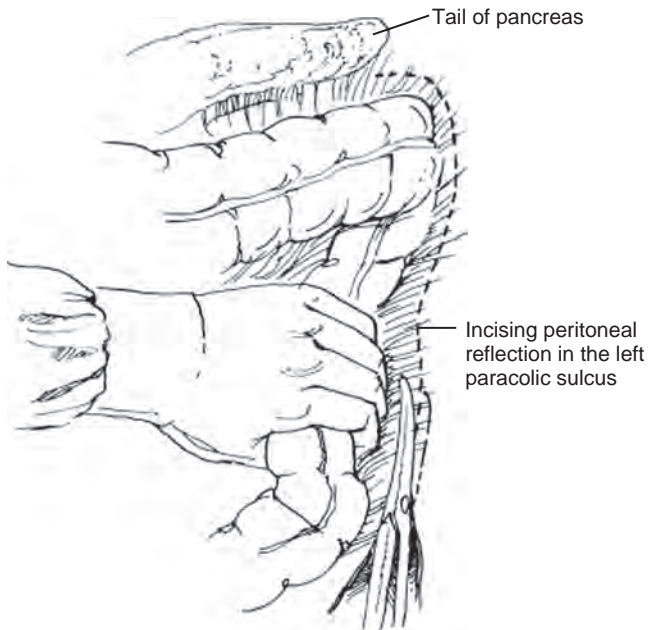


Figure 60-17. For left-sided tumors, the white line of Toldt is incised from the splenic flexure to the common iliac artery and the descending colon is reflected medially. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

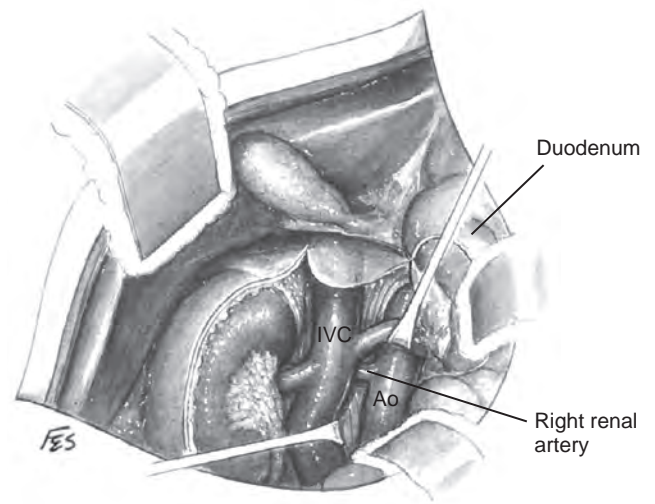


Figure 60-19. Exposure of right renal artery behind overlying left renal vein. Ao, aorta; IVC, inferior vena cava. (© The Lahey Clinic.)

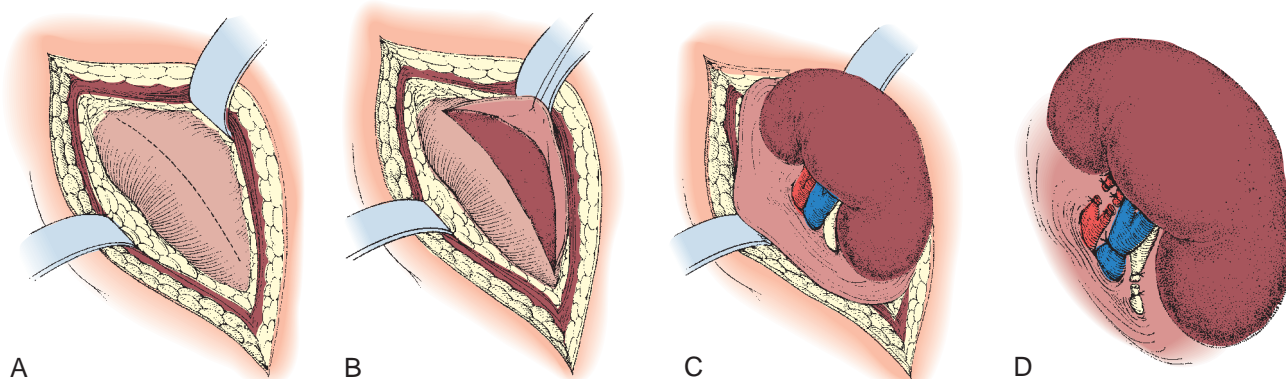


Figure 60-21. A to D, Technique of subcapsular nephrectomy.

nephrectomy with inferior vena cava (IVC) tumor thrombectomy. Exposure of the renal pedicles and great vessels is outstanding. The incision starts at the tip of the 11th rib, extends approximately two fingerbreadths below and parallel to the costal margin, curves superiorly in the midline, travels parallel to the contralateral costal margin, and terminates at the tip of the contralateral 11th rib.

SURGERY FOR BENIGN DISEASES

Simple Nephrectomy

Simple nephrectomy—removal of the kidney within the Gerota fascia—is used to manage nonmalignant diseases of the kidney (Fig. 60-20 on the Expert Consult website). Indications for simple nephrectomy include durable nonfunction or poor function of a kidney as a result of obstruction, infection, trauma, stones, nephrosclerosis, vesicoureteral reflux, polycystic kidney, or congenital dysplasia. Simple nephrectomy of a functional kidney may be employed to relieve intractable symptoms or associated problems, such as bleeding, pain, hypertension, or persistent infection.

Using one of the incisions described above, typically a flank incision, access to the retroperitoneal cavity is obtained. A self-retaining retractor (Finochietto, Bookwalter, or Omni-Tract retractor) is used to expose the visceral organs. The posterior layer of the renal fascia is bluntly dissected from the muscles of the posterior abdominal wall. The anterior layer of renal fascia is dissected from the colonic mesentery and peritoneum, leaving a fascial compartment in which the kidney, adrenal gland, and perirenal fat lie. The renal fascia is incised and the perirenal fat is separated from the kidney using a combination of blunt dissection and electrocautery. Improper entry into the subrenal capsule must be avoided as this can lead to additional bleeding and difficulty in identifying the appropriate surgical planes. The surgeon must beware of aberrant vessels, typically found near the poles and in areas resistant to blunt dissection. In cases in which posterior dissection is difficult because of adherence of the kidney to the psoas muscle, inclusion of the psoas fascia in the dissection may be helpful and necessary. In cases of a large hydronephrotic kidney, in which exposure can be difficult, puncture and aspiration of the renal pelvic contents may decompress and aid mobilization of the kidney. Next, the adrenal gland is dissected from the upper pole of the kidney by maintaining the dissection plane directly on the renal capsule. The superior attachments of the kidney to the spleen, pancreas, and liver are freed to allow safe caudal retraction of the kidney.

Next, the lower pole of the kidney is mobilized and the ureter isolated, and the gonadal vein, usually found adjacent to the ureter, is identified. Care should be taken to mobilize the gonadal vein medially in order to avoid traction injury and avulsion of the vein. Once the inferior pole is mobilized, the ureter can be divided in between surgical clips or 2-0 silk ties. Division of the ureter provides access to the posterior part of the kidney and better exposure of the

renal hilar structures. From a caudocranial approach, the renal vein is usually identified after division of the ureter. Combination of blunt and sharp dissections will allow identification of the renal artery posterior to the renal vein (Fig. 60-21).

Partial Nephrectomy for Benign Disease

Partial nephrectomy, in addition to its common utilization for treatment of small-sized renal cancer, can sometime be used for benign diseases. Some clinical scenarios in which partial nephrectomy may be indicated in benign diseases include hydronephrosis with parenchymal atrophy, atrophic pyelonephritis in a duplicated kidney, infected calyceal diverticulum, segmental traumatic renal injury with irreversible damage, and removal of benign renal tumors (angiomyolipoma or oncocytoma).

Partial nephrectomy for benign disease entities can be approached by excision of the renal capsule from the diseased site. The excised renal capsule can be successfully used for renorrhaphy (Fig. 60-22). Further details and techniques of partial nephrectomy are described in the section on surgery for malignant disease.

Open Nephrostomy

With the advancement in percutaneous nephrostomy tube placements, open surgical insertion of nephrostomy tubes is rare. However, when percutaneous nephrostomy tube placement is not technically feasible and endoscopic placement of a ureteral stent is not an option, open surgical placement of a nephrostomy tube can be a lifesaving procedure (Fig. 60-23 on the Expert Consult website).

Through a retroperitoneal flank incision the Gerota fascia is identified and incised. The kidney is mobilized within the Gerota fascia to expose the posterior surface, and the ureter is identified inferiorly. The ureter is followed superiorly in order to identify the renal pelvis. The renal pelvis is incised after placement of two 2-0 absorbable Vicryl (Ethicon, Cincinnati, OH) holding sutures away from the ureteropelvic junction. Using a hooked scalpel or sharp tenotomy scissors, a 2-cm incision is made parallel to the long axis of the kidney between the holding sutures. Next, a stone forceps is passed through the pyelotomy incision into the lower pole calyx. The tip of the forceps is aimed at the convex border of the kidney, because a nephrostomy on the anterior or posterior surface of the kidney has a higher risk of hemorrhage from damage to intrarenal vessels. While pressure is applied with the forceps, the tip of the forceps is palpated at the convex border of the kidney. A radial capsulotomy is made over the tip of the forceps. The tract through the parenchyma is widened. From the exterior surface of the kidney a Malecot catheter with a threaded 0 silk suture at the tip is guided through the renal parenchyma; the tip is placed in the renal pelvis and the guiding 0 silk suture is removed. The Malecot catheter is secured to the renal capsule using a 3-0 absorbable purse-string suture, and the pyelotomy is closed with 4-0 Vicryl sutures and the

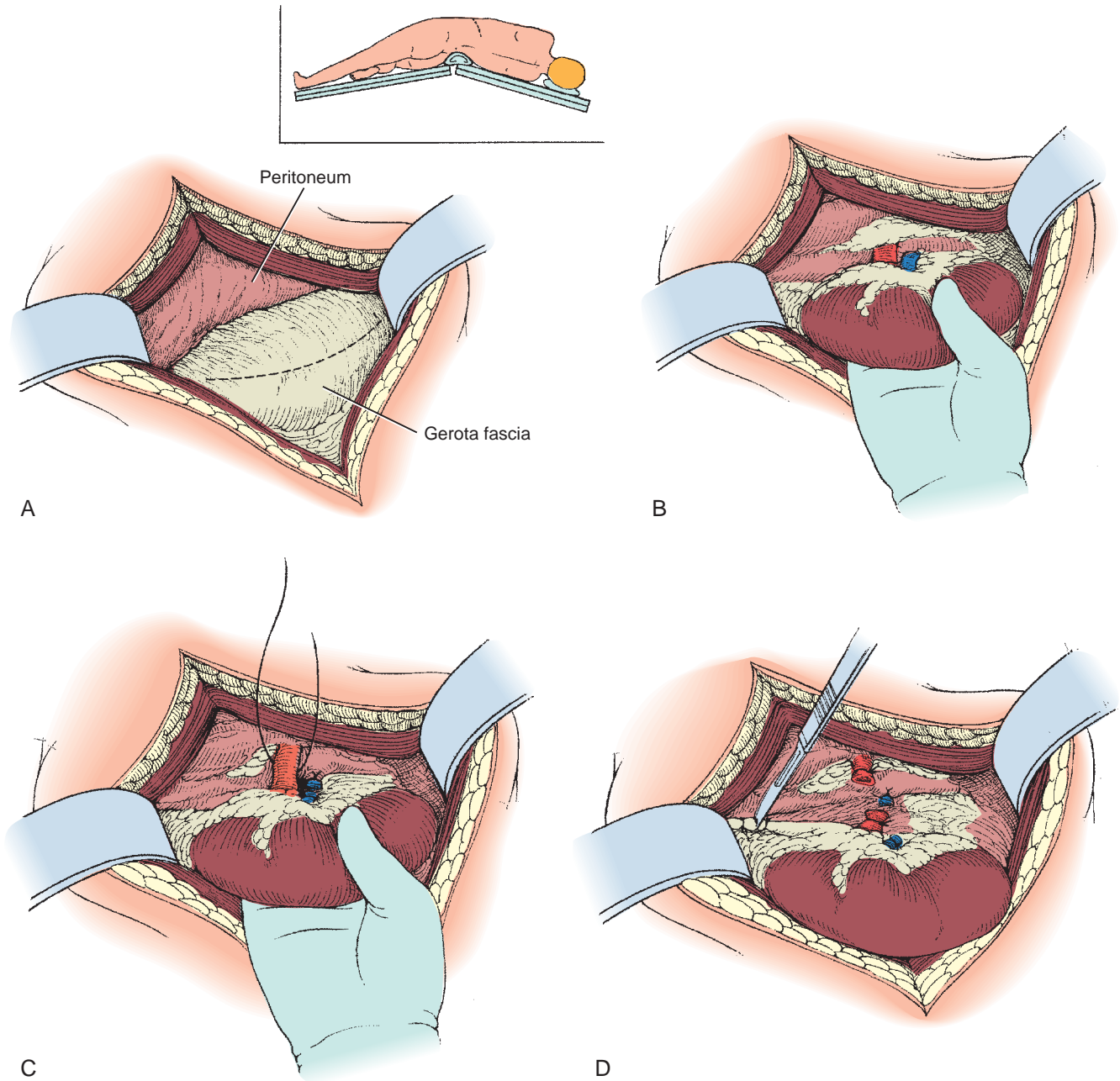


Figure 60-20. A to D, Technique of simple left nephrectomy through an extraperitoneal flank incision.

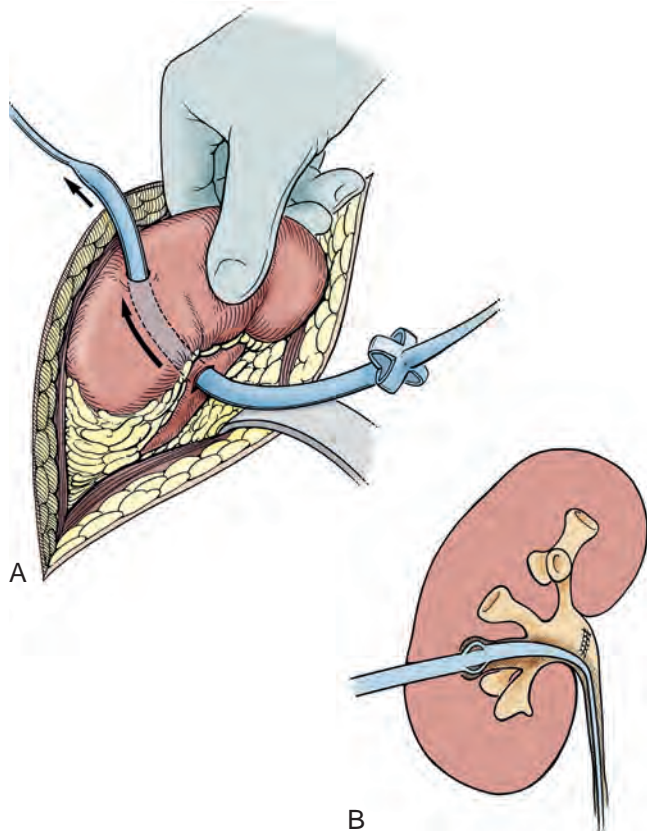


Figure 60-23. A and B, Technique of open nephrostomy tube placement.

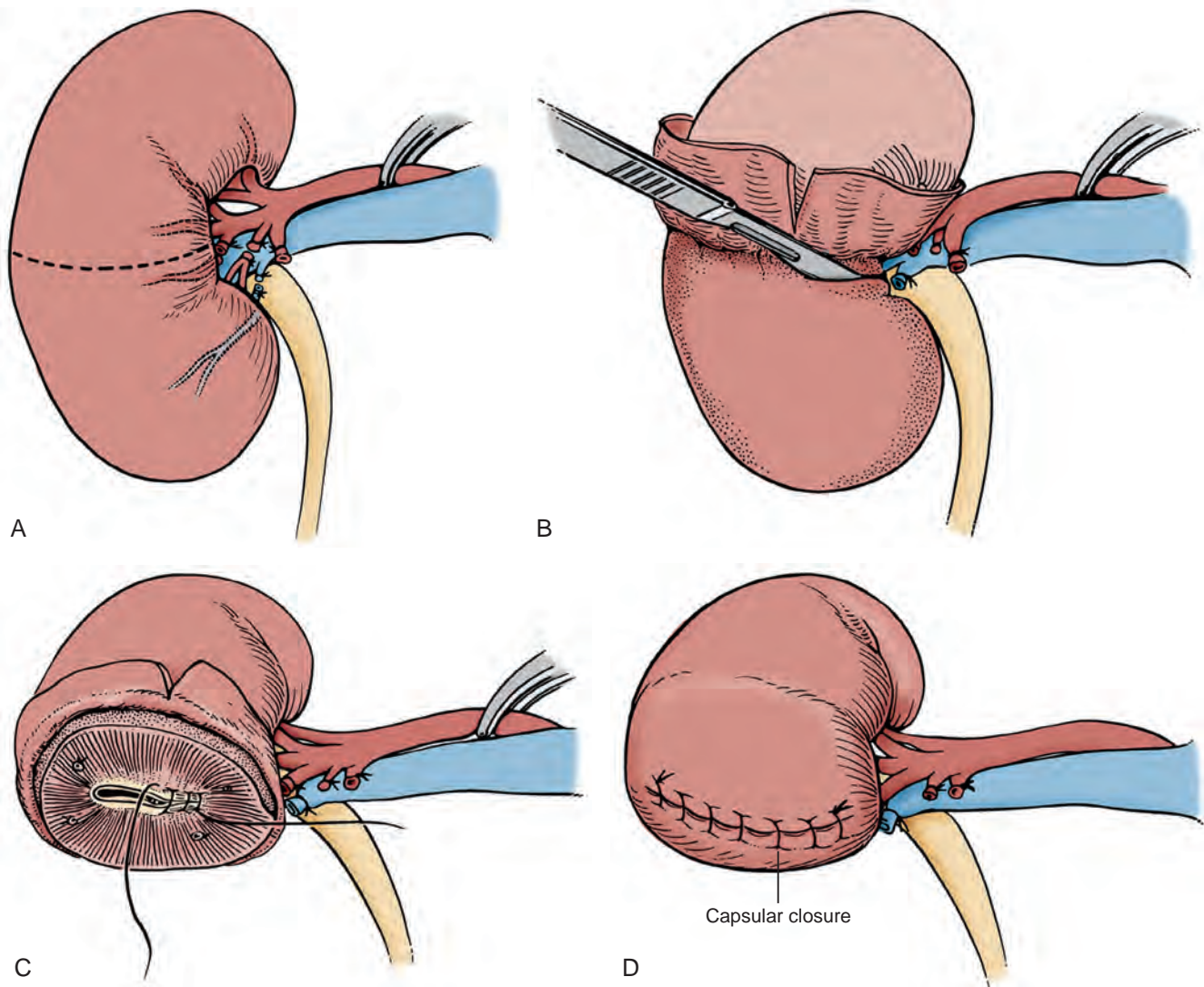


Figure 60-22. A to D, Technique of transverse renal resection for a benign disorder. The renal capsule from the diseased parenchyma is preserved and used to cover the transected renal surface.

holding sutures are removed. The distal end of the Malecot catheter is externalized through a stab incision from the anterior flank, avoiding kinking of the tube to ensure proper drainage. The Malecot catheter is secured to the skin externally using a drain stitch (2-0 silk or 3-0 nylon). A Penrose drain or Jackson-Pratt drain (Cardinal Health, Dublin, OH) is placed in the perinephric area and the flank incision is closed.

Extracorporeal Renal Surgery

Extracorporeal renal surgery (ECRS) with autotransplantation is an operative technique that is rarely used in contemporary urologic practice, since open *in situ* renal exposure with vascular clamping and hypothermia provides excellent access to the kidney for nearly all forms of renal surgery. The advantages of ECRS are better exposure and illumination, a bloodless surgical field, the ability to protect the kidney from prolonged ischemia, and the opportunity to use an operating microscope (Ota et al, 1967; Husberg et al, 1975; Putnam et al, 1975). Currently, ECRS is reserved for reconstruction of complex renal pathologies in cases of a solitary kidney, when percutaneous approaches are not appropriate or possible, and when routine *in situ* operative exposure is inadequate (Fig. 60-24). Additionally, ECRS is used when addressing anatomic problems in a donated kidney that is destined for allogeneic transplantation.

Specific indications for which ECRS may be a valid option are listed below:

Renovascular diseases

- Prolonged ischemia (>45 minutes) is anticipated
- Segmental renal artery disease
- Multivessel disease
- Arteriovenous malformations refractory to embolization
- Large intrarenal arterial aneurysms

Renal transplantation

- Repair of vascular anomaly
- Repair of collecting system anomaly

Malignancy in solitary kidney

- Large, central mass encroaching on the renal pelvis
- Large, central renal pelvic tumor
- Multiple subcortical neoplasms

Preoperative Considerations

Thorough abdominal imaging studies (CT scan and/or magnetic resonance angiogram) should be obtained to fully evaluate the renal parenchyma, collecting system, and vasculature. In select cases, digital subtraction arteriography may be used to evaluate the vascular anatomy.

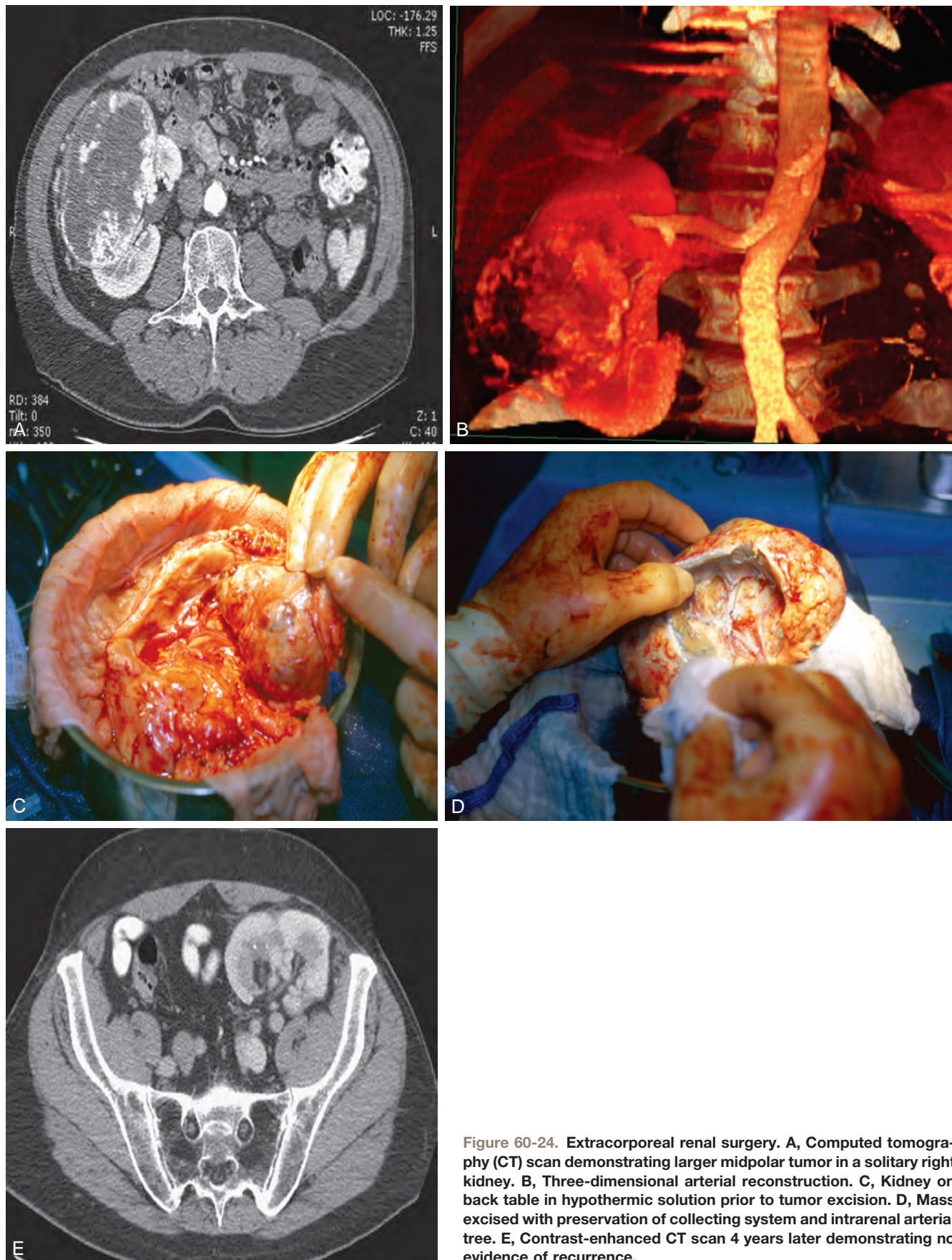


Figure 60-24. Extracorporeal renal surgery. A, Computed tomography (CT) scan demonstrating larger midpolar tumor in a solitary right kidney. B, Three-dimensional arterial reconstruction. C, Kidney on back table in hypothermic solution prior to tumor excision. D, Mass excised with preservation of collecting system and intrarenal arterial tree. E, Contrast-enhanced CT scan 4 years later demonstrating no evidence of recurrence.

The patient's renal function is assessed by serum creatinine level. Strong consideration should be given to obtaining a preoperative nephrology consultation to help maximize renal function preoperatively and to make necessary preparations in case of hemodialysis postoperatively.

A seated operative bench should be available with ice slush, renal transplant preservation solution (e.g., Euro-Collins or UW solution), and microvascular instruments.

Surgical Procedure

Since access to both the retroperitoneum and iliac fossa (for autotransplantation) is required, a number of different single- or double-incision approaches are possible. Following incision and abdominal exploration, the kidney is exposed as for a living related donor nephrectomy. When the kidney is mobilized and the only remaining attachments are the ureter, renal vein, and renal artery, 12.5 g of mannitol and 20 mg of furosemide are rapidly infused intravenously. The ureter is ligated as far distally as possible and transected, preserving as much periureteral tissue as possible. Although the ureter can be preserved intact, we do not favor this approach since it limits positioning the autotransplanted kidney in the opposite iliac fossa, and the long length of ureter is prone to ischemia and kinking leading to obstruction. Vascular clamps are applied to each renal vessel directly where they exit the aorta and IVC (a C-shaped clamp is useful to gain length on the right renal vein) and the renal vessels are transected directly on the clamps.

Immediately after dividing the renal vessels, the kidney is placed on the workbench in a pan of ice slush covered with a towel. The kidney is flushed intra-arterially by gravity flow with renal preservation solution at 6° C. Flushing the kidney should continue until it is cooled and the renal effluent is clear (~500 to 1000 mL). The kidney is kept in the ice slush basin during the procedure to maintain hypothermia.

For renovascular disease, the vasculature of the renal hilum is dissected and vascular repair is done. For neoplasms, the Gerota fascia and the perirenal fat are removed and partial nephrectomy is undertaken. After reconstruction of the renal vasculature or the nephrectomy parenchymal defect is achieved, the renal artery and vein are flushed independently with preservation solution to assess for potential sites of bleeding. Retrograde flushing of the ureter is done to assess for collecting system leaks, which should be repaired if identified.

The kidney may be transplanted into either lower quadrant. The kidney is transferred to the iliac fossa, and the renal vein is anastomosed to the external iliac vein. The renal artery anastomosis can be achieved by either end-to-end anastomosis to the hypogastric artery or end-to-side anastomosis with the external iliac artery.

During the anastomosis, the vessels should be irrigated with heparin solution (10,000 units of heparin in 100 mL of normal saline), and the surgeon should consider injecting 10 mg of verapamil into the renal artery following the anastomosis to help vasodilation. The ureter is implanted into the dome of the bladder with a tension-free anastomosis. Prior to completion of the ureteral anastomosis, a ureteral stent is placed. Finally, a closed suction drain is placed.

SURGERY FOR MALIGNANCY

Radical Nephrectomy

Radical nephrectomy refers to complete removal of the kidney outside the Gerota fascia together with the ipsilateral adrenal gland and complete regional lymphadenectomy from the crus of the diaphragm to the aortic bifurcation as described by [Robson and colleagues in 1969](#) for management of renal malignancy. Today, the adrenal gland is typically spared when technically possible, since removal of the adrenal gland, when not involved by tumor, has not been shown to improve survival of patients with renal cancer. Extensive lymphadenectomy is only done in select cases when it is strongly felt that it may contribute to improved patient survival without adding complications to patient's recovery.

Radical nephrectomy is reserved for renal tumors that are not amenable to partial nephrectomy. Indications for radical nephrectomy include tumors in nonfunctional kidneys, large tumors replacing the majority of renal parenchyma, tumors associated with detectable regional lymphadenopathy, or tumors associated with renal vein thrombus.

All renal tumors suspicious of malignancy should be staged with abdominopelvic CT or MRI and chest imaging with chest x-ray or chest CT ([Fig. 60-25](#)) ([Bradley et al, 2011](#); [Chen and Uzzo, 2011](#)). If any sign of metastatic disease is present, a bone scan and head CT should also be obtained. The cross-sectional imaging should be closely evaluated for tumor thrombus, enlarged retroperitoneal nodes, and any embryologic abnormalities of the renal collecting system and vasculature.

Prior to surgery, percutaneous renal biopsy can be considered in patients with another malignancy to evaluate for potential metastatic disease, to evaluate for the possibility of lymphoma in cases of infiltrative-appearing renal masses on imaging studies and solid masses that will be managed nonoperatively with percutaneous modalities (radiofrequency or cryotherapy), or in nonoperative cases when the histology may dictate the type of systemic therapy ([Volpe et al, 2007](#); [Pandharipande et al, 2010](#); [Psutka et al, 2013](#)). In cases of bilateral renal tumors, percutaneous renal biopsy should be considered in order to guide management ([Blute et al, 2000](#)).

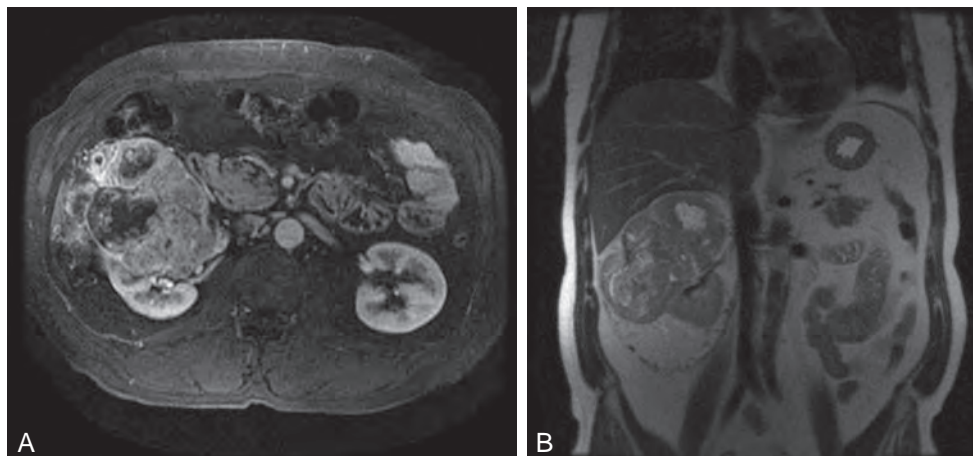


Figure 60-25. Axial (A) and coronal (B) magnetic resonance images of a right-sided renal mass.

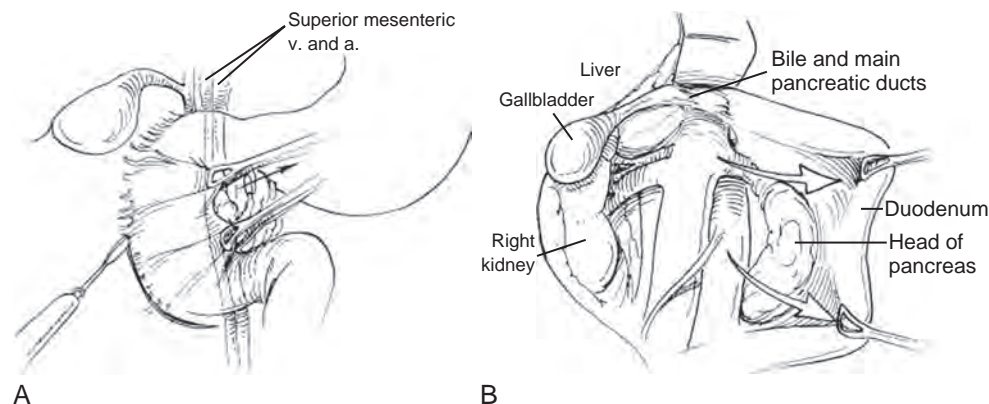


Figure 60-26. A and B, Kocher maneuver. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

At times, preoperative angioembolization is undertaken for the kidney with a large renal mass and regional lymphadenopathy (Schwartz et al, 2007). Potentially, angioembolization can reduce the amount of intraoperative blood loss and provide the ability to ligate the renal vein before the renal artery, which may be necessary as a result of extensive hilar lymphadenopathy. Angioembolization may also reduce the size of the primary tumor, thereby technically improving the feasibility of nephrectomy. Disadvantages of angioembolization include postinfarction painful syndrome, risk of tumor lysis syndrome, risk of embolization of tumor thrombi, and risk of vascular trauma.

Ipsilateral adrenalectomy should be considered in large upper pole tumors when the surgical plane between the kidney and adrenal gland may be compromised. Otherwise, routine adrenalectomy is not required since the overall incidence of adrenal metastasis is less than 5%. Because preoperative CT and MRI may miss 20% to 25% of adrenal metastases, one must consider clinical indicators of adrenal involvement to guide surgical practice (Siemer et al, 2004). Typically, adrenalectomy would be indicated when there is diffuse involvement by tumor, large tumor size (>10 cm), extrarenal tumor extension, tumor thrombus, lymphadenopathy and regional metastasis, or an adrenal mass on imaging.

Regional lymphadenectomy is not required in every radical nephrectomy, since the overall incidence of lymph node disease is about 5%. Regional lymphadenectomy should be considered in those patients who may have a reasonable chance of benefiting from the added surgery. The probability of regional nodal involvement is discussed by Blute and coworkers (2004a) and Crispen and colleagues (2011). Indications for regional lymphadenectomy include enlarged lymph nodes on imaging, cytoreductive surgery for metastatic disease, tumor size greater than 10 cm, nuclear grade 3 or greater, sarcomatoid histology, presence of tumor necrosis on imaging, extrarenal tumor extension, and tumor thrombus and direct tumoral invasion of adjacent organs.

In cases of adjacent organ involvement (colon and/or spleen), preoperative planning for splenectomy and/or partial colectomy is important (Blute et al, 2004a). Owing to the presence of its bilaminar capsule, the liver is not usually directly invaded by renal tumors despite preoperative imaging studies that may suggest extension of right-sided renal tumors to the liver. However, in rare circumstances when a right-sided renal tumor does directly invade the liver, appropriate preoperative surgical planning is essential.

Surgical Procedure

The most commonly used incisions for radical nephrectomy are subcostal flank incisions, which are described above. In brief, for a subcostal approach, the patient is placed in a modified lateral decubitus position. After incising through the skin and muscular layers, a Balfour, Bookwalter, or Omni-Tract retractor is placed and, for a

right-sided approach, the liver and gallbladder are packed away superiorly. When additional mobilization of the liver is required, the avascular right triangular ligament is incised. The posterior parietal peritoneum on the white line of Toldt is incised from the pelvis (region of the iliac artery) to the right upper quadrant (region of hepatic flexure). The anterior pararenal space is developed by dissecting in the plane between the anterior renal fascia and the mesentery of the ascending colon. With large inflammatory masses, the anterior pararenal space may be difficult to develop. It is important to avoid injury to the ascending mesocolon, since injury to the right colic and ileocolic arteries may devitalize this segment of colon. It is important to resect the renal fascia in its entirety for the best chance of surgical cure and to avoid any intra-abdominal tumor spillage.

After mobilizing the hepatic flexure of the colon using sharp and blunt dissection, the second part of the duodenum is mobilized medially using the Kocher maneuver (Fig. 60-26). With medially located tumors, mobilization of the duodenum should be performed with extreme care in order to avoid injury.

After mobilization of the duodenum, the IVC is identified posteriorly. Dissection anterior to the IVC will enable identification of the renal vein and gonadal vein (on the right side). Placement of a vessel loop will enable gentle traction of the renal vein. The renal vein is palpated for any tumor thrombus. Next the renal artery is identified posterior to the renal vein. If identification of the renal artery is difficult, attention is turned to the lower pole of the kidney to identify the ureter and gonadal vein. If technically feasible, the gonadal vein is spared. However, often because of the large size of the renal tumor, the gonadal vein cannot be safely left intact without the risk of avulsion from the IVC (right side) or left renal vein. With ligation of the ureter, the kidney is lifted from a posterior to an anterior position in order to aid in identification of the renal artery posterior to the kidney.

Another option for identifying the right renal artery in difficult hilar dissections is to dissect in the interaortocaval region at its takeoff from the aorta (Fig. 60-27). The right renal artery can be ligated with 0 silk suture or in emergent cases with a surgical clip. With the renal artery controlled, the right kidney and tumor will decrease in size and engorgement, easing the dissection of the kidney at the hilum and the remaining sites. The right renal vein, which should now be flaccid, is examined for any tumor thrombus and subsequently doubly ligated with 0 silk tie and 2-0 silk suture ligature and divided. Identification of the renal artery should be technically much easier lateral to the IVC, which can now be doubly ligated and divided. Attention should be given to the lumbar veins, which enter the IVC (Fig. 60-28 on the Expert Consult website). If avulsed, bleeding should be controlled with suture ligatures and not surgical clips since surgical clips do not provide adequate hemostasis for the lumbar veins. These veins can retract, thereby exacerbating the degree of retroperitoneal bleeding, which will be difficult to access and control.

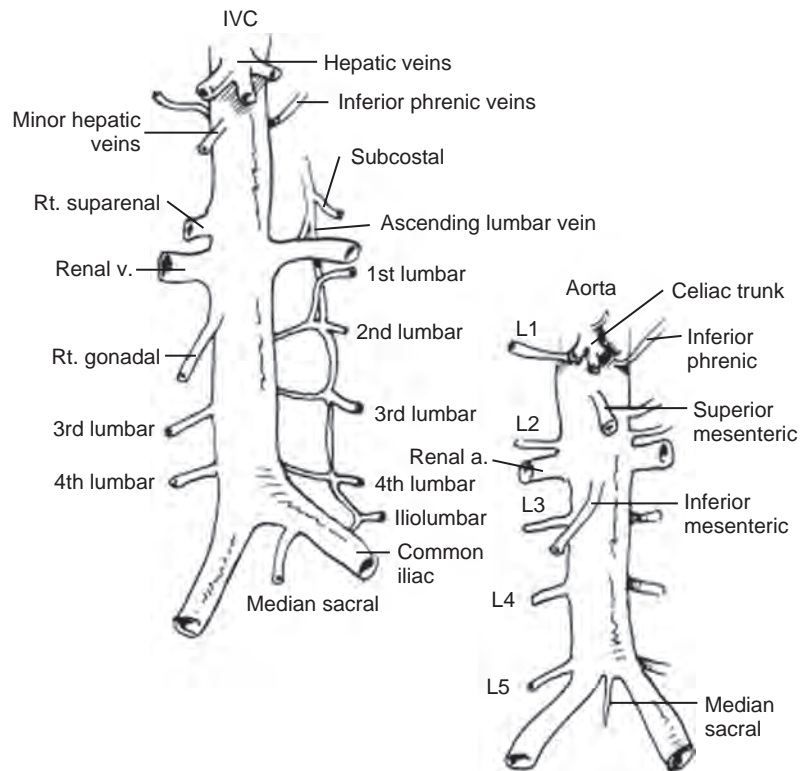


Figure 60-28. Branches of the inferior vena cava (IVC) and aorta. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

For left radical nephrectomy, after incision of the white line of Toldt from the splenic flexure to the common iliac artery, the descending colon is reflected medially. The renocolic ligament is divided and extreme care is taken to avoid injury to the tail of the pancreas. The left renal vein is identified using the anterior surface of the aorta as a guide. The left renal artery is usually located cranial and posterior to the left renal vein. After further mobilization of the lower pole of the kidney, the left ureter and the left gonadal vein are identified. The left gonadal vein can be traced to its insertion to help identify the left renal vein. Depending on the size and location of the tumor, the surgeon determines whether the left gonadal vein should be left intact or tied off and transected to help with mobilization of the kidney. The ureter is divided, and the inferior and posterior surface of the kidney is mobilized to identify the left renal artery. Once the left renal artery and vein are identified, the renal artery is ligated with two right-angle clamps and divided. Preferably, the

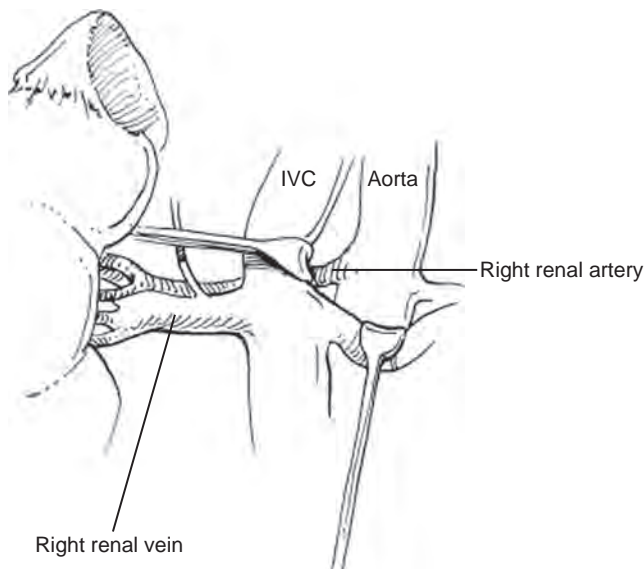


Figure 60-27. The anteromedial surface of the inferior vena cava (IVC) can be used as a guide to identify the short right renal vein. The right renal artery is usually located deep to the right renal vein and is sometimes easier to identify in the interaortocaval groove. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

proximal end of the renal artery is clamped with two right-angle clamps and the distal end with one right-angle clamp. The renal artery is divided using a fine scalpel. The proximal end is ligated with 0 silk suture and further secured with 2-0 silk suture ligature; the distal end is tied with 0 silk tie. With the renal artery secured and divided, the renal vein is secured and divided in a similar fashion.

At times, the renal artery and vein may not be able to be separated individually because of significant hilar lymphadenopathy. Then, a whole-pedicle clamp technique may be utilized to control the hilar vessels (Fig. 60-29 on the Expert Consult website). While a risk of arteriovenous fistula may be associated with en bloc ligation of the whole renal pedicle (Lacombe, 1985), some small clinical series have not found any evidence of such fistulas in patients undergoing nephrectomy who have been managed by en bloc stapling of the renal hilum (Ou et al, 2008; Chung et al, 2013). The vascular pedicle is bluntly dissected until the pedicle has a 2- to 3-cm diameter. Long curved vascular clamps (e.g., Satinsky clamps) or renal pedicle clamps (e.g., Crawford, Young, Mayo) are used to clamp the renal artery and vein together. The pedicle is pinched and the first clamp is placed at the lowermost aspect of the pedicle to ensure adequate length for ligation of the pedicle and that the clamp extends far enough beyond the structures within the pedicle to engage the suture. A second clamp is placed above and adjacent to the first under direct vision. A third clamp is placed on the pedicle near the renal parenchyma. The pedicle is divided between the second and the third clamps, leaving vascular stumps protruding. A 0 silk suture is looped below the lower clamp to tie off. It is prudent to tie the pedicle twice and also use suture ligature to minimize the risk with silk ties, which may slip off the vascular pedicle. Various other techniques can be utilized for controlling the vascular pedicles (Figs. 60-30 and 60-31).

In the emergent condition of loss of control of the renal hilar vascular pedicle, it is important to stay calm. The surgeon must inform the anesthesiologist and all operating room personnel of major bleeding and request aggressive hydration and availability of blood products. Compression can be applied using a fingertip or sponge stick to achieve hemostasis as best as possible so that the rest of the operating room staff can prepare. Compression can also be applied on the IVC and/or aorta to control bleeding. Two Yankauer suction tubes can be used to clear the surgical wound. Vascular occlusion clamps are used to clamp and ligate actively bleeding vessels. Clamping should not be done blindly; rather, one should suction, pack, retract, and dissect to get better exposure. If the bleeding is occurring from the renal artery, the surgeon can compress the aorta above the renal artery, clamp the arterial stump with a vascular clamp, and repair the defect with two layered running vascular sutures. If the bleeding is occurring from the IVC because of an avulsed or lacerated renal vein, or avulsed gonadal or

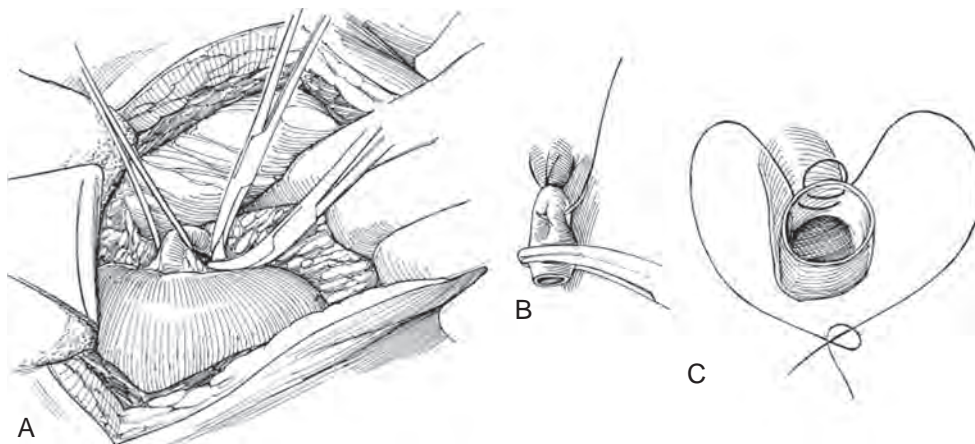


Figure 60-30. A to C, "Cut first, ligate second" method for securing the renal hilum. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

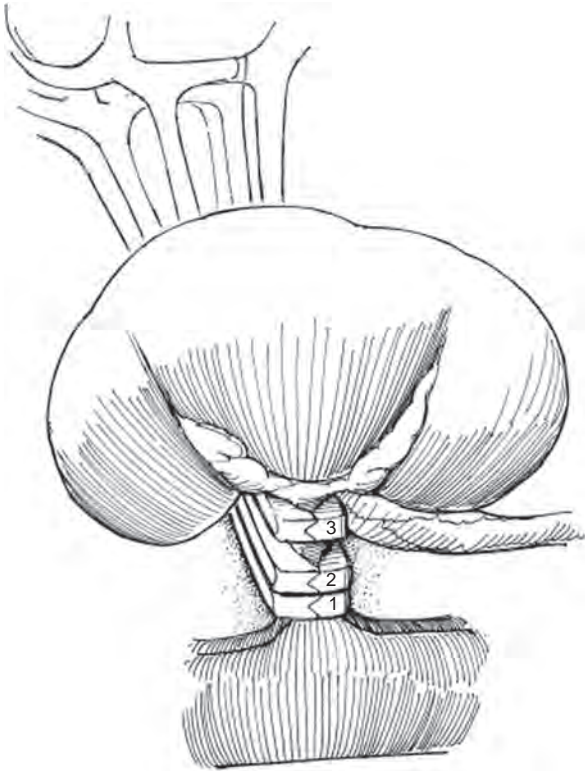


Figure 60-29. Whole-pedicle clamp method for securing the renal hilum. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

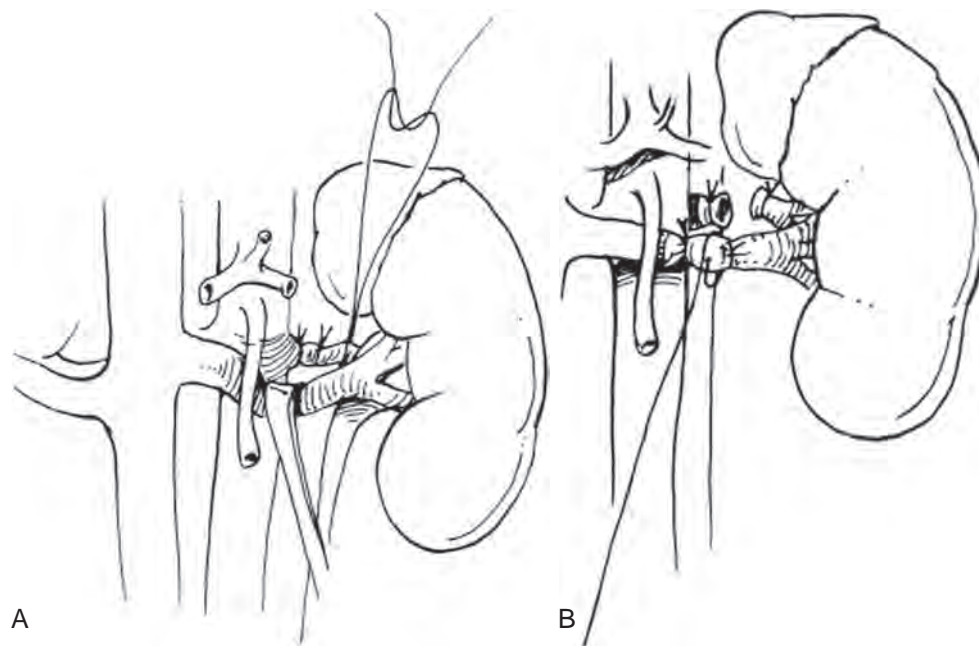


Figure 60-31. A and B, “Ligate first, cut second” method for securing the renal hilum. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman’s atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

lumbar vein, a finger can be placed on the hole until the hole can be grasped with an Allis clamp (Scanlan International, St. Paul, MN). Pulling up on the clamp will normally stop the bleeding, allowing the defect to be visualized for repair.

For repair, polypropylene (Prolene) sutures (Ethicon, Cincinnati, OH)—typically 30 inch or 36 inch (75 cm or 90 cm)—are used; 3-0 or 4-0 sutures can be used for IVC or aortic repairs and 4-0 or 5-0 sutures can be used for renal vessel repairs. We recommend using double-armed sutures with tapered needles— $\frac{3}{8}$ circle BB (17 mm) for arterial repair (they are less likely to fracture a calcific arterial plaque) and $\frac{1}{2}$ circle RB-1 (17 mm) or SH (26 mm) for venous repair.

Regional Lymphadenectomy for Renal Cancer

The role of regional lymphadenectomy for renal cell carcinoma (RCC) has remained controversial. Multiple retrospective studies have suggested a possible benefit to regional lymphadenectomy for carefully selected patients (Blute et al, 2004a; Kim et al, 2004; Lam et al, 2004, 2006; Crispen et al, 2011; Capitanio et al, 2013; Sun et al, 2014). A prospective randomized trial that was carried out by the European Organization for Research and Treatment of Cancer included 772 patients. Patients were randomly assigned to two groups—one that underwent regional lymphadenectomy and one that did not. While no overall survival benefit was shown for patients who underwent regional lymphadenectomy for management of RCC, the study included a high percentage of patients with localized small and low-stage tumors who may not have benefited from lymphadenectomy at all (Blom et al, 2009).

For right-sided renal masses when lymphadenectomy is considered, the paracaval, precaval, retrocaval, and interaortocaval nodes from the right crus of the diaphragm to the bifurcation of the IVC are sampled (Fig. 60-32). A right-angle clamp and electrocautery are used to split the lymphatic tissue from the anterior surface of the IVC. The lymphatic tissue is cleared cranially from the right crus of the diaphragm (located 3 to 4 cm above the right renal vein) and caudally until the bifurcation of the IVC. The right gonadal vein is ligated at its insertion into the IVC with 2-0 silk suture, in order to avoid avulsion of the vein. Next the lymphatic tissue is cleared off the lateral aspect of the IVC (paracaval nodes). The IVC is gently

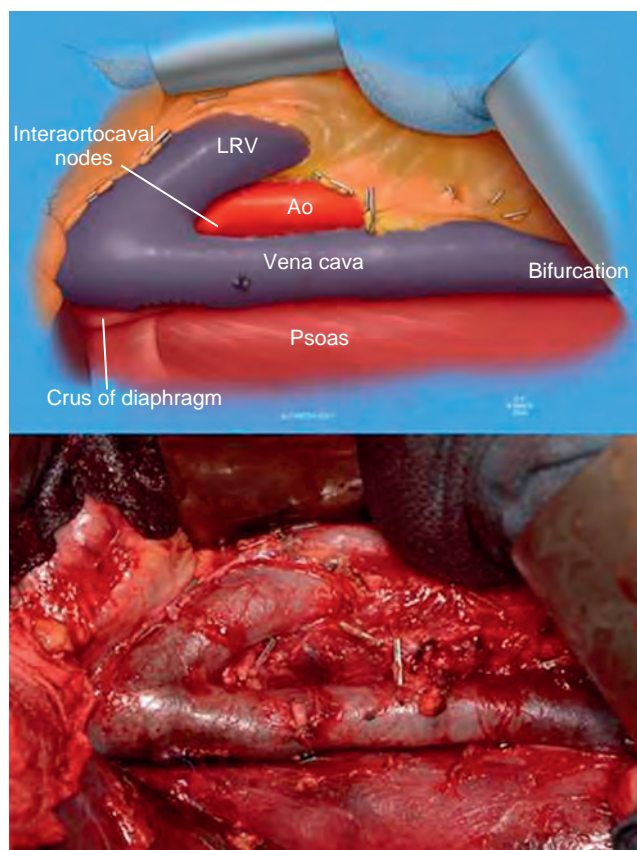


Figure 60-32. Extended lymphadenectomy for right-sided renal masses. Ao, aorta; LRV, left renal vein.

elevated with a vein retractor to expose the lumbar branches. The lumbar veins (typically four or five branches on either side of the IVC) are carefully ligated with 3-0 silk ties and transected. The lymphatic trunks located above the renal vein are ligated with surgical clips. Care to adequately ligate the lymphatic trunks is essential since large quantities of lymph and chyle drain through the cisterna chyli and thoracic duct, and failure to appropriately control them can result in chylous ascites (Fig. 60-33 on the Expert Consult website). Once the lumbar veins are secured and the superior aspect of the lymphatic trunk above the renal vein is secured, the assistant rolls the IVC medially with gentle pressure using two sponge sticks. Next the lymphatic tissue is cleared off the retrocaval region. The nodal tissue overlying the anterior surface of the aorta is then split and divided to the superior border of the left renal vein. Division of the nodal packet is followed to the medial border of the IVC and the aortocaval nodal packet is cleared to the level of the common iliac vessels.

For left-sided renal masses, the lymphatic tissue on the antero-medial surface of the aorta is clipped and divided and rolled laterally (Fig. 60-34). The split is continued cranially along the aorta to the level of the superior mesenteric artery (SMA) and caudally past the inferior mesenteric artery (IMA) to the bifurcation of the aorta. While the IMA and the celiac trunk have to be preserved, the IMA can be tied and divided in case of involved lymphadenopathy. Once the lymphatics are dissected off the anterior and lateral surface of the aorta, the assistant gently elevates the aorta on either side to expose, secure, and divide the lumbar arteries. Once the lumbar arteries are properly secured, the aorta is rolled medially and the tissue between the anterior longitudinal vertebral ligament and the aorta (retroaortic lymph nodes) is resected. The interaortocaval nodes are resected only if they are palpable or visualized on preoperative imaging, or if there is extensive nodal involvement around the aorta.

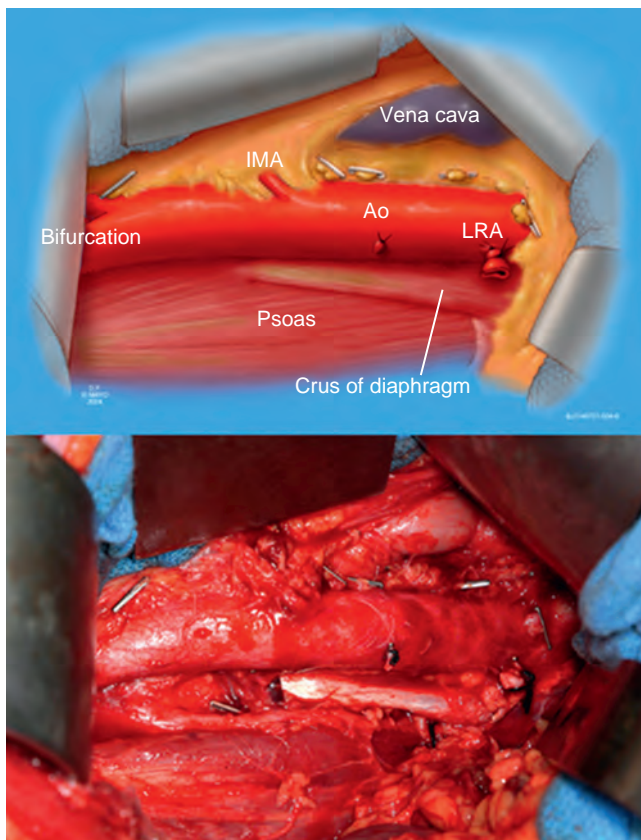


Figure 60-34. Extended lymphadenectomy for left-sided renal masses. IMA, inferior mesenteric artery; LRA, left renal artery.

Wound Closure

Once the surgical procedure is completed, the surgeon should investigate for hemostasis and evaluate adjacent organs for any signs of injury. The diaphragm and pleura are tissues that can be inadvertently injured secondary to retraction during radical open renal surgery. To test for pleural injury, the retroperitoneum is filled to the level of the flank incision with saline. The anesthesiologist then inflates the lungs with high inspiratory volumes. Bubbling of saline irrigation in the retroperitoneum with deep inspiration would suggest a pneumothorax. In case of a small pleural injury, the pleural cavity can be closed with running nonabsorbable sutures. Prior to complete closure of the pleura, the tip of a 14-Fr red rubber catheter is placed in the pleural cavity. The end of the catheter is placed in a saline-filled bowl. The anesthesiologist provides a deep inspiratory breath to evacuate any air from the pleural cavity through the red rubber catheter and into the saline bowl. Once the air is evacuated from the pleural cavity as evidenced by bubbles in the saline bowl, the red rubber catheter is removed and the assistant cinches the pleural incision tight for an airtight closure. A postoperative chest radiograph is essential to assess for any significant pneumothorax, even in cases when pneumothorax is not suspected.

The fascial layers are approximated typically in two layers—the transversus abdominis and internal oblique fasciae are approximated together, and the external oblique fascia is approximated as a separate layer. A 1:1 mixture of bupivacaine (0.5%) and lidocaine (1%) solutions is injected into the wound for pain control. The subcutaneous tissue is approximated using 3-0 absorbable sutures. The skin is approximated with skin staples or subcuticular 4-0 poliglecaprone 25 (Monocryl) suture (Ethicon, Cincinnati, OH).

Intra- and Postoperative Complications

Damage during Suprahilar and Retrocrural Lymphadenectomy. Dissecting the lymphatic tissue located above the left renal vein (suprahilar and retrocrural nodes) in the interaortocaval space should be undertaken with great caution and care because the duodenum, pancreas, superior mesenteric artery, celiac trunk, superior mesenteric autonomic plexus, and cisterna chyli can all be easily damaged in this area with serious sequelae. In general, we consider dissecting this area if the nodes are noticeably palpable or enlarged on preoperative imaging.

Injury to the Vasculature of the Gut. During radical nephrectomy, a number of important gastrointestinal blood vessels may be encountered that have become involved by tumor, resulting in iatrogenic injury. The inferior mesenteric artery provides the blood supply to the distal transverse, descending, and sigmoid colon. It can be safely ligated as long as the marginal artery of the colon (marginal artery of Drummond, arch of Rioloan) is patent and can supply blood from the SMA to the left colonic arcades. The SMA provides the blood supply to the entire small bowel as well as to the cecum and ascending and transverse colon, whereas the celiac trunk feeds the esophagus, stomach, pancreas, liver, spleen, and part of the duodenum. Ligation of either the SMA or the celiac trunk is a catastrophic event that occurs predominantly with left-sided nephrectomy and that must be rapidly reversed if the patient is to survive. A vascular surgeon should be immediately called to the operating room and the vessel in question should be repaired.

The inferior mesenteric vein (IMV) is found in the mesentery of the descending colon, immediately lateral to the ligament of Treitz. It is a useful landmark for mobilization of the right colon and small bowel mesentery to access the retroperitoneum, because the posterior peritoneum is incised immediately medial to the IMV. The IMV can be safely ligated during surgery without consequence.

In contrast, the superior mesenteric vein (SMV) should not be ligated unless that is the only surgical option. It runs in the root of the small bowel mesentery and joins the splenic vein and IMV to form the portal vein. Repair of an SMV laceration is done by first clipping the small venous branches entering the SMV and then isolating the injury with atraumatic vascular clamps. Venorrhaphy

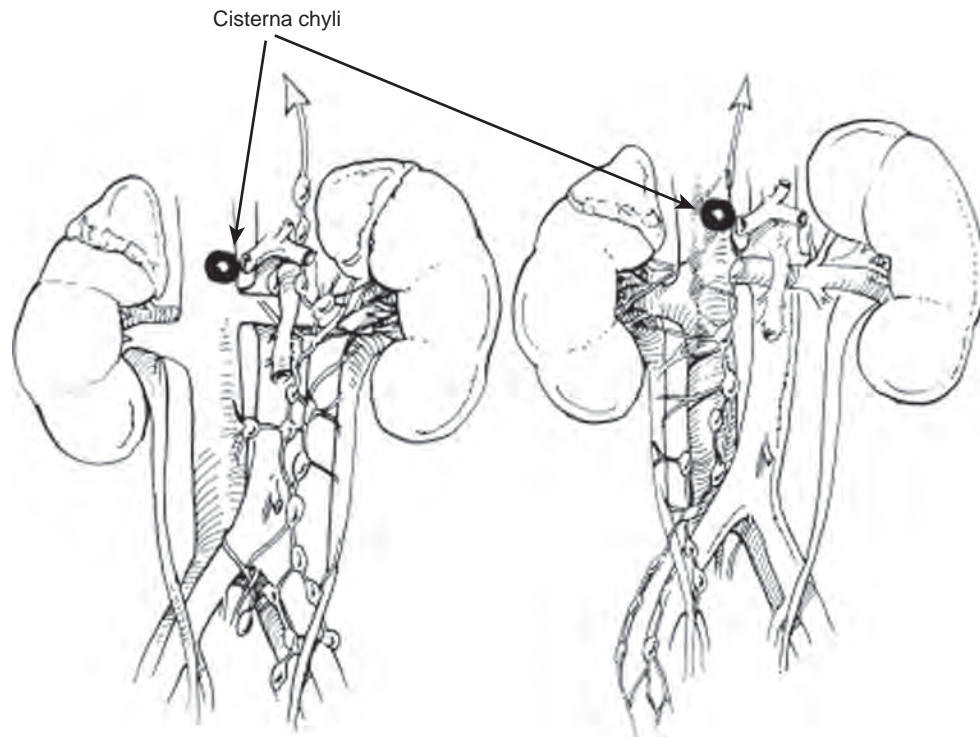


Figure 60-33. Renal lymphatic drainage and location of the cisterna chyli. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

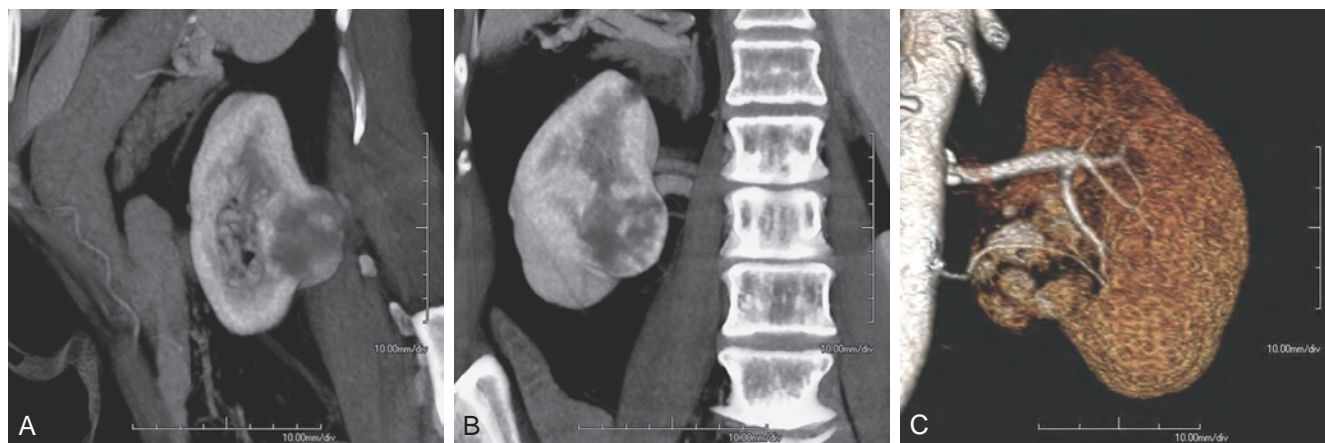


Figure 60-35. A, Contrast-enhanced computed tomography scan demonstrating right renal mass. B, Three-dimensional reconstruction demonstrates a large intrarenal component to the mass. C, Arterial reconstruction shows lower pole renal artery in close proximity to the renal mass.

using 6-0 Prolene is usually adequate to repair the vein. If the vein has been ligated and transected, serious bowel edema and venous engorgement will result, which can impair venous return through the portal venous system. The net result is the development of systemic hypotension/splanchnic hypertension syndrome, which is characterized by venous thrombosis, bowel ischemia, and necrosis. If possible, a ligated SMV should be reanastomosed primarily or repaired using autologous venous grafting. Gore-Tex vascular grafts (W. L. Gore & Associates, Flagstaff, AZ) should only be used when autologous veins are not available because the thrombosis rate is high. The abdomen should not be closed primarily in cases of SMV injury because abdominal compartment syndrome will occur.

Injury to the Liver and Spleen. Small hepatic injuries (capsular tears and minor lacerations) can usually be managed effectively by argon beam coagulation or electrocautery. Fibrin glue and topical hemostatic meshes (e.g., Surgicel Absorbable Hemostat, Ethicon, Cincinnati, OH) are useful adjuncts. More serious splenic injuries can be managed by splenorrhaphy or splenectomy. Minor hepatic lacerations can be repaired using the same basic principles as for a partial nephrectomy closure, with a synthetic absorbable suture on a $\frac{1}{2}$ circle tapered needle and Nu-Knit pledgets as described later (see [Enucleation for Small Cortical Tumors](#)).

Injury to the Duodenum. Most intramural hematomas of the duodenum should be managed expectantly. However, if the hematoma is large and narrowing the duodenal lumen, incision of the serosa and muscularis (but not the mucosa) can be performed to drain the hematoma and achieve hemostasis. The defect should be closed in one layer with interrupted 3-0 silk sutures. The involved segment may initially appear nonviable; however, no resection should be performed since the initial perception is false. Consultation with a general surgeon or gastrointestinal surgeon can be very helpful.

Minor electrocautery or laceration injuries should be managed by careful debridement of the nonviable tissue and closure in two layers, the mucosal layer with continuous 4-0 chromic or Vicryl suture on a $\frac{1}{2}$ circle tapered needle, and the serosa and muscularis layer with 3-0 silk interrupted suture on a $\frac{1}{2}$ circle tapered needle. An omental flap is placed over the injury and a closed suction drain is inserted.

Injury to the Pancreas. The first step in management of pancreatic injury is a thorough inspection of the organ. Superficial lacerations and contusions can usually be managed by applying fibrin glue and inserting a closed suction drain. The drain is monitored for an alkaline pH and lipase/amylase levels to determine whether a pancreatic fistula is developing. If the injury to the pancreas is deep and/or involves the pancreatic duct, consultation with a

gastrointestinal surgeon is essential for appropriate repair and management.

Pulmonary Complications. Large postoperative pleural effusions can be managed by aspiration initially, followed by chest tube drainage if necessary.

Partial Nephrectomy for Malignant Disease

When technically feasible, partial nephrectomy is the preferred method of choice for managing most renal masses in order to preserve maximum renal function ([Fig. 60-35](#)). While in the past partial nephrectomy was reserved for specific conditions (bilateral tumors, tumor in a solitary kidney, patient at high risk of future renal failure) and small tumors less than 4 cm in diameter ([Novick et al, 1991](#)), indications for partial nephrectomy have considerably widened to include most renal masses that can be safely and completely removed independent of their size ([Blute et al, 2003](#); [Gill et al, 2007](#); [Blute and Inman, 2012](#)).

Relative contraindications to partial nephrectomy include:

Technical issues

- Cold ischemia time greater than 45 minutes (consider extracorporeal approach)
- Less than 20% of global nephron mass retained

Cancer-related issues

- Diffuse encasement of renal pedicle by tumor
- Diffuse invasion of central collecting system
- Tumor thrombus involving major renal veins
- Adjacent organ invasion (stage cT4)
- Regional lymphadenopathy (stage cTxN1)

Preoperative Considerations

In addition to the preoperative considerations for radical nephrectomy, there are additional concepts to consider related to partial nephrectomy.

Hyperfiltration Injury. When a significant portion of renal parenchyma is removed, the renal blood flow is delivered to a smaller number of nephrons, which can lead to increased glomerular capillary perfusion pressure that results in an increased single-nephron glomerular filtration rate called *hyperfiltration* ([Steckler et al, 1990](#); [Goldfarb, 1995](#)). Over decades, the hyperfiltration can injure the remaining nephrons, resulting in focal segmental glomerulosclerosis and the clinical manifestations of proteinuria and progressive renal failure. Hyperfiltration injury is most common when the total nephron mass of both kidneys is reduced by more than 80%.

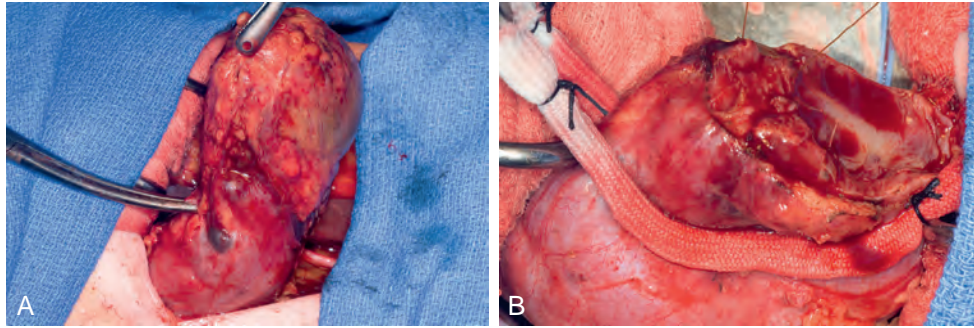


Figure 60-36. A and B, Partial nephrectomy for a large polar tumor using a Satinsky clamp on the renal parenchyma for ischemia.

Renal Ischemia and Hypothermia. To minimize blood loss and allow for adequate surgical visibility, it is often necessary to employ vascular compression during partial nephrectomy. Options include manual compression, a renal compression clamp (Kaufmann clamp), selective clamping of the renal artery, and en bloc clamping of the entire renal pedicle. Manual and clamp compression of renal parenchyma is preferable, since vascular clamping is associated with a higher incidence of renal complications (Fig. 60-36). It is unclear whether leaving the renal vein unclamped for retrograde renal perfusion offers any tangible benefit. Attempting to limit warm ischemia to 20 minutes and cold ischemia to 35 minutes helps maintain renal function (Thompson et al, 2007).

Adequate renal hypothermia (core renal temperature of 20° C) takes at least 15 minutes to achieve if the kidney is packed with ice slush. To help prevent acute postoperative renal failure, intravenous mannitol (12.5 g) and furosemide (20 mg) should be infused about 15 minutes before renal artery clamping (Hanley and Davidson, 1981; Tiggeler et al, 1985). While evidence supporting this practice is somewhat limited, both drugs are quite safe as long as the patient is well hydrated (Novick et al, 1991).

Enucleation and Surgical Margin. Simple tumor enucleation can be safely conducted in small renal tumors while preserving a small rim of normal tissue and a negative surgical margin (Carini et al, 2006).

Multifocality and Tumor Size. The incidence of multifocality is approximately 2% for clear cell and chromophobe RCC and 10% for papillary RCC (Fig. 60-37). Multifocal tumors are also more common as the primary tumor size increases (Blute et al, 2003). Careful inspection of the entire renal surface should be done at the time of partial nephrectomy to ensure that intraoperative findings corroborate preoperative imaging studies. If additional unanticipated renal mass(es) are encountered intraoperatively, partial nephrectomy is still the treatment of choice for multifocal tumors as long as they can be safely resected with clear surgical margins.

Hereditary Renal Malignancy. Hereditary renal tumors are usually multifocal and bilateral, with high likelihood of recurrence. Except for patients with hereditary leiomyomatosis and RCC who should be aggressively treated with wide excision, most patients with hereditary syndromes can be safely observed with little chance of metastasis until the renal tumors reach 3 cm in size (Maher et al, 1991; Seizinger, 1991; Richards et al, 1993). When partial nephrectomy is performed, the perirenal fat and renal fascia should be preserved. The entire renal surface should be visualized and all visible tumors should be resected. Intraoperative ultrasound can be used to identify any subcortical tumors that could also be resected (Fig. 60-38 on the Expert Consult website). Hypothermia is advisable to minimize injury to the renal parenchyma.

Enucleation for Small Cortical Tumors

The surgeon should ensure that renal cooling is available, even though ischemia time seldom exceeds 30 minutes. Two cylinder-shaped cigarette-like bolsters are prepared by rolling Nu-Knit



Figure 60-37. Three-dimensional computed tomography reconstruction demonstrating a hilar tumor and peripheral tumor.

Absorbable Hemostat (Ethicon, Cincinnati, OH) and tying each end with absorbable sutures. Two pledgets are prepared by folding Nu-Knit into a double-layer strip 5 to 10 cm wide and 1 cm long. We prefer Nu-Knit because it is absorbable and it maintains its integrity without immediate shrinkage when wet. In addition, it has excellent tensile strength when sutured.

The kidney is exposed using either the anterior subcostal or flank approach as described earlier. The entire surface of the kidney is freed of perirenal fat, with the exception of the perirenal fat overlying the tumor. While removing the perirenal fat, special care should be taken to avoid injury to the ureter, particularly for lower pole tumors. Intravenous mannitol and furosemide are administered and the renal pedicle is exposed sufficiently to allow safe application of a vascular clamp if necessary. Vessel loops are placed around the renal vein and artery individually.

The renal cortex surrounding the tumor is marked circumferentially using electrocautery. The plane outside the tumor pseudocapsule and within the normal parenchyma is identified and bluntly dissected with small closed Metzenbaum scissors. For enucleation of small lesions, renal occlusion is usually not necessary. However, if there is excessive bleeding that hampers proper visualization of the resection margin, then manual compression of the kidney or clamping of the renal pedicle can help. When small vessels within the kidney are encountered they are divided sharply with scissors. The tumor is excised and the margins are examined for gross evidence of a positive surgical margin; the deep margin of the excised tumor is assessed by frozen-section analysis. Small bleeding vessels

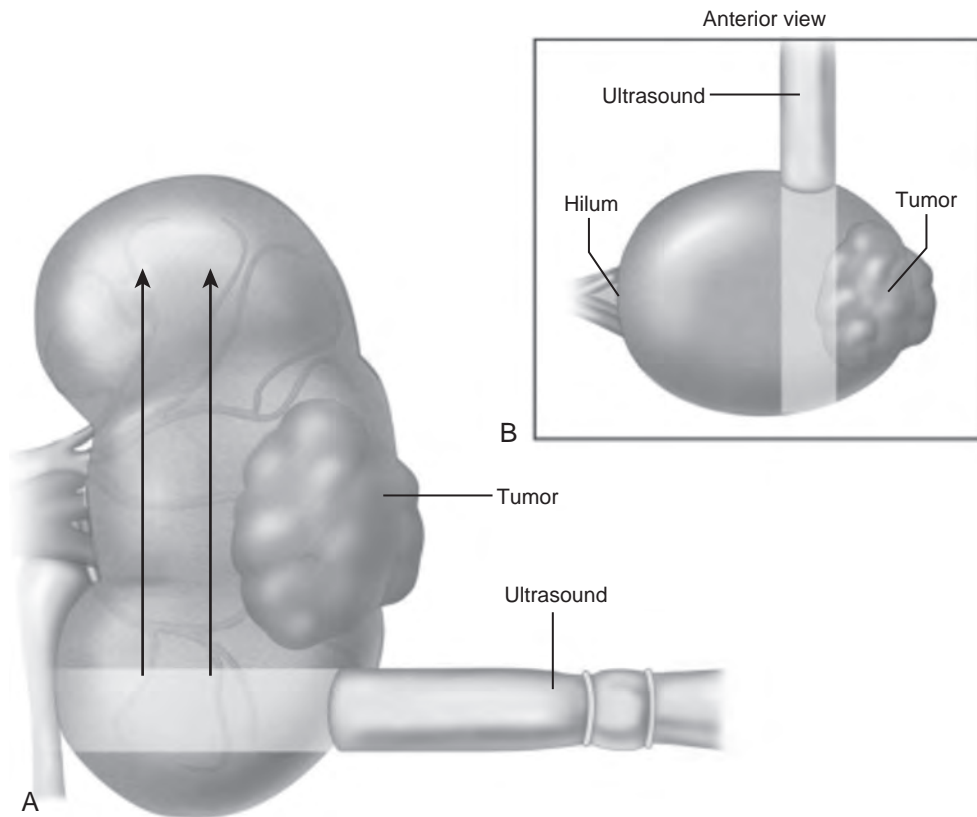


Figure 60-38. A and B, When performing intraoperative ultrasound for assessment of the renal tumor, the probe is passed over the kidney in radial angles to the center of the tumor. This allows assessment of the subcortical extent of the tumor in each angle, by assessing the transition from normal kidney to tumor interface in multiple planes. On the basis of this assessment, the position and line of incision are selected. (From Graham SD Jr, Keane TE, editors. Glenn's urologic surgery. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2010.)

in the renal parenchyma are controlled with 4-0 absorbable figure-of-eight sutures on a tapered needle or by coagulation with an argon beam coagulator or bipolar electrocautery. The integrity of the collecting system is verified by checking for injury and repairing with absorbable suture if necessary (Fig. 60-39).

A Nu-Knit pledget that was prepared earlier is placed along each border of the excised renal parenchyma and in the bottom of the

excised parenchyma (Fig. 60-40). The defect is closed with 2-0 absorbable horizontal mattress sutures on a long tapered $\frac{1}{2}$ circle needle. The suture is placed through the pledget and about 1 to 2 cm into the renal parenchyma to prevent capsular and parenchymal tearing. The pledgets allow even distribution of tension along the renal capsule, reducing the likelihood of tearing the capsule. If clamping was used, the pedicle is unclamped and inspection is

Collecting system involved

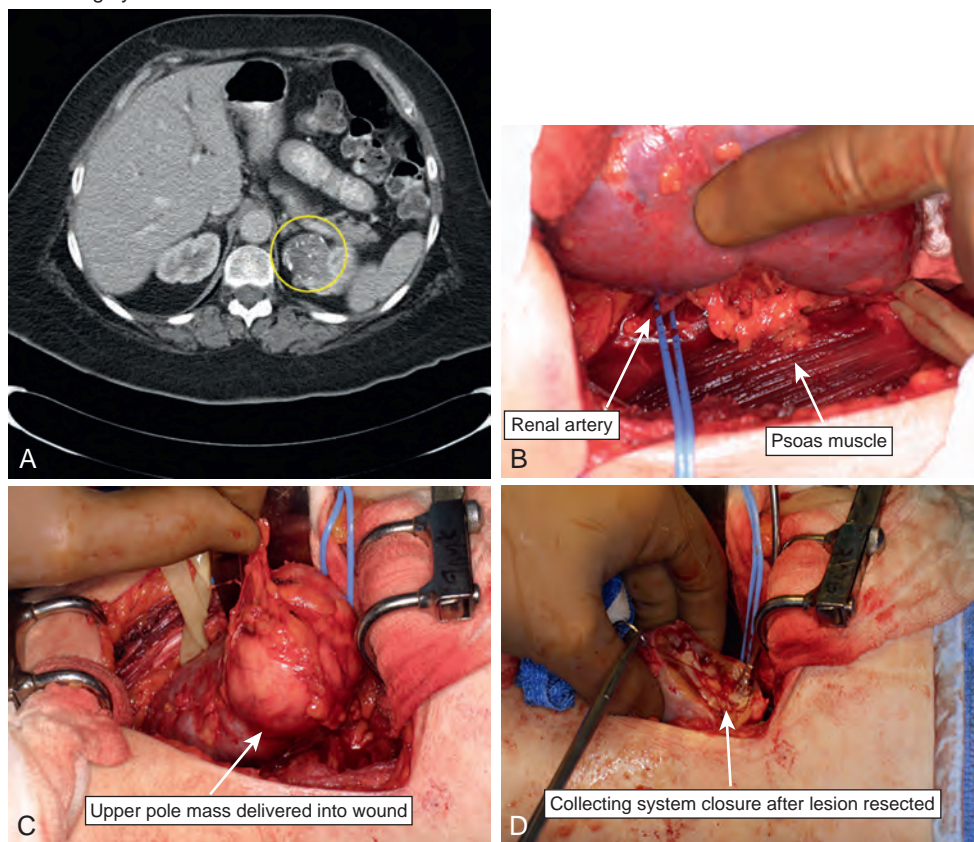


Figure 60-39. A, Renal tumor involving the collecting system demonstrated on computed tomography scan. B, Securing the renal artery. C, Identifying the upper pole mass. D, Repair of the collecting system after lesion resected.

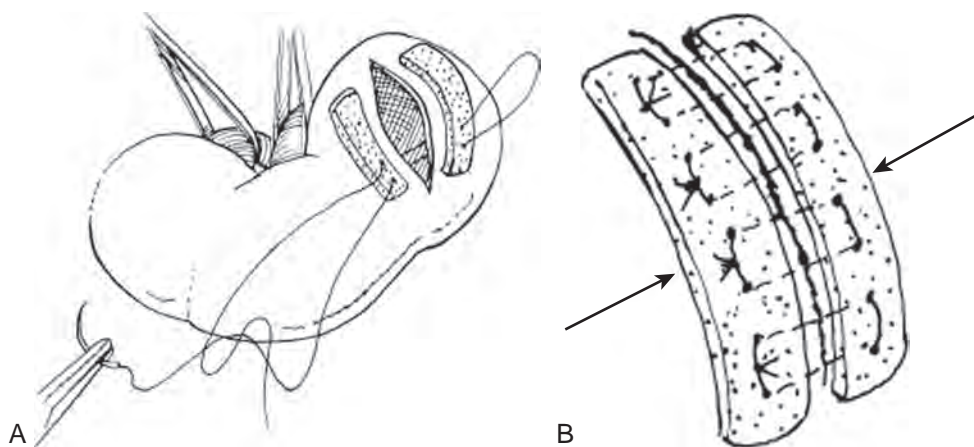


Figure 60-40. A and B, A Nu-Knit pledget is placed along each border of the crater and a Nu-Knit bolster is placed into the bottom of the crater (not required if the defect is very small). The defect is closed with a 2-0 absorbable horizontal mattress suture. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

done for bleeding, ischemia, or urine leakage of the kidney and for adjacent organ trauma.

The perirenal fat and renal fascia are replaced around the kidney. A closed suction drain in the pararenal space is placed to monitor for bleeding and urine leaks. The closed suction drain is removed after 2 to 5 days when the output is minimal. A Foley catheter is used to monitor the urine output. Unless there is a large renal collecting system defect, a ureteral stent is not typically required.

Wedge Resection for Large Cortical Tumors

For large tumors, intravenous mannitol and furosemide are administered, then the renal artery is clamped with a vascular bulldog clamp. Based on the surgeon's preference, when partial nephrectomy is being performed for larger tumor sizes or lesions that are close to the renal hilum, the renal vein may also be clamped after clamping the renal artery to provide better hemostasis during partial nephrectomy (Fig. 60-41). A plastic bag or sheet is placed around the kidney and filled with ice slush. The kidney is allowed to cool to 20° C (approximately 15 minutes).

The renal capsule is circumferentially incised 5 to 10 mm peripheral to the tumor with electrocautery. Using a combination of blunt and sharp dissection with Metzenbaum scissors, the tumor is

excised with a small rim of normal parenchyma. The specimen is inspected for visible tumor at the resection margin, then submitted for frozen-section analysis.

Bleeding vessels are controlled with figure-of-eight sutures or with argon beam or bipolar electrocautery. The deep resection margin of the kidney must be inspected for any residual tumor or any sign of collecting system injury. If there is any doubt about collecting system injury, 10 to 20 mL of diluted indigo carmine is injected into the renal pelvis while occluding the ureter to assess for leaks. The collecting system is closed with 4-0 absorbable suture on a tapered needle.

The renal parenchymal defect is reconstructed using Nu-Knit bolsters and pledgets as described above. Fibrin glue is applied to the renal parenchymal defect. Finally, the renal vessels are unclamped—if the renal vein as well as the renal artery is clamped, the renal vein is unclamped first followed by unclamping the renal artery.

Segmental Nephrectomy for Large Polar Tumors

Intravenous mannitol and furosemide are administered and the renal pedicle is completely dissected, including the segmental branches (Fig. 60-42; Fig. 60-43 on the Expert Consult website).

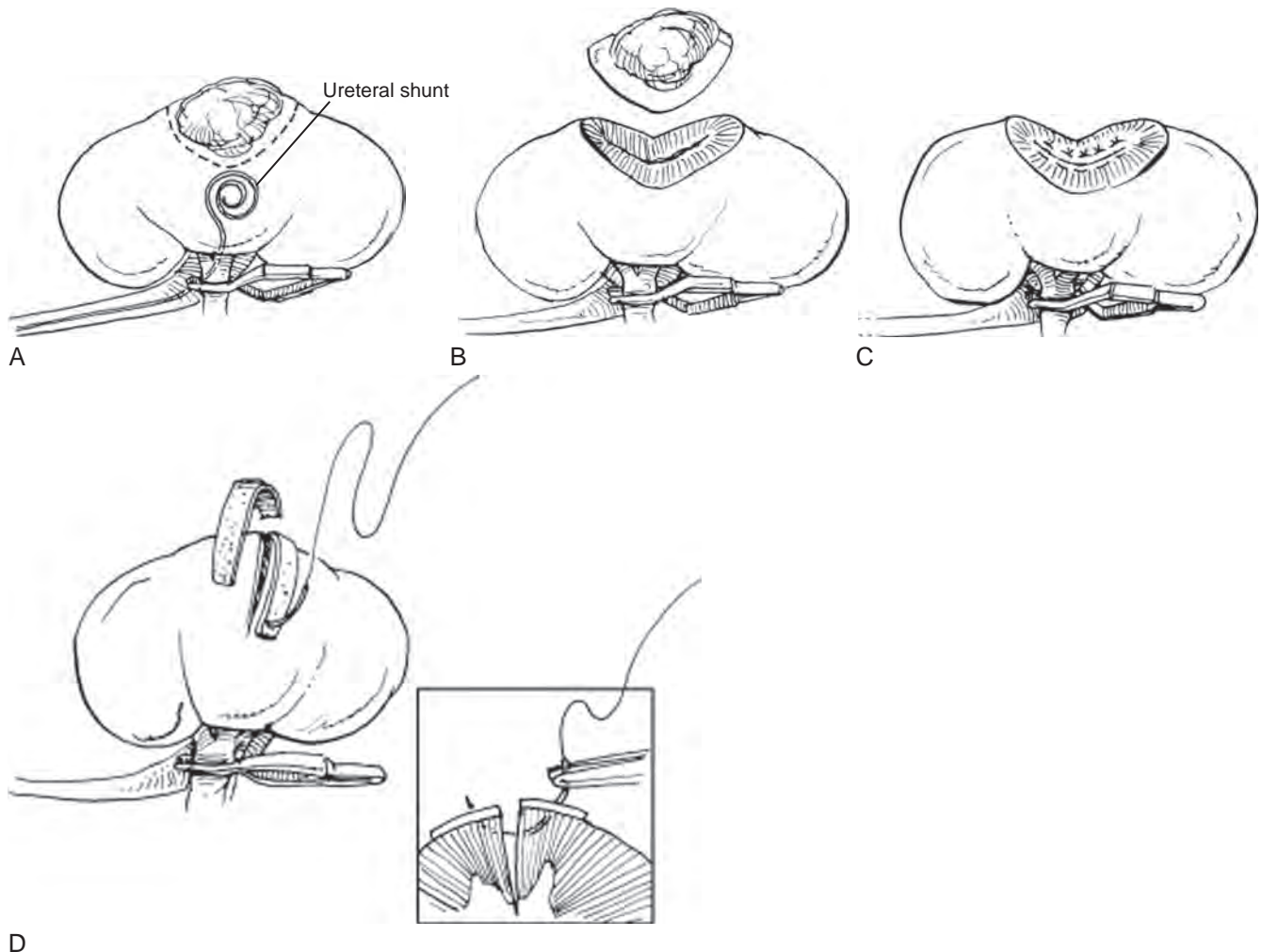


Figure 60-41. A, The renal capsule is circumferentially incised 5 to 10 mm peripheral to the tumor with electrocautery. B, A combination of blunt and sharp dissection with Metzenbaum scissors is used to excise the tumor with a small rim of normal parenchyma. C, Bleeding vessels are controlled and the collecting system is closed. D, The defect is reconstructed using Nu-Knit bolsters and pledgets. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

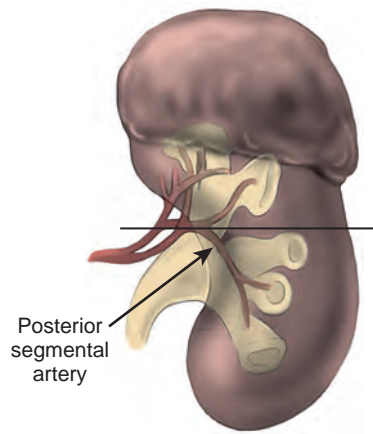


Figure 60-43. Injury to the posterior segmental artery must be avoided.

A bulldog clamp is applied to the apical segmental artery (or basilar segmental artery for lower pole tumors) and the line of ischemia is observed. The avascular line can be further demarcated by injecting 5 mL of indigo carmine directly into the clamped artery (Fig. 60-44 on the Expert Consult website). The line of ischemia is the optimal site for transection of the kidney and should be lightly marked with electrocautery. The apical segmental artery is ligated, then the renal pedicle is clamped en bloc with a curved Satinsky clamp. A plastic bag or sheet is placed around the kidney and filled with ice slush to cool the kidney to 20° C (approximately 15 minutes). The renal capsule is incised along the line of ischemia with electrocautery. Using blunt dissection, the pole of the kidney is excised (Fig. 60-45). Bleeding vessels are controlled, working expeditiously and accurately. The clamp is released to check for uncontrolled bleeders. If

hemostasis is adequate, collecting system repair is begun; otherwise the pedicle is reclamped and vascular control resumed.

The collecting system is inspected for injury. If the defect in the collecting system is large, a guidewire is inserted into the defect and manually guided into the ureter and bladder. A 6-Fr double-J ureteral stent is inserted over the guidewire with the proximal coil in the renal pelvis. The collecting system is closed with a running 4-0 absorbable noncutting suture.

The renal capsule is closed using Nu-Knit pledgets and horizontal mattress sutures as described earlier. Because the defect is large, we use a larger needle (e.g., XLH, GS-27) for segmental polar nephrectomies and heminephrectomies than for enucleation and wedge resections. Nephropexy should be considered if the kidney is quite mobile; however, injury to retroperitoneal nerves overlying the psoas and quadratus lumborum muscles must be avoided (Fig. 60-46 on the Expert Consult website). The kidney is covered with perirenal fat and renal fascia and a closed suction drain is placed to monitor output postoperatively. The indwelling Foley catheter is removed when the patient is mobile and stable. Depending on the output of the closed suction drain, it can be removed 5 to 10 days postoperatively. If a ureteral stent is used, it should not be removed for 4 to 6 weeks postoperatively. After removal of the indwelling Foley catheter, if the output of the closed suction drain is increased, the transurethral indwelling Foley catheter is reinserted to reduce the intrapelvic urine pressure, which should minimize the output from the closed suction drain.

Complications Associated with Partial Nephrectomy

Urinary Fistulae. Partial nephrectomies that involve incision of the collecting system, because of the size and location of the tumor, increase the possibility of urinary leakage. Most urinary fistulae present themselves in about 1 week postoperatively. Therefore, in cases of deep renal resections, it is advisable to keep the closed suction abdominal drain in place for 7 to 10 days. If a urinary fistula is suspected, the diagnosis is confirmed by checking the effluent for creatinine, which will be present at a level manyfold higher than the serum creatinine level. Alternatively, an intravenous ampule of indigo carmine, when injected and collected in the closed suction drain, can also confirm the diagnosis.

If a closed suction drain is not present and a urinary fistula is suspected, a urinary collection in the retroperitoneum can become



Figure 60-42. Left renal mass in the lower pole on computed tomography scan.

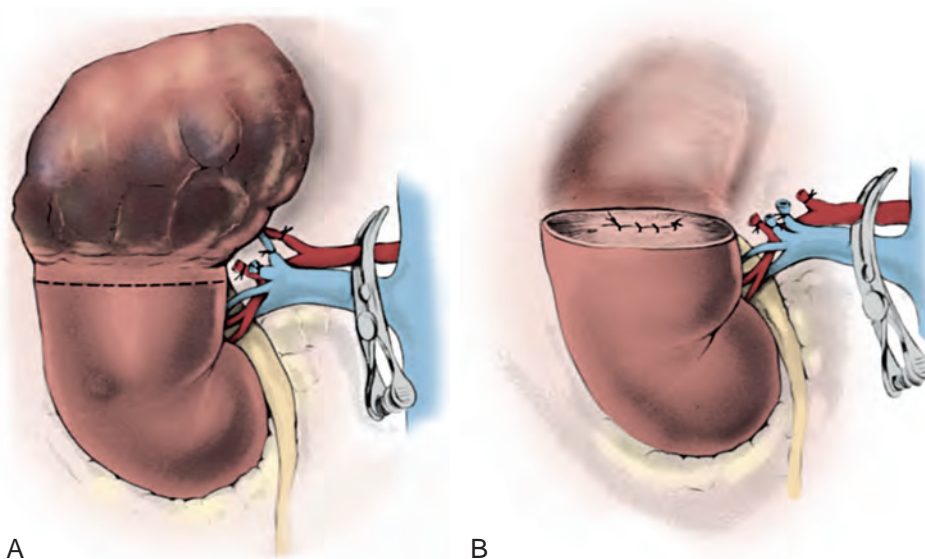


Figure 60-45. A and B, Technique of transverse resection for a tumor involving the upper half of the kidney. (From Novick AC: Partial nephrectomy for renal cell carcinoma. *Urol Clin North Am* 1987;14:419.)

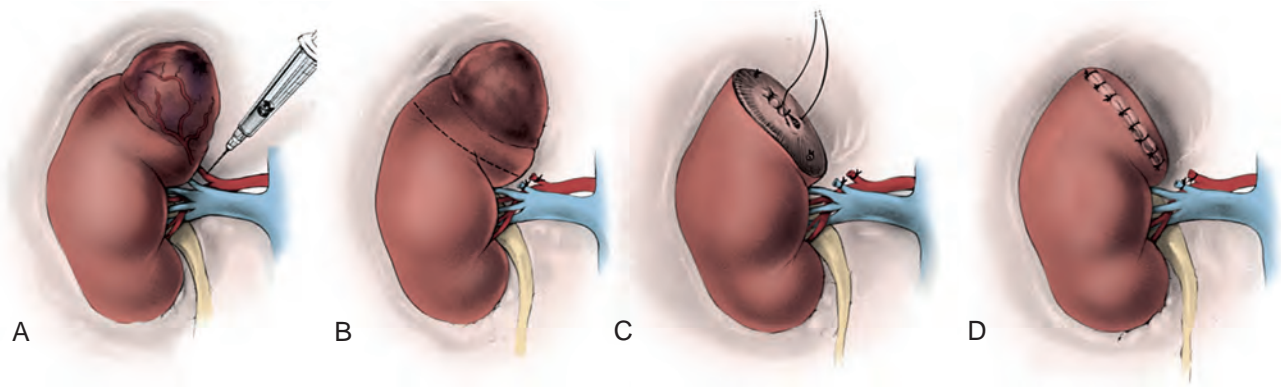


Figure 60-44. A to D, Technique of segmental (apical) polar nephrectomy with preliminary ligation of apical arterial and venous branches. (From Novick AC. Partial nephrectomy for renal cell carcinoma. *Urol Clin North Am* 1987;14:419.)

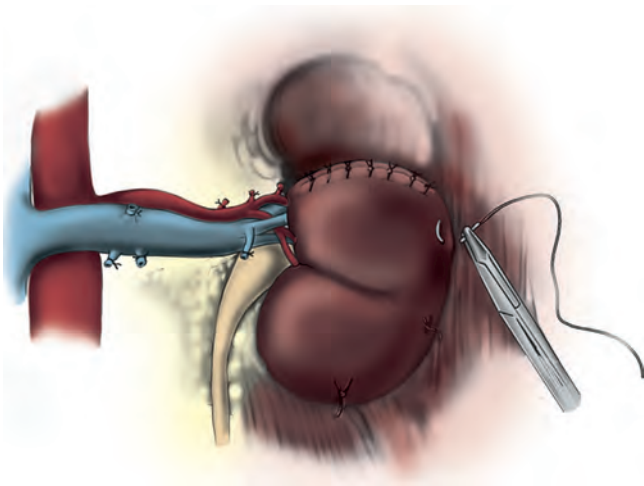


Figure 60-46. Nephropexy of the remnant kidney to the retroperitoneum is achieved with several interrupted sutures.

symptomatic. Abdominal imaging is used to confirm the diagnosis. The treatment of urinary fistulae requires three tubes: (1) a retroperitoneal closed suction drain to collect the urinoma, (2) a double-J ureteral stent that is placed after retrograde pyelography, and (3) a Foley catheter to keep the entire collecting system at low pressure. Most fistulas resolve within 4 to 6 weeks with conservative management, and reoperation is rarely required.

Postoperative Bleeding. Delayed bleeding can occur following partial nephrectomy, particularly in patients who require postoperative anticoagulation therapy. If a drain is in place, initial management is conservative and consists of bed rest, hydration, close clinical monitoring, and serial evaluations of blood counts. In situations when more than 1 to 2 units of transfused blood products are required, renal angioembolization should be attempted. Usually, bleeding segmental and subsegmental arteries can be selectively embolized and the kidney salvaged without need for complete nephrectomy. Life-threatening hemorrhage can also occur and require complete angioinfarction of the kidney or reoperative exploration.

Renal Insufficiency. Acute renal failure may follow partial nephrectomy in a solitary kidney, related to large size of the tumor, excessive removal of renal parenchyma, and prolonged ischemic time. Obstruction of the collecting system, drug toxicity, vascular thrombosis, and vascular disruption are other causes that should be considered. While most cases of postoperative renal insufficiency are mild and temporary, some cases require hemodialysis for electrolyte and fluid management. Hyperfiltration injury can also cause a gradual decrease in renal function over time, typically associated with proteinuria.

Vena Caval Thrombectomy

Tumor thrombus within the venous drainage system of the kidney can occur with many retroperitoneal tumors. In children, Wilms tumor, clear cell sarcoma of the kidney, adrenocortical carcinoma, and neuroblastoma can all be associated with IVC thrombi. In adults, urothelial carcinoma of the renal pelvis, lymphoma, retroperitoneal sarcoma, adrenocortical carcinoma, pheochromocytoma, and angiomyolipoma are all potential sources of an IVC thrombus. RCC is the most common cause associated with IVC tumor thrombus, accounting for 18% of all tumors that have venous thrombi (Blute et al, 2004b). The two components associated with IVC thrombi are tumor thrombus (tumor cells contained within bland thrombus) and bland thrombus (blood coagulum without tumor cells). Venous drainage is hampered by venous thrombus encouraging formation of bland thrombus. Distinction between these two forms of venous thrombus is critical and forms the basis of operative management for IVC thrombi.

Management of a tumor with associated IVC thrombus can be technically challenging. In the case of RCC with venous thrombus, 10% have associated positive regional lymph nodes, 25% have associated metastases, and 50% have perirenal fat invasion. Usually, IVC thrombectomy is accompanied by radical nephrectomy and regional lymph node dissection.

Preoperative Considerations

Pulmonary Embolism, Anticoagulation, and IVC Filters. Patients with renal tumors are at increased risk of pulmonary embolism as a result of malignancy-associated hypercoagulability and venous thrombus embolization. We suggest anticoagulation with intravenous or low-molecular-weight heparin to be started as soon as tumor thrombus is detected. Although evidence supporting the use of preoperative anticoagulation is limited, several potential benefits include reduced risk of pulmonary embolism, tumor thrombus shrinkage, and bland thrombus shrinkage and/or prevention. Temporary suprarenal IVC filters are also an option for patients with level 0, I, and II tumor thrombi. However, because of the risk of contralateral renal and hepatic vein thrombosis, the risk of provoking embolization, and the impediment that these devices can pose to future IVC thrombectomy, we do not recommend use of supra-

renal IVC filters. Given the risk of intraoperative thrombus detachment and the possibility of interval thrombus growth in the period immediately preceding surgery, we recommend the use of transesophageal echocardiography (TEE) for level II to IV thrombi.

Preoperative angioembolization can be considered since tumor thrombi have an independent blood supply arising from the renal artery and/or aorta in one third of cases. Angiographic infarction of the blood supply to the tumor thrombus can help shrink a large thrombus to a more manageable size, potentially avoiding the need for bypass or extensive mobilization of the liver. Angioembolization can be considered when caval thrombi appear to invade the IVC, when the thrombus invades the intrahepatic or suprahepatic veins and cannot be excised, when the thrombus is associated with a bleeding kidney, and when deep hypothermic arrest is planned since the patency of the coronary arteries can be simultaneously assessed. The optimal timing for angioembolization is unknown but at most centers, when undertaken, it is usually performed 1 day prior to surgery. There is a potential risk of causing iatrogenic pulmonary embolization of the tumor thrombus when angiography is performed; however, this risk appears to be minimal. We seldom use angioembolization but, if performed, it is associated with ischemia-related flank pain and tumor lysis syndrome.

Urologists who do not routinely handle the IVC and aorta should consult a vascular surgeon for level II and III thrombi to aid in vena caval control and reconstruction. Consultation with a cardiothoracic surgeon preoperatively for all level III and IV thrombi is essential, since access to the mediastinal compartment for vascular bypass and thrombus removal may be required. Involvement of a cardiologist or cardiac anesthesiologist is essential for level II to IV thrombi to allow for intraoperative TEE.

Tumor Thrombus Level. Traditionally, IVC thrombi have been defined and managed according to the cranial extent of the tumor thrombus (Fig. 60-47). MRI provides excellent overall assessment of the level of tumor thrombus involvement; however, reconstructed CT angiograms can also produce excellent images to determine the level of the tumor thrombus. Assessment of the bland thrombus, a grouping system that complements the traditional tumor thrombus levels, can help with intraoperative decision making (Tables 60-1 and 60-2). The key addition of this grouping system is the consideration of the location and extent of bland thrombus and its impact on IVC management (Fig. 60-48).

Level I Vena Caval Thrombectomy: Right-Sided Tumor

Usually, level I thrombi are partially occlusive, are nonadherent, and do not require extensive IVC dissection or any form of bypass. Some groups mobilize the kidney after the thrombectomy is complete, in order to minimize the risk of embolization, while others mobilize the kidney first followed by thrombectomy.

Using an anterior midline, anterior subcostal, or modified flank incision, access is gained to the kidney as previously described. The great vessels and the renal hilum are exposed. Using care not to manipulate the renal vein or IVC too much, the renal artery is identified in the interaortocaval region and secured with 0 silk ligature or a large clip. Ligating the renal artery early will help reduce the blood flow to the kidney and minimize the amount of potential blood loss. The kidney is mobilized outside the renal fascia and the IVC is dissected above the right renal vein. The left renal vein, suprarenal IVC, and infrarenal IVC are identified and secured with vessel loops. To help with temporary ligation of these vessels, 3- to 6-inch portions of an 18-Fr red rubber catheter are passed through the vessel loop and used as Rummel tourniquets (Fig. 60-49 on the Expert Consult website). While this degree of vascular control may not be necessary for all level I thrombi, it is prudent to have adequate vascular control if there is any doubt about the extension of the level of thrombus. Starting cranially, the IVC is gently pinched closed, and then the Rummel tourniquets are applied so that the infrarenal IVC, left renal vein, and suprarenal IVC are closed in that order. The IVC is milked with the left hand toward the ostium of the right renal vein. A C-shaped Satinsky vascular clamp is placed

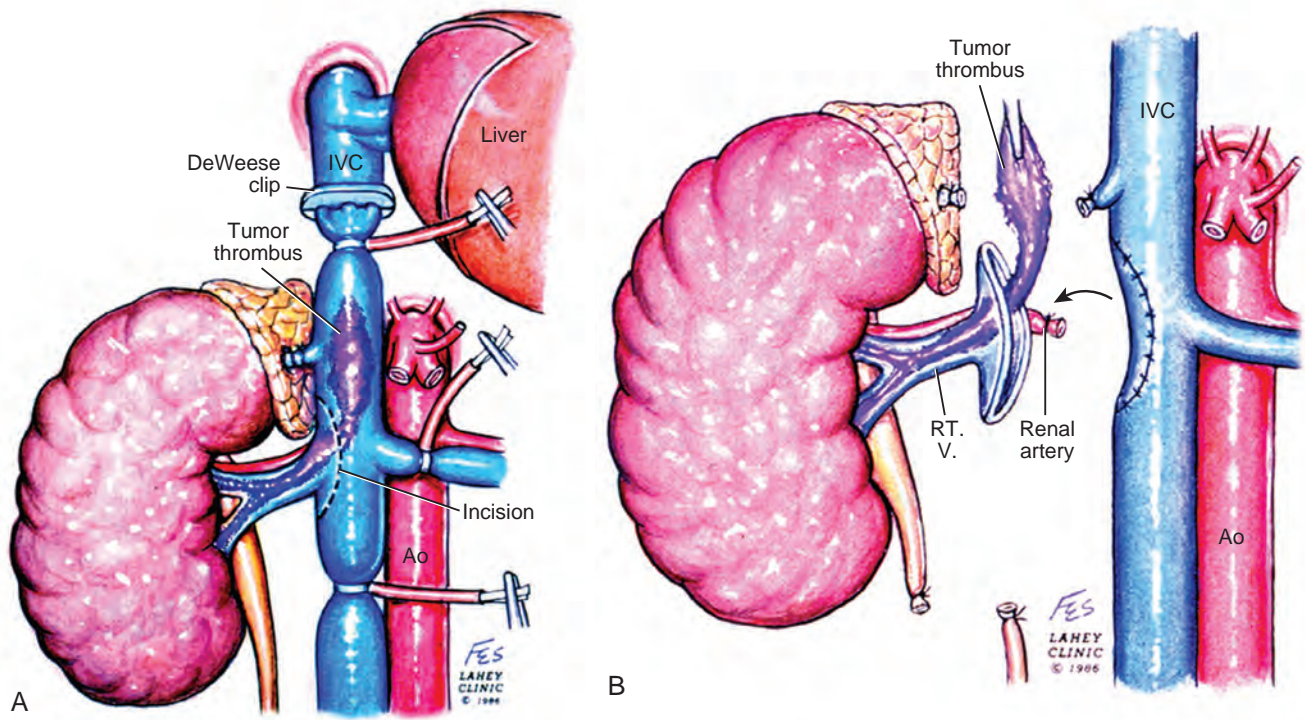


Figure 60-49. A and B, Technique for removing infrahepatic tumor thrombus with assistance of Rummel tourniquets, avoiding cardiopulmonary bypass. Ao, aorta; IVC, inferior vena cava; RT. V, right vein. (© The Lahey Clinic.)

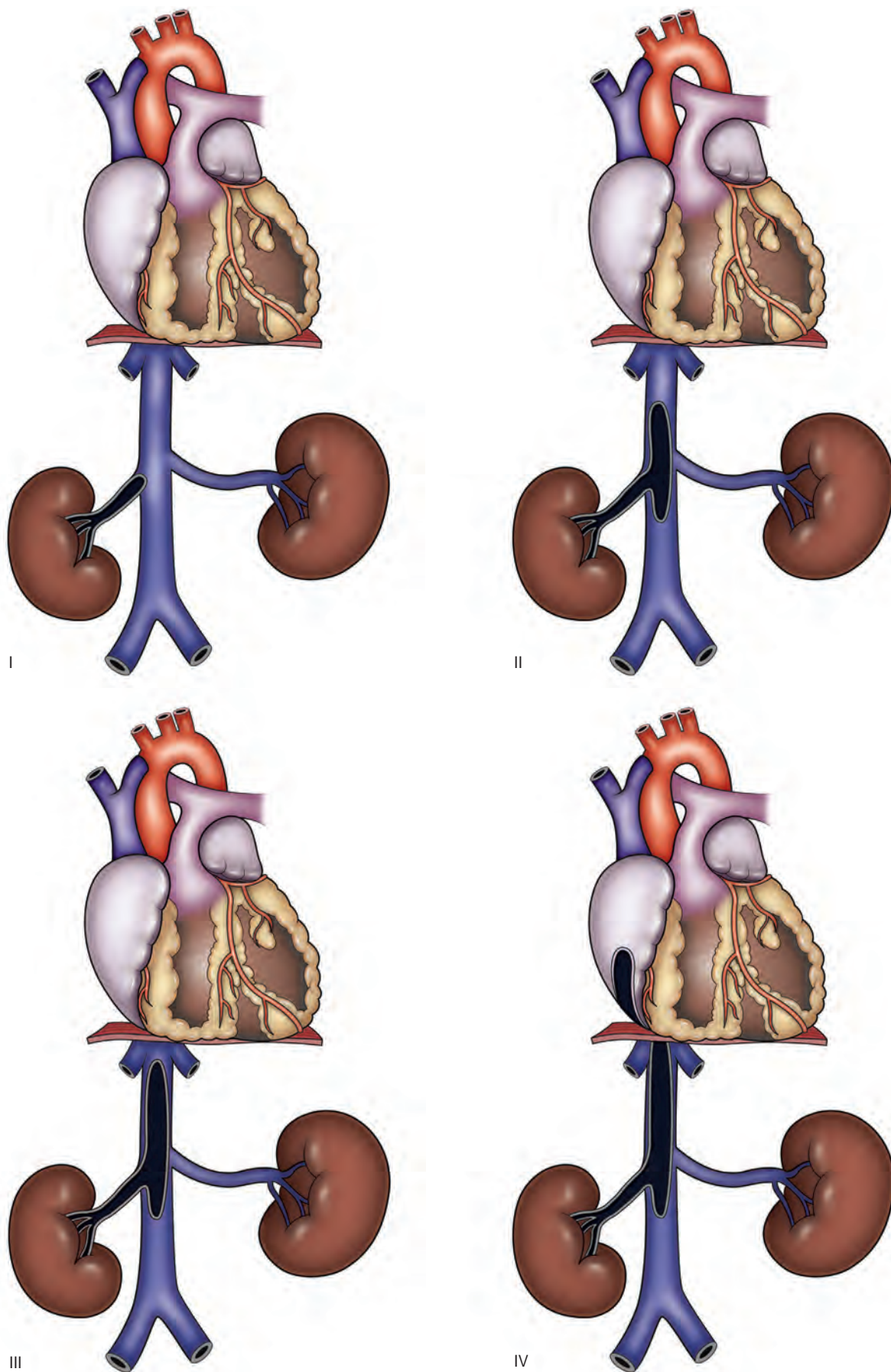


Figure 60-47. Classification of venous tumor thrombus extension. (From Wang GJ, Carpenter JP, Fairman RM, et al. Single-center experience of caval thrombectomy in patients with renal cell carcinoma with tumor thrombus extension into the inferior vena cava. *Vasc Endovasc Surg* 2008;42:335–40.)

TABLE 60-1 Traditional Staging and Management of Inferior Vena Cava (IVC) Thrombi

THROMBUS LEVEL	INCIDENCE RATE IN RCC	PROPORTION OF THROMBI	CRANIAL EXTENT OF THROMBUS	MANAGEMENT OF TUMOR THROMBUS
0	12%	65%	Confined to renal vein	Radical nephrectomy
I	2%	10%	Within 2 cm of renal vein ostium	IVC milking, partial IVC occlusion, ostial cavotomy
II	3%	15%	Below hepatic veins	Complete IVC mobilization/control, infrahepatic cavotomy
III	1%	5%	Between hepatic veins and diaphragm	Complete occlusion: suprahepatic IVC clamping, infrahepatic cavotomy Partial occlusion: veno-venous bypass, infrahepatic cavotomy
IV	1%	5%	Above diaphragm	Deep hypothermic arrest, infrahepatic cavotomy, right atriotomy

RCC, renal cell carcinoma.

Data from Blute ML, Leibovich BC, Lohse CM, et al. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. *BJU Int* 2004;94:33–41.

TABLE 60-2 Mayo Clinic Thrombus Grouping System for Inferior Vena Cava (IVC) Thrombi

MAYO THROMBUS GROUP	INCIDENCE RATE IN RCC	PROPORTION OF THROMBI	ASSOCIATED BLAND THROMBUS	ADDITIONAL IVC MANAGEMENT
A	17%	90%	None	None
B	<1%	1%	At or below common iliac veins	Infrarenal IVC filter (e.g., Greenfield)
C	1%	5%	Infrarenal IVC, separate from tumor thrombus	Infrarenal IVC interruption with vena cava clip
D	0.5%	4%	Infrarenal IVC, mixed with tumor thrombus	Infrarenal IVC resection

RCC, renal cell carcinoma.

Data from Blute ML, Leibovich BC, Lohse CM, et al. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. *BJU Int* 2004;94:33–41.

around the ostium of the right renal vein partially occluding the IVC (Fig. 60-50), ensuring that the thrombus is located within the jaws of the clamp before complete closure. The IVC is palpated for evidence of any other thrombus. Suction and two sponge sticks (to compress the IVC if necessary) are readied and laparotomy sponges are placed around the renal vein to collect any spillage of tumor thrombus after opening of the renal vein. The renal ostium is circumferentially incised using a scalpel or fine-tipped Metzenbaum or Potts scissors. At least half of the width of the IVC must be maintained for proper closure.

The thrombus is extracted by gentle downward traction on the renal vein. A gauze is wrapped around the renal vein stump and secured with a silk ligature to prevent tumor spillage (Fig. 60-51). The medial attachments of the kidney are dissected, ligating the renal artery again before division.

The IVC is inspected for evidence of residual thrombus, irrigating its lumen with heparinized saline (100 units/mL) for improved visualization. The IVC defect is closed with a running closure using a 4-0 Prolene suture on a BB vascular needle (Fig. 60-52). Prior to tying the knot, the anesthesiologist should apply positive airway pressure, pinch the infrarenal IVC closed, and then release the Satinsky clamp. The surgeon should allow 5 to 10 mL of blood to escape from the caval defect to flush out any residual thrombus fragments and debris before pulling the suture tight and tying the closure. A right regional lymphadenectomy is performed, irrigating the wound copiously with sterile water. The surgeon may consider placement of a closed suction catheter to monitor for bleeding.

Level II Vena Caval Thrombectomy: Left-Sided Tumor

Exposure for a tumor thrombus associated with a left-sided tumor is more difficult since the IVC is best accessed from the right retroperitoneum. Both the right and the left colon have to be mobilized to get adequate exposure. The anterior midline and chevron incisions provide the best access for left-sided tumors associated with tumor thrombi in the IVC.

After a subcostal chevron incision is made, the left colon is mobilized and the left anterior pararenal space is developed. The left renal artery is then identified and ligated near its origin close to the aorta. The adrenal, lumbar, and gonadal branches of the left renal vein are ligated and divided. These branches are often dilated and friable and occasionally contain thrombi. The kidney is mobilized outside the renal fascia and the ureter is divided.

The right colon and small bowel are mobilized, a Kocher maneuver is performed, and the right anterior space is developed and the great vessels are exposed. The IVC is carefully dissected to its bifurcation, ligating the right gonadal vein on its anterior surface. Vascular control is obtained sequentially in the following order: (1) the ipsilateral (left) renal artery is ligated, (2) the infrarenal IVC is clamped, (3) the contralateral (right) renal vein is clamped, (4) the suprarenal IVC is clamped, and (5) accessory hepatic veins are ligated to the caudate lobe (this is an optional maneuver to gain 2 to 3 cm of extra infrahepatic IVC exposure) (Fig. 60-53 on the Expert Consult website). Optionally, one can clamp the contralateral renal artery to prevent renal engorgement while the venous



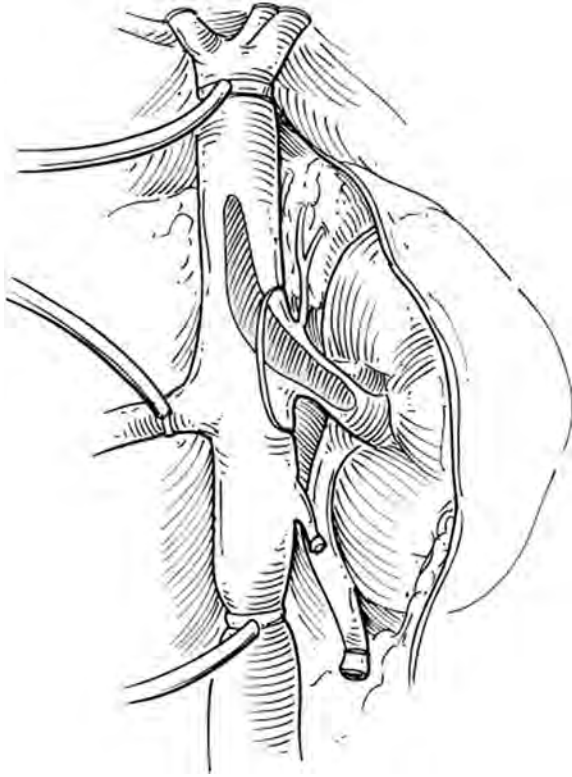


Figure 60-53. Left-sided level II tumor thrombus. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

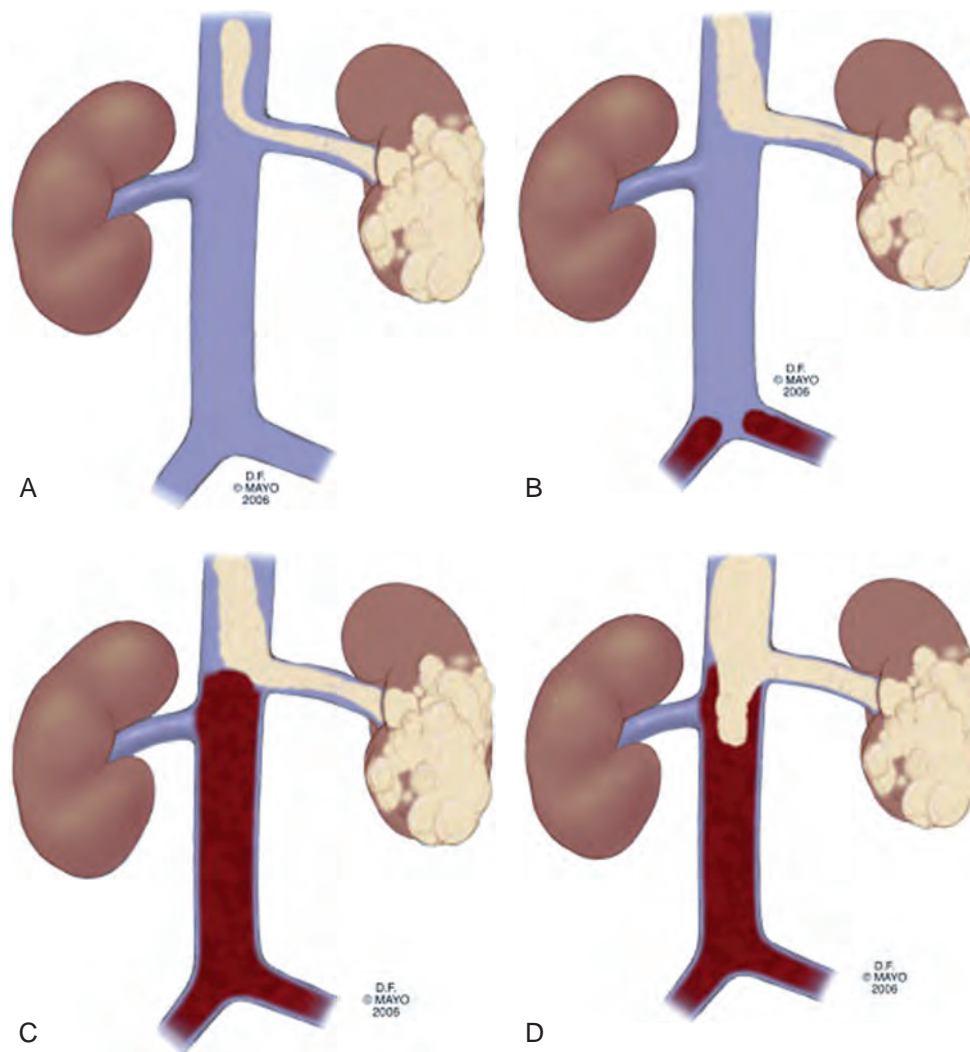


Figure 60-48. Mayo Clinic Thrombus Classification system. (From Blute ML, Boorjian SA, Leibovich BC, et al. Results of inferior vena caval interruption by Greenfield filter, ligation or resection during radical nephrectomy and tumor thrombectomy. *J Urol* 2007;178:440-5. Reprinted with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

outflow is temporarily clamped. This is more of an issue for left-sided tumors since the right kidney does not have significant venous collateralization to shunt blood when the right renal vein is clamped. While obtaining vascular control, one must be very gentle to avoid dislodging the thrombus. The lumbar veins are ligated and divided as required. Prior to clamping, some may use 0.5 mg/kg of intravenous heparin to prevent clamp-related thrombotic complications. Our experience has been that bleeding, not clotting, is the principal problem encountered with vena caval thrombectomy and we do not routinely heparinize our patients.

The renal vein ostium is circumferentially excised and the incision is extended superiorly onto the anterior surface of the IVC using Potts scissors (Fig. 60-54). A Penfield dissector is used to carefully extract the tumor thrombus from the IVC. Lumbar veins can be a source of troublesome bleeding at this stage and should be ligated or sutured as needed. The gross tumor thrombus and kidney are removed en bloc. The IVC is flushed with heparinized saline and the intima inspected for signs of caval invasion. Any suspicious areas should be biopsied or resected. The IVC lumen can be safely narrowed to about 50% of its preoperative size without requiring special measures. The caval defect is closed with a running 4-0 Prolene suture. Prior to tying the knot, the infrarenal clamp is released and 5 to 10 mL of blood is allowed to seep from the

cavotomy to clear the IVC of air and debris. After tying the suture, the contralateral renal clamp is released followed by the suprarenal IVC clamp. Regional lymphadenectomy is performed, consideration is given to leaving a closed suction drain, and the wound is irrigated and the incision closed.

Level III-IV Vena Caval Thrombectomy: Intra-abdominal Approach

Intrahepatic tumor thrombi are very challenging cases to treat. The operating room should be set up for possible cardiopulmonary bypass (CPB), including deep hypothermic arrest. Intraoperative TEE should be available to measure the cranial extent of the thrombus and to monitor the thrombus for fracture and embolization (Fig. 60-55). Cardiac function is evaluated with TEE so that the anesthesiologist can appropriately manage the patient's hemodynamics.

The key decision for level III thrombi is whether to attempt an intra-abdominal thrombus extraction with complete hepatic mobilization or use a combined intrathoracic/intra-abdominal approach with bypass. This decision can only be made intraoperatively, after the renal artery is ligated, the liver is mobilized, and the IVC is

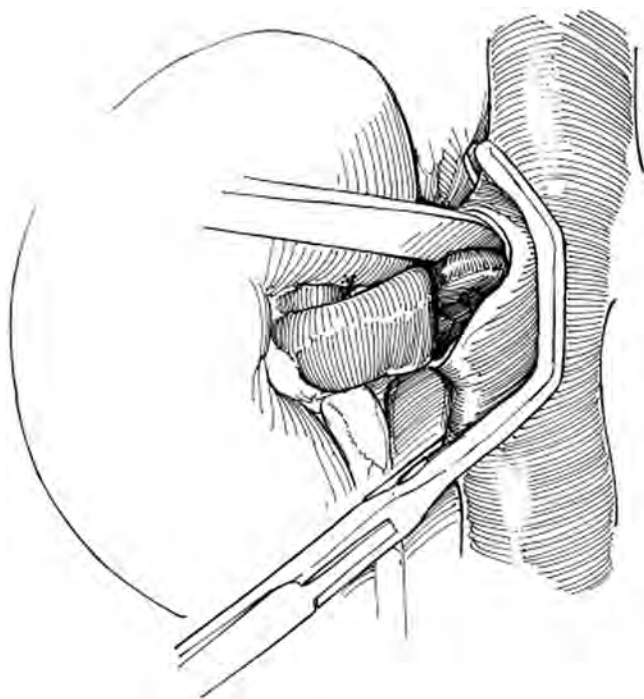


Figure 60-50. Right-sided level I tumor thrombus. A C-shaped Satinsky vascular clamp is placed around the ostium of the right renal vein, partially occluding the inferior vena cava. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

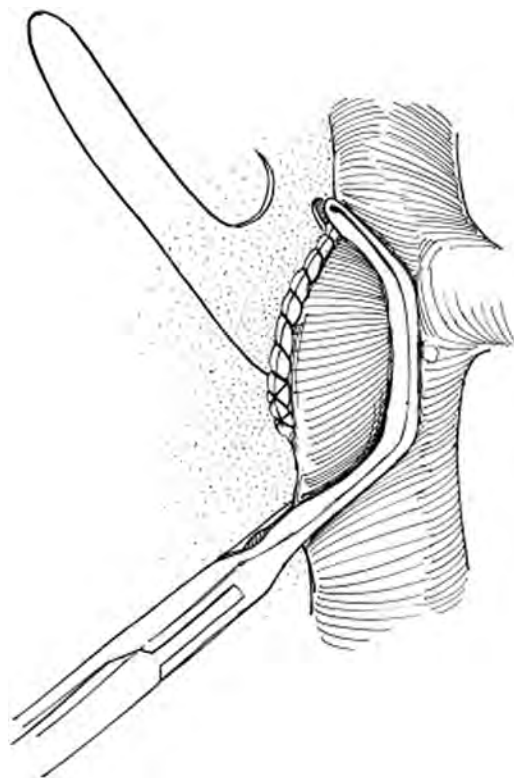


Figure 60-52. Right-sided level I tumor thrombus. Closing the inferior vena cava defect. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

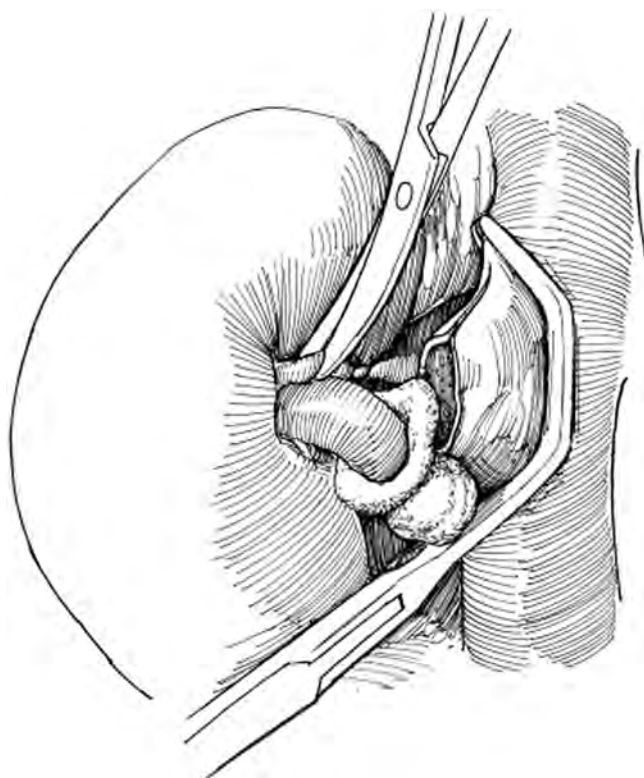


Figure 60-51. Right-sided level I tumor thrombus. Preventing tumor spillage. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

exposed and evaluated. If the IVC can be clamped below the hepatic veins this is preferable, since the venous return from the liver is significant. As a rule of thumb, patients with free-floating partially occlusive thrombi will not tolerate suprahepatic clamping very well and should probably undergo bypass. Contrarily, patients with completely occlusive thrombi will typically have developed extensive collateral venous drainage networks and therefore tolerate clamping much better (Fig. 60-56). Occasionally, a level IV thrombus can be milked into the abdomen through a small diaphragmatic incision and treated intra-abdominally. It is crucial that IVC control not compromise the operation since bleeding and hypotension can lead to an incomplete tumor resection, a result that is universally fatal. Techniques of bypass are discussed in a later section.

We prefer the anterior midline incision for level III and IV thrombi; however, a chevron incision with added sternotomy can also be used. The right kidney and great vessels are exposed as described for a level I thrombus and the right renal artery is ligated in the interaortocaval area. The infrahepatic IVC is gently dissected. The infrahepatic IVC and left renal vein are isolated and Rummel tourniquets are placed around them.

The liver is mobilized by ligating and dividing the ligamentum teres, the remnant of the obliterated left umbilical vein that is located at the lower free border of the falciform ligament. The falciform ligament is divided with electrocautery up to the upper border of the liver where it branches into the coronary ligament on the right and the left triangular ligament on the left (see Fig. 60-12). The superior layer of the coronary ligament is divided with scissors or electrocautery, taking care not to injure the liver or the IVC, which is located just behind the ligament in the bare area of the liver. Division of the superior layer of the coronary ligament continues along the right border of the liver until it forms the right triangular ligament (the fused superior and inferior layers of the coronary ligament), which should also be divided. Mobilization of the right lobe of the liver is completed by dividing the inferior layer of the

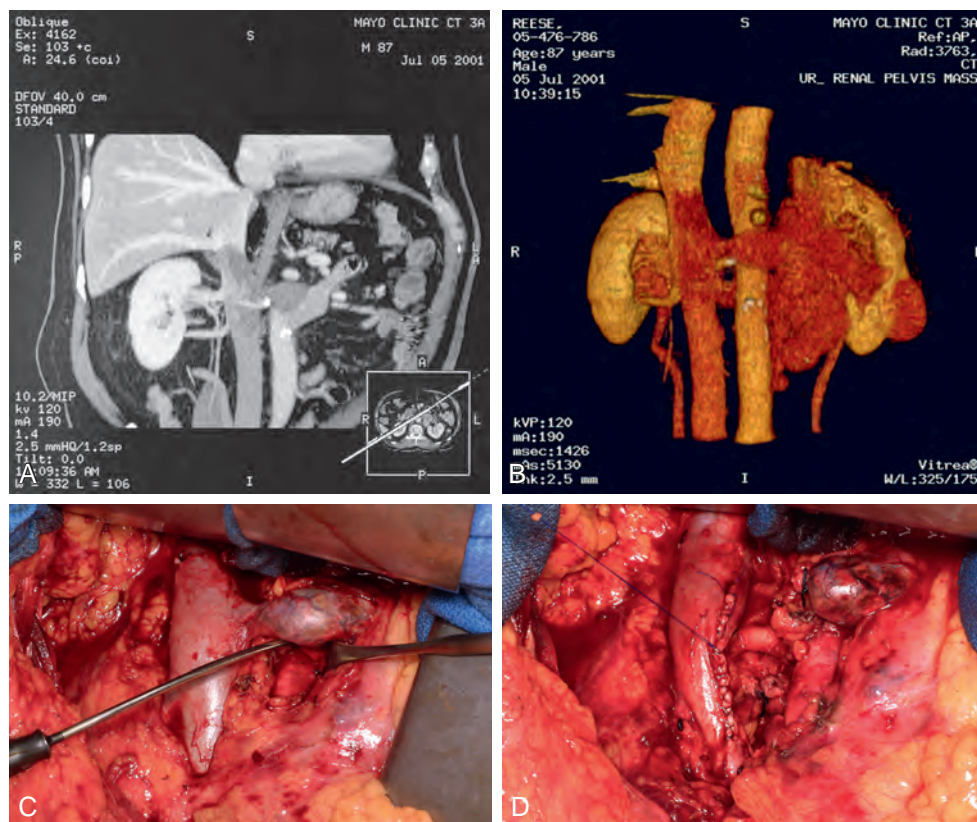


Figure 60-54. Coronal computed tomography scan (A) and three-dimensional reconstruction (B) of a level II left-sided tumor thrombus. C, Securing vascular control. D, Repair of inferior vena cava defect.

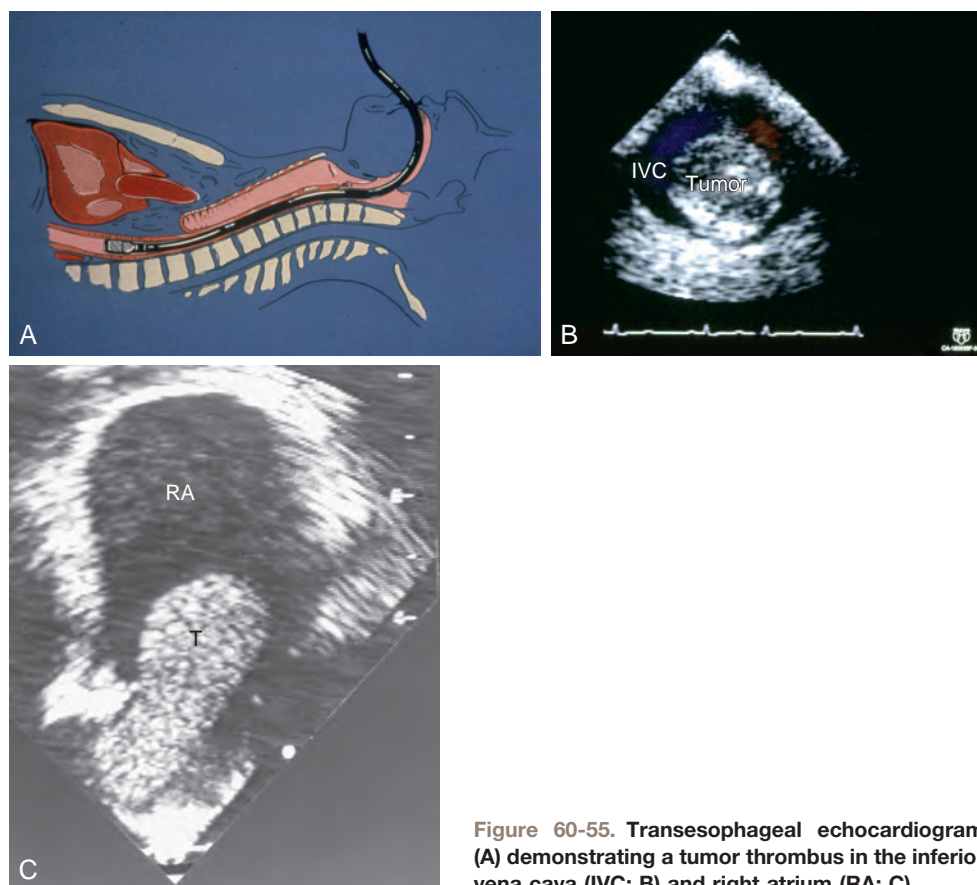


Figure 60-55. Transesophageal echocardiogram (A) demonstrating a tumor thrombus in the inferior vena cava (IVC; B) and right atrium (RA; C).

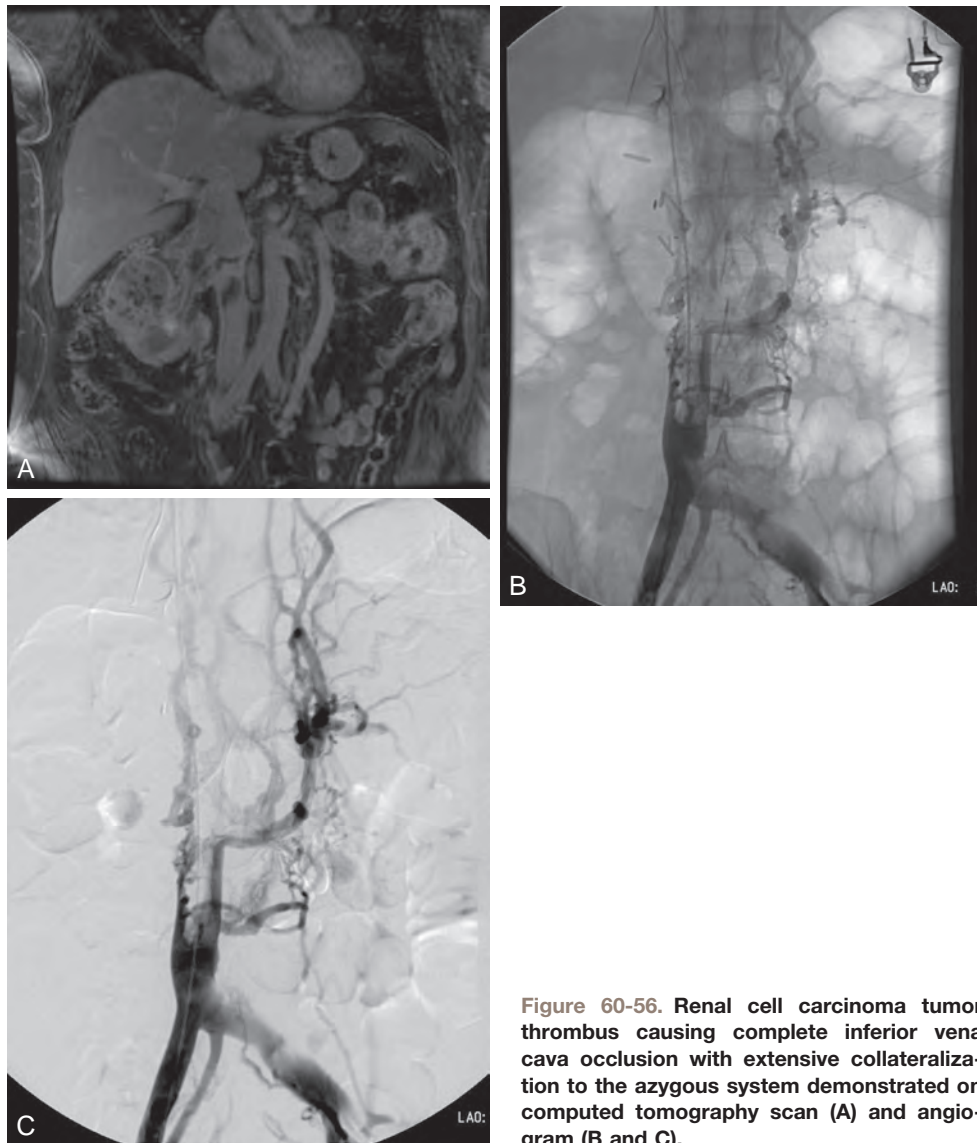


Figure 60-56. Renal cell carcinoma tumor thrombus causing complete inferior vena cava occlusion with extensive collateralization to the azygous system demonstrated on computed tomography scan (A) and angiogram (B and C).

coronary ligament, the attachment that ties the liver to the diaphragm, upward toward the IVC.

The left triangular ligament is divided anteriorly and hepatic mobilization is completed by dividing the posterior aspects of the left triangular ligament toward the IVC. The right lobe of the liver can now be safely and gently rotated toward the midline so that the IVC can be evaluated on the posterior surface of the liver (Fig. 60-57). For tumors of the left kidney, it may be necessary to divide the diaphragmatic attachments of the spleen so that it can be rotated toward the midline with the pancreas without being traumatized.

The plane between the posterior surface of the liver and the anterior surface of the IVC is developed. The help of a hepatic surgeon with this portion of the procedure should be considered. This plane contains venous branches from the liver that are divided into upper and lower groups. The most important group is the upper group that contains the right, middle, and left hepatic veins, the principal outflow from the liver, and therefore cannot be divided. Tumor thrombus can extend into these veins and they must be carefully inspected and cleared of any thrombus during thrombectomy. Obstruction of these three veins leads to the Budd-Chiari syndrome. The lower group of hepatic veins (the accessory hepatic veins) drain blood principally from the caudate lobe (with a small contribution from the right lobe) and can be safely divided. The accessory hepatic veins are ligated with 2-0 silk and the plane

between the IVC and the liver is developed. Additionally, the lumbar veins are ligated with 2-0 silk and the plane between the IVC and the posterior abdominal wall is developed. The IVC should now be fully mobilized.

A window is created in the lesser omentum and the porta hepatis (also called the portal triad or hepatic pedicle), which contains the portal vein, common hepatic artery, and common bile duct, is encircled with a Rummel tourniquet. Clamping the porta hepatis (the Pringle maneuver) is necessary to prevent massive blood loss if the IVC is clamped above the major hepatic veins (Fig. 60-58 on the Expert Consult website). Clamping the IVC above and below the hepatic veins while performing a Pringle maneuver is called total hepatic vascular occlusion. If the IVC is clamped below the major hepatic veins and the accessory hepatic veins are ligated, the Pringle maneuver may not be necessary. Under normothermic conditions, the porta hepatis can be clamped for up to 60 minutes, although a clamping time of 20 minutes or less is preferred since ischemic hepatic injury and portal vein thrombosis can ensue. Another complication of the Pringle maneuver is splenic engorgement and rupture as a result of backup of venous drainage from the splenic vein, which normally empties into the portal vein.

The resectability of the tumor and thrombus is determined using TEE and a thorough intraoperative assessment of the anatomy. If the thrombus is below the hepatic veins or can be milked below these veins, it is usually safe to proceed without bypass. If the

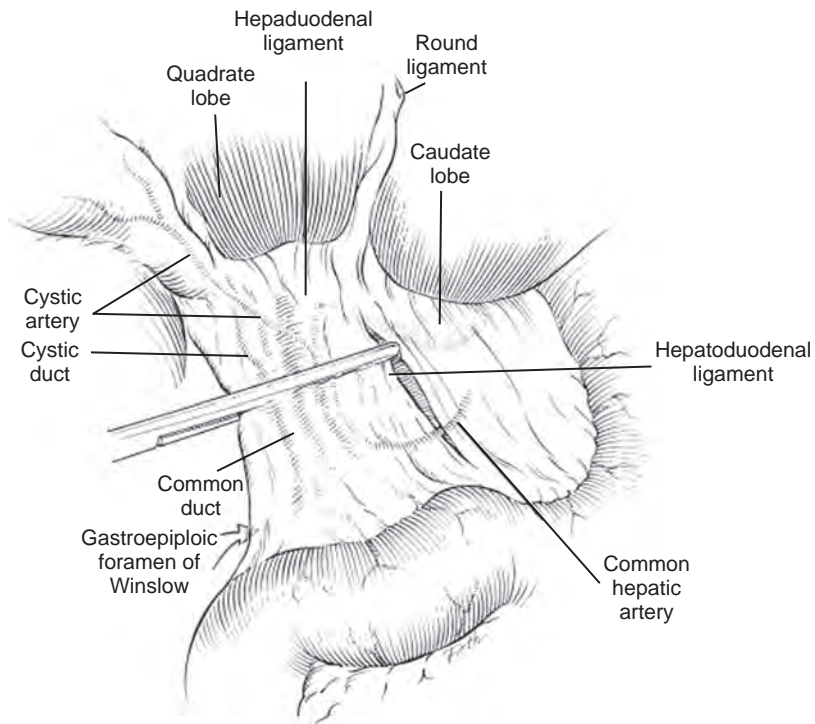


Figure 60-58. The Pringle maneuver. (From Asensio J, Trunkey D. *Current therapy of trauma and surgical critical care*. Philadelphia: Mosby; 2008.)

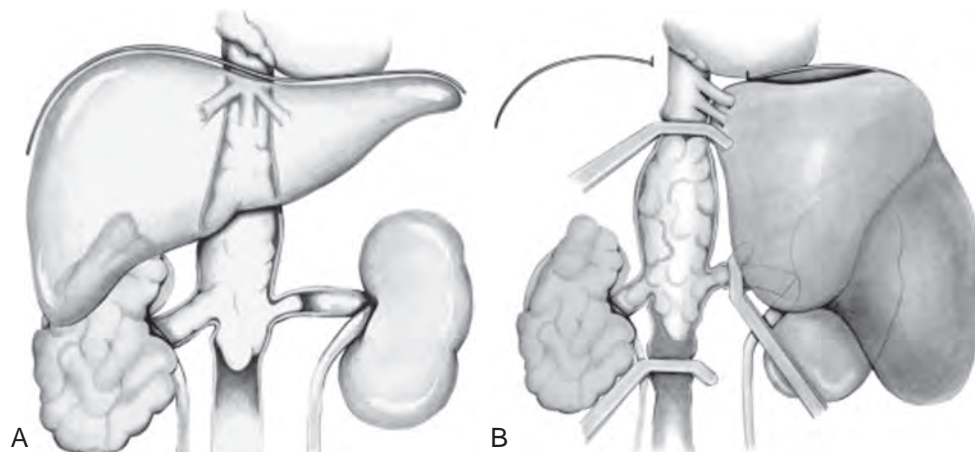


Figure 60-57. A and B, Mobilizing the liver to expose the inferior vena cava for management of tumor thrombus. (From Ciancio G, Livingstone AS, Soloway M. Surgical management of renal cell carcinoma with tumor thrombus in the renal and inferior vena cava: the University of Miami experience in using liver transplantation techniques. *Eur Urol* 2007;51:988–95.)

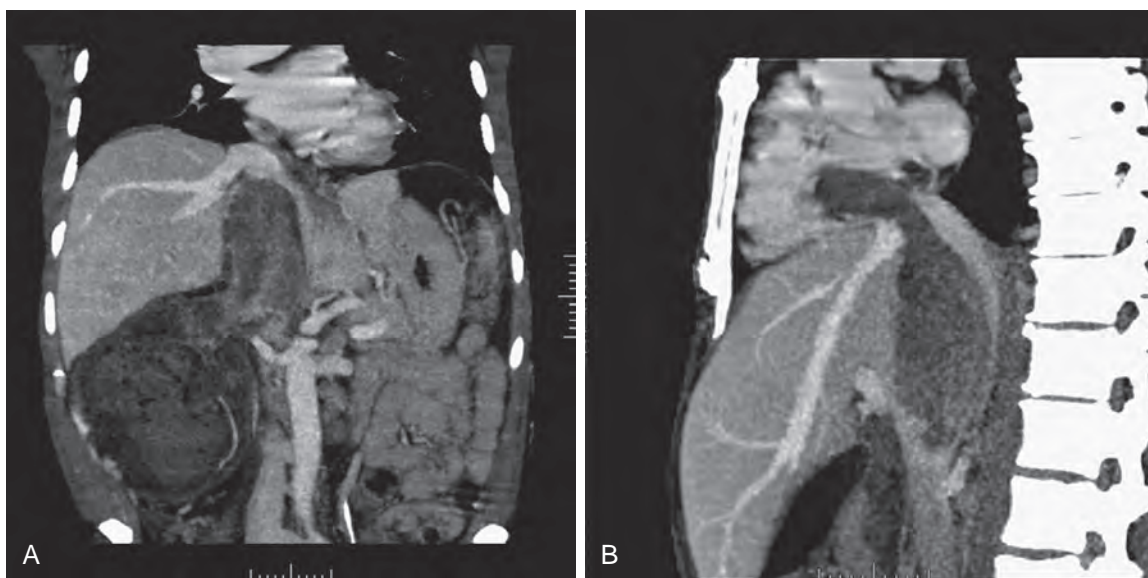


Figure 60-59. A, Coronal magnetic resonance (MR) image demonstrates tumor extending to the level of the diaphragm. B, Sagittal MR reconstruction demonstrates thrombus that extends farther into the right atrium. The patient would eventually require cardiopulmonary bypass and deep hypothermic circulatory arrest.

thrombus involves the hepatic veins or extends above the liver, bypass is often required (Fig. 60-59). The IVC is occluded above the liver and thrombus and the patient's hemodynamic response is observed over 2 to 5 minutes. Clamping the suprahepatic IVC results in a 60% reduction in cardiac preload, an increase in peripheral vascular resistance of 80%, an increase in heart rate of 50%, a drop in cardiac output of 40%, and a drop in mean arterial blood pressure of 10% to 20%. If the cardiac output drops more than 50% or the mean arterial blood pressure drops more than 30%, the patient will not tolerate suprahepatic IVC clamping. Options for managing this situation include bypass (our preference) and clamping of the supraceliac aorta. If the IVC clamping trial is tolerated and the thrombus can be removed in less than 30 minutes, it is safe to proceed with the intra-abdominal procedure.

In sequence, the infrarenal IVC, the contralateral (left) renal vein, the porta hepatis, and the suprahepatic IVC are clamped. For left-sided tumors, the right renal artery should be clamped prior to the right renal vein since there is no good collateral venous drainage

for the right kidney. The ostium of the right renal vein is circumferentially incised and the incision is extended upward toward the intrahepatic IVC. The incision should be large enough to permit extraction of all of the tumor thrombus and careful inspection of the intima of the IVC. The thrombus and kidney are excised (Fig. 60-60). With the help of a Penfield dissector the IVC is cleared of adherent thrombus. A Fogarty balloon catheter (Edwards Lifesciences Corporation, Irvine, CA) or 20-Fr Foley catheter can be used as an embolectomy catheter if the thrombus is out of reach. If involved with tumor that cannot be scraped away, the IVC should be completely or partially resected and reconstructed (see [Patching, Replacing, and Interrupting the Inferior Vena Cava](#)). During deep hypothermic arrest a cystoscope can be used to inspect the hepatic veins and suprahepatic IVC, which allows for a smaller caval incision. The IVC is closed as described for level II thrombus. The hepatic ligaments are tacked back into place to prevent torsion of the liver. A regional lymphadenectomy is performed and a closed suction drain is inserted.

Level III-IV Vena Caval Thrombectomy: Combined Intra-abdominal and Intrathoracic Approach

Level III thrombi that cannot be removed intra-abdominally and most level IV thrombi are managed with a combined intra-abdominal and intrathoracic approach. Thoracoabdominal, chevron laparotomy with sternotomy, and anterior midline laparotomy with sternotomy incisions can be used to provide access to the chest and abdomen (Fig. 60-61 on the Expert Consult website). Our preference is for the anterior midline laparotomy with sternotomy. A cardiothoracic surgeon needs to participate with the planned operation.

The abdominal portion of the case is identical to the intra-abdominal approach described above. Once the abdominal phase

is completed, the cardiothoracic surgeon is called to the operating room and a median sternotomy is performed. The pericardium is opened and the right heart exposed. Often, mobilization of the liver and IVC is easier once the sternotomy is completed (Fig. 60-62).

The blood supply is bypassed using one of the techniques described below. Once on bypass, the ostium of the renal vein is circumferentially excised, the incision is extended cranially on the IVC, and the thrombus is extracted. A right atriotomy is usually performed to help remove the suprahepatic thrombus. The atrium and IVC are then closed. The patient is taken off bypass and thoracotomy tubes and closed suction abdominal drains are placed. The hepatic ligaments are tacked back into place to prevent torsion of the liver and regional lymphadenectomy is performed.

Bypass Techniques for Inferior Vena Cava Surgery

The requirement of bypass significantly complicates and prolongs IVC thrombectomy. However, bypass is often critical to performing the procedure safely and completely and should be used whenever required. Bypass should be considered in patients in whom the IVC cross-clamping trial causes significant hypotension, as well as in patients in whom there is preoperative cardiac or hepatic dysfunction, contralateral renal dysfunction, or portal venous hypertension, and when there is major intraoperative bleeding that is difficult to control.

Venovenous Bypass. This is the least invasive bypass technique for IVC thrombi and involves shunting the venous blood from below the renal veins to the venous return of the heart with the aid of a pump. Venovenous bypass (VVB) can be done without opening the chest, which is a key advantage that it has over traditional CPB. Two main options are available for infrarenal cannulation: a percutaneous approach through the femoral vein or a direct intraoperative approach through the IVC just above its bifurcation. When cannulating the IVC, it is important to position the tip of the cannula as far from the tumor thrombus as possible to avoid dislodging it, which can cause a massive pulmonary embolism, and to



Figure 60-60. Resected renal mass and intact inferior vena cava thrombus.

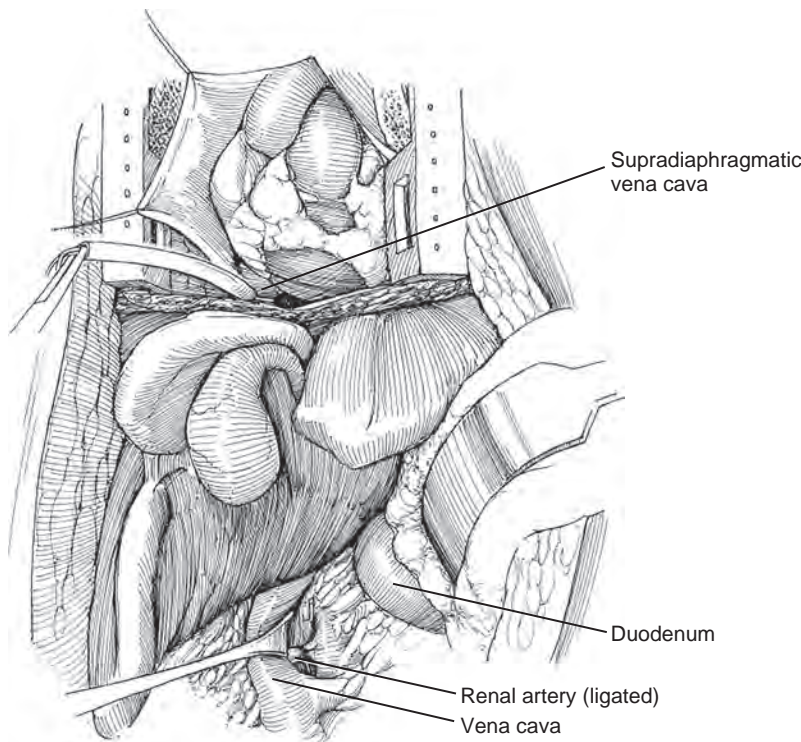


Figure 60-62. Median sternotomy with pericardium opened exposing the right heart. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

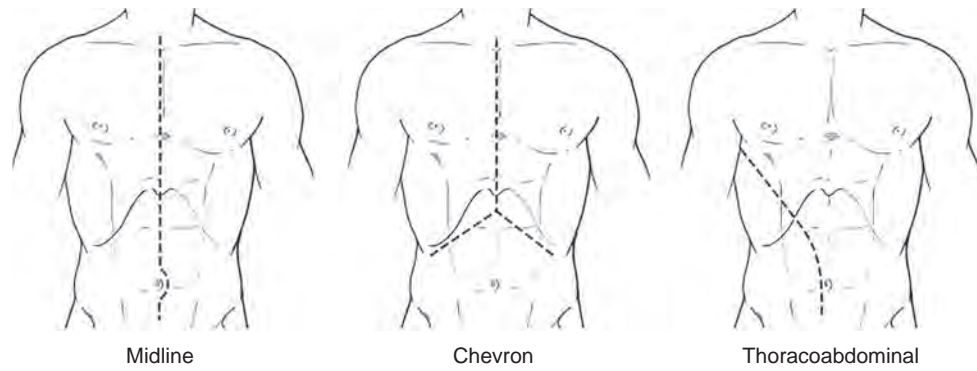


Figure 60-61. Surgical incisions for combined intra-abdominal and intrathoracic approach to vena caval tumor thrombi. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

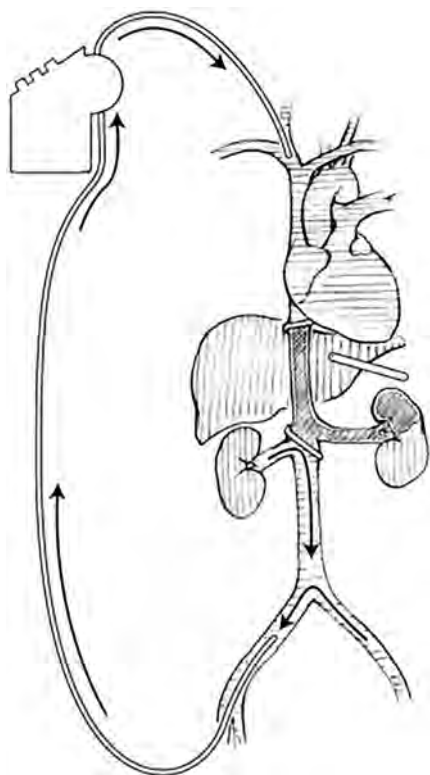


Figure 60-63. Percutaneous venovenous bypass. (From Smith JA Jr, Howards SS, Preminger GM, editors. *Hinman's atlas of urologic surgery*. 3rd ed. Philadelphia: Saunders; 2012.)

avoid aspirating and recirculating tumor cells. Several options are available for delivering the shunted blood back to the heart: a percutaneous approach via the internal jugular vein, a cutdown approach to the brachial/axillary vein, and a direct intraoperative approach through the right atrium. One advantage of VVB is that full heparinization is not required, which may help minimize post-operative bleeding problems. However, a key disadvantage is that the blood flow to the intercostal and lumbar arteries and the intercostal and lumbar veins is not interrupted during VVB, a problem that can lead to major bleeding once the cavotomy is performed to extract the thrombus. VVB should not be used when atrial thrombi cannot be completely milked into the IVC, when there is extensive bland thrombus in the iliac veins or infrarenal IVC, or when there is preexisting Budd-Chiari syndrome.

For percutaneous VVB, immediately following intubation, the anesthesiologist should insert an 8- to 18-Fr heparin-bonded arterial cannula into the internal jugular vein using the Seldinger technique (Fig. 60-63). A 6-cm, 18-gauge hollow needle is inserted into the femoral vein, a guidewire is placed, the tract is dilated, and a 14- to 20-Fr heparin-bonded arterial cannula is advanced into the common iliac vein. Both cannulae are connected to a perfusion pump using heparin-bonded tubing. The portal vein can also be cannulated with a 20-Fr cannula and its venous flow returned to the pump, though this is usually not necessary. The incision is performed and the kidney and IVC are dissected. Once all the vessels are clamped, the perfusion pump is started and the thrombectomy is performed under pump, ligating any troublesome lumbar and intercostal veins. Once thrombectomy and IVC repair are complete, the vessels are unclamped in the same order they were clamped.

For open VVB, the kidney and IVC are dissected, the liver is mobilized, and a sternotomy is performed (Fig. 60-64 on the Expert Consult website). A 20-Fr cannula is inserted into the infrarenal IVC well away from the tumor thrombus and then a 14- to 20-Fr cannula is inserted into the auricle of the right atrium. The infrarenal IVC, renal vein, porta hepatis, and suparenal IVC are clamped,

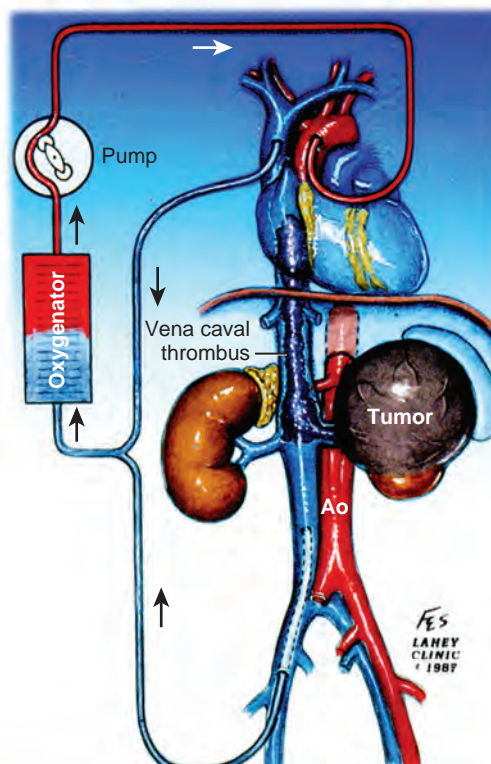


Figure 60-65. Traditional median sternotomy approach with cannulation of the aortic arch, superior vena cava, and right femoral vein for cardiopulmonary bypass. Ao, aorta. (© The Lahey Clinic.)

and then bypass is started. Thrombectomy is performed as quickly as possible.

Cardiopulmonary Bypass with and without Deep Hypothermic Arrest. CPB can be performed with or without deep hypothermic arrest (Fig. 60-65). CPB with hypothermic arrest involves stopping the heart and starting bypass, cooling the patient to 16° C to 18° C, and draining all of the blood from the patient. Although very invasive, CPB with hypothermic arrest offers several benefits. First, it can be used in cases in which the thrombus cannot be milked below an intrapericardial IVC clamp. Second, there is no need to clamp the aorta or porta hepatis or to ligate as many lumbar and hepatic veins since blood flow to these structures is no longer present. However, all vessels that have been traumatized or transected must be controlled since they will bleed once the patient is taken off bypass. Third, the absence of active blood flow allows for complete inspection of the IVC and hepatic veins, thereby aiding in achieving a complete thrombectomy. Fourth, the risk of embolization during thrombectomy is lower. Fifth, the surgeon is allowed up to 60 minutes to perform thrombectomy (although <40 minutes is certainly a better target), whereas IVC clamping without bypass is only tolerated for about 30 minutes.

For CPB with deep hypothermia, the kidney and IVC are dissected and the liver is mobilized. The cardiothoracic surgeon performs the sternotomy, opens the pericardium, and exposes the heart and its vessels. Heparin-bonded cannulae are placed in the infrarenal IVC and the right atrium to collect venous blood and a cannula is placed into the aortic arch for outflow. The patient is heparinized and bypass is started. The aorta is clamped and cardioplegia solution is administered. The temperature of the recirculated blood is dropped to 10° C to 14° C and the patient is cooled for 15 to 30 minutes until a core temperature of 16° C to 18° C is reached. Intraoperative electroencephalography should be performed to determine when the brain has been adequately cooled. When sufficient cooling has been achieved, the perfusion pump is stopped and 95% of the patient's blood volume is drained into the pump reservoir. Tumor thrombectomy should be performed as fast as

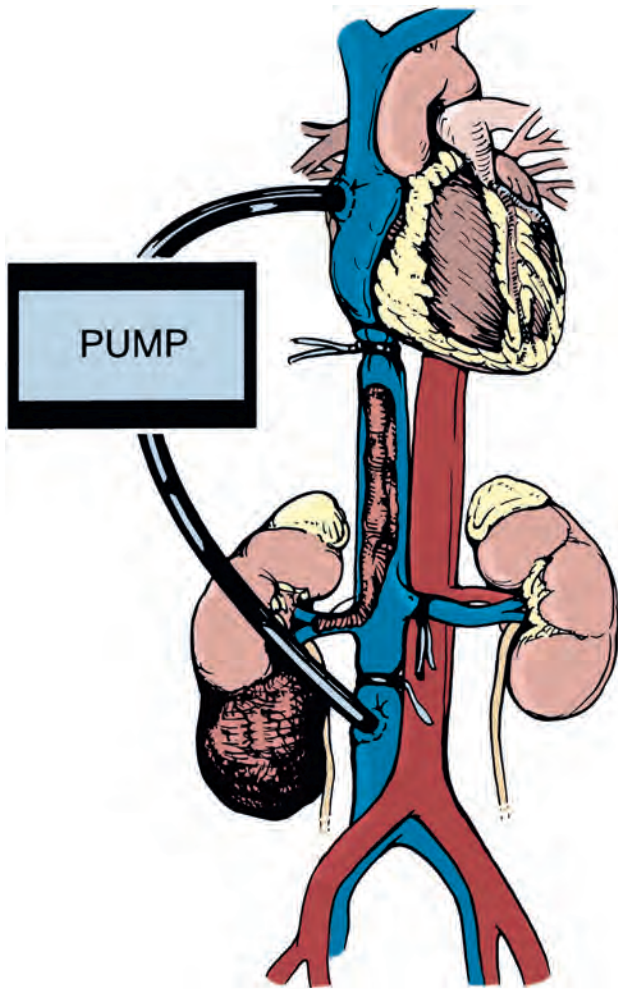


Figure 60-64. Technique of open venovenous bypass for removal of supradiaphragmatic vena caval tumor thrombus.

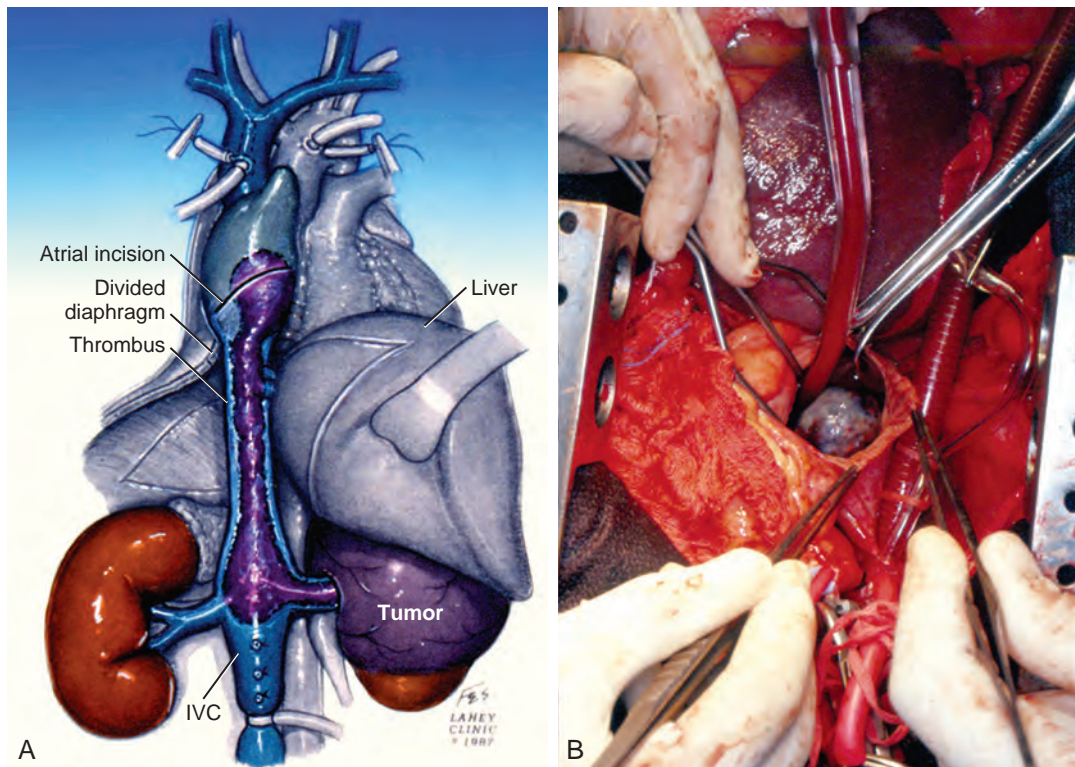


Figure 60-66. A and B, Tumor thrombus extension into right atrium removed using traditional median sternotomy approach and an atriotomy for retrieval of thrombus. IVC, inferior vena cava. (A, © The Lahey Clinic; B, from Wotkowicz C, Libertino JA, Sorcini A, et al. Management of renal cell carcinoma with vena cava and atrial thrombus: minimal access vs. median sternotomy with circulatory arrest. *BJU Int* 2006;98:289–97.)



possible, taking great care to ligate all potential bleeders (Fig. 60-66; Fig. 60-67 on the Expert Consult website). If the patient has known coronary artery disease, coronary artery bypass can be performed at the same time. If the resection is taking longer than anticipated, the surgeon should consider allowing a 10-mL/kg/min trickle of blood to flow to the organs or using retrograde cerebral perfusion.

Once the IVC and right atrium are repaired, warm blood is reinfused from the pump reservoir and CPB is restarted. Hemostasis is performed while the patient warms to 37°C over the next 30 to 45 minutes. Once the heart has restarted pumping, bypass is stopped, the cannulae are removed, and protamine sulfate is administered. Coagulopathy is common and fresh frozen plasma, platelets, and packed red blood cells should be available to administer. Thoracostomy tubes and closed suction abdominal drains are inserted.

Patching, Replacing, and Interrupting the Inferior Vena Cava

Patch Cavoplasty. If the IVC is expected to be less than 50% of its original size, a patch cavoplasty is necessary to prevent IVC stenosis and thrombosis-related events (Fig. 60-68). Autologous and bovine pericardium, polytetrafluoroethylene (PTFE), collagen-impregnated Dacron (DuPont, Wilmington, DE), and autologous saphenous vein are materials that can be used for patch cavoplasty.

The patch is sized to a bit larger dimension than the caval defect, typically configured to an oval shape. A double-armed 5-0 Prolene suture on a BB needle is used to sew the patch in place. Small and regular suture bites will assure a tight closure. Intraluminal inversion of the edges of the patch should be avoided to prevent excess thrombogenesis. Some surgeons prefer tacking both apices of the defect first and then running a strand of suture from each apex to the midpoint between the apices, which requires four knots. Alternatively, the graft can be parachuted into position and sewn into place circumferentially, requiring only one knot. Minimal

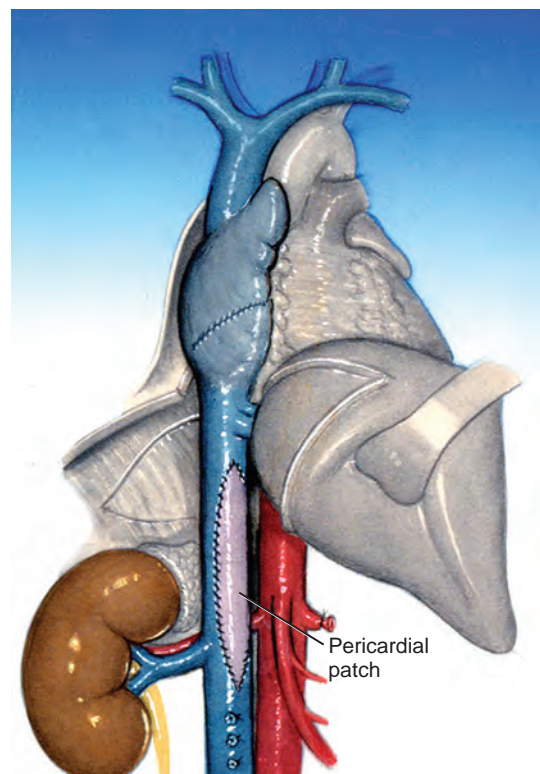


Figure 60-68. Vena cava reconstruction using a pericardial patch graft.

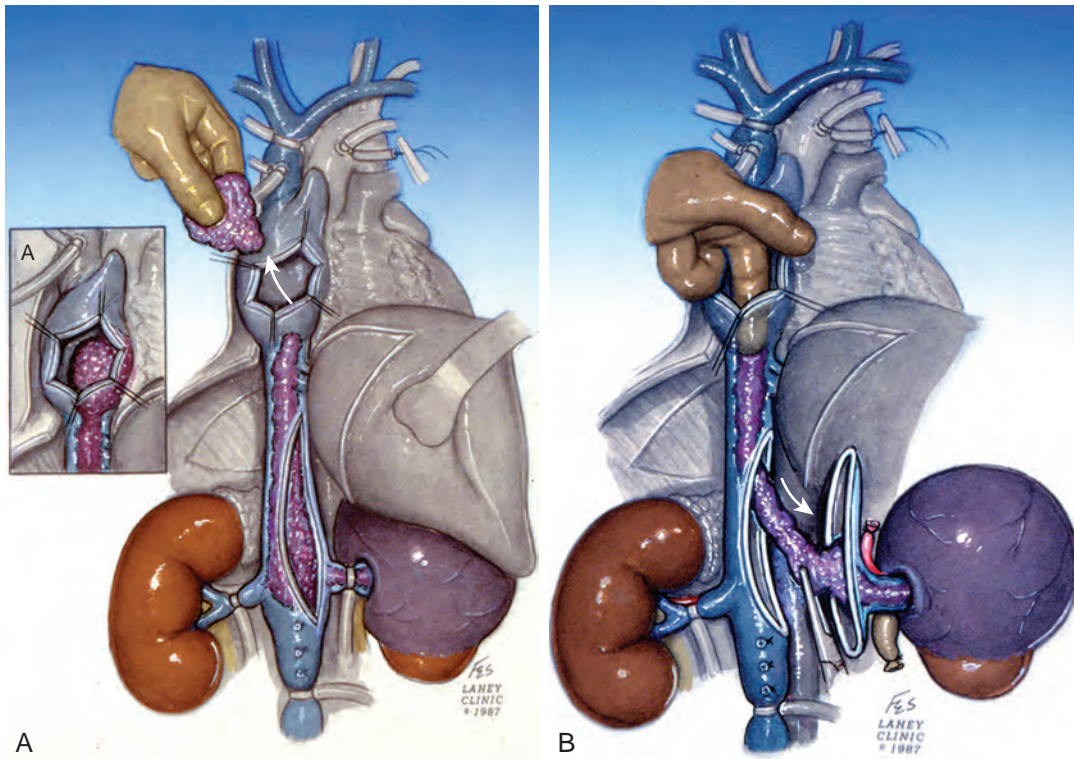


Figure 60-67. A and B, Tumor thrombus finger fracture and removal after formal atriotomy with retraction sutures (inset A). Manual displacement from atrium through diaphragm and removal through anterior cavotomy. (© The Lahey Clinic.)

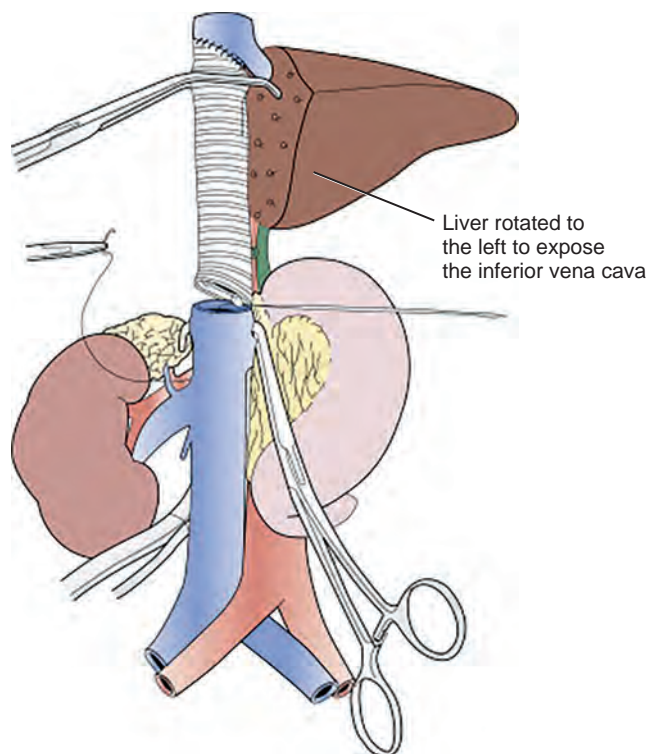


Figure 60-69. Vena cava replacement with polytetrafluoroethylene graft. (From Bower TC, Nagorney DM, Toomey BJ, et al. Vena cava replacement for malignant disease: is there a role? *Ann Vasc Surg* 1993;7:51-62.)

manipulation of the patch is helpful to prevent inadvertent damage to the patch and caval edge. Liberal use of heparinized saline can help with visualization. Prior to the final closure of the cava, the caudal IVC clamp should be released and 5 to 10 mL of venous blood allowed to escape from the cavotomy, providing for removal of air, debris, and clot prior to unclamping the cranial caval clamp.

Vena Caval Replacement. In situations when a circumferential section of IVC has been removed or if a vena cava defect is too large for simple patching, vena caval replacement is necessary (Fig. 60-69). Typically, we use PTFE grafts to replace the IVC, although others have described spiraled saphenous vein, superficial femoral vein, and tubularized pericardium as options (Helfand et al, 2011; Hyams et al, 2011; Quinones-Baldrich et al, 2012; Pulitano et al, 2013). Typically a graft size of 16 to 20 mm in diameter is required. The large diameter of the graft reduces the risk of thrombosis.

The liver is mobilized and the IVC exposed completely. Vascular bypass is used if clinically indicated, and 5000 units of intravenous heparin is administered. The IVC is clamped and the affected portion is excised. The cranial IVC-patch anastomosis is completed first. Subsequently, the graft is clamped followed by releasing the cranial IVC clamp to test the upper IVC-patch anastomosis. Next the graft is sized and cut to fit the IVC defect and the caudal IVC-patch anastomosis is completed. Prior to closure of the lower IVC anastomosis, the graft is unclamped and 5 to 10 mL of blood is allowed to escape from the graft through the cavotomy. The graft is then reclamped and the infrarenal IVC is unclamped, and 5 to 10 mL of blood is allowed to escape from the infrarenal IVC. Closure of the anastomosis is completed by tying the final knot and the IVC is unclamped. The graft is wrapped with omentum or retroperitoneal fat and then the hepatic ligaments are reapproximated to prevent torsion of the IVC graft.

Postoperatively, low-dose intravenous heparin or a reduced dosage of low-molecular-weight heparin is given. Once the patient's bowel function has recovered, lifelong oral warfarin is used with a target international normalized ratio of 2 to 3.

Inferior Vena Cava Filtration and Permanent Interruption for Bland Thrombus

Occasionally, a patient with an infrarenal bland thrombus requires management at the time of tumor thrombectomy. For bland thrombus that is limited to the pelvic veins, intraoperative placement of an infrarenal vena cava filter is indicated. When the bland thrombus diffusely involves the infrarenal IVC, the optimal management is permanent interruption of the IVC. Necessary intraoperative care is required to preserve the collateral lumbar venous drainage, since these vessels provide a "release valve" for the impaired caval blood flow. When the infrarenal IVC is occluded with bland thrombus that is distinct and separate from the tumor thrombus, the best form of management is usually permanent interruption without resection since attempts at complete removal of diffuse organized bland thrombus are almost always unsuccessful and often result in vascular injury. Options for permanent interruption of the IVC include serrated vena cava clips (e.g., Adams-DeWeese clip, Moretz clip), cross stapling with a vascular GIA stapler (Covidien Ltd., Mansfield, MA), suture plication, and suture ligation. Serrated vena cava clips and vascular staplers offer the advantage of easy application, while serrated vena cava clips allow partial blood flow through the IVC.

When the bland thrombus in the infrarenal IVC is admixed with tumor thrombus that has undergone retrograde growth, segmental resection of the IVC with permanent interruption of the IVC will maximize the chance of cure. Since it is not possible to accurately dissect tumor thrombus from bland thrombus and assure complete resection of tumor, resection of the IVC below the level of the contralateral renal vein ostium is recommended. Resection should be as close to the renal vein ostium as possible to prevent turbulent and thrombogenic flow in the upper stump. In addition, maximal preservation of the lumbar veins in the lower stump is important to ensure good collateral drainage.

Perioperative Complications

Air Embolism. Air embolism to the right heart and pulmonary arteries is a serious and potentially lethal complication associated with caval thrombectomy. Risk of air embolism can be significantly reduced by releasing the caudal IVC clamp first and allowing air and some blood (5 to 10 mL) to escape from the IVC repair site prior to removing the cranial clamp.

Acute Pulmonary Embolism. Tumor and bland thrombus can embolize during and after surgery. Minimizing intraoperative manipulation of the kidney and IVC before vascular control helps reduce the likelihood of acute thrombotic pulmonary embolism. Early preoperative or intraoperative placement of a Greenfield filter (Boston Scientific, Natick, MA) in a patient with pelvic bland thrombus can also help reduce the risk of pulmonary embolism. If respiratory distress is encountered during surgery, strong consideration should be given to prompt thoracotomy, pulmonary arteriotomy, and extraction of the thrombus.

Massive Hemorrhage. Major bleeding can occur during and after the surgery. If uncontrolled major bleeding occurs in a patient who is not on bypass, the surgeon should consider clamping the aorta above the celiac trunk or initiating deep hypothermic CPB. However, CPB can also lead to major coagulopathy, potentially worsening the degree of hemorrhage. Fresh frozen plasma, platelets, and red blood cells should be transfused liberally as indicated. Using a Cell Saver (Haemonetics Corporation, Braintree, MA) is not recommended for oncologic surgery since tumor cells can be disseminated.

Hepatic Dysfunction. Temporary hepatic dysfunction, characterized by elevated transaminases and alkaline phosphatase, is common in patients with levels III and IV thrombi that require suprahepatic IVC clamping and/or bypass. Minimizing clamping of the porta hepatis as much as possible can reduce hepatic ischemia and thereby the degree of postoperative hepatic dysfunction. Liver enzymes typically peak 2 to 3 days postoperatively and slowly resolve thereafter.

Organ Ischemia. Cardiac ischemia is most common in patients undergoing suprahepatic IVC clamping without bypass. Patients

with poor preoperative cardiac function are probably best managed by CPB. Renal and intestinal ischemia can also result during thrombectomy, requiring close postoperative monitoring.

KEY POINTS

- The origin of the right renal artery is posterior to the left renal vein and IVC. During a difficult right radical nephrectomy, the right renal artery may be more accessible posterior and medial to the IVC, near the site of origin from the aorta.
- While the right gonadal and adrenal veins drain into the IVC, the drainage of the left gonadal and left adrenal veins is different as they drain into the left renal vein.
- Simple nephrectomy, removal of the kidney within the Gerota fascia, is used for management of benign renal entities.
- The key elements of radical nephrectomy are early ligation of the renal artery and vein and removal of the kidney outside of the Gerota fascia. When technically feasible, the ipsilateral adrenal gland should be spared.
- For left radical nephrectomy, particularly for upper pole renal masses, identification of the left renal artery from the posterior approach is recommended to avoid inadvertent ligation of the superior mesenteric artery, which is on the anterior surface of the aorta 1 to 2 cm cephalad to the left renal vein.
- Regional lymphadenectomy extending from the crus of the diaphragm to the aortic bifurcation is employed in select cases of advanced local disease and when technically feasible.
- The impact of lymphadenectomy on progression-free and overall survival is controversial.
- In order to maintain the maximum number of functioning nephrons, partial nephrectomy is the treatment of choice for stage T1 renal tumors when technically feasible, even in the absence of identifiable renal insufficiency.
- The goal of partial nephrectomy is complete excision of the tumor with negative surgical margins and maximal preservation of benign adjacent parenchyma. Various techniques have been used, including enucleation, polar segmental nephrectomy, transverse resection, wedge resection, and extracorporeal partial nephrectomy with renal autotransplantation.
- In patients with known IVC tumor thrombus, intraoperative TEE should be utilized after the patient is anesthetized and intubated to appropriately assess the distal extent of the tumor thrombus before initiating the surgical procedure.
- When performing right radical nephrectomy with tumor thrombectomy, the suprarenal IVC can be resected, but only if the left renal vein has been ligated distal to its venous tributaries (i.e., gonadal, lumbar, and adrenal veins).
- Given the lack of venous tributaries on the right side, the suprarenal IVC should not be resected for a left-sided tumor unless one provides alternative venous drainage for the right kidney with autotransplantation or a saphenous vein graft to the splenic, portal, or inferior mesenteric vein.
- Alternatives to CPB may include venovenous bypass and extensive liver mobilization.
- When reconstructing the IVC, the lumen can be safely narrowed by half and closed primarily. To maintain the lumen in larger resections the cava can be reconstructed with a pericardial graft or PTFE.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.



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Overview

Patient Evaluation and Preparation

Surgical Approaches and Obtaining Access

Simple Nephrectomy

Surgery for Renal Cystic Disease

Renal Biopsy for Medical Renal Disease

Nephropexy

Calyceal Diverticulectomy

Nephrolysis

Radical Nephrectomy

Partial Nephrectomy

Laparoscopic Ablative Techniques

Laparoendoscopic Single-Site Surgery of the Kidney

Complications of Laparoscopic Renal Surgery

Penetrance of Minimally Invasive Renal Surgery among Urologists

Summary

OVERVIEW

Surgical treatment is central to addressing many urologic conditions affecting the kidneys. Decades of experience have demonstrated the efficacy and durability of operative extirpation for malignant processes, as well as operative reconstruction for obstruction. Although effective, traditional open surgical approaches to the kidney are associated with significant postoperative discomfort and convalescence. Laparoscopy, compared with open renal surgery, has been shown to result in less change in muscle volume and a lower rate of flank bulge, paresthesias, and numbness postoperatively (Crouzet et al, 2014). Studies have demonstrated that many patients can have permanent body surface alterations with flank incisions resulting in significantly larger postoperative surface area and volume changes on the operated flank compared with the uninvolved flank. Patients report dissatisfaction with the body changes that occur in up to 60% of flank incisions, with a preference toward minimally invasive techniques (Chatterjee et al, 2004; Kobayashi et al, 2004; Park et al, 2011).

Minimally invasive surgical approaches were born out of the desire to address secondary issues related to surgery, including incisional pain, convalescence, and cosmesis. Initially applied for the treatment of stone disease, advances in video technology and surgical tools have now been used to treat the most complex of renal pathologies, with less morbidity compared with standard operative approaches. Clayman and associates initiated this revolution in renal surgery in 1990 when they introduced the laparoscopic nephrectomy (Clayman et al, 1991). This was performed in an octogenarian with a kidney mass, and although the procedure took over 7 hours, its impact on postoperative recovery was immediately apparent compared with the conventional open approach. Subsequently, this minimally invasive approach has been applied to every aspect of operative renal disease as an alternative to open surgery.

Multiple studies have demonstrated that laparoscopic renal surgery provides recuperative as well as cosmetic advantages in contrast to open surgery (Kerbl et al, 1994a; Dunn et al, 2000; Gill et al, 2007; Tan et al, 2011). With experience, all manner of laparoscopic renal surgeries are now routinely accomplished without

compromise to surgical outcomes. Accordingly, the laparoscopic technique, where available, has evolved into a standard in treating a variety of surgical diseases of the kidney. This chapter will discuss indications, present techniques, review results, and outline potential complications of laparoscopy and robotic-assisted laparoscopy as applied to the kidney.

PATIENT EVALUATION AND PREPARATION

Basic principles of laparoscopic surgery are thoroughly discussed in Chapter 10 of the text. Fundamentals of patient selection and preparation for renal surgery largely parallel those of open surgical options for treatment of the underlying pathology. A pertinent history and physical examination are necessary to identify potential issues that could arise during surgery. **Prior abdominal, retroperitoneal, or renal surgery is not a contraindication to laparoscopic surgery; however, the type and extent of prior abdominal surgery may direct technique, positioning, trocar placement, and selection of a transperitoneal versus extraperitoneal point of access** (Chen et al, 1998; Cadeddu et al, 1999). In addition, the patient's body habitus may influence the type of access obtained and the location and configuration of trocar placement (Fugita et al, 2004; Kapoor et al, 2004; Romero et al, 2008). Surgeon experience and availability of equipment will facilitate or deter from use of the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) in treating renal pathology via a laparoscopic approach. Informed consent is obtained with a detailed discussion of potential complications including the potential for intraoperative conversion to open surgery.

Coagulopathies should be corrected to minimize chances of perioperative bleeding. With the increased use of cardiac stenting, more patients are maintained on chronic antiplatelet therapy. These cases warrant discussion with the patient's cardiologist to delineate risks and benefits of continuing or temporarily holding antiplatelet therapy. The decision should be individualized, taking into account the intended renal surgery, type of vascular stent used, and interval since placement in order to minimize the risks of bleeding and

perioperative coronary artery thrombosis. If necessary, complex laparoscopic renal procedures can be performed safely while patients continue antiplatelet therapy (Kefer et al, 2008).

Uremic patients with prolonged bleeding time may benefit from desmopressin acetate (1-desamino-8-D-arginine vasopressin [DDAVP] 0.3 to 0.4 µg/kg) given intravenously an hour before surgery to improve platelet function (Mannucci et al, 1983). However, one must consider a potential side effect of DDAVP therapy, iatrogenic hyponatremia, which is well recognized and has been reported in patients undergoing laparoscopic renal surgery (Humphries et al, 1993; Pruthi et al, 2002).

Laboratory and imaging studies are obtained as indicated by each individual patient's medical history and physical examination. Patients should have blood typed and screened. Crossmatching of blood is at the discretion of each surgeon based on operative experience and expected complexity of the intended procedure. Evidence suggests that mechanical or antibiotic preoperative bowel preparation does not improve outcomes. Hence, the use of bowel preparation is left to the discretion and practice patterns of the surgeon (Sugihara et al, 2013).

Imaging studies that define the pathology should be present in the operative suite to define anatomy and, in conjunction with preoperative site marking, minimize the risk of wrong-side surgery. Angiography, embolization, and stent placement are not routine for laparoscopic renal surgery but may be undertaken in preparation for specific pathologies or procedures.

Anesthetic Considerations for Laparoscopy

Most laparoscopic renal procedures require a general anesthetic, and a patient's pulmonary and cardiac function must tolerate this anesthetic approach (Monk and Weldon, 1992). The pneumoperitoneum can affect patients with severe cardiopulmonary disease by compromising ventilation and venous return (Arthure, 1970; Hodgson et al, 1970; Nunn, 1987; Lew et al, 1992). Patients with chronic pulmonary disease may not be able to compensate for the pneumoperitoneum-induced hypercarbia and may require working at lower pressures, use of helium as an insufflant, specialized laparoscopic trocars minimizing carbon dioxide reabsorption, or open conversion (Monk and Weldon, 1992; Wolf et al, 1996; Makarov et al, 2007; Herati et al, 2009, 2011).

Considerations in Obese Patients

Obesity is not a contraindication to laparoscopic surgery but can make retraction and identification of anatomic structures more challenging. It is for these reasons that laparoscopy in obese patients is associated with an increased risk of open conversion when compared with nonobese patients (Fazeli-Matin et al, 1999). In addition, although complication rates for laparoscopy in obese patients are higher when compared with laparoscopy in the general population (Mendoza et al, 1996; Aboumarzouk et al, 2012), pulmonary and wound complications are lower with laparoscopy when compared with an open approach (Kapoor et al, 2004; Montgomery et al, 2005). Other factors to account for in the obese population include the increased distance to the operative field, which calls for modifying trocar location and number, as well as the use of longer instrumentation (Doublet and Belair, 2000; Jacobs et al, 2000). Consideration must also be given to the weight of the pannus, which may raise the intra-abdominal pressure and further limit working space. The potential for rhabdomyolysis, a rare but devastating complication in the obese as well as very muscular individuals undergoing prolonged procedures, must also be considered (Troppmann and Perez, 2003; Glassman et al, 2007).

Considerations in Elderly Patients

The ever-increasing use of laparoscopy in urology has demonstrated benefits in all patient populations irrespective of age. Laparoscopy has been shown to be safe and effective in elderly individuals (McDougall and Clayman, 1994), and its use is now commonplace

in patients of all age groups and risk stratification (Salami et al, 2013). The well-documented advantages of laparoscopy compared with open surgery including reduced postoperative pain, decreased analgesic requirements, and more rapid convalescence are particularly welcome in elderly patients who are often at higher risk of perioperative complications. Limited nutritional, pulmonary, and cardiovascular reserve relative to younger patients gives rapid convalescence particular importance in this patient population. Minimization of narcotic use, early mobilization, and physical therapy (when warranted) are important management principles in this patient population.

SURGICAL APPROACHES AND OBTAINING ACCESS

There are currently five laparoscopic approaches to renal surgery: transperitoneal, retroperitoneal, hand assisted, robotic, and laparo-endoscopic single-site surgery (LESS) and natural orifice transluminal endoscopic surgery (NOTES). Each approach can have discrete advantages and limitations depending on the patient factors, pathology and clinical situation, and surgeon familiarity with each approach. To date, no studies have shown a definitive recuperative advantage of any one of these approaches. Potential differences in cosmesis may exist, but have also not been consistently demonstrated thus far.

Transperitoneal Approach

The transperitoneal approach is the traditional and most widely used laparoscopic method of addressing renal pathology. It provides the largest working space, facilitates orientation by providing readily identifiable anatomic landmarks, affords greater versatility in angles and location of laparoscopic trocars and instruments, and can result in the smallest size and number of ports used. The equipment is mature and techniques are well defined, but as with any approach, it requires significant expertise in instrument manipulation and suturing.

Patient Positioning and Trocar Placement

For most transperitoneal renal surgery, the patient is initially positioned supine for intravenous (IV) access, the induction of general anesthesia, and endotracheal intubation. A urinary drainage catheter and an orogastric tube are placed for decompression of the bladder and stomach during insufflation, trocar placement, and dissection. Sequential compression stockings are placed for deep venous thrombosis prophylaxis. For transperitoneal procedures, including robotic-assisted laparoscopy surgery and LESS, patients are positioned in a 30- to 45-degree flank-up position. Care is taken to pad all pressure points to minimize risk of nerve injury and reduce the incidence of tissue breakdown and rhabdomyolysis. The patient is secured to the operating table to allow lateral tilting of the table (Fig. 61-1). Tilting the table away from the affected kidney will help move bowel out of the operative field. There is no need

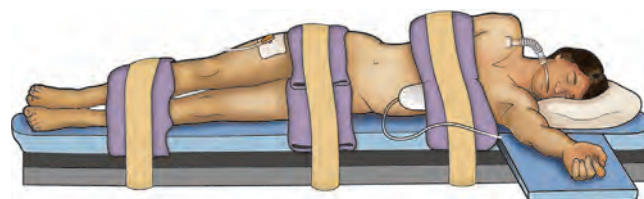


Figure 61-1. The patient is placed in a modified flank position, with the operative side tilted up 30 to 45 degrees using a gel roll or a rolled blanket supporting the back. The lower arm is placed on a padded arm rest, and the other arm is flexed at the elbow and rested over the chest. Wide cloth or silk tape is used to secure the patient to the operating table to allow for table rotation during the surgery.

to flex the table or elevate the kidney rest as there is with open surgery. The equipment in the operating room is situated to maximize the use of space and allow all members of the surgical team to view the procedure (Fig. 61-2). The entire flank and abdomen are included in the field of skin preparation and draping, in case conversion to an open procedure is required.

Once a pneumoperitoneum is established, three to five trocars are initially placed to complete the dissection (Fig. 61-3). A variety of trocar configurations are effective for each type of renal procedure.

A 12-mm trocar is placed in the anterior axillary line at the level of the umbilicus. This trocar is used for instrumentation and the passage of sutures, bulldog clamps, or staplers to secure and divide hilar vessels. In shorter patients, this may be placed in the midline, halfway between the umbilicus and pubis. A 10-mm trocar is placed at the umbilicus for camera manipulation, and a 5- or 10-mm port is inserted in the midline 2 cm below the xiphoid process. In obese patients, all trocar sites are shifted laterally (see Fig. 61-3C). Additional trocars for retraction may be needed for visualization or assistance with organ entrapment (Fig. 61-4). Additional low midline 10- or 12-mm trocars can be used for assistants to retract or use clamps or stapler devices. This low midline port site can be extended at the end of the case as a low midline extraction site.

Retroperitoneal Approach

The retroperitoneal approach mimics open surgery because the peritoneal cavity is avoided. A potential space is created to visualize the surgical field. This approach may be preferred for selected cases of laparoscopic partial nephrectomy (LPN), cyst marsupialization, pyeloplasty, or renal biopsy or in patients who have had peritonitis or who have undergone multiple prior abdominal surgeries resulting in significant intraperitoneal adhesions.

Patient Positioning and Trocar Placement

With this approach, patients are placed in a full-flank position. Modest table flexion can help increase the distance between the ribs

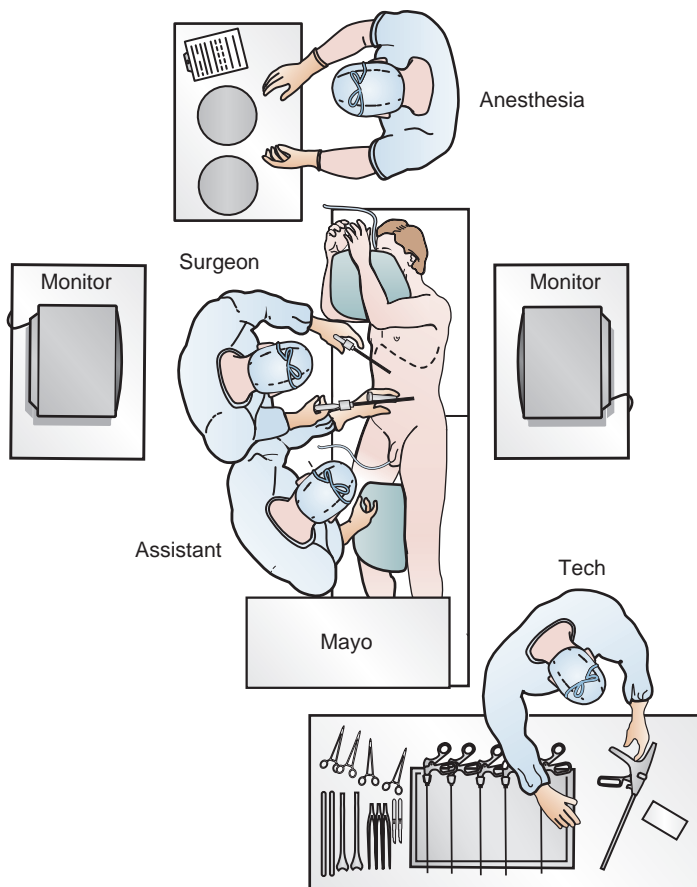


Figure 61-2. The operating room configured for left nephrectomy. Two monitors allow the assistant to follow the procedure. The scrub technician (Tech) is positioned to easily assist with instrument passage and exchange.

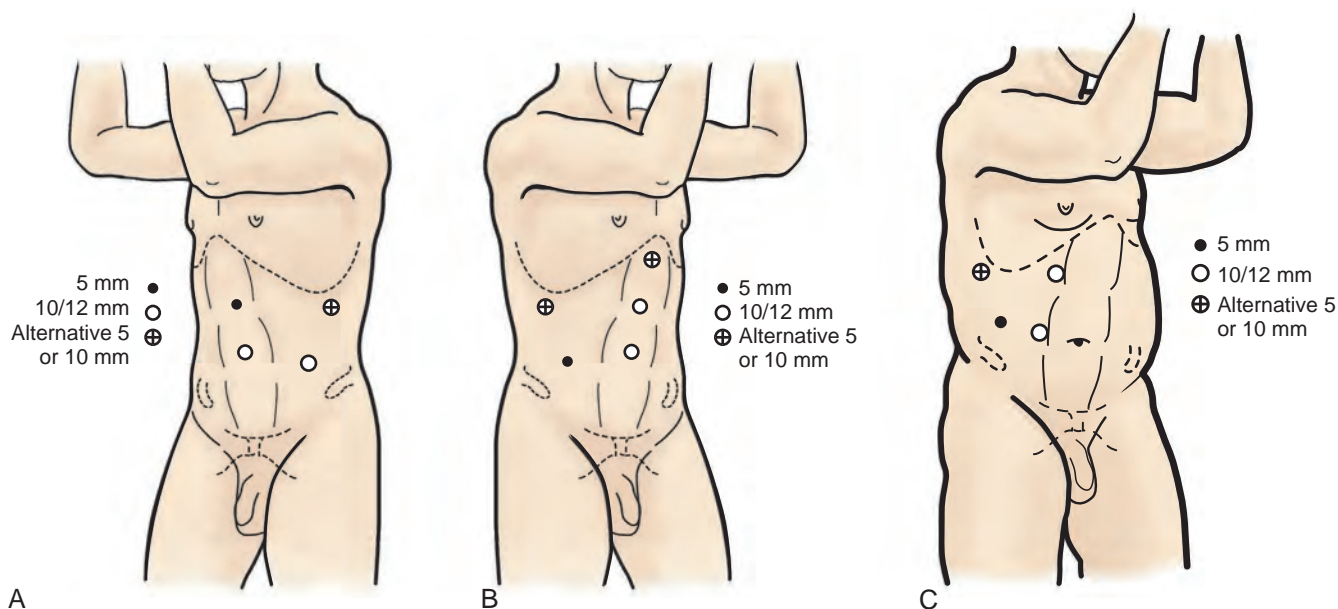


Figure 61-3. Trocar sites for left-sided (A) and right-sided (B) procedures. A 12-mm trocar is placed lateral to the rectus at the level of the umbilicus, a second 10-mm trocar is placed at the umbilicus, and a 5-mm trocar is inserted in the midline between the umbilicus and the xiphoid process. C, In obese patients, all trocars are shifted laterally. Optional accessory subcostal, subxiphoid, and low midline trocar positions, which may be helpful for retraction, are also shown.

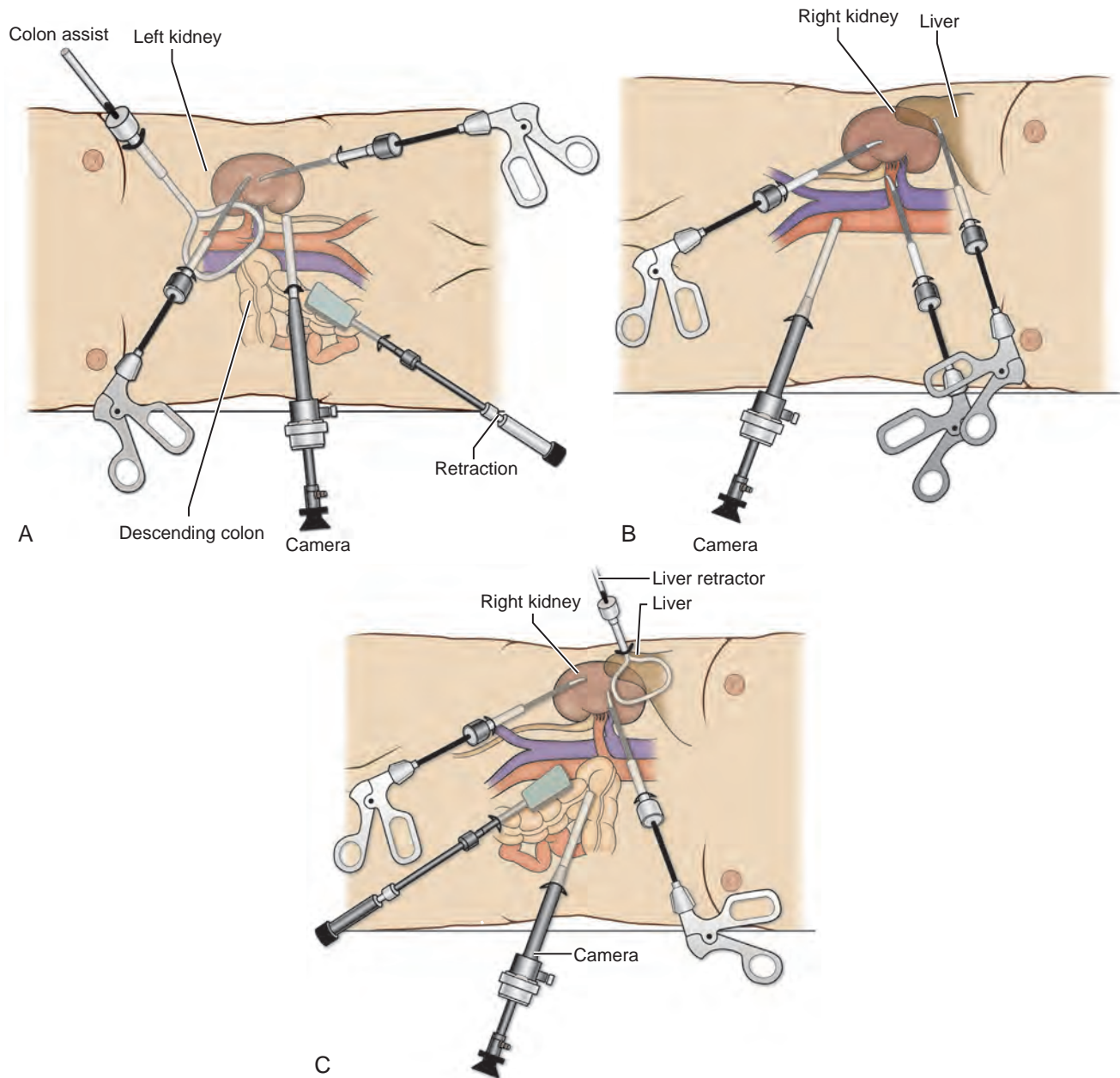


Figure 61-4. Options for additional trocar placement and instrumentation. A, Additional retraction during left-sided procedures can be accomplished with the use of a blunt instrument passed through a 5- or 10-mm trocar placed above the symphysis pubis, or a 5-mm instrument and retractor passed through a subcostal incision. B, In right-sided procedures, the liver and bowel can be retracted through a 3- or 5-mm trocar placed in the midline. C, In right-sided procedures, the liver and bowel can be retracted through a 5-mm trocar with a 5-mm instrument. An optional 10-mm lower midline trocar may also be placed for retraction, freeing the two other working hands for dissection.

and iliac crest to facilitate trocar placement. An axillary roll is required, and great care is taken in securing the patient to the bed. Arms may be secured on pillows or a purpose-built arm rest. A 15-mm transverse incision is made in the posterior axillary line, midway between the tip of the 12th rib and the iliac crest (Fig. 61-5A). After the dissection is deepened downward through the lumbodorsal fascia, the retroperitoneum is entered, and a working space may be developed using blunt dissection with the tip of a finger in the space between the psoas muscle and the kidney (Fig. 61-5B). A simple balloon created from two fingers of a size 8 or 9 glove may then be inserted and filled with CO₂ or saline, or alternatively, a purpose-built trocar with an integrated balloon may be

used to dissect the fat away from the overlying musculature. Either will further aid in developing the retroperitoneal working space (Fig. 61-5C). A Blunt Tip Trocar (US Surgical, Norwalk, CT) is then passed through the incision, and the trocar cuff is expanded and cinched to the skin to prevent leakage of CO₂ (Fig. 61-5D). An alternative entry approach involves entry with the 0-degree lens and visual obturator through the initial incision (Fig. 61-6A). Entry into the retroperitoneum may be confirmed by the appearance of the characteristic yellow retroperitoneal fat; insufflation is initiated, and blunt dissection using only the laparoscope is performed to develop a working space (Fig. 61-6B). Caution must be used not to enter too anteriorly because inadvertent peritoneal entry or colon injury

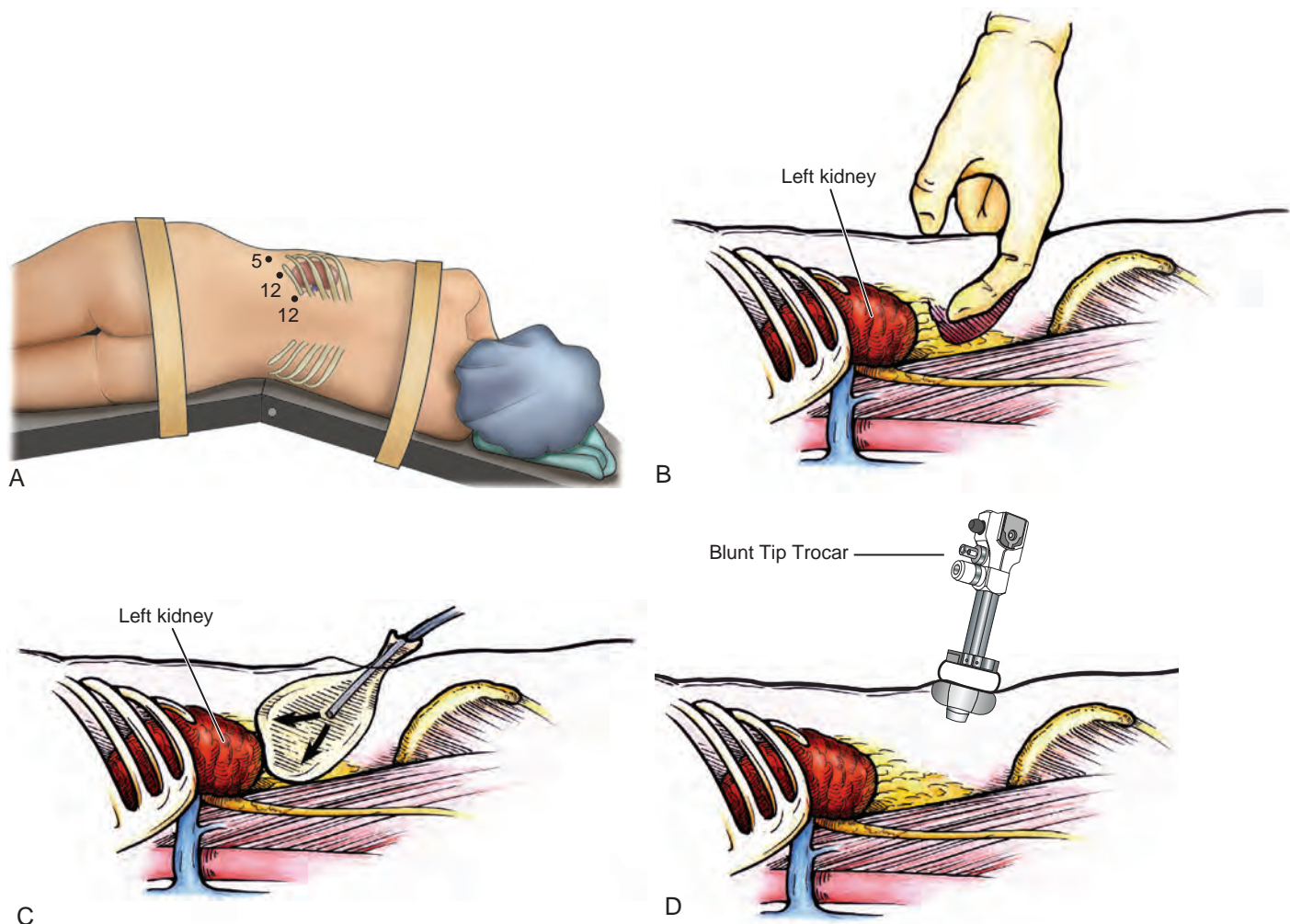


Figure 61-5. Trocar placement for retroperitoneal kidney surgery. A, With the patient in the full lateral position, the hips flexed, and the kidney rest elevated, a 15-mm incision is made 2 cm below the tip of the 12th rib, between the rib and the anterior superior iliac spine. B, The index finger is inserted through the incision and used for blunt dissection to create a hole from the skin through the muscle into the retroperitoneal space. If the finger is in the correct position, the surgeon should feel the smooth surface of psoas muscle and the lower pole of the kidney covered by Gerota fascia. C, To quickly create the working space, insert a balloon created from the finger of a size 8 or 9 glove, secured with silk suture over a simple red rubber catheter. The balloon is then filled with 600 to 800 mL of saline. D, A Blunt Tip Trocar (US Surgical, Norwalk, CT) is used to seal the trocar site. Because of its low profile, it will not obstruct the view or take up useful space in the retroperitoneum. The balloon and collar configuration eliminates the need for sutures and allows 360-degree rotation.

may occur; entering too posteriorly may result in bleeding from entry into the quadratus lumborum or psoas muscles. Once the working space has been established through either approach, pertinent structures may be identified for orientation and additional trocar placement. Typically, a 5-mm trocar is placed just off the tip of the 12th rib, and a 12-mm trocar is placed posteriorly and superiorly relative to the camera port, both under laparoscopic visualization (see Fig. 61-5A).

The greatest limitations of the retroperitoneal approach are the limited working space and more subtle anatomic landmarks. The smaller working space limits the distance between trocars, potentially leading to decreased triangulation and challenging hand positioning, similar to LESS procedures. Also, with the area of surgical dissection much closer to the lens, frequent smudging of the laparoscope tip may occur. If additional space is needed during the procedure, initial retroperitoneal access can be expanded to a transperitoneal approach by opening the peritoneum under direct vision.

Despite these limitations, the retroperitoneal approach may be preferred in some cases, and with adequate experience a wide variety of laparoscopic renal surgical procedures may be performed via this approach.

Modifications for Hand-Assisted Laparoscopy

Hand assistance offers a bridge between open surgery and pure laparoscopy (Nakada et al, 1997). It offers more intuitive assistance from the surgeon's hand in performing dissection and retraction, with simultaneous tactile feedback. Several manufacturers make devices for this purpose. An incision large enough for the hand must be created and can also be used as an extraction site at the culmination of the case. This technique may be advantageous for the novice laparoscopist and in treating patients with significant scarring around the kidney or in cases for which a difficult dissection is anticipated. Hand assistance may also be used in the event of an

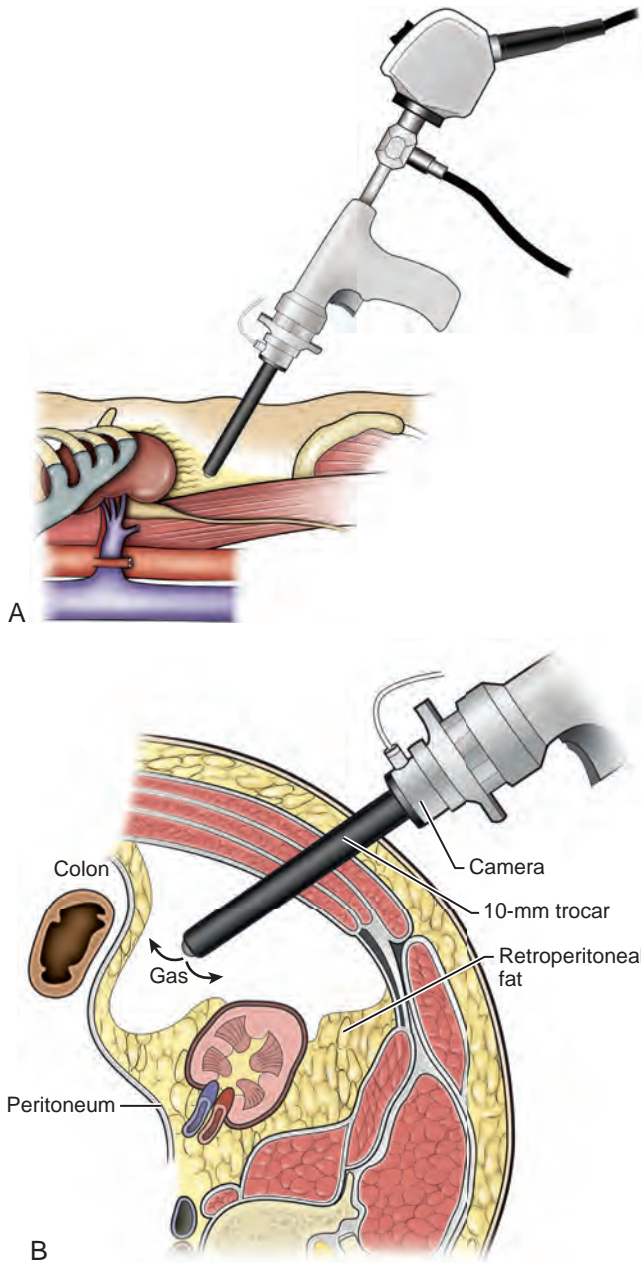


Figure 61-6. A, Standing behind the patient, the surgeon initially develops a space bluntly between the psoas muscle and the kidney using the visual obturator with the 0-degree laparoscope through it. B, Together, they are used to bluntly push the peritoneum medially, creating a working space large enough to allow placement of additional trocars.

emergency, such as bleeding, by extending a trocar site and placing a hand port to assist in achieving vascular control and repair.

Patient Positioning and Trocar Placement

The patient positioning is similar to that for transperitoneal laparoscopic kidney surgery. The initial incision for the hand port is made through the skin and fascia and into the peritoneal cavity. Location will depend on handedness of the surgeon, operative side, and body habitus of the patient (Figs. 61-7 and 61-8). Care must be taken to avoid making the incision too large because leakage of the pneumoperitoneum may occur, making the procedure more difficult owing to decreased working space. Once the hand-assistance device is placed, the pneumoperitoneum is

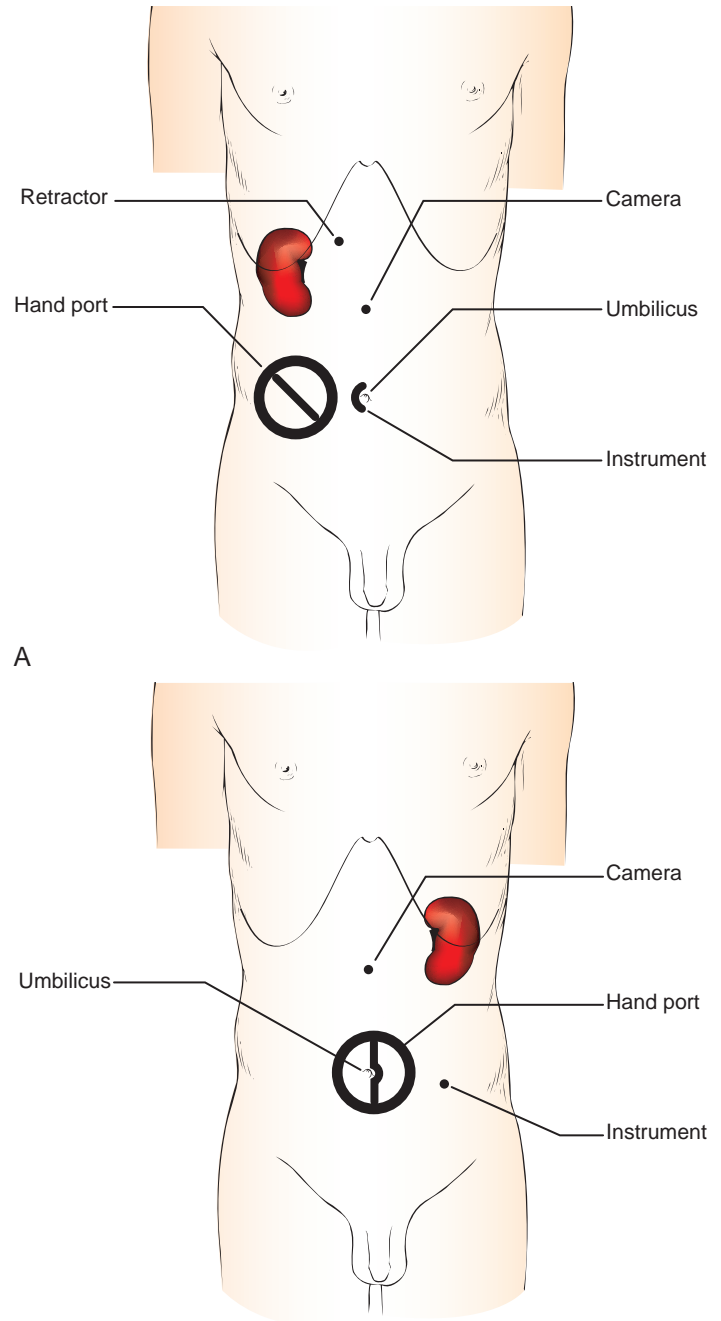


Figure 61-7. Port placement for a right-handed surgeon for hand assistance. A, For a right-sided kidney, the hand-assisted device is placed in the right lower quadrant for insertion of the left hand, and dissection is performed with instruments in the right hand placed through an umbilical trocar. The camera is placed several centimeters above the umbilicus in the midline. On the right side, retraction of the liver is usually necessary to allow visualization and dissection of the renal hilum. A liver or bowel retractor can be placed through a subcostal trocar to assist with visualization or irrigation and aspiration. B, For the left kidney, the hand-assisted device and left hand are placed through a periumbilical incision, and dissection is performed with the right hand using an instrument placed in the subcostal margin just medial to the nipple. The camera is placed several centimeters lateral to the edge of the actual hand-assisted device (not the edge of the incision). Additional assistance can be delivered through the most lateral trocar site.

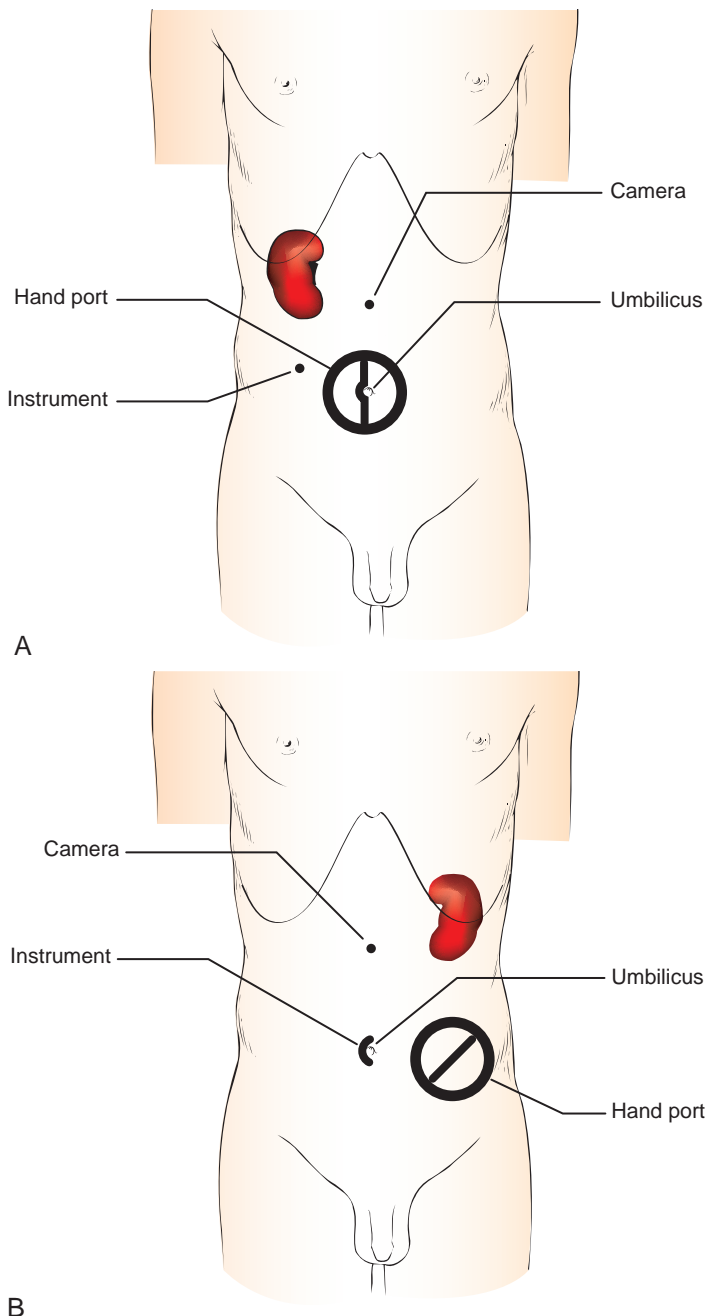


Figure 61-8. Port placement for a left-handed surgeon for hand assistance **A**, When operating on the right kidney, a left-handed surgeon places the hand-assisted port in the periumbilical location for insertion of the right hand. The working port for the left hand is placed lateral to the rectus muscle, in line with or just inferior to the level of the umbilicus. The camera is placed through a lateral trocar in the anterior axillary line. Additional assistance with retraction of the liver can be accomplished through a subcostal trocar. **B**, For a left-handed surgeon operating on the left kidney, the hand-assisted port is placed in the left lower quadrant for insertion of the right hand. The left hand works with the instrument passed through an umbilical trocar, and the camera is placed midway between the umbilicus and the xiphoid process. Additional assistance with retraction or aspiration can be accomplished through a fourth trocar placed at the subcostal margin.

established, and additional trocars are placed under direct laparoscopic visualization by passing the camera through the hand port.

There are some limitations in location of port placement, and the hand may potentially get in the way of visualization or dissection instrumentation. In addition, these devices exert 30 to 100 mm Hg of pressure on the arm, which may account for surgeons developing tingling, numbness, or pain in the forearm or hand (Monga et al, 2004; Ost et al, 2006).

Modifications for Robotic-Assisted Laparoscopy

The da Vinci computer-aided surgical system (Intuitive Surgical) has been used to perform what has commonly become known as *robotic surgery*. This device uses a computer system and a series of mechanical arms to translate surgeon movements to a laparoscopic platform. Instrument movement of right and left is preserved, as opposed to pure laparoscopic surgery, in which it is reversed. Also, hand-eye association is preserved, and a dual lens system provides 3-dimensional (3D) visualization with depth perception. The addition of intracorporeal instrument articulation facilitates fine dissection, suturing, and other challenging laparoscopic tasks. These additions have reduced the need for advanced laparoscopic skills, allowing more surgeons to offer a minimally invasive approach to their patients, albeit at increased cost. Whereas robotic procedures require a skilled bedside assistant and more trocars than standard laparoscopy, most laparoscopic renal procedures can be completed in a solo fashion using a mechanical endoscope holder and two working trocars (Wang and Bhayani, 2009). The robotic platform provides more surgeons the ability to offer a minimally invasive approach to patients and has increased the use of robotics relative to pure laparoscopic kidney surgery (Patel et al, 2013).

Patient Positioning and Trocar Placement

Patient positioning will depend, in part, on tumor location (in cases of partial nephrectomy) and choice of a transperitoneal or retroperitoneal approach. In addition, the point in the operation at which the robotic device is docked must be considered because additional table rotation is not possible with the robot docked. The entire procedure may be performed with the aid of the robot, or, as in cases of partial nephrectomy, the initial portions of the operation may be performed using standard laparoscopy, with use of the robot for hilar dissection or in some cases only for tumor excision and renorrhaphy.

Most surgeons report using a flank position with the table modestly flexed, although a modified flank position without flexing the table has also been described in several series (Deane et al, 2008; Benway et al, 2009a; Boris et al, 2009; Kaouk et al, 2012). Inclining the table may provide additional space at the back of the patient for the robot and other equipment (Fig. 61-9).

Robotic trocars for instrumentation and camera are used for the procedure in addition to bedside assistant ports. A port-in-port technique of robotic-assisted partial nephrectomy (RaPN) has also been described, wherein the robotic 8-mm ports are inserted through standard 12-mm ports (Aron et al, 2008). This arrangement allows use of 10-mm instruments via standard laparoscopy before and after docking the robotic platform. It may also be advantageous in the event of an intraoperative complication or robotic malfunction, when emergent conversion to pure laparoscopic surgery is necessary. The robot can be undocked and a standard laparoscopic procedure can be completed without requiring additional time to insert new ports or working through 8-mm robotic ports that preclude passage of larger instruments such as stapler devices or CT-1 or CT-X needles.

A three-arm configuration includes a total of four or five trocars: a 12-mm periumbilical camera port, an 8-mm subcostal robotic trocar in the anterior axillary line, an 8-mm robotic trocar in the posterior axillary line placed above the iliac crest, and one 12-mm assistant trocar in the low midline to allow passage of sutures, bulldog clamps, stapler devices, suction, or retraction. An additional 5- or 12-mm subxiphoid trocar may be used, if necessary, for

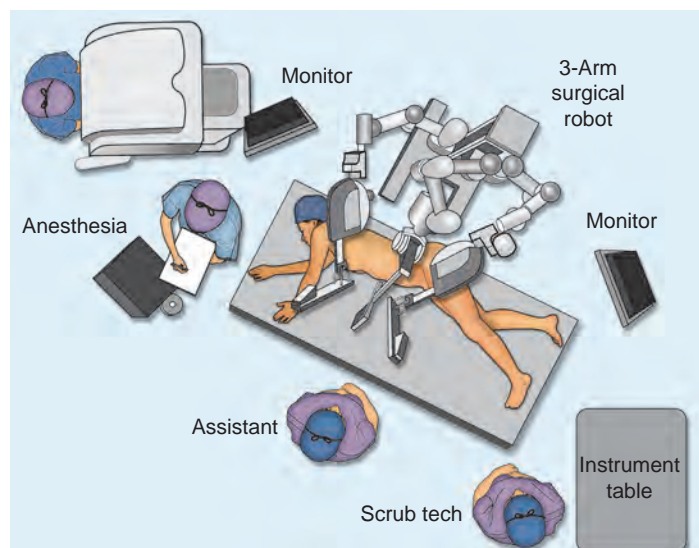


Figure 61-9. Operating room configured for left-sided robotic-assisted laparoscopic partial nephrectomy.



Figure 61-11. Laparoendoscopic single-site surgery performed using three low-profile trocars inserted through a single small extraction incision. A flexible laparoscope and flexible instrumentation may be used. (From Tracy CR, Raman JD, Cadeddu JA, et al. Laparoendoscopic single-site surgery in urology: where have we been and where are we heading? *Nat Clin Pract Urol* 2008;5:561–8.)

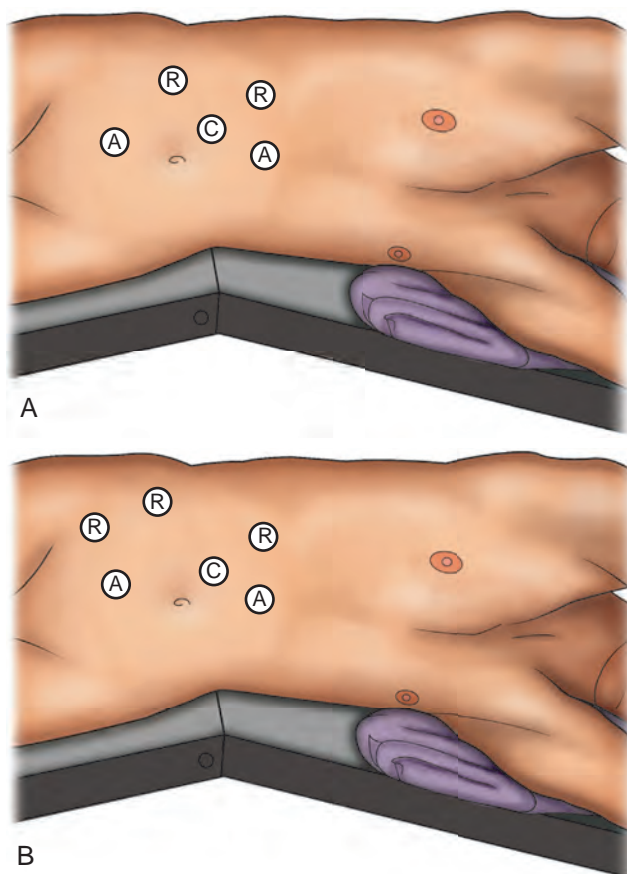


Figure 61-10. Trocar placement for robotic-assisted laparoscopic renal surgery. A, Three-arm system configuration. B, Four-arm system configuration. A, assistant trocar; C, camera port; R, robotic trocar.

additional bedside assistance, if the angle is more optimal (Fig. 61-10A). A four-arm configuration involves a total of five or six trocars, using the same general configuration as the three-arm technique, but shifting the robotic trocars to avoid clashing of the robot arms (Fig. 61-10B).

Laparoendoscopic Single-Site Surgery and Natural Orifice Transluminal Endoscopic Surgery

LESS refers to laparoscopic techniques that consolidate all ports within a single skin incision, often concealed within the umbilicus (Box et al, 2008). This approach to renal surgery has evolved with the goal of further improving cosmesis and reducing postoperative pain relative to standard laparoscopic surgery. Clustering standard laparoscopic ports, purpose-built homemade multichannel access devices, and commercially available multichannel working ports can be used, typically placed in the umbilicus or below the waistline to minimize visible scars (Rais-Bahrami et al, 2009; Kaouk et al, 2011). To date, virtually all extirpative and reconstructive renal procedures have now been performed via LESS.

Patient Positioning and Trocar Placement

A variety of accepted methods of positioning and trocar use have been reported and are currently used for LESS procedures. Modified flank and full-flank positions have been described, mirroring positioning for standard transperitoneal or retroperitoneal laparoscopic kidney surgery, respectively. Once the pneumoperitoneum has been established, one may cluster multiple traditional low-profile trocars close together within a single, small extraction incision (Fig. 61-11). Alternatively, newer purpose-specific access devices (Fig. 61-12) may be used in combination with conventional laparoscopic or flexible instrumentation. The devices are secured using preplaced fascial sutures or with an inner and outer ring drawn together with a cylindrical sleeve. Characteristics of various single-site access options are described in Table 61-1.

LESS approaches are technically challenging, largely because of the limited triangulation afforded by the clustering of instruments entering the intracorporeal working space, making LESS the most difficult of the minimally invasive techniques. To date, randomized series comparing LESS with conventional laparoscopy have demonstrated comparative improvement in postoperative pain and potentially decreased analgesic use and shorter hospitalization (Tugcu et al, 2010; Kurien et al, 2011; Richstone et al, 2013). Adapting LESS for the context of robotic assistance and other specialized instrumentation has gradually increased the application and dissemination of this approach to minimally invasive renal surgery (Autorino et al, 2013).

NOTES involves using a natural orifice to perform the entire operation. In the gastrointestinal (GI) and surgical literature, the



Figure 61-12. Purpose-specific device for laparoendoscopic single-site surgery. The TriPort system (Advanced Surgical Concepts, Bray, Ireland) allows for passage of multiple instruments through a single incision.

mouth, vagina, and rectum have been used to remove organs such as the appendix and gallbladder (Rao and Reddy, 2005; Zorron et al, 2007; Palanivelu et al, 2008). In renal surgery, to date, experience with pure NOTES surgery in humans is limited (Kaouk et al, 2009a). Several authors have reported a hybrid NOTES approach with standard laparoscopic assistance, using the vagina as an access and extraction site during nephrectomy (Branco et al, 2008; Alcaraz et al, 2011; Paparel and Golfier, 2012). More recently, development of successful transvesical renal surgery in animal models has been reported (Metzelder et al, 2009; Bin et al, 2012).

SIMPLE NEPHRECTOMY

Laparoscopic simple nephrectomy is indicated in the treatment of most benign renal diseases. **Renovascular hypertension that is not correctable with medication or angiographic repair** may be managed with simple nephrectomy. Patients with **chronic pain syndromes** may benefit from nephrectomy, including **symptomatic acquired renal cystic disease**, **autosomal dominant polycystic kidney disease (ADPKD)**, **chronic hydronephrosis not amenable to surgical repair**, and **loin pain-hematuria syndrome**. **Chronic infectious processes** that are recalcitrant to antibiotic therapy may also be approached laparoscopically, including **chronic refractory pyelonephritis**, **xanthogranulomatous pyelonephritis (XGP)**, and **renal tuberculosis**. These conditions are associated with higher rates of conversion to open surgery as a result of perinephric inflammatory changes and loss of tissue planes (Gupta et al, 1997; Ber-cowsky et al, 1999). In some cases, a subcapsular nephrectomy may be necessary to safely complete the procedure. Hand assistance may also be of benefit and avoid open conversion in cases involving dense scar tissue formation or inflammatory reaction (Rosoff et al, 2006). Successful retroperitoneal laparoscopic simple nephrectomy has also been reported in 30 of 31 patients with nonfunctioning kidneys secondary to tuberculosis (Lee et al, 2002). Other benign conditions that may call for nephrectomy include patients with a multicystic dysplastic kidney or a symptomatic failed renal transplant. Again, in this latter case, a subcapsular dissection may be required because of significant perinephric scarring.

Procedure

Reflection of the Colon

For a left nephrectomy and all renal surgery, the line of Toldt is incised from below the lower pole of the kidney inferiorly to above the spleen superiorly (Fig. 61-13). The inferior limit of this incision may be extended further inferiorly if the colon does not sufficiently reflect medially. The lienocolic ligament should be incised to allow the spleen to fall medially along with the pancreas and the colon (see Fig. 61-13). Care must be taken to avoid injuring the diaphragm with this maneuver. The thin colorenal attachments are incised and the colon is swept medially, taking great care to avoid making a hole in the colonic mesentery (Fig. 61-14). Mesenteric fat has a brighter hue of yellow compared with the retroperitoneal or Gerota fat, which allows for identification of the correct plane of dissection. If the operative field is not adequately visualized, a paddle retractor may be placed through an additional lower midline trocar to aid in retracting the colon, pancreas, and spleen medially (see Fig. 61-4A). Blunt and sharp dissection is necessary to move these structures off the anterior surface of the kidney and renal hilum.

During a right-sided nephrectomy, the peritoneal incision is carried medially and parallel to the lateral border of the vena cava and duodenum. A lateral (anterior axillary line) or high midline port may be needed to retract the liver anteriorly (see Fig 61-4B and C). Care must be taken to avoid thermal injury to the duodenum and gallbladder during incision of the peritoneal lining. Medial traction on the colon reveals colorenal attachments that must be divided to complete the colon reflection. Again, a low midline retractor may be helpful for visualization. A Kocher maneuver may be required to fully expose the medial portion of the kidney and the connective tissue overlying the renal hilum and inferior vena cava (Fig. 61-15). This should be done without electrocautery adjacent to the duodenum.

Dissection of the Ureter

Once the colon has been adequately mobilized, the psoas muscle and tendon should be identified inferior to the lower pole of the kidney. Following the psoas medially, the gonadal vessels are usually encountered first. These should be swept medially—the ureter is usually located just deep to these vessels. Peristalsis of the ureter can help differentiate between the ureter and adjacent vascular structures. **Once identified, the ureter is elevated and followed proximally to the lower pole of the kidney. The ureter is not divided at this time, because it can be used to help elevate the kidney (Fig. 61-16).** The tissue posterior to the ureter and lower pole of the kidney is swept anteriorly to further expose the anterior surface of the psoas muscle. Care should be taken to stay above the psoas fascia to minimize postoperative thigh numbness. The instrument in the subxiphoid trocar is used to slide under the kidney through to the sidewall. This allows the surgeon to lift the kidney anteriorly and laterally, placing medial lymphatic and vascular attachments on stretch.

Identification of the Renal Hilum

Safe dissection of the renal hilum requires medial retraction of the colon and bowel by gravity or an additional retractor, as well as anterior-lateral retraction of the kidney, lifting it out of the renal fossa. With the ureter and lower pole of the kidney elevated, vessels entering the renal hilum can be identified and bluntly dissected using the tip of the irrigator-aspirator. **Firm elevation of the kidney to provide hilar traction is a key principle of laparoscopic renal surgery and assists in identification and safe dissection of the renal hilar vessels (Fig. 61-17).** This is accomplished by gently placing the lateral grasper under the ureter and kidney until it abuts the abdominal sidewall. It is important to be sure that the grasper is against the muscle and not into the renal parenchyma. A gentle, layer-by-layer dissection is performed with the irrigator-aspirator until the renal vein is uncovered. There is usually an anterior

TABLE 61-1 Access Options for Laparoendoscopic Single-Site (LESS) Surgery

ACCESS TYPE	DESCRIPTION
Keyhole	Use of three closely approximated periumbilical trocars placed side by side in a single skin incision or three separate incisions. No additional purpose-built device required. Typically used with articulating camera and specialized instrumentation. Insufflation through one of the trocars.
TriPort +/-TriPort 15/QuadPort + (Advanced Surgical Concepts, Bray, Ireland)	Open or closed access, may be used with multiple incision sizes, typically 2.5- to 5-cm fascial incision. Anchored by inner (intra-abdominal) and outer rings drawn together with cylindric sleeve. Three-port (one 12-mm and two 5-mm) and four-port (two 12-mm and two 5-mm) configurations available. Insufflation through valve housing.
Uni-X (Pnavel Systems, Cleveland, OH)	Open access technique, requires 2-cm fascial incision. Anchored with preplaced fascial sutures. Single port encompassing three 5-mm access ports. Typically used with articulating camera and specialized instrumentation. Insufflation through valve housing.
GelPort/GelPoint (Applied Medical, Rancho Santa Margarita, CA)	Open access technique, requires 2.5- to 5-cm fascial incision. Anchored by inner and outer rings drawn together with cylindric sleeve. Can accommodate all trocar sizes. May allow for wider spacing of trocars. Insufflation through trocar placed through device.
AirSeal (SurgiQuest, Milford, CT)	Various trocar sizes up to 27 mm, oval-shaped trocar accommodating multiple instruments. High-velocity CO ₂ recycling system to maintain pneumoperitoneum pressures without mechanical valve.
SILS (Covidien, Mansfield, MA)	Single biconcave piece of foam with a valve for insufflation and three holes to accommodate trocars (three 5-mm low profile trocars or two 5-mm trocars and one 10- to 12-mm trocar). Inserted via open Hasson technique through minimum 2-cm fascial incision with the aid of a Péan clamp.
SPIDER (TransEnterix, Morrisville, NC)	Single-access device allowing for the use of flexible instruments passed through articulating instrument delivery tubes. Additional working channels allow for use of conventional laparoscopic instruments as well.
Homemade port (using Applied Medical [Rancho Santa Margarita, CA] wound retractor)	Similar to GelPoint trocar using a wound retractor from the same company in addition to a sterile surgical glove. Surgical glove secured to the wound retractor using suture or sterile rubber bands. Trocars can be passed through each of the fingers of the surgical glove portion of the access device.
OCTO Port (DalimSurgNET, Seoul, Korea)	Available in two base sizes requiring fascial incisions ranging from 1.5 to 5 cm. Uses a wound retractor and multiple attachments allowing for up to four ports.
Single Site Laparoscopy (SSL) Access System (Ethicon Endo-Surgery, Somerville, NJ)	Similar to other access devices in using a wound retractor base with an attachment cap. Integrates channels (two 5-mm instruments and a 10- to 12-mm instrument) with no trocar components protruding above the low-profile cap that can rotate. Placed through 2- to 4-cm fascial openings and able to traverse abdominal wall thickness up to 7 cm.

bundle of connective tissue that needs to be incised to fully expose and visualize the anterior surface of the vein. Gonadal, lumbar, and accessory venous branches can be clipped and divided as necessary.

Securing the Renal Blood Vessels

By clearing off inferior attachments and lymphatics, one can identify the renal artery, most commonly posterior to the vein. Care should be taken to identify the location and number of renal arteries based on preoperative imaging as available. If the irrigator-aspirator tip is not precise enough for meticulous dissection, a hook electrode or laparoscopic DeBakey forceps can be used to dissect the lymphatic

vessels free of the vein and artery. **With an endovascular gastrointestinal anastomosis (GIA) stapler, first the artery is ligated and divided, then the vein (Fig. 61-18).** In some instances clips may be needed, in which case multiple clips are recommended on the remnant patient-side of the vessels. In 2006 and 2011, the manufacturer of Weck Hem-o-lok Ligating Clips (Teleflex Medical) and the Food and Drug Administration respectively issued alerts stating that **Weck Hem-o-lok Ligating Clips are contraindicated for the ligation of the renal artery** during laparoscopic donor nephrectomy owing to several donor deaths linked to failure of the clips in ligating the vessel. Given these recommendations, we advocate for the use of either vascular stapling devices or multiple titanium clips for the ligation of the renal artery in all laparoscopic renal surgery.

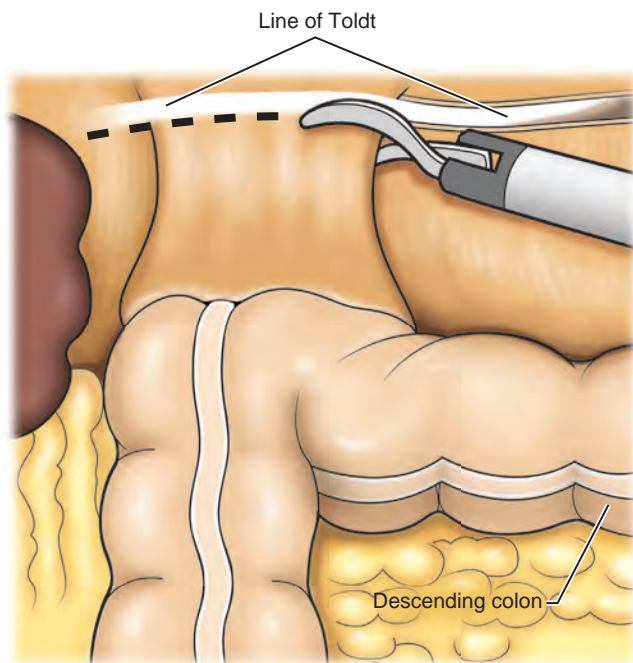


Figure 61-13. Incision of the white line of Toldt with endoshears, bipolar cautery, or ultrasonic energy allows reflection of the colon. Continuing superiorly allows incision of the lienocolic ligament, facilitating reflection of the spleen, pancreas, and colon.

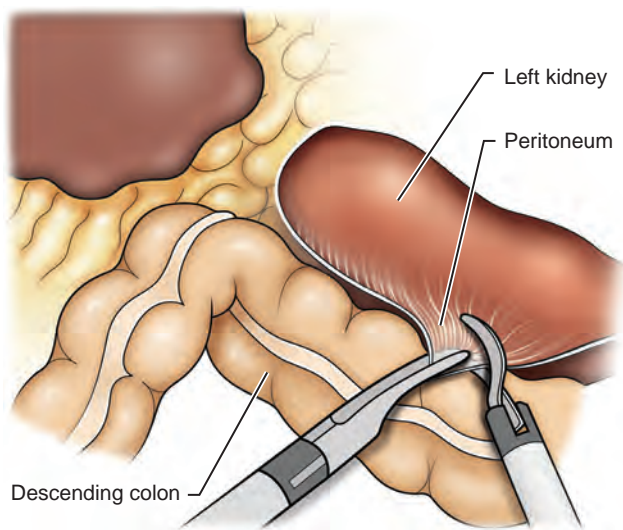


Figure 61-14. Medial traction on the colon helps identify additional colorenal attachments and assists in differentiating the undersurface of the large bowel mesentery. Care must be taken at this step to avoid creating a mesenteric window.

Isolation of the Upper Pole

Once the hilar vessels have been divided, the dissection continues posteriorly and superiorly to the upper pole. The adrenal gland is preserved in cases of simple nephrectomy by staying close to the upper pole (Fig. 61-19). This is accomplished by incising the Gerota fascia anteriorly, just above the hilum. The perinephric fat is then gently peeled off circumferentially above the upper pole of the kidney. At this point during the dissection, it may be necessary to clip and transect the ureter. This allows the kidney to be rotated anteriorly above the liver (right) or spleen (left) to facilitate incision of the uppermost attachments under direct vision. In cases of

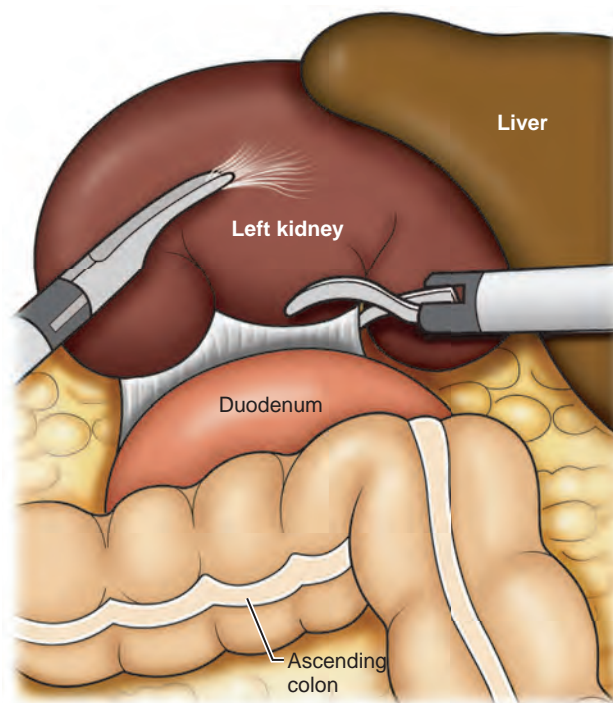


Figure 61-15. On the right side, the colon is reflected, and a Kocher maneuver may be performed to completely expose the kidney and the renal hilum.

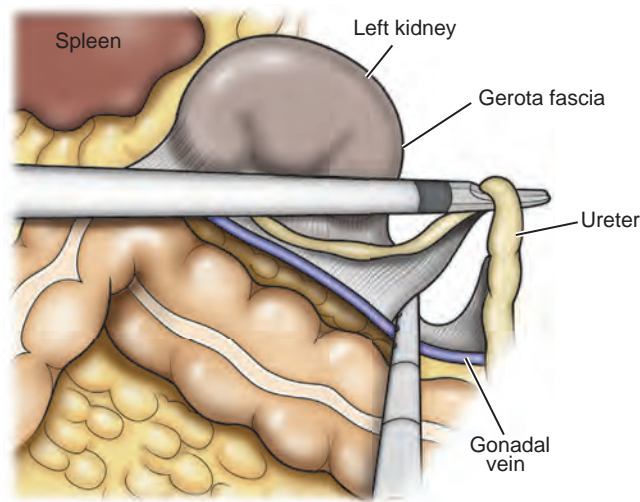


Figure 61-16. A curved dissector, in the left hand, is placed beneath the ureter and used to provide anterolateral elevation. On the right side the angle of insertion from the gonadal vein to the vena cava can be a source of significant bleeding if torn during elevation.

extreme fibrosis, a subcapsular nephrectomy can be performed once the artery and vein have been controlled (Moore et al, 1998). Long, blunt instruments, such as the 10-mm LigaSure Atlas (Valleylab, Boulder, CO), are particularly well suited for reaching and bluntly dissecting free the upper pole attachments. Care should be taken to avoid a diaphragmatic injury. Once the upper pole is free, the ureter can be ligated and lateral attachments taken with electrocautery.

Organ Entrapment and Extraction

The kidney can be removed intact or through morcellation. When morcellation is performed in cases of malignancy, the specimen

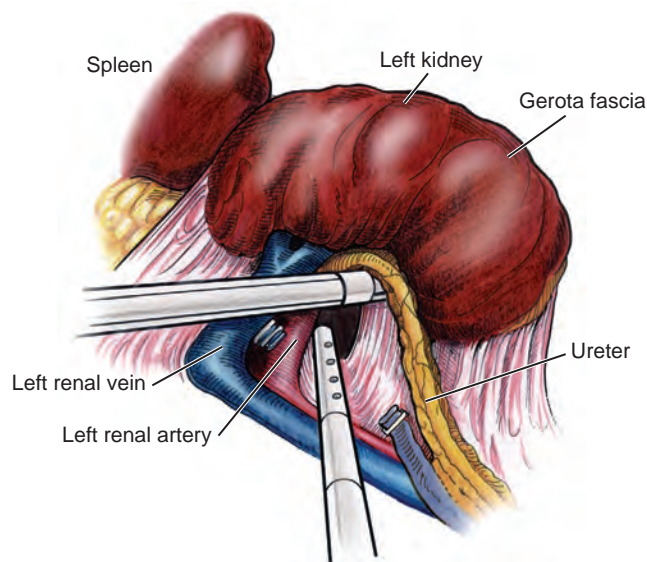
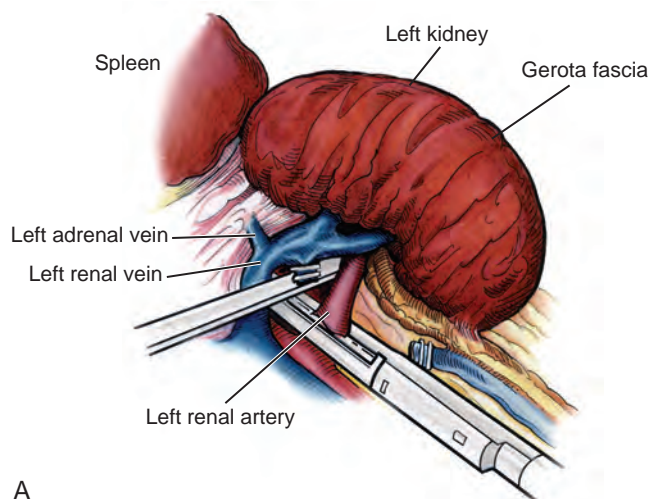
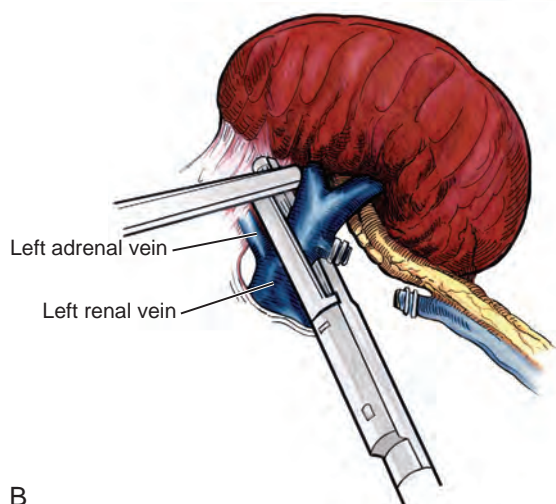


Figure 61-17. The lower pole of the kidney and ureter are firmly retracted anterolaterally, placing the hilum on stretch. The left gonadal vein has been ligated and divided.



A



B

Figure 61-18. A, First, the renal artery is stapled using an endovascular gastrointestinal anastomosis (GIA) stapler. B, The renal vein is secured lateral to the adrenal vein with the GIA stapler. If clips are used on the gonadal or adrenal vessels, the surgeon must be careful to exclude them from the jaws of the stapler.

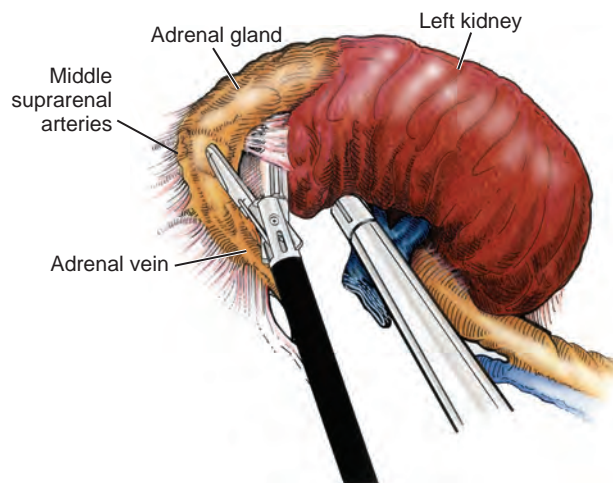


Figure 61-19. The adrenal gland can be preserved during simple nephrectomy or radical nephrectomy as indicated by dissecting it from the superior pole of the kidney.

should be placed into a sturdy entrapment sac (Urban et al, 1993). This minimizes the risk of rupture during mechanical morcellation of the tissue (Landman et al, 2000a; Pautler et al, 2002). With use of ring forceps and a Kocher clamp, the kidney and collecting system can be morcellated and removed in small pieces (Fig. 61-20). Purpose-built morcellators have become increasingly controversial owing to rare cases of port-site metastasis or tumor spread during surgery when malignancy is unsuspected. If used, great care must be taken to avoid engaging other organs or leaving tissue behind. Alternatively, the kidney can be removed intact through an incision after placement into a sac (Fig. 61-21). The kidney can be worked out of an extended trocar site or Pfannenstiel incision.

Postoperative Management

The orogastric tube is removed at the conclusion of the procedure. The patient can begin a diet as tolerated. The Foley catheter should be removed once the patient is comfortably ambulating. Depending on patient reliability and surgeon preference, the patient may be discharged either when tolerating a regular diet in the hospital or with instructions to begin a regular diet at home once passing flatus. Unrestricted activity can usually be resumed according to patient comfort, although in patients with an extraction incision, heavy lifting is often restricted until after 4 to 6 weeks of convalescence.

Results

The postoperative results of laparoscopic nephrectomy are comparable to those of open surgery, with less pain and shorter convalescence. Postoperative pain control requirements are approximately four times less than with traditional open incisions. Hospital stays have been decreased by 50%, and the time to full convalescence has been reported to be markedly less than with open removal. In early series, the mean operative times were greater than 300 minutes. However, with advances in technique, experience, and equipment, current operative times have decreased dramatically (Kerbl et al, 1994b; Nicol et al, 1994; Parra et al, 1995; Baba et al, 1996; Rassweiler et al, 1998a).

SURGERY FOR RENAL CYSTIC DISEASE

Renal cysts are extremely common and are present in more than one third of patients older than 50 years (Laucks and McLachlan, 1981; Carrim and Murchison, 2003). They rarely require surgical intervention, but indications include cyst-associated pain, infection, or obstruction (Hoenig et al, 1997; Wolf, 1998; Roberts et al,

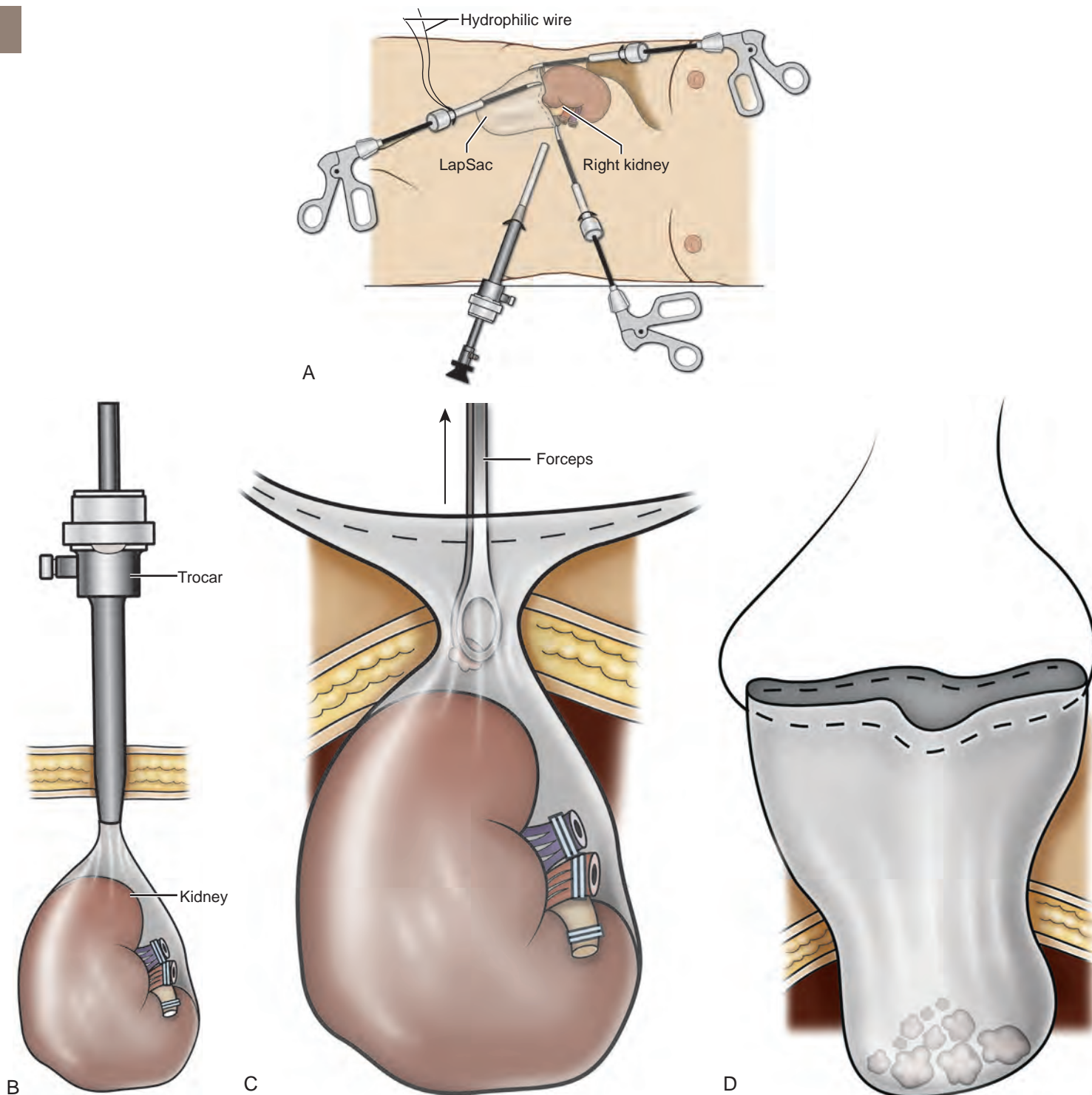


Figure 61-20. Removal of the morcellated specimen. A, The LapSac (Cook Urological, Spencer, IN) entrapment sac is introduced through the lateral 10-mm trocar site after passage of a hydrophilic wire through the opening of the LapSac. The entrapment sac is then released within the abdomen. The wire facilitates opening of the bag and placement of the specimen. A lateral 5- or 3-mm port may be necessary to assist with holding placement of the specimen inside the LapSac. B, Once the specimen is within the LapSac, the wire is removed, the bag cinched closed, and the opening withdrawn through the 10-mm trocar site. C, The entrapment sac is pulled tightly up against the abdominal wall, with two hands pushing part of the specimen to appear through the opening of the LapSac. After the site is carefully draped, manual morcellation with ring forceps or a Kelly clamp can be used. D, The entrapment sac is removed once the remaining specimen fragments are small enough to be extracted through the trocar site. Only the tissue visible from the opening is grasped. Blind passes into the bag may injure surrounding bowel segments.

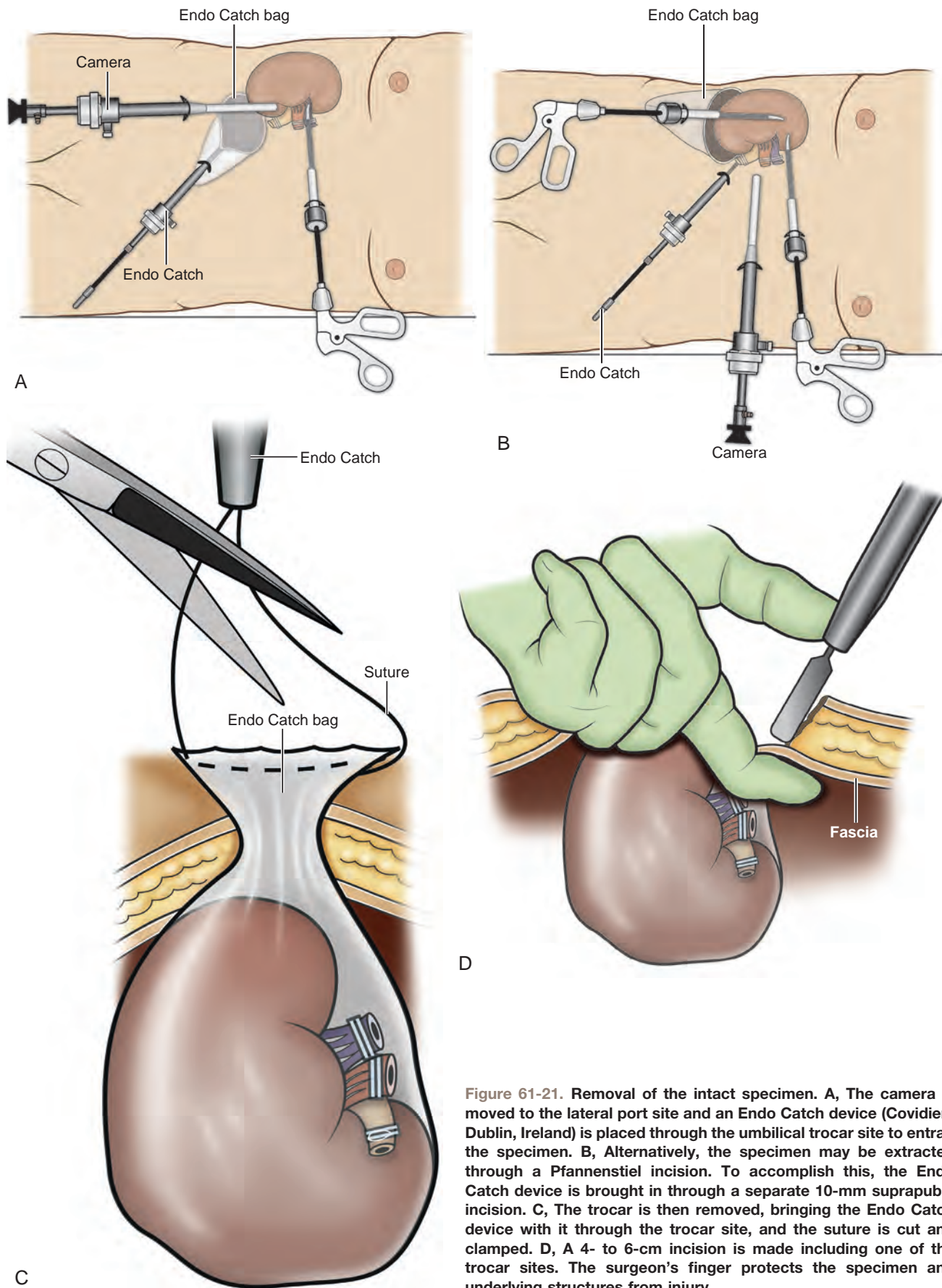


Figure 61-21. Removal of the intact specimen. **A,** The camera is moved to the lateral port site and an Endo Catch device (Covidien, Dublin, Ireland) is placed through the umbilical trocar site to entrap the specimen. **B,** Alternatively, the specimen may be extracted through a Pfannenstiel incision. To accomplish this, the Endo Catch device is brought in through a separate 10-mm suprapubic incision. **C,** The trocar is then removed, bringing the Endo Catch device with it through the trocar site, and the suture is cut and clamped. **D,** A 4- to 6-cm incision is made including one of the trocar sites. The surgeon's finger protects the specimen and underlying structures from injury.

TABLE 61-2 Renal Cyst Classification Based on Updated Bosniak Criteria

TYPE	DESCRIPTION	RECOMMENDED MANAGEMENT
I	A benign simple cyst with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density and does not enhance.	No follow-up necessary
II	A benign cyst that may contain a few hairline thin septa in which “perceived” [*] enhancement may be present. Fine calcification or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high-attenuation lesions (3 cm) (so-called high-density cysts) that are well margined and do not enhance are included in this group.	No follow-up necessary
II F	Cysts that may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Perceived enhancement of their septa or wall may be present. Their wall or septa may contain calcification that may be thick and nodular, but no measurable contrast enhancement is present. In general, these lesions are well margined. Totally intrarenal nonenhancing high-attenuation renal lesions >3 cm are also included in this category.	Follow-up imaging required
III	“Indeterminate” cystic masses that have thickened irregular or smooth walls or septa in which measurable enhancement is present. These are surgical lesions, although some will prove to be benign (e.g., hemorrhagic cysts, chronically infected cysts, and multiloculated cystic nephroma) and some will be malignant, such as cystic renal cell carcinoma and multiloculated cystic renal cell carcinoma.	Surgical treatment
IV	These are clearly malignant cystic masses that can have all the criteria of category III, but also contain enhancing soft-tissue components adjacent to, but independent of, the wall or septum. These lesions include cystic carcinomas and require surgical removal.	Surgical treatment

From Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. *Urology* 2005;66:484–8.

^{*}Not measurable enhancement.

2001; Doumas et al, 2004; Camargo et al, 2005). The increased use of cross-sectional imaging has also increased the detection of indeterminate renal cystic lesions and complex renal cysts, bringing an increased number to the attention of urologists. Classification schemata have been developed to help clinicians make determinations regarding management, the most popular being the Bosniak system (Table 61-2) (Israel and Bosniak, 2005). Although this imaging schema can be extremely useful, they are not always diagnostic, and surgery may be required in some cases to exclude malignancy.

First-line therapy and diagnosis of symptomatic renal cysts often involve percutaneous image-guided needle aspiration, with or without the use of a sclerosing agent, to reduce risk of recurrence. If symptoms temporarily resolve and recur when fluid reaccumulates, this increases the likelihood that surgical treatment will be successful in resolving the pain (Rané, 2004). Caution should be exercised in use of cyst aspiration and sclerosing agents in peripelvic cysts, because fibrosis may occur (Wehle and Grabstald, 1986; Hulbert et al, 1988; Santiago et al, 1998; McDougall, 2000).

In addition to causing pain, cysts may compress the renal parenchyma or other adjacent organs, cause ureteral obstruction and obstructive uropathy, spontaneously bleed, cause hypertension, or become infected. Laparoscopic cyst decortication or unroofing may be used to treat these cysts, which are typically simple in character (Fig. 61-22). Cysts with complex appearance, such as thickened septa, calcification, or enhancement (Bosniak class III to IV), may be explored and sampled laparoscopically to rule out renal cell carcinoma (RCC) owing to their increased risk of harboring malignancy (Cloix et al, 1996; Santiago et al, 1998). Options include cryoablation, enucleation, partial nephrectomy, and radical nephrectomy. If there is any question of cyst proximity to the collecting system, cystoscopy and placement of an open-ended ureteral catheter may be performed to ensure the integrity of the collecting system after cyst excision via partial nephrectomy.

A subset of patients with ADPKD may develop cyst-associated pain. Laparoscopic cyst decortication, marsupialization, or unroofing can be of benefit to these patients by offering a minimally invasive treatment that is successful in relieving pain in up to 83% of cases (Lifson et al, 1998; Dunn et al, 2001; Lee et al, 2003).



Figure 61-22. Axial computed tomography scan in delayed phase after intravenous contrast administration, demonstrating peripelvic cysts in a patient with left flank pain.

In patients with end-stage renal disease, bilateral synchronous laparoscopic nephrectomy may be performed in patients with enlarged, symptomatic, or infected kidneys (Gill et al, 2001; Rehman et al, 2001; Bendavid et al, 2004; Desai et al, 2008; Martin et al, 2012). Because an incision will be required to remove kidneys that are often quite enlarged, a hand port may be placed in the midline and used bilaterally to facilitate the dissection (Rehman et al, 2001; Jenkins et al, 2002; Eng et al, 2013).

Procedure

Depending on cyst location, a transperitoneal or retroperitoneal approach may be used as previously described. Intraoperative ultrasonography may be used to identify the cyst or cysts in question. It is usually easier to dissect the cyst wall free of surrounding

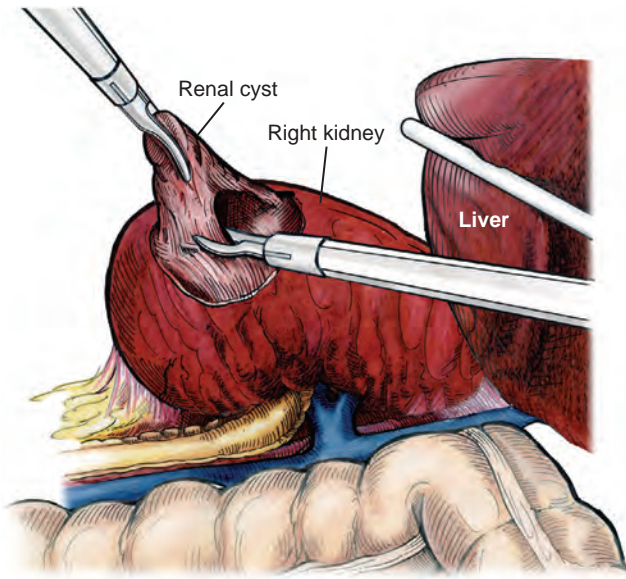


Figure 61-23. The cyst fluid is aspirated with a laparoscopic aspiration needle. After decompression of the cyst, the wall can easily be grasped and manipulated. The cyst is elevated with a grasper and scissors or ultrasonic shears to circumferentially excise the cyst wall. The edge of the cyst is carefully inspected, and biopsies are performed using the 5-mm laparoscopic biopsy forceps as needed.

connective tissue before evacuating fluid. The wall of the cyst can then be grasped and excised, cutting along the junction between the cyst wall and the renal parenchyma (Fig. 61-23). If suspicious lesions are noted in the base, biopsy specimens may be taken using the 5-mm biopsy forceps. If no evidence of malignancy is seen, the remaining cyst wall may be fulgurated with either electrocautery or the argon beam coagulator. Care should be taken when ablating the surface, because inadvertent or occult entry into the collecting system can easily occur (Cherullo et al, 1999). Moreover, these surfaces can be friable and prone to significant bleeding. Packing with hemostatic agents or suturing may be necessary. One should have a low level of suspicion for entry into the collecting system and therefore a low threshold for leaving a drain (Fig. 61-24). If malignancy is noted, extirpative surgery or cryoablation may be used to treat the remainder of the lesion.

When treating central or perihilar cysts, it may not be feasible to remove a large portion of the cyst wall. In these cases, it is helpful to place a pedicle of autologous fat into the defect to act as a wick (Nieh and Bihrlé, 1993).

Results

Laparoscopic treatment of symptomatic renal cysts has been found to be effective in both decompression and pain control. A study evaluating treatment durability at a mean follow-up of 26 months demonstrated a 100% pain-free rate in patients treated for a solitary symptomatic renal cyst (Lifson et al, 1998). In a separate study with a mean follow-up of 60 months, 80% to 90% of patients had complete resolution of pain after laparoscopic cyst decortication. In patients with ADPKD, additional benefits of cyst decortication have been noted, including decreased blood pressure (Dunn et al, 2001; Lee et al, 2003). Recurrence of pain in this group is higher than in patients with simple cysts, and durability is moderate (Brown et al, 1996). No significant changes in renal function were noted postoperatively.

Patients undergoing surgery for cystic renal disease are inherently a heterogeneous group, made up of patients with simple renal cysts, complex or indeterminate cysts, and ADPKD. Interpretation

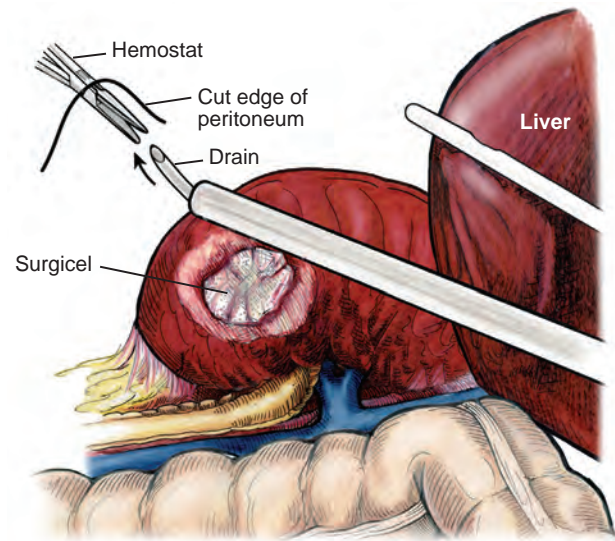


Figure 61-24. Drain placement after renal cyst excision. If the collecting system has been entered, it is closed and a drain placed. To insert the drain, a hemostat is passed through a small stab incision in the side and advanced into the abdominal cavity under direct vision. A drain is placed through a trocar site and advanced toward the open hemostat using the trocar to direct the drain. The colon is brought back over the kidney and attached to the sidewall to “reperitonealize” the kidney and drain.

of incidence reports of RCC in these series must take this fact into account. That said, the reported incidence of RCC in cystic lesions is 3% to 20% (Rubenstein et al, 1993; Lifson et al, 1998; Roberts et al, 2001; Limb et al, 2002).

RENAL BIOPSY FOR MEDICAL RENAL DISEASE

Histologic information is a key component in making treatment decisions and for prognosis in patients with proteinuria or unexplained renal insufficiency (Morel-Maroger, 1982; Gault and Muehrcke, 1983; Manaligod and Pirani, 1985). Although the modality of choice is typically ultrasound-guided or CT-guided percutaneous renal biopsy, laparoscopic biopsy may be preferred in certain situations, such as failed attempts at percutaneous biopsy, renal anatomic anomalies hindering image-guided percutaneous biopsy, heightened risk of bleeding complications, morbid obesity, multiple renal cysts, or a solitary kidney.

Procedure

The patient is placed in the full-flank position with the table flexed to increase working space between the costal margin and the iliac crest. Retroperitoneal access is preferred and obtained using techniques described earlier in this chapter. Renal biopsy is accomplished with the use of two trocars. With blunt dissection, the Gerota fascia is opened, and the lower pole of the kidney is exposed (Fig. 61-25A). In obese patients, intraoperative ultrasonography may be required to localize the kidney when copious retroperitoneal or perinephric fat is present. Five-millimeter biopsy forceps are used to take samples of cortical tissue; hemostasis is achieved with Bovie electrocautery or the argon beam coagulator; and adjunctive hemostatic measures are used as necessary (Fig. 61-25B).

Results

A multi-institutional series reporting on outcomes of laparoscopic renal biopsy in 74 patients over 9 years showed a mean operative

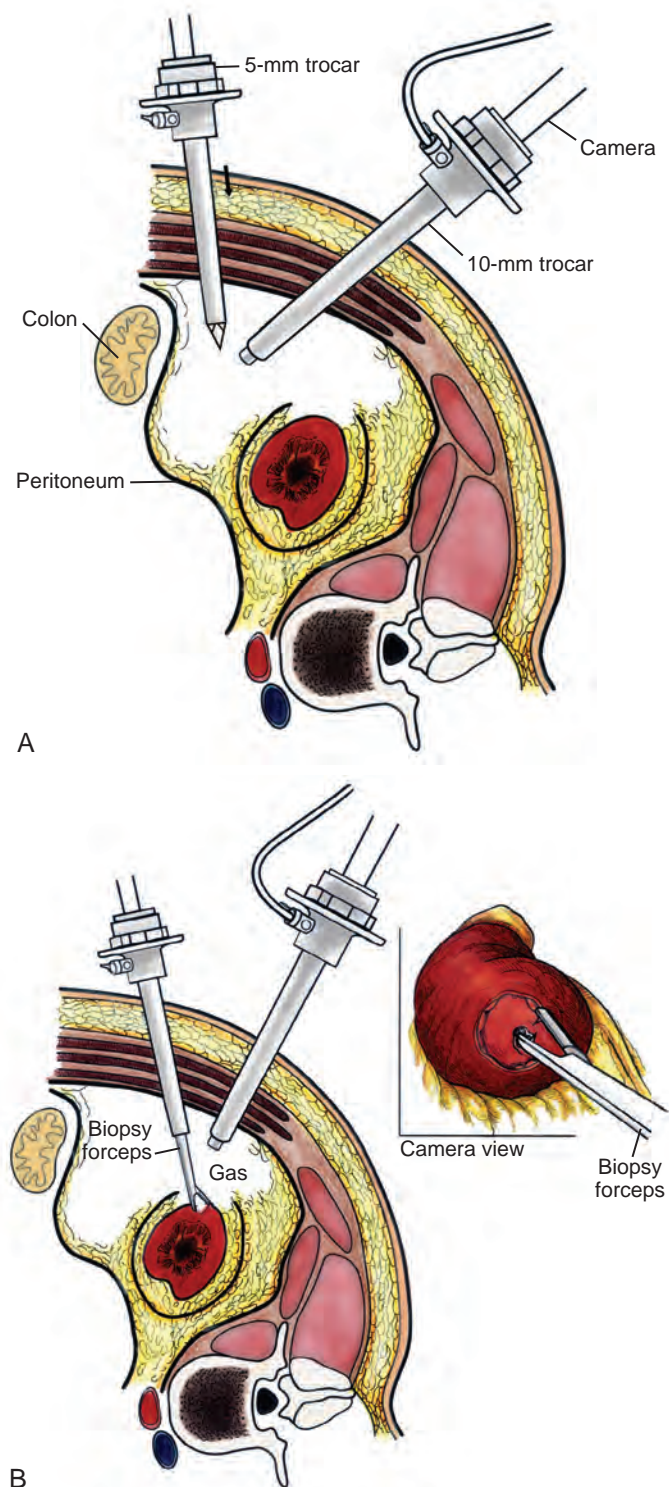


Figure 61-25. A, After establishment of a working space, a 5-mm trocar is placed under direct vision. The working instruments are passed through this port. The camera can be used to assist with dissection and is frequently cleaned to maintain adequate visualization. B, Gerota fascia is opened with the use of the scissors. With 5-mm two-tooth laparoscopic biopsy forceps, two or three samples are taken from the lower pole of the kidney.

time of 123 minutes, mean estimated blood loss of 67 mL, and discharge within 24 to 48 hours unless other preexisting medical conditions required a longer stay (Shetye et al, 2003). Tissue obtained from 96% of patients was adequate for diagnosis, with a complication rate of 13.5%. The authors concluded that laparoscopic renal biopsy may be performed safely with a high success rate, and that as experience grows, the complication rate and operative duration would likely decrease. In another series of 17 patients, use of balloon dilatation to create the working space demonstrated 100% success in obtaining renal tissue adequate for diagnosis. Mean operative time was 35 minutes (excluding anesthesia time), complication rate was 11%, and 15 of 17 patients were discharged within 24 hours. In published series of laparoscopic renal biopsy, hemorrhage is the most common complication. Caution should be used in resumption of anticoagulation in patients who require it postoperatively. If signs or symptoms of postoperative anemia or hypovolemia occur, a low threshold should be used to evaluate the patient with computed tomography (CT).

NEPHROPEXY

Renal ptosis, although rare, is a real cause of chronic flank or upper abdominal pain. The precise origin of symptoms is unknown but is likely secondary to either transient ischemia or urinary obstruction (Moss, 1997). The typical patient with a ptotic kidney is a young, thin female who complains of pain while in an upright position. Supine and erect intravenous pyelography (IVP) can be used for diagnosis, with the finding of interest being ptosis, defined as descent of the symptomatic kidney by two vertebral bodies (Fig. 61-26). Nuclear imaging may also quantify obstruction of blood flow or drainage in the upright position. Color Doppler sonography in both the supine and upright positions can also be used to evaluate differential blood flow. If a ptotic kidney is present, the expected finding would be diminished blood flow while in the erect position. Before surgical repair, obstruction, decreased blood flow, or significant descent correlating with pain should be documented.

Procedure

Surgical repair is performed using either a standard transperitoneal or retroperitoneal approach to fully mobilize the affected kidney and expose the fascia overlying the psoas and quadratus lumborum muscles (Chueh et al, 2002; Matsui et al, 2004) (Fig. 61-27). Beginning at the upper pole, interrupted sutures are placed to secure the lateral edge of the renal capsule to the fascia overlying the muscle (Fig. 61-28). Sutures may also be placed between the anterior renal capsule and the parietal peritoneum for additional support. Using sutures with preplaced Lapra-Ty clips (Ethicon, Cincinnati, OH), the initial pass is made through the fascia or peritoneum, and a second clip is placed on the suture after the pass through the kidney. An alternative technique describes the use of tension-free vaginal tape to secure the kidney (Hübner et al, 2004). By placement of the needles such that the tape is passed around the lower pole of the kidney and out through the abdominal wall, the kidney is secured. Sometimes this is found in conjunction with a ureteropelvic junction obstruction that should be addressed simultaneously (Boylu et al, 2009).

Results

A retrospective study of 30 patients undergoing laparoscopic nephropexy with a median follow-up of 5.9 years demonstrated improvement in all patients, 11 with complete relief of symptoms (Plas et al, 2001). Significant improvement in differential renal function was measured by renal scan in 9 of 10 patients undergoing the study postoperatively. Two patients developed a recurrent ptotic kidney with greater than 5 cm of descent documented by IVP. An additional study of 48 patients, with a median follow-up of just over 8

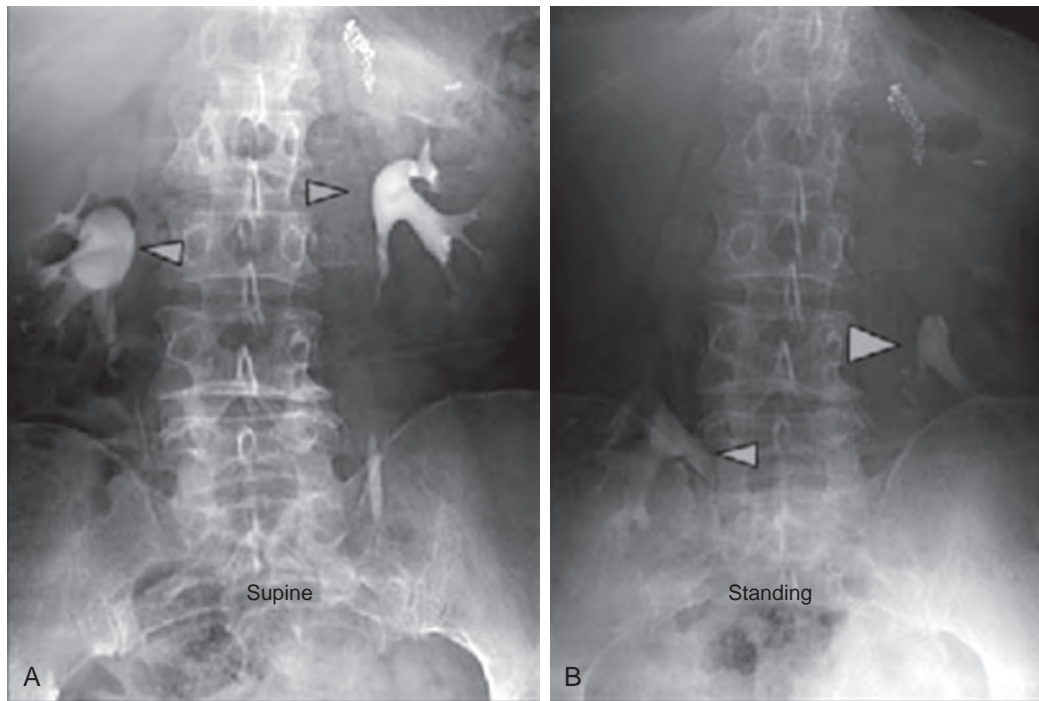


Figure 61-26. Intravenous pyelogram demonstrating bilateral ptotic kidneys in the supine (A) and standing (B) positions. (From El-Moula MG, Izaki H, Kishimoto T, et al. Laparoscopic nephropexy. *J Laparoendosc Adv Surg Tech A* 2008;18:230–6.)

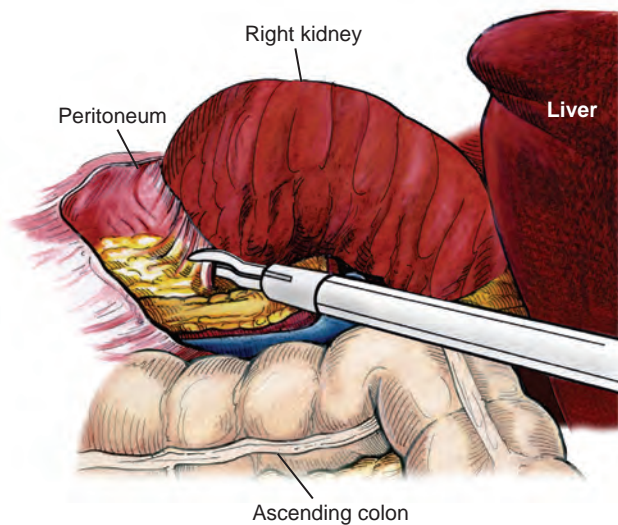


Figure 61-27. The kidney is stripped of overlying Gerota fascia down to the surface of the renal capsule. All remaining attachments are divided, allowing full mobility for repositioning.

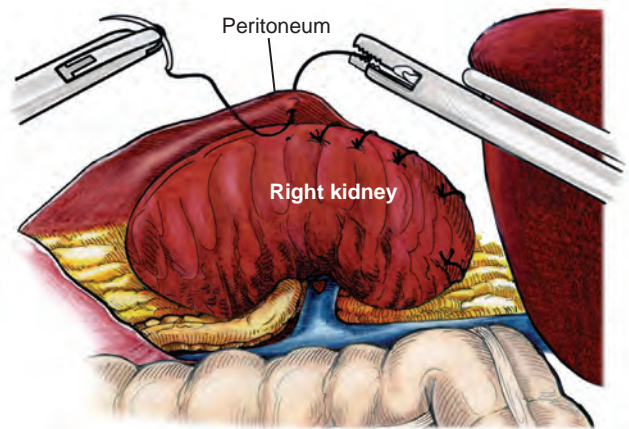


Figure 61-28. Nephropexy. Once the kidney is free of lateral and posterior attachments, multiple 2-0 sutures are placed into the capsule and the lateral edge of the fascia overlying the abdominal wall. Sutures may also be placed between the anterior renal capsule and the parietal peritoneum for additional support.

years, revealed that 94% of patients had no signs of significant ptosis on postoperative imaging, and 91% of patients had improvement in their pain symptoms (Gözen et al, 2008). Mean operative time was 95 minutes, and mean estimated blood loss was 50 mL. Patient satisfaction was high, and the authors concluded that laparoscopic nephropexy provided a minimally invasive approach to these patients with good long-term clinical outcomes. More recently, robotic assistance and LESS approaches to laparoscopic nephropexy have also been reported, mimicking similar techniques and reporting similar outcomes, although not directly compared with conventional laparoscopy (Boylu et al, 2009; Tsai et al, 2010; Baldassarre et al, 2011).

CALYCEAL DIVERTICULECTOMY

Patients with symptomatic calyceal diverticula containing stones can be managed laparoscopically. Extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy may be used, but because of infundibular stenosis, stone clearance rates are low (Jones et al, 1991; Pang et al, 1992; Stream and Yost, 1992). The principles of treatment include the removal of stones and widening of the infundibular stenosis to prevent urinary stasis or performing ablation of the diverticula cavity altogether. In the past, symptomatic calyceal diverticula have been managed with partial nephrectomy, with marsupialization and fulguration of the diverticulum, and

occasionally with simple nephrectomy. More recently, percutaneous treatment has been used, but stones or symptoms may recur if the cavity is not fully ablated (Donnellan et al, 1999). A laparoscopic approach may be indicated with large, peripheral diverticula, or for centrally located diverticula with proximity to the renal hilum.

Procedure

The location of the diverticula will be the primary driver for choosing either a transperitoneal or a retroperitoneal approach. Once the renal dissection has been completed, locating the diverticulum may prove difficult. Dense adhesions on the surface of the kidney overlying the diverticulum may be present along with a “dimpling” effect on the renal capsule. Intraoperative ultrasonography may also be used to aid in the location of the diverticulum or to confirm a suspected location. Once localized, the overlying parenchyma is incised and opened to expose the diverticulum, which is subsequently opened with cautery. Stones within the cavity may then be removed, and the argon beam coagulator or monopolar cautery device can be used to fulgurate the diverticular lining. The infundibulum in communication with the collecting system is closed with suture, and perirenal fat may be placed into the defect to further decrease the likelihood of recurrence. A drain is usually left in place after closure of the collecting system defect.

Results

Published reports on laparoscopic calyceal diverticulectomy are limited to small series and case reports. Excellent results have been reported by numerous authors, demonstrating the definitive nature of this treatment modality (Gluckman et al, 1993; Ruckle and Segura et al, 1994; Harewood et al, 1996; Wolf, 2000; Miller et al, 2002; Canales and Monga, 2003; Wyler et al, 2005; Gonzalez et al, 2011). Probably due to the rarity of this surgery and small case series in the literature, complications are also rare and not consistently reported.

NEPHROLYSIS

Nephrolysis has been used to treat loin pain, hematuria syndrome, and chyluria. The first indication has limited data. Chyluria is caused by lymphatic rupture or fistulous connection into the pyelocalyceal system. It is a rare problem worldwide but is commonly seen in tropical countries where filariasis (*Wuchereria*

bancrofti or *Brugia malayi*), the most common cause, is endemic (Tandon et al, 2004). Rarely, schistosomiasis may also be a cause of chyluria, and nonparasitic chyluria is rare. Other reported causes include tuberculosis (Wilson and White, 1976), idiopathic lymphorenal fistula (Eisner et al, 2009), prior surgery (Kim and Joudi, 2009), pregnancy (Onyeije et al, 1997), thoracic duct obstruction (Garrido et al, 1995), mesenteric adenitis (Cohen et al, 1984), renal vasculitis (El-Reshaide et al, 1998), and metanephric adenoma (McNeil et al, 2008).

Diagnosis of Chyluria

Patients typically have milky white urine and may have nephrotic range proteinuria. Initial evaluation includes urinalysis and culture, urine for chyle, and complete blood count to check for eosinophilia. Evaluation to localize the fistula may include cystoscopy with retrograde pyelogram, CT, magnetic resonance imaging (MRI), or lymphangiography (Fig. 61-29).

Treatment

Chyluria is often self-limited, and many patients may be managed conservatively. In filariasis-associated cases, this involves treatment with a course of diethylcarbamazine (DEC) in combination with a low-fat diet (Tandon et al, 2004). Retrograde instillation of silver nitrate or povidone iodine into the collecting system as a sclerosing agent has also been described, and these agents are commonly used as first-line treatment with comparable success rates of approximately 80% (Dalela et al, 2004b; Goel et al, 2004). When conservative management fails or if cases are particularly severe, surgical intervention is undertaken.

Procedure and Results

Nephrolysis involves the complete mobilization of the kidney and skeletonization of the renal hilar vessels and upper ureter with ligation of the lymphatic channels. The procedure may be performed laparoscopically with either a transperitoneal or a retroperitoneal approach and ensures complete lymphatic dissociation of the affected kidney (Chiu et al, 1995; Gomella et al, 1998). The use of an omental wrap around the hilum has also been described to provide an additional barrier against recurrence (Dalela et al, 2004a). It has been reported to be safe and efficacious even in the context of complex renal vasculature (Zhang et al, 2012). Authors commonly performing this procedure report excellent success rates approaching 100%.

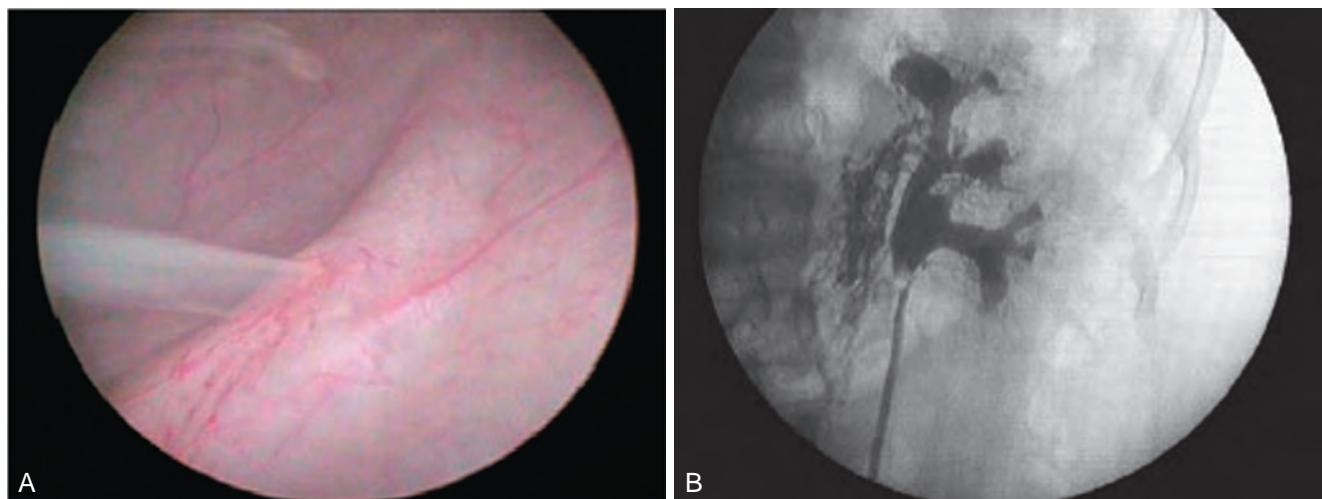


Figure 61-29. Chyluria. A, Cystoscopy demonstrating milky white efflux from the left ureteral orifice. B, Retrograde pyelogram demonstrating lymphorenal fistula. (From Eisner BH, Tanrikut C, Dahl DM. Chyluria secondary to lymphorenal fistula. *Kidney Int* 2009;76:126.)

RADICAL NEPHRECTOMY

Laparoscopic approaches to malignancy have been performed for over 20 years. The oncologic indications for laparoscopic radical nephrectomy (LRN) are similar to those for open surgery. Kidneys with tumors as large as 25 cm have been successfully removed laparoscopically, and cytoreductive nephrectomy has been performed in patients with metastatic disease (Walther et al, 1999). Moreover, tumors with caval thrombi have also been removed (Martin et al, 2008; Hoang et al, 2010; Bansal et al, 2014).

Transperitoneal

Procedure

Access and trocar placement are similar to what has been described for simple nephrectomy. With larger masses, caval involvement, or organ invasion, additional trocars or a hand port may be needed. The procedure for LRN is essentially identical to laparoscopic simple nephrectomy. The main distinguishing feature is that the Gerota fascia and fat are left intact during dissection. The adrenal may be removed en bloc with the kidney when indicated (Fig. 61-30A). To aid in this, the renal vein is taken medial to the take-off of the adrenal vein. In adrenal-sparing surgery, the fascia is opened over the upper medial aspect of the kidney (Fig. 61-30B). Suspect lymph nodes may be removed, and a full hilar or retroperitoneal dissection can be carried out if deemed necessary based on preoperative imaging, tumor location, and histologic subtype if known based on preoperative biopsy, prior surgery pathology, or hereditary predisposition. Excision of part of the adjacent muscle or involved organ, such as the diaphragm, pancreas, liver, spleen, and

bowel, has also been reported (Molina et al, 2004; Huscher et al, 2012).

Results

Long-term cancer-specific survival data are now widely available from multiple centers around the world that perform LRN (Table 61-3). Five- and 10-year outcomes show oncologic equivalence to open radical nephrectomy in treatment of renal cancer. Indeed, LRN has become the standard of care for most renal malignancies previously treated with open radical nephrectomy.

A multi-institutional study from centers performing LRN compared the surgical and disease-specific outcomes between open and LRN, with long-term follow-up (Portis et al, 2002). Median follow-up was 54 months, and recurrence-free survival rates were 91% and 92%, respectively, for the two groups at 5 years. The 5-year cancer-specific survival was 98% for the laparoscopic cohort and 92% for the open cohort.

A comparative analysis of 67 patients undergoing LRN, with 54 patients undergoing open radical nephrectomy, evaluated perioperative and oncologic outcomes (Permpongkosol et al, 2005). The LRN group showed a longer mean operative time (256 vs. 193 minutes). However, this finding likely reflects the learning curve for laparoscopy, because the first 34 patients and last 33 patients in the LRN group had a significant operative time difference. Complications occurred in 15% of patients in the LRN and open groups, and blood transfusions were required in 6% and 20% of the patients, respectively. Most important, the calculated disease-free survival rates for laparoscopic and open radical nephrectomy were 95% and 89%, respectively, at 10 years. The actuarial survival rates for laparoscopic and open radical nephrectomy were 87% and 75%,

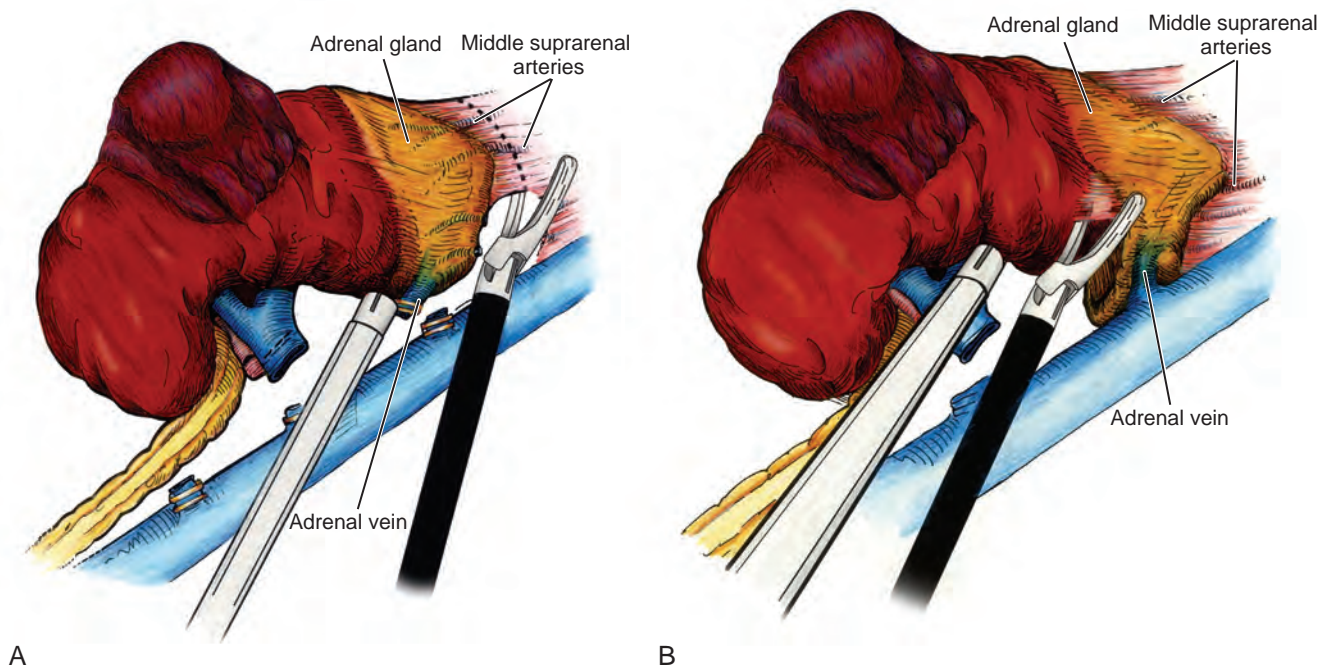


Figure 61-30. A, Inclusion of the adrenal gland during right laparoscopic radical nephrectomy can be readily accomplished using ultrasonic or bipolar shears to control the multiple arterial branches to the adrenal gland. Inferior retraction of the specimen facilitates exposure of this surgical plane. B, Adrenal-sparing, right radical nephrectomy. Use of a blunt instrument above the hilum to put anterior and inferior traction on the kidney helps to expose the correct plane and place the connective tissue on stretch. Ultrasonic or bipolar shears are again useful to avoid any bleeding that may be encountered in this plane.

TABLE 61-3 Oncologic Outcomes of Laparoscopic Radical Nephrectomy

A. COMPARATIVE SERIES ANALYZING LAPAROSCOPIC AND OPEN RADICAL NEPHRECTOMY															
AUTHOR	APPROACH	TOTAL NO. OF PATIENTS	NO. OF PATIENTS WITH RCC	MEAN AGE AT SURGERY	MEAN TUMOR SIZE	CLINICAL STAGE ≥T2	PATIENTS WITH FUHRMAN GRADE 3 OR 4		MEDIAN FOLLOW-UP	LOCAL RECURRENCE	PROGRESSION TO METASTATIC DISEASE	MEAN TIME TO RECURRENCE OR METASTASIS	CANCER-SPECIFIC DEATHS	5-YEAR RECURRENT-FREE/CANCER-SPECIFIC/ OVERALL SURVIVAL	10-YEAR RECURRENT-FREE/CANCER-SPECIFIC/ OVERALL SURVIVAL
Dunn et al, 2000	Laparoscopic	60	44	63.5 yr	5.3 cm	NR	NR	NR	25 mo (mean)	1 (2.3%)	2 (4.5%)	Not specified	2	—	—
	Open	30	30	61.8 yr	7.4 cm	NR	NR	NR	27 mo (mean)	0 (0%)	3 (10%)	Not specified	0	—	—
Ono et al, 2001	Laparoscopic	103	103	57.2 yr	3.1 cm	0%	3.9%	3.9%	29 mo	1 (1%)	3 (2.9%)	31.5 mo	0	95.1%/NR/95%	—
	Open	46	46	56.7 yr	3.3 cm	0%	6.5%	6.5%	39 mo	0 (0%)	3 (6.5%)	22.3 mo	2	89.7%/NR/95.6%	—
Portis et al, 2002	Laparoscopic	64	64	60.6 yr	4.3 cm	14.1%	9.4%	9.4%	54 mo	1 (1.6%)	3 (4.7%)	31.8 mo	1	92%/98%/81%	—
	Open	69	69	61.3 yr	6.2 cm	34.8%	13.0%	13.0%	69 mo	1 (1.4%)	10 (14.5%)	47.5 mo	6	91%/92%/89%	—
Saika et al, 2003	Laparoscopic	195	195	57.3 yr	3.7 cm	NR	4.1%	4.1%	40 mo	1 (0.5%)	10 (5.1%)	33.6 mo	5	91%/NR/94%	—
	Open	68	68	58.4 yr	4.4 cm	NR	7.3%	7.3%	65 mo	0 (0%)	10 (14.7%)	Not specified	6	87%/NR/94%	—
Harano et al, 2005	Laparoscopic	96	96	61.1 yr	4.3 cm	NR	NR	NR	25 mo	0 (0%)	3 (3.1%)	24.3 mo	0	88%/NA/100%*	—
	Open	86	86	58.5 yr	4.9 cm	NR	NR	NR	86 mo	0 (0%)	5 (5.8%)	Not specified	0	93%/NA/100%*	—
Permpongkosol et al, 2005	Laparoscopic	67	67	61 yr	5.1 cm	31.3%	26.9%	26.9%	73 mo	0 (0%)	4 (6%)	29.5 mo	2	94%/97%/85%	94%/97%/76%
	Open	54	54	59 yr	5.4 cm	25.9%	29.6%	29.6%	80 mo	0 (0%)	7 (13%)	Not specified	6	87%/89%/72%	87%/86%/58%
Hemal et al, 2007†	Laparoscopic	41	39	52.5 yr	9.9 cm	100%	NR	NR	51 mo	0 (0%)	3 (7.7%)	Not specified	2	92.6%/95.1%/87.8%	—
	Open	71	68	52.7 yr	10.1 cm	100%	NR	NR	57 mo	0 (0%)	7 (10.3%)	Not specified	4	90.1%/94.4%/88.7%	—
Hattori et al, 2009†	Laparoscopic	52	52	56 yr	8.8 cm	100%	11.5%	11.5%	41 mo	1.9%	19.2%	Not specified	6	75%/90%/NR	60%/90%/NR
	Open	79	79	62 yr	8.9 cm	100%	11.4%	11.4%	51 mo	2.5%	20.3%	Not specified	20	77%/87%/NR	70%/75%/NR
B. NONCOMPARATIVE SERIES OF LAPAROSCOPIC RADICAL NEPHRECTOMY															
AUTHOR	NO. OF PATIENTS WITH RCC	MEDIAN AGE AT SURGERY	MEAN TUMOR SIZE	PATIENTS WITH FUHRMAN GRADE 3 OR 4		MEDIAN FOLLOW-UP	LOCAL RECURRENCE	PROGRESSION TO METASTATIC DISEASE	MEAN TIME TO RECURRENCE OR METASTASIS	CANCER-SPECIFIC DEATHS	5-YEAR RECURRENT-FREE/CANCER-SPECIFIC/ OVERALL SURVIVAL	10-YEAR RECURRENT-FREE/CANCER-SPECIFIC/ OVERALL SURVIVAL			
Cadeddu et al, 1998	157	61 yr	NR	8.9%	19.2 mo (mean)	1 (0.6%)	4 (2.5%)	14.8 mo	0	91%/NA/NA	NA	NA			
Wille et al, 2004	118	63 yr	5.1 cm	NR	23.5 mo	0 (0%)	3 (2.5%)	9.7 mo	NR	NR	NA	NA			
Hemal et al, 2007	132	51.6 yr	6.9 cm	7.6%	56 mo	0 (0%)	17 (12.9%)	34.1 mo	16	87.1%/87.9%/85.6%	NA	NA			
Bandi et al, 2008	65	59 yr	5.8 cm	14.0%	46 mo (mean)	1 (1.5%)	4 (6.2%)	18 mo	3	90.2%/94.4%/80%	NA	NA			
Berger et al, 2009	73	59 yr	5 cm	24.6%	131 mo	0 (0%)	8.2%	74 mo	8	NR	86%/92%/65%	86%/92%/65%			
Pierorazio et al, 2012†	166	58.2 yr	9 cm	51.7%	36 mo	4 (2.4%)	35 (21.1%)	NA	NA	62.4%/92.9%/NA	NA	NA			
Luciani et al, 2013†	222	64 yr	8.5 cm	43%	42	4 (1.8%)	42 (18.9%)	14 mo	28	66%/78%/76%	NA	NA			

*Four-year survival reported in this series.

†Series inclusive of tumors only ≥7 cm in size.

NA, not available; NR, not reported; RCC, renal cell carcinoma.

respectively, at 10 years. These differences were not found to be statistically significant.

More recently, 10-year oncologic outcomes data following LRN were reported. Recurrence-free, cancer-specific, and overall survival rates were 86%, 92%, and 65%, respectively, at 10 years postnephrectomy (Berger et al, 2009). Of 73 patients undergoing LRN, no patient developed local recurrence, and 6 (8.2%) developed metastatic disease at a mean time to recurrence of 74 months. Although outcomes in this study were not compared with an open radical nephrectomy cohort, results are quite comparable to those for open surgery.

Perioperative outcomes in contemporary groups undergoing laparoscopic and open radical nephrectomy have also been extensively studied. In a report comparing minimally invasive radical nephrectomy with open radical nephrectomy in the National Surgical Quality Improvement Program database, 5459 radical nephrectomy cases were identified. Significantly lower operative times, need for blood transfusion, length of hospitalization, and postoperative complications were noted in the laparoscopic patient cohort (Liu et al, 2014a). Similarly, in a well-matched cohort comparing laparoscopic with open radical nephrectomy, the laparoscopic approach was shown to have less blood loss, shorter hospital course, lower analgesic requirement, and shorter return to convalescence (Gill et al, 2000). Consistently, similar findings have been reported by multiple authors over the past three decades (Kerbl et al, 1994a; McDougall et al, 1996; Hemal et al, 2007).

Retroperitoneal

Procedure

The patient is positioned, and trocars are placed for retroperitoneal access as described earlier in the chapter. After identification of the psoas muscle and tendon, medial dissection in this plane will reveal the ureter. Elevation of the ureter will allow visualization and subsequent elevation of the lower pole of the kidney. This will place the main renal vessels on stretch, facilitating their dissection. The arterial pulsation may be indirectly visualized through overlying connective tissue, and just as with the transperitoneal approach, gentle layer-by-layer dissection with the suction-irrigator will allow the renal vessels to come more directly into view. Use of the right-angle dissector will allow the artery to be circumferentially freed from the surrounding tissue, and the endovascular stapler or clips are used to divide the artery and vein sequentially. During surgery on the left kidney, a lumbar vein will typically require dissection, ligation, and division to allow unencumbered access to the main hilum. Care must be taken to continuously reorient to anatomic relationships to ensure that the inferior vena cava is not mistakenly identified as the renal vein.

Results

When compared with transperitoneal LRN, outcomes of the retroperitoneal approach are similar with regard to complication rates, analgesic requirements, hospital course, and return to convalescence.

A randomized study comparing transperitoneal and retroperitoneal laparoscopic approaches was performed in 102 patients (52 transperitoneal, 50 retroperitoneal) with a mean tumor size of 5 cm (Desai et al, 2005). No difference was seen in blood loss, narcotic requirement, hospital stay, or complication rate. However, there was a significant difference noted in operative time, which favored the retroperitoneal approach (150 vs. 207 minutes). A second randomized study of 40 patients compared the number and size of trocars, pathologic stage, blood loss, operative time, complication rate, and hospital stay (Nambirajan et al, 2004). No statistical difference was noted in any of these outcomes, including operative time. A recent systematic review including prospective randomized controlled trials as well as retrospective observational studies comparing the outcomes of the two approaches demonstrated no significant difference in operative times, time to first oral intake, postoperative

analgesic requirement, postoperative complications, open conversion, need for blood transfusion, or oncologic outcomes (Fan et al, 2013).

Hand-Assisted

Procedure

The patient is positioned, and the hand port and trocars are placed as previously described. The steps in hand-assisted laparoscopic nephrectomy (HALN) are similar to those for pure laparoscopic surgery, but the nondominant hand is used throughout for retraction and blunt dissection. To incise the white line of Toldt, the nondominant hand retracts the colon medially while the dominant hand uses laparoscopic scissors to divide the attachments (Fig. 61-31). The irrigator-aspirator is then used to help identify and dissect the correct plane posterior to the large bowel mesentery and anterior to the Gerota fascia. The surgeon's hand and fingers may be used to simultaneously place lateral traction on the kidney and medial traction on the bowel, helping to demonstrate the correct plane. For a left-sided renal procedure, the hand may also be used to gently retract the spleen and pancreas medially while the lienorenal attachments are divided. Similarly, on the right, the hand is used to retract the liver anteriorly, exposing the upper pole and facilitating its dissection.

After the colon is sufficiently mobilized, the psoas muscle is identified, which will allow the ureter to be elevated. On the left the gonadal vein is typically elevated in the packet along with the ureter, but on the right the gonadal vein is reflected medially. With the ureter elevated, the hand can bluntly dissect and elevate the entire kidney off the psoas muscle, and the ureter is then followed up to the renal hilum. The fingers are then used to place anterolateral traction on the kidney while the thumb pushes the bowel and mesentery medially. The hilum should begin to come into view at this point, and the irrigator-aspirator can be used to gently dissect the overlying connective tissue while the hand is used to keep the vessels on stretch. Once the vessels are sufficiently skeletonized, the endovascular stapler or clips are used to ligate and divide the artery

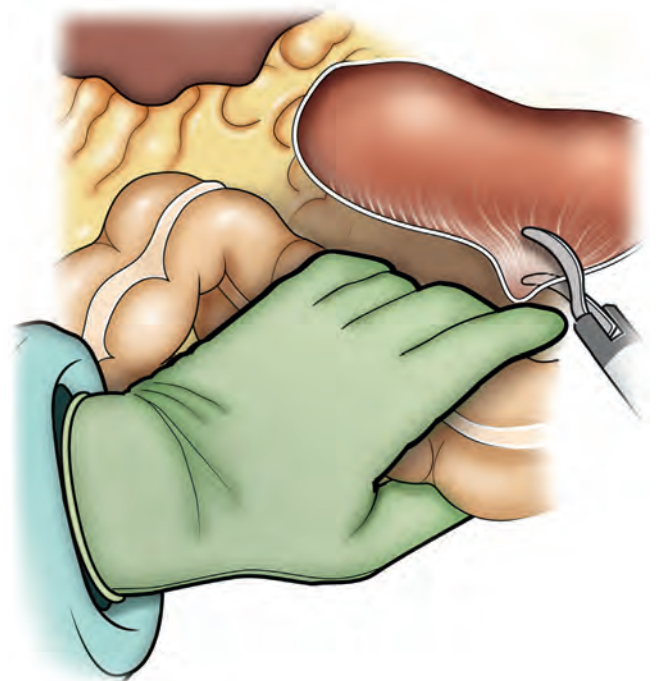


Figure 61-31. The nondominant hand is used to retract the colon medially and to dissect tissue planes, while the dominant hand uses endoscopic scissors to divide colon attachments.

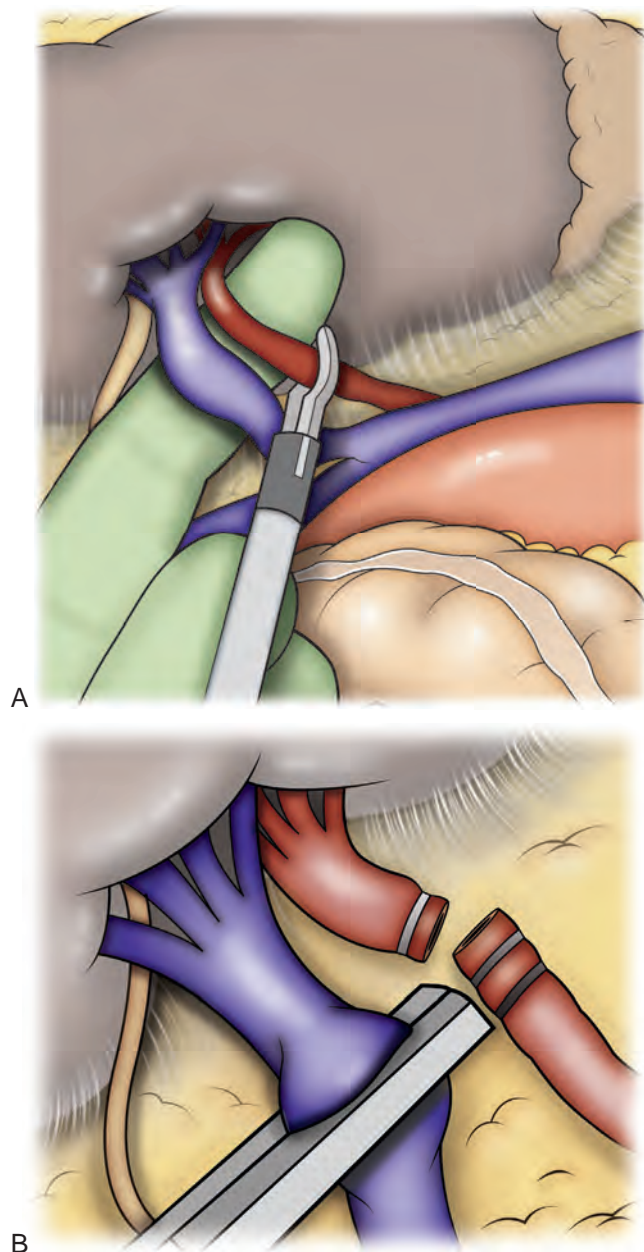


Figure 61-32. A, With the renal hilum on stretch and the bowel retracted medially to expose the vessels, the fingers can be used to palpate the renal artery and guide a stapler or clip applicator to secure and divide the artery. B, Once the artery is divided, the renal vein is freed circumferentially and divided with an endovascular stapler.

and vein sequentially (Fig. 61-32). The lateral and superior attachments may then be divided, using a LigaSure device or Harmonic scalpel (Ethicon) while the hand keeps them on traction. The hand should not be used to bluntly dissect the adrenal gland free from the upper pole of the kidney, because this will typically result in bleeding. Ultrasonic energy, LigaSure, or bipolar cautery may be used to divide the fragile attachments between the kidney and the adrenal gland, just as with pure laparoscopy.

A rolled laparotomy sponge is often placed through the hand port at the beginning of the procedure to assist with retraction, absorb blood, and allow the surgeon to hold pressure if needed. In addition, the tip of the irrigator-aspirator can be placed into the compressed sponge to facilitate suction when needed. It is critical to remember removal of the sponge at the end of the case. The previously made hand-port incision allows rapid removal of sponge and the intact specimen. However, hand-port metastases have been

reported, and it is recommended to place the specimen in a removal device before extraction to minimize any possibility of direct contact of the extraction specimen with wound edges.

The inserted hand can also facilitate closure of trocar sites greater than 10 mm with a suture-passing device. Wound complications such as hernias and infections have been reported at the hand-port site, with hernias typically manifesting 3 months or more after surgery and with an overall 4% incidence (Okeke et al, 2002; Wolf, 2005). Care must be taken to copiously irrigate and close the hand-port incision, ideally closing the peritoneum separately from the fascia to minimize the chance of injuring intraperitoneal structures and hernia formation.

Results

Most outcomes are comparable between pure laparoscopy and the hand-assisted technique, including efficacy, operative times, complication rates, narcotic requirements, length of hospital stay, and return to convalescence. Some comparative studies between laparoscopic and hand-assisted techniques have demonstrated that the hand-assisted procedures can require shorter operative times, but patients had more abdominal pain and wound complications (Nelson and Wolf, 2002).

Comparative studies between HALN and standard laparoscopic approaches have shown that choice of approach does not affect oncologic outcome. Gabr and colleagues (2009) studied and compared 147 patients who underwent standard laparoscopic nephrectomy and 108 who underwent HALN. Patients were followed for a mean of 35.2 months, and multivariate analysis showed that the approach did not affect recurrence-free, cancer-specific, or overall survival. A multi-institutional study of 95 patients undergoing HALN evaluated the impact of tumor size on outcome (Stifelman et al, 2003). Patients were grouped into those with tumors larger than 7 cm and those with tumors smaller than 7 cm. Short-term outcomes at mean follow-up of 12 months were not different between the two groups, including positive margin rate, local recurrence, and metastasis.

Special Considerations

Large Tumors

Experience with laparoscopy for large tumors (>7 cm) has grown substantially as confidence with renal laparoscopy has increased (Steinberg et al, 2004; Hemal et al, 2007; Berger et al, 2008; Rosoff et al, 2009; Luciani et al, 2013). Large tumors present several surgical challenges. The bulk of the mass can decrease working space and alter normal anatomic landmarks. This can result in disorientation with potentially higher risk of injury to surrounding structures. Continuous intraoperative reference to preoperative imaging as well as use of intraoperative ultrasonography is helpful. Flexible endoscopes may be used to better visualize portions of the surgical field that would otherwise not be visible via a conventional rigid laparoscope. The weight of large tumors may cause the surgeon to apply additional force for manipulation, potentially resulting in tumor rupture. It may be beneficial to use a hand port or additional trocars in these instances to allow for more widely distributed retraction of the kidney. Consideration may also be given to lymphadenectomy with larger, higher-stage tumors.

En Bloc Hilar Vessel Stapling

En bloc stapling of the renal hilum has been reported from several centers. An evaluation of 80 patients with mean follow-up of 35.2 months after either open radical nephrectomy or LRN, with routine use of en bloc hilar stapling, demonstrated no clinical evidence of arteriovenous fistula (White et al, 2007). Half of the patients also underwent CT arteriography at a minimum interval of 12 months postoperatively, and no patient had radiographic evidence of arteriovenous fistula. Another study evaluated patient outcomes in 433 patients undergoing LRN or nephroureterectomy, of whom 26 (6%)

underwent en bloc stapling only when hilar dissection was deemed difficult by the surgeon (Rapp et al, 2004). No cases of arteriovenous fistula were noted at a mean follow-up of 26 months. More recently, a randomized controlled trial of 70 patients undergoing either en bloc stapling of the renal hilum or separate ligation of the artery and vein reported no significant difference in postoperative blood pressure, heart rate, presence of bruit, or clinical or radiographic evidence of arteriovenous fistulization at 12 months' follow-up. Shorter operative times and lower estimated blood loss were noted in the en bloc ligation cohort (Chung et al, 2013). However, arteriovenous fistula may possibly occur as a more long-term complication after en bloc hilar stapling, and thus longer follow-up is needed to properly assess patients undergoing this form of hilar vascular management.

Port-Site Recurrence

Since the inception of laparoscopy and its application for surgical management of urologic malignancies, port-site seeding with recurrence has been of concern. In an international survey of 20 centers performing 2604 laparoscopic radical nephrectomies, no port-site seeding was reported (Micali et al, 2004). A review of all reported cases of port-site seeding in laparoscopy for urologic malignancy revealed a total of 28 cases. The majority involved aggressive upper tract transitional cell carcinoma, and 6 involved RCC (Eng et al, 2008). A more recent report of 133 laparoscopic radical nephrectomies demonstrated port-site metastases in 2 patients, both with higher pathologic stage with evidence of nodal metastases (Kumar et al, 2012). The cause of port-site recurrence is thought to be multifactorial and related to tumor aggressiveness, immune status of the patient, local wound factors, and surgical technique. The effects of pneumoperitoneum, aerosolization of tumor cells, insufflation gas type, and laparoscopic wound closure techniques have been studied by multiple authors and have been shown to be noncontributory (Ikramuddin et al, 1998; Tsivian et al, 2000; Gupta et al, 2002; Burns et al, 2005; Halpin et al, 2005; Jingli et al, 2006). As with open surgery, the most common cause is technical error and associated tumor spillage. Animal studies demonstrate that direct contact between tumor and port site enhances tumor growth (Bouvy et al, 1996), and hence the use of an impermeable specimen retrieval bag is recommended in all cases. Although the overall incidence of port-site metastasis is low—estimated at 0.09% to 0.18% (Rassweiler et al, 2003; Micali et al, 2004)—care should be taken in specimen handling and extraction to help minimize risk factors over which the surgeon has the most control.

Specimen Extraction

An area of controversy surrounding specimen extraction has been morcellation owing to the concerns for inadequate pathology assessment and staging, theoretic heightened risk of peritoneal or port-site seeding, bag rupture during morcellation, and overall recurrence. Although there is an advantage in terms of shorter incision length, there has been no benefit demonstrated in postoperative analgesic requirement (Hernandez et al, 2003). A multi-institutional study of the safety and efficacy of specimen morcellation in 188 patients with clinical stage T1 or T2 RCCs revealed 11 patients with recurrent disease (10 metastatic to lungs or viscera and 1 patient with port-site, renal fossa, and lymph node recurrence) (Wu et al, 2009). This demonstrates that mechanical morcellation may be safely performed in selected patients, although it is not considered standard of care. However, the ability to properly stage the patient remains in question, with studies demonstrating conflicting results. The feasibility of pathologic evaluation has been studied in comparative fashion by evaluating both fresh and formalin-fixed specimens before and after morcellation (Landman et al, 2000b). No alteration in determination of histology, grade, or local invasiveness of tumor was seen. Only specimen size could not be assessed after morcellation. A separate study of 23 morcellated specimens concluded that pathologic tumor stage in both renal cell and transitional cell carcinoma is severely limited by morcellation and must

rely partially on diagnostic imaging for lesion size, capsule, and renal vein involvement (Rabban et al, 2001). In addition, the incidence of pathologic stage T3a tumors was evaluated retrospectively in a series of 1781 patients and found to be 7.2% overall (Granberg et al, 2007). Imaging in the overwhelming majority of these patients did not predict stage pT3a disease. The authors concluded that without imaging that can more reliably predict fat invasion, accurate staging would be difficult if morcellation were performed.

If the specimen is to be morcellated, the surgeon should strictly adhere to proper technique including the use of a purpose-built sac, adequate draping, and change of gowns, gloves, and instruments after morcellation. The LapSac (Cook Urological, Spencer, IN) has been shown to be impermeable to bacteria and tumor cells, even after its use for morcellation (Urban et al, 1993). The sac is prepared by passing a moistened hydrophilic wire alternating through every third hole in the sac, which is then rolled from the bottom up and passed through a 12-mm trocar site. The trocar is replaced, leaving the wire and drawstrings outside the trocar. Graspers are used to place the specimen in the sac, which is held open by the wire, and the wire is removed (Wakabayashi et al, 2003). The drawstrings are grasped and brought through the periumbilical incision along with the neck of the sac, which is held tightly against the abdomen. Enlarging the trocar site by 1 cm will allow small amounts of tissue to protrude through the mouth of the sac. The morcellation process is performed with a ring forceps, working with alternating bites on the protruding tissue. Deep passes with the forceps should be avoided to prevent unintentional incorporation of bowel into the forceps. Pneumoperitoneum and direct laparoscopic visualization should also be maintained during the process to allow monitoring of the sac intracorporeally to avoid injury to structures resting against the sac or sac perforation.

Lymphadenectomy

Lymphadenectomy at the time of nephrectomy for presumed RCC, open or laparoscopic, remains controversial and is not commonly performed (Filson et al, 2012). It has been shown that presence of two or more adverse pathologic predictors (grade, sarcomatoid features, tumor size, stage, and necrosis) results in a higher likelihood of lymph node metastasis (Blute et al, 2004). In addition, patients with preoperatively or intraoperatively suspicious lymph nodes have been shown to have improved survival (median of 5-month benefit) when undergoing a lymph node dissection (LND) compared with those who did not (Pantuck et al, 2003). A retrospective study of 50 patients undergoing LRN alone versus 50 undergoing LRN with LND determined that 10% of the patients undergoing LND had positive nodes (Chapman et al, 2008). All patients were preoperatively node negative by cross-sectional imaging evaluation, and those with positive nodes all had high-grade lesions, stage T3 or T4. However, a randomized study comparing groups undergoing radical nephrectomy, with or without lymphadenectomy at the time of surgery, demonstrated no survival benefit of LND in patients with clinically negative lymph nodes (Blom et al, 2009).

It is clear that not every patient with RCC requires lymphadenectomy. However, a subset of patients with clinically suspicious lymph nodes, based on preoperative imaging criteria, preoperative biopsy pathology, intraoperative findings, or hereditary predisposition to aggressive pathology, may derive benefit from lymphadenectomy. Of note, there is no consensus on the extent of node dissection to be performed. The additional group that may benefit includes those with higher-stage tumors in the absence of suspicious lymph nodes, although survival data to support lymphadenectomy in this population are lacking.

Local Recurrence

The incidence of isolated local recurrence after nephrectomy with curative intent is approximately 1.8% (Itano et al, 2000; Margulis et al, 2009). Isolated local recurrence is defined as recurrence in the ipsilateral retroperitoneal lymph nodes, renal fossa, or adrenal gland without evidence of distant metastasis (Fig. 61-33). In a study



Figure 61-33. Renal fossa recurrence. (From Nóbrega de Jesus CM, Silva Casafus FA, et al. Surgical treatment of renal cell carcinoma recurrence at the renal fossa following radical nephrectomy. *Sao Paulo Med J* 2008;126:194–6.)

of 54 patients with isolated local recurrence managed with open surgical resection, median recurrence-free and cancer-specific survival rates of 11 and 61 months, respectively, were observed (Margulis et al, 2009). Perioperative systemic therapy with various combinations of immunotherapy, chemotherapy, and targeted tyrosine kinase inhibitors was used in 69% of cases. Given the rarity of these recurrences, published laparoscopic experience in surgically addressing them is quite limited to date. A series of 5 patients (1 open conversion for vena caval invasion) undergoing a hand-assisted approach to isolated local recurrence demonstrated that the procedure may be safely performed in selected patients (Bandi et al, 2008). At a mean follow-up of 43 months, cancer-specific and disease-free survival rates were 60% and 20%, respectively. The small number of patients in this report makes the results difficult to interpret. An open surgical resection can offer durable local control and cancer-specific survival in carefully selected patients; larger comparative laparoscopic series with sufficient follow-up are clearly needed to determine the efficacy of laparoscopy in these scenarios.

Renal Vein and Caval Tumor Thrombus

Several centers have now published their experiences with laparoscopy for renal cancers with associated tumor thrombus into the renal vein or inferior vena cava (Desai et al, 2003a; Hsu et al, 2003; Martin et al, 2008; Guzzo et al, 2009; Hoang et al, 2010; Bansal et al, 2014). After complete laparoscopic mobilization of the kidney and ligation of the renal artery, a laparoscopic DeBakey, vessel loop, or hand-assistance procedure is typically used to “milk” the tumor thrombus back toward the kidney. This allows either the endovascular stapler to be deployed on the renal vein excluding the thrombus, or a laparoscopic Satinsky clamp to be placed to isolate a cuff of the vena cava such that the cuff may be excised to allow intact specimen extraction without tumor at the margin. In cases in which a cuff of the inferior vena cava is excised en bloc with the renal vein stump, this cavotomy may then be oversewn using Prolene suture mirroring the open procedure. The use of intraoperative ultrasonography has also been described to aid in assessing the location of the extent of the tumor thrombus (Hsu et al, 2003). For higher thrombi, the cava is isolated as in open surgery and bulldog clamps or alternative methods are used to gain control during the cavotomy, extraction, and repair. To date, the approach has been largely limited to low- to mid-level caval thrombi, with reported results comparable with the open surgical experience.

Cytoreductive Nephrectomy

Patients with advanced RCC may require cytoreductive nephrectomy before the initiation of systemic secondary therapies. A comparative study of open versus laparoscopic cytoreductive nephrectomy in a selected group of patients with metastatic disease—but without local invasion, venous involvement, or bulky adenopathy—demonstrated similar 1-year survival between the two groups (61% vs. 65%) (Rabets et al, 2004). In addition, the laparoscopic group had less blood loss, shorter hospital stay, and shorter interval between surgery and the initiation of systemic therapy (36 vs. 61 days). Other studies have shown similar results (Eisenberg et al, 2006; Matin et al, 2006b; Blick et al, 2010), although the shorter interval to systemic therapy has not been consistently observed.

Surgical Salvage after Failed Ablative Therapies

Nephrectomy after ablation is technically challenging owing to resulting loss of tissue planes surrounding the lesion. A multi-institutional review of treatment outcomes for primary radiofrequency ablation (RFA) or cryotherapy revealed residual or recurrent disease in a median of 8.7% of patients (Matin et al, 2006a). Although a subgroup of these patients will undergo successful salvage ablative therapy, some may not be candidates for repeat ablation because of disease progression, tumor size, or failed repeat ablation. A report of 10 patients undergoing salvage surgery in this patient population showed that laparoscopic nephrectomy was only possible in 4 patients, and the remainder required either open partial or radical nephrectomy (Nguyen et al, 2008). Other studies have demonstrated laparoscopic salvage nephrectomy as feasible, but partial nephrectomy after ablation is often exceedingly challenging based on the literature (Kowalczyk et al, 2009; Breda et al, 2010). Extensive perinephric fibrosis was cited as the main factor complicating surgery in the postablation setting.

PARTIAL NEPHRECTOMY

The increased use of cross-sectional imaging has caused a downward stage migration and changed the paradigm for the typical presentation of kidney cancer. It has become the exception for kidney tumors to manifest with symptoms as had been the classic teaching for decades. **Kidney tumors are now most commonly diagnosed incidentally, at a small size and early stage, in asymptomatic healthy patients** (Jayson et al, 1998; Luciani et al, 2000; Leslie et al, 2003; Chow and Devesa, 2008). Although the majority of imaging-detected incidentally found renal lesions are benign simple cysts, one must be vigilant to not miss an early renal cancer. The prevalence of unsuspected, early-stage chronic kidney disease (CKD) underscores an important point: renal functional preservation and nephron-sparing strategies are important considerations when making management decisions in patients with a small renal mass (SRM) (Huang et al, 2006; Jeon et al, 2009). The desire to provide a minimally invasive alternative to treat patients with SRMs led to the application of laparoscopic techniques to nephron-sparing surgery (NSS).

Indications

The first transperitoneal LPN was reported in 1993 by Winfield and colleagues, with the retroperitoneal approach introduced 1 year later (Gill et al, 1994). Initially, LPN was applied to treat small clinical T1a exophytic renal masses (Fig. 61-34). With increasing experience, the indications of LPN have been expanded to include almost all patients with challenging tumor anatomy in complex clinical settings. The RENAL nephrometry score has in recent years become a popular method of characterizing the complexity of renal masses (Kutikov and Uzzo, 2009). Taking into account the (R) tumor diameter, (E) exophytic or endophytic character of the lesion, (N) nearness to the collecting system, (A) anterior or posterior location, and (L) location relative to the polar line, this system has



Figure 61-34. Computed tomography scan with intravenous contrast demonstrating a partially exophytic mid-pole clinical T1a lesion in the right kidney.

facilitated discussion of tumor complexity and series comparisons within the partial nephrectomy literature. Data have been conflicting regarding correlation of RENAL nephrometry score as a predictor of complications, but most evidence does suggest that increasing nephrometry score is associated with complication risk in minimally invasive approaches for management of the SRM (Mayer et al, 2012; Okhunov et al, 2012; Ellison et al, 2013; Schmit et al, 2013; Tanagho et al, 2013).

Clinical Stage T1b and Greater Tumors

LPN was initially restricted to patients with tumors 4 cm or smaller and clinically staged as T1a. Technical advances in laparoscopic techniques, along with demonstration of equivalent results to open surgery for T1a tumors, provided the groundwork for approaching larger lesions (Leibovich et al, 2004; Dash et al, 2006; Mitchell et al, 2006; Rais-Bahrami et al, 2008; Gupta et al, 2013). Simmons and colleagues (2009a) reported perioperative outcomes of LPN in 58 patients for T1b tumors. Mean tumor size was 6 cm, and 55% of tumors were centrally located. Although patients with pT1b tumors more often underwent pelvicalyceal repair ($P = .004$) and heminephrectomy ($P < .001$), they had similar operative time, blood loss, and hospital stay but longer warm ischemia time than patients with tumors smaller than 4 cm. Tumor size greater than 4 cm did not increase risk for positive cancer margins, intraoperative complications, or postoperative urologic complications. Of note, in patients with tumors smaller than 2 cm, 2 to 4 cm, and 4 to 7 cm (stage \geq III), CKD existed preoperatively in 31%, 35%, and 44% of patients, respectively, and postoperatively in 52%, 53%, and 63%, respectively ($P =$ nonsignificant). Also, other reports of LPN for cT1b tumors have corroborated the renal functional benefits compared with radical nephrectomy, even in the setting of a normal contralateral kidney (Simmons et al, 2009b; Deklaj et al, 2010). This underscores the importance of attempting a nephron-sparing approach in all patients when feasible. Given adequate laparoscopic experience and appropriate patient selection, the perioperative outcomes of LPN for clinical T1b tumors appear comparable to those achieved for clinical T1a tumors.

Recently, Lane and colleagues (2013) evaluated long-term oncologic outcomes of LPN compared with open partial nephrectomy (OPN) for clinical stage T1 tumors. Combining cases of cT1a and cT1b tumors, their study investigating follow-up on 1541 patients demonstrated that the operative approach (laparoscopic vs. open) was not an independent predictor of metastasis ($P = .42$) or all-cause mortality ($P = .13$). Also, the median decrease in glomerular filtration rate was not significantly different comparing those who underwent LPN versus OPN ($P = .50$).

Laparoscopic Heminephrectomy

Finelli and colleagues (2005) compared outcomes of laparoscopic heminephrectomy (excising greater than 30% of renal parenchyma) in 41 patients, with a contemporary group of 41 consecutive patients who underwent LPN with less than 30% resection. Except for a longer ischemia time (39 vs. 33 minutes) in the heminephrectomy cohort, there were no differences between the two groups regarding blood loss, operating room time, analgesic requirement, hospital stay, postoperative serum creatinine, and overall complications. All surgical margins were negative. A similar report evaluating 24 patients who underwent laparoscopic heminephrectomy with other LPN done at the same institution over the same time period showed comparable results (Sobey et al, 2012). The indications for the cases of laparoscopic heminephrectomy in this study were larger tumors with higher nephrometry scores. Operative times and warm ischemia times were significantly higher in the cohort of patients undergoing heminephrectomy, but estimated blood loss, length of hospitalization, complications, and change in renal function were equivalent.

Specific technical considerations inherent to laparoscopic heminephrectomy include routinely performing deeper renal parenchymal resections, transection of sizable intraparenchymal blood vessels, and intentional entry into the pelvicalyceal system (PCS). The primary goals of laparoscopic heminephrectomy and LPN are the same: achieve negative surgical margins, perform clipping or suture repair to secure renal vessels, and, where necessary, repair the collecting system while minimizing ischemia time.

Central and Hilar Tumors

Central tumors are defined as those abutting or invading the central renal sinus fat and/or the collecting system on preoperative imaging. These tumors deeply infiltrate the renal parenchyma, and their excision requires intentional entry into and potentially suture-repair of the PCS along with complex parenchymal reconstruction, all within the time constraints of renal ischemia. The technical complexity of such cases depends on the location of the individual tumor and the type of suturing angles available for laparoscopic instruments in the dominant and nondominant hands. Frank and colleagues (2006) compared experience with LPN for 154 central tumors with LPN for 209 peripheral tumors. Although blood loss was similar, central tumors were associated with somewhat longer operative time, ischemia time, and hospital stay, and more early postoperative complications. There was only one positive margin for cancer in each group. In series of completely intraparenchymal tumors, Chung and colleagues (2011) compared these cases with three other tumor groups—completely exophytic tumors, tumors infiltrating up to sinus fat, and tumors infiltrating but not up to sinus fat—and found that there was no statistically significant difference among the groups in rate of complications, positive margins, operative blood loss, or tumor excision or warm ischemia times.

Hilar tumors, defined as tumors located in the renal hilum in direct contact with the renal artery and/or vein on cross-sectional imaging, were initially considered to be a contraindication to LPN, but with increased experience these challenging tumors have been successfully managed with LPN by several groups. In 2005, an initial experience with LPN outcomes for hilar tumors in 25 patients was reported (Gill et al, 2005). Mean tumor size was 3.7 cm (range 1 to 10.3). LPN was successful in all cases, without any open conversions or operative reinterventions. Postoperative hemorrhage occurred in 3 early patients. Preoperative 3D video reconstruction of triphasic spiral CT was important in detailing the number, inter-relationship, anatomic course, and position of the renal vessels in relation to the tumor. George and colleagues (2014) reported their experience with 43 LPNs for hilar tumors compared with a contemporary series of 445 LPNs for nonhilar tumors, finding no significant difference in any perioperative parameter investigated including warm ischemia time and postoperative renal functional outcomes at 6 months' follow-up.

Tumor in a Solitary Kidney

Partial nephrectomy for tumor in a solitary kidney is challenging, whether performed via the open or the laparoscopic approach. The margin for error is small because a complication could result in temporary dialysis, or worse, render the patient anephric. A multi-institutional analysis by [Hillyer and colleagues \(2013\)](#) reported on 26 patients undergoing robotic-assisted laparoscopic partial nephrectomy (RaLPN) for a tumor in a solitary kidney; the majority (62%) rendered solitary from prior surgery for renal malignancy. No cases were converted to open surgery, median warm ischemia time was 17 minutes, and at a median 6-month follow-up the estimated glomerular filtration rate (eGFR) was not significantly affected. Prior report of 22 patients undergoing conventional LPN in a solitary kidney at a single institution reported mean warm ischemia time of 29 minutes, two procedures (9%) electively converted to open surgery, and one kidney lost because of delayed postoperative hemorrhage ([Gill et al, 2006](#)). Authors of both studies concluded that minimally invasive partial nephrectomy for management of tumors in a solitary kidney was feasible and offered reliable preservation of renal function.

Management of Multiple Tumors

NSS is increasingly considered the preferred treatment for patients with multiple, ipsilateral tumors owing to the potential for contralateral involvement or recurrence. LPN has been applied in this clinical setting as well. [Abreu and colleagues \(2013\)](#) published their experience of 33 patients who underwent LPN, with or without robotic assistance, for multiple ipsilateral renal tumors matched with 33 patients treated for a single renal tumor. Perioperative results demonstrated significantly longer operative times and length of hospitalization, with no significant difference in warm ischemia times, blood loss, rate of transfusion, or conversion to radical nephrectomy.

Other Indications

LPN has also been performed in the following unique clinical settings: adrenal involvement from an upper pole tumor requiring excision with concomitant adrenalectomy ([Ramani et al, 2003](#)); repair of concomitant renal artery disease ([Steinberg et al, 2003](#)); tumors in congenitally anomalous kidney, such as horseshoe kidney ([Tsivian et al, 2007](#)); in obese patients ([Romero et al, 2008](#)); after prior ipsilateral renal surgery ([Turna et al, 2008](#); [Boris et al, 2013](#)); and in the setting of hereditary kidney cancer syndromes ([Rogers et al, 2008](#)). Although each of these unique settings poses different challenges, the use of LPN in any clinical setting should realistically be able to achieve the central goals of safely removing the malignant tumor while sparing normal renal parenchyma, minimizing ischemia and operative times, and minimizing postoperative complications.

Procedure

Technical Issues

The principal technical challenge during LPN stems from the complexity of laparoscopic tumor excision and sutured renal reconstruction in a time-sensitive manner. The primary objectives are to complete tumor excision with negative margins, achieve hemostasis, and minimize warm ischemia time. Successful LPN for complex tumors requires an in-depth understanding of 3D renal anatomy, real-time intraoperative appreciation of visual cues, and precise, efficient intracorporeal suturing.

Transperitoneal Laparoscopic Partial Nephrectomy

The transperitoneal approach offers many features that are crucial for performance of advanced LPN: larger working space, more familiar landmarks, greater versatility of instrument angles, and technical ease of suturing. The initial portion of the procedure is

performed as previously described for transperitoneal access to the kidney.

Retroperitoneal Laparoscopic Partial Nephrectomy

Although most LPN surgeons prefer the transperitoneal approach for almost all renal tumors, some use the retroperitoneal approach, which has advantages for select posteriorly located upper pole apical tumors. After entry into the retroperitoneum and establishment of a working space as previously described, the kidney may be lifted anteriorly off the psoas muscle to allow visualization of the arterial pulsation. The dissection of the renal hilum can then proceed to facilitate bulldog clamp placement when deemed necessary. In a comparison of 32 retroperitoneal with 19 transperitoneal LPNs, choice of approach was based on tumor location ([Wright and Porter, 2005](#)). The retroperitoneal approach was associated with shorter operating time, decreased blood loss, more rapid return of bowel function, and shorter hospitalization. A comparison of 100 transperitoneal with 63 retroperitoneal LPNs demonstrated that blood loss, perioperative complications, postoperative serum creatinine, analgesic requirements, and histologic outcomes were comparable in the two groups ([Ng et al, 2005](#)). Accordingly, the choice of a transperitoneal or retroperitoneal LPN approach is dictated primarily by surgeon experience and tumor location. Other factors that may influence the decision include tumor size, number of tumors, number of arteries supplying the kidney, amount of visceral fat surrounding the kidney, and route of any prior open surgery on the quadrant of interest.

Robotic-Assisted Laparoscopic Partial Nephrectomy

RaLPN has been used by several centers as an extension of conventional LPN, reducing difficulty of fine intracorporeal tissue manipulation including tumor resection and renorrhaphy. This has broadened the cohort of urologic surgeons able to offer a minimally invasive approach to partial nephrectomy to include those surgeons without advanced laparoscopic skills ([Gettman et al, 2004](#); [Caruso et al, 2006](#); [Kaul et al, 2007](#); [Rogers et al, 2008](#)). Many surgeons with advanced laparoscopic skills also use robotic assistance to facilitate skeletonization of renal arterial branches when selective clamping is to be used. Potential differences in cost aside, the addition of robotic assistance to LPN is considered to be comparable to conventional LPN. Randomized trials comparing the two modalities are lacking.

The beginning of the case is often conducted with conventional laparoscopy to varying degrees, sometimes to the point of tumor resection when the robotic platform is docked. Others use the robotic assistance throughout the case, starting immediately after trocar insertion.

The responsibilities of the bedside assistant often include aiding in clamping the renal hilum, providing suction and retraction to maintain a clean operative field, delivery and cutting of sutures, and clip placement as needed. Newer robotic instrumentation has allowed the surgeon at the console to perform many of these maneuvers, but additional exchanges of robotic instruments are necessary. The surgeon at the console also performs tumor excision, hemostatic suturing, and pelvicalyceal and parenchymal suture reconstruction. On completion of renal reconstruction, the hilum is unclamped, and additional parenchymal sutures are placed, as needed, to ensure hemostasis. The robot is undocked and laparoscopic exit completed.

Tumor Localization and Excision

Regardless of the approach (transperitoneal LPN, retroperitoneal LPN, or RaLPN) the techniques of tumor localization and excision are essentially identical. Once the initial dissection is complete, including isolation of the hilar vessels, intraoperative ultrasonography is used to confirm location, width, and depth of the tumor ([Fig. 61-35](#)). Ultrasonography may also be used to confirm absence of additional lesions in the kidney. The Gerota fascia is entered away from the lesion to expose the renal capsule. Using the monopolar

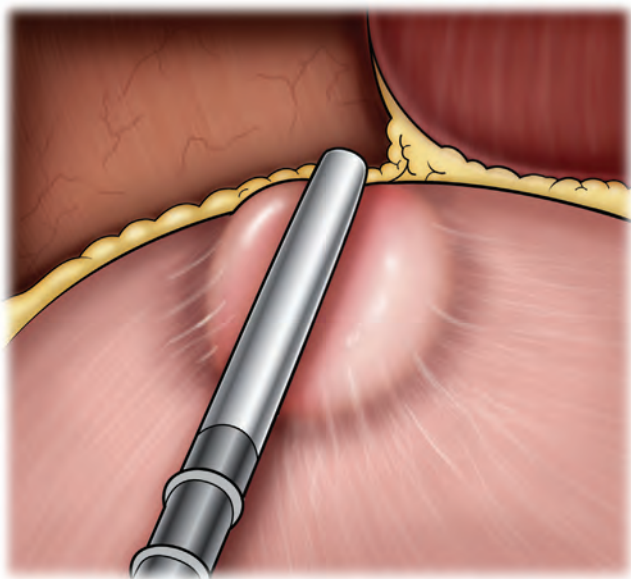


Figure 61-35. Intraoperative ultrasonography is used to confirm location, width, and depth of the tumor.

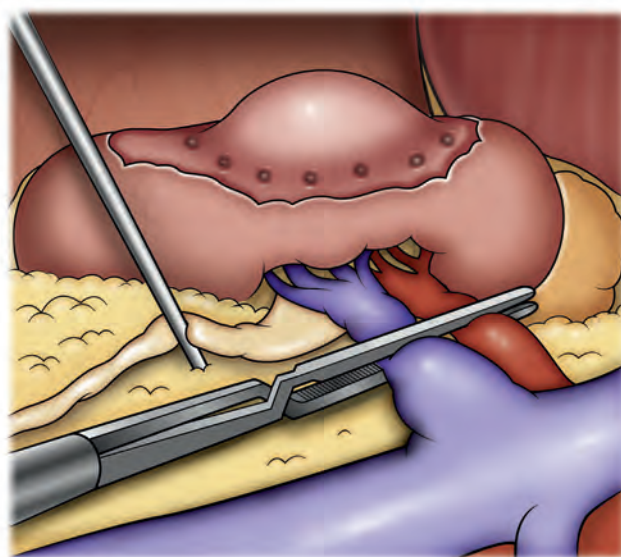


Figure 61-37. Once the margin around the tumor has been scored, the hilum is clamped en bloc using a laparoscopic Satinsky clamp, or the artery and vein are clamped separately using bulldog clamps.

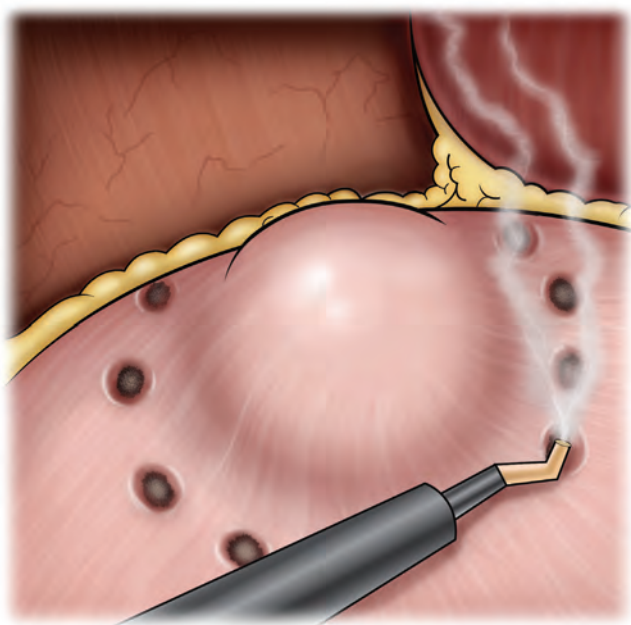


Figure 61-36. After the Gerota fascia is cleared to expose the lesion and the renal capsule, with use of monopolar scissors or hook cautery, the capsule is scored circumferentially around the tumor.

scissors, the capsule is scored circumferentially around the tumor (Fig. 61-36), and the hilum is classically then clamped using laparoscopic bulldog clamps (Fig. 61-37). The scored line may then be incised using cold shears (Fig. 61-38), and with the assistance of a suction-irrigator device to provide both countertraction and a clear operative field, the tumor excision is completed. In some patients, adherent fat not easily dissecting off the renal capsule will necessitate a subcapsular dissection to visually identify the borders of the tumor before resection.

Hemostasis

The most widely used technique to achieve hemostasis of the partial nephrectomy bed is suture renorrhaphy. Suturing techniques range from suturing the base with or without adjunctive

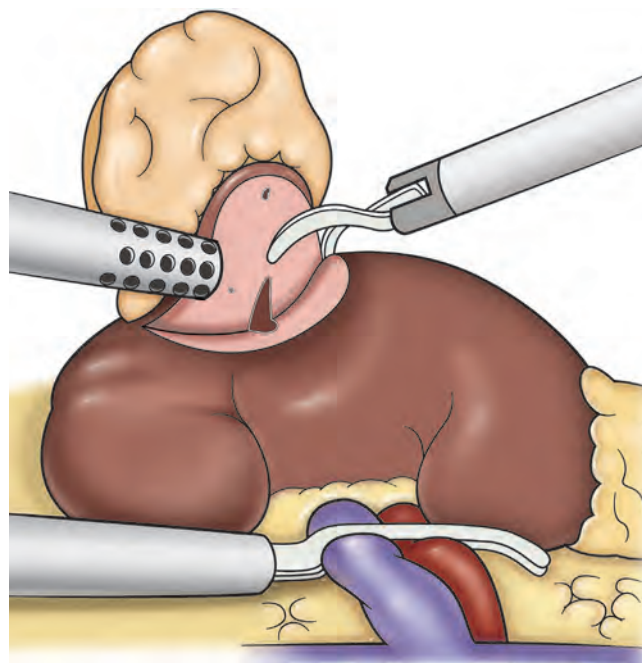


Figure 61-38. The scored margin around the tumor is incised using cold shears with the renal hilum clamped. The suction-irrigator both provides countertraction and helps to maintain a clear operative field and adequate margin of normal renal tissue.

biologic hemostatic or sealing agents, or a Surgicel bolster (Johnson and Johnson, New Brunswick, NJ), to using only a horizontal mattress suture to close the capsular and parenchymal defect (Fig. 61-39). During extrication, surgical clips may be used to ligate any visualized vessels while coming across the surface of the parenchyma. A number of tissue sealants are available and used based on surgeon preference: gelatin matrix thrombin sealant (FloSeal; Baxter, Deerfield, IL), fibrin glue (Tisseel; Baxter), fibrin sealant (Evicel; Ethicon), polyethylene glycol hydrogel (Coseal; Baxter), cyanoacrylate glue (Dermabond; Ethicon), BioGlue (CryoLife; Atlanta, GA), and homemade versions of similar matrix materials immersed in hemostatic solutions. Of note, no study published to date has clearly demonstrated the true benefit of the use of any of these agents.

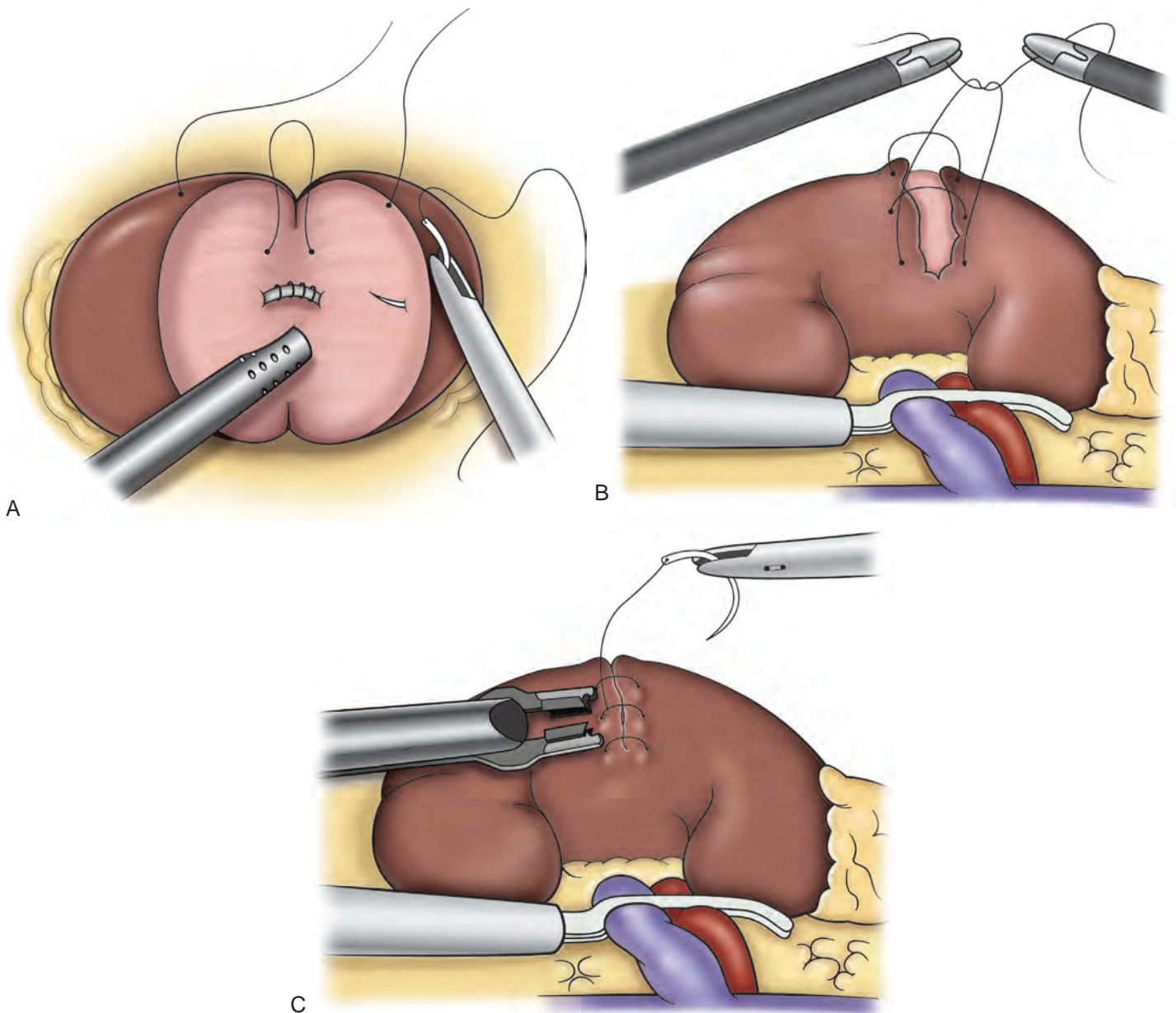


Figure 61-39. A, After use of the argon beam coagulator on the exposed parenchyma, interrupted absorbable sutures are placed for the renorrhaphy. The collecting system has already been repaired and the suction-irrigator serves to provide countertraction and maintain a clear operative field. B, The sutures may be laparoscopically tied with optional pledgets to help prevent capsular tearing during closure. C, Alternatively, sutures with preplaced Lapra-Ty clips (Ethicon, Cincinnati, OH) at the tail are used and secured with an additional Lapra-Ty clip after the needle is passed and tension on the closure is adjusted.

During LPN for selected small, superficial, exophytic tumors, various thermal (radiofrequency, microwave, ultrasonic) and novel alternative (laser, water-jet) energy sources have been used for hemostasis clinically and in the laboratory (Lotan et al, 2004; Herrell and Levin, 2005; Moinzadeh et al, 2005; Hindley et al, 2006; Liu et al, 2006; Thomas et al, 2013).

Collecting System Repair

Central tumors abutting the renal sinus fat and collecting system may require deliberate entry into the PCS to ensure negative surgical margins during tumor excision. For this reason, PCS entry is a common occurrence in contemporary LPN practice. Prospective comparison of perioperative outcomes in 27 LPNs with

pelvicalyceal entry with 37 LPNs with no pelvicalyceal entry (Desai et al, 2003b) revealed similar operating room time, tumor excision time, and blood loss. However, PCS suture repair was associated with longer warm ischemia time and hospital stay. None of the patients undergoing PCS suture repair developed a urinary leak. The results of this early study showed that intentional entry into the PCS for central tumors could be safely and effectively repaired (Fig. 61-40). Zorn and colleagues (2007) also reported that cases with PCS repair compared with those not requiring PCS repair demonstrated longer operative times and warm ischemia times, without significant differences in intraoperative or postoperative complications including urine leak and need for transfusion. Suture repair of the PCS with running 3-0 or 4-0 polyglactin can be used. Alternatively, one may close the renal parenchyma and capsule over the

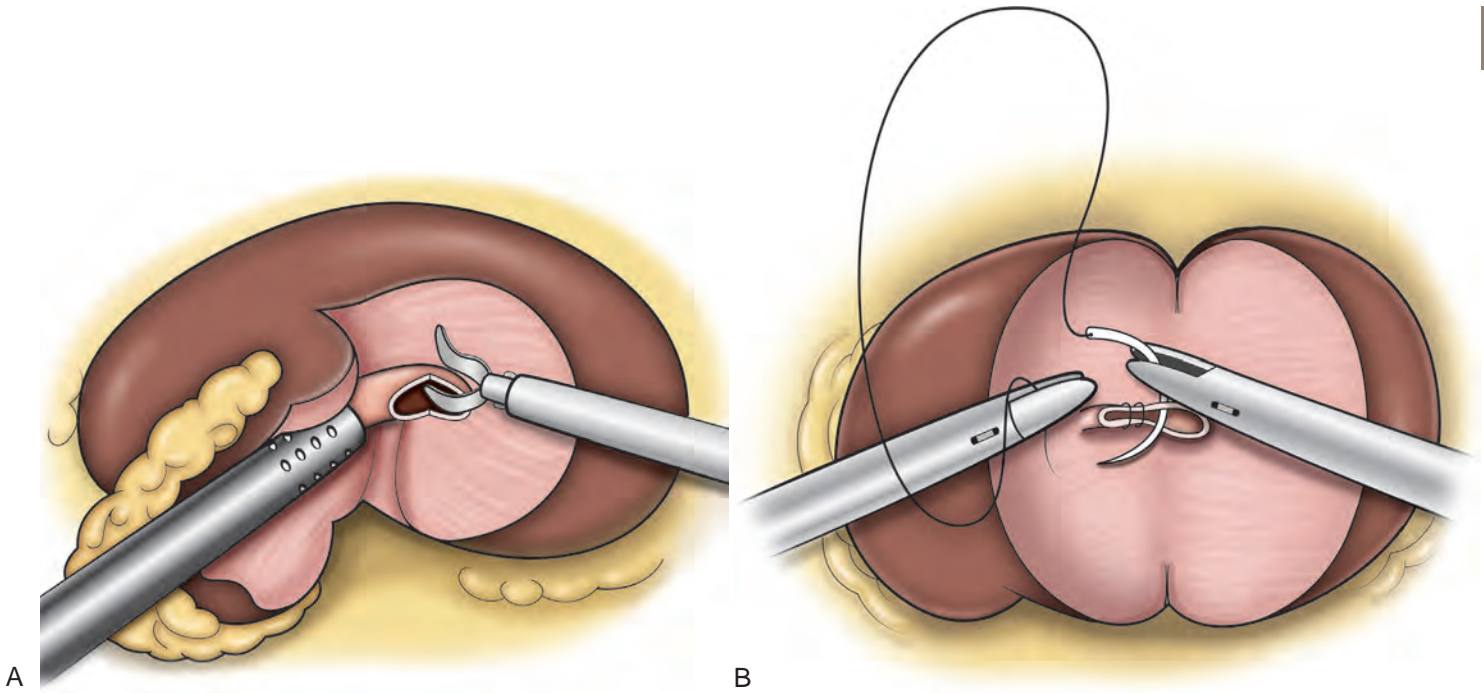


Figure 61-40. A, When deep resection is required, the collecting system will often be transected. With occlusion of the renal vessels, these defects can easily be identified and closed using absorbable sutures. The cut edge of the collecting system is identified with the tip of the needle and elevated. B, An interrupted figure-of-eight suture or running suture is used to completely close the collecting system. The integrity of the repair can be determined by intravenous indigo carmine administration or retrograde instillation, if a ureteral catheter was placed at the beginning of the case. Care must be taken not to destroy the suture, if argon beam coagulation of the parenchyma surface will be performed.

defect without primary PCS repair. In either case, a drain should be placed to reduce the risk of perinephric urinoma. No randomized studies of closure versus nonclosure of the collecting system exist to show the necessity of repairing the PCS.

Renal Hypothermia

Multiple techniques have been described for laparoscopic renal hypothermia: surface cooling with ice slush, instillation of cold saline through a retrograde ureteral catheter, and intra-arterial perfusion of cold isotonic solution (Marley et al, 2011; Abe et al, 2012; Saitz et al, 2013). Although all of these techniques are clinically feasible and reasonably effective, they are rarely used in routine practice. This is not only because of their complexity, but also because the majority of tumors subjected to LPN do not require an inordinately long period of warm ischemia for resection and reconstruction. Greater consideration of hypothermic techniques may be given in settings of a solitary kidney or significant renal insufficiency, depending on surgeon preference, tumor complexity, and expected ischemia time (if any).

Warm Ischemia and Hilar Control

The limit of safe renal warm ischemia time has historically been considered to be 30 minutes. Although supported by canine and anecdotal clinical data, no scientifically rigorous clinical study has defined an ischemic dose-response curve to date. Indeed, data exist suggesting that up to 90 minutes may be reasonable (Orvieto et al, 2005). The difficulty in understanding the effects of surgical renal ischemia is related to insufficient data and many confounding variables affecting global renal function. While this issue is being debated, efforts should be made to minimize warm ischemia time to the greatest extent possible.

From a technical standpoint, hilar control can be achieved by using bulldog clamps individually on the renal vessels, the renal

artery alone without clamping the vein, or a laparoscopic Satinsky clamp for en bloc hilar clamping. Several techniques have also been investigated in an effort to reduce renal ischemia and further minimize any loss of renal function that might occur as a result of NSS.

Traditionally during LPN, the entire tumor excision and renal repair are performed in the ischemic kidney, with the hilar vessels clamped. Early unclamping is a modification of the traditional technique with the primary goal of decreasing warm ischemia time (Nguyen and Gill, 2008). In this technique, the renal hilum is clamped only up to placement of the initial, central, running suture in the resection bed. Results suggest that this technique does indeed reduce warm ischemia time with comparable estimated blood loss and transfusion rates relative to conventional hilar clamping (Peyronnet et al, 2014).

Off-Clamp Laparoscopic Partial Nephrectomy Technique. Select tumors can be excised during LPN without hilar clamping. Typically, tumors best suited for this technique are more superficial, exophytic, noninfiltrating lesions. In 2003, Guillonnet and colleagues compared LPN with ($n = 12$) and without ($n = 16$) hilar clamping using ultrasonic shears and bipolar cautery, concluding that hilar clamping provided decreased blood loss, shorter operating time, and superior surgical performance. A recent study compared 150 off-clamp LPNs with 289 traditional clamped LPNs (George et al, 2013). Significant differences ($P < .05$) in the off-clamp group relative to the on-clamp group included smaller, more relatively exophytic tumors. The group of off-clamp cases had significantly larger estimated blood loss (338.4 mL vs. 276.8 mL, $P = .023$) and less decrease in eGFR at 6-month follow-up (-3.9 vs. -11.7 , $P = .035$) with no difference in operative time, length of hospitalization, positive margins, or transfusions. As experience improves, an increasing number of procedures may be performed off-clamp to optimize renal perfusion and potentially renal functional outcomes. Several groups have demonstrated the feasibility and safety of various iterations of performing off-clamp LPN, including its use for treatment of more challenging lesions (Novak

et al, 2012; Kaczmarek et al, 2013; Salami et al, 2014). Tumors that are larger, deeper, central, or hilar may require more substantial dissection and reconstruction, but may also be safely excised off-clamp with adequate experience. Several of these experiences have been reviewed, with overall support of the safety of the approach with potential renal functional benefits (Simone et al, 2013; Liu et al, 2014b).

Selective Renal Arterial Clamping. Extensive hilar dissection beyond that traditionally performed for main renal artery clamping can provide the surgeon with the option of selectively clamping a single or multiple arterial branches supplying the area of the tumor without causing ischemia to the renal remnant. This technique has the theoretic advantage of providing a relatively bloodless field for tumor resection, without compromising blood flow to the entire kidney. Studies have demonstrated longer operative times and higher perioperative transfusion rates relative to main artery clamping (Desai et al, 2014). Near-infrared fluorescence imaging has been used in conjunction with selective arterial clamping to confirm ischemia to the desired area of the kidney (Borofsky et al, 2013).

Renal Artery-Only versus Artery-Plus-Vein Clamping. It is theorized that artery-only clamping during partial nephrectomy would allow retrograde venous blood flow with potentially partial oxygenation to the renal parenchyma. In a solitary kidney pig model, Orvieto and associates (2007) found that artery-only clamping resulted in lower serum creatinine rises during postoperative days 1 to 3 than in animals that underwent complete hilar occlusion. It is interesting to note that this effect was not observed in animals that underwent laparoscopic surgery. It was concluded that artery-only clamping provided immediate postoperative benefit, and that this benefit was likely offset by pneumoperitoneum-induced venous compression during laparoscopy. In contrast, the same group found a benefit to artery-only clamping in a case-control study of patients undergoing LPN with artery-only clamping ($n = 25$) versus simultaneous clamping of the artery and vein ($n = 53$) (Gong et al, 2008). A significant decrease in serum creatinine and creatinine clearance was observed in patients undergoing simultaneous clamping of the artery and vein compared with preoperative levels. This effect was not observed in those undergoing artery-only clamping. In addition, there were no statistically significant differences observed in either blood loss or positive margin rate between the groups.

Parenchymal Compression and Clamping versus Vascular Clamping. Similar in concept to selective arterial clamping, manual compression or clamping of the kidney during tumor excision and renorrhaphy can theoretically allow continued perfusion of the renal remnant while providing ischemia to the area of parenchyma containing the tumor and a bloodless operative field. The time-sensitivity of tumor excision and renorrhaphy is also reduced. Manual compression can be effective for small exophytic tumors, although the renal vasculature should always be accessible to allow emergent clamping in the case of hemorrhage. Issues to consider include the possibility of tissue trauma caused by excessive compression, and the limitation of this approach to peripheral tumors during open and hand-assisted laparoscopic procedures only. Manual compression techniques would not be feasible in partial nephrectomy of central, hilar, or large tumors, or for pure laparoscopic surgery without specialized instrumentation. Several authors have published their initial experiences in a small number of patients using techniques of parenchymal clamping in selected patients with peripheral renal cortical tumors (Verhoest et al, 2007; Simon et al, 2009). All patients in these studies had negative surgical margins, and no changes in renal function were reported. The primary limitation of the technique is that only selected patients with peripherally located tumors are candidates.

Laparoscopic Partial Nephrectomy: Contemporary Outcomes

It is important to consider comparisons of LPN patients with patients who have undergone radical nephrectomy or OPN to

effectively gauge outcomes. Oncologic outcomes, perioperative complications, renal functional outcomes, and overall survival are all critical metrics in determining the safety and efficacy of the techniques.

Series comparing radical versus partial nephrectomy for T1 solitary lesions suggest that a nephron-sparing approach is as effective as radical nephrectomy for cancer treatment over the long term (Lau et al, 2000; Lee et al, 2000; Thompson et al, 2009). Retrospective studies have also suggested that patients undergoing partial nephrectomy may experience improved overall survival relative to patients undergoing radical nephrectomy (Thompson et al, 2008), possibly secondary to reduced rates of renal insufficiency and cardiovascular morbidity and mortality (Huang et al, 2006). More recently, the only randomized trial comparing radical versus partial nephrectomy for the treatment of renal tumors smaller than 5 cm failed to demonstrate an overall survival benefit for patients undergoing partial nephrectomy (Van Poppel et al, 2011). The group undergoing partial nephrectomy was seen to have higher risk of cardiovascular death, although the explanation for this finding is unclear and the authors acknowledge that the study was not designed to evaluate differences in cardiovascular outcomes. Although this result certainly should prompt additional investigation, the authors acknowledge that their findings contradict those of prior retrospective analyses and they continue to encourage a minimally invasive nephron-sparing approach when possible.

An 1800-patient retrospective multi-institutional study compared a mature series of 1029 OPN cases with the initial LPN cases for solitary T1 tumors 7 cm or smaller (Gill et al, 2007). Tumors in the OPN group were larger (3.3 vs. 2.6 cm), and more often located centrally (53% vs. 34%) or in a solitary kidney ($P < .001$ for all comparisons). LPN had less blood loss and shorter operative time, hospital stay, and convalescence ($P < .001$ for all comparisons). Overall postoperative complications (25% vs. 19%) and conversion to radical nephrectomy (1% vs. 0%) were somewhat greater in the LPN group. It is important to note that LPN and OPN were similar with regard to intraoperative complications (1.8% vs. 1%), positive surgical margins for cancer (1.6% vs. 1%), 3-year oncologic outcomes, and 3-year renal functional outcomes. However, LPN had a 10-minute longer ischemia time (30 vs. 20 minutes), and somewhat higher postoperative hemorrhage (4.2% vs. 2%) and reintervention rate.

With increasing LPN experience and more common use of techniques to reduce warm ischemia time (early unclamping, off-clamp partial nephrectomy, selective arterial clamping, and parenchymal clamping), contemporary LPN outcomes have improved significantly. Specifically, the two remaining concerns for higher postoperative hemorrhage and longer ischemia time with LPN have now been addressed, leading to significantly decreased ischemia time and reduced occurrence of postoperative hemorrhage. **Surgical experience and improvements in instrumentation have allowed continued progress in reducing warm ischemia time, perioperative complications, and renal functional outcomes even with increasing complexity of tumors being addressed with LPN** (Gill et al, 2011; George et al, 2013; Salami et al, 2014). **Outcomes of LPN parallel those of OPN while reducing perioperative morbidity.**

Positive Surgical Margins

The clinical significance of a pathologic positive surgical margin after partial nephrectomy, whether laparoscopic or open, has prompted several studies evaluating outcomes specifically in these patients. In a group of 1344 patients undergoing OPN, positive surgical margins were noted in 77 (5.5%) (Yossefowitch et al, 2008). The 10-year probability of freedom from local recurrence and progression to metastatic disease was 93% for both. There were no significant differences noted between those with positive and negative margins. Several laparoscopic surgeons have reported similar results with positive margin rates ranging from 1% to 1.8% with no increased risk of local recurrence or metastasis (Permpongkosol et al, 2006a; Lane et al, 2013). A recent multi-institutional report found contradictory results in the 2.2% of 943 patients who underwent RaLPN with positive margins on final pathology; the

hazard ratio (HR) of recurrence and metastasis was 18.4 relative to those with negative margins (Khalifeh et al, 2013). Although these data demonstrate that many patients with pathologically positive margins may be observed, negative surgical margins should always be the goal in any oncologic procedure.

Long-Term Outcomes

Long-term data on LPN are now available (Table 61-4), and appear similar to those for OPN. Five-year cancer-specific survival after LPN has been reported up to 100% (Lane et al, 2007). Most recently, a comparative study of 10-year outcomes compared 625 patients undergoing LPN with 916 patients undergoing OPN for single clinical stage T1 (≤ 7 cm) tumors from 1999 to 2007 (Lane et al, 2013). There were statistically significant differences in the LPN and OPN cohorts noted, including preoperative renal function (eGFR 82 vs. 74 mL/min/1.73 m²), smaller radiographic tumor size (2.6 vs. 3.5 cm), and absolute indication for partial nephrectomy. Pathologic features were also noted to be different between the LPN and OPN groups, including smaller tumor size (2.5 vs. 3 cm), larger percentage of benign lesions (26% vs. 19%), and fewer pT1b lesions (14% vs. 33%). Patients with pathologically confirmed RCC had comparable 5-year recurrence-free survival in both the pT1a (97.8% vs. 97.1%) and pT1b (93.1% vs. 92.7%) subgroups. A total of 45 patients undergoing LPN and 254 patients undergoing OPN had 10-year follow-up with 78% and 72% overall survival, respectively. The recurrence rate in the OPN cohort was higher relative to LPN; however, this is likely a reflection of the inherent differences between the cohorts noted earlier. On multivariable analysis, predictors of metastasis included larger tumor size, absolute indication, and comorbidity, but not LPN (HR 0.72; confidence interval [CI] 0.36 to 1.34; $P = .32$). The authors concluded that LPN and OPN provide similarly excellent long-term overall survival, with the vast majority of patients experiencing metastasis-free survival.

In experienced hands, LPN is equivalent to OPN, with shorter ischemia times, equivalent complication rates, and comparable renal functional outcomes. As a result, large-volume centers routinely offer LPN for the majority of renal tumors. These include technically challenging SRMs, including tumors that are hilar, central, completely intrarenal, larger (4 to 7 cm, pT1b), or located in a solitary kidney (Leslie et al, 2013).

LAPAROSCOPIC ABLATIVE TECHNIQUES

As the incidence of the SRM has increased with the prevalence of cross-sectional imaging, a stage migration has occurred such that a rising number of patients have incidentally been found to have low-stage disease. Cancer-specific survival rates in excess of 95% (Frank et al, 2005; Lane et al, 2007) with cryoablation and RFA have given credence to use of ablation as an alternative treatment. High-intensity focused ultrasonography, microwave therapy, and high-intensity focused radiation have also been investigated. The primary goals of these ablative techniques are complete tumor destruction with minimization of morbidity. The potential advantages include less blood loss, decreased need for dissection, and fewer complications. Indications are similar for all the ablative technologies and include lesions in patients with significant comorbidities, solitary kidneys, and hereditary RCC. The percutaneous approach is preferred for treatment of SRMs owing to its lower morbidity, but in some instances it may not be possible because of tumor location or proximity to adjacent organs. For these reasons, laparoscopy is required for direct visualization and manipulation to make treatment delivery feasible and safe. Because cryoablation and RFA are the most prevalent in clinical applications, these ablative techniques are discussed here in further detail.

Cryoablation

Laparoscopic cryoablation may be delivered using either a transperitoneal or retroperitoneal approach, with the decision resting

primarily on tumor location. The kidney is mobilized and the Gerota fascia is opened in a manner similar to that used for LPN. The fat overlying the tumor may be excised and placed in a specimen bag for extraction and pathologic analysis. Biopsy samples of the tumor itself may also be taken with a 14- or 18-gauge biopsy needle for histopathologic diagnosis. Placement of the cryoablation probes into the tumor can be performed percutaneously, leaving the laparoscopic ports free for instrumentation and tissue manipulation. Direct visualization of probe placement and depth of placement are confirmed with laparoscope and intraoperative ultrasonography, respectively. Number and spacing of probes are dictated by probe-specific ablative shape and diameter, and they should be positioned to ensure cryolesion overlap, typically parallel to one another in a triangular or quadrangular configuration. The tip of the probes should be advanced just beyond the deepest margin of the tumor.

The progress of the iceball formation may be monitored in real time using intraoperative ultrasonography, and the iceball should extend approximately 1 cm beyond the edge of the tumor. Keeping in mind that the progress of the iceball cannot be abruptly stopped, caution should be exercised to avoid contact of the iceball with the renal collecting system, ureter, renal vasculature, or adjacent organs. After the freeze-thaw cycles are complete, the probes are removed with a gentle twisting motion. If any bleeding occurs, it can usually be controlled by applying pressure or, if necessary, hemostatic agents such as fibrin glue or Floseal.

Radiofrequency Ablation

Similar to cryoablation, RFA may be administered laparoscopically using either a transperitoneal or a retroperitoneal approach. After ultrasound confirmation of tumor location and size and biopsy of the overlying fat and tumor tissue, as with cryoablation, the RFA probe is introduced into the tumor, and the tines are deployed to a diameter that ensures ablation of the tumor and a 1-cm margin of normal renal tissue. The size of the thermal lesion is determined by temperature- or impedance-based monitoring. The probe uses an alternating current of high-frequency radio waves, causing ion vibration. The resistance in the tissue causes generation of sufficient heat to result in thermal tissue damage—tumor coagulation, protein denaturation, and cell membrane disintegration all occur (Goldberg et al, 2000; Aron and Gill, 2007). Immediate histopathology after RFA shows hypereosinophilia and pyknosis, which is subsequently replaced by coagulative necrosis within days to weeks (Crowley et al, 2001). For achievement of these effects, optimal temperatures for ablation range from 60° C to 100° C and avoid tissue vaporization, which may occur at temperatures over 105° C (Goldberg et al, 2000; Crowley et al, 2001).

Unfortunately, unlike with cryoablation, real-time ultrasonography cannot be used to monitor the thermal lesion induced by RFA. RFA itself may interfere with ultrasound imaging, and the affected tissue does not have any immediate change in echotexture. Color Doppler ultrasonography has been evaluated during RFA but does not reliably contribute to monitoring the lesion (Crowley et al, 2001). Although MRI, allowing for real-time thermometry, has been used to monitor the changing appearance of ablated lesions at the time of percutaneous treatment (Lewin et al, 2004), there is no current imaging technique that effectively monitors the progress of RFA lesions intraoperatively. Questions have been raised about temperature-based monitoring of the lesion owing to the observation that temperatures measured at the limit of the ablated area are actually 20° C to 30° C cooler than what is measured by the probe thermocouples. A potential solution involves the use of independent temperature probes to monitor temperature at the edge of the desired treatment area (Wingo et al, 2008). This allows a more definitive end point in the ablation cycle. Alternatively, an impedance-based system may be used. Instead of direct temperature measurement, this method relies on tissue impedance; sufficiently desiccated tissue becomes an insulator, and at an impedance level of 200 Ω , further progression of the thermal lesion is unlikely to occur (Lewin et al, 1998).

TABLE 61-4 Oncologic Outcomes of Laparoscopic Partial Nephrectomy

A. COMPARATIVE SERIES ANALYZING LAPAROSCOPIC AND OPEN PARTIAL NEPHRECTOMY													
AUTHOR	APPROACH	TOTAL NO. OF PATIENTS	NO. OF PATIENTS WITH RCC	MEAN AGE AT SURGERY	MEAN TUMOR SIZE	PATIENTS WITH FUHRMAN GRADE 3 OR 4		MEDIAN FOLLOW-UP	NO. OF POSITIVE MARGINS (RATE)	PROGRESSION TO METASTATIC DISEASE		MEAN TIME TO RECURRENCE OR METASTASIS	5-YEAR RECURRENCE-FREE/CANCER-SPECIFIC/OVERALL SURVIVAL
						FUHRMAN GRADE 3	OR 4			LOCAL RECURRENCE	TO METASTATIC DISEASE		
Permpongkosol et al, 2006a	Laparoscopic	85	85	58.2 yr	2.4 cm	17.6%	40.5 mo (mean)	2 (2.35%)	2 (2.35%)	1 (1.18%)	31.1 mo	1	91.4%/NR/93.8%
	Open	58	58	57 yr	2.9 cm	6.7%	49.7 mo (mean)	1 (1.72%)	1 (1.72%)	1 (1.72%)	43.3 mo	0	97.6%/NR/95.8%
Gill et al, 2007	Laparoscopic	771	554	59.4 yr	2.7 cm	28.9%	14.4 mo	12 (1.6%)	1.4%	0.9%	NR	NR	97.7%/99.3%/NR (3-year)
	Open	1028	853	61.6 yr	3.5 cm	34.0%	33.6 mo	10 (1.0%)	1.5%	2.1%	NR	NR	96.4%/99.2%/NR (3-year)
Marszalek et al, 2009	Laparoscopic	100	81	62.3 yr	2.8 cm	NR	43.2 mo (mean)	4.0%	2 (2.4%)	1 (1.2%)	NR	NR	96.2%/NR/96%
	Open	100	66	62.5 yr	2.9 cm	NR	42 mo (mean)	2.0%	1 (1.5%)	3 (4.5%)	NR	NR	94.5%/NR/85%
Lane et al, 2013	Laparoscopic	625	461	60 yr	2.5 cm	31%	NR	5 (1%)	NR	NR	NR	NR	96.9%/NR/78%*
	Open	916	742	61 yr	3.0 cm	36%	NR	2 (0.3%)	NR	NR	NR	NR	92.3%/NR/72%*

B. NONCOMPARATIVE SERIES OF LAPAROSCOPIC PARTIAL NEPHRECTOMY FOR MALIGNANCY													
AUTHOR	TOTAL NO. OF PATIENTS	NO. OF PATIENTS WITH RCC	MEAN AGE AT SURGERY	MEAN TUMOR SIZE	MEDIAN FOLLOW-UP	PATIENTS WITH FUHRMAN GRADE 3 OR 4		POSITIVE MARGIN RATE	LOCAL RECURRENCE	PROGRESSION TO METASTATIC DISEASE		MEAN TIME TO RECURRENCE OR METASTASIS	5-YEAR RECURRENCE-FREE/CANCER-SPECIFIC/OVERALL SURVIVAL
						FUHRMAN GRADE 3	OR 4			LOCAL RECURRENCE	TO METASTATIC DISEASE		
Allaf et al, 2004 Moinzadeh et al, 2006	48	48	59.7 yr	2.4 cm	37.7 mo (mean)	20.8%	1 (2.1%)	2 (4.2%)	0 (0%)	0 (0%)	32 mo	0	—
	100	68	65 yr	3.1 cm	42 mo	23.5%	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	NA	0	100%/100%/86%
Lane et al, 2007 Pyo et al, 2008	58	37	64 yr	2.9 cm	68.4 mo	NR	1 (2.7%)	1 (2.7%)	0 (0%)	0 (0%)	12 mo	0	97.3%/100%/86%
	110	70	62 yr	2.4 cm	23.4 mo (mean)	16.5%	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	12 mo	0	—
Gill et al, 2010	800	594	59.5 yr	3.1 cm	36 mo	19.5%	6 (1.0%)	NR	NR	NR	NR	NR	97.8%/99%/92.5%

*Ten-year metastasis-free/cancer-specific/overall survivals reported in this study.
NA, not available; NR, not reported; RCC, renal cell carcinoma.

Treatment Outcomes

Several studies have reported promising oncologic outcomes of laparoscopic cryoablation (Cestari et al, 2004; Weld et al, 2007; Malcolm et al, 2009). A study of 62 patients undergoing laparoscopic cryoablation, with a median tumor size of 2.52 cm and mean follow-up of 76 months, demonstrated a 6-year Kaplan-Meier estimated disease-free survival of 80%, cancer-specific survival of 100%, and overall survival of 76.2% among patients with biopsy proof of RCC (Tanagho et al, 2012).

A comparison of 145 patients undergoing laparoscopic cryoablation with 118 patients undergoing percutaneous cryoablation demonstrated equivalent oncologic control as measured by recurrence-free survival and overall survival with a mean follow-up of 71.4 and 38.6 months for the two groups, respectively (Kim et al, 2014).

A recent systematic review and meta-analysis comparing laparoscopic cryoablation with LPN and RaLPN found significantly shorter operative times, lower estimated blood loss, shorter length of stay, and a lower risk of complications; however, there was an increased risk of local and metastatic tumor progression, prompting the authors to conclude that cancer control should be balanced with the risk of perioperative complications in proper patient counseling and selection (Klatte et al, 2014).

A multi-institutional study of RFA and cryoablation outcomes in 616 patients demonstrated residual or recurrent disease in 13.4% of patients undergoing RFA and 3.9% of patients undergoing cryoablation (Matin et al, 2006a). Overall, primary therapy failed in 8.7% of patients, and after salvage ablative therapy the failure rate was reduced to 4.2%. The authors noted that the majority of failures were detected after less than 3 months, and that cross-sectional imaging should be obtained three or four times at spaced intervals for the first year after treatment. A subsequent meta-analysis of patients undergoing partial nephrectomy, ablative therapies, or observation noted a higher risk of recurrence in patients undergoing cryoablation (relative risk [RR] = 7.45) or RFA (RR = 18.23) when compared with partial nephrectomy (Kunkle et al, 2008). Treatment failure was also linked to tumor size. However, no significant difference in rates of progression to metastatic disease was observed, regardless of treatment modality (Kunkle et al, 2008). More recently, Ramirez and colleagues (2014) published on 79 patients who underwent RFA of 111 SRMs with a median tumor size of 2.2 cm over a 10-year period and had a median follow-up of 59 months. These patients had an estimated 5-year recurrence-free survival of 93.3%.

Complications

A multi-institutional experience with 148 laparoscopic cryoablation procedures on 144 patients reported a complication rate of 15.5% (Laguna et al, 2009). Significant independent predictors of negative outcomes and complications included tumor size, preexisting cardiac disease, and female gender. A second multi-institutional study investigated complications of both percutaneous and laparoscopic cryoablation and RFA of small renal tumors (Johnson et al, 2004). A total of 139 cryoablations were performed along with 133 RFAs. An overall 11% complication rate was observed, with 1.8% classified as major and 9.2% as minor. Major complications included significant hemorrhage, ileus, ureteropelvic junction obstruction necessitating nephrectomy, urinoma, conversion to open surgery, and death (aspiration pneumonia). In the laparoscopic group (90 patients), a 9% complication rate was reported, with the most common complication being pain or paresthesia at the ablation probe insertion site.

LAPAROENDOSCOPIC SINGLE-SITE SURGERY OF THE KIDNEY

Clinical Experience of Renal Laparoendoscopic Single-Site Surgery

Initially reported for nephrectomy in the urologic literature (Raman et al, 2007), LESS has now been used to perform a wide variety of

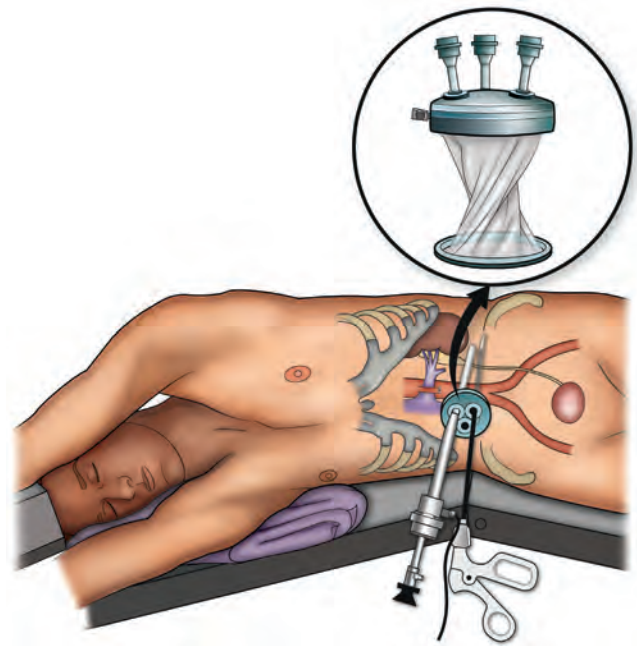


Figure 61-41. Laparoendoscopic single-site surgery donor nephrectomy using a purpose-specific device with multichannel instrument access. A 2-mm instrument is also used to aid in retraction, hilar dissection, and extraction.

urologic procedures (Kaouk et al, 2011). Adjunctive 3- to 5-mm subxiphoid ports and 2-mm needlescopic ports have been required in some cases for liver retraction and aiding in laparoscopic suturing. Reported operative times and complication rates have been comparable to those of earlier experiences of traditional laparoscopy (Fig. 61-41), although it should be noted that surgeons attempting LESS renal procedures are often highly experienced in traditional laparoscopy.

The most extensive LESS series are reports of an international multi-institutional effort reporting over 1000 patients, wherein LESS has been used to perform a variety of different urologic surgeries (Kaouk et al, 2011; Autorino et al, 2012). A wide range of procedures have been successfully performed including pyeloplasty, simple nephrectomy, donor nephrectomy, radical nephrectomy, nephroureterectomy, partial nephrectomy, renal cyst decortication, renal cryoablation, simple prostatectomy, radical prostatectomy, radical cystectomy, sacrocolpopexy, adrenalectomy, varicocelectomy, and ureterolithotomy. Most cases highlighted in this extensive experience consist of LESS renal procedures.

The follow-up study focused on the risks of conversion and complications in this urologic LESS experience (Autorino et al, 2012). The authors reported oncologic indications, pelvic surgery, robotic approach, high difficulty score, extended operative time, and intraoperative complications as independent predictors of conversion, in addition to finding that reconstructive procedures, high difficulty score, and extended operative time predicted high-grade complications, which occurred in only 2.4% of the entire cohort, comparable to conventional laparoscopic series.

After gaining substantial experience with LESS techniques, several centers have now reported the use of LESS with more time-sensitive surgeries such as donor nephrectomy and partial nephrectomy. Two randomized studies comparing LESS with conventional laparoscopic donor nephrectomies have shown similar perioperative parameters including operative time, estimated blood loss, rate of transfusion, rate of complications, rate of conversion, and change in eGFR in both studies (Kurien et al, 2011; Richstone et al, 2013). One study demonstrated an increased warm ischemia time with LESS, whereas the other study found no significant difference, and both reports had findings of decreased patient-reported pain

scores in the LESS patient cohort compared with conventional laparoscopy.

The largest series of LESS partial nephrectomies is a multi-institutional consortium of 11 institutions reporting on 190 patients with a mean tumor size of 2.6 cm and median warm ischemia time of 16.5 minutes resulting in a median estimated blood loss of 150 mL (Greco et al, 2013). Of these cases, 36.8% were successfully performed off-clamp. Oncologic outcomes for this patient cohort were published by Springer and colleagues (2014) and demonstrated disease-free survival of 98%, 97%, and 97% at 12, 24, and 36 months and overall survival of 99%, 97%, and 88% at 12, 24, and 36 months, respectively.

Other comparative studies of LESS versus conventional laparoscopic renal surgery have been reported for nephrectomy, yielding similar findings to those of the donor nephrectomy literature wherein LESS is feasible and yields similar perioperative and short-term results to cases in which the conventional laparoscopic approach is used (Raman et al, 2009; Tugcu et al, 2010). Randomized controlled trials comparing LESS with conventional laparoscopy for both nephrectomy and pyeloplasty have shown a significantly earlier return to normal activities, lower visual analog pain scale scores, and lower postoperative use of analgesics (Tugcu et al, 2010; Tugcu et al, 2013).

Robotic Laparoendoscopic Single-Site Surgery

The da Vinci-S Robotic System (Intuitive Surgical) has been used in conjunction with the LESS approach to urologic surgery by a number of groups since the initial report by Kaouk and colleagues (2009b) documenting successful robotic laparoendoscopic single-site surgery (R-LESS) radical prostatectomy, pyeloplasty, and radical nephrectomy. It has been proposed that the benefits of robotic assistance may overcome some of the challenges inherent to LESS, including the limited triangulation needed for precise dissection and tissue manipulation including retraction and reconstruction (Samarasekera and Kaouk, 2013). Extracorporeal “clashing” of robotic arms has been noted since the earliest experience of R-LESS and persists, although it has been lessened with techniques used to “chopstick” or cross the robotic arms and reverse the handedness of the robotic console controls to correct the visual association of the affected instruments within the operative field. R-LESS has been performed using the GelPort/GelPoint laparoscopic access system (Applied Medical, Rancho Santa Margarita, CA) as well as other purpose-built LESS access platforms (Stein et al, 2010; Autorino et al, 2013). Nevertheless, there is a continued need for further advances in the robotic platform designed to facilitate single-site surgery as well as novel, purpose-built robotic instrumentation-friendly access platforms to optimize the ease of use of R-LESS. With widespread availability of operative robotic platforms, R-LESS will potentially be more practical than standard LESS procedures with their inherent technical challenges.

COMPLICATIONS OF LAPAROSCOPIC RENAL SURGERY

Complications are an unavoidable consequence of surgical practice and even the most experienced clinicians will face problems. Organic factors related to the patient, operating room environment, and chaotic forces can lead to an untoward event. Thus, efforts at prevention through knowledge of each given procedure and its potential pitfalls should be maximized. Moreover, patient education about the potential risks of surgery is essential.

Patient selection is important to minimize risk of complications. This needs to be paired with each surgeon’s experience and ability. Several situations require caution when considering a laparoscopic approach. True contraindications include an uncorrected coagulopathy, untreated infection, and hypovolemic shock (Capelouto and Kavoussi, 1993). Previous surgery is not a contraindication to laparoscopic renal surgery. However, prior abdominal surgery may result in intra-abdominal adhesions and increased possibility of bowel injury during insufflation, trocar placement, or

dissection. The initial entry site in these patients should be away from scars and prior surgical fields. If Veress needle access is used for creating the pneumoperitoneum, the desired site of first trocar insertion can be first assessed with placement of a second Veress needle at that site to ensure evacuation of gas suggesting a lack of adhesions or bowel in that area. Also, open trocar placement or a retroperitoneal approach may be necessary to minimize access injuries and avoid adhesions (Hasson, 1971).

Patients with large, dilated loops of bowel from either functional or obstructive ileus should be approached cautiously, because the dilated intestinal segments can limit the working space and may be injured during access, dissection, and trocar site closure (Borten, 1986).

Care is taken to keep anatomic orientation at all times, because confusion in landmarks can lead to catastrophic consequences. Prior surgery or bulky pathology can alter normal anatomic relationships. It is thus necessary to have preoperative imaging studies available in the room. Intraoperative ultrasonography can be a valuable tool to further help identify structures. When visual clues are inadequate to allow safe progress, palpation by hand assistance may provide additional information. Alternatively, open conversion may be indicated.

When complications occur, the consequences can often be minimized through early recognition and appropriate intervention. Laparoscopic renal surgeries share several potential risks with traditional open approaches. However, there are differences in the type and presentation of these complications. It must be kept in mind that all situations are individual, and unique problems may arise and call for innovative actions.

General complications of laparoscopic surgery are covered in Chapter 10; however, specific pitfalls require review. Reported complications of laparoscopic kidney surgery are reviewed in Box 61-1.

BOX 61-1 Reported Complications of Laparoscopic Kidney Surgery
Vascular injury
Adjacent organ injury (liver, spleen, pancreas, bowel, stomach, diaphragm)
Wound infection
Abscess
Seroma
Wound dehiscence
Internal hernia
Incisional hernia
Pulmonary complications (pneumothorax, pulmonary edema, pleural effusion, pneumonia)
Pulmonary embolism
Deep vein thrombosis
Neuromuscular pain
Postoperative bleeding and transfusion
Atrial fibrillation
Myocardial infarction
Adrenal insufficiency
Testicular infarction or ischemia
Epididymitis
Ureteral stricture
Nonelective open conversion
Chylous ascites
Urinoma
Completion nephrectomy (after partial nephrectomy)
Tumor fragmentation
Renal insufficiency (transient or chronic)
Delayed bleeding
Urinary tract infection
Urinary retention



Figure 61-42. Computed tomography (CT) scan taken 9 days after partial nephrectomy when the patient visited the clinic for routine follow-up complaining of distention and worsening abdominal pain for the previous 3 days, low-grade fever, leukopenia, and pain out of proportion at a single trocar site. CT shows dilated loops of large bowel and significant amounts of free air. Exploration revealed a small perforation in the cecum.

The combined incidence of bowel injury in the urologic literature is 0.8%, and injury may occur at any point during the dissection (Schwartz et al, 2010). When reflecting the colon or duodenum, avoid thermal energy adjacent to the bowel. This is the most common cause of unrecognized injury and may not be diagnosed until postoperative day 3 to 5. When recognized intraoperatively, superficial thermal injuries may be oversewn with 3-0 silk suture to imbricate the affected area. Transmural injuries should be debrided and, as with primary sharp injury, may be closed primarily in two layers. The area should be irrigated thoroughly and inspected to rule out a through and through injury. Drain placement is encouraged and oral intake is withheld until bowel function has returned.

One of the most significant complications occurring as a result of laparoscopic surgery is unrecognized bowel injury (Fig. 61-42). Only a small portion of the laparoscopic instrument is in the visual field, so injuries can occur out of the surgeon's view during introduction or retraction of instruments. In the urologic literature, the overall incidence of bowel injury during laparoscopic surgery of the retroperitoneum, both recognized and unrecognized, is 0.65% (Schwartz et al, 2010). Unrecognized injuries result in high-grade complications in 100% of cases in series reporting on laparoscopic bowel injuries. Blunt, sharp, and cautery dissections account for the majority of bowel injuries (60%), whereas access-related injuries are far less common (6%). The presentation of bowel injuries in patients undergoing laparoscopy differs from that described with open surgery. Patients with unrecognized bowel injury after laparoscopy typically have persistent and increased trocar-site pain at the site closest to the bowel injury. The area around this site becomes edematous and doughy in consistency. Signs and symptoms may also include abdominal distention, nausea, diarrhea, anorexia, low-grade fever, persistent bowel sounds, and a low or normal white blood cell count. The patient's condition can rapidly deteriorate to hemodynamic instability and death, if the injury is not recognized and appropriately treated (Bishoff et al, 1999). CT with oral contrast is the initial diagnostic modality of choice (Cadeddu et al, 1997), and

open exploration is usually required to evacuate bowel spillage and perform the necessary repair. In rare cases, when a controlled fistula develops, conservative management with bowel rest and hyperalimentation may be used, but this can take months to resolve.

In reflecting the bowel on the left side, care must be taken to avoid making a hole in the mesentery. Any mesenteric defects should be closed because postoperative bowel herniation is possible (Regan et al, 2003). During closure of the mesentery, care also should be taken to avoid compromising the vascular supply to the colon. Retractors not in the operative field may also injure the bowel, and one should check for inadvertent injury at the conclusion of the procedure.

Vascular injuries are the most common complication of urologic laparoscopy (Permpongkosol et al, 2007). Life-threatening vascular injuries can occur during laparoscopic renal surgery and usually occur during dissection of the renal hilum. Injury to arteries, veins, branches, and accessory vessels can result in bleeding that may require conversion to open surgery. The renal vein can have multiple branches that can easily be torn. Care should be taken in ensuring ligation and transection without tension. Venous bleeding can be brisk and quickly lead to hemodynamic instability. Often, applying direct pressure with gauze for several minutes will be sufficient to control venous bleeding. Resist the temptation to continually explore the area of venous bleeding, if all is quiescent once the gauze has been removed. On the right side, the vena cava can be injured. Avulsion of the gonadal or adrenal vein can cause significant bleeding. If a hole is visible, placement of a clip or suture may be attempted once a grasper has controlled the situation. Blind clip placement or suturing can lead to a worsening of the situation and additional complications. Again, direct pressure with gauze over several minutes may abate bleeding. Dissection may continue with the gauze in place.

Arterial injuries can occur when structures are not fully identified before transection. Also, past pointing of scissors can cut an underlying vessel. If the opening is identified, suture placement or clips may be used for control. A hand may be placed in a lower abdominal midline incision to hold pressure if bleeding is brisk. In this manner, laparoscopic suturing or open conversion can proceed in a controlled manner.

Cases of inadvertent stapling of important anatomic structures have been reported. The vena cava and aorta have been mistaken for the renal vessels (McAllister et al, 2004). Several instances of transection of the small mesenteric artery (SMA) or contralateral renal vessels have also occurred. This can occur readily with the novice who is unfamiliar with the retroperitoneal approach. Unfortunately, many of these are not recognized intraoperatively and the risk of mortality is high. The best way to avoid this complication is through continuous anatomic orientation and vigilant self-questioning.

Equipment failure can result in bleeding. A multi-institutional review of endovascular stapler complications showed a malfunction rate of 1.8% (10 of 565), with 8 cases involving the renal vein and 2 cases the renal artery (Chan et al, 2000). Blood loss resulting from the malfunction was 200 to 1200 mL. Conversion to open surgery for hemostasis was required in 20% of the malfunction cases. Stapler failure was caused directly by the instrument in 3 cases and had preventable causes in 7 cases. Preventable causes included stapling over clips or incomplete transection resulting from incorrect placement. The abdominal cavity should be inspected for bleeding at the conclusion of surgery, and decreasing intraperitoneal insufflation pressures may assist in unmasking occult venous bleeding. Common areas of postoperative intra-abdominal bleeding include the bed of the dissection, adrenal gland, mesentery, gonadal vessels, and ureteral stump.

Postoperative hemorrhage can occur after partial nephrectomy. Hypotension with associated tachycardia and a drop in hematocrit may imply postoperative bleeding. After partial nephrectomy, an arteriovenous malformation or pseudoaneurysm may form (Benway et al, 2009b; Shapiro et al, 2009; Hyams et al, 2011; Montag et al, 2011). These patients have persistent gross hematuria, hypotension, and tachycardia. If there is uncertainty

regarding the source of hemorrhage, CT scanning may be appropriate in identifying the site of bleeding. However, in the majority of patients, especially in a delayed hemorrhage setting with gross hematuria, immediate renal angiography with embolization of the bleeding site is indicated (Montag et al, 2011).

Persistent urine leakage may occur after a partial nephrectomy or cyst ablation. Unless there is distal obstruction to the site of leakage, most will resolve with conservative therapy after several weeks (Meeks et al, 2008). After approximately 1 week, a controlled fistula develops, and the drain can be taken off continuous suction and checked intermittently to be sure fluid is not accumulating. If conservative management fails, as in cases of distal obstruction, additional intervention may be required, such as percutaneous drainage of a perinephric urinoma or a combination of ureteral stenting and bladder decompression.

Upper pole renal dissection can result in diaphragmatic injury. This is usually immediately recognized because peak airway pressures suddenly increase, and ventilation of the patient becomes difficult. The diaphragm can be seen billowing via laparoscopic inspection. Immediate treatment is needed to prevent development of a tension pneumothorax. The diaphragm can be sutured directly while a central line catheter is placed into the ipsilateral anterior second intercostal space and placed to a water seal. At the conclusion of the procedure, the patient is ventilated, a chest radiograph is obtained, and, if the pneumothorax is resolved, the catheter is removed. When significant pneumothorax persists, a chest tube can be inserted (Del Pizzo et al, 2003; Aron et al, 2007).

On the left side, splenic and pancreatic injuries may occur. Bleeding from the spleen is usually controlled with topical hemostatic agents and argon beam coagulation (Canby-Hagino et al, 2000; McGinnis et al, 2000). Injuries to the pancreas may be insidious, and inspection is needed at the conclusion of surgery. Superficial pancreatic injuries can be managed conservatively with drain placement. Deeper injuries may require formal repair or isolation of the segment with a GIA stapler (Varkarakis et al, 2004b). Right-sided dissections may cause injury to the liver or gallbladder. Liver injuries are managed with topical hemostatic therapy and argon beam coagulation. Gallbladder injuries are best managed by concurrent cholecystectomy.

Patients undergoing laparoscopic renal surgery are at risk of intravascular volume overload if fluid replacement is not modified relative to open surgery. The laparoscopic approach is associated with far less insensible fluid loss compared with open procedures, and there is also a vascular-mediated oliguria. Accordingly, urine output should not be a barometer of fluid resuscitation status as it is with open surgical procedures. Typically, IV fluids should be minimized with the exception of laparoscopic donor nephrectomy. Aggressive replacement can result in volume overload in patients with diminished cardiac reserve and can result in postoperative congestive heart failure. Poor urine output or hemodynamic instability in the postoperative period should initiate an evaluation to rule out bleeding; if the workup is negative, diuresis can be induced if clinically indicated.

Several authors have reported cases of chronic pain syndrome or nerve injury after LRN. Patients may experience a burning discomfort in the ipsilateral flank; paresthesias around port sites or over the thigh and upper extremity can occur (Wolf et al, 2000; Oefelein and Bayazit, 2003). In a series of 381 laparoscopic donor nephrectomies, ipsilateral orchialgia was reported in 10% of patients (Kim et al, 2003). Onset of pain occurred at a mean of 5 days after surgery (range 6 to 52 months), and at 6 months 50% had complete spontaneous resolution. Thigh paresthesias may be avoided by preserving the psoas fascia during posterior renal dissection. Additional reported complications include incisional hernia after intact specimen removal, port-site hernia, prolonged ileus, pulmonary embolus, and pneumonia.

In a multi-institutional review of 185 patients, Gill and coworkers (1995) reported an overall complication rate of 12% for benign disease, with 5% of patients requiring conversion to open surgery. In this series the incidence of complications decreased markedly with increasing experience. In fact, 70% of

the complications occurred during the first 20 cases at each institution. A learning curve of approximately 20 laparoscopic nephrectomy cases is also supported by other reports (Keeley and Tolley, 1998; Rassweiler et al, 1998b; Fahlenkamp et al, 1999). In a series of laparoscopic partial nephrectomies reported in 2010, the complication rate continued to decrease even after 750 cases (Gill et al, 2010). This implies a longer learning curve for more complex procedures.

In a series of 482 laparoscopic nephrectomies (444 procedures for benign disease) performed by 20 surgeons at 14 different European medical centers, a 6% overall complication rate was reported, with 10% of the cases converted to open surgery (Rassweiler et al, 1998b). The majority of patients converted to open surgery had infectious causes of renal abnormality as the leading indication for kidney removal. Bleeding was the most common cause of open conversion in these cases, followed by the surgeon's inability to visualize the renal hilum for safe, complete dissection.

In series comparing open, hand-assisted, and laparoscopic nephrectomy for malignancy, the complication rates were 10%, 17%, and 12% respectively ($P = .133$) (Chan et al, 2001; Shuford et al, 2004).

Two comparative studies examining complication rates in the elderly population—older than 75 and older than 80 years—found no difference in surgical or long-term morbidity when compared with younger patient populations (Varkarakis et al, 2004a; Thomas et al, 2009). In patients at high risk for perioperative complications, as determined by an American Society of Anesthesiologists score greater than or equal to 3, there were no significant differences in complication rates among hand-assisted, laparoscopic, and open radical nephrectomy (Baldwin et al, 2003).

PENETRANCE OF MINIMALLY INVASIVE RENAL SURGERY AMONG UROLOGISTS


Studies have demonstrated the serious underutilization of laparoscopic and nephron-sparing techniques (Permpongkosol et al, 2006b; Miller et al, 2008; Liu et al, 2014). After variables such as demographics, tumor size, and comorbidities were controlled for, surgeon-attributable factors were consistently the most significant predictor of the type of surgery performed. However, there has been a noticeable trend toward increased implementation of partial nephrectomy, both open and laparoscopic, and a trend toward laparoscopic and robotic-assisted laparoscopic renal surgery over time (Poon et al, 2013). Laparoscopic procedures such as cholecystectomy and appendectomy are quite commonplace and were rapidly adopted by general surgeons. Historically, urologists have been receptive to new technology, a fact clearly demonstrated by the rapid increase in the number of robotic prostatectomies performed in the United States. However, the relatively slower pace of widespread adoption of laparoscopic renal surgery, despite its longevity and proven benefits, would suggest additional barriers to the diffusion of its implementation. A complex array of reasons may account for this observation, including the differential incidence of kidney and prostate cancer, marketing of robotics, referral patterns, and consumer demand (Richstone and Kavoussi, 2008). The incorporation of robotic assistance in laparoscopic renal surgery may facilitate broader implementation of minimally invasive renal surgery (Patel et al, 2013).

SUMMARY

Laparoscopy is the preferred treatment modality for many types of renal pathology. Patients have undoubtedly gained from the benefits laparoscopy offers in terms of perioperative morbidity without sacrificing therapeutic outcomes. As surgical tools continue to evolve, even more minimally invasive options may become more pervasive and potentially offer additional perioperative benefit to patients.

KEY POINTS

- Laparoscopy can be used to treat most renal pathology with efficacy equal to that of open surgery while resulting in less pain, shorter convalescence, and improved cosmesis.
- Basic principles of oncologic surgery must be maintained when using a laparoscopic approach to treat renal tumors.
- Unrecognized bowel injuries are associated with high-grade complications including high mortality. It must be recognized that the presentation of unrecognized bowel injuries in patients undergoing laparoscopy may differ from that described with open surgery. Presentation is typically characterized by normal to low white blood count, focal abdominal pain (often worst at the trocar site nearest the injury), mild ileus, and lack of fever.

 Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Cryoablation

Radiofrequency Ablation

Surgical Technique

Treatment Success and Follow-Up Protocol after Tumor Ablation

Oncologic Outcomes

Complications

New Ablation Modalities

Conclusions

The incidence of localized renal cell carcinoma (RCC) is rising as a result of the increasing use of cross-sectional imaging.

According to the Surveillance, Epidemiology, and End Results Program (SEER), in North America the age-adjusted incidence rate of kidney cancer was estimated at 15.6 per 100,000 person-years in 2012, representing a greater than twofold increase since 1975 (National Cancer Institute, 2012). Along with the increasing incidence in the diagnosis of renal masses, there has been a parallel down-staging of newly detected renal masses, such that more than 70% are small and organ confined (clinical stage T1) (Volpe et al, 2004; Chen and Uzzo, 2011). The overall result is a paradigm shift in the management of RCC over the last decade, with an increasing focus on minimally invasive treatment and nephron-sparing surgery. Accordingly, in addition to cancer-specific survival (CSS), emphasis is now placed on preservation of renal function and avoidance of treatment-related morbidity in the management of early-stage RCC. Therefore the 2009 American Urologic Association (AUA) guidelines for the management of clinical stage 1 renal masses recommends nephron-sparing surgery as standard of care, with consideration of ablative therapies as valid alternatives for older patients or those with substantial comorbidities (Novick et al, 2009).

Partial nephrectomy is the gold standard for the treatment of small renal tumors because it provides comparable oncologic outcomes (>95% CSS) compared with radical nephrectomy and is associated with improved preservation of renal function, superior cardiac outcomes, and improved overall survival (Thompson et al, 2008; Huang et al, 2009; Zini et al, 2009). Moreover, nephron-sparing surgery avoids overtreatment of indolent or benign tumors, a particularly germane concern given that nearly 20% of small renal masses are pathologically benign, 55% to 60% are malignant but display indolent behavior, and only 20% to 25% have highly aggressive histologic features (Frank et al, 2003; Russo, 2008; Thompson et al, 2009). Irrespective of an open or laparoscopic surgical approach, nephron-sparing surgery is underused in the United States owing to the comparative risks and attendant technical demands associated with the procedure (Abouassaly et al, 2009). Recent SEER data found that partial nephrectomy use is increasing, yet 72% of patients with localized renal tumors still undergo radical nephrectomy (Smaldone et al, 2012). Thus, to increase the number of patients offered nephron-sparing surgery and broaden the minimally invasive treatment options available to patients with small renal tumors, energy-based, in-situ tumor ablation technologies were introduced in the 1990s.

Focal ablative therapies offer several advantages compared with extirpative surgery. First, these modalities are less technically demanding than open, laparoscopic, or robotic partial nephrectomy, because renorrhaphy and hilar dissection are not obligatory.

Consequently, renal tumor ablation is associated with shorter convalescence and fewer complications than extirpative surgery (Desai et al, 2005). Equally important, several studies clearly demonstrated minimal impact on postablation renal function, with comparable or better postoperative renal function found when compared to that with partial nephrectomy (Shingleton and Sewell, 2003; Lucas et al, 2008; Raman et al, 2008b). Finally, all of the ablation modalities offer treatment versatility because they can be deployed in open, laparoscopic, or percutaneous procedures. Given these advantages, well-recognized indications for ablative treatment include patients with small renal tumors who are either poor surgical candidates or at risk for renal insufficiency, including patients with solitary kidneys, bilateral renal tumors, hereditary syndromes such as von Hippel-Landau disease, and renal insufficiency. However, because of the excellent results with ablation in these selected patients, there is now growing experience with the treatment of the sporadic small renal tumors in healthy patients (Stern et al, 2009). Together with improved treatment guidance systems, more robust operator experience, and improved patient selection, renal ablative technologies are now a viable treatment alternative for small renal tumors.

CRYOABLATION

Background and Mode of Action

Cryoablation (CA), or cryotherapy, refers to the practice of using extreme cold temperatures to treat a wide variety of pathologic conditions. The use of cold therapy in medicine can be traced back to the early Egyptians, who used cold to treat inflammatory conditions as early as 2500 BC. However, CA was not used with a goal of tissue destruction until the mid-1800s, when an English physician, Dr. James Arnott, described using a combination of ice and salt to obtain temperatures (-18°C to -24°C) sufficient to treat breast, cervical, and skin cancers (Arnott, 1850). Over the course of the ensuing decades, multiple investigators described the use of cooled gases for treatment of various skin conditions, beginning with liquified air (-190°C), followed by solidified carbon dioxide (-78.5°C), liquid oxygen (-182.9°C), and then eventually liquid nitrogen (-196°C) (Freiman and Bouganin, 2005). In 1963, Cooper and Lee developed the first modern cryoprobe using pressurized liquid nitrogen passed through a three-channel probe (one inflow and two outflow) to achieve controlled temperatures of -196°C (Cooper, 1963). This revolutionary probe opened the possibility of treating less accessible areas rather than relegating cryotherapy solely to superficial areas such as the skin.

Although Cooper's design allowed for intra-abdominal treatment of large volumes, its use was limited by an inability to control

or monitor the extent of the cryolesion. Without the availability of intraoperative imaging to visualize the expanding frozen tissue or “ice ball” physicians routinely relied on physical examination to monitor treatment, such as digital rectal examination during prostate cryotherapy, which often led to irreparable collateral damage (Weber and Lee, 2005). In the mid-1980s, Onik and colleagues (1984, 1985) discovered that the cryogenic ice-tissue interface was highly echogenic on ultrasonography when used in the liver, allowing for the fusion of CA with real-time image guidance and opening the door for controlled treatment of intra-abdominal malignancies. Further animal studies confirmed a close correlation between the sonographically visible ice ball and the zone of cell death, providing a reliable and reproducible method of targeting and destroying tumors without attendant collateral damage (Steed et al, 1997; Campbell et al, 1998; Weber et al, 1998).

Although the fusion of the nitrogen-based cryoprobe and ultrasound guidance improved the treatment of intra-abdominal tumors, the next significant breakthrough came with the development of argon gas–based probes, which relied on the Joule-Thomson principle (low temperatures are achieved by the rapid expansion of high-pressure, inert gas) to generate temperatures of -185.7°C within the treatment tissues. In addition to providing a reliable target temperature, argon-based systems are more efficient than nitrogen-based probes, with target temperatures reached faster and with a steeper internal thermal gradient (Rewcastle et al, 1999). The majority of commercially available CA units now employ argon gas–based systems (CryoHit, Galil Medical, Plymouth Meeting, PA; CryoCare, CryoCare CS, Endocare, Irvine, CA; SeedNet, Oncura, Philadelphia, PA).

Tissue destruction during CA occurs during both the freezing and thawing processes. Rapid freezing in the area closest to the cryoprobe forms ice crystals within the intracellular space that cause direct cellular injury through mechanical trauma to plasma membranes and organelles, leading to subsequent cell death mediated by ischemia and apoptosis (Mazur, 1977; Ishiguro and Rubinsky, 1994; Hoffmann and Bischof, 2002; Baust and Gage, 2005). As the freezing process expands further from the cryoprobe, the cooling process is slower, which encourages extracellular ice crystals to form and leads to a depletion of extracellular water and an osmotic gradient that causes further intracellular damage through dehydration and membrane rupture. During the thawing phase, extracellular osmolarity decreases as ice crystals melt, allowing an influx of water back into cells, which causes cellular edema and further disruption of cell membranes (Erinjeri and Clark, 2010). In addition to direct cellular damage, injury to blood vessel endothelium during the freezing process results in platelet activation, vascular thrombosis, and tissue ischemia (Weber et al, 1997; Kahlenberg et al, 1998; Rupp et al, 2002). The summative pathologic consequence of treatment is coagulative necrosis, cellular apoptosis, and eventual fibrosis and scar formation.

Treatment Temperature

Tissue destruction during CA requires a certain threshold temperature, which is unique to the cell type and cellular environment of the target tissue. Whereas normal renal parenchyma is typically destroyed at -19.4°C , small animal models of CA indicate that temperatures as low as -50°C may be necessary to guarantee complete cellular death of cancerous tissue because of its more fibrous nature (Chosy et al, 1998; Gage and Baust, 1998; Larson et al, 2000). Therefore the preferred target tissue temperature during CA is at or below -40°C . Importantly, the temperature of the progressing ice ball is not uniform, with temperatures increasing the further the distance from the cryoprobe. Campbell and colleagues (1998) measured intrarenal temperatures during CA and referenced these to the leading edge of the ice-tissue interface. At the edge of the ice ball, the temperature was measured at 0°C , correlating with the onset of the freezing process. Temperatures of -20°C were reached 2.0 mm within the ice-tissue interface, while temperatures consistently below -20°C were not reached until 3.1 mm inside. Based on these findings, most authors advocate

creating an ice ball treatment zone that is at least 5 to 10 mm beyond the edge of the target lesion. Alternatively, small temperature probes may be positioned around the tumor periphery to ensure that adequate treatment temperatures (-40°C) are achieved (Rukstalis et al, 2001). Depending on the size of the lesion and the type and size of probe used, reaching the appropriate target temperature within the entire mass may require the use of multiple cryoprobes (Breen et al, 2013). Additionally, freezing is subject to the “heat sink” phenomenon, in which large blood vessels adjacent to the tumor may dissipate ice formation and require more extreme temperatures or longer periods of cooling (see section on radiofrequency ablation and heat sink in next section for further details).

Freeze-Thaw Cycles

In-vivo animal studies initially demonstrated adequate cell kill in normal tissue employing a single freeze-thaw cycle (Weber et al, 1997). However, further studies on implanted tumor cells in mice, then in dogs, found that multiple freeze-thaw cycles promoted a larger and more adequate area of liquefactive necrosis, improving subsequent cure rates (Neel et al, 1971; Woolley et al, 2002). Therefore, when treating renal malignancies, the current recommendation is to perform a double freeze-thaw cycle to ensure complete cellular death. The thawing process is also instrumental in cellular death and may be performed in a passive or active manner. Passive thawing, which relies on the ice ball melting without any intervention after the cessation of argon gas through the cryoprobe, is more time-consuming than active thawing, where helium gas (rather than argon) is forced through the cryoprobe creating a warming effect secondary to the Joule-Thomson principle. Although clearly more efficient, there are conflicting data on whether an active thaw is as effective as a passive thaw (Woolley et al, 2002; Klossner et al, 2007). In addition to decreasing operating room time, an active thaw during at least the second thaw cycle may allow the surgeon to more rapidly address post-treatment bleeding (White and Kaouk, 2012).

Duration of Treatment

The duration of treatment to produce complete cellular death in humans is unknown. Auge and colleagues (2006) performed a prospective study in nine female farm pigs with CA performed for 5, 10, or 15 minutes. Although all lesions demonstrated complete cellular necrosis 5 mm from the probe, only animals treated for 10 or 15 minutes had necrosis extending 10 mm or more beyond the probes. Furthermore, animals treated for only 5 minutes had excessive bleeding, whereas those treated for 15 minutes had an increased risk for tumor fracture and subsequent hemorrhage. Based on these findings, most contemporary series use a freeze cycle of 8 to 10 minutes (Breen et al, 2013; Kim et al, 2013).

KEY POINTS: CRYOABLATION

- CA employs argon gas–based systems to achieve treatment temperatures of less than -40°C through the Joule-Thomson principle.
- CA of renal tumors should be performed under real-time imaging, with the treatment area approximately 5 to 10 mm beyond the margin of the tumor.
- A double freeze-thaw cycle, each 8 to 10 minutes in duration, is currently the standard of care during renal tumor CA.

RADIOFREQUENCY ABLATION

Background and Mode of Action

Radiofrequency ablation (RFA) refers to the use of radiofrequency energy to heat tissue to the point of cellular death. RFA uses monopolar alternating electric current that is delivered directly into the

target tissue at a frequency of 450 to 1200 kHz, leading to vibration of ions within tissue and resulting in molecular friction and heat production. Increasing temperature within the target tissue leads to cellular protein denaturation and cell membrane disintegration (Hsu et al, 2000; Tracy et al, 2010). Importantly, heat is not directly supplied by the probe itself, but rather by the agitation of ions within the tissue (Cosman et al, 1984). Although not as old as cryotherapy, study of the effect of radiofrequency energy dates back over 100 years to 1891 when d'Arsonval described the ability of radiofrequency waves to heat living tissue. Without a clear understanding of the technology and an inability to effectively control the energy, the use of radiofrequency energy in surgery did not become more mainstream until 1928, when Cushing and Bovie developed the electrocautery knife. Using radiofrequency energy they described an ability to cauterize or cut tissue, ushering in the development of the modern-day electrocautery probe, which desiccates tissue at the point of contact when alternating current passes through the patient and then dissipates to a remotely placed grounding pad on the patient's lower extremities. These principles led to further development of RFA and opened the door for use in a broader number of surgical procedures (Organ, 1976).

In 1990 two individual groups of researchers simultaneously reported the development of probes that could be used for percutaneous ablation (McGahan et al, 1990; Rossi et al, 1990). These probes consisted of a layer of insulation down to an exposed metal tip, which allowed for percutaneous passage of the needle to deeper target tissues. Using these needles, the amount of tissue destruction could be controlled along the central axis of the lesion by adjusting the length of the exposed, uninsulated portion of the needle. Although effective in ablating along the long axis of the lesion, these initial probes were limited in their ability to create circumferential tissue damage, preventing their use in lesions greater than 1.5 cm. Further refinements using these initial designs led to the development of modern RFA generators and probes, which are capable of treating larger and more complex lesions.

Variations in Radiofrequency Ablation Equipment

RFA can be performed with either a temperature-based or impedance-based monitoring system. Temperature-based systems work by measuring tissue temperatures at the tip of the electrode and are based on achieving a specific temperature for a given period. These systems accurately measure the temperature of the tissue at the electrode tip; however, they do not measure the temperature of the surrounding parenchyma. Alternatively, impedance-based systems measure the tissue impedance (resistance to alternating current) at the electrode tip and are based on achieving a predetermined impedance level that indicates complete tissue ablation. Although these systems are able to measure actual tissue desiccation at the electrode tip, they have been associated with incomplete ablation in animal models (Gettman, 2002a). **There are no explicit clinical data that support the superiority of impedance or temperature-based systems.**

The original ablation probes, which were designed as single electrode monopolar probes controlled by varying the exposed uninsulated tip, were capable of treating tumors no greater than 2 cm (McGahan et al, 1993). Therefore the treatment of larger tumors or the acquisition of an adequate tumor margin often required additional probes or re-treatment of overlapping regions. Multiple systems have been developed in an attempt to achieve a larger overall treatment volume. LeVeen (1997) introduced an insulated monopolar probe (Boston Scientific, Natick, MA) with 12 deployable tines that function as radiofrequency antennas for the wider dispersion of current. These tines are deployed in an umbrella shape to create a spherical lesion. When high impedance is encountered at one prong, current is redirected to areas of lower impedance. The Christmas tree-shaped RITA device (AngioDynamics, Queensbury, NY) uses thermistors embedded in five of the nine electrical tines to modulate energy based on the temperature of each electrode as well as the average temperature of the electrodes in aggregate. Finally, the Valleylab system (Mansfield, MA) uses an

impedance-based system composed of a single 17-gauge ("cool tip") electrode that is cooled internally with chilled saline to prevent charring of tissue adjacent to the probe. A direct comparison of these systems in the porcine liver demonstrated larger zones of ablation with the "cool tip" systems, more spherical ablation volumes with the 12-tine electrodes, and better reproducibility with the 9-tine electrodes (Pereira et al, 2004). Clinical validation studies have suggested more complete necrosis and superior treatment outcomes with multitine electrodes (Rossi et al, 1998; Curley et al, 2000; Rehman et al, 2004).

Another major classification in RFA technology is the differentiation between "dry" and "wet" RFA. As tissue desiccation increases in the target lesion, the charring effect (carbonization) on tissue leads to increased impedance and resistance to the alternating current of the electrode, limiting the size of the ablation zone with a single electrode to less than 4 cm. "Wet" RFA probes deliver a constant saline infusion into the tissue and in proximity to the probe to lower the temperature at the probe tip, thus mitigating the charring effect and corresponding premature rise in impedance, allowing for larger zones of ablation (Goldberg et al, 1996; Lorentzen et al, 1997; Collyer et al, 2001; Pereira et al, 2004). Additionally, interstitial hypertonic saline infusion forms a virtual "liquid electrode" beyond the metal electrode so that the total electrode surface area is augmented (Ni et al, 1999). **Although lesions tend to be larger using "wet" RFA, there is less control of the exact size of ablation, which may lead to overtreatment of the target zone and disruption of adjacent normal parenchyma (Frich and colleagues, 2005).**

Radiofrequency energy also can be delivered through either bipolar or monopolar electrodes. Compared to traditional monopolar radiofrequency devices, which work based on electrical transmission through the exposed probe tip with dissipation to a grounding pad on the skin of the patient, bipolar radiofrequency devices generate current between two separate electrodes (one active and one negative), within the target tissue. The purported advantage of bipolar energy is that significantly higher temperatures are induced compared with those of monopolar devices (Nakada et al, 2003). In addition, heat is generated not only at the active probe but also adjacent to the ground needle and between the two electrodes (McGahan et al, 1996), resulting in a focus of coagulation necrosis that is larger than with a conventional monopolar electrode. The use of two separate electrodes, however, produces an elliptical area of coagulation necrosis rather than spherical; because most renal tumors are spherical, this technology has not been widely adapted for RFA of renal masses.

Treatment Temperature

The ability of RFA to ablate the target tissue relies on power delivered to the probe, the maximum temperature obtained, and the duration of the ablation (McGahan and Dodd, 2001). As stated, alternating radiofrequency current creates cellular agitation and, as a result of electrical impedance of the tissue, local heating. Provided that electrical impedance remains low, an expanding sphere of tissue damage emanates outward from the treatment probe. If current is administered too rapidly or the amount of radiofrequency energy applied is too high, charring occurs, which reduces the water content of the tissue. Charring and dehydration then may lead to increased electrical impedance, blocking energy transfer and halting the heating process (Djavan et al, 2000; Finelli et al, 2003). To prevent this phenomenon, which may lead to incomplete or nonuniform ablation, target temperatures during RFA are generally kept at or below 105°C. It is also important to reach a minimum target temperature at which cellular death occurs. In in-vitro studies using human prostate tissue, Bhowmick and associates (2004a, 2004b) achieved irreversible cell injury when benign and malignant cell lines were heated to 45°C for 60 minutes, 55°C for 5 minutes, and 70°C for 1 minute. Similarly, Walsh and colleagues (2007) found that even short exposures at temperatures higher than 70°C are lethal to human RCC in vitro. **To maximize cellular death without carbonization, most modern**

temperature-based generators are programmed to reach a target temperature of 105°C, and ablation should not be considered successful unless a minimum of 70°C is reached during the treatment cycle. Impedance-based systems are typically started at 40 to 80 W and increased at 10 W/min to a maximum of 130 to 200 W until an impedance of 200 to 500 ohms is reached.

The ability of the radiofrequency (or CA) to reach its target temperature within the tissue depends not only on the probe itself and the energy delivered but also on the surrounding treatment environment (Goldberg et al, 2000). In particular, when the target zone is highly vascularized or is adjacent to large vessels, thermal energy is preferentially dispersed to the comparatively cooler blood within these vessels. This heat sink effect may therefore spare tumor cells in close proximity to large blood vessels and lead to treatment failures. Temporary renal ischemia during RFA experimentally increases the size of the initial treatment lesion and shortens the time to reach target temperature (Corwin et al, 2001). However, hilar occlusion is not currently recommended because of the risk for arterial thrombosis and ischemia-reperfusion injury to normal parenchyma. To prevent complications of vascular clamping, some authors advocate selective arterial embolization when performing RFA. Hall and colleagues (2000) reported an innovative combination of embolization with polyvinyl alcohol and percutaneous RFA in a 67-year-old patient with a 2.5-cm × 3.0-cm tumor in a solitary kidney. A computed tomography (CT) scan performed at 8 weeks after ablation showed a complete lack of contrast enhancement in the treated area. At 3 months after ablation, a biopsy revealed fibrous tissue and necrotic cellular debris with no evidence of malignancy. The authors have successfully employed this same technique in a few central or large (>4 cm) tumors to reduce the circulatory heat sink.

Although most studies show cellular death with a single RFA treatment, studies in animals using CA have demonstrated improved cell death with multiple cycles. Therefore, when employing a temperature-based system, we typically recommend using two separate RFA cycles separated by a minimum 30-second cool-down period (Park et al, 2006a).

Intraoperative Monitoring

Although it is possible to visualize placement of the RFA probe using ultrasonography, magnetic resonance imaging (MRI), or CT guidance, there is currently no reliable manner to evaluate the zone of treatment radiographically (Rendon et al, 2001; Renshaw, 2004). In contrast to CA, where the expanding ice ball indicates the zone of treatment, the RFA treatment zone is determined solely by the probe choice, accurate placement, and measurement of electrical impedance or temperature (embedded thermistors) measured by the generator itself. An alternative method, which also may be used with CA, is to place nonconducting temperature probes around the periphery of the tumor or at the deep margin to measure real-time treatment temperatures independent of the RFA device. Using this method, Carey and Leveillee (2007) demonstrated 100% clinical success in treating tumors up to 5 cm in diameter. Experimental imaging modalities, including real-time contrast-enhanced ultrasonography (Johnson et al, 2005; Chen et al, 2013) and magnetic resonance elastography (Li and colleagues, 2013) have shown some promise experimentally, but have not been properly evaluated in the clinical setting. The successful ablation of a renal lesion with RFA therefore is highly dependent (likely more so than with CA) on exact probe placement, and outcome is typically determined only by feedback from the generator, thermal probes, the presence of gas bubbles within the tumor, and the absence of contrast enhancement during percutaneous CT-guided RFA.

SURGICAL TECHNIQUE

Transperitoneal and Retroperitoneal Laparoscopic Renal Cryoablation and Radiofrequency Ablation

See Chapter 61 for these modalities.

KEY POINTS: RADIOFREQUENCY ABLATION

- Transfer of radiofrequency energy generates ionic friction and agitation within tissue that results in heating. When temperatures exceed 60°C, irreversible coagulative necrosis and tissue desiccation occurs.
- Treatment may be either thermal based or impedance based.
- Real-time monitoring of ablation depends on measurement of electrical impedance and temperature rather than visual or radiographic cues.

Percutaneous Renal Cryoablation and Radiofrequency Ablation

Depending on treating physician preference, percutaneous tumor ablation is performed under either conscious sedation with local anesthesia or general endotracheal anesthesia. Regardless, the procedure is generally performed on an outpatient basis or 23-hour observation. General endotracheal anesthesia enables control of respiration during probe placement and tumor biopsy that may translate into more accurate targeting and improved overall outcomes (Gupta et al, 2009). Conversely, conscious sedation minimizes the morbidity and time of the procedure. After administration of intravenous prophylactic antibiotics, the patient is positioned in either a prone or modified flank position on the CT gantry, with the choice of position largely dictated by the tumor location. CT guidance is by far the preferred and most common targeting technique, although ultrasound and magnetic resonance guidance also have been reported (Shingleton and Sewell 2001; Davis et al, 2012).

A noncontrast CT image is obtained first to confirm tumor size and position in the prone or lateral position, and a contrast-enhanced CT image is then often obtained to better delineate the tumor. A radiographic grid placed on the patient's skin can help localize placement of the needle. A 20-gauge "finder needle" or access sheath may be inserted under CT guidance near the expected location of the tumor, with position confirmed through repeated imaging. Using this finder needle as a guide, the ablation probe(s) is then positioned to treat the tumor. The number of probes and the duration of treatment are determined based on lesion size in accordance with the manufacturer's recommendations. Serial imaging is used to confirm the placement of all treatment probes/tines. If a tumor biopsy has not been performed, an 18-gauge core biopsy needle is inserted percutaneously and positioning is again confirmed with repeat imaging. Biopsy specimens are obtained and sent for permanent section before the initiation of therapy. Importantly, the treatment probes should be placed into the tumor before the biopsy because perinephric hematoma formation may obscure visualization of the tumor. Probe and biopsy needle positioning and adjustments are all performed with breath holding to standardize the position of the mobile kidney with each sequential pass of the needle.

Monitoring of treatment efficacy during CA employs imaging of the ablation zone. Although each cryoprobe tip reaches temperatures of -140°C to -190°C, there is a steep temperature gradient that falls to 0°C at the edge of the ice ball. Temperatures of less than -20°C are achieved at a distance of 3.1 mm inside the edge of the ice ball (Campbell et al, 1998). Because tumor cell death is reliably achieved at target temperatures of -40°C (Campbell et al, 1998), the ice ball should propagate 5 to 10 mm beyond the tumor margin to ensure complete treatment. The ice ball appears as a distinct hypodense zone on CT imaging (Fig. 62-1). As previously mentioned in the section on mechanism of action, two freeze-thaw cycles are performed to obtain more complete tissue necrosis (Woolley et al, 2002). Unlike RFA, with which lesions are typically treated for a predetermined period, there is no standard duration for a freeze cycle as long as the intended ablation zone size is attained. Ten minutes is commonly used during the initial cycle, and the second cycle is generally shorter (6 to 8 minutes) based on

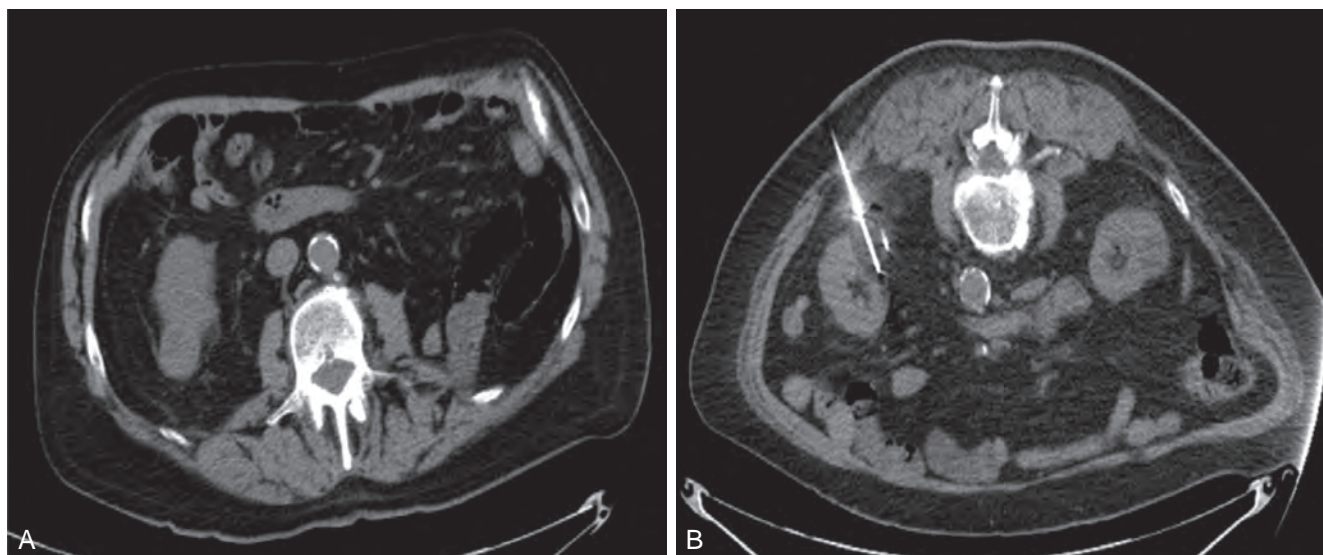


Figure 62-1. Percutaneous cryoablation. A, Preoperative imaging demonstrates a 2.6-cm exophytic renal cell carcinoma on the posterior aspect of the right kidney. B, Intraoperative image during percutaneous ablations shows low attenuation area corresponding to the ice ball. (Courtesy Ardeshir Rastinehad, MD, Department of Urology, North Shore-Long Island Jewish Health system.)

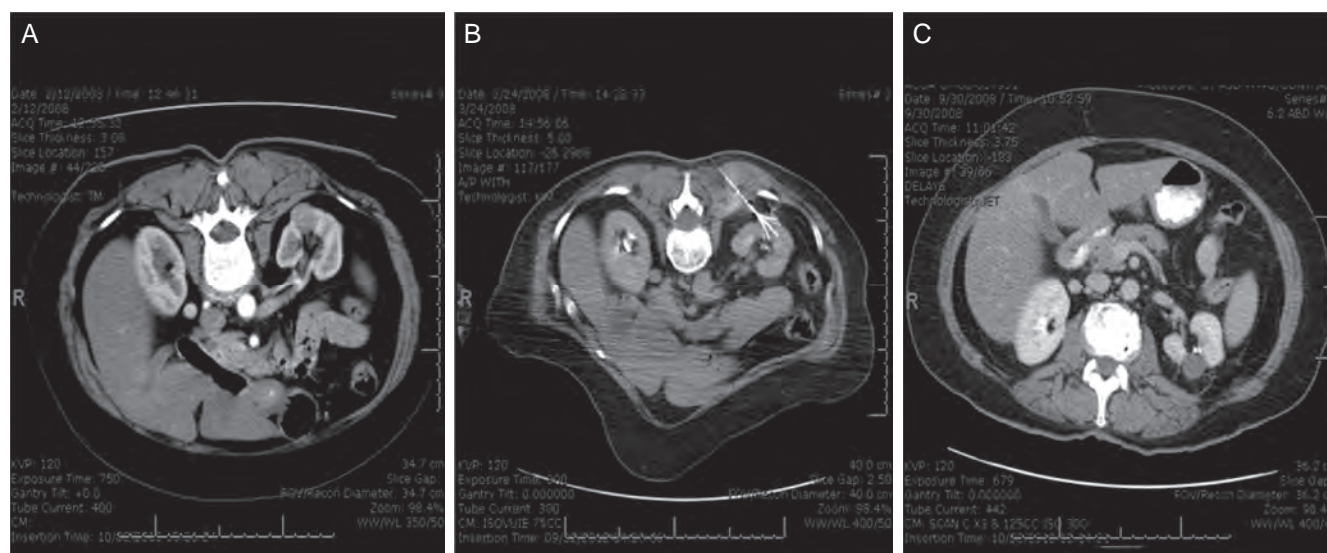


Figure 62-2. Radiofrequency ablation (RFA) probe positioning and postablation findings. A, Posterior left renal tumor before ablation. B, RFA probe positioned. C, Six months after ablation imaging with characteristic periablation halo sign.

animal evidence demonstrating inadequate necrosis at 5 minutes and increased tissue fracture at 15 minutes. Thus 10-minute freeze cycles represent an optimal compromise with adequate tumor necrosis and fewer complications (Auge et al, 2006). Each freeze cycle is followed by either an active (helium-based) or passive thaw. Although there is conflicting evidence regarding an active versus passive thaw, some authors suggest an active thaw during at least the second thaw cycle to decrease operative time and allow the surgeon to more rapidly address post-treatment bleeding (White and Kaouk, 2012). After the second cycle thaw, the probe is gently twisted, and, if there is no resistance, it is removed atraumatically. A contrast-enhanced CT is repeated after treatment to assess completeness of ablation and rule out complications.

Monitoring of treatment efficacy during RFA employs measurement of tissue temperature or impedance, using either single multi-

tined probes (with incorporated thermistors) or multiple single-shaft probes that measure tissue impedance as the end point. At our institutions, a 14-gauge Starburst XL (AngioDynamics, Queensbury, NY) RFA probe is deployed and its position is adjusted to ensure complete lesion coverage plus a peritumoral margin of at least 5 mm (Fig. 62-2). This is done using serial limited CT scans through the kidney employing 3-mm cuts. When necessary, after probe positioning, an 18-gauge CT-guided core biopsy is obtained as previously described. Ablation cycles of 5, 7, and 8 minutes at a target temperature of 105°C are then delivered for tine deployments of less than 2 cm, 2 to 3 cm, and 3 to 4 cm, respectively. After a 30-second cool-down, a second cycle of similar duration is performed. During the initial and secondary cool-down cycles, the passive tissue temperature in each quadrant should be at least 70°C, confirming the absence of a large heat sink. Contrast-enhanced CT

is repeated after treatment to assess completeness of ablation and rule out complications. If inadequately treated areas are identified, the radiofrequency probe is repositioned and the treatment is repeated in a similar fashion. Depending on the manufacturer, the probe tract is ablated during probe withdrawal. For ablation of larger lesions, some authors have described the use of nonconducting temperature probes placed at the peripheral and deep margins of the tumor for active temperature monitoring (Carey and Leveillee, 2007). Rather than multitined probes, multiple individual probes also can be used in overlapping ablations (Karam et al, 2011). Patients who undergo percutaneous CA or RFA under general anesthesia or conscious sedation are discharged in a same-day fashion, whereas those with significant comorbidities or complication typically are admitted overnight.

TREATMENT SUCCESS AND FOLLOW-UP PROTOCOL AFTER TUMOR ABLATION

Interpretation of treatment success after renal tumor ablation had been a controversial subject but with maturing experience and standardization of follow-up protocols, radiographic cross-sectional imaging alone is now the accepted measure of treatment efficacy (Matin et al, 2006). Routine postablative biopsy may serve a role in corroborating radiographic findings. However, the interpretation of biopsy findings after ablation is highly contentious and the overall utility of biopsy in this setting is unresolved. When enhancement and involution are incongruent or recurrence is suspected, multisite-directed core biopsies are appropriate.

Radiographic Interpretation of Success

No pathologic margins are rendered with in-situ ablation; therefore imaging characteristics serve as a surrogate marker of treatment efficacy. In general, the complete loss of contrast enhancement on follow-up CT or MRI is considered evidence of complete tissue destruction and attendant treatment success (Matsumoto et al, 2004; McAchran et al, 2005). At most centers, the first postablation CT or MRI image is obtained at 4 to 12 weeks. If persistent enhancement is identified in any portion of the treated lesion on initial imaging, it is classified as an incomplete ablation and repeat ablation is scheduled (Fig. 62-3). Conversely, if a lesion

demonstrates an initial complete loss of contrast enhancement and later demonstrates enlargement of the lesion and/or contrast enhancement, this is considered local tumor recurrence or progression (Matin, 2010).

In addition to contrast-related characteristics, lesions that undergo CA or RFA demonstrate characteristic but strikingly different appearances on follow-up imaging. The majority of lesions treated with CA demonstrate a greater than 50% reduction in size in the first year after treatment (Deane and Clayman, 2006; Kawamoto et al, 2009). This contraction is due to cellular breakdown and phagocytosis. Conversely, lesions treated with RFA often demonstrate minimal postablative contraction and have a distinctive fibrotic halo or circular demarcation around the treatment zone when performed percutaneously (see Fig. 62-2C), representing a foreign-body giant cell fibrotic response (Park et al, 2006b). Enlargement of a lesion, regardless of the treatment modality or the enhancement characteristics, should be considered a tumor recurrence and biopsy and/or treatment (observation vs. repeat ablation vs. extirpative surgery) should be strongly considered.

Recommended Radiographic Follow-Up Protocol

The AUA guidelines for the follow-up of an ablated renal tumor recommend that CT or MRI with intravenous contrast should be performed at 3 and 6 months after ablation and then annually thereafter for 5 years (Donat et al, 2013). There are no available data suggesting the superiority of MRI or CT in routine follow-up, although some experts contend that CT better distinguishes tumor margins and enhancement in the evaluation of renal tumors (Cadeddu, 2008). Ultrasonography should not be routinely employed to evaluate lesions after ablation unless specific protocols are in place for contrast-enhanced ultrasonography.

Role of Preablation and Postablation Biopsy

To establish a diagnosis and provide uniformity and improved outcomes-based data, the AUA Small Renal Mass and the Follow-up for Clinically Localized Renal Neoplasms Guidelines Panels recently recommended that tumor biopsy be universally performed at or before the time of ablation (Novick et al, 2009; Donat et al, 2013). The diagnostic accuracy in specimen interpretation is high (Schmidbauer et al, 2008) and will help define the frequency of

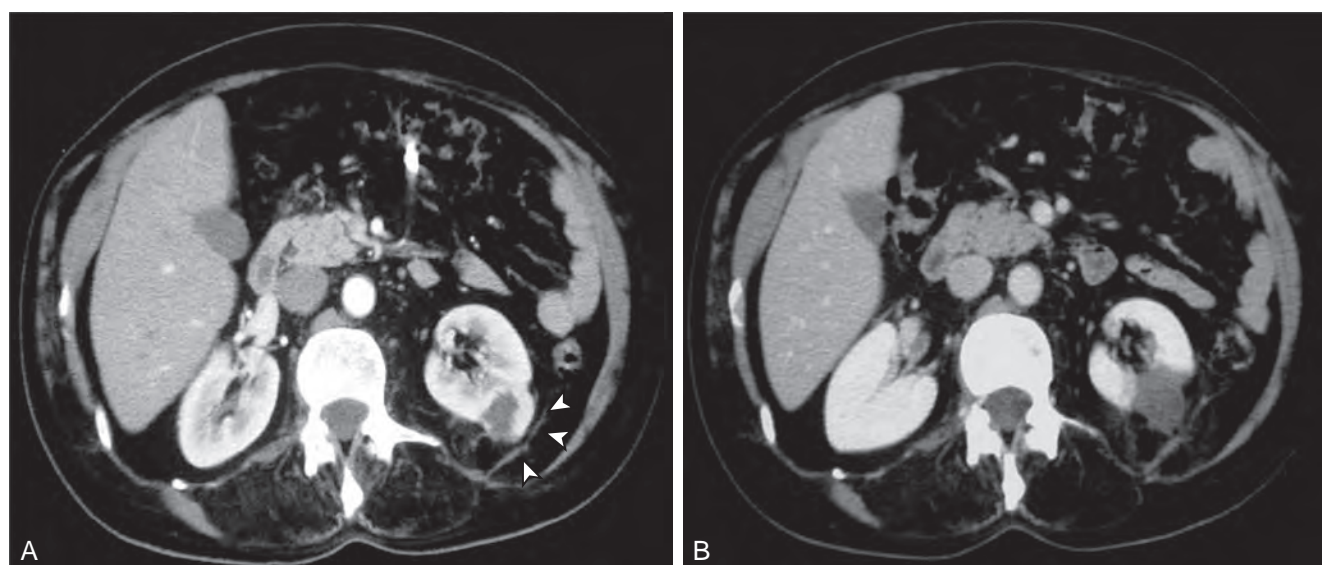


Figure 62-3. Incomplete ablation with radiofrequency ablation. A, Six-week follow-up computed tomography scan shows contrast enhancement of a left renal cell carcinoma indicative of an incomplete ablation (arrowheads). B, After repeat ablation, the tumor shows no further enhancement on subsequent 6-week follow-up.

postablation follow-up. Conversely, one of the chief criticisms of in-situ renal ablation has been the inability to render definitive pathologic evidence of treatment success. Efficacy with ablative technologies is therefore predicated solely on indirect radiographic interpretation, as previously discussed. The role of a routine postablation biopsy is controversial, and studies have yielded conflicting data on its utility (Matlaga et al, 2002; Lin et al, 2004; Klingler et al, 2007; Raman et al, 2008a; Weight et al, 2008). Considering the dual limitations of imaging studies and biopsy findings, a recent multi-institutional study on the incidence and patterns of recurrence after energy ablative therapy concluded that radiographic detection of residual or recurrent disease was the current state of the art when performed correctly (Matin, 2010).

The controversy surrounding the oncologic accuracy of routine postablation biopsy centers on the histologic interpretation, inherent sampling error, and poor correlation with long-term oncologic results. Much of the debate during the last decade focused on the utility of radiographic imaging alone and the need for postablation biopsy in patients who underwent RFA. In the largest study addressing this controversy, Weight and colleagues (2008) attempted to correlate the radiographic appearance of ablated renal masses with pathologic outcomes. The group examined a total of 109 renal lesions in 88 patients who underwent percutaneous RFA and 192 lesions in 176 patients who underwent laparoscopic CA. At 6 months after treatment, radiographic success (no evidence of contrast enhancement) was noted in 90% of patients who underwent CA and in 85% of patients who underwent RFA. Biopsy at 6 months was then performed in 134 lesions (45%). Pathologic evidence of success was 93.8% with CA and only 64.8% with RFA. Of note, 6 of the 13 patients who underwent RFA and demonstrated viable residual tumor on follow-up biopsy demonstrated no contrast enhancement on follow-up imaging. Conversely, all CA patients who had residual tumor on follow-up biopsy demonstrated definitive contrast enhancement. The authors concluded that radiographic imaging results after CA correlated well with pathologic results, whereas a poor correlation was noted between radiographic imaging and pathologic results after RFA. Routine biopsy after RFA was advocated by the authors.

The study by Weight and colleagues (2008) generated significant debate regarding the efficacy of RFA and need for postablation biopsy, but it was subsequently criticized for selection bias and possible errors in histologic interpretation. Most importantly, the authors used standard hematoxylin and eosin (H&E) staining, which can be misleading after RFA, because cellular architecture is largely preserved despite cell death (Margulis et al, 2004). The duration of this “architectural preservation” has not been defined but is likely 6 months or more. Stern and colleagues (2008) performed tumor biopsy on 20 radiographically negative lesions at least 1 year after RFA and found no evidence of tumor with routine H&E staining. The authors concluded that RFA imparts definitive cellular necrosis and radiographic imaging results correlate well with histopathologic findings at 1 year. To assess shorter term ablation success, cell viability stains, primarily reduced nicotinamide adenine dinucleotide (NADH) diaphorase, have been proposed as a more accurate method of determining cell death after tumor ablation. Marcovich and coworkers (2003) performed a porcine study in which renal tumors were treated with RFA and later resected and examined histologically. Tumor architecture was variably preserved on H&E staining (as discussed), but no NADH diaphorase staining was noted (implying complete cell death). Clinically, Davenport and colleagues (2009) reported on 28 tumors ablated with RFA that had no radiographic evidence of disease. A biopsy sample at 2 months was analyzed using H&E and NADH staining. No viable tumor was identified, confirming the experience of Stern and colleagues (2008).

ONCOLOGIC OUTCOMES

CA and RFA are relatively new compared to extirpative procedures, and thus long-term results are just now being described. Based on

KEY POINTS: FOLLOW-UP AFTER TUMOR ABLATION

- Complete loss of contrast enhancement on follow-up CT or MRI is considered evidence of complete tissue destruction and treatment success.
- The majority of lesions treated with CA demonstrate a greater than 50% reduction in size in the first year after treatment. Lesions treated with RFA demonstrate minimal postablative contraction and have a distinctive fibrotic halo or circular demarcation around the treatment zone. Enlargement of a lesion, regardless of the treatment modality or the enhancement characteristics, should be construed as an ominous sign of local tumor recurrence.
- The AUA Guidelines Panel recommends that a pretreatment tumor biopsy be universally performed before or at the time of ablation.
- The same Guidelines Panel recommends that a CT or MRI scan with intravenous contrast should be performed at 3 and 6 months after ablation and then annually thereafter for 5 years.

these results, the indications for these minimally invasive ablative techniques are rapidly evolving. Therefore the AUA has recently recognized ablative therapies as a treatment alternative for small renal masses in a select group of patients (Novick et al, 2009). Specifically, the role of ablation was noted for patients with primarily T1a (<4 cm) tumors who have risk factors that may increase surgical morbidity. In addition, based on the success of ablation, the AUA Guidelines also now recommend that CA and RFA be discussed with healthy patients as an alternative to partial or radical nephrectomy, with an understanding that tumor recurrence may be more likely and that surgical salvage may be difficult.

Several confounding variables in the literature complicate the interpretation of oncologic success after thermal ablation, including small cohort sizes, short follow-up, inclusion of patients with benign masses, lack of preablation biopsy, inclusion of patients with confounding features for RCC recurrence such as hereditary cancer syndromes, use of various (and evolving) technologies, and variable definitions of recurrence. Fortunately, as the ablative literature continues to mature, the quality of evidence has continued to improve, with most series now controlling for some of these variables. Tables 62-1 and 62-2 summarize RCC-specific outcomes for RFA and CA, respectively, in select series with intermediate- to long-term follow-up. For RFA, local recurrence-free outcomes range between 88% and 92% and corresponding rates for CA are 80% to approximately 86%. Metastasis-free survival and CSS exceed 90% in virtually all series. Although a direct comparison between ablation and partial nephrectomy is limited by patient, tumor, and surgeon selection biases, as well as inconsistent definitions of postablation recurrence, data to date suggest that progression-free survival and disease-specific survival are similar for energy ablative therapy and extirpative therapy in the intermediate term, exceeding 90% in each case. In a head-to-head comparison of RFA and partial nephrectomy in patients with sporadic unilateral T1a RCC, 5-year actual local recurrence-free survival, overall disease-free survival, and progression-free survival were statistically similar between cohorts when including patients who may have required a second ablation for incomplete primary treatment (Olweny et al, 2012). Similar studies to date comparing oncologic outcomes for CA and partial nephrectomy in matched cohorts are limited by inclusion of patients with benign histologic findings, rendering interpretation of recurrence outcomes inconclusive (Klatte et al, 2011; Guillotreau et al, 2012; Whitson et al, 2012). A review of many of these studies follows.

Local Recurrence-Free Survival

The definition of local recurrence-free survival is likely the most contested point with regard to comparing CA, RFA, and partial

TABLE 62-1 Intermediate-Term to Long-Term Outcomes after Radiofrequency Ablation of Biopsy-Proved Renal Cell Carcinoma

AUTHOR	NO. PATIENTS (NO. TUMORS)	FOLLOW- UP (yr) (RANGE)	TUMOR SIZE (cm) (RANGE)	TECHNIQUE	% LOCAL RECURRENCE- FREE SURVIVAL	% METASTATIC RECURRENCE	% OVERALL DISEASE-FREE SURVIVAL	% CANCER- SPECIFIC SURVIVAL	% OVERALL SURVIVAL
Psutka et al, 2013	185 (185)	Median 6.43 (0.5–13.4)	Median 3 (1–6.5)	Perc	5-yr: 95.2	5-yr MFS 99.4	5-yr DFS 87.6	5-yr CSS 99.4	5-yr OS 73.3
Tracy et al, 2010	160 (179)	Mean 2.25 (0.13–7.5)	Mean 2.4 (1.0–5.4)	Perc and Lap	5-yr: 90	5-yr MFS 95	—	5-yr CSS 99	5-yr OS 85*
Zagoria et al, 2011	41 (48)	Median 4.67 (IQR 3–5.3)	Median 2.6 (0.7–8.2)	Perc	5-yr: 88	5-yr MFS 93	5-yr DFS 83†	1/41 (2.4) died of RCC	5-yr OS 66
Olweny et al, 2012	37 (37)	Median 6.5 (IQR 5.8–7.1)	Median 2.1 (IQR 1.8–2.8)	Perc and Lap	5-yr: 91.7	5-yr MFS 97.2	5-yr DFS 89	5-yr CSS 97.2	5-yr OS 97.2
Levinson et al, 2008	18 (18)	Mean 4.8 (3.4–6.7)	Mean 2.1 (1–4)	Perc	5-yr: 79.9	5-yr MFS 100	5-yr DFS 79.9	5-yr CSS 100	5-yr OS 58.3
McDougal et al, 2005	16 (20)	Mean 4.6 (4–6)	Mean 3.2 (1.1–7.1)	Perc	4-yr: 91	4-yr MFS 100	—	4-yr CSS 100	4-yr OS 68.7
Atwell et al, 2013	222 (256)	Mean 2.8 (1.2–4.1)	Mean 1.9 (0.6–3)	Perc	5-yr: 98.1	5 yr: 98.1‡	—	5 yr: 98.7‡	—

*Overall survival for entire cohort, including 22% with nondiagnostic or benign histology.

†No recurrences observed in patients with tumors less than 4 cm in size.

‡Patients with no history of RCC.

CSS, cancer-specific survival; DFS, disease-free survival; IQR, interquartile range; Lap, laparoscopic; MFS, metastasis-free survival; OS, overall survival; Perc, percutaneous; RCC, renal cell carcinoma.

TABLE 62-2 Intermediate-Term to Long-Term Outcomes after Cryoablation for Biopsy-Proved Renal Cell Carcinoma

AUTHOR	NO. PATIENTS (NO. TUMORS)	FOLLOW UP (yr) (RANGE)	TUMOR SIZE (cm) (RANGE)	APPROACH	% LOCAL RECURRENCE- FREE SURVIVAL	% METASTATIC RECURRENCE	% OVERALL DISEASE-FREE SURVIVAL	% CANCER- SPECIFIC SURVIVAL	% OVERALL SURVIVAL
Aron et al, 2010	55 (55)	Median 7.8 (5-11)	Mean 2.3 (0.9-5.0)	Lap	87.3	89 MFR	5-yr DFS 81	5-yr CSS 92	5-yr OS 84
Guazzoni et al, 2010	44	Mean 5.1	Median 2.14 (0.5-4)	Lap	93.2*	95.5 MFS	—	5-yr CSS 100	5-yr OS 93.2
Tanagho et al, 2012	35	Mean 6.3 (SD 3.3)	Mean 2.5 (SD 0.98)	Lap	6-yr RFS 80	6-yr MFS 100	6-yr DFS 80	6-yr CSS 100	6-yr OS 76.2

*Although these patients received salvage therapy by radiofrequency ablation or radical nephrectomy, the authors did not include them in their analysis of recurrences.
CSS, cancer-specific survival; DFS, disease-free survival; Lap, laparoscopic; MFS, metastasis-free survival; OS, overall survival; RFS, recurrence-free survival.

nephrectomy. In addition to varying time points for defining success ranging from days to months, surgical approach may confound initial success rates. In particular, compared to partial nephrectomy and cryotherapy, which has been generally reported in the literature using either an open or laparoscopic technique, the majority of RFA cases are performed percutaneously. Because percutaneous treatments are considered to be easily repeatable, physicians performing the procedure may be less aggressive with their initial treatment compared to those approaching a malignancy in an open or laparoscopic fashion. Surgeons performing percutaneous ablation, therefore, may be more accepting of persistent disease on short-term follow-up, presuming that the tumor may be completely ablated with a second, minimally invasive procedure. Indeed, several studies have demonstrated similar recurrence-free survival rates between CA and RFA when taking into account the percutaneous versus laparoscopic approach (Matin et al, 2006; Permpongkosol et al, 2006). Conversely, others comparing laparoscopic and percutaneous ablation have demonstrated inferior initial treatment outcomes with the percutaneous approach compared to the laparoscopic approach but without any difference in CSS or recurrence-free survival (Derweesh et al, 2008; Hui et al, 2008; Malcolm et al, 2009).

Several meta-analyses have evaluated the risk for local tumor recurrence after CA and RFA (Kunkle et al, 2008; Novick et al, 2009; El Dib et al, 2012). For these studies, local recurrence was most often defined as any evidence of residual disease remaining in the treated kidney after the primary ablation procedure. Using this definition, the AUA Guidelines Panel examined 10 studies of CA and 10 studies of RFA and determined a local recurrence-free survival of 90.6% (83.8% to 94.7%) for CA and 87.0% (83.2% to 90%) for RFA (Novick et al, 2009). When compared to alternative extirpative treatments, both CA and RFA demonstrated significantly higher rates of local recurrence despite a shorter overall duration of follow-up, with no significant difference in local recurrence-free survival between CA and RFA and no difference in metastasis-free survival or CSS between ablation and surgical excision. Similarly in a more recent meta-analysis, El Dib and associates (2012) reviewed 31 case series (20 CA, 11 RFA) and found no difference in the clinical efficacy (89% vs. 90%) between CA and RFA, respectively.

Several authors sought to compare the two ablation methods to one another as well as to extirpative surgery. Kunkle and colleagues (2008), using less stringent inclusion criteria than the previously mentioned study by El Dib and associates (2012), performed a meta-analysis comparing outcomes with partial nephrectomy, CA, RFA, and active surveillance, including 40 studies and 936 tumors undergoing ablation. The relative risk for local recurrence was significantly higher with CA (relative risk [RR] 7.45) and RFA (RR 18.23), respectively, when compared to partial nephrectomy, although there was no difference in metastasis-free survival among any approaches. A follow-up study by the same authors, in which 77% of CA cases were performed open or laparoscopically compared to just 6% of RFA cases, reported a local tumor progression of 5.2% after CA and 12.9% after RFA. Again, there was no significant difference in the incidence of metastases associated with any of the tested variables by univariate or multivariate regression analyses, including ablation modality. A recent cohort study using data from the SEER registry found that patients undergoing nephron-sparing surgery had a 5-year disease-specific survival that was improved by 1.7% over ablation (Whitson et al, 2012). However, there was no significant difference in the risk for death when comparing the two ablative technologies. Interestingly, the authors noted that the difference in disease-specific survival between nephron-sparing surgery and ablation has decreased over time, possibly indicating improved outcomes from ablative procedures as a result of increased experience, improved patient selection, and technical modifications.

In addition to surgical factors and their influence on outcomes after ablative procedures, long-term follow-up data suggest that tumor size is a significant indicator of ablation success. Best and associates (2012) found that the 5-year overall

local recurrence-free survival in 108 biopsy-proved RCCs was 95% for those with tumors smaller than 3 cm, but only 78% for those with tumors 3 cm or larger ($P = .002$). Similarly, Psutka and colleagues (2013) demonstrated a 5-year local recurrence-free survival and overall disease-free survival of 96.1% and 91.5% with tumors smaller than 4 cm (T1a) compared with 91.9% and 74.5% in a comparative group of 42 patients with tumors larger than 4 cm (T1b). With regard to CA, Tanagho and colleagues (2012) demonstrated a 6-year overall disease-free survival of 80%, with tumor size 2.6 cm or greater found to be the only significant predictor of oncologic failure on multivariate analysis.

Metastatic Recurrence-Free Survival

For the purpose of evaluating metastasis-free survival, the AUA Guidelines Panel defined metastatic recurrence as any disease present in the body other than in the treated kidney or associated renal fossa after primary treatment. Based on this definition, mean metastatic recurrence-free survival was 95.3% (91.1% to 97.5%) for CA and 97.5% (94.8% to 98.8%) for RFA (Novick et al, 2009). There was no significant difference in metastatic recurrence-free survival between tumor ablation and extirpative treatments, including laparoscopic and open partial and radical nephrectomy. Importantly, ablative procedures had the shortest follow-up, underscoring the need for more long-term follow-up of patients undergoing thermal ablation.

As seen in Tables 62-1 and 62-2, over the last several years, multiple centers have reported on their intermediate- to long-term outcomes, including multiple series with more than 5 years of follow-up for RFA (Tracy et al, 2010; Zagoria et al, 2011; Best et al, 2012; Olweny et al, 2012; Psutka et al, 2013) and CA (Aron et al, 2010; Tanagho et al, 2012). Although the presence of confounding factors precludes meaningful comparisons among these studies, these data seem to support the fact that outcomes for ablative procedures are durable beyond 5 years and up to 10 years.

Cancer-Specific Survival

The AUA meta-analysis published in 2009 evaluated the risk for dying from RCC after CA or RFA and concluded that CSS was 95.2% (89.2% to 97.9%) with CA and 98.1% (95.2% to 99.2%) with RFA. CSS was significantly higher with laparoscopic partial nephrectomy than for CA, but there was no significant difference in CSS between laparoscopic partial nephrectomy and RFA. There also was no significant difference in CSS between CA and RFA. Again, selection bias and short duration of follow-up may confound these results. More recent publications reporting on long-term outcomes have verified a CSS ranging from 78% to 100% for CA (Aron et al, 2010; Tanagho et al, 2012) and approximately 98% for RFA (Zagoria et al, 2011; Olweny et al, 2012; Psutka et al, 2013).

Overall Survival

Patients undergoing ablative procedures tend to be older and have more comorbidities than those undergoing extirpative surgery (Novick et al, 2009). Thus the mean overall survival rate after ablative procedures is typically 75% to 85% at 5 years (Tracy et al, 2010; Zagoria et al, 2011; Psutka et al, 2013). The higher overall survival rates previously published by the AUA Guidelines Panel for CA (95.8%) and RFA (93.7%) likely reflect the shorter follow-up of studies used in their analysis. There does not appear to be any significant difference in overall survival between CA and RFA. Interestingly, the Guidelines Panel did find a higher overall survival for patients undergoing open partial nephrectomy than radical nephrectomy, which may be related to a deleterious effect of chronic kidney disease associated with open radical nephrectomy (Tan et al, 2012). As ablative procedures have shown similar, if not improved, renal function when compared to partial nephrectomy, long-term data in younger cohorts may show a potential overall improved survival rate for ablation compared to radical nephrectomy (Faddegon et al, 2013).

Cryoablation versus Radiofrequency Ablation

Any debate regarding the superiority of CA versus RFA is subject to the same faults, confounders, and ambiguities as the aforementioned comparisons between in-situ tumor ablation and extirpation. Beyond issues of ill-defined radiologic and pathologic end points, there is considerable variability in patient selection, tumor size and location, technique, and approach (laparoscopic vs. percutaneous), as well as inherent bias for a particular ablative modality. To date, there are no data that directly compare percutaneous and laparoscopic CA to its respective RFA counterparts.

Two large single-institution studies with significant experience with both CA and RFA have reported comparable oncologic outcomes, impact on renal function, and complication rates. In 2006, [Hegarty and colleagues](#) compared outcomes in a somewhat disparate cohort of 164 laparoscopic CA procedures and 82 percutaneous RFA procedures. Although there was no significant difference in tumor size between the two groups, the RFA cohort contained more patients with central tumors and tumors in solitary kidneys, which likely accounted for the higher radiographic evidence of disease persistence or recurrence noted in patients who underwent percutaneous RFA (11% vs. 2% for laparoscopic CA). Importantly, there was no significant impact on renal function with either modality and the short-term CSS for CA and RFA were comparable at 98% and 100%, respectively. Recently, [Atwell and associates \(2013\)](#) reported their single-institution contemporary outcomes comparing percutaneous ablation with either RFA or CA. Overall, in their experience with 445 tumors 3 cm or smaller over a 10-year period (256 RFA, 189 CA), the local tumor recurrence rate was 3.2% for RFA at a mean of 2.8 years and 2.8% for CA at a mean of 0.9 year. In patients with biopsy-proved RCC, there was no difference in local recurrence-free survival at 1 (100% vs. 97.3%), 3 (98.1% vs. 90.6%), and 5 years (98.1% vs. 90.6%), when comparing RFA and CA, respectively.

Ultimately, the result of these three recent meta-analyses offer the most insight into the comparative oncologic merit and potential limitations of CA and RFA ([Kunkle and Uzzo, 2008](#); [Novick et al, 2009](#); [El Dib et al, 2012](#)). It appears that there is no significant difference in the risk for local tumor recurrence, disease progression/metastasis, CSS, and overall survival between CA and RFA.

Laparoscopic versus Percutaneous Renal Tumor Ablation

One limitation when comparing series of renal tumor ablation to each other is the variability in technique. The assumption that the success of a laparoscopic and percutaneous ablation is comparable remains debatable. Indeed, until recently the vast majority of CA procedures were approached laparoscopically, whereas more than 95% of RFA procedures are performed percutaneously. [Crouzet and colleagues \(2009\)](#) retrospectively compared similar cohorts of 244 laparoscopic renal CA procedures with 63 percutaneous renal CA procedures. There was no significant difference in renal functional outcomes between the two groups, and patients undergoing percutaneous ablation had a shorter length of stay. With a minimum follow-up of 2 years, the percutaneous cohort demonstrated a higher incomplete treatment rate and need for re-treatment; however, there was no difference in overall survival, CSS, and recurrence-free survival between the two groups. Similar studies comparing laparoscopic and percutaneous tumor ablation have confirmed these findings for both RFA and CA ([O'Malley et al, 2006](#); [Derweesh et al, 2008](#); [Hinshaw et al, 2008](#); [Hui et al, 2008](#); [Malcolm et al, 2009](#)).

In comparison to these studies, [Finley and colleagues \(2008\)](#) reported their 4-year experience with laparoscopic and percutaneous renal CA in 37 patients with 43 tumors. Operative time and duration of hospitalization were significantly shorter with the percutaneous approach, but there was no significant difference in the number of incomplete ablations. Similarly, [Leveillee and colleagues \(2013\)](#) reported their experience with laparoscopic and percutaneous RFA in 274 patients with 292 tumors. The radiographic recurrence rate for either approach was only 4%.

KEY POINTS: ONCOLOGIC OUTCOMES

- The interpretation of oncologic outcomes after renal tumor ablation is challenging and subject to confounding variables such as the inclusion of nonmalignant tumors.
- When compared to alternative extirpative treatments, both CA and RFA demonstrate significantly higher rates of local recurrence, albeit they can be salvaged with repeat ablation or surgery.
- There is no apparent significant difference in metastatic recurrence-free survival when comparing RFA and CA to each other or against extirpative treatments.
- Any discussion of oncologic efficacy regarding ablative technologies must focus on long-term markers of success, such as metastasis-free survival, CSS, renal function preservation, and quality-of-life outcomes.

COMPLICATIONS

As part of the recently published small renal mass guidelines from the AUA, a meta-analysis comparing urologic and nonurologic complications after CA, RFA, and alternative extirpative approaches was performed ([Novick et al, 2009](#)). The incidence of major urologic complications with renal CA and RFA was 4.9% (range 3.3% to 7.4%) and 6.0% (4.3% to 8.2%), respectively. Major nonurologic problems occurred in 5% (3.5% to 7.2%) of patients undergoing CA and 4.5% (3.2% to 6.2%) of those undergoing RFA. The risk for major urologic complications was lower with ablative techniques than with either laparoscopic or open partial nephrectomy. There was no significant difference in urologic complications with CA versus RFA.

The majority of complications that occur with renal ablation are minor, with major complications occurring in as few as 2% of cases ([Johnson et al, 2004](#)). However, up to 20% of complications may require hospital readmission, procedural intervention, or transfusion ([Johnson et al, 2004](#)). Laparoscopic ablation tends to have a higher rate of complications than percutaneous ablation, with an estimated one third of laparoscopic ablation complications occurring as a result of laparoscopic technique ([Johnson et al, 2004](#)). Complications decrease significantly, regardless of surgical approach, with increasing operative experience.

To objectively determine the risk for complications, several authors reported on the use of standardized scoring systems for determining complication severity as well as the risk for complications. Several studies on extirpative surgery for renal malignancy have demonstrated that the RENAL nephrometry score ([Kutikov and Uzzo, 2009](#)) can predict both surgeon preference and postoperative complications ([Canter et al, 2011](#); [Rosevear et al, 2012](#)). Accordingly, in a retrospective review of 77 laparoscopic CAs performed at three high-volume centers, [Okhunov and colleagues \(2012\)](#) reported their complication rates based on low (4 to 6), moderate (7 to 19) or high (10 to 12) nephrometry scores. Overall, their cohort had a complication rate of 19.5%, including 9.5% with major complications. There was a significant association with tumor complexity and complications, with no complications in the low complexity cohort compared to 35% and 100% of those with moderate or high nephrometry scores, respectively. Similarly, [Schmit and colleagues \(2013\)](#) reported their extensive experience with 679 percutaneous tumor ablations, stratifying patients by renal complexity based on nephrometry score to predict outcomes and complications of percutaneous ablation (both CA and RFA). In their series, 5.6% of patients developed major complications, as graded by the Clavien-Dindo classification system ([Dindo et al, 2004](#)), including 7.8% of CAs and 2.7% of RFAs. Patients with complications had a higher mean nephrometry score than those who did not experience complications (8.1 vs. 6.8). Patients with high-complexity tumors (nephrometry score 10 to 12) had a risk of 14.3% for major complications. Although there was a clear difference between complications with regard to ablative technology (CA

vs. RFA), the results were difficult to compare because the authors typically performed CA on larger, more complex lesions and RFA on more exophytic and smaller lesions. A subsequent report from our institution examining only RFA (both percutaneous and laparoscopic) indicated an overall complication rate of 7.5%, with major complication rate of 2% (Seidman et al, 2013). Overall there was no significant difference in postoperative complications based on nephrometry complexity in this group of RFA-only patients.

The most common complication after renal tumor ablation is pain or paresthesia at the percutaneous probe insertion site, occurring in up to 8% of patients (Farrell et al, 2003b). The current generation of cryoprobes comes with thermal insulation along the shaft, which has led to a decrease in freezer burns as were seen with prior generations. The active portion of the RFA probe is only along the most distal aspect. However, with RFA, to prevent inadvertent nerve damage, tract ablation should be performed only long enough to remove the probe from the kidney and surrounding the Gerota fascia. Electrical skin burns after RFA, which may occur at the site of the grounding pads, should be incredibly rare and can be avoided by placing the pads at the exact same level on the patient's posterior thigh (McDougal et al, 2005). Because energy returning to the generator travels in the shortest arc, the pads should be placed perpendicular to the long axis of the thigh to increase surface area for energy dissipation.

Complications from damage to surrounding intra-abdominal organs can be minimized through appropriate patient selection, preoperative planning, and good surgical technique. Cross-sectional preoperative imaging is essential to determine if a tumor should be managed with a laparoscopic or percutaneous approach. For patients in whom there may be a concern regarding adjacent organs, additional imaging can be obtained with the patient in various positions to plan an appropriate needle path. Patients with anterior tumors, tumors close to the collecting system, or without a suitable access tract on preoperative imaging, should be scheduled for laparoscopic ablation or have consideration for displacement of organs using intraprocedural hydrodissection. **Ideal patients for percutaneous treatment are those with posterior tumors, those with tumors located more than 0.5 cm from the ureteropelvic junction or renal pelvis, and those with tumors at least 1 cm from surrounding bowel.**

Urothelial damage may manifest as minor hematuria, hematuria with significant clots, or urinary tract obstruction. Patients with hematuria should be managed conservatively, unless they present with significant hemorrhage, at which time they can be managed with selective angioembolization. There have been several reports of urinary fistula or collecting system injury after RFA as well as CA (Gervais et al, 2005a, 2005b; Janzen et al, 2005; Brown and Bhayani, 2007). **Permanent urothelial damage may manifest as either calyceal obstruction or ureteral obstruction if damage occurs at the ureteropelvic junction or distally (Johnson et al, 2003).** In extreme cases, damage to the urinary tract may result in perirenal urinoma formation or cutaneous urinary fistula. Patients with ureteral obstruction or urine leakage from the collecting system may be managed conservatively or with insertion of an indwelling ureteral stent (Fig. 62-4). Patients with significant urinoma accumulation should have a percutaneous drain placed.

Injury to the pleural cavity resulting in pneumothorax or hemothorax can occur if probes are placed above the twelfth rib to treat upper pole lesions. These complications are typically recognized either during the procedure as breathing difficulties or, with percutaneous access, on routine imaging during tumor treatment. If a simple pneumothorax is identified, it may be treated by aspiration using a small needle inserted into the pleural space at the conclusion of the case. In the absence of a large or persistent pneumothorax, placement of a chest tube should be performed sparingly. Postoperatively, chest pain or shortness of breath should trigger suspicion of pneumothorax and prompt performance of an upright chest radiograph.

Colon injury after renal mass ablation is exceedingly rare and should be largely preventable with appropriate surgical technique. During percutaneous access, tumors within close proximity to

bowel may be dissected free from the treatment area by injecting saline to hydrodissect tissues and develop a safe working space around the tumor (Farrell et al, 2003a; Clark et al, 2006; Lee et al, 2006) (Fig. 62-5). However, reproducibility and surgeon familiarity with the patient's anatomy may make these lesions more suitable for the laparoscopic approach by which the bowel can be safely removed from the operative field. Patients with colon damage should be managed along with a general surgical consultation. Patients with a controlled colon-nephric fistula should be initially managed with placement of a ureteral stent, whereas those with a persistent fistula or with colon-cutaneous fistulas may require surgical diversion or a trial of total peripheral nutrition (Vanderbrink et al, 2007). Patients with frank colon perforation and signs of peritonitis should be managed with prompt surgical exploration.

When treating posterior tumors percutaneously, damage to the nerves running along the posterior abdominal wall can lead to self-limiting neuralgia or neuroapraxias (Lee et al, 2006; Baker, 2007). This complication can be avoided by positioning the patient so that the tumor falls away from the body wall or by hydrodissecting the plane between kidney and body wall (Lee et al, 2006). For patients with multiple posterior tumors or with limited perinephric fat between the kidney and body wall, strong consideration should be given to the laparoscopic approach, in which the kidney can be physically relocated away from the body wall.

Intraoperative or postoperative hemorrhage may occur in up to 11% to 27% of patients undergoing ablative renal procedures (Finley et al, 2008), with transfusion rates of 3.2% (2% to 4.9%) with CA and 2.4% (1.4% to 4%) with RFA (Novick et al, 2009). **The primary risk factor for hemorrhage is the use of multiple probes for treatment of larger renal masses (Lehman et al, 2008).** To decrease the risk for tumor fracture during CA, probes should be given adequate time to thaw, because premature removal increases the risk for tumor fracture and hemorrhage. Bleeding during needle placement may be controlled by proceeding with the ablation, especially with the coagulative nature of RFA. Bleeding during laparoscopic ablation can be managed with the use of hemostatic agents combined with direct pressure. If bleeding continues after ablation, consideration should be given to selective angioembolization. As with any percutaneous needle placement, percutaneous ablation risks damage to the abdominal wall vasculature, and thus care should be taken to avoid intercostal arteries. When injury does occur, it is typically visualized during the procedure with routine imaging. The expanding hematoma may be observed with serial imaging (if rapidly expanding) or serial hematocrit levels (if stable), with only the rare case requiring angiographic embolization.

Postoperative infection after tumor ablation, in the absence of a large hematoma or urinoma, is exceedingly rare, but may be lethal (Schmit et al, 2013). Patients at risk for infection are those with chronic colonization of the urinary tract (e.g., ileal conduit) or active infection at the time of procedure (Bandi et al, 2007; Brown and Bhayani, 2007). When infectious complications do occur, they typically manifest from 1 to 6 months later as a chronic drainage or retroperitoneal abscess. Patients at risk for urinary tract infection (UTI) should be screened by urine culture and treated appropriately before their ablation procedure. Whereas we routinely administer perioperative prophylactic antibiotics at the time of the surgery, some authors suggest broad-spectrum coverage 2 days before and 2 weeks after surgery for patients at high risk for infection (Wah et al, 2008).

NEW ABLATION MODALITIES

High-Intensity Focused Ultrasonography

As an acoustic wave is propagated through tissue, a portion of its energy is absorbed and converted into heat (Madersbacher et al, 1995; Vricella et al, 2009). When the ultrasound waves are focused with an appropriately shaped transducer the temperature at the focal point can exceed the threshold for cell death, while adjacent tissue is spared. At sufficiently high intensities ($>3500 \text{ W/cm}^3$),

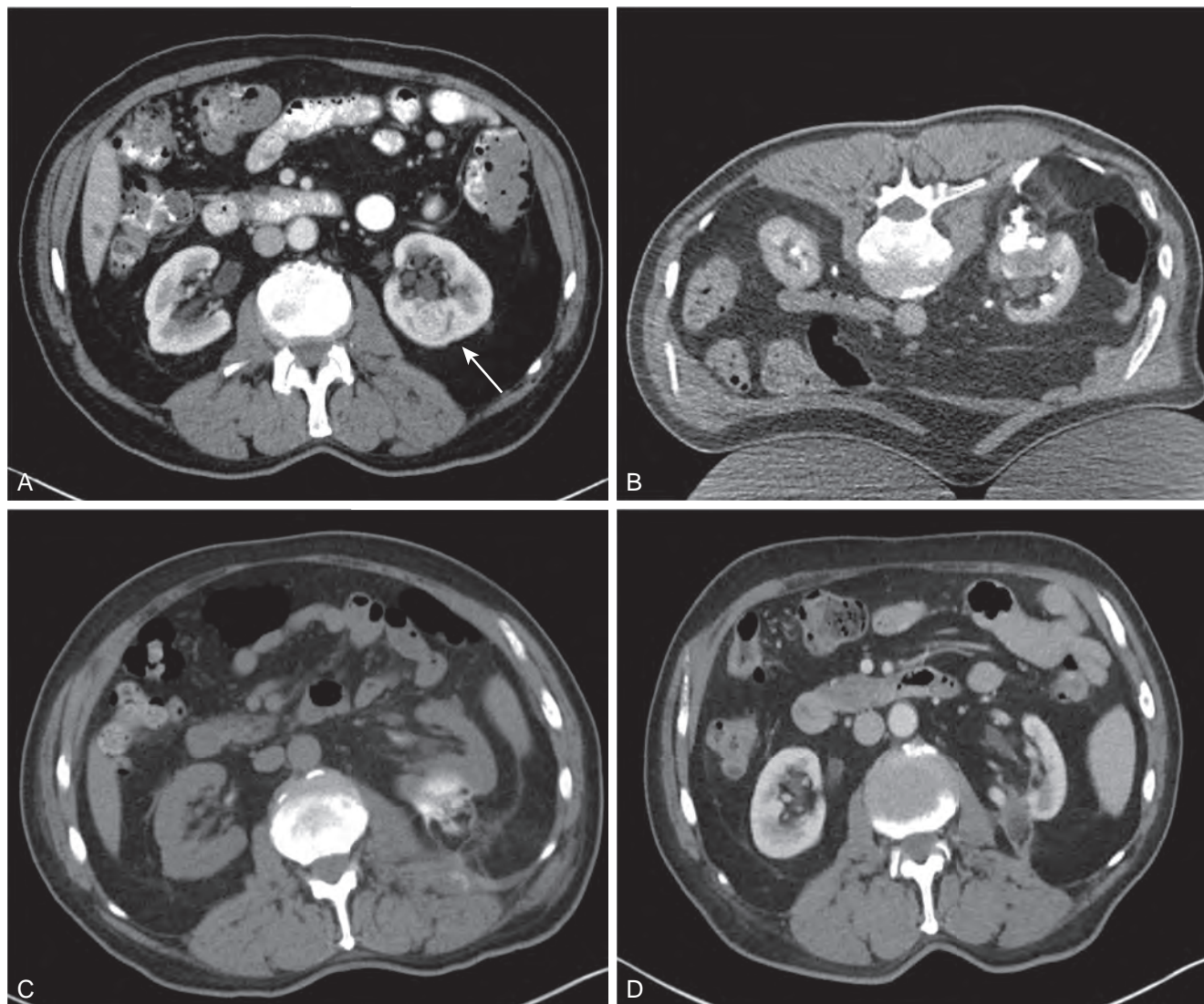


Figure 62-4. Urine leak after percutaneous radiofrequency ablation (RFA). **A**, Preoperative imaging shows 2.5-cm endophytic left renal mass (*arrow*). **B**, Immediate postoperative image after ablation shows urinary extravasation at the site of RFA. **C**, Postoperative day 1 computed tomography (CT) image shows no change in the fluid collection. **D**, Three-year follow-up CT shows involution of the treated area with postoperative halo.

KEY POINTS: COMPLICATIONS FOLLOWING TUMOR ABLATION

- The risk for major urologic complications is lower with ablative techniques (~5%) than with either laparoscopic or open partial nephrectomy. There is no significant difference in urologic complications between CA and RFA.
- For CA, postoperative hemorrhage is the most commonly cited major adverse risk.
- Bleeding is less common with RFA than CA and may be ideally suited for those at risk for postoperative hemorrhage.
- The risk for complications with CA may be predicted by nephrometry score, whereas the same may not hold true for RFA.
- Commonly cited minor complications with CA and RFA include pain and paresthesia at the probe insertion site, UTIs, damage to surrounding structures, and self-limited hematuria.

cavitation and microbubble formation occur that yield extremely high temperatures and a mechanically disrupting “shock wave” effect similar to that seen with extracorporeal shock wave lithotripsy (Kieran et al, 2007). Termed high-intensity focused ultrasound (HIFU), it is a unique thermal ablation technology in that it can be administered in an entirely noninvasive, extracorporeal fashion minimizing or eliminating the risk for tumor seeding, hemorrhage, or urinary extravasation.

HIFU employs a transducer that is used for treatment and monitoring. Under real-time guidance, the HIFU beam is focused on the treatment zone and a defined area is ablated. The transducer is then refocused to ablate overlapping volumes and “paint” a larger overall volume of tissue. Treatment times can be lengthy, with a mean reported duration of nearly 5.5 hours (1.5 to 9 hours) (Köhrmann et al, 2002; Marberger et al, 2005; Häcker et al, 2006). A myriad of parameters, including focal length, type of transducer employed, and type of treatment system have been investigated and are beyond the scope of this chapter.

Although early clinical trials have established the feasibility of transcutaneous HIFU, based on the data available and the existing

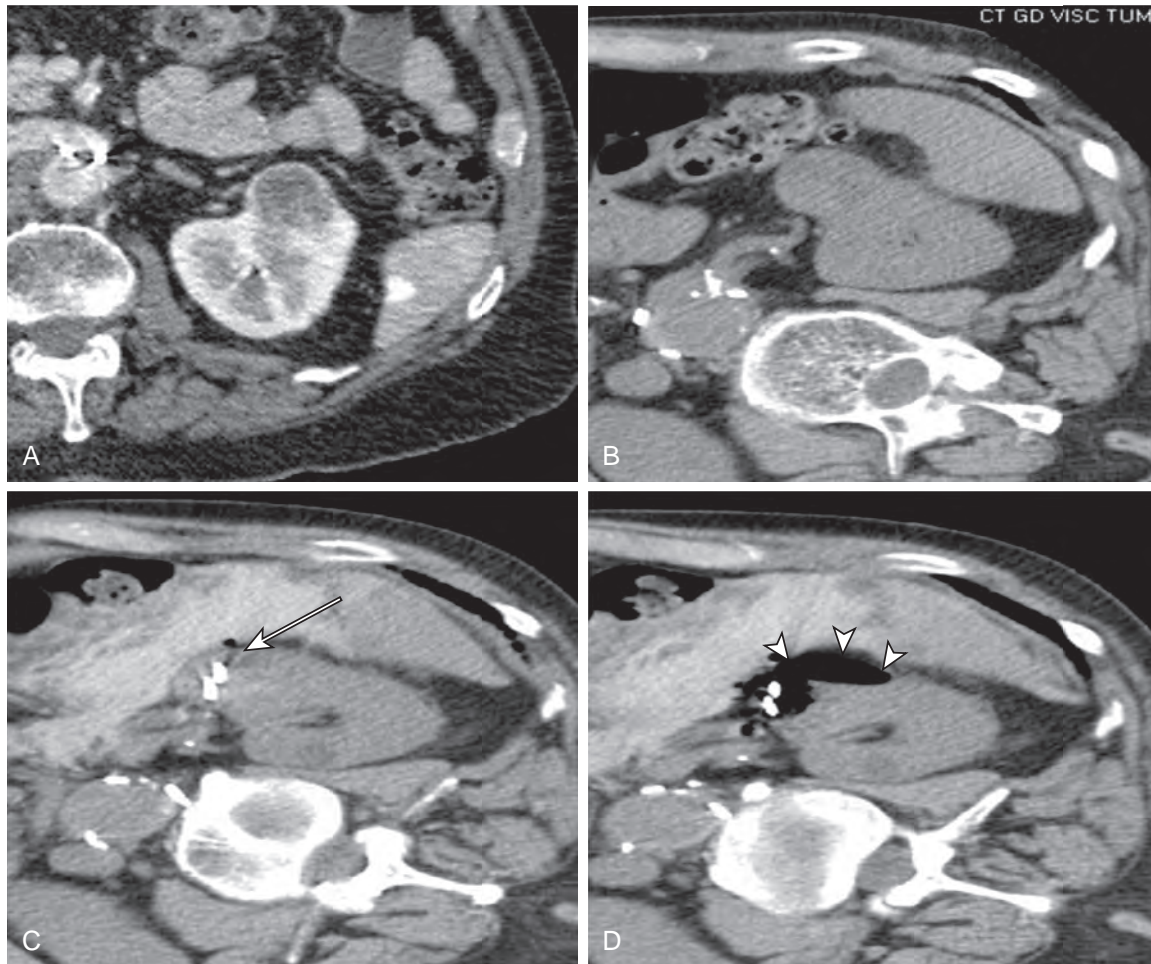


Figure 62-5. Intraoperative hydrodissection for anterior tumor. **A**, Preoperative imaging shows a 3-cm anterior renal mass. **B**, Intraoperative imaging demonstrates large bowel anterior to the lesion. **C**, D5 + contrast is injected percutaneously to hydrodissect bowel and create a window for placement of two cryoprobes (arrow). **D**, Ice ball is demonstrated by hypodense lesion adjacent to the cryoprobes (arrowheads). (Courtesy Fred Lee Jr, MD, University of Wisconsin.)

clinical hurdles, it should be considered only investigational at this time. Two important ablate-and-resect studies have noted incomplete treatment in all specimens, highlighting the challenge of accurate targeting. Vallancien and colleagues (1993) performed transcutaneous HIFU in eight patients, with approximately 10% of the cohort exhibiting skin burns and all specimens demonstrating pathologic evidence of viable tumor. Similarly, Marberger and colleagues (2005) treated 18 renal units with HIFU, and incomplete ablation was noted in all cases at surgery. Ritchie and colleagues (2010) reported a very limited experience with transcutaneous HIFU ablation and subsequent intermediate-term radiographic follow-up. MRI 2 weeks after treatment suggested viable tumor in 8 of 15 treated tumors. Of 14 patients with at least 6 months' follow-up, 10 appeared to have tumor involution with loss of enhancement and shrinkage (mean follow-up 36 months). Purported explanations for these collective incomplete treatments have included poor targeting secondary to respiratory movement and acoustic interference (acoustic shadowing, reverberation, and refraction) and lack of effective intraoperative monitoring of treatment progress. To circumvent these issues, laparoscopic HIFU has been investigated, and though results are favorable its viability as a treatment modality is questionable because it would compete with established laparoscopic CA and RFA techniques (Klingler et al, 2008). In summary, outcomes with renal HIFU have proved inferior to alternative ablative technologies and its use in this regard should be considered investigational.

Radiation Therapy

Historically, radiation therapy was considered ineffective in the treatment of RCC. It remains unclear whether poor outcomes with radiation therapy for RCC are due to an inherent resistance to radiation or to limitations with radiation delivery (Camphausen and Coia, 2008). There are many technical challenges associated with treatment of kidney tumors, including limited radiation tolerance of the normal parenchyma, significant scatter with attendant damage to the surrounding tissues, and difficulty of target localization. Furthermore, conventional external-beam radiation systems are inadequately designed to deliver high doses in a focal manner.

Stereotactic ablative body radiation (SABR) is an emerging treatment paradigm defined by the American Society of Therapeutic Radiology and Oncology as a "treatment method to deliver a high dose of radiation to the target, using either a single dose or a small number of fractions with a high degree of precision within the body" (Potters et al, 2010). As opposed to conventional radiation delivery techniques, modern stereotactic treatment systems employ three-dimensional coordinates to target and compensate for respiratory movement and radiation scatter by automatically tracking, detecting, and correcting for tumor and/or organ movement without interrupting the treatment or repositioning the patient. This tracking system is image guided and dependent on a constant reference point (e.g., fiducial marker) that is continually recognized by the linear accelerator. High-dose radiation beams move in real time

with the respiratory cycle and are therefore extremely accurate (Ponsky et al, 2007). Not only is radiation scatter minimized, but higher doses may be applied in a focal manner that effectively ablates masses in the kidney without compromising overall renal function. Ponsky and colleagues (2003) first evaluated stereotactic radiosurgery in the porcine kidney using the CyberKnife (Accuray, Palo Alto, CA) treatment system. Treatment doses between 24 to 40 Gy resulted in complete necrosis in the treatment zone with no collateral damage to adjacent tissue. Building on this initial animal experience, Ponsky and colleagues (2007) subsequently performed a phase I study on three human patients with a mean renal tumor size of 2 cm. A total of 16 Gy was administered in a fractionated fashion. Patients were followed for 8 weeks, after which a partial nephrectomy was performed. No adverse events or radiation toxicities were noted. Histopathology demonstrated residual RCC in two patients and no evidence of viable tumor in the remaining patient.

Svedman and colleagues (2006) performed a retrospective study evaluating the efficacy and safety of stereotactic radiosurgery in the management of inoperable or metastatic primary RCC. Thirty patients with 82 lesions underwent treatment with varied dose/fractionation schedules. At a median follow-up of 52 months, complete response was noted in 21% of patients, with another 58% demonstrating a partial/stable response.

A critical and systematic review of SABR for primary RCC recently identified 10 studies consisting of 126 patients treated with between one and six fractions (Siva et al, 2012). The most common treatment regimen was 40 Gy over five fractions. Median or mean follow-up ranged from 9 to 57 months. Local control was defined only radiologically and was estimated at 94% at 2 years. The weighted rate of grade 3 or higher adverse effects was only 3.8% with the most common being radiation dermatitis and enteritis.

Certainly, the responsiveness of RCC to stereotactic radiosurgery in the aforementioned trials argues against its radioresistant reputation. Presently its use should be considered experimental because there is no consensus for dose fractionation or technique. With improved treatment protocols and well-designed prospective trials, SABR ultimately may play a significant role in the treatment of RCC.

Microwave Ablation

Microwave ablation (MWA) delivers energy through semiflexible probes that are inserted directly into the target lesion and functions in a similar fashion to RFA. Medical applications of microwave energy operate in the 900-MHz to 2.45-GHz range of the electromagnetic spectrum and create rapid water ion oscillation in the tissue and frictional heat. The degree of tissue penetration and heat produced is related to the water content of the target tissue, which can be more difficult to predict in the heterogeneous kidney parenchyma environment (Rehman et al, 2004; Moore et al, 2010). MWA is capable of achieving treatment temperatures ($>60^{\circ}\text{C}$) with greater rapidity than RFA and is not limited by tissue charring and desiccation as experienced with RFA. These qualities may translate into more efficient treatment times and may make MWA less susceptible to the heat sink phenomenon (Liang and Wang, 2007).

MWA technology was initially designed for the percutaneous treatment of liver tumors and has enjoyed considerable success in this capacity. Its use in the management of renal tumors remains investigational, with no standardized protocols for its use and with only sporadic clinical feasibility studies reported. Clark and colleagues (2007) performed a phase I study in which 10 patients underwent MWA of suspected RCC at the time of radical nephrectomy. When examined pathologically, lesions as large as 5.7 cm \times 4.7 cm \times 3.8 cm were achieved with complete and uniform tissue necrosis. In 2008, Liang and colleagues first reported a percutaneous ablation experience in 12 patients under ultrasound guidance. No significant adverse events were reported, and at a median follow-up of 11 months, no cancer recurrence was noted on imaging. In contradistinction, Castle and colleagues (2011) reported more sobering 38% recurrence rate in 10 patients over an 18-month follow-up period. Most recently, the only direct comparison of MWA to partial

nephrectomy reported comparable 3-year recurrence-free survival of 90% and 97%, respectively (Guan et al, 2012).

At this point, MWA offers considerable promise as an alternative thermal ablative technology. However, larger prospective studies are necessary to better understand the optimal tumor characteristics, risks, and morbidity. At this time it should remain investigational.

Laser Interstitial Thermal Therapy

Laser interstitial thermal therapy (LITT) employs specialized laser fibers to deliver energy directly into tissue. These fibers emit laser light that is converted to heat, achieving tissue necrosis. Thus far, LITT has relied on neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers and diode lasers. Results have been difficult to interpret owing to the small number of treated patients and a lack of clinical follow-up (Williams et al, 2000; Dick et al, 2002; Gettman et al, 2002b). The use of LITT remains investigational.

Irreversible Electroporation

Irreversible electroporation (IRE), is a novel nonthermal method for ablation of living tissue that potentially offers advantages over RFA and CA. Electroporation is a process whereby an electric field applied across cells generates nanoscale pores within cellular membranes that can be either reversible or lethally irreversible depending on the magnitude of electricity applied. IRE is produced through a series of electrical pulses delivered by a single (bipolar) or multiple (monopolar) electrodes. With appropriate modulation it is able to ablate a substantial and reproducible amount of tissue by increasing cell membrane permeability that ultimately leads to cell death (Edd et al, 2006). The result is a nonthermal effect that preserves the extracellular matrix, tissue scaffolding, ductal structures, and large blood vessels (Edd et al, 2006; Deodhar et al, 2011).

Because of the potential to avoid the shortcomings of thermal ablation, there is a great deal of interest in applying IRE to ablation of renal tumors. Although IRE has been shown to be effective in ablating liver and prostate tissue, these results cannot be readily extrapolated to the kidney, which is substantially different given the vigorous arterial blood supply, complex collecting system, and presence of urinary solutes. The efficacy of IRE ablation of renal parenchyma was first described by Tracy and colleagues (2011). When IRE bipolar and monopolar electrodes (Angiodynamics, Queensbury, NY) were used to perform laparoscopic ablations on porcine kidneys, histopathologic evaluation revealed absence of cellular viability immediately after IRE treatment that evolved to diffuse cellular necrosis by 7 days and chronic inflammation, cellular contraction, and fibrosis by day 14. In addition to its effect on the parenchyma, IRE appeared to provide some urothelial sparing with initial ulceration followed by signs of early repair and viability.

Other authors subsequently confirmed these findings using image-guided percutaneous placement of IRE electrodes. Deodhar and associates (2011) used CT-guided placement of monopolar electrodes and reported that the IRE lesions were characterized by nonenhancing hypodense ablation zones immediately after treatment with no identifiable ablation zone by 3 weeks in the majority of animals. Additionally, there were no cases of urinary extravasation or evidence of collecting system injury in any of the cases, confirming the potential connective tissue-sparing effects of IRE.

There is very limited clinical experience with IRE. Pech and coworkers (2011) designed a phase I trial evaluating safety of the technology in six patients with tumors 2.5 to 3.5 cm scheduled for extirpative surgery (partial or radical nephrectomy). Electrodes were placed under ultrasound guidance and delivered using cardiac synchronization. All patients tolerated the procedure well, with no changes identified during the procedure in regard to pulse rate, mean blood pressure, central venous pressure, or changes in ST segment on electrocardiogram. Acutely, 15 minutes after treatment ablated lesions were examined with H&E staining, which showed cellular swelling but was inadequate at assessing postablative cellular viability. In summary, the experience with IRE ablation of

renal tumors is very limited and its use in this regard should be considered investigational.

Targeted Embolization and Ablation

Owing to the heat sink phenomenon with RFA, highly vascular central lesions or lesions positioned adjacent to the renal hilum are often inadequately ablated. Studies estimate treatment failures to be as high as 40%. In an attempt to address conductive heat loss, investigators have performed selective arterial embolization before RFA (Yamakado et al, 2006; Gebauer et al, 2007; Mahnken et al, 2009). Theoretically, selective embolization should allow for more homogeneous heating and improved tissue necrosis. Clinical reports are sporadic and anecdotal. Therefore the use of targeted angioembolization before RFA remains investigational.

KEY POINTS: NEW ABLATION TECHNOLOGIES

- Although there are a number of promising ablation modalities on the horizon, the majority of these should be considered investigational at this time.
- The most promising future ablation modalities appear to be stereotactic radiosurgery, microwave thermotherapy, and IRE. However, significant study is required to further determine their potential benefits compared to the well-established methods of CA and RFA.

CONCLUSIONS

Once considered experimental and appropriate only for patients with significant comorbidities, CA and RFA are currently considered viable alternatives to extirpative management. In-situ ablation confers less treatment-related morbidity than either open or laparoscopic partial nephrectomy and offers comparable renal function preservation compared with partial nephrectomy. CA and RFA are technically less challenging than other nephron-sparing approaches, though learning curves exist for patient selection, tumor targeting, probe deployment, and generator use. Results from recent meta-analyses demonstrate modestly inferior local tumor control compared with partial and radical nephrectomy, but with equivalent cancer-specific and overall survival. Interpretation of treatment

success remains challenging with existing protocols, and long-term follow-up is needed to confirm these findings. No prospective literature currently exists that addresses the superiority of CA or RFA. Ultimately, the decision to treat a small renal mass with an ablative technology should take into account tumor-related characteristics, patient demographics and comorbidities, and the values and desires of the patient.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Prognostic Factors

Surgical Management of Metastatic Renal Cell Carcinoma

Immunologic Approaches in the Management of Advanced Clear Cell Renal Cell Carcinoma

Molecular Basis for Targeted Approaches in Clear Cell Renal Cell Carcinoma

Targeted Molecular Agents in Clear Cell Renal Cell Carcinoma

Systemic Therapy for Non–Clear Cell Variants of Renal Cell Carcinoma

Renal cell carcinoma (RCC) is a term that includes a variety of cancers arising in the kidney and encompasses several histologically, biologically, and clinically distinct entities (Linehan et al, 2007, 2009). An estimated 63,920 new cases of cancer arising in the kidney or renal pelvis were diagnosed in 2014 in the United States (Siegel et al, 2014). Approximately one third of all newly diagnosed RCC patients present with synchronous metastatic disease and an additional 20% to 40% of patients with clinically localized disease at diagnosis will eventually develop metastases (Skinner et al, 1971; Rabinovitch et al, 1994; Bukowski, 1997). Metastatic RCC is almost always fatal, with 10-year survival rates of less than 5% (Bukowski, 1997; Motzer et al, 1999, 2000; Motzer and Russo, 2000; Négrier et al, 2002); patients with metastatic disease account for the majority of deaths (approximately 13,860 a year in the United States) related to RCC (Siegel et al, 2014).

Advances in our understanding of the genetic and molecular changes underlying the individual subtypes of RCC have led to the development of novel agents designed to reverse or modulate aberrant pathways contributing to renal oncogenesis. These “targeted” therapeutic strategies have largely supplanted other treatment modalities in the management of metastatic clear cell kidney cancer; however, surgery, irradiation, and cytokine therapy remain appropriate choices in the management of selected patients with advanced clear cell RCC. More recently, the recognition that agents modulating T-cell function may have activity against a variety of solid tumors, including RCC, has reinvigorated interest in immune-based strategies; the efficacy of several immune “checkpoint” inhibitors in clear cell RCC is currently being evaluated in several phase III studies. Lastly, the advent of techniques that allow comprehensive interrogation of the cancer genome have allowed identification of hitherto unrecognized alterations affecting diverse cellular functions, including carbohydrate and amino acid metabolism as well as chromatin remodeling, in clear cell RCC. Although the precise contribution of these changes in the genesis and progression of kidney cancer remains to be determined, it is hoped that a better understanding of these pathways will spawn additional strategies to combat what remains an incurable group of malignancies.

Although agents effective in clear cell RCC are often used in patients with other subtypes of RCC, there is scant evidence from prospective studies to justify their utility in non–clear cell RCC variants. Elucidation of aberrant oncogenic pathways in papillary, chromophobe, and other variants of RCC has paved the way for evaluation of targeted therapeutic approaches in these histologic subtypes (Linehan et al, 2009).

PROGNOSTIC FACTORS

Patients with metastatic RCC generally have a poor prognosis, with the majority succumbing to their disease. Ten-year survival in patients diagnosed with metastatic disease was estimated to be less than 5% in the era of cytokine therapy and is unlikely to change significantly with the advent of targeted therapy. However, several clinical features, such as a long time interval between initial diagnosis and appearance of metastatic disease and presence of fewer sites of metastatic disease, have been observed to be associated with better outcome. Conversely, poor performance status and the presence of lymph node and/or liver metastases have long been recognized to be associated with shorter survival. Investigators at the Memorial Sloan Kettering Cancer Center (MSKCC) evaluated a variety of clinical and laboratory parameters in 670 patients enrolled in various clinical trials of chemotherapy or immunotherapy from 1975 to 1996 in an effort to identify those pretreatment factors that were able to best predict outcome (Motzer et al, 1999). In a multivariate analysis, a poor performance status (Karnofsky score <80), an elevated serum lactate dehydrogenase level (>1.5 times the upper limit of normal), a low hemoglobin (less than the lower limit of normal), an elevated corrected calcium concentration (>10 g/dL), and lack of prior nephrectomy were independent predictors of a poor outcome (Table 63-1 and Fig. 63-1). Patients could be stratified into three distinct prognostic groups based on these five poor prognostic factors (see Table 63-1). The overall survival (OS) times in patients with no adverse factors (favorable-risk group), one to two risk factors (intermediate-risk group), and more than three risk factors (poor-risk group) were 20 months, 10 months, and 4 months, respectively (Motzer et al, 1999). Subsequently, the same group of investigators identified poor performance status, high serum calcium, low hemoglobin, elevated lactate dehydrogenase, and a short time interval from initial diagnosis to initiation of systemic therapy (<1 year) as factors that could best predict a poor outcome in 463 patients receiving interferon-based therapy in the first-line setting (Motzer et al, 2002). This prognostic model was found to be predictive of survival in an independent data set derived from patients treated at the Cleveland Clinic, providing independent, external validation of the proposed model (Mekhail et al, 2005). Similar prognostic schemes have also been proposed by the Groupe Français d’Immunothérapie (Négrier et al, 2002), the International Kidney Cancer Working Group (Manola et al, 2011), and investigators from the University of California, Los Angeles (Tsui et al, 2000).

Modifications of these prognostic schemes as well as identification of reliable molecular markers are under investigation as

TABLE 63-1 Adverse Prognostic Factors and Risk Stratification Based on Adverse Prognostic Factors in 670 Patients Treated with Chemotherapy or Immunotherapy at the Memorial Sloan Kettering Cancer Center

ADVERSE PROGNOSTIC FACTORS		
Karnofsky performance score <80%		
Elevated lactate dehydrogenase (>1.5 times upper limit of normal)		
Low hemoglobin (< lower limit of normal)		
Elevated corrected calcium (>10 mg/dL)		
Absence of prior nephrectomy		
RISK STRATIFICATION BASED ON ADVERSE PROGNOSTIC FACTORS		
RISK GROUP	NO. OF ADVERSE PROGNOSTIC FACTORS	MEDIAN OVERALL SURVIVAL
Good	0	20 months
Intermediate	1-2	10 months
Poor	3-5	4 months

Data from Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999;17:2530–40.

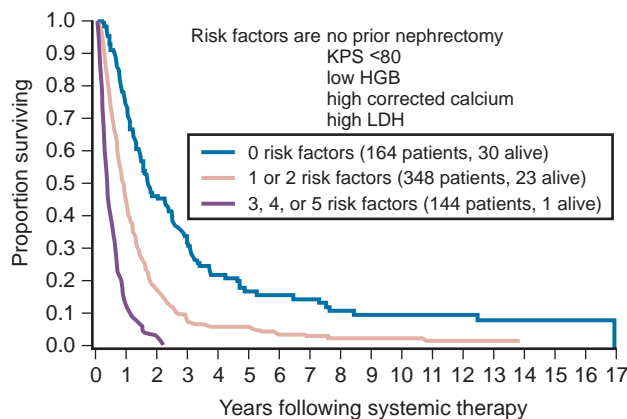


Figure 63-1. Survival analysis stratified according to risk group in 670 patients treated with chemotherapy or immunotherapy at the Memorial Sloan Kettering Cancer Center (n = 656; 14 patients missing one or more of the five risk factors were excluded). HGB, hemoglobin; KPS, Karnofsky performance score; LDH, lactate dehydrogenase. (From Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999;17:2530–40.)

suitable predictors of response to and survival after therapy with newer targeted agents against vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathway components (Choueiri et al, 2007, 2008b; Motzer et al, 2008a). The most comprehensive effort to define prognostic factors in patients undergoing therapy with VEGF pathway antagonists was undertaken by the International Metastatic Renal Cell Carcinoma Database Consortium. Using data from a group of 645 patients treated with first-line VEGF-targeted agents at several U.S. and Canadian centers, the Database Consortium investigators confirmed the prognostic relevance of several components of the MSKCC model (performance status, hypercalcemia, anemia, and time from diagnosis to treatment); neutrophilia and thrombocytosis were identified as additional, independent predictors of poor outcome (Heng et al, 2009). Patients were divided into three risk categories based on the

TABLE 63-2 Adverse Prognostic Factors and Risk Stratification Based on Adverse Prognostic Factors in 849 Patients Treated with First-Line Vascular Endothelial Growth Factor (VEGF) Targeted Therapy

ADVERSE PROGNOSTIC FACTORS		
Karnofsky performance score <80%		
Neutrophilia (> upper limit of normal)		
Low hemoglobin (< lower limit of normal)		
Elevated corrected calcium (> upper limit of normal)		
Thrombocytosis (> upper limit of normal)		
<1 year from diagnosis to VEGF-targeted therapy		
RISK STRATIFICATION BASED ON ADVERSE PROGNOSTIC FACTORS		
RISK GROUP	NO. OF ADVERSE PROGNOSTIC FACTORS	MEDIAN OVERALL SURVIVAL
Good	0	43.2 months
Intermediate	1-2	22.5 months
Poor	3-6	7.8 months

Data From Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol* 2013;14:141–8.

number of adverse prognostic factors associated with their disease. This model was validated by the same group in an independent cohort of 849 patients and also shown to be comparable to other prognostic models such as the MSKCC model. In their updated analysis, median OS was 43.2 months in patients with no risk factors, 22.5 months in those with one or two risk factors and 7.8 months in those with three or more risk factors (Heng et al, 2013) (Table 63-2). Validated prognostic models are used in clinical practice to help make appropriate management decisions as well as in the design and interpretation of clinical trials.

SURGICAL MANAGEMENT OF METASTATIC RENAL CELL CARCINOMA

Debulking or Cyto-reductive Nephrectomy in Patients with Metastatic Renal Cell Carcinoma

The role of cytoreductive nephrectomy preceding systemic therapy has been extensively studied in the era of cytokine therapy. The impetus for exploring this approach in metastatic RCC was provided both by the perception that bulky tumors might inhibit key components of the immune system critical for combating cancer and by observations suggesting that removal of large primary tumors may provide clinical benefit. To support this practice, early proponents of cytoreductive nephrectomy had cited (1) the rare but well-described occurrence of spontaneous regression of metastatic lesions after nephrectomy (Bloom, 1973; Middleton, 1980; Snow and Schellhammer, 1982; Marcus et al, 1993); (2) preclinical data suggesting that large primary tumors may inhibit T-cell function (Kudoh et al, 1997; Bukowski et al, 1998; Ling et al, 1998; Uzzo et al, 1999a, 1999b); and (3) the inability of systemic agents, particularly cytokines, to induce meaningful responses in primary renal tumors in most patients (Sella et al, 1993; Rackley et al, 1994; Wagner et al, 1999). However, the risk of perioperative morbidity and mortality and the inability of a significant proportion of patients undergoing nephrectomy to subsequently receive systemic therapy clearly underlined the need for unequivocal evidence of clinical benefit as well as the ability to identify patients likely to benefit from this approach.

Nephrectomy as the sole therapeutic intervention in the context of metastatic disease is unlikely to alter outcome, as

suggested by small retrospective analyses (Dekernion et al, 1978). However, several retrospective studies have demonstrated the feasibility of a combined modality approach in which nephrectomy is followed by cytokine therapy, with some suggesting that this approach may favorably impact response and survival. Investigators from the National Cancer Institute (NCI) reported their experience in 195 patients undergoing nephrectomy followed by high-dose interleukin-2 (IL-2) therapy between the years 1985 and 1996 (Walther et al, 1997b). An overall response rate of 18% (including a complete response rate of 4%) after IL-2 therapy was observed in this study. A notable finding that emerged from this study was that although the majority of patients underwent successful resection of the primary tumor, only 107 of 195 (55%) went on to receive IL-2 therapy. Rapid postoperative disease progression and perioperative surgical and medical morbidity were the most common factors preventing delivery of systemic therapy, suggesting that careful patient selection may play an important role in the successful application of this combined modality approach. The impact of patient and/or disease characteristics on outcome was further highlighted by a retrospective study addressing this issue. In Bennett and associates' (1995) series of 30 patients, which included several patients with unfavorable performance status (Eastern Cooperative Oncology Group [ECOG] 2) and multiple metastatic sites, including patients with brain or liver metastases, only 7 (23%) were able to proceed with IL-2 after nephrectomy. Conversely, in a series that included only patients with favorable clinical/prognostic factors (e.g., good performance status, minimal comorbidity, no liver or brain metastases), the majority of patients were able to proceed to systemic therapy after nephrectomy, with high response rates (35% to 40%) and OS (median 20 to 22 months) after cytokine-based treatment (Fallick et al, 1997; Figlin et al, 1997). More recently, in a population-based analysis of more than 5000 patients with metastatic kidney cancer identified in the Surveillance, Epidemiology, and End Results database, cytoreductive nephrectomy appeared to be associated with a better overall and cancer-specific survival (Zini et al, 2009). Although these retrospective analyses and small single-arm prospective studies confirmed the feasibility of a tandem surgical-cytokine therapeutic approach, their major contribution was in laying the foundation for controlled, prospective studies to determine if outcomes with cytokine therapy could be improved by prior nephrectomy.

The most compelling evidence in support of cytoreductive nephrectomy is provided by two randomized phase III studies

conducted by the Southwest Oncology Group (SWOG) and the European Organisation for Research and Treatment of Cancer (EORTC). The larger of the two studies, SWOG trial 8949, randomized 241 patients with metastatic RCC to receive interferon alfa-2b either as initial therapy or after cytoreductive nephrectomy (Flanigan et al, 2001). Salient eligibility criteria included a histologic diagnosis of kidney cancer (all histologic subtypes were allowed); good performance status (ECOG 0 or 1); presence of a resectable primary renal tumor; no prior chemotherapy, irradiation, or immunotherapy; and adequate organ function. Although there were no significant differences in the response rates to interferon observed in the two study arms, OS was improved in the surgery-plus-interferon arm (median 11.1 vs. 8.1 months for interferon alone, $P = .05$) (Fig. 63-2). These data were recapitulated in a smaller EORTC trial (a total of 85 patients randomized to interferon alone or interferon after nephrectomy) that used a similar design and reported a survival advantage favoring the surgery-plus-interferon arm (median OS 17 vs. 7 months, $P = .03$) (Mickisch et al, 2001). A combined analysis of both trials revealed data that were consistent with those reported in the individual trials (Flanigan et al, 2004). These data support the use of cytoreductive nephrectomy in carefully selected patients with metastatic RCC who are likely candidates for subsequent cytokine therapy (data summarized in Table 63-3). Although some patients with non-clear cell histologic subtypes of RCC were included in the aforementioned trials, the role of nephrectomy before systemic therapy in these patients is unclear.

Although widely employed in standard clinical practice, the impact of cytoreductive nephrectomy on outcome in patients receiving VEGF or mTOR pathway inhibitors remains to be determined and is the subject of ongoing prospective randomized trials. At least one retrospective series suggests that patients with metastatic clear cell RCC benefited from undergoing cytoreductive nephrectomy prior to initiation of systemic therapy (Choueiri et al, 2011). Of 314 patients who had received VEGF pathway antagonists, 201 underwent prior cytoreductive surgery, while the remainder ($n = 113$) proceeded to systemic therapy without surgical debulking of their primary tumor. In a univariate analysis, cytoreductive surgery was associated with a more favorable outcome (median OS 19.8 vs. 9.4 months, hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.32 to 0.59, $P < .01$), a difference that persisted after adjusting for confounding prognostic/risk factors (HR 0.68, 95% CI 0.46 to 0.99, $P = .04$). While these data should be interpreted

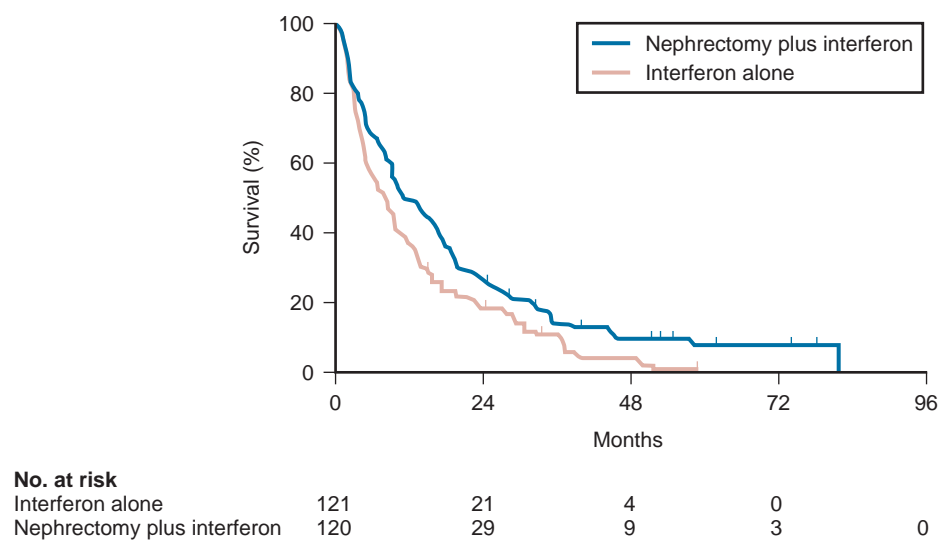


Figure 63-2. Actuarial survival among 241 patients with metastatic renal cell carcinoma randomized to either interferon alfa-2b alone or interferon alfa-2b after cytoreductive nephrectomy. (From Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001;345:1655–9.)

TABLE 63-3 Summary of Outcome in Randomized Studies of Interferon Alfa-2b Alone or Interferon Alfa-2b after Cyto-reductive Nephrectomy in Patients with Metastatic Kidney Cancer

STUDY	NO. OF ELIGIBLE PATIENTS			RESPONSE RATE AFTER IFN (%)			MEDIAN OVERALL SURVIVAL (mo)		
	TOTAL	IFN	NX PLUS IFN	IFN	Nx PLUS IFN	P	IFN	Nx PLUS IFN	P
Flanigan et al, 2001	241	121	120	3.6	3.3	NS	8.1	11.1	.05
Mickisch et al, 2001	83	42	41	12	19	.38	7	17	.03
Flanigan et al, 2004	331	163	161	5.7	6.9	.60	7.8	13.6	.002

IFN, interferon alfa-2b; NS, not significant; Nx, cytoreductive nephrectomy.

with caution because of the inherent bias associated with analyses of this nature, these data nonetheless provide some justification for clinicians who continue the practice of cytoreductive nephrectomy in the era of targeted systemic therapy.

Resection of Metastases

Most patients with metastatic RCC will not achieve a cure or long-term disease remission with currently available systemic agents. However, resection of limited metastatic disease has been reported by several groups to be associated with long disease-free intervals and OS in some patients. It should be emphasized that metastasectomy has not been evaluated systematically in a prospective, randomized fashion and that the favorable outcome ascribed to resection in patients with oligometastatic disease may reflect patient selection bias, inherent differences in tumor biology, and natural history or other confounding factors.

Most studies detailing outcome after metastasectomy are retrospective series. In most series, isolated pulmonary metastases were the lesions most commonly amenable to resection with curative intent. The OS of patients undergoing complete resection of limited metastatic disease is quite impressive, with reported median 5-year survival rates of 35% to 50% in many series (Middleton, 1967; Skinner et al, 1971; Tolia and Whitmore, 1975; O'Dea et al, 1978; Pogrebnik et al, 1992; Kierney et al, 1994; Friedel et al, 1999; Murthy et al, 2005; Russo et al, 2007). The larger of these studies have also attempted to identify patients most likely to benefit from this approach. In a series of 278 patients with recurrent RCC treated at MSKCC, 211 were reported to have undergone either complete (141 patients) or incomplete (70 patients) resection of recurrent tumor from a variety of metastatic sites (Kavolius et al, 1998). In this series, complete or "curative" resection was associated with a longer OS (44% 5-year survival vs. 14% in patients undergoing incomplete resection); multivariate analysis also identified the presence of a solitary metastatic lesion, age younger than 60 years, and a disease-free interval of more than 1 year as favorable prognostic indicators. In addition, some studies have suggested that pulmonary metastases, smaller tumor size (<4 cm in one series), and metachronous lesions are predictors of better outcome after metastasectomy (Friedel et al, 1999; Piltz et al, 2002; Murthy et al, 2005). In a retrospective single-institution study of 125 patients who had one or more metastatic lesions surgically removed, Alt and colleagues (2011) confirmed that patients who underwent complete metastasectomy had improved outcomes; furthermore, complete metastasectomy appeared to be both feasible and predictive of improved cancer-specific survival even in patients with multiple metastatic lesions. Although not supported by convincing evidence of survival benefit from prospective studies, resection of isolated metastatic lesions is a reasonable and widely employed practice in selected RCC patients.

Palliative Surgery

Cytoreductive nephrectomy can be performed with palliative intent in patients with intractable pain, hematuria, constitutional symptoms, or a variety of paraneoplastic manifestations

such as hypercalcemia, erythrocytosis, secondary thrombocytosis, or hypertension. Symptoms such as pain and laboratory abnormalities, including hypercalcemia, can often be effectively managed medically, whereas symptoms such as hematuria may be amenable to alternative treatment approaches (e.g., angioembolization). Furthermore, resection of the primary renal tumor does not always result in clinical benefit; for instance, in one series, only a little over half the patients (7 of 12) with hypercalcemia experienced clinically meaningful reductions in serum calcium levels (Walther et al, 1997a). Cytoreductive nephrectomy with palliative intent is therefore performed relatively infrequently but is appropriate in some patients.

Resection of metastases to alleviate pain or to forestall potentially life-threatening or debilitating complications is indicated in a variety of situations. Patients who may benefit from noncurative resection of metastatic lesions include those with solitary brain metastases, metastatic lesions in weight-bearing bones or joints, or vertebral metastatic lesions with impending spinal cord or radicular compromise (Sundaresan et al, 1986; Kollender et al, 2000; Sheehan et al, 2003). Surgical resection is often combined with radiation and/or systemic therapy in many of the aforementioned situations.

KEY POINTS: CYTOREDUCTIVE NEPHRECTOMY IN METASTATIC RENAL CELL CARCINOMA

- Two randomized studies have demonstrated improved survival in carefully selected metastatic RCC patients undergoing cytoreductive nephrectomy followed by cytokine therapy (interferon- α) compared with those receiving cytokine therapy alone.
- Several patient and/or disease characteristics appear to influence outcome; patients with poor performance status, comorbid medical conditions, rapidly progressive disease, and presence of brain metastases are unlikely to benefit from this approach.
- The role of cytoreductive nephrectomy as a prelude to systemic therapy with currently available novel targeted agents is unclear and is being prospectively studied in ongoing clinical trials. A retrospective analysis appears to suggest benefit for cytoreductive nephrectomy in patients treated with first-line sunitinib.

IMMUNOLOGIC APPROACHES IN THE MANAGEMENT OF ADVANCED CLEAR CELL RENAL CELL CARCINOMA

The host immune system has long been believed to play an important role in the causation and control of RCC. A report detailing spontaneous regression of metastatic lesions after radical nephrectomy provides perhaps the earliest evidence implicating the immune system in the regulation of kidney cancer. The phenomenon of

KEY POINTS: METASTASECTOMY

- Resection of isolated metastatic lesions is appropriate in selected patients.
- Several retrospective studies have suggested that patients undergoing complete resection of isolated metastatic foci may experience long disease-free intervals, with median overall survival rates of 35% to 50% in some reports.
- Several factors are associated with an improved outcome after metastasectomy, including complete resection, presence of solitary metastatic lesions, age younger than 60 years, smaller tumor size, presence of pulmonary metastases, and development of metachronous metastatic disease.
- There are no prospective, randomized studies demonstrating a favorable outcome with metastasectomy. It is therefore possible that the favorable outcome after resection of limited metastatic disease may be a reflection of patient selection bias, differences in tumor biology and natural history, or other confounding factors not related to resection.

KEY POINTS: PALLIATIVE SURGERY IN ADVANCED RENAL CELL CARCINOMA

- In some patients with advanced RCC, cytoreductive nephrectomy may help alleviate symptoms related to the primary tumor (e.g., intractable pain, hematuria) or paraneoplastic manifestations.
- However, nonsurgical options are often effective in palliating symptoms associated with RCC; cytoreductive nephrectomy is hence infrequently performed with purely palliative intent.
- Resection of metastatic lesions (often in combination with radiation or systemic therapy) is sometimes performed for relief of symptoms or to prevent life-threatening or disabling sequelae.

spontaneous regression, thought to represent T- or B-cell-mediated antitumor immunity, has sparked great enthusiasm over the years and generated several reports describing this phenomenon (Braren et al, 1974; Silber et al, 1975; Middleton, 1980; Robson, 1982; Snow and Schellhammer, 1982; Kavoussi et al, 1986; Marcus et al, 1993; Edwards et al, 1996). Although rare (it is estimated that the true incidence of spontaneous regression is less than 1%) and often transient, the presumed immunologic mechanisms underlying this event have nonetheless played an important part in the development of immunotherapeutic approaches in kidney cancer. The presence of immune cells, notably cytotoxic T lymphocytes, in resected tumors and the identification of tumor-associated antigens that can serve as human leukocyte antigen (HLA)-restricted targets

on tumor cells for T cell-mediated cytotoxicity have also kindled interest in immune-based strategies in RCC (Finke et al, 1994; Boon et al, 1997; Ada, 1999; Rosenberg, 1999; Takahashi et al, 2008). Early clinical studies explored the efficacy of agents believed to act as nonspecific stimulators of the host immune system, such as cytokines, with or without adoptive cellular therapy. More recently, investigators have evaluated a variety of novel approaches, including allogeneic immunotherapy, vaccines, and modulators of T-cell function. Most immunotherapy strategies have been directed at clear cell RCC, and the utility of these approaches in non-clear cell variants remains to be explored.

Interferons

The interferons are a group of proteins with diverse biologic functions, including immunomodulatory properties. Interferon- α was one of the earliest cytokines to be evaluated for activity in RCC. Initial trials with interferon utilized leukocyte-derived interferon. The subsequent availability of recombinant interferon- α in the early to mid 1980s allowed investigators to evaluate higher doses of this cytokine in a series of phase II trials. Initial trials demonstrated overall response rates of 16% to 26% in patients treated with interferon- α , and several subsequent trials have confirmed the activity of this agent, with response rates generally in the 10% to 15% range (deKernion et al, 1983; Quesada et al, 1983, 1985; Umeda and Nijijima, 1986; Muss et al, 1987; Rosenberg et al, 1987; Figlin et al, 1988; Quesada, 1989; Minasian et al, 1993; Motzer et al, 2002). The limited long-term survival data available suggest that durable complete responses with this agent are relatively rare (<2%). A variety of dosing schedules and routes have been evaluated to determine the optimal interferon regimen; no single mode of administration or dosing schedule has so far demonstrated superiority over others (Kirkwood et al, 1985; Umeda and Nijijima, 1986; Muss et al, 1987; Minasian et al, 1993). Similarly, the addition of chemotherapy or other cytokines to interferon- α has failed to improve the outcomes seen with single-agent therapy (Rosenberg et al, 1989a; Sella et al, 1992; Ravaud et al, 1994, 1998; Ellerhorst et al, 1997; Tourani et al, 1998, 2003; Dorval et al, 1999; Négrier et al, 2000a, 2000b).

Several prospective, randomized trials evaluating the efficacy of interferon- α have demonstrated a modest but statistically significant improvement in outcome after treatment with this agent. A randomized phase III study that assigned 335 patients to receive either interferon alfa or medroxyprogesterone demonstrated a higher response rate (14% vs. 2%) and OS (median 8.5 vs. 6 months, HR 0.72, $P = .017$) favoring the interferon arm of the study (Medical Research Council Renal Cancer Collaborators, 1999). A second study randomized 160 patients with metastatic RCC to receive vinblastine alone or in combination with interferon alfa-2a; a higher response rate (16% vs. 2.5%) and improved OS (median 16 vs. 9 months, $P = .0049$) with the addition of interferon was observed in this study (Table 63-4) (Pyrrhonen et al, 1999). Two additional randomized studies suggested that vinblastine is unlikely to have contributed significantly to the activity of this combination

TABLE 63-4 Summary of Results from Selected Randomized Trials of Interferon- α in Metastatic Renal Cell Carcinoma

STUDY	AGENT(S)	PHASE	NO. OF PATIENTS: TOTAL (RANDOMIZED)	OVERALL RESPONSE RATE (%)	OVERALL SURVIVAL	
					MEDIAN (mo)	P
Medical Research Council Renal Cancer Collaborators, 1999	IFN vs. MPA	3	335 (167 vs. 168)	13 vs. 7	8.5 vs. 6.0	<.01
Pyrrhonen et al, 1999	IFN + vinblastine vs. vinblastine	3	160 (79 vs. 81)	16 vs. 2.5	15.8 vs. 8.8	<.01
Neidhart et al, 1991	IFN vs. IFN + vinblastine	3	165 (82 vs. 83)	13 vs. 13	NA	NS
Fossa et al, 1992	IFN vs. IFN + vinblastine	3	178 (87 vs. 91)	11 vs. 24	12 vs. 12	NS

IFN, interferon alfa; MPA, medroxyprogesterone acetate; NA, not available; NS, not significant.

by showing that survival was not improved with the addition of vinblastine to interferon alfa (Neidhart et al, 1991; Fossa et al, 1992). Lastly, a meta-analysis of randomized trials of interferon against a variety of agents suggested that interferon-based therapy conferred a survival advantage (Coppin et al, 2005). Despite its relatively modest activity, based on the just-described data and relative ease of administration compared with IL-2, interferon was commonly the agent of choice in the initial treatment of metastatic RCC until the advent of VEGF pathway antagonists.

Interleukin-2

Clinical trials in the early 1980s initially identified IL-2 as an active agent in RCC, with some IL-2-based regimens leading to objective response rates in excess of 30% (Rosenberg et al, 1989b, 1993). In a subsequent report detailing 255 patients treated in a series of phase II trials at the NCI, a more modest overall response rate of 15% (37 of 255 patients) was noted (Fyfe et al, 1996). Several trials conducted by the NCI and the Cytokine Working Group as well as meta-analyses of published data have consistently demonstrated response rates in the range of 15% to 20% (Lotze et al, 1986; Rosenberg et al, 1987, 1989b, 1993; Fisher et al, 1988; Dutcher et al, 1997a). More importantly, 7% to 9% of patients receiving high-dose IL-2 are reported to have achieved complete regression of all metastatic tumor, with the majority of complete responders (>60%) demonstrating no evidence of disease recurrence on long-term follow-up (Fisher et al, 1997, 2000; Rosenberg et al, 1998). There have also been reports of long-term disease-free remission in partial responders whose limited disease burden after IL-2 therapy rendered them amenable to resection of localized metastases. High-dose IL-2 was approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic kidney cancer in 1992, based largely on its ability to induce durable complete responses in some patients.

The initial studies with IL-2 were conducted using an intravenous bolus regimen with doses of 600,000 or 720,000 IU/kg administered every 8 hours as tolerated to a maximum of 15 doses. A major limitation of this dosing regimen is the considerable associated toxicity that has limited its widespread use. Vascular leak syndrome and the resulting hypotension, third-space fluid retention, respiratory compromise, and multiorgan damage are some of the more problematic concomitants of IL-2 therapy and led to an unacceptably high treatment-related mortality rate (2% to 5%) in early studies with this agent (Rosenberg et al, 1987; Kammula et al, 1998). Subsequently, careful patient selection, intensive monitoring schemes, and early interventions with intravenous

fluids, vasopressors, and antibiotics have served to significantly reduce mortality associated with IL-2 (Kammula et al, 1998). However, the significant morbidity and expense associated with delivering bolus high-dose IL-2 have led several investigators to explore alternative regimens aimed at reducing toxicity without compromising efficacy. Numerous single-arm phase II studies have evaluated a variety of alternative regimens, including daily subcutaneous administration and continuous intravenous infusion (Escudier et al, 1994a, 1994b, 1995; Négrier et al, 2000b, 2005, 2008; Atkins et al, 2001). Many of these studies have reported overall response rates of 10% to 30%, suggesting comparable efficacy to high-dose bolus administration based on data from historical controls. However, two randomized studies have demonstrated that, although well tolerated, lower-dose regimens are associated with lower overall response rates, as well as with fewer durable, complete responses (Table 63-5) (Yang et al, 2003b; McDermott et al, 2005). Based on these data, we only recommend high-dose IL-2 regimens in patients being considered for cytokine therapy.

Attempts to enhance the efficacy of IL-2 therapy have led investigators to explore combination therapy with other cytokines, cytotoxic chemotherapy, and adoptive cellular immunotherapy. Early experience with combination cytokine therapy was promising, with one study reporting a 31% overall response rate in patients treated with high-dose bolus IL-2 and interferon (Rosenberg et al, 1989a). However, subsequent studies have indicated that this combination is more toxic and no more effective than IL-2 alone (Ravaud et al, 1994; Bukowski et al, 1997; Dutcher et al, 1997b; Tourani et al, 1998, 2003). A multicenter, randomized phase III study compared the efficacy of intermediate-dose IL-2 administered by continuous intravenous infusion with interferon alfa-2a or the combination in 425 patients with metastatic clear cell RCC (Négrier et al, 1998). Although the combination of IL-2 and interferon resulted in a higher response rate (18.6%) and 1-year event-free survival (EFS; 20%) compared with IL-2 (overall response rate 6.5%, 1-year EFS 15%) or interferon (overall response rate 7.5%, 1-year EFS 12%) alone, there was no significant difference in survival between the groups (Fig. 63-3). Combination therapy also resulted in higher toxicity than either agent given alone. Regimens combining IL-2 and cytotoxic chemotherapy (particularly 5-fluorouracil [5-FU]) have been the subject of numerous studies. Unfortunately, reports of high response rates in initial studies (49% in a study using IL-2, interferon, and 5-FU) could not be reproduced in later studies (Atzpodi et al, 1993; Ellerhorst et al, 1997; Dutcher et al, 2000; Négrier et al, 2000a). Similarly, despite the promise of preclinical and early clinical studies, the addition of ex vivo expanded tumor-infiltrating lymphocytes or lymphokine-activated killer cells to

TABLE 63-5 Summary of Results from Selected Randomized Trials of Interleukin-2 in Metastatic Renal Cell Carcinoma

STUDY	TREATMENT ARMS	NO. OF PATIENTS	DOSE, ROUTE, AND SCHEDULE	RESPONSE		OVERALL SURVIVAL	
				ORR	P	MEDIAN (mo)	P
Négrier et al, 1998	IL-2	138	18×10^6 IU/m ² /day \times 5 days, CIV	6.5		12	
	IFN	147	18×10^6 IU tiw, SC	7.5		13	.55
	IL-2 + IFN	140	IL-2: 18×10^6 IU/m ² /day \times 5 days, CIV IFN: 6×10^6 IU tiw, SC	18.6	.01	17	
Yang et al, 2003b	IL-2	156	720,000 U/kg q8h \times 5 days, IV bolus	21		NA	
	IL-2	150	72,000 U/kg q8h \times 5 days, IV bolus	13	.048	NA	.41
	IL-2	94	250,000 U/day \times 5 days, SC, wk 1 125,000 U/day \times 5 days, SC, wk 2-6	10	.033	NA	.38
McDermott et al, 2005	IL-2	96	600,000 U/kg q8h \times 5 days, IV bolus	23		17	
	IL-2+ IFN	96	IL-2: 5×10^6 IU/m ² q8h \times 3, then 5×10^6 IU/m ² /day \times 5 days/wk, SC IFN: 5×10^6 IU tiw, SC	10	.018	13	.21

CIV, continuous intravenous infusion; IFN, interferon- α ; IL-2, interleukin-2; IV, intravenous; NA, not available; ORR, overall response rate; SC, subcutaneous; tiw, three times a week.

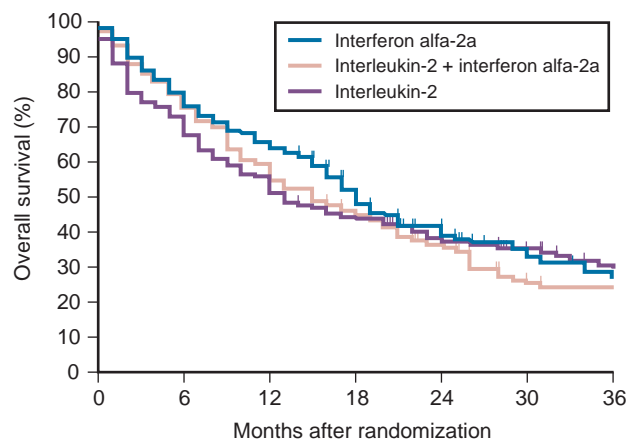


Figure 63-3. Kaplan-Meier curves for overall survival among 425 patients randomized to receive interleukin-2 alone, interferon alfa-2a alone, or both. (From Négrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunothérapie. *N Engl J Med* 1998;338:1272-8.)

high-dose IL-2 has not reliably demonstrated improved clinical benefit and these approaches have been largely abandoned (Rosenberg et al, 1993; Law et al, 1995; Figlin et al, 1999).

Given the considerable toxicity associated with high dose IL-2 and the relatively small proportion of patients who derive benefit from this therapy, identification of predictors of response and long-term outcome has received considerable attention. The predictive value of a variety of histologic, clinical, laboratory, and molecular parameters has been studied. Patients with clear cell RCC appear most likely to benefit from IL-2 therapy, although the exceedingly small number of patients with non-clear cell histologies typically enrolled in studies of IL-2 makes it difficult to draw definitive conclusions about efficacy in this subgroup of patients. Patient performance status, number of metastatic sites, site of metastases, prior nephrectomy, and time from nephrectomy to systemic therapy are some of the factors that may impact outcome. In one study, patients with more than one site of metastasis, those with metastatic disease within 1 year of diagnosis, and those with liver metastases had the worst outcome, with a median survival of 6 months (Négrier et al, 2002). Overexpression of carbonic anhydrase IX (CA-IX or G250) has been observed in a retrospective analysis to be associated with a higher probability of response to IL-2 (Atkins et al, 2005); however, a prospective trial of 120 advanced kidney cancer patients designed to evaluate the impact of prespecified "good risk" clinical features or biomarkers (i.e., CA-IX) on outcome revealed that CA-IX expression was not predictive of response (McDermott et al, 2010). The role of cytokine therapy in the current management of kidney cancer has changed with the availability of novel inhibitors of VEGF and mTOR pathways with activity in clear cell RCC. Single-agent interferon, the previous standard in many institutions, is no longer used in the first-line treatment of clear cell RCC. However, given the inability of newer targeted agents to induce durable responses, high-dose intravenous IL-2 remains a reasonable option in the initial therapy of carefully selected patients with metastatic clear cell RCC.

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation allows the replacement of host or recipient immune and hematopoietic systems with those of a healthy, HLA-compatible donor. The therapeutic potential of hematopoietic stem cell transplantation lies largely in the ability of the transplanted donor graft to generate an allogeneic antitumor immune response known as the graft-versus-tumor effect. This approach has been used successfully with curative

intent in a variety of hematologic malignancies (Thomas et al, 1977; Weiden et al, 1979, 1981). The ability of a variety of immune-based approaches to induce remissions in patients with RCC and evidence suggesting that the host immune system in these patients may be compromised and/or tolerant to tumor cells have led several investigators to evaluate allogeneic hematopoietic stem cell transplantation in kidney cancer.

The approach was initially studied by investigators at the National Heart, Lung and Blood Institute exploring the efficacy of reduced-intensity hematopoietic stem cell transplantation in patients with treatment-refractory metastatic RCC. Eligible patients underwent reduced-intensity conditioning with cyclophosphamide (120 mg/kg) and fludarabine (125 mg/m²) followed by infusion of a granulocyte colony-stimulating factor-mobilized peripheral blood stem cell graft from a 5 of 6 or 6 of 6 HLA-matched sibling donor. The initial experience with hematopoietic stem cell transplantation in metastatic RCC was published by Childs and colleagues (2000). Ten of the first 19 patients treated with this transplant approach had tumor shrinkage, including 3 who had a complete response and 7 who had a partial response. As more recently reported, 74 patients have undergone hematopoietic stem cell transplantation for RCC at the National Institutes of Health. Of these, 73 patients have demonstrated durable engraftment, achieving 100% donor T-cell chimerism by day 100 post-transplant. Twenty-nine of 74 patients (39%) have had a disease response, including 7 complete (9%) and 22 partial (30%) responders (Takahashi et al, 2008). Preliminary data suggest that disease response after hematopoietic stem cell transplantation is a clinically meaningful phenomenon because regression of metastatic RCC appears to be associated with a trend toward improved survival. Survival in nonresponders has been less than 6 months, in contrast to those achieving a partial response, who survived a median 2.5 years post-transplant. Several durable responses have been noted, and the first patient who underwent a transplant remains in complete remission more than 10 years after the procedure. Hematopoietic stem cell transplantation is associated with a variety of adverse events typically associated with conditioning chemotherapy (e.g., pancytopenia), a variety of opportunistic infections, and graft-versus-host disease (GVHD). Eight patients in the just-mentioned series died of transplant-related causes (transplant-related mortality of 11%), most due to GVHD and its attendant infectious complications.

Several other trials have since confirmed the efficacy of this approach in RCC (Table 63-6) (Rini et al, 2001, 2002; Bregni et al, 2002; Artz et al, 2005; Barkholt et al, 2006). However, a Cancer and Leukemia Group B (CALGB) intergroup trial evaluating the feasibility of performing hematopoietic stem cell transplantation for metastatic RCC in a multi-institutional setting in the United States reported no responses in 22 patients undergoing hematopoietic stem cell transplantation from an HLA-matched sibling donor after cyclophosphamide/fludarabine-based conditioning (Rini et al, 2006). Median OS was only 5.5 months, with most patients dying of disease progression (median time to progression of 3 months). Inclusion of a number of patients with multiple adverse prognostic factors, sparing use of donor lymphocyte infusions (only 2 of 22 patients received donor lymphocyte infusions despite disease progression in the majority), and inclusion of patients with non-clear cell histology are some of the factors that may account for the poor outcome observed in this trial. This trial clearly highlights the importance of appropriate patient selection and the need for identifying prognostic factors likely to predict for a favorable outcome. In a European multicenter study of 106 patients undergoing transplantation, chronic GVHD, good performance status (Karnofsky score = 80), administration of donor lymphocyte infusions, and fewer than three sites of metastatic disease were identified as factors favorably impacting survival (Barkholt et al, 2006). Given the high morbidity and mortality with this approach, careful patient selection is of great importance. Hematopoietic stem cell transplantation remains an experimental approach in the management of RCC; strategies for minimizing the toxicity associated with this procedure and maximizing

TABLE 63-6 Summary of Results from Selected Trials of Allogeneic Hematopoietic Stem Cell Transplantation in Metastatic Renal Cell Carcinoma

STUDIES	CONDITIONING AGENTS	GVHD PROPHYLAXIS	aGVHD (II-IV)	cGVHD	TRM	RESPONSE (PR or CR)
Childs et al, 2000; Takahashi et al, 2008	Cy + Flu	CSP (first 25 patients) CSP + MMF (subsequent patients)	55%	21%	11%	39%
Artz et al, 2005; Rini et al, 2001, 2002	Cy + Flu	Tacro + MMF	22%	39%	14%	22%
Bregni et al, 2002	Cy + Flu + thiotepa	CSP + MTX	86%	71%	0%	57%
Barkholt et al, 2006	Multiple Flu-based regimens	CSP ± MMF or MTX	40%	33%	16%	32%
Rini et al, 2006	Flu + Cy	Tacro + MTX	32%	23%	9%	0%

aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CR, complete response; CSP, cyclosporine; Cy, cyclophosphamide; Flu, fludarabine; MMF, mycophenolate mofetil; MTX, methotrexate; PR, partial response; Tacro, tacrolimus; TRM, treatment-related mortality.

antitumor effects are being explored and are required to render this approach more widely applicable.

Immune “Checkpoint” Inhibitors

The host immune response to tumors is a highly complex process that is regulated at multiple levels. The interplay between multiple stimulatory and inhibitory processes determines the nature and extent of the antitumor response generated by the host immune system. Over the last few years, it has become increasingly evident that several inhibitory receptors on effector immune cells, such as CD8⁺ T lymphocytes, play a key role in tightly regulating the immune response to tumors. Furthermore, antitumor responses can be downregulated by activation of T-cell receptors such as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and those mediating programmed death-1 (PD-1).

Pharmacologic targeting of immune checkpoints such as CTLA-4 and the PD-1 axis is being explored currently in many solid tumors, including RCC. A single-arm phase II study of ipilimumab, a monoclonal antibody targeting CTLA-4, demonstrated activity in patients with clear cell RCC, including in some who had previously progressed following IL-2 therapy (Yang et al, 2007). The most notable side effects associated with this agent included autoimmune events such as enteritis and hypophysitis. While autoimmune adverse events were highly predictive of response, they were sufficiently severe enough (grade 3-4 in up to a third of the patients) to dampen enthusiasm for further development of this agent in RCC.

More recently, both PD-1 and its ligands (PD-L1, PD-L2) have attracted attention as potential antitumor targets. While PD-1 is expressed on CD⁺ T cells, PD-L1 and PD-L2 are expressed on the surface of tumor cells; patients whose tumors contain PD-1-positive tumor-infiltrating lymphocytes are more likely to have larger tumors, higher grade tumors, advanced-stage RCC, and sarcomatoid differentiation than patients without PD-1-positive tumor-infiltrating lymphocytes (Thompson et al, 2007). Engagement of PD-1 on T cells by its ligand leads to downregulation of antigen-driven immune responses (Fife et al, 2009; Sznol et al, 2013).

Several antibodies targeting the PD-L1 checkpoint are currently in clinical evaluation (Brahmer et al, 2012; Topalian et al, 2012; Drake et al, 2013). In a large phase I study with multiple expansion cohorts, patients with advanced melanoma, non-small cell lung cancer, castration-resistant prostate cancer, colorectal cancer, or renal cancer were treated with nivolumab (anti-PD-1 antibody) (Topalian et al, 2012). A total of 33 RCC patients were enrolled, and 9 patients (27%) had an objective response. Despite the fairly short follow-up, several durable responses were evident, with five patients demonstrating a response lasting 1 year or more. Furthermore, stable disease lasting 24 weeks or more was seen in an

additional nine patients (27%). Interestingly, pretreatment tumor specimens from 42 patients (5 with RCC) were analyzed for PD-L1 expression on the surface of tumor cells. None of the 17 patients with PD-L1-negative tumors experienced a response while 9 of 25 (36%) with PD-L1 expression had an objective response, suggesting that PD-L1 expression should be further evaluated as a predictive biomarker. As anticipated, several patients experienced adverse events of possible autoimmune etiology, including diarrhea, hypophysitis, and vitiligo.

A second phase I, dose-escalating study evaluating inhibition of the PD-1 checkpoint was conducted with BMS-936559, a PD-L1-specific monoclonal antibody, in patients with advanced solid tumors (Brahmer et al, 2012). Of 75 patients, 17 had RCC; 2 of the 17 RCC patients (12%) had an objective response lasting 4 and 17 months, respectively. Seven additional patients (41%) had stable disease lasting at least 24 weeks.

While promising, these data were obtained from small patient cohorts with a short follow-up duration and must be interpreted with caution. Data from more definitive, ongoing trials of PD-1 and PD-L1 inhibitors are awaited and will determine if the enthusiasm engendered by the phase I data is justified.

MOLECULAR BASIS FOR TARGETED APPROACHES IN CLEAR CELL RENAL CELL CARCINOMA

The development of antagonists of the VEGF pathway in the treatment of clear cell RCC is an often-cited paradigm in the evolution of rational targeted therapeutic strategies and represents a logical progression from identification of an oncogenic cellular pathway to rational drug design and structured clinical evaluation. The earliest clues to the central role played by VEGF in renal oncogenesis came from studies attempting to identify the genetic basis of the von Hippel-Lindau familial kidney cancer syndrome. In the early 1990s, investigators at the NCI studying families with von Hippel-Lindau disease used genetic linkage analysis to identify germline mutations or deletions in the von Hippel-Lindau gene (*VHL*) as the basis for this disease (Latif et al, 1993). Individuals carrying germline *VHL* mutations are at increased risk for developing tumors in multiple organs, including bilateral, multifocal clear cell kidney cancer. The *VHL* gene is a classic tumor suppressor gene, with inactivation of the normal *VHL* allele in affected tissues by a somatic “second hit” required for tumor formation.

The *VHL* gene resides on the short arm of chromosome 3 and encodes the von Hippel-Lindau protein (VHL), which can be synthesized as two alternatively spliced variants (Latif et al, 1993; Gnarr et al, 1996; Iliopoulos et al, 1998; Linehan, 2003). One

of the better-understood functions of the VHL protein is its association with elongins B and C and Cullin 2 (CUL2) to form a protein complex that serves to tag certain cellular proteins for delivery to and degradation by the ubiquitin system (Duan et al, 1995; Pause et al, 1997; Stebbins et al, 1999; Linehan, 2003; Kaelin, 2004). Proteins targeted for ubiquitin-mediated degradation include the α subunits of a group of transcriptionally active proteins known as hypoxia-inducible factors (HIFs) (Iliopoulos et al, 1996; Pause et al, 1997; Maxwell et al, 1999; Cockman et al, 2000; Ohh et al, 2000; Ivan et al, 2001; Jaakkola et al, 2001). In cells with intact VHL function, HIF levels are primarily controlled by ambient oxygen tension. In normoxic conditions, hydroxylation of key proline residues on HIF promotes its association with the VHL/elongin/CUL complex and subsequent degradation; conversely, hypoxia impedes prolyl hydroxylation of HIF and its subsequent degradation, leading to intracellular accumulation of HIF α subunits. Mutations in *VHL* interfere with its binding to either HIF or elongin/CUL2 and promote HIF accumulation even under normoxia. HIF accumulation, in turn, leads to the upregulation of a variety of proangiogenic and growth factors, including VEGF, platelet-derived growth factor (PDGF), transforming growth factor- α , glucose transporter 1, and erythropoietin, which are believed to play critical roles in the development and progression of clear cell RCC (Fig. 63-4) (Duan et al, 1995; Iliopoulos et al, 1996; Kaelin, 2004; Linehan et al, 2007, 2010a). Although originally identified as a germline defect in von Hippel-Lindau families, evidence of somatic *VHL* inactivation by mutation or promoter hypermethylation has been observed in a high proportion of sporadic clear cell tumors (91% in a recent series) (Herman et al, 1994; Gnarr et al, 1996; Zhuang et al, 1996a, 1996b; Nickerson et al, 2008). The recognition of VHL loss as a central event in renal oncogenesis has paved the way for the development of novel agents targeting components of this pathway in the management of metastatic clear cell RCC.

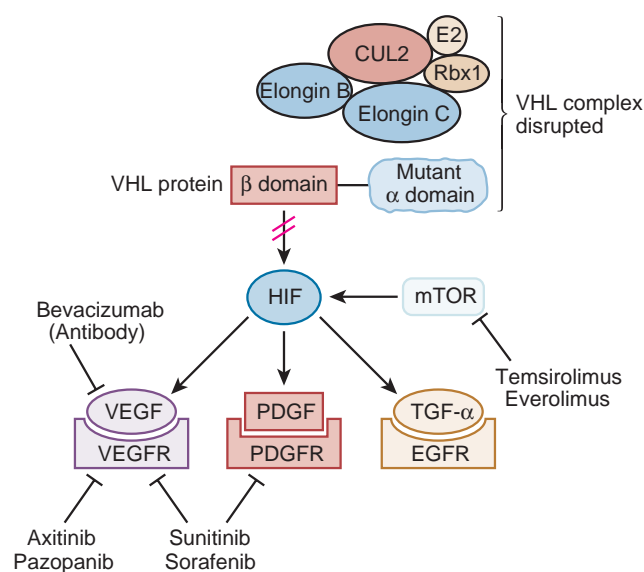


Figure 63-4. Targeting the von Hippel-Lindau (VHL) pathway in clear cell renal cell carcinoma. Loss of VHL activity leads to accumulation of hypoxia-inducible factor (HIF) and several proangiogenic and growth factors that can serve as targets for anticancer drugs. HIF can also be upregulated by mammalian target of rapamycin (mTOR), which promotes HIF translation. EGFR, epidermal growth factor receptor; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; TGF- α , transforming growth factor- α ; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. (Modified from Linehan WM, Bratslavsky G, Pinto PA, et al. Molecular diagnosis and therapy of kidney cancer. *Annu Rev Med* 2010;61:329–43.)

TARGETED MOLECULAR AGENTS IN CLEAR CELL RENAL CELL CARCINOMA

Antagonists of the Vascular Endothelial Growth Factor Pathway

Bevacizumab

Bevacizumab, a humanized monoclonal antibody against VEGF-A, was the first VEGF pathway antagonist used in clinical trials to test the hypothesis that modulation of aberrantly expressed components of the VHL pathway would be associated with clinical activity in clear cell RCC. In a three-arm phase II study, patients with metastatic clear cell RCC whose disease had progressed after prior cytokine therapy were randomized to receive either one of two dose levels of bevacizumab (10 mg/kg or 3 mg/kg administered every 2 weeks intravenously) or placebo (Table 63-7) (Yang et al, 2003a). An interim efficacy analysis performed after 116 patients (of a planned 240 patients) were enrolled in the study demonstrated a significantly longer progression-free survival (PFS) in patients assigned to 10 mg/kg bevacizumab compared with those receiving placebo (4.8 vs. 2.5 months, $P < .001$) (Fig. 63-5). There was no corresponding improvement in OS, although the crossover design used in this trial (patients progressing on placebo were allowed to cross over to bevacizumab) may have influenced this outcome. The overall response rate in patients receiving bevacizumab was modest (objective response rate of 10%, all in patients assigned to the 10-mg/kg dose). The agent was well tolerated, with bleeding, hypertension, fatigue, and proteinuria being some of the more common adverse events reported. Single-agent bevacizumab has not been compared with either cytokines (often used in first-line treatment before the advent of VEGF pathway antagonists) or other VEGF pathway antagonists such as sunitinib in prospective trials.

Several strategies for improving the efficacy of bevacizumab have been explored, including combination with cytokines (interferon- α) and other targeted agents (e.g., erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase activity). A single-arm phase II study of bevacizumab plus erlotinib showed promising activity with an overall response rate of 25% (higher than would be expected with bevacizumab alone based on historical data) and median PFS of 11 months (Hainsworth et al, 2005). However, a subsequent randomized phase II study failed to demonstrate the superiority of this combination (median PFS 9.9 months) over bevacizumab alone (median PFS 8.5 months, $P = .58$) in patients with advanced clear cell RCC (Bukowski et al, 2007). Two large randomized phase III studies have compared the combination of bevacizumab and interferon α to interferon α alone (see Table 63-7). In the CALGB 90206 study of 752 patients with previously untreated metastatic clear cell RCC randomized to one of two treatment arms, a higher response rate (25.5% vs. 13.1%, $P < .0001$) and PFS (8.5 vs. 5.2 months, $P < .0001$) were observed in patients assigned to bevacizumab plus interferon α compared with those receiving interferon α alone (Rini et al, 2008a). A multicenter European trial (AVOREN) with a similar design also reported similar results with PFS (10.2 vs. 5.4 months, $P = .0001$) and an objective response rate (31% vs. 13%) favoring the combination arm (Fig. 63-6) (Escudier et al, 2007b). Updated survival data from both trials were reported, demonstrating no improvement in overall survival associated with the addition of bevacizumab to interferon (Escudier et al, 2010; Rini et al, 2010). While neither study permitted crossover of patients assigned to interferon α at progression, a significant number of patients (>60%) subsequently received anticancer therapy off protocol, potentially confounding overall survival analysis. Both trials reported a higher incidence of some grade 3 adverse events such as hypertension, fatigue, anorexia, and asthenia in patients receiving combination therapy. The CALGB and AVOREN trials were large, well-designed, and well-conducted multicenter studies that suggest that the addition of bevacizumab to interferon may be associated

TABLE 63-7 Summary of Selected Studies of Bevacizumab-Based Regimens in Metastatic Renal Cell Carcinoma

STUDY	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (mo)*	MEDIAN OS (mo)*
Yang et al, 2003a	Bev (10 mg/kg) vs. Bev (3 mg/kg) vs. placebo	Randomized, 3-arm phase II	Cytokine-refractory clear cell	116	10% vs. 0% vs. 0%	4.8 vs. 3.0 vs. 2.5	
Escudier et al, 2007b	Bev + IFN- α vs. IFN- α	Randomized phase III	Previously untreated clear cell	649	31% vs. 13%	10.2. vs. 5.4	NR vs. 19.8
Rini et al, 2008a	Bev + IFN- α vs. IFN- α	Randomized phase III	Previously untreated clear cell	732	25.5% vs. 13.1%	8.5. vs. 5.2	NA
Bukowski et al, 2007	Bev + erlotinib vs. Bev	Randomized phase III	Previously untreated clear cell	104	14% vs. 13%	9.9 vs. 8.5	20 vs. NR

Bev, bevacizumab; IFN- α , interferon alfa; NA, not available; NR, not reached; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

*Statistically significant differences indicated in bold.

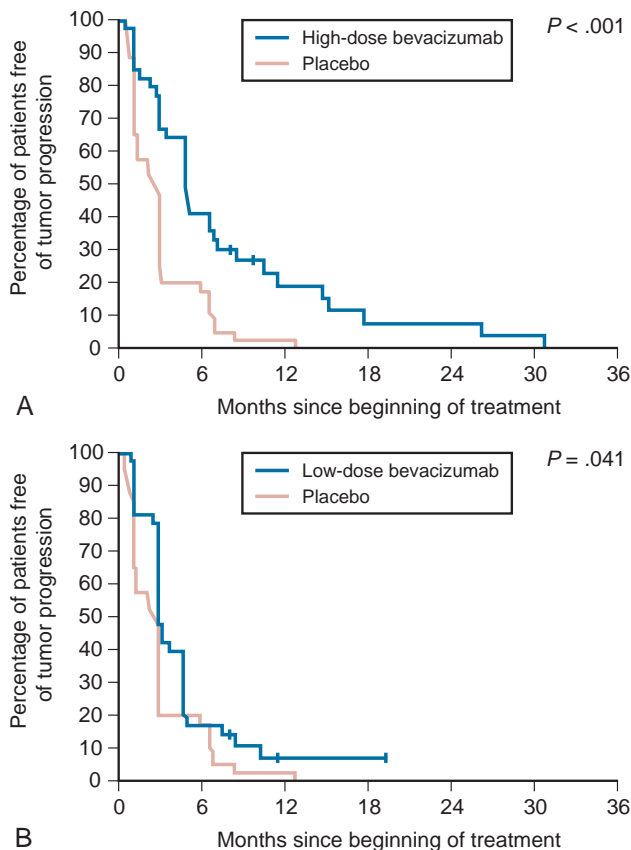


Figure 63-5. Kaplan-Meier analysis of 39 patients assigned to high-dose bevacizumab (10 mg/kg; A) and 37 patients assigned to low-dose bevacizumab (3 mg/kg; B) compared with 40 patients assigned to receive placebo. (From Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427–34.)

with clinical benefit (i.e., improvement in PFS). However, these trials did not include an arm with bevacizumab alone (owing to insufficient evidence of single-agent activity at the time these trials were designed to justify a bevacizumab-only arm), making it difficult to determine if inclusion of interferon in this regimen, with its attendant toxicities, adds meaningful clinical benefit. Interestingly,

the median PFS observed in the combination arm of the CALGB trial (8.5 months) is similar to that observed with bevacizumab alone in a phase II trial of previously untreated patients with clear cell RCC (Bukowski et al, 2007). Lastly, bevacizumab (either alone or in combination with interferon) has not been compared prospectively with VEGF receptor (VEGFR) antagonists such as sunitinib or pazopanib, arguably the current standard of care for most newly diagnosed patients with metastatic clear cell RCC. Bevacizumab is not widely used as a single agent in the initial therapy for metastatic clear cell RCC but may have a role in patients who have failed standard therapy with first-line VEGFR antagonists, either alone or in combination with other agents, particularly interferon. Ongoing and future trials may help determine the best use of this agent in the overall management of patients with clear cell RCC.

Sorafenib

Sorafenib is an oral receptor kinase inhibitor with activity against VEGFR-2, PDGF receptor- β (PDGFR- β), and raf-1. A phase II trial using a randomized discontinuation design provided initial evidence that sorafenib is active in RCC (Table 63-8) (Ratain et al, 2006). Two hundred and two patients were enrolled in this trial, and all of them received 400 mg of sorafenib twice daily for the first 12 weeks. Sixty-five patients who demonstrated stable disease at the end of this period (defined in this trial as within $\pm 25\%$ of baseline) were then randomized either to continued treatment with sorafenib or to placebo. Patients randomized to sorafenib had a superior PFS (24 weeks) versus those receiving placebo (6 weeks, $P = .0087$). A global, multicenter, placebo-controlled randomized phase III trial with 903 patients (the TARGET study) was subsequently undertaken to evaluate the efficacy of sorafenib in patients with metastatic RCC who had previously received cytokine therapy (Fig. 63-7) (Escudier et al, 2007a). This trial echoed the results seen in the phase II trial, with patients randomized to receive sorafenib experiencing a longer PFS (median 5.5 months) versus those receiving placebo (2.8 months, $P < .01$) at a planned interim analysis. After this interim analysis, patients progressing on placebo were allowed to cross over to receive sorafenib. Mature survival data from this trial were subsequently presented and demonstrated no significant difference in OS between the two groups (17.8 months for sorafenib vs. 15.3 months with placebo, $P = .146$) in an intent-to-treat analysis (see Fig. 63-7) (Escudier et al, 2009a). However, if patients who crossed over from placebo to sorafenib were censored, the survival data demonstrated a statistically significant advantage favoring sorafenib (median OS 17.8 vs. 14.3 months, $P = .029$). Results from this exploratory “pre-cross-over” survival analysis suggest that the

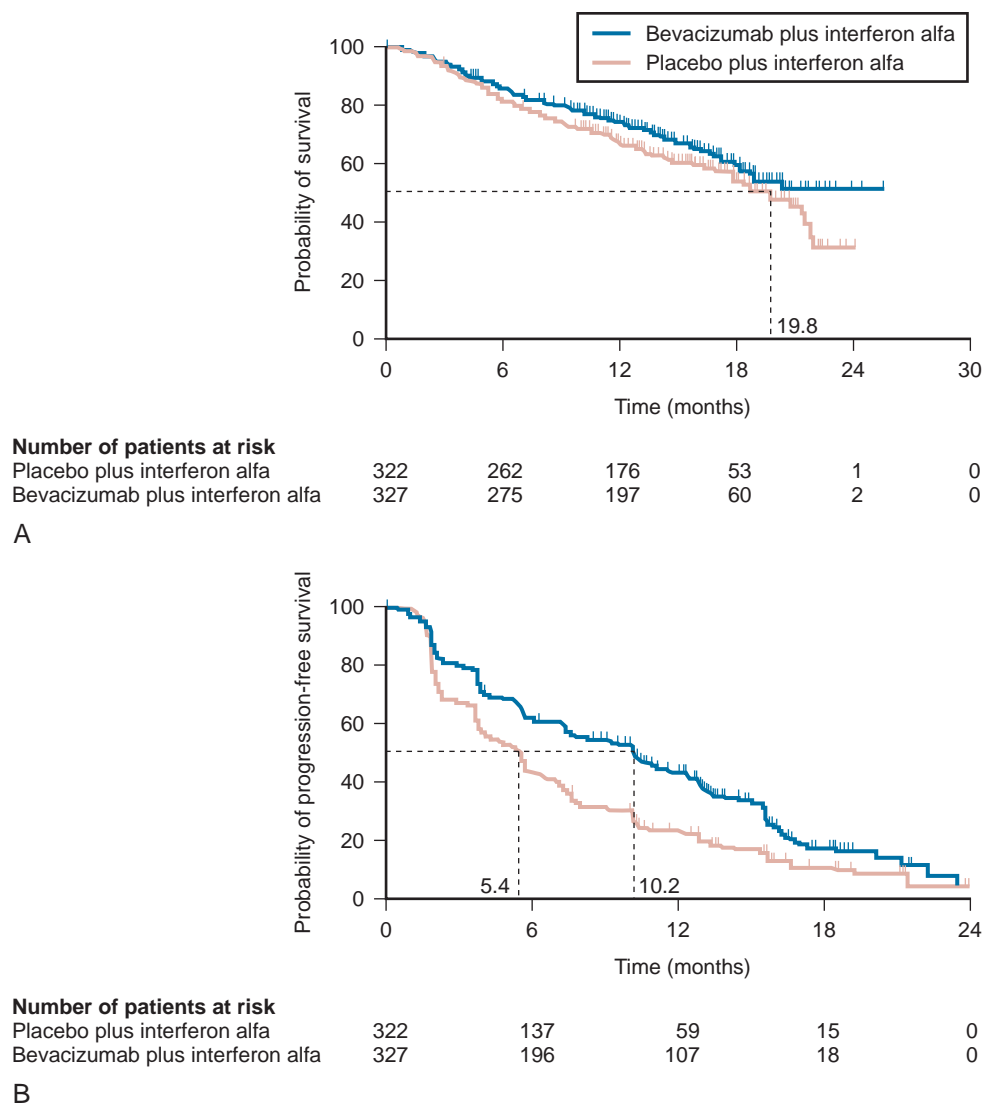


Figure 63-6. Kaplan-Meier analysis of (A) overall survival and (B) progression-free survival in 649 patients assigned to receive interferon alfa alone or in combination with bevacizumab. (From Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007;370:2103–11.)

TABLE 63-8 Summary of Selected Studies of Sorafenib in Metastatic Renal Cell Carcinoma

STUDIES	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (mo)*	MEDIAN OS (mo)*
Ratain et al, 2006	Sorafenib vs. placebo	Phase II randomized discontinuation	Treatment-refractory, all histologic subtypes	202		6 vs. 1.5	NA
Escudier et al, 2007a, 2009a	Sorafenib vs. placebo	Randomized phase III	Cytokine-refractory clear cell	903	10% vs. 2%	5.5 vs. 2.8	17.8 vs. 15.2
Escudier et al, 2009b	Sorafenib vs. IFN- α	Randomized phase II	Previously untreated clear cell	189	5% vs. 9%	5.7 vs. 5.6	NA

IFN- α , interferon alfa-2a; NA, not available; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors. *Statistically significant differences indicated in bold.

survival end point may have been influenced by the crossover design. Overall response rate to sorafenib in this trial was relatively low, with 10% of patients experiencing a partial response; however, more than 70% of patients receiving sorafenib had some degree of tumor regression.

The side effect profile of sorafenib is comparable to that of other agents in this class and includes hypertension, fatigue, rash, hand-foot syndrome, and diarrhea. The efficacy of sorafenib in the first-line setting was investigated in a randomized phase II study that assigned 189 previously untreated patients with

metastatic clear cell RCC to receive either sorafenib or interferon alfa-2a (Escudier et al, 2009b). Although patients receiving sorafenib had a higher likelihood of achieving tumor regression (68% vs. 39%), PFS in the two groups was nearly identical (median 5.7 months for sorafenib vs. 5.6 months for interferon, $P = \text{NS}$) (see Table 63-8). Although sorafenib is FDA-approved for the treatment of advanced kidney cancer, its precise role in the management of these patients remains to be determined

in view of the plethora of VEGFR antagonists currently available or under investigation. Dose-intensive regimens of sorafenib (up to 800 mg twice daily) have been explored in an attempt to enhance the efficacy of this agent, but to date there is no convincing evidence that higher doses offer additional clinical benefit. Currently, sorafenib is infrequently used in the first-line setting. Anecdotal evidence and small case series suggest that patients whose disease has progressed on other VEGFR inhibitors may respond favorably to sorafenib, and the agent is commonly used in patients whose disease has progressed on sunitinib or similar agents.

Sunitinib

Sunitinib is an oral VEGFR kinase inhibitor widely used in the initial treatment of metastatic clear cell RCC. It is a potent inhibitor of VEGFR-2, PDGFR- β , c-Kit, and fms-like tyrosine kinase 3 (Flt3). As with sorafenib, simultaneous targeting of VEGF and PDGF pathways by this agent is likely to act synergistically in inhibiting tumor angiogenesis, by directly disrupting VEGF-mediated vascular endothelial development and proliferation and by interfering with vascular pericyte function, which is dependent on the integrity of PDGF signaling. Initial evaluation of sunitinib was undertaken with two single-arm open-label phase II trials in patients with metastatic RCC, most of whom had previously received cytokine therapy (Motzer et al, 2006a, 2006b). Sunitinib was administered orally at a dose of 50 mg/day during the first 4 weeks of a 6-week cycle in both trials (Table 63-9). Remarkably high overall response rates (30% to 40%) with a median PFS of more than 8.5 months were observed in these trials, leading to the approval of this agent for treatment of advanced RCC by the FDA. A landmark phase III randomized trial comparing sunitinib with interferon- α as first-line therapy in patients with metastatic clear cell RCC further demonstrated the activity of sunitinib in this patient population (Motzer et al, 2007). In this study, 750 patients were randomized to receive either sunitinib or interferon alfa. An interim analysis based on independent, third-party radiologic assessment demonstrated a significantly superior PFS (median 11 vs. 5 months, $P = .001$) and overall response rate (31% vs. 6%, $P = .001$) favoring the sunitinib arm (Fig. 63-8). Gastrointestinal events, particularly diarrhea, dermatologic manifestations such as rash and hand-foot syndrome, constitutional symptoms such as fatigue and asthenia, and hypertension were the most common adverse events associated with sunitinib; bone marrow suppression and hypothyroidism were other notable side effects. Sunitinib also performed better than interferon in a quality-of-life assessment conducted as part of the study. Mature survival data from this study were subsequently reported and demonstrated a clear trend toward superior OS in the sunitinib study arm based on an intent-to-treat analysis (median OS 26.4 vs. 21.8 months, $P = .051$) (Motzer et al, 2009). Based on these data, sunitinib is widely used in the initial management of metastatic clear cell RCC patients in the United States.

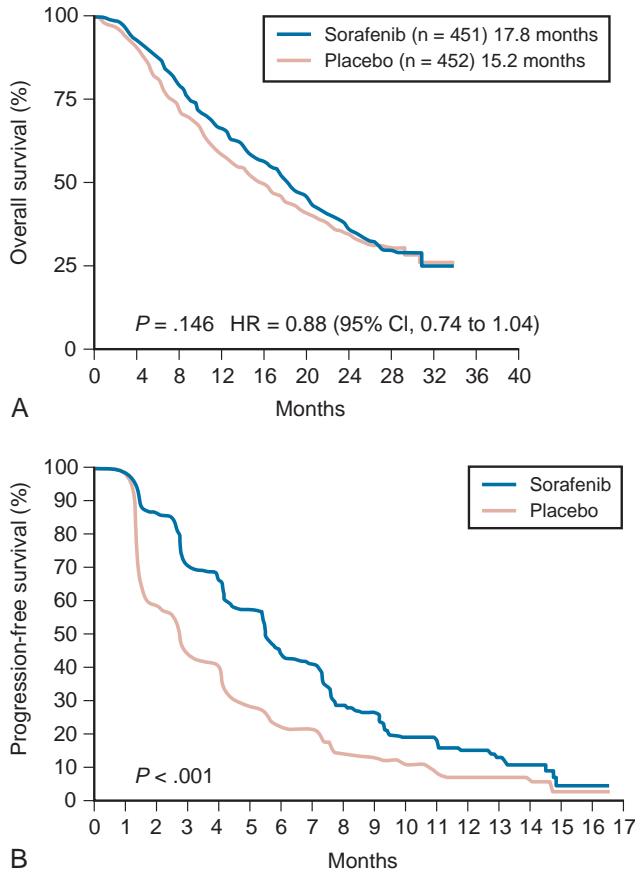


Figure 63-7. Kaplan-Meier analysis of overall survival (A) and progression-free survival (B) in 903 metastatic renal cell carcinoma patients randomized to sorafenib or placebo. CI, confidence interval; HR, hazard ratio. (From Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009;27:3312–8; and Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125–34.)

TABLE 63-9 Summary of Selected Studies of Sunitinib in Metastatic Renal Cell Carcinoma

STUDIES	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (mo)*	MEDIAN OS (mo)*
Motzer et al, 2007, 2009	Sunitinib vs. IFN- α	Randomized phase III	Previously untreated clear cell	750	31% vs. 6%	11 vs. 5	26.4 vs. 21.8
Motzer et al, 2006a	Sunitinib	Single-arm phase II	Cytokine-refractory clear cell	63	40%	8.7	NA
Motzer et al, 2006b	Sunitinib	Single-arm phase II	Cytokine-refractory clear cell	106	44%	8.1	NA

IFN- α , interferon alfa; NA, not available; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors. *Statistically significant differences indicated in bold.

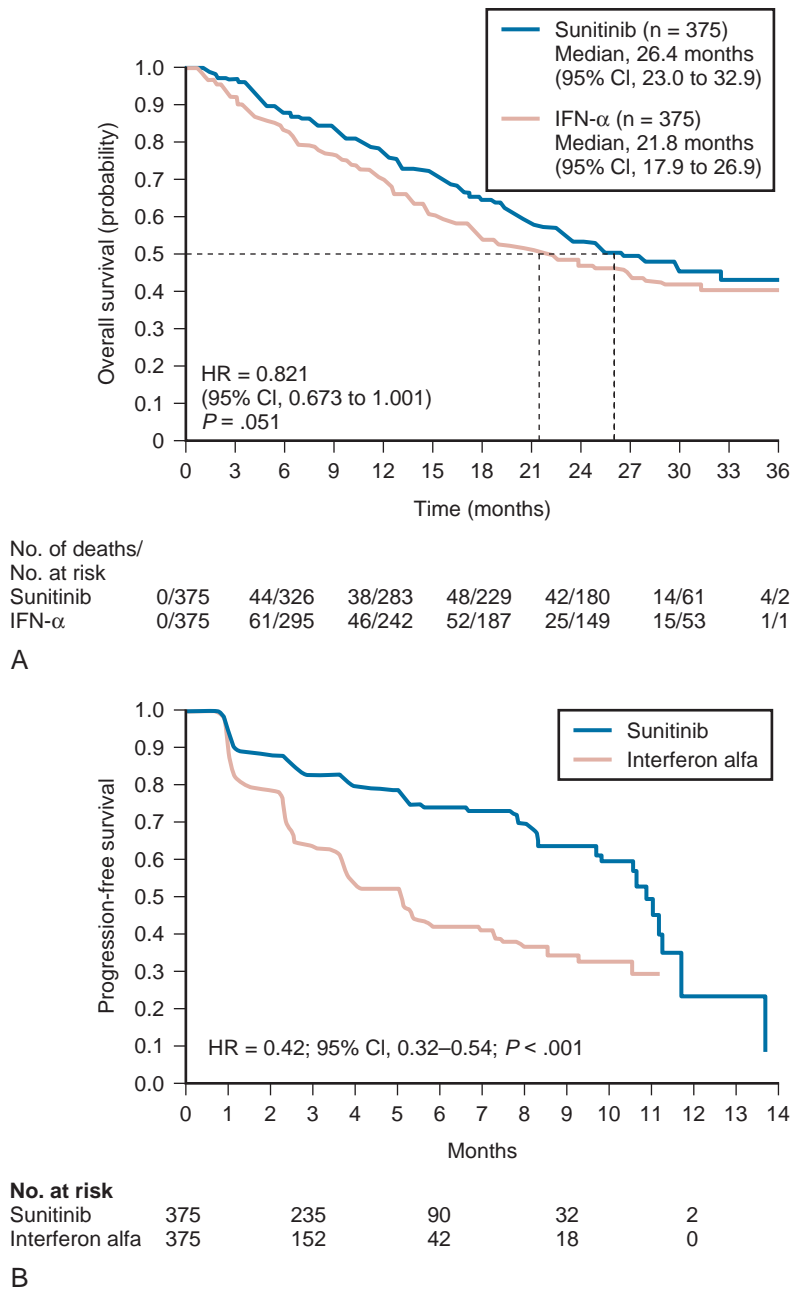


Figure 63-8. Kaplan-Meier analysis of overall survival (A) and progression-free survival (B) in 750 previously untreated patients with metastatic renal cell carcinoma receiving either sunitinib or interferon- α (IFN- α). CI, confidence interval; HR, hazard ratio. (From Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584–90; and Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115–24.)

Pazopanib

Agents such as sunitinib and sorafenib have activity against a wide array of target molecules, some of which may not be relevant in clear cell RCC. Although these agents are relatively well tolerated when compared with conventional cytotoxic chemotherapy, dose reductions and termination of treatment because of toxicity are not infrequently warranted in patients receiving these drugs. A variety of newer agents with selective activity against the VEGFR family have recently gained attention as a possible means of diminishing the side effects associated with therapy without compromising efficacy (Table 63-10). One agent in this class, pazopanib, is a potent inhibitor of the VEGF receptors but retains activity against PDGFR.

Pazopanib was evaluated in a randomized, double-blind, placebo-controlled phase III trial in patients with metastatic clear cell RCC who had received no or one prior cytokine-based therapy (Sternberg et al, 2010). In the 435 patients randomized (2:1) to receive either pazopanib or placebo, PFS (median 9.2 vs. 4.2 months, $P = .0000001$) and response rates (30% vs. 3%) clearly favored the pazopanib study arm. Pazopanib was associated with superior outcomes in both the treatment-naïve subpopulation ($N = 233$, median PFS 11.1 vs. 2.8 months, HR 0.40, 95% CI 0.27 to 0.60, $P < .0001$) and the cytokine-pretreated subpopulation ($N = 202$, median PFS 7.4 vs. 4.2 months, HR 0.54, 95% CI 0.35 to 0.84, $P < .001$). Furthermore, reported toxicities were mild, with very few grade 3 and 4 adverse events encountered. However,

TABLE 63-10 Summary of Selected Studies of Selective VEGFR Antagonists in Metastatic Renal Cell Carcinoma

STUDY	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (mo)*	MEDIAN OS (mo)*
Sternberg et al, 2010, 2013	Pazopanib vs. placebo	Randomized phase III	Metastatic clear cell patients with 0-1 prior cytokine therapy	435	30% vs. 3%	9.2 vs. 4.2	22.9 vs. 20.5
Motzer et al, 2013d	Tivozanib vs. sorafenib	Randomized phase III	Metastatic clear cell; 0-1 prior therapies	517	33% vs. 23%	11.9 vs. 9.1	28.8 vs. 29.3
Rini et al, 2011;	Axitinib vs. sorafenib	Randomized phase III	Second-line clear cell	723	19% vs. 9%	6.7 vs. 4.7	20.1 vs. 19.2
Motzer et al, 2013b							
Motzer et al, 2013c	Pazopanib vs. sunitinib	Randomized phase III	Previously untreated clear cell	1110	31% vs. 25%	10.5 vs. 10.2	28.4 vs. 29.3

NA, not available; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; VEGFR, vascular endothelial growth factor receptor.

*Statistically significant differences indicated in bold.

mature survival data from this trial demonstrated that OS was not significantly better in the pazopanib arm compared to placebo (median OS 22.9 vs. 20.5 months, HR 0.91, 95% CI 0.71 to 1.16, one-sided $P = .224$) ([Sternberg et al, 2013](#)).

The efficacy and/or tolerability of pazopanib and sunitinib were subsequently compared in at least two studies. In a recently published multicenter phase III randomized trial (COMPARZ) of 1110 patients with previously untreated metastatic clear cell kidney cancer comparing the efficacy and safety of the two agents, patients were randomized to receive either pazopanib 800 mg once daily ($N = 557$) or a standard sunitinib regimen (50 mg once daily for 4 weeks followed by 2 weeks with no treatment, $N = 553$) ([Motzer et al, 2013c](#)). The primary end point was PFS and the study was powered to evaluate noninferiority of pazopanib versus sunitinib. Secondary end points included OS, quality of life, and safety. Median PFS in patients treated with pazopanib was 8.4 months compared to 9.5 months for sunitinib. Based on predefined criteria, PFS with pazopanib was determined to be noninferior to sunitinib (HR 1.05, 95% CI 0.90 to 1.22). OS was comparable in the two groups, with a median OS of 28.4 months in the pazopanib group versus 29.3 months in the sunitinib group (HR 0.91, 95% CI 0.76 to 1.08). However, differences were noted between the two groups in the adverse event profile and patient tolerability. Patients treated with sunitinib had a higher incidence of fatigue (63% vs. 55%), thrombocytopenia (78% vs. 41%), and hand-foot syndrome (50% vs. 29%), while increased levels of alanine aminotransferase were more common in the pazopanib group (60% vs. 43%). Quality-of-life assessments related to fatigue or soreness in the mouth, throat, and hands or feet during the first 6 months of treatment favored pazopanib. Results from a second, smaller study evaluating patient preference between pazopanib and sunitinib (PISCES) were reported in abstract form ([Escudier et al, 2012](#)). One hundred and sixty-eight previously untreated patients with metastatic clear cell RCC were randomized to receive pazopanib for 10 weeks followed by a 2-week washout and then sunitinib for 10 weeks (on a 4-week-on/2-week-off schedule) or vice versa. After completing 22 weeks of therapy, the patients were asked to complete a questionnaire assessing which agent they preferred. Pazopanib was preferred by 70% of the patients, while sunitinib was preferred by 22% of the patients (8% had no specific preference between the agents). **Based on these data, pazopanib is a reasonable first-line option for patients with advanced clear cell RCC. Although pazopanib appears to be better tolerated than sunitinib by the majority of patients, it appears to be associated with an increased incidence of hepatotoxicity and must be used with caution in patients at risk for this complication. It should be further noted that at least**

some patients found sunitinib more tolerable than pazopanib. Decisions regarding which of these agents should be initiated in a given patient should be made after careful, individualized evaluation of each patient.

Axitinib

Axitinib is a highly selective oral small molecule tyrosine kinase inhibitor of VEGF receptors VEGFR-1, VEGFR-2, and VEGFR-3. In a phase II trial of axitinib in 52 patients with advanced kidney cancer, an overall response of 44%, including two complete responses (4%), and a median time to progression of 15.7 months were reported ([Rixe et al, 2007](#)). Most patients treated in this study displayed some degree of tumor shrinkage, and many had been pretreated with either IL-2 or interferon. Diarrhea, fatigue, and hypertension were the most commonly encountered grade 3 and 4 adverse events and were amenable to medical management in most patients. Axitinib was the subject of a recently concluded phase III trial (AXIS) that compared its efficacy to sorafenib (a first-generation VEGFR and RAF inhibitor) in the second-line setting ([Rini et al, 2011; Motzer et al, 2013b](#)). In this study, 723 patients with clear cell RCC who progressed on one first-line therapy containing sunitinib, bevacizumab, temsirolimus, or cytokines were randomized to receive axitinib (starting dose of 5 mg orally twice daily, $N = 361$) or sorafenib (400 mg orally twice daily, $N = 362$). Patients in the axitinib arm were allowed to receive higher doses (up to 10 mg orally twice daily) if lower dose levels were well tolerated; there was no dose escalation in the sorafenib arm. Median PFS, as measured by Response Evaluation Criteria in Solid Tumors (RECIST), was 6.7 months in the axitinib arm compared to 4.7 months in the sorafenib arm (HR 0.665, 95% CI 0.544 to 0.812, $P < .0001$). The benefit from axitinib was most pronounced in patients who had previously received cytokines (median PFS 12.1 months for axitinib vs. 6.5 months for sorafenib, HR 0.464, 95% CI 0.318 to 0.676, $P < .0001$). Patients previously treated with a VEGF pathway antagonist also appeared to benefit, although the improvement in PFS was modest. For instance, in patients who had received sunitinib in the first-line setting, median PFS was 4.8 months with axitinib and 3.4 months with sorafenib (HR 0.741, 95% CI 0.573 to 0.958, $P = .0107$). Overall survival in the two arms was comparable, with a median OS of 20.1 months (95% CI 16.7 to 23.4) with axitinib and 19.2 months (95% CI 17.5 to 22.3) with sorafenib (HR 0.969, 95% CI 0.800 to 1.174, one-sided $P = .3744$). **Based on the improved PFS compared to sorafenib in the AXIS trial, axitinib was approved by the FDA for use in the second-line setting in patients with advanced RCC. In**

both the AXIS trial and prior studies of axitinib, significant inter-patient variability in pharmacokinetics and drug exposure was observed, with higher exposures associated with superior activity. A phase II study in previously untreated clear cell RCC patients employed a dose titration scheme based on clinical tolerability in an attempt to enhance activity by optimizing drug dosing and exposure (Rini et al, 2013). A total of 213 patients were enrolled in this trial, with 112 patients tolerating the drug well enough at the starting dose (5 mg PO bid) to be eligible for dose escalation. These patients were randomized to either an axitinib dose titration arm (7 mg PO bid, increased to 10 mg PO bid if well tolerated; n = 56) or a placebo titration arm (patients remained on 5 mg PO bid; n = 56). Response rates were significantly higher in the dose titration arm (overall response rate = 54%) compared to the placebo arm (overall response rate = 34%, one sided $P = .019$); however, the higher response rates did not translate to an improved PFS. Although these data suggest the possibility that dose titration in individual patients based on tolerability may be advantageous, this approach requires further study.

Other Agents Targeting the VEGF Pathway

Tivozanib, yet another highly selective inhibitor of VEGFR-1, -2, and -3, was evaluated in a phase II randomized discontinuation trial with demonstration of activity in RCC as well as an appealing adverse event profile (Bhargava et al, 2009). Subsequently, Motzer and colleagues (2013d) compared the activity of tivozanib versus sorafenib in advanced RCC in a phase III randomized, open-label, multicenter trial. Patients with advanced RCC with a clear cell component and no prior exposure to VEGF- or mTOR-targeted agents were randomized to receive either tivozanib (N = 260) or sorafenib (N = 257). Tivozanib was associated with a statistically meaningful improvement in PFS (median 11.9 months for tivozanib vs. 9.1 months for sorafenib, HR 0.797, 95% CI 0.639 to 0.993, $P = .042$). The overall response rate was 33% for tivozanib versus 23% for sorafenib ($P = .037$). However, there was a trend toward improved survival in the sorafenib arm (median 29.3 vs. 28.8 months, HR 1.245, 95% CI 0.954 to 1.624, $P = .105$). While results from this trial clearly establish the activity of tivozanib in clear cell RCC, given the profusion of available agents targeting this pathway, further studies are required to define the optimal use of this agent in the context of the current treatment landscape.

Despite advances in our ability to target the VEGF pathway in a clinically meaningful manner, most patients with clear cell RCC eventually progress and die from their disease. Identifying mechanisms mediating both primary and acquired or adaptive resistance to VEGF pathway inhibition is an area of active investigation. Activation of alternative means of promoting and supporting angiogenesis in the face of VEGF inhibition has emerged as a possible contributor to resistance in preclinical models. Fibroblast growth factor (FGF) receptors (FGFR-1 and FGFR-2) have been proposed as important mediators of resistance following effective VEGF pathway inhibition in some models (Korc and Friesel, 2009; Welti

et al, 2011). A recent noncomparative phase II study evaluated the use of sunitinib and **nintedanib**, a small angiokinase inhibitor with activity against VEGFR-1, -2, and -3, PDGFR- α/β , FGFR-1, -2, and -3, RET, and Flt-3 (Eisen et al, 2013). Ninety-nine patients with advanced clear cell RCC who had not received prior systemic therapy were treated with either nintedanib or sunitinib in a 2:1 ratio until disease progression as defined by RECIST 1.1 or the onset of unacceptable drug-related adverse events. The primary end point was PFS at 9 months, as well as the incidence of significant Q-Tc interval change in the nintedanib group. **There was no significant difference in PFS at 9 months between the two groups (43% in the nintedanib arm vs. 45% in the sunitinib arm, $P = .85$).** Secondary efficacy end points were also similar between the two groups, including response rate (18.8% vs. 31.3%, $P = .19$), median OS (20.4 vs. 21.2 months, $P = .63$), and median time to progression (8.5 months in both groups). **Dovitinib**, an oral inhibitor of VEGFR, PDGFR, and FGFR, was studied in an open-label randomized phase III trial in patients with clear cell RCC who had received one prior VEGF and one prior mTOR therapy (Motzer, 2013). A total of 570 patients were randomized 1:1 to dovitinib or sorafenib with PFS as the primary end point. Most patients had received an anti-VEGF agent (92%) followed by an mTOR agent before enrolling in the trial. PFS was comparable, with a median of 3.7 and 3.6 months (HR 0.86, 95% CI 0.72 to 1.94, $P = .063$) in the dovitinib and sorafenib arms, respectively. Median OS (HR 0.96, 95% CI 0.75 to 1.22, $P = .357$) was also similar (11.1 and 11 months in the dovitinib and sorafenib arms, respectively). While the two aforementioned studies dampen enthusiasm for further evaluation of FGFR inhibitors in RCC, it must be noted that there was no attempt made in these studies to select patients based on evidence of FGFR pathway activation in their tumors. Additionally, no pharmacodynamic end points were reported, rendering it impossible to determine if effective FGFR-1 inhibition was achieved with either of these drugs.

Inhibitors of the Mammalian Target of Rapamycin

mTOR is a key intracellular protein that is a component of several signaling cascades, including those mediating the effects of some growth factors. It appears to play a role in regulating translation and stability of HIF-1 α , and preclinical models have suggested that growth inhibition occurring in response to mTOR inhibitors correlates with a block in HIF-1 α translation (Hudson et al, 2002; Thomas et al, 2006). Two analogues of sirolimus, **temsirolimus** and **everolimus**, have been clinically evaluated with demonstrable activity in RCC.

A phase II trial of **temsirolimus** evaluated three different doses (25 mg, 75 mg, and 250 mg per week administered intravenously) in 111 patients assigned randomly to one of the dose levels (Table 63-11). The overall response rate observed in this trial was modest (7%, including one patient with a complete response), and the median PFS was 15 months (Atkins et al, 2004). Responses and PFS appeared to be independent of temsirolimus dose. An exploratory subgroup analysis based on stratification of patients according to

TABLE 63-11 Summary of Selected Studies of mTOR Inhibitors in Metastatic Renal Cell Carcinoma

STUDY	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (mo)*	MEDIAN OS (mo)*
Hudes et al, 2007	Tem vs. IFN- α vs. tem/IFN- α	Randomized phase III	Poor prognosis, previously untreated, all histologic subtypes	626	8.6% vs. 4.8% vs. 8.1%	5.5 vs. 3.1 vs. 4.7	10.9 vs. 7.3 vs. 8.4
Motzer et al, 2008b	Everolimus vs. placebo	Randomized phase III	Clear cell refractory to VEGF-targeted therapy	410	1% vs. 0%	4.0 vs. 1.9	NR vs. 8.8

IFN- α , interferon alfa; mTOR, mammalian target of rapamycin; NR, not reached; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; tem, temsirolimus; VEGF, vascular endothelial growth factor.

*Statistically significant differences indicated in bold.

MSKCC risk groups revealed that patients in the poor-risk group had a longer median OS compared with historical controls receiving interferon- α (8.2 vs. 4.9 months). Based on this observation, a three-arm randomized phase III trial of 626 patients with three or more predefined poor-risk features was undertaken (Hudes et al, 2007). Patients with previously untreated metastatic kidney cancer of all histologic subtypes were eligible and randomized to receive temsirolimus alone (25 mg intravenously every week), interferon alfa alone (up to 18 million units subcutaneously three times a week), or temsirolimus (15 mg intravenously every week) plus interferon alfa (6 million units subcutaneously three times a week). PFS was superior in both temsirolimus-containing arms compared with interferon alone (median 3.8 vs. 1.9 months). Importantly, the trial also demonstrated a significantly higher OS in the temsirolimus arm compared with the interferon-only arm (median OS 10.9 vs. 7.3 months, $P = .008$), while the addition of temsirolimus did not appear to significantly alter OS compared with interferon alone (median OS 8.4 vs. 7.3 months, $P = .70$) (Fig. 63-9). Temsirolimus was fairly well tolerated, and most common adverse events such as mucositis, fatigue, rash, hyperglycemia, hypophosphatemia,

hypercholesterolemia, and pulmonary complications were amenable to medical and/or supportive measures. Based on these data, temsirolimus was approved by the FDA for the treatment of patients with metastatic RCC, and the agent is a reasonable frontline choice in patients presenting with poor-risk features.

Everolimus is an orally bioavailable inhibitor of mTOR. It was the subject of a phase III trial in patients with metastatic clear cell RCC whose disease had progressed after therapy with sunitinib, sorafenib, or both (Motzer et al, 2008b). Patients were randomized to receive either everolimus, 10 mg once daily ($n = 272$), or placebo ($n = 138$) (see Table 63-11). The trial was stopped after an interim analysis demonstrated superior PFS in the everolimus arm (median 4 months) compared with the placebo arm (median 1.9 months) (Fig. 63-10). At the time of this analysis, median survival had not been reached in the everolimus group and was 8.8 months for the placebo group; OS was not significantly different in the two groups. Although the agent offers only a modest improvement in PFS in patients progressing on first-line VEGFR antagonists, it is nonetheless a reasonable therapeutic option and has been approved by the FDA for this indication.

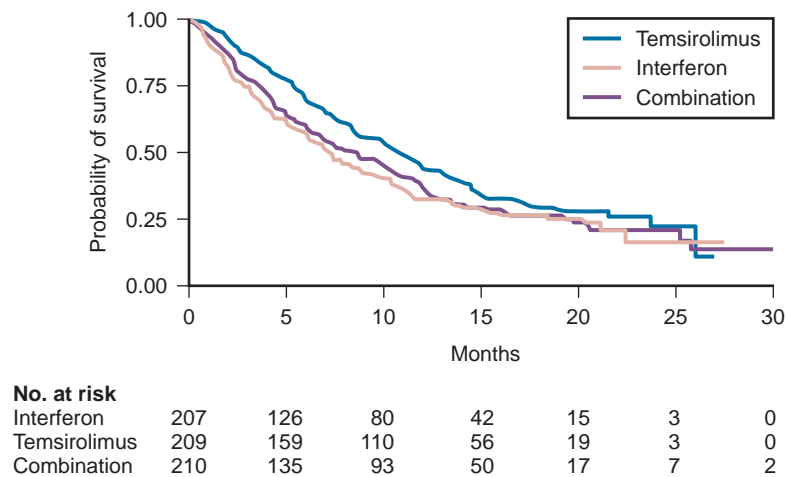


Figure 63-9. Kaplan-Meier estimates of overall survival in 626 metastatic renal cell carcinoma patients with adverse prognostic features randomized to receive temsirolimus alone, interferon- α alone, or combination therapy. (From Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; 356:2271–81.)

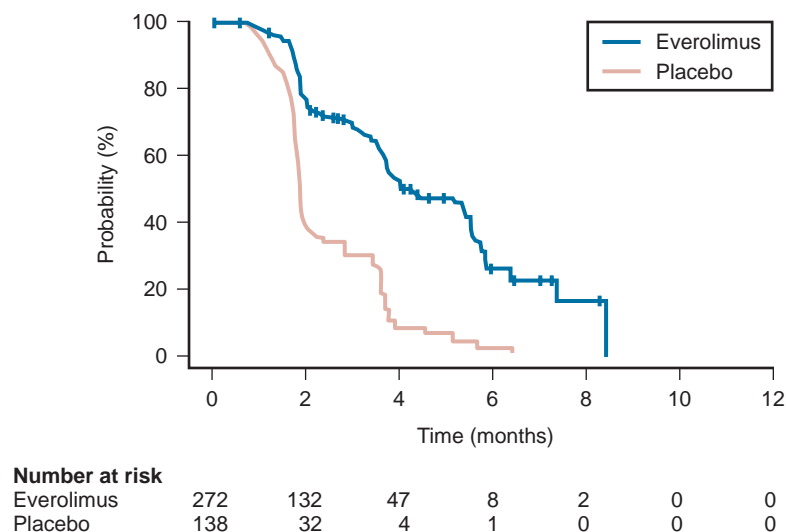


Figure 63-10. Kaplan-Meier estimates of progression-free survival in 410 patients with metastatic renal cell carcinoma randomized to everolimus or placebo. (From Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008;372:449–56.)

Combination and Sequential Therapy with Agents Targeting the von Hippel-Lindau Pathway

Combinations of two or more classes of agents with activity centered on different components of the VHL pathway provide an attractive strategy that might serve to increase efficacy as well as eliminating potential mechanisms of resistance. A major limitation of this approach is the overlapping toxicity profile of several drugs, necessitating significant dose reductions of individual drugs (Feldman et al, 2009; Patel et al, 2009). Several combinations of mTOR and VEGF pathway antagonists have been evaluated in phase I trials. In general, combinations of first-generation VEGFR inhibitors such as sunitinib with an mTOR inhibitor are associated with significant toxicity, discouraging their evaluation in phase II/III studies (Feldman et al, 2009; Patel et al, 2009). However, bevacizumab-based combinations appear to be better tolerated and have been evaluated in several trials.

The activity of bevacizumab in combination with everolimus was evaluated in a phase II trial of metastatic clear cell RCC patients (n = 80); both treatment-naïve patients (n = 50) and patients who had previously received sunitinib and/or sorafenib were eligible (Hainsworth et al, 2010). Median PFS in the treatment-naïve and previously treated populations was 9.1 and 7.1 months, respectively. The combination was further evaluated in a phase III trial (RECORD-2) that compared its efficacy to that of bevacizumab plus interferon- α (Ravaud et al, 2013). This study demonstrated similar median PFS, OS, and safety profiles in both groups, which suggests no additional advantage to replacing interferon- α with everolimus in combination with bevacizumab. The INTORACT trial compared the combination of either temsirolimus or interferon- α to bevacizumab (Rini et al, 2014). Seven hundred and ninety-one patients with previously untreated metastatic clear cell RCC were randomized to one of the aforementioned groups; the primary end point of the trial was PFS. There was no significant difference between the temsirolimus and interferon- α groups in median PFS (9.1 vs. 9.3 months, HR 1.1, 95% CI 0.9 to 1.3, $P = .80$), OS (25.8 vs. 25.5 months, HR 1.0, 95% CI 0.9 to 1.3, $P = .6$), or objective response rates (27.0% vs. 27.4%, risk ratio 1.0, 95% CI 0.8 to 1.3, $P = 1.0$). The combination of temsirolimus plus bevacizumab, however, appeared to be better tolerated, with superior symptom scores as assessed by the validated Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI)-15 and FKSI-Disease Related Symptoms, without a significant difference in global health outcomes. Based on these studies, combinations of bevacizumab with an mTOR inhibitor do not appear to offer additional activity compared to established standard-of-care options in the first-line setting. Whether these combinations are substantively different from single-agent bevacizumab remains to be addressed.

Given the profusion of agents with single-agent activity in RCC, identifying the optimal sequencing of these agents is a question of considerable importance. A randomized study has demonstrated that everolimus can prolong PFS compared with placebo in patients who have progressed on first-line VEGFR antagonists (Motzer et al, 2008b). Smaller retrospective analyses have suggested that a proportion of patients who have progressed on one VEGF pathway inhibitor may benefit from a second agent targeting the same pathway (Rini et al, 2008b; Tamaskar et al, 2008).

A commonly employed treatment paradigm is to offer patients an mTOR inhibitor after disease progression on a first-line VEGFR–tyrosine kinase inhibitor, based on the RECORD-1 trial, which showed a longer PFS in patients treated with everolimus compared with placebo after failure of front-line VEGF therapy (Motzer et al, 2008b). This paradigm was further tested in the RECORD-3 trial, which addressed the issue of whether the sequence in which VEGF and mTOR pathway agents were administered might impact outcome (Motzer et al, 2013a). Four hundred and seventy-one patients with metastatic RCC (any risk category; 85.4% had clear cell histology) without prior systemic therapy were randomized to receive either first-line sunitinib or everolimus until disease progression, at which point they crossed over to the alternate drug. The

primary end point was to assess whether first-line everolimus resulted in a PFS that was not inferior to first-line sunitinib. Median PFS was significantly better in patients receiving first-line sunitinib (10.7 months, 95% CI 8.2 to 11.5) compared to those receiving everolimus as initial therapy (7.9 months, 95% CI 5.6 to 8.2, HR 1.43, range 1.15 to 1.77). At the time of the analysis, there was also a trend toward worse OS in the first-line everolimus group (median OS 22.4 months) versus the first-line sunitinib group, (32.0 months, HR 1.24, 95% CI 0.94 to 1.64). These data suggest that the standard sequence used commonly in clinical practice, particularly in patients with standard-risk disease (first-line VEGFR–tyrosine kinase inhibitor followed by mTOR agent upon disease progression) results in better outcomes than using an mTOR agent first.

Carefully designed clinical trials are required to identify the most effective strategies for sequencing multiple agents, as well as to categorize patients most likely to benefit from a given sequence based on molecular characterization of their tumors.

Other Treatment Options in Patients with Clear Cell Renal Cell Carcinoma

Chemotherapy

Conventional cytotoxic chemotherapy has been largely ineffective in the management of clear cell RCC. Numerous chemotherapeutic agents, including 5-FU, platinum compounds, gemcitabine, vinblastine, and bleomycin, have been evaluated as single agents in this disease but have failed to demonstrate clinically meaningful activity; a wide array of combination chemotherapy regimens have fared little better (Haas et al, 1976; Hahn et al, 1977; Zaniboni et al, 1989; Mertens et al, 1993, 1994; Amato, 2000; Rini et al, 2000, 2005; Stadler et al, 2006). Comprehensive meta-analyses of chemotherapy trials in RCC indicate the overall response rate is 5.5% to 6.0% (Yagoda et al, 1995). Although the mechanisms underlying this profound chemoresistance have not been fully elucidated, overexpression of the multidrug resistance gene (MDR) has been proposed as one possible culprit (Fojo et al, 1987). However, the addition of MDR inhibitors such as toremifene, cyclosporine, and verapamil to conventional chemotherapeutic agents has failed to improve their efficacy, suggesting that other, as yet unrecognized, factors may be at play (Braybrooke et al, 2000). Cytotoxic chemotherapy has no role in the current management of most patients with clear cell RCC. One situation in which chemotherapy may bear further investigation is in patients whose tumors demonstrate a sarcomatoid component; a small case series has suggested promising activity for gemcitabine-based chemotherapy in this setting, prompting further study of this approach (Nanus et al, 2004).

Hormonal Therapy

Hormonal therapy had been the subject of trials in RCC in the 1970s and 1980s, preceding the advent of cytokines. These studies were prompted both by the lack of effective therapies for kidney cancer and by the belief that a male preponderance (kidney cancer occurs approximately twice as frequently in males) implied a hormonal basis for this malignancy. Hormonal agents such as medroxyprogesterone have been noted to induce tumor regressions in a small minority of patients, but overall response rates are too low (approximately 2%) to have meaningful clinical impact in most patients (Harris, 1983; Schomburg et al, 1993; Medical Research Council Renal Cancer Collaborators, 1999; Braybrooke et al, 2000). Progesterational and other hormonal agents have no role in the current management of RCC.

SYSTEMIC THERAPY FOR NON-CLEAR CELL VARIANTS OF RENAL CELL CARCINOMA

Non-clear cell subtypes of kidney cancer are relatively rare (constituting approximately 15% to 25% of all kidney cancer) and have been the subject of few prospective studies. Given the unavailability

of agents of proven efficacy in papillary, chromophobe, and other rare histologic subtypes, patients with non-clear cell renal tumors often receive agents with activity in clear cell RCC.

VEGFR inhibitors active in clear cell RCC have only modest efficacy in papillary RCC. Sorafenib and sunitinib were shown to have minimal activity in retrospective studies of papillary RCC patients (Choueiri et al, 2008a). Prospective phase II trials with sunitinib have demonstrated that this agent is associated with low response rates (5% to 10%) in papillary RCC. The Southwest Oncology Group reported an 11% overall response rate with erlotinib, an oral epidermal growth factor receptor (EGFR) inhibitor, in 52 patients with metastatic papillary RCC with a 6-month PFS of only 29%.

An exploratory subgroup analysis of patients enrolled in a large randomized phase III study evaluating the efficacy of temsirolimus versus interferon in “poor prognosis” patients suggests that mTOR inhibitors may have activity in some non-clear cell variants. Approximately 20% of the patients enrolled in this trial had non-clear cell histologies (predominantly papillary RCC). The outcome of 37 patients with non-clear cell RCC treated with temsirolimus (both OS and PFS) was found to be better than that of 36 patients receiving interferon in this subgroup analysis. Although these data suggest that temsirolimus may have activity in some non-clear cell variants, these conclusions are limited by the fact that this is a subgroup analysis (Dutcher et al, 2009). Everolimus was evaluated in a relatively large open-label, multicenter phase II clinical trial as a first-line agent in patients with metastatic papillary RCC (RAPTOR); results from this trial were recently reported in abstract form (Escudier et al, 2013). At the time of a preliminary intent-to-treat analysis ($n = 83$), median PFS was 3.7 months (95% CI 2.4 to 5.5), while median OS was 21 months (95% CI 15.4 to 28) by independent radiology review. Common grade 3 or 4 adverse events included asthenia (10.6%), fatigue (5.4%), and anemia (5.4%). Around 27.2% of the patients discontinued treatment because of adverse events. A second phase II trial of everolimus in patients with

metastatic non-clear cell RCC was recently published (Koh et al, 2013). Of the 49 patients enrolled, 29 (59%) had papillary RCC and 23 (47%) had had prior anti-VEGF therapy. Partial response was noted in 5 (10%), stable disease in 25 (51%), and disease progression in 16 (32.7%) of the 49 patients. Interestingly, two of five patients with objective response to everolimus had chromophobe RCC, whereas two had papillary RCC and one had an unclassified RCC variant. The median PFS in this study was 5.2 months, and patients with chromophobe RCC had a trend toward longer PFS compared to other non-clear cell RCC patients ($P = .084$). Based on the two foregoing trials, everolimus appears to have modest activity in patients with papillary/non-clear cell RCC.

Recent advances in our understanding of the genetic and molecular alterations underlying several RCC subtypes have begun to lead to a more rational and individualized approach to their management. As with clear cell RCC, hereditary forms of papillary and chromophobe RCC hold the key to the identification of critical molecular events leading to these tumors in both familial and sporadic settings (Linehan, 2003; Linehan et al, 2009). Hereditary papillary renal cell carcinoma (HPRCC) is a familial condition characterized by the predisposition of affected individuals to develop bilateral, multifocal papillary type I RCC. HPRCC is characterized by the presence of activating germline mutations in the tyrosine kinase domain of the proto-oncogene *MET*, which is located on chromosome 7; this is usually accompanied by non-random duplication of the chromosome containing the mutated allele in the tumors (Schmidt et al, 1997, 1998, 1999, 2004; Zhuang et al, 1998; Linehan, 2003; Linehan et al, 2009). *MET* is a cell surface receptor that is normally activated on binding its ligand, hepatocyte growth factor (HGF), but is rendered constitutively active in the presence of mutations in the kinase domain of this protein (Bottaro et al, 1991; Dharmawardana et al, 2004; Peruzzi and Bottaro, 2006; Giubellino et al, 2009). The HGF/*MET* pathway is involved in regulating a variety of biologic functions, including cell growth, proliferation, and motility (Fig. 63-11) (Jeffers et al,

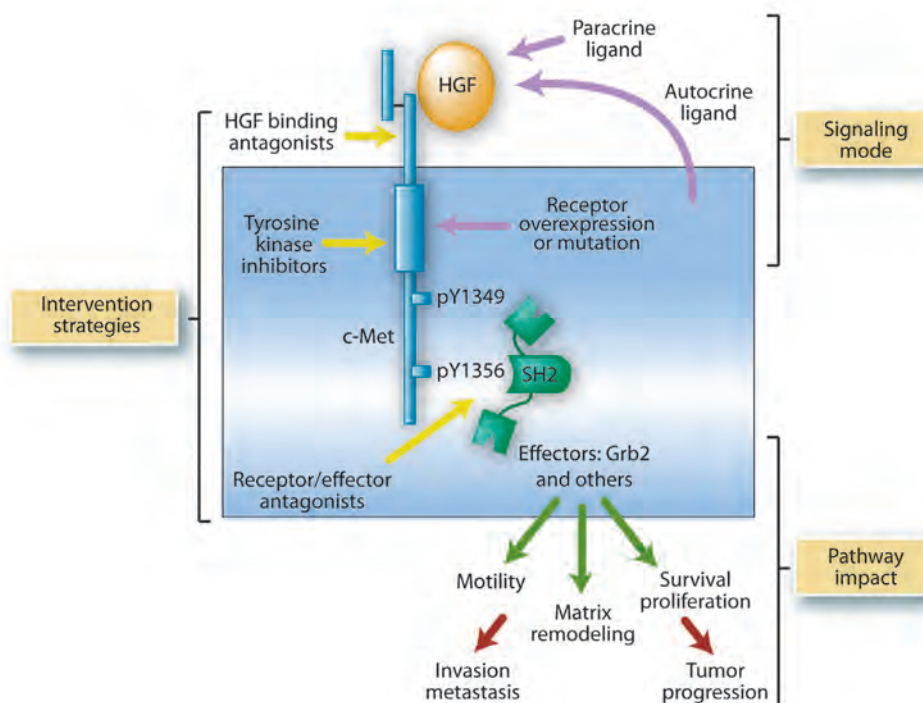


Figure 63-11. MET oncogenic signaling pathway. Important downstream biochemical and biologic consequences of MET activation, by hepatocyte growth factor (HGF) binding or by constitutive activation of the receptor tyrosine kinase activity by mutation, are represented. The MET ligand (HGF), MET tyrosine kinase activity, and downstream effectors (such as Grb-2) are potential targets for drugs in tumors with aberrant pathway activation. (From Peruzzi B, Bottaro DP. Targeting the c-Met signaling pathway in cancer. Clin Cancer Res 2006;12:3657–60.)

1998; Giubellino et al, 2009). Somatic MET alterations have been noted in a proportion of patients with sporadic papillary RCC, with activating mutations identified in approximately 13% of papillary tumors in one series. Gain of chromosome 7 (both *HGF* and *MET* are located on chromosome 7) has been described in more than two thirds of papillary tumors and may represent an alternative mechanism contributing to activation of the MET pathway in these tumors (Kovacs et al, 1991; Henke and Erbersdobler, 2002).

The realization that MET activation may play an important role in some forms of papillary RCC has led to the evaluation of foretinib, a novel tyrosine kinase inhibitor with activity against MET and VEGFR-2 in this RCC subtype. In a phase II study by Choueiri and colleagues (2013), two dosing regimens were evaluated in sequential patient cohorts: cohort A (n = 37) received an intermittent dosing regimen of 240 mg of foretinib given on days 1 through 5 of every 14-day cycle, and cohort B (n = 37) received a continuous daily dosing regimen of 80 mg/day. The primary end point was overall response rate based on RECIST. An overall response rate of 13.5% with a median PFS of 9.3 months was reported in the entire study population. A subgroup analysis was undertaken to determine if MET pathway activation was associated with treatment outcome. The presence of a germline *MET* mutation was associated with a high likelihood of response, with 5 of 10 patients (50%) demonstrating a PR in this group compared to 5 of 57 responders (9%) in the absence of germline alterations. The side effect profile for foretinib appeared similar to that of other anti-VEGFR agents, with hypertension being the most commonly reported adverse effect. Although the primary end point of overall response rate greater than 25% was not met, foretinib has activity in papillary RCC, notably in the germline *MET* mutation cohort, indicating that MET inhibition might be a viable treatment option for a subset of patients with papillary RCC.

A second form of hereditary papillary RCC is associated with alterations in the fumarate hydratase gene (*FH*), which encodes a tricarboxylic acid cycle enzyme that catalyzes the conversion of fumarate to malate. Germline *FH* mutations are seen in patients with hereditary leiomyomatosis and renal cell carcinoma (HLRCC), a condition associated with a highly aggressive variant of type II papillary RCC (Launonen et al, 2001; Lehtonen et al, 2006; Grubb et al, 2007; Merino et al, 2007; Linehan et al, 2010b). It has long been recognized that accumulation of fumarate, resulting from FH inactivation, leads to a VHL-independent upregulation of intracellular HIF and transcriptional activation of downstream proangiogenic and growth factors (Isaacs et al, 2005). Loss of FH activity promotes a metabolic shift in these tumors, characterized by disruption of the Krebs cycle and a consequent reliance on aerobic glycolysis to satisfy cellular bioenergetic requirements (Shuch et al, 2013). Investigators at the NCI have recently attempted to therapeutically exploit the exquisite sensitivity of this variant of papillary RCC to glucose deprivation (Yang et al, 2010). They hypothesized that a combination of bevacizumab (a monoclonal antibody to VEGF) and erlotinib (inhibitor of EGFR kinase activity) would severely constrain glucose delivery to the tumor microenvironment and disrupt critical cellular processes. The combination of bevacizumab and erlotinib is currently being evaluated in patients with metastatic papillary RCC, and interim data from this trial were recently presented (Stamatakis et al, 2013). This interim analysis

included the first 34 individuals enrolled, of whom 20 had sporadic papillary RCC and 14 had HLRCC-associated kidney cancer. Sixteen patients had received at least one prior systemic therapy regimen. The overall RECIST response rate was 32% (11 of 34) in the entire cohort, with a disease control rate (partial response and stable disease) of 65%. Partial responses were seen in 6 of 14 (43%) individuals with HLRCC and 5 of 20 (25%) individuals with sporadic papillary RCC. After a median follow-up of 10.7 months, median PFS was 10.5 months (95% CI 7.4 to 18.6). While these results are promising and suggest that the combination of bevacizumab and erlotinib is highly active in some forms of papillary RCC, further follow-up is required to clearly define the efficacy of this regimen in this population.

Cytotoxic chemotherapy has been used with modest success in collecting duct carcinoma, a rare kidney cancer variant with similarities to urothelial malignancies. In a series of 23 patients with metastatic collecting duct carcinoma, a response rate of 26% (including one complete response) was reported with a regimen comprising gemcitabine and carboplatin. Median PFS (7.1 months) and OS (10.5 months) were modest (Oudard et al, 2007). In summary, there is no standard approach of proven efficacy for most patients with non-clear cell RCC, although some promising approaches are being evaluated. Enrollment in suitable trials should be considered for all patients with non-clear cell RCC.

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64

Surgical and Radiologic Anatomy of the Adrenals

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Anatomic Relationships

Surgical Landmarks

Adrenal Vasculature

Adrenal Nerves

Embryology

Histology

Radiology

Conclusion

The adrenal glands are retroperitoneal endocrine organs that are unique from other retroperitoneal structures because of their embryology, anatomy, and the critical role they play in homeostasis. Physiologically, the adrenals are responsible for the production of mineralocorticoids, glucocorticoids, androgenic steroids, and catecholamines. The absence of both adrenal glands, without supplementation of these critical hormones, is not compatible with life. This chapter focuses on the surgical and radiographic anatomy of the adrenal glands (Fig. 64-1A to D).

ANATOMIC RELATIONSHIPS

The adrenal glands are paired organs located cephalad to the kidneys in the retroperitoneum. The position of these glands varies from right to left. Both are located at the level of the 11th or 12th ribs, with the right gland located more superiorly and the left gland extending as low as the first lumbar space. The adrenals are enclosed within the perirenal (Gerota) fascia and are completely surrounded by perirenal adipose tissue. Each gland is separated from the upper pole of the ipsilateral kidney by a thin layer of connective tissue. Grossly, the adrenals are yellow-orange and are noticeably more orange than the surrounding adipose tissue. The dimensions of the glands range from 2 to 3 cm in width and are 4 to 6 cm in length (Mitty, 1988). The weight of each gland is approximately 5 g, and the weight ranges from 2 to 6 g with no variation between genders (Mills, 2007).

SURGICAL LANDMARKS

Dorsolaterally, the adrenal glands are in close proximity to the crus of the diaphragm. The right gland is triangular and is located nearly directly cranial to the upper pole of the right kidney. The adjacent structures include the underside of the liver anterolaterally, the duodenum anteromedially, the lateral margin of the inferior vena cava (IVC) medially, and the psoas muscle posteriorly (Fig. 64-2, top left). The left adrenal gland is more crescentic in shape and its lateral surface is in contact with the medial aspect of the upper pole of the left kidney. The adjacent structures include the splenic vessels and body of the pancreas anteriorly, the aorta medially, and the psoas muscle posteriorly (Fig. 64-2, bottom right).

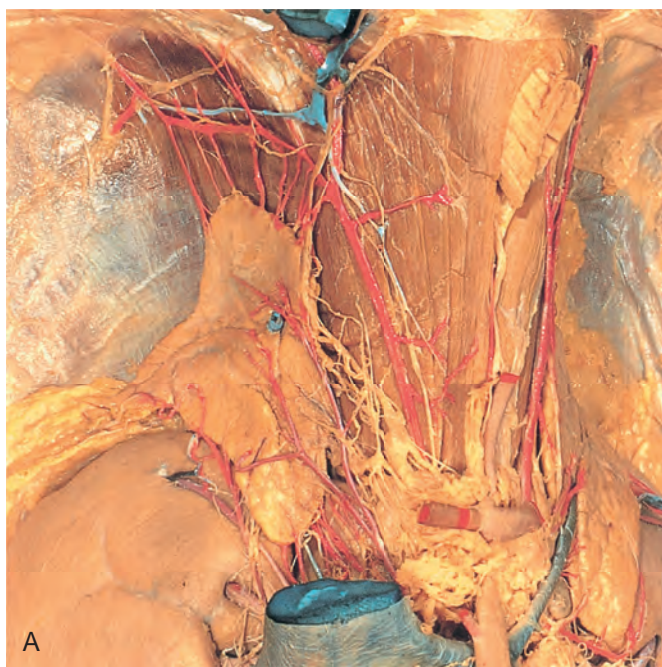
The anatomic relationships between the adrenal glands and the surrounding intra-abdominal and retroperitoneal organs are important when considering a surgical approach. The cross-sectional anatomy of the adrenal gland (Fig. 64-3) demonstrates the relationship of the right adrenal gland with the liver and IVC, and the left adrenal gland relates to the splenic vasculature and the pancreas.

ADRENAL VASCULATURE

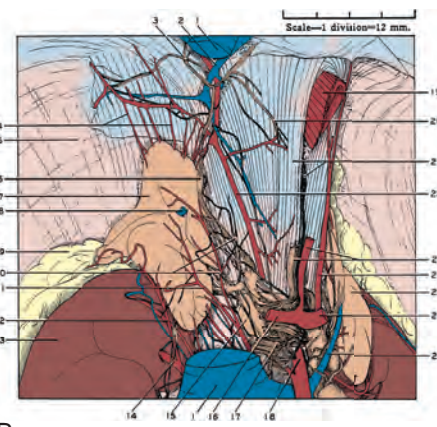
The vasculature of the adrenal glands is unique because the arterial and venous anatomy is highly variable. The arterial supply to the adrenal originates from three sources (Fig. 64-4). Superiorly, the adrenal is typically supplied by the inferior phrenic artery, and rarely by the aorta, celiac axis, or intercostal arteries. The middle adrenal artery typically arises from the lateral aspect of the aorta and rarely from the inferior phrenic artery or renal artery. The inferior adrenal artery typically arises from the superior aspect of the ipsilateral renal artery (Toni and Mosca, 1988). The three main adrenal arteries each branch into cascades of 10 to 50 smaller arteries that then penetrate the adrenal capsule.

There are three patterns of blood distribution within the adrenal gland (Fig. 64-5). Capsular arteries only supply the adrenal capsule and do not penetrate more deeply into the tissue. Fenestrated cortical sinusoidal capillaries supply the cortex and then drain into fenestrated medullary capillary sinusoids. Medullary arterioles travel within the trabeculae of the adrenal gland to deliver blood to the medullary capillary sinusoids. The medulla has two blood supplies: arterial blood from the medullary arterioles and venous blood from the cortical sinusoid capillaries that have already supplied the adrenal cortex with arterial blood (Ross et al, 1995). This dual vascular supply is important for the medullary production of catecholamines. As venous blood from the adrenal cortex reaches the medullary tissue, it contains a high concentration of glucocorticoids, and this situation plays a role in epinephrine synthesis (Bloom and Fawcett, 1986). The complex vascular supply to the adrenal gland is composed of the cortical vascular supply (cortical sinusoids draining into the medullary capillaries, and the medullary vein) and the medullary vascular supply (medullary arterioles and cortical sinusoids) (Gray et al, 1995).

The venous drainage of the adrenals varies by side, although both adrenal glands are drained by a single central vein that exits



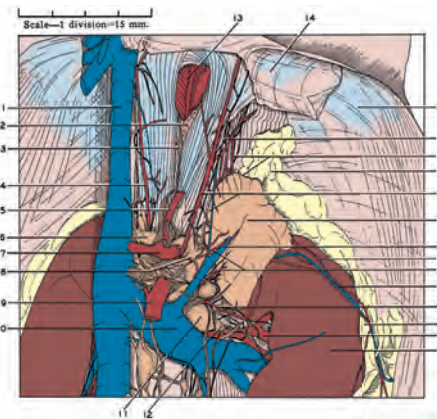
A



B



C



D

Figure 64-1. A, Right adrenal gland dissected. The inferior vena cava has been excised to fully expose the gland. The celiac arterial trunk, its branches, and associated autonomic nervous plexus are also well demonstrated. B, 1, Inferior vena cava (cut). 2, Right inferior phrenic vein. 3, Right phrenic nerve. 4, Superior adrenal arteries (branching from right inferior phrenic artery). 5, Diaphragm. 6, Inferior phrenic ganglion. 7, Right adrenal gland. 8, Right adrenal vein (cut). 9, Pararenal retroperitoneal fat. 10, Autonomic nerves to adrenal gland. 11, Middle adrenal artery (from aorta). 12, Inferior adrenal artery (from renal artery). 13, Right kidney. 14, Branch of right renal artery. 15, Celiac ganglion. 16, Common hepatic artery. 17, Celiac autonomic nervous plexus. 18, Superior mesenteric artery. 19, Esophagus (cut). 20, Branch of phrenic nerve. 21, Upper pointer, right crus of diaphragm; lower pointer, vagus nerve. 22, Right inferior phrenic artery. 23, Upper pointer, left gastric artery; lower pointer, superior extension of celiac autonomic nervous plexus. 24, Left inferior phrenic artery. 25, Left adrenal gland. 26, Splenic artery. 27, Left adrenal vein. C, Left adrenal gland dissected. D, 1, Inferior vena cava. 2, Esophageal hiatus. 3, Vagus nerve. 4, Right inferior phrenic artery. 5, Left gastric artery. 6, Right celiac ganglion. 7, Celiac artery. 8, Left celiac ganglion. 9, Superior mesenteric artery. 10, Left renal vein. 11, Renal hilar lymph node. 12, Renal autonomic nervous plexus. 13, Esophagus (cut). 14, Peritoneum (cut). 15, Diaphragm. 16, Phrenic autonomic nervous plexus. 17, Upper pointer, superior adrenal arteries (from inferior phrenic artery); lower pointer, superior margin of left adrenal gland. 18, Perinephric fat. 19, Upper pointer, left inferior phrenic artery; lower pointer, medial margin of left adrenal gland. 20, Left adrenal gland. 21, Left adrenal vein. 22, Inferior adrenal artery (in this case branching from perinephric/capsular artery of kidney). 23, Middle adrenal arteries (from aorta). 24, Perinephric blood vessels within Gerota fascia. 25, Inferior adrenal artery (from renal artery). 26, Perinephric fat. 27, Branch of left renal artery. 28, Left kidney.

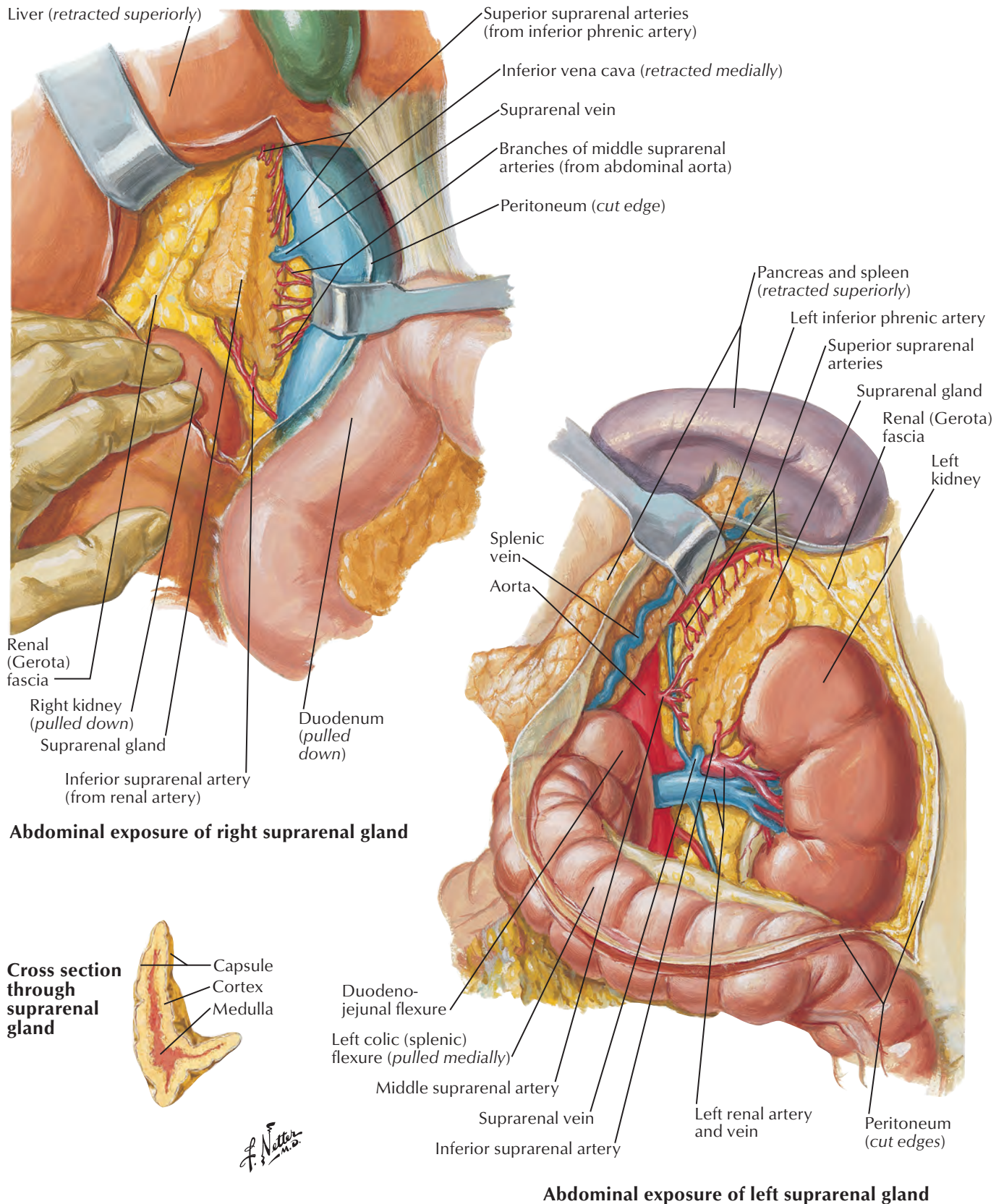


Figure 64-2. Top left, Abdominal exposure of right adrenal gland. Bottom right, Abdominal exposure of left adrenal gland. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

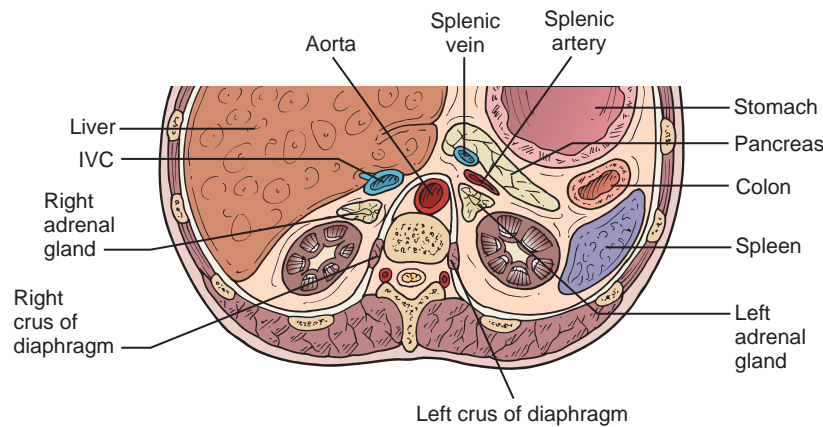


Figure 64-3. Cross-sectional anatomy of the adrenal glands and their relationships to nearby structures. IVC, inferior vena cava. (Modified from Mitty HA. Embryology, anatomy, and anomalies of the adrenal gland. *Semin Roentgenol* 1988;23:271–9.)

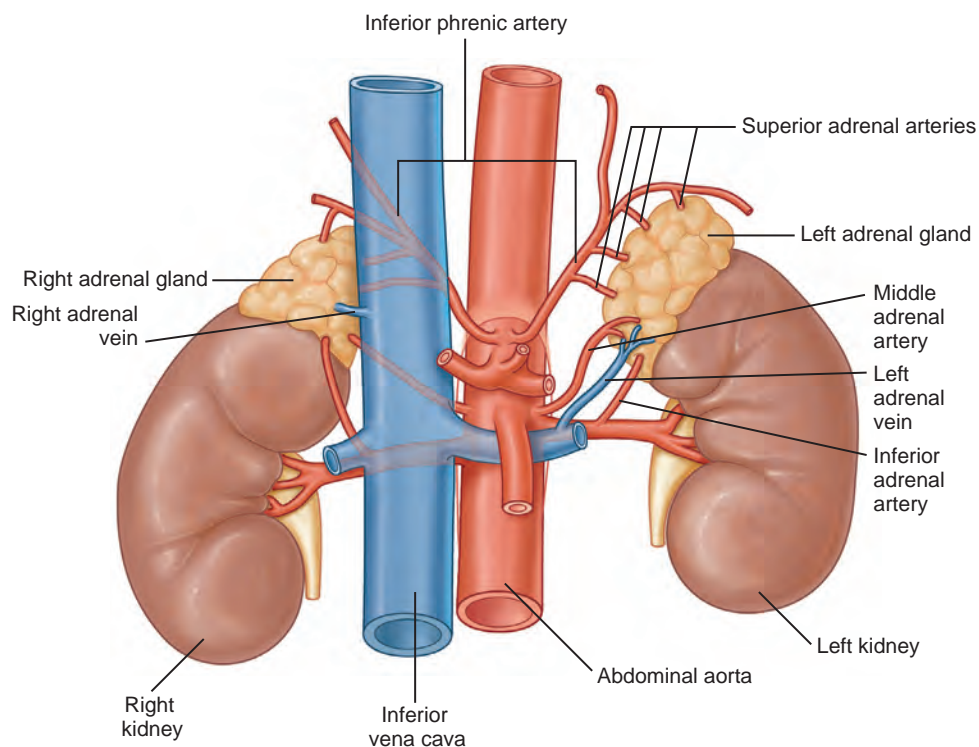


Figure 64-4. Arterial supply to the adrenal glands. (From Drake RL, Vogl W, Mitchell AWM. *Gray's anatomy for students*. Philadelphia: Elsevier; 2005.)

the adrenal anteromedially, with emissary veins connecting the central vein to the pericapsular adrenal arterial plexus (Mitty, 1988). The right adrenal vein is short and enters the posterior aspect of the IVC. The longer left adrenal vein joins with the inferior phrenic vein and enters the cranial aspect of the left renal vein (Fig. 64-6) (Avisse et al, 2000).

ADRENAL NERVES

Innervation of the adrenal gland is important for release of catecholamines from the chromaffin cells of the medulla (Fig. 64-7). Preganglionic sympathetic nerve fibers from the lower thoracic and lumbar spinal cord travel through the sympathetic chain to

reach a nerve plexus at the adrenal capsule. These nerves then traverse the cortex to reach the medulla (Bloom and Fawcett, 1986). The secretory products released from the adrenal medulla enter systemic circulation via fenestrated capillaries (Ross et al, 1995). Cholinergic innervation of the adrenal cortex has also been described, although it is not as well characterized as the innervation of the medulla (Charlton et al, 1991).

EMBRYOLOGY

The processes involved in the development of the adrenal glands were hypothesized until 1911 when the anatomy of adrenal glands from various stages of human development was initially described.

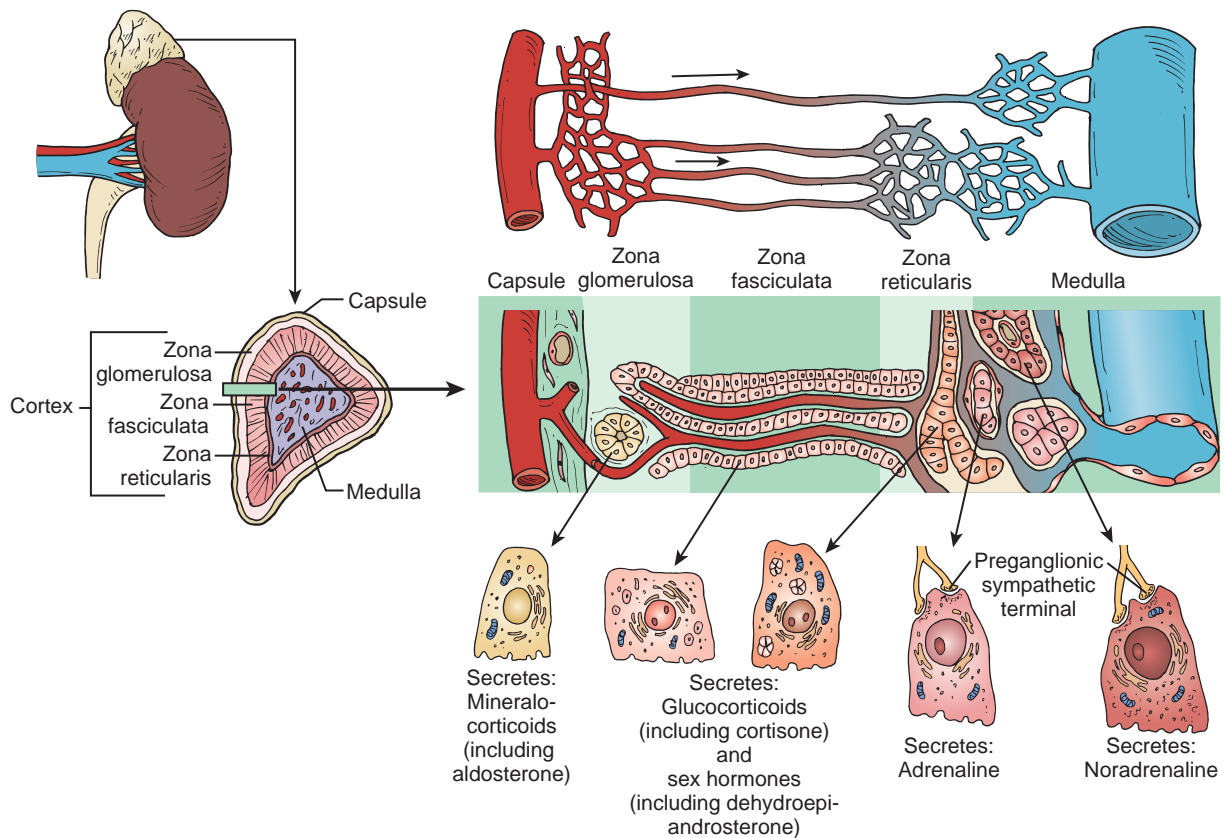


Figure 64-5. The complex vascular supply of the adrenal gland. (From Gray H, Williams PL, Bannister LH. *Gray's anatomy: the anatomical basis of medicine and surgery*. New York: Churchill Livingstone; 1995.)

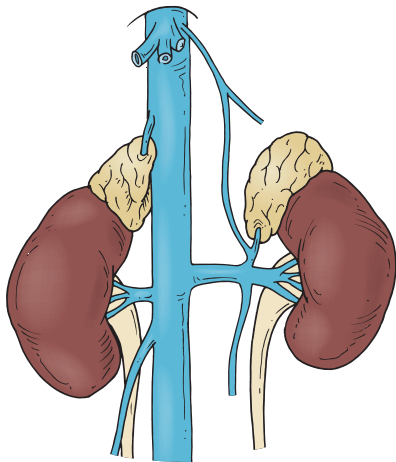


Figure 64-6. Venous drainage of the right and left adrenal glands. The right adrenal vein enters the posterior aspect of the inferior vena cava. The left adrenal vein joins with the inferior phrenic vein and enters the cranial aspect of the left renal vein. (From Vaughan ED Jr, Carey RM, editors. *Adrenal disorders*. New York: Thieme Medical; 1989.)

The original illustration of the human fetal adrenal gland described an early fetal zone composed of immature cortical cells and groups of sympathogonia (Malendowicz, 2010). The fetal zone is an important part of development, and after birth this portion of the adrenal dramatically decreases in size.

The development of the adrenal gland begins at approximately the third or fourth week of fetal development, when columns of coelomic epithelium start to condense. During the next 2 weeks, these cells proliferate and begin to migrate to the cranial end of the mesonephros to form the adrenogonadal ridge, the common precursor to both the adrenals and the gonads. The adrenal cortex arises from the cephalic portion of the ridge, whereas precursor cells of the future gonads arise from the caudal portion of the ridge (Fig. 64-8).

Morphologic differentiation into a definitive zone and a fetal zone occurs between 8 and 10 weeks' development. Mesenchymal cells surrounding the fetal cortex form the adrenal capsule, and neural crest-derived cells migrate to the medial region to form the eventual adrenal medulla. At this time, blood vessels and nerves of the adrenal gland develop.

At birth the adrenal glands are relatively large and weigh twice the weight of the adult glands (Kempná and Flück, 2008). The fetal zone involutes during the first year of life, and is replaced by the definitive zone. This zone develops into the adrenal cortex regions named the zona glomerulosa (ZG) and the zona fasciculata, under the influence of adrenocorticotropic hormone secreted by the pituitary gland. With regression of the fetal zone, chromaffin cells that were scattered throughout the fetal zone aggregate to form the adrenal medulla (Ross et al, 1995). The medulla is homologous to a sympathetic ganglion without postganglionic processes. The zona reticularis (ZR), located between the zona fasciculata (ZF) and the medulla, is a relatively minor component of the adrenal cortex until early childhood. Between 6 and 8 years of life, the ZR expands to its adult volume (Sucheston and Cannon, 1968; Havelock et al, 2004; Else and Hammer, 2005; Kempná and Flück, 2008).

Several unique clinical findings occur with the aberrant development of the adrenal glands and neighboring structures. The

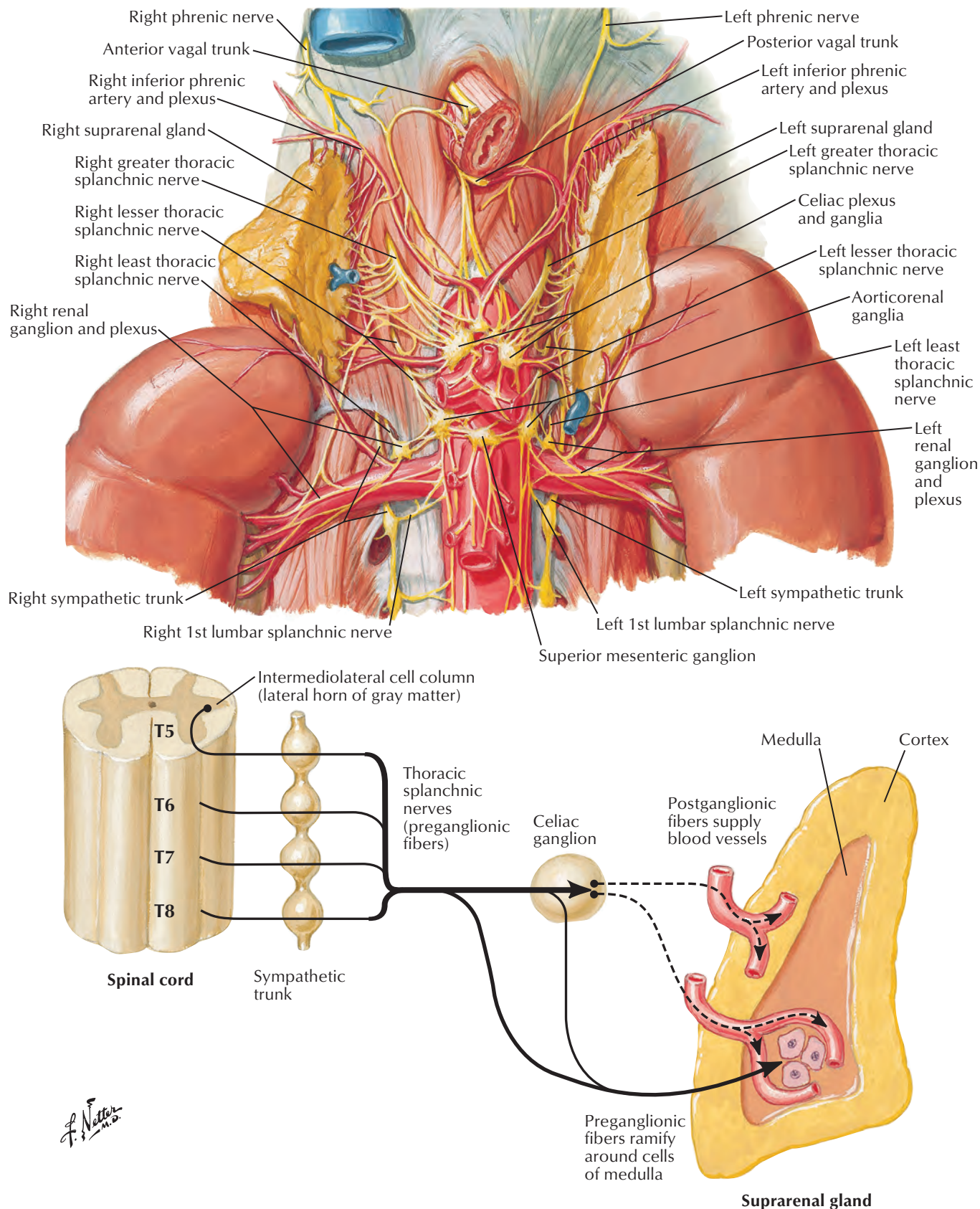


Figure 64-7. Innervation of the adrenal glands. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

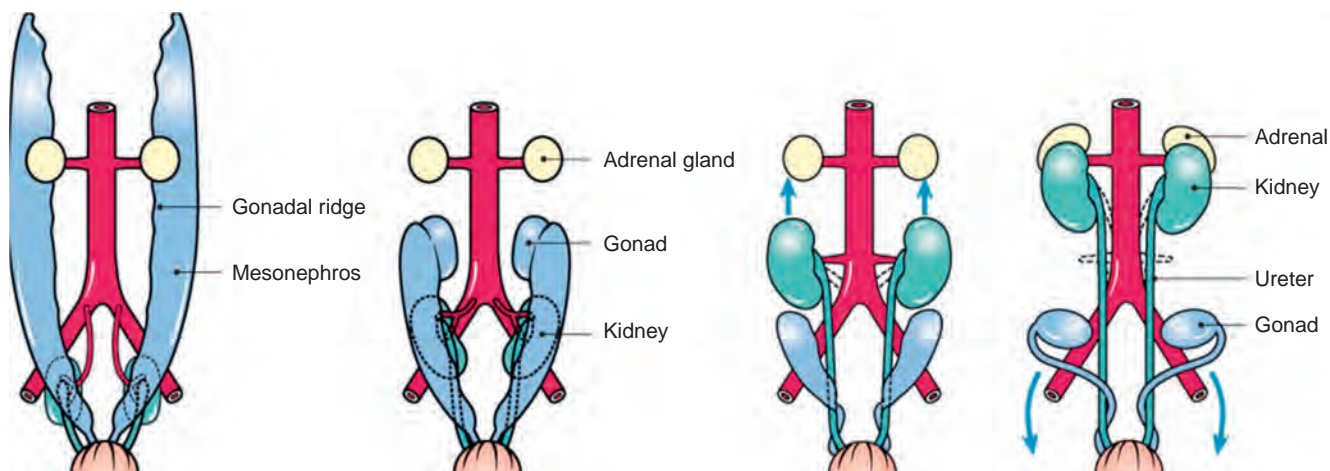


Figure 64-8. Development of the adrenal gland. Note the close relationship between the gonadal ridge and the developing adrenal gland. (From Barwick TD, Malhotra A, Webb JA, et al. *Embryology of the adrenal gland and its relevance to diagnostic imaging*. Clin Radiol 2005;60: 953–9.)

developing kidneys ascend from the pelvis to unite with the adrenal glands at approximately 8 weeks of development (Moore and Persaud, 1998). In the setting of renal agenesis, the adrenal glands are found in their orthotopic positions, but they might be discoid instead of their normal triangular or crescent shapes (Mitty, 1988). Adrenal rests are ectopic tissue derived from either adrenal cortex or medulla. Adrenal rests are found in 1% of adults, and are typically located in the vicinity of the adrenals in proximity to the celiac axis (Graham, 1953). These rests can also be found along the path of gonadal descent. Adrenal rests associated with the gonad are found in 7.5% to 15% of neonates, and they usually regress with time (Graham, 1953). In cases of congenital adrenal hyperplasia, these rests can sometimes present as testes masses. The clinical significance of ectopic adrenal tissue may be important for compensatory hypertrophy after adrenalectomy, inadvertent excision of a heterotopic adrenal gland during unrelated surgery, or neoplastic transformation (Schechter, 1968).

HISTOLOGY

The adult adrenal gland consists of an outer cortex, which makes up approximately 90% of the adrenal mass, and an inner medulla. The gland is surrounded by a capsule composed of hypocellular fibrous tissue [(Mills, 2007). The adrenal cortex consists of three concentric zones (Fig. 64-9): the outer ZG comprising approximately 15% of the cortex, the middle ZF, which includes 80% of the cortex, and the inner ZR including 5% to 7% of the cortex (Ross et al, 1995). The zones are distinct and each is identifiable by the typical appearance of the cells and the ultrastructure of the cellular arrangements.

The ZG is composed of small, polyhedral cells arranged in ovoid clusters and curved columns, which are surrounded by sinusoidal capillaries. The cells are notable for less abundant cytoplasm and a large amount of lipid in the cytoplasm, which results in a vacuolated appearance. These cells are characterized by a higher nuclear-to-cytoplasmic ratio. Aldosterone is synthesized in these cells in the smooth endoplasmic reticulum and the mitochondria (Bloom and Fawcett, 1986; Ross et al, 1995; Cormack, 1998; Mills, 2007). The ZF, which is the largest of the three cortical zones, contains large pale polyhedral cells arranged in long straight cords, separated by capillaries. These cells contain a higher amount of lipid than the other zones, and they are referred to as “clear cells” because of their histologic appearance (Mills, 2007). The ZR is composed of smaller cells arranged in anastomosing cords.

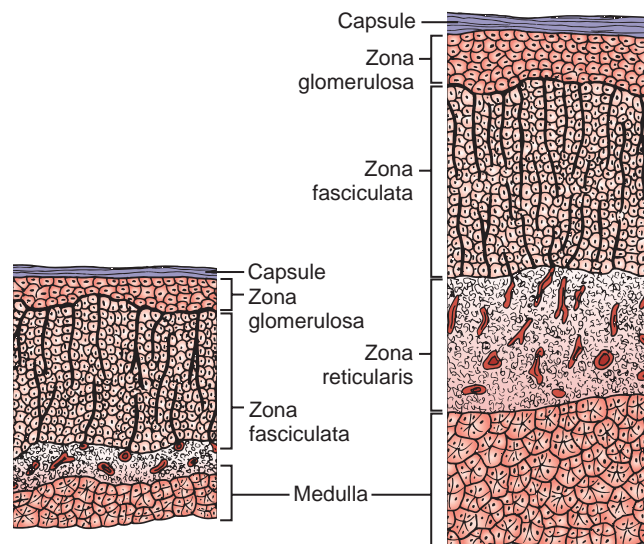


Figure 64-9. Cross-sections through the infant and adult adrenal gland. (From Bloom W, Fawcett DW. *Bloom and Fawcett: textbook of histology*. Philadelphia: Saunders; 1986.)

The adrenal medulla is composed of chromaffin cells arranged in ovoid clusters and cords. This portion of the adrenal gland provides 10% of the weight and volume of the total adrenal gland (Mills, 2007). The medullary cells are large and epithelioid in appearance, and they are closely associated with medullary capillaries. They are often poorly outlined and are arranged in vague clusters with nuclei of varying sizes (Mills, 2007). Chromaffin cells are postganglionic sympathetic neurons that have lost their axons and dendrites (Paulsen, 1996). Staining and electron microscopy of these cells can differentiate between those that secrete epinephrine and those that secrete norepinephrine (Bloom and Fawcett, 1986).

RADIOLOGY

Several imaging modalities are used to image the adrenal gland and its pathology. These include computed tomography (CT), magnetic

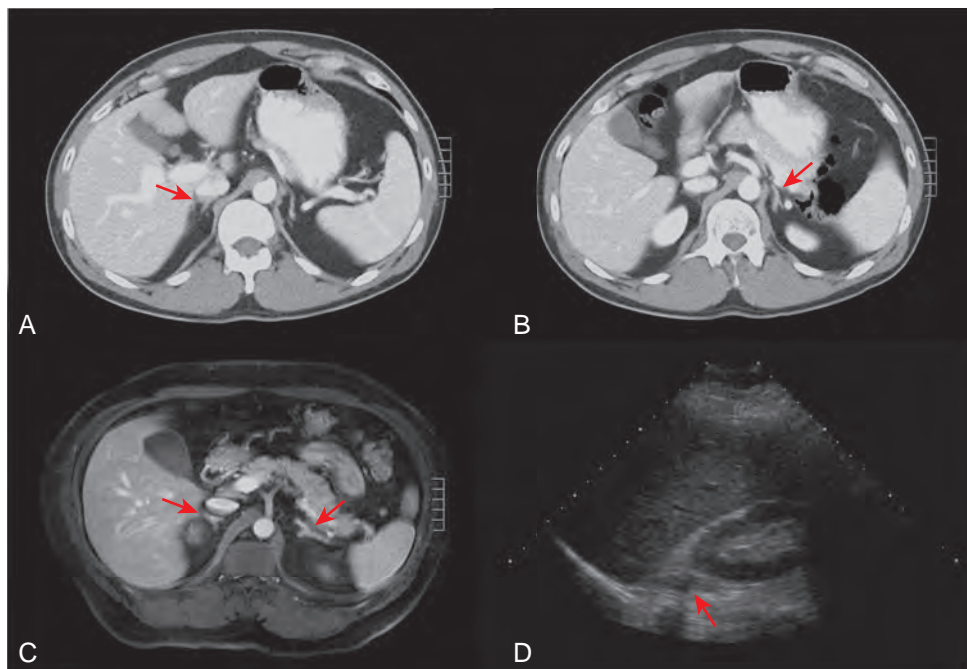


Figure 64-10. Radiographic images of the adrenal glands. A, Axial computed tomography (CT) image of abdomen with arrow indicating right adrenal gland. B, Axial CT image of abdomen with arrow indicating left adrenal gland. C, T1-weighted axial magnetic resonance image of abdomen with arrows indicating right and left adrenal glands. D, Ultrasound image of right upper quadrant with arrow indicating right adrenal gland.

resonance imaging (MRI), ultrasonography (US), angiography, metaiodobenzylguanidine scan, and positron emission tomography. Adrenal imaging is beneficial for the evaluation of abnormal adrenal morphology or function, and it is discussed in further detail in other chapters. This section reviews normal adrenal anatomy using CT, MRI, US, and angiography.

Computed Tomography

CT is the most widely used imaging modality for imaging the adrenal glands. The perinephric adipose tissue allows for clear visualization of the adrenal gland with outstanding resolution. Although CT provides excellent morphologic information, it does not provide functional data. On axial sections, the adrenal glands present the appearance of an inverted “V” or “Y.” The limbs of the normal adrenal gland are usually thinner than the adjacent diaphragmatic crura, with a width of approximately 3 to 6 mm. The right adrenal gland lies just superior to the upper pole of the right kidney and posterolateral to the IVC (Fig. 64-10A). The left adrenal gland is slightly more caudal and lies anterior and medial to the upper pole of the left kidney and posterior to the splenic vessels (Fig. 64-10B). Normal adrenal tissue has a density of less than or equal to 10 Hounsfield units (HU) on noncontrast CT imaging.

Magnetic Resonance Imaging

MRI of the adrenal glands is slightly inferior to CT in terms of spatial resolution, but MRI is a useful adjunct in selected cases of abnormal pathology. Coronal or sagittal images may confirm the adrenal origin of a mass when axial images are equivocal. Contrast resolution of MRI, via T1-weighted and T2-weighted images, is superior to that of CT and enables differentiation of adrenal masses. The technique of flow-related enhancement allows excellent evaluation of the arterial and venous vasculature. The transverse imaging plane is most commonly used to evaluate the adrenal gland at an MRI slice thickness of less than or equal to 3 mm. On T1-weighted images, the normal adrenal gland has a uniform

intermediate signal intensity that is slightly less intense than that of the liver and renal cortical tissue (Fig. 64-10C). On T2-weighted images, the normal adrenal gland is difficult to distinguish from retroperitoneal adipose tissue because of the presence of intracellular lipid within the gland.

Ultrasonography

US imaging of the adrenal glands is typically performed to identify abnormalities. When the normal adrenal glands are visualized with this modality, they appear as hypoechoic structures (Fig. 64-10D). The retroperitoneal adipose tissue can make it difficult to differentiate normal adrenal tissue from the surrounding structures. As a result, US imaging is more commonly used for differentiating between solid and cystic masses of the adrenal gland.

Angiography

Adrenal venous sampling is performed to provide functional information by obtaining blood samples for metabolic assay. Inferior vena cavography can be performed to evaluate the intraluminal component of an adrenal malignancy when CT, MRI, and US are equivocal. Adrenal arteriography is rarely performed or required, because CT and MRI nearly always provide the essential morphologic information required for surgical planning.

CONCLUSION

The adrenal glands have unique anatomic, embryologic, and histologic characteristics. The adrenal gland's anatomic and histologic transformation from fetal development through adulthood is unlike any other organ. An appreciation of their vascular and anatomic relationships is critical both for surgical approaches to the adrenal glands and also to nearby organs. As radiographic imaging of the adrenal glands has evolved, normal and pathologic adrenal anatomy can be better characterized.

KEY POINTS

- Embryologically, the adrenals are distinct from the kidneys, and developmental abnormalities of one organ do not affect the other.
- The adrenal gland is divided into the cortex and the medulla.
- The adrenal cortex is composed of three distinct areas: the ZG, the ZF, and the ZR.
- The adrenal medulla receives preganglionic sympathetic input that stimulates the release of catecholamines from the medullary chromaffin cells.
- Arterial supply to the adrenals arises from branches of the inferior phrenic artery, aorta, and renal artery.
- Venous drainage of the adrenals varies by side, with the right adrenal vein entering the IVC and the left adrenal vein entering the left renal vein.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Historical Background

Adrenal Anatomy and Embryology

Adrenal Physiology

Adrenal Disorders

Evaluation of Adrenal Lesions in Urologic Practice

Conclusions

The adrenal glands are small and deceptively simple. Formerly known as the *suprarenal glands*, given their location above the kidneys, this paired triangular organ sits at an anatomic crossroads in the upper abdomen adjacent to major vessels, nerves, and other vital organs, which the adrenal glands help to monitor and regulate. The complexities of adrenal endocrine and neurocrine function only recently have been more fully recognized. Indeed, **adrenals are now known to be central to homeostasis**. Moreover, pathology involving the glands is responsible for major human ailments.

Given the varied systemic adrenal functions and dysfunctions, medical management is primarily within the purview of endocrinologists, nephrologists, and cardiologists. Similarly, surgical management of adrenal diseases historically has been divided among urologists, general surgeons, surgical oncologists, and, more recently, endocrine surgeons, with referral patterns often dependent on traditions established at individual institutions (Simhan et al, 2012b). With the urologist's advanced minimally invasive surgical skills, comfort with both retroperitoneal anatomy and surgical approaches to retroperitoneal organs, and the close relationship between renal and adrenal pathophysiology, **it is natural that the evaluation and surgical management of adrenal disorders remain firmly in the domain of practicing urologic surgeons.**

HISTORICAL BACKGROUND

The diminutive adrenal glands were easily overlooked by early physicians. Distinguished anatomists such as Galen, da Vinci, and Vesalius omitted the adrenal glands in their descriptions of the retroperitoneum. Bartholomaeus Eustachius was the first to describe the organs in the mid-16th century (Scott, 1990). Not until the mid-19th century was the critical importance of the adrenal recognized when Thomas Addison, an English physician, described a series of patients with the condition of **adrenal insufficiency** that now carries his name. He linked the disease to the adrenal glands on careful inspection of the organs at autopsy (Addison, 1855). Soon thereafter, Charles Brown-Séquard, through a series of animal experiments, demonstrated that **bilateral adrenalectomy uniformly resulted in death**, suggesting that the adrenals were indispensable to the survival of the host (Brown-Séquard, 1856). William Osler was the first to report treatment of Addison disease with hormonal replacement in 1896. He administered crude extract from the adrenal glands of pigs to a patient with Addison disease and produced significant weight gain in this one individual (Oliver and Sharpey-Schafer, 1895). In the ensuing half-century, "adrenalin"

was discovered, and its production was localized to the adrenal medulla (Oliver and Sharpey-Schafer, 1895). The ability of adrenalin to produce a sustained rise in blood pressure was subsequently determined (Abell and Crawford, 1897). Moreover, the failure of this substance, later termed "epinephrine," to sustain life after bilateral adrenalectomy underscored the complexity and multifunctionality of the adrenal gland and established Addison disease as an ailment of the adrenal cortex (Scott, 1990; Porterfield et al, 2008). Discovery and isolation of cortisol from the adrenal gland in the 1930s and subsequent work on its use to treat rheumatoid arthritis produced a 1950 Nobel Prize in Physiology or Medicine for Edward Kendall, Philip Hench, and Tadeus Reichstein (Scott, 1990). Aldosterone was ultimately isolated from the bovine adrenal in 1952 (Grundy et al, 1952). The latter part of the 20th century witnessed a rapid transformation in our understanding and treatment of adrenal disorders led by pioneers such as Jerome Conn, Lawson Wilkins, Grant Liddle, and Earl Sutherland (Scott, 1990).

ADRENAL ANATOMY AND EMBRYOLOGY

Overview

The adrenal glands are paired retroperitoneal organs composed of a cortex and medulla. Gross examination reveals a distinct spiculated mustard-yellow-colored cortex that is distinct from the surrounding perinephric fat and the inner medulla, which can be distinguished macroscopically on cross section by its central brown color (see Figs. 65-1 and 65-2 on the Expert Consult website). The normal adrenal glands weigh an average of 4 to 5 g each and range in size from 4 to 6 cm in length and 2 to 3 cm in width (Mitty, 1988; Silverman and Lee, 1989; Avisse et al, 2000). Morphologically, the right adrenal gland is triangular, whereas the left adrenal gland is crescent-shaped (Avisse et al, 2000). They may sit either immediately superior to the kidney, "capping" the upper pole, or superior medially to the upper pole, "cradled" by the kidney just above the renal vessels. Once understood, this difference can be appreciated through either computed tomography (CT) scan or magnetic resonance imaging (MRI) and is a relevant surgical distinction, particularly in patients with substantive perinephric fat and on the left side when identifying the adrenal vein.

Embryology

The adrenal cortex and the medulla are two embryologically and functionally distinct units. The cortex is derived from the intermediate mesoderm of the urogenital ridge (Mitty, 1988; Barwick et al,

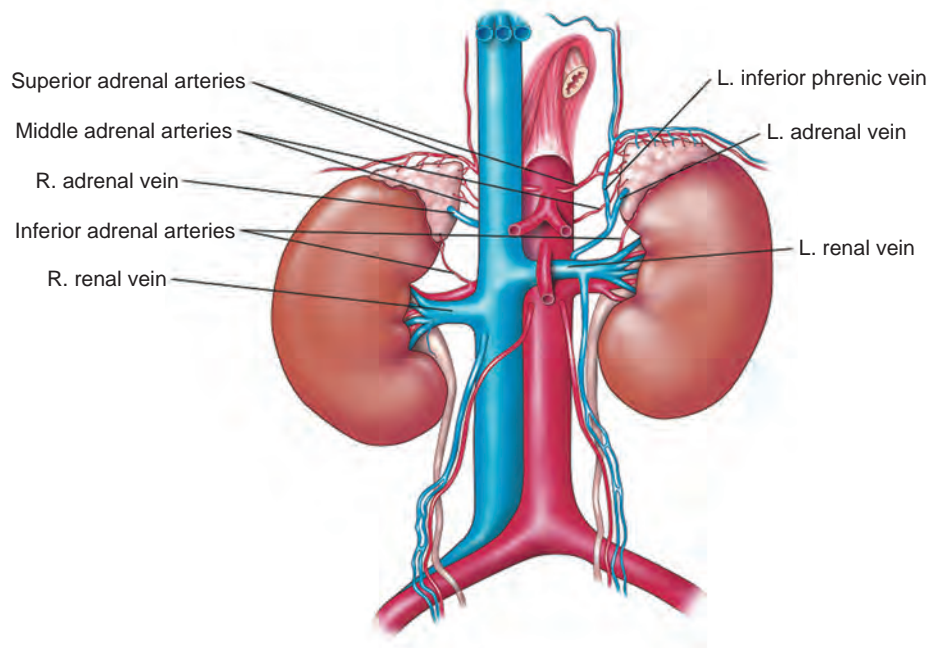


Figure 65-1. Adrenal vascular supply demonstrating inflow from the superior, middle, and inferior adrenal arteries bilaterally. Whereas the right adrenal vein drains directly into the posterior inferior vena cava, the left adrenal vein will often communicate with the inferior phrenic vein before draining into the left renal vein. (Courtesy the University of Kentucky.)

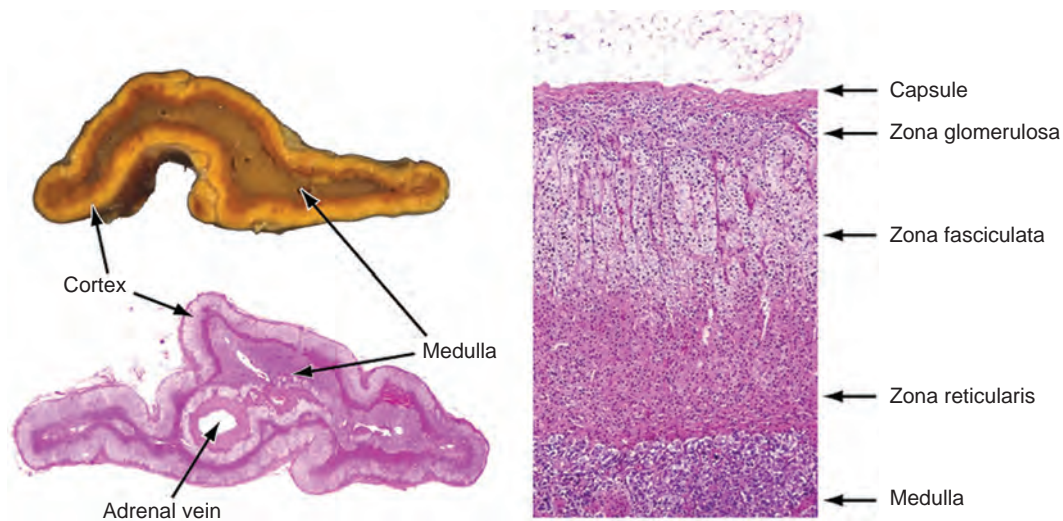


Figure 65-2. Normal adrenal gland histology. Macroscopic and low-power microscopic views of the adrenal cortex and medulla. The three layers of the adrenal medulla (glomerulosa, fasciculata, and reticularis) produce mineralocorticoids (aldosterone), glucocorticoids (cortisol), and sex steroids (adrenal androgens and estrogens), respectively. The acronym *GFR = ACE* summarizes this relationship (glomerulosa, fasciculata, reticularis = aldosterone, cortisol, estrogen) nicely. (Courtesy Dr. Thomas J. Sebo, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.)

2005). Beginning in the 5th week of gestation, mesenchymal cells located at the urogenital ridge and the root of the mesentery proliferate and form the cortex of the fetal adrenal gland. During the 6th and 7th weeks of gestation, additional mesothelial cells surround the fetal adrenal cortex, which will later form the adult adrenal cortex (Mitty, 1988; Barwick et al, 2005). By the end of the 8th week of gestation the mesothelial cells forming the cortex are encapsulated by connective tissue and have separated from the peritoneal mesothelium. In distinction, the adrenal medulla is derived from neural crest cells, located in adjacent sympathetic ganglia, which migrate into the medial aspect of the fetal adrenal cortex by the 9th week of gestation (Kempna and Fluck, 2008). The neural crest cells continue to invade the adrenal cortex until they achieve a central position surrounding the adrenal vein by the 18th week of gestation. This embryologic relationship explains the brown stippling of the adrenal cortex.

At birth, the fetal adrenal gland is twice the weight of an adult adrenal gland but has not completed development. After birth, the fetal cortex begins to atrophy and will be completely resorbed by 12 months of age (Mitty, 1988). As the fetal cortex is being resorbed, the zona glomerulosa and fasciculata of the adult cortex continue to develop, but the zona reticularis will not complete differentiation until 3 years of age, reflecting the relative late importance of sex steroid production by this part of the adrenal cortex (Barwick et al, 2005; Kempna and Fluck, 2008).

Cases of unilateral adrenal agenesis are rare and are often associated with unilateral renal agenesis (Nakada et al, 1988; Else and Hammer, 2005). However, because adrenal and renal development are separate processes, this association is likely spurious and is the result of limited radiographic evaluation of the ipsilateral adrenal gland in cases of renal agenesis. **Most often, adrenal gland development occurs normally in the absence of ipsilateral renal unit development, malrotation, or malascence. In these cases, the adrenal glands are often discoid in shape and located in their normal position within the retroperitoneum (Mitty, 1988).**

More common anomalies of adrenal gland development include accessory adrenal tissue and adrenal heterotopia. Accessory renal tissue, also known as *adrenal rests*, can be composed of cortical or medullary tissues. Owing to the close proximity of the adrenal gland and genitourinary organ development, adrenal rests can be found anywhere along the path of gonadal descent within the retroperitoneum. Although adrenal rests can be found in up to 50% of neonates, the tissue typically atrophies and is found in only approximately 1% of adults (Barwick et al, 2005). In cases of congenital adrenal hyperplasia (CAH), adrenal rest within the testis may become hyperplastic and manifest as a testicular mass. This is an important consideration before performance of an orchiectomy for a testicular mass in patients with CAH. Adrenal heterotopia results from incomplete separation of primitive adrenal mesoderm from adjacent organs such as the liver or kidney, resulting in partial or complete incorporation of the gland into the adjacent organ.

Anatomy

The right and left adrenal glands are located within the Gerota fascia at the levels of the 11th and 12th ribs and share several important anatomic relationships, including being located cephalad to the upper pole of the kidneys and anterior to the crus of the diaphragm. The right adrenal is bounded medially by the inferior vena cava (IVC) and anteriorly by the liver; the left adrenal gland is bounded medially by the aorta and anteriorly by the stomach, pancreas, and splenic vessels. The close juxtaposition of these organs to the adrenal explains why lesions of adjacent organs, such as leiomyomas of the greater curvature of the stomach, may be confused for an adrenal mass.

As with most endocrine organs, the blood supply to the adrenal gland is redundant. Although variable, the arterial supply of each adrenal gland may arise from three main sources: superior adrenal arteries (branches from the inferior phrenic arteries), middle adrenal arteries (direct visceral branches from the aorta), and inferior adrenal arteries (branches from the ipsilateral renal artery (see Fig.

65-1). The main adrenal arteries then branch to form a subcapsular plexus. From the subcapsular plexus some branches continue directly to the medulla, and others form sinusoids supplying the adrenal cortex. On the venous side, medullary veins coalesce to form the adrenal vein, which is surrounded by medullary tissue within the adrenal gland. The short right adrenal vein drains directly into the vena cava. On the left, the adrenal vein is long compared with the right and is joined by the inferior phrenic vein before draining into the left renal vein. The overlapping of both arterial and venous anatomy makes partial adrenalectomy possible with little risk of subsequent adrenal infarction. The principal lymphatic drainage of the adrenal glands is through the paracaval lymph nodes on the right and the para-aortic lymph nodes on the left.

The autonomic innervation of the adrenal glands includes predominantly preganglionic sympathetic fibers off the sympathetic trunk directly to the chromaffin cells of the adrenal medulla, whereas postganglionic fibers originating from the splanchnic ganglia provide innervation to the adrenal cortex. Parasympathetic innervation to the adrenal cortex and medulla is not well defined; however, animal models suggest that parasympathetic branches originating from the vagus nerve may be present.

Histology

Each adrenal gland is enclosed within a fibrous capsule (see Fig. 65-2). Directly beneath the capsule is the cortex, which consists of three zones: the zona glomerulosa, the zona fasciculata, and the zona reticularis. The zona glomerulosa consists of small polyhedral cells with scant eosinophilic cytoplasm and dark round nuclei. The essential function of the glomerulosa is the production of mineralocorticoids, predominantly aldosterone. The broad layer of large pale cells arranged in vertical columns beneath the zona glomerulosa is the zona fasciculata responsible for the production of glucocorticoids such as cortisol. The zona reticularis, the innermost layer of the cortex, consists of round dark-staining cells and predominantly produces sex steroids, such as adrenal estrogens and androgens (Mitty, 1988; MacLennan et al, 2003) (Table 65-1).

KEY POINTS: ANATOMY AND EMBRYOLOGY

- The adrenal glands are composed of two embryologically and functionally distinct components: the cortex and the medulla (the former endocrine, the latter neurocrine).
- The arterial supply of the adrenal glands is variable and can arise from several sources. However, the venous drainage is more predictable, with the right adrenal vein emptying into the IVC and the left adrenal vein draining into the left renal vein in the majority of patients.

ADRENAL PHYSIOLOGY

Other than their juxtaposed anatomic associations, the adrenal cortex and the adrenal medulla are best conceptualized as two distinct organs, the former endocrine and the latter neurocrine.

Adrenal Cortex Physiology

As part of a multistep synthetic pathway, numerous enzymes of the adrenal cortex catalyze conversion of essential steroid hormones from the common precursor cholesterol. Low-density lipoprotein (LDL) serves as the primary source of cholesterol for the adrenals (Arlt and Stewart, 2005). **Ratios and types of enzymes in each zone of the adrenal cortex vary, resulting in different hormonal products for each region (Fig. 65-3) (Rainey, 1999).**

Steroid hormone receptors are absent on cellular membranes of target tissues. Instead, steroids diffuse passively into the cell and bind to their respective receptors intracellularly. Gene transcription is then modulated by direct binding of the hormone receptor

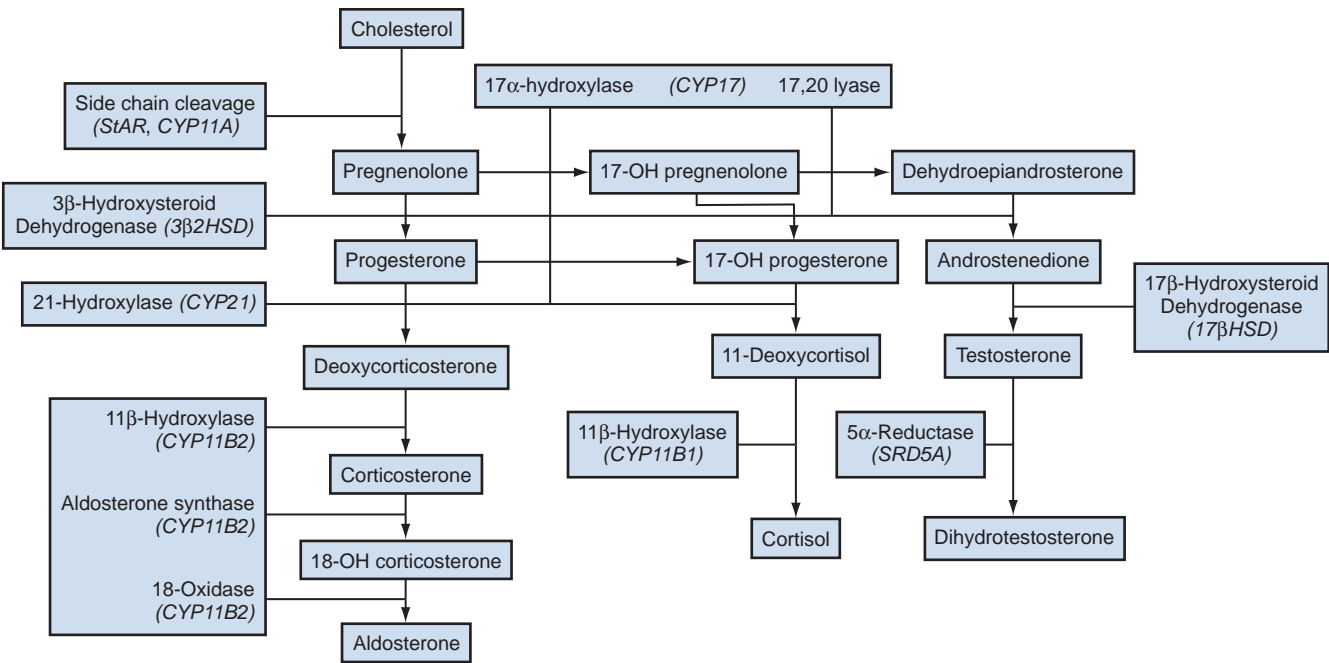


Figure 65-3. Steroid hormone synthesis beginning with cholesterol and resulting in mineralocorticoid, glucocorticoid, and androgen production in the adrenal cortex. Enzymes are listed in boxes and genes in parentheses. (From Hyun G, Kolon TF. A practical approach to intersex in the newborn period. *Urol Clin North Am* 2004;31:435–43.)

TABLE 65-1 Primary Effects of Mineralocorticoids

ACTION	EFFECT	SITE OF ACTION
Renal sodium reabsorption	Increased blood volume Increased blood pressure Decreased urine sodium	Distal tubule Connecting segment Collecting duct
Renal chloride reabsorption	Increased serum chloride Decreased urine chloride	Distal tubule Connecting segment Collecting duct
Renal potassium secretion	Decreased serum potassium Increased urine potassium	Distal tubule Connecting segment Collecting duct
Renal proton secretion	Increased urine NH ₄	Collecting duct—a result of sodium reabsorption

NH₄, ammonia.

complex to target DNA (Arlt and Stewart, 2005). As discussed previously, the three main zones of the adrenal cortex are the zona glomerulosa, zona fasciculata, and zona reticularis, with each zone primarily responsible for mineralocorticoid (100 to 150 µg/day), glucocorticoid (10 to 20 mg/day), and androgen synthesis (>20 mg/day), respectively (Arlt and Stewart, 2005).

Zona Glomerulosa

The zona glomerulosa is the outermost region of the adrenal cortex and is the only zone of the adrenal gland that contains

the enzyme aldosterone synthase (CYP11B2). As a result, the glomerulosa cells of this tissue are the sole source of aldosterone—the primary human mineralocorticoid (Rainey, 1999). Aldosterone regulates electrolyte metabolism by stimulating epithelial cells of the distal nephron to reabsorb Na⁺ and Cl[−], while secreting H⁺ and K⁺. Although aldosterone levels have a profound effect on total body Na⁺, concentration of the ion does not change, whereas reabsorption of sodium is accompanied by reuptake of free water. Therefore aldosterone primarily affects total body volume and not sodium concentration (White, 1994; Arlt and Stewart, 2005). Electrolyte balance in epithelial cells of the submaxillary salivary glands and the large intestine are also under mineralocorticoid control; however, the physiologic importance of this phenomenon is likely minimal (Bastl and Hayslett, 1992).

Aldosterone levels are primarily regulated by angiotensin II through the renin-angiotensin-aldosterone system (RAAS) and directly by serum potassium levels. A rise in adrenocorticotrophic hormone (ACTH) can also increase aldosterone secretion, but this is a much less potent stimulus (White, 1994; Arlt and Stewart, 2005). For this reason the zona glomerulosa is the only region of the adrenal cortex that does not atrophy on pituitary failure (Hubbard et al, 1990). Atrial natriuretic peptide is the main inhibitory regulator of aldosterone secretion, providing an important link among cardiac, adrenal, and renal function—although somatostatin, dopamine, and others may also play a role (Spat and Hunyady, 2004). A working knowledge of the RAAS is critical in conceptualizing and managing hyperaldosteronism. The pathophysiology of this pathway is discussed in the section on Conn syndrome.

Zona Fasciculata

The zona fasciculata is the site of glucocorticoid production as a result of zonal expression of 17α-hydroxylase, 21-hydroxylase, and 11β-hydroxylase enzymes (see Fig. 65-3) (Arlt and Stewart, 2005). Cortisol is the primary glucocorticoid in humans, and its secretion is under tight control of the ACTH. Accordingly, cortisol and ACTH are a part of a classic hormonal negative feedback system that features the hypothalamus, the pituitary gland, and the adrenal glands. The physiology of this axis is discussed in more detail in the

TABLE 65-2 Primary Effects of Glucocorticoids

EFFECTS	CLINICAL IMPLICATIONS
Enhance skeletal and cardiac muscle contraction	Absence results in weakness.
Cause protein catabolism	Excess results in muscle wasting and weakness.
Inhibit bone formation	Excess decreases bone density.
Inhibit collagen synthesis	Excess causes thin skin and fragile capillaries.
Increase vascular contractility and decrease permeability	Absence makes it difficult to maintain blood pressure.
Have anti-inflammatory activity	Exogenous steroid is useful in treating inflammatory diseases.
Have anti-immune system activity	Exogenous steroids are useful in promoting transplant tolerance and in treating autoimmune disorders.
Maintain normal glomerular filtration rate	Absence reduces glomerular filtration rate.

From Howards SS, Carey RM. The adrenals. In: Gillenwater JY, Grayhack JT, Howards SS, et al, editors. Adult and pediatric urology. 2nd ed. Chicago: Year Book; 1991.

section on Cushing syndrome (Jacobson, 2005). Production of cortisol by the adrenal glands follows a strict circadian schedule, with the majority of the hormone being secreted in the early morning (Jacobson, 2005). Glucocorticoids are essential to life and modulate complex physiologic pathways that include metabolism, immunity, maintenance of intravascular volume, regulation of blood pressure, and complex modulation of the central nervous system with significant effects on mood, sleep, and potentially memory (Arlt and Stewart, 2005) (Table 65-2).

Zona Reticularis

The zona reticularis is the innermost zone of the adrenal cortex. The presence of 17 α -hydroxylase and 17,20-lyase results in the production of dehydroepiandrosterone (DHEA), sulfated DHEA (DHEA-S), and androstenedione to this region, although some androgen synthesis also occurs in the zona fasciculata. Adrenal androgen secretion appears to be under control of ACTH, and, like cortisol, exhibits circadian patterns (Arlt and Stewart, 2005). DHEA, DHEA-S, and androstenedione comprise the greatest portion of steroid hormone that is produced by the adrenals (>20 mg/day), but appear to be the least important for adult physiologic homeostasis (Nguyen and Conley, 2008); however, pharmacologic manipulation of adrenal androgen production remains a viable and increasingly targeted strategy for advanced prostate cancer (see Chapter 121). Moreover, aberrations in production of these hormones during development are responsible for significant pathology and result in the clinical entity known as *congenital adrenal hyperplasia* (Finkelstein and Shaefer, 1979; Hubbard et al, 1990). CAH is discussed in detail in Chapter 150.

Adrenal Medulla Physiology

The adrenal medulla comprises less than 10% of total adrenal mass. Neither its function nor its embryology is related to the neighboring cortex. Instead, this portion of the adrenal gland, which lies at the center of the gland, is an integral part of the autonomic nervous system. Chromaffin cells of the medulla are innervated by preganglionic sympathetic fibers of T11 through L2,

making them analogous to cells of the sympathetic ganglia. The medulla secretes epinephrine (80%), norepinephrine (19%), and dopamine (1%). These substances, collectively known as *catecholamines*, are produced from the amino acid tyrosine and modulate the systemic stress response (Fig. 65-4) (Robertson, 1990; de Diego et al, 2008). The effects of these catecholamines are mediated through their binding to adrenoreceptors located on target organs. The nature of these effects depends on the adrenoreceptor types or subtypes located and stimulated on a particular end organ (Table 65-3) (Robertson, 1990; Guimaraes and Moura, 2001). It is interesting to note that the enzyme phenylethanolamine-N-methyltransferase (PNMT), which catalyzes the conversion of norepinephrine to epinephrine, is relatively unique to the adrenal medulla (the brain and organ of Zuckerkandl also express this enzyme). The function of this enzyme is potentiated by the presence of glucocorticoids, thereby creating one of the few physiologic links between the adrenal cortex and the medulla. **Localization of PNMT to the adrenal medulla explains why the gland is the primary source of systemic epinephrine**, despite the presence of similar chromaffin cells elsewhere in the sympathetic nervous system (Robertson, 1990). Similar to the physiology that controls norepinephrine release at synaptic nerve terminals, the storage and release of adrenal catecholamines involves intracellular vesicles. Liberation of these vesicles through exocytosis results in release of adrenal catecholamines into the bloodstream (Eisenhofer et al, 2004b).

The metabolism of catecholamines is complex, and some controversy still exists about the physiologic relevance of each pathway (Eisenhofer et al, 2004b). The majority of adrenal catecholamine metabolism occurs at the scene of production in cells of the adrenal medulla themselves (Eisenhofer et al, 2003a). For clinical purposes, three metabolites (metanephrine, normetanephrine, and vanillylmandelic acid [VMA]) and two enzymes (catechol-O-methyltransferase [COMT] and monoamine oxidase [MAO]) are important. Metanephrine and normetanephrine result from respective methylation of epinephrine and norepinephrine by COMT. Although large amounts of this enzyme are present in the liver and kidneys, the majority of adrenal catecholamine metabolites are methylated by COMT within the cells of the adrenal medulla (Eisenhofer et al, 2003a). Indeed, over 90% of metanephrine (epinephrine metabolite) and some 20% or more of normetanephrine (a norepinephrine metabolite) in the bloodstream are derived from the adrenal medulla. Therefore a measurable rise in the level of these metabolites is very useful when diagnosing potential pheochromocytomas (see section on *assessment of function of adrenal masses*) (Eisenhofer et al, 1995). In the urine, most of these metabolites are excreted in a sulfonated form. Furthermore, MAO and other enzymes subsequently participate in the conversion of catecholamine metabolites to VMA, the primary catecholamine metabolic end product that is largely formed by the liver. Nonadrenal catecholamines from the sympathetic nervous system are similarly converted to VMA (Eisenhofer et al, 2004b). Figure 65-4 summarizes the most clinically relevant aspects of the catecholamine metabolism pathway.

ADRENAL DISORDERS

Disorders of Increased Adrenal Function

Cushing Syndrome

Overview and Epidemiology. Hypercortisolism secondary to excessive production of glucocorticoids by the adrenal cortex is defined as Cushing syndrome (Orth and Liddle, 1971). The disease is rare and occurs in 2 to 5 of every million people per year (Lindholm et al, 2001; Findling and Raff, 2005). Diagnosis and treatment of Cushing syndrome is multifaceted, often requiring cooperation of internists, endocrinologists, neurosurgeons, and adrenal surgical experts (Newell-Price et al, 2006). The urologist must understand the comprehensive pathophysiology of hypercortisolism and have particularly advanced expertise in the aspects of this complex disease for which adrenalectomy is required.

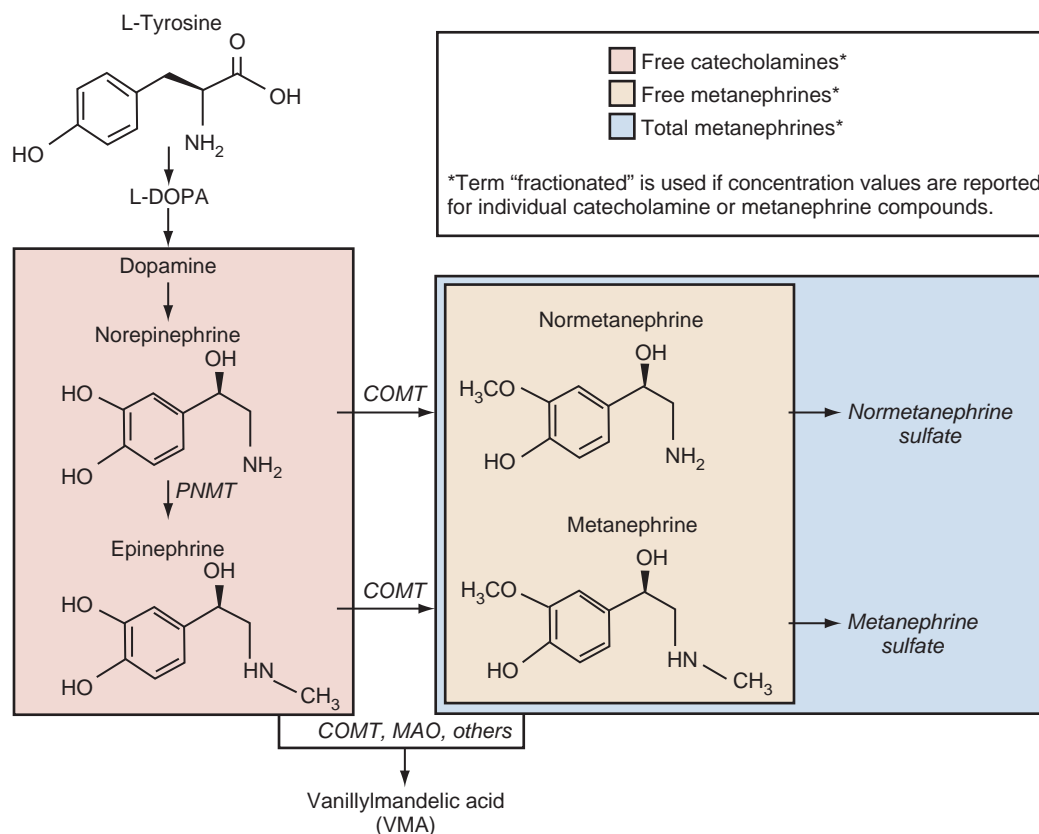


Figure 65-4. Summary of catecholamine metabolism. The figure simplifies the metabolic pathway of norepinephrine and epinephrine degradation to highlight those metabolic products that play a role in routine clinical practice. Note: The central role that the monoamine oxidase (MAO) enzyme plays in catecholamine degradation is not fully reflected in this figure, because most metabolites that are produced by MAO catalysis are not routinely measured in laboratory assessments for pheochromocytoma. Key enzymes involved in catalysis of metabolic conversions are indicated in *italic font*. COMT, catechol-*O*-methyltransferase; PNMT, phenylethanolamine-*N*-methyltransferase.

KEY POINTS: PHYSIOLOGY

- Adrenal cortex and the adrenal medulla are best conceptualized as two distinct organs, the former endocrine and the latter neurocrine.
- Three main zones of the adrenal cortex are the zona glomerulosa, zona fasciculata, and zona reticularis, with each zone primarily responsible for mineralocorticoid, glucocorticoid, and androgen synthesis, respectively.
- Ratios and types of enzymes in each zone of the adrenal cortex vary, resulting in different hormonal products for each region.
- Aldosterone levels are primarily regulated by angiotensin II through the RAAS and directly by serum potassium levels. ACTH is less important in regulation of this region's function; therefore the zona glomerulosa is the only region of the adrenal cortex that does not atrophy on pituitary failure.
- Cortisol is the primary glucocorticoid in humans, and its secretion is under tight ACTH control.
- Pharmacologic manipulation of adrenal androgen production is an increasingly targeted strategy for treatment of advanced prostate cancer.
- Substances collectively known as *catecholamines*—epinephrine, norepinephrine, and dopamine—are produced from the amino acid tyrosine and modulate the systemic stress response.

Pathophysiology. The zona fasciculata of the adrenal cortex secretes more than 20 mg of cortisol every day (Arlt and Stewart, 2005). Regulation of this secretion is controlled through the hypothalamic-pituitary-adrenal (HPA) axis (Jacobson, 2005). A fluent understanding of this classic neuroendocrine negative feedback system is critical for the successful management of every Cushing patient.

Normal Hypothalamic-Pituitary-Adrenal Axis Physiology. Corticotrophic cells of the anterior pituitary secrete ACTH, also known as *corticotropin*, under the influence of neuronal innervations from the hypothalamus. Synthesis of ACTH is a result of cleavage of the pro-opiomelanocortin (POMC) precursor molecule. Physiologically, the most important promoter of ACTH release is corticotropin-releasing hormone (CRH), but oxytocin and vasopressin also play a role (Jacobson, 2005; Sam and Frohman, 2008). Stress, whether physiologic or psychologic, appears to be the most important variable in modulating activity of the HPA axis (Jacobson, 2005).

ACTH not only is responsible for promoting production of glucocorticoids and androgens by the adrenal cortex, but it also plays a critical role in maintaining adrenal cortical vitality. Indeed, without ACTH (e.g., when its secretion is suppressed by exogenous steroid intake), all but the mineralocorticoid-producing cells of the adrenal cortex arrest hormone production and undergo apoptosis (Arlt and Stewart, 2005; Jacobson, 2005). In addition to ACTH, splanchnic nerves that innervate the adrenals also appear to affect glucocorticoid production (Jacobson, 2005).

TABLE 65-3 Primary Effects of Catecholamines

EFFECTOR ORGANS	RECEPTOR TYPE	RESPONSES	MOST RELEVANT CLINICAL MANIFESTATIONS
Eye			
Radial muscle, iris	α_1	Contraction (mydriasis) ++	Blurry vision
Ciliary muscle	β_2	Relaxation for far vision +	
Heart			
SA node	β_1, β_2	Increase in heart rate ++	Palpitations, angina
Atria	β_1, β_2	Increase in contractility and conduction velocity ++	Palpitations, angina
AV node	β_1, β_2	Increase in automaticity and conduction velocity +++	Palpitations, angina
His-Purkinje system	β_1, β_2	Increase in automaticity and conduction velocity +++	Palpitations, angina
Ventricles	β_1, β_2	Increase in contractility, conduction velocity, automaticity, and rate of idioventricular pacemakers +++	Palpitations, angina
Arterioles			
Coronary	$\alpha_1, \alpha_2, \beta_2$	Constriction +; dilations ++	Angina
Skin and mucosa	α_1, α_2	Constriction +++	Pallor
Skeletal muscle	α, β_2	Constriction ++; dilations ++	Hypertension
Cerebral	α_1	Constriction (slight)	Stroke
Pulmonary	α_1, β_2	Constriction +; dilations ++	Edema
Abdominal viscera	α_1, β_2	Constriction +++; dilations +	For example, bowel ischemia
Salivary glands	α_1, α_2	Constriction +++	
Renal	$\alpha_1, \alpha_2, \beta_1, \beta_2$	Constriction +++; dilations +	Renal failure
Veins (systemic)	$\alpha_1, \alpha_2, \beta_2$	Constriction ++; dilations ++	Orthostatic hypotension
Lung			
Tracheal and bronchial muscle	β_2	Relaxation +	
Bronchial glands	α_1, β_2	Decreased secretion; increased secretion	
Stomach			
Motility and tone	$\alpha_1, \alpha_2, \beta_2$	Decrease (usually) +	Early satiety, discomfort
Sphincters	α_1	Contraction (usually) +	
Intestine			
Motility and tone	$\alpha_1, \alpha_2, \beta_1, \beta_2$	Decrease +	Constipation, ileus
Sphincters	α_1	Contraction (usually) +	
Secretion	α_2	Inhibition	Constipation
Gallbladder and ducts	β_2	Relaxation +	Gallstones
Kidney			
Renin secretion	α_1, β_2	Decrease +; increase ++	
Urinary bladder			
Detrusor	β_2	Relaxation (usually) +	Urinary retention
Trigone and sphincter	α_1	Contraction ++	Urinary retention
Ureter			
Motility and tone	α_1	Increase	
Uterus	α_1, β_2	Pregnant; contraction; relaxation Nonpregnant; relaxation	
Sex organs, male	α_1	Ejaculation ++	
Skin			
Pilomotor muscles	α_1	Contraction ++	Sweating
Sweat glands	α_1	Localized secretion +	
Spleen capsule	α_1, β_2	Contraction +++; relaxation +	
Skeletal muscle	β_2	Increased contractility; glycogenolysis; K^+ uptake	Hyperglycemia, glycosuria
Pancreas			
Acini	α	Decreased secretion +	Hyperglycemia, glycosuria Hypoglycemia Feeling warm
Islets (β cells)	α_2	Decreased secretion +++	
	β_2	Increased secretion +	
Fat cells	$\alpha_2, \beta_1, \beta_2$	Lipolysis +++ (thermogenesis)	
Salivary glands	α_1	K^+ and water secretion +	
	β	Amylase secretion +	
Lacrimal glands	α	Secretion +	Lacrimation
Pineal gland	β	Melatonin synthesis	
Posterior pituitary	β_1	Antidiuretic hormone secretion	Decreased diuresis

Highest (+++) to lowest (+) intensity of adrenergic nerve activity in the control of various organs and functions listed. Where (+) is not given, intensity is not specified.

AV, atrioventricular; SA, sinoatrial.

Modified from Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab 2007;92:4069–79.

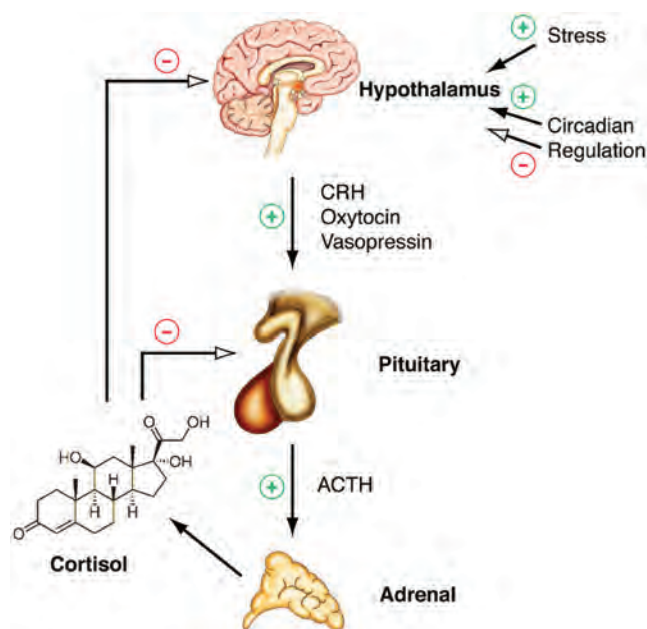


Figure 65-5. The hypothalamic-pituitary-adrenal axis and feedback loop. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

Glucocorticoids bind receptors in the hypothalamus and the pituitary and complete the negative feedback loop by inhibiting production of CRH and ACTH by these structures, respectively (Jacobson, 2005). Figure 65-5 summarizes the salient features of the HPA axis.

It is important to understand that CRH secretion is under tight control of the hypothalamic suprachiasmatic nucleus and follows circadian patterns. The highest level of cortisol in healthy subjects is detected in the mornings, and the nadir is observed at approximately 11 PM. Even small perturbations of this physiologic rhythm are considered pathologic (Jacobson, 2005; Sam and Frohman, 2008).

Overview of Cushing Syndrome. Given the sophistication of the HPA axis, hypercortisolism can result from a number of different pathologies that result in oversecretion of cortisol by the adrenal glands. Causes of Cushing syndrome can be divided into three main groups: (1) exogenous, (2) ACTH dependent, and (3) ACTH independent (Fig. 65-6). Exogenous Cushing syndrome is a result of iatrogenic glucocorticoid administration. ACTH-dependent disease results from an elevated serum corticotropin level caused by pathology extrinsic to the adrenal gland and accounts for up to 85% of cases of endogenous Cushing syndrome. ACTH-independent hypercortisolism, on the other hand, results from unregulated overproduction of glucocorticoids by the adrenal(s) and is relatively rare. The adrenal surgeon has long been involved in management of ACTH-independent disease, but with the advent of laparoscopy, adrenal surgery for ACTH-dependent Cushing syndrome is becoming more commonplace (Porterfield et al, 2008).

Exogenous Cushing Syndrome. Exogenous Cushing syndrome is the most common cause of hypercortisolism in patients of the Western world (Newell-Price et al, 2006). Synthetic glucocorticoids are frequently used in treatment of many conditions, and Cushing syndrome can result from the administration of even low doses of exogenous steroids orally, topically, or by inhaled preparations (Hopkins and Leinung, 2005; Newell-Price et al, 2006). A careful patient history is therefore essential in the evaluation of all patients with Cushing syndrome. The clinician also must be cognizant of the possibility that the patient either is unaware of his or her steroid use (e.g., use of herbal remedies, nasal sprays) or is surreptitiously self-administering glucocorticoids (e.g., for performance enhancement) (Hopkins and Leinung, 2005).

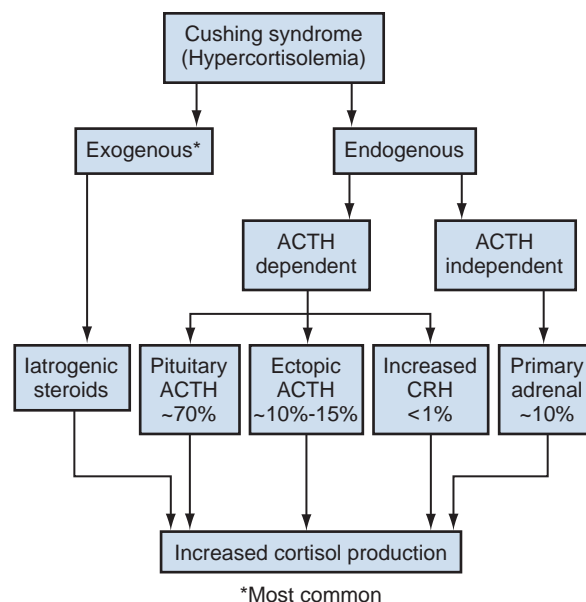


Figure 65-6. Clinically relevant causes of excess cortisol production. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

Adrenocorticotropic Hormone–Dependent Cushing Syndrome

Overview. ACTH-dependent hypercortisolism accounts for 80% to 85% of endogenous Cushing syndrome. Approximately 80% of ACTH-dependent disease results from primary pituitary pathology and is known as *Cushing disease*. Ectopic ACTH production is the other main cause of ACTH-dependent hypercortisolism (Newell-Price et al, 2006). Ectopic CRH syndrome is a third cause of ACTH-dependent Cushing syndrome and is extremely uncommon (see Fig. 65-6) (Orth, 1995).

Cushing Disease. Described by the neurosurgical pioneer Harvey Cushing in 1932, Cushing disease causes hypercortisolism through excessive secretion of ACTH by the pituitary gland (Cushing, 1932). The condition accounts for nearly 70% of endogenous Cushing syndrome. The most common culprit is a corticotropin-producing microadenoma. Large macroadenomas 1 cm or greater are found in only about 5% of cases (Newell-Price et al, 2006). Fifteen percent of functional pituitary adenomas exhibit the ability to secrete ACTH (Shimon and Melmed, 1998). Hyperplasia of ACTH-producing cells and pituitary carcinoma can also oversecrete ACTH but are extremely rare (Orth, 1995). Up to two thirds of individuals with Cushing disease are female (Scott and Orth, 1990).

Ectopic Adrenocorticotropic Hormone Syndrome. Production of ACTH by nonpituitary tumors can also result in hypercortisolism. These corticotropin-producing tissues are nearly always malignant and account for approximately 10% of Cushing syndrome (Porterfield et al, 2008). Liddle and associates first described the phenomenon in the early 1960s and termed it *ectopic ACTH syndrome* (Meador et al, 1962; Scott and Orth, 1990). The timing and onset of hypercortisolism varies and can precede the diagnosis of an extra-adrenal malignancy by many years, resulting in diagnostic difficulties and the clinical conundrum wherein a subclinical pituitary adenoma is suspected but not radiographically identified (Aniszewski et al, 2001). Moreover, hypercortisolism in end-stage debilitated cancer patients is almost certainly underdiagnosed (Orth, 1995). As a result of higher ACTH levels, the adrenal glands of patients with ectopic ACTH syndrome are usually more markedly hyperplastic and thereby larger than those of patients with Cushing disease (Jenkins et al, 1999). Table 65-4 summarizes primary malignancies implicated in ectopic ACTH production, which notably includes pheochromocytoma.

TABLE 65-4 Sources of Ectopic Adrenocorticotrophic Hormone

PARAMETER	CURRENT STUDY	FINDLING AND TYRRELL, 1986*	IMURA ET AL, 1975	DOPPMAN ET AL, 1989	HOWLETT ET AL, 1986
No. of patients	106	49	30	28	16
No tumor found (%)	16	12		32	
Islet cell tumor (%)	16	4	7	11	13
Bronchial carcinoid (%)	25	49	7	46	38
Thymic carcinoid (%)	5	16			13
Medullary thyroid cancer (%)	8				
Disseminated neuroendocrine tumor (%)	7				
Disseminated gastrointestinal carcinoid (%)	1				
Small cell lung cancer (%)	11	10	33		19
Miscellaneous (%)	8	6	17		13†
Pancreatic adenocarcinoma (%)		2			
Adenocarcinoma of the bronchus (%)			10		
Squamous cell carcinoma of the bronchus (%)			3		
Undifferentiated carcinoma of the bronchus (%)			10		
Malignant thymoma (%)			13		
Pheochromocytoma (%)	3			11	6
TOTAL	100	100	100	100	100

*Includes a literature review.

†Carcinoid of the gallbladder and colon cancer.

Modified from Aniszewski JP, Young WF Jr, Thompson GB, et al. Cushing syndrome due to ectopic adrenocorticotrophic hormone secretion. *World J Surg* 2001;25(7):934–40.

Ectopic Corticotropin-Releasing Hormone. Production of CRH by malignancies is extremely rare and is responsible for less than 1% of cases of Cushing syndrome. Bronchial carcinoma is the most common culprit, and concurrent ACTH secretion is not unusual (Carey et al, 1984; Orth, 1995).

Adrenocorticotrophic Hormone-Independent Cushing Syndrome. Uncontrolled hypersecretion of cortisol by adrenal tissues accounts for a minority of endogenous hypercortisolism and is classified as ACTH-independent Cushing syndrome. Adrenal neoplasms and rare forms of bilateral adrenal disease are responsible for this group of conditions (Lacroix and Bourdeau, 2005; Newell-Price et al, 2006).

Adrenal Tumors. Cortisol-secreting benign adenomas of the adrenal gland are responsible for approximately 10% of Cushing syndrome and often result from a dominant unilateral hyperplastic nodule, although multifocal bilateral functional adrenal hyperplasia may also occur. Less than 10% of adrenal masses are bilateral and often present a diagnostic challenge (Lacroix and Bourdeau, 2005; Porterfield et al, 2008; Young et al, 2008). Radiographically undetectable benign adrenal cortisol-producing lesions may also be responsible for cases of subclinical Cushing syndrome (Rossi et al, 2000). Cortisol production by adrenocortical carcinomas (ACCs) accounts for approximately 8% of patients with Cushing syndrome and appears to be an independent predictor of poor outcome for patients with ACC (Lindsay and Nieman, 2005a; Berruti et al, 2014). Cushingoid phenotype resolves for most patients within 7 to 9 months after adrenalectomy; however, it can persist for several years in some individuals (Sippel et al, 2008).

Adrenocorticotrophic Hormone-Independent Macronodular Adrenal Hyperplasia. ACTH-independent bilateral macronodular adrenal hyperplasia (AIMAH) gives rise to less than 1% of Cushing syndrome. The condition is characterized by multiple large (up to 4 cm) nodules replacing the glands, with each adrenal weighing over 60 g (Lacroix and Bourdeau, 2005; Iacobone et al, 2008).

Weights in excess of 200 g have been reported for each gland affected by AIMAH (Swain et al, 1998). It is essential that this disease entity be distinguished from adrenal enlargement caused by chronic adrenal stimulation in ACTH-dependent Cushing syndrome; radiographic images of the adrenals appear similar in both conditions. Bilateral macronodular hyperplasia is observed as a feature of the McCune-Albright syndrome, which also includes polyostotic fibrous dysplasia, dermatologic manifestations, and other endocrine abnormalities (Lacroix and Bourdeau, 2005).

Primary Pigmented Nodular Adrenocortical Disease. Like AIMAH, primary pigmented nodular adrenocortical disease (PPNAD) is exceedingly rare, accounting for less than 1% of cases of Cushing syndrome. Unlike AIMAH, however, the adrenal glands in this condition remain normal in size and exhibit black or brown cortical nodules (Young et al, 1989). The cortical tissue surrounding the nodules is atrophic, and the adrenal medulla is free of disease (Lacroix and Bourdeau, 2005). Approximately half of PPNAD is found in patients with the autosomal dominant Carney complex, which is also responsible for spotty skin and mucous membrane lesions, and a variety of neoplasms that include Sertoli cell tumors. The other half of cases of PPNAD are nonhereditary with no known cause (Lacroix and Bourdeau, 2005).

Clinical Characteristics

Classical Cushing Syndrome. Clinical characteristics of Cushing syndrome vary considerably among affected patients. Many of the classic symptoms of hypercortisolism, such as central obesity, moon facies, buffalo hump, proximal muscle weakness, easy bruisability, and abdominal striae, are nonspecific. It is the combination of these and other clinical signs that should raise suspicion and prompt potential screening for Cushing syndrome (Findling and Raff, 2005). Cushing syndrome also results in systemic symptomatology, such as central obesity, dyslipidemia, insulin resistance, and hypertension, that is identical to the highly-prevalent metabolic syndrome (Pivonello et al, 2005,

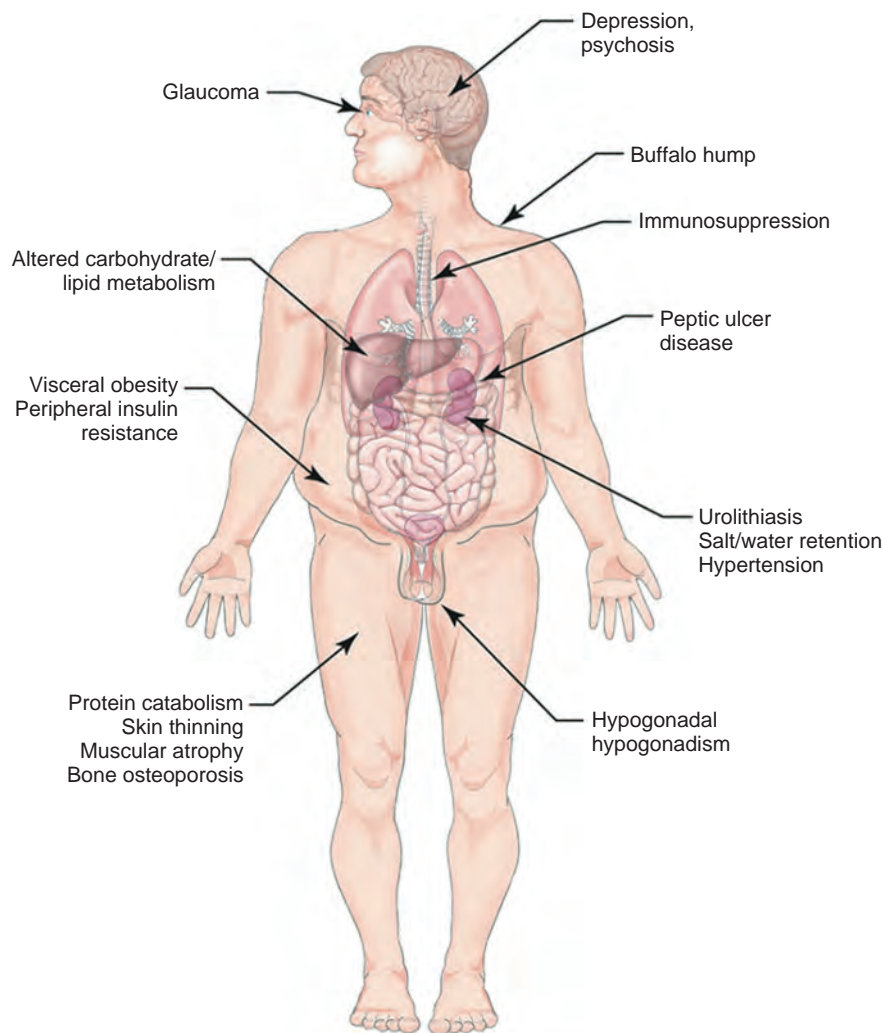


Figure 65-7. Diverse effects of hypercortisolism on organ systems.

2008). Figure 65-7 depicts the effects of glucocorticoids on organ systems, and Table 65-5 summarizes signs and symptoms of the disease and indicates their frequency. Screening for Cushing syndrome is usually beyond the scope of urologic practice; however, it is important for urologists to appreciate the **relatively common occurrence of hypogonadal hypogonadism in men with Cushing syndrome**. A low threshold for initiating a hypercortisolism workup should exist for these men with libido or erectile problems, low testosterone, and low gonadotropin levels (Findling and Raff, 2005; Pivonello et al, 2008). **Up to 50% of patients with Cushing syndrome exhibit urolithiasis**; therefore stone formers with cushingoid features also should receive a hypercortisolemia evaluation. It is interesting to note that definitive treatment of Cushing syndrome in these patients reduces the risk of stone formation but does not bring the risk back to that of the general population (Faggiano et al, 2003).

Subclinical Cushing Syndrome. Subclinical Cushing syndrome is a relatively new disease entity consisting of hypercortisolemia in the absence of an overt cushingoid phenotype. Obvious clinical signs of Cushing syndrome are absent, and the diagnosis is made when a metabolic workup for an incidentally discovered adrenal mass reveals hypercortisolemia (Sippel and Chen, 2004). In the past, the disease entity was referred to as *pre-Cushing syndrome*, *noncushingoid Cushing syndrome*, and *preclinical Cushing syndrome*; however, the term *subclinical Cushing syndrome* has gained acceptance. The term *subclinical autonomous glucocorticoid hypersecretion* also has been introduced (Tsagarakis et al, 2006). Classically, the disease entity applies to patients who are found to have elevated cortisol levels

on a metabolic workup of an adrenal incidentaloma. **Nearly 10% of patients in one large series of adrenal incidentalomas were found to have the condition** (Mantero et al, 2000). Patients can also fall under the umbrella of this diagnosis when Cushing syndrome is discovered during screening. For instance, when patients with type 2 diabetes and poor glucose control are screened for hypercortisolism, some 2% have subclinical Cushing syndrome (Catargi et al, 2003).

Adrenalectomy in the setting of subclinical Cushing syndrome may improve glucose control and hypertension and result in weight loss (Midorikawa et al, 2001; Mitchell et al, 2007). Surgical indications and benefits for subclinical Cushing syndrome, however, are still a matter of debate (Sippel and Chen, 2004; Tsagarakis et al, 2006). Some authors argue that adrenalectomy should be performed only in patients who are potentially symptomatic and exhibit clinical signs, such as hypertension, obesity, glucose intolerance, or osteopenia. Others propose that surgery must be offered to all patients to prevent the sequelae of hypercortisolism (Sippel and Chen, 2004; Pivonello et al, 2005; Tsagarakis et al, 2006). Patients with subclinical Cushing syndrome may be at higher risk for postadrenalectomy adrenal insufficiency than patients with non-cortisol-secreting adrenal pathologies, because functionality of the contralateral gland may be suppressed (Tsagarakis et al, 2006).

Diagnostic Tests. The diagnosis of Cushing syndrome is one of the most complex and difficult tasks in clinical endocrinology and most often falls outside of the realm of medical or surgical urologic practice (Findling and Raff, 2005). Nevertheless, the urologist must be familiar with these diagnostic strategies and how they relate to

TABLE 65-5 Signs and Symptoms of Cushing Syndrome

SYMPTOMS AND SIGNS	PREVALENCE (%)
Central obesity	90-100
Rounded face (“moon face”)	
Facial plethora	
Decreased libido	70-90
Purple striae	
Menstrual disturbances	
Hirsutism	
Erectile dysfunction	50-70
Hypertension	
Muscle weakness	
Posterior neck fat deposit (“buffalo hump”)	
Body bruising	
Glucose intolerance, diabetes	20-50
Osteopenia, osteoporosis	
Emotional lability, depression	
Headache	
Backache	
Limb edema	
Recurrent infections	0-20
Hypokalemic alkalosis	
Nephrolithiasis	
Acne	
Alopecia	

Modified from Pivonello R, De Martino MC, De Leo M, et al. Cushing's syndrome. *Endocrinol Metab Clin North Am* 2008;37(1):135–49, ix.

the etiology of hypercortisolism. Moreover, the urologist who offers adrenalectomy must be well versed in the basic metabolic evaluation for Cushing syndrome in patients with adrenal masses.

Establishing the Diagnosis of Cushing Syndrome. When the diagnosis of Cushing syndrome is suspected, the clinician can choose among several laboratory studies. The two evaluations performed most frequently are the 24-hour urinary free cortisol (UFC) evaluation and the overnight low-dose dexamethasone suppression test (LD-DST). The sensitivity of the former test, however, may not be adequate for screening patients with incidentalomas (Nieman et al, 2008). Late-night salivary cortisol is a test that is becoming increasingly popular. Second-line tests include the 2-day LD-DST and midnight plasma cortisol testing (Arnaldi et al, 2003; Newell-Price et al, 2006; Nieman et al, 2008; Pivonello et al, 2008). The physiologic principles underlying these tests are important to understand and are described in this section (Findling and Raff, 2005). The section on evaluation of adrenal pathology in urologic practice outlines practical algorithms for the metabolic evaluation of adrenal lesions. Tests such as random serum cortisol, plasma ACTH level, urinary 17-ketosteroid level, insulin tolerance testing, and loperamide testing have fallen out of favor and are no longer recommended (Nieman et al, 2008).

Administration of low-dose dexamethasone followed by measurement of serum cortisol the next morning probes the patient's glucocorticoid negative feedback system. In subjects without hypercortisolism, dexamethasone acts on the corticotrophic cells of the anterior pituitary, suppresses ACTH production, and thereby results in a reduction of serum cortisol levels (Findling and Raff, 2005). A key element to understanding this test is that despite the “low-dose” designation, the dose of dexamethasone administered for this study corresponds to threefold to fourfold levels of physiologic glucocorticoid. It is important to note that the exogenous dexamethasone is not detected by the serum cortisol assay. The fact that patients with ACTH-independent Cushing syndrome and those

with ectopic ACTH secretion fail to suppress cortisol production during such testing is intuitive; however, the reason for the failure of patients with ACTH-producing pituitary adenomas (Cushing disease) to suppress cortisol secretion after low-dose dexamethasone administration is less obvious. The phenomenon is best understood by the relative insensitivity of pituitary adenomas to the inhibitory effects of glucocorticoid stimulation (Raff and Findling, 2003). In summary, a patient's failure to suppress cortisol levels after an overnight low-dose dexamethasone administration is indicative of Cushing syndrome. **This test does not delineate the cause of hypercortisolism, but simply suggests its presence.** Administration of low-dose dexamethasone over a 48-hour period is less practical and is reserved for second-line testing.

The UFC evaluation is a 24-hour direct measurement of free bioavailable cortisol. Unlike serum cortisol testing, which measures both free and bound cortisol, urinary cortisol measurements are independent from the variables that influence corticosteroid-binding globulin levels (Arnaldi et al, 2003). Moreover, the test is an integrated measurement of cortisol secretion over a 24-hour period. This feature of the study is critical, because serum cortisol levels exhibit some circadian variation even in many patients with Cushing syndrome (Orth, 1995). **The urologist must be cognizant that this test may not possess sufficient sensitivity for diagnosis of subclinical Cushing syndrome, and the Endocrine Society recommends against it for metabolic evaluation of adrenal incidentalomas (Nieman et al, 2008).**

Late-night salivary cortisol and midnight plasma cortisol measurements take advantage of a common feature of all causes of Cushing syndrome—a perturbation and in some cases complete disruption in the diurnal variation of cortisol levels. The abnormality, even in very mild cases of Cushing syndrome, is the inability to suppress cortisol levels at night. As previously mentioned, peak morning cortisol levels in patients with Cushing syndrome are often within the normal range; however, persistent elevation at night may signal the loss of diurnal variance associated with Cushing syndrome. Although midnight plasma cortisol measurements are clinically impractical in an outpatient setting, late-night salivary cortisol measurements are becoming a popular diagnostic tool for identification of hypercortisolism (Raff and Findling, 2003; Findling and Raff, 2005).

It is important to note that other conditions can stimulate the HPA axis and emulate Cushing syndrome (Box 65-1); therefore endocrinologic expertise is recommended when definitively diagnosing hypercortisolism (Nieman et al, 2008).

Identifying the Cause of Cushing Syndrome. Once Cushing syndrome has been diagnosed, its cause must be localized. Because of the nuanced complexity of this process, some authors believe that this is best done by endocrinologists at major referral centers (Newell-Price et al, 2006). Briefly, the algorithm is as follows.

First, ACTH-dependent disease must be distinguished from the ACTH-independent causes. This is done by measurement of serum ACTH. Low serum ACTH points to ACTH-independent pathology, and abdominal imaging is indicated to identify the adrenal source. If the adrenals are unremarkable on cross-sectional imaging, exogenous steroids as a cause of Cushing syndrome, or much less commonly PPAD, must be suspected (Arnaldi et al, 2003). It is interesting to note that the presence of PPAD often can be confirmed by a delayed “paradoxical rise” in the 24-hour urinary cortisol sampling after dexamethasone administration (Lacroix and Bourdeau, 2005). Up to 10% of patients with adrenal Cushing syndrome have bilateral adrenal lesions (Lacroix, 2008). Adrenal venous sampling may be helpful in this setting (Young et al, 2008).

The true diagnostic difficulty lies in distinguishing Cushing disease from the ectopic ACTH syndrome for patients who have high serum ACTH levels. This problem stems from the fact that both pituitary microadenomas and ACTH-producing tumors can be very difficult to localize with modern imaging. Meanwhile, incidental imaging findings in the lungs, pancreas, and pituitary are relatively common, often clouding the diagnostic waters (Newell-Price et al, 2006). For instance, 10% of the general population exhibit an abnormality on imaging of the pituitary gland, whereas some 50%



Figure 65-8. Bilateral adrenal enlargement in a patient with advanced metastatic adenocarcinoma of the pancreas.

BOX 65-1 Causes of Hypercortisolism in the Absence of Cushing Syndrome

Some clinical features of Cushing syndrome may be present:

- Pregnancy
- Depression
- Alcohol dependence
- Glucocorticoid resistance
- Morbid obesity
- Poorly controlled diabetes mellitus

Unlikely to have any clinical features of Cushing syndrome:

- Physical stress (hospitalization, surgery, pain)
- Malnutrition, anorexia nervosa
- Intense chronic exercise
- Hypothalamic amenorrhea
- Corticosteroid-binding globulin excess (increased serum but not in urine cortisol)

Although Cushing syndrome is unlikely in these conditions, it may rarely be present. If there is a high clinical index of suspicion, the patient should undergo testing, particularly those within the first group.

Modified from Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93(5):1526–40.

of patients with Cushing disease have no abnormality on pituitary MRI (Fig. 65-8) (Arnaldi et al, 2003; Porterfield et al, 2008).

Direct measurements of ACTH in a downstream venous plexus that drains the pituitary—the inferior petrosal sinus—after CRH stimulation has become the gold standard approach for distinguishing ectopic ACTH production from Cushing disease. High levels of ACTH in the inferior petrosal sinus, when compared with those in peripheral blood, indicate Cushing disease, whereas levels similar to peripheral plasma suggest an ectopic ACTH source (Findling and Raff, 2006; Porterfield et al, 2008).

High-dose dexamethasone suppression testing was used in the past to differentiate pituitary and ectopic ACTH sources, but the value of the test is limited. The study is based on the principle that high enough doses of dexamethasone should suppress ACTH production by pituitary adenomas, whereas ectopic ACTH

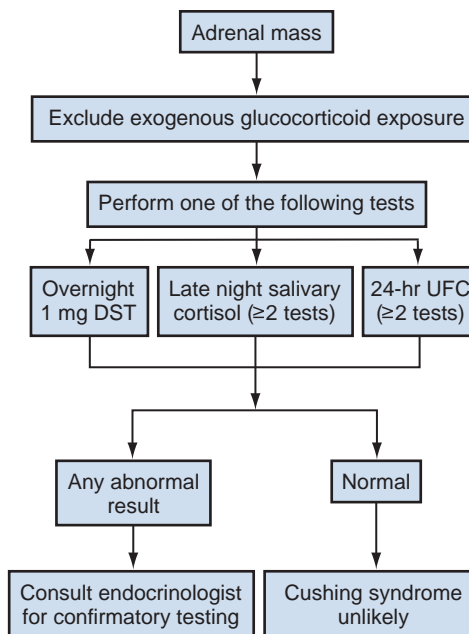


Figure 65-9. Testing algorithm for ruling out hypercortisolemia secondary to an adrenal mass. In case of a positive result during late-night salivary cortisol or 24-hour urinary free cortisol evaluations, repeat testing is often prudent. DST, dexamethasone suppression test; UFC, urinary free cortisol.

production continues despite the high-dose glucocorticoid administration (Arnaldi et al, 2003). Unfortunately, it is now clear that some nonpituitary ACTH-producing tumors possess the glucocorticoid receptor and also reduce ACTH production on high-dose dexamethasone administration (Aron et al, 1997; Raff and Findling, 2003). Currently, high-dexamethasone suppression testing is not routinely used (Fig. 65-9) (Findling and Raff, 2006; Porterfield et al, 2008).

Treatment. The treatment of Cushing syndrome must be approached as a multidisciplinary endeavor. Primary care physicians, endocrinologists, neurosurgeons, and the adrenal surgical experts must effectively communicate not only with the patient but also with one another. Treatment goals involve correction of hypercortisolemia, restoration of the HPA axis, and management of Cushing syndrome sequelae (Porterfield et al, 2008).

Exogenous Cushing Syndrome. Correction of exogenous Cushing syndrome, when appropriate, must be handled with proper care. Cessation of glucocorticoid administration must be gradual, so that the HPA axis has ample time to recover. The process can take weeks to months and varies greatly from patient to patient. The physician must be aware of the clinical entity known as *steroid withdrawal syndrome*, wherein the patient cannot tolerate steroid dose reduction despite apparent normalization in HPA axis testing (Hopkins and Leinung, 2005).

Adrenocorticotrophic Hormone-Dependent Disease

Cushing Disease. The current standard of care for ACTH-secreting pituitary adenomas is trans-sphenoidal surgical resection (see Fig. 65-10 on the Expert Consult website). Unfortunately, cure is seen in only 60% to 80% of patients (Newell-Price et al, 2006; Pivonello et al, 2008). Furthermore, long-term follow-up is necessary, because up to 25% of individuals relapse (Patil et al, 2008). In addition, macroadenomas are resistant to neurosurgical treatment, and less than 15% of patients are cured after excision of tumors 1 cm or larger (Newell-Price et al, 2006). After resection, a severe Addisonian state is common, and careful glucocorticoid replacement is necessary in the year after surgery (Utz et al, 2005). Hypopituitarism after resection of a pituitary adenoma is a known complication, with rates varying from less than 5% to more than 50% for the various pituitary metabolic products in various surgical series. Careful patient monitoring by expert endocrinologists is

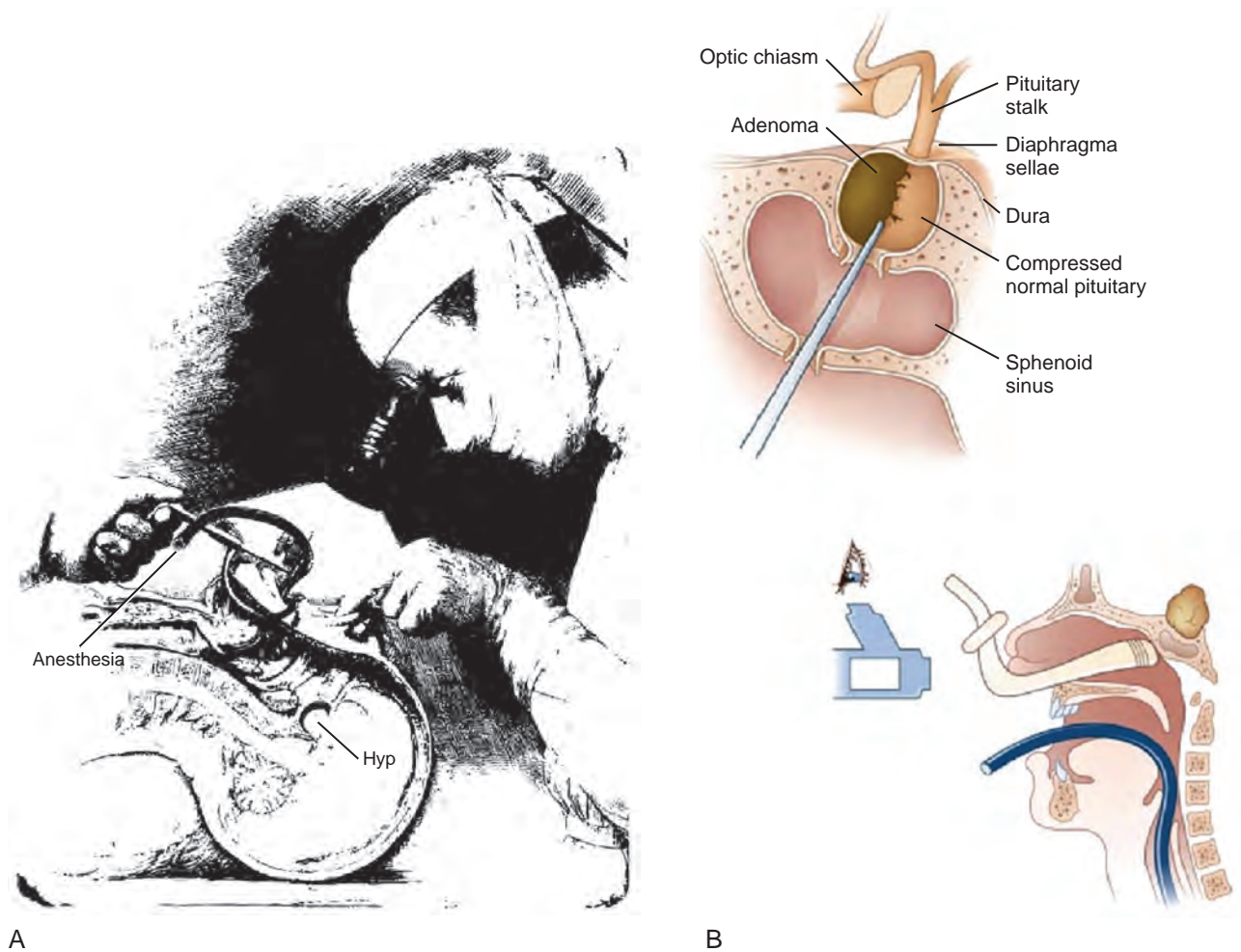


Figure 65-10. A, Harvey Cushing performing a trans-sphenoidal hypophysectomy. B, Diagram of trans-sphenoidal access to the pituitary. Hyp, hypothalamus. (From Schwartz SI, Fisher JE, Spencer FC, et al, editors. *Principles of surgery*. 7th ed. New York: McGraw-Hill; 1998; and Melmed S, Kronenberg HM. Anterior pituitary. In: Kronenberg HM, Melmed S, Polonsky KS, et al, editors. *Williams textbook of endocrinology*. 11th ed. Philadelphia: Saunders; 2008.)

essential (Utz et al, 2005; Porterfield et al, 2008). Neurosurgical reoperation after initial failure is challenging, and success rates vary. Moreover, the risk of hypopituitarism also significantly rises with secondary resections (Utz et al, 2005; Porterfield et al, 2008). Salvage radiation therapy is an option, but the patient must be warned about significant delays in reduction of ACTH secretion and the possibility of hypopituitarism (Estrada et al, 1997; Utz et al, 2005; Porterfield et al, 2008).

The urologist must be involved when adrenalectomy is contemplated or required. Currently, bilateral adrenalectomy is most often recommended when at least one attempt to treat the primary tumor has failed. It is also necessary in rare instances when hypercortisolism is life-threatening and swift definitive treatment is mandatory. The advantages of the procedure include a lack of postoperative hypopituitarism and an extremely high success rate with rapid resolution of hypercortisolism (Vella et al, 2001; Chow et al, 2008; Lacroix, 2008). Nevertheless, lifelong mineralocorticoid and glucocorticoid replacement is required in all patients. Moreover, the patients are at risk for progressive growth of their pituitary adenoma, mainly resulting in complications such as ocular chiasm compression, oculomotor deficiencies, and, rarely, a rise in intracranial pressure (Assie et al, 2007). This results in the Nelson-Salassa syndrome (also known as Nelson syndrome), which is found in 8% to 29% of patients who have undergone bilateral adrenalectomy in large series. Prophylactic radiation therapy has been shown to prevent the phenomenon in some but not all published reports (Gil-Cárdenas et al, 2007). Currently, routine use of prophylactic radiotherapy to prevent Nelson syndrome after bilateral adrenalectomy is controversial (Porterfield et al, 2008). When counseling patients regarding bilateral adrenalectomy for ACTH-dependent Cushing syndrome, the urologist must also warn of the rare possibility of residual, functioning adrenal tissue remaining after the procedure (Kemink et al, 1992).

Ectopic Adrenocorticotrophic Hormone Syndrome. Resection of the primary ACTH-producing tumor is the single best therapeutic approach to normalizing cortisol levels in patients with ectopic ACTH syndrome. In large series, however, primary tumor resection is possible in only approximately 10% of patients (Aniszewski et al, 2001). For patients with unresectable primary tumors or whose primary ACTH-producing tissue cannot be identified (up to 35% of patients), bilateral adrenalectomy with lifelong replacement therapy is an excellent therapeutic option (Aniszewski et al, 2001; Porterfield et al, 2008).

Adrenocorticotrophic Hormone-Independent Disease. Patients with unilateral cortisol-secreting adrenal masses are treated with ipsilateral adrenalectomy. Partial adrenalectomy is possible when preservation of adrenal tissue is deemed essential (Walz, 2004). Case reports of bilateral partial adrenalectomies for cortisol-producing masses exist in the literature (Inoue et al, 2006). The current standard of care for AIMAH and PPNAD patients is bilateral adrenalectomy with lifelong replacement therapy. Success with unilateral resection of the largest gland in AIMAH patients also has been reported (Iacobone et al, 2008).

Medical Treatment of Hypercortisolism. Medical therapy for hypercortisolism is used for bridging a patient to surgery or when surgical intervention is not possible. Medications that block enzymes of steroid synthesis, such as metyrapone, aminoglutethimide, trilostane, ketoconazole, and etomidate, are often used. Mitotane, a medication that is discussed in further detail in the section on adrenal carcinomas, can also be used (Porterfield et al, 2008). In the future, inhibitors of 17 α -hydroxylase (CYP17), such as abiraterone, may also be of some use; however, at this point such use of these drugs remains largely unexplored (Attard et al, 2009). Medical treatment of hypercortisolemia requires significant expertise and should be left to expert endocrinologists.

Prognosis. Life expectancy for patients with Cushing syndrome falls short of that of patients with normal cortisol levels. Normalization of hypercortisolemia may reduce but not eradicate this risk (Swearingen et al, 1999; Pivonello et al, 2005). Aggressive management of cardiovascular risk factors under the watchful eyes of

experienced medical experts is paramount even in patients whose laboratory values return to normal after successful treatment.

Summary. Cushing syndrome is a complex disorder that requires a multidisciplinary approach. The urologist plays a critical role in management of the hypercortisolemic patient when unilateral or bilateral adrenalectomy is required. A thorough understanding of relevant pathophysiology is necessary not only for diagnosis and treatment, but also for appropriate perioperative counseling of patients with Cushing syndrome.

KEY POINTS: CUSHING SYNDROME

- Serum cortisol levels are under tight control. In healthy subjects, peaks occur in the morning and the nadir is observed at approximately 11:00 PM.
- Adrenal tumors that secrete cortisol cause ACTH-independent Cushing syndrome and account for approximately 10% of Cushing syndrome that is not caused by steroid intake.
- Patients with undiagnosed Cushing syndrome can have hypogonadal hypogonadism or urolithiasis on presentation to the urologist.
- Testing of adrenal masses for cortisol hypersecretion is mandatory.

Primary Aldosteronism

Overview and Epidemiology. Dr. Jerome Conn first described primary aldosteronism in 1955 in a 34-year-old woman with hypertension and hypokalemia (Conn, 1955). Urine assays demonstrated a markedly elevated level of mineralocorticoid activity. The patient's condition greatly improved after the removal of a 4-cm unilateral adrenal tumor. Since this initial case report, several subtypes of primary aldosteronism, which require distinct evaluation and treatment, have been identified. Primary aldosteronism is the most common form of secondary hypertension, with a prevalence ranging from 5% to 15% of hypertensive patients in contemporary series; thus it is important for urologists to be familiar with appropriate diagnostic and management strategies (Mulatero et al, 2004; Rossi et al, 2006a; Young, 2007a; Jansen et al, 2014).

Pathophysiology. The RAAS is a key regulator of blood pressure and extracellular fluid volume (Fig. 65-11). The release of renin from the juxtaglomerular cells is the rate-limiting step in the RAAS cascade. Under normal physiologic conditions, renin release is stimulated by low renal perfusion pressure, increased renal sympathetic nervous activity, and low sodium concentration sensed by the macula densa (Gibbons et al, 1984). Renin then cleaves angiotensinogen to angiotensin I, which in turn is cleaved by angiotensin-converting enzyme (ACE) to angiotensin II. Angiotensin II both functions as a potent vasoconstrictor and triggers the release of aldosterone from the zona glomerulosa. Additional regulators of aldosterone release include potassium and ACTH. In primary aldosteronism, aldosterone secretion is independent of the RAAS, and plasma renin levels will be suppressed. This finding is in contrast to patients with secondary hyperaldosteronism, in whom elevated renin levels are the cause of elevations in aldosterone secretion. This distinction between plasma renin levels in primary and secondary hyperaldosteronism is a critical concept used when screening for primary aldosteronism (see diagnosis section, later).

After release from the adrenal cortex, aldosterone increases sodium reabsorption and potassium secretion in the distal nephron (Nyirenda and Padfield, 2007). Hyponatremia does not occur because sodium reabsorption is accompanied by water uptake, thereby maintaining isotonicity. The resultant volume expansion is limited by mineralocorticoid escape. Mineralocorticoid escape is mediated by pressure-natriuresis, atrial natriuretic peptide secretion, and changes in electrolyte transporters in the distal nephron,

which result in limiting volume expansion to approximately 1.5 kg or less (Burnett et al, 1985; Yokota et al, 1994; Knepper et al, 2003).

Although the finding of increased plasma aldosterone and decreased plasma renin activity (PRA) is common to all patients with primary aldosteronism, individual subtypes of the disorder have distinct underlying pathophysiology. Differentiation between subtypes of primary aldosteronism is essential to ensure proper treatment. The causes of primary aldosteronism are presented in Figure 65-12. Idiopathic hyperplasia and aldosterone-producing adenomas are by far the most common subtypes encountered, accounting for over 95% of cases. Although idiopathic hyperplasia is the most common subtype diagnosed, the prevalence of aldosterone-producing adenomas may be greater than previously thought owing to lack of routine lateralization studies in patients diagnosed with primary aldosteronism (Mulatero et al, 2004).

The underlying pathophysiology of idiopathic hyperplasia, also referred to as *bilateral adrenal hyperplasia*, remains unknown. Macronodular hyperplasia is rare, with most cases attributed to micronodular hyperplasia (Schirpenbach and Reincke, 2007). Clinically, patients with idiopathic hyperplasia have less severe hypertension and are less likely to be hypokalemic compared with patients with aldosterone-producing adenomas (Rossi et al, 2006a). Whereas

both adrenal glands are responsible for increased aldosterone production in idiopathic hyperplasia, unilaterally adrenalectomy is not therapeutic. Unilateral adrenal hyperplasia is distinctly uncommon, but when appropriately diagnosed is potentially curable with adrenalectomy after confirmation of lateralizing aldosterone secretion (see the section on *subtype differentiation*). In comparison with idiopathic hyperplasia, aldosterone-producing adenomas are associated with more profound hypertension and hypokalemia (Rossi et al, 2006a).

Less common causes of primary aldosteronism include ACCs, ectopic aldosterone-producing tumors, and familial hyperaldosteronism (FH). Primary aldosteronism associated with ACC is rare, representing less than 1% of cases of primary aldosteronism and 2.5% to 5% of ACCs (Ng and Libertino, 2003; Seccia et al, 2005). Ectopic aldosterone-producing tumors are extremely rare and should raise suspicion for the presence of accessory adrenal tissue or adrenal heterotopia (Abdelhamid et al, 1996).

Three types of FH have been described: type I, type II, and type III (Viola et al, 2013). FH type I, also known as glucocorticoid-remediable aldosteronism, is an autosomal dominant genetic disorder driven by the chimeric fusion of the promoter region of the 11 β -hydroxylase gene (*CYP11B1*) and the coding region of the aldosterone synthase gene (*CYP11B2*). This combination results in aldosterone synthase activity being controlled by ACTH. Thus aldosterone is secreted according to the circadian rhythm of ACTH instead of the RAAS (Lifton et al, 1992). Patients with FH type I will often have early-onset refractory hypertension and a family history of early onset hypertension or cerebral vascular accidents (Litchfield et al, 1998; McMahon and Dluhy, 2004). FH type II is a genetically heterogeneous disease with an autosomal dominant inheritance pattern. Affected families will demonstrate either idiopathic hyperplasia or aldosterone-producing adenomas that are clinically and morphologically indistinguishable from sporadic cases of primary aldosteronism. Linkage analysis suggests that mutations in the 7p22 region are responsible for FH type II in some families (Mulatero et al, 2004; So et al, 2005). FH type III is characterized by bilateral adrenal hyperplasia, refractory hypertension, severe hypokalemia, and the overproduction of hybrid steroids (Geller et al, 2008). Genetic mutations of *KCNJ*, which encodes for a potassium channel, have been identified as the cause of FH type III (Charmandari et al, 2012; Mulatero et al, 2012).

Clinical Characteristics. The diagnosis of primary aldosteronism is usually made during the third to sixth decades of life in patients being evaluated for refractory hypertension. The degree of hypertension is typically graded as moderate to severe, with a mean blood pressure of 184/112 noted in a retrospective series of 262 patients with primary aldosteronism (Young and Klee, 1988). In the prospective series by Rossi and colleagues (2006a), which evaluated the prevalence of primary aldosteronism in 1125 newly diagnosed hypertensive patients, the mean blood pressure (154/98) was significantly higher than in patients without primary aldosteronism

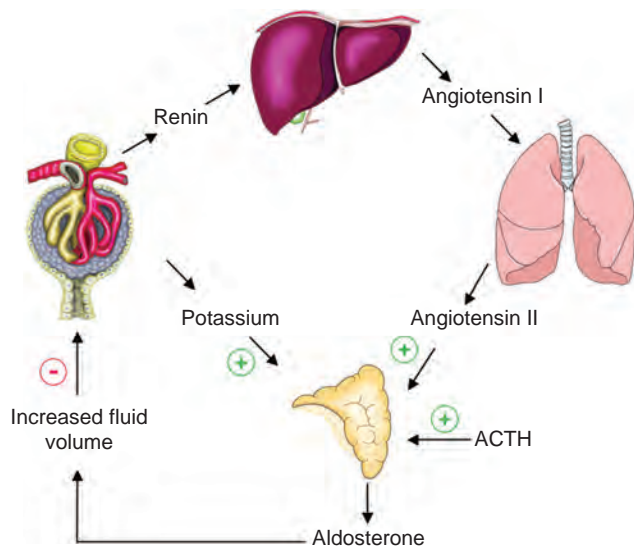


Figure 65-11. Renin-angiotensin-aldosterone system. Under normal conditions, aldosterone secretion is under the control of angiotensin II, serum potassium levels, and adrenocorticotropic hormone (ACTH). In primary aldosteronism, aldosterone is autonomously released, resulting in decreased plasma renin levels.

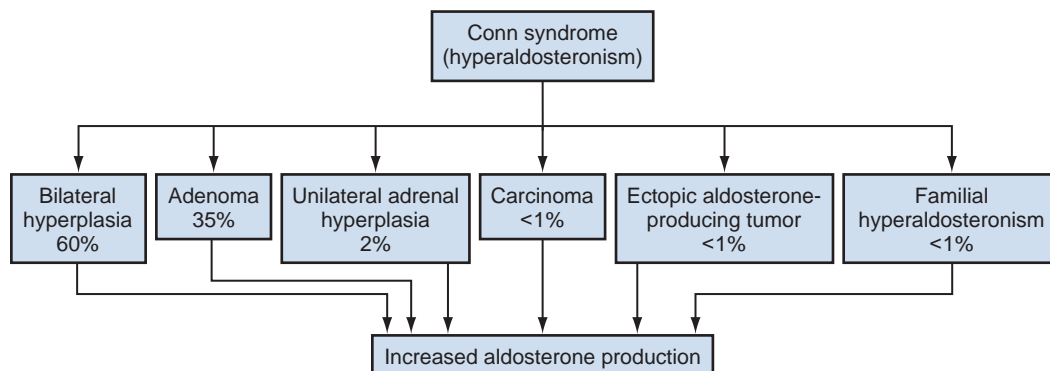


Figure 65-12. Subtypes of primary aldosteronism. (Modified from Young WF. Primary aldosteronism: renaissance of a syndrome. Clin Endocrinol [Oxf] 2007;66:607–18.)

(147/95) (Rossi et al, 2006a). The association between primary aldosteronism and the severity of hypertension has been demonstrated by Mosso and colleagues (2003), who noted a 2%, 8%, and 13% prevalence of primary aldosteronism in hypertensive patients stratified as stage 1 (140 to 159/90 to 99), stage 2 (160 to 179/100 to 109), and stage 3 ($>180/>110$) hypertension, respectively.

Although hypokalemia has been classically described as a common finding in primary aldosteronism, in contemporary series 63% to 91% of newly diagnosed patients are normokalemic at the time of diagnosis (Mulatero et al, 2004). In a minority of patients, hypokalemia is associated with symptoms including headaches, polydipsia, palpitations, polyuria, nocturia, and muscle weakness (Young, 2007a). Because of mineralocorticoid escape, hypernatremia is an uncommon finding in primary aldosteronism, with serum sodium levels similar to those in other forms of hypertension (Rossi et al, 2006a; Young, 2007a).

Cardiovascular and renal damage is a concern for all patients with hypertension and underlies the need for treatment. The incidence and severity of target organ damage appears to be increased in patients with primary aldosteronism compared with other forms of hypertension (Mulatero et al, 2013). Cardiac abnormalities, including left ventricular filling and diastolic dysfunction, increased left ventricular mass measurement, and prolonged QP interval have all been associated with primary aldosteronism (Rossi et al, 1996; Tanabe et al, 1997). These findings may help to explain the significant increase of cardiovascular events noted in patients with primary aldosteronism by Milliez and colleagues. In a retrospective series of patients with hypertension, patients with primary aldosteronism were 4 times more likely to be diagnosed with a stroke, 6.5 times more likely to be diagnosed with a myocardial infarction, and 12 times more likely to be diagnosed with atrial fibrillation compared with patients with essential hypertension (Milliez et al, 2005; Gonzaga and Calhoun, 2008). The increased risk of cardiovascular disease may be associated with the increased prevalence of metabolic syndrome that has been noted in this patient population (Fallo et al, 2006). Fortunately, appropriate treatment of primary aldosteronism has been associated with left ventricular remodeling, which may decrease the risk of future cardiac events (Rossi et al, 2014). In addition, patients with primary aldosteronism demonstrate increased rates of proteinuria and development of type 2 diabetes when compared with patients with essential hypertension (Fox et al, 2006; Rossi et al, 2006b; Mulatero et al, 2013).

Diagnostic Tests. The diagnosis of primary aldosteronism requires screening, confirmatory testing, and subtype differentiation. Indications for screening are listed in Box 65-2. The accurate diagnosis of primary aldosteronism and subtype differentiation is critical because of the associated increased risk of target organ damage, proper selection of antihypertensives, and potential for surgical cure in appropriately selected patients.

BOX 65-2 Indications for Primary Aldosterone Screening

- Hypertension with hypokalemia
- Resistant hypertension (three or more oral agents with poor control)
- Adrenal incidentaloma with hypertension
- Early-onset hypertension (<20 years) or stroke (<50 years)
- Severe hypertension ($\geq 160/\geq 110$)
- Whenever considering secondary causes of hypertension (i.e., pheochromocytoma or renovascular disease)
- Unexplained hypokalemia (spontaneous or diuretic induced)
- Evidence of target organ damage disproportionate to degree of hypertension
- Hypertension with family history of primary aldosteronism

Screening. Before screening is initiated, hypokalemia should be corrected and all contraindicated medications discontinued. Although patients can continue the majority of antihypertensive agents during screening, mineralocorticoid receptor antagonists are contraindicated and should be stopped at least 6 weeks before testing (Seifarth et al, 2002; Young, 2007a). Patients requiring these agents for control of severe hypertension should be transitioned to agents, such as α_1 -receptor blockers or long-acting calcium channel blockers, with minimal effects on screening test results (Rossi et al, 2008a). Other antihypertensive agents can alter screening values, but not to the extent that mandates their discontinuation (see Fig. 65-32, later).

Screening for primary aldosteronism begins by obtaining a morning (between 8 and 10 AM) plasma aldosterone concentration (PAC) and PRA (Funder et al, 2008). From these tests, the PAC and aldosterone-to-renin ratio (ARR) are used to screen for autonomous aldosterone secretion. Whereas the ARR is dependent on PRA, it is recommended that the lowest PRA value be set at 0.2 ng/mL/hr to avoid falsely elevated ratios (Rossi et al, 2006a). The PACs and ARRs that define a positive screen and suggest the diagnosis of primary aldosteronism are subject to laboratory variability; thus, standard thresholds have not been established. Reported sensitivities and specificities for use of ARRs in screening for primary aldosteronism range from 66% to 100% and 61% to 96%, respectively (Jansen et al, 2014). The National Institutes of Health (NIH) Consensus Statement (2002) on the management of the clinically inapparent adrenal mass suggests cutoffs of greater than 30 for the ARR and greater than 20 ng/dL for the PAC. However, other institutions have recommended lowering the cutoffs to greater than 20 and greater than 15 ng/dL, respectively (Young, 2007a; Rossi et al, 2008a). Although lowering the thresholds for a positive screening test result may increase the rate of false positives, all positive test results must be confirmed with further testing before the diagnosis of primary aldosteronism is made.

Measurement of PRA can be time-consuming and varies among different laboratories. For this reason, plasma renin concentration has been evaluated as a possible replacement for PRA in screening for primary aldosteronism (Ferrari et al, 2004; Perschel et al, 2004). Although initial series evaluating the usefulness of plasma renin concentration in primary aldosteronism screening have demonstrated promise, these findings require further standardization and validation before widespread use (Young, 2007a; Rossi et al, 2008b). **Confirmatory Testing.** After a positive screening test result, a confirmatory test must be performed before the diagnosis of primary aldosteronism is secured, owing to the known variability of aldosterone and PRA levels secondary to day-to-day oscillation, posture, diet, and antihypertensives (Salva et al, 2012). Of patients with positive screening test results, only 50% to 87% will be diagnosed with primary aldosteronism on confirmatory testing (Mosso et al, 2003; Seiler et al, 2004; Giacchetti et al, 2006; Nanba et al, 2012). As with screening for primary aldosteronism, proper patient preparation is required, with the correction of hypokalemia and discontinuation of mineralocorticoid receptor antagonists. Of the confirmatory tests available, the majority evaluate the suppression of aldosterone after sodium loading. The underlying theory behind the sodium loading tests is that loading will decrease plasma renin and aldosterone production in patients without autonomous aldosterone secretion (Mattsson and Young, 2006). Additional confirmatory tests, including captopril suppression test, furosemide-upright test, and the ACTH stimulation test, have been described but are not widely accepted or used (Hirohara et al, 2001; Sonoyama et al, 2011). The selection of the confirmatory test used depends on individual patient characteristics and physician preferences. Blood pressure should be monitored closely in all patients during confirmatory testing.

The fludrocortisone suppression test requires the administration of the synthetic mineralocorticoid fludrocortisone (0.1 mg every 6 hours) and sodium chloride (2 g every 8 hours) for 4 days. After 4 days of fludrocortisone and sodium loading, PAC is measured in the upright position. Failure to suppress PAC to less than 6 ng/dL is diagnostic of primary aldosteronism. Once considered

the gold standard in the diagnosis of primary aldosteronism, the fludrocortisone suppression test has been supplanted by the oral sodium loading test and the intravenous infusion test owing to the risks of severe hypertension and hypokalemia (Schirpenbach and Reincke, 2007).

The oral sodium loading test is conducted by administering a high-sodium diet for 3 days, followed by 24-hour urine measurements of aldosterone, sodium, and creatinine. Supplemental sodium chloride can be given to ensure the intake of at least 12.8 g of sodium per day. Twenty-four-hour sodium should be greater than 200 mmol to ensure adequate sodium loading. The diagnosis of primary aldosteronism is then made when the 24-hour aldosterone is greater than 12 µg/day.

The intravenous saline infusion test spares the patient from several days of sodium loading by the administration of 2 L of 0.9% sodium chloride intravenously over 4 hours. The infusion is performed in the morning after an overnight fast, while the patient is in a recumbent position. After the intravenous infusion of saline, PAC is measured; a level greater than 5 ng/dL is diagnostic of primary aldosteronism, and levels greater than 10 ng/dL are suggestive of aldosterone-producing adenomas (Mulatero et al, 2005; Young, 2007a).

The captopril suppression test evaluates for the suppression of the ARR after the administration of an ACE inhibitor. Measurement of PAC is performed after administration of 25 to 50 mg of the ACE inhibitor captopril while the patient remains recumbent. Suppression of the RAAS should be noted in patients without primary aldosteronism after the administration of captopril, whereas those with autonomous aldosterone secretion will have persistently elevated PACs greater than 15 ng/dL (Young and Klee, 1988). Further standardization and validation of the captopril suppression test are needed before it is used routinely when sodium loading tests are available and not contraindicated as in patients with cardiac and renal disease, which largely prohibit sodium loading (Giacchetti et al, 2008).

Subtype Differentiation. After diagnosis of primary aldosteronism, attention is then paid to defining the cause of autonomous aldosterone secretion. Subtype differentiation of primary aldosteronism is essential in selecting the appropriate therapy, because surgical therapy is successful for only select subtypes (Box 65-3). In patients who are not surgical candidates, subtype differentiation is of little consequence because medical therapy will be instituted; thus these patients can forgo further evaluation, and medical management can be initiated (Fig. 65-13). Given the rarity of familial primary aldosteronism, genetic screening should not be performed in all patients. However, patients with a family history of primary aldosteronism, early age of onset (<20 years), or with a family history of cerebral vascular accidents at a young age should be considered for genetic testing (Fig. 65-14). Cross-sectional abdominal imaging should be performed in all patients with primary aldosteronism who are potential surgical candidates.

BOX 65-3 Subtypes of Primary Aldosteronism

SURGICALLY CORRECTABLE

Aldosterone-producing adenoma
Primary unilateral adrenal hyperplasia
Ovarian aldosterone-secreting tumor
Aldosterone-producing carcinoma

NOT CORRECTABLE BY SURGERY

Bilateral adrenal hyperplasia
Familial hyperaldosteronism type I
Familial hyperaldosteronism type II
Familial hyperaldosteronism type III

Although imperfect in delineating the subtype of primary aldosteronism, an adrenal CT scan should be obtained to evaluate for the presence of adrenal nodules. Radiographic characteristics of aldosterone-producing adenomas include the presence of a unilateral low-density nonenhancing lesion of less than 10 Hounsfield

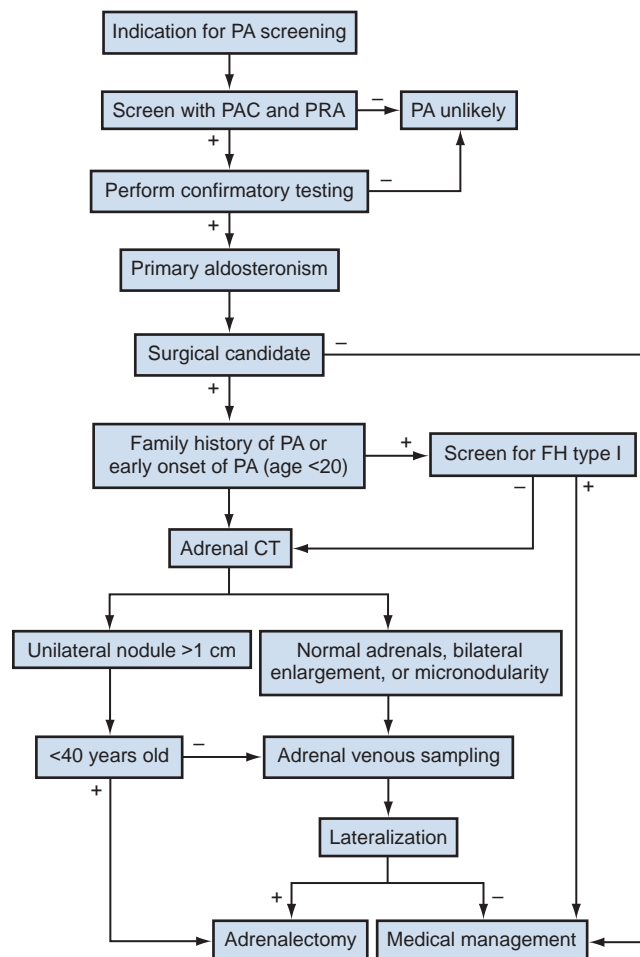


Figure 65-13. Primary aldosteronism diagnosis and treatment algorithm. CT, computed tomography; FH, familial hyperaldosteronism; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

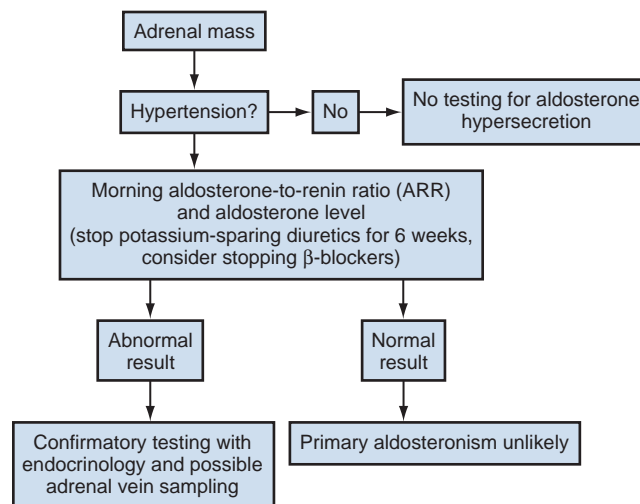


Figure 65-14. Testing algorithm for aldosterone hypersecretion by an adrenal mass.

units (HU), with an average size of 1.6 to 1.8 cm and a normal-appearing contralateral adrenal gland. However, given that approximately 20% of aldosterone-producing adenomas will be smaller than 1 cm, lateralization is not based on CT findings alone (Simon and Palese, 2008). Radiographic characteristics of idiopathic hyperplasia can include the presence of multiple unilateral or bilateral adrenal nodules, bilateral adrenal enlargement with increased limb size, or the presence of normal-appearing glands. The combination of the small-size, aldosterone-producing adenomas and the potential for the presence of nonfunctional adrenal adenomas makes CT imaging flawed in delineating lateralization of aldosterone hypersecretion. Because MRI does not offer an advantage in delineating primary aldosteronism subtypes and is associated with increased cost, routine use is not currently recommended.

To establish lateralization of aldosterone secretion in surgical candidates, adrenal vein sampling should be performed. By establishing lateralization, one can differentiate between subtypes of primary aldosteronism and identify patients in whom adrenalectomy is potentially beneficial. The value of adrenal vein sampling in evaluating the presence of lateralized aldosterone secretion was illustrated by Young and colleagues (2004), who noted that 22% of patients would have been incorrectly excluded from adrenalectomy, and 25% would have been inappropriately recommended to undergo adrenalectomy based on CT findings instead of adrenal vein sampling studies. As with all other evaluations performed for primary aldosteronism, proper patient selection, proper patient preparation, and an accurate interpretation of results are essential (Young and Stanson, 2009). A decision-making strategy when performing adrenal vein sampling is depicted in Figure 65-15.

Patients with confirmed PA should undergo adrenal vein sampling when adrenalectomy is being considered. Exceptions include patients younger than 40 years with a clear unilateral adrenal adenoma and normal contralateral adrenal gland on cross-sectional imaging and patients suspected of having an ACC (Rossi et al, 2014). Because the results of adrenal vein sampling can be affected by multiple factors, attention to preprocedural and procedural details is mandatory. Proper patient preparation is essential and includes 1 hour of recumbency, correction of hypokalemia, and discontinuation of antihypertensive agents, which may affect aldosterone and renin levels. After appropriate patient selection and preparation, adrenal vein sampling is performed in the morning after an overnight fast. Percutaneous access to the femoral vein is obtained, and catheter tips are positioned to collect samples from three sites: the right adrenal vein, left adrenal vein, and IVC (see Fig. 65-15A). Samples are then evaluated for aldosterone and cortisol concentrations. Appropriate specimen collection from the adrenal vein is determined by comparing the cortisol concentrations from the adrenal vein samples with the cortisol concentration from the IVC sample. The ratio of adrenal vein cortisol to IVC cortisol should be greater than 1:1 to 5:1, depending on the use of cosyntropin stimulation (Young and Stanson, 2009). If cosyntropin stimulation is used, a higher ratio is expected in properly collected samples. Adrenal vein sampling that demonstrates adrenal vein-to-IVC ratios below the cutoff, on either side, should be considered “nonselective” and discarded. An adrenal vein-to-IVC ratio above the cutoff, bilaterally, is considered “selective,” and comparisons between aldosterone concentrations can be made to determine the presence of lateralization.

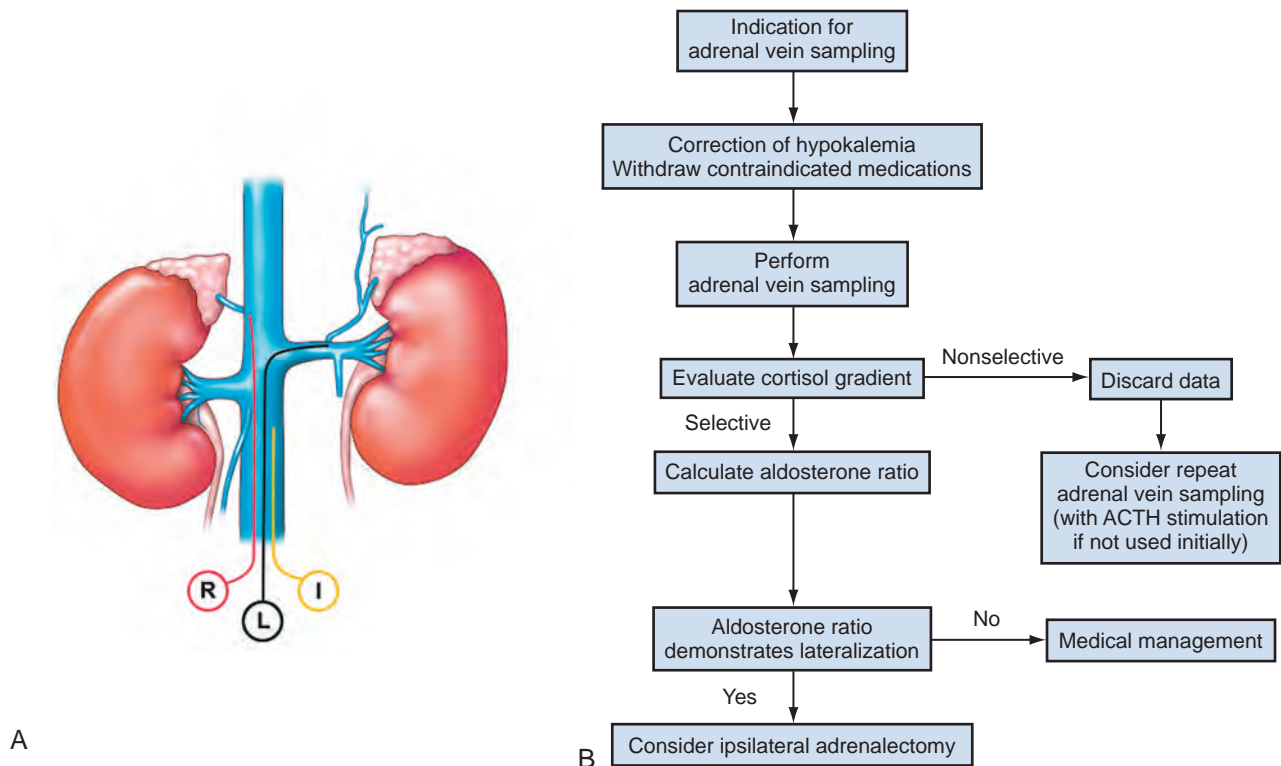


Figure 65-15. Adrenal vein sampling protocol. **A**, Proper catheter positioning for sampling right adrenal vein sample (R), left adrenal vein sample (L), and inferior vena cava (I) sample. **B**, After sample collection, the cortisol gradient is evaluated using the ratios $R_{\text{cortisol}}/I_{\text{cortisol}}$ and $L_{\text{cortisol}}/I_{\text{cortisol}}$. If the cortisol gradients confirm appropriate sample collection, lateralization of aldosterone secretion can be evaluated. Lateralization of aldosterone secretion is determined by the ratio of aldosterone secretion of the dominant to the nondominant adrenal gland while correcting for ipsilateral cortisol secretion using the formula $(A_{\text{dominant}}/C_{\text{dominant}})/(A_{\text{nondominant}}/C_{\text{nondominant}})$, where A = plasma aldosterone concentration and C = cortisol. ACTH, adrenocorticotropic hormone.

Lateralization of aldosterone secretion is determined by comparing the aldosterone-to-cortisol ratios of the dominant to nondominant sides using the formula $(A_{\text{dominant}}/C_{\text{dominant}})/(A_{\text{nondominant}}/C_{\text{nondominant}})$. Aldosterone secretion is considered to be lateralized if the ratio is greater than 2:1 to 4:1, depending on the use of cosyntropin stimulation (Young and Stanson, 2009; Rossi et al, 2014). When performed and interpreted correctly, adrenal vein sampling has a sensitivity of 95% and a specificity of 100% in detecting lateralized autonomous aldosterone secretion (Young et al, 2004).

The routine use of cosyntropin stimulation during adrenal vein sampling is controversial. Potential advantages of cosyntropin stimulation include minimizing stress-induced fluctuations in aldosterone secretion, maximizing the cortisol gradient, and maximizing the aldosterone secretion from aldosterone-producing adenomas (Young, 2007a; Young and Stanson, 2009; Rossi et al, 2014). In a prospective study investigating these potential benefits, cosyntropin stimulation was noted to facilitate the ascertainment of proper specimen collection for evaluation of the cortisol gradient between adrenal and IVC specimens. However, the authors also noted that cosyntropin stimulation was also associated with a small risk (3% to 12%) of incorrectly assigning the side of lateralization of aldosterone-producing adenomas, and a moderate risk (36% to 37%) of incorrectly classifying aldosterone-producing adenomas as idiopathic hyperplasia (Seccia et al, 2009).

When adrenal vein sampling is inconclusive because of sampling error, alternative studies are available that may help guide treatment decisions, including nuclear scintigraphy, postural stimulation testing, and measurement of cortisol metabolites. Of these modalities, only nuclear scintigraphy can provide both functional and anatomic data, which are necessary when considering surgical intervention.

Iodine-131 (^{131}I)-6 β -iodomethyl-norcholesterol (NP59) is a cortisol analog that can label adrenal cortical cells to evaluate for areas of hypersecretion (Heinz-Peer et al, 2007). Before injection of the radiotracer, saturated potassium iodine (Lugol solution) is administered to protect the thyroid from uptake of free ^{131}I . In addition, suppression of ACTH with dexamethasone (1 mg every 6 hours for 7 days) is necessary. Evaluation of radiotracer uptake is begun 4 days after NP59 injection and may continue through day 10. Characteristics that suggest the presence of aldosterone-producing adenomas include unilateral uptake of radiotracer less than 5 days after injection, whereas bilateral uptake is suggestive of idiopathic hyperplasia (Simon and Palese, 2008). The ability to detect a hyperfunctioning adenoma using NP59 is directly proportional to the tumor size and function, with a diminished ability to detect lesions smaller than 1.5 cm (Hogan et al, 1976; Nomura et al, 1990; Mansoor et al, 2002). To overcome some of the known limitations of NP59 imaging, NP59 single-photon emission computed tomography (SPECT-CT) has been evaluated and has demonstrated improved sensitivity in detecting smaller adenomas (Yen et al, 2009).

The posture stimulation test is designed to distinguish between aldosterone-producing adenomas and idiopathic hyperplasia based on changes in PAC levels in response to changes in posture. The test is performed by comparing PAC levels after the patient has been recumbent overnight, and again after 4 hours of being upright. In theory, the increase of angiotensin induced with being upright leads to an increase of PAC in normal patients that is twofold to fourfold greater when compared with recumbent levels. In comparison, patients with idiopathic hyperplasia will demonstrate an increase of at least 33% over baseline, and patients with aldosterone-producing adenomas or FH type I will not demonstrate an increase in PAC levels with changes in posture (Ganguly et al, 1973; Young, 2007a). Although the test can be helpful in distinguishing between aldosterone-producing adenomas and idiopathic hyperplasia, it does not provide information regarding the location of the adenoma (right vs. left). In addition, the reliability of the posture stimulation test is limited by the observation that 30% to 50% of aldosterone-producing adenomas demonstrate an increase of PAC, whereas 20% of idiopathic hyperplasia patients do not demonstrate any elevation

with postural changes (Mulatero et al, 2004; Schirpenbach and Reincke, 2007).

Another potential method for differentiating aldosterone-producing adenomas from idiopathic hyperplasia is the measurement of 18-hydroxycorticosterone (18-OHB). 18-OHB is formed by the 18-hydroxylation of corticosterone and may be the immediate precursor of aldosterone (Mulatero et al, 2013). Elevated 18-OHB (>100 ng/dL) suggests an aldosterone-producing adenoma, whereas levels below 100 ng/dL suggest idiopathic hyperplasia (Biglieri and Schambelan, 1979). However, the accuracy of this test in distinguishing aldosterone production from an adenoma versus hyperplasia is thought to be less than 80%. In addition, the test does not provide information about tumor location (right vs. left) in cases of functional adenomas (Young and Klee, 1988).

Treatment and Prognosis. The goal of treatment in primary aldosteronism is to control and prevent the morbidity associated with mineralocorticoid excess. Therefore the treatment strategies used in therapy aim to remove the source of mineralocorticoid excess or block the effect of aldosterone on target organs (Young, 2007a). Treatment strategies for primary aldosteronism are primarily dependent on subtype classification and surgical candidacy (see Fig. 65-13). Patients who are acceptable surgical candidates and have been diagnosed with a surgically correctable subtype of primary aldosteronism can be offered unilateral adrenalectomy; other patients can be managed effectively with medical therapy.

In patients with confirmed lateralizing aldosterone secretion, adrenalectomy should be considered. Given the small size of aldosterone-producing adenomas, the majority of patients are candidates for a laparoscopic adrenalectomy. In patients suspected of having hypersecretion of aldosterone associated with ACC, an open procedure may be recommended (Kebebew et al, 2002; Gonzalez et al, 2005; Schlamp et al, 2007). Improvements in blood pressure are noted in the majority of patients undergoing adrenalectomy for primary aldosteronism, with 33% to 73% of patients not requiring antihypertensives postoperatively (Sawka et al, 2001; Meyer et al, 2005; Schirpenbach and Reincke, 2007). Several predictors of persistent hypertension after adrenalectomy for primary aldosteronism have been described, including age older than 50 years, male gender, high body mass index, the use of two or more antihypertensive agents preoperatively, having a first-degree relative with hypertension, prolonged duration of hypertension before adrenalectomy, degree of cardiovascular remodeling, and renal insufficiency (Celen et al, 1996; Sawka et al, 2001; Wang et al, 2012; Rossi et al, 2014). In patients younger than 40 years with a unilateral adenoma larger than 1 cm, a unilateral adrenalectomy can be performed without adrenal vein sampling because of the rarity of incidental adenomas in this population (Schirpenbach and Reincke, 2007; Young, 2007a; Zarnegar et al, 2008). In the immediate postoperative period, PAC and ARR should be evaluated to ensure biochemical cure. In addition, patients should maintain a high-sodium diet and be monitored for hyperkalemia for several weeks after surgery (Mattsson and Young, 2006; Funder et al, 2008).

Medical treatment of primary aldosteronism is indicated in patients with nonsurgically correctable subtypes and those who are not surgical candidates. The aldosterone receptor antagonists spironolactone and eplerenone are successful in lowering the blood pressure and are the antihypertensive agents of choice in patients with primary aldosteronism. Spironolactone therapy is initiated at doses of 25 to 50 mg/day and can be titrated up to 400 mg/day, depending on blood pressure, serum potassium levels, and side effects. Side effects of spironolactone include gynecomastia, impotence, and menstrual disturbances. Eplerenone may provide a more favorable side-effect profile compared with spironolactone owing to increased selectivity for the aldosterone receptor. Treatment should be initiated with 25 mg per day and titrated up to 100 mg/day. Despite treatment with an aldosterone receptor antagonist, other antihypertensive agents will often be needed. In addition, several lifestyle modifications may contribute to the success of medical therapy, including weight loss, a low-sodium diet, and a regular exercise program (Young, 2007a).

Unlike other forms of primary aldosteronism, FH type I can be treated with oral glucocorticoids. Glucocorticoid administration will reduce ACTH release, leading to decreased aldosterone production in this select group of patients. In FH type I patients whose blood pressure is not controlled with glucocorticoids alone or in those who develop iatrogenic Cushing syndrome, the addition of an aldosterone receptor antagonist should be considered (Funder et al, 2008).

Summary. Successful identification and treatment of primary aldosteronism is critical because of the increased risk of cardiovascular morbidity associated with the diagnosis. Because primary aldosteronism consists of several distinct subtypes that significantly affect management strategy, subtype differentiation is critical before surgical intervention.

KEY POINTS: PRIMARY ALDOSTERONISM

- Most patients with primary aldosteronism in contemporary series are normokalemic.
- Primary aldosteronism is associated with an increased risk of end-organ damage compared with essential hypertension.
- Accurate subtype differentiation is essential to ensure appropriate treatment of primary aldosteronism.

Pheochromocytoma

Overview and Epidemiology. Pheochromocytoma is a tumor of the catecholamine-producing cells of the adrenal medulla. Approximately 1 to 2 per 100,000 individuals are diagnosed annually with pheochromocytoma, albeit reports on incidence vary (Bravo and Tagle, 2003). Given its rarity, it is estimated that pheochromocytoma is responsible for only approximately 0.5% of cases of hypertension (Lenders et al, 2005). Among patients with incidental adrenal masses, approximately 5% will have a pheochromocytoma (Mantero et al, 2000; Young, 2000). Indeed, incidentally discovered lesions now account for 10% to 25% of all pheochromocytomas diagnoses (Bravo and Tagle, 2003; Lenders et al, 2005).

Some 1% to 25% of pheochromocytomas originate outside of the adrenal gland (Fig. 65-16). These extra-adrenal pheochromocytomas are known as *paragangliomas*, because they arise from paraganglia, a network of chromaffin-producing neural crest tissue that anatomically parallels the sympathetic and parasympathetic ganglia (Scott et al, 1990; Ilias and Pacak, 2004). Paragangliomas can arise in the head, neck, thorax, abdomen, and pelvis (including bladder). The chromaffin bodies that lie between the aortic bifurcation and the root of the inferior mesenteric artery are known as the *organ of Zuckerkandl* and are a common site for paragangliomas (Scott et al, 1990). Of note, some authors reserve the term *paraganglioma* for tumors only in the head and neck, locations where extra-adrenal pheochromocytomas tend to be nonfunctional (Neumann et al, 2004).

Pathophysiology

Overview. As discussed in the section on adrenal physiology, cells of the adrenal medulla are analogous to the chromaffin cells of the

sympathetic ganglia. Unlike sympathetic ganglia cells, however, cells of the adrenal medulla, and therefore of adrenal pheochromocytomas, possess the enzyme PNMT, which gives them the ability to synthesize epinephrine from norepinephrine (Eisenhofer et al, 2004b). Pheochromocytomas vary in their enzymatic composition and in their ability to self-metabolize the catecholamines within each tumor's secretory vesicles. Therefore there is great variability in the amount and ratio of catecholamines secreted by pheochromocytomas (Eisenhofer et al, 2001). Indeed, these differences in norepinephrine, epinephrine, and dopamine secretion explain the heterogeneity in clinical behavior of pheochromocytomas. For instance, patients with the rare tumors that secrete primarily epinephrine (usually limited to those that arise from the adrenals or from the organ of Zuckerkandl) tend to experience syncopal or hypotensive episodes because of epinephrine's vasodilatory action through the β_2 receptor, whereas patients with predominantly norepinephrine-secreting tumors (e.g., patients with von Hippel-Lindau [VHL] syndrome) have hypertension and sweating, given the compound's affinity for the vasoconstricting α adrenoreceptor (Pacak, 2007).

Pathophysiology of Hereditary Pheochromocytoma. Familial cases account for nearly one third of pheochromocytomas (Benn and Robinson, 2006). Indeed, a significant percentage of cases that initially appear sporadic are later deemed hereditary on genetic testing. In a 2002 report, Neumann and colleagues (2002) demonstrated that 24% of patients ($n = 271$) with isolated pheochromocytoma who lacked any significant family history exhibited a germline mutation that predisposed them to the disease. At least five genes—rearranged transfection proto-oncogene (*RET*), von Hippel-Lindau (*VHL*), neurofibromatosis type 1 (*NF1*), and mitochondrial succinate dehydrogenase subunits D and B genes (*SDHD*, *SDHB*)—are now associated with familial pheochromocytomas. Some investigators believe that these genetic abnormalities all modulate neuronal apoptosis and are related through signal transduction pathways downstream from the nerve growth factor (NGF) (Nakamura and Kaelin, 2006). Nevertheless, the phenotypes produced by each gene mutation are quite diverse. Table 65-6 summarizes the clinical features associated with each gene mutation.

In general urologic practice, VHL is the most relevant syndrome associated with pheochromocytoma, because these patients usually are already under urologic care owing to their propensity to develop renal cell carcinoma (RCC). Patients with VHL and no family history of pheochromocytoma are classified as having the type 1 variant of the syndrome, whereas type 2 patients are those who carry a family history of pheochromocytoma. In addition, the type 2 variant of VHL is further subdivided. Type 2A patients are those without concomitant RCC, and type 2B patients are those who do exhibit evidence of renal malignancy (Linehan and Ricketts, 2013). A type 2C variant is defined as patients with pheochromocytoma in the setting of a *VHL* mutation, but no other stigmata of the VHL syndrome (Hes et al, 2003). It is interesting to note that a genotype phenotype has been established with VHL-associated pheochromocytomas (type 2), wherein these patients are more likely to exhibit a missense mutation of the *VHL* gene (Walther et al, 1999). Whereas VHL type 2C patients appear to maintain hypoxia-inducible factor (HIF) regulation, pheochromocytoma pathogenesis may occur through HIF-independent pathways (Nakamura and Kaelin, 2006). Furthermore, pheochromocytomas in patients with VHL, unlike those in cases of sporadic or multiple endocrine neoplasia type 2 (MEN-2)-related disease, tend to produce less epinephrine. As a result, metanephrine (but not normetanephrine) levels in these patients are nearly always normal (Eisenhofer et al, 1999; Walther et al, 1999; Pacak, 2007).

Pathophysiology of Malignant Pheochromocytoma. Malignant pheochromocytoma is an aggressive life-threatening neoplasm. Currently, malignancy can only be defined by the presence of clinical metastases. Pathologic appearance and even local invasion are of only limited value in determining metastatic potential of a given lesion (Scholz et al, 2007). A number of pathologic criteria to differentiate benign from malignant disease have been proposed, but to date there is no single histologic criterion agreed

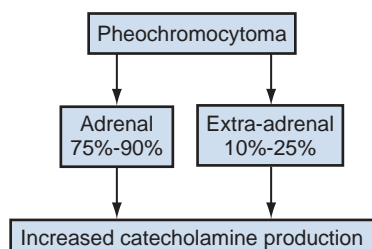


Figure 65-16. Causes of excess catecholamines.

TABLE 65-6 Hereditary Forms of Pheochromocytoma

SYNDROME	CLINICAL CHARACTERISTICS	RISK OF PHEOCHROMOCYTOMA	GENE	CHROMOSOME AND INHERITANCE	PROTEIN	GERMLINE MUTATION IN APPARENTLY SPORADIC CASES (%)	RATE OF MALIGNANT DISEASE
Multiple endocrine neoplasia type 2A	Medullary cancer of thyroid Hyperparathyroidism Cutaneous lichen Amyloidosis	50%	<i>RET</i>	10q11.2 Autosomal dominant	Tyrosine kinase receptor	<5	3
Multiple endocrine neoplasia type 2B	Medullary cancer of thyroid Multiple neuromas Marfanoid body habitus Rare hyperparathyroidism	50%	<i>RET</i>	10q11.2 Autosomal dominant	Tyrosine kinase receptor	<5	3
von Hippel-Lindau syndrome type 2	Renal cell carcinomas and renal cysts CNS and retinal hemangioblastomas Pancreatic cysts Epididymal cystadenomas Endolymphatic cyst tumors	10%-20%	<i>VHL</i>	3p25.26 Autosomal dominant	pVHL19 pVHL30	2-11	5
Neurofibromatosis type 1	Neurofibromas Café-au-lait skin spots	1%	<i>NF1</i>	17q11.2 Autosomal dominant	Neurofibromin	Unknown	11
Familial paraganglioma syndrome type 4 (PGL-4)	Carotid body tumors (chemodectomas) Vagal, jugular, tympanic, abdominal, thoracic paragangliomas	Approximately 20%	<i>SDHB</i>	1p36.13 Autosomal dominant	Catalytic iron-sulfur protein	3-10	30-50
Familial paraganglioma syndrome type 1 (PGL-1)	Carotid body tumors (chemodectomas) Vagal, jugular, tympanic, abdominal, thoracic paragangliomas	Approximately 20%	<i>SDHD</i>	11q23 Maternal imprinting	CybS (membrane-spanning subunit)	4-7	<3

CNS, central nervous system.

Data from Dluhy RG. Pheochromocytoma—death of an axiom. *N Engl J Med* 2002;346(19):1486-8; and Lenders JW, Eisenhofer G, Mannelli M, et al. Pheochromocytoma. *Lancet* 2005;366(9486):665-75.

on (Thompson, 2002; Kimura et al, 2005; Pacak et al, 2007; Scholz et al, 2007). Some pathologic criteria use immunohistochemical strategies including Ki-67 staining, which may be the best indicator of malignancy thus far, although it has not yet been validated owing to methodologic heterogeneity (Kimura et al, 2005; Pacak et al, 2007).

Malignant pheochromocytoma in patients with MEN-2 and VHL is exceedingly rare (see Table 65-6). The *SDHB* mutation is the single genetic abnormality most strongly associated with malignancy. In one international series, 11 of 32 patients with this mutation exhibited clinically malignant pheochromocytoma (Neumann et al, 2004).

Clinical Characteristics

Overview. Classically, pheochromocytoma has been called the “10% tumor”: 10% extra-adrenal, 10% familial, 10% bilateral, 10% pediatric, and 10% malignant (Scott et al, 1990; Dluhy, 2002; Lenders et al, 2005). However, this rule has been challenged repeatedly. As already mentioned, up to 25% of pheochromocytomas can be extra-adrenal (Ilias and Pacak, 2004). Similarly, familial cases account for up to 30% of tumors at presentation (Benn and Robinson, 2006). Malignancy is rare in both sporadic cases of adrenal pheochromocytoma (up to 5%) and in most cases of hereditary disease (see Table 65-6). However, for unclear reasons, it occurs in over one third of patients with extra-adrenal disease (Lenders et al, 2005). Nonhereditary cases of pheochromocytoma are most often diagnosed in the fourth and fifth decades of life, whereas familial tumors tend to occur at a younger age (Lenders et al, 2005). Despite being uncommon, pediatric pheochromocytoma is the most frequently encountered endocrine neoplasm in children. Up to 40% of such tumors are familial, and over 20% are bilateral (Pacak et al, 2007; Havekes et al, 2009). For reasons that are unclear, tumors arising from the right adrenal are more common, tend to be larger, and recur more frequently than those that arise in the left gland (Amar et al, 2005b).

Paroxysmal hypertension is the classic presenting sign in patients with pheochromocytoma. Nevertheless, such episodic spikes in blood pressure are documented in only approximately 30% to 50% of patients and can occur in the backdrop of baseline essential hypertension. The remainder of patients demonstrate persistently elevated blood pressure, and a minority are entirely normotensive (Scott et al, 1990). The triad of headache, episodic sudden perspiration, and tachycardia is a classic hallmark of pheochromocytoma (Bravo and Tagle, 2003). Table 65-7 lists common clinical signs and symptoms of pheochromocytoma. More than 20% of patients can be asymptomatic (Adler et al, 2008). Indeed, depend-

ing on the catecholamine milieu of each tumor, its ability to self-metabolize the catecholamine reserve, and patients' varied responses to catecholamine surges, symptomatology can drastically differ from patient to patient (Pacak, 2007). This heterogeneity in mode of presentation and symptomatology and the difficulty in establishing firm diagnostic criteria for pheochromocytoma are illustrated by an autopsy series that included 54 patients over a 50-year period from the Mayo Clinic, wherein more than 75% of tumors were not suspected before the patient's death (Sutton et al, 1981).

Clinical Characteristics of Hereditary Pheochromocytoma. Hereditary pheochromocytomas occur at a younger age and tend to be multifocal and/or bilateral at presentation (Adler et al, 2008). Table 65-6 summarizes the clinical features of each gene mutation. Pheochromocytomas in patients with MEN-2 nearly always arise from the adrenal gland, whereas tumors in patients with VHL and neurofibromatosis type 1 (NF-1) are outside the adrenal in approximately 12% and 6% of cases, respectively (Lairmore et al, 1993; Walther et al, 1999; Benn and Robinson, 2006; Karagiannis et al, 2007). *SDHB* and *SDHD* mutations mostly result in extra-adrenal and often multifocal phenotypes; nevertheless, solitary adrenal masses, as a result of these genetic abnormalities, may also arise (Neumann et al, 2004; Pacak et al, 2007). Unlike other hereditary forms of pheochromocytoma, mutations in the *SDHB* gene are associated with a very high risk of malignancy (Neumann et al, 2004). As mentioned previously, pheochromocytomas in patients with VHL mainly secrete norepinephrine and lack significantly elevated epinephrine secretion. As a result, normetanephrine, but not metanephrine, levels are elevated in these patients (Eisenhofer et al, 1999; Walther et al, 1999; Pacak, 2007).

Clinical Characteristics of Malignant Pheochromocytoma. Metastatic disease is much more common in extra-adrenal lesions (Scholz et al, 2007). The *SDHB* mutation is the one genetic abnormality that is strongly associated with metastatic disease (see Table 65-6). Classically, the majority of patients with an *SDHB* abnormality exhibit extra-adrenal disease; however, a significant proportion of patients (28% of patients in one series) have adrenal lesions at presentation (Neumann et al, 2004). Malignant lesions are more likely to exhibit elevated dopamine levels and tend to be larger (>5 cm); however, as mentioned previously, in the absence of metastatic deposits, a preclinical diagnosis of malignant potential is not possible (John et al, 1999; Lenders et al, 2005). Bone, lungs, liver, and lymph nodes constitute the most common sites of metastases (Scholz et al, 2007).

Metastatic pheochromocytoma can be present at diagnosis or be detected during surveillance after excision of the primary tumor. Most metastases are discovered within 5 years of the original diagnosis, but metastatic spread more than 15 years after initial excision has been reported (Eisenhofer et al, 2004a; Lenders et al, 2005).

Diagnostic Tests. Biochemical testing is the first step in the evaluation of patients suspected of having pheochromocytoma. If metabolic testing results are positive, appropriate imaging is undertaken to localize the source of the catecholamine excess (Adler et al, 2008). Timely and appropriate diagnosis of pheochromocytoma continues to be a clinical challenge (Zendron et al, 2004; Harding et al, 2005; Yu et al, 2009). In urologic practice, diagnosis of pheochromocytoma typically begins with the evaluation of an adrenal mass as a catecholamine-hypersecreting lesion. Given the potentially catastrophic consequences of misdiagnosis, the possibility of pheochromocytoma must also be considered in patients with a known history of malignancy, and with a solitary adrenal mass in those in whom a metastatic adrenal lesion is suspected (Weismann et al, 2006; Adler et al, 2007). Clinical evaluation depends on both radiographic imaging and, more important, biochemical testing.

Imaging. Here we briefly discuss imaging of pheochromocytoma. Please refer to the section on imaging of adrenal masses for further details on adrenal imaging.

Cross-Sectional Imaging. On cross-sectional imaging, adrenal pheochromocytomas appear as well-circumscribed lesions. Given their rich vascularity and low lipid content, pheochromocytomas typically measure an attenuation of greater than 10 HU on unenhanced CT (mean approximately 35 HU). This property affords

TABLE 65-7 Clinical Manifestations of Pheochromocytoma

MANIFESTATION	FREQUENCY (%)
Headache	60-90
Palpitations	50-70
Sweating	55-75
Pallor	40-45
Nausea	20-40
Flushing	10-20
Weight loss	20-40
Tiredness	25-40
Psychological symptoms (anxiety, panic)	20-40
Sustained hypertension	50-60
Paroxysmal hypertension	30
Orthostatic hypotension	10-50
Hyperglycemia	40

Modified from Lenders JW, Eisenhofer G, Mannelli M, et al. Pheochromocytoma. *Lancet* 2005;366(9486):665-75.

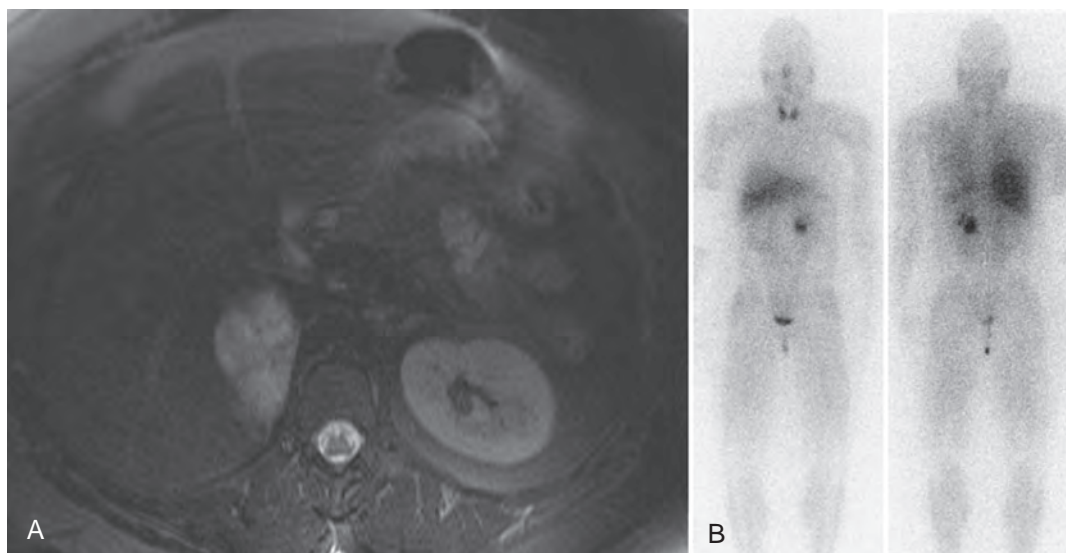


Figure 65-17. Imaging of pheochromocytoma. A, Axial T2-weighted magnetic resonance image of a right adrenal mass that proved to be pheochromocytoma. B, Metaiodobenzylguanidine (MIBG) scan of a different patient with a localized left pheochromocytoma. Normal uptake can be seen in the liver, salivary glands, thyroid, and bladder. It is important to note that fluorodeoxyglucose positron emission tomography appears to be superior to the MIBG scan with a notable exception of patients with known multiple endocrine neoplasia type 2 (A, Courtesy Dr. Rosaleen Parsons, Fox Chase Cancer Center, Philadelphia; B, courtesy Dr. Michael Yu, Fox Chase Cancer Center, Philadelphia.)

the ability to differentiate them from lipid-rich adenomas (Motta-Ramirez et al, 2005). Furthermore, pheochromocytomas can be distinguished from lipid-poor adenomas through use of CT contrast washout strategies. Although nonspecific, pheochromocytomas, unlike adenomas, do not exhibit rapid contrast washout on delayed imaging (Szolar et al, 2005); rare examples of low-density pheochromocytomas that exhibit an unenhanced attenuation of less than 10 HU and demonstrate brisk contrast washout have been reported (Blake et al, 2003, 2005). Such examples underscore the importance of a complete metabolic evaluation for every adrenal mass. In the past, iodinated intravenous contrast was believed to be a possible trigger for a hypertensive crisis. No evidence exists to support this misconception (Pacak, 2007).

Similar to CT, MRI is an excellent imaging modality for characterizing adrenal lesions. Again, differentiation of pheochromocytoma from adenoma centers on an assessment of the lesion's lipid content. Unlike lipid-rich adenomas, pheochromocytomas do not exhibit signal dropout on out-of-phase sequences (Namimoto et al, 2001). Classically, bright signal intensity on T2-weighted imaging (best seen on fat suppression sequences)—termed the “light bulb” sign—was believed to be diagnostic for pheochromocytoma. It is now clear that this imaging characteristic is neither specific nor sensitive enough to secure a diagnosis and must be interpreted with caution (Varghese et al, 1997; Elsayes et al, 2005).

Functional Imaging

¹⁸F-Fluorodeoxyglucose Positron Emission Tomography. Fluorine-18 fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) recently has emerged as the gold standard imaging modality for definitive staging in patients with pheochromocytoma. Initially ¹⁸F-FDG PET was shown to be a useful clinical tool for patients with the *SDHB* mutation (Timmers et al, 2007a, 2007b); however, a recent report of over 200 patients with adrenal and extra-adrenal pheochromocytoma from investigators from the NIH documented that ¹⁸F-FDG PET has far superior test characteristics to CT, MRI, and metaiodobenzylguanidine (MIBG) scintigraphy. ¹⁸F-FDG PET exhibited better accuracy than ¹²³I-MIBG in nearly all patients, especially for identification of metastatic disease. Notable exceptions were individuals with MEN-2 germline mutations, for whom

sensitivity of ¹⁸F-FDG PET was low (<50%) and in whom the procedure was far inferior to ¹²³I-MIBG. It is interesting to note that PET avidity was independent of the tumor's biochemical vigor or “phenotype” (Timmers et al, 2012).

Metaiodobenzylguanidine Scintigraphy. MIBG is a small-molecule analog of norepinephrine. With MIBG tagged with either ¹³¹I or ¹²³I, MIBG scintigraphy has been used since the 1980s to evaluate patients with pheochromocytoma. ¹²³I-MIBG—the preferred agent—affords a high sensitivity (83% to 100%) and superb specificity (95% to 100%) for identification of pheochromocytoma (Fig. 65-17) (Ilias and Pacak, 2004). Details regarding this imaging modality are discussed in the imaging section of this chapter. Here, we review clinical applications of MIBG.

MIBG historically has been an integral part of a thorough workup for patients with extra-adrenal, metastatic, or recurrent pheochromocytoma; however, new data suggest that ¹⁸F-FDG PET may be a superior modality for non-MEN-2 patients (Timmers et al, 2007b, 2012). MIBG is also often used to localize disease in patients with biochemical evidence of pheochromocytoma but negative cross-sectional imaging. Nevertheless, currently no consensus exists on the role of MIBG in the most common and urologically most relevant clinical scenario—a solitary adrenal mass on cross sectional imaging in the setting of a biochemical evaluation indicative of pheochromocytoma (Pacak et al, 2007; Koch, 2009). Advocates for MIBG testing argue that in this context, MIBG and, more recently, ¹⁸F-FDG PET afford the opportunity to verify that the mass in question is indeed a pheochromocytoma and that metastatic disease was not missed on cross-sectional imaging (Ilias and Pacak, 2004). Some clinical data, however, suggest that MIBG or ¹⁸F-FDG PET in this situation can safely be omitted because these functional studies only serve to confirm what is already known and do not alter management (Miskulin et al, 2003; Bhatia et al, 2008; Greenblatt et al, 2008). Nevertheless, MIBG or ¹⁸F-FDG PET imaging for large (>5 cm) tumors is likely prudent to assess for presence of metastatic disease before surgery and thereby counsel the patient appropriately (Lenders et al, 2005). Rarely, MIBG scanning may also be used when metabolic workup of an adrenal mass reveals exclusive excess of norepinephrine and normetanephrine but not epinephrine or

TABLE 65-8 Test Characteristics for Diagnosis of Pheochromocytoma from a Large Multicenter Cohort Study (N = 858: 214 Patients with Pheochromocytoma and 644 Controls)

	SENSITIVITY (%)		SPECIFICITY (%)	
	HEREDITARY	SPORADIC	HEREDITARY	SPORADIC
Plasma free metanephrines	97 (74/76)	99 (137/138)	96 (326/339)	82 (249/305)
Catecholamines	69 (52/75)	92 (126/137)	89 (303/339)	72 (220/304)
Urinary fractionated metanephrines	96 (26/27)	97 (76/78)	82 (237/288)	45 (73/164)
Catecholamines	79 (54/68)	91 (97/107)	96 (312/324)	75 (159/211)
Total metanephrines	60 (27/45)	88 (61/69)	97 (91/94)	89 (79/89)
Vanillylmandelic acid	46 (30/65)	77 (66/86)	99 (310/312)	86 (132/153)

From Lenders J, Pacak K, Walther M, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287(11):1427–34.

metanephrine. In such unusual circumstances, MIBG scanning can at times demonstrate that the actual functioning lesion is extra-adrenal (Pacak et al, 2007).

Other Functional Imaging Modalities. Whole-body functional imaging with MIBG has its limitations. For instance, tumors in patients with *VHL* and *SDHB* gene mutations may exhibit cold MIBG scans (Timmers et al, 2007b; Havekes et al, 2008). ^{18}F -FDG PET, nevertheless, is exquisitely sensitive in these individuals (Timmers et al, 2012). Furthermore, aggressive metastatic lesions may lose their ability to accumulate MIBG (Havekes et al, 2008). As discussed in the section on imaging, several modalities using radiolabeled somatostatin analogs and PET radiopharmaceuticals have been developed to serve as alternatives to MIBG or ^{18}F -FDG PET in these instances. Most have limited clinical usefulness; however, PET imaging with ^{18}F -dopamine has been explored at some institutions (Timmers et al, 2007a).

Biochemical Evaluation

Overview. Catecholamines and their metabolites, including metanephrines, are conjugated with a sulfate moiety in the bloodstream. The term *free* refers to compounds that are not conjugated and lack this sulfate group. In the past, assays that measured “total” amounts of catecholamine metabolites were used. These assays were not able to discriminate between “free” and “sulfonated” compounds and were largely inferior in their test characteristics compared with current methods (Eisenhofer et al, 2003a). Moreover, in the past, assays did not always distinguish compound subtypes and reported the aggregate level of catecholamines or metanephrines. Today, the term *fractionated* is used when the laboratory report details not only the amount of each compound type (e.g., metanephrines), but also the relative concentrations of each compound (e.g., normetanephrine and metanephrine) (Eisenhofer et al, 2004b) (Table 65-8).

Catecholamine Testing. Catecholamines—dopamine, norepinephrine, and epinephrine—are produced by pheochromocytomas in varying amounts. Release of these compounds into the bloodstream is often paroxysmal. In the past, measurement of both urinary and serum catecholamine levels was the mainstay for evaluation of pheochromocytoma. Because of the sensitivity (approximately 85%) and specificity (approximately 85%) of these tests, this strategy has been largely replaced by measurements of levels of metanephrines—the methylated metabolites of catecholamines (Lenders et al, 2002, 2005). Measurement of urinary catecholamines, nevertheless, is still recommended in conjunction with urinary fractionated metanephrine testing (Young, 2007b).

Metanephrine Testing. O-methylation of catecholamines is catalyzed by the COMT enzyme. O-methylation of norepinephrine produces normetanephrine, whereas epinephrine’s methylation results in formation of metanephrine. Together, normetanephrine and metanephrine are known as *metanephrines* (see Fig. 65-4) (Eisenhofer et al, 2001). Historically, formation of metanephrines was believed to take place by COMT in the liver and kidneys after catecholamines were released into the peripheral circulation by the tumor. Now it is clear that the vast majority of metanephrine

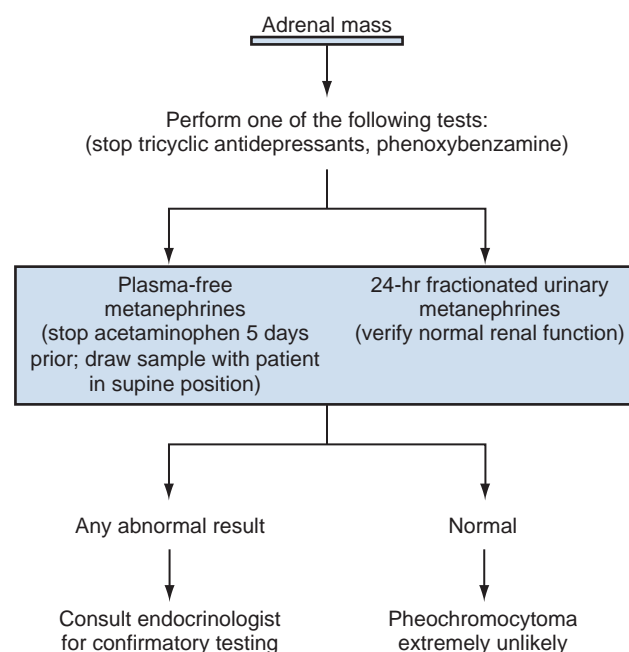


Figure 65-18. Testing algorithm to evaluate adrenal mass for catecholamine secretion.

synthesis occurs within the adrenal medulla and/or pheochromocytoma, and only then do metanephrines enter the bloodstream (Eisenhofer et al, 1998, 2004b). Because this conversion of catecholamines to metanephrines is an uninterrupted process within pheochromocytomas, measurement of plasma concentration of metanephrines is a much more sensitive means of tumor detection than the measurement of rises in plasma catecholamines, which may be paroxysmal (Eisenhofer et al, 2003a, 2003b). Today, measurement of metanephrine levels in plasma or urine represents the foundation for pheochromocytoma diagnosis and is extremely sensitive (Fig. 65-18). Controversy exists regarding whether measurement of plasma free metanephrines versus urinary fractionated metanephrines should be used as the initial test (Lenders et al, 2002; Sawka et al, 2003; Young, 2007b; Eisenhofer et al, 2008). Please refer to the section Testing for Catecholamine Hypersecretion (in the Assessment of Function of Adrenal Masses section) for a complete discussion of the two testing strategies. Traditionally, when tests for fractionated urine or total metanephrines are ordered, urine catecholamine levels are also obtained (Eisenhofer et al, 2003a).

Vanillylmandelic Acid Testing. Because VMA is the primary end metabolite of catecholamines, its measurement in urine has long been used for diagnosis of pheochromocytoma. Nevertheless, synthesis of VMA requires deamination of catecholamines, or their

metabolites, by the MOA enzyme and occurs not only in the adrenal medulla but also in the sympathetic nervous system. Moreover, the sympathetic nervous system lacks the ability to produce epinephrine owing to the absence of the PNMT enzyme and therefore contributes to the serum level of only normetanephrine (from norepinephrine) but not metanephrine (from epinephrine). Therefore the relative rise of VMA levels in the presence of a pheochromocytoma is much less dramatic than the rise seen in the levels of metanephrines, and the sensitivity of urine VMA levels is therefore low (below 65% in some series) (Lenders et al, 2005). However, the specificity of the test is high, especially in nonfamilial cases (99%) (Lenders et al, 2002).

Clonidine Suppression Testing. Clonidine, an α_2 agonist, suppresses catecholamine (specifically norepinephrine) production by the sympathetic nervous system but not by pheochromocytoma. Comparison of normetanephrine levels before and after clonidine administration has been shown to yield results with favorable test characteristics (Eisenhofer et al, 2003b). This evaluation is suggested by some experts for secondary testing in patients with pheochromocytoma who exhibit mild or borderline elevations in metanephrine levels. When embarking on clonidine suppression testing, one must be cognizant that clonidine administration can result in significant hypotension in certain patients (Eisenhofer et al, 2003b).

Chromogranin A Testing. Chromogranin A belongs to a group of compounds known as granins, which exist in the secretory vesicles of the neuroendocrine and the nervous systems. Elevation of serum chromogranin A levels has been documented in patients with pheochromocytoma. Although the sensitivity of the test for detecting pheochromocytoma is suboptimal (approximately 85%), some have suggested that the evaluation of chromogranin A level has a role in confirmatory testing in patients who have mild or moderate (less than a fourfold) elevation in free plasma metanephrine levels (Bravo and Tagle, 2003; Algeciras-Schimmich et al, 2008). Chromogranin A is renally cleared, and the specificity of the test decreases significantly in patients with glomerular filtration rates less than 80 mL/min (Bravo and Tagle, 2003).

Screening for Hereditary Pheochromocytoma. A hereditary pattern is responsible for more than one third of pheochromocytomas. Furthermore, nearly one quarter of patients who appear to have sporadic nonfamilial disease at diagnosis demonstrate germline mutations on genetic testing (Neumann et al, 2002; Benn and Robinson, 2006). Despite this, the consensus of the First International Symposium on Pheochromocytoma in 2005 did not endorse universal genetic testing in all patients diagnosed with pheochromocytoma. Instead, this panel of experts established guidelines for screening and evaluation for pheochromocytoma. Figure 65-19 summarizes how clinical history and disease characteristics at presentation should guide genetic testing. Others have suggested similar algorithms (Amar et al, 2005a). All patients younger than 50 should receive genetic testing for the *RET*, *VHL*, *SDHB*, and *SDHD* gene mutations (Pacak, 2007). Routine testing for the *NF1* gene is not recommended in patients who do not meet clinical criteria for neurofibromatosis (Plouin and Gimenez-Roqueplo, 2006b). Before initiating genetic testing, the patient should be counseled about implications and benefits of genetic testing. Professional genetic counseling is strongly recommended (Pacak, 2007).

Treatment

Overview. Pheochromocytoma is a surgical disease. Complete resection of the tumor is advised whenever possible (Khorram-Manesh et al, 2005). Laparoscopic adrenalectomy constitutes the standard of care for most tumors, although open approaches have been advocated for large and/or surgically difficult tumors (Pacak et al, 2007). Please see Chapter 66 regarding surgical considerations when treating patients with pheochromocytoma. The urologist must be familiar with the perioperative management of catecholamine-producing tumors before taking the patient to the operating room. Lifelong follow-up is necessary for all patients. Patients with familial and malignant disease require a tailored approach that should include cardiology, endocrinology, and, if needed, medical oncology.

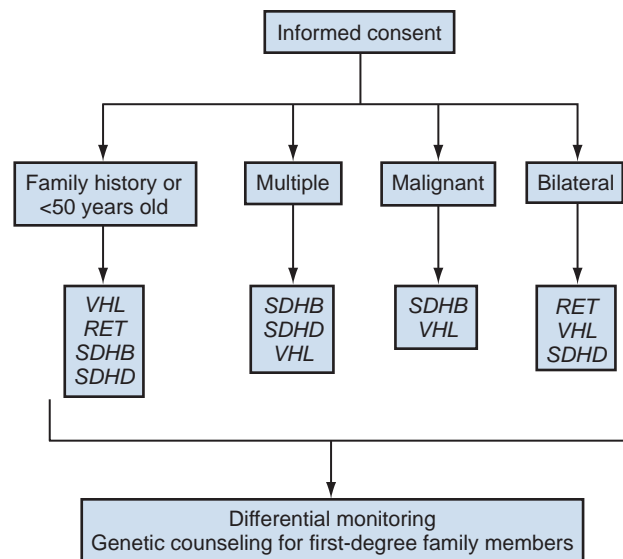


Figure 65-19. Algorithm for genetic screening of patients with pheochromocytoma with risk factors for hereditary disease. (From Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab 2007;92:4069–79.)

Preoperative Management

Overview. Catecholamine release during intraoperative tumor manipulation can result in hazardous blood pressure elevation and cardiac arrhythmias. In the era before routine initiation of preoperative catecholamine blockade, some reported mortality rates as high as 50% (Pacak et al, 2001b). In 2005, the First International Symposium on Pheochromocytoma recommended that all patients with pheochromocytoma and an abnormal metabolic evaluation undergo preoperative catecholamine blockade, including patients who do not exhibit evidence of blood pressure elevation and lack classic symptomatology (Pacak, 2007). Contemporary series demonstrate mortality rates of less than 3%, which has been attributed in part to optimized anesthetic care and routine preoperative blockade (Lenders et al, 2005). In the absence of appropriately conducted clinical studies comparing preoperative management strategies, no level 1 evidence exists regarding optimal preoperative or perioperative management (Pacak, 2007). Here, we review preoperative blockade strategies relevant to aggressive α -blockade, a central theme recommended by the team from the NIH. Option 1 in Figure 65-20 summarizes the team's approach. We also outline an alternative strategy (see Fig. 65-20, option 2) that focuses on calcium channel blockade and that has been popularized by other authors (Ulchaker et al, 1999). Other permutations on approaches to preoperative catecholamine blockade exist but are less widely discussed in the literature (Pacak, 2007).

Thoughtful preoperative cardiac evaluation is paramount, because patients with pheochromocytoma are at risk for cardiomyopathy. Some experts recommend routine preoperative echocardiography (Kinney et al, 2002). We suggest that the patient undergo either a cardiology or an anesthesia consultation before surgery.

α -Blockade. Phenoxybenzamine is the most common α -blocker used for preoperative catecholamine blockade of pheochromocytoma. The agent irreversibly blocks the α receptor. Accordingly, intraoperative catecholamine surges typically do not override its actions, because reversal of the blockade is possible only through synthesis of new receptor molecules (Pacak, 2007). Phenoxybenzamine is started 7 to 14 days before surgery. Oral administration of 10 mg twice daily is initiated and titrated by increases of 10 to 20 mg to a blood pressure of 120 to 130/80 mm Hg in a seated position. Mild postural hypotension with systolic pressure greater than 80 mm Hg is acceptable (Kinney et al, 2002). Experience shows that a final dose of 1 mg/kg is usually sufficient to achieve adequate blockade (Pacak, 2007). In children,

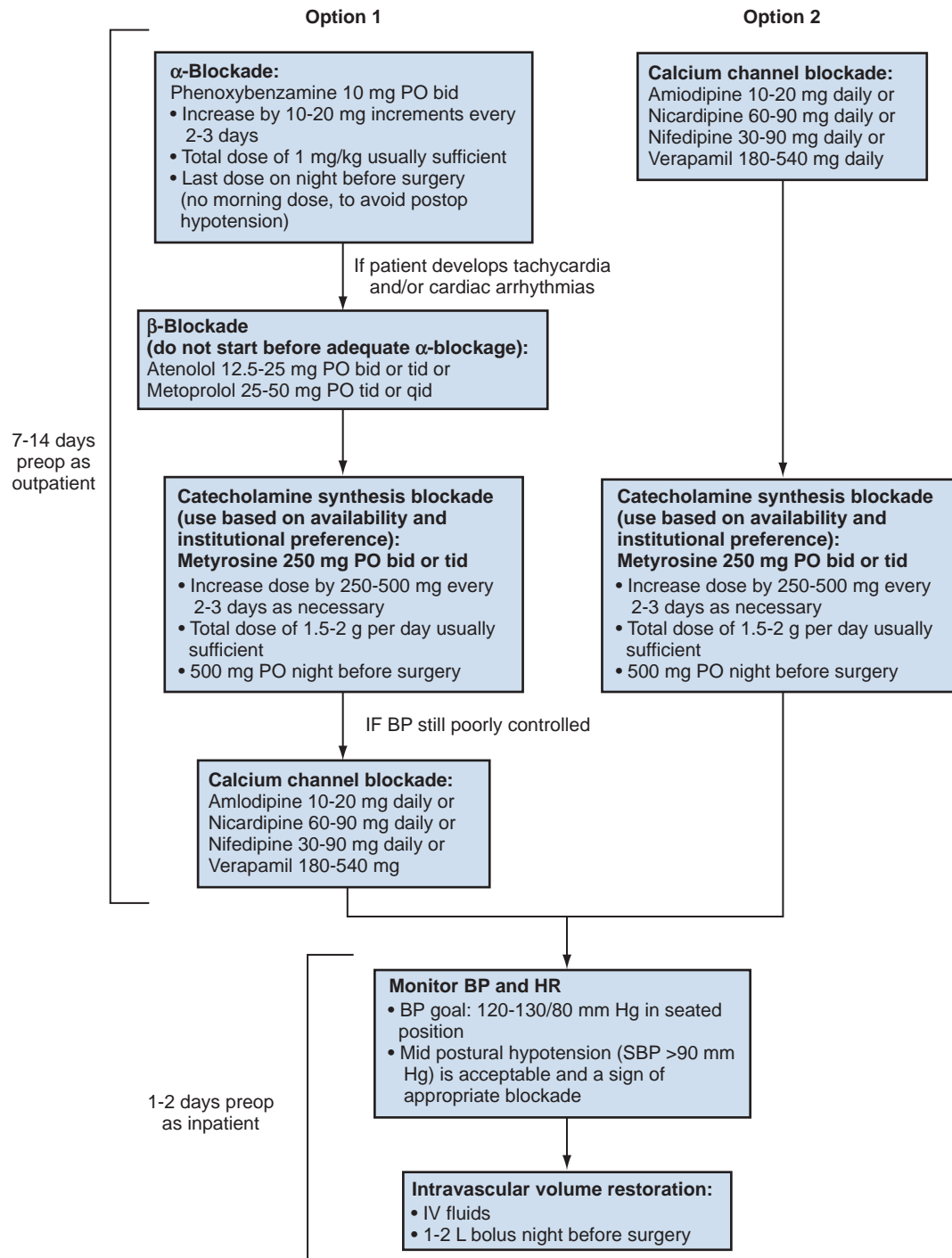


Figure 65-20. Preoperative medical management in patients with pheochromocytoma. BP, blood pressure; HR, heart rate; IV, intravenous; PO, by mouth; SBP, systolic blood pressure. (Modified from Pacak K. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab* 2007;92:4069–79.)

0.2 mg/kg (maximum dose of 10 mg) four times daily with increases in 0.2-mg/kg increments is recommended (Lenders et al, 2005). Because of the irreversible nature of α -blockade, after tumor resection patients may require transient blood pressure support (Pacak, 2007).

Selective reversible α_1 -blockers, such as terazosin, doxazosin, or prazosin, are used at some centers in lieu of or in combination with phenoxybenzamine. Although these agents may have fewer side effects than phenoxybenzamine, data regarding their efficacy are contradictory (Lenders et al, 2005; Pacak, 2007). Moreover, recent compelling data are emerging that in normotensive asymptomatic

patients, preoperative α -blockade may not be necessary. In one report a large cohort of asymptomatic normotensive patients with incidentaloma and a metabolic workup suggestive of pheochromocytoma was offered either α -blockade with doxazosin ($n = 38$) or no preoperative blockade ($n = 21$) (Shao et al, 2011). No differences in blood pressure control or perioperative outcomes were seen between the two groups. The group that received doxazosin was more likely to require intraoperative administration of vasoactive agents (Shao et al, 2011). Although these data are provocative, they require validation from other centers, ideally in a prospective randomized fashion.

β -Blockade. β -Blockade should be used with caution in patients with pheochromocytoma; however, its use is at times necessary because of reflex tachycardia and arrhythmias that can result on initiation of α -blockade. It is important to understand that **β -blockade should never be started before appropriate α -blockade.** Indeed, in the absence of α -blockade, β antagonists cause a potentiation of the action of epinephrine on the α_1 receptors owing to blockade of the arteriolar dilation at the β_2 receptor. For this reason, selective β_1 adrenoreceptor blockers, such as atenolol and metoprolol, are usually preferred. Dosages for these agents are summarized in Figure 65-20 (Pacak, 2007).

Catecholamine Synthesis Blockade. α -Methyltyrosine, better known as *metyrosine*, blocks the rate-limiting step in the biosynthesis of catecholamines by inhibiting the tyrosine hydroxylase enzyme and thereby preventing the conversion of tyrosine to L-dihydroxyphenylalanine (L-DOPA) (see Fig. 65-4) (Pacak et al, 2001b). Approximately 3 days are necessary to achieve full clinical effect after initiation of this agent. Because blockade of catecholamine synthesis is incomplete, the use of metyrosine is usually coupled with α -blockade by phenoxybenzamine. Use of this agent largely depends on institutional preferences and availability. Some centers avoid routine use of this agent and reserve it for refractory or metastatic patients because of its central nervous system side effects, including sedation, mood depression, and galactorrhea. Extrapyramidal symptoms resembling parkinsonism can result and necessitate cessation of phenoxybenzamine use if present (Pacak et al, 2007). Dosage and titration strategies are summarized in Figure 65-20.

Calcium Channel Blockade. Calcium channel blockade in the context of catecholamine excess lowers blood pressure by generating smooth muscle relaxation (Ulchaker et al, 1999). The use of agents such as nicardipine has been suggested by some as an adjunct to traditional α -blockade therapy in refractory patients. Other groups, however, report that sole use of calcium channel blockers (see Fig. 65-20, option 2) is sufficient for safe pheochromocytoma resection (Ulchaker et al, 1999; Lebuffe et al, 2005). Indeed, advocates of this strategy argue that this approach avoids the reflex tachycardia and postoperative hypotension that are seen with use of phenoxybenzamine (Ulchaker et al, 1999). The team from the NIH suggests that this strategy (see Fig. 65-20, option 2) be reserved for patients with only mild symptomatology at presentation (Pacak, 2007).

Intravascular Volume Management. Restoration of intravascular volume is perhaps the most important component of preoperative management of patients with pheochromocytoma. Intake of salt and fluid is encouraged once catecholamine blockade has been initiated (Lenders et al, 2005). Moreover, most centers admit patients the day before surgery and initiate aggressive intravenous fluid resuscitation. The last dose of phenoxybenzamine and/or metyrosine is usually given on the night before surgery, and the next morning's dose is withheld. This approach minimizes potentially prolonged hypotension after tumor resection (Pacak, 2007).

Postoperative Management. In the immediate postoperative period, the patient must be actively monitored. If phenoxybenzamine was used for preoperative α -blockade, hypotension is common, given the lasting effects of the agent (Pacak et al, 2001b). Moreover, in a high catecholamine state, α_2 -adrenoreceptor stimulation inhibits insulin release. The withdrawal of this adrenergic stimulus after tumor resection may result in rebound hyperinsulinemia and subsequent hypoglycemia (Kinney et al, 2002). Hence, given the necessity for close monitoring, some experts advise overnight admission to the intensive care unit after pheochromocytoma resection (Lenders et al, 2005).

Follow-Up. Repeat metabolic testing should be performed approximately 2 weeks after adrenalectomy to document normalization of chromaffin cell function (Pacak et al, 2007). In patients in whom metanephrine levels remain elevated, MIBG imaging may be helpful. MIBG uptake by previously unseen metastases may be unveiled after resection of the primary tumor (Plouin and Gimenez-Roqueplo, 2006a).

Long-term vigilant postoperative follow-up of patients with pheochromocytoma is essential (Lenders et al, 2005; Pacak et al,

2007). Lifelong screening for recurrence is recommended by some experts, because 10-year recurrence rates are as high as 16% in some series of fully resected lesions (Amar et al, 2005b; Plouin and Gimenez-Roqueplo, 2006a). Indeed, recurrent disease has been noted in patients more than 15 years after resection of the original tumor (Plouin et al, 1997; Goldstein et al, 1999). Annual biochemical follow-up is mandatory for all patients with resected pheochromocytoma (Eisenhofer et al, 2004a; Lenders et al, 2005). No consensus on follow-up protocols exists; however, biochemical testing at 6 months after surgery, followed by annual testing, has been suggested (Pacak et al, 2001b, 2007). Postoperative cross-sectional imaging is reasonable to document tumor resection and appropriate healing of the resection bed. Need for subsequent imaging should be guided by results of biochemical testing (Pacak et al, 2001b).

Treatment of Hereditary Pheochromocytoma. Patients with hereditary pheochromocytoma require a unique approach. Given that for patients with MEN-2 and VHL, the risk of malignancy is low (see Table 65-6) whereas the risk of bilateral disease is significant, partial cortical-sparing adrenalectomy has been advocated. This strategy is used to avoid lifelong hormonal replacement, with its associated morbidity (Løvås et al, 2002; Yip et al, 2004; Diner et al, 2005). Successful surgical outcomes require advanced surgical expertise and careful preoperative radiographic planning (Mitterberger et al, 2006). Nevertheless, the patient must be counseled that hormonal replacement may still be necessary despite a seemingly successful cortex-sparing procedure. Life-threatening addisonian crisis can also occur despite close postoperative monitoring (Yip et al, 2004; Asari et al, 2006). Close long-term biochemical and radiographic follow-up is essential, whereas recurrence rates are poorly defined but appear to be significant (Yip et al, 2004; Asari et al, 2006).

Treatment of Malignant Pheochromocytoma. Currently therapy for metastatic pheochromocytoma is largely palliative. Surgical metastasectomy of resectable disease is the standard of care; however, little evidence exists to demonstrate that it prolongs patient survival or is more effective for symptomatic relief than medical treatment with α/β -blockade and α -methyl-*p*-tyrosine (Eisenhofer et al, 2004a; Lenders et al, 2005; Pacak, 2007). Local palliative tumor control using ablation techniques and embolization has also been described (Pacak et al, 2001a; Eisenhofer et al, 2004a).

Given the selective uptake of MIBG by pheochromocytoma cells, systemic treatment of metastatic disease with radioactive ^{131}I -MIBG may be instituted. Before initiation of therapy, MIBG uptake by tumor targets should be demonstrated with traditional MIBG imaging (Scholz et al, 2007). Symptomatic response is seen in up to 2 of 3 patients. Over 40% of patients exhibit a reduction in catecholamine levels. Tumor volume reduction occurs in approximately 30% of patients, but complete responses are seen in less than 5% (Loh et al, 1997; Scholz et al, 2007). High-dose therapy has been reported. Rose and colleagues (2003) described a multi-institutional study in which 12 patients were treated with ^{131}I -MIBG at 2 to 3.5 times its usual dose. Although toxicity was not trivial, 25% of patients ($n = 3$) exhibited a lasting complete response. Two of these patients had both bony and soft-tissue metastatic lesions. Given the significant toxicity, routine use of high-dose MIBG radiotherapy continues to be controversial (Lenders et al, 2005; Pacak et al, 2007; Scholz et al, 2007).

The best-studied chemotherapy regimen for malignant pheochromocytoma entails a combination of cyclophosphamide, vincristine, and dacarbazine (CVD). Although response rates can be significant (over 50% radiographic tumor response and nearly 75% biochemical response), they are typically short-lived (2 years) (Scholz et al, 2007; Huang et al, 2008). Chemotherapy is primarily used in patients in whom MIBG therapy has failed or in those whose tumors do not demonstrate MIBG uptake on initial MIBG imaging studies. Combination therapy with CVD and MIBG has been explored, but, to date, its risks and benefits remain poorly defined (Scholz et al, 2007).

Prognosis. After surgical resection, patients with pheochromocytoma typically do exceedingly well. Surgical mortality rates in the current era are less than 3% (Lenders et al, 2005). Hypertension

usually resolves after resection, but not in all cases (Plouin et al, 1997). Despite an excellent prognosis, the disease can recur many years after resection in up to 16% of patients, necessitating vigilant lifelong follow-up (Plouin et al, 1997; Goldstein et al, 1999; Eisenhofer et al, 2004a; Amar et al, 2005b). In one large series, patients with extra-adrenal disease (hazard ratio [HR] 11.2), hereditary pheochromocytomas (HR 3.4), right adrenal tumors (HR 3.1), bilateral tumors (HR 1.4), and larger tumors (HR 1.2 per centimeter of diameter) were more likely to recur. Some 50% of the recurrences were malignant (Amar et al, 2005b).

In some patients metastatic disease progresses rapidly, whereas others exhibit nonaggressive disease and can live in excess of 20 years (Huang et al, 2008). Bone metastases appear to carry the most benign prognosis (Pacak, 2007; Scholz et al, 2007). For all-comers, 5-year survival statistics vary but are believed to be approximately 50% (John et al, 1999; Lenders et al, 2005; Pacak et al, 2007; Scholz et al, 2007).

Summary. Pheochromocytoma is a rare catecholamine-producing tumor. Awareness of its potential presence and familiarity with its management are critical for every urologist. Misdiagnosis or mismanagement is often associated with dire consequences. Pheochromocytoma must be considered in every adrenal mass and referral to a tertiary care facility made if the physician is unfamiliar with the care of these complex patients.

KEY POINTS: PHEOCHROMOCYTOMA

- Nearly 25% of cases of pheochromocytoma that initially appear sporadic are later deemed hereditary on genetic testing.
- Testing for urinary or serum metanephrines (normetanephrine and metanephrine) represents the underpinning of modern biochemical testing for pheochromocytoma.
- Malignancy of pheochromocytoma can be defined only by presence of metastases. Pathologic appearance is unreliable. Long-term follow-up is paramount, because recurrences are reported even 15 years after the initial resection of a localized lesion.
- Familiarity with perioperative management of patients with pheochromocytoma is paramount.

Disorders of Decreased Adrenal Function

Overview and Epidemiology

Adrenal insufficiency, also known as *Addison disease*, is a condition whose management typically is beyond the scope of most urologic practices. Nonetheless, a working knowledge of the condition is essential for the urologic surgeon because the disease may result from either resection or pharmacologic inhibition of functioning adrenal tissues. Failure to consider and diagnose is potentially lethal and therefore warrants review. **Indeed, if the condition is not anticipated and appropriate proactive therapies are not instituted, addisonian crises following simultaneous or staged bilateral adrenalectomy can result in death (Asari et al, 2006).**

Adrenal insufficiency may be caused by primary adrenal failure or may occur secondary to extra-adrenal mechanisms. Its estimated prevalence is 39 to 60 per million (Oelkers, 1996).

Pathophysiology

In the Western world, the most frequent cause of primary adrenal insufficiency is autoimmune adrenalitis. This condition can occur in isolation or as a constellation of pathologies known as autoimmune polyendocrine syndrome (APS), wherein adrenal

insufficiency coexists with hypoparathyroidism, autoimmune thyroid disease, hypogonadism, diabetes, and other autoimmune conditions. Depending on the extent of endocrinologic involvement, APS is classified as either type 1 or the more common type 2 (Arlt and Allolio, 2003). In developing countries, as was true in the age of Thomas Addison, tuberculosis remains the major cause of adrenal failure (Løvås and Husebye, 2005). Other infectious causes, such as cytomegalovirus in the setting of human immunodeficiency virus (HIV) infection and rare fungal adrenalities, can also destroy the adrenal cortex. Bilateral adrenal hemorrhage or infiltrative diseases, such as amyloidosis, sarcoidosis, and hemochromatosis may also affect the function of the glands (Oelkers, 1996). Bilateral metastatic disease involving the adrenals, although classically described as a potential cause of adrenal insufficiency, is a very rare cause of clinically significant Addison disease (Lutz et al, 2000). In urologic practice, relevant clinical scenarios include simultaneous or staged surgical loss of bilateral adrenal tissue after treatment of adrenal or renal disease, and pharmacologic adrenalectomy with inhibitors of steroid hormone synthesis, such as ketoconazole, or new 17 α -hydroxylase (CYP17) inhibitors such as abiraterone (Arlt and Allolio, 2003). Although low postoperative day 1 cortisol levels (<3.4 μ g/dL) are not uncommon in patients after unilateral adrenalectomy (Mitchell et al, 2009), the clinical significance of such findings is unclear, and steroid replacement appears largely unnecessary for those without preoperative hypercortisolism (Shen et al, 2006). Nevertheless, a high index of suspicion for adrenal insufficiency must always remain in patients whose adrenal unit is removed.

Secondary adrenal insufficiency is caused by abnormalities in the pituitary gland or, less frequently, the hypothalamus. Tumors, radiation, autoimmune conditions, pituitary apoplexy (also known as *Sheehan syndrome* when it occurs peripartally), and trauma are less common causes of the condition. Rare congenital conditions marked by a metabolic error in the production of pituitary hormones, including ACTH, are rare causes of secondary Addison disease (Arlt and Allolio, 2003). Figure 65-21 summarizes the major causes of Addison disease. Important, given that aldosterone secretion by the adrenals does not depend on ACTH, the zona glomerulosa continues to function appropriately in patients with secondary adrenal insufficiency. **Mineralocorticoid deficiency is therefore present only in patients with primary Addison disease (White, 1994).**

Exogenous chronic administration of glucocorticoids accompanied by suppression of the HPA axis, resulting in secondary adrenal insufficiency, is particularly relevant to the surgeon (Krasner, 1999). Although overt adrenal crises caused by this clinical scenario are exceedingly rare, the possibility exists in surgical patients on chronic steroids (Axelrod, 2003). Postoperatively the urologist must also be cognizant of HPA axis failure in critically ill patients. This condition, recently termed *critical illness-related corticosteroid insufficiency*, is an important, albeit controversial, clinical entity (Marik et al, 2008; Marik, 2009).

Clinical Characteristics

Clinical signs and symptoms of Addison disease are usually nonspecific and constitutional in most outpatients, who may complain of profound fatigue and anorexia for many months before definitive diagnosis. Hyperpigmentation, a hallmark of primary adrenal insufficiency, results from high serum concentrations of ACTH in response to increased hypothalamic release of POMC-derived peptides that stimulate the melanocortin (MC1) receptor of the skin (Arlt and Allolio, 2003). Table 65-9 summarizes the clinical manifestations of adrenal insufficiency.

Acute adrenal insufficiency, or adrenal crisis, is a life-threatening condition often preceded by hypotension unresponsive to fluid resuscitation. Patients are easily and often misdiagnosed with an acute abdomen, whereas abdominal pain, nausea, vomiting, and fever frequently accompany hypovolemia in these individuals. Pediatric patients can exhibit hypoglycemic seizures (Arlt and Allolio, 2003; Bouillon, 2006).

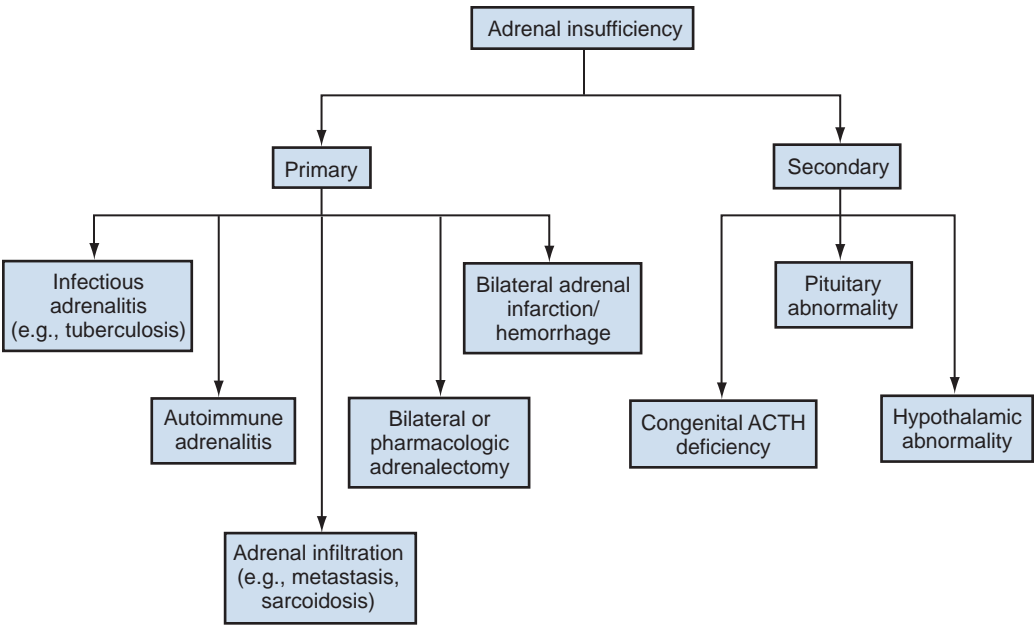


Figure 65-21. Causes of adrenal insufficiency. ACTH, adrenocorticotrophic hormone.

TABLE 65-9 Clinical Manifestations of Adrenal Insufficiency

	PATHOPHYSIOLOGY
SYMPTOMS	
Fatigue, lack of energy or stamina, reduced strength	Glucocorticoid deficiency, adrenal androgen deficiency
Anorexia, weight loss (in children, failure to thrive)	Glucocorticoid deficiency
Gastric pain, nausea, vomiting (more frequent in primary adrenal insufficiency)	Glucocorticoid deficiency, mineralocorticoid deficiency
Myalgia, joint pain	Glucocorticoid deficiency
Dizziness	Mineralocorticoid deficiency, glucocorticoid deficiency
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Dry and itchy skin (in women)	Adrenal androgen deficiency
Loss or impairment of libido (in women)	Adrenal androgen deficiency
SIGNS	
Skin hyperpigmentation (primary adrenal insufficiency only)	Excess of pro-opiomelanocortin–derived peptides
Alabaster-colored pale skin (secondary adrenal insufficiency only)	Deficiency of pro-opiomelanocortin–derived peptides
Fever	Glucocorticoid deficiency
Low blood pressure (systolic RR <100 mm Hg), postural hypotension (pronounced in primary adrenal insufficiency)	Mineralocorticoid deficiency, glucocorticoid deficiency
Raised serum creatinine (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Hyponatremia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to syndrome of inappropriate antidiuretic hormone secretion [SIADH])
Hyperkalemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Anemia, lymphocytosis, eosinophilia	Glucocorticoid deficiency
Increased thyroid-stimulating hormone (primary adrenal insufficiency only)	Glucocorticoid deficiency (or autoimmune thyroid failure)
Hypercalcemia (primary adrenal insufficiency only)	Glucocorticoid deficiency (mostly concurrent hyperthyroidism)
Hypoglycemia	Glucocorticoid deficiency
Loss of axillary or pubic hair (in women), absence of adrenarche or pubarche in children	Adrenal androgen deficiency

From Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361(9372):1881–93.

TABLE 65-10 Perioperative Glucocorticoid Administration in Patients on Chronic Steroid Therapy

DEGREE OF SURGICAL STRESS	DEFINITION	GLUCOCORTICOID DOSE
Minor	Procedure under local anesthesia and less than 1 hour in duration (e.g., inguinal hernia repair)	Hydrocortisone 25 mg or equivalent.
Moderate	Procedure such as vascular surgery of a lower extremity or a total joint replacement	Hydrocortisone 50-75 mg or equivalent. This could be continuation of usual daily steroid dose (e.g., prednisone 10 mg/day) and hydrocortisone 50 mg intravenously during surgery.
Major	Procedure such as esophagogastrectomy or operation on cardiopulmonary bypass	Usual glucocorticoid (e.g., prednisone 40 mg or the parenteral equivalent within 2 hr before surgery) and hydrocortisone 50 mg intravenously q8h after the initial dose for the first 48-72 hr of the postoperative period.

Data from Salem M, Tainsh RE Jr, Bromberg J, et al. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. *Ann Surg* 1994;219(4):416-25; and Axelrod L. Perioperative management of patients treated with glucocorticoids. *Endocrinol Metab Clin North Am* 2003;32(2):367-83.

Adrenal insufficiency (an Addisonian state) after adrenalectomy in the setting of a normally functioning contralateral adrenal gland is unlikely, but possible. This is especially true for patients who are undergoing adrenalectomy for a cortisol-secreting lesion, because functionality of the contralateral gland can be suppressed (Shen et al, 2006; Tsagarakis et al, 2006; Mitchell et al, 2009; Phitayakorn and McHenry, 2012). Furthermore, patients with a history of contralateral partial or radical nephrectomy clearly represent a high-risk group. The integrity of the adrenal gland on the side of previous surgery may be compromised, or that gland may be altogether absent. Close examination of preoperative imaging and review of old operative and pathology reports for information regarding the status of the adrenal gland in the previous surgical field are paramount.

Diagnostic Tests

The diagnosis of primary adrenal insufficiency is primarily made on clinical grounds, with a high index of suspicion given a patient's history, examination findings, and laboratory evaluation. It is ultimately secured by measurements of morning serum cortisol and ACTH. Patients with primary Addison disease exhibit abnormal aldosterone and renin levels. Confirmatory testing involves assessing the adrenal response to ACTH stimulation in the form of the corticotropin test. The majority of patients with autoimmune adrenalitis demonstrate detectable levels of anti-21-hydroxylase antibodies (Oelkers et al, 1992; Arlt and Allolio, 2003).

The appropriate workup for secondary adrenal insufficiency often requires sophisticated probing of the HPA axis that goes beyond the scope of this text and requires endocrinologic expertise. In-depth reviews of the topic are available (Oelkers et al, 1992, 1996).

Treatment

The treatment of Addison disease involves adrenal hormonal replacement. Cortisol is replaced with hydrocortisone or with cortisone acetate. To mimic physiologic circadian glucocorticoid cycling, the majority (half or two thirds) of the daily dose is given in the morning, with the rest administered in one or two doses later in the day (Arlt and Allolio, 2003). Mineralocorticoid replacement is required only for patients with primary adrenal insufficiency and is achieved with fludrocortisone (Løvås and Husebye, 2005). Supplementation of adrenal androgens is advised by some experts, but is often limited to those who experience constitutional complaints despite adequate glucocorticoid and mineralocorticoid supplementation (Arlt and Allolio, 2003). Careful monitoring of patients on

hormone replacement for adrenal insufficiency is required and is often best left to experienced endocrine experts.

The necessity of perioperative stress-dose steroid administration continues to be controversial. Although continuing the patient's usual steroid dose is usually sufficient, given the negligible downside of perioperative steroid coverage and the potential catastrophic consequences of failure to prevent an adrenal crisis, surgeons continue to administer stress-dose steroids perioperatively. Tables 65-10 and 65-11 summarize contemporary recommendations (Salem et al, 1994; Krasner, 1999; Axelrod, 2003). Again, because aldosterone physiology is not altered in these patients, mineralocorticoid replacement is unnecessary (White, 1994).

Prognosis

The impact on life expectancy in cases of primary adrenal insufficiency has not been established; however, a significant impact on a patient's quality of life has been demonstrated (Løvås et al, 2002). Many patients complain of decreased energy, loss of libido, and psychologic maleffects (Arlt and Allolio, 2003). Secondary adrenal insufficiency from hypopituitary disease is an established cause of premature death (Tomlinson et al, 2001).

Summary

In urologic practice, adrenal insufficiency can result from simultaneous or staged surgical excision or pharmacologic ablation with steroid hormone synthesis blockade agents. Diagnosis requires a high index of suspicion. Patients having undergone ipsilateral partial or radical nephrectomy who are to undergo contralateral surgery constitute an at-risk population. Obtaining old operative or pathology reports and examining cross-sectional imaging for the presence or absence of adrenal tissue are essential in this setting. Postoperative adrenal insufficiency must be considered in patients on chronic glucocorticoid therapy or in the critically ill. There should be a low threshold to consult advanced endocrinologic expertise, given the complexity and the potentially grave consequences of the condition.

Disorders of Abnormal Adrenal Function

Congenital Adrenal Hyperplasia

CAH is a disorder that is characterized by low cortisol production caused by a metabolic enzymatic abnormality in the cholesterol-steroid biosynthesis pathway (see Fig. 65-3). The disorder is autosomal recessive and associated with a deficiency in the enzyme

TABLE 65-11 Relative Potency of Common Glucocorticoid Preparations

NAME	BIOLOGIC HALF-LIFE (hr)	RELATIVE ANTI-INFLAMMATORY POTENCY	APPROXIMATE ADULT PHYSIOLOGIC REPLACEMENT DOSE (mg/day)
Hydrocortisone (cortisol)	8-12	1	20
Cortisone acetate		0.8	25
Prednisone	18-36	4	5
Prednisolone		4	5
Methylprednisolone		5	4
Triamcinolone		5	4
Dexamethasone	36-54	25-50	0.5

Modified from Krasner AS. Glucocorticoid-induced adrenal insufficiency. JAMA 1999;282(7):671-6.

KEY POINTS: ADRENAL INSUFFICIENCY

- Mineralocorticoid deficiency is present only in patients with primary Addison disease (e.g., autoimmune adrenalitis, surgical absence of adrenal tissue). Abnormalities in the pituitary gland or, less frequently, the hypothalamus (e.g., in patients with suppressed ACTH secretion from chronic steroid use) do not result in suppression of aldosterone production.
- Any patient who has undergone ipsilateral partial or radical nephrectomy and is undergoing contralateral renal or adrenal surgery is at risk for a postoperative adrenal crisis. Obtaining old operative or pathology reports and examining cross-sectional imaging for the presence or absence of adrenal tissue are essential in this setting.

21-hydroxylase in over 95% of cases. In the absence of negative feedback, ACTH production by the pituitary is increased, resulting in hyperplasia of the adrenal cortex and overproduction of adrenal androgens (Merke and Bornstein, 2005). Diagnosis of the condition is most often established in childhood and is discussed in detail in Chapter 150. Patients with known CAH, as well as carriers of the CAH gene, appear to have a high propensity for developing benign adrenal cortical adenomas but are not at known increased risk for malignant adrenal lesions (Jaresch et al, 1992; Barzon et al, 2007). Patients with undiagnosed nonclassic 21-hydroxylase deficiency can develop adrenal neoplasms later in life (Ravichandran et al, 1996; Nigawara et al, 2008). Given the relatively low incidence, genetic screening of patients with adrenal incidentalomas has not demonstrated an increased incidence of undiagnosed CAH. Therefore screening of incidentaloma patients for CAH is not indicated (Kjellman et al, 1999; Barzon et al, 2003; Wagnierova et al, 2008).

Adrenal Lesions

Malignant

Adrenal Carcinoma

Overview and Epidemiology. ACC is a rare malignancy with an incidence of 0.5 to 2 per million (Aubert et al, 2002; Roman, 2006; Fassnacht et al, 2013). It has a bimodal age distribution that peaks in children in the first decade of life and adults in the fourth to fifth decades of life, although most patients with ACC are adults, with a slight female predominance of 1.5 to 2.1 (Roman, 2006). Several important differences exist between the pediatric and adult ACC populations, including symptoms at presentation, staging systems used, and prognosis. Compared with the adult population, children with ACC on presentation will more often have lower-stage functional tumors associated with improved survival (Liou and Kay, 2000).

The majority of ACCs are sporadic and unilateral; however, 2% to 6% of patients will have bilateral disease that may be associated with a hereditary disorder (Ng and Libertino, 2003). Although the cause of sporadic ACC remains unknown, several syndromes are associated with an increased incidence of ACC, including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, Lynch syndrome, Carney complex, MEN-1, and McCune-Albright syndrome (Else, 2012; Raymond et al, 2013). Although the underlying molecular defect of these syndromes has advanced our understanding of the tumorigenesis of ACC, significant improvements in treatment regimens and survival are yet to be realized. Currently, surgical resection remains the cornerstone of treatment and, when localized, offers the best chance of cure; however, multimodal therapy including systemic chemotherapy and radiation therapy are often required for locally advanced and metastatic disease. Over the last two decades there has been a lack of stage and size migration in patients diagnosed with ACC, despite “incidental screening” of the adrenal gland that has resulted from rising rates of cross-sectional imaging. Furthermore, ACC survival rates have also failed to improve (Kutikov et al, 2011a).

Pathophysiology. Two hereditary disorders, Li-Fraumeni syndrome and Beckwith-Wiedemann syndrome, have provided valuable insight into the tumorigenesis of sporadic ACC. Loss of TP53 function, as found in Li-Fraumeni syndrome, has been noted in 20% to 33% of sporadic ACC cases compared with 0% to 6% of adrenal cortical adenomas. Increased insulin-like growth factor (IGF) expression, as found in Beckwith-Wiedemann syndrome, has been noted in up to 90% of sporadic cases of ACC, compared with only 8.5% of adrenal cortical adenomas (Herbet et al, 2009). These findings suggest that loss of TP53 function and increased IGF expression represent late events in the tumorigenesis of sporadic ACC. Another common alteration noted in ACC is constitutive activation of the Wnt/ β -catenin pathway, which has been noted in 30% of cases (Lerario et al, 2014). Alterations of multiple other oncogenes and peptides have been associated with the ACC; however, the importance of how these alterations influence carcinogenesis, progression, and response to treatment of ACC remains unknown (Boulle et al, 1998; Kolomecki et al, 2001; Beuschlein et al, 2004; Sarkaria et al, 2004; Lehmann and Wrzesinski, 2012; Papotti et al, 2014).

Clinical Characteristics. Incidental detection of ACC has increased with the routine use of cross-sectional imaging; however, the majority of patients still have advanced disease and tumor-related symptoms on presentation. Figure 65-22 shows a CT image of a large right-sided ACC. Tumor-related symptoms of ACC can be secondary to local or systemic disease burden and/or hypersecretion of adrenal hormones, which has been noted in 50% to 79% of adult and 90% of pediatric ACCs (Roman, 2006). ACCs that are associated with the hypersecretion of adrenal hormones are characterized as being functional. However, the presence of a functional tumor does not always lead to clinical symptoms, as in the case of tumors that secrete high concentrations of steroid precursors. This

TABLE 65-12 Functional Breakdown of Adrenal Cortical Carcinomas

Nonfunctional	21%-50%
Functional	50%-79%
Cushing syndrome	33%-53%
Cushing syndrome plus virilization	20%-24%
Virilization alone	10%-20%
Feminization	6%-10%
Hyperaldosteronism	2.5%-5%

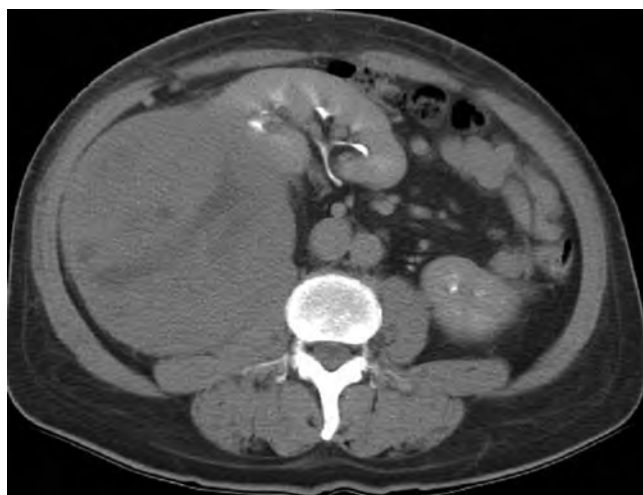


Figure 65-22. Axial cut in excretory phase of a computed tomography scan demonstrating a large right adrenal carcinoma. The right kidney is shifted anteriorly and medially. Similar-sized masses that arise from the kidney itself usually do not displace the renal unit. Important, even at this large size the adrenal carcinoma appears relatively homogeneous and well circumscribed—features deceptively camouflaging its deadly biologic potential. Surgical resection demonstrated a 25-cm, stage II (pT2N0M0), localized adrenocortical carcinoma. (Courtesy Dr. David Y. T. Chen, Fox Chase Cancer Center, Philadelphia.)

is especially relevant given the increasing sensitivity of assays used when evaluating serum hormone levels. Furthermore, it is common to have several hormones secreted by a single tumor, and it has been theorized that a tumor's functional status and hormones secreted may change throughout the tumor's development and growth (Phan, 2007).

The most common hormone secreted by ACC is cortisol, resulting in the clinical manifestations of Cushing syndrome (Table 65-12). Hypercortisolism in ACC is ACTH-independent, and the Cushing-associated virilization has been noted to be more pronounced compared with that resulting from functional adenomas. Recent data suggest that symptomatic hypercortisolemia is an independent prognosticator of survival in patients with resected localized ACC (Berruti et al, 2014). The observed increase in virilization may be the result of increased rates of cosecretion of 17-ketosteroids and DHEA in patients with ACC (Roman, 2006). Androgen-secreting tumors in women can lead to virilization, characterized by male-pattern baldness, hirsutism, and oligomenorrhea, which are typically related to elevated 17-ketosteroids. When virilization is present in the absence of elevated 17-ketosteroids, free testosterone hypersecretion from an adrenal or ovarian source should be considered. Feminization in men, characterized by testicular atrophy and gynecomastia, may result from peripheral conversion of androstenedione to estrogen and is highly suggestive of malignancy when present. Although hypersecretion of aldosterone is

TABLE 65-13 Functional Evaluation of Adrenal Tumors Suspected to Be Adrenocortical Carcinoma

TYPE OF ADRENAL HYPERSECRETION	FUNCTIONAL EVALUATION
Glucocorticoid excess	Low-dose dexamethasone suppression test or Late night salivary or 24-hour urine cortisol
Sexual steroids and steroid precursors	DHEA-S 17-OH-progesterone Androstenedione Testosterone 17 β -estradiol (only in men and postmenopausal women)
Catecholamine excess	Serum or urinary metanephrines
Mineralocorticoid excess	Aldosterone-to-renin ratio (only in patients with hypertension or hypokalemia)

DHEA-S, dehydroepiandrosterone sulfate.

Modified from Fassnacht M, Kenn W, Allolio B. Adrenal tumors: how to establish malignancy? *J Endocrinol Invest* 2004;27(4):387–99.

rarely associated with ACC, when present it is associated with profound hypertension and hypokalemia. Moreover, the symptoms of hypertension and hypokalemia are more likely secondary to other adrenal steroids produced by ACC, rather than the hypersecretion of aldosterone. Although considered functional, ACCs can result in high levels of steroid precursors, such as androstenedione and 17 α -hydroxyprogesterone, which may not cause any overt clinical symptoms (Fassnacht and Allolio, 2009). Nonfunctional ACCs may cause more generalized tumor-related symptoms, such as abdominal fullness, back pain, nausea, vomiting, or other constitutional symptoms.

Diagnostic Tests. Suspicion for ACCs is based on clinical symptoms or radiographic findings and warrants the complete extent of disease evaluation, given the implications of this malignancy. Evaluating the functional status of adrenal tumors suspicious for ACC is essential, not only for making the diagnosis of ACC but also for consideration of postoperative cortisol replacement and the potential use of tumor-secreted hormones as markers during postoperative surveillance. When considering the functional status of a tumor that raises suspicion for ACC, glucocorticoid, mineralocorticoid, catecholamine, sexual steroid, and steroid precursor excesses should be evaluated as outlined in Table 65-13.

The radiographic characteristics of an adrenal tumor provide valuable information regarding the lesion's malignant potential and may be obtained using several modalities including CT, MRI, and ¹⁸F-FDG PET imaging. On cross-sectional imaging, ACCs tend to be larger than benign adrenal tumors, with an average size of 10 to 12 cm on presentation. Indeed over 90% of ACCs are larger than 5 cm (Ng and Libertino, 2003; Fassnacht and Allolio, 2009). In incidentally detected adrenal tumors, size is a relative indicator of malignancy, with 4% to 5% of tumors smaller than 4 cm, 10% of tumors larger than 4 cm, and 25% of tumors larger than 6 cm found to be adrenal carcinomas (Sturgeon and Kebebew, 2004; Walz et al, 2005). Given the relationship between adrenal tumor size and malignancy, it is currently recommended that adrenal tumors larger than 4 to 6 cm be surgically excised (Scheingart et al, 2005). Although a complete metastatic evaluation should be completed for all adrenal tumors that raise suspicion for ACC, the presence of lymphadenopathy and local tumor extension into the

IVC and other adjacent organs are ominous indicators of locally advanced or distant metastatic disease. The most common sites of metastases in adrenal carcinoma are the lung and liver. Therefore metastatic evaluation at presentation should include cross-sectional imaging of the chest, abdomen, and pelvis. Evaluation for bone and central nervous system metastases need be performed only in patients with site-specific symptoms. **Common radiographic characteristics of adrenal carcinomas on CT imaging include the presence of irregular borders, irregular enhancement, calcifications, and necrotic areas with cystic degeneration. Mean attenuation on noncontrast CT scan in ACC is significantly higher (39 HU) compared with adenomas (8 HU). Classically, ACC does not exhibit brisk iodinated contrast washout characteristic of adenomas; however, these conclusions are based on limited data, and exceptions have been reported (Szolar et al, 2005; Roman, 2006; Simhan et al, 2012a) (see imaging section).**

MRI provides valuable information for evaluating adrenal tumors. ACCs appear isointense relative to the liver or spleen on T1-weighted images and demonstrate intermediate to increased intensity on T2-weighted images. On gadolinium-enhanced images, adrenal carcinomas demonstrate marked contrast uptake (Ilias et al, 2007). In cases of suspicion for venous tumor thrombus, MRI can be an essential tool in detecting the presence of a tumor clot and delineating its extent.

Available data suggest that ACC tends to be ^{18}F -FDG PET avid (Tenenbaum et al, 2004; Boland et al, 2011). However, given the established value of cross-sectional imaging in distinguishing benign from malignant disease, routine use of ^{18}F -FDG PET must be clinically calibrated.

In diagnosing ACCs, percutaneous needle biopsy is usually not performed before surgical excision owing to a clinically unacceptable risk of needle-tract seeding (Fassnacht et al, 2004; Schteingart et al, 2005). In cases of surgically resectable disease, the information obtained from biochemical and radiographic evaluation should be enough to justify extirpation. The primary indication for needle biopsy is in cases of unresectable, locally advanced, or metastatic disease, to confirm the diagnosis before systemic medical therapy.

Pathologic Evaluation. During the histologic evaluation of an adrenal tumor, tumor origin and malignancy are the two most important considerations. In cases in which tumor origin is questioned, SF1 expression can be evaluated, with positive staining suggesting adrenocortical origin (Fassnacht et al, 2013). Although the presence of distant metastasis and local invasion are clear indications of malignancy, the differentiation between benign and malignant neoplasms in organ-confined tumors can be pathologically challenging (Fig. 65-23). The Weiss criteria, developed in 1984, were established to distinguish benign from malignant adrenal tumors using nine pathologic features (Weiss, 1984). The classification system is based on tumor structure, cytology, and invasion (Box 65-4). The presence of three or more of the Weiss criteria is associated with malignancy, with a sensitivity of 100% and a specificity of 96% (Aubert et al, 2002). In cases of pediatric adrenal tumors, and in adult adrenal tumors that demonstrate oncocytic features, the Weiss criteria should be used with caution, and alternative diagnostic criteria are recommended (Lau and Weiss, 2009).

Staging. The American Joint Committee on Cancer (AJCC) staging of ACC is based on size of the primary tumor, degree of local invasion, and spread to regional lymph nodes or distant sites (Table 65-14). Stage I and II tumors are confined to the adrenal gland and are distinguished by a size cutoff of 5 cm. Stage III disease includes tumor extension into adjacent adipose tissue or the presence of regional lymph node involvement. Stage IV disease includes tumors invading adjacent organs and the presence of distant metastatic disease. The European Network for the Study of Adrenal Tumors (ENSAT) staging system of ACC is similar to the AJCC staging system; however, it differs in the grouping of patients with advanced disease. The ENSAT staging system maintains the tumor-node-metastasis (TNM) classifications used in the AJCC staging system (version 6); however, stage III disease includes patients with positive lymph nodes (N1), infiltration of surrounding tissues (T3 and T4),

and venous tumor thrombus, whereas stage IV disease is reserved for any tumor associated with distant metastatic disease (Fassnacht et al, 2009).

Management. Unfortunately, the majority of patients with ACCs have advanced disease on presentation (see Table 65-14), and those who do have localized disease are at a high risk of local recurrence and metastatic progression. For this reason, treatment of ACC often includes multimodal therapy directed by a team of surgeons, medical oncologists, endocrinologists, and radiation oncologists. Despite aggressive surgical resection, adrenal carcinoma is associated with a high rate (60% to 80%) of recurrent disease (Pommier and Brennan, 1992; Stojadinovic et al, 2002; Meyer et al, 2004). Thus, local and systemic adjuvant therapy is often administered, in spite of the lack of clear evidence demonstrating improved survival. Furthermore, given the low incidence of ACC, only one randomized trial has been completed evaluating the efficacy of current treatment regimens in patients with metastatic disease; thus the remaining treatment strategies are based on the collective experience of nonrandomized retrospective series.

Surgery. Complete surgical excision is essential in the management of ACC and offers the best chance of cure, control of symptoms secondary to hypersecretion of adrenal hormones, and other tumor-related symptoms in patients with localized disease. En bloc resection of surrounding organs involved with locally advanced disease should be performed whenever possible. Regional retroperitoneal lymph node dissection can provide additional disease control and staging information. Cases of venous tumor thrombus involving the IVC may require vascular bypass techniques, IVC replacement, and/or IVC interruption. Given the extent of resection frequently

BOX 65-4 Weiss Pathologic Criteria for Differentiating Benign and Malignant Adrenal Tumors

- High nuclear grade (Furman grade 3 to 4)
- High mitotic rate (greater than 5 mitoses per high-power field)
- Presence of atypical mitoses
- Character of cytoplasm (low percentage of clear cells)
- Diffuse architecture of tumor cells
- Presence of necrosis
- Invasion of venous structures
- Invasion of sinusoidal structures
- Invasion of tumor capsule

From Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 1984;8(3): 163-9.

TABLE 65-14 Staging of Adrenocortical Carcinoma Including Stage at Diagnosis and 5-Year Survival Data

STAGE	2004 UICC/WHO	AT DIAGNOSIS	5-YEAR SURVIVAL
I	T1N0M0	3%-4%	33%-66%
II	T2N0M0	29%-46%	20%-58%
III	T1-2N1M0 T3N0M0	11%-19%	18%-24%
IV	T1-4N0-1M1 T3N1M0 T4N0-1M0	39%-49%	<5%

T1, <5 cm; T2, >5 cm; T3, infiltration of surrounding adipose tissue; T4, invasion into adjacent organs.

UICC, Union Internationale Contre Le Cancer; WHO, World Health Organization.

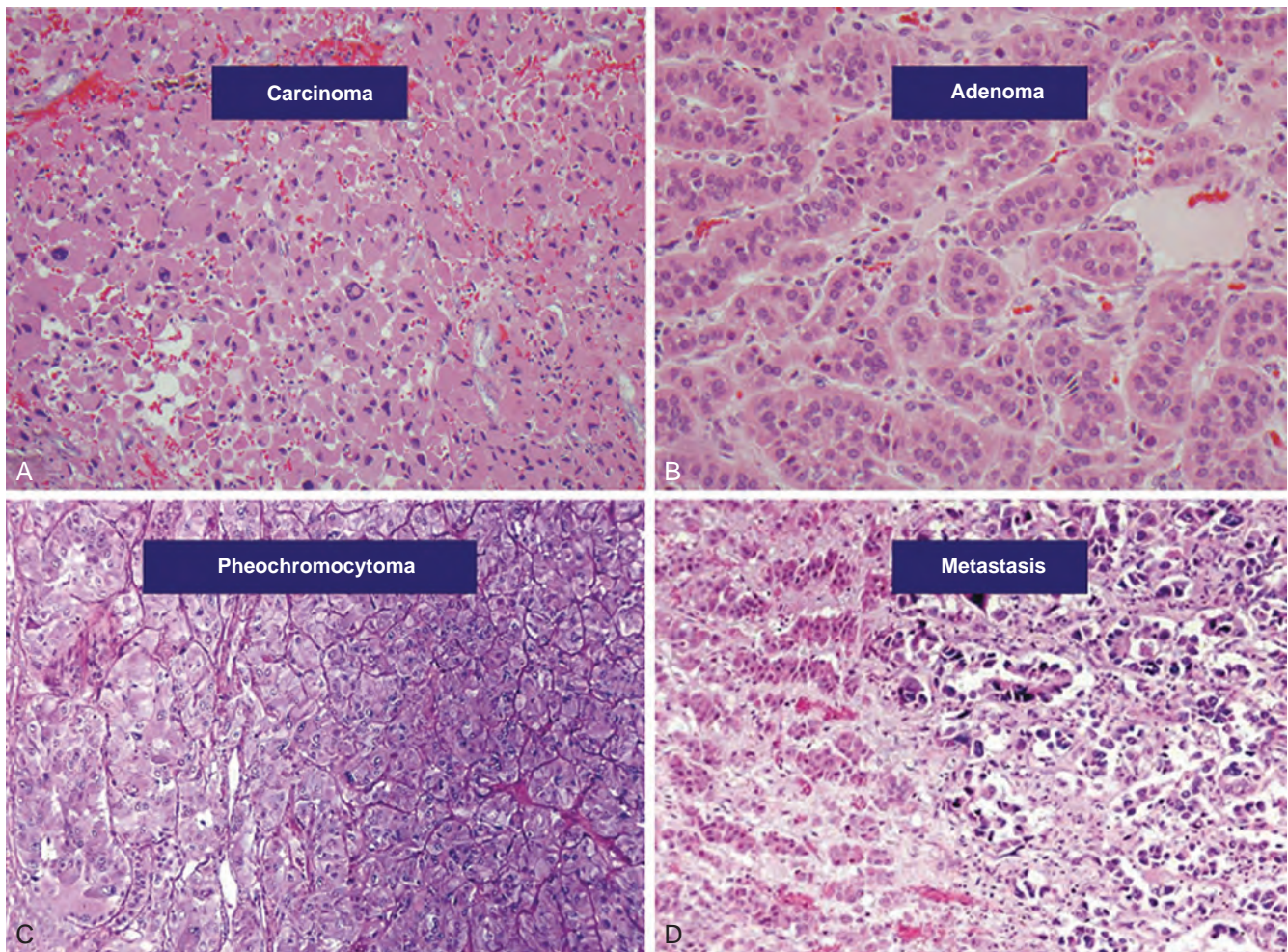


Figure 65-23. Histologic appearance of adrenal tumors (hematoxylin and eosin staining). **A**, Adrenocortical carcinoma: high-grade nuclear atypia with necrosis in other sections. **B**, Adrenocortical adenoma: well-organized trabecular pattern with relatively uniform cells and minimal atypia. **C**, Pheochromocytoma: alveolar and trabecular pattern, eosinophilic, and amphophilic finely granular cytoplasm. **D**, Metastatic adenocarcinoma: hyperchromatic pleomorphic cells (right) compared with the eosinophilic cells with organized trabecular pattern (left) of the residual adrenal gland. (Courtesy Tahseen Al-Saleem, MD, Department of Pathology, Fox Chase Cancer Center, Philadelphia, PA, and Dr. Thomas J. Sebo, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.)

required, open abdominal or retroperitoneal exploration is commonly performed. Smaller radiographically organ-confined disease can be approached laparoscopically, but the procedure should be performed with caution owing to the risk of tumor spillage (Kebebew et al, 2002; Gonzalez et al, 2005; Schlamp et al, 2007). In cases of metastatic adrenal carcinoma, cytoreductive removal of the primary tumor and debulking metastasectomy should be considered if more than 90% of the disease burden can be removed (Schteingart et al, 2005). Although debulking surgery may not improve survival, it may alleviate tumor-related side effects and facilitate additional therapies (Fassnacht et al, 2004). Local or distant disease recurrences after initial resection should be considered for surgical excision and have been associated with improved survival in retrospective series (Meyer et al, 2004; Dattice et al, 2012; Fassnacht et al, 2013). Locally recurrent disease and select metastatic lesions may be treated with ablative therapy using radiofrequency ablation or angioembolization, if surgical excision cannot be performed (Wood et al, 2003; Schteingart et al, 2005; Soga et al, 2009).

Follow-up should include CT examination of the chest, abdomen, and pelvis every 3 months for the first 2 years. The value of routine

PET imaging in disease surveillance has not been established. In patients with evidence of functional tumors, measurement of the initially elevated hormones postoperatively may help to reveal early disease recurrence despite negative radiographic studies. After a disease-free interval of 2 years, surveillance should continue, but the frequency of imaging may decrease (Schteingart et al, 2005; Fassnacht et al, 2013).

Radiation. Currently there is a limited role for radiation therapy in the treatment of primary ACCs; however, radiation therapy remains the treatment of choice in the management of bone and CNS metastasis (Schteingart et al, 2005). Adjuvant radiation has been noted to decrease local recurrence rates after complete tumor resection, with reported local recurrence rates of 14% and 79%, with and without adjuvant radiation therapy, respectively (Fassnacht et al, 2004; Polat et al, 2009). Unfortunately, a significant improvement in disease-free or overall survival was not observed. Patients believed to benefit the most from adjuvant radiation therapy are those without evidence of metastatic disease and positive or indeterminate surgical margins.

Medical Therapy. Mitotane is an oral synthetic derivative of the insecticide dichlorodiphenyltrichloroethane (DDT) and is the most

commonly used chemotherapeutic agent in the treatment of ACC. The agent has demonstrated clinical benefit in the adjuvant setting after surgical resection and in patients with metastatic disease (Phan, 2007). Three mechanisms of action of mitotane against ACC have been proposed: direct cytotoxicity of cells in the adrenal cortex, oxidative damage through the production of free radicals, and/or inhibition of enzymes involved with steroid synthesis (Fassnacht and Allolio, 2009). Owing to the adrenolytic effect of mitotane, steroid replacement is typically necessary during therapy. In addition to adrenal insufficiency, common side effects include gastrointestinal upset, lethargy, depression, feminization in males, rash, elevation of hepatic enzymes, elevation of hormone-binding globulins, hypothyroidism, dyslipidemia, and thrombocytopenia. Given its significant adverse effect profile and its marginal therapeutic benefit, administration must be closely monitored and dosage titrated according to patient tolerability and serum levels (Fassnacht and Allolio, 2009).

The efficacy of adjuvant mitotane following surgical resection has been evaluated by several small retrospective series with varying results. A more contemporary retrospective series by Terzolo and colleagues (2007) evaluated the impact of adjuvant mitotane on recurrence-free survival and overall survival in 177 patients with ACC. A significant increase in recurrence-free survival and overall survival was noted in patients receiving mitotane compared with controls, after multivariate adjustments. In addition, treatment-related toxicity appeared acceptably low. Currently, significant questions remain regarding the routine use of adjuvant mitotane after surgical resection, including which patients will derive the greatest benefit from adjuvant therapy, and the optimal dosage and duration of adjuvant mitotane therapy (Terzolo et al, 2007, 2009; Else et al, 2014).

In patients who are not candidates for complete tumor debulking, surgery should not be performed because it will delay systemic therapy. Currently, mitotane remains the primary systemic therapy, either as a single agent or in combination with other cytotoxic drugs for ACCs. As a single agent, overall responses to mitotane range from 14% to 36%, with few studies demonstrating a significant survival benefit (Roman, 2006; Phan, 2007). A series by Khan and colleagues (2000), investigating the combination of mitotane and streptozotocin, noted a response rate of 36%. In a report by Berruti and colleagues (2005), a response rate of 49% was noted with the combination of mitotane, etoposide, doxorubicin, and cisplatin. The First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) randomized patients to receive mitotane in combination with streptozotocin or etoposide, doxorubicin, and cisplatin (M-EDP) (Fassnacht et al, 2012). Overall survival was similar between groups; however, patients receiving M-EDP were noted to have improved objective response rates and progression-free survival. Based on the results of this trial, M-EDP is now being considered the first-line regimen of choice in patients requiring systemic therapy. With the known limited success of first-line therapy for advanced disease, salvage therapy is often required. Multiple ongoing trials are investigating targeted therapies and other agents in patients in whom the disease progresses after first-line systemic therapy (Roman, 2006; Lebastchi et al, 2012; Fassnacht et al, 2013).

Control of symptoms secondary to the hypersecretion of hormones is often necessary in patients with metastatic disease. Although mitotane has adrenolytic activity, given its delayed onset of action and associated toxicity, other agents are often necessary to help control symptoms of hormone hypersecretion. Adrenostatic drugs such as ketoconazole, metyrapone, aminoglutethimide, and etomidate have been used to decrease circulating levels of cortisol in symptomatic patients (Fassnacht et al, 2004).

Prognosis. Overall 5-year survival in ACCs is poor, ranging from 20% to 47% (Roman, 2006; Fassnacht and Allolio, 2009). The observed poor prognosis associated with ACC reflects the advanced stage frequently noted at presentation, the high rate of recurrent disease in patients with localized disease, and the limited efficacy of current systemic treatment regimens. Administrative datasets reveal that tumor size at resection in patients with localized disease

fails to show a strong relationship with overall survival (Canter et al, 2013). Five-year survival based on tumor stage is presented in Table 65-14. In addition to advanced stage, several clinicopathologic features have been associated with decreased survival, including tumor size greater than 12 cm, age, high mitotic rate, tumor necrosis, atypical mitotic figures, and high Ki-67 staining (Fassnacht and Allolio, 2009; Ayala-Ramirez et al, 2013). The impact of a tumor's functional status on outcome has been widely debated and remains controversial (Luton et al, 1990; Favia et al, 2001; Chen et al, 2004; Vaughan, 2004).

Pediatric Adrenocortical Carcinoma. The presentation, staging, and prognosis of pediatric ACC differ from those in adults (Liou and Kay, 2000). More than 90% of ACCs in children are functional at the time of presentation, with virilization being the most common clinical manifestation, occurring in 55% to 70% of patients. Unlike in adults, the female-to-male ratio is equal in children younger than age 12; it sharply increases to 6:1 in children aged 13 to 20. Genetic syndromes should be considered in pediatric cases of adrenal carcinoma, particularly Li-Fraumeni syndrome, because a high rate of TP53 mutations has been noted in prior series. The staging system in pediatric patients defines stage I and II tumors as being completely excised with negative margins and with a tumor weight of greater than 200 g differentiating stage I and II disease. Stage III disease is defined by the presence of microscopic or macroscopic residual disease after surgical resection or inoperable tumors; stage IV disease is defined by the presence of hematogenous metastasis. The overall 5-year survival rate is 54.2%, with several clinicopathologic features associated with diminished survival, including tumors weighing more than 400 g, tumor size greater than 10.5 cm, necrosis, frequent and atypical mitotic bodies, and presentation after 5 years of age (Michalkiewicz et al, 2004; McAteer et al, 2013).

Summary. ACC is a rare malignancy requiring multispecialty care. Given the aggressive natural history of the disease, ACC must be considered in the differential diagnosis in all patients with an adrenal tumor, particularly if larger than 6 cm. Evaluation of tumor functional status is critical for preoperative planning and supportive care, even in asymptomatic patients. Complete surgical resection of the primary tumor and any associated metastatic lesions should be performed whenever possible. Adjuvant therapy or enrollment into a clinical trial should be considered in most patients, given the high rate of local recurrence and metastatic progression despite complete surgical resection. Systemic therapy with mitotane therapy alone, or in combination with other cytotoxic agents, is recommended as first-line therapy in patients with metastatic ACC. Unfortunately, the prognosis for patients with ACC is poor, and improved therapeutic regimens are needed to improve outcomes.

KEY POINTS: ADRENAL CORTICAL CARCINOMA

- Increasing adrenal tumor size is significantly associated with an increased risk of malignancy.
- The majority of ACCs will be functional at the time of presentation.
- Multimodal treatment, surgical resection, radiation therapy, and systemic chemotherapy are often necessary for patients with ACC.

Neuroblastoma. Neuroblastoma, a malignancy derived from the cells of the neural crest, which give rise to the adrenal medulla and sympathetic ganglia, is the most common solid extracranial tumor of childhood. Chapter 155 is dedicated to the clinical and pathologic features of this entity (Park et al, 2008).

Metastases

Overview and Epidemiology. The adrenal glands are a common site of metastases. Large autopsy series have demonstrated that over 25% of patients with melanoma and lung carcinoma have metastases to their adrenals (Bullock and Hirst, 1953). RCC, breast cancer, medullary thyroid carcinoma, contralateral ACC, gastrointestinal

malignancies, prostate adenocarcinoma, cervical cancer, basal cell carcinoma, pancreatic tumors, cholangiocarcinoma, urothelial carcinoma, squamous cell carcinoma, seminoma, thymoma, chronic myelogenous leukemia, and other malignancies can all exhibit metastatic deposits within the adrenals (Bullock and Hirst, 1953; Lenert et al, 2001). Indeed, diagnostic challenges arise when an adrenal incidentaloma is discovered in patients with a known malignancy. It has been estimated that in patients with a history of a previous malignancy, over 50% of newly discovered adrenal lesions are metastatic (Lenert et al, 2001; Frilling et al, 2004). Current imaging modalities supplemented by adrenal biopsy, when necessary, can frequently differentiate metastases from a primary adrenal tumor.

RCC can involve the adrenal by direct invasion or systemic metastases (Lau et al, 2003; Antonelli et al, 2006). O'Malley and colleagues (2009) provide a recent review of these data as they relate to the need for adrenalectomy during surgery for RCC. Management of solitary metastases to the adrenal from other malignancies often falls within the purview of the practicing urologist. Indeed, for some malignancies, specifically melanoma and non-small cell lung carcinoma, a survival benefit has been suggested in patients who undergo resection of an isolated adrenal metastasis (Mercier et al, 2005; Collinson et al, 2008; Mittendorf et al, 2008; Tanvetyanov et al, 2008).

Pathophysiology and Clinical Characteristics. Remarkably few patients with metastatic disease to the adrenal gland exhibit evidence of adrenal insufficiency. Indeed, although an Addisonian state secondary to metastatic carcinoma was described by Addison in his original series, the scenario is exceedingly rare (Addison, 1855; Lutz et al, 2000). Some reports suggest that bulky (>4 cm) bilateral disease is necessary to produce biochemical evidence of adrenal insufficiency (Lutz et al, 2000). The statement that adrenal insufficiency exists in 20% of patients with metastatic RCC is, at times, quoted in the urologic literature. This supposition is based on an isolated report from the 1980s (involving a cohort of 15 patients) that, to our knowledge, has been published only in abstract form (Schorr et al, 1986). Indeed, patients with advanced malignancy may exhibit symptoms of an Addisonian state (i.e., nausea, vomiting, fatigue, weight loss, and so on) in the absence of biochemical evidence of adrenal insufficiency (Lutz et al, 2000).

Diagnostic Tests. Radiographically metastatic lesions, similar to benign adenomas, appear well circumscribed and homogeneous and most often lack areas of macroscopic necrosis (Boland et al, 2008). Nevertheless, metastatic disease often can be differentiated from the typical adrenal adenoma based on its lack of substantial lipid content. As is discussed in the imaging section of this chapter, metastatic lesions exhibit greater than 10 HU in attenuation on noncontrast imaging and fail to demonstrate significant contrast loss on adrenal washout studies (Fig. 65-24) (Boland et al, 2008). Recent literature, however, suggests that without characteristics of RCC and hepatocellular carcinoma metastases can mimic those of lipid-poor adenomas. Accordingly, when metastases from these primary tumor sites are suspected, adrenal nodule growth kinetics become critical in formulating clinical decision (Choi et al, 2013). Furthermore, adrenal biopsy can be helpful with newly found adrenal lesions in the setting of a known history of malignancy when imaging is equivocal. Unlike with metastases to the kidney, which are frequently associated with widespread metastatic disease, metastases to the adrenals can occur early and may be the sole focus of radiographically identifiable disease, making therapeutic resection feasible. (See the section on adrenal biopsy for more details.)

Nonetheless, a standard metabolic workup is warranted to rule out functionality of any new adrenal lesion (Lenert et al, 2001). Indeed, some small series report no difference in the incidence of metabolically active tumors, when patients with and without a history of extra-adrenal malignancy are compared (Tsvetov et al, 2007). It is important to note that reports of pigmented pheochromocytomas being mislabeled as metastatic melanoma exist in the literature (Lenert et al, 2001).

Treatment and Prognosis. Resection of metastases to the contralateral or ipsilateral adrenal gland from RCC is advocated in the

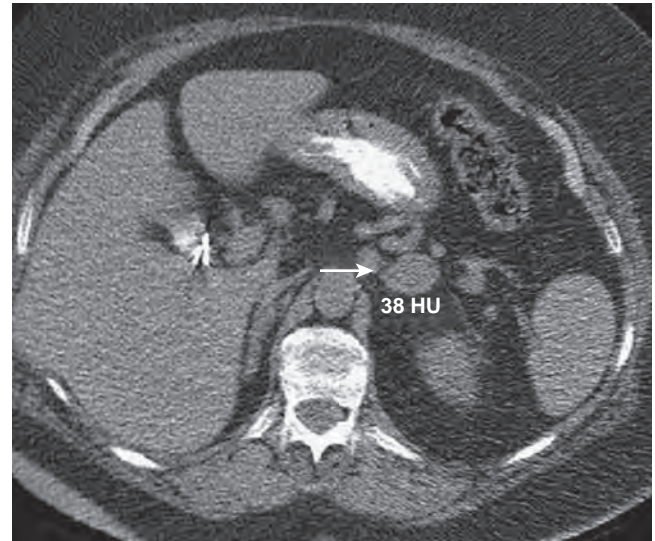


Figure 65-24. Unenhanced computed tomography scan of a patient with a left adrenal metastasis from right-sided renal cell carcinoma (RCC) that had been resected several years earlier. At presentation, unenhanced imaging revealed a lesion with an attenuation of greater than 10 Hounsfield units (HU), indicating that the adrenal mass was not a lipid-rich adenoma. Recent data reveal that RCC metastases may exhibit washout characteristics similar to lipid-poor adenomas. Metabolic evaluation ruled out pheochromocytoma. Laparoscopic adrenalectomy confirmed metastatic RCC.

context of a cytoreductive approach for a select group of patients. Nevertheless, benefits to adrenal metastasectomy are as yet unproven in a prospective fashion. Moreover, the role of resection may change with antiangiogenic targeted therapies (Lau et al, 2003; Antonelli et al, 2006; O'Malley et al, 2009). Treatment of metastatic disease of the adrenals in patients with nonurologic malignancies requires a multidisciplinary approach. The urologist must work closely with the patient's primary medical oncologist regarding the surgical and biologic prudence of resection. Lenert and colleagues (2001) have reported their experience with adrenalectomy for solitary adrenal metastases from over 20 separate primary malignancies. Currently, the best data regarding adrenal metastasectomy exist for patients with non-small cell lung carcinoma and melanoma (Branum et al, 1991; Mittendorf et al, 2008).

In patients with non-small cell lung cancer, adrenal metastases are most frequently encountered in the setting of systemic disease. An isolated adrenal metastasis is rare and may be the result of nonhematogenous lymphatic spread (Tanvetyanov et al, 2008). Surgical resection of solitary adrenal metastases has been associated with 5-year overall survival rates of over 25% (Mercier et al, 2005; Strong et al, 2007; Tanvetyanov et al, 2008). Although the prognosis after resection in patients with metachronous metastasis and longer disease-free intervals is thought to be better than in patients found to have an isolated adrenal metastasis at the time of their initial diagnosis, a meta-analysis from 2008 demonstrated that the 5-year overall survival is equivalent in both groups (Tanvetyanov et al, 2008). In patients with metastatic melanoma, adrenalectomy has been reported to be associated with long-term survival and even rare regression of distant disease (Branum et al, 1991; Collinson et al, 2008). Nevertheless, data are limited to retrospective reports describing highly selected patient populations (Mittendorf et al, 2008).

Summary. Metastatic disease to the adrenal is common and must be suspected when patients with a history of malignancy are found to have adrenal incidentaloma. Radiographic and functional studies are essential and often secure the diagnosis. Percutaneous biopsy is safe, but its success depends on the size and location of the lesion and the technical aspects of the procedure. Adrenalectomy for

patients with solitary adrenal metastasis is a viable option for a select group of individuals.

KEY POINTS: ADRENAL METASTASES

- Metastatic disease to the adrenals is common, yet it appears that bilateral and bulky disease (>4 cm) is necessary to produce biochemical evidence of adrenal insufficiency.
- More than 50% of newly discovered adrenal lesions in patients with a history of previous malignancy represent metastatic disease; nevertheless, metabolic workup in these patients is recommended.

Malignant Pheochromocytoma. Malignant pheochromocytomas are discussed in the section on pheochromocytoma under Disorders of Increased Adrenal Function.

Benign

Adenoma

Overview and Epidemiology. Adenomas are the most common neoplasms arising from the adrenal gland and are most often associated with the cortex. These lesions are found in approximately 6% of patients at autopsy (Kloos et al, 1995). Clinically, adrenal adenomas are most often incidentally discovered on cross-sectional imaging obtained for other indications and are thus termed *incidentalomas*. More than 85% of adrenal neoplasms incidentally discovered on imaging are ultimately clinically proven to be adenomas (Young, 2000, 2007b). The incidence of adenomas rises with age, as inferred from the observation that incidentalomas are found in less than 0.5% of individuals in their 20s and in up to 7% of those aged 70 years or older (Young, 2000). Similar trends are observed in historical autopsy series (Commons and Callaway, 1948; Russell et al, 1972). Despite benign behavior, a small percentage of adrenal adenomas can exhibit metabolic activity and therefore can represent “surgical” lesions. The essential evaluation of the small adrenal mass requires differentiating the nonfunctional benign adenoma from functional or malignant lesions.

Pathophysiology and Clinical Characteristics. Adenomas possess a yellowish color on gross pathologic examination owing to the presence of abundant lipid. Histologically, they may be difficult to distinguish from adrenal adenocarcinomas. As discussed earlier (see Box 65-4), pathologists use a set of criteria proposed by Weiss along with modern immunohistochemical methods to differentiate the two clinical entities (Weiss, 1984; Aubert et al, 2002; Sasano et al, 2006).

Adrenal adenomas are by definition benign, and the vast majority is metabolically silent. An analysis of the 13 largest series of incidental adrenal masses (N = 2005) reveals that nearly 90% (n = 1779) of these lesions were clinically benign adenomas. Of these, only 127 lesions (7.1% of adenomas) exhibited metabolic activity, 107 (6% of adenomas) hypersecreted glucocorticoids, and 20 (1.1% of adenomas) were functioning hyperaldosteronomas. The overwhelming majority (93%) of adenomas displayed no evidence of metabolic activity (Young, 2000, 2007b). Hypersecretion of sex steroids by benign adrenal adenomas is exceedingly rare but has been reported. It is interesting to note that these rare lesions may secrete testosterone and possess Reinke crystals, normally identified in testosterone-producing Leydig cells of the testes (Ryan et al, 1995). The implications of glucocorticoid and mineralocorticoid hypersecretion by adrenal adenomas are discussed in detail in the sections on Cushing syndrome and primary aldosteronism, respectively. Finally, it has been hypothesized that nonfunctional adrenal adenomas may be associated with physiologic derangements, such as insulin resistance and left ventricular dysfunction; however, such reports are isolated to small single-institution series and await confirmation (Midorikawa et al, 2001; Ermetici et al, 2008).

The growth kinetics of adrenal adenomas is reviewed later (see discussion on incidentalomas). In brief, an analysis of 18 reported series following over 850 patients with adrenal incidentalomas revealed that the vast majority of these benign masses remained stable in size; however, approximately 9% of lesions increased by more than 1 cm in diameter over a mean follow-up of 3 years (Barzon et al, 2003). The size and growth of adrenal lesions are discussed in detail in a later section of this chapter.

The current literature suggests that adenomas that are initially metabolically inert are unlikely to gain function. An analysis of 18 published series reporting more than 1100 incidental adrenal masses (not all of them adenomas) revealed that only 1.7% became metabolically active in follow-up, including 0.65% that developed subclinical Cushing syndrome, 0.3% with subsequent overt Cushing syndrome, and 0.05% that were identified as becoming functional secretors of catecholamines. No lesion produced new-onset hyperaldosteronism during endocrinologic reevaluation (Barzon et al, 2003).

Diagnostic Tests. The evaluation of incidental adrenal lesions, the primary way that adenomas come to clinical attention, is discussed in detail elsewhere in this chapter. In this section, we review the salient points of the clinical workup as it relates to adenomas. The goal in evaluating any adrenal lesion is twofold: (1) rule out the possibility of malignancy and (2) document metabolic inactivity of the lesion in question.

Noncontrast CT scan is arguably the most valuable imaging study for the diagnosis of an adrenal adenoma. CT affords accurate measurements of a lesion’s density, uniformity, and size. The vast majority of adrenal adenomas are smooth-bordered, homogeneous tumors that are less than 4 cm in diameter (Grumbach et al, 2003). High intracytoplasmic lipid content is unique to adenomas, and this attribute affords accurate differentiation of adenomas from other adrenal lesions on cross-sectional imaging. According to an NIH 2002 consensus panel, an adrenal mass with an attenuation of less than 10 HU on unenhanced CT is “strongly suggest[ive of] a benign adrenal adenoma” (Grumbach et al, 2003). Indeed, a large contemporary series of resected adrenal masses from the Cleveland Clinic demonstrated 100% specificity when the threshold of less than 10 HU was applied to lesions in this cohort (Hamrahian et al, 2005). The 100% specificity for adenoma was retained if only masses equal to 4 cm were considered and the threshold was raised to 20 HU (Hamrahian et al, 2005). Nevertheless, not all adenomas have sufficient intracytoplasmic fat content to result in attenuation below 10 HU on noncontrast CT. Approximately 30% of adrenal adenomas register a density greater than 10 HU on unenhanced CT (Korobkin et al, 1998; Pena et al, 2000; Szolar et al, 2005). However, even in these cases a diagnosis of adenoma is still possible with use of the “washout” technique, whereby loss of attenuation of the lesion is noted on delayed contrast-enhanced CT imaging. Lesions that wash out more than 40% to 60% of gained enhancement can be identified as adenomas with extremely high specificity (Fig. 65-25) (Korobkin et al, 1998; Pena et al, 2000; Szolar et al, 2005; Heinz-Peer et al, 2007). The urologist must be aware, however, that RCC and hepatocellular carcinoma metastases may exhibit washout characteristics similar to lipid-poor adenomas (Choi et al, 2013). MRI also can be used to successfully characterize adrenal adenomas. Chemical shift ratios relating to in- and out-of-phase imaging substitute for CT attenuation values. Although, in general, adenomas do not exhibit significant FDG uptake on PET imaging, exceptions exist. Accordingly, increased standardized uptake values (SUVs) of an adrenal lesion with otherwise benign imaging characteristics must be interpreted in the context of each clinical scenario, especially when pretest probability of malignancy is low (Boland et al, 2011; Canter et al, 2011). Refer to the imaging section for further details on imaging of adrenal adenomas (Outwater et al, 1996; Hussain and Korobkin, 2004; Heinz-Peer et al, 2007).

Classically, incidentalomas are evaluated for excess cortisol and catecholamine secretion. In patients with a history of hypertension, hyperaldosteronemia also should be ruled out (Grumbach et al, 2003). Adenomas themselves have the potential to secrete only cortisol or aldosterone; therefore, strictly speaking, if

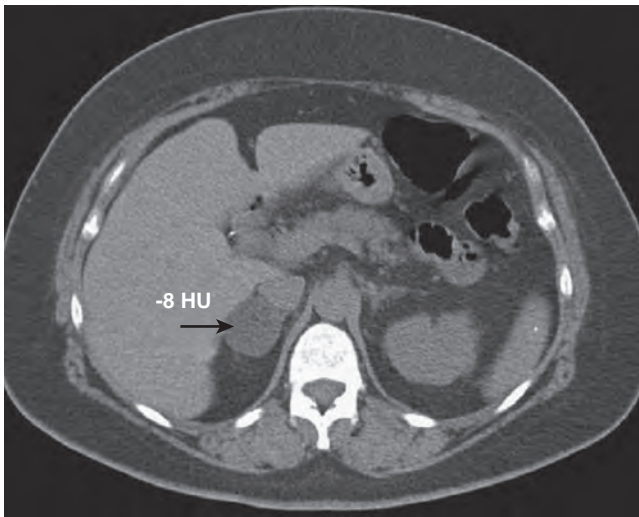


Figure 65-25. Axial cut of an unenhanced computed tomography scan in a patient with a 3.5-cm, right, lipid-rich adrenal adenoma, demonstrating an attenuation of less than 10 Hounsfield units (HU).

a diagnosis of adenoma is unequivocal on imaging, metabolic workup for pheochromocytoma risks false-positive results given the imperfect specificity of testing. Nevertheless, current recommendations suggest serum or urine metanephrine testing for all adrenal lesions (Grumbach et al, 2003; Young, 2007b). Indeed, pheochromocytomas that mimic adenomas on imaging have been reported, validating the recommendation for metanephrine testing of all adrenal lesions (Blake et al, 2003). Despite the 2002 NIH consensus statement that all adrenal lesions larger than 1 cm should undergo a metabolic evaluation, current literature suggests that more than 80% of adrenal masses are not appropriately radiographically or functionally evaluated in routine clinical practice (Eldeiry and Garber, 2008).

Treatment. Adenomas that are metabolically active should undergo resection in acceptable surgical candidates. In patients with nonfunctional adenomas, the size of lesion and its growth characteristics dictate management. Notwithstanding benign imaging features, experts suggest that resection of all adrenal masses larger than 6 cm is prudent, given that adenomas of this size are rare and the risk of malignancy is substantial. The one exception to this may be a definitively diagnosed adrenal myelolipoma (Grumbach et al, 2003). Others argue that a cutoff of 4 cm should be used (Young, 2007b). Lesions that are not resected should undergo at least initial radiographic follow-up to ascertain growth kinetics. Reimaging at 6, 12, and, potentially, 24 months has been recommended to verify benign clinical biology and indolent growth (Grumbach et al, 2003; Young, 2007b). Suspicious and unusual tumors may necessitate imaging at earlier or more frequent intervals or removal (Young, 2007b). As already discussed, although reports in the literature vary, on average approximately 2% of incidentalomas that are initially metabolically silent result in superphysiologic hormone production during follow-up (Barzon et al, 2003). Despite this low rate of “metabolic transformation,” the most recent consensus statement by a panel of NIH-convened experts suggests that annual metabolic hormonal screening for the first 3 to 4 years after diagnosis is prudent, especially for masses that are equal to 3 cm in diameter (Grumbach et al, 2003). Nevertheless, given lack of strong data supporting this recommendation, the need for metabolic reevaluation of adrenal adenomas in patients who show no clinical signs of hormonal hypersecretion remains controversial (Barry et al, 1998; Bulow et al, 2006; Young, 2007b).

Prognosis. Normalization of serum cortisol levels after resection of adenoma likely reduces but does not eradicate heightened cardiovascular risk in patients with Cushing syndrome (Swearingen et al, 1999; Pivonello et al, 2005). For patients with hyperaldosteronism,

serum aldosterone and blood pressure often return to normal within 3 months of adrenalectomy (Young, 2007a), although those with baseline essential hypertension may remain medication-dependent. In general, patients with nonfunctional adrenal adenomas appear to be unaffected by their diagnoses. A large surveillance series from the Mayo Clinic (N = 231) demonstrated that no patients died as a result of a condition that could be ascribed to adrenal pathology after a mean follow-up of 7 years (Barry et al, 1998).

Summary. Adrenal adenomas account for more than 80% of incidental adrenal neoplasms. Because of their abundance of intracellular lipid, these lesions possess characteristic imaging features. More than 90% of these lesions are metabolically silent and require no treatment; however, all should be subjected to an initial metabolic evaluation. Lesions larger than 4 to 6 cm and metabolically active lesions should be resected in patients who are appropriate surgical candidates.

KEY POINTS: ADENOMA

- Incidence of adrenal adenoma rises with age.
- Approximately 7% of adrenal adenomas exhibit metabolic hyperactivity. Those that are metabolically inert at diagnosis only rarely (<2%) gain function on follow-up.
- Radiographic diagnosis of adrenal adenoma pivots on its high lipid content.

Oncocytoma

Overview and Epidemiology. Oncocytomas are familiar to the urologist, given their relatively common renal origin (Chang and Harawi, 1992). Oncocytic tumors can also arise from the salivary gland and the endocrine organs. Adrenal lesions are exceedingly rare (Bisceglia et al, 2004), with approximately 50 cases having been reported in the literature (Juliano et al, 2008).

Pathophysiology and Clinical Characteristics. Like oncocytic tumors in other organs, oncocytic adrenal lesions are characterized histologically by mitochondria-rich, large, eosinophilic cells with abundant granulations (Chang and Harawi, 1992). The pathogenesis of oncocytic neoplasias is poorly understood (Chang and Harawi, 1992). Females have been reported to be affected 2.5 times more frequently than males, and left-sided lesions outnumber those in the right adrenal 3.5 to 1. Tumors can grow up to 20 cm, and at least two cases have been reported in pregnancy (Bisceglia et al, 2004; Juliano et al, 2008). Most lesions that are documented in the literature are metabolically inactive; however, some oncocytic adrenal neoplasms (n = 6, or approximately 10% of all cases reported) hypersecrete sex steroids, cytokines, and/or cortisol (Akatsu et al, 2008; Juliano et al, 2008; Lee et al, 2008). Classically, these lesions have been considered benign (Vaughan and Blumenfeld, 2007); however, over 30% of reported lesions have been classified as malignant, with an additional 23% having been designated as pathologically indeterminate (Juliano et al, 2008). These reports include a lesion that locally invaded the IVC (El-Naggar et al, 1991).

Diagnostic Tests and Treatment. Because the diagnosis of adrenal oncocytic tumor is nearly always made on surgical resection, the evaluation and treatment of oncocytic lesions follow the same strategy as that of other adrenal masses. On imaging, adrenal oncocytic lesions are not reported to regularly possess the central stellate scar that may characterize such cases in the kidney (Lee et al, 2006). The optimal treatment for malignant oncocytic lesions is unknown; however, in at least one report, metastasectomy and radiation treatment for local recurrence may play a role (Juliano et al, 2008).

Prognosis. Given the emerging appreciation for the heterogeneity of the biologic behavior of adrenal oncocytic lesions, the prognosis of patients with these lesions is uncertain but leans toward the more benign. Some reports suggest that even patients with widely metastatic disease can exhibit slow disease progression with long-term survival (Juliano et al, 2008).

Summary. Adrenal oncocytic tumors are extremely rare neoplasms. Despite predominantly benign classical descriptions, a proportion of lesions can exhibit malignant potential.

KEY POINT: ONCOCYTOMA

- Unlike renal oncocytomas, a large proportion of adrenal lesions are malignant.

Myelolipoma

Overview and Epidemiology. Myelolipomas are rare, benign, metabolically silent lesions that arise primarily from the adrenal gland and arise in patients in all age groups (Han et al, 1997). Based on historical autopsy series, the incidence of these lesions is estimated at less than 0.1% percent (Olsson et al, 1973; Bishop et al, 2006). Some reports suggest that 15% of all myelolipomas are extra-adrenal, with up to half of these arising in the presacral area. Thoracic, retroperitoneal, pelvic, renal, hepatic, and gastric lesions have all been reported (Patel et al, 2006).

Pathophysiology. Myelolipomas appear to result from clonal stem cell proliferation and are composed of an unusual mixture of mature adipose tissue and relatively normal trilineage hematopoietic elements (Bishop et al, 2006). Overabundance of megakaryocytes has been reported. Unlike in normal bone marrow, cellularity within myelolipomas varies greatly and does not decrease with increasing patient age. These lesions do not appear to contribute hematopoietic cells to the circulation, which may be a result of irregularities in stromal support and a lack of appropriate microvasculature. Specifically, normal capillary venous sinuses that are critical to functional bone marrow are nearly always absent in myelolipomas (Bishop et al, 2006).

Experimentally, myelolipoma generation has been induced in the adrenals of rats after injection with necrotic tumor tissues and ACTH (Seyle and Stone, 1950). This observation has resulted in the hypothesis that myelolipomas are a result of an adrenal stress response. Additional theories exist, and the cause of these unusual tumors remains unknown (Han et al, 1997; Bishop et al, 2006).

Clinical Characteristics. Men and women are affected with relatively equal frequency. The tumor does not appear to have a predilection for either the right or left adrenal. Bilateral lesions have been reported (Bishoff et al, 1997; Han et al, 1997; Russell et al, 2000). Tumors vary greatly in size and can grow in excess of 10 cm. In a single institutional series of 21 lesions, the average tumor size was

5.1 cm (Han et al, 1997). As with most retroperitoneal tumors, these lesions are usually asymptomatic, although some patients do seek medical attention with abdominal or flank pain (Han et al, 1997). Spontaneous rupture of myelolipomas has been reported; however, this event is rare. Indeed, the mean tumor size of myelolipomas that have ruptured exceeds 10 cm (range 6.3 to 14.7 cm) (Russell et al, 2000).

Classically, myelolipomas are metabolically nonfunctional lesions. Nevertheless, the literature contains over two dozen cases in which myelolipomas are associated with adrenal metabolic hyperactivity. The most common abnormality appears to be hypercortisolemia (Hisamatsu et al, 2004). In the majority of patients, the myelolipoma is not the source of excess hormone production but coexists with a hyperfunctional adrenal adenoma. Indeed, some have suggested that these cases substantiate the early animal model wherein rat adrenal hyperstimulation with pituitary extract resulted in myelolipoma formation (Seyle and Stone, 1950; Hisamatsu et al, 2004).

Diagnostic Tests. In the majority of cases, diagnosis of myelolipoma can be made accurately on cross-sectional imaging. CT reveals a well-circumscribed adrenal lesion with varying amounts of mature adipose tissue (30 HU) interdigitated with higher-density myeloid components, which enhance on contrast administration (Fig. 65-26). Over a quarter of the lesions may exhibit evidence of calcifications, and a large proportion have areas of hemorrhage (Kenney et al, 1998). Macroscopic adipose tissue can also be easily identified within myelolipomas on MRI (Cyran et al, 1996). The presence of macroscopic fat in an adrenal mass is virtually diagnostic of a myelolipoma. Nevertheless, exceedingly rare exceptions exist, and adrenal lipomas, teratomas, angiomyolipomas, metastases, and liposarcomas with macroscopic fat on imaging have been reported (Han et al, 1997; Lam and Lo, 2001). Careful interpretation of cross-sectional imaging is mandatory to distinguish an adrenal myelolipoma from an upper pole renal angiomyelolipoma. In contrast to the benign appearance of a myelolipoma, liposarcomas tend to be aggressive lesions that lack regular borders and have a propensity for infiltrating surrounding tissues (Schaeffer and Kavoussi, 2005). When the diagnosis is in doubt, some experts believe that percutaneous biopsy may be helpful (Han et al, 1997).

As discussed earlier, although myelolipomas are themselves metabolically silent, they have been associated with metabolically active adenomas and pheochromocytomas that may not be readily differentiated on imaging. Therefore it is not unreasonable to perform a standard adrenal metabolic workup in the rare patient who is diagnosed with a myelolipoma (Daneshmand and Quek,

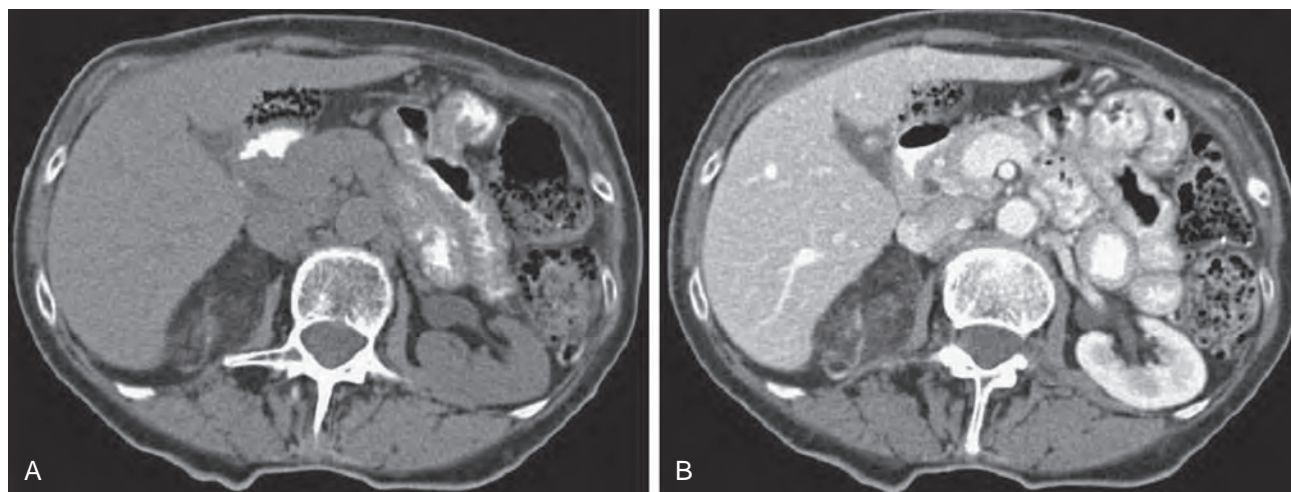


Figure 65-26. Precontrast (A) and postcontrast (B) axial cuts of a computed tomography scan demonstrating a right 6-cm × 3.5-cm adrenal myelolipoma in a 76-year-old, otherwise asymptomatic woman. (Courtesy Dr. Rosalia Viterbo, Fox Chase Cancer Center, Philadelphia.)

2006; Patel et al, 2006). Nevertheless, some experts believe a metabolic workup is necessary only when the index of suspicion for a concomitant metabolically active tumor is high (Han et al, 1997). The NIH consensus panel on adrenal incidentaloma concluded that myelolipoma can be regarded as an exception to the mandatory metabolic workup of a newly discovered adrenal mass (Grumbach et al, 2003).

Treatment. Classically asymptomatic myelolipomas are treated conservatively. No standard protocols for reimaging exist, but serial reevaluation with ultrasonography or CT every several years has been suggested (Han et al, 1997). Surgery is usually reserved for symptomatic lesions (Schaeffer and Kavoussi, 2005).

Prognosis. Tumor growth rates vary. Not only do some lesions remain stable, but some may actually decrease in size over time (Han et al, 1997). Based on available literature, resections are considered definitive. As discussed previously, although spontaneous rupture of myelolipomas has been reported, this event appears to be extremely rare and, on average, has been reported in lesions larger than 10 cm (range 6.3 to 14.7 cm) (Russell et al, 2000).

Summary. Myelolipoma is a rare lesion of the adrenal gland that contains hematopoietic elements and mature adipose tissues. Extra-adrenal lesions have also been reported. In general, lesions do not require resection and follow a benign clinical course.

KEY POINTS: MYELOLIPOMA

- Myelolipomas possess tissue components identical to healthy bone marrow.
- The clinical course is benign, and surgery is indicated only for extremely large or symptomatic lesions.

Ganglioneuroma

Overview and Epidemiology. Ganglioneuromas are extremely rare benign neuroectodermal neoplasms that are composed of ganglion and Schwann cells (Enzinger and Weiss, 1995). Although uncommon, the diagnosis must be considered during the evaluation of an adrenal mass (Mawaja et al, 2007). In one large series (N = 88), 21% of cases arose from the adrenal gland itself. Other sites of origin included the mediastinum (39%) and retroperitoneum (31%), and isolated cases occurred in the pelvis and neck (Enzinger and Weiss, 1995). The tumor appears to have a predilection for the young, with only 20% of cases affecting individuals over age 40, and some 50% of cases found in patients 10 to 29 years of age (Enzinger and Weiss, 1995).

Pathophysiology/Clinical Characteristics. Ganglioneuromas are benign, but isolated cases of ganglioneuromas undergoing malignant transformation have been reported (Enzinger and Weiss, 1995). Furthermore, cases of peripheral nerve sheath tumors (PNST) arising within ganglioneuromas, and composite tumors of ganglioneuroma and pheochromocytoma, also exist in the literature (Radin et al, 1997). It is interesting to note that reports of ganglioneuroma cells in lymph nodes surrounding an apparently benign tumor exist, and some authors presume that such cases represent neuroblastomas that have matured (Enzinger and Weiss, 1995).

Tumors can grow extremely large and have a propensity to encase vessels without impinging on the vessel lumen (Radin et al, 1997). Ganglioneuromas have been reported to secrete vasoactive intestinal polypeptide (VIP), and some patients complain of diarrhea (Enzinger and Weiss, 1995). Nevertheless, the majority of individuals with ganglioneuromas are largely asymptomatic (Radin et al, 1997).

Diagnostic Tests. On both enhanced and unenhanced CT, ganglioneuromas exhibit attenuation less than that of muscle (Radin et al, 1997). Calcifications within the tumor are not uncommon and have been reported to be present in as many as a third of ganglioneuromas (Enzinger and Weiss, 1995; Radin et al, 1997). Some authors have suggested that a metabolically silent adrenal mass with

unenhanced attenuation of less than 40 HU and presence of stippled calcifications should raise suspicion for a ganglioneuroma (Mawaja et al, 2007).

Treatment and Prognosis. Because the diagnosis of ganglioneuroma is nearly always made on resection, natural history of unresected ganglioneuromas has not been clearly defined. Nevertheless, the urologist must be aware that the tumors can grow quite large and can surround critical structures such as retroperitoneal vessels (Radin et al, 1997).

Summary. Ganglioneuromas are rare tumors that can arise from the adrenal gland. Diagnosis is largely pathologic, and the clinical course is nearly always benign.

KEY POINT: GANGLIONEUROMA

- Ganglioneuromas are rare, benign tumors that tend to occur in the young and can grow to encase critical structures.

Adrenal Cysts

Overview and Epidemiology. Adrenal cysts have been noted in 0.064% to 0.18% of patients in autopsy series and account for 1% to 22% of incidentally detected adrenal lesions (Elsayes et al, 2004; Guo et al, 2007; Song et al, 2008; Wedmid and Palese, 2010). Cystic adrenal lesions can be diagnosed throughout life and as early as the prenatal period. Cyst size can range widely from several millimeters to greater than 20 cm, with either unilocular or multilocular components. Although the majority of adrenal cysts are unilateral, bilateral cysts have been noted in 8% to 10% of cases (Rozenblit et al, 1996). An increased incidence of adrenal cysts has been noted in women, with a peak incidence between the third and sixth decades of life (Sanal et al, 2006). Several medical conditions have been associated with adrenal cysts, including polycystic renal disease, Klippel-Trénaunay-Weber syndrome, and Beckwith-Wiedemann syndrome (Erickson et al, 2004).

Pathophysiology. Four histologic types of adrenal cysts have been described: pseudocysts, endothelial cysts, epithelial cysts, and parasitic cysts. Among these, the most common are pseudocysts and endothelial adrenal cysts. Adrenal pseudocysts do not possess a cellular lining and are believed to be the result of previous intra-adrenal hemorrhage or infarction in most cases. Endothelial cysts lack proliferating endothelium and include lymphangiomatous and angiomatous subtypes. Epithelial cysts are lined by a true epithelium and can be further characterized as glandular cysts, embryonal cysts, and cystic adenomas based on pathogenesis. Parasitic adrenal cysts may occur in association with disseminated *Echinococcus* infections; however, it is extremely rare for a parasitic adrenal cyst to be the only site of infection (Otal et al, 1999; Guo et al, 2007; Wedmid and Palese, 2010).

It can be difficult to distinguish a benign adrenal cyst from cystic adrenal neoplasms. This is especially true of adrenal neoplasms with associated hemorrhage or cystic degeneration, which may radiographically resemble an adrenal pseudocyst. In a series of 41 adrenal lesions macroscopically characterized as cysts, 7 were associated with adrenal neoplasms, including 2 ACCs, 2 adenomas, and 3 pheochromocytomas (Erickson et al, 2004). Furthermore, 6 of the 7 adrenal neoplasms in this series were associated with adrenal pseudocysts. A review of multiple series accounting for 515 adrenal cysts noted that 7% of the lesions were associated with malignancy, all of which were pseudocysts (Neri and Nance, 1999). In addition, cases of cystic adrenal carcinoma and pheochromocytomas have been reported (Rozenblit et al, 1996). Compared with benign cysts, cystic adrenal neoplasms tend to be larger (>7 cm) and have thicker walls. In considering the reported incidence of malignancy associated with adrenal cysts, it should be noted that histology in most series is based on surgical specimens, so the incidence of malignancy may be overestimated because small radiographically benign lesions likely remain unresected.

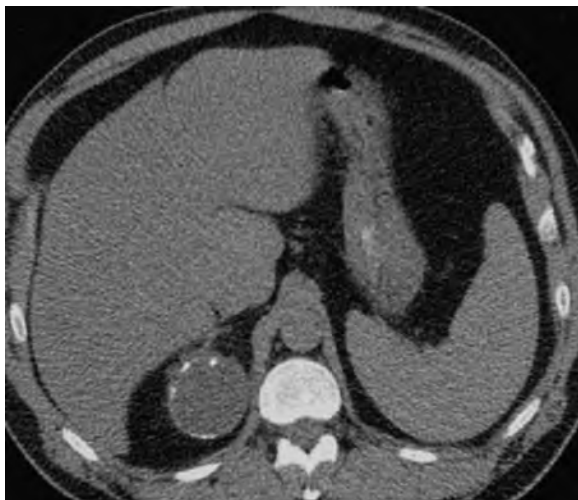


Figure 65-27. Unenhanced computed tomography scan of a right adrenal cyst. Stippled calcifications within the cyst wall are not unusual in these lesions, as can be seen in this particular lesion.

Clinical Characteristics. Although most adrenal cysts are diagnosed incidentally, some become large in size and are symptomatic on presentation. The origin of large adrenal cysts is often difficult to distinguish from other organs, including the kidney, pancreas, spleen, and liver (Otal et al, 1999).

Diagnostic Tests. Although the majority of adrenal cysts are benign and nonfunctional, routine endocrinologic evaluation should be performed to exclude active lesions. Owing to the relative rarity of adrenal cysts, well-defined diagnostic criteria have not been established. The suggested radiographic criteria for diagnosing an adrenal cyst include a well-defined, sharply marginated mass of fluid attenuation without any evidence of enhancement (Fig. 65-27). Cysts with higher fluid attenuation (>30 HU) may be attributed to hemorrhage, intracystic debris, or calcification (Rozenblit et al, 1996; Sanal et al, 2006). The presence of peripheral calcifications has been noted in 15% to 70% of adrenal cysts (Song et al, 2008). Calcifications are typically rimlike, but occasionally will be nodular in appearance (Rozenblit et al, 1996). When evaluated with MRI, simple cysts will appear hypointense on T1-weighted images and hyperintense on T2-weighted images. Unfortunately, radiographic criteria alone cannot rule out malignancy in adrenal cystic lesions; thus cyst aspiration or surgical excision is often performed to rule out malignancy. Aspiration of cystic adrenal lesions should be performed only after chemical evidence of pheochromocytoma has been excluded. Adrenal cyst aspiration may be both diagnostic and potentially therapeutic in select patients (Pradeep et al, 2006). If aspiration is performed, the collected fluid should be sent for Gram stain, cytology, triglycerides, cortisol, and amylase (for left-sided cysts). In addition, a contrast injection of the cyst cavity (cystogram) can be performed at the time of aspiration to evaluate the cyst wall texture.

Treatment. Factors influencing the treatment of adrenal cysts include functional status, chances of incidental malignancy, and cyst-related symptoms. With the known, albeit low, risk of associated malignancy with cystic adrenal lesions, active surveillance must be done with caution. Small, asymptomatic thin-walled lesions containing homogeneous near-water attenuation may be safely observed, and future surveillance of cystic lesions is warranted (Rozenblit et al, 1996). Adrenal cysts that are heterogeneous, larger than 5 cm, thick walled, or symptomatic warrant further evaluation and surgical excision (Wedmid and Palese, 2010). Because of the known risk of associated malignancy, simple decortication is not advocated and should be undertaken with caution. Owing to the inadequacies of radiographic evaluation, surgical resection remains the standard of care in patients with a normal-appearing contralateral adrenal gland.

Prognosis. The prognosis and subsequent follow-up after resection of an adrenal cyst are dependent on histology. Benign adrenal cysts warrant follow-up to monitor potential reaccumulation, and warrant re-treatment if symptoms return. Adrenal cysts associated with malignancy require follow-up in accordance with the malignant histology detected.

Summary. Adrenal cysts are rare, and their diagnosis can be challenging. Symptomatic adrenal cysts should be surgically removed, whereas small nonfunctional asymptomatic lesions with benign radiographic appearance may be treated conservatively with regular follow-up.

KEY POINT: ADRENAL CYSTS

- Because of the known chance of associated malignancy, observation of adrenal cysts must be done with caution.

Benign Pheochromocytoma. Benign pheochromocytomas are discussed in the section on pheochromocytoma under Disorders of Increased Adrenal Function.

EVALUATION OF ADRENAL LESIONS IN UROLOGIC PRACTICE

In urologic practice, the evaluation of adrenal pathology is typically in the setting of patients referred with a diagnosis of a new adrenal mass or in existing patients in whom a new adrenal mass is discovered incidentally. Occasionally, patients are identified by astute clinicians based on clinical symptoms in the absence of prior radiographic identification of an adrenal lesion. This section of the chapter reviews clinically relevant evaluation and management of adrenal masses. It is important to note that the pregnant patient diagnosed with an adrenal mass requires a carefully planned, multidisciplinary, tailored approach. This subject matter is beyond the scope of this chapter; however, reviews on this topic are available (Harrington et al, 1999; Lindsay and Nieman, 2005b; Klibanski et al, 2006; Lindsay and Nieman, 2006).

Overview of the Adrenal Incidentaloma

Adrenal incidentalomas are unsuspected adrenal masses greater than 1 cm in diameter identified on cross-sectional imaging performed for seemingly unrelated causes. Strictly speaking, patients who are undergoing a staging evaluation for another malignancy or who are later found to have symptoms relating to the adrenal lesion are excluded from the term *adrenal incidentaloma*, given the possible relationship of the primary indication for the study and the adrenal lesion (Young, 2000, 2007b; Mazzaglia and Monchik, 2009). The frequency of adrenal incidentalomas is relatively high, with contemporary imaging series reporting an incidence of approximately 5% (Song et al, 2008), similar to that found in historical autopsy data (Commons and Callaway, 1948; Russell et al, 1972). The incidence of the incidental adrenal mass increases with age, with a risk of less than 0.5% in individuals in their 20s and up to 7% in those 70 years of age or older (Young, 2000).

It is important to emphasize that “incidental” does not mean “insignificant.” Table 65-15 summarizes collective data available regarding pertinent clinical characteristics of over 2000 newly discovered adrenal lesions and demonstrates that nearly 20% of adrenal incidentalomas are found to be potential surgical lesions. The two characteristics of primary clinical relevance are imaging and metabolic activity or functional status. Biopsy is rarely indicated but can be a useful tool in specific clinical circumstances. This section of the chapter describes in details the clinical indications and processes of imaging, biopsy, and metabolic testing.

TABLE 65-15 Characteristics of Incidental Adrenal Masses as Described in a Systematic Review of Published Series of Adrenal Incidentalomas That Include 20 or More Patients (N = 2005)

ADRENAL LESION	PERCENT OF TOTAL (N = 2005)
Metabolically active	11.2%
Cortisol-producing adenoma	5.3%
Aldosterone-producing adenoma	1.0%
Pheochromocytoma	5.1%
Malignant	7.2%
Adrenocortical carcinoma	4.7%
Metastasis	2.5%
TOTAL POTENTIALLY SURGICAL LESIONS	18.4%

Data from Young WF Jr. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. *Endocrinol Metab Clin North Am* 2000;29(1):159–85, x; and Young WF Jr. The incidentally discovered adrenal mass. *N Engl J Med* 2007;356(6):601–10.

Imaging of Adrenal Masses

Imaging Modalities

Appropriate management and follow-up of the adrenal incidentaloma largely depend on ordering the proper test, carrying out accurate image-acquisition protocols, and interpreting the information obtained. Urologists must be well versed in adrenal imaging modalities and limitations and be able to speak knowledgeably to their radiology colleagues. Numerous imaging modalities can be used to assess both morphologic and functional features of adrenal masses. This section summarizes the salient features of each imaging modality as it pertains to characterization of adrenal incidentalomas. Please also refer to the section on adrenal lesions for details regarding imaging characteristics of each specific type of adrenal lesion.

Ultrasonography. Ultrasonography is a suboptimal imaging modality for detecting and fully characterizing adrenal lesions. Nevertheless, many incidentalomas will be discovered on ultrasound imaging performed for unrelated reasons. Indeed, in parts of the world where ultrasonography is used as the primary imaging modality, the majority of adrenal incidentalomas are discovered through use of this modality (Bhargava et al, 2008). Moreover, in series wherein ultrasonography is responsible for identifying individuals with adenomas, right-sided lesions appear to be more common, whereas ultrasonography is less sensitive in identifying left-sided adrenal lesions than those in the right gland, based on anatomic differences. On the right, the IVC and liver provide a better window to the adrenal gland on ultrasonography, whereas on the left the adrenal can be overlooked or mistaken as part of the splenic, pancreatic, para-aortic lymphatic, or gastric anatomy (Barzon et al, 2003).

Computed Tomography and Magnetic Resonance Imaging. CT and MRI permit cross-sectional and reconstructed anatomic image characterization of the adrenals and serve as the cornerstone for adrenal evaluation. Size, laterality, homogeneity, density, vascularity (enhancement and washout), and anatomic relationships can be accurately assessed using these modalities. Indeed, the size of an adrenal lesion, a characteristic reliably assessed by cross-sectional imaging, is a primary factor driving management decisions (see discussion in the section on [size and growth](#)). Often the differential diagnosis of an adrenal lesion can be immediately narrowed based on the imaging characteristics. For instance, the presence of macroscopic fat identifies an adrenal myelolipoma, whereas large heterogeneous masses that invade surrounding structures are

most indicative of adrenal adenocarcinomas (Cyran et al, 1996). Adrenal cysts and acute or subacute hemorrhage also exhibit characteristic imaging findings (Burks et al, 1992). Nevertheless, most adrenal incidentalomas are small homogeneous masses with regular contours that cannot be immediately given a pathologic label. Further characterization of these common lesions relies on the ability of modern cross-sectional imaging to identify the presence of intracytoplasmic lipid that differentiates a benign adrenal adenoma from other adrenal pathology (Korobkin et al, 1996b). Although adenomas can be differentiated from nonadenomas based on this single imaging characteristic, the need for a metabolic workup is not eliminated based on identification of lipid within an adrenal mass. Radiographic differentiation between metabolically functional and nonfunctioning adenomas has been investigated, and, to date, no reliable radiographic test or characteristic is sensitive enough to obviate endocrinologic evaluation based solely on imaging (Korobkin et al, 1996b; Fujiyoshi et al, 2003; Hussain and Korobkin, 2004).

Unenhanced Computed Tomography. An unenhanced CT scan is the first, and perhaps single best, and most easily interpreted test for intracellular lipid and therefore can diagnose an adrenal adenoma in more than 70% of cases. Low attenuation (<10 HU) on unenhanced CT corresponds to high intracytoplasmic lipid content and is diagnostic for an adrenal adenoma (Lee et al, 1991; Korobkin et al, 1996b). Using a threshold of 0 HU or less, there is 100% specificity for an adrenal adenoma, meaning that if the lesion meets this criterion, it is always an adenoma. Unfortunately, the sensitivity of noncontrast CT density measurements is imperfect, meaning that not all adenomas will meet this criterion. Indeed only 41% of adenomas exhibit an attenuation of 0 HU (Boland et al, 1998), and therefore a threshold of 10 HU is currently used. This cutoff affords a sensitivity of 71% and a specificity of 98% for the diagnosis of adrenal adenomas (Boland et al, 1998, 2008). In other words, 98% of lesions that exhibit an attenuation of 10 HU or less on noncontrast CT are adrenal adenomas, whereas less than 30% of adrenal adenomas are lipid poor (also known as *atypical adenomas*) and exhibit an attenuation of greater than 10 HU. Similar test characteristics have been confirmed in purely surgical series (Hamrahian et al, 2005). In urologic practice, this criterion on unenhanced CT is quite useful, because the vast majority of renal imaging for stones or lesions of the upper urinary tracts includes an unenhanced precontrast phase. Despite the high specificity of the 10-HU cutoff, few low-density (<10 HU) pheochromocytomas have been reported, underscoring the importance of a metabolic workup for all adrenal lesions (Blake et al, 2003, 2005). It should be mentioned that in an era of digital radiology, density measurements of adrenal lesions can easily be undertaken at the time of evaluation, even when the interpreting radiologist may not provide the values in the dictation. Diligence in this regard by the clinician is essential to avoid additional unnecessary imaging tests, even if improperly recommended.

Enhanced Computed Tomography. Some adrenal masses may be discovered on contrast-enhanced imaging without the benefit of precontrast films. Unfortunately, the diagnostic information that can be obtained from attenuation values of these single-phase studies (approximately 1 minute after the contrast bolus) is limited. Unlike unenhanced CT, there is tremendous overlap in postcontrast attenuation values of adenomas and nonadenomas (Korobkin et al, 1996a; Szolar and Kammerhuber, 1998).

Nevertheless, enhanced CT may indeed contain diagnostic information that is helpful. Data reveal that morphologic features such as irregular margins and an enhancing rim can be quite specific for malignancy (Song et al, 2013). Furthermore, histogram analysis of the lesion's region of interest (ROI) may be useful in identifying lipid-rich adenomas on enhanced CT. This technique is available on most modern workstations, and it graphs the quantity of pixels in an ROI against their attenuation value (Boland et al, 2008). Some suggest that if more than 10% of pixels exhibit a density below 0 HU, the lesion is likely an adenoma (Bae et al, 2003; Boland et al, 2008). Combination of a histogram analysis and ¹⁸F-FDG-PET CT also harbors promise (Perri et al, 2011).

Computed Tomography Washout Study. Approximately 30% of adrenal adenomas exhibit an attenuation of greater than 10 HU on unenhanced CT owing to their lower lipid content. These “atypical adenomas” are indistinguishable from nonadenomas on noncontrast CT density measurements alone (Boland et al, 1998). Fortunately, lipid-poor adenomas possess identical properties to lipid-rich adenomas regarding their rapid loss (washout) of enhancement after CT contrast load (Caoili et al, 2000; Pena et al, 2000). Indeed, in the last decade, washout of contrast enhancement has become a routine technique to differentiate lipid-poor adenomas from other adrenal lesions (Korobkin et al, 1998; Szolar and Kammerhuber, 1998; Szolar et al, 2005). An absolute percent washout (comparing noncontrast values with 15-minute postcontrast density values) of greater than 60%, or a relative percent washout (RPW) (comparing arterial phase density measurements with 15-minute postcontrast density values) of greater than 40% on delayed (washout) imaging, is indicative of adenoma (Fig. 65-28) (Caoili et al, 2002; Boland et al, 2008). Remarkably, test characteristics for these CT washout studies are highly sensitive and specific (Boland et al, 2008). Figure 65-29 summarizes when CT washout studies should be used and how the percent washout is calculated. It is important to note, however, that washout characteristics may have limitations in differentiating lipid-poor adenomas from RCC and hepatocellular carcinoma metastases (Choi et al, 2013). Furthermore, data on washout characteristics of ACC are limited, largely because of the large size at presentation and lack of necessity in performing such studies. Although, classically, ACC can be differentiated from adenoma on 15-minute CT washout studies, some exceptions have been reported (Simhan et al, 2012a).

Reports on washout studies using a 10- instead of a 15-minute delay exist. Originally, an RPW of greater than 50% was believed to be necessary to diagnose adenomas using such protocols (Pena et al, 2000). Although some reports suggest that just as with a 15-minute delayed study, an RPW of more than 40% is sufficient (Blake et al, 2005), imaging experts currently recommend use of 15-minute delayed protocols, despite the potential added efficiency of a 10-minute study (Boland et al, 2008; Boland, 2010b).

Given these data, it is imperative that the knowledgeable urologist order a proper adrenal CT study to include noncontrast 5-mm images through the adrenal with enhanced (1-minute postbolus imaging) and 15-minute washout imaging and that he or she speak to the radiologists to ensure that the test uses the proper protocol. In the absence of a properly performed test, nondiagnostic images may lead to a recommendation for subsequent unnecessary and anxiety-provoking tests.

Magnetic Resonance Imaging. Similar to adrenal imaging by CT, MRI of the adrenal incidentaloma relies on its ability to accurately quantify the lesion’s lipid content. Whereas CT uses unenhanced attenuation to identify lipid-rich adenomas, MRI harnesses the interference between signal collected from fat and water tissue to evaluate for intracellular lipid content (Hussain and Korobkin, 2004). On such opposed phase chemical shift imaging, signal intensity loss on out-of-phase sequences, when compared with in-phase imaging, signifies the presence of intracellular lipid and definitively identifies the lesions in question is an adenoma (Korobkin et al, 1996b; Namimoto et al, 2001). The loss of signal intensity can be quantified by several methods (e.g., use of the spleen as an internal reference); however, in clinical practice, qualitative

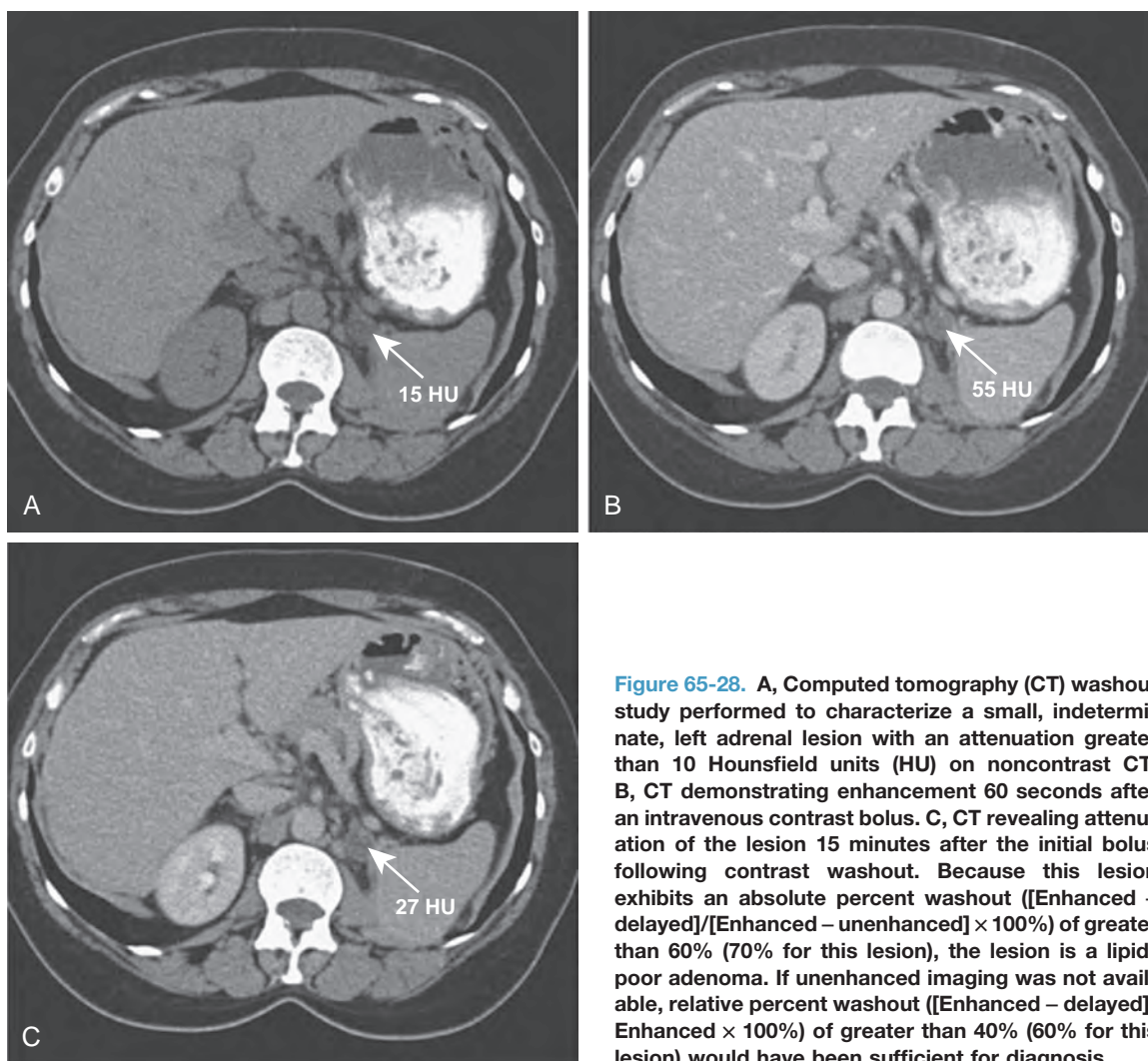


Figure 65-28. A, Computed tomography (CT) washout study performed to characterize a small, indeterminate, left adrenal lesion with an attenuation greater than 10 Hounsfield units (HU) on noncontrast CT. B, CT demonstrating enhancement 60 seconds after an intravenous contrast bolus. C, CT revealing attenuation of the lesion 15 minutes after the initial bolus following contrast washout. Because this lesion exhibits an absolute percent washout $\left(\frac{[\text{Enhanced} - \text{delayed}]}{[\text{Enhanced} - \text{unenhanced}]} \times 100\%\right)$ of greater than 60% (70% for this lesion), the lesion is a lipid-poor adenoma. If unenhanced imaging was not available, relative percent washout $\left(\frac{[\text{Enhanced} - \text{delayed}]}{\text{Enhanced}} \times 100\%\right)$ of greater than 40% (60% for this lesion) would have been sufficient for diagnosis.

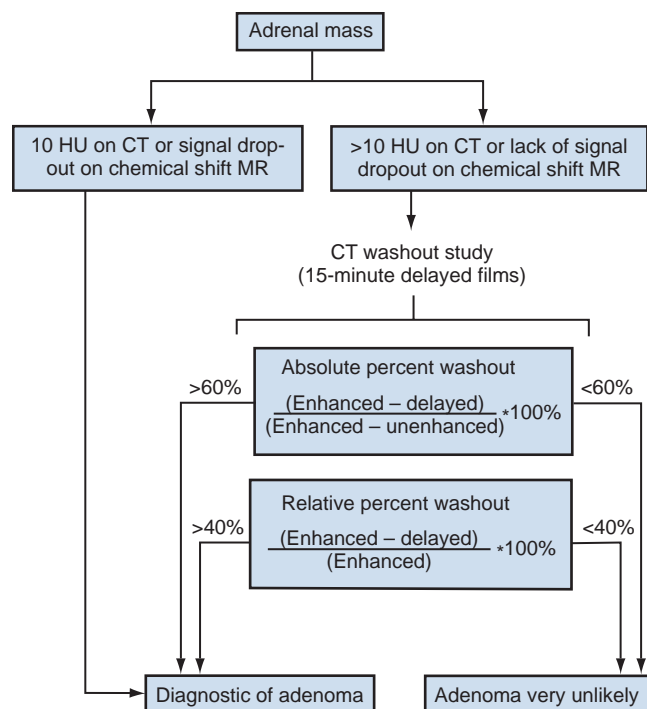


Figure 65-29. Summary of evaluation of adrenal mass using modern cross-sectional imaging. CT, computed tomography; HU, Hounsfield units; MR, magnetic resonance.

assessments are most often used (Outwater et al, 1996; Fujiyoshi et al, 2003; Boland et al, 2008). Most reports demonstrate that the test characteristics of chemical shift MRI are similar to those of unenhanced CT, albeit significantly more expensive. Although some reports suggest that MRI may be superior to unenhanced CT in characterizing lipid-poor adenomas (Haider et al, 2004; Israel et al, 2004), most experts believe that the two modalities are largely equivalent (Boland, 2010b). Nevertheless, CT washout studies are considered the gold standard and appear to surpass opposed phase chemical shift MRI in their sensitivity for identifying adenomas (Caoili et al, 2000; Hussain and Korobkin, 2004; Park et al, 2007a; Boland et al, 2008; Boland, 2010a, 2010b). It is important to note that gadolinium-enhanced MRI washout studies do not exhibit the diagnostic strength of iodine-based CT washout studies and are not currently used in clinical practice. This shortcoming of MRI may be explained by the fact that gadolinium-induced signal intensity is less dose-dependent than enhancement from iodinated contrast on CT imaging (Hussain and Korobkin, 2004).

Functional Imaging. The high diagnostic accuracy provided by biochemical evaluation and cross-sectional radiographic imaging of adrenal incidentalomas limits the indications for the routine use of functional imaging. However, functional adrenal imaging can provide valuable information when the origin of the adrenal tumor is unclear or when malignancy is highly suspected but has not been confirmed with other diagnostic modalities (Avram et al, 2006; Gross et al, 2009).

Radionuclide scintigraphy with the radiolabeled cholesterol analog NP59 can help determine whether or not an adrenal lesion originated in the adrenal cortex or is from another source, because adrenocortical cells demonstrate increased uptake of the cholesterol analog. Based on the pattern of NP59 uptake, adrenal adenomas can be distinguished from other space-occupying lesions of the adrenal gland with high sensitivity and specificity (Kloos et al, 1995, 1997). Although the characterization of lesions greater than 2 cm is limited with planar scintigraphy, the use of SPECT-CT may enhance the ability of NP59 to detect smaller lesions (La Cava et al, 2003). Despite the apparent benefits of NP59 scintigraphy in detecting adrenal adenomas, the test is time-consuming and is not

currently approved by the U.S. Food and Drug Administration. Moreover, it cannot reliably exclude the presence of ACC (Tauchmanova et al, 2004).

Another radiotracer used to identify tumors of adrenocortical origin is carbon-11 (^{11}C)-metomidate. Metomidate is an inhibitor of 11β -hydroxylase and aldosterone synthase that is preferentially taken up by adrenocortical cells (see Fig. 65-3). Although several studies have demonstrated the ability of ^{11}C -metomidate PET to correctly identify tumors of adrenocortical origin, the test is significantly limited by its inability to differentiate benign adrenal adenomas from ACCs (Minn et al, 2004; Hennings et al, 2006).

The role of functional imaging for the diagnosis of pheochromocytoma is limited, given that most pheochromocytomas can be accurately diagnosed with cross-sectional imaging and metabolic evaluation for catecholamines and their metabolites. Therefore ^{131}I -MIBG imaging has a limited role in the routine evaluation of adrenal incidentalomas. MIBG is a functional and structural analog of norepinephrine that is incorporated into catecholamine storage vesicles. Increased uptake of MIBG suggests the presence of a chromaffin tumor, such as a pheochromocytoma or paraganglioma. In a small series of 23 patients with nonfunctioning adrenal masses, ^{131}I -MIBG scintigraphy was performed before pathologic evaluation and demonstrated a sensitivity of 100% and a specificity of 94% in identifying the presence of pheochromocytomas and paragangliomas (Maurea et al, 2001). Although there are alternatives to MIBG imaging for the detection of pheochromocytomas, including ^{18}F -dopamine PET and the somatostatin analog indium-111 (^{111}In)-octreotide, their usefulness in the routine evaluation of adrenal incidentalomas has not been evaluated to date (Mayo-Smith et al, 2001; Timmers et al, 2007a). As discussed previously, ^{18}F -FDG PET is largely replacing MIBG in staging non-MEN-2 patients with known pheochromocytoma (Timmers et al, 2012).

The differentiation of benign and malignant adrenal tumors may be facilitated by the use of ^{18}F -FDG PET. Multiple reports have demonstrated a high sensitivity (93% to 100%) and specificity (80% to 100%) of use of ^{18}F -FDG PET to identify malignant adrenal tumors, including ACCs and metastatic lesions to the adrenal (Yun et al, 2001; Blake et al, 2006; Chong et al, 2006; Boland et al, 2011). However, the use of ^{18}F -FDG PET is best reserved for cases in which CT imaging and clinical data are inconclusive (Boland et al, 2008, 2011). Indeed, some data suggest that CT washout studies are more helpful than ^{18}F -FDG PET in evaluating patients with an adrenal mass and known malignancy (Park et al, 2007b). Nevertheless, caution must be exercised in patients with known RCC and hepatocellular carcinoma, because adrenal metastases from these primary tumors can exhibit iodinated contrast washout characteristics similar to those of lipid-poor adenomas (Choi et al, 2013).

KEY POINTS: IMAGING

- Low attenuation on unenhanced CT (<10 HU) corresponds to high intracellular lipid and is extremely specific for identification of adrenal adenoma.
- MRI is similar in its test characteristics to unenhanced CT.
- CT washout studies are considered the gold standard for adrenal imaging. Rapid loss of contrast enhancement can differentiate even lipid-poor adenomas (approximately 30% of adenomas) from other lesions. Gadolinium-enhanced MRI washout studies do not exhibit the diagnostic strength of iodine-based CT washout studies and are not currently used in clinical practice.
- RCC metastases may exhibit washout characteristics similar to those of lipid-poor adenomas.

Size and Growth

The retroperitoneal space allows for relatively asymptomatic growth of most adrenal lesions, which may reach beyond 20 cm

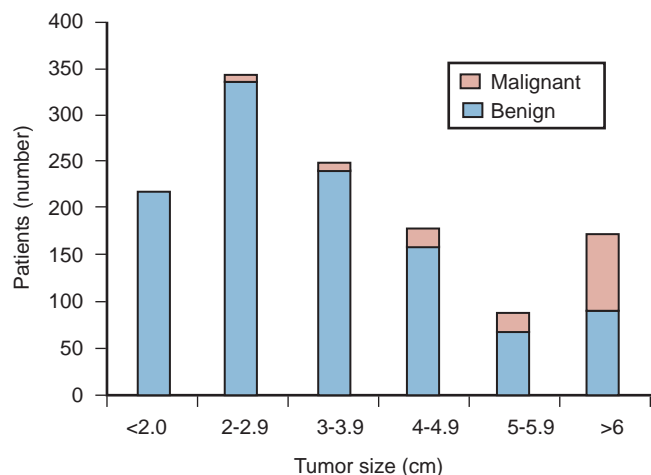


Figure 65-30. Distribution of benign versus malignant adrenal masses based on lesion size (N = 1322). (Modified from Barzon L, Sonino N, Fallo F, et al. Prevalence and natural history of adrenal incidentalomas. *Eur J Endocrinol* 2003;149:273–85.)

in size before clinically manifesting. Nevertheless, at presentation the median radiographic diameter of an adrenal incidentaloma is approximately 3 cm (Mantero et al, 2000). A relationship does exist between the size of an adrenal lesion and its malignant potential, with larger masses more likely to exhibit adverse clinical and pathologic features (Angeli et al, 1997). Figure 65-30 summarizes the relationship between adrenal mass size and its risk of malignancy in over 1300 reported incidentalomas (Barzon et al, 2003). Masses smaller than 4 cm are considered to possess low malignant potential (2% are adrenal carcinomas) and, if nonfunctional, can be observed safely (Grumbach et al, 2003; Cicala et al, 2008). Masses that exceed 6 cm should be considered malignant until proven benign, which usually requires definitive resection. Management of incidentalomas between 4 cm and 6 cm is more controversial. In this intermediate size range, the rate of malignancy is estimated to be only 6% (Cicala et al, 2008). Nonetheless, in otherwise healthy individuals with acceptable perioperative risk profile, most experts recommend 4 cm as the cutoff diameter that warrants resection (Barry et al, 1998; Mantero et al, 2000; Young, 2000; Thompson and Young, 2003; Young, 2007b). In the largest adrenal incidentaloma series to date (N = 1004), Mantero and colleagues (2000) reported that the 4-cm cutoff afforded a 93% sensitivity and 42% specificity for detecting malignancy. Sensitivity dropped to 74% and specificity rose to 73% when a 6-cm cutoff was applied. It is important to note that the relationship between the radiographic and pathologic size of an adrenal lesion is imperfect, with pathologic assessment usually resulting in a larger measurement (Cerfolio et al, 1993; Kouriefs et al, 2001). Furthermore, administrative data reveal only a weak relationship between tumor size at presentation and rates of concomitant metastatic disease in patients with ACC. Also, although analyses from administrative data sets must be interpreted with caution, a robust relationship between survival and size of localized ACC at resection is difficult to identify (Canter et al, 2013).

The urologic oncologist must remember that the incidence of benign adrenal adenomas increases with age; therefore adrenal lesions in younger patients, even those smaller than 4 cm, must be managed with greater caution than similar lesions in an older patient. Likewise, lesions larger than 4 cm in older patients with significant comorbidities may be better served with observation than resection (Young, 2007b). Moreover, the radiographic characteristics of individual adrenal lesions (regularity of borders, enhancement) must be considered in addition to the lesion's size when deciding whether to treat. In the absence of level 1 evidence, large population-based reports must be integrated with sound clinical judgment.

The growth kinetics of unresected adrenal lesions should be followed, although most lesions that are resected because of increased growth kinetics ultimately prove benign. In a prospectively followed multi-institutional Swedish cohort (N = 229, median follow-up 25 months), 7.4% (17) of masses grew at least 5 mm, with 5.2% (12) adding at least 1 cm to their diameter. All patients who underwent resection because of an increase in lesion size exhibited benign pathology (Libe et al, 2002). Similarly, an earlier review of the literature (N = 873) revealed that at a mean follow-up of 3 years, 9% of adrenal incidentalomas grew over 1 cm in diameter and a smaller number decreased in size. In this series, only one lesion proved malignant. The authors concluded that the rate of malignant transformation of adrenal incidentalomas is approximately 1 in 1000 (Barzon et al, 2003). Reimaging at 6, 12, and, as possible, 24 months is currently recommended to verify oncologic indolence (Grumbach et al, 2003; Young, 2007b). Suspicious and unusual tumors may require imaging at earlier or more frequent intervals, whereas small (<2 cm) homogeneous, well-circumscribed, nonfunctional lesions can be followed less closely (Young, 2007b). A rather arbitrary criterion of 1 cm of growth has been proposed as an indication for resection; however, the patient must be counseled that the chance of malignancy is low if growth kinetics are flat (Young, 2007b).

KEY POINTS: SIZE AND GROWTH

- Masses larger than 6 cm should be considered malignant until proved otherwise. Although management of masses between 4 cm and 6 cm is controversial, thought leaders in the field advise that in otherwise healthy individuals, masses 4 cm or larger should be resected.
- Kinetics of growth should be followed. The current recommendation is to resect masses that grow over 1 cm; however, incidence of malignancy among these patients is low.

Biopsy of Adrenal Masses

Overview

The role of adrenal biopsy has been limited for the following reasons: (1) modern imaging in the context of clinical characteristics affords superb diagnostic capabilities, (2) histologically, adenomas cannot be reliably differentiated from adrenal carcinomas, and (3) adrenal biopsy is not without risk (Thompson and Young, 2003; Young, 2007b). Nevertheless, it is useful to review data that are available with regard to safety and diagnostic usefulness of adrenal biopsy, and the procedure can occasionally be a useful tool in the diagnostic armamentarium of the adrenal surgeon.

Test Characteristics of Biopsy

Welch and colleagues (1994) reported on 277 percutaneous biopsies performed at the Mayo Clinic. Most biopsies in the series were performed in patients with a known nonadrenal malignancy. The authors report a sensitivity of 81% and specificity of 99%. The accuracy of right-sided biopsies was higher than those on the left (94% vs. 87%). Larger biopsy needles (18 or 19 gauge) resulted in better diagnostic yield and equivalent complication rates when compared with biopsies performed with smaller needles.

The reported positive predictive value of adrenal biopsy is high, meaning that a positive biopsy for malignancy has a high correlation on final pathology. This is especially relevant in patients with a history of an unrelated primary malignancy and in whom an adrenal metastasis is suspected (Silverman et al, 1993; Harisinghani et al, 2002). Although the overall specificity is imperfect, in the same clinical scenario the test's negative predictive value is nevertheless impressive when nondiagnostic biopsies are excluded (Silverman et al, 1993; Harisinghani et al, 2002). In a series of 225 adrenal

biopsies performed in patients with a known primary malignancy at Massachusetts General Hospital, 18% of biopsy specimens demonstrated adrenal tissue without evidence of malignancy. The authors reported the negative predictive value of these negative biopsy findings based on lack of tumor growth at follow-up, autopsy findings, or a rebiopsy result of 100%, although selection and research biases may have existed (Harisinghani et al, 2002). In skilled hands, nondiagnostic biopsies appear infrequent when the majority of sampling is performed with 18-gauge needles (Paulsen et al, 2004).

The probability of a positive adrenal biopsy for metastatic disease appears highest in patients with known lung carcinoma (>90%) and RCC (80%) (Mazzaglia and Monchik, 2009). In contrast, an adrenal mass in a patient without a previous history of malignancy and without evidence of a synchronous nonadrenal mass is highly unlikely to be present as a metastasis (Lutz et al, 2000). Biopsy in this setting is rarely helpful. Instead, other criteria, such as radiographic morphology and size, must be used to characterize adrenal masses in such patients (Thompson and Young, 2003; Mazzaglia and Monchik, 2009).

Complications of Biopsy

The complication rates of adrenal biopsies in some large series are as low as 2.8% (Welch et al, 1994). Bleeding is the most common postbiopsy issue, with pneumothoraces and hemothoraces also being reported (Silverman et al, 1993; Welch et al, 1994; Quayle et al, 2007). Needle-track seeding in patients with ACC remains a concern, and some authors suggest that biopsy should be avoided in patients in whom adrenal carcinoma is suspected (Quayle et al, 2007). Surgically, there has been a suggestion that biopsy, especially if followed by hemorrhage, can complicate or even prevent laparoscopic resection (Quayle et al, 2007).

The NIH consensus statement mandates that the possibility of pheochromocytoma be metabolically excluded before biopsy; percutaneous biopsies of pheochromocytomas have been reported to result in life-threatening hypertensive crises (Grumbach et al, 2003; Quayle et al, 2007). It is interesting to note that inadvertent biopsy of pheochromocytomas has resulted in no ill effects in some patients (Quayle et al, 2007); however, in real-world practice, due diligence to rule out pheochromocytoma before biopsy is prudent (Mazzaglia and Monchik, 2009).

Clinical Usefulness of Biopsy

Despite the fact that adrenal biopsies—when used to differentiate benign from metastatic disease—afford favorable accuracy, some clinicians argue that most adrenal biopsies performed today are unnecessary (Quayle et al, 2007; Mazzaglia and Monchik, 2009). For instance, Quayle and colleagues retrospectively reviewed their experience with patients who were sent to their tertiary referral center after an adrenal biopsy performed in the community. The researchers concluded that in no case did the biopsy affect the clinical management of these patients. Moreover, these and other investigators have raised the issue of radiology reports recommending adrenal biopsies or stating that the lesions are “amenable” to biopsy. The authors suggested that such language in radiology reports must be strongly discouraged, because it leads to unnecessary and, at times, deleterious procedures by physicians who are not familiar with standard management of the adrenal mass (Quayle et al, 2007; Mazzaglia and Monchik, 2009).

In conclusion, adrenal biopsy should be pursued only when limitations of imaging have been reached and when the physician and patient are certain that the result of biopsy will influence management. Indeed, perhaps the biggest role for adrenal mass biopsy is in patients with primary malignancies that have potentially recurred in the adrenal gland and whose management will be affected by the biopsy results. Figure 65-31 summarizes the salient points that must be considered when making a decision regarding whether to perform a biopsy of a patient's adrenal mass.

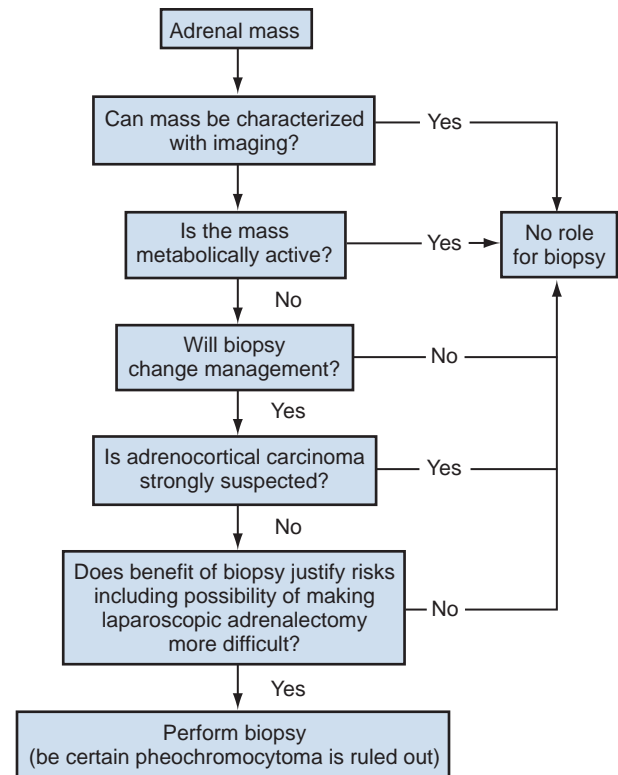


Figure 65-31. Algorithm summarizing decision making regarding whether to subject the patient to an adrenal biopsy. Perhaps the most clinically valuable role for adrenal mass biopsy is in patients with primary malignancies that have potentially recurred in the adrenal gland and whose management will be affected by the biopsy results.

KEY POINTS: BIOPSY OF ADRENAL MASSES

- When used to differentiate benign from metastatic disease, adrenal biopsy carries favorable test characteristics.
- Always exclude possibility of pheochromocytoma before biopsy.

Assessment of Function of Adrenal Masses

Overview

The NIH consensus statement recommends metabolic testing for all adrenal incidentalomas (Grumbach et al, 2003). This recommendation is supported by the observation that more than 10% of adrenal incidentalomas are metabolically active (see Table 65-15). Current practice is to test all new adrenal masses for cortisol and catecholamine hypersecretion. In patients with a history of hypertension, aldosterone hypersecretion should also be assessed (Grumbach et al, 2003; Young, 2007b). Despite this recommendation as a standard of care, routine clinical practice remains inadequate in this domain, whereas it is estimated that more than 80% of adrenal masses do not receive appropriate evaluation (Eldeiry and Garber, 2008).

Testing for Cortisol Hypersecretion

A systematic review of the literature reveals that 5% to 8% of adrenal incidentalomas produce excessive glucocorticoids (Young, 2000; Barzon et al, 2003). The NIH consensus guidelines state that all adrenal lesions should be tested for glucocorticoid hypersecretion (Grumbach et al, 2003). Three first-line tests are available to

screen patients with incidentalomas for Cushing syndrome: (1) LD-DST, (2) a late-night salivary cortisol test, and (3) a 24-hour UFC evaluation. A meta-analysis of the published literature demonstrates that these tests afford relatively equivalent accuracy; however, the UFC and the LD-DST are supported by more abundant evidence than the late-night salivary cortisol approach (Elamin et al, 2008). Nonetheless, reports suggest that UFC is not sufficiently sensitive to detect subclinical Cushing syndrome (Tsagarakis et al, 2006; Mitchell et al, 2007). Indeed, recent practice guidelines from the Endocrine Society recommend the use of either the LD-DST or the late-night salivary cortisol test to screen patients with adrenal incidentalomas as part of a complete endocrinologic evaluation (Nieman et al, 2008). The section on Cushing syndrome reviews the physiologic rationale for both first-line testing discussed here and other testing that may be necessary. In this section, we review practical considerations of evaluating adrenal incidentalomas for excess glucocorticoid secretion within the scope of urologic practice. As mentioned in prior sections, the physician must verify that exogenous steroids, including creams and nasal sprays, are not in use by the patient before testing.

Overnight Low-Dose Dexamethasone Suppression Test. Administration of low-dose dexamethasone followed by measurement of serum cortisol probes the patient's glucocorticoid negative feedback system (see the section on Cushing syndrome for a discussion of physiology). A patient's failure to suppress cortisol levels after low-dose dexamethasone administration is indicative of Cushing syndrome (Findling and Raff, 2005).

Despite the test's arguably complex physiologic considerations, its administration is remarkably simple. The patient is given a prescription for 1 mg of dexamethasone and instructed to take it between 11 PM and 12 AM (Newell-Price et al, 2006). The next morning, serum cortisol is measured between 8 AM and 9 AM. In patients without hypercortisolemia, the cortisol level should be suppressed below 5 µg/dL (140 nmol/L). Specificity at this threshold is greater than 95% (Nieman et al, 2008). The trade-off, however, is sensitivity. In some reports, up to 18% of patients with Cushing syndrome exhibited false-negative results (Findling et al, 2004). Therefore a threshold suppressed cortisol level of 1.8 µg/dL (50 nmol/L) has been suggested, raising the sensitivity to over 90% (Findling et al, 2004) with a specificity of 80% (Nieman et al, 2008). The test's performance is similar to that of other first-line tests used to diagnose Cushing syndrome and is recommended as an alternative to the late-night salivary cortisol test for initial screening of incidentalomas (Elamin et al, 2008; Nieman et al, 2008).

Unlike 24-hour UFC testing, LD-DST is not affected by the patient's glomerular filtration rate (GFR). Box 65-5 lists the most common pharmacologic agents that can alter testing. Most important, the urologist must be aware that the test can yield as high as a 50% false-positive rate in women using oral contraceptives, because the contraceptives increase total (but not bioavailable) cortisol levels by raising the patient's cortisol-binding globulin concentrations (Nickelsen et al, 1989). Administration of low-dose dexamethasone over a 48-hour period is less practical but may improve accuracy and is preferred by some endocrinologists.

Late-Night Salivary Cortisol. Late-night cortisol measurements probe the perturbation or, in some cases, complete disruption in the diurnal variation of cortisol levels that is seen in Cushing syndrome. The abnormality, even in very mild cases of Cushing syndrome, is the inability to suppress cortisol levels at night (Raff and Findling, 2003; Findling and Raff, 2005). Because late-night serum cortisol measurements are impractical, salivary testing has gained acceptance, because salivary cortisol levels reflect near real-time serum cortisol levels. Measurements of cortisol in saliva samples collected between 11 PM and midnight or at bedtime should not exceed 145 ng/dL when the liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay is used (Nieman et al, 2008). The sensitivity and specificity of the test exceed 90% and are similar to both UFC and LD-DST; however, a large meta-analysis concluded that the data supporting salivary cortisol testing, to date, are inferior to the data available for UFC and the LD-DST (Elamin et al, 2008; Nieman et al, 2008). Furthermore, the test's usefulness in diagnosing

BOX 65-5 Pharmaceuticals That Affect Testing for Cushing Syndrome

DRUGS THAT ACCELERATE DEXAMETHASONE METABOLISM BY INDUCTION OF CYP3A4

Phenobarbital
Phenytoin
Carbamazepine
Primidone
Rifampin
Rifapentine
Ethosuximide
Pioglitazone

DRUGS THAT IMPAIR DEXAMETHASONE METABOLISM BY INHIBITION OF CYP3A4

Aprepitant, fosaprepitant
Itraconazole
Ritonavir
Fluoxetine
Diltiazem
Cimetidine

DRUGS THAT INCREASE CORTISOL-BINDING GLOBULIN AND MAY FALSELY ELEVATE CORTISOL RESULTS

Estrogens
Mitotane

DRUGS THAT INCREASE URINE FREE CORTISOL RESULTS

Carbamazepine
Fenofibrate (increase if measured by high-performance liquid chromatography)
Some synthetic glucocorticoids (immunoassays)
Drugs that inhibit 11β-hydroxysteroid dehydrogenase type 2 (licorice, carbenoxolone)

This should not be considered a complete list of potential drug interactions. Data regarding CYP3A4 obtained from <http://medicine.iupui.edu/flockhart/table.htm>.

From Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93:1526–40.

subclinical Cushing syndrome has been questioned (Nunes et al, 2009).

Unacceptably high false-positive rates may occur in patients with depression, altered sleep patterns, and chronic illness, because normal circadian variation in cortisol levels can be altered in these individuals. Tobacco use can affect salivary cortisol levels and should be avoided on the day of testing (Nieman et al, 2008). Some clinicians instruct patients to avoid oral food or liquid intake, brushing teeth, or undergoing stimulating activity within 30 minutes of salivary collection. Collection is rescheduled if the patient feels ill (Nunes et al, 2009). Some experts advise repeating salivary testing at least twice, regardless of the initial result (Nieman et al, 2008).

24-Hour Urinary Free Cortisol Evaluation. The UFC evaluation is a 24-hour direct measurement of free bioavailable cortisol. This test is an integrated measurement of cortisol secretion over a 24-hour period and does not depend on variables that influence corticosteroid-binding globulin levels (e.g., oral contraceptives) (Arnaldi et al, 2003). This study has been recommended as an initial test to screen patients with incidentalomas for Cushing syndrome (Orth, 1995); however, some recent evidence suggests that the study may not be sensitive enough to detect subtle glucocorticoid metabolism perturbations in patients with cortisol-secreting

adrenal lesions (Terzolo et al, 2005; Tsagarakis et al, 2006; Mitchell et al, 2007). Practice guidelines issued by the Endocrine Society in 2008 recommend that the dexamethasone suppression test or the late-night salivary cortisol test supplant the 24-hour UFC evaluation in initial metabolic screening of patients with incidentalomas (Nieman et al, 2008). Nevertheless, this test remains the test of choice in pregnant patients. In the second and third trimester, cutoff values twofold to threefold above the normal laboratory threshold must be used to account for the physiologic hormonal changes associated with pregnancy (Nieman et al, 2008).

As in all 24-hour urine collections, the patient is instructed to discard the morning's first voided urine and begin to collect all subsequent voided samples. The last sample that is collected is the first morning's void of the following day. Collection and analysis of two separate samples from each patient is advised. The test is most accurate in patients with a GFR greater than 60 mL/min because false-negative results may arise in patients with poor renal function (Nieman et al, 2008). Creatinine levels in the collection must be checked to verify completeness of the collection.

As for all tests, sensitivity and specificity of the UFC depend on the population that is being tested and the normal cutoff values that are selected. Normal cutoff values of approximately 50 μ g to 100 μ g per 24 hours of urine volume are usually used, but these vary depending on the laboratory where the test is performed and the assay used (Orth, 1995; Lin et al, 1997; Pecori Giraldi et al, 2007). Again, cutoff values in the second and third trimesters of pregnancy must be raised approximately threefold to account for physiologic changes. As stated previously, the sensitivity of UFC for patients proven to exhibit hypercortisolism secondary to an adrenal adenoma has been reported to be as low as 85% (Invitti et al, 1999), whereas the specificity of the test in a population of patients with suspected Cushing syndrome appears to be in the 90% range (Pecori Giraldi et al, 2007).

Testing for Aldosterone Hypersecretion

Hypersecretion of aldosterone by adrenal masses is extremely rare, with only approximately 1% of adrenal adenomas responsible for Conn syndrome (Young, 2000). Nevertheless, data demonstrate that nearly 5% of newly hypertensive patients may harbor an aldosterone-secreting adenoma (Rossi et al, 2006a). Indeed, testing of hypertensive patients with adrenal lesions for hyperaldosteronemia is clinically recommended. Testing of nonhypertensive patients, however, currently is not recommended. The section on **primary aldosteronism** describes the physiologic rationale for each test. In this section, we review the practical implications of evaluating adrenal incidentalomas for excess aldosterone secretion.

In the past, low serum potassium level has been used as a screening tool to assess for presence of aldosterone hypersecretion. Despite this prior teaching, contemporary series reveal that less than 40% of patients with hyperaldosteronism exhibit hypokalemia (Mulatero et al, 2004). Today the screening test of choice for Conn syndrome is the ratio of morning plasma aldosterone (ng/dL) to renin (ng/mL/hr). An ARR of 20 (some suggest 30) along with a concomitant aldosterone concentration above 15 ng/mL is indicative of Conn syndrome (Grumbach et al, 2003; Mulatero et al, 2004; Vierhapper, 2007; Young, 2007b). The concurrent elevated aldosterone level appears important for cases in which the ARR is elevated simply because of a low renin level. The test's characteristics have not been fully defined; however, sensitivities and specificities in the 90th percentile have been reported (Montori and Young, 2002; Young, 2007a).

Blood samples should be drawn between 8 AM and 10 AM, preferably with the patient in the sitting position. Note that this timing is also ideal for drawing the morning cortisol level for an LD-DST. Some experts believe that hypokalemia may result in false-positive results owing to physiologic aldosterone elevation, and therefore patients with low potassium levels should undergo repletion before testing (Young, 2007a). Potassium-sparing diuretics such as amiloride, and especially mineralocorticoid receptor blockers such as spironolactone, alter the RAAS and will affect test results.

β -Blockers — consider discontinuing for several weeks before testing

$$\frac{\text{Aldosterone} \leftrightarrow}{\text{Renin} \downarrow} = \text{ARR} \uparrow \text{ (possible false positive)}$$

ACE inhibitors — no need to discontinue before testing (see text)

$$\frac{\text{Aldosterone} \downarrow\downarrow}{\text{Renin} \uparrow} = \text{ARR} \downarrow \text{ (small chance of false negative)}$$

Calcium channel blockers — no need to discontinue before testing

$$\frac{\text{Aldosterone} \leftrightarrow}{\text{Renin} \leftrightarrow} = \text{ARR} \leftrightarrow$$

Figure 65-32. Effect of antihypertensives on screening for hyperaldosteronism. Potassium-sparing diuretics and mineralocorticoid receptor blockers are not included in the figure, because they greatly alter the renin-angiotensin-aldosterone axis and should be stopped at least 6 weeks before aldosterone-renin ratio (ARR) testing. The ARR must be interpreted in the context of the aldosterone and renin levels (see text). ACE, angiotensin-converting enzyme.

These agents should be stopped approximately 6 weeks before testing (Young, 2007a). Also, historically, there has been great concern about ARR reliability in patients who are on other antihypertensive medications. Indeed, until recently, cessation of all antihypertensive therapy was recommended for a minimum of several days before ARR testing. Data now suggest that this may be unnecessary. Figure 65-32 summarizes the effects of various antihypertensive agents on aldosterone and renin levels and on the ARR. The urologist must remember that patients on β -blockers who continue therapy through testing may show a false-positive rise in ARR. Interpretation in these cases should be unaffected because the concurrent aldosterone level remains within normal limits (Young, 2007a). Nevertheless, some experts recommend cessation of β -blockade before testing (Seifarth et al, 2002). ACE inhibitors and angiotensin receptor blockers (ARBs) can lower aldosterone levels while raising renin levels in normal individuals. The ARR in patients with and without hyperaldosteronism who are on these medications has been shown to fall. Cessation of ACE inhibitors and ARBs, however, is not required. First, aldosterone levels are unlikely to fall in patients with hypersecreting adrenal lesions in the setting of ACE inhibitor or ARB use, owing to the fact that this hypersecretion is independent of the RAAS. Second, undetectable renin levels can be used as an additional screen for the diagnosis of hyperaldosteronism. Indeed, renin levels rise in normal individuals, and undetectable renin concentrations should be used as a trigger for secondary (confirmatory) testing even in the setting of an ARR within the normal limits (Seifarth et al, 2002; Young, 2007a).

Confirmatory testing is mandatory in patients who test positive during the initial screen for Conn syndrome. Briefly, this testing involves a 72-hour oral sodium challenge followed by measurements of a 24-hour urinary aldosterone level. The intravenous saline infusion test and the fludrocortisone suppression tests are also used for confirmatory testing by some experts, although the latter test has fallen out of favor (Mulatero et al, 2004; Young, 2007a). We strongly recommend that the patient be referred to an experienced endocrinologist at this point in his or her care. Once hyperaldosteronism is confirmed, further workup with adrenal vein sampling may be necessary. Please refer to the section on **primary aldosteronism** for further discussion.

Testing for Adrenal Sex Steroid Hypersecretion

Hypersecretion of adrenal sex steroids by adrenal masses, especially incidentalomas, is exceedingly rare. The most common adrenal mass that hypersecretes sex steroid is an adrenal carcinoma that concomitantly exhibits cortisol hypersecretion (Wajchenberg et al, 2000; Cordera et al, 2003). Tumors that exclusively hypersecrete androgens—testosterone and/or 17-ketosteroids—have been reported primarily in women. Approximately 50% of such lesions ultimately prove benign (Cordera et al, 2003; Moreno et al, 2004). Routine testing of incidentalomas for sex hormones is currently not recommended (Grumbach et al, 2003; Stanczyk, 2006; Young, 2007b).

Previously for patients with virilization, dexamethasone suppression testing was used to differentiate adrenal androgen excess from an ovarian androgen source; however, this approach has proven unreliable and has been largely replaced by radiographic imaging strategies (Derksen et al, 1994; Cordera et al, 2003).

Testing for Catecholamine Hypersecretion

Pheochromocytoma is found in approximately 5% of patients with adrenal incidentaloma. Therefore all patients, including those in whom metastatic disease is suspected, should undergo functional testing to rule out pheochromocytoma (Adler et al, 2007; Young, 2007b). The section on pheochromocytoma describes the physiologic rationale for each test. Here we discuss the practical details regarding testing.

Free fractionated plasma metanephrines and the 24-hour urinary fractionated metanephrine test constitute the mainstay for pheochromocytoma testing, given their superb sensitivity and suitable specificity. Indeed, the 2005 International Symposium on Pheochromocytoma concluded that one of these two tests should be used for initial diagnosis and screening for pheochromocytoma (Grossman et al, 2006; Pacak et al, 2007). Currently there is an ongoing debate regarding which one of these tests is superior (Young, 2007b; Eisenhofer et al, 2008).

Plasma Free Metanephrines. The measurement of plasma free (fractionated) metanephrines has gained popularity owing to ease of testing and excellent test characteristics. In a study of over 850 patients (214 with pheochromocytoma, 644 without pheochromocytoma), Lenders and colleagues (2002) concluded that the test is superior to all other methods for diagnosing and excluding pheochromocytoma. Investigators in this multicenter study showed that

the test affords nearly perfect sensitivity in cases of sporadic (99%) and familial (97%) pheochromocytoma. Specificity was reported to be 82% for sporadic and 96% for familial cases (Lenders et al, 2002). Indeed, the test's low specificity (reportedly as low as 77%) in patients older than 60 may lead to false-positive results. For this reason, some experts advise against first-line use of plasma free metanephrines in all patients with incidentalomas (Sawka et al, 2003; Young, 2007b). Nevertheless, supporters of the test contend that the true specificity of the test is closer to 92% and that insufficient evidence exists to prove superiority of urinary testing and to eliminate plasma free metanephrines from routine first-line use (Eisenhofer et al, 2008). Further arguments for and against use of plasma free metanephrines are summarized in Table 65-16.

Ideally, patients should not consume food or liquids after midnight before the study. Caffeinated beverages must be avoided especially (Lenders et al, 2002). Acetaminophen can produce a false-positive result owing to cross reactivity in the assay and should be stopped for at least 5 days before testing. Tricyclic antidepressants and phenoxybenzamine should also be stopped, because these have been shown to be responsible for false-positive results (Eisenhofer et al, 2003b). Usual antihypertensive therapy can be continued. Although β -blockade can potentially result in a false-positive test result, the current recommendation is to stop the medication only on repeat testing (Eisenhofer et al, 2003b). Ideally, the serum sample should be drawn with the patient in the supine position after at least 20 minutes of supine rest. Position is especially important if a positive result has been obtained and confirmatory testing is being performed (Grossman et al, 2006).

The upper limit of normal for the test is usually set at 0.61 nmol/L (112 ng/L) for normetanephrine and 0.31 nmol/L (61 ng/L) for metanephrine (Lenders et al, 2002; Eisenhofer et al, 2003a, 2003b; Pacak et al, 2007). Elevation beyond 2.2 nmol/L (400 ng/L) for normetanephrine and/or 1.2 nmol/L (236 ng/L) for metanephrine is substantial and is highly indicative of pheochromocytoma. Lesser elevation in plasma free metanephrine levels necessitates repeat testing (Eisenhofer et al, 2003b). No consensus exists regarding the best strategy for repeat testing; however, such strategies as repeating plasma free metanephrine under ideal conditions (i.e., supine for 20 minutes, off β -blockers, and so on), performing urinary fractionated metanephrine testing, evaluating for elevated chromogranin A levels, and subjecting the patient to clonidine suppression testing have all been suggested (Eisenhofer et al, 2003b; Lenders et al, 2005; Algeciras-Schimmich et al, 2008). At this point

TABLE 65-16 Relative Merits for and against Use of Plasma Free Metanephrines and Urinary Fractionated Metanephrines in Diagnosis of Pheochromocytoma

URINARY FRACTIONATED METANEPHRINES	PLASMA FREE METANEPHRINES
Well-established, widely available test.	Relatively new test with limited availability.
Urinary concentrations (200-2000 nmol) make analysis relatively easy.	Plasma concentrations (0.1-0.5 nmol) can make analysis difficult.
Easy for clinicians to implement with minimal expenditure of time and effort.	Blood collections require some time and effort by medical staff.
Twenty-four-hour collections can be inconvenient for patients.	Blood sampling relatively more convenient for patients.
Problems with reliability of incomplete timed urine collections.	Collection and handling of blood samples can be better regulated.
Difficult to control dietary and daily life influences on sympathoadrenal function.	Influences of diet and sympathoadrenal function more easily controlled.
In children, 24-hour collections are difficult to interpret without age-appropriate reference intervals.	In children, blood sampling may be stressful, but results are more easily interpreted without age-appropriate reference intervals.
Urine collections may be inappropriate in patients with renal failure.	Test is applicable in patients with renal failure.

From Grossman A, Pacak K, Sawka A, et al. Biochemical diagnosis and localization of pheochromocytoma: can we reach a consensus? *Ann N Y Acad Sci* 2006;1073:332-47.

in the patient's care, we strongly suggest involving an experienced endocrinologist.

24-Hour Urinary Fractionated Metanephrines. Some experts believe that 24-hour urinary fractionated metanephrines along with fractionated urinary catecholamine testing represent the best first-line test for pheochromocytoma (Perry et al, 2007; Young, 2007b). When measured with tandem mass spectrometry, and when an elevation in metanephrine (>1531 nmol/day), normetanephrine (>4001 nmol/day), or total metanephrines (>1563 nmol/day) level is considered as a positive result, sensitivity for detecting pheochromocytoma is reported to exceed 97% with a specificity of approximately 91%. Supporters contend that given this specificity, the test is superior to plasma free metanephrines because it avoids unnecessary false-positive results, especially in patient populations with relatively low pretest probabilities, such as those with incidentaloma (Sawka et al, 2003; Perry et al, 2007; Young, 2007a, 2007b). Nevertheless, critics argue that high specificity is achieved by raising reference limits, potentially compromising sensitivity (Eisenhofer et al, 2008). Furthermore, they point to results of Lenders and colleagues (2002) that showed urinary fractionated metanephrine to be inferior to plasma free metanephrines. Given strong opinions on both sides of the argument, the 2005 International Symposium on Pheochromocytoma failed to reach a consensus regarding the superiority of either test (Grossman et al, 2006; Pacak et al, 2007). Table 65-16 summarizes some additional arguments for and against urinary metanephrine testing.

As in all 24-hour urine collections, the patient is instructed to discard the morning's first voided urine and begin to collect all subsequent voided samples. The last sample that is collected is the first morning's void of the following day. Creatinine levels in the collection must be checked to verify completeness of the collection. The test is most accurate in patients with normal renal function. Tricyclic antidepressants and phenoxybenzamine should be stopped.

Follow-Up

A small percentage (approximately 2%), of metabolically silent adrenal incidentalomas are reported to show new metabolic activity during follow-up evaluation (Barzon et al, 2003). The most recent consensus statement by a panel of experts recommends

annual metabolic hormonal screening for the first 3 to 4 years after diagnosis, especially for masses that are 3 cm in diameter (Grumbach et al, 2003). Nevertheless, given a lack of strong data for this recommendation, the need for metabolic reevaluation of adrenal adenomas in patients who show no clinical signs of hormonal hypersecretion remains controversial (Barry et al, 1998; Bulow et al, 2006; Young, 2007b).

KEY POINTS: ASSESSMENT OF FUNCTION OF ADRENAL MASSES

- All adrenal incidentalomas demand a metabolic evaluation.
- Annual follow-up for 3 to 4 years is recommended for metabolically silent masses; however, de novo development of metabolic activity is rare.

Summary of Surgical Indications

Every urologist must clearly understand the indications for surgical intervention in patients with adrenal pathology. The decision-making and management algorithm for patients with adrenal incidentalomas is summarized in Figure 65-33. Box 65-6 also details the major surgical indications for resection of the adrenal gland. The table also includes existing recommendations for adrenal resection during renal surgery (Lane et al, 2009; O'Malley et al, 2009; Kutikov et al, 2011b; Weight et al, 2011).

CONCLUSIONS

The adrenal glands have long been recognized for their essential role in regulation of critical homeostatic functions. Indeed, these deceptively simple glands are central to myriad essential life-sustaining human functions. Despite the frequency of incidental adrenal lesions, relative to other essential organs, the adrenal glands are infrequent primary initiators of human diseases. Nonetheless, clinically significant abnormalities of the adrenal gland require

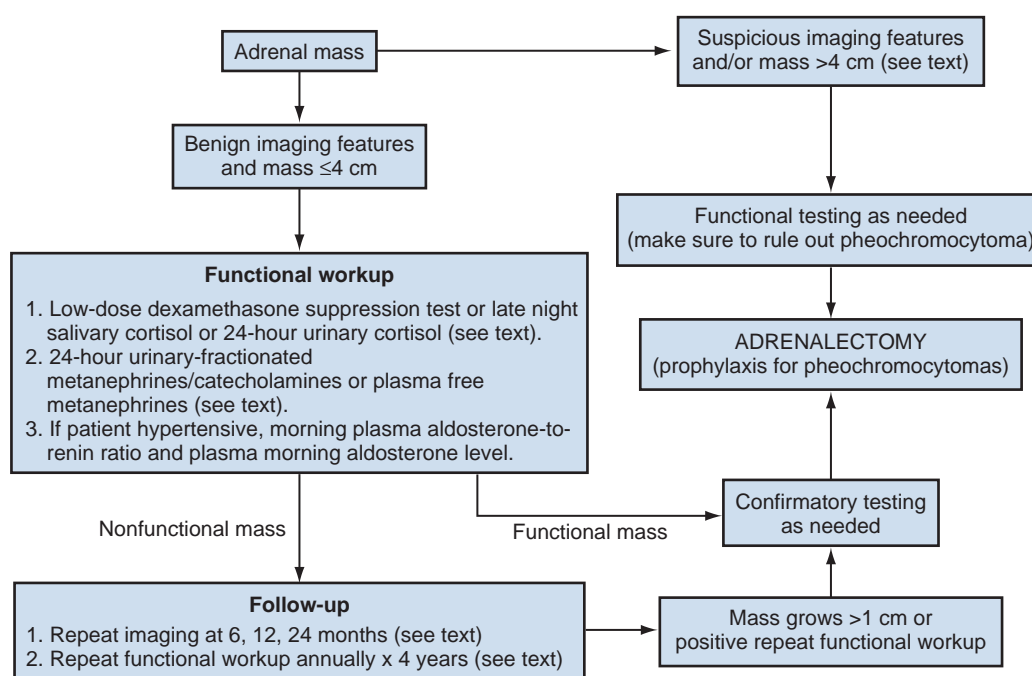


Figure 65-33. Management algorithm for newly diagnosed incidental adrenal mass.

BOX 65-6 Summary of Surgical Indications for Adrenalectomy

- Functional adrenal mass
 - Cortisol hypersecretion
 - Pheochromocytoma
 - Aldosterone hypersecretion
- Mass > 4 cm (see section on size and growth under [Imaging of Adrenal Masses](#)) with exception of myelolipoma
- Mass with imaging findings that are suggestive of malignancy (e.g., lipid poor, heterogeneous, irregular borders, infiltrates surrounding structures)
- Adrenal incidentaloma that grows more than 1 cm on follow-up imaging
- Extremely large and/or symptomatic myelolipoma (see section on [myelolipoma](#) under [Adrenal Lesions: Benign](#))
- Isolated adrenal metastasis (multidisciplinary decision making required)
- During renal surgery for renal cell carcinoma if:
 - Adrenal abnormal or not visualized because of large renal tumor size on imaging
 - Vein thrombus to level of adrenal vein
- Failed neurosurgical treatment of Cushing disease, necessitating bilateral adrenalectomy
- Select patients with ectopic adrenocorticotrophic hormone (ACTH) syndrome, requiring bilateral adrenalectomy
- ACTH-independent macronodular adrenal hyperplasia (AIMAH)
- Primary pigmented nodular adrenocortical disease (PPNAD)

a systematic multidisciplinary approach. With the urologist's advanced minimally invasive surgical skills, his or her comfort with both retroperitoneal anatomy and surgical approaches to retroperitoneal organs, and the close relationship between renal and adrenal pathophysiology, it is natural that the urologist participate in the evaluation of adrenal disorders and provide primary surgical management for these patients.

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The complete reference list is available online at www.expertconsult.com.

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Evolution of Adrenal Surgery

Surgical Anatomy

Clinical Indications for Adrenalectomy

Indications and Contraindications for Laparoscopic Adrenalectomy

Preoperative and Perioperative Management

Open Adrenalectomy

Laparoscopic Adrenalectomy

Robot-Assisted Adrenalectomy

Hand-Assisted Surgery

Laparoendoscopic Single-Site (LESS) Adrenalectomy

Natural Orifice Transluminal Endoscopic Surgery (NOTES)–Assisted
Laparoscopic Adrenalectomy

Partial Adrenalectomy

Outcomes

Complications

Ablative Therapy for Adrenal Tumors

Future of Adrenal Surgery

Surgery of the adrenal gland is usually performed to control endocrine derangement after failed medical management or to treat malignancies. The first open adrenal surgery was performed in the late 19th century, and over the last century various operative techniques and surgical approaches had been developed and refined. The late 20th and early 21st centuries ushered the entrance of minimally invasive techniques for surgery of the adrenal gland. Although minimally invasive techniques have largely supplanted the open approach, the essential surgical principles of adrenal surgery remain unchanged and the open approach is still vital in the management of large, invasive adrenal carcinoma. Moreover, all urologic surgeons must be familiar with open techniques in the event that emergent open conversion is necessary.

The evolution of adrenal surgery is far from over and the future remains exciting. Virtual reality, computer simulation, and three- or four-dimensional reconstruction techniques, with their incorporation into existing robotic platforms, promise to push adrenal surgery to greater heights. In addition, minimally invasive nonsurgical approaches such as percutaneous ablative techniques may obviate not only scars but also the skills of the surgeon. Nevertheless, it is important that the urologist remain in the treatment team, either as a direct practitioner of the technique or in direct consultation guiding therapy.

EVOLUTION OF ADRENAL SURGERY

The early history of adrenal surgery is obscure because of the confusing nomenclature, the rarity of adrenal neoplasms, the lack of accurate diagnosis, and the ignorance of hormonal presentations associated with adrenal disorders. Indeed, the commonly used term *hypernephroma* was first proposed by Grawitz (1883), who erroneously believed that these neoplasms arose from adrenocortical tissue within the kidney.

Knowsly Thornton was credited with performing the first successful adrenal surgery in 1889 on a 36-year-old hirsute woman

with a large abdominal mass (Thornton, 1890). Although Thornton was unaware of the adrenal origin of the patient's tumor, a 20-pound left adrenal malignant tumor was resected en bloc with her left kidney. Despite a stormy postoperative recovery complicated by subphrenic abscesses, she survived 2 years before tumor recurrence. Sargent performed the first planned adrenalectomy in 1914 for a large adrenal adenoma. The first adrenalectomy was performed via a T-shaped subcostal incision, and most of these early adrenal surgeries employed incisions used for renal surgeries. Consequently, these incisions were usually too low for optimal access to the adrenal gland. Therefore surgeons began to site their incisions progressively higher, usually involving resection of the 11th or 12th ribs. In 1927, Charles Mayo performed the first flank adrenalectomy for a tumor from a retroperitoneal nerve, which was subsequently found to be a pheochromocytoma (Mayo, 1927). In 1932, Broster utilized a transpleural, transdiaphragmatic approach through a long, posterior intercostal incision, providing excellent access for adrenalectomy (Broster et al, 1932).

The anterior approach permitted a full exploration of the abdominal cavity and is helpful in surgeries involving large tumors but has its associated disadvantages owing to entry into the peritoneum. Lateral or flank incisions provide excellent access, but bilateral pathology such as Cushing syndrome caused by adrenal hyperplasia requires patient repositioning to access the contralateral side. Young described a "hockey stick" posterior approach in 1936 to access both adrenal glands simultaneously (Young, 1936). Although excellent for resecting smaller bilateral tumors, surgical access was difficult for larger lesions. The thoracoabdominal incision for large retroperitoneal masses was first described by Chute and colleagues (1949).

The year 1991 marked the beginning of the era of minimally invasive adrenal surgery when Gagner performed the first laparoscopic transperitoneal adrenalectomy (Gagner et al, 1992). In 1992 Gaur developed the first device for balloon dilation of the retroperitoneum (Gaur, 1992), and in 1995 Mercan reported the first case of retroperitoneoscopic adrenalectomy (Mercan et al, 1995). The

first robot-assisted laparoscopic adrenalectomies were reported by [Piazza and coworkers \(1999\)](#) and [Hubens and associates \(1999\)](#). In recent years, several techniques such as laparoendoscopic single-site (LESS) adrenalectomy and natural orifice transluminal endoscopic surgery (NOTES)-assisted laparoscopic adrenalectomy have moved to the forefront of the quest for smaller incisions or even “scarless” adrenal surgery.

SURGICAL ANATOMY

The adrenal glands are paired retroperitoneal organs situated within the Gerota fascia, residing on the superomedial aspect of each kidney. The adrenal cortex can be readily differentiated from the surrounding adipose tissue by its characteristic bright chrome yellow color with a finely granular surface and firm consistency.

The right adrenal gland is pyramidal in shape and is usually more cephalad than the left. It is bordered by the bare area of the right lobe of the liver anteriorly, the vena cava medially, the duodenum anteromedially, the diaphragm and pleura posteriorly, and the upper pole of right kidney inferiorly ([Fig. 66-1](#)). Unlike the left adrenal gland, the right is often fixed in its position and does not move down when the kidney is retracted downward. The right adrenal gland derives its arterial supply through the superior, middle, and inferior adrenal arteries from the inferior phrenic artery, the abdominal aorta, and the renal artery, respectively. The right adrenal vein takes a short (1-cm) transverse route at an angle of 45 degrees to empty into the posterior segment of the inferior vena cava and is usually not exposed until the adrenal gland is mobilized. **Consequently, meticulous dissection of the right adrenal vein is essential to avoid nicking the inferior vena cava.** The right inferior phrenic vein and aberrant smaller veins that are found in 5% to 10% of right adrenal glands may drain into the right hepatic or renal vein. These veins should be recognized intraoperatively to avoid accidental ligation of the right renal vein ([Fig. 66-2](#)).

The left adrenal gland is crescentic in shape and is bordered by the abdominal aorta medially, the cardiac part of the stomach and the body of the pancreas anteriorly, the spleen superiorly, the kidney inferiorly, and the diaphragm and pleura posteriorly. The arterial supply of the left adrenal gland is identical to its right counterpart. The left adrenal vein takes a longer course of 2 to 3 cm, passing downward from the lower medial aspect of the gland, receiving the left inferior phrenic vein before draining into the left renal vein. Occasionally, the left adrenal vein empties into the left inferior phrenic vein before entering the left renal vein or courses over the aorta to enter the inferior vena cava directly. The longer course of the left adrenal vein facilitates venous control during left adrenalectomy.

The lymphatic drainage from the adrenal glands empties into the lateral aortic lymph node chain extending from the diaphragm

to the ipsilateral renal artery and may end in the thoracic duct or the posterior mediastinal nodes after piercing the crura of the diaphragm.

CLINICAL INDICATIONS FOR ADRENALECTOMY

In general, adrenalectomy is indicated in functional adrenal masses or suspected adrenal malignancy, either primary adrenal cortical carcinoma or solitary metastasis from nonadrenal sources, the most common being lungs, breasts, kidneys, and skin (melanomas). The indications for adrenalectomy are summarized in [Box 66-1](#).

The increased use of abdominal imaging such as ultrasonography or computed tomography (CT) has led to increased incidence

BOX 66-1 Indications for Adrenalectomy

FUNCTIONAL ADRENAL TUMORS

Aldosterone-secreting adenomas (Conn syndrome)
Cortisol-secreting adenomas (Cushing syndrome)
Pituitary-dependent Cushing disease unsuccessfully managed by transsphenoidal surgery
Bilateral adrenal hyperplasia
Pheochromocytomas
Adrenal androgens/estrogen-producing tumors causing virilization/feminization

NONFUNCTIONAL ADRENAL TUMORS

Histologically confirmed adrenal cortical carcinoma
Symptomatic adrenal masses such as cysts, myelolipomas
Incidentally discovered adrenal tumors (adrenal incidentalomas)
Size criteria:

- Incidentaloma ≥ 6 cm
- Incidentaloma between 4 and 6 cm and enlarging on serial imaging
- Incidentaloma < 4 cm that is rapidly enlarging (> 1 cm in 1 year)

Hounsfield criteria:

- > 10 HU in an unenhanced CT scan
- Enhancement washout of $< 50\%$ and delayed attenuation of > 35 HU

Solitary adrenal metastasis from nonadrenal primary

CT, computed tomography; HU, Hounsfield units.

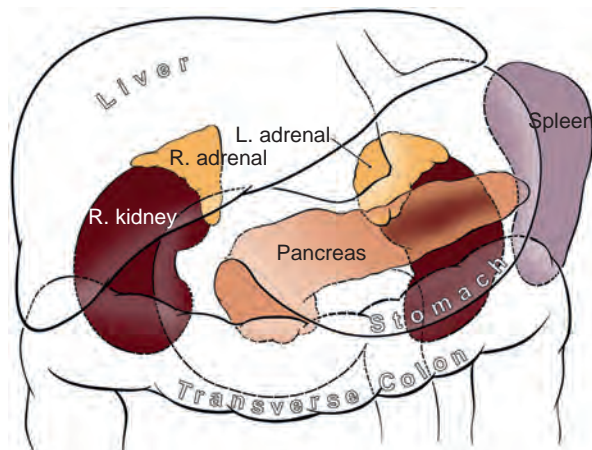


Figure 66-1. Regional anatomy of adrenal glands.

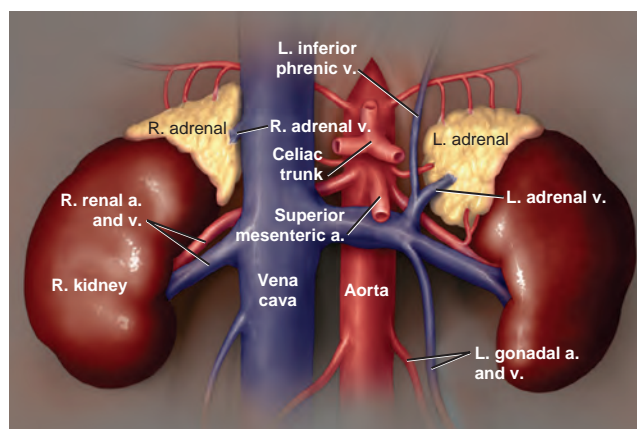


Figure 66-2. Vascular supply of adrenal glands.

of incidental adrenal masses. These adrenal “incidentalomas,” defined as any adrenal mass 1 cm or greater in diameter detected on radiologic imaging performed for indications other than primary adrenal disease, are reported in up to 4% of CT scans of the abdomen, with incidence increasing with age (Young, 2007). The size of an incidentaloma is a major determinant for surgical excision. Twenty-five percent of adrenal lesions greater than 6 cm are adrenal cortical carcinomas, and these larger lesions should be resected (NIH state-of-the-science statement, 2002). Risk of malignancy in lesions less than 4 cm is 2% and, if deemed low risk by imaging criteria, these lesions could be monitored. Approximately 6% of adrenal lesions between 4 and 6 cm are malignant, and surgical resection can be considered in appropriate individuals. Increase in lesion size of greater than 1 cm in 1 year is another consideration for adrenalectomy (National Comprehensive Cancer Network, 2014).

INDICATIONS AND CONTRAINDICATIONS FOR LAPAROSCOPIC ADRENALECTOMY

Over the last decade, there has been a slow paradigm shift from open adrenalectomy toward laparoscopic adrenalectomy for most adrenal lesions. There is a growing body of evidence from literature published by major laparoscopic centers around the world to indicate that laparoscopic adrenalectomy is replacing open adrenalectomy as the standard of care for surgical management of most adrenal lesions. The indications for laparoscopic adrenalectomy are summarized in Box 66-2.

Contraindications to laparoscopic adrenalectomy would be indications for open adrenalectomy (see Box 66-2). Although the current indications for open adrenalectomy are few, the choice of open approach over laparoscopic approach is dictated by the sur-

geon’s experience and expertise. A recent review of the Nationwide Inpatient Sample reported that in the United States, during the period of 1998 to 2006, the majority of adrenalectomies (83%) were still performed using the open approach, which occurred mainly in smaller nonteaching hospitals with an annual case volume of fewer than six cases per year (Murphy et al, 2010).

Absolute contraindications to adrenalectomy would include extensive metastatic disease, uncorrected coagulopathy, and severe cardiopulmonary disease that precludes anesthesia.

Past Surgical and Medical History

Previous abdominal surgeries may lead to intra-abdominal adhesions and scarring, which may render the laparoscopic approach difficult if not impossible. Siddiqui and coworkers (2010) reported an overall adhesiolysis rate of about 23% after any previous abdominal surgeries. However, this problem may be circumvented by modifying the laparoscopic approach according to the patient’s past surgical history. A retroperitoneal laparoscopic approach may be ideal in a patient with history of transperitoneal surgery while a transperitoneal laparoscopic approach may be the approach of choice in a patient with a previous flank, retroperitoneal surgery. Furthermore, Gill and colleagues (2001) have demonstrated the feasibility of a transthoracic laparoscopic approach that involves entering the thoracic cavity thoracoscopically and incising the diaphragm to approach the adrenal superiorly.

Conventionally, laparoscopic surgeries required the establishment of pneumoperitoneum that may lead to hemodynamic, metabolic, and neurologic adverse effects in patients with significant cardiopulmonary and neurologic diseases. Contraindications to establishment of pneumoperitoneum include patients with severe cardiac insufficiency, advanced chronic obstructive bronchitis, renal function insufficiency, acute glaucoma, recurrent spontaneous pneumothorax, vascular endocranial malformation, and hypertensive retinopathy. Giraudo and associates (2009) have described a gasless technique that made it possible for these patients to undergo laparoscopic adrenalectomy instead of the open approach.

Tumor Size

Large tumor size is considered a relative contraindication to laparoscopic adrenalectomy. A larger size increases the chance that the tumor is malignant and also distorts the regional anatomy, making laparoscopic resection more difficult. Although most laparoscopic surgeons are comfortable with tumor sizes of up to 6 to 7 cm, there is no clear upper limit to the size at which the laparoscopic approach would be contraindicated. However, available literature seems to suggest an arbitrary upper limit of about 10 to 12 cm in diameter (Henry et al, 2002; MacGillivray et al, 2002; Zografos et al, 2010). The studies by MacGillivray and colleagues (2002) and Zografos and coworkers (2010) showed no difference in short-term morbidity in patients with larger tumor sizes (≥ 6 to 8 cm) compared to those with smaller tumors. A point to note is that CT can underestimate the size of adrenal tumors by as much as 12% to 23% compared with actual size determined by pathologic examination (Lau et al, 1999).

In contrast, Hobart and colleagues (2000) noted increased operative time, blood loss, complication rates, and open conversion rates in larger tumors removed laparoscopically (mean 8 cm vs. 2.2 cm). However, they reported that operative time, blood loss, hospital stay, and complication rates were lower with laparoscopic adrenalectomy compared to open surgery. More recently, Bittner and coworkers (2013) reported similar findings in favor of laparoscopic adrenalectomy over the open approach in a larger cohort.

Conversion to open surgery has been found to be associated with size of tumor and infiltrative adrenal cortical carcinoma. MacGillivray and colleagues (2002) concluded that preoperative CT scanning can identify those infiltrative tumors that are likely to be invasive carcinoma. Bittner and coworkers (2013) found that a tumor size of greater than 8 cm increases the risk of open conversion during laparoscopic adrenalectomy significantly (by 14 times).

BOX 66-2 Indications and Contraindications for Laparoscopic Adrenalectomy

INDICATIONS

Functional adrenal tumors

- Aldosterone-secreting adenoma
- Cortisol-secreting adenoma
- Bilateral adrenal hyperplasia
- Pheochromocytoma

Symptomatic benign adrenal cyst or myelolipoma

Small incidentaloma without clinical or radiologic evidence of malignancy and local invasion

CONTRAINDICATIONS

Relative

Large tumor (>6 cm)

Localized adrenal cortical carcinoma without adrenal vein or vena caval involvement

Morbid obesity

Malignant pheochromocytoma

Virilizing adrenal tumor (70%-80% of these tumors are actually functional adrenal cortical carcinoma)

Significant abdominal adhesion

History of recurrent pyelonephritis

Pregnancy

Absolute

Local recurrence of a previously resected adrenal mass

Invasive adrenal cortical carcinoma with evidence of invasion of neighboring organs or renal artery or vena caval involvement

Severe cardiopulmonary disease

BOX 66-3 Oncologic Principles of Resection for Adrenal Cortical Carcinoma

1. No touch technique
2. Preservation of the intact peritoneum on the anterior surface of the adrenal gland if no evidence of invasion through the overlying peritoneal layer
3. En bloc resection of tumor with a wide margin of surrounding benign tissue outside the tumor capsule
4. Strict preservation of an intact tumor capsule
5. Exclusion of the remainder of the peritoneal cavity as much as possible using barriers such as laparotomy pads, plastic barriers, or drapes
6. Minimizing of bleeding and fluid spillage into the peritoneal cavity
7. Change of gloves, gowns, and instruments after removal of the tumor and prior to closure of the abdomen.

Modified from Porpiglia F, Miller BS, Manfredi M, et al. A debate on laparoscopic versus open adrenalectomy for adrenocortical carcinoma. *Horm Cancer* 2011;2:372–7.

Adrenal Cortical Carcinoma

Laparoscopic adrenalectomy in adrenal cortical carcinoma is currently controversial. In a consensus statement from the Third International Adrenal Cancer Symposium, the oncologic principles for resection of adrenal cortical carcinoma were outlined as summarized in [Box 66-3](#) ([Porpiglia et al, 2011](#)). Strict adherence to these principles of resection is difficult during laparoscopic adrenalectomy and thus the open approach seems to be the technique of choice. The thin tumor capsule is prone to rupture during inevitable manipulation of tumor during dissection, resulting in tumor spillage and subsequent recurrence. Furthermore, en bloc dissection of the retroperitoneal fat around the tumor is more difficult using laparoscopic techniques. However, this is often necessary because microscopic tumor extension cannot be accurately identified pre- and intraoperatively and there are currently no effective adjuvant treatments if margins are positive.

To determine whether the surgical approach for adrenal cortical carcinoma is a risk factor for peritoneal carcinomatosis, [Leboulleux and colleagues \(2010\)](#) reviewed 64 patients with stages I to IV disease with a median follow-up of 35 months. Of these, 58 patients underwent open adrenalectomy and 6 underwent laparoscopic adrenalectomy. The 4-year rate of peritoneal carcinomatosis was 67% for laparoscopic adrenalectomy and 27% for the open approach, with surgical approach being identified as the only risk factor. Data reported from the MD Anderson Cancer Center in 2005 showed similar outcomes with regard to increased risk of peritoneal carcinomatosis after laparoscopic adrenalectomy ([Gonzalez et al, 2005](#)). [Miller and coworkers \(2010\)](#) demonstrated in a retrospective review that 17 patients who underwent laparoscopic adrenalectomy showed significantly faster local recurrence time and higher rates of tumor spillage and positive surgical margins when compared to 71 patients who underwent open adrenalectomy. Although the local and overall recurrence rates were similar in both groups, they concluded that laparoscopic resection should not be attempted in patients with tumors suspicious for or known to be adrenal cortical carcinoma.

In contrast, a study from the German Adrenocortical Carcinoma Registry Group comparing 117 patients undergoing open adrenalectomy and 35 patients undergoing laparoscopic adrenalectomy for stages I to III adrenal cortical carcinoma showed no significant difference in disease-specific and recurrence-free survivals, tumor capsule violation, and peritoneal carcinomatosis ([Brix et al, 2010](#)). However, this study was limited by having more patients with higher stage tumors in the open adrenalectomy group, short follow-up duration, and incomplete data, especially on resection

margin status. [Porpiglia and colleagues \(2010\)](#) concluded that open and laparoscopic adrenalectomy may be comparable in terms of recurrence-free survival for patients with stages I and II adrenal cortical carcinoma based on a retrospective analysis of 43 patients. A major limitation of this study was that patients who had macroscopically incomplete resection, tumor capsule violation, open conversion from laparoscopic approach, and microscopic periadrenal fat invasion on postoperative pathologic examination were excluded, introducing significant selection bias. In addition, the follow-up period of less than 1 year in some patients is relatively short for diagnosis of tumor recurrence.

There is currently no consensus opinion on the role of laparoscopic adrenalectomy in adrenal cortical carcinoma. The 2014 National Comprehensive Cancer Network (NCCN) guidelines recommended open adrenalectomy for adrenal cortical carcinoma ([NCCN, 2014](#)). The Third International Adrenal Cancer Symposium ([Porpiglia et al, 2011](#)) suggested that **laparoscopic adrenalectomy can be considered in small incidentalomas, indeterminate large incidentalomas without necrosis or evidence of invasion, and small adrenal cortical carcinoma only if surgery is limited to referral centers with at least 20 cases of laparoscopic adrenalectomy per year and oncologic principles are adhered to, with avoidance of tumor violation and extraction of tumor without fragmentation.**

PREOPERATIVE AND PERIOPERATIVE MANAGEMENT

In general, preoperative management for adrenal surgery is similar to most general abdominal surgeries. Preoperative anesthetic consultation and optimization of the patient's medical conditions are essential. Mechanical bowel preparation and orogastric/nasogastric tube insertion are recommended in open or laparoscopic transperitoneal surgery and are optional for retroperitoneal approaches. The placement of a urinary catheter prior to surgery is helpful to measure urine output and to decompress the bladder. For functional tumors, special considerations are required ([Box 66-4](#)).

Pheochromocytoma

Excessive secretion of catecholamines from chromaffin tissue may result in tachycardia, diaphoresis, headache, hypertension, cardiac arrhythmias, left ventricular dysfunction, and impaired glucose tolerance. Preoperative cardiac workup, including electrocardiography and echocardiography, and assessment of hypertension-induced end-organ dysfunction are indicated. Preoperative sympatholytic therapy with α -adrenergic blockers for at least 2 weeks before surgery helps in both hemodynamic and glucose control and should be continued until the day of surgery. Phenoxybenzamine is time proven to be safe and effective but has its associated problems. Its nonselective nature may lead to tachycardia and β -adrenergic blockade may be necessary. Being an irreversible non-competitive α -adrenergic blocker, prolonged hypotension in the immediate postoperative period and central nervous system effects such as somnolence may be expected. Newer selective and competitive α_1 -adrenergic blockers such as doxazosin, prazosin, and terazosin obviate the drug-induced need for β -blockade. **β -Adrenergic blockade, if needed, must be given with caution in patients with myocardial depression and started only after phenoxybenzamine therapy.**

Intraoperatively, hypertensive episodes should be anticipated and can be controlled with intravenous drugs with rapid onset and short half-life such as nitroprusside, phentolamine, nitroglycerin, and nicardipine. Temporary cessation of surgical manipulation of the pheochromocytoma may be necessary. Short-acting β -blockers such as labetalol and esmolol are also good choices. Aggressive fluid management with volume repletion is necessary after removal of pheochromocytoma because hypotension can occur as a result of sudden loss of tonic vasoconstriction.

Postoperatively, fluid administration and use of vasopressors such as phenylephrine, guided by invasive monitoring, are useful

BOX 66-4 Preparation of Patients for Adrenal Surgery**PRIMARY ALDOSTERONISM**

Magnesium and potassium repletion
 Normalization of intravascular fluid status
 Blood pressure control
 Stress dose of cortisol

CUSHING SYNDROME

Inhibition of glucocorticoid production with metyrapone when there is severe manifestation
 Control of diabetes
 Preoperative antibiotics
 Cardiopulmonary workup
 Operative steroid administration

INCIDENTALOMAS

Anesthetic preparation for pheochromocytoma; 5% have normal diagnostic studies
 Full endocrinology workup

ADRENAL CARCINOMA

Consent for adjacent organ removal
 Failure to identify vena cava involvement

PHEOCHROMOCYTOMA

Preoperative catecholamine blockade
 Consider β -blockers if necessary
 Volume expansion
 Anesthetic consultation

Modified from Vaughn ED. Complications of adrenal surgery. In: Taneja SS, Smith RB, Ehrlich RM, editors. *Complications of urologic surgery: prevention and management*. 3rd ed. Philadelphia: Saunders; 2001. p. 363.

to manage hypotension. Electrolyte abnormalities and hypoglycemia should be corrected. It is not uncommon for patients to remain hypertensive postoperatively, and antihypertensive management should be continued.

Conn Syndrome

Primary hyperaldosteronism can lead to electrolyte and acid-base disturbances such as hypokalemia, hypomagnesemia, and alkalosis; fluid depletion or retention; refractory hypertension; and cardiac dysfunction and arrhythmias. These issues should be resolved preoperatively. An aldosterone antagonist (spironolactone) should be started at least 1 to 2 weeks before surgery, especially in patients on long-term angiotensin-converting enzyme inhibitors (Winship et al, 1999). Correction of hypomagnesemia may be indicated in cases of refractory hypokalemia. Diuretics or fluid repletion should be tailored according to fluid status. If bilateral adrenal manipulation or resection is planned, a stress dose of cortisol should be considered preoperatively and continued for 24 hours.

Postoperatively, monitoring of electrolytes should be continued regularly because hypokalemia may persist for up to a week after surgery. Persistent hypertension requires pharmacologic treatment, and a temporary or permanent mineralocorticoid or glucocorticoid might be necessary in patients with bilateral adrenalectomy.

Cushing Syndrome

Hypercortisolism can lead to obesity, hypertension, diabetes, myopathy, hypokalemia, fluid retention, and cardiac dysfunction. Obesity is associated with obstructive sleep apnea and may result in airway

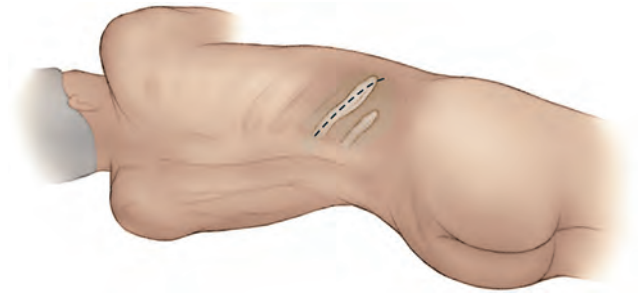


Figure 66-3. Surgical incision over 11th rib for flank adrenalectomy. The patient is in flexion, with the kidney rest deployed to maximally expose the right retroperitoneum.

and ventilatory problems during anesthesia. Myopathy and intestinal motility abnormalities can result in postoperative respiratory problems and aspiration pneumonia. Preoperative anesthetic and cardiopulmonary consultations should be sought. Preoperative optimization of fluid status, blood pressure, and glucose control and correction of electrolyte abnormalities are necessary. Use of spironolactone or inhibitors of steroid production such as mitotane and aminoglutethimide can be considered. Proton pump inhibitors and prokinetics such as metoclopramide can be considered to reduce risk of aspiration.

Postoperatively, patients must be monitored for respiratory depression. Epidural analgesia is recommended to minimize use of systemic opiate analgesia, which can lead to respiratory depression. Breathing exercises should be initiated early, and nonsteroidal analgesics can be considered. In patients with bilateral adrenalectomy, steroid replacement therapy should be initiated at the time of tumor resection and continued postoperatively. Cardiovascular instability and electrolyte abnormalities can occur and must be monitored.

OPEN ADRENALECTOMY

Open adrenalectomy can be broadly classified into transperitoneal and retroperitoneal approaches. Transperitoneal approaches include the anterior transabdominal and thoracoabdominal approaches, where the main advantages lie in excellent surgical exposure and better access to the hilum and great vessels, at the expense of higher risk of intra-abdominal organ injury and ileus. Retroperitoneal approaches include the flank and posterior lumbodorsal approaches, which result in a smaller operative field but are associated with less ileus and shorter hospitalization. In addition, the retroperitoneal approach is ideal for the morbidly obese patient in whom the abdominal panniculus will fall forward in a flank or prone position.

Flank Retroperitoneal Approach

Positioning. The patient is placed in the lateral decubitus position with the side with adrenal pathology up. The table is flexed at the level of the costal margin and a kidney rest is employed to maximize the distance between the costal margin and the iliac crest. An axillary roll is placed under the axilla with the arm closest to the table extended secured on an armboard and the upper arm slightly flexed at the elbow and placed on an elevated arm rest. The lower leg is flexed and the upper leg straight with pillows placed between them. All bony prominences are padded and the patient is secured to the operating table.

Incision. The course of the 11th rib is palpated and the incision is made along the rib as shown in Figure 66-3. The latissimus dorsi, external and internal oblique, and transversus abdominis muscles overlying the rib are divided until the anterior surface of the rib is exposed (Fig. 66-4).

11th Rib Excision. The anterior periosteum of the rib is scraped off using the periosteal elevator and the periosteum on the superior

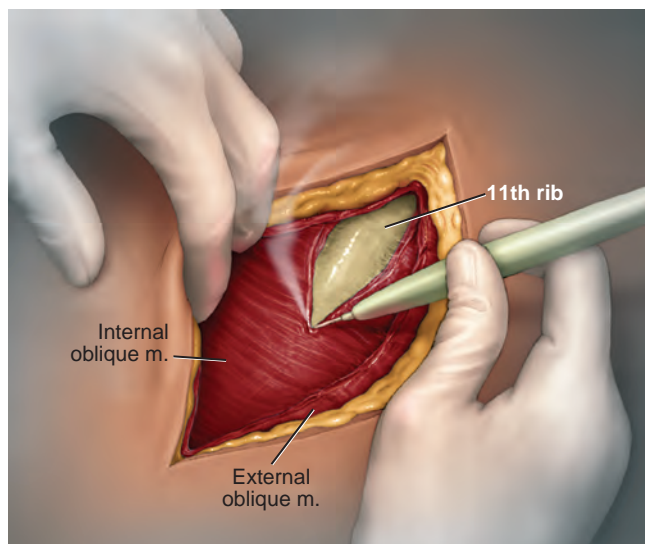


Figure 66-4. Flank approach. Incision of muscle overlying 11th rib.

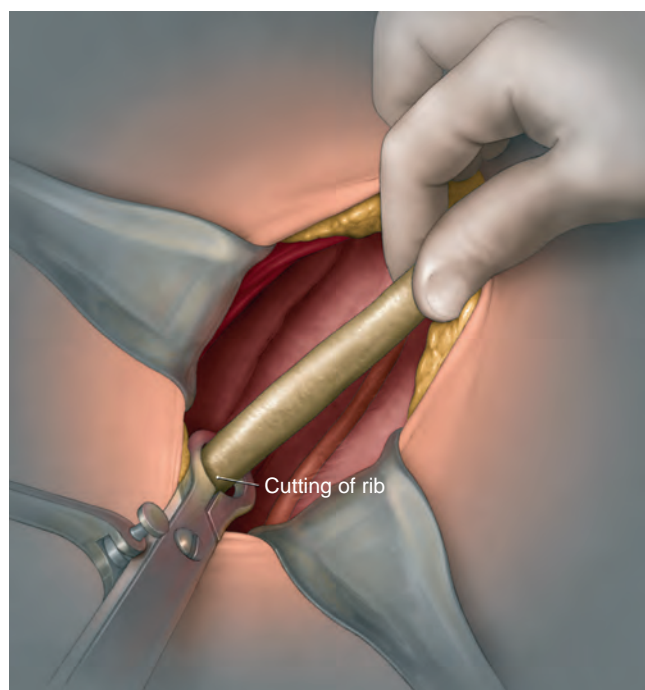


Figure 66-5. Flank approach. Excision of 11th rib.

and inferior aspects of the rib is visualized. The periosteum posterior to the rib can be scraped off in a similar manner with the periosteal elevator, taking care not to injure the neurovascular bundle that runs along the inferior aspect of the rib. After stripping the periosteum from the tip of the rib back to the paraspinal muscles, the 11th rib is cut with the rib cutter (Fig. 66-5). The rib stump is then smoothed with a rongeur and hemostasis is secured with the aid of cautery or bone wax. The neurovascular bundle is then freed athermally to avoid injury during subsequent dissection and closure (Fig. 66-6).

Creating the Retroperitoneal Space. The lumbodorsal fascia is entered and blunt dissection is used to dissect the peritoneum off the transverse fascia anteriorly. The muscles are divided and the plane between the Gerota fascia and the peritoneum is identified. This plane is then maximally developed with blunt dissection, reflecting the peritoneum anteromedially. A plane between the diaphragm and retroperitoneum is then developed, facilitating entry

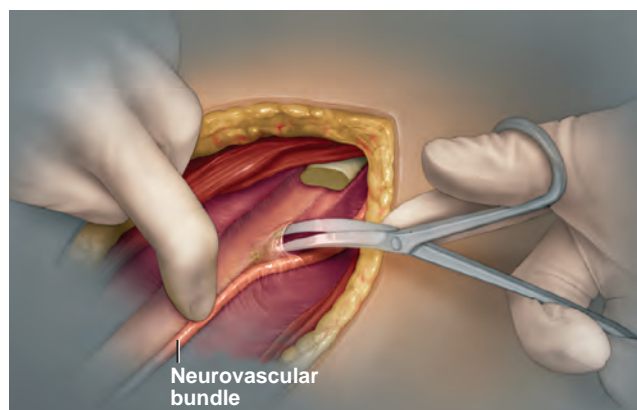


Figure 66-6. Flank approach. Mobilization of the intercostal neurovascular bundle from the 11th rib. This is performed with a combination of blunt dissection with a Kittner dissector and sharp dissection with Metzenbaum scissors.

into the retroperitoneal space. Once the peritoneum is fully mobilized, the vena cava or aorta can be visualized. Further cephalad dissection will expose the adrenal gland and renal vein. Self-retaining retractors can now be placed with maximal exposure.

Dissection of Adrenal Gland. On the right side, dissection typically starts with the division of the peritoneal layer overlying the vena cava, along the medial border of the gland. The plane between the medial surface of the adrenal gland and the lateral vena cava is then bluntly dissected to expose the adrenal vein. The adrenal vein is then isolated with the aid of a right-angle instrument such as a Mixer forceps. The adrenal vein can then be ligated between silk ties or surgical clips. In the event of accidental avulsion of the vein resulting in hemorrhage from the vena cava, vascular control of the vena cava proximal and distal to the tear by vessel clamps or sponged forceps can be applied. The tear can then be repaired in the usual manner with 4-0 or 5-0 Prolene sutures (Ethicon, Cincinnati, OH).

The adrenal gland can now be dissected out starting with its superior attachments. Care must be taken to handle the friable adrenal gland via its surrounding adventitia to avoid tissue spillage, seeding, or autotransplantation. Actual arterial branches to the gland usually are not identified but can be safely cauterized during dissection of the gland. Clips or surgical ties should be employed if any vessels are identified. Inferomedial attachments to the kidney are then taken with sharp dissection or cautery and the freed adrenal gland is removed from the surgical field. Dissection of the left adrenal gland is similar except that the aorta is encountered and the left adrenal vein runs a longer course, typically originating from the renal vein.

Closure. After ensuring good hemostasis of the adrenal bed, the incision is closed in two layers with a running looped polydioxanone suture. The deeper layer consists of the transverse abdominal and internal oblique muscles and fascia and the outer layer consists of the external oblique muscle and fascia. Skin closure can be completed with staplers or absorbable/nonabsorbable sutures.

Posterior Lumbodorsal Approach

The posterior approach is the most direct route to the adrenal glands and no major muscles are divided, thus reducing dissection required to expose the adrenal glands. The prone position allows for ready access to both adrenal glands through two separate incisions. However, surgical exposure is limited and hence is usually reserved for smaller tumors or bilateral adrenal hyperplasia. In addition, access to the adrenal vein and great vessels is more difficult, which may be problematic in the event of excessive intraoperative bleeding. Finally, the prone position increases ventilatory difficulties. **This approach should not be used for large tumors or adrenal cortical carcinoma.**



Figure 66-7. Posterior approach—possible locations for lumbodorsal incisions.

Positioning. The patient is positioned in a prone position after intubation, with the operating table flexed at the level of the 12th rib. Pillows are placed under the abdomen and lower limbs and care is taken to avoid compression on the eyes in the prone position.

Incision and Rib Excision. Incisions can be made along the course of the 11th or 12th rib, or a hockey stick incision made about 5 cm lateral to the midline of the vertebral column, progressing downward and outward in a curvilinear fashion at the level of 10th rib, extending over or slightly below the 12th rib toward the iliac crest (Fig. 66-7). The technique of 12th rib excision on the right side is as follows. After the skin incision, division of the subcutaneous tissue and the latissimus dorsi and sacrospinalis muscles in layers exposes the 12th rib. The sacrospinalis is retracted medially and its attachment to the 12th rib is divided. Sequential division of the lumbodorsal fascia and then the posterior subcostal ligament releases the pleura from the 12th rib. The pleura dips below the 12th rib in the region of the costovertebral angle and may be perforated if the rib is elevated near the vertebral column. The 12th rib is then excised in a fashion similar to that described in the earlier section on the Flank Retroperitoneal Approach, with careful preservation of the neurovascular bundle. The 11th rib is then retracted upward to expose the retroperitoneum. If a bilateral procedure is undertaken, a Finochietto retractor can be used to assist in bilateral exposure (Fig. 66-8).

Dissection of Adrenal Gland. With division of the final hepatic attachments, the adrenal gland and the vena cava are visualized. The right adrenal vein is identified at its posterolateral origin and ligated between clips or ties. The arterial branches are then ligated and the adrenal gland is mobilized posteriorly away from the paraspinal muscles and dissected out, starting superiorly and progressing caudally.

Anterior Transabdominal Approach

The anterior transabdominal approach is indicated in cases of large or potentially malignant tumors for which adequate expo-

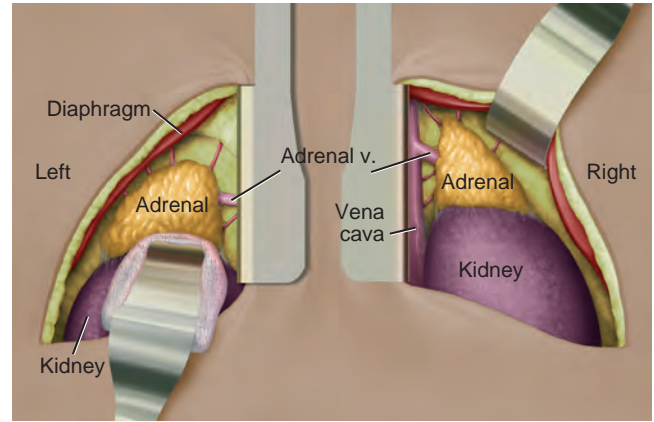


Figure 66-8. Bilateral posterior approach—anatomic relations to the adrenal gland as seen from behind.

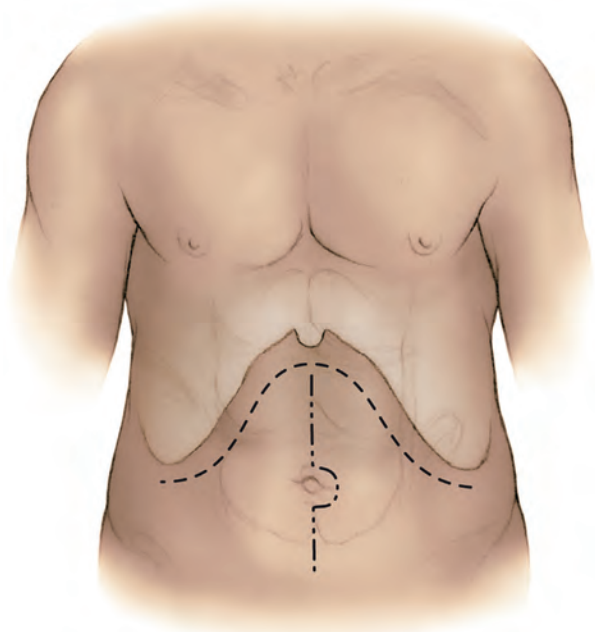


Figure 66-9. Anterior approach. The transperitoneal approach may be attempted through a midline incision or subcostal incision. The subcostal incision can be extended into a full chevron for bilateral adrenalectomy or if a large unilateral tumor is encountered.

sure for extensive dissection is needed. It is also mandatory in cases of inferior vena caval or extensive nodal involvement. The anterior transabdominal approach may be attempted through a subcostal, chevron, or midline approach (Fig. 66-9). The subcostal or chevron incision provides better exposure of the superior and lateral aspects of the adrenal gland than the midline approach. The midline approach is generally reserved for cases in which an extra-adrenal pheochromocytoma is suspected along the great vessels or in the pelvis.

Left Adrenalectomy

Positioning and Incision. The patient is positioned supine with a body roll placed under the back at the level of the costal margin to accentuate the costal margin. For left adrenalectomy, the skin incision is made two fingerbreadths below the costal margin and

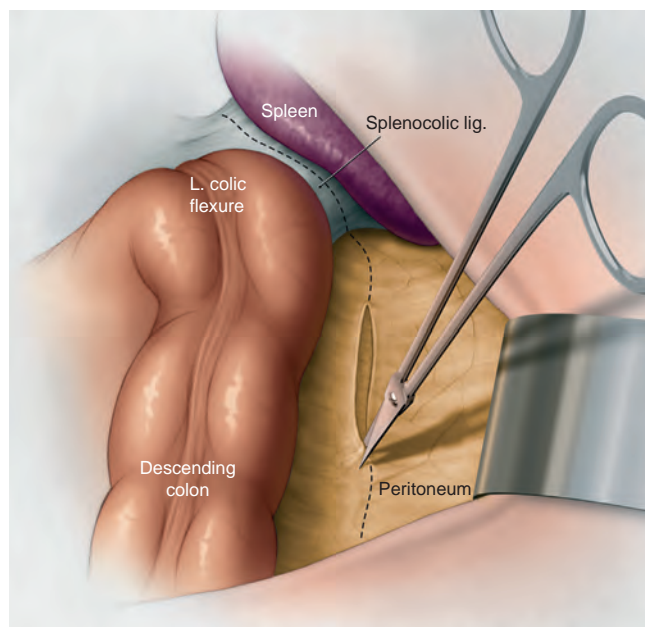


Figure 66-10. Anterior approach. Peritoneum lateral to the left colon is incised at the line of Toldt and extended cephalad to the splenocolic ligament and inferiorly.

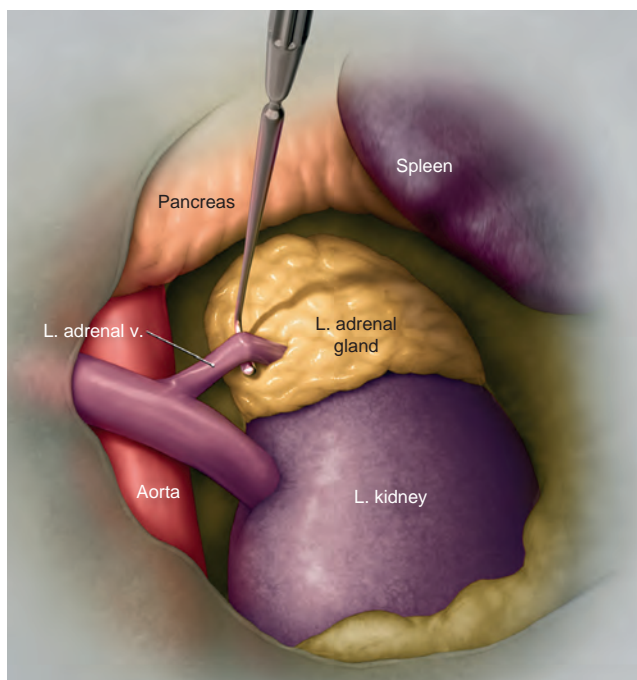


Figure 66-11. Anterior approach. The left adrenal vein is dissected out and ligated.

extends medially to the midline. The external oblique, internal oblique, and transverse abdominal muscles are divided laterally and the rectus muscle and sheath are divided medially. The peritoneum is entered with sharp dissection and the falciform ligament is ligated.

Approach to Left Adrenal Gland. There are four different approaches to the left adrenal gland:

- Through the gastrocolic ligament
- Through the lienorenal ligament
- Through the transverse mesocolon
- Through the lesser omentum

The lienorenal ligament approach is described here. The line of Toldt is incised and the descending colon is mobilized medially. The splenic flexure is then taken down by dividing the splenocolic ligament (Fig. 66-10). Subsequent division of the lienorenal ligament and opening of the retroperitoneum along the inferior border of the pancreas will allow superior retraction of the spleen and pancreas with exposure of the left adrenal vein. The left adrenal vein is identified as it courses from the inferomedial border of the left adrenal gland into the left renal vein, and is ligated and divided (Fig. 66-11). The medial attachments to the aorta can now be taken either with monopolar diathermy on a long right-angle instrument or with a harmonic scalpel while applying gentle lateral traction on the gland. The lateral and inferior attachments to the kidney are taken by blunt and sharp dissection off the renal capsule, taking care to avoid the vasculature to the renal upper pole.

Closure. Closure of the incision is performed with a running No. 1 polydioxanone suture in two layers. The deep layer consists of the transverse abdominal muscle, transverse fascia, internal oblique muscle and fascia, and posterior rectus sheath. The superficial layer consists of the external oblique muscle and fascia and the anterior rectus sheath.

Right Adrenalectomy

After entering the peritoneum, the hepatic flexure is mobilized inferiorly and the liver is retracted superiorly. The Kocher maneuver is performed to mobilize the second part of the duodenum sharply, and the inferior vena cava is exposed (Fig. 66-12). The rest of the dissection is similar to that on the left side.

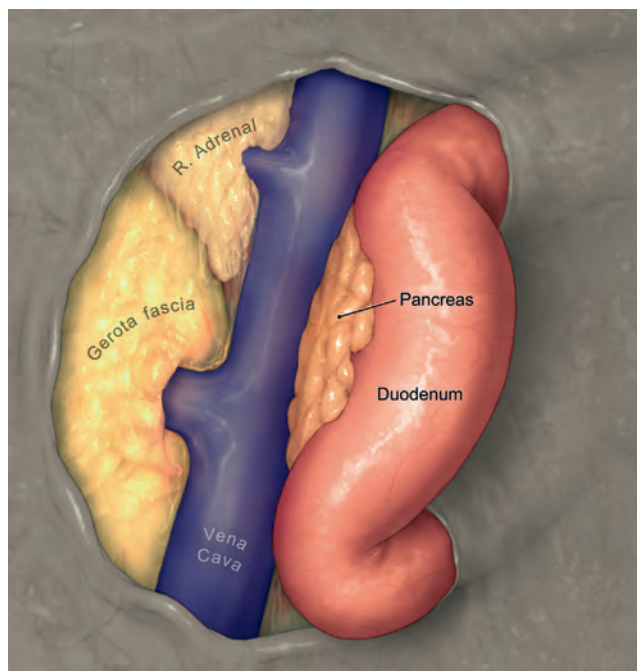


Figure 66-12. Kocher maneuver. The peritoneum is incised, and sharp dissection and blunt dissection are used to mobilize the second stage of the duodenum away from the renal hilum.

Thoracoabdominal Approach

The thoracoabdominal approach offers the best surgical exposure of the retroperitoneum, adrenal gland, and great vessels but may cause more morbidity, such as incisional pain, pulmonary morbidities, phrenic nerve injury during division of the diaphragm, and the need for a chest tube. This approach is generally reserved for large and invasive tumors with extensive involvement of surrounding structures or vena cava that cannot be safely removed.

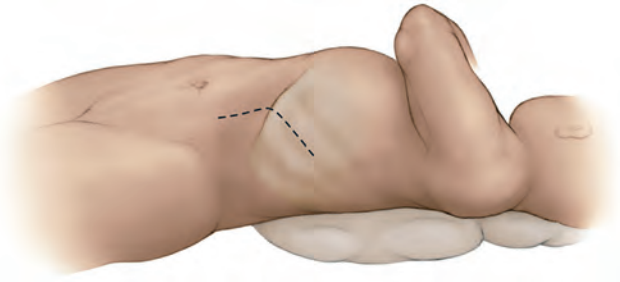


Figure 66-13. Positioning for thoracoabdominal surgery. A body roll elevates the flank on the side of surgery, and the arm and shoulder are rotated away, supported by a sling.

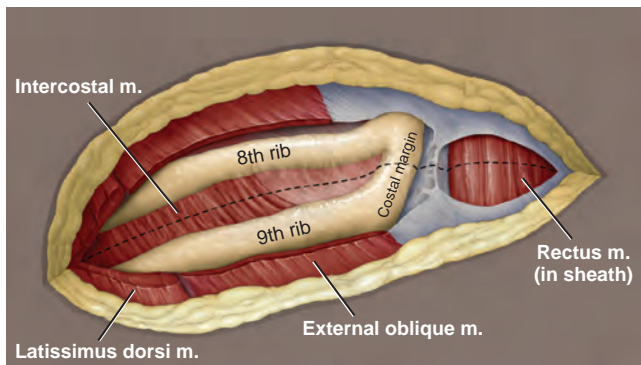


Figure 66-14. Thoracoabdominal approach. Incision at the eighth intercostal space. The costal margin, external intercostal muscle and fascia, and anterior rectus sheath are divided.

via the anterior transabdominal approach. The thoracoabdominal approach is particularly useful in right-sided tumors since the liver and inferior vena cava can limit exposure whereas, on the left side, the spleen and pancreas can generally be elevated to provide adequate exposure.

Positioning. The patient is placed in a semioblique position at an angle of 45 degrees to the table with the operating side upward and the opposite side decubitus. A body roll or pillow is placed longitudinally along the hemithorax and flank to achieve and maintain this position. The ipsilateral arm is placed across the chest on a padded arm rest and the other arm is secured to an armboard (Fig. 66-13).

Incision and Dissection of Adrenal Gland. The incision is made along the eighth or ninth intercostal space extending from the posterior axillary line and curving over the costal margin into the abdomen (Fig. 66-14). The latissimus dorsi, serratus anterior, and intercostal muscles are divided. The costal cartilage is then divided with cautery and the incision is carried through the anterior and posterior rectus sheaths and the rectus abdominis muscle. The pleura is entered along the superior margin of the rib to avoid injury to the neurovascular bundle and the lung is packed away (Fig. 66-15). The diaphragm is divided in a circumferential fashion along its periphery. The surgeon must not cut directly to the center of the diaphragm because the phrenic nerve can be damaged. Marking sutures can be placed on either side of the divided diaphragm to aid alignment during closure. Once the diaphragm is divided, a Finochietto self-retaining retractor is placed. The rest of the dissection is similar to the previously described techniques. The relationship of the thoracoabdominal incision to the adrenal gland is illustrated in Figures 66-16 and 66-17.

Closure. A chest tube is placed and the diaphragm is closed with either running suture or interrupted figure-of-eight stitches with nonabsorbable sutures. In order to take tension off the diaphragmatic closure, the ribs should be reapproximated with several

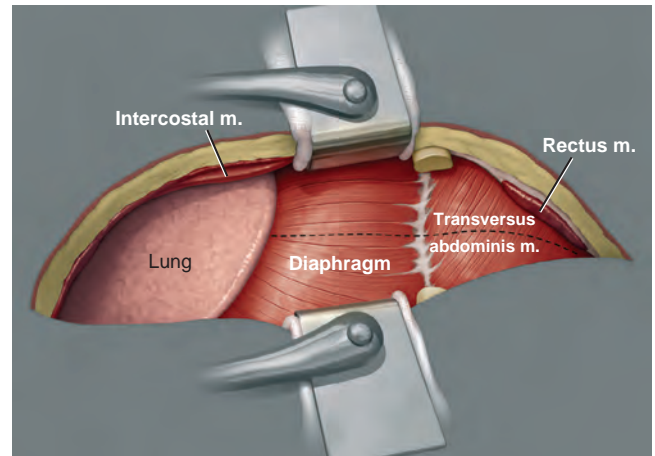


Figure 66-15. Thoracoabdominal approach. The Finochietto retractor is placed to expose the anatomy. The lung visible in this view is packed away with laparotomy sponges.

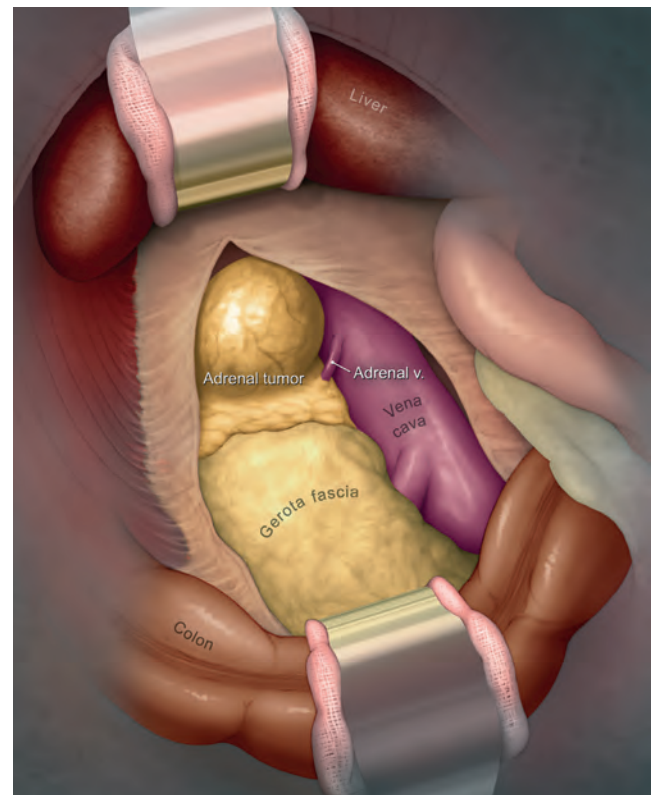


Figure 66-16. Thoracoabdominal approach. Exposure of the adrenal.

interrupted No. 0 chromic sutures on blunt-tip liver needles around the superior border of the eighth rib and inferior border of the ninth rib. A No. 0 Prolene suture is placed through the cut costal cartilage to bring the costal margin together, followed by closure of the serratus anterior and latissimus dorsi muscles in two layers. The chest tube is then placed to a water seal and suction.

LAPAROSCOPIC ADRENALECTOMY

Transperitoneal Approach

Transperitoneal laparoscopic adrenalectomy can be performed with the patient in a supine or lateral position. In general, the

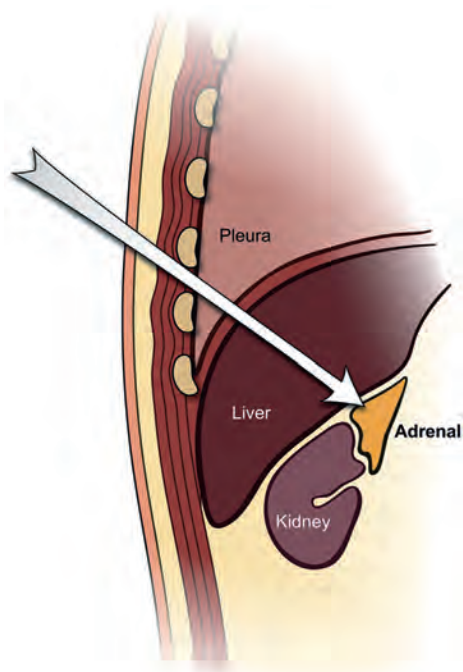


Figure 66-17. Demonstration of the route of surgical dissection via thoracoabdominal incision.

transperitoneal approach allows for a greater working space and a better visualization of the operative field and surrounding anatomic structures as compared to the retroperitoneal approach. The lateral transperitoneal approach allows for a greater working space as gravity aids in moving the bowels away from the surgical field. The supine approach permits bilateral adrenalectomy without repositioning the patient. However, more dissection and retraction of surrounding organs are generally needed with the supine approach, so it is usually reserved for bilateral adrenalectomy.

Transperitoneal Lateral Approach: Left Adrenalectomy

Positioning and Ports Placement. After general anesthesia, a urinary catheter and a nasogastric tube are inserted to decompress the bladder and the stomach. The patient can be positioned in either a full lateral position with the operating side upward or a modified lateral position angled at 45 to 60 degrees. The table can be straight or minimally flexed to increase the distance between the costal margins and the iliac crest. Care should be taken to avoid excessive flexion because this may lead to neuromuscular problems and decreased venous return. All bony prominences must be adequately padded and the patient strapped in position.

The initial 10-mm camera port can be inserted either with the open technique or with the aid of the Veress needle. After insufflation of the abdomen with CO₂, two or three other trocars are inserted under vision in the configuration shown in Figure 66-18. The 5-mm port at the anterior axillary line can be replaced with a 10- to 12-mm port for larger instruments and ease of specimen retrieval. The splenic flexure may need to be mobilized prior to insertion of this port. The optional fourth 2- or 5-mm port may be inserted to aid retraction in difficult dissection.

Mobilization of Colon and Spleen. The line of Toldt is incised and the colon is mobilized inferiorly (Fig. 66-19). The splenocolic and lienorenal ligaments are incised toward the diaphragm to the level of the gastric cardia, allowing for full medial rotation of the spleen away from the surgical field. Care should be taken to avoid injury to the stomach and diaphragm at this stage. A sudden loss of pneumoperitoneal pressure with increases in ventilation pressures may signify diaphragmatic perforation. With the spleen

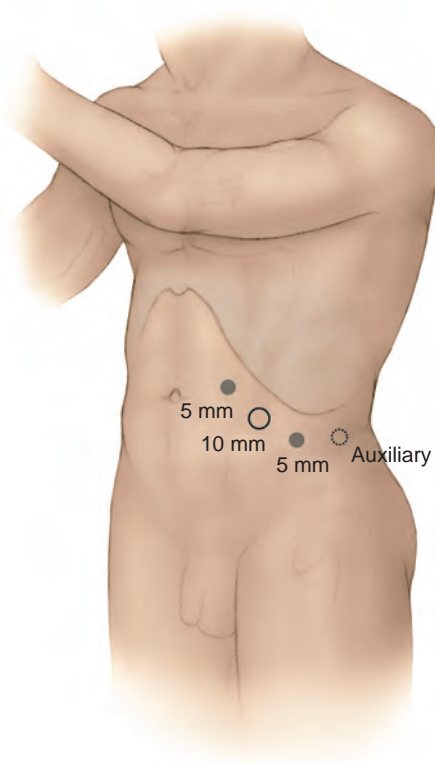


Figure 66-18. Four-trocar configuration for left transperitoneal laparoscopic adrenalectomy.

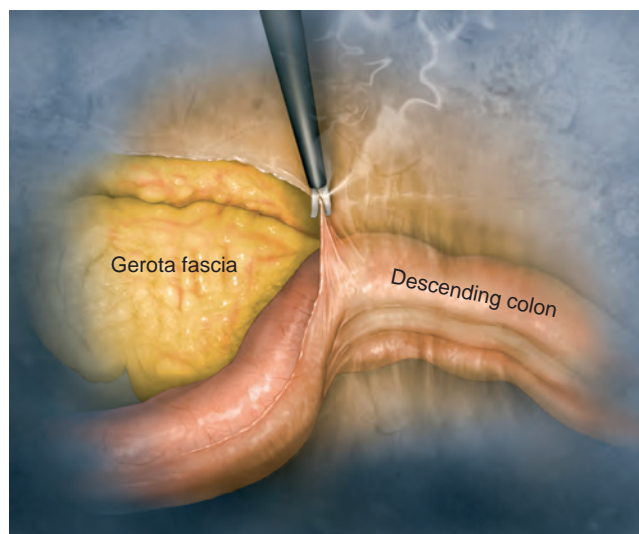


Figure 66-19. Transperitoneal laparoscopic adrenalectomy. Incision of the line of Toldt and medial dissection of the left colon with cautery endoscopic scissors.

rotated away and the tail of the pancreas dissected off, the left adrenal gland will come into view. Occasionally, especially in patients with Cushing syndrome, dense retroperitoneal fat may obscure the adrenal gland. A laparoscopic ultrasound probe can be inserted through the 10- to 12-mm port for localization of the adrenal gland.

Ligation of Left Adrenal Vein and Mobilization of the Left Adrenal Gland. The left renal vein is identified and traced along its superior border to reach the point of entry of the left adrenal

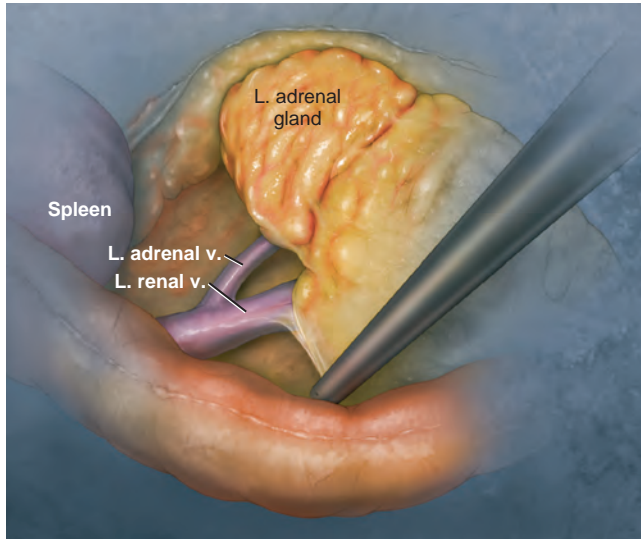


Figure 66-20. Transperitoneal laparoscopic adrenalectomy. Exposure and dissection of the renal vein and left adrenal vein.

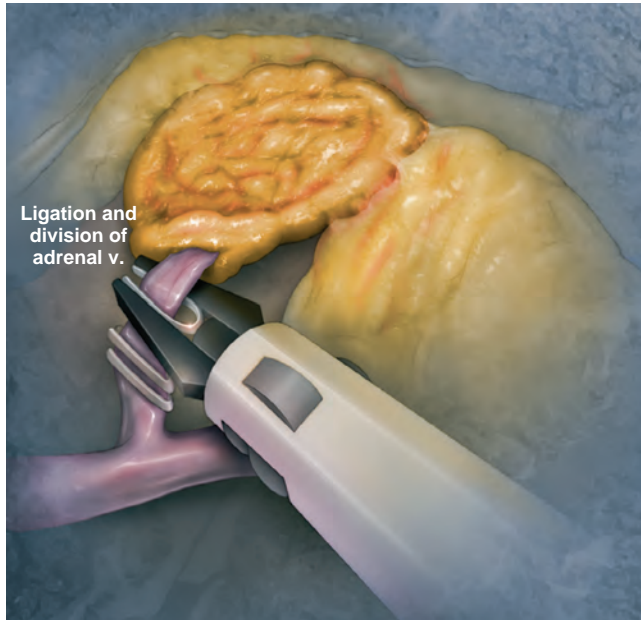


Figure 66-21. Transperitoneal laparoscopic adrenalectomy. Ligation and division of left adrenal vein.

vein (Fig. 66-20). The left adrenal vein is carefully isolated and ligated. It is advisable to place at least two clips on the stay side of the adrenal vein (Fig. 66-21). Care has to be taken to avoid any upper pole branch of the left renal artery, which may lie behind the adrenal vein. It is also important to recognize that the inferior phrenic vein may occasionally join the adrenal vein prior to its entry into the left renal vein. The adrenal arterial supply is divided either with cautery or a harmonic scalpel as the adrenal is dissected free (Figs. 66-22 and 66-23). Grasping on the adrenal gland should be avoided as the gland is fragile and tears easily, leading to increased intraoperative bleeding.

Closure. Once the adrenal gland is freed, it is placed in an endoscopic bag and removed via the 10- to 12-mm port (Fig. 66-24). Pneumoperitoneal pressure is reduced to 5 mm Hg and the surgical bed inspected for hemostasis. All port sites larger than 5 mm are closed in layers with fascial approximation and skin closure.

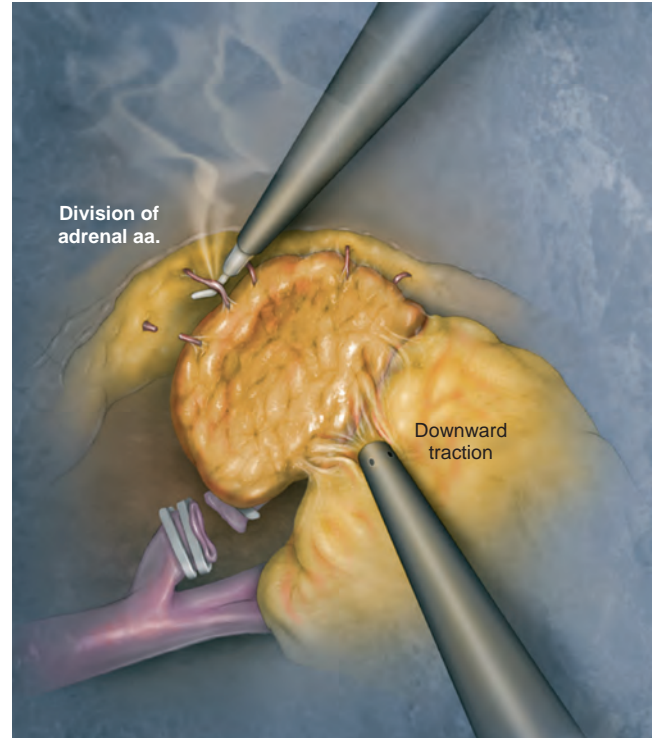


Figure 66-22. Transperitoneal laparoscopic adrenalectomy. Division of adrenal arterial supply and superomedial dissection with downward traction on the kidney.

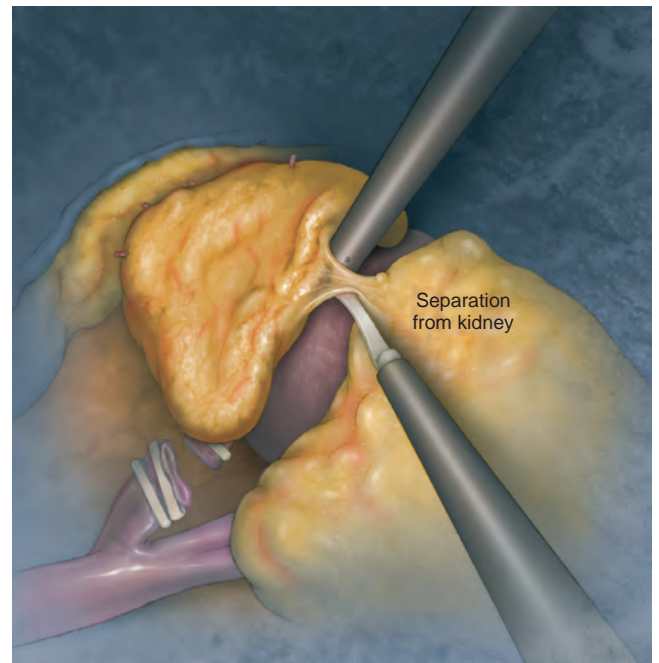


Figure 66-23. Transperitoneal laparoscopic adrenalectomy. The adrenal gland is mobilized off the medial aspect of the kidney.

Transperitoneal Lateral Approach: Right Adrenalectomy

The port configuration for transperitoneal laparoscopic lateral right adrenalectomy is shown in Figure 66-25. An additional 2- or 5-mm port sited most superomedially is used for liver retraction. After creation of pneumoperitoneum, the first step is to mobilize the liver by dividing the triangular ligament laterally and inferiorly. The liver

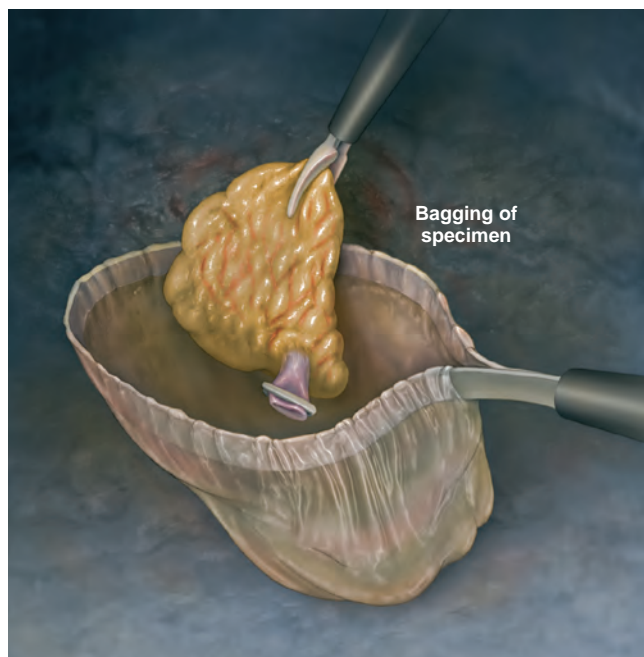


Figure 66-24. Transperitoneal laparoscopic adrenalectomy. Placement of specimen in endoscopic extraction sac.

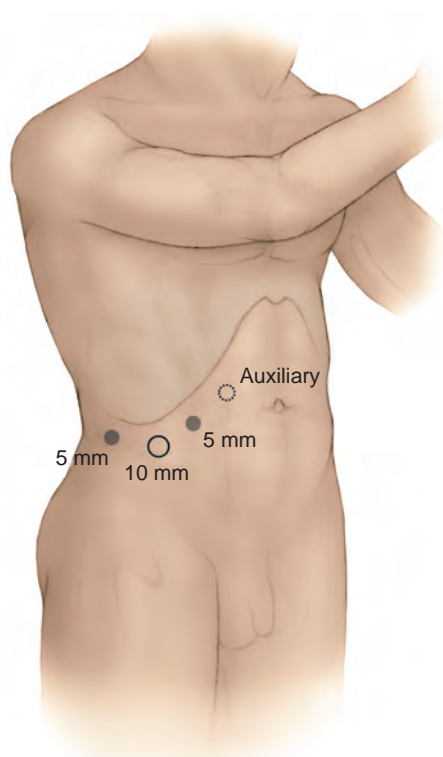


Figure 66-25. Four-trocar configuration for right transperitoneal laparoscopic adrenalectomy. Auxiliary site can be used for liver retraction.

is then retracted anterosuperiorly using the shaft of a 2- or 5-mm laparoscopic ratcheted locking forceps (Fig. 66-26). The lateral parietal peritoneum is grasped by the forceps, creating an assistant-free self-retaining retraction of the liver. A Kocher maneuver is then performed to mobilize the second part of the duodenum. This permits the visualization of the inferior vena cava and the right

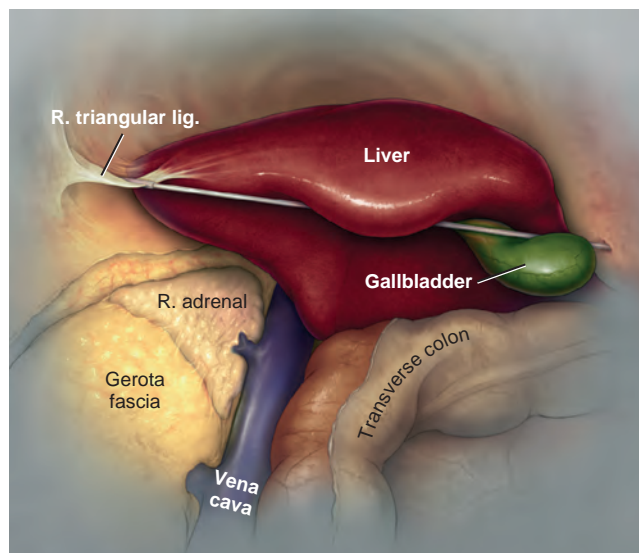


Figure 66-26. A 2-mm trocar and locking grasping forceps can be used instead of a larger-caliber fan retractor to act as a self-retaining liver retractor. It is important that the trocar be placed just below the xiphoid process to ensure adequate retraction.

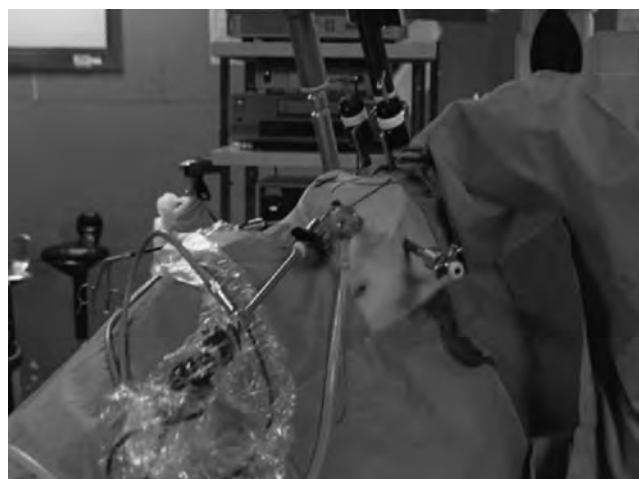


Figure 66-27. The LaparoTenser (L&T Lucini, Milan, Italy). (From Giraudo G, Pantuso G, Festa F, et al. Clinical role of gasless laparoscopic adrenalectomy. *Surg Laparosc Endosc Percutan Tech* 2009; 19:329–32.)

adrenal gland. The rest of the dissection is similar to that described on the left side.

Gasless Laparoscopic Transperitoneal Approach

Pneumoperitoneum is associated with several negative hemodynamic, metabolic, neurologic, and humoral effects. These include decreased venous return and cardiac output, elevated systemic arterial blood pressure, increased inspiratory and expiratory airway pressures and end-tidal carbon dioxide levels, decreased renal blood flow, and possible gas embolism. Pneumoperitoneum is thus contraindicated in certain groups of patients with preexisting cardiac, pulmonary, or neurologic diseases.

Giraudo and colleagues (2009) described their gasless laparoscopic adrenalectomy techniques using an abdominal wall lifting platform. The LaparoTenser (L&T Lucini, Milan, Italy) (Fig. 66-27) was used as an abdominal wall retractor, with two curved needles

(Aghi Pluriplan) placed in the subcutaneous tissue of the anterolateral abdominal wall. The intraperitoneal space was created by lifting of the abdominal wall, which eliminates the need for pneumoperitoneum. Three or four trocars are then inserted and dissection of the adrenal gland proceeds in a manner similar to that described earlier. The main suggested benefit of this technique is that it allows laparoscopic transperitoneal adrenalectomy to be performed as an alternative to open surgery in patients with contraindications to pneumoperitoneum.

Retroperitoneal Approach

Laparoscopic retroperitoneal adrenalectomy can be performed using either the prone or the lateral approach. The main advantage of the retroperitoneal approach is that entry into the peritoneum is avoided and thus complications such as visceral and bowel injuries are minimized. In the absence of pneumoperitoneum, hemodynamic and respiratory morbidities are also reduced. In addition, dense intraperitoneal adhesions arising from previous surgery or inflammation are averted by operating in the retroperitoneum. The main disadvantage of the retroperitoneal approach is the limited working space that makes dissection of large tumors difficult. Furthermore, because of the smaller skin surface area for port placement, the risk of improper port placement leading to colonic injury is increased (Liapis et al, 2008). Finally, the lack of anatomic landmarks and the abundant retroperitoneal adipose tissues may pose a significant challenge to surgeons inexperienced with the retroperitoneum.

The main advantage of the lateral approach over the posterior approach is the ease of conversion into the transperitoneal approach should difficulties be encountered. In contrast, the prone retroperitoneal approach allows for bilateral adrenalectomy without patient repositioning.

Retroperitoneal Lateral Adrenalectomy: Left Adrenalectomy

Positioning and Ports Placement. The patient is placed in the lateral position with the left side up with a kidney rest under the body and the operating table flexed to accentuate the left flank. A 1.5-cm incision is made near the tip of the 12th rib under the 11th rib. The underlying muscle and fasciae are divided with cautery until the lumbodorsal fascia is visible. This lumbodorsal fascia is then incised sharply and a finger is inserted to confirm access into the retroperitoneal space. The inner surface of the 12th or 11th rib should be palpable superiorly and the iliac crest felt inferiorly. Blunt finger dissection is used to create a plane between the psoas muscle and the posterior Gerota fascia by sweeping the kidney anteriorly and the peritoneum medially. This retroperitoneal space is then widened with a retroperitoneal dissection balloon inflated under direct vision by inserting the laparoscope into its transparent shaft. The balloon dissector is directed along the posterior abdominal wall in a cephalic direction. The psoas muscle is usually identifiable and this serves as a landmark for longitudinal orientation. A balloon-tip trocar is secured in position into this space and insufflation of the retroperitoneum is generated. A 5- or 10-mm trocar is placed at the angle of the paraspinal muscle and the origin of the 12th rib. Another 5- or 10-mm trocar is placed about two finger-breadths above the iliac crest near the anterior superior iliac spine (Fig. 66-28).

Ligation of Left Adrenal Vein and Mobilization of Left Adrenal Gland. By dissecting medially, the great vessels can be identified by their pulsation and their course parallel to the psoas. The renal hilum is then identified by the pulsation of the posteriorly situated renal artery. The superior border of the renal artery is dissected to expose the left adrenal vein as it courses anterior and cephalad to the renal artery toward the inferomedial border of the left adrenal gland (Fig. 66-29). The left adrenal vein is subsequently doubly clipped and ligated (Fig. 66-30). Small arterial branches arising from the aorta are ligated with cautery or a harmonic scalpel, mobilizing the medial border of the gland. The inferior and lateral borders of the gland are then mobilized in a similar manner from

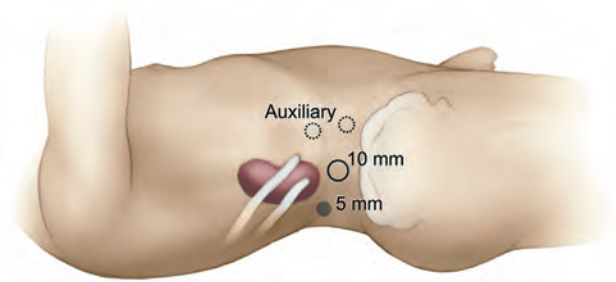


Figure 66-28. Trocar placement for retroperitoneal laparoscopy. The dotted circles represent alternative sites for placement of a third port.

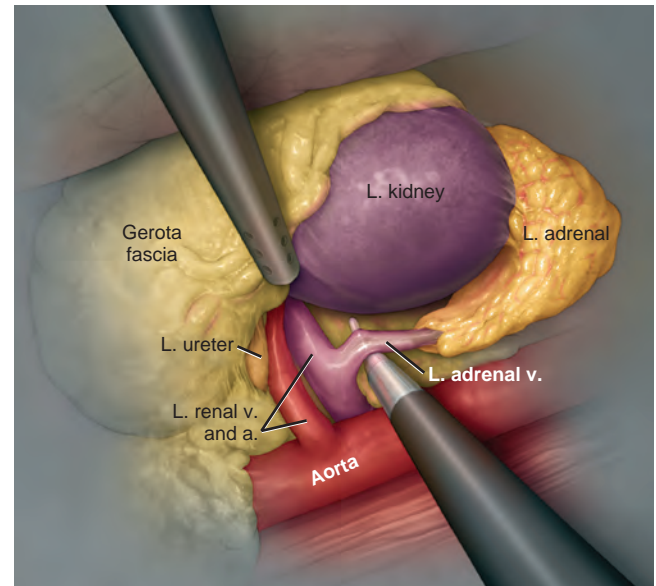


Figure 66-29. Retroperitoneal laparoscopic adrenalectomy. Dissection of the left adrenal vein by the retroperitoneal approach.

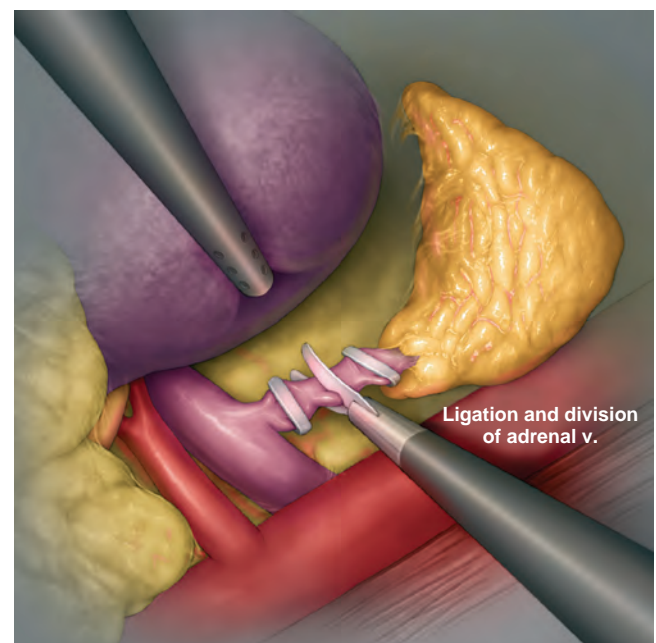


Figure 66-30. Retroperitoneal laparoscopic adrenalectomy. Ligation and division of left adrenal vein. The kidney is dissected away from the adrenal gland.

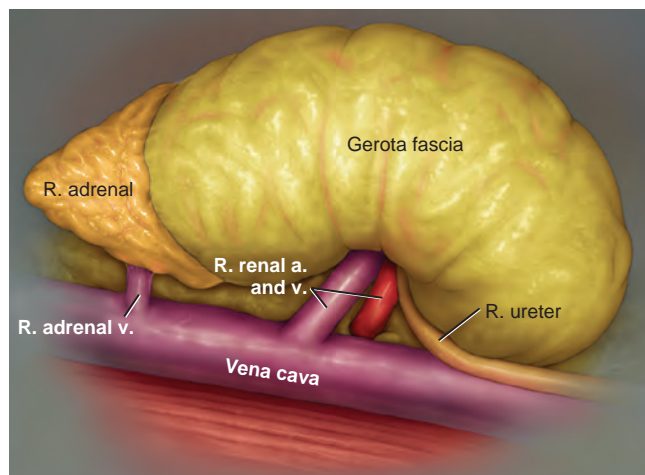


Figure 66-31. Anatomic view of right adrenal gland from laparoscopic retroperitoneal approach.

the upper pole of the left kidney. Finally, the anterior and superior borders of the gland are freed. The inferior phrenic vein may course along the anteromedial border of the gland to join the left adrenal vein. If encountered, it should be clipped and ligated.

Closure. The specimen is placed in an endoscopic bag and extracted through a 10-mm port. After ensuring adequate hemostasis, the trocar sites are closed in the standard fashion as described earlier.

Retroperitoneal Lateral Adrenalectomy: Right Adrenalectomy

The right adrenalectomy is performed in a similar fashion, dissecting cephalad along the inferior vena cava to reach the renal hilum and right adrenal vein. The anatomic relationships of this approach are illustrated in [Figure 66-31](#).

ROBOT-ASSISTED ADRENALECTOMY

Currently, the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) is the only commercially available platform for robotic surgery. Since the first robot-assisted adrenalectomy in 1999, many centers around the world have jumped onto the bandwagon of robot-assisted adrenalectomy. The main benefits of the robotic system over conventional laparoscopy lie in superior ergonomics, three-dimensional (3D) magnification of the operative field, tremor filtering, and enhanced degrees of freedom of the EndoWrist (Intuitive Surgical, Sunnyvale, CA) instruments. These advantages of the robotic platform render it ideal in handling the fragile adrenal gland in a deep narrow space surrounded by major vessels and viscera where injury may lead to catastrophic consequences.

Robot-Assisted Lateral Transperitoneal Adrenalectomy

After insertion of a nasogastric tube and urinary catheter, the patient is positioned in an oblique lateral position with the affected side elevated on a kidney rest at an angle of 30 to 45 degrees from the table. The bony prominences are padded and the patient is strapped securely onto the table. The table is then tilted in the opposite direction to achieve a supine position for port placement. A longitudinal 1.2-cm supraumbilical incision is made and pneumoperitoneum is established with a Veress needle. A 12-mm optical port is inserted for the camera. Two 8-mm robotic ports and a 12-mm assistant port are inserted under vision in the configuration shown in [Figure 66-32](#). For right adrenalectomy, an additional 5-mm port is inserted just inferior to the xiphoid process for liver retraction ([Fig. 66-33](#)). In general, the distance between the camera and each robotic port should be at least 8 cm to reduce instrument clashing internally and

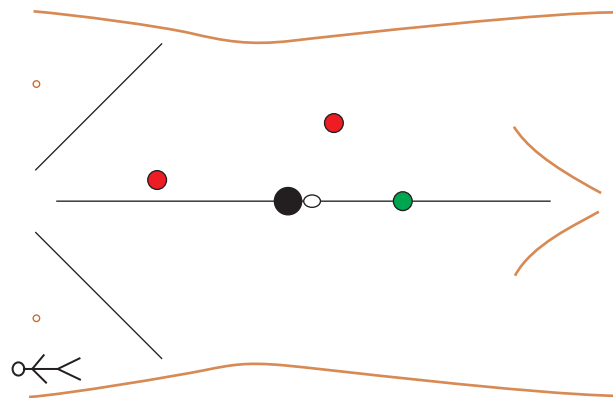


Figure 66-32. Left robotic adrenalectomy trocar placement. A total of four ports are placed: one 12-mm camera port (●), one 12-mm assistant port (●), and the two 8-mm robotic arm ports (●). The distance between each port should be at least 8 cm.

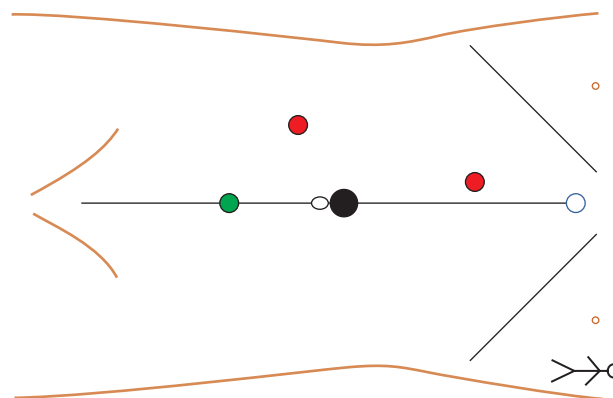


Figure 66-33. Right robotic adrenalectomy trocar placement. A total of five ports are used: one 12-mm camera port (●), one 12-mm assistant port (●), two 8-mm robotic arm ports (●) are established, and to retract the liver, a 5-mm trocar (○) is placed with a retraction device.

robotic arms clashing externally. The table is now tilted so that the patient lies in a full lateral position with the affected side upward. To facilitate access to the upper areas of the retroperitoneum, the robot is docked at an angle at the head of the table as outlined in [Figure 66-34](#).

The dissection and mobilization of the adrenal gland are similar to the transperitoneal laparoscopic techniques described earlier.

HAND-ASSISTED SURGERY

Hand assistance during laparoscopic surgery introduces enhanced tactile sensation and greater degrees of freedom of movement as compared to laparoscopic instruments. This may result in easier dissection, added security in the event of bleeding complications, and a shorter learning curve. With the introduction of the robotic system, hand-assisted adrenalectomy may have fallen out of favor in recent years, with publications limited to case reports and small case series published in the early 2000s. Hand-assisted adrenalectomy may be indicated in bilateral adrenalectomy or with large adrenal tumors that may require a larger incision for extraction. There may also be a role for hand-assisted surgery as an alternative to open conversion should laparoscopic dissection prove difficult or for bleeding complications.

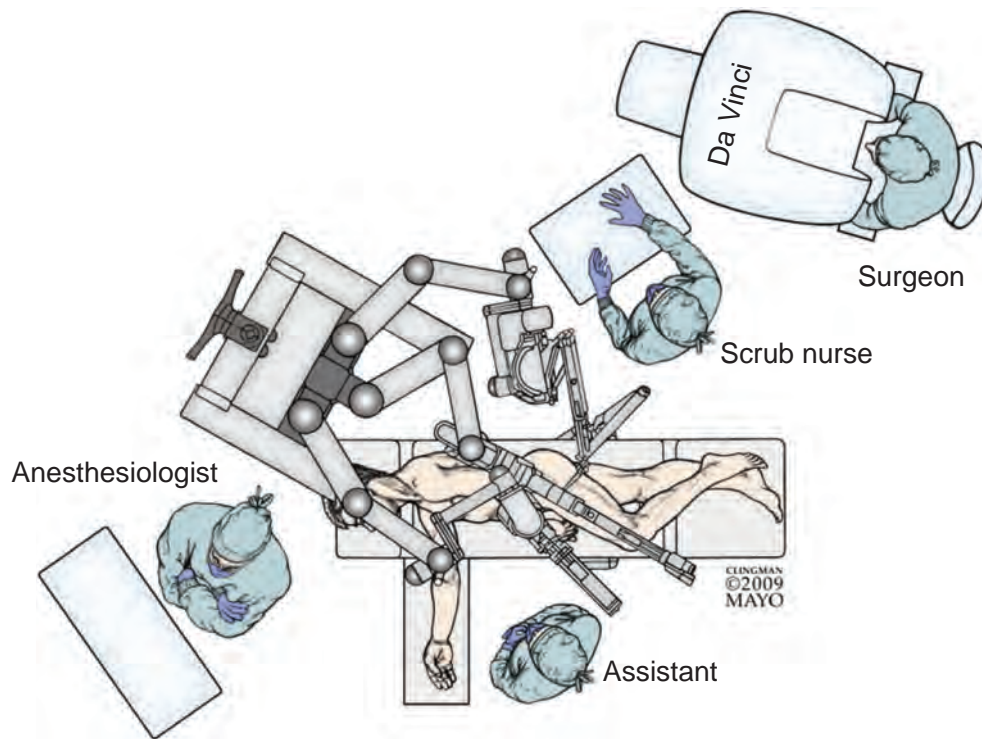


Figure 66-34. Surgical room set-up for left robotic adrenalectomy. The slave unit of the robot is brought in over the patient's left shoulder as indicated in the diagram. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

LAPAROENDOSCOPIC SINGLE-SITE (LESS) ADRENALECTOMY

Laparoendoscopic single-site (LESS) surgery has recently been developed based on the principle that, with a smaller number of incisions and ports, enhancement of cosmesis and reduction of associated port site complications such as bleeding, organ injury, and incisional hernias can be attained. In general, all patients eligible for laparoscopic adrenalectomy can be considered for LESS depending on the surgeon's experience. However, because of the technical difficulties, LESS is most commonly performed for small (≤ 4 cm) and benign tumors.

Like conventional laparoscopic adrenalectomy, both transperitoneal and retroperitoneal approaches for LESS adrenalectomy have been described. Single multiluminal access ports are commercially available for LESS access. The umbilicus is the most common location for LESS access owing to the superior cosmetic results. However, the longer distance and the more tangential approach from the umbilicus to the adrenal gland render the surgery much more challenging. Alternative sites such as the subcostal margin or retroperitoneum have been described, albeit with less cosmetically appealing results. Moreover, the limited working space in the retroperitoneum makes the use of articulating and curved instruments more difficult when compared to the transperitoneal approach.

The inherent disadvantages of LESS surgery include reduced working space and loss of instrument triangulation leading to clashing, crossover, and paradoxical movement of instruments, as well as suboptimal approach to the adrenal gland and inadequate traction and countertraction. These disadvantages may translate into longer operative time and increased risk of tissue injuries and complications. Jeong and colleagues (2009) reported the first matched case-control study comparing 9 patients who underwent LESS adrenalectomy with 17 patients who underwent conventional laparoscopic adrenalectomy. Although the LESS adrenalectomy group required reduced postoperative analgesia, it was associated with a

non-statistically significant longer operative time and a case of bowel injury. Similarly, Shi and coworkers (2011) and Walz and associates (2010) reported a longer median operative time and lower analgesic requirements after LESS adrenalectomy compared to conventional adrenalectomy. Ishida and colleagues (2013) showed that tissue regrasping was more frequently observed (16.2 vs. 2.2 times) during LESS than in conventional adrenalectomy. Hu and colleagues (2013) summarized in their meta-analysis comparing LESS adrenalectomy and conventional laparoscopic adrenalectomy that, although LESS adrenalectomy is associated with a longer operative time, estimated blood loss and complications are similar. In addition, patients who underwent LESS adrenalectomy had a shorter hospital stay and reduced requirement for analgesia.

NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY (NOTES)-ASSISTED LAPAROSCOPIC ADRENALECTOMY

Natural orifice transluminal endoscopic surgery (NOTES) utilizes natural orifices such as the mouth, urethra, vagina, or anus as entry points to perform intra-abdominal surgeries. In pure NOTES, access points are strictly limited to natural orifices. Hybrid-NOTES allows for additional incisions to be made, usually around the umbilicus, to facilitate surgery. Like LESS, the aims of NOTES are to improve cosmetic outcomes and convalescence and reduce hospitalization stay and analgesia requirements without compromising safety and efficacy.

Fritscher-Ravens and colleagues (2008) were among the first to attempt NOTES adrenalectomy. By using the transesophageal or transgastric route with the aid of endoscopic ultrasonography, they failed to remove the adrenal gland in all procedures in which it was attempted. Perretta and coworkers (2009) successfully performed bilateral adrenalectomy in two female pigs and two female

cadavers through a transvaginal retroperitoneal approach. The first report of hybrid-NOTES came from [Zou and colleagues \(2011\)](#), who presented their series of 11 female patients, with a median tumor size of 4.7 cm, who underwent transvaginal NOTES adrenalectomy. Injury to the spleen occurred in one patient necessitating open conversion and splenectomy. Median estimated blood loss was 80 mL. Almost all published literature describes NOTES adrenalectomy via the transvaginal route. Recently, [Eyraud and associates \(2013\)](#) described their transrectal robot-assisted NOTES techniques in a male cadaver. Despite these reports, NOTES adrenalectomy is still in its infancy and should only be considered as experimental.

PARTIAL ADRENALECTOMY

Unilateral adrenalectomy is often well tolerated and should be considered as the gold standard in the treatment of functioning or malignant adrenal tumors. Patients with bilateral adrenalectomy will require lifelong adrenal replacement therapy. Unfortunately, fixed daily dosing of steroids is associated with overdosing, which may result in osteoporosis, obesity, and Cushing syndrome, and with underdosing in times of stress. Life-threatening Addisonian crisis can occur. Patients after bilateral adrenalectomy continue to report poorer quality of life as compared to the general population ([Hawn et al, 2002](#); [van Aken et al, 2005](#)). Therefore partial adrenalectomy should be considered in patients with bilateral adrenal tumors, solitary adrenal gland, or familial syndromes such as von Hippel-Lindau disease, familial pheochromocytoma, and multiple endocrine neoplasia type IIA.

Partial adrenalectomy can be performed in any of the open, laparoscopic, or robot-assisted approaches described earlier. A major and important difference is that the adrenal gland is exposed but not mobilized. In open surgery, the tumor can usually be visualized or palpated. In laparoscopic or robotic surgery, lesions larger than 1 cm can usually be visualized. In any of these approaches, the use of intraoperative ultrasonography can help accurately localize and identify the tumor. Once the lesion is identified, only the affected portion is mobilized. The arterial supply of the adrenal gland forms a plexus circumferentially around the gland and can usually be removed without fear of devascularizing the adrenal cortex, and the gland will remain viable as long as it remains attached to the kidney or to an area of unmobilized connective tissue. The venous system drains into a central adrenal vein. Opinions are divided as to whether the main adrenal vein should be left intact during partial adrenalectomy. Some authors believe that removing the main adrenal vein will result in congested remnant adrenal tissues and difficult hemostasis, thus advocating its preservation ([Janetschek et al, 1998](#); [Imai et al, 1999](#)). In our experience and as concurred by other authors, the main adrenal vein can be removed as long as the remnant adrenal gland remains in situ without mobilization ([Walz et al, 1998](#); [Kaouk et al, 2002](#)). However, it would be prudent to preserve the main adrenal vein as long as it is safe and adequate margins can be obtained.

Partial adrenalectomy can be performed with either an endoscopic stapler ([Imai et al, 1999](#)), a harmonic scalpel ([Walz et al, 1998](#); [Sasagawa et al, 2000](#)), or cautery or cold endoscissors with clips or suture ligation. The use of the endoscissors allows for clear identification of the tumor plane and precise dissection but may lead to more bleeding. Finally, the cut surface can be sealed with fibrin glue or Surgicel (Ethicon, Cincinnati, OH) to prevent delayed bleeding. Frozen section is recommended if available; if not, intraoperative ultrasonography can be performed to confirm gross complete resection.

The amount of adrenal tissue that must be left behind after partial adrenalectomy to avoid insufficiency is not known. It has been suggested previously that at least 20% of the adrenal gland should be preserved ([Lee et al, 1996](#)). However, Lee and colleagues were unable to correlate the amount of adrenal tissue preserved with the presence of adrenal insufficiency.

OUTCOMES

Open versus Laparoscopic Adrenalectomy

There have been no prospective randomized controlled studies comparing open with laparoscopic adrenalectomy. It is highly doubtful that such a trial will ever be conducted because laparoscopic adrenalectomy is emerging as the gold standard technique for benign lesions and surgeons are pushing the boundaries for laparoscopic management of malignant tumors. Many large retrospective studies have consistently demonstrated superior outcomes of laparoscopic adrenalectomy over open surgery in terms of analgesia, hospital stay, blood loss, and complication rates. As surgeons gain more experience with laparoscopic surgeries, operative times have also decreased tremendously.

In an early meta-analysis of close to 100 studies comparing laparoscopic with open adrenalectomy, Brunt reported that, although the rate of bleeding complications was higher in laparoscopic (4.7%) than open (3.7%) adrenalectomy, total complication rates were lower in laparoscopic (10.9%) than open (25.2%) adrenalectomy ([Brunt, 2002](#)). Of note, open adrenalectomy was associated with significantly higher rates of associated organ injury and wound, pulmonary, cardiac, and infectious complications. There was also a higher non-statistically significant rate of mortality after open adrenalectomy (0.9% vs. 0.3%). Using the Veterans Affairs National Surgical Quality Improvement Program database to compare laparoscopic with open adrenalectomy, [Lee and colleagues \(2008\)](#) demonstrated that open procedures had increased operative times, transfusion requirements, reoperations, length of stay, and 30-day morbidity rates. Open adrenalectomy had also resulted in more pneumonia, unplanned intubation, unsuccessful ventilator wean, systemic sepsis, cardiac arrest, renal insufficiency, and wound infections. The 30-day morbidity rate was still higher even after adjusting for confounding factors. A Nationwide Inpatient Sample from the United States involving more than 40,000 patients who underwent adrenalectomy echoed similar findings of fewer complications and shorter length of stay in patients who underwent laparoscopic adrenalectomy over their open adrenalectomy counterparts ([Murphy et al, 2010](#)).

Most recently, using a contemporary cohort from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) data, [Elfenbein and colleagues \(2013\)](#) concluded that patients undergoing laparoscopic adrenalectomy had significantly lower postoperative morbidity and shorter length of stay than patients undergoing an open procedure after adjustment for patient- and procedure-related factors, including malignancy.

Laparoscopic Transperitoneal versus Retroperitoneal Approach

Multiple retrospective studies have been performed that seem to suggest an advantage in terms of lesser blood loss and shorter convalescence time of the retroperitoneal approach over the transperitoneal approach. In a meta-analysis of 22 eligible studies ([Constantinides et al, 2012](#)), the laparoscopic retroperitoneal approach was associated with a significantly shorter hospital stay when compared to the transperitoneal approach. The authors attributed this to the decrease in postoperative pain and ileus associated with the retroperitoneal approach because the peritoneum is not breached. There were no differences in duration of operation, blood loss, time to ambulation and oral intake, or complication rates between techniques. Another meta-analysis by [Chen and colleagues \(2013\)](#) identified nine eligible retrospective studies reporting that the retroperitoneal approach was associated with shorter operative time, less intraoperative blood loss, shorter hospital stay, and shorter time to first ambulation. There was no significant difference in open conversion rates, time to first oral intake, and major postoperative complication rates.

Three randomized prospective studies were carried out to compare these two approaches. [Fernández-Cruz and coworkers](#)

(1996) randomized 21 laparoscopic adrenalectomy patients into transperitoneal and retroperitoneal approaches. They showed that the transperitoneal approach resulted in a greater rise in the PaCO₂ level compared with the retroperitoneal approach at 30 minutes, together with a significant increase in mean arterial pressure. However, operation time, blood transfusion and analgesia requirements, hospital stay, return to normal activities, and complication rates were similar between the two approaches. The authors concluded that the retroperitoneal approach might be a better option in patients with previous abdominal surgery and preexisting cardiopulmonary diseases. In another prospective randomized trial by Rubinstein and colleagues (2005) in which all baseline patient and operative factors were matched, the only significant difference was a shorter convalescence time in the retroperitoneal group. All other parameters such as blood loss, operative time, analgesia requirements, open conversion, and complication rates were similar. Finally, a prospective randomized study involving a more contemporary cohort concurred with the previous findings that the transperitoneal approach was comparable to the retroperitoneal approach in terms of operative time, estimated blood loss, time to ambulation, hospital stay, and analgesic requirement but was associated with longer time to oral intake resumption and longer convalescence period (Mohammadi-Fallah et al, 2013).

Laparoscopic versus Robot-Assisted Adrenalectomy

As described previously, the robotic platform offers several advantages over conventional laparoscopy but current literature has yet to show conclusively that these advantages have translated into better clinical outcomes. The only prospective randomized study comparing robot-assisted with laparoscopic adrenalectomy was published in the early years of robot-assisted surgeries. Morino and coworkers (2004) randomized 20 consecutive patients with benign adrenal tumors to either traditional laparoscopic or robotic surgery. The robot-assisted approach was associated with a longer operative time and higher 30-day complication rate compared to the laparoscopic approach. In addition, cost analyses revealed that robotic procedures were more expensive than laparoscopic procedures. The authors concluded that laparoscopic adrenalectomy was superior to robot-assisted adrenalectomy in terms of feasibility, morbidity, and cost. In separate studies, Brunaud and colleagues concurred that patients' quality of life after robotic surgery was similar to that after laparoscopic surgery (Brunaud et al, 2004) but robotic surgery was 2.3 times more expensive (Brunaud et al, 2008).

Robot-assisted surgery requires the insertion of more trocars and docking of the robotic arms when compared to conventional laparoscopy, and these additional steps may lead to longer operative time (Morino et al, 2004; Wu et al, 2008; Pineda-Solís et al, 2013). Robotic surgery is highly dependent on the expertise of the assistant and the whole robotic team, including the scrub nurses. As robotic teams go beyond the initial learning curve of 10 to 20 cases, operative times have been shown to approach those clocked by the conventional laparoscopic approach (Brunaud et al, 2008; Agcaoglu et al, 2012a; Karabulut et al, 2012). Karabulut and colleagues went further to time each individual step of adrenalectomy and reported similar timings for each step of robotic and laparoscopic adrenalectomy, except for shorter hemostasis time in the robotic group (Karabulut et al, 2012).

Multiple studies have demonstrated that perioperative outcomes such as estimated blood loss, hospital stay, postoperative analgesia, and complication and mortality rates are similar between the two approaches. In fact, robot-assisted adrenalectomy may be preferred in certain circumstances. For tumors greater than 5 cm, Agcaoglu and associates (2012b) reported shorter operative time and hospital stay and lower open conversion and morbidity rates in robot-assisted as compared with conventional laparoscopy. In a separate study by Karabulut and colleagues (2012), the morbidity was 10% in the laparoscopic and 2% in the robotic group despite the fact that tumors in the robotic group were significantly larger. For obese patients with body mass index 30 kg/m² or greater, Aksoy and colleagues (2013) found no differences in operative time, estimated

blood loss, and hospital stay between robot-assisted and laparoscopic adrenalectomy. However, there was a lower conversion rate (0 vs. 5.2%) and a non-statistically significantly lower 30-day morbidity rate (4.8% vs. 7%, $P = .06$) in favor of the robotic approach (Aksoy et al, 2013).

COMPLICATIONS

Intraoperative

Box 66-5 summarizes the intraoperative complications that can occur. As expected, adrenal surgery, both open and laparoscopic, can involve injury to adjacent organs. Hemorrhage is a potentially catastrophic complication of adrenal surgery. Bleeding can result from injury to the adrenal vein, inferior vena cava, lumbar vein, or renal vein. These injuries are managed initially by application of direct pressure to the injury. Grasping a small injury with an Allis clamp (Scanlan International, St. Paul, MN) and closing it with suture or by placement of a vascular clamp for a larger vena cava injury may be curative. In the early days of laparoscopic adrenalectomy, open conversion was the typical consequence of vascular injury. However, with increasing experience with laparoscopic suturing techniques, these injuries are often managed as in the open surgery.

Ischemic injuries can occur as well. An upper pole renal artery branch can be divided inadvertently during dissection. If the branch is small and supplies a minimal portion of the kidney, it can be ignored. More substantial injuries may require a revascularization

BOX 66-5 Intraoperative Complications of Adrenal Surgery

ACCESS RELATED

Abdominal wall hemorrhage
Cutaneous nerve injury
Visceral injury by Veress needle or trocar

HEMORRHAGE

Inferior vena cava or aorta
Adrenal vein
Lumbar vein
Hepatic vein
Remnant adrenal gland after partial adrenalectomy

ISCHEMIA

Ligation of renal artery or vein
Ligation of superior mesenteric artery and vein

INJURY TO NEIGHBORING ORGANS AS A RESULT OF THERMAL ENERGY OR INCORRECT PLANE OF DISSECTION

Lung—pneumothorax
Pancreas
Liver
Spleen
Stomach and bowel, especially duodenum
Kidney

HEMODYNAMIC INSTABILITY

Pheochromocytoma

Modified from Vaughn ED. Complications of adrenal surgery. In: Taneja SS, Smith RB, Ehrlich RM, editors. Complications of urologic surgery: prevention and management. 3rd ed. Philadelphia: Saunders; 2001. p. 366.

attempt. If the patient has a large tumor there can be distortion of the regional anatomy, and inadvertent ligation of the superior mesenteric vein or artery is possible. This is a potentially fatal injury, and one must have a high index of suspicion to restore vascular supply to the bowel as soon as possible.

The adjacent organs can be injured during dissection of the adrenal gland. The liver can be injured during right adrenalectomy. Liver lacerations can be treated with argon beam coagulation and application of hemostatic agents such as methylcellulose. More serious injuries may require hemostatic sutures with a blunt-tip liver needle. The spleen can be injured during left adrenalectomy. As with hepatic injury, argon beam coagulation and hemostatic agents can be used to control bleeding. If this is not sufficient, splenorraphy can be attempted. If these measures are unsuccessful, splenectomy may be necessary. **It is important to remember to give pneumococcus, *Haemophilus influenzae* type B (Hib), and meningococcus vaccinations to these patients during postoperative care.**

The pancreas can be injured during surgery on either the right or left adrenal gland. If an injury to the tail of the pancreas occurs, distal pancreatectomy may be performed. If the injury is to the pancreatic duct, this may be repaired and surgical drains left. If there is uncertainty of pancreatic injury, leaving closed-suction surgical drains behind is advisable. Postoperative drainage high in triglycerides is indicative of pancreas injury. Management consists of bowel rest with parenteral nutrition. The administration of octreotide can decrease pancreatic secretions while the pancreas heals.

The proximity of the kidney to the adrenal gland can be a problem in cases of large adrenal cortical carcinomas. **It is imperative for all patients undergoing surgery for large adrenal masses to be counseled about the possibility of concurrent en bloc nephrectomy.**

During 11th-rib or higher flank adrenalectomy, it is not unusual for pleural injury to be incurred. These injuries can be repaired with a purse-string chromic suture and a red rubber catheter to water seal. Expulsion of air from the pleura followed by cinching of the purse-string suture usually repairs the defect. Postoperative chest radiography should be routinely performed after flank or thoracoabdominal nephrectomy. If a significant pneumothorax is present, a chest tube should be placed.

With pheochromocytoma, blood pressure fluctuations can be life threatening. The anesthesiologist typically manages high blood pressure with short-acting β -blockade, α -blockers, or nitroprusside. Arrhythmias are usually treated with β -blockers. When the adrenal vein is ligated, there can be a sudden drop in blood pressure. It is important to inform the anesthesiologist just before the adrenal vein is ligated to avoid any nasty surprises. Fluid repletion and pressors may be necessary to bring the pressure to normal.

With the emergence of minimally invasive surgery, access-related complications can occur. Bleeding from the abdominal wall can occur following trocar insertion. Care should be exercised to avoid visible superficial veins during trocar site insertion. Although bleeding usually stops from the tamponade effect of the trocar and pneumoperitoneum, it is imperative to inspect all trocar sites laparoscopically upon trocar withdrawal at end of surgery to ensure hemostasis. Cutaneous nerve injury is less likely to occur than in open surgery because of smaller incisions. Finally, visceral injury by the Veress needle can occur. Closed access technique using the Veress needle must be done with caution in patients with previous abdominal surgery as bowels may be adherent to the abdominal wall and can be injured. The open (Hasson) access technique can be a safer alternative in these cases.

Postoperative

Box 66-6 summarizes the postoperative complications that can occur. Disease-specific complications must be accounted for to ensure an uneventful postoperative course.

Patients with primary hyperaldosteronism require close monitoring of potassium levels because they can be either hypokalemic or hyperkalemic. Hyperkalemia, secondary to contralateral adrenal zona glomerulosa suppression, should be managed medically with

BOX 66-6 Postoperative Complications of Adrenal Surgery

PRIMARY ALDOSTERONISM

Hypokalemia: secondary to continued potassium loss immediately postoperative

Hyperkalemia: secondary to failure of contralateral adrenal to secrete aldosterone

CUSHING SYNDROME

Inadequate steroid replacement leading to hypocorticism

Fracture secondary to osteoporosis

Hyperglycemia

Poor wound healing

Increased risk of infections

PHEOCHROMOCYTOMA

Hypotension secondary to α -adrenergic blockade after tumor removal

GENERIC COMPLICATIONS

Hemorrhage

Pneumothorax

Pancreatitis

Pneumonia

Prolonged ileus

Intra-abdominal collections

Modified from Vaughn ED. Complications of adrenal surgery. In: Taneja SS, Smith RB, Ehrlich RM, editors. Complications of urologic surgery: prevention and management. 3rd ed. Philadelphia: Saunders; 2001. p. 368.

the typical hyperkalemia regimens. Hypokalemia can persist in the immediate period after adrenalectomy, and this should be corrected with potassium repletion. In patients who had only one adrenal gland to begin with, mineralocorticoid replacement with fludrocortisone is essential.

Patients with Cushing syndrome will require steroid replacement after surgery, until the contralateral gland recovers function. Measurements of plasma cortisol can be useful in determining when steroid replacement can be tapered. Furthermore, these patients have increased risk of fracture secondary to osteoporosis, hyperglycemia, and poor wound healing.

Patients with pheochromocytoma may have hypotension secondary to α -blockade. These patients need to be monitored closely until α -blockade wears off, often in the intensive care unit. If α -blockade was not used preoperatively, as is the protocol at the Cleveland Clinic, intensive care stay is unnecessary in most cases.

ABLATIVE THERAPY FOR ADRENAL TUMORS

Current indications for ablative therapy for adrenal tumors include patients with small tumors not keen on or suitable for surgery and palliation of painful metastases not amenable to resection. The three major thermal ablative techniques currently used are radiofrequency ablation (RFA), cryoablation, and microwave ablation. RFA utilizes frictional energy created by oscillating tissue ions to supply destructive heat to target tissue, with target tissue temperature ranging from 60° C to 100° C resulting in protein and enzymatic degradation and cell death. Microwave ablation creates an alternating electric field that causes oscillation of surrounding water dipoles resulting in tissue heating. Some authors have suggested that advantages of microwave ablation include the potential for larger ablation volumes, decreased procedural pain, and the potential to treat cystic

lesions (Simon et al, 2005). Cryoablation relies on rapid freezing and thawing to cause rupture of cell membranes resulting in cell death. The main advantage of this technique is the ability to follow iceball formation in real time with CT imaging.

It is generally recommended to perform a biopsy of the tumor either prior to or at the same session as ablative therapy because histologic results might influence follow-up management. Systemic catecholamine release resulting in hypertensive crisis and cardiac arrest has been reported during ablative treatment of adrenal metastases and pheochromocytomas (Chini et al, 2004; Mamlouk et al, 2009; Tsoumakidou et al, 2010). Since catecholamine release can be caused by thermal injury to the adrenal in the absence of pheochromocytoma, some authors advocate premedication with α -blockade prior to the ablation procedure. Welch and colleagues (2011) demonstrated a significant increase in systolic blood pressure, pulse pressure, and mean arterial pressures in patients undergoing adrenal cryoablation, even with prior α -blockade. Continuous blood pressure monitoring with an arterial line and general anesthesia with a rapid-acting vasodilatory drug on standby may be prudent.

Mendiratta-Lala and colleagues (2011) treated 13 hyperfunctioning small adrenal tumors with RFA. At a mean follow-up of about 21 months, all patients experienced resolution of clinical symptoms or syndrome and normalization of biochemical markers. The majority of current literature on ablative therapy is centered on treatment of metastases in the adrenal gland. The largest of these studies by Wolf and coworkers (2012) reported that 19 of 23 tumors treated showed no evidence of local progression and tumor enhancement at mean follow-up of 45.1 months after RFA or microwave ablation. Other studies also mirrored excellent short-term local progression-free and enhancement-free rates ranging from 83% to 100% after RFA, microwave ablation, or cryoablation (Mayo-Smith and Dupuy, 2004; Carrafiello et al, 2008; Wang et al, 2009; Welch et al, 2011). Nevertheless, evidence of long-term follow-up and outcomes are still lacking.

FUTURE OF ADRENAL SURGERY

Contemporary computer-based image acquisition systems are able to perform accurate 3D reconstruction of an organ or body region. Surgeons are now able to manipulate these 3D images such that the organ or body region could be viewed from almost all angles, allowing surgeons to acquire a mental picture of the regional anatomy they will be dealing with prior to surgery. Currently, virtual reality systems are being developed that will allow for the creation of a virtual environment where organs and structures can be represented in a fully 3D manner, in which surgeons can interact with the images as though they truly exist and perform tasks and surgical manipulations (Marescaux et al, 2005). In addition, the differentiation between the structure of the normal gland and pathologic lesions can be enhanced with high contrast and color, allowing for accurate localization of pathologic lesions and their relationship with the surrounding structures.

There are a few potential clinical applications for these virtual reality systems (Marescaux et al, 2005). First, by integrating with surgical simulators, residents and junior surgeons are able to gain surgical experience in a completely safe environment where errors could be made without detrimental consequences to the patient. Second, the integrated system can allow the surgeon to have an individualized “dry run” of a patient’s surgery prior to the actual

procedure, allowing for better planning as well as anticipation of possible dangers and identification of the optimal plane for dissection or resection. Finally, by integrating these virtual reality systems with advanced surgical robots in future, the digital data of the best simulated procedure performed by an expert could be recorded and transmitted to a distant remote location where a robot reproduces the surgery automatically on a patient.

The future of adrenal surgery remains exciting and fascinating.

KEY POINTS

- Adrenalectomy is indicated in functional adrenal masses or suspected adrenal malignancy, either primary adrenal cortical carcinoma or solitary metastasis from nonadrenal sources.
- Preoperative and postoperative medical management is essential for optimal surgical outcome for functional adrenal tumors.
- Laparoscopic adrenalectomy is the current standard of care for adrenal lesions with the exception of invasive adrenal cortical carcinoma or adrenal cortical carcinoma with caval thrombus.
- Open adrenal surgery is indicated for lesions contraindicated for or not amendable to minimally invasive techniques (e.g., large invasive carcinomas, great vessel involvement, severe cardiopulmonary diseases).
- It is imperative for all patients undergoing surgery for large adrenal masses to be counseled about the possibility of concurrent en bloc nephrectomy.
- It is recommended to perform a biopsy of the tumor either prior to or at the same session as ablative therapy.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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67

Surgical, Radiographic, and Endoscopic Anatomy of the Female Pelvis

Larissa V. Rodriguez, MD, and Leah Yukie Nakamura, MD

Bony Pelvis

Fascia and Peritoneum

Ligaments

Muscles of the Pelvic Floor

Vasculature of the Pelvis

Lymphatic Drainage

Innervation

Perineum

Anal Perineum

External Genitalia

Female Pelvic Organs

Pelvic Organ Support

Urethra

Radiographic Anatomy

Female pelvic anatomy is one of the most complex areas of urosurgical anatomy. Pictures and descriptions alone are not enough to grasp fully the anatomy, as there is significant patient variation and many of the muscles and supportive structures are not clearly defined. There is also significant controversy and disagreement between the sources of terminology and the function of structures. This chapter aims to highlight the pertinent pelvic floor anatomy in a normal female. Many of the key structures will also be outlined in Chapter 68, and the current chapter will focus primarily on the important differences in females as compared to males. The radiographic and endoscopic anatomy will also be reviewed.

BONY PELVIS

The bony pelvis is the foundation that anchors the support structures of the female pelvis (Fig. 67-1). The true pelvis is made up of two hip bones or innominate bones (ilium, ischium, and pubis), as well as the sacrum and coccyx. The ilium is the fan-shaped portion of the hip bone that has an ala (wing) and body. The iliac crest is the rim of the ala between the anterior and posterior iliac spines. The ramus of the ischium forms part of the obturator foramen. **The ischial spine is a small posterior point between the ramus and the body of the ischium and is an important surgical landmark in pelvic reconstruction surgery.**

The pubic rami, ischial spines, and sacrum are some of the major anchoring points for the attachment of ligaments that support the bony pelvis. **The anterior and posterior compartments are divided by a line drawn between the two ischial spines.**

The pelvis is divided into the greater or false pelvis and the lesser or true pelvis by the plane at the level of the sacral promontory posteriorly and the terminal lines or pelvic brim. The pelvic brim also defines the pelvic inlet. The greater pelvis is a part of the lower abdominal cavity. The lesser or true pelvis is

the location of all the pelvic viscera and the area between the pelvic inlet and outlet.

Females have a wider diameter and a more oval inlet as compared to males. This aids in parturition but also contributes to weakness of the pelvic floor (Herschorn, 2004). The bones are also lighter and thinner compared to the male. Men have more clearly demarcated areas of muscular attachment, and women have smaller iliac fossa (MacLennan, 2012).

When the pelvis is visualized in the standing position, the anterior superior iliac spine and pubic symphysis lie parallel to each other (Barber, 2005). **The pelvic inlet faces anteriorly, which allows most of the pressure of the intra-abdominal and pelvic contents to be directed toward the bony pelvis rather than toward the muscles and the fascia (Fig. 67-2).** This is in contrast to the surgical anatomy, which is most commonly described in the lithotomy position.

FASCIA AND PERITONEUM

The fascia is divided into three strata:

1. Inner stratum
2. Intermediate stratum
3. Outer stratum

The rectal fascia is part of the inner stratum and covers the anterior and lateral rectal wall, vessels, and nerves forming part of Denonvilliers fascia. The intermediate stratum encases the uterus and supporting vessels and provides additional pelvic support. **Most of the support of the pelvic organs comes from the retroperitoneal connective tissue derived from the intermediate stratum.** This includes the pubovesical and pubocervical fascia that surround the vagina. The fascia attached to the uterus is referred to as the parametrium and that surrounding the vagina is the paracolpium (Wei and DeLancey, 2004) (Fig. 67-3).

The transversalis fascia is part of the outer stratum and is continuous with the endopelvic and lateral pelvic fascia. Both the

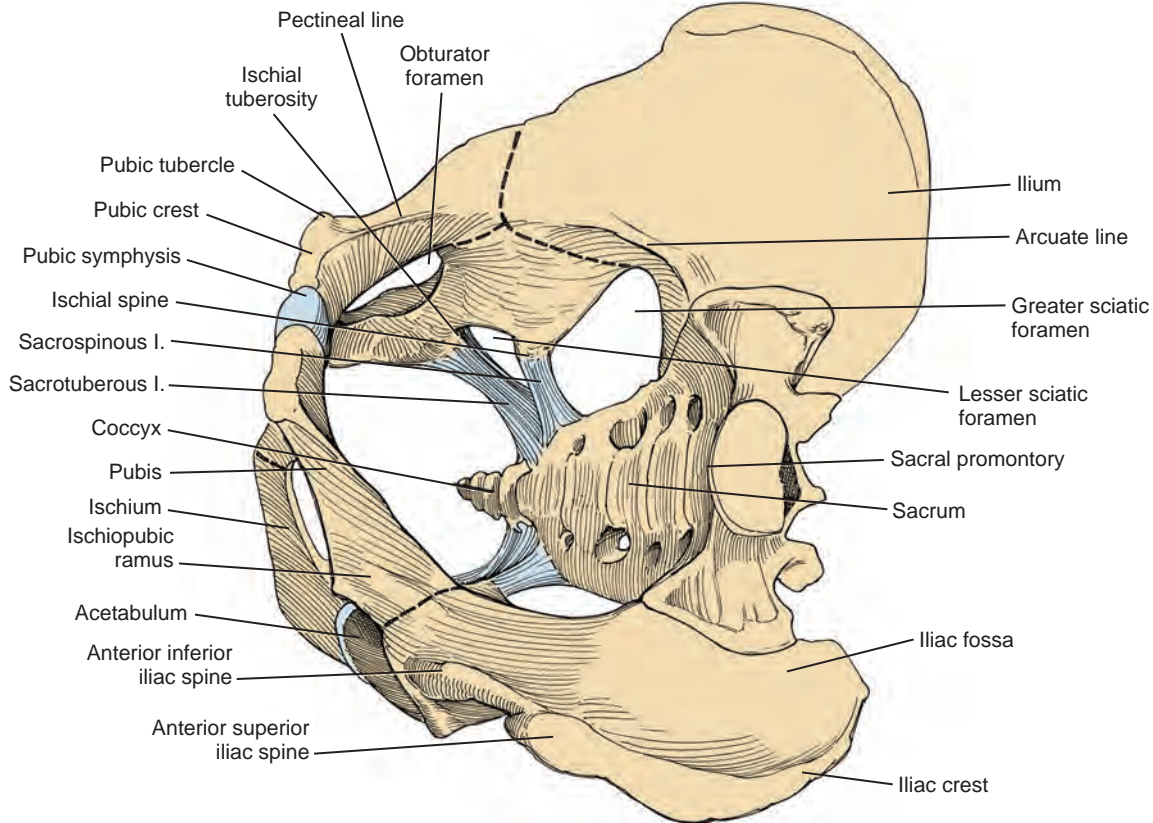


Figure 67-1. The bones and ligaments of the pelvis. l., ligament. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

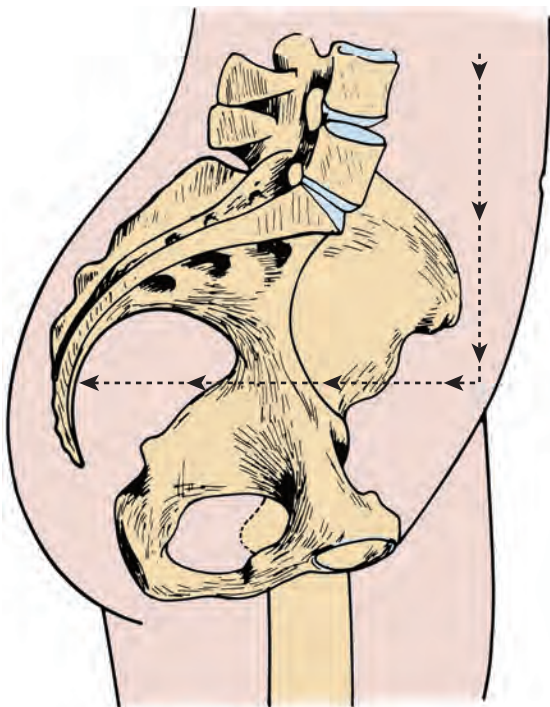


Figure 67-2. Pelvis in standing position. The axis of the pelvic cavity is horizontal because of the lumbar lordosis. (From Zacharin RF. *Pelvic floor anatomy and the surgery of pulsion enterocele*. New York: Springer-Verlag; 1985.)

transversalis and endopelvic fascia play important roles at the exit points of the pelvic organs. The endopelvic fascia extends from the uterine artery down to where the vagina and levator ani fuse. The iliac fascia is also part of the outer stratum and covers the iliacus and psoas muscles. It attaches to the iliac crest and runs down to the tendinous arch (white line) and is continuous with the posterior portion of the inguinal ligament. It is also continuous with the pectineal fascia and obturator fascia. The obturator fascia covers the obturator internus and piriformis muscles.

The thickened band of the pelvic fascia that runs from the ischial spine to the pubic bone is called the tendinous arch or the arcus tendineus. It is also known as the **arcus tendineus fasciae pelvis (ATFP)** where many of the important fascial layers attach. It originates from the pubic bone laterally and is connected to the pubovesical ligament medially and the tendinous arch of the levator ani (Fritsch et al, 2012). This is the remnant of the degenerate tendon of iliococcygeus. This should not be confused with an adjacent structure that bears a similar name. The **arcus tendineus levator ani (ATLA)** is where the muscles of the levator ani attach. The ATLA is the aponeurotic portion of the obturator fascia covering the obturator internus muscle.

The inferior pelvic fascia is continuous with the obturator fascia and fascia of the pudendal canal. It covers the surface of the levator ani. The superior pelvic fascia arises from the outer stratum and the obturator fascia. It runs from the pubic symphysis laterally to the ischial spine. The fascia is thinner over the muscles and organs, allowing more mobility.

There are six main potential spaces that exist among the pelvic organs. In the midline, there are the vesicovaginal and the rectovaginal spaces. The vesicovaginal space is contained by the adventitia of the bladder anteriorly and vagina posteriorly. The space ends where the vagina fuses with the distal urethra and at the vesicocervical ligament (fusion of the bladder with the vagina and cervix). The prevesical space is between the fascia covering the bladder and the endopelvic fascia behind the pubis. This space extends laterally to

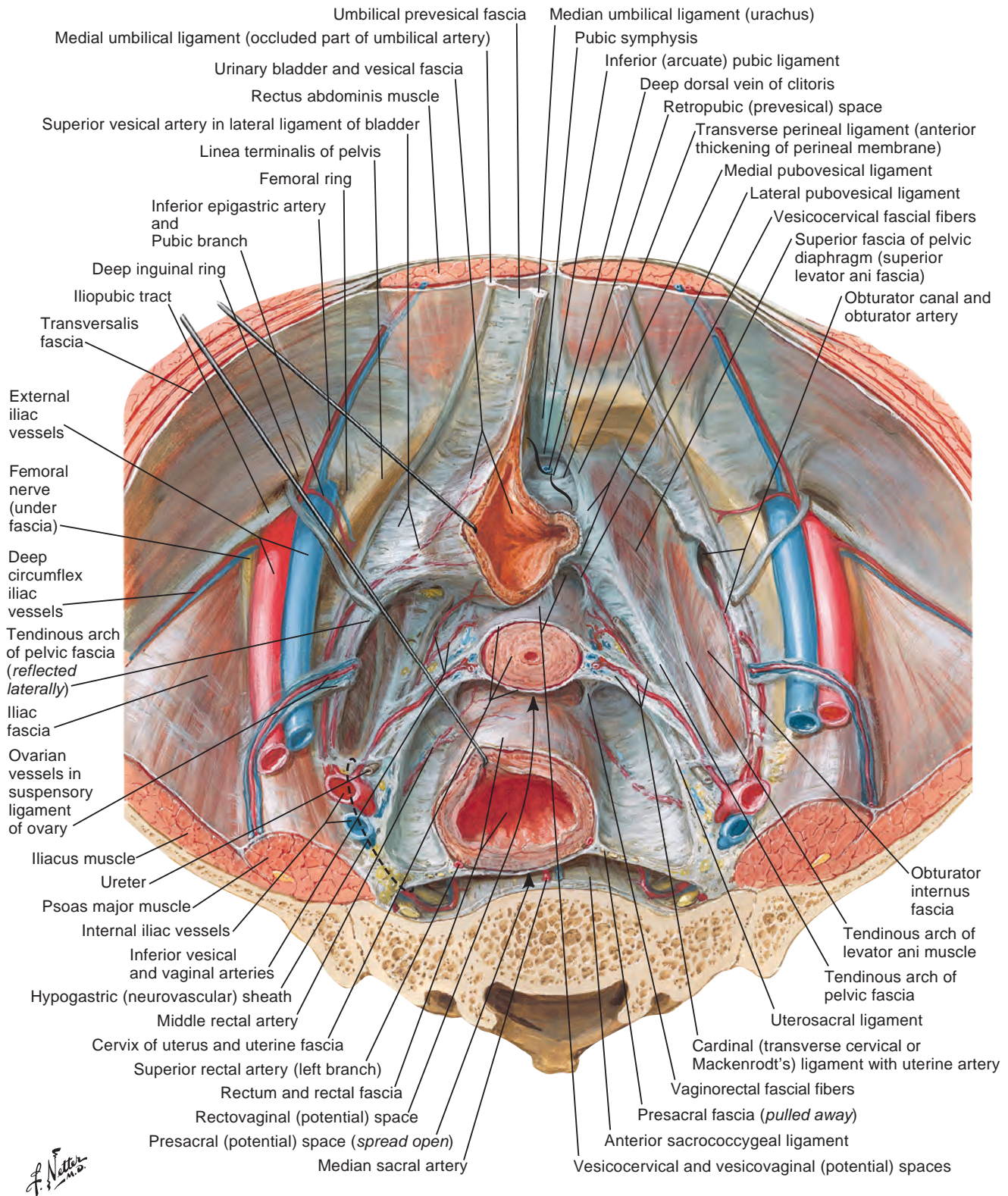
Female: superior view (peritoneum and loose areolar tissue removed)

Figure 67-3. Fascia of the pelvis and potential spaces. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

the obliterated umbilical artery. The **retrorectal space** is between the rectal fascia and transversalis fascia over the sacrum. Laterally there are the **paravesical** and **pararectal spaces**, which sit adjacent to their respective organs.

The **pouch of Douglas** or **rectouterine pouch** is formed by a fold of peritoneum (rectovaginal fold) that extends between the

uterus and rectum. It is bound by the uterus, posterior vaginal fornix, rectum, and uterosacral ligaments. The **vesicouterine pouch** is demarcated by a fold of peritoneum (utero-vesical fold) reflected onto the bladder from the uterus located just at the junction of the uterine body and cervix. The peritoneum also forms the **uterosacral fold** between the pararectal and paravesical fossae.

LIGAMENTS

There are several pelvic ligaments of importance to urosurgical anatomy: the **sacrospinous**, **sacrotuberous**, and **sacroiliac** ligaments. The sacrospinous ligament attaches from the ischial spine to the lateral border of the sacrum and crosses in front of the sacrotuberous ligament, fusing with it medially. The **coccygeus muscle covers the sacrospinous ligament**. Above this lies the **sciatic nerve and plexus**, which is an important structure to avoid during vault suspensions. The sacrotuberous ligament attaches from the ilium and ischium to the sacrum. It runs from the posterior iliac spine along the sacral border and attaches to the ischial tuberosity. The greater and lesser sciatic foramina run above and below this ligament (Rosenblum et al, 2005).

Posteriorly there are also short and long dorsal sacroiliac ligaments that connect the sacrum to the ilium. The sacrospinous ligament lies in continuity with the sacrococcygeal ligament. The iliolumbar ligament connects the fifth lumbar vertebrae to the ilium (Fig. 67-4).

In addition, condensations of the transversalis fascia form ligamentous structures that help to support the pelvic organs. These include the pubovesical ligaments, vesicopelvic ligaments, pubocervical fascia, and cardinal and uterosacral ligaments.

The **pubovesical ligaments (pubourethral ligament)** are homologous to the **puboprostatic ligaments** in males and run from the pubic bone to the bladder neck. They are important structures in retropubic suspension; they hold the bladder neck in place when it contracts, and they provide a hammocklike support to the mid-urethra. The **vesicopelvic ligament or fascia is formed from fusion of the perivesical and endopelvic fascia**. It extends from the base of the bladder and anterior vaginal wall and attaches to the tendinous arch. It is continuous with the periurethral fascia and the uterine cervix and cardinal ligaments. Defects in this fascia or ligament can result in lateral cystocele defects (MacLennan, 2012).

The **broad ligament** contains the fallopian tube and ovary and lies on the posterolateral surface of the uterus attaching it to the pelvic wall. It is formed by peritoneum extending from the anterior and posterior surfaces of the uterus. Within the mesometrium of

the broad ligament are the uterine artery, veins, and nerves. The broad ligament also contains the mesosalpinx, which has a vascular network between the uterine tube and ovary. The **round ligament (present within the broad ligament)** exits at the internal inguinal ring and crosses over the external iliac artery and terminates in the mons pubis of the labium majus. It attaches the lateral walls of the uterine body to the pelvic sidewalls. It contains the ovarian ligaments and is homologous to the gubernaculum of the male. Behind the broad ligament lies the infundibulopelvic ligament (suspensory ligament of the ovary), which runs from the ovary to the lateral surface of the uterus beneath the entrance of the fallopian tube. It contains the ovarian vessels (Fig. 67-5).

Within the parametrium are the important **cardinal and uterosacral ligaments**. There are blood vessels, nerves, smooth muscle, adipose, and connective tissue that lie near these ligaments. Nerves from the pelvic plexus travel through the cardinal and uterosacral ligaments with the vessels, and damage to these during a hysterectomy can result in bladder dysfunction. The **uterosacral (sacrouterine) ligaments** originate from the greater sciatic foramen and insert into the lateral aspect of the fascia that encircles the cervix, isthmus of the uterus, and vaginal wall. They contain fibrous tissue and smooth muscle. They are often used as anchoring structures in apical suspensions. The **ureter lies lateral to the anterior portion of the uterosacral ligament** (closest at the area of the cervix). There is potential for sacral nerve entrapment (S1 and S2 to S4 nerve trunks) during a suspension as the nerve crosses over these areas dorsally (Ramanah et al, 2012).

The **cardinal ligaments** fuse posteriorly with the uterosacral ligaments and stabilize the uterus, cervix, and upper vagina (Fig. 67-6). They originate from S2 to S4 and insert into the posterolateral aspect of the pericervical fascia and lateral vaginal wall. They run under the rectovaginal peritoneum and contain the major blood vessels from the internal iliac artery. The paracolpium suspends the superior aspect of the vagina to the pelvic wall.

The **ureter is vulnerable to injury as it passes near the ligaments that support the uterus and ovary (Fig. 67-7)**. It crosses the infundibulopelvic ligament under the ovarian artery and is just medial to the uterine artery. It also passes near the cardinal ligament and lies in close proximity to the cervix.

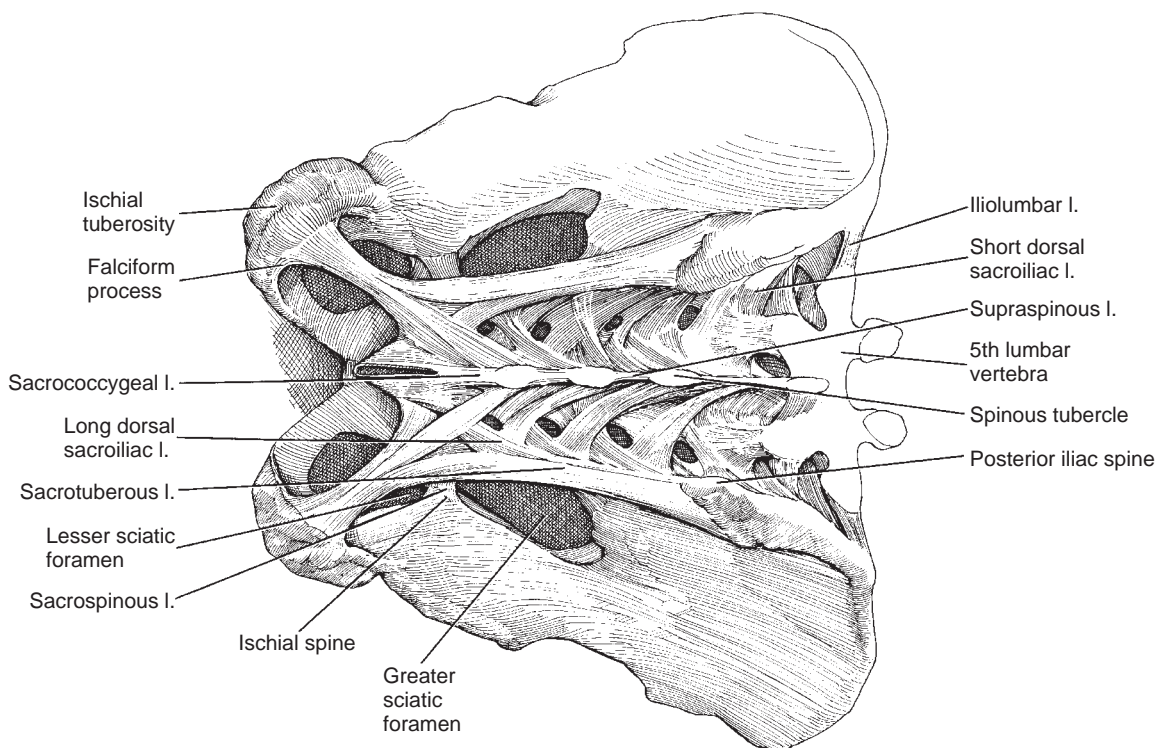


Figure 67-4. Ligaments of the pelvis. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

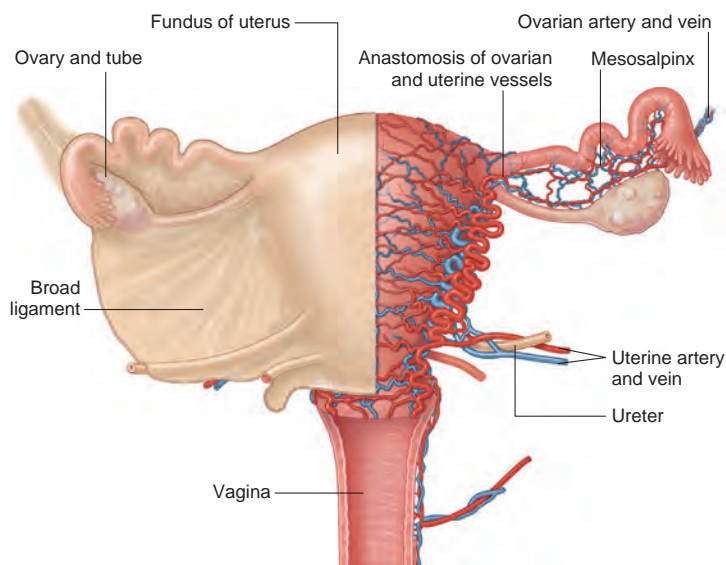


Figure 67-5. The broad ligament of the uterus and its contents. (From Standring S. *Gray's anatomy: the anatomical basis of clinical practice*. 40th ed. London: Churchill Livingstone; 2008.)

MUSCLES OF THE PELVIC FLOOR

Pelvic Sidewalls

The walls of the pelvis are formed by the obturator internus, iliacus, psoas major and minor, levator ani system, and the coccygeus.

The obturator internus covers most of the lateral pelvic sidewall. It passes through the lesser sciatic foramen and attaches to the greater trochanter of the femur. The piriformis muscle covers and pads the pelvic wall posterolaterally. It passes through the greater sciatic foramen to attach to the greater trochanter of the femur and is associated with the sacral plexus medially.

Pelvic Floor

The pelvic floor is composed of the pelvic diaphragm, which extends from the pubis anteriorly to the coccyx posteriorly. **It is composed of the levator ani muscles and plays an important role in support of the urogenital viscera as well as their function.** The levator ani complex consists of the **pubococcygeus, puborectalis, and iliococcygeus**. The name of each of its components is derived from their attachments. The **pubococcygeus originates at the posterior portion of the pubis and arcus tendineus** and attaches to the visceral organs and anococcygeal raphe. It can be subdivided into smaller muscles that are not well delineated and can be named after the structures they surround. These include the pubourethralis, pubovaginalis, and puboanalis (together referred to as the pubovisceralis). The pubococcygeus plays an active role in visceral control. It forms a sling around the urethra and vagina and is known as the pubovaginal muscles. The puborectalis is part of the pubococcygeus and originates on the pubic bone and forms a muscular sling around the vagina, rectum, and perineal body. **The iliococcygeus originates at the obturator fascia and ischial spine.** The muscles meet in the midline to form the anococcygeal ligament or raphe. The opening of the levator ani muscle group is referred to as the levator hiatus and allows passage of the urethra, vagina, and rectum. The fascial attachments provide additional support to the viscera. **The levator plate is created by the fusion of the levator ani muscles in the midline and serves as a shelf on which the viscera rest.** Weakening of the levator ani may cause the plate to sag and open the hiatus, predisposing to pelvic organ prolapse (Herschorn, 2004).

The ischiococcygeus is sometimes referred to as the coccygeus. This muscle extends from the ischial spine to the coccyx and sacrum and contributes to the posterior part of the pelvic diaphragm. It sits anterior to the sacrospinous ligament. The coccygeus and iliococ-

cygeus are thought to be innervated by divisions of the pudendal nerve, inferior rectal nerve, and perineal nerve, but more recent studies describe its innervation solely from the levator ani nerve originating from S3, S4, and S5, which travels medial to the ischial spine and ATLA (Barber, 2005).

There is a constant resting tone to the pelvic floor muscles that help support the pelvic viscera, resist increases in intra-abdominal pressure, and play an important role in passive control of urinary and fecal continence. When there is loss of this tone resulting from muscle or nerve injury, the urogenital hiatus becomes more lax and there is a lessening of the horizontal orientation of the levator plate (Barber, 2005) (Fig. 67-8).

VASCULATURE OF THE PELVIS

The vascular anatomy will be reviewed in detail in Chapter 33, but there are some pertinent differences in the female pelvic vascular anatomy that need to be noted.

The internal iliac artery (hypogastric artery) branches into a posterior and anterior division. **The uterine artery arises from the anterior trunk and enters the broad ligament and cardinal ligament.** It branches into an ascending branch that anastomoses with the ovarian and fallopian tube arteries as well as with a descending limb that supplies the cervix and vagina. **The uterine artery passes in front of the ureter, making the ureter vulnerable to iatrogenic injury during division of the uterine pedicle.**

The venous drainage of the pelvis parallels the arteries but contains an intricate network of plexuses (uterine, vaginal, retropubic, vesical, rectal). The internal iliac vein is the main venous drainage from the pelvis running posteromedial to the artery. The internal pudendal vein drains the corresponding structures that the artery supplies and drains directly into the internal iliac vein. The obturator vein lies posterior to the artery and ureter and drains into the internal iliac vein. The superior and inferior gluteal veins, lateral sacral veins, and middle rectal and rectal venous plexuses also drain directly into the internal iliac vein. The clitoral veins drain into the retropubic plexus, which is much smaller relative to the Santorini plexus in the male. The retropubic plexus drains through the vesical plexus, which lies over the anterior portion of the bladder (in continuity with the uterine plexus) and subsequently drains into the internal iliac vein. The retropubic plexus also receives blood from the external genitalia and rectum. The uterine and vaginal plexuses communicate with each other and drain into the internal iliac vein.

The external iliac vein is a continuation of the femoral vein and drains the inferior epigastric vein, deep circumflex iliac, and pubic veins (Fig. 67-9).

LYMPHATIC DRAINAGE

The internal iliac nodes lie near the origin of the uterine, pudendal, and middle hemorrhoidal arteries. They drain the bladder, uterus, rectum, and perineum. They then communicate and drain into the middle chain of the common iliac nodes.

The external iliac nodes are divided into three chains: external, middle, and internal. The clitoris and abdominal wall drain into the superficial and deep inguinal nodes that feed the external chain. The bladder, uterus, and vagina drain into the middle chain that lies over the external iliac artery. The internal chain drains the lower abdominal wall, clitoris, superficial and deep inguinal nodes, bladder neck, and urethra. More details of lymphatic drainage will be highlighted throughout the remainder of the chapter.

INNERVATION

The innervation is also reviewed in Chapter 68. The sacral plexus is formed from the ventral rami of L4 to L5 and S1 to S3 and lies on the piriformis muscle deep to the endopelvic fascia and posterior to the internal iliac vessels. **It exits the pelvis through the greater**

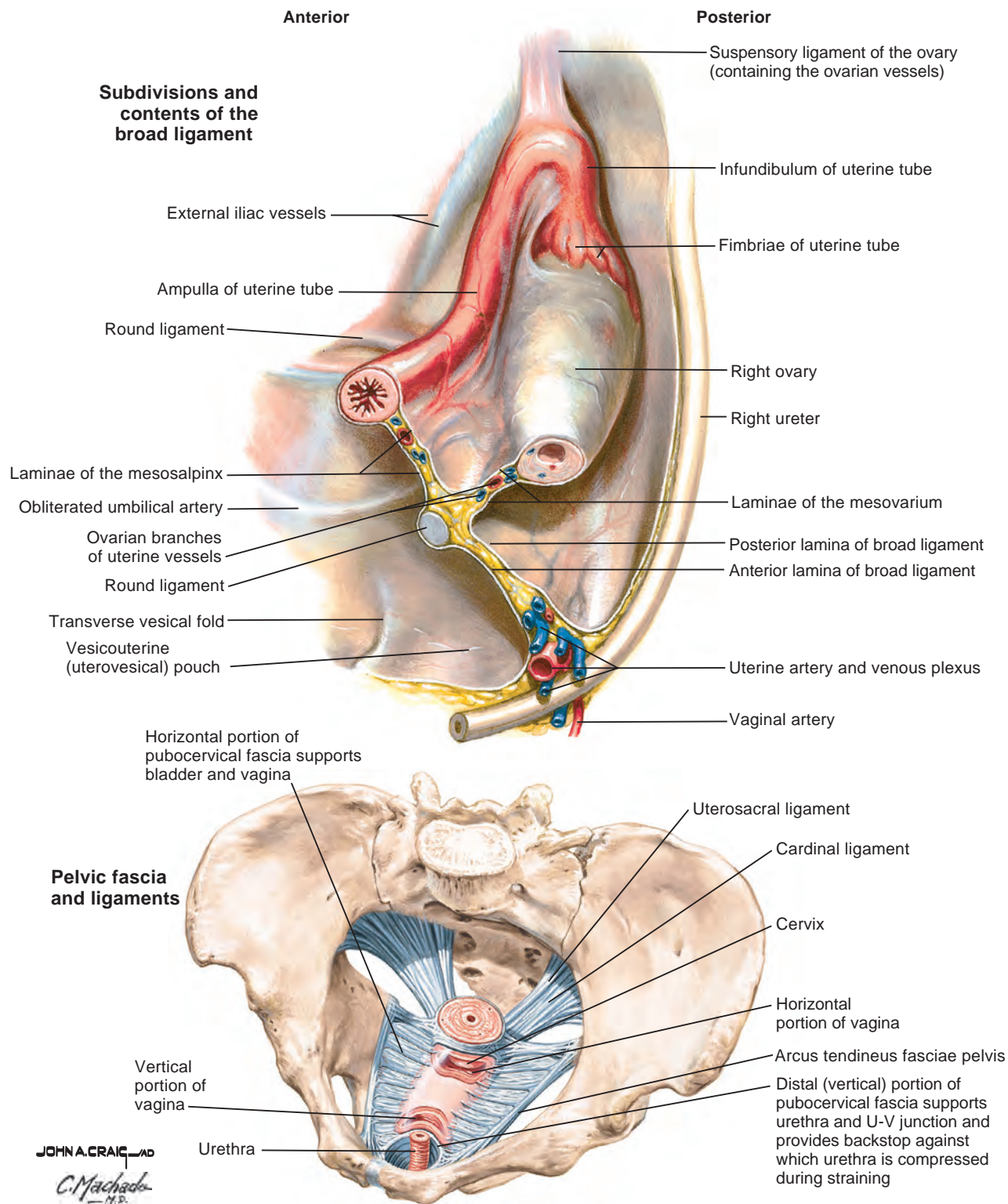


Figure 67-6. Ligament and support of the vagina and uterus. (Copyright 2016 Elsevier Inc. All rights reserved. www.netterimages.com.)

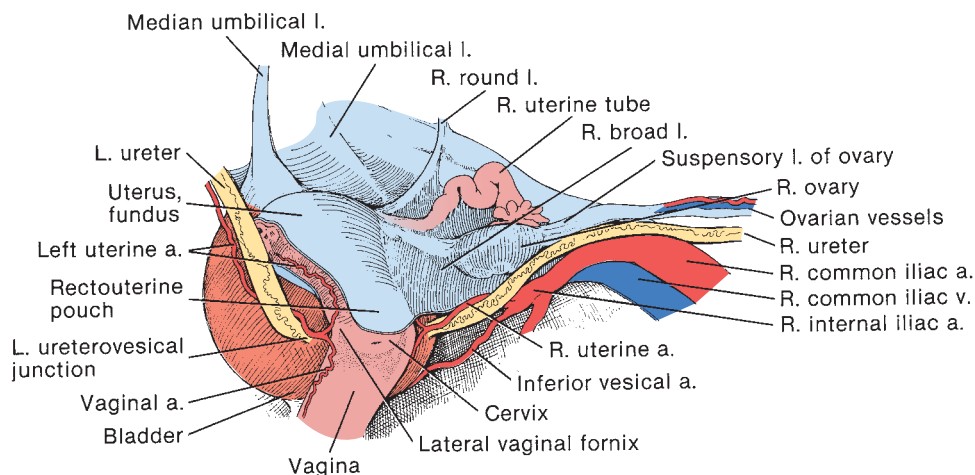
sciatic foramen immediately posterior to the sacrospinous ligament and can be injured during a sacrospinous culdosuspension. It supplies motor and sensory innervation to the posterior thigh and lower leg. Exaggerated lithotomy position may stretch this nerve or place pressure on its peroneal branch at the fibular head to produce foot drop.

Pelvic and perineal branches of the sacral plexus include the posterior femoral cutaneous nerve (S2, S3) that passes through the

greater sciatic foramen and has a sensory branch to the perineum. It also includes the pelvic somatic efferent nerves from the ventral rami of S2, S3, and S4. They travel on the pelvic surface of the levator ani, innervating these muscles as well as the striated urethral sphincter.

The pudendal nerve arises from S2 to S4 just above the sacrotuberous ligament and ischiococcygeus. It passes through the greater sciatic foramen and crosses the piriformis and

Figure 67-7. Close relationship of ureter to the uterine structures. a., artery; l., ligament. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)



the bladder base, which then yields the vesical plexus and utero-vaginal plexus that sends fibers through the broad ligament. The parasympathetic fibers usually lie deeper to the sympathetic fibers within the intermediate stratum.

PERINEUM

The borders of the perineum are the pubic symphysis anteriorly, pubic rami and ischial rami anterolaterally, ischial tuberosities laterally, sacrotuberous ligaments posterolaterally, and sacrum and coccyx. It is divided into the anal triangle posteriorly and urogenital triangle anteriorly by a line connecting the ischial tuberosities. The perineal membrane (previously called the urogenital diaphragm) is a sheet of fascia that lies between the two sides of the pubic arch. The urethra and vagina pass through the urogenital hiatus of the perineal membrane to exit at the vestibule.

The perineal membrane divides the urogenital hiatus into a superficial and deep perineal space. It attaches laterally to the ischiopubic rami, and its apex is attached to the arcuate ligament of the pubis. The posterior border is fused with the perineal body. The deep space contains the external urethral sphincter, urethrovaginalis, compressor urethrae, and deep transverse perineal muscles. The inferior fascia of the urogenital diaphragm is what lays the groundwork for the deep space. The superficial space is made up of the superficial perineal muscles, clitoris, vestibular bulbs (bulbospongiosus), and Bartholin glands. Bartholin glands are homologous to Cowper glands but lie more superficially. Colles fascia or the membranous layer of the superficial fascia covers the superficial perineal space. It attaches laterally to the pubic rami and the ischial tuberosities. Posteriorly it meets the perineal membrane and anteriorly covers the clitoris similar to the dartos fascia in the male. The deep perineal fascia lies over the superficial muscles of the perineum and fuses with the suspensory ligament of the clitoris and fascia of the rectus sheath and external oblique muscles.

The perineal body is at the central point of the perineum and consists of muscle and collagenous and elastic fibers. It is the convergence of the bulbospongiosus, external anal sphincter, and superficial and deep transverse perineal muscles. It is posterior to the vestibule of the vagina and anterior to the anal canal and attaches to the posterior border of the perineal membrane. Damage to the perineal body during parturition can result in damage to the fibers of the external anal sphincter. An episiotomy is angled laterally to avoid damage to these fibers.

The bulbospongiosus splits to surround the introitus and attaches anteriorly to the clitoris. It attaches to the perineal body and covers the vestibular bulbs. They contract to constrict the vaginal orifice and express vestibular gland secretions. The ischio-cavernosus also covers one crus of the clitoris and promotes its erection. The superficial transverse perineal muscles overlie the posterior portion of the vagina.

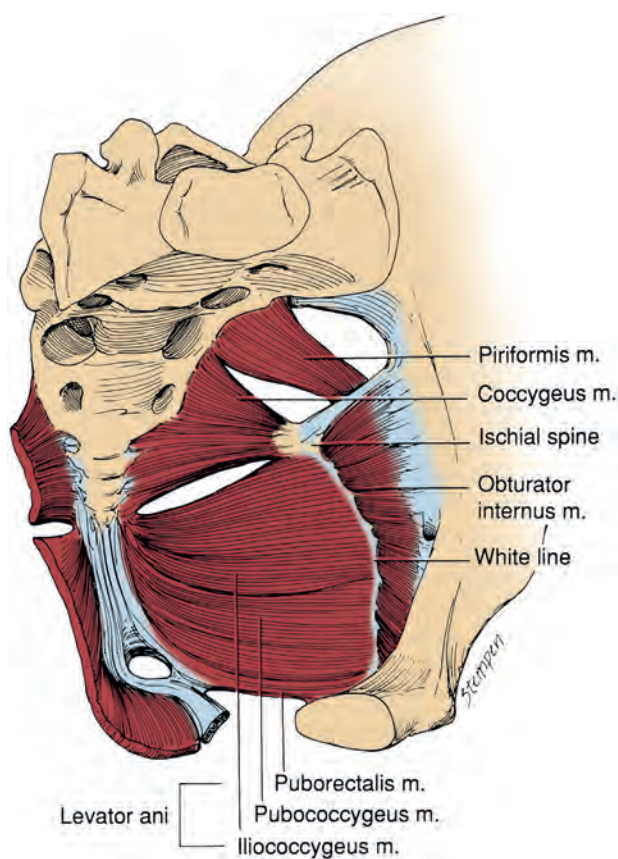


Figure 67-8. Muscles of the true pelvis (three-quarter view).

ischiococcygeus as well as the sacrospinous ligament close to the area where it attaches to the ischial spine. This also makes it vulnerable to injury during a sacrospinous ligament culdosuspension. It then runs medially to the internal pudendal vessels as they travel through the lesser sciatic foramen into the Alcock canal. The pudendal nerve has three branches: (1) inferior rectal nerve, (2) perineal nerve, and (3) dorsal nerve of the clitoris. The perineal branch divides into the posterior labial branch to supply the labium majus, superficial and deep transverse perineal muscles, external anal sphincter, and levator ani. The pudendal branches carry efferent impulses to muscles of the pelvic floor and proprioceptive afferent signals and sensation from the urethra.

The superior hypogastric plexus arises from the aortic plexus below the aortic bifurcation at L5. It bifurcates into the left and right hypogastric nerves that unite with the pelvic splanchnic nerves. The right and left pelvic (hypogastric) plexuses lie near

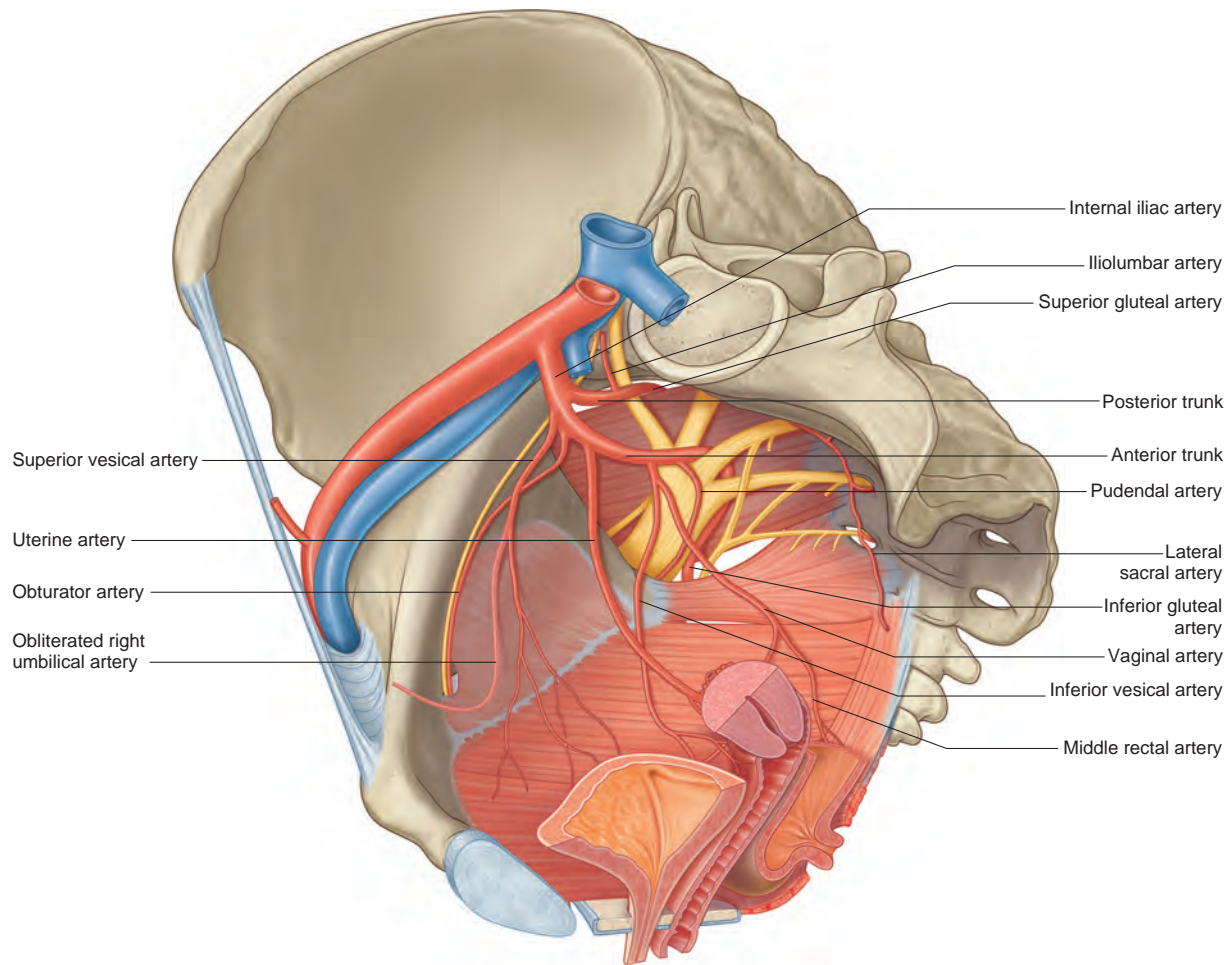


Figure 67-9. Arterial supply of the pelvis. (From Standring S. *Gray's anatomy: the anatomical basis of clinical practice*. 40th ed. London: Churchill Livingstone; 2008.)

The perineum is supplied by the internal pudendal artery, which travels through the perineal membrane and branches into the posterior labial branches, the artery of the bulb to the erectile tissue of vestibular bulbs, and the arterial supply to the clitoris and corpus cavernosum (Fig. 67-10).

ANAL PERINEUM

The rectum is covered in pararectal fascia that connects the anorectal junction to the sacrum. Anteriorly there is rectovesical fascia and posterolaterally there are lateral ligaments of the rectum that run with the middle rectal vessels. The anococcygeal ligament also provides anal canal support and runs between the middle of the external anal sphincter and the coccyx.

The ischioanal fossa contains fat and Colles fascia and is bound by the external anal sphincter, ischial tuberosity, urogenital diaphragm, and gluteus maximus. The internal pudendal vessels run on the lateral wall of the fossa inside Alcock canal. The internal rectal venous plexus lies between the rectum and puborectalis and levator ani muscles. The external plexus lies deep to the sphincters. They both drain into the middle rectal vein. The superior rectal vein drains into the inferior mesenteric vein and the inferior rectal vein drains into pudendal vein.

The external anal sphincter is composed of striated muscle and has three parts. From distal to proximal, they include the subcutaneous external anal sphincter, the superficial external sphincter, and the deep external sphincter. The deep external anal sphincter is adjacent to the deep transverse perineal muscles and the levator ani. The external anal sphincter is innervated by

the inferior rectal nerve and by branches of the pudendal nerve. The internal anal sphincter is a circular nonstriated muscle lying outside the internal rectal venous plexus. It receives autonomic innervations from branches of the iliohypogastric plexus. Fecal continence is complex and depends on the integrated function of the internal and external anal sphincters, the puborectalis muscle, intact neurosensory pathways, rectal compliance, anorectal sensation, and anal sphincter resting tone.

EXTERNAL GENITALIA

The **mons pubis** is the hair-bearing area of skin overlying the pubic symphysis. The hymen is composed of folds of mucous membranes that lie at the entrance of the vagina. The **labia majora** frame the vagina laterally and fuse anteriorly at the hood of the clitoris and are the homolog of the scrotum. The mons pubis is continuous with the labia. The **labia minora** are fat free and hairless and immediately surround the vestibule of the vagina. They contain erectile tissue, and blood vessels are connected by the frenulum or fourchette.

The clitoris is bounded by the labia minora, by the prepuce dorsally, and ventrally by the frenulum. It is composed of a root, body, and glans. There are two corpora cavernosa that split as crura proximally to attach to the inferior ischiopubic rami and are surrounded by the ischiocavernosus. They fuse distally and terminate as the glans, which is composed of spongy erectile tissue and is connected to the bulbs by bands of erectile tissue. The erectile bodies are composed of the bulbar commissure ventrally and the bulbs of the vestibule, which are covered by bulbospongiosus

Figure 67-10. Female superficial perineal pouch. Left, the muscles have been removed to show the vestibular bulb and Bartholin gland. (From Williams PL, Warwick R. *Gray's anatomy*. 35th British ed. Philadelphia: Saunders; 1973.)

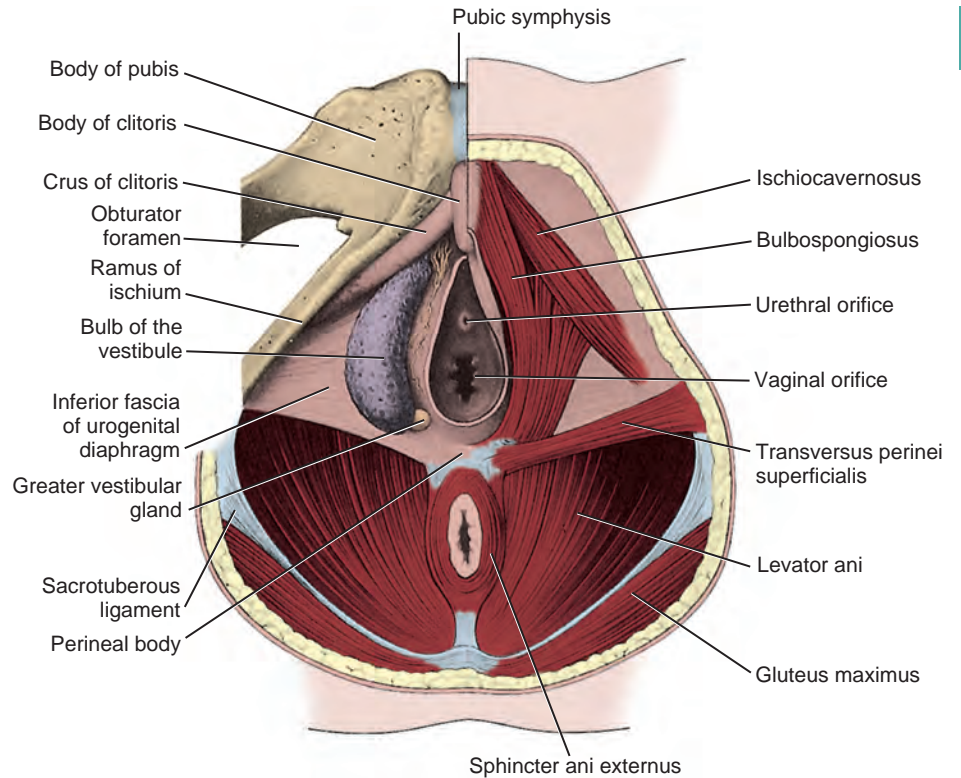
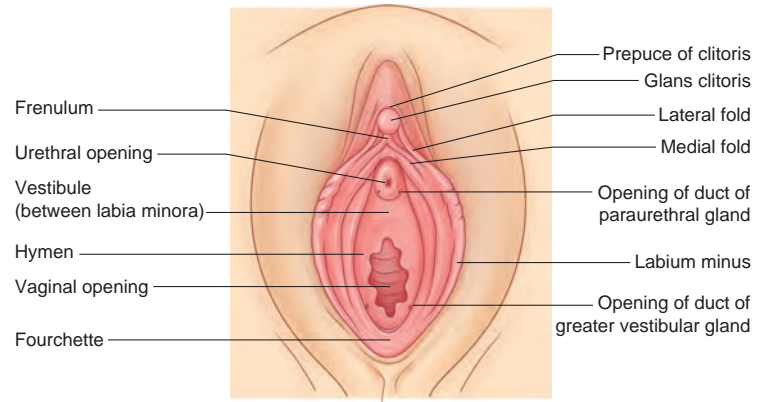


Figure 67-11. Female vulva and external genitalia. (From Standring S: *Gray's anatomy: the anatomical basis of clinical practice*. 40th ed. London: Churchill Livingstone; 2008.)



muscle. Bartholin glands are at the end of each bulb and travel 2 cm to empty through the groove between the hymen and labia minora. These glands can become obstructed and present as Bartholin gland cysts.

The vulva has lymphatic drainage into the superficial inguinal glands. These then drain to the deep inguinal nodes that travel to the pelvic nodes. The clitoris and labia minora drain to the deep inguinal nodes and may pass to the internal iliac nodes (from the clitoris).

The innervation to the anterior labium majus comes from branches of the ilioinguinal nerve, which arises from T12. Branches from the perineal nerve innervate the posterior two thirds. Laterally there is also innervation from the perineal branch of the cutaneous nerve of the thigh. Parasympathetic stimulation results in increased vaginal secretion, erection of the clitoris, and engorgement of the erectile tissues (Figs. 67-11 and 67-12).

FEMALE PELVIC ORGANS

The uterus is composed of the uterine body and the cervix and is normally anteverted and anteflexed. The cervix terminates as the

os into the vagina. It is surrounded by the vaginal wall that is shallow anteriorly (ventral fornix) and deeper posteriorly (dorsal fornix) along with lateral fornices. The cervix is usually 2.5 cm long (Standring, 2008). The cervix is adjacent to the bladder and is separated only by the parametrium. **The body of the uterus is composed of three layers.** The outermost layer is the **perimetrium**, which is the peritoneum and thin connective tissue (parametrium). The **myometrium** is broken down into three additional layers: outer longitudinal layer continuous with the ovarian and round ligament, middle circular layer, and inner longitudinal layer. The blood vessels and nerves are located in this layer. The innermost layer of the uterus is the **endometrium** or mucosal layer.

The uterine artery is a branch off the anterior branch of the internal iliac artery. It crosses the ureter close to the cervix and also provides a small branch to the ureter. It passes through the broad ligament and feeds the fallopian tube, and it then runs laterally and joins the ovarian artery. There are branches to the cervix and the cervix terminates as the azygos arteries of the vagina. The uterus drains into a uterine plexus that runs in the broad ligament and joins the vaginal and ovarian plexuses to drain eventually into the internal iliac vein. Innervation is from the uterovaginal plexus, which originates from the inferior hypogastric plexus.

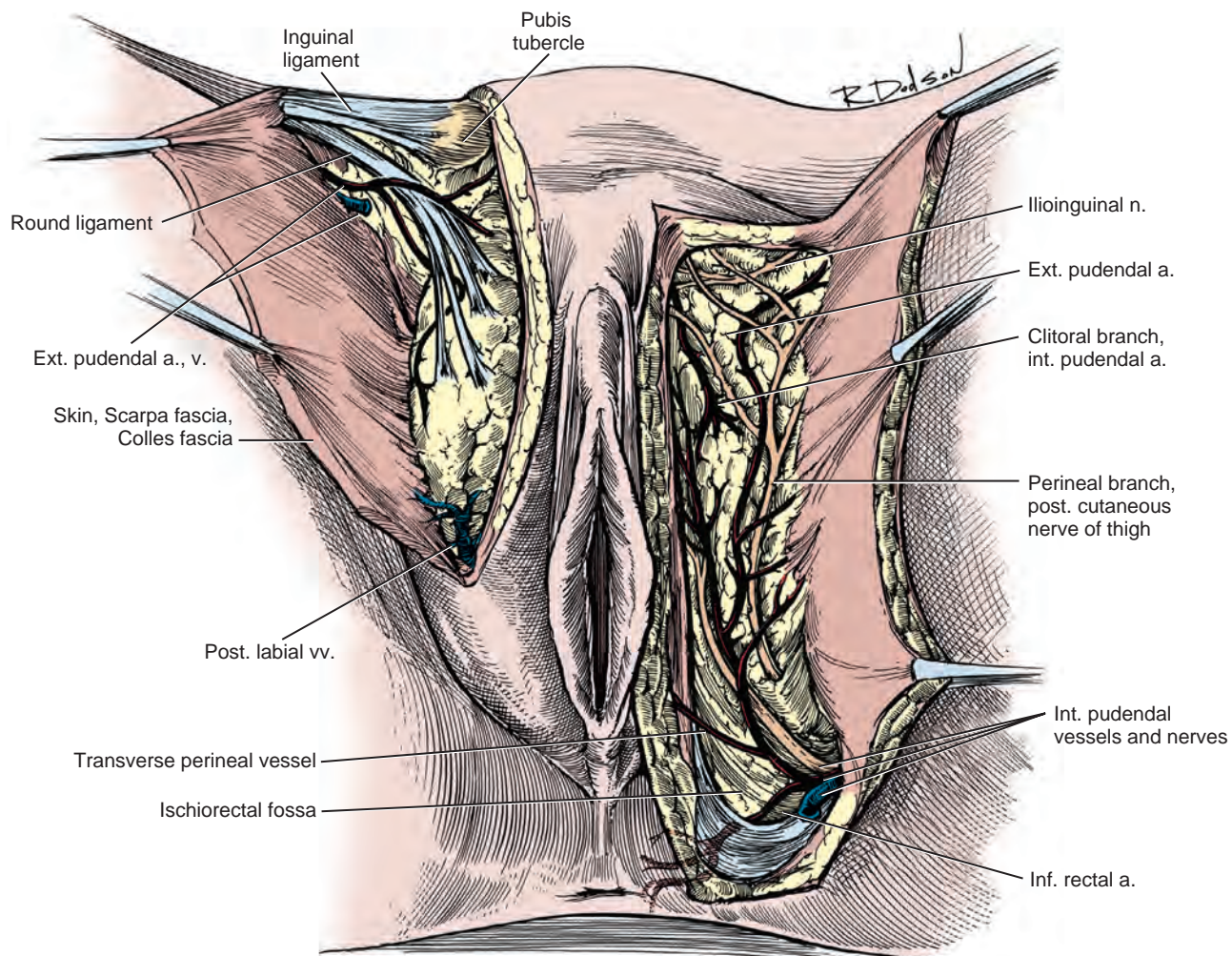


Figure 67-12. Arteries and nerves of the female perineum. (From Doherty MG. Clinical anatomy of the pelvis. In: Copeland LJ, editor. Textbook of gynecology. Philadelphia: Saunders; 1993. p. 51.)

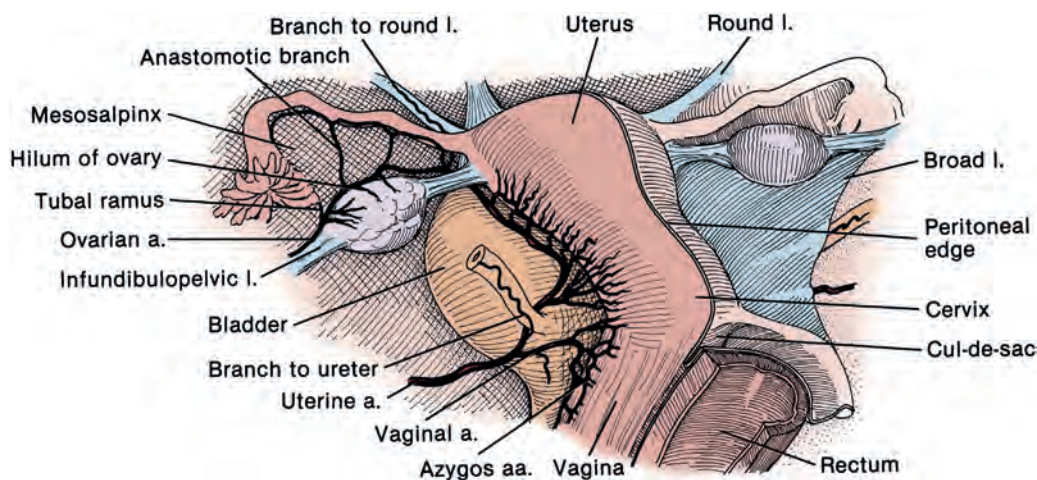


Figure 67-13. Female internal genitalia, from behind. The ureter passes beneath the uterine artery. a., artery; l., ligament. (From MacLennan GT. Hinman's atlas of urosurgical anatomy. 2nd ed. Philadelphia: Saunders; 2012.)

The lymphatic drainage of the uterus is complex. The cervix drains into the external and internal iliac nodes as well as the sacral nodes. The upper part of the uterus and fallopian tubes follow the ovary drainage into the lateral aortic and preaortic nodes. Around the area of the round ligament, there is drainage into the superficial

inguinal nodes. The uterine body drains into the external iliac nodes. The fundus drains into the para-aortic and lateral aortic nodes (Fig. 67-13).

The uterine or fallopian tubes are 10 to 12 cm in length and are draped in the broad ligaments. They open posteromedially

and are divided into four parts: uterine interstitial segment, isthmus, ampulla, and infundibulum. They terminate with fimbriae. They enter the uterus bilaterally at the uterine cornua. There is arterial supply from both the ovarian and uterine arteries. The lateral two thirds drain into the ovarian veins and the medial portion drains into the uterine plexus. Lymphatic drainage is to the para-aortic nodes (ovarian vessels), internal iliac chain (uterine vessels), and inguinal nodes (round ligament). Innervation is by autonomic fibers from the ovarian and uterine plexuses.

The ovaries are supported by the mesovarium and are in the ovarian fossa in the posterior peritoneum, which is bordered by the obliterated umbilical artery, ureter, and internal iliac artery. The ovary is attached to the posterior aspect of the broad ligament and is suspended by the infundibulopelvic ligament, which contains the ovarian vessels. It is also attached to the uterus by the ovarian ligament. The ovarian artery arises directly from the aorta and passes in the infundibulopelvic ligament into the hilum of the ovary. It then passes through the broad ligament supplying the fallopian tube and joins the uterine artery. The venous drainage of the ovary is to a pampiniform plexus that merges into the ovarian vein. Similar to the testicle, the drainage of the right vein drains directly into the vena cava below the renal vein and the left drains into the left renal vein. Innervation is from the ovarian plexus and inferior mesenteric plexus and it follows the path of the ovarian artery. The lymphatic drainage is also similar to the testicle and drains into the lateral aortic and preaortic nodes near the kidneys.

The vagina appears H shaped when cross sectioned and contains rugae or folds. There are columns that run on the anterior and posterior walls terminating at the urethrovaginal ridge or carina. The vagina is composed of a mucous membrane and lamina propria that are fixed to the muscular layer. The muscle has an outer longitudinal and an inner circular layer that are attached to the rectovesical fascia on either side. The muscle is lined by nonkeratinized stratified squamous epithelium. The vaginal wall is attached to the cervix higher on the posterior wall compared to the anterior wall. Therefore the anterior wall is about 7.5 cm on average, and the posterior wall is 9 cm. There are remnants of the ducts of Gartner that can protrude through the lateral fornices of the vagina, and when obstructed they can lead to Gartner cysts.

The vagina is attached anteriorly by the levator ani at the arcus tendineus and posteriorly to the rectovaginal septum. The apex is covered by the peritoneum from the rectouterine pouch. The base of the bladder rests on the vaginal wall and is tethered together by smooth muscle fibers that need to be opened to access the vesicovaginal space. The ureters pass close to the lateral fornices of the vagina and are anterior to the vagina as they enter the bladder. Access to the retropubic space can be obtained by incising the anterior vaginal wall on either side of the urethra.

The vessels and nerves lie on the anterolateral surface of the vagina deep to the ATFP. The uterine arteries supply the superior part of the vagina. The middle and inferior portion of the vagina are supplied by the vaginal arteries (branches of the uterine and middle rectal artery). The inferior portion is supplied by the internal pudendal artery. The vaginal venous plexus joins the uterine plexus to form the uterovaginal venous plexus. The superior portion of the vagina includes lymphatic drainage into the internal and external iliac lymph nodes. The middle portion drains into the internal iliac lymph nodes, and the inferior portion into the sacral and common iliac nodes as well as the superficial inguinal nodes.

The vagina has autonomic innervation from the uterovaginal plexus (sympathetic, parasympathetic, and visceral afferent fibers), which travels at the base of the broad ligament. The lower one fourth of the vagina also has somatic innervation from the pudendal nerve and is sensitive to touch and to temperature changes.

PELVIC ORGAN SUPPORT

The pubovesical ligaments help support the urethra and bladder neck but may also play a role in relaxation of the bladder neck

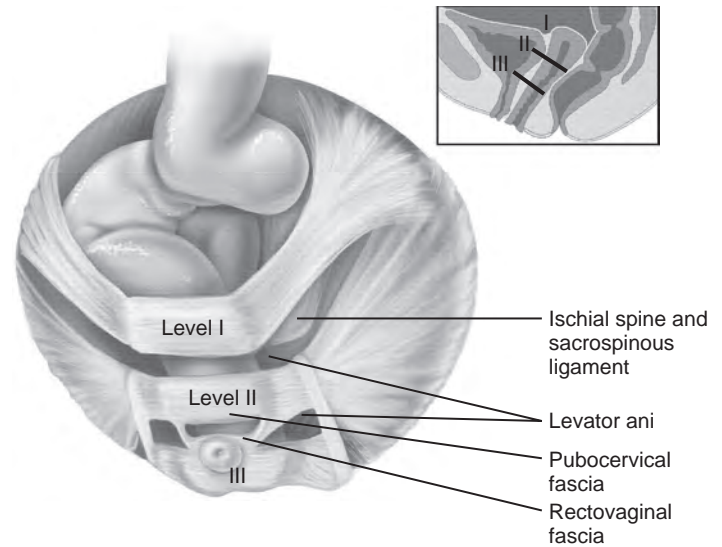


Figure 67-14. Vaginal and visceral supportive structures as defined by DeLancey. The fibers of level I support are oriented vertically and suspend the uterus and upper vagina. Level II support is more horizontal in its orientation and is attached to the mid vagina. Distally, level III support fuses directly into the support structures. (From DeLancey JO. Anatomic aspects of vaginal eversion after hysterectomy. *Am J Obstet Gynecol* 1992;166:1717–28.)

during micturition (Herschorn, 2004). Whether or not there is any true fascia at the anterior vaginal wall is controversial. However, the anterior vagina does provide support to the urethra through its lateral attachment to the pubococcygeus and ATFP. The pubocervical fascia that extends from the pubic symphysis to the cervix (another disputable structure) may provide additional support to the bladder base (Herschorn, 2004).

The parametrium and paracolpium provide support to the vagina and uterus. The cardinal ligaments and uterosacral ligaments also provide additional support to the uterus, cervix, and upper vagina. This is level I support as originally described by DeLancey (Wei and DeLancey, 2004), which supports the uterus and the vaginal apex. The broad ligament and round ligament do not play a significant role in pelvic organ support (Barber, 2005). Weakness of the lateral attachments of the cardinal ligaments or vesicopelvic ligaments leads to lateral cystocele defects. The posterior vaginal wall is supported by the paracolpium that attaches to the rectovaginal fascia (Herschorn, 2004). This sheet of fascia at its medial aspect of the vagina is sometimes referred to as the rectal pillars (Ashton-Miller and DeLancey, 2007). Level II support is from the paravaginal attachments to the ATFP (Barber, 2005) and to the arcus tendineus rectovaginalis. Level II support is for the anterior vaginal wall, and loss of this support can lead to anterior wall prolapse. The distal vagina is directly attached to the surrounding structures fusing with the urethra and perineal membrane (Level III support). Laterally it attaches to the levator ani muscles and fuses with the perineal body. Level III support relates to the urethra, and disruption of this support results in urethral hypermobility (Fig. 67-14).

URETHRA

The anatomic length of the female urethra is about 4 cm from the internal to the external urethral meatus. The urethra lies just anterior to the vagina below the pubic bone.

The urethra is composed of three anatomic layers: (1) epithelium, (2) submucosa, and (3) mucosa. The urethra is made up of the transitional epithelium with multiple infoldings that allow distensibility and coaptation on closure. This transitions to the pseudostratified and squamous epithelium at the most distal portion. It is

surrounded by a spongy tissue of vascular networks that make up the submucosa, which is similar to the corpus spongiosum in a male. Surrounding this is a thin periurethral fascia. **The mucosa and submucosa are the primary contributors to urethral closure pressure and are estrogen dependent.** There is a proximal and distal venous plexus that runs under the epithelium that may also play a role in urethral closure. Aneurysms may form in these plexuses.

There are many periurethral glands around the urethra that, when obstructed, can give rise to diverticula. The most prominent are Skene glands, which open distally just inside the meatus.

External to the urethra are two layers of smooth muscle, an inner longitudinal and an outer circular, which are continuous with the muscle layers of the bladder and constitute the involuntary urethral sphincter. These muscle layers are surrounded by elastic tissue and collagen. The longitudinal fibers shorten the urethra and increase the diameter for voiding (MacLennan, 2012). **At the distal two thirds of the urethra, the voluntary sphincter is present, which is composed of striated muscle.** At the most proximal portion (midurethra) it forms a horseshoe around the urethra. This is where the urethral closing pressure is highest. **There are muscle fibers on the lateral sides of the urethra that are continuous with the anterior and lateral walls of the vagina (urethral compressor).** When they contract, it results in closure of the urethra against the anterior vaginal wall. There are additional fibers that surround both the urethra and the vagina that compose the urethrovaginal sphincter. When these fibers contract, they tighten the urogenital hiatus. The pubococcygeus runs alongside the urethra on either side and has some function to increase resistance in the urethra. Innervation comes from both pudendal and somatic nerves that travel on the lateral vaginal wall. The somatic nerves innervate the striated urethral sphincter through the ventral root of S3 and some from S2.

Blood supply to the urethra comes from the inferior vesical, vaginal, and internal pudendal arteries. The venous drainage is carried through the inferior, middle, and superior vesical veins as well as the clitoral plexus into the internal pudendal veins. The distal one third of the urethra (anterior urethra) drains into the superficial and deep inguinal lymph nodes. The proximal two thirds (posterior urethra) drains into the iliac and obturator lymph nodes (Fig. 67-15).

RADIOGRAPHIC ANATOMY

There are many different modality images that are used to visualize the female pelvis and its contents.

KEY POINTS: SURGICAL ANATOMY OF THE FEMALE PELVIS

- The bony pelvis should be visualized in the supine position. Here the pelvis is oriented in such a fashion that allows most of the pressure of the intra-abdominal and pelvic contents to be directed toward the bony pelvis.
- The ATPF and ATLA are two distinct structures that should not be confused with each other.
- The ureter is vulnerable to injury during a hysterectomy because it comes into close proximity to the cervix and to the blood supply of the uterus and ovaries.
- The levator ani muscles (pubococcygeus, puborectalis, and iliococcygeus) and coccygeus make up the pelvic floor muscles and have a constant resting tone that helps support the pelvic viscera and resist increases in intra-abdominal pressure. They also play a role in fecal and urinary continence.
- Both the sacral plexus and the pudendal nerve are at risk of injury during a sacrospinous culdosuspension.

Fluoroscopy

Fluoroscopy is often used to obtain real-time imaging, especially to capture dynamic pictures of the bladder and urethra during voiding. It uses a low dose of radiograph beams that pass to an image intensifier (Raman and Boyadzhyan, 2008b) and to a high-resolution monitor. A cystogram is performed by taking static images of the bladder in different views after contrast is instilled. It usually includes a postdrainage picture of the bladder. It is used to diagnose bladder perforations, intravesical filling defects, and diverticula. Low-pressure fistulae to the bladder can also be visualized.

A voiding cystourethrogram (VCUG) takes dynamic pictures during voiding after contrast is instilled into the bladder and the Foley is subsequently removed. This test is often used concurrently with urodynamics (videourodynamics) to correlate dynamic with radiographic findings. This is especially helpful to evaluate the urethra and bladder outlet anatomy during voiding. Vesicoureteral reflux and vesical fistulae can also be diagnosed on VCUG. Urethral obstruction and diverticula can also be seen. High-grade cystoceles are easily seen on VCUG as well.

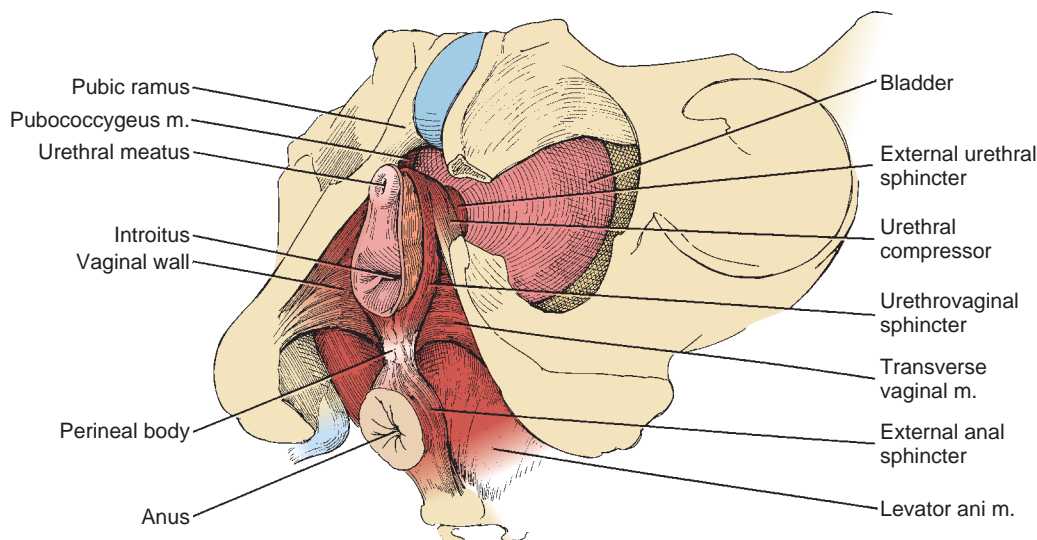


Figure 67-15. Urethra and its supportive structures that help to maintain continence. m., muscle. (From MacLennan GT. *Hinman's atlas of urosurgical anatomy*. 2nd ed. Philadelphia: Saunders; 2012.)

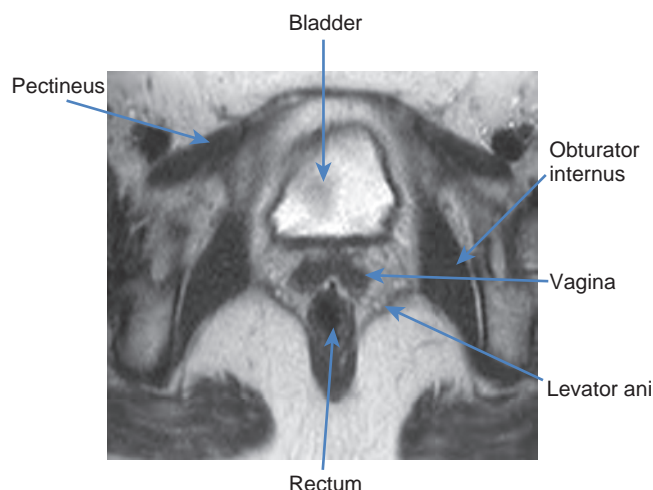


Figure 67-16. Axial T2 half-Fourier acquisition single-shot turbo spin-echo magnetic resonance imaging of normal female pelvic anatomy.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is one of the most helpful tools to visualize pelvic floor structures without the use of radiation. It provides well-delineated imaging of tissues such as muscle, fat, fluid, and blood (Raman and Boyadzhyan, 2008a). In pelvic floor imaging, the half-Fourier acquisition single-shot turbo spin-echo (HASTE) or single-shot fast spin-echo (SSFSE) T2-weighted sequences are often used. These provide quick, noninvasive multiplanar surveys of the abdomen and pelvis as well as dynamic studies to visualize the pelvic floor during relaxed and strained states (Raman and Boyadzhyan, 2008a). The obturator internus and levator ani muscles are well visualized by MRI (Fig. 67-16). T1-weighted imaging with gadolinium contrast is useful for visualization of the kidneys and ureters. T2-weighted imaging is useful to differentiate masses, cysts, and tissue parenchyma.

Pelvic MRI is useful in differentiating cystic lesions in the vagina and urethra. Some benign vaginal cysts include müllerian cysts, epidermal inclusion cysts, Gartner duct cysts, Bartholin gland cysts, and Skene gland cysts. MRI is the best imaging technique to visualize and localize urethral diverticula and to differentiate them from other benign vaginal cysts (Walker et al, 2011).

The uterus is imaged on T2-weighted MRI, which delineates its three zones: endometrium, junctional zone, and myometrium (Fig. 67-17). The endometrium and uterine cavity have high signal, whereas the junctional zone has low signal. The outer myometrium has medium to high signal. It is a great imaging modality to assess for leiomyomas and adenomyosis as well as to determine the vascular supply and staging endometrial and cervical cancer (Raman and Boyadzhyan, 2008b). Endometrial implants can also be diagnosed on MRI as well. Although adnexal imaging is performed primarily via ultrasonography, MRI can help provide better definition in certain cases such as differentiating malignancy from benign adnexal masses.

MRI can be used for the diagnosis and staging of pelvic organ prolapse. Midsagittal and parasagittal resting and straining supine views are obtained for evaluating the different compartments, pelvic floor muscles, and pelvic organs (Fig. 67-18). These images are often looped as a cine stack and are measured to fixed anatomic landmarks to determine the grade of pelvic organ prolapse and pelvic floor relaxation (Comiter, 2005). Measurements obtained include the “H-line,” or levator hiatus width, measured from the pubis to the posterior anal canal. The “M-line,” or muscular pelvic floor relaxation, measures the distance from the levator plate to the pubococcygeal line. The “O” classification is then assigned to the degree of prolapse beyond the “H-line” as 0, 1, 2, or 3 (no, mild, moderate, or severe) (Comiter et al, 1999).

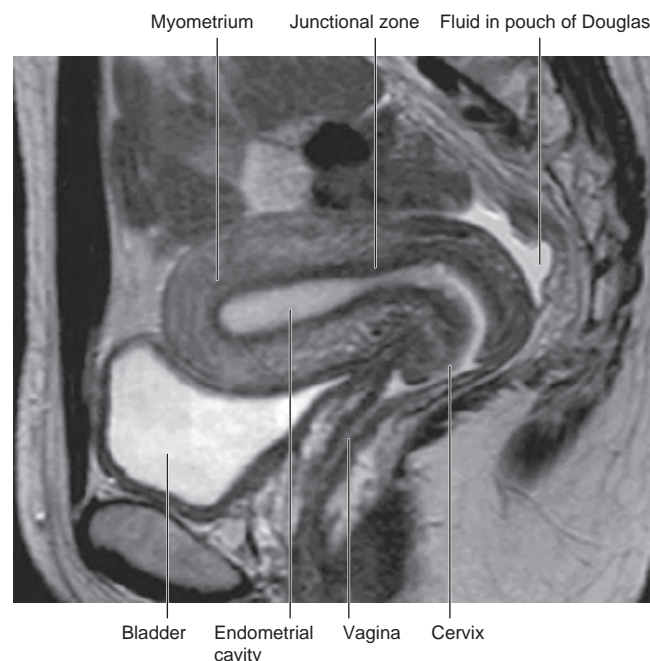


Figure 67-17. Normal anatomy of the pelvic structures on T2-weighted magnetic resonance image showing the zonal anatomy of the uterus. (From Standing S. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. London: Churchill Livingstone; 2008.)

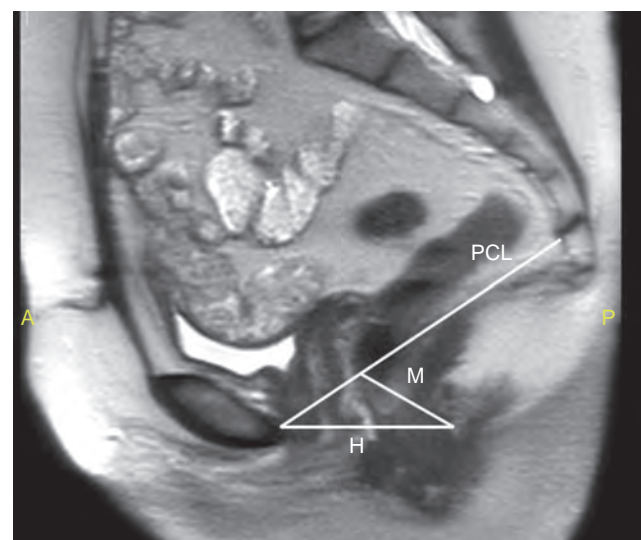


Figure 67-18. Dynamic half-Fourier acquisition single-shot turbo spin-echo sequence T2-weighted magnetic resonance image in a patient with minor prolapse. H-line measures levator hiatus, M-line measures descent of the levator plate, and PCL measures pubococcygeal line. A, anterior; P, posterior.

Ultrasonography

Ultrasound is one of the most readily available imaging instruments to assess pelvic anatomy. Transabdominal, transperineal, transrectal, translabial, and transvaginal approaches have been used (Dietz, 2008).

Transperineal or translabial ultrasonography is often used because of its noninvasive approach and a technique that does not distort or compress many structures. The pubic symphysis, urethra, bladder neck, vagina, rectum, and anal canal are visualized routinely on translabial ultrasound. The levator plate and pubovisceral

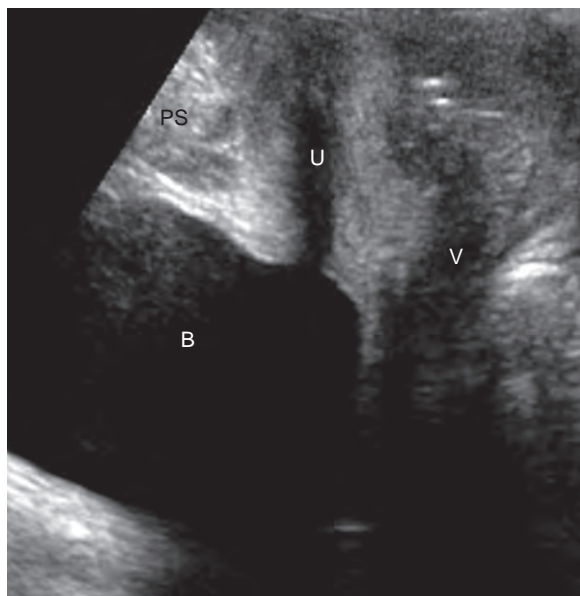


Figure 67-19. Two-dimensional translabial ultrasound image in the midsagittal plane. B, bladder; PS, pubic symphysis; U, urethra; V, vagina.

muscles are seen as a hyperechogenic area behind the anorectal junction (Dietz, 2004). The cul-de-sac can contain fluid, fat, or small bowel. Bladder neck mobility is assessed via real-time imaging while performing a Valsalva maneuver in the supine position. Bladder wall thickness and pelvic organ prolapse can also be measured via translabial ultrasonography (Dietz, 2004). One of the other common uses of the translabial ultrasonography is to evaluate various implants such as urethral bulking agents or transvaginal mesh. Newer probes have allowed for three-dimensional imaging reconstruction to occur, which provides the added benefit of visualizing structures in the axial view rather than just the midsagittal view (Fig. 67-19).

When evaluating fecal incontinence, anorectal ultrasonography can assess for anal sphincter defects. The internal sphincter defects are seen as an echogenic discontinuity in the hypoechoic muscle between the vagina and the rectum (Hull and Zutshi, 2008). The external sphincter injury appears as a hypoechoic lesion in a normally echogenic structure. When the sphincter is in spasm or hypertrophy (as in the case of obstructed defecation), it can often have a thickened appearance (Fig. 67-20).

Endoscopic Anatomy

The caliber of the normal urethra appears to be between 14 and 20 Fr (Keegan et al, 2008). It is usually evaluated with a rigid or flexible cystoscope. The labia are spread and the urethral meatus is identified to advance the cystoscope into the urethra. The entire urethra as well as the external sphincter and bladder neck should be visualized in both a retrograde and an antegrade fashion, usually best seen with a 0-degree lens (Akorn et al, 2005). This is best performed with the irrigation flowing to distend the urethra. Great care needs to be taken to inspect the urethra, especially in women with recurrent urinary tract infections, dysuria, or obstruction. One can visualize foreign bodies, stones, and occasionally the ostia of a urethral diverticulum.

Cystoscopy allows the operator the ability to visualize the entire bladder mucosa from the dome down to the bladder neck, which is best done in a complete fashion with a 70-degree lens. The trigone and ureteral orifices are also well visualized. Often at the trigone

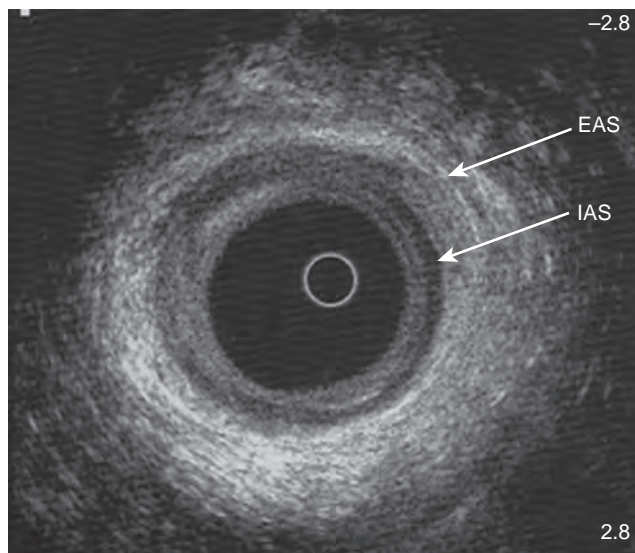


Figure 67-20. Endoanal ultrasound image in a normal female. EAS, external anal sphincter; IAS, internal anal sphincter.

and base of the bladder, premenopausal women can exhibit normal signs of squamous metaplasia (Clouston and Lawrentschuk, 2013). This is a nonkeratinizing metaplasia or vaginal metaplasia that is hormonally responsive and is a normal variant. Other potential findings on cystoscopy include tumors, masses, foreign bodies, fistula openings, or stones. Females of reproductive age may have an external impression at the dome of the bladder from their uterus. Bladder diverticula, cellulites, and trabeculations in women with urinary retention or obstruction can be seen on cystoscopy.

KEY POINTS: RADIOGRAPHIC ANATOMY

- MRI is the best imaging technique to visualize and differentiate anterior vaginal wall masses—especially a urethral diverticulum.
- Ultrasonography is an important imaging modality used in female pelvic medicine because of the lack of radiation and the ability to visualize almost all of the important female pelvic anatomic structures. It is also useful in visualizing foreign bodies such as bulking agents or synthetic mesh.

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Bony Pelvis

Anterior Abdominal Wall

Soft Tissues of the Pelvis

Pelvic Circulation

Pelvic Innervation

Pelvic Viscera

Perineum

This chapter provides a general anatomic framework to guide the pelvic surgeon. The bony, ligamentous, and muscular framework of the pelvis is presented first. Next the pelvic vessels and nerves and the genital, urinary, and gastrointestinal viscera are discussed. Finally the perineum and external genitalia are reviewed.

BONY PELVIS

The pelvic bones are the sacrum (the termination of the axial skeleton) and the two innominate bones. The latter are formed by the fusion of the iliac, ischial, and pubic ossification centers at the acetabulum (see Fig. 67-1 in Chapter 67). The ischium and pubis also meet below, in the center of the inferior ramus, to form the obturator foramen. The weight of the upper body is transmitted from the axial skeleton to the innominate bones and lower extremities through the strong sacroiliac (SI) joints. As a whole, the pelvis is divided into a bowl-shaped false pelvis, formed by the iliac fossae and largely in contact with intraperitoneal contents, and the circular true pelvis wherein lie the urogenital organs. At the pelvic inlet, the true and false pelvis are separated by the arcuate line, which extends from the sacral promontory to the pectineal line of the pubis. The lumbar lordosis that accompanies erect posture tilts the axis of the pelvic inlet so that it parallels the ground; the pelvic inlet faces anteriorly, and the inferior ischiopubic rami lie horizontally (see Fig. 67-2 in Chapter 67). When approaching the pelvis through a low midline incision, the surgeon gazes directly into the true pelvis.

The anterior and posterior iliac spines, the iliac crests, the pubic tubercles, and the ischial tuberosities are palpable landmarks that orient the pelvic surgeon (see Fig. 67-1 in Chapter 67). Cooper (pectineal) ligament overlies the pectineal line and offers a sure hold for sutures in hernia repairs and urethral suspension procedures (Fig. 68-1). The ischial spine is palpable transvaginally and attaches to the pelvic diaphragm and the sacrospinous ligament. The sacrospinous ligament separates the greater and lesser sciatic foramina. Together with the sacrotuberous ligament, it stabilizes the SI joint by preventing downward rotation of the sacral promontory. The SI joint, synovial in type, gains additional strength from anterior and posterior ligaments. In pelvic trauma, fractures virtually never involve this joint, but they occur adjacent to it. The pubes, the thinnest of the pelvic bones, are nearly always fractured, and their fragments may injure the adjacent bladder and urethra. Resection or congenital nonunion of the pubes (e.g., bladder exstrophy) does not affect ambulation because of the strength of the SI joint (Waterhouse et al, 1973; Golimbu et al, 1990).

ANTERIOR ABDOMINAL WALL

Skin and Subcutaneous Fasciae

To minimize scarring, incisions of the anterior abdominal wall and flank should follow Langer lines of cleavage. These lines parallel dermal collagen fibers and are oriented along lines of stress. They correspond to the segmental thoracic and lumbar nerves. The skin is backed by Camper fascia, a loose layer of fatty tissue that varies in thickness with the nutritional status of the patient. The superficial circumflex iliac, external pudendal, and superficial inferior epigastric vessels branch from the femoral vessels to run in this layer (Figs. 68-2 and 68-3). The superficial inferior epigastric vessels are encountered during inguinal incisions and can cause troublesome bleeding during placement of pelvic laparoscopic ports.

Scarpa fascia forms a distinct layer deep to Camper fascia, although it may be difficult to discern in older patients. It blends superiorly and laterally with Camper fascia. It fuses inferiorly with the deep fascia of the thigh 1 cm below the inguinal ligament along a line from the anterior superior iliac spine to the pubic tubercle. Medially, it is continuous with Colles fascia of the perineum (see Fig. 68-2). Colles fascia attaches to the posterior edge of the urogenital diaphragm and the inferior ischiopubic rami. It is continuous with the dartos fascia of the penis and scrotum. These fasciae can limit both the spread of infection in necrotizing fasciitis of the scrotum (Fournier gangrene) and the extent of urinary extravasation in an anterior urethral injury. For instance, blood and urine can accumulate in the scrotum and penis deep to the dartos fascia after an anterior urethral injury. In the perineum, their spread is limited by the fusions of Colles fascia to the ischiopubic rami laterally and to the posterior edge of the perineal membrane; the resulting hematoma is therefore butterfly shaped. Because of these fasciae, bleeding, infection, or urinary extravasation will not extend down the leg or into the buttock but can freely travel up the anterior abdominal wall deep to Scarpa fascia to the clavicles and around the flank to the back.

Abdominal Musculature

The abdominal musculature lies immediately below Scarpa fascia. The origins of the external oblique, internal oblique, and transversus abdominis muscles and the orientation of their fibers are presented in Chapter 42. These muscles terminate on the anterior abdominal wall as broad, tough aponeurotic sheets that fuse in the midline (linea alba) and form the rectus sheath (see Fig. 68-3). The linea alba is avascular and is a convenient point of access

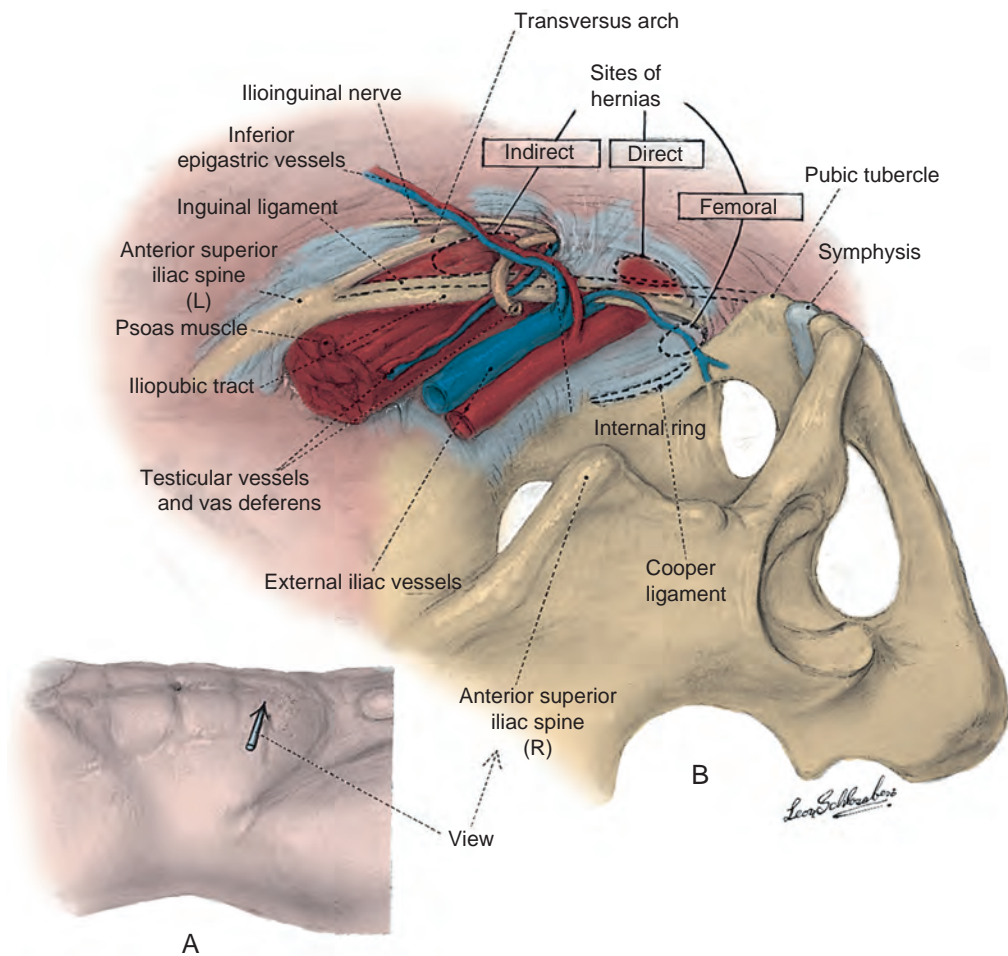


Figure 68-1. Topography (A) and posterior wall (B) of the left inguinal canal, viewed from the preperitoneal space. The location of three types of inguinal hernia is demonstrated. L, left; R, right. (From Schlegel PN, Walsh PC. Simultaneous preperitoneal hernia repair during radical pelvic surgery. *J Urol* 1987;137:1180-3.)

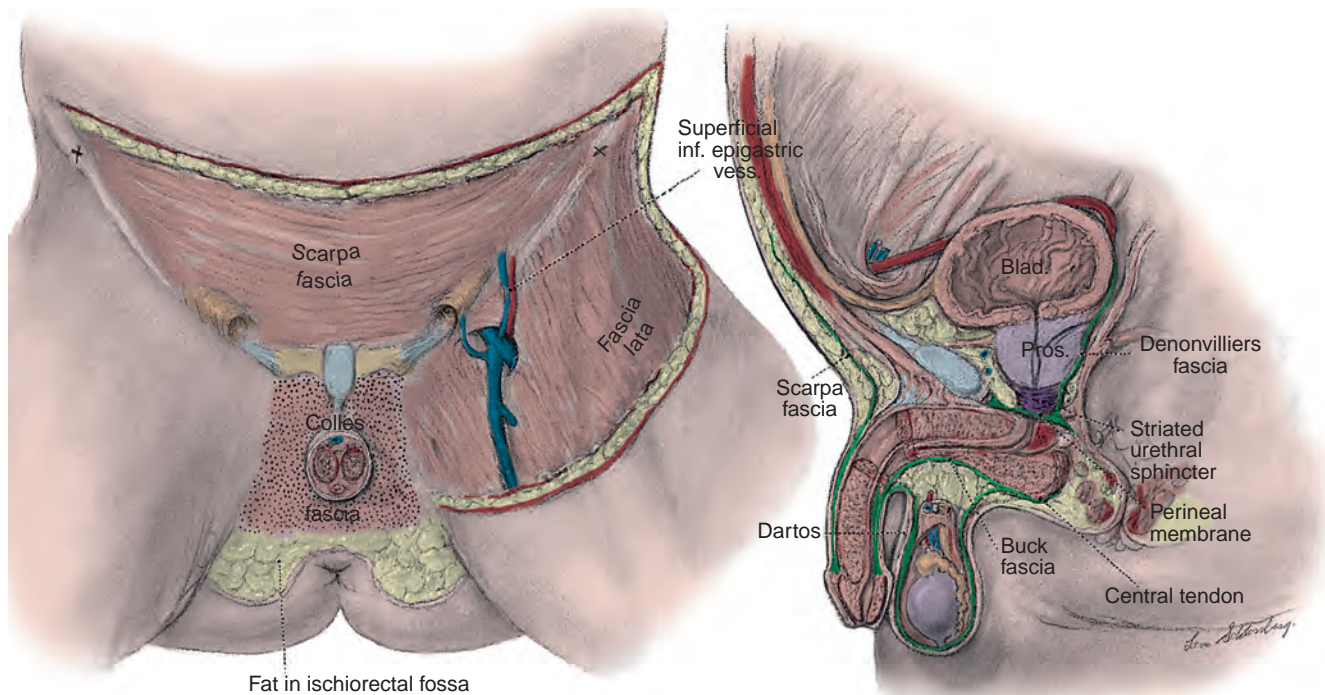


Figure 68-2. Left, Anterior view of the deep fasciae of the abdomen, perineum, and thigh. Note the superficial inferior epigastric artery passing superiorly in Camper fascia. Right, Midline sagittal view of the pelvic fasciae and their attachments.

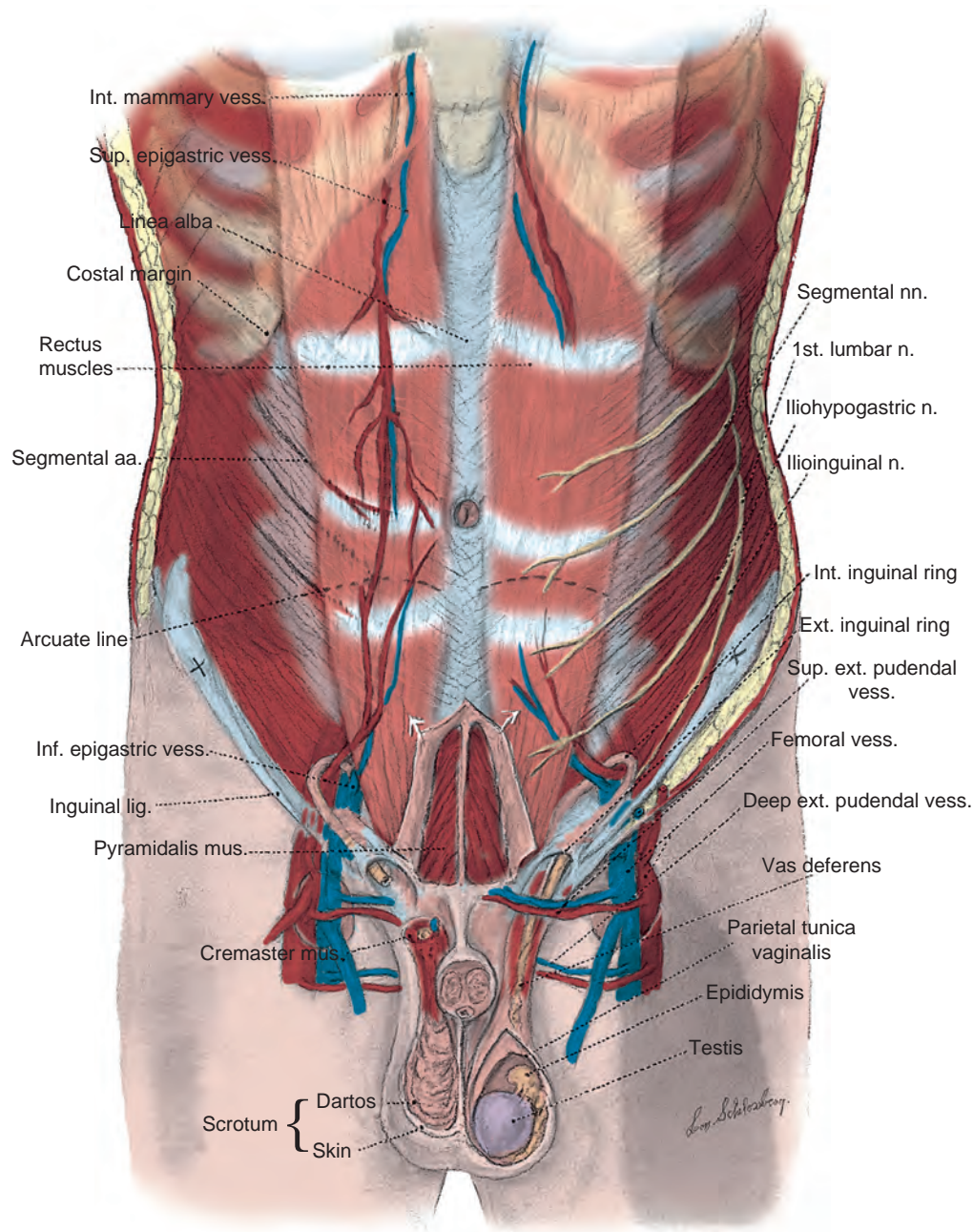


Figure 68-3. Muscles, vessels, and nerves of the anterior abdominal wall.

to the peritoneal and pelvic cavities. In its upper portion, the anterior rectus sheath is formed by the aponeurosis of the external oblique muscle and a portion of the internal oblique muscle (Fig. 68-4). The posterior sheath is derived from the remaining internal oblique aponeurosis and the transversus abdominis aponeurosis. At a location that is two thirds of the distance between the pubis and the umbilicus, the arcuate line is formed, as all aponeurotic layers abruptly pass anterior to the rectus abdominis, leaving this muscle clothed only by transversalis fascia and peritoneum posteriorly.

The rectus abdominis arises from the pubis medial to the pubic tubercle and inserts on the xiphoid process and adjacent costal cartilages. The muscle is crossed by three or four tendinous intersections that are firmly attached to the anterior rectus sheath; thus the muscle can be divided transversely without significant retraction. It is supplied by the last six thoracic segmental nerves that enter it laterally. Paramedian incisions lateral to the rectus

divide these nerves, cause atrophy of the rectus, and predispose to ventral hernia. Anterior to the rectus and within its sheath, the triangle-shaped pyramidalis muscle arises from the pubic crest and inserts into the linea alba (see Fig. 68-3). It is supplied by the subcostal nerve (T12).

Inguinal Canal

The inguinal canal transmits the spermatic cord and the ilioinguinal nerve in the male (Fig. 68-5; see also Fig. 68-3). The external oblique muscle, which folds over at its inferior edge as the inguinal ligament, forms its anterior wall and floor. Above the pubic tubercle, the fibers of the external oblique aponeurosis split to form the lateral edges (crura) of the external inguinal ring. Transverse (intercrural) fibers bridge the crura to form the superior edge of the external ring. By dividing the intracruial fibers, the external oblique can be separated along its fibers to gain access to the cord.

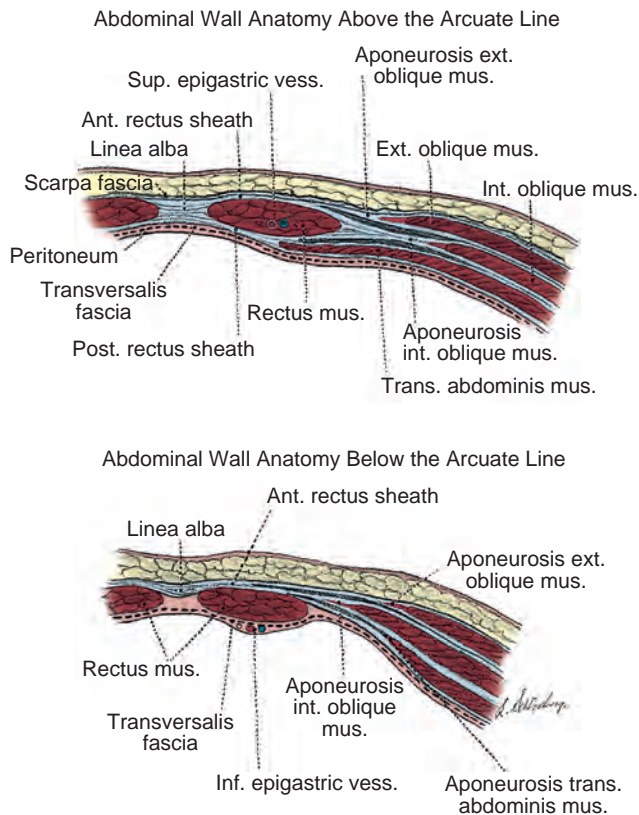


Figure 68-4. Cross section of the rectus sheath. **Top, Above the arcuate line,** the aponeurosis of the external oblique muscle forms the anterior sheath, and the transversus aponeurosis forms the posterior sheath. The internal oblique muscle splits to contribute to both the anterior and the posterior sheaths. **Bottom, Below the arcuate line,** all aponeuroses pass anterior to the rectus.

Transversalis fascia, which lines the inner surface of the abdominal wall, forms the posterior wall of the canal. The cord structures pierce this fascia lateral to the inferior epigastric vessels at the internal inguinal ring (see Fig. 68-5). The internal inguinal ring lies midway between the anterior superior iliac spine and the pubic tubercle, above the inguinal ligament, and 4 cm lateral to the external ring. Fibers of the internal oblique and transversus abdominis arise from the iliopsoas fascia and inguinal ligament lateral to the internal ring and arch over the canal to form its roof. They fuse as the conjoint tendon and pass posterior to the cord, and insert into the rectus sheath and pubis. The conjoint tendon reinforces the posterior wall of the inguinal canal at the external ring. With contraction of the internal oblique and transversus muscles, the roof of the canal closes against the floor, preventing herniation of intra-abdominal contents into the canal. Hernias into the canal may occur medial (direct) or lateral (indirect) to the inferior epigastric vessels (see Figs. 68-1 and 68-5).

Internal Surface of the Anterior Abdominal Wall

Approached laparoscopically, three elevations of the peritoneum, referred to as the **median**, **medial**, and **lateral** umbilical folds, are visible on the anterior abdominal wall below the umbilicus (Fig. 68-6). The median fold overlies the median umbilical ligament (urachus), a fibrous remnant of the cloaca that attaches the bladder to the anterior abdominal wall. The obliterated umbilical artery in the medial umbilical fold serves as an important landmark for the surgeon. It may be traced to its origin from the internal iliac artery to locate the ureter, which lies on its medial side. During transperitoneal laparoscopic pelvic lymph node dissection, the obturator packet is accessed by incising the peritoneum lateral to the

obliterated umbilical artery. In addition, during the performance of transperitoneal laparoscopic or robotic radical prostatectomy, the medial umbilical folds are used as landmarks to guide the dissection of the bladder to expose the space of Retzius. The lateral umbilical fold contains the inferior epigastric vessels as they ascend to supply the rectus abdominis.

SOFT TISSUES OF THE PELVIS

Pelvic Musculature

Muscles and fascia line the true pelvis and form its floor. The **obturator internus** arises from the inner surface of the obturator foramen and the obturator membrane and passes through the lesser sciatic foramen to insert on the femur (see Fig. 68-6). The fascia on the pelvic surface of this muscle is thickened into a tough line extending from the lower half of the pubis to the ischial spine. This tendinous arch of the levator ani serves as the origin of the muscles of the pelvic diaphragm: pubococcygeus and iliococcygeus (see Fig. 67-8 in Chapter 67). These muscles are not truly separable, and they form a diaphragm that closes the pelvic outlet. Anteriorly, a narrow U-shaped hiatus remains through which the urethra and rectum exit in the male (Fig. 68-7). The muscle bordering this hiatus has been referred to as *pubovisceral* because it provides a sling for (pubourethralis, puborectalis), inserts directly into (puboanalis, levator prostatae), or inserts into a structure intimately associated with the pelvic viscera (Lawson, 1974). The pubovisceral group provides strong fixation and support for the pelvic viscera. The coccygeus muscle extends from the sacrospinous ligament to the lateral border of the sacrum and coccyx to complete the pelvic diaphragm. Muscles of the pelvic diaphragm contain type I (slow-twitch) fibers, which provide tonic support to pelvic structures, and type II (fast-twitch) fibers for sudden increases in intra-abdominal pressure (Gosling et al, 1981). The piriformis muscle arises from the lateral aspect of the sacrum and passes through and fills the greater sciatic foramen to form the posterolateral wall of the pelvis.

It is important to recognize that the pelvic diaphragm is not flat or bowl shaped, as it is frequently depicted. At the urogenital and anal hiatus, the muscles lie in a near-vertical configuration and are thickened inferiorly (see Fig. 68-7) (Brooks et al, 1998; Myers et al, 1998). Behind the anus, they flatten to form a nearly horizontal diaphragm referred to as the *levator plate*.

Pelvic Fasciae

The pelvic fasciae are not merely collagenous; they are also rich in elastic tissue and smooth muscle. This suggests that they are active in the support, and possibly the function, of the pelvic viscera. The pelvic fasciae are continuous with the retroperitoneal fasciae and have been categorized somewhat arbitrarily into outer, intermediate, and inner strata. The outer stratum, or endopelvic fascia, lines the inner surface of the pelvic muscles and is continuous with the transversalis layer of the abdomen. It is fixed to the arcuate line of the pelvis, Cooper ligament, the sacrospinous ligament, the ischial spine, and tendinous arch of the levator ani. The intermediate stratum embeds the pelvic viscera in a fatty, compressible layer that accommodates their filling and emptying. Its tissues are easily swept aside to show the retropubic, paravesical, rectogenital, and retrorectal potential spaces. All pelvic vessels and some pelvic nerves travel in this stratum and are subject to injury when these potential spaces are developed at surgery. The intermediate stratum coalesces around vessels and nerves supplying the pelvic organs to form named ligaments (e.g., lateral and posterior vesical) that suspend and tether these organs in the pelvis. This fascia also thickens around the pelvic urogenital organs to form their visceral fascia. These are not true ligaments but are a meshwork of connective tissue and smooth muscle investing the visceral neurovascular pedicles (DeCaro et al, 1998). The inner stratum lies just beneath the peritoneum and is associated with the entire gastrointestinal tract. In the pelvis, it covers the rectum and the dome of the bladder and forms the rectogenital septum (Denonvilliers fascia). This septum

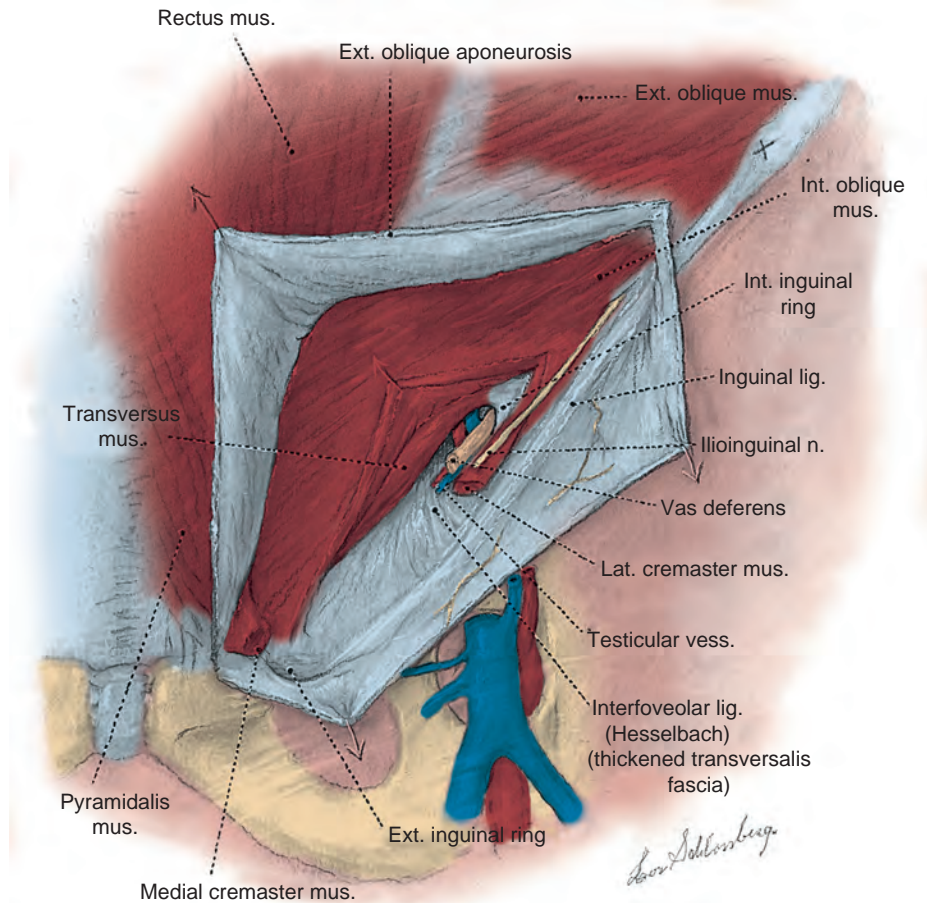


Figure 68-5. Deep structures of the left inguinal canal, viewed from the front.

is the developmental remains of the rectogenital pouch of peritoneum that extended between the rectum and the internal genitalia to the pelvic floor.

The pelvic fasciae have been given a confusing array of appellations by anatomists and surgeons. **There are three important components of the pelvic fasciae:** (1) **Anteriorly the puboprostatic ligaments** attach to the lower fifth of the pubis, lateral to the symphysis, and to the junction of the prostate and external sphincter. (2) Laterally the **arcus tendineus fasciae pelvis** extends from the puboprostatic ligament to the ischial spine. This fascia forms at the junction of the endopelvic and visceral fasciae. It should not be confused with the **arcus tendineus levator ani**, which lies above its anterior portion. In the male, the **arcus tendineus fasciae pelvis** is found at the base of a sulcus between the pelvic sidewall and the prostate and bladder. The lateral branches of the dorsal venous complex are directly beneath the **arcus tendineus fasciae pelvis**; thus the endopelvic fascia should be opened lateral to this landmark in radical prostatectomy. (3) Posterior to the ischial spine, the fascia fans out to either side of the rectum and attaches to the pelvic sidewall as the lateral and posterior vesical ligaments. The peritoneum over these ligaments forms discrete folds (rectovesical in the male) that can be appreciated at cystectomy (Fig. 68-8). Taken as a whole, the pelvic fasciae form a Y-shaped scaffolding for the pelvic viscera.

Fasciae of the Perineum and the Perineal Body

The weakest point in the pelvic floor, the urogenital hiatus, is bridged by the urogenital diaphragm, a structure unique to humans (see Fig. 68-7). The fibrous perineal membrane lies at the center of, and defines, the urogenital diaphragm (Fig. 68-9; see also Fig. 68-2). It is triangular and spans the inferior ischiopubic rami

from the pubis to the ischial tuberosities. Posteriorly it ends abruptly; the superficial and deep transverse perinei run along its free edge (Fig. 68-10). The external genitalia attach to its inferior surface; superiorly it supports the urethral sphincter (discussed later). The perineal body represents the point of fusion between the free posterior edge of the urogenital diaphragm and the posterior apex of the urogenital hiatus. This pyramid-shaped structure forms the hub of pelvic support. Virtually every pelvic muscle (superficial and deep transverse perinei, bulbocavernosus, levator ani, rectourethralis, external anal sphincter, striated urethral sphincter) and fascia (perineal membrane, Denonvilliers, Colles, and endopelvic) insert into the perineal body. At the core of the perineal body are abundant elastin and richly innervated smooth muscle, which suggests that it may have a dynamic role in support. Damage to the perineal body during perineal prostatectomy risks postoperative urinary incontinence.

PELVIC CIRCULATION

Arterial Supply

Major arteries of the pelvis are summarized in Table 68-1. At the bifurcation of the aorta, the **middle sacral artery** arises posteriorly and travels on the pelvic surface of the sacrum to supply branches to the sacral foramina and the rectum. The common iliac arteries arise at the level of the fourth lumbar vertebra, run anterior and lateral to their accompanying veins, and bifurcate into the external and internal iliac arteries at the SI joint (Fig. 68-11). The external iliac artery follows the medial border of the iliopsoas muscle along the arcuate line and leaves the pelvis beneath the inguinal ligament as the femoral artery (Fig. 68-12). Its inferior epigastric artery is given off proximal to the inguinal ligament and ascends medial to

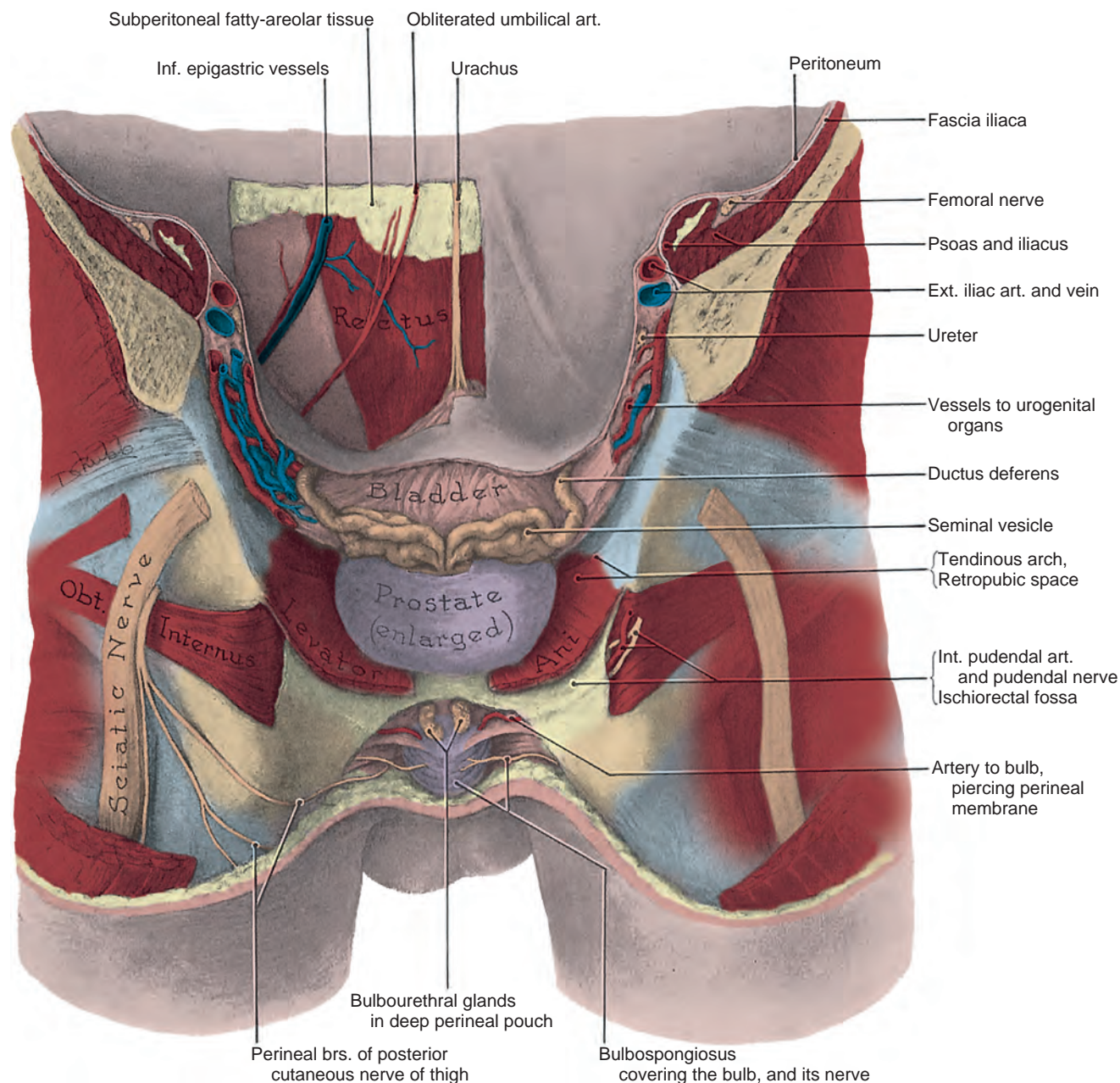


Figure 68-6. Male pelvis and anterior abdominal wall viewed from behind. The sacrum and ilia have been removed. (From Anderson JE. *Grant's atlas of anatomy*. 7th ed. Baltimore: Williams & Wilkins; 1978.)

the internal inguinal ring to supply the rectus muscle and overlying skin. Because the rectus is richly collateralized from above and laterally, the inferior epigastric arteries may be ligated with impunity. A rectus myocutaneous flap based on this artery has been used to correct major pelvic and perineal tissue defects. Near its origin, the inferior epigastric artery sends a deep circumflex iliac branch laterally and a pubic branch medially. Both vessels travel on the iliopubic tract and may be injured during inguinal hernia repair. Its cremasteric branch joins the spermatic cord at the internal inguinal ring and forms a distal anastomosis with the testicular artery. In 25% of people, an accessory obturator artery arises from the inferior epigastric artery and runs medial to the femoral vein to reach the obturator canal. This vessel must be avoided during obturator lymph node dissection.

The internal iliac (hypogastric) artery descends in front of the SI joint and divides into an anterior and a posterior trunk (see Fig. 68-11). The posterior trunk gives rise to three parietal branches:

(1) the superior gluteal, which exits the greater sciatic foramen; (2) the ascending lumbar, which supplies the posterior abdominal wall; and (3) the lateral sacral, which passes medially to join the middle sacral branches at the sciatic foramina.

The anterior trunk yields seven parietal and visceral branches: (1) The superior vesical artery arises from the proximal portion of the obliterated umbilical artery and gives off a vesiculodeferential branch to the seminal vesicles and vas deferens. The artery of the vas deferens travels the length of the vas to meet the cremasteric and testicular arteries distally. Because of these anastomoses, the testicular artery may be sacrificed without compromising the viability of the testis. (2) The middle rectal artery gives small branches to the seminal vesicles and prostate and anastomoses with the inferior and superior rectal arteries in the rectal wall. (3) The inferior vesical branches supply the lower ureter, the bladder base, the prostate, and the seminal vesicles. (5) The internal pudendal artery leaves the pelvic cavity through the greater sciatic foramen,

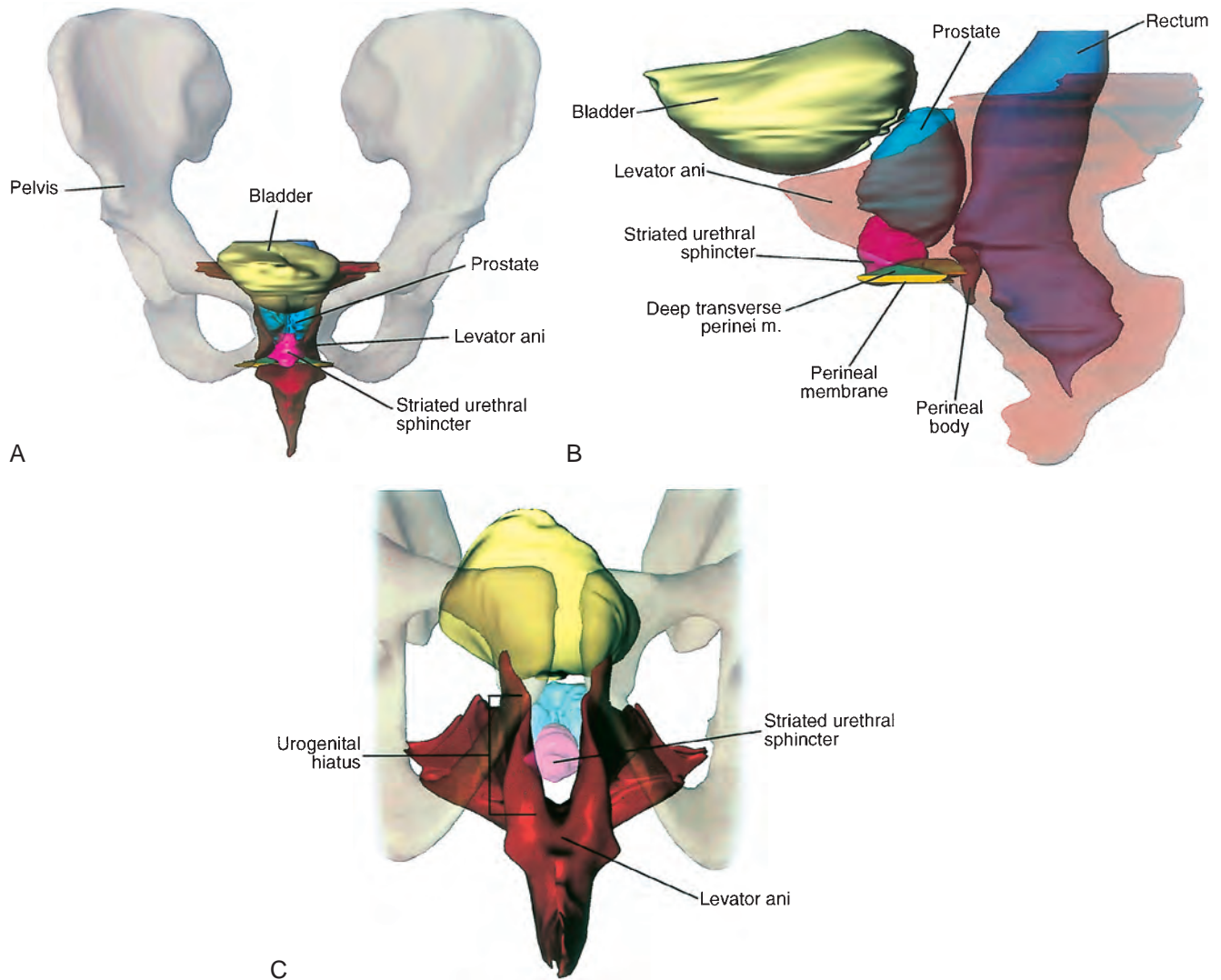


Figure 68-7. Location and contour of the levator ani and pelvic viscera. **A,** Anterior view demonstrating the near-vertical orientation of the lateral walls of the levator ani and the horizontal wings at its posterior superior aspect. **B,** Lateral view in which the levator ani has been made transparent. The perineal membrane bridges the urogenital hiatus, and the urethral sphincter fills much of the hiatus. **C,** View of the levator ani from below showing the urogenital hiatus and the thickened inferior border of the levator ani. The perineal body and related structures are not shown. (From Brooks JD, Chao WM, Kerr J. Male pelvic anatomy reconstructed from the visible human data set. *J Urol* 1998;159:868-72.)

passes around the sacrospinous ligament, and enters the lesser sciatic foramen to gain access to the perineum. Its perineal course is discussed later. (6) The obturator artery, variable in origin, travels through the obturator fossa medial and inferior to the obturator nerve and passes through its canal to supply the adductors of the thigh (see Fig. 68-12). (7) The inferior gluteal artery travels through the greater sciatic foramen to supply the buttock and thigh.

The internal iliac artery can be ligated to control severe pelvic hemorrhage. Ligation decreases the pulse pressure, allowing hemostasis to occur more readily. Internal iliac blood flow does not stop but reverses its direction because of critical anastomoses (lumbar segmentals to iliolumbar; median sacral to lateral sacral; and superior rectal and middle rectal). Bilateral ligation almost invariably produces vasculogenic impotence.

Venous Supply

The dorsal vein of the penis passes between the inferior pubic arch and the striated urinary sphincter to reach the pelvis, where

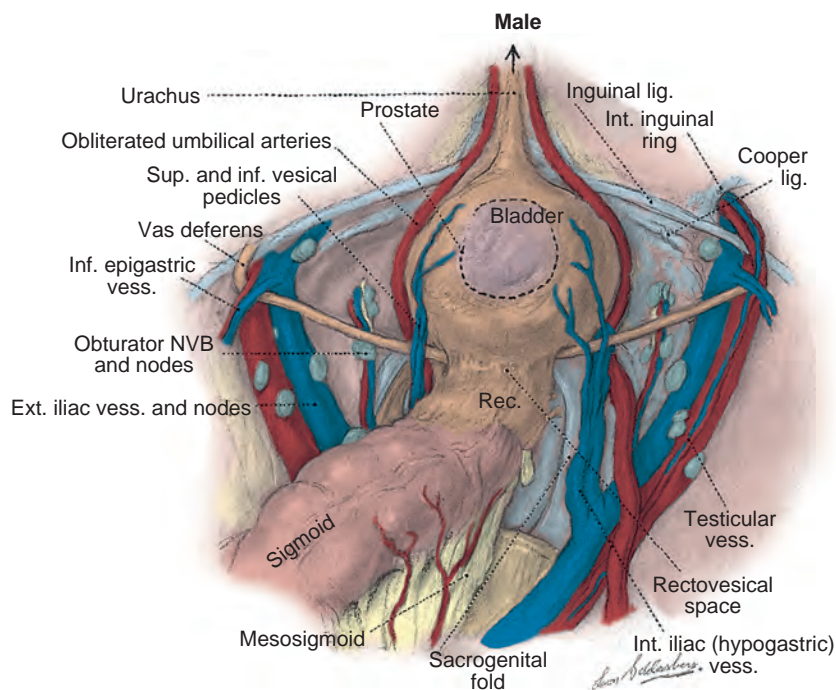
it trifurcates into a central superficial branch and two lateral plexuses (Reiner and Walsh, 1979) (Fig. 68-13). To minimize blood loss at radical retropubic prostatectomy, the dorsal vein complex is best divided distally before its ramification. Part of this complex runs within the anterior and lateral wall of the striated sphincter; thus care must be taken not to injure the sphincter when securing hemostasis. The superficial branch pierces the visceral endopelvic fascia between the puboprostatic ligaments and drains the retropubic fat, the anterior bladder, and the anterior prostate (see Fig. 68-13).

The lateral plexuses sweep down the sides of the prostate, receiving drainage from it and the rectum, and communicate with the vesical plexuses on the lower part of the bladder. Three to five inferior vesical veins emerge from the vesical plexus laterally and drain into the internal iliac vein.

The internal iliac vein is joined by tributaries corresponding to the branches of the internal iliac artery and ascends medial and posterior to the artery. This vein is relatively thin walled and at risk for injury during dissection of the artery or the nearby pelvic ureter. The external iliac vein travels medial and inferior to its artery and

TABLE 68-1 Arteries of the Pelvis

ARTERY NAME	ORIGIN	SUPPLIES
Middle sacral	Aorta	Sacral nerves and sacrum
EXTERNAL ILIAC BRANCHES		
Inferior epigastric	External iliac	Rectus abdominis muscle and overlying skin and fascia
Deep circumflex iliac	Inferior epigastric	Inguinal ligament and surrounding structures laterally
Pubic	Inferior epigastric	Inguinal ligament and surrounding structures medially
Cremasteric	Inferior epigastric	Vas deferens and testis
INTERNAL ILIAC BRANCHES		
Superior gluteal	Posterior trunk	Gluteus muscles and overlying skin
Ascending lumbar	Posterior trunk	Psoas and quadratus lumborum muscles and adjacent structures
Lateral sacral	Posterior trunk	Sacral nerves and sacrum
Superior vesical	Anterior trunk	Bladder, ureter, vas deferens, and seminal vesicle
Middle rectal	Anterior trunk	Rectum, ureter, and bladder
Inferior vesical	Anterior trunk	Bladder, seminal vesicle, prostate, ureter, and the neurovascular bundle
Internal pudendal	Anterior trunk	Rectum, perineum, and external genitalia
Obturator	Anterior trunk	Adductor muscles of the leg and overlying skin
Inferior gluteal	Anterior trunk	Gluteus muscles and overlying skin

**Figure 68-8.** Peritoneal surfaces of the male pelvis. NVB, neurovascular bundle.

joins the internal iliac vein behind the internal iliac artery. In half the patients, one or more accessory obturator veins drain into the underside of the external iliac vein and can be easily torn during lymphadenectomy (see Fig. 68-12).

Pelvic Lymphatics

The pelvic lymph nodes can be difficult to appreciate on gross examination because they are embedded in the fatty and fibrous tissue of the intermediate stratum. Three major lymph node groups are associated with the pelvic vessels (Fig. 68-14). A substantial portion of pelvic visceral lymphatic drainage passes through the internal iliac nodes and their tributaries: the presacral, obturator, and internal pudendal nodes. The external iliac nodes lie lateral, anterior, and medial to the vessels and drain the anterior abdominal wall, urachus, bladder, and, in part, internal genitalia.

The external genitalia and perineum drain into the superficial and deep inguinal nodes. The inguinal nodes communicate directly with the internal and external iliac chains. The common iliac nodes receive efferent vessels from the external and internal iliac nodes and the pelvic ureter and drain into the lateral aortic nodes.

PELVIC INNERVATION

Lumbosacral Plexus

The lumbosacral plexus and its rami are well illustrated in Chapter 42; only the pelvic courses of its nerves are reviewed here (Table 68-2; see also Fig. 68-5). The iliohypogastric nerve (L1) travels between, and supplies, the internal oblique and the transversus muscles and pierces the internal and external oblique

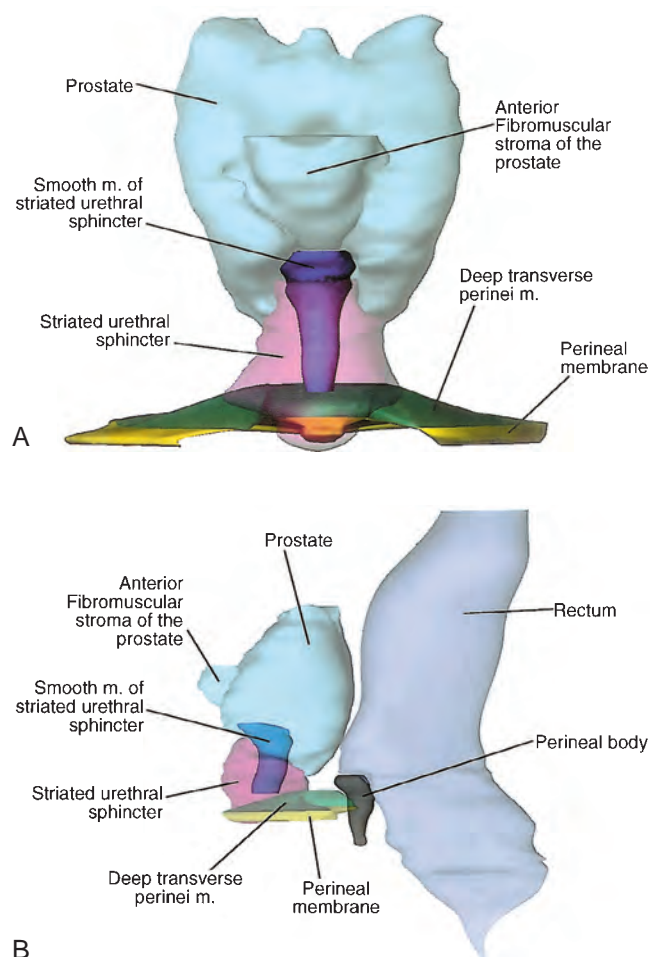


Figure 68-9. Structure of the male striated urethral sphincter. A, Anterior projection shows the cone shape of the sphincter and the smooth muscle of the sphincter. B, Viewed laterally, the anterior wall of the sphincter is nearly twice the length of the posterior wall, although both are of comparable thickness. (From Brooks JD, Chao WM, Kerr J. Male pelvic anatomy reconstructed from the visible human data set. *J Urol* 1998;159:868–72.)

muscles 3 cm above the external inguinal ring to supply sensation over the lower anterior abdomen and pubis (see Fig. 68-3). The ilioinguinal nerve (L1) passes through the internal oblique muscle to enter the inguinal canal laterally. This nerve travels anterior to the cord and exits the external ring to provide sensation to the anterior scrotum (see Figs. 68-3 and 68-5). The genitofemoral nerve (L1, L2) pierces the psoas muscle to reach its anterior surface in the retroperitoneum and then travels to the pelvis and splits into genital and femoral branches. The latter supplies sensation over the anterior thigh below the inguinal ligament. The genital branch follows the cord through the inguinal canal, supplies the cremaster muscle, and supplies sensation to the anterior scrotum.

For most of its pelvic course, the femoral nerve (L2, L3, L4) travels within the substance of the psoas muscle and then exits its lateral side to pass under the inguinal ligament (Fig. 68-15). It supplies sensation to the anterior thigh and motor innervation to the extensors of the knee. During a psoas hitch, sutures should be placed in the direction of the nerve (and the psoas muscle fibers) to avoid nerve damage or entrapment. Retractor blades must not rest on the psoas muscle because they can produce a femoral nerve palsy, a potentially dangerous setback after pelvic surgery. The lateral femoral cutaneous nerve (L2, L3) may be seen lateral to the psoas in the iliacus fascia.

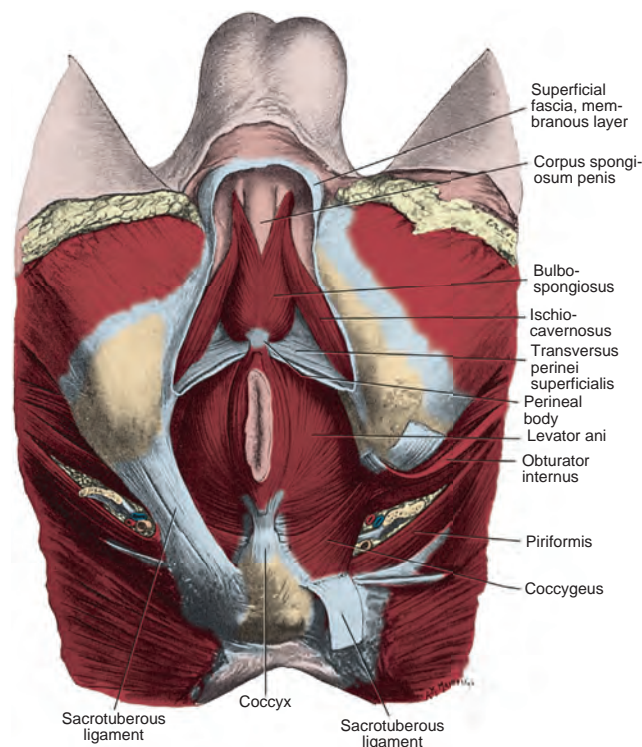


Figure 68-10. Muscles of the male perineum. The transversus perinei and ischiocavernosus frame the urogenital diaphragm. (From Williams PL, Warwick R. *Gray's anatomy*. 35th British ed. Philadelphia: Saunders; 1973.)

The obturator nerve (L2, L3, L4) emerges in the true pelvis from beneath the psoas muscle, lateral to the internal iliac vessels, and passes through the obturator foramen to the obturator canal. In the fossa, it is lateral and superior to the obturator vessels and is surrounded by the obturator and internal iliac lymph nodes. Damage to this nerve during pelvic lymphadenectomy weakens the adductors of the thigh.

The lumbosacral trunk (L4, L5) passes into the true pelvis behind the psoas and unites with the ventral rami of the sacral segmental nerves to form the sacral plexus. This plexus lies on the pelvic surface of the piriformis deep to the endopelvic fascia and posterior to the internal iliac vessels (see Fig. 68-11). It leaves the pelvis through the greater sciatic foramen immediately posterior to the sacrospinous ligament and supplies motor and sensory innervation to the posterior thigh and lower leg. An exaggerated lithotomy position may stretch this nerve or place pressure on its peroneal branch at the fibular head to produce foot drop. Pelvic and perineal branches of the sacral plexus include (1) the posterior femoral cutaneous nerve (S2, S3), which, after passing through the greater sciatic foramen, gives an anterior sensory branch to the perineum and posterior scrotum; (2) the pudendal nerve (S2, S3, S4), which follows the internal pudendal artery to the perineum (to be discussed); (3) the nervi erigentes (S2, S3, S4) to the autonomic plexus; and (4) pelvic somatic efferent nerves from the ventral rami of S2, S3, and S4 (Fig. 68-16). The latter nerves travel on the pelvic surface of the levator ani in close association with the rectum and prostate and are separated from the pelvic autonomic plexus by the endopelvic fascia. They supply the levator ani and extend anteriorly to the striated urethral sphincter (Lawson, 1974; Zvara et al, 1994).

Pelvic Autonomic Plexus

The presynaptic sympathetic cell bodies that project to the pelvic autonomic plexus reside in the lateral column of gray matter in the last three thoracic and first two lumbar segments of the spinal

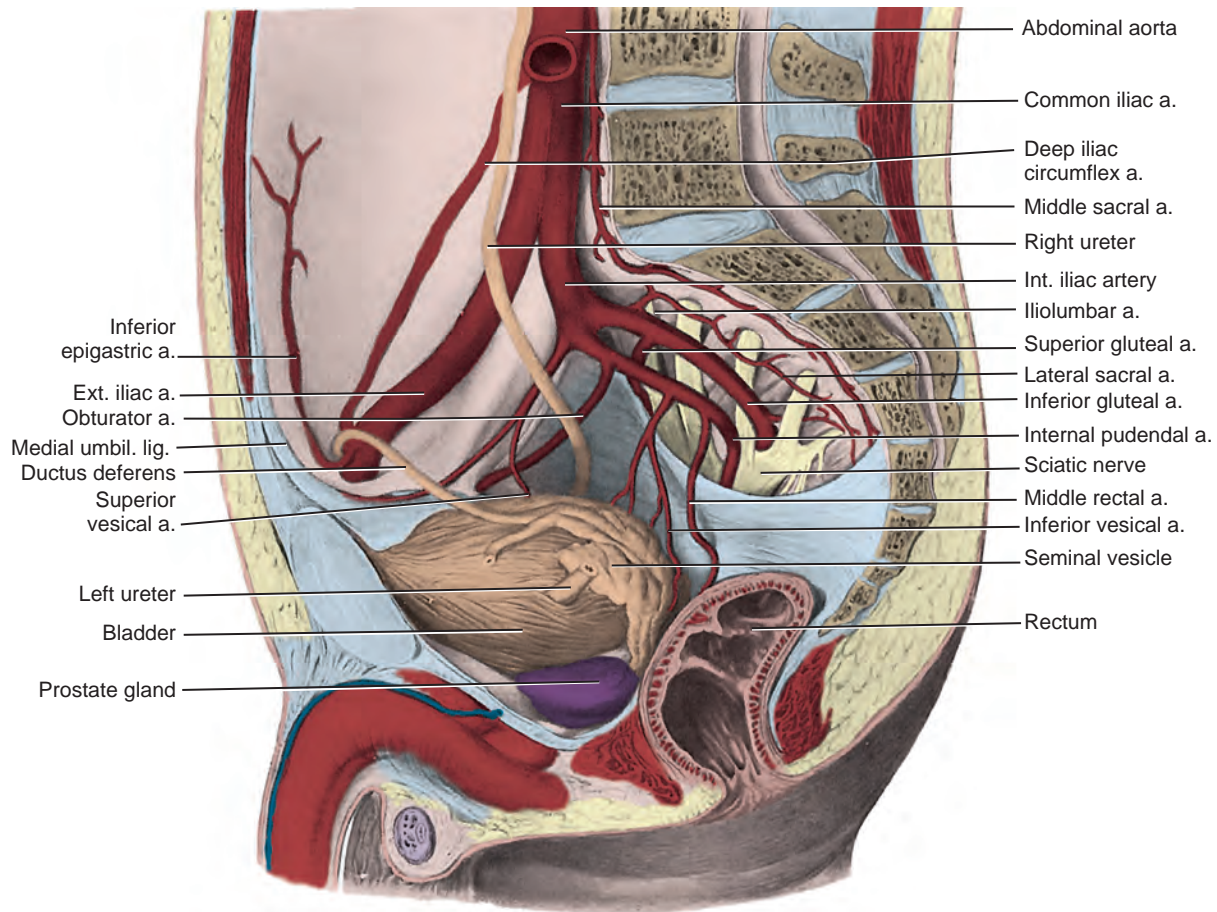


Figure 68-11. Right internal and external iliac arteries. The ureter and vas deferens pass medial to the vessels. (From Clemente CD. Gray's anatomy. 30th American ed. Philadelphia: Lea & Febiger, 1985.)

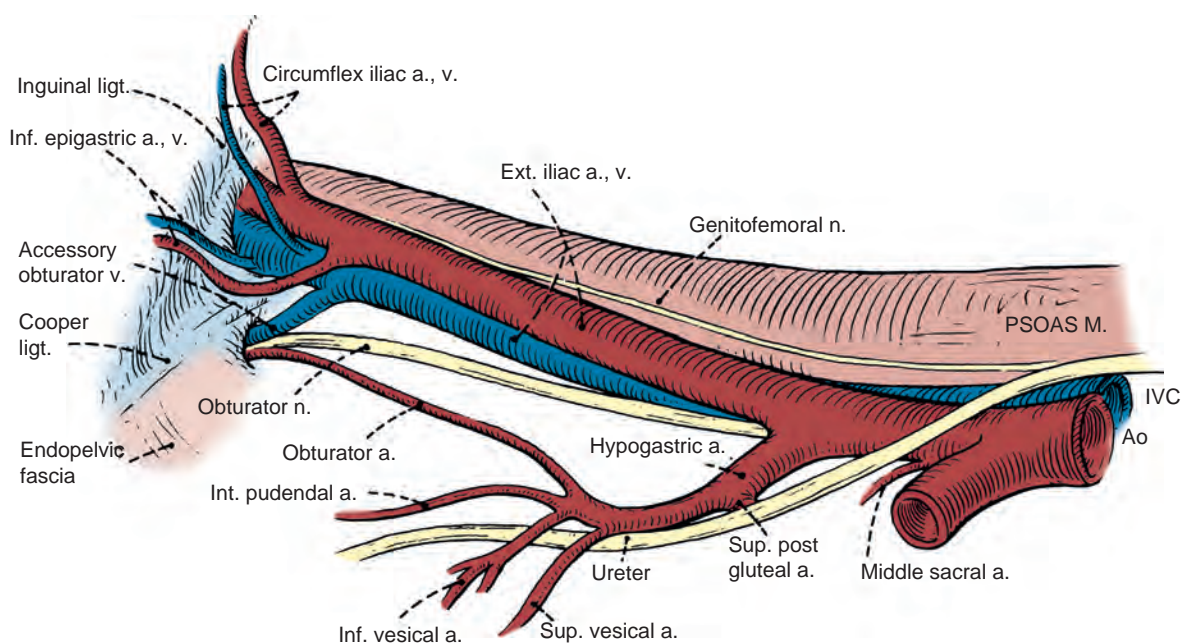


Figure 68-12. Right obturator fossa showing the iliac vessels and obturator nerve. Ao, aorta; IVC, inferior vena cava. (From Skinner DG. Pelvic lymphadenectomy. In: Glenn JF, editor. Urological surgery, 2nd ed. New York: Harper & Row; 1975. p. 591.)

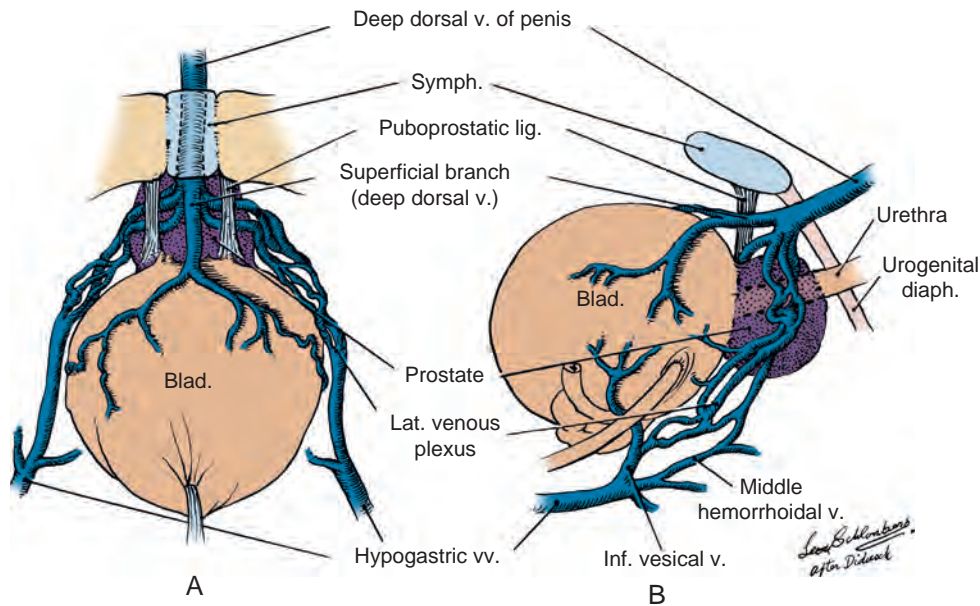


Figure 68-13. Pelvic venous plexus. A, Trifurcation of the dorsal vein of the penis, viewed from the retropubic space. The relationship of the venous branches to the puboprostatic ligaments is shown. B, Lateral view of the pelvic venous plexus after removal of the lateral pelvic fascia. Normally these structures are difficult to see because they are embedded in pelvic fascia. (From Reiner WG, Walsh PC. An anatomical approach to the surgical management of the dorsal vein and Santorini's plexus during radical retropubic surgery. *J Urol* 1979;121:198–200.)

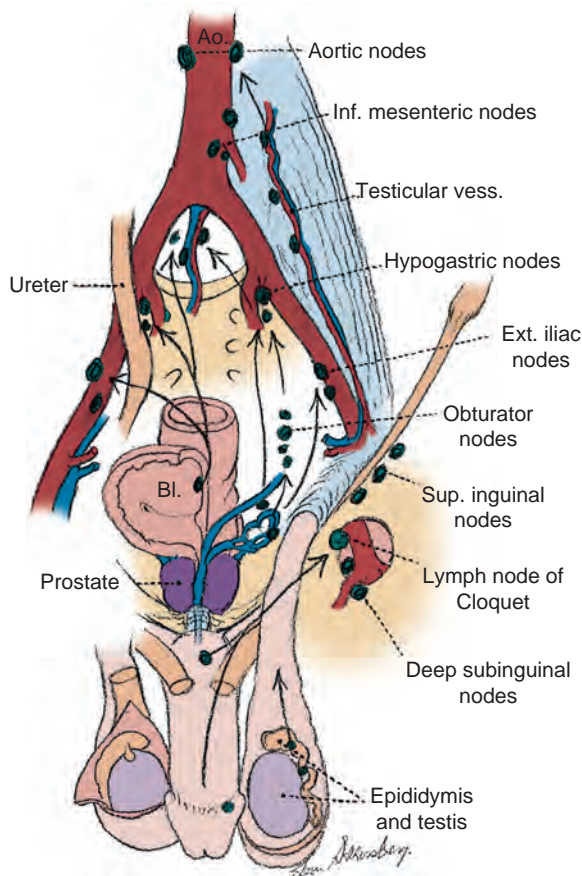


Figure 68-14. Lymphatic drainage of the male pelvis, perineum, and external genitalia. Ao., aorta; Bl., bladder.

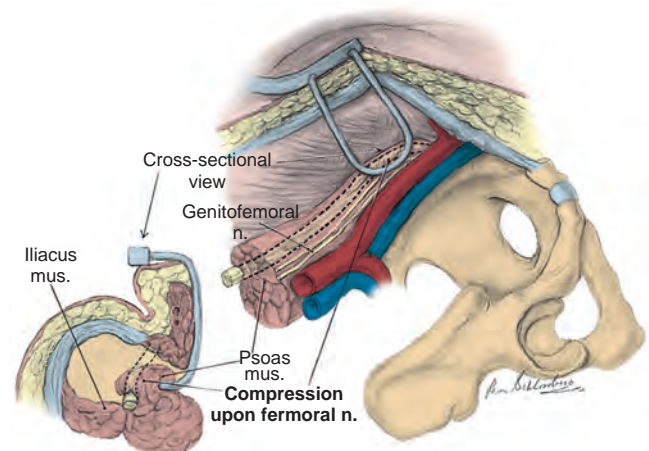


Figure 68-15. Femoral nerve as it relates to the psoas muscle. Retractor blades may compress this nerve to produce a femoral nerve palsy. (From Burnett AL, Brendler CB. Femoral neuropathy following major pelvic surgery: etiology and prevention. *J Urol* 1994; 151:163–5.)

cord. They reach the pelvic plexus by two pathways: (1) The superior hypogastric plexus is formed by sympathetic fibers from the celiac plexus and the first four lumbar splanchnic nerves (Fig. 68-17). Anterior to the bifurcation of the aorta, it divides into two hypogastric nerves that enter the pelvis medial to the internal iliac vessels, anterior to the sacrum, and deep to the endopelvic fascia. (2) The pelvic continuations of the sympathetic trunks pass deep to the common iliac vessels and medial to the sacral foramina and fuse in front of the coccyx at the ganglion impar (see Fig. 68-17). Each chain comprises four to five ganglia that send branches anterolaterally to participate in the formation of the pelvic plexus.

Presynaptic parasympathetic innervation arises from the intermediolateral cell column of the sacral cord. Fibers emerge from

TABLE 68-2 Somatic Nerves of the Lower Abdomen and Pelvis

NERVE NAME	ORIGIN	SUPPLIES
Iliohypogastric	L1	Motor supply to internal oblique, transversus muscles, sensation over lower anterior abdominal wall
Ilioinguinal	L1	Sensation over anterior pubis (mons) and anterior scrotum
Genitofemoral	L1, L2	Genital branch: motor supply to cremaster muscle, sensation to anterior scrotum Femoral branch: sensation to anterior thigh
Femoral	L2, L3, L4	Motor supply to extensors of the knee, sensation to anterior thigh
Obturator	L2, L3, L4	Motor supply to adductors of the thigh, sensation to medial thigh
Lumbosacral trunk	L4, L5	Joins the sacral nerves to form the lumbosacral plexus that supplies motor and sensory innervation to the lower extremities
Posterior femoral cutaneous	S2, S3	Sensation to perineum, posterior scrotum, and posterior thigh
Pudendal	S2, S3, S4	Motor to levator ani, muscles of the urogenital diaphragm, anal and striated urethral sphincter, sensation to the perineum, scrotum, penis
Pelvic somatic efferents	S2, S3, S4	Motor supply to levator ani and striated urethral sphincter
Nervi erigentes	S2, S3, S4	Parasympathetic fibers from the sacral cord that supply the pelvic viscera

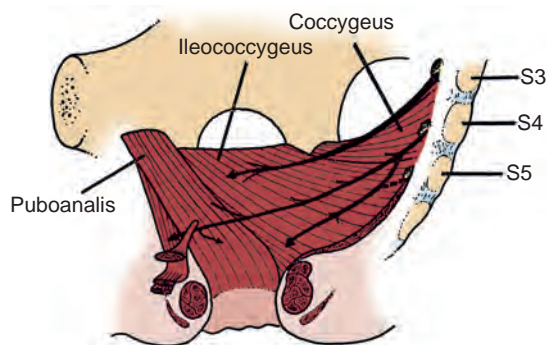


Figure 68-16. Pelvic floor somatic efferent nerves extending anteriorly on the pelvic surface of the levator ani to supply this muscle and the striated urethral sphincter. (From Lawson JO. *Pelvic anatomy. I. Pelvic floor muscles.* Ann R Coll Surg Engl 1974;54:244–52.)

the second, third, and fourth sacral spinal nerves as the pelvic splanchnic nerves (nervi erigentes) to join the hypogastric nerves and branches from the sacral sympathetic ganglia to form the inferior hypogastric (pelvic) plexus (see Fig. 68-17). Some pelvic parasympathetic efferent fibers travel up the hypogastric nerves to the inferior mesenteric plexus, where they provide parasympathetic innervation to the descending and sigmoid colon.

The pelvic plexus is rectangular, approximately 4 to 5 cm long, and its midpoint is at the tips of the seminal vesicles (Schlegel and Walsh, 1987). It is oriented in the sagittal plane on either side of the rectum and is pierced by the numerous vessels going to and from the rectum, bladder, seminal vesicles, and prostate (Fig. 68-18). Division of these vessels (the so-called lateral pedicles of the bladder and prostate) risks injury to the pelvic plexus with attendant postoperative impotence (Walsh and Donker, 1982; Walsh et al, 1983). The right and left components of the pelvic plexus communicate behind the rectum and anterior and posterior to the vesical neck. Branches of the pelvic plexus follow pelvic blood vessels to reach the pelvic viscera, although nerves to the ureter may join it directly as it passes nearby. Visceral afferent and efferent nerves travel on the vas deferens to reach the testis and epididymis.

The most caudal portion of the pelvic plexus gives rise to the innervation of the prostate and the important cavernosal nerves (Walsh and Donker, 1982). After passing the tips of the seminal vesicles, these nerves lie within leaves of the lateral endopelvic fascia near its juncture with, but outside, Denonvilliers fascia (Lepor et al, 1985). They travel at the posterolateral border of the

prostate on the surface of the rectum and are lateral to the prostatic capsular arteries and veins (see Fig. 68-18). Because the nerves are composed of multiple fibers not visible on gross inspection, these vessels serve as a surgical landmark for the course of these nerves (the neurovascular bundle of Walsh). During radical prostatectomy, the nerves are most vulnerable at the apex of the prostate, where they closely approach the prostatic capsule at the 5 and 7 o'clock positions. On reaching the membranous urethra, the nerves divide into superficial branches, which travel on the lateral surface of the striated urethral sphincter at the 3 and 9 o'clock positions, and deep fibers, which penetrate the substance of this muscle and send twigs to the bulbourethral glands. As the nerves reach the hilum of the penis, they join to form one to three discrete bundles, related to the urethra at the 1 and 11 o'clock positions, superficial to the cavernous veins and dorsomedial to the cavernous arteries (Lue et al, 1984; Breza et al, 1989). With the arteries, they pierce the corpora cavernosa to supply the erectile tissue. Small fibers also join the dorsal nerves of the penis as they course distally.

PELVIC VISCERA

Rectum

The rectum begins with the disappearance of the sigmoid mesentery opposite the third sacral vertebra. Peritoneum continues anteriorly over the upper two thirds of the rectum as the rectovesical pouch in males (Fig. 68-19). Incision of the anterior wall of this peritoneal pouch exposes the seminal vesicles behind the bladder. Inferior to this pouch, the anterior rectum is related to its fascial continuation (the rectogenital or Denonvilliers fascia) down to the level of the striated urethral sphincter (see Figs. 68-2 and 68-19). The rectum describes a gentle curve on the sacrum, coccyx, and levator plate (see Fig. 68-17) and receives innervation from the laterally placed pelvic autonomic plexus and blood supply from the superior (from inferior mesenteric), middle (from internal iliac), and inferior (from internal pudendal) rectal arteries.

The rectal wall is composed of an inner layer of circular smooth muscle and a virtually continuous sheet of outer longitudinal smooth muscle derived from the taenia of the colon. In its lowest part, the rectum dilates to form the rectal ampulla. At the most inferior portion of the ampulla, anterior fibers of the longitudinal muscle leave the rectum to join Denonvilliers fascia and the posterior striated urethral sphincter in the apex of the perineal body (Brooks et al, 2002). During perineal prostatectomy, these fibers, the rectourethralis muscle, are 2 to 10 mm thick and must be divided to gain access to the prostate (Fig. 68-20). The apices of the prostate and rectal ampulla are in close proximity, and rectal

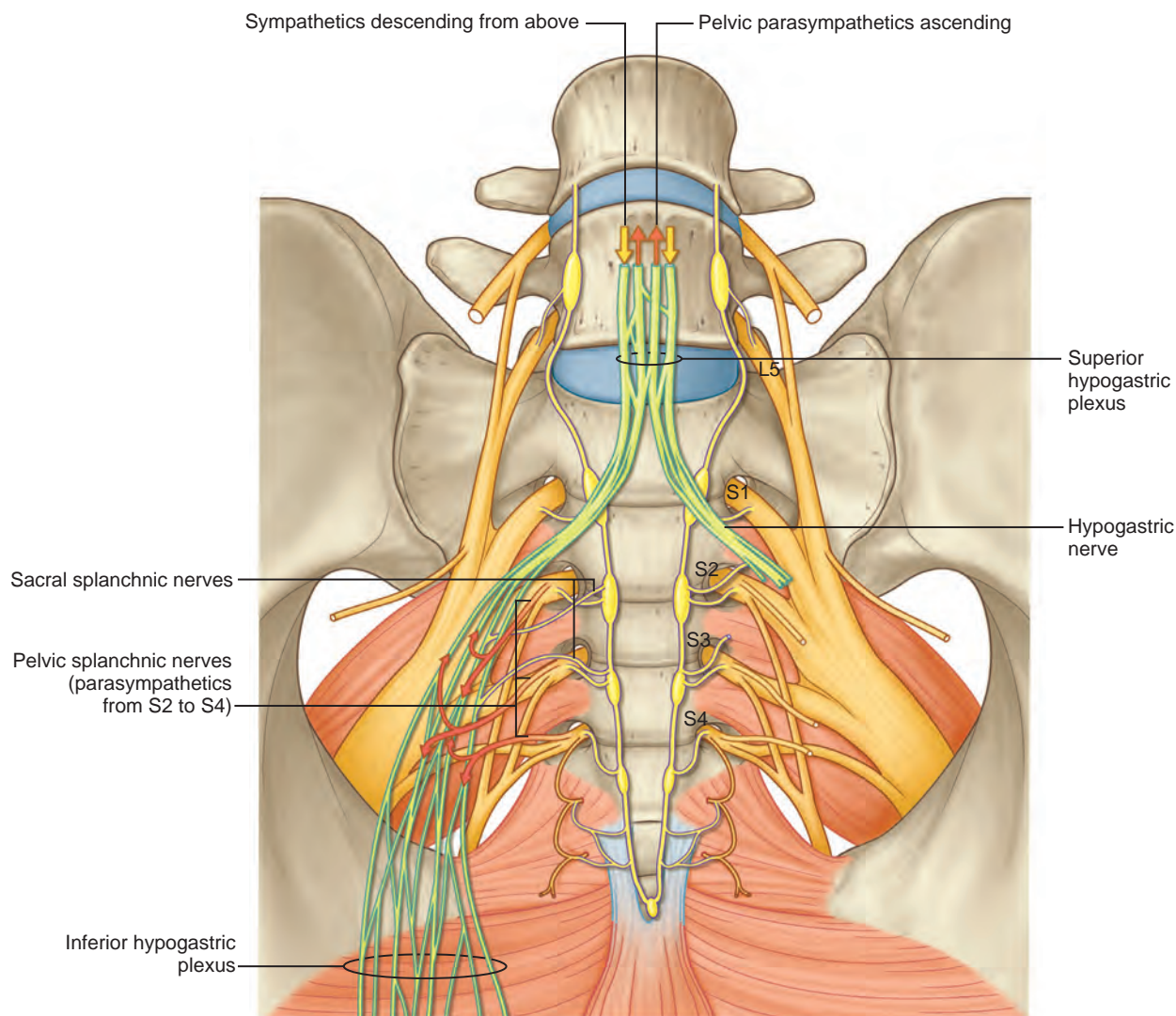


Figure 68-17. Sympathetic and parasympathetic contributions to the pelvic autonomic nervous plexus.

injuries during radical prostatectomy commonly occur at this location. As the rectourethralis is given off, the rectum makes a right-angle turn posteroinferiorly to exit the pelvis at the anal canal (see Fig. 68-7). The anatomy of the anal canal is considered with the perineum.

Pelvic Ureter

The ureter is divided into abdominal and pelvic portions by the common iliac artery. The structure of the ureter and its abdominal course are reviewed in Chapter 42. Intraoperatively the ureter is identified by its peristaltic waves and is readily found anterior to the bifurcation of the common iliac artery. At ureteroscopy, pulsations of this artery can be seen in the posterior ureteral wall. Pyeloureterography discloses a narrowing of the ureter at the iliac vessels, and ureteral calculi frequently become lodged at this location. Because the ureter and iliac vessels rest on the arcuate line, the ureter is subject to compression and obstruction by the gravid uterus and by masses within the true pelvis.

The ureters come within 5 cm of each other as they cross the iliac vessels. On entering the pelvis, they diverge widely along the pelvic sidewalls toward the ischial spines. The ureter travels on the anterior surface of the internal iliac vessels and is related laterally to the branches of the anterior trunk. Near the ischial spine, the ureter turns anteriorly and medially to reach the bladder. In

men, the anteromedial surface of the ureter is covered by the peritoneum, and the ureter is embedded in retroperitoneal connective tissue, which varies in thickness (see Fig. 68-8). As the ureter courses medially, it is crossed anteriorly by the vas deferens and runs with the inferior vesical arteries, veins, and nerves in the lateral vesical ligaments. Viewed from the peritoneal side, the ureter is just lateral and deep to the rectogenital fold. The intramural ureter is discussed with the bladder in this chapter.

The pelvic ureter receives abundant blood supply from the common iliac artery and most branches of the internal iliac artery. The inferior vesical and uterine arteries usually supply the ureter with its largest pelvic branches. **Blood supply to the pelvic ureter enters laterally; thus the pelvic peritoneum should be incised only medial to the ureter.** Intramural vessels of the ureter run within the adventitia and generally follow one of two patterns. In approximately 75% of specimens, longitudinal vessels run the length of the ureter and are formed by anastomoses of segmental ureteral vessels. In the remaining ureters, the vessels form a fine interconnecting mesh (plexiform) with less collateral flow (Shafik, 1972). Therefore primary repair of injuries to the pelvic ureter fare poorly and are more prone to stricture formation (Hinman, 1993). Lymphatic drainage of the pelvic ureter is to the external, internal, and common iliac nodes. Pathologic enlargement of the common and internal iliac nodes can encroach on and obstruct the ureter.

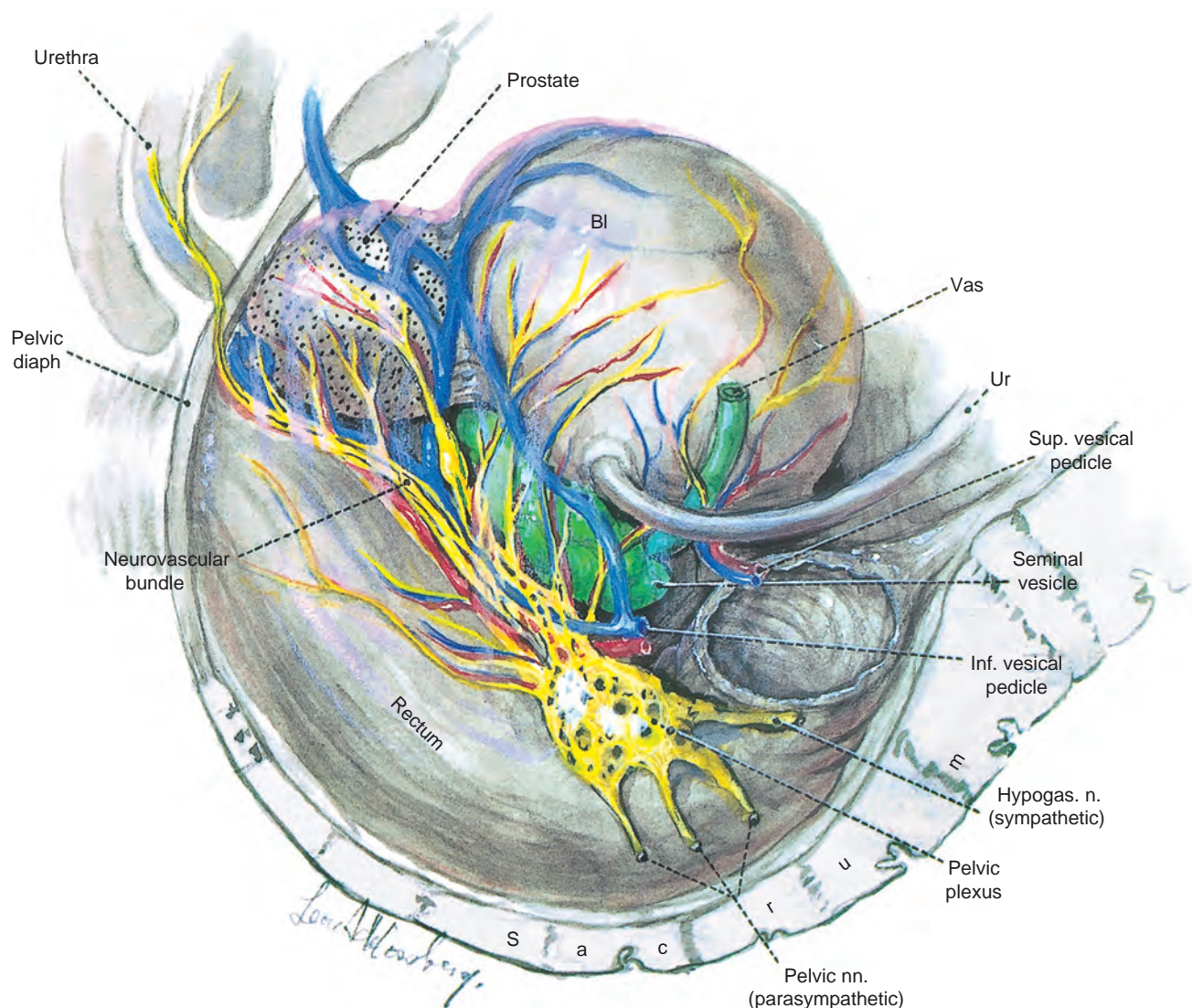


Figure 68-18. Lateral view showing the left pelvic autonomic nervous plexus and its relation to the pelvic viscera. Bl, bladder; Ur, urethra. (From Schlegel PN, Walsh PC. Neuroanatomical approach to radical cystoprostatectomy with preservation of sexual function. *J Urol* 1987;138:1402–6.)

The pelvic ureter has rich adrenergic and cholinergic autonomic innervation derived from the pelvic plexus. The functional significance of this innervation is unclear, inasmuch as the ureter continues to contract peristaltically after denervation. Afferent neural fibers travel through the pelvic plexus and account for the visceral quality of referred pain from ureteral irritation or acute obstruction.

Bladder

Relationships

When filled, the bladder has a capacity of approximately 500 mL and assumes an ovoid shape. The empty bladder is tetrahedral and is described as having a superior surface with an apex at the urachus, two inferolateral surfaces, and a posteroinferior surface or base with the bladder neck at the lowest point (see Fig. 68-19).

The urachus anchors the bladder to the anterior abdominal wall (see Fig. 68-6). There is a relative paucity of bladder wall muscle at the point of attachment of the urachus, predisposing to diverticula formation. The urachus is composed of longitudinal smooth muscle bundles derived from the bladder wall. Near the

umbilicus, it becomes more fibrous and usually fuses with one of the obliterated umbilical arteries. Urachal vessels run longitudinally, and the ends of the urachus must be ligated when it is divided. An epithelium-lined lumen usually persists throughout life and uncommonly gives rise to aggressive urachal adenocarcinomas (Begg, 1930). In rare instances, luminal continuity with the bladder serves as a bacterial reservoir or results in an umbilical urinary fistula.

The superior surface of the bladder is covered by the peritoneum. Anteriorly the peritoneum sweeps gently onto the anterior abdominal wall (see Fig. 68-8). With distention, the bladder rises out of the true pelvis and separates the peritoneum from the anterior abdominal wall. It is therefore possible to perform a suprapubic cystostomy without risking entry into the peritoneal cavity. Posteriorly, the peritoneum passes to the level of the seminal vesicles and meets the peritoneum on the anterior rectum to form the rectovesical space.

Anteroinferiorly and laterally, the bladder is cushioned from the pelvic sidewall by retropubic and perivesical fat and loose connective tissue. This potential space (of Retzius) may be entered anteriorly by dividing the transversalis fascia, and it provides access to the pelvic viscera as far posteriorly as the iliac

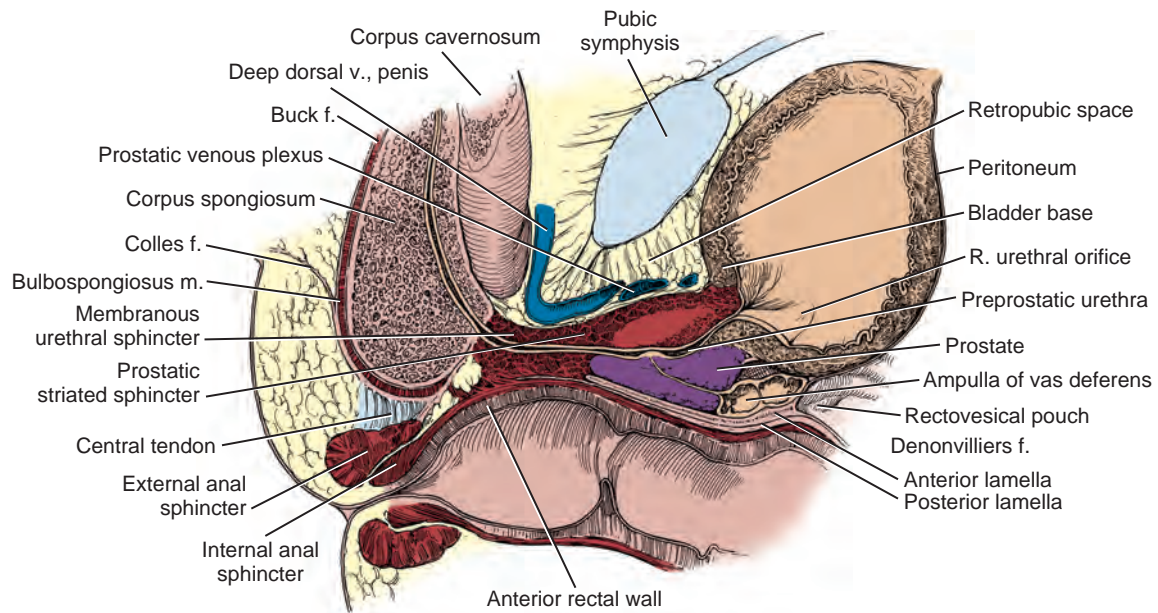


Figure 68-19. Sagittal section through the prostatic and membranous urethra, demonstrating the midline relations of the pelvic structures. (From Hinman F Jr. *Atlas of urosurgical anatomy*. Philadelphia: Saunders; 1993.)

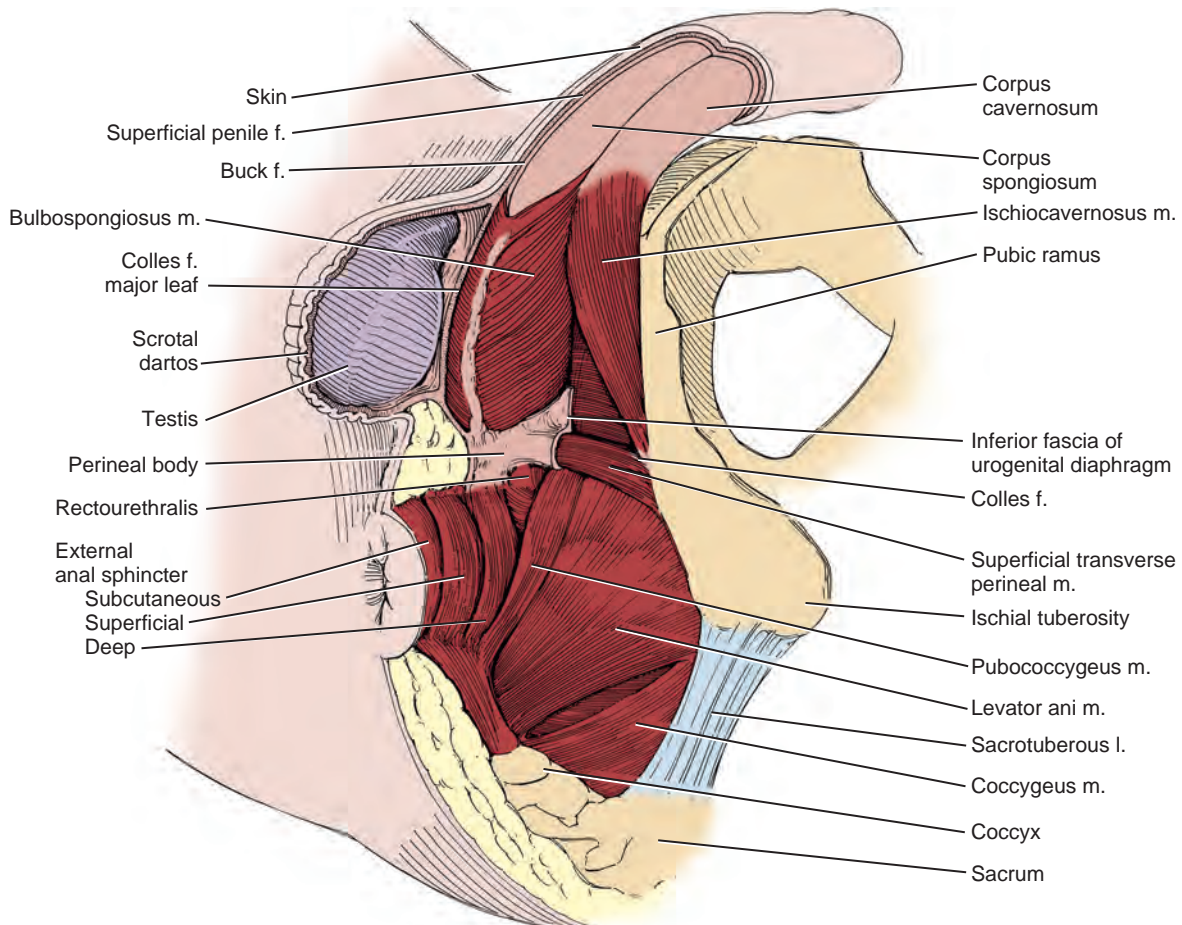


Figure 68-20. Muscles and superficial fasciae of the male perineum. (From Hinman F Jr. *Atlas of urosurgical anatomy*. Philadelphia: Saunders; 1993.)

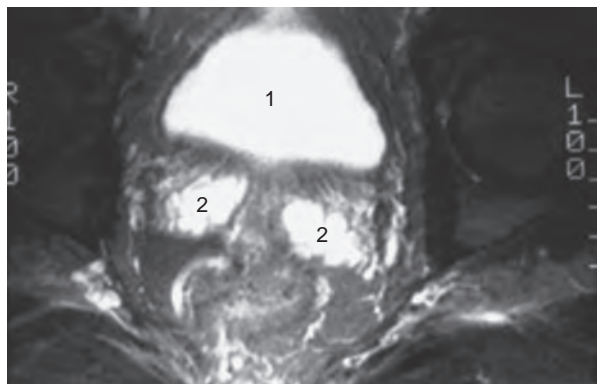


Figure 68-21. Axial T2-weighted magnetic resonance image of the male pelvis illustrating the bladder (1) and the seminal vesicles (2).

vessels and ureters. The bladder base is related to the seminal vesicles, ampullae of the vasa deferentia, and the terminal ureter (Fig. 68-21). The bladder neck, located at the internal urethral meatus, rests 3 to 4 cm behind the midpoint of the symphysis pubis. It is firmly fixed by the pelvic fasciae (see earlier discussion) and by its continuity with the prostate; its position changes little with varying conditions of the bladder and rectum.

In infants, the true pelvis is shallow and the bladder neck is level with the upper border of the symphysis. The bladder is a true intra-abdominal organ that can project above the umbilicus when full. By puberty, the bladder has migrated to the confines of the deepened true pelvis.

Structure

The internal surface of the bladder is lined with the transitional epithelium, which appears smooth when the bladder is full but contracts into numerous folds when the bladder empties. This urothelium is usually six cells thick and rests on a thin basement membrane. Deep to this, the lamina propria forms a relatively thick layer of fibroelastic connective tissue that allows considerable distention. This layer is traversed by numerous blood vessels and contains smooth muscle fibers collected into a poorly defined muscularis mucosae. Beneath this layer lies the smooth muscle of the bladder wall. The relatively large muscle fibers form branching, interlacing bundles loosely arranged into inner longitudinal, middle circular, and outer longitudinal layers (Fig. 68-22). However, in the upper aspect of the bladder, these layers are clearly not separable, and any one fiber can travel between each of the layers, can change orientation, and can branch into longitudinal and circular fibers. This meshwork of detrusor muscle is ideally suited for emptying the spherical bladder.

Near the bladder neck, the detrusor muscle is clearly separable into the three layers described earlier. Here the smooth muscle is morphologically and pharmacologically distinct from the remainder of the bladder, for the large-diameter muscle fascicles are replaced by much finer fibers. The structure of the bladder neck appears to differ between men and women. In men, radially oriented inner longitudinal fibers pass through the internal meatus to become continuous with the inner longitudinal layer of smooth muscle in the urethra.

The middle layer forms a circular preprostatic sphincter that is responsible for continence at the level of the bladder neck (Fig. 68-23). The bladder wall posterior to the internal urethral meatus and the anterior fibromuscular stroma of the prostate form a continuous ringlike structure at the bladder neck (Brooks et al, 1998). The fact that perfect continence can be maintained in men in whom the striated urethral sphincter is destroyed attests to the efficacy of this sphincter (Waterhouse et al, 1973). This muscle is richly innervated by adrenergic fibers, which, when stimulated, produce closure of the bladder neck (Uhlenhuth, 1953). Damage to the sympathetic

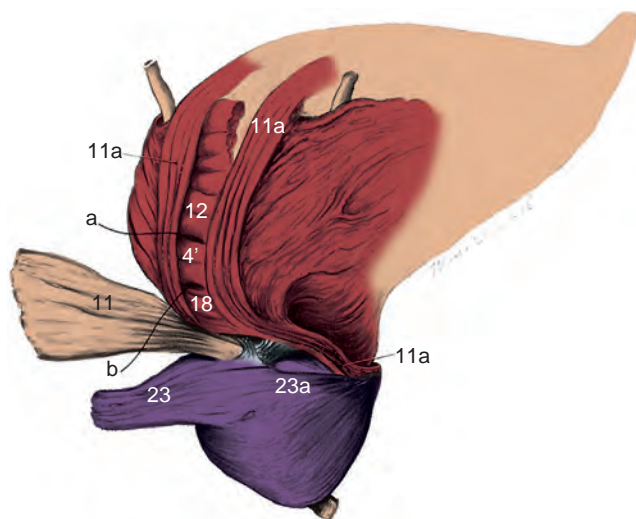


Figure 68-22. Dissection of the male bladder. 11, Posterior outer longitudinal detrusor, which forms the backing of the ureters (folded back); 11a, posterolateral portion of the outer longitudinal muscle forming a loop around the anterior bladder neck; 4', 12, and 18, middle circular layer backing the trigone; 23 and 23a, lateral pedicle of the prostate. (From Uhlenhuth E. *Problems in the anatomy of the pelvis*. Philadelphia: JB Lippincott; 1953.)

nerves leading to the bladder, as a result of diabetes mellitus or retroperitoneal lymph node dissection for testis cancer, can cause retrograde ejaculation.

The outer longitudinal fibers are thickest posteriorly at the bladder base. In the midline, they insert into the apex of the trigone and intermix with the smooth muscle of the prostate to provide a strong trigonal backing. Laterally the fibers from this posterior sheet pass anteriorly and fuse to form a loop around the bladder neck (see Fig. 68-22). This loop is thought to participate in continence at the bladder neck. On the lateral and anterior surfaces of the bladder, the longitudinal fibers are not as well developed. Some anterior fibers course forward to join the puboprostatic ligaments in men. These fibers contribute smooth muscle to these supports and are speculated to contribute during micturition to the bladder neck opening (DeLancey, 1989).

Ureterovesical Junction and the Trigone

As the ureter approaches the bladder, its spirally oriented mural smooth muscle fibers become longitudinal. Two to 3 cm from the bladder, a fibromuscular sheath (of Waldeyer) extends longitudinally over the ureter and follows it to the trigone (Tanagho, 1992). The ureter pierces the bladder wall obliquely, travels 1.5 to 2 cm, and terminates at the ureteral orifice (Figs. 68-24 and 68-25). As it passes through a hiatus in the detrusor (intramural ureter), it is compressed and it narrows considerably. This is a common site in which ureteral stones become impacted. The intravesical portion of the ureter lies immediately beneath the bladder urothelium and therefore is quite pliant; it is backed by a strong plate of detrusor muscle. With bladder filling, this arrangement is thought to result in passive occlusion of the ureter, like a flap valve. Indeed, reflux does not occur in fresh cadavers when the bladder is filled (Thomson et al, 1994). Vesicoureteral reflux is thought to result from insufficient submucosal ureteral length and poor detrusor backing. (Fig. 68-26) Chronic increases in intravesical pressure resulting from bladder outlet obstruction can cause herniation of the bladder mucosa through the weakest point of the hiatus above the ureter and can produce a "Hutch diverticulum" and reflux (Hutch et al, 1961).

The triangle of smooth urothelium between the two ureteric orifices and the internal urethral meatus is referred to as the

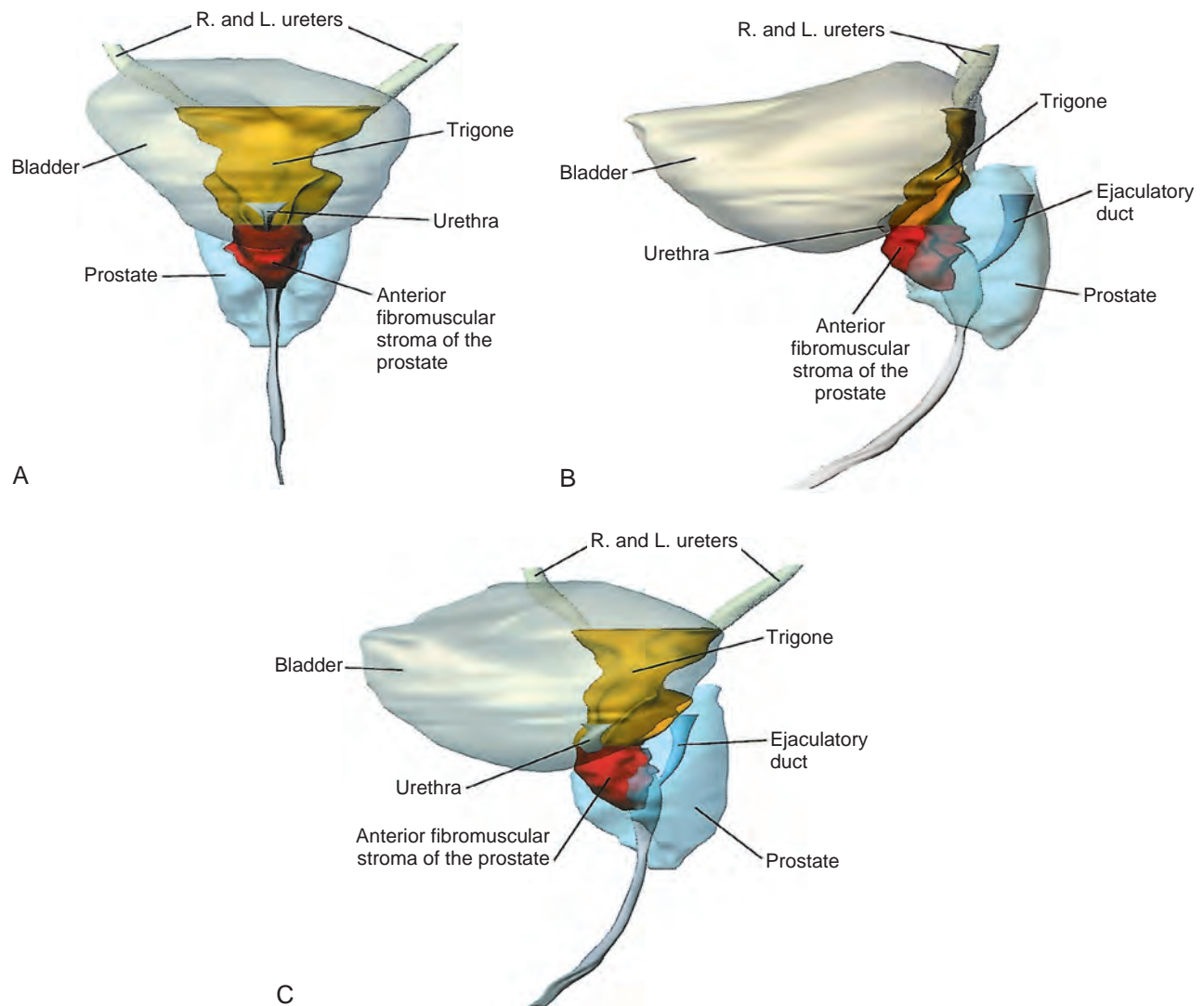


Figure 68-23. Structure of the male bladder neck and trigone. **A**, Anterior view shows that the trigone narrows below the ureteric orifices and then widens at the bladder neck to become continuous with the anterior fibromuscular stroma of the prostate. **B**, Lateral projection shows that the trigone and anterior fibromuscular stroma are in continuity. The trigone thickens near the bladder neck as it meets the anterior fibromuscular stroma. **C**, Oblique view shows this structure at the bladder neck, where it forms the internal urethral sphincter. (From Brooks JD, Chao WM, Kerr J. Male pelvic anatomy reconstructed from the visible human data set. *J Urol* 1998;159:868–72.)

trigone of the bladder (see Fig. 68-24). The fine longitudinal smooth muscle fibers from each ureter fan out over the base of the bladder to form a triangular sheet of muscle that extends from the two ureteric orifices to the internal urethral meatus. The edges of this muscular sheet can be thickened between the ureteric orifices (the interureteric crest or Mercier bar) and between the ureters and the internal urethral meatus (Bell muscle).

The muscle of trigone forms three distinct layers: (1) a superficial layer, derived from the longitudinal muscle of the ureter, which extends down the urethra to insert at the verumontanum; (2) a deep layer, which continues from the Waldeyer sheath and inserts at the bladder neck; and (3) a detrusor layer, formed by the outer longitudinal and middle circular smooth muscle layers of the bladder wall. Through its continuity with the ureter, the superficial trigonal muscle anchors the ureter to the bladder. During ureteral reimplantation, this muscle is tented up and divided to gain access to the space between the Waldeyer sheath and the ureter. In this space, only loose fibrous and muscular connections are found. This

anatomic arrangement helps prevent reflux during bladder filling by fixing and applying tension to the ureteric orifice. As the bladder fills, its lateral wall telescopes outward on the ureter, thereby increasing intravesical ureteral length (Hutch et al, 1961).

The urothelium overlying the muscular trigone is usually only three cells thick and adheres strongly to the underlying muscle by a dense lamina propria. During filling and emptying of the bladder, this mucosal surface remains smooth.

Bladder Circulation

In addition to the vesical branches, the bladder may be supplied by any adjacent artery arising from the internal iliac artery. For convenience, surgeons refer to the vesical blood supply as the *lateral* and *posterior* pedicles, which, when the bladder is approached from the rectovesical space, are lateral and posteromedial to the ureters, respectively. These pedicles are the lateral and posterior vesical ligaments in the male (see Fig. 68-8). The veins of

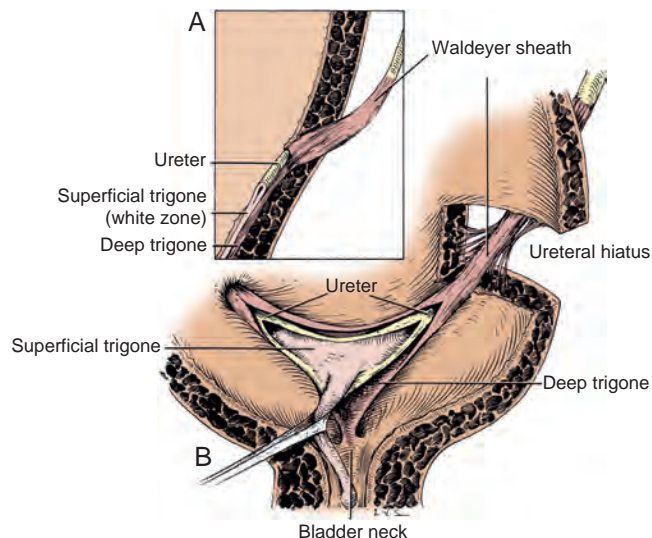


Figure 68-24. Normal ureterovesical junction and trigone. **A**, Section of the bladder wall perpendicular to the ureteral hiatus shows the oblique passage of the ureter through the detrusor and also shows the submucosal ureter with its detrusor backing. Waldeyer sheath surrounds the prevesical ureter and extends inward to become the deep trigone. **B**, Waldeyer sheath continues in the bladder as the deep trigone, which is fixed at the bladder neck. Smooth muscle of the ureter forms the superficial trigone and is anchored at the verumontanum. (From Tanagho EA, Pugh RCB. The anatomy and function of the ureterovesical junction. *Br J Urol* 1963;35:151–65.)

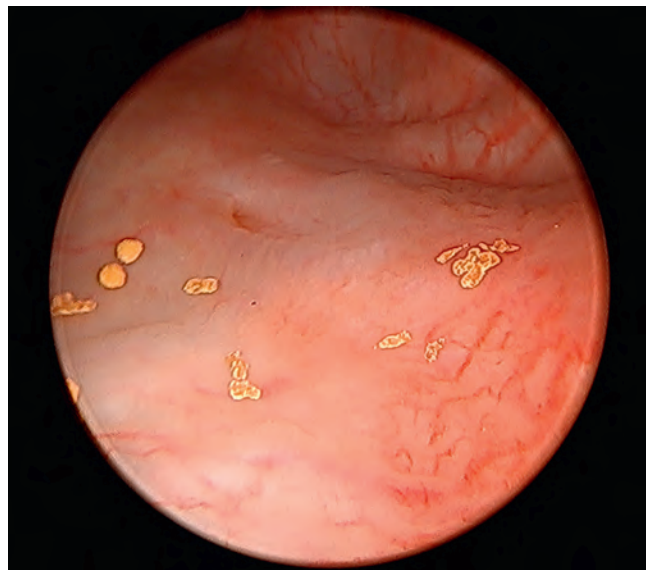


Figure 68-25. Right ureteric orifice and right hemitrigone with scattered small calculi.

the bladder coalesce into the vesical plexus and drain into the internal iliac vein. Lymphatics from the lamina propria and muscularis drain to channels on the bladder surface, which run with the superficial vessels within the thin visceral fascia. Small paravesical lymph nodes can be found along the superficial channels. The bulk of the lymphatic drainage passes to the external iliac lymph nodes (see Fig. 68-14). Some anterior and lateral drainage may go through the obturator and internal iliac nodes, whereas portions of the bladder base and trigone may drain into the internal and common iliac groups.



Figure 68-26. Cystogram demonstrating left-sided vesicoureteral reflux into dilated ureter.

Bladder Innervation

Autonomic efferent fibers from the anterior portion of the pelvic plexus (the vesical plexus) bypass the lateral and posterior ligaments to innervate the bladder. The bladder wall is richly supplied with parasympathetic cholinergic nerve endings and has abundant postganglionic cell bodies. Sparse sympathetic innervation of the bladder has been proposed to mediate detrusor relaxation but probably lacks functional significance. A separate nonadrenergic, noncholinergic (NANC) component of the autonomic nervous system participates in activating the detrusor, although the neurotransmitter has not been identified (Burnett, 1995). As mentioned, the male bladder neck receives abundant sympathetic innervation and expresses α_1 -adrenergic receptors. The female bladder neck has little adrenergic innervation. Nitric oxide synthase-containing neurons have been identified in the detrusor, particularly at the bladder neck, where they facilitate relaxation during micturition. The trigonal muscle is innervated by adrenergic and nitric oxide synthase-containing neurons. Like the bladder neck, it relaxes during micturition. Afferent innervation from the bladder travels with both sympathetic (via the hypogastric nerves) and parasympathetic nerves to reach cell bodies in the dorsal root ganglia located at thoracolumbar and sacral levels. As a consequence, presacral neurectomy (division of the hypogastric nerves) is ineffective in relieving bladder pain.

PERINEUM

The perineum lies between the pubis, thighs, and buttocks and is limited superiorly by the levator ani. Viewed from below, the symphysis pubis, ischial tuberosities, and coccyx outline the diamond shape of the perineum; the inferior ischiopubic rami and sacrotuberous ligaments form its bony and ligamentous walls (Figs. 68-27 and 68-28; see also Fig. 68-20). A line drawn through the ischial tuberosities divides the perineum into an anal and a urogenital triangle.

Anal Triangle

At the apex of the prostate, the rectum turns approximately 90 degrees posteriorly and inferiorly to become the anus (see

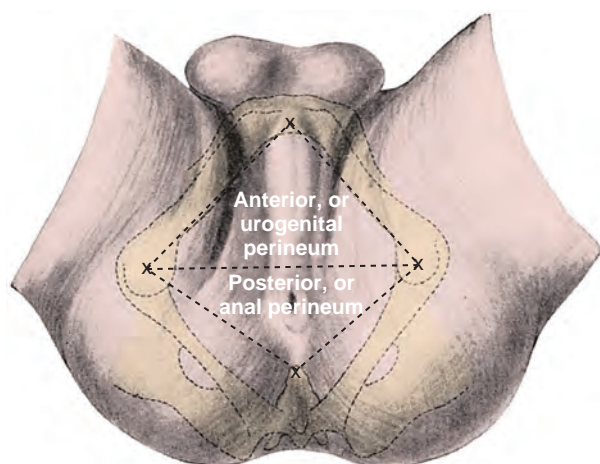


Figure 68-27. Male perineum. (From Anson BJ, McVay CB. *Surgical anatomy*. 6th ed. Philadelphia: Saunders; 1984.)

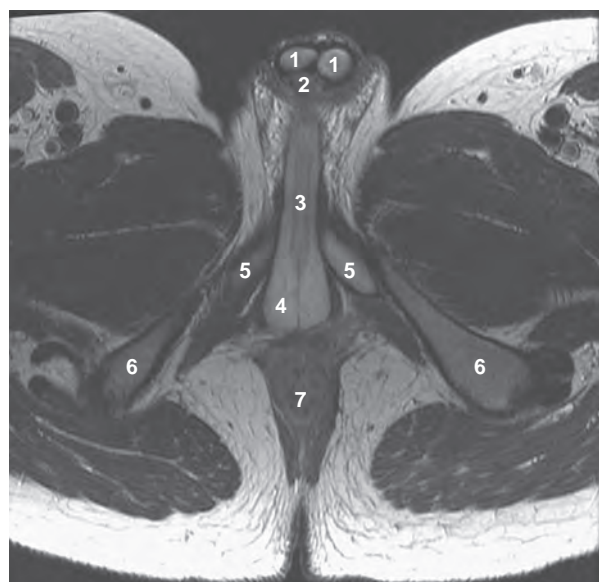


Figure 68-28. Axial T1-weighted MRI of male pelvis. 1, Corpora cavernosa in cross section; 2, corpus spongiosum in cross section; 3, corpus spongiosum in perineum; 4, bulbospongiosus muscle, which facilitates urine or seminal fluid expulsion from bulbar urethra; 5, crura of corpora cavernosa—note divergence of crura as they insert on pubic bone; 6, ischial tuberosities; 7, rectum.

Figs. 68-7 and 68-9). It traverses 4 cm to reach the skin near the center of the anal triangle. The subcutaneous fat that surrounds the anus is continuous with that of the urogenital triangle, buttocks, and medial thigh. Laterally the fat fills the ischioanal fossa, a space bounded by the levator ani medially, and the obturator internus, and the sacrotuberous ligament laterally (see Fig. 68-10). Anteriorly this space extends into a recess above the urogenital diaphragm; posteriorly it is continuous with the intermediate stratum of the pelvis through the sciatic foramina. Through this continuity, infections may travel between the perineum and the pelvic cavity.

The anal sphincter is divided into internal and external components. The internal sphincter represents a thickening of the inner circular smooth muscle layer of the rectum. The outer longitudinal smooth muscle thins beyond the rectourethralis and blends with the external sphincter, although a few fibers insert in the skin around the anus (corrugator cutis ani) to produce a puckered appearance. The external sphincter surrounds the internal and is

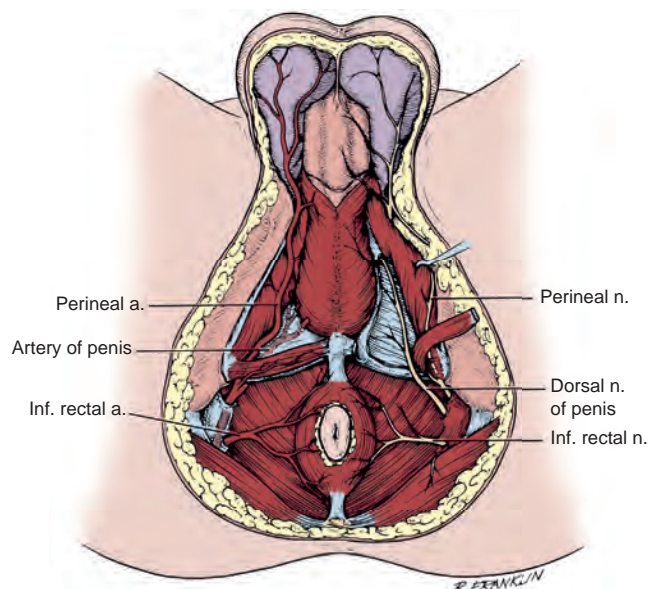


Figure 68-29. Male perineum, illustrating the internal pudendal artery and its branches on the left and the pudendal nerve and its branches on the right.

divided into subcutaneous, superficial, and deep portions. The subcutaneous part attaches to the perineal body by collagenous and muscular fibers that are thickest superficially and are referred to as the *central tendon of the perineum*. The superficial sphincter attaches to the perineal body and coccyx. At the posterior inflection of the rectum, the deep sphincter blends with the puborectalis sling of levator ani. At this level, a firm band may be felt on rectal examination and corresponds to the internal and external sphincter. Division of this muscular band results in fecal incontinence. The prostate may be accessed anterior to the sphincter by dividing the central tendon and the sphincteric attachments to the perineum (Young procedure) or by following the anterior rectal wall beneath the external anal sphincter (Belt procedure).

Male Urogenital Triangle

The entire urogenital triangle is bridged by the urogenital diaphragm. The scrotum hangs from the anterior aspect of the urogenital triangle; in the posterior aspect, skin and subcutaneous fat overlie Colles fascia. The perineal membrane and the posterior and lateral attachments of Colles fascia limit a potential space known as the superficial pouch (see Figs. 68-2, 68-10, and 68-20). In this space, the three erectile bodies of the penis have their bony and fascial attachments (the root of the penis). The paired corpora cavernosa attach to the inferior ischiopubic rami and perineal membrane and are surrounded by the ischiocavernosus muscles. The corpus spongiosum dilates as the bulb of the penis and is fixed to the center of the perineal membrane. It is encompassed by the bulbospongiosus muscles (see Fig. 68-28) that arise from the perineal body and from a central tendinous raphe and pass around the bulb to attach to the perineal membrane and dorsum of the penis. Contraction of the ischiocavernosus and bulbospongiosus muscles compresses the erectile bodies and potentiates penile erection. The transversus perinei muscles (superficial and deep) run along the posterior edge of the perineal membrane and are thought to stabilize the perineal body. Deep to the perineal membrane rests the striated urethral sphincter (discussed earlier).

Blood supply to the anal and urogenital triangles is derived largely from the internal pudendal vessels (Fig. 68-29). After entering the perineum through the lesser sciatic foramen, the artery runs in a fascial sheath on the medial aspect of obturator internus, which is the pudendal canal (of Alcock). Early in its course, it yields

three or four inferior rectal branches to the anus. Its perineal branch pierces Colles fascia to supply the muscles of the superficial pouch and continues anteriorly to supply the back of the scrotum. The internal pudendal terminates as the common penile artery.

The internal pudendal veins communicate freely with the dorsal vein complex by piercing the levator ani. These communicating vessels enter the pelvic venous plexus on the lateral surface of the prostate and are a common, often unexpected, source of bleeding during apical dissection of the prostate. The inferior rectal veins anastomose with the middle and superior rectal veins and produce an important connection between the portal and the systemic circulation. Obstruction of the portal or systemic venous system may cause shunting of collateral venous drainage through the portal system, manifested by hemorrhoids.

The pudendal nerve follows the vessels in their course through the perineum (see Fig. 68-29). Its first branch, the dorsal nerve of the penis, travels ventral to the main pudendal trunk in Alcock canal. Several inferior rectal branches supply the external sphincter muscle and provide sensation to perianal skin. The perineal branches follow the perineal artery into the superficial pouch to supply the ischiocavernosus, bulbospongiosus, and transversus perinei muscles. A few of these branches continue anteriorly to supply sensation to the posterior scrotum. Additional perineal branches pass deep to the perineal membrane to supply the levator ani and striated urethral sphincter.

Perineal Lymphatics

The penis, scrotum, and perineum drain into the inguinal lymph nodes. These nodes may be divided into a superficial and a deep group, which are separated by the deep fascia of the thigh (fascia lata). In relation to the external pudendal, superficial inferior epigastric, and superficial circumflex iliac vessels, the superficial nodes lie at the saphenofemoral junction. At the saphenous opening (fossa ovalis) in the fascia lata, the greater saphenous vein joins the femoral vein, and the superficial nodes communicate with the deep group. Most of the deep inguinal nodes lie medial to the femoral vein and send their efferents through the femoral ring (beneath the inguinal ligament) to the external iliac and obturator nodes. Just outside the femoral ring, a large node (Cloquet or Rosenmüller node) is consistently present.

The scrotal lymphatics do not cross the median raphe and drain into the ipsilateral superficial inguinal lymph nodes. Lymphatics from the shaft of the penis converge on the dorsum and then ramify to both sides of the groin. Those of the glans pass deep to Buck fascia dorsally and drain to superficial and deep groups in

both sides of the groin. Anatomists have proposed direct lymphatic channels from the glans to the pelvic nodes, which bypass the inguinal nodes; however, clinical studies have not confirmed their existence. Other studies have suggested that all penile lymphatic drainage passes through “sentinel nodes,” which lie medial to the superficial inferior epigastric veins. Clinical studies have also called this speculation into question (Catalona, 1988). The perineal skin and fasciae drain into superficial inguinal nodes; the structures of the superficial pouch likely drain into the superficial and deep inguinal node groups.

KEY POINTS

- The pelvic cavity is divided into the false pelvis superiorly and the true pelvis inferiorly, wherein lie all of the pelvic organs.
- The bony prominences and ligaments of the pelvis and lower abdomen will orient the surgeon during physical examination and in the operating room.
- The pelvic floor is closed off by the levator ani and urogenital diaphragm and the muscles and fasciae of the pelvic floor provide critical support for the pelvic organs.
- The rectum, bladder, prostate, seminal vesicles, and penis receive blood supply from the anterior trunk of the internal iliac artery and innervation from the pelvic autonomic plexus.
- The urethra and anus exit through the perineum in association with the external genitalia.
- Detailed knowledge of the relationships of the pelvic organs to one another and to the bones and muscles of the pelvis, as well as the locations of the blood supply and innervation of all pelvic and perineal structures, is critical for performing all pelvic operations safely.

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Lower Urinary Tract Anatomy

Bladder Compartments

Overview of Urethra

Urothelial Physiology

Smooth Muscle Physiology

Bladder Mechanics

Neural Control of the Lower Urinary Tract

Pharmacology

Clinical Relevance

Future Research

This chapter reviews physiologic mechanisms that regulate lower urinary tract (LUT) function. The LUT is composed of the bladder and urethra, and the two defining functions of the LUT are urinary storage and emptying. Although not the focus of this chapter, another LUT function is protection of the kidneys from ascending pathogenic microorganisms, which involves appropriate functioning of the urothelium and presence of a community of microorganisms (microbiome).

Urinary storage (continence) and urinary emptying (micturition) depend on the integrated function of many components, including the central nervous system (CNS), the peripheral nervous system, bladder smooth muscle, bladder stroma, suburothelial and intradetrusor interstitial cells, bladder urothelium, urethral smooth muscle, pelvic floor striated muscles, and the external urethral sphincter (EUS). An understanding of LUT physiology is essential for management of lower urinary tract dysfunction (LUTD), such as urinary incontinence, lower urinary tract symptoms (LUTS), overactive bladder (OAB), nocturia, neurogenic bladder, and underactive bladder. Improvements in physiologic understanding will improve diagnostic and phenotyping abilities and help discover the next generation of LUTD treatments.

Laboratory investigations into LUT physiology have used animal models, and most of the data discussed in this chapter are from animal studies. This is reasonable because there are limited interventions or experiments one can do in human subjects. **However, several reasons may mitigate the relevance of animal findings to humans.** The first consideration is use of lower-order mammals (i.e., mice and rats) as a model for human LUT function. Rodents are nocturnally active and their circadian rhythm is opposite of humans. Micturition is a behavior in which some animals mark their territory, a conduct that does not apply to humans. Whereas the clinical management of LUTS is almost entirely symptom based, LUTS are difficult (if not impossible) to quantify in animals, so surrogate parameters (such as micturition frequency and volume, urodynamics) that might not relate to symptoms have been used. Another consideration is whether research data were obtained from anesthetized or awake animals, because anesthesia can alter continence and micturition reflexes. But animal models, no matter the potential drawbacks, will always be needed to improve our understanding of human LUTS. Novel findings can arise from findings in animal models (Gillespie, 2005). However, the importance of translational research, which seeks a bidirectional link between the bedside and bench, whether it is validating animal findings in humans or replicating a human phenotype in animals, is crucial in improving the treatment of LUTD.

The process of control of urinary storage and emptying is classically summarized as a complex of neural circuits in the brain and

spinal cord that coordinate the activity of smooth and striated muscles in the bladder and urethra (Torrens and Morrison, 1987; de Groat et al, 1993; Yoshimura and de Groat, 1997). These neural circuits act as switches that enable the bladder to alternate between urinary storage and elimination. Although this concept is important, translating physiologic understanding of LUT function into improved care for LUTD should be the ultimate goal. Furthermore, LUTD may not always arise from primary defects in nerves and/or muscles. Other biologic mechanisms can adversely affect LUT function, such as endocrine dysregulation (e.g., metabolic syndrome and obesity), inflammation (e.g., urothelial response to microorganisms), bladder or urethral fibrosis, and ischemia. Therefore, LUTD can be a manifestation of mechanisms arising separately from the LUT.

The mechanisms underlying control of detrusor contractility and LUT sensation remain two major areas that would benefit from continued research because of the potential for clinical impact. Many conditions encountered in LUTD relate to these two parameters. A complexity of normal LUT function is that the bladder and urethra function necessarily in an opposite manner, thus making treatments that target only the bladder or only the urethra potentially ineffective and/or causing them to have unwanted side effects. For example, treatments directed at increasing bladder contractility for detrusor underactivity may not work if the treatments do not concomitantly relax the urethra. On the other hand, an example of how a more complete understanding of a single area can improve both storage and emptying disorders is in the area of sensory (afferent) function. **Modulation of sensory mechanisms could serve two purposes: Reducing afferent signals could help those with LUTS, whereas augmenting afferent signals could help those with detrusor underactivity (Suskind and Smith, 2009; Eastham and Gillespie, 2013).** Thus, manipulation of the sensory pathway could preserve the requirement of coordinated yet simultaneously opposite bladder and urethral functions.

Although the management of LUTD is primarily symptom based at this time, use of biomarkers may come into play based on better physiologic understanding of the LUT. Ultimately, we should look forward to a time when targeted therapies and even prevention strategies may take their places in the management of LUTD patients.

LOWER URINARY TRACT ANATOMY

The bladder can be divided into several parts: a body lying above the ureteral orifices and a base consisting of the trigone and bladder neck; the two areas are different but homogeneous within

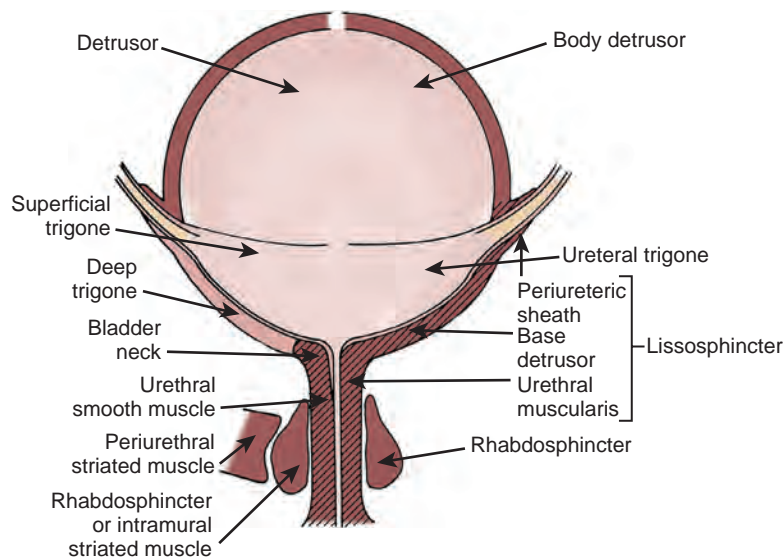


Figure 69-1. Anatomy of the bladder and its outlet, as defined by Gosling and Dixon (*left*) versus Elbadawi and coworkers (*right*). (From Torrens M, Morrison JF. *The physiology of the urinary bladder*. New York: Springer-Verlag; 1987.)

themselves regarding neuromorphology and neuropharmacology (Elbadawi and Schenk, 1966). The bladder base has a laminar architecture with a superficial longitudinal layer lying beneath the trigone (Fig. 69-1). A muscle layer deep to the superficial layer is continuous with the detrusor (Tanagho, 1982; Dixon and Gosling, 1987; Zderic et al, 1996). The smaller muscle bundles of the deep muscle layer in the bladder base exhibit a predominantly circular orientation. Histology of the full-thickness bladder is shown in Figure 69-2A. A complete and competent ring of smooth muscle at the male bladder neck has been described (Gosling, 1999). No such collar of muscle is identified in the female. The bladder neck serves an important function in reproduction. In men, closure of the bladder neck facilitates antegrade ejaculation. This is accompanied through a rich noradrenergic innervation by sympathetic nerves that actively contract the bladder neck during ejaculation. However, in women the density of adrenergic innervation in the bladder neck is reportedly less than that in men (de Groat and Booth, 1993).

The urethra is part of the bladder outlet, along with the pelvic floor musculature. The urethra has components of smooth muscle and striated muscle (rhabdosphincter or EUS) (see Fig. 69-1). The periurethral striated muscle is part of the pelvic floor muscle complex.

BLADDER COMPARTMENTS

Urothelium

The urothelium is a multilayered epithelium with a basal, intermediate, and apical layer of cells. The apical cells (umbrella cells) comprise the layer that is in contact with urine and microorganisms. The histology of the polarized urothelium is shown in Figure 69-2B; the urothelium is about seven layers thick, with the largest cells being the apical (umbrella) cells, which are sometimes multinucleated. Although the anatomy of the urothelium is relatively straightforward, there are several physiologic functions including barrier function (impermeability) and urothelial-afferent signaling, which are covered in later sections.

A scanning electron microscope (SEM) image of human apical urothelium, viewed from the luminal surface, is shown in Figure 69-3. The SEM image was obtained from a biopsy forceps cystoscopic biopsy. Note the hexagonal shape of the apical urothelial cells and the microvilli on the surface. The apical cells are also

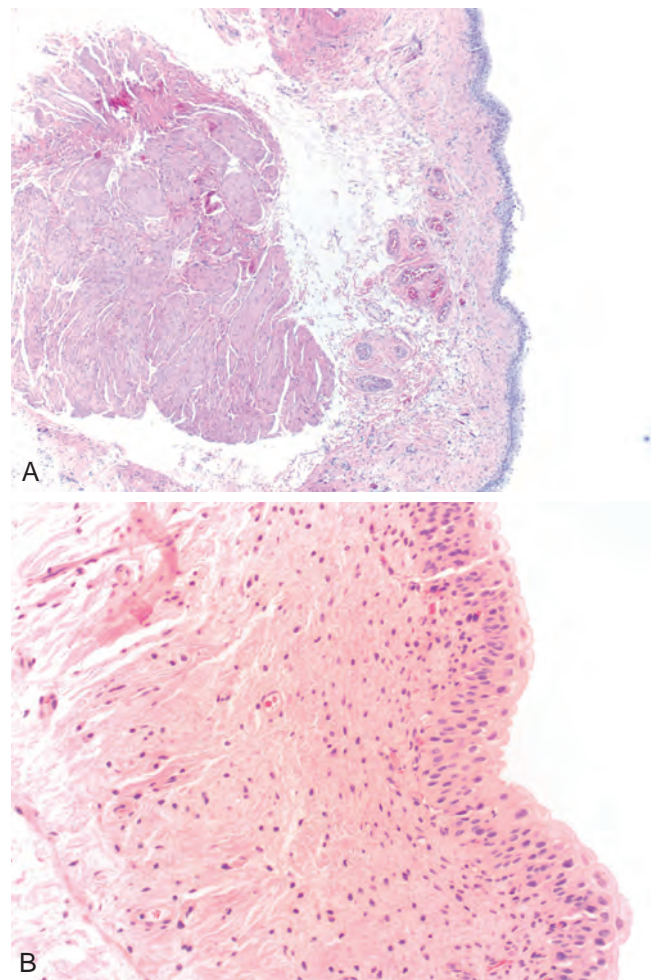


Figure 69-2. Histologic sections from a human bladder obtained from cystectomy. A (40 \times magnification) shows the entire bladder wall including urothelium, lamina propria, and muscularis propria. B (200 \times magnification) shows the urothelium and lamina propria. (Courtesy Adebawale Adeniran, MD, Yale Department of Pathology.)

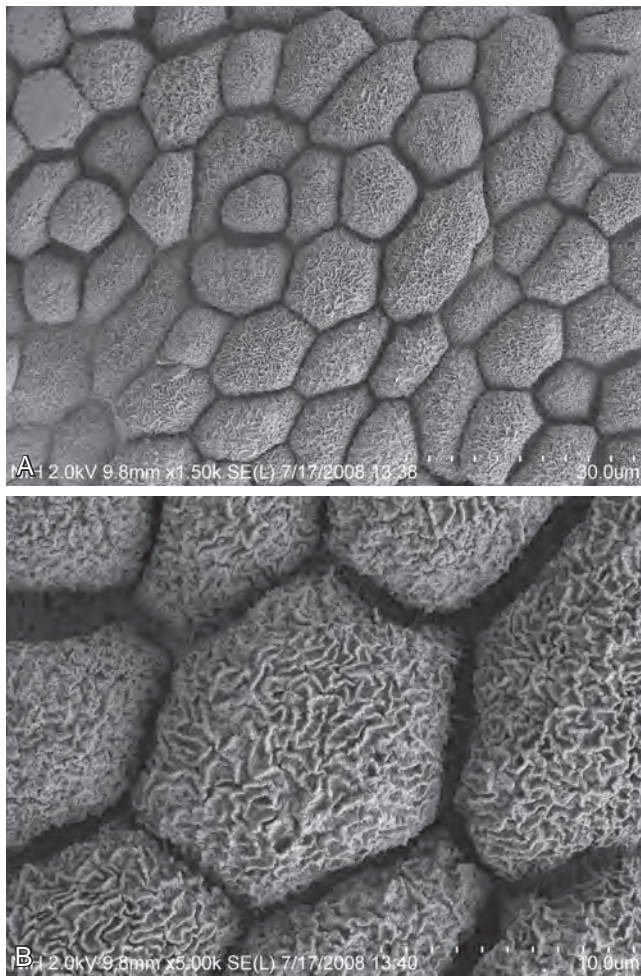


Figure 69-3. Scanning electron microscope image of human apical urothelial cells: A, 1500× magnification; B, 5000× magnification.

unique in their expression of an assembly of a specialized class of proteins called *uroplakins*. The uroplakins are assembled within the apical membrane of the apical urothelial cells within specialized areas called *plaques*. The plaques have a membrane outer leaflet that is thicker than the inner leaflet, resulting in asymmetry. Thus, the plaque region is also termed the *asymmetrical unit membrane* (AUM). The areas between the plaques are symmetrical in terms of the outer and inner leaflet thickness; this area is called the *hinge region*. Inside the AUM are chainmail-like ultrastructural hexagonal particles composed of uroplakins (Fig. 69-4). These ultrastructural particles are important in barrier function. The attachment of *Escherichia coli* type 1 fimbriae to uroplakins also initiates the host-pathogen interaction, initiating a cascade of host events (Wu et al, 1996; Mulvey et al, 1998; Thumbikat et al, 2009). More details of barrier function and urothelial-afferent crosstalk of the urothelium is described in later sections.

Lamina Propria and Vasculature

The lamina propria has been recently theorized to be the “functional center” for localized control of the bladder, coordinating the activities of the urothelium and detrusor smooth muscle (Anderson and McClosky, 2014). Within the lamina propria, there is a diffuse plexus of unmyelinated nerve fibers making contact with urothelium, blood vessels, and detrusor smooth muscle. TRPV1 and P2X₃ receptors exist on nerve fibers that traverse the muscularis layer (Yiangou et al, 2001). In addition to the nerve fibers, other important structures in the lamina propria include interstitial cells (myofibroblasts) and microvasculature. The role of suburothelial myofibroblasts in detrusor contractility is discussed in a later

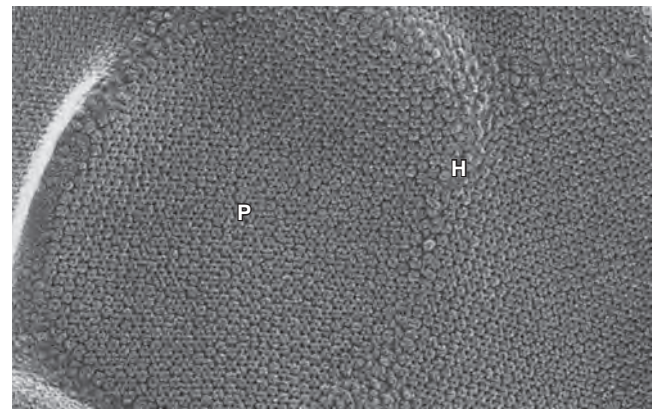


Figure 69-4. Hexagonal chainmail-like ultrastructural units composed of uroplakins. H, hinge area; P, plaque area. (From Kachar B, Liang F, Lins U, et al. Three-dimensional analysis of the 16 nm urothelial plaque particle: luminal surface exposure, preferential head-to-head interaction, and hinge formation. *J Mol Biol* 1999;285:595–608.)

section. These myofibroblasts positioned in the lamina propria are primed to modulate physiologic interactions between the urothelium and detrusor smooth muscle.

The anatomy of the microvasculature of the bladder in human and rabbit was studied using corrosion cast studies (Hossler and Monson, 1995; Miodoński and Litwin, 1999). The corrosion technique “fixes” the blood vessels by immediate vascular perfusion of the excised whole bladder with a fixative (e.g., a resin). Then all other tissue components of the bladder (smooth muscle, nerves, urothelium, stromal cells) were chemically digested, leaving only the vascular tree cast, which was imaged with scanning electron microscopy. The human bladder tissue studies showed a large horizontal plexus of blood vessels located in the lamina propria (termed the *mucosal plexus*) and another plexus just under the basal urothelial layer (termed the *subepithelial plexus*). Scanning electron microscopy of the mucosal vascular anatomy is shown in the Figure 69-5A, which shows a dense and rich submucosal plexus of vessels that lie immediately underneath the urothelium, the subepithelial capillary plexus. These are the vessels that would be typically seen during cystoscopy. Figure 69-5B shows a schematic of what happens to the bladder vasculature during bladder filling and emptying. Blood flow through the subepithelial plexus might also be, in part, regulated by the urothelium. Furthermore, the subepithelial plexus could play a role for substances that are transported through or secreted by the urothelium.

Because of the large increase in surface area of the bladder wall during filling, the blood vessels must be able to change length considerably. To maintain good blood flow, mechanisms may be needed to ensure that the overall resistance of the vessels, as they lengthen, does not increase sufficiently to reduce the effective perfusion of the tissue. Several groups have investigated the effects of bladder filling on the blood flow. The majority of reports have shown that the blood flow is reduced by distention (Batista et al, 1996; Greenland and Brading, 1996). In patients with low bladder compliance, there is a marked increase in the intravesicular pressure and a more pronounced decrease in bladder blood flow compared with normal controls (Ohnishi et al, 1994). The principal determinant of blood flow in the bladder wall seems to be intramural tension. During normal filling, the blood flow is able to adapt to the large increase in surface area until the pressure in the bladder increases (Greenland and Brading, 1996).

When the detrusor is deprived of oxygen or a metabolic substrate, as would occur in ischemia, its contractile ability rapidly declines (Levin et al, 1983; Zhao et al, 1991; Pessina et al, 1997; Levin et al, 2003). It has been suggested that ischemia and reperfusion might lead to damage to intramural neurons and result in the patchy denervation and altered smooth muscle function

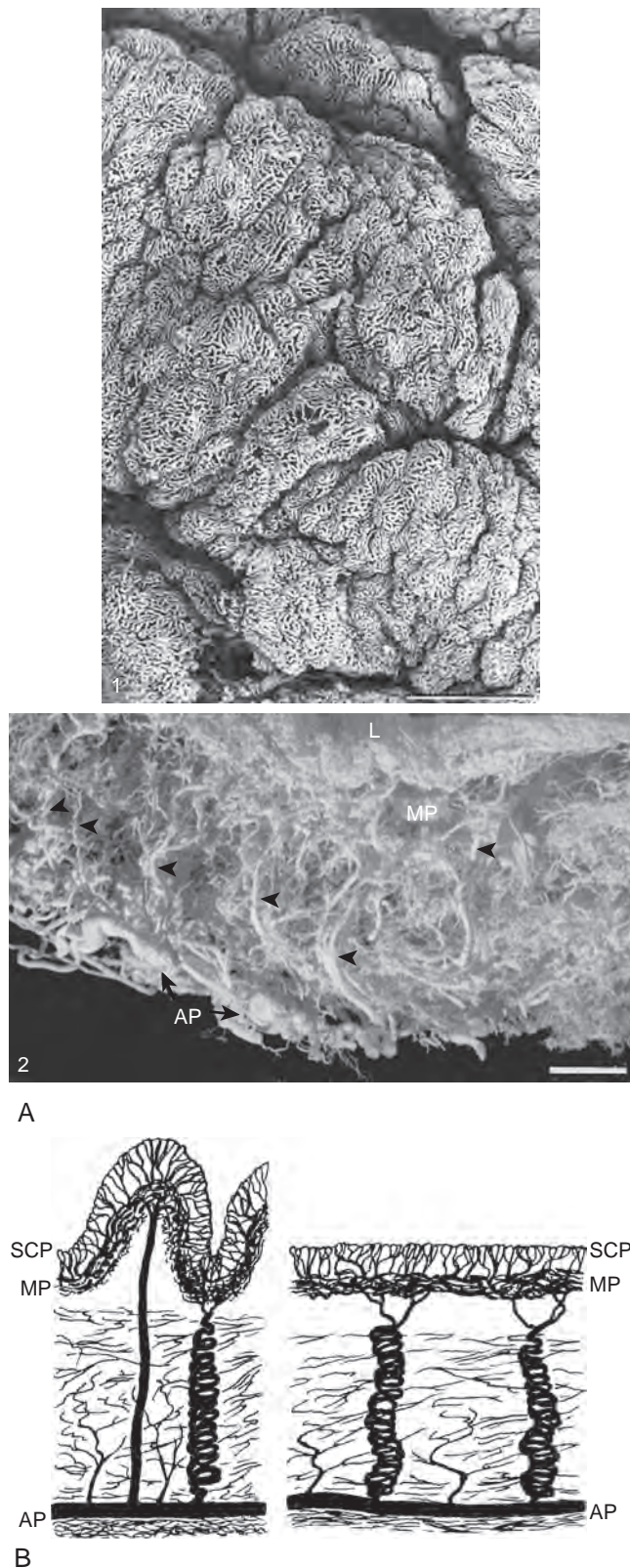


Figure 69-5. A, Scanning electron microscope image of human bladder blood vessels after corrosion cast preparation (see text). This is viewed from the luminal side and shows the high density of the vessels that comprise the subepithelial capillary network (scale = 1000 μ m). B, Schematic of vasculature of empty bladder (left) and full bladder (right). Mucosal plexus (MP) and subepithelial capillary plexus (SCP) are in lamina propria. AP, adventitial plexus. (From Miodoński AJ, Litwin JA. Microvascular architecture of the human urinary bladder wall: a corrosion casting study. *Anat Rec* 1999;254: 375–81.)

seen in bladders of patients with detrusor overactivity (DO) (Brading, 1997a).

Stroma

The main constituents of bladder wall stroma are collagen and elastin in a matrix composed of proteoglycans. The main cells are fibroblasts. The passive mechanical properties of the bladder wall depend on the viscoelastic properties of the stroma and of the relaxed detrusor muscle (Cortivo et al, 1981). The stroma has commonly been considered a passive low-metabolic tissue that fills out the space among muscle bundles, vessels, and nerves. In recent years there has been increased appreciation for the role of the stroma in the adaptation of the bladder to pathophysiologic conditions (Macarak and Howard, 1999). Bladder hypertrophy is likely to involve an interaction of stroma and smooth muscle. In arteries, disruption of elastin in the stroma can stimulate proliferation of smooth muscle (Li et al, 1998). Although no such mechanisms are yet known in the bladder, it is possible that there could be a more intimate relationship between changes in the composition of the stroma and muscle function and growth than is appreciated at present.

Bladder Wall Collagen

Most of the bladder wall collagen is found in the connective tissue outside the muscle bundles. Changes in the relative amounts of muscle and nonmuscle tissue in the bladder wall would therefore influence collagen concentration. A number of different collagen types have been identified. In the bladder, **types I, III, and IV are the most common** (Macarak et al, 1995; Andersson and Arner, 2004). Landau and coworkers (1994) developed morphometric and histochemical techniques to determine the percentage volume of connective tissue in the bladder wall and to measure the two major types (I and III) of collagen. These methods quantitate three parameters of bladder ultrastructure: percentage volume of connective tissue, ratio of connective tissue to smooth muscle, and ratio of type III to type I collagen. These parameters have been shown to be abnormally elevated in patients with bladder disease compared with normal patients. Landau and associates further studied the ultrastructural changes that occur in the wall of dysfunctional bladders to determine the ability of new urodynamic techniques to reliably detect the clinical effect of these histologic changes. The study included 29 consecutive patients undergoing bladder augmentation. Preoperative urodynamic evaluation included measurement of the total bladder capacity, assessment of pressure-specific bladder volume, and dynamic analysis of bladder compliance. Full-thickness bladder biopsy specimens were obtained from the dome of the bladders during augmentation. The percentage of connective tissue and the ratio of connective tissue to smooth muscle were determined for all patients. These histologic results were compared with previously established normal values. All 29 patients had decreased bladder compliance, even though 9 had a normal bladder capacity. The ratio of connective tissue to smooth muscle was significantly increased in poorly compliant versus normal bladders. The ratio of type III to type I collagen was also significantly elevated. One can conclude that the poor storage function of poorly compliant bladders is secondary to an alteration in the connective tissue content of the bladder wall, especially increased collagen type III.

In the rat, infravesical obstruction or bladder denervation induces hypertrophy of the detrusor smooth muscle and, in turn, a decrease in the collagen concentration (Uvelius and Mattiasson, 1984, 1986). Aging is associated with a relative decrease in smooth muscle, in both men and women, relative to collagen content (Susset et al, 1978; Lepor et al, 1992). This could perhaps be related to the decreased packing density of submucosal collagen during aging (Levy and Wight, 1990).

Perhaps the most comprehensive work on bladder collagen was performed by Macarak and Howard (1999), who speculated that connections must exist between the tension-generating elements

(i.e., the smooth muscle cells) and the other components of the bladder. In bladders that become noncompliant (e.g., from spinal cord injury), it is likely that there is some interference with the ability of the collagen fibers to alter their tortuosity. This, predictably, would reduce total bladder capacity. Further studies are required to establish the relationship between compliance changes and the passive mechanical elements of the bladder wall that make up its structural protein matrix.

Bladder Wall Elastin and Matrix

Elastic fibers are amorphous structures composed of elastin and a microfibrillar component located mainly around the periphery of the amorphous component (Rosenbloom et al, 1995). In the mature fiber, the amorphous component makes up about 90%. The microfibrils contain a number of glycoproteins. Elastin fibers are sparse in the bladder compared with collagen but are found in all layers of the bladder wall (Murakumo et al, 1995). In spinal cord-injured rats, the elastin-to-collagen ratio increases over the first 6 weeks after injury. During this 6 weeks, the bladder compliance increases and the bladder becomes overdistended. Then the ratio is reduced as bladder compliance is decreased as a result of the emergence of DO 10 weeks after injury, suggesting a potential role for elastin in the modulation of bladder compliance (Nagatomi et al, 2005; Toosi et al, 2008).

The nonfibrillar matrix in the stroma is largely composed of a gel of proteoglycans and water. Proteoglycans are glycoproteins with glycosaminoglycans (GAGs) covalently attached. The arrangement of the proteoglycans in the matrix creates a compartment of tissue water that has a viscous behavior when it is subjected to deformation.

Smooth Muscle

Histologic examination of the bladder body reveals that myofibrils are arranged into fascicles (bundles) in random directions (Donker et al, 1982). The individual cells within a bundle are connected together to form a functional syncytium. This architecture differs from the discrete circular and longitudinal smooth muscle layers in the ureter or gastrointestinal tract.

Bladder smooth muscles have no cross striations visible under the microscope. Each detrusor smooth muscle cell contains a single nucleus. The individual smooth muscle cells in the bladder wall are small spindle-shaped cells with a central nucleus; fully relaxed, they are several hundred micrometers long with a 5- to 6- μ m maximum diameter (Smet et al, 1996). The cell membranes of smooth muscle contain caveolae—flask-shaped invaginations of the membrane—and elements of the intracellular sarcoplasmic reticulum (SR) are often associated with caveolae.

The motor innervation of the bladder smooth muscle is from the postganglionic parasympathetic nerve fibers, although intramural ganglia can exist within the bladder wall. Figure 69-6 shows the varicosities (rounded nodes) that wrap around the smooth muscle fiber. Varicosities can release a variety of neurotransmitters including acetylcholine (ACh) and adenosine triphosphate (ATP). It is unlikely that every smooth muscle cell receives direct synaptic contact; the presence of gap junctions allows excitation to propagate throughout the smooth muscle syncytium. Postjunctional receptors, such as muscarinic and purinergic receptors, are present on the smooth muscle cell. When activated by their respective agonists, these receptors initiate the excitation-contraction events (see later section) of the smooth muscle. Some investigators have found that the detrusor smooth muscle has afferent innervation that could mediate afferent signals related to smooth muscle activity (Gillespie et al, 2006).

OVERVIEW OF URETHRA

Male Urethra

The urethra begins at the bladder neck and extends to the external meatus and is composed of striated and smooth muscle. In the male, four segments are readily identified. The first is the preprostatic portion, or the bladder neck. The prostatic urethra then extends throughout the length of the gland, terminating at the prostatic apex. The membranous urethra extends from the prostatic apex through the pelvic floor musculature (including the EUS) until it becomes the bulbous and penile urethra at the base of the penis (Fig. 69-7). The male EUS covers the ventral surface of the prostate as a crescent shape proximal to the verumontanum, then assumes

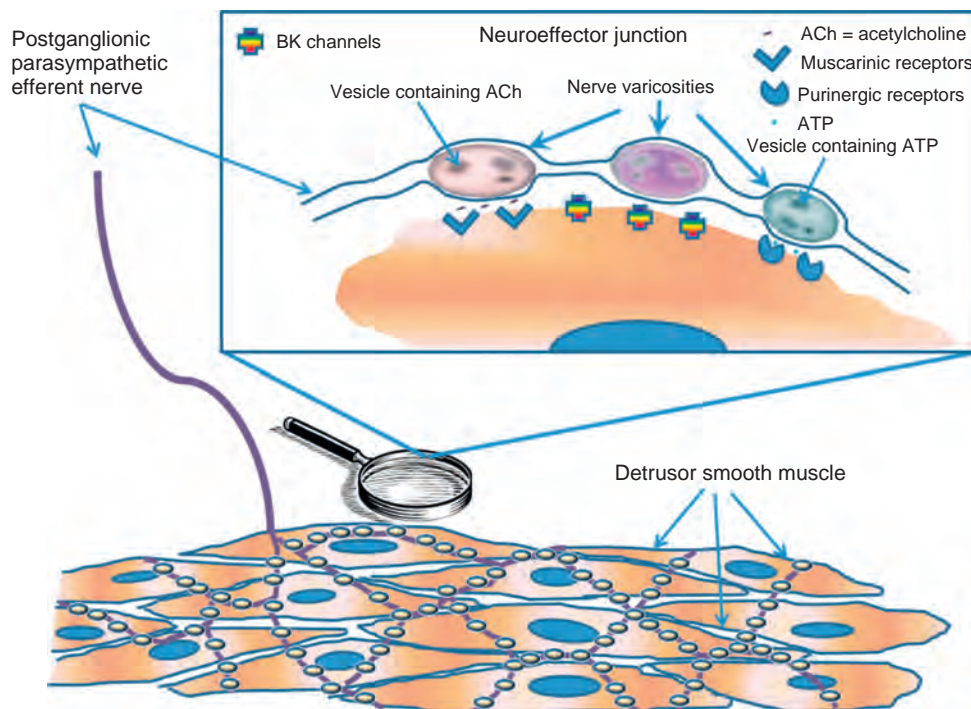


Figure 69-6. Motor nerve innervation of a detrusor muscle fascicle. See text for description.

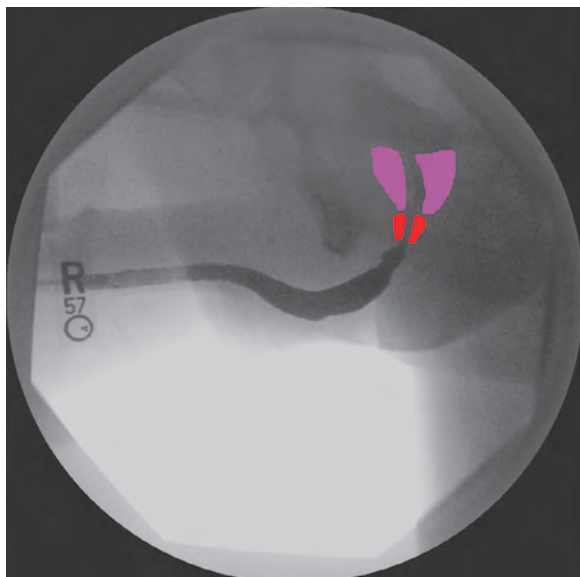


Figure 69-7. Anatomy of male urethra seen on retrograde urethrogram with patient in lateral oblique position. The red area is the external urethral sphincter, and the purple area is the prostate.

a horseshoe shape distal to the verumontanum and is crescent in shape at the bulbar urethra.

Female Urethra

In women, the urethra extends throughout the distal third of the anterior vaginal wall from the bladder neck to the meatus. Detailed anatomic descriptions of structures along the female urethra are shown in Figure 69-8. The urethra is composed of tissues that aid continence in addition to the urethral sphincter. A network of vascular subepithelial tissue in women contributes to a urethral seal effect and promotes continence. The EUS or rhabdosphincter (striated muscle) is under voluntary control and is part of the pelvic floor musculature. The female EUS covers the ventral surface of the urethra in a horseshoe configuration.

Urinary continence is maintained during elevations in intra-abdominal pressure by three processes. First, there is passive transmission of abdominal pressure to the proximal urethra. A guarding reflex involving an active contraction of striated muscle of the EUS can transiently help continence (Enhörning, 1961; Tanagho, 1982). However, mere transmission of abdominal pressure to proximal urethra does not account for the entire increase in urethral pressure (Constantinou and Govan, 1982). Urethral pressure rises before cough transmission. These findings implicate an active urethral continence (neural) mechanism in women (Constantinou and Govan, 1982). DeLancey proposed the “hammock hypothesis”—that abdominal pressure transmitted through the proximal urethra presses the anterior wall against the posterior wall. The posterior wall remains rigid if there is adequate pelvic support from muscle and connective tissues. More distally, based on morphologic data, DeLancey and colleagues (DeLancey, 1989,

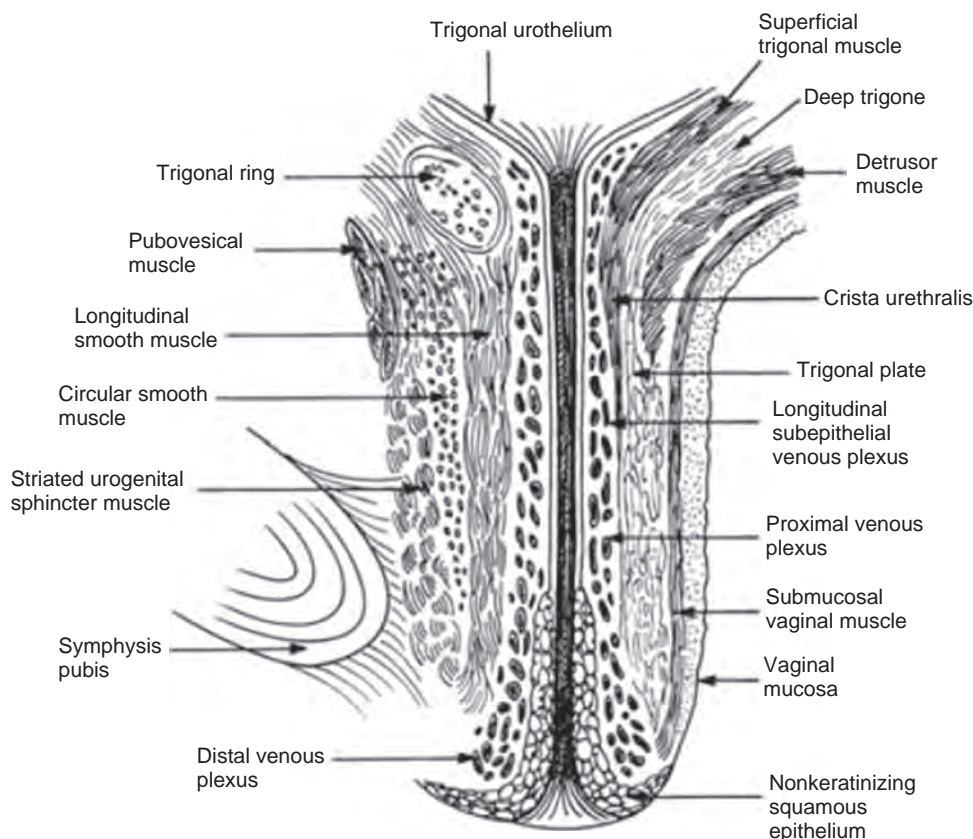


Figure 69-8. Female urethra showing importance of the multiple tissues in aid of continence including striated sphincter, smooth sphincter, and subepithelial venous plexus. (From Ashton-Miller JA, DeLancey JO. Functional anatomy of the female pelvic floor. *Ann N Y Acad Sci* 2007;1101:266–96.)

1997; Sampselle and DeLancey, 1998) postulated that the urethral attachments to the pubis (pubourethral) and vaginal connections to pelvic muscles and fascia actively change the position of the bladder neck and proximal urethra with voiding. This arrangement compresses the urethra against the pubis during bladder filling and straining. These attachments contain both fascia and smooth muscle (Oelrich, 1983; DeLancey, 1988, 1989). Thus urinary continence results from the combination of active muscle tone and passive anatomic coaptation.

Anatomy Common to Both Genders

Normal pelvic dissections of human urethral sphincters during different phases of gestational development were studied anatomically (Yucel and Baskin, 2004). The findings of this study were that development of the urethral sphincteric complex is similar in both genders. The urethral complex is derived from musculature from bladder detrusor, bladder trigone, and urethral muscles, each of different embryonic origin. These investigators found that the levator ani pelvic floor muscle does not surround the ventral aspect of the urethra in either gender, and the role of the levator ani in continence was questioned.

Urethral Tone

There is controversy about the relative roles of the urethral smooth and striated circular muscles and the lamina propria in generating the urethral pressure profile, but it seems likely that both contribute (Thind, 1995). Blocking striated sphincter activity with nicotinic neuromuscular blocking agents has variable effects and may reduce urethral tone, but rarely by more than 40%, suggesting that the smooth muscles are important. Blocking sympathetic tone with α -adrenoceptor blockers may also reduce urethral pressure by about a third (Torrens and Morrison, 1987). There is little evidence for the involvement of the cholinergic innervation in generating urethral pressure.

Despite the horseshoe configuration with the open end in the posterior direction, urethral pressure recording at the external sphincter during bladder filling increases uniformly along the entire circumference like an iris (Morita and Tsuchida, 1989). Norepinephrine or hypogastric nerve stimulation augments this pressure, suggesting a role for adrenergic receptors and sympathetic nerves in the function of the EUS (Kakizaki et al, 1991).

The urethral stroma contains primarily longitudinally arranged collagen fibers and elastin fibers (Hickey et al, 1982; Huisman, 1983). The vascular filling of the urethral lamina propria is known to be of importance for urinary continence, although the magnitude of its contribution to continence is still not understood (Rud et al, 1980). Estrogen is known to increase the urethral blood flow, resulting in increased distention of the lamina propria blood vessels (Brading, 1997a).

Impaired arterial blood supply to the urethra decreases the intraluminal pressure (Rud et al, 1980), but at present it is not known whether it is the decrease in vascular filling or the urethral hypoxia that mediates the decrease in urethral pressure. It has been suggested that both these mechanisms may be involved because it was shown that the initial drop in urethral pressure was mediated through decreased vascular filling, whereas the later phase was the result of a hypoxic effect on the urethral smooth muscle (Greenland and Brading, 1996).

Results are divergent regarding the clinical significance of connective tissue outside the urethra. Paraurethral tissue biopsy specimens from premenopausal women with stress incontinence contain 30% more collagen, and the diameter of the fibrils is 30% larger than in controls (Falconer et al, 1998a). Postmenopausal stress-incontinent women, on the other hand, have no difference in collagen concentration compared with their age-matched controls (Falconer et al, 1998b). Others, however, have found a decreased periurethral collagen concentration (Rechberger et al, 1993) and a decreased ratio of collagen I to collagen III (Keane et al, 1997) in patients with stress incontinence.

Fiber Types of Urethral Striated Muscle

Striated muscles are characterized as **slow type** and **twitch type**. Twitch-type myofibrils can be further classified as **slow** and **fast** on the basis of functional and metabolic characteristics (Padykula and Gauthier, 1967). Slow-twitch fibers seem ideally suited to maintaining sphincter tone for prolonged periods, whereas fast-twitch fibers may be needed to add to sphincter tone rapidly to maintain continence when intra-abdominal pressure is abruptly increased. Similar to smooth muscle, contraction of striated muscle fibers is governed by intracellular calcium, through interactions with troponin.

The fast-twitch fibers can be recruited rapidly but also fatigue rapidly, and perform predominantly anaerobic metabolism (Markwardt and Isenberg, 1992). Fast-twitch fibers exhibit rapid bursts of contractile force and are rich in myosin ATPase that catalyzes the actin-myosin interaction. The speed of contraction may be correlated with the histochemical reaction of this ATPase and alkaline pH. In addition, fast-twitch muscles are supplied with a fast isoform of the Ca^{2+} -ATPase, which translocates the cytosolic calcium into the abundant SR to allow rapid relaxation.

In contrast, slow-twitch fibers are found in greater percentage in muscles that require sustained tension, such as the pelvic levators and urethral sphincter. These muscle fibers are recruited and fatigue slowly and can perform high rates of oxidative metabolism because they possess less of the myosin ATPase activity and contain an increased expression of a slow isoform of the Ca^{2+} -ATPase (Markwardt and Isenberg, 1992). These fibers give rise to the background electromyographic activity seen during a urodynamic evaluation.

The rhabdosphincter (EUS) is a skeletal muscle that is present in the walls of the urethra and is separate from the periurethral skeletal muscle of the pelvic floor. The muscle cells are smaller than ordinary skeletal muscle, being 15 to 20 μm in diameter. The EUS is composed of two parts. The periurethral striated muscle of the pelvic floor contains both fast-twitch and slow-twitch fibers. The striated muscle of the distal sphincter mechanism contains predominantly slow-twitch fibers (Elbadawi, 1984) and provides more than 50% of the static resistance (Tanagho et al, 1989). Gosling and colleagues (2000) presented histochemical evidence in humans that striated muscle within the distal urethra is composed primarily of slow-twitch myofibrils in contrast to the periurethral striated muscles of the pelvic floor, which contain fast-twitch and slow-twitch fibers. In the male, the rhabdosphincter consists of 35% fast-twitch and 65% slow-twitch fibers (Padykula and Gauthier, 1970). In the female, the ratio of slow-twitch to fast-twitch fibers is 87% slow-twitch and 13% fast-twitch fibers.

The majority of the fast-twitch fibers and about a fourth of the slow-twitch fibers in the intramural striated muscle of the human membranous urethral sphincter show positive staining for nitric oxide (NO) synthase (NOS) in the sarcolemma (Ho et al, 1998). Moreover, the striated periurethral muscles of the pelvic floor are adapted for the rapid recruitment of motor units required during increases in abdominal pressure. It has been speculated that the successful treatment of stress incontinence by pelvic floor exercises or electrostimulation is caused by the conversion of fast-twitch to slow-twitch striated muscle fibers (Bazeed et al, 1982).

In addition to striated muscle, the external sphincter appears to contain smooth muscle, which receives noradrenergic innervation. Investigators have shown that stimulation of the hypogastric nerve elicits myogenic potentials in the EUS (Kakizaki et al, 1991). Whether this activity is the result of smooth or striated muscle is unclear. Because these potentials persist after α -adrenergic blockade, investigators postulate that the activity arises from striated muscle.

UROTHELIAL PHYSIOLOGY

Although the primary role of the urothelium is to form a relatively impermeable barrier to protect the underlying stroma of the bladder,

other roles of the bladder urothelium include sentinel defense against uropathogenic bacterial infections, afferent signaling, and modulation of detrusor smooth muscle contractility.

Barrier Function

Epithelial permeability, including that of the urothelium, depends on a number of factors. These are passive diffusion, osmotically driven diffusion, active transport, and inertness of the membrane to the solutes to which it is exposed.

Descriptions of finite passage of substances across the urothelium are well known. In 1856, Kaupp reported that the composition and volume of urine were altered with 12-hour voiding patterns instead of hourly voiding. These changes in volume have also been noted in rats during isovolumetric cystometrograms during 3-hour periods (Sugaya et al, 1997), and the rate of water loss has also been estimated by direct measurement of passive water diffusion in vitro in the rabbit (Negrete et al, 1996). There is a passive permeability to most substances in the blood or urine (Hicks, 1975). In studies using an in vivo rat model, the bladder urothelium was permeable to urea, sodium, potassium, and chloride (Spector et al, 2011, 2013). The authors of these studies contend that the bladder modifies the final urinary concentration of these solutes and that this modification depends on the hydration status and dietary protein (Spector et al, 2012).

The human bladder urothelium is also permeable to water, because of expression of the water transport protein aquaporin (Rubenwolf et al, 2009, 2012). Water permeability value in humans was measured at 6.5×10^{-5} cm/sec (Fellows and Marshall, 1972). This value was obtained by estimating the absorption of tritiated water into the plasma after instillation of the tritiated water into the bladder of volunteers. A direct measurement of urothelial diffusive permeability in the human has not yet been made. A measurement tool may help better phenotype LUTD that might be associated with increased urothelial permeability.

Breakdown of the apical (umbrella) cells in animal models of cystitis has shown increased water and urea permeability. Presumably, leakage of urinary solutes into the lamina propria is also responsible for the symptoms of cystitis (Lavelle et al, 1998, 2000). This increase in urothelial permeability with cystitis is increased further by distention of the bladder. The hypothesis is that with distention of the bladder, the weakened urothelium with denuded

apical umbrella cells and no real barrier in the intermediate or basal cells is further disrupted, thus allowing further egress of urine constituents into the detrusor. Similar breakdown of the apical cells is thought to occur in most forms of infectious cystitis and also in radiation cystitis.

Direct measurements of the osmotic effect on permeability have not been performed on urothelium. However, the urothelium maintains an osmotic gradient between plasma (approximately 300 mOsm/kg) and urine (100 to 1500 mOsm/kg), depending on the level of water balance and diuresis of the individual. In the normal bladder, the osmotic effects of the urine appear to go unnoticed, and the patients have few or no symptoms. However, once the bladder is inflamed, as in bladder pain syndrome and interstitial cystitis (BPS/IC), the effects of osmotic gradients become important (Gao et al, 1994).

Patients with spinal cord injury or with myelodysplasia tend to have chronic cystitis with bacteriuria and inflamed urothelium. When detrusor activity was increased in the rat by instillation of hyperosmolar compounds, this was accompanied by neurogenic inflammation, including plasma extravasation of Evans blue that could be decreased by pretreatment with the C-fiber afferent neurotoxin capsaicin (Maggi et al, 1990), indicating that hyperosmolar solutions excite afferent nerves. With increased osmolality, detrusor contractions were much stronger and accompanied by blood pressure elevations. These effects were enhanced when the bladder was pretreated with dimethyl sulfoxide to simulate cystitis conditions (Hohlbrugger and Lentsch, 1985; Hohlbrugger, 1987).

Tight junction (TJ) proteins also contribute to the impermeability of the bladder urothelium. TJ proteins include zona occludens-1 (ZO-1), occludin, claudin-4, claudin-8, and claudin-12 (Acharya et al, 2004). TJs are present between cells to prevent paracellular (between the cell) permeability (Fig. 69-9). These TJ proteins adapt to stretch of the urothelium during filling and voiding without affecting permeability (of small molecules biotin, fluorescein, and ruthenium red), although there was a 10-fold drop in transepithelial resistance (TER) during urothelial stretch (Carattino et al, 2013). This drop in TER reflected increased ionic paracellular transport via claudin permeation pathway. In addition to these physiologic functions (barrier function, host response to pathogens) of the urothelium, the roles of urothelial-afferent signaling and modulation of smooth muscle contractility are covered in later sections.

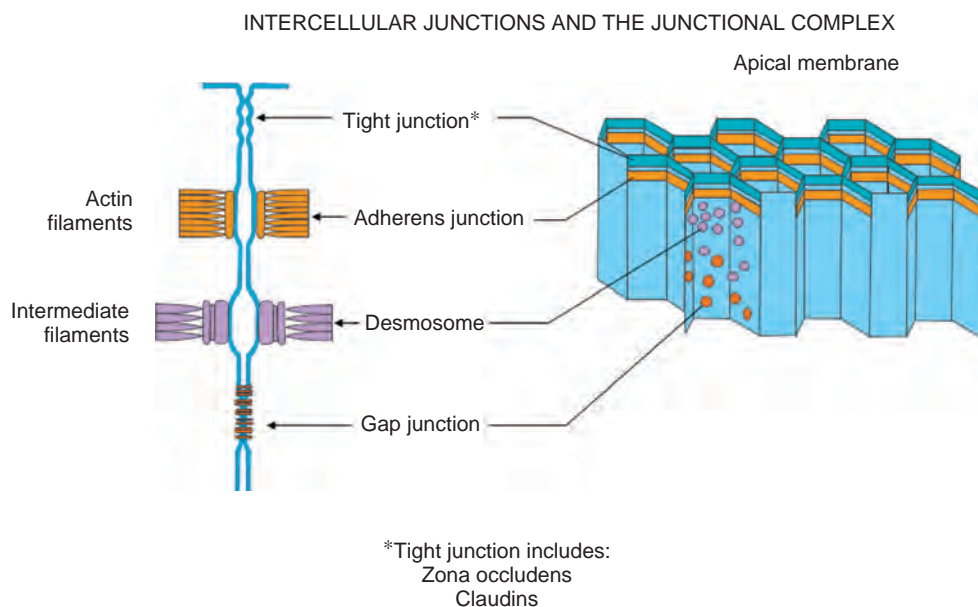


Figure 69-9. Junctional complexes between cells include tight junctions, adherens, desmosomes, and gap junctions. Gap junctions include proteins such as zona occludens and claudins.

The GAG layer, which has been described to be located on the luminal surface of the apical urothelial cell, has been a controversial subject of research into urothelial barrier function. GAG refers to a structure composed of 100% carbohydrate (polysaccharide). GAG is not produced through a template reaction as a protein is (DNA → RNA → protein), but rather through a series of enzymatic reactions within the cell. For this reason, GAG can be highly heterogeneous in molecular weight and composition. This GAG theory arose from findings of increased bacterial adherence to rabbit bladder urothelium after topical acid treatment and return to normal function with decreased adherence within 24 hours after acid injury, suggesting a “secretory” factor produced by the urothelium protecting the urothelium against bacterial adherence (Parsons et al, 1975). The secretory factor was reported to be GAG, based on the histology of rabbit bladders (Mulholland et al, 1976). However, using a different approach, it was found that the secretory factor was a glycoprotein (mucin glycoprotein MUC-1) rather than a polysaccharide (GAG) (Buckley et al, 1996; Higuchi et al, 2000). In an indirect method of examining the role of the GAG layer, Madin-Darby canine kidney (MDCK) cells were transfected with MUC-1. After this treatment, no difference in the transcellular water and urea permeability was found (Lavelle et al, 1997). Immunofluorescence study of human urothelium showed that chondroitin sulfate was the main GAG component, although the role of GAG in creating impermeability was studied in monolayer of cultured pig urothelial cells (Janssen et al, 2013). In summary, the GAG layer may have importance in bacterial antiadherence and in prevention of urothelial damage by large macromolecules. However, there is no definite evidence that the GAG layer acts as the primary epithelial barrier between urine and plasma in the human urothelium.

Ionic Transport

The apical membrane of the urothelium has a high electrical resistance (Lavelle et al, 1998, 2000), whereas the basolateral membrane resistance is approximately 10-fold lower (Clausen et al, 1979). Active sodium transport across the urothelium has been demonstrated (Wickham, 1964; Lewis and Diamond, 1976). Na⁺ channels that exist on the apical surface of the umbrella cells and in the cytoplasmic vesicles below the apical surface are primarily amiloride sensitive (inhibition) and aldosterone responsive. However, amiloride-insensitive, cation-selective, as well as amiloride-insensitive, unstable cation channels have also been identified. Both of these channels were found to be degradation products of the amiloride-sensitive Na⁺ channel. The amiloride-sensitive Na⁺ channel is hydrolyzed by serine proteases such as kallikrein and urokinase and plasmin (normally found in the urine but produced by the kidney) (Lewis et al, 1995). Studies of rat bladders have shown that urea, sodium, potassium, and chloride can all cross the bladder urothelium and be taken up by suburothelial blood vessels (Spector et al, 2011, 2012, 2013).

Sodium that is transported into the cell is removed at the basolateral membrane by an Na⁺-K⁺ exchanger. This leaves the cell with a negative intracellular charge. The basolateral membrane contains K⁺ and Cl⁻ channels, Na⁺-H⁺ exchangers, and Cl⁻-HCO₃⁻ exchangers. These channels and exchangers are important in recovery of cell volume during an increase in serosal osmolality (Donaldson and Lewis, 1990). Unfortunately, the precise role of the Na⁺ channel in the apical membrane of the umbrella cell is unknown. It is possible that the degradation of the channel might follow the filling of the bladder and that the changes in conductance of sodium may be a signaling factor for the bladder and micturition when it reaches capacity. Alternatively, it may be involved in the signaling pathway that allows insertion or removal of apical membrane on expansion of the bladder.

Sensor-Transducer Function of the Urothelium

Whereas the urothelium has historically been viewed primarily as a barrier, there is increasing evidence that urothelial cells display a number of properties similar to sensory neurons (nociceptors

and mechanoreceptors) and that both types of cells use diverse signal-transduction mechanisms to detect physiologic stimuli. Examples of “sensor molecules” (i.e., receptors and ion channels) associated with neurons that have been identified in urothelium include receptors for bradykinin (Chopra et al, 2005), neurotrophins (TrkA and p75) (Murray et al, 2004), purines (P2X and P2Y) (Lee et al, 2000; Hu et al, 2002; Birder et al, 2004; Sun and Chai, 2004; Tempest et al, 2004; Chopra et al, 2008), norepinephrine (α and β) (Birder et al, 1998, 2002), ACh (nicotinic and muscarinic) (Chess-Williams, 2002; Beckel et al, 2006; Kullmann et al, 2008b), protease-activated receptors, amiloride-mechanosensitive Na⁺ channels such as ENaC (Smith et al, 1998; Wang et al, 2003; Araki et al, 2004), and a number of TRP channels (TRPV1, TRPV2, TRPV4, TRPM8) (Birder and de Groat, 1998; Birder et al, 2001, 2002; Stein et al, 2004; Birder et al, 2007a; Gevaert et al, 2007).

When urothelial cells are activated through these receptors and ion channels in response to mechanical as well as chemical stimuli, they can, in turn, release chemical mediators such as NO, ATP, ACh, and substance P (SP) (Ferguson et al, 1997; Birder et al, 1998; Burnstock, 2001a; Birder et al, 2003; Chess-Williams, 2004). These agents are known to have excitatory and inhibitory actions on afferent nerves that are close to or in the urothelium (Bean et al, 1990; Dmitrieva et al, 1998; Birder et al, 2001; Yoshimura et al, 2008). A video of urothelial cells responding to increasing doses of extracellular carbachol, a nonselective muscarinic agonist, with increasing concentrations of intracellular Ca²⁺ (fura-2 ratio), is shown in the microfluorometry video on the Expert Consult website.

Chemicals released from urothelial cells may act directly on afferent nerves or indirectly through an action on suburothelial interstitial cells (also referred to as myofibroblasts) that lie in close proximity to afferent nerves. Myofibroblasts are extensively linked by gap junctions and can respond to chemicals that in turn modulate afferent nerves (Fowler et al, 2008). Thus it is believed that urothelial cells and myofibroblasts can participate in sensory mechanisms in the urinary tract by chemical coupling to the adjacent sensory nerves.

NO can be released by the urothelium, particularly during inflammation (Birder et al, 1998). The release of NO may be evoked by the calcium ionophore A-23187, norepinephrine, and capsaicin. SP also acts on receptors on urothelial cells to release NO. The adrenergic release of NO from bladder strips was reduced by 85% after removal of the urothelium. Denervation of the bladder did not completely block the release of capsaicin-induced NO production, suggesting other sites of production. This is consistent with the observations that capsaicin released NO from cultured rat, cat, rabbit, and human urothelial cells and that the TRPV1 capsaicin receptor is expressed in cultured urothelial cells. NOS expression in afferent neurons is also increased in chronic bladder inflammation. Given that NO does not have much effect on the detrusor muscle but does inhibit Ca²⁺ channels in rat bladder afferent neurons (Yoshimura et al, 2001), the role of NO in the urothelium has still to be clarified. However, NO released locally in the bladder appears to have an inhibitory effect on afferent activity in the bladder because suppression of endogenous NO by intravesical oxyhemoglobin, an NO scavenger, or L-NAME, a NOS inhibitor, enhances bladder activity in rats (Pandita et al, 2000; Masuda et al, 2007).

ATP released from urothelial cells during stretch can activate a population of suburothelial bladder afferents expressing P2X₃ receptors, signaling changes in bladder fullness and pain (Ferguson et al, 1997; Burnstock, 2001a). Accordingly, P2X₃ null mice exhibit a urinary bladder hyporeflexia, suggesting that this receptor, as well as neural-epithelial interactions, are essential for normal bladder function (Cockayne et al, 2000). This type of regulation may be similar to epithelium-dependent secretion of mediators in airway epithelial cells, which are thought to modulate submucosal nerves and bronchial smooth muscle tone and may play an important role in inflammation (Homolya et al, 2000; Jallat-Daloz et al, 2001). Thus it is possible that activation of bladder nerves and urothelial cells can modulate bladder function directly or indirectly

by the release of chemical factors in the urothelial layer. ATP released from the urothelium or surrounding tissues may also play a role in the regulation of membrane trafficking. This is supported by studies in the urinary bladder in which urothelium-derived ATP release purportedly acts as a trigger for exocytosis, in part by autocrine activation of urothelial purinergic (P2X, P2Y) receptors (Wang et al, 2005). These findings suggest a mechanism whereby urothelial cells sense or respond to ATP and thereby translate extracellular stimuli into functional processes.

A study showed that human bladder urothelial tissue behaved similarly to guinea pig bladder urothelium. Both urothelia released ATP in response to both muscarinic and purinergic stimulation (Sui et al, 2014). The released ATP induced contraction of the urothelial mucosal tissue. Aging was associated with increased ATP release. These findings continue to support the hypothesis that the urothelium is capable of sensing and transducing signals and likely modulates overall bladder function.

Prostaglandins are also released from the urothelium. These are assigned two possible functions: regulation of detrusor muscle activity and cytoprotection of the urothelium, based on effective treatment of hemorrhagic cystitis by prostaglandins (Jeremy et al, 1987). The predominant forms found in human urothelium from biopsy specimens are 6-oxo-prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) more than PGE_2 more than $PGF_{2\alpha}$ more than thromboxane B_2 , PGL_2 (prostacyclin) is also produced. These findings were confirmed and further developed in the guinea pig, in which it was found that the major production of prostaglandins occurred in the urothelium. The production of prostaglandins also increased greatly with inflammation (Saban et al, 1994). Prostaglandin synthesis also occurs in the ureter, where it is speculated to be important in the regulation of ureteral peristalsis and also in reducing the development of blood clots in the lumen of the ureter (Ali et al, 1998).

Evidence also suggests that the involvement of the muscarinic receptor in bladder function extends beyond detrusor contractility and into afferent sensory functioning. Muscarinic receptors are found on the urothelium at high density (Hawthorn et al, 2000), and there is a basal release of ACh from the urothelium that is increased by stretch and aging (Yoshida et al, 2006). Thus activation of the muscarinic receptors in the urothelium releases substances that modulate afferent nerves and smooth muscle activity (Hawthorn et al, 2000; de Groat, 2004; Kullmann et al, 2008a).

The urothelium also releases substances called **urothelium-derived inhibitory factors**, which decrease the force of detrusor muscle contraction in response to muscarinic stimulation (Hawthorn et al, 2000; Kumar et al, 2005). The molecular identity of this factor is not known; however, pharmacologic studies suggest that it is not NO, a prostaglandin, prostacyclin, adenosine, catecholamine, γ -aminobutyric acid (GABA), or a factor that acts through apamine-sensitive, small-conductance K^+ channels. It has been shown that an inhibitory response through this factor is attenuated in a fetal model of bladder outlet obstruction (BOO) (Thiruchelvam et al, 2003). Further studies are required to clarify the identity of this substance and its role in bladder function.

Suburothelial Interstitial Cells

In the human bladder, subepithelial interstitial cells, which are also called **myofibroblasts**, are located just below the basal layer of the urothelium. These myofibroblasts stain for vimentin and α -smooth muscle actin but not for desmin (Fry et al, 2004). These cells are linked by gap junctions consisting of connexin 43 (Cx43) proteins and make close appositions with C-fiber nerve endings in the submucosal layer of the bladder, suggesting that there is a network of functionally connected interstitial cells immediately below the urothelium that may be modulated by other nerve fibers (Fry et al, 2004) (Fig. 69-10). ATP can induce inward currents associated with elevated intracellular Ca^{2+} in isolated suburothelial interstitial cells (Fry et al, 2007).

Immunohistochemical studies show the expression of P2Y receptors, most notably P2Y₆ receptors, and M₃ muscarinic receptors

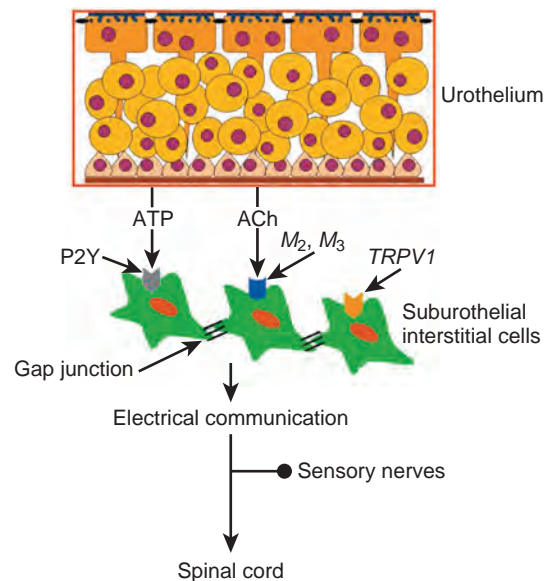


Figure 69-10. Schematic representation of suburothelial interstitial cells, which are also called **myofibroblasts**. Substances released from the basolateral surface during stretch, such as adenosine triphosphate (ATP) and acetylcholine (ACh), activate afferents in the suburothelial layer through the intermediation of suburothelially located interstitial cells, which express purinergic P2Y receptors, muscarinic M₂ and M₃ receptors, or capsaicin TRPV1 receptors, and are connected to one another by gap-junction proteins.

in suburothelial interstitial cells from guinea pigs (Fry et al, 2007; Grol et al, 2009). In the human bladder, increased expression of muscarinic M₂ and M₃ receptors in vimentin-stained suburothelial interstitial cells is found and correlates with the urgency score in humans with idiopathic detrusor overactivity (IDO) (Mukerji et al, 2006). Because ATP or ACh is known to be released from the urothelium during bladder stretch, suburothelial interstitial cells are in an ideal position between the urothelium and nerve endings to modify a sensory feedback mechanism. Application of an NO donor sodium nitroprusside (SNP) also attenuates an increase in intracellular Ca^{2+} and current responses to ATP in guinea pig interstitial cells, suggesting the cyclic guanosine monophosphate (cGMP)-dependent inhibition of cell activity (Sui et al, 2008).

KEY POINTS: UROTHELIUM

- Uroplakin proteins and TJ proteins play key parts in urothelial barrier function.
- Uroplakins have also been shown to act as the primary attachment site of type 1 piliated uropathogenic *E. coli*.
- The GAG layer may have importance in bacterial antiadherence, but there is no definite evidence that the GAG layer serves impermeability function.
- Urothelial cells can release and respond to neurotransmitters.
- Myofibroblasts mediate interaction between urothelial cells and afferent nerves.

SMOOTH MUSCLE PHYSIOLOGY

Studies on bladder smooth muscle physiology have been a mainstay for understanding micturition function, because the detrusor smooth muscle needs to contract for the bladder to empty efficiently and normally. Understanding the factors that regulate smooth muscle quiescence could be applicable to clinical conditions characterized by DO such as OAB, neurogenic bladder, and

TABLE 69-1 Comparison of the Properties of Skeletal and Smooth Muscle

PROPERTY	SKELETAL MUSCLE	SMOOTH MUSCLE
Cell characteristics	Long cylindric cells with many nuclei	Spindle-shaped cells with a single nucleus
Maximum cell size (length × diameter)	30 cm × 100 μm	200 μm × 5 μm
Visible striations	Yes	No
Ultrastructure	Sarcomere pattern No immediate filaments	No sarcomere pattern Intermediate filaments Dense bodies
Motor innervation	Somatic	Autonomic
Type of contracture	Phasic	Mostly tonic, some phasic
Contractile activity	Disinhibition of tropomyosin Sliding filaments Rapid contraction	Active myosin phosphorylation ? Sliding filaments Formation of “latch state”
Calcium regulation	Rapid Ca ²⁺ influx via T tubule	Voltage- and receptor-operated Ca ²⁺ channels Release from internal stores
Basic muscle tone	Neural activity	Intrinsic, extrinsic factors
Force of contraction regulated by hormone	No	Yes

underactive detrusor. Function of the smooth muscle, like striated muscle, is regulated by motor nerves (though autonomic rather than somatic), but unlike striated muscle, smooth muscle function can be also be modulated by circulating hormones, local paracrine factors such as NO, and factors released by the urothelium. Although the coordinated and efficient contractions of the detrusor smooth muscle require neural control, detrusor muscle can generate spontaneous and rhythmic activity without neural input. The differences between smooth muscle versus striated muscle properties are shown in Table 69-1 (Chacko et al, 1999). The next several sections will cover physiologic aspects of detrusor smooth muscle function starting at the individual smooth muscle cell and moving to the whole organ level.

Contractile Proteins

Bladder (detrusor) smooth muscle cells contract by the interaction of thick and thin filaments within the intracellular cytoskeletal network. Thick filaments (15-nm diameter) are composed of myosin. Thin filaments (6- to 8-nm diameter) are composed mainly of actin. Bound to actin are tropomyosin (TM) and caldesmon (CaD), both of which are important in regulation of contraction. Intermediate filaments (10 nm in diameter) are composed of desmin and vimentin. Whereas contraction of smooth muscle cells is caused by the cross-bridge cycling between the thick and thin filaments, intermediate filaments can modulate the contractile response (see review by Tang, 2008). The thin and thick filaments of smooth muscle fibers are arranged as myofibrils that cross the fibers obliquely in a lattice-like arrangement, rather than the organized linear fashion of the sarcomere in striated muscle fibers. The thin and intermediate filaments attach to multiple sites within the cytoplasm (sarcolemma) at locations called *dense bodies* (Fig. 69-11). The filaments of contractile proteins are also attached to the plasma membrane at junctional complexes between neighboring cells, which allow smooth muscle cells to contract as a syncytium.

Thick filaments are made up of myosin II—two intertwined myosin heavy chains (MHCs) (Fig. 69-12) (as opposed to myosin I, which contains only one MHC). There are two areas of myosin II: the rod portion, which contains the coil region, and the head region, which contains globular domains of the two MHCs, with an intervening hinge region between the coil and head. Alternative splicing of MHCs pre-mRNA at the 5'-end produces SM-A and SM-B isoforms of MHC, whereas alternative splicing at the 3'-end produces SM-1 and SM-2 isoforms of MHC. The bladder smooth

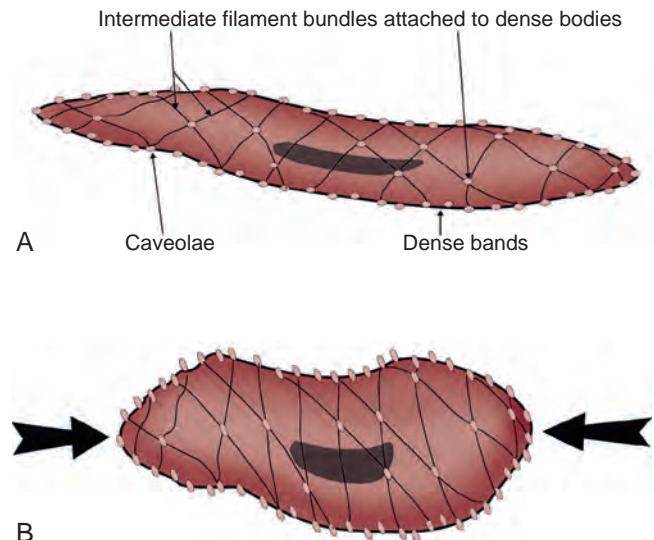


Figure 69-11. The organization of the contractile elements of smooth muscle fibers by a simple model of the contraction of smooth muscle. **A**, Relaxed smooth muscle cell. **B**, Contracted smooth muscle cell. Intermediate filaments, dense bodies, and dense bands of smooth muscle fibers harness the pull generated during myosin cross-bridge activity. Intermediate and thin filaments attach to dense bodies scattered throughout the sarcoplasm and occasionally anchor to the dense bands situated between caveolae (invaginations of the sarcolemma). As the obliquely running contractile elements contract, the muscle shortens.

muscle contains almost 100% SM-B. SM-B has a higher ATPase activity than SM-A; therefore SM-B can move actin filaments faster in an in vitro assay (Rovner et al, 1997).

Contained within each globular region of the MHC are two myosin light chains (MLCs), MLC20 (20 kDa) and MLC17 (17 kDa). These two MLC isoforms are encoded by different genes, but only one relates to contractility. Two MLC17 variants occur as a result of alternative splicing of a single MLC17 gene. Cross-bridge cycling depends on the phosphorylation of MLC20, which increases the activity of an enzyme, myosin ATPase.

Although studies of interactions between actin and myosin in cross-bridge cycling have been canonical in understanding smooth muscle contractility, the unique role of actin has been only recently recognized and reviewed (Gunst and Zhang, 2008). The structure and organization of filamentous actin was thought to remain relatively constant during a contractile event. Furthermore, it was assumed that actin filaments anchored at adhesion sites at the plasma membrane and at dense bodies within the cytosol (see Fig. 69-11), which provides a fixed and stable network on which the myosin or thick filaments move during shortening and tension development. However, intracellular actin polymerization is now

recognized as a seminal event in smooth muscle contraction. This actin polymerization further serves to catalyze recruitment of structural proteins that connect actin filaments and transmembrane integrin proteins to adhesion junctions (Fig. 69-13).

The interaction between actin and myosin in smooth muscle contractions is modulated by the actin-binding (actin-associated) proteins caldesmon (CaD) and tropomyosin (TM) (Fig. 69-14). These two proteins control access points on the actin filament to allow myosin II heads to form cross-bridges. Figure 69-14 shows that CaD interacts with all of the contractile proteins and also calmodulin (CaM). CaD was first isolated from chicken gizzard smooth muscle in 1981 (Sobue et al, 1981). There are two isoforms of CaD: heavy CaD (h-CaD), which is associated with all smooth muscle, and light CaD (l-CaD), which is found in non-smooth muscle cells. CaD is an inhibitor of actinomyosin ATPase and motility, and both actin binding and CaD inhibition are greatly enhanced in the presence of TM. Detailed descriptions of CaD functions have been reviewed (Wang, 2008). CaD is modulated by another protein, CaM. Although CaM is technically not a contractile protein, CaM is the protein that interacts with intracellular Ca^{2+} to initiate the contraction.

Actinomyosin Cross-Bridge Cycling

The key step in smooth muscle cellular contraction is cross-bridge formation of myosin II heads to actin, which is dependent on rise of intracellular Ca^{2+} . When an action potential (AP) occurs in the smooth muscle cell, there is a rise in intracellular Ca^{2+} , which then binds to CaM, thereby activating myosin light chain kinase (MLCK) (Hai and Murphy, 1989; Gunst et al, 1993;

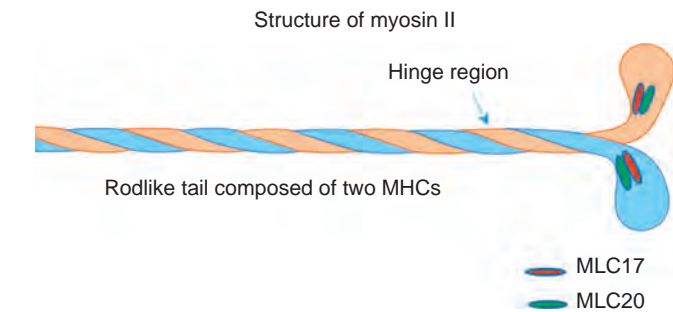


Figure 69-12. Structure of myosin II, composed of two intertwined myosin heavy chains (MHCs). MLC17 and MLC20 are two myosin light chains located on heads of myosin II.

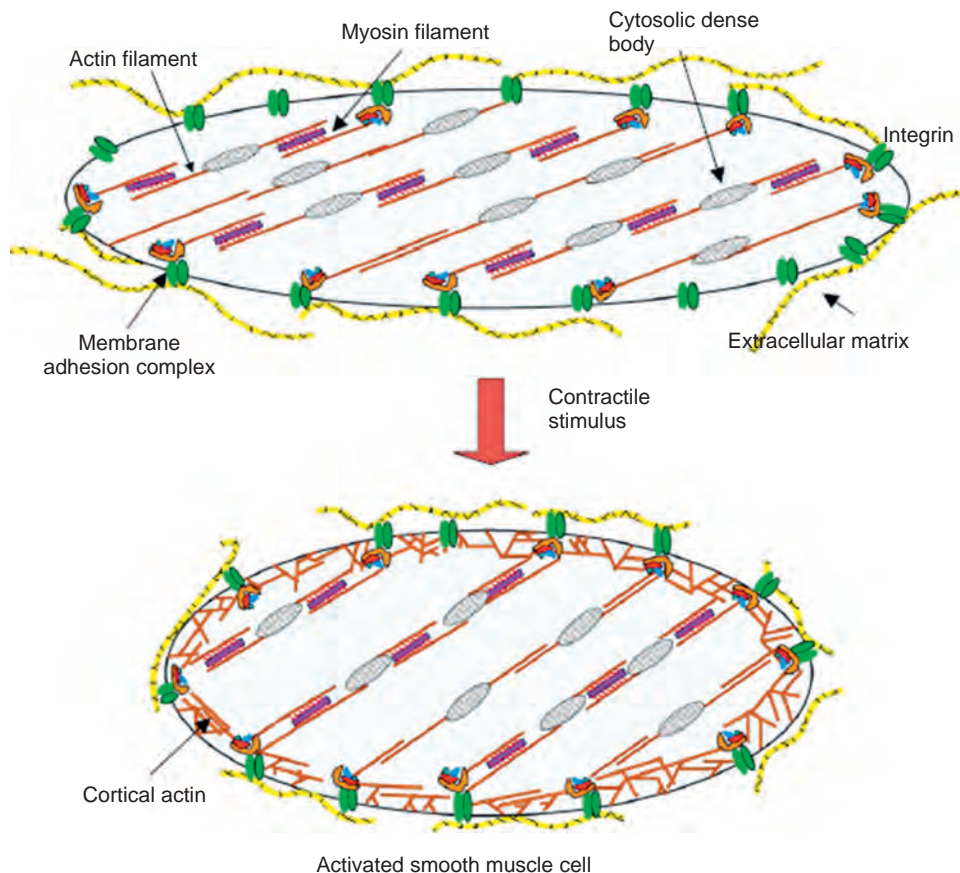


Figure 69-13. Figure shows a single myocyte going from relaxation to contraction. The importance of actin polymerization at the periphery of the cell is that this network strengthens the membrane for force transmission from the actinomyosin cross-bridges. The regulation of actin polymerization is distinct and separate from actinomyosin cross-bridge cycling. (From Gunst SJ, Zhang W. Actin cytoskeletal dynamics in smooth muscle: a new paradigm for the regulation of smooth muscle contraction. *Am J Physiol Cell Physiol* 2008;295:C576–87.)

Andersson and Arner, 2004). MLCK phosphorylates MLC20, which is in the head region of myosin II, cleaving a phosphate moiety in ATP, thus converting ATP to adenosine diphosphate (ADP) in the process. Phosphorylated MLC20 forms cross-bridges with (i.e., binds to) actin, leading to force generation (White et al, 1993; Chacko et al, 1994; Andersson and Arner, 2004). Dephosphorylation of MLC20 is catalyzed by myosin light chain phosphatase (MLCP), leading to detachment of the myosin II heads from actin and relaxation. An animation of these interactions is shown on the Expert Consult website. Key points in the smooth muscle contraction sequence are also presented in Box 69-1.

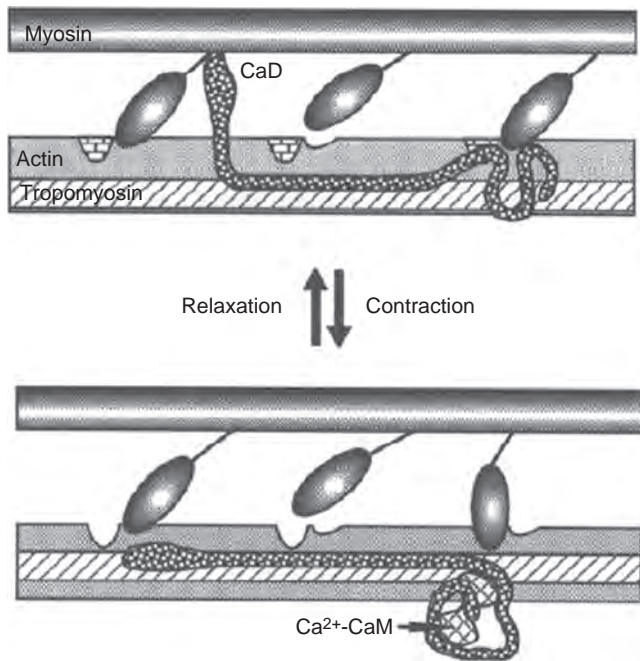


Figure 69-14. Caldesmon (CaD) and tropomyosin are actin-bound proteins that regulate actinomyosin cross-bridging. CaD and tropomyosin move along the actin filament to expose actin binding sites for the head region of myosin II to generate contraction. (From Shirinsky VP, Vorotnikov AV, Gusev NB. Caldesmon phosphorylation and smooth muscle contraction. In: Kohama K, Sasaki Y, editors. Molecular mechanisms of smooth muscle contraction. Austin [TX]: R.G. Landes Company; 1999.)

The determination of smooth muscle tone is therefore dependent on the balance of intracellular Ca^{2+} and the balance between MLCK and MLCP activities. Although Ca^{2+} is needed for MLCK activity, regulation of MLCP activity plays an important role in smooth muscle contractility. **Inhibition of MLCP activity promotes contractility and tone in the smooth muscle cell in the absence of increases in intracellular Ca^{2+} changes (calcium sensitization).** It has been shown that MLCP activity is under control of a series of complex molecular events related to two proteins, RhoA and Rho kinase (ROK).

RhoA is part of a family of proteins known as *small GTPases*. The activity of RhoA (active vs. inactive forms) is based on the form of guanine phosphate bound to RhoA. Inactive RhoA is bound to guanosine diphosphate (GDP) (Rho-GDP), and active RhoA is bound to guanosine triphosphate (GTP) (Rho-GTP). Three classes of regulatory proteins control the cycling between active RhoA and inactive RhoA forms: (1) guanine nucleotide exchange factors (GEFs), which convert RhoA-GDP to Rho-GTP; (2) GTPase-activating proteins (GAPs), which convert Rho-GTP to Rho-GDP; and (3) guanine nucleotide dissociation inhibitors (GDIs), which bind to RhoA-GDP and prevent action of GEFs and prevent RhoA-GDP from translocating from cytosol to cellular membrane, which inhibits the activity of RhoA (Puetz et al, 2009).

Activated RhoA, RhoA-GTP, binds to ROK at the cellular membrane to activate ROK. Activated ROK phosphorylates MLCP, inactivating MLCP, thus tipping the balance toward contraction of the smooth muscle cell. Another mechanism in which activated ROK can inactivate MLCP is via phosphorylation of another protein, CPI-17 (Eto et al, 1997). Phosphorylated CPI-17 then can directly phosphorylate MLCP, thus inactivating MLCP. Thus RhoA and ROK promote smooth bladder contractility by inactivation of MLCP (Fig. 69-15).

BOX 69-1 Detrusor Smooth Muscle Contraction Sequence

- Ca^{2+} binds to calmodulin (CaM), activating it.
- CaM activates the kinase enzyme (myosin light-chain kinase).
- The kinase enzyme catalyzes phosphate transfer from adenosine triphosphate to myosin, allowing myosin to interact with actin of the thin filaments.
- Smooth muscle relaxes with intracellular decrease in Ca^{2+} levels.

RhoA/RhoA kinase (ROK) inactivation of MLCP by phosphorylation

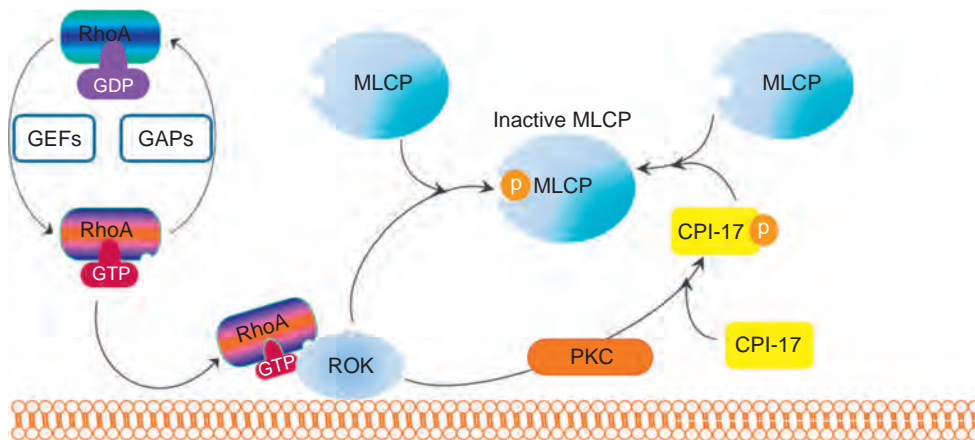


Figure 69-15. Pathways for RhoA and Rho kinase (ROK) interaction with myosin light chain phosphatase (MLCP) in regulating smooth muscle contractility. See text for details. GAPs, GTPase-activating proteins; GDP, guanosine diphosphate; GEFs, guanine nucleotide exchange factors; GTP, guanosine triphosphate; MLCP, myosin light chain phosphatase; PKC, protein kinase C.

Membrane Electrical Properties and Action Potentials

Smooth muscle cellular membrane potential is critical in regulating contraction because smooth muscle cells are excitable (can generate APs) and contractility is dependent on the membrane potential. One must keep in mind that studies of membrane properties of single smooth muscle cells do not take into account that the detrusor functions as a syncytium of cells involving gap junctions that allow electrical coupling among the cells. Furthermore, it is likely that in certain species, detrusor muscle interstitial cells, with their own intrinsic pacemaker activities, modulate smooth muscle cell excitability. Therefore, although single cell smooth muscle studies allow the ability to perform patch-clamp electrophysiologic experiments to study membrane properties, these findings are not necessarily reflective of the behavior of the syncytium of smooth muscle cells.

The membrane potential of a cell, in millivolts (mV), is created primarily by concentration differences between intracellular and extracellular spaces of the ions Na^+ , K^+ , and Cl^- . The approximate concentrations of these ions are as follows:

ION CONCENTRATION (mEq/l)	Na^+	K^+	Cl^-
Intracellular	5-15 (low)	130-140 (high)	4-30 (low)
Extracellular	130-140 (high)	3-5 (low)	105-115 (high)

The equation for calculating membrane potential is determined by the Goldman-Hodgkin-Katz voltage equation, as follows:

$$E_m = \frac{RT}{F} \ln \left(\frac{P_{\text{Na}}[\text{Na}]_o + P_{\text{K}}[\text{K}]_o + P_{\text{Cl}}[\text{Cl}]_i}{P_{\text{Na}}[\text{Na}]_i + P_{\text{K}}[\text{K}]_i + P_{\text{Cl}}[\text{Cl}]_o} \right)$$

where

E_m = membrane potential

R = universal gas constant

T = absolute temperature

F = Faraday constant

P_{Na} , P_{K} , or P_{Cl} = permeability to that ion in arbitrary units

$[\dots]_o$ = concentration of that ion, outside (extracellular)

$[\dots]_i$ = concentration of that ion, inside (intracellular).

At rest, most cells are permeable to K^+ but impermeable to Na^+ and Cl^- (P_{Na} and $P_{\text{Cl}} = 0$); thus the aforementioned equation for resting membrane potential essentially becomes the reversal potential for K^+ , which is -62 mV. However, if the membrane becomes permeable Na^+ and Cl^- , the membrane potential will reflect the contribution of the electrochemical gradient of all these ions. The reversal potentials for Na^+ and Cl^- are approximately $+65$ mV and -85 mV, respectively. The resting membrane potential of human detrusor muscle cells varies and has been measured at -50 to -60 mV (Montgomery and Fry, 1992; Fry et al, 2002), although more recent measurements in cultured human detrusor smooth muscle cells were more depolarized at -28 mV (Hristov et al, 2011).

Guinea pig smooth muscle cell APs were studied in detail by Klöckner (Klöckner and Isenberg, 1985). Pulse current (current passed from inside the cell to outside) via a patch electrode induced an AP, and continuous current resulted in a train of repetitive APs. The morphology of the AP tracings was typical of that of excitable cells, with four phases: phase 0, slow depolarization; phase 1, fast upstroke; phase 2, repolarization; and phase 3, hyperpolarization (Fig. 69-16). With use of voltage clamping techniques and pharmacologic channel blockers or changes in ion concentrations in extracellular buffer, the types of ionic currents that make up the phases of smooth muscle AP tracing were determined (see Fig. 69-16). Phase 1 fast upstroke of the AP is composed of a Ca^{2+} inward current (abbreviated I_{Ca}). Phases 2 repolarization and 3 hyperpolarization of AP are the result of a K^+ outward current (abbreviated I_{K}). These ionic currents are mediated by various ion channels.

The I_{K} that occurs during phases 2 and 3 of the AP is the result of K^+ flowing out of the cell through different K^+ channels including small and large conductance calcium-activated K^+ channels (SK and BK, respectively) and voltage-gated K^+ channels (Kv) (Heppner et al, 1997; Hristov et al, 2011). Blockage or inhibition of any of these K^+ channels would promote myocyte contractility and increase

BLADDER SMOOTH MUSCLE CELL ACTION POTENTIAL AND SIMULTANEOUS CURRENT TRACING

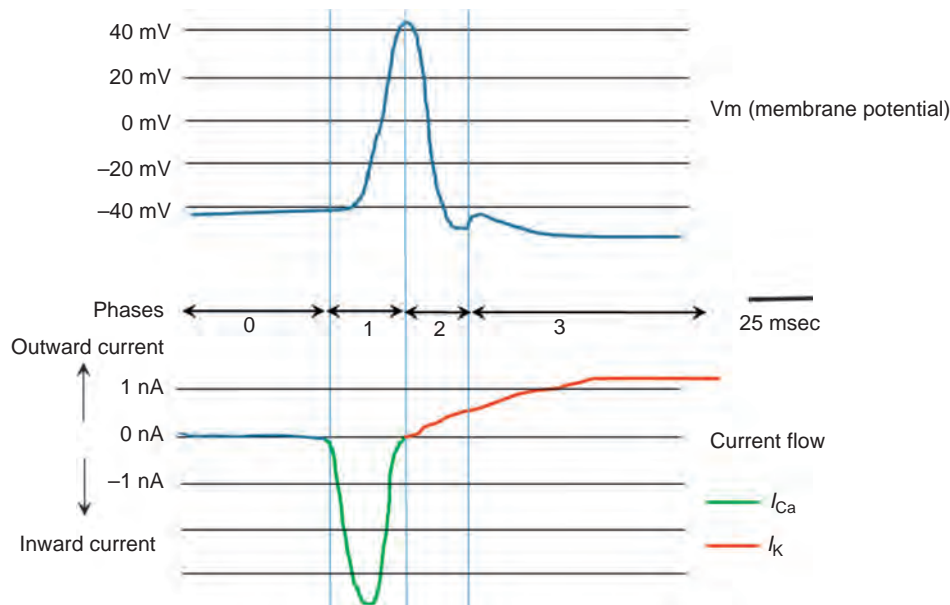


Figure 69-16. The membrane potential (*upper panel*) and the current flow (*lower panel*) in a detrusor myocyte action potential (AP). There are four phases of the action potential, and each phase is mediated by a different ionic current. Phase 0 is slow depolarization. Phase 1 is the fast upstroke of the AP mediated by Ca^{2+} inward current (I_{Ca}). Phases 2 and 3 are hyperpolarization of the AP mediated by K^+ outward current (I_{K}).

the propensity for spontaneous myocyte activity. Of these different types of K^+ channels, BK is the most critical. BK regulates myocyte contractility by regulating the membrane potential, which in turn determines activity of the L-type voltage-dependent calcium channel (VDCC), which in turn determines $(Ca^{2+})_i$ and therefore the contractility of the myocyte.

Excitation-Contraction Coupling

When ACh, released by postganglionic parasympathetic nerve terminals, activates smooth muscle muscarinic M_3 receptors, smooth muscle intracellular Ca^{2+} concentration increases through two mechanisms: extracellular entry through VDCC L-type Ca^{2+} channels (Andersson and Arner, 2004; Andersson and Wein, 2004; Schneider et al, 2004a, 2004b; Nausch et al, 2010) and release of intracellular Ca^{2+} stores via G-protein activation with resultant inositol triphosphate (IP_3) production (Iacovou et al, 1990; Eglen et al, 1994; Harriss et al, 1995; Hashitani et al, 2000; Fry et al, 2002; Braverman et al, 2006a). Because the M_3 receptor is a canonical G_q -coupled protein (seven transmembrane domains), the downstream mechanisms after M_3 activation resulting in release of intracellular Ca^{2+} are reviewed in detail (Fig. 69-17). Other canonical receptors that share the same G_q -activated downstream mechanisms include all the odd muscarinic receptor subtypes (M_1 , M_3 , M_5), α_1 -adrenoreceptors, angiotensin II receptors, histamine H_1 receptors, and 5-HT₂ serotonin receptors, although this is not the complete list (the 2012 Nobel Prize in Chemistry was awarded to Drs. Brian Kobilka and Robert Lefkowitz for their work in unraveling how G-coupled receptors work). Once the M_3 receptor is activated by ACh, it activates the α subunit of the G_q protein. The activated G protein then activates the membrane-bound enzyme, phospholipase C (PLC). Activated PLC cleaves a membrane phospholipid, PIP_2 (phosphatidylinositol 4,5-bisphosphate), to form

cytosolic IP_3 (inositol triphosphate). IP_3 binds to its receptor at the SR, which causes stored Ca^{2+} to be released. The other product of PIP_2 cleavage is diacylglycerol (DAG), which remains membrane bound. DAG binds to protein kinase C (PKC), which is bound to the membrane, thereby activating PKC. PKC is a protein kinase that goes on to phosphorylate myriad proteins to induce secondary signals. Figure 69-17 shows a diagram of the two categories of secondary messenger pathway that all G-coupled receptors follow: One pathway is the IP_3 /PKC pathway, and the other is the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) pathway. The M_2 receptor subtype is coupled to $G_{i/o}$ and results in increased cAMP and activation of PKA. It has been shown in transgenic animals, where selective deletion of either M_2 or M_3 receptors is created, that M_3 is the subtype that mediates the bladder contractions in the mouse and humans (Matsui et al, 2000; Fetscher et al, 2002; Stengel et al, 2002).

The dogma that the release of intracellular stores of Ca^{2+} is the main driver for nerve-induced smooth muscle contraction has been challenged. Investigators have shown in mouse detrusor smooth muscle that Ca^{2+} entering through L-type VDCCs is the only driver of contraction (Nausch et al, 2010) after nerve stimulation with electric field stimulation (EFS), which causes efferent nerves to release neurotransmitters. EFS-induced smooth muscle contraction was reduced with an anticholinergic (atropine) and VDCC blocker (diltiazem), but EFS-induced contractions were not reduced by blocking IP_3 -mediated signaling or inhibition of PLC. In this study, all purinergic components were blocked by using α,β -methylene ATP in the experiments, so only the muscarinic component was being studied.

Although the normal contraction in the human detrusor smooth muscle is mediated by ACh, in disease states the excitation neurotransmitter could possibly be caused by ATP. Human bladders from obstructed and OAB subjects were studied and found

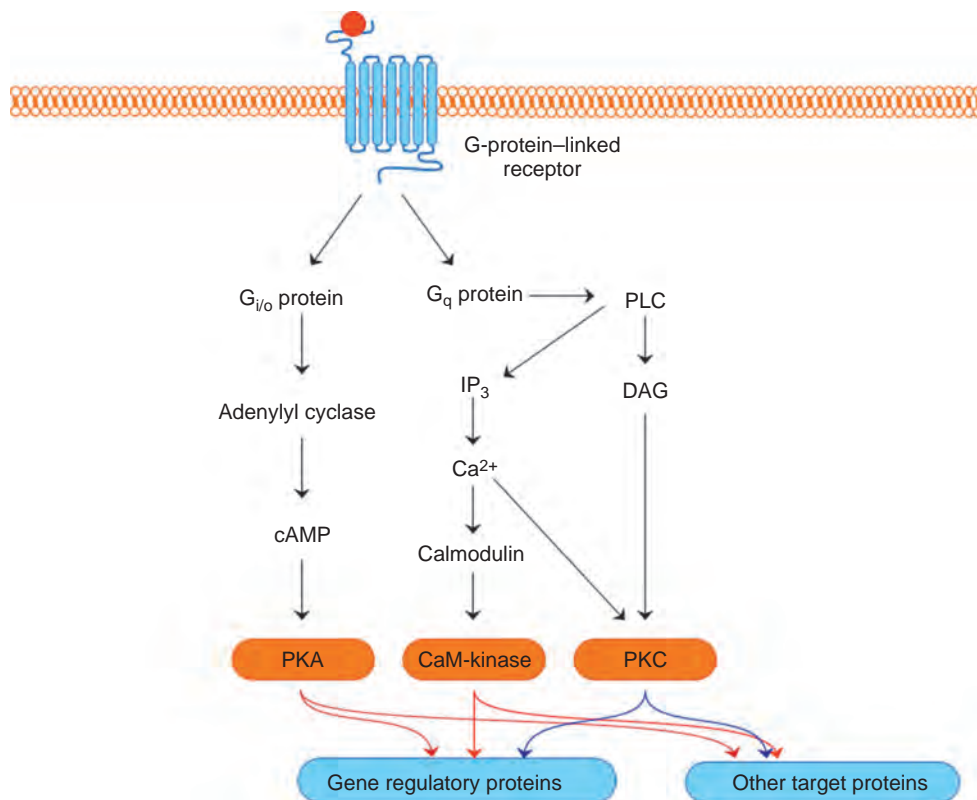


Figure 69-17. Paradigm for G-protein-linked receptor downstream mechanisms. Even muscarinic subtype receptors (M_2 , M_4) are $G_{i/o}$ -protein coupled. Odd muscarinic subtype receptors (M_1 , M_3 , M_5) are G_q protein coupled. CaM, calmodulin; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP_3 , inositol triphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C.

to have atropine-resistant contractions that were blocked by the ATP-receptor blocker α,β -methylene ATP, suggesting a purinergic excitatory component to the pathologic bladder contractions (Bayliss et al, 1999). In this study, normal human bladders had no purinergic excitation-coupling signaling. More recent investigations in mouse smooth bladder revealed that both P2X₁ and M₃ receptors contribute to the muscle contractions, but it is interesting to note that there appeared to be an element of suppression of the muscarinic excitation-contraction coupling by the purinergic activation (Heppner et al, 2009). These investigators used their experimental findings to propose a hypothesis of how both DO (LUTS) and underactivity can occur simultaneously in a patient, as with detrusor hyperactivity with impaired contractility (DHIC) (Resnick and Yalla, 1987). It has already been shown that purinergic signaling is increased in the human aging bladder (Yoshida et al, 2001). And if the interplay between purinergic and muscarinic signaling occurs in human as it does in mice, then this increased purinergic signaling detected in elderly human bladders can explain the occurrence of LUTS and overactivity (through increased purinergic-activated afferent activity; see later) with simultaneous incomplete bladder emptying (detrusor underactivity or impaired contractility through suppression of muscarinic signaling). This describes DHIC. Furthermore, this interplay gives rise to the possibility of treating DHIC by blocking purinergic signaling.

Calcium Signaling in Detrusor Myocyte

Because contractility of the smooth muscle is dependent on Ca^{2+} , there are many control mechanisms regulating intracellular Ca^{2+} . I_{Ca} (Ca^{2+} inward current) occurring during the phase 1 fast upstroke of APs is mediated by voltage-dependent Ca^{2+} channels (gene name is *CaV* or *CACNA1*). As discussed in the previous section, Ca^{2+} entry through the VDCC is likely the main contributor to the contraction. There are several types of VDCCs, but the two types that are important in bladder smooth muscle contraction are L-type (L = long lasting) and T-type (T = transient). The classic VDCC, the L-type, which is blocked by traditional Ca^{2+} blockers such as nifedipine (a dihydropyridine), diltiazem (a nondihydropyridine), and verapamil (a phenylalkylamine), is present on smooth muscle cells and is activated by AP-induced depolarization (Rivera and Brading, 2006; Nausch et al, 2010). T-type VDCCs responded to lower magnitudes of depolarization, had smaller conductance, and have no highly specific blockers yet (Fry and Jabr, 2014). The participation of T-type VDCCs in bladder smooth muscle physiology may allow a finer control of the excitation coupling and/or be important in detrusor contractile pathologies. Calcium imaging is a technique whereby one can visualize changes in single-cell intracellular Ca^{2+} concentrations ($[\text{Ca}^{2+}]_i$) by using calcium dyes that fluoresce with intensities directly correlated with $(\text{Ca}^{2+})_i$. Calcium imaging during the course of a smooth muscle cell contraction reveals a “calcium flash” caused by a sudden large increase in $(\text{Ca}^{2+})_i$ followed by mechanical contraction with shortening of the cell. This influx of Ca^{2+} through both types of VDCC initiates the actinomyosin cross-bridge cycling as detailed in the previous section.

When $(\text{Ca}^{2+})_i$ rises via entry through VDCCs during the AP, this causes the SR to release its stores of Ca^{2+} (internal stores) through ryanodine receptors (RyRs)—a phenomenon called *calcium-induced calcium release* (CICR). Internal stores of Ca^{2+} released are visualized as “calcium sparks” (from microfluorometry) that were first discovered in arterial smooth muscle (Nelson et al, 1995). These calcium sparks activate (open) the nearby membrane-associated calcium-activated large conductance potassium channel (BK or gene name *KCNMA1*), which lets potassium out of the cell, thus hyperpolarizing the cell and relaxing the smooth muscle cell (see next paragraph about I_K portion of the AP). These calcium sparks are the cause of the spontaneous transient outward currents (STOCs) of K^+ mediated by the BK channel. Calcium sparks were studied in detrusor smooth muscle (Collier et al, 2000; Herrera et al, 2001). In bladder myocytes, the calcium sparks (e.g., RyR openings) were not tightly linked to the gating of L-type VDCCs, as in cardiac myocytes, because the SR is not as physically close to the VDCC in the bladder

myocytes as in the cardiac myocytes. Similar to arterial myocytes, the calcium sparks in detrusor myocytes also activate BK channels. These interactions are shown in the animation on the Expert Consult website.

Intracellular Ca^{2+} also activates a variety of cellular responses when it enters the cytoplasm of a cell. To be effective as a signal, its concentration must be returned to submicromolar levels, driven by ATP pumps. The Ca^{2+} pump is a membrane-bound, Ca^{2+} -activated ATPase, similar to the Na^+ - K^+ pump that controls ion balance and membrane potential in all animal cells. These pumps belong to a superfamily of ATPases known as *P type*, because they depend on the autophosphorylation of a conserved aspartic acid residue using ATP. The rise in intracellular Ca^{2+} can be lowered by pumping Ca^{2+} back into the SR or mitochondria or out into the extracellular space (Fig. 69-18).

When intracellular stores of Ca^{2+} within the SR are depleted, the myocyte has a mechanism by which another type of Ca^{2+} channel (ORAI) opens, thus allowing influx of extracellular Ca^{2+} to refill the SR stores. This process is called the *store-operated Ca^{2+} entry* (SOCE) or capacitive Ca^{2+} entry. The sensor for SR Ca^{2+} concentration is the protein called STIM (stromal interaction molecule) (Roos et al, 2005). When STIM senses low Ca^{2+} concentrations, STIM proteins aggregate to form discrete membrane clusters that tether the plasma membrane protein ORAI, allowing tetramers of ORAI to form a pore for extracellular Ca^{2+} entry into the cell (Penna et al, 2008). This Ca^{2+} channel composed of multiunits of ORAI is called CRAC (calcium release-activated channel). The electrophysiologic current measured from Ca^{2+} entry through CRAC is denoted I_{CRAC} . Although SOCE has been shown to be present in various other smooth muscles, SOCE has not been measured yet in detrusor myocytes but is likely to exist.

Propagation of Electrical Responses

Specialized proteins called **connexin 43 (gap-junction proteins)** are expressed between the membranes of connected smooth muscle cells. The basic unit (monomer) of Cx43 is composed of four transmembrane domains with the carboxy-terminal and amino-terminal intracellular (Fig. 69-19). Six monomers of Cx43 are arranged as a hexamer unit with a central pore channel. The hexameric unit Cx43 of two neighboring myocytes will have to dock to align the central pore so that ions can flow from one myocyte to another. The electrically coupled myocytes can be measured using double whole-cell patch (DWCP) electrophysiology. This technique was performed on cultured human myocytes and gap junction currents were detected; also, Western blots confirmed the presence of Cx43 (Wang et al, 2006).

However, lack of fused tetanic contractions in normal detrusor smooth muscle strips suggests that there is poor electrical coupling between smooth muscle cells (Uvelius and Mattiasson, 1986). Measurements of tissue impedance support the observation that the detrusor is less well coupled electrically than other smooth muscles (Brading and Mostwin, 1989; Parekh et al, 1990). Poor coupling could be a feature of a normal detrusor that prevents synchronous activation of the smooth muscle cells during bladder filling. Nevertheless, some degree of coupling within a muscle bundle clearly does exist, because it is possible to measure the length constant of a bundle (Seki et al, 1992). There is also evidence for gap-junction coupling between detrusor cells in humans and guinea pigs, detected by whole-cell patch clamp recordings (Wang et al, 2006) and Ca^{2+} imaging (Neuhaus et al, 2002), respectively. Significant expression of Cx43 and Cx45 gap-junction proteins is found in human detrusor muscles (John et al, 2003; Wang et al, 2006). However, electrical couplings between detrusor cells seem to be reduced during postnatal development because coordinated, large-amplitude, low-frequency contractile activity as seen in the neonate rat bladder declines and is replaced by low-amplitude, high-frequency, more irregular activity in older rats, which appears to depend on the disruption of the intercellular smooth muscle communication (Szell et al, 2003). It has also been suggested that a change in the properties of the cell coupling may

MECHANISMS OF MAINTAINING CALCIUM LEVEL IN THE MYOCYTE

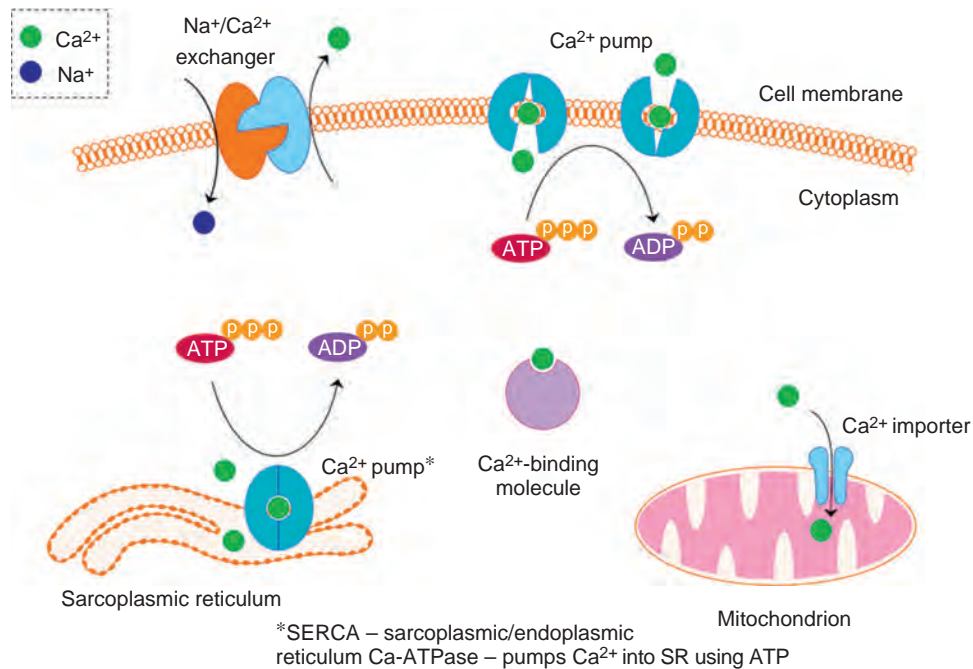


Figure 69-18. Intracellular calcium (green circles) in the detrusor myocyte can be regulated by various mechanisms: (1) exchanging for Na⁺ ion; (2) pumping out of cell using adenosine triphosphate (ATP); (3) pumping into sarcoplasmic reticulum (SR) with SERCA/ATP; (4) binding to calcium-binding molecule; (5) pumping into mitochondria. ADP, adenosine diphosphate.

MOLECULAR STRUCTURE AND FUNCTION OF THE GAP JUNCTIONS

Connexin has four transmembrane domains

Six connexin molecules form the channel of the connexin

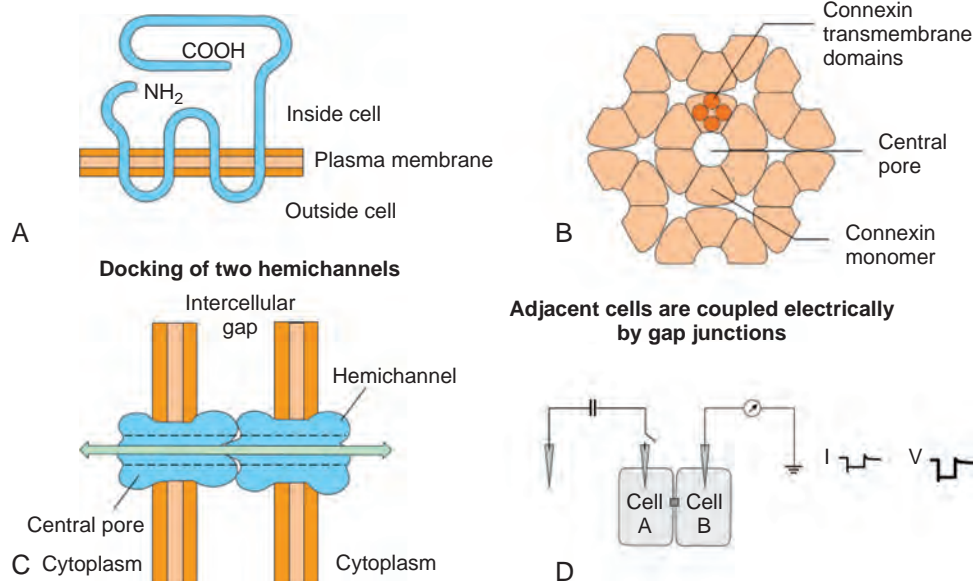


Figure 69-19. The molecular structure of a gap junction (e.g., connexin 43 [Cx43]). A, Each connexin unit (monomer) has four transmembrane domains. B, Six connexin units (monomers) form a hemichannel with a central pore. C, Two hemichannels dock together to form a channel that allows passage of ions between cells. D, Patch clamp can reveal electrically coupled cells.

underlie the generation of the uninhibited detrusor contractions occurring in overactive and aging bladders (Seki et al, 1992; Brading, 1997b, 2006).

Detrusor Interstitial Cells

Recent evidence suggests that the “normal” bladder may be spontaneously active and that exaggerated spontaneous contractions could contribute to the development of DO. In a rat model for DO, local areas of spontaneous contractions are increased and more coordinated in rat bladders with partial outlet obstruction (Drake et al, 2003). However, it is still not clear which cells generate spontaneous activity in the bladder. As mentioned before, detrusor myocytes could be spontaneously active, and electrical coupling through gap junctions could trigger spontaneous contractions (Brading, 1997b, 2006). Alternatively, another population of cells in the bladder known as *interstitial cells* or *myofibroblasts* has been proposed for a pacemaking role in spontaneous activity of the bladder (Andersson and Arner, 2004; Kumar et al, 2005). Interstitial cells have been identified in the human and guinea pig ureter, urethra, and bladder body (Kumar et al, 2005; Hashitani, 2006; Fry et al, 2007).

Interstitial cells, in addition to being located in the suburothelial layer, are also found in the detrusor layer and have been shown to be spontaneously active (Kumar et al, 2005). These cells are stained for c-KIT and located along both boundaries of muscle bundles in the guinea pig bladder (McCloskey and Gurney, 2002; Hashitani et al, 2004; Hashitani, 2006). These cells can fire Ca^{2+} waves in response to cholinergic stimulation by M_3 muscarinic receptor activation and can be spontaneously active, suggesting that they could act as pacemakers or intermediaries in transmission of nerve signals to smooth muscle cells (McCloskey and Gurney, 2002; Johnston et al, 2008) (Fig. 69-20). However, Hashitani and colleagues (2004) have also suggested that interstitial cells in the detrusor may be more important for modulating the transmission of Ca^{2+} transients originating from smooth muscle cells than for being the pacemaker of spontaneous activity because spontaneous Ca^{2+} transients occur independently in smooth muscles and interstitial cells. It has also been demonstrated that the c-KIT tyrosine kinase inhibitor imatinib (Glivec) decreased the amplitude of spontaneous contractions in the guinea pig bladder (Kubota et al, 2004, 2006) and in muscle

strips from the overactive human bladder, in which c-KIT-positive cells were increased compared with normal subjects (Biers et al, 2006), suggesting that targeting these receptors expressed in intradetrusor interstitial cells may provide a new approach for treating OAB. In addition, after application of SNP (an NO donor), interstitial cells throughout the bladder, but not detrusor muscle cells, demonstrate cGMP immunoreactivity (Smet et al, 1996; Gillespie et al, 2004). Thus, increased levels of cGMP found in interstitial cells by using phosphodiesterase-5 (PDE5) inhibitors, for example, may diminish synchronicity between detrusor muscle bundles (Hashitani, 2006). These cells are also a source of PGE_2 because of their expression of cyclooxygenase and a reduction in spontaneous activity of bladder muscle strips by use of PGE_2 receptor (EP) antagonists in rabbits (Collins et al, 2009).

Investigators have found a new class of intradetrusor cells with pacemaker-like properties (Koh et al, 2012; Lee et al, 2014). These cells were not c-KIT positive, but rather expressed platelet-derived growth factor receptor (PDGFR)- α . The reason these investigators searched for this type of cell in the bladder was because the PDGFR- α -positive cells in the gastrointestinal tract have been found to inhibit neurotransmission in the myenteric neural plexus (Cobine et al, 2011; Kurahashi et al, 2011). Although purines, such as ATP, induce initial contraction of the bladder muscle (see the section on **excitation-contraction coupling**), there is also a prolonged relaxation that could be related to the suppression of the muscarinic excitation-coupling (Heppner et al, 2009). However, investigators found that the detrusor PDGFR- α cells, through P_2Y_1 signaling, were the reason for the prolonged relaxation induced by purines (Lee et al, 2014). These investigators theorized that a “dual receptive field”—an excitatory field via P_2X_1 on the smooth muscle and one inhibitory field via P_2Y_1 on the PDGFR- α cells—provides finer regulation of detrusor contractility.

Further research is required to fully understand the role of suburothelial and intradetrusor interstitial cells and their contribution to spontaneous contractions or DO.

KEY POINTS: SMOOTH MUSCLE MECHANICS

- Muscarinic receptors induce detrusor contraction, in response to ACh released from parasympathetic nerve terminals, by calcium entry through Ca^{2+} channels
- Although calcium serves the same triggering role in all muscle types, the mechanism of activation is different in smooth muscle. The contractile response is slower and longer lasting than that of skeletal and cardiac muscle.
- Recent evidence suggests that the “normal” bladder may be spontaneously active and that exaggerated spontaneous contractions could contribute to the development of an OAB. A population of cells within the detrusor layer, known as *interstitial cells* or *myofibroblasts*, has been proposed to have a pacemaking role in spontaneous activity of the bladder.

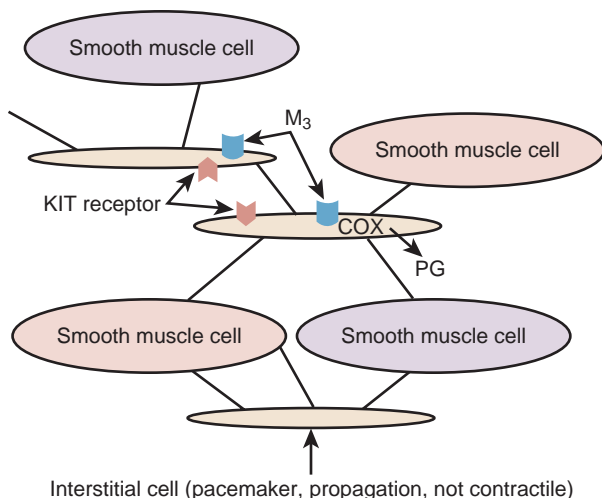


Figure 69-20. Schematic representation of interstitial cells in the detrusor muscle layers. These cells are not contractile but may be pacemakers with spontaneous activity and propagate signals between detrusor muscles. They also express KIT receptors and muscarinic M_3 receptors, and can produce prostaglandins (PG), such as PGE_2 , through activation of cyclooxygenase (COX).

BLADDER MECHANICS

Urinary Storage (Filling)

During urine filling of the bladder, the viscoelastic behavior of the bladder depends on both neuromuscular and mechanical properties. Mechanical properties are extremely sensitive to tissue structure and composition of the bladder wall. In addition to smooth muscle, the human bladder is composed of roughly 50% collagen and 2% elastin. With injury, obstruction, or denervation, collagen content increases (Macarak and Howard, 1999). When contractile protein content exceeds collagen, greater distensibility is achieved (compliance). Conversely, when collagen levels increase, compliance falls. The changes in the thickness of the lamina propria and the detrusor are mechanical requirements for the bladder to accommodate increasing urine volume. During filling, the lamina propria thins at a faster rate than the muscle wall. It has been proposed that bladder wall thinning during filling is the result

of a rearrangement of the muscle bundles and also alteration of collagen coil structure (Macarak and Howard, 1999). A combination of muscle and connective tissue spatial changes is required to accommodate urine at low intravesical pressures (Chang et al, 1999). During filling, the detrusor reorganizes and muscle bundles shift position from a top-to-bottom to a side-to-side configuration. During reorganization, the coiled type III collagen fibers connecting the muscle bundles orthogonally become extended, longer, and taut and assume an orientation such that the fibers become oriented parallel to the lumen.

Bladder compliance (C) is defined as the change in volume (V) relative to the corresponding change in intravesical pressure (P):

$$C = \Delta V / \Delta P$$

Filling the bladder at a slow physiologic rate maintains an intravesical pressure of less than 10 cm H₂O (Klevmark, 1974). However, the compliance of the bladder is dependent on the rate at which fluid is instilled into the bladder (Coolsaet, 1985). This phenomenon can be seen in urodynamics when the intravesical pressure can drop when filling is slowed or stopped. The pressure-volume curve during filling of the bladder is dependent on several factors including (1) collagen, elastin, and smooth muscle as passive structures; (2) active properties of the smooth muscle; and (3) geometry of the bladder. Therefore, when there is decreased compliance of the bladder (steep filling curve), it may be the result of multiple factors including (1) fast filling rate; (2) change in composition of the bladder wall (e.g., more collagen, less elastin); (3) hyperactivity of the smooth muscle; and (4) a combination of any of these factors. The compliance of a typical bladder in 559 women with stress incontinence was measured with standardized urodynamics (50 mL/min filling rate). The data showed that the mean maximum cystometric capacity (MCC) was 392 mL; intravesical pressure (Pdet) rose from 2 cm H₂O at the beginning of fill to 6 cm H₂O at MCC (Nager et al, 2007).

Acute spinal transection of the bladder did not alter bladder compliance, although pelvic nerve transection did decrease compliance (Langley and Whiteside, 1951). However, recent animal studies have suggested that central neural input is required for bladder compliance and that this is an active afferent neural process (Smith et al, 2012b). These investigators theorized that afferent signals arising from the bladder wall during filling of the bladder are relayed to the CNS, which in turn inhibits spontaneous smooth muscle contractility, thus maintaining high bladder compliance during filling. In other words, the nervous system, in addition to viscoelastic properties of the bladder wall, has a role in maintaining bladder compliance during filling.

The bladder muscle has a broad length-tension relationship, allowing tension to be developed over a large range of resting muscle lengths (Uvelius and Gabella, 1980). The tissue shows viscoelasticity that influences muscle tension and manifests as total bladder wall tension (Venegas, 1991). Isolated detrusor strips show spontaneous mechanical activity to a variable extent. It is more frequently seen in bladders from small mammals (Sibley, 1984) but can also be seen in muscle strips from human detrusor. However, spontaneous fused tetanic contractions, such as those commonly seen in smooth muscles from the gastrointestinal tract and uterus, are almost never seen in normal bladders.

Voiding Mechanics

Intravesical pressure reflects the combined factors of abdominal (Pabd) and detrusor (Pdet) pressures. Therefore,

$$P_{det} = P_{ves} - P_{abd}$$

Micturition relies on a neurally mediated detrusor contraction, causing Pdet to rise without a significant change in Pabd. To assess the strength of a detrusor contraction, Pdet alone is an insufficient measure. A muscle can use energy either to generate force or to shorten its length. Because the bladder is a hollow viscus, the force

developed contributes to Pdet, whereas the velocity of shortening relates to urine flow (Q). There is a trade-off between generating Pdet and urine flow. This has been nicely reviewed by Griffiths (1988). If urethral resistance is low, as in women with sphincter insufficiency and even in normal continent women, Pdet may be almost undetectable; yet, these women with modest Pdet would have normal flow rates. In a population of 384 stress-incontinent women, the mean Pdet at Qmax on pressure-flow urodynamics study was 19 cm H₂O (Nager et al, 2007). In a group of 30 healthy men who underwent ambulatory urodynamics, Pdet at Qmax ranged from 60 to 70 cm H₂O (Schmidt et al, 2004). The trade-off between Pdet and Q resembles a curve for constant mechanical power (W) in which

$$W = P_{det} \times Q$$

The equation explains why a woman could have normal detrusor contractility and normal detrusor power despite low voiding pressure. During micturition, Pdet reflects outlet resistance. When the urethra opens widely with a high flow (Q), little Pdet is needed to achieve the work necessary to empty the bladder. The key message is that low voiding pressure in a woman does not equate with impaired detrusor contractility; she may simply be able to open her urethra widely. Moreover, pressure-flow nomograms developed for men for diagnosis of obstruction should not be applied to women without validation.

Motor Sensory Network in Detrusor Muscle

Based on anatomic immunohistochemical localization studies of nerve fibers in the guinea pig, Gillespie has proposed a "motor sensory" network within the detrusor muscle wall (Gillespie et al, 2006) (Fig. 69-21). This network involves the presence of sensory fibers (green and red lines in Fig. 69-21) next to detrusor myocytes and intradetrusor interstitial cells. Because the detrusor has spontaneous activity (as micromotions and/or nonvoiding contractions), the spontaneous smooth muscle contractions trigger sensory signals to the host. An increase in spontaneous activity of the detrusor smooth muscle could be interpreted as an urgency episode. Certainly, this model could help explain how decreasing smooth muscle spontaneous activity (e.g., with antimuscarinics) could decrease sensory input. The effect of tolterodine (antimuscarinic) and mirabegron (β_3 agonist) in decreasing nonvoiding contractions in a partial urethral obstruction animal model has been shown (Gillespie et al, 2012). However, the investigators did not measure the pelvic afferent output to determine whether that was reduced with the reduction of the nonvoiding contractions. Bladder wall micromotions were measured in women with sensory urgency, though the sample size was small (N = 6) (Drake et al, 2005). This motor sensory network ties in the concept that it is not easy to separate the function of the bladder organ into simple efferent and afferent activities, because these two events are inexorably linked.

NEURAL CONTROL OF THE LOWER URINARY TRACT

Peripheral Nervous System

The LUT is innervated by three sets of peripheral nerves involving the parasympathetic, sympathetic, and somatic nervous systems (Fig. 69-22). Pelvic parasympathetic nerves arise at the sacral level of the spinal cord, excite the bladder, and relax the urethra. Lumbar sympathetic nerves inhibit the bladder body and excite the bladder base and urethra. Pudendal nerves excite the EUS. These nerves contain afferent (sensory) as well as efferent axons (Wein, 1992; de Groat et al, 1993; Sugaya et al, 1997; Yoshimura et al, 2008).

Parasympathetic Pathways

Parasympathetic preganglionic neurons innervating the LUT are located in the lateral part of the sacral intermediate gray matter in

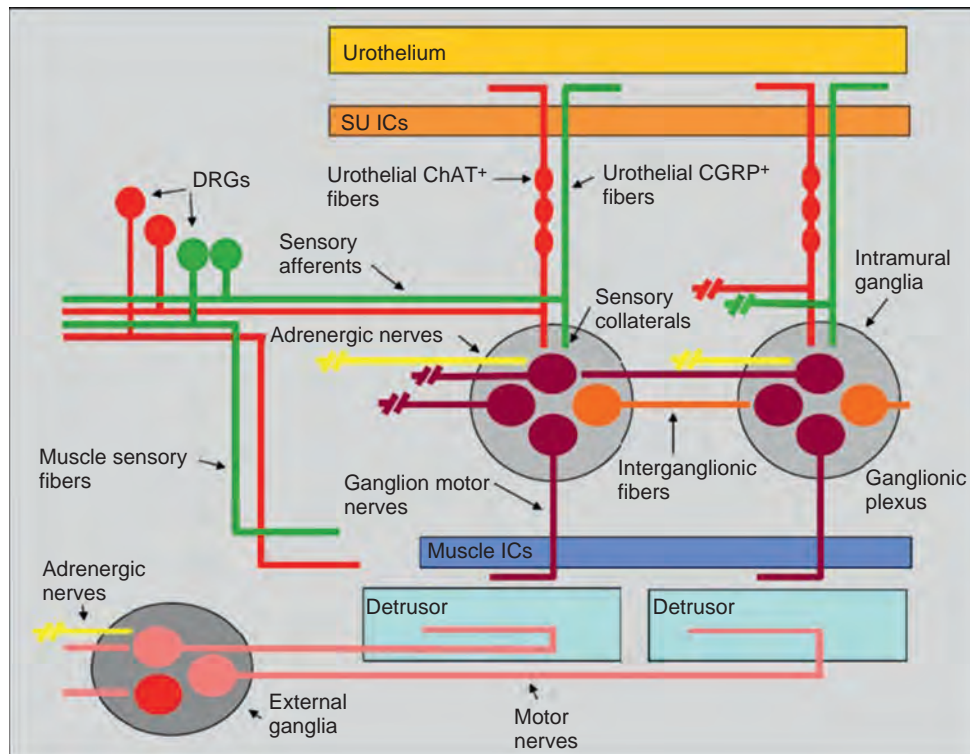


Figure 69-21. Motor sensory network within the detrusor muscle wall. Sensory afferents surround detrusor myocytes. Gray circles represent (1) intradetrusor ganglia that supply postganglionic efferents to detrusor muscle and (2) external ganglia. Detrusor myocyte spontaneous activity can trigger sensory afferents. CGRP, calcitonin gene-related peptide; ChAT, choline acetyltransferase; DRGs, dorsal root ganglia; ICs, interstitial cells; SU, suburothelial.

a region termed the *sacral parasympathetic nucleus* (Nadelhaft et al, 1980; Morgan et al, 1981; de Groat et al, 1993; Morgan et al, 1993; de Groat et al, 1996). Parasympathetic preganglionic neurons send axons through the ventral roots to peripheral ganglia, where they release the excitatory transmitter ACh (de Groat and Booth, 1993). Parasympathetic postganglionic neurons in humans are located in the detrusor wall layer as well as in the pelvic plexus. This is an important fact to remember because patients with cauda equina or pelvic plexus injury are neurologically decentralized but may not be completely denervated. Cauda equina injury allows possible afferent and efferent neuron interconnection at the level of the intramural ganglia (de Groat et al, 1993, 1996).

Sympathetic Pathways

Sympathetic outflow from the rostral lumbar spinal cord provides a noradrenergic excitatory and inhibitory input to the bladder and urethra (Andersson, 1993). Activation of sympathetic nerves induces relaxation of the bladder body and contraction of the bladder outlet and urethra, which contribute to urine storage in the bladder. The peripheral sympathetic pathways follow a complex route that passes through the sympathetic chain ganglia to the inferior mesenteric ganglia and then through the hypogastric nerves to the pelvic ganglia.

Somatic Pathways

The EUS motoneurons are located along the lateral border of the ventral horn, commonly referred to as the *Onuf nucleus* (Fig. 69-23) (Thor et al, 1989). Sphincter motoneurons also exhibit transversely oriented dendritic bundles that project laterally into the lateral funiculus, dorsally into the intermediate gray matter, and dorsomedially toward the central canal.

Afferent Pathways

Overview: Properties of Afferent Neurons. The bladder and LUT serve to store and evacuate urine and are controlled by a complex interaction of neural mechanisms organized by local, spinal, and brain circuits. The majority of time is spent in storage mode, during which the bladder accommodates urine and maintains continence via reflexes that prevent contraction of bladder smooth muscle and promote contraction of the urethral sphincter. This switches during micturition when the bladder contracts and the sphincter relaxes to facilitate voiding. This switch relies on sensory signals, which provide the input to the reflex circuits that control bladder filling and emptying and are also the source of both nonpainful sensations of fullness and pain. Dysfunction leads to a number of disorders such as OAB syndrome and BPS/IC, with symptoms including urgency, pain, and urinary incontinence. Currently available therapeutic approaches are aimed primarily at reducing bladder contraction to relieve intravesical pressure and maintain continence. More recently, interest in bladder afferent signaling has been driven by the realization that symptoms are a feature of dysregulated storage sensations rather than exaggerated contractile responses and therefore targeting afferent mechanisms may be a rational approach to treatment.

Pathways to the Spinal Cord. Afferent fibers innervate the LUT via pelvic, hypogastric (lumbar splanchnic), and pudendal nerves. These nerves are mixed nerves that also contain the efferent parasympathetic, sympathetic, and motor fibers supplying the bladder, urethra, and sphincters. Axonally transported dyes taken up by afferent nerves are transported to the afferent cell bodies in the lumbosacral dorsal root ganglia (DRG) and the afferent terminations in the dorsal horn of the spinal cord. The primary afferent neurons of the pelvic and pudendal nerves are contained in sacral DRG, whereas afferent innervation in the hypogastric

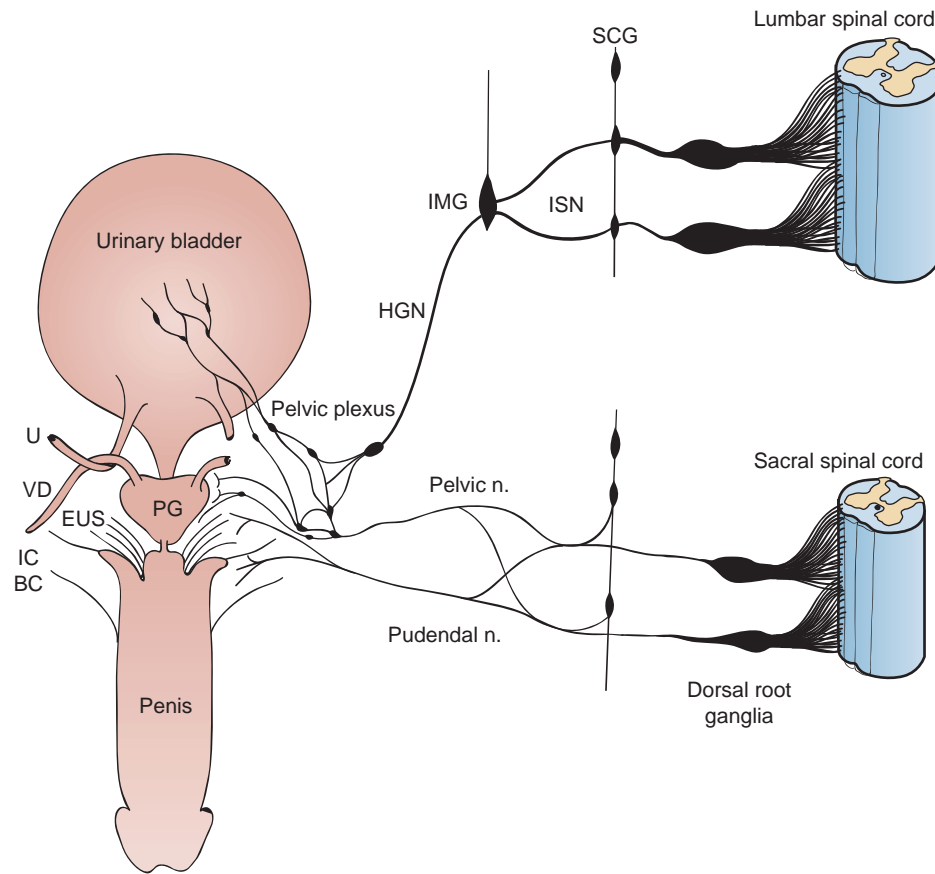


Figure 69-22. Diagram showing the sympathetic, parasympathetic, and somatic innervation of the urogenital tract of the male cat. Sympathetic preganglionic pathways emerge from the lumbar spinal cord and pass to the sympathetic chain ganglia (SCG) and then through the inferior splanchnic nerves (ISN) to the inferior mesenteric ganglia (IMG). Preganglionic and postganglionic sympathetic axons then travel in the hypogastric nerve (HGN) to the pelvic plexus and the urogenital organs. Parasympathetic preganglionic axons that originate in the sacral spinal cord pass in the pelvic nerve to ganglion cells in the pelvic plexus and to distal ganglia in the organs. Sacral somatic pathways are contained in the pudendal nerve, which provides an innervation to the penis and the ischiocavernosus (IC), bulbocavernosus (BC), and external urethral sphincter (EUS) muscles. The pudendal and pelvic nerves also receive postganglionic axons from the caudal sympathetic chain ganglia. These three sets of nerves contain afferent axons from the lumbosacral dorsal root ganglia. PG, prostate gland; U, ureter; VD, vas deferens.

nerves arises in the rostral lumbar DRG. The central axons of the DRG neurons carry the sensory information from the LUT to second-order neurons in the spinal cord (Morgan et al, 1981; de Groat, 1986; Thor et al, 1989; de Groat et al, 1996). These second-order neurons provide the basis for spinal reflexes and ascending pathways to higher brain regions involved in micturition, continence, and mediation of sensation.

Pelvic nerve afferents, which monitor the volume of the bladder and the amplitude of the bladder contraction, consist of myelinated (Aδ) and unmyelinated (C) axons (Table 69-2, Fig. 69-24). During neuropathic conditions (spinal cord injury) and possibly inflammatory conditions, there is recruitment of C fibers that form a new functional afferent pathway that can cause urgency incontinence and possibly bladder pain (Fig. 69-25).

There is great interest in understanding the nature and origins of bladder sensation. "Sensing" bladder volume is of particular relevance during bladder storage. Nathan (1956) described the sensations of awareness and desire to micturate involving bladder distention (stretch) and contraction and suggested that these could be mapped to the urinary bladder. In contrast, the sensation of imminent micturition may originate not in the urinary bladder, but rather from the urethra. More recent ideas link bladder filling with

episodic bursts of sensation (correlating with afferent discharge) that increase in intensity during filling, with the final episodes being the most intense and often described as "urgency" (Chapple and Wein, 2005). Afferent discharges that occur during a bladder contraction have an important reflex function and appear to reinforce the central drive that maintains the detrusor contraction. Afferent nerves that respond to both distention and contraction—that is, "in-series tension receptors"—have been identified in the pelvic and hypogastric nerves of cats and rats (Iggo, 1955; Floyd et al, 1976; Morrison, 1997). Afferents that respond only to bladder distention have been identified in the rat bladder (Morrison et al, 1998) and appear to be volume receptors, possibly sensitive to stretch of the urothelium. In the cat bladder, the presence of in-series tension receptors has also been reported (Downie and Armour, 1992). In the rat, there is evidence that many C bladder afferents are stretch receptors that do not respond to bladder contractions, a property that distinguishes them from in-series tension receptors (Morrison et al, 1998).

Functional Properties of Bladder Afferents. In the human bladder, ultrastructural studies have identified only unmyelinated nerves in the urothelium and immediate suburothelial layer, with small myelinated nerves being closely associated with the smooth

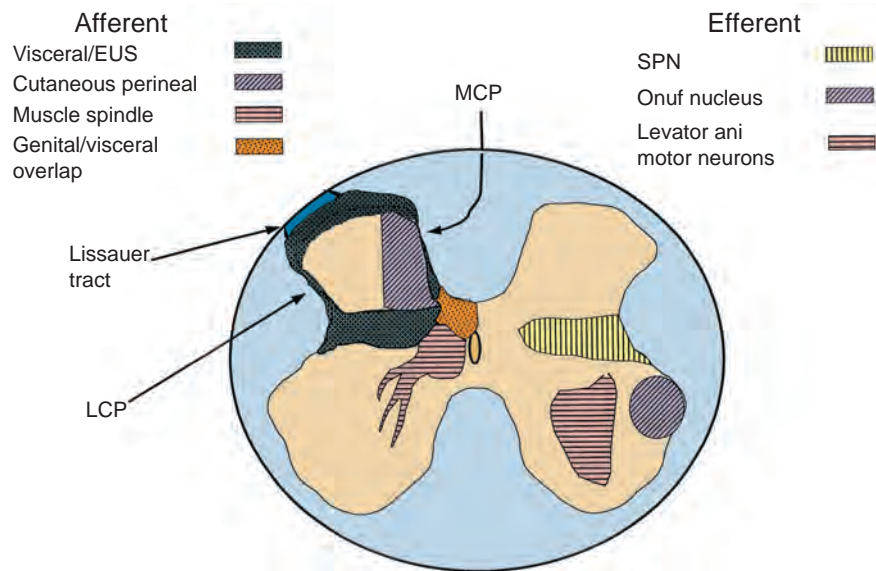


Figure 69-23. Cross section of sacral spinal cord; neuroanatomic distribution of primary afferent and efferent components of storage and micturition reflexes. For purposes of clarity, afferent components are shown only on the *left*, and efferent components are shown only on the *right*. Both components are, of course, distributed bilaterally and thus overlap extensively. Visceral afferent components represent bladder, urethral, and genital (glans penis or clitoris) afferent fibers contained in the pelvic and pudendal nerves. Cutaneous perineal afferent components represent afferent fibers that innervate the perineal skin contained in the pudendal nerve. Muscle spindle afferent components represent Ia/b afferent fibers contained in the levator ani nerve that innervate muscle spindles in the levator ani muscle. EUS, external urethral sphincter; LCP, lateral collateral projection; MCP, medial collateral projection; SPN, sacral parasympathetic nucleus.

TABLE 69-2 Bladder Afferent Properties

FIBER TYPE	LOCATION	NORMAL FUNCTION	INFLAMMATION EFFECT
Aδ (finely myelinated axons)	Smooth muscle	Sense bladder fullness (wall tension)	Increase discharge at lower pressure threshold
C fiber (unmyelinated axons)	Mucosa	Respond to stretch (bladder volume sensors)	Increase discharge at lower threshold
C fiber (unmyelinated axons)	Mucosa muscle	Nociception to overdistention Silent afferent	Sensitive to irritants Become mechanosensitive and unmask new afferent pathway during inflammation

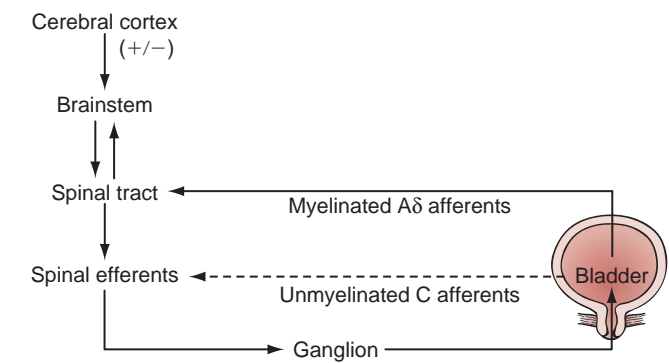


Figure 69-24. Illustration depicting the predominant Aδ afferent contribution to the normal micturition reflex. C-fibers (*dotted line*) are normally silent unless turned on by pathology.

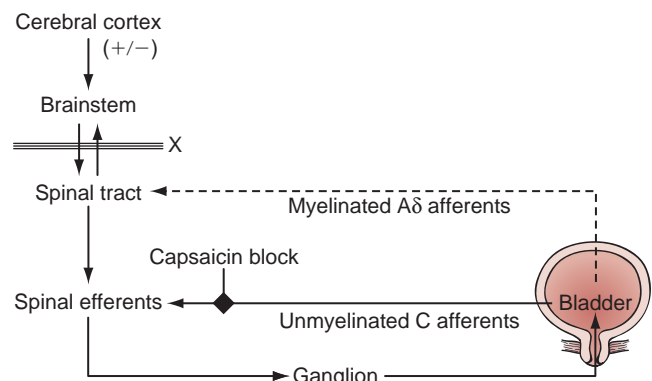


Figure 69-25. Illustration depicting the switch in afferent contribution to the micturition reflex from Aδ-fiber predominant to C-fiber predominant with neurologic diseases, aging, and possibly inflammatory disease. Note that capsaicin (and other vanilloids) can block the C-fiber contribution under these conditions.

muscle layers (Wiseman et al, 2002). The plexus of afferent nerves in the lamina propria is thickest in bladder neck and in the initial portion of the urethra, and becomes progressively less dense in adjacent regions such that the cranial region of the bladder has no afferent axons. In contrast, the afferent innervation of the musculature is more uniform throughout the bladder.

Recording from bladder afferents has revealed the diversity of afferent populations described earlier based on morphology, receptive field site, mechanical and chemical sensitivity, and electrophysiological characteristics. **Conduction velocity measurements confirm the predominance of fibers conducting APs in the A δ and C-fiber range.** The majority of these fibers are mechanosensitive, responding with a range of thresholds from volumes that would be encountered under normal bladder filling to extreme levels of distention that would be considered noxious and give rise to pain. Those with lower activation thresholds have small myelinated axons, whereas unmyelinated fibers in general have higher thresholds for activation. In addition, other afferents do not respond to bladder filling but can be activated by intraluminal chemicals such as hypertonic saline, capsaicin, or ATP, suggesting they may function as chemoreceptors. Still other subpopulations may be so-called silent afferents that have been described elsewhere, including the gastrointestinal tract. These afferents can be sensitized during inflammation, suggesting a role in signaling pain.

In the mouse pelvic nerve, four classes of bladder afferents (serosal, muscular, muscular/urothelial, and urothelial) have been identified based on responses to receptive field stimulation with different mechanical stimuli, including probing, stretch, and stroking the urothelium. Both low-threshold, representing 65% to 80% of the total population, and high-threshold stretch-sensitive muscular afferents are present (Daly et al, 2007; Xu and Gebhart, 2008). The muscular afferents can be sensitized by application of a combination of inflammatory mediators (bradykinin, serotonin, prostaglandin, and histamine at pH 6.0) (Xu and Gebhart, 2008).

A series of studies have used open-sheet preparations of guinea pig bladder to examine the diversity of bladder afferents and to attempt to correlate structure with function. Low-threshold

afferents have terminals in the muscle, described as “antenna-like” endings, and are referred to as *stretch-sensitive muscular mechanoreceptors* (Zagorodnyuk et al, 2006, 2007). These afferents, termed *tension receptors*, also respond to contraction of the detrusor muscle as well as tension generated by elongation during stretch and shortening during contraction. High-threshold afferents are also likely to terminate in the deeper muscle layers or in the serosa. These mechanosensitive endings have receptive fields (located by mechanical probing) associated with blood vessels. Thus, high-threshold afferents respond to high levels of bladder stretch but may also become sensitized in response to inflammation.

Species differences, as well as differences in nomenclature, might account for some of the variations in reported properties of bladder afferents. For example, the conduction velocity that differentiates A δ and C fibers is 2 m/sec in the cat, whereas it is 1.3 m/sec in the rat (Waddell et al, 1989). In the cat, bladder A δ afferents appear to be low-threshold mechanoreceptors (Häbler et al, 1993), whereas bladder C afferents (Häbler et al, 1990) are, in general, mechanosensitive (“silent C fibers”) (see Table 69-2). Some of the latter may be nociceptive and found to be sensitized by intravesical administration of chemicals (such as high potassium), low pH, high osmolality, and irritants such as capsaicin (Maggi et al, 1987; McMahon and Abel, 1987; Wen et al, 1994; Zagorodnyuk et al, 2009) (Fig. 69-26). After exposure to these substances, the sensitivity of bladder mechanoreceptors to distention increases, and some silent afferents become mechanoreceptive.

The bladder neck and proximal urethra contain the largest density of bladder nerves (Yokokawa et al, 1985; Gabella and Davis, 1998). In the urethra, afferent nerves have been reported between the muscle fibers, surrounding blood vessels, within the urothelium, and in a dense suburothelial plexus (Crowe et al, 1986; Tainio, 1993; Fahrenkrug and Hannibal, 1998). The striated sphincter muscle surrounding the urethra receives a very sparse afferent innervation that is localized primarily to nerve bundles passing between the muscle bundles. Specialized tension receptors (muscle spindles) that are innervated by large-diameter myelinated group IA afferents and that are prominent in most striated muscles are

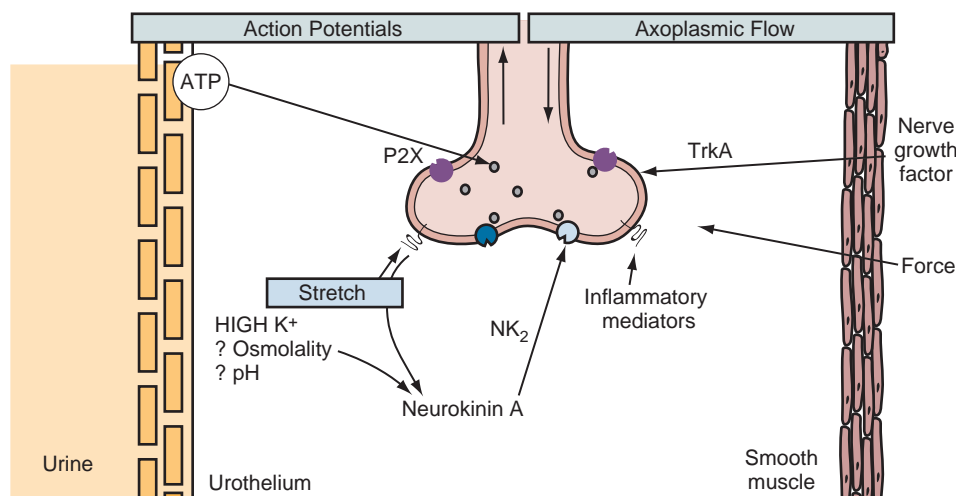


Figure 69-26. Actions of chemical mediators that may sensitize mechanosensory nerve endings in the bladder mucosa. Adenosine triphosphate (ATP) can be released from the urothelium and may sensitize the mechanoreceptors, which respond to stretch of the mucosa during bladder distention. Neuropeptides transported to the sensory ending by axoplasmic transport may be released during distention and chemical stimulation, and neurokinin A can act on NK₂ autoreceptors, which sensitize the mechanosensitive endings. This mechanism can be induced by high urinary potassium concentrations and possibly by other sensitizing solutions within the bladder lumen, such as those with high osmolality or low pH; the presence in the tissues of inflammatory mediators may also sensitize the endings. The smooth muscle can generate force that may influence some mucosal endings, and the production of nerve growth factor is another mechanism that can influence the mechanosensitivity of the sensory ending through the tyrosine kinase (TrkA) receptor.

absent (Gosling et al, 1981) or are present in low density (Lassmann, 1984) in striated sphincter muscles.

Afferent nerves may extend in some species to the luminal surface of the urothelium. In contrast, the urethral epithelium is likely to be part of a signaling system involving projections of neuroendocrine cells, interstitial cells, and sensory nerve endings. There is speculation that these urethral-neuroendocrine cells (often termed *paraneurons*) (Hashimoto et al, 1999) could release mediators such as neuropeptides or serotonin, which via activation of adjacent sensory nerves can stimulate urethral reflexes. Such types of cells are not unlike those in other types of epithelia, such as the trachea, where a cell type termed *brush cells* has been described, which are likely chemoreceptive and make contact with nearby sensory nerve fibers (Saunders et al, 2013). In addition, there are also reports that have identified and characterized functional properties of sacral afferents responding to flow through the urethra (Snellings et al, 2012). These are important observations whereby properties of these flow-responsive afferents seem to parallel those of cutaneous afferents. This could be important in terms of restoration of bladder emptying after spinal cord injury.

Modulators of Afferent Sensitivity. A number of parameters including stimulus-response function can be used to define the features of the various subpopulations of afferents that supply the LUT. The relationship between stimulus and response can be altered or modified according to the mechanical and chemical environment of the sensory ending. For example, bladder contractions can distort the afferent ending, whereas connective tissue elements will transmit or dissipate stimulus energy within the tissue, determining whether a response is rapidly or slowly adapting to maintained stretch. Similarly, a number of chemical mediators released from a variety of cells within the bladder wall, such as the urothelium and underlying lamina propria, will influence afferent firing.

Many mediators are released during inflammation, injury and ischemia, as well as from a number of cell types such as mast cells, fibroblasts, and neurons. Some mediators act directly on sensory nerve terminals, whereas others act indirectly, causing release of yet other agents from nearby cells. Thus, this can lead to augmented sensitivity of nerve endings to both mechanical and chemical stimuli and may also contribute to chronic pain states. Examples of local mediators include neurotrophins, purines, proteases, prostanooids, and cytokines. They produce their effects on visceral afferent nerves by three distinct processes. First, they can act directly, by opening ion channels on the nerve terminals. Second, they can sensitize endings without causing direct stimulation but causing hyperexcitability to other chemical and mechanical stimuli. Third, as is the case with neurotrophins, they can change the phenotype of the afferent nerve over long periods. For example, they may alter expression of channels, receptors, or mediators in the sensory neuron (Vergnolle, 2008). The result of sensitization is a leftward shift in the stimulus-response function. This means that for any given level of stimulation, a greater afferent barrage is generated. Peripheral sensitization normally develops rapidly and is relatively short-lived. However, in the presence of maintained injury or inflammation, the sensitization can be prolonged by changes in gene expression. Genes influenced in this way include those that determine the amount and pattern of neurotransmitter release by central nerve terminals in the brain and spinal cord. This alters the way that sensory signals are processed within the CNS and contributes to central sensitization (Woolf, 2011).

In contrast, ineffective or inefficient bladder emptying may be caused by a number of changes including damage or injury to bladder (afferent) pathways. Although mechanisms underlying detrusor underactivity are not well explored or defined, conditions including diabetes mellitus, classically referred to as a *diabetic cystopathy*, have been linked with impaired sensory function and increased residual urine (Ellenberg, 1980; Xiao et al, 2013). A number of factors including ischemia, altered glucose metabolism, and/or free radical formation may play a role in diabetic neuropathy and decreased sensation. Studies in aged rats have revealed a decreased afferent sensitivity to changes in bladder volume and a decreased level of afferent neuropeptide expression (Hotta et al,

1995; Mohammed and Santer, 2002). Also, studies in humans have revealed an age-related decreased response to bladder filling in brain regions that play a role in bladder sensation (Griffiths et al, 2007). Therefore, decreased afferent sensitivity or excitability in a number of conditions in addition to normal aging may be an important factor leading to impaired voiding (Smith, 2010; Miyazato et al, 2013).

Nitric Oxide. NO has been identified as a major inhibitory transmitter mediating relaxation of the urethral smooth muscle during micturition (Andersson et al, 1992; Andersson, 1993; Andersson and Persson, 1995; Bennett et al, 1995). In addition, NO is also involved in controlling bladder afferent nerve activity. Inhibitors of NOS, given systemically or intrathecally, do not affect normal micturition in conscious or anesthetized rats. However, DO that accompanies irritation is ameliorated by spinal application of NOS inhibitors (Rice, 1995; Kakizaki and de Groat, 1996; Lagos and Ballejo, 2004). Aizawa and colleagues (2011) examined the effect of NO on sensory signaling by directly recording afferent activity arising from the bladder in vivo. Release of NO can be inhibited using nonmetabolizable analogs that compete with L-arginine as substrate for NOS. On such inhibitor, L-NAME, increased the afferent response to bladder filling by about 50%, which was reversed by activation of NO pathways with L-arginine. These data suggest that NO is able to inhibit afferent activity, an observation consistent with earlier cystometric analysis of the effect of activating the NO pathway (Ozawa et al, 1999). In addition to studying NO mechanisms in the normal bladder, Aizawa and colleagues also showed that application of L-arginine significantly inhibited hypersensitivity induced by the cyclophosphamide metabolite acrolein, which is used experimentally as a model for BPS/IC.

The actions of NO are mediated through elevation of the intracellular second messenger cGMP (Fig. 69-27). The second messengers cAMP and cGMP are synthesized from the corresponding nucleoside triphosphates by their respective membrane-bound or soluble adenylate or guanylate cyclases. cAMP and cGMP are inactivated by phosphodiesterases (PDE) by hydrolytic cleavage of the 3'-ribose phosphate bond. Therefore the level of intracellular second messengers can be regulated by PDE isoenzymes (Truss et al, 1999, 2001). For example, PDE5 terminates the action of NO, and PDE inhibitors can be used therapeutically to prolong the action of NO at a number of sites including the bladder, prostate, and blood vessels. Behr-Roussel and colleagues found that inhibition of PDE5 attenuated bladder afferent activity in a rat model of spinal cord injury (Behr-Roussel et al, 2011). Thus, in addition to an important role for PDEs in regulation of smooth muscle tone, available data suggest that these agents might represent a target for treatment of hypersensitivity disorders of the bladder such as BPS/IC and OAB.

Purinergic Signaling. It is well established that the urothelium releases ATP in response to stretch and that this acts in a paracrine fashion to influence the function of myofibroblasts and bladder afferent nerves (Fig. 69-28). P2X₂ and P2X₃ receptors are expressed on unmyelinated afferent fibers innervating the bladder, and thus the hypothesis has been put forward that mechanosensitivity, at least in those afferents in proximity to the urothelium, involves ATP release by stretch and activation of P2X₂ and P2X_{2/3} receptors on the afferents (Ferguson et al, 1997; Vlaskovska et al, 2001). In the normal bladder, it is believed that a balance between the excitatory effects of ATP and inhibitory effects of NO may determine micturition thresholds and urinary frequency and that this balance may be disturbed in bladder disorders. Elevated ATP levels have been demonstrated in patients with DO and BPS/IC (Kumar et al, 2007). Munoz and colleagues, using a rat model of DO (diabetic bladder), found increased levels of ATP but normal levels of NO (Munoz et al, 2010). Conversely in an underactive bladder model induced by chronic sugar intake, NO levels were increased whereas ATP remained normal. This suggests that the balance between ATP and NO is altered in bladder dysfunction.

Transient Receptor Potential Cation Channels. A number of different members of the transient receptor potential (TRP) channel family are expressed in the bladder, mostly in association with

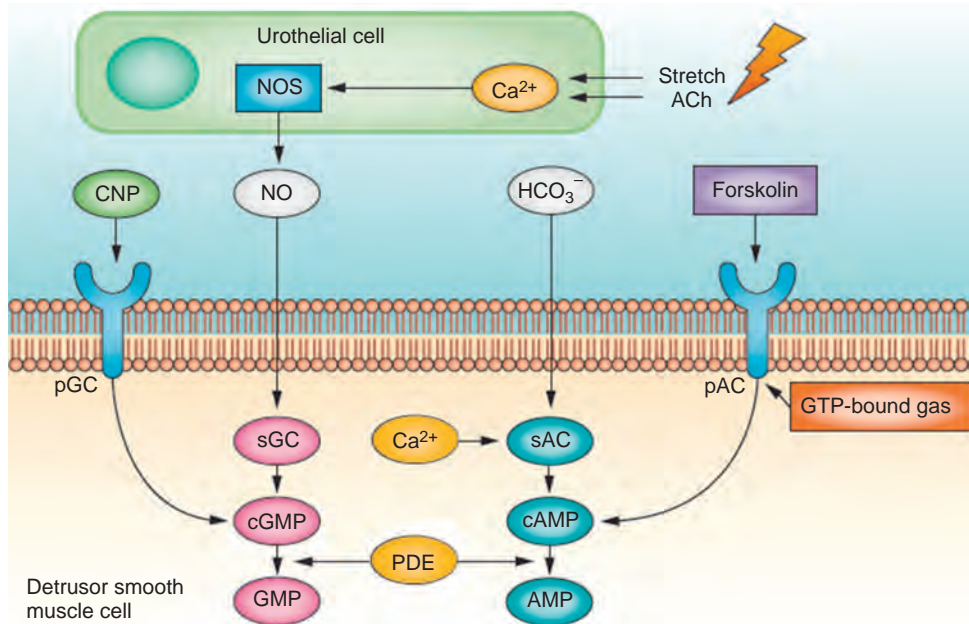


Figure 69-27. Schematic diagram of the cyclic nucleotide signaling pathways. Stretch stimuli, or acetylcholine release, increase internal Ca^{2+} levels in nitric oxide synthase (NOS)-expressing urothelial cells. NOS produces nitric oxide (NO), which signals to detrusor smooth muscle cells. NO is thought to have a modulatory role in the lower urinary tract, including the relaxation of urethral smooth muscle, modulation of neurotransmitter release from efferent nerves, regulation of urothelial permeability, and modulation of afferent nerve activity. Moreover, a pathophysiologic role of NO has been suggested because injury or chronic inflammation can upregulate the expression of inducible NOS. Guanylyl cyclases located in the cytoplasm or plasma membrane synthesize cyclic guanosine monophosphate (cGMP) in response to NO or C-like natriuretic peptide (CNP), respectively. Cyclic adenosine monophosphate (cAMP) is synthesized by adenylyl cyclases, either associated with G protein-coupled receptors in the plasma membrane, or in the cytoplasm. Membrane-associated adenylyl cyclases are activated by guanosine triphosphate (GTP)-bound G_α and forskolin, whereas cytoplasmic adenylyl cyclases are regulated by HCO_3^- and Ca^{2+} but insensitive to forskolin or activated G_α . cAMP and cGMP are hydrolyzed to AMP and GMP, respectively, by phosphodiesterases (PDEs). ACh, acetylcholine; pAC, particulate (plasma membrane) adenylyl cyclase; pGC, particulate (plasma membrane) guanylyl cyclase; sAC, soluble (cytoplasmic) adenylyl cyclase; sGC, soluble guanylyl cyclase. (From Rahnama'i MS, Ückert S, Hohnen R, et al. The role of phosphodiesterases in bladder pathophysiology. *Nat Rev Urol* 2013;10:414–24.)

sensory nerve fibers involved in mechanotransduction and nociception. TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1 are expressed in varying levels within the bladder. TRPV1, the most extensively studied TRP channel, is expressed on capsaicin-sensitive afferent pathways, predominantly C-fiber nociceptors, and responds to increases in temperature to the noxious range ($>43^\circ\text{C}$) and to protons, suggesting that it functions as a transducer of painful thermal stimuli and acidity in vivo. Thus, C fibers signal inflammatory or noxious events in the bladder. TRPV1 has been shown to play an integral role in modulating the excitability of bladder afferents and the generation of hypersensitivity, induced by bladder inflammation (Birder et al, 2002; Apostolidis et al, 2005a). It is through desensitization of this receptor that agents such as resiniferatoxin (RTX) act to treat symptoms in OAB (Kissin and Szallasi, 2011). TRPV1 is predominantly expressed on sensory nerves and has been identified within nerve plexuses running in both the muscle layer and suburothelium as well as within the urothelium itself.

RTX is the principal active ingredient in the drug euphorbium, which is derived from the air-dried latex (resin) of the cactus-like plant *Euphorbia resinifera*. In 1975 the principal active ingredient in euphorbium was isolated and named *resiniferatoxin* (Hergenhahn et al, 1975). In 1989, RTX was recognized as an ultrapotent analog of capsaicin; however, it has unique pharmacologic effects as well (Szallasi and Blumberg, 1990), such as desensitization without prior excitation of the pulmonary chemoreflex pathway (Szolcsanyi,

1990). In patients with spinal cord injury-induced DO, clinical response to intravesical therapy with RTX showed changes in nerve fiber staining as well as marked improvements on cystometry and other parameters (Brady et al, 2004). Furthermore, it has also been shown that intravesical application of high-dose capsaicin as well as RTX is effective for treating painful symptoms in IC patients (Lazzeri et al, 1996, 2000), although a prospective, randomized clinical trial using intravesical RTX application showed no effect in patients with IC (Payne et al, 2005).

TRPV4 is a member of vanilloid TRPV channels and a nonselective cation channel activated by mechanical pressure, osmolarity (hypotonicity), moderate warmth ($>27^\circ\text{C}$), and chemical stimuli such as phorbol esters. Interest in TRPV4 has been fueled by the observation of impaired voiding behavior in knockout mice (Gevaert et al, 2007). This channel shows mechanosensitivity and is proposed to play a role in the micturition reflex by activating C-fiber afferents (Aizawa et al, 2012). However, the site of action of TRPV4 agonists may in fact be the urothelium, which expresses the TRPV4 channel (Birder et al, 2007a), particularly in association with adherence junctions, where they may be preferentially activated by stretch and lead to the release of ATP (Yamada et al, 2009). Inhibition of TRPV4 has recently been shown to improve symptoms in a model of experimental cystitis (Everaerts et al, 2010).

TRPA1 is the only member of the ankyrin TRP channel and a receptor for several pungent chemicals that evoke pain, such as allyl

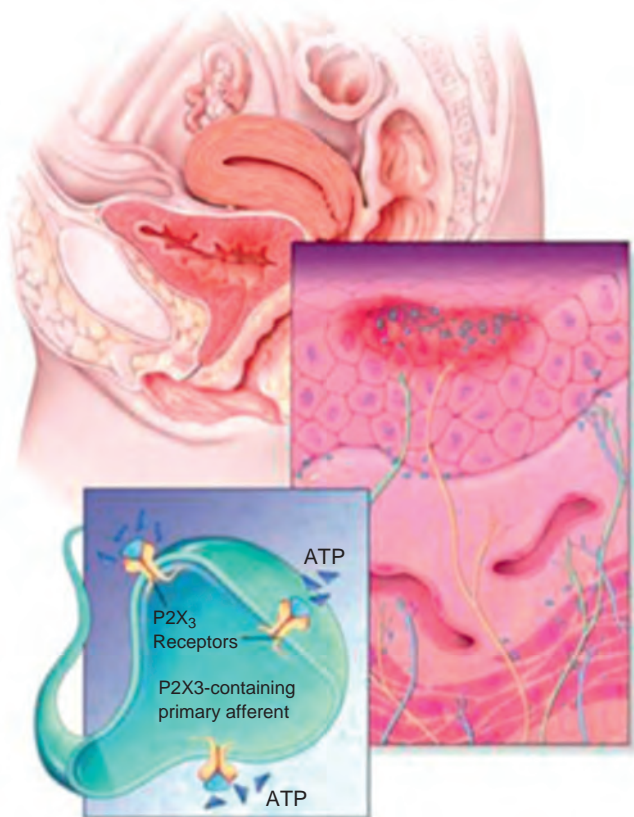


Figure 69-28. Morphology and wiring of the lower urinary tract (LUT). In the LUT, adenosine triphosphate (ATP) (shown as blue triangles) is present in large extracellular concentrations, is released by various cells including epithelia, fibroblasts, and smooth muscles, and can activate C-fiber afferent and promote sensitization. Release of ATP is augmented in conditions of stress, injury, inflammation, and infection. (From Ford AP, Udem BJ. The therapeutic promise of ATP antagonism at P2X3 receptors in respiratory and urological disorders. *Front Cell Neurosci* 2013;7:267.)

isothiocyanate (the pungent compound in mustard oil), allicin (garlic), cinnamaldehyde (in cinnamon), and acrolein (a metabolite of cyclophosphamide). TRPA1 also functions as a receptor-operated channel that can be activated by growth factors or proinflammatory peptides such as bradykinin, which increases intracellular Ca^{2+} levels using G protein-coupled receptors. TRPA1 is also expressed in the bladder and is particularly associated with C-fiber endings in the suburothelium that co-localize calcitonin gene-related peptide (CGRP). Agonists acting at the receptor cause bladder overactivity and are suggested to play a role in mechanotransduction and in signaling pain. TRPA1 has also been demonstrated in the urothelium at both transcriptional and protein levels. Expression is increased in a spinal cord injury model, and both pharmacologic blockade and RNA knockdown of TRPA1 were effective in normalizing bladder reflex function (Andrade et al, 2011).

TRPM8 is a member of the temperature-sensitive TRP channels that responds to cold temperature of less than 23°C . Pharmacologic agents that evoke cool sensation, such as menthol and ilicin, can activate TRPM8. Interest in its role in the bladder stems from the observation that instillation of cold saline into the bladder elicits a contractile response (at pressures or volumes below the threshold for normal voiding). This response to a cooling stimulus (which has been referred to as the *bladder cooling reflex*) was originally thought to indicate a supraspinal neurologic lesion, and the test (termed the *ice-water test*) has been used in the diagnosis of bladder disorders such as OAB and BOO (Chai et al, 1998). Expression of TRPM8 has been identified on bladder afferent fibers and on the cell bodies in the DRG where it co-localizes with nociceptive

markers such as CGRP and IB4 (Hayashi et al, 2009a). Previously Lashinger and colleagues (2008) showed that application of a TRPM8 channel blocker decreased voiding frequency and abdominal motor responses in the rat, suggesting that in addition to cold sensing, TRPM8 may also be involved in the afferent control of micturition and nociception.

Cannabinoids. The multicenter Cannabinoids in Multiple Sclerosis (CAMS) study reported that the use of cannabis-based extracts significantly improved symptoms of urge incontinence and DO in patients with multiple sclerosis. This observation has provoked interest in the study of expression and function of cannabinoid (CB) receptors in the bladder. In the human bladder, both receptors could be identified in the urothelium and detrusor, where CB1 receptors were more abundant than CB2 (Tyagi et al, 2009). In patients with BPS/IC and IDO, a significant increase in nerve fibers expressing CB1 in the urothelium was observed, strongly suggesting a role for CB1 in OAB (Mukerji et al, 2010). Functional experiments also found a reduction in distention-evoked afferent firing in response to application of a CB1 agonist. In particular, high-threshold afferents typically associated with noxious stimuli were directly affected. In contrast, Gratzke and colleagues (2009) found CB2 receptors predominated in the urothelium and suburothelium and on sensory nerve fibers and found that CB2 agonists inhibited nerve-induced contractions of the bladder, providing evidence that CB2 receptors are important in micturition. Taken together, these studies suggest that CB receptors in the bladder may have a modulatory role in sensory afferent signaling, a greater understanding of which could lead to new therapeutic strategies for treatment of bladder disorders.

Pelvic Organ Interactions: Crosstalk between Bladder and Bowel. Patients with irritable bowel syndrome (IBS) often report LUT symptoms including nocturia, frequent and urgent micturition, and incomplete emptying (Whorwell et al, 1986). The counterpart is also true with patients with BPS/IC who have bowel symptoms (Alagiri et al, 1997). These observations are consistent with the concept of cross-organ sensitization, which extends to different abdominal and pelvic structures and contributes to a more generalized chronic pelvic pain syndrome (Brumovsky and Gebhart, 2010). In experimental models, colonic inflammation has been shown to lead to increased frequency of bladder contractions and altered micturition reflexes (Pezzone et al, 2005). Similarly, experimental bladder inflammation has been reported to sensitize the bowel to distention (Bielefeldt et al, 2006). Such cross-organ sensitization has also been demonstrated among the uterus, pelvic urethra, and vagina. In men there is the potential for cross-organ sensitization between the prostate and other pelvic organs.

The mechanisms underlying cross-organ sensitization have not been fully elucidated, but there are potentially several levels at which the sensory innervation to the different pelvic structures can interact. In terms of peripheral mechanisms there is evidence that afferent fibers branch extensively to innervate multiple target structures. Axonal tracing studies using different retrograde tracers injected into the bladder and bowel reveal a number of DRG neurons carrying both labels, although the numbers are low. Similarly, dichotomizing afferents have been shown to innervate the colon and uterus with DRGs expressing TRPV1 and P2X₃ receptors, implying a role in nociception. Sensitization of the endings in one organ by local inflammation would likely affect overall sensitivity after upregulation in excitability in all terminal receptive fields. Central sensitization may also contribute to cross-organ sensitization. Excitability of spinal neurons receiving afferent input from the bladder has been shown to respond to afferent input from other pelvic structures such as the colon (Fig. 69-29) (Malykhina, 2007; Clemens et al, 2008). Second-order neurons in the spinal cord therefore receive convergent input from various visceral structures as well as somatic inputs. The latter explains the phenomenon of referred pain wherein sensations from the viscera are experienced in the associated somatic sensory field, the classic example being angina. Such viscerosomatic convergence has been extensively investigated, and only recently has viscerovisceral referral received attention. Nevertheless, convergent inputs would explain the poor

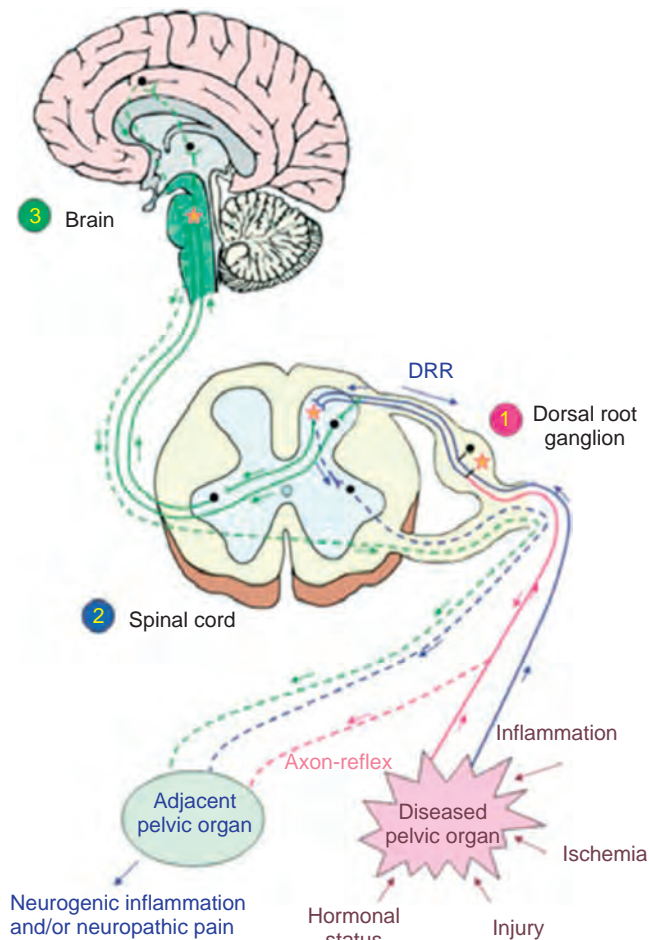


Figure 69-29. Schematic representation of convergent afferent pathways. 1, Convergence of sensory neural pathways within a dorsal root ganglion (red route). The propagation of noxious stimulus from a diseased pelvic organ to a normal adjacent structure occurs via dichotomizing afferents as a result of an “axon-reflex” mechanism. Axon-reflex–antidromic propagation of action potentials (APs) from dorsal root ganglion to the periphery. 2, Convergence of afferent information in the spinal cord (blue route). DRR refers to dorsal root reflexes (antidromic conduction via sensory fibers from the spinal cord to the periphery). Note that an output neuron belongs to the population of intermediolateral neurons (not motoneurons) localized mostly in laminae VI to VII. 3, Convergence of afferent inputs from two different pelvic organs in the brain (green route). Convergent neurons within the dorsal root ganglion, in the spinal cord, and in the brain are shown by star symbol. Orthodromic propagation of APs from pelvic organs to the points of convergence is depicted by solid lines and arrows in respective color for each route. Anterograde AP propagation from the brain, the spinal cord, and the dorsal root ganglion to the periphery is shown by dotted lines. (From Malykhina AP. Neural mechanisms of pelvic organ cross-sensitization. *Neuroscience* 2007;149:660–72.)

localization of pelvic pain and the difficulty in diagnosis and treatment.

Efferent Pathways to the Bladder

Three main neural pathways regulate LUT efferent activity: (1) Sacral parasympathetic (pelvic) nerves provide excitatory input to the bladder; (2) thoracolumbar sympathetic (hypogastric) nerves provide inhibitory input to the bladder and excitatory input to the bladder neck and urethra; and (3) sacral somatic (pudendal) nerves innervate the striated muscles of the sphincters and pelvic floor (Fig. 69-30) (Kluck, 1980). Parasympathetic postganglionic fibers termi-

KEY POINTS: AFFERENT PATHWAYS

- Studies of the properties of bladder afferents in the pelvic nerve, particularly in the rat, indicate that in-series tension receptors, volume receptors, and silent afferents (including nociceptors) are present.
- Intravesical irritant chemicals reduce the pressure thresholds of most of these endings, including the high-threshold receptors.
- A substantial proportion of the C-fiber afferent population is silent (i.e., insensitive to normal distention). However, these fibers become mechanosensitive after the action of various chemical mediators.
- During inflammation and possibly other pathologic conditions, there is recruitment of mechanosensitive C fibers that form a new functional afferent pathway. This is the rationale for intravesical C-fiber neurotoxin capsaicin and RTX therapy (Chancellor and de Groat, 1999).

nate predominantly at the detrusor muscle and release ACh, resulting in detrusor contraction during voiding. Studies in animals have shown that sympathetic postganglionic fibers release noradrenaline (NA) and contribute to bladder relaxation during storage (via stimulation of β -adrenergic receptors expressed in detrusor).

Terminal Nerve Fibers. Smooth muscle cells in the bladder are grouped into fascicles, several of which make up a muscle bundle. They receive a dense innervation, which runs in line with the axis of the fascicle and is derived from coarse nerve trunks in the connective tissue around the fascicles and bundles. This innervation mediates the widespread coordinated detrusor contraction accompanying voiding. The nerve supply is illustrated in Figure 69-6 (Maas et al, 2005), and the anatomic relationship between the preterminal innervation and the muscle fascicles has been described in a serial sectioning study in the human bladder (Drake et al, 2003).

The majority of nerves innervating the detrusor express acetylcholinesterase and vesicular acetylcholine transferase (VACHT) (Ek et al, 1977; Dixon et al, 1983; Maas et al, 2005) and are thought to be parasympathetic. EFS studies have been used to elucidate the neurotransmitter content from muscle strips (with or without the mucosa). ACh and ATP appear to provide the majority of the excitatory input, because EFS responses are blocked by muscarinic receptor antagonists combined with purinergic antagonists. Both transmitters are released in the innervated muscle layer and persist after mucosal removal. Apart from ACh and ATP, there are additional substances present in parasympathetic efferents (vasoactive intestinal polypeptide [VIP], NOS, galanin), which allow immunohistochemical subclassification of nerve fibers and raise the question as to whether additional transmitters (other than ACh and ATP) have a role in normal micturition function or disease pathophysiology. In addition, cholinergic nerves are also present in the suburothelium, where most also contain neuropeptide Y (NPY) and tyrosine hydroxylase and some also contain NOS. In the muscle of the trigone, the most common axons contain both VIP and NPY, with noradrenergic axons forming only a sparse supply. Indeed, noradrenergic neurons are rare in the detrusor and absent in the urothelium (Wanigasekara et al, 2003).

Spinal Ascending and Descending Influences:

Transmitters

Glutamate. Glutamate is present in the terminals of primary afferent neurons in the spinal cord along with interneurons and fibers originating in the medulla oblongata. In general, glutamatergic neurons tend to be excitatory, contrasting with generally inhibitory effects of glycinergic neurons; however, excitatory and inhibitory effects of transmitters can be reversed by the nature of the postsynaptic neuron. Thus, glutamatergic neurons can indirectly have an inhibitory effect if an inhibitory neuron is interposed before the ultimate target (de Groat and Yoshimura, 2001). Glutamate acts on spinal neurons through a variety of receptor subtypes

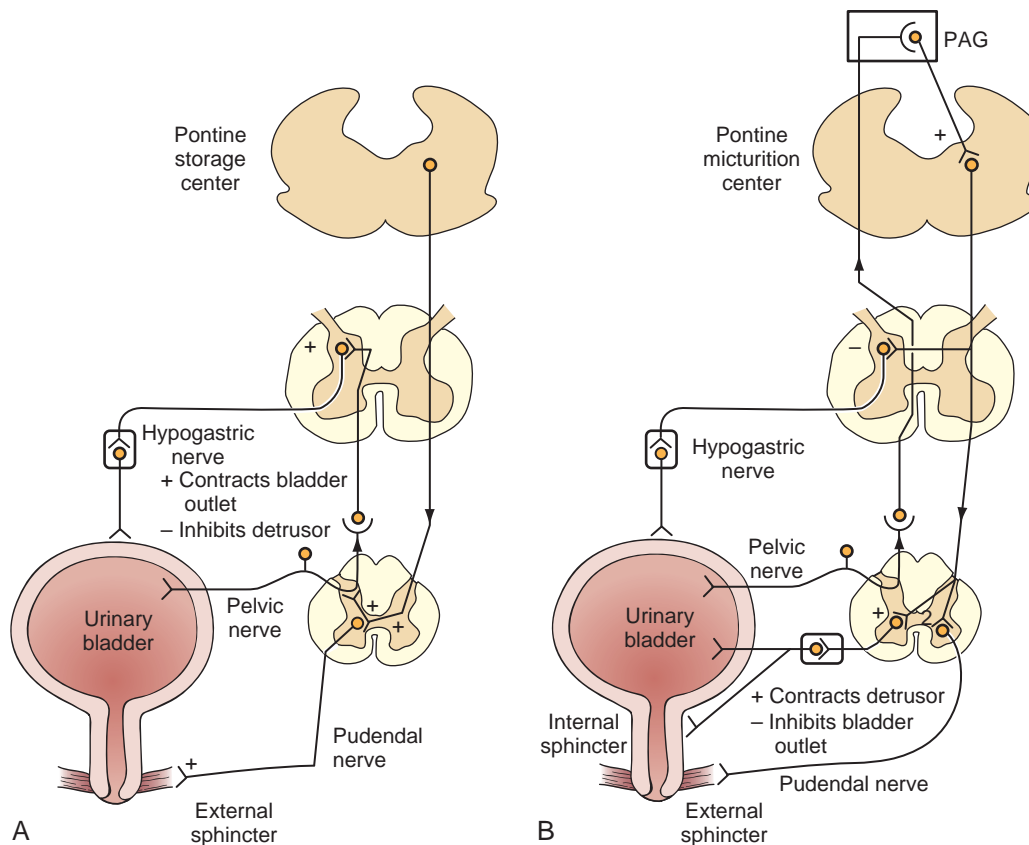


Figure 69-30. Mechanism of storage and voiding reflexes. **A, Storage reflexes.** During the storage of urine, distention of the bladder produces low-level bladder afferent firing. Afferent firing, in turn, stimulates the sympathetic outflow to the bladder outlet (base and urethra) and pudendal outflow to the external urethral sphincter. These responses occur by spinal reflex pathways and represent “guarding reflexes,” which promote continence. Sympathetic firing also inhibits detrusor muscle and transmission in bladder ganglia. **B, Voiding reflexes.** At the initiation of micturition, intense vesical afferent activity activates the brainstem micturition center, which inhibits the spinal guarding reflexes (sympathetic and pudendal outflow to the urethra). The pontine micturition center also stimulates the parasympathetic outflow to the bladder and internal sphincter smooth muscle. Maintenance of the voiding reflex is through ascending afferent input from the spinal cord, which may pass through the periaqueductal gray matter (PAG) before reaching the pontine micturition center.

including *N*-methyl-D-aspartate (NMDA) receptors, which are important in controlling polysynaptic reflex pathways at the lumbosacral levels (Fig. 69-31). With aging, there is a decrease in the density of glutamatergic synaptic inputs, which may influence urinary tract function (Ranson et al, 2007).

Glycine and γ -Aminobutyric Acid. Glycinergic and GABAergic interneurons have a major role in neural control processes mediating bladder function (Shefchyk, 2002). Glycinergic and GABAergic projections to the lumbosacral cord inhibit the micturition reflex and also inhibit glutamatergic neurons (Miyazato et al, 2013). Clinically, DO can be inhibited by GABA receptor activation (Miyazato et al, 2008b, 2008c). Rectal distention prolongs the interval, decreases the amplitude, and shortens the duration of bladder contractions in rats; this effect is not seen after simultaneous intrathecal injection of low-dose strychnine (a selective glycine-receptor antagonist) and bicuculline (GABA-A receptor antagonist), suggesting that the inhibitory rectovesical reflex involves glycinergic and GABAergic mechanisms in the lumbosacral spinal cord, which may be synergistic (Miyazato et al, 2004).

Serotonin. Spinal reflex circuits involved in voiding function have a dense serotonergic (5-hydroxytryptamine [5-HT]) innervation (de Groat, 2002). Immunocytochemical studies in rats, cats, and primates show that lumbosacral sympathetic and parasympathetic autonomic nuclei receive serotonergic inputs from the raphe nuclei

(Mizukawa, 1980; Kojima et al, 1983; Skagerberg and Bjorklund, 1985; Rajaofetra et al, 1992). Activation of the central serotonergic system can suppress voiding by inhibiting the parasympathetic excitatory input to the urinary bladder, and 5-HT elicits a prolonged activation of thoracic sympathetic preganglionic neurons. Stimulation of the raphe nuclei in the cat inhibits reflex bladder activity (McMahon and Spillane, 1982; Chen et al, 1993; Sugaya et al, 1998). 5-HT_{1A} and 5-HT₂ receptors are present in the sacral parasympathetic nucleus. However, in different species, serotonin (5-HT) may have varying functions in the central nervous control of bladder activity. For example, activation of 5-HT_{1A} receptors facilitates reflex bladder activity in rats (Lecci et al, 1992; de Groat, 2002) and has been used to reverse the effects of diabetes mellitus (Gu et al, 2012).

Duloxetine, a combined norepinephrine and 5-HT reuptake inhibitor (Sharma et al, 2000), has been shown, in a bladder-irritated model, to increase the neural activity of both the urethral sphincter and the bladder (Thor and Katofiasc, 1995; Thor and Donatucci, 2004). Duloxetine appears to have effects on both the bladder and the sphincter and has been proposed for treatment of both stress incontinence and urgency incontinence (Cannon et al, 2003; Thor and Donatucci, 2004). Duloxetine increases the neural activity to the EUS and decreases bladder activity through effects on the CNS in cats (Thor and Donatucci, 2004). In a rat study, duloxetine also enhances the urethral continence reflex

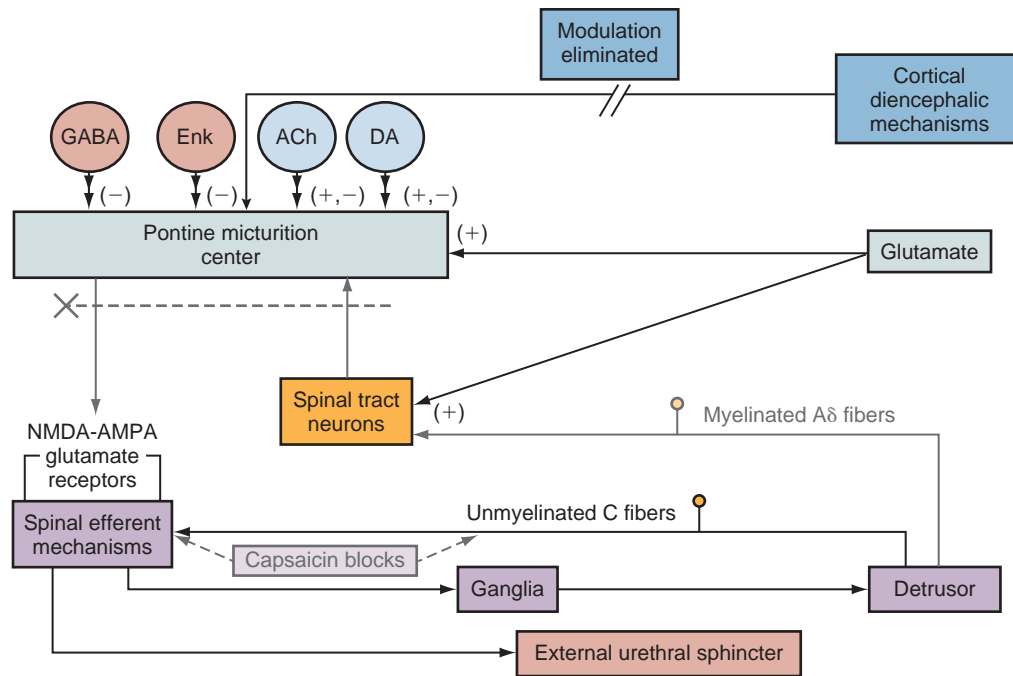


Figure 69-31. Diagram of the central reflex pathways that regulate micturition in the cat. Normally, micturition is initiated by a supraspinal reflex pathway passing through the pontine micturition center (PMC) in the brainstem. The pathway is triggered by myelinated afferents (A δ) connected to tension receptors in the bladder wall (detrusor). Spinal tract neurons carry information to the brain. During micturition, pathways from the PMC activate the parasympathetic outflow to the bladder and inhibit the somatic outflow to the urethral sphincter. Transmission in the PMC is modulated by cortical-diencephalic mechanisms. Interruption of these mechanisms leads to bladder instability. In spinal cord-transected animals, connections between the brainstem and the sacral spinal cord are interrupted and micturition is initially blocked. In animals with chronic spinal cord injury, a spinal micturition reflex emerges that is triggered by unmyelinated (C-fiber) bladder afferents. The C-fiber reflex pathway is usually weak or undetectable in animals with an intact nervous system. Stimulation of the C-fiber bladder afferents by instillation of ice water into the bladder (cold stimulation) activates voiding reflexes in patients with spinal cord injury. Capsaicin (20 to 30 mg/kg subcutaneously) blocks the C-fiber reflexes in cats with chronic spinal cord injury but does not block micturition reflexes in intact cats. Intravesical capsaicin also suppresses bladder instability and cold-evoked reflexes in patients with neurogenic bladder dysfunction. Glutamic acid is the principal excitatory transmitter in the ascending and descending limbs of the micturition reflex pathway, as well as in the reflex pathway controlling sphincter function. Glutamate acts on both *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamatergic receptors. Other neurotransmitters that regulate transmission in the micturition reflex pathway include γ -aminobutyric acid (GABA), enkephalins (Enk), acetylcholine (ACh), and dopamine (DA). Acetylcholine and dopamine have both excitatory and inhibitory effects on the pathway: excitatory (+) and inhibitory (-) synapse.

during sneezing as evidenced by an increase in sneeze-induced pressure responses at the middle urethra, although the effect appears to be mainly mediated by α_1 adrenoceptors (Miyazato et al, 2008a).

Adrenergic Transmitters. Descending catecholaminergic neurons are primarily located in the upper medulla or pons (Ranson et al, 2003). In clinical use, nonselective α_1 -adrenergic antagonists influence urine flow and LUTS; the two effects probably occur by different mechanisms, and central or peripheral locations may be responsible (Somogyi et al, 1995). Reflex bladder activity is modulated by at least two spinal α_1 -adrenergic mechanisms. Firstly, there is inhibitory control of reflex bladder contractions, probably by modulation of afferent processing. Second, there is excitatory modulation of the amplitude of bladder contractions as a result of regulation of the descending glutamatergic limb of the spinobulbospinal bladder reflex pathway (de Groat et al, 1999; Yoshiyama et al, 2000). α_{1A} Adrenoceptors constitute 70% and α_{1B} adrenoceptors constitute 30% of the α -adrenergic receptors in the rat lumbar spinal cord (Wada et al, 1996), whereas α_{1D} adrenoceptors do not appear to have a significant role.

Blood pressure, vascular resistance, and tissue blood flow are also regulated by α -adrenergic receptors. Aging is thought to affect pelvic blood flow and thus bladder function. Pharmacologic blockade of the vascular α_{1B} adrenoceptor may increase pelvic blood flow and contribute to an improvement in bladder dysfunctions associated with aging and/or hypertension (Yono et al, 2011). β_3 Adrenoceptors, although well documented peripherally, are also present at a number of sites peripherally as well as in the rat sacral spinal cord. A number of studies have demonstrated that these agonists (via effects on bladder afferents and detrusor smooth muscle) may be a promising treatment for OAB (Chapple et al, 2014).

Purinergic Transmitters. ATP acting via purinergic receptors modulates bladder function mediated by both afferent and efferent pathways involved in urine storage and emptying. ATP is released together with NA and NPY from sympathetic nerves. It is also released as a cotransmitter with ACh from parasympathetic nerves supplying the bladder. Cotransmission likely offers subtle, local variations in neurotransmission and neuromodulation

mechanisms (Burnstock, 2009). Purinergic contribution to parasympathetic stimulation has been shown to exist in a variety of species including rat, rabbit, and guinea pig (Burnstock et al, 1972; Chancellor et al, 1992; Burnstock, 1996). In contrast, there is less evidence that purinergic neurotransmission exists in humans, at least regarding normal responses to stimulation, but it may play a role in pathologic conditions such as DO or BOO (Palea et al, 1993; Burnstock, 2001b; O'Reilly et al, 2001a).

ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G protein–coupled receptor family (P2Y) (Inoue and Brading, 1990; Inoue and Gabella, 1991; McMurray et al, 1997). Seven P2X subtypes and eight P2Y subtypes have been identified. Analysis of the structure-activity relationships of a series of excitatory purinergic agonists on the guinea pig bladder revealed an order of potency consistent with P2X₁ or P2X₂ receptors (Burnstock, 2001a; Zhong et al, 2001). In other species various studies suggested that multiple purinergic excitatory receptors are present in the bladder (Burnstock, 2001b).

Immunohistochemical experiments with specific antibodies for different P2X receptors showed that P2X₁ receptors are the dominant subtype in membranes of rat detrusor muscle and vascular smooth muscle in the bladder (Lee et al, 2000). The predominant expression of P2X₁ receptors has also been confirmed in the human bladder (O'Reilly et al, 2001a, 2001b). Investigators also found that the amount of P2X₁ receptors was increased in the obstructed bladder compared with the control bladder, suggesting upregulated purinergic mechanisms mediating OAB due to BOO (O'Reilly et al, 2001a).

KEY POINTS: SPINAL CIRCUITRY NEUROTRANSMITTERS

- Glutamate plays an important role in the spinal efferent circuitry supporting micturition.
- The spinal noradrenergic system, mediated by α_1 adrenoceptors, has a modulatory role in controlling micturition by inhibiting afferent inputs from the bladder and facilitating the descending limb of the spinal micturition reflex to increase bladder contractility.
- Transmitters such as 5-HT, purines, glycine, and GABA appear to selectively modulate the volume threshold by actions in the sacral spinal cord. The role of other potential excitatory transmitters remains to be examined.
- These mechanisms seem to be favorable for development of novel drug therapies.
- Glutamate appears to be involved as an excitatory transmitter in the supraspinal circuitry controlling micturition.
- Glutamate may also be a mediator of DO after neural injury.
- Several substances can exert significant modulatory influences on the supraspinal circuits (see Fig. 69-31) and can have dramatic influences on micturition.
- The receptors for these substances represent potential sites for therapeutic intervention.

Reflex Circuitry Controlling Continence and Micturition. Multiple reflex pathways organized in the brain and spinal cord mediate coordination between the urinary bladder and the urethra. The central pathways controlling LUT function are organized as simple on-off switching circuits (Fig. 69-32) that maintain a reciprocal relationship between the urinary bladder and the urethral outlet (de Groat, 1975; de Groat et al, 1993). Some reflexes promote urine storage, whereas others facilitate voiding (see Fig. 69-30). It is also possible that individual reflexes might be linked together in a serial manner to create complex feedback mechanisms. For example, the bladder-to-EUS guarding reflex that triggers sphincter contractions during bladder filling could, in turn, activate sphincter muscle afferents that initiate an inhibition of

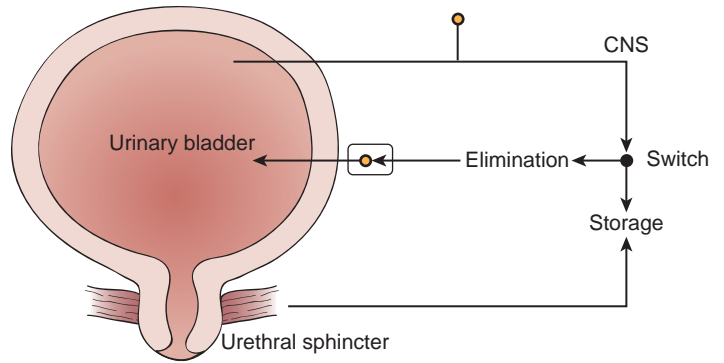


Figure 69-32. Diagram illustrating the anatomy of the lower urinary tract and the “switchlike” function of the micturition reflex pathway. During urine storage, a low level of afferent activity activates efferent input to the urethral sphincter. A high level of afferent activity induced by bladder distention activates the switching circuit in the central nervous system (CNS), producing firing in the efferent pathways to the bladder, inhibition of the efferent outflow to the sphincter, and urine elimination.

the parasympathetic excitatory pathway to the bladder. Thus a bladder-to-sphincter-to-bladder reflex pathway could, in theory, contribute to the suppression of bladder activity during urine storage. Alterations in these primitive reflex mechanisms may contribute to neurogenic bladder dysfunction. Direct activation of these reflexes by electric stimulation of the sacral spinal roots very likely contributes to therapeutic effects of sacral nerve root neuromodulation (Dijkema et al, 1993; Chancellor and Chartier-Kastler, 2000).

Storage Phase of the Bladder. Intravesical pressure measurements during bladder filling in both humans and animals reveal low and relatively constant bladder pressures when bladder volume is below the threshold for inducing voiding (Fig. 69-33). The accommodation of the bladder to increasing volumes of urine is dependent on the intrinsic properties of the vesical smooth muscle and stroma, as well as the quiescence of the parasympathetic efferent pathway (Torrens and Morrison, 1987; de Groat et al, 1993; Yoshimura et al, 2008). In addition, the urothelium also plays an important role in accommodating urine storage via changes in the apical (umbrella) cell membrane and release of a number of neuromediators that can influence bladder smooth muscle tone (Wang et al, 2005). The bladder sympathetic reflex also contributes as a negative feedback or urine storage mechanism that promotes closure of the urethral outlet and inhibits neurally mediated contractions of the bladder during bladder filling (de Groat and Theobald, 1976) (Table 69-3). Reflex activation of the sympathetic outflow to the LUT can be triggered by afferent activity induced by distention of the urinary bladder (de Groat and Theobald, 1976; de Groat et al, 1993). This reflex response is organized in the lumbosacral spinal cord and persists after transection of the spinal cord at the thoracic levels (Fig. 69-34). However, this bladder sympathetic mechanism to suppress bladder contractions during urine storage may be weak in humans, given that bilateral retroperitoneal lymph node dissection, in which the sympathetic chains are destroyed, results in no discernible alteration of filling or storage function in humans.

During bladder filling, the activity of the sphincter electromyogram also increases (see Fig. 69-33), reflecting an increase in efferent firing in the pudendal nerve and an increase in outlet resistance that contributes to the maintenance of urinary continence. Pudendal motoneurons are activated by bladder afferent input (the guarding reflex) (Park et al, 1997), whereas during micturition the motoneurons are reciprocally inhibited (de Groat et al, 1993). EUS motoneurons are also activated by urethral or perineal afferents in the pudendal nerve (Fedirchuk et al, 1992). This reflex may represent, in part, a continence mechanism that is activated by proprioceptive afferent input from the urethra or pelvic

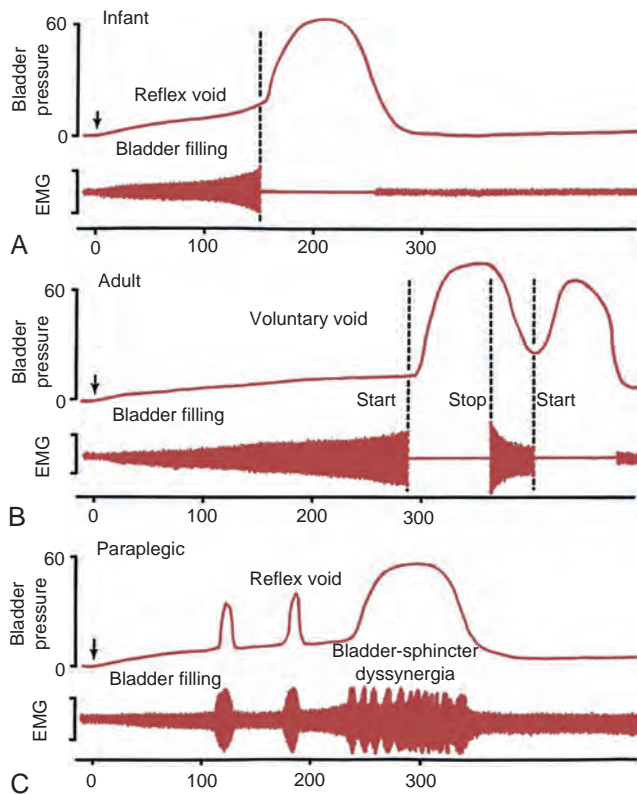


Figure 69-33. Combined cystometrograms and sphincter electromyogram (EMG) comparing reflex voiding responses in an infant (A) and in a paraplegic patient (C) with a voluntary voiding response in an adult (B). The x-axis in all records represents bladder volume in milliliters, and the y-axis represents bladder pressure in centimeters of water and electrical activity of the electromyographic recording. On the left side of each trace, the arrows indicate the start of a slow infusion of fluid into the bladder (bladder filling). Vertical dashed lines indicate the start of sphincter relaxation that precedes by a few seconds the bladder contraction in A and B. In B, note that a voluntary cessation of voiding (stop) is associated with an initial increase in sphincter electromyographic activity followed by a reciprocal relaxation of the bladder. A resumption of voiding is again associated with sphincter relaxation and a delayed increase in bladder pressure. On the other hand, in the paraplegic patient (C), the reciprocal relationship between bladder and sphincter is abolished. During bladder filling, transient uninhibited bladder contractions occur in association with sphincter activity. Further filling leads to more prolonged and simultaneous contractions of the bladder and sphincter (bladder-sphincter dyssynergia). Loss of the reciprocal relationship between bladder and sphincter in paraplegic patients interferes with bladder emptying. (From de Groat WC. Basic neurophysiology and neuropharmacology. In: Abrams P, Khoury S, Wein A, editors. Incontinence. Plymouth [U.K.]: Health Publications; 1999. p. 112.)

floor and that induces closure of the urethral outlet. These excitatory sphincter reflexes are organized in the spinal cord. Inhibition of EUS reflex activity during micturition is dependent, in part, on supraspinal mechanisms, because it is weak or absent in chronically spinalized animals and humans, resulting in simultaneous contractions of bladder and sphincter (i.e., detrusor-sphincter dyssynergia) (Rossier and Ott, 1976; Blaivas, 1982).

Sphincter to Bladder Reflexes. It is well known that stimulation of somatic afferent pathways projecting in the pudendal nerve to the caudal lumbosacral spinal cord can inhibit voiding function. The inhibition can be induced by activation of afferent input from various sites, including the penis, vagina, rectum, perineum, urethral sphincter, and anal sphincter (de Groat et al, 1979, 1993, 2001). Electrophysiologic studies in cats showed that the inhibition was mediated by suppression of interneuronal pathways in the

sacral spinal cord and also by direct inhibitory input to the parasympathetic preganglionic neurons (de Groat et al, 1982).

On the basis of experiments in the laboratory and the review of medical literature, contractions of the EUS, and possibly other pelvic floor striated muscles, are likely to stimulate firing in muscle proprioceptive afferents, which then activate central inhibitory mechanisms to suppress the micturition reflex (see Fig. 69-33). A similar inhibitory mechanism has been identified in monkeys by directly stimulating the anal sphincter muscle (McGuire et al, 1983). In monkeys, at least part of the inhibitory mechanism must be localized in the spinal cord, because it persisted in T4 chronically paraplegic animals.

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Somatic to Visceral Reflexes. There is evidence that stimulation of the sacral nerve roots using implanted electrodes (sacral neuromodulation) may be effective in patients with refractory OAB as well as in nonobstructive urinary retention, in patients refractory to conventional methods. Though the specific site of action is still unknown, various mechanisms have been described including the modulation of CNS pathways (including somatic afferent inhibition of sensory processing) and the restoration of brainstem autoregulation (Leng and Chancellor, 2005; Thompson et al, 2010). Although more comprehensive evaluation is needed, another method that has been used as effective treatment for OAB and nonobstructive urinary retention is posterior tibial nerve stimulation (PTNS). Studies in anesthetized cats revealed that continuous tibial nerve stimulation (TNS) inhibited bladder activity that persisted after termination of the stimulus (Tai et al, 2011), suggesting a role for treatment in bladder overactivity. In addition, this group also found evidence that an interaction between opioid and metabotropic glutamate receptor mechanisms may play a role in mechanisms underlying TNS-induced inhibition of bladder overactivity (Matsuta et al, 2013).

Emptying Phase of the Bladder. The storage phase of the bladder can be switched to the voiding phase either involuntarily (reflexively) or voluntarily. The former is readily demonstrated in the human infant or in patients with neuropathic bladder when the bladder wall tension caused by increased volume of urine exceeds the micturition threshold. At this point, increased afferent firing from tension receptors in the bladder reverses the pattern of efferent outflow, producing firing in the sacral parasympathetic pathways and inhibition of sympathetic and somatic pathways. The expulsion phase consists of an initial relaxation of the urethral sphincter (see Fig. 69-33) followed in a few seconds by a contraction of the bladder, an increase in bladder pressure, and the flow of urine. Relaxation of the urethral smooth muscle during micturition is mediated by activation of a parasympathetic pathway to the urethra that triggers the release of NO, an inhibitory transmitter (Andersson, 1993), and by removal of excitatory inputs to the urethra. Secondary reflexes elicited by flow of urine through the urethra facilitate bladder emptying (Torrens and Morrison, 1987; de Groat et al, 1993; Jung et al,

TABLE 69-3 Reflexes to the Lower Urinary Tract

AFFERENT PATHWAY	EFFERENT PATHWAYS	CENTRAL PATHWAY
URINE STORAGE Low-level vesical afferent activity (pelvic nerve)	External sphincter contraction (somatic nerves) Internal sphincter contraction (sympathetic nerves) Detrusor inhibition (sympathetic nerves) Ganglionic inhibition (sympathetic nerves) Sacral parasympathetic outflow inactive	Spinal reflexes
MICTURITION High-level vesical afferent activity (pelvic nerve)	Inhibition of external sphincter activity Inhibition of sympathetic outflow Activation of parasympathetic outflow to the bladder Activation of parasympathetic outflow to the urethra	Spinobulbospinal reflex

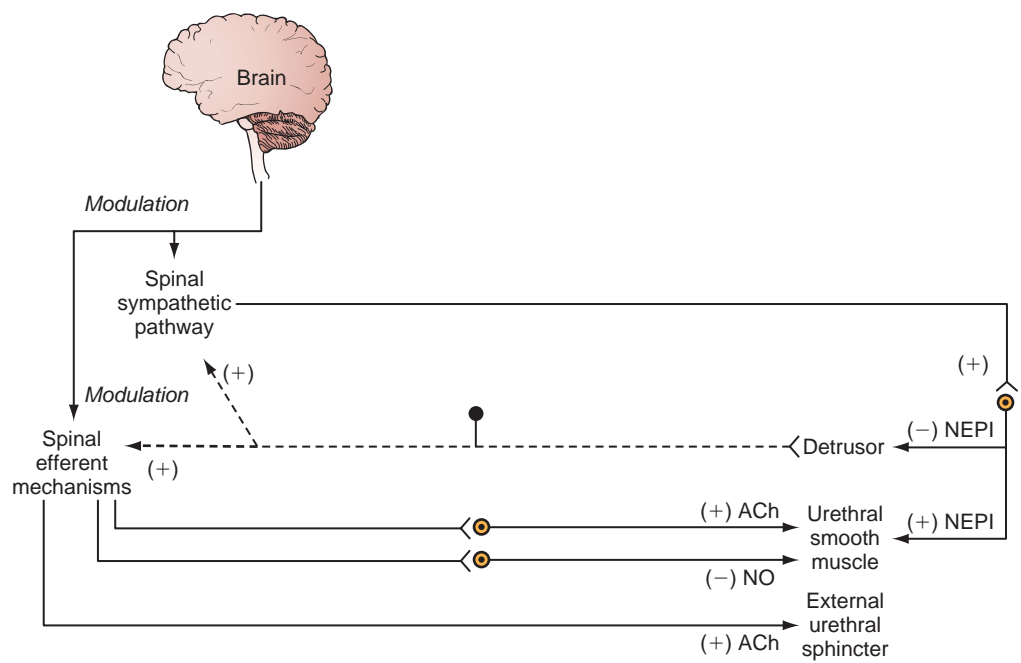


Figure 69-34. Diagram showing bladder to urethra reflex pathways. Afferent pathway (dashed line) from the detrusor activates spinal reflex mechanisms that induce firing in somatic cholinergic nerves to the external urethral sphincter, sympathetic adrenergic nerves to the urethral smooth muscle, and cholinergic and nitrergic nerves to the urethral smooth muscle. Bulbospinal pathways from the brain can modulate these spinal reflex mechanisms. ACh, acetylcholine; NEPI, norepinephrine; NO, nitric oxide; +, excitatory mechanism; –, inhibitory mechanism.

1999). These reflexes require the integrative action of neuronal populations at various levels of the neuraxis. The parasympathetic outflow to the detrusor and urethra has a more complicated central organization involving spinal and spinobulbospinal pathways passing through a micturition center in the pons (pontine micturition center [PMC]).

Urethra to Bladder Reflexes. A landmark in the historical progress of neurobiology is the contribution of Barrington. Using his keen observational skills, Barrington (1931, 1941) reported that urine flow or mechanical stimulation of the urethra with a catheter could excite afferent nerves that, in turn, facilitated reflexive bladder contractions in the anesthetized cat (see Fig. 69-35). He proposed that this facilitatory urethra-to-bladder reflex could promote complete bladder emptying. Barrington identified two components of this reflex. One component was activated by a somatic afferent pathway in the pudendal nerve and produced facilitation by a supraspinal mechanism involving the PMC (see Fig. 69-35) (Bar-

rington, 1931). Studies have confirmed the existence of this type of reflex by the pudendal nerve because low-frequency electric stimulation of afferent axons in the pudendal nerve in humans, or the deep perineal nerve (a caudal branch of the pudendal nerve) in cats, can initiate reflexive bladder contractions and voiding (Shefchyk and Buss, 1998; Boggs et al, 2005). The other component was activated by a visceral afferent pathway in the pelvic nerve and produced facilitation by a spinal reflex mechanism (Barrington, 1941).

Studies in the anesthetized rat have also provided additional support for Barrington's findings (Dokita et al, 1991). Measurements of reflexive bladder contractions, under isovolumetric conditions during continuous urethral perfusion (0.075 mL/min), revealed that the frequency of micturition reflexes was significantly reduced when urethral perfusion was stopped or after infusion of lidocaine (1%) into the urethra. Intraurethral infusion of NO donors (S-nitroso-N-acetylpenicillamine [SNAP] or nitroprusside, 1 to 2 mM) markedly decreased urethral perfusion pressure

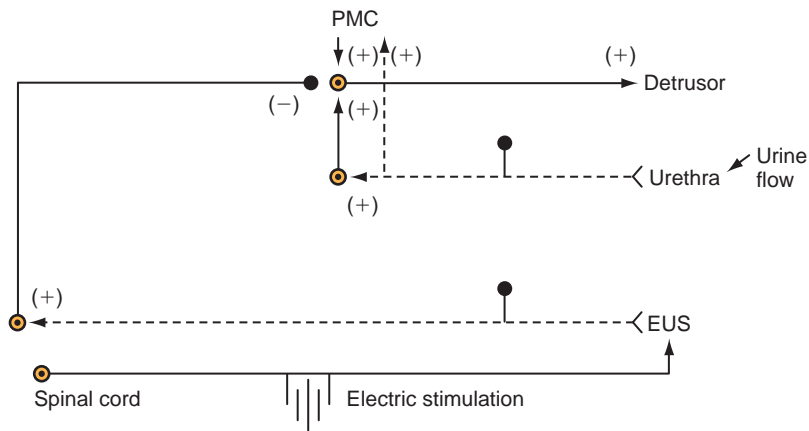


Figure 69-35. Urethra to bladder reflexes. Activity in afferent nerves (dashed lines) from the urethra can facilitate parasympathetic efferent outflow to the detrusor by means of a supra-spinal pathway passing through the pontine micturition center (PMC), as well as a spinal reflex pathway. Afferent input from the external urethral sphincter (EUS) can inhibit parasympathetic outflow to the detrusor through a spinal reflex circuit. Electric stimulation of motor axons in the S1 ventral root elicits an EUS contraction and EUS afferent firing that, in turn, inhibits reflex bladder activity. +, excitatory mechanism; –, inhibitory mechanism.

(approximately 30%) and decreased the frequency of reflex bladder contractions (45% to 75%) but did not change the amplitude of bladder contractions (Fig. 69-36). Desensitization of the urethral afferent with intraurethral capsaicin also dramatically altered the micturition reflex (Fig. 69-37). It was concluded that activation of urethral afferents during urethral perfusion could modulate the micturition reflex in the rat.

Supraspinal Pathways

Pontine Micturition Center and Brainstem Modulatory Mechanisms. The integral role of the brainstem in bladder function was initially realized by the demonstration in cats that micturition was abolished by lesions at the level of the inferior colliculus, whereas lesions anterior to the colliculus facilitated micturition, presumably by removing inhibitory influences (Barrington, 1921, 1925). Anatomic and physiologic studies in both rat and cat have delineated midbrain–pontine–spinal cord circuits in reflexes controlling filling, storing and emptying of the bladder (Fig. 69-38). The roles of pontine nuclei revealed by animal models translate well to humans as indicated by brain imaging during micturition (Fukuyama et al, 1996; Blok et al, 1997; Kershen et al, 2003) and clinical cases showing that specific pontine lesions can result in either bladder continence or incontinence problems (Fukuyama et al, 1996; Sakakibara et al, 1996; Charil et al, 2003).

The dorsal pontine tegmentum has been firmly established as an essential control center for micturition in normal subjects. First described by Barrington (1921), it has subsequently been called the *Barrington nucleus*, the *pontine micturition center* (Blok and Holstege, 1997) or the *M region* (Blok and Holstege, 1996; Holstege et al, 1996) because of its medial location. In 1925 Barrington was the first to describe a pontine control center for micturition in the cat after lesion studies (Barrington, 1921, 1925). This region was better localized to a nucleus in the dorsal pons (now termed the *Barrington nucleus*) using more discrete lesions that abolished micturition and caused urinary retention in cats and rats (Tang, 1955; Satoh et al, 1978). Lesions in humans as a result of stroke or multiple sclerosis in an analogous region similarly result in urinary retention (Komiya et al, 1998).

Physiologic studies have confirmed the role of the Barrington nucleus in micturition. Both electrical and chemical activation of Barrington nucleus neurons in rats and cats initiates bladder contractions and relaxes the urethral sphincter (Holstege et al, 1986; Mallory et al, 1991; Pavcovich and Valentino, 1995; Tanaka et al, 2003). Precise mapping of sites at which chemical stimulation

elicits bladder contractions demonstrates a well-defined area localized to the Barrington nucleus (Pavcovich and Valentino, 1995). Single unit recordings in rat pons revealed three types of responses to bladder contraction: an excitation that occurred only before contraction, an excitation that occurred before and was maintained during contraction, and an inhibition during contraction (Tanaka et al, 2003). Neurons that were activated just before contraction and that maintained activation during contraction were found in Barrington nucleus whereas the other two types of neurons were scattered throughout the pontine tegmentum.

Micturition also requires an inhibition of the urethral sphincter to be coordinated with detrusor contraction. The striated urethral sphincter (rhabdosphincter) is controlled by the interaction between upper motor neurons and the lower motoneurons of the Onuf nucleus. Barrington nucleus neurons do not project to Onuf nucleus. Rather, in the cat a diffuse region ventrolateral to Barrington nucleus, termed the *L-region*, is thought to provide pontine control of sphincter function through its projections to Onuf nucleus (Holstege et al, 1979). For coordination between the detrusor and sphincter, there should be some form of reciprocal communication between these regions. However, a lack of connections between Barrington nucleus and the L-region argue against sphincter regulation by Barrington nucleus through this route (Blok and Holstege, 1999). Rather, it has been proposed that Barrington nucleus indirectly inhibits Onuf nucleus neurons through excitatory projections to GABA premotor interneurons in the dorsal gray commissure (Blok and Holstege, 1999). In addition, Barrington nucleus projections onto inhibitory interneurons located in the intermediolateral cell column at the sacral segmental level have been described and may provide an inhibitory influence over Onuf nucleus; both glycine and GABA are thought to play a role here (Blok and Holstege, 1998; Sie et al, 2001). Together, the anatomic and physiologic findings just described point to Barrington nucleus as being the command center for initiating and orchestrating the act of bladder emptying.

Central Circuitry Regulating Bladder Function by Transneuronal Tracing. Transneuronal retrograde tracing from end organs with pseudorabies virus (PRV) has been an invaluable tool in delineating the central circuitry that regulates visceral function (Loewy, 1998). The population of rat brain neurons labeled from PRV injections in either the bladder wall or urethra of the rat exhibits an overlap and similar time course of labeling, supporting a close coordination of detrusor and urethral muscle function by brain circuits as previously suggested (Nadelhaft et al, 1992; Vizzard et al, 1995; Nadelhaft and Vera, 1996; Marson, 1997). The first neurons

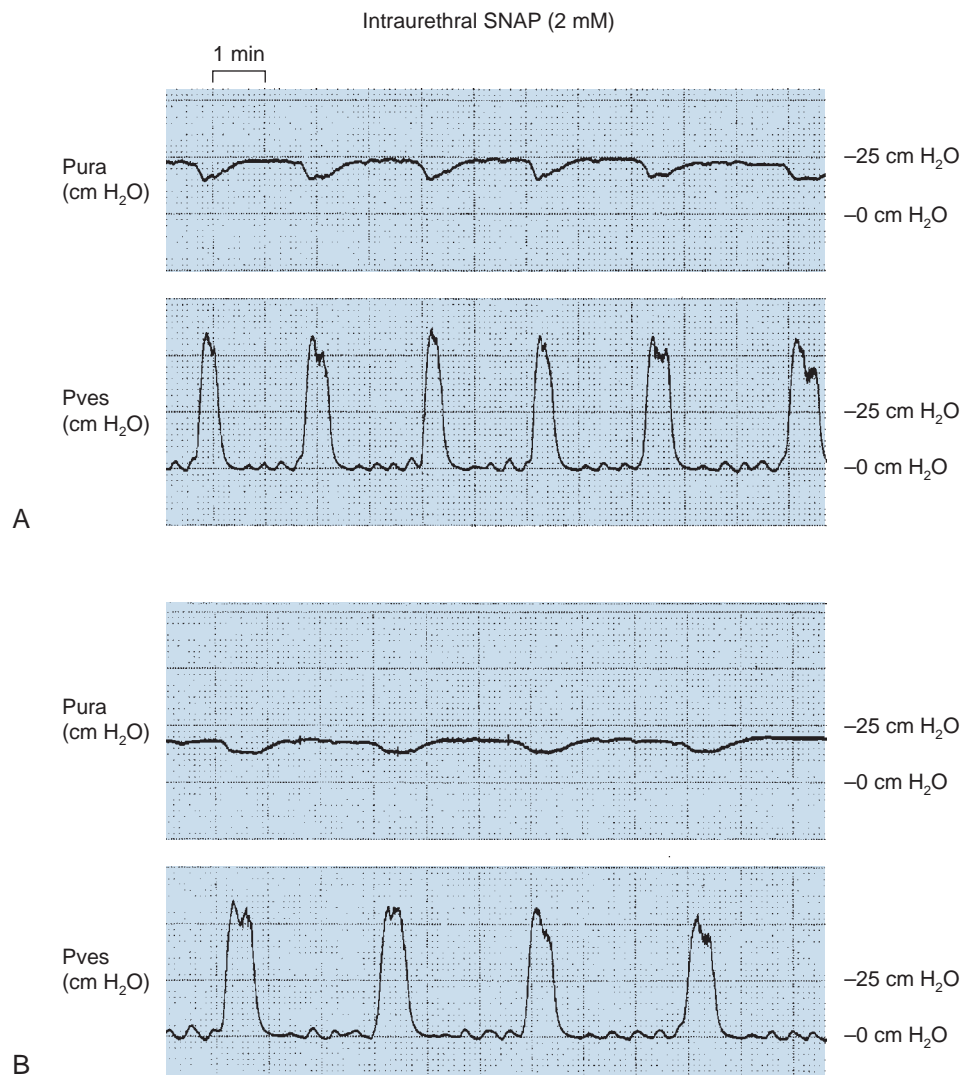


Figure 69-36. Effects of intraurethral S-nitroso-N-acetylpenicillamine (SNAP) on the bladder pressure (Pves) and urethral pressure (Pura) in normal female rats. **A,** Before treatment. **B,** After intraurethral administration of SNAP (2 mM). Urethral perfusion pressure immediately decreased. In addition, bladder contraction frequency was significantly decreased. The duration of reflexive urethral relaxation was increased. (From Jung SY, Fraser MO, Ozawa H, et al. Urethral afferent nerve activity affects the micturition reflex: implication for the relationship between stress incontinence and detrusor instability. *J Urol* 1999;162:204–12.)

to be labeled in brain from bladder or urethra and therefore the most direct links to the spinal efferents are the ventral medullary raphe, parapyramidal reticular formation, A5, and Barrington nucleus. The periaqueductal gray (PAG), hypothalamus, and medial preoptic nucleus, which are prominent afferents to Barrington nucleus, are labeled at a slightly later time when the locus ceruleus (LC), cortex, and red nucleus are also labeled. It is interesting to note that PRV labeling from other pelvic viscera including the distal colon yields a similar pattern and time course, suggesting a certain degree of central coordination of these functions (Marson and Carson, 1999; Rouzade-Dominguez et al, 2003).

The PRV studies provide information regarding some hierarchy of neurons that is anatomically linked to the bladder and/or urethra. However, the PRV technique does not imply precise information about connectivity or functionality. This must be delineated by additional tract tracing between putatively connected brain nuclei and physiologic studies. For example, studies in humans indicate that voluntary control of voiding is dependent on connections between the frontal cortex and the septal-preoptic region of the hypothalamus, as well as on connections between the paracentral lobule and the brainstem. Lesions to these areas of cortex appear

to directly increase bladder activity by removing cortical inhibitory control (de Groat et al, 1993). Of the brain regions that are initially labeled with PRV from the bladder or urethra, most anatomic, electrophysiologic, and imaging studies to date have implicated the Barrington nucleus as pivotal in regulating bladder function in both animals and man.

Neurotransmitters and Modulators within Brainstem Networks. Knowledge of the neurochemical signals within the central circuits controlling micturition is important for understanding how these circuits function and how they can be manipulated for the treatment of bladder dysfunctions. These were reviewed in detail by Holstege (2005) and by Fowler and colleagues (2008). Much of the current knowledge is based on studies using cats; less is known regarding rats and primates. Glutamate is thought to be the primary neurotransmitter within Barrington nucleus neurons that innervate the preganglionic parasympathetic neurons responsible for detrusor contraction. Both NMDA and non-NMDA receptors have been implicated in this response (Matsumoto et al, 1995a; 1995b; Yoshiyama et al, 1995; Yoshiyama and de Groat, 2005).

Barrington nucleus neurons express corticotropin-releasing factor (CRF) mRNA and protein and a dense CRF terminal field

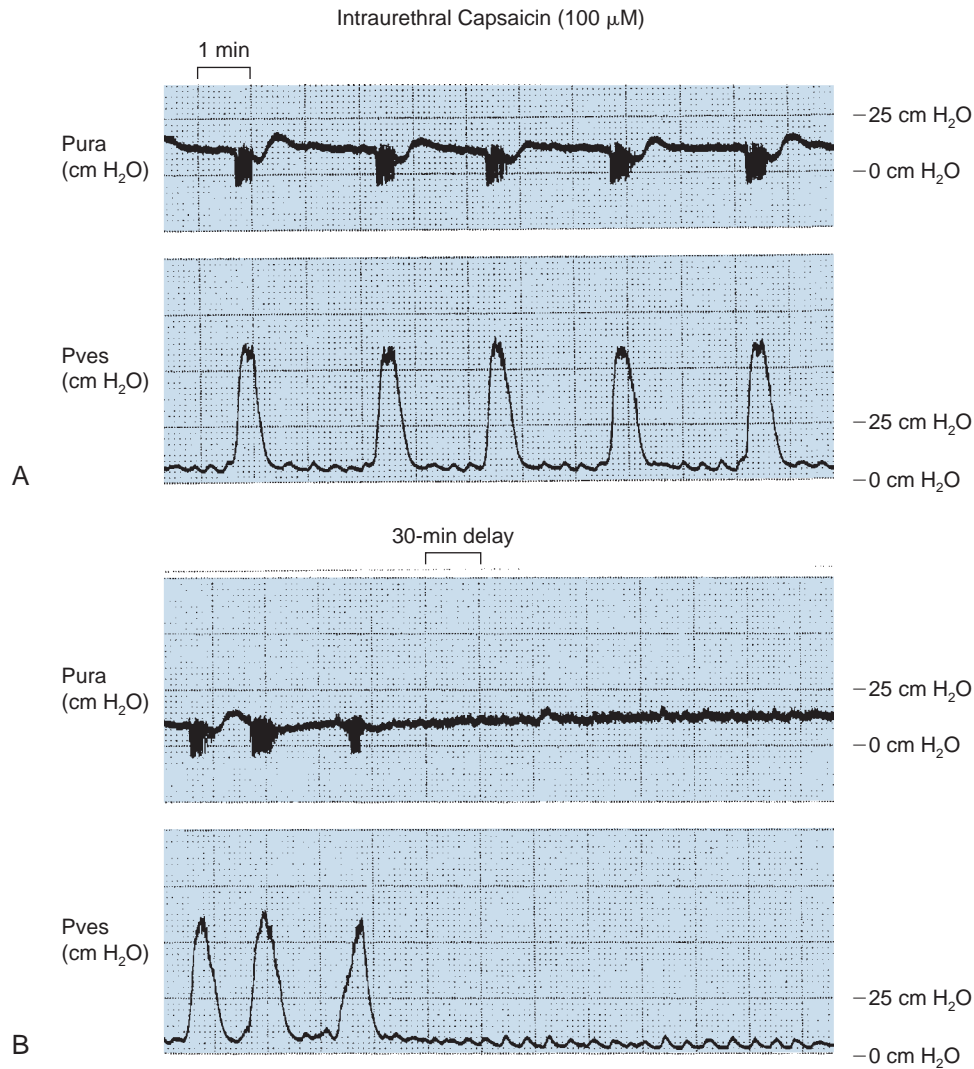


Figure 69-37. Effects of intraurethral capsaicin on the bladder pressure (Pves) and urethral pressure (Pura) in normal female rats. **A,** Before treatment. **B,** After intraurethral administration of capsaicin (100 μ M). Initially, intraurethral capsaicin instillation increased the bladder contraction frequency, but 30 minutes after continuous infusion, the activity was blocked. (From Jung SY, Fraser MO, Ozawa H, et al. Urethral afferent nerve activity affects the micturition reflex: implication for the relationship between stress incontinence and detrusor instability. *J Urol* 1999;162:204–12.)

is present in the region of preganglionic parasympathetic neurons of the rat lumbosacral spinal cord (Imaki et al, 1992; Valentino et al, 2000). Recent findings suggest that CRF has an inhibitory influence in this same pathway (Pavcovich and Valentino, 1995). Thus, discrete chemical activation of Barrington nucleus neurons elicits bladder contraction that is enhanced by blocking the CRF influence in the lumbosacral spinal cord with a CRF antagonist. Serotonin appears to affect nervous control of bladder function at multiple levels including sensory processing of bladder wall afferents within the dorsal horn of the spinal cord and at the level of the spinal motoneurons. In all cases this appeared to be an inhibitory influence on detrusor muscle activity but excitatory on urethral sphincter (Burgard et al, 2003). It was proposed that 5-HT_{1A} receptors were located on the terminals of sensory afferent fibers to depress neurotransmitter release.

Human Brain Imaging Studies. In the last decade, the areas of the brain involved in the control of micturition have been examined in human brain imaging studies using single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) (DasGupta et al, 2007; Griffiths and Tadic, 2008)

(Fig. 69-39). All these methods provide indirect measures of regional blood flow, assumed to be related to local neuronal activity, but PET is good for measuring long-lasting states of a system, whereas fMRI is better for following relatively fast events. SPECT has rather poor temporal and spatial resolution.

Cerebral Control of Voiding. During human voiding the urethral sphincter relaxes, facilitating urine flow, and the detrusor contracts so as to expel urine. This coordinated relaxation and contraction of urethra and bladder respectively is driven by a long-loop spinobulbospinal reflex (Fowler et al, 2008). As the bladder fills, increasingly strong bladder afferents travel via synapses in the sacral cord to the brainstem and midbrain, where they synapse in the central PAG and possibly Barrington nucleus or PMC. Although there are differing views about how the brainstem circuitry is organized, regardless, if the trigger level is exceeded, efferent signals from the PMC descend to the sacral cord, where they excite an indirect inhibitory pathway via the nucleus of Onuf that leads to sphincter relaxation (Blok and Holstege, 1998) and an excitatory pathway to the bladder that leads to detrusor contraction; thus voiding occurs. Therefore the spinobulbospinal voiding-reflex pathway functions as a switch, either “off” (storage) or “on” (voiding). In the absence of higher control,

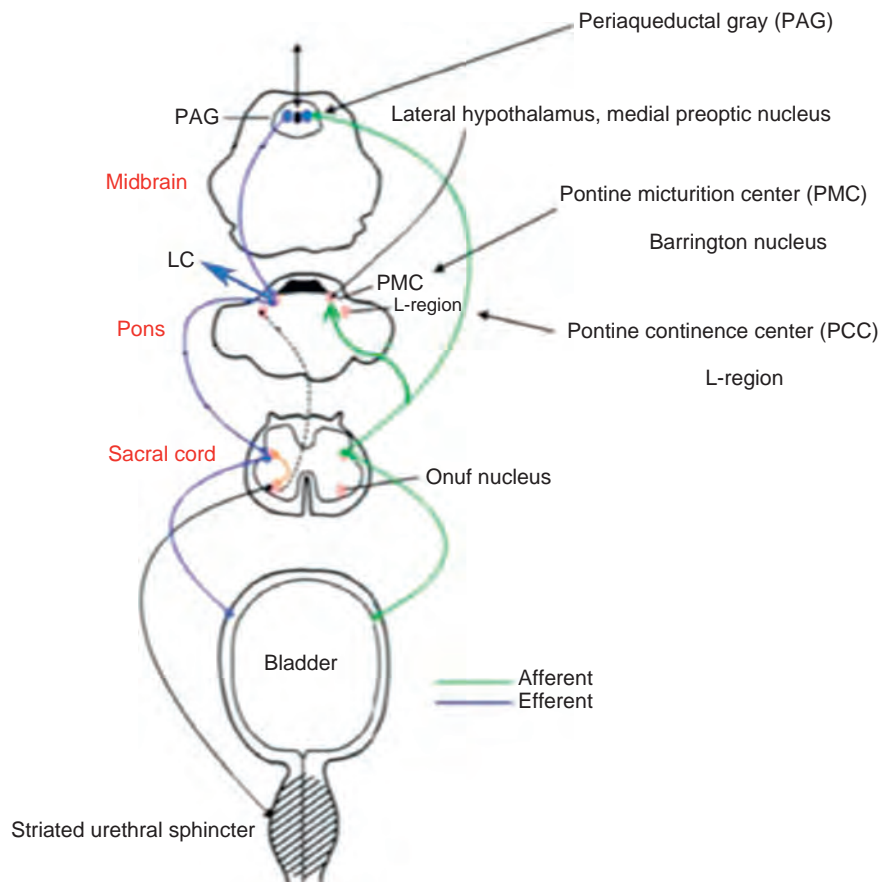


Figure 69-38. Schematic depicting information flow among the bladder, spinal cord, and brain. In the rat, spinal cord interneurons relay information about the bladder to the pontine micturition center (PMC), Barrington nucleus, and PAG. The PMC also gets input from the PAG, lateral hypothalamus, and medial preoptic nucleus. PMC neurons project to the locus ceruleus (LC) and preganglionic parasympathetic neurons of the lumbosacral spinal cord that innervate the detrusor. There are also projections to premotor neurons in the dorsal gray commissure that innervate Onuf's nucleus, which projects to the urethral sphincter. A pontine continence center (PCC) has been proposed in the cat and is localized to the L-region of the pons. Neurons here project to the Onuf nucleus.

this switching behavior would lead to involuntary bladder emptying (i.e., incontinence) whenever the bladder volume reached a critical level sufficient to trigger the brainstem switch.

White-matter damage that causes permanent incontinence appears to do so by disrupting a pathway (from medial frontal cortex to brainstem, either direct or via the thalamus) carrying the signal that maintains continence by tonically inhibiting the voiding reflex during storage. Imaging studies using PET (Blok et al, 1997, 1998a; Nour et al, 2000; Athwal et al, 2001; Matsuura et al, 2002) or fMRI (Griffiths et al, 2005; Blok et al, 2006; Di Gangi Herms et al, 2006; Kunze et al, 2006) are in agreement that during bladder filling, storage, and withholding of urine, there is activity in the right inferior frontal or dorsolateral prefrontal cortex, perhaps extending into the lateral part of the superior frontal cortex. There is some right-sided predominance. In contrast, there is little evidence for activation of the medial parts of the frontal cortex during storage. These observations are consistent with the concept that functional imaging reveals gray-matter activation or deactivation, whereas lesions may damage critical links in white-matter connecting pathways also.

Additional Regions. PET scan studies in normal men and women revealed that during voiding two cortical areas (the dorsolateral prefrontal cortex and anterior cingulate gyrus) were active (i.e., exhibited increased blood flow). The hypothalamus, including the preoptic area, as well as the pons and the PAG also showed activity in concert with voluntary micturition (Blok et al, 1997, 1998a).

Another PET study during voiding also confirmed that micturition was associated with increased activity in the pons, inferior frontal gyrus, hypothalamus, and PAG, while also showing activity in several other cortical areas (postcentral gyrus, superior frontal gyrus, thalamus, insula, and globus pallidus) and the cerebellar vermis (Nour et al, 2000).

Many functional imaging studies have observed responses (mostly activations) in ACG to bladder filling, storage, or withholding (Blok et al, 1997, 1998a; Athwal et al, 2001; Matsuura et al, 2002; Griffiths et al, 2005; Yin et al, 2006; Komesu et al, 2011). Response to bladder filling in the dorsal ACG and adjacent supplementary motor area (SMA) is abnormally pronounced in patients with urge incontinence (Griffiths et al, 2007) when, with full bladder but without any actual bladder contraction, they experience the abnormal sensation of urgency (a compelling desire to void that is difficult to inhibit [Abrams et al, 2002], also associated with fear of leakage, i.e., embarrassment) (Abrams et al, 1988). Thus urgency is a powerful homeostatic and social emotion that provides strong motivation to void together with motor output aimed at suppressing incontinence until a socially acceptable location can be reached. fMRI observations in rats confirm activation in the cingulate cortex during bladder filling (Tai et al, 2009), although whether this region is homologous with the human dorsal anterior cingulate cortex (dACC) and whether rats ever experience urgency are not known.

The demonstration by Barrington (1925) in the cat that a center necessary for activation of micturition existed at the level of the

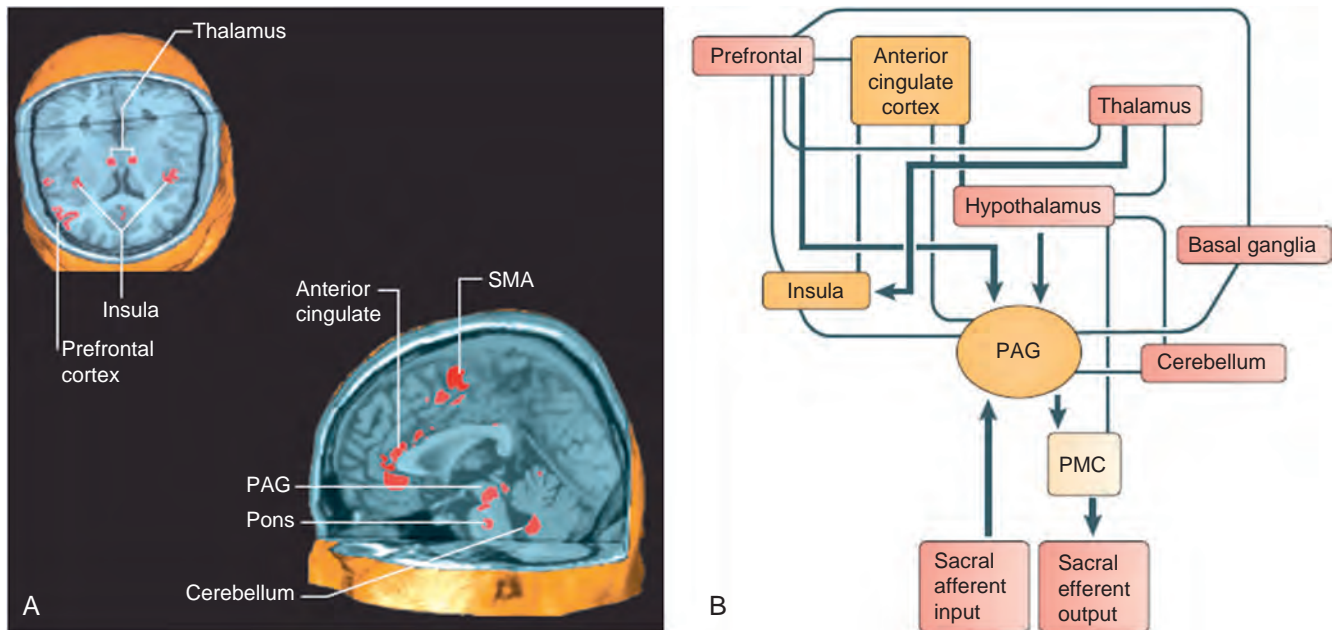


Figure 69-39. Brain areas involved in the regulation of urine storage. **A**, A meta-analysis of positron-emission tomography and functional magnetic resonance imaging studies that investigated which brain areas are involved in the regulation of micturition reveals that the thalamus, the insula, the prefrontal cortex, the anterior cingulate, the periaqueductal gray (PAG), the pons, the medulla, and the supplementary motor area (SMA) are activated during urinary storage. **B**, A preliminary conceptual framework, based on functional brain-imaging studies, suggesting a scheme for the connections among various forebrain and brainstem structures that are involved in the control of the bladder and the sphincter in humans. Arrows show probable directions of connectivity but do not preclude connections in the opposite direction. PMC, pontine micturition center. (From Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. *Neuroscience* 2008;6:453–66.)

pons provided the background for recognizing a comparable center in humans and the early report of the association of difficulty with micturition with posterior fossa tumors. Later histories of individual cases of discrete pontine lesions (Betts et al, 1992; Manente et al, 1996; Sakakibara et al, 1996; Komiya et al, 1998) and reports of difficulties with micturition or retention as a feature of brainstem gliomas in children (Ueki, 1960; Renier et al, 1980) or vascular lesions (Sakakibara et al, 1996) confirmed the likely existence of a comparable center in humans. Studies using MRI to visualize the precise location of the responsible lesions sited this in the dorsolateral pons, including the pontine reticular nucleus and the reticular formation, adjacent to the medial parabrachial nucleus and locus ceruleus (Sakakibara et al, 1996). Lesions in this location are frequently associated with disturbances of consciousness and respiration, and bladder symptoms may therefore be overlooked.

Other regions relevant to bladder control and revealed only by functional imaging include parts of parietal and frontoparietal cortices, posterior cortex (precuneus, posterior cingulate cortex), parts of the limbic system (hippocampal complex, amygdala), and the cerebellum. Functional imaging has occasionally shown activity in the basal ganglia, particularly the striatum and putamen (Griffiths et al, 2009). Correspondingly, dopamine pathways are thought to have a profound inhibitory effect on the PMC in health that is lost in Parkinson disease (Winge and Fowler, 2006).

Model of Brain-Bladder Control and Normal Continence Mechanism. The brain regions involved in bladder control are believed to be organized in neural circuits that perform different tasks related to homeostasis, answering questions regarding the adequacy of bladder filling, and the safety and social appropriateness of voiding, as well as the reflex or mechanical aspects dealt with by the brainstem switch. We should therefore expect forebrain control of the switch to involve both limbic circuits (concerned with basic emotion and safety) and cortical circuits (concerned with

social propriety [Amodio and Frith, 2006] and conscious decision making). In the working model, the PAG and PMC form the brainstem switch (Fig. 69-40). The PMC is the final efferent brain nucleus involved in bladder control. The PAG receives numerous projections from forebrain regions (Mantyh, 1982; Mouton and Holstege, 2000) including the medial and orbital prefrontal cortex (An et al, 1998).

During urine storage, as the bladder fills it generates afferent signals that are transmitted to the brainstem switch but do not trigger it. They are relayed from the PAG via the thalamus to the insula (red circuit) and, if activation is strong enough, generate a desire to void. Propagation of this insular activity to the lateral and medial prefrontal cortex enables both a conscious decision about voiding and an assessment of social propriety and possible embarrassment. If no voiding is planned, a return pathway from the medial frontal cortex to the brainstem tonically suppresses the voiding reflex. The pathway may run directly or via the thalamus in the anterior thalamic radiation. The result is postulated to be the normal continence mechanism. When there is a normal sensation of bladder filling, it exerts negative feedback on the brainstem switch, preventing incontinence. Interruption of the negative feedback—for example, by white-matter damage in the medial prefrontal cortex–periaqueductal gray (mPFC–PAG) pathway—leads to incontinence. During normal daily life, however, there is usually no conscious awareness of the bladder at all.

PHARMACOLOGY

Muscarinic Mechanisms

Detrusor strips from normal human bladders are contracted by cholinergic muscarinic receptor agonists and by electric stimulation of intrinsic cholinergic nerves. Contractile responses can be completely abolished by atropine (Sibley, 1984). There are at least five

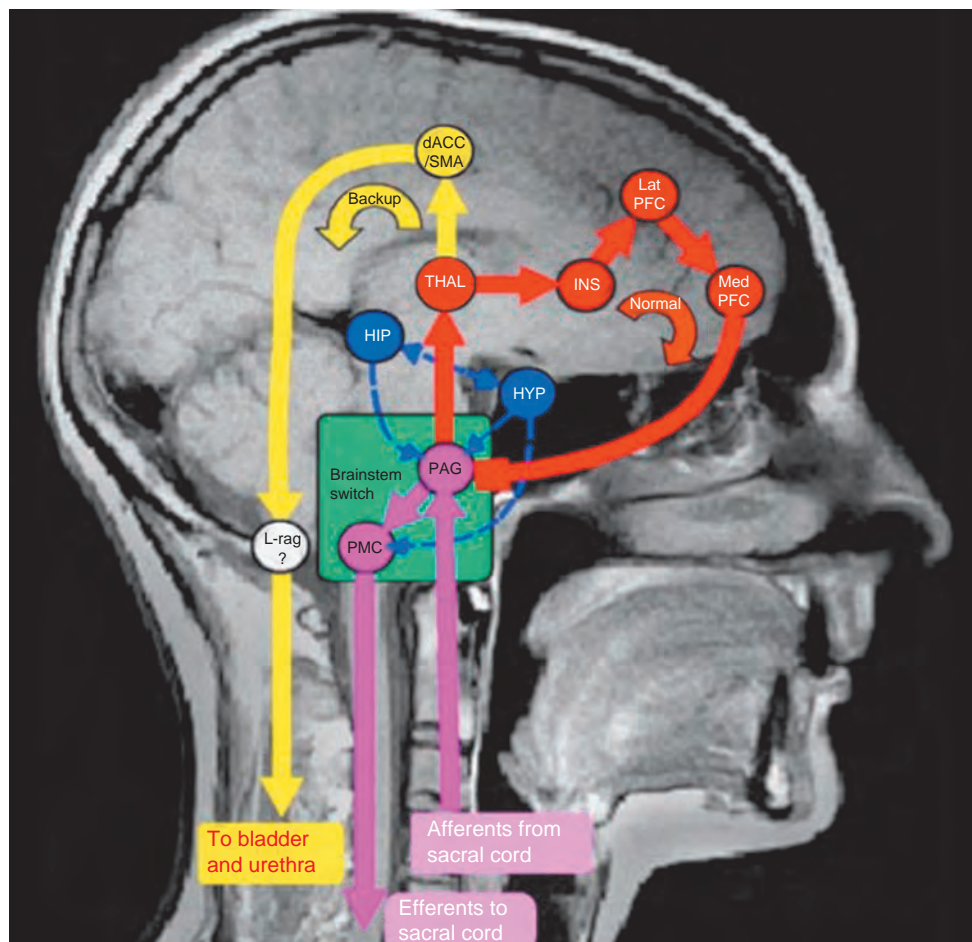


Figure 69-40. Working model of forebrain control of micturition, showing the brainstem switch and neural circuits that mediate two possible continence mechanisms. The normal mechanism (red) operates when there is a normal sensation of bladder filling. It depends on tonic inhibition of the brainstem switch via a long return pathway from the medial prefrontal cortex to the brainstem switch (probably via the anterior thalamic radiation, but shown for simplicity as a direct connection to the periaqueductal gray [PAG]). The inhibition is switched off for voiding. A backup mechanism (yellow) corresponds to the abnormal sensation or urgency. It may operate via brainstem nuclei such as an L-region (pontine storage center) or by modulating the sympathetic input to bladder and urethra. The dashed blue arrows show a possible circuit concerned with monitoring safety and/or maintaining continence without conscious sensation. dACC, dorsal anterior cingulate cortex; HIP, (para)hippocampal complex (may include amygdala, inferior parts of temporal lobe, and parts of posterior cortex); HYP, hypothalamus; INS, insula; Lat, lateral; L-reg, L-region; med, medial; PAG, periaqueductal grey; PFC, prefrontal cortex; PMC, pontine micturition center; SMA, supplementary motor area; THAL, thalamus.

receptor subtypes based on molecular cloning and four different receptor subtypes based on pharmacology (M_1 to M_5) (Somogyi et al, 1994; Wang et al, 1995; Eglen et al, 1996; Yamaguchi et al, 1996; Hegde et al, 1997).

Pharmacologically, M_1 , M_2 , and M_3 receptor subtypes have been found in the human bladder by receptor binding assays (Kondo et al, 1995); all M_1 to M_5 receptor mRNAs are detected by reverse transcription polymerase chain reaction assays (Andersson and Wein, 2004; Mansfield et al, 2005). Although ligand and receptor binding studies revealed that M_2 receptors predominate, M_3 receptors mediate cholinergic contractions (Eglen et al, 1994; Harriss et al, 1995; Yamaguchi, 1996; Hegde et al, 1997; Lai et al, 1998). Stimulation of M_3 receptors by ACh leads to IP_3 hydrolysis as a result of PLC activation and then to the release of intracellular calcium and smooth muscle contraction (Harriss et al, 1995; Fry et al, 2002) (see Figs. 69-15, 69-17, and 69-18). The involvement of transmembrane flux of calcium ions through nifedipine-sensitive L-type Ca^{2+} channels has also been indicated in M_3 receptor-mediated detrusor muscle contractions because the

L-type Ca^{2+} channel inhibitor nifedipine strongly suppressed carbachol-induced detrusor contractions, whereas the PLC inhibitor or the store-operated Ca^{2+} channel inhibitor caused little inhibition in rats and humans (Andersson and Arner, 2004; Andersson and Wein, 2004; Schneider et al, 2004a, 2004b; Frazier et al, 2008) (see earlier section on calcium signaling in detrusor myocyte). However, other studies have indicated the major contribution of the PLC-mediated mechanism to M_3 receptor-induced detrusor contractions, because PLC inhibitors significantly suppressed carbachol-induced detrusor contractions in rats (Braverman et al, 2006a, 2006b), and intracellular calcium elevation after carbachol application was observed without membrane depolarization in human bladders, which is required for the opening of L-type Ca^{2+} channels (Fry et al, 2002). Hashitani and colleagues (2000) reported that the stimulation of muscarinic receptors activates both calcium influx through L-type Ca^{2+} channels and calcium release from intracellular calcium stores in guinea pig bladders.

It has also been proposed (Hegde et al, 1997; Ehler et al, 2005) that coactivation of M_2 receptors could enhance the response to

M₃ stimulation by (1) inhibition of adenylate cyclase, thereby suppressing sympathetically mediated depression of detrusor muscle; (2) inactivation of K⁺ channels; or (3) activation of non-specific cation channels. In addition, because the specific ROK inhibitor Y-27632 reportedly suppresses carbachol-induced detrusor contractions in rats and humans, muscarinic receptor activation in detrusor smooth muscles is likely to stimulate the ROK pathway, leading to a direct inhibition of myosin phosphatase that induces calcium sensitization to enhance the ability of the muscle to generate the same contractile force with lower levels of intracellular calcium (Andersson and Wein, 2004; Schneider et al, 2004a, 2004b; Frazier et al, 2008). Although the involvement of M₃ receptors for ROK activation has been suggested (Andersson and Arner, 2004; Andersson and Wein, 2004; Schneider et al, 2004a) (see Fig. 69-15), a study has also suggested the participation of M₂ receptors in this mechanism because Y-27632 not only suppressed carbachol-induced muscle contractions but also increased the affinity of darifenacin, an M₃ receptor antagonist with approximately a 30-fold selectivity for M₃ over M₂ receptors, for inhibiting carbachol-induced contractions of rat bladders (Braverman et al, 2006a, 2006b). It has also been reported that the muscarinic receptor subtype-mediated detrusor contractions shift from M₃ to M₂ receptor subtype in certain pathologic conditions, such as obstructed or denervated hypertrophied bladders in rats (Braverman and Rugieri, 2003; Braverman et al, 2006a, 2006b), as well as in bladder

muscle specimens from patients with neurogenic bladder dysfunction (Pontari et al, 2004).

Studies using constructed mutant mice lacking the M₃ receptor or the M₂ and M₃ receptors have demonstrated that this subtype plays key roles in salivary secretion, pupillary constriction, and detrusor contractions (Matsui et al, 2000, 2002; Igawa et al, 2004). However, M₃-mediated signals in digestive and reproductive organs are dispensable, probably because of redundant mechanisms through other muscarinic ACh receptor subtypes or other mediators (Matsui et al, 2000). In addition, it has also been found that male M₃ knockout mice had a distended bladder and larger bladder capacity compared with females, indicating a considerable sex difference in the micturition mechanism (Matsui et al, 2002; Igawa et al, 2004). Thus M₃ or M₂ and M₃ double-knockout mice should provide a useful animal model for the DO pathophysiology and pharmacology.

The muscarinic receptor antagonists tolterodine and oxybutynin (Table 69-4) are widely prescribed drugs for urinary incontinence. Oxybutynin is a nonspecific muscarinic antagonist with additional smooth muscle relaxant properties. The smooth muscle relaxation properties of oxybutynin may be clinically relevant only with intravesical instillation of the drug. In addition, botulinum toxin A injections in children and adolescents diagnosed with neurogenic DO are associated with decreased muscarinic receptor muscular expression (Schulte-Baukloh et al, 2013). Thus, because new

TABLE 69-4 Drugs with Bladder Action

CLASSIFICATION	EXAMPLES	PHARMACOLOGIC ACTION
Anticholinergic agents	Atropine Glycopyrrolate Oxybutynin Propantheline Tolterodine	Inhibit muscarinic receptors, thus reducing the response to cholinergic stimulation; used to reduce pressure during bladder filling and for the treatment of unstable bladder contractions.
Smooth muscle relaxants	Dicyclomine Flavoxate	Direct smooth muscle relaxation reduces intravesical pressure during filling and reduces severity and presence of unstable bladder contractions; most of these agents have some degree of anticholinergic action.
Calcium antagonists	Diltiazem Nifedipine Verapamil	Used in the treatment of unstable bladder contractions to reduce the magnitude of the spikes by reducing the entrance of calcium during an action potential.
Potassium channel openers	Cromakalim Pinacidil	Act to increase the membrane potential and thus reduce the myogenic initiation of unstable bladder contractions.
Prostaglandin synthesis inhibitors	Flurbiprofen	Prostaglandins have been implicated in increased smooth muscle tone and in the induction of spontaneous activity. Inhibition of prostaglandin synthesis could promote relaxation of the bladder during filling and decrease spontaneous activity of the bladder.
β-Adrenergic agonists	Isoproterenol Terbutaline	Stimulation of β receptors induces relaxation of the bladder body, resulting in a decrease in intravesical pressure during filling.
Tricyclic antidepressants	Amitriptyline Imipramine	These agents have anticholinergic, direct smooth muscle relaxant, and norepinephrine reuptake inhibition properties.
α-Adrenergic agonists	Ephedrine Phenylpropanolamine Midodrine Pseudoephedrine	Increase urethral tone and closure pressure by direct stimulation of α-adrenergic receptors.
Afferent nerve inhibitors	DMSO Capsaicin Resiniferatoxin	Reduce the sensory input from bladder and thereby increase bladder capacity and reduce detrusor overactivity.
Estrogen	Estradiol	Direct application to the vagina or oral therapy may increase the thickness of the urothelial mucosa, making a better seal and reducing the incidence of incontinence. Other actions may include increasing adrenergic effects on the urethra and increasing blood flow.

DMSO, dimethyl sulfoxide.

antimuscarinic and other therapies are continually being developed by the pharmaceutical industry, all urologists should be aware of the existence of muscarinic receptor subtypes and their distribution in the LUT and other organs.

We will briefly present two additional issues regarding the effect of antimuscarinic drugs on the bladder and salivary glands that have clinical relevancy. First, antimuscarinic drugs are metabolized, and their metabolites have pharmacologic effects. It has been shown that oxybutynin has less of a dry mouth effect than does its metabolite desethyloxybutynin (Gupta and Sathyan, 1999). Therefore the controlled-release formulation of oxybutynin maintains the efficacy of immediate-release oxybutynin but with significantly fewer side effects. Tolterodine and solifenacin have been shown in cats and rats, respectively, to have less activity on the salivary gland muscarinic receptors than on the bladder muscarinic receptors (Nilvebrant et al, 1997; Ohtake et al, 2004). Second, the site and speed of antimuscarinic metabolism appear to have profound effects in terms of clinical efficacy and side effects.

Muscarinic Selectivity

Pharmacologically defined subtype-selective drugs have been developed. Darifenacin and vamicamide have been demonstrated to be relatively selective for the M_3 subtype (Yamamoto et al, 1995; Andersson, 1997; Steers, 2006). However, they are not necessarily tissue selective, because salivary glands and other tissues also contain M_3 muscarinic receptors. Tolterodine appears to be a muscarinic antagonist that has selectivity for the bladder compared with the salivary gland, even though it may not be an M_3 subtype-selective antagonist (Nilvebrant et al, 1997; Andersson, 1998). More recently, solifenacin has also shown selectivity to the bladder over the salivary gland; the receptor selectivity of solifenacin to M_3 receptors over M_2 receptors (10-fold) is similar to that of oxybutynin (Ikeda et al, 2002; Ohtake et al, 2004). Thus, therapeutically, it is more important to be tissue selective than subtype selective (Nilvebrant et al, 1997; Andersson, 1998). A truly bladder-selective antimuscarinic drug with no side effects is the “Holy Grail” of OAB drug therapy.

In addition, a number of studies have indicated that urothelial cells have the ability to release a variety of neurotransmitters including both ACh and ATP. Both mechanical stimuli and cholinergic agonists can evoke non-neuronal ACh release. Furthermore, stimulating ACh receptors leads to release of ATP, whereas blocking these receptors can reduce this release (Hanna-Mitchell et al, 2007; McLatchie et al, 2014). These and other data suggest that release of ACh can modulate the release of additional transmitters that may help to explain in part the mechanism of action for muscarinic antagonists in reducing symptoms of bladder disorders.

KEY POINTS: MUSCARINIC MECHANISMS

- There are at least five muscarinic receptor subtypes. Pharmacologically, M_1 , M_2 , and M_3 receptor subtypes have been found in the human bladder.
- Stimulation of M_3 receptors by ACh induces calcium influx through L-type Ca^{2+} channels, as well as IP_3 hydrolysis as a result of PLC activation, resulting in the release of intracellular calcium, both of which contribute to a smooth muscle contraction.
- Muscarinic receptor subtype-mediated detrusor contraction shift from M_3 to M_2 receptor subtype has been reported in bladder muscle specimens from neurogenic bladder dysfunction patients.

Adrenergic Mechanisms

β -Adrenergic Receptors

Stimulation of β_2 - and β_3 -adrenergic receptors that exist in the human detrusor results in the direct relaxation of the detrusor

smooth muscle (Andersson, 1993; Morita et al, 1993; Levin and Wein, 1995; Nishimoto et al, 1995). In addition, β -adrenergic-stimulated relaxation is mediated through the stimulation of adenylate cyclase and the accumulation of cAMP (Levin et al, 1986; Andersson, 1993; Andersson and Arner, 2004). Because β -adrenoceptor-mediated relaxation of the human detrusor was not blocked by selective β_1 - or β_2 -adrenoceptor antagonists, such as dobutamine and procaterol, but was blocked by selective β_3 -adrenoceptor antagonists, the relaxation induced by adrenergic stimulation of the human detrusor is mediated mainly through β_3 -adrenoceptor activation (Igawa et al, 1999; Yamaguchi, 2002; Andersson and Arner, 2004). A quantitative analysis by reverse transcription polymerase chain reaction has also confirmed that the β_3 -adrenergic receptor is the most highly expressed subtype among α - and β -adrenoceptor subtypes at the mRNA level in human bladders (Nomiya and Yamaguchi, 2003).

For these and other reasons, the β_3 -receptor agonist mirabegron has been approved as a new treatment option for OAB with symptoms of urge incontinence (Andersson and Arner, 2004; Bridgeman et al, 2013). This agent has been shown to provide an alternative for patients with contraindications or intolerance to existing therapy, although combination therapy (mirabegron and the antimuscarinic solifenacin) has also been shown to be effective (Abrams et al, 2015). The mechanism of action may be related to effects on a number of cell types including bladder afferent activity (Aizawa et al, 2015). Findings in rodents have revealed that β_3 adrenoceptor stimulation with mirabegron increased bladder compliance and shortened the intervoid interval; this regulation may be a result of the effect at a number of sites including reduction of nonmicturition contractions and decreased afferent nerve activation (Sadananda et al, 2013; Aizawa et al, 2015).

A second pharmacologic method of increasing levels of cyclic nucleotide monophosphates (cAMP or cGMP) is use of PDE inhibitors. PDE enzymes catalyze the hydrolysis of cAMP or cGMP (Andersson, 1997; Longhurst et al, 1997; Rahnama'i et al, 2013). There are several classes of PDEs that have individual substrate affinities, specific species and tissue distributions, and pharmacologic selectivities (Truss et al, 1996; Longhurst et al, 1997). Currently, there is considerable research trying to identify the specific isoform of PDE present in the bladder as opposed to that in the penis (Truss et al, 1996). For example, in the isolated guinea pig bladder, the frequency of agonist-induced phasic activity is slowed by cAMP, and degradation of intracellular cAMP in the cells responsible for phasic activity appears to involve primarily PDE4 (Gillespie, 2004). PDE4 inhibitors are shown to suppress DO in a rat model of BOO induced by partial urethral ligation (Kaiho et al, 2008). Although a number of preclinical studies have been done, to date the PDE1 and PDE5 inhibitors have been used clinically for management of storage or voiding disorders.

α -Adrenergic Receptors

Although α -adrenergic stimulation is not prominent in the normal bladder, recent evidence indicates that under pathologic conditions, such as DO associated with BOO, the α -adrenergic receptor density, especially the α_{1D} -receptor subtype, can increase to such an extent that the norepinephrine-induced responses in the bladder are converted from relaxation to contraction (Andersson and Arner, 2004). In rats with outflow obstruction, the proportion of α_{1D} -receptor subtype in the total α_1 -receptor mRNA in the bladder is increased to 70% from 25% in normal rat bladders (Hampel et al, 2002), and urinary frequency is suppressed by an inhibition of α_{1D} and α_{1A} receptors by tamsulosin, whereas α_{1A} -receptor suppression by 5-methyl-urapidil has no effect. Moreover, α_{1D} -receptor knockout mice have larger bladder capacity and voided volumes than do their wild-type controls, which supports an important role of α_{1D} receptors in the control of bladder function (Chen et al, 2005). However, in humans, there is the predominant expression of α_{1D} receptors already in the normal bladder (Malloy et al, 1998), and the level of expression of α -adrenoceptor mRNA, which is considerably low compared with β_3 adrenoceptors in normal bladders, was

not increased in the bladder with outflow obstruction (Nomiya and Yamaguchi, 2003). Thus the contribution of α_{1D} receptors to DO observed in a variety of pathologic conditions, including obstructive uropathy and incontinence, still needs to be established (Andersson and Arner, 2004).

α -Adrenergic mechanisms are more important in urethral function. Substantial pharmacologic and physiologic evidence indicates that urethral tone and intraurethral pressure are influenced by α -adrenergic receptors. The presence of α_1 and α_2 adrenoceptors has been shown in the urethra of various species including humans. Among α_1 adrenoceptors, the α_{1A} adrenoceptor is the major subtype expressed in urethral smooth muscle at the mRNA and protein levels (Yono et al, 2004; Michel and Vrydag, 2006). Isolated human urethral smooth muscle contracts in response to α -adrenergic agonists (Yalla et al, 1977; Awad et al, 1978; Nordling, 1983; Mattiasson et al, 1984). It is also reported in the rabbit that the urethral contraction is mediated by the α_{1A} -adrenoceptor subtype (Testa et al, 1993; Michel and Vrydag, 2006). Likewise, hypogastric nerve stimulation and α -adrenergic agonists raise intraurethral pressure, which is blocked by α_1 -adrenergic antagonists (Awad et al, 1976; Yalla et al, 1977). These findings provide the rationale for use of α -adrenergic agonists to promote urine storage by increasing urethral resistance.

Conversely, α -adrenergic receptor antagonists facilitate urine release in conditions of functionally increased urethral resistance, such as benign prostatic hyperplasia (BPH). Although the α_{1A} adrenoceptor is the major subtype in the prostate and urethra, highly selective α_{1A} -adrenoceptor antagonists (e.g., RS-17053) do not alter LUTS scores in men with BPH, but these agents are effective at relaxing prostate smooth muscle and increasing urine flow in men (Schwinn and Roehrborn, 2008). In contrast, α_1 -adrenoceptor antagonists that contain α_{1D} -adrenoceptor blocking activity improve bladder-based symptoms in humans (Nishino et al, 2006), suggesting the important role of the α_{1D} -adrenoceptors for storage symptoms associated with BOO, receptors potentially located at the bladder or the spinal cord (Schwinn and Roehrborn, 2008).

α_2 -Adrenergic antagonists increase the release of norepinephrine from urethral tissues through a presynaptic mechanism, but this does not affect the contractility of urethral smooth muscle in vitro (Mattiasson et al, 1984; Willette et al, 1990; Michel and Vrydag, 2006). The human urethra lacks postjunctional α_2 -adrenergic receptors, although in vitro prejunctional activation of these receptors produces a feedback inhibition of norepinephrine release. Pharmacologic and electrophysiologic data suggest that adrenergic nerves influence excitatory cholinergic transmission in pelvic ganglia. de Groat and Booth (1993) have shown in the cat that hypogastric nerves inhibit excitatory cholinergic transmission in vesical ganglia by activation of α_2 -adrenergic receptors (Fig. 69-41). Conversely, β -adrenergic agonists facilitate transmission in vesical ganglia.

KEY POINTS: ADRENERGIC MECHANISMS

- β -Adrenergic-stimulated relaxation is mediated through the activation of adenylate cyclase and the accumulation of cAMP.
- The β_3 -adrenergic receptor is the most highly expressed subtype among α - and β -adrenoceptor subtypes, and β_3 -receptor agonists are in clinical trials for treatment of DO.
- In the human, there is a predominant expression of α_{1D} receptors present in the normal bladder, and the level of expression of α -adrenoceptor mRNA, which is considerably low compared with β_3 adrenoceptors in normal bladders, was not increased in the bladder with outflow obstruction.
- Urethral tone and intraurethral pressure are influenced by α -adrenergic receptors. The α_{1A} adrenoceptor is the major subtype in the prostate and urethra, and all three α_1 -adrenoceptor subtypes (α_{1A} , α_{1B} , α_{1D}) are present in blood vessels.

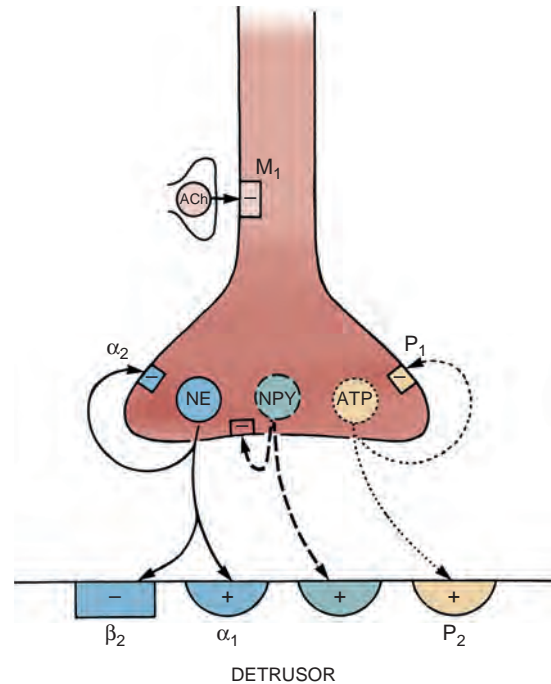


Figure 69-41. Diagram of possible transmitters in an adrenergic terminal supplying the bladder or urethra. Norepinephrine (NE) release can activate α_1 -adrenergic receptors and produce contraction (+) or β receptors and cause relaxation (-) of the detrusor. Feedback inhibition of NE release through α_2 receptors can also occur. Neuropeptide Y (NPY) can produce smooth muscle contraction (+) or inhibit acetylcholine (ACh) release (not shown), or feedback can inhibit NE release. Adenosine triphosphate (ATP) can activate P_2 receptors in the detrusor, which elicit contraction (+) or inhibit (-) further ATP release through P_1 prejunctional receptors. ACh release from terminals in synaptic contact with an adrenergic varicosity can inhibit firing of adrenergic axons by activation of M_1 receptors.

Urethral Tone in Women

Taki and associates (1999) separated the entire length of the human female urethra into several parts and studied the regional contractile effect of norepinephrine, clonidine, ACh, and potassium chloride. Their findings suggest that sympathetic innervation helps maintain resting urethral tonus, mainly through α_1 adrenoceptors. With the recent identification of at least three distinct subtypes of α_1 adrenoceptors with distinct pharmacologic profiles, it may be possible to develop urethra-specific pharmacologic agonists for the treatment of stress urinary incontinence (SUI). A small-scale, placebo-controlled clinical study has demonstrated that activation of the $\alpha_{1A/1L}$ -adrenoceptor subtype, which is a pharmacologic isoform of the α_{1A} -adrenoceptor gene product, was effective in reducing the number of incontinence episodes in women with mild-to-moderate SUI (Musselman et al, 2004), suggesting an important role of α_1 adrenoceptors in the urethral continence mechanism, although the data are still preliminary.

Afferent Neuropeptides

Afferent neurons innervating the LUT exhibit immunoreactivity for various neuropeptides, such as SP, CGRP, pituitary adenylate cyclase-activating polypeptide (PACAP), leucine enkephalin, CRP, and VIP (de Groat, 1986, 1989; Keast and de Groat, 1992; Maggi, 1993; Vizzard, 2001, 2006), as well as growth-associated protein-43 (GAP43), NOS (Vizzard et al, 1996), glutamic acid, and aspartic acid (Keast and Stephensen, 2000). These substances have been identified in many species and at one or more locations in the afferent pathways including (1) afferent neurons in lumbosacral DRG, (2) afferent nerves in the peripheral organs, and (3) afferent

axons and terminals in the lumbosacral spinal cord (Kawatani et al, 1985, 1986, 1996; Morrison et al, 2005). The majority (>70%) of bladder DRG neurons in rats appear to contain multiple neuropeptides—CGRP, SP, and PACAP being the most common. In cats, VIP is also contained in a large percentage of bladder DRG neurons (de Groat, 1989).

Many of these peptides, which are contained in capsaicin-sensitive, C-fiber bladder afferents, are released in the bladder by noxious stimulation and contribute to inflammatory responses by triggering plasma extravasation, vasodilation, and alterations in bladder smooth muscle activity (Maggi, 1993; Ishizuka et al, 1994, 1995). These agents also function as transmitters at afferent terminals in the spinal cord.

Tachykinins

The tachykinins are a family of small peptides sharing a common C-terminal sequence, Phe-Xaa-Gly-Leu-Met-NH₂, whose main members are SP, neurokinin A, and neurokinin B. Tachykinins are found in both central and peripheral nervous systems. In the peripheral nerves, tachykinins are predominantly located in the terminals of nonmyelinated, sensory C fibers. The diverse biologic effects of the tachykinins are mediated through three receptors, designated NK₁, NK₂, and NK₃, which belong to the superfamily of seven transmembrane-spanning G protein-coupled receptors (Khawaja and Rogers, 1996). SP is the most potent tachykinin for the NK₁ receptor, whereas neurokinin A exhibits the highest affinity for the tachykinin NK₂ receptor, and neurokinin B for the tachykinin NK₃ receptor (Table 69-5). All receptor subtypes have been identified in the bladder of humans and animals such as rats, mice, and dogs (Lecci and Maggi, 2001; Andersson and Arner, 2004).

Tachykinins released from capsaicin-sensitive sensory C fibers in response to irritation in the bladder can act on (1) NK₁ receptors in blood vessels to induce plasma extravasation and vasodilation, (2) NK₂ receptors to stimulate bladder contractions, and (3) NK₃ receptors on primary afferent terminals to increase the excitability during bladder filling or during bladder inflammation (de Groat, 1989; Andersson, 1993; Morrison et al, 1995; Lecci and Maggi, 2001). A study by Kamo and associates (2005) also demonstrated that activation of NK₃ receptors on capsaicin-sensitive C-fiber afferents in the rat bladder can increase the excitability during bladder filling.

Intrathecal administration of NK₁ antagonists (RP 67580 and CP 96345) or systemic application of centrally acting NK₁ antagonists (GR 205171 and CP 99994) increased bladder capacity in normal rats and guinea pigs, respectively, without changing voiding pressure, whereas NK₂, NK₃, or peripherally acting NK₁ antagonists were ineffective (Lecci et al, 1993; Yamamoto et al, 2003). DO in rats induced by chemical cystitis, intravesical administration of capsaicin, or intravenous injection of L-dopa was also suppressed by intrathecal injection of NK₁ antagonists (Ishizuka et al, 1994; Lecci et al, 1994; Ishizuka et al, 1995). DO induced by capsaicin was reduced by an NK₂ antagonist (SR 48965) that did not influence normal voiding (Lecci et al, 1997). In anesthetized guinea pigs, TAK-637, an NK₁ receptor antagonist, administered orally or intravenously also increased the volume threshold for inducing micturition and inhibited the micturition reflex induced by capsaicin applied topically to the bladder (Doi et al, 1999). In a clinical study, an NK₁ receptor antagonist, aprepitant, has also been shown to effectively decrease the average daily number of micturitions and urgency episodes compared with placebo at 8 weeks in women with

idiopathic OAB (Green et al, 2006). These results indicate that sensory input to the spinal cord from non-nociceptive bladder afferents is mediated by tachykinins acting on NK₁ receptors, whereas input from nociceptive afferents in the bladder can be mediated by NK₁, NK₂, and NK₃ receptors. In addition, tachykinin NK₃ receptor activation in the spinal cord can inhibit the micturition reflex through an activation of the spinal opioid mechanism (Kamo et al, 2005).

Autofeedback mechanisms may also be important at afferent nerve terminals. As mentioned earlier, some stimuli are known to release neuropeptides from afferent nerves, and these neuropeptides may, in turn, sensitize the afferents. NK₂ agonists were found (Wen and Morrison, 1996) to sensitize bladder mechanoreceptors by acting on NK₂ autoreceptors in the sensory endings in the bladder mucosa to produce the combination of effects found previously for other sensitizing agents (Morrison et al, 1998). The NK₂ receptor blocker SR 48968 decreases the sensitivity of bladder mechanoreceptors and also blocks the sensitization produced by NK₂ agonists and high urinary potassium levels. This suggests that the sensitization produced by intravesical chemical stimuli may be caused by a mechanism using the NK₂ receptor. On the basis of these findings, it could be hypothesized that high urinary potassium concentration or higher levels of bladder distention release neurokinin A from sensory endings, and that the sensitization is the result of the action of the peptide on local NK₂ autoreceptors on the sensory endings. It has also been shown that sensory neurons obtained from rat DRG can be excited by NK₂ agonists and inhibited by NK₃ agonists through modulation of Ca²⁺ channel activity mediated by PKC activation (Sculptoreanu and de Groat, 2003). NK₂ receptor activation also leads to PKC-induced phosphorylation of TRPV1 channels, resulting in an increase in capsaicin-evoked currents in rat DRG neurons (Sculptoreanu and de Groat, 2007; Sculptoreanu et al, 2008).

Prostanoids

Prostanoids (prostaglandins and thromboxanes), which comprise a family of oxygenated metabolites of arachidonic acid, by the enzymatic activity of cyclooxygenases 1 and 2, are manufactured throughout the LUT and have been implicated in bladder contractility, inflammatory responses, and neurotransmission. Biopsy specimens of human bladder mucosa contain PGI₂, PGE₂, PGE_{2w}, and thromboxane A. In decreasing order of potency, PGF_{2w}, PGE₂, and PGE₂ contract the human detrusor (Andersson, 1993; Andersson and Arner, 2004). The actions of prostanoids are mediated by specific receptors on cell membranes. The receptors include the DP, EP, FP, IP, and TP receptors that preferentially respond to PGD₂, PGE₂, PGF_{2w}, PGI₂, and thromboxane A₂, respectively. Furthermore, EP is subdivided into four subtypes: EP₁, EP₂, EP₃, and EP₄ (Breyer et al, 2001, 2003). The slow onset of action for these substances suggests a modulatory role for prostaglandins. Some prostaglandins may affect neural release of transmitters, whereas others inhibit acetylcholinesterase activity. These actions provide mechanisms whereby prostaglandins could potentially augment the amplitude of cholinergic-induced detrusor contractions (Borda et al, 1982).

Attempts to use prostaglandins to facilitate voiding have had mixed results. Intravesical PGE₂ has been shown to enhance bladder emptying in women with urinary retention and patients with neurogenic voiding dysfunction (Bultitude et al, 1976; Vadyanaathan et al, 1981; Tammela et al, 1987). Others have failed to find PGE₂ useful to facilitate complete evacuation of the bladder (Delaere et al, 1981; Wagner et al, 1985). Intravesical PGE₂ does produce urgency and involuntary bladder contractions (Schussler, 1990). Consistent with this finding, inhibition of prostaglandin synthesis with indomethacin reduces DO (Cardozo and Stanton, 1980).

Endothelins

Endothelins (ETs), a family of 21-amino acid peptides (originally isolated from bovine aortic endothelial cells), include ET-1, ET-2, and ET-3, which are encoded by separate genes and mediate a

TABLE 69-5 Tachykinins and Tachykinin Receptors

TACHYKININ	RECEPTOR
Substance P	NK ₁
Neurokinin A	NK ₂
Neurokinin B	NK ₃

variety of biologic actions through two distinct G protein-coupled receptor subtypes, the endothelin-A (ET_A) and the endothelin-B (ET_B) receptor (Yanagisawa et al, 1988; Masaki, 2004). The ET_A receptor subtype has a higher affinity for ET-1 and ET-2 than for ET-3; the ET_B receptor subtype binds all ETs with equal affinity (Rubanyi and Polokoff, 1994). ET-1, which is known to be primarily produced by human endothelial cells, can induce prolonged contractile responses in isolated urinary bladder muscle strips in various species (Maggi et al, 1990; Khan et al, 1999). In humans and rabbits, ET-like immunoreactivity is identified in almost all cell types in the bladder, including bladder epithelium, vascular endothelium, detrusor, and vascular smooth muscles, and fibroblasts; it plays a role in control of bladder smooth muscle tone, regulation of local blood flow, and bladder wall remodeling in pathologic conditions (Saenz de Tejada et al, 1992). In a rabbit model of BOO, ET-1 and ET_A receptor binding sites in detrusor smooth muscle and urothelium, as well as ET_B receptor binding sites in detrusor smooth muscle, were significantly increased (Khan et al, 1999). In addition, the ET-converting enzyme inhibitor WO-03028719, which suppresses ET-1 production, can improve voiding efficiency and suppress DO in a rat model of BOO (Schroder et al, 2004). YM598, a selective ET_A receptor antagonist, also reduces DO in urethral obstructed rats (Ukai et al, 2006). These results suggest that the increase in ET-1 expression and ET receptors could be involved in detrusor hyperplasia and overactivity seen in patients with BOO resulting from BPH.

There is also evidence that ETs have a role in modulation of sensory function in the peripheral nervous system and CNS. The activation of ET_A receptors in capsaicin-sensitive C-fiber afferents in the bladder induces DO, whereas ET_A receptor activation in the spinal cord can inhibit the micturition reflex through activation of a spinal opioid mechanism in rats (Ogawa et al, 2004). In spinal cord-injured rats, the bladder ET-1 level was increased, and the application of ABT-627, an ET_A antagonist, suppressed C fiber-mediated DO. Accordingly, modulation of ET_A receptor activity in bladder afferent pathways or the spinal cord could be effective in treating bladder overactivity or painful conditions (Ogawa et al, 2008).

Sex Steroids

Differences in responses of human and animal bladders to the effect of drugs suggest that sex steroids play a role in detrusor contractility. It is not unusual for women to note changes in voiding, bladder pain, or continence at different times of their menstrual cycle. Sex steroids do not directly affect bladder contractility, but they modulate receptors and influence growth of bladder tissues. Estrogen receptors are expressed by the trigone in women (Iosif et al, 1981). Levin and associates (1980) noted that bladder body muscle from young female rabbits treated with estrogens exhibits increased responsiveness to α -adrenergic, cholinergic, and purinergic agonists. Others have seen a decreased density of adrenergic and muscarinic receptors in the bladder after estrogen administration (Shapiro, 1986; Batra and Andersson, 1989). In contrast to the study by Levin and coworkers (1980), Elliott and associates (1992) showed that bladder smooth muscle from estrogen-treated rats exhibited decreased contractions.

Estrogens also increase adrenergic receptors in the urethra (Calahan and Creed, 1985). Ekstrom and associates (1993) reported that estrogen administration to ovariectomized rabbits unmasked contractile responses to α -adrenergic agonists, whereas contracted and normal rabbit bladders demonstrated no response to these agents. Some clinicians have combined these agents to elevate urethral pressure in patients with stress incontinence (Wilson et al, 1987). However, the clinical efficacy of the combined use of estrogen with α agonists has been questioned (Walter et al, 1978). The effect of estrogens on urinary continence in females probably reflects the multiple actions of this hormone on adrenergic receptors, vasculature, and urothelium. In addition, progesterone increases electrical and cholinergic contractions of the bladder. Exogenous estrogens and progesterones also induce NOS

activity in bladders of female guinea pigs (Ehren et al, 1995). This effect is postulated to contribute to relief of DO with hormonal treatment. However, the use of estrogens alone to treat either SUI or urgency incontinence has given disappointing results (Abrams et al, 2005), and studies have suggested that estrogen may be associated with an increase in urinary incontinence in postmenopausal women (Hendrix et al, 2005).

Androgen treatment in the male rat has been reported to have similar effects on synaptic connections, as well as effects on motoneuronal somatic and dendritic size in the androgen-sensitive motoneurons innervating the bulbocavernosus and levator ani muscles of the rat (Jordan, 1997; Matsumoto, 1997). Testosterone treatment can also influence the size of postganglionic neurons in the major pelvic ganglion of the male rat (Keast and Saunders, 1998). Thus further studies are needed to evaluate the influence of changes in hormonal environment on the neural pathways controlling the LUT.

CLINICAL RELEVANCE

The following section discusses different LUTD conditions encountered by urologists that involve perturbation of the physiologic mechanisms presented in this chapter. Some of these conditions arise as a result of injuries to innervation, obstruction, or infection of the LUT. On a logical level, the ideal treatment for these conditions would be to reverse the neurologic injury, relieve the obstruction, or eradicate the infection. When LUTD, manifesting with LUTS, increased postvoid residual volume, and/or DO, has no identifiable pathology, then the treatment becomes empirical and driven primarily by LUTS relief. A variety of diagnostic terms have been used to describe idiopathic LUTD conditions—OAB, IC/PBS, and underactive bladder to name a few. Many of these idiopathic LUTD conditions reflect an increased or augmented sensory input from the LUT, leading to the term *afferent neurolurology* in describing these conditions (Clemens, 2013). Although idiopathic nonobstructive urinary retention (underactive detrusor) may be primarily a failure of efferent signaling, the resultant decreased motor sensory pathway (Eastham and Gillespie, 2013) could exacerbate or prolong this condition. The ability to augment or inhibit sensory afferent mechanisms in treating these afferent neurolurologic conditions could advance treatment for LUTD.

One overarching paradigm to explain afferent neurolurologic conditions involves C-fiber afferent activation via neurotrophic cytokine, such as nerve growth factor (NGF), signaling. Changes in bladder innervation orchestrated by neurotrophins manufactured by detrusor smooth muscle are temporally linked with DO (Fig. 69-42). The ability of local anesthetics, intravesical afferent neurotoxins, and destruction of afferent nerves in the bladder neck and prostate to reduce urgency, frequency, and urgency incontinence indicates an important role for afferent-evoked reflexes (Chalfin and Bradley, 1982). The development of a spinal reflex (ice-water test response) in patients with neurogenic bladders (Geirsson et al, 1999), as well as in patients with BOO (Chai et al, 1998; Hirayama et al, 2003, 2005), suggests a common underlying plasticity in nerves supplying the bladder. Moreover, the association between elevated blood pressure and LUTS in patients with BPH (Pool, 1994; Sugaya et al, 2003) provides a link between changes in sympathetic tone and voiding complaints.

Mechanisms of Idiopathic Detrusor Overactivity and Overactive Bladder

The classic model of OAB is that of urodynamically demonstrated DO, although DO was found in only 11% of a contemporary cohort of subjects with OAB symptoms (Diamond et al, 2012). Nevertheless, various models have been used to explore the pathogenesis of DO and to formulate treatments for urgency incontinence associated with OAB. Animal models for DO that do not involve damage or injury to bladder, urethra, or spinal cord include

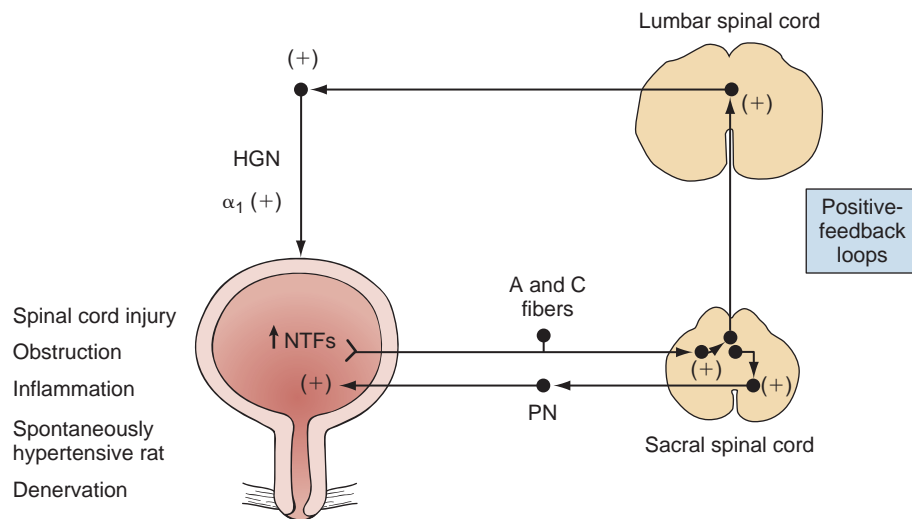


Figure 69-42. Possible mechanisms underlying plasticity in bladder reflex pathways induced by various pathologic conditions. Bladders from rats with chronic spinal cord injury, urethral obstruction, chronic inflammation, and bladder denervation and those that are spontaneously hypertensive exhibit increased level of neurotrophic factors (NTFs), such as nerve growth factor. NTFs can increase the excitability of C-fiber bladder afferent neurons and alter reflex mechanisms in parasympathetic excitatory pathways in the pelvic nerve (PN), as well as in sympathetic pathways in the hypogastric nerve (HGN). These reflex circuits are organized in the spinal cord as positive-feedback loops that induce involuntary bladder activity. In certain situations, such as the spontaneously hypertensive rat, peripheral efferent mechanisms are also altered: Excitatory α_1 -adrenoceptor mechanisms are upregulated, providing an additional excitatory input to the bladder.

the spontaneously hypertensive rat (Steers et al, 1999), serotonin reuptake transporter knockout (Cornelissen et al, 2005), constitutive BK channel knockout (Meredith et al, 2004), urothelially restricted NGF knock-in (Schnegelsberg et al, 2010), and urothelially restricted β_1 -integrin knockout (Kanasaki et al, 2013). Other molecular targets, using transgenic animals, have been used to study LUT function, although none of these models has specifically addressed the clinical problem of DO or OAB. These animal models include knockout mice lacking muscarinic receptors (M_1 to M_5) (Matsui et al, 2002; Igawa et al, 2004), purinergic receptors ($P2X_2$, $P2X_3$) (Cockayne et al, 2000, 2005), and TRPV1 (Birder et al, 2002). With some of these models, a mechanistic theme is alterations in growth factors leading to plasticity in micturitional neural and smooth muscle contractile pathways.

NGF has been a biomarker for LUTD since the description of NGF upregulation by bladder smooth muscle after BOO and increased diuresis (Steers et al, 1991; Steers and Tuttle, 2006). The role of increased urinary NGF as a biomarker for OAB has been studied (Liu et al, 2009, 2011; Liu and Kuo, 2012; Seth et al, 2013). Although the source of the urinary NGF is uncertain, it is less likely to come from the bladder stroma because of the necessity of NGF having to traverse the lamina propria and the entire urothelium. However, the role of increased NGF expressed by the bladder urothelium in mediating a change in bladder function was studied in transgenic mice with overexpression of NGF restricted to the urothelium (Schnegelsberg et al, 2010). These animals had increased urinary frequency, pelvic pain, and prominent neuronal hypertrophy in the lamina propria. Investigators failed to detect increased urothelial tissue NGF in DO subjects and paradoxically less urothelial tissue NGF in subjects with increased urinary frequency (Birder et al, 2007b). It remains to be seen how NGF can be used in evaluation, phenotyping, and/or treatment of OAB, and further studies are needed (Ochodnick et al, 2011).

Urothelial dysfunction associated with idiopathic OAB has also been studied using human urothelial cells grown in culture. The findings from using human cells in these *in vitro* studies included increased urothelial polyamine signaling (Li et al, 2013) leading to block of urothelial BK channels (Li et al, 2009). Other findings

include increased TRPV1 signaling in the cultured OAB cells (Li et al, 2011). Whether these urothelial abnormalities related to altered bladder urothelial-afferent signaling remains to be seen.

Investigators found that subjects with OAB and urgency incontinence had decreased urethral afferent function (Kenton et al, 2007, 2010) when measured with urethral CPT (current perception threshold) testing. Furthermore, 2 weeks after successful sacral neuromodulation treatment, urethral CPT measures did not change (Gleason et al, 2013). These findings are counterintuitive because one would expect augmented urethral afferent function in OAB. An animal model in which urethral afferent signaling can be selectively modulated (augmented or diminished) would help shed light on the impact of urethral afferent signaling on micturitional behavior.

The role of bladder smooth muscle pathophysiology in OAB and DO has also been studied. In the constitutive BK knockout mouse, development of OAB micturitional behavior phenotype was seen (Meredith et al, 2004). The ability to obtain detrusor smooth muscle strips in idiopathic urgency incontinence patients is limited, so confirmation of this phenomenon would be difficult, unlike the case of neurogenic DO (see next section). Other investigators have examined derangements in regulation of (Ca^{2+})_i from detrusor myocytes isolated from both idiopathic and neurogenic DO subjects (Sui et al, 2009). These investigators found that myocytes from DO had increased resting (Ca^{2+})_i, and more spontaneous increases in (Ca^{2+})_i arising from influx of extracellular Ca^{2+} from L-type and T-type VDCCs. There was a suggestion that neurogenic DO had greater dysregulation of (Ca^{2+})_i than IDO.

The role of suburothelial myofibroblasts has been also explored in OAB. Immunofluorescent studies of these myofibroblasts from both idiopathic and neurogenic DO subjects revealed increased gap junction (Cx43) expression in the myofibroblasts (Roosen et al, 2009). Furthermore, these changes were not reversed, even with successful treatment with onabotulinumtoxinA (OBTX). The links among myofibroblasts; detrusor myocytes; cytokines including interleukin-4 (IL-4), IL-6, IL-10; tumor necrosis factor- α (TNF- α); and transforming growth factor- β 1 (TGF- β 1); and Cx43 were investigated (Heinrich et al, 2011). These investigators found that these

cytokines increased expression of Cx43 in both myofibroblasts and myocytes, suggesting a mechanism for increased cellular connectivity in OAB (and IC/PBS) that is related to these cytokines. Although NGF was not tested in this study, investigators using PC12 cells (neuronal cells) found that NGF increased Cx43 connectivity in these cells (Cushing et al, 2005), which suggests that NGF could possibly also increase Cx43 expression in detrusor myocytes and myofibroblasts.

Stress Urinary Incontinence

Traditionally, SUI in women has been thought to be a urethral anatomic and not a urethral physiologic problem. The urethral integral theory of Petros and Ulmsten (1993) led to the development of the mid-urethral sling, the current standard surgical treatment for SUI. However, SUI in women is unlikely to be caused only by anatomic laxity of the anterior vaginal wall. DeLancey presented data that showed intrinsic sphincteric function (physiologic function) to be more important for maintenance of stress continence than anatomic integrity (anatomic support) (DeLancey, 2010). Pathophysiologic studies of urethral function in women have centered on the mechanisms surrounding urethral injury at time of childbirth using vaginal distention animal models, including pudendal nerve injuries (Damaser et al, 2007; Pan et al, 2009). Chemokines and receptors involved in stem cell homing, such as CCL7, CXCR4, CXCL12, CD195, and CD193 were upregulated with vaginal distention or after vaginal birth in rats (Lenis et al, 2013). Increased expression of monocyte chemoattractant protein-3 (MCP-3) at the urethra after vaginal distention provides a homing signal for stem cells, because MCP-3 is a stem cell homing chemokine (Woo et al, 2007). A possible method to diminish SUI after childbirth is to maximize healing of urethral injuries (both muscular and neurologic) soon after childbirth.

The ability to use biomarkers to predict success or failure after mid-urethral slings was studied (Chai et al, 2014). This study found that higher urinary NTx (N-telopeptide cross-linked collagen) was associated with a significantly higher failure rate after slings. NTx is a marker for bone metabolism; higher NTx levels reflect greater bone turnover and osteoporosis (Garnero, 2008). It remains to be seen whether leveraging this knowledge can reduce the failure rate of mid-urethral slings, which at 1 year is about 23% (Richter et al, 2010).

Serotonin-norepinephrine reuptake inhibitors, such as duloxetine, increase efferent output at the Onuf nucleus at the sacral spinal cord, thus increasing urethral smooth muscle tone and decreasing SUI (Thor and Katofiasc, 1995). Clinical trials of duloxetine have shown benefits over placebo in treating mild-to-moderate SUI (Millard et al, 2004; van Kerrebroeck et al, 2004). Duloxetine is approved in Europe, but not the United States, for use in SUI. Duloxetine has also been studied in male postprostatectomy SUI and was found to have statistically significant efficacy over placebo, although the sample size was small (Cornu et al, 2011).

Spinal Cord Injury and Neurogenic Detrusor Overactivity

Damage to the spinal cord above the sacral spinal level results in DO (Kaplan et al, 1991; Chancellor, 1997). Acute spinal cord injury disrupts normal supraspinal circuits that control urine storage and release. After the spinal shock period of urinary retention that typically lasts a few weeks, neurogenic DO develops. Electrophysiologic data reveal that this DO is mediated by a spinal micturition reflex that emerges in response to a reorganization of synaptic connections in the spinal cord (de Groat, 1975; de Groat et al, 1981, 1990; Araki and de Groat, 1997; Yoshimura, 1999). In addition, bladder afferents that are normally unresponsive to low intravesical pressures become more mechanosensitive, leading to the development of DO.

Normal micturition is associated with a spinobulbospinal reflex mediated by lightly myelinated A δ afferents (de Groat et al, 1975, 1993). These fibers represent only 30% of bladder afferents in some species. Compared with A δ fibers, the more prevalent

unmyelinated C fibers are relatively insensitive to gradual distention of the urinary bladder, at least in the cat (Häbler et al, 1990). Most C fibers in this species remain silent during normal filling of the bladder, although in the rat, some studies indicate that C fibers can fire at low pressures (Sengupta and Gebhart, 1994), whereas other studies (Morrison, 1998) showed firing at higher intravesical pressures of approximately 30 mm Hg. After spinal cord injury, a capsaicin-sensitive C fiber-mediated spinal reflex develops (see Fig. 69-25). These C-fiber afferents are thought to play a role in the development of DO after spinal cord injury. Capsaicin-sensitive C fibers have also been implicated in DO after upper motoneuron diseases, such as spinal cord injury and multiple sclerosis (Fowler et al, 1992, 1994; Geirsson et al, 1995; Szallasi and Fowler, 2002). Studies in multiple sclerosis and spinal cord-injured patients with DO also revealed an increased density of TRPV1 and P2X₃ immunoreactivity in suburothelial nerves and increased TRPV1 immunoreactivity in the basal layer of the urothelium (Brady et al, 2004; Apostolidis et al, 2005b). Treatment of these patients with intravesical capsaicin or another C-fiber neurotoxin, RTX, reversed these abnormalities (Brady et al, 2004).

Insight into the mechanisms underlying the increased mechanosensitivity of C fibers after spinal cord injury has been gained by examination of the DRG cells innervating the bladder. Plasticity of these afferents manifests with enlargement of these DRG cells (Kruse et al, 1995) and increased electrical excitability (Yoshimura and de Groat, 1997; Yoshimura, 1999). Upregulation of tetrodotoxin (TTX)-sensitive Na⁺ channels and downregulation of TTX-resistant Na⁺ channels, as well as low-threshold A-type K⁺ channels, occur after spinal cord injury (Yoshimura and de Groat, 1997; Yoshimura, 1999).

Plasticity in bladder afferents after spinal cord injury and upper motoneuron lesions may involve the retrograde transport of substances from either the spinal cord or the bladder to the DRG neuron. NGF has been implicated as a chemical mediator of disease-induced changes in C-fiber afferent nerve excitability and reflex bladder activity (Yoshimura, 1999; Vizzard, 2000). Chronic administration of NGF into bladder afferent pathways induced bladder overactivity and increased the firing frequency of dissociated bladder afferent neurons in rats (Yoshimura et al, 2006), and the production of neurotrophic factors, including NGF, increased in the bladder after spinal cord injury (Vizzard, 2000). Thus it seems that target organ-neural interactions mediated by neurotrophic factors, such as NGF, produced in the bladder may contribute to changes in C-fiber bladder afferent pathways that induce DO and detrusor-sphincter dyssynergia after spinal cord injury. In addition, increased NGF in the spinal cord after spinal cord injury is also responsible for inducing hyperexcitability of C-fiber bladder afferent pathways, and intrathecal application of NGF antibodies, which neutralizes NGF in the lumbosacral spinal cord and DRG, suppresses DO and detrusor-sphincter dyssynergia in spinal cord-injured rats (Seki et al, 2002). Intrathecal administration of NGF antibodies also blocks autonomic dysreflexia in paraplegic rats (Krenz et al, 1999). Thus NGF and its receptors in the bladder or the spinal cord are potential targets for new therapies to suppress DO and detrusor-sphincter dyssynergia after spinal cord injury.

Other neurogenic disorders associated with urgency incontinence respond to intravesical therapy with capsaicin or RTX, suggesting that plasticity in C-fiber afferents could form the neurogenic basis for DO (Geirsson, 1993; Fowler et al, 1994; Szallasi and Fowler, 2002). The emergence of a spinal reflex circuit activated by C-fiber bladder afferents represents a positive feedback mechanism (see Fig. 69-42) that may be unresponsive to voluntary control by higher brain centers and thereby be able to trigger involuntary voiding. The bladder ice-water urodynamic test has been suggested as a method to assess the C fiber-mediated micturition reflex. Although the ice-water test is consistent in a strictly controlled research environment, it has not been adequately sensitive or specific in routine clinical use (Chai et al, 1998; Chancellor et al, 1998).

Neurogenic DO has also been associated with decreased expression and decreased activity of BK channels in the bladder smooth

muscle (Hristov et al, 2013). BK channel activity (opening) underlies phase 2 and 3 hyperpolarization of the smooth muscle AP (see Fig. 69-16) and serves to quell detrusor myocyte excitability. Therefore, reduced expression and/or lessened function of the BK channels would necessarily lead to increased bladder contractions, hence DO. Although decreased BK expression and function in neurogenic DO help explain the mechanism behind neurogenic DO, the cause of decreased BK expression and function was not explored. This reference theorized that teleologically, decreased BK expression or function may be a consequence of a compensatory or adaptive mechanism in spinal cord injury patients that leads to increased detrusor smooth muscle contractility, allowing optimization of bladder emptying in the absence of normal innervation.

KEY POINTS: NEUROGENIC BLADDER

- Normal micturition is associated with a spinobulbospinal reflex mediated by lightly myelinated A δ afferents.
- Unmyelinated C fibers are normally relatively insensitive to gradual distention of the urinary bladder.
- After spinal cord injury, a capsaicin-sensitive C fiber-mediated spinal reflex develops and may play a role in the development of DO.
- Treatment of neurogenic DO patients with intravesical capsaicin or another C-fiber neurotoxin, RTX, produces symptomatic improvement in a subpopulation of these patients and reduces the density of TRPV1 immunoreactivity in nerve fibers and urothelium.
- The bladder ice-water urodynamic test has been suggested as a research method to assess the C fiber-mediated micturition reflex but is not practiced clinically.

Nocturia

It is becoming recognized that nocturia, especially when occurring in isolation from other LUTS, represents a symptom with its own unique set of possible physiologic causes (van Kerrebroeck and Andersson, 2014) including global polyuria, nocturnal polyuria, reduced bladder capacity, sleep disorders, heart failure, and circadian clock disorders. It has been recently shown that the mouse bladder itself exhibits circadian rhythms in expression of Cx43 (Negoro et al, 2012) and furthermore that Cx43 regulates bladder capacity in dark and light cycles of the mouse. During the light cycle, when the mouse is not active (equivalent to the human sleep cycle), Cx43 is downregulated, leading to increased bladder capacity (increased measure of volume voided per micturition). Conversely, during the dark cycle, when the mouse is awake and active, Cx43 is upregulated and bladder capacity is reduced (decreased volume voided per micturition). Transgenic animals with one of the circadian transcriptional regulators, *Cry*, knocked out developed loss of circadian oscillations of bladder capacity associated with loss of Cx43 expression oscillations. This study suggested that loss of the biologic clock mechanism in regulating Cx43 within the bladder may be a contributing mechanism to nocturia and nocturnal enuresis.

Bladder Outlet Obstruction

It is important to understand that the bothersome symptoms of patients with urethral obstruction are in most cases caused by the bladder. BOO, such as that in patients with BPH, often produces detrusor hypertrophy and DO (Gosling et al, 2000; Andersson and Wein, 2004). After chronic partial obstruction of the urethra in rats, the bladder enlarges and is about 15 times heavier, but it has the same shape as in control rats; the growth is mainly accounted for by muscle hypertrophy. The outer surface of the hypertrophic bladder is increased sixfold over that of the controls; the muscle is increased threefold in thickness and is more compact. Mitoses are not found, but there is a massive increase in muscle cell size

(Gabella and Uvelius, 1990). Obstruction-induced DO with irritative voiding symptoms has been attributed to denervation supersensitivity, because increased contractile responses of the bladder smooth muscle to cholinergic agonists have been observed (Speakman et al, 1987; Andersson and Wein, 2004). Alterations in detrusor contractility may also result from changes in contractile proteins (Uvelius et al, 1989; Cher et al, 1990; Chacko et al, 1999, 2004). Changes in the contractile proteins occur in developing bladders and also during bladder hypertrophy (Wang et al, 1995; Wu et al, 1995; Sjuve et al, 1996). Obstructed bladders induced expression of SM-A (DiSanto et al, 2003). The obstructed bladder developed higher levels of force, but with reduced cross-bridge cycling rates (Su et al, 2003). The ratio of SM1 to SM2 isoforms was also changed by BOO (Cher et al, 1996).

Brading and Turner (1994) proposed that all cases of DO have a common feature—detrusor smooth muscle change that predisposes it to unstable contraction. They have demonstrated that DO, as shown in a pig model of obstruction, may occur without participation of a micturition reflex. Mills and coworkers (2000) have also implicated abnormalities in the detrusor muscle and its pattern of innervation in IDO. Compared with the bladder wall in control subjects, there was evidence in the detrusor smooth muscle of altered spontaneous contractile activity consistent with increased electrical coupling of cells, patchy denervation of the detrusor, and potassium supersensitivity (Mills et al, 2000). One of the manifestations of this abnormality is a partial denervation of the detrusor smooth muscle. In rats with BOO induced by partial urethral ligation, acetylcholine release during electric stimulation of obstructed bladder muscle strips was significantly decreased 3 to 6 months after obstruction, along with a reduction in the number of nerve fibers in the obstructed bladder compared with control rats (Murakami et al, 2008). Partial denervation in obstructed bladder leads to various functional changes in smooth muscles including denervation supersensitivity of cholinergic (muscarinic) receptors (Speakman et al, 1987) and increases in purinergic receptor-mediated contractile responses as well as expression of purinergic receptors such as P2X₁ (Boselli et al, 2001; O'Reilly et al, 2001a). Changes in the cell-to-cell communication in detrusor muscles have also been indicated as a mechanism inducing DO, because there is an upregulation of Cx43, a gap-junction protein, in rats with DO induced by BOO (Christ et al, 2003; Mori et al, 2005; Li et al, 2007; Imamura et al, 2009; Miyazato et al, 2009). Increased expression of Cx43 is also identified in the bladders from patients with neurogenic DO (Haferkamp et al, 2004) or with urgency symptoms (Neuhaus et al, 2005). Thus increases in receptor-mediated muscle contractility and interaction among smooth muscle cells can result in coordinated myogenic contraction of the entire bladder and DO.

In addition, another population of cells in the bladder, known as *interstitial cells*, has been proposed to have a pacemaking role in spontaneous activity of the bladder (Andersson and Arner, 2004). Because it has been reported that the number of interstitial cells is increased in a guinea pig model of BOO (Kubota et al, 2008) and that c-KIT tyrosine kinase inhibitors, which inhibit interstitial cell activity, decreased the amplitude of spontaneous contractions in the guinea pig and human bladder (Biers et al, 2006; Kubota et al, 2006), interstitial cells may also be involved in the emergence of DO as a result of enhanced autonomous detrusor muscle activity.

Alterations also occur in neural networks in the CNS after obstruction of the LUT. BOO in rats causes enhancement of a spinal reflex (Steers and de Groat, 1988). Similarly, in humans with obstruction, a capsaicin-sensitive spinal reflex can be detected by the ice-water test (Chai et al, 1998; Hirayama et al, 2003, 2005). Within the spinal cord, obstruction stimulates an increased expression of GAP43 that has been associated with axonal sprouting after injury (Steers et al, 1996). These observations suggest an enhancement or de novo development of new spinal circuits after obstruction. Similar to spinal cord injury, obstruction causes hypertrophy of bladder afferent and efferent neurons (Steers et al, 1990, 1991). A hypothesis proposed is that these newly formed spinal circuits (neuroplasticity), once formed, do not reverse easily even if

obstruction is relieved because of persistent increased voiding frequency after relief of obstruction (Chai et al, 1999). An immunohistochemical analysis of the distribution and density of GAP43 showed that this protein was increased in the spinal cord in the region of the sacral parasympathetic nucleus in rats with BOO (Steers et al, 1996). Because this protein is a marker for axonal sprouting, its upregulation provides further indirect support for morphologic plasticity in afferent pathways after BOO. Nevertheless, these findings are not mutually exclusive of changes in the bladder smooth muscle, which are also likely to participate in the development of DO (Turner and Brading, 1997).

BOO appears to initiate the morphologic and electrophysiologic afferent plasticity through a mechanism involving NGF (see Fig. 69-42). NGF is responsible for the growth and maintenance of sympathetic and sensory neurons and has been shown to be responsible for neuronal regrowth after injury. NGF content is increased in obstructed bladders in animals and in humans (Steers et al, 1991). This increase in NGF content precedes the enlargement of bladder neurons and the development of urinary frequency (Steers et al, 1990, 1991). Moreover, blockade of NGF action with autoantibodies prevents the neural plasticity and urinary frequency after obstruction (Steers et al, 1996). In animals with persistent urinary frequency after relief of obstruction, NGF remains elevated in the bladder. These findings suggest a cause-and-effect relationship between NGF-mediated changes in bladder afferents and an enhanced spinal micturition reflex and urinary frequency associated with obstruction. Increased levels of urinary NGF have also been detected in BOO patients exhibiting OAB symptoms. Total urinary NGF levels were low in controls (0.5 pg/mL) and in patients with BOO without OAB symptoms (1 pg/mL), but considerably higher in patients with BOO and OAB symptoms (41 pg/mL) or BOO and DO (50 pg/mL). Investigators have examined urinary NGF before and after mid-urethral slings in females and found significantly increased NGF, corrected for creatinine, after mid-urethral slings (Chai et al, 2014), consistent with the finding that mid-urethral slings have a urodynamic cause of increased PdetQ-max (Kraus et al, 2011).

KEY POINTS: BLADDER OUTLET OBSTRUCTION

- Obstruction-induced DO with irritative voiding symptoms has been attributed to denervation supersensitivity, because increased contractile responses of the bladder smooth muscle to cholinergic agonists have been observed. Alterations in detrusor contractility may also result from changes in contractile proteins.
- Increases in receptor-mediated muscle contractility and interaction among smooth muscle cells have been observed with BOO.
- BOO in rats causes enhancement of a spinal reflex.
- Bladder tissue and urine NGF content is increased in obstructed bladders in animals.

Bladder Pain Syndrome and Interstitial Cystitis

BPS/IC is a syndrome characterized primarily by pain attributable to the bladder associated with urinary frequency and urgency. This condition has no defined cause, although this section will present data from animal studies that offer some theoretical origins. In Europe, the diagnosis of BPS/IC typically requires a bladder biopsy showing overt inflammation, so it is no surprise that histologic analysis of bladders from European patients with BPS/IC revealed marked edema, vasodilation, proliferation of nerve fibers, and infiltration of mast cells (Johansson and Fall, 1997). However, the diagnosis of BPS/IC in the United States is driven primarily by symptoms of chronic bladder pain and urinary frequency and urgency in the absence of urinary tract infection (UTI). In the United States, the diagnostic test, if performed, usually is hydrodistention of the bladder; and if a biopsy is performed,

rarely is it a deep biopsy of the bladder stroma. The appearance of glomerulations (petechiae) after hydrodistention of the bladder as a diagnostic criterion for BPS/IC was first described by Messing and Stamey (1978), although the diagnostic specificity of glomerulations was questioned (Waxman et al, 1998). It appears that the diagnostic approach to BPS/IC varies between the United States and Europe.

Traditionally, BPS/IC is categorized as an inflammatory bladder disease, although the cause of the inflammation remains elusive (and some question whether BPS/IC is even an inflammatory disease). Cyclophosphamide-induced hemorrhagic cystitis has been used to model for BPS/IC, although there is no relationship between these two entities. Although the chemical cystitis model is important in understanding the neurobiologic response to inflammation, the relevance to BPS/IC remains to be validated in translational clinical trials.

Chemical cystitis resulted in sensitizing mechanosensitive afferents and/or recruitment of afferents normally unresponsive to mechanical stimulation (i.e., silent C fibers) (Häbler et al, 1990; Sengupta and Gebhart, 1994; Dmitrieva and McMahon, 1996; Dmitrieva et al, 1997) and results in bladder inflammation. Proinflammatory agents, such as PGE₂, serotonin (5-HT), histamine, bradykinin, and adenosine, as well as neurotrophic factors such as NGF, which are released during chemical irritation, can induce bladder hyperactivity, as well as functional and chemical changes in C-fiber afferents that can lead to hyperexcitability (Dmitrieva and McMahon, 1996; Gold et al, 1996). For example, chronic chemical irritation of the bladder changes ion channel function in bladder afferent neurons and also increases the expression of various markers, including NOS (Vizzard et al, 1996), GAP43 (Vizzard and Boyle, 1999), PACAP, SP (Vizzard, 2001), and protease-activated receptors (Dattilio and Vizzard, 2005). The density of peptidergic afferent nerves also increases in the bladder mucosa and detrusor muscle (Dickson et al, 2006), and afferent peptidergic axons and parasympathetic efferent axons and varicosities are commonly observed in close contact, suggesting that sprouting of peripheral nerves occurs during chronic cystitis.

Cystitis also induces chemical changes in the spinal cord. Acute or chronic bladder irritation increases immediate early gene expression (*c-FOS*) in spinal neurons (Birder and de Groat, 1993), as well as increasing in GFR α 1-IR in the spinal dorsal horn and in areas associated with autonomic neurons (Forrest and Keast, 2008). There was a much smaller increase in GFR α 3-IR and no change in GFR α 2-IR. Changes in spinal cord mitogen-activated protein (MAP) kinases (extracellular signal-related kinases 1 and 2 [ERK1 and ERK2]) may also play a role in the facilitation of reflex voiding after bladder inflammation. Immunohistochemical studies revealed that, in noninflamed rat bladders, noxious but not non-noxious stimulation significantly increased phospho-ERK immunoreactivity (Cruz et al, 2007). After bladder inflammation, innocuous and noxious bladder distention increased the number of spinal neurons exhibiting phospho-ERK-immunoreactivity. ERK inhibition with intrathecal injection of PD98059 decreases reflex bladder activity and spinal *c-FOS* expression in animals with inflamed bladders but not in normal animals (Cruz et al, 2007). The results suggest that activation of spinal cord ERK contributes to acute and chronic inflammatory pain perception and mediates reflex bladder overactivity accompanying chronic bladder inflammation.

Direct evidence linking chronic bladder inflammation with functional changes in C-fiber afferents has been obtained in rat chronic cystitis models induced by cyclophosphamide or hydrochloric acid. In these models, the electrical properties of bladder afferent neurons (dissociated from L6 and S1 DRG), as well as the activity of the inflamed bladder, were measured. The majority of bladder afferent neurons from both control and cyclophosphamide-treated rats are capsaicin sensitive and exhibit high-threshold TTX-resistant APs and Na⁺ currents. However, neurons from rats with cystitis exhibit significantly lower thresholds for spike activation and show tonic rather than phasic firing characteristics (Hayashi et al, 2009b). Other significant changes in bladder afferent neurons from cystitis rats include increased somal diameter, increased input capacitance,

and decreased density of slowly inactivating A-type K^+ (K_A) currents (Yoshimura and de Groat, 1999; Hayashi et al, 2009b). In addition, the reduction in K_A currents in the hydrochloric acid-induced cystitis model was associated with reduced expression of the Kv1.4 α -subunit protein (which can form K_A channels) in bladder afferent neurons (Hayashi et al, 2009b), suggesting that the Kv1.4 subunit may be a molecule responsible for reduced K_A currents and increased excitability of bladder afferent neurons after cystitis. Previous experiments using cats with naturally occurring feline-type IC have also demonstrated that capsaicin-sensitive dorsal root ganglion neurons exhibit an increase in cell size and increase in firing rates of depolarizing current pulses because of a reduction in low-threshold K^+ currents (Sculptoreanu et al, 2005). Accordingly, chronic inflammation in BPS/IC could induce both cell hypertrophy and hyperexcitability of C-fiber bladder afferent neurons. If these changes in neuronal cell bodies also occur at C-fiber afferent terminals in the bladder wall, such hyperexcitability may represent an important mechanism for inducing pain in the inflamed bladder. This is supported by some clinical studies showing that C-fiber desensitization induced by intravesical application of capsaicin or RTX is effective for treating painful symptoms in patients with BPS/IC (Lazzeri et al, 1996, 2000), although a previous prospective, randomized clinical trial using intravesical RTX application was not effective in patients with BPS/IC (Payne et al, 2005).

There is little information available about the neuroplasticity of A δ -fiber bladder afferents in BPS/IC. However, a previous study (Roppolo et al, 2005) using single nerve fiber recordings has documented that A δ -fiber bladder afferents in cats with feline-type IC are more sensitive to bladder pressure changes than afferents in normal cats, suggesting that, in addition to neuroplasticity of C-fiber afferents, A δ -fiber bladder afferents might also undergo functional changes in BPS/IC.

Chronic bladder inflammation can also induce changes in functional properties of chemosensitive receptors such as TRPV1 in sensory neurons. Sculptoreanu and colleagues (2005) reported that DRG neurons obtained from cats with feline IC exhibit capsaicin-induced responses that are larger in amplitude and desensitize more slowly compared with those obtained from normal cats, and that altered TRPV1 receptor activity in cats with feline IC is reversed by an application of an inhibitor of PKC, suggesting that BPS/IC can alter TRPV1 activity owing to enhanced endogenous PKC activity. Because TRPV1 receptors are reportedly responsible, at least in part, for bladder overactivity elicited by cyclophosphamide-induced cystitis (Dinis et al, 2004), enhanced activity of TRPV1 receptors could contribute to bladder pain in BPS/IC. Studies in mice have also demonstrated a role of TRPV1 in cystitis. Systemic treatment with cyclophosphamide or intravesical administration of acrolein (the irritant metabolite of cyclophosphamide) produces not only bladder hyperactivity but also a sensitization of the paw withdrawal responses to mechanical stimulation of the paw (mechanical hyperalgesia). These responses do not occur in TRPV1 knockout mice (Charrua et al, 2007; Wang et al, 2008). In addition, GRC-6211, a new oral-specific TRPV1 antagonist, has been shown to decrease bladder overactivity and noxious bladder input in cystitis animal models (Charrua et al, 2009).

Afferent mechanisms can also explain coexistence of pelvic organ hyperalgesia, such as BPS/IC and IBS. The animal model for this phenomenon is pelvic organ cross-sensitization. In this model, the rectum is exposed to a chemical irritant, with the resultant development of bladder afferent sensitivity, involvement of the C-fiber afferents, and bladder mast cell activation (Ustinova et al, 2006; Pan et al, 2010; Ustinova et al, 2010; Asfaw et al, 2011; Malykhina et al, 2013).

NGF has also attracted attention as a mediator in the link between experimentally induced inflammation and pain signaling in BPS/IC. NGF is expressed widely in various cells, including urothelial cells, smooth muscle cells, and mast cells, and can activate mast cells to degranulate and proliferate. In the cyclophosphamide-induced chronic cystitis model in rats, increased expression of neurotrophic growth factors, such as NGF, brain-derived neurotrophic factor (BDNF), and CNTF in the bladder, as

well as phosphorylation of tyrosine kinase receptors (TrkA, TrkB) in bladder afferent neurons, has also been presented as direct evidence for increased neurotrophin-mediated signaling in chronic bladder inflammation (Vizzard, 2000; Qiao and Vizzard, 2002). The enhanced neurotrophic factor mechanisms are also associated with increased phosphorylated cAMP response-element binding protein (CREB) in bladder afferent neurons. Phosphorylated CREB, which is a transcription factor in the neurotrophin intracellular signaling pathway, is coexpressed with phosphorylated TrkA in a subpopulation of bladder afferent neurons (Qiao and Vizzard, 2004). RTX, a C-fiber neurotoxin, reduced cyclophosphamide-induced upregulation of phosphorylated CREB in DRG cells, suggesting that cystitis is linked with altered CREB phosphorylation in capsaicin-sensitive C-fiber bladder afferents (Qiao and Vizzard, 2004). These results suggest that upregulation of phosphorylated CREB may be mediated by a neurotrophin/TrkA signaling pathway, and that CREB phosphorylation may play a role as a transcription factor in LUT plasticity induced by chemical cystitis. In patients with BPS/IC, neurotrophins, including nerve growth factor, neurotrophin-3 (NT-3), and glial cell-derived neurotrophic factor (GDNF), have been detected in the urine (Okragly et al, 1999). Increased expression of NGF is also present in bladder biopsy specimens from women with IC (Lowe et al, 1997; Liu et al, 2014).

Exogenous NGF can induce bladder nociceptive responses and bladder overactivity in rats when applied acutely into the bladder lumen (Dmitrieva et al, 1997; Chuang et al, 2001) or chronically to the bladder wall or intrathecal space (Lamb et al, 2004; Yoshimura et al, 2006; Zvara and Vizzard, 2007). Conversely, application of NGF-sequestering molecules (TrkA-IgG or REN1820) can reduce referred thermal hyperalgesia elicited by bladder inflammation induced by intravesically applied turpentine oil (Jaggar et al, 1999) or bladder overactivity elicited by cyclophosphamide-induced cystitis (Hu et al, 2005), suggesting that increased NGF expression is directly involved in the emergence of bladder-related nociceptive responses in cystitis. A urothelially restricted NGF expression transgenic animal has also been created (Schneegelsberg et al, 2010). This animal has increased voiding frequency and evidence of increased pelvic pain. The suburothelial nerve fibers also vastly expanded with hyperinnervation of the bladder with significantly increased mast cells in the bladder stroma, consistent with the trophic effects of NGF on this cell type. However despite these data, targeted treatment with monoclonal anti-NGF antibody, tanezumab, did not prove efficacious in BPS/IC patients (Evans et al, 2011). This may be a result of phenotyping issues in enrollment, and perhaps an entry criterion of threshold level of increased NGF would be required to show an effect. As discussed in a prior section, the use of NGF as a biomarker in evaluation and management of LUTD is still unresolved (Ochodnick et al, 2011).

Purinergic mechanisms may also contribute to the bladder dysfunction in BPS/IC. ATP release from the urothelium is enhanced in patients and cats with BPS/IC (Sun et al, 2001; Birder et al, 2003). In conscious rats with cyclophosphamide-induced cystitis, purinergic receptor antagonists (pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid [PPADS] and A-317491) reduced nonvoiding contractions and decreased voiding frequency (Ito et al, 2008). In in vitro whole-bladder pelvic afferent nerve preparations from rats with cyclophosphamide-induced cystitis, afferent nerve firing induced by bladder distention or by direct electric stimulation was markedly increased compared with firing in normal rats (Yu and de Groat, 2008). Exogenous purinergic agonists mimic the facilitatory effects of cyclophosphamide treatment, and P2X purinergic receptor antagonists suppress the effects of purinergic agonists and cystitis. These results suggest that endogenous purinergic agonists released in the inflamed bladder can enhance the excitability of bladder afferent nerves by activating P2X receptors. Patch clamp studies on bladder afferent neurons from rats revealed that chronic cyclophosphamide treatment increases the currents induced by purinergic agonists in both thoracolumbar and lumbosacral neurons (Dang et al, 2008). Analysis of the kinetics of the currents indicated that increased receptor expression and/or properties of homomeric P2X₃ in thoracolumbar neurons and P2X_{2/3} in

lumbosacral neurons contributes to the enhanced responses during cystitis. Investigations with human BPS/IC bladder urothelial specimens found that stretch of cultured bladder urothelial cells resulted in significantly increased ATP release (Sun et al, 2001) and increased P2X₃ expression on the cells (Sun and Chai 2004; Tempest et al, 2004).

Another animal model for BPS/IC is chronic psychological stress inflicted by water avoidance stress (WAS) testing. In this model, a rat is placed on a narrow surface suspended over water. The rat becomes stressed because it must maintain balance to avoid getting wet. Changes in bladder neurophysiology then can be studied after chronic WAS. It was found that chronic WAS significantly enhanced visceral organ, including bladder, nociceptive responses (Bradesi et al, 2005; Robbins et al, 2007; Smith et al, 2011). Chronic WAS was noted to cause increased mast cell activity in the bladder, which was blocked with treatment with melatonin and montelukast (Cikler et al, 2005). Because stress mechanisms involve the brain, it could be theorized that the development of visceral hyperalgesia with chronic WAS involves brain mechanisms, which now can be imaged with fMRI, in maintenance of the chronic pain state (Phillips and Clauw, 2011).

A search for urinary factors that might be a cause of BPS/IC resulted in discovery of antiproliferative factor (APF) by Keay and colleagues (1996, 1998). APF's structure was found to be a sialated glyconapeptide with sequence homology to a portion of the frizzled 8 protein of the Wnt signaling pathway (Keay et al, 2004). APF's receptor in the urothelial cell was found to be cytoskeletal-associated protein, CKAP4/p63 (Conrads et al, 2006). CKAP4/p63 is a palmitoylated protein that physically links the endoplasmic reticulum to the microtubules (Vedrenne et al, 2005). It is also a cell surface receptor for tissue plasminogen activator (Razzaq et al, 2003) and surfactant protein A (Gupta et al, 2006). CKAP4/p63 is a major substrate for a putative tumor suppressor enzyme, palmitoyl acyltransferase DHHC2 (Zhang et al, 2008), which may help explain APF's antiproliferative activity against urothelial cells. A mouse model in which intravesical application of APF resulted in similar bladder urothelial changes detected in human urothelium was published (Keay et al, 2012). Whether the understanding of APF biology can be integrated into care of BPS/IC patients remains to be seen.

KEY POINTS: BLADDER PAIN SYNDROME AND INTERSTITIAL CYSTITIS

- Histologic analysis of bladders from patients with BPS/IC often revealed marked edema, vasodilation, proliferation of nerve fibers, and infiltration of mast cells.
- NGF appears to be a key player in the link between inflammation and altered pain signaling. NGF is expressed widely in various cells, including urothelial cells, smooth muscle cells, and mast cells, and can activate mast cells to degranulate and proliferate.
- Application of NGF-sequestering molecules can reduce bladder overactivity elicited by cyclophosphamide-induced cystitis.
- Direct evidence linking chronic bladder inflammation with functional changes in C-fiber afferents has been obtained in rat chronic cystitis models. Chronic bladder inflammation can also induce changes in functional properties of chemosensitive receptors, such as TRPV1 in sensory neurons.

Aging

LUTS, such as increased voiding frequency, urgency, urgency incontinence, and poor bladder emptying, are common and troublesome problems in older men and women (Resnick, 1995; Naughton and Wyman, 1997; Nuotio et al, 2002). Previous studies have reported various changes in LUT function, including a reduction in bladder capacity, increased bladder sensation, and DO (Diokno et al, 1986;

Homma et al, 1994; Hald and Horn, 1998; Madersbacher et al, 1998, 1999; Nuotio et al, 2002). However, few studies have addressed the normal changes in the LUT that occur with aging. Studies by Pfisterer and colleagues (2006) have examined age-related changes in bladder function among 85 community-dwelling female volunteers and demonstrated that detrusor contractility, bladder sensation, and urethral pressure decline with age and that a reduction in bladder capacity associated with age may be related to DO rather than to aging itself, because bladder capacity did not decrease with age, but was smaller in subjects with DO (Pfisterer et al, 2006). Thus aging appears to induce hypofunction of the bladder and urethra in humans.

In animal studies, impaired bladder function, as evidenced by increased voided volume per micturition associated with a high micturition-pressure threshold, has also been demonstrated in aged rats compared with the young counterpart (Chun et al, 1988; Chai et al, 2000). In addition, aged rats exhibit reduced sensitivity of pelvic nerve afferents in response to increased bladder volume, but not pressure, and a reduction in the maximal bladder pressure generated during pelvic nerve stimulation (Hotta et al, 1995). In aging mice, bladder contractility was normal, but bladder afferent signaling was diminished (Smith et al, 2012a).

A significant linear reduction in the amount of acetylcholinesterase-positive nerve was observed with increasing age in the human bladder (Gilpin et al, 1986), suggesting reduced parasympathetic innervation of the aged bladder. It was also shown that expression of neuropeptides, such as CGRP and SP in lumbosacral DRG neurons, decreases with age (Mohammed and Santer, 2002) and that there is a marked reduction in the density of PACAP innervation of the subepithelial plexus and of the muscle layer of the bladder base, as well as slight reductions in CGRP and SP innervation of the muscle layer in old rats (Mohammed et al, 2002). Taken together, these results suggest that impaired activity of the aged bladder is likely, at least in part, a result of reduced activity of efferent and afferent nerves innervating the bladder.

Changes in the CNS in relation to LUT function have also been demonstrated in aged animals. Immunohistochemical analyses in aged rats revealed significant age-associated declines in the serotonergic (5-HT) and adrenergic innervation of various spinal cord regions, including the intermediolateral cell nucleus, sacral parasympathetic nucleus, dorsal gray commissure, and the ventral horn nucleus that contains the Onuf nucleus. However, 5-HT innervation of the sacral parasympathetic nucleus and tyrosine hydroxylase-like immunoreactivity in the ventral horn nucleus were maintained (Ranson et al, 2003). It was also shown that sympathetic preganglionic neurons in the L1-L2 spinal cord that project to the major pelvic ganglion exhibit a number of degenerative changes, such as reductions in the cell number, the length of their dendrites, and the synaptic contact made by glutamate-immunoreactive boutons onto the dendrites in aged rats, although these changes are not seen in parasympathetic preganglionic neurons in the L6-S1 spinal cord (Santer et al, 2002). Chai and colleagues also reported that frequent voiding produced by apomorphine-induced dopamine receptor activation is more pronounced in aged rats compared with young rats, suggesting that aged rats are more susceptible to altered central processing to induce bladder overactivity despite decline of baseline bladder function with aging (Chai et al, 2000). Hypoactivity of the bladder or the underactive bladder represents an unmet medical need moving forward in light of the aging populations in developed countries (Chancellor and Kaufman, 2008).

In contrast to altered nerve activity, there appears to be no significant change in detrusor contractile responses to cholinergic or electric stimulation between young and old animals (Chun et al, 1989; Longhurst et al, 1992; Yu et al, 1996; Lieu et al, 1997; Lin et al, 1997; Schneider et al, 2004b), although old rats have a reduced density of muscarinic receptors in the bladder (Schneider et al, 2004b). In contrast, there are some reports of age-related changes of the detrusor response to adrenergic stimulation (Latifpour et al, 1990). Most studies showed that detrusor contractile responses to α -adrenergic stimulation increased in old male and female rats (Saito et al, 1991, 1993; Nishimoto et al, 1995; Lin et al,

1997) in association with upregulation of α_{1D} -receptor expression in the bladder (Dmitrieva et al, 2008). However, another study showed no age-dependent changes in α_1 -adrenoceptor properties, such as phenylephrine-induced contractile responses, total receptor density, and mRNA expression of α_1 -adrenoceptor subtypes (α_{1A} , α_{1B} , and α_{1D}) in the rat bladder base and dome (Yono et al, 2006). The detrusor response to β -adrenergic stimulation is reduced in old male rats (Nishimoto et al, 1995; Lin et al, 1997), along with a reduction in the density of β -adrenergic receptors and decreased cAMP production (Nishimoto et al, 1995) in response to β -adrenergic stimulation. The combination of increased α -adrenergic excitatory response and decreased β -adrenergic inhibitory response results in a net contracting effect of norepinephrine on the aged bladder, in contrast to the relaxing effect of norepinephrine in the young bladder (Lin et al, 1997). However, the contribution of these changes in adrenoceptor properties to age-related alterations in LUT function is still to be determined.

KEY POINTS: AGING

- Bladder sensation and urethral pressure decline with age, and a reduction in bladder capacity associated with age may be related to DO rather than to aging itself, because bladder capacity was not seen to decrease with age but was smaller in subjects with DO. Thus aging appears to induce hypofunction of the bladder and urethra in humans.
- In contrast to altered nerve activity, there appears to be no significant change in detrusor contractile responses to cholinergic or electric stimulation between young and old animals.
- Most studies have shown that detrusor contractile responses to α -adrenergic stimulation increase and that detrusor-relaxing responses to β -adrenergic stimulation decrease in old rats.

Neuromodulation

Hypothesis of Mechanism of Action of Sacral Neuromodulation

Neuromodulation of the sacral nerves and, more recently, pudendal and posterior tibial nerves is now used for the treatment of

refractory OAB and urinary retention relating to pelvic floor dysfunction (Das et al, 2004; Leng and Chancellor, 2005; Herbison and Arnold, 2009). Some have criticized the inconsistency that electric stimulation of the sacral nerve can paradoxically inhibit the OAB and conversely promote bladder emptying in patients with idiopathic nonobstructive urinary retention. The effects of sacral neuromodulation may depend on electric stimulation of afferent axons in the spinal roots, which in turn modulate voiding and continence reflex pathways in the CNS. The afferent system is the most likely target, because beneficial effects can be elicited at intensities of stimulation that do not activate movements of striated muscles (Vadusek et al, 1986; Thon et al, 1991; de Groat et al, 1997). Sacral neuromodulation activates somatic afferent axons that modulate sensory processing and micturition reflex pathways in the spinal cord. Urinary retention and dysfunctional voiding can be resolved by inhibition of the guarding reflexes. DO can be suppressed by direct inhibition of bladder preganglionic neurons. Inhibition of interneuronal transmission in the afferent limb of the micturition reflex can also block DO. Thus the principle behind sacral neuromodulation can be summarized as somatic afferent inhibition of sensory processing in the spinal cord.

Rationale for Neuromodulation to Facilitate Voiding

In adults, brain pathways are necessary to turn off sphincter and urethral guarding reflexes to allow efficient bladder emptying. Thus spinal cord injury produces bladder-sphincter dyssynergia and inefficient bladder emptying by eliminating the brain mechanisms involved (Fig. 69-43). This may also occur after more subtle neurologic lesions in patients with idiopathic urinary retention, such as after a bout of prostatitis or UTI. Before the development of brain control of micturition, at least in animals, the stimulation of somatic afferent pathways passing through the pudendal nerve from the perineum can initiate efficient voiding by activating bladder efferent pathways and turning off the excitatory pathways to the urethral outlet (de Groat et al, 1993; Kruse and de Groat, 1993). Tactile stimulation of the perineum in the cat also inhibits the bladder-sympathetic reflex component of the guarding reflex mechanism. The sacral nerve stimulation may elicit similar responses in patients with urinary retention, and it may turn off excitatory outflow to the urethral outlet and promote bladder emptying. Because sphincter activity can generate afferent input to the spinal cord that can, in turn, inhibit reflex bladder activity, an indirect

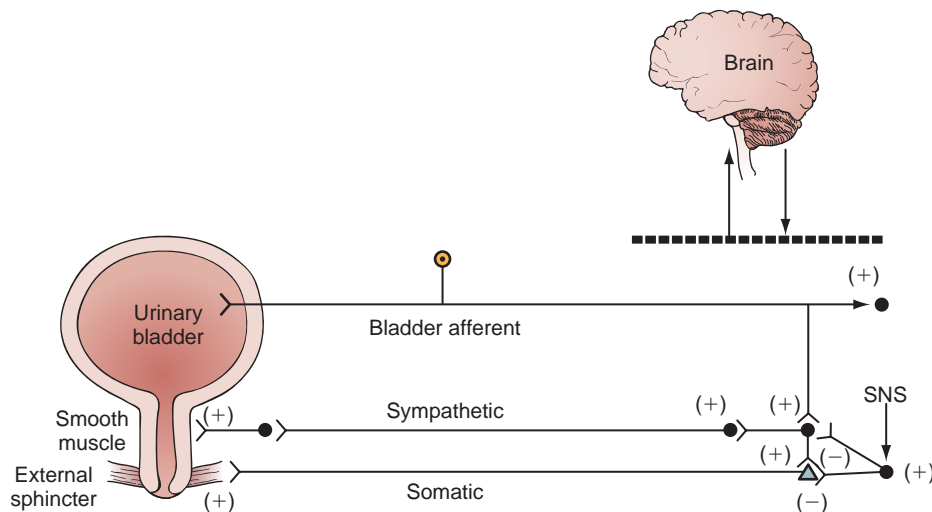


Figure 69-43. When there is a sudden increase in intravesical pressure, such as during a cough, the urinary sphincter contracts by means of the spinal guarding reflex to prevent urinary incontinence (guarding reflex). The spinal guarding reflexes can be turned off by the brain for urination. In cases of neurologic diseases, the brain cannot turn off the guarding reflex, and retention can occur. Sacral nerve stimulation (SNS) restores voluntary micturition in cases of voiding dysfunction and urinary retention but inhibits the guarding reflex.

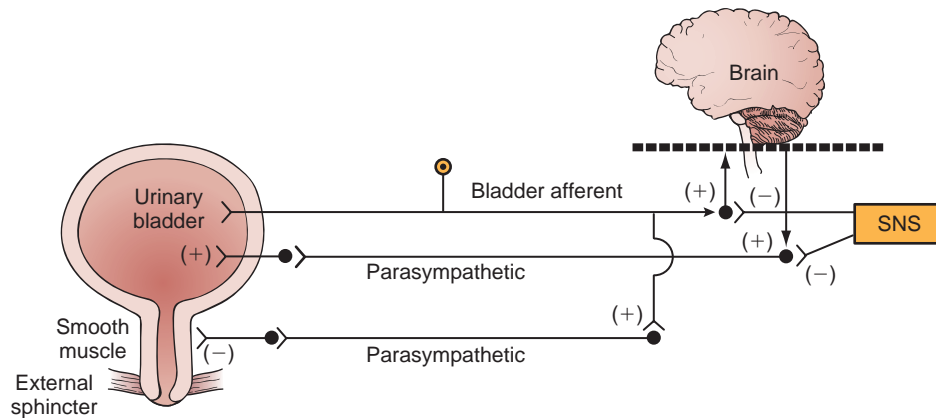


Figure 69-44. The voiding reflex involves afferent neurons from the bladder that project on spinal tract neurons that ascend to the brain. Descending pathways connect to parasympathetic efferent nerves to contract the bladder (bladder-bladder reflex). A spinal bladder-urethra reflex is activated by a similar bladder afferent innervation. In cases of supraspinal dysfunction, overactive micturition reflexes occur. Sacral nerve stimulation (SNS) inhibits urinary urgency, frequency, and urge incontinence by inhibiting the bladder-bladder and bladder-urethra reflexes.

benefit of suppressing sphincter reflexes would be a facilitation of bladder activity.

Rationale for Neuromodulation to Inhibit the Overactive Bladder

Several reflex mechanisms may be involved in the sacral neuromodulation suppression of DO. Afferent pathways projecting to the sacral cord can inhibit bladder reflexes in animals and humans. The source of afferent input may be from sphincter muscles, distal colon, rectum, anal canal, vagina, uterine cervix, and cutaneous afferents from the perineum (Fig. 69-44). As mentioned previously, two mechanisms have been identified in animals for somatic and visceral afferent inhibition of bladder reflexes. The most common mechanism is suppression of interneuronal transmission in the bladder reflex pathway (de Groat and Theobald, 1976; Kruse et al, 1990; Kruse and de Groat, 1993). It is assumed that this inhibition occurs, in part, on the ascending limb of the micturition reflex and therefore blocks the transfer of information from the bladder to the PMC. This action would prevent involuntary (reflex) micturition but not necessarily suppress voluntary voiding that would be mediated by descending excitatory efferent pathways from the brain to the sacral parasympathetic preganglionic neurons. A second inhibitory mechanism is mediated by a direct inhibitory input to the bladder preganglionic neurons. This can be induced by electric stimulation of the pudendal nerve or by mechanical stimulation of the anal canal and distal bowel. It is not elicited by tactile stimulation of penile or perineal afferents; this mechanism would be much more effective in turning off bladder reflexes, because it would directly suppress firing in the motor outflow from the spinal cord.

Pudendal Nerve Stimulation

The pudendal nerve is a peripheral branch of the sacral nerve roots, and stimulating the pudendal allows afferent stimulation to all three of the sacral nerve roots (S2, S3, S4), and that may raise the stimulation threshold needed for micturition and inhibit detrusor activity. Because this is a more peripheral nerve, it is less likely that stimulation of the sciatic and sural nerves will occur, thus decreasing the potential risk for discomfort in the thighs, calves, and feet as seen on occasion with sacral stimulation at the S3 nerve root. The pudendal nerve arises from the sacral plexus within the pelvis; it must go around the pelvic floor to reach the ischioanal fossa. In the pelvis, it runs on the piriformis and then passes laterally through

the greater sciatic foramen to enter the gluteal region. Here it lies inferior to the piriformis as does the sciatic nerve, the inferior gluteal neurovascular bundle, and the nerve to the quadratus femoris. The pudendal nerve curls around the spine of the ischium, lying superficial to the sacrospinous ligament, and then passes into the lesser sciatic notch to enter the ischioanal fossa. The nerve then divides into the inferior rectal, the perineal, and the dorsal nerve of the penis or clitoris.

Afferent pudendal nerve stimulation has been demonstrated to inhibit the micturition reflex, abolish uninhibited detrusor contractions, and increase bladder capacity in animals and humans (Fall and Lindstrom, 1991). Peters and colleagues (2005) compared the effectiveness of sacral and pudendal nerve stimulation for voiding dysfunction in a prospective, single-blind, randomized crossover trial including 30 patients (22 with urgency or frequency, 5 with urgency incontinence, and 3 with urinary retention) scheduled for sacral implantation of a tined quadripolar lead who consented to the placement of a second pudendal lead. Twenty-four of the 30 patients demonstrated a significant clinical response and had an implantable pulse generator placed. Sacral nerve stimulation resulted in 46% improvement in symptoms, whereas pudendal nerve stimulation demonstrated 63% improvement in symptoms. Urgency-incontinence episodes were reduced by approximately 47%; however, this did not reach statistical significance because of small sample size ($n = 5$).

Inhibitory and Excitatory Stimulation Frequencies of the Pudendal-Bladder Reflexes

The exact mechanism of action of neuromodulation is unknown. In addition, there are no studies involving neuromodulation that look at programming parameters (pulse width, intensity, or frequency) and their impact on voiding function. The pudendal nerve may have a dual mechanism depending on the frequency and continuity of stimulation. A recent study by Tai and colleagues (2007) in anesthetized spinal cord-injured cats demonstrated that at 3 Hz, stimulation of the pudendal nerve inhibited bladder function and decreased bladder pressures, whereas intermittent stimulation at 20 Hz improved the efficiency of the bladder to empty (Tai et al, 2007). Furthermore, the clinical outcomes of continuous (which potentially can fatigue the urethral sphincter and accommodate the nerve) and intermittent stimulation have not been explored. It would directly suppress firing in the motor outflow from the spinal cord.

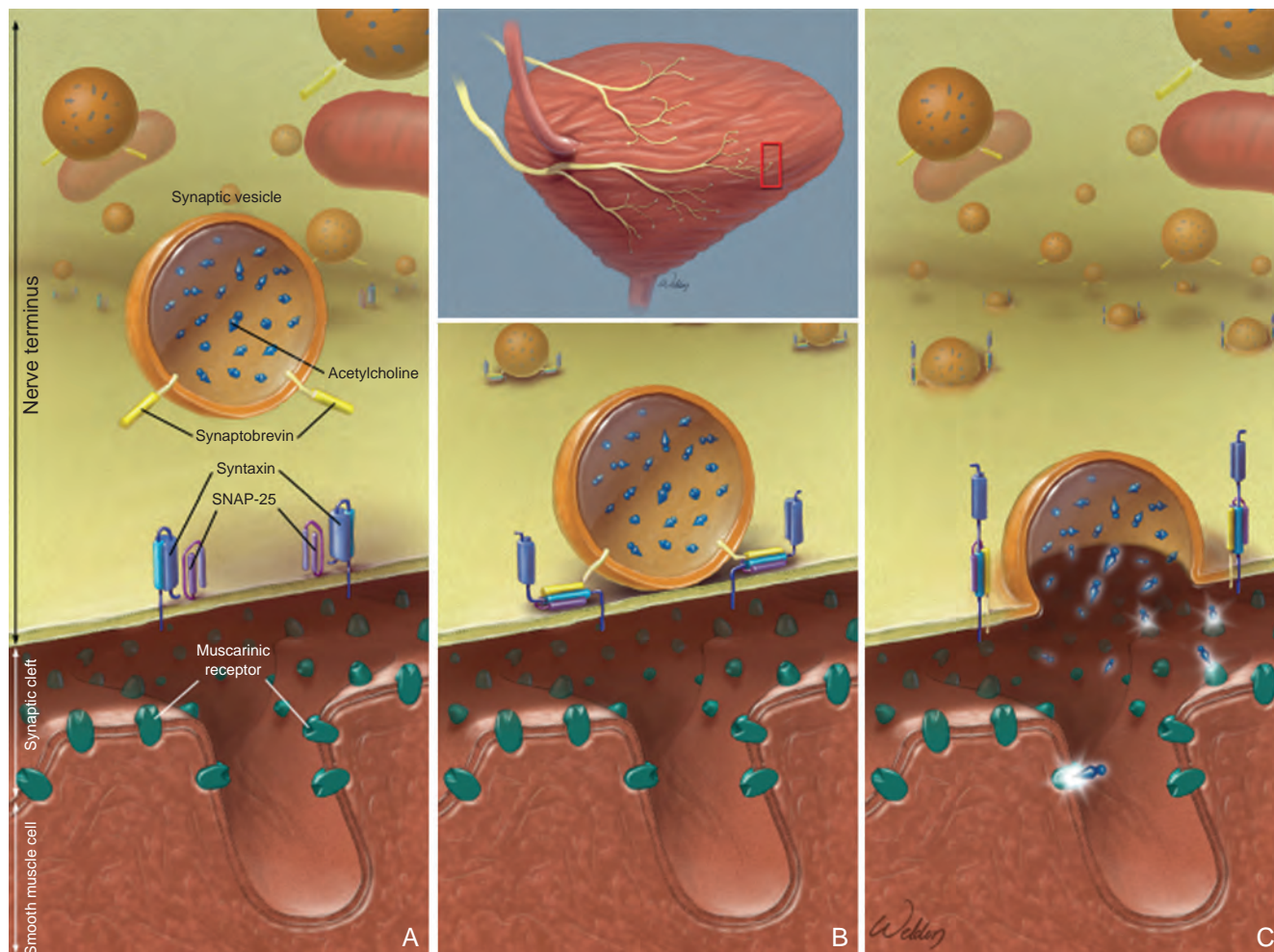


Figure 69-45. Schematic diagram demonstrating normal fusion and release of acetylcholine from nerve terminals through interaction of vesicle and membrane-bound (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor [SNARE]) proteins. Parasympathetic nerves innervate the urinary bladder (*inset*) with (A) nerve terminal in an unactivated state displaying numerous vesicles containing the neurotransmitter acetylcholine. B, After nerve activation, assembly of the SNARE protein complex (e.g., synaptobrevin, SNAP-25, and syntaxin) leads to (C) release of acetylcholine and activation of postjunctional muscarinic receptors, resulting in bladder contraction.

OnabotulinumtoxinA Neuromodulation

In recent years, there has been increasing evidence for the therapeutic efficacy of OBTX for the treatment of various urethral and bladder dysfunctions (Smith and Chancellor, 2004; Apostolidis and Fowler, 2008).

Botulinum toxins act by inhibiting ACh release at the presynaptic cholinergic nerve terminal, thereby inhibiting striated and smooth muscle contractions. The toxins are synthesized as single-chain polypeptides with a molecular weight of about 150 kD (Das-Gupta, 1994). Initially, the parent chain is cleaved into its active dichain polypeptide form, consisting of a heavy chain (approximately 100 kD) connected by a disulfide bond to a light chain (approximately 50 kD) with an associated zinc atom (Schiavo et al, 1992). Four steps are required for toxin-induced paralysis: binding of the toxin heavy chain to an as yet unidentified nerve terminal receptor, internalization of the toxin within the nerve terminal, translocation of the light chain into the cytosol, and inhibition of neurotransmitter release. Neurotransmitter release involves the ATP-dependent transport of the vesicle from the cytosol to the plasma membrane (Barinaga, 1993). Vesicle docking requires the interaction of various cytoplasm, vesicle, and target membrane proteins (i.e., soluble *N*-ethylmaleimide-sensitive factor attachment

protein receptor [SNARE] proteins), some of which are specifically targeted with clostridial neurotoxins (Fig. 69-45). For example, OBTX cleaves the cytosolic translocation protein SNAP-25, thus preventing vesicle fusion with the plasma membrane (Fig. 69-46) (Schiavo et al, 1993).

Seven immunologically distinct neurotoxins are designated types A, B, C, D, E, F, and G. Clinically, the urologic community has used commercial preparations of OBTX to treat patients with neurogenic and IDO (Dykstra et al, 1988; Dykstra and Sidi, 1990; Schurch et al, 1996; Petit et al, 1998; Schurch et al, 2000; Apostolidis et al, 2009). Although ACh release from bladder parasympathetic efferent terminals is a likely target of OBTX treatment, suppression of bladder afferent activity with OBTX treatment is also evident because the reduction of urgency symptom in patients with neurogenic detrusor overactivity and IDO is associated with reduced expression of the capsaicin receptor (TRPV1) and the ATP receptor (P2X₃) in C fibers (Apostolidis et al, 2005a). In addition, in basic research, botulinum toxins are shown to suppress not only efferent nerve activity by inhibition of the release of ACh but also afferent nerve activity by release of inhibition of neurotransmitters, such as SP and CGRP, from sensory terminals (Chuang et al, 2004; Dressler et al, 2005; Ikeda et al, 2012). There is also evidence that the toxin can reduce the release of ATP (and

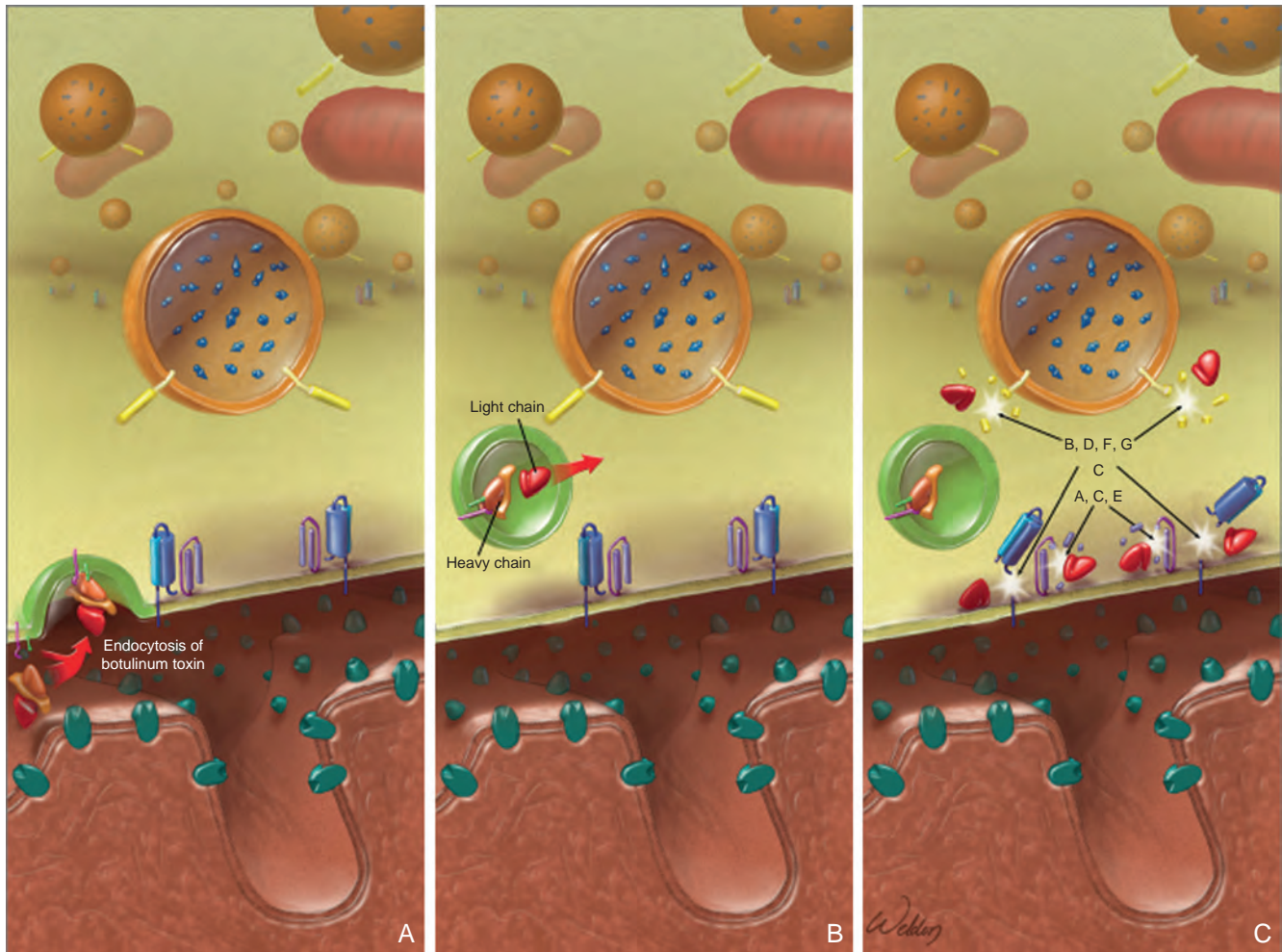


Figure 69-46. Diagram of parasymphathetic nerve terminal demonstrating (A) binding of the toxin heavy chain to an as yet unidentified receptor and internalization of the toxin within the nerve terminal; (B) translocation of the light chain into the cytosol; and (C) inhibition of neurotransmitter release by cleavage of specific synaptosome-associated membrane receptor proteins. A to G represent different botulinum toxin serotypes.

possibly other mediators) from urothelial cells in control urothelial cells (Hanna-Mitchell et al, 2015) and in spinalized rats (Khera et al, 2004; Smith et al, 2005, 2008). A recent study using lipotoxin (liposomes as a carrier for OBTX) demonstrated that the urothelium is also a site of action for this treatment (Kuo et al, 2014). Thus the use of the toxins has been expanded to treat women with pelvic floor spasticity, as well as patients with non-neurogenic OAB and even BPS (Smith et al, 2003; Smith and Chancellor, 2004; Smith et al, 2005; Apostolidis and Fowler, 2008). The efficacy of botulinum toxins has also been identified in patients with BPH, in whom OBTX injection into the prostate induced an atrophy of the prostate by inducing apoptosis, inhibiting proliferation, and downregulating α_{1A} -adrenergic receptors (Chuang et al, 2006). However, in a large phase 2 randomized, placebo-controlled, dose-ranging OBTX (transperineal or transrectal intraprostatic injection of OBTX into transitional zone) trial for BPH symptoms, the findings were primarily negative (Marberger et al, 2013). There was no difference in the outcomes between placebo and any of the dose ranges of OBTX (100 U, 200 U, and 300 U) used. Only in a subanalysis of the 200-U OBTX dose, and only in subjects with prior α -blocker use, did the investigators find a significant difference between placebo and OBTX.

The use of intradetrusor OBTX injection versus oral antimuscarinics in idiopathic OAB with urgency incontinence was studied in a randomized comparative efficacy trial (Visco et al, 2012). Reduction in urgency incontinence episodes per day was not different

between OBTX and antimuscarinics, but the rate of complete resolution of urgency incontinence was significantly higher in the OBTX-treated subjects. The antimuscarinic-treated subjects had a higher rate of dry mouth, but lower rates of catheter use and UTI.


FUTURE RESEARCH

Research holds the key to advancing the evaluation, treatment, and prevention of LUTD. As research delves deeper into physiology and pharmacology of the LUT, it is vitally important to continually translate research findings into clinical advances. A continuing dialogue between the clinician and scientist must be maintained. Newer treatments such as OBTX, β_3 -agonists, sacral neuromodulation, and posterior tibial neurostimulation have been implemented into our armamentarium, but what is next on the horizon? Although traditional physiologic, pharmacologic, and neurobiologic approaches will continue to be important, this field will require innovations that have advanced other fields. These would include incorporation of "omics" techniques—genomics, proteomics, transcriptomics, and metabolomics. These techniques use the latest high-throughput technology to screen the entire genome or all of the proteins, mRNA, or metabolites within a biologic specimen in attempts to find signature abnormalities that could point to biologic causes for the condition being studied. Through use of this technology, coupled with "omics" techniques, we will have to

develop more accurate phenotyping of patients with LUTD. Currently, we are “stuck” on refining symptom phenotyping, when all other fields are moving to biologic phenotyping. Phenotyping based on biology might help prognosticate outcomes of LUTD treatment, determine history of LUTD conditions, and point to new biologic pathways involved in LUTD.

The questions for future research may include the following:

1. Can we prevent development of any form of LUTD based on our understanding of pathophysiologic mechanisms?
2. Can we develop biomarkers to better phenotype different forms of LUTD?
3. Can the biomarkers be used to prognosticate treatment outcomes?
4. Can the biomarker search result in novel targets for treatment?
5. Can genomics studies point to susceptibility genes for the development of LUTD?
6. Can the afferent signals from the LUT be modulated to treat afferent neurourology conditions?
7. Is the bladder urothelium targetable to treat different forms of LUTD?
8. Will a pharmacologic or physiologic intervention be developed that will successfully treat the underactive detrusor so self-catheterization is obsolete?

 Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.



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Normal Lower Urinary Tract Function: Overview

Mechanisms Underlying the Two Phases of Function: Overview

Micturition Cycle: Simplification and Overview

Abnormalities of Filling/Storage and Emptying/Voiding: Overview of Pathophysiology

Classification Systems

The lower urinary tract (LUT) functions as a group of inter-related structures whose joint function in an adult is to bring about efficient and low-pressure bladder filling, low-pressure urine storage with perfect continence, and periodic complete voluntary urine expulsion also at low pressure. Appropriate sensation should accompany the function of the LUT, meaning that a sense of deferrable bladder fullness should gradually occur between voluntary voids up to a volume that is sufficient to prevent urinary frequency and without any pain or sudden compelling desires to void that are difficult to defer (urgency). Because the LUT in adults is normally under voluntary neural control, it is clearly different from other visceral organs innervated by the autonomic nervous system, whose regulation is solely by involuntary mechanisms.

For the purposes of description and teaching, the micturition cycle is best divided into two relatively discrete phases: bladder filling/urine storage and bladder emptying/voiding. The micturition cycle normally displays these two modes of operation in a simple on-off fashion. The cycle involves switching from inhibition of the voiding reflex and activation of the storage reflexes to inhibition of the storage reflexes and activation of the voiding reflex and back again. This chapter begins with a functional, physiologic, and pharmacologic overview of normal and abnormal LUT function. A simple way of looking at the pathophysiology of all types of voiding dysfunction is then presented, followed by a discussion of various systems of classification and categorization. Consistent with my own philosophy and prior attempts to make the understanding, evaluation, and management of voiding dysfunction as logical and simple as possible (Wein, 1981; Wein and Barrett, 1988; Wein, 2002), a functional and practical approach is favored.

As an apology and explanation to significant contributors to the field whose works have not been specifically referenced by name as frequently as they could have been, citations have been chosen primarily because of their comprehensive review or informational content and not because of originality or initial publication on a particular subject except where noted.

NORMAL LOWER URINARY TRACT FUNCTION: OVERVIEW

Two-Phase Concept of Function: Filling/Storage and Emptying/Voiding

Whatever disagreements exist regarding the anatomic, morphologic, physiologic, pharmacologic, and mechanical details involved in the storage and the expulsion of urine by the LUT, I have always

taken the simple view that the “experts” would agree on certain general points (Wein, 1981; Wein and Barrett, 1988; Wein, 2007; Wein and Moy, 2007). The first is that the micturition cycle involves two relatively discrete processes: (1) bladder filling and urine storage and (2) bladder emptying or voiding. The second is that, whatever the details involved, one can succinctly summarize these processes from a conceptual point of view as follows:

Bladder filling and urine storage require:

- Accommodation of increasing volumes of urine at a low detrusor pressure (normal compliance) and with appropriate sensation.
- A bladder outlet that is closed at rest and remains so during increases in intra-abdominal pressure.
- Absence of involuntary bladder contractions (detrusor overactivity [DO]).

Bladder emptying/voiding requires:

- A coordinated contraction of the bladder smooth musculature of adequate magnitude and duration.
- A concomitant lowering of resistance at the level of the smooth and striated sphincter (no functional obstruction).
- Absence of anatomic (as opposed to functional) obstruction.

The **smooth sphincter** refers to the smooth musculature of the bladder neck and proximal urethra. This is a physiologic but not an anatomic sphincter and one that is not under voluntary control. The **striated sphincter** refers to the striated musculature that is a part of the outer wall of the proximal urethra in males and females (this portion is often referred to as the **intrinsic or intramural striated sphincter or rhabdosphincter**) and the bulky skeletal muscle group that closely surrounds the urethra at the level of the membranous portion in males and primarily the middle segment in females (often referred to as the **extrinsic or extramural striated sphincter**). The extramural portion is the classically described **external urethral sphincter** and is under voluntary control (for a detailed discussion see Chapter 69) (Brading et al, 2001; DeLancey et al, 2002; Zderic et al, 2002; Bircar et al, 2013).

MECHANISMS UNDERLYING THE TWO PHASES OF FUNCTION: OVERVIEW

This section briefly summarizes pertinent points regarding the physiology and pharmacology of the various mechanisms underlying normal bladder filling/storage and emptying/voiding that constitute

the pathophysiologic mechanisms seen in the various types of dysfunction of the LUT. The general information is consistent with that detailed in Chapter 69 and in previous source materials and their supporting references (Wein and Barrett, 1988; de Groat et al, 1993, 1999; de Groat and Yoshimura, 2001; Zderic et al, 2002; Andersson and Arner, 2004; Andersson and Wein, 2004; Morrison et al, 2005; Mostwin et al, 2005; de Groat, 2006; Yoshimura and Chancellor, 2007; Fowler et al, 2008; Michel and Barendrecht, 2008; Beckel and Holstege, 2011; Birder et al, 2013; Koelbl et al, 2013; Ochodnick et al, 2013; and Andersson, 2014). Other specific references are provided only when particularly unique or applicable.

Bladder Response during Filling

The normal adult bladder response to filling at a physiologic rate is an almost imperceptible change in intravesical and detrusor pressure. During at least the initial stages of bladder filling, after unfolding of the bladder wall from its collapsed state, this high compliance (Δ volume/ Δ pressure) of the bladder is due primarily to its elastic and viscoelastic properties. Elasticity allows the constituents of the bladder wall to stretch to a certain degree without any increase in tension. Viscoelasticity allows stretch to induce an increase in tension followed by a decay ("stress relaxation") when the filling (stretch stimulus) slows or stops. The viscoelastic properties are considered to be primarily due to the characteristics of the extracellular matrix in the bladder wall. Andersson and Arner (2004) cite references demonstrating that the main extracellular components are elastic fibers and collagen fibrils present in the serosa, between muscle bundles, and between the smooth muscle cells in the muscle bundles. Brading and colleagues (1999) state that they believe there is continuous contractile activity in the smooth muscle cells to adjust their length during filling but without the type of synchronous activity that would increase intravesical pressure, would impede filling, and could cause urinary leakage. Clinically and urodynamically, the bladder seems "relaxed." The urothelium also expands but must preserve its barrier function while doing so.

There may also be a non-neurogenic active component to the storage properties of the bladder. Hawthorn and colleagues (2000) have suggested that an as yet unidentifiable relaxing factor is released from the urothelium during filling and storage, and Andersson and Wein (2004) and Andersson (2014) have suggested that urothelium-released nitric oxide may have an inhibitory effect on afferent mechanisms as well.

The viscoelastic properties of the stroma (bladder wall less smooth muscle and epithelium) and the urodynamically non-contractile state of the detrusor muscle account for the passive mechanical properties and normal bladder compliance seen during filling. The main components of the stroma are collagen and elastin. In the usual clinical setting, filling cystometry seems to show a slight increase in intravesical pressure, but Klevmark (1974, 1999) elegantly showed that this pressure increase is a function of the fact that cystometric filling is carried out at a greater than physiologic rate and that, at physiologic filling rates, there is essentially no increase in bladder pressure until bladder capacity is reached.

When the collagen component of the bladder wall increases, compliance decreases. This can occur with chronic inflammation, bladder outlet obstruction, neurologic decentralization, and various other types of injury. Bladder muscle hypertrophy, which can result from outlet obstruction, can also result in decreased compliance because hypertrophic muscle is said to be less elastic than normal detrusor; it also can synthesize increased amounts of collagen (Mostwin, 2006). Once decreased compliance has occurred because of a replacement by collagen of other components of the stroma, it is generally unresponsive to pharmacologic manipulation, hydraulic distention, or nerve section. Most often, under those circumstances, augmentation cystoplasty is required to achieve satisfactory reservoir function.

Does the nervous system affect the normal bladder response to filling? At a certain level of bladder filling, spinal sympathetic reflexes facilitatory to bladder filling/storage are clearly evoked in

animals, a concept developed over the years by de Groat and others (see Chapter 69) (de Groat et al, 1993; de Groat and Yoshimura, 2001; Chancellor and Yoshimura, 2002; Zderic et al, 2002; Yoshimura and Chancellor, 2007), who have also cited indirect evidence to support such a role in humans. This inhibitory effect is thought to be mediated primarily by sympathetic modulation of cholinergic ganglionic transmission. Through this reflex mechanism, two other possibilities exist for promoting filling/storage. One is neurally mediated stimulation of the predominantly α -adrenergic receptors (α_1) in the area of the smooth sphincter, the net result of which would be to cause an increase in resistance in that area. The second is neurally mediated stimulation of the predominantly β -adrenergic receptors (β_3 inhibitory) in the bladder body smooth musculature, which would cause a decrease in bladder wall tension. McGuire and colleagues (1983) have also proposed a direct inhibition of detrusor motor neurons in the sacral spinal cord during bladder filling related to increased afferent pudendal nerve activity generated by receptors in the striated sphincter. Good evidence also seems to exist to support an inhibitory effect of other neurotransmitters (e.g., glycine, γ -aminobutyric acid, opioids, purines, the noradrenergic system) on the micturition reflex at various levels of the neural axis. Bladder filling and consequent wall distention may also result in the release of factors from the urothelium that may influence contractility (e.g., acetylcholine, adenosine triphosphate, nitric oxide, prostaglandins, other peptides, as yet unidentified inhibitory factors).

Outlet Response during Filling

There is a gradual increase in proximal urethral pressure during bladder filling, contributed to at least by the striated sphincteric element and perhaps by the smooth sphincteric element as well. The increase in urethral pressure seen during the filling/storage phase of micturition can be correlated with an increase in efferent pudendal nerve impulse frequency and in electromyographic activity of the striated sphincter. This constitutes the efferent limb of a spinal somatic reflex, the so-called **guarding reflex**, which results in a gradual increase in striated sphincter activity during normal bladder filling and storage. Although it seems logical and compatible with neuropharmacologic, neurophysiologic, and neuromorphologic data to assume that the muscular component of the smooth sphincter also contributes to the change in urethral response during bladder filling, probably through sympathetically induced contraction, it is extremely difficult to prove this experimentally or clinically. The direct and circumstantial evidence in favor of such a hypothesis has been summarized by Wein and Barrett (1988), Brading (1999), Andersson and Wein (2004), Birder and colleagues (2013), and Andersson (2014).

The passive properties of the urethral wall warrant mention because these undoubtedly play a role in the maintenance of continence (Zinner et al, 1983; Brading, 1999). Urethral wall tension develops within the outer layers of the urethra; however, urethral pressure is a product not only of the active characteristics of smooth and striated muscle but also of the passive characteristics of the elastic, collagenous, and vascular components of the urethral wall because this tension must be exerted on a soft or plastic inner layer capable of being compressed to a closed configuration—the **"filler material"** representing the submucosal portion of the urethra. The softer and more pliable this area is, the less pressure is required by the tension-producing area to produce continence. Finally, whatever the compressive forces, the lumen of the urethra must be capable of being obliterated by a watertight seal. This **"mucosal seal mechanism"** explains why a thin-walled rubber tube requires less pressure to close an open end when the inner layer is coated with a fine layer of grease than when it is not, the latter case being akin to scarred or atrophic urethral mucosa.

Voiding with a Normal Bladder Contraction

Although many factors are involved in the initiation of micturition, in adults, increased intravesical pressure producing the sensation

of distention is primarily responsible for the initiation of normal voluntarily induced emptying of the LUT. Although the origin of the parasympathetic neural outflow to the bladder, the pelvic nerve, is in the sacral spinal cord, the actual coordinating center for the micturition reflex in an intact neural axis is in the rostral brainstem. The complete neural circuit for normal micturition includes the ascending and descending spinal cord pathways to and from this area and the facilitatory and inhibitory influences from other parts of the brain, particularly the cerebral cortex. The final step in voluntarily induced micturition involves inhibition of the somatic neural efferent activity to the striated sphincter and an inhibition of all aspects of any spinal sympathetic reflexes evoked during filling. Efferent parasympathetic pelvic nerve activity is ultimately what is responsible for a highly coordinated contraction of the bulk of the bladder smooth musculature.

A decrease in outlet resistance occurs with adaptive shaping or funneling of the relaxed bladder outlet. Besides the inhibition of any continence-promoting reflexes that have occurred during bladder filling, the change in outlet resistance may also involve an active relaxation of the smooth sphincter area through a noradrenergic noncholinergic mechanism, proposed to be mediated by nitric oxide (Andersson and Arner, 2004; Andersson and Wein, 2004; Birder et al, 2013; Andersson, 2014). The adaptive changes that occur in the outlet are probably also due at least in part to the anatomic interrelationships of the smooth muscle of the bladder base and proximal urethra. Longitudinal smooth muscle continuity (see Chapter 69) (Mostwin, 2006) would promote shortening and widening of the proximal urethra during a coordinated emptying bladder contraction. Other reflexes that are elicited by bladder contraction and by the passage of urine through the urethra may reinforce and facilitate complete bladder emptying. Superimposed on these autonomic and somatic reflexes are complex, modifying supraspinal inputs from other central neuronal networks. These facilitatory and inhibitory impulses, which originate from several areas of the nervous system, allow the full conscious control of micturition in the adult.

Urinary Continence during Abdominal Pressure Increases

During voluntarily initiated micturition, the bladder pressure becomes higher than the outlet pressure, and certain adaptive changes occur in the shape of the bladder outlet with consequent passage of urine into and through the proximal urethra. One could reasonably ask: **Why do such changes not occur with increases in intravesical pressure that are similar in magnitude but that are produced only by changes in intra-abdominal pressure such as straining or coughing?** First, a coordinated bladder contraction does not occur in response to such stimuli, emphasizing the fact that increases in total intravesical pressure are by no means equivalent to emptying ability. Second, for urine to flow into and through the proximal urethra in an individual who does not have sphincteric incontinence, there must be (1) an increase in intravesical/detrusor pressure that is primarily a product of a coordinated, neurally mediated bladder contraction and that is (2) associated with characteristic tension and conformational changes in the bladder neck and proximal urethral areas.

Assuming that the bladder outlet is competent at rest, a major factor required for the prevention of urinary leakage during increases in intra-abdominal pressure is the presence of **at least equal pressure transmission to the proximal urethra (the mid-urethra as well in women) during such activity.** This phenomenon was first described by Enhorning (1961) and has been confirmed in virtually every urodynamic laboratory since that time. **Failure of this mechanism is an invariable correlate of effort-related urinary incontinence in women and men.** The urethral closure pressure increases with increments in intra-abdominal pressure, indicating that active muscular function related to a reflex increase in striated sphincter activity or other factors that increase urethral resistance is also involved in preventing such leakage. Tanagho (1978) was the first to provide direct evidence of this. A more complete

description of the factors involved in sphincteric incontinence can be found later in this chapter, in Chapters 69 and 74, and in the work of Koelbl and associates (2013).

Sensory Aspects

Most of the afferent input from the bladder and urethra reaches the spinal cord through the pelvic nerve and dorsal root ganglia, and some reaches the spinal cord through the hypogastric nerve. Afferent input from the striated muscle of the sphincter and pelvic floor travels in the pudendal nerve. The most important afferents for initiating and maintaining normal micturition are those in the pelvic nerve, relaying to the sacral spinal cord. These convey impulses from tension, volume, and nociceptive receptors located in the serosal, muscle, and urothelial and suburothelial layers of the bladder and urethra. In a neurologically normal adult, the sensation of filling and distention, but not urgency or pain, develops during normal filling/storage and initiates the reflexes responsible for emptying/voiding (see Chapter 69) (de Groat and Yoshimura, 2001; Chancellor and Yoshimura, 2002; Morrison et al, 2005; Birder et al, 2013). Alterations in this finely tuned pathway can be responsible for significant alterations in LUT function.

MICTURITION CYCLE: SIMPLIFICATION AND OVERVIEW

Filling/Storage

Bladder accommodation during filling is a primarily passive phenomenon dependent on the elastic and viscoelastic properties of the bladder wall and the lack of parasympathetic excitatory input. An increase in outlet resistance occurs by means of the striated sphincter somatic guarding reflex. In some species, a sympathetic reflex also contributes to storage by (1) increasing outlet resistance through increased tension in the smooth sphincter, (2) inhibiting bladder contractility through an inhibitory effect on parasympathetic ganglia, and (3) causing a decrease in tension of bladder body smooth muscle. Continence is maintained during increases in intra-abdominal pressure by the intrinsic competence of the bladder outlet (bladder neck and proximal urethra/mid-urethra) and the pressure transmission ratio to this area with respect to the intravesical contents. A further increase in striated sphincter activity, on a reflex basis, is also contributory.

Emptying/Voiding

Emptying (voiding) can be voluntary or involuntary and involves an inhibition of the spinal somatic and sympathetic reflexes and activation of the vesical parasympathetic pathways, the organizational center for which is in the rostral brainstem. Initially, there is a decrease in outlet resistance, mediated not only by the cessation of the somatic and sympathetic spinal reflexes but possibly also by a relaxing factor released by parasympathetic stimulation or by some effect of bladder smooth muscle contraction itself. A highly coordinated parasympathetically induced contraction of the bulk of the bladder smooth musculature occurs, with shaping or funneling of the relaxed outlet, owing at least in part to smooth muscle continuity between the bladder base and the proximal urethra. With amplification and facilitation of the bladder contraction from other peripheral reflexes and from spinal cord supraspinal sources, and in the absence of anatomic or functional obstruction between the bladder and urethral meatus, complete emptying occurs.

BOX 70-1 Simple Functional Classification of Lower Urinary Tract Dysfunction

FAILURE TO STORE

Because of the bladder
Because of the outlet

FAILURE TO EMPTY

Because of the bladder
Because of the outlet

ABNORMALITIES OF FILLING/STORAGE AND EMPTYING/VOIDING: OVERVIEW OF PATHOPHYSIOLOGY

Excluding psychological reasons, the pathophysiology of failure of the LUT in an adult to fill with or store urine adequately or to empty adequately must logically be secondary to reasons related to the bladder, the outlet, or a combination (Wein, 1981; Wein and Barrett, 1988). This division provides a logical rationale for discussion and classification of all types of LUT dysfunction. (Box 70-1).

There are some types of dysfunction that represent combinations of filling/storage and emptying/voiding abnormalities (e.g., DO and sphincter dyssynergia in a patient with suprasacral spinal cord injury; DO during filling/storage, detrusor underactivity during emptying), but within this scheme these have become readily understandable and detectable, and the treatment dilemmas have been logically described. Failure in either category is not absolute but more often is relative. The system can be easily expanded and made more detailed to include etiologic or specific urodynamic connotations (Box 70-2). However, the simplified system is perfectly workable and avoids argument in complex situations in which the exact etiology or mechanism for a dysfunction cannot be agreed on.

Using this concept, all aspects of urodynamic and video-urodynamic evaluation can be conceptualized as to exactly what they evaluate in terms of either bladder or outlet activity during filling/storage or emptying/voiding (Table 70-1). Treatments can be classified under these broad categories as to whether they facilitate filling/storage or emptying/voiding and whether they do so by acting primarily on the bladder or on one or more components of the bladder outlet (Boxes 70-3 and 70-4).

Filling/Storage Failure

Absolute or relative failure of the bladder to fill with and store urine adequately results from bladder overactivity (involuntary contraction and/or decreased compliance), decreased outlet resistance, heightened or altered sensation, or a combination.

Bladder Overactivity

Overactivity of the bladder during filling/storage can be expressed as phasic involuntary contractions, as low compliance, or as a combination. Involuntary contractions are most commonly seen in association with neurologic disease or injury, bladder outlet obstruction, stress urinary incontinence (perhaps because of sudden entry of urine into the proximal urethra, eliciting a reflex contraction), or aging (probably related to neural degeneration) or

TABLE 70-1 Urodynamics Simplified

	BLADDER	OUTLET
Filling/storage phase	Pves ¹ Pdet ² (FCMG ³) DLPP ⁴	UPP ⁵ VLPP ⁶
Emptying phase	Pves ⁸ Pdet ⁹ (VCMG) ¹⁰	FLUORO ⁷ MUPP ¹¹ FLUORO ¹² EMG ¹³
	(_____)	
	_____ FLOW ¹⁴ _____	
	_____ RU ¹⁵ _____	

This functional conceptualization of urodynamics categorizes each study as to whether it examines bladder or outlet activity during the filling/storage or emptying phase of micturition. In this scheme, uroflow and residual urine integrate the activity of the bladder and the outlet during the emptying phase.

^{1,2}Total bladder (Pves) and detrusor (Pdet) pressures during a filling cystometrogram (FCMG).

³Filling cystometrogram.

⁴Detrusor leak point pressure.

⁵Urethral pressure profilometry.

⁶Valsalva leak point pressure.

⁷Fluoroscopy of outlet during filling/storage.

^{8,9}Total bladder and detrusor pressures during a voiding cystometrogram (VCMG).

¹⁰Voiding cystometrogram.

¹¹Micturitional urethral pressure profilometry.

¹²Fluoroscopy of outlet during emptying.

¹³Electromyography of periurethral striated musculature.

¹⁴Flowmetry.

¹⁵Residual urine.

may be truly idiopathic. However, they may also be associated with increased afferent input related to inflammation or irritation of the bladder or urethral wall or an increased sensitivity (decreased threshold of activation to a normal amount of transmitter). Excitatory neurotransmitters may be released from the urothelium during filling/storage and activate afferent receptors/nerves, ultimately resulting, in some individuals, in involuntary contractions or altered (heightened) sensation: a premature sensation of distention or fullness, true urgency (a sudden compelling desire to void, which is difficult to defer), or pain. If an individual has urgency urinary incontinence, it can be assumed that an involuntary contraction (DO) has occurred. The symptom of urgency without incontinence suggests DO, but this is often not demonstrable on urodynamic study. Conversely, urodynamically demonstrable DO may not be associated with clinically troublesome filling/storage symptoms.

The possible pathophysiologies of the symptom syndrome “overactive bladder” (defined by the International Continence Society [ICS] as urgency with or without urge incontinence, usually with frequency and nocturia) can be summarized as (1) reduced suprapontine inhibition, (2) damaged axonal paths in the spinal cord, (3) damaged axonal paths in the periphery, (4) loss of peripheral inhibition, (5) enhancement of excitatory neurotransmission in the micturition reflex pathway, (6) increased LUT afferent input, and (7) idiopathic. Staskin (2001) and Mostwin and colleagues (2005) also hypothesized that decreased stimulation from the pelvic floor can contribute to phasic bladder overactivity. Decreased compliance during filling/storage may be secondary to neurologic injury or disease, usually at a sacral or infrasacral level, but may result from any process that impairs or destroys the viscoelastic or elastic properties of the bladder wall.

Filling/Storage Failure due to Altered Sensation

Bladder-related storage failure may also occur in the absence of overactivity because of increased afferent input from inflammation,

BOX 70-2 Expanded Functional Classification of Lower Urinary Tract Dysfunction

- I. Failure to store
 - A. Because of the bladder
 - 1. Overactivity
 - a. Involuntary contractions (detrusor overactivity)
 - (1) Neurologic disease, injury, or degeneration
 - (2) Bladder outlet obstruction
 - (3) Increased afferent input or sensitivity
 - (4) Inflammation
 - (5) Increased neurotransmitter release
 - (6) Increased sensitivity to transmitter
 - (7) Decreased inhibitory pelvic floor activity
 - (8) Idiopathic
 - b. Decreased compliance
 - (1) Neurologic disease or injury
 - (2) Fibrosis
 - (3) Bladder muscle hypertrophy
 - (4) Idiopathic
 - c. Combination
 - 2. Hypersensitivity
 - a. Inflammatory/infectious
 - b. Neurologic
 - c. Increased neurotransmitter release or sensitivity
 - d. Psychological
 - e. Idiopathic
 - 3. Underactivity (with retention and overflow incontinence)
 - 4. Combination
 - B. Because of the outlet
 - 1. Genuine stress urinary incontinence
 - a. Lack of suburethral support
 - b. Pelvic floor laxity, hypermobility
 - 2. Intrinsic sphincter deficiency
 - a. Neurologic disease or injury
 - b. Fibrosis
 - 3. Combination (genuine stress urinary incontinence and intrinsic sphincter deficiency)
 - C. Combination (bladder and outlet factors)
 - D. Fistula
- II. Failure to empty
 - A. Because of the bladder (underactivity)
 - 1. Neurogenic
 - 2. Myogenic
 - 3. Psychogenic
 - 4. Idiopathic
 - B. Because of the outlet
 - 1. Anatomic
 - a. Prostatic obstruction
 - b. Bladder neck contracture
 - c. Urethral stricture
 - d. Urethral compression, fibrosis
 - 2. Functional
 - a. Striated sphincter dyssynergia (neurogenic)
 - b. Smooth sphincter dyssynergia or dysfunction (bladder neck dysfunction)
 - c. Dysfunctional voiding (non-neurogenic)
 - C. Combination

irritation, other causes of hypersensitivity, and pain. The causes may be chemical, psychological, or idiopathic. One classic example is termed *bladder pain syndrome* (also known as *interstitial cystitis*; see Chapter 14). Increased afferent activity can be responsible for true DO (an involuntary contraction), true urgency without DO, a premature feeling of fullness or distention without urgency or DO, or the sensation of pain during filling.

Outlet Underactivity

Decreased outlet resistance may result from any process that damages the innervation of structural elements of the smooth or striated sphincter, or both, or damages or impairs the support of the bladder outlet in women. This process may occur with neurologic disease or injury, surgical or other mechanical trauma, or aging. Classically, sphincteric incontinence in a woman was categorized into relatively discrete entities: (1) so-called *genuine stress incontinence* and (2) *intrinsic sphincter deficiency (ISD)*, originally described as “type III stress incontinence” (DeLancey, 1994; Mostwin et al, 2005; Koelbl et al, 2013) (see Chapters 69, 74, 82, and 84). *Genuine stress incontinence in women* was described as associated with hypermobility of the bladder outlet because of poor pelvic support and with an outlet that was competent at rest but lost its competence only during increases in intra-abdominal pressure. ISD described a nonfunctional or poorly functional bladder neck and proximal urethra at rest. The implication of classic ISD was that a surgical procedure designed to correct only urethral hypermobility would have a relatively high failure rate, as opposed to one designed to improve urethral coaptation and compression. The contemporary view is that most cases of effort-related incontinence in women involve varying proportions of

support-related factors and ISD. It is possible to have outlet-related incontinence that is due only to ISD but not due solely to hypermobility or poor support—some ISD must exist.

Stress or effort-related urinary incontinence is a symptom that arises primarily from **damage to muscles, nerves, or connective tissue, or a combination, within the pelvic floor** (DeLancey et al, 2002; Mostwin et al, 2005; Koelbl et al, 2013). Urethral support is important in women, the urethra normally being supported by the action of the levator ani muscles through their connection to the endopelvic fascia of the anterior vaginal wall. Damage to the connection between this fascia and this muscle, damage to the relevant nerve supply, or direct muscle damage can influence continence. Bladder neck function is likewise important, and loss of normal bladder neck closure can result in incontinence despite normal urethral support. Previously, the urethra was sometimes ignored as a factor contributing to continence in women, and the site of continence was thought to be exclusively the bladder neck. However, in approximately 50% of continent women, urine enters the urethra during increases in abdominal pressure. The continence point in these women (highest point of pressure transmission) is at the mid-urethra.

Urethral hypermobility implies weakness of the pelvic floor support structures. During increases in intra-abdominal pressure, there is descent of the bladder neck and proximal urethra. If the outlet opens concomitantly, stress urinary incontinence ensues. In the classic form of urethral hypermobility, there is rotational descent of the bladder neck and urethra. The urethra may also descend without rotation (it shortens and widens), or the posterior wall of the urethra may be pulled (sheared) open while the anterior wall remains fixed. However, urethral hypermobility is often present in women who are not incontinent, and the mere presence of urethral

BOX 70-3 Functional Categorization of Therapy to Facilitate Urine Storage/Bladder Filling

- I. Bladder related (decreasing intravesical pressure, inhibitors, detrusor contractility, increasing bladder capacity)
 - A. Behavioral therapy (including any or all of the following)
 1. Education
 2. Bladder training
 3. Timed bladder emptying or prompted voiding
 4. Fluid restriction
 5. Pelvic floor physiotherapy ± biofeedback
 - B. Pharmacologic therapy (oral, intravesical, intradetrusor)
 1. Antimuscarinic agents
 2. Drugs with mixed actions
 3. β -Adrenergic agonists
 4. Botulinum toxin
 5. Calcium antagonists
 6. Potassium channel openers
 7. Prostaglandin inhibitors
 8. α -Adrenergic antagonists
 9. Tricyclic antidepressants; serotonin and norepinephrine reuptake inhibitors
 10. Dimethyl sulfoxide
 11. Polysynaptic inhibitors
 12. Capsaicin, resiniferatoxin, and similar agents
 - C. Bladder overdistention
 - D. Electrical stimulation (sacral neuromodulation, posterior tibial and other peripheral nerve stimulation)
 - E. Acupuncture and electroacupuncture
 - F. Interruption of innervation
 1. Very central (subarachnoid block)
 2. Less central (sacral rhizotomy, selective sacral rhizotomy)
 3. Peripheral motor and/or sensory
- G. Augmentation cystoplasty (autoaugmentation, bowel, tissue engineering)
- II. Outlet related (increasing outlet resistance)
 - A. Behavioral therapy (see I. A.)
 - B. Electrical stimulation
 - C. Pharmacologic therapy
 1. α -Adrenergic agonists
 2. Tricyclic antidepressants; serotonin and norepinephrine reuptake inhibitors
 3. β -Adrenergic antagonists, agonists
 - D. Vaginal and perineal occlusive and/or supportive devices; urethral plugs
 - E. Nonsurgical periurethral bulking
 1. Synthetics
 2. Tissue engineering
 - F. Retropubic vesicourethral suspension ± prolapse repair (female)
 - G. Sling procedures ± prolapse repair (female)
 - H. Mid-urethral tapes ± prolapse repair (female)
 - I. Perineal sling procedure (male)
 - J. Artificial urinary sphincter
 - K. Myoplasty (muscle transposition)
 - L. Bladder outlet closure
- III. Circumventing the problem
 - A. Absorbent products
 - B. External collecting devices
 - C. Antidiuretic hormone-like agents
 - D. Short-acting diuretics
 - E. Intermittent catheterization
 - F. Continuous catheterization
 - G. Urinary diversion

hypermobility is insufficient to make a diagnosis of a sphincter abnormality unless urinary incontinence is also demonstrated. The “hammock hypothesis” of DeLancey (1994) proposes that for stress incontinence to occur with hypermobility, there must be a lack of stability of the suburethral supportive layer. This theory proposes that the effect of abdominal pressure increases on the normal bladder outlet, if the suburethral supportive layer is firm, is to compress the urethra rapidly and effectively. If the supportive suburethral layer is lax and/or movable, compression is not as effective. **Intrinsic sphincter dysfunction** denotes an intrinsic malfunction of the urethral sphincter mechanism itself. In its most overt form, it is characterized by a bladder neck that is open at rest and a low abdominal leak point pressure and urethral closure pressure (see Chapter 73) and is usually the result of prior surgery, trauma with scarring, or a neurologic lesion.

Urethral instability refers to the rare phenomenon of episodic decreases in outlet pressure unrelated to increases in bladder or abdominal pressure. Although rarely seemingly demonstrable, many authors believe that the decrease in urethral pressure usually represents simply the urethral component of what would otherwise be a bladder contraction/urethral relaxation in an individual whose bladder does not measurably contract, for either myogenic or neurogenic reasons. Little has appeared about this entity since the last edition of this text.

In theory at least, categories of outlet-related incontinence in men are similar to the categories in women. However, sphincteric incontinence in men is not associated with hypermobility of the bladder neck and proximal urethra but is similar to what is termed *intrinsic sphincter dysfunction* in women. There is essentially no information on the topic of urethral instability in men.

The treatment of filling/storage abnormalities is directed toward inhibiting bladder contractility, decreasing sensory output, mechanically increasing bladder capacity, or increasing outlet resistance, the last either continuously or just during increases in intra-abdominal pressure.

Emptying/Voiding Failure

Absolute or relative failure to empty the bladder results from decreased bladder contractility (a decrease in magnitude, coordination, or duration), increased outlet resistance, or a combination.

Bladder Underactivity

Absolute or relative failure of bladder contractility may result from temporary or permanent failure or impairment in one of the neuromuscular mechanisms necessary for initiating and maintaining a normal detrusor contraction. Inhibition of the voiding reflex in a neurologically normal individual may also occur; it may be by a reflex mechanism secondary to increased afferent input, especially from the pelvic and perineal areas, or may be psychogenic. **Non-neurogenic causes** also include impairment of bladder smooth muscle function, which may result from

BOX 70-4 Functional Categorization of Therapy to Facilitate Bladder Emptying/Voiding

- I. Bladder related (increasing intravesical pressure or facilitating/augmenting bladder contractility)
 - A. External compression, Valsalva
 - B. Promotion or initiating of reflex contraction
 1. Trigger zones or maneuvers
 2. Bladder “training”; tidal drainage
 - C. Pharmacologic therapy (oral, intravesical)
 1. Parasympathomimetic agents
 2. Prostaglandins
 3. Blockers of inhibition
 - a. α -Adrenergic antagonists
 - b. Opioid antagonists
 - D. Electrical stimulation
 1. Directly to the bladder or spinal cord
 2. Directly to the nerve roots
 3. Intravesical (transurethral)
 4. Neuromodulation
 - E. Reduction cystoplasty
 - F. Bladder myoplasty (muscle wrap)
 - G. Tissue engineering
- II. Outlet related (decreasing outlet resistance)
 - A. At a site of anatomic obstruction
 1. Pharmacologic therapy—decrease prostate size or tone
 - a. α -Adrenergic antagonists
 - b. α -Reductase inhibitors
 - c. Luteinizing hormone-releasing hormone agonists/antagonists
 - d. Antiandrogens
 2. Prostatectomy, prostatotomy (diathermy, heat, laser, stapling)
 3. Bladder neck incision or resection
 4. Urethral stricture repair or dilation
 5. Intraurethral stent
 6. Balloon dilation of stricture/contracture
 - B. At level of smooth sphincter
 1. Pharmacologic therapy
 - a. α -Adrenergic antagonists
 - b. β -Adrenergic agonists
 - c. Botulinum toxin (injection)
 2. Transurethral resection or incision
 3. Reconstruction
 - C. At level of striated sphincter
 1. Behavioral therapy \pm biofeedback
 2. Pharmacologic therapy
 - a. Benzodiazepines
 - b. Baclofen
 - c. Dantrolene
 - d. α -Adrenergic antagonists
 - e. Botulinum toxin (injection)
 3. Urethral overdilation
 4. Surgical sphincterotomy
 5. Urethral stent
 6. Pudendal nerve interruption
 - D. Circumventing the problem
 1. Intermittent catheterization
 2. Continuous catheterization
 3. Urinary diversion (conduit or reservoir)

overdistention, various centrally or peripherally acting drugs, severe infection, or fibrosis.

Outlet Overactivity or Obstruction

Pathologically increased outlet resistance is much more common in men than in women. Although it is most often secondary to anatomic obstruction, it may be secondary to a failure of relaxation or active contraction of the striated or smooth sphincter during bladder contraction (see Chapter 75). **Striated sphincter dyssynergia** is a common cause of functional (nonanatomic as opposed to fixed anatomic) obstruction in patients with neurologic disease or injury. Except for the true smooth sphincter contraction, which occurs in conjunction with autonomic hyperreflexia (see Chapter 75), true dyssynergia at the level of the bladder neck-proximal urethra is unusual. Incomplete opening of an anatomically normal bladder neck during voluntary or involuntary voiding is termed *bladder neck dysfunction* and is an uncommon entity found almost exclusively in young and middle-aged men (also sometimes known as *primary bladder neck obstruction* or *dysfunctional bladder neck*) (see Chapter 75). Common causes of **anatomic outlet obstruction in men** include prostatic enlargement, bladder neck contracture, and urethral stricture. A common cause of **outlet obstruction in women** is compression or fibrosis after surgery for sphincteric incontinence.

The treatment of emptying failure generally consists of maneuvers to increase intravesical/detrusor pressure, facilitate the micturition reflex, decrease outlet resistance, or a combination. If other means fail or are impractical, intermittent (or continuous) catheterization is an effective way to circumvent emptying failure.

CLASSIFICATION SYSTEMS

On the basis of the data obtained from the neurourologic evaluation, a given LUT dysfunction can be categorized in an ever-increasing number of descriptive systems. The **purpose of any classification system** should be to facilitate understanding and management and to avoid confusion among those who are concerned with the problem for which the system was designed. A good classification system should serve as **intellectual shorthand** and should convey, in a few key words or phrases, the essence of a clinical situation. An ideal system for all types of voiding dysfunction would include or imply several factors: (1) the conclusions reached from urodynamic testing, (2) expected clinical symptoms, and (3) approximate site and type of a neurologic lesion or lack of one. If the various categories accurately portray pathophysiology, treatment options should be obvious, and a treatment “menu” should be evident. **Most classification systems for voiding dysfunction were formulated primarily to describe dysfunction secondary to neurologic disease or injury. The ideal system should be applicable to all types of voiding dysfunction.** On the basis of the data obtained from the neurourologic evaluation, a given voiding dysfunction can be categorized in many descriptive systems. **No one system is perfect.** The major systems or types of systems in use are reviewed here with their advantages and applicability. Understanding the rationale and shortcomings of each system significantly improves one’s knowledge of LUT function and dysfunction.

Functional System

Classification of voiding dysfunction can be formulated on a simple functional basis, describing the dysfunction in terms of whether the deficit produced is primarily one of the filling/storage or the emptying/voiding phase of micturition (see Box 70-1) (Wein, 1981; Wein and Barrett, 1988). The genesis of such a system was proposed initially by Scott’s group (Quesada et al,

1968). This simple scheme assumes only that, whatever their differences, all “experts” would agree on the two-phase concept of micturition (filling/storage and emptying/voiding), on the simple overall mechanisms underlying the normality of each phase (see previous discussion), and on the possibilities for dysfunction.

The expansion of this concept to encompass all types of LUT dysfunction (see Box 70-2) and categorize urodynamic and video-urodynamic studies (see Table 70-1) has been previously discussed. In addition, one can easily classify all known treatments for voiding dysfunction under the broad categories of whether they facilitate filling/storage and emptying/voiding and whether they do so by an action primarily on the bladder or on one or more of the components of the bladder outlet (see Boxes 70-3 and 70-4).

Failure in either category generally is not absolute but more often is relative. Such a functional system can easily be “expanded” and made more complicated to include etiologic or specific urodynamic connotations (see Box 70-4). However, the simplified system is workable and avoids argument in complex situations in which the exact etiology or urodynamic mechanism for a voiding dysfunction cannot be agreed on.

Proper use of the functional system for a given voiding dysfunction requires a reasonably accurate notion of what the urodynamic data show. However, an exact diagnosis is not required for treatment. Some patients do not have only a discrete storage or emptying failure, and the existence of combination deficits must be recognized to use this system classification properly. For example, the “classic” T10 paraplegic patient after spinal shock generally exhibits a relative failure of storage because of involuntary bladder contraction and a relative failure to empty the bladder because of striated sphincter dyssynergia. With such a combination deficit, to use this classification system as a guide to treatment, one must assume that one of the deficits is primary and that significant improvement will result from its treatment alone or that the voiding dysfunction can be converted primarily to a disorder of either storage or emptying by means of nonsurgical or surgical therapy. The resultant deficit can then be treated or circumvented. Using this example, the combined deficit in a T10 paraplegic patient can be converted primarily to a storage failure by procedures directed at the dyssynergic striated sphincter; the resultant storage failure (secondary to involuntary contraction) can be circumvented (in a man) with an external collecting device. Alternatively, the deficit can be converted primarily to an emptying failure by pharmacologic or surgical measures designed to abolish or reduce the involuntary contraction, and the resultant emptying failure can be circumvented with clean intermittent catheterization. Other examples of combination deficits include impaired bladder contractility or overactivity with sphincter dysfunction, bladder outlet obstruction with DO, bladder outlet obstruction with sphincter malfunction, and detrusor filling/storage overactivity with impaired emptying contractility.

One advantage of this functional classification is that it allows the clinician the liberty of “playing” with the system to suit his or her own preferences without an alteration in the basic concept of “keep it simple but accurate and informative.” For instance, one could easily substitute the terms *overactive* or *oversensitive bladder* and *underactive outlet* for *because of the bladder* and *because of the outlet* under “Failure to Store” in Box 70-1. One could choose to categorize the bladder reasons for overactivity (see Box 70-2) further in terms of neurogenic, myogenic, or anatomic causes and subcategorize neurogenic further in terms of decreased inhibitory control, increased afferent activity, and increased sensitivity to efferent activity. The system is flexible.

The classification system proposed by the ICS (Box 70-5) is in essence an extension of a urodynamic classification system. The storage and voiding phases of micturition are described separately, and, within each phase, various designations are applied to describe bladder and urethral function (Abrams et al, 1988, 1992). Some of the definitions were changed by the standardization subcommittee of the ICS in 2002, and the relevant changes are indicated here (Abrams et al, 2002, 2003). Normal bladder function during

BOX 70-5 International Continence Society Classification

STORAGE PHASE

Bladder Function

Detrusor activity
Normal or stable
Overactive
Neurogenic
Idiopathic

Bladder sensation

Normal
Increased or hypersensitive
Reduced or hyposensitive
Absent

Bladder capacity

Normal
High
Low

Bladder Compliance

Normal
High
Low

Urethral Function

Normal closure mechanism
Incompetent closure mechanism

VOIDING PHASE

Bladder Function

Detrusor activity
Normal
Underactive
Acontractile
Areflexic

Urethral Function

Normal
Abnormal
Mechanical obstruction
Overactivity
Dysfunctional voiding
Detrusor sphincter dyssynergia
Nonrelaxing urethral sphincter dysfunction

Modified from Abrams P, Blaivas J, Stanton S, et al. ICS standardization of terminology of LUT function. *Scand J Urol Nephrol* 1988;114:5–19; Abrams P, Blaivas J, Stanton S, et al. ICS 6th report on the standardization of terminology of LUT function. *Neurol Urodyn* 1992;11:593–603; and Abrams P, Cardozo L, Fall M, et al. The standardization of terminology in LUT function: report from the standardization subcommittee of the International Continence Society. *Neurol Urodyn* 2002;21:167–78.

filling/storage implies no significant increases in detrusor pressure (stability). Overactive detrusor function indicates the presence of “involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked.” If the condition is caused by neurologic disease, the term *neurogenic detrusor overactivity* (previously, *detrusor hyperreflexia*) is applied. If not, the term *idiopathic detrusor overactivity* (previously, *detrusor instability*) is applied. Bladder sensation can be categorized only in qualitative terms as indicated. Bladder capacity and compliance (Δ volume/ Δ pressure) are cystometric measurements. Bladder capacity can refer to cystometric capacity, maximum cystometric capacity, or maximum anesthetic cystometric capacity (Abrams et al, 2002). Normal urethral function during filling/storage indicates a positive urethral closure pressure (urethral pressure minus bladder pressure) even with increases in intra-abdominal pressure, although it may be overcome by DO. Incompetent urethral function during filling/storage implies urine leakage in the absence of a detrusor contraction. This leakage may be due to genuine stress incontinence, intrinsic sphincter dysfunction, a combination, or an involuntary decrease in urethral pressure in the absence of detrusor contraction.

During the voiding/emptying phase of micturition, normal detrusor activity implies voiding by a voluntarily initiated sustained contraction that leads to complete bladder emptying within a normal time span. An underactive detrusor defines a contraction of inadequate magnitude or duration, or both, to empty the bladder within a normal time span. An *accontractile detrusor* is one that cannot be demonstrated to contract during urodynamic testing. *Areflexia* is defined as *accontractility* secondary to an abnormality of neural control, implying the complete absence of centrally

coordinated contraction. **Normal urethral function** during voiding indicates a urethra that opens and is continuously relaxed to allow bladder emptying at a normal pressure. **Abnormal urethral function during voiding** may be due to either mechanical obstruction or urethral overactivity. **Dysfunctional voiding** describes an intermittent or fluctuating flow rate secondary to involuntary intermittent contractions of the periurethral striated muscle in neurologically normal individuals. **Detrusor sphincter dyssynergia** defines a detrusor contraction concurrent with an involuntary contraction of the urethral or periurethral striated muscle, or both. **Nonrelaxing urethral sphincter obstruction** usually occurs in individuals with a neurologic lesion and is characterized by a nonrelaxing obstructing urethra resulting in reduced urine flow.

LUT dysfunction in a patient with classic T10-level paraplegia after spinal shock has passed would be classified in the ICS system as follows:

- Storage phase—overactive neurogenic detrusor function, absent sensation, low capacity, normal compliance, normal urethral closure function
- Voiding phase—overactive obstructive urethral function, overactive detrusor function

The micturition dysfunction of a patient with stroke and urgency incontinence would most likely be classified during storage as overactive neurogenic detrusor function, normal sensation, low capacity, normal compliance, and normal urethral closure function. During voiding, the dysfunction would be classified as normal detrusor activity and normal urethral function, assuming that no anatomic obstruction existed.

Urodynamic Classification

As urodynamic techniques have become more accepted and sophisticated, systems of classification have evolved solely on the basis of objective urodynamic data (Box 70-6). Among the first to popularize this concept were Krane and Siroky (1984). When exact urodynamic classification is possible, such a system can provide an exact description of the voiding dysfunction that occurs. If a normal or hyperreflexic (overactive) detrusor exists with coordinated smooth and striated sphincter function and without anatomic obstruction, normal bladder emptying should occur. **Detrusor hyperreflexia** (now termed *neurogenic detrusor overactivity* in ICS parlance) is most commonly associated with neurologic lesions above the sacral spinal cord. **Striated sphincter dyssynergia** is most commonly seen after complete suprasacral spinal cord injury, following the period of spinal shock. **Smooth sphincter dyssynergia** is seen most classically in autonomic hyperreflexia (see Chapter 75) when it is characteristically associated with DO and striated sphincter dyssynergia. **Detrusor areflexia** (this category includes acontractile and areflexic

bladder) may be secondary to bladder muscle decompensation or to various other conditions that produce inhibition at the level of the brainstem micturition center, the sacral spinal cord, bladder ganglia, or bladder smooth muscle. Patients with a voiding dysfunction secondary to detrusor areflexia generally attempt bladder emptying by abdominal straining, and their continence status and the efficiency of their emptying efforts are determined by the status of their smooth and striated sphincter mechanisms.

This classification system is easiest to use when detrusor hyperreflexia (overactivity) or normoreflexia exists. A patient with typical T10-level paraplegia after spinal shock exhibits detrusor hyperreflexia, smooth sphincter synergy, and striated sphincter dyssynergia. When a voluntary or a hyperreflexic contraction cannot be elicited, the system is more difficult to use because it is not appropriate to speak of true sphincter dyssynergia in the absence of an opposing bladder contraction. There are many variations and extensions of such a system. **Such systems can work well only when total urodynamic agreement exists among classifiers. There are many dysfunctions that do not fit neatly into a urodynamic classification system that is agreed on by all experts. Compliance is not mentioned in this particular version, nor is sensation or the concept of deficient, but not absent, detrusor contractile function.** As sophisticated urodynamic technology and understanding improve, this type of classification system may be more commonly used. The ICS system (see previous discussion) is in reality a logical and more complete extension of such a system.

Lapides's Classification

Lapides (1970) contributed significantly to the classification and care of patients with neuropathic voiding dysfunction by slightly modifying and popularizing a system originally proposed by McLellan (1939) (Box 70-7). Lapides's classification differs from that of McLellan in only one respect, and that is the division of the group of "atonic neurogenic bladder" into sensory neurogenic and motor neurogenic bladder. This is a familiar system to urologists and nonurologists because it describes in recognizable shorthand the clinical and cystometric conditions of many types of neurogenic voiding dysfunction.

A **sensory neurogenic bladder** results from disease that selectively interrupts the sensory fibers between the bladder and the spinal cord or the afferent tracts to the brain. **Diabetes mellitus, tabes dorsalis, and pernicious anemia** are the diseases most responsible. The first clinical changes are described as impaired sensation of bladder distention. Unless voiding is initiated on a timed basis, varying degrees of bladder overdistention can result with hypotonicity. If bladder decompensation occurs, significant amounts of residual urine result, and at that time the cystometric curve generally demonstrates a large-capacity bladder with a flat, high-compliance, low-pressure filling curve.

A **motor paralytic bladder** results from disease processes that destroy the parasympathetic motor innervation of the bladder. **Extensive pelvic surgery or trauma** may produce this. **Herpes zoster** has been listed as a cause as well, but more recent evidence suggests that the voiding dysfunction seen with herpes may be related more to a problem with afferent input (see Chapter 75). The early symptoms of a motor paralytic bladder may vary from painful urinary retention to only a relative inability to initiate and maintain normal micturition. Early cystometric filling is normal but without

BOX 70-6 Urodynamic Classification

DETRUSOR HYPERREFLEXIA (OR NORMOREFLEXIA)

Coordinated sphincters
Striated sphincter dyssynergia
Smooth sphincter dyssynergia
Nonrelaxing smooth sphincter

DETRUSOR AREFLEXIA

Coordinated sphincters
Nonrelaxing striated sphincter
Denervated striated sphincter
Nonrelaxing smooth sphincter

Modified from Krane RJ, Siroky MB. Classification of voiding dysfunction: value of classification systems. In: Barrett DM, Wein AJ, editors. *Controversies in neuro-urology*. New York: Churchill Livingstone; 1984. p. 223–38.

BOX 70-7 Lapides Classification

Sensory neurogenic bladder
Motor paralytic bladder (motor neurogenic bladder)
Uninhibited neurogenic bladder
Reflex neurogenic bladder
Autonomous neurogenic bladder

a voluntary bladder contraction at capacity. Chronic overdistention and decompensation may occur, resulting in a large-capacity bladder with a flat, low-pressure filling curve; a large amount of residual urine may result.

An **uninhibited neurogenic bladder** was described originally as resulting from injury or disease to the “corticoregulatory tract.” The sacral spinal cord was presumed to be the micturition reflex center, and this corticoregulatory tract was believed normally to exert an inhibitory influence on the sacral micturition reflex center. A destructive lesion in this tract would then result in overfacilitation of the micturition reflex. **Cerebrovascular accident, brain or spinal cord tumor, Parkinson disease, and demyelinating disease** were listed as the most common causes in this category. The voiding dysfunction is most often characterized symptomatically by frequency, urgency, and urge incontinence and urodynamically by normal sensation with involuntary contraction at low filling volumes. Residual urine is characteristically low unless anatomic outlet obstruction or true smooth or striated sphincter dyssynergia occurs. The patient generally can initiate a bladder contraction voluntarily but is often unable to do so during cystometry because sufficient urine storage cannot occur before involuntary contraction is stimulated.

Reflex neurogenic bladder refers to the post-spinal shock condition that exists after complete interruption of the sensory and motor pathways between the sacral spinal cord and the brainstem. Most commonly, this condition occurs in **traumatic spinal cord injury and transverse myelitis**, but it may occur with **extensive demyelinating disease or any process that produces significant suprasacral (cord) spinal cord destruction**. Typically, there is no bladder sensation, and there is inability to initiate voluntary micturition. Incontinence without sensation generally results from low-volume involuntary contraction. Striated sphincter dyssynergia is the rule. This type of lesion is essentially equivalent to a complete upper motor neuron (UMN) lesion in the Bors-Comarr system (see later).

An **autonomous neurogenic bladder** results from complete motor and sensory separation of the bladder from the sacral spinal cord. This condition may be caused by **any disease that destroys the sacral cord or causes extensive damage to the sacral roots or pelvic nerves**. There is inability to initiate micturition voluntarily, no bladder reflex activity, and no specific bladder sensation. This type of bladder is equivalent to a complete lower motor neuron (LMN) lesion in the Bors-Comarr system and is the type of dysfunction seen in patients with spinal shock. The characteristic cystometric pattern is initially similar to the late stages of the motor or sensory paralytic bladder, with a marked shift to the right of the cystometric filling curve and a large bladder capacity at low intravesical pressure. However, decreased compliance may develop, secondary either to chronic inflammatory change or to the effects of denervation/decentralization with secondary neuromorphologic and neuropharmacologic reorganizational changes. Emptying capacity may vary widely, depending on the ability of the patient to increase intravesical pressure and on the resistance offered during this increase by the smooth and striated sphincters.

These classic categories in their usual settings are generally understood and remembered, and this is why this system provides an excellent framework for teaching some fundamentals of neurogenic voiding dysfunction to students and nonurologists. However, **many patients do not fit exactly into one or another category**. Gradations of sensory, motor, and mixed lesions occur, and the patterns produced after different types of peripheral denervation/defunctionalization may vary widely from the patterns that are classically described. **The system is applicable only to neuropathic dysfunction.**

Bors and Comarr (1971) made a remarkable contribution by logically deducing a classification system from clinical observation of their patients with traumatic spinal cord injury (**Box 70-8**). This system, primarily of historical interest at present, applies only to patients with neurologic dysfunction and considers three factors: (1) the anatomic localization of the lesion, (2) the neurologic completeness or incompleteness of the lesion, and (3) whether

BOX 70-8 Bors-Comarr Classification

Sensory neuron lesion
Incomplete, balanced
Complete, balanced
Motor neuron lesion
Balanced
Imbalanced
Sensorimotor neuron lesion
Upper motor neuron lesion
Complete, balanced
Complete, imbalanced
Incomplete, balanced
Incomplete, imbalanced
Lower motor neuron lesion
Complete, balanced
Complete, imbalanced
Incomplete, balanced
Incomplete, imbalanced
Mixed lesion
Upper somatomotor neuron, lower visceromotor neuron
Lower somatomotor neuron, upper visceromotor neuron
Normal somatomotor neuron, lower visceromotor neuron

LUT function is *balanced* or *unbalanced*. The last terms are based solely on the percentage of residual urine relative to bladder capacity. **Unbalanced** signifies the presence of greater than 20% residual urine in a patient with a UMN lesion or 10% in a patient with an LMN lesion. This relative residual urine volume was ideally meant to imply coordination (synergy) or dyssynergia between the smooth and the striated sphincters of the outlet and the bladder during bladder contraction or during attempted micturition by abdominal straining or the Credé maneuver. The determination of the completeness of the lesion is made on the basis of a thorough neurologic examination.

The system erroneously assumes that the sacral spinal cord is the primary reflex center for micturition. LMN implies collectively the preganglionic and postganglionic parasympathetic autonomic fibers that innervate the bladder and outlet and originate as preganglionic fibers in the sacral spinal cord. The term is used in an analogy to efferent somatic nerve fibers such as those of the pudendal nerve, which originate in the same sacral cord segment but terminate directly on pelvic floor striated musculature without the interposition of ganglia. UMN is used in a similar analogy to the somatic nervous system to describe the descending autonomic pathways above the sacral spinal cord (the origin of the motor efferent supply to the bladder).

In this system, **UMN bladder** refers to the pattern of micturition that results from an injury to the suprasacral spinal cord after the period of spinal shock has passed, assuming that the sacral spinal cord and the sacral nerve roots are intact and that the pelvic and pudendal nerve reflexes are intact. **LMN bladder** refers to the pattern resulting if the sacral spinal cord or sacral roots are damaged and the reflex pattern through the autonomic and somatic nerves that emanate from these segments is absent. This system implies that if skeletal muscle spasticity exists below the level of the lesion, the lesion is above the sacral spinal cord and is by definition a UMN lesion. This type of lesion is characterized by involuntary bladder contraction during filling. If flaccidity of the skeletal musculature below the level of a lesion exists, an LMN lesion is assumed to be present, implying that detrusor areflexia is present. Exceptions occur and are classified in a “**mixed lesion group**” characterized either by involuntary bladder contraction with a flaccid paralysis below the level of the lesion or by detrusor areflexia with spasticity

or normal skeletal muscle tone neurologically below the lesion level.

The use of this system is illustrated as follows. A “**UMN lesion, complete, imbalanced**” implies a neurologically complete lesion above the level of the sacral spinal cord that results in skeletal muscle spasticity below the level of the injury. Involuntary bladder contraction occurs during filling, but a residual urine volume of greater than 20% of the bladder capacity is left after bladder contraction, implying obstruction in the area of the bladder outlet during the involuntary detrusor contraction. This obstruction is generally due to striated sphincter dyssynergia, typically occurring in patients who are paraplegic or quadriplegic with lesions between the cervical and the sacral spinal cord. Smooth sphincter dyssynergia may be seen as well in patients with lesions above the level of T6, usually associated with autonomic hyperreflexia (see Chapter 75). An “**LMN lesion, complete, imbalanced**” implies a neurologically complete lesion at the level of the sacral spinal cord or of the sacral roots, resulting in skeletal muscle flaccidity below that level. Detrusor areflexia results, and whatever measures the patient may use to increase intravesical pressure during attempted voiding are insufficient to decrease residual urine to less than 10% of bladder capacity.

This classification system applies best to spinal cord injury patients with complete neurologic lesions after spinal shock has passed. It is difficult to apply to patients with multicentric neurologic disease and cannot be used at all for patients with non-neurologic disease. The system fails to reconcile the clinical and urodynamic variability exhibited by patients who, by neurologic examination alone, seem to have similar lesions. The period of spinal shock that immediately follows severe cord injury is generally associated with bladder areflexia, whatever the status of the sacral somatic reflexes. Temporary or permanent changes in bladder or outlet activity during filling/storage and emptying/voiding may occur as a result of numerous factors, such as chronic overdistention, infection, and reinnervation or reorganization of neural pathways after injury or disease; such changes make it impossible to predict LUT activity accurately solely on the basis of the level of the neurologic lesion. Finally, although the terms *balanced* and *imbalanced* are helpful, in that they describe the presence or absence of a certain relative percentage of residual urine, they do not imply the true functional significance of a lesion, which depends on the potential for damage to the lower or upper urinary tracts and on the social and vocational disability that results.

Hald-Bradley Classification

Hald and Bradley (1982) described what they termed a simple neurotopographic classification (Box 70-9). The system is of historical interest only. A **suprasacral lesion** is characterized by synergy between detrusor contraction and the smooth and striated sphincters, but defective inhibition of the voiding reflex exists. Involuntary bladder contraction generally occurs, and sensation is usually preserved. However, depending on the site of the lesion, detrusor areflexia and defective sensation may be seen. A **suprasacral spinal lesion** is roughly equivalent to what is described as a UMN lesion in the Bors-Comarr classification. An **infrasacral lesion** is roughly equivalent to an LMN lesion. **Peripheral autonomic neuropathy** is most frequently encountered in diabetic patients and is character-

ized by deficient bladder sensation, gradually increasing residual urine, and ultimate decompensation, with loss of detrusor contractility. A **muscular lesion** can involve the detrusor itself, the smooth sphincter, or any portion, or all, of the striated sphincter. The resultant dysfunction depends on which structure is affected. Detrusor dysfunction is the most common and generally results from decompensation following long-standing bladder outlet obstruction. In my opinion, this system is as confusing as the word neurotopographic and adds little to the understanding of LUT dysfunction.

Bradley Classification

Bradley’s “**loop system**” of classification is a primarily neurologic system based on his conceptualization of central nervous system control of the LUT that identifies four neurologic “loops” (Hald and Bradley, 1982). Dysfunctions are classified according to the loop affected. Occasional reference is made to this system, primarily by nonurologists.

Loop 1 consists of neuronal connections between the cerebral cortex and the pontine mesencephalic micturition center; this coordinates voluntary control of the detrusor reflex. **Loop 1 lesions** are seen in conditions such as **brain tumor, cerebrovascular accident or disease, and cerebral atrophy with dementia**. The final result is characteristically **involuntary bladder contractions**.

Loop 2 includes the intraspinal pathway of detrusor muscle afferents to the brainstem micturition center and the motor impulses from this center to the sacral spinal cord. Loop 2 is thought to coordinate and provide for a detrusor reflex of adequate temporal duration to allow complete voiding. Partial interruption by spinal cord injury results in a detrusor reflex of low threshold and in poor emptying with residual urine. **Spinal cord transection of loop 2 acutely produces detrusor areflexia and urinary retention—spinal shock. After this has passed, involuntary bladder contractions result.**

Loop 3 consists of the peripheral detrusor afferent axons and their pathways in the spinal cord; these terminate by synapsing on pudendal motor neurons that ultimately innervate periurethral striated muscle. Loop 3 was thought to provide a neurologic substrate for coordinated reciprocal action of the bladder and striated sphincter. **Loop 3 dysfunction could be responsible for detrusor striated dyssynergia or involuntary sphincter relaxation.**

Loop 4 consists of two components. Loop 4A is the suprasacral afferent and efferent innervation of the pudendal motor neurons to the periurethral striated musculature. Loop 4B consists of afferent fibers from the periurethral striated musculature that synapse on pudendal motor neurons in Onuf nucleus—the segmental innervation of the periurethral striated muscle. Bradley conceptualized that, in contrast to the stimulation of detrusor afferent fibers, which produced inhibitory postsynaptic potentials in pudendal motor neurons through loop 3, pudendal nerve afferents produced excitatory postsynaptic potentials in those motor neurons through loop 4B. These provided for contraction of the periurethral striated muscle during bladder filling and urine storage. The related sensory impulses arise from muscle spindles and tendon organs in the pelvic floor musculature. **Loop 4 provides for volitional control of the striated sphincter.** Abnormalities of the suprasacral portion result in abnormal responses of the pudendal motor neurons to bladder filling and emptying, manifested as detrusor striated sphincter dyssynergia and/or loss of the ability to contract the striated sphincter voluntarily.

The Bradley system is sophisticated and reflects the ingenuity and neurophysiologic expertise of its originator, himself a neurologist. For neurologists, this method may be an excellent way to conceptualize the neurophysiology involved, assuming that there is agreement on the existence and significance of all four loops—a big assumption. Most urologists find this system difficult to use for many types of neurogenic LUT dysfunction and not applicable to non-neurogenic LUT dysfunction. Urodynamically, it may be extremely difficult to test the intactness of each loop system, and multicentric and partial lesions are difficult to describe.

BOX 70-9 Hald-Bradley Classification

- Suprasacral lesion
- Suprasacral spinal lesion
- Infrasacral lesion
- Peripheral autonomic neuropathy
- Muscular lesion

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The complete reference list is available online at www.expertconsult.com.

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Definition and Impact of Pelvic Floor Disorders

Diagnostic Evaluation

Management

Conclusion

DEFINITION AND IMPACT OF PELVIC FLOOR DISORDERS

Pelvic floor disorders (PFDs), which include urinary incontinence, fecal incontinence, and pelvic organ prolapse (POP), pose a prevalent worldwide health concern. (For the purposes of this chapter, *incontinence* will refer to urinary leakage unless otherwise specified.) A detailed overview of the epidemiology and pathophysiology of pelvic floor disorders appears in Chapter 74.

The impact of PFDs is far-reaching, carrying a significant potential to affect patient quality of life (QoL), notwithstanding the psychological burden they produce. Additionally, incontinence creates a tremendous cost to the individual and to society. [Hu and colleagues \(2004\)](#) estimated that the evaluation and management of incontinence and productivity lost as a result of the condition resulted in a \$19.5 billion (year 2000 dollars) cost to society, although sensitivity analysis suggested a potential cost range of \$9.32 to \$28 billion. Contemporary numbers might predictably be higher, although Hu's most recent analysis demonstrated a 26% cost decrease compared to their 1995 report, which estimated \$26.29 billion. The decrease was speculated to be due to various factors, including decreased hospital stays and adjusted methods of assessing nursing home stays, routine care product use, and prevalence data. Other reports have demonstrated that medical expenditures for incontinence in the female Medicare population nearly doubled between 1992 and 1998, the result primarily of increased outpatient expenditure from 9.1% to 27.3% of total Medicare costs in approximately the same timeframe ([Thom et al, 2005](#); [Anger et al, 2006](#)). Contemporary estimates of the economic burden imparted by PFDs range widely. [Chong and associates \(2011\)](#) reported an annual cost of over \$12 billion for stress urinary incontinence (SUI). [Milsom and colleagues \(2014\)](#) reported a cost of \$66 billion per year for urinary urgency incontinence in 2007, and [Ganz and coworkers \(2010\)](#) projected a total annual cost of \$76.2 billion in 2015 and \$82.6 billion in 2020. [Sung and colleagues \(2010\)](#) reported a cost of \$412 million, including deductibles and copayments for PFDs, in 2005 and 2006.

[Wu and colleagues \(2009\)](#) used U.S. Census Bureau population projections to forecast the change in PFD prevalence in women between 2010 and 2050. The current estimate of 28.1 million women with at least one PFD in 2010 is projected to increase substantially to 43.8 million in 2050. Accordingly, the same group predicted an increase in surgical treatment of SUI and POP during the same period of 47.2% and 48.2%, respectively ([Wu et al, 2009](#)).

As a result of increasing awareness of the societal impact of PFDs in addition to the growing emphasis on maximizing QoL in our aging population, tremendous research efforts are under way to improve our understanding of the pathophysiology of

these disorders, thereby improving both diagnostic and therapeutic techniques. The importance of evidence-based medicine and meticulous follow-up of patients is driving improvement in the science on which advancements in this subspecialty of urology are being made.

DIAGNOSTIC EVALUATION

General Considerations

A recent upsurge in research efforts has resulted in the emergence of new diagnostic and therapeutic techniques to address PFDs. As QoL impact has become a focus, much of current research efforts include detailed QoL assessment and attempts to quantify and assess the relationship between PFDs and their effects on QoL. Correlating the bother caused by a given PFD with the risk of available therapies is an important consideration. The purpose of evaluation of patients with urinary incontinence includes documentation and characterization of the incontinence, consideration of the differential diagnosis, prognostication and facilitation of treatment selection ([Dmochowski et al, 2010](#)). Additionally, proper evaluation helps assess symptom bother and establish a patient's expectations of potential outcomes.

The type of incontinence affecting an individual must be defined and quantified to guide proper treatment planning. Transient or unrelated conditions that can cause leakage should be identified before proceeding with definitive therapy. [Box 71-1](#) contains a mnemonic of transient causes of incontinence ([Resnick, 1984](#)). [Table 71-1](#) lists current International Urogynecological Association (IUGA)/International Continence Society (ICS) nomenclature regarding urinary incontinence symptoms ([Abrams et al, 2002, 2009b](#); [Haylen et al, 2010](#)). The terminology continues to adjust to reflect the evolving understanding of the condition. The importance of this flexibility has been realized and acknowledged by leaders in the subspecialty of pelvic floor medicine ([Chapple, 2009](#)). Accordingly, the IUGA/ICS terminology has been updated since its inception and most recently has been expanded to include not only terminology for lower urinary tract (LUT) function and urodynamics (UDS) but also POP, LUT pain, sexual dysfunction, anorectal dysfunction, and pelvic imaging ([Haylen et al, 2010](#)).

The classification of POP is categorized according to the affected compartment. Simply put, anterior compartment prolapse (cystocele) generally involves descent of the bladder toward the vaginal lumen, posterior prolapse (rectocele) involves the rectum compressing the posterior vaginal wall into the vagina, and apical prolapse is associated with descent of the uterus (uterine procidentia) and/or the bowel (enterocele) at the top of the vagina. Several grading systems exist to quantify the severity of POP and are discussed later and illustrated in [Figure 71-1](#).

BOX 71-1 Causes of Transient Incontinence (DIAPPERS)

- Delerium
- Infection (urinary tract infection)
- Atrophic vaginitis/urethritis
- Psychological (e.g., severe depression, neurosis)
- Pharmacologic
- Excess urine production
- Restricted mobility
- Stool impaction

Regarding incontinence specifically, the substantiation of a proper diagnosis requires direct observation of urinary leakage by the clinician (Nitti and Blaivas, 2007). It is the belief of many experts that no patient should undergo invasive or irreversible therapies without definitive establishment of the cause of their incontinence and demonstration of leakage in the specific case of SUI. Complete and extensive evaluation can facilitate accurate diagnosis of PFDs to promote optimal treatment planning and counseling of patients.

History

A careful history should always be obtained from the patient. However, several studies have indicated that patient history alone

TABLE 71-1 Standard International Urogynecological Association/International Continence Society Terminology of Urinary Incontinence Symptoms

TERMINOLOGY	DESCRIPTION
Urinary incontinence	Complaint of any involuntary leakage of urine
Stress urinary incontinence	Complaint of involuntary leakage on effort or exertion or on sneezing or coughing
Urgency	Complaint of a sudden compelling desire to pass urine, which is difficult to defer
Urgency incontinence	Complaint of involuntary leakage accompanied by or immediately preceded by urgency
Postural incontinence	Complaint of voluntary loss of urine associated with change of body position (e.g., rising from a seated or lying position)
Nocturnal enuresis	Complaint of involuntary loss of urine that occurs during sleep
Mixed incontinence	Complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing
Continuous urinary incontinence	Complaint of continuous leakage
Insensible incontinence	Complaint of urinary incontinence in which the woman is unaware of how it occurred
Coital incontinence	Complaint of involuntary loss of urine with coitus

Data from Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-Committee of the International Continence Society. *Neurourol Urodyn* 2002;21:167–78.

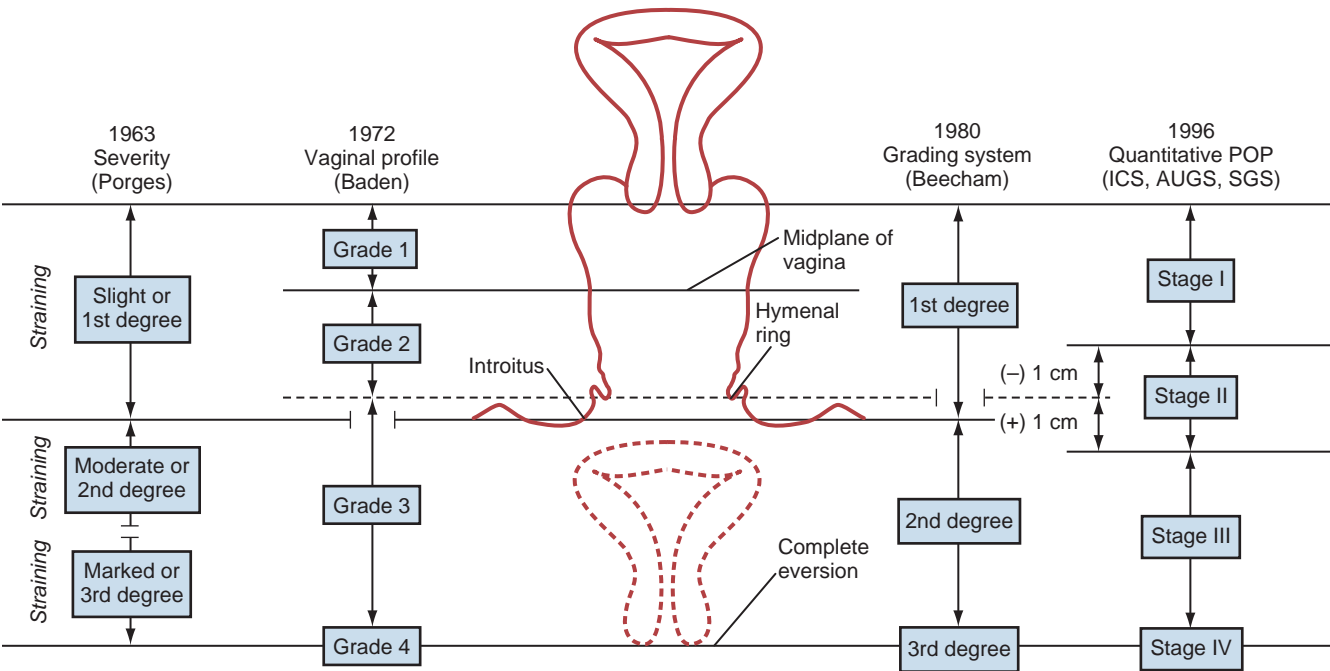


Figure 71-1. Visual comparison of systems used to quantify pelvic organ prolapse (POP). AUGS, American Urogynecologic Society; ICS, International Continence Society; SGS, Society of Gynecologic Surgeons. (From Theofrastous JP, Swift SE. The clinical evaluation of pelvic floor dysfunction. *Obstet Gynecol Clin North Am* 1998;25:783–804.)

KEY POINTS: GENERAL CONSIDERATIONS

- PFDs are a prevalent worldwide health concern.
- Careful history and physical examination are integral in the proper evaluation of patients with PFDs.
- Supplementary evaluation including urinalysis (UA), post-void residual (PVR), UDS, endoscopy, and radiologic imaging can be helpful in arriving at a complete and accurate diagnosis.
- A variety of surgical and nonsurgical treatment options are available for treatment of urinary incontinence and POP.

is not completely accurate as the sole determinant of incontinence type (Summitt et al, 1992; Jensen et al, 1994). Bates and associates (1973) are credited with the dictum, “The bladder is an unreliable witness,” which has been corroborated by many investigators in various forms. Accordingly, all available information, including that obtained by supplementary examinations, should be integrated into the diagnosis.

History of Present Illness

A thorough history is imperative in the evaluation of incontinence. Several queries should be included in a continence and pelvic floor history to best portray the patient’s symptoms (Holroyd-Leduc et al, 2008). The incontinence first should be characterized subjectively. Does the leakage occur: With physical activity? With a sense of urgency? Without sensory awareness? If the nature of the incontinence is mixed, does one component cause more bother or occur more frequently than the other? Second, the leakage should be quantified if possible. Appraisal of the degree of leakage before therapy can be helpful during postoperative assessment of treatment impact. For the purposes of routine outpatient assessment, this quantification can be achieved based on the number of pads used per day or the frequency of clothing changes because of urinary leakage. In the setting of research or an academic practice, more stringent and objective measures such as pad weight testing are often used (see Supplemental Evaluation). Third, the voiding pattern should be defined. What is the frequency of urination during the day? During the night? Are there any obstructive symptoms? Does the patient have to wait for the stream to start (hesitancy)? Does the patient feel as though the bladder has emptied completely? Is the stream strong or does it “trickle”? Does the stream fluctuate during the void? Is it necessary to push or strain or change posture to void or empty the bladder? Fourth, establishment of the duration of symptoms and any inciting events that contributed to the onset of leakage is important. Did the leakage follow a pregnancy or a vaginal delivery? How long ago? Did the leakage start after a strain, a fall, or trauma? Has the patient undergone pelvic or back surgery? In males, has there been prostate or urethral surgery for benign or malignant disease? Has there been LUT instrumentation? Are there any accompanying neurologic symptoms, such as numbness or tingling in the extremities, blurry/double vision, balance or coordination changes, or tremor? It is helpful to determine the impact that the leakage has on the patient’s daily life and activities. Does the incontinence limit the individual’s activity? Has he or she made lifestyle changes because of the threat of leakage? Finally, the American Urological Association (AUA) guidelines emphasize the importance of establishing patient expectation of treatment and an understanding of the balance between the benefits and risks/burden of available treatment options (Dmochowski et al, 2010).

Regarding pelvic prolapse specifically, important questions focus on whether the patient is aware of any prolapse and what, if any, symptomatology and bother the prolapse may be causing. Does the patient feel that anything is falling down out of place in the vagina? Does she need to reduce the prolapse for comfort? Or to empty her bladder completely? Or to facilitate evacuation of her bowels?

Past Medical and Surgical History

Past medical and surgical histories are vital to the assessment of incontinence insofar as medical conditions and surgeries can affect urinary tract function. Childhood and adult urologic history should be obtained, as should a neurologic history. Neurologic conditions such as Parkinson disease, multiple sclerosis, stroke, spinal cord injury, back surgery, and myelodysplasia can have a considerable impact on LUT function. Medical diagnoses, such as diabetes mellitus and dementia, can affect continence. Similarly, a history of radiation therapy or neurologic or urologic trauma can affect LUT function, specifically with regard to outlet resistance and/or bladder contractility, stability, and compliance. Although outlet resistance may be compromised by trauma or LUT surgery, urethral strictures related to trauma or neurologic dysfunction that abnormally increase outlet resistance during voiding can cause obstruction and secondary symptoms related to the obstruction.

In women, the gynecologic and obstetric history, including gravity, parity, and hormonal status is important. Determination of whether the patient is premenopausal, perimenopausal, or postmenopausal and whether she has used any exogenous hormones such as oral contraceptives or local or systemic hormone replacement therapy can be helpful in her overall assessment. As mentioned previously, although beneficial effects of local hormone replacement therapy are well-established, there have been reports that exogenous systemic hormone therapy can actually increase the risk for SUI (Townsend et al, 2009; Cody et al, 2012).

Clearly, previous pelvic surgery can affect LUT function. Anti-incontinence surgery, POP repair, and hysterectomy can contribute to a variety of urinary symptoms in women. Similarly, a history of prostate surgery can give rise to voiding or leakage complaints in men. Abdominoperineal resection can result in neurologic injury that can affect the function of either the bladder or the sphincter (Petrelli et al, 1993), and back surgery can cause a variety of symptoms depending on the level affected.

Medications

An accurate assessment of medications is critical, particularly in the elderly patient population in whom polypharmacy is common. Many agents can affect urine production, LUT function, and mental status, all of which can have an impact on continence. Special attention should be focused on agents that can affect bladder/sphincteric function. Table 71-2 categorizes some commonly used classes of medications by mechanism of action and potential effect on the LUT.

TABLE 71-2 Pharmacologic Agents That Can Affect the Lower Urinary Tract

PHARMACOLOGIC EFFECTS	POTENTIAL EFFECTS ON URINARY TRACT
Sympathomimetics	Can increase outlet resistance and exacerbate obstructive symptoms/overactive bladder symptoms Can decrease detrusor contractility and precipitate retention
Sympatholytics	Can decrease outlet resistance and exacerbate stress incontinence
Anticholinergics	Can contribute to urinary retention, particularly in patients with outlet obstruction
Diuretics	Do not affect bladder directly, but because of increased urine production, can aggravate incontinence problems

Other

Because **genetics** can influence connective tissue integrity, it stands to reason that there may be a potential hereditary role in continence and POP (Twiss et al, 2007b). Therefore inquiry about family history of POP may be helpful. Additionally, a thorough review of systems may reveal symptoms that suggest other conditions that could have an impact on pelvic floor function.

Male incontinence, also a very prevalent health issue, should be assessed in much the same way as female incontinence, although specific consideration of the impact of the anatomy specific to the male should be considered. **Benign prostatic hyperplasia**, the evaluation of which is covered in detail in Chapter 104, can cause secondary urgency and urgency incontinence in addition to more “typical” obstructive symptoms, such as a decreased force of stream, urinary hesitancy, intermittency, and incomplete bladder emptying. **Prostate surgery for benign or malignant disease** can contribute to SUI. With this in mind, full assessment of male LUT symptoms (LUTS) should be performed to facilitate proper treatment planning.

KEY POINTS: HISTORY

- A thorough history is essential in the diagnostic evaluation of patients with PFDs.
- Queries specific to the character, severity, duration, and quantity of incontinence and other symptoms related to pelvic floor function should be performed.
- Attention should be paid to the impact of PFD symptoms on QoL.
- When appropriate, the clinician should present questions specific to the female with potential POP and the male with potential prostate issues.
- Queries regarding past medical and surgical history, obstetric and gynecologic history, radiation therapy, trauma, and medications may provide important information.

Physical Examination

The general appearance of a patient, including details such as age, gait, stature, and fragility, can provide important information regarding performance status, neurologic status, and other factors that may direct proper treatment planning. Similarly, an abdominal examination evaluating for incisions, hernias, organomegaly or bladder distention, and habitus is important, particularly if any abdominal surgery may be considered.

Per Medicare coding guidelines (Centers for Medicare and Medicaid Services, 1997), a female pelvic examination includes at least 7 of the 11 bulleted items listed in Box 71-2. The external genitalia should be evaluated with regard to general appearance, estrogen status, lesions, and labial size, and adhesions. Estrogen status can be evaluated based on the presence or absence of a urethral caruncle, urethral prolapse, and/or labial adhesions, all of which, if present, may indicate estrogen deficiency. Likewise, attention to the overall tissue appearance and color is important. Hormonally deficient vaginal tissue has a pale, flat, dry appearance with no rugae, as opposed to the healthy, pink rugated tissue of well-estrogenized tissue.

Urethral position and mobility should be assessed at rest and with straining and coughing. The **Q-tip test** was developed to objectify the evaluation of urethral mobility (Bergman and Bhatia, 1987; Walters and Diaz, 1987). The discomfort caused to the patient during insertion of the Q-tip can be minimized with the use of intraurethral lidocaine jelly. With the patient in the lithotomy position, a Q-tip is inserted into bladder through the urethra and the angle that the Q-tip moves from horizontal to its final position with straining is measured. Hypermobility is defined as a Q-tip angle of more than 30 degrees from horizontal.

Connective tissue support of the pelvis and the pelvic viscera was described by DeLancey in three levels. Levels I, II, and III represent

BOX 71-2 Components of a Focused Pelvic Examination

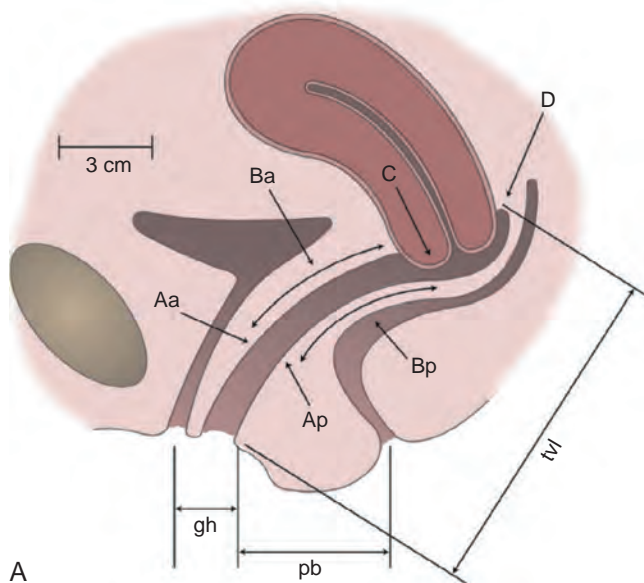
- Inspection and palpation of breasts (e.g., masses or lumps, tenderness, symmetry, nipple discharge)
- Digital rectal examination, including sphincter tone, presence of hemorrhoids, rectal masses
- Pelvic examination (with or without specimen collection for smears and cultures), including:
 - External genitalia (e.g., general appearance, hair distribution, lesions)
 - Urethral meatus (e.g., size, location, lesions, prolapse)
 - Urethra (e.g., masses, tenderness, scarring)
 - Bladder (e.g., fullness, masses, tenderness)
 - Vagina (e.g., general appearance, estrogen effect, discharge, lesions, pelvic support, cystocele, rectocele)
 - Cervix (e.g., general appearance, lesions, discharge)
 - Uterus (e.g., size, contour, positions, mobility, tenderness, consistency, descent or support)
 - Adnexa/parametria (e.g., masses, tenderness, organomegaly, nodularity)
 - Anus and perineum

At the time of this writing, 7 of 11 bullet points listed above are required to be considered a complete female genitourinary examination. However, other organ systems/body areas not limited to the genitourinary system may be included in a report to accomplish the requirements of various levels of examination.

Data from Centers for Medicare and Medicaid Services. Single organ system examination: genitourinary—1997 Documentation Guidelines for Evaluation and Management (E/M) Services, jointly approved by the American Medical Association and HCFA with revisions. Baltimore, November 1997.

the proximal, middle, and distal vaginal support, respectively, in this classification system that is now used worldwide. Level I involves the uterosacral and cardinal ligaments and supports the vaginal vault; level II supports the mid-vagina via attachment of the anterior and posterior endopelvic fascia to the lateral pelvic side walls; and level III support depends on the fusion of the endopelvic fascia to the pubic symphysis and perineal body (DeLancey, 1992). Assessment of prolapse ideally should be performed in both the lithotomy and standing positions, the latter facilitated by having the patient stand with one foot elevated on a short stool. Each compartment—the anterior, posterior, and apical (uterus/cervix or vaginal cuff)—should be evaluated methodically and the perineal body assessed for laxity. A complete systematic examination is performed using two posterior blades of a split Grave speculum with and without straining. First, one blade is used to retract the posterior wall to facilitate anterior compartment examination. The blade is then repositioned to retract anteriorly for examination of the posterior compartment. Finally, both blades are inserted simultaneously, one anteriorly and one posteriorly, to isolate the vaginal apex and facilitate examination of the cervical or cuff support. The posterior blade is slowly withdrawn to examine the posterior wall. Next, with the posterior blade in place, the patient is asked to strain. Foreshortening of the posterior wall causes expulsion of the blade and suggests a compromise in the level I support (DeLancey, 1992) (cardinal-uterosacral ligament complex) of the vault; if the blade remains in place, this could represent an isolated rectocele or enterocele without vault prolapse. Evaluation for occult SUI should be performed with the anterior wall supported. SUI can be masked if significant prolapse “kinks” the urethra and outlet.

Several classification systems are used to quantify POP, the most widely used of which are the **Baden-Walker classification** (Baden et al, 1968) and the **Pelvic Organ Prolapse-Quantification system**, known as the POP-Q (Bump et al, 1996). The two systems are



A

Point	Description	Range of values
Aa	Anterior vaginal wall 3 cm proximal to the hymen	−3 cm to +3 cm
Ba	Most distal position of remaining upper anterior vaginal wall	−3 cm to +tvL
C	Most distal edge of cervix or vaginal cuff scar	—
D	Posterior fornix (N/A if posthysterectomy)	—
Ap	Posterior vaginal wall 3 cm proximal to the hymen	−3 cm to +3 cm
Bp	Most distal position of remaining upper posterior vaginal wall	−3 cm to +tvL
gh (genital hiatus)	Measured from middle of external urethral meatus to posterior midline hymen	—
pb (perineal body)	Measured from posterior margin of gh to middle of anal opening	—
tvL (total vaginal length)	Depth of vagina when point D or C is reduced to normal position	—

B

Figure 71-2. A, Landmarks for the POP-Q system. B, POP-Q points of reference. (A, From Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:10–7.)

juxtaposed in Figure 71-1. In the POP-Q system, which was created in an effort to provide objectivity to POP quantification, nine specific points of measurement are obtained in relation to the hymenal ring, as illustrated in Figure 71-2. Six vaginal points labeled Aa, Ba, C, D, Ap, and Bp are measured during Valsalva maneuver. Points above the hymen are considered negative, and points below the hymen are positive. The genital hiatus (gh) represents the size of the vaginal opening, while the perineal body (pb) represents the distance between the vagina and the anus. The total vaginal length (tvL) is measured by reducing the prolapse and measuring the depth of the vagina. Table 71-3 contains the POP-Q staging criteria, a simplified presentation of the POP-Q system, and Figure 71-3 illustrates an example of the application of the system.

A neurologic examination is important in any patient with a known or suspected neurologic condition. Attention to the patient's gait, speech, cognitive status, facial symmetry, sensation in the lower extremities, perineal and perianal regions, lower extremity motor strength, and vaginal and pelvic floor strength can provide helpful

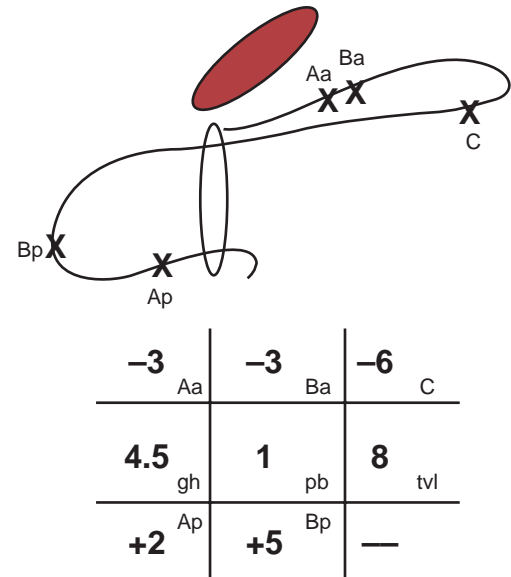


Figure 71-3. Line drawing example of posterior support defect. The anterior compartment is well supported. Bp is the leading point of the prolapse relative to the reference point of the hymen. At +5, Bp is 5 cm beyond the hymen. Point C designates the cuff position. Taking into consideration a total vaginal length (tvL) of 8 cm, the cuff has descended 2 cm. (From Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:10–7.)

TABLE 71-3 POP-Q Staging Criteria

STAGE	CRITERIA
0	Aa, Ap, Ba, Bp at −3 cm and C or D ≤ −(tvL − 2) cm
I	Stage 0 criteria not met and leading edge < −1 cm
II	Leading edge ≥ −1 cm but ≤ +1 cm
III	Leading edge > +1 cm but < +(tvL − 2) cm
IV	Leading edge ≥ +(tvL − 2) cm

information. Mobility and cognitive status can play a role in urinary continence insofar as both can affect a patient's ability to reach the facilities in a timely fashion. The **bulbocavernosus reflex (BCR)**, which is representative of sacral nerve root levels 2 to 4 (S2–4), is present in 70% of normal females and 100% of normal males. The BCR is considered positive when squeezing of the glans penis or clitoris results in anal and pelvic floor contraction that can be detected visually or by rectal examination. Alternatively, applying traction to an indwelling Foley catheter to pull the balloon against bladder neck should also precipitate a BCR.

A digital rectal examination (DRE) is important in men to assess the prostate for size, nodularity, or tenderness. In the female, the DRE can facilitate assessment of the rectovaginal septum. Demonstration of a rectocele can be facilitated via anterior pressure applied by a finger placed in the rectum. Anal sphincter tone, which is a reflection of the function at S2–4, is particularly important in neurologic patients with PFD. Patients are asked to voluntarily tighten the pelvic floor as if attempting to stop the flow of urine midstream. Laxity in the rectal sphincter tone may suggest a possible neurologic defect, but it also may be due to patient lack of understanding regarding how to voluntarily control the specific muscle groups necessary for contraction.

In men, genitourinary examination as it pertains to voiding function also should include evaluation of the penis for meatal stenosis and, particularly in the postprostatectomy patient, visible urinary leakage with coughing and straining. Examination for leakage is ideally performed with the patient in the standing position.

KEY POINTS: PHYSICAL EXAMINATION

- A properly performed physical examination is imperative in the evaluation of patients with PFDs.
- The Centers for Medicare and Medicaid Services require specific elements of both male and female genitourinary examination to meet coding guidelines (see [Box 71-2](#)).
- Assessment of POP ideally should be performed in both the supine and standing positions.
- Several classification and quantification systems are available for assessment of POP, the most widely used of which (Baden-Walker and POP-Q) are illustrated in [Figures 71-1 and 71-2](#).
- Neurologic and rectal examinations should be performed in appropriate patients to obtain complete clinical information important in the assessment of lower urinary tract and pelvic floor function.

Supplemental Evaluation

A variety of measures are available to supplement the history and physical examination in patients with PFDs. Instruments exist to quantify symptoms, their effects on QoL, and the degree of bother experienced by patients with PFDs. **Most experts concur that a urinalysis (UA) and PVR measurement should be considered in the majority of patients undergoing evaluation for incontinence.** However, beyond this, there are no universally agreed-upon standards regarding the roles of other studies, such as endoscopy, UDS, radiographic imaging, and various modalities of symptom quantification, including voiding diaries, pad tests, and questionnaires ([Zimmern et al, 2010](#)). In an effort to address this, the AUA and the Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) published guidelines based on the current literature ([Dmochowski et al, 2010](#); [Gormley et al, 2012](#); [Winters et al, 2012](#)).

According to the guidelines, a UA is part of the minimum requirement for proper evaluation of the patient with an overactive bladder (OAB). Urine culture and PVR can be obtained at the discretion of the clinician. The guidelines state that UDS, cystoscopy, and renal ultrasound should not be a part of the initial evaluation of the patient with uncomplicated OAB ([Gormley et al, 2012](#)). Evaluation of the index patient with SUI should include PVR assessment. UA, UDS, pad tests, cystoscopy, and imaging can be considered ([Dmochowski et al, 2010](#)) in specific situations such as those outlined in [Box 71-3](#). In circumstances in which further investigation is considered, the value and accuracy (sensitivity and specificity) of the information provided by the given assessment method should be considered in relation to the cost and morbidity of the examination.

BOX 71-3 Circumstances That Warrant Consideration of Supplemental Evaluation

Inability to establish a diagnosis based on the patient's symptoms and initial evaluation
 Concomitant overactive bladder symptoms
 Prior lower urinary tract surgery including anti-incontinence surgery
 Known or suspected neurogenic bladder
 Negative stress test
 Abnormal urinalysis (e.g., unexplained hematuria or pyuria)
 Elevated postvoid residual
 High-grade pelvic prolapse (\geq grade 3)
 Evidence of dysfunctional voiding

Symptom Quantification Instruments

Voiding Diaries. Instruments such as voiding diaries, questionnaires, and pad tests have been developed to aid in the quantification of urinary loss, both symptomatically and volumetrically. **Voiding diaries can provide both diagnostic and therapeutic advantages. The use of diaries often helps patients realize their pattern of urination and is more accurate than recall** ([McCormack et al, 1992](#); [Siltberg et al, 1997](#); [Stav et al, 2009](#)). Furthermore, the diary can provide patients with insights into those behaviors that can be altered to decrease urinary frequency ([Burgio, 2004](#)).

Several studies have demonstrated the adjunctive role that diaries can have in the diagnosis and management of incontinence. Diaries can be helpful over routine subjective history because it has been demonstrated that patient recall is not often as accurate as a formal voiding diary in ascertaining urinary frequency. In a retrospective review of 601 patients who underwent sling surgery and completed bladder diaries, only 47% were accurate about their daytime frequency; 51% overestimated their diurnal frequency, and this overestimation was exaggerated in those who reported voiding more than 10 times per day ([Stav et al, 2009](#)). Overestimation rates were similar between patients with and without OAB symptoms. Interestingly, 93% of women in this study were accurate about their nighttime frequency. In another study of women with urinary incontinence, it was noted that the overestimation of incontinence episode frequency occurred more often in those patients who were more bothered by their incontinence. Conversely, Ku and associates ([Ku et al, 2004](#)) found a poor correlation between subjective nocturnal frequency and that noted by 164 patients on their frequency volume charts. [Wyman and colleagues \(1988\)](#) similarly showed a higher correlation of diary-reported frequency in the daytime versus the night.

[Martin and associates \(2006b\)](#) performed a meta-analysis of 121 in 6099 papers that compared two or more diagnostic techniques for incontinence and showed that diaries are most cost-effective when used in conjunction with history, particularly in patients undergoing treatment for detrusor overactivity. It should be noted, however, that diaries should not substitute for more formal studies in selected patients. One study that retrospectively assessed the Larsson frequency/volume chart as compared to the cystometrogram in 216 patients demonstrated the sensitivity and specificity of the chart with regard to detrusor overactivity to be 52% and 70%, respectively, and with regard to SUI, 66% and 65%, respectively ([Tincello and Richmond, 1998](#)). For daily clinical practice, 24-hour diaries should suffice to obtain valuable clinical information regarding LUT function; in academic studies, longer diaries may be requested, but this should be balanced with the well-established knowledge that the more complex a given instrument is (i.e., the more data requested), the lower patient compliance will be in completing it ([Groutz et al, 2000](#)).

Questionnaires and Quality of Life Instruments

Questionnaires can provide a very helpful complement to the patient history and patient-reported outcomes. A plethora of instruments to evaluate symptoms, degree of bother, and QoL in patients with incontinence and PFDs have been developed in an effort to provide optimal assessment of outcomes and eliminate the confounding issue of physician bias; many have been validated. [Table 71-4](#) contains validated questionnaires highly recommended by the International Consultation on Incontinence (ICI). One such instrument, the modular ICIQ, was developed by the ICI in an effort to collaboratively develop a universally applicable instrument that could be used internationally to assess pelvic floor function in both clinical practice and research settings ([Abrams et al, 2005a, 2005b](#)) and has accordingly been translated in 38 languages. The short form of the ICI questionnaire (ICIQ-SF) has been shown to correlate nicely with both the 1-hour ([Franco et al, 2008](#)) and 24-hour ([Karantanis et al, 2004](#)) pad tests for evaluation of the severity of SUI. Another comparison of the 24-hour pad test, the ICIQ-SF, the International Prostate Symptom Score (IPSS), and the Post-operative

TABLE 71-4 Instruments Highly Recommended by the Fourth International Consultation on Incontinence for Urinary Incontinence, Overactive Bladder, Lower Urinary Tract Symptoms, and Pelvic Organ Prolapse Patient Reported Outcomes

QUESTIONNAIRE	POPULATION	PURPOSE OF INSTRUMENT
HEALTH-RELATED QUALITY OF LIFE (HRQOL)		
BFLUTS (Bristol Female Lower Urinary Tract Symptoms Questionnaire) (also named ICIQ-FLUTS) (Jackson et al, 1996)	Women, incontinence	To assess female LUTS, particularly incontinence, measure impact on QoL and evaluate treatment outcome
DAN-PSS-1 (Danish Prostatic Symptom Score) (Hansen et al, 1995)	Men, BPH	To evaluate males with LUTS suggestive of uncomplicated BPH
ICIQ-UI-SF (ICIQ Urinary Incontinence Short Form) (Avery et al, 2004)	Men and women, urinary symptoms	To assess symptoms and impact of urinary incontinence in clinical practice and research
ICSmale (ICIQ-MLUTS) (Donovan et al, 1996)	Men with LUTS and possible BPH	To provide evaluation of occurrence and bother of LUTS and their impact on the lives of men with BPH
ICS-QoL (Donovan et al, 1997)	Men with LUTs and possible BPH	To assess impact of LUTS on the lives of men with LUTS
IIQ (Incontinence Impact Questionnaire) (Wyman et al, 1987)	Women, UI, SUI	To assess impact of incontinence on HRQOL, primarily in patients with SUI
IIQ-7 (IIQ-short form) (Uebersax et al, 1995)	Women, UI, SUI	To assess impact of urinary incontinence on HRQOL
I-QOL (ICIQ-Uiqol) (urinary incontinence-specific QoL instrument) (Wagner et al, 1996)	Women, UI	To assess QoL of women with urinary incontinence
KHQ (King's Health Questionnaire) (ICIQ-LUTSqol) (Kelleher et al, 1997)	Men and women, OAB	To assess the impact of LUTS on HRQOL
N-QoL (ICIQ-Nqol; Nocturia QoL) (Abraham et al, 2004)	Men and women	To assess the impact of nocturia on QoL
OABq-SF (Coyne et al, 2002)	Men and women, OAB	Shortened version of OAB-q to evaluate both continence and incontinence symptoms of OAB and their impact on QoL
OAB-q (ICIQ-OABqol) (Coyne et al, 2002)	Men and women with OAB wet and OAB dry	To evaluate both OAB-wet and OAB-dry symptoms and their impact on HRQOL
PRAFAB (Protection, Amount, Frequency, Adjustment, Body image) (Hendriks et al, 2007)	Women, UI	To evaluate treatment effects for UI in women
UISS (Urinary Incontinence Severity Score) (Stach-Lempinen et al, 2001)	Women, UI	To assess symptom severity and impact of urinary incontinence on everyday life
Urolife (BPH-QoL9) (Lukacs et al, 1997)	Men, BPH	To assess the impact of BPH and its treatment on the QoL of patients
SCREENERS		
B-SAQ (Bladder-Self-Assessment Questionnaire) (Basra et al, 2007)	Women	Screening tool for the presence of bothersome LUTS in women
LUSQ (Leicester Urinary Symptom Questionnaire) (Shaw et al, 2002)	Men and women, LUTS	Condition-specific screener of storage LUTS (urgency, frequency, nocturia, and incontinence)
OAB-SS (OAB Symptom Score) (Blaivas et al, 2007)	Men and women, LUTS with and without OAB	7-item tool to measure overall symptom severity resulting from the four index symptoms of OAB
OAB-V8 (OAB Awareness Tool) (Coyne et al, 2005)	Men and women, OAB	8-item screening tool for use in primary care setting to identify patients who may have OAB
QUID (Questionnaire for Urinary Incontinence Diagnosis) (Bradley et al, 2005)	Women, UI and SUI	6-item tool to diagnose SUI and UI
SYMPTOM BOTHER		
PPBC (Patient Perception of Bladder Condition) (Coyne et al, 2006)	Men and women	To assess patients' subjective impression of their current urinary problems Developed as a global assessment of bladder condition
UDI-6 (Urogenital Distress Inventory-6/short form) (Uebersax et al, 1995)	Women	To assess LUTS bother, including incontinence, in women

Continued

TABLE 71-4 Instruments Highly Recommended by the Fourth International Consultation on Incontinence for Urinary Incontinence, Overactive Bladder, Lower Urinary Tract Symptoms, and Pelvic Organ Prolapse Patient Reported Outcomes—cont'd

QUESTIONNAIRE	POPULATION	PURPOSE OF INSTRUMENT
URGENCY		
IUSS (Indevus Urgency Severity) (Nixon et al, 2005)	OAB with urgency incontinence, men and women	To quantify the level of urgency associated with each toilet void as measured during standard voiding diaries
POP SYMPTOMS AND QOL		
PFDI (Pelvic Floor Distress Inventory) (Barber et al, 2001)	Women	To quantify the symptoms caused by pelvic prolapse
PFIQ (Pelvic Floor Impact Questionnaire) (Barber et al, 2001)	Women	To quantify the effects of pelvic prolapse on quality of life

BPH, benign prostatic hyperplasia; HRQOL, health-related QOL; ICIQ, International Consultation on Incontinence Questionnaire; ICS, International Continence Society; MLUTS/FLUTS, male/female lower urinary tract symptoms; OAB, overactive bladder; QoL, quality of life; SF, short form; SUI, stress urinary incontinence; UI, urgency incontinence.

Data from Staskin DR. In: Patient-Reported Outcome Assessment. Fourth International Consultation on Incontinence, report of Committee 5, part 5B. 2009. p. 363–412.

Patient Global Impression of Improvement (PGI-I) score in 26 men after perineal sling placement confirmed the construct validity of these instruments (Twiss et al, 2007a). There was a strong correlation demonstrated between the ICIQ-SF and PGI-I scores and the percentage reduction in 24-hour pad weight. At the time of this writing, available validated ICI symptom modules include the ICIQ-MLUTS (male LUTS) long and short forms, ICIQ-FLUTS (female LUTS) long and short forms, ICIQ-UI short form, ICIQ-N (nocturia), ICIQ-OAB, and ICIQ-VS (vaginal symptoms). Validated QOL modules applying to LUTS (ICIQ-LUTSqol), urinary incontinence (ICIQ-UIqol), OAB (ICIQ-OABqol), and nocturia (ICIQ-Nqol), as well as modules that assess male and female sexual function related to urinary symptoms (ICIQ-MLUTSsex and ICIQ-FLUTSsex), are also available for use. Additional modules covering bowel function, pediatric LUTS, and neurogenic LUTS, as well as modules assessing QoL symptoms pertaining to the same, and additional sexual function and treatment satisfaction modules are under development (Abrams et al, 2010; Bristol Urological Institute, 2014).

A study examining the incontinence- and non-incontinence-related pelvic floor symptoms evaluated by two widely used symptom tools, the UDI-6 and the ICIQ-UI, demonstrated that both symptom questionnaires were sound and correlated with each other and independently with the QoL scores, as measured by the ICIQ-7 and I-QOL (van de Vaart et al, 2010). This study also uncovered the interesting finding that the delay in time to consultation with a physician was associated with greater bother, emphasizing the importance of heightened awareness of PFDs in the female patient population.

In the meta-analysis by Martin and colleagues (2006b), two studies showed a high sensitivity (.82 to .92) of question 3 in the Urogenital Distress Inventory for SUI; the specificity was .51 to .69. In this study, history alone had a pooled sensitivity of .92 (95% confidence interval [CI]) and a specificity of .56 for the diagnosis of SUI and a sensitivity of .61 and specificity of .87 for the diagnosis of detrusor overactivity. It should be borne in mind, however, that for higher risk interventions, such as surgery, the most accurate testing available remains multichannel UDS studies.

Pad Tests

Pad tests are generally used for academic purposes. The ICS recommends both a 3-day bladder diary and pad weight test as proper measures for symptom quantification in incontinence research (Lose et al, 2001). However, although pad tests can be helpful in quantifying leakage, they are tedious and cumbersome for the

patients. Moreover, they do not provide information that is necessary for daily routine clinical practice. The Fourth ICI Committee on initial assessment did not recommend pad tests as part of the initial evaluation in the incontinent patient (Staskin, 2009). From an academic standpoint, however, many investigators advocate for pad tests in clinical trials, because pad tests can provide objective, precise information for assessment of actual volume of urine lost over an established period.

According to the Third ICI, greater than 1.3 g of urine loss is considered a positive 24-hour pad test (Tubaro, 2005), whereas others consider up to 8 g of urine loss in 24 hours to be normal (Lose et al, 1989). This variability poses a potential limitation on the utility of the pad test; many investigators use the pad test for research purposes. Vaginal secretions should be taken into consideration, although the volume attributable to normal vaginal secretions may be as low as 0.3 g in 24 hours (Karantanis et al, 2003). O'Sullivan and colleagues (2004) evaluated 110 women with incontinence with two 1-hour pad tests and 7 consecutive days of 24-hour pad tests. The severity of the leakage was analyzed in relation to UDS parameters, age, parity, and pelvic floor muscle strength, showing increased severity with increasing age and parity and in those women who demonstrated detrusor overactivity. The authors proposed that 24-hour loss of 1.3 to 20 g, 21 to 74 g, and greater than 75 g to signify "mild," "moderate," and "severe" incontinence, respectively. Another study of 144 randomly selected Danish women who underwent 24-hour pad testing revealed a similar loss of urine in the self-reported continent and incontinent groups or 3.1 and 3.3 g, respectively (Ryhammer et al, 1998).

It is generally agreed that the 24-hour pad test is a clinically more useful tool than the 1-hour pad test (Lose et al, 1989; Matharu et al, 2004); in fact, the test-retest reliability and the predictive value of the 1-hour test in the diagnosis of female incontinence have been shown to be poor (Lose et al, 1986, 1988; Simons et al, 2001; Constantini et al, 2008). Others have advocated the opposite extreme, suggesting that a 20-minute pad test with a standardized bladder volume of 250 mL instilled into the bladder via catheterization had superior sensitivity compared to the 1-hour test conducted via the ICS standardized method of pad testing (Wu et al, 2006). The ICS method, described in 1988, requires the patient to drink 500 mL of sodium-free liquid in 15 minutes followed by a 30-minute resting period before proceeding with the recommended physical activity (Abrams et al, 1988). One potential concern about this method is the lack of standardization of bladder volume.

Parenthetically, pad use per day obtained in the patient history is a measure frequently used to quantify urine loss, but one study

demonstrated that this is an unreliable measure of incontinence (Dylewski et al, 2007). A retrospective chart review of 145 males and 116 females who underwent artificial urinary sphincter placement and sling surgery, respectively, and who had completed a self-reported pad-use query was performed and the patients were asked to bring three pads into their clinic visit: one dry “reference” pad and the incontinence pads used for the 24-hour periods preceding and including the day of their visit. The pads were quantified and weighed to determine the grams of urine per pad. All patients also underwent a 24-hour pad weight test. Only a very weak correlation was found between reported pad usage and the 24-hour pad weight, with pad usage measuring only 38% of the variability of incontinence volume. Additionally, whereas the pads per day decreased, the grams of urine per pad increased with increasing age.

Dye Testing

Dye testing can be helpful to verify that the leakage represents urine versus another fluid such as vaginal discharge or peritoneal fluid and to substantiate the diagnosis of urinary tract fistulae. **Oral phenazopyridine** 100 to 200 mg three times per day colors the urine orange, and this simple test can confirm that the leaking fluid is indeed urine. Diagnosis of a vesicovaginal or urethrovaginal fistula can be supported by blue or orange staining of an intravaginal tampon after **intravesical instillation of methylene blue or pyridium dissolved in sterile water or saline**. In the case of a suspected *ureterovaginal* fistula, **intravesical methylene blue with concurrent oral pyridium** can elucidate the fistula location based on the staining pattern on the vaginal tampon. Orange staining suggests a ureteral communication, whereas blue staining connotes a bladder communication (Raghavaiah, 1974). The clinician must keep in mind that simultaneous vesicovaginal and ureterovaginal fistulae can occur.

KEY POINTS: SUPPLEMENTAL EVALUATION

- It has been demonstrated that patient subjective history alone often does not reflect an accurate or complete picture of their symptomatology complex.
- Several instruments designed to facilitate symptom quantification have been developed and include tools such as voiding diaries, symptom and QoL questionnaires, and pad tests.
- Voiding diaries can be both diagnostic and therapeutic, because they can provide patients with insights into behaviors that may be contributing to their voiding symptoms.
- Pad tests may be helpful, particularly in the academic setting, to quantify incontinence symptoms. Loss of up to 8 g of urine in 24 hours may be considered normal, although the ICI considers loss of greater than 1.3 g to be a positive 24-hour test.
- Validated questionnaires are available to assess symptoms and QoL in patients with PFDs.

Urinalysis

It is generally agreed that UA plays a fundamental role in the evaluation of the incontinent patient or the patient with LUTS (Abrams et al, 2009a). The UA provides information such as the presence of hematuria, pyuria, glucosuria, or proteinuria that can be indicative of conditions that can cause *secondary* incontinence. As indicated by the screening dipstick analysis, a microanalysis and/or culture should be performed that may provide guidance regarding further testing or therapy for conditions related to or independent of urinary incontinence.

Postvoid Residual

The volume of urine left in the bladder after routine voiding is termed the *postvoid residual (PVR)*, and some authors have sug-

gested that PVR should be evaluated in all incontinent patients (Tubaro, 2005; Gormley, 2007). This simple test, which can be performed via in-and-out catheterization or using noninvasive transabdominal ultrasonography, evaluates the bladder's emptying ability and can be helpful in the diagnosis of overflow incontinence. The 2012 AUA/SUFU SUI guidelines state that clinicians considering invasive therapy in patients with SUI should assess PVR to evaluate bladder emptying, because patients with elevated PVRs preoperatively are at increased risk for developing voiding difficulties postoperatively (Winters et al, 2012). It is important to establish baseline bladder emptying, particularly in patients with stress incontinence who may be considered for an anti-incontinence procedure or patients with urinary urgency who may be candidates for therapies aimed at decreasing bladder contractility.

A number of studies have demonstrated that ultrasonography is comparable to catheterization in evaluating the PVR, although there are no officially established volumes that define normal or impaired emptying. The Agency for Healthcare Research and Quality (AHRQ) suggests that PVR less than 50 mL represents adequate emptying and PVR greater than 200 mL represents inadequate emptying (U.S. Department of Health and Human Services, 1992). There is no consensus recommendation regarding the significance of PVR between 50 and 200 mL. In one study, Gehrich and associates (2007) enrolled 96 healthy women who presented for routine well-woman checkup. Exclusion criteria included urinary incontinence more than twice per week, urinary retention, neurologic disease, or symptomatic POP. The mean and median PVRs were 19 mL (0 to 145 mL) and 24 ± 29 mL. Fifteen percent had a PVR greater than 50 mL, and 95% had PVR less than 100 mL. Another study compared PVR measurements obtained by three-dimensional (3D) bladder scan versus catheterization in 170 women who were undergoing evaluation for SUI but who had never undergone previous pelvic surgery (Tseng et al, 2008); 35.5% had PVR greater than 50 mL, and 15.9% had PVR greater than 100 mL. Ultrasonography offered a sensitivity of 64.7% and a specificity of 94.3% in detecting PVR above 100 mL. Although several studies support the accuracy of the bladder scan (Al-Shaikh et al, 2009), some suggest that certain sonographic devices may provide more accurate information than others (Chani et al, 2008).

Cystoscopy

Endoscopic examination of the bladder is important as a means to evaluate for intravesical or intraurethral pathology that may be contributing to the patient's symptomatology. Bladder tumors, bladder stones, cystitis, and intravesical or intraurethral foreign bodies such as mesh or suture can contribute to irritative voiding symptoms, recurrent urinary tract infections (UTIs), and incontinence. Patients with a history of previous pelvic floor reconstructive surgery should be evaluated for eroded materials into the LUT. The ureteric orifices should be identified and evaluated for morphology, position, number, and efflux. The bladder mucosa is examined for trabeculation (which can be suggestive of bladder outlet obstruction [BOO] and/or detrusor overactivity) and estrogen status, and the urethra is assessed for foreign bodies, stricture, diverticulum or fistula, and position.

The role of preoperative cystourethroscopy has been addressed by few authors. Anger and associates (2007) analyzed Medicare claims data to assess the effects of preoperative cystoscopy and UDS studies on sling outcomes. The data of a random 5% sample of Medicare beneficiaries during an established 18-month period were used to assess the likelihood of undergoing postoperative studies in those who did and did not undergo the same studies preoperatively. Although patients who underwent preoperative cystoscopy were less likely to undergo postoperative cystoscopy (23.4% vs. 35.2%, $P < .0001$) or UDS (19.3% vs. 34.0%, $P < .0001$), there were no significant differences in complications or repeat incontinence procedures between the groups. However, Cundiff and Bent (1996) reported that cystoscopy changed the diagnosis and management in 6 of 84 women (7%) who underwent both cystoscopy and UDS for evaluation of LUT dysfunction. Findings included transitional

cell carcinoma, cystitis glandularis, intravesical suture, and a urethral diverticulum.

Although the use of routine cystoscopy is not advocated in the evaluation of the “index” SUI patient, it should be considered in patients who present with urinary urgency, hematuria, or other irritative symptoms, particularly if they have undergone a previous anti-incontinence procedure, pelvic radiation, or pelvic prolapse repair.

Urodynamics

Similar to cystourethroscopy, the routine use of UDS is the subject of much discussion; however, one should or may consider UDS in patients who are considering invasive, potentially morbid or irreversible surgery; have failed previous pelvic floor reconstruction; or have mixed incontinence, urinary urgency, or obstructive symptoms; and in patients who have elevated PVRs or neurologic disease. UDS is also useful to confirm or refute a diagnosis and can facilitate patient selection and counseling. The benefit of UDS in these situations is to establish baseline bladder capacity, compliance, sensation, stability, and sphincter function before further surgical or therapeutic manipulation. A comprehensive review of UDS is presented in Chapter 73.

LUT function can be simply categorized into storage and emptying. Each of these categories is affected by the bladder (detrusor) and the outlet. Two main questions should be considered in the evaluation of the incontinent patient. (1) Is the problem at hand a storage issue, an emptying issue, or a combination of the two? (2) Is the cause of the identified problem a detrusor issue, an outlet issue, or a combination of both?

“Eyeball UDS” is a simple, economically favorable alternative to full multichannel UDS that can be helpful in selected patients. The study can determine bladder sensation, compliance, stability, and capacity, as well as outlet competence and PVR (Blaivas, 1996). After voiding, the patient is placed in the lithotomy position, a Foley catheter is placed, and the PVR is measured. A 60-mL catheter-tip syringe with the barrel removed is placed into the end of the catheter. With the syringe held upright, the bladder is filled with sterile fluid through the syringe. The height of the meniscus above the bladder represents the intravesical pressure. The volumes at first sensation and first desire, normal desire, strong desire to void are recorded. During the filling phase, the meniscus in the syringe is observed for a rise and fall that may represent bladder overactivity or a consistent gradual rise that suggests compromised detrusor compliance. The absence of the abdominal pressure (Pabd) channel limits the ability to accurately determine any abdominal contribution to a change in the water volume in the syringe. The catheter is removed, and a cough stress test is performed by observing the urethra for incontinence during coughing and straining.

Multichannel UDS offers an extensive evaluation of LUT function. The degree of accuracy provided by multichannel UDS is important in a variety of circumstances, including when conservative treatment methods fail; when the diagnosis is unclear; when previous diagnostic procedures are inconclusive; in patients with clinical pictures complicated by radiation therapy, neurologic disease, or prior failed pelvic floor reconstruction or anti-incontinence surgery; or when patients describe symptoms that cannot be confirmed by the clinician. A complete UDS study evaluates the filling/storage phase by filling cystometrogram and the voiding/emptying phase by uroflowmetry.

Catheters are placed into the bladder and the rectum. The bladder catheter measures the actual pressure within the bladder, termed the vesical pressure (Pves). The rectal catheter measures the abdominal pressure (Pabd). The detrusor pressure (Pdet) is a calculated value ($P_{ves} - P_{abd}$) that represents the pressure created by the detrusor independent of the influences of intra-abdominal pressure. During the filling phase, the Pdet is expected to remain low and stable to allow for low-pressure bladder filling. Poorly compliant bladders will show a gradual steady rise in the Pdet as the bladder volume increases. Detrusor overactivity is manifest by

intermittent and unpredictable rises in the Pdet. During the voiding phase, the Pdet may rise as the urine flows. Many women void normally with virtually no rise in Pdet. High Pdet with low flow during voiding suggests BOO. Inability to produce a flow with no Pdet, particularly when accompanied by abdominal straining (represented by an undulant Pabd), may indicate an atonic or hypotonic detrusor.

When making the diagnosis of urodynamic SUI, urethral function should be assessed (Winters et al, 2012). Quantitative measurements such as the Valsalva leak point pressure or maximal urethral closure pressure can be used to guide treatment decisions in patients suspected of having SUI who do not demonstrate leakage with stress maneuvers; stress testing should be repeated with the urethral catheter removed. In patients with high-grade POP without symptoms of SUI, stress testing should be performed with the POP reduced to evaluate for occult SUI.

Electromyography (EMG) and fluoroscopic imaging (video-urodynamics [VURDS]) are helpful adjuncts to the UDS study in selected patients and are covered in detail in Chapter 73. EMG activity is reflective of the activity of the striated muscles of the urethral and anal sphincters and the perineal musculature and can be measured using either surface electrodes or needle electrodes. Although the latter provides more accurate readings, the discomfort caused to the patient and the expertise required for the technique render it far less popular than surface electrodes. The coordination of the EMG and detrusor activity is most helpful during the voiding phase, when failure to relax the pelvic floor can be indicative of pathologic processes. Similarly, recruitment of activity should be noted with BCR and increased abdominal pressure, such as occurs during coughing. VURDS can be useful in the demonstration of anatomy in the upright position and because the bladder and outlet are visualized in real time, VURDS can confirm incontinence in patients in whom the diagnosis is difficult and can provide an accurate measure of leak point pressure. It is also helpful to assess the bladder outlet in patients in whom dysfunctional voiding, primary bladder neck obstruction, or detrusor-sphincter dyssynergia are suspected. Patients also can be evaluated for vesicoureteral reflux (VUR) and bladder or urethral diverticula. Assessment of detrusor pressures in the face of reflux or a large bladder diverticulum can provide important information that would be missed without video imaging.

Recent attention has been placed on scientifically establishing the role and clinical value of UDS. The worth of a test is not solely in its diagnostic accuracy but is also in the improvement of the outcomes of subsequent interventions. UDS is frequently used in the evaluation of patients with PFDs and can be helpful in counseling. Suboptimal outcomes of anti-incontinence procedures are generally attributed to intrinsic sphincter deficiency, detrusor overactivity, or baseline dysfunctional voiding. The deliberation regarding the merit of these theories and the ability of UDS to accurately establish these conditions continues. In a study of 655 women with positive stress tests, 10% did not demonstrate urodynamic-SUI (UDS-SUI) (Nager et al, 2007). A meta-analysis based on a Medline search of the literature between 1975 and 1998 suggested that UDS has a positive predictive value (PPV) of only 56% and 79% for pure SUI and SUI with other abnormalities, respectively, and a positive cough test has PPVs for the same of 55% and 91%, respectively (Harvey and Versi, 2001). The Urinary Incontinence Treatment Network (UITN) reported that UDS did not predict postoperative voiding dysfunction or the risk for need of postoperative surgical intervention (Lemack et al, 2008). In another retrospective study in women who underwent retropubic midurethral sling placement for treatment of mixed incontinence, the median opening detrusor pressure was higher in women with postoperative detrusor overactivity than in those with normal postoperative UDS (Panayi et al, 2009).

Much of the literature to date has been limited by the retrospective design and small cohorts of the available studies. The UITN found that the success of anti-incontinence surgery in patients who demonstrated UDS-SUI was nearly twice that of those with non-UDS-SUI, although this trend did not reach statistical significance

(Nager et al, 2008). The same group showed that treatment outcomes at 1 year for women with uncomplicated demonstrable stress incontinence were not inferior in patients who did not undergo preoperative UDS compared to those who did (Nager et al, 2009, 2012). Although a study by Anger and associates (2007) did not definitively establish an effect of preoperative UDS specifically on sling outcomes, there was a clear demonstration of a two-fold (significant) increased likelihood of undergoing postoperative UDS studies in those patients who did not undergo the study preoperatively compared to those who did.

With the implementation of health care reform in 2014, cost-effectiveness is at the forefront of discussion. Based on decision-analytic (hypothetical) models, one group deemed UDS not cost-effective relative to the basic office evaluation (Weber and Walters, 2000; Weber et al, 2002). However, one must remain mindful that UDS provides information, not only about the overall diagnosis, but also regarding important subtle findings that may direct the clinician in treatment planning and counseling (Summitt et al, 1992; Patel and Chapple, 2008). Although it has been suggested that UDS may not be necessary or useful in patients with straightforward non-neurologic conditions who would be considered for initial conservative management (Colli et al, 2003; National Institute for Health and Clinical Excellence, 2006; Winters et al, 2012), others have shown that as many as 20% of patients with presumed pure SUI may have UDS findings that might alter their treatment or outcomes (Digesu et al, 2009).

Reproducibility of UDS studies and interpretation of the examination has been questioned by several studies (Van de Beek et al, 1997; Gupta et al, 2004; Zimmern et al, 2006; Gacci et al, 2007). Others have demonstrated that intraobserver interpretation (interpretation repeated by the same individual) is superior to interobserver interpretation (same study read by two different individuals) for both pressure-flow analyses (Digesu et al, 2003) and filling/voiding studies (Whiteside et al, 2006). Still others have demonstrated no difference in interobserver and intraobserver interpretation, but that live interpretation of a study provides different readings than post-hoc interpretation, suggesting that intangible experiential factors may play a role in the interpretation of UDS studies (Smith et al, 2009).

Approximately 40% of patients with POP describe SUI symptoms (Grody, 1998), and UDS-SUI is demonstrated in 70% to 75% of patients with prolapse (Roovers and Oelke, 2007). Occult SUI unmasked by reduction of prolapse is reported to be present in 36% to 80% (Richardson et al, 1983; Bergman et al, 1988; Chaikin et al, 2000), and 11% to 50% of clinically continent patients will develop de novo SUI after repair of high-grade prolapse (Bergman et al, 1988; Borstad and Rud, 1989; Gallentine and Cespedes, 2001). Women who demonstrated preoperative UDS-SUI before sacrocolpopexy were more likely to develop postoperative SUI irrespective of whether they received a concomitant Burch colposuspension (Visco et al, 2008). Conversely, after a retrospective review of the records of 76 patients who underwent POP repair, Roovers and colleagues (2007) reported that no UDS parameters predicted postoperative incontinence. In an effort to determine the need for prophylactic sling placement in patients undergoing surgery for high-grade POP, Ballert and coworkers (2009) followed a UDS protocol designed to address the urethra in a standardized fashion. They concluded that in patients who did not subjectively describe or urodynamically demonstrate SUI preoperatively, the risk of intervention because of BOO after sling placement was equivalent to the risk of intervention for SUI in patients who did not receive a sling. The Colpopexy and Urinary Reduction Efforts (CARE) trial was designed to evaluate whether a Burch colposuspension performed at the time of sacrocolpopexy for prolapse in stress-continent women reduced postoperative SUI. The large prospective randomized study was stopped after the first interim analysis at 3 months when 23.8% of the women in the Burch group and 44.1% of the control group met criteria for SUI ($P < .001$) (Brubaker et al, 2006). The cohort was continued at 2 (Brubaker et al, 2008) and 7 (Nygaard et al, 2013) years postoperatively, demonstrating a continued advantage of prophylactic Burch for SUI

at both time points, though the failure rates of sacrocolpopexy increased in both groups by the 7-year follow-up.

In select patients, particularly those with OAB symptoms and/or known neurogenic bladder, UDS can be helpful in determining the risk for progression to upper tract deterioration. Detrusor overactivity, poor compliance, detrusor-external sphincter dyssynergia, high detrusor storage pressures, VUR, and BOO represent potential risk factors for the development of upper tract disease, particularly in patients with sustained Pdet greater than 40 cm H₂O (McGuire et al, 1981; Blaivas and Barbalias, 1984; Choniem et al, 1989, 1990).

Although multichannel UDS remains the most accurate tool with which to evaluate LUT function, it is clear that multi-institutional randomized prospective studies are of dire importance in addressing many of the unanswered questions regarding the role and contribution of UDS to patient care, counseling, and optimization of treatment modalities. Further evaluation of the accuracy of the study and most importantly, the impact of UDS on patients, treatments, and treatment outcomes must be pursued. The UDS guidelines provide parameters around the use of UDS based on an exhaustive review of the current literature.

KEY POINTS: URODYNAMICS

- UDS is the most accurate tool available for the assessment of LUT function and provides information regarding urine storage and emptying as they are affected by the bladder and the bladder outlet.
- Although the use of routine UDS for straightforward incontinence is a topic of discussion, UDS should be strongly considered before intervention in patients who have a complex clinical picture because of failed previous treatment or surgery, mixed incontinence, obstructive symptoms, significantly elevated PVR, neurologic disease, or other medical conditions that may contribute to the LUT function, such as diabetes mellitus, pelvic prolapse, or history of radiation therapy.
- "Eyeball UDS" may provide an approximate picture of the bladder capacity, sensation, stability, compliance, and outlet resistance when formal UDS is not available.
- Multichannel UDS offers extensive evaluation of LUT function. It involves direct measurement of bladder and intra-abdominal pressure (Pves and Pabd, respectively) and a calculated assessment of detrusor pressure that is independent of abdominal pressure (Pdet). $Pves - Pabd = Pdet$.
- Fluoroscopic imaging provides useful adjunctive information, such as the position and status of the bladder base and bladder neck, the presence of VUR, and direct visualization of urinary leakage under real-time circumstances. Video imaging should be considered when the diagnosis cannot be made with certainty without simultaneous understanding of the anatomy in conjunction with the functional findings.

Radiographic Imaging

Voiding Cystourethrogram. Standard imaging studies are not necessary in the initial evaluation of women with uncomplicated incontinence (Artibani et al, 2002; Artibani and Cerruto, 2005). However, upper and lower urinary tract imaging in patients in whom renal damage or pelvic pathologic conditions are suspected should be performed. Voiding cystourethrogram (VCUG) is optional in patients with recurrent UTIs, but can be helpful in the diagnosis of a urethral diverticulum or VUR. VCUG can provide valuable information regarding the contour of the bladder, the presence of VUR, the position of the bladder base with and without straining with the patient in an upright posture, and the position

and configuration of the bladder neck during voiding. Fluoroscopic imaging also can provide visualization of subtle leakage with coughing or Valsalva maneuver that may be difficult to detect with direct examination.

Ultrasonography. Upper tract imaging is recommended in patients with chronic urinary retention, suspected extraurethral incontinence, untreated severe POP, and neurogenic detrusor dysfunction considered to be at high risk for renal damage. Patients with high-grade POP can develop upper tract obstruction and hydronephrosis related to ureteral kinking resulting from the prolapse. Ultrasonography provides a noninvasive sensitive and specific method of assessing the upper tracts for hydronephrosis. Ultrasonic imaging of the bladder neck for urinary leakage and descent during stress also has been used to diagnose SUI with documented pooled sensitivity and specificity rates in the range of .84 to .89 and .82 to .89, respectively (Martin et al, 2006b).

Magnetic Resonance Imaging. Magnetic resonance imaging (MRI) has been proposed as an ideal method by which to evaluate the anatomy of the bladder neck and urethra with good correlation with functional studies (Macura, 2006; Macura et al, 2006; Macura and Genadry, 2008). MRI has also been advocated for evaluation of pelvic floor relaxation and POP (Boyadzhyan et al, 2008), particularly in patients undergoing evaluation for complex multicompartmental pelvic floor reconstruction (Macura, 2006; Boyadzhyan et al, 2008) and has been shown to identify changes related to the uterosacral ligaments before and after surgical repair of prolapse (Martin et al, 2006a). MRI also may be helpful in identifying patients in whom a urethral diverticulum may be present. Although urethral diverticula can cause symptoms of urinary leakage, pelvic pain, obstructive voiding symptoms, recurrent UTIs, dyspareunia, and a multitude of nonspecific symptoms, up to 20% of diverticula may be completely asymptomatic (Rovner, 2007). In patients with reports of SUI who are found to have a urethral diverticulum, a simultaneous anti-incontinence surgery may be considered, in which case proper radiographic imaging, such as can be obtained with MRI, can provide anatomic information germane to optimal surgical planning.

High-resolution MRI allows detailed visualization of the urethra, the external sphincter, and the supporting structures. MRI evaluation focusing specifically on the muscle volume of the sphincter, defects in the sphincteric musculature, funneling of the bladder neck, symmetry of the pubococcygeus muscle or urethral supporting ligaments, increase in the size of the retropubic space or urethrovesical angle, and abnormal vaginal shape may be helpful in the diagnosis of SUI resulting from intrinsic sphincter deficiency or urethral hypermobility (Macura, 2006). To facilitate assessment of POP using MRI, the HMO (H-line, M-line, organ prolapse) system was developed (Pannu et al, 2000).

Evaluation is performed using rapid half-Fourier T2-weighted images in the midsagittal plane during maximal patient straining. There are three fixed points in the HMO system: A, the inferior margin of the pubic symphysis; B, the posterior levator plate; and C, the junction between the first and second coccygeal segments. Two fixed reference points include point B and the pubococcygeal line (PCL), drawn between points A and C. Line H, drawn between A and B, represents the anterior-posterior hiatal dimension. Line M, which is the shortest distance between point B and the PCL, represents the degree of pelvic descent. The O component comprises the shortest distance between the H line and the most caudal aspect of the evaluated organ during Valsalva maneuver. Prolapse is graded based on the organ location relative to the H-line in centimeters.

Dynamic MRI can provide integral information in the preoperative assessment of POP, particularly in patients in whom the pelvic examination is difficult and inconclusive. The sensitivity, specificity, and PPV of MRI for cystoceles has been reported to be 70% to 100%, 83% to 100%, and 97% to 100%, respectively; 42% to 100%, 54% to 81%, and 33% to 60%, respectively, for vaginal vault prolapse; 87% to 100%, 80% to 83%, and 75% to 91%, respectively, for enteroceles; 83%, 100%, and 100%, respectively, for uterine prolapse, and 87%, 72%, and 66%, respectively, for

rectoceles (Gousse et al, 2000; Deval et al, 2003). Other authors have found that dynamic MRI does not correlate well with clinical findings in patients with middle compartment (i.e., apical) prolapse, and much of the literature suggests that the study should be used only as an adjunct to clarify anatomy in complex cases (Cortes et al, 2004) or under investigational circumstances (Tubaro, 2005). Similarly, many authors agree that the posterior compartment is not as easily visualized on dynamic MRI. A study using intrarectal air during MRI did not demonstrate any value of dynamic MRI for evaluation for rectoceles over videoproctography, the latter of which was more sensitive in identifying rectoceles (Matsuoka et al, 2001). For optimal visualization of rectoceles, intrarectal gel is used to provide hyperintensity on T2-weighted images (Macura, 2006; Boyadzhyan et al, 2008; Law and Fielding, 2008).

MANAGEMENT

Incontinence Treatment Overview

The approach to treatment of incontinence is contingent on a clear understanding of the cause and pathophysiology underlying the patient's symptoms. The clinician must first determine whether the cause of the symptomatology complex is a bladder or an outlet problem, or, not uncommonly, a combination of both. Therapeutic options should be considered with the goal of providing an individualized patient-directed treatment plan based on the patient goals and risk-benefit and cost-benefit ratios. **Proper representative counseling is paramount to properly align patient expectations and goals and what is possible to achieve.** Adjunctive studies such as UDS may be performed (and in select situations *should* be performed) to provide complete information on which clinical decisions can be made as outlined in the SUI, OAB, and UDS guidelines (Dmochowski et al, 2010; Gormley et al, 2012; Winters et al, 2012).

Management of incontinence can be categorized into nonsurgical and surgical options. Underlying causes such as UTI, BOO, bladder stones, foreign body, or bladder tumor should be identified and addressed first. Box 70-3 in Chapter 70 provides an overview of the treatment options available for the management of incontinence; a detailed review of the various therapeutic options is presented in Chapters 79 through 87.

Treatment of incontinence must be tailored to the patient's needs, goals, and expectations and requires proper counseling on the part of the clinician. Some patients may be satisfied with protective garments and/or urine collection devices, such as indwelling or condom catheters, or barriers, such as urethral plugs or external occlusion devices. Intervention for patients with urgency incontinence may range from behavioral and dietary modification to biofeedback or pharmacotherapy. **Per the OAB guidelines, behavioral therapy (e.g., fluid management, dietary modification, and bladder training) is considered to be the first line of therapy (Gormley et al, 2012).** Medications can be added subsequently, but are technically considered to be second-line therapy. Sacral neuromodulation, onabotulinumtoxinA detrusor injection, and enteric augmentation of the bladder may be considered in patients with refractory symptoms.

Similarly, patients with SUI may benefit variably from conservative measures using pelvic floor muscle exercises, biofeedback, electrical stimulation, and pharmacotherapy. Urethral bulking injection therapy can provide an intermediate option between nonsurgical and surgical therapies, but surgery remains the mainstay of treatment for SUI. Although needle suspensions remain only as a point of historic discussion, retropubic suspensions have persisted as a reasonable treatment option for SUI. However, slings, using a variety of materials, insertion approaches, and anchoring techniques, have effectively become the standard options for women with SUI. In 2011 the U.S. Food and Drug Administration (FDA) released a safety communication regarding mesh placed transvaginally specifically for the repair of pelvic prolapse (U.S. Food and Drug Administration, 2011a, 2011b, 2013). Unfortunately, subsequent media communication regarding mesh litigation created

patient confusion and concern, prompting a joint response from SUFU and the American Urogynecologic Society (AUGS) in 2014 (AUGS and SUFU, 2014).

Injection therapy has not proved a particularly viable option for the treatment of male SUI (which occurs most commonly after prostatectomy for treatment of adenocarcinoma of the prostate), and follow-up of the outcomes with male slings is still early. In a review of the literature, Cerruto and colleagues (2013) reported on a pooled cure rate from 160 studies, none of which were controlled; 77.4% were “cured” at a median follow-up of 15 months. The artificial urinary sphincter remains the prevailing treatment option for post-prostatectomy incontinence. The artificial urinary sphincter has been used rarely for treatment of SUI in women. In the fortunately rare cases of complete urethral devastation, bladder neck closure or urinary diversion can be considered.

Pelvic Prolapse Treatment Overview

New techniques have been explored to improve on the traditional pelvic floor reconstructive approaches that depend on the inherently compromised tissues of the patient with POP. The use of synthetic and biologic graft materials to improve the integrity and durability of POP repairs has become popularized over the past decade, though graft use remains a point of robust discussion and debate. Novel anatomic approaches and kits have been developed and have resulted in a dramatic increase in the number of clinicians participating in pelvic floor reconstruction, but controversy surrounding the safety of synthetic mesh grafts has quickly changed the landscape again.

The goal of POP repair is to restore the normal anatomy and function of the vagina and the lower urinary and gastrointestinal tracts. The decision regarding whether to proceed with a transvaginal or a transabdominal approach depends on which of the three compartments is affected, the degree of prolapse, and patient and surgeon preference. Apical prolapse involving the uterus typically results in a hysterectomy, although uterine sparing techniques can be performed. Post-hysterectomy apical prolapse can be addressed transvaginally with a uterosacral ligament suspension or a sacrospinous ligament fixation. Several contemporary devices that aim to facilitate high prolapse reduction have been introduced, but follow-up is early. Nevertheless, the sacrocolpopexy, a transabdominal approach that can be performed either open or minimally invasively using laparoscopy or robotic assistance, remains the gold standard repair for apical prolapse. A Y-shaped mesh typically composed of polypropylene is attached to the apex of the vagina and bridged to the sacrum to return the vagina to its normal axis.

New techniques of pelvic floor reconstruction continue to emerge parallel with increasing efforts to understand pelvic floor anatomy and function. A comprehensive overview of current surgical management of pelvic prolapse is presented in Chapter 83.

CONCLUSION

The ultimate goal of pelvic floor reconstruction is to restore the normal anatomy and function of the vagina, bladder, and surrounding structures. Proper evaluation of the pelvic floor anatomy and function should theoretically maximize the probability of favorable outcomes. Additionally, with a growing emphasis on QoL enrichment and a simultaneously increasing cost of health care, along with the implementation of the Patient Protection and Affordable

Care Act, economically sound and durable treatments are the aspiration. Accordingly, efforts to develop methods by which to evaluate and quantify symptoms and assess outcomes continue. New techniques designed to provide safe and successful options to achieve maximal symptom relief and QoL improvement continue to evolve, and tissue engineering is an exciting new frontier. As our comprehension of the pelvic floor advances, further approaches to treat PFDs will undoubtedly arise.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Types of Urinary Incontinence

Evaluation

Urinary incontinence (UI) is defined by the International Continence Society as the **involuntary loss of urine** (Abrams et al, 2002) or, in other words, any leakage of urine. It is part of storage lower urinary tract symptoms (LUTS) and can result from a variety of causes. It is therefore important to understand the etiology of the UI and to evaluate and assess appropriately the men who are suffering with UI to manage them accordingly, as this condition can be a social and hygienic problem that affects quality of life (QoL).

UI should be **described by specifying relevant factors** such as type, frequency, severity, precipitating factors, social impact, effect on hygiene and QoL, the measures used to contain the leakage, and whether or not the individual seeks or desires help because of UI. The condition must be distinguished from sweating or urethral discharge.

UI in men is prevalent but less so than in women. Prevalence in men varies from 1% to 39% depending on the definition used, variation in populations, response options, and participation rates (Tikkinen et al, 2013). In a population survey in Canada, 5.4% of male respondents presented with UI (26% had stress urinary incontinence [SUI], 15% had mixed urinary incontinence [MUI], and 58% had urgency urinary incontinence [UUI]) (Bettez et al, 2012). In the EpiLUTS study (Coyne et al, 2012), the prevalence of UI in men was 46%. However, this included various forms of urinary symptoms, such as postmicturition incontinence, nocturnal enuresis, and urinary leakage with no definable cause. A total of 5.6% of men reported UUI only, 0.8% SUI only, 1.4% MUI, 6.3% UUI and another form of UI, and 1.2% SUI and another form of UI.

TYPES OF URINARY INCONTINENCE

There are different types of UI (Abrams et al, 2002) and it is important to know the differences among them, as these differences would affect management.

Stress Urinary Incontinence

SUI is the complaint of involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing (Abrams et al, 2002). In other words, SUI is effort-related or activity-related incontinence, and this appellation might be preferred in some languages to avoid confusion with psychological stress. SUI occurs when the intra-abdominal pressure exceeds the intraurethral pressure. SUI is more common in women than in men and usually

Treatment

Conclusion

occurs in men only after a prostatectomy in which the external urethral sphincter is damaged.

Urgency Urinary Incontinence

UUI is the complaint of involuntary loss of urine associated with urgency. It was formerly known as urge urinary incontinence (Abrams et al, 2002). However, because it must be preceded by urgency, the terminology has changed to urgency urinary incontinence (Abrams et al, 2009; Tooze-Hobson et al, 2012). It is part of the **overactive bladder (OAB) syndrome**, and 90% of men who experience UUI will have detrusor overactivity (DO) on urodynamics (Hashim and Abrams, 2006). Patients who suffer with UUI have *wet OAB*.

Mixed Urinary Incontinence

MUI is the complaint of involuntary loss of urine associated with urgency and also associated with effort, physical exertion, sneezing, or coughing. Thus those with MUI experience both UUI and SUI (Abrams et al, 2002). This condition is uncommon in men although it may occur after prostatectomy.

Nocturnal Enuresis

Nocturnal enuresis is the complaint of **involuntary urinary loss of urine that occurs during sleep** (van Kerrebroeck et al, 2002). In other words, it is wetting the bed at night while asleep and not being aware of it. Nocturnal enuresis is differentiated from nocturia, which is intentionally getting out of bed to pass urine at night and is preceded and followed by sleep.

Nocturnal enuresis has an estimated prevalence of nearly 10% in children aged 7 years. However, in 2% to 3% of children it may persist into adulthood (Vande Walle et al, 2012). Nocturnal enuresis may also manifest later in life and it is an important symptom, especially in men, as it may indicate that these men are in high-pressure chronic urinary retention, which is usually associated with upper tract dilation and the risk of renal failure.

Continuous Urinary Incontinence

Continuous urinary incontinence describes the complaint of **continuous involuntary loss of urine** (Tooze-Hobson et al, 2012). This is a rare symptom and only exists when there is a fistula, for example a prostate-rectal fistula. Sometimes men describe severe incontinence as continuous, when the underlying etiology may be related to SUI, UUI, or MUI.

Postmicturition Leakage or Dribble

This condition evokes complaints of involuntary leakage of urine following the completion of micturition and occurring after the man has dressed himself, usually after he has left the toilet (Abrams et al, 2002).

Insensible Urinary Incontinence

Insensible urinary incontinence is a complaint of UI when the patient is unaware of how it occurs but becomes aware that he is wet (Tooze-Hobson et al, 2012).

Other Types of Urinary Incontinence

These types may be situational; for example, the report of incontinence during sexual intercourse in women is termed coital incontinence. Giggle incontinence occurs when girls are giggling. Both of these types are rare in male patients.

KEY POINTS: TYPES OF URINARY INCONTINENCE IN MEN

- SUI
- UUI
- MUI
- Nocturnal enuresis
- Postmicturition dribble
- Continuous UI
- Insensible UI

EVALUATION

History

Men presenting with symptoms of UI must be evaluated with a **thorough history and directed physical examination**. It is important to enquire about:

- When do they leak? For example, when they cough, when they have urgency, at night while asleep, or other times.
- How often do they leak? For example, every night, daily, or another frequency.
- Are there any precipitating factors that make leakage worse? For example, cold weather, putting the key in the door (latch-key incontinence), or other factors.
- Was there any previous surgery to the prostate or bladder or was there major abdominal surgery that could have led to damage to the sacral plexus?
- How much do they leak? For example, wet the underwear, flood the outer clothing or floor, or other amounts.
- Does the patient wear pads? If so, what type of pads, how many pads, what size of pads, or what other containment products are used, such as condom catheter or perhaps a change of underwear in the event of a leak?
- Has the patient tried any medications, and what medications does he take?
- Are there any neurologic problems and/or back pain that might suggest a neurologic cause for UI?
- How is the patient's sexual, erectile, and bowel function?

A general medical, surgical, and social history must be obtained, including drug allergies, smoking habits, and quantifying any alcohol or caffeine intake.

Physical Examination

An examination, with the patient in a lying position, should include:

- The abdomen to feel for any masses and especially for a distended bladder and hernias.

- The external genitalia to examine the foreskin and external urethral meatus, as some men may be suffering with *overflow incontinence* resulting from a stenosis of the external urethral meatus or a severe phimosis.
- The prostate via a digital rectal examination to feel the size and consistency of the prostate, as well as asking the patient to perform a pelvic squeeze to assess the strength of the pelvic floor.
- The anal canal and lower rectum to feel for anal tone and sensation and to assess rectal emptying.
- Lower-limb neurologic examination to check reflexes, muscle strength, and sensation.
- Cough test: After the previous examinations are completed, ask the patient to cough to see if there is any leakage, and then ask the patient to stand and to cough again to check for SUI.

First-Line Investigations

After the clinical examination is completed, bedside investigations must be performed.

Measurement of Height and Weight to Calculate Body Mass Index

The **body mass index (BMI)** is a good measure of obesity, and, in men who suffer with SUI, providing advice about weight loss may be helpful. However, there is little evidence that weight loss in men is useful; the evidence is extrapolated from women suffering with SUI. Also, related to men with SUI who have an artificial urinary sphincter (AUS), the less pressure there is intra-abdominally, and therefore the less pressure transmitted to the bladder, the less likely that these men would leak through the inflated artificial sphincter. This is because the AUS is a mechanical device, usually inserted with a pressure-regulating balloon of 61 to 70 cm H₂O, and if the intra-abdominal pressure exceeds that, then the patient will leak.

Urinalysis

Urinalysis is usually performed using a dipstick with multiple parameters including leukocytes and nitrites (to check for infection), glucose (to check for diabetes), blood (to check for hematuria), specific gravity (to ensure adequate fluid intake), pH (to see if the urine is basic or acidic), and ketones.

If there is any abnormality on the dipstick urinalysis, then the specimen is sent for microscopy, culture, and sensitivity. Appropriate investigations are also then initiated such as a flexible cystoscopy and ultrasound scan of the renal tract if there is hematuria.

Bladder Diary

The **bladder diary** (Fig. 72-1) is a vital investigational tool, as it provides objective information on the number of episodes the patient is leaking and the number of pads being used, how many times the patient is passing urine during the day and night, the average and maximum voided volumes and hence bladder capacity, the type and amount of fluid being drunk, assessment for nocturnal polyuria, and whether or not there is any urgency.

Several different bladder diaries are available. However, none of these diaries has been fully validated except for the International Consultation on Incontinence Questionnaire Bladder Diary (ICIQ-BD) (Bright et al, 2012).

The number of days a bladder diary must be completed has also been the subject of several publications, and the most recent recommendation is that a 3-day bladder diary would offer the same information as a 7-day one without being too exhaustive for patients (Dmochowski et al, 2005). It is important, however, to tell patients to try to complete the diary so that they include a combination of weekdays and weekends, and the entries should be representative

ICIQ-BLADDER DIARY

Please complete this 3-day bladder diary. Enter the following in each column against the time. You can change the specified times if you need to. In the time column, please write BED when you went to bed and WOKE when you woke up.

Drinks Write the amount you had to drink and the type of drink.

Urine output Enter the amount of urine you passed in milliliters (mL) in the urine output column, day and night. Any measuring jug will do. If you passed urine but couldn't measure it, put a tick in this column. If you leaked urine at any time, write LEAK here.

Bladder sensation Write a description of how your bladder felt when you went to the toilet using these codes:

0 - If you had no sensation of needing to pass urine, but passed urine for "social reasons"; for example, just before going out, or unsure where the next toilet is.

1 - If you had a normal desire to pass urine and no urgency.

"Urgency" is different from normal bladder feelings and is the sudden compelling desire to pass urine that is difficult to defer, or a sudden feeling that you need to pass urine, and, if you don't, you will have an accident.

2 - If you had urgency but it had passed away before you went to the toilet.

3 - If you had urgency but managed to get to the toilet, still with urgency, but did not leak urine.

4 - If you had urgency and could not get to the toilet in time, so you leaked urine.

Pads If you change a pad, put a tick in the pads column.

Here is an example of how to complete the diary:

Time	Drinks		Urine output (mL)	Bladder sensation	Pads
	Amount	Type			
6 am WOKE			350 mL	2	
7 am	300 mL	ice			
8 am			✓	2	
9 am					
10 am	cup	water	leak	3	✓

NAME _____

DAY 1 DATE: / /					
Time	Drinks		Urine output (mL)	Bladder sensation	Pads
	Amount	Type			
6 am					
7 am					
8 am					
9 am					
10 am					
11 am					
Midday					
1 pm					
2 pm					
3 pm					
4 pm					
5 pm					
6 pm					
7 pm					
8 pm					
9 pm					
10 pm					
11 pm					
Midnight					
1 am					
2 am					
3 am					
4 am					
5 am					

DAY 2 DATE: / /					
Time	Drinks		Urine output (mL)	Bladder sensation	Pads
	Amount	Type			
6 am					
7 am					
8 am					
9 am					
10 am					
11 am					
Midday					
1 pm					
2 pm					
3 pm					
4 pm					
5 pm					
6 pm					
7 pm					
8 pm					
9 pm					
10 pm					
11 pm					
Midnight					
1 am					
2 am					
3 am					
4 am					
5 am					

DAY 3 DATE: / /					
Time	Drinks		Urine output (mL)	Bladder sensation	Pads
	Amount	Type			
6 am					
7 am					
8 am					
9 am					
10 am					
11 am					
Midday					
1 pm					
2 pm					
3 pm					
4 pm					
5 pm					
6 pm					
7 pm					
8 pm					
9 pm					
10 pm					
11 pm					
Midnight					
1 am					
2 am					
3 am					
4 am					
5 am					

Bladder sensation codes

0 - No sensation of needing to pass urine, but passed urine for "social reasons"

1 - Normal desire to pass urine and no urgency

2 - Urgency but it had passed away before you went to the toilet

3 - Urgency but managed to get to the toilet, still with urgency, but did not leak urine

4 - Urgency and could not get to the toilet in time, so you leaked urine

Figure 72-1. International Consultation on Incontinence Questionnaire Bladder Diary (ICIQ-BD).

of patients' day-to-day lifestyles. The ICIQ-BD validation has shown that 3 days is the appropriate length to include the day-to-day changes in frequency and so forth.

Quality-of-Life Questionnaires and Patient-Reported Outcome Measures

Patients are unlikely to suffer significant morbidity from most types of UI, but UI does cause significant impact on QoL. It is therefore prudent to assess the impact of UI on a patient's QoL with a validated questionnaire.

The International Prostate Symptom Score (IPSS or AUA-SI) is the most commonly used questionnaire for men. However, this questionnaire is useless for men with UI, simply because the IPSS does not measure incontinence.

The ICIQ-UI short form (ICIQ-UI-SF; Fig. 72-2) is a simple, short questionnaire that helps differentiate between SUI and UUI (Avery et al, 2004). The alternative is the longer form ICIQ-male LUTS questionnaire (ICIQ-MLUTS; Fig. 72-3 on the Expert Consult website), which includes the advantages of asking about the storage and voiding symptoms covered by the IPPS and asking about the bother of each (Abrams et al, 2006).

Both the bladder diary and QoL questionnaire not only help in the assessment of patients but also help in looking at treatment effects if repeated after the patient has been treated.

Pad Testing

There is much controversy about the use of **pad testing** and the duration of time for which it should be performed. Should it be done for 1 hour or 24 hours? How many days should it be

performed? Do pretreatment pad loss volumes predict outcomes? All these are questions that have not yet been answered by high-quality research. Also, pad testing does not help to differentiate between the different types of incontinence, especially UUI and SUI.

Most guidelines have not recommended the use of pad testing. However, pad testing can be useful in attempting to quantify the amount of leakage a patient experiences and perhaps in planning treatment accordingly. There is also disagreement in the literature as to what the definition of mild, moderate, and severe incontinence is, and whether or not the number of pads should be used to classify UI severity, or whether urine loss measured by pad weights should be used. Some would suggest that the use of one pad is considered mild, two to four pads is moderate, and more than four pads is severe, but patients sometimes change pads because of hygienic reasons rather than for necessity (Tsui et al, 2013). Increased pad weight is therefore probably a better measure of the severity of UI, and usually less than 200 g/day is considered mild, 200 to 400 g/day is moderate, and more than 400 g/day is severe (Kumar et al, 2009). However, it should be emphasised that these cut points have not been properly validated.

Urine Flow Rate and Postvoid Residual

Urine flow rates help in showing the pattern of the flow and the speed at which the patient is voiding, and ultrasound after voiding measures the postvoid residual (PVR). These measurements are inexpensive and easy to perform, and they are noninvasive. It is important, however, to learn how to interpret the measurements. A fast-rising flow rate may indicate an OAB, and a slow-rising one with a long tail on the flow curve may indicate obstruction. If there is a high PVR, the obstruction might cause

<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Initial number	ICIQ-MLUTS Long Form 08/04 CONFIDENTIAL	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> DAY MONTH YEAR Today's date
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Urinary symptoms

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

DAY MONTH YEAR

2a. During the day, how many times do you urinate, on average?

one to six times	<input type="checkbox"/>	0
seven to eight times	<input type="checkbox"/>	1
nine to ten times	<input type="checkbox"/>	2
eleven to twelve times	<input type="checkbox"/>	3
thirteen times or more	<input type="checkbox"/>	4

2b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0	1	2	3	4	5	6	7	8	9	10
not at all										a great deal

3a. During the night, how many times do you have to get up to urinate, on average?

none	<input type="checkbox"/>	0
one	<input type="checkbox"/>	1
two	<input type="checkbox"/>	2
three	<input type="checkbox"/>	3
four or more	<input type="checkbox"/>	4

3b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0	1	2	3	4	5	6	7	8	9	10
not at all										a great deal

4a. Do you have a sudden need to rush to the toilet to urinate?

never	<input type="checkbox"/>	0
occasionally	<input type="checkbox"/>	1
sometimes	<input type="checkbox"/>	2
most of the time	<input type="checkbox"/>	3
all of the time	<input type="checkbox"/>	4

4b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0	1	2	3	4	5	6	7	8	9	10
not at all										a great deal

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Figure 72-3. International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms (ICIQ-MLUTS).

Continued

ICIQ-MLUTS Long Form 08/04

5a. Does urine leak before you can get to the toilet?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

5b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

6a. Do you have pain in your bladder?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

6b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

7a. Does urine leak when you cough or sneeze?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

7b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

8a. Do you ever leak for no obvious reason and without feeling that you want to go?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

8b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

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Figure 72-3, cont'd

ICIQ-MLUTS Long Form 08/04

9a. Is there a delay before you can start to urinate?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

9b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

10a. Do you have to strain to start urinating?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

10b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

11a. Do you have to strain to continue urinating?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

11b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

12a. Do you usually urinate standing up or sitting down?

standing up ☐ 0
sitting down ☐ 1

12b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

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Figure 72-3, cont'd

Continued

ICIQ-MLUTS Long Form 08/04

13a. Would you say that the strength of your urinary stream is...

normal ☐ 0
occasionally reduced ☐ 1
sometimes reduced ☐ 2
reduced most of the time ☐ 3
reduced all of the time ☐ 4


13b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

14. Do you think you have *always* had a weak stream?

no ☐ 0
yes ☐ 1

15. Would you say that the strength of your urinary stream is...
(please ring one number)



Which is it?

4 3 2 1

(from Peeling, 1989)

16a. Do you stop and start more than once while you urinate?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

16b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

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Figure 72-3, cont'd

ICIQ-MLUTS Long Form 08/04

17a. Do you have a burning feeling when you urinate?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

17b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

18a. How often do you feel that your bladder has not emptied properly after you have urinated?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

18b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

19a. Does your urine stream end with a dribble?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

19b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

20a. How often have you had a slight wetting of your pants a few minutes after you had finished urinating and had dressed yourself?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

20b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

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Figure 72-3, cont'd

Continued

ICIQ-MLUTS Long Form 08/04

21a. Do you leak urine when you are asleep?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

21b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

22a. If you leak urine during the day, do you have to change your clothes or wear pads?

no, urine does not leak ☐ 0
yes, change underpants ☐ 1
yes, change clothes ☐ 2
I wear pads ☐ 3

22b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

23a. Do you have to urinate again (within 15 minutes) after you thought you had finished urinating?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

23b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

24. Have you ever blocked up completely so that you could not urinate at all and had to have a catheter passed to drain the bladder ?

no ☐ 0
yes, once ☐ 1
yes, twice ☐ 2
yes, more than twice ☐ 3

© ICSmale

Thank you very much for answering these questions.

Copyright © "ICIQ Group" ; the ICIQ-MLUTS Long Form is based on the ICSmale

Figure 72-3, cont'd

Initial number

ICIQ-UI SF

CONFIDENTIAL

DAY MONTH YEAR

Today's date

Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1 Please write in your date of birth:

DAY MONTH YEAR

2 Are you (tick one):

Female ☐ Male ☐

3 How often do you leak urine? (Tick one box)

never ☐ 0
 about once a week or less often ☐ 1
 two or three times a week ☐ 2
 about once a day ☐ 3
 several times a day ☐ 4
 all the time ☐ 5

4 We would like to know how much urine you think leaks.
How much urine do you usually leak (whether you wear protection or not)?
 (Tick one box)

none ☐ 0
 a small amount ☐ 2
 a moderate amount ☐ 4
 a large amount ☐ 6

5 Overall, how much does leaking urine interfere with your everyday life?
 Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

ICIQ score: sum scores 3+4+5

6 When does urine leak? (Please tick all that apply to you)

never – urine does not leak ☐
 leaks before you can get to the toilet ☐
 leaks when you cough or sneeze ☐
 leaks when you are asleep ☐
 leaks when you are physically active/exercising ☐
 leaks when you have finished urinating and are dressed ☐
 leaks for no obvious reason ☐
 leaks all the time ☐

Thank you very much for answering these questions.

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Figure 72-2. International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form (ICIQ-UI-SF).

chronic retention and if this is associated with high bladder-filling pressures then nighttime UI during sleep may occur.

It is recommended that at least two flows be performed to ensure that they are representative of the manner in which the patient normally voids (Reynard et al, 1996; Garcia-Mora et al, 2013).

Measurement of Prostate-Specific Antigen

There is much controversy about prostate-specific antigen (PSA) testing, which will not be discussed here. However, if the testing is not going to change management, and if the digital rectal examination was normal, it should not be performed unless the patient requests it and is fully counseled about PSA testing.

Blood Tests

Blood tests should be tailored according to the patient history and examination. If a patient is diabetic then renal function tests and glucose are indicated. In general, if it is an index case of UI or SUI with no PVR, then blood tests are not indicated; however the clinician may opt to perform blood tests because they are helpful in assessing renal function and it would be difficult to select those patients with renal insufficiency (Madersbacher et al, 2004).

Endoscopy and Imaging

Cystoscopy and imaging with radiograph or urinary tract ultrasound are not indicated in patients with UI unless there is

concern that the patient may be suffering with a urethral stricture or another pathology seen on urinalysis, such as blood, or flow tests such as a high PVR.

Urodynamic Studies

Urodynamic studies (UDS), or urodynamics, include studies of the physics and physiology of the lower urinary tract (LUT). Technically this includes flow rates. In everyday practice, however, the term *UDS* means filling cystometry and voiding pressure/flow studies.

The general underlying principle when performing urodynamics is that it should not be performed unless it is going to change the management of the patient and unless it would provide the clinician with more information that would alter his or her management of the patient. Hence, following baseline investigations, most major international guidelines including the International Consultation on Incontinence, the European Association of Urology, and the American Urological Association recommend that patients be treated with conservative therapy and medical therapy before performing urodynamics, and if these treatments fail to control the patient's symptoms and the patient would like to have, or needs, a surgical intervention, then that is when urodynamics is performed—that is, before invasive therapy (Winters et al, 2012).

Urodynamics should be considered in the following situations:

- to identify factors contributing to LUT dysfunction and to assess their relevance
- to predict the consequences of LUT dysfunction on the upper tracts
- to predict the consequences and outcomes of therapeutic intervention
- to confirm and/or understand the effects of interventional techniques
- to investigate the reasons for treatment failure

Filling cystometry aims to define how the bladder and urethra behave during the storage phase. In other words, in an index non-neurologic patient, the bladder can either be normal, or there is DO, or there is poor compliance. If the patient leaks during filling cystometry when a DO wave exists, that then is termed *detrusor overactivity incontinence* (DOI). It is important to mark on the urodynamics trace whether urgency was experienced at that time and whether there were any provocative maneuvers.

The urethra, that is, the external urethral sphincter, can either be competent or incompetent during filling cystometry. If it is competent then the patient will be continent and will not experience SUI. The patient is usually asked to perform Valsalva maneuvers or repeated coughs in the upright position when 200 mL of fluid have been instilled into the bladder. If the patient leaks, then the urethra is incompetent and the pressure at which leakage starts, the abdominal (Valsalva or cough) leak-point pressure, is recorded. Valsalva and coughs are also repeated at the end of the test at maximum capacity if the patient did not leak at 200 mL of bladder filling. If the patient leaks on increasing intra-abdominal pressure, then he is said to have urodynamic stress incontinence (USI) as opposed to SUI; USI is a symptomatic clinical diagnosis before urodynamics is performed.

One important scenario that can occur during urodynamics is cough-induced DOI, which happens when the patient coughs, and this action initiates an involuntary detrusor contraction (DO), and the patient leaks because of the DO contraction rather than because of the raised intra-abdominal pressure generated by the cough. Clinically it sounds as if the patient is leaking because of SUI, whereas the urodynamics shows that he has cough-induced DOI.

If during UDS it is difficult to be certain whether the man has USI or cough-induced DOI then it might be helpful to fill the bladder with the man in a lying position, as then DO is less likely to occur. Then ask him to cough to determine whether he leaks in the absence of DO, which would confirm the diagnosis of USI. If he does not leak with coughing, that is then good evidence that he only has DOI. If he leaks while lying down without DO, then the

patient also has USI and therefore has both DOI and USI, that is, mixed urodynamically proven UI.

After urodynamics is performed and the diagnosis is confirmed, invasive surgical treatment can be offered.

KEY POINTS: INITIAL EVALUATION OF PATIENTS WITH URINARY INCONTINENCE

ESSENTIAL

- History and examination
- Measurement of height and weight to calculate BMI
- Dipstick urinalysis
- Bladder diary, for example ICIQ-BD
- QoL questionnaire, for example ICIQ-UI-SF
- Urine flow rate and measurement of PVR

OPTIONAL

- PSA
- Blood tests, for example urea and electrolytes
- Renal tract imaging
- UDS

TREATMENT

Treatment (Fig. 72-4) of patients suffering with UI can be divided into:

- Conservative
- Medical
- Minimally invasive
- Major surgery

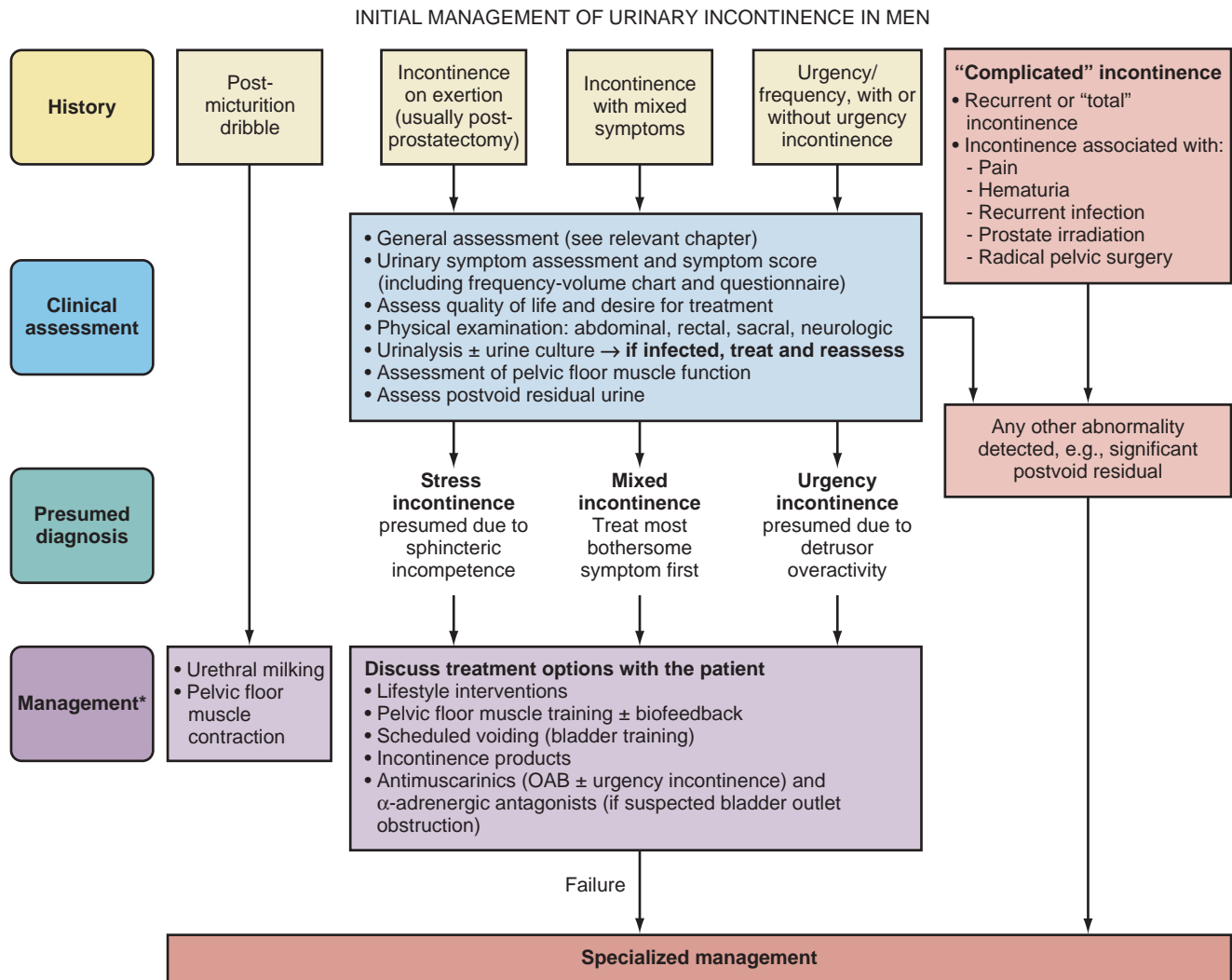
Treatment of Urgency Urinary Incontinence

Initial conservative treatment of UII includes behavioral modifications and lifestyle changes such as reducing fluid input by 25% as long as the patient is drinking more than 1 L/day (Hashim and Abrams, 2008), stopping smoking, reducing weight, and avoiding caffeinated and fizzy drinks that may irritate the bladder. The patient is also taught bladder training and pelvic floor muscle training to supplement the bladder training. These treatments need to be attempted for at least 6 weeks to obtain benefit, and they should ideally be tried for 3 months.

If the previously outlined treatment fails, the patient can then be offered antimuscarinic therapy if there are no contraindications. At least two antimuscarinics must be tried for at least 4 weeks each, starting at a low dose and building up to a maximum dose. There are seven antimuscarinics on the market in the United Kingdom (oxybutynin, tolterodine, fesoterodine, solifenacin, darifenacin, Propiverine, and trospium chloride). Most are oral tablets but oxybutynin is also available in a topical gel formulation (in the United States) and as a skin patch. Each has advantages and disadvantages, and the choice of one in favor of the other depends on several factors, including licensing in the respective country, local guidelines, and clinician and patient preferences. All of the antimuscarinics have Level 1 evidence and Grade A recommendations for their use.

If patients are unable to tolerate antimuscarinics or the antimuscarinics have failed to control symptoms, then patients can be prescribed mirabegron, which is a β_3 agonist that has been licensed for the treatment of OAB in some countries including the United States, the United Kingdom and other European countries, and Japan.

Trials are currently being conducted on combination therapy of an antimuscarinic with a β_3 agonist. In theory, as they work on different receptors they can be used in combination. A phase II trial has shown that the combination therapy of mirabegron and solifenacin is superior to monotherapy with a safe side-effect profile



A

*At any stage of the patient's care pathway, management may need to include continence products.

Figure 72-4. International Consultation on Incontinence algorithm on initial (A) and specialized (B) management of urinary incontinence in men. (From Abrams P, Andersson KE, Artibani W, et al. 5th international consultation on incontinence, recommendations of the International Scientific Committee: evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. In: Abrams P, Cardozo L, Khoury S, et al, editors. *Incontinence. Paris: International Consultation on Urological Diseases and European Association of Urology; 2013. p. 1895-911.*)

(Abrams et al, 2013). More often than not, both conservative and medical therapies are initiated at the same time to provide patients with a quicker and better relief of symptoms.

If conservative and medical therapies fail to control symptoms and the patient requests further treatment, invasive urodynamics is then performed to confirm DO and/or DOI, and minimally invasive surgery, where indicated and available, is offered. This can either be in the form of cystoscopic intradetrusor injections of botulinum toxin-A, percutaneous sacral nerve stimulation (SNS), or percutaneous tibial nerve stimulation (PTNS).

Botox is the only licensed formulation of botulinum toxin A, for idiopathic UII at 100 units, and for neurogenic DO at 200 units. Patients using Botox should be warned of the risk of urinary retention and they should be able and willing to perform intermittent catheterization. In addition, the injections must be repeated on average every 9 months.

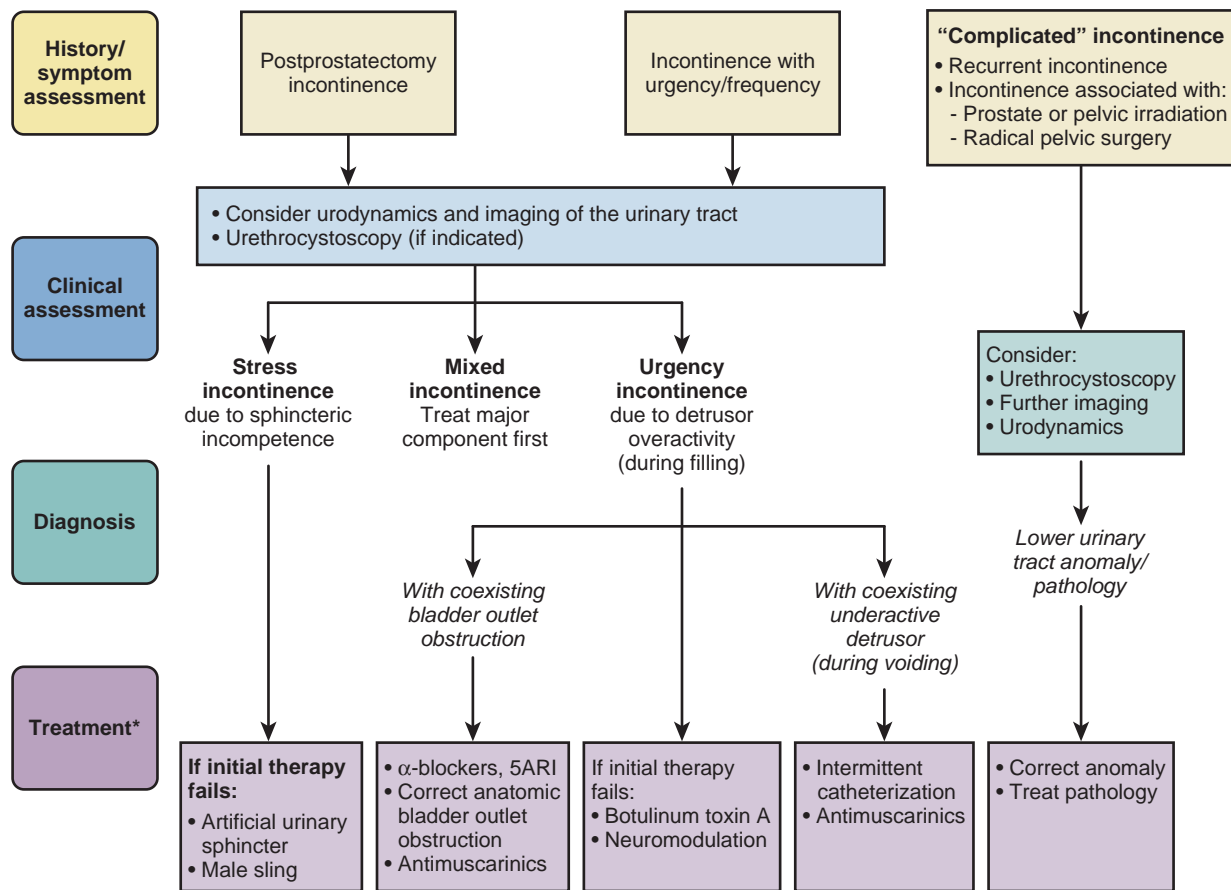
SNS involves a test phase with a wire and external stimulator for 1 week, and a second stage with a tined lead and battery if the first one is successful, which is usually defined as more than a 50% improvement in symptoms. The mechanism of action of SNS is not

clear; however, it is believed that it modulates the nerves supplying the bladder. The battery is changed every 7 years, on average, depending on the amount of use. The cure rate of UII is 39% and an improvement of greater than 50% is seen in 67% of patients. Long-term success has been evaluated with more than 10 years' follow-up with sustained results (Bettez et al, 2012).

PTNS, on the other hand, although licensed for OAB in some countries, does not seem to offer the same degree of benefit as Botox or SNS and as such PTNS is not widely used. The response rate is 54% to 81% (Bettez et al, 2012). PTNS involves inserting a needle into the ankle on the tibial nerve, similar to acupuncture. It is administered as 30-minute sessions once per week for 12 weeks and then it is maintained after that once per month. Patients find it laborious especially if it means traveling for long distances to receive treatment. In theory, this treatment can be self-administered if the patients are taught how to do it. The cost is higher than antimuscarinics therapy and there are no long-term outcome data available.

If these minimally invasive treatments fail and the patient continues to be bothered by symptoms, then the only treatments

SPECIALIZED MANAGEMENT OF URINARY INCONTINENCE IN MEN



B

*At any stage of the patient's care pathway, management may need to include continence products.

Figure 72-4, cont'd

remaining are major surgical operations, unless the patient prefers to use containment products such as pads or a permanent suprapubic catheter. **Surgical options include augmentation cystoplasty, in its various forms, or an ileal conduit with or without a sub-total cystectomy.** In adults, autoaugmentation is no longer recommended for the treatment of DO, because the long-term success of this procedure is not high.

Treatment of Stress Urinary Incontinence

SUI is treated initially with pelvic floor muscle training for at least 3 months. Ideally the training should be supervised to allow the best chance of success (Hay-Smith et al, 2012). If this treatment fails to control symptoms then surgical options should be considered.

The most common cause for SUI in men occurs following prostatectomy. **After radical prostatectomy, it is recommended that no surgical treatment be considered until at least 6 to 12 months subsequently, as some patients will continue to improve (Herschorn et al, 2010).** While they are waiting to improve, patients can use a penile clamp such as *Dribble-Stop*, or, more frequently, containment products are used such as a condom catheter, urethral or suprapubic catheter, or incontinence pads.

Duloxetine, a serotonin norepinephrine reuptake inhibitor, can also be tried (Tsakiris et al, 2008). However, this is an off-license use of the medication that has only been licensed in several countries around the world to women who are experiencing moderate to severe incontinence. The efficacy data for men are limited.

If these treatments fail to control the incontinence and patients are still bothered, then surgical treatment is often offered, usually using an AUS, which is the gold-standard treatment, or using one

of the other options, which include the male sling and, occasionally, the ProACT balloon (see Chapter 91).

Treatment of Mixed Urinary Incontinence

Treatment of MUI is more challenging. It should be aimed at treating the most bothersome symptom. Diagnosis of the SUI component, even on urodynamics, is sometimes difficult if UII is the predominant type of incontinence. Initial treatment usually involves treating DO with antimuscarinics and even with Botox, and then repeating the urodynamics to determine if there is an SUI component.

Treatment of Other Types of Urinary Incontinence

The other types of UI are treated based on the etiology and treatment of the underlying cause.

Enuresis

Patients with high-pressure urinary retention causing nocturnal enuresis are treated by initial catheterization to relieve the pressure, followed by appropriate assessment with a view to using endoscopic surgery to resect, to vaporize, or to enucleate the prostate, or open removal of the prostate.

Nocturnal enuresis, without residual urine, may be related to the OAB. This can be treated with antimuscarinics and potentially with desmopressin in the melt formulation. It can also be related to relaxation of the pelvic floor during sleeping in patients with a neobladder following cystoprostatectomy. These patients sometimes only leak at night and treatment is usually conservative.

Postmicturition Dribble

Treatment of postmicturition dribble has not been well studied and there are no medications available that have been approved for this indication. The main form of treatment is pelvic floor muscle training with a strong pelvic squeeze at the end of voiding and also urethral milking (Paterson et al, 1997; Dorey et al, 2004). The man is asked to wait for a few seconds after passing urine to ensure that the bladder is empty. Then he must place the fingertips of one of his hands three-finger breadths behind the scrotum and apply gentle pressure in the midline and gently move the fingertips toward the base of the penis under the scrotum. The aim is to push the urine forward into the middle part of the penis. From then on, the penis is milked, squeezed, and shaken to empty any remaining urine. The process is repeated twice to ensure that no further urine remains in the urethra.

KEY POINTS: TREATMENT OF URINARY INCONTINENCE

URGENCY URINARY INCONTINENCE

- Fluid manipulation and lifestyle changes
- Bladder training and pelvic floor muscle training
- Antimuscarinics and/or β_3 agonists
- Botox
- SNS
- Augmentation cystoplasty
- Urinary diversion, for example, ileal conduit

STRESS URINARY INCONTINENCE

- Weight loss and lifestyle changes
- Pelvic floor muscle training
- Duloxetine (off-license)
- Penile clamp
- AUS (gold standard)
- Male suburethral sling
- ProACT balloon

CONCLUSION

UI in men can be related to a number of conditions. It is important to assess these patients appropriately to formulate a management plan that will help improve the patient's QoL. Depending on the etiology, initial treatment is usually conservative, and medical and surgical therapies are reserved for those who fail initial treatment and in whom the UI is affecting their QoL.

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The Role of Urodynamic Testing in Clinical Practice

Functional Classification of Voiding Dysfunction: Applicability to Urodynamic Testing

Conducting a Urodynamic Study: Patient and Technical Factors

Components of the Urodynamic Study

Urodynamic Equipment

The Urodynamic Study: Analysis and Interpretation

Filling and Storage Phase

Voiding and Emptying Phase

Video-Urodynamics

Ambulatory Urodynamics

Clinical Utility of Ambulatory Urodynamics

Clinical Applications of Urodynamic Studies: Evidence-Based Review

Evaluation of Women with Stress Incontinence

Evaluation of Men and Women with Lower Urinary Tract Symptoms

Evaluation of Neurogenic Lower Urinary Tract Dysfunction

Urodynamic (UDS) is the term used to describe testing and measurements of the function of the urinary tract. Today, UDS is most commonly done to assess the function of the lower urinary tract (LUT). The LUT has two essential functions: the storage of urine at low pressure and the voluntary evacuation of urine. Low-pressure storage is essential to protect the kidneys and ensure continence, and voluntary evacuation allows for the elimination of urine in socially acceptable situations without fear of leakage or overdistention. It is clear that a number of conditions and diseases affect the LUT and disrupt the storage and/or evacuation of urine. This can lead to bothersome symptoms (e.g., urinary frequency, urgency, and incontinence; slow or interrupted stream) or in some cases potentially harmful sequelae. In many cases, a precise assessment of storage and emptying is necessary to optimally treat patients. **UDS is the dynamic study of the transport, storage, and evacuation of urine. It comprises a number of tests that individually or collectively can be used to gain information about urine storage and evacuation.** UDS involves the assessment of the function and dysfunction of the urinary tract and includes the actual tests that are performed (UDS studies) and the observations during the testing (UDS observations) (Abrams et al, 1988, 2002).

The principles of UDS and the technical performance and interpretation of urodynamic studies has not changed since the 10th edition of *Campbell-Walsh Urology*. What is new is that there is new level 1 evidence regarding the value of UDS in certain clinical conditions. In addition, an American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) Urodynamic Guideline has been published (Winters et al, 2012) and the European Association of Urology (EAU) has published guidelines on neurogenic LUT dysfunction (NLUTD) (Pannek et al, 2013) and urinary incontinence (Lucas et al, 2013), both of which contain recommendations regarding UDS. **The AUA/SUFU Urodynamics Guideline findings and recommendations are “intended to assist the clinician in the appropriate selection of urodynamic tests, following evaluation and symptom characterization.”** We have incorporated the latest literature and guideline recommendations into this chapter, with emphasis on practical use and clinical utility. We will discuss the

different types of urodynamic tests and how they apply to specific conditions of the LUT.

Urodynamic principles, equipment, and performance details apply to both adults and children. We will limit our discussion of UDS in specific conditions to adults. However, several important things should be considered with regard to UDS in children. Many of the conditions for which UDS is used in children involve anatomic and neurologic abnormalities in which LUT function is variable and unpredictable. UDS is used to establish as clearly as possible the baseline situation, so that changes as a result of treatment and/or growth can be assessed and some guidance be obtained in the choice of treatment even if the result of UDS testing is not necessarily the deciding factor (Hosker et al, 2009). In the pediatric population, the aim of UDS is not only to provide precise knowledge of LUT function but also to provide an understanding of the current and future condition to the caregiver and to the patient (and his or her parents). Of course, it is still imperative that the testing should be relevant, reliable, and reproducible. The reader is referred to Chapter 136 for a more detailed discussion of specific conditions in children.

THE ROLE OF URODYNAMIC TESTING IN CLINICAL PRACTICE

UDS has been used for decades, yet level 1 evidenced-based “indications” for its use are limited. There are a number of reasons for this. It is difficult to conduct proper randomized controlled trials on UDS for conditions in which lesser levels of evidence and expert opinion strongly suggest clinical utility and in which empirical treatment is potentially harmful or even life-threatening (e.g., NLUTD). Additionally, symptoms can be caused by a number of different conditions, and it is difficult to study pure or homogeneous patient populations. Recently two trials, which are discussed later, have provided some level 1 evidence for the use of UDS before surgery in women with stress urinary incontinence (SUI) (Nager et al, 2012; van Leijssen et al, 2013). We believe that **given the current state of evidence for UDS studies, what is most important is that the**

clinician has clear-cut reasons for performing the study and that the information obtained will be used to guide treatment of the patient. Therefore it is probably more useful to describe the role of UDS in clinical practice rather than precise indications for its use.

In 2012, the AUA and SUFU produced their first guideline for UDS (Winters et al, 2012). There are also newly published guidelines from the EAU on urinary incontinence (Lucas et al, 2013) and neurogenic LUT dysfunction (NLUTD) (Pannek et al, 2013), both of which make recommendations regarding the use of UDS to assist the clinician in the appropriate selection tests after evaluation and symptom characterization. The AUA/SUFU Guideline was “intended to review the literature regarding urodynamic testing in common LUT conditions and assist clinicians in the proper selection and application of urodynamic tests, following an appropriate evaluation and symptom characterization.” The EAU Guidelines offer practical advice based mostly on expert opinion. We, like the AUA/SUFU guidelines panel, believe that UDS guidelines do not necessarily establish the standard of care, but rather should encourage compliance by practitioners with current best practices related to the condition being treated. Individual health care providers must take into account individual patient situations that can include patient willingness to be treated, variations in resources, and patient tolerances, needs, and preferences.

In practical terms, UDS is most useful when history, physical examination, and simple tests are not sufficient to make an accurate diagnosis and/or institute treatment. This has clinical applicability in the following two general scenarios:

1. To obtain information needed to make an accurate diagnosis for what condition(s) is causing the symptoms (e.g., LUT symptoms [LUTS] or urinary incontinence).
2. To determine the impact of a disease that has the potential to cause serious and irreversible damage to the upper and lower urinary tracts (e.g., neurologic conditions such as spinal cord injury, multiple sclerosis, radiation cystitis). Sometimes, profound abnormalities can be found in the relative absence of symptoms.

Rather than refer to a list of indications for UDS that often are not evidence-based at all, it is more useful for clinicians to think of how UDS should be used in a broader clinical perspective. In keeping with that theme, the role of UDS in clinical practice has been nicely summarized by Hosker and colleagues (2009) and updated by Rosier and associates (2013) for the following situations:

1. To identify or rule out factors contributing to LUTD (e.g., urinary incontinence) and assess their relative importance
2. To obtain information about other aspects of LUT function or dysfunction, whether or not expressed as a symptom or a recognizable sign
3. To allow a prediction of the possible consequences of LUTD for the upper urinary tract (see Box 73-1 for UDS findings that are risk factors for upper tract decompensation)
4. To allow a prediction of the outcome, including undesirable side effects, of a contemplated treatment
5. To confirm the effects of intervention or understand the mode of action of a particular type of treatment for LUTD, especially a new and or experimental (preroutine) one

BOX 73-1 Urodynamic Risk Factors

The following urodynamics findings are potentially dangerous and usually require intervention to prevent upper and lower urinary tract decompensation:

1. Impaired compliance
2. Detrusor external sphincter dyssynergia (DESD)
3. Detrusor internal sphincter dyssynergia (DISD)
4. High-pressure detrusor overactivity present throughout filling
5. Elevated detrusor leak point pressure (>40 cm H₂O)
6. Poor emptying with high storage pressures

6. To understand the reasons for failure of previous treatments for urinary incontinence or for LUTD in general (after unsatisfactory treatment)

It is important to remember that UDS is only one part of the comprehensive evaluation of symptoms and LUT function and that the main goal of UDS is to reproduce the patient's symptoms, when present, and determine the cause of these symptoms by urodynamic measurements or observations. To use UDS in a practical and effective way it is important that the clinician has the proper expertise to know when and why to perform a UDS study. Despite many technical advances in the recording, processing, and printing of UDS studies, careful attention to technical details to ensure accurate collection of data remains the cornerstone of a good study. Because not all patients undergo UDS for the same reasons, the clinician should customize UDS to the patients' symptoms and condition. That means deciding on the questions to be answered before starting each study and designing that study to obtain the answers to those questions. It is important to remember that UDS is performed in an “unnatural setting” and therefore does not always duplicate real-life situations. A UDS study that does not duplicate complaints or symptoms when an abnormality is recorded is not necessarily diagnostic. In addition, failure to record an abnormality does not always rule out its existence (e.g., failure to demonstrate detrusor overactivity (DO) in a patient with urgency incontinence). Finally, not all UDS observations are clinically significant. Therefore it is important to interpret UDS studies in the context of the patient's history, including symptoms and concomitant diseases/conditions, and other information such as postvoid residual (PVR) volumes and frequency volume charts (voiding and intake diaries) when clinically applicable.

KEY POINTS: URODYNAMICS DEFINITION AND GUIDELINES

- UDS is the dynamic study of the transport, storage, and evacuation of urine.
- UDS comprises tests that individually or collectively can be used to gain information about urine storage and evacuation.
- AUA/SUFU UDS Guidelines are intended to assist the clinician to select appropriate urodynamic tests, after evaluation and symptom characterization.

FUNCTIONAL CLASSIFICATION OF VOIDING DYSFUNCTION: APPLICABILITY TO URODYNAMIC TESTING

To formulate a set of questions to be answered by a urodynamic test, an understanding of the possible causes of symptoms and the possible urodynamic manifestations of a preexisting condition is necessary. To accomplish this, a practical classification of voiding dysfunction is invaluable. The system proposed and popularized by Wein (1981) is simple and allows classification of voiding dysfunction according to urodynamic findings. Functionally, abnormalities of the LUT can be divided into the following:

1. Storage dysfunction (failure to properly store urine)
2. Emptying dysfunction (failure to empty the bladder normally)
3. Combined dysfunction (failure to store and empty)

In addition, functional abnormalities can be subclassified to the anatomic region of the LUT that is affected and how it is affected. Thus storage and emptying abnormalities can be caused by the following:

1. Bladder dysfunction
 - a. Overactive (causing failure to store)
 - b. Underactive (causing failure to empty)

2. Bladder outlet dysfunction

- a. Overactive (causing failure to empty)
- b. Underactive (causing failure to store)

3. Combined bladder and bladder outlet dysfunction

The beauty of a functional classification system is that it helps clarify treatment options for a given patient. Thus, in practical terms, the UDS evaluation should help determine if there is bladder or bladder outlet dysfunction (or both) and whether there is a storage and/or emptying problem. By providing answers to these simple questions UDS can lead to a correct diagnosis and, equally as important, institution of appropriate treatment. Obviously, an understanding of the physiology of urine storage and voiding and the pathophysiology of voiding dysfunction (see Chapter 70) is required to formulate appropriate questions to be answered by a urodynamic study. However, all too often clinicians get caught up in the intricate neurophysiologic aspects of voiding and storage dysfunction and fail to think in practical terms. One should always focus on the possible urodynamic findings in a given case and how each of the findings may ultimately affect the patient and treatment. Symptoms and/or underlying conditions or diseases will determine these potential findings.

KEY POINT: FUNCTIONAL CLASSIFICATION SYSTEM

- The functional classification system can help clarify treatment options for a given patient. Thus, in practical terms, the UDS evaluation should be performed to help determine if there is bladder or bladder outlet dysfunction (or both) and whether there is a storage and/or emptying problem.

CONDUCTING A URODYNAMIC STUDY: PATIENT AND TECHNICAL FACTORS

Preparing for a Urodynamic Study: Clinician, Patient, and Facility

Once the decision has been made to perform UDS on a particular patient it is important to consider what information is expected from the test. The simple fact that a patient has symptoms or a disorder that may affect the LUT is not sufficient to start the UDS evaluation. **A list of problems or questions that should be solved or answered by UDS should be made before any testing is performed.** All patients are not alike, and therefore each urodynamic evaluation may be different depending on the information needed to answer the questions relevant to a particular patient. **We follow these three important rules before starting the UDS evaluation (Nitti and Combs, 1998):**

1. Decide on questions to be answered before starting a study.
2. Design the study to answer these questions.
3. Customize the study as necessary.

By following these simple rules the chance of obtaining useful information from a study can be maximized. If a particular question is not answered, the study can be repeated in the same session. Most people who perform UDS regularly would concur that a urodynamic test is not always perfect in answering all important questions, but by defining the information needed before starting the study, unanswered questions can be kept to a minimum. We cannot emphasize enough that one of the most important parts of UDS is its proper performance with careful attention to technical details so that accurate interpretation is possible. It is beyond the scope of this chapter to describe the proper performance of UDS in detail; however, the reader is referred to the articles by [Schafer and colleagues \(2002\)](#) for good urodynamic practices and [Abrams and associates \(2002\)](#) for terminology. The International Continence Society (ICS) has now defined the term *urodynamic observations* to denote observations that occur during and are measured by the UDS test. To be consistent, it is recommended that all clinicians

performing and interpreting UDS use the current ICS terminology ([Abrams et al, 2002](#)). A list of common UDS terms is provided in [Box 73-2](#).

Ideally a room of suitable size should be dedicated to UDS ([Nitti and Combs, 1998](#)). This area does not have to be exclusively for UDS, but when a study is being performed, there should not be distractions from people walking into and out of the area for other reasons. A quiet private area is best. It is difficult enough to recreate a natural environment during testing without outside distractions. The room should be large enough to allow for the patient to lie down to have catheters placed and also to be able to stand and sit on a commode as necessary. Many patients undergoing urodynamic testing will have neurologic problems that limit mobility and will require assistance with positioning. This includes patients in wheelchairs. This must be considered when determining the size of the room. Centers that perform video-urodynamics (VUDS) will require a larger area to allow for x-ray equipment.

The importance of a well-trained, attentive, and supportive staff involved with the UDS study cannot be overemphasized. With that said, in general, UDS is well tolerated. **However, patients should be properly prepared and told why the test is being done, how the results may affect treatment, and what to expect during the actual UDS test.** [Scarpero and colleagues \(2005\)](#) used a questionnaire-based study to assess patient expectations of anxiety, pain, embarrassment, and apprehension before UDS and compared it to the patient's actual experience. They found that UDS was associated with minimal-to-moderate degrees of anxiety, discomfort, and embarrassment. After testing, most respondents (>90% per question) thought that the test was the same or better than expected and it was associated with an expected or less than expected level of pain and embarrassment. This did not vary between the sexes, but a higher number of younger individuals found that the test experience was worse than expected and a higher number of older individuals found that it was better than expected. Therefore younger patients may require more reassurance and attention in preparation for the procedure. Similarly, [Yokoyama and coworkers \(2005\)](#) found UDS to be quite tolerable based on a questionnaire study. Patients experienced minimal degrees of pain, embarrassment, and physical burden from UDS. On a visual analog scale of 0 to 10 (*not at all to unbearable*) in 154 consecutive patients (56% men) the mean (standard deviation) degrees of pain, embarrassment, and physical burden were 2.27 (2.53), 2.59 (2.69), and 1.76 (2.43), respectively, and 73.6% of men and 80.6% of women were willing to repeat UDS. The most common complaint after UDS was micturition pain. Urinalysis showed that 4.6% of men and 7.5% of women had leukocyturia after the investigation.

Many patients undergoing urodynamic testing will have been placed on medications that can affect bladder function (e.g., anti-muscarinics). For such patients the clinician should decide in advance what information is desired and whether the study should be done on or off medication. For example, if the goal of the study is to determine the therapeutic effect of a medication, obviously the UDS should be done with the patient on a regular dosing schedule for that medication. On the other hand, if medication was started empirically to treat symptoms and the goal of the urodynamic test is to uncover the cause of those symptoms, consideration can be given to discontinuing the medication before testing because this may give the highest yield.

COMPONENTS OF THE URODYNAMIC STUDY

Before discussing the details of the UDS test itself it is useful to be familiar with the test components. These tests within the test can be used individually or in combination depending on the information desired. For the purposes of this chapter we will discuss each component as part of the entire multichannel UDS or VUDS study. Uroflow and PVR determination are two simple, noninvasive tests that can be used to evaluate voiding function and perhaps prompt further testing. In addition, both are part of a multichannel UDS study.

BOX 73-2 Terminology for Common Urodynamic Terms and Observations According to the International Continence Society Standardization Subcommittee

The International Continence Society (ICS) has now defined the term *urodynamic observations* to denote observations that occur during and are measured by the urodynamics (UDS) test itself. To be consistent, it is recommended that all clinicians performing and interpreting UDS use the current ICS terminology (Abrams et al, 2002).

Two principal methods of urodynamic investigation exist:

Conventional urodynamic studies: Normally take place in the urodynamic laboratory involving artificial bladder filling.

Ambulatory urodynamic studies: A functional test of the lower urinary tract using natural filling and reproducing the subject's everyday activities.

The following are required of both types of studies:

Intravesical pressure: The pressure within the bladder.

Abdominal pressure: The pressure surrounding the bladder; currently it is estimated from rectal, vaginal, or extraperitoneal pressure or a bowel stoma.

Detrusor pressure: The component of intravesical pressure created by forces on the bladder wall that are both passive and active.

Filling cystometry: The method by which the pressure and volume relationship of the bladder is measured during bladder filling.

Physiologic filling rate: A filling rate less than the predicted maximum. Predicted maximum is the body weight in kilograms divided by 4 and expressed as milliliters per minute.

Nonphysiologic filling rate: A filling rate greater than the predicted maximum.

Bladder sensation during filling cystometry:

Normal bladder sensation, defined by three points noted during filling cystometry and evaluated in relation to the bladder volume at that moment and in relation to the patient's symptomatic complaints.

First sensation of bladder filling: The volume at which the patient first becomes aware of the bladder filling.

First desire to void: The feeling during filling cystometry that would lead the patient to pass urine at the next convenient moment.

Strong desire to void: A persistent desire to void without the fear of leakage.

Increase that occurs at low bladder volumes and persists.

Reduced bladder sensation: Diminished sensation throughout bladder filling.

Absent bladder sensation: The individual has no bladder sensation.

Nonspecific bladder sensation: The individual is aware of bladder filling because of other sensations such as abdominal fullness or vegetative symptoms.

Bladder pain: A self-explanatory term that is abnormal.

Urgency: A sudden compelling desire to void.

Normal detrusor function: Allows bladder filling with little or no change in pressure, no involuntary contractions despite provocative maneuvers.

Detrusor overactivity: Involuntary detrusor contractions during the filling phase, spontaneous or provoked.

Phasic detrusor overactivity: A characteristic waveform that may or may not lead to urinary incontinence.

Terminal detrusor overactivity: A single involuntary detrusor contraction occurring at cystometric capacity that cannot be suppressed, resulting in incontinence with bladder emptying.

Detrusor overactivity incontinence: Incontinence related to involuntary detrusor contractions. This may be qualified according to cause.

Neurogenic detrusor overactivity: Overactivity accompanied by a neurologic condition; this term replaces the term *detrusor hyperreflexia*.

Idiopathic detrusor overactivity: Detrusor overactivity without concurrent neurologic cause. This term replaces the term *detrusor instability*.

Provocative maneuvers: Techniques used during urodynamic border to provoke detrusor overactivity.

Cystometric capacity: The bladder volume at the end of the filling cystogram when permission to void is given.

Maximum cystometric capacity: The volume at which the patient feels he or she can no longer delay micturition and has a strong desire to void.

Maximum anesthetic bladder capacity: The volume to which the bladder can be filled under deep general or spinal anesthesia. This should be qualified as to what type of anesthesia is used, the rate of filling, the length of time of filling, and the pressure to which the bladder is filled.

Normal urethral closure mechanism: This maintains a positive urethral closure pressure during bladder filling even in the presence of increased abdominal pressure.

Incompetent urethral closer mechanism: This is defined as one allowing leakage of urine in the absence of detrusor contraction.

Urethral relaxation incontinence: Leakage related to urethral relaxation in the absence of raised abdominal pressure or detrusor overactivity.

Urodynamic stress incontinence: Noted during filling cystometry and defined as the involuntary leakage of urine during increased abdominal pressure in the absence of a detrusor contraction. This currently replaces genuine stress incontinence.

Urethral pressure measurements:

Urethral pressure: The fluid pressure needed to just open a closed urethra.

Urethral pressure profile: A graph indicating the intraluminal pressure along the length of the urethra.

Urethral closure pressure profile: The subtraction of intravesical pressure from urethral pressure.

Maximum urethral pressure: The maximum pressure of the measured profile.

Maximum urethral closure pressure (MUCP): The maximum difference between the urethral pressure and the intravesical pressure.

Functional profile length: The length of the urethra along which the urethral pressure exceeds intravesical pressure in women.

Pressure transmission ratio: The increment in urethral pressure on stress as a percentage of the simultaneously recorded increment in intravesical pressure.

Abdominal leak point pressure: The intravesical pressure at which urine leakage occurs because of increased abdominal pressure in the absence of a detrusor contraction.

BOX 73-2 Terminology for Common Urodynamic Terms and Observations According to the International Continence Society Standardization Subcommittee—cont'd

Detrusor leak point pressure: The lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure.

Pressure-flow studies: The method by which the relationship between pressure in the bladder and urine flow rate is measured during bladder emptying.

Pressure measurements during pressure-flow studies:

Premicturition pressure: The pressure recorded immediately before the initial isovolumetric contraction.

Opening pressure: The pressure recorded at the onset of urine flow.

Opening time: The elapsed time from original rise in detrusor pressure to onset of flow.

Maximum pressure: The maximum value of the measured pressure.

Pressure at maximum flow: The lowest pressure recorded at maximum measured flow rate.

Closing pressure: The pressure measured at the end of measured flow.

Minimum voiding pressure: The minimum pressure during measurable flow.

Flow delay: The time delay between a change in bladder pressure and the corresponding change in measured flow rate.

From Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. *Neurourol Urodyn* 2002;21:167–78; and Schafer W, Abrams P, Liao L, et al. Good urodynamic practices: uroflowmetry, filling, cystometry, and pressure-flow studies. *Neurourol Urodyn* 2002;21:261–74.

PVR is an excellent assessment of bladder emptying. It can be performed by ultrasound (bladder scan) or catheterization. Elevation of PVR indicates a problem with emptying but does not indicate the reason. An elevated PVR may prompt further testing.

Uroflowmetry is measurement of the rate of urine flow over time. It is also an assessment of bladder emptying. Multiple data points can be reported from noninvasive uroflowmetry. These include the following:

- Voided volume (VV in milliliters)
- Flow rate (Q in milliliters per second)
- Maximum flow rate (Qmax in milliliters per second)
- Average flow rate (Qave in milliliters per second)
- Voiding time (total time during micturition in seconds)
- Flow time (the time during which flow occurred in seconds)
- Time to maximum flow (onset of flow to Qmax in seconds)

In addition to these objective measurements, it is also important to observe the pattern or shape of the uroflow curve. A normal uroflow curve is bell-shaped (Fig. 73-1). Uroflow curve interpretation is somewhat subjective because of difficulty in qualitatively judging a pattern (Boone and Kim, 1998). When the flow rate is reduced or the pattern is altered, this could indicate bladder (underactivity) or bladder outlet (anatomic or functional obstruction) dysfunction (see Fig. 73-1). Although certain patterns are suggestive of certain voiding dynamics (e.g., an interrupted or straining pattern with detrusor underactivity [DU], and a flattened pattern with a fixed obstruction), specific underlying abnormalities cannot be definitively identified without detrusor pressure data (see later discussion of invasive pressure-flow UDS).

Cystometry (CMG) or, more appropriately, filling CMG is the method by which the pressure/volume relationship of the bladder is measured during bladder filling. The filling phase starts when filling commences and ends when the patient and urodynamicist decide that permission to void has been given (maximum cystometric capacity). CMG can be performed by the single measurement of bladder pressure via a bladder catheter (urethral or suprapubic); however, changes in bladder pressure can represent a change in detrusor pressure (Pdet) or a change in abdominal pressure (Pabd) (see later). Therefore it is recommended that CMG be performed by measuring both the total vesical pressure (Pves) and Pabd (measured by a catheter placed in the rectum or vagina). To calculate Pdet the following equation is used (Fig. 73-2):

$$P_{det} = P_{ves} - P_{abd}$$

Electromyography (EMG) is the study of the electronic potentials produced by the depolarization of muscle membranes. In the case

of UDS, EMG measurement of the striated sphincteric muscles of the perineum is done to evaluate possible abnormalities of pelvic floor muscle function, which are often associated with LUTS and LUTD. EMG activity is measured during both filling and emptying. EMG is performed via electrodes placed in (needle electrodes) or near (surface electrodes) the muscle to be measured.

The **urethral pressure profile** (UPP) is a graph indicating the intraluminal pressure along the length of the urethra. Urethral pressure is defined as the fluid pressure needed to just open a closed urethra. UPP is obtained by withdrawal of a pressure sensor (catheter) along the length of the urethra.

Pressure-flow studies of voiding are the method by which the relationship between Pdet and urine flow rate is measured during bladder emptying (voiding). Pdet is measured as described previously with the simultaneous measurement of flow rate by uroflowmeter. The voiding phase starts when permission to void is given, or when uncontrollable voiding begins, and ends when the patient considers voiding has finished.

URODYNAMIC EQUIPMENT

Urodynamic Systems

A variety of different urodynamic systems are available today. They range in cost depending on their features and complexity. Current UDS systems are computer-based digital systems that allow for easy data storage and postprocessing of the study. In addition they allow for hardware and software upgrades as necessary. It is beyond the scope of this chapter to describe in detail the options available for UDS systems. However, it is recommended that, when choosing a system, the patient population and spectrum of diseases frequently encountered, space, convenience of operation (if a factor), and the need for data storage and processing be considered. In addition it is recommended that a multichannel system be used where channels are available to measure Pves, Pabd (and subtracted Pdet), and flow rate. Some clinicians also may desire channels for EMG and urethral pressure measurement. The UDS system and software market is constantly changing, so what is state-of-the-art today may seem outdated tomorrow. However, despite all the advances, the clinician performing the study remains the most important constant in data collection and interpretation. For the most realistic assessment, the infusant should be a liquid (e.g., normal saline or radiographic contrast) that most approximates urine. The use of gas, such as carbon dioxide, is not recommended. Many advanced urodynamic centers now perform VUDS. Adding this capability is costly, but it allows the most comprehensive study possible. In

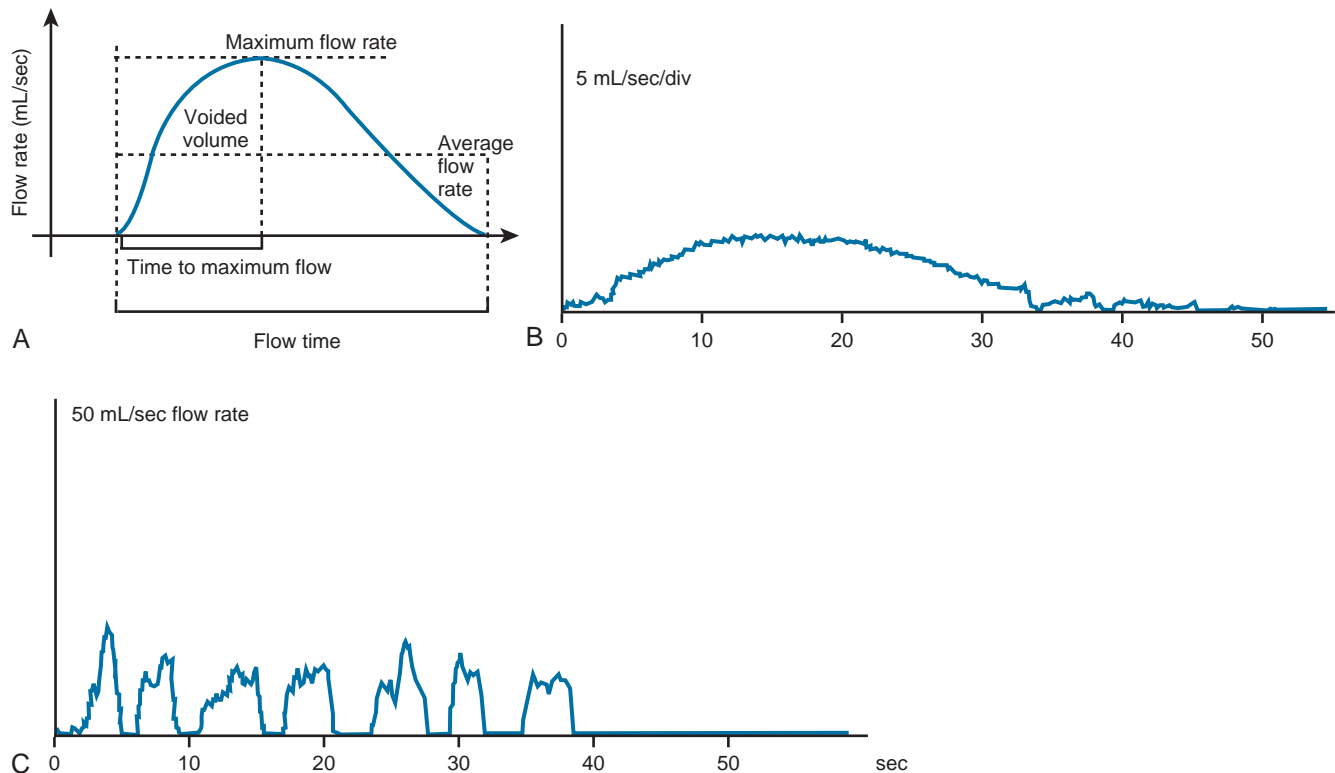


Figure 73-1. Examples of uroflow curves. **A**, Normal bell-shaped flow curve of flow rate versus time. **B**, Flattened pattern usually indicative of obstruction. **C**, Interrupted or straining pattern, which can be seen with impaired bladder contractility, obstruction, or voiding with or by abdominal straining. (A, From Wein AJ, English WS, Whitmore KE. Office urodynamics. *Urol Clin North Am* 1988;15:609; B and C, from Boone TB, Kim YH. Uroflowmetry. In: Nitti VW, editor. *Practical urodynamics*. Philadelphia: Saunders; 1998. p. 28–51.)

certain clinical settings VUDS is the test of choice (see later). In addition to the necessary urodynamic hardware and software, a fluoroscopy unit and room of adequate size are required. Obviously, this is not practical or necessary in every setting. VUD studies also require a greater time commitment on the part of the clinician to ensure accurate data collection. Thus VUDS is ideally performed in centers with a specific interest in complex storage and voiding dysfunction. For specific recommendations regarding UDS equipment performance, the reader is referred to the recently published ICS document on this subject (Gammie et al, 2014).

Signal Transmission and Transducers

Transducers are the hardware that allows pressure in the patient to be measured and measurements transferred to the UDS system. External strain gauge transducers located between the patient and the urodynamic machine have been popular for years. Pressurized tubing (to avoid damping or dissipating the pressure) extends from the pressure transducer to the catheters placed in the patient. An electronic cable or wireless transmission brings the signal from the transducer to the urodynamic machine. Traditionally a water-filled system was used in which the entire system from transducer to patient is filled with water. Because this system depends on the transmission of pressure through fluid (water), it is crucial that there are no air bubbles in the transducer or tubing. The pressurized tubing transmission lines should be lucent to allow for easy recognition of air in the line. The transducers are usually set at the level of the patient's bladder (symphysis pubis) at the start of the study. This is important, because if the patient changes position during the test (e.g., standing to sitting), the height of the transducer can be adjusted so that it remains at the level of the bladder.

More recently, **air-charged catheters** (T-Doc, Wenonah, NJ) have become popular for pressure measurement. Air-charged catheters

use a miniature air-filled balloon placed circumferentially around a polyethylene catheter. External forces on the balloon of the catheter are transmitted to the air-filled catheter lumen and communicated to an external semiconductor transducer. The technology of the balloon system allows circumferential measurement readings. The catheters are disposable and for single use. Air-charged catheters have several practical advantages over fluid-filled pressure lines because there is no fluid connection between the patient and the urodynamic equipment, just air. This means there is no hydrostatic pressure effect to account for, so there is no need to position anything at the level of the symphysis pubis and no need to flush the system through to exclude air (essential when using a fluid-filled system). Also, there are no artifactual fluctuations in pressure produced when the patient moves. It must be remembered that **many UDS nomograms and other standards of measurement were determined using fluid-filled systems. There is comparative evidence for the use of air-charged catheters to measure urethral pressure and Valsalva leak point pressure**, with one study showing comparable performance between air-charged and microtip catheters (Pollak et al, 2004) and one study concluding that they cannot be used interchangeably, because air-charged catheters showed systematically higher readings (Zehnder et al, 2008).

Cooper and colleagues (2011), in an experimental model, showed that **air-charged and water-filled catheters respond to pressure changes in dramatically different ways**. Water-filled catheters acted as an underdamped system, resonating at 10.13 ± 1.03 Hz and attenuating signals at frequencies higher than 19 Hz. They demonstrated significant motion and hydrostatic artifacts. Air-charged catheters acted as an overdamped system and attenuated signals at frequencies higher than 3.02 ± 0.13 Hz. They demonstrated significantly less motion and hydrostatic artifacts than water-filled catheters. The authors point out that most urodynamic signals occur below 3 Hz, and thus air-charged systems could be beneficial

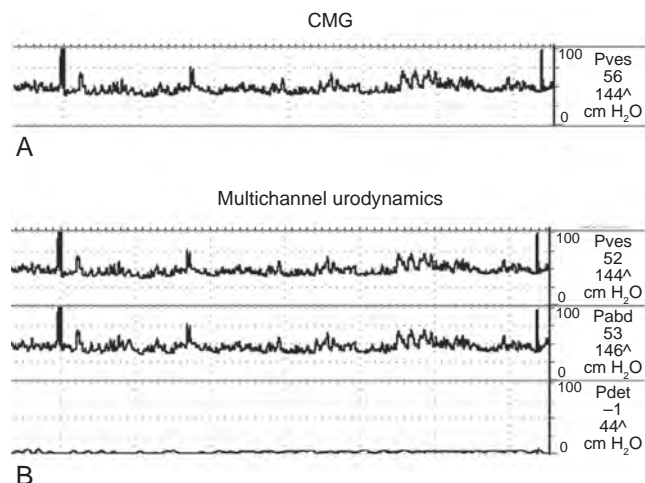


Figure 73-2. Cystometrography (CMG) measures the pressure in the bladder as the bladder fills over time. Standard fill rates in adults are 30 to 100 cm H₂O per minute. Adding intra-abdominal pressure monitoring gives a better representation of the true detrusor pressure (Pdet). A, Single-channel CMG in which only the total vesical pressure (Pves) is measured. Note the multiple spikes and rises in pressure. Without having simultaneous monitoring of intra-abdominal pressure (Pabd), it is impossible to know if these pressure spikes are due to a rise in detrusor or abdominal pressure. B, The same tracing with Pabd monitoring added (multichannel urodynamics). This allows for the determination of (subtracted) Pdet. Here it can be clearly seen that changes in Pves were due to the changes in Pabd (movement, coughing, etc.). The Pdet curve is noted to be flat and without any rises in pressure. (From Nitti VW. Cystometry and abdominal pressure monitoring. In: Nitti VW, editor. *Practical urodynamics*. Philadelphia: Saunders; 1998. p. 38–51.)

because most of the higher frequency noise is damped. However, urodynamic signals can have frequency components greater than 3 Hz, particularly when using rapidly changing signals, such as coughs. The authors concluded that “knowledge of the characteristics of the pressure-measuring system is essential to finding the best match for a specific application.” The conclusions of the 5th International Consultation on Incontinence (Rosier et al, 2013) are that air-charged catheters may provide an acceptable alternative for measuring the closure pressure of the female urethra, but there have been no studies to show that air-charged catheters provide a superior alternative to fluid-filled lines for measuring intravesical and intra-abdominal pressure. Thus it is recommended that investigators planning to use air-charged catheters for intravesical and intra-abdominal pressure monitoring check for themselves that they have an equivalent performance to their current system for measuring pressure (Rosier et al, 2013).

Finally, a microtip or fiberoptic system can be used to process pressure transmission. In this system the transducer is contained within the catheter. This in turn is connected directly into the urodynamic machine via a cable. These catheters are quite expensive and reusable and must be sterilized before each use.

Uroflowmeters

Urine flow rate, or uroflow, can be determined by a number of different types of devices or uroflowmeters. Modern uroflowmeters use weight, electrical capacitance, or a rotating disc to determine urinary flow rates. The two most common techniques today are the weight transducer or load cell method and the rotating disc method. With the load cell the voided weight is measured and then differentiated with respect to time to determine the flow rate. In the rotating disc method the urine stream is directed onto a rotating disc and the power necessary to keep a disc rotating at a constant rate is mea-

sured. This power is proportional to the flow rate. The electronic dipstick flowmeter measures the electrical capacitance of a dipstick mounted in a collecting chamber. The output of the signal is proportional to the accumulated volume, and the volumetric flow rate is determined by differentiation. Each of these methods has advantages and disadvantages. The weight transducer method is simple, reliable, and accurate, regardless of the site of stream impact, but requires that the density of urine must be set. The rotating disc method is also reliable and accurate and provides a direct measurement without need for differentiation of volume with respect to time. Electronic flowmeters provide a range of electronically read flow parameters with graphic depiction of the uroflow and have sufficient precision for clinical use with error rates of 1% to 8% in voided volume and 4% to 15% in flow rate (Susset, 1983). Variations in specific gravity of the fluid voided (infusant when doing UDS studies) can affect the calculated flow rate. Most systems allow for calibrations for various fluids such as radiographic contrast agent.

Electromyography

Muscle depolarization must be detected by an electrode placed in or near the muscle. Several different methods are available, including surface electrodes, needle electrodes (which are the two most common methods), and anal plug or urethral catheter-mounted electrodes (O'Donnell, 1998). Surface electrodes are self-adhesive skin patch electrodes that are applied over the skin of the anal sphincter (Barrett, 1980). Except in some neurologic diseases, external anal sphincter EMG will be the same as the external urethral sphincter EMG. Surface electrodes have a significant advantage compared with the needle electrode regarding patient convenience and comfort. However, the surface electrodes provide an inferior signal source and must be precisely placed to provide an adequate signal source. Most clinicians think the concentric needle electrode is the superior technique for obtaining a signal source of EMG activity of the striated external sphincter muscles. Compared with the surface electrode, placement of the needle electrode has the disadvantage of being uncomfortable for the patient, especially if more than one attempt at placement of the electrode is required to obtain an adequate signal. Also, the needle electrode is easily dislodged and may require replacement during the study. Patients typically have a low tolerance for replacement of the needle electrode during urodynamic studies (Brucker et al, 2012). The performance of EMG and the selection of the type of electrode to be used depend on the UDS question to be answered.

KEY POINTS: URODYNAMICS PERFORMANCE AND INTERPRETATION

- There should be a clearly defined reason to perform a UDS study. The intention should be that the information that may be obtained could be used to guide patient treatment.
- UDS is only one part of the comprehensive evaluation of symptoms and LUT function, and the main goal of UDS is to reproduce patient symptoms, when present, and determine the cause of the symptoms by urodynamic measurements or observations.
- UDS studies should be interpreted in the context of patient history, including symptoms, concomitant diseases/conditions, and other information, such as PVR volumes and frequency volume charts (voiding and intake diaries) when clinically applicable.
- Proper urodynamic practices and appropriate terminology should be used when possible.
- Well-trained, attentive, and supportive staff involved with the UDS study cannot be overemphasized. Patients should be properly prepared and told why the test is being done, how the results may affect treatment, and what to expect during the actual UDS test.

THE URODYNAMIC STUDY: ANALYSIS AND INTERPRETATION

We have found it useful to divide the UDS test into filling/storage and voiding phases. This allows for ease of classification of voiding dysfunction according to the functional classification system mentioned previously. The filling/storage phase consists primarily of CMG and provocative testing (e.g., measurement of abdominal leak point pressure [ALPP]), and urethral pressure measurement during storage. The voiding phase evaluates bladder contractility, bladder outlet resistance, and sphincter coordination by pressure-flow analysis and EMG.

FILLING AND STORAGE PHASE

The CMG assesses the bladder's response to filling. It can measure filling pressure, sensation, involuntary contractions, compliance, and capacity. Sensation is the part of CMG that is truly subjective and therefore requires an alert and attentive patient and clinician. Several subjective parameters can be recorded during filling that are recognized by the ICS (see Box 73-2). Categorizing LUT sensation during bladder filling (e.g., urinary urgency or early filling sensation) is now thought to be more clinically important than previously thought. Some treatments are thought to have a specific influence on sensation (de Wachter et al, 2011; Heeringa et al, 2011).

Normal Filling and Storage

Normally, the bladder should store urine at a low pressure and not contract involuntarily. Once capacity is reached or voluntary voiding is desired, intravesical pressure will increase (voluntary detrusor contraction). In actuality this is preceded by a relaxation of the external sphincter. A normalized adult CMG image is shown in Figure 73-3. Normally Pdet should remain near zero during the entire filling cycle until voluntary voiding is initiated. That means baseline pressure stays constant (and low) and there are no involuntary contractions.

As mentioned previously, the simultaneous measurement of Pabd, usually by a rectal or vaginal catheter, and Pves during UDS provides a means of calculating the true Pdet. The ability to calculate subtracted Pdet allows distinguishing between a true rise in Pdet (via either a contraction or loss of compliance) and the

effect of increased Pabd (e.g., straining, Valsalva). This is especially important when rises in Pdet are small or when they are accompanied by changes in Pabd.

Abnormalities of Bladder Filling: Detrusor Overactivity and Impaired Compliance

During filling, involuntary detrusor contractions (IDCs) can occur. These are often associated with urgency and even urgency incontinence. DO is a urodynamic observation characterized by IDCs during the filling phase that may be spontaneous or provoked (Fig. 73-4). DO may be further characterized as neurogenic DO when it is associated with a relevant neurologic condition (e.g., spinal cord injury, multiple sclerosis) or idiopathic DO when there is no defined cause (non-neurogenic) (Abrams et al, 2002). The term *idiopathic DO* is a bit of a misnomer, in that the cause of DO in a non-neurogenic patient may be readily apparent (e.g., bladder outlet obstruction [BOO], inflammatory process) or may be truly unknown. Thus, from a practical standpoint, the terms *neurogenic* and *non-neurogenic* DO make more sense, but do not fit the ICS definitions. (It should be noted that the term *neurogenic DO* replaced the term *detrusor hyperreflexia* and the term *idiopathic DO* replaced the term *detrusor instability* in the last ICS terminology). Neurogenic and idiopathic DO may look identical on CMG. These terms are strictly defined by patient neurologic status and not the appearance of the IDCs on CMG.

The presence of DO during UDS must be interpreted in the context of patient symptoms and condition. Ideally, patient symptoms should be reproduced during UDS, so DO would be expected to be accompanied by urgency or urgency incontinence, although it can occur and be significant without being symptomatic, particularly in neurogenic DO. However, DO also can be test induced or clinically insignificant. It has been reported in 14% to 18% of healthy asymptomatic volunteers undergoing UDS (van Waalwijk van Doorn et al, 1992; Robertson, 1999; Wyndaele et al, 2002). This is even more dramatic in ambulatory UDS studies in which the presence of DO has been found in as many as 69% of asymptomatic females (van Waalwijk van Doorn et al, 1996). Conversely, failure to demonstrate DO on UDS does not rule out its existence. It is well known that up to 50% of women with urgency incontinence do not demonstrate DO on UDS. However, the ability to suppress DO during UDS testing may in and of itself be significant. For example, Osman (2003) demonstrated that patients with mixed incontinence and normal CMG findings (no DO) not only had excellent cure rates for stress incontinence but also had an 87% cure rate for urgency incontinence (compared to only 43%

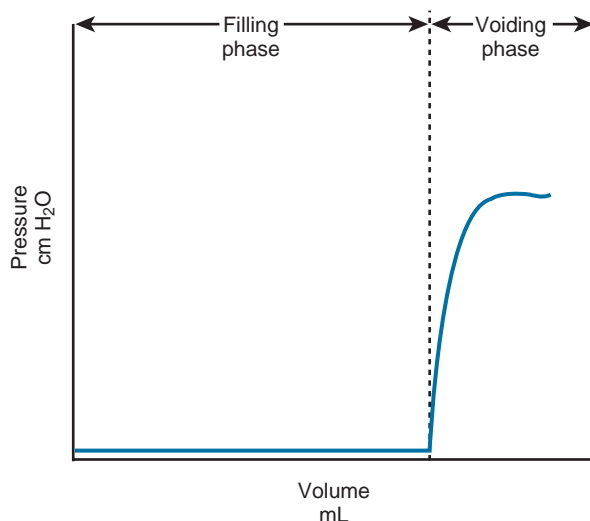


Figure 73-3. Normal, idealized adult cystometrogram with low pressure storage until the patient is given the command to void and the voiding phase starts. Note that the baseline bladder pressure is near zero (compliant) and there are no involuntary contractions.

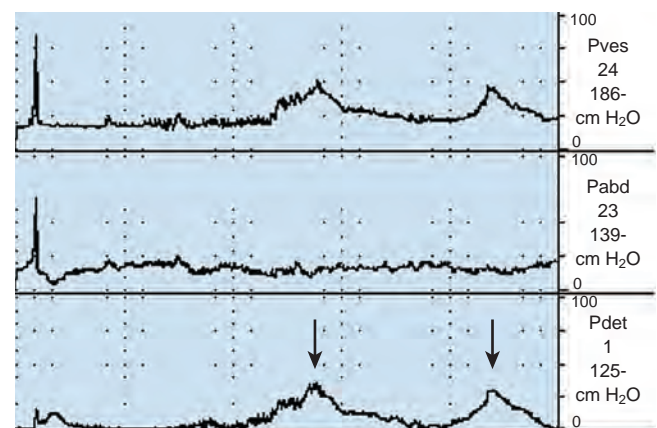


Figure 73-4. Detrusor overactivity. In this tracing there are two involuntary detrusor contractions (arrows). There is a rise in Pves with no associated rise in Pabd, and therefore the subtracted Pdet looks identical to the Pves.

ture for urgency incontinence for women randomized to receive antimuscarinic medication instead of stress incontinence surgery).

It is important that the person performing the UDS study be absolutely sure that the contraction is indeed involuntary. Sometimes patients may become confused during the study and actually void as soon as they feel the desire. The volume at which contractions occur and the pressure of the contractions should be recorded. It is often worthwhile to repeat CMG at a slower filling rate if the patient experiences uncharacteristic symptoms associated with DO. If the patient experiences incontinence during an involuntary contraction (DO incontinence), this should be noted.

In addition to the presence of DO, its characteristics can be noted. DO can be observed as a single event or as multiple IDCs. It can be phasic (continuous), sporadic, or terminal (occurring at the end of filling near capacity). It also can be suppressed or non-abortable and may lead to leakage or precipitant micturition. Classifying DO in such a way can be valuable in certain circumstances. For example, overactive bladder symptoms associated with obstruction have been shown to have a higher likelihood of resolving with intervention (e.g., transurethral resection of the prostate [TURP]) when DO occurs as a single terminal IDC rather than continuous or sporadic IDCs (Kageyama et al, 2000).

The detection of DO can be influenced by the patient's position. A review of studies on the influence of patient position found that 14 of 16 showed a higher incidence of DO in the vertical position (supine or standing) or onset of DO when changing to a vertical position versus supine (Al-Hayek et al, 2008). Thus, when the detection/documentation of DO is clinically important, it would seem appropriate to test patients in the position in which they experience specific symptoms.

In summary, DO is often a significant UDS observation and may explain a number of storage symptoms. In addition to its presence, the characteristics of DO should be noted. It is also important that clinicians recognize normal test-retest variation and also that "usual LUT behavior" is not always replicated in the test setting.

The vesicoelastic properties of the bladder, based on its composition of smooth muscle, collagen, and elastin, normally produce a highly compliant structure. Therefore as the bladder fills there is little change in pressure (see normalized CMG, Fig. 73-3). Compliance is the relationship between change in bladder volume and change in Pdet ($\Delta \text{volume}/\Delta \text{pressure}$) and is measured in milliliters per centimeters of H₂O. The ICS recommends two standard points, the Pdet at start of bladder filling (usually zero) and the Pdet at cystometric capacity or before the start of any detrusor contraction that results in significant leakage (Abrams et al, 2002). Both points are measured, excluding any detrusor contractions. It is difficult to define what "normal compliance" is in terms of milliliters per centimeters of H₂O. Several authors have shown that mean values for compliance in healthy subjects range from 46 to 124 mL/cm H₂O (Sorensen et al, 1988; van Waalwijk van Doorn et al, 1992; Hosker, 2004). However, there is great variation; for example, van Waalwijk van Doorn and colleagues (1992) showed a variation of compliance from 11 to 150 mL/cm H₂O (mean 46 mL/cm H₂O) in 17 healthy subjects. Some of the variation in a "normal" bladder is likely due to the fact that compliance per se depends on bladder capacity. Furthermore, various definitions of impaired compliance have been used (e.g., between 10 and 20 mL/cm H₂O); however, there is not a consistent definition based on milliliters per centimeters of H₂O. Stöhrer and associates (1999) suggest that a value less than 20 mL/cm H₂O is consistent with impaired compliance and implies a poorly accommodating bladder. However, examples can be cited (e.g., small cystometric capacity) in which this may not be the case. Therefore, in practical terms, absolute pressure is probably more useful than a compliance number or value. For example, it has been shown that storage greater than 40 cm H₂O is associated with harmful effects on the upper tract (McGuire et al, 1981) (Fig. 73-5). Also, depending on the clinical scenario, a particular compliance in terms of milliliters per centimeters of H₂O can mean very different things (Fig. 73-6). As a general rule, prolonged storage at high pressures can lead to upper tract deterioration. Elevated

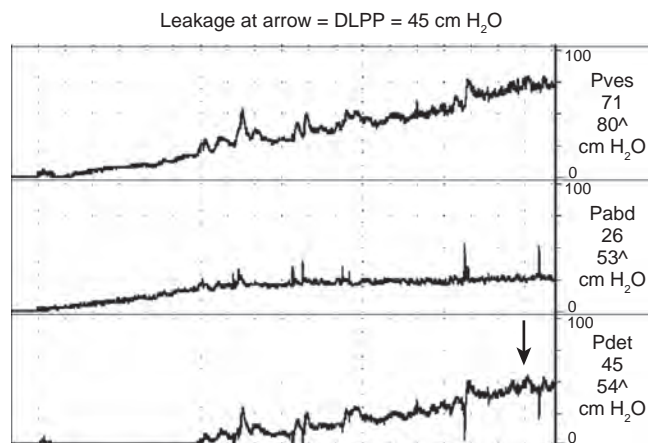


Figure 73-5. Impaired compliance. Note the rise in Pves (and Pdet) with bladder filling. The Pdet at the end of filling is approximately 45 cm H₂O, which is a potentially dangerous situation. In this case the bladder was filled to a volume of 300 mL, so the compliance is 6.67 mL/cm H₂O. The arrow is the point at which incontinence was demonstrated, which is the detrusor leak point pressure (DLPP).

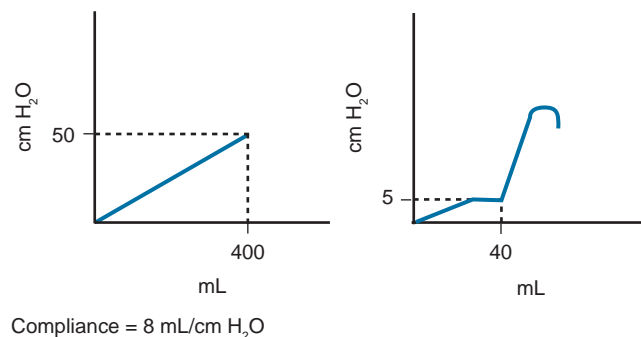


Figure 73-6. A problem with measuring compliance. Two theoretical cystometrography (CMG) images are shown. The one on the left demonstrates impaired compliance with a constant rise in Pdet throughout filling. At 400 mL the Pdet is 50 cm H₂O (8 mL/cm H₂O), a dangerous situation. There is significant storage time in which the Pdet is greater than 40 cm H₂O. The CMG on the right could represent a small capacity bladder with detrusor overactivity and precipitant micturition. At a volume of only 40 mL, an involuntary detrusor contraction occurs. The Pdet just before this was only 5 cm H₂O. The calculated compliance would be 6 mL/cm H₂O, the same as the one on the left. Yet the CMG on the right does not demonstrate a dangerous situation, just a highly symptomatic (incontinent) patient.

storage pressures and impaired compliance should be interpreted in the context of the clinical scenario. It appears that conventional CMG may provoke filling pressures higher than natural filling in some cases. Robertson (1999) showed that for six patients with neuropathic bladder and severely impaired compliance on conventional CMG, compliance was actually normal on ambulatory monitoring with natural filling.

Impaired compliance is seen in a variety of neurologic conditions (spinal cord injury/lesion, spina bifida) and usually results from increased outlet resistance (e.g., detrusor external sphincter dyssynergia [DESD]) or decentralization in the case of lower motor neuron lesions. It also can result from long-term BOO (e.g., from benign prostatic obstruction) (Leng and McGuire, 2003) or structural changes such as radiation cystitis or tuberculosis. Impaired compliance with prolonged elevated storage pressures is a urodynamic risk factor and usually needs to be treated to prevent renal damage (see Box 73-1).

The measurement of compliance can be affected by a number of factors. Sometimes an increase in Pdet during CMG is seen as a result of rapid filling (filling during CMG is almost always faster than physiologic filling). This is more of an accommodation problem than a true decrease in compliance. When Pdet is seen to be rising, filling may need to be stopped or reduced to see if the effect is real. An IDC, particularly if of a sustained and low amplitude, can be confused with impaired compliance. If filling is stopped, and the pressure returns to baseline, the compliance is not impaired. Finally there are a number of pop-off mechanisms that can make compliance seem better than it actually is. Vesicoureteral reflux (VUR) and bladder diverticulum are two examples. With VUR, pressure is actually transferred to the refluxing renal unit and may be harmful. We have seen instances in which the upper tract holds more urine than the bladder. VUDS (see later) is very useful in these cases. A bladder diverticulum is actually part of the bladder, and thus it may provide a protective effect for the upper tracts. Finally, an incompetent outlet may be a pop-off mechanism. This may become apparent only when outlet resistance is increased. This can be done during CMG by occluding the outlet, but may not be seen until the outlet resistance is surgically increased (e.g., with an artificial urinary sphincter or sling procedure).

Leak Point Pressures

There are two distinct types of leak point pressures that can be measured in the incontinent patient: ALPP and detrusor leak point pressure (DLPP). The two are independent of each other and conceptually measure completely different things.

ALPP is a measure of sphincter strength or the ability of the sphincter to resist changes in Pabd (McGuire et al, 1993). ALPP is defined as the intravesical pressure at which urine leakage occurs as a result of increased Pabd in the absence of a detrusor contraction (Abrams et al, 2002). This measure of intrinsic urethral function is applicable to patients with stress incontinence. An ALPP can be demonstrated only in a patient with SUI. Conceptually, the lower the ALPP, the weaker is the sphincter. There is no normal ALPP, because patients without stress incontinence will not leak at any physiologic Pabd. ALPP should be measured as the total Pabd required to cause leakage, not the change in pressure (McGuire et al, 1993). Therefore, if ALPP is measured in the standing position, it should include the baseline Pabd (or Pves), which is usually approximately 20 to 40 cm H₂O. Classically, the reading is taken from the Pves channel as long as there is no involuntary contraction (Fig. 73-7). In cases in which patients do not leak with a urethral catheter in place, the ALPP can be measured from the Pabd channel either rectally or vaginally (Stöhrer et al, 1999). The original description of ALPP was done at an arbitrary

bladder volume of 150 mL; however, in some cases it is necessary to fill the bladder more. The volume at which ALPP is determined should be noted, because some investigators have found that it decreases at higher volumes (Faerber and Vashi, 1998). As a general rule, we will start testing at 150 mL and then every 50 mL thereafter until SUI is demonstrated. If no SUI is demonstrated at capacity, the urethral catheter is removed and ALPP is measured via the rectal catheter (provided there is no increase in Pdet from DO or impaired compliance).

Attempts have been made to quantify intrinsic sphincter deficiency (ISD) in women using ALPP. In 1993, McGuire and associates measured ALPP in 125 women with SUI. When the ALPP was less than 60 cm H₂O, all patients had high-grade incontinence, with 81% having continuous leakage and 75% having a fixed urethra (no urethral hypermobility). When ALPP was between 61 and 89 cm H₂O, 80% had pronounced urethral hypermobility and moderate to high-grade incontinence. When ALPP was 90 cm H₂O or greater, patients had lesser grades of incontinence and minimal to gross urethral hypermobility. The inference is that:

ALPP < 60 cm H₂O signifies ISD

ALPP between 60 and 90 cm H₂O is equivocal
(there is a component of ISD)

ALPP > 90 cm H₂O indicates little or no ISD

Current technology does not permit a method to distinguish between ISD in the face of urethral hypermobility in women. Therefore, although these ALPP values are often used as guidelines, they should be interpreted with caution. For example, if there is no urethral hypermobility, SUI must be caused by ISD, regardless of the ALPP. Furthermore, Fleischmann and colleagues (2003) found that urethral hypermobility was equally common in women with lower versus higher ALPP. ISD and urethral hypermobility may coexist, and they do not define discrete classes of patients with SUI. Thus an isolated measure of ALPP without considering other factors such as CMG and urethral mobility is of limited utility in predicting success for commonly performed female SUI procedures (Hosker et al, 2009; Rosier et al, 2013). The use of ALPP in the diagnosis and treatment of female SUI is discussed further in that section (see later).

The term ALPP has been used interchangeably with Valsalva leak point pressure (VLPP); however, this is not entirely correct. An ALPP can be measured during UDS testing by a voluntary Valsalva maneuver (VLPP) or by a cough (cough leak point pressure [CLPP]). In the same person, VLPP tends to be significantly lower than CLPP. Therefore exact terminology and methods should be used when describing an ALPP. ALPP also can be influenced by the presence or the size of a urethral catheter (Bump et al, 1995; Huckabay et al, 2005; Türker et al, 2010). It has been shown in women with SUI that the larger the catheter, the lower the ALPP. ALPP also can be measured without a urethral catheter by assessing the Pabd via a rectal (or vaginal catheter). It has been shown that 15% of women with SUI (Türker et al, 2010) and 35% of men with SUI after prostatectomy (Huckabay et al, 2005) will demonstrate an ALPP only with the urethral catheter removed.

The second type of leak point pressure is the DLPP, which is a measure of Pdet in a patient with decreased bladder compliance. It is defined as the lowest Pdet at which urine leakage occurs in the absence of either a detrusor contraction or increased Pabd (Abrams et al, 2002) (see Fig. 73-5). The higher the urethral resistance, the higher the DLPP will be. One can imagine that in a poorly compliant bladder, if outlet resistance is low, incontinence will occur at a relatively low or "safe" pressure. However, if outlet resistance is high, the pressure in the bladder will continue to increase as the bladder fills. There is potentially less incontinence, but eventually the pressure is transmitted to the upper tracts (Fig. 73-8).

From a clinical perspective, DLPP is most useful in patients with upper motor neuron lesions with high storage pressures (usually secondary to DO and DESD), in patients with lower motor neuron

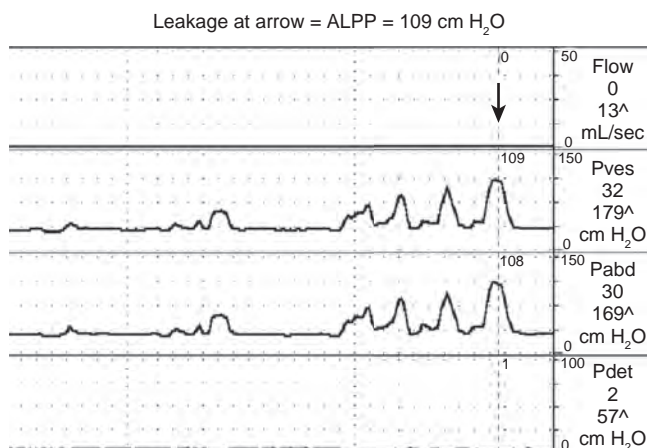


Figure 73-7. Abdominal leak point pressure measurement (ALPP). After progressive Valsalva maneuvers, leakage is demonstrated on the last one at 109 cm H₂O (arrow). There is no rise in Pdet.

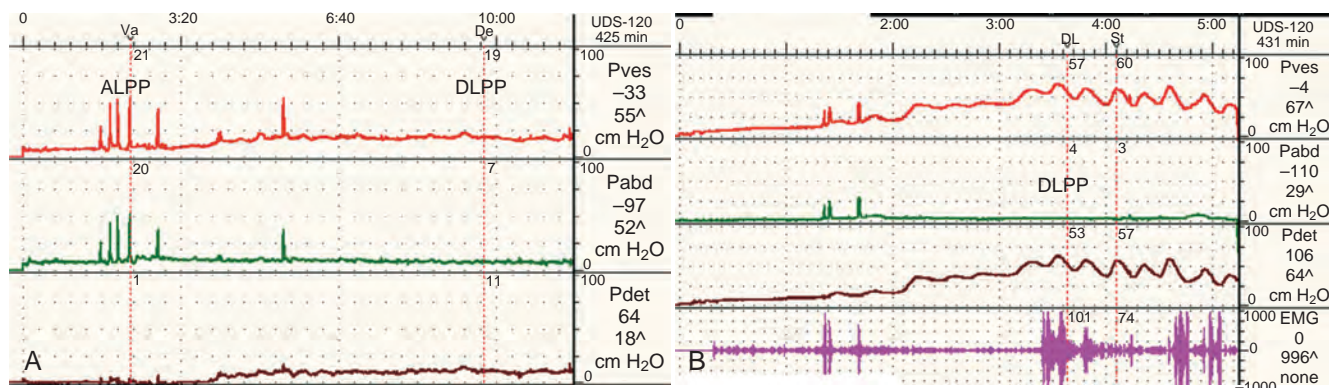


Figure 73-8. Outlet resistance causes impaired compliance. Urodynamics (UDS) studies of two children with the same neurologic problem and symptoms, but dramatically different findings. **A**, UDS tracing of a young boy with spina bifida who is incontinent between catheterizations. The study shows a low-pressure system with poor outlet resistance and stress incontinence (abdominal leak pressure point [ALPP] demonstrated) and a low detrusor leak pressure point (DLPP). His upper tracts are protected. **B**, UDS tracing of a young girl with spina bifida who is incontinent between catheterizations. The study shows a high-pressure system with strong outlet resistance and a high DLPP. There was no stress incontinence. Her upper tracts are at risk. The difference in these two cases is difference in storage pressures caused by the difference in outlet resistance.

disease causing “decentralization,” and in non-neurogenic patients with low bladder compliance (after multiple bladder surgeries, radiation, and tuberculous cystitis). The higher the DLPP, the more likely is upper tract damage as intravesical pressure is transferred to the kidneys. McGuire and associates (1981) documented the deleterious effects that a high DLPP has on the upper urinary tracts; a DLPP greater than 40 cm H₂O resulted in hydronephrosis or VUR in 85% of myelodysplastic patients. Although 40 cm H₂O clearly appears to be detrimental in the pediatric population that was studied, most experts would agree that there is limited evidence that an absolute cutoff of 40 cm H₂O should be used to determine a “safe” storage pressure. In reality, when treating impaired compliance, expert opinion leans toward the concept of aiming for as low a pressure as is “reasonably achievable” (Rosier et al, 2013). This would be considerably below 40 cm H₂O in most cases.

The significance of an elevated DLPP is that bladder pressures are getting too high before the pop-off mechanism of urethral leakage occurs. In most cases treatment is aimed at lowering bladder pressures so the DLPP is never reached. In some cases DLPP can be lowered by decreasing outlet resistance—for example, with a sphincterotomy in a patient with DESD.

In summary, ALPP and DLPP, although both called *leak point pressure*, are completely different. The ALPP measures the sphincter response to increased Pabd. The lower the ALPP, the weaker the sphincter. The DLPP measures the injured bladder response to increased outlet resistance. The higher the resistance (e.g., DESD), the higher the DLPP, which is potentially dangerous to the upper tracts.

Stress-Induced Detrusor Overactivity

Sometimes DO can be triggered by a rise in Pabd (Fig. 73-9). Thus the symptom may appear to be stress incontinence, but the condition causing the symptom is actually an involuntary contraction, not sphincteric weakness. In a patient with stress-induced DO (SIDO) it is important to note if there is also urodynamic SUI and/or DO independent of the SIDO.

Occult Stress Incontinence

Stress incontinence on prolapse reduction, also referred to as *occult incontinence* or *latent stress incontinence*, is stress inconti-

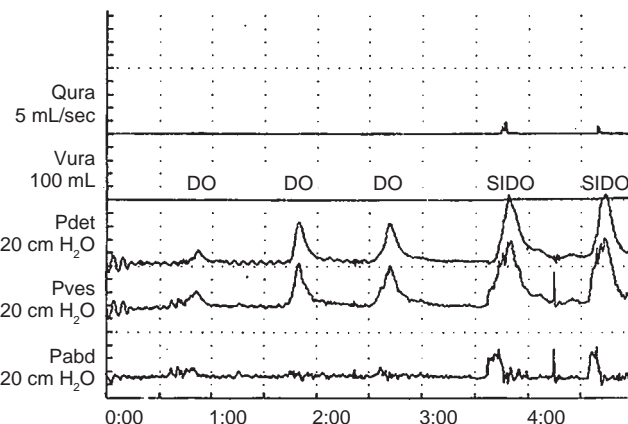


Figure 73-9. Stress-induced detrusor overactivity (SIDO). In this case, there are three episodes of detrusor overactivity (DO) preceding two episodes of SIDO. In the case of SIDO, note that as Pabd increases so does Pves. Shortly after this, Pdet rises and continues long after Pabd returns to baseline. With both episodes of SIDO, incontinence occurred, as can be seen on the flow (Qura) curve. Vura, urine volume voided. (From Nitti VW. Cystometry and abdominal pressure monitoring. In Nitti VW, editor. Practical urodynamics. Philadelphia: Saunders; 1998. p. 38–51.)

nence that is demonstrated in a clinically continent woman with pelvic prolapse, only when the prolapse is reduced (Ballert et al, 2009; Haylen et al, 2010). Prolapse reduction can be done with a pessary, packing, forceps, or manually. Technically, if this is demonstrated during urodynamic testing, it may be referred to as *urodynamic occult SUI*.

Urethral Pressure Profilometry

The method of urethral pressure profilometry (UPP) was popularized by Brown and Wickman in 1969 using a small catheter with lateral apertures through which fluid is continuously infused. Simultaneous bladder and urethral pressure is measured as the catheter is slowly withdrawn along the course of the urethra. The urethral pressure transducer measures the fluid pressure required to

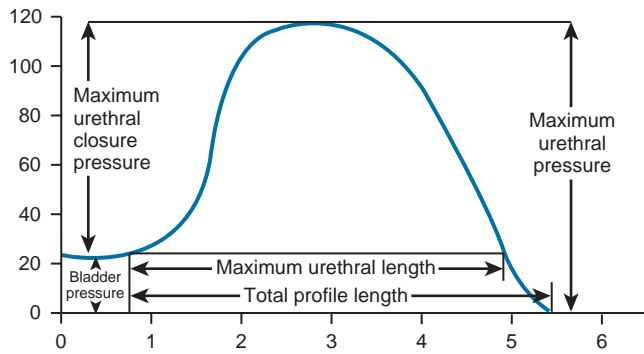


Figure 73-10. Urethral pressure profile with appropriate parameters identified.

lift the urethral wall off the catheter side holes and thus elevates the circumferential and radial stresses induced by the presence of the catheter in the urethra and the slow urethral profusion. Thus urethral pressure is defined as the fluid pressure needed to just open a closed urethra (Abrams et al, 2002). Accurate measurements are recorded only in cases in which the urethra is distensible and therefore able to create a perfect seal.

Despite an abundant literature on urethral profilometry, its clinical relevance is controversial. Many urologists do not routinely perform urethral profilometry. The UPP represents the intraluminal pressure along the length of the urethra in graphic form (Fig. 73-10). Several parameters can be obtained from the UPP:

- The urethral closure pressure profile is given by the subtraction of intravesical pressure from urethral pressure.
- Maximum urethral pressure is the highest pressure measured along the UPP.
- Maximum urethral closure pressure (MUCP) is the maximum difference between the urethral pressure and the intravesical pressure.
- Functional profile length is the length of the urethra along which the urethral pressure exceeds intravesical pressure in women.

In most continent women the functional urethral length is approximately 3 cm and the MUCP is 40 to 60 cm H₂O, but normal values vary widely. MUCP also has been used to define ISD. McGuire (1981) performed a retrospective evaluation of women who failed SUI surgery and found that a preoperative MUCP of 20 cm H₂O or less resulted in higher surgical failure rates. These patients represented a specific subtype of SUI caused by a fixed, open urethra (type III SUI). In 1992, the term was redefined as ISD. Many authors have used the definition of MUCP of 20 cm H₂O or less to define ISD; however, this definition has many of the same problems as ISD definitions for ALPP. Another caveat of UPP is that its measurement does not diagnose stress incontinence and SUI is not required to measure it (contrary to ALPP). MUCP in incontinent women has been shown to be lower than in continent women, but there is certainly overlap (Schick et al, 2004). In addition, MUCP is not always indicative of the severity of incontinence. For example, there is a difference between the urethra of an incontinent patient whose MUCP was 38 cm H₂O and that of a continent woman with the same MUCP.

In 2002, the ICS standardization subcommittee concluded that the clinical utility of urethral pressure measurement is unclear (Lose et al, 2002). Furthermore, there are no urethral pressure measurements that (1) discriminate urethral incompetence from other disorders; (2) provide a measure of the severity of the condition; or (3) provide a reliable indicator to surgical success and return to normal after surgical intervention (Lose et al, 2002). In 2013, Rosier and associates reported that since the 2002 ICS report there is no new evidence, nor evidence regarding newer techniques, that intrinsic urethral pressure measuring quality has improved to a clinically relevant level with regard to sensitivity, specificity, and reliability.

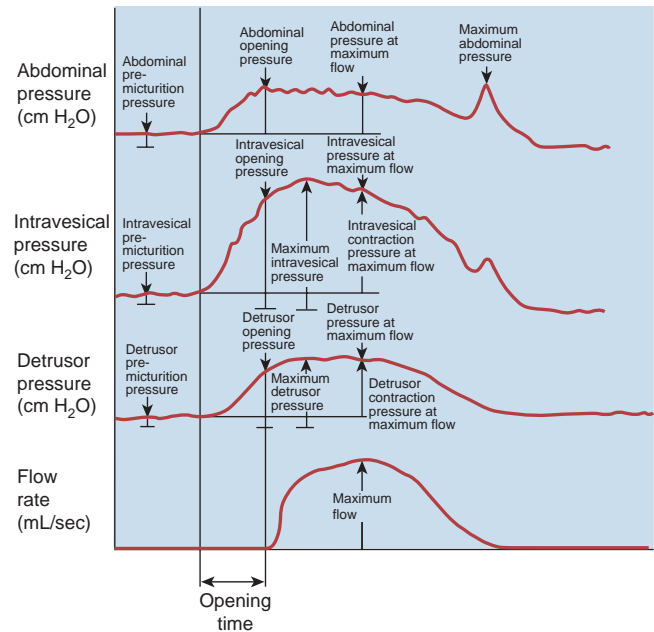


Figure 73-11. Schematic pressure flow study labeled with recommended terminology.

VOIDING AND EMPTYING PHASE

Normal Voiding and Emptying

Evaluation of the voiding phase provides an assessment of both detrusor contractility and bladder outlet resistance, the two parameters that are critical for normal bladder emptying. In simple terms, abnormalities of bladder emptying are caused by “overactivity” of the bladder outlet (too much outlet resistance), “underactivity” of the detrusor (weak detrusor contraction force, short detrusor contraction duration, impaired contraction velocity), or a combination of both. The simultaneous measurement of Pdet and urinary flow rate during voluntary voiding, known as a pressure-flow study, is the most accurate way to access these two critical parameters (Fig. 73-11).

To understand the relationship between bladder contractility and outlet resistance, one must start with an understanding of the normal micturition process. Normal voiding is accomplished by activation of micturition reflex, which involves the following (Fig. 73-12):

1. Relaxation of striated urethral sphincter
2. Contraction of detrusor muscle
3. Opening of vesical neck and urethra
4. Onset of urine flow

This occurs as a result of coordination between pontine and sacral micturition centers with suprapontine input that allows for voluntary control of the micturition reflex.

UDS can evaluate the critical parameters during the voiding phase, which include detrusor contractility, relaxation of the bladder outlet, and coordination of sphincters (Fig. 73-13).

According to the ICS, normal detrusor function is characterized by a voluntarily initiated continuous contraction that leads to complete bladder emptying within a normal time span and in the absence of obstruction. DU is defined as when there is a contraction of reduced strength and/or duration resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span. Finally, an acontractile detrusor is when there is no demonstrable contraction during UDS (Abrams et al, 2002). The term *areflexia* has been used in the case of a neurologic cause of an acontractile detrusor, but it is now suggested that this be replaced by *neurogenic acontractile detrusor*, when appropriate (Haylen et al, 2010).

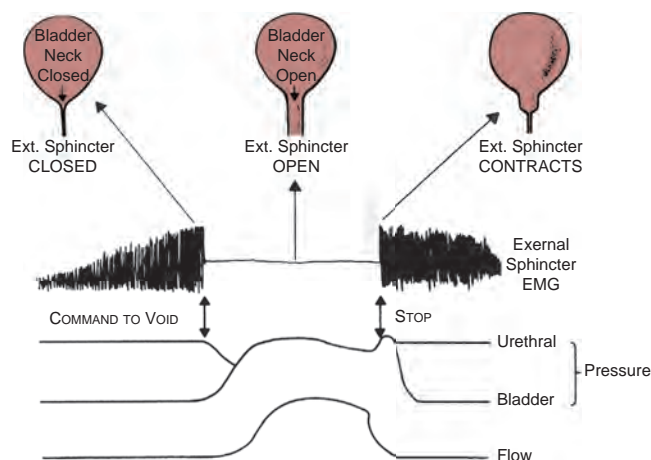


Figure 73-12. Physiology of micturition. See text for details. EMG, electromyography; ext, external. (From Blaivas JG. Pathophysiology of lower urinary tract dysfunction. Clin Obstet Gynaecol 1985;12:295–309.)

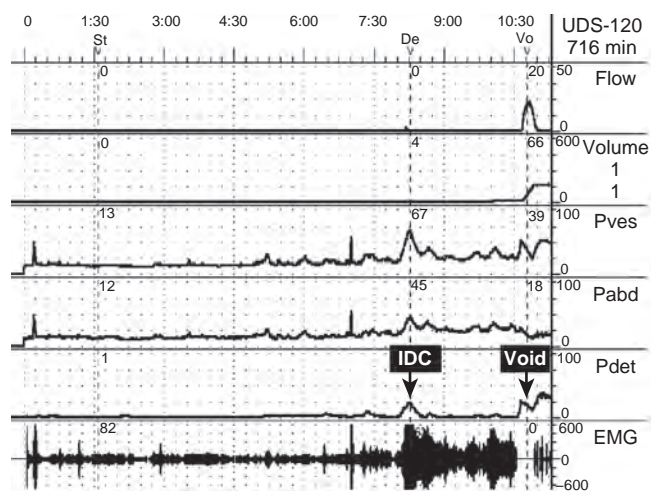


Figure 73-13. Multichannel urodynamics study showing filling and voiding phases with pressure and electromyography (EMG) readings. In this case, the patient experienced an involuntary detrusor contraction (IDC), which led to increased external sphincter contraction and an increase in EMG activity (guarding reflex). However, shortly after that the patient is given permission to void. First there is quieting of the EMG (sphincter relaxation) followed by an increase in Pdet and volitional voiding with a normal appearing uroflow curve.

The current definition of *detrusor underactivity* is hampered by the subjective interpretation of what constitutes reduced strength, reduced length of contraction, or prolonged emptying (Osman et al, 2014). Normal detrusor function and DU are somewhat nebulously defined in terms of absolute pressure because bladder pressure is influenced by outlet resistance. When evaluating detrusor function urodynamically, UDS must be correlated with clinical findings. For example, if a patient who normally voids is unable to void during a UDS study, a definitive diagnosis of acontractile detrusor cannot be made. Specific measures of detrusor contractility are mentioned later in the text.

Urinary flow rate in combination with PVR is a useful clinical tool to assess emptying. Reduced flow rate or elevated PVR indicates that emptying is not complete but does not inform as to why (e.g., obstruction vs. impaired contractility). Flow rate also depends on voided volume because there is a linear relationship between Qmax and voided volume, with a voided volume above and a hyperbolic relationship below a voided volume of 150 mL (Drach et al, 1979).

Therefore many authors recommend a minimum voided volume of 150 mL to accurately assess uroflow. However, establishing a minimum voided volume puts major limitations on uroflowmetry because any patients with voiding dysfunction do not routinely void large enough volumes to be evaluable. The corrected form of Qmax—Qmax divided by the square root of voided volume—may provide useful information in such patients (Boone and Kim, 1998). Over the years several nomograms have been developed to define normal flow rates for a specified population and correct for voided volume. These include the Siroky nomogram (Siroky et al, 1979, 1980) for men and the Liverpool nomogram (Haylen et al, 1989) for men and women.

The **bethanechol supersensitivity test** has been used to help distinguish the cause of DU as neurogenic or myogenic. It is based on the Cannon law of denervation, which states that denervated structures develop increased sensitivity to chemical stimulation. This concept was applied to the bladder by Lapidès and associates (1962). The original bethanechol supersensitivity test described by these authors was performed by infusing liquid at a rate of 1 mL/sec to a volume of 100 mL, where the pressure is measured. This can be done up to three times and the pressure values averaged. The patient is then given 2.5 mg of bethanechol chloride (later revised to 0.035 mg/kg) subcutaneously and the study is repeated at 10, 20, and 30 minutes. A normal bladder (or myogenically impaired bladder) should show an increase of less than 15 cm H₂O above control value at 100 mL at 30 minutes. This is considered a negative study result. A positive study result, indicating a sensory or motor paralytic bladder, is a response of at least 15 cm H₂O above the control value. More recent studies have indicated that the bethanechol supersensitivity test is rather unreliable in predicting neurogenic bladder. Blaivas and colleagues (1980) reported only 76% sensitivity and 50% specificity in doing this. Another problem is that even if the test is able to differentiate between neurogenic and myogenic dysfunction, treatment is often the same (e.g., clean intermittent catheterization). Bethanechol chloride, whether administered subcutaneously or orally, has not proved to be a consistently effective treatment for the underactive detrusor (Wein et al, 1978, 1980). In addition a positive test does not predict improved voiding when it is used therapeutically. Therefore we feel that there is a very limited role for the use of the bethanechol supersensitivity test.

Voiding Pressure-Flow Studies

Once the bladder is filled to cystometric capacity, the voiding portion of the pressure-flow study can begin. This examines the emptying phase of micturition. The same bladder and rectal (or vaginal catheter in women) catheters are used while simultaneously collecting pressure data along with uroflowmetry. Ideally, such a study should assess a voluntary void. When there is flow of urine during an IDC, patients may contract the pelvic floor to prevent leakage. Such an event should be annotated on study. In addition, some patients may have a difficult time voiding on demand in a public setting and with invasive monitoring in place. These stressors and the artificial environment of the testing need to be accounted for when interpreting the test.

As mentioned previously, Pdet during voiding is a function of outlet resistance. For a normal detrusor, the greater the outlet resistance, the higher the Pdet during voiding will be. This is accompanied by a reduced flow rate. A healthy bladder is able to overcome obstruction by contracting more forcefully, and although flow may be slower the bladder is able to empty itself. Over time, the detrusor may decompensate and may no longer be able to generate the necessary pressure to overcome obstruction. When this occurs the result will be incomplete bladder emptying or retention of urine.

The voiding pressure-flow study helps assess two critical parameters related to the bladder and bladder outlet: detrusor activity (normal vs. impaired) and outlet resistance (obstructed vs. unobstructed). In general the pressure-flow study can identify the following three fundamental conditions:

1. Low (or normal) Pdet and high (or normal) flow rate (normal, unobstructed voiding)
2. High Pdet and low (or normal) flow rate (obstruction)
3. Low Pdet with low flow rate (DU)

It is important to remember that these three categories are broad and general and a final diagnosis should be made after considering UDS findings and the patient's clinical presentation (see later). It is also important to note that in cases of DU (i.e., low Pdet and low flow) obstruction may coexist with DU, but making the urodynamic diagnosis of obstruction may not be possible if the detrusor is too decompensated.

The urodynamic manifestation of BOO is high-pressure and low-flow voiding (or more practically speaking increased pressure and reduced flow). Over time, if bladder decompensation results, DU or impaired contractility can result.

To use the common measures of obstruction and impaired contractility that are used today it is important to understand basic bladder output and urethral resistance relations (URRs). Attempts to mathematically define urethral resistance date back to 1962 (Gleason and Lattimer, 1962). Early equations calculating urethral resistance followed standard hydrodynamic formulae calculating outlet resistance. These concepts failed to consider that the urethra is not a rigid tube but rather has an active and distensible nature. They also failed to consider the importance of bladder volume. Rigid tube hydrodynamics were abandoned in favor of more dynamic ways to analyze micturition. In 1972, Griffiths introduced bladder output relation (BOR), which depicts the interrelations between bladder pressure and uroflow at a given volume and essentially measures the function of the bladder independent of the function of the urethra (Griffiths, 1973). Griffiths further defined a method to evaluate urethral resistance independent of bladder function, the URR. According to this relation, as bladder pressure rises the flow rate will be zero until the intrinsic bladder pressure equals the intrinsic urethral pressure. At this point flow will start and the flow rate will rise rapidly, with further increases in the intrinsic bladder pressure. If pairs of simultaneously measured values of Pdet and flow rate are plotted against one another throughout the course of a micturition event, a curve is obtained that shows the resistance to flow independent of detrusor function, representing the URR. If the urethra were relaxed or tightened during voiding, the URR would move toward the left or right, respectively. Because the BOR represents the function of the bladder independent of the urethra and the URR depicts urethral function independent of bladder function, the actual Pdet and flow rate are determined by the intersection of the BOR and the URR, which is the point at which intrinsic bladder pressure equals urethral pressure (Fig. 73-14). A change in one of these relations during micturition would not affect the curve representing the other relation but would result in the point of intersection to moving along that curve.

In cases of suspected DU a stop test can be performed. This is done by voluntary or mechanical interruption of urine flow during voiding (i.e., occluding the urethra). This allows for an estimation of isovolumetric Pdet (Piso) (Sullivan and Yalla, 2007). In a voluntary stop test, patients interrupt flow midstream by contracting the external urethral sphincter. In a mechanical stop test, interruption involves blocking the urethra by pulling a catheter balloon against the bladder neck during midstream or clamping or squeezing the urethra. In a continuous occlusion test, the outflow is occluded before the onset of detrusor contraction and the patient is asked to void against the occlusion. The three techniques show good correlation with each other in both men (Sullivan et al, 1995) and women (Tan et al, 2003). However, the voluntary stop test gives a lower Piso than the other two (Sullivan et al, 1995).

Bladder Outlet Obstruction and Detrusor Underactivity in Men

The value of making a precise diagnosis of obstruction in men comes from the assumption that the outcomes of surgery to treat benign prostatic hyperplasia (BPH) and its consequent LUTS are

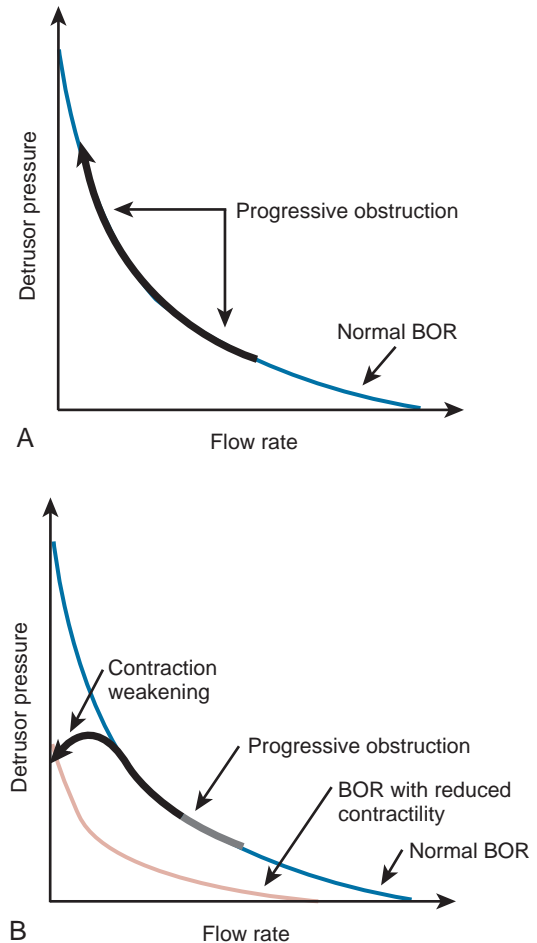


Figure 73-14. Relationship between Pdet and flow in a given person—the bladder outlet relation (BOR). See text for details. (From Griffiths DJ. The mechanics of the urethra and of micturition. *Br J Urol* 1973;45:497–507.)

improved when obstruction can be documented. BPH and benign prostatic obstruction (BPO) are highly prevalent conditions, so it was intuitive to use them as a model for defining obstruction. Most of the analytical work has focused on defining obstruction-based pressure-flow studies. Three well-known nomograms based on pressure-flow studies have been described to diagnose men as obstructed, equivocal, or unobstructed. These are the Abrams-Griffiths nomogram (Abrams and Griffiths, 1979), the Urethral Resistance Factor (URA) (Griffiths et al, 1989), and the Linear Passive Urethral Resistance Relation or Schafer nomogram (Schafer, 1990). The categories of obstruction described in these nomograms are based on observations of men who underwent surgery for LUTS (mainly TURP). After surgery the Pdet at maximum flow (PdetQmax) was reduced in the obstructed group, reduced unpredictably in the equivocal group, and unchanged in the unobstructed group. Subsequently, Lim and Abrams (1995) showed that patients were similarly classified by all three methods. They described a number, the Abrams-Griffiths (AG) number (now known as the bladder outlet obstruction index [BOOI]) derived from the equation for the slope of the line dividing obstructed from equivocal in the Abrams-Griffiths nomogram, which is the same line dividing obstructed from slightly obstructed in the Schafer nomogram: $BOOI = PdetQ_{max} - 2(Q_{max})$. Subsequently Griffiths and colleagues (1997) (Fig. 73-15) described the ICS provisional nomogram, which is now suggested for use for the diagnosis of obstruction in men with LUTS suggestive of BPH (Abrams, 1999). Men are considered obstructed if the BOOI is 40 or greater, unobstructed if the BOOI is 20 or less, and equivocal if the BOOI is 20 to 40.

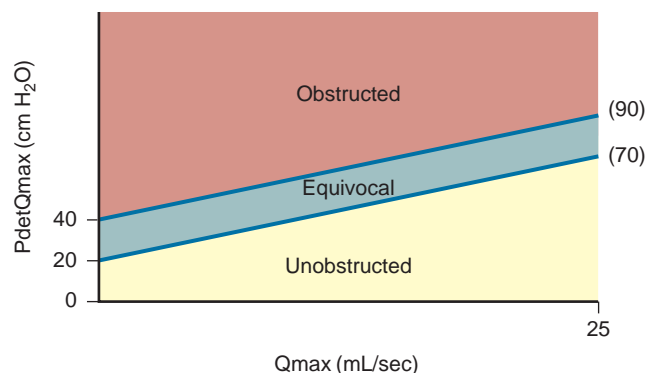


Figure 73-15. The Provisional International Continence Society nomogram. See text for details.

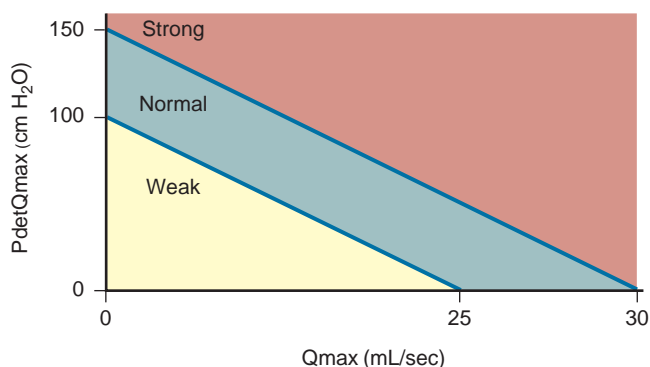


Figure 73-16. The Bladder Contractility Nomogram. See text for details.

Voiding pressure-flow studies show consistent reproducibility in the diagnosis of BOO in men. In a review of the topic, [Abrams and colleagues \(2001\)](#) concluded that random variations of approximately 9 to 14 cm H₂O in pressure measurement and approximately 0.4 to 2 mL/sec in maximum flow rate occur. In repeated studies during the same session there is usually a systematic decrease of up to 4 cm H₂O in Pdet and 0.4 mL/sec in maximum flow rate. These variations have little clinical importance because they cause only 10% to 16% of patients to change classification on the ICS nomogram, and in all but approximately 1% that change is only by 1 class (e.g., from equivocal to unobstructed or from obstructed to equivocal).

Although much effort has focused on defining outlet resistance (i.e., obstruction), an index for bladder contractility also can be derived from the contractility groups [Schafer \(1995\)](#) described (strong, normal, weak, very weak). The slope of Schafer's lines, now known as the bladder contractility index (BCI), is given by the formula: $PdetQmax + 5(Qmax)$ ([Abrams, 1999](#)). Strong contractility is a BCI greater than 150, normal contractility with a BCI of 100 to 150, and weak contractility with a BCI of less than 100 ([Fig. 73-16](#)). The BCI is the most common measure of bladder contractility used today because of its easy calculation and relationship to the BOOI and ICS nomogram.

Although contractility and obstruction can be independently measured, it is sometimes impossible to diagnose obstruction in the face of DU using the ICS or other nomograms. For example, to make a diagnosis of unequivocal obstruction, BOOI must be at least 40 cm H₂O. That means that a Pdet of at least 40 cm H₂O must be generated and that assumes flow is zero. If the Qmax is 5 mL/sec, then PdetQmax must be at least 50 cm H₂O. Thus the ICS nomogram can exclude obstructed patients whose impaired contractility is the result of long-term obstruction. In such cases clinical judgment becomes important.

Another measure of detrusor function is the Watts factor (WF), a quantification of detrusor power by a formula that estimates the power per unit area of bladder surface generated by the detrusor, corrected for the finite power required for either isometric contraction or for shortening against no load.

$$WF = [(Pdet + a)(Vdet + b) - ab] / 2\pi$$

where Vdet represents detrusor shortening velocity and a and b are fixed constants ($a = 25$ cm H₂O; $b = 6$ mm/sec), obtained from experimental and clinical studies ([Griffiths, 1991](#)).

Because Pdet and velocity vary during the voiding phase, so too does the WF. Two points have been proposed as the most representative of detrusor contractility: the maximum WF (WFmax) ([Griffiths et al, 1989](#)) and the WF at maximum flow (Wqmax). An advantage of the WF calculation is that it depends minimally on bladder volume ([Griffiths, 1991](#)) and is not affected by the presence of BOO ([Lecanwasam et al, 1998](#)). However, it does not provide a measure of contraction sustainability and involves a complex calculation, limiting its use in clinical practice ([Osman et al, 2014](#)). In addition, threshold values for normal have not been validated; however, some have suggested using a Wmax value of 7.0 W/m² ([van Koeveeringe et al, 2011](#)).

BOO is associated with abnormalities of storage as well. This is presumably due to changes in ultrastructure that occur with obstruction. DO and impaired compliance occur in conjunction with obstruction. For example, approximately two thirds of men with symptomatic BPO have DO that resolves 50% to 67% of the time with treatment of obstruction ([Abrams et al, 1979](#)). Reduced compliance is also associated with obstruction and has been shown to improve with treatment of obstruction (TURP) ([Leng and McGuire, 2003](#)).

An alternative to voiding pressure-flow studies as a way of measuring outlet resistance is the micturitional urethral pressure profile (MUPP), or voiding profilometry. This technique, popularized by [Yalla and colleagues \(1980, 1981\)](#), can both diagnose and localize obstruction. The MUPP is performed with a triple-lumen catheter under fluoroscopic guidance, similar to the static UPP described previously. During voiding the catheter is slowly withdrawn and the pressure is measured from the bladder neck through the anterior urethra ([Steele et al, 1998](#)). Normally, during voiding the pressure in the bladder is isobaric with the prostatic urethra and then pressure decreases across the membranous urethra and gradually decays along the rest of the anterior urethra. The membranous urethra is the narrowest segment of the bladder outlet during voiding, which accounts for the expected pressure drop of 20 to 30 cm H₂O. In patients with obstruction secondary to BPH, the MUPP is quite different. A pressure disparity somewhere along the prostatic urethra typically will be seen. When this pressure disparity is greater than 5 cm H₂O, obstruction at the point of pressure drop is present. MUPP has been shown to be as effective in diagnosing BOO as standard pressure-flow studies ([DuBeau et al, 1995](#)). An analysis of patients with symptomatic BPH has shown that successful treatment outcomes have been achieved with treatment based on MUPP results ([Lecanwasam et al, 1994](#)).

In cases in which it is difficult to differentiate obstruction from DU by standard pressure-flow dynamics (e.g., in men with inefficient emptying in whom neither obstruction nor DU can be diagnosed by standard pressure-flow studies), Piso can be measured by a stop test (see earlier discussion). In men a Piso less than 50 cm H₂O is uncommon and has been considered to be diagnostic of DU ([Comiter et al, 1996](#); [Sullivan and Yalla, 1996](#)).

Bladder Outlet Obstruction in Women

BOO in women can present more of a diagnostic dilemma than in men. Because there is no highly prevalent condition (such as BPH) that causes female obstruction it is difficult to establish nomograms. Furthermore, nomograms derived for men cannot be applied to women because voiding dynamics differ. In addition, anatomic differences allow many women to empty their bladders by simply

relaxing the pelvic floor and some will augment voiding by abdominal straining. Minor elevations in Pdet or decreases in flow rate, which might be considered insignificant in the male population, might signify BOO in women. Accordingly, clinicians must have a high index of suspicion based on the presence of LUTS, incomplete emptying, persistent UTIs, and a history of anti-incontinence surgery, prolapse, or other conditions.

In an effort to develop cutoff values for pressure and flow for the diagnosis of obstruction in women, Chassagne and associates (1998) studied a group of "clinically obstructed women" (after incontinence surgery, secondary to cystocele, or "other etiologies") and compared them to a group of controls (women with stress incontinence). Using receiver operating characteristic (ROC) curve analysis, they found the optimum sensitivity and specificity for predicting obstruction was obtained with a Qmax 15 mL/sec or less and a PdetQmax of 20 cm H₂O or greater (74.3% sensitivity and 91.1% specificity). In 2000, with an expanded population, the authors (Lemack and Zimmern, 2000) revised this to Qmax 11 mL/sec or less and PdetQmax 21 cm H₂O or greater, as optimal for the selection of patients with BOO. In the most recent publication (Defreitas et al, 2004), these authors used normal asymptomatic women as the control group and found the highest sensitivity and specificity for predicting obstruction was obtained with Qmax 12 mL/sec or less and PdetQmax 25 cm H₂O or greater. These cut-point studies have some limitations; namely, obstruction was predefined clinically and only patients with anatomic obstruction were included. Women with functional obstruction (e.g., from primary bladder neck obstruction or dysfunctional voiding) were not included in any of the cut-point analyses. This would be a difficult group of women to define clinically without any testing.

In 1999, Nitti and coworkers showed that the addition of fluoroscopic imaging to UDS was helpful in diagnosing female BOO (see section on VUDS). In this study, patients were classified as obstructed if there was radiographic evidence of obstruction between the bladder neck and distal urethra in the presence of a sustained detrusor contraction of any magnitude. In addition to diagnosing BOO it also localizes the site of obstruction and allows for the diagnosis of obstruction in the face of impaired contractility if indeed the site can be localized. With both the video-urodynamic and cut-points criteria there is a significant difference in mean Qmax and PdetQmax in the group of obstructed versus the group of unobstructed women, but there is a large overlap of values between obstructed and unobstructed patients. This demonstrates that absolute pressure and flow values are imprecise and that another parameter (e.g., radiographic or clinical evidence of obstruction) is necessary for diagnosis.

Blaivas and Groutz (2000) presented a nomogram for defining female BOO. Citing the fact that in their series there was a significantly higher flow rate in the same woman without a catheter, they choose to use noninvasive flow rate in their nomogram. Also, because they found no statistical difference between PdetQmax and Pdetmax in obstructed or unobstructed patients, they chose Pdetmax as the pressure parameter. Using cluster analysis to classify patients with low- and moderate-grade obstruction, they formulated the nomogram. The nomogram places women into four zones: no, mild, moderate, and severe obstruction. An obvious criticism of the nomogram is that it is based on two separate voids (invasive and noninvasive) and one must assume that the pressure characteristics of the void are the same. Akikwala and colleagues (2006) compared the three methods of diagnosing BOO in women and found good concordance between the video-urodynamic and cut-points criteria. They also noted that the Blaivas-Groutz nomogram overdiagnosed obstruction compared to the other two methods.

Obstruction in women cannot be defined by the ICS nomogram or the BOOI because these will grossly underestimate female BOO. This is because normally women void at much lower pressures than men and therefore the obstructed female bladder outlet may not respond as dramatically (or at least with the same pressures) as in males. Unfortunately, there is no condition in women that causes BOO as commonly as BPO in men and therefore creating a consistent standard is difficult. Thus the concepts are the

same (higher pressure and lower flow), but the values are different and less well defined. Those who are interested are referred to suggested readings (Nitti et al, 1999; Blaivas and Groutz, 2000; Defreitas et al, 2004; Akikwala et al, 2006).

Theoretically, one can consider measuring Piso via a stop test in women to measure detrusor strength and help differentiate between DU and obstruction. Piso has not been used to accurately characterize women. However, it is known that in older women Piso values are significantly lower than in men. Tan and colleagues (2003) showed mean Piso in women at least 53 years of age with urgency incontinence was 31.2, 47.2, and 48.7 cm H₂O for voluntary, mechanical, and continuous stop test, respectively.

Sphincter Coordination

The External Sphincter

Normal voiding requires external sphincter relaxation followed by contraction of the detrusor. The external sphincter (and internal sphincter) should remain relaxed until voiding is complete. In normal voluntary voiding, a rise in Pdet is preceded by a fall in urethral pressure and relaxation of the external sphincter as measured by EMG. The sphincter and urethral pressure remain low during voiding and then increase when voiding is completed (Fig. 73-17). Failure of the sphincter to relax or stay completely relaxed during micturition is abnormal (Abrams et al, 2002). Thus normally EMG activity decreases before a voluntary bladder contraction; however, it is not abnormal for EMG activity to increase with an involuntary contraction as part of a guarding reflex to inhibit the IDC (see Fig. 73-13).

There are several abnormalities related to external sphincter relaxation (or lack thereof). DESD occurs when there is an involuntary increase of external sphincter activity associated with DO and also with voiding (Fig. 73-18). It is caused by a neurologic lesion in the suprasacral spinal cord. DESD can produce profound changes as the detrusor involuntarily contracts against a relatively closed sphincter. This will result in high pressures and can even cause impaired bladder compliance over time. Because long periods of elevated Pdet during bladder filling or (abnormally prolonged) voiding put the upper urinary tract at risk (McGuire et al, 1996; Kurzrock and Polse, 1998; Tanaka et al, 1999). DESD may be considered a urodynamic risk factor for upper tract deterioration (see Box 73-1). True DESD occurs only

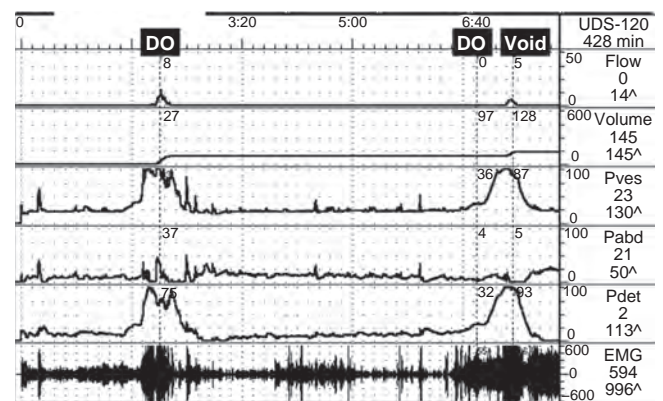


Figure 73-17. Uroynamics (UDS) tracing of a patient with myelodysplasia and neurogenic detrusor overactivity (DO) and detrusor external sphincter dyssynergia (DESD). Note the initial involuntary detrusor contraction associated with DESD and incontinence (measured on the flow channel). With refilling there is again DO with DESD, and then the patient is told to voluntarily void and there is persistent increased electromyography (EMG) activity. As a result there is high-pressure, low-flow voiding (obstruction from the dyssynergic sphincter).



Figure 73-18. Primary bladder neck obstruction in a 35-year-old woman with obstructive voiding symptoms and intermittent urinary retention. Note the failure of the bladder neck to open at all, despite a detrusor contraction of greater than 60 cm H₂O. (From Nitti VW. Primary bladder neck obstruction in men and women. *Rev Urol* 2005;7[Suppl. 8]:S12–7.)

when there is a known neurologic lesion above the sacral micturition center. The higher the lesion, the more likely it is that DESD will occur (Blaivas, 1982). If there is no neurologic lesion, the dyssynergia is considered to be a learned behavior and is known as **dysfunctional voiding**. The term *dysfunctional* describes malfunction (failure to relax or involuntarily contraction of the external sphincter) during the voiding phase only and says nothing about the storage phase (Nevéus et al, 2006). However, it is entirely possible and quite common for a patient to experience storage symptoms (and UDS abnormalities) associated with dysfunctional voiding. Although the condition has been extensively described in children, it also has been described in adult men (Kaplan et al, 1997; Nitti et al, 2001; He et al, 2010) and women (Carlson et al, 2001) and can be a major cause of LUTS. It is recommended that when dysfunctional voiding is diagnosed by UDS, the flow pattern (reduced and/or intermittent) is confirmed by noninvasive uroflowmetry to rule out a test-induced phenomenon (Barrett and Wein, 1981; Carlson et al, 2001). He and colleagues (2010) used the following diagnostic criteria in men: nothing abnormal detected in the history and no symptoms on an examination for neurologic diseases; transient and intermittent closure of the external sphincter during voiding detected by EMG and fluoroscopic cystourethrography; and a higher external sphincter EMG activity with no Pabd increase in the voiding phase. Uroflowmetry was assessed individually to show any discontinuity in a diagram of urinary flow, in conditions with as little external interference as possible.

The Internal Sphincter

Just as there can be a lack of coordination of the detrusor and external sphincter, so too can there be dyscoordination of the internal sphincter or bladder neck. In the case of neurologic disease, if a suprasacral spinal cord lesion is above the level of the sympathetic ganglia (T10 to L1) detrusor internal sphincter dyssynergia may occur in conjunction with external sphincter dyssynergia (Pan et al, 2009). In non-neuropathic men, women, and children the phenomenon of bladder neck dyssynergia or primary bladder neck obstruction is a well-known cause of LUTS, although its exact cause is not known (Diokno et al, 1984; Norlen and Blaivas, 1986; Combs et al, 2005). Conditions of internal sphincter dysfunction require VUDS for an exact diagnosis and are described in the next section.

KEY POINTS: URODYNAMICS PARAMETERS

- Normally, Pdet should remain near zero during the entire filling cycle until voluntary voiding is initiated.
- The ability to calculate subtracted Pdet allows distinguishing between a true rise in Pdet (either via a contraction or loss of compliance) and the effect of increased Pabd.
- It is important that the person performing the UDS study be absolutely sure that a bladder contraction is indeed involuntary. Sometimes patients may become confused during the study and actually void as soon as they feel the desire.
- “Usual LUT behavior” is not always replicated in the test setting.
- As a general rule, prolonged storage at high pressures can lead to upper tract deterioration.
- ALPP and DLPP, although both called *leak point pressure*, are completely different. The ALPP measures the sphincter response to increased Pabd. The lower the ALPP, the “weaker” is the sphincter. The DLPP measures the injured bladder response to increased outlet resistance. The higher the resistance, the higher is the DLPP, which is potentially dangerous to the upper tracts.
- According to the ICS, normal detrusor function is characterized by a voluntarily initiated continuous contraction that leads to complete bladder emptying within a normal time span and in the absence of obstruction.
- According to the ICS, DU is defined as when there is a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span.
- The urodynamic manifestation of BOO is high-pressure and low-flow voiding.
- Normally EMG activity decreases before a voluntary bladder contraction; however, it is not abnormal for EMG activity to increase with an involuntary contraction as part of a guarding reflex to inhibit the IDC.
- True DESD occurs only when there is a known neurologic lesion above the sacral micturition center.

VIDEO-URODYNAMICS

VUDS consists of the simultaneous measurement of UDS parameters and imaging of the lower urinary tract. It provides the most precise evaluation of voiding function and dysfunction and is particularly useful when anatomic structure and function are important (McGuire et al, 1996). Examples of situations in which VUDS is useful include the localization of obstruction, detecting incontinence not seen on physical examination, and evaluating VUR during storage and/or voiding. It can be particularly useful in cases of neuropathic voiding dysfunction. VUDS is the only way to evaluate bladder neck dysfunction and can confirm sphincteric dysfunction diagnosed by EMG. Also, there are instances in which a known anatomic abnormality exists and simultaneous imaging can determine if that abnormality is playing a role in voiding dysfunction (e.g., bladder or urethral diverticulum, VUR).

VUDS can be performed using a variety of different methods. Most commonly fluoroscopy is employed using a C-arm. This gives the most flexibility in allowing patient positioning. However, a fixed unit with a fluoroscopy table that can move from 90 to 180 degrees also may be used. It is important that the patient be able to be positioned properly to evaluate the desired function and anatomy. For example, SUI in men and women is best evaluated in the standing position. Voiding is best evaluated in the position that the patient characteristically voids (usually sitting for women and standing for men). It is always recommended that fluoroscopy time be limited and focus on situations of high yield, such as during provocative maneuvers to demonstrate SUI, during rises in pressure associated with impaired compliance or involuntary contractions, and during voiding.

VUDS can be extremely useful for the diagnosis of BOO in women (Nitti et al, 1999; Blaivas and Groutz, 2000). In 1999, Nitti and colleagues described the VUDS criteria for the diagnosis of obstruction where radiographic evidence of obstruction between the bladder neck and urethral meatus during voluntary voiding defines and localizes obstruction. **Primary bladder neck obstruction can be diagnosed only on VUDS.** Figures 73-18 and 73-19 distinguish between the two most common causes of functional obstruction in women, primary bladder neck obstruction and dysfunctional voiding.

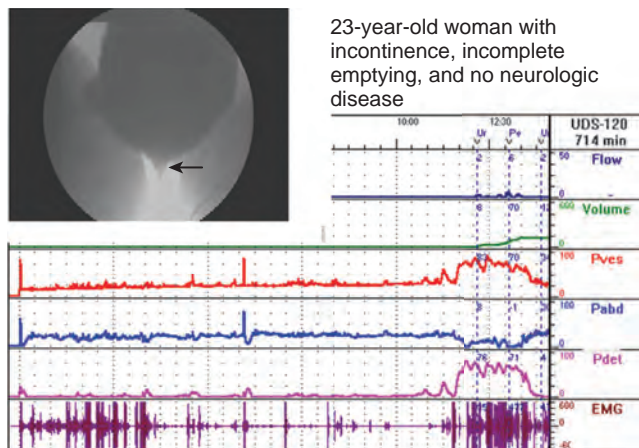


Figure 73-19. Dysfunctional voiding. Uroynamics study of a 23-year-old woman with urgency incontinence, incomplete emptying, and no neurologic disease. Just before voiding there is an involuntary detrusor contraction. With voiding there is increased electromyography (EMG) activity. The fluoroscopic picture taken during voiding shows a characteristic “spinning top urethra” with the level of obstruction at the external sphincter. The high-pressure and low-flow voiding is also characteristic of obstruction.

Similarly, VUDS can be used to evaluate LUTS in young men and in particular make a diagnosis of primary bladder neck obstruction (Norden and Blaivas, 1986; Kaplan et al, 1996). Although obstruction can be diagnosed by pressure-flow studies alone, many surgeons would not feel comfortable performing surgical intervention on a young man without localizing that obstruction. In addition, sometimes bladder neck obstruction can present without the classic findings of high pressure and low flow. Three distinct types have been described (Nitti et al, 2001): classic high pressure–low flow (type I), normal pressure–low flow with narrowing at the bladder neck (type II), and delayed opening of the bladder neck (type III). Figure 73-20 shows types I and II male primary bladder neck obstruction. Fluoroscopy is critical to the diagnosis, especially in types II and III. In fact, simultaneous fluoroscopy during UDS can localize the anatomic site of obstruction in many conditions (e.g., BPO, bladder neck contracture, urethral stricture) once the urodynamic diagnosis of obstruction is confirmed.

VUDS has been shown to be very useful in diagnosing voiding phase dysfunction in women and can be more accurate than surface electrodes in determining EMG activity. We recently found that VUDS was more accurate than surface EMG in diagnosing dysfunctional voiding and differentiating it from primary bladder neck obstruction in women (Brucker et al, 2012). In this study it was assumed that VUDS would be the most accurate method to diagnose voiding phase dysfunction in women. We found that if the surface EMG findings alone were used, the incorrect diagnosis would have been made in 20.6% of the women with dysfunctional voiding diagnosed by VUDS. In contrast, increased EMG activity during voiding was seen in 14.3% of women with primary bladder neck obstruction by VUDS (e.g., a patient voiding with high pressure and low flow without any funneling or opening of the bladder neck and during voiding).

In cases of severe neurogenic and non-neurogenic storage phase dysfunction, VUDS can be helpful if upper urinary tract effects (e.g., hydronephrosis) are present. It has been previously mentioned that upper tract deterioration depends on storage pressures and that reduced bladder compliance is associated with such changes. However, if VUR occurs as a result of high bladder storage pressures, this can result in a pop-off mechanism causing true

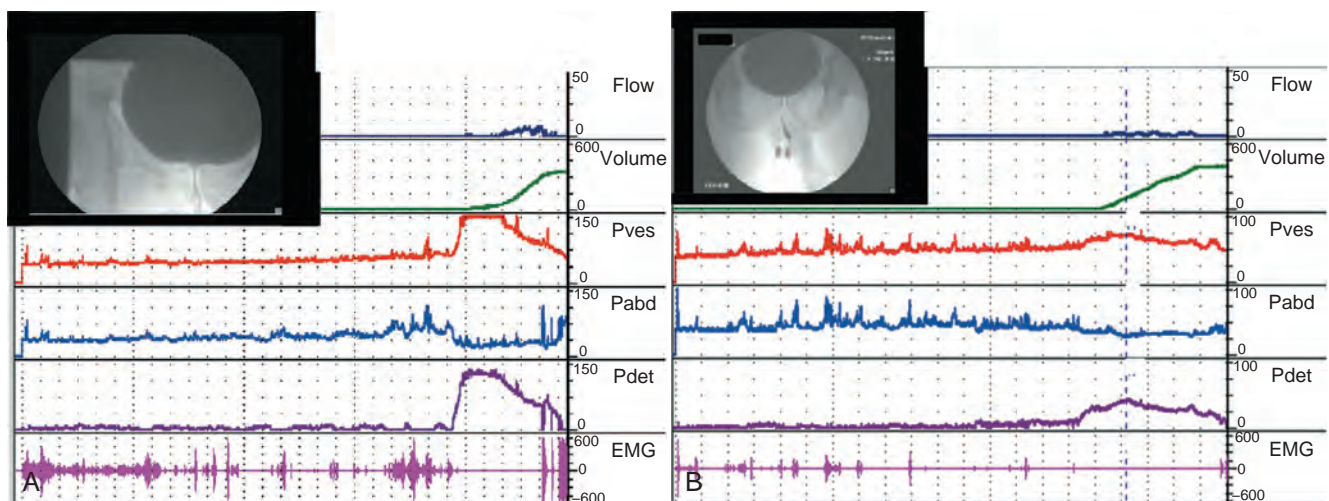


Figure 73-20. Primary bladder neck obstruction (dysfunction). A, Type 1: High-pressure, low-flow voiding in a 45-year-old man with severe lower urinary tract symptoms (LUTS), including frequency, urgency, and decreased force of stream. Image is taken during voiding. Note the incompletely opened bladder neck. B, Type 2: Normal-pressure, low-flow voiding in a 35-year-old man with LUTS similar to those in the patient in A. There is also an incompletely open bladder neck during voiding. The much lower voiding pressures compared to those in A should still be enough to empty normally, though there may be a component of impaired contractility because the bladder was unable to compensate for the increased resistance at the bladder neck. (From Nitti VW. Primary bladder neck obstruction in men and women. *Rev Urol* 2005;7[Suppl. 8]:S12-7.)

bladder compliance to not be a reflection of the measured pressure because one of the upper urinary tracts now absorbs the pressure. If reflux is not diagnosed, reduced bladder compliance can be missed. VUDS is very useful in situations in which reflux is suspected or if hydronephrosis is present (Fig. 73-21).

The AUA/SUFU Urodynamic Guideline supports the use of VUDS in young men and women without an obvious anatomic cause of obstruction, because it can differentiate between functional causes of obstruction such as primary bladder neck obstruction and dysfunctional voiding (Winters et al, 2012). They further state that VUDS is the only diagnostic tool that can document pressure/flow parameters and localize functional bladder neck obstruction. However, the panel recognized that studies have not been performed comparing treatment outcomes of men and women diagnosed with VUDS versus those who had treatment but no VUDS.

VUDS is an important aid in diagnosing neuropathic voiding dysfunction as well as other conditions that may cause elevated

storage pressures. In cases in which VUR occurs, the volume and pressure at which it starts can be documented. In fact, in cases of impaired compliance, in which there is compensation by the pop-off mechanism of VUR, the impaired compliance might not be identified unless the reflux is also recognized by fluoroscopy. In addition, an accurate DLPP can be obtained in cases in which it would otherwise be impossible to position a patient to observe leakage (e.g., some tetraplegics). Furthermore, in cases of possible internal sphincter dyssynergia (often found in conjunction with external sphincter dyssynergia), VUDS is the only way to make the diagnosis and can dramatically change treatment (Fig. 73-22). The EAU Guidelines state that VUDS is the gold standard for invasive UDS in patients with NLUTD (Pannek et al, 2013). If VUDS is not available, a filling CMG plus pressure-flow study should be done. The AUA/SUFU Urodynamics Guideline also recognizes the value of VUDS in patients with NLUTD (Winters et al, 2012). The panel concluded that adding simultaneous fluoroscopy during CMG and

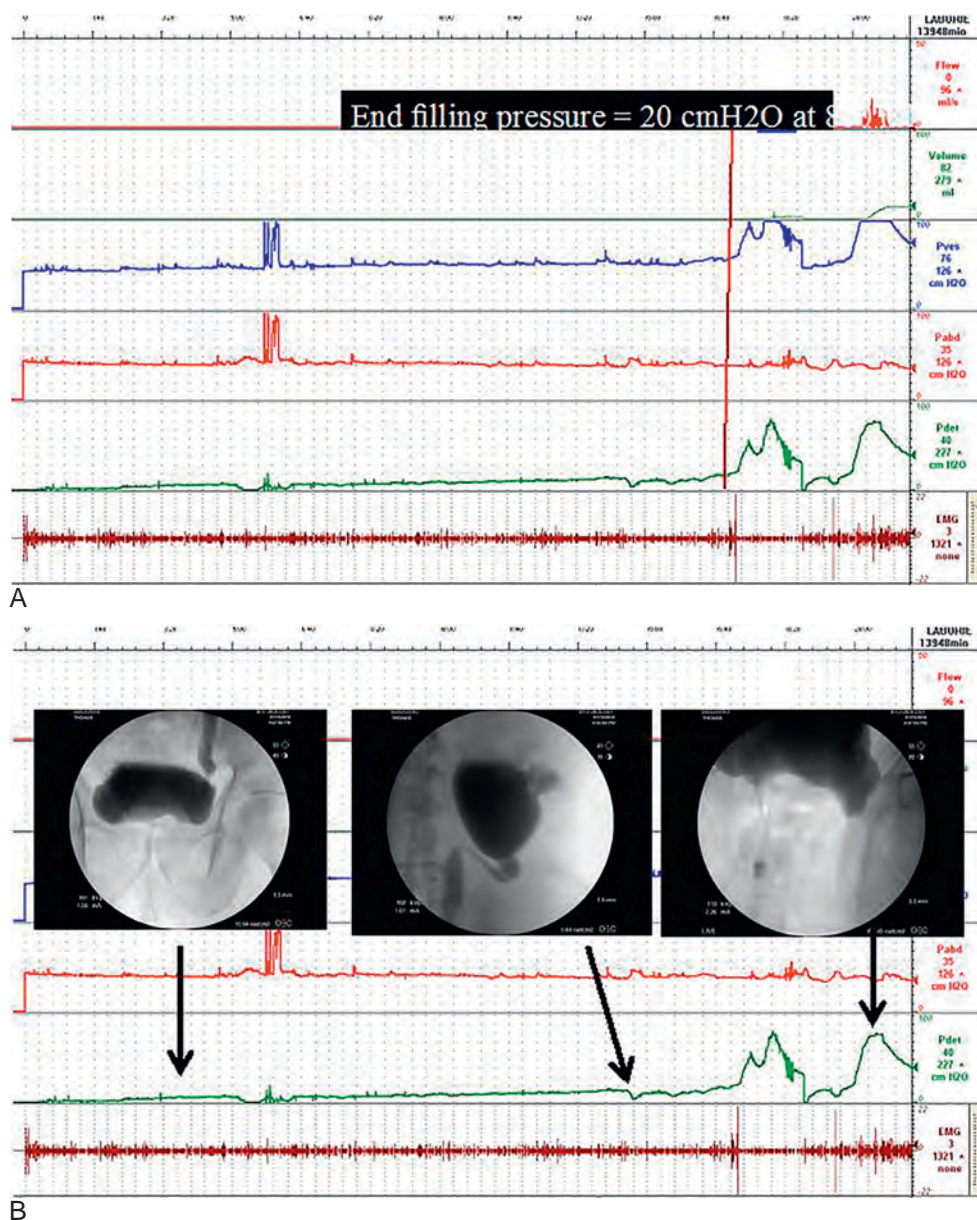


Figure 73-21. A, Urodynamics study of a 75-year-old man with elevated postvoid residual and left hydronephrosis. The end filling pressure is 20 cm H₂O indicating “safe” storage pressures. B, Video-urodynamics shows early reflux at low bladder pressures and significant reflux as bladder filling continues. This represents a “pop-off” mechanism, and the true “functional” bladder compliance is actually significantly more impaired than would be determined by bladder pressure alone.

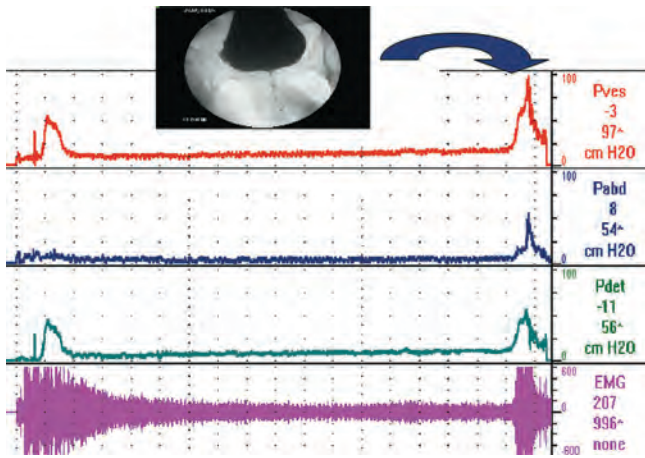


Figure 73-22. Video-urodynamics evaluation of a man with cervical spine injury with neuropathic voiding dysfunction with incontinence and incomplete emptying. The urodynamics tracing clearly shows detrusor overactivity with detrusor external sphincter dyssynergia (DESD) (increased electromyography [EMG] activity with involuntary contraction). However, it is only with the fluoroscopic view of the bladder outlet during an involuntary contraction that DESD is diagnosed (the bladder neck remains relatively closed).

pressure-flow study provided additional worthwhile diagnostic information beyond what either study alone could provide. However, they also warn that because radiation exposure is additive, studies should be done in a manner that provides the desired clinical information at the lowest possible radiation dose to the patient.

Although VUDS can be helpful in many cases, it is not readily available to all physicians. VUDS is the procedure of choice for documenting bladder neck dysfunction in men and women. In addition, patients at high risk for complicated voiding dysfunction, such as those with known or suspected NLUTD, unexplained urinary retention in women, prior radical pelvic surgery, urinary diversion, prerenal or postrenal transplant status, or prior pelvic radiation, should be considered for referral to a center with VUDS capabilities if a complete and accurate diagnosis cannot otherwise be obtained (Scarpero et al, 2009).

KEY POINT: VIDEO-URODYNAMICS IN NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

- VUDS is usually considered the gold standard for invasive UDS in patients with NLUTD.

AMBULATORY URODYNAMICS

Ambulatory urodynamic studies are defined as a functional test of the LUT, using natural filling, and reproducing the subject's daily activities (Abrams et al, 2002). The development of natural and slow filling urodynamic studies was initially undertaken in the investigation of patients with NLUTD by Comarr (1957) using diuresis-induced natural filling. He demonstrated an increase in bladder capacity and decreases in bladder pressures during natural filling when compared to retrograde filling CMG. Similar investigations of patients with spinal cord injury (SCI) by Tsiju and coworkers (1960) demonstrated increased phasic DO associated with incontinence during natural filling. Today it is a well-established method for investigating LUT function under the conditions of normal daily activities. Ambulatory UDS has its greatest value in patients in whom conventional UDS is not suitable or is unable to reproduce symptoms in question.

In 2000, the ICS published guidelines for the performance of ambulatory UDS (van Waalwijk van Doorn et al, 2000). Before the

investigation, patients receive detailed information describing the test and the necessary preparation. Patients are instructed on how to accurately record symptoms and how to identify catheter displacement and hardware failure. A sample diary is given to record all relevant events so that UDS findings can be correlated with symptoms. Most systems employ microtip transducer catheters, which allow the most mobility. These are placed transurethral to record bladder pressure and transrectally to record Pabd. These catheters are firmly secured to the patient and are connected to a portable recording device. Some systems contain a third channel, which can be used for measuring urinary leakage objectively using an absorbent electronic (capacitance change) nappy pad (Robertson and Neil, 1998). This allows accurate data to be obtained on the relationship of urinary leakage to detrusor activity. Home uroflowmetry units also are available. After the completion of testing, ambulatory UDS tracings are analyzed, which can be a time-consuming process depending on the length of the study. This must be done with great care and frequent quality checks to make sure that urethral and abdominal catheters are properly transducing pressure (e.g., using cough tests). In addition, the reader must be able to identify physiologic artifacts (after contractions and aberrant rectal pressures) and technical artifacts (movement or variation in pressure and lack of balance in the transducer lines), which could have an impact on the interpretation of the study. The ambulatory study should be designed to reproduce symptoms. For example, if the patient complains of stress incontinence, a standard protocol of exercises can be performed and recorded (e.g., jumping up and down, squatting, coughing).

CLINICAL UTILITY OF AMBULATORY URODYNAMICS

Ambulatory UDS is performed in an effort to capture more realistic or more physiologic observations, especially of incontinence episodes (Hosker et al, 2009). It attempts to increase sensitivity by providing a longer time for DO (and other abnormalities) to manifest. Practically speaking, ambulatory UDS is most useful when standard UDS is inconclusive and diagnosis and, more importantly, treatment are uncertain. Ambulatory UDS has been most commonly used to diagnose the cause of urinary incontinence but also has been applied to the diagnosis of male BOO and NLUTD. However, ambulatory UDS is not without limitations. Aside from obvious potential technical challenges, Rosier and associates (2013) noted that there are no published data on the reproducibility or test-retest differences of ambulatory UDS studies nor is there any report that evaluates the investigator dependence on the post-test analysis of recorded data. Further, a Cochrane review looking for randomized or quasi-randomized trials did not show adequate evidence that one technique of UDS was superior to the other (Glazer and Lapitan, 2012).

It has been shown that ambulatory monitoring detects more actual incontinence in symptomatically incontinent patients than retrograde filling CMG (Cassidenti and Ostergard, 1999). Dokmeci and colleagues (2010) prospectively classify incontinent women into three groups (urgency incontinence, stress incontinence, and mixed incontinence) using the UDI-6 questionnaire. Both conventional UDS and ambulatory UDS were prospectively performed. Overall, ambulatory UDS findings matched the classification in 77.3% of women, compared to 6.8% using conventional UDS ($P = .001$). The authors suggested that conventional UDS has a higher false-negative rate than conventional UDS. It is important to note that during this study the conventional UDS were performed with the patients in the supine position (and then the seated position), but not in the standing position, which is often recommended. Another limitation was the measure of incontinence during ambulatory UDS and was based only on the patient-controlled event marker. This introduces a bias, and thus the results must be interpreted cautiously.

Several studies have shown ambulatory UDS to be more sensitive than conventional CMG for the diagnosis of DO (Robertson et al, 1994; Heslington and Hilton, 1996). Radley and associates (2001)

found that ambulatory monitoring revealed DO in 70 of 106 women with symptoms suggestive of DO (twice as many as conventional CMG with provocation by hand washing), and that it detected DO incontinence in 40 of the 70. The observation of DO incontinence was correlated with symptom severity, but it was not clear how many women reporting urgency incontinence showed DO incontinence. Thus the sensitivity is unknown. The finding of higher rates (and sensitivity) of DO on ambulatory monitoring must be weighed against the fact that ambulatory UDS has also found higher rates of DO in asymptomatic volunteers. The rates of DO found in asymptomatic females were noted as high as 69% versus 18% for conventional CMG (van Waalwijk van Doorn et al, 1996) and 38% versus 17% in asymptomatic men and women (Robertson et al, 1994). Thus some degree of DO may be normal in the setting of a urethral catheter for a prolonged period, making some sort of standardization important.

In a review of 422 female ambulatory UDS studies over a 12-year period, Patravali (2007) argued for the value of the study. It was seen that 85% of patients reporting urinary incontinence showed detectable leakage with a diagnosable mechanism on ambulatory study; in 77% of 74 women with a normal CMG, ambulatory UDS diagnosed the cause of incontinence and provided “clear added value.” DO was a component in 42 of these 57 patients (76%). What is not known is exactly what is meant by “clear added value” and how treatment was affected. In a smaller study of 25 patients, Pannek and Pieper (2008) had similar findings but a more useful interpretation of those findings. They found that ambulatory UDS was helpful (vs. conventional UDS) in diagnosing LUTD in 72% of the evaluable examinations. However, 24% of the studies done were not evaluable owing to technical problems or catheter dislocation. Thus ambulatory UDS was clinically useful in only 48% of the patients who underwent this examination. When a diagnosis was made on ambulatory UDS, successful treatment was established in 42% of the patients. However, when ambulatory UDS was not helpful and patients were treated based on clinical symptoms, 33.3% were treated successfully. Gorton and Stanton (2000) also looked at the effect of ambulatory UDS on clinical management. In a retrospective review of 71 women there were technical difficulties in 42% of the studies, with 2 being noninterpretable. DO was found in 45% and nearly all were treated with medication. Among the remainder without DO, fewer received medication. However, fewer than half of those who received medication improved. The authors concluded that ambulatory UDS was not very helpful in deciding on management.

Ambulatory UDS has been used for the diagnosis of obstruction in men with LUTS and inconclusive (borderline or nondiagnostic) conventional pressure-flow studies. Rosario and coworkers (1999) reclassified 24% of such patients as either obstructed or nonobstructed. However, Robertson and colleagues (1996) found no difference in the classification of patients with ambulatory versus conventional pressure-flow studies.

It has been demonstrated that storage pressures in patients with NLUTD (and chronic obstruction) are lower on ambulatory, natural fill UDS than on conventional CMG (Webb et al, 1989, 1991, 1992). Patients with poor compliance (high filling pressures) and hydronephrosis on conventional CMG were found to have normal compliance, but significant phasic neurogenic DO on ambulatory monitoring. It has been suggested that phasic neurogenic DO and not impaired compliance may lead to upper tract deterioration in these patients. Although this may be true, it needs to be proved in a series of patients followed over time; for now, based on the available evidence, it must still be concluded that significantly impaired compliance on conventional CMG is a risk factor for upper tract damage.

Martens and associates (2010) looked at 27 patients with SCI and symptoms suggestive of neurogenic DO. These patients underwent both conventional and ambulatory UDS (for 6 hours). It was reported that a greater percentage of patients were found to have neurogenic DO on the ambulatory study (92% vs. 69%, $P = .031$), but there was no difference in the bladder pressure during the IDC. Comparing each method to the “clinical diagnosis of DO” ambula-

tory UDS had a sensitivity to detect neurogenic DO of 85% and conventional UDS had a sensitivity of 75%, but this was not significant ($P = .375$). The authors also found that the interindividual agreement to diagnose neurogenic DO was higher for the conventional UDS compared to the ambulatory UDS. They did look at how the studies altered management recommendations and concluded that although ambulatory UDS did not need to be used as a standard tool for risk assessment in patients with SCI, ambulatory UDS remain indicated if conventional UDS are not conclusive for treatment decisions.

VUDS are often considered the gold standard for the evaluation of patients with NLUTD (Pannek et al, 2013), but most studies in this population have compared ambulatory UDS to conventional UDS, but not VUDS. Virseda-Chamorro and associates (2014) compared ambulatory UDS (with a single natural fill cycle) in 69 patients with SCI. The patients were grouped by findings noted on fluoroscopy, including having an open bladder neck at rest, DESD, and VUR (in this population representing 25%, 64%, and 6% of patients, respectively); they found no association with ambulatory UDS findings. The only statistically significant finding was patients with an open bladder neck on VUDS had a higher percentage of neurogenic DO (67%) on ambulatory UDS compared to patients whose bladder neck was closed at rest (35%) ($P = .025$). This study also found lack of agreement in most other filling parameters when comparing other VUDS parameters to ambulatory UDS parameters. The cytometric capacity on ambulatory UDS (275 mL) aligned more closely with frequency volume chart bladder capacity (296 mL). VUD capacity was noted to be higher (416 mL). It is not clear that this information alters management or affecting outcomes.

When considering the use of ambulatory UDS in the clinical evaluation of NLUTD the possibility of autonomic dysreflexia deserves mention (Cameron, 2011). It was suggested that prolonged periods of catheterization and irritation from multiple catheters could be an issue, but the data about frequency of autonomic dysreflexia episodes and the ability to recognize and adequately manage autonomic dysreflexia has not been systematically evaluated.

Attempts have been made to modify the ambulatory urodynamic equipment needed and have shown some promising results in identifying neurogenic DO (Kim et al, 2010; Kim and Song, 2012). Aside from technical advances and accuracy, cost, convenience and patient experience must also be considered moving forward.

In conclusion, ambulatory UDS may be useful in a select group of patients in whom conventional UDS is nondiagnostic and the information provided would affect treatment, counseling, or follow-up. Ambulatory UDS and its interpretation are time-consuming and technically challenging. The data obtained for ambulatory UDS studies must be weighed against the fact that for many findings, standards—both normal and abnormal—have not been established. More data are needed on the reproducibility of ambulatory UDS. The impact that ambulatory UDS has on altering management and changing both patient-reported and objective outcomes should be investigated across varied patient populations.

KEY POINT: AMBULATORY URODYNAMICS

- Ambulatory UDS may be useful in a select group of patients in whom conventional UDS is nondiagnostic and the information provided would affect treatment, counseling, or follow-up.

CLINICAL APPLICATIONS OF URODYNAMIC STUDIES: EVIDENCE-BASED REVIEW

Thus far in this chapter we have described the technical aspects of UDS and general indications for use. In this final section, we will

provide an evidence-based review of UDS for different common clinical applications. In many situations there is not enough evidence in the literature to conclude how useful UDS is for a particular case, and thus its use should be based on a clinical impression. Nevertheless, there are some instances and indications in which the evidence is strong enough to provide guidance as to how useful UDS will be. In cases in which recommendations are made, these are based on the Oxford system: Grade A recommendation usually depends on consistent level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway. Grade B recommendation usually depends on consistent level 2 and or 3 evidence studies, or “majority evidence” from randomized controlled trials. Grade C recommendation usually depends on level 4 evidence studies or majority evidence from level 2/3 studies or from expert opinion. We will specifically address four areas in which UDS is commonly used for evaluation and enough evidence exists to make valid conclusions or recommendations: women with SUI, men and women with LUTS, and NLUTD.

EVALUATION OF WOMEN WITH STRESS INCONTINENCE

For the last decade, it generally has been thought that **for women with pure SUI without urgency symptoms who empty normally and demonstrated SUI on physical examination, UDS will not provide much useful information.** For example, in the Stress Incontinence Surgical Treatment Efficacy (SISTER) trial, a randomized trial comparing the efficacy of the Burch procedure versus the pubovaginal sling in 655 *selected* women with pure or predominant SUI and no obvious emptying problems, UDS, including ALPP and presence of DO, added little to help determine surgical outcomes with respect to efficacy (Nager et al, 2008) or postoperative voiding dysfunction (Lemack et al, 2008). In 2006, in the United Kingdom, the National Institute of Health and Clinical Excellence issued guidelines that UDS was recommended before surgery for urinary incontinence only if there is a clinical suspicion of DO, if there has been previous surgery for stress incontinence or anterior compartment prolapse, or if there are symptoms suggestive of voiding dysfunction. In the past several years there have been two randomized controlled trials that were designed to answer the question of how useful UDS is in the evaluation of women with straightforward SUI.

The Value of Urodynamic Evaluation Trial (ValUE) was a multicenter, randomized noninferiority trial involving women with uncomplicated, stress-predominant urinary incontinence who were planning to undergo surgery to determine whether outcomes at 1 year among women who underwent only an office evaluation were inferior to those among women who also underwent preoperative urodynamic studies (Nager et al, 2012). The study included a select group of women who had pure or stress-predominant SUI based on a validated questionnaire, a PVR less than 150 mL, a negative urinalysis or urine culture, or urethral mobility with a positive provocative stress test. Women with previous surgery for incontinence, a history of pelvic irradiation, pelvic surgery within the previous 3 months, and significant anterior or apical pelvic organ prolapse were excluded. A total of 630 women were equally randomized to office evaluation plus UDS versus office evaluation alone. The primary outcome was surgical treatment success measured as a reduction in the Urogenital Distress Inventory score from baseline to 12 months of 70% or more and a Patient Global Impression of Improvement response of “very much better” or “much better” at 12 months. The proportion in which treatment was successful was 76.9% in the urodynamic-testing group versus 77.2% in the evaluation-only group (difference, −0.3 percentage points; 95% confidence interval [CI] −7.5 to 6.9), which was consistent with noninferiority. The authors did note that based on UDS, 18 women had the type of surgery changed from transobturator to retropubic midurethral sling (12) or from retropubic to transobturator sling (6). It is not clear if these changes affected outcomes. The authors concluded that for women with uncomplicated, demonstrable SUI,

preoperative office evaluation alone was not inferior to evaluation with urodynamic testing for outcomes at 1 year. In a follow-up study (Zimmern et al, 2014), the authors found that for patients who underwent UDS, physician confidence for the diagnosis of ISD, overactive bladder wet and dry (presumably DO), and voiding phase dysfunction, but not SUI, increased. However, this did not correlate with treatment success.

In another study to investigate the value of UDS before SUI surgery, van Leijssen and associates (2013) conducted a multicenter diagnostic cohort study with an embedded noninferiority randomized controlled trial in 6 academic and 24 nonacademic Dutch hospitals. All women in the trial had SUI or stress predominant mixed incontinence and underwent UDS. Those who had UDS that were discordant with clinical assessment (SUI was not confirmed, DO, weak flow, elevated PVR, small cystometric maximum capacity, or a reduced bladder sensation), were then randomly allocated to receive either immediate surgery or individually tailored therapy based on UDS. Possible treatment options included anticholinergics for DO, prolonged pelvic floor exercises or bladder training in cases of dysfunctional voiding, a pessary, expectant management, intravesical botulinum toxin injections, or pretibial nerve stimulation at the physician's discretion. Of the 578 included women, 268 women (46%) had urodynamic findings that were discordant with clinical history and physical examination. Consent for randomization was obtained from 126. Of the patients randomized to individualized treatment, 57 of 62 received surgery as the initial treatment. The mean improvement on the Urogenital Distress Inventory UI subscale was 39 points (± 25) in the group who received individually tailored treatment compared with 44 points (± 24) in the group receiving immediate surgery. The difference in mean improvement was 5 points in favor of the group receiving immediate surgery, confirming noninferiority for either one of the strategies. Subjective cure as measured with the Urogenital Distress Inventory and objective cure as measured with the stress test and bladder diary were not different between the two arms. In the surgery group, subjective cure was 43 of 58 (74%) and in the individual treated group was 42 of 56 (75%) (relative risk [RR] 0.99, 95% CI 0.80 to 1.23). Objectively cured were 37 of 38 women (97%) in the surgery group and 33 of 34 women (97%) in the individual treated group (RR 1.00, 95% CI 0.93 to 1.09). The authors concluded that in women with uncomplicated SUI, an immediate midurethral sling operation is not inferior to individually tailored treatment based on urodynamic findings.

These two well-done studies suggest that UDS is not essential before surgical treatment of stress-predominant urinary incontinence in women when SUI is seen clinically. However, many women with SUI who are considering surgical correction have mixed symptoms or emptying difficulties and it is here that UDS probably has its most significant role for female SUI. In addition, previous studies found significant variation of the predictive value of symptoms in identifying the three UDS observations of urodynamic SUI, DOI, and mixed urinary incontinence (Harvey and Versi, 2001; Homma, 2002; Agur et al, 2009). This variation is probably explained by the nonhomogeneous patient populations and an inconsistency in the clinical and the UDS diagnosis among the studies.

We believe that UDS does have a valuable and definitive role in the preoperative evaluation of patients with SUI and significant urgency symptoms. In fact, several studies have shown excellent cure rates for both stress and urgency symptoms in women with urodynamic SUI and a normal CMG (no DO) for pubovaginal sling (Chou et al, 2003), Burch procedure (Osman, 2003) and tension-free vaginal tape (Rezpour and Ulmsten, 2001). It should be noted that the trials that have shown no difference in success of treatment with or without DO were primarily done in patients with stress-predominant SUI. The presence or absence of DO in women with more significant urgency symptoms may play a more significant role in predicting outcomes.

Based on a thorough review of the literature the AUA Urodynamics Guideline Panel has made the following statements (Winters et al, 2012):

1. "Clinicians who are making the diagnosis of urodynamic stress incontinence should assess urethral function. (Recommendation; Evidence Strength: Grade C)." The committee recommends that if UDS is performed, an assessment of urethral function (e.g., ALPP or MUCP) should be performed. This seems reasonable as an ALPP may for some surgeons affect the type of surgery performed, because inferior outcomes have been found for some procedures in patients with low ALPP and/or MUCP.
2. "Surgeons considering invasive therapy in patients with SUI should assess PVR urine volume. (Expert Opinion)." An elevated PVR may prompt a change in treatment for additional testing such as UDS.
3. "Clinicians may perform multichannel UDS in patients with both symptoms and physical findings of SUI who are considering invasive, potentially morbid, or irreversible treatments. (Option; Evidence Strength: Grade C)." This statement allows the clinician to make a decision on the selective use of preoperative UDS based on patient symptoms, how the study will influence choice of surgery, and the degree of confidence that the surgeon has in the diagnosis.
4. "Clinicians should perform repeat stress testing with the urethral catheter removed in patients suspected of having SUI who do not demonstrate this finding with the catheter in place during urodynamic testing. (Recommendation; Evidence Strength: Grade C)." It is well established that some women will not demonstrate SUI with a catheter in place. This maneuver is especially important in a woman who does not demonstrate SUI on physical examination.
5. "In women with high-grade pelvic organ prolapse but without the symptom of SUI, clinicians should perform stress testing with reduction of the prolapse. Multichannel UDS with prolapse reduction may be used to assess for occult stress incontinence and detrusor dysfunction in these women with associated LUTS. (Option; Evidence Strength: Grade C)." Prolapse reduction is extremely important if the demonstration of occult SUI on UDS will influence the type of prolapse surgery performed (i.e., a simultaneous anti-incontinence with prolapse repair).

The EAU Guidelines on UDS are not specific to SUI in women, but, nevertheless, make a number of practical recommendations, which are consistent with the AUA Guideline (Lucas et al, 2013).

Clinicians carrying out UDS in patients with urinary incontinence should:

1. Ensure that the test replicates the patient's symptoms (grade C).
2. Interpret results in context of the clinical problem (grade C).
3. Advise patients that the results of UDS may be useful in discussing treatment options, although there is limited evidence that performing UDS will alter the outcome of treatment for urinary incontinence (grade C).
4. Do not routinely carry out UDS when offering conservative treatment for urinary incontinence (grade B).
5. Perform UDS if the findings may change the choice of invasive treatment (grade B).
6. Do not routinely carry out urethral pressure profilometry (grade C).

Both AUA and EAU Guidelines give the clinician the discretion to perform UDS before surgery, based on the individual patient, clinical scenario, and whether UDS will ultimately affect the choice of treatment (the latter varies based on the individual clinician). It is our practice that for cases of straightforward SUI with no or minimal urgency symptoms and with normal bladder emptying, it seems reasonable to forego UDS evaluation because it does not affect our choice of treatment or the outcomes of that treatment. We find UDS most useful in women who have significant urgency and/or urgency incontinence, bladder emptying problems, prior stress incontinence surgery, uncertain diagnosis or inability to demonstrate SUI on physical examination, history of pelvic radiation, neurologic disease, and very severe symptoms (total or near total). We also find UDS useful in elderly women, because we do not believe that the existing literature has investigated this group sufficiently to suggest that UDS is not useful.

EVALUATION OF MEN AND WOMEN WITH LOWER URINARY TRACT SYMPTOMS

The cause of LUTS in men and women is multifactorial, comprising at least four conditions: (1) BOO, (2) DU, (3) DO, and (4) sensory urgency (Blaivas, 1988). Often storage symptoms of frequency and urgency accompany voiding symptoms of decreased force of stream and hesitancy. Urgency incontinence also can occur as a result of DO with or without BOO. LUTS are common among men of 50 years and over. It has been established that coexistence of BOO and DO in men increases with age and with the degree of BOO (Vesely et al, 2003; Oelke et al, 2008). In such cases, UDS can be helpful to establish the underlying bladder and/or bladder outlet abnormality.

Noninvasive testing such as PVR and uroflowmetry can be helpful in the evaluation of men and women with LUTS and also may prompt further invasive UDS testing. The AUA Urodynamics Guideline (Winters et al, 2012) states that, "Clinicians may perform PVR in patients with LUTS as a safety measure to rule out significant urinary retention both initially and during follow-up (Clinical Principle)." Although it is true that PVR cannot differentiate between obstruction and nonobstructive conditions (e.g., DU) and that there is no agreed-upon definition of exactly what volume constitutes an elevated PVR, most urologists would agree with this statement. The Guideline also states that uroflow may be used by clinicians in the initial and ongoing evaluation of male patients with LUTS that suggest an abnormality of voiding/emptying (recommendation; evidence strength: grade C). Like PVR, an abnormal uroflow cannot differentiate between obstruction and DU; however, it can be helpful in instituting or not instituting certain therapies or in prompting further testing.

The question of how much help UDS is in the evaluation and treatment of male LUTS has been debated for years. How necessary is a diagnosis of BOO before transurethral prostate resection, for example? The answer depends on how comfortable the clinician is in making a diagnosis and treating with less invasive and less definitive testing. Few would argue that, to institute an α -receptor blocker for the treatment of LUTS in a man with relatively normal bladder emptying, UDS is not required. However, as the scenario becomes more complex and the treatment more invasive and potentially morbid, a precise diagnosis will be helpful in many cases. Often it is ultimately up to the clinician to decide how much information is useful or necessary to make a treatment decision and properly counsel patients.

It is well documented that in men with BOO, surgery such as TURP (by any means) reduces obstruction and relieves symptoms. However, storage symptoms such as urgency frequency and urgency incontinence will persist in approximately one third of cases. It has been shown that when storage symptoms are associated with DO and BOO, UDS can help predict resolution of those symptoms. In such a scenario, storage symptoms have a higher likelihood of resolving with intervention (e.g., TURP) when DO occurs as a single terminal IDC rather than continuous or sporadic IDCs (Kageyama et al, 2000). Such information can be quite valuable when counseling patients. For example, given the same UDS presentation of BOO plus continuous IDCs, a patient primarily concerned with the inability to empty may opt for surgery whereas a patient who is primarily concerned about overactive bladder symptoms may not.

As for the utility of UDS before surgical treatment or no treatment of LUTS thought to be secondary to BPH, the literature is mixed, with several studies supporting its necessity (Javle et al, 1998; Rodrigues et al, 2001; Porru et al, 2002; Thomas et al, 2004) and others concluding that UDS is not necessary (Pannek et al, 1998; Kanik et al, 2004) or necessary only in inconclusive cases (Ignjatovic, 1997). Other reviews (Abrams et al, 2001; Homma, 2001; Clemens, 2003; Brucker and Jaffe, 2009) suggest that UDS has some, but not strong, predictive value for the outcome of treatment. Another review, by Bhargava and coworkers (2004), concluded that conventional urodynamic studies are useful in providing preoperative information about detrusor function and to exclude

patients less likely to benefit from prostate surgery. Despite this, some regard the need for performing urodynamic evaluation routinely, before TURP, as still controversial. This led the experts at the 6th International Consultation on New Developments in Prostate Cancer and Diseases to conclude that almost all evidence for the advantages of UDS before invasive therapy for benign prostatic obstruction (BPO) is level 3 (good-quality retrospective case-control studies or case series), and the quantity of evidence allows a grade B recommendation (Abrams et al, 2006). In a similar statement, the AUA Urodynamics Guideline (Winters et al, 2012) states that, "Clinicians should perform pressure-flow studies in men when it is important to determine if urodynamic obstruction is present in men with LUTS, particularly when invasive, potentially morbid, or irreversible treatments are considered (Standard; Evidence Strength: Grade B)."

Most of the time when BOO is treated it is done because of symptoms. However, asymptomatic BOO, if not relieved in time, may lead to progression of the disease and affect organ function. For many years attention was paid only to the backpressure effects of obstruction on the kidneys (from high voiding pressures and/or impaired compliance). However, it is now known that BOO affects bladder function, leading to structural changes. Because the changes may eventually become irreversible, some would argue that management should be directed toward early relief of significant obstruction (Flanigan et al, 1998; Lu et al, 2000; Brierly et al, 2003). However, at this time, a critical level of obstruction (e.g., based on the BOOI) has not been defined. There are no evidence-based studies to suggest when surgical relief is indicated to prevent bladder decompensation. Many papers have shown, however, that if there is no evidence of obstruction on pressure-flow studies, the results of surgical relief are not as good (Porru et al, 2002; Thomas, 2004). Significantly impaired compliance remains the only absolute urodynamic indication for treating BOO.

At times it may be important to diagnose DO or more importantly impaired compliance that is associated with LUTS. In addition to BOO, conditions such as radiation cystitis and certain inflammatory diseases (e.g., tuberculosis) can cause impaired compliance. Impaired compliance, however, can be diagnosed only by CMG. In such cases, the diagnosis of impaired compliance can result in the institution of therapy independent of symptoms. Thus, in cases in which impaired compliance is suspected, we recommend UDS testing. This is consistent with the following AUA Guidelines statements:

1. "Clinicians may perform multichannel filling cystometry when it is important to determine if altered compliance, DO or other urodynamic abnormalities are present (or not) in patients with urgency incontinence in whom invasive, potentially morbid, or irreversible treatments are considered. (Option; Evidence Strength: Grade C)"
2. "Clinicians may perform multi-channel filling cystometry when it is important to determine if DO or other abnormalities of bladder filling/urine storage are present in patients with LUTS, particularly when invasive, potentially morbid, or irreversible treatments are considered is consistent with the available information (Expert Opinion)."

As in men, women with emptying problems (poor emptying and/or voiding symptoms) may benefit from UDS with voiding pressure-flow studies. This can help differentiate obstruction from impaired contractility. UDS is particularly helpful when the cause of obstruction is not obvious. Anatomic obstruction (high-grade prolapse, incomplete emptying after incontinence surgery, urethral mass) is usually obvious. However, functional obstruction such as dysfunctional voiding or primary bladder neck obstruction is not obvious on physical examination or endoscopy and requires evaluation during voiding. We agree with the AUA Urodynamics Guideline statement (Winters et al, 2012) that "Clinicians may perform pressure-flow studies in women when it is important to determine if obstruction is present. (Recommendation; Evidence Quality: Grade C)." We find VUDS to be particularly helpful because it can diagnosis and localize obstruction (see earlier section on Video-Urodynamics).

EVALUATION OF NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

NLUTD usually manifests clinically as incontinence and/or inability to empty the bladder. Incontinence may be of bladder origin (DO or impaired compliance) or sphincter origin. Poor emptying also can be of bladder origin (DU or acontractile bladder) or sphincter origin (dyssynergia). In addition to symptomatic presentation, NLUTD can present as upper urinary tract decompensation with hydroureteronephrosis and renal insufficiency without bothersome symptoms. The goal of management in these patients is to prevent upper tract decompensation and relieve symptoms. A specific understanding of the pathophysiology of the condition in each individual is essential for the correct choice of therapy (Stöhrer, 1990; Stöhrer et al, 1994; Rivas and Chancellor, 1995). UDS probably has its most important role in the evaluation and management of patients with neurogenic voiding dysfunction.

The aims of therapy for NLUTD are to achieve physiologic filling (and if possible voiding) conditions as well as to control symptoms and create a management situation acceptable to the patient in daily life. Much of the evidence base for management of the LUT in the neurogenic patient consists of level 3 or lower evidence. This is primarily because of the potential negative consequences of untreated neurogenic dysfunction. Thus, randomized controlled trials are thought by many to be dangerous and unethical. Because prolonged periods of elevated Pdet during bladder filling or abnormally prolonged elevated pressures during voiding have been found to put the upper urinary tract at risk (McGuire et al, 1996; Kurzrock and Polse, 1998; Tanaka et al, 1999), the primary aim of therapy in patients with such problems is conversion to a low-pressure bladder during filling, even if this leads to incomplete emptying and the need to supplement emptying with catheterization. Adequate therapy depends on whether the detrusor is overactive or has reduced compliance, and only UDS can answer those questions unequivocally. In addition to the prevention and amelioration of upper and lower urinary tract abnormalities/decompensation, timely and adequate diagnosis of DO and impaired compliance is thought to be of paramount importance for the patient's quality of life (Stöhrer, 1990; Stöhrer et al, 1994; Bomalaski et al, 1995; Cardenas et al, 1995). UDS is also essential for assessing the response to treatment and following any sequelae of the disease and its management (Hosker et al, 2009).

Not all NLUTD requires UDS before observation or treatment. Conditions in which high storage pressures are not suspected (e.g., urgency incontinence after a stroke or women with multiple sclerosis with a low PVR) often can be managed initially without UDS. But in cases in which the neurologic condition/lesion can cause potentially harmful storage situations (spinal cord injury, myelomeningocele), UDS is essential both before treatment and also in ongoing follow-up of the condition and to monitor the response to treatment. In the middle are situations in which UDS can be helpful in guiding management (e.g., men with possible BPO and Parkinson disease or multiple sclerosis). The AUA Guidelines contains the following five very important and practical statements regarding UDS in NLUTD:

1. Clinicians should perform PVR assessment, either as part of complete urodynamic study or separately, during the initial urologic evaluation of patients with relevant neurologic conditions (e.g., spinal cord injury, myelomeningocele), and as part of ongoing follow-up when appropriate (Standard; Evidence Strength: Grade B).
2. Clinicians should perform a complex CMG during initial urologic evaluation of patients with relevant neurologic conditions with or without symptoms and as part of ongoing follow-up when appropriate. In patients with other neurologic diseases, physicians may consider CMG as an option in the urologic evaluation of patients with LUTS (Recommendation; Evidence Strength: Grade C).
3. Clinicians should perform pressure-flow analysis in patients with relevant neurologic disease with or without symptoms or in patients with other neurologic disease and elevated PVR

or urinary symptoms (Recommendation; Evidence Strength: Grade C).

4. When available, clinicians may perform VUDS in patients with relevant neurologic disease at risk for NLUTD or in patients with other neurologic disease and elevated PVR or urinary symptoms (Recommendation; Evidence Strength: Grade C).
5. Clinicians should perform EMG in combination with CMG with or without pressure-flow studies in patients with relevant neurologic disease at risk for NLUTD or in patients with other neurologic disease and elevated PVR or urinary symptoms (Recommendation; Evidence Strength: Grade C).

KEY POINTS: URODYNAMICS BEST PRACTICES

- There is mounting evidence that UDS is not essential before surgical treatment of stress-predominant urinary incontinence in women when SUI is seen clinically.
- According to the AUA Guidelines, pressure-flow studies are performed in men when it is important to determine if urodynamic obstruction is present with LUTS, particularly when invasive, potentially morbid, or irreversible treatments are considered.
- As in men, women with emptying problems (poor emptying and/or voiding symptoms) may benefit from UDS with voiding pressure-flow studies. This can help differentiate obstruction from impaired contractility. UDS is particularly helpful when the cause of obstruction is not obvious.
- UDS probably has its most important role in the diagnosis and management of patients with neurogenic voiding dysfunction.

▶ Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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▶ The complete reference list is available online at www.expertconsult.com.

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Definition and Classification of Urinary Incontinence

Terminology of Lower Urinary Tract Symptoms and Incontinence

Epidemiology of Urinary Incontinence in Women

Risk Factors for Urinary Incontinence in Women

Epidemiology of Urinary Incontinence in Men

Definitions and Classification of Pelvic Organ Prolapse

Epidemiology of Pelvic Organ Prolapse

Relationship between Urinary Incontinence and Pelvic Organ Prolapse

Consequences of Urinary Incontinence and Prolapse

Physiology of Urinary Continence

Pathophysiology of Urinary Incontinence: General Principles

Pathophysiology of Stress Urinary Incontinence in Women

Pathophysiology of Insensible Incontinence

Pathophysiology of Pelvic Organ Prolapse

DEFINITION AND CLASSIFICATION OF URINARY INCONTINENCE

Introduction and Overview of the Lower Urinary Tract

The economic, social, and emotional burden of urinary incontinence (UI) profoundly impacts patients' lives, heavily contributes to health care spending, and results in millions of office visits, diagnostic studies, and therapeutic interventions each year. And although the number of visits and procedures related to UI has steadily increased throughout the past several decades, in fact the number of symptomatic yet undiagnosed women remains substantial (Miller et al, 2009). The challenge for urologists is to identify patients with UI appropriately, to decipher the type of UI present, and in some cases to determine the etiology of the condition. In so doing, one can then begin the discussion of treatment alternatives.

The lower urinary tract is composed of the bladder and urethra, supported by a complex system of neural innervation and musculo-fascial support in the lower pelvis. Lower urinary tract symptoms (LUTS), including UI, might develop as a result of anatomic abnormalities in the lower urinary tract that might be at the macroscopic, microscopic, or ultrastructural level. Such abnormalities include functional disturbances in the various components of the LUT (e.g., the urothelium, detrusor musculature, sphincteric unit) or abnormalities of the surrounding structures impacting the ability of the LUT to perform its normal functions. Those normal functions, which principally involve storing urine at low intravesical pressures during the vast majority of times and expelling urine at socially appropriate and convenient times, may indeed be inexorably influenced by a variety of coexisting urologic and nonurologic conditions, demographic/environmental risks, lifestyle choices, and genetic factors.

Signs, Symptoms, and Urodynamic Observations of Urinary Incontinence

When evaluating the LUT it is essential to distinguish between signs, symptoms, and (urodynamic) observations. These distinc-

tions are necessary particularly because symptoms of LUT dysfunction are often nonspecific. That is to say, varying etiologies of LUT dysfunction can result in very similar LUTS. Urinary urgency, for example, can represent underlying overactive bladder (OAB), bladder outlet obstruction (BOO), prolapse, and interstitial cystitis/painful bladder syndrome, as well as other conditions. The extent to which the urologist must go to clarify the etiology varies by condition, invasiveness/risk of the proposed intervention, and, to a certain extent, comfort level of the clinician and patient. Suffice it to say, however, that in many cases, the more definitive the diagnosis, the more effective the proposed treatment strategy will likely be.

A sign of LUT dysfunction is considered as one that is observable by the clinician. For the purpose of LUT dysfunction, this might include, for example, the finding of UI during a supine stress test or the finding of pelvic organ prolapse (POP) in a woman who complains of pelvic pressure. Signs are reproducible and objective.

Symptoms are the subjective complaint, made directly by the patient or reported by a caregiver/family member, of a change in condition from what was previously experienced. By their nature, symptoms are descriptive/experiential, and they reflect noticeable alterations in the patient's perception of their LUT function. Symptoms can be self-reported, or they can be determined through the use of a variety of validated questionnaires, many of which are developed for the sole purpose of attempting to make more objective what is, at its essence, a very subjective report. Symptoms, including incontinence, do not necessarily indicate bother, which is a critical distinction to make, because quality-of-life (QoL) impact is the most common reason to intervene for LUTS. In the absence of QoL change, treatment may not necessarily be indicated.

Observations may be urodynamic or nonurodynamic. Nonurodynamic observations include, for example, information gleaned from patient-completed frequency-volume charts. Urodynamic observations are specific findings made during urodynamic studies that speak to the underlying physiology of lower urinary tract function. Specific guidelines for performing and interpreting urodynamic studies were reviewed (Rosier et al, 2013). Abnormalities of storage (obtained during the cystometrogram portion), voiding (obtained during the pressure flow portion), and post-micturition

TABLE 74-1 Lower Urinary Tract Symptom Definitions

SYMPTOM	DESCRIPTION
Stress urinary incontinence	Complaint of involuntary urinary loss with physical exertion, sneezing/coughing, or other activities raising intra-abdominal pressure
Urgency urinary incontinence	Complaint of involuntary urinary loss associated with sensation of urgency
Mixed urinary incontinence	Complaint of involuntary urinary loss associated with physical exertion/rise in intra-abdominal pressure <i>and also</i> with urgency
Nocturnal enuresis	Complaint of involuntary urine loss during sleep
Continuous urinary incontinence	Complaint of continuous urine loss, day and night
Insensible urinary incontinence	Complaint of urine loss without knowledge of what precipitated the event or when it occurred
Urinary frequency	Complaint that micturition occurs more frequently than deemed normal
Urinary urgency	Complaint of sudden compelling desire to urinate that is difficult to defer
Overactive bladder syndrome	Complaint of urinary urgency, with or without urgency incontinence, typically with frequency and nocturia
Nocturia	Complaint of interruption of sleep resulting from the need to void, where the interruption is preceded and followed by sleep

may be ascertained during the study. Although it is the goal of urodynamics to recreate the symptoms reported by the patient, it is clear that this is neither always feasible, nor perhaps is it necessary. For example, patients with symptoms of pure stress incontinence will often be found to have divergent urodynamic findings—it then becomes the role of the clinician to determine if the urodynamic observations or the patient-reported symptoms are more appropriate to treat (Digesu et al, 2009).

TERMINOLOGY OF LOWER URINARY TRACT SYMPTOMS AND INCONTINENCE

The terminology used to describe LUT dysfunction in women has undergone much iteration during the last several years (Table 74-1). The most recent standardization was developed through a joint effort of the International Continence Society (ICS) and International Urogynecological Association, and includes the terminology that is currently in use (Haylen et al, 2010). Although LUTS are the focus of the present chapter, this important document and its precedent manuscript (Abrams et al, 2002) also include standard terminology used for characterizing prolapse, as well as for performing and interpreting urodynamic investigations. Symptom terminology is typically broken down into abnormalities associated with incontinence, with bladder storage, with bladder sensation, with voiding, and post-micturition disturbances.

Incontinence

UI is the symptomatic complaint regarding the involuntary loss of urine. When assessing UI, it is essential to establish the nature (type), severity, impact on QoL, duration, and frequency with which the incontinence occurs. Validated questionnaires, frequency volume charts, physical examination, and urodynamic testing are all used to evaluate UI symptoms better and to distinguish the type of incontinence present (Fig. 74-1). None of these tools alone is capable of answering these essential questions regarding UI, and their combined use is often helpful in developing treatment strategies.

Stress urinary incontinence (SUI) is the complaint of involuntary loss of urine with physical exertion (i.e., walking, straining, exercise) or with sneezing/coughing or other activities that cause a rise in intra-abdominal pressure. It can be witnessed on exam as involuntary leakage per urethra synchronous with effort, physical exertion, or coughing. This provocative testing is often performed during an office supine stress test. Urodynamic stress incontinence refers to the finding of involuntary urine leakage during filling

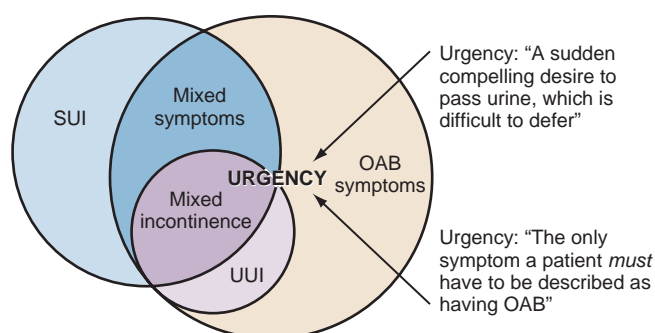


Figure 74-1. Overlap between conditions. OAB, overactive bladder; SUI, stress urinary incontinence; UII, urgency urinary incontinence. (From Wein AJ, Rackley, RR. Overactive bladder: a better understanding of pathophysiology, diagnosis and management. J Urol 2006;175:S5–10.)

cystometry associated with an increase in intra-abdominal pressure, and in the absence of a detrusor contraction.

Urgency urinary incontinence (UII) is the complaint of involuntary urine loss associated with urgency. It can be noted on physical exam as the observation of involuntary leakage from the urethra synchronous with the sensation of a sudden, compelling desire to void that is difficult to defer. Whereas urgency incontinence may be diagnosed urodynamically, it need not be present with any specific urodynamic finding such as detrusor overactivity, bladder oversensitivity, or diminished maximum bladder capacity. Detrusor overactivity incontinence, a urodynamic diagnosis, may be present in patients with UII, although it need not be present to establish the diagnosis of UII.

Mixed urinary incontinence (MUI) is the complaint of involuntary urine loss associated with urgency and is also associated with effort, physical exertion, sneezing, or coughing. Mixed symptoms may be urge predominant, stress predominant, or equal. Postural UI is the complaint of involuntary urine loss associated with a change in position (often from sitting/lying down to standing). Nocturnal enuresis is the complaint of involuntary urine loss occurring during sleep and should be distinguished from urgency incontinence, which may occur during the night after being awakened to void but having insufficient time to get to the bathroom to void. Continuous UI is the complaint of continuous urine loss, day and night. This is the type of UI typically seen with fistula of the lower urinary tract involving the vagina (i.e., vesicovaginal and ureterovaginal fistulae). Patients often will have little

to no volitional voids with continuous incontinence. **Insensible UI** is the complaint of urine loss when the patient is unaware of how or precisely when the urine loss occurred. Coital incontinence is the complaint of involuntary loss of urine with sexual intercourse. It may occur with penetration, intromission, and/or during orgasm.

Bladder Storage and Sensation

These symptoms are associated with abnormalities of bladder filling and are not characterized by loss of urine. Symptoms associated with bladder storage include increased daytime frequency, which is the complaint that micturition occurs more frequently than previously deemed normal. In general, eight or more voids within a 24-hour period are considered more than normal, although this finding alone does not necessarily imply bladder dysfunction. **Nocturia** is the complaint of interruption of sleep because of the need to void, where each interruption is preceded and followed by sleep. **Urgency** is the sudden compelling desire to urinate, which is difficult to defer. Urge, by comparison, is a normal bladder sensation that occurs and signals the need to micturate. **OAB syndrome** includes urinary urgency, with or without urgency incontinence, typically accompanied by frequency and nocturia.

Increased bladder sensation implies that the patient experiences the desire to void earlier than previously deemed normal and differs from urgency in that voiding can be postponed. **Reduced bladder sensation**, in contrast, implies that the desire to void comes later than that previously experienced by the patient, despite the fact that the patient is aware that the bladder is filling. **Absent bladder sensation** involves the complaint that both the sensation of bladder filling and the desire to void are absent.

EPIDEMIOLOGY OF URINARY INCONTINENCE IN WOMEN

General Comments

Epidemiologic studies on the topic of UI must be closely scrutinized when determining their relevance. Several factors must be considered when evaluating these types of data. Among the most important of these factors is the definition of UI—indeed altering the definition will result in widely divergent estimates of disease prevalence. In a condition that does not rely on pathologic diagnosis, and one in which the diagnosis may often be made appropriately by history alone, estimates clearly vary widely.

Questionnaires to assess incontinence differ greatly in specificity, length, and complexity, which often results in very different estimates of prevalence. **Questionnaires used in characterizing incontinence differentiate the type of incontinence present, identify the frequency with which it occurs, and address the severity of the condition.** Thus, for example, asking a woman if she has leaked in the past month will result in very different findings than if the timeframe is narrower. **Additionally, a questionnaire that inquires about bother associated with leakage to define UI will yield varying findings from a questionnaire that merely assesses the presence of the condition.** In a nonmorbid condition such as UI, the impact of the condition on QoL (associated bother) would appear to be of paramount importance. Similarly, studies that rely on the physical demonstration of UI, either on exam or during urodynamics, are likely to report very different findings regarding condition prevalence than those based on questionnaires alone. It is imperative to analyze carefully the incontinence definition used.

Patient populations may also be quite different when assessing epidemiologic aspects of UI. Examining a group of young, nulliparous women, for example, will yield different findings than examining octogenarians living in skilled nursing facilities (O'Halloran et al, 2012). **Clearly, analysis of population gender, comorbidities, access to health care, as well as many other factors will impact the findings greatly.** It is also clear that the geographic location of the study will affect findings—which itself may be a

result of several factors. Although one cannot rule out genetic or environmental factors influencing incontinence rates, the impact of social mores, treatment availability, and education should not be underestimated.

The **type of study** must also be considered. **Case-control studies** are observational studies in which patients are identified who have the condition (incontinence) and are compared retrospectively to patients without the condition. Incidence rates and prevalence rates cannot be generated from this type of study, although one can establish an odds ratio (OR) for associated factors potentially associated with the condition. **Cohort studies** are also observational studies that follow through time a group of patients with a condition. These studies can be either prospective or retrospective and can generate incidence data. **Cross-sectional studies** occur at a single point in time, evaluating for the condition in question, and these studies can generate prevalence data for the condition. Causation, or relative risk, of contributing factors or conditions cannot be established from these types of studies. Although all of the previously mentioned trial designs are susceptible to either various types of bias or confounding factors, **randomized controlled trials (RCTs)** are optimally suited to avoid these pitfalls. RCTs are prospective interventional trials that are ideally designed to not only evaluate outcome of intervention, but also potentially assess relative risk factors for condition prevalence, as well as factors associated with treatment success.

KEY POINTS: FACTORS INFLUENCING THE REPORTED PREVALENCE OF URINARY INCONTINENCE

- Study type
 - Case-control
 - Cohort
 - Cross-sectional
 - Randomized controlled trials
- Demographic factors
 - Age
 - Gender
 - Race
 - Location/nationality
- Presence of comorbidities
- Time period assessed
- Assessment tool used
 - Validated questionnaire
 - Symptom bother assessed
 - Symptom presence assessed
 - Single item on broad health assessment inventory
 - Direct (face-to-face) questioning

Prevalence of Urinary Incontinence in Adult Women

A comprehensive review of epidemiologic aspects of UI summarized data from worldwide studies, focusing on those with favorable (>60%) response rates (Milson et al, 2013). A variety of surveys and survey methods was used in the studies quoted. Overall prevalence rates ranged from as low as 2.8% in a study of younger African women (Ojengbede et al, 2011) to as high as 58.8% in a report from the Netherlands (Sliker-ten Hove et al, 2010). **The majority of studies appear to indicate a prevalence rate for UI between 25% and 40% (Hershorn et al, 2008; Lee et al, 2008; Minassian et al, 2008),** although the rates are age-dependent and studies focusing on younger respondents show lower prevalence rates (Nygaard et al, 2008). As a fraction of incontinence overall, approximately 50% of women reporting leakage will describe stress incontinence, with a slightly lower percentage reporting mixed incontinence, and somewhat fewer describing urgency incontinence. These rates are heavily influenced by the study population, as younger cohorts tend to have more SUI overall, whereas the differences are quite a bit less distinct in older populations (Wehrberger et al, 2012). **Overall,**

prevalence rates of SUI tend to be higher (10% to 25%) than either UUI (3% to 10%) or MUI (5% to 20%).

KEY POINTS: PREVALENCE OF URINARY INCONTINENCE IN WOMEN

- Prevalence rates for UI in women vary considerably depending on the study, but typically range between 20% and 40%.
- Overall, about 50% of reported UI in women is in the form of SUI, with slightly less in the form of MUI, and somewhat less as UUI.
- Younger populations tend to have a greater prevalence of SUI overall, and the differences in prevalence of the different forms of UI tend to be less apparent with older populations.
- Approximately 10% of women experience UI episodes at least weekly.

Because the prevalence rates seem to vary so widely, and study populations often differ considerably, it is inappropriate to generate generalized conclusions from prevalence data. Furthermore, the time interval during which the patients are asked to recount their frequency of leakage tends to differ widely among studies, so even the reported incontinence prevalence rates truly reflect different patient responses. **Ultimately, the majority of the evidence seems to suggest that approximately 10% of women experience at least weekly incontinence episodes**, with certain subpopulations experiencing considerably more. In fact, data suggest that the prevalence of UI, at least in the United States, has risen somewhat during the past decade from 49% in 2001 to 53% in 2008 (Markland et al, 2011). Others have suggested that prevalence rates for pelvic floor disorders, including incontinence, have remained stable recently, although these conditions are still common (Wu et al, 2014) (Fig. 74-2). International estimates appear to be proportionally lower at 21%, although trends suggest that developing nations will be responsible for the majority of new incontinence cases during the coming years (Fig. 74-3) (Irwin et al, 2011).

Incidence and Remission Rates of Urinary Incontinence in Women

Longitudinal studies offer the advantage of the ability to follow groups for potentially extended periods to determine when incontinence is most likely to develop during a woman's lifetime, to determine whether other factors associated with aging might contribute, and to determine whether remission occurs at any time. Studies examining incidence and remission rates of UI may be even more vulnerable to bias and misinterpretation given the high overall prevalence of this condition compared to the relatively low incidence rate. Time between inquiries regarding incontinence, age of the population studied, duration of time that the patient is queried regarding the last time she experienced leakage, and the very nature of the questions asked will often differ considerably among studies. All of these issues must be considered when evaluating reported incidence rates.

When considering middle-aged women (40 to 60), annual UI incidence rates appear to range from 1% to 10%, with higher rates noted when women consider monthly leakage episodes rather than weekly episodes. One extended study following 40-year-old women for 10 years showed that 40% developed new-onset incontinence during this period (Jahanlu and Hunskaar, 2011). As one would expect, SUI is most commonly reported among younger cohorts reporting new symptoms (responsible for 50% of new cases). Interestingly, the incidence of SUI, but not UUI or severe UI, was noted to increase with the menopausal transition from ages 48 to 54 (Mishra et al, 2010). In general, older cohorts have been found to have higher annualized incidence rates—typically between 10% and 20% (Herzog and Fultz, 1990). Among middle-aged or older women, Caucasians, compared to African-Americans, appear more likely to develop UI when followed throughout 5 years (Thom et al, 2010). Those Caucasian women with higher body mass index (BMI) at baseline, and those with weight gain during the survey period, appeared to be at greatest risk. **Annualized resolution rates typically remain less than 5%, although these are noted clearly and consistently in most longitudinal studies.** Higher remission rates have been noted in several studies and may be more typical of studies following younger patients at baseline (Botlero et al, 2011). Interestingly, remission rates may be highest among African-American women (Townsend et al, 2011). The fact that remission

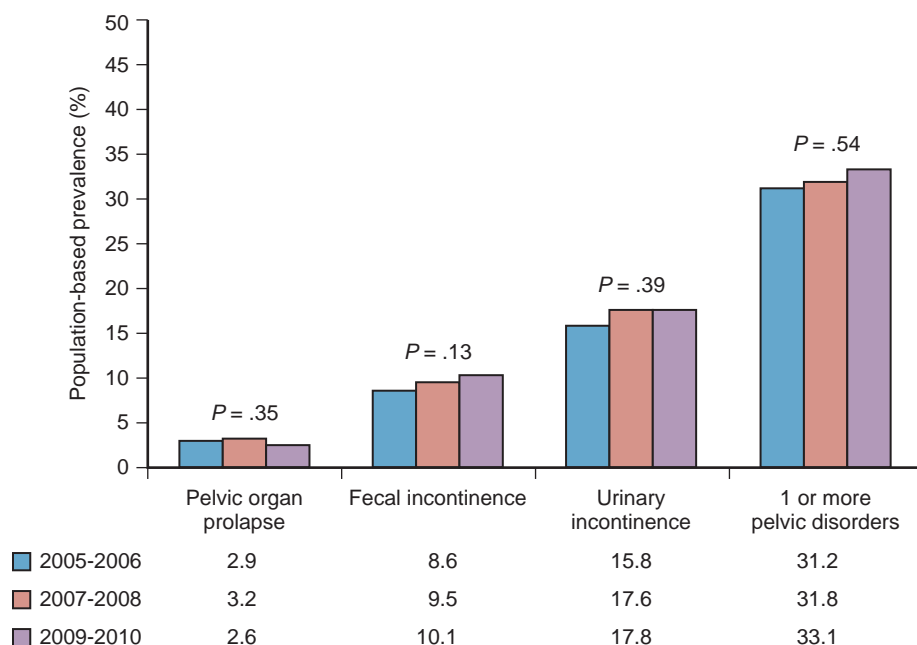


Figure 74-2. Population-based prevalence trends in pelvic floor disorders among nonpregnant women in the United States.

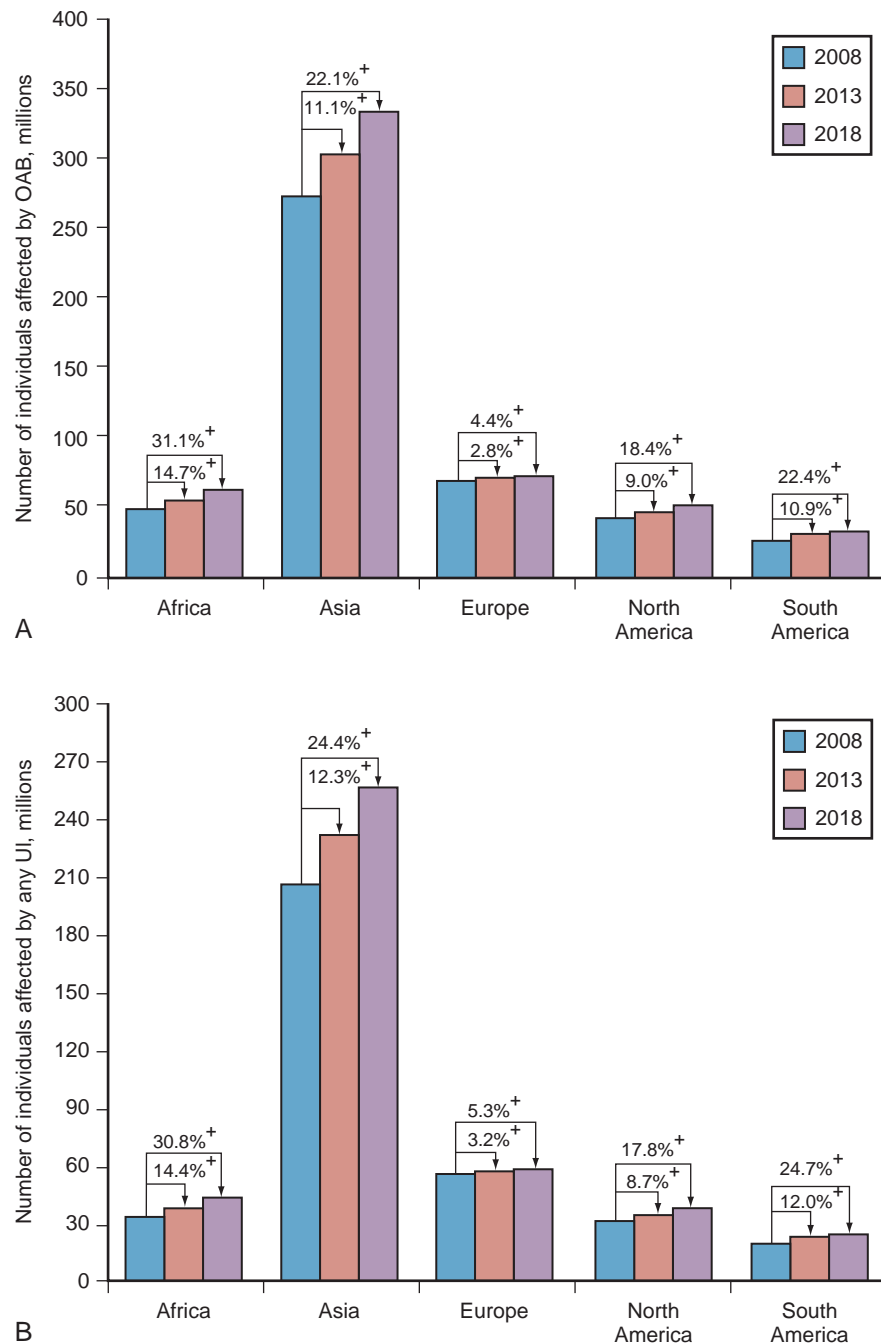


Figure 74-3. Estimated numbers of individuals in major world regions affected by (A) overactive bladder and (B) urinary incontinence.

has been reported emphasizes the existence of transient causes of incontinence, the subjective nature of the condition, and the possibility of recall bias.

KEY POINTS: INCIDENCE AND REMISSION OF URINARY INCONTINENCE

- Annualized incidence rates for UI in women vary between 1% and 10% and are heavily influenced by the population surveyed and the survey tool used.
- A remission rate for UI in women of 1% to 5% has been reported. Remission appears to be higher in younger women.
- Remission rates for men with UI are considerably higher.

RISK FACTORS FOR URINARY INCONTINENCE IN WOMEN

Aging

Although aging alone should not be considered as inevitably linked to UI, it is clear that the vast majority of studies of UI demonstrate a clear association with age that may go beyond the menopausal years—a time when many epidemiologic studies do demonstrate a sharp rise. And although some of the incontinence reported in elderly patients may indeed be attributed to comorbidities, cognitive function, and medication use (as discussed later), age has been recognized as an independent risk factor for UI. In a study of more than 5000 Medicare beneficiaries (all >65) 37% reported UI. There was a clear association with aging noted, even among this

older group (Hawkins et al, 2011). Another survey of nearly 800 community-dwelling women aged more than 65 years showed that 28% of women reported urgency incontinence occasionally or often, whereas 21% reported a similar degree of stress incontinence (Sims et al, 2011). These findings highlight the change in incontinence type that tends to occur with aging, with a shift away from SUI toward MUI and UUI noted in most studies. Interestingly, among older women (>75) UUI appears to be associated with impaired physical mobility, whereas SUI is not (Fritel et al, 2013). Among nonagenarians, UI has been independently linked to frailty and has been established as an independent risk factor for death, suggesting that treatment may be warranted even among the oldest of our patients (Berardelli et al, 2013).

Women living in long-term care facilities (LTCFs) may be at the greatest risk for UI. Several studies have demonstrated the high prevalence of UI in women living in LTCFs (Ouslander et al, 1982; Sgadari et al, 1997; Hunskaar et al, 1998; Saxer et al, 2008). An analysis of nearly 5000 women living in residential care facilities found an incontinence prevalence of more than 40% at admission (De Gagne et al, 2013). Most importantly, severe impairment in the activities of daily living had the strongest association with the presence of UI (OR 21.59). Poor nutritional status, impaired mobility, and increased dementia symptoms all have been correlated with the severity of UI. Importantly, intervening with a group-based behavioral exercise program has been shown to decrease incontinence in women in LTCFs (Tak et al, 2012).

Pregnancy and Postpartum

The prevalence of UI, and in particular SUI, increases during pregnancy and in general increases with gestational age. Overall, the prevalence of SUI during pregnancy is approximately 40%, with more than 50% of affected women reporting a significant impact on QoL (Dolan et al, 2004). By 3 months postpartum, the prevalence of UI drops to approximately 30% and appears to be relatively less severe and imposes much less impact on QoL for most women (Thom et al, 2010). Still, compared to age-matched nulliparous women, primiparous women appear to have a threefold increased likelihood of UI during pregnancy that remains 2.5 times higher 1 year after delivery (Hansen et al, 2012). Interestingly, the magnitude of weight gain during pregnancy does not appear to influence greatly the degree of UI during pregnancy or postpartum, but weight loss postpartum may hasten recovery of continence (Wesnes et al, 2010). In that regard, several studies have demonstrated the protective effect of a properly performed pelvic floor muscle training (PFMT) program in reducing the risk both of UI during pregnancy (Boyle et al, 2008; Stafne et al, 2012) and UI when PFMT is performed immediately postpartum (Ahlund et al, 2013). Regardless of the impact of PFMT postpartum, or the eventual improvement/resolution of UI seen in most women after delivery, the development of UI during pregnancy does reflect a greater likelihood of developing symptomatic UI later in life.

Aspects of Delivery

Whereas pregnancy itself confers an increased risk of UI, mode, duration, and nature of the delivery also appear to influence the risk of UI later in life. Cesarean delivery appears to confer an advantage over normal spontaneous vaginal delivery with regard to the development of UI and SUI (Findik et al, 2012). Five years after delivery, primiparous women who had undergone cesarean section were significantly less likely to report UI overall, although these women may be more bothered by UUI when it occurs than their counterparts (Liang et al, 2013). Similarly a study of women followed for 12 years after delivery noted that, although cesarean section did confer a decreased likelihood of UI, this was only the case if all deliveries were by this method—if other deliveries were vaginal, any protective effect was lost (MacArthur et al, 2011). Other factors such as length of delivery, use of forceps, type of anesthesia,

and use of episiotomy have all been suggested as factors potentially associated with the development of either transient or long-standing UI after delivery, although no conclusive evidence exists to support modifying obstetrical practice based on these findings. In contrast, any history of vaginal birth of a large baby with increased birth weight has been fairly consistently associated with an increased likelihood for developing UI (Connolly et al, 2007; Thom et al, 2011). For example, among women who had at least one child with a birth weight of more than 4 kg, the OR of experiencing weekly UI later in life was 1.47 when compared to those without large babies.

Parity

A single pregnancy and subsequent delivery significantly increase a woman's risk for UI in later life, with an OR of approximately 1.5. Subsequent deliveries increase this risk further (Rortveit et al, 2001; Grodstein et al, 2003; Danforth et al, 2006; Waetjen et al, 2007). Overall, the OR of experiencing any quantity of incontinence later in life among women with 5 or more births, for example, is 1.72 or higher. This risk appears to be accentuated by the timing of the first birth, with those women having their first child closer to the age of 20 seeming to be at greatest risk in most studies, although controversy exists on this topic. As one might suspect, the association between incontinence and parity appears to be strongest for SUI.

Race/Ethnicity

Most cross-sectional studies have indicated that Caucasian women have an increased prevalence of UI and an increased risk for developing incident UI/SUI when compared to African-American women and Asian women (Townsend et al, 2010). Although various explanations exist for this finding, at least one group has noted higher urethral closure pressures in African-American women (DeLancey et al, 2010). This difference in prevalence is less clear when compared to other populations, including Hispanic women. Differences in MUI and UUI based on race are less obvious in comparison and, in fact, are likely inconsequential overall. It appears that Caucasian and African-American women are equally likely to seek care for UI (Berger et al, 2011), although this difference is clearly affected by the degree of leakage (Lewicky-Gaupp et al, 2009). Population-based studies of different cultures, especially those outside the United States, report striking differences in the prevalence of UI in different populations, although these findings are often difficult to interpret based on varying cultural norms and other differences in survey methods.

Hormonal Therapy

Data from several studies suggest that oral estrogen treatment with or without progestogens is associated with the development of UI in middle-aged and older women (Brown et al, 1999). When compared to placebo, the rate of incident incontinence nearly doubled during a 1-year period in a well-conducted large clinical trial of postmenopausal women treated with placebo, estrogen, or estrogen and progestin therapy (Hendrix et al, 2005). By comparison, topical estrogen use is not clearly linked to the development of SUI, and it has proven its efficacy in treating women with vaginal atrophy and recurrent urinary tract infections (UTIs).

Obesity

Both the presence and severity of UI are strongly associated with obesity in women. Although the association appears to be strongest for SUI and MUI, all types of UI have been associated with the development of obesity in women. BMI in excess of 30 has been shown to more than double a woman's risk of UI (Hannestad et al, 2003; Danforth et al, 2006). Whereas symptomatic SUI appears to be more severe and more common in obese women, Valsalva leak point pressure (VLPP) values are higher in women

who are considering surgery for SUI, indicating gradual accommodation of the pelvic floor in women with SUI (Lemack et al, 2007). Incontinence associated with weight gain may be reversible, however, because both surgically induced weight loss and weight loss experienced as a result of a carefully executed weight-loss program have been associated with improvements in UI symptoms that are maintained as long as the weight is kept off (Bump et al, 1992; Richter et al, 2005).

Smoking

Although data remain inconsistent, several compelling studies have demonstrated a link between UI and smoking. A Finnish study of more than 2000 women noted a clear association between symptoms of urinary urgency and frequency and current smoking status. In fact, heavy smoking was associated with more severe urgency symptoms than light smoking (Tahtinen et al, 2011). In a cross-sectional study of more than 80,000 nurses, severe incontinence was associated with current smoking (OR 1.34) (Danforth et al, 2006). Lastly, among women scheduled for SUI surgery, incontinence severity was clearly correlated with current tobacco use. Overall, current smokers had 56% more incontinence episodes than nonsmokers (Richter et al, 2005). Various causes for this link have been suggested, and although some data do question the relationship between smoking and incontinence, there appears to be a growing consensus that some relationship exists.

Diet

Certain foods have been purported to be associated with UI. Overall data are inconsistent, with the association between caffeine (coffee in particular) intake and symptoms of urgency incontinence, mixed incontinence, or OAB generating the most compelling data. Recent data appear to have solidified this link, particularly in men (Davis et al, 2013). There is no consistent link between dietary intake and SUI in most studies. Carbonated beverages and artificial sweeteners have also been primarily associated with urgency symptoms, though confirmatory studies are lacking (Jura et al, 2011).

Medical Conditions

UI appears to be more prevalent among women with certain medical conditions, including diabetes mellitus (DM) and depression. The prevalence of UI among type 2 diabetic women may be as high as two times greater than age-matched nondiabetic women, with emerging evidence suggesting the same finding in women with type 1 DM (Lifford et al, 2005; Phelan et al, 2009a). Among more than 9000 nurses with type 2 DM who were surveyed, 48% reported at least monthly UI, with 29% reporting at least weekly incontinence episodes. Obesity enhanced the risk of UI significantly in this cohort of women (Devore et al, 2012). Similar findings were noted in an interventional trial (weight loss) of obese women with type 2 DM, in whom 27% reported weekly incontinence (Phelan et al, 2009b). The National Health and Nutrition Examination Survey (NHANES) cross-sectional study of 1400 women with type 2 DM additionally identified macroalbuminuria and peripheral neuropathic pain as independent risk factors for UI in patients with type 2 diabetes (Brown et al, 2006). Data from women with type 1 DM is less robust, although a study of more than 500 women demonstrated weekly incontinence in 17% of them, which was a far greater rate in comparison to a nondiabetic cohort from the NHANES analysis (Sarma et al, 2009).

Depression has also been associated with UI in women. It remains unclear whether this association is related to increased bother potentially associated with UI in women with depression, whether incontinence leads to symptoms of depression, or whether there is a common pathophysiologic mechanism for the two. Several studies have demonstrated that the presence of depression leads to an increased likelihood of the later development of UI in women (Thom et al, 1997).

KEY POINTS: RISK FACTORS FOR URINARY INCONTINENCE IN WOMEN

- **Age:** Aging is clearly demonstrated as a potent risk factor for the development of UI in women. Advancing age is clearly linked with a greater likelihood of incontinence and a shift away from SUI to, more commonly, MUI or UUI.
- **LTCFs:** Distinct from aging, maintaining residence in an LTC facility is an independent risk factor for UI. Similarly, severe impairment in activities of daily living has a particularly strong association with UI.
- **Pregnancy and postpartum:** Prevalence of SUI, in particular, increases during pregnancy and increases with gestational age during pregnancy. Prevalence decreases considerably within 3 months postpartum. Properly performed PFMT has been shown to decrease the likelihood of developing SUI.
- **Aspects of delivery:** Cesarean section, when compared to vaginal delivery, appears to confer an advantage with regard to the later development of UI. This advantage may be lost with even one vaginal delivery in addition to the cesarean section. Birth weight of the largest child also appears to be positively correlated with an increased risk of later UI. Other factors such as forceps use and length of delivery have been proposed as risk factors for UI, although overall the association is less clear.
- **Parity:** Whereas a single vaginal delivery increases the risk of UI (and SUI in particular), subsequent deliveries further increase this risk. Age at time of delivery also appears to augment this risk, and those women who are younger when first exposed to pregnancy and delivery appear to be at greatest risk.
- **Race/ethnicity:** An increased prevalence of UI and SUI is noted in Caucasian women when compared to African-American and Asian women. Differences compared to Hispanic populations are less clear. Rates of seeking treatment for UI are similar between African-American and Caucasian women.
- **Hormonal therapy:** Oral estrogen use with or without progestogen is associated with the development of SUI in middle-aged and older women. Topical estrogen has not been clearly associated with this finding, and it can be used for the treatment of vaginal atrophy and, frequently, associated UTIs.
- **Obesity:** The presence and severity of UI is positively correlated with obesity. SUI and MUI are most strongly linked to BMI overall. UI related to weight gain may be reversible in most instances, with either surgical treatment or regimented weight-loss programs providing evidence of substantial improvements in UI.
- **Smoking:** Several compelling studies suggest that symptoms of urinary urgency/frequency, as well as SUI severity (in a surgical cohort), are associated with active smoking. Heavy smokers may be at greatest risk. Data on the impact of smoking cessation are scant.
- **Diet:** The most convincing data with regard to diet and incontinence concern the link between caffeine (coffee in particular) and urgency incontinence/OAB. No clear association exists with SUI. Carbonated beverages and artificial sweeteners have also been associated with UUI, although less clearly so.
- **Medical conditions:** Diabetes and depression are the two most common medical conditions frequently associated with UI. For diabetes, the risk appears to be present in both insulin- and noninsulin-dependent forms, although these are more heavily studied in type 2. Depression in the early years or midlife appears to increase the risk of developing UI later in life.

EPIDEMIOLOGY OF URINARY INCONTINENCE IN MEN

Prevalence, Incidence, Remission Rates

The overall prevalence of UI in men is considerably lower than the rate found in women. In particular, SUI is uncommon in men, with the exception of men who have previously undergone radical pelvic surgery (e.g., radical prostatectomy [RP] or abdominoperineal resection), who have undergone endoscopic transurethral resection of the prostate (TURP) surgery, or who have a neurologic condition that might predispose them to SUI. UUI and MUI are more common in men than SUI, and in many cases these conditions may be attributable to BOO from benign prostatic hyperplasia, other outlet disorders, OAB, or other inflammatory or infectious processes. **Prevalence estimates for UI in men have ranged from 11% to 34% in older men, with up to 11% reporting daily incontinence.** In a telephone survey of more than 14,000 men older than age 40 (mean age 60), 46% reported UI within the previous 4 weeks, although the vast majority reported “other incontinence,” which may have included postvoid dribbling (Buckley et al, 2010; Markland et al, 2010; Coyne et al, 2012). Matched for age, UUI or MUI are more prevalent forms of UI in men than in women, particularly for younger men. As with women, estimates vary considerably dependent on the tool used to assess for UI, the timeframe used, and the population surveyed.

The likelihood of developing UI is age dependent. Several studies have indicated an incidence rate of approximately 1% to 10% annually in men from 60 to 70 years of age followed for 5 to 10 years (Herzog and Fultz, 1990). The remission rate for UI tends to be higher in men than in women. This is largely because of the fact that leakage in men is more typically urgency related, which may have several reversible (infectious/inflammatory) causes. **Depending on the age studied, remission rates as high as 40% have been noted in men with UI (McGrother et al, 2004).**

Risk Factors for Urinary Incontinence in Men

Age appears to be the strongest independent risk factor for UI developing in men—an association that might be even stronger than that noted in women (Diokno et al, 2007). Men appear to be particularly vulnerable to UI with infectious processes such as acute cystitis and prostatitis, the prevalence of which are also clearly associated with aging. Similar to findings in women, altered cognition, diminished mobility, and the presence of other comorbidities are all associated with an increased likelihood of UI. Certain neurologic conditions more commonly found in aging populations (Parkinson disease, cerebrovascular accident [CVA]) are also associated with incontinence in men, most commonly UUI.

RP and other radical pelvic surgeries have been associated with the development of UI in men. The likelihood of UI varies considerably, with overall estimates ranging from 8% to 60% at 1 year following RP (Ficarra et al, 2009). **The absence of preexisting LUTS/previous TURP, technique of surgery (bladder neck sparing and neurovascular bundle sparing), and younger age at the time of surgery have all been shown to be associated with a lower risk of postoperative UI, although conflicting data exist (Gupta et al, 2011).** The postoperative impact of robotic-assisted approaches to RP on UI incidence rates has been modest, with the most recent studies noting incontinence rates comparable to the open approach. When compared to a laparoscopic approach, robot-assisted RP appears to result in earlier return to continence and overall improved continence (95% vs. 83% at 1 year) (Porpligia et al, 2013). In comparison, TURP, whether performed with electrosurgical cauterization or using the potassium titanyl phosphate (KTP) laser approach, is associated with a low (1%) likelihood of developing UI postoperatively.

KEY POINTS: EPIDEMIOLOGIC ASPECTS OF URINARY INCONTINENCE IN MEN

- UI is considerably less prevalent in men than in women.
- UUI is the most common form of UI in men, followed by MUI and then SUI.
- SUI in men is associated with previous radical pelvic surgery (in particular RP) and certain neurologic diseases.
- SUI prevalence rates following RP range from 8% to 60%.
- Robotic prostatectomy leads to an earlier return to continence and lower UI overall compared to the laparoscopic approach. There is no clear consensus that the robotic approach has led to a lower incidence of postoperative UI compared to an open approach.
- Remission rates for UI are considerably higher in men than in women. Remission rates as high as 40% have been reported.
- Age is even more closely associated with the development of UI in men than in women.

DEFINITIONS AND CLASSIFICATION OF PELVIC ORGAN PROLAPSE

POP refers to “downward descent of the female pelvic organs, including the bladder, uterus, or posthysterectomy vaginal cuff, and the small or large bowel, resulting in protrusion of the vagina, uterus, or both” (Jelovsek et al, 2007). **Anterior compartment prolapse** refers to a weakness of the anterior vaginal wall often associated with the descent of the bladder (cystocele). **Posterior compartment prolapse** is a weakness of the posterior vaginal segment often associated with bulging of the rectum into the vagina (rectocele) but can include the small intestine (enterocele). Rectoceles are usually associated with perineal descent, or weakening of the perineal body. **Apical prolapse** entails descent of the uterus, or in the posthysterectomy patient, the vaginal cuff. **Enterocoele** is a true hernia of the intestines into the vaginal wall. Enterocoeles may be an asymptomatic consequence of apical vaginal prolapse, but can also be associated with significant defecatory dysfunction when they are located between the posterior vagina and rectum (Takahashi et al, 2006), even when the apex is well supported. **Uterine procidentia** refers to total vaginal eversion with stage IV uterine prolapse.

Symptoms of Pelvic Organ Prolapse

A multitude of symptoms can be attributed to POP. However, **sensation of a vaginal bulge remains the only symptom that is strongly associated with prolapse at or below the hymenal ring (Tan et al, 2005).** Other symptoms, including UI and fecal incontinence, voiding and defecatory difficulty, and sexual dysfunction, frequently coexist with POP, but they correlate weakly with the severity or site of POP (Ellerkmann et al, 2001). If a woman presents with pelvic pain or pressure primarily, it is imperative to consider other sources of her symptoms, such as endometriosis, adnexal masses, or other forms of pelvic pathology. Placement of a pessary can help to determine whether pain or other vague symptoms of pressure are a result of prolapse. If the pessary relieves symptoms, then the POP is the likely cause of symptoms. Rectocele symptoms are easily confused with defecatory dysfunction resulting from constipation. **In general, defecatory symptoms alone in the absence of specific sensation of a vaginal bulge would only rarely be an adequate reason to intervene surgically for posterior compartment prolapse.** Hence a specific inquiry should be made about whether defecatory symptoms persist even in the absence of constipation, and whether the patient feels as though bowel movements get caught “in a pocket” (the rectocele defect) during defecation. Women with symptomatic rectoceles may, on their own accord, place fingers in the vagina or

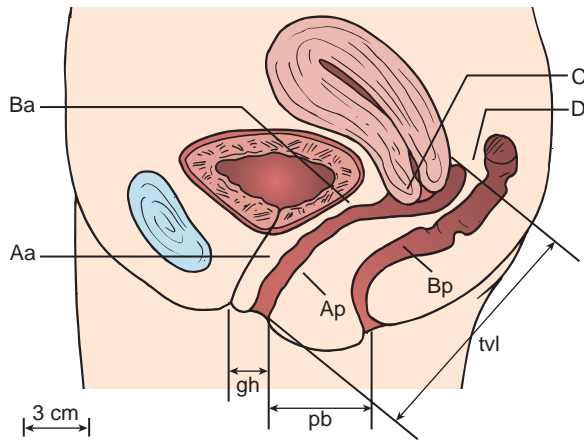


Figure 74-4. Pelvic Organ Prolapse Quantification system and specific points measured. gh, genital hiatus; pb, perineal body; tvl, total vaginal length.

perineum to help evacuate a bowel movement, which is a behavior known as “splinting.”

Physical Examination of Pelvic Organ Prolapse

The Baden-Walker halfway scoring system for the evaluation of POP uses the hymen as the reference point. Grade 0 is considered normal, grade 1 descent halfway to the hymen, grade 2 descent to the hymen, grade 3 descent halfway past the hymen, and grade 4 maximum possible descent for each site. Although widely used, interobserver agreement is variable with the Baden-Walker system, and there is a lack of information about the exact location of specific sector defects (Persu et al, 2011).

In 1993 an international multidisciplinary group composed of members of the ICS, the American Urogynecologic Society, and the Society of Gynecologic Surgeons developed a standardization document that was then adopted by these specialty societies, was published in 1996 (Bump et al, 1996), and was updated in 2002 (Abrams et al, 2002). The Pelvic Organ Prolapse Quantification (POPQ) system provides a precise, objective description of a woman's pelvic support that defines POP relative to a fixed reference point, the hymen. Negative numbers refer to points inside the introitus, and positive numbers reflect prolapse outside the introitus (Fig. 74-4). Point Aa refers to a point on the anterior vaginal wall that is 3 cm proximal to the urethral meatus. It is meant to estimate the position of the bladder neck/proximal urethra junction in most women. Aa ranges from -3 cm to $+3$ cm (-3 cm in the absence of prolapse or urethral hypermobility). Urethral hypermobility can be measured using the POPQ system, eliminating the need to perform a Q-tip test. Point Ba refers to the most dependent portion of anterior vaginal wall prolapse (from the vaginal apex to point Aa). Two points reflect the vaginal apex, which are point C (either the cervix or the vaginal cuff/hysterectomy scar) and point D (the point denoting the posterior fornix in a woman who still has a cervix). Point D, when compared to point C, will differentiate cervical elongation from uterine prolapse. The posterior vaginal wall points include point Bp (the most distal prolapse of the posterior vaginal wall) and Ap (the point located 3 cm from the hymen), which is meant to parallel the Aa point. The genital hiatus (gh) is measured from the middle of the urethral meatus to the posterior midline hymen. The perineal body (pb) is measured from the posterior margin of the genital hiatus to the midanal opening. The total vaginal length (tvl) is the greatest depth of the vagina in centimeters when the vagina is fully reduced. Points Aa, Ba, Ap, Bp, C, and D are measured with the patient straining, so as to accentuate maximal prolapse during the examination. See the video on the Expert Consult website for instructions on how to conduct a POPQ exam.

anterior wall Aa	anterior wall Ba	cervix or cuff C
genital hiatus gh	perineal body pb	total vaginal length tvl
posterior wall Ap	posterior wall Bp	posterior fornix D

Figure 74-5. The 9-point Pelvic Organ Prolapse Quantification scoring system placed on a 3×3 grid. gh, genital hiatus; pb, perineal body; tvl, total vaginal length.

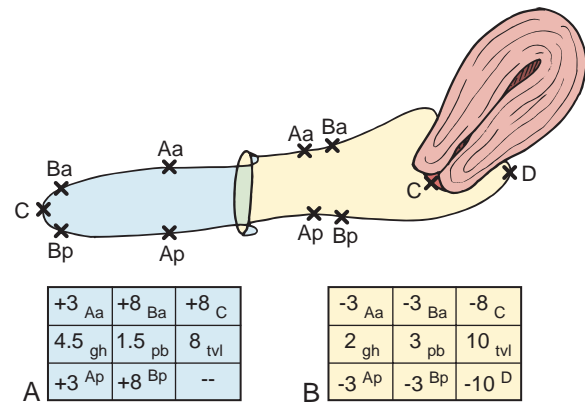


Figure 74-6. A, Pelvic Organ Prolapse Quantification (POPQ) description of patient with total vault eversion posthysterectomy. B, Woman with no prolapse (normal POPQ measurements). gh, genital hiatus; pb, perineal body; tvl, total vaginal length.

The 9-point scoring system is placed on a three-by-three grid (Fig. 74-5) (Bump et al, 1996). Measurements may also be recorded as a line of numbers for points Aa, Ba, C, D, Bp, Ap, tvl, gh, and pb, respectively. Stages are assigned to the most severe portion of the prolapse when the full extent of the prolapse has been demonstrated (usually with straining). Stage 0 is without prolapse (points Aa, Ap, Bp are all at -3 , and point C or D is between $-tvl$ and $-[tvl - 2]$ cm). In stage 1 POP, the distal portion of the prolapse is more than 1 cm above the level of the hymen. In stage 2, the distalmost aspect of the POP is found within 1 cm on either side of the hymen. In stage 3, the distalmost portion of the prolapse is more than 1 cm below the hymen but not totally everted (no further than 2 cm less than tvl, or $> +1$ cm but $< +[tvl - 2]$ cm). Stage 4 is complete vaginal eversion ($\geq +[tvl - 2]$ cm). Figure 74-6 demonstrates POPQ measurements in a woman with normal anatomy and a woman with stage 4 posthysterectomy vaginal vault eversion.

For most clinicians, radiologic studies play a relatively small role in the evaluation of POP; the physical examination with the POPQ system quantifies most defects such that further information is often not needed for treatment planning. A static cystogram followed by a voiding cystourethrogram, performed in the standing position is used by some clinicians to establish urethral position, and may assist in assessing the impact of prior procedures on the urethral axis. Resting and straining magnetic resonance imaging (MRI) has become integrated into the diagnostic workup of POP in some centers and can specifically aid in diagnosing the presence of an enterocele (Fig. 74-7A and B). Defecography is also valuable in determining the presence of enterocele in women with defecatory dysfunction, and this procedure likely has better sensitivity than MRI because women are in the upright position during defecography, which may better demonstrate pelvic prolapse. MRI

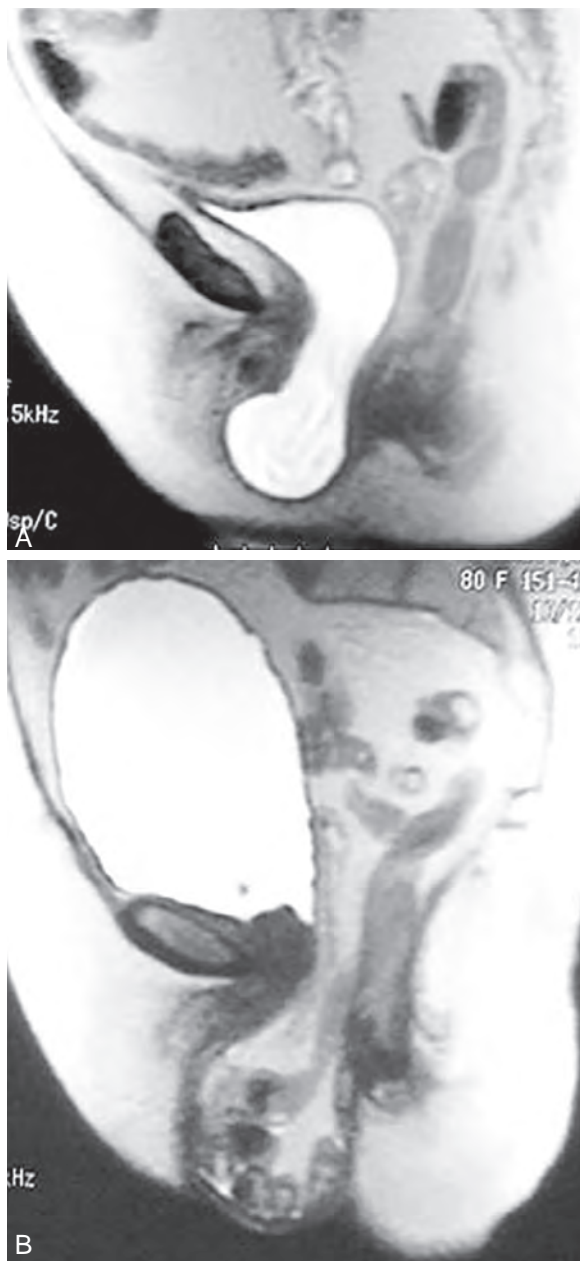


Figure 74-7. A, Magnetic resonance image (MRI) of female pelvis with isolated cystocele defect. B, MRI of female pelvis with isolated enterocele defect. (From De Almeida FG, Rodriguez LV, Raz S. Magnetic resonance imaging in the diagnosis of pelvic floor disorders. *Int Braz J Urol* 2002;28:553–9.)

defecography is a new tool that also has been used in certain centers to characterize prolapse better, particularly in the differentiation of enterocele. The cost effectiveness and overall benefit of radiologic studies in the evaluation of women with POP have not been carefully scrutinized and therefore still should be used at the discretion of the treating physician. For the majority of patients, a careful POPQ physical examination and, if necessary, reassessment at the time of surgery remain the cornerstones of POP assessment.

EPIDEMIOLOGY OF PELVIC ORGAN PROLAPSE

Prevalence and Incidence

Identifying POP based on self-reported symptoms is difficult because of the lack of specificity and sensitivity of most symptoms

attributed to POP (Ellerkmann et al, 2001). The greatest challenge in studying the prevalence of POP rests in the fact that POP develops well before it becomes symptomatic, and POP above the hymenal ring is usually asymptomatic. In fact, in a multicenter observational study of 1004 women aged 18 to 83 years seen for routine annual gynecological examinations, the prevalence of stages 0 to 3 POP was 24%, 38%, 35%, and 2%, respectively (Swift et al, 2005). Therefore asymptomatic stages 1 to 2 POP are considered normal in adult women. Similarly, in the Women's Health Initiative, which measured prolapse in postmenopausal women with physical examination, the overall presence of prolapse was 41% for women with a uterus and 38% of women posthysterectomy (Hendrix et al, 2002).

Additionally, individual women experience symptoms of prolapse differently in that some women may be symptomatic with stage 2 POP whereas other women will have no symptoms. A study suggests that ethnic background may influence symptoms associated with POP (Dunivan et al, 2014b). In this study, the authors noted that degree of bother from stage 2 POP was higher in Hispanic and Native American women compared with Caucasians. Because treatment is generally indicated for women with symptoms, the distinction between symptomatic and asymptomatic POP is relevant.

The prevalence of POP based on a sensation of a mass bulging into the vagina or observed on pelvic examination is between 4% and 12.2% (Hunskar et al, 2005; Sliker-ten Hove et al, 2009). In contrast, questionnaire-based estimates likely under-report the true prevalence of POP based on physical examination. Few studies report on the incidence of POP. In a subgroup analysis of women enrolled in the Women's Health Initiative Estrogen Plus Progestin Trial, Handa and colleagues (2004) found that the annual incidence of new cystoceles was 9.3 cases per 100 women-years, rectocele 5.7 cases, and uterine prolapse 1.5 based on physical examination. Most epidemiologic analyses suggest that prolapse occurs most frequently in the anterior compartment, followed by the posterior compartment, and least commonly in the apex. Although this finding is well supported in the epidemiologic literature, it is clear that both high-grade anterior and posterior prolapse are frequently associated with coexisting apical descent.

Risk Factors

Well-established risk factors for POP include parity, age, and obesity. Childbirth is associated with an increased risk of POP later in life, and current evidence suggests that parity also contributes. In the Oxford Family Planning Study, which is a prospective cohort study of more than 17,000 women, parity was the strongest risk factor for the development of POP with an adjusted relative risk of 10.85 (95% confidence interval [CI] 4.65 to 33.81) (Mant et al, 1997). Although the risk increased with each delivery, the rate of increase slowed after the first two deliveries. Nonetheless, a case-control study by Moalli and colleagues (2003) showed that women who had a vaginal delivery had 2.9 times the risk of undergoing surgery for POP or UI (95% CI 0.9 to 10.0) and women who had forceps delivery had 5.4 times the risk (vs. cesarean delivery, 95% CI 1.6 to 18.4). Although cesarean delivery is associated with a decreased risk of POP compared to vaginal delivery, the degree to which cesarean delivery prevents the development of POP is unknown, especially after multiple cesarean deliveries. As with UI, both the incidence and prevalence of POP increase with age (Hunskar et al, 2005). Surgery for POP and UI also increase with age, reaching a peak in the seventh decade (Olsen et al, 1997). Obesity is not only a risk factor for the development of POP, but it is associated with early recurrence of anterior vaginal wall prolapse after anterior colporrhaphy (OR 2.5, 95% CI 1.2 to 5.3) (Kawasaki et al, 2013).

Several other important, yet less well-established, POP risk factors exist. These include race/ethnicity and increasing weight of the vaginally delivered fetus. Two studies that examined POP by race showed that black women had the lowest prevalence of POP and Hispanic women the highest prevalence after controlling for other possible confounding factors. Based on symptoms, Rortveit

and colleagues (2001) found adjusted ORs of 9.4 (95% CI 0.2 to 0.8) for black and 1.3 (95% CI 0.8 to 2.2) for Hispanic women, with white women as the reference group. Based on physical examination, Hendrix and colleagues (2002) similarly found adjusted ORs of 0.6 (95% CI 0.5 to 0.8) for black women and 1.2 (95% CI 1.0 to 1.5) for Hispanic women. An association between **maximum birth weight** and the development of POP has also been found (Samuelsson et al, 1999). **Hysterectomy and other pelvic surgery** may increase the risk of POP (Hunnskaar et al, 2005). In fact, hysterectomy performed for POP is a strong predictor of the need for repeat pelvic floor surgery, although this in part might be a result of failure to perform concomitant vaginal vault suspension at the time of hysterectomy. Based on twin studies, POP includes **familial transmission** patterns mediated by genetic factors (Hunnskaar et al, 2005). Other identified risk factors for the development of POP include **smoking, chronic constipation, and menopause/hormonal effects**.

KEY POINTS: EPIDEMIOLOGY OF PELVIC ORGAN PROLAPSE

- The prevalence of symptomatic prolapse ranges from 4% to 12%, although asymptomatic prolapse is present in the majority of adult women.
- Both the incidence and prevalence of POP increase with age, as do rates of surgery for POP.
- Parity is associated with an increased risk for POP later in life. Current evidence also suggests that an increasing number of childbirths increases the risk of POP, although the rate of increase slows after the first two deliveries.
- Obesity is not only a risk factor for the development of POP, but it is associated with early recurrence of anterior vaginal wall prolapse after anterior colporrhaphy.
- Hysterectomy and other pelvic surgery may increase the risk for POP, and hysterectomy for POP is a strong predictor of secondary pelvic floor surgery.
- Cesarean delivery is associated with a decreased risk for subsequent pelvic floor morbidity in comparison to giving vaginal birth, but whether cesarean delivery prevents the development of POP remains uncertain.
- POP is more common in Caucasian and Hispanic women when compared with African-American women.

RELATIONSHIP BETWEEN URINARY INCONTINENCE AND PELVIC ORGAN PROLAPSE

Many of the etiologic risk factors that contribute to SUI are similar to those described for POP. In fact, more than 40% of women with SUI will have a significant anterior vaginal prolapse (Cardozo and Stanton, 1980). In addition, **high-stage cystocele might mask "occult" SUI by creating urethral obstruction**. Often, as anterior prolapse stage progresses in severity, previously incontinent women will notice an improvement in their SUI symptoms. Our understanding about why some women develop symptoms of SUI without POP and others develop POP without SUI is limited (Bidmead et al, 2001). POP can **exacerbate storage symptoms**, and the two conditions are frequently associated. Enhorning found that women with mild cystoceles experienced a 20% incidence of detrusor overactivity (Enhorning, 1961). This increased to 52% among women with moderate to severe cystoceles. **Improvement of OAB symptoms can be expected after POP surgery in a significant proportion of patients** (de Boer and Vierhout, 2011). In fact, Fletcher and coworkers (2010) found that anterior compartment repair resulted in a reduction of frequency (by 33%), UUI (49%), and difficulty voiding (74%) at a median of 21 months' follow-up. Persistent UUI after repair was related to a higher preoperative P(det)Q(max) (OR 1.056, 95% CI 1.003 to 1.11, $P = .04$).

Failure to recognize POP at the time of UI treatment might greatly increase the need for subsequent surgery for POP (Anger et al, 2007). Data from a 5% national random sample of 1999 to 2001 Medicare claims for patients undergoing UI surgery showed that urologists performed concomitant prolapse repairs at the time of sling in 29.1% of cases, whereas gynecologists performed prolapse repairs in 55.7% ($P < .0001$). In the 12 months following sling surgery, patients who underwent surgery by a urologist were more likely to undergo a repeat surgery for prolapse repair (26.0% vs. 12.2%, $P < .0001$). These findings emphasize the importance of identifying and managing symptomatic prolapse when evaluating patients with UI.

In addition, **procedures for UI can exacerbate certain types of POP**. The classic Burch colposuspension, which corrects SUI and anterior prolapse by suspending the anterior vagina at the level of the bladder neck to Cooper ligament, has been shown to contribute to the later development of uterine prolapse and/or enterocele by changing the vaginal axis and bringing it to a more anterior position (Langer et al, 1988).

Women with high-stage anterior vaginal wall prolapse are also at risk of developing "de novo" SUI should they undergo surgery for POP. In fact, a multicenter trial by the Pelvic Floor Disorders Network randomized women without symptoms of SUI to receive a concomitant midurethral sling (vs. sham) at the time of vaginally approached prolapse surgery (Wei et al, 2012). At 1 year after surgery, 27.3% of women in the sling group experienced incontinence vs. 43% in the sham group ($P = .002$). However, complications were increased among those who underwent a sling, including bladder perforation in 6.7% (vs. 0%), UTIs (31.0% vs. 18.3%), major bleeding complications (3.1% vs. 0%), and incomplete bladder emptying 6 weeks after surgery (3.7% vs. 0%, $P \leq .05$ for all comparisons). Other risks of sling placement, such as de novo urgency, although not mentioned, should also be carefully considered in a patient without incontinence symptoms. **This study emphasizes the relationship between anterior vaginal prolapse and SUI, and also the need to consider prophylactic sling placement at the time of POP surgery for women who do not report SUI, while carefully weighing the potential for additional risks associated with this approach.**

KEY POINTS: CONDITIONS ASSOCIATED WITH PELVIC ORGAN PROLAPSE

- More than 40% of women with SUI will have a significant cystocele.
- Occult SUI is urethral sphincteric incompetence masked by the presence of high-stage anterior POP. Failure to address occult SUI at the time of surgery for POP may lead to more severely symptomatic SUI postoperatively.
- POP may be associated with defecatory dysfunction and fecal incontinence. Disorders of defecation, including fecal incontinence and urgency, should be carefully evaluated before considering POP surgery.
- Sexual dysfunction is often associated with both POP and UI. Treatment of these conditions may ameliorate symptoms of sexual dysfunction. Still, dyspareunia has been associated with some types of POP repair, and, as such, changes in sexual function are an important aspect of preoperative counseling.

CONSEQUENCES OF URINARY INCONTINENCE AND PROLAPSE

Societal Costs of Urinary Incontinence

The cost of diagnosing and treating UI is significant. Estimates of cost are difficult to make, as they include many variables not easily quantified in health care cost analyses, including many

out-of-pocket expenses that place the financial burden squarely on individuals rather than on government or third-party payers. Therefore, in addition to the costs of diagnostic studies, office visits, medications, surgeries and other interventions, and treatment of related UTIs or care for skin breakdown, one must take into account personal expenses related to absorbent products, increased laundering related to leakage, missed work, and other personal costs. A review of the financial burden associated with the management of female SUI alone reported annual costs in excess of \$12 billion in the United States, with more than 70% considered out-of-pocket expenses (Chong et al, 2011). A report from the Urinary Incontinence Treatment Network noted that women with severe incontinence had \$900 of out-of-pocket expenses annually for incontinence routine care (absorbent products, laundry, and so forth) (Subak et al, 2006). With regard to OAB, if one uses a prevalence estimate of 42 million Americans affected, a societal cost of \$25 billion annually has been estimated, based on outpatient visits, medical treatments, work time lost, as well as other related expenses (Onukwugha et al, 2009).

Social Impact of Urinary Incontinence

The impact of UI and OAB on patients' lives has been studied in detail. Nearly every aspect of a patient's life is affected by the development of UI (Coyne et al, 2012). Relationships are clearly affected, and sexual activity may be severely limited by the threat of UI. It is clear that young and old, patient and partner, are all affected by the impact of UI on sexual activity, and that surgery to improve incontinence has a positive effect on sexual function (Brubaker et al, 2009; Nilsson et al, 2009). Patients often restrict travel, even for short distances, because of the fear of major leakage episodes when not in close proximity to a toilet. UI affects what patients eat and drink (avoiding foods they may enjoy), what they wear (wearing dark clothing to guard against obviating leakage), and with whom they associate (avoiding people they do not know). They may have decreased work productivity because they need to urinate often (or desire to urinate to try to avoid leakage episodes). Because sleep disturbances are more common in some forms of UI, daytime alertness and productivity might be affected as well.

UI appears to affect the QoL of patients at all ages. Young nulligravid women with incontinence report greatly diminished overall well-being compared to age-matched women without UI (O'Halloran et al, 2012). Elderly patients are affected as well, with the severity of UI rather than the type of UI primarily responsible for the impact on QoL (Aguilar-Navarro et al, 2012; Barentsen et al, 2012). The impact of UI is seen in nearly all QoL domains, and the severity of impact may be greater than that seen with other common conditions associated with aging, including arthritis and diabetes (Hawkins et al, 2011).

KEY POINTS: CONSEQUENCES OF URINARY INCONTINENCE

- Societal costs of UI are difficult to estimate because of the considerable burden on patients not covered by conventional third-party insurers. Tens of billions of dollars are estimated at a minimum for the societal costs associated with UI.
- Interpersonal relationships are affected in a variety of ways. Sexual activity may be curtailed because of concerns regarding incontinence. This finding is true regardless of age.
- Virtually all QoL domains are impacted by UI. Travel, leisure, and recreational activities are often restricted. Diet is often adjusted (particularly in patients with OAB symptoms).
- Sleep disturbances are often associated with certain types of UI.
- Loss of work productivity has been associated with UI.

Societal and Personal Costs and Consequences of Pelvic Organ Prolapse

Olsen and coworkers (1997) reported an 11% lifetime risk of surgery for POP or UI in a Kaiser Permanente population of women in the Pacific Northwest. Reoperation for failed procedures was 29%. Smith and coworkers (2010) reported a 19% lifetime risk of undergoing prolapse surgery in Western Australia. POP is the most common noncancer indication for hysterectomy among menopausal women in the United States (Wilcox et al, 1994; Swift et al, 2005). In the United States, more than 300,000 surgical procedures for POP are performed annually, with 25% undergoing reoperations (Maher et al, 2013). The annual incidence of POP surgery ranges from 1.5 to 4.9 cases per 1000 woman-years (Hunnskaar et al, 2005). The incidence rises with age, approaching 3.3 cases per 1000 woman-years among women aged 50 and older (Boyles et al, 2003). U.S. costs for POP and UI are more than \$1 billion per year (Olsen, 1997). In 1997, the direct costs of POP surgery were \$1.012 billion, including \$494 million (49%) for vaginal hysterectomy, \$279 million (28%) for cystocele and rectocele repair, and \$135 million (13%) for abdominal hysterectomy (Subak et al, 2001). Using the 2007 Nationwide Inpatient Sample and the 2006 National Survey of Ambulatory Surgery, Wu and colleagues (2011) calculated the rates for inpatient and outpatient SUI and POP surgery and estimated that the number of those who will have surgery for prolapse will increase from 166,000 in 2010 to 245,970 in 2050. Even if the overall surgery rates for pelvic floor disorders remain unchanged, it has been predicted that the number of surgeries for UI and POP will increase substantially during the next 40 years.

POP has a significant negative impact on QoL. Similar to UI, POP is not discussed freely in public, and therefore women often experience shame about the condition and do not discuss it with others (Dunivan et al, 2014a). POP is associated with both decreased body image (Jelovsek and Barber, 2006) and sexual dysfunction. In fact, in a population of women with UI, women with both POP and UI were more likely to report decreased libido, decreased sexual excitement, and difficulty achieving orgasm when compared to women with UI alone (Ozel et al, 2006). Although POP is generally considered a QoL condition with few medical sequelae, untreated prolapse can become advanced to a point when a woman can develop urinary retention from urethral compression and, rarely, renal failure from ureteral compression (Young et al, 1984).

PHYSIOLOGY OF URINARY CONTINENCE

Overview of Normal Continence Mechanisms

Urinary continence is maintained via an interplay of complex neural, structural, and ultrastructural mechanisms involving the lower urinary tract and surrounding structures. Failure of any one of these contributing factors can lead to UI. Some common pathologies may affect more than one of these mechanisms, leading to fairly severe UI. For example, the effects of external-beam radiation may be realized years, even decades, following initial treatment. In addition to profound effects on nerve structure and function (which can affect bladder sensation and induce overactivity), radiation can affect bladder storage pressures by increasing bladder wall rigidity through changes in smooth muscle elasticity and extracellular matrix composition.

Neural Control of the Lower Urinary Tract

Bladder storage at its very essence is a neurologically mediated event. Parasympathetic transmission (via the pelvic nerve) is suppressed and sympathetic transmission (via the hypogastric nerve) is active, and both are imperative to the creation of a low-pressure reservoir that is maintained during the entirety of the filling phase. Spinal reflex mechanisms allow afferent signaling from the bladder (via A delta myelinated nerves) to promote sympathetic-mediated closure of the bladder neck, a closure mechanism that is decidedly stronger in men than in women. The pontine micturition

center in the brainstem integrates afferent input and ultimately is responsible for parasympathetic-mediated bladder contraction (Drake et al, 2010). However, before a coordinated contraction, tonic inhibition of coordinated parasympathetic activity by suprapontine centers prevents bladder contraction. Additionally, ongoing pudendal nerve activation (via Onuf nucleus in the sacral cord) of the external sphincter mechanism results in the continuous resistance required to maintain continence during bladder filling.

The Bladder: An Organ Capable of Significant Expansion at Low Pressures

The position of the bladder itself also provides a unique ability to allow for significant expansion, while placing the vulnerable sphincteric unit in a more protected environment where external forces are less likely potentially to influence the ability of the outlet to maintain continence (particularly in men). The dome of the bladder can expand well into the peritoneal cavity with relatively no extravescical force opposing this expansion. In contrast, the bladder base and neck sit in a stable retropubic location. In men, this position is essentially fixed and immobile, and unless neurologic/traumatic/operative events occur, only a direct impact on the sphincteric unit itself will result in leakage. In women, where pelvic floor laxity can impact bladder neck position and function, incontinence may result, at least in part, from changes in the position of the bladder outlet.

The structure of the bladder wall and characteristics of smooth muscle cells allow for passive filling without increases in pressure that would create undue forces on the bladder outlet. Relatively poor coupling between detrusor smooth muscle cells appears to contribute to the ability of the bladder to avoid the propagation of unplanned spontaneous smooth muscle contractions into a coordinated bladder contraction during filling. Although individual smooth muscle cells may be triggered to contract by stretching during bladder fill, in most situations a sustained bladder contraction requires coordinated parasympathetic stimulation. The multiple-layered mucosal lining of the bladder itself further enhances the ability of the bladder to store urine, as the urothelial cell layers (“umbrella cells”) can flatten considerably with filling. Further, the extracellular matrix composition of the bladder wall, and in particular the type of collagen (type I favored in normally compliant bladders), as well as the collagen-to-elastic ratio, are critical to the maintenance of a low-pressure state in the bladder during normal filling.

KEY POINTS: FACTORS CONTRIBUTING TO LOW-PRESSURE RESERVOIR DURING BLADDER FILLING

- **Neural:** Parasympathetic suppression, sympathetic activation promotes detrusor relaxation.
- **Anatomic (gross):** Intraperitoneal position of bladder dome permits unimpeded expansion.
- **Anatomic (micro):**
 - Multilayered mucosal layer of bladder promotes expansion with filling, collapse with emptying.
 - Poor coupling between detrusor smooth muscle cells dissipates aberrant contractions.
 - Extracellular matrix composition promotes minimal change in bladder pressure by enhancing bladder elasticity. Collagen type I is major collagen subtype.

Bladder Outlet/Sphincteric Mechanisms

Maintenance of a low-pressure reservoir would be of no value in assuring continence if not for the presence of sufficient outlet resistance (higher than storage pressures). A competent bladder outlet results from specific urethral mucosa attributes, which are the so-called internal sphincter (intrinsic properties of the

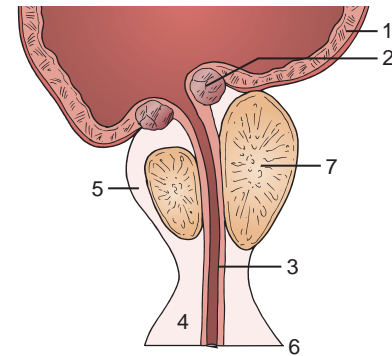


Figure 74-8. Male urethral sphincter complex. 1, Bladder musculature. 2, Proximal part of internal sphincter. 3, Distal part of internal sphincter. 4, Rhabdosphincter. 5, Prostatic part of rhabdosphincter. 6, Perineal membrane. 7, Prostate.

bladder neck/proximal urethra) and the distal (rhabdo) sphincter. Urethral mucosal longitudinal folds allow for both distensibility (for opening during voiding) and contribute to the creation of a mucosal “seal” that enhances urethral closure during bladder filling. The well-vascularized spongy submucosal layer contributes to the distensibility of the urethral lumen. Additionally there are important structural and functional differences characterizing the sphincteric units in men and women that help to explain further how incontinence can be maintained in each of the sexes.

Male Sphincteric Mechanisms

The internal sphincter is a contributory continence mechanism extending from the bladder neck to the distal verumontanum. In the absence of disease or injury, urine commonly does not descend beyond the bladder neck to the level of the external sphincter. Dryness created by the forces at the bladder neck is, in part, a result of α -adrenergic activation of smooth muscle at the bladder neck (sometimes called the lissosphincter) and within the prostatic urethra. This smooth muscle extends distally and then toward the rhabdosphincter where the greatest intraurethral forces are generated (Koraitim, 2008) (Fig. 74-8). Sympathetic innervation of this zone, when combined with β -adrenergic-stimulated relaxation of the bladder body, promotes dryness. Other aspects of the internal sphincter continence unit include the prostate itself, which further enhances outlet resistance. Because of these factors, loss of external sphincter function, such as with traumatic pelvic injury, may not result in incontinence in men with an intact bladder neck. This is in contradistinction to the bladder neck in women, which is relatively weak, making women more vulnerable to incontinence with any deficiency of external sphincter function.

The external sphincter is largely composed of skeletal muscle and as such has the ability to create intense compressive forces. Indeed, pressures at the rhabdosphincter are in excess of 40 cm water continuously during bladder filling, and these pressures can rise considerably further with voluntary contraction. Pudendal nerve injury or denervation can result in the loss of external sphincter strength and subsequent UI (Sajadi et al, 2012; Gill et al, 2013). The strength of the external sphincter is highlighted in the presence of the failure of and/or the injury to the bladder neck (i.e., during TURP), in which case the presence of an intact rhabdosphincter nearly always results in the maintenance of continence. The rhabdosphincter is a concentric muscle composed largely of type I (slow-twitch) skeletal muscle, although smooth muscle fibers are noted to intermingle with the more prominent skeletal muscle bundles. The presence of slow-twitch fibers is what is largely responsible for the tonic ability of the sphincter to maintain urethral closure essentially in a continuous fashion during bladder filling. Fast-twitch fibers found in the surrounding levator musculature contribute then to the ability transiently to enhance voluntary closure during times of increased stress on the sphincteric

unit. Further anatomic support of the rhabdosphincter is derived from the pubourethral ligaments, which serve to anchor the sphincteric unit solidly in an anterior position. Ventral support of the sphincter comes from the condensation of musculofascial elements that ultimately fuse at the perineal body. This unique arrangement of the male sphincteric unit stabilizes and protects the sphincter from the impact of external forces.

KEY POINTS: CONTINENCE MECHANISMS OF THE BLADDER OUTLET AND URETHRA IN MEN

- Internal sphincter:
 - α -adrenergic activation of bladder neck and prostatic smooth muscle
 - Prostatic restrictive forces on urethra
- External sphincter:
 - Rhabdosphincter (largely slow-twitch type I skeletal muscle) provides tonic compression
 - Levator muscular elements (fast-twitch) assist during times of increased stress on external sphincter
 - Anterior fixation by pubourethral ligaments
 - Posterior support of musculofascial plate fusing at perineal body

Female Sphincteric Mechanisms

Unlike the powerful continence zone created at the level of the bladder neck in men, continence in women is largely a result of forces created along the proximal urethra and/or midurethra, in addition to somewhat less forceful distal urethral muscular contributions. **Indeed it is fairly common for the bladder neck to be incompetent in women, although continence remains intact (Chapple et al, 1989; Versi et al, 1990).** As in men, longitudinal smooth muscle courses toward the external sphincter, although the bulk of the muscle responsible for sphincteric control in women is circular striated muscle located in the proximal urethra and/or midurethra. Muscular forces (primarily striated muscle) create a nearly complete circumferential compression of the midurethra (DeLancey, 1988) under the influence of tonic pudendal innervation. Experimental studies in rats have demonstrated both transverse and longitudinal orientation of striated muscle inserting directly into the connective tissue of the urethral wall (Mondet et al, 2003) (indicating both circular and longitudinal muscle orientation). Pudendal denervation and resultant sphincteric weakness, potentially occurring as a result of prolonged labor, is one mechanism by which incontinence may result from the effects of labor and delivery.

More distally, striated muscular fibers are not oriented circularly but are located ventrally. These muscular fibers contribute to the compressor urethra (which originates in the perineal membrane) and urethrovaginal sphincter (which originates in the vaginal wall). These further contribute to the sphincteric unit in women. Unlike the relative stability and immobility of the male external sphincter, the female sphincteric unit is most certainly vulnerable to common external forces.

A combination of attributes of the female urethra itself contributes to urinary continence. **Intrinsic properties of the urethral mucosa and urethral wall are an important part of maintaining continence in women. The spongy nature of estrogen-sensitive urethral submucosa enhances the apposition of urethral mucosa, which aids in the creation of an effective watertight seal.** In fact, it has been estimated that up to 30% of the forces responsible for continence are derived from this seal (Raz et al, 1972).

Surrounding musculofascial elements further support continence mechanisms in women. **A strong muscular backing (anterior vaginal wall) provides posterior support and additional compression of the midurethra.** Laxity in vaginal support can result in anterior vaginal prolapse and a shearing effect in the continence zone, particularly if anterior ligamentous support at the

proximal urethra (pubourethral ligaments) is intact. **Indeed fixation of the urethra by ligamentous support (pubourethral ligaments) normally minimizes movement of the proximal urethra, further contributing to continence by helping to prevent abdominal forces to be transmitted to the remainder of the urethra.** The urethropelvic ligaments further anchor the urethra to the tendinous arc bilaterally. It is the combined effect of these extraurethral forces, intrinsic urethral properties, and muscular elements that promotes continence, and loss of any one, or several in most cases, can result in UI in women.

KEY POINTS: CONTINENCE MECHANISMS OF THE OUTLET IN WOMEN

- External sphincter mechanisms:
 - Circular striated muscle of the external sphincter in the midurethra under pudendal innervation supplies the majority of active midurethral compression by the external sphincter
 - More distally, longitudinal striated muscle arising from the vagina and perineal membrane contribute to sphincteric forces
- Urethral attributes:
 - Mucosa of urethral wall tends to adhere to itself
 - Spongy, vascular nature of urethral submucosal layer promotes apposition of the urethral wall
- Surrounding support structures:
 - Anterior vaginal wall provides firm posterior support of the urethra allowing compression of the midurethra
 - Fixation of the midurethra anteriorly by the pubourethral ligaments helps prevent transmission of intra-abdominal forces to the remainder of the urethra
 - Further anchoring of the urethra laterally to the arcus tendineus is provided by the urethropelvic ligaments

PATHOPHYSIOLOGY OF URINARY INCONTINENCE: GENERAL PRINCIPLES

Factors Affecting Bladder Storage

UI resulting from bladder dysfunction is induced by a variety of neurologic, iatrogenic, and common demographic risk factors. **Any neurologic process interrupting the normal suprapontine inhibition of the pontine micturition center may result in neurogenic detrusor overactivity (NDO) and cause UII.** CVAs, multiple sclerosis, and Parkinson disease are among the more common neurologic processes that might result in UII. DM, even early in diagnosis, has been associated with NDO and UII. Obstruction resulting from anti-incontinence surgery in women can lead to de novo UII secondary to induced detrusor overactivity (DO). In men, BOO induced by prostatic enlargement (or other obstructive process) can be associated with DO and resultant UII.

Poor emptying from detrusor underactivity or detrusor areflexia (causing overflow incontinence) might also cause UI. This type of detrusor dysfunction is common with neurologic diseases affecting the lumbosacral cord or conus medullaris. Systemic diseases, which can result in peripheral neuropathies such as diabetes, tabes dorsalis, and alcoholism, can similarly cause overflow incontinence. So whereas early in the disease process DM can lead to UII, later in the process sensation can be altered as can detrusor contractility, resulting in impaired bladder emptying, UTIs, and UI. Radical pelvic surgeries (i.e., radical hysterectomy, abdominoperineal resection) can also result in significant, sometime permanent, neurogenic detrusor dysfunction leading to urinary retention and overflow incontinence. Pelvic external beam radiation (commonly used in the treatment of prostate cancer and other pelvic malignancies) can alter bladder compliance, increase detrusor leak point pressure, and contribute to UI.

Factors Affecting Sphincteric Function

The most common causes of **intrinsic sphincteric deficiency (ISD)** are iatrogenic, although, less commonly, neurologic disease can directly impact sphincter function. Traumatic or vascular injury to the lumbosacral cord can impair sphincter function and can result in ISD (Gomelsky et al, 2003). Multiple systems atrophy typically results in loss of intrinsic sphincteric function in men and a high likelihood ($\geq 20\%$) of UI following TURP in men who are considering this surgery. Other processes such as traumatic cervical or upper thoracic spinal cord injury can cause **detrusor sphincter dyssynergia**, creating impaired bladder emptying and UI, particularly when coupled with NDO. Medications used purposely to enhance voiding (α -blockers) can reduce outlet resistance sufficiently to cause leakage in vulnerable patients. Any medication with either α -antagonistic properties or skeletal muscle relaxant properties can also cause UI by inhibiting outlet resistance.

In women, urethral surgery or anti-incontinence surgery can lead to urethral scarring, periurethral fibrosis, and ISD. The likelihood of ISD appears to increase with an increased number of failed surgeries previously. Advanced prolapse surgery performed without concomitant treatment of the bladder outlet appears to result in an increased likelihood of postoperative UI. This appears to be true of both abdominal sacrocolpopexy and vaginal surgery for significant anterior prolapse (Brubaker et al, 2008; Wei et al, 2012). Still, the risks of incontinence surgery, and the reality that some patients who never would have developed UI (and thus are overtreated) must be weighed against the risk of needing future surgery or the impairment of QoL associated with ongoing leakage.

Labor and delivery can also impact sphincter function in women. **Prolonged labor, third-degree lacerations, large birth weight, multiparity, and forceps deliveries are all aspects of labor and delivery that have been associated with sphincteric dysfunction.** The mechanisms by which labor appears to result in UI include direct injury to ligamentous/fascial support, ischemic injury to the pelvic floor as a result of prolonged compression, pelvic or pudendal denervation induced by compression, and direct genitourinary injury. This finding is further corroborated by the study of women followed for decades after cesarean section compared to women who had a single vaginal delivery. Twenty years following delivery, women who underwent vaginal delivery are more likely to experience MUI, SUI, and UUI, and are more likely to report severe forms of UI (Gyhagen et al, 2013).

RP, the most common surgical cause of incontinence in men, generally causes leakage via a direct impairment of sphincter function. Among incontinent men studied urodynamically, ISD is the predominant finding in approximately 70%, whereas DO and altered compliance are less common causes, although they may contribute to the condition in more than 30% of cases (Dubbelman et al, 2012). It is clear, however, that the finding of DO is common among men following RP (more than 50% of men 3 years following RP), regardless of the presence of UI (Song et al, 2010). Following RP, decreases in functional urethral length (64%) and maximum urethral closure pressure (MUCP, 41%) have been noted. In this regard, higher baseline MUCP has been associated with earlier urinary control and lower likelihood of postprostatectomy incontinence (PPI) (Dubbelman et al, 2012). Although the approach of RP (open vs. robotic) does not appear to affect greatly the risk of ISD, preservation of the bladder neck and, in particular, nerve sparing for both open and robotic approaches to RP seems to hasten the recovery of continence and to lower the overall likelihood of PPI (Campodonico and Manuputty, 2012; Srivastava et al, 2013).

PATHOPHYSIOLOGY OF STRESS URINARY INCONTINENCE IN WOMEN

Original theories explaining the pathophysiology of UI in women focused on the descent of the proximal urethra and bladder neck, and the implications of moving away from an intra-abdominal location with anterior pelvic prolapse. It was believed that as the

urethra became hypermobile, intraperitoneal forces could no longer constrict the urethra and incontinence resulted (Enhörning, 1961). The pressure transmission theory was the basis of several effective operations (i.e., Marshall-Marchetti-Krantz and Burch colposuspension) designed to restore the urethra to its normal anatomic location.

Loss of Urethral Support

Gradually the understanding of the urethral support mechanisms and causative factors for SUI evolved. It became clear that urethral support emanated from the endopelvic fascia and was enhanced by anterior support (pubourethral ligament) and posterior support (vaginal wall), all of which normally prevent excessive urethral mobility. Proponents of the current theory thought it best to explain incontinence resulting from urethral hypermobility as the “hammock hypothesis,” based on the work of John DeLancey (DeLancey, 1994). This theory suggests that posterior musculo-fascial support of the urethra from the anterior vaginal wall itself and extending laterally from the vagina to the levator ani and arcus tendineus fascia pelvis contribute to the maintenance of continence seen at times of increases in intra-abdominal pressure (Figs. 74-9 and 74-10). It is compression of the urethra against this firm posterior backing (hammock) that enables the urethra to prevent urinary loss with stress maneuvers. Loss of backing from this musculo-fascial support leads to incontinence because of an inability to compress the urethra, particularly if combined with intact anterior support (creating a shearing effect) and loss of compressive sphincteric forces (Mostwin et al, 1995). Hence this theory suggests that repositioning the urethra, previously

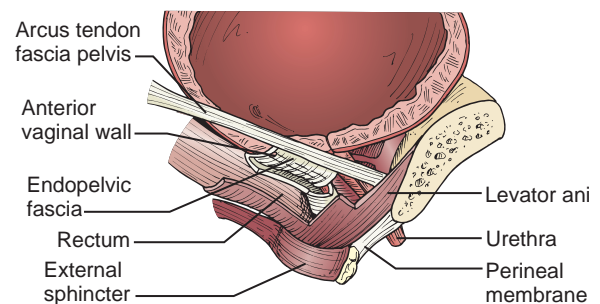


Figure 74-9. Structures involved in urethral support drawn from dissection and three-dimensional reconstruction made from serial sections. Note the connection of the endopelvic fascia and the vaginal wall that lies under the urethra to the arcus tendineus fasciae pelvis and its connection to the levator ani muscle.

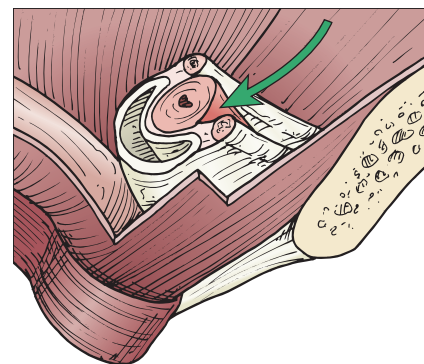


Figure 74-10. Lateral view of the pelvic floor with urethra, vagina, and fascial tissues transected at the level of the vesical neck drawn from three-dimensional reconstruction, indicating compression of the urethra by downward force (arrow) against supportive tissues indicating the influence of abdominal pressure on urethra.

considered to be essential, is not necessarily essential to restoring continence in women who leak with SUI. The essential element to restoring continence, then, rests with restoring the layer of support to the posterior urethra and therefore allowing the urethra to be compressed adequately (DeLancey, 1997).

Petros and Ulmsten (1990) proposed an additional explanation for both stress and urge incontinence. The “integral theory” pinpoints the site of the maximal continence zone in the midurethra at the pubourethral ligaments. During times of bladder storage, anterior forces from the pubococcygeus muscle pull the vagina up against the pubourethral ligament to close the urethra. Additionally, backward forces stretch the vagina and bladder neck in a plane around the pubourethral ligament to allow proximal urethral closure (Petros and Skilling, 2001; Petros and Woodman, 2008). The authors contend that laxity of these forces secondary to connective tissue damage leads to the loss of urine with stress and, further, that muscular forces stretching the vaginal membrane against the ligaments activate stretch receptors causing them to fire prematurely. This last event is thought to contribute to urinary urgency and UUI. The concept of midurethral tension-free sling procedures to treat symptomatic SUI was largely based on treating the anatomic deficiencies proposed by Petros and Ulmsten (1990) in their discussion of the integral theory.

Intrinsic Sphincteric Deficiency

Despite the breakthrough in understanding urethral anatomy, function, and support, it remained clear that even with extensive pelvic relaxation and urethral hypermobility, some women were completely continent. More importantly, some women with no hypermobility had fairly severe SUI, particularly those with scarred urethras or certain types of neurogenic disease. The concept of intrinsic sphincteric deficiency (ISD) was introduced in the urologic literature by McGuire and Lytton (1978) in their initial description of the use of autologous fascial slings for patients with SUI resulting from absent or poor urethral function, typically secondary to previous urethral surgeries. In this landmark article, the authors noted significant improvements in the vast majority of patients with severe urethral dysfunction (diagnosed urodynamically) treated by pubovaginal sling, without apparent obstruction in early assessment. Blaivas and Olsson further characterized ISD later (Blaivas and Olsson, 1988) as type III UI to distinguish it from forms of incontinence involving urethral mobility. ISD implies the sphincter activity itself is dysfunctional, whether because of a neural or a structural problem. Patients with ISD have classically been described as having a “pipe stem” urethra, meaning a fixed urethra with little intrinsic closure function. This finding may result from previous surgery and is typically iatrogenic in some way. Subtler forms of ISD, which typically coexist with the finding of urethral hypermobility, are more commonly found and are likely responsible for most forms of SUI. ISD in this setting may be secondary to ischemic injury (birth or other trauma) or other forms of progressive pudendal nerve damage.

ISD was historically identified urodynamically using the concept of VLPP (McGuire et al, 1996). VLPP testing describes the abdominal pressure required to cause urethral incontinence. VLPP measurement cannot be made in the presence of a detrusor contraction or altered bladder compliance. Low VLPP (less than 60 cm water) has been associated with ISD, and this has been used in the past to dictate specific treatments for ISD, such as bulking agents or pubovaginal sling. Both of these treatments may address sphincteric abnormalities and thus were presumed to be more appropriate treatment selections for patients without hypermobility. Our current understanding is that most forms of SUI likely involve some degree of ISD, even if urethral hypermobility is present. This fact underlies the finding that even among patients with hypermobility, treatments such as pubovaginal sling, midurethral sling, and even bulking agents appear to have reasonable efficacy (Blaivas and Chaikin, 2011). It is clear, however, that the reverse is untrue—that treatments aimed specifically at the correction of hypermobility may be less helpful in the presence of severe ISD and limited

mobility. It is for this reason that Burch colposuspension and various needle suspension procedures, for example, have limited usefulness in the treatment of ISD, particularly in the setting of a fixed urethra.

KEY POINTS: THEORIES ON THE PATHOPHYSIOLOGY OF STRESS URINARY INCONTINENCE IN WOMEN

- **Pressure transmission theory**—proposes that descent of the urethra from its protected intraperitoneal position increases the forces placed on more distal urethral continence mechanisms and promotes SUI. Supported by Enhorning (1961) and others, these theories contend that the proximal urethra functionally becomes contiguous with the bladder and, as such, transmission of intra-abdominal forces is placed directly on the urethra. More distal sphincteric mechanisms may not adequately protect against incontinence.
- **Hammock hypothesis**—proposed by DeLancey (1994). Suggests that the urethra is not truly in an intraperitoneal position, rather that firm posterior and lateral support allows compression of the urethra at times of increased intra-abdominal pressure, when combined with active midurethral sphincteric mechanisms. Loss of this support permits the development of SUI. This theory combines elements of previous theories on urethral hypermobility into a more cohesive, anatomically based explanation.
- **Integral theory**—proposed by Petros and Ulmsten (1990). Suggests that both urge and SUI are caused by laxity in the vaginal wall itself and/or surrounding structures (such as pubourethral ligaments). Stretch receptors in the bladder neck, activated at times of increased abdominal pressure with urine deposition in the proximal urethra/bladder neck, are proposed to contribute to urgency incontinence.

PATHOPHYSIOLOGY OF INSENSIBLE INCONTINENCE

Although in most instances women will be able to discern when urine loss occurs, in other cases the timing of incontinence may be unclear. Particularly when incontinence cannot be demonstrated on examination, or cannot be discerned from a thorough history, urodynamic studies and other diagnostic tests might help to determine the cause of leakage. In most cases, the common types of incontinence will still be responsible even if urine loss is insensible, such as sphincteric deficiency or detrusor overactivity incontinence. Other less common causes, however, must be considered, particularly when standard nonoperative measures fail to improve the symptom. Other causes such as urethral diverticula (typically postvoid urine loss), ectopic ureter (typically continuous urine loss), and overflow incontinence (typically small-volume frequent urine loss, urinary frequency, and small volume voids) should be considered. Although urodynamics should identify overflow incontinence, it may miss the other sources, and it may be nondiagnostic in a relatively frequent number of cases (Brucker et al, 2013). Thus in unique circumstances, pelvic MRI (to identify suspected urethral diverticula) and upper tract studies (to identify ureteral ectopy) should be considered in the evaluation of women with insensible urine loss.

PATHOPHYSIOLOGY OF PELVIC ORGAN PROLAPSE

Pelvic support defects are similar to hernias in that they have disruptions in the continuity of their supporting connective tissue (Shull, 1999). However, with the exception of enteroceles, POP is not usually associated with protrusions of the peritoneal sac containing intra-abdominal materials.

Normal pelvic support mechanisms can be separated into three levels, as eloquently described in a cadaver dissection study by John DeLancey (1992) (Fig. 74-11). The upper third of the vagina

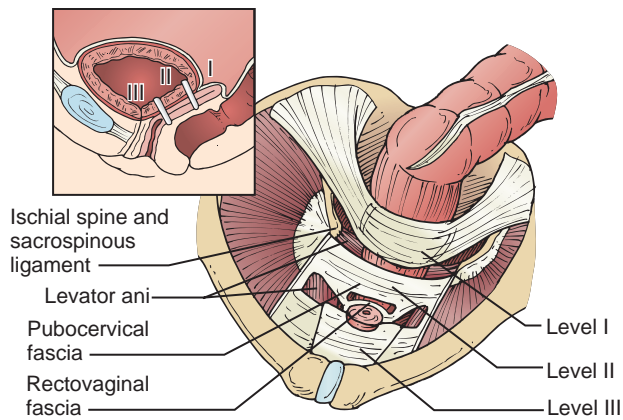


Figure 74-11. Levels of support, as described by DeLancey (1992). In level I, the paracolpium suspends the vagina from the lateral pelvic walls. In level II, the vagina is attached to the arcus tendineus of the pelvic fascia and superior fascia of the levator ani muscles. The vagina's lower third fuses with the perineal membrane, levator ani muscles, and perineal body (level III).

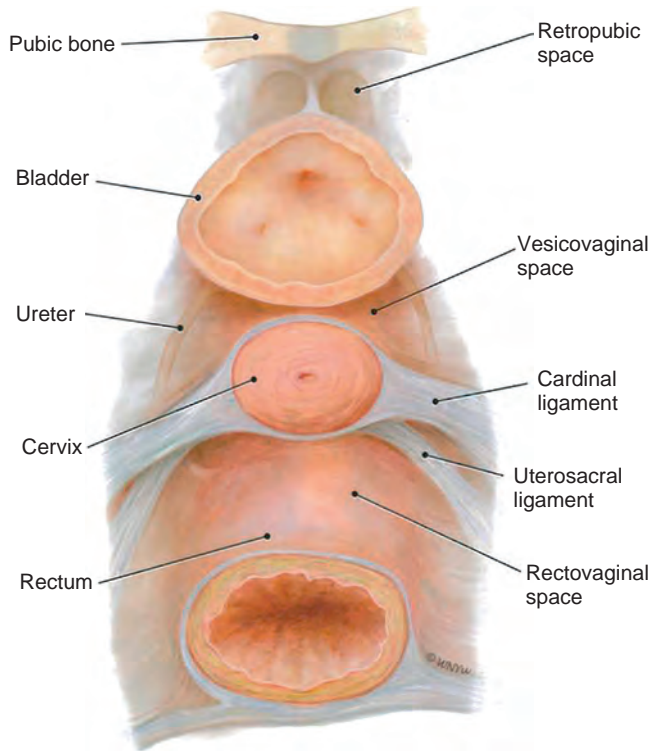


Figure 74-12. The cardinal and uterosacral ligaments provide support to the cervix and indirectly to the bladder base. The retropubic, vesicovaginal, and rectovaginal spaces are seen at the level of the cervix. (Modified from Raz S, Stothers L, Chopra A. Vaginal reconstructive surgery for incontinence and prolapse. In: Walsh PC, Retik AB, Vaughan Jr ED, et al, editors. Campbell's urology. 7th ed. Philadelphia: Saunders; 1998. p. 1059–94.)

(level I) is suspended by a continuation of the cardinal ligament known as the paracolpium or the uterosacral ligament/cardinal ligament complex. Level I support suspends the uterus and upper vagina to the sacrum and lateral pelvic sidewall. Level II support includes the paravaginal attachments of the middle third of the vagina laterally to the superior fascia of the levator ani muscle and the arcus tendineus fascia pelvis (Fig. 74-12). Loss of level II support contributes to anterior vaginal wall prolapse/cystocele. The vagina's

lower third fuses with the perineal membrane, levator ani muscles (superficial and deep perineal muscles), and perineal body (level III). Loss of level III support anteriorly results in urethral hypermobility, whereas loss of posterior level III support results in a distal rectocele or perineal descent. According to DeLancey, the paracolpium's vertical fibers in level I form the critical factor that differentiates vaginal eversion from posthysterectomy cystocele, rectocele, or enterocele in which the vaginal apex remains well suspended. Enteroceles are often an asymptomatic consequence of vaginal vault prolapse in that the small bowel simply fills the space previously occupied by the uterus. However, when the small bowel enters the cul-de-sac between the vagina and the rectum in a woman with a relatively well-supported vaginal apex, severe defecatory dysfunction and straining may occur.

Cystoceles have classically been characterized as either those with a central defect (weakness in the midline perivesical fascia) and those with a lateral defect (those with defects in lateral vaginal attachments resulting in paravaginal defects (Shull and Baden, 1989). In all likelihood, the majority of cystocele defects are a combination of both defects. Of note, the loss of apical support (level I) is highly correlated with the development of high-stage cystoceles, and the identification of apical prolapse is crucial in optimizing cystocele management. Rooney and colleagues (2006) used POPQ measurements and found that high-stage cystocele defects are invariably associated with apical prolapse. This fact underlies the high failure rate of anterior colporrhaphy in the treatment of high-stage anterior POP, because the apical defect is essentially ignored. In fact, in a study of Medicare claims by Eilber and colleagues (2013) isolated cystocele repairs were found to have a 20% reoperation rate during a period of 10 years. This number was reduced to 11% when the initial cystocele repair was combined with an apical support procedure.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Objectives

General Patterns of Neuropathic Voiding Dysfunction

Disease at or above the Brainstem

Diseases Primarily Involving the Spinal Cord

Disease Distal to the Spinal Cord

Miscellaneous Neurologic Diseases Causing Lower Urinary Tract Dysfunction

Miscellaneous Conditions Definitely, Probably, or Possibly Related to Neuromuscular Dysfunction

Treatment of Neurogenic Lower Urinary Tract Dysfunction: Overview

OBJECTIVES

The first part of this chapter is a summary of the abnormalities of the micturition cycle produced by different types of neuromuscular disease, injury, or dysfunction. The background material for the central and peripheral factors involved in the pathophysiology and pharmacology of lower urinary tract (LUT) function (and dysfunction) are discussed in Chapters 69 and 79. An understanding of the physiology and pharmacology of normal urinary storage and emptying, as well as the patterns and location of neuropathic insults, will usually, but not always, enable one to easily infer the associated lower tract dysfunction. The second part of the chapter summarizes certain secondary factors that can modify the type of observed LUT dysfunction. These secondary factors are important to consider because they cause persistence of both storage and voiding abnormalities, even after the initial precipitating factors have resolved or have been corrected. The third part of the chapter describes in detail the specific types of LUT dysfunction that occur secondary to the most common categories of neuromuscular disease, injury, or dysfunction. Ideally, in any such discussion, the expected states of the following urodynamic parameters should be described (see Chapter 73 for specific definitions of terms) (Abrams et al, 2003):

- Sensation (normal, absent, impaired)
- Detrusor activity (normal, overactive, areflexic, impaired contractility)
- Detrusor compliance (normal, decreased, increased)
- Smooth sphincter activity (synergic, dyssynergic)
- Striated sphincter activity (synergic, dyssynergic, bradykinetic, impaired voluntary control, fixed tone)

Table 75-1 is a summary of many of these dysfunctions, grouped by the status of the aforementioned urodynamic parameters and the most common type of abnormal pattern resulting from a given disease or injury. This abbreviated classification is not meant to be all-inclusive but to simply indicate that, for the most part, an individual with a specific neurologic abnormality and subsequent LUT dysfunction will typically have the type of dysfunction listed.

The chapter concludes with a general consideration of the principles that should guide the selection of therapeutic interventions for the types of dysfunctions considered. Other chapters cover in detail the individual therapies and their potential consequences. The types of LUT dysfunction in the pediatric age group and their management are specifically covered in Chapter 142.

As an apology to others in the field whose works have not been specifically cited or have not been cited as frequently as they could have been, please note that citations have generally not been chosen, except where noted, because of initial publication or origi-

nal thinking on a particular subject but primarily because of their review or informational content.

GENERAL PATTERNS OF NEUROPATHIC VOIDING DYSFUNCTION

In general, discrete neurologic lesions affect the filling and storage and the emptying and voiding phases of LUT function in a relatively consistent manner. This nature of the impact is dependent on (1) the area(s) of the nervous system affected; (2) the physiologic function(s) and the contents and location of the area(s) affected; and (3) whether the lesion or process is destructive, inflammatory, or irritative. It is important to note that the acute dysfunction produced may, for a variety of reasons, be different from the chronic one.

KEY POINT: LESIONS ABOVE THE BRAINSTEM

- Neurologic lesions above the brainstem (with rare exceptions) that have an impact on micturition typically result in involuntary bladder contractions (detrusor overactivity) with coordinated sphincter function (smooth and striated sphincter synergy). Sensation and voluntary striated sphincter function are usually preserved, but sensation may be deficient or delayed. Detrusor areflexia may, however, occur, either initially or as a permanent dysfunction. Urinary incontinence may occur owing to the detrusor overactivity.

KEY POINT: COMPLETE SPINAL CORD LESIONS FROM SPINAL CORD LEVEL T6 TO S2

- After recovering from a period of spinal shock, patients with complete lesions of the spinal cord between spinal cord level T6 and S2 usually exhibit absent sensation, involuntary bladder contractions (detrusor overactivity), and smooth sphincter synergy, but striated sphincter dyssynergia. In addition, patients with lesions above spinal cord level T6 may experience smooth sphincter dyssynergia and autonomic hyperreflexia. Incontinence may occur owing to detrusor overactivity; however, the outlet obstruction resulting from striated sphincter dyssynergia can also cause urinary retention and overflow incontinence.

TABLE 75-1 Most Common Patterns of Voiding Dysfunction Seen with Various Types of Neurologic Disease or Injury*

DISORDER	DETRUSOR ACTIVITY	COMPLIANCE	SMOOTH SPHINCTER	STRIATED SPHINCTER	OTHER
Cerebrovascular accident	Ov	N	S ±VC	S	There may be decreased sensation of lower urinary tract events.
Brain tumor	Ov	N	S	S	There may be decreased sensation of lower urinary tract events.
Cerebral palsy	Ov	N	S	S D (25% of those with detrusor overactivity) ±VC	
Parkinson disease	Ov I	N	S	S Bradykinesia	
Multiple system atrophy	Ov I	N ↓	Op	S	Striated sphincter may exhibit denervation.
Multiple sclerosis	Ov	N	S	S D (30%-65%)	Dyssynergia figures refer to percentage of those with detrusor activity.
Spinal cord injury Suprasacral	Ov	N	S	D	Smooth sphincter may be dyssynergic if lesion is above T7.
Sacral	A	N ↓ (may develop)	CNR Op (may develop)	F	
Autonomic hyperreflexia	Ov	N	D	D	
Myelodysplasia	A	N O	Op ↓ (may develop)	F	Findings vary widely in different series. Striated sphincter commonly shows some evidence of denervation.
Tabes, pernicious anemia	I A	N ↑	S	S	Primary problem is loss of sensation. Detrusor may become decompensated secondary to overdistention.
Disk disease	A	N	CNR	S	Striated sphincter may show evidence of denervation and fixed tone.
Radical pelvic surgery	I A	↓ N	Op	F	
Diabetes	I A Ov	N ↑	S	S	Sensory loss contributes, but there is a motor neuropathy as well.

Compliance: N, normal; ↓, decreased; ↑, increased.

Detrusor activity: A, areflexia; I, impaired; Ov, overactive.

Smooth sphincter: CNR, competent, nonrelaxing; D, dyssynergic; Op, open, incompetent at rest; S, synergic.

Striated sphincter: D, dyssynergic; F, fixed tone; S, synergic; ±VC, voluntary control may be impaired.

*See chapter content for percentages of patients with dysfunction.

KEY POINT: TRAUMA OR DISEASE BELOW SPINAL CORD LEVEL S2

- Patients with significant nerve root trauma or injury or disease below spinal cord level S2 typically do not manifest involuntary bladder contractions. After the period of spinal shock resolves, persistent detrusor areflexia is the rule. Various forms of decreased compliance during filling (usually resulting from bladder wall fibrosis) may occur and will depend on the type and extent of neurologic insult. An open smooth sphincter area may result, but whether this is caused by sympathetic or parasympathetic decentralization or defunctionalization (or both or neither) has never been determined. Various types of striated sphincter dysfunction may occur, but commonly an injury in this area is associated with a residual resting sphincter tone (not the same as dys-synergia) and striated sphincter activity is not under voluntary control.

KEY POINT: INTERRUPTION OF PERIPHERAL REFLEX ARC

- Processes that affect or interrupt the peripheral reflex arc (coordination among spine, bladder, and urethra) may cause storage or emptying dysfunctions that resemble those seen after distal spinal cord or nerve root injury. Detrusor areflexia often develops, and low compliance may result. The smooth sphincter may be relatively incompetent, and the striated sphincter may exhibit fixed residual tone that does not voluntarily relax. True peripheral neuropathy can be motor or sensory, and, at least initially, the usual sequelae can be expected.

Plasticity

When engaging in a discussion of the nervous system and the structures it innervates, *plasticity* refers to the inherent capacity to undergo structural and functional modification. These induced changes can be reflected on a number of levels: structural, metabolic, and neurologic. In addition, the neurologic changes can then be reflected on a number of levels: morphologic, neurochemical, electrical, and organizational. Each of these changes can be studied at a variety of different levels, from investigation of the end product (e.g., the clinical manifestations) to exploration of the initial molecular correlates and the factors that induce or affect them. The chronic clinical manifestations that we associate with a particular voiding dysfunction may in fact be the ultimate results of the phenomena that fall under the rubric “plasticity.” Up to a certain point the changes may be reversible, but after a certain point they may not be. Thus plasticity may account for the persistence of clinical symptoms after the initial stimulus for dysfunction has been eliminated or corrected.



A more detailed explanation of plasticity as it applies to the neuromuscular dysfunction of the LUT can be found on the Expert Consult website.

DISEASE AT OR ABOVE THE BRAINSTEM**Cerebrovascular Disease****Cerebrovascular Accident (Stroke)**

Cerebrovascular accident (CVA) is a common cause of death and one of the most common causes of disability in the world. CVA is the most devastating manifestation of cerebrovascular disease, with an annual incidence in the United States that has been cited as approximately 795,000 (www.strokecenter.org) and 15 million

worldwide (www.strokecenter.org). Approximately one quarter to one third of CVAs are fatal, and another third necessitate long-term nursing care ([Marinkovic and Badlani, 2001](#)). The prevalence of stroke in persons older than 65 years has been cited as approximately 60 in 1000, and in persons 75 years of age and older, 95 per 1000 ([Khan et al, 1990](#); [Public health and aging, 2003](#)). [Wyndaele and colleagues \(2005, 2009\)](#) estimated that 1 in 200 individuals will sustain a CVA. Although CVA is the third leading cause of death in the United States ([Marinkovic and Badlani, 2001](#)), approximately 75% of stroke victims survive ([Blaivas et al, 1998a](#)). Of the survivors, only 10% are unimpaired, whereas 40% have mild residual effects, 40% have significant disability, and 10% require institutionalization ([Arunable and Badlani, 1993](#)). Thrombosis, occlusion, and hemorrhage are the most common causes of stroke, leading to ischemia and infarction of variably sized areas in the brain, usually around the internal capsule. [Marinkovic and Badlani \(2001\)](#) cite evidence that arterial occlusion is found in 80% of patients.

After an initial acute CVA, urinary retention from detrusor areflexia often occurs. The neurophysiology of this “cerebral shock” is unclear. After a variable degree of recovery from the neurologic lesion, a fixed deficit may become apparent over a few weeks or months. The most common long-term expression of LUT dysfunction after CVA is phasic detrusor overactivity ([Wein and Barrett, 1988](#); [Khan et al, 1990](#); [Fowler, 1999](#); [Wyndaele et al, 2005](#)). Sensation is variable but most typically intact, and thus the patient has urinary urgency and frequency with detrusor overactivity. The appropriate response to detrusor overactivity is to try to inhibit the involuntary bladder contraction by voluntarily and forcefully contracting the striated sphincter. If this can be accomplished, only urgency and frequency result; if not, the result is urgency urinary incontinence.

The exact acute and chronic incidence of any voiding dysfunction after CVA is difficult to cull from the literature. The cited prevalence of urinary incontinence ranges from 32% to 79% on hospital admission for CVA, 25% to 28% on discharge, and 12% to 19% several months later ([Brittain et al, 1998](#)). Based on their experience and that of others, [Sakakibara and associates \(1999\)](#) estimate that some LUT dysfunction occurs in 20% to 50% of patients with focal brain lesions from tumor and CVA. They cite nocturnal frequency as the most common manifestation, affecting 36% of their patients. Urgency urinary incontinence occurred in 29%, “voiding difficulty” in 25%, urgency without incontinence in 25%, diurnal frequency in 13%, and enuresis in 6%. Acute urinary retention occurred in only 6%. [Fowler \(1999\)](#) cited studies showing that the presence of urinary incontinence within 7 days of a stroke is a more powerful prognostic indicator for poor survival and functional dependence than a depressed level of consciousness. [Cariballa \(2003\)](#) found that urinary incontinence at admission had a hazard ratio of 2.8 as a predictor of death from CVA at 3 months. Stroke patients who were incontinent had an increased risk of infectious complications and were malnourished, possible confounders of the increased death risk. [Patel and colleagues \(2001\)](#) reported that urinary incontinence was associated with age older than 75 years, dysphagia, visual field defect, and motor weakness. Certain specific types of strokes also appear to be associated with unusual forms of incontinence. Lenticulocapsular strokes have been noted to be associated with incontinence. Fifty-two percent of patients with strokes in this area of the brain demonstrated post-stroke emotional incontinence, which was not related to other aspects of stroke or gender ([Kim, 2002](#)). The prevalence of urinary and fecal incontinence after hemispheric vascular accident has ranged from 21% to 56% in earlier studies. Urinary incontinence associated with fecal incontinence is the most prevalent condition on admission to rehabilitation units after a vascular event, being prevalent in approximately 33% of patients. Isolated urinary incontinence follows at a rate of 12% and finally isolated fecal incontinence with 8%. At the completion of rehabilitation, combined fecal and urinary incontinence decreases to 15%, isolated urinary incontinence to 8%, and isolated fecal incontinence to approximately 5%. The most prevalent form of urinary incontinence is impaired awareness (insensate or delayed awareness of voiding

Perhaps the most obvious changes that occur as a result of plasticity are (1) chronic changes in neural organization of the micturition reflex that occur after complete spinal cord transection above the level of S2 and (2) the changes in peripheral neural organization that occur after damage to or transection of the peripheral parasympathetic innervation of the LUT. Specific details are contained in the relevant sections of this chapter.

What may be less obvious as a phenomenon related to plasticity are many of the changes that occur subsequent to bladder outlet obstruction. The most obvious changes that occur are those related to muscle and collagen content. However, these are themselves initiated by molecular events that ultimately cause increased contractile protein synthesis and hypertrophic bladder tissue growth (Levin et al, 1995). The initial stimulus might be stretch from overdistention (Cheng et al, 1999) or ischemia, likewise from distention (Chen et al, 1996). Compensation of the bladder smooth muscle cells to initially overcome the increased demand associated with obstruction is associated with alterations in the expression and function of many proteins involved in excitation-contraction coupling and active force generation of bladder smooth muscle (Chacko et al, 1999). Although urodynamic studies reflect obstruction, satisfactory emptying is usually preserved. Changes in the composition of the extracellular matrix occur as well, presumably also caused by an initial stretch stimulus. The ratio of type III collagen to type I collagen increases, and the localization of type III collagen changes as well (within some muscle bundles as well as around them) (Macarak and Howard, 1999). The increase in connective tissue could be related to an increase in certain growth factors emanating from the smooth muscle or to a decrease in the activity of certain metabolic pathways contributing to the breakdown of various forms of collagen (Borer et al, 1999). Ischemia, which itself can be caused by obstruction or by atherosclerosis, has also been hypothesized to contribute to remodeling of the extracellular matrix and fibrosis (Azadzoi et al, 1999; Mostwin et al, 2005).

Bladder outlet obstruction has also been postulated to be associated with partial denervation, owing to damage to the intrinsic innervation of the bladder smooth muscle from a combination of pressure and ischemia (Turner and Brading, 1997; Mostwin et al, 2005). With all of these potential adverse changes occurring, it seems almost miraculous that the bladder is able to maintain its function, but it does for variable periods of time under different circumstances. However, there does come a point when the ability to fill and store and empty is adversely affected, but not necessarily to the same extent. Filling and storage changes seem related primarily to (1) changes in the extracellular matrix, leading to decreased compliance, and (2) the appearance of phasic bladder overactivity. This overactivity could be myogenic in origin (caused by partial denervation—see Turner and Brading, 1997), or it could be neurogenic and related to another facet of plasticity. Afferent neuroplasticity mediated by nerve growth factors (NGFs) occurs experimentally in response to bladder outlet obstruction, a phenomenon that is inhibited by autoimmunization against NGF (Steers et al, 1996). The ability to empty can be adversely affected by factors related to neurogenic or myogenic mechanisms. The myogenic mechanisms could include a reversal of the compensatory changes that initially occur (see Chacko et al, 1999) or a breakdown of the structure and function of the proteins that enable the smooth muscle cells to take up, store, and release calcium, affecting the calcium activation of the contractile apparatus (Zderic et al, 1998; Chacko et al, 1999).

Furthermore, these neurogenic changes associated with outflow obstruction may alter the neurotransmitter milieu of the LUT. In a model of fetal sheep bladder outlet obstruction, ligation of the urachus at mid-gestation in fetal sheep for 1 month resulted in a shifting of muscarinic, purinergic, and nitrergic mechanisms normally present during fetal development and growth. With outflow obstruction, bladder hypocontractility was induced and contractile forces decreased during stimulated conditions, consistent with denervation and the possibility of atropine resistance. Normal urothelial exerted negative ionotropic effects (nitric oxide mediated) were also lost after obstruction. In addition, loss of compliance resulted in reduced elasticity in the obstructed bladders, consistent with denervation (Thiruchelvam et al, 2003). At this time, one cannot reverse certain precipitating factors for the initiation of LUT dysfunction, such as spinal cord transection and peripheral nerve injury. Hence the fact that the changes that result from the neuroplasticity induced by these insults are permanent is not surprising. However, **there are instances in which the initiating “cause” of a particular voiding dysfunction can be removed and yet the symptoms do not entirely disappear. This may be another instance in which neuroplasticity is a major factor.** For instance, irritative lower urinary tract symptoms (LUTS) fail to disappear in a certain percent of patients with outlet obstruction who undergo surgical correction. Chai and coworkers (1998) found an increased incidence of a positive ice-water test result in patients with bladder outlet obstruction, indicating the presence of a primitive reflex circuitry capable of mediating an abnormal micturition reflex. Because the ice-water test is mediated by C-afferent fibers, the findings support the hypothesis that bladder outlet obstruction is associated with afferent neuroplasticity, detectable in this case by ice-water cystometry. Furthermore, persistence of this afferent neural plasticity after relief of the obstruction could account for at least a proportion of the symptomatic treatment failures after urodynamically successful outlet reduction.

Vizzard (1999, 2000a, 2000b, 2000c, 2000d) and Qiao and Vizzard (2004) have written prolifically about various aspects of neuroplasticity, specifically on the occurrence and potential role of such changes in altered LUT dysfunction after spinal cord injury (SCI) and irritant-induced cystitis. Changes in spinal cord protein expression from retrogradely transported bladder neurotrophic factors could play a role in the neurochemical, electrophysiologic, and organizational properties of the LUT seen in both of these conditions and could account, in the latter case, for persistence of symptomatic and/or urodynamic abnormalities after the irritating stimulus has been removed (e.g., in patients with interstitial cystitis). Those especially interested in this area should consult Vizzard's articles and associated references.

events), occurring in 12% to 58% of individuals, as compared with pure urge, which occurs in 9% to 42%. This impaired awareness incontinence is a more significant negative prognostic indicator for resolution of symptoms as compared with patients who retain the sensation of urgency (Kovindha et al, 2010; McKenzie and Badlani, 2012).

In a nationwide Danish assessment of patients after acute stroke, at 1 month after the stroke, patients were asked to assess the severity of their urinary symptoms as well as bother related to each symptom. A total of 482 eligible patients were assessed; 94% of patients had had at least one urinary symptom in the prior 2 weeks, with nocturia being the most frequent (76%), followed by urgency (70%) and urinary daytime frequency (59%). Urgency was the symptom associated with the most bother, followed by nocturia and finally frequency. If a patient had at least one symptom, bother was at least 78%. Bother caused by urinary symptoms was associated with severity of lower extremity paresis, as well as use of analgesics. The overall conclusion was that LUTS were very highly prevalent and also had significant impact on overall bother in this population (Tibaek et al, 2008).

Previous descriptions of LUT dysfunction patterns after CVA have overwhelmingly cited detrusor overactivity with coordinated striated and smooth sphincter activity (Kolominsky-Rabas et al, 2003; Wyndaele et al, 2005; Drake et al, 2013). It is difficult to reconcile this with the relatively high rates of urinary incontinence in these patients, despite the probability that a percentage of these patients already had an incontinence problem before the CVA. Tsuchida and coworkers (1983) and Khan and associates (1990) made early significant contributions in this area by correlating the urodynamic and computed tomographic pictures after CVA. They concluded that patients with lesions in only the basal ganglia or thalamus have normal sphincter function. This indicates that these patients could voluntarily contract the striated sphincter and abort or minimize the effect of an abnormal micturition reflex when an impending involuntary contraction was sensed. Most patients with involvement of the cerebral cortex, internal capsule, or both were unable to forcefully contract the striated sphincter under these circumstances. Although the authors and others have called this problem “uninhibited relaxation of the sphincter” (Marinkovic and Badlani, 2001), this term is a misnomer. In actuality, the term implies that a profound abnormality exists in the cerebral to corticospinal circuitry that is necessary for voluntary control of the striated sphincter. In an assessment of 192 stroke patients, of whom 69 had undergone urodynamic evaluation, minor urodynamic differences were noted among patients with strokes in the dominant versus nondominant hemisphere versus bilateral hemispheric strokes. Of the dominant hemispheric stroke patients, 64.2% demonstrated detrusor overactivity; detrusor underactivity was present in 35% of the patients. In contradistinction, nondominant hemispheric stroke resulted in detrusor overactivity in 66% of patients and detrusor underactivity in 33%, whereas of bilateral stroke patients, 60% demonstrated detrusor overactivity and 40% detrusor underactivity. Therefore no significant difference was noted between location of stroke and urodynamic findings (Kim et al, 2010).

In a summary of findings obtained from electrical stimulation, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), Griffiths (2004) implicated the Barrington nucleus, the so-called M region, as responsible for normal voiding (coordinated striated sphincter relaxation followed by detrusor contraction). His findings indicate that a second region in the pons—the L region—may be responsible for maintaining striated sphincter tone between voids, although the evidence for this is less convincing. Griffiths (1998), studying the results of single-photon emission computer tomography (SPECT) in a group of geriatric patients with established urinary incontinence, found urgency incontinence in approximately 50%; half of these patients had reduced sensation of bladder filling, more pronounced in men than in women. True urgency urinary incontinence with reduced bladder sensation was associated with global underperfusion of the cerebral cortex, specifically on the right side and the frontal areas. Thus, there are two possible mechanisms for the incontinence

associated with involuntary bladder contractions in patients who have sustained a CVA: (1) impaired striated sphincter control and (2) lack of appreciation of bladder filling and impending bladder contraction.

In general, the smooth sphincter is unaffected after CVA and remains synergic. Some authors describe striated sphincter dys-synergia in 5% to 21% of patients who manifest brain disease and voiding dysfunction (Sakakibara et al, 1999); however, this appears to be incompatible with accepted neural circuitry. True detrusor striated sphincter dyssynergia does not occur in this situation, although pseudodyssynergia has been found to occur during urodynamic testing of these patients (Wein and Barrett, 1982). This finding refers to an electromyographic sphincter “flare” during filling cystometry that is secondary to attempted inhibition of an involuntary bladder contraction by voluntary contraction of the striated sphincter. The guarding reflex in these patients usually remains intact (Siroky and Krane, 1982).

Detrusor hypocontractility or areflexia may rarely persist after CVA. The exact incidence of areflexia as a cause of chronic voiding symptoms after CVA is uncertain, but some estimates place it as high as 20% (Arunable and Badlani, 1993). Linsenmeyer and Zorowitz (1992) found that 35% of men who were incontinent after a CVA had involuntary bladder contractions with urodynamic evidence of bladder outlet obstruction and 6% had detrusor areflexia. In comparison, 13% of women in this group had involuntary contraction with a large residual urine volume and 19% had areflexia. Poor flow rates and high residual urine volumes in a man with LUTS before CVA usually indicate prostatic obstruction. However, a full urodynamic evaluation to exclude detrusor overactivity with impaired contractility as a cause of symptoms is advisable before committing such a patient to surgical reduction of bladder outlet obstruction.

KEY POINT: LOWER URINARY TRACT DYSFUNCTION AFTER CEREBROVASCULAR ACCIDENT

- In the functional system of classification (see Chapter 70), the most common type of LUT dysfunction after CVA would be characterized as a failure to store secondary to detrusor overactivity, specifically involuntary bladder contractions. In the International Continence Society (ICS) classification system, the dysfunction would most likely be classified as overactive neurogenic detrusor function, normal sensation, low capacity, normal compliance, and normal urethral closure function during storage; regarding voiding, the description would be normal detrusor activity and normal urethral function, assuming that no anatomic obstruction existed. Treatment, in the absence of coexisting significant bladder obstruction or significantly impaired contractility, is directed at decreasing bladder contractility and increasing bladder capacity (see Table 70-1 and Box 70-3 in Chapter 70).

Because strokes are often a condition sustained by the elderly, the presentation and management of these patients may be more complex owing to preexistent LUT pathology. Although the urinary symptoms may have been manageable before the CVA, they may become significantly worse afterward. As Andrews (1994) noted, other aspects of the brain damage can affect general rehabilitation and control of the LUT dysfunction. These may include cognitive impairment, dysphasia, inappropriate and aggressive behavior, impaired mobility, and low motivation. In addition, the LUT dysfunction may be significantly and adversely affected by treatment regimens that concentrate on detrusor overactivity alone (e.g., anticholinergic or antispasmodic therapy). Vigorous pharmacologic therapy of detrusor overactivity with agents that cross the blood-brain barrier and inhibit M₁ muscarinic receptors may worsen preexisting confusion, disorientation, and other problems of mentation.

The underlying basic mechanisms of bladder overactivity after CVA remain unclear. Experimental models of middle cerebral artery occlusion have been described, followed by reperfusion to simulate the clinical condition (Pehrson et al, 2003). Shimizu and associates (2003) described the development of a rat model involving an electrolytic lesion of the right basal forebrain. After middle cerebral artery occlusion, neural signaling changes seem to involve glutaminergic, dopaminergic, and γ -aminobutyric acid (GABA)-ergic mechanisms (Kanie et al, 2000; Yokoyama et al, 2002). In addition, Fu and coworkers (2004) have shown upregulation of proinflammatory cytokines and the neuronal nitric oxide synthase gene in the spinal cord and bladder after acute vascular injury. Such findings raise interesting theoretic possibilities for central pharmacologic management. Cerebrovascular injury manifesting with suprapontine injury also can result in an alteration of urinary urgency perception, producing symptomatic frequency and urge incontinence. The underlying pathophysiology of this effect may be elimination of cortical ambulatory control of the pontine micturition center (PMC), possibly combined with facilitation of excitatory control. These aberrant signaling pathways may arise from abnormalities in acetylcholine, dopamine, and glutamate regulatory changes with upregulation or downregulation of excitatory and inhibitory pathways resulting in the overactivity associated with diagnosis (Yokoyama et al, 2009).

Brainstem Stroke

Sakakibara and associates (1996d) reported on 39 patients with brainstem stroke, of whom 19 had LUTS. Problems were more common after damage from bleeding than from infarction. The major problems were nocturnal frequency and voiding difficulty in 6, urinary retention in 8, and urinary incontinence in 3. Symptoms did not occur in those with strictly midbrain lesions but occurred in 18% of patients with medullary stroke and in 35% of patients with pontine lesions. Detrusor overactivity was found in 8 of the 11 symptomatic patients who underwent urodynamic evaluation, and low compliance was found in 1 patient. What was interpreted as striated sphincter dyssynergia was reported in 5 of the 11 patients, and what was called uninhibited sphincter relaxation occurred in 3. The authors concluded that lesions of the dorsolateral pons involving the pontine reticular nucleus, reticular formation, and locus ceruleus were mainly responsible for the micturition disturbances in patients with brainstem lesions. Furthermore, the authors felt that these findings corroborated the presence of a PMC in humans, corresponding to the pontine storage and micturition centers reported in animal studies.

Dementia

Dementia is a poorly understood disease complex involving atrophy and the loss of both gray and white matter of the brain, especially in the frontal lobes, causing deficits with memory and the performance of tasks requiring intellectual mentation. Associated conditions include widespread vascular disease, Alzheimer disease, Pick disease, Creutzfeldt-Jakob disease, syphilis, heat trauma, and encephalitis. Alzheimer disease is the principal cause of dementia in the elderly (Wyndaele et al, 2005; Drake, et al, 2013). Although urinary dysfunction does not consistently accompany dementia, when voiding dysfunction occurs the result is typically incontinence. It is difficult to ascertain whether the pathophysiology and considerations are similar to those in the stroke patient or whether the incontinence reflects a situation in which the individual has simply lost the awareness of the desirability of voluntary urinary control. Even if the person has voluntary sphincter control, such individuals may void when and where they please, because impaired mentation fails to dictate why they should not. Such activity may be caused by detrusor overactivity or an otherwise normal, but inappropriately timed, micturition reflex. An accurate estimate of the prevalence of dementia-associated incontinence is confounded by the difficulty in distinguishing this from age-related changes in the bladder and from other concomitant diseases, as

pointed out by Wyndaele and colleagues (2005) and Drake and coworkers (2013), who cite figures of 30% to 100%. Treatment can be difficult and the outcomes frustrating without a desire for improvement. In addition, therapy that inhibits muscarinic brain receptors may be contraindicated in Alzheimer disease if current theories about its cause are valid (cortical cholinergic loss).

Traumatic Brain Injury

Traumatic brain injury has been cited as the most common form of severe neurologic impairment resulting from trauma (Blaivas and Chancellor, 1995a). As with many neurologic insults, there may be an initial period of detrusor areflexia when LUT dysfunction occurs. With lesions above the PMC, detrusor overactivity and coordinated sphincter function are the most frequent manifestations of chronic LUT dysfunction. In patients who have more isolated brainstem injuries with involvement below the PMC, additional findings may include detrusor striated sphincter dyssynergia.

Chua and colleagues assessed 66 males and 18 females within 6 weeks of acute traumatic brain injury. Of these patients, 62% had urinary incontinence on admission, with urinary retention (defined as postvoid residual volume greater than 100 mL) noted in 9.5%. Sixty-two percent required either indwelling catheters or external collecting devices for urinary maintenance. Urinary incontinence was associated with poor functional status and bilateral lesions, whereas urinary retention was more commonly noted in patients with comorbid diabetes mellitus or fecal impaction. After rehabilitation, 36% remained incontinent (Chua et al, 2003).

Brain Tumor

Disturbances of bladder function have been associated with both primary and metastatic brain tumors. When dysfunction results, it is related to the localized area involved rather than to the tumor type. The areas that are most frequently involved with associated micturition dysfunction are the superior aspects of the frontal lobe (Blaivas, 1985). When LUT dysfunction occurs, it usually consists of detrusor overactivity and urinary incontinence. These individuals may have a markedly diminished awareness of all LUT events and, if so, may be totally unable to even attempt suppression of the micturition reflex. In general, smooth and striated sphincters are synergic, whereas pseudodyssynergia may occur during urodynamic testing. In a review of frontal lobe lesions and bladder control, Fowler (1999) cites instances of improvement of micturition symptoms for a period of time after tumor resection, raising the question of whether the phenomenon of tumor-associated bladder overactivity was a positive one (activating some system) rather than a negative one (releasing a system from control). Urinary retention has also been described in patients with space-occupying lesions of the frontal cortex, in the absence of other associated neurologic deficits (Lang et al, 1996). Posterior fossa tumors may be associated with voiding dysfunction (32% to 70%, based on references cited by Fowler, 1999). Retention or difficulty voiding is the rule, with incontinence being a rare finding.

Cerebellar Ataxia

Cerebellar ataxia refers to a group of diseases involving pathologic degeneration of the nervous system, usually involving the cerebellum but with possible extension to the brainstem, spinal cord, and dorsal nerve roots (Leach et al, 1982). Cerebellar involvement often results in poor coordination, depressed deep tendon reflexes (DTRs), dysarthria, dysmetria, and choreiform movements. LUT dysfunction typically manifests with incontinence, usually associated with detrusor overactivity and sphincter synergy. Retention or high postvoid residual urine volume may occur as well. When present, impaired emptying is most commonly caused by detrusor areflexia, but it may also be associated with detrusor striated sphincter dyssynergia, presumably a result of spinal cord

involvement. Sakakibara and associates (1998b) reported micturition symptoms in 184 patients with spinocerebellar degeneration, of whom 29 (15.8%) had stress urinary incontinence. Although 20 of these 29 also had detrusor overactivity, low compliance, and/or elevated residual urine, the remaining 9 had none of these findings. The authors speculated that, in the absence of other findings, spinal lesions affecting the Onuf nucleus and consequently pudendal nerve function were responsible for the development of stress urinary incontinence.

Normal-Pressure Hydrocephalus

Normal-pressure hydrocephalus is a condition of progressive dementia and ataxia occurring in patients with normal cerebrospinal fluid pressure and distended cerebral ventricles, but with no passage of air over the cerebral convexities on pneumoencephalography (Blaivas, 1985). When voiding dysfunction occurs, it is usually incontinence secondary to detrusor overactivity with synergic sphincters.

Cerebral Palsy

Cerebral palsy (CP) is a nonprogressive injury of the brain that typically occurs during the first year of life (but potentially up to 3 years of age) and produces neuromuscular disability and/or specific symptom complexes of cerebral dysfunction. In general, the cause is infection or a period of hypoxia. Affected children exhibit delayed gross motor development, abnormal motor performance, altered muscle tone, abnormal posture, and exaggerated reflexes. **Most children and adults with only CP have urinary control and what seems to be normal storage and emptying.** The actual incidence of LUT dysfunction in the CP population is unclear, because the few available series report findings predominantly in those with LUTS. Andrews (1994) estimates that a third or more of children with CP have urinary symptoms, whereas Roijen and coworkers (2001) surveyed children and adolescents from six rehabilitation centers and cited the prevalence of "primary urinary incontinence" as 23.5%. The most important factors influencing the occurrence of incontinence were spastic tetraplegia and low intellectual capacity. Wyndaele and colleagues (2005) and Drake and coworkers (2013) cite the occurrence of LUT dysfunction as 36%. When an adult with CP has an acute or subacute change in voiding status, however, it is most likely unrelated to CP.

Reid and Borzyskowski (1993) described findings in 27 patients (ages 3 to 20 years) who were referred because of LUT dysfunction. Incontinence (74%), urinary frequency (56%), and urgency (37%) were the most common presenting symptoms, and detrusor overactivity was the most common urodynamic abnormality (87% of those undergoing urodynamics), with 25% of these exhibiting apparent striated sphincter dyssynergia. Mayo (1992) reported on 33 CP patients referred for evaluation of micturition dysfunction, of whom 10 were older than 20 years. Difficulty urinating was the predominant symptom in about half the patients, but half of these also had overactivity and urgency when the bladder was full. The cause of the difficulty in voluntarily initiating micturition was thought to be a problem with relaxing the pelvic floor and not true striated sphincter dyssynergia. Incontinence was the major presenting symptom in the other half, with associated detrusor overactivity in 14 of 16. All patients exhibited normal voiding otherwise. Decreased sensation was reported in 17 of 23 patients younger than 20 years of age and in 4 of 10 older than 20. The more serious manifestations, such as retention, were found only in the adults, prompting the authors to suggest that difficulty urinating may progress in adulthood. In another study of 37 children (21 girls and 16 boys) ranging in age from 1 to 17 undergoing urodynamic as well as urologic assessment, reduced functional bladder capacity was noted in 54%, whereas detrusor overactivity was observed in 35%. Residual volume was increased in 13.5% and diminished bladder compliance was noted in 10.8% of the patients. In this trial, however, approximately one third of patients with CP and urinary tract symptoms were found to have normal urodynamic

findings (Silva et al, 2009). In another assessment of a CP cohort, Richardson and Palmer evaluated 32 children (15 boys and 16 girls) with urodynamics. Social continence was highly associated with larger capacity bladder with lower storage pressures (presumably improved compliance), lack of uninhibited contractions, and coordinated (lack of pseudodyssynergia) sphincter activity. Bladder sensation differed substantially in continent versus incontinent patients. The main difference between continent and incontinent groups appeared to be delayed bladder sensation in the incontinent group (Richardson and Palmer, 2009).

Reid and Borzyskowski (1993) noted that incontinence can be significantly improved in most CP patients and that, in their experience, intellectual delay is not a barrier to successful management. However, the severe degree of mental delay encountered in some of these individuals makes their management very difficult, such that any evaluation or treatment that requires cooperation becomes virtually impossible. **In individuals with CP who exhibit significant dysfunction, the type of damage that one would suspect from the most common urodynamic abnormalities seems to be localized anatomically above the brainstem. Therefore this is most commonly reflected by phasic detrusor overactivity and coordinated sphincters. However, spinal cord damage can occur, and perhaps this accounts for those individuals with CP who seem to have evidence of striated sphincter dyssynergia or of a more distal type of neural axis lesion.**

Parkinson Disease

Parkinson disease (PD) is a neurodegenerative disorder of unknown cause that affects primarily the dopaminergic neurons of the substantia nigra but also heterogeneous populations of neurons in other locations (Lang and Lozano, 1998). The most important site of pathology is the substantia nigra pars compacta, the origin of the dopaminergic nigrostriatal tract to the caudate nucleus and putamen. **Dopamine deficiency in the nigrostriatal pathway accounts for most of the classic clinical motor features of PD, a symptom complex referred to as parkinsonism, the major signs of which are tremor, skeletal rigidity, and bradykinesia.** Other pathways that may contribute to abnormal neural physiology in PD include the corpus striatum, thalamus, periaqueductal gray matter (PAG), and L and M regions of the PMC, as well as the ventral tegmental area (VTA) of the midbrain (Barbalat, 2010). The role of alterations in dopaminergic receptor subtypes has been assessed in animal models of PD. Treatment with dopamine D₂ agonists and D₁ antagonists appears to result in a reduction of bladder capacity in these models. Brusa and colleagues studied a group of 87 patients with mild PD who were evaluated by symptomatic change and urodynamics after administration of selective dopaminergic agents. Use of agents causing central acute D₂ stimulation resulted in a reduction in bladder capacity and worsened detrusor overactivity, as compared with peripheral dopaminergic antagonists (Brusa et al, 2006). Lang and Lozano (1998) compiled an excellent review of conditions causing parkinsonism other than PD and clinical features of these conditions distinguishing them from PD. These other causes consist of (1) multiple system atrophy (MSA) (includes striatonigral degeneration, sporadic olivopontocerebellar atrophy, and Shy-Drager syndrome); (2) progressive supranuclear palsy; (3) cortical-basal ganglionic degeneration; (4) so-called vascular parkinsonism; and (5) Lewy body dementia. **The combination of asymmetry of symptoms and signs, the presence of a resting tremor, and a good response to levodopa best differentiates PD from parkinsonism produced by other causes, although none of these is individually specific for PD (Fowler, 2007).** Wyndaele and colleagues (2005) and Drake and colleagues (2013) endorsed additional criteria that favor MSA as a cause of LUTS rather than PD: (1) urinary symptoms that precede or occur with onset of parkinsonism; (2) presence of urinary incontinence; (3) significant postvoid residual volume; (4) initial erectile dysfunction; and (5) abnormal striated sphincter electromyographic findings. In addition, 5% of patients initially diagnosed with PD are found to have Parkinson-plus syndromes, characterized by early dementia and/or

falls, symmetrical symptoms, wide-based gait, normal eye movements, autonomic dysfunction, and marked disability. These variants tend to have a worse prognosis than does idiopathic PD, and urinary function is not well described in this subgroup of patients (Nutt and Wooten, 2005).

The gold standard for the diagnosis of PD is the neuropathologic examination. In addition to the characteristic pattern of the loss of selected populations of neurons, there is the presence of degenerating ubiquitin-positive neuronal processes or neurites (Lewy neurites) found in all affected brainstem regions. The Lewy body is an intracytoplasmic eosinophilic hyaline inclusion consistently observed in selectively vulnerable neuronal populations. Lewy bodies are not specific to PD and may be found in small numbers in other neurodegenerative disorders. PD affects both sexes roughly equally and the prevalence is cited as 0.3% of the general population and 3% of people older than 65 years (Lang and Lazano, 1998).

Depending on the definition, LUT dysfunction occurs in 35% to 70% of patients with PD (Berger et al, 1990; Sotolongo, 1993; Blaivas et al, 1998a; Wein and Rovner, 1999; Wyndaele et al, 2005). Preexisting detrusor dysfunction or bladder outlet abnormalities may be present, and the symptomatology may be affected by various types of treatment for the primary disease. LUTS is a frequent manifestation of PD. The time from onset of PD to initiation of LUTS in most studies averages 5 years. The most frequent symptoms include nocturia in 86% of patients, followed by frequency in 71% of patients and urgency in 68% of patients. It has been hypothesized that dopamine modulates the normal micturition reflex, and therefore neurogenic degeneration in the nigrostriatal pathway leads to the significant LUT dysfunction associated with PD (Campeau et al, 2011). One early manifestation of PD may be deficient perception of sensory information in visceral neuronal pathways resulting in delayed perception of bladder filling. Studies have demonstrated that the deep brain stimulation used for improvement of moving function in patients with PD may also benefit this sensory perception (Herzog et al, 2006).

When LUT dysfunction does occur, 50% to 75% of the time symptoms consist of urgency, frequency, nocturia, and urgency incontinence. The remainder of patients have obstructive symptoms or a combination of storage and voiding symptoms. The most common urodynamic finding is detrusor overactivity. The pathophysiology of detrusor overactivity most widely proposed (Fowler, 1999) is that the basal ganglia normally have an inhibitory effect on the micturition reflex, which is abolished by the cell loss in the substantia nigra. It is currently unclear whether the dopamine D₁ or D₂ receptor (or both) is primarily responsible. It has been suggested that loss of inhibitory D₁-like receptors causes detrusor overactivity, allowing D₂ receptors to facilitate micturition (Andersson, 2004). The smooth sphincter is synergic. There is some confusatory recording electromyographic interpretation. Sporadic involuntary activity in the striated sphincter during involuntary bladder contraction has been reported in as many as 60% of patients; however, this does not cause obstruction and cannot be termed *true* detrusor sphincter dyssynergia (DSD), which in general does not occur. Pseudodyssynergia may occur, as well as a delay in striated sphincter relaxation (bradykinesia) at the onset of voluntary micturition, both of which can be urodynamically misinterpreted as *true* dyssynergia. Impaired detrusor contractility may also occur, either in the form of low amplitude or poorly sustained contractions or a combination. Detrusor areflexia is relatively uncommon in PD. PET revealed changes in nine patients in brain activation associated with detrusor overactivity, specifically in the periaqueductal gray, supplementary motor area, cerebellar vermis, insula, putamen, and thalamus. The most prominent degree of increased activation was noted in the cerebellum, with no change in pons during detrusor overactivity (Kitta et al, 2006).

It should be noted, however, that many cases of "PD" in the older literature may actually have been MSA, and citations regarding symptoms and urodynamic findings may therefore not be accurate. A good and important example of this is the inference from the publication by Staskin and coworkers (1988)

that transurethral resection of the prostate (TURP) in the patient with PD is associated with a high incidence of urinary incontinence because of poor striated sphincter control. Retrospective interpretation (Fowler, 1999, 2001; Wyndaele et al, 2005; Drake et al, 2013) has shown that these were patients with MSA and not PD and that TURP should not be contraindicated in patients with PD, because external sphincter acontractility is extremely rare in such patients. However, irrespective of similar studies, one must be cautious with such patients, and a complete urodynamic or video-urodynamic evaluation is advisable. Poorly sustained bladder contractions, sometimes with slow sphincter relaxation, should make one less optimistic regarding the results of outlet reduction in the male.

Christmas and coworkers (1988) demonstrated that subcutaneous administration of a dopamine receptor agonist (apomorphine) can reliably and rapidly reverse parkinsonian "off" periods (periods of worsening symptoms mainly caused by the timing of previous medication doses and the unpredictable nature of motor fluctuations). By repeating video-urodynamic studies during the motor improvement after administration of apomorphine, bladder outlet obstruction secondary to benign prostatic obstruction (BPO) may be able to be distinguished from voiding dysfunction secondary to PD. The authors also point out that apomorphine might be useful in such patients who have severe off-phase voiding dysfunction, such as those with disabling nocturnal frequency and incontinence. LUT dysfunction secondary to PD defies routine classification within any system. It manifests mostly with storage failure secondary to bladder overactivity, but detailed urodynamic evaluation is mandatory before any but the simplest and most reversible therapy is initiated. The therapeutic menus (see Table 70-1 and Box 70-3 in Chapter 70) are perfectly applicable, but the disease itself may impose certain limitations on the use of certain treatments (e.g., limited mobility for rapid toilet access, hand control insufficient for clean intermittent catheterization [CIC]). The role of medications used to treat PD and exacerbation of LUTS in these patients has been postulated. Some studies have shown a relationship between the degree of neurologic impairment associated with PD and associated LUTS. Quality of life has been shown to be directly linked to the severity of LUTS, with urinary frequency and nocturia having the most deleterious impact. Overall, in a study of 110 patients, 63 (57.3%) were symptomatic from the urinary tract standpoint. No impact on LUTS was associated with use of levodopa, anticholinergics, or dopamine receptor agonists. Similar symptomatic impact occurred in both genders (Sammour et al, 2009). Bromocriptine may have a role in the exacerbation of urgency in PD patients. In a prospective trial of 8 patients with stable PD, bromocriptine was administered followed by urodynamic and systematic assessment. Urinary urgency was found to be symptomatically exacerbated after bromocriptine administration, and this was accompanied by increased detrusor overactivity. However, there was improvement in bladder emptying associated with enhanced detrusor contractility and decreased bladder outlet resistance (Uchiyama et al, 2009). Animal models of PD have been developed, using injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or 6-hydroxydopamine into the nigrostriatal pathway (Yoshimura et al, 2003; Andersson, 2004; Wyndaele et al, 2005; Drake et al, 2013).

Subthalamic nucleus deep brain stimulation has been shown to be effective for motor symptoms and dyskinesias in patients with moderate to severe PD. Clinical studies have shown that this type of stimulation improves urinary function in these patients by ameliorating bladder sensation and also improving functional bladder capacity. Herzog and colleagues studied 11 patients undergoing deep brain stimulation with PET scans of regional cerebral blood flow. In addition, subjects were studied with urodynamics both with stimulation on and stimulation off. At urodynamic capacity, significant increases in anterior cingulate regional blood flow were noted and were increased when deep brain stimulation was off. At bladder capacity, there was also an increase in lateral frontal cortical blood flow with stimulation off. These results were felt to be indicative of deep brain stimulation improvement of bladder function by the

modulation of afferent bladder information to cortical and subcortical areas (Herzog et al, 2006). Further evidence of the effect of deep brain stimulation on PD was recently reported by Winge and colleagues (Winge and Nielsen, 2012). A cohort of patients received oral medications only and was compared with a group of individuals being treated either with deep brain stimulation or with apomorphine pump for control of symptoms. A total of 170 patients were available, and outcomes reported were symptom scores (International Prostate Symptom Score [IPSS] and Danish Prostate Symptom Score [DanPSS]). There was no significant difference between the treatment groups in terms of overall symptom scores. Bladder symptom score did correlate to the stage of disease progression except for those individuals treated with deep brain stimulation, in whom symptom severity correlated to deep brain stimulation duration. Deep brain stimulation significantly decreased the amount of nocturia patients experienced (Winge and Nielsen, 2012).

Other therapies have been reported for the treatment of LUTS associated with PD. Botulinum toxin has demonstrated benefit in patients with PD; varying the doses of different toxin serotypes has demonstrated improvements in urinary frequency and quality of life as well as incontinence episodes for up to 9 months (Giannantoni et al, 2009; Kulaksizoglu and Parman, 2010). In addition, peripheral intermittent neuromodulation (posterior tibial nerve stimulation) has demonstrated improvements in detrusor overactivity and improved mean cystometric capacity in five of seven patients undergoing intervention (Kabay et al, 2009). Another therapy that has demonstrated some benefit for LUT dysfunction in PD is repetitive transcranial magnetic stimulation (rTMS). In eight patients with advanced PD, this therapy demonstrated temporary improvement in LUTS as well as improvement in bladder capacity and first sensation on cystometric filling. The beneficial effect of this therapy was noted to last for approximately 2 weeks, consistent with findings associated with other temporary forms of neuromodulation (Brusa et al, 2009).

Multiple System Atrophy

MSA results from glial α -synucleinopathy and is a progressive neurodegenerative disease of unknown cause. The symptoms encompass parkinsonism and cerebellar, autonomic (including urinary and erectile problems), and pyramidal cortical dysfunction in a multitude of combinations. The clinical features and the differentiation from PD are nicely described in a consensus statement by Gilman and associates (1999). These investigators advocate a designation of MSA-P if parkinsonian features predominate and one of MSA-C if cerebellar features predominate. Older names such as *striatonigral degeneration*, *sporadic olivopontocerebellar atrophy*, and *Shy-Drager syndrome* (Wein, 2002a, 2002b) should be discarded in favor of these terms.

The neurologic lesions of MSA consist of cell loss and gliosis in widespread areas and occur to a significantly greater degree than with PD. This more diffuse nature of cell loss probably explains why bladder symptoms may occur earlier and be more severe than in PD, and why erectile function may be affected as well (Kirby et al, 1986; Beck et al, 1994; Chandiramani et al, 1997). Affected areas have been identified in the cerebellum, substantia nigra, globus pallidus, caudate, putamen, inferior olives, intermediolateral columns of the spinal cord, and Onuf nucleus. Males and females are equally affected, with the onset in middle age. MSA is usually progressive and associated with a poor prognosis.

Shy-Drager syndrome has been described in the past as characterized clinically by orthostatic hypotension, anhidrosis, and varying degrees of cerebellar and parkinsonian dysfunction. Voiding and erectile dysfunction are common. Some consider this to be late-stage MSA (Chandiramani et al, 1997).

Chandiramani and coworkers (1997) compared the clinical features of 52 patients with probable MSA and 41 patients with PD. Sixty percent of patients with MSA had their urinary symptoms precede or occur with their symptoms of parkinsonism; 94% of patients with PD had been diagnosed for several years before the onset of urinary symptoms. In patients with MSA, urinary

incontinence was a significant complaint in 73%; 19% had only frequency and urgency without incontinence, and 66% had a significant postvoid residual volume (100 to 450 mL). In patients with PD, frequency and urgency were the predominant symptoms in 85%, incontinence was the primary complaint in 15%, and the postvoid residual volume was elevated in only 5 of the 32 patients in whom it was measured. Eleven men with MSA underwent TURP, and 9 of these had deterioration of their urinary incontinence afterward. All 3 women with MSA were incontinent after pelvic floor repair. Five men with PD underwent prostatectomy, and 3 reported a good result. Of 27 men with MSA questioned about erectile function, 93% reported erectile failure, and in 13 of these (48%) the erectile dysfunction preceded the diagnosis of MSA. Seven of the 21 men with PD had erectile failure, but in all of these men the diagnosis of erectile dysfunction followed the diagnosis of PD by 1 to 4 years. The urogenital criteria favoring a diagnosis of MSA (Fowler, 2001) are (1) urinary symptoms that precede or occur with parkinsonism; (2) male erectile dysfunction that precedes or occurs with parkinsonism; (3) urinary incontinence; (4) significant postvoid residual volume; and (5) worsening LUT dysfunction after urologic surgery. Others have reported the progressive nature of LUTS associated with MSA. With time, incontinence and significant postvoid residual volume become more problematic, with steady progression of the condition in all patients (Papatsoris et al, 2008).

The initial urinary symptoms of MSA are urgency, frequency, and urgency incontinence, occurring up to 4 years before the diagnosis is made. As would be expected from the central nervous system (CNS) areas affected, detrusor overactivity is frequently found; however, decreased compliance may also occur, reflecting distal spinal involvement of the locations of the cell bodies of autonomic neurons innervating the LUT. As the disease progresses, difficulty in initiating and maintaining voiding may occur, probably from pontine and sacral cord lesions, and this usually is associated with a poor prognosis. Cystourethrography or video-urodynamic studies may reveal an open bladder neck, and many patients exhibit evidence of striated sphincter denervation on motor unit electromyography. The smooth and striated sphincter abnormalities predispose women to sphincteric incontinence and make prostatectomy hazardous in men. Berger and coworkers (1990) described a useful urodynamic differentiation of what was termed *Shy-Drager syndrome* (probable late-stage MSA) from PD. In general, parkinsonian patients with voiding dysfunction have detrusor overactivity and normal compliance. An open bladder neck was seen only in patients with Shy-Drager syndrome, excluding patients with PD who had had a prostatectomy. Electromyographic evidence of striated sphincter denervation was seen much more commonly in those diagnosed as having Shy-Drager syndrome.

The treatment of significant LUT dysfunction caused by MSA is difficult and seldom satisfactory. Treatment of detrusor overactivity during filling may worsen problems initiating voluntary micturition or worsen impaired contractility during emptying. Patients usually have sphincteric insufficiency; therefore an outlet-reducing procedure is rarely indicated. Conversely, drug treatment for sphincteric incontinence may further worsen emptying problems. In general, the goal in these patients is to facilitate storage, and CIC would often be desirable. Unfortunately, patients with advanced disease often are not candidates for CIC. Some patients do respond well to desmopressin administration for predominant nocturia; however, the majority of the patients do not respond well to antimuscarinic or other types of therapy (Wenning and Stefanova, 2009).

DISEASES PRIMARILY INVOLVING THE SPINAL CORD

Multiple Sclerosis

Multiple sclerosis (MS) is primarily a disease of adults ages 20 to 50 years with a twofold predilection for women. Litwiler and colleagues (1999) detailed prevalence rates for MS as 1 per 1000 Americans, 2 per 1000 northern Europeans, and 20 to 40 per 100,000 first-degree relatives of patients with MS. The World Health

Organization (WHO) in 2008 estimated that 2 to 2.5 million people worldwide had MS (WHO, 2008). Most commonly the age of onset is 30 to 38 years of age for relapsing, remitting, and progressive phases. Common symptoms include optic nerve dysfunction, pyramidal tract abnormalities (hyper-reflexia), ataxia, bowel dysfunction, neurogenic bladder, and bowel and sexual dysfunction. Primary and secondary progressive MS are predominately spinal diseases, and their activity affects LUT function.

Although the cause is not clear, the disease is believed to be immune mediated and is characterized by neural demyelination in the brain and spinal cord; it is characterized, in general, by axonal sparing (Noseworthy et al, 2000). This demyelination causes impairment of saltatory conduction and conduction velocity in axonal pathways, resulting in various neurologic abnormalities that are subject to exacerbation and remission. Lesions, known as *plaques*, range from 1 mm to 4 cm and are scattered throughout the white matter of the nervous system (Chancellor and Blaivas, 1993; Clanet, 2008). The demyelinating process most commonly involves the lateral corticospinal (pyramidal) and reticulospinal columns of the cervical spinal cord, and it is thus not surprising that LUT dysfunction and sphincter dysfunction are so common. Autopsy studies have revealed almost constant evidence of demyelination in the cervical spinal cord, but involvement of the lumbar and sacral cord may occur in approximately 40% and 18%, respectively (Blaivas and Kaplan, 1988). Lesions may also occur in the optic nerve and in the cerebral cortex and midbrain, the latter accounting for the intellectual deterioration and/or euphoria that may accompany physical findings (Kirby, 1994; Noseworthy et al, 2000) in as many as 43% to 65% of patients (Litwiler et al, 1999). A rat model for a demyelinating disease resembling MS has been described using myelin basic protein as an antigen for inducing experimental allergic encephalomyelitis (Mizusawa et al, 2000).

Some patients with MS demonstrate intravesical changes in receptor density and type. In a study of 18 patients with LUTS associated with MS, patients underwent evaluation with urologic assessment and urodynamics. Two groups were identified: one with pronounced neurogenic detrusor overactivity and minimal outflow obstruction, and the second with some degree of neurogenic detrusor overactivity or detrusor hypocontractility during voiding and a high degree of bladder outflow obstruction. Cold-cup biopsies were performed on all patients, and the density of calcitonin gene-related peptide (CGRP)- and substance P (SP)-positive nerve fibers was noted to be higher in the first group, suggesting that denser innervation is present in patients with milder degrees of outflow obstruction and retention of detrusor contractility as compared with individuals without these findings (Radziszewski et al, 2009).

The incidence of LUT dysfunction in MS is related to the disability status. Of patients with MS, 50% to 90% report voiding symptoms at some time; the prevalence of incontinence is cited as 37% to 72% (Wyndaele et al, 2005; Drake et al, 2013). In a comprehensive review of the literature, Litwiler and coworkers (1999) cited symptoms of frequency or urgency in 31% to 85% of patients, incontinence in 37% to 72%, and obstructive symptoms with urinary retention in 2% to 52%. LUT involvement may constitute the sole initial complaint or may be part of the presenting symptom complex in up to 15% of patients, typically with a presentation of acute urinary retention of unknown cause or as an acute onset of urgency and frequency (Wyndaele et al, 2005).

In terms of urodynamic findings, detrusor overactivity is the most common abnormality detected, occurring in 34% to 99% of patients in reported series (Blaivas and Kaplan, 1988; Chancellor and Blaivas, 1993; Sirls et al, 1994; Litwiler et al, 1999). Striated sphincter dyssynergia coexists with overactivity in 30% to 65% of patients. The prevalence of coexistent impaired detrusor contractility or areflexia ranges from 12% to 38% (Wyndaele et al, 2005; Drake et al, 2013), a phenomenon that can considerably complicate treatment efforts. More recent estimates suggest that 62% of patients with MS have neurogenic detrusor overactivity with bladder outlet obstruction, 25% have neurogenic detrusor overactivity with DSD, 20% have detrusor underactivity, and 10% have no initial abnormal urodynamic findings. It is important to note that

the variability and potential multiplicity of lesions associated with MS may prohibit accurate diagnosis based on urodynamics alone (Ukkonen et al, 2004).

In general, the smooth sphincter is synergic. Chancellor and Blaivas (1993) reviewed urodynamic findings in multiple series of patients with MS and voiding dysfunction and cited the incidence of detrusor overactivity with striated sphincter synergia to be 26% to 50% (average, 38%), detrusor overactivity with striated sphincter dyssynergia to be 24% to 46% (average, 29%), and detrusor areflexia to be 19% to 40% (average, 26%). Litwiler and coworkers (1999) report approximately the same ranges in a review of 22 studies. It is also possible to see relative degrees of sphincteric flaccidity caused by MS. Although this finding is relatively rare and occurs in fewer than 15% of patients (Litwiler et al, 1999), it could contribute to and predispose patients to sphincteric incontinence. De Ridder and colleagues (1998) reported weakness of pelvic floor contraction in almost all of the 30 women with MS whom they studied. Spasticity of the pelvic floor was present in all patients with striated sphincter dyssynergia but in none with detrusor overactivity alone. Up to 80% of patients will have neurogenic vesicourethral dysfunction at some point during the course of their disease (Fletcher and Lemack, 2009).

Because sensation is frequently intact in these patients, one must be careful to distinguish urodynamic pseudodyssynergia from true striated sphincter dyssynergia. Blaivas and associates (1981) subcategorized true striated sphincter dyssynergia in patients with MS and identified some varieties that are more worrisome than others. For example, a brief period of striated sphincter dyssynergia during detrusor contraction in a woman with MS may be relatively inconsequential, as long as it does not result in excessive intravesical pressure during voiding, substantial postvoid residual urine volume, or secondary detrusor hypertrophy. However, more sustained episodes of striated sphincter dyssynergia that result in high bladder pressures of long duration are most associated with urologic complications. Giannantoni and colleagues (1998) likewise concluded that there was a significant relationship between the maximum amplitude of the involuntary bladder contractions and upper urinary tract deterioration in their MS population of 116 patients. Chancellor and Blaivas (1993) emphasized what they believed were the most important parameters predisposing patients with MS to significant urologic complications: (1) striated sphincter dyssynergia in men; (2) high detrusor filling pressure; and (3) an indwelling catheter. It is interesting to note that Wyndaele's committee (Wyndaele, 2005; Drake et al, 2013) concluded that progressive neurologic disease in patients with MS rarely causes upper urinary tract damage, even when severe spasticity and disability exist. The reason for this is unknown, but the committee proposed that the situation and concerns with respect to MS were unlike those for SCI.

KEY POINT: MULTIPLE SCLEROSIS

- The most common functional classification applicable to patients with LUT dysfunction secondary to MS would be storage failure secondary to detrusor overactivity. This is commonly complicated by striated sphincter dyssynergia, with varying sequelae based on the patient's ability to empty completely at acceptable voiding pressures. Other abnormalities, and especially combined deficits, are obviously possible.
- Once the dysfunction is broadly characterized, the treatment options should be obvious from the therapeutic menus (see Table 70-1 and Box 70-3 in Chapter 70).

Aggressive and anticipatory medical management can obviate most of the significant complications. Sirls and associates (1994) reported that less than 10% of their patients required surgical intervention resulting from failure of aggressive medical management and that none developed hydronephrosis on such therapy. The

regimens used were (1) medications to decrease detrusor overactivity plus CIC (57%); (2) medications alone (13%); (3) CIC alone (15%); and (4) behavioral therapy. **Caution should be exercised in recommending irreversible therapeutic options, because a significant proportion of patients with MS, both with and without new symptoms, will develop changes in their detrusor compliance and urodynamic pattern (Ciancio et al, 2001).** No factors appear to be predictive of upper tract changes in MS. In a 4-year follow-up of 113 MS patients, 66 underwent both urodynamic and renal ultrasound testing. Eleven of the 66 patients (17%) had abnormal ultrasound findings, with the most significant finding being minor caliectasis of no clinical significance. Neither creatinine nor urodynamic findings were associated with the abnormal renal ultrasound findings (Lemack et al, 2005). Others have noted the lack of predictability of urinary symptoms for disease status, making baseline testing with urodynamics critical to disease assessment and management (Nakipoglu et al, 2009). Surgical intervention for MS appears to be diminishing with improved pharmacologic management and the realization of the alternating neurologic picture of lower urinary dysfunction associated with MS (Ukkonen et al, 2004; Togami et al, 2013).

Physiotherapeutic management has demonstrated success for this condition. In a recent Australian trial with 73 patients with MS, 40 patients were randomized to an individualized bladder rehabilitation program that included baseline assessment (3-day voiding charts, fluid balance, intake restrictions, postvoid residual measurement, and urodynamics). Subsequently, bladder reeducation, pelvic floor exercises, and instruction in techniques for improved bladder emptying and a bowel program were instituted. A nonintervention group served as control. Substantial improvements in all subjective quality-of-life indicators were noted in the intervention group, as compared with the nonintervention group, demonstrating the benefit of a bladder and bowel regimen in this population (Khan et al, 2009).

At present there is no consensus on optimal bladder management for patients with MS, and management is most commonly predicated on symptomatic and urodynamic findings. On the basis of expert consensus, De Ridder and associates (2005) concluded that in early MS, anticholinergics and CIC were considered to be the cornerstones of therapy. For patients with advanced MS (with an Expanded Disability Status Scale [EDSS] score >7), specific guidelines remain lacking. In general, Credé voiding or Valsalva voiding are contraindicated, especially in the presence of DSD. The committee further recommended that indwelling catheters be reserved for patients for whom all other possible treatments have failed. In the approximately 30% of patients with MS using indwelling urinary catheters, the suprapubic route is the preferred route in both men and women. This form of management is considered reasonable for that subpopulation, as long as vigilant long-term follow-up is maintained (De Ridder et al, 2005).

The emerging role of onabotulinum toxin therapy for bladder overactivity related to MS has been recently reported. Detrusor overactivity suppressed with onabotulinum toxin injection can provide social continence and improved quality of life. Stability of response and safety have been reported over treatment periods as long as five cycles. Kennelly and colleagues reported long-term experience with 387 patients with neurogenic detrusor overactivity caused by either MS or SCI and found that 73% to 94% of patients reported incontinence episode reductions of at least 50% depending on treatment cycle assessed (Kennelly et al, 2013).

Spinal Cord Injury

Epidemiology, Morbidity, General Concepts

SCI may occur as a consequence of acts of violence, fracture, or dislocation of the spinal column secondary to motor vehicle collisions, diving accidents or falls, vascular injuries or surgical repairs, infection, disk prolapse, or sudden and/or severe hyperextension from other causes. Altered LUT and sexual function frequently occur secondary to SCI and have a significant impact on quality of life.

SCI patients are at risk urologically for urinary tract infection (UTI), sepsis, upper urinary tract and LUT deterioration, upper urinary tract and LUT calculi, autonomic hyperreflexia (dysreflexia), skin complications, and depression (which can complicate urologic management). Failure to properly address the LUT dysfunction can lead to significant morbidity and mortality. There is great variation in urologic practice regarding initial evaluation, follow-up, and surveillance among spinal injury units (Bycroft et al, 2004), a problem that Boone (2004) properly attributes to a lack of evidence-based decision making.

Complete anatomic transection of the spinal cord is rare, and the degree of neurologic deficit varies with the level and severity of the injury. **Spinal column (bone) segments are numbered by the vertebral level, and these have a different relationship to the spinal cord segmental level at different locations. One must be careful to specify cord or column level when discussing SCI. The sacral spinal cord begins at about spinal column level T12 to L1. The spinal cord terminates in the cauda equina at approximately the spinal column level of L2.** Multiple-level injuries may occur, and, even with a single isolated initial injury, cord damage may not remain confined to a single cord segment and may extend cephalad, caudad, or both.

Stover and Fine (1987) reviewed the epidemiology and other general aspects of SCI. The annual rate was reported as 30 to 32 new SCIs per million persons at risk in the United States; the prevalence was approximately 906 per million. This coincides roughly with the estimate by DeVivo (1997) of approximately 10,000 new cases of SCI in the United States yearly and an estimate of 12,000 per year by Rabchevsky and Smith (2001). More recent estimates concur with these earlier studies (National Spinal Cord Injury Statistical Center, Birmingham, AL. Office of Special Education and Rehabilitative Services, U.S. Department of Education, Washington, DC 2012). The most common mechanisms of injury, as collected by the National Spinal Cord Injury Statistical Center, are motor vehicle accidents (39.2%), violence (14.6%), falls (28.3%), and sports-related injuries (8.2%). Males account for 71% to 81% of patients with SCI. From 1973 to 1979, the average age at injury was 28.7 years, and most injuries occurred between the ages of 16 and 30. However, as the median age of the general population of the United States has increased by approximately 9 years since the mid 1970s, the average age at injury has also steadily increased over time. Since 2005, the average age at injury is 41.0 years. Children constitute 3% to 5% of all patients with SCI (Generao et al, 2004). Stover and Fine (1987) reported that neurologically incomplete quadriplegics constituted the largest group of SCI patients at the time of hospital admission (28%), followed by complete paraplegics (26%), complete quadriplegics (24%), and incomplete paraplegics (18%). Since 2005, the most frequent neurologic category at discharge of persons reported to the database is incomplete tetraplegia (40.8%), followed by complete paraplegia (21.6%), incomplete paraplegia (21.4%), and complete tetraplegia (15.8%). Less than 1% of persons experienced complete neurologic recovery by hospital discharge. The majority of SCIs occur at or above the T12 spinal column (vertebral) level, with injury to one of the eight cervical segments accounting for the patients with tetraplegia and with patients with paraplegia having injury in the thoracic, lumbar, or sacral regions of the spinal cord. SCI is associated with long-term urologic functional compromise. In an assessment of 236 patients with follow-up of mean 24 years, 43% of patients continue to report incontinence at time of follow-up, with paraplegics reporting daily incontinence more frequently than tetraplegics (presumably because of catheter dependence of the latter group). Only 19% of patients used some form of medication for assistance in management of their incontinence. Surprisingly, CIC was associated with higher rates of incontinence than other types of bladder drainage techniques (Hansen et al, 2010).

Although earlier data (Hackler, 1977) indicated that renal disease was the major cause of death, at least in the paraplegic patient, a retrospective study of more than 5000 patients who sustained SCI between 1973 and 1980 revealed that the leading causes of death at that time were pneumonia, septicemia,

pulmonary emboli, heart disease, accidents, and suicide (Stover and Fine, 1987; Soden et al, 2000). These figures seemingly indicate a distinct improvement in the urologic care of these patients. Impaired mobility is commonly noted in the SCI patient and may substantially affect urinary habits and continence (Biering-Sorensen et al, 2004). Urologic phenomena also figure prominently in chronic SCI; approximately 7% of patients will develop an initial kidney stone within 10 years after initial injury. The greatest risk occurs during the first 3 months after injury, and 98% of these stones will be apatite or struvite in composition. There appear to be two specific time frames for stone formation in this population, one being the acute phase associated with immobilization and immobilization hypercalciuria. A more chronic phase stone formation period that usually is associated with chronic catheter management occurs years after injury and predominately involves the LUT (Post and Noreau, 2005).

Controlled and coordinated LUT function depends on an intact neural axis. Bladder contractility and the occurrence of reflex contractions depend on an intact sacral spinal cord and its afferent and efferent connections (see Chapter 69).

KEY POINT: SPINAL CORD INJURY

- In general, complete SCI above the sacral spinal cord but below the area of the sympathetic outflow results in detrusor overactivity, absent sensation below the level of the lesion, smooth sphincter synergy, and striated sphincter dyssynergia. Lesions at or above the spinal cord level of T7 or T8 (the spinal column level of T6) may result in smooth sphincter dyssynergia as well. However, despite the strong correlation between neurologic and urodynamic findings, it is not perfect, and a neurologic examination is no substitute for a urodynamic evaluation in these patients when one is determining risk factors and treatment.



There is an impressive amount of literature that is continuously building on the neurobiology of the spinal cord and its acute and chronic alteration after SCI. A section can be found on the Expert Consult website.

Sexual and reproductive dysfunction in the patient with SCI is a topic that deserves much attention in the overall rehabilitation plan. Pertinent general and specific concepts of sexual and reproductive dysfunction and their normalization in this special group of patients can be found in Chapters 26, 30, and 32. Other excellent reviews on the specifics of sexual function in SCI can be found by Bennett and coworkers (1988), Stone and MacDermott (1989), Smith and Bodner (1993), and Biering-Sorensen and Sonksen (2001), and on infertility by Linsensmeyer and Perkash (1991), Rajaskaran and Monga (1999), and Rutkowski and colleagues (1999).

Spinal Shock

A period of "spinal shock" may be expected after a significant SCI, defined as decreased excitability of spinal cord segments at and below the level of the lesion. There is **absent somatic reflex activity and flaccid muscle paralysis below this level**. Although classic teaching refers to generalized areflexia below the level of the lesion for days to months, Thomas and O'Flynn (1994) confirm that the most peripheral somatic reflexes of the sacral cord segments (the anal and bulbocavernosus reflexes) may never disappear or, if they do, may return within minutes or hours of the injury. However, functions proximal to the level of the injury may be depressed as well (Atkinson and Atkinson, 1996). Although the course of spinal shock is well known, the actual phenomenon remains poorly understood, with few or no recent additions to basic research.

Spinal shock includes a suppression of autonomic activity as well as somatic activity, and the bladder is acontractile and areflexic. Radiologically, the bladder has a smooth contour with no evidence of trabeculation. The bladder neck is usually closed and competent, unless there has been prior surgery or the patient has

sustained a potential thoracolumbar and presumably sympathetic injury (Sullivan and Yalla, 1992). The smooth sphincter mechanism appears to be functional. Some electromyographic activity may be recorded from the striated sphincter, and the maximum urethral closure pressure is lower than normal but still maintained at the level of the external sphincter zone. However, the normal guarding reflex (striated sphincter response during filling) is absent and there is no voluntary control (Fam and Yalla, 1988). Because sphincter tone exists, urinary incontinence usually does not result unless there is gross overdistention with overflow. In evolving lesions, every attempt should be made to preserve as low a bladder storage pressure as possible and to avoid any measures that might impair this. Urinary retention is the rule, and catheterization is necessary to circumvent this problem. Although virtually all would agree that CIC is an excellent and preferred method of management during this period, Lloyd and coworkers (1986) reported their own experience and that of others that indicate no differences in outcome when a small-bore indwelling urethral catheter or suprapubic tube is used at this stage.

If the distal spinal cord is intact but is simply isolated from higher centers, there is usually a return of reflex detrusor contractility. At first, such reflex activity is poorly sustained and produces only low-pressure changes, but the strength and duration of such involuntary contractions typically increase, producing involuntary voiding, usually with incomplete bladder emptying. This return of reflex bladder activity typically manifests with involuntary voiding between catheterizations and occurs along with the recovery of lower extremity deep tendon reflexes (DTRs). Spinal shock usually lasts 6 to 12 weeks in complete suprasacral spinal cord lesions but may last up to 1 or 2 years. It may last a shorter period of time in incomplete suprasacral lesions and only a few days in some.

Suprasacral Spinal Cord Injury

There is no consensus agreement on the neurobiology of the development of reflex bladder contraction in response to bladder distention after suprasacral SCI. de Groat and colleagues (1997) have studied this phenomenon extensively in cats and listed four potential mechanisms for the recovery of such micturition and the development of C-fiber afferent evoked bladder reflexes (see also the description in Chapter 69): (1) elimination of bulbospinal inhibitory pathways; (2) strengthening of existing synapses, or formation of new synaptic connections from axonal sprouting in the spinal cord; (3) changes in synthesis, release, or actions of neurotransmitters, and (4) alterations in afferent input (afferent axonal sprouting) from peripheral organs. Recent reports of specific alterations in animal models are summarized by Morrison and colleagues (2005) as (1) increased sensitivity of C-fiber afferents, possibly involving NGF; (2) enlargement of dorsal root ganglion cells; (3) increased electrical excitability of afferents associated with a shift in expression of sodium channels from a high-threshold tetrodotoxin-resistant type to a low-threshold tetrodotoxin-sensitive type. Other findings possibly related to the development of LUT dysfunction after SCI have been reported as (1) increased concentrations of glutamate, glycine, and taurine (Smith et al, 2002); (2) disruption of bladder epithelium barrier function (Apodaca et al, 2003); (3) change from low affinity M₁ to high affinity M₃ receptors at prejunctional cholinergic nerve endings (Somogyi et al, 2003); (4) increased release of adenosine triphosphate (ATP) from bladder urothelium (Khera et al, 2004); (5) increased spinal cord NGF (Seki et al, 2004); and (6) alterations in smooth muscle myosin heavy chain gene expression (Wilson et al, 2005). Recently, in murine models of acute SCI, nicotinic or purinergic receptor mechanisms have been shown to be the primary mechanism for ATP release as atropine has been shown to be only partially effective in stimulating ATP release (predominantly a muscarinic receptor phenomenon in the absence of injury). These findings further indicate a change in receptor-mediated bladder activity associated with SCI (Salas et al, 2007). Yet another mechanism of bladder dysfunction may arise from modulation of TRPA-1 receptors, which has been shown to attenuate bladder overactivity in SCI models, indicating

Bladder dysfunction associated with acute SCI has been investigated in a variety of animal models. In rodent models using a moderate contusion injury at three different thoracic levels—T1, T4, or T9—versus complete crush injury at T1 and T9, differences in bladder function were noted. T4 and T9 contusions were associated with a relative increase in urinary retention, whereas T1 defects had less impact on retained volume. Lesions at T1 spared a critical descending modulating pathway for voiding in rats. Crush injuries were associated with much more defect emphasis (David and Steward, 2010). Receptor behavior has also been noted to change in SCI. Differential expression of channel receptors has been demonstrated in muscle strips from neurogenic patients. K_{ATP} calcium channels appear to regulate spontaneous hyperactivity in neurogenic patients as compared with normal individuals. However BK_{Ca} channels are more involved in regulation of normal patients as compared with neurogenic patients (Oger and AlKhawajah, 2010).

These topics are not further specifically considered in detail here, nor are the ramifications of this information relative to potential improvement of SCI after stem cell implant or reinnervation. Reviews can be found by Olson (1997); Fawcett (1998); Kakulas (1999); Rabchevsky and Smith (2001) (this also includes a discussion of pathophysiology and experimental models); Cao and coworkers (2002) (stem cell repair); Fawcett (2002) (repair of SCI); Rossi and Cattaneo (2002) (stem cell therapy); Mitsui and colleagues (2003) (stem cell repair); Kakulas (2004) (neuropathology and natural history of the spinal cord changes); and Livshits and associates (2004) (reinnervation).

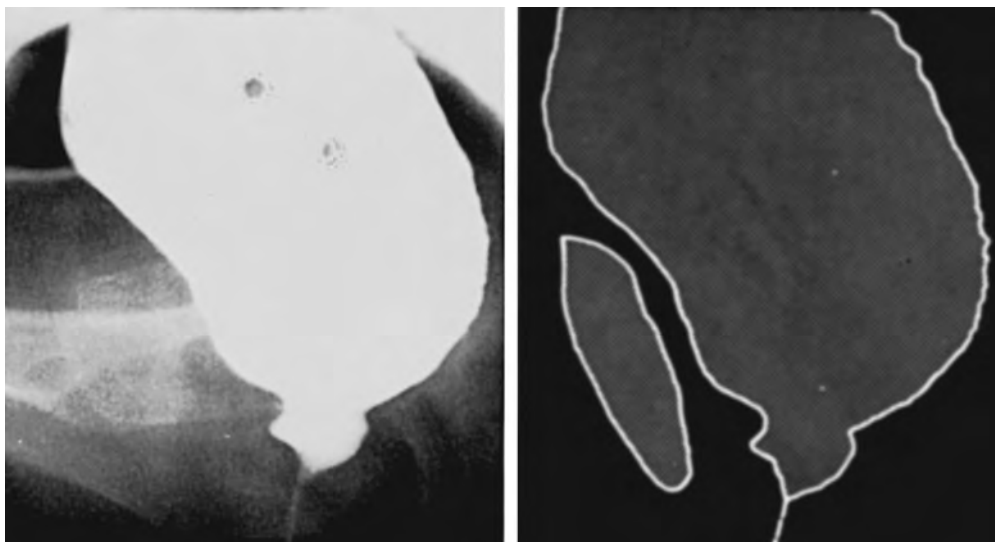


Figure 75-1. Cystourethrogram in a 19-year-old woman with detrusor-striated sphincter dyssynergia secondary to a complete spinal cord injury at vertebral level T11. Image was taken during an involuntary bladder contraction with exaggerated bladder neck opening caused by the obstruction below. (From Nordling J, Olesen KP. Basic urographic and cystourethrogram patterns. In: Pollack HM, editor. *Clinical urography*. Philadelphia: Saunders; 1990. p. 1953.)

the importance of these receptors in the spinal cord-injured bladder (Andrade et al, 2011).

The characteristic pattern in a patient with a complete lesion above the sacral spinal cord is detrusor overactivity, smooth sphincter synergy (with lesions below the sympathetic outflow), and striated sphincter dyssynergia (Sullivan and Yalla, 1992; Thomas and O'Flynn, 1994; Chancellor and Blaivas, 1995a). Neurologic examination shows spasticity of skeletal muscle distal to the lesion, hyperreflexic DTRs, and abnormal plantar responses. There is impairment of superficial and deep sensation. Figures 75-1 to 75-3 typify the cystourethrogram and urodynamic patterns. The guarding reflex is absent or weak in most patients with a complete suprasacral SCI. In incomplete lesions the reflex is often preserved but quite variable (Morrison et al, 2005). The striated sphincter dyssynergia causes a functional obstruction with poor emptying and high detrusor pressure. In an effort to subclassify detrusor sphincter dyssynergia, Karsenty and colleagues (2005) retrospectively evaluated video-urodynamic recordings of patients with complete SCI with untreated neurogenic overactive bladder and detrusor sphincter dyssynergia. They identified two time periods within the tracings, with Delay A being defined as that period between the onset of external urethral sphincter (EUS) pressure increase and the subsequent onset of bladder pressure increase. Delay B was defined as the period between the onset of urethral sphincter pressure increase and the moment at which bladder pressure increase reached a level of 10 cm H₂O or greater above the baseline value. The recordings of 20 patients were assessed, with the Delay A timeframe found to be significant in 16 of 20 patients, with a meantime for delay of 2.2 seconds. There was a positive association between this delay and the completeness of the SCI and the presence of continuous DSD on electromyogram. Delay B was positive in all patients with a mean delay time of 7.6 seconds. The authors concluded that EUS contraction starts before the onset of bladder contraction in most patients with coexistent SCI and detrusor sphincter dyssynergia.

The presence of striated sphincter dyssynergia causes a functional obstruction with poor emptying and high detrusor pressures. Occasionally, incomplete bladder emptying may result from what seems to be a poorly sustained or absent detrusor contraction. This seems to occur more commonly in lesions close to the conus medullaris than with more cephalad lesions. This may result from a second occult lesion or may be caused by locally



Figure 75-2. Typical cystourethrogram configuration of a synergic smooth sphincter and a dyssynergic striated sphincter in a man during a bladder contraction. (From Nanninga JB. Radiological appearances following surgery for neuromuscular diseases affecting the urinary tract. In: Pollack HM, editor. *Clinical urography*. Philadelphia: Saunders; 1990. p. 2003.)

functioning reflex arcs, which result in detrusor inhibition from strong striated pelvic floor muscle contraction, or by a loss of higher center-mediated detrusor facilitation, which normally occurs after the initial increase in pressure during a bladder contraction (Thomas and O'Flynn, 1994). Once reflex voiding is established, it can be initiated or reinforced by the stimulation of certain dermatomes, such as by tapping the suprapubic area. The urodynamic and upper tract consequences of the striated sphincter dyssynergia vary with severity (usually worse in complete lesions), duration (continuous contraction during detrusor activity is worse than intermittent contraction), and anatomy (male is worse than female) (Linszenmeyer et al, 1998).

The type of dyssynergia also appears to be associated with degree of injury and potential for progression of dysfunction. Schurch and

colleagues evaluated 105 male patients with SCI and noted a correlation between type of DSD and completeness of spinal cord lesion. Men with incomplete sensory and motor lesions more commonly had type 1 DSD, whereas complete sensory and motor lesions were more commonly associated with either type 2 or type 3 DSD. There was no correlation, however, noted between the type of DSD and the lesion level. At long-term follow-up, DSD type was noted to evolve from type 2 or type 3 DSD in approximately a quarter of the studied patients, whereas 65% of patients remained stable with the same type of DSD at follow-up (Schurch et al, 2005).

KEY POINT: MANAGEMENT OF PATIENTS WITH SUPRASACRAL SPINAL CORD INJURY

- From a functional standpoint, the voiding dysfunction most commonly seen in suprasacral SCI represents both a filling or storage and an emptying or voiding failure. Although the urodynamics are “safe” enough in some individuals to allow only periodic stimulation of bladder reflex activity, many will require some form of additional treatment. If bladder pressures are suitably low or if they can be sufficiently and safely lowered with nonsurgical or surgical management, the problem can be treated primarily as an emptying failure. CIC can then be continued as a safe and effective way of satisfying many of the goals of treatment. The role of additive antimuscarinic administration appears to be supported by the preponderance of evidence in this patient population (Madersbacher et al, 2012). Recent consensus opinion has stressed the conservative use of antibiotics in patients using long-term CIC. Wyndaele and colleagues opined on the importance of demonstrating definitive evidence of UTI before initiating antimicrobial therapy in the population using this technique (Wyndaele, 2012). Alternatively, sphincterotomy, urethral stenting, or intrasphincteric injection of onabotulinumtoxinA can be used in males to lower the detrusor leak point to an acceptable level and render the patient incontinent, thus converting the dysfunction primarily to a storage failure (incontinence), which can be obviated either by timed stimulation or with an external collecting device. In the dexterous SCI patient, the former approach using CIC is becoming predominant. Electrical stimulation of the anterior sacral roots with some form of deafferentation is also now a distinct reality (Creasey et al, 2001; Seif et al, 2004). Although used sparingly, as with all patients with neurologic impairment, a careful initial evaluation and periodic, routine follow-up evaluation must be performed to identify and correct the following risk factors and potential complications: bladder overdistention, high-pressure storage, high detrusor leak point pressure, vesicoureteral reflux (VUR), stone formation (lower and upper tracts), and complicating infection, especially in association with reflux.

Sacral Spinal Cord Injury

After the patient has recovered from spinal shock, there is typically a depression of DTRs below the level of a complete lesion with varying degrees of flaccid paralysis. Sensation is usually absent below the lesion level. Detrusor areflexia with high or normal compliance is the common initial result. However, decreased compliance may also develop, a finding in some distal SCI lesions that most likely represents a complex response to neurologic decentralization probably involving reorganization and plasticity of neural pathways (Fam and Yalla, 1988; de Groat et al, 1997; Blaivas et al, 1998b). There is surprisingly little consensus on the evolution of the appearance or function of the bladder neck or smooth sphincter area after sacral SCI. The classic outlet findings are described as a competent but nonrelaxing smooth sphincter and a striated sphincter that retains some fixed tone but is not under voluntary control. Closure pressures are decreased in both areas

(Sullivan and Yalla, 1992; Thomas and O’Flynn, 1994). It is interesting to note that the late appearance of the bladder neck may be “open” (Kaplan et al, 1991). Attempted voiding by straining or Credé maneuver results in “obstruction” at the level of the potentially closed bladder neck or at the distal sphincter area if the sphincter tone is fixed (Fam and Yalla, 1988; Thomas and O’Flynn, 1994). Figure 75-4 illustrates the typical cystourographic and urodynamic pictures of the late phases of such a complete lesion.

Neurologic and Urodynamic Correlation

Although generally correct, the correlation between somatic neurologic findings and urodynamic findings in suprasacral and sacral SCI patients is not exact. A number of factors should be considered in this regard. First, whether a lesion is complete or incomplete is sometimes a matter of definition, and a complete lesion, somatically speaking, may not translate into a complete lesion anatomically and vice versa. In addition, multiple injuries may actually exist at different levels, even though what is seen somatically may reflect a single level of injury. Even considering these examples, all such discrepancies are not readily explained. In an assessment of 236 patients, with follow-up of mean 24 years, 43% of patients continue to report incontinence at time of follow-up with paraplegics reporting more frequently daily incontinence than tetraplegics (presumably because of catheter dependence of the latter group). Only 19% of patients used some form of medication for assistance in management of their incontinence. Surprisingly, CIC was associated with higher rates of incontinence than other types of bladder drainage techniques (Hansen et al, 2010). Further demonstration of the unpredictability of LUT status in patients with incomplete lesions was reported by Patki and colleagues (2006), who assessed a group of 43 men and 21 women with incomplete SCI (American Spinal Injury Association [ASIA] grades D and E) during a 2-year period. Forty patients initially assessed as having a bladder not at risk for deterioration ultimately experienced deterioration requiring CIC. Conversely, 5 of 20 patients who initially required CIC no longer required this with time. In long-term follow-up, 68% of patients continued to have abnormal urodynamic findings, and 37% of patients required a change in urologic management in the absence of perceptible change in neurologic status, indicating the potential for continued bladder changes in the absence of other detectable neurologic disease (Patki et al, 2005).

KEY POINT: MANAGEMENT OF PATIENTS WITH SACRAL CORD INJURY

- Potential risk factors and complications are those previously described, with particular emphasis on storage pressure, which can result in silent upper tract decompensation and deterioration in the absence of VUR. The treatment of such a patient is usually directed toward producing or maintaining low-pressure storage while circumventing emptying failure with CIC when possible. Pharmacologic and electrical stimulation may be useful in promoting emptying in certain circumstances (see Table 70-1 and Box 70-3 in Chapter 70).

In a classic article, Blaivas (1982) correlated clinical and urodynamic data from 550 patients with LUT dysfunction. In 155 patients with complete and incomplete suprasacral neurologic lesions, physiologically normal voiding was reported in 41%. DSD was demonstrated in 34%, and, surprisingly (and seemingly paradoxically), detrusor areflexia was noted in 25%. Other authors have noted detrusor areflexia with suprasacral SCI or disease, and the causes have been hypothesized to be a coexistent distal spinal cord lesion or a disordered integration of afferent activity at the sacral root or cord level (Light et al, 1985; Beric and Light, 1992). DSD was reported in 45% of 119 patients with suprasacral spinal cord lesions, whereas none of 36 patients with supraspinal neurologic

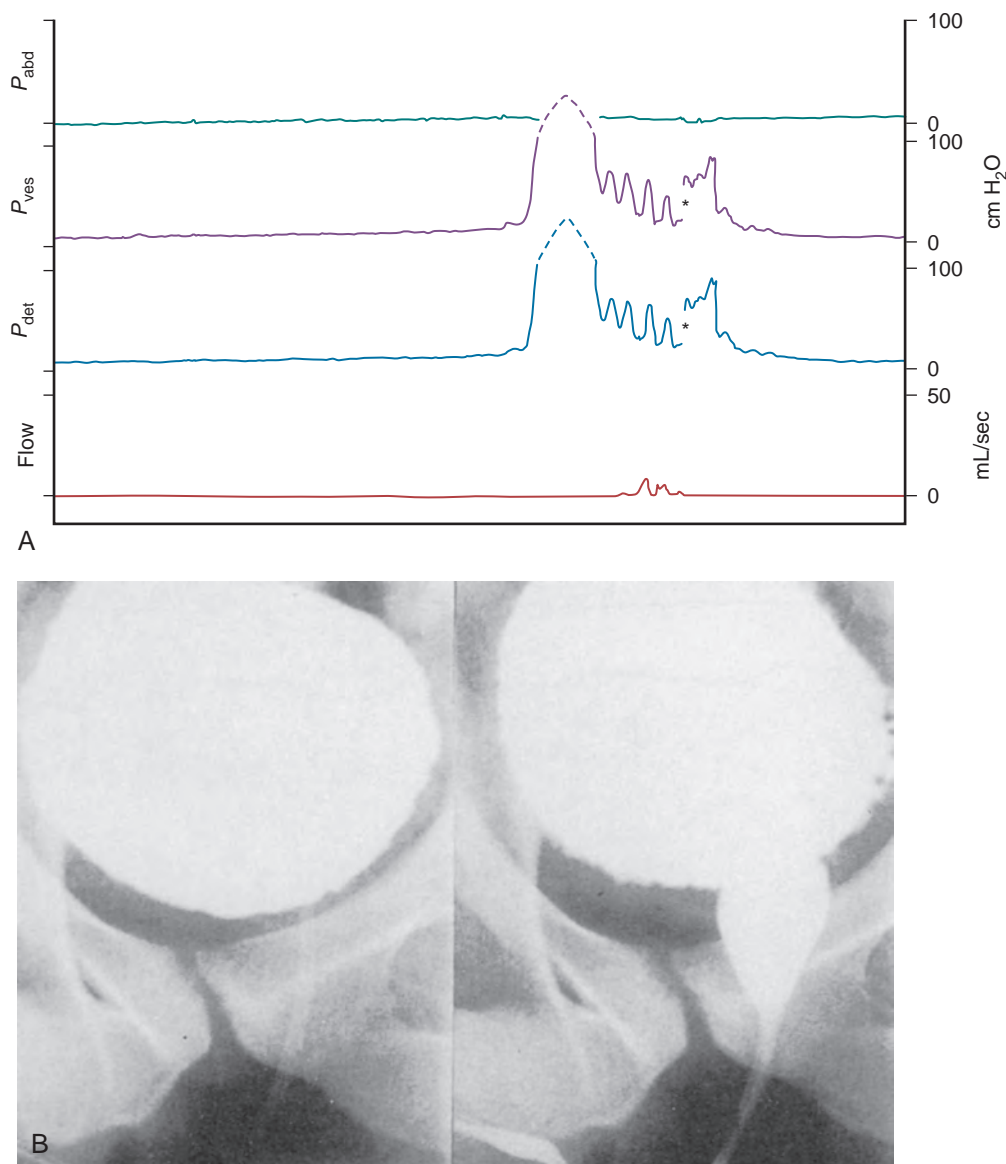


Figure 75-3. Video images in B at corresponding points of the urodynamic tracings in A. Detrusor hyperreflexia (P_{det} 150 cm H_2O), synergic bladder neck, dyssynergic striated sphincter. The asterisk represents a range change from a scale of 0 to 100 cm H_2O . (From Lawrence WT, Thomas DC. Urodynamic techniques in the neurologic patient. In: O'Reilly PH, George NJR, Weiss RM, editors. Diagnostic techniques in urology. Philadelphia: Saunders; 1990. p. 360.)

lesions had DSD. These data certainly support prior conclusions that (1) coordinated voiding is regulated by neurologic centers above the spinal cord and (2) a diagnosis of striated sphincter dyssynergia implies a neurologic lesion that interrupts the neural axis between the pontine-mesencephalic reticular formation and the sacral spinal cord. All 27 patients with neurologic lesions above the pons who were able to void did so synergistically (i.e., with relaxation of the striated sphincter followed by detrusor contraction). Twenty of these patients had detrusor overactivity, but 12 of the 20 had voluntary control of the striated sphincter, supporting a thesis of separate neural pathways governing voluntary control of the bladder and of the periurethral striated musculature. Most of these patients with detrusor overactivity secondary to suprapontine lesions were able to voluntarily contract the striated sphincter, but without abolishing bladder contraction. This seems to indicate that the inhibition of bladder contraction by pudendal motor activity is not merely a simple sacral reflex, but rather a complex neurologic event. Twenty-two of these patients had evidence of either sacral or infrasacral neurologic impairment of bladder function with

suprasacral control of striated sphincter function or vice versa. This provides a clinical correlate to the separate anatomic locations of the parasympathetic motor nucleus and the pudendal nucleus in the sacral spinal cord (see Chapter 69).

A subsequent study from the same center analyzed the results of urodynamic evaluation in 489 consecutive patients with either congenital or acquired SCI or spinal cord disease and correlated these with the diagnosed neurologic deficit (Kaplan et al, 1991). Although there was a general correlation between the neurologic level of injury and the expected vesicourethral function, the relationship was neither absolute nor specific. Twenty of 117 patients with cervical lesions exhibited detrusor areflexia, 42 of 156 with lumbar lesions had DSD, and 26 of 84 patients with sacral lesions had either detrusor overactivity or DSD. The patients were further classified on the basis of the integrity of the sacral dermatomes (intact sacral reflexes or not), which may explain some, but not all, of the apparent discrepancies. Of the patients with suprasacral cord lesions who had detrusor areflexia, 84% also had abnormal sacral cord signs (absent bulbocavernosus reflex, lax anal sphincter tone, or

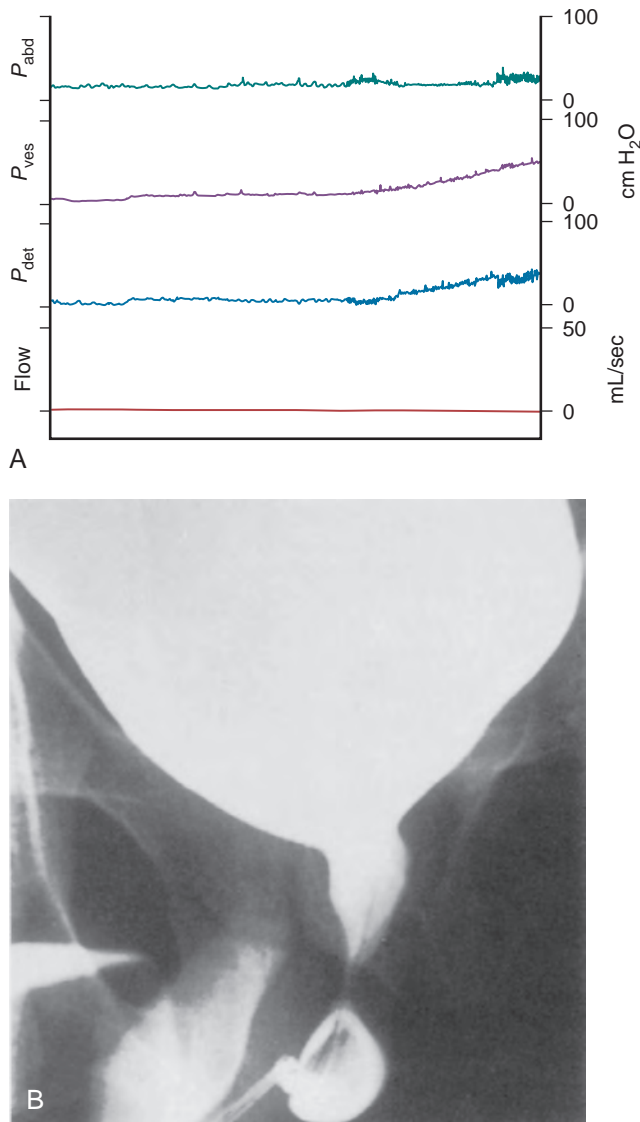


Figure 75-4. Simultaneous video (B) and urodynamic study (A) from a 28-year-old man whose bladder has been filled with 420 mL of contrast material. There is low compliance; the bladder neck is incompetent; and with straining the distal sphincter mechanism does not open—a pattern often seen in sacral spinal cord or efferent nerve root injury or disease. (From Lawrence WT, Thomas DC. *Urodynamic techniques in the neurologic patient*. In: O'Reilly PH, George NJR, Weiss RM, editors. *Diagnostic techniques in urology*. Philadelphia: Saunders; 1990. p. 362.)

sphincter electromyographic abnormalities indicative of lower motor neuron degeneration). All suprasacral cord lesion patients who had no evidence of sacral cord involvement had either detrusor overactivity or DSD.

Patients were also classified according to the three most common neurologic causes for their lesion: trauma, myelomeningocele, and spinal stenosis. Of the 284 trauma patients, all with thoracic cord lesions had either detrusor overactivity or DSD and absence of sacral cord signs. In contrast, patients with traumatic lesions affecting other parts of the spinal cord had a wide distribution of both urodynamic and sacral cord sign findings. For example, 38% of patients with traumatic lumbar cord injury had detrusor areflexia and positive sacral cord signs, 25% had DSD and negative sacral cord signs, 25% had detrusor overactivity and negative sacral cord signs, and 14% had either detrusor overactivity or DSD and negative sacral cord signs. Twenty of 25 patients with lumbar myelomeningocele had either detrusor areflexia or DSD, whereas all patients

with lumbar myelomeningocele and detrusor areflexia had positive sacral cord signs. Thirty-seven of 48 patients with sacral myelomeningocele had detrusor areflexia, and 35 had positive sacral cord signs. Of 54 patients with spinal stenosis, all those with cervical and thoracic cord lesions had either detrusor overactivity or DSD and negative sacral cord signs. Patients with a lumbar cord stenosis had no consistent pattern of detrusor activity or sacral cord signs. An open bladder neck at rest was found in 21 patients. All had either lumbar or sacral SCI. Sixteen of these had sacral cord lesions and detrusor areflexia. Decreased bladder compliance was noted in 54 patients, 41 of whom had sacral cord injury and 43 of whom had detrusor areflexia.

Wyndaele (1997) correlated the neurologic and urodynamic data in 92 patients with SCI and came to the same general conclusion: Although there was a general correlation between the neurologic level of injury and the expected vesicourethral function, it was neither absolute nor specific, especially in the group of patients with paraplegia resulting from spinal cord lesions at column level T10 to L2. With reference to this latter group, Pesce and coworkers (1997) reported on 46 patients with complete SCIs from vertebral lesions between T11 and L2. Fifty percent of the patients had detrusor areflexia and 50% had detrusor overactivity. Of the patients with detrusor overactivity, 16 also had DSD. Of 22 patients with lesions above vertebral level L1, 8 showed areflexia and 14 showed detrusor overactivity, of whom 9 demonstrated DSD. Of 9 patients with a lesion between T12 and L1, 3 showed detrusor areflexia and 6 overactivity, of whom 4 showed DSD. Of 15 patients with a lesion at L1 or lower, 3% showed detrusor overactivity and DSD.

Based on their review of 243 post-traumatic SCI patients who underwent complete spinal computed tomography (CT) or MRI, Weld and Dmochowski (2000) agreed that the correlation between somatic neurologic findings or spinal imaging studies and urodynamic findings in SCI patients is not exact. It should be noted that the authors' correlation between level of injury and urodynamic findings was better than those previously reported, most likely attributable to the precision of the radiologic imaging studies. Of 196 patients with suprasacral injuries, 94.9% demonstrated overactivity and/or DSD, 41.8% had low bladder compliance (defined as 12.5 mL/cm H₂O), and 40.3% had detrusor leak point pressures greater than 40 cm H₂O. Of the 14 patients with sacral injuries, 85.7% demonstrated detrusor areflexia; 78.6%, low compliance; and 85.7%, high leak point pressures. Of 33 patients with combined suprasacral and sacral injuries, 68% demonstrated detrusor overactivity and/or DSD, 27% had areflexia, 58% had low compliance, and 61% had high leak point pressures.

Other factors such as underlying histology may also contribute to upper tract deterioration. Ozkan performed full-thickness bladder biopsies in a group of patients undergoing augmentation cystoplasty for neurogenic detrusor overactivity. A relationship between the degree of and severity of detrusor fibrosis was noted to be a significant risk factor for upper tract deterioration. In addition, leak-point pressures of greater than 75 cm H₂O were also found to be consistent with upper tract deterioration (Ozkan et al, 2006).

In summary, all of these data suggest that management of the urinary tract in such patients must be based on urodynamic principles and findings rather than inferences from the neurologic history and evaluation. The presence of ambulation does not preclude significant urodynamic study abnormalities (Bellucci et al, 2012). Conversely, one should not make neurologic conclusions solely on the basis of urodynamic findings, although the information regarding "classic" complete lesions is for the most part valid (Cameron et al, 2012; Lenherr and Clemens, 2013).

Autonomic Hyperreflexia (Dysreflexia)

First described by Guttmann and Whitteridge in 1947, autonomic hyperreflexia (autonomic dysreflexia) is a potentially fatal emergency unique to the SCI patient. Excellent source materials include the reviews by Trop and Bennett (1991), Vaidyanathan and colleagues (1998), and Karlsson (1999). Autonomic hyperreflexia

represents an acute massive disordered autonomic (primarily sympathetic) response to specific stimuli in patients with SCI above the cord level of T6 to T8 (the sympathetic outflow). It is more common in cervical (60%) than thoracic (20%) spinal cord injuries. Onset after injury is variable—usually soon after spinal shock, but it may occur up to years after injury, and distal spinal cord viability is a prerequisite.

Symptomatically, autonomic hyperreflexia is a syndrome of exaggerated sympathetic activity in response to stimuli below the level of the lesion. The symptoms include pounding headache, hypertension, and flushing and sweating of the face and body above the level of the lesion. Bradycardia is a typical accompaniment, although tachycardia or arrhythmia may be present. Hypertension may vary in severity from causing a mild headache before voiding to life-threatening cerebral hemorrhage or seizure. The stimuli for this exaggerated response commonly arise from the bladder or rectum and typically involve distention. Precipitation may be the result of simple LUT instrumentation, tube change, catheter obstruction, or clot retention, and in such cases the symptoms resolve quickly if the stimulus is withdrawn. Additional causes or exacerbating factors may include other upper urinary tract or LUT pathology (e.g., calculi), gastrointestinal pathology, long bone fracture, sexual activity, electrocoagulation, and decubitus ulcers. In addition, with more SCI patients participating in athletic pursuits, the instigation of this condition related to sports activities is also being increasingly recognized (Krassioukov, 2012).

DSD invariably occurs, and, at least in males, smooth sphincter dyssynergia is also usually a part of the syndrome. The pathophysiology is that of nociceptive stimulation via afferent impulses that ascend through the cord and elicit reflex motor outflow, causing arteriolar, pilomotor, and pelvic visceral spasm and sweating. Normally, the reflexes would be inhibited by secondary output from the medulla, but because of the SCI this does not occur below the lesion level. Vaidyanathan and colleagues (1998) emphasized that the SCI disrupts control of the sympathetic preganglionic neurons because bulbospinal input has been lost, and the remaining regulation is accomplished by spinal circuits consisting of dorsal root afferent and spinal interneurons. Karlsson (1999), however, points out that the underlying pathogenic mechanisms may not be as simple as they first appear. The amplitude of the blood pressure reaction indicates involvement of a large vascular bed, perhaps larger than that of the skin and skeletal muscle. It may be that the splanchnic vascular bed is involved as well, either from the standpoint of active vasoconstriction or simply from a lack of the ability to exhibit compensatory vasodilatation. Afferent and efferent plasticity in the sympathetic nervous system may also be involved.

Urodynamics continues to be a critical component of the evaluation of the LUT in SCI. A study of 120 patients with suprasacral SCI undergoing urodynamics assessed the incidence of autonomic dysreflexia (defined as systolic blood pressure increase of 20 mm Hg or more); 42.6% of patients with injuries at T6 or above met criteria for the diagnosis of autonomic dysreflexia. Overall, 36.7% of patients experienced this condition. Surprisingly, 15.4% of patients with lesions below T6 experienced blood pressure elevations. Significant blood pressure increases were more commonly associated with DSD occurring continuously during bladder filling or in individuals with severely impaired bladder compliance as compared with individuals without those two variables. Most patients in this trial (75%) did not experience significant pulse rate changes (10 beats per minute), and, surprisingly, only 22.7% of those with the diagnosis of autonomic dysreflexia actually experienced bradycardia. The finding of dysreflexia in patients with lesions below the classically defined T6 level serves as a signal for close surveillance of SCI patients receiving LUT evaluation (Huang et al, 2011).

Ideally, any endoscopic procedure in susceptible patients should be done using spinal anesthesia or carefully monitored general anesthesia. Acutely, the hemodynamic effects of this

syndrome may be managed with β - and/or α -adrenergic blocking agents. Ganglionic blockers were once the mainstay of treatment (Wein, 2002a), but their usage has essentially been abandoned. Sublingual nifedipine is capable of alleviating this syndrome when given during cystoscopy (10 to 20 mg) and of preventing it when given orally 30 minutes before cystoscopy (10 mg) (Dykstra et al, 1987). The rationale for giving this medicine was that smooth muscle contraction would be prevented through its calcium antagonist properties, and the increase in peripheral vascular resistance normally seen with sympathetic stimulation would likewise be prevented. Before electroejaculation, Steinberger and colleagues (1990) recommended oral prophylaxis with 20 mg of nifedipine, finding this markedly lowered pressure rises during treatment. The use of sublingual nifedipine, however, has been prohibited in many medical centers.

Other rapidly acting agents have been reported to be beneficial, and labetalol is recommended by many anesthesiologists (Bycroft et al, 2005). Captopril, hydralazine, and diazoxide are still occasionally recommended but may be less advantageous (Furlan, 2013).

It is interesting to note that there seems to be no consensus on the acute pharmacologic management of autonomic dysreflexia when necessary. Krassioukov and colleagues (2009) extensively reviewed the level of evidence for various management strategies at the time and concluded that nifedipine, nitrates, and captopril were the most commonly used and recommended agents and were supported by level 2, 5, and 4 evidence, respectively.

Chancellor and colleagues (1994) reported on the use of terazosin (a selective α_1 -adrenergic blocker) for long-term management (3-month study) and prophylaxis of autonomic hyperreflexia. A nightly dose of 5 mg reduced severity, whereas erectile function and blood pressure were unchanged. Vaidyanathan and colleagues (1998) confirmed the success of prophylactic terazosin. They treated 18 tetraplegic adults and 3 paraplegics with gradually increasing doses of the drug, ultimately varying from 1 to 10 mg daily. The authors reported complete resolution of dysreflexic symptoms in all patients; only 1 tetraplegic patient required drug discontinuation because of persistent dizziness. Such prophylaxis may be particularly important in view of the fact that significant elevations in blood pressure can occur without other symptoms of autonomic hyperreflexia (Linsenmeyer et al, 1996).

Similar salubrious results have also been reported with prazosin as prophylaxis for this condition (Bycroft et al, 2005).

Prophylaxis, however, does not eliminate the need for careful monitoring during provocative procedures. There are patients with severe dysreflexia that is intractable to oral prophylaxis and correction by urologic procedures. For these unfortunate individuals, a number of neurologic ablative procedures have been used—sympathectomy, sacral neurectomy, sacral rhizotomy, cordectomy, and dorsal root ganglionectomy (Trop and Bennett, 1991). Hohenfellner and associates (2001) advocate sacral bladder denervation by sacral rhizotomy as a moderately invasive, relatively low risk procedure that, along with intermittent catheterization, produces good results in refractory patients.

Vesicoureteral Reflux

Surprisingly little is written about VUR in the SCI patient. The reported incidence varies between 17% and 25% of such patients (Thomas and Lucas, 1990), and the condition is more common in those with suprasacral SCI. Contributing factors include (1) elevated intravesical pressure during filling and emptying and (2) infection. Persistent reflux can lead to chronic renal damage and may be an important factor in the long-term survival of SCI patients. Hackler and coworkers (1965) reported that persistent reflux was present in 60% of SCI patients dying of renal disease. In patients with only transient VUR over a 5- to 15-year period, urography was normal or minimally changed in 83%. It should be noted that high storage and voiding pressures irrespective of VUR can be responsible for renal damage (McGuire, 1984; Vega and Pascual,

2001). Ku and associates reported on 179 men with SCI at a mean follow-up after injury of 29 years. The incidence of VUR in this group was 15.1%, whereas 34% of patients were diagnosed with pyelonephritis at some point during their follow-up. Nearly 25% developed renal stones, and 32% experienced upper tract deterioration as manifested by hydronephrosis. Upper tract degeneration was more prevalent in those managed with urethral catheters (51%) than in those managed with either spontaneous voiding or CIC. Urethral catheter drainage was inferior to all other forms of bladder drainage in terms of protecting the upper tracts, underscoring the inadvisability of chronic urethral catheterization in this patient population (Ku et al, 2005).

The best initial treatment for VUR in a patient with voiding dysfunction secondary to neurologic disease or injury is to normalize LUT urodynamics (i.e., decrease storage pressures and decrease outlet resistance) as much and as quickly as possible. Depending on the clinical circumstances, this may be achieved by pharmacotherapy, urethral dilatation (in the myelomeningocele patient), neuromodulation, deafferentation, augmentation cystoplasty, or sphincterotomy (Flood et al, 1994; Perkash et al, 1998). If this fails, the question of whether to operate on such patients for correction of the reflux or to correct the reflux while performing another procedure (e.g., augmentation cystoplasty) is not an easy one, because correction of reflux in a frequently very thickened bladder may not be an easy task.

Transureteroureterostomy for unilateral reflux is feasible, but even experienced urologists have had difficulties with ureteral calculi trapping, recurrent VUR, and obstruction at the vesicoureteral junction after such procedures in this difficult group of patients (Van Arsdalen et al, 1983). Submucosal trigonal injection of bulking substances has recently added a new dimension to the treatment of this difficult problem. Despite increased awareness of renal dysfunction related to high-pressure reflux in the SCI population, the prevalence of renal functional compromise in this population remains significant (Fischer et al, 2012).

Occasionally, bladder neck closure and permanent suprapubic drainage are indicated in the case of the severely dysfunctional or destroyed urethra arising from long-term indwelling catheterization (Colli and Lloyd, 2011). Urinary diversion continues to be a common method for management of LUT complications in this patient population (Peterson et al, 2012). However, in some cases, alternative diversion techniques using detubularized bowel segments may be successful (Khavari et al, 2012).

Finally, one must remember the potential artifact that significant reflux can introduce into urodynamic studies. Measured bladder capacity appears artifactually large, and measured pressures at given inflow volumes may appear lower than those after reflux correction. The apparent significance of detrusor overactivity may thus be underestimated.

Urinary Tract Infection

UTI is relatively common in patients with SCI. UTI or bacteriuria may occur in up to 57% of patients with SCI in the first year after initial hospitalization (Morton et al, 2002). Recurrent infections may be a manifestation of upper or lower tract calculi, symptomatic or silent pyelonephritis, or LUT dysfunction causing persistently elevated residual urine. In conjunction with poor urodynamic function, UTI can lead to high morbidity, poor quality of life, and decreased life expectancy in patients with SCI (Sauerwein, 2002). The use of antibiotics in SCI patients remains a topic of controversy. A consensus reached by the National Institute on Disability and Rehabilitation Research Group in 1992 stated that bacteriuria should be treated only when the patient has signs or symptoms of a UTI (Penders et al, 2003). In a comprehensive review, Biering-Sorensen and coworkers (2001) recommended the following: (1) Treat bacteriuria only if symptomatic; (2) use antimicrobial agents, if possible, with little or no impact on normal flora; (3) treat at least 5 days, and 7 to 14 days for those with reinfection or relapse; (4) repair structural and functional risk factors; (5) use prophylaxis

only in those with recurrent UTI when no underlying cause can be found and especially in those patients with dilated upper tracts; and (6) do not use antibiotics to prevent UTI in patients with an indwelling catheter. They regard the use of prophylactic antibiotics in patients on CIC as controversial.

Morton and coworkers (2002) concluded from a meta-analysis of 15 controlled trials that prophylactic antibiotics were not generally helpful, but added that they could not exclude a clinically important effect, especially in those who had recurrent UTI that limited their functioning and well-being. Sauerwein (2002) recommended beginning antibiotic prophylaxis in patients on CIC and stopping after 1 year if there has been one UTI or fewer. Some (Burns et al, 2001) believe that significant pyuria, defined as 8 to 10 or more white blood cells per high-power field, denotes tissue invasion and is an indication for antibiotic treatment. At the end of the day, there are few evidence-based data in this area (Hooton et al, 2010). In addition, the role of catheter type and infection risk has extensively been assessed, with evidence supporting the use of hydrophilic catheters (Bermingham et al, 2013; Li et al, 2013).

Spinal Cord Injury in Women

There are many aspects of management of the LUT affected by SCI that are specific to women (Yang and Cardenas, 2001). The incidence of SCI is highest among young men and older women (McColl, 2002). The body composition of women with SCI shows deficient protein and bone mass and excess fat, predisposing them to an increased risk of skin breakdown and incidence of fractures, a finding compounded by osteoporosis. The symptoms of menopause (e.g., hot flashes) may be difficult to distinguish from those of autonomic dysreflexia, and incontinence and UTIs worsen with age in women in the general population and particularly in those with SCI (Kalpakjian et al, 2010).

Suitable bladder reservoir function can usually be achieved either pharmacologically or surgically, and paraplegic women can usually master CIC; however, special difficulty is encountered in these patients owing to the lack of an appropriate external collecting device. Although some tetraplegic women can be trained to perform CIC, there is no practical alternative to indwelling catheterization for most (Lindan et al, 1987). Although there are reports of long-term drainage with an indwelling urethral catheter being well tolerated in the long term, McGuire and Savastano (1986) point out that this may often not be the case because of significant incontinence around the catheter and the development of upper tract changes (Kalpakjian et al, 2010).

For those spinal cord-injured female patients who can perform CIC or who have around-the-clock medical or family care, creation of adequate bladder reservoir function is reasonable. For those not in this category, the alternatives are limited and challenging. Bennett and associates (1995) compared the incidence of major complications in a group of female SCI patients who were managed long term by (1) CIC; (2) reflex voiding and incontinence padding; and (3) an indwelling catheter. There were 10 major complications in the 25 patients in group 2, 58 in the 22 patients in group 3, and only four major complications in group 1. Singh and Thomas (1997) looked at the results of treatment in a group of female tetraplegics. Twenty-three of 27 patients with complete lesions wound up using an indwelling catheter, 3 underwent diversion, and in 1 patient the caregiver performed CIC. In 20 patients with incomplete lesions, all with poor functional recovery, 14 had permanent indwelling catheters, 3 were able to perform CIC, and 3 used reflex voiding by triggering. Of 37 patients with incomplete lesions with good functional recovery, only 3 required indwelling catheterization, 4 used CIC, and most were able to use reflex voiding by triggering. The authors noted also that 55% of the women with permanent catheters had bladder calculi, 35% had leakage around the catheter, and 33% had recurrent symptomatic infection. Although upper tract changes were seen in only 5%, it is obvious that the authors consider that, for the most part, female patients

with voiding dysfunction secondary to cervical SCI who exhibit poor functional recovery represent urologic failures of management. Surgical intervention for stress urinary incontinence in this population also may be beneficial in well-selected patients. Mid-urethral tapes have been reported to produce reasonable outcomes in selected women with SCI (Pannek, 2012). Other groups have reported durable and safe results using autologous tissue as the sling type (Athanasopoulos et al, 2012).

Spinal Cord Injury (Neurogenic Bladder) and Bladder Cancer

There is a strong association between the development of bladder cancer and long-term indwelling catheterization. Kaufman and colleagues (1977) initially reported squamous cell carcinoma of the bladder in 6 of 59 patients with SCI who had long-term indwelling catheters. Four of these patients had no obvious tumors visible at endoscopy, and the diagnosis was made by bladder biopsy. Five of these patients also had transitional cell elements in their tumor. Broecker and associates (1981) surveyed 81 consecutive SCI patients with an indwelling urinary catheter for more than 10 years, and, although the investigators did not find frank carcinoma in any patient, they found squamous metaplasia of the bladder in 11 and leukoplakia in 1. Locke and coworkers (1985) noted 2 cases of squamous cell carcinoma of the bladder in 25 consecutive SCI patients catheterized for a minimum of 10 years. Bickel and colleagues (1991) reported 8 cases of bladder cancer in men with SCI, although the denominator was uncertain. Four of the men had been managed by indwelling catheterization for 7, 10, 14, and 19 years, respectively. All of these 4 had transitional cell carcinoma, whereas in the other 4 men there were 2 cases of transitional and 2 of squamous cell carcinoma. In Chao and colleagues' series (1993), 6 patients developed bladder cancer, 3 of whom had indwelling catheters (of a total of 32) and 3 of whom (of 41) did not. Stonehill and associates (1996) retrospectively reviewed all bladder tumors in their SCI patients for 7 years and compared these with matched controls. They found 17 malignant and 2 benign bladder tumors, with indwelling catheters and a history of bladder calculi being statistically significant risk factors.

Hess and associates (2003) reported their own series and summarized one view of the literature regarding SCI and bladder cancer: (1) The relative risk in SCI patients is 16% to 28% greater than the general population; (2) the overall incidence is 2.3% to 10%; (3) there is a higher proportion of squamous cell than transitional cell carcinoma; (4) the prevalence peaks at an earlier age than in the general population; (5) diagnosis is often made at a more advanced stage; (6) risk factors include chronic indwelling catheterization, bladder stones, and chronic UTI; (7) neither cystoscopy nor cytology is an entirely reliable diagnostic tool; and (8) those with multiple risk factors should have a more aggressive evaluation.

Tempering these views are reports by Pannek (2002), who reviewed the data from 43,561 SCI patients in three countries and concluded that the incidence of bladder cancer is comparable to that of the general population; however, more than 60% of those affected had muscle invasive disease on initial presentation. Chronic indwelling catheters and persistent or recurrent UTI are suggested as risk factors rather than the SCI itself. Subramonian and associates (2004), in an assessment of spina bifida patients, reported similar conclusions regarding age-standardized incidence of bladder cancer relative to the general population. They reported a lifetime risk of 2.4% in their reported population. This compares with a lifetime risk estimation of 30.7 to 720 per 100,000. Seventy-five percent of the affected patients in the series had indwelling catheters for 18 to 32 years.

The incidence of bladder cancer in MS patients with indwelling catheters is estimated to be 0.29%, as compared with 0.004% in the general population of females and 0.018% in the population of males. The incidence of bladder cancer in SCI patients has been recorded to range from 0.27% to 9.6%; however, in larger series the overall incidence is 0.27% to 0.37%. The natural history of bladder cancer is thought to be more highly aggressive in neurogenic

patients and is responsible for 0.3% to 2.8% of known deaths in the SCI population.

Follow-Up

Linszenmeyer and Culkin (1999) reported the American Paraplegia Society (APS) guidelines for urologic care of SCI. Annual follow-up is recommended for the first 5 to 10 years after injury, and if the patient is doing well, then follow-up every other year is advised. Upper and lower tract evaluation should be done initially, yearly for 5 to 10 years, and then every other year. Burns and associates (2001) recommended at least plain films and nuclear renal scans, with a decrease of more than 20% in renal plasma flow warranting further investigation. Urodynamic evaluation was recommended by the APS at the same intervals as upper and lower tract screening. Cystoscopy was recommended annually in those with an indwelling catheter.

In 2006, the Consortium for Spinal Cord Medicine detailed a set of guidelines for bladder management in adults with SCI and stated only that, in general, a urologic evaluation should be done yearly, although no studies exist on the optimum frequency of such examinations or the tests that should be included (Consortium for Spinal Cord Medicine, 2006).

The European Association of Urology (EAU) guidelines for follow-up of all neurogenic LUT dysfunctions call for meticulous and regular re-evaluations at intervals of no more than 1 to 2 years, and more frequently for patients with MS and acute SCI and other unstable conditions. They include the following guidelines: (1) Supply the patient with urinary dipsticks to check the urine at least every 2 months and whenever a urinary infection is suspected; (2) perform upper urinary tract and bladder morphology every 6 months (ultrasonography), along with residual urine determination; (3) conduct physical examinations and blood chemistries yearly; (4) obtain detailed specialist investigation every 1 to 2 years and on demand when risk factors emerge (Pannek et al, 2011).

Cervical Myelopathy

Cervical myelopathy is usually caused by compression, secondary to spondylosis, ossification of the posterior longitudinal ligament, or cervical disk herniation (Sakakibara et al, 1995a; Mochida et al, 1996). Sakakibara and associates (1995a) studied 128 affected patients, of whom 95 had voiding symptoms, 61 had storage symptoms, 71 had obstructive symptoms, and 25 had urinary incontinence. Urodynamic studies revealed detrusor overactivity in 61 patients and DSD in 22. On the other hand, Mochida and colleagues (1996) reported that 22 of 60 (37%) patients undergoing surgery for cervical myelopathy were found to have neuropathic bladder dysfunction on urodynamic evaluation. Of these, 9 (41%) were found to have detrusor overactivity, but 13 (59%) were characterized as having an underactive detrusor. Because these findings are at odds with what one would expect with only cervical spinal cord pathology, the need for urodynamic study to optimally guide therapy in patients with neurogenic bladder is reinforced.

Acute Transverse Myelitis

Acute transverse myelitis is a rapidly developing condition with motor, sensory, and sphincter abnormalities, usually with a well-defined upper sensory limit and no signs of spinal cord compression or other neurologic disease (Kalita et al, 2002). It may result from a variety of mechanisms—parainfectious, autoimmune, vascular, or demyelinating (Ganesan and Borzyskowski, 2001). The condition usually stabilizes within 2 to 4 weeks and is not progressive afterward; however, recovery may be variable and some residual neurologic deficits are possible. Although recovery is more variable, and the prognosis, in general, is more favorable, the development and nature of voiding dysfunction have been reported to be similar, level by level, to those of SCI (Sakakibara et al, 1995b). Kalita and colleagues (2002) reported on 18 patients with acute transverse

myelitis whose 6-month outcome included persistent retention in 6 and storage symptoms in 10, of whom 5 had emptying problems as well. Only 2 patients had regained normal voiding. In the acute state, urodynamics showed an areflexic or contractile bladder in 10, detrusor overactivity with poor compliance in 2, and DSD in 3. Seventeen had had urinary retention on presentation. As in SCI, urodynamic studies are necessary to guide irreversible therapy because the activity of the bladder and outlet during storage and emptying does not always correspond to the expected pattern based on the level of pathology.

Neurospinal Dysraphism

Neurospinal dysraphism is covered primarily in Chapter 142; however, certain considerations regarding the adult with these abnormalities should be mentioned. *Spinal dysraphism* refers to the malformation of the vertebral arches and, commonly, malformation of the neural tube. The term includes spina bifida occulta, which involves only a bony (vertebral) arch defect; and spina bifida cystica (aperta), which involves a bony defect and a neural tube (spinal cord) defect. The two primary subclasses of spina bifida cystica are myelomeningocele (the nerve roots or portions of the spinal cord have evaginated beyond the vertebral bodies) and meningoceles (which contain only a herniated meningeal sac with no neural elements). If fatty tissue is present in the sac in either case, the prefix *lipo-* is added (Churchill et al, 2001). Myelomeningocele accounts for more than 90% of spina bifida cystica and is the most devastating condition in terms of sequelae. Of myelomeningoceles, 2% are cervical, 5% thoracic, 26% lumbar, 47% lumbosacral, and 20% sacral. The level(s) of the lesion correlate(s) poorly with urodynamic findings (Churchill et al, 2001). Myelomeningocele occurs in approximately 1 per 1000 live births (Wyndaele et al, 2005; Drake et al, 2013). The incidence of LUT dysfunction is not absolutely documented, but most studies suggest an incidence of over 90% (Wyndaele et al, 2005; Drake et al, 2013). The incidence of spina bifida has decreased in recent years owing to the recognition of the importance of folate ingestion in pregnant women and also advanced prenatal diagnostic capabilities resulting in selective termination of pregnancies. However, up to 85% of patients with spina bifida do survive to adulthood, and therefore this condition is becoming a more significant chronic care issue in the general population. Transitional care from childhood through adolescence to adulthood now is becoming a focus of specialized clinics despite the fact that many barriers do exist (Summers et al, 2014).

McGuire and Denil (1991) and Woodhouse (2005) point out that, owing to progress in the overall care of children with myelodysplasia, urologic dysfunction often becomes a problem of the adolescent or adult with this disease. In McGuire and Denil's (1991) experience, the "typical" myelodysplastic patient shows an areflexic bladder with an open bladder neck. The bladder usually fills until the resting residual fixed external sphincter pressure is reached, and then leakage occurs. Stress incontinence may also occur owing to changes in intra-abdominal pressure. A small percentage (10% to 15%) of patients demonstrate DSD, but these individuals show normal bladder neck function that, if detrusor reflex activity is controlled, may be associated with urinary continence. After puberty, most authors report that the majority of myelodysplastic patients note an improvement in continence, but at that age and afterward they are less inclined than children to tolerate any degree of incontinence. In adult patients the problems encountered in myelodysplastic children still exist but are often compounded by prior surgery, upper tract dysfunction, and one form of urinary diversion or another.

Perhaps the most important intervention for myelomeningocele is amelioration of the initial impact of the disease. A recent prenatal intervention trial was discontinued before study completion when the primary outcome of fetal or neonatal death or the need for cerebrospinal fluid shunt by age of 12 months was substantially less in the treated group. An additional primary outcome of overall mental development and motor function at age 30 months

showed that in individuals undergoing prenatal surgery, substantial improvement was encountered as compared with those receiving only postnatal interventions. In the prenatal surgery group, 40% of patients required cerebrospinal fluid shunts, whereas 82% of those in the postnatal group did. In addition, highly significant improvement in motor function and mental development was noted in the prenatal as compared with the postnatal group. A variety of secondary outcomes also were improved in this group, including the risk of hindbrain herniation at 12 months and ambulation by 30 months. However, there was an increased risk of preterm delivery and uterine dehiscence at delivery in the prenatal group as compared with the postnatal group. Nonetheless, this randomized trial of prenatal versus postnatal repair showed significant benefits to prenatal repair, resulting in termination of this trial on elevation of this intervention to a primary consideration for the condition of prenatally diagnosed myelomeningocele (Adzick et al, 2011).

The treatment strategy in women is to increase urethral sphincter efficiency without causing an increase in urethral closing pressure significant enough to result in a change in bladder compliance (McGuire and Denil, 1991). Periurethral injection therapy may be a safer option than the pubovaginal sling and artificial urethral sphincter in this case. The authors also believe that stress incontinence in men with myelodysplasia may follow similar general rules as in women, and bulking agents may give good results in this group as well. When the urethra is very widely dilated and somewhat rigid, and neither procedure alone will provide sufficient coaptation, it may be possible to combine a "prostatic sling" with periurethral bulking. Continent individuals will remain on CIC.

Nowhere is the failure of a neurologic examination to predict urodynamic behavior more obvious than in patients with myelomeningocele. Van Gool and colleagues (2001) categorized the urodynamic findings in 188 children with myelomeningocele into five groups: (1) normal detrusor and sphincter activity (7%); (2) detrusor overactivity and an inactive sphincter (11%); (3) detrusor overactivity and an overactive sphincter (45%); (4) inactive detrusor and inactive sphincter (23%); and (5) an inactive detrusor and an overactive sphincter (14%). In 16 adults with myelomeningocele, Sakakibara and associates (2003a) reported detrusor overactivity in 38%, low compliance in 81%, impaired bladder sensation in 25%, DSD in 50%, low maximum urethral pressure in 56%, and silent sphincter electromyographic findings in 25%. Webster and colleagues (1986) reported that 62% of their patients with myelomeningocele had detrusor overactivity, whereas 38% had detrusor areflexia. Thirty of 34 patients in the latter group had low compliance with high terminal filling pressures. Striated sphincter behavior was characterized as follows: true DSD in 15%, an apparently innervated but fixed nonrelaxing sphincter in 15%, and some evidence of striated sphincter denervation in 69%. Regardless of the pattern of LUT dysfunction in the adult, the main goal of therapy is the avoidance of high storage pressures (McGuire and Denil, 1991; Persun et al, 1999; Woodhouse, 2005).

LUT dysfunction secondary to occult spinal dysraphism may not manifest in childhood, and such patients may be referred as adults for symptoms as commonplace as urinary incontinence or recurrent UTIs. Delayed diagnosis of such voiding dysfunction has been reported by several authors (Jakobsen et al, 1985; Yip et al, 1985) and the specific dysfunction is dependent on the level and extent of the neurologic injury.

The urologic rehabilitation of patients with spinal dysraphism relies primarily on medical management and intravesical injection of onabotulinumtoxinA, with the selective use of augmentation enterocystoplasty or urinary diversion if failure occurs. However, surgery does not necessarily yield superior results. In a review of 421 patients managed for complications relating to spina bifida, 45% were treated medically, either with CIC, spontaneous voiding, or no specific method, and 55% were treated surgically. Overall incontinence episodes were higher in the surgical management group; however, these outcomes may have been reflective of the aggressiveness of management as well as the severity of disease (Lemelle et al, 2006). A recent evaluation of individuals being

followed long term for myelomeningocele (20-year follow-up) found that 7 patients (13% of the original 52 followed) had unilateral renal dysfunction and 8 (15%) had bilateral overall renal dysfunction. Those with bilateral dysfunction had a significantly higher risk of detrusor overactivity during childhood urodynamic evaluation (63%) compared with those with normal function (24%). Overall, 48% of patients were continent at follow-up. Eight patients required surgical intervention sometime during the course of their condition. Nine used regular antimuscarinic ingestion, and 3 had had intravesical botulinum toxin injection. In addition, 27 required intermittent catheterization for management. Therefore urodynamic findings may be predictive of long-term consequences (Thorup et al, 2011). Surgery remains a salvage option for those not optimally managed by medical intervention. A recent assessment of national data practices using administrative data sets from a nationwide inpatient sample assessed patients undergoing bladder augmentation versus ileal conduit urinary diversion over a 7-year timeframe (1998 to 2005) for the primary diagnosis of spina bifida. Overall, 3403 patients underwent bladder augmentation, whereas 772 underwent ileal loop diversion. The bladder augmentation group tended to be younger patients (16 vs. 36 years) and more commonly male (52%). Urinary diversion was more commonly associated with the female patients as well as older patients. Overall, those undergoing urinary diversion had higher health care expenses and longer hospital stays. There was some difference in care choice based on insurance status (Wiener et al, 2011).

Recently, neural rerouting has been proposed as a potential option for some of these individuals. Ziao and colleagues have performed microanastomosis of the fifth lumbar ventral root to the third sacral ventral root to bypass low-level spina bifida injury. Initial improvements in bladder compliance and urinary incontinence were noted in patients and paralleled similar findings in patients with SCI (Joseph, 2005).

Tethered cord syndrome (TCS) is defined as a stretch-induced functional disorder of the spinal cord with its caudal part anchored by inelastic structures and restricting vertical movement. The anchoring structures can include scar from prior surgery, fibrous or fibroadipose filum terminale, a bony septum, or tumor (Yamada et al, 2004a, 2004b). Adults with TCS can be divided into those with a prior history of spinal dysraphism with a previously stable neurologic status who present with subtle progression in adulthood and those without associated spinal dysraphism who present with new-onset subtle neurologic symptoms (Yamada et al, 2004a, 2004b). Symptoms can include back pain, leg weakness, foot deformity, scoliosis, sensory loss, and bowel or LUT dysfunction (Phuong et al, 2002). TCS is reported to occur in 3% to 15% of patients with myelomeningocele. There is no typical dysfunction in TCS, and treatment must be based on urodynamic evaluation. LUT dysfunction may not be present until the teenage years or later (Kaplan and Blaivas, 1988; Husmann, 1995). Giddens and colleagues (1999) point out that, whereas children often develop symptoms of tethered cord after growth spurts, in adults the presenting symptomatology often follows activities that stretch the spine, such as sports or motor vehicle accidents. In adults, urologic presentation can include storage or voiding symptoms, incontinence, or complete retention. In a group of adult patients, urgency (67%) and urgency incontinence (50%) were the most common findings at presentation. Pretreatment urodynamics in 18 patients revealed detrusor overactivity in 72%, DSD in 22%, decreased sensation in 22%, decreased compliance in 17%, and what was termed a "hypocontractile" detrusor in 11%. It is interesting that postoperative urodynamic findings improved in only 29% and were unchanged in 71%. Steinbok and associates (2007) assessed eight children undergoing section of the filum that induced the tethered cord and compared them with seven children who had abnormal urodynamic findings and did not undergo filum release. Clinical improvement occurred in seven of the eight children at a mean follow-up of 3 years with improved urodynamics in four of seven children tested after surgery. These improvements were also associated with nonurologic functional

improvements (i.e., motor leg function). Two patients in the non-surgical group had urologic improvement at a mean follow-up of 3 years; however, three patients required surgical intervention and five had persistence of nonurologic symptoms. Thus, section of the cord appeared to improve function as compared with conservative, nonsurgical management.

Not all symptoms of tethered cord are remediated by surgery. In a retrospective assessment of 29 patients undergoing first-time tethered cord release, clinical symptoms were evaluated at 1 and 3 months after surgery as well as every 6 months thereafter. Garces-Ambrossi and coworkers (2009) addressed rates of improvement in motor and urinary dysfunction over time. The most common causes of tethered cord included lipomyelomeningocele (10%), tight filum (10%), lumbosacral lipoma (14%), intradural tumor (10%), and previous surgery in 7%. In addition, 48% of patients had had previous repair of myelomeningocele defects. Symptoms before intervention occurred for a mean of 5 months. Symptomatic presentation included diffuse pain and paresthesias in both lower extremities (45%) or perineum (62%). Lower extremity weakness was noted in patients with gait disturbances (59%) and bladder dysfunction (48%). Multilevel laminectomy accompanied by duraplasty (30% of patients) was performed as the primary intervention. At 18 months postoperatively, 47% of the patients with urinary symptoms had improvement in those symptoms, 69% had improvement in the lower extremity weakness, and 79% had improved painful dysesthesias. Mean time for improvement was 1 month for pain and 2.3 months for motor symptoms. Urinary symptoms lagged at 4.3 months. The majority of patients demonstrated improvement within 6 months of surgery (96%). After 1 year, only 4% showed no improvement (Garces-Ambrossi et al, 2009).

Recent emphasis on transitional aspects of care from childhood to adulthood has centered on the need for meticulous follow-up and optimization of bladder and renal function in light of social stigma, patient concerns, independence, and also bowel-related dysfunction. Consensus agreement stresses the need for established algorithmic approaches for follow-up inclusive of annual surveillance for early identification of urinary tract deterioration. These assessments should include renal and bladder ultrasonography and urodynamics when indicated (by symptomatic change or clinical physical examination finding). In addition, serum creatinine and renal scintigraphy may be performed when upper tract changes are suspected. Goals of therapy include reduction in detrusor pressure and maintenance of bladder compliance and social continence (de Kort et al, 2012).

Tabes Dorsalis, Pernicious Anemia

Although syphilitic myelopathy is rapidly disappearing as a major neurologic problem, involvement of the spinal cord dorsal columns and posterior sacral roots can result in a loss of bladder sensation and large postvoid residual urine volumes and therefore can be a cause of "sensory neurogenic bladder" (see Chapter 70). Although this represents the classic tabetic bladder (Wheeler et al, 1986), Hattori and coworkers (1990) reported on some patients with only tabes as an obvious cause of their LUT dysfunction who had low compliance or detrusor overactivity. Another spinal cord cause of the classic "sensory bladder" is the now uncommon pernicious anemia that produced this disorder by virtue of subacute combined degeneration (SACD) of the dorsolateral columns of the spinal cord. Pernicious anemia is a disease caused by impaired uptake of vitamin B₁₂ resulting from the lack of intrinsic factor in the gastric mucosa.

Poliomyelitis

Although not always present, when voiding dysfunction is seen in patients with polio it is that of a typical "motor neurogenic bladder" (see Chapter 70), with urinary retention, detrusor areflexia, and intact sensation. The reported incidence of LUT dysfunction in patients with polio was described as ranging from 4% to 42% by Bors and Comarr (1971).

DISEASE DISTAL TO THE SPINAL CORD

Disk Disease

Goldman and Appell (2000a, 2000b) nicely summarize the anatomic and neurologic considerations applicable to voiding dysfunction from lumbar disk disease. In the adult, the sacral segments of the spinal cord are at the level of the L1 and L2 vertebral bodies. In this distal end of the spinal cord (conus medullaris), the spinal cord segments are named for the vertebral body at which the nerve roots exit the spinal canal. Thus, although the sacral spinal cord segment is located at vertebral segment L1, its nerve roots run in the subarachnoid space posterior to the L2 to L5 vertebral bodies until reaching the S1 vertebral body, at which point they exit the canal. Therefore all of the sacral nerves that originate at the L1 and L2 spinal column levels run posterior to the lumbar vertebral bodies until they reach their appropriate site of exit from the spinal canal. This group of nerve roots running at the distal end of the spinal cord is commonly referred to as the *cauda equina*.

Usually, disk prolapse is in a posterolateral direction, which does not affect the majority of the cauda equina. However, in 1% to 15% of the cases (Goldman and Appell, 2000b), central disk prolapse occurs and compression of the cauda equina may result. Thus, disk prolapse anywhere in the lumbar spine could interfere with the parasympathetic and somatic innervation of the LUT, striated sphincter, and other pelvic floor musculature, and afferent activity from the bladder and affected somatic segments to the spinal cord. Most disk protrusions compress the spinal roots in the L4 to L5 or L5 to S1 vertebral interspaces. When LUT dysfunction is present, it typically occurs with the usual clinical manifestations of low back pain radiating in a girdle-like fashion along the involved spinal root areas. The most characteristic findings on physical examination are sensory loss in the perineum or perianal area (S2 to S4 dermatomes), sensory loss on the lateral foot (S1 to S2 dermatomes), or both.

In a review of the literature on LUT dysfunction associated with lumbar disk disease, Goldman and Appell (2000b) found that the incidence ranged from 27% to 92%, although the true incidence is unknown because many series describe findings only in patients with LUT dysfunction. Bartolin and colleagues (1998) found detrusor areflexia in 27% and normal detrusor activity in the remaining 73% of 114 patients with lumbar disk protrusion. All 31 patients with detrusor areflexia reported difficulty voiding with straining, and patients with voiding dysfunction generally presented with these symptoms or in urinary retention. The most consistent urodynamic finding was that of a normally compliant areflexic bladder associated with normal innervation or findings of incomplete denervation of the perineal floor musculature. In a later report, Bartolin and colleagues (2002) describe findings in 122 patients with lumbar disk protrusion. Detrusor areflexia was found in 32 (26%) and normal bladder urodynamic findings in 90 (74%). All with areflexia complained of difficulty voiding; 8 could not void at all, 14 had an interrupted flow, and 10 had a continuous but low flow. Occasionally, patients may show detrusor overactivity, attributed to irritation of the nerve roots (O'Flynn et al, 1992).

The detrusor areflexia associated with lumbar disk protrusion shows a lower incidence of concomitant decreased compliance than in the voiding dysfunction associated with myelomeningocele. Sandri and coworkers (1987) offered two possible explanations for this difference: (1) The effect of the disk represents a more incomplete lesion of the preganglionic parasympathetic fibers, and (2) the lesion is more sensory than motor, implying that the decreased compliance seen with the type of neural lesion in myelomeningocele is primarily caused by injury of the preganglionic parasympathetic motor fibers to the bladder.

Laminectomy may not improve LUT function in many cases, and prelamination urodynamic evaluation is prudent because it may be difficult postoperatively to separate causation of voiding dysfunction resulting from the disk sequelae from changes secondary to the surgery. In a group of patients with lumbar disk protrusion who underwent corrective surgery, Bartolin

and colleagues (1999) reported that detrusor activity returned to normal in only 6 of 27 patients with preoperative detrusor areflexia. Of the 71 patients with normal urodynamic findings preoperatively, 4 developed detrusor overactivity and 3 developed postoperative detrusor areflexia. The medicolegal implications of a presurgical and postsurgical urodynamic evaluation are obvious.

Cauda equina syndrome is a term applied to the clinical picture of perineal sensory loss with loss of voluntary control of both anal and urethral sphincter and of sexual responsiveness. This can occur not only secondary to disk disease (severe central posterior disk protrusion) but also to other pathologic processes affecting the spinal canal. Yamanishi and associates (2003) place the incidence of cauda equina syndrome at 1% to 5% of all prolapsed lumbar disks. All eight patients undergoing emergency corrective surgery had an acontractile detrusor with no bladder sensation, and four of seven had an inactive sphincter electromyogram. Follow-up urodynamics showed that all still had an acontractile detrusor and three had normal electromyographic activity. Three patients had electromyographic activity, but with denervation potentials in two and low activity in two. The clinical picture in cauda equina syndrome can vary widely, from minimal to maximal sensory and motor involvement.

Spinal Stenosis

Spinal stenosis is a term applied to any narrowing of the spinal canal, nerve root canals, or intervertebral foramina. It may be congenital, developmental, or acquired. Compression of the nerve roots or cord by such a problem may lead to neuronal damage, ischemia, or edema. Spinal stenosis may occur without disk prolapse. Symptoms may range from those consequent to cervical spinal cord compression to a cauda equina syndrome, with corresponding urodynamic findings (Smith and Woodside, 1988). Back and lower extremity pain, cramping, and paresthesias related to exercise and relieved by rest are the classic symptoms of lumbar stenosis caused by lumbar spondylosis and are believed to result from a sacral nerve root ischemia. The urodynamic findings are dependent on the level and the amount of spinal cord or nerve root damage. Deen and coworkers (1994) reported subjective improvement in over 50% of such patients with bladder dysfunction who were treated by decompressive laminectomy. In cervical spondylitic spinal stenosis, detrusor overactivity or underactivity may occur, depending on whether the primary pathologic process affecting the micturition neural axis is compression of the inhibitory reticulospinal tracts or myelopathy in the posterior funiculus, which carries proprioceptive sensation (Tammela et al, 1992). Because there is no consistent pattern of dysfunction with any type of spinal stenosis, urodynamic studies again should serve as the cornerstone of therapy. In a study of 26 patients undergoing urodynamic assessment of spinal stenosis preoperatively and postoperatively, substantive improvements were noted in postvoid residual volume, maximal cystometric capacity, and flow rate postoperatively after successful surgical intervention in all patients. Urodynamic evaluation was important from a diagnostic standpoint to identify patients who were experiencing LUT compromise (Cong et al, 2010). Podnar and colleagues (2006) assessed 65 cauda equina patients with neurologic examination, electromyography, and urodynamics. Severe LUT dysfunction was noted in 14% of women and 15% of men, whereas moderate dysfunction was noted in 27% of men and 46% of women. Incomplete emptying was the most common symptom (>90%), and urinary incontinence was next with 56% of men and 71% of women. Reduced capacity was noted in 9% and 15%, respectively. Poor detrusor contractility was noted in 59% of men and 85% of women. Using multiple linear regression, perianal sensory loss and female gender had the most significant positive predictive value for urinary incontinence.

Radical Pelvic Surgery

The inferior hypogastric plexus (pelvic plexus) which innervates the viscera of the pelvic cavity is a paired structure located on the side

of the rectum in males and at the sides of the rectum and vagina in females. LUT dysfunction after pelvic plexus injury occurs most commonly after abdominoperineal resection (APR) and radical hysterectomy. The true incidence of neurogenic vesicourethral dysfunction after various types of pelvic surgery is unknown because there are few prospectively studied series of patients with preoperative and postoperative urodynamic evaluation. The incidence has been estimated to range from 20% to 68% of patients after APR, 16% to 80% after radical hysterectomy, 20% to 25% after anterior resection, and 10% to 20% after proctocolectomy (Blaivas and Chancellor, 1995b). These are estimates drawn from past literature, and the current incidence is most likely significantly lower, owing to the use of nerve-sparing techniques during these types of pelvic procedures. It has been estimated that the LUT dysfunction remains permanent in 15% to 20% of affected individuals (McGuire, 1984; Mundy, 1984). The injury may occur from denervation or neurologic decentralization, tethering of the nerves or encasement in scar, direct bladder or urethral trauma, or bladder devascularization. Adjuvant treatment, such as chemotherapy or irradiation, may compound the damage. The type of LUT dysfunction that occurs is dependent on the specific nerves involved, the degree of injury, and any pattern of reinnervation or altered innervation that occurs over time (see Chapter 69 and the previous section on neuroplasticity). Therapeutic and disease-related effects on pelvic nerves have substantive effects on long-term functional outcomes after treatment for anal-rectal carcinomas. Approximately one third of patients have some element of urinary tract dysfunction (urinary frequency, urgency, and/or poor detrusor contraction resulting in retention and incomplete emptying). This can be related to surgical, radiotherapeutic, and chemotherapeutic effects. Abdominoperineal resection has the greatest impact on function, most likely because of autonomic nerve injury at time of resection. Other dysfunctions related to sexual activity, ejaculatory dysfunction in men, and vaginal dryness and dyspareunia in women are also commonly associated with the management of this malignancy (Lange and van de Velde, 2011).

Literature on the effects of parasympathetic decentralization on neuromorphology and neuropharmacology of the LUT in many animal models is abundant (Wein and Barrett, 1988).

Parasympathetic decentralization has been reported to lead to a marked increase in adrenergic innervation of the bladder in some experimental models, with the resultant conversion of the usual β (relaxant) response of the bladder body in response to sympathetic stimulation to the α (contractile) effect (Sundin et al, 1977). Hanno and colleagues (1988) confirmed that, in the cat model, parasympathetic decentralization does result in adrenergic hyperinnervation of the detrusor but that pelvic plexus neurectomy alone or parasympathetic decentralization plus hypogastric neurectomy yields no detectable increase in adrenergic innervation. In their experimental model, decentralization did result in synaptic reorganization in bladder wall ganglia with new cholinergic excitatory inputs from the hypogastric nerves. Koyanagi was the first to call attention to what he referred to as supersensitivity of the urethra to α -adrenergic stimulation in a similar group of patients with neurologic decentralization of the LUT, implying a similar change in adrenergic receptor function in the urethra after parasympathetic decentralization (Koyanagi et al, 1988). Nordling and colleagues (1981) described a similar change in women after radical hysterectomy and ascribed this change to damage to the sympathetic innervation of the LUT.

When permanent LUT dysfunction occurs after radical pelvic surgery, the pattern is usually one of impaired bladder contractility or a failure of the bladder to voluntarily contract. Urodynamically, obstruction may be seen from likely residual fixed striated sphincter tone, which is not subject to voluntarily induced relaxation. Often, the smooth sphincter is open and nonfunctional. Whether this appearance of the bladder neck and proximal urethra is caused by parasympathetic damage or terminal sympathetic damage or whether it results from the hydrodynamic effects of obstruction at the level of the striated sphincter is debated and unknown. Decreased compliance is common in these patients,

and, with the “obstruction” caused by fixed residual striated sphincter tone, may result in both storage and emptying failure. These patients often experience leakage across the distal sphincter area and are unable to empty the bladder, because, although intravesical pressure may be increased, they cannot mount a true bladder contraction. The patient often has urinary incontinence that is characteristically and most commonly initiated with increases in intra-abdominal pressure. This is usually most obvious in women, because the prostatic bulk in men often masks an equivalent deficit in urethral closure function. Alternatively, patients may have variable degrees of urinary retention.

Urodynamic studies may show decreased compliance, poor proximal urethral closure function, loss of voluntary control of the striated sphincter, and a positive bethanechol supersensitivity test, findings similar to those in Figure 75-4. Upper tract risk factors are related to intravesical pressure and the detrusor leak point pressure, and the therapeutic goal is always low-pressure storage with periodic emptying. In men, the temptation to perform a prostatectomy should be avoided unless a clear bladder outlet obstruction is demonstrated at this level. Otherwise, prostatectomy simply decreases urethral sphincter function and thereby may result in the occurrence or worsening of sphincteric urinary incontinence.

We strongly urge caution in the early postoperative period, because the temptation to “do something” other than perform CIC initially after surgery in these patients is often strong, especially in those patients with little or no preexistent voiding dysfunction. Most of these dysfunctions will be transient, and our general practice in these patients is to discharge them on CIC with full urodynamic evaluation at a later date. Frequently, 6 to 12 months may elapse before detrusor function returns to an acceptable level (Blaivas and Chancellor, 1995b). Many of the changes after radical pelvic surgery are similar to those seen in sacral cord injury or disease. In an excellent study on decreased bladder compliance after decentralization, Sislow and Mayo (1990) noted a higher prevalence of this finding in patients who had undergone radical pelvic surgery than in those who had sustained conus medullaris or cauda equina injury.

Questions remain as to whether nonradical pelvic surgery such as simple hysterectomy can be ultimately responsible for storage or emptying abnormalities on the basis of neurologic damage. At this time there is no consensus opinion, and more series that include sophisticated preoperative and early and late postoperative urodynamic evaluation are necessary.

There is, as yet, no clear consensus as to the independent effects of childbirth and hysterectomy on LUT function. A variety of explanations have been put forth regarding whether or not, in fact, LUT dysfunction is induced by these events and, if so, what the underlying pathophysiology may be. In a multicenter Danish trial (Gimbel et al, 2005), a total of 319 women with benign disease were randomized to undergo either total abdominal hysterectomy (158) or subtotal abdominal hysterectomy (161). At 1-year follow-up after intervention, urinary incontinence was less often noted in patients undergoing total abdominal hysterectomy. Both groups, however, did experience an increase in incomplete emptying requiring double voiding. It is interesting to note that both groups experienced an overall decrease in urinary incontinence frequency as compared with baseline.

To date, there have been no prospective trials documenting a long-term follow-up relationship between urinary dysfunction and method of delivery, and no prospective clinical trials have been done to determine if cesarean section is protective against the development of incontinence. The debate regarding cesarean section as an alternative to spontaneous vaginal delivery and impact of each on the LUT also continues. The Epidemiology of Incontinence in the County of Nord-Trøndelag (EPINCONT) study assessed 15,307 women for the development of voiding dysfunction during longitudinal follow-up. The risk of urinary incontinence of all types was noted to be higher in women who had had cesarean sections as compared with nulliparous women and those who had had vaginal deliveries. However, the risk of moderate-to-severe incontinence

was actually less in patients who had undergone cesarean sections than in those who had delivered vaginally. Urgency incontinence was the only exception, being equal across all groups. The adjusted ratio for any incontinence in women after cesarean section was 1.5 versus 1.7 for women with vaginal deliveries. Stress incontinence appeared to be associated with mode of delivery (Rortveit et al, 2003a, 2003b).

McKinnie and associates (2005) studied 1004 women over an 18-month period to determine the relationship between urinary and fecal incontinence and type of delivery. In this study, pregnancy increased the overall risk of urinary and fecal incontinence, and there was no apparent relationship to mode of delivery.

Simple and Radical Hysterectomy

In a study of the effects of hysterectomy on LUT function, 430 women who underwent either vaginal or abdominal hysterectomy for benign conditions (without prolapse as an indication) were assessed. Patients completed validated questionnaires before surgery and up to 10 years after surgery. Significant differences were noted between the vaginal and abdominal approaches in terms of symptoms as measured by the Urogenital Distress Inventory and Defecation Distress Inventory questionnaires. Women who underwent hysterectomy by the vaginal approach were more likely to have micturition symptoms as compared with abdominal approach patients (18% vs. 8%). In addition, defecation symptoms also appeared to be more common after vaginal hysterectomy (58% vs. 46%) (Sultan and Thakar, 2006; Lakeman et al, 2011). As compared with simple hysterectomy, radical hysterectomy may have more debilitating effects on bladder and bowel function. In a study of 209 patients undergoing radical hysterectomy for malignant disease with a survey return rate of 32% (66 of 209) (Brooks et al, 2009), 42% of patients undergoing radical hysterectomy reported mild incontinence symptoms as compared with 50% of controls. Moderate symptoms were seen in 34% of subjects and 35% of controls. Moderate-to-severe symptoms were noted in 18% of subjects and 14% of controls. Fecal symptoms did not differ between subjects and controls. Radical hysterectomy in this group did not appear to be associated with more long-term bladder or anorectal dysfunction (Brooks et al, 2009).

Herpesvirus Infections

Invasion of the sacral dorsal root ganglia and posterior nerve roots with herpes zoster virus may produce urinary retention and detrusor areflexia days to weeks after the other primary viral manifestations (Rytto et al, 1985). In general, painful cutaneous eruptions secondary to the virus are also present, but initially the patient may have only fever, malaise, perineal and thigh paresthesias, and obstipation. Urinary incontinence secondary to detrusor overactivity may also occur, but the pathophysiology is unclear. It may be related to nerve root irritation, inflammation of the meninges or spinal cord, or "zoster cystitis" (Broseta et al, 1993). Cystoscopy may reveal vesicles in the bladder mucosa similar to those seen on the skin. Spontaneous resolution usually occurs in 1 to 2 months. Out of 57 patients with herpes zoster infection, 15 (26%) showed urologic manifestations, but only 2 had frank urinary retention (Broseta et al, 1993). Three patients demonstrated urinary incontinence, and all 3 demonstrated detrusor overactivity on urodynamics. Ten patients demonstrated irritative storage symptoms with dysuria and frequency.

Out of 423 patients admitted with a diagnosis of herpes zoster LUT, 17 (4%) had voiding dysfunction (Chen et al, 2002). Excluding those with cranial rather than spinal nerve involvement, the incidence was 8.8%; however, when only patients with lumbosacral dermatome distribution were considered, the figure rose to 28.6%. The authors subdivided the bladder disorders into three types. Twelve of the 17 affected patients (71%) had voiding dysfunction caused by herpetic cystitis and had dysuria, frequency, retention, pyuria, or hematuria on presentation. Four of the 17 patients (24%) had neuritis-associated voiding dysfunction, presumably affecting

the sacral motor neurons, and on presentation had urinary retention with a "flaccid bladder." One patient had myelitis-associated voiding dysfunction with spinal cord involvement, with detrusor overactivity on presentation. All 17 patients regained a normal or "balanced bladder" within 8 weeks, and no major urologic sequelae were noted.

Urinary retention has also been reported to occur in association with anogenital herpes simplex virus infection. Caplan and colleagues (1977) reported 11 such patients with the typical clinical picture of herpes genitalis, all of whom developed urinary retention 2 to 7 days after the genital eruption. Three such patients showed pleocytosis of the cerebrospinal fluid, a finding that Hemrika and associates (1986) believed was indicative of CNS involvement. They termed the coexistence of bilateral involvement of the sacral nerve roots of rapid onset accompanied by sphincteric incontinence with cerebrospinal fluid pleocytosis the *Elsberg syndrome* and tabulated 47 such cases reported before their article. Haanpaa and Paavonen (2004) added 2 patients, both of whom had transient urinary retention but developed chronic neuropathic pain in the sacral area. As with herpes zoster, the LUT dysfunction was transient.

Diabetes Mellitus

Diabetes is the most common cause of peripheral neuropathy in Europe and North America. The exact prevalence of diabetes in the United States is between 1% and 6%, depending on whether one includes only diagnosed patients and on what fasting blood glucose criteria are used for inclusion (the higher estimate of prevalence represents a recent reduction in blood glucose criteria to 126 mg/dL) (Chancellor and Blaivas, 1995a; Goldman and Appell, 2000a). The clinical spectrum of LUT dysfunction thought to be caused by diabetes has been extensively reviewed by a number of authors, each of whom has cited the same historical articles up to their date of publication and added their personal experience at that time (Kaplan and Blaivas, 1988; Beck et al, 1994; Chancellor and Blaivas, 1995a; Kaplan et al, 1995; Wein and Rovner, 1999; Goldman and Appell, 2000a). The exact incidence of LUT dysfunction caused by diabetes is uncertain; however, 5% to 59% of patients with diabetes report symptoms of LUT dysfunction. In attempting to estimate the true incidence and types of LUT dysfunction specifically associated with diabetes, one has to carefully discriminate between articles that consider patients referred for voiding symptoms versus those that have evaluated unselected patients from a population known to have diabetes. In the Nurses' Health Study, urinary incontinence was found to be more prevalent in women with diabetes (8.7% vs. 5.3% of controls). The odds of urinary incontinence developing increased by 20% with diabetes. The predominant type of associated incontinence noted in this study was urge incontinence; no association between diabetes and stress incontinence was recognized (Danforth et al, 2009).

KEY POINT: DIABETES MELLITUS

- Cai Frimodt-Moller (1976) coined the term *diabetic cystopathy* to describe the involvement of the LUT by this disease. The classic description of voiding dysfunction secondary to diabetes is that of a peripheral and autonomic neuropathy that first affects sensory afferent pathways, causing the insidious onset of impaired bladder sensation. As the classic description continues, a gradual increase in the time interval between voiding results, which may progress to the point at which the patient voids only once or twice a day without ever sensing any real urgency. If this continues, detrusor distention, overdistention, and decompensation ultimately occur. Detrusor contractility, therefore, is classically described as being decreased in the end-stage diabetic bladder. More recently, however, detrusor overactivity has been cited as the most frequent urodynamic finding. This could be a result of a difference in the time of diagnosis with reference to the natural history of the effects of diabetes on the LUT.

Current evidence points to both a sensory and a motor neuropathy as being involved in the pathogenesis, with the motor aspect contributing to the impaired detrusor contractility. **The classic urodynamic findings include impaired bladder sensation, increased cystometric bladder capacity, decreased bladder contractility, impaired uroflow, and, later, increased residual urine volume.** At least in men, the main differential diagnosis is bladder outlet obstruction, because both conditions commonly produce a low urinary flow rate; however, pressure-flow urodynamic studies easily differentiate the two. **Smooth or striated sphincter dyssynergia usually is not seen in classic diabetic cystopathy,** but these diagnoses can easily be erroneously made on a poor or incomplete urodynamic study (e.g., voiding may involve abdominal straining, which will produce an interference electromyographic pattern [pseudodyssynergia], and abdominal straining alone will not open the bladder neck area).

Other authors have suggested that findings seen in classic diabetic cystopathy may not represent the predominant form of LUT dysfunction. In a group of 19 female and 4 male elderly diabetic nursing home patients with symptoms of urinary dysfunction, 61% were found to have involuntary bladder contractions, 17% to have voluntary contractions of decreased magnitude, and 13% to have normal detrusor contractility, and 9% were unable to initiate a detrusor contraction at all (Starer and Libow, 1990). In another group of diabetic patients referred because of voiding symptoms, Kaplan and coworkers (1995) found that 55% had involuntary bladder contractions, 23% had impaired detrusor contractility, 10% had detrusor areflexia, and 11% had "indeterminate findings." Of the 42 patients with sacral cord neurologic signs, 50% had impaired detrusor contractility and 24% had detrusor areflexia. Chancellor and Blaivas (1995a) detailed the urodynamic findings in 43 diabetic patients at Chancellor's institution, with 33% having involuntary bladder contractions with normal contractility, 23% having involuntary bladder contractions with impaired contractility but were able to void, 9% having impaired bladder contractility alone but were able to void, 23% having detrusor areflexia, and only 12% having a normal urodynamic study. Ueda and associates (1997) also found involuntary bladder contractions in a moderate percentage of diabetic patients (25%), but noted that all these patients had a history of cerebrovascular disease and that no patient had involuntary bladder contractions who did not have such a history. Although it is obvious that some (or even many) of the patients with diabetes who exhibited involuntary bladder contractions may have had factors other than diabetes to account for their bladder overactivity, the importance of urodynamic study in diabetic patients before the institution of therapy cannot be overemphasized.



A variety of animal models have been able to replicate the diabetic state; however, different models demonstrate different patterns of disease expression. These and a discussion of potential pathophysiologic mechanisms involved in effects of diabetes on LUT function are found on the Expert Consult website.

Early institution of timed voiding will avoid some of the impaired detrusor contractility from chronic distention and detrusor decompensation. Experimental studies are currently directed at inhibiting the proposed mechanisms by which hyperglycemia produces neuropathy (Clark and Lee, 1995). Ayan and colleagues (1999) cite references showing that intensive therapy for diabetes can slow its progression and slow the development of abnormal autonomic tests. On a short-term basis, the authors showed that insulin therapy in alloxan-induced diabetic rabbits prevented the urodynamic effects (e.g., increased bladder capacity and compliance) and histopathologic changes seen in a similar but non-insulin-treated group of animals. Insulin reversed most of the changes reported by Cardozo and coworkers (2002). Despite improvement in other organ systems with enhanced glycemic control, LUTS in patients with type 1 diabetes do not appear to respond well to other otherwise well-documented glycemic control (Van Den Eeden et al, 2009).

A recent prospective evaluation of women with type 2 diabetes assessed urodynamic findings as compared with responses to A δ

and C fibers in the bladder using intravesical current responses to threshold frequencies at 250 and 5 Hz, respectively. Of the 86 women evaluated, 34.9% had detrusor underactivity, 14% (12) had detrusor overactivity, 12.8% (11) had bladder outlet obstruction by the criteria of the trial, and 38.4% (33) had normal detrusor function. With the normal detrusor function group used as a comparator, the underactivity group showed not only decreased emptying capabilities, but also decreased sensation on both cystometry and intravesical current perception threshold testing. The overactivity group demonstrated impaired storage and emptying function but had no significant changes in intravesical current reception. In this trial, an increase in current perception threshold values was associated with a decrease in bladder voiding efficiency at both 5 and 250 Hz. These data underscored the evidence that impaired A δ - as well as C-fiber function had direct effect on bladder pathways for emptying in patients with diabetes mellitus (Lee et al, 2009).

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a **potentially life-threatening, inflammatory demyelinating disorder of the peripheral somatic and autonomic nervous system.** It is described as a recognizable clinical entity characterized by rapidly evolving symmetrical limb weakness, loss of tendon reflexes, absent or mild sensory signs, and variable autonomic dysfunctions (Hahn, 1998). It results from aberrant immune responses directed against peripheral nerve components (Hartung et al, 1995; Hahn, 1998) and is triggered by a preceding bacterial or viral infection, with the immune responses directed toward the infecting organisms cross-reacting with neural tissues. The immune reactions against Schwann cell surface membrane or myelin result in acute inflammatory demyelinating neuropathy (accounting for 85% of cases), whereas reactions against axonal membrane components cause acute motor-sensory axonal neuropathy, accounting for the remaining 15%. Two thirds of patients report an antecedent acute infectious illness, most commonly a respiratory tract infection or gastroenteritis that has resolved by the time the neurologic symptoms begin. Several anecdotal case reports have linked GBS to vaccination by temporal association alone. About 75% of cases reach their nadir within 2 weeks, and 94% within 4 weeks. After a brief plateau phase, paralysis gradually resolves over weeks to months. In general, the outcome is favorable, but Hahn (1998) quotes a mortality rate of 5% to 8% despite the most aggressive management. **Autonomic neuropathy is a common complication.** Cardiac arrhythmia, hypertension and hypotension, and bowel, bladder, and sexual dysfunction may occur. **The prevalence of LUT dysfunction ranges from 25% to over 80% (Wyndaele et al, 2005).** Zochodne (1994) reviewed multiple series and reported a urinary retention rate of 11% to 30%. Of the 7 of 28 GBS patients with voiding dysfunction, 3 had transient urinary retention; 2 had urgency, nocturia, and urge incontinence; 1 had stress incontinence; and 1 had otherwise unexplained voiding difficulty (Sakakibara et al, 1997a, 2009). Although many of these patients may have an indwelling catheter in the acute setting, **their voiding dysfunction should be managed by reversible therapy** (e.g., CIC, anticholinergic therapy) pending resolution. The urinary symptoms associated with GBS are multifaceted. In other reports, approximately 27% of patients with GBS have demonstrated urinary symptoms, with urinary retention being present in 9.2% of patients. Defecatory dysfunction and urinary dysfunction are highly related to the motor grade of GBS symptomatology. Antibody titers have no relationship to symptomatic urinary dysfunction. The most common urinary findings include increased postvoid residual volume, followed by decreased bladder sensation, detrusor overactivity, diminished bladder compliance, and underactive detrusor contraction, as well as sphincteric dyssynergia. These findings underscore the difficulty in prediction of LUTS based on condition diagnosis only (Sakakibara et al, 2009). In another study of GBS patients, 38 patients were assessed using Hughes motor grading, Overall Disability Sum Score (ODSS), and Medical Research Council (MRC) sum score with urodynamics at baseline and at 2 months. Ten of 38 patients had urinary symptoms; 23 of the 38 had

Alloxan-induced diabetic rats demonstrate detrusor overactivity, whereas sucrose-fed rats demonstrate normal bladder contractions. In addition, streptozotocin-induced diabetic rats more commonly demonstrate pyuria, raising the question of an inflammatory component. Therefore the type of model used should be considered when attempting to interpret experimental findings (Yoshimura et al, 2003). Liu and Daneshgari (2005) concluded that the bladders of diabetic and diuretic rats weighed more than control animals and that diabetes and diuresis caused a significant increase in overall fluid intake, urine output, and bladder size. An increased response after field stimulation was noted in both diabetic and diuretic conditions and a reduced response to cholinergic activity was noted as compared with controls. The authors noted that this finding indicated the possibility of neurogenically mediated bladder contraction in the diabetic rat. Numerous authors have proposed potential pathophysiologic mechanisms that could account for the various types of voiding dysfunction seen in diabetic patients. Clark and Lee (1995) describe the basic mechanism of interference with physiologic mechanisms as increases in blood glucose increasing the intercellular accumulation of both glucose and its subsequent metabolic products. Hyperglycemia is then proposed to lead to microvascular and neurologic complications, with the neurologic sequelae ultimately resulting in a loss of myelinated and unmyelinated fibers, wallerian degeneration, and blunted nerve fiber reproduction and function. The proposed mechanisms include increased accumulation of polyols (sorbitol) from glucose through the aldolase-reductase pathway, inhibiting both glomerular and neural synthesis of myo-inositol. The decrease in myo-inositol synthesis depresses phosphoinositide metabolism, decreasing Na^+/K^+ -ATPase activity. Hyperglycemia also leads to the formation of advanced glycosylation end products, inhibition of the formation of which in animals has been shown to improve response to functional and structural abnormalities of peripheral nerves. NGF and other nerve trophic factors also appear to play a role in regulation of the pathogenesis of diabetic voiding dysfunction. In addition, nitrergic and adrenergic mechanisms also contribute to the ultimate pathophysiologic cascade of this condition (Torimoto et al, 2009). In another report of streptozotocin-induced diabetic rats, the diabetic condition was associated with increased bladder weight. This was associated with a decreased blood vessel density that occurred on a time-dependent basis. In a comparator group of polyuric animals, similar changes were noted. These findings appeared to support not only direct change, but also diuretic-induced changes as being an additional physiologic consequence of the diabetic condition (Liu et al, 2010).

Another aspect of diabetic bladder dysfunction may occur at the organelle level. In rodent models morphologic changes in chronic diabetes have also included mitochondrial abnormalities, particularly in the urothelium. Increased collagen was noted to be deposited in capillary walls, with an interruption or extensive widening of the gap junctions between myocytes in the bladder muscularis. Reduced mitochondrial counts were noted in the urothelium and bladder muscle. Degenerated nerve fibers and myelin bodies were identified between myocytes, with increased collagen and mast cell inflammatory aggregates noted in the stroma of diabetic rats as compared with nondiabetic controls. The duration of diabetes appeared to amplify these changes, and the authors concluded that diabetic changes were a time-dependent phenomenon (Rizk et al, 2006).

In addition to this overall hypothesis, there are tantalizing “chunks” of data from various investigators that may or may not prove to be involved in the pathogenesis of diabetic voiding dysfunction. In streptozotocin-induced diabetic rats, Hashitani and Suzuki (1996) reported reduced spontaneous spike activity, failure of neuromuscular transmission, reduced potency of the smooth muscle sodium-potassium pump, and the development of a post-junctional, muscarinic supersensitivity, without alteration of the ATP receptor sensitivity. Tong and colleagues (1999) reported an upregulation of M_2 receptor protein in the bladder of streptozotocin-induced diabetic rats and an upregulation of M_2 receptor protein in bladder body tissue (Tong and Cheng, 2002). Presumably, this

could be related to detrusor overactivity and conceivably account for a differential effect of various anticholinergic agents, depending on their receptor specificity. Mumtaz and coworkers (1999) reported an impairment of nitric oxide-mediated urethral smooth muscle relaxation in alloxan-induced diabetic rabbits along with a significant impairment of nonadrenergic noncholinergic nerve-mediated relaxation in this area. They hypothesize that nitric oxide may be functionally inactive and/or unavailable in this type of diabetes, and this lack may contribute to non-benign prostatic hyperplasia (BPH)-related outlet obstruction in patients with long-term diabetes and to detrusor overactivity, although it is a bit unclear as to how changes in only the outlet might influence overactivity. Gupta and colleagues (1996) and Gupta and Wein (1999) suggested that diabetes diminishes sodium pump activity, thereby inhibiting agonist-induced contractions in bladder smooth muscle by an increase in intracellular sodium concentration, the latter acting to diminish calcium influx. In abstract form, Chacko's group (1999) hypothesized a translocation of protein kinase C isoforms as being involved in decreased detrusor contractility in alloxan-induced diabetes in rabbits. Cardozo and coworkers (2002) reported enhancement of bladder contractions to SP and des-Arg-BK in a streptozotocin model. Sasaki and associates (2002) described decreased NGF in bladder tissue and L6 to S1 dorsal root ganglia. In alloxan-induced diabetic animals, Khan and colleagues (2002) noted decreased apoptosis of bladder urothelial cells. In this same model, Su and associates (2004) reported increased myosin light chain phosphorylation and decreased sensitivity to activator calcium. Changolkar and coworkers (2005) reported decreased smooth muscle force associated with increased lipid peroxides and sorbitol and an overexpression of aldolase reductase and polyol pathway activation. Another interesting pathophysiologic explanation is one that is attributed to autoimmune phenomena. Antibody-mediated bladder dysfunction in type 1 diabetes has been identified in a murine model, in which anti-voltage-gated calcium channel antibodies induce urodynamic findings such as phasic detrusor contractions and also loss of bladder wall compliance compatible with overactive bladder. The autoimmune dysfunction was reversed by the administration of agonists for voltage-gated calcium channels. The possible reversibility of this phenomenon remains intriguing for early stage treatment (Wan et al, 2007).

Hyperglycemia-induced oxidative stress in detrusor smooth muscle resulting in microvascular and macrovascular events has been postulated to contribute to urologic symptoms and complications associated with diabetes (Kirschner-Hermanns et al, 2012). In addition, further evidence of oxidative stress has been identified by comparative gene expression studies. When nondiabetic versus streptozotocin-induced-diabetic in animals were assessed for oxidative stress via a variety of protein-based metabolic assays (glutathione and S-transferase activity, lipid peroxidation, and carbonylation and nitrosylation of proteins), global gene expression in the diabetic animals demonstrated a significant increase in markers for oxidative stress. This was subsequently further hypothesized to have a downstream effect on protein damage and apoptosis. This hypothesis was confirmed by demonstrating an increase in protein degradation product (Nedd-4 and LC3B) in diabetic bladders. The conclusion was that oxidative stress resulted in aberration and protein-based pathways resulting directly from oxidative stress (Kanika et al, 2011).

In a trial using rodent (mouse) exposure to streptozotocin in an M_2 muscarinic receptor knockout model as compared with wild-type specimens, the M_2 receptor was found to modulate bladder overdistention associated with streptozotocin-induced neuropathy and therefore preserve function. The difference between function in the wild-type versus the knockout model approximated a 70% difference in those animals with retained M_2 receptors (Pak et al, 2010a). With the same study construct (wild type versus M_2 muscarinic receptor knockout exposure to streptozotocin), rodents were exposed to oxotremorine-M (an M_2 muscarinic agonist). In the wild-type animals, contractile function was maintained by enhanced mediation by M_2 contractile activity despite loss of M_3 activity in these animals (Pak et al, 2010b).

Smooth muscle ultrastructural and functional changes in detrusor smooth muscle associated with streptozotocin-induced bladder dysfunction in mice has been attributed to the contribution of the L-type voltage-operated channels (L-VOCCs). The presence of these receptors and an increased density of M_3 receptors were noted in streptozotocin-induced diabetic animals. The role of these L-VOCC channels continues to be explored ([Leiria et al, 2011](#)).

Therefore, the pathophysiology of diabetic cystopathy can be attributed to five possible sources. Alterations in muscarinic receptor densities specifically with overexpression of M_2 receptors may be one mode of dysfunction. Direct neural damage caused by hyperglycemia resulting in glycosylated end products may accelerate microvascular disease as well as inducing endothelial dysfunction and causing a deleterious effect on nitric oxide release. In addition, the production of sorbitol in a hyperglycemic environment may increase reactive oxygen species, resulting in oxidative stress at the muscle cell level. Hyperglycemia may, as well, increase the production of diacylglycerol, resulting in the activation of protein kinase C, which affects transcription of a variety of connective tissue constituents including type IV collagen, contractile proteins, and fibronectin, as well as damaging local endothelial and neural cells. Finally, there may be a decrease in NGF, which has been previously hypothesized to protect bladder activity ([Nanigian et al, 2007](#)).

urodynamic abnormalities, with the most significant being detrusor underactivity in 15 patients. DSD was found in 6 patients, bladder acontractility in 5, and detrusor overactivity in 3. There was a correlation between disability based on these scoring systems and urodynamic findings (Naphade et al, 2012).

MISCELLANEOUS NEUROLOGIC DISEASES CAUSING LOWER URINARY TRACT DYSFUNCTION

Lyme Disease

The associated neurologic symptoms of Lyme disease (neuroborreliosis) fall broadly into three syndromes: (1) encephalopathy, (2) polyneuropathy, and (3) leukoencephalitis. The Lyme spirochete can also (rarely) invade the bladder itself. Chancellor and colleagues (1993) described seven patients who also had LUT dysfunction. Five had detrusor overactivity, none had dyssynergia, and two had detrusor areflexia. In two women, urinary retention was the presenting symptom of Lyme disease. Other subjective symptoms noted were urgency, frequency, nocturia, and urge incontinence. Follow-up at 6 months to 2 years after treatment revealed residual urgency and frequency in three patients.

Hereditary Spastic Paraplegia

Hereditary spastic paraplegia (HSP) is a genetically transmitted disorder, usually autosomal dominant, less commonly autosomal recessive, and rarely sex linked. There is a pattern of central demyelination with axon loss and progressive lower extremity spasticity with muscle weakness. Bushman and coworkers (1993) described three patients, two of whom had detrusor overactivity (one with striated sphincter dyssynergia), one who had significantly decreased compliance, and one who was urodynamically normal except for a high maximum urethral pressure of uncertain significance. Pure forms of this disease are associated with primary lower extremity spasticity at presentation, but variance exists.

Jensen and colleagues (1998) reported the voiding characteristics of 11 patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p21-p24. These patients were culled from six of eight families with the disorder; the authors commented that LUTS were present in 16 of 44 definitely affected family members. One patient had an indwelling catheter, and thus an accurate description of symptomatology was not possible. For the other patients, urinary urgency and frequency were the dominant complaints, with 6 of these 10 patients regularly experiencing urgency urinary incontinence. Urodynamically, 3 patients showed detrusor overactivity, 6 demonstrated normal detrusor activity, and 1 demonstrated "hyporeflexia" with delayed first sensation. Satisfactory sphincter electromyographic recordings were obtained from 7 patients, and all were normal. Postvoid residual urine volumes were elevated in 8 of 10 patients. The bulbocavernosus reflex was absent in 6 patients and was truly normal in only 1 patient. The authors commented that the frequency of urinary symptoms in their patients (36%) correlated well with other reports in the literature. They proposed that the LUTS (along with bowel and sexual dysfunction) in patients with this disorder are caused by a combination of somatic and autonomic nervous system involvement, supporting a multisystem involvement. LUT dysfunction is well recognized in this condition and is associated with high prevalence rates in those of Eastern European extraction (approaching 77%). In a study of 29 HSP patients, the primary urinary symptom was urgency in 72%, followed by frequency in 65%, incontinence in 55%, and hesitancy in 51%. Urodynamic findings included detrusor overactivity in 51% and sphincter dyssynergia in 66%, with increased postvoid residual volume in 41%. However, there was no significant risk of upper tract complications related to this condition (Fourtassi et al, 2012). In another study of patients with HSP, 49 patients were assessed and 38 (77.6%) had some urinary concern. LUT dysfunction occurred similarly in the pure and complex forms of the disease. The most common symptoms associated with this condition were urinary incontinence of any type (69.4%), urinary hesitancy (59.2%),

increased frequency (55.1%), and associated urinary urgency (51.0%). Incomplete bladder emptying was the least common (36.7% of patients). Increased LUT dysfunction was more commonly associated with the female gender (Braschinsky et al, 2010).

Tropical Spastic Paraparesis

Tropical spastic paraparesis is primarily a spinal cord myelopathy caused by a retrovirus (human T-cell leukemia virus 1 [HTLV-1]) that is similar to human immunodeficiency virus (HIV). Progressive lower limb weakness and back pain are typically the primary complaints, but LUT dysfunction occurs in up to 60% of those affected (Walton and Kaplan, 1993). Eardley and associates (1991) studied six such patients with LUT dysfunction. Two had detrusor areflexia and three had overactivity, one of whom also had dyssynergia. Walton and Kaplan (1993) found that four of five consecutive patients had detrusor overactivity and DSD, whereas one had overactivity and synergy. The type of voiding dysfunction depends on whether the damage is primarily to the descending spinal tracts, to the sacral nuclei, or to the sacral outflow. The disease must be distinguished from other myelopathic conditions associated with LUT dysfunction, such as MS.

Acquired Immunodeficiency Syndrome

Infection with HIV can affect both the central and the peripheral nervous systems, and so it is not unexpected that symptoms of LUT dysfunction occur. As with many other conditions, there is some disagreement as to the overall prevalence of such symptoms in this population. AIDS-related neurogenic voiding dysfunction is associated with a poor outcome, with a mortality rate of approximately 40% within 8 months of development of urologic symptoms (Heyns and Fisher, 2005). Khan and coworkers (1992) were among the first to report on the types of LUT dysfunctions seen in 11 patients with AIDS. Urinary retention occurred in 6, whereas on urodynamic evaluation, 3 had detrusor overactivity, 4 had detrusor areflexia, 2 had a hypocontractile detrusor, and 2 had outlet obstruction secondary to BPO. In a prospective study of 39 patients with HIV infection and voiding symptoms, clinical symptoms included frequency, urgency, and incontinence in 41% of patients, acute urinary retention in 28%, dysuria and frequency in 18%, and decreased flow in 13% (Hermieu et al, 1996). Seventeen of the patients had involuntary bladder contractions, and, of these, 8 had DSD or a lack of sphincter relaxation during micturition, 5 had detrusor areflexia, 4 had what was termed a "hypertonic urethra," 3 had "hypersensitivity," and 5 had a normal urodynamic evaluation. The authors characterized the voiding dysfunctions broadly as inability to void in 41% of the cases and frequency, urgency, or incontinence in 41%. Furthermore, the authors proposed that the appearance of neurogenic voiding disturbances heralded a poor prognosis. Eighteen HIV-positive patients, 13 with acquired immunodeficiency syndrome (AIDS), with voiding dysfunction were urodynamically characterized by Kane and coworkers (1996). Chief presenting complaints were daytime frequency in 8 patients, retention in 3, nocturia in 2, and having to strain to void, feeling incompletely empty, and having incontinence, a split stream, or groin pain in 1 each. Five patients (28%) showed detrusor overactivity, 5 showed DSD, and 1 (6%) showed detrusor areflexia. The authors remarked that there is a correlation among cytomegalovirus infection, polyradiculopathy, and detrusor areflexia, a phenomenon reported by others as well. Lima and colleagues (2002) evaluated a group of 26 men with HIV-induced bladder dysfunction. Eighty percent of those patients demonstrated detrusor overactivity, and 34% had detrusor-sphincter dyssynergia. These findings are indicative of the myopathy associated with HIV (Lima et al, 2002). Other common causes of LUT dysfunction exist as well; 5 patients had outlet obstruction, 4 secondary to BPO and 1 from urethral stricture. The fact that HIV can cause demyelination at any site in the nervous system complicates symptom-based management of the HIV-infected patient and mandates sufficient LUT evaluation as a guide for therapy (Delgado et al, 2014). Renal functional

impairment may result from LUT dysfunction or from primary renal involvement by the disease (Tonolini et al, 2013). Gyrtrup and colleagues (1995) prospectively investigated voiding function in 77 men and 4 women with HIV infection or AIDS consecutively attending an outpatient clinic. Eight of these (10%) had moderate subjective voiding problems, whereas two (2%) had severe problems. The authors believed that in only 4% of patients did the nature of the disturbance warrant urodynamic examination and concluded that urinary voiding symptoms are only a modest problem overall in an HIV/AIDS population. They concluded that neuropathic bladder dysfunction is rare and occurs mostly in the late stages of the disease.

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory demyelinating disorder of the CNS of unknown cause. It is also sometimes known as *parainfectious* or *postinfectious encephalomyelitis*. The locations of lesions are multifocal and can include the cerebral white matter, cerebellum, brainstem, and spinal cord. Of 11 patients with ADEM, 9 had urinary retention; the other 2 had urgency, frequency, nocturia, and difficulty voiding (Sakakibara et al, 1996b). One patient in the latter group had enuresis and urgency incontinence as well. The urodynamic findings are difficult to correlate with the presenting symptoms, because in 4 of the patients the studies were done considerably after the onset of the disease. During the follow-up period, 7 of the 9 patients who originally had retention became able to urinate. Five had difficulty voiding, and four developed irritative symptoms. Six of the patients ultimately had a near-complete neurologic recovery, but voiding symptoms persisted in 3. The authors concluded that the supranuclear and nuclear types of pelvic and pudendal nerve dysfunction were primarily responsible for the micturitional disturbances in patients with this disease and that voiding dysfunction was very common in these patients.

Syringomyelia

Syringomyelia is a chronic disorder of the spinal cord characterized by dissociated sensory loss and brachial amyotrophy. It usually affects the cervical spinal cord but can extend caudally. LUT dysfunction has been reported in 9% to 25% of patients. Fourteen patients with syringomyelia were studied urologically by Sakakibara and associates (1996c). Eleven of these had urinary symptoms: difficulty voiding in 8, retention in 3, nocturnal and daytime frequency in 3, incontinence in 2, and urgency and enuresis in 1. The urinary symptoms appeared from 2 months to 13 years after the initial neurologic symptoms. Urodynamic studies revealed detrusor overactivity in 7, DSD in 4, detrusor areflexia in 4, and "uninhibited sphincter relaxation" in 2. It is interesting that motor unit electromyographic recordings disclosed findings compatible with denervation of the striated sphincter in 5 of 6 patients. The authors concluded that both supranuclear and nuclear types of peripheral autonomic and somatic nerve dysfunction are responsible for the LUT dysfunctions seen. It is also interesting that the micturitional status gradually improved in 4 of 6 patients after syringosubarachnoid shunts.

Schistosomal Myelopathy

Schistosomiasis may cause LUT dysfunction from bladder neck obstruction and impaired muscle contractility as a result of infiltration of the bladder smooth muscle itself. In addition, it can rarely cause spinal cord involvement, either as a granulomatous intrathecal mass or as an acute transverse myelitis (Razdan et al, 1997). Two such patients had urinary incontinence as their chief urologic complaint, and both had detrusor overactivity, 1 without dyssynergia and with minimal motor weakness and 1 with DSD and a T11 sensory level. It was believed that the findings in the former patient were characteristic of a partial spinal cord or cerebral lesion and that the second patient had a suprasacral transverse myelopathy. In the first patient, the urinary symptoms developed approximately 2

months after exposure and after the development of systemic symptoms, whereas in the second case, symptoms developed some 5 years after the initial diagnosis. Gomes and associates (2002) reviewed the records of 14 patients with schistosomal myelopathy referred because of LUT dysfunction. Of 5 patients with acute disease, 3 had retention and 2 had incontinence. Urodynamics were performed in 3 of these. Two (1 in retention, 1 with hesitancy and incontinence) demonstrated detrusor areflexia, and 1 (with retention) showed detrusor overactivity and DSD. Of the 9 patients with chronic disease, 5 showed detrusor overactivity with DSD, 1 had decreased compliance, 2 had overactivity with synergic sphincters, and 1 had detrusor areflexia with decreased compliance. In another study of 26 patients with schistosomiasis, all patients had chronic neurologic and urologic symptoms secondary to this diagnosis. The most common urinary symptoms were difficulty in bladder emptying in 65% of the patients followed by incontinence in 54% and urgency and frequency in 50% of the patients, UTI in 30% of patients, and bilateral hydronephrosis in 19%. Detrusor overactivity associated with sphincter dyssynergia was present in 54% of the patients, with detrusor areflexia being present in 23% of the patients. Patients with dyssynergia had a much higher incidence of upper tract decompensation. These findings are consistent with classically defined involvement of spinal cord as a common complication of this disease (Gomes et al, 2005).

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a disease with a likely autoimmune origin in which there is widespread inflammatory change in the connective tissues and small vessels of the skin and systemic organs (Hahn cited by Sakakibara et al, 2003b). The prevalence of nervous system involvement ranges from 18% to 75%, and myelopathy occurs in 1% to 3% of SLE patients. Sakakibara and associates (2003b) reported on eight patients with SLE with LUT dysfunction, six with voiding difficulty (two of whom had retention), and four with urinary incontinence. Five exhibited decreased flow, three had increased residual urine, five had detrusor overactivity, five had impaired detrusor contractility, four had DSD, and two of four patients studied exhibited abnormal striated sphincter electromyographic potentials. Sensation was impaired in two. Although three patients had subacute encephalomyelopathy (one subacute myelopathy, four chronic myelopathy), the LUT dysfunction seemed to have been related mainly to the myelopathy.

Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy (RSD) is a disabling syndrome characterized by severe pain with autonomic changes, such as vasomotor disturbances. The condition usually follows a traumatic injury; the exact cause and pathogenesis are unclear. The prevalence of LUT dysfunction in patients with RSD is unknown, but it must be more than a rare occurrence because Chancellor and colleagues (1996) were able to collect 20 consecutive patients with neurologically verified RSD who were referred because of new-onset voiding symptoms. Seven of the patients had urinary retention, although some of these had undergone various types of surgery designed to treat the symptoms of the dystrophy. Five presented with urgency incontinence, one of whom also had stress incontinence. Six had urgency as a primary complaint, 1 had daytime frequency, and 1 had severe nocturia. Detrusor overactivity was demonstrated in 8 patients, DSD in 1, detrusor areflexia in 8, and hypersensitivity on filling in 3. Because the authors excluded patients who acutely developed voiding dysfunctions after back surgery and those with herniated disks, one must conclude that significant LUT dysfunction can develop as a direct result of, or in association with, RSD. However, the cause-and-effect relationship is so far unclear.

Tuberculosis

Spinal tuberculosis has been associated with significant evidence of micturition disturbances including high postvoid residual volume

and urinary symptoms. In a recent assessment of patients undergoing clinical urodynamics and spinal MRI, 30 spinal tuberculosis patients were assessed; 15 had some form of micturition disturbance (urinary incontinence or storage disorder). Four of the 15 also demonstrated retention; 2, stress incontinence; 6, urinary hesitancy; 11, urgency; and 9, urge incontinence. These symptoms were associated with a significant incidence of either paraparesis or quadriparesis (13 patients). Detrusor overactivity with high-pressure voiding was present in 6. Detrusor areflexia was present in 4, with the remainder having increased postvoid residual volumes. After intervention, those patients with prior micturition disturbances had poor functional recovery as compared with patients without micturition disturbances. There was a strong relationship between bladder symptomatology and severity of paraplegia, horizontal sensory level, and signal abnormality in the cord; these variables were associated with poorer outcome than in those patients without them (Kalita et al, 2010).

MISCELLANEOUS CONDITIONS DEFINITELY, PROBABLY, OR POSSIBLY RELATED TO NEUROMUSCULAR DYSFUNCTION

Detrusor Sphincter Dyssynergia

Dyssynergia refers to the kinesiological disassociation of two groups of muscles that, in general, work in harmony. *Sphincter dyssynergia* refers to an involuntary contraction, or lack of relaxation, of either the striated sphincter (the striated muscle surrounding the proximal urethra and the striated muscle that forms a part of the urethra for a variable distance from the “urogenital diaphragm” to the bladder neck) or the smooth sphincter (the smooth muscle of the bladder neck and proximal urethra). *Detrusor sphincter dyssynergia*, unless specified otherwise, refers to dyssynergia of the striated sphincter and is sometimes abbreviated DSD or DESD. This is discussed in Chapter 70 and in the earlier parts of this chapter, especially in the section on SCI. It is discussed as a separate entity here as well to emphasize its importance in terms of recognition and proper management in patients with neurogenic voiding dysfunction.

True DSD should exist only in patients who have an abnormality in pathways between the sacral spinal cord and the brainstem PMC and is usually caused by neurologic injury or disease (Blaivas, 1982; Rudy, 1993; Chancellor and Rivas, 1995; Wein and Rovner, 1999). The diagnosis of DSD should be suspected in any patient with a neurologic lesion in this area. Common causes include traumatic SCI, MS, and transverse myelitis. Conversely, in patients without such a lesion, this diagnosis should always be viewed with skepticism, and, without such apparent pathology, such a patient deserves exhaustive study to exclude a neural diagnosis. One exception to this precept is in infants and children with dysfunctional voiding or the Hinman syndrome (see later).

Blaivas and coworkers (1981) have described three categories of DSD. In type 1 there is a concomitant increase in both detrusor pressure and electromyographic activity; at the peak of the detrusor contraction, the sphincter suddenly relaxes and unobstructed voiding occurs. In type 2 there are sporadic contractions of the striated sphincter throughout the detrusor contraction. In type 3 there is a crescendo-decrescendo pattern of sphincter contraction that results in outlet obstruction throughout the entire detrusor contraction. Schurch and colleagues (2005) have correlated neurologic status and DSD type after SCI and found that those with an incomplete sensory and motor lesion typically have type 1 DSD, whereas those patients with complete sensory and motor lesions have type 2 and type 3. Weld and associates (2000) prefer to classify DSD as intermittent or continuous, but note that in their experience the clinical significance of DSD type is not crucial because both types require urodynamic surveillance and expedient treatment to minimize complications. No significant association between type and level of injury was found; however, continuous DSD was more associated with complete injuries.

It is important to remember that sphincter electromyographic activity that increases simultaneously with intravesical or detrusor pressure does not always indicate true DSD. These instances are referred to as *pseudodyssynergia* (Wein and Barrett, 1982), and such a misdiagnosis may be accompanied by adverse therapeutic consequences. Common causes of pseudodyssynergia include (1) abdominal straining to either initiate or augment a bladder contraction or in response to discomfort, and (2) attempted inhibition of a bladder contraction either because of its involuntary nature or because of discomfort. Rudy (1993) reported that pseudodyssynergia can reliably be differentiated from true DSD urodynamically by analyzing the patterns of detrusor and electromyographic activity, but others have not consistently found this to be the case.

Without proper treatment, over 50% of men with DSD will develop significant complications, such as VUR, upper tract deterioration, urolithiasis, urosepsis, and ureterovesical obstruction (Chancellor and Rivas, 1995). In women, these complications are much less common, most likely a result of the lower detrusor pressures generated. Using Blaivas's categorization, type 1 DSD is usually managed with observation alone unless there is persistent VUR, hydronephrosis, or autonomic hyperreflexia, whereas types 2 and 3, in general, require treatment. In assessing success or failure of treatment, Kim and colleagues (1998) used bladder leak point pressure greater than 40 cm H₂O as an indicator of the failure of sphincterotomy, because in their experience there was a significantly higher incidence of upper tract damage and persistent DSD in such patients. This most likely applies to other treatments as well. Therapy for DSD is designed to either eliminate or significantly minimize the abnormal sphincter activity or to bypass the sphincter itself. Oral medical therapy directed toward the striated sphincter has not enjoyed wide success. The most common treatment approaches currently are (1) CIC (usually combined with therapy to control detrusor overactivity), (2) sphincterotomy, (3) stent placement across the sphincter, (4) injection of onabotulinumtoxinA into the sphincter, (5) continuous indwelling catheterization, and (6) urinary diversion.

Dysfunctional Voiding

Dysfunctional voiding is more extensively considered in Chapter 143 but is mentioned here because individuals with a history of unexplained LUT dysfunction symptomatology may not be seen by the urologist or be definitively diagnosed with this entity until adulthood. This syndrome, also described by various authors as *non-neurogenic neurogenic bladder*, *occult voiding dysfunction*, *occult neuropathic bladder*, *learned voiding dysfunction*, and *Hinman syndrome*, demonstrates what urodynamically appears to be involuntary obstruction at the striated sphincter level existing in the absence of demonstrable neurologic disease (Hinman, 1986). It is very difficult to prove urodynamically that an individual has this entity, and it should further be noted that the diagnoses in many of the patients reported have been made on the basis of only history, isolated flowmetry, isolated measurements of total intravesical pressure, and pelvic floor electromyographic activity (Wein and Barrett, 1988). Unequivocal demonstration of this entity requires pressure-flow electromyographic evidence of bladder emptying occurring simultaneously with involuntary striated sphincter contraction in the absence of any element of abdominal straining, either in an attempt to augment bladder contraction or as a response to discomfort during urination. Such reports do exist and confirm the existence of this syndrome. The cause is uncertain and may represent a persistent transitional phase in the development of micturitional control or persistence of a reaction phase to the stimulus of LUT discomfort during voiding, long after the initial cause of the problem has disappeared (Jorgensen et al, 1982).

Bladder Neck Dysfunction

Bladder neck dysfunction is defined here as an incomplete opening of the bladder neck during voluntary or involuntary voiding. It

has also been referred to as *smooth sphincter dyssynergia*, *proximal urethral obstruction*, *primary bladder neck obstruction*, and *dysfunctional bladder neck*. The term *smooth sphincter dyssynergia* or *proximal sphincter dyssynergia* is usually used when referring to this urodynamic finding in an individual with autonomic hyperreflexia. In male patients with autonomic hyperreflexia, the neurologic pathophysiology is clear. The term *bladder neck dysfunction* more often refers to a poorly understood, non-neurogenic condition first described over a century ago but first fully characterized by [Turner-Warwick and associates in 1973](#). The dysfunction is found almost exclusively in young and middle-aged men, who characteristically report long-standing voiding and storage symptoms ([Webster et al, 1980](#); [Norlen and Blaivas, 1986](#); [Wein and Barrett, 1988](#); [Trockman et al, 1996](#); [Yamanishi et al, 1997](#)). These patients have often been seen by many urologists and have been diagnosed as having psychogenic voiding dysfunction because of a normal prostate on rectal examination, a negligible residual urine volume, and a normal endoscopic bladder appearance. The differential diagnosis also includes anatomic bladder neck contracture, benign prostatic enlargement (BPE) or BPO, dysfunctional voiding, prostatitis, neurogenic micturition dysfunction, and low pressure and low flow (see later). Objective evidence of outlet obstruction in these patients is easily obtainable by urodynamic study. Once obstruction has been diagnosed, it can be localized to the level of the bladder neck by video-urodynamic study, cystourethrography during a bladder contraction, or micturitional urethral profilometry (see Chapter 73). The diagnosis may also be made indirectly by the urodynamic findings of outlet obstruction in the absence of urethral stricture, prostatic enlargement, and DSD. [Noble and associates \(1994\)](#) cite the incidence of concomitant involuntary bladder contractions or decreased compliance as 50%; [Trockman and colleagues \(1996\)](#) quote it as 34%.

The exact cause of this problem is unknown. Some have proposed that there is an abnormal arrangement of musculature in the bladder neck region, such that coordinated detrusor contractions cause bladder neck narrowing instead of the normal funneling ([Bates et al, 1975](#)). The occurrence of this problem in young, anxious, and “high-strung” individuals, and its partial relief by α -adrenergic blocking agents, have prompted some to speculate that it may in some way be related to sympathetic hyperactivity. When prostatic enlargement develops in individuals with this problem, a double obstruction results, and [Turner-Warwick \(1984\)](#) has coined the term *trapped prostate* to describe these patients. Because the lobes of the prostate cannot expand the bladder neck, they expand into the urethra. In general, a patient so affected has a lifelong history of voiding dysfunction that has gone relatively unnoticed because he has always accepted this as normal, and exacerbation of these symptoms may occur during a relatively short and early period of prostatic enlargement. Although α -adrenergic blocking agents provide improvement in some patients with bladder neck dysfunction, definitive relief in men is best achieved by a bladder neck incision. In patients with this and a trapped prostate, marked relief is typically effected by a small prostatic resection or ablation that includes the bladder neck, or a transurethral incision of the bladder neck and prostate. Such patients often note afterward that they have “never” voided as well as after their treatment.

Bladder Outlet Obstruction in Women

The female counterpart of male non-neurogenic bladder neck dysfunction is rare but does exist. **Bladder outlet obstruction in women in general is uncommon.** [Diokno and coworkers \(1984\)](#) were among the first to clearly define this entity in women on the basis of video-urodynamic studies. [Nitti and coworkers \(1999\)](#) evaluated the video-urodynamic studies of 261 of 331 women who underwent multichannel studies for non-neurogenic voiding dysfunction. They defined *bladder outlet obstruction* as radiographic evidence of obstruction between the bladder neck and the distal urethra in the presence of a sustained detrusor contraction of any magnitude, which is usually associated with reduced or

delayed urinary flow rate. Obstruction at the level of the bladder neck was diagnosed when the bladder neck was closed or narrowed during voiding. Obstruction of the urethra was diagnosed as a discrete area of narrowing associated with proximal dilatation. Strict pressure-flow criteria were not used to classify cases as obstructed or not obstructed. Using these criteria, the authors found 76 (23%) of their cases to be obstructed and of those, only 12 (16%) were diagnosed as having primary bladder neck obstruction (the counterpart to non-neurogenic bladder neck dysfunction in the male). Thirty-three percent of the cases of obstruction were caused by dysfunctional voiding, 28% by cystocele, 14% by obstruction created by prior incontinence surgery, 4% by urethral stricture, 3% by uterine prolapse, and 1% each by urethral diverticulum and rectocele. [Groutz and associates \(2000\)](#) defined obstruction as a persistent low, noninvasive maximum flow rate less than 12 mL/sec on repeated study combined with a detrusor pressure at maximum measured flow rate of more than 20 cm H₂O in a pressure-flow study. Of the 587 consecutive women referred for urodynamic evaluation of voiding symptoms, only 38 (6.5%) met these criteria of bladder outlet obstruction. Of those, only 3 women (8%) were characterized as having primary bladder neck obstruction. Ten women (26%) had obstruction on the basis of prior anti-incontinence surgery, 24% because of severe genital prolapse, 13% because of urethral stricture, 5% because of dysfunctional voiding, 5% because of true DSD, and 3% because of urethral diverticulum; in 16% there was no identifiable cause. Most authors would agree that surgical treatment of this problem in women should be approached with caution because sphincteric incontinence is a significant risk. [Smith and Appell \(2006\)](#) commented on the importance of urodynamics in distinguishing dysfunctional voiding versus bladder neck dysfunction. They commented on the importance of evaluation inclusive of symptom assessment, uninstrumented uroflow patterns, simultaneous urodynamic and EMG assessment of voiding, as well as the addition of fluoroscopy to assess function of the bladder neck during voiding. They further stressed multidisciplinary therapy including pelvic floor therapy (biofeedback), behavioral modification, and the addition of pharmacotherapy.

Low-Pressure and Low-Flow Voiding in Younger Men: Bashful Bladder

Low-pressure and low-flow voiding can be the result of a number of causes, most notably a decompensating detrusor (usually from bladder outlet obstruction—see Chapters 73 and 104) or as a part of the syndrome known as *detrusor hyperactivity with impaired contractility* (DHIC—see Chapters 73 and 88). When this occurs in a young man, it is usually characterized by frequency, hesitancy, and a poor stream. The entity is readily demonstrated on urodynamic assessment and with no coexisting endoscopic abnormality. The patient usually notes marked hesitancy when attempting to initiate micturition in the presence of others, and some have therefore described this condition as an “anxious bladder” or a “bashful bladder.” The estimate of the incidence of this problem in younger male patients referred for urodynamic assessment varies from 6% ([Barnes et al, 1985](#)) to 19% ([George and Slade, 1979](#)).

[Barnes and associates \(1985\)](#) suggested that, psychologically, these men tend to be obsessional rather than anxious. They suggest that these individuals have a lifelong tendency to over-control the process of micturition and are thus vulnerable to LUTS under stress. The authors recommend that a behavioral modification program be considered. [Rosario and colleagues \(2000\)](#) performed ambulatory urodynamic studies on 40 consecutive symptomatic men with a mean IPSS of 19 who were unable to “perform” during conventional video-urodynamic study. They concluded that a surgically correctable cause of the symptoms could be found in only 20% of men, and only in those 40 years of age and older. They concluded that the contribution of ambulatory urodynamic monitoring in such cases in men younger than 40 years was negligible. As with previous studies, these authors thought that a significant proportion

of such nonobstructed cases would respond to drug therapy or behavioral intervention.

Urinary Retention: Fowler Syndrome in Young Women

Although urinary retention is encountered fairly commonly in men with anatomic obstruction from BPE, urinary retention in women is unusual, but not rare. As in men, the potential causes are classically cited as neurologic, pharmacologic, anatomic, myopathic, functional, and psychogenic. A comprehensive review and algorithm for evaluation and treatment of the various causes of urinary retention in women has been published by Smith and coworkers (1999).

Fowler syndrome (Fowler et al, 1988; Noble et al, 1994; Fowler, 1999; Swinn and Fowler, 2001; Fowler, 2003) refers specifically to urinary retention in young women in the absence of overt neurologic disease. The typical history is that of a woman younger than 30 years who has found herself unable to void for a day or more with no urinary urgency but increasing lower abdominal discomfort. A bladder capacity of over 1 L with no sensation of urgency is necessary for the diagnosis. There are no neurologic or laboratory features to support a diagnosis of any neurologic disease. MRI scans of the brain and the entire spinal cord have been reported to be normal. However a recent MRI assessment of patients with Fowler syndrome has suggested exaggerated cortical procontinence behavior attributable to increased afferent activity emanating from the urethra inhibiting bladder afferents at the sacral level. This increased afferent activity is partially modulated by successful sacral neuromodulation resulting in decreased overall sphincteric activity (Griffiths and Fowler, 2010).

On concentric needle electrode examination of the striated muscle of the urethral sphincter, however, Fowler and associates described a unique electromyographic abnormality. This abnormal activity, localized to the urethral sphincter, consists of a type of activity that would be expected to cause inappropriate contraction of the muscle. Sphincter activity consists of two components: complex repetitive discharges and decelerating bursts. This abnormal activity impairs sphincter relaxation. These patients often have polycystic ovaries, raising the possibility that the activity is linked in some way to impaired muscle membrane stability. This, in turn, allows direct spread of electrical impulses throughout the muscle, possibly from a hormonal abnormality. Thus, the disorder may possibly be the manifestation of a focal, hormonally dependent "channelopathy." This would potentially explain why the condition is seen only in premenopausal women. Efforts to treat this condition by hormonal manipulation, pharmacologic therapy, or injections of onabotulinumtoxinA have been unsuccessful. This condition is highly responsive to neuromodulation, with a success rate approaching 70% even in women who have had urinary retention for many months or years.

The urodynamic finding is detrusor acontractility; however, the same electromyographic abnormality is found sometimes in women with obstructed voiding. This type of electromyographic activity is not uncommon; FitzGerald and associates (2000) cite an incidence of 8% in a series of women undergoing routine urodynamic and electromyographic studies, but its correlation with complete retention is relatively rare.

In one of the largest reports of Fowler syndrome, 247 women with a presumptive diagnosis of Fowler syndrome were assessed. Overall, the diagnosis was confirmed in 57.5% of patients. However, distressingly, in 32% of the patients the authors were not able to determine an ultimate diagnosis. Of the study group, 4.8% had congenital intestinal pseudo-obstruction (associated in some patients with ingestion of high-dose opiates). Other cases of voiding dysfunction included detrusor failure (1.6%), pain or structural abnormality in the LUT (1.6%), recurrent obstruction after surgery for sphincteric incontinence in 1.2%, and a neurologic abnormality other than Fowler syndrome in 1.2% of patients. The authors based their diagnosis on the classic Fowler syndrome (nonpainful urinary retention in women 20 to 35 years of age); patients frequently had polycystic ovaries and relatively mild LUT dysfunction. They further

identified urodynamic findings including a very high urethral closure pressure (greater than 100 cm H₂O) and increased sphincter volume based on ultrasonographic assessment, perhaps suggesting a hormonal-based effect on channel receptors. The authors reported a success rate of 40% to 68% for peripheral nerve evaluation with neuromodulation, followed by a 60% complete success rate after formal implantation and an additional 14% partial success rate in their population. The possibility of autonomic dysfunction as being contributory to this condition was also raised (Kavia et al, 2006).

De Ridder and colleagues (2007) reported 62 women who underwent sacral nerve stimulation, 30 of whom had findings compatible with Fowler syndrome and 32 with idiopathic retention. Somatoform disorder was found in 26% of the Fowler syndrome patients and 43.8% of the idiopathic group. Depression was also higher in the Fowler syndrome group (30% vs. 18.8%). Neither of these findings, however, had correlation with outcome. Nine patients with Fowler syndrome (compared to 19 patients without Fowler syndrome) failed neuromodulation. The authors concluded that Fowler syndrome was actually a positive predictive factor for SNS response in patients with female urinary retention.

Postoperative Urinary Retention

Postoperative urinary retention is a well-recognized but poorly understood event. Its incidence is usually quoted to be 4% to 25% overall. It occurs more frequently after LUT and perineal, gynecologic, and anorectal surgery. In the placebo arms of four trials of adrenergic blocker prophylaxis after these types of surgery, the incidence of postoperative retention ranged from 18.8% to 57% (Velanovich, 1992). Although not mutually exclusive, contributing factors include the following:

1. Traumatic instrumentation
2. Bladder overdistention
3. Diminished awareness of bladder sensation
4. Decreased bladder contractility
5. Increased outlet resistance
6. Decreased micturition reflex activity
7. Nociceptive inhibitory reflex
8. Preexistent outlet pathology (e.g., BPH)

Anesthesia and analgesia can contribute to factors 2, 3, 4, and 6. The idea of a nociceptive inhibitory reflex initiated by pain or discomfort is an attractive one, because a sympathetic efferent limb could directly affect factors 4, 5, and 6 (see Chapter 69).

Bladder decompression for 18 to 24 hours postoperatively decreased the incidence of retention in patients undergoing joint replacement surgery by 52% versus 27% (Michelson et al, 1988) and 65% versus 0% (Carpiniello et al, 1988), compared with CIC. The incidence of urinary infection with continuous catheterization was no different in the study by Michelson and colleagues (15% vs. 11%) and was less in the study by Carpiello and coworkers (16% vs. 43%), in which CIC was carried out in the recovery room as well. The avoidance of acute bladder overdistention to prevent postoperative urinary retention is supported by the experimental observation of a reduced bladder response to sacral neural stimulation during overdistention (>80% reduction) and, as well, after overdistention (19% reduction) (Bross et al, 1999).

Historically, prophylactic adrenergic blockade with phenoxybenzamine has seemed effective in decreasing the incidence of postoperative retention. Velanovich (1992) performed a meta-analysis on the use of phenoxybenzamine and concluded that this agent reduced the occurrence by 29.1%. In a retrospective review of colorectal patients treated with and without phenoxybenzamine, Goldman and colleagues (1988) found a 54.7% incidence of retention in patients not given this agent versus a 19.2% incidence in those who were. The regimen for those not catheterized preoperatively was 10 mg orally the evening before and 1 hour before surgery, 2 hours after, and 10 mg twice daily for 3 days. For those who were catheterized before the procedure, the regimen was 10 mg twice daily, initiated the day before catheter removal. The mechanism of action is uncertain. If an inhibitory nociceptive reflex is initiated, and this is similar to the sympathetic reflex elicited by

bladder filling (see Chapter 69), the mechanism is likely multifactorial. Alternatively, the drug may act only on the outlet to decrease resistance, which may be pathologically increased by anxiety, pain, and other factors related to surgery. Whether other adrenergic blockers are as effective is uncertain (Cataldo and Senagore, 1991).

Hyperthyroidism

Patients with thyrotoxicosis often have symptoms caused by sympathetic overactivity and autonomic nervous system imbalance. Hyperthyroidism has an association with LUTS, especially in women. Autonomic dysfunction may play a contributory role. In an assessment of 65 newly diagnosed untreated women with hyperthyroidism compared with 62 age-matched controls, the women with hyperthyroidism demonstrated significantly higher mean symptom scores for incomplete emptying, frequency, straining, and overall total symptoms. More than 80% demonstrated high total symptom scores and diminished peak flow rates. In follow-up, LUTS and flow times improved significantly after therapy.

There is no relationship between LUTS and serum thyroid levels, hormone levels, or other hyperthyroid symptoms (Ho et al, 2011). Goswami and associates (1997) reported that 12 of 30 patients (40%) experienced the onset of voiding symptoms 1 to 6 months after the onset of the symptoms of thyrotoxicosis. Four of these patients had enuresis. Of the 5 patients who underwent urodynamic studies, all had reduced flow rates and 4 had a significant postvoid residual volume, 3 of whom had an enlarged bladder capacity and increased perineal electromyographic activity during voiding. The LUT dysfunction and urodynamic abnormalities resolved after resolution of the hyperthyroidism. The bladder symptoms were more common in females than in males. A higher incidence of bladder symptoms was noted in patients with thyrotoxicosis: a 7% incidence of urgency with or without hesitancy and a 1% incidence of enuresis.

Schizophrenia

Bonney and coworkers (1997) proposed that a significant subset of schizophrenic patients have involuntary bladder contractions secondary to brain pathology. In a previous study (Gupta et al, 1995), the same group demonstrated involuntary bladder contractions in 4 of 10 evaluable patients with schizophrenia who were referred because of voiding dysfunction or incontinence. All of these patients had a history of significant childhood incontinence, urge incontinence, bedwetting, and a diminished bladder capacity. In the later report (Bonney et al, 1997), the prevalence of urinary incontinence and related symptoms in a group of chronic schizophrenic patients was compared with a group of comparable patients hospitalized with mood disorders. There was a significantly higher prevalence of urge incontinence (34% vs. 17%) and bedwetting (46% vs. 20%) in the schizophrenic group, whereas there were no significant differences in urinary urgency, overall voiding dysfunction, fecal incontinence, or sexual dysfunction. The hypothesis of a neurobiologic correlation between schizophrenia and the occurrence of involuntary bladder contractions is an intriguing one.

Gastroparesis

Gastroparesis is a condition characterized by symptoms from impaired transit of intraluminal gastric contents into the duodenum in the absence of mechanical obstruction. It may be caused by diabetes, occur after gastric surgery, or be idiopathic. Goldman and Dmochowski (1997) characterized the voiding dysfunction of 17 patients with gastroparesis who were referred because of voiding symptoms, 10 of whom had idiopathic gastroparesis and in 7 of whom the condition was secondary to diabetes. Seven patients had abnormal detrusor contraction and delayed sensation, 5 had poor detrusor function and normal sensation, 3 had normal detrusor function and poor sensation, and 2 had normal detrusor contraction and sensation. There was no difference in the occurrence of the

dysfunctions between the two groups. Predominant symptoms were urinary frequency in 7 and difficulty emptying in 10. Patients with idiopathic gastroparesis were more likely to note difficulty emptying (70%), whereas those with diabetic gastroparesis were more likely to have urinary frequency (71%). The authors postulated an association between idiopathic gastroparesis and bladder dysfunction and proposed that a common autonomic neuropathic syndrome may account for the bladder dysfunction in both the idiopathic and the diabetic forms of this syndrome.

Myasthenia Gravis

Any neuromuscular disease that affects the tone of the smooth or striated muscle of the distal sphincter mechanism can predispose an individual to a greater chance of urinary incontinence after even a well-performed transurethral or open prostatectomy. Myasthenia gravis is an autoimmune disease caused by autoantibodies to acetylcholine nicotinic receptors. This leads to neuromuscular blockade and subsequent weakness in a variety of striated muscle groups. The incidence of incontinence after prostatectomy is indeed greatly increased in patients with this disease (Greene et al, 1974; Khan and Bhola, 1989). In addition, Sandler and associates (1998) reviewed three cases of de novo voiding dysfunction in patients with myasthenia gravis (one woman with intrinsic sphincter deficiency, poor pelvic muscle contractility, and detrusor overactivity; one man with detrusor hyporeflexia who reported urgency and incontinence; and one young woman with an acontractile bladder). The authors add a personal report of a fourth patient with urinary retention from detrusor areflexia. They hypothesize that such autonomic dysfunction in a patient with myasthenia might indicate a unique subset with a worse prognosis.

Isaacs Syndrome

Isaacs syndrome is a rare neurologic disorder characterized by continuous muscle contraction, fasciculations, myokymia, excessive sweating, and elevated creatine kinase level. It is caused by antibodies possibly directed against potassium channels on peripheral nerves and is associated with peripheral neuropathy, autoimmune diseases, malignancies, and endocrine disorders. Tiguet and coworkers (1999) present a case with urinary retention associated with a picture of acute demyelinating neuropathy. Their patient had painful urinary and fecal retention; the urinary retention was thought to be caused by spasm of the periurethral striated sphincter and was diagnosed by an inability to pass a catheter beyond this area. Rectal sphincter spasm was also diagnosed. The condition was treated with plasmapheresis and pharmacologic agents to relax the skeletal muscle. Suprapubic drainage was instituted. The condition subsided, and normal urinary function was ultimately restored.

Wernicke Encephalopathy

Wernicke encephalopathy is a rare but well-documented condition caused by a deficiency in thiamine (vitamin B₁) in both alcoholic and nonalcoholic populations. Pathologic lesions are characteristically distributed periventricularly at the levels of the third and fourth ventricles, including the mammillary body, medial thalamic nucleus, hypothalamus, superior cerebellar vermis, PAG, and mid-brain tegmentum. The two major clinical manifestations of thiamine deficiency involve the cardiovascular and neurologic systems, with the latter manifesting in general as a peripheral neuropathy, also known as Wernicke encephalopathy. The initial symptoms of the polyneuropathy range from burning feet to muscle weakness. Sakakibara and associates (1997b) report a case of a pregnant woman with multiple neurologic manifestations of central and peripheral neuropathy and urgency incontinence, manifesting urodynamically with involuntary bladder contractions and a decreased bladder volume. **Resolution of the urinary symptoms occurred after thiamine replacement.** The authors hypothesized that lesions in the medial thalamic-hypothalamic area and PAG were primarily

responsible for the micturitional disturbance. [Tjandra and Janknegt \(1997\)](#) reported a case of a chronic alcoholic man with seemingly isolated erectile and voiding dysfunction. The emptying complaints correlated with a prolonged void with a peak flow rate of 6.4 mL/sec and an interrupted pattern during flowmetry, suggesting poor detrusor contractility. The erectile dysfunction was determined to be neurogenic, and both resolved with thiamine replacement.

Systemic Sclerosis (Scleroderma)

Scleroderma is a disease of the connective tissue characterized by thickening and fibrosis of the skin, abnormalities of the small arteries, and involvement of the gastrointestinal tract, heart, lung, and kidneys. The pathogenesis is unknown but thought to be caused by overexpression of the collagen gene DNA that contributes to excessive production of collagen in these patients. [Lazzeri and colleagues \(1995\)](#) reported the urodynamic assessment and histologic evaluation of nine such women, of whom five had hesitancy, four had decreased stream, two had frequency and nocturia, and two had suprapubic pain. Four patients had detrusor areflexia, one of whom also had decreased compliance. Another patient with a decreased stream also had decreased compliance. Three of the patients with areflexia demonstrated collagen accumulation on histologic examination of bladder biopsies. The authors reviewed five literature reports of various aspects of LUT function and histology in patients with scleroderma but failed to find a consistent pattern. They hypothesized that the areflexia resulted from impaired neurologic modulation owing to the histologic changes in the detrusor tissue.

Conversely, [Minervini and associates \(1998\)](#) evaluated 23 females with systemic sclerosis and found urodynamic alterations in only 3 of 9 patients who reported urinary symptoms. They were unable to correlate voiding symptoms, urodynamic changes, and the degree of bladder wall fibrosis or visceral involvement. Evidence of autonomic nervous system dysfunction was found outside the urinary tract in 13 of these patients. The authors speculate that when LUT dysfunction occurs, it could be caused by the fibrotic replacement of bladder smooth muscle. However, they did not exclude some degree of autonomic dysfunction, as well.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome refers to a heterogeneous group of disorders characterized by inherited abnormalities of connective tissue. The main clinical manifestations are skin fragility, skin hyperextensibility, and joint mobility. More than 10 subtypes of the syndrome have been defined based on clinical, genetic, and biochemical criteria. Bladder diverticula have been associated with this disorder, with operative repair characterized by a higher recurrence rate than would ordinarily be expected. [Deveaud and associates \(1999\)](#) reviewed the literature on this subject and reported on one such patient with a large left-sided, nonemptying diverticulum, along with a greatly enlarged bladder capacity and high postvoid residual urine. Simultaneously, they reported a second patient without Ehlers-Danlos syndrome who had a UTI and left pyelonephritis. This patient also reported a decreased force of stream, and evaluation disclosed left VUR with a left (presumably congenital) periureteral diverticulum. The diverticulum enlarged with voiding, and the patient had a large postvoid residual volume. Both patients were successfully treated surgically. The authors thought the tissue from the nonperiureteral diverticulum was more closely related to the pathophysiology of Ehlers-Danlos syndrome, noting the tissue from that diverticulum to be more compliant. They attributed this to changes in the extracellular matrix protein caused by the Ehlers-Danlos syndrome.

Myotonic Dystrophy

Myotonic dystrophy is an autosomal dominant hereditary multiorgan disease characterized by myotonia and distal muscle atrophy. In addition, this condition in later stages is characterized by

cataracts, endocrine disturbances, mental retardation or dementia, testicular atrophy and infertility, progressive frontal alopecia, and disturbances in cardiac conduction. Although myotonic activity has not been found in the sphincter or pelvic floor, many patients have voiding complaints. [Bernstein and coworkers \(1992\)](#) reported on 10 patients, 8 of whom had urinary complaints by history (4 infrequent voiders, 1 with urgency and stress incontinence, 1 with urge and urgency incontinence, 1 with slight urgency without incontinence, and 1 with obstructive symptoms only in the morning). There were no characteristic urodynamic patterns observed, and urodynamic findings did not correlate particularly well with symptoms. [Sakakibara and associates \(1995b\)](#) also reported LUTS in such patients; however, there is **no characteristic pattern of dysfunction**. Thus, such patients need to be characterized urodynamically before any assumptions are made regarding therapy based on symptoms alone.

Corticobasal Degeneration

Corticobasal degeneration is a rare neurodegenerative disorder of the corticobasal tracts in the cerebral cortex and basal ganglia. The disorder tends to have a unilateral predominance and is most likely present in the supranuclear parasympathetic system. Cortical, extrapyramidal, long-tract, and urinary symptoms are commonly noted in this disease process. [Sakakibara and associates \(2004b\)](#) assessed 10 patients with this disorder and compared them with 11 age-matched controls. As compared with controls, the degeneration patients had more common urinary symptoms (80% of study group). Urinary symptoms usually appeared within 1 to 3 years after onset of the disease and became more common with longer disease duration. Nocturnal frequency tended to be the initial urinary symptom, followed by incontinence, urgency, and frequency. Urodynamic findings included decreased bladder capacity, detrusor overactivity (most common), detrusor hypocontractility, and low compliance in individual patients. DSD was not noted.

Sacral Coccygeal Teratoma

Sacral coccygeal teratoma can produce significant neurolgic dysfunction and can be associated with upper tract deterioration as a result of high-grade reflux and abnormal bladder storage pressures. [Ozkan and colleagues \(2006\)](#) identified 14 patients with sacral coccygeal teratoma, of whom 8 had detrusor overactivity and 2 had underactivity. There was also abnormal urethral sphincteric activity in 54% of the patients and 38% demonstrated DSD. Eleven of 14 patients required CIC for bladder emptying, and 5 required anticholinergics. Six patients had hydronephrosis and 7 had reflux ([Ozkan et al, 2006](#)).

Subacute Combined Degeneration

SACD is a condition arising from vitamin B₁₂ deficiency resulting in degeneration of the spinal cord, frontal cortex, and peripheral nerves. Visual dysfunction is also a prominent finding. The condition is associated with deficient dietary intake (vegetarianism and old age), gut malabsorption, gastrectomy, fish tapeworm infestation, and autoimmune disorders. In a study of eight patients with this condition, multiple nonurologic symptoms were associated with the condition including ambulation problems in addition to joint spasticity. Urinary symptoms represented a mix of storage (five of eight patients), voiding (seven of eight patients), and combined dysfunctions (four of eight patients). Urodynamic evaluation revealed detrusor areflexia in two patients, neurogenic detrusor overactivity in three, and normal studies in the remainder. After treatment with vitamin B₁₂ supplementation, detrusor areflexia improved in two patients, dysfunction improved in three patients completely, and four had partial recovery. MRI findings include T2 hyperintensity in the posterior spinal column and subcortical white matter defects in two patients ([Misra et al, 2008](#)).

Williams-Beuren Syndrome

Williams-Beuren syndrome (WBS) is an autosomal disorder associated with cardiovascular abnormalities, facial changes, cognitive dysfunction resulting in mental retardation, and developmental delay. In a study of individuals with this syndrome, 28 children (16 boys, 12 girls) were assessed with a complete urologic workup including renal functional studies, voiding cystourethrography, and urodynamics; 78% of patients had urinary symptoms (urinary frequency 66.7%, enuresis 50%, and urge incontinence 42%). Fifty percent of patients had urinary tract abnormalities, with bladder diverticula being most common (43%). Urodynamic findings demonstrated detrusor overactivity in 60% of patients and sphincteric dyssynergia with detrusor overactivity in 14%. Decreased cystometric capacity was identified in 28% of patients. The exact site of neural compromise associated with this condition (caused by chromosomal deletion 7q11.23) is unknown (Sammour et al, 2006).

Amyloidosis

Subtypes of amyloidosis are associated with neurologic disorders. Familial amyloidotic polyneuropathy, Portuguese type, has been identified as one of these subtypes. In a study of 54 patients with this condition, generalized muscle atrophy and weakness resulting in impairment of gait capabilities were identified. Autonomic and sensory neuropathy occurred early in the course of the condition. There was early development of gastrointestinal symptoms. With disease progression, marked effects were noted in detrusor contractility (deleterious), thought to be caused by amyloid infiltration of peripheral nerves. In addition, a sensory deficit resulting in chronic overdistention injury was postulated as contributory to this finding. Bladder and sphincteric dysfunction appears to occur in the early stage in this disease and produces a progressive dysfunction with the appearance of stress incontinence in both genders as a result of sphincteric dysfunction. Residual urinary volume increase was related to chronic overdistention (Andrade, 2009).

Machado-Joseph Disease

A variant of spinocerebellar degeneration is spinocerebellar ataxia type 3, otherwise known as Machado-Joseph (MJ) disease. This is the most common hereditary spinocerebellar ataxia dominant disease. It is associated with a defined expansion of the *MJD1* gene from the 14q32.1 chromosome. Symptoms include pyramidal spasticity, extrapyramidal rigidity, athetosis, dystonia, visual movement disorder (ophthalmoplegia), eyelid retraction, amyotrophy, and impairment of global sensory function. In a study of 122 patients with this disorder, 17 (13.9%) experienced LUT dysfunction. The mean age of occurrence of the disease was the mid-fifth decade, with urgency being the predominant symptom in 15 and incontinence found in 9 patients. The most common urodynamic finding was detrusor overactivity in 8 patients, areflexia in 1, and normal contractility in 4. Bladder sensory disorder defined by delayed perceptions was identified in 6 patients. Postvoid residual volumes greater than 100 mL were noted in 9 (Musegante et al, 2011).

Radiation

Vale and associates (1993) summarized their experience with the occurrence of voiding dysfunction after external-beam irradiation. They describe an early radiation reaction most prominent at 4 to 6 weeks, with an incidence as high as 70%. Storage symptoms are most common, and urodynamic studies have demonstrated reduced volume at first desire to void, reduced cystometric capacity, and reduced compliance. These parameters tend to return to pretreatment values by 6 months. Symptoms associated with later radiation effects are less common but may be progressive and intractable. Storage symptoms again predominate, and urodynamic studies, when positive, demonstrate reductions in first desire to void and maximum cystometric capacity, presence of involuntary bladder contractions in up to a third of patients, and

an increase in maximum subtracted detrusor pressure during filling. Historical explanations have concentrated on urothelial injury and ulceration with fibrosis. In an experimental rat model, the authors found a biphasic reduction in compliance, with the first reduction developing at 4 to 6 weeks after irradiation, followed by recovery. A second reduction phase in compliance started at 10 to 12 weeks and persisted. It is interesting to note that only half of the irradiated bladders demonstrated fibrotic infiltration of muscle bundles, and there was no association between the presence of fibrosis and the magnitude of reduction and compliance. Mast cells were more abundant in irradiated bladders than in controls. Electron microscopic studies in the irradiated bladders showed the presence of areas displaying focal degeneration of smooth muscle cells, with these cells demonstrating disaggregation of filaments and, in some cases, cytoplasmic organelles free in the intracellular space. In scattered foci, selective degeneration of unmyelinated axon profiles was noted, ranging from marked to lesser degrees of axonal injury. Thus the authors were unable to confirm a fibrosis-based hypothesis of postirradiation bladder dysfunction in their experimental model, but did reveal other changes that could contribute to such dysfunction (neural degeneration and changes in the detrusor muscle itself).

Choo and colleagues (2002) reported on video-urodynamic parameters in 15 of 17 patients completing studies at baseline and at 3 and 18 months after external-beam irradiation for prostate cancer. Between baseline and 18 months there were no statistically significant changes in detrusor pressure, peak flow rate, voided volume, postvoid residual, compliance, occurrence of detrusor overactivity, or outlet obstruction. There was a mean reduction in bladder capacity of 100 mL in the supine position and 54 mL in the upright position. There was no change in self-assessed qualitative urologic function (IPSS, quality-of-life assessment index, and urinary frequency). There were, however, individual patients who developed decreased compliance (4 patients) and detrusor overactivity (2 patients), urgency (5 patients), and urgency incontinence (3 patients).

The Defunctionalized Bladder

The timing of bladder defunctionalization and the age of the individual at time of defunctionalization may be predictive of bladder functionality. In fetal sheep, urinary diversion results in loss of overall bladder weight with marked connective tissue infiltration and loss of smooth muscle organization. Also, a reduced response to carbachol stimulation and increased response to field stimulation was noted in tissue from animals undergoing early diversion (Matsumoto et al, 2003).

The previously normal defunctionalized bladder will often show decreased capacity and involuntary bladder contractions and/or decreased compliance. Previously abnormal bladders will usually demonstrate their prior pathology, many times with these additional abnormalities. Rehabilitation of a defunctionalized bladder is certainly possible and should definitely be attempted by cycling with progressively increasing volumes. Serrano and associates (1996) considered this subject while evaluating the outcome of transplantation in five long-term defunctionalized bladders. Successful bladder rehabilitation was accomplished, and the transplantation was successful without bladder augmentation, although one patient required CIC. Normal compliance was inferred by the fact that there was no evidence of hydronephrosis after long-term allograft function up to 10 years. The authors proposed that transplantation can be accomplished into a previously defunctionalized bladder when a capacity greater than 100 mL and a voiding pressure less than 100 cm H₂O are demonstrated during bladder rehabilitation. The presence of a defunctionalized bladder may not prevent subsequent renal transplantation. In an assessment of 12 pediatric patients with markedly diminished-capacity (defunctionalized) bladders, transplantation was performed without pretransplant bladder augmentation. The overall transplant survival rates in this group were 100%. Minimal reflux was noted. In addition, all patients were able to void spontaneously without incontinence (Alexopoulos et al, 2011).

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is associated with mixed urinary symptoms. [Davies and colleagues \(2005\)](#) studied 19 women with CAH, of whom 16 had undergone childhood feminizing surgery. Compared with age-matched controls, the CAH population had a higher incidence of urgency incontinence (68%) and stress incontinence (47%). The effects of CAH are uncertain and may be either the result of feminizing surgery secondary to a direct neuropraxia induced by surgery or a primary effect of CAH.

Aging

LUTS and LUT disorders are prevalent and bothersome in the elderly population. These problems are specifically and extensively considered in Chapter 88. When considering the effects of aging on the LUT, one cannot separate the effects of chronologic age itself from the various anatomic, neuromorphologic, neurophysiologic, neuropharmacologic, metabolic, and hormonal changes that coexist with aging, along with the effects of other coexistent disease processes. In addition, neurologic phenomena may masquerade as LUTS associated with bladder outlet obstruction. These phenomena may include multiple cerebral infarctions, cervical spondylosis, and lumbar spondylosis, all findings noted in the Olmsted County longitudinal study and indicative of the need for urodynamics in older men with complex urinary symptoms ([Woderich and Fowler, 2006](#)). In addition to the material contained in Chapter 88, there is an excellent review of this topic by the Committee on Pathophysiology of the Urinary Bladder and Obstruction and Aging for the 4th International Consultation on BPH ([Nordling et al, 2001](#)).

Benign Joint Hypermobility Syndrome

Benign joint hypermobility syndrome has an apparent association with urinary incontinence. [Manning and colleagues \(2003\)](#) prospectively evaluated 1000 women referred for urodynamic evaluation and noted benign joint hypermobility to be associated with increasing bowel dysfunction and a higher degree of urinary tract symptomatology. Also noted was a significant childhood history for both of these phenomena. In a study of 38 women with joint hypermobility as compared with normal controls, symptom questionnaires were administered to both groups; 18 of 30 (60%) with benign joint hypermobility demonstrated urinary incontinence as compared to an incidence of 30% in the controls. In addition, 23% of the women with joint hypermobility also demonstrated anal incontinence as compared to none of the controls. These findings have been attributed to disorders of collagen metabolism; however, the absolute cause has not been clearly delineated ([Jha et al, 2007](#)).

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) occurs in 3% to 5% of children, and LUTS are common in this group. In a study of 75 children with ADHD with voiding dysfunction, all children had daytime enuresis and urgency. In addition, 88% of the children had urinary frequency and 87% had sleep enuresis. Complete resolution of symptoms occurred in 30.4% of patients, and 53.6% had partial response with therapy using a combination of behavior modification and antimuscarinic agents ([Kaye and Palmer, 2010](#)).

Other Conditions

The effect of disordered function of other organs within the pelvis is also potentially contributory to LUT dysfunction. Some of this disordered function may arise as a result of altered afferent neurologic activity induced by other organ disorders. The potential for visceral “crosstalk” has been proposed as a cause of LUT dysfunction and includes syndromes such as interstitial cystitis and irritable bowel syndrome. [Noronha and colleagues \(2007\)](#) assessed the short- and long-term effects of acid-induced colitis on bladder

function in a rodent model. Detrusor muscle contractility and histology were evaluated, both acutely and subacutely after induction of chemical colitis. During the active phase (3 days postinjury), bladder muscle structure appeared histologically normal and inflammation was absent. However, some abnormalities in detrusor muscle contractility in response to electric field stimulation were noted. During the subacute period and after recovery of colitis (15 and 30 days), bladder muscle contractility returned to control levels with no discernible histologic change. These reversible changes were postulated to result from altered afferent input from the colon, resulting in “field” type changes affecting the bladder.

Any neurologic disease or injury can affect LUT function. Many have been mentioned in this chapter, but case reports and small series exist that document many others. The dysfunction produced by some is logically deducible on the basis of similarity to other neurologic lesions. For others, the LUT dysfunctions are inconsistent and seemingly at odds with what would be predicted on the basis of neuroanatomic and neurophysiologic principles. For those who wish to further pursue this subject, the following referenced list may be helpful:

- Adrenoleukodystrophy ([Silveri et al, 2004](#))
- Adrenomyeloneuropathy ([Sakakibara et al, 1998a](#))
- Adult polyglucosan body disease ([Gray et al, 1988](#))
- Behçet disease ([Theodorou et al, 1999](#); [Saito and Miyagawa, 2000](#); [Sakakibara et al, 2000](#))
- Brown-Séquard syndrome ([Sakakibara et al, 2001](#))
- Central cord syndrome ([Newey et al, 2000](#); [Smith et al, 2000](#))
- Incontinence in cystic fibrosis ([Dodd and Langman, 2005](#))
- Down syndrome ([Handel et al, 2003](#))
- Duchenne muscular dystrophy ([MacLeod et al, 2003](#))
- Familial dysautonomia ([Saini et al, 2003](#))
- Intramedullary epidermoid cyst ([Ferrara et al, 2003](#))
- Lambert-Eaton myasthenic syndrome ([Satoh et al, 2001](#))
- Neurofibromatosis ([Brownlee et al, 1998](#))
- Pituitary adenomas and urinary symptoms ([Yamamoto et al, 2005](#))
- Sjögren syndrome ([Kovacs et al, 2003](#))
- Spinal cord tumors ([Uchiyama et al, 2004](#))
- Spinal muscular atrophy ([von Gontard et al, 2001](#))

TREATMENT OF NEUROGENIC LOWER URINARY TRACT DYSFUNCTION: OVERVIEW

In later chapters, the various therapies available for the treatment of LUT dysfunction are discussed. Only a discrete number of such therapies are available, and these are easily categorized on a functional “menu” basis according to whether they are used primarily to facilitate urine filling and storage or voiding and emptying and according to whether their primary effect is on the bladder or on the outlet (see Table 70-1 and Box 70-3 in Chapter 70).

The initial choice of a mode of management for a given problem is multifactorial, and **certain goals of management for LUT dysfunction are beyond debate (Box 75-1)**. The fact that these goals have remained relatively unchanged over the past few editions of this text attest to their general validity. As a corollary, absolute or relative indications for changing or augmenting a particular regimen

BOX 75-1 Voiding Dysfunction: Goals of Management

- Upper urinary tract preservation or improvement
- Absence or control of infection
- Adequate storage at low intravesical pressure
- Adequate emptying at low intravesical pressure
- Adequate control
- No catheter or stoma
- Social acceptability and adaptability
- Vocational acceptability and adaptability

BOX 75-2 Reasons to Change or Augment a Given Regimen

Upper urinary tract deterioration
 Recurrent sepsis or fever of urinary tract origin
 Lower urinary tract deterioration
 Inadequate storage
 Inadequate emptying
 Inadequate control
 Unacceptable side effects
 Skin changes secondary to incontinence or collecting device

BOX 75-3 Patient Factors to Consider in Choosing Therapy

Prognosis of underlying disease, especially if progressive or malignant
 General health
 Limiting factors: inability to perform certain tasks (e.g., hand dexterity, ability to transfer, body habitus)
 Mental status
 Motivation
 Desire to remain catheter or appliance free
 Desire to avoid surgery
 Sexual activity status
 Reliability
 Educability
 Psychosocial environment, interest, reliability, and cooperation of family
 Economic resources

exist, and, likewise, there is general agreement on these, although the relative importance of the indication for change might be disputed (Box 75-2). It should be remembered that the term *inadequate*, when applied to storage and emptying, applies not only to volumes (capacity, voided volume, residual) but also to unacceptably high detrusor pressures during either or both of the two phases of the micturition cycle. In the planning of goals of therapy and reasons for change, the concept of a “hostility score,” such as that of Galloway (1989), is attractive. His hostility score includes five urodynamic characteristics—bladder compliance, overactivity, dys-synergia, outlet resistance, and VUR. Each is allocated a score of 0, 1, or 2. The best possible score is 0 and implies normal compliance, no inappropriate detrusor activity, a synergic sphincter, a low leak pressure, and no reflux.

The results of treatment of voiding dysfunction are rarely perfect, and they do not have to be. The goals are satisfaction and avoidance of adverse outcomes. A very flexible approach must be adopted in choosing therapy that takes into account the individual wishes of each patient and family and the practicality of each proposed solution for that particular patient (Box 75-3). The therapeutic decisions are thus made with the patient and with the family. In every case, within the limits of practicality, the following should be discussed: reversibility, side effects that occur with some regularity, ultimate best and worst possible scenario, frequency and extent of follow-up, and alternate methods of management. Treatment should always begin with the simplest, most reversible form(s) of therapy, proceeding gradually up the ladder of complexity, but with the knowledge that it is only the patient (and/or family) who is (are) empowered to say when “enough is enough.” Again, satisfaction and avoidance of adverse outcomes are the primary goals. A combination of therapeutic maneuvers can some-

times be used to achieve a particular end, especially if these modalities act through different mechanisms and their side effects are not synergistic or additive. There are circumstances and locales in which health care resources and hospital bed use must also be considered.

The importance of graded intervention for neurogenic disease with the ultimate goals of control of bladder pressures, preservation of renal function, control of UTI, and social continence has been recently underscored by two guidelines (Consortium for Spinal Cord Medicine, 2006; Pannek et al, 2011). Recent consensus guidelines stress the importance of intermittent catheterization as the foundational strategy in the management of the willing and motivated patient or health care provider. Catheterization volumes should be kept below 500 mL (consensus). Credé or Valsalva is not a recommended technique for improving bladder emptying, given concerns regarding outlet resistance. When chronic catheterization is required, suprapubic management is preferable to indwelling urethral catheterization. However, CIC remains the gold standard (EAU guidelines). Recent ICI-RS (International Consultation on Incontinence–Research Society) evaluation of the extant literature on the management of neurologic bladder found that the level of evidence guiding therapy is of poor quality and that more special research is necessary. However, the basis of progressive therapy from medical ascending through surgical is a foundational concept (Wyndaele et al, 2010). Urodynamics may provide a useful guide for directing intervention. Differences in bladder compliance may be predictive of intervention success. Type A (total) versus type C (end fill) compliance patterns respond differently to antimuscarinic management, with resultant impacts on bladder storage pressures and upper tract function (Park and Linsenmeyer, 2001).

Optimal management of the bladder in spinal cord injuries has, in general, focused on the use of CIC where available. In a study of 179 patients undergoing management either with suprapubic or urethral catheterization, both groups had complications related to management technique. Tube revision and incontinence through the suprapubic tract were common in the group so managed. In the urethral management group, urethral erosion and incontinence were also common. The rates of UTI, bladder calculi, and bladder cancer were similar between the two groups (Katsumi et al, 2010). A prospective randomized assessment of spinal cord-injured patients using CIC was recently performed to address the rate of UTI with this condition. The time to first UTI requiring antibiotic management was significantly lengthened in patients using hydrophilic-coated catheters as compared with uncoated catheters. A 33% daily risk for symptomatic infection in those using the hydrophilic catheters was identified. In institutional settings, the use of these catheters reduced infection rate by approximately 21% (Cardenas et al, 2011). Although limited to select male patients, when sphincter ablation is necessary, sphincterotomy using laser treatment is considered the ideal method (however, this is indicated in a very small number of patients) (Linsenmeyer, 2007).

New therapies continue to be proposed for patients with neurogenic LUT dysfunction refractory to medical therapies. The use of dorsal penile or clitoral nerve stimulation for controlled neurogenic detrusor overactivity has been described. Hansen and colleagues (2005) studied a group of 16 patients (2 women and 14 men) with neurogenic detrusor overactivity and diminished bladder capacity associated with complete or incomplete SCI. After stimulation of the dorsal nerve, 13 of 16 were noted to have increased bladder capacity and improved storage pressures during stimulation. The average bladder capacity increase was 53% in the study group. Detrusor pressures were also modulated below those associated with ureterovesical reflux.

Pudendal nerve stimulation has been used for improving neurogenic voiding dysfunction. Spinelli and associates (2005) treated 15 patients with varied types of neurogenic voiding dysfunction. After pudendal stimulation, there was a significant decrease in incontinence episodes, with 8 of 15 patients becoming continent during stimulation, and 2 with improvement approximating 90%. Twelve of 15 ultimately progressed to permanent implantation. In the chronically implanted patients, maximal cystometric capacity

was noted to significantly increase and maximum detrusor pressure was also noted to decrease substantially. Neurophysiologic guidance was considered critical for adequate implantation.

Another form of neuromodulatory therapy for which more experience is being reported in SCI is anterior root stimulation. One of the largest experiences with sacral deafferentation and anterior root stimulator implantation was reported by [Kutzenberger and colleagues \(2005\)](#). A total of 464 paraplegic patients received this intervention, with most patients receiving the intradural approach. At a mean of 6.6 years, 440 of these patients were available for long-term follow-up. Complete deafferentation was successful in 94% of patients; 420 patients used the sacral anterior root stimulator for voiding, and 401 used it for defecation. Overall, 364 (83%) patients were continent. Postoperatively, UTIs decreased from a mean of six to a mean of one and kidney function remained stable in this population. Complications included cerebrospinal fluid leaks in 6 patients and infected implants in 5. In addition, later complications included device failure or cable failure in 35 patients. It is interesting to note that autonomic dysreflexia also disappeared or was resolved in most of these cases. Recently, the Dutch experience with the Brindley bladder stimulator compared with a matched control group was reported; 93 stimulator-implanted patients were compared with a control group of 70 new patients with SCI and neurogenic detrusor overactivity. The main outcomes in the study were quality of life as assessed by the Qualiveen metric. In those patients implanted, long-term stimulators were still used for voiding dysfunction in 63% of the patients (46 patients). Those patients with functional stimulator implants had substantially improved symptom scores and general quality-of-life ratings in addition to improved continence and fewer UTIs as compared with the control group. Apparently, the associated rhizotomy appeared to benefit even patients who had deactivated their stimulator device. The follow-up for these individuals after implant ranged from 1 to 3 years ([Martens et al, 2011](#)).

The future of urinary tract dysfunction related to SCI may be dependent on advances in the use of stem cells for spinal cord repair. However, difference in study type, model used, type of stem cells, and techniques used for stem cell implantation and perpetuation have yet to be standardized for purposes of assessing the potentials of this therapy for impact on long-term urinary function ([Snyder and Teng, 2012](#)).

As a treatment of last resort, urinary diversion may provide significant functional improvement in addition to improved quality of life in selected patients with neurologic dysfunction (e.g., those unable to catheterize). One method for management of incontinence or other refractory storage issues related to neurogenic bladder is bladder neck closure associated with chronic suprapubic catheter management. In a retrospective review of 35 patients undergoing this intervention for a variety of conditions (SCI, 71%; MS, 23%; CVA, 9%) the majority of patients had adequate response to therapy. Only 2 patients were incontinent at follow-up. Overall complications were experienced by 17% of patients ([Colli, 2011](#)). In another assessment of bladder neck closure and suprapubic tube placement, 29 patients were assessed for the efficacy of this intervention (MS, 48%; SCI, 28%; myelodysplasia, 17%). Bladder neck closure was performed via a retropubic approach in most patients at the time of suprapubic tube placement. Eight of 29 patients had persistent incontinence, 2 with peristomal leakage and 6 with urethral leakage. Catheter complications were associated with 7 of the

8 urinary leaks. Perineal bladder neck closure was associated with much higher fistula rates than retropubic approaches. In addition, poor catheter management also resulted in worse success rates ([Ginger et al, 2010](#)). [Stein and colleagues \(2005\)](#) reported on 24 patients undergoing Mainz pouch diversion. Urinary diversion was associated with stability of the upper tracts and daytime continence but with some nocturnal incontinence per stoma. Comparing this group with a separate group of patients undergoing bladder augmentation with suburethral fascial sling, all patients in the augmentation group had stability of the upper tracts and 8 of 10 were continent. Both alternatives were considered adequate for neurogenic voiding dysfunction. Ileovesicostomy also is an option for the management of the neurogenic bladder. In a report of 15 individuals undergoing ileovesicostomy (7 open and 8 robotic), surgical robotic operative times were substantially longer than with open cases; however, there were trends toward less blood loss and shorter hospital stays in the robotic group. With both procedures, there was an improvement in urinary continence from baseline and a trend toward decreased UTI. Overall costs were substantially greater with the robotic versus the open group despite differentials in length of stay. This further underscores the need for further larger studies to assess the possible role of advanced minimally invasive technology for this condition ([Vanni and Stoffel, 2011](#)).

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The complete reference list is available online at www.expertconsult.com.



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Terminology and Definitions

Pathophysiology and Etiology

Prevalence and Costs

Clinical Assessment

Initial Treatment Outline

Specialized Evaluation and Management Outline

Specialized Treatment Outline

TERMINOLOGY AND DEFINITIONS

The International Continence Society (ICS) Standardization Committee categorized the symptom syndromes suggestive of lower urinary tract dysfunction (Abrams et al, 2002). They stated that urinary urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as the overactive bladder (OAB) syndrome, urge syndrome, or urgency-frequency syndrome if there is no proven infection or other obvious pathology. To be consistent with the individual component lower urinary tract symptoms (LUTS), “urgency incontinence” (Abrams et al, 2009) and “increased daytime frequency” should be in the descriptions used in place of “urge incontinence” and “frequency,” respectively. Thus the current definition of OAB is urinary urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology.

The definitions of the component storage LUTS included in OAB were also standardized by the ICS. Urgency is the complaint of a sudden compelling desire to void that is difficult to defer. It is the OAB symptom with the greatest impact on patients (Milsom et al, 2012). Urgency is an abnormal sensation and should not be confused with the normal sensation of a strong desire to void. Urgency is a term used for sensations reported by patients with OAB, but also by patients with bladder pain syndrome (BPS). The sudden compelling desire to void in these separate patient groups probably differs in character. In OAB, patients may feel as if they are going to leak, even if they say they never have, and they commonly express anxieties exemplified by phrases such as:

- “When I’ve got to go, I’ve got to go.”
- “When I want to go, I have to rush because I think I may wet myself.”

Hence “fear of leakage” is an important concept to OAB patients. In BPS, the compelling desire to void is driven by fear of pain emerging if the bladder is allowed to fill further, but not “for fear of leakage.” In both OAB and BPS, urgency, increased daytime frequency, and nocturia can be present (Fig. 76-1).

Urgency urinary incontinence (UUI) is defined as involuntary leakage of urine, accompanied or immediately preceded by urgency (Abrams et al, 2002). UUI should be diagnosed regardless of whether it causes problems such as social or hygiene effects. In a prevalence survey, 69% of women experienced “any incontinence,” but only 30% found this a “social or hygienic problem” (Swithinbank et al, 1999).

The symptom of increased daytime frequency is the complaint by the patient who considers that he or she voids too often by day. There is no minimum number of voids included in the

standardized definition, and there is currently insufficient research evidence on which to base a threshold for defining increased daytime frequency. The symptom of **nocturia is the complaint that the individual has to wake at night one or more times to void.**

The introduction of the standardized definitions addressed a confusing situation that hampered research and management. The English-speaking world had adopted Patrick Bates’s term *unstable bladder* to describe involuntary detrusor contractions seen during urodynamic studies as the bladder was filled, whereas the Scandinavians used the term *detrusor hyperreflexia*. To resolve the discrepancy, the ICS designated the term *unstable bladder* to be applied where there was no obvious cause for the contractions and *detrusor hyperreflexia* for patients whose involuntary contractions were caused neurologically (Bates et al, 1980a, 1980b). Nonetheless, the use of different terms in neurologic and non-neurologic patient groups became increasingly difficult. “Overactive Bladder” was used as the title of a consensus conference, and a formal definition was proposed in 1999 (Abrams and Wein, 1999), culminating in the unified ICS definition used currently (Abrams et al, 2002). For women, another terminology document, jointly drafted by the International Urogynecology Association and the ICS, was published more recently (Haylen et al, 2010).

The current definition of OAB is based on symptoms; in contrast, detrusor overactivity (DO) is a urodynamic observation, characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked (Abrams et al, 2002). OAB and DO are thus not interchangeable terms, signified by the recognition that OAB patients undergoing urodynamic testing may not have DO (especially continent OAB patients). Conversely DO seen during urodynamics may not be associated with any sensation.

KEY POINTS: OVERACTIVE BLADDER TERMINOLOGY

- The current definition of OAB is urinary urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology.
- OAB is a symptomatic diagnosis and is distinct from DO, which is a urodynamic observation.
- Urgency is an abnormal sensation, defined as the complaint of a sudden compelling desire to void that is difficult to defer.
- “Fear of leakage” and “fear of pain” distinguish urgency in OAB from BPS.

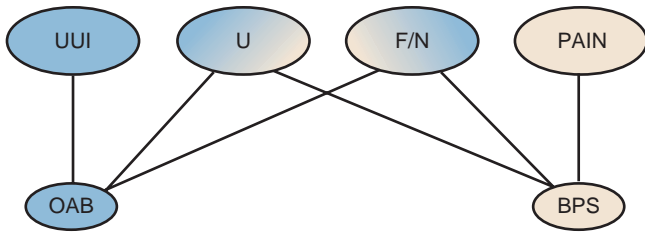


Figure 76-1. Overactive bladder (OAB) and bladder pain syndrome (BPS) both give rise to urgency (U), frequency (F), and nocturia (N); pain, but not urgency urinary incontinence (UUI), is seen in BPS.

PATHOPHYSIOLOGY AND ETIOLOGY

Basic science research into OAB has to use indirect or surrogate markers, because the basis of the condition relies on a subjective symptom of urgency. Thus there is no animal model of OAB, because reporting of subjective symptoms in animals is not possible (Parsons et al, 2011). Accordingly research focus has particularly concentrated on three key aspects: sensory activity, motor control, and reflexes of the lower urinary tract.

- Understanding abnormalities of **sensory nerve (afferent) signaling** is appropriate as it is presumed that urgency sensation largely derives from afferent input. The processes involved are signal transduction, afferent traffic, gating, sensitization, and conscious perception. The role of urothelium and the suburothelial layers of the bladder are now considered substantial contributors to the signal transduction and the afferent traffic through the release of mediators (Birder and Andersson, 2013), cellular interactions (Birder et al, 2010) and release of cytokines and growth factors (Andersson and McCloskey, 2014). Sensitization of bladder nerves by inflammation in the gut innervation has been demonstrated experimentally (Malykhina et al, 2012). Conscious perception is not well understood, but functional brain imaging has highlighted centers in the central nervous system (CNS) that could yield valuable information in the future.
- **Contractile (motor) function** comprises the motility of the detrusor muscle and also relevant drivers—for example efferent nerves, interstitial cells, and locally released mediators. Increasingly the focus has been to evaluate how these aspects summate in the contractility of the whole bladder, which is what determines the urodynamic observations. The whole organ can manifest areas of localized micromotions adjacent to quiescent areas in a constantly changing play of activity (Fig. 76-2). Thus full understanding of intravesical pressure will not be achieved until properties of the overall motile and nonmotile areas can be explained.
- The sensory information ascending in afferents is **integrated at several levels in the CNS** (Drake et al, 2010), where it converges with information from other relevant structures (Fig. 76-3). The integration of this information underpins the coordinated motor behavior of LUT reflexes. In the sacral spinal cord, there is some integration enabling reflex voiding, which is relevant in neonates and in neurologic disease. **The main regulatory region is at the level of the midbrain and brainstem**, where the periaqueductal gray and pontine micturition center integrate the key elements of vegetative function, including the voiding reflex. **At the higher levels of the CNS, more sophisticated aspects are integrated, for example consciousness (LUT sensations, as opposed to subconscious sensory information), awareness of environmental suitability, and voluntary initiation.** There is probably some basic integration in the periphery as well, where interactions may occur between urothelium, interstitial cells, and detrusor muscle (Drake, 2007).

The development of functional brain imaging technology allows estimation of gross activity in specific brain areas and has been used to study bladder filling in normal and symptomatic individuals

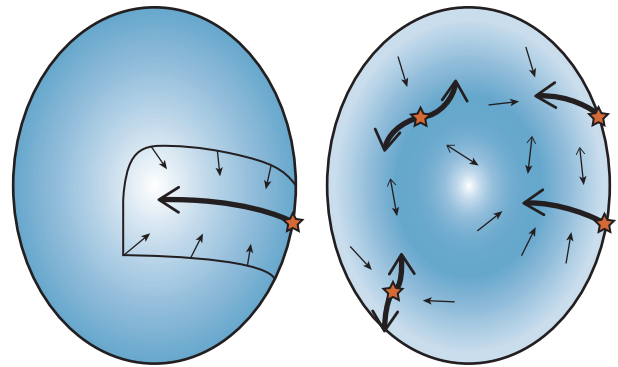


Figure 76-2. *Left*, Schematic representation of a whole bladder during urinary storage, illustrating a localized “micromotion” contraction, starting from an initiation point (star), and spreading to a limited part of the bladder wall. Such activity is characteristic of the normal isolated bladder in all species tested (including human), and it is associated with only small fluctuations in bladder pressure (Drake et al, 2003a, 2003b), presumably because the noncontracting part of the bladder stays relaxed. In the overactive bladder (*right*), multifocal trigger points lead to continuous activity; this enhances the effect on bladder pressure (as the bulk of the bladder is active) and stimulates afferents by the extensive distorting movements.

(Griffiths, 2011). Intriguing insights into contributions from various parts of the cerebral cortex such as the insula and the prefrontal cortex have resulted. Alterations in the regional brain activity of symptomatic individuals with OAB have been reported (Griffiths et al, 2007). Understanding brain responses to lower urinary tract activity through autonomic afferent processing networks, as is already under investigation for the gastrointestinal tract, will be crucial in the endeavor to improve insight into the clinical setting.

Afferent Mechanisms in Overactive Bladder and Detrusor Overactivity

In theory, increased sensory activity may give rise to increased sensation, and hence OAB. Thus the properties of the bladder afferents and factors that influence them are highly relevant in OAB. **The afferent nerve endings are widely distributed in the bladder wall and are particularly dense in the connective tissue underneath the urothelium.** The urothelium itself possesses sensory and signaling properties somewhat resembling the characteristics of the afferent nerves. Suburothelial interstitial cells lie in close physical proximity to the nerve fibers, suggesting that these cells may also participate in sensory transduction or its regulation (Wiseman et al, 2003). Accordingly, transduction of sensory stimuli in the bladder into afferent activity probably comes from the interaction of several cell types (Birder and Andersson, 2013).

The afferent nerve fibers include fast-conduction A delta fibers and slower-conducting unmyelinated C fibers. A delta fibers largely respond to passive bladder distention and active detrusor contraction (“in series” mechanoreceptors (Iggo, 1955), thus conveying information about bladder filling (Janig and Morrison, 1986). C fibers are regarded as responding primarily to chemical irritation of the bladder mucosa (Habler et al, 1990) or to thermal stimulus (Fall et al, 1990). Accordingly they may be less active in the physiologic state than the A delta fibers. Nonetheless there is almost certainly considerable overlap in the sensory information carried by the two types of afferent, and the C fibers may take on a more prominent role in pathophysiologic states (Juszczak et al, 2009).

The afferents express a wide range of surface proteins, which may generate or modulate sensory activity. Several members of the transient receptor potential (trp) superfamily are seen on bladder afferents (Avelino et al, 2013), and they provide a tool for studying physiologic properties. One of the best known is the

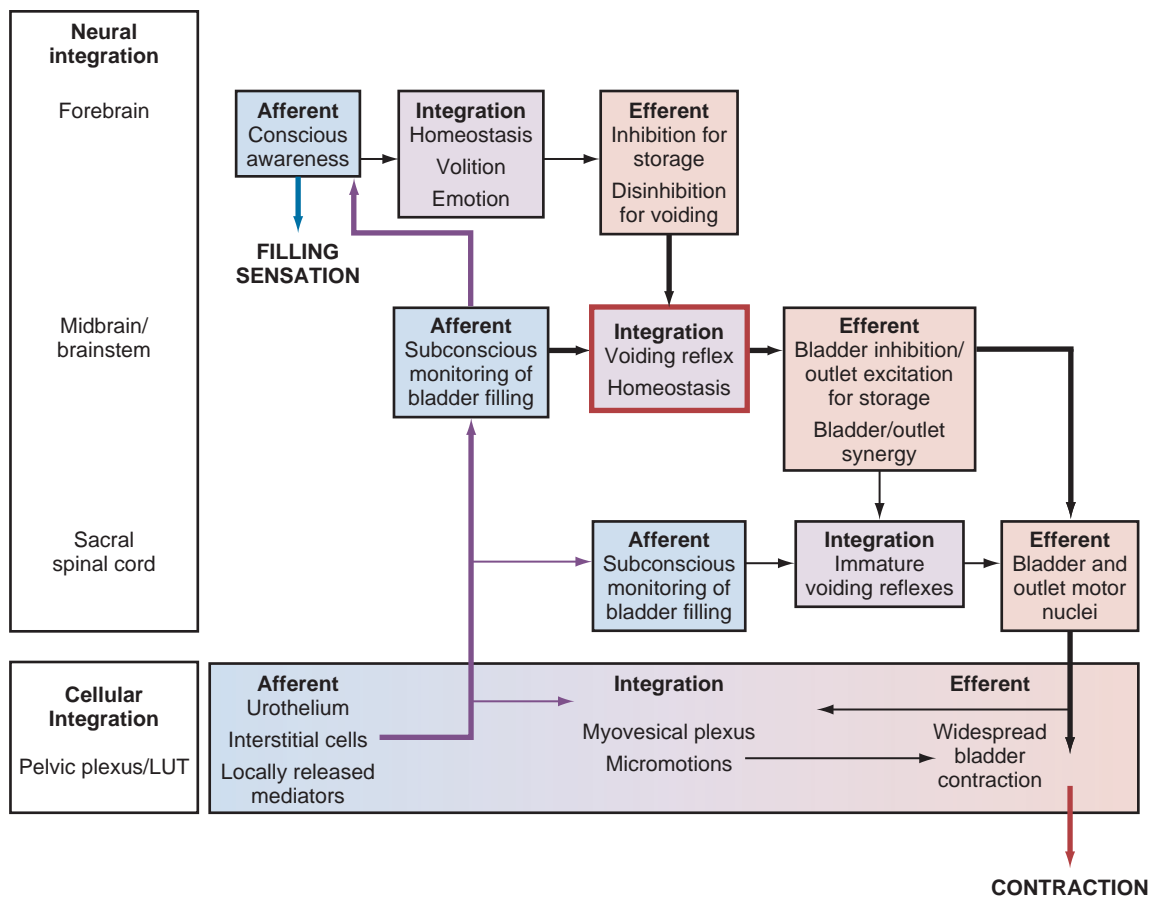


Figure 76-3. Central nervous system circuitry controls the lower urinary tract (LUT) at multiple levels. Sensory information in afferent is affected by peripheral factors, such as mediators and urothelium. It is carried centrally with some input to the sacral cord, which is important for voiding in infants, and it ascends to the midbrain where it inputs to the pontine micturition center (PMC). At this level there is widespread integration of information from vegetative organs, which is crucial for homeostasis. Sensory information is relayed on to the forebrain, where conscious awareness (sensation) is mediated. The forebrain also mediates voluntary control, including the active decision not to pass urine (storage) or to initiate voiding in the right circumstances. Descending forebrain inputs to the PMC allow the switching from storage to voiding phase, with the synergic regulation of the sacral nuclei responsible for bladder contraction and outlet relaxation. There is also possible integration of sensory information in the periphery, contributing to the generation of bladder motility.

vanilloid receptor (trp-V1), which is the target of capsaicin and resiniferatoxin—two compounds previously used for clinical management of neurogenic bladder dysfunction. Purinergic receptors can also influence bladder afferent activity (Munoz et al, 2012). Indeed a range of targets is feasible, but it is unclear whether there are any whose distribution in the body is sufficiently confined so that they could be suitable for treating LUT dysfunction. The trophic influence of growth factors in maintaining the afferent nerves is important physiologically, and some research suggests downregulation of nerve growth factor may mitigate surrogate markers of OAB in animal models (Kashyap et al, 2013).

In theory, OAB may arise if the level of sensory activity is inappropriately high for any given degree of bladder distention, resulting from pathologically sensitized or abnormally numerous afferent nerve endings. The interaction among afferents, urothelium, and interstitial cells is thus interesting, in that modulating their interactions may result in amelioration of symptom severity.

Hypotheses of Detrusor Overactivity

Hypothetical reasoning has been used to conceptualize the clinical observations, particularly for DO. The **neurogenic hypothesis** states that DO arises from generalized, nerve-mediated excita-

tion of the detrusor muscle (de Groat, 1997). Nerve-mediated detrusor excitation is normal during voiding, where it is associated synergically with relaxation of the bladder outlet. However, nerve-mediated detrusor excitation should not occur during urine storage because of inhibitory influences within the CNS. **Emergence of inappropriate excitation during storage implies loss of inhibition, re-emergence of primitive spinal bladder reflexes, acquisition of new reflexes, or sensitization of afferents.** The extent to which inappropriate bladder contraction during storage is associated with outlet relaxation will depend on the precise changes present.

The **myogenic hypothesis** suggests that overactive detrusor contractions result from a combination of an increased likelihood of spontaneous excitation within the smooth muscle of the bladder and enhanced propagation of this activity to affect an excessive proportion of the bladder wall (Brading and Turner, 1994; Brading, 1997). Patchy denervation is a common observation in DO, regardless of etiology (German et al, 1995; Charlton et al, 1999; Drake et al, 2000; Mills et al, 2000). A smooth muscle cell deprived of its innervation shows an upregulation of surface membrane receptors and may have altered membrane potential, which increases the likelihood of spontaneous contraction in that cell. DO is also associated with structural changes (Elbadawi et al, 1993;

Haferkamp et al, 2003a, 2003b), which could facilitate the excessive spread of spontaneous contractions throughout a wider proportion of the bladder than normal. Although the observations in different models of DO and from clinical specimens do not uniformly describe these features, understanding of altered smooth muscle behavior remains a relevant factor for understanding DO.

The integrative hypothesis suggests that a range of triggers can generate localized detrusor contractions, which can spread in the bladder wall through various routes of propagation. Consequently, urgency is a result of distortions in the bladder wall, and it is associated with urodynamic DO if the contractions spread to a sufficient proportion of the bladder wall (Drake et al, 2001). Coolsaet and colleagues (1993) described localized contractions ("micromotions") in pigs, and these contractions were postulated as a basis for urinary urgency. They have been widely reported in normal animals and humans. Importantly, such micromotions are exaggerated in models of DO and in human OAB (Van Os-Bossagh et al, 2001; Drake et al, 2003a, 2003b; Gillespie et al, 2003; Drake et al, 2005). The thinking is that the normal small distortions caused by micromotions are detected by afferents, hence generating the sensation of bladder filling without change in detrusor pressure (see Fig. 76-2). In OAB, the distortions may be excessive as a result of exaggerated micromotions, and they will be associated with DO if the movements become coordinated across a substantial proportion of the bladder. There is considerable overlap between the myogenic and integrative hypothesis, as both allude to the increased peripheral excitability and propagation as key aspects of OAB and DO. The major difference is that the integrative hypothesis exploits the increasing knowledge of cellular physiology in the bladder to draw in the urothelium and interstitial cells as possible contributors in triggering and distributing both normal and pathologic excitation.

Etiology

Female gender is associated with a higher prevalence of OAB, particularly in younger people. A small influence of racial factors is also present; for men, prevalence among African-Americans is 20%, Hispanics 18%, and whites 15%, with the figures for women being 32%, 29%, and 29%, respectively (Coyne et al, 2013).

Neurologic disease is associated with a high prevalence of LUT dysfunction, and this is to be anticipated from the fundamental regulatory influence of the innervation on the bladder and its outlet. Given that most of the time people are storing urine (rather than voiding), it is likely that the CNS exerts continuous inhibitory influence on the bladder contractility. For example, the sympathetic nervous system may inhibit the detrusor muscle directly through β_3 adrenoceptors (Sadananda et al, 2013), or indirectly by inhibiting parasympathetic ganglia (de Groat, 1997). Thus neurologic disease may affect the continuous inhibition, leading to emergence of DO. Aging is clearly associated with increased LUTS, including OAB; the wide range of changes in cellular function and the CNS means that increasing OAB with aging is probably multifactorial. Partial bladder outlet obstruction (BOO) has long been considered an etiologic factor in the generation of DO and OAB, and BOO is a widely used means of generating enhanced nonmicturition contractions as an animal model of DO. However, the relationship between BOO and DO or OAB in humans is not clear-cut. Prevalence of OAB in women, in whom BOO is rare, is broadly similar to that in men in whom BOO is common because of prostate enlargement. Furthermore, DO rarely resolves with prostate surgery. Overall, BOO is probably a relevant factor, but the influence of BOO may be indirect, perhaps by accelerating some of the changes brought on by aging.

The overlap with other functional syndromes and other health influences indicates the need to recognize wider contributory factors to mechanisms underlying the emergence of OAB and its clinical assessment, particularly in relation to bowel function (Daly and Chapple, 2013; Kaplan et al, 2013), metabolic syndrome (Kirby et al, 2010), fibromyalgia (Chung et al, 2013), and hormonal status (Robinson et al, 2013).

KEY POINTS: OVERACTIVE BLADDER PATHOPHYSIOLOGY AND ETIOLOGY

- Sensory nerve activity is influenced by the urothelium and cytokines and is the basis of normal and OAB sensations.
- Efferent nerves and interstitial cells drive bladder contractility; micromotions are normal during the storage phase, but they can become multifocal and exaggerated in OAB.
- Integration of sensory information at multiple levels of the CNS underpins reflex control of the urinary tract, particularly in the midbrain and brainstem.
- The neurogenic hypothesis of DO suggests it arises from generalized, nerve-mediated excitation of the detrusor muscle.
- The integrative hypothesis suggests that a range of triggers can generate localized detrusor contractions, which spread in the bladder wall by various routes; triggering and propagation can occur primarily in the smooth muscle (myogenic hypothesis).
- Aging, neurologic disease, female gender, BOO, and metabolic disease are potential influences on OAB etiology.

PREVALENCE AND COSTS

Using the standardized ICS definition of OAB, the EPIC study (a population-based, cross-sectional telephone survey of adults aged ≥ 18 years in five countries) reported on the prevalence of OAB in four European countries and in Canada, indicating an overall OAB prevalence of 11.8% in the context of a prevalence of 64.3% for at least one of the LUTS (Irwin et al, 2006). The EPIC study also catalogued the multidimensional impact including effects on employment (Coyne et al, 2008b; Irwin et al, 2009). UUI prevalence has been estimated at 1.7% to 36.4% in U.S. populations, 1.8% to 30.5% in European populations, and 1.5% to 15.2% in Asian populations, with the prevalence dependent on age and gender (Milsom et al, 2014). Of 6000 subjects randomly identified from the population in Finland, the presence of any urgency was reported by 54% of respondents (Vaughan et al, 2011). A total of 11% of men and 26% of women reported any UUI. One in seven of all respondents with urgency and fewer than one in three with UUI reported at least moderate bother.

Older studies must be interpreted according to the definitions that the researchers used for LUTS. One prevalence study (Milsom et al, 2001) reported a prevalence of OAB symptoms that "occurred singly or in combination," estimating overall OAB prevalence at 16%. In the studied population, 9.2% experienced urgency, and this is perhaps closer to the true prevalence of OAB in the community.

The National Overactive Bladder Evaluation (NOBLE) study (Stewart et al, 2003) established the prevalence of OAB in more than 5000 community-dwelling individuals in the United States using a validated computer-assisted telephone interview. Men and women had the same prevalence of OAB overall (16.0% and 16.9%, respectively) as defined by the ICS. However, men were shown to have a higher prevalence of "OAB dry" (13.4% as opposed to 7.6% in women) and women had a higher prevalence of "OAB wet" (9.3% as opposed to 2.6% in men). It is assumed that the difference in the prevalence of incontinence is a result of the relative weakness of the bladder neck and the urethral sphincter mechanism in women, particularly in those who have had children, and the additional outlet resistance in men because of the presence of the prostate and the greater urethral length. In women, the prevalence of "OAB wet" rose from 2.0% in the youngest group (ages 18 to 24) to 19.1% in those 65 to 74 years of age. Men, on the other hand, did not experience an increase in "OAB wet" until they were older: 8.22% for those 65 to 74 and 10.2% for those 75 years and older.

The natural history of OAB is varied. Overall there is an increased prevalence of OAB that is associated with aging, and there is progression from "OAB dry" to UUI with the passage of time in

general populations (Irwin et al, 2010). For individuals, OAB can be stable for prolonged periods and remission can occur (Heidler et al, 2011).

In addition to simple prevalence, effects on quality of life need to be evaluated. These effects can occur through wide-ranging influences, for example, increased anxiety levels (Knight et al, 2012) and detrimental impact on sexual function (Cohen et al, 2008; Heidler et al, 2010), and quality of life is also affected by patient attitudes such as the expectation of cure (Renganathan et al, 2010). OAB is a long-term condition, and ongoing quality-of-life impairment can be anticipated in many patients (Garnett et al, 2009).

In some studies, the symptom of urgency was shown to have a greater effect on quality of life than incontinence (Coyne et al, 2004, 2008a, 2008b). EpiLUTS was an Internet-based survey of 30,000 people in the United States, United Kingdom, and Sweden, which documented symptoms, symptom bother, and health-related quality of life. It derived a substantial amount of information about the impact of LUTS, and it identified that storage symptoms were associated with significantly greater impact than other LUTS (Sexton et al, 2009).

Estimates of the overall costs of OAB must be considered with caution, as they depend on the accuracy of prevalence data and the cost components included in the analysis model (Coyne et al, 2014). In 2007, average annual per capita costs of OAB were \$1925, suggesting an overall total national cost in the United States of \$66 billion, of which \$49 billion were direct medical costs (Ganz et al, 2010). Health resource use is increased by indirect impacts, such as impaired productivity (Goren et al, 2014) and falls that occur when patients go to the toilet in urgency situations (Kurita et al, 2013). Costs to the patient include expenditure on containment products and laundry bills.

KEY POINTS: OVERACTIVE BLADDER PREVALENCE AND COSTS

- Overall prevalence of OAB is about 12% in the EPIC study, but estimated prevalence of OAB and UIUI varies widely among studies.
- Aging is associated with higher OAB prevalence in both men and women.
- OAB is generally progressive, but long-term stability and remissions can occur.
- Storage LUTS have a greater impact on health-related quality of life than other LUTS.
- Both genders have similar rates of OAB, but "OAB wet" is more prevalent in women and "OAB dry" is more prevalent in men.
- Substantial expenditure on OAB results from direct and indirect health care costs and patient expenses.

CLINICAL ASSESSMENT

OAB is a syndrome relating several of the storage LUTS, offering an empirical diagnosis that enables health care professionals to initiate preliminary treatment (Abrams et al, 2002). Patients with OAB may present to health care workers in various disciplines in either the community or the hospital services. The American Urological Association/Society for Urodynamics and Female Urology joint Guideline for OAB advocates the clinical principle that the clinician should engage in a diagnostic process to document symptoms and signs that characterize OAB and to exclude other disorders that could cause the patient's symptoms; the minimum requirements for this process are a careful history, physical exam, and urinalysis (Gormley et al, 2012). Because of the relatively nonspecific nature of storage LUTS, it is crucial that physicians consider the possibility of malignancy, neurologic disease or systemic disease. In some patients, additional procedures and measures may be necessary to validate an OAB diagnosis, exclude other disorders, and fully inform the treatment plan (Gormley et al, 2012).

History should cover the following:

1. Presence or absence, incidence, severity, bother, and effect on quality of life for each of the OAB symptoms (urgency, urgency incontinence, increased daytime frequency, and nocturia). Patients with urgency tend to describe frequent voids with a low typical voided volume. Nocturia is somewhat variable in OAB. Voiding and postmicturition LUTS, dysuria, hematuria, and LUT pain should also be assessed. **The most time-efficient and systematic way to explore contributory LUTS is to use a symptom assessment questionnaire.**
2. Nature and volume of fluid intake, recognizing that stimulants and polydipsia affect LUTS, and that patients may adapt their intake to reduce the impact of symptoms.
3. Whether occult neurologic disease could be present; for example, recent onset of OAB with symptoms of erectile dysfunction or tremor.
4. Obstetric and gynecologic history, previous surgery and/or radiotherapy, bowel symptoms, and medication history.
5. Other medical issues (e.g., poorly controlled closed-angle glaucoma, cognitive impairment, history of urinary retention, and impaired gastric emptying are relative contraindications to antimuscarinic therapy).

Focused physical examination requires abdominal and pelvic examination, general examination (e.g., peripheral edema), and basic neurologic examination. Assessment of bladder emptying is necessary (most simply by palpating the lower abdomen if the patient is slim). **Urinalysis is important in all patients** to exclude urinary tract infection, hematuria, and leukocyturia. However, **urodynamics, cystoscopy, and diagnostic renal and bladder ultrasound should not be used in the initial workup of the uncomplicated patient** (Gormley et al, 2012).

The algorithms from the fifth International Consultation on Incontinence (ICI) 2012 (Abrams et al, 2013) summarize the basic assessment necessary in the evaluation of lower urinary tract dysfunction in men, women, and the frail elderly (Fig. 76-4).

Instruments for Measuring Bladder Sensations and Storage Symptoms

Normal LUT sensations during cystometry are (1) first sensation of filling, (2) normal desire to void, and (3) strong desire to void (Wyndaele and De Wachter, 2002). Whether an individual with OAB also experiences normal sensations is not yet established but seems likely. In addition to the urinary tract sensations, cognitive aspects substantially influence voiding behavior (Harvey et al, 2012). Tools for evaluating urgency thus have to address the subjective nature of the symptom, the habit of preemptive voiding at low bladder volumes, and the consequent increased frequency with low levels of urgency, further complicated by adaptive behaviors such as restricting fluid intake. A validation process is necessary to ensure that the tools used are suitable for clinical or research situations (Avery et al, 2004; Abrams et al, 2006).

The urinary sensation scale (Abrams et al, 2005a) is as follows:

1. No urgency: "I felt no need to empty my bladder but did so for other reasons."
 2. Mild urgency: "I could postpone voiding as long as needed without fear of wetting myself."
 3. Moderate urgency: "I could postpone voiding for a short time without fear of wetting myself."
 4. Severe urgency: "I could not postpone voiding but had to rush to the toilet in order not to wet myself."
 5. Urgency incontinence: "I leaked before arriving at the toilet."
- Score 1 on the urinary sensation scale appears in line with a "convenience void," which has been defined as "a void without desire to void" (Honjo et al, 2010).

The urgency percentage scale (Cardozo et al, 2002) includes three possible responses:

1. I am usually not able to hold urine.
2. I am usually able to hold urine until I reach the toilet if I go immediately.

	MEN	WOMEN	FRAIL ELDERLY
	INITIAL MANAGEMENT		
HISTORY	Urgency/frequency, with or without incontinence	Incontinence with mixed symptoms	Active case finding
CLINICAL ASSESSMENT	<p>General assessment</p> <p>Urinary symptom assessment and symptom score (including FVC and questionnaire)</p> <p>Assessment QoL and desire for treatment</p> <p>Urinalysis ± urine culture; if infected, treat and reassess</p>	<p>Physical examination; abdominal, pelvic and perineal</p> <p><i>If appropriate</i></p> <p>Cough test to demonstrate stress incontinence</p> <p>Assess estrogen status and treat as appropriate</p> <p>Assess voluntary pelvic floor muscle contraction</p> <p>Assess postvoid residual volume</p>	<p>Assess, treat and reassess potentially treatable conditions, including relevant comorbidities and ADLs</p> <p>Assess QoL, desire for treatment, goals for treatment, patient and caregiver preference</p> <p>Targeted physical exam including cognition, mobility, neurologic and rectal exams</p> <p>Urinalysis</p> <p>Consider frequency volume charts or wet checks, especially if nocturia present</p>
Presumed diagnosis	OAB with or without URGENCY INCONTINENCE	MIXED INCONTINENCE (treat most bothersome symptom first)	
Management	<p>DISCUSS TREATMENT OPTIONS WITH THE PATIENT</p> <p>Lifestyle interventions</p> <p>Pelvic floor muscle training ± biofeedback</p> <p>Scheduled voiding (bladder training)</p> <p>Incontinence products</p> <p>Antimuscarinics (OAB ± urgency incontinence) and alpha adrenergic antagonists (if also bladder outlet obstruction)</p>	<p>Lifestyle interventions</p> <p>Pelvic floor muscle training for SUI or OAB</p> <p>Bladder retraining for OAB</p> <p>Antimuscarinic (OAB ± urgency incontinence)</p>	<p>Lifestyle interventions</p> <p>Behavioral therapies</p> <p>Consider additional trial of antimuscarinic drug</p> <p>Treat significant postvoid residual</p> <p>If insufficient improvement, reassess for treatment of contributing comorbidity ± functional impairment</p>
	Failure		
	SPECIALIST MANAGEMENT		
HISTORY	Incontinence with urgency/frequency	Incontinence with mixed symptoms	
CLINICAL ASSESSMENT	Consider urodynamics and imaging of the urinary tract	Assess for pelvic organ mobility/prolapse	If continued insufficient improvement or severe associated symptoms are present, consider specialist referral as appropriate per patient preferences and comorbidity
Diagnosis	Urgency incontinence due to DO	Urodynamics	
Management	<p>Mixed incontinence</p> <p>Treat major component first</p>	<p>Mixed incontinence (SUI/DOI)</p> <p>DOI</p> <p>Treat most bothersome symptom first</p>	
	<p>α-Blockers, 5ARI</p> <p>Correct anatomic BOO</p> <p>Antimuscarinics</p>	<p>Intermittent catheterization</p> <p>Antimuscarinics</p>	<p>If initial therapy fails:</p> <p>Stress incontinence surgery</p> <p>Bulking agents</p> <p>Tapes and slings</p> <p>Colposuspension</p>
		<p>If initial therapy fails:</p> <p>Botulinum toxin</p> <p>Neuromodulation</p> <p>Bladder augmentation</p>	

Figure 76-4. Overactive bladder in men, women, and the frail elderly; assessment and management derived from the respective algorithms of the fifth International Consultation on Incontinence (Abrams et al, 2013). ADLs, activities of daily living; 5ARI, 5α-reductase inhibitor; BOO, bladder outlet obstruction; DO, detrusor overactivity; DOI, detrusor overactivity incontinence; FVC, frequency volume chart; OAB, overactive bladder; QoL, quality of life; SUI, stress urinary incontinence; USI, urodynamic stress incontinence.

Delirium

Infection

Pharmaceuticals

Psychological

Excess urine output

Reduced mobility

Stool impaction and other factors

Don't overtreat asymptomatic bacteriuria

3. I am usually able to finish what I am doing before going to the toilet.

The Indevus “Urgency Severity Scale” (Bowden et al, 2003), used in trials of tiroprism, includes four responses:

0. None, no urgency.
1. Mild, awareness of urgency but easily tolerated.
2. Moderate, enough urgency/discomfort that it interferes with usual activities/tasks.
3. Severe, extreme urgency/discomfort that abruptly stops all activities/tasks.

A related strategy used an “urgeometer” (Oliver et al, 2003) in cystometry, which instructs patients to press sequentially a series of five buttons during bladder filling according to their degree of urgency:

0. None.
1. Mild.
2. Moderate.
3. Strong.
4. Desperate.

However, the lower three descriptions on these scales do not explain to patients how urgency is defined; thus the buttons are perhaps inappropriately named because they actually measure intensity of bladder sensation in differing parts of the sensation spectrum. Other measures such as “warning time” (between first sensation of urgency and eventual voiding) also depend on the patients and the clinicians reaching a consensus about the meaning of urgency (Cardozo and Dixon, 2005).

Storage symptoms questionnaires are now available in a modular format, developed to address recommendations made by the International Consultation on Incontinence Questionnaire (ICIQ) group (Abrams et al, 2006). The ICIQ group has adopted several validated tools and has developed new ones where necessary. The King’s Health Questionnaire (Kelleher et al, 1997) and the OAB-q (Coyne et al, 2002) have been adopted as ICIQ modules. A shortened form of the OAB-q has been validated more recently (Coyne et al, 2015).

Urgency assessment is a component of the more generic assessment tools for LUTS and may be of more practical use in clinical practice. For example, the “Patient Perception of Bladder Condition” is a straightforward means to administer and capture the clinical significance that patients attribute to their OAB (Coyne et al, 2008a).

The frequency volume chart (FVC) (Abrams and Klevmark, 1996) remains the principal method for evaluating frequency and nocturia in an objective way. In OAB, the pattern of voided volumes is characteristically erratic. On the FVC, frequency is defined as the number of voids recorded during waking hours including the last void before sleep and the first void after waking and rising in the morning (Abrams et al, 2002). The FVC is valuable for highlighting factors that may hinder successful OAB management, such as nocturia caused by nocturnal polyuria, or other causes of sleep disturbance (Cornu et al, 2012). The maximum voided volume on an FVC can be used as a measure of OAB severity, and it has also been used to estimate severity of DO (Miller et al, 2002). The bladder diary additionally collects information on fluid intake and incontinence episodes. A symptom scale has been evaluated for use in conjunction with a bladder diary validated by the ICIQ group in nonselected populations (Bright et al, 2012, 2014) (Table 76-1).

The Patient Perception of Intensity of Urgency Scale (PPIUS) is a five-point scale designed to rate the level of urinary urgency for each void during completion of a micturition diary (Cartwright et al, 2011).

0. No urgency: I felt no need to empty my bladder but did so for other reasons.
1. Mild urgency: I could postpone voiding for as long as necessary without fear of wetting myself.
2. Moderate urgency: I could postpone voiding for a short while without fear of wetting myself.
3. Severe urgency: I could not postpone voiding but had to rush to the toilet in order not to wet myself.
4. Urge incontinence: I leaked before arriving at the toilet.

TABLE 76-1 Bladder Sensation Scale Used in the International Consultation on Incontinence Questionnaire Bladder Diary

SCALE	DESCRIPTION
0	If you had no sensation of needing to pass urine, but passed urine for “social reasons,” for example, just before going out or because you are unsure where the next toilet is
1	If you had a normal desire to pass urine and no urgency. Urgency is different from normal bladder feelings and is the sudden compelling desire to pass urine that is difficult to defer, or a sudden feeling that you need to pass urine and if you don’t you will have an accident
2	If you had urgency but it passed before you had to visit the toilet
3	If you had urgency and managed to get to the toilet, still with urgency, but did not leak urine

From Bright E, Cotterill N, Drake M, et al. Developing a validated urinary diary: phase 1. *Neurourol Urodyn* 2012;31(5):625–33.

During cystometry, subjects are usually asked to report sensations and are questioned by the investigator about the sensations. These sensations are then mapped onto the following categories: **first sensation of bladder filling** (defined as the first awareness of bladder being filled), **first desire to void** (defined as the desire to pass urine at the next convenient moment but voiding can be delayed if necessary), **strong desire to void** (defined as a persistent desire to void without the fear of leakage), and **urgency** (defined as a sudden compelling desire to void). This approach is consistent when retested after an interval of 1 week (Van Meel and Wyndaele, 2011). A visual analog scale has been described for assessing sensation (Dompeyre et al, 2007). The latter study suggested that the filling sensation is a continuum, which means that it is a single sensation of a desire to void that increases continually during filling.

Increased frequency may be a behavioral response to urgency, as patients attempt to reduce the incidence of severe urgency or incontinence, and this can be assessed with additional interpretations of the measures mentioned previously. The total urgency and frequency score (TUFS) (Chapple et al, 2014) is calculated by adding the PPIUS scores of every void by a patient in the patient’s urinary diary, and dividing this number by the number of days recorded in the diary. The OAB symptom composite score (Zinner et al, 2005) is derived by summation from the Indevus Urgency Severity Scale, but it has not been validated.

Mixed Symptoms Incorporating Urinary Urgency

OAB can coexist with stress urinary incontinence (SUI). Mixed urinary incontinence (MUI) is the **complaint of involuntary leakage associated with urgency and with exertion, effort, sneezing, or coughing** (Abrams et al, 2002). Thus in MUI, both SUI and urgency incontinence (“OAB wet”) are present in the same person. A person with SUI and “OAB dry” does not have MUI; no suitable phrase has yet been standardized for this situation, so such a patient’s mixed symptoms should be categorized descriptively. For example, it may be necessary to state that the patient experiences SUI and urgency but does not have UUI.

The coexistence of urinary and anal incontinence can be referred to as “mixed incontinence,” and it should not be confused with MUI. Figure 76-5 describes the relationships among SUI, MUI, and OAB. In general, MUI is associated with more severe levels of leakage, although the relative contributions of the two types of incontinence can be difficult to clarify. Clarity of communication is necessary to ensure all parties are aware of the specific situation for each individual under consideration.

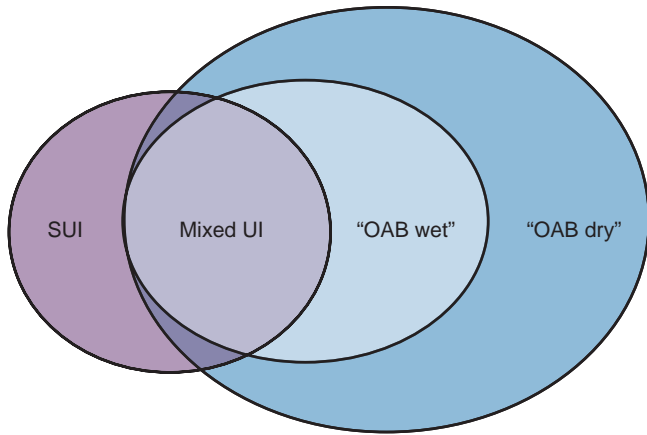


Figure 76-5. Incontinence may be stress urinary incontinence (SUI), mixed urinary incontinence (MUI), or urgency urinary incontinence (“overactive bladder [OAB] wet”), especially in women. SUI can coexist with “OAB dry,” giving rise to mixed symptoms of stress incontinence and urgency.

Distinguishing Overactive Bladder from Bladder Pain Syndrome

Older standardizations defined urgency as a strong desire to void accompanied by the fear of leakage or the fear of pain (Abrams et al, 1988). However, the urgency of OAB characteristically does not include pain; where pain causing urgency is reported, it is categorized as BPS (see Fig. 76-1) (Abrams et al, 2005b; Hanno et al, 2008). BPS is defined as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology. The relationship between urgency and filling sensation is different in OAB and BPS (Fig. 76-6).

Differences that help to distinguish BPS include the painful nature of symptoms, the steady increase in pain with filling, the more consistent voided volumes compared with OAB, and the ability to defer voiding (albeit at the cost of greater pain). In BPS, suprapubic pain is usual and additional perineal (urethral/vaginal/penile) discomfort and/or pain can also occur (FitzGerald et al, 2005); in OAB, urgency is typically felt in the perineum/base of penis or vagina/urethra.

KEY POINTS: OVERACTIVE BLADDER CLINICAL ASSESSMENT

- The minimum requirements to document symptoms and signs of OAB and to exclude other potential causative disorders are a careful history, physical exam, and urinalysis.
- Physicians must consider the possibility of malignancy, neurologic disease, systemic disease, or a significant postvoid residual.
- The most time-efficient and systematic way to evaluate OAB is to use a symptom assessment questionnaire.
- The FVC is the principal method for evaluating frequency and nocturia in an objective way.
- Urodynamics, cystoscopy, and diagnostic renal and bladder ultrasound should not be used in the initial workup of the uncomplicated patient.
- MUI is the complaint of involuntary leakage associated with urgency and with exertion, effort, sneezing, or coughing.
- Unlike OAB, in BPS there is a steady increase in pain with filling, more consistent voided volumes, and the ability to defer voiding.

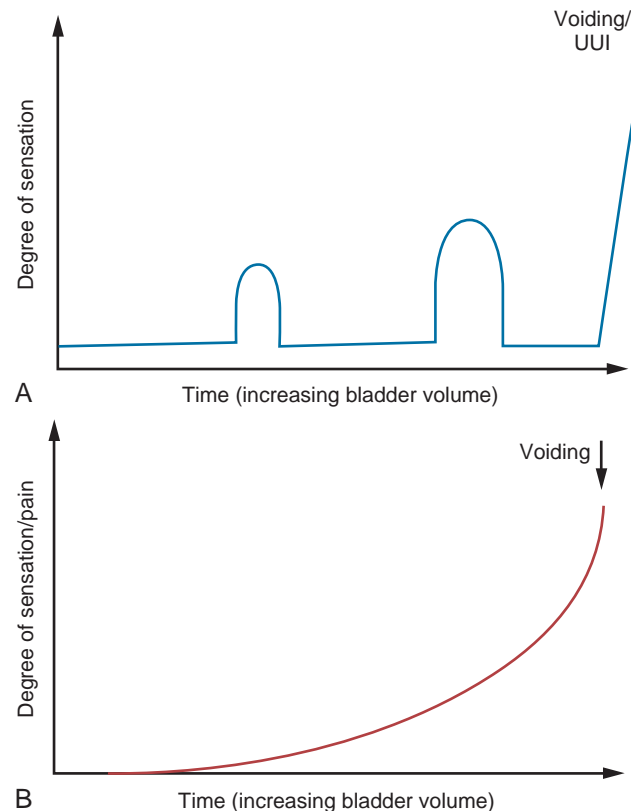


Figure 76-6. The differences in the development of bladder sensation in overactive bladder (OAB) and bladder pain syndrome (BPS). A, In OAB, phasic increases in urgency arise and recede as filling progresses, until severe urgency compels the patient to void or an urgency urinary incontinence (UUI) episode sets in. B, In BPS, pain increases throughout filling, accelerating as filling progresses.

INITIAL TREATMENT OUTLINE

After the diagnosis and baseline severity of OAB have been evaluated, initial treatment can be instigated according to the patient's desire for treatment. It is common practice to use conservative management and oral pharmacotherapy without a urodynamic diagnosis. Because “cure” is not a realistic aspiration, and the condition is generally progressive, appropriate expectations and honest explanation are crucial.

1. After assessment has been performed to exclude conditions requiring treatment and counseling, “no treatment” is an acceptable choice made by some patients and caregivers (Gormley et al, 2012).
2. Lifestyle interventions such as education about the condition, attention to the nature and volume of fluid intake, dietary irritants, and cessation of smoking foster in patients a sense of engagement in their own care.
3. Bladder training and pelvic floor muscle training help patients to reestablish inhibitory control over bladder storage and allow patients to resist and abort urgency episodes.
4. **Drug treatments should be used after conservative approaches have been undertaken**, and these are described in more detail in Chapter 79. If recommending antimuscarinic medication, prescribers should warn the patient about potential side effects including dry mouth, constipation, cognitive effects, visual impairment, and others (Leone Roberti Maggiore et al, 2012). A range of agents and doses is available, and patients should be advised that the idiosyncratic nature of responses means that it may take some adjustment to find an optimum regimen. **Extended release formulations should preferentially be prescribed in favor of short-acting formulations** because of lower rates of dry mouth (Gormley et al, 2012), and if a patient

experiences inadequate symptom control and/or unacceptable adverse drug events with one antimuscarinic medication, then a dose modification or a different antimuscarinic medication may be tried. A β_3 -adrenergic agonist has been introduced for the treatment of OAB, and this provides a new approach to the pharmacotherapy of OAB (Nitti et al, 2013). For men, α_1 -adrenergic blockers are widely used, and they are first-line drug therapy if voiding symptoms are also present (Oelke et al, 2013). For men with LUTS suggestive of OAB pathophysiology, inclusion of an antimuscarinic in first-line therapy is an appropriate option (Drake, 2012). The use of an antimuscarinic in the treatment of a man with BOO and concomitant OAB seems to ameliorate the symptoms and to provide a moderate improvement in quality of life (Athanasopoulos et al, 2011). Incidence of acute urinary retention in men receiving antimuscarinics with or without an α_1 -adrenergic blocker is up to 3% (Kaplan et al, 2011). The availability of various medications for OAB, along with drugs for voiding LUTS in men, provides the potential for combination therapies, which are likely to evolve substantially in the foreseeable future.

In evaluating response, repeat use of the symptom assessment questionnaire is valuable in providing objective markers before and after therapy initiation, as subjective perceptions and recollections of LUTS can be unreliable.

KEY POINTS: INITIAL THERAPY OF OVERACTIVE BLADDER

- After the diagnosis and baseline severity of OAB have been evaluated, initial treatment can be instigated according to the patient's desire for treatment. Repeat use of the symptom assessment questionnaire is more reliable than patient impression in identifying treatment response.
- It is common practice to use conservative management and oral pharmacotherapy without a urodynamic diagnosis.
- Some patients might elect not to receive treatment for OAB.
- First-line treatment is lifestyle intervention, bladder training, and pelvic floor muscle training, and these should precede drug treatments.
- Drug options for both genders include antimuscarinics and a β_3 -adrenergic agonist, and treatment needs to be tailored according to efficacy and adverse effects.
- For men, α_1 -adrenergic antagonists are an additional option.
- Combination therapies may yield additional benefits, for which research is ongoing.

SPECIALIZED EVALUATION AND MANAGEMENT OUTLINE

Where the initial treatment response is deemed inadequate and specialist referral is made, the specialist clinician must review the diagnosis, look for complicating factors, and ensure that suitable initial therapy has been provided. Before urodynamic tests are requested, the potential reasons for "failure" of drug therapy should be explored:

1. Failure to undertake conservative measures before drug prescription.
2. Insufficient duration of prescription.
3. Poor patient compliance.
4. Insufficient dose; individual patients absorb and metabolize drugs differently, so dose titration may be necessary to achieve a therapeutic level. Presence of dry mouth symptoms is a useful rule of thumb for deciding whether dose is adequate.
5. Variability of response; some people appear to find better efficacy with certain agents.
6. Partial response; if urgency and increased daytime frequency have improved, persisting nocturia may reflect either a refractory OAB symptom or the multifactorial nature of nocturia (Gulur et al, 2011).

7. Adverse effects; some patients do exhibit therapeutic improvement in symptoms but tolerate adverse effects poorly.

For each circumstance, altered drug dose, different agent, or combination therapy may achieve sufficient improvement to obviate the need to consider more invasive investigation and treatment. Only when considerable efforts have been made should conservative therapy and antimuscarinic medications be considered unsuccessful.

Urodynamic Testing

The fifth ICI (Abrams et al, 2013) indicates that urodynamic evaluation and imaging should be considered as part of specialist assessment. This applies where conservative and drug therapy fails adequately to manage OAB in a patient who is sufficiently healthy and is considering more invasive therapeutic interventions because of the impact of the symptoms on his or her quality of life. Urethrocystoscopy might be indicated.

The comprehensive symptom score questionnaire, FVC, free flow rate and postvoid residual should be assessed before cystometry and pressure flow studies (see Chapter 73). Whether to discontinue antimuscarinic drugs before urodynamic testing can be argued either way; stopping the drugs provides the best chance of observing DO if present, whereas continuing them allows evaluation of the mechanism underlying residual refractory symptoms.

The primary aim of urodynamic studies is to reproduce the patient's symptoms and to identify additional factors likely to influence management decisions. The two main urodynamic diagnoses associated with OAB are DO (Fig. 76-7) and increased filling sensation. DO presents a variety of patterns on urodynamic traces. The ICS report describes two types:

1. **Phasic DO** is the characteristic pattern seen in most idiopathic DO. It exhibits a characteristic waveform and may or may not lead to incontinence (see Fig. 76-7). It tends to be characterized by contractions of increasing amplitude as the bladder volume increases.
2. **Terminal DO** is a single involuntary detrusor contraction occurring at cystometric capacity, which causes incontinence, often resulting in complete bladder emptying. It is most characteristically seen in the elderly person with "precipitant voiding," such as in elderly patients who have suffered a cerebrovascular accident. Such patients appear to lose awareness of impending micturition and the ability to inhibit what turns out to be a voiding contraction.

Nonphasic changes in detrusor pressure before micturition should be regarded as changes in bladder compliance rather than as DO. Note that some patients with DO are asymptomatic (i.e., they do not experience OAB). Any phasic detrusor contraction during filling constitutes DO, regardless of amplitude (Abrams et al, 2002). Earlier ICS reports (Bates et al, 1980a, 1980b) stated that, to diagnose "detrusor instability" (the old term for DO), the contraction should be at least 15 cm H₂O. However, it was later recognized that involuntary detrusor contractions of lower amplitude could be clinically significant, so the 1988 ICS report (Abrams et al, 1988) was altered accordingly.

It is worth emphasizing that DO may not be present in some patients with OAB, especially in women (Hashim and Abrams, 2006). Figure 76-8 illustrates the relationship between the symptom-based diagnosis of OAB and the urodynamic-based diagnosis of DO. Where DO is absent the patient will usually report increased bladder sensation, that is, an early and persistent desire to void (Abrams et al, 2002). If DO is not seen during filling, the investigator should attempt to use any provocations that the patient says lead to OAB symptoms, such as the sound of running water. Filling rate needs to be considered carefully; a short period of rapid filling can provoke the emergence of DO. However, fast filling can mask DO and cause low compliance, particularly in neurogenic DO.

Urodynamic testing may additionally detect urodynamic stress incontinence (USI) (MUI or mixed storage LUTS). In some patients considered to have OAB based on their symptoms, the ultimate diagnosis turns out to be USI. This might be because contact of

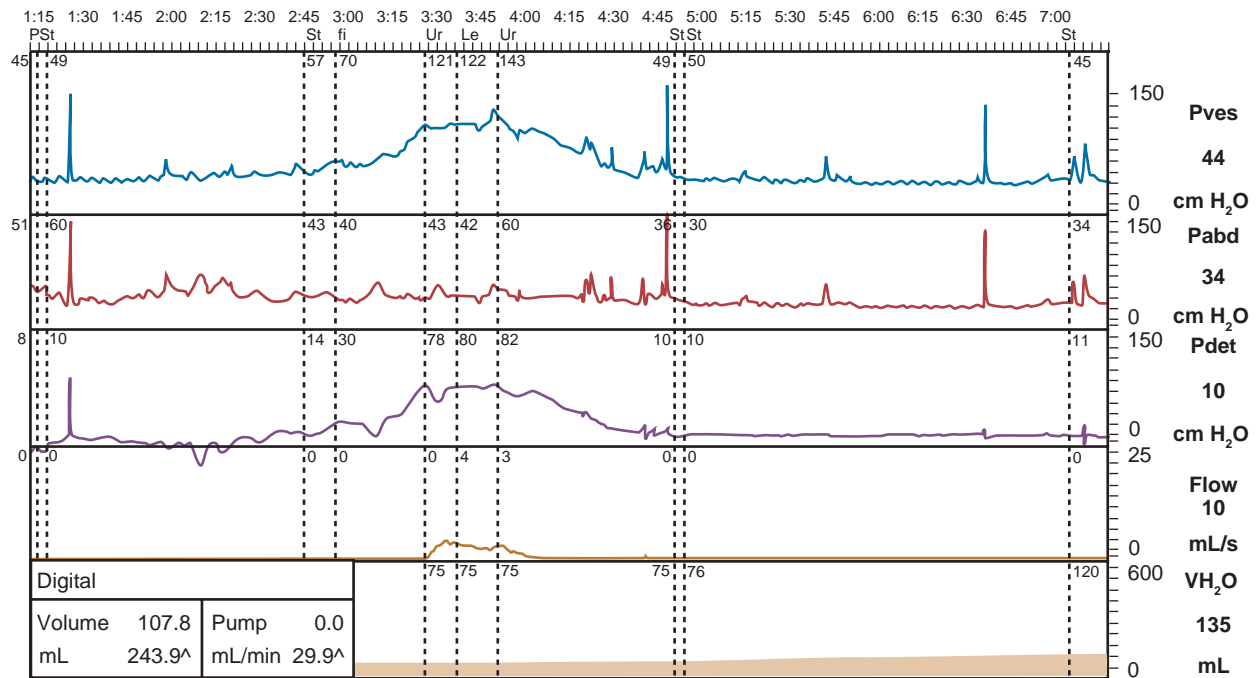


Figure 76-7. Filling cystometry urodynamic trace showing detrusor overactivity incontinence. *Blue*, Bladder pressure (Pves; top). *Red*, Rectal pressure (Pabd). *Purple*, Detrusor pressure (Pdet). *Light brown*, Flow. *Orange*, Filling (VH₂O; bottom). The bladder pressure and detrusor pressure rise substantially from baseline, and between 3 minutes 30 seconds and 4 minutes (top axis) there is incontinence seen in the flow trace that is associated with urgency (Ur).

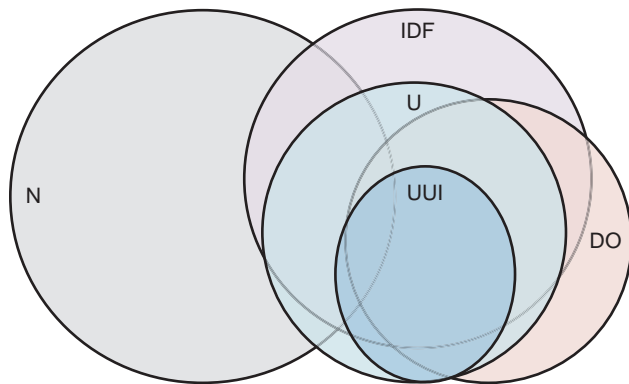


Figure 76-8. Correlation between the symptom-based diagnosis of overactive bladder (increased daytime frequency [IDF], urgency [U], nocturia [N], and urgency urinary incontinence [UUI]) and the urodynamic diagnosis of detrusor overactivity (DO). The correlation is best for UUI and worst for N.

urine with urethral receptors caused by USI can stimulate urethral receptors, causing an urgency sensation and perhaps a secondary bladder contraction. However, care is needed to ensure that the symptoms are fully reproduced during the test, and that sufficient provocation maneuvers are undertaken to elicit DO. In some individuals, DO can be elicited by asking the patient to cough; this stress-provoked DO (where cough sets off DO, which causes leakage) must not be confused with USI (where the cough causes an immediate leak and no DO is seen).

Pressure flow urodynamics may detect BOO or inefficient bladder emptying. This is crucial, as OAB treatment measures that aim at improving bladder reservoir function may impair voiding, perhaps necessitating intermittent self-catheterization. Some clinicians believe that DO can arise as a consequence of BOO, but the causal relationship is not clear-cut. Prevalence of DO is 60% in men

who have had transurethral resection of the prostate previously (Thomas et al, 2005), despite the fact that they remain unobstructed. Accordingly, relief of BOO does not lead to permanent disappearance of DO. Although symptomatic improvement is seen in many of these men, it is probably less reliable than in men without DO.

Ideally the patient should be seated or standing for filling cystometry, because OAB symptoms are usually experienced when upright. However, where there is severe DO at low volumes, it may be difficult to ascertain if USI is also present. In these patients, a second filling cycle in the supine position generally reduces DO (Al-Hayek et al, 2008), making it easier to detect USI if present.

The urodynamic report must clearly state whether the patients' symptoms were reproduced completely, reproduced in part, or not reproduced to ensure that due caution is exercised in major treatment decisions where there is diagnostic uncertainty. Technical artifacts should be recognized and handled immediately (Hogan et al, 2012). Artifact can easily result if a patient or the equipment is moved during urodynamics.

Ambulatory urodynamics may be considered where conventional cystometry fails to reproduce symptoms. However, DO is then difficult to interpret, as DO might appear in up to 60% of asymptomatic women during ambulatory urodynamics (Heslington and Hilton, 1996).

SPECIALIZED TREATMENT OUTLINE

The fifth ICI (Abrams et al, 2013) has produced a comprehensive review of the spectrum of incontinence management, weighted according to levels of evidence, and providing grades of recommendation (Abrams and Khoury, 2010). The care pathways for OAB and DO in the initial and specialized management algorithms for incontinence in women, men, and the frail elderly are illustrated in Figure 76-4. A more detailed description of the management of OAB is covered elsewhere in this book. In brief, therapy for OAB can be divided into four classes of treatment:

1. Conservative management including weight loss, cessation of smoking, and dietary factors (decreased use of caffeine, decreased fluid intake, decreased alcohol intake, changes in food and drink). Lifestyle interventions include pelvic floor muscle training, to resist and occasionally to terminate overactivity when it arises, and bladder retraining to encourage inhibitory influences on the lower urinary tract.
2. Pharmacotherapy; the antimuscarinics are the mainstay of treatment and can be administered orally or transdermally. A β_3 -adrenergic agonist is now also available. Vanilloid agonists, exemplified by capsaicin and resiniferatoxin, have been used in neurogenic DO; although not currently in use, analogous treatments might become available in the future.
3. Surgical therapy; sacral nerve stimulation, tibial nerve stimulation, intravesical botulinum neurotoxin-A injections, augmentation cystoplasty, and detrusor myectomy.
4. Containment; for intractable OAB, options are appliances, catheters (urethral or suprapubic), urethral closure, and urinary diversion.

Careful assessment of contributory factors and patient capacity is essential to optimize response and to minimize adverse consequences. For example, treatments likely to impair voiding contractility substantially should not be used if intermittent catheterization is not feasible, or indwelling catheterization will not be tolerated.

KEY POINTS: SPECIALIZED EVALUATION AND MANAGEMENT

- The specialist clinician must review the diagnosis, look for complicating factors, and ensure that suitable initial therapy has been provided.
- Urodynamic evaluation should be considered where conservative and drug therapy fails adequately to manage OAB in a patient who is sufficiently healthy and who is considering more invasive therapeutic interventions.
- Comprehensive symptom score questionnaire, FVC, free flow rate, and postvoid residual should be assessed.
- The primary aim of urodynamic studies is to reproduce the patient's symptoms and to identify additional factors likely to influence management decisions.
- The two main urodynamic diagnoses associated with OAB are DO and increased filling sensation. USI and BOO are additional factors of importance in deciding treatment.
- The urodynamic report must state whether the patients' symptoms were reproduced completely, reproduced in part, or not reproduced.
- Therapy options include conservative measures, pharmacotherapy, surgery, and containment. Assessment of contributory factors and patient capacity is essential to optimize response and to minimize adverse consequences of treatment.

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The complete reference list is available online at www.expertconsult.com.



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Terminology, Definitions, and Symptoms

Epidemiology

Etiopathogenesis

Diagnosis

Management

Conclusions

An impaired ability to empty the bladder is common in both men and women with aging. It may be attributable to increased resistance of the bladder outlet and/or a reduction in the ability to generate an efficient bladder contraction, referred to as *detrusor underactivity* (DUA) by the International Continence Society (ICS), although the symptomatic condition could be labeled the underactive bladder. Increased bladder outlet resistance, far more common in men because of the effect of benign prostatic hyperplasia (BPH) with aging, has been the target of most therapeutic interventions for lower urinary tract symptoms (LUTS) in men. By contrast, DUA mostly lacks any effective treatment other than catheterization (preferably by intermittent self-catheterization [ISC]), when the postvoid residual (PVR) is raised. Despite its common prevalence, which increases with age, in patients with LUTS referred to urologists, the underlying cause and pathophysiologic mechanisms are poorly understood. Recently there has been a resurgence of interest in this poorly understood condition (van Koeveinge et al, 2011; Miyazato et al, 2013; Osman et al, 2014). In this chapter we summarize and discuss the contemporary evidence relating to symptomatology, epidemiology, cause, diagnosis, and management of the underactive bladder.

TERMINOLOGY, DEFINITIONS, AND SYMPTOMS

A confusing multitude of terms are used to describe impaired bladder voiding function, including *impaired detrusor contractility*, *detrusor areflexia*, and *detrusor failure*. The ICS standardization document in 2002 termed the problem DUA defined on the basis of a urodynamic study (UDS) as “a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span” (Abrams et al, 2002) (Fig. 77-1A). What constitutes reduced strength, reduced length of contraction, or prolonged emptying is not specified. If no contraction occurs, the term *acocontractile detrusor* is used (see Fig. 77-1B). In clinical practice it is important to distinguish this from an isolated inability to void during a UDS (or “bashful bladder”), which is common and often can be correlated with a history of being unable to void in public restrooms.

Defining DUA in purely urodynamic terms is problematic, because this currently necessitates an invasive test that is neither available nor appropriate in all health care settings. These were some of the reasons why the overactive bladder (OAB) symptom complex was introduced as an adjunct to the urodynamic concepts. Nevertheless the two situations are not entirely analogous, because OAB can be defined by the presence of urinary urgency (albeit variably correlated to detrusor overactivity (DOA)). A **symptom syndrome of underactive bladder** is difficult to define because of the absence of individual symptoms that can be considered pathog-

nomonic of the underlying detrusor abnormality. In particular the symptoms of DUA are diverse and overlap significantly with those seen in OAB and associated with bladder outlet obstruction (BOO). During the voiding phase, patients may experience weak stream, intermittency, hesitancy, and straining. After voiding, some report a feeling of incomplete bladder emptying. In the storage phase, some experience urinary frequency and nocturia whereas others may have a loss of the normal urge to void (the opposite of urinary urgency) and report infrequent voiding. In the presence of a very large PVR, patients may experience incontinence (especially during sleep). One could speculate that the reason for these very different clinical pictures is related to the degree of residual bladder sensation, with patients with very poor sensation typically being infrequent voiders and those with intact sensation voiding frequently in the presence of a raised PVR (Fig. 77-2). A further problem at present relates to the lack of consensus over what represents a clinically significant residual volume in the bladder, with the suggestion being that the threshold is more than 40% of the functional capacity (volume voided + residual).

EPIDEMIOLOGY

Epidemiologic studies have demonstrated that LUTS have a high prevalence in the population, increasing significantly with age. However, the extent to which DUA is a contributing factor is unknown. The Epidemiology of LUTS (EpiLUTS) study, conducted in the United Kingdom, United States, and Sweden, included 30,000 participants over 40 years of age and showed that storage LUTS (occurring at least sometimes) are present in 45.7% of men and 66.8% of women. Voiding LUTS (occurring at least sometimes) were documented in 57.1% of men and 48% of women (Sexton et al, 2009). Postmicturition symptoms occur with a similar prevalence in both men and women. Although it is clearly likely that multiple factors contribute to this clinical picture, it is difficult to establish on a population basis to what extent DUA is a cause of these symptoms because of the lack of a simple noninvasive marker.

In men, voiding LUTS, raised PVR or reduced urinary flow rate, individually or collectively, cannot be used as proxy measures for DUA, because they could be attributed to BOO. Similarly, in women, voiding LUTS such as straining often can occur in the context of frequency and low voided volumes associated with OAB. However, if voiding LUTS occur in association with more objective evidence such as reduced flow rate and raised PVR, underlying DUA becomes more likely as a result of the extremely low incidence of BOO in women (2.7% to 8% of those referred for UDS) (Carr and Webster, 1996).

In the absence of epidemiologic data, clinical studies indicate that in patients with LUTS referred for urodynamic assessment DUA

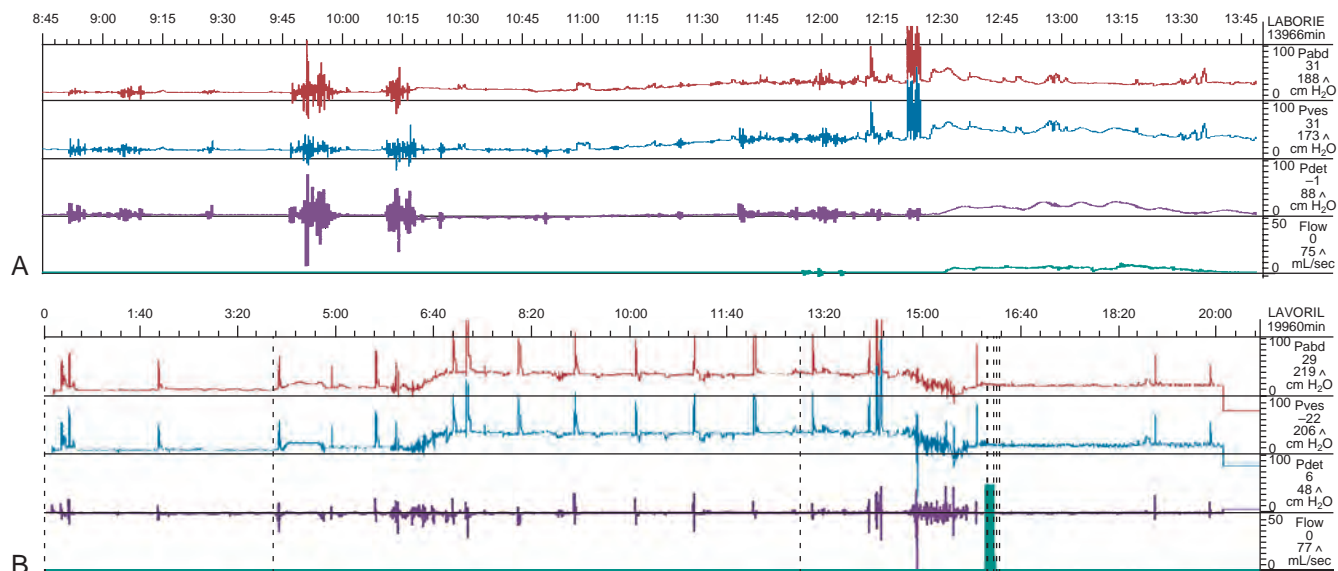


Figure 77-1. Urodynamic traces. **A**, A 67-year-old man with benign prostatic enlargement and predominant voiding lower urinary tract symptoms. Voiding phase demonstrates low detrusor pressure, prolonged detrusor contraction, and prolonged voiding time. The postvoid residual was 100 mL, and the diagnosis is detrusor underactivity. **B**, A 29-year-old woman with a history of lower back injury and urinary retention managed with intermittent self-catheterization. The diagnosis is acontractile detrusor. Pabd, abdominal pressure; Pdet, detrusor pressure; Pves, intravesical pressure.

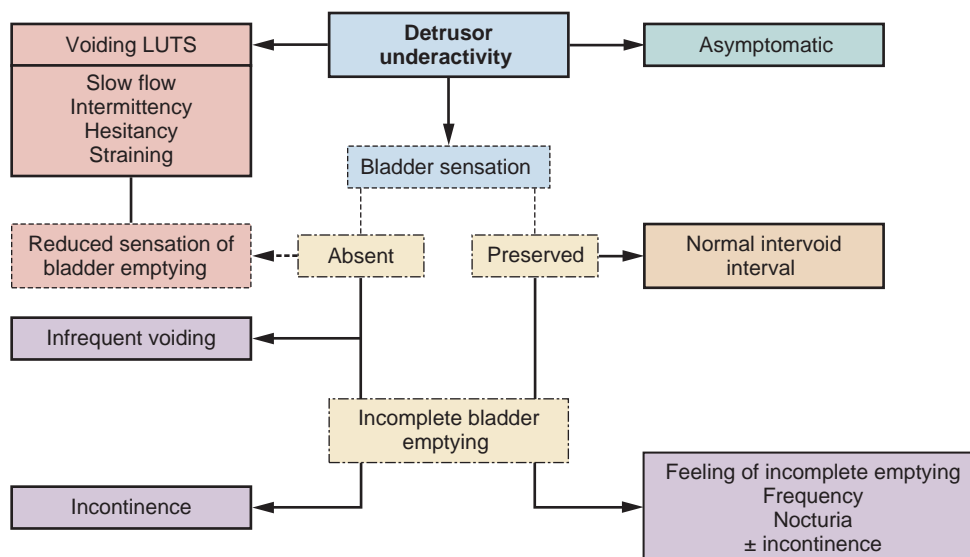


Figure 77-2. Lower urinary tract symptoms (LUTS) in detrusor underactivity (DUA). DUA may manifest with a spectrum of voiding, storage, and postmicturition LUTS or cause no symptoms. Patients with significantly impaired bladder sensation void infrequently and, if bladder emptying is reduced, may have incontinence, typically more pronounced during nighttime (urethral relaxation during sleep). Patients who have preserved bladder sensation can have a normal intervoid interval provided bladder emptying is normal. If bladder emptying is poor, these patients typically experience a sensation of incomplete emptying after voiding, urinary frequency, and nocturia \pm incontinence. This wide variation in symptomatology and its overlap with LUTS/benign prostatic hyperplasia and overactive bladder hampers the development of a reliable symptom-based definition.

TABLE 77-1 Prevalence of Detrusor Underactivity in Clinical Studies

STUDY	POPULATION	SIZE	AGE RANGE OR MEAN AGE (yr)	DIAGNOSTIC CRITERIA	PREVALENCE OF DUA + (% OF ACONTRACTILE DETRUSORS)
Fusco et al, 2001	Male	541	26-89	Pdet@Qmax \leq 30 cm H ₂ O and Qmax \leq 12 mL/sec	10
Kuo, 2007b	Male	1407	46-96	Relaxed sphincter EMG with open membranous urethra during voiding and low flow rate	10.6
Nitti et al, 2002	Male	85	18-45	Bladder outlet obstruction index $<$ 20 cm H ₂ O and uroflow $<$ 12 mL/sec	9
Wang et al, 2003	Male	90	18-50	Pdet@Qmax $<$ 30 cm H ₂ O and Qmax $<$ 15 mL/sec	10
Kaplan et al, 1996	Male	137	18-50	Pdet@Qmax $<$ 45 cm H ₂ O and Qmax $<$ 12 mL/sec	23 (5)
Karami et al, 2011	Male	456	18-40	ICS definition	12.9 (10.5)
Abarbanel and Marcus, 2007	Male	82	$>$ 70	Pdet@Qmax $<$ 30 cm H ₂ O and Qmax $<$ 10 mL/sec	48
Jeong et al, 2012	Female	99	$>$ 70		12
	Male	632	$>$ 65	Bladder contractility index $<$ 100 (men)	40.2
	Female	547	$>$ 65	Qmax \leq 12 mL/sec and Pdet@Qmax \leq 10 cm H ₂ O (women)	13.3
Resnick et al, 1989	Male	17	87	In the absence of obstruction, underactive detrusor: "Failure to empty in the absence of an increase in abdominal pressure"	41.2
	Female (institutionalized)	77		DHIC: "Involuntary detrusor contraction that emptied less than half of volume instilled"	37.7
Resnick et al, 1996	Female (institutionalized)	97	87.6	"Reproducible failure of the involuntary contraction to empty at least half of bladder contents in the absence of straining, urethral obstruction, and detrusor-sphincter dyssynergia"	45
Groutz et al, 1999	Female	206	62.6 \pm 15.8 yr	ICS definition	19
Valentini et al, 2011	Female	442	$>$ 55	"Impaired detrusor contraction leading to prolonged voiding time and high residual volume"	13.8

DUA, detrusor underactivity; EMG, electromyography; ICS, International Continence Society.

From Osman NI, Chapple CR, Abrams P, et al. Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *Eur Urol* 2014;65:389–98.

is very common, particularly in the older age groups (Table 77-1). DUA is diagnosed in 9% to 28% of males under 50 years of age and 48% in those over 70 years. In females, DUA is present in 12% to 45%, being more common in elderly nursing home residents who often have concomitant DOA, an entity described as detrusor hyperactivity impaired contractility (DHIC) (Resnick et al, 1989). It must be borne in mind that these data cannot be extrapolated to the general population and are limited by the inconsistency in definitions used in these studies, the populations studied, and the post-hoc data interpretation.

One of the largest clinical urodynamic series demonstrated that DUA often coexists with other LUT dysfunctions (LUTDs) in the elderly (Jeong et al, 2012). In their study of 1179 patients older than 65 years, 46.5% of males with DUA also had DOA or BOO and 72.6% of the females with DUA also had DOA or urodynamic stress urinary incontinence (Fig. 77-3). In our opinion this is further support for the case for urodynamic assessment before surgical intervention for LUTS in this group.

Very little is known of the natural history of DUA. In a 10-year study of 69 men with non-neurogenic DUA (with a maximal urinary flow rate [Qmax] of $<$ 15 mL/sec and detrusor pressure [Pdet] at Qmax [Pdet@Qmax] of $<$ 40 cm H₂O) managed conservatively,

there was minimal symptomatic or urodynamic progression (Thomas et al, 2005b). In this cohort, 11 patients underwent transurethral resection of the prostate (TURP), 3 for acute urinary retention and 8 for worsening LUTS (all of whom showed no change in Qmax preoperatively compared to the baseline values).

KEY POINTS: TERMINOLOGY, DEFINITIONS, AND SYMPTOMS, AND EPIDEMIOLOGY

- DUA is a common clinical problem associated with a range of storage, voiding, and postmicturition LUTS.
- The population prevalence of DUA is not known, because of the lack of a noninvasive marker.
- DUA affects 9% to 28% of men under 50 years of age and 48% in those over 70 years undergoing UDS and is more prevalent among the institutionalized elderly.
- In women DUA is found in 12% to 45% undergoing UDS and is more prevalent among the institutionalized elderly.
- DUA commonly coexists with other LUTDs.

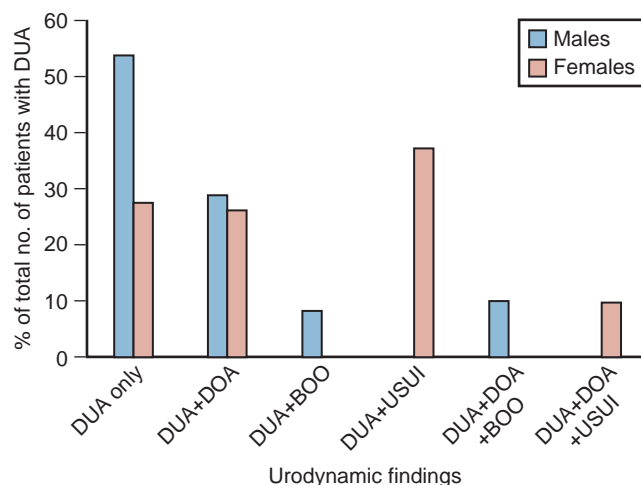


Figure 77-3. The overlap between detrusor underactivity (DUA), detrusor overactivity (DOA), and bladder outlet obstruction (BOO) in 1179 patients (632 men and 547 women) older than 65 years in a Korean clinical series of urodynamic studies. DUA was defined as a bladder contractility index less than 100 in men and Qmax 12 mL/sec or less and Pdet@Qmax 10 cm H₂O or less in women. In total, 40.2% of men and 13.3% of women were classified as having DUA. The data suggest a significant overlap between DUA and other urodynamic diagnoses. USUI, urodynamic stress urinary incontinence. (Raw data provided by Dr. Sang Eun Lee. From Jeong SJ, Kim HJ, Lee YJ, et al. Prevalence and clinical features of detrusor underactivity among elderly with lower urinary tract symptoms: a comparison between men and women. *Korean J Urol* 2012;53:342–8.)

ETIOPATHOGENESIS

DUA occurs in both sexes and diverse clinical groups. Several distinct etiologic factors are recognized, such as diabetes mellitus and cauda equina compression. In clinical practice many patients do not have any obvious cause for DUA, neurologic or otherwise, suggesting that DUA may occur secondary to common age-related changes. In particular, an age-related decline in detrusor function with normal aging is likely, although it has not been conclusively demonstrated.

Direct measurement of the contractility of bladder muscle strips from rodents, comparing younger to older animals, has yielded contradictory results that are difficult to extrapolate to humans because of differences in functional innervation. The few studies that used human bladder muscle strips often have failed to demonstrate a decline in contractile responses to electrical stimulation and a variety of agonists (Mark et al, 1992; Yoshida et al, 2001; Fry et al, 2011). Some clinical urodynamic data suggest an age-related reduction in Pdet and flow rate accompanied with an increase in PVR (Pfisterer et al, 2006; Smith et al, 2009; Valentini et al, 2011). Most studies have included symptomatic individuals with probable underlying pathophysiologic abnormalities that could be expected to progress with time. It is to be expected that there would be a more pronounced decline in detrusor contractility in men because of bladder wall changes (increased connective tissue and reduced smooth muscle) occurring as a result of BOO; however, these changes are also seen in women suggesting that they may be partly attributable to normal aging (Lepor et al, 1992; Holm et al, 1995) (Fig. 77-4A to C).

The mechanisms by which different causes result in DUA can be classified as (1) myogenic, affecting the cellular functions of detrusor myocytes or the surrounding extracellular matrix; or (2) neurogenic, affecting the afferent pathways, efferent pathways, or brain circuits involved in the micturition reflex. (These mechanisms and the probable major etiologic factors are summarized in Fig. 77-5.)

Myogenic Factors

Processes that alter the normal structure and function of the detrusor muscle extracellular matrix may result in diminution of transmitted contractile force. The intrinsic ability of detrusor muscle cells to generate contractile activity may be compromised by dysfunction of cellular mechanisms (e.g., ion storage/exchange, excitation-contraction coupling, calcium storage, energy generation) such that even in the presence of normal extrinsic neuronal activity, a reduced contraction may occur (Brierly et al, 2003).

Morphologic changes have been reported to occur in the detrusor with normal aging and disease. Elbadawi and colleagues (1993a, 1993b, 1993c) proposed that distinct ultrastructural patterns observed by electron microscopy characterized the normally contractile aging detrusor and different bladder dysfunctions, including DUA. Although the applicability of this classification system is disputed, other groups have noted similar findings (Hindley et al, 2002; Brierly et al, 2003). This degeneration pattern, which consists of widespread disrupted detrusor myocytes and axonal degeneration, has been associated with DUA (Elbadawi et al, 1993a). Whether detrusor myocyte disruption is the cause of DUA or a consequence of a pathologic insult is not clear (see Fig. 77-4D to E).

Neurogenic Factors

Brain Circuits

The central neural control mechanism governing micturition involves key processes including perception and integration of storage and voiding that, if disturbed, may result in DUA (Suskind and Smith, 2009). The micturition reflex is facilitated by the spino-bulbo-spinal pathway passing through the sacral parasympathetic nucleus and the pontine micturition center (PMC). The PMC receives input from higher centers in the cerebral cortex and in particular the limbic system. Many insights have been gained from functional neuroimaging studies in animals (de Groat et al, 1998; Sugaya et al, 2003, 2005). Certain populations of PMC neurons ("direct neurons"), appear to become activated immediately before and during reflex bladder contractions, whereas outside these periods they are completely inactive. A large number of these neurons pass to the lumbosacral spinal cord, suggesting a role in the micturition reflex. Human functional neuroimaging suggests similar areas of the brainstem and cortex are implicated—the insula, hypothalamus, periaqueductal gray, and PMC (Blok et al, 1997). Any lesion affecting these regions could in theory result in DUA, albeit a clinical correlation between the site of a neurologic lesion and the urodynamic finding is not always apparent in all diseases (Kim et al, 1998).

Bladder Efferent Pathways

Interruption or impairment of efferent signaling in the sacral cord, sacral roots, and pelvic nerves may manifest as absent or reduced detrusor contraction. There is evidence to suggest that a reduction in autonomic innervation occurs in human bladders as a consequence of normal aging (Gilpin et al, 1986). A range of diseases and injuries can result in disturbance of efferent signaling (discussed later in this section).

Bladder and Urethral Afferent Pathways

Intact bladder sensation is critical to the functioning of the efferent limb of the micturition reflex. Bladder afferents monitor both volumes during bladder filling in the storage phase of the micturition cycle and the magnitude of detrusor contractions during the voiding phase. Urethral afferents have an important role in the perception of both flow through the urethra and detrusor contraction (Feber et al, 1998; Bump, 2000). An impairment in afferent function (from bladder or urethra) is likely to reduce or prematurely end the micturition reflex, leading to impairment or

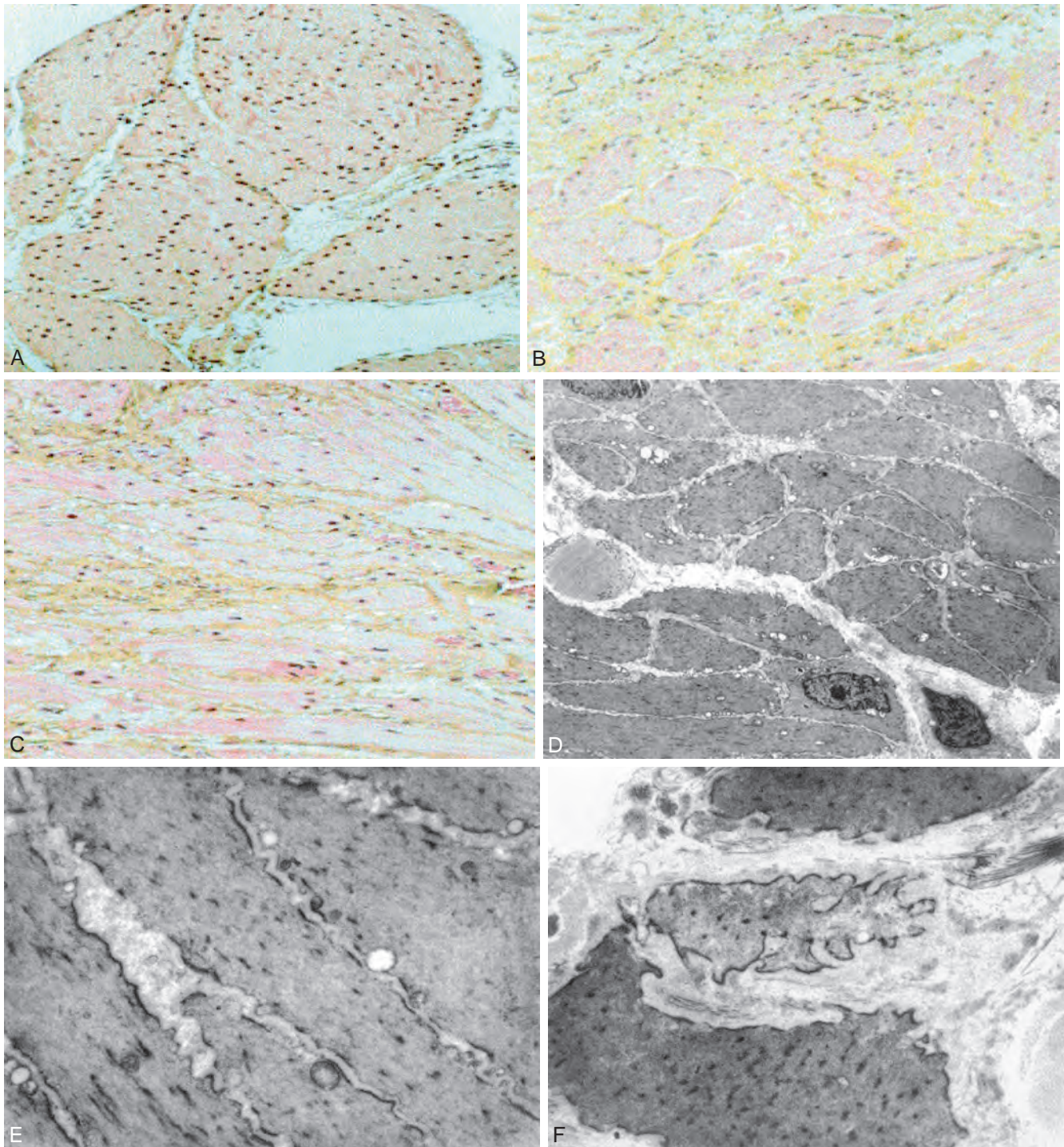


Figure 77-4. Morphologic detrusor changes in aging and disease. Light microscopy: A to C. A, Normal detrusor. B, Man with bladder outlet obstruction, showing an increase in muscle mass and increase in fibrous tissue deposition inside and between muscle bundles. C, Elderly woman without lower urinary tract symptoms showing similar deposition of fibrous tissue suggesting extracellular matrix changes also occur with aging. Electron microscopy: D to F. D, Normal detrusor muscle showing two muscle bundles, a wide collagen-rich septum dividing the bundles is seen. Within the bundles are individual fascicles separated by a thin microseptum (magnification $\times 6000$). E, Normal muscle cells at higher power magnification; smooth intact sarcolemma with a thin interstitium between adjacent cells. F, Degeneration pattern. A disruptive cell, with a shriveled appearance and sarcolemma breakdown, with debris and collagen deposition in the interstitium. (A to C from Nordling J. The aging bladder: a significant but underestimated role in the development of lower urinary tract symptoms. *Exp Gerontol* 2002;37:991–9; D to F from Briery RD, Hindley RG, McLarty E, et al. A prospective controlled study of ultrastructural changes in the underactive detrusor. *J Urol* 2003;169:1374–8.)

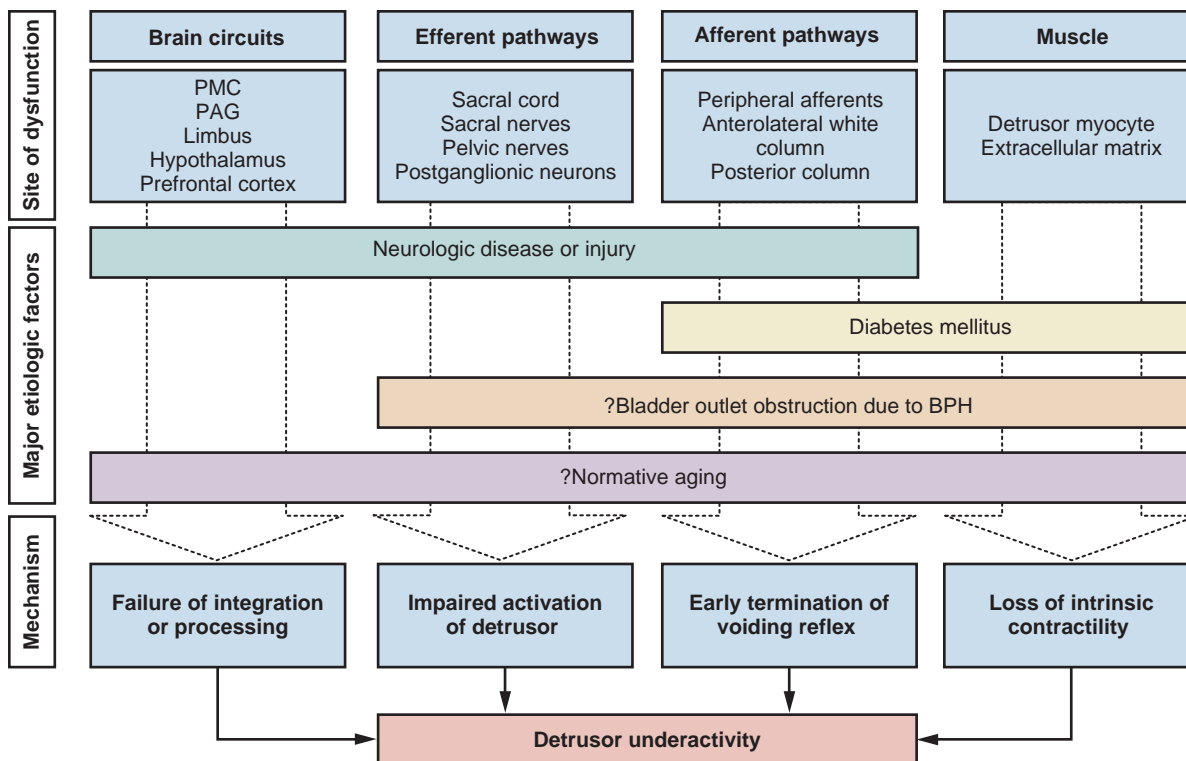


Figure 77-5. Etiopathogenesis of detrusor underactivity (DUA). The mechanisms by which the likely major etiologic factors lead to DUA. Bladder outlet obstruction and normative aging are probable rather than definite factors. BPH, benign prostatic hyperplasia; PAG, periaqueductal gray; PMC, pontine micturition center.

loss of voiding efficiency (Suskind and Smith, 2009). There is evidence that normal aging is associated with a decline in sensory function in the LUT. In support of this, an age-related increase in the thresholds for reaching bladder capacity was observed in women (Pfisterer et al, 2006, 2007) and functional magnetic resonance imaging in asymptomatic older people has shown a reduced response to bladder filling in the insula (the region that maps visceral sensation).

Given that both tissue changes and a decline in sensory function appear to occur with aging, it is likely that both factors contribute to DUA in the elderly. An interesting hypothesis that integrates both aspects has been proposed (Smith, 2010). It is based on the concept that afferent outflow is a function of bladder wall stress and suggests that increased connective tissue deposition and smooth muscle disruption results in a loss of bladder elasticity that leads to changes in the normal passive compliance curve. There would also be impairment of normal sensory innervations resulting from connective tissue infiltration into the bladder wall. Conceptually the bladder progressively loses the property of receptive relaxation and becomes more akin to a stiff balloon. Such a stiff-walled bladder will exhibit a precipitous rise in wall stress with physiologic filling. Clinically this would be manifested by delayed bladder sensation and soon after this the sensation of urgency as the functional bladder capacity is reached. After a small volume of urine is passed, wall stress is dramatically reduced, with a reduction in afferent stimulation resulting in premature termination of the detrusor contraction before the bladder is emptied and an increased PVR. This is a potential explanation for the finding of DHIC, which has been described to occur with aging (Resnick and Yalla, 1987).

Specific Etiologic Factors

See Box 77-1.

Bladder Outlet Obstruction

DUA also may occur as consequence of a series of changes in the detrusor induced by the increased work requirements to overcome bladder outlet obstruction (BOO). In rodent models of partial BOO, the sequence of events leading to DUA is well described and has been separated into three stages. Initially a surgically created BOO (e.g., ring or ligature) increases bladder outlet resistance and results in bladder distention. The detrusor muscle then undergoes compensatory hypertrophy and hyperplasia, with bladder weight increasing sharply over the next few weeks before stabilizing. During this time tissue blood supply also increases. The contractile function at this point is almost normal, and the bladder is said to have entered the compensated stage—in which mass and function remain relatively stable. After a period of variable length, detrusor contractile function declines and bladder emptying is impaired, marking the decompensation phase (Levin et al, 1992, Saito et al, 1997). This is characterized by reduced response to electrical stimulation and agonists and replacement of bladder muscle with connective tissue (fibrosis). Typically, if the obstruction is not relieved before the stage of decompensation and connective tissue deposition, permanent contractile dysfunction ensues. In such an obstructed bladder, laser Doppler estimation of blood flow has demonstrated this to be decreased, further contributing to the bladder wall dysfunction by a direct effect on both neural and muscular dysfunction (Greenland and Brading, 1996). Other work has demonstrated that there is denervation of the bladder as a consequence of BOO in both humans and an animal model (Harrison et al, 1987; Sibley, 1987).

Clearly the hypothesis for the sequential changes observed in animals centers on ischemic/reperfusion injury and pathologic connective tissue infiltration consequent on increased intravesical pressure being necessary to overcome outlet resistance. This results in increased bladder wall tension during contraction (the law of

BOX 77-1 Etiologic Factors**IDIOPATHIC**

Normal aging
Unknown factor in younger people

NEUROGENIC INJURY AND DISEASE

Vascular
Stroke (early phase)
Degenerative
Parkinson disease
Multisystem atrophy
Demyelinating neuropathies
Multiple sclerosis
Peripheral neuropathies
Guillain-Barré syndrome
Neurosyphilis (tabes dorsalis)
Herpes-zoster and herpes simplex
Diabetes mellitus
Acquired immunodeficiency syndrome
Spinal cord and cauda equina
Intravertebral disk prolapse
Cauda equina lesions
Spinal cord tumors
Spinal canal stenosis
Spinal cord injury
Sacral fracture
Pelvic fracture
Pudendal nerve injury (bilateral)

MYOGENIC

Bladder outlet obstruction
Diabetes

IATROGENIC

Radical pelvic surgery
Radical prostatectomy
Radical hysterectomy
Anterior resection, abdominoperineal resection
Detrusor myomectomy
Intravesical phenol injections
Radiation therapy

FUNCTIONAL

Fowler syndrome
Dysfunctional voiding

PHARMACOTHERAPY

Drugs with anticholinergic effects
Antimuscarinics
Antihistamines
Antipsychotics
Anti-Parkinson medications
Antispasmodics
Tricyclic antidepressants
Opioids

Laplace). This leads to compression of bladder wall vessels, tissue ischemia, and hypoxia. Cycles of ischemia and reperfusion during the micturition cycle (as the bladder empties and then fills) lead to generation of reactive oxygen species (Erdem et al, 2005) and release of free intracellular calcium. These factors cause activation of proteases, phospholipases, and membrane lipid peroxidation, which damages cellular and subcellular membranes, including nerve cells, synaptic membranes, mitochondria, and sarcoplasmic reticulum. The outcome of these processes is impaired cellular function and denervation, leading to decompensation of detrusor function (Schroder et al, 2001).

Relating the insights from this work to humans is problematic, because the animals studied are usually immature and often female; the obstruction is acute and certainly not representative of the clinical scenario. Indeed, the sequential changes that have been described, with consistency, do not correlate with the diverse outcomes men with BOO experience clinically. In addition, this sequence of events is not seen in patients presenting with a urethral stricture and does not explain the genesis of the similar bladder dysfunction seen clinically in female patients.

A longitudinal study has demonstrated that prolonged BOO commonly does not necessarily result in clinical decompensation. In a cohort of 170 men with BOO followed for a mean of 13.9 years, no significant deterioration was found in urodynamic parameters (no change in p_{det}@Q_{max} (detrusor pressure at maximum flow) and a reduction in Q_{max} (maximum flow rate) of only 1 mL/sec) and only 17% required any form of intervention (Thomas et al, 2005a). Of men who decompensate their bladders acutely (i.e., develop acute urinary retention), most have preserved detrusor function. Even among men with chronic retention there are some who have preserved contractility and typically poor compliance and upper renal tract changes (high-pressure chronic retention) (George et al, 1983, Djavan et al, 1997). The pathophysiologic explanation for these divergent clinical outcomes remains unknown.

Some aspects of the pathophysiology relating to BOO remain unclear. Animal models do not predict or explain what is seen in the clinical setting. It is likely that the clinical picture in any individual patient is multifactorial and thus unlikely to be explained by any single hypothesis.

Diabetes Mellitus

Diabetes mellitus may impair detrusor function through a combination of myogenic and neurogenic mechanisms. Diabetes-induced bladder dysfunction (DBD), classically termed *diabetic cystopathy*, results in a reduction in emptying efficiency in a time-dependent fashion during the course of the disease (Lee et al, 2004; Lifford et al, 2005). This is traditionally attributed to an autonomic neuropathy occurring as a result of axonal degeneration and segmental demyelination resulting in diminished bladder sensation (Hill et al, 2008). The mechanisms underlying this process are thought to occur as consequences of hyperglycemia. These include activation of the polyol pathway, increases in the generation of free radicals, activation of protein kinase C, and formation of advanced glycated end products (Daneshgari et al, 2009; Miyazato et al, 2013). It has been suggested that a reduction in nerve growth factor (essential for maintaining normal sympathetic and sensory nerve function) is also implicated in DBD. In support of this, studies in streptozotocin-induced diabetes mellitus in rats have shown reduced levels of nerve growth factor in the dorsal root ganglia associated with increased PVR and bladder capacity (Hellweg et al, 1994; Sasaki et al, 2002).

DBD also may result from detrusor myocyte dysfunction occurring as a result of alterations in intercellular connections and excitability, intracellular signaling, receptor density, and distribution. These mechanisms are poorly understood; most insights are derived from animal studies, which have demonstrated both increases and reductions in bladder contractility. Daneshgari and colleagues

(2009) suggested this may be explained by time-dependent changes occurring in the bladder wall, the DBD temporal theory. This theory postulates that initially osmotic diuresis induced by hyperglycemia causes bladder wall stretching, which with increased intravesical pressure results in compensatory bladder hypertrophy. This stage would correspond clinically to storage symptoms early in the disease time course. It is suggested that as the disease progresses, accumulation of toxic products of oxidative stress results in bladder decompensation, clinically manifested as poor bladder sensation and impaired voiding function with associated LUTS.

Neurologic Disease or Injury

A range of neurologic diseases or injuries affecting the brain, spinal cord, or peripheral nerves can lead to DUA (see Box 77-1). Although neurogenic DOA is the most common chronic urologic sequela of cerebrovascular accident, in the acute phase approximately half of patients develop urinary retention (attributed to “cerebral shock”); 75% of these have acontractile detrusors (Burney et al, 1996). Similarly in Parkinson disease DUA is far less common than DOA, occurring in less than 20% of cases (Araki et al, 2000).

Anticholinergic parkinsonian medication may be an important contributor; in a study in which these were withdrawn before urodynamic assessment, DUA was not demonstrated in any patient (Stocchi et al, 1997). Multisystem atrophy, otherwise known as Shy-Drager syndrome, is a condition often confused with Parkinson disease, in which 52% to 95% of patients demonstrate DUA on UDS (Bloch et al, 2010; Yamamoto et al, 2014) as a result of atrophy of efferent parasympathetic nerves, and clinically the majority of these patients develop urinary retention. DUA occurs in 20% of patients with multiple sclerosis (Litwiller et al, 1999), particularly when plaques affect the lumbosacral cord.

Injury at the level of lumbosacral spinal cord, the cauda equina, and sacral and pelvic nerves can occur as a result of trauma or a prolapsed intervertebral disk and also commonly results in DUA related to cauda equina syndrome. In particular, radical pelvic surgery can lead to injury to the pelvic plexus (located near the

anterolateral wall of the lower rectum) or postganglionic fibers that traverse the lateral wall of the upper vagina.

A systematic review found that the overall incidence of LUTD after radical hysterectomy was 72% (Plotti et al, 2011). Although high incidences were reported in older series of patients undergoing rectal cancer surgery, more recently lower rates have been reported (<5%) (Maurer et al, 2001), which can be attributed to the adoption of nerve-sparing techniques. The true incidence of DUA in this context is difficult to define because of the lack of studies correlating preoperative and postoperative urodynamic findings. Nevertheless many patients appear to recover bladder function by 1 year after surgery. In support of this, a study of feline pelvic plexus extirpation suggests this may be due to restitution of intrinsic cholinergic nerves and muscle cell regeneration after an initial injury-related degeneration (Elbadawi, 1988).

In neurologic disorders associated with infective causes, DUA can be either entirely reversible, such as in Guillain-Barré syndrome and herpes zoster (shingles), or permanent, as seen with progressive problems such as acquired immunodeficiency syndrome or neurosyphilis (tabes dorsalis) as was common in the preantibiotic era.

DIAGNOSIS

The only accepted modality for clinically estimating detrusor voiding function is an invasive UDS; however, there are currently no universally agreed criteria for diagnosing DUA. Current methods of estimating detrusor voiding function almost exclusively focus on detrusor contraction strength (Table 77-2), neglecting other potentially important aspects such as the speed and sustainability of a detrusor contraction.

Detrusor Contraction Strength

A detrusor contraction generates both pressure and flow (Griffiths, 2003); thus many authors have used two parameters to diagnose DUA: Qmax and Pdet@Qmax. Reductions in both are considered

TABLE 77-2 Summary of Diagnostic Methods and Criteria

TYPE	METHOD	ADVANTAGES	LIMITATIONS
Mathematical calculations	Watts factor	1. Measure of bladder power 2. Minimally dependent on volume of urine 3. Not affected by presence of BOO	1. Lengthy and complex calculation 2. No validated thresholds 3. Does not measure sustainability of contraction
	Detrusor shortening velocity	1. May identify early-stage DUA	
Indices	Detrusor contraction coefficient (DECO)	1. Simple to use 2. Measurement easy to obtain	1. Does not measure sustainability of contraction
	Bladder contractility index (BCI)	3. Estimation of isovolumetric contraction	2. May not be applicable to other groups
Occlusion testing	Voluntary stop test	1. Real-time indication of isovolumetric contraction strength	1. Uncomfortable or painful for patients
	Mechanical stop test Continuous occlusion	2. No calculations	2. Impractical 3. No information on sustainability of contraction in (in continuous occlusion) 4. May underestimate isovolumetric pressure (stop test) 5. Unusable in some patient groups
Ranges of urodynamic measurements	Pdet@Qmax (e.g., <40) Qmax (e.g., <15)	1. Simple to use	1. No widely accepted “normal” ranges 2. Underestimate contraction strength 3. Does not conceptually consider coexistence of BOO and DUA

BOO, bladder outlet obstruction; DUA, detrusor underactivity; Pdet, detrusor pressure.

From Osman NI, Chapple CR, Abrams P, et al. Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *Eur Urol* 2014;65:389–98.

KEY POINTS: EITOPATHOGENESIS

- The etiopathogenesis of DUA is incompletely understood; a diverse range of factors and pathophysiologic mechanisms are likely to be implicated.
- Confirmed etiologic factors include neurologic injury/disease and diabetes mellitus; BOO and normal aging are probable rather than definite contributory factors.
- These factors may cause DUA by impairing or disrupting processes that are essential for the generation of an efficient voiding contraction.
- The pathophysiologic mechanisms can be classified as follows:
 - Myogenic: Affecting detrusor myocytes or their surrounding extracellular matrix
 - Neurogenic: Affecting the central neural control mechanisms governing the voiding reflex by an action on either afferent or efferent nerves

to be below the lower limits of the normal ranges for the particular patient group. For men these ranges were derived from series of patients undergoing bladder outlet surgery (Abrams and Griffiths, 1979; Schäfer et al, 1989). In healthy men and women these ranges are less well characterized (Schmidt et al, 2002; Pfisterer et al, 2006; Rosario et al, 2008).

There are two limitations with this approach. First, it is likely to underestimate the contraction strength because of bladder outlet relation (BOR), the normal inverse relationship between Pdet and urine flow (Griffiths, 1973). The BOR is an adaptation of the Hill equation for actively contracting muscle and can be summarized as during voiding when flow is low the pressure is high and vice versa. On this basis the Pdet@Qmax actually represents the point of least pressure. Second, the variability in bladder outlet resistance that also can affect flow rate is not considered. The clinical implications of this are that when Pdet is low, a low Qmax also can be attributed to increased outlet resistance (e.g., BOO caused by BPH) or alternatively a normal Qmax can result from reduced outlet resistance (e.g., postprostatectomy incontinence).

To more accurately assess contraction strength, methods that estimate isovolumetric pressure were developed. These are based either on post-hoc mathematical calculations or volitional or mechanical interruption to the flow of urine during UDS (Griffiths, 2004). Many of these are complicated, time-consuming, or impractical limiting their use in clinical practice.

The Watts factor (WF) is an estimate of the power per unit area of bladder surface that is generated by the detrusor, corrected for the finite power required for either isometric contraction or for shortening against no load. It is calculated by the formula: $WF = [(P_{det} + a)(V_{det} + b) - ab] / 2\pi$ where V_{det} is detrusor shortening velocity and a and b are fixed constants ($a = 25$ cm H₂O, $b = 6$ mm/sec), derived from experimental and clinical data (Griffiths, 1991). Throughout micturition the WF varies because of the variation in Pdet and Vdet; the points proposed to best represent detrusor contraction strength is the point at which the WF peaks, the maximal WF (WFmax). The major advantages of the WF are that it minimally depends on volume (Griffiths, 1991) and that it is not affected by increased outlet resistance (Lecamwasam et al, 1998). However, as of yet there are no validated cutoffs for the normal range, but based on expert opinion a WFmax of 7 W/m² was deemed to represent the threshold for reduced contractility (van Koeveeringe et al, 2011), although some authors use a value of 10 W/m² (Mitsui et al, 2012). Ultimately the WF found little use in everyday clinical practice because of the complexity of the calculation and as with all current measures it does not consider the sustainability of a contraction.

Schäfer (1995) proposed an alternative method of estimating isometric contraction strength that is based on superimposing the BOR on his pressure-flow nomogram. The BOR is simplified to a straight line and “projected” back to the y-axis (Pdet) from the point representing Pdet@Qmax to obtain the isovolumetric

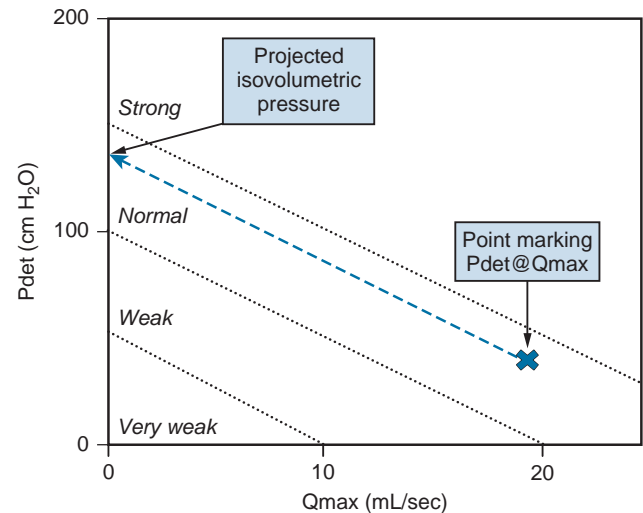


Figure 77-6. Method of determining the projected isovolumetric pressure. The point marking the detrusor pressure (Pdet) @Qmax is plotted on Schäfer's contractility nomogram and is projected back to the y-axis. In this case the pressure is 130 cm H₂O, which is in the normal contractility range.

pressure (Fig. 77-6). This projected isovolumetric pressure (PIP) can be calculated by the formula $PIP = P_{det}@Q_{max} + KQ_{max}$, where K is a fixed constant representing the slope of the BOR (Schäfer, 1995). The value of K depends on the specific population studied. In men with BPH it is taken as 5 cm H₂O/mL/sec, whereas in older women 1 cm H₂O/mL/sec was found to be more accurate (Griffiths, 2004).

Based on this the suggested formula for use in men in clinical practice is as follows:

$$PIP = P_{det}@Q_{max} + 5 Q_{max}$$

A PIP greater than 150 represents strong contractility, 100 to 150 normal contractility, 50 to 100 weak contractility, and less than 50 very weak contractility. The corresponding BORs at these cutoffs were plotted on the Schäfer pressure-flow nomogram, to give subdivisions for contractility (see Fig. 77-6).

Although there are two other reported variations of PIP, all three are essentially the same. The detrusor coefficient is the PIP divided by 100, where a value less than 1 signifies weak contraction.

$$PIP = P_{det}@Q_{max} + 5 Q_{max} / 100$$

The bladder contractility index, described by Abrams, is calculated using the same formula as PIP and includes three groupings (strong > 150, normal 100 to 150, and weak < 100) (Abrams, 1999). Evidently all these methods are fairly easy and quick to calculate but tend to overestimate PIP, because such adjustments need to be made for use in different populations. Although test-retest reliability is thought to be acceptable, it is less consistent than measures that directly record isovolumetric pressures (Tan et al, 2003).

Isovolumetric pressure can be measured directly by mechanically obstructing the flow of urine (Sullivan, 2007). This can be achieved through either (1) a stop test, interruption of urine flow after it has begun, or (2) continuous occlusion test, in which the urine outflow is blocked before and during the course of the voiding contraction.

There are two types of stop test: a voluntary stop test, in which the patient voluntarily contracts the urethral sphincter, and a mechanical stop test, in which the bladder outflow is occluded by the investigator (e.g., by tugging a catheter balloon against the bladder neck). These techniques correlate well with each other in both sexes

(Tan et al, 2003), but the voluntary stop test tends to produce a lower value for isovolumetric pressure by approximately 20 cm H₂O. This is probably explained by the reflex detrusor inhibition induced by urethral sphincter contraction (Sullivan et al, 1995). The voluntary stop test is difficult and sometimes impossible to conduct in patients with urethral sphincter weakness. The continuous occlusion testing has greater test-retest reliability and allows assessment of sustainability of contraction, although the consequence is that a representative flow measurement during that particular contraction is not obtained. Although it correlates well with the ability of bladder to empty (Sullivan and Yalla, 1996), continuous occlusion is potentially painful and has found little applicability outside of a research setting.

Detrusor Contraction Speed

A bladder that contracts more slowly could in theory result in clinical symptoms, although this is not part of the ICS definition. A reduction in detrusor shortening velocity (calculated by the formula $V_{det} = Q/2[3/(V + V_t)/4\pi]^{0.66}$, where Q represents the flow rate [milliliters per seconds], V represents bladder volume [in milliliters], and V_t represents the volume of noncontracting bladder wall tissue) was found to precede reduction in WF in series of longitudinal studies in both males (Cucchi et al, 2007, 2010) and females (Cucchi et al, 2008).

Detrusor Contraction Duration

A detrusor contraction of reduced duration is suggested by the ICS as part of the definition of DUA (Abrams et al, 2002); however, the limits of a normal voiding detrusor contraction are not defined. There are only a few studies that assess contraction duration as a urodynamic parameter. In a study of men with BPH, unobstructed patients with poor contractility actually had significantly longer contraction durations than those with no obstruction and normal contractility (Ameda et al, 1998). It is likely that the contraction duration reflects the underlying pathophysiologic mechanisms—for example, an early termination of the micturition reflex could presumably lead to a shorter duration. A standardized method for measuring duration of the detrusor contraction is needed before any conclusions can be reached.

Bladder Sensation

An assessment of bladder sensation is clearly relevant to the evaluation of DUA because the afferent nerves play such a central role in the initiation and maintenance of a detrusor contraction. This is most commonly undertaken using the patient's perceptions of bladder filling (first sensation, first desire, strong desire, and capacity).

Thresholds in normal individuals are available (Wyndaele, 1998), although this method can be criticized because patients may report bladder sensation even when the bladder is not being filled (Erdem et al, 2004; De Wachter et al, 2008); as with any subjective measure, there is substantial individual variation because of the circumstances of a UDS and the anxiety level of the study subject. Testing sensory responses to the passage of electrical current through the bladder wall (current perception threshold testing) may provide a more objective measure but is clearly rather an invasive approach and is as yet an unvalidated research technique.

Ambulatory Urodynamics

Patients often fail to void during UDS because of anxiety or a so-called bashful bladder. It is thought this arises as a result of poor pelvic floor relaxation and reflex detrusor inhibition. Alternatively the patient may have true DUA or acontractile detrusor. A careful history is usually sufficient to differentiate the two situations. Where doubt exists, ambulatory UDS may be useful (Rosario et al, 2000). van Koeveering and colleagues (2010) demonstrated that 84% of patients who failed to generate a detrusor contraction during

standard UDS had evidence of demonstrable contraction during an ambulatory study.

KEY POINTS: DIAGNOSIS

- There is no published consensus on the diagnostic criteria for DUA.
- Most available criteria focus on the strength of contraction as determined by the Pdet during UDS.
- Several indices and formulas to estimate isometric detrusor strength are available, most of which are unvalidated and are not applicable to all patient groups.
- Urodynamic stop and occlusion tests are more reliable but may be painful and impractical.
- The significance of other aspects of detrusor contraction such as speed and duration is unclear.

MANAGEMENT

The goals of managing the patient with DUA are to improve symptoms and quality of life and reduce the risk for the complications of impaired bladder emptying. These include urinary tract infections (UTIs), bladder stones, ureteric reflux leading to back-pressure on the upper urinary tract, and skin damage from urinary overflow incontinence associated with chronic retention. There is a profound lack of effective treatments to improve detrusor function and thereby facilitate bladder emptying. Thus management commonly entails bladder drainage techniques (e.g., catheterization) or therapies aimed at reducing bladder outlet resistance, for example, by relaxing the external urethral sphincter mechanism. The clinical approach and therapies that are available in contemporary clinical practice as well as potential experimental approaches are reviewed in the next sections (Fig. 77-7).

Initial Assessment

The assessment of patients with symptoms suggestive of DUA entails routine urologic evaluation (bladder diary, digital rectal examination, urinalysis, uroflowmetry, PVR estimation using ultrasound) and neurologic assessment (sacral dermatomes anal tone, the bulbocavernosus reflex, lower limb reflexes). Neurologic deficits require further specialist evaluation; magnetic resonance imaging of the spine is commonly performed in particular to assess the lumbar spinal cord and cauda equina. A careful drug history should be taken to identify medications that impair bladder contractility (agents with anticholinergic or opioid effects) (see Box 77-1) or that increase outlet resistance (e.g., α -adrenoreceptor agonists). Fecal impaction/constipation may contribute to poor bladder emptying by a direct obstructive effect, and, if identified, its treatment may facilitate improved bladder emptying (Charach et al, 2001).

Conservative Management

Behavioral interventions in patients with DUA aim to reduce the symptoms and complications of incomplete bladder emptying. Scheduled voiding can be instituted to increase the frequency of voids in patients with sensory impairment. Double voiding to improve bladder emptying may help reduce bothersome frequency, and patients often use this strategy before seeking treatment. Bladder expression techniques such as Valsalva voiding or the Credé maneuver are used in only very specific neurogenic situations (i.e., DUA with incompetent sphincter) and are otherwise not recommended because of the risk for generating high vesical pressure, causing vesicoureter reflux or reflux into the prostate and seminal vesicles.

Pelvic floor physiotherapy and biofeedback have been used to successfully treat children and adults with dysfunctional

	In routine clinical use	Experimental	Not recommended
Drainage	Time voiding/double voiding		Compression
	Catheterization		Reflex voiding
	Urine diversion		Valsalva voiding
↓ Outlet resistance	Pelvic floor physiotherapy and biofeedback	Intrasphincter botulinum toxin	
	α-Blockers Muscle relaxants		
	Bladder outlet surgery		
↑ Detrusor function	Sacral neuromodulation	Intravesical prostanoids	Anticholinesterase
		Intravesical electrotherapy	
	Anterior sacral root stimulator	Detrusor myoplasty	Muscarinic agonists
		Reduction cystoplasty	

Figure 77-7. Management options in detrusor underactivity.

voiding (de Jong et al, 2007; Minardi et al, 2010). In this group, poor relaxation of the pelvic floor muscles and the external urethral sphincter mechanism may obstruct urine flow and cause reflex inhibition of detrusor contraction. In a study by van Koeveeringe and colleagues (2010), 24% of patients with acontractile detrusors on conventional UDS who subsequently demonstrated contractility on ambulatory studies were successfully treated with physiotherapy.

ISC is the preferred method of establishing bladder drainage in patients with problematic high PVR. Provided cognition and dexterity are adequate, this method is safe and effective, with lower infection rates than with indwelling catheters. Specific problems include urethral bleeding (one third of patients) (Webb et al, 1990) and production of false passages. Additionally, the technique may be time-consuming and socially restricting; some patients may be unable to overcome the psychological barriers such as a fear of inflicting harm or infection (Mangnall, 2012). An indwelling urethral catheter is best avoided in the long term, and in this context a suprapubic catheter is the best long-term option in patients unwilling or unable to perform ISC.

Pharmacotherapies

Parasympathomimetics for Underactive Bladder

Acetylcholine is the principal neurotransmitter mediating bladder contraction, acting on muscarinic (M_3) receptors. Parasympathomimetic agents, including direct muscarinic receptor agonists or anticholinesterases, have been used with the aim of increasing bladder contractility. Bethanechol and carbachol, the most common compounds studied, are quaternary amines that are selective for the muscarinic receptor but not receptor subtype selective. In mechanistic terms these compounds are more likely to be effective if the problem is reduced or absent contractile stimulus (e.g., reduced efferent input, impaired acetylcholine release from parasympathetic nerves, increased acetylcholine breakdown). Anti-

cholinesterases (e.g., distigmine) would require the presence of at least some endogenous acetylcholine, to amplify its effect. Conversely if the underlying cause is reduced tissue responsiveness to stimulation (e.g., detrusor muscle cell dysfunction, bladder wall fibrosis), parasympathomimetics are less likely to benefit. Similarly, if the problem is loss of the detrusor muscle, no pharmacotherapy is likely to be effective.

The efficacy of parasympathomimetics has been assessed in a small group of heterogeneous studies, mainly for the prevention and treatment of postoperative urinary retention. A systematic review of this literature (Barendrecht et al, 2007) found only 4 of 10 randomized clinical trials included (two of the four in patients with DUA) showed a significant benefit over placebo. However, all of these studies could be considered to be underpowered. Bethanechol was used in all four (dose of 10 to 50 mg up to four times daily). A further three studies failed to show any advantage with use of this agent. One study found that distigmine (5 mg) actually increased PVR compared to placebo. It was concluded there is little, if any, benefit in using parasympathomimetics.

When bethanechol is given to neurologically normal individuals it causes a rise in bladder wall stiffness and sensory perception (De Wachter and Wyndaele, 2001). De Wachter and associates (2003) also noted that women with DUA responding to bethanechol demonstrated significant reductions in bladder sensory thresholds. Hence, intact sensory pathways may be a prerequisite for improvement in voiding with muscarinic agonists, which may explain their lack of efficacy in unselected groups. Alternatively it could be that the doses used are simply too low because of the concern with side effects. Parasympathomimetics are associated with significant dose-dependent systemic side effects, including nausea, bronchospasm, abdominal cramping, diarrhea, increased salivation, flushing, and visual disturbance. A rare but potentially lethal side effect is severe cardiac depression resulting in cardiac arrest. In contemporary practice, parasympathomimetic agents are generally avoided because of their questionable efficacy and potentially serious side effects.

α-Adrenoreceptor Antagonists

α-Adrenoreceptor antagonists have been used to reduce bladder outlet resistance in children and adults with both neurogenic bladder and dysfunctional voiding. [Chang and associates \(2008\)](#) studied the use of tamsulosin (0.2 mg) in 52 women with DUA (Pdet@Qmax <10 cm H₂O), finding 38.5% had a greater than 50% improvement in voiding LUTS, 53.8% had a greater than 30% improvement in Qmax, and 32.7% were judged to have had a good therapeutic response ([Chang et al, 2008](#)). Combination therapy with an α-adrenoreceptor antagonist and a parasympathomimetic has long been considered a therapeutic possibility ([Khanna and Gonick, 1975](#)). In a prospective single-blind randomized study of 119 patients with DUA, urapidil alone did not result in a reduction in Qmax in either sex and led to a reduction in PVR in women only ([Yamanishi et al, 2004](#)). By contrast a combined regimen of urapidil (60 mg) with either bethanechol (60 mg) or distigmine (15 mg) led to significantly improved flow rates (by 2.66 mL/sec in women, $P < .01$, and 4.33 mL/sec in men, $P < .05$) and significantly reduced PVR in women (by 54.1 mL/sec, $P < .01$) ([Yamanishi et al, 2004](#)).

Prostanoids

Prostanoids are a subclass of signaling molecules that may be implicated in the micturition reflex. The efficacy of prostanoids in treating DUA is not clear. Most clinical studies have evaluated the effect of intravesical prostaglandin (PG) instillation in the prevention of postoperative urinary retention.

There are five principal endogenous prostanoids (PGE₂, PGF_{2α}, PGI₂, PGD₂, and thromboxane A) that are all synthesized in the bladder wall and released into the general circulation when the bladder is stretched ([Maggi, 1992](#); [Rahnama'i et al, 2012](#)). Detrusor contraction in response to acetylcholine and adenosine triphosphate stimulation is enhanced by prostanoid production. Conversely, nonsteroidal anti-inflammatory agents (inhibitors of prostanoid synthesis) cause a loss of tone in the isolated bladder that is reversed with the administration of prostanoids. PGF_{2α}, PGE₁, and PGE₂ all enhance detrusor contraction; PGE₁ and PGE₂ cause urethral relaxation, and PGF_{2α} results in urethral contraction ([Rahnama'i et al, 2012](#)).

The clinical studies conducted to date have demonstrated mixed outcomes ([Wagner et al, 1985](#); [Tammela et al, 1987](#); [Koonings et al, 1990](#); [Bergman et al, 1992, 1993](#)); however, a recent pooled analysis of the results of two randomized trials assessing PGE₂ and a third assessing PGF_{2α} demonstrated a statistically significant association between instillation and successful voiding (risk ratio 3.07) ([Buckley and Lapitan, 2010](#)). Both PGE and PGF series also stimulate contraction of the uterus, a potential side effect of treatment ([O'Brien, 1995](#)).

Future Prospects in Pharmacotherapy

In the absence of any effective compound, there are several avenues aimed at increasing bladder contractility that can be explored, as follows:

- Parasympathomimetics could yet be an option; however, their side-effect profile is concerning. Development of a bladder-specific agent could avoid these effects permitting dose escalation. However, this is unlikely to be possible based on contemporary knowledge.
- Novel muscarinic receptor manipulation such as postsynaptic allosteric receptor enhancement or the presynaptic M₂-receptor antagonist could be promising.
- Exogenous prostanoids require further investigation; agents with selectivity for the urinary tract over the uterus and gastrointestinal tract are under development; however, whether they will be effective if taken orally is an important question.
- Agonists of transient receptor potential (TRP) channels, such as TRPV4 agonist GSK1016790A, can increase contractility and are worthy of further investigation.

- Treatments of analogous conditions affecting other organ systems, such as cardiac inotropes in cardiac failure or prokinetics for intestinal dysmotility, could provide alternative options to increase contractility.
- Improving bladder sensation using sensory sensitizers could hypothetically help patients with impaired afferent signaling.

To develop effective drug therapies there is a need to better understand the pharmacologic principles that underpin normal detrusor contraction and the mechanisms of detrusor dysfunction underlying DUA.

Electrical Stimulation

A variety of electrical stimulation techniques have been applied in DUA of different causes. [Brindley and associates \(1982, 1986\)](#) developed the sacral root stimulator for patients with complete spinal cord injury to activate the anterior sacral roots and achieve volitional bladder emptying. For the procedure to be successful there is a need for intact peripheral efferents and the absence of myogenic dysfunction. This is confirmed by the presence of reflex detrusor contractions on bladder filling preoperatively. The anterior sacral roots are stimulated through an implantable receiver, stimulation wires, and external transmitter. Stimulation also activates urethral somatic efferents; this is overcome by using intermittent stimulation patterns that exploit the longer relaxation time of smooth muscle compared to skeletal muscle to generate a sustained detrusor contraction with short intermittent periods of sphincter contraction. Clinically this results in an interrupted void pattern. [Sauerwein \(1990\)](#) subsequently modified the technique by combining it with total sacral root rhizotomy, thereby abolishing all reflex activity.

[Katona and Berenyi \(1975\)](#) popularized the technique of applying electrical current to the bladder wall through a transurethral electrode in 1958, termed *intravesical electrotherapy* (IVE). The bladder is filled with saline, and current is passed through an electrode (cathode) at the tip of the catheter; the circuit is completed by a neutral electrode applied to the skin in an area of normal sensation. Daily sessions of stimulation are undertaken, usually of 1 hour or more, with 10 to 15 sessions considered a trial period.

Animal experiments have shown that IVE activates mechanosensitive bladder afferents (myelinated Aδ fibers) and, as a consequence, central reflex activation of the detrusor ([Ebner et al, 1992](#)). It is postulated that repeat activation of this pathway upregulates its performance during bladder filling and volitional voiding, resulting in improved sensation and emptying. On this basis, where the underlying cause is complete denervation or bladder wall fibrosis, IVE is considered unlikely to be successful.

IVE has been studied primarily in the pediatric age group, with some encouraging results, but is still considered a controversial therapy. There is considerable heterogeneity in inclusion criteria and technical aspects, and most studies include only small numbers, limiting definitive conclusions as to efficacy. In children with both neurogenic and idiopathic DUA, voiding was normalized after treatment in as many as 85% of cases ([Gladh, 2002](#)). In adults with predominately neurogenic DUA, 39% of those without a detrusor contraction and 75% without bladder sensation before treatment experienced a restoration of these parameters ([Primus et al, 1996](#)). Several studies have failed to show benefit, including the only sham controlled randomized prospective study ([Boone et al, 1992](#)). Moreover, IVE often is undertaken alongside an intensive bladder training/biofeedback regimen, which may partially explain the positive outcomes ([Madersbacher, 1990](#)). Although not associated with significant complications (except a small risk for UTI), its principal limitations are the significant time and resource requirements. An average of 47 sessions was required for a durable effect in a cohort of children followed for 10 years after treatment ([Kaplan, 2000](#)).

Sacral neuromodulation (SNM) was first introduced over 30 years ago by [Tanagho and Schmidt \(1982\)](#). It has been used with good efficacy in the group of patients with nonobstructive

urinary retention and DUA (Everaert et al, 1997; Swinn et al, 2000). It is postulated that abnormal afferent signals generated from the urethral sphincter (because of pelvic floor/sphincter disorders) have an inhibitory effect on bladder afferents at the level of the sacral spinal cord, preventing their transmission in the periaqueductal gray and higher brain centers. SNM is thought to inhibit urethral afferent signals and allow restoration of normal afferent flow to the brain and the resumption of normal bladder sensation and detrusor contractions. A direct effect on bladder efferents is possible but less likely (DasGupta and Fowler, 2004).

Botulinum Toxin

Botulinum neurotoxin A (BoNT-A) injected into the urethral sphincter has been used to reduce outlet resistance and improve bladder emptying in patients with detrusor-sphincter dyssynergia (Dykstra et al, 1988; Schurch et al, 1996; Phelan et al, 2001). The potential rationale for its use in DUA is to relax the urethral sphincter mechanism, thereby overcoming reflex inhibition of detrusor function (Park et al, 1997), or to facilitate Valsalva-induced voiding.

Kuo (2003) reported the results of urethral BoNT-A (50 U in 4 mL of normal saline) in 20 patients with DUA of mixed causes. The toxin was injected cystoscopically in men and periurethrally in women. Seven patients who previously required indwelling catheters could void with low PVRs (≤ 150 mL). In the 7 patients performing ISC at baseline it could be stopped or reduced in frequency after injection. The same author also reported the effects of urethral BoNT-A (50 U or 100 U in 4 mL and 8 mL of normal saline, respectively) in 27 patients (5 men and 22 women) with idiopathic detrusor underactivity (low or no Pdet and Qmax of <10 mL/sec and PVR >150 mL) (Kuo, 2007a). An increase in Pdet and Qmax with a decrease in PVR occurred in 13 patients (48%), all of whom could void without abdominal straining. Analysis of baseline characteristics identified the responders as having significantly better bladder sensation. Patients with evidence of poor sphincter relaxation before treatment were more likely to improve (87%) compared to patients with DUA only (33%) or DHIC (30%).

The evidence available suggests that the action of BoNT-A when injected into the urethral sphincter mechanism is short-lived, and to date no adequate clinical studies have been conducted to evaluate the appropriate dose. In this context it is not licensed for use and cannot be used outside of a clinical trial setting.

Surgery

Bladder Outlet Surgery

The role of bladder outlet surgery in the management of men with non-neurogenic DUA is a controversial topic in which there is a lack of high-level evidence to guide clinical decision making.

It is important to differentiate between two common clinical scenarios: the patient with DUA with a low or minimal PVR whose primary complaint is symptoms and the patient with DUA who is catheter dependent (i.e., chronic retention). In the former, although BOO cannot be definitively excluded, because of the limitations of urodynamic analysis discussed earlier, it is generally less likely to be significant as the patient is able to empty the bladder with a low Pdet. In this situation, outlet surgery is generally considered to be unlikely to significantly improve voiding LUTS. This supposition is supported by a study that followed 22 men with DUA treated with TURP for a mean of 11.3 years (Thomas et al, 2004). The majority of patients underwent TURP on the basis of symptoms (3 of 22 after acute retention). There was no significant improvement in any symptoms. A small reduction of questionable clinical significance in the BOO index ($\text{BOOI} = \text{Pdet@Qmax} - 2 \text{Qmax}$) did occur but was not associated with an improvement in flow rate or voiding efficiency. It can be concluded that when compared to patients with DUA undergoing conservative treatment, outlet surgery confers no significant improvement in symptoms or urodynamic

parameters. Other studies with shorter follow-up support these findings (Rollema and Van Mastrigt, 1992; Javle et al, 1998).

In the situation in which the patient with DUA is catheter dependent and has arguably reached a later stage of detrusor decompensation, even less evidence is available as to the benefit of outlet surgery. Surgery is performed with the aim of reducing outlet resistance enough to permit bladder emptying, albeit the flow rate and PVR rarely return to normal in this scenario. Predictors of poor outcome include low voiding pressures (<45 cm H₂O) (Ghalayini et al, 2005), older age (>80 years), and high residual volume (>1500 mL) (Djavan et al, 1997). Although the limited evidence suggests men with DUA and chronic retention do less well after bladder outlet surgery (Ghalayini et al, 2005), a significant proportion resume spontaneous voiding (Monoski et al, 2006). In the absence of any other effective treatments some advocate surgery in the younger, medically fit patient who wishes to become catheter free.

The use of urethral dilation for women with DUA and significant residuals has been advocated but lacks an adequate evidence base to permit clear conclusions to be drawn (Basu and Duckett, 2010). Resection or incision of the bladder neck in women with DUA is not recommended, because this may lead to significant problems with either incontinence or bladder neck stenosis.

Urinary Diversion

Because of the general acceptability and safety of both ISC and indwelling catheterization techniques, urinary diversion is rarely performed for DUA outside of the neurogenic population. When urethral clean intermittent catheterization is not possible and the patient wishes to avoid a suprapubic catheter, as is often the case in young women with idiopathic urinary retention refractory to SNM, a continent catheterizable stoma can be performed. An incontinent diversion (e.g., ileal conduit) is occasionally performed when there are signs of renal deterioration resulting from obstruction to the intramural ureters secondary to a thick-walled bladder.

Reconstructive Surgery

Few reports of reconstructive surgical procedures for DUA are available. Stenzl and colleagues (1998) reported the first series of latissimus dorsi detrusor myoplasty in patients with DUA in 1998. The muscle is harvested, and its pedicle is anastomosed to the inferior epigastric vessels, with the nerve coapted to the intercostal branch. The muscle is wrapped in a spiral configuration around the bladder, covering over three quarters of its surface. It is then anchored to the pelvic floor fascia and ligaments. The long-term outcomes of this technique in 24 catheter-dependent patients with acontractile detrusor have been reported (Gakis et al, 2011). Seventeen patients recovered the ability to void (mean PVR = 25 mL). The mean bladder contractility index increased from 20.1 ± 7.6 to 176.2 ± 25.4 ($P < .001$). Complications occurred in a third of patients, including thromboembolism, pelvic abscess, and wound infection, though there were no long-term problems. Partial cystectomy (or reduction cystoplasty) has been reported as an alternative approach, in a few series (Weinberg et al, 1974; Klarskov et al, 1988), with no recent reported studies and is no longer considered in contemporary practice.

CONCLUSIONS

DUA is a not uncommon problem that can pose a difficult challenge for both patients and physicians because of the lack of simple and effective treatments. This problem has received little attention in clinical and basic science research in comparison to other common LUTD such as OAB and DOA. Defining the problem in symptom-based terms is difficult because of the wide spectrum of manifesting symptoms, underlying clinical conditions, and absence of accurate noninvasive markers. Clinical studies suggest that the problem is highly prevalent in both men and women with LUTS

KEY POINTS: MANAGEMENT

- There are no effective pharmacotherapies for the treatment of DUA.
- Parasympathomimetic agents have questionable efficacy, are associated with potentially fatal systemic effects, and are not used in routine practice.
- Intravesical electrotherapy has shown promising results in restoring detrusor contraction; however, it is time- and resource-consuming.
- SNM is effective in restoring voiding in patients with DUA associated with urethral sphincter/pelvic floor disorders.
- Bladder outlet surgery has a high risk for failure in men with DUA not reliant on catheters. Men with DUA and chronic retention dependent on catheter drainage experience poorer outcomes than those with normal detrusor function; however, they still may benefit from surgery.

presenting to urologists. A variety of causes are implicated, affecting all aspects of the micturition reflex. There is a lack of any simple and effective treatments. Preserved bladder sensation appears to predict better responses to treatment. There is need for a greater understanding of the mechanisms governing normal detrusor con-

traction and how these are affected by disease. Until this is achieved it will be difficult to develop compounds that enhance detrusor strength and duration of contractility or enhance bladder sensation. In the future developments in regenerative medicine, stem cell and gene therapy may provide interesting avenues for further research, but a prerequisite for this will be to develop a better understanding of both normal structure and function of the LUT and the way in which this is altered in cases of DUA.

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The complete reference list is available online at www.expertconsult.com.

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Rationale for Evaluation and Management

Evaluation

Nocturia, defined as waking because of the desire to void during intended sleep, can be the result of an abnormality in the genitourinary tract or a symptom of an underlying medical condition. Because of its numerous causes, uncovering the cause of a patient's nocturia and treating it appropriately can be a diagnostic and therapeutic challenge for the urologist. A systematic approach, including a thorough history and physical examination, is essential to help find the underlying cause(s). Therapeutic options are numerous and include conservative/behavioral management, pharmacotherapy, phytotherapy, and invasive procedures. Tailoring appropriate therapy to an accurate diagnosis should lead to effective treatment and patient satisfaction.

RATIONALE FOR EVALUATION AND MANAGEMENT

Nocturia Is Bothersome

The International Continence Society (ICS) defines **nocturia as voiding that occurs during the hours of sleep (i.e., voiding that is preceded and followed by sleep)** (van Kerrebroeck et al, 2002). Key terms are listed in Table 78-1. Some clinicians do not consider one void during the night to be clinically significant. This may be because several studies have shown that less than two voids per night does not generate bother and that two or more voids per night can impair quality of life (Häkkinen et al, 2006; Hernández et al, 2008; Tikkinen et al, 2009b). **The definition of nocturia does not take into account the patient's degree of bother.** For example, one patient who voids once per night may report being very bothered versus another patient who voids 2 or 3 times per night who may report little bother. **Degree of bother influences quality of life.** According to the Boston Area Community Health (BACH) Survey, a population-based study of 5502 men and women 30 to 79 years of age, nocturia is associated with a decreased quality of life and an increased prevalence of depressive symptoms in both men and women (Kupelian et al, 2012). Compared to those with low bother, patients reporting high levels of nocturia-specific bother were found to be significantly more likely to have difficulty initiating sleep (47.7 minutes \pm 34.4 vs. 23.5 minutes \pm 13.6, $P = .05$), difficulty returning to sleep (28.9 minutes \pm 16.1 vs. 15.4 minutes \pm 9.6, $P = .03$), and greater morning fatigue (3.3 \pm 0.7 vs. 2.5 \pm 1.0, $P = .04$). Subjective morning fatigue and sleep ratings scale ranges from 1 to 7; higher scores equate to worse fatigue or sleep characteristics (Vaughan et al, 2012). In a prospectively analyzed study of various sleep parameters and nocturia in a cohort of community-dwelling men and women, nocturia, common among older individuals with insomnia, was associated with both increased subjective nocturnal and decreased daytime wakefulness (Zeitzer et al, 2013).

Nocturia Is Common

Nocturia affects people of different ages, races, and genders all over the world. The BACH Survey, composed of 5502 men and women

Cause and Management

between the ages of 30 and 79, found that the overall **prevalence of nocturia (>1 void per night) was 28.4%, 25.2% among men and 31.3% among women** (Fitzgerald et al, 2007). A review of 43 pertinent articles revealed that prevalence rates of nocturia in younger men (20 to 40 years) were one or more voids in 11% to 35% and two or more voids in 2% to 17%. In older men (>70 years), rates were one or more voids in 69% to 93% and two or more voids in 29% to 59%. Prevalence rates in younger women were one or more voids in 20% to 44% and two or more voids in 4% to 18%. In older women, rates were one or more voids in 74% to 77% and two or more voids in 28% to 62%. It is noteworthy that **one in every five or six people 20 to 40 years of age wakes two or more times per night and that up to nearly three in every five people older than 70 years wake to void two or more times nightly** (Bosch and Weiss, 2010). The Fujiwara-Kyo study included 4427 men and women over the age of 65. Nocturia was defined as awakening to void two or more times per night. In this population, the prevalence was reported to be 47% at baseline and 50% 1 year later. The incidence was found to be 20% and the remission rate was 15%. The authors showed that women and younger patients were more likely to spontaneously remit (Hirayama et al, 2013).

The prevalence of nocturia in both men and women increases with age (Bosch and Weiss, 2010). In a survey of 1424 elderly individuals (ages 55 to 84 years), 53% of the sample listed nocturia as a self-perceived cause of nocturnal sleep disturbance every night or almost every night (Bliwise et al, 2009). Data acquisition methodology regarding nocturia may influence calculated prevalence. In the Krimpen study, a Dutch cohort of community-dwelling men 50 to 78 years of age, the International Prostate Symptom Score (IPSS) nocturia question overestimated the percentage with nocturia three times or more compared with recordings on frequency-volume charts, in younger men (younger than 60 years). In contrast, older men (older than 60 years) underestimated their nighttime frequency when scoring the IPSS nocturia question. Nocturia was three times more prevalent in men with a low functional bladder capacity (<300 mL) in the Krimpen study than men with greater capacity (Bosch and van Doorn, 2012).

Association of Nocturia with Early Mortality

Nocturia affects both quality and quantity of life. Several studies have implicated nocturia in overall survival. In the Third National Health and Nutrition Examination Survey (NHANES III), a U.S. population-based sample of 7455 men and 8533 women, two or more voids per night were associated with worse survival compared to zero to one voids per night. This was particularly true in subjects younger than 65 years of age (Kupelian et al, 2011). In a community sample of 784 Japanese individuals 70 years or older, subjects with nocturia were at greater risk for skeletal fracture and death than those without nocturia during the 5-year observation period (even when adjusting for covariates including diabetes, smoking status, history of coronary disease, renal disease, and stroke and use of

TABLE 78-1 Key Terms and Definitions

TERM	DEFINITION
Night	The period between going to bed with the intention of sleeping and waking with the intention of arising
Nocturia	Waking one or more times to void during the hours of sleep; each void is preceded and followed by sleep
Total urine volume (TUV)	Total volume of urine produced during a 24-hour period
First morning void	The first void after waking with the intention of rising
Nocturnal urine volume (NUV)	Total volume of urine passed during the night, including the first morning void
Maximum voided volume (MVV)	The largest single voided volume in a 24-hr period
Nighttime frequency or actual number of nightly voids (ANV)	The number of voids recorded from the time the individual goes to bed with the intention of sleeping, to the time the individual wakes with the intention of rising
Nocturia index (Ni)	$Ni = NUV/MVV$; when $Ni > 1$ NUV exceeds maximum storage capacity and nocturia or enuresis occurs
Nocturnal polyuria	Nocturnal volume $>20\%$ – 33% of total 24-hr volume (age dependent), other definitions include: NUV >6.4 mL/kg NUV >0.9 mL/min (54 mL/hr) NUV >1.5 mL/min (>90 mL/hr)
Nocturnal polyuria index (NPI)	$NPI = NUV/TUV$; if $NPI > 0.20$ – 0.33 (age dependent); patient has nocturnal polyuria
Predicted number of nightly voids (PNV)	$PNV = Ni - 1$, used for calculation of NBCi
Nocturnal bladder capacity index (NBCi)	$NBCi = ANV - PNV$; $NBCi > 0$ indicates that nocturia will occur at voided volumes $< MVV$. $NBCi > 2$ associated with severe nocturia
Global polyuria	24-hour voided volume of >2.8 L in a 70-kg adult (>40 mL/kg)
Nocturnal enuresis	Voiding occurring during sleep

Modified from van Kerrebroeck P. Standardization of terminology in nocturia: commentary on the ICS report. BJU Int 2002;90(Suppl 3):16–7.

tranquilizers, hypnotics, and diuretics) (Nakagawa et al, 2010). In contrast, the Krimpen study, here analyzing 1114 men 50 to 78 years of age based on frequency-volume chart data, determined that the association between nocturia and mortality was explained by confounding factors including age, chronic obstructive pulmonary disease, smoking, and hypertension (age being the most profound). Specifically, nocturia was associated with increased mortality in the univariate analysis, but was not associated with mortality in multivariate analysis (van Doorn et al, 2012).

Nocturia affects sleep efficiency and sleep latency. Sleep efficiency is defined as actual time asleep (minutes) divided by total time of intended sleep (minutes); normal is considered greater than 85%. Sleep latency is defined as the time it takes to go from being completely awake to being completely asleep. Dew and colleagues (2003) showed that older adults with certain electroencephalography (EEG) sleep characteristics have an increased risk for dying independent of age, gender, and medical comorbidities. Individuals with sleep latency times of greater than 30 minutes were found to have greater than twice the risk for death, and those with sleep efficiency less than 80% were found to have nearly twice the risk for death when controlling for age, gender, and medical burden. Vaughan and associates (2013) prospectively analyzed 63 patients with Parkinson disease using IPSS and polysomnography. Of the 60 having completed the IPSS, 37 (61%) reported two or more episodes of nocturia. These patients demonstrated lower polysomnography-defined sleep efficiency and whole-night total sleep time than patients with zero to one episode of nocturia per night. Also, patients who reported two or three episodes of nocturia with high bother on the IPSS demonstrated lower whole-night total sleep time (281 ± 116 minutes vs. 373 ± 59 minutes, $P = .03$) and worse sleep efficiency ($59\% \pm 23\%$ vs. $76\% \pm 11\%$, $P = .04$) compared to participants who reported two or three episodes of nocturia with low bother. These results show that individuals with higher

bother on the IPSS experience poorer sleep as defined by polysomnography and that patients with Parkinson disease and nocturia have poor sleep in general.

It is not surprising that nocturia is associated with an increased risk for mortality, because nocturia can be a symptom of serious systemic illnesses including hypertension, diabetes, heart disease, and kidney disease (Ancoli-Israel et al, 2012). Sleep loss can negatively affect health by decreasing immune function, increasing the risk for cardiovascular disease, and increasing the risk for developing obesity and type 2 diabetes (Spiegel et al, 2004; Asplund, 2005). This can be better understood by defining the various states and stages of sleep. Sleep is divided into two states: rapid eye movement (REM) and non-rapid eye movement (NREM). NREM accounts for approximately 75% of total sleep time and is divided into 4 stages. Stage 1 accounts for the transition from wakefulness to sleep; stage 2 accounts for light sleep; and stages 3 and 4 consist of deep, restorative sleep or slow-wave sleep (SWS) (Keenan, 1999). The normal sleep cycle alternates between stages 1 and 4 of NREM and REM sleep (Roehrs, 2000). Each night consists of roughly four to six sleep cycles. In the beginning of the night, SWS predominates, whereas in the later hours of the night REM predominates. Waking up during REM sleep is more natural and may still leave one feeling rested compared to waking during SWS, which leaves one to experience daytime fatigue and discomfort irrespective of the total length of sleep time (Lentz et al, 1999). Because the first nocturia episode often occurs within the first 2 to 3 hours of sleep on average, SWS may be interrupted by nocturia, which may explain why nocturics often experience decreased quality of life (van Kerrebroeck et al, 2007).

SWS plays a role in glucose homeostasis. Tasali and colleagues (2008) demonstrated that suppression of SWS for 3 nights impairs glucose tolerance and insulin sensitivity. This explains why aging individuals with impaired SWS are at higher risk for developing type

2 diabetes. The body's regulation of SWS is a homeostatic process as well. This was illustrated by a study that monitored the EEG activity of both control subjects and subjects receiving acoustic stimulation during the first 3 hours of sleep to decrease the amount of SWS. Individuals who had decreased SWS early in the night because of acoustic stimulation were noted to have inadequately compensated amounts of SWS later in the night (Dijk, 2009). In a related study, when the first void occurred during the first two sleep cycles, patients had (on average) 37 minutes of SWS compared to those in whom the first void occurred after the first two sleep cycles, tallying (on average) 56 minutes of SWS ($P = .023$). The actual number of nightly voids (ANV) also affected SWS. Patients who experienced no to one void per night had an average of 62 minutes of SWS compared to those who experienced two or more voids per night, who had an average of 40 minutes of SWS ($P = .014$) (Torimoto et al, 2013). In the Sleep Heart Health Study, 2813 men and 3097 women between the ages of 40 and 100 years of age were enrolled in a community-based prospective study that examined the cardiovascular consequences of sleep-disordered breathing. Usual sleep durations were obtained by questionnaire, and hypertension was defined as systolic BP greater than 104 mm Hg, diastolic BP greater than 90 mm Hg, or the use of medication to treat hypertension. Usual sleep duration above or below the median of 7 to 8 hours per night was associated with an increased risk for hypertension, particularly in individuals who sleep less than 6 hours per night (Gottlieb et al, 2006). **Sleep duration less than 6 hours or more than 8 hours may be a factor predisposing to the metabolic syndrome.** Compared to those sleeping 7 to 8 hours per night, those sleeping longer or shorter were at least 45% more likely to have metabolic syndrome (Hall et al, 2008). A recent analysis of the BACH survey revealed that among baseline lower urinary tract symptoms (LUTS), only nocturia was associated with incident sleep problems at 5-year follow-up (odds ratio [OR] 1.98 with or without body mass index adjustment, $P < .001$) (Araujo et al, 2014). In a U.S. cohort of 2447 men (40 to 79 years of age) who were followed for a median of 17.1 years, nocturia was found to be a marker for coronary heart disease in men younger than 60 years (adjusted OR 1.36) and a marker for death in men 60 years of age or older (OR 1.48) (Lightner et al, 2012). **In summation, present evidence points to nocturia as a risk factor for future development of both metabolic syndrome and early mortality owing to its proxy effect on sleep impairment.**

Nocturia is among the LUTS most strongly associated with falls (Parsons et al, 2009) and is a risk for hip fractures (regardless of age). In an Austrian study, 1820 men 40 to 80 years of age completed the IPSS. Although the IPSS was not correlated with the occurrence of hip fractures, nocturia (two or more voids per night) was an age-independent risk factor for hip fractures (OR 1.36; 95% confidence interval [CI] 1.03, 1.80; $P = .03$) (Temml et al, 2009). Hip fractures have been associated with an in-hospital mortality rate of 5.3%, hence providing explanation for early mortality related to nocturia (Alvarez-Nebreda et al, 2008). What is not clear is whether successful therapy for nocturia could diminish falls, fractures, metabolic syndrome, or early mortality.

Costs to Society

Assuming that 28 million people 25 years of age or older in the United States experience nocturia (more than two voids per night) and this results in a productivity loss of 127 hours per individual, then based on the average U.S. wage of \$17.38 per hour (based on small-size, private industry salaries), the economic value of productivity lost in 2008 was \$61 billion (Holm-Larsen et al, 2010). In a Swedish study, productivity, vitality, and quality of life were assessed in more than 200 professionally active adults with one or more voids per night. Compared with controls, patients with nocturia had significantly increased work impairment (assessed using a work productivity and activity impairment questionnaire) and increased impairment in nonwork activities ($P < .001$). Patients with nocturia also had significantly reduced vitality (based on responses to Short Form-36) and reduced overall quality of life (based on responses

to EQ-5D) compared with controls ($P < .001$). It also was found that work impairment increased and vitality decreased in proportion to nocturia severity ($P < .05$, $< .01$ respectively) (Kobelt et al, 2003). Nocturnal awakenings were found to be associated with sleepiness, naps, and sick leave in the general adult population in a study in which 76% of respondents reported needing to go to the toilet as the reason for awakening (i.e., true nocturia) (Ohayon, 2008).

KEY POINTS: RATIONALE FOR EVALUATION AND MANAGEMENT

- Nocturia is waking during intended sleep because of the desire to void.
- Two or more voids per night appears to be clinically significant.
- The prevalence of nocturia increases with age.
- Nocturia is costly to society because it can lead to decreased productivity, increased time away from work, and increased falls and fractures.
- Nocturia impairs sleep efficiency, sleep latency, and SWS and is associated with increased mortality.
- Nocturia can be a symptom of serious systemic illness, including hypertension, diabetes, heart disease, and kidney disease, leading to metabolic syndrome.

EVALUATION

The cause of nocturia can be multifactorial and complex; therefore the evaluation of nocturia should be thorough and systematic, beginning with a complete history and physical examination. By way of example, a history of medication use, such as lithium, should alert the clinician to the possibility of global polyuria as a result of drug-induced nephrogenic diabetes insipidus. Physical findings pertinent to an evaluation of nocturia might include peripheral edema resulting from cardiac disease, nephrotic syndrome, or venous insufficiency and be associated with nocturnal polyuria. Physical findings such as obesity and short neck might be suggestive of obstructive sleep apnea (OSA); the latter also is associated with nocturnal polyuria. In the population-based Finnish National Nocturia and Overactive Bladder (FINNO) study, numerous risk factors for nocturia were identified, such as urinary urgency, benign prostatic hyperplasia (BPH), snoring, obesity, antidepressant usage, restless leg syndrome, and prostate cancer in men and obesity, urinary urgency, snoring, diabetes, restless leg syndrome, and coronary artery disease in women. However, none of the identified risk factors were associated with nocturia in more than 50% of the affected subjects of both sexes, highlighting the multifactorial cause of nocturia (Tikkinen et al, 2009a). Hence, it is essential that clinicians consider factors beyond the LUT when treating bothersome nocturia.

Some of the questions to consider when evaluating nocturia are: How is nighttime defined? Is the patient awakened by the need to void, or does the patient void because he or she is already awake? A recent study by Weinberger and coworkers (2013) showed that 92% of men and 90% of women are awakened by the urge to void, leaving the remainder as incidental nocturnal convenience voids. **Nighttime is defined as the period between going to bed with the intention of sleeping and waking up with the intention of arising** (van Kerrebroeck et al, 2002). This definition becomes relevant when explaining to the patient how to complete a 24-hour voiding diary or **frequency-volume chart**, the most valuable objective instrument in evaluating nocturia. When completing a frequency-volume chart, the patient must be aware that nocturnal voids are preceded and followed by the intention of sleep regardless of time of day. Because at least 16% of the U.S. population consists of shift workers who occasionally sleep during the day, it is important to remember that nocturia may occur during the day (Beers, 2000). Changing time zones (jet lag) also complicates the

definition of nighttime. Before having a patient complete a frequency-volume chart, it is best to allow sufficient recovery time to eliminate the effect of jet lag.

Although the first morning void after a night's sleep is counted toward daytime (diurnal) frequency rather than the ANV, the volume of the first morning void is included in the tally of nocturnal voided volume. Hence, nocturnal urine volume (NUV) is the sum of all nocturnally voided volumes plus that of the first morning void, because the urine in the latter void is produced during the hours of sleep. An untested assumption is that most patients void before bedtime. Hence the first nocturia-related void is also assumed to have been excreted during the hours of sleep. **Maximum voided volume (MVV)** is the largest voided volume of urine during a 24-hour period. The nocturia index (Ni) is calculated by dividing NUV by MVV (Weiss et al, 1999). When NUV is greater than MVV, the Ni is greater than 1, in which case nocturia must occur if the patient awakens and, if not, enuresis will occur.

Nocturnal polyuria is increased production of urine at night that is offset by lowered daytime urine production, such that 24-hour urine volume remains within normal limits (Asplund, 1995). Because urine is normally produced in an age-dependent circadian pattern, it is worthwhile to determine the nocturnal polyuria index (NPI), which is the percentage of urine produced during nighttime (calculated as $\text{NUV}/\text{total 24-hour urine volume}$). In healthy adults 21 to 35 years of age, mean NPI = 0.14 versus patients aged 65 years and older, whose mean NPI = 0.34 (Rembratt et al, 2002). The NPI for middle-aged adults lies between 0.14 and 0.34. Accordingly, to simplify the definition, the ICS has defined NP as NPI greater than 20% (0.20) in young adults and greater than 33% (0.33) in patients older than 65 years when 24-hour urine production is within normal limits (van Kerrebroeck et al, 2002). Other definitions of nocturnal polyuria include NUV greater than 6.4 mL/kg and NUV greater than 0.9 mL/min (54 mL/hr) (Matthiesen et al, 1996). Blanker and associates (2002) defined nocturnal polyuria as greater than 1.5 mL/min (>90 mL/hr), which was 2 standard deviations above the mean of 60 mL/hr in their study of men 50 to 78 years of age. Van Doorn and colleagues (2013) found that prevalence, incidence, and resolution rates of nocturnal polyuria vary greatly depending upon which definition is used. When analyzing the cohort of 1688 men 50 to 78 years of age in the Krimpen study, men who had nocturnal polyuria defined as nocturnal urine production greater than 90 mL/hr (NUP90) had a baseline prevalence of 15.0% that increased to 21.7% after 6.5 years. When nocturnal polyuria was defined as NUV greater than 33% of 24-hour voided volume (NUV33), baseline prevalence was 77.8% and increased to 80.5% after 6.5 years. At baseline, NUV33 was prevalent in 91.9% of men with nocturia and in 70.1% of men without nocturia and NUP90 was prevalent in 27.7% of men with nocturia and 8.0% of those without nocturia (van Doorn et al, 2013). A universally accepted definition of nocturnal polyuria has yet to be defined.

Another cause of nocturia is **decreased bladder capacity**. This can result from either a global decrease in bladder capacity as expressed by a low MVV or simply a decrease in nocturnal bladder capacity. In both instances, NUV exceeds nocturnal bladder capacity and the patient arises because of the need to void. The **nocturnal bladder capacity index (NBCi)** is a useful means to examine the relationship between the patient's own bladder capacity and nocturnal voided volumes during a 24-hour period. NBCi is calculated by subtracting the predicted number of nightly voids (PNV) from the ANV. The PNV is calculated by subtracting 1 from Ni or (NUV/MVV). If Ni is greater than 1, nocturia occurs because functional bladder capacity (MVV) is exceeded. Therefore $\text{PNV} = (\text{Ni} - 1)$ and $\text{NBCi} = (\text{ANV} - \text{PNV})$. If NBCi is greater than 0, then nocturia occurs at volumes less than MVV (Weiss, 2012). As an example, a patient who voids eight times per night (ANV = 8), who voids a total of 800 mL during the intended hours of sleep (NUV = 800 mL), and who has an MVV of 200 mL would have an Ni of 4 ($\text{Ni} = \text{NUV}/\text{MVV} = 800 \text{ mL}/200 \text{ mL} = 4$). This patient's $\text{PNV} = \text{Ni} - 1 = 4 - 1 = 3$. Therefore this patient's $\text{NBCi} = \text{ANV} - \text{PNV} = 8 - 3 = 5$. An NBCi of 5 indicates a substantially diminished nocturnal bladder capacity. Although there is a significant association between patients with

severe nocturia and NBCi greater than 2 (Weiss et al, 1999), an analysis of a sample of normal volunteers suggested that nocturia is related to diminished nocturnal bladder capacity when NBCi is greater than 1.3 (Burton et al, 2011).

Global polyuria also can cause an individual to wake to void during the hours of sleep. **Global polyuria is defined as 24-hour urine output greater than 40 mL/kg causing both daytime urinary frequency and nocturia** (Oelke and van Kerrebroeck, 2012). For example, a 75-kg patient would be considered to have global polyuria if the 24-hour urine output exceeded 3000 mL ($75 \text{ kg} \times 40 \text{ mL/kg} = 3000 \text{ mL}$). It is worthwhile to note that nocturia can have a mixed cause, as well; that is, a patient may awake to void during the hours of sleep because of diminished nocturnal bladder capacity combined with either nocturnal polyuria or global polyuria.

KEY POINTS: EVALUATION

- A thorough evaluation of nocturia should include a complete history and physical examination.
- A frequency-volume chart or a voiding diary is the single most useful tool in evaluating and classifying the cause of nocturia.
- When NUV is greater than MVV, the Ni is greater than 1, and nocturia will occur if the patient awakens. If the patient does not awaken, enuresis will occur.
- Nocturnal polyuria is increased production of urine at night and has several definitions.
- Global polyuria is defined as 24-hour urine output greater than 40 mL/kg causing both daytime urinary frequency and nocturia.

CAUSE AND MANAGEMENT

Classification of nocturia using a frequency-volume chart, along with a thorough history and physical examination, unlocks up to 17 different underlying medical conditions that may potentially contribute to its genesis (Table 78-2). Diary-based classification of

TABLE 78-2 Diary-Based Classification of Nocturia and Respective Underlying Medical Conditions

NOCTURIA CATEGORY	UNDERLYING MEDICAL CONDITIONS
Nocturnal polyuria	Excessive nighttime fluid intake Peripheral edema Obstructive sleep apnea Diabetes mellitus Congestive heart failure
Diminished global or low nocturnal bladder capacity	Ureteral calculi Bladder calculi Pharmacologic agents Anxiety disorders Learned voiding dysfunction Cancer of bladder, prostate, or urethra Neurogenic bladder Nocturnal detrusor overactivity Prostatic obstruction
Global (24 hour) polyuria	Primary polydipsia Diabetes insipidus Diabetes mellitus

Modified from Weiss JP. Assessment of nocturia and nocturnal polyuria. In: Oelke M, van Kerrebroeck P, editors. Current aspects on diagnosis and treatment of nocturia. London: UNI-MED Verlag AG; 2012 p. 72.

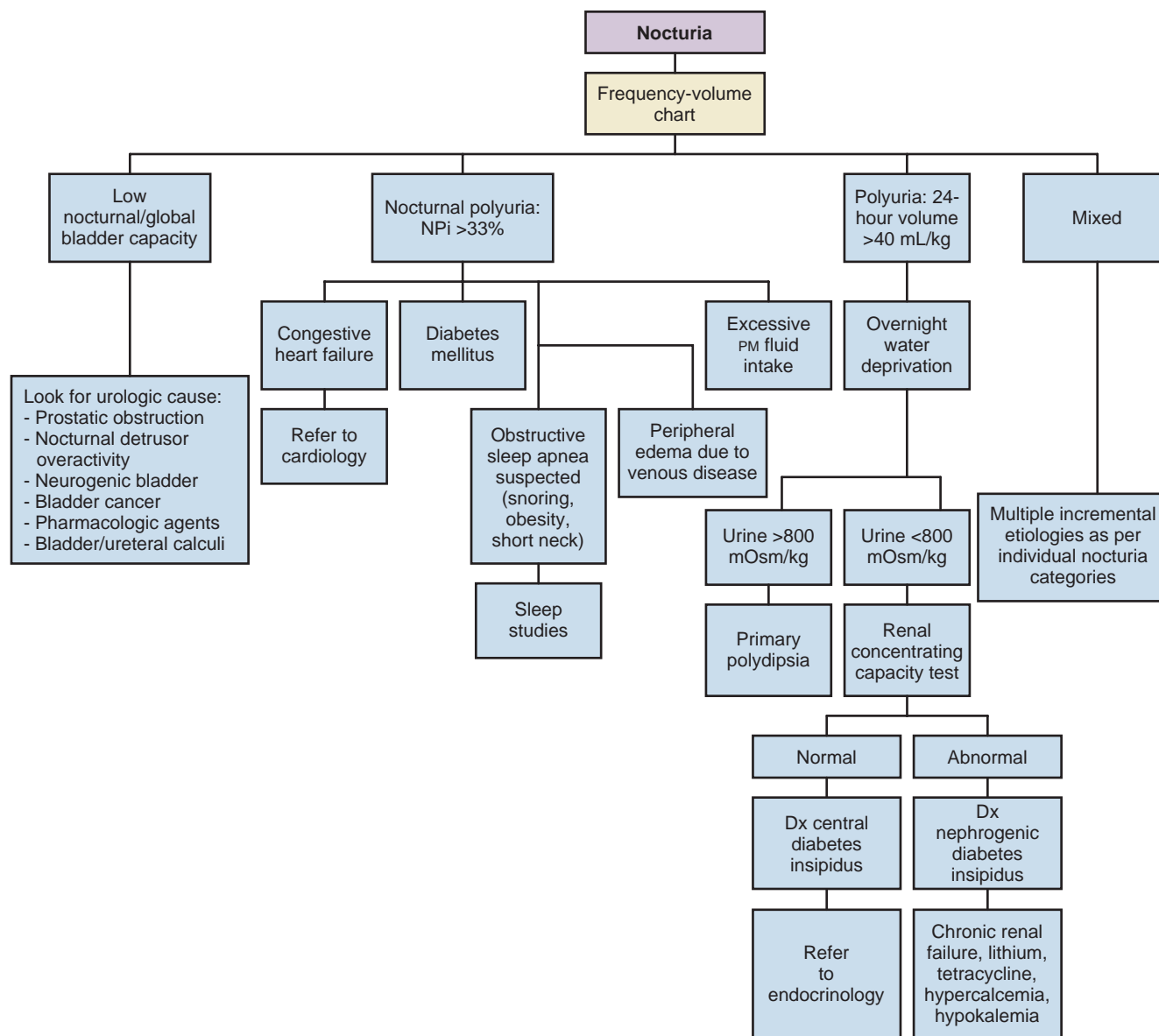


Figure 78-1. Flowchart depicting comprehensive evaluation of nocturia and algorithm for treatment. Dx, diagnosis; NP_i, nocturnal polyuria index. (Modified from Weiss JP. Assessment of nocturia and nocturnal polyuria. In: Oelke M, van Kerrebroeck P, editors. Current aspects on diagnosis and treatment of nocturia. London: UNI-MED Verlag AG; 2012. p. 73.)

nocturia also can help the urologist follow a treatment algorithm (Fig. 78-1). Although unproved, it is assumed that more accurate classification leads to better treatment outcomes.

Nocturnal Polyuria

Epidemiology and Causes

The definition of nocturnal polyuria has a major impact on its perceived prevalence. Among patients with nocturia, nocturnal polyuria seems to be quite common. In a population recruited for a pharmacologic study of nocturia, 819 (88%) of 934 subjects with nocturia (more than two voids per night) who completed a voiding diary had nocturnal polyuria (NUV >33% of 24-hour volume) (Weiss, 2009). On the other hand, in analyzing the Krimpen database, Blanker and associates (2000) found that nocturnal polyuria prevalence for men 50 to 54 and 65 to 69 years of age was 44% and 54%, respectively, at baseline and increased to 51% and 65% after 6.5 years of follow-up when nocturnal polyuria was defined

as NUV/24-hour urine volume greater than 33%. When the nocturnal polyuria definition was changed to NUV greater than 90 mL/hr, the prevalence for men 50 to 54 and 65 to 69 years of age was 14% and 23% and increased to 19% and 26%, respectively, after 6.5 years of follow-up. In an effort to prevent the overestimation of nocturnal polyuria prevalence, van Haast and Bosch (2012) proposed that nocturnal polyuria exists when the NP_i exceeds 53%.

The physiology of renal water handling is relevant to an understanding of the pathophysiology of nocturnal polyuria and its treatment. Normal circadian urine production is age dependent. In those younger than 25 years of age, NUV/total = 14%, and in those older than 65 years of age, NUV/total = 34% (Rembratt et al, 2002). Water is the largest component of the human body; the major determinant of body water is arginine vasopressin (AVP)-regulated water excretion by the kidneys. AVP is stimulated by high serum hyperosmolality, hypovolemia, and angiotensin II and is inhibited by natriuretic peptides and negative feedback via baroreceptors. AVP causes vasoconstriction via V_{1a} receptors and causes renal reabsorption of water through its action on V₂ receptors as follows: AVP

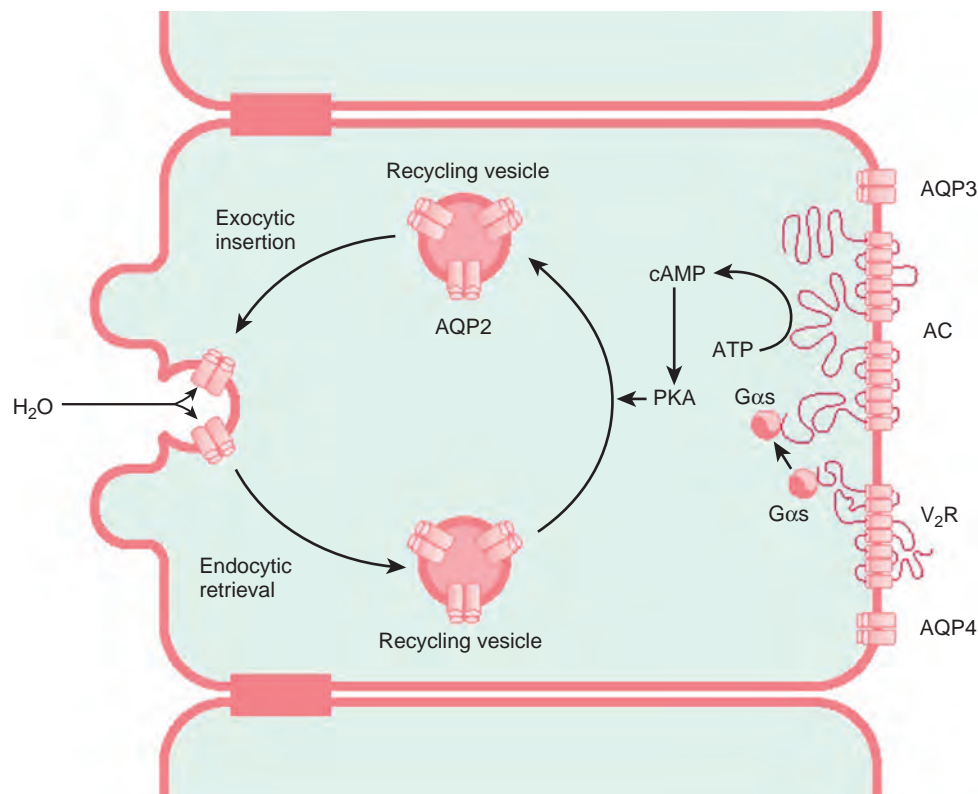


Figure 78-2. Schematic diagram depicting arginine vasopressin regulation of water reabsorption from renal tubular cells. Schematic representation of aquaporin 2 trafficking within a cell. AC, adenyl cyclase; AQP, aquaporin; ATP, adenosine triphosphate; cAMP, cyclic 3'-5'-adenosine monophosphate; PKA, protein kinase A; V₂R, V₂ receptor. (From Nielsen S. Renal aquaporins: an overview. *BJU Int* 2002;90[Suppl. 3]:1-6.)

stimulation of V₂ receptors, located in the basolateral membrane of the renal tubular cell, activates a G_s subtype of guanine nucleotide-binding protein (guanosine triphosphate [GTP]), which in turn activates adenylate cyclase. The result is an increased concentration of cyclic 3'-5'-adenosine monophosphate (cAMP), as well as activation of protein kinase A (PKA). PKA triggers the vesicles that contain aquaporin 2 (AQP2) to fuse with the luminal plasma membrane of the collecting tubule, thereby allowing water to enter the cell. Passive resorption of water through the basolateral membrane (aquaporins 3 and 4) along osmotic gradients by way of other water channels into the vasa recta ultimately leads to water retention (Fig. 78-2). Other factors that inhibit ADH and cause diuresis (inhibit water reabsorption) include prostaglandin E₂ (PGE₂), atrial natriuretic peptide (ANP), hypercalcemia, hypokalemia, lithium, and tetracyclines (Nielsen et al, 1999). Reversal of water diuresis, accordingly, may occur through stimulation of V₂ receptors, either by endogenous AVP or a congener thereof, such as desmopressin. Therefore low antidiuretic hormone (ADH) levels cause a larger volume of dilute urine to be produced. During sleep hours, this translates into a greater likelihood for nocturia.

OSA is a common cause of nocturnal polyuria. OSA is defined as the sudden cessation of respiration during sleep because of airway obstruction. Older adults with severe sleep disordered breathing have a greater number of nocturia episodes (Yalkut et al, 1996; Endeshaw et al, 2004). The mechanism behind this is as follows. Increased airway pressures lead to hypoxia, which in turn causes pulmonary vasoconstriction, the latter leading to increased right atrial transmural pressure with resulting increase in ANP production and ultimately increased renal sodium and water excretion. OSA is more likely as nocturia worsens in severity; the sleep apnea incidence in men with no, one, two, and three or more episodes of nocturia is 10%, 13%, 17%, and 20%, respectively. The sleep apnea

incidence in women with no, one, two, and three or more episodes of nocturia is 7%, 9%, 12%, and 19%, respectively (Hashim et al, 2011). Those with three or more voids per night are more likely to have severe OSA (Kaynak et al, 2004).

Management

Treating nocturnal polyuria should begin with a conservative approach. Directly address the nocturnal polyuria itself by recommending cessation of fluid intake 4 hours before bedtime, the use of compressive lower extremity stockings and/or administration of diuretics in the mid-afternoon for edema states, and antidiuretic therapy at bedtime. Individuals who have insomnia and nocturia may benefit from behavioral therapy directed at improving the insomnia. Tyagi and associates (2014) showed that individuals with insomnia and nocturia saw a greater improvement in number of nocturnal voids when treated with behavioral therapy versus receiving printed materials (information control). The behavioral therapy group saw a decrease in total number of nocturnal voids by 6.5 ± 4.8 over a 14-day period, whereas the information control group saw an increase of nocturnal voids by 1.3 ± 1.7 ($P = .05$). In addition, treating sleep disturbances, hypertension, and obesity in patients with nocturia also may decrease the number of nightly voids and improve quality of life (Sağlam et al, 2013).

A large roster of pharmaceutical agents may contribute to nocturia (Box 78-1). Further, timing of certain medications can influence nocturnal urine output. Diuretics work by preventing water accumulation and forcing water out of the system; they are indicated in patients with lower limb venous insufficiency and congestive cardiac failure. Timing of diuretic administration should be during the mid-afternoon, to allow for elimination of lower extremity excess body fluid during normal waking hours. In a small

BOX 78-1 Drug Effects Causing Nocturia**INCREASED URINE OUTPUT**

Diuretics

SSRIs (block ADH secretion)*†

Calcium channel blockers (increase ANP, block sodium reabsorption in PCT)‡

Tetracycline (attenuates ADH via decreases in cAMP accumulation and action)§

Lithium (decreases AQP2)||

INSOMNIA AND CNS EFFECTS

CNS stimulants

Dextroamphetamine

Methylphenidate

Antihypertensives

α-Blockers

β-Blockers

Methyldopa

Respiratory

Albuterol

Theophylline

Decongestants

Phenylephrine

Pseudoephedrine

Hormones (corticosteroids, thyroid)

Psychotropics

MAOIs

SSRIs

Atypical antidepressants

Dopaminergic agonists (carbidopa)

Antiepileptics (phenytoin)

DIRECT LOWER URINARY TRACT EFFECTS

Ketamine

Direct bladder toxin

Tiaprofenic acid (Surgam)

Toxic cystitis

Cyclophosphamide

ADH, antidiuretic hormone; ANP, atrial natriuretic peptide; AQP, aquaporin; cAMP, cyclic 3'5'-adenosine monophosphate; CNS, central nervous system; MAOIs, monoamine oxidase inhibitors; PCT, proximal convoluted tubule; SSRIs, selective serotonin reuptake inhibitors.

*Rottmann CN. SSRIs and the syndrome of inappropriate antidiuretic hormone secretion. *Am J Nurs* 2007;107:51–8; quiz 58–9.

†Asplund R, Johansson S, Henriksson S, et al. Nocturia, depression and antidepressant medication. *BJU Int* 2005;95:820–3.

‡Otsuka K, Tanaka H, Horinouchi T, et al. Functional contribution of voltage-dependent and Ca²⁺ activated K⁺ (BK[Ca]) channels to the relaxation of guinea-pig aorta in response to natriuretic peptides. *J Smooth Muscle Res* 2002;38:117–29.

§Guzzo J, Cox M, Kelley AB, et al. Tetracycline-induced inhibition of Na⁺ transport in the toad urinary bladder. *Am J Physiol* 1978;235:F359–66.

||Marples D, Christensen S, Christensen EI, et al. Lithium-induced down-regulation of aquaporin-2 water channel expression in rat kidney medulla. *J Clin Invest* 1995;95:1838–45.

randomized double-blind, placebo-controlled trial, 49 men (older than 50 years of age) with nocturnal polyuria were randomized to receive 40 mg of furosemide 6 hours before sleep versus placebo. Among the 43 men who completed the study, the reduction in nocturnal episodes was 0.5 versus 0.0 (furosemide vs. placebo, $P = .014$). There was also a significant reduction in percentage of nighttime voided volume: –18% versus 0% (furosemide vs. placebo, $P <$

.001). Therefore men with nocturnal polyuria may benefit from diuretic therapy 6 hours before sleep (Reynard et al, 1998).

Imipramine is a tricyclic antidepressant with a complex pharmacologic profile, including nonsubtype-selective antimuscarinic effect, also shown to have varied effects in modulating AVP release and potentiating renal proximal tubular sodium and water reabsorption in children. (Tomasi et al, 2001). Imipramine should be used with caution because it has been shown to prolong the PR, QRS, and QTc intervals, increase heart rate, and lower T-wave amplitude during a 4-week treatment course (Giardina et al, 1979). There have been rare reports of torsades de pointes and sudden death resulting from imipramine administration (Swanson et al, 1997).

The influence of nocturnal polyuria on nocturia therapy with antimuscarinics has been addressed in four pooled 3-month phase III randomized control trials, in which 2534 of 3032 patients reported nocturia at baseline (62% of these patients were classified as having nocturnal polyuria). These patients were randomized to receive solifenacin 5 mg, 10 mg, or placebo. In patients without nocturnal polyuria there was a statistically significant reduction in nocturia: –0.18 episode reduction advantage for 5 mg versus placebo and –0.18 episode reduction advantage for 10 mg versus placebo. Nocturia episode reduction in patients with nocturnal polyuria was not significant. However, failure to achieve statistically significantly decreased nocturia between drug and placebo in the nocturnal polyuria group appeared to be due to unexpectedly high performance of placebo in the latter arm (Brubaker and Fitzgerald, 2007).

Weiss and colleagues (2012) defined a clinically significant improvement in nocturia as one that improves the Nocturia Quality of Life (N-QoL) score. The N-QoL questionnaire consists of 13 statements in two domains (sleep/energy and bother/concern). Patients ranked each statement from 1 (lowest QoL) to 4 (highest QoL). One fewer nocturnal void was associated with a 4.68 increase in total N-QoL score, and a 1-hour increase in the first period of undisturbed sleep was associated with a 3.68 increase in total N-QoL. This study revealed that reducing nocturia improves quality of life.

Bal and coworkers (2012) found that nocturia mainly occurs during superficial/REM sleep and that OSA severity is directly related to both nocturia severity and daytime sleepiness and inversely related to sleep efficiency and total sleep time. **Treatment of OSA with continuous positive airway pressure (CPAP) can improve nocturia.** In a study of 88 men with OSA, the average number of nightly voids before treatment was 3.8 ± 0.4 voids per night and after treatment with CPAP decreased to 0.7 ± 0.3 voids per night (Guilleminault et al, 2004). A significant improvement in nocturia by treating OSA with CPAP also has been observed in women (Fitzgerald et al, 2006).

Because ADH is essential in controlling urinary concentration, it is not surprising that synthetic antidiuretics have been used to treat nocturia in addition to being standard replacement therapy for polyuric conditions such as central diabetes insipidus and primary nocturnal enuresis (PNE). Desmopressin (DDAVP) is a selective V₂-receptor agonist that retains the antidiuretic properties of vasopressin but lacks its unwanted pressor activity (Vilhardt, 1990). **When bound to V₂ receptors in the renal collecting tubules, desmopressin increases water permeability, enhances water reabsorption, dilutes extracellular fluid, and concentrates urine (Hammer and Vilhardt, 1985).** There have been multiple clinical trials of nocturia patients treated with desmopressin (Table 78-3). Desmopressin currently has the following recommendations for the treatment of nocturia:

- ICI: Grade A (level 1 evidence) (Andersson et al, 2013)
- European Association of Urology (EAU): Grade A (level 1b evidence) (Gravas et al, 2015)

For maximum concentration of urine, large amounts of urea must be deposited in the interstitium of the inner renal medulla. V₂ receptor activation (e.g., by DDAVP) increases urea permeability by 400% in the terminal portions of the inner medullary collecting duct by activating an AVP-regulated urea transporter, most likely by means of PKA-induced phosphorylation

TABLE 78-3 Clinical Trials Involving Desmopressin Treatment in Patients with Nocturia

STUDY	TARGET POPULATION	MEAN AGE (RANGE)	EFFECTIVE DOSES	ROUTE OF DELIVERY	CLINICAL RESPONDERS IN TREATMENT ARM (%)	CLINICAL RESPONDERS IN PLACEBO ARM (%)	P VALUE	INCIDENCE OF HYPONATREMIA (%)
Mattiasson et al, 2002	Men	65.1 (24.2-87.6)	0.1, 0.2, 0.4 mg (dose titration)	Oral	34	3	<.001	8
Lose et al, 2003	Women	57.1 (20.6-88.7)	0.1, 0.2, 0.4 mg (dose titration)	Oral	44	4	<.0001	12
Lose et al, 2004	Men and women	60.5 (21-88)	0.1, 0.2, 0.4 mg (dose titration)	Oral	67	N/A	N/A	14
Van Kerrebroeck et al, 2007	Men and women	63.4 (19.8-94.0)	0.1, 0.2, 0.4 mg (dose titration)	Oral	33	11	.0014	3
Weiss et al, 2012	Men and women	62.0 (N/A)	100 µg (25 µg in women)	Sublingual	71	47	<.0001*	3
Rembratt et al, 2003	Men and women	75.5† (66-90)	0.2 mg	Oral	82	N/A	N/A	5
Kuo, 2002	Men and women	75.4 (65-84)	0.1 mg	Oral	66.7	N/A	N/A	3
Wang et al, 2011	Men	74.0 (65-88)	0.1 mg	Oral	61.4	13.8	<.001	16
Weiss et al, 2013a	Men	60.4 (N/A)	50 µg or 75 µg	Sublingual	2.04‡	N/A	.0004	3

*For 100-µg dose only.

†Median age.

‡Odds ratio for achieving >33% decrease in number of nocturnal voids at 75 µg.

From Friedman FM, Weiss JP. Desmopressin in the treatment of nocturia: clinical evidence and experience. Ther Adv Urol 2013;5:310-7.

(Sands, 2003). Desmopressin tablet studies have shown long-term reduction in nocturnal voids compared to baseline in both men (48% to 58%) and women (55% to 59%) (Lose et al, 2004) while increasing the initial sleep period by 2 hours in both (Mattiasson et al, 2002; Lose et al, 2003). Hyponatremia is a well-known undesired effect of desmopressin. In high-dose desmopressin tablet studies, 4.9% of all patients developed hyponatremia (defined as serum sodium <130 mmol/L). Patients with hyponatremia were older, smaller, and moderately more polyuric and had slightly lower basal serum sodium level and moderately lower creatinine clearance rate than those without hyponatremia. Nearly all patients who developed hyponatremia in the tablet studies were 65 years of age or older (Rembratt et al, 2006). More recently, studies have been completed with the intraorally dispersible preparation of desmopressin ("melt"). Melt was found to decrease overall nocturia severity and to increase the 33% responder rate. In a 4-week randomized, double-blind study, 757 patients who reported three or more voids per night (90% of whom had nocturnal polyuria) received 10, 25, 50, or 100 µg of melt or placebo. Those who received placebo, 10, 25, 50, or 100 µg of melt had the following reduction in number of nocturnal voids from baseline respectively: -0.86, -0.83, -1.00, -1.18*, and -1.43* and had the following percent increase in 33% responder rate: 47%, 47%, 50%, 53%, 71%* (Weiss et al, 2012). In both men at 50 µg and women at 25 µg desmopressin melt, the odds of increasing the first uninterrupted sleep period to 4 hours or longer was significantly greater than placebo at 1 week and after months 1, 2, and 3 ($P < .0001$) (Sand et al., 2013; Weiss et al, 2013b). In a follow-up study designed to investigate the lowest possible therapeutically effective dose of desmopressin, the efficacy and safety of desmopressin orally disintegrating tablets (ODT) 50 µg and 75 µg in men with nocturia (two or more nocturnal voids) was investigated. In men treated with 50 µg of desmopressin, there was a -0.37 difference in reduction of nightly voids versus placebo ($P = .0003$). In men treated with 75 µg of desmopressin, there was a -0.41 difference in reduction of nightly voids versus placebo ($P < .0001$). In those treated with 50 µg, 0% had serum sodium from 126 mmol/L to 129 mmol/L and 2% had serum sodium less than 125 mmol/L. In those treated with 75 µg, 4% had serum sodium from 126 mmol/L to 129 mmol/L and 3% had serum sodium less than 125 mmol/L (Weiss et al, 2013b). From these data it could be concluded that 50 µg of desmopressin melt may be the lowest therapeutically beneficial dose for men. In a related study, 261 women (age range 19 to 87 years) with an average of three voids per night were given 25 µg desmopressin ODT. Desmopressin ODT reduced nocturia by -1.46 (treatment difference vs. placebo: -0.22; $P = .028$) and increased odds of a 33% or greater response (from baseline nocturia severity) versus placebo by 85% (OR 1.85; $P = .006$) at month 3. This low dose of desmopressin melt increased mean time to first nocturnal void by 155 minutes (treatment difference vs. placebo: 49 min; $P = .003$) and reduced NUV by 235 mL (treatment difference vs. placebo: 83 mL; $P = .003$) at month 3. There were no serum sodium drops less than 125 mmol/L or treatment withdrawals as a result of hyponatremia (Sand et al, 2013).

Women appear to be more sensitive (by a factor of at least 2) to desmopressin than men in terms of effects on nocturnal urine production (Juul et al, 2011) and duration of action (Yamaguchi et al, 2013). This may be because the gene for the V_2 receptor is located on the X chromosome. It is hypothesized that the gene for V_2 can escape inactivation that results in a higher density of V_2 receptors in women and thus a greater response to desmopressin. The phenomenon of gender differential sensitivity to desmopressin may explain why women seem to fare as well with a lower dose of the melt preparation than men (25 µg vs. 50 µg minimum effective dosages, respectively, based on the most recent studies as described herein).

Bae and colleagues (2013) demonstrated that desmopressin is a useful treatment in men with nocturia refractory to treatment with α -blockers. There were 216 patients enrolled in this study (76% with nocturnal polyuria, 7.2% with decreased nocturnal bladder capacity, and 16.8% with mixed cause). The number of nocturnal voids decreased from a mean of 7.0 to 5.7 episodes for 3 days at the 24-week visit (Bae et al, 2013).

In summary, when considering the use of desmopressin to treat nocturia, voiding diary analysis should immediately follow a standard urologic history and physical examination. Patients found to have global polyuria should be excluded for further evaluation. Patients with low volumes per void and no nocturnal polyuria may need nonantidiuretic treatment approaches. **Current thinking is that desmopressin would be most appropriate therapy for patients with nocturia related to nocturnal polyuria.** There is a gender sensitivity differential between genders (men appear to require a higher dose than women). Even though the risk for hyponatremia is less than 1% in those younger than 65 and 8% in those older than 65 years of age, it is always wise to obtain a baseline serum sodium before commencing therapy. Desmopressin should not be given to elderly patients (younger than 65 years of age) with baseline hyponatremia. It is advisable to monitor the serum sodium within 7 days and then 28 days after initial or incremental dosing, then continuing to check sodium levels every 6 months or more often as indicated. Table 78-4 presents a complete summary of medications used to treat nocturnal polyuria, including desmopressin.

Diminished Global and Nocturnal Bladder Capacity

Cause

Diminished bladder capacity has many causes, including infra-vesical obstruction, idiopathic nocturnal detrusor overactivity (NDO), neurogenic bladder, cystitis (bacterial, interstitial, tuberculous, radiation), and cancer of the bladder, prostate, or urethra. NDO occurs in association with nocturia in most patients with detrusor overactivity plus overactive bladder (OAB). NDO does not normally occur during sleep, is not due to sleep disturbance, and is not linked to nocturnal polyuria (Krystal et al, 2010). Additional causes of low global or nocturnal bladder capacity include learned voiding dysfunction, anxiety disorders, bladder calculi, ureteral calculi, and drugs such as xanthines (caffeine, theophylline) and β -blockers (Weiss, 2012). Low bladder compliance is also a risk factor for nocturia severity (Tsui et al, 2013).

Management

Treating bladder outlet obstruction (BOO) is thought to improve nocturia by lowering postvoid residual (PVR) volume, increasing functional bladder capacity, and reducing urinary frequency. Reducing BOO also diminishes input from afferents in the bladder neck and the prostatic urethra (Cumming and Chisholm, 1992; Margel et al, 2007; Housami and Abrams, 2008). Tamsulosin therapy and transurethral resection of prostate (TURP) significantly reduced the number of episodes of nocturia in 17.9% and 32.2% of patients, respectively (Yoshimura et al, 2003), and by an average of 1.3 episodes per night in patients treated with TURP (Antunes et al, 2009). Outlet reduction also may act by increasing hours of uninterrupted sleep, with commensurate benefit to nocturia-specific quality of life. In patients who underwent simple prostatectomy, nocturia episodes decreased from a baseline of 3.4 to 2.6, 2 to 3 months postoperatively ($P < .001$) and hours of uninterrupted sleep increased from 1.83 at baseline to 2.74, 2 to 3 months postoperatively ($P < .001$) (Margel et al, 2007). In a retrospective analysis of 1258 men, improvement in nocturia-related quality of life was studied after various forms of treatment for BPH, including watchful waiting, α -blockers, TURP, and transurethral microwave treatment (TUMT). After 6 to 12 months, watchful waiting, α -blockers, TURP, and TUMT yielded reduction in nocturia episodes by 7%, 17%, 75%, and 32%, respectively. Improvements in nocturia-related quality of life were most strongly associated with

* $P < .05$.

TABLE 78-4 Summary of Pharmacotherapeutic Agents Used to Treat Nocturnal Polyuria

DRUG NAME	DOSE	SIDE EFFECT(S)	CONTRAINDICATION(S)
Furosemide*	40 mg PO 6 hr before sleep (Dose range 20-80 mg PO in adults. The study mentioned in this text used only 40 mg in the context of nocturia.)	Anorexia Nausea/vomiting Constipation Cramping Diarrhea Blurred vision Hearing loss Tinnitus Headaches Orthostatic hypotension Hypokalemia Dehydration Metabolic alkalosis Muscle cramps SLE exacerbation	Hypersensitivity Anuria Hepatic coma Hypovolemia Severe hypokalemia
Imipramine*	20 mg PO qhs	Prolong the PR interval Prolong QRS interval Prolong QTc interval Increase the heart rate Lower T-wave amplitude Torsades de pointes Sudden death	Hypersensitivity Usage of MAOI within 14 days Acute recovery period after MI
Desmopressin*	Intranasal: 10 µg/spray; max 40 µg/day (central DI indication only) Oral: 0.1-mg tablets; max 0.6 mg/day for PNE Melt: 60-, 120-, 240-µg melt tabs Melt "low dose": 25 µg (women) and 50-100 µg (men)	Water intoxication Hyponatremia Flushing Vulval pain Diarrhea Mild abdominal cramps Nausea Increased SGOT Thrombosis Cough Dyspnea Drowsiness Dizziness Headache Abnormal thinking Seizures	Hypersensitivity CrCl <50 mL/min Hyponatremia History of hyponatremia Von Willebrand disease, type IIB

*RxDrugs Drug Index. Accessed January 2014.

CrCl, creatine clearance; DI, diabetes insipidus; MAOI, monoamine oxidase inhibitor; MI, myocardial infarction; PNE, primary nocturnal enuresis; SGOT, serum glutamic oxaloacetic transaminase; SLE, systemic lupus erythematosus.

treatment-associated declines in nocturia severity (van Dijk et al, 2010). Other reports point out that nocturia still persists despite bladder outlet-reducing surgery. The NHANES III in the United States showed that among those who undergo TURP, nocturia (two or more voids per night) persists for 41% of people 60 to 69 years of age and 50% of those 70 years or older (Platz et al, 2002).

TURP appears to be superior to tamsulosin for treatment of BPH-related nocturia. In a single-center study, 66 men with LUTS (mean age 68.9 years) were randomized to receive **TURP or tamsulosin 0.4 mg orally at bedtime** for management of nocturia. Nocturia severity was assessed at baseline, 3 months, and 1 year. TURP was associated with a significant improvement compared to tamsulosin in the number of nocturnal awakenings, IPSS, International Consultation on Incontinence Questionnaire Nocturia (ICIQ-N), and ICIQ-N Quality of Life (N-QoL) scores. Hours of uninterrupted sleep increased in both groups but were not statistically different (Simaioridis et al, 2011).

A secondary analysis of the Department of Veterans Affairs Cooperative Study Trial studied the changes in nocturia in a cohort of 1078 men with BPH who were randomly assigned to receive **terazosin, finasteride, combination, or placebo**. Overall, episodes of nocturia decreased from a baseline mean of 2.5 to 1.8, 2.1, 2.0, and 2.1 episodes in the terazosin, finasteride, combination, and placebo groups, respectively. Mean reduction of nocturia episodes from treatment with terazosin alone was significantly different from that with treatment with combination therapy ($P = .03$), finasteride ($P = .0001$), and placebo ($P = .0001$). Terazosin and combination therapy reduced the number of nocturia episodes in men with BPH, although the advantage of terazosin over placebo was only a net reduction of 0.3 episode (Johnson et al, 2003).

Using as a model the "typical" patient with OAB who has 12 voids per day, one to four episodes of arising from sleep to void, and 50% of the voids occurring with urgency, an effective antimuscarinic would be expected to reduce the episodes of urgency by half

of 50%, or 25%. This would amount to a reduction in nocturia from 4 to 3, 3 to 2.25, and 2 to 1.5. Clearly the benefit would be most appreciated by those more severely afflicted with nocturia, if the theory is correct. In a subgroup analysis of 962 patients of both sexes older than 20 years of age with OAB studied for response to solifenacin 5 mg and 10 mg, solifenacin 10 mg decreased nocturia “significantly” by 0.12 episodes and increased volume per nocturnal micturition by 28 mL. Hence, the clinical outcomes appear to be ineffective (Yokoyama et al, 2011).

In a 12-week randomized, controlled study, 850 patients were given 4 mg **tolterodine extended release** (Tolt ER) or placebo once daily 4 hours before going to bed. All subjects had eight or more micturitions per 24 hours with or without urge incontinence and nocturia (mean of 2.5 episodes per night). Tolt ER did not significantly reduce the total number of nocturnal micturitions; however, it did significantly reduce OAB-related and severe OAB-related nocturnal micturitions versus placebo. Tolt ER did not affect non-OAB nocturnal micturitions (Rackley et al, 2006). The suggestion here was that antimuscarinic therapy would benefit nocturic voids that are characterized by severe urgency.

A randomized, controlled trial of 658 patients at 52 sites were given either placebo or **tropium chloride** 20 mg twice daily in this 12-week, multicenter, parallel, double-blind, placebo-controlled study. After 12 weeks a significant decrease was found in the mean number of nocturic episodes per night: 0.29 episode for placebo versus 0.57 episode for drug (baseline was two episodes per night) (Rudy et al, 2006).

Fesoterodine significantly improved all diary end points compared with placebo except for nocturnal voids and nocturnal urgency episodes (Nitti et al, 2007; Dmochowski et al, 2010; Herschorn et al, 2010). However, in a study powered to determine the effect of fesoterodine on nocturnal urgency as a primary end point, **fesoterodine** did decrease the number of nocturnal urgency episodes and the number of nocturnal voids when compared to placebo. This particular study looked at change from baseline to week 12 in the number of nocturnal urgency episodes per 24 hours. Urgency was defined as an intense and/or sudden need to urinate. The subject rated the feeling of urgency associated with each micturition episode using the 5-point Urinary Sensation Scale (USS) (Coyne et al, 2011), where 1 = no feeling of urgency and 5 = unable to hold and leaked urine. Nocturnal urgency episodes were defined as those with a USS rating of 3 or greater. The mean reduction from baseline to week 12 in nocturnal urgency episodes per 24 hours was statistically significantly greater with fesoterodine than placebo (−1.29 vs. −1.06, $P = .0030$). Mean reduction from baseline to week 12 in nocturnal micturitions per 24 hours was significantly greater with fesoterodine than placebo (−1.02 vs. −0.84, $P = .0112$) (Weiss et al, 2013a).

A prospective randomized trial was conducted with 2583 men with one or more episodes of nocturia at baseline who were treated with doxazosin, finasteride, combination therapy (doxazosin + finasteride), or placebo. Treatment effectiveness was measured by a self-reported number of nocturia episodes at 1 and 4 years after treatment. After 1 year, mean nocturia was reduced by 0.35, 0.40, 0.54, and 0.58 in the placebo, finasteride, doxazosin, and combination groups, respectively; reductions with combination therapy and with doxazosin were statistically greater than with placebo ($P < .05$). After 4 years, the number of nocturia episodes was also significantly reduced in patients treated with doxazosin and combination therapy versus placebo ($P < .05$). In a subgroup of men older than 70 years of age ($n = 495$), all of the drugs significantly reduced nocturia at 1 year (finasteride 0.29, doxazosin 0.46, and combination 0.42) compared to placebo (0.11, $P < .05$). This study confirmed that α -blockers alone are as effective as α -blockers in combination with 5 α -reductase inhibitors (5-ARIs) for treatment of nocturia (Johnson et al, 2007).

A randomized, double-blind, placebo-controlled study was carried out in which patients were assigned to one of four groups for 12 weeks: placebo ($n = 222$), 4 mg Tolt ER ($n = 217$), 0.4 mg tamsulosin ($n = 215$), and combination Tolt ER + tamsulosin ($n = 225$). The combination of Tolt ER + tamsulosin significantly reduced

the number of micturitions per night versus placebo (−0.59 vs. −0.39, $P = .02$) (Kaplan et al, 2006).

In conclusion, α -blockers, 5-ARIs, antimuscarinics, and antimuscarinics plus α -blockers have occasionally been found to have a statistically significant reduction in nocturia episodes, but clinical significance appears to be minimal. When 5-ARIs and α -blockers are used in combination, they have the same degree of success as α -blockers alone. The optimal patients to treat with medications that target the bladder and the prostate appear to be those who have a large number of nocturia episodes (mostly resulting from severe urgency).

There have also been various alternative treatments for nocturia, including cyclooxygenase-2 inhibitors combined with α -blockers (Gorgel et al, 2013), sedatives (Song and Ku, 2007; Sugaya et al, 2007), melatonin (Drake et al, 2004; Sugaya et al, 2007), and phytotherapy. A systematic review of 1562 men from 18 randomized control trials examined the effect of *Pygeum africanum* on various BPH symptoms, including nocturia. There was no comparison of *P. africanum* to other pharmacologic treatments for BPH, including α -blockers and 5-ARIs. Compared to men taking placebo, those taking *P. africanum* reported a 19% reduction in nocturia (weighted mean difference [WMD] of −0.9 times per evening, $P > .05$) (Wilt and Ishani, 1998).

Another phytotherapeutic, Cernilton, is prepared from the ryegrass pollen *Secale cereale*. A systematic review was conducted to assess the efficacy of Cernilton on urinary symptoms in men with BPH. Cernilton reduced nocturia compared with placebo and another neutraceutical, Paraprost. Versus placebo, the weighted risk ratio for improvement of nocturia was 2.05 (95% CI = 1.41 to 3.00); thus those taking Cernilton were approximately two times more likely to have their nocturia improve over those taking placebo. Versus Paraprost, the WMD was −0.40 nocturic episodes per evening (95% CI = −0.73 to −0.07). Data were collected from a self-rated urinary symptom survey. The limitations of these trials were short duration, limited number of enrollees, gaps in reported outcomes, quality control of preparations, and lack of a proved active control (Wilt et al, 2011).

Mirabegron, a β_3 -adrenergic agonist approved by the U.S. Food and Drug Administration to treat OAB, showed an improvement in nocturia measured by the OAB symptom score at 3 and 6 months after beginning treatment in female patients over 70 years of age who did not respond to anticholinergics (Nakanishi, 2013). For a complete list of medications used to treat diminished global or nocturnal bladder capacity, including mirabegron, see Table 78-5.

Mixed Nocturnal Polyuria and Diminished Global and Nocturnal Bladder Capacity

In a review of 194 consecutive patients with nocturia, 13 (7%) had nocturnal polyuria (NPi >0.35), 111 (57%) had decreased nocturnal bladder capacity, and 70 (36%) had “mixed” cause. Forty-five (23%) also had polyuria (defined as 24-hour urine output >2500 mL). Nocturnal polyuria was a significant component of nocturia in 43% of the patients. Thus the cause of nocturia was found to be multifactorial and often unrelated to an underlying urologic condition (Weiss et al, 1998). In a U.S. veteran population of men 50 years of age and older, Vaughan and colleagues (2009) demonstrated a significant improvement in ANV ($P < .001$), bother ($P < .001$), time to initiating sleep ($P = .003$), time to return to sleep ($P = .03$), and quality of sleep ($P < .001$) after single or combined pharmacotherapy and/or behavioral modification to address the mixed etiologic category of nocturia. Behavioral modification included reduced caffeine and alcohol intake, limited nighttime fluid intake, and improved sleep hygiene through moderate exercise and attention to room temperature, noise, and lighting. Additional interventions included early evening leg elevation and compression stockings if patients had bilateral lower extremity edema. Also, if patients had BPH-related symptoms (American Urology Association symptom score ≥ 8 , maximum uroflow [Qmax] 4 to 15 mL/sec), terazosin was titrated as tolerated/needed to 10 mg daily. If

TABLE 78-5 Pharmacotherapeutic Agents Used to Treat Diminished Global and Nocturnal Bladder Capacity

DRUG NAME	DOSE	SIDE EFFECT	CONTRAINDICATION(S)
Tamsulosin*	0.4 mg, 0.8 mg PO qhs	Orthostatic hypotension Syncope Dizziness Asthenia Somnolence Headache Insomnia Diarrhea Abnormal ejaculation Intraoperative floppy iris syndrome Rhinitis Pharyngitis Sinusitis Cough Priapism Back pain Chest pain	Hypersensitivity
Terazosin*	1-5 mg PO qhs Max dose: 20 mg/day	Headache Dizziness Somnolence Vertigo Asthenia Nervousness Depression Paresthesias Hypotension Palpitations Syncope Supraventricular tachycardia Atrial fibrillation Postural hypotension Weight gain Peripheral edema Thrombocytopenia Dyspnea Nasal congestion Rhinitis Sinusitis Nausea Blurred vision Amblyopia Intraoperative floppy iris syndrome Impotence UTI Decreased libido Priapism	Hypersensitivity
Finasteride*	5 mg/day PO	Orthostatic/postural hypotension Peripheral edema Asthenia Headache Dizziness Somnolence Decreased libido Impotence Rhinitis Dyspnea Decreased ejaculate volume Gynecomastia Breast cancer	Hypersensitivity Women and children Pregnancy

TABLE 78-5 Pharmacotherapeutic Agents Used to Treat Diminished Global and Nocturnal Bladder Capacity—cont'd

DRUG NAME	DOSE	SIDE EFFECT	CONTRAINDICATION(S)
Solifenacin*	5 mg/day, 10 mg/day PO	Dizziness Depression Dry mouth Constipation Nausea Colonic obstruction Severe fecal impaction Intestinal obstruction Dyspepsia Upper abdominal pain Vomiting Hypertension QT prolongation Torsades de pointes Cough Blurred vision Dry eyes Urinary retention UTI Fatigue	Hypersensitivity Urinary retention Gastric retention Uncontrolled narrow-angle glaucoma Severe hepatic impairment
Tolterodine*	1-2 mg PO bid LA formulation: 2-4 mg/day PO	Dizziness Headache Somnolence Chest pain Dry mouth Constipation Dyspepsia Abnormal vision Xerophthalmia Urinary retention Dysuria Dry skin Arthralgia Sinusitis Weight gain Flulike symptoms Fatigue	Hypersensitivity Urinary retention Gastric retention Uncontrolled narrow-angle glaucoma Potassium salts
Tropium chloride*	Adults younger than 75 yr: 20 mg PO bid Adults older than 75 yr: 20 mg PO qhs (based on tolerability)	Dry mouth Constipation Flatulence Abdominal pain Abdominal distention Dyspepsia Headache Fatigue Rash Stevens-Johnson syndrome Nasopharyngitis Dry eyes Nasal dryness Abnormal vision Urinary retention Rhabdomyolysis Fever Heat stroke Influenza Anaphylaxis	Hypersensitivity Urinary retention Gastric retention Uncontrolled narrow-angle glaucoma Severe renal impairment

Continued

TABLE 78-5 Pharmacotherapeutic Agents Used to Treat Diminished Global and Nocturnal Bladder Capacity—cont'd

DRUG NAME	DOSE	SIDE EFFECT	CONTRAINDICATION(S)
Fesoterodine*	4-8 mg/day PO If on potent CYP3A4 inhibitors: 4 mg/day PO	Dry mouth Constipation Nausea Abdominal pain Dyspepsia Gastroenteritis Cough Dry throat Upper respiratory tract infection Tachycardia Angina Chest pain QT prolongation Dysuria Urinary retention UTI Rash Dry eyes Back pain Edema Heat stroke	Hypersensitivity Urinary retention Gastric retention Uncontrolled narrow-angle glaucoma Severe hepatic impairment
Doxazosin*	Immediate release: 1-8 mg/day PO Extended release: 4-8 mg/day PO	Dizziness Headache Drowsiness Weakness Mental depression Syncope Vertigo Orthostatic hypotension Hypotension Arrhythmias Palpitations Edema Dyspnea Syncope Blurred vision Reddened sclera Epistaxis Dry mouth Nasal congestion Rash Vomiting Diarrhea Nausea Abdominal cramps	Hypersensitivity
Mirabegron†	25-50 mg/day PO	Hypertension Urinary retention	Hypersensitivity

*RxDrugs Drug Index. Accessed 1.14.

†Astellas Pharma US package insert.

LA, long-acting; UTI, urinary tract infection.

patients reported eight or more voids in 24 hours, Tolt ER 2 mg to 4 mg daily was initiated. If return to sleep required 30 minutes or more after an awakening, zaleplon 5 mg nightly after the first nocturia episode between 11:00 PM and 3:00 AM was recommended. This proved to be a structured, multimodal approach with little risk (one trip to an emergency room for hypotension after taking terazosin) (Vaughan et al, 2009). Multicomponent treatment was further found to be an effective strategy to treat nocturia in a study

by Johnson and coworkers (2013) in which men on α -blockers received individually titrated drug therapy (extended-release oxybutynin) or multicomponent behavioral treatment (pelvic floor muscle training and delayed voiding and urge suppression techniques). Participants with two or more episodes of nocturia at baseline showed larger changes with behavioral treatment compared with antimuscarinic therapy (mean reduction = 1.26 vs. 0.61, respectively; $P = .008$).

Polyuria

Etiology

Polyuria is defined as 24-hour urine output greater than 40 mL/kg. Once a steady state is reached, polyuria is associated with excessive oral intake of fluids (polydipsia). This results in urinary frequency both day and night because of the global overproduction of urine in excess of bladder capacity. Nocturia is often the manifesting symptom of patients with polyuria of any cause. Hence, it behooves the urologist to understand both its cause and diagnostic measures to sort out its various causes. Common underpinnings of polyuria include diabetes mellitus, diabetes insipidus, and primary polydipsia (dipsogenic and psychogenic).

Diabetes insipidus is a disorder of water balance in which inappropriate excretion of water leads to polydipsia in an effort to prevent circulatory collapse. Diabetes insipidus can be central or nephrogenic. Central diabetes insipidus occurs when there is a deficiency in the synthesis or secretion of endogenous ADH. This can be due to loss of neurosecretory neurons in the hypothalamus or the posterior pituitary gland as a result of trauma, primary pituitary tumors (e.g., craniopharyngioma), metastatic disease (e.g., breast, lung), infiltrative diseases (e.g., sarcoid), infarction (e.g., Sheehan syndrome postpartum), or infection (e.g., tuberculosis, meningitis) or can be idiopathic (Shapiro and Weiss, 2012). Nephrogenic diabetes insipidus is diuresis in the setting of normal ADH secretion, but the kidneys do not respond appropriately to the hormone, as in some patients with chronic kidney disease. Some extrarenal causes of diabetes insipidus include PGE₂, ANP, hypercalcemia, hypokalemia, lithium, and tetracyclines. This mechanism may explain how nonsteroidal anti-inflammatory drugs can improve nocturia, because of the effect of these drugs in blocking PGE₂-mediated diuresis (Araki et al, 2004).

The diagnostic algorithm for polyuria begins with an overnight water deprivation test (OWDT). To perform an OWDT, the patient is told not to drink anything during the night. It is normal if the first morning urine osmolality is greater than 800 mOsm/kg H₂O. Normal implies that there is an appropriate secretion of ADH and an appropriate renal response. If the OWDT is normal, polyuria is due to primary polydipsia (neurogenic or dipsogenic). If the OWDT is abnormal, the patient has diabetes insipidus. To distinguish central from nephrogenic diabetes insipidus, a renal concentrating capacity test (RCCT) may be performed. The RCCT is performed by giving 40 µg of desmopressin intranasally or 0.4 mg orally. The patient's bladder is emptied and urine osmolality is tested 3 to 5 hours later. Water is restricted for the first 12 hours after the drug is administered. The RCCT is normal if the urine osmolality rises to at least 800 mOsm/kg H₂O (Weiss, 2012). If the RCCT is normal, the patient has central diabetes insipidus and can be treated with desmopressin replacement therapy. If the RCCT is abnormal, the patient has nephrogenic diabetes insipidus, which has no specific treatment.

Management

Patients who have a 24-hour urine production greater than 30 mL/kg may benefit from water restriction during the day and night. Tani and associates (2014) showed that adjusting water and food intake so that 24-hour urine production is less than 30 mL/kg reduced NUV and nocturnal urinary frequency with no adverse events. This illustrates that guidance on water intake may be a safe and effective conservative lifestyle management strategy.

A patient with **primary (dipsogenic or psychogenic) polydipsia** will have normal urine osmolality on water deprivation tests. **Dipsogenic polydipsia** is associated with a history of a central neurologic abnormality such as a history of brain trauma

or radiation. Psychogenic polydipsia is a long-term behavioral or psychiatric disorder. It is important to identify the cause of a patient's polyuria to treat it effectively. For example, if a patient with polyuria has diabetes mellitus, controlling glycosuria may improve the polyuria. Central diabetes insipidus may be treated with synthetic vasopressin analogues. Patients without diabetes insipidus who are found to have polydipsia and are compulsive water drinkers may benefit from psychotherapy (Weiss, 2012). Nocturia as a manifesting complaint is expected to benefit from appropriate therapy for polyuria.

KEY POINTS: EVALUATION AND MANAGEMENT OF NOCTURIA

- Classification of nocturia using a frequency-volume chart yields up to 17 different underlying medical conditions that may potentially contribute to its genesis.
- OSA is a common cause of nocturnal polyuria.
- The normal circadian pattern of nocturnal urine production is age dependent.
- Treating nocturnal polyuria should focus on underlying contributing medical comorbidities.
- There are many causes of diminished bladder capacity, including infravesical obstruction, idiopathic nocturnal detrusor overactivity, neurogenic bladder, cystitis (bacterial, interstitial, tuberculous, radiation), and cancer of the bladder, prostate, or urethra.
- Treating BOO is thought to improve nocturia by lowering PVR volume, increasing functional bladder capacity, and reducing urinary frequency.
- α -Blockers, 5-ARIs, antimuscarinics, and antimuscarinics plus α -blockers have been found to have a statistically but questionably clinically significant reduction in nocturia episodes.
- When 5-ARIs and α -blockers are used in combination, they have the same degree of success as α -blockers alone.
- The optimal group to treat with medications that target the bladder and the prostate appear to be those who have a large number of nocturia episodes (mostly as a response to severe urgency) and not from nocturnal polyuria.
- Polyuria is defined as 24-hour urine output greater than 40 mL/kg and thus must be diagnosed through use of frequency-volume charts. Treatment of conditions underlying polyuria should benefit nocturia.
- Patients with nocturnal polyuria unrelated to specific causes such as peripheral edema or sleep apnea may benefit from treatment with desmopressin.
- Desmopressin should be avoided in elderly patients (older than 65 years of age) and those with baseline hyponatremia.

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The complete reference list is available online at www.expertconsult.com.



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Pharmacologic Therapy to Facilitate Bladder Filling and Urine Storage

The function of the lower urinary tract (LUT) is to effect efficient and low-pressure bladder filling, low-pressure urine storage with normal sensation and perfect continence, and periodic complete voluntary emptying, again at low pressure. The structures involved include the smooth musculature of the bladder and the bladder outlet, and striated muscle, both intrinsic (to the bladder outlet) and extrinsic (the striated musculature surrounding the bladder outlet and the striated musculature of the pelvic floor). These component structures are controlled by a complex interplay among the central and peripheral nervous systems and local regulatory factors. **Pharmacologic alteration of LUT function can occur at any point along the afferent or efferent limb of this complex neuromuscular cascade, by receptor activation or stimulation or blockade, by affecting the concentration of neurotransmitter at an activation site, or by stimulating or inhibiting signal transduction mechanisms** (Andersson and Wein, 2004; Andersson et al, 2009; Birder et al, 2009; Fry et al, 2009; Andersson et al, 2013a; see also Chapter 69).

This chapter considers the pharmacologic management of bladder filling and storage and bladder emptying and voiding dysfunction. The conceptual basis of the organization is that of the expanded functional classification shown in Boxes 70-1 and 70-2 in Chapter 70 and the division of therapies in the relatively simple manner of those that facilitate urine storage and bladder filling and those that facilitate bladder emptying and voiding (see Boxes 70-3 and 70-4 in Chapter 70). Although the principles expressed are generally applicable to patients of all ages, specifics concerning usage in the pediatric age groups and in the elderly are considered in detail in Chapters 142 and 143. Specific information regarding the pharmacologic management of LUT dysfunction secondary to obstruction by benign prostatic enlargement (BPE) is considered in detail in Chapter 104, whereas drug therapy for the treatment of bladder and pelvic pain disorders is considered in detail in Chapters 13 and 14.

As an apology in explanation to significant contributors to the field whose works have not been specifically referenced by name as frequently as they could have been, please note that the citations have been chosen primarily because of their comprehensive review or specific informational content and not because of originality or initial publication on a particular subject, except where noted.

PHARMACOLOGIC THERAPY TO FACILITATE BLADDER FILLING AND URINE STORAGE

Inhibiting Bladder Contractility, Decreasing Sensory Input, Increasing Bladder Capacity

Bladder Contraction and Muscarinic Receptors

The major portion of the neurohumoral stimulus for physiologic bladder contraction is acetylcholine (ACh)-induced stimulation of

Pharmacologic Therapy to Facilitate Bladder Emptying

postganglionic parasympathetic muscarinic cholinergic receptor sites in the bladder (detrusor smooth muscle and possibly other sites) (see Chapter 69). **Atropine and atropine-like agents will depress normal bladder contractions and involuntary bladder contractions (detrusor overactivity [DO]) of any cause** (Andersson, 1988, 1993; Andersson and Wein, 2004). **In patients with involuntary contractions, the volume to the first DO will usually be increased, the amplitude of the contraction decreased, and the total bladder capacity increased** (Jensen, 1981).

It has been stated that bladder compliance in normal individuals and in those with neurogenic detrusor overactivity (NDO) (Abrams et al, 2002), in whom the initial slope of the filling curve on cystometry is normal before the involuntary contraction, does not seem to be significantly altered by antimuscarinic agents and that the effect of pure antimuscarinics in patients who exhibit only decreased compliance had not been well studied. Regarding the subject of bladder tone during filling, Andersson (1999a, 1999b, 2004, 2011b) and Andersson and Yoshida (2003) have pointed out that although it is widely accepted that there is normally no sacral parasympathetic outflow to the bladder during filling, antimuscarinic drugs increase, and anticholinesterase inhibitors decrease, bladder capacity. **Because antimuscarinic drugs do seem to affect the sensation of urgency during filling, this suggests an ongoing ACh-mediated stimulation of detrusor tone** (see later). If this is correct, agents that inhibit ACh release or activity would be expected to contribute to bladder relaxation or the maintenance of low bladder tone during filling with a consequent decrease in filling and storage symptomatology unrelated to the occurrence of DO. **Outlet resistance, at least as reflected by urethral pressure measurements, does not seem to be clinically affected.**

Although the antimuscarinic agents usually produce significant clinical improvement in patients with DO and associated symptoms, they typically produce only partial inhibition. In many animal models, atropine only partially antagonizes the response of the whole bladder to pelvic nerve stimulation and of bladder strips to field stimulation, although it does completely inhibit the response of bladder smooth muscle to exogenous cholinergic stimulation. This phenomenon, which is called *atropine resistance*, is secondary to release of a transmitter other than ACh (see Andersson, 1993; Andersson et al, 1999; Andersson and Wein, 2004; see also Chapter 69). Atropine resistance is the most common hypothesis invoked to explain the clinical difficulty in eradicating DO with antimuscarinic agents alone, and it is also invoked to support the rationale of combined treatment of DO with agents that have different mechanisms of action (Andersson, 2006).

Andersson and Wein (2004) cite references stating that atropine resistance seems to be of little importance in normal human bladder muscle, but point out that atropine-resistant (nonadrenergic, noncholinergic [NANC]) contractions have been reported in human detrusor smooth muscle and in morphologically and/or functionally changed bladders in individuals with various types

of voiding dysfunction. Thus, the importance or unimportance of an atropine-resistant component to detrusor contraction in the treatment of DO in humans remains to be established.

Muscarinic Receptors

In the human bladder, where the mRNAs for all the five pharmacologically defined muscarinic receptors, M_1 to M_5 , have been demonstrated (Sigala et al, 2002; Abrams et al, 2006a; Giglio and Tobin, 2009; Andersson, 2011a), there is a predominance of mRNAs encoding M_2 and M_3 receptors (Yamaguchi et al, 1996; Sigala et al, 2002; Abrams et al, 2006a; Giglio and Tobin, 2009; Andersson, 2011a). This seems to be the case also in the animal species investigated (Hegde and Eglén, 1999; Chess-Williams, 2002; Andersson and Arner, 2004). Both M_2 and M_3 receptors can be found on detrusor muscle cells, where M_2 receptors predominate at least 3:1 over M_3 receptors, but also in other bladder structures, which may be of importance for detrusor activation. Thus, muscarinic receptors can be found on urothelial cells, on suburothelial nerves, and on other suburothelial structures, such as interstitial cells (Chess-Williams, 2002; Gillespie et al, 2003; Gillespie, 2004; Mansfield et al, 2005; Bschiepfer et al, 2007; Giglio and Tobin, 2009; Andersson, 2011a).

In human as well as animal detrusor, the M_3 receptors are believed to be the most important for contraction (Andersson, 1993; Chess-Williams, 2002; Abrams et al, 2006a; Giglio and Tobin, 2009; Andersson, 2011a). No differences between genders could be demonstrated in rat and human bladders (Kories et al, 2003). The functional role for the M_2 receptors has not been clarified, and even in M_3 receptor knockout (KO) mice they seem responsible for less than 5% of the carbachol-mediated detrusor contraction (Matsui et al, 2000). Stimulation of M_2 receptors has been shown to oppose sympathetically (β -adrenoceptor [β -AR]) mediated smooth muscle relaxation (Hegde et al, 1997). However, based on animal experiments, M_2 receptors have been suggested to directly contribute to contraction of the bladder in certain disease states (denervation, outflow obstruction). Experiments on human detrusor muscle by Stevens and coworkers (2007) could not confirm this, however. Pontari and colleagues (2004) analyzed bladder muscle specimens from patients with neurogenic bladder dysfunction to determine whether the muscarinic receptor subtype mediating contraction shifts from M_3 to the M_2 receptor subtype, as found in the denervated, hypertrophied rat bladder. They concluded that normal detrusor contraction is mediated by the M_3 receptor subtype, whereas contractions can be mediated by the M_2 receptors in patients with neurogenic bladder dysfunction.

Muscarinic receptors are coupled to G proteins, but the signal transduction systems may vary. In general, M_1 , M_3 , and M_5 receptors are considered to couple preferentially to $G_{q/11}$, activating phosphoinositide hydrolysis, in turn leading to activation of intracellular calcium. M_2 and M_4 receptors couple to pertussis toxin-sensitive $G_{i/o}$, resulting in inhibition of adenylate cyclase activity. In the human detrusor, Schneider and colleagues (2004a), confirming that the muscarinic receptor subtype mediating carbachol-induced contraction is the M_3 receptor, also demonstrated that the phospholipase C inhibitor U-73122 did not significantly affect carbachol-stimulated bladder contraction, despite blocking inositol trisphosphate (IP_3) generation. They concluded that carbachol-induced contraction of human urinary bladder is mediated via M_3 receptors and largely depends on Ca^{2+} entry through nifedipine-sensitive channels and activation of the Rho-kinase pathway. Thus, it may be that the main pathways for muscarinic-receptor activation of the detrusor via M_3 receptors are calcium influx via L-type calcium channels, and increased sensitivity to calcium of the contractile machinery via inhibition of myosin light chain phosphatase through activation of Rho-kinase.

The signaling mechanisms for the M_2 receptors are less clear than those for M_3 receptors. As mentioned previously, M_2 receptor stimulation may oppose sympathetically induced smooth muscle relaxation, mediated by β -ARs via inhibition of adenylyl cyclase

(Hegde et al, 1997). In agreement with this, Matsui and colleagues (2003) suggested, based on results obtained in M_2 receptor KO mice, that a component of the contractile response to muscarinic agonists in smooth muscle involves an M_2 receptor-mediated inhibition of the relaxant effects of agents that increase cyclic adenosine monophosphate (cAMP) levels. M_2 -receptor stimulation can also activate nonspecific cation channels and inhibit K_{ATP} channels through activation of protein kinase C (Bonev and Nelson, 1993; Kotlikoff et al, 1999).

Muscarinic receptors may also be located on the presynaptic nerve terminals and participate in the regulation of transmitter release. The inhibitory prejunctional muscarinic receptors have been classified as muscarinic M_2 in the rabbit (Tobin and Sjögren, 1995) and rat (Somogyi and de Groat, 1992) and M_4 in the guinea pig (Alberts, 1995) and in the human bladder (D'Agostino et al, 2000). Prejunctional facilitatory muscarinic receptors appear to be of the M_1 subtype in the bladders of rat, rabbit (Somogyi and de Groat, 1992; Tobin and Sjögren, 1995), and humans (Somogyi and de Groat, 1999; Giglio and Tobin, 2009; Andersson, 2011b). The muscarinic facilitatory mechanism seems to be upregulated in overactive bladders (OABs) from chronic spinal cord-transected rats. The facilitation in these preparations is primarily mediated by M_3 muscarinic receptors (Somogyi and de Groat, 1999).

The relative roles of the different presynaptic and postsynaptic receptor subtypes in normal and abnormal bladder function still require clarification, and thus speculation regarding optimal drug therapy based only on in vitro receptor selectivity profiles represents, at the very least, a gross oversimplification of assumptions regarding the muscarinic regulation of bladder function. The muscarinic receptor functions may be changed in different urologic disorders, such as outflow obstruction, neurogenic bladders, DO without overt neurogenic cause, and diabetes (Andersson, 2000a, 2011b). However, it is not always clear what the changes mean in terms of changes in detrusor function.

In general, all drug therapy for LUT dysfunction is hindered by a concept that can be expressed in one word: *uroselectivity* (Andersson, 1998). The clinical usefulness of available antimuscarinic agents is limited by their lack of selectivity, responsible for the classic peripheral antimuscarinic side effects of dry mouth, constipation, blurred vision, and increase in heart rate (HR) and for the effects on cognitive functions (Table 79-1). Although M_3 -receptor selective agents have the potential to eliminate some of these side effects, it would appear that the M_3 receptors in tissues of the LUT are identical to those elsewhere in the body (Caulfield and Birdsall, 1998). It may be speculated, however, that there is some heterogeneity among M_3 receptors, and this has prompted many pharmaceutical companies to continue to search for the "ideal" antimuscarinic agent to treat DO, one that would be relatively selective for muscarinic receptors involved in the regulation of bladder contraction. Receptor selectivity, however, is not the only basis on which a drug may be uroselective. From a clinical standpoint, it would seem particularly important to be able to describe in relative terms the ratio between a drug dose required for a desired therapeutic action and the dose that produces side effects. A differential effect could be based not only on receptor selectivity but also on other known and as yet undefined physiologic, pharmacologic, or metabolic characteristics. Organ selectivity would thus seem to be the "holy grail" of such therapy. The same problematic set of concepts applies to virtually all drugs used for the treatment of LUT dysfunction.

Prevalence of Lower Urinary Tract Symptoms

The prevalence of lower urinary tract symptoms (LUTS), including OAB syndrome, varies with the criteria for diagnosis. According to Irwin and colleagues (2006), using the 2002 International Continence Society (ICS) definition, the overall prevalence of OAB was 11.8% (the EPIC study). The rates were similar in men and women and increased with age. A similar study by Herschorn and colleagues (2008) found the OAB prevalence to be 13% in Canadian men and 14% in women. Irwin and colleagues (2011)

TABLE 79-1 Muscarinic Receptors: Distribution and Function

REGION	SUBTYPE OF MUSCARINIC RECEPTOR	FUNCTION
Bladder	M ₂ > M ₃ (3:1)	M ₃ : mediates human detrusor contraction
Salivary glands, parotid gland	M ₁ , M ₃	M ₁ : high-viscosity lubrication M ₃ : salivation
Gastrointestinal tract	M ₂ > M ₃ (4:1)	M ₃ : stimulation of gastrointestinal motility
Brain	M ₁ to M ₅ (M ₃ sparse)	Involved in higher cognitive processes such as learning and memory (mostly M ₁)
Eye	M ₁ to M ₂ (M ₃ predominates)	Controls iris sphincter contraction
Heart	M ₂	Modulates pacemaker activity, atrioventricular conduction, and the force of contraction

Data from Abrams P, Andersson KE, Buccafusco JJ, et al. Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol* 2006;148:565–78.

estimated and predicted the worldwide and regional prevalence of LUTS, OAB, urinary incontinence (UI), and LUTS suggestive of bladder outlet obstruction (LUTS/BOO) in 2008, 2013, and 2018 based on current ICS symptom definitions in adults older than 20 years. An estimated 45.2%, 10.7%, 8.2%, and 21.5% of the 2008 worldwide population (4.3 billion) were affected by at least one LUTS, OAB, UI, and LUTS/BOO, respectively. By 2018, an estimated 2.3 billion individuals will be affected by at least one LUTS (18.4% increase), 546 million by OAB (20.1%), 423 million by UI (21.6%), and 1.1 billion by LUTS/ BOO (18.5%).

LUTS may be the result of several different mechanisms, both myogenic and neurologic (Morrison et al, 2002; Birder et al, 2009; Koelbl et al, 2009; Banakhar et al, 2012), and abundant drugs have been used for treatment. The 5th International Consultation on Incontinence (2013) assessed drugs used for treatment of incontinence (Andersson et al, 2013a). The assessment criteria (Table 79-2) were based on the Oxford guidelines, and the drugs included are listed in Tables 79-3 and 79-4.

Antimuscarinic (Anticholinergic) Agents

Mechanism of Action. For many years, antimuscarinic drugs have been the gold standard for treatment of OAB. Still, the ways by which they exert their beneficial effect have not yet been established.

ACh stimulates both muscarinic and nicotinic receptors (Abrams and Andersson, 2007). Antimuscarinics block selectively muscarinic receptors. They are currently the mainstay of treatment of OAB symptoms, even if new therapeutic options have been introduced (Andersson et al, 2013a). The **traditional view** is that in OAB and DO, the drugs act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by ACh, released from activated cholinergic (parasympathetic) nerves. Thereby, they decrease the ability of the bladder to contract. **However, antimuscarinic drugs act mainly during the storage phase, decreasing urgency and increasing bladder capacity, and during this phase, there is normally no parasympathetic input to the LUT** (Morrison et al, 2002;

TABLE 79-2 International Consultation on Incontinence: Oxford Guidelines (Modified)

LEVELS OF EVIDENCE	
LEVEL	DESCRIPTION
Level 1	Systematic reviews, meta-analyses, good quality RCTs
Level 2	RCTs, good-quality prospective cohort studies
Level 3	Case-control studies, case series
Level 4	Expert opinion
GRADES OF RECOMMENDATION	
GRADE	DESCRIPTION
Grade A	Based on level 1 evidence (highly recommended)
Grade B	Consistent level 2 or 3 evidence (recommended)
Grade C	Level 4 studies or “majority evidence” (optional)
Grade D	Evidence inconsistent or inconclusive (no recommendation possible) or the evidence indicates that the drug should not be recommended

RCTs, randomized controlled trials.
From Andersson KE, Chapple CR, Cardozo L, et al. Pharmacology treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, et al, editors. *Incontinence*. Paris: European Association of Urology and International Consultation on Urological Diseases; 2013. p. 625–728.

Andersson, 2004). Furthermore, antimuscarinics are usually competitive antagonists. This implies that when there is a massive release of ACh, as during micturition, the effects of the drugs should be decreased; otherwise the reduced ability of the detrusor to contract would eventually lead to urinary retention. Undeniably, high doses of antimuscarinics can produce urinary retention in humans, **but in the dose range used for beneficial effects in OAB and DO, there is little evidence for a significant reduction of the voiding contraction** (Finney et al, 2006) (Fig. 79-1). There is indirect clinical evidence for release of ACh during bladder filling in certain abnormal conditions. Smith and colleagues (1974) found that in patients with recent spinal cord injury (SCI), inhibition of ACh breakdown by use of cholinesterase inhibitors could increase resting tone and induce rhythmic contractions in the bladder. Yossepowitch and colleagues (2001) inhibited ACh breakdown with edrophonium in a series of patients with disturbed voiding or UI. They found a significant change in sensation and decreased bladder capacity, induction or amplification of involuntary detrusor contractions, or significantly decreased detrusor compliance in 78% of the patients with the symptom pattern of OAB, but in no patients without specific complaints suggesting DO. Thus, **during the storage phase, ACh may be released from both neuronal and non-neuronal sources** (e.g., the urothelium and suburothelium) and directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium and within the detrusor. There is also good experimental evidence that antimuscarinics act during the storage phase by decreasing the activity in afferent nerves (both C and Aδ fibers) from the bladder (De Laet et al, 2006; Iijima et al, 2007).

Muscarinic receptors are found on bladder urothelial cells, where their density can be even higher than in detrusor muscle. The role of the urothelium in bladder activation has attracted much interest (Andersson, 2002a; de Groat, 2004; Birder and de Groat, 2007; Birder et al, 2009; Giglio and Tobin, 2009; Andersson, 2011b), but whether the muscarinic receptors on urothelial cells can influence micturition has not yet been established. Yoshida and colleagues (2004, 2006, 2008) found that there is basal ACh release in human bladder. This release was resistant to tetrodotoxin and much

TABLE 79-3 Drugs Used in the Treatment of Lower Urinary Tract Symptoms (LUTS), Overactive Bladder (OAB), and Detrusor Overactivity (DO): Assessments According to the Oxford System (Modified)

	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION		LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
ANTIMUSCARINIC DRUGS			β-ADRENERGIC RECEPTOR AGONISTS		
Atropine, hyoscyamine	3	C	Terbutaline (β ₂)	3	C
Darifenacin	1	A	Salbutamol (β ₂)	3	C
Fesoterodine	1	A	Mirabegron (β ₃)	1	B
Imidafenacin	1	B			
Propantheline	2	B	PHOSPHODIESTERASE TYPE 5 (PDE5) INHIBITORS*		
Solifenacin	1	A	Sildenafil, tadalafil, vardenafil	1	B
Tolterodine	1	A			
Trospium	1	A	CYCLOOXYGENASE (COX) INHIBITORS		
DRUGS WITH MIXED ACTIONS			Indomethacin	2	C
Oxybutynin	1	A	Flurbiprofen	2	C
Propiverine	1	A			
Flavoxate	2	D	TOXINS		
DRUGS ACTING ON MEMBRANE CHANNELS			Botulinum toxin (neurogenic)†	1	A
Calcium antagonists	2	D	Botulinum toxin (idiopathic)†	1	B
Potassium channel openers	2	D	Capsaicin (neurogenic)‡	2	C
ANTIDEPRESSANTS			Resiniferatoxin (neurogenic)‡	2	C
Imipramine	3	C			
Duloxetine	2	C	OTHER DRUGS		
α-ADRENERGIC RECEPTOR ANTAGONISTS			Baclofen§	3	C
Alfuzosin	3	C			
Doxazosin	3	C	HORMONES		
Prazosin	3	C	Estrogen	2	C
Terazosin	3	C	Desmopressin	1	A
Tamsulosin	3	C			
Silodosin	3	C			
Naftopidil	3	C			

*Male LUTS/OAB.

†Bladder wall.

‡Intravesical.

§Intrathecal.

||Nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly!

From Andersson KE, Chapple CR, Cardozo L, et al. Pharmacology treatment of urinary incontinence. In Abrams P, Cardozo L, Khoury S, Wein A, editors: Incontinence. Paris: European Association of Urology and International Consultation on Urological Diseases; 2013. p. 625–728.

diminished when the urothelium was removed; thus, the released ACh was probably of non-neuronal origin and at least partly generated by the urothelium. Thus during the storage phase, ACh and adenosine triphosphate (ATP) may be released from both neuronal and non-neuronal sources (e.g., the urothelium) and directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium and within the detrusor. These mechanisms may be important in the pathophysiology of OAB and represent possible targets for antimuscarinic drugs.

Pharmacologic Properties. In general, antimuscarinics can be divided into tertiary and quaternary amines (Guay, 2003; Abrams and Andersson, 2007). They differ with regard to lipophilicity, molecular charge, and even molecular size, tertiary compounds typically having higher lipophilicity and molecular charge than quaternary agents. Atropine, darifenacin, fesoterodine (and its active metabolite 5-hydroxymethyl tolterodine [5-HMT]), imidafenacin, oxybutynin, propiverine, solifenacin, and tolterodine, are tertiary amines. They are generally well absorbed from the gastrointestinal tract and should theoretically be able to pass into the central nervous system (CNS), dependent on their individual

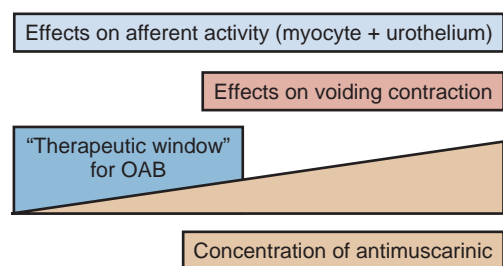
physicochemical properties. High lipophilicity, small molecular size, and less charge will increase the possibilities to pass the blood-brain barrier, but for some of the drugs this is counteracted by active transport out of the CNS by P-glycoprotein. Quaternary ammonium compounds, such as propantheline and trospium, are not well absorbed, pass into the CNS to a limited extent, and have a low incidence of CNS side effects (Guay, 2003). They still produce well-known peripheral antimuscarinic side effects, such as accommodation paralysis, constipation, increase in HR, and dryness of mouth.

Many antimuscarinics are metabolized by the P450 enzyme system to active and/or inactive metabolites (Guay, 2003). The most commonly involved P450 enzymes are CYP2D6 and CYP3A4. The metabolic conversion creates a risk for drug-drug interactions, resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate competition) plasma concentration or effect of the antimuscarinic and/or interacting drug. Antimuscarinics secreted by the renal tubules (e.g., trospium) may theoretically be able to interfere with the elimination of other drugs using this mechanism.

TABLE 79-4 Drugs Used in the Treatment of Stress Urinary Incontinence: Assessments According to the Oxford System (Modified)

DRUG	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
Clenbuterol	3	C
Duloxetine	1	B
Ephedrine	3	D
Estrogen	2	D
Imipramine	3	D
Methoxamine	2	D
Midodrine	2	C
Norephedrine (phenylpropanolamine)	3	D

From Andersson KE, Chapple CR, Cardozo L, et al. Pharmacology treatment of urinary incontinence. In Abrams P, Cardozo L, Khoury S, Wein A, editors: *Incontinence*. Paris: European Association of Urology and International Consultation on Urological Diseases; 2013. p. 625–728.

**Figure 79-1.** Rationale for use of antimuscarinic agents in overactive bladder (OAB).

Antimuscarinics are still the most widely used treatment for urgency and urgency incontinence (Andersson, 2004; Andersson et al, 2009, 2013a). However, currently used drugs lack selectivity for the bladder, and effects on other organ systems may result in side effects that limit their usefulness. For example, all antimuscarinic drugs are contraindicated in untreated narrow-angle glaucoma.

One way of avoiding many of the antimuscarinic side effects is to administer the drugs intravesically. However, this is practical in only a limited number of patients.

Clinical Use. The clinical relevance of efficacy of antimuscarinic drugs relative to placebo has been questioned (Herbison et al, 2003). However, large meta-analyses of studies performed with the currently most widely used drugs (Chapple et al, 2005a, 2008a; Novara et al, 2008) clearly show that antimuscarinics are of significant clinical benefit. It was recommended that because the pharmacologic profiles of each drug (see later) and dosages differ, these factors should be considered in making treatment choices.

The durability of the effects of antimuscarinics is not known, and the relapse rate of symptoms after discontinuation of treatment has not been systematically studied. In 173 women with OAB symptoms for longer than 6 months, Lee and colleagues (2011) studied in a prospective, randomized, open-label trial what happened 3 months after the patients had been successfully treated for 1, 3, or 6 months. The relapse rate was 62%, and the request for re-treatment was 65%, indirectly suggesting an efficacy of treatment.

None of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin, tolterodine, or trospium) is ideal as a first-line treatment for all OAB or DO patients. Optimal treatment should be individualized, implying that the patient's comorbidities and

concomitant medications, and the pharmacologic profiles of the different drugs, should be taken into consideration (Chapple et al, 2008a).

To compare the effects of different antimuscarinic drugs for OAB symptoms, Madhuvrata and colleagues (2012) analyzed 86 trials, 70 with parallel and 16 with crossover designs (31,249 adults), drawing attention to the significance of the adverse effect of dry mouth. They concluded that when the prescribing choice is between oral immediate-release (IR) oxybutynin or tolterodine, tolterodine might be preferred for reduced risk of dry mouth. Also, extended-release (ER) preparations of oxybutynin or tolterodine might be preferred to IR preparations because there is less risk of dry mouth. Comparing solifenacin and IR tolterodine, solifenacin might be preferred for better efficacy and less risk of dry mouth. Fesoterodine might be preferred over ER tolterodine for superior efficacy but has a higher risk of withdrawal because of adverse events in general, but in particular a higher risk of dry mouth.

Several studies have documented that the persistence with prescribed antimuscarinic therapy for OAB is low (Kelleher et al, 2005; Basra et al, 2008; Sears et al, 2010; Wagg et al, 2012). The most common causes seem to be lack of efficacy and adverse effects. However, there is some evidence suggesting that the tolerability of the different antimuscarinics may differ. Wagg and colleagues (2012) analyzed prescription data for patients receiving antimuscarinics for treatment of the OAB syndrome over a 12-month period. At 12 months, they found that the proportions of patients still on their original treatment were as follows: solifenacin, 35%; tolterodine ER, 28%; propiverine, 27%; oxybutynin ER, 26%; trospium, 26%; tolterodine IR, 24%; oxybutynin IR, 22%; darifenacin, 17%; and flavoxate, 14%. The longest mean persistence was reported for solifenacin (187 days vs. 77 to 157 days for the other treatments). Gomes and colleagues (2012) compared the persistence of oxybutynin or tolterodine therapy among older patients newly prescribed one of these drugs. This was a retrospective cohort study of Ontarians aged 66 years and older. Persistence with treatment was defined on the basis of refills for the drug within a grace period equal to 50% of the prescription duration. The authors identified 31,996 patients newly treated with oxybutynin and 24,855 newly treated with tolterodine. After 2 years of follow-up, persistence on oxybutynin (9.4%) was significantly lower than that on tolterodine (13.6%, $P < .0001$). The median times to discontinuation of oxybutynin and tolterodine were 68 and 128 days, respectively. Kessler and colleagues (2011) analyzed 69 trials enrolling 26,229 patients with OAB; the aim was to compare adverse events of antimuscarinics using a network meta-analytic approach that overcomes shortcomings of conventional analyses. They found similar overall adverse event profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride, but not for oxybutynin orally administered when currently used starting dosages were compared. They concluded that most currently used antimuscarinics seem to be equivalent first-choice drugs to start the treatment of OAB, except for oral oxybutynin doses of 10 mg/day or more, which may have more unfavorable adverse event profiles.

Adverse Effects. Even if the use of antimuscarinics is associated with many adverse effects, they are generally considered to be "safe" drugs. However, among the more serious concerns related to their use is the risk of cardiac adverse effects, particularly QT prolongation and induction of polymorphic ventricular tachycardia (torsades de pointes), and increases in HR (Andersson and Olshansky, 2007; Andersson, 2011c; Rosa et al, 2013). QT prolongation and its consequences are not related to blockade of muscarinic receptors, but rather linked to inhibition of the hERG potassium channel in the heart (Roden, 2004). Thus, QT prolongation is not a class effect of antimuscarinics. However, the experiences with terodiline, an antimuscarinic drug that caused torsades de pointes in patients (Connolly et al, 1991; Stewart et al, 1992), have placed the whole drug class under scrutiny.

The parasympathetic actions on the heart oppose the excitatory actions of the sympathetic nervous system and slow the HR. An elevated resting HR has been linked to overall increased morbidity

and mortality, particularly in patients with cardiovascular diseases. The prevalence of cardiovascular comorbidities was found to be significantly higher in patients with than without OAB (Andersson et al, 2010b). Because mean changes in HR reported in population studies might not be applicable to an individual patient, and particularly in patients at risk of cardiac disease, even moderate increases in HR might be harmful. The potential of the different antimuscarinic agents to increase HR and/or prolong the QT time has not been extensively explored for all agents in clinical use. Differences among drugs cannot be excluded, but risk assessments based on available evidence are not possible.

Another concern is that antimuscarinic drugs commonly used to treat OAB can be associated with CNS side effects including cognitive dysfunction, memory impairment, dizziness, fatigue, and headache. With the exception of oxybutynin IR, CNS-related side effects are not commonly found when investigated. The potential to cause CNS-related adverse effects may differ among drugs, but in the absence of comparative trials, relative risk assessments are not possible.

Antimuscarinics with Specific Action

Here, data on the different antimuscarinics are presented. These drugs are assumed to block only muscarinic receptors (motivating the term *specific*). The amount of information for the individual drugs varies, and so does the degree of detail from the different studies presented. However, the information has been chosen to give a reasonable efficacy and adverse effect profile of each individual drug.

Atropine Sulfate. Atropine (*dl*-hyoscyamine) is rarely used for treatment of OAB or DO because of its systemic side effects, which preclude its use as an oral treatment. However, in patients with NDO, intravesical atropine may be effective for increasing bladder capacity without causing any systemic adverse effects, as shown in open pilot trials (Ekström et al, 1992; Glickman et al, 1995; Deaney et al, 1998; Enskat et al, 2001; Fader et al, 2007). It appears that intravesical atropine may be as effective as intravesical oxybutynin in patients with NDO (Fader et al, 2007).

The pharmacologically active antimuscarinic component of atropine is L-hyoscyamine. Although still used, few clinical studies are available to evaluate the antimuscarinic activity of L-hyoscyamine sulfate (Muskat et al, 1996). For assessment, see Table 79-3.

Darifenacin Hydrobromide. Darifenacin is a tertiary amine with moderate lipophilicity, well absorbed from the gastrointestinal tract after oral administration, and extensively metabolized in the liver by the cytochrome P450 isoforms CYP3A4 and CYP2D6, the latter saturating within the therapeutic range (Skerjanec, 2006). UK-148993, UK-73689, and UK-88862 are the three main circulating darifenacin metabolites, of which only UK-148993 is said to have significant antimuscarinic activity. However, available information suggests that various metabolites of darifenacin contribute little to its clinical effects (Michel and Hegde, 2006). The metabolism of darifenacin by CYP3A4 suggests that coadministration of a potent inhibitor of this enzyme (e.g., ketoconazole) may lead to an increase in the circulating concentration of darifenacin (Kerbusch et al, 2003).

Darifenacin is a relatively selective muscarinic M₃-receptor antagonist. In vitro, it is selective for human cloned muscarinic M₃ receptors relative to M₁, M₂, M₄, or M₅ receptors. Theoretically, drugs with selectivity for the M₃ receptor can be expected to have clinical efficacy in OAB and DO with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes (Andersson, 2002b). However, the clinical efficacy and adverse effects of a drug are dependent not only on its profile of receptor affinity, but also on its pharmacokinetics, and on the importance of muscarinic receptors for a given organ function.

Darifenacin has been developed as a controlled-release formulation, which allows once-daily administration. Recommended doses are 7.5 and 15 mg/day. The clinical effectiveness of the drug has been documented in several randomized controlled trials (RCTs) (Haab et al, 2004; Cardozo and Dixon, 2005; Chapple et al, 2005b;

Foote et al, 2005; Steers et al, 2005; Haab et al, 2006; Hill et al, 2006; Zinner et al, 2006; Chapple et al, 2007a; Abrams et al, 2008; Chancellor et al, 2008b; Dwyer et al, 2008; for reviews, see Guay, 2005; Zinner, 2007; Chapple et al, 2008a; Novara et al, 2008). Haab and colleagues (2004) reported a multicenter, double-blind, placebo-controlled, parallel-group study that enrolled 561 patients (19 to 88 years; 85% female) with OAB symptoms for more than 6 months, and included some patients with prior exposure to antimuscarinic agents. After washout and a 2-week placebo run-in, patients were randomized (1:4:2:3) to once-daily oral darifenacin controlled-release tablets, 3.75 mg (n = 53), 7.5 mg (n = 229), or 15 mg (n = 115), or matching placebo (n = 164) for 12 weeks. Using an electronic diary during weeks 2, 6, and 12 (directly preceding clinic visits), patients recorded daily incontinence episodes, micturition frequency, bladder capacity (mean voided volume [MVV]), frequency of urgency, severity of urgency, incontinence episodes resulting in change of clothing or pads, and nocturnal awakenings caused by OAB. Tolerability data were evaluated from adverse event reports. Darifenacin 7.5 mg and 15 mg had a rapid onset of effect, with significant improvement compared with placebo being seen for most parameters at the first clinic visit (week 2). Darifenacin 7.5 mg and 15 mg were significantly superior to placebo for (median) improvements in micturition frequency (7.5 mg, -1.6; 15 mg, -1.7; placebo, -0.8), frequency of urgency per day (-2.0; -2.0; -0.9), and number of incontinence episodes leading to a change in clothing or pads (-4.0; -4.7; -2.0). There was no significant reduction in nocturnal awakenings caused by OAB. The most common adverse events were mild-to-moderate dry mouth and constipation, with a CNS and cardiac safety profile comparable to placebo. No patients withdrew from the study as a result of dry mouth, and discontinuation related to constipation was rare (0.6% for placebo vs. 0.9% for darifenacin).

In a dose titration study on 395 OAB patients, darifenacin, allowing individualized dosage (7.5 or 15 mg), was found to be effective and well-tolerated (Steers et al, 2005). A 2-year open-label extension study of these investigations (Haab et al, 2004; Steers et al, 2005), confirmed a favorable efficacy, tolerability, and safety profile (Haab et al, 2006).

A review of the pooled darifenacin data from the three phase III, multicenter, double-blind clinical trials in patients with OAB was reported by Chapple and colleagues (2005b). After a 4-week washout and run-in period, 1059 adults (85% female) with symptoms of OAB (urgency incontinence, urgency, and frequency) for at least 6 months were randomized to once-daily oral treatment with darifenacin 7.5 mg (n = 337) or 15 mg (n = 334) or matching placebo (n = 388) for 12 weeks. Efficacy was evaluated using electronic patient diaries that recorded incontinence episodes (including those resulting in a change of clothing or pads), frequency and severity of urgency, micturition frequency, and bladder capacity (volume voided). Safety was evaluated by analysis of treatment-related adverse events, withdrawal rates, and laboratory tests. Relative to baseline, 12 weeks of treatment with darifenacin resulted in a dose-related significant reduction in median number of incontinence episodes per week (7.5 mg, -8.8 [-68.4%; placebo -54%, $P < .004$]; 15 mg, -10.6 [-76.8%; placebo 58%, $P < .001$]). Significant decreases in the frequency and severity of urgency, micturition frequency, and number of incontinence episodes resulting in a change of clothing or pads were also apparent, along with an increase in bladder capacity. Darifenacin was well tolerated. The most common treatment-related adverse events were dry mouth and constipation, although together these resulted in few discontinuations (darifenacin 7.5 mg, 0.6% of patients; darifenacin 15 mg, 2.1%; placebo, 0.3%). The incidence of CNS and cardiovascular adverse events were comparable to placebo. The results were confirmed in other RCTs, including also a pooled analysis of three phase III studies in older patients (≥ 65 years), showing that darifenacin (7.5 and 15 mg) had an excellent efficacy, tolerability, and safety profile (Foote et al, 2005; Zinner et al, 2005; Hill et al, 2006).

The time to effect with darifenacin was analyzed in a pooled analysis of efficacy and safety data from 1059 patients participating

in three double-blind 12-week studies (Khullar et al, 2011). Darifenacin significantly improved all OAB symptoms as early as 6 to 8 days.

One of the most noticeable clinical effects of antimuscarinics is their ability to reduce urgency and allow patients to postpone micturition. A study was conducted to assess the effect of darifenacin on the warning time associated with urinary urgency. Warning time was defined as the time from the first sensation of urgency to the time of voluntary micturition or incontinence. This was a multicenter, randomized, double-blind, placebo-controlled study consisting of 2 weeks' washout, 2 weeks' medication-free run-in, and a 2-week treatment phase (Cardozo and Dixon, 2005). Warning time was defined as the time from the first sensation of urgency to voluntary micturition or incontinence and was recorded via an electronic event recorder at baseline (visit 3) and study end (visit 4) during a 6-hour clinic-based monitoring period, with the subject instructed to delay micturition for as long as possible. During each monitoring period, up to three urgency-void cycles were recorded. Of the 72 subjects who entered the study, 67 had warning time data recorded at both baseline and study end and were included in the primary efficacy analysis (32 on darifenacin, 35 on placebo). Darifenacin treatment resulted in a significant ($P < .004$) increase in mean warning time, with a median increase of 4.3 minutes compared with placebo (darifenacin group from 4.4 to 1.8 minutes; placebo from 7.0 to -1.0 minutes). Overall, 47% of darifenacin-treated subjects compared with 20% receiving placebo achieved a 30% or greater increase in mean warning time. There were methodologic problems associated with this study; it used a dose of 30 mg (higher than the dose recommended for clinical use), the treatment period was short, it was conducted in a clinical-centered environment, the methodology carried with it a significant potential training effect, and the placebo group had higher baseline values than the treatment group. In another warning time study (Zinner et al, 2006) on 445 OAB patients, darifenacin treatment (15 mg) resulted in numeric increases in warning time; however, these were not significant compared with placebo.

Further studies have demonstrated that darifenacin treatment is associated with clinically relevant improvements in health-related quality of life (QoL) in patients with OAB (Abrams et al, 2008), and such improvements were sustained as shown in a 2-year extension study (Dwyer et al, 2008). It was shown that neither the positive effects on micturition variables nor those on health-related QoL produced by darifenacin (7.5 and 15 mg) were further enhanced by a behavioral modification program including timed voiding, dietary modifications, and Kegel exercises (Chancellor et al, 2008b).

Because darifenacin is a substrate for the P-glycoprotein drug efflux transporter (Miller et al, 2011; Chancellor et al, 2012), which is present in both the blood-brain and the blood-ocular barriers, several clinical studies have been devoted to investigate possible effects of darifenacin on cognition. Neither in healthy volunteers aged 19 to 44 years and healthy patients 60 years or older nor in volunteers 65 years or older could any effect of darifenacin (3.75 to 15 mg daily) be demonstrated, compared with placebo (Kay and Wesnes, 2005; Lipton et al, 2005; Kay et al, 2006; Kay and Ebinger 2008; Chancellor et al, 2012).

To study whether darifenacin had any effect on QT and QTc intervals, Serra and colleagues (2005) performed a 7-day, randomized, parallel-group study ($n = 188$) in healthy volunteers receiving once-daily darifenacin at steady-state therapeutic (15 mg) and supratherapeutic (75 mg) doses, alongside controls receiving placebo or moxifloxacin (positive control, 400 mg) once daily. No significant increase in QTcF interval could be demonstrated compared with placebo. Mean changes from baseline at pharmacokinetic T_{max} versus placebo were -0.4 and -2.2 msec in the darifenacin 15-mg and 75-mg groups, respectively, compared with +11.6 msec in the moxifloxacin group ($P < .01$). The conclusion was that darifenacin does not prolong the QT or QTc interval.

Darifenacin 15 mg/day given to healthy volunteers did not change HR significantly compared with placebo (Olshansky et al, 2008).

Assessment. Darifenacin has a well-documented beneficial effect in OAB and DO (see Table 79-3), and tolerability and safety seem acceptable.

Fesoterodine Fumarate. Fesoterodine functions as an orally active prodrug that is converted to the active metabolite 5-HMT by nonspecific esterases (Michel, 2008; Malhotra et al, 2009b). This compound, which is chemically identical to the 5-hydroxy metabolite of tolterodine, is a non-subtype selective muscarinic-receptor antagonist (Ney et al, 2008). All of the effects of fesoterodine in man are thought to be mediated via 5-HMT, because the parent compound remains undetectable after oral administration. 5-HMT is metabolized in the liver, but a significant part of 5-HMT is excreted renally without additional metabolism. Because the renal clearance of 5-HMT is about 250 mL/min, with more than 15% of the administered fesoterodine dose excreted as unchanged 5-HMT, this raises the possibility that 5-HMT also could work from the luminal side of the bladder (Michel, 2008). The bioavailability of fesoterodine, averaging 52%, was independent of food intake, and the drug may be taken with or without a meal (Malhotra et al, 2009c). Peak plasma concentration of 5-HMT is reached at 5 hours after oral administration, and the agent has a half-life of 7 to 9 hours (Malhotra et al, 2008). The suggested starting dose, 4 mg/day, can be used in patients with moderately impaired renal or hepatic function because of the combination of renal excretion and hepatic metabolism of 5-HMT (Malhotra et al, 2009a; de Mey et al, 2011).

The clinical efficacy and tolerability of fesoterodine have been documented in several RCTs (Chapple et al, 2007b; Nitti et al, 2007; Dmochowski et al, 2010c; Herschorn et al, 2010; Nitti et al, 2010; Kaplan et al, 2011; Dell'Utri et al, 2012). In a multicenter, double-blind, double-dummy RCT with tolterodine ER, 1132 patients were enrolled and received treatment (Chapple et al, 2007b). The trial showed that both the 4- and 8-mg doses of fesoterodine were effective in improving symptoms of OAB, with the 8-mg dose having a greater effect at the expense of a higher rate of dry mouth. There appeared to be little difference between fesoterodine 4 mg and tolterodine ER. Only 1 patient from the fesoterodine 8-mg group and 1 patient from the tolterodine ER group withdrew from the study because of dry mouth. The dose-response relationship was confirmed in another study that pooled data from two phase III RCTs (Khullar et al, 2008). Fesoterodine 8 mg performed better than the 4-mg dose in improving urgency and urge UI as recorded by 3-day bladder diary, offering the possibility of dose titration.

A head-to-head placebo-controlled trial has been completed comparing fesoterodine 8 mg with tolterodine ER 4 mg and placebo (Herschorn et al, 2010). The study randomized 1590 patients to assess the primary outcome of reduced urgency incontinence episodes at 12 weeks. Fesoterodine produced statistically significant improvements in urgency incontinence episodes, complete dry rates (64.0% vs. 57.2%, $P = .015$), and MVV per void (+32.9 mL vs. +23.5 mL, $P = .005$) and in patients' assessments of bladder-related problems as measured by OAB questionnaire (except sleep domain), Patient Perception of Bladder Condition (40% vs. 33% with >2-point improvement, $P < .001$), and Urgency Perception Scale (46% vs. 40% with improvement, $P = .014$) compared with tolterodine. The clinical significance of these statistically significant findings is questionable because there was no difference between agents with respect to number of micturitions, urgency episodes, and frequency-urgency sum per 24 hours. The improved efficacy of fesoterodine came at the cost of greater dry mouth (27.8% vs. 16.4%), headache (5.6% vs. 3.4%), constipation (5.4% vs. 4.1%), and withdrawal rates (6% vs. 4%). Nonetheless, this first head-to-head trial comparing two drugs in class supports the use of fesoterodine 8 mg for additional benefit over tolterodine ER 4 mg.

Wyndaele and colleagues (2009) reported the first flexible-dose open-label fesoterodine trial, which was conducted at 80 different centers worldwide and included 516 participants (men and women) older than 18 years who self-reported OAB symptoms for at least 3 months before screening and had been treated with either tolterodine or tolterodine ER within 2 years without symptom improvement. Approximately 50% opted for dose escalation to 8 mg at

week 4. Significant improvements from baseline to week 12 were observed in micturitions, urgency urinary incontinence (UUI) episodes, micturition-related urgency episodes, and severe micturition-related urgency episodes per 24 hours. Significant improvements from baseline were observed in QoL parameters. Dry mouth (23%) and constipation (5%) were the most common adverse events; no safety issues were identified.

The largest double-blind, double-dummy, flexible-dose fesoterodine RCT, which was conducted at 210 different centers with a total of 2417 patients enrolled, was performed by [Kaplan and colleagues \(2011\)](#). All patients were healthy, older than 18 years, and self-reported OAB symptoms for at least 3 months. The 960 patients who received fesoterodine 8 mg showed significantly greater mean improvements at week 12 in most efficacy parameters (diary variables)—UUI and urgency episodes, micturition frequency, and MVV—than those receiving either tolterodine ER or placebo. No statistically significant changes were shown in reduction of nocturnal micturitions compared with the tolterodine group, whereas when comparing the mean changes in nighttime micturition with the placebo group a significant difference was found. This phase III study confirmed the superiority of fesoterodine 8 mg over tolterodine ER 4 mg for improving UUI and urgency episodes and 24-hour micturitions but not for MVV and nocturia. In another RCT of flexible-dose fesoterodine, [Dmochowski and colleagues \(2010c\)](#) reported statistically significant improvements at week 12 in the mean number of micturition per 24 hours and in both UUI and urgency episodes. Between groups, difference in nocturnal micturition was not statistically significant.

[Nitti and colleagues \(2010\)](#) determined whether the presence of DO in patients with OAB and UUI was a predictor of the response to treatment with fesoterodine in a phase II randomized, multicenter, placebo-controlled trial. They concluded that regardless of the presence of DO, the response to fesoterodine treatment was dose proportional and associated with significant improvements in OAB symptoms, indicating that **the response to OAB pharmacotherapy in patients with UUI was independent of the urodynamic diagnosis of DO.**

[Kelleher and colleagues \(2008\)](#) evaluated the effect of fesoterodine on health-related QoL in patients with OAB syndrome. Pooled data from two randomized placebo-controlled phase III studies ([Chapple et al, 2007b](#); [Nitti et al, 2007](#)) were analyzed. Eligible patients were randomized to placebo or fesoterodine 4 or 8 mg for 12 weeks; one trial also included tolterodine ER 4 mg. By the end of treatment, all active-treatment groups had significantly improved health-related QoL compared with those on placebo. In a post hoc analysis of data pooled from these studies, significant improvements in all King's Health Questionnaire (KHQ) domains, International Consultation on Incontinence Questionnaire Short Form (ICIQ-IUSF) scores, and bladder-related problems were observed at months 12 and 24 compared with open-label baseline ([Kelleher et al, 2012](#)). The authors concluded that treatment satisfaction was high throughout the open-label treatment regardless of gender and age.

[Malhotra and colleagues \(2010\)](#) performed a thorough QT study to investigate the effects of fesoterodine on cardiac repolarization in a parallel-group study. Subjects were randomly assigned to receive double-blind fesoterodine 4 mg, fesoterodine 28 mg, or placebo or open-label moxifloxacin 400 mg (positive control) for 3 days. Electrocardiograms (ECGs) were obtained on days 1 (baseline) and 3. The primary analysis was of the time-averaged changes from baseline for Fridericia's corrected QT interval (QTcF) on day 3. Among 261 subjects randomized to fesoterodine 4 mg ($n = 64$), fesoterodine 28 mg ($n = 68$), placebo ($n = 65$), or moxifloxacin 400 mg ($n = 64$), 256 completed the trial. The results indicated that fesoterodine is not associated with QTc prolongation or other ECG abnormalities at either therapeutic or supratherapeutic doses.

Assessment. Fesoterodine has a well-documented beneficial effect in OAB (see [Table 79-3](#)), and the adverse event profile seems acceptable.

Imidafenacin. Imidafenacin (KRP-197/ONO-8025, 4-[2-methyl-1H-imidazol-1-yl]-2,2-diphenylbutanamide) is an antagonist for

the muscarinic ACh receptor with higher affinities for M_3 and M_1 receptors than for the M_2 receptor. Metabolites of imidafenacin (M-2, M-4 and M-9) had low affinities for muscarinic ACh receptor subtypes ([Kobayashi et al, 2007](#)). The drug blocks prejunctional as well as postjunctional muscarinic receptors and was shown to block both detrusor contractions and ACh release ([Murakami et al, 2003](#)). The receptor binding affinity of imidafenacin in vitro was found to be significantly lower in the bladder than submaxillary gland or colon ([Yamada et al, 2011](#)), and in rats orally administered imidafenacin distributes predominantly to the bladder and exerts more selective and longer-lasting effect there than on other tissues. Whether this can be translated to the human situation has to be established before claims of clinical bladder selectivity can be made.

Imidafenacin is well absorbed from the gastrointestinal tract, and its absolute bioavailability in humans is 57.8% ([Ohmori et al, 2007](#); [Ohno et al, 2008](#)). It is rapidly absorbed with maximum plasma concentration occurring 1 to 3 hours after oral administration ([Ohno et al, 2008](#)). Metabolites in the plasma are produced mainly by first-pass effects. The major enzymes responsible for the metabolism of the drug are CYP3A4 and UGT1A4. The oxidative metabolism is reduced by concomitant administration of CYP3A4 inhibitors. In contrast, imidafenacin and its metabolites have no inhibitory effect on the CYP-mediated metabolism of concomitant drugs ([Kanayama et al, 2007](#)).

[Kitagawa and colleagues \(2011\)](#) reported that the subjective efficacy of imidafenacin was observed from 3 days after the commencement of administration and that mean total Overactive Bladder Symptom Score decreased gradually during 2 weeks after administration.

A randomized, double-blind, placebo-controlled phase II dose-finding study in Japanese OAB patients was performed to evaluate the efficacy, safety and tolerability, and dose-response relationship of imidafenacin ([Homma et al, 2008](#)). Overall, 401 patients were enrolled and randomized for treatment with 0.1 mg of imidafenacin per day (99 patients), 0.2 mg of imidafenacin per day (100), 0.5 mg of imidafenacin per day (101), or a placebo (101). After 12 weeks of treatment, the number of incontinence episodes was reduced in a dose-dependent manner, and a significant difference between the imidafenacin treatment and the placebo groups was observed ($P < .0001$). Compared with the placebo, imidafenacin caused significant reductions in urgency incontinence, voiding frequency, and urinary urgency, and a significant increase in the urine volume voided per micturition. Imidafenacin was also well tolerated. The incidence of dry mouth in the imidafenacin groups increased in a dose-dependent manner. Even though the percentage of patients receiving 0.5 mg/day who discontinued treatment because of dry mouth was high (8.9%), the percentages in the 0.1 mg/day and 0.2 mg/day groups (1.0% and 0.0%, respectively) were comparable with that in the placebo group (0.0%).

A randomized, double-blind, placebo- and propiverine-controlled trial of 781 Japanese patients with OAB symptoms was conducted by Homma and coworkers ([Homma and Yamaguchi, 2009](#)). Patients were randomized to imidafenacin (324), propiverine (310), or a placebo (147). After 12 weeks of treatment, a significantly larger reduction in the mean number of incontinence episodes was observed in the imidafenacin group than in the placebo group ($P < .0001$). The noninferiority of imidafenacin compared with propiverine was confirmed for the reduction in UI episodes ($P = .0014$; noninferiority margin, 14.5%). Imidafenacin was well tolerated. The incidence of adverse events with imidafenacin was significantly lower than with propiverine ($P = .0101$). Dry mouth, the most common adverse event, was significantly more common in the propiverine group than in the imidafenacin group. There were no significant increases in either the imidafenacin or the placebo group in the mean QTc interval, whereas there was a significant increase in the mean QTc interval in the propiverine group ($P < .0001$). However, clinical arrhythmia and clinical arrhythmic events were not seen in any of the treatment groups.

The long-term safety, tolerability, and efficacy of imidafenacin were studied in Japanese OAB patients ([Homma and Yamaguchi, 2008](#)), of whom 478 received treatment and 376 completed a

52-week program. Imidafenacin was well tolerated, the most common adverse event being a dry mouth (40.2% of the patients). Long-term treatment did not produce an increase in the frequency of adverse events compared with short-term treatment. A significant efficacy of the drug was observed from week 4 through week 52. After 52 weeks, imidafenacin had produced mean changes from baseline in the number of incontinence episodes (−83.51%), urgency incontinence episodes (−84.21%), voiding frequency (−2.35 micturitions per day), urgency episodes (−70.53%), and volume voided per micturition (28.99 mL). There were also significant reductions from baseline in all domains of the KHQ. Imidafenacin had no significant effects on the corrected QT interval, vital signs, results from laboratory tests, or postvoid residual (PVR) volume).

A 52-week prospective, open randomized comparative study to evaluate the efficacy and tolerability of imidafenacin (0.2 mg/day) and solifenacin (5 mg/day) was conducted in a total of 41 Japanese patients with untreated OAB (Zaitsu et al, 2011). They were randomly assigned to imidafenacin and solifenacin groups. There were no differences in OAB and KHQ scores between the two groups, but the severity and incidence of adverse events caused by the drugs showed increased differences between the groups with time. The severity of dry mouth and the incidence of constipation were significantly lower in the imidafenacin group ($P = .0092$ and $P = .0013$, respectively). An important limitation of this study is the low number of patients. Only 25 patients (17 male, 8 female) were available for long-term analysis.

Assessment. Imidafenacin seems to be effective and to have an acceptable tolerability. However, the documentation is relatively scarce and the drug is not yet available in the Western countries.

Propantheline Bromide. Propantheline is a quaternary ammonium compound, nonselective for muscarinic receptor subtypes, which has a low (5% to 10%) and individually varying biologic availability. It is metabolized (metabolites inactive) and has a short half-life (less than 2 hours) (Beermann et al, 1972). It is usually given in a dose of 15 to 30 mg four times daily, but to obtain an optimal effect, individual titration of the dose is necessary, and often higher doses are required. Using this approach in 26 patients with DO contractions, Blaivas and colleagues (1980) in an open study obtained a complete clinical response in all patients but 1, who did not tolerate more than propantheline 15 mg four times daily. The range of doses varied from 7.5 to 60 mg four times daily. In contrast, Thüroff and colleagues (1991), comparing the effects of oxybutynin 5 mg three times daily, propantheline 15 mg three times daily, and placebo in a randomized, double-blind, multicenter trial on the treatment of frequency, urgency, and incontinence related to DO (154 patients), found no differences between the placebo and propantheline groups. In another randomized comparative trial with crossover design (23 women with idiopathic detrusor overactivity [IDO]) and with dose titration, Holmes and colleagues (1989) found no differences in efficacy between oxybutynin and propantheline. Six controlled randomized trials reviewed by Thüroff and colleagues (1998) confirmed a positive but varying response to the drug.

Assessment. Although the effect of propantheline on OAB and DO has not been well documented in controlled trials satisfying standards of today, it can be considered effective, and may, in individually titrated doses, be clinically useful (see Table 79-3). No new studies on the use of this drug for treatment of OAB and DO seem to have been performed during the last decade.

Solifenacin Succinate. Solifenacin succinate (YM905) is a tertiary amine that is well absorbed from the gastrointestinal tract (absolute bioavailability 90%). The mean terminal half-life is 45 to 68 hours (Kuipers et al, 2002; Smulders et al, 2002, 2004). It undergoes significant hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4). In patients who received a single oral dose of 10 mg solifenacin on day 7 of a 20-day regimen of ketoconazole administration (200 mg), C_{max} and AUC_{0-inf} were increased by only approximately 40% and 56%, respectively (Swart et al, 2006). Solifenacin has a modest selectivity for M₃ over M₂ (and M₁) receptors (Abrams and Andersson, 2007).

Supporting an effect of solifenacin on sensory function, 15 women with DO receiving 10 mg of the drug per day showed an increase in the area under the bladder-volume sensation curve (Lowenstein et al, 2012). Solifenacin also increased maximum bladder capacity, a finding in agreement with other studies (Tanaka et al, 2010; Hsiao et al, 2011).

Two large-scale phase II trials with parallel designs, including men and women, were performed (Smith et al, 2002; Chapple et al, 2004a). The first dose-ranging study evaluated solifenacin 2.5 mg, 5 mg, 10 mg, and 20 mg and tolterodine (2 mg twice daily) in a multinational placebo-controlled study of 225 patients with uroynamically confirmed DO (Chapple et al, 2004a). Patients received treatment for 4 weeks followed by 2 weeks of follow-up. Inclusion criteria for this and subsequent phase III studies of patients with OAB included at least eight micturitions per 24 hours and either one episode of incontinence or one episode of urgency daily as recorded in 3-day micturition diaries. Micturition frequency, the primary efficacy variable, was statistically significantly reduced in patients taking solifenacin 5 mg (−2.21), 10 mg (−2.47), and 20 mg (−2.75), but not in patients receiving placebo (−1.03) or tolterodine (−1.79). This effect was rapid, with most of the effect observed at the earliest assessment visit, 2 weeks after treatment initiation. In addition, there were numerically greater reductions in episodes of urgency and incontinence when compared with placebo. Study discontinuations caused by adverse events were similar across treatment groups, albeit highest in the 20-mg solifenacin group. Because the 5-mg and 10-mg doses caused lower rates of dry mouth than tolterodine and had superior efficacy outcomes relative to placebo, these dosage strengths were selected for further evaluation in large-scale phase III studies.

The second dose-ranging study of solifenacin 2.5 mg to 20 mg was carried out in the United States (Smith et al, 2002). This trial included 261 evaluable men and women receiving solifenacin or placebo for 4 weeks followed by a 2-week follow-up period. Micturition frequency was statistically significantly reduced relative to placebo in patients receiving 10 mg and 20 mg of solifenacin. The number of micturitions per 24 hours showed reductions by day 7 and continued to decrease through day 28; day 7 was the earliest time point tested in solifenacin trials, and these findings demonstrate efficacy as early as 1 week. The 5-mg, 10-mg, and 20-mg dosage groups experienced statistically significant increases in volume voided; the 10-mg solifenacin dose was associated with statistically significant reductions in episodes of incontinence.

In one of the early RCTs, 1077 patients were randomized to 5-mg solifenacin, 10-mg solifenacin, tolterodine (2 mg twice daily), or placebo (Chapple et al, 2004b). It should be noted that this study was powered only to compare active treatments with placebo. Compared with placebo (−8%), mean micturitions per 24 hours were significantly reduced with solifenacin 10 mg (−20%), solifenacin 5 mg (−17%), and tolterodine (−15%). Solifenacin was well tolerated, with few patients discontinuing treatment. Incidences of dry mouth were 4.9% with placebo, 14.0% with solifenacin 5 mg, 21.3% with solifenacin 10 mg, and 18.6% with tolterodine 2 mg twice daily.

Cardozo and colleagues (2004b) randomized 911 patients to 12-week once-daily treatment with solifenacin 5 mg, solifenacin 10 mg, or placebo. The primary efficacy variable was change from baseline to study end point in mean number of micturitions per 24 hours. Secondary efficacy variables included changes from baseline in mean number of urgency, nocturia, and incontinence episodes per 24 hours, and MVV per micturition. Compared with changes obtained with placebo (−1.6), the number of micturitions per 24 hours was statistically significantly decreased with solifenacin 5 mg (−2.37) and 10 mg (−2.81). A statistically significant decrease was observed in the number of all incontinence episodes with both solifenacin doses (5 mg, −1.63, 61%; 10 mg, −1.57, 52%), but not with placebo (−1.25, 28%). Of patients reporting incontinence at baseline, 50% achieved continence after treatment with solifenacin (based on a 3-day micturition diary, placebo responses not given). Episodes of nocturia were statistically significantly decreased in patients treated with solifenacin 10 mg versus placebo. Episodes of

urgency and MVV per micturition were statistically significantly reduced with solifenacin 5 mg and 10 mg. Treatment with solifenacin was well tolerated. Dry mouth, mostly mild in severity, was reported in 7.7% of patients receiving solifenacin 5 mg and 23% receiving solifenacin 10 mg (vs. 2.3% with placebo). A 40-week follow-up of these studies (Cardozo et al, 2004b; Chapple et al, 2004b) demonstrated that the favorable profile, both in terms of efficacy and tolerability, was maintained over the study period (Haab et al, 2005).

The STAR trial (Chapple et al, 2005c, 2007c) was a prospective, double-blind, double-dummy, two-arm, parallel-group, 12-week study conducted to compare the efficacy and safety of solifenacin 5 or 10 mg and tolterodine extended release (TOLT-ER) 4 mg once daily in OAB patients. The primary effect variable was micturition frequency. After 4 weeks of treatment patients had the option to request a dose increase, but were dummied throughout because approved product labeling allowed an increase only for those on solifenacin. The results showed that solifenacin, with a flexible dosing regimen, was noninferior to tolterodine with regard to the primary effect variable, micturition frequency. However, solifenacin showed significant greater efficacy to tolterodine in decreasing urgency episodes (−2.85 vs. −2.42), incontinence (−1.60 vs. −.83), urgency incontinence (−1.42 vs. −0.83), and pad use (−1.72 vs. −1.19). More solifenacin-treated patients became continent by study end point (59% vs. 49%) and reported improvements in perception of bladder condition (−1.51 vs. −1.33) assessments. However, this was accompanied by an adverse event incidence that was greater with solifenacin than with tolterodine. Dry mouth and constipation (mild, moderate, or severe) were the most common (solifenacin, 30 [6.4%]; tolterodine, 23 [2.5%]). The majority of side effects were mild to moderate in nature, and discontinuations were comparable and low (5.9% and 7.3%) in both groups.

Luo and colleagues (2012) performed a systematic review and meta-analysis of solifenacin RCTs and provided a comprehensive assessment regarding the efficacy and safety of the drug. Their results, which largely confirmed what could be deduced from previously published information, indicated that solifenacin significantly decreased the number of urgency episodes per 24 hours, micturitions per 24 hours, incontinence episodes per 24 hours, nighttime micturitions per 24 hours, and UUI episodes per 24 hours and improved volume voided per micturition compared with the placebo or tolterodine treatment.

A number of studies and reviews have further documented the effects of solifenacin (Cardozo et al, 2006; Chapple et al, 2006, 2007; Maniscalco et al, 2006; see also Chapple et al, 2008b; Novara et al, 2008; Toglia et al, 2009; Vardy et al, 2009; Serels et al, 2010; Luo et al, 2012), including in men with OAB without BOO (Kaplan et al, 2010). In a pooled analysis of four RCTs, Abrams and Swift (2005) demonstrated positive effects on urgency, frequency, and nocturia symptoms in OAB dry patients. In an analysis of four phase III clinical trials, Brubaker and FitzGerald (2007) confirmed a significant effect of solifenacin 5 and 10 mg on nocturia in patients with OAB (reductions of nocturia episodes with 5 mg, −0.6, $P < .025$; with 10 mg, −0.6, $P < .001$; vs. placebo, −0.4) but without nocturnal polyuria (NP). A positive impact on nocturia and sleep quality in patients with OAB treated with solifenacin has also been reported in other studies (Takao et al, 2011; Yokoyama et al, 2011). Kelleher and colleagues (2006) and Staskin and Te (2006) presented data showing efficacy in patients with mixed incontinence.

A pooled analysis of four studies confirmed the efficacy and tolerability of solifenacin 5 and 10 mg in elderly (65 years or older) patients and also showed a high level of persistence in a 40-week extension trial (Wagg et al, 2006). Post hoc analysis of two 12-week, open-label, flexible-dosage studies on 2645 patients older than 65 years with OAB revealed that solifenacin was associated with improvements in measures assessing patients' perception of their bladder problems, symptom bothersomeness, and aspects of health-related QoL (Capo' et al, 2011). Solifenacin was equally well tolerated in younger (<65 years) and older (>65 years) patients (Herschorn et al, 2011b). An exploratory pilot study with single doses of solifenacin 10 mg administered to 12 elderly volunteers

suggested no clear propensity to impair cognitive functions (Wesnes et al, 2009).

Improvement of QoL by solifenacin treatment has been documented in several studies (Kelleher et al, 2005; Garely et al, 2006). In 30 patients with multiple sclerosis, van Rey and Heesakkers (2011) improved OAB symptoms as well as neurogenic disease-specific QoL measures.

Information on solifenacin treatment in children is scarce. In a prospective open-label study in 72 children (27 with neurogenic bladders), Bolduc and colleagues (2010) improved urodynamic capacity and improved continence. Chart review of 138 children with therapy-resistant OAB treated with solifenacin increased MVV and improved continence (Hoebeke et al, 2009).

In female volunteers, aged 19 to 79 years, the effect of 10-mg and 30-mg solifenacin on the QT interval was evaluated at the time of peak solifenacin plasma concentration in a multidose, randomized, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg) trial. The QT interval–prolonging effect appeared greater for the 30-mg (8 msec, 4, 13 [90% confidence interval (CI)]) compared with the 10-mg (2 msec, −3, 6) dose of solifenacin. Although the effect of the highest solifenacin dose (three times the maximum therapeutic dose) studied did not appear as large as that of the positive control moxifloxacin at its therapeutic dose, the CIs overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels (Astellas prescribing information for VESicare, July 2010).

Michel and colleagues (2008) studied cardiovascular safety and overall tolerability of solifenacin in routine clinical use in a 12-week, open-label, postmarketing surveillance study. They concluded that “in real-life conditions, i.e., with inclusion of large numbers of patients with cardiovascular co-morbidities and taking comedications, therapeutically effective doses of solifenacin did not increase heart rate or blood pressure.”

Assessment. Solifenacin has a well-documented beneficial effect in OAB and DO (see Table 79-3), and the adverse event profile seems acceptable.

Tolterodine Tartrate. Tolterodine is a tertiary amine, rapidly absorbed and extensively metabolized by the cytochrome P450 system (CYP2D6). The major active 5-hydroxymethyl metabolite (5-HMT) has a similar pharmacologic profile as the mother compound (Nilvebrant et al, 1997b) and significantly contributes to the therapeutic effect of tolterodine (Brynne et al, 1997, 1998). Both tolterodine and 5-HMT have a plasma half-life of 2 to 3 hours, but the effects on the bladder seem to be longer lasting than could be expected from the pharmacokinetic data. Urinary excretion of tolterodine accounted for less than 1% to 2.4% of the dose; 5% to 14% of 5-HMT is eliminated in the urine (Brynne et al, 1997). Whether or not the total antimuscarinic activity of unchanged tolterodine and 5-HMT excreted in urine is sufficient to exert any effect on the mucosal signaling mechanisms has not been established. However, the preliminary studies by Kim and colleagues (2006) and Chuang and colleagues (2008) do not support such an effect.

The relatively low lipophilicity of tolterodine and even lesser one of 5-HMT imply limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects (Hills et al, 1998; Clemett and Jarvis, 2001; Salvatore et al, 2008). However, tolterodine may disturb sleep in subjects unable to form the even less lipophilic 5-HMT because of a low activity of CYP2D6 (Diefenbach et al, 2008).

Tolterodine has no selectivity for muscarinic receptor subtypes but is claimed to have functional selectivity for the bladder over the salivary glands (Stahl et al, 1995; Nilvebrant et al, 1997a). In healthy volunteers, oral tolterodine at a high dose (6.4 mg) had a powerful inhibitory effect on micturition and also reduced stimulated salivation 1 hour after administration of the drug (Stahl et al, 1995). However, 5 hours after administration, the effects on the urinary bladder were maintained, whereas no significant effects on salivation could be demonstrated.

Animal experiments have suggested that antimuscarinics may affect signaling from the bladder (Andersson et al, 2011b). Confirming data in humans were found by Vijaya and colleagues (2012). In

a randomized, placebo-controlled study, they evaluated the effect of tolterodine on urethral and bladder afferent nerves in women with DO compared with placebo, by studying the changes in the current perception threshold (CPT). They found a significantly increased CPT value at 5 (described as urgency) and 250 Hz on both urethral and bladder stimulation after 1 week of treatment. When compared with placebo, women taking tolterodine had significantly increased bladder CPT values at 5 Hz ($P < .05$).

Tolterodine is available in IR (TOLT-IR; 1 or 2 mg; twice-daily administration) and ER (TOLT-ER) forms (2 or 4 mg; once-daily administration). The ER form seems to have advantages over the IR form in terms of both efficacy and tolerability (Van Kerrebroeck et al, 2001).

Several randomized, double-blind, placebo-controlled studies on patients with OAB and DO (both IDO and NDO) have documented a significant reduction in micturition frequency and number of incontinence episodes (Hills et al, 1998; Clemett and Jarvis, 2001; Salvatore et al, 2008). Comparative RCTs such as the OBJECT (Overactive Bladder: Judging Effective Control and Treatment) and OPERA (Overactive Bladder: Performance of Extended Release Agents) studies have further supported its effectiveness.

The OBJECT trial compared oxybutynin ER (OXY-ER) 10 mg once daily with TOLT-IR 2 mg twice daily (Appell et al, 2001) in a 12-week randomized, double-blind, parallel-group study including 378 patients with OAB. Participants had 7 to 50 episodes of urgency incontinence per week and 10 or more voids in 24 hours. The outcome measures were the number of episodes of urgency incontinence, total incontinence, and micturition frequency at 12 weeks adjusted for baseline. At the end of the study, OXY-ER was found to be significantly more effective than TOLT-IR in each of the main outcome measures adjusted for baseline (see also the later discussion of *oxybutynin chloride*). Dry mouth, the most common adverse event, was reported by 33% and 28% of participants taking OXY-ER and TOLT-IR, respectively. Rates of CNS and other adverse events were low and similar in both groups. The authors concluded that OXY-ER was more effective than TOLT-IR and that the rates of dry mouth and other adverse events were similar in both treatment groups.

In the OPERA study (Diokno et al, 2003), OXY-ER at 10 mg/day or TOLT-ER at 4 mg/day were given for 12 weeks to women with 21 to 60 urgency incontinence episodes per week and an average of 10 or more voids per 24 hours. Episodes of incontinence (primary end point), total incontinence (urgency and nonurgency), and micturition were recorded in seven 24-hour urinary diaries at baseline and at weeks 2, 4, 8, and 12 and compared. Adverse events were also evaluated. Improvements in weekly urgency incontinence episodes were similar for the 790 women who received OXY-ER (391) or TOLT-ER (399). OXY-ER was significantly more effective than TOLT-ER in reducing micturition frequency, and 23.0% of women taking OXY-ER reported no episodes of UI compared with 16.8% of women taking TOLT-ER. Dry mouth, usually mild, was more common with OXY-ER. In general, adverse events were mild and occurred at low rates, with both groups having similar discontinuation of treatment because of adverse events. The conclusions were that reductions in weekly urgency incontinence and total incontinence episodes were similar with the two drugs. Dry mouth was more common with OXY-ER, but tolerability was otherwise comparable, including adverse events involving the CNS.

In the Antimuscarinic Clinical Effectiveness Trial (ACET) (Sussman and Garely, 2002), which consisted of two trials, patients with OAB were randomized to 8 weeks of open-label treatment with either 2 mg or 4 mg of once-daily TOLT-ER (study one) and to 5 mg or 10 mg of OXY-ER (study two). A total of 1289 patients were included. Fewer patients prematurely withdrew from the trial in the TOLT-ER 4-mg group (12%) than either the OXY-ER 5-mg (19%) or OXY-ER 10-mg groups (21%). More patients in the OXY-ER 10-mg group than in the TOLT-ER 4-mg group withdrew because of poor tolerability (13% vs. 6%). After 8 weeks, 70% of patients in the TOLT-ER 4-mg group perceived an improved bladder condition, compared with 60% in the TOLT-ER 2-mg group, 59% in the OXY-ER 5-mg group, and 60% in the OXY-ER 10-mg group. Dry

mouth was dose-dependent with both agents, although differences between doses reached statistical significance only in the oxybutynin trial (OXY-ER 5 mg vs. OXY-ER 10 mg; $P = .05$). Patients treated with TOLT-ER 4 mg reported a significantly lower severity of dry mouth compared with OXY-ER 10 mg. The conclusion that the findings suggest improved clinical efficacy of TOLT-ER (4 mg) than of OXY-ER (10 mg) is weakened by the the open-label design of the study.

Zinner and colleagues (2002) evaluated the efficacy, safety, and tolerability of TOLT-ER in older (≥ 65) and younger (< 65) OAB patients, in a 12-week RCT including 1015 patients with urgency incontinence and urinary frequency. Patients were randomized to treatment with TOLT-ER 4 mg once daily (507) or placebo (508) for 12 weeks. Efficacy, measured with micturition charts (incontinence episodes, micturitions, volume voided per micturition) and subjective patient assessments; safety; and tolerability end points were evaluated relative to placebo. Compared with placebo, significant improvements in micturition chart variables with TOLT-ER showed no age-related differences. Dry mouth (of any severity) was the most common adverse event in both the TOLT-ER and placebo treatment arms, irrespective of age (< 65 : ER 22.7%, placebo 8.1%; ≥ 65 : ER 24.3%, placebo 7.2%). A few patients ($< 2\%$) experienced severe dry mouth. No CNS (cognitive functions were not specifically studied), visual, cardiac (per ECG), or laboratory safety concerns were noted in this study. Withdrawal rates caused by adverse events on TOLT-ER 4 mg qd were comparable in the two age cohorts (< 65 : 5.5%; ≥ 65 : 5.1%).

The central symptom in the OAB syndrome is urgency. Freeman and colleagues (2003) presented a secondary analysis of a double-blind, placebo-controlled study evaluating the effect of once-daily TOLT-ER on urinary urgency in patients with OAB. Patients with urinary frequency (eight or more micturitions per 24 hours) and urgency incontinence (five or more episodes per week) were randomized to oral treatment with TOLT-ER 4 mg once daily ($n = 398$) or placebo ($n = 374$) for 12 weeks. Efficacy was assessed by use of patient perception evaluations. Of patients treated with TOLT-ER, 44% reported improved urgency symptoms (compared with 32% for placebo) and 62% reported improved bladder symptoms (placebo, 48%). The proportion of patients unable to hold urine on experiencing urgency was decreased by 58% with TOLT-ER, compared with 32% with placebo ($P < .001$).

In the Improvement in Patients: Assessing Symptomatic Control with Tolterodine ER (IMPACT) study (Elinoff et al, 2006), the efficacy of TOLT-ER for patients' most bothersome OAB symptom was investigated in an open-label primary care setting. Patients with OAB symptoms for 3 months or longer received TOLT-ER (4 mg once daily) for 12 weeks. By week 12, there were significant reductions in patients' most bothersome symptom: incontinence, urgency episodes, or nocturnal and daytime frequency. The most common adverse events were dry mouth (10%) and constipation (4%), and it was concluded that in primary care practice, bothersome OAB symptoms can be effectively and safely treated with TOLT-ER, even in patients with comorbid conditions.

Various aspects of the efficacy and tolerability of tolterodine have been further documented in a number of RCTs (Dmochowski et al, 2007a, 2007b; Bharucha et al, 2008; Choo et al, 2008; Coyne et al, 2008; Rogers et al, 2008; Rovner et al, 2008b; see also Chapple et al, 2008b; Novara et al, 2008). It is important to note that the QTc effects of tolterodine were determined in a crossover-designed QT study of recommended (2 mg twice daily) and supratherapeutic (4 mg twice daily) doses of tolterodine, moxifloxacin (400 mg once daily), and placebo. No subject receiving tolterodine exceeded the clinically relevant thresholds of 500-msec absolute QTc or 60-msec change from baseline, and it was concluded that tolterodine does not have a clinically significant effect on QT interval (Malhotra et al, 2007).

Olshansky and colleagues (2008) compared the effects on HR of TOLT-ER 4 mg/day with those of darifenacin 15 mg/day in healthy volunteers. They found that tolterodine, but not darifenacin, significantly increased mean HR per 24 hours. The proportion of subjects with an increase of more than 5 beats/min was

significantly greater in those receiving TOLT-ER (25%) than with darifenacin (8.9%).

Hsiao and colleagues (2011) compared the urodynamic effects, therapeutic efficacy, and safety of solifenacin (5 mg) versus tolterodine ER (4 mg) treatment in women with the OAB syndrome. Both solifenacin and tolterodine had similar urodynamic effects, therapeutic efficacy, and adverse events; however, tolterodine had a greater effect in increasing HR than solifenacin.

In a prospective, open study, Song and colleagues (2006) compared the effects of bladder training (BT) and/or tolterodine as first-line treatment in female patients with OAB. One hundred and thirty-nine female patients with OAB were randomized to treatment with BT, tolterodine (2 mg twice daily), or both for 12 weeks. All treatments were effective; however, combination therapy was the most effective. Mattiasson and colleagues (2003) compared the efficacy of tolterodine 2 mg twice daily plus simplified BT with tolterodine alone in patients with OAB in a multicenter single-blind study. At the end of the study the median percentage reduction in voiding frequency was greater with tolterodine plus BT than with tolterodine alone (33% vs. 25%; $P < .001$), whereas the median percentage increase in volume voided per void was 31% with tolterodine plus BT and 20% with tolterodine alone ($P < .001$). There was a median of 81% fewer incontinence episodes than at baseline with tolterodine alone, which was not significantly different from that with tolterodine plus BT (−87%). It was concluded that the effectiveness of tolterodine 2 mg twice daily can be augmented by a simplified BT regimen. However, Millard and the Asia Pacific Tolterodine Study Group (2004) investigated whether the combination of tolterodine plus a simple pelvic floor muscle exercise program would provide improved treatment benefits compared with tolterodine alone in 480 patients with OAB. Tolterodine therapy for 24 weeks resulted in significant improvement in urgency, frequency, and incontinence; however, no additional benefit was demonstrated for a simple pelvic floor muscle exercise program. In a 16-week, multicenter, open-label study, tolterodine ER plus behavioral intervention resulted in high treatment satisfaction and improved bladder diary variables in patients who had previously been treated and were dissatisfied with tolterodine or other antimuscarinics (Klutke et al, 2009).

Abrams and colleagues (2006c) studied the safety and tolerability of tolterodine for the treatment of OAB symptoms in men with BOO. They found that tolterodine did not adversely affect urinary function in these men. Urinary flow rate was unaltered, and there was no evidence of clinically meaningful changes in voiding pressure and PVR or urinary retention. It was suggested that antimuscarinics can be safely administered in men with BOO. Lee and colleagues (2008a) reviewed the safety and efficacy of antimuscarinic agents in treating men with BOO and OAB and emphasized their safety and efficacy. They also concluded that combination therapy with antimuscarinics and α_1 -adrenoceptor (α_1 -AR) antagonists improves the symptoms effectively without increasing the incidence of acute urinary retention (AUR).

The beneficial effect of TOLT-ER in men with BPE and LUTS, including OAB, has been well documented. Both as monotherapy, but particularly in combination with α_1 -AR antagonists, TOLT-ER was found effective (Kaplan et al, 2006, 2008a, 2008b; Höfner et al, 2007; Roehrborn et al, 2008a; Rovner et al, 2008a). This effect was obtained irrespective of prostate size and was not associated with increased incidence of AUR (Roehrborn et al, 2008a). A large, 26-week, multicenter, randomized, double-blind, placebo-controlled, three-period crossover study enrolled women aged 18 years or older who were diagnosed with OAB and reported eight or more micturitions per 24 hours and four or more urgency episodes per week on 5-day bladder diary at baseline (Marenca et al, 2011). Patients were randomized to 1 of 10 treatment sequences and received three of five treatments, each for 4 weeks with 4-week washout periods: standard-dose pregabalin/tolterodine ER (150 mg bid/4 mg qd; $n = 102$); pregabalin alone (150 mg bid; $n = 105$); tolterodine ER alone (4 mg qd; $n = 104$); low-dose pregabalin/tolterodine ER (75 mg bid/2 mg qd; $n = 105$); and placebo ($n = 103$). Patients completed 5-day diaries at the end of treatment and

washout periods. The primary end point was change from baseline to week 4 in MVV per micturition. Baseline-adjusted changes in MVV were significantly greater after treatment with standard-dose pregabalin/tolterodine ER (39.5 mL) versus tolterodine ER alone (15.5 mL; $P < .0001$) and with pregabalin alone (27.4 mL) versus tolterodine ER alone ($P = .005$) and placebo (11.9 mL; $P = .0006$). Treatments were generally well tolerated; discontinuation rates because of adverse events were 4%, 2%, 5%, 0%, and 1% with standard- and low-dose pregabalin/tolterodine ER, pregabalin, tolterodine ER, and placebo, respectively. See section on combination therapies for further information.

Assessment. Both the IR and ER forms of tolterodine have a well-documented effect in OAB and DO (see Table 79-3) and are well tolerated.

Trospium Chloride. Trospium is a quaternary ammonium compound with a biologic availability of less than 10% (Fusgen and Hauri, 2000; Doroshenko et al, 2005). The drug has a plasma half-life of approximately 20 hours, and is mainly (60% of the dose absorbed) eliminated unchanged in the urine. The concentration obtained in urine seems to be enough to affect the mucosal signaling system in a rat model (Kim et al, 2006). Whether or not it contributes to the clinical efficacy of the drug remains to be established.

Trospium is not metabolized by the cytochrome P450 enzyme system (Beckmann-Knopp et al, 1999; Doroshenko et al, 2005). It is expected to cross the blood-brain to a limited extent because it is a substrate for the drug-efflux transporter P-glycoprotein, which restricts its entry into the brain (Davis et al, 2014). This was demonstrated by Staskin and colleagues (2010), who showed that trospium chloride levels in cerebrospinal fluid (CSF) samples were undetectable on day 10 at steady-state peak plasma concentration concurrent with measureable peak plasma values. Clinically, trospium seems to have no negative cognitive effects (Fusgen and Hauri, 2000; Todorova et al, 2001; Wiedemann et al, 2002; Staskin et al, 2010; Chancellor et al, 2012).

Trospium has no selectivity for muscarinic receptor subtypes. In isolated detrusor muscle, it was more potent than oxybutynin and tolterodine to antagonize carbachol-induced contractions (Uckert et al, 2000).

Several RCTs have documented positive effects of trospium both in NDO (Stöhrer et al, 1991; Madersbacher et al, 1995; Menarini et al, 2006) and non-neurogenic DO (Alloussi et al, 1998; Cardozo et al, 2000; Jünemann and Al-Shukri, 2000; Halaska et al, 2003; Zinner et al, 2004; Rudy et al, 2006; Staskin et al, 2007; Dmochowski et al, 2008). In a placebo-controlled, double-blind study on patients with NDO (Stöhrer et al, 1991), the drug was given twice daily at a dose of 20 mg over a 3-week period. It increased maximum cystometric capacity, decreased maximal detrusor pressure, and increased compliance in the treatment group, whereas no effects were noted in the placebo group. Side effects were few and comparable in both groups. In another RCT including patients with spinal cord injuries and NDO, trospium and oxybutynin were equipotent; however, trospium seemed to have fewer side effects (Madersbacher et al, 1995).

The effect of trospium in urgency incontinence has been documented in several RCTs. Alloussi and colleagues (1998) compared the effects of the drug with those of placebo in 309 patients in a urodynamic study of 3 weeks' duration. Trospium 20 mg was given twice daily. Significant increases were noted in volume at first involuntary contraction and in maximum bladder capacity. Cardozo and colleagues (2000) investigated 208 patients with DO who were treated with trospium 20 mg twice daily for 2 weeks. Also in this study, significant increases were found in mean volume at first unstable contraction (from 233 to 299 mL; placebo, 254 to 255 mL) and in maximum bladder capacity (from 329 to 356 mL; placebo, 345 to 335 mL) in the trospium-treated group. Trospium was well tolerated with similar frequency of adverse effects as in the placebo group. Jünemann and Al-Shukri (2000) compared trospium 20 mg twice daily with tolterodine 2 mg twice daily in a placebo-controlled double-blind study on 232 patients with urodynamically proven DO, urgency incontinence without demonstrable DO, or mixed incontinence. Trospium reduced the frequency of micturition,

which was the primary end point, more than tolterodine and placebo, and also reduced the number of incontinence episodes more than the comparators. Dry mouth was comparable in the trospium and tolterodine groups (7% and 9%, respectively).

Halaska and colleagues (2003) studied the tolerability and efficacy of trospium chloride in doses of 20 mg twice daily for long-term therapy in patients with urgency syndrome. The trial included a total of 358 patients with urgency syndrome or urgency incontinence. After randomization in the ratio of 3:1, participants were treated continuously for 52 weeks with either trospium chloride (20 mg twice daily) or oxybutynin (5 mg twice daily). Urodynamic measurements were performed at the beginning and at 26 and 52 weeks to determine the maximal cystometric bladder capacity. Analysis of the micturition diary clearly indicated a reduction in the micturition frequency, incontinence frequency, and the number of urgency episodes in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 mL after 26 weeks and 115 mL after 52 weeks ($P = .001$). Further comparison with oxybutynin did not reveal any statistically significant differences in urodynamic variables between the drugs. Adverse events occurred in 65% of the patients treated with trospium and 77% of those treated with oxybutynin. The main symptom encountered in both treatment groups was dryness of the mouth. An overall assessment for each of the drugs revealed a comparable efficacy level and a better benefit-risk ratio for trospium than for oxybutynin resulting from better tolerability.

Zinner and colleagues (2004) treated 523 patients with symptoms associated with OAB and urgency incontinence with 20 mg trospium twice daily or placebo in a 12-week, multicenter, parallel, double-blind, placebo-controlled trial. Dual primary end points were change in average number of toilet voids and change in urgency incontinence episodes per 24 hours. Secondary efficacy variables were change in average volume per void, voiding urgency severity, urinations during day and night, time to onset of action, and change in Incontinence Impact Questionnaire score. By week 12, trospium significantly decreased average frequency of toilet voids per 24 hours (-2.37) and urgency incontinence episodes 59% compared with placebo (-1.29 ; 44%). It significantly increased average volume per void (32 mL; placebo, 7.7 mL), and decreased average urgency severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 (-0.43 ; placebo, -0.17), and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%; placebo 6.5%), constipation (9.5%; placebo 3.8%), and headache (6.5%; placebo 4.6%). In a large U.S. multicenter trial with the same design and including 658 patients with OAB, **Rudy and colleagues (2006)** confirmed the data by **Zinner and colleagues (2004)**, with respect to both efficacy and adverse effects.

Dose escalation seems to improve therapeutic efficacy. In a 12-week, randomized, double-blind, phase IIIb study including 1658 patients with urinary frequency plus urgency incontinence, patients received trospium chloride 15 mg tid ($n = 828$) or 2.5 mg oxybutynin hydrochloride tid ($n = 830$). After 4 weeks, daily doses were doubled and not readjusted in 29.2% (242 of 828) of patients in the trospium group and in 23.3% (193 of 830) in the oxybutynin group, until the end of treatment. At study end, there were no relevant differences between the "dose adjustment" subgroups and the respective "no dose adjustment" subgroups (trospium, $P = .249$; oxybutynin, $P = .349$). After dose escalation, worsening of dry mouth was higher in both dose-adjusted subgroups compared with the respective "no dose adjustment" subgroups ($P < .001$). Worsening of dry mouth was lower in the trospium groups than in the oxybutynin groups (**Bödeker et al, 2010**).

An ER formulation of trospium allowing once-daily administration has been introduced (**Silver et al, 2010**), and its effects have been tested in controlled trials (**Staskin et al, 2007**; **Dmochowski et al, 2008**; **Chancellor et al, 2010**; **MacDiarmid et al, 2011**; **Sand et al, 2011a, 2011b**; **Zinner et al, 2011**). These studies demonstrated similar efficacy as found with previous formulations, but include

experiences in, for example, elderly patients (>75 years), obese patients, and patients who use multiple concomitant medications. The most frequent side effects were dry mouth (12.9%; placebo, 4.6%) and constipation (7.5%; placebo, 1.8%) (**Dmochowski et al, 2008**).

Intravesical application of trospium may be an interesting alternative. **Frölich and colleagues (1998)** performed a randomized, single-blind, placebo-controlled, monocenter clinical trial in 84 patients with urgency or urgency incontinence. Compared with placebo, intravesical trospium produced a significant increase in maximum bladder capacity and a decrease of detrusor pressure accompanied by an increase of residual urine. There was an improvement in uninhibited bladder contractions. No adverse events were reported. It is interesting to note that intravesical trospium does not seem to be absorbed (**Walter et al, 1999**), thus offering an opportunity for treatment with minimal systemic antimuscarinic effects.

Assessment. Trospium has a well-documented effect in OAB and DO, and tolerability and safety seem acceptable (see **Table 79-3**).

Antimuscarinics with "Mixed" Action

Some drugs used for treatment of OAB and DO have been shown to have more than one mechanism of action. They all have a more-or-less pronounced antimuscarinic effect and, in addition, an often poorly defined "direct" action on bladder muscle. For several of these drugs, the antimuscarinic effects can be demonstrated at much lower drug concentrations than the direct action, which may involve blockade of voltage-operated Ca^{2+} channels. Most probably, the clinical effects of these drugs can be explained mainly by an antimuscarinic action. Among the drugs with mixed actions was terodiline, which was withdrawn from the market because it was suspected to cause polymorphic ventricular tachycardia (torsades de pointes) in some patients (**Connolly et al, 1991**; **Stewart et al, 1992**).

Oxybutynin Chloride. Oxybutynin is a tertiary amine that is well absorbed and undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the cytochrome P450 system (CYP3A4) into multiple metabolites. The primary metabolite, *N*-desethyloxybutynin, has pharmacologic properties similar to those of the parent compound (**Waldeck et al, 1997**) but occurs in much higher concentrations after oral administration (**Hughes et al, 1992**). It has been implicated as the major cause of the troublesome side effect of dry mouth associated with the administration of oxybutynin. It seems reasonable to assume that the effect of oral oxybutynin to a large extent is exerted by the metabolite. The occurrence of an active metabolite may also explain the lack of correlation between plasma concentration of oxybutynin itself and side effects in geriatric patients reported by **Ouslander and colleagues (1988)**. The plasma half-life of the oxybutynin is approximately 2 hours, but with wide interindividual variation (**Douchamps et al, 1988**; **Hughes et al, 1992**).

Oxybutynin has several pharmacologic effects in vitro, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions. The latter may be of importance when the drug is administered intravesically, but probably play no role when it is given orally. In vitro, oxybutynin was 500 times weaker as a smooth muscle relaxant than as an antimuscarinic agent (**Kachur et al, 1988**). Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug. Oxybutynin has a high affinity for muscarinic receptors in human bladder tissue and effectively blocks carbachol-induced contractions (**Nilvebrant and Sparf, 1988**; **Waldeck et al, 1997**). The drug was shown to have slightly higher affinity for muscarinic M_1 and M_3 receptors than for M_2 receptors (**Nilvebrant and Sparf, 1986**; **Norhona-Blob and Kachur, 1991**), but the clinical significance of this is unclear.

The IR form of oxybutynin (OXY-IR) is recognized for its efficacy, and most of the newer antimuscarinic agents have been compared with it once efficacy over placebo has been determined. In general, the new formulations of oxybutynin and other antimuscarinic

agents offer patients efficacy roughly equivalent to that of OXY-IR, and the advantage of the newer formulations lies in improved dosage schedules and side effect profile (Appell et al, 2001; Dmochowski et al, 2002; Diokno et al, 2003). An OXY-ER once-daily oral formulation and an oxybutynin transdermal delivery system (OXY-TDS) are available. OXY-TDS offers a twice-weekly dosage regimen and the potential for improved patient compliance and tolerability. Some of the available formulations of oxybutynin were overviewed by McCrery and Appell (2006).

Immediate-Release Oxybutynin. Several controlled studies have shown that OXY-IR is effective in controlling DO, including NDO (Yarker et al, 1995; Andersson and Chapple, 2001). The recommended oral dose of the IR form is 5 mg three times daily or four times daily, even if lower doses have been used. Thüroff and colleagues (1998) summarized 15 randomized controlled studies on a total of 476 patients treated with oxybutynin. The mean decrease in incontinence was recorded as 52% and the mean reduction in frequency per 24 hours was 33% (data on placebo not presented). The overall “subjective improvement” rate was reported as 74% (range 61% to 100%). The mean percent of patients reporting an adverse effect was 70% (range 17% to 93%). Oxybutynin, 7.5 to 15 mg/day, significantly improved QoL of patients with OAB in a large open multicenter trial. In this study, patient compliance was 97% and side effects, mainly dry mouth, were reported by only 8% of the patients (Amarenco et al, 1998). In 75 nursing home residents, Ouslander and colleagues (1995) found that oxybutynin did not add to the clinical effectiveness of prompted voiding in a placebo-controlled, double-blind, crossover trial. On the other hand, in another controlled trial in 57 elderly subjects, oxybutynin with BT was found to be superior to BT alone (Szonyi et al, 1995).

Several open studies in patients with spinal cord injuries suggested that oxybutynin, given orally or intravesically, can be of therapeutic benefit (Kim et al, 1996; Szollar and Lee, 1996).

The therapeutic effect of OXY-IR on DO is associated with a high incidence of side effects (up to 80% with oral administration). These are typically antimuscarinic in nature (dry mouth, constipation, drowsiness, blurred vision) and are often dose limiting (Baigrie et al, 1988; Jonville et al, 1992). The effects of oxybutynin on the ECG were studied in elderly patients with UI (Hussain et al, 1996); no changes were found. It cannot be excluded that the commonly recommended dose of 5 mg \times 3 is unnecessarily high in some patients, and that a starting dose of 2.5 mg \times 2 with subsequent dose titration would reduce the number of adverse effects (Amarenco et al, 1998).

Extended Release Oxybutynin. The OXY-ER formulation was developed to decrease liver metabolite formation of desethyloxybutynin (DEO) with the presumption that it would result in decreased side effects, especially dry mouth, and improve patient compliance with remaining on oxybutynin therapy (Arisco et al, 2009). The formulation uses an osmotic system to release the drug at a controlled rate over 24 hours distally primarily into the large intestine where absorption is not subject to first-pass metabolism in the liver. This reduction in metabolism is meant to improve the rate of dry mouth complaints when compared with OXY-IR. DEO is still formed through the hepatic cytochrome P450 enzymes, but clinical trials have indeed demonstrated improved dry mouth rates compared with OXY-IR (Appell et al, 2003). Salivary output studies have also been interesting. Two hours after administration of OXY-IR or TOLT-IR, salivary production decreased markedly and then gradually returned to normal. With OXY-ER, however, salivary output was maintained at predose levels throughout the day (Chancellor et al, 2001).

The effects of OXY-ER have been well documented (Siddiqui et al, 2004). In the OBJECT study (Appell et al, 2001), the efficacy and tolerability of 10-mg OXY-ER was compared with a twice-daily 2-mg dose of TOLT-IR. OXY-ER was statistically more effective than the TOLT-IR in weekly urgency incontinence episodes (OXY-ER from 25.6% to 6.1%; TOLT-IR 24.1% to 7.8%), total incontinence (OXY-ER from 28.6% to 7.1%; TOLT-IR 27.0% to 9.3%), and frequency (OXY-ER from 91.8% to 67.1%; TOLT-IR 91.6% to 71.5%),

and both medications were equally well tolerated. The basic study was repeated as the OPERA study (Diokno et al, 2003) with the difference that this study was a direct comparison of the two ER forms, OXY-ER (10 mg) and TOLT-ER (4 mg) and the results were quite different. In this study there was no significant difference in efficacy for the primary end point of urgency incontinence; however, TOLT-ER had a statistically lower incidence of dry mouth. OXY-ER was statistically better at 10 mg than TOLT-ER 4 mg in only the reduction of the rate of urinary frequency. These studies made it clear that in comparative studies, IR entities of one drug should no longer be compared with ER entities of the other.

Greater reductions in urgency and total incontinence have been reported in patients treated in dose-escalation studies with OXY-ER. In two randomized studies, the efficacy and tolerability of OXY-ER were compared with those of OXY-IR. In the 1999 study (Anderson et al, 1999), 105 patients with urgency or mixed incontinence were randomized to receive 5 to 30 mg of OXY-ER once daily or 5 mg of OXY-IR one to four times per day. Dose titrations began at 5 mg, and the dose was increased every 4 to 7 days until one of three end points was achieved. These were (1) the patient reported no urgency incontinence during the final 2 days of the dosage period; (2) the maximum tolerable dose was reached; or (3) the maximum allowable dose (30 mg for OXY-ER or 20 mg for OXY-IR) was reached. The mean percent reduction in weekly urgency and total incontinence episodes was statistically similar between OXY-ER and OXY-IR, but dry mouth was reported statistically more often with OXY-IR. In the 2000 study (Versi et al, 2000), 226 patients were randomized between OXY-ER and OXY-IR with weekly increments of 5 mg daily up to 20 mg daily. As in the 1999 study, OXY-ER again achieved a greater than 80% reduction in urgency and total incontinence episodes, and a significant percentage of patients became dry. A negative aspect of these studies is that there were no naive patients included; all patients were known responders to oxybutynin. Similar efficacy results have been achieved, however, with OXY-ER in a treatment-naive population (Gleason et al, 1999).

In an RCT comparing different daily doses of oxybutynin (5, 10, and 15 mg), Corcos and colleagues (2006) found a significant dose-response relationship for both urgency incontinence episodes and dry mouth. The greatest satisfaction was with 15 mg of oxybutynin per day.

In a multicenter, prospective, observational, flexible-dosing Korean study, Yoo and colleagues (2012) investigated the prescription pattern and dose distribution of OXY-ER in patients with the OAB syndrome in actual clinical practice. The dose for each patient was adjusted after discussions of efficacy and tolerability between doctor and patient, over a 12-week treatment period. Efficacy was measured by administering the Primary OAB Symptom Questionnaire (POSQ) before and after treatment. Patients were also administered a patient perception of treatment benefit (PPTB) questionnaire at the end of the study. Of the 809 patients enrolled, 590 (73.2%) continued to take study medication for 12 weeks. Most patients were prescribed 5 to 10 mg of oxybutynin ER per day as both starting and maintenance doses, with a dose escalation rate of only 14.9%. All OAB symptoms evaluated by the POSQ were improved; 94.1% of patients reported benefits from treatment, and 89.3% were satisfied.

Transdermal Oxybutynin. Transdermal delivery also alters oxybutynin metabolism, reducing DEO production to an even greater extent than OXY-ER. A study (Davila et al, 2001) comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinence episodes (from 7.3 to 2.3 [66%] for OXY-TDS; and 7.4 to 2.6 [72%] for OXY-IR), but much less dry mouth (38% for OXY-TDS and 94% for OXY-IR). In another study (Dmochowski et al, 2002) the 3.9-mg daily-dose patch significantly (vs. placebo) reduced the mean number of daily incontinence episodes (from 4.7 to 1.9; placebo from 5.0 to 2.9) while reducing average daily urinary frequency, confirmed by an increased average voided volume (from 165 to 198 mL; placebo from 175 to 182 mL). Furthermore, dry mouth rate was similar to placebo (7% vs. 8.3%). In a third study (Dmochowski et al, 2003b) OXY-TDS

was compared not only with placebo but with TOLT-ER. Both drugs equivalently and significantly reduced daily incontinence episodes and increased the average voided volume, but TOLT-ER was associated with a significantly higher rate of antimuscarinic adverse events. The primary adverse event for OXY-TDS was application site reaction pruritus in 14% and erythema in 8.3%, with nearly 9% feeling that the reactions were severe enough to withdraw from the study despite the lack of systemic problems.

The pharmacokinetics and adverse effect dynamics of OXY-TDS (3.9 mg/day) and OXY-ER (10 mg/day) were compared in healthy subjects in a randomized, two-way crossover study (Appell et al, 2003). Multiple blood and saliva samples were collected and pharmacokinetic parameters and total salivary output were assessed. OXY-TDS administration resulted in greater systemic availability and minimal metabolism to DEO compared with OXY-ER, which resulted in greater salivary output in OXY-TDS patients and less dry mouth symptomatology than when taking OXY-ER.

Dmochowski and colleagues (2005), analyzing the combined results of two RCTs, concluded that transdermal oxybutynin was shown to be efficacious and well tolerated. The most common systemic side effect was dry mouth (7.0% vs. placebo 5.3%). Application site erythema occurred in 7% and pruritus in 16.1%. Also Cartwright and Cardozo (2007), reviewing published and presented data, concluded that transdermal oxybutynin has a good balance between efficacy and tolerability with a rate of systemic antimuscarinic side effects that is lower than with oral antimuscarinics; however, this benefit was offset by the rate of local skin reaction. The reviews of Sahai and colleagues (2008) and Staskin and Salvatore (2010) largely confirmed these conclusions, which also have been supported by further studies (Cartwright et al, 2011).

Oxybutynin Topical Gel. Given the efficacy and tolerability of the transdermal application, limited only by skin site reactions, a gel formulation was developed. Oxybutynin topical gel (OTG) was approved by the U.S. Food and Drug Administration (FDA) in January 2009. OTG is applied once daily to the abdomen, thigh, shoulder, or upper arm area (Staskin et al, 2009). The 1-g application dose delivers approximately 4 mg of drug to the circulation, with stable plasma concentrations and a "favorable" *N*-desethyloxybutynin metabolite-oxybutynin ratio, believed to minimize antimuscarinic side effects (Staskin and Robinson, 2009). In a multicenter RCT, 789 patients (89% women) with urgency-predominant incontinence were assigned to OTG or placebo once daily for 12 weeks (Staskin et al, 2009). The mean number of urgency episodes, as recorded by 3-day voiding diary, was reduced by 3.0 episodes per day versus 2.5 in the placebo arm ($P < .0001$). Urinary frequency decreased by 2.7 episodes per day, and voided volume increased by 21 mL (vs. 2.0 episodes [$P = .0017$] and 3.8 mL [$P = .0018$], respectively, in the placebo group). Dry mouth was reported in 6.9% of the treatment group versus 2.8% of the placebo group. Skin reaction at the application site was reported in 5.4% of the treatment group versus 1.0% in the placebo arm. It was felt that improved skin tolerability of the gel over the OXY transdermal patch delivery system was secondary to lack of adhesive and skin occlusion. The gel dries rapidly on application and leaves no residue; person-to-person transference via skin contact is largely eliminated if clothing is worn over the application site (Dmochowski et al, 2011). The evolution of the transdermal gel allows greater patient tolerability and improved compliance. This was confirmed by Sand and colleagues (2012a), who showed that in 704 women with OAB, OTG significantly reduced the number (mean \pm standard deviation [SD]) of daily incontinence episodes (OTG, -3.0 ± 2.8 episodes; placebo, -2.5 ± 3.0 episodes), reduced urinary frequency, increased voided volume, and improved select health-related quality-of-life domains versus placebo. Dry mouth was the only drug-related adverse event significantly more common with OTG (7.4%) than with placebo (2.8%).

Other Administration Forms. Rectal administration (Collas and Malone-Lee, 1997) was reported to have fewer adverse effects than the conventional tablets.

Administered intravesically, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical

improvement with few side effects, both in neurogenic and in other types of DO, and in both children and adults (Lose and Norgaard, 2001; Fader et al, 2007; George et al, 2007; Guerra et al, 2008), although adverse effects may occur (Kasabian et al, 1994; Palmer et al, 1997).

Effects on Cognition. Several studies have documented the possibility that oxybutynin may have negative effects on cognitive functions, particularly in the elderly population but also in children (see, e.g., Kay et al, 2006; Klausner and Steers, 2007; Kay and Ebinger, 2008). This factor should be taken into consideration when prescribing the drug.

Assessment. Oxybutynin has well-documented efficacy in the treatment of OAB and DO (see Table 79-3). Despite the adverse effect profile, it is still an established therapeutic option.

Propiverine Hydrochloride. Several aspects of the preclinical, pharmacokinetic, and clinical effects of propiverine have been reviewed by Madersbacher and Murz (2001). The drug is rapidly absorbed (T_{max} 2 hours) but has a high first-pass metabolism, and its biologic availability is about 50%. Propiverine is an inducer of hepatic cytochrome P450 enzymes in rats in doses about 100 times above the therapeutic doses in humans (Walter et al, 2003). Several active metabolites that quantitatively and qualitatively differ from the mother compound are formed (Haustein et al, 1988; Müller et al, 1993; Wuest et al, 2006; Sugiyama et al, 2008; Zhu et al, 2008). Most probably these metabolites contribute to the clinical effects of the drug, but their individual contributions have not been clarified (Michel and Hegde, 2006). The half-life of propiverine itself is about 11 to 14 hours. An ER preparation was shown to be effective (Jünemann et al, 2006; May et al, 2008). Oral absorption of propiverine is site dependent and influenced by dosage form and circadian time-dependent elimination processes (May et al, 2008).

Propiverine has combined antimuscarinic and calcium antagonistic actions (Haruno, 1992; Tokuno et al, 1993). The importance of the calcium antagonistic component for the drug's clinical effects has not been established. Propiverine has no selectivity for muscarinic receptor subtypes. The effects of propiverine on cardiac ion channels and action potentials were investigated by Christ and colleagues (2008). Propiverine blocked, in a concentration-dependent manner, hERG channels expressed in HEK293 cells, as well as native I(Kr) current in ventricular myocytes of guinea pig. However, action potential duration was not prolonged in guinea pig and human ventricular tissue, and the investigators concluded that their results did not provide evidence for an enhanced cardiovascular safety risk with the drug.

Propiverine has been shown to have beneficial effects in patients with DO in several investigations. Thüroff and colleagues (1998) analyzed nine randomized studies on a total of 230 patients and found a 17% reduction in micturitions per 24 hours, a 64-mL increase in bladder capacity, and a 77% (range 33% to 80%) subjective improvement. Side effects were found in 14% (range 8% to 42%). In patients with NDO, controlled clinical trials have demonstrated propiverine's superiority over placebo (Stöhrer et al, 1999). Propiverine also increased bladder capacity and decreased maximum detrusor contractions. Controlled trials comparing propiverine, flavoxate, and placebo (Wehnert et al, 1989) and propiverine, oxybutynin, and placebo (Wehnert et al, 1992; Madersbacher et al, 1999) have confirmed the efficacy of propiverine, and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin. In a comparative RCT including 131 patients with NDO, propiverine and oxybutynin were compared (Stöhrer et al, 2007). The drugs were found to be equally effective in increasing bladder capacity and lowering bladder pressure. Propiverine caused a significantly lower frequency of dry mouth than oxybutynin.

Also in children and adolescents with NDO, propiverine was found to be effective (Grigoleit et al, 2006; Schulte-Baukloh et al, 2006), with a low incidence rate of adverse events ($<1.5\%$) (Grigoleit et al, 2006). A randomized, double-blind, placebo-controlled trial with parallel-group design in children aged 5 to 10 years was performed by Marschall-Kehrel and colleagues (2009). Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. Decrease in voiding frequency per day was the primary efficacy

parameter; secondary end points included voided volume and incontinence episodes. There was a significant decrease in voiding frequency episodes for propiverine versus placebo. Superiority could also be demonstrated for voided volume and incontinence episodes per day. Propiverine was well tolerated; 23% of patients reported side effects for propiverine and 20% for placebo.

In a randomized, double-blind, multicenter clinical trial, patients with IDO were treated with 15 mg of propiverine twice daily or 2 mg of TOLT-IR twice daily over a period of 28 days (Jünemann et al, 2005). The maximum cystometric capacity was determined at baseline and after 4 weeks of therapy. The difference of both values was used as the primary end point. Secondary end points were voided volume per micturition, evaluation of efficacy (by the investigator), tolerability, PVR urine, and QoL. It was found that the mean maximum cystometric capacity increased significantly ($P < .01$) in both groups. The volume at first urgency and the frequency and volume chart parameters also showed relevant improvements during treatment. The most common adverse event, dry mouth, occurred in 20 patients in the propiverine group and in 19 patients in the tolterodine group. The scores for QoL improved comparably in both groups.

Madersbacher and colleagues (1999) compared the tolerability and efficacy of propiverine (15 mg three times daily), oxybutynin (5 mg twice daily), and placebo in 366 patients with urgency and urgency incontinence in a randomized, double-blind, placebo-controlled clinical trial. Urodynamic efficacy of propiverine was judged similar to that of oxybutynin, but the incidence of dry mouth and the severity of dry mouth were judged to be less with propiverine than with oxybutynin. Dorschner and colleagues (2000) investigated in a double-blind, multicenter, placebo-controlled, randomized study the efficacy and cardiac safety of propiverine in 98 elderly patients (mean age 68 years) with urgency, urgency incontinence, or mixed urgency-stress incontinence. After a 2-week placebo run-in period, the patients received propiverine (15 mg three times daily) or placebo (three times daily) for 4 weeks. Propiverine caused a significant reduction of the micturition frequency (from 8.7 to 6.5) and a significant decrease in episodes of incontinence (from 0.9 to 0.3 per day). The incidence of adverse events was very low (2% dryness of the mouth under propiverine—2 out of 49 patients). Resting and ambulatory ECGs indicated no significant changes. The cardiac safety of propiverine was further studied by Donath and colleagues (2011) in two comprehensively designed monocentric ECG studies (including 24 healthy women, followed by a second study on 24 male patients with coronary heart disease (CHD) and a pathologic Pardee Q wave on the ECG). Both studies were placebo controlled and compared the effects of single-dose (30 mg *sid*) and multiple-dose (15 mg *tid*) administration of propiverine hydrochloride in a crossover design over 6 and 13 days, respectively. They were performed to investigate the influence of propiverine hydrochloride and its main metabolite, propiverine *N*-oxide, on cardiac function with regard to QTc prolongation, QTc dispersion, and T-wave shape. No negative effects on cardiac safety could be demonstrated.

Abrams and colleagues (2006b) compared the effects of propiverine and oxybutynin on ambulatory urodynamic monitoring (AUM) parameters, safety, and tolerability in OAB patients. Seventy-seven patients received two of the following treatments during two 2-week periods: propiverine 20 mg once daily, propiverine 15 mg three times daily, oxybutynin 5 mg three times daily, and placebo. The researchers found that oxybutynin 15 mg was more effective than propiverine 20 mg in reducing symptomatic and asymptomatic involuntary detrusor contractions in ambulatory patients. Oxybutynin had a higher rate of dry mouth, and propiverine had a more pronounced effect on gastrointestinal, cardiovascular, and visual function.

Yamaguchi and colleagues (2007) performed a multicenter, 12-week, double-blind phase III trial in Japanese men and women with OAB (1593 patients were randomized and 1584 were treated), comparing solifenacin 5 or 10 mg, propiverine 20 mg, and placebo. Changes at end point in number of voids per 24 hours, urgency, incontinence, urgency incontinence and nocturia episodes, volume

voided per void, restoration of continence, and QoL were examined. It was found that at end point there were greater reductions in mean (SD) voids per 24 hours with all drug regimens than with placebo. All active treatments improved the volume voided and QoL versus placebo; solifenacin 10 mg reduced nocturia episodes and significantly improved urgency episodes and volume voided versus propiverine 20 mg, and solifenacin 5 mg caused less dry mouth. Solifenacin 10 mg caused more dry mouth and constipation than propiverine 20 mg. Wada and colleagues (2011) performed a prospective nonrandomized crossover study of female OAB patients, assigned alternately to treatment with propiverine (20 mg) for 8 weeks then solifenacin (5 mg) for 8 weeks or solifenacin for 8 weeks then propiverine for 8 weeks. At baseline, 8th week, and 16th week, symptoms were assessed using OAB Symptom Score. Of the 121 patients enrolled, 83 were analyzed. Both drugs were effective. Urgency was further improved after switching from propiverine to solifenacin, but not after switching from solifenacin to propiverine. Solifenacin was better tolerated than propiverine.

In another multicenter, prospective, parallel, double-blind, placebo-controlled trial, Lee and colleagues (2010) studied the effects of 30 mg of propiverine per day in 264 OAB patients (mean age 52.2 years), 221 of whom had efficacy data available from baseline and at least one on-treatment visit with greater than 75% compliance. The study was focused on improving urgency. Overall, among patients treated with propiverine, 39% rated their treatment as providing “much benefit,” compared with 15% in the placebo group. Adverse events reported by 32 (22.5%) and 10 (12.7%) patients in the propiverine and placebo group were all tolerable.

Masumori and colleagues (2011) examined prospectively the efficacy and safety of propiverine in patients with OAB who responded poorly to previous treatment with solifenacin, tolterodine, or imidafenacin. Of 73 patients enrolled (29 men and 44 women, median age 71 years), 52 completed the protocol treatment. The OAB Symptom Score was significantly improved by propiverine treatment. The scores of OAB symptoms (nighttime frequency, urgency, and urge incontinence) except daytime frequency also improved significantly. No increase in PVR was observed. The most frequent adverse event was dry mouth (13.7%), followed by constipation (6.8%).

In a noncontrolled study in patients with wet OAB, the efficacy of propiverine on symptoms and QoL was confirmed (Komatsu et al, 2009).

Assessment. Propiverine has a documented beneficial effect in the treatment of OAB and DO (see Table 79-3) and seems to have an acceptable side effect profile. It is not approved for use in the United States.

Flavoxate Hydrochloride. Flavoxate is often discussed as a drug with mixed actions; however, its main mechanism of action may not be antimuscarinic. Flavoxate is well absorbed, and oral bioavailability appeared to be close to 100% (Guay, 2003). The drug is extensively metabolized and plasma half-life was found to be 3.5 hours (Sheu et al, 2001). Its main metabolite (3-methylflavone-8-carboxylic acid [MFCA]) has been shown to have low pharmacologic activity (Cazzulani et al, 1988; Caine et al, 1991). The main mechanism of flavoxate's effect on smooth muscle has not been established. The drug has been found to possess a moderate calcium antagonistic activity, to have the ability to inhibit phosphodiesterase (PDE), and to have local anesthetic properties; no antimuscarinic effect was found (Guarneri et al, 1994). Uckert and colleagues (2000), on the other hand, found that in strips of human bladder, the potency of flavoxate to reverse contraction induced by muscarinic receptor stimulation and by electrical field stimulation was comparable. It has been suggested that pertussis toxin-sensitive G proteins in the brain are involved in the flavoxate-induced suppression of the micturition reflex, because intracerebroventricularly or intrathecally administered flavoxate abolished isovolumetric rhythmic bladder contractions in anesthetized rats (Oka et al, 1996).

The clinical effects of flavoxate in patients with DO and frequency, urgency, and incontinence have been studied in both open and controlled investigations, but with varying rates of success (Ruffman, 1988). Stanton (1973) compared emeprenium bromide

and flavoxate in a double-blind crossover study of patients with DO and reported improvement rates of 83% and 66% after flavoxate or emepronium bromide, respectively, both administered at 200 mg three times daily. In another double-blind crossover study comparing flavoxate 1200 mg/day with oxybutynin 15 mg/day in 41 women with idiopathic motor or sensory urgency, and using both clinical and urodynamic criteria, [Milani and colleagues \(1993\)](#) found both drugs effective. No difference in efficacy was found between them, but flavoxate had fewer and milder side effects. Other investigators comparing the effects of flavoxate with those of placebo have not been able to show any beneficial effect of flavoxate at doses up to 400 mg three times daily ([Briggs et al, 1980](#); [Chapple et al, 1990](#); [Dahm et al, 1995](#)). In general, few side effects have been reported during treatment with flavoxate. On the other hand, its efficacy compared with other therapeutic alternatives is not well documented (see [Table 79-3](#)).

Assessment. No RCTs seem to have been performed with flavoxate during the last decade. The scarcity of evidence regarding documented clinical efficacy should be considered before use of the drug.

KEY POINTS: ANTIMUSCARINIC THERAPY

- Drugs can alter LUT function by acting at any point along the afferent or efferent limb of innervation by reception activation or blockade, or by affecting the concentration of the neural transmitter at an activation site, or by stimulating or inhibiting signal transduction mechanisms. Functionally, these actions can be divided into those that facilitate bladder filling or urine storage versus those that facilitate bladder emptying or voiding. Furthermore, these actions can be subdivided into those that primarily affect the bladder or outlet. Some drugs will have an effect on both. Atropine and atropine-like agents that inhibit muscarinic receptors are the most commonly used agents to inhibit involuntary contractions. They also act to maintain low bladder tone during filling with a consequent decrease in filling and storage symptoms that are unrelated to the occurrence of an involuntary contraction. They do so primarily by the inhibition of muscarinic receptors, located on detrusor muscle cells, urothelial cells, suburothelial nerves, and interstitial cells. There are five pharmacologically defined muscarinic receptors; the M_2 receptor is the most common in the human bladder, but the M_3 receptor is the most important for contraction. As opposed to the traditional view that antimuscarinics in the usual administered clinical doses act by blocking the muscarinic receptors on the detrusor muscle, they appear to act mainly during the storage phase, decreasing urgency and increasing bladder capacity. In the dosage range used for treatment of the symptoms of OAB or DO, there is little evidence for a significant reduction of the voiding contraction. Higher doses can and will produce a reduction of the voiding contraction.
- In general, drug therapy for LUT dysfunction is hindered by *uroselectivity*, a term that originated with Karl-Erik Andersson.
- Antimuscarinics are of significant clinical benefit in the treatment of OAB and related symptoms. There are numerous such agents available, and the pharmacologic profiles of each drug and their individual characteristics differ. None, however, is ideal as a first-line treatment for all patients with OAB or DO.
- Persistence with current antimuscarinic agents for such treatment is low, owing to a combination of relative lack of efficacy and adverse effects.
- Some drugs are labelled as primarily antimuscarinic but with a mixed action, meaning there is often a poorly defined direction of action bladder smooth muscle; however, most probably the clinical effects of such drugs can be explained primarily by the antimuscarinic action.

Drugs Acting on Membrane Channels

Calcium Antagonists. Activation of detrusor muscle, through both muscarinic-receptor and NANC pathways, seems to require influx of extracellular Ca^{2+} through Ca^{2+} channels as well as via mobilization of intracellular Ca^{2+} ([Andersson, 1993](#); [Andersson and Arner, 2004](#)). The influx of extracellular calcium can be blocked by calcium antagonists, blocking L-type Ca^{2+} channels, and theoretically this would be an attractive way of inhibiting DO and regulating detrusor smooth muscle tone ([Berridge, 2008](#)). Two major groups of calcium channels include the voltage-gated ([Catterall et al, 2003](#)) and the store-operated channels ([Leung et al, 2008](#)). Although both can contribute to the maintenance of smooth muscle tone in general, store-operated calcium channels apparently contribute only to a limited, if any, extent to the regulation of bladder smooth muscle tone ([Schneider et al, 2004a, 2004b](#)). On the other hand, various types of voltage-operated calcium channels have been implicated in the regulation of bladder smooth muscle including Q-type ([Frew and Lundy, 1995](#)) and L-type channels ([Wuest et al, 2007](#)). The latter appear to be of particular importance because inhibitors of L-type channels have repeatedly been shown to inhibit bladder contraction in vitro with tissue from multiple mammalian species, including humans ([Frazier et al, 2008](#)). However, the relative importance of L-type channels may be somewhat less in humans than in other mammalian species ([Wuest et al, 2007](#)). In confirmation of the role of L-type calcium channels, it has been shown that KO mice lacking a crucial subunit of this channel exhibit a markedly impaired bladder contractility ([Wegener et al, 2004](#)).

Although these in vitro data suggest a possible role for calcium channel inhibitors, particularly those of L-type channels, in the treatment of DO and incontinence, only limited clinical studies are available in this regard. One urodynamic study compared the effects of intravesical instillation of the calcium channel inhibitor verapamil, the muscarinic-receptor antagonists oxybutynin and trospium, and placebo in patients with urgency or urgency incontinence. Whereas the two muscarinic-receptor antagonists significantly increased bladder capacity, verapamil treatment was not associated with relevant changes in bladder function ([Fröhlich et al, 1998](#)). In a clinical study of limited size, the calcium channel inhibitor nimodipine (30 mg/day) did not significantly improve the number of incontinence episodes as compared with placebo ([Naglie et al, 2002](#)). It should be noted that despite a long-standing and widespread use of calcium channel inhibitors in the treatment of cardiovascular disease, there are no major reports on impaired bladder contractility as a side effect of such treatment. The reasons for the discrepancy between the promising in vitro data and the lack of clinical data are not fully clear, but they may relate to pharmacokinetic properties of the currently used drugs, which may insufficiently either reach or penetrate bladder tissue in therapeutically administered doses. At present, there is no clinical evidence to support a possible use of calcium channel inhibitors in the treatment of bladder dysfunction (see [Table 79-3](#)).

Potassium Channel Openers. Potassium channels contribute to the membrane potential of smooth muscle cells and hence to the regulation of smooth muscle tone. Numerous types of potassium channels exist in the bladder ([Gutman et al, 2003](#); [Petkov, 2011](#)). With regard to bladder function, ATP-dependent (K_{ATP}) and big calcium-activated (BK_{Ca}) channels have been studied most intensively. The BK_{Ca} channels also appear to be important physiologically because their activation can cause hyperpolarization of bladder smooth muscle cells, and by this mechanism they can contribute to the relaxation of bladder smooth muscle by, for example, β -AR agonists ([Frazier et al, 2008](#)). Openers of both K_{ATP} ([Howe et al, 1995](#); [Hu and Kim, 1997](#); [Martin et al, 1997](#)) and BK_{Ca} channels ([Hu and Kim, 1997](#); [Sheldon et al, 1997](#)) have been shown to induce bladder smooth muscle relaxation in various mammalian species, but the density of some types of potassium channels may differ markedly among species. Some potassium channel openers have also been shown to suppress nonvoiding detrusor contractions in vivo in animal models of DO ([Howe et al, 1995](#); [Martin et al,](#)

1997; Tanaka et al, 2003), and this also includes activators of the KCNQ type of potassium channels (Streng et al, 2004). Although potassium channel openers are believed to mainly act directly on smooth muscle cells (Gopalakrishnan and Shieh, 2004; Petkov, 2011), they may also at least in part affect bladder function by modulating the activity of afferent neurones (Tanaka et al, 2003).

Although the aforementioned data demonstrate the potential of potassium channel openers to inhibit nonvoiding detrusor contractions, these channels are expressed not only in bladder, but also in, for example, vascular smooth muscle. Therefore potassium channel openers may also affect cardiovascular function, and in effective doses may considerably lower blood pressure (Howe et al, 1995; Shieh et al, 2007). Whereas some compounds of this class have a certain degree of selectivity for the bladder as compared with the cardiovascular system, it remains unclear whether the degree of selectivity offers a sufficiently large therapeutic window for clinical use. This consideration has led to a considerable hesitancy to study potassium channel openers in OAB patients. Nevertheless, one randomized, placebo-controlled clinical study on the K_{ATP} opener ZD0947 has been reported (Chapple et al, 2006). ZD0947 at the chosen dose did not lower blood pressure or cause adverse events typical for a vasodilating drug, but it also failed to achieve superiority relative to placebo for the treatment of OAB symptoms. Therefore, despite promising preclinical efficacy data, potassium channel openers at present are not a therapeutic option and may never become one owing to a lack of selectivity for bladder over cardiovascular tissues (see Table 79-3).

Another way to use potassium channels to normalize bladder function was suggested by Christ and colleagues (2001) in a rat model of detrusor hyperactivity. They injected “naked” hSlo/pCDNA3 (maxiK channel) into the bladder and found a significant amelioration of the hyperactivity. Whether this principle can be therapeutically useful in humans is currently under investigation.

α -Adrenoceptor Antagonists

It is well documented that α_1 -AR antagonists can ameliorate LUTS in men (Andersson, 2002b; Michel, 2010; McVary et al, 2011; Lepor et al, 2012; Ishizuka et al, 2013; Oelke et al, 2013; Yuan et al, 2013). Currently used α_1 -AR antagonists are considered effective for treatment of both storage and voiding symptoms in men with LUTS associated with or suggestive of benign prostatic hyperplasia (BPH) (Lepor et al, 2012; Soler et al, 2013). However, in a study in which tamsulosin was given alone or together with tolterodine to patients with male LUTS and OAB symptoms, monotherapy with the drug was not effective (Kaplan et al, 2006). Doxazosin monotherapy resulted in only minimal effects in International Prostate Symptom Score (IPSS) storage subscore and urgency episodes and no improvement in patient perception of bladder condition (Lee et al, 2011).

A pivotal question is whether better efficacy and/or tolerability can be achieved by highly subtype-selective drugs than with the commonly used alternatives. α_1 -ARs include three receptor subtypes, α_{1A} , α_{1B} , and α_{1D} , that are structurally and pharmacologically distinct and have different tissue distributions (Andersson and Gratzke, 2007; Yamada and Ito, 2011; Nishimune et al, 2012). α_{1A} -ARs are the predominant subtype in the human prostate, where they mediate smooth muscle contraction. A fourth subtype, α_{1L} , also found in human prostate, is derived from the same gene as the α_{1A} subtype, but α_{1L} and α_{1A} receptors have different pharmacologic properties and bind some α -AR antagonists with different affinities. The precise structural relationship between the two subtypes remains to be elucidated. Selectivity for α_{1B} -AR has been considered disadvantageous from a cardiovascular point of view (Schwinn et al, 2004; Schwinn and Roehrborn, 2008). Kojima and colleagues (2008) studied the expression of α_1 -AR in the transitional zone of prostates from 55 patients with BPH, comparing patients treated with tamsulosin, presumed to block α_{1A} -ARs, and naftopidil, presumed to block α_{1D} -ARs. However, the selectivity of

naftopidil for α_{1D} -ARs versus α_{1A} -ARs is modest (Take et al, 1998), and its use as a tool to differentiate among α_1 -AR subtypes is questionable. Nevertheless, the tamsulosin and naftopidil groups were classified as α_{1A} -AR dominant (22 and 12 patients) and α_{1D} -AR dominant (11 and 16, respectively). The efficacy of tamsulosin and naftopidil differed depending on the dominant expression of the α_1 -AR subtype in the prostate. Tamsulosin was more effective in patients with dominant expression of the α_{1A} -AR subtype, whereas naftopidil was more effective in those with dominant expression of the α_{1D} -AR subtype. In another study, the same group assessed whether there was a direct correlation between the prostatic expression of α_1 -AR subtype mRNA and severity of LUTS or BOO (Kojima et al, 2011). They found no direct correlation between the expression of α_1 -AR subtype mRNA in the prostate and severity of LUTS or BOO, although there was a significant regression of this expression with patient age. Kojima and colleagues (2011) concluded that the expression level of α_1 -AR subtype mRNA in the prostate could be a predictor of the efficacy of subtype-selective α_1 -AR antagonists in patients with BPH and suggested that genetic differences were responsible for the diverse responses to the drugs.

Silodosin (KD-3213), which has a high selectivity for α_{1A} -ARs (Tatemichi et al, 2006a, 2006b; Lepor and Hill, 2010; Yoshida et al, 2011), had clinically good effects on both voiding and storage symptoms in men with BPH (Kawabe et al, 2005; Yoshida et al, 2007; Marks et al, 2009a, 2009b; Morganroth et al, 2010; Chapple et al, 2011; Yoshida et al, 2011). Chapple and colleagues (2011) conducted a multicenter double-blind, placebo- and active-controlled parallel group study comparing silodosin, tamsulosin, and placebo. A total of 1228 men 50 years of age or older with an IPSS of 13 or higher and a urine maximum flow rate (Qmax) greater than 4 and less than or equal to 15 mL/sec were selected at 72 sites in 11 European countries. The patients were entered into a 2-week washout and a 4-week placebo run-in period. A total of 955 patients were randomized (2:2:1) to silodosin 8 mg (n = 381), tamsulosin 0.4 mg (n = 384), or placebo (n = 190) once daily for 12 weeks. Its overall efficacy was not inferior to tamsulosin. Only silodosin showed a significant effect on nocturia over placebo. There was no significant difference among the two α_1 -AR antagonists and the placebo in terms of Qmax. There was also no difference between the two α -AR antagonists for the QoL parameter, although both were better than the placebo. Active treatments were well tolerated, and discontinuation rates resulting from adverse events were low in all groups (2.1%, 1.0%, and 1.6% with silodosin, tamsulosin, and placebo, respectively). The most frequent adverse event with silodosin was a reduced or absent ejaculation during orgasm (14%), a reversible effect as a consequence of the potent and selective α_{1A} -AR antagonism of the drug. The incidence was higher than that observed with tamsulosin (2%); however, only 1.3% of silodosin-treated patients discontinued treatment because of this adverse event. Silodosin treatment improved DO and obstruction grade by decreasing detrusor opening pressure, detrusor pressure at Qmax, BOO Index score, and Schafer obstruction class significantly (Yamanishi et al, 2009). In a different open, nonblinded prospective study, silodosin 8 mg led to a significant increase in bladder capacity at first desire to void with no significant change in maximum cystometric capacity. In the voiding phase, mean detrusor pressure at maximum flow significantly decreased, mean BOO Index score decreased significantly, and obstruction grade as assessed by the Schaefer nomogram improved significantly (Matsukawa et al, 2009).

It thus seems that selective blockade of α_{1A} -ARs is a clinically effective approach, and silodosin is an effective and well-tolerated treatment for the relief of both voiding and storage symptoms in male patients with LUTS, even if treatment is associated with a high incidence of ejaculatory dysfunction.

Interest has also been focused on the α_1 -ARs (α_{1D}), specifically in the bladder (Schwinn et al, 2004; Schwinn and Roehrborn, 2008), on the assumption that these receptors were responsible for storage symptoms. However, the inter-relationship between the α_{1D} -ARs in the human detrusor smooth muscle and the pathophysiology of LUTS is unclear. Naftopidil was shown to

significantly improve the OAB Symptom Score (Sakai et al, 2011) and urgency episodes (Yokoyama et al, 2009). Ikemoto and colleagues (2003) gave tamsulosin and naftopidil to 96 patients with BPH for 8 weeks in a crossover study. Whereas naftopidil monotherapy decreased the IPSS for storage symptoms, tamsulosin monotherapy decreased the IPSS for voiding symptoms. However, this difference (which was suggested to depend on differences in affinity for α_1 -AR subtypes between the drugs) could not be reproduced in a randomized head-to-head comparison between the drugs (Gotoh et al, 2005). Based on available evidence, it therefore cannot be concluded that the α_{1D} -ARs on the detrusor smooth muscle are the main therapeutic target. However, α_{1D} -ARs may have effects on different locations in the bladder aside from the detrusor smooth muscle: the detrusor vasculature, the urothelium, and the afferent and efferent nerve terminals and intramural ganglia (Andersson and Gratzke, 2007; Yamada and Ito, 2011; Moro et al, 2013). The importance and functional role of this observation remain to be established.

In women, treatment of OAB symptoms with α_1 -AR antagonists seems to be ineffective. In an RCT including 364 women with OAB, no effect of tamsulosin versus placebo could be demonstrated (Robinson et al, 2007). On the other hand, voiding symptoms in women with functional outflow obstruction or LUTS were treated (with modest success) with an α_1 -AR antagonist (Kessler et al, 2006; Low et al, 2008). It should be remembered that in women, these drugs may produce stress incontinence (Dwyer and Teele, 1992).

In patients with NDO, treatment with α_1 -AR antagonists was moderately successful (Abrams et al, 2003).

β -Adrenoceptor agonists

Background. The three cloned subtypes of β -ARs (β_1 , β_2 , and β_3) have been identified in the detrusor of most species, including humans (Andersson and Arner, 2004; Michel and Vrydag, 2006). In addition, the human urothelium contains all three receptor subtypes (Otsuka et al, 2008). Studies using real-time reverse transcription polymerase chain reaction (RT-PCR) have revealed a predominant expression of β_3 -AR mRNA in human detrusor muscle (Nomiya and Yamaguchi, 2003; Michel and Vrydag, 2006; Igawa et al, 2010), and the functional evidence for an important role in both normal and neurogenic bladders is convincing (Fujimura et al, 1999; Igawa et al, 1999; Takeda et al, 1999; Morita et al, 2000; Igawa et al, 2001; Biers et al, 2006; Michel and Vrydag, 2006; Leon et al, 2008; Igawa et al, 2010). The human detrusor also contains β_2 -ARs, and most probably both receptors are involved in the physiologic effects (relaxation) of noradrenaline (NA) in this structure (Andersson and Arner, 2004; Michel and Vrydag, 2006; Igawa et al, 2010).

The generally accepted mechanism by which β -ARs induce detrusor relaxation in most species is activation of adenylyl cyclase with the subsequent formation of cAMP. However, there is evidence suggesting that in the bladder, K^+ channels, particularly BK_{Ca} channels, may be more important in β -AR mediated relaxation than cAMP (Hudman et al, 2000; Frazier et al, 2005; Uchida et al, 2005; Frazier et al, 2008). Aizawa and colleagues (2012) showed that the β_3 -AR agonist mirabegron could inhibit filling-induced activity in both mechanosensitive A δ - and C-fiber primary bladder afferents of the rat bladder.

Because β -ARs are present in the urothelium, their possible role in bladder relaxation has been investigated (Murakami et al, 2007; Otsuka et al, 2008). However, to what extent a urothelial signaling pathway contributes in vitro and in vivo to the relaxant effects of β -AR agonists in general, and β_3 -AR agonists specifically, remains to be elucidated.

The in vivo effects of β_3 -AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinics), β_3 -AR agonists increase bladder capacity with no change in micturition pressure and the residual volume (Fujimura et al, 1999; Woods et al, 2001; Kaidoh et al, 2002; Takeda et al, 2002; Igawa et al, 2010). For example, Hicks and colleagues (2007) studied the effects

of the selective β_3 -AR agonist GW427353 in the anesthetized dog and found that the drug evoked an increase in bladder capacity under conditions of acid-evoked bladder hyperactivity, without affecting voiding.

Clinical Use. The selective β_3 -AR agonist mirabegron has been approved for treatment of OAB in Japan (Betanis), the United States (Myrbetriq), and Europe (Betmiga), and its properties and clinical effects have been extensively reviewed (Sacco and Bientinesi, 2012; Andersson et al, 2013b; Bridgeman et al, 2013; Chapple et al, 2014b). There are proof-of-concept studies for other β_3 -AR selective agonists such as solabegron and ritobegron (Igawa and Michel, 2013). However, the development of ritobegron has been ceased because it failed to reach the primary efficacy end point in phase III studies. Other agents—for example, TRK-380 (Kanie et al, 2012)—are in preclinical development for the treatment of the OAB syndrome.

Mirabegron

Pharmacokinetics. Mirabegron is rapidly absorbed after oral administration. It circulates in the plasma as the unchanged form, its glucuronic acid conjugates and other metabolites, the metabolites being inactive (Takusagawa et al, 2012b). Of the administered dose, 55% is excreted in urine, mainly as the unchanged form, and 34% is recovered in feces, almost entirely as the unchanged form. Mirabegron is highly lipophilic and is metabolized in the liver via multiple pathways, mainly by cytochrome P450 3A4 and 2D6 (CYP3A4, CYP2D6) (Takusagawa et al, 2012a, 2012c). It may therefore be subject to clinically relevant drug-drug interactions and should be used with caution in patients who are taking ketoconazole or other potent CYP3A4 inhibitors.

T_{max} in both extensive and poor metabolizers was about 2 hours, and the terminal elimination half-life ($t_{1/2}$) approximately 23 to 25 hours (Eltink et al, 2012; Krauwinkel et al, 2012).

Efficacy. Several phase II RCTs have shown that in OAB patients mirabegron consistently improved mean number of micturitions in 24 hours and number of continence episodes in 24 hours (Chapple et al, 2013a, 2013b, 2013c). Mirabegron was further evaluated in three pivotal phase III, 12-week RCTs in patients with OAB symptoms of UII, urgency, and urinary frequency (Herschorn et al, 2013; Khullar et al, 2013; Nitti et al, 2013a). These trials had basically similar design. Entry criteria required that patients had symptoms of OAB for at least 3 months' duration, at least eight micturitions per day, and at least three episodes of urgency with or without incontinence over a 3-day period. The majority of patients were Caucasian (94%) and female (72%) with a mean age of 59 years (range 18 to 95 years).

In the study by Nitti and colleagues (2013a), 1329 patients were randomized to receive placebo or mirabegron 50 or 100 mg once daily for 12 weeks. Coprimary end points were change from baseline to final visit (study end) in the mean number of incontinence episodes per 24 hours and micturitions per 24 hours. At the final visit, mirabegron 50 and 100 mg showed statistically significant improvements in the coprimary efficacy end points and MVV per micturition compared with placebo.

Khullar and colleagues (2013) performed a similarly designed study enrolling 1978 patients. The study included a fourth arm in which tolterodine sustained release (SR) 4 mg was used as a comparator. As in the study of Nitti and colleagues (2013a), it was found that mirabegron caused a statistically significant improvement from baseline compared with placebo in the number of urgency incontinence episodes and number of micturitions per 24 hours. Mirabegron 50 and 100 mg were statistically superior to placebo, whereas tolterodine was not, in these two key OAB symptoms, but the study was not powered for head-to-head evaluation.

In a third phase III study in which Herschorn and colleagues (2013) evaluated the effects of 25 and 50 mg of mirabegron, both doses were associated with significant improvements in efficacy measures of incontinence episodes and micturition frequency.

Nitti and colleagues (2013c) reported on the effects of mirabegron on maximum urinary flow rate and detrusor pressure at maximum flow rate in a urodynamic safety study on male patients with BOO and LUTS. Two hundred men with OAB symptoms and

a BOO Index score above 20 were randomized to receive placebo, mirabegron 50 mg, or mirabegron 100 mg once daily for 12 weeks. Mirabegron did not adversely affect flow rate, detrusor pressure at maximum flow rate, or bladder contractile index and was well tolerated.

Chapple and colleagues (2013c) compared the safety and efficacy of long-term administration of mirabegron 50 and 100 mg and tolterodine in a 12-month three-armed, parallel group study (no placebo arm). A total of 812 (50 mg) and 820 (100 mg) patients were randomized to receive mirabegron, and 812 patients received tolterodine ER 4 mg. The primary variable was incidence and severity of treatment-emergent adverse, and secondary variables were changes from baseline at months 1, 3, 6, 9, and 12 in key OAB symptoms. Both mirabegron and tolterodine improved key OAB symptoms from the first measured time point of 4 weeks, and efficacy was maintained throughout the 12-month treatment period.

Tolerability and Adverse Effects. In a proof-of-concept study of mirabegron 100 and 150 mg bid (Chapple et al, 2013a), adverse events were experienced by 45.2% of the patients—the incidence was similar among those treated with placebo (43.2%) and mirabegron (43.8% to 47.9%). The most commonly reported adverse events considered to be treatment related were gastrointestinal disorders, including constipation, dry mouth, dyspepsia, and nausea. There was no patient-reported acute retention. No significant difference in ECG parameters between the groups was demonstrated. However, a small but significant increase in mean pulse rate was observed after mirabegron 100 mg and 150 mg (1.6 and 4.1 beats/min, respectively), although this was not associated with an increase in cardiovascular adverse events in this study. The overall discontinuation rate resulting from adverse events was 3.2% (placebo 3.0% vs. mirabegron 2.4% to 5.3%).

In the study of Khullar and colleagues (2013), the incidence of adverse effects was similar across the placebo and mirabegron 50- and 100-mg groups (50.1%, 51.6%, and 46.9%, respectively). The most common ($\geq 3\%$) adverse effects in any treatment group were hypertension (6.6%, 6.1%, and 4.9%, respectively), urinary tract infection (1.8%, 2.7%, and 3.7%), headache (2.0%, 3.2%, and 3.0%), and nasopharyngitis (2.9%, 3.4%, and 2.5%). The incidence of dry mouth was similar in the placebo and mirabegron groups (2.6% vs. 2.8%) and lower than observed in patients receiving tolterodine SR (10.1%). The incidence of constipation was similar in all treatment groups (placebo, 1.4%; mirabegron, 1.6%), including tolterodine (2.0%).

In the 12-month safety and efficacy study of mirabegron referred to previously (Chapple et al, 2013c), the incidence and severity of treatment-emergent and serious adverse effects (primary outcome parameters) were similar across the mirabegron 50-mg (59.7%), mirabegron 100-mg (61.3%), and tolterodine SR 4-mg (62.6%) groups. The most frequent treatment-emergent adverse effects were hypertension, constipation, and headache, which occurred at a similar incidence across all treatment groups; the incidence of dry mouth was more than threefold lower compared with the tolterodine SR 4-mg group (Chapple et al, 2013c).

One concern with the use of β_3 -AR agonists has been the possibility of negative cardiovascular effects. In healthy subjects, mirabegron (50 to 300 mg/day for 10 days) increased blood pressure in a dose-dependent manner (Mirabegron prescribing information, 2012). However, in the studies on OAB patients, the mean increase (compared with placebo) in systolic and diastolic blood pressure after therapeutic doses of mirabegron once daily was approximately 0.5 to 1 mm Hg and was reversible on discontinuation of treatment.

In a study of healthy volunteers, mirabegron increased heart rate in a dose-dependent manner. Maximum mean increases in HR from baseline for the 50-mg, 100-mg, and 200-mg dose groups compared with placebo were 6.7 beats/min, 11 beats/min, and 17 beats/min, respectively, in healthy volunteers (Mirabegron prescribing information, 2012). However, in the clinical efficacy and safety studies, the change from baseline in mean pulse rate for mirabegron 50 mg was approximately 1 beat/min and reversible on discontinuation of treatment.

The cardiac safety of mirabegron was evaluated in a thorough QT/QTc (HR-corrected QT interval) study, including supratherapeutic dose. This was a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-treatment-arm parallel crossover study (Malik et al, 2012), and the design followed the recommendations of the International Conference on Harmonisation (ICH). Equal numbers of men and women were enrolled in each treatment group, and the pharmacokinetic and pharmacodynamic analyses included 333 and 317 subjects, respectively. The effect of multiple doses of mirabegron 50 mg, 100 mg, and 200 mg once daily on QTc interval was studied, and according to ICH E14 criteria, mirabegron did not cause QTcI prolongation at the 50-mg therapeutic and 100-mg supratherapeutic doses in patients of either sex. Mirabegron prolonged QTcI interval at the 200-mg supratherapeutic dose (upper one-sided 95% CI >10 msec) in women, but not in men.

Even if the cardiovascular effects of mirabegron observed in clinical studies have been minimal and clinically not relevant, effects on HR and blood pressure need to be monitored when the drug is prescribed and patients with cardiovascular morbidities are treated.

Phosphodiesterase Inhibitors

Drugs stimulating the generation of cAMP are known to relax smooth muscles, including the detrusor (Andersson et al, 1999; Andersson and Wein, 2004). It is also well established that drugs acting through the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) system can relax the smooth muscle of the bladder outflow region (Andersson and Arner, 2004). Use of PDE inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscles (detrusor prostate, urethra) should then be a logical approach (Andersson et al, 2007; Andersson, 2011c; Ückert et al, 2013). There are presently 11 families of PDEs, some of which preferentially hydrolyze either cAMP or cGMP (Ückert et al, 2006; Rahnama'i et al, 2013).

As a basis for PDE inhibitor treatment of LUTS, Ückert and colleagues (2006) investigated human bladder tissue, revealing mRNA for PDE types 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A; most of these PDE types preferably inhibit the breakdown of cAMP. In vitro, human detrusor muscle responded poorly to sodium nitroprusside and to agents acting via the cGMP system (Truss et al, 2000). However, significant relaxation of human detrusor muscle, paralleled by increases in cyclic nucleotide levels, was induced by papaverine, vinpocetine (a low-affinity inhibitor of PDE type 1 [PDE1]), and forskolin (stimulating the generation of cAMP), suggesting that the cAMP pathway and PDE1 may be important in regulation of detrusor smooth muscle tone (Truss et al, 2001). Significant dose-dependent relaxations were also induced by human cAMP analogues (Truss et al, 2001). With these studies as a background, Truss and colleagues presented preliminary clinical data for vinpocetine in patients with urgency and urgency incontinence or low-compliance bladders who were not responding to standard antimuscarinic therapy (Truss et al, 2000). This initial open pilot study suggested a possible role for vinpocetine in the treatment of OAB. However, the results of a larger RCT in patients with DO showed that vinpocetine only showed statistically significant results for one parameter (Truss et al, 2001). Studies with PDE1 inhibitors other than vinpocetine (which may not be an optimal drug for elucidation of the principle) do not seem to have been performed.

PDE4 (which also preferably hydrolyzes cAMP) has been implicated in the control of bladder smooth muscle tone. PDE4 inhibitors reduced the in vitro contractile response of guinea pig (Longhurst et al, 1997) and rat (Kaiho et al, 2008) bladder strips and also suppressed rhythmic bladder contractions of the isolated guinea pig and rat bladder (Gillespie and Drake, 2004; Nishiguchi et al, 2007). Previous experiences with selective PDE4 inhibitors showed emesis to be a dose-limiting effect (Giembycz, 2005). If this side action can be avoided, PDE4 inhibition seems to be a promising approach.

Oger and coworkers showed that the PDE5 inhibitor sildenafil-induced relaxation of human detrusor smooth muscle involved cGMP-, cAMP- and K⁺ channel-dependent signaling pathways, with a minor contribution from NO (Oger et al, 2010). In combination with the α_1 -AR antagonist doxazosin, sildenafil reduced adrenergic tone of prostatic and cavernosal smooth muscle, and their combination provided a significant benefit when targeting relaxation of both tissues (Oger et al, 2008).

In vivo, several studies have indicated a role for PDE5 inhibitors in the regulation of micturition function. Systemic vardenafil reduced both nonvoiding contractions and bladder afferent nerve firing in unanesthetized, decerebrate, spinal cord-injured rats, indicating potential mechanisms by which PDE5 inhibitors improve storage symptoms in SCI patients (Behr-Roussel et al, 2010). The effect of vardenafil on OAB symptoms could be related to a cGMP-dependent RhoA/ROCK signaling inhibition, as shown in spontaneously hypertensive rats (Morelli et al, 2009a, 2009b). Using the same animal model, bladder hypoxia was significantly reduced by acute vardenafil treatment (Morelli et al, 2009b). Thus, in addition to relaxing muscular wall, PDE5 inhibition may positively affect urinary bladder blood perfusion. In the same respect, tadalafil was shown to increase prostate tissue oxygenation in spontaneously hypertensive rats, and human vesicular-deferential artery is characterized by a high expression and activity of PDE5, which was inhibited by tadalafil in vitro; these results suggest another possible mechanism through which PDE5 inhibitors exert beneficial effects on LUTS (Morelli et al, 2011).

NO has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra, and its relaxant effect is associated with increased levels of cGMP (Andersson and Arner, 2004). However, few investigations have addressed the cAMP- and cGMP-mediated signal transduction pathways and the key enzymes of the cGMP system in the mammalian urethra. Morita and colleagues (1994) examined the effects of isoproterenol, prostaglandin E₁ (PGE₁) and PGE₂, and sodium nitroprusside on the contractile force and tissue content of cAMP and cGMP in the rabbit urethra. They concluded that both cyclic nucleotides can produce relaxation of the urethra. Werkström and colleagues (2006) characterized the distribution of PDE5, cGMP, and protein kinase PKG1 in female pig and human urethra and evaluated the effect of pharmacologic inhibition of PDE5 in isolated smooth muscle preparations. After stimulation with the NO donor, DETA NONOate, the cGMP-immunoreactivity in urethral and vascular smooth muscles increased. There was a wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles. PDE5 immunoreactivity could be demonstrated within the urethral and vascular smooth muscle cells, but also in vascular endothelial cells that expressed cGMP immunoreactivity. Nerve-induced relaxations of urethral preparations were enhanced at low concentrations of sildenafil, vardenafil, and tadalafil, whereas there were direct smooth muscle relaxant actions of the PDE5 inhibitors at high concentrations. Fibbi and colleagues (2009) confirmed that the highest expression and biologic activity of PDE5 was found in the bladder. However, consistent PDE5 expression and activity were also found in prostatic urethra. In contrast, the prostate gland showed the lowest PDE5 abundance, and cultures derived from this tissue were less sensitive to vardenafil. Using a different animal model associated with C-fiber afferent activation, it was shown that the NO/cGMP signaling pathway is involved in the regulation of the micturition reflex, with an action that seems more predominant on the sensory rather than on the motor component of the micturition reflex (Caremél et al, 2010).

The observation that patients treated for erectile dysfunction (ED) with PDE5 inhibitors had an improvement of their LUTS has sparked a new interest in using these drugs also for treatment of LUTS and OAB. After the report in an open study that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS (Sairam et al, 2002), this observation has been confirmed in several well-designed and well-conducted RCTs.

To date, several RCTs have been published comparing the effect of PDE5 inhibitors alone with placebo, and the combination of

α_1 -AR antagonists and PDE5 inhibitors versus α_1 -AR antagonists alone (Kaplan et al, 2007; McVary et al, 2007a, 2007b; Bechara et al, 2008; Roehrborn et al, 2008b; Stief et al, 2008; Liguori et al, 2009; Porst et al, 2009; Tamimi et al, 2010; Tuncel et al, 2010; Porst et al, 2011; Gacci et al, 2012). In these studies, different PDE5 inhibitors and different doses were administered.

PDE5 inhibitors significantly improve IPSS and International Index of Erectile Function (IIEF) scores, but not Qmax, when compared with placebo. According to a recent meta-analysis by Gacci and coworkers (2012), differences in IPSS score were significantly lower in older and obese patients. The combination of PDE5 inhibitors and α -blockers led to significant improvements of the IPSS and IIEF scores as well as Qmax when compared with the use of α -blockers alone. Dmochowski showed that tadalafil once daily for LUTS had no significant effect on bladder function as measured by detrusor pressure at maximum urinary flow rate or maximum detrusor pressure and BOO Index score while improving IPSS (Dmochowski et al, 2010b). PDE5 inhibitors were shown to be generally safe and well tolerated.

The mechanism behind the beneficial effect of the PDE inhibitors on LUTS and OAB and their site(s) of action largely remain to be elucidated (Andersson et al, 2011b; Giuliano et al, 2013). If the site of action were the smooth muscles of the outflow region (and the effect relaxation), an increase in flow rate should be expected. No such effect was found in urodynamic studies (Dmochowski et al, 2010b, 2013). However, there are several other structures in the LUT that may be involved, including those in the urothelial signaling pathway (urothelium, interstitial cells, and suburothelial afferent nerves). In general, it is believed that major mechanisms contributing to LUTS include reduced NO/cGMP signaling pathway, increased RhoA-kinase pathway activity, autonomic overactivity, increased bladder afferent activity, and pelvic ischemia (Andersson et al, 2011b). Nomiya and colleagues (2013) found in a rat model of chronic bladder ischemia that tadalafil had a marked protective effect, preventing both functional and morphologic bladder changes induced by progressive ischemia. This is in line with the proposal by Cellek and colleagues (2013) linking the effectiveness of PDE5 inhibitors on BPH and LUTS (and ED) to microvascular dysfunction within the pelvic organs. They suggested that a combination of endothelial and neural dysfunction may lead to a vicious cycle of hypoxia, vasoconstriction, altered smooth muscle contractility, and degeneration of autonomic neurons and ganglia.

It has to be mentioned that as of the time of this writing, only tadalafil has been approved for the treatment of LUTS caused by benign prostatic obstruction (BPO); long-term experience with PDE5 inhibitors in patients with LUTS is still lacking (Oelke et al, 2014). In addition, insufficient information is available on the combination of PDE5 inhibitors with other LUTS medications such as 5 α -reductase inhibitors.

Antidepressants

Some clinicians believe that tricyclic antidepressants, particularly imipramine (Tofranil, others), are useful agents for facilitating urine storage, both by decreasing bladder contractility and by increasing outlet resistance (Wein, 1995a; 1995b). These agents have been the subject of a voluminous amount of highly sophisticated pharmacologic investigation to determine the mechanisms of action responsible for their varied effects (Maggi et al, 1989a; Richelson, 1994; Baldessarini, 2006). Most data have been accumulated as a result of trying to explain the antidepressant properties of these agents and are thus primarily from CNS tissue. The results, conclusions, and speculations inferred from the data are extremely interesting, but it should be emphasized that it is essentially unknown whether they apply to or have relevance for the LUT.

Tricyclic antidepressants possess varying degrees of at least three major pharmacologic actions: (1) They have central and peripheral antimuscarinic effects at some, but not all, sites; (2) they block the active transport system in the presynaptic nerve ending that is responsible for the reuptake of the released amine

neurotransmitters norepinephrine and serotonin; and (3) they are sedatives, an action that occurs presumably on a central basis but is perhaps related to antihistaminic properties (at H_1 receptors, although they also antagonize H_2 receptors to some extent). There is also evidence that they desensitize at least some α_2 - and some β -ARs. Paradoxically, they also have been shown to block some α -ARs and 5-HT₁ receptors.

Several antidepressants have been reported to have beneficial effects in patients with DO (Martin and Schiff, 1984; Lose et al, 1989). However, the use of antidepressants was shown to be an independent risk factor for LUTS suggestive of BPH in a community-based population of healthy aging men (Kok et al, 2009).

Imipramine. Imipramine is the only drug that has been widely used clinically to treat storage symptoms. Imipramine has complex pharmacologic effects, including marked systemic antimuscarinic actions (Baldessarini, 2006) and blockade of the reuptake of serotonin and NA (Maggi et al, 1989b), but its mode of action in DO has not been established (Hunsballe and Djurhuus, 2001). Even if it is considered that imipramine is a useful drug in the treatment of DO, no good-quality RCTs that can document this have been retrieved. It has been known for a long time that imipramine can have favorable effects in the treatment of nocturnal enuresis in children, with a success rate of 10% to 70% in controlled trials (Hunsballe and Djurhuus, 2001; Glazener et al, 2003). It is well established that therapeutic doses of tricyclic antidepressants, including imipramine, may cause serious toxic effects on the cardiovascular system (orthostatic hypotension, ventricular arrhythmias). Imipramine prolongs QTc intervals and has an antiarrhythmic (and proarrhythmic) effect similar to that of quinidine (Bigger et al, 1977; Giardina et al, 1979). Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants (Baldessarini, 2006). The risks and benefits of imipramine in the treatment of voiding disorders do not seem to have been assessed. Very few studies have been performed during the last decade (Hunsballe and Djurhuus, 2001; Natalin et al, 2009). No good-quality RCTs have documented that the drug is effective in the treatment of DO. However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

A prospective (no controls) study of the impact of the “three-drug therapy” (antimuscarinic, α -blocker, and tricyclic antidepressants) on refractory DO showed a significant increase in bladder capacity and decreases in urgency, urge incontinence, and frequency. Objective urodynamic data as well as symptom score improved significantly with triple therapy (Natalin et al, 2009).

Doxepin. Doxepin is another tricyclic antidepressant that was found to be more potent, using in vitro rabbit bladder strips, than other tricyclic compounds with respect to antimuscarinic and muscletropic relaxant activity (Levin and Wein, 1984). Lose and colleagues (1989), in a randomized, double-blind crossover study of women with involuntary bladder contractions and frequency, urgency, or urgency incontinence, found that this agent caused a significant decrease in urine loss (pad-weighing test), and in the cystometric parameters of first sensation and maximal bladder capacity. The dose of doxepin used was either a single 50-mg bedtime dose or this dose plus an additional 25 mg in the morning. The number of daytime incontinence episodes decreased in both doxepin and placebo groups, and the difference was not statistically significant. Doxepin treatment was preferred by 14 patients, whereas 2 preferred placebo. Three patients had no preference. Of the 14 patients who stated a preference for doxepin, 12 claimed that they became continent during treatment, whereas 2 claimed improvement; the 2 patients who preferred placebo claimed improvement. The Agency for Health Care Policy and Research (AHCPR) guidelines combine results for imipramine and doxepin, citing only three RCTs, with an unknown percent of female patients. Percent cures (all figures refer to percent drug effect minus percent effect on placebo) are listed as 31%, percent reduction in urgency incontinence as 20% to 77%, and percent side effects as 0% to 70% (AHCPR, 1992).

Milnacipran Hydrochloride and Paroxetine Hydrochloride. Milnacipran hydrochloride, a serotonin-norepinephrine reuptake inhibitor

(SNRI), and paroxetine hydrochloride, a selective serotonin reuptake inhibitor (SSRI), were analyzed in a prospective open trial in neurogenic OAB patients (Sakakibara et al, 2008). Milnacipran reduced daytime urinary frequency, improved the QoL index score, and increased bladder capacity as shown in urodynamic studies. No such changes were noted in the other categories of the LUTS questionnaire or urodynamic studies, or in the paroxetine group.

Duloxetine. Duloxetine is an NA-serotonin reuptake inhibitor that has been shown to significantly increase sphincteric muscle activity during the filling and storage phase of micturition in the cat acetic acid model of irritated bladder function (Thor and Katofiasc, 1995; Katofiasc et al, 2002). Bladder capacity was also increased in this model, with both effects mediated centrally through both motor efferent and sensory afferent modulation (Fraser et al, 2003). The effects of duloxetine were studied in a placebo-controlled study of 306 women (aged 21 to 84 years) with OAB, randomly treated with placebo (153) or duloxetine (80 mg/day for 4 weeks, which was increased to 120 mg/day for 8 weeks) (Steers et al, 2007). The primary efficacy analysis compared the treatment effects on mean change from baseline to end point in the mean number of voiding episodes per 24 hours. Patients randomized to duloxetine had significant improvements over those randomized to placebo for decreases in voiding and incontinence episodes (−1.81 vs. −0.62), for increases in the daytime voiding intervals (29 vs. 7 minutes), and for improvements in Incontinence Quality of Life (I-QoL) scores at both doses of duloxetine. Urodynamic studies showed no significant increases in maximum cystometric capacity or in the volume threshold for DO. The most common treatment-emergent adverse events with duloxetine (nausea 31% [placebo 4.6%], dry mouth 16% [placebo 1.3%], dizziness 14% [placebo 0.7%], constipation 14% [placebo 3.3%], insomnia 13% [placebo 1.3%], and fatigue 11% [placebo 2.0%]) were the same as those reported by women with stress urinary incontinence (SUI) (see later) and were significantly more common with duloxetine than placebo. Also, in women with mixed incontinence, improvement of the OAB component has been demonstrated (Bent et al, 2008; Schagen van Leeuwen et al, 2008). For assessment, see Table 79-3.

Side Effects and Cardiovascular Risks. With the typically larger doses used for antidepressant effects, the most frequent side effects of the tricyclic antidepressants are those attributable to their systemic antimuscarinic activity (Richelson, 1994; Baldessarini, 2006). Allergic phenomena, including rash, hepatic dysfunction, obstructive jaundice, and agranulocytosis may also occur, but rarely. CNS side effects may include weakness, fatigue, Parkinsonian effect, a fine tremor noted most in the upper extremities, a manic or schizophrenic picture, and sedation, probably from an antihistaminic effect. Postural hypotension may also be seen, presumably on the basis of selective blockade (a paradoxical effect) of α_1 -ARs in some vascular smooth muscle. Tricyclic antidepressants can also cause excess sweating of obscure cause and a delay of orgasm or orgasmic impotence, the cause of which is likewise unclear. They can also produce arrhythmias and interact in deleterious ways with other drugs, so caution must be observed in their use in patients with cardiac disease (Baldessarini, 2006). Whether cardiotoxicity will prove to be a legitimate concern in patients receiving the smaller doses (than for treatment of depression) for LUT dysfunction remains to be seen but is a potential matter of concern. Consultation with a patient’s internist or cardiologist is always helpful before instituting such therapy in questionable situations. It is well established that therapeutic doses of tricyclic antidepressants, including imipramine, may cause serious toxic effects on the cardiovascular system (orthostatic hypotension, ventricular arrhythmias). Imipramine prolongs QTc intervals and has an antiarrhythmic (and proarrhythmic) effect similar to that of quinidine (Bigger et al, 1977; Giardina et al, 1979). Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants (Baldessarini, 2006).

With respect to the potential cardiovascular risks of antidepressant medication, two additional points need to be made. First of all, it may be depression itself that is associated with an increased

risk of myocardial infarction, cardiovascular disease, and all-cause mortality (see references in [Cohen et al, 2000](#)). Although treatments for depression, including antidepressive medications, are certainly a potential factor underlying this association, the separation from disease association and treatment association is difficult at best. The second point relates to whether there is a difference in this regard between the use of tricyclic antidepressants and SSRIs. Data presented by [Cohen and coworkers \(2000\)](#) suggest that with respect to long-term adverse cardiovascular outcome, there is an association between the use of tricyclic antidepressants but not SSRIs, a conclusion that differs from earlier data, indicating no significant differences in the safety or efficacy of these two groups of agents (AHCPR report, cited by [Cohen et al, 2000](#)). As a closing statement on this subject, it should be noted that data in the literature refer to therapeutic doses of these medications for depression and not the smaller (in comparison) doses of imipramine used for the treatment of voiding dysfunction.

The use of imipramine is contraindicated in patients receiving monoamine oxidase inhibitors, because severe CNS toxicity can be precipitated, including hyperpyrexia, seizures, and coma. Some potential side effects of the antidepressants may be especially significant for the elderly, specifically weakness, fatigue, and postural hypotension. Psychotropic drugs in general have been shown to increase the risk of falls and hip fractures in the elderly ([Liu et al, 1998](#)). If imipramine or any of the tricyclic antidepressants is to be prescribed for the treatment of voiding dysfunction, the patient should be thoroughly informed of the fact that this is not the usual indication for this drug and that potential side effects exist. Reports of significant side effects (severe abdominal distress, nausea, vomiting, headache, lethargy, and irritability) after abrupt cessation of high doses of imipramine in children would suggest that the drug should be discontinued gradually, especially in patients receiving high doses.

Cyclooxygenase Inhibitors

Human bladder mucosa has the ability to synthesize eicosanoids ([Jeremy et al, 1987](#)), and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma ([Downie and Karmazyn, 1984](#); [Leslie et al, 1984](#)). Even if prostaglandins cause contraction of human detrusor ([Andersson, 1993](#)), it is still unclear whether prostaglandins contribute to the pathogenesis of DO. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. However, clinical evidence for this is scarce.

[Cardozo and colleagues \(1980\)](#) performed a double-blind controlled study of 30 women with DO using the prostaglandin synthesis inhibitor flurbiprofen at a dose of 50 mg three times daily. The drug was shown to have favorable effects, although it did not completely abolish DO. There was a high incidence of side effects (43%) including nausea, vomiting, headache, and gastrointestinal symptoms. [Palmer \(1983\)](#) studied the effects of flurbiprofen 50 mg \times 4 versus placebo in a double-blind crossover trial in 37 patients with IDO (27% of the patients did not complete the trial). Active treatment significantly increased maximum contractile pressure, decreased the number of voids, and decreased the number of urgent voids compared with baseline. Indomethacin 50 to 100 mg daily was reported to give symptomatic relief in patients with DO compared with bromocriptine in a randomized, single-blind crossover study ([Cardozo and Stanton, 1980](#)). The incidence of side effects was high, occurring in 19 of 32 patients. However, no patient had to stop treatment because of side effects.

The few controlled clinical trials on the effects of prostaglandin synthesis inhibitors in the treatment of DO, and the limited number of drugs tested, makes it difficult to evaluate their therapeutic value. No new RCTs on the effects of cyclooxygenase

(COX) inhibitors in OAB and DO patients seem to have been published during the last decade.

Although these early clinical studies with nonselective COX inhibitors showed some promise in the treatment of these disorders, the drugs were not further developed for this indication, mainly because of side effects. The interest in the use of selective COX-2 inhibitors was hampered by concerns about long-term cardiovascular toxicity with these drugs.

KEY POINTS: DRUGS FOR OVERACTIVE BLADDER

- Theoretically, calcium antagonists and potassium channel openers would be attractive methods to inhibit DO and regulate detrusor smooth muscle tone. However, there is no current clinical evidence to support the use of either class of drug in the treatment of bladder dysfunction. The use of α -adrenergic antagonists to treat storage symptoms in men, as distinct from their effect on voiding symptoms, is somewhat unclear. Some studies suggest no effect of commonly used agents, whereas other studies suggest that selective blockade of α_{1A} -ARs is clinically effective, albeit associated with a high incidence of ejaculatory dysfunction. In women, treatment of OAB filling and storage symptoms with α_{1A} antagonists seems ineffective.
- The most recent drug approved for the treatment of OAB is a β_3 -AR agonist, mirabegron, which acts both to relax and maintain low detrusor tone during filling and also to inhibit activity in sensory afferents in an animal model. In such a model, these drugs increase bladder capacity but do not change voiding pressure or voiding volume. Clinically, mirabegron, the only such agent currently available, improves OAB symptoms without affecting emptying parameters. The side effect profile is quite different from that of the antimuscarinic agents, and some concern exists regarding negative cardiovascular effects (blood pressure and HR); in clinical studies these have been minimal and clinically not relevant, but it has been recommended that these be monitored during treatment.
- There are logical theoretic mechanisms whereby PDE inhibitors should enhance the relaxation of LUT smooth muscle. PDE5 inhibitors have been shown to have beneficial effects on LUTS, including those of OAB, although their site(s) and mechanism(s) remains to be established.
- Although there are theoretic mechanisms by which tricyclic antidepressants, particularly imipramine, should facilitate storage, both by decreasing bladder contractility and increasing outlet resistance, there are no good-quality randomized controlled trials to adequately test this hypothesis. Duloxetine, primarily a noradrenalin-serotonin reuptake inhibitor, has been shown to increase some significant storage symptoms, but trials directed specifically toward this effect are lacking. Although there are theoretic mechanisms by which prostaglandin synthesis inhibitors could affect filling and storage symptoms, clinical evidence for this is scarce.

Other Drugs

Dimethyl Sulfoxide. Dimethyl sulfoxide (DMSO) is a relatively simple, naturally occurring organic compound that has been used as an industrial solvent for many years. It has multiple pharmacologic actions (membrane penetrant, anti-inflammatory, local analgesic, bacteriostatic, diuretic, cholinesterase inhibitor, collagen solvent, vasodilator) and has been used for the treatment of arthritis and other musculoskeletal disorders, usually in a 70% solution. The formulation for human intravesical use is a 50% solution. [Sant \(1987\)](#) has summarized the pharmacology and clinical use of DMSO and has tabulated "good to excellent" results in 50% to 90% of collected series of patients treated with intravesical instillation for interstitial cystitis. However, DMSO has not been shown to be

useful in the treatment of NDO or IDO or in any patients with urgency or frequency but without interstitial cystitis. The subject of interstitial cystitis and its treatment is considered in Chapter 14. **Baclofen.** γ -Aminobutyric acid (GABA) is a ubiquitous inhibitory neurotransmitter in the CNS that can inhibit the micturition reflex at several points along its central pathway (de Groat, 1997; Pehrson and Andersson, 2002). Experimental data suggest the GABAergic system as an interesting target for bladder dysfunction therapy. Baclofen intrathecally attenuated oxyhemoglobin-induced DO, suggesting that the inhibitory actions of GABA-B-receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium (Pehrson and Andersson, 2002). In spinal-intact rats, intrathecal application of bicuculline induced detrusor-sphincter dyssynergia (DSD)-like changes, whereas intrathecal application of baclofen induced urethral relaxation during isovolumetric bladder contractions (Miyazato et al, 2008). Miyazato and colleagues (2008) found signs of hypofunction of the GABAergic system after SCI (glutamate decarboxylase 67 mRNA levels in the spinal cord and dorsal root ganglia were decreased), and showed that activation of GABA-A and GABA-B receptors in the spinal cord inhibited DO as evidenced by a reduction in nonvoiding contractions. GABA-B-receptor activation preferentially reduced DO before inhibiting voiding contractions, whereas GABA-A-receptor activation inhibited DO and voiding contraction at the same concentration.

As a GABA agonist on GABA-B receptors, baclofen was used orally in IDO patients. However, its efficacy was poor, eventually dictated by the fact that baclofen does not cross the blood-brain barrier (Taylor and Bates, 1979). Baclofen is one of the most effective drugs for the treatment of spasticity after SCI, traumatic or hypoxic brain injury, and cerebral palsy (Ochs, 1993), and intrathecal baclofen was shown to be useful in some patients with spasticity and bladder dysfunction (Bushman et al, 1993). Baldo and colleagues (2000) found a rapid (24 hours) and persistent increment in the volume to first detrusor contraction (FDC) and of the maximal cystometric capacity, whereas maximal detrusor pressure decreased. At 10 days the volume to FDC had increased from 143 mL to 486 mL. In selected patients with spasticity and bladder dysfunction, intrathecal baclofen seems to be an effective therapy.

Combinations

α_{1A} -Adrenergic-Receptor Antagonists with Antimuscarinics. Traditionally, male LUTS were thought to result from BPO secondary to BPE. However, male LUTS may arise from prostatic pathology, bladder dysfunction, or both. Thus, diagnosis and appropriate treatment of men with OAB symptoms are complex and difficult. α_1 -AR antagonists remain the most widely used pharmacologic agents for relief of bladder outflow resistance, as they relax prostatic and urethral smooth muscle tone, the dynamic component of BPO (Andersson and Gratzke, 2007; Lepor et al, 2012). In contrast, antimuscarinics, which function by competitively blocking the muscarinic receptors, are the first-line pharmacologic treatment for OAB (Andersson et al, 2009). Given the prevalence of combined voiding and OAB symptoms as well as the finding that the QoL of these patients is affected primarily by the symptoms of OAB, it might be logical for this category of patients to be given antimuscarinic drugs (Ruggieri et al, 2005).

A variety of such combinations have been evaluated. Several randomized, controlled trials demonstrated that the combination treatment of antimuscarinic drugs and α_1 -AR antagonists was more effective at reducing male LUTS than α_1 -AR antagonists alone in men with OAB and coexisting BPO (Saito et al, 1999; Athanasopoulos et al, 2003; Lee et al, 2004, 2005; Kaplan et al, 2006, 2007). Therapeutic benefit of combining an antimuscarinic agent (propiverine) with an α_1 -AR antagonist (tamsulosin), as compared with an α_1 -AR antagonist alone, was reported by Saito and colleagues (Saito et al, 1999). The rates of improvement in daytime frequency, incontinence, and urgency were greater in the combination group than the α_1 -AR antagonist-alone group. The PVR was

unchanged in both groups, and there was only one case (1.5%) of AUR with the combined treatment.

Subsequently, Lee and colleagues (2005) compared the efficacy and safety of combination therapy with propiverine and doxazosin in 211 men with urodynamically confirmed BOO and OAB symptoms for 8 weeks. Compared with the doxazosin arm, the patients in the combination therapy group showed greater improvement in urinary frequency, average micturition volume, and storage and urgency scores of IPSS. Patient satisfaction was significantly higher in the combination group. There was also a significant increase in PVR (+20.7 mL) in the combination group, but no case of urinary retention was reported.

A large-scale, multicenter, randomized, double-blind, placebo-controlled trial (the TIMES study) demonstrated the efficacy and safety of tolterodine ER alone, tamsulosin alone, and the combination of both in 879 men with OAB and BPO (Kaplan et al, 2006). In the primary efficacy analysis, 172 men (80%) receiving tolterodine ER plus tamsulosin reported treatment benefits by week 12 ($P < .001$ vs. placebo; $P = .001$ vs. tolterodine ER; $P = .03$ vs. tamsulosin). In the secondary efficacy analysis, patients receiving tolterodine ER plus tamsulosin compared with placebo experienced small but significant reductions in urgency incontinence, urgency episodes, daytime frequency, and nocturia. However, there were no significant differences between tamsulosin monotherapy and placebo for any diary variables at week 12. Patients receiving tolterodine ER plus tamsulosin demonstrated significant improvements in total IPSS (−8.02 vs. placebo −6.19, $P = .003$) and QoL (−1.61 vs. −1.17, $P = .003$). Although there were significant improvements in the total IPSS among patients who received tamsulosin alone, the differences in total IPSS among patients who received tolterodine ER versus placebo were not significant. The combination of antimuscarinics and α_1 -AR antagonists may be the most effective therapy in men with OAB symptoms in the presence of BPO.

A subanalysis (Rovner et al, 2008a) of data from the TIMES study focused on the urgency perception scale and concluded that the group of 217 men who received tolterodine plus tamsulosin showed significantly improved urgency variables and patient-reported outcomes. Moreover, this group of patients reported increased satisfaction with the treatment as well as willingness to continue the treatment. Another subanalysis (Kaplan et al, 2008a) of data from the TIMES study examined the effects of the drugs on urinary symptoms as assessed by the IPSS. Based on this subanalysis, the authors concluded that tolterodine ER plus tamsulosin was significantly more effective than placebo in treating storage LUTS, including OAB symptoms. However, these results should be considered with caution because they were derived from post hoc analysis of the TIMES data.

Maruyama and colleagues (2006) reported different results in their prospective, randomized, controlled study in which naftopidil (25 to 75 mg/day), an α_{1D} -AR antagonist, alone or in combination with propiverine hydrochloride (10 to 20 mg/day) or oxybutynin hydrochloride (2 to 6 mg/day), was administered for 12 weeks to 101 BPH patients. In the study, the IPSS and QoL index score improved significantly in both groups, with no marked differences between groups. Qmax and PVR tended to improve in both groups, again with no differences between groups. However, median post-therapeutic PVR was significantly larger in the combination group (45.0 mL) than in the monotherapy group (13.5 mL, $P = .021$). There were significantly more patients with increased residual urine volume relative to unchanged residuals in the combination therapy (22.9%) group versus the monotherapy group (5.0%, $P = .038$). The authors of this study concluded that combination therapy with a low-dose antimuscarinic agent was not more effective than monotherapy. Moreover, although they did not encounter any cases of urinary retention, the percentage of patients with increased residual urine volume was significantly greater in the combination therapy group than in the monotherapy group.

The results of another study using low-dose antimuscarinic therapy was published by Kang and colleagues (2009). They evaluated the efficacy and safety of combined treatment with tamsulosin

0.2 mg and propiverine hydrochloride 10 mg compared with tamsulosin monotherapy. After 3 months, both groups showed significant improvements in IPSS, QoL, voided volume, Qmax, and PVR, but only the QoL index was significantly different between groups in favor of the combination group. No cases of AUR were recorded in this low-dose study.

Medical therapy to reduce DO in a neurogenic bladder has focused on antimuscarinic therapy, which increases bladder capacity, decreases bladder filling pressure, and improves compliance (Goessl et al, 1998; Stöhrer et al, 2009). Although use of antimuscarinics combined with clean intermittent catheterization (CIC) is the most commonly recommended medical therapy for neurogenic bladder, the results are sometimes unsatisfactory, and many patients continue to have poor bladder compliance and remain incontinent (Razdan et al, 2003). McGuire and Savastano (1985) reported that α_1 -AR antagonists decreased bladder pressure with filling and increased capacity, and that the addition of an antimuscarinic enhanced these effects, indicating that α_1 -AR antagonists and the antimuscarinic had a synergistic effect on detrusor tone in the decentralized bladder. This finding led to the widespread use of α_1 -AR antagonists in the treatment of neurogenic bladder (Chancellor et al, 1994; Swierzewski et al, 1994; Abrams et al, 2003). Swierzewski treated 12 patients with SCI who had poor bladder compliance, despite therapy with CIC and an antimuscarinic, with 5 mg of terazosin for bladder management (Swierzewski et al, 1994). After 4 weeks, compliance increased by 73%, bladder pressure decreased by 36 cm H₂O, and capacity increased by 157 mL. These results support the assumption that α_1 -AR antagonists and antimuscarinics may have an additional synergistic effect on the bladder in the neurogenic population.

In a retrospective chart review, combination therapy with an antimuscarinic agent, an α_1 -AR antagonist, and imipramine produced superior results to those obtained using a single agent in patients with neurogenic bladder dysfunction (Cameron et al, 2009). These patients showed significant improvement in clinical parameters and compliance and decreased bladder pressures at capacity. It has been shown that in the decentralized human detrusor, there may be an increase in α -AR sites and a switch to α -AR-mediated contractile function from the typical β -AR-mediated relaxation function during bladder filling (Sundin et al, 1977). Imipramine is a systemic muscarinic-receptor antagonist and a direct smooth muscle inhibitor that also blocks the reuptake of serotonin and NA. This suggests that targeting multiple receptors may maximize the effectiveness of pharmacologic treatment of neurogenic bladder and should be considered in patients in whom treatment with antimuscarinics alone fails.

β_3 -Adrenergic-Receptor Antagonists with Antimuscarinics. β_3 -AR agonists exert their therapeutic effects through stimulation of adenyl cyclase and activation of potassium K⁺ channels. The former leads to an increase in cAMP and the latter to hyperpolarization, both of which result in relaxation. The beneficial effects of modulation of these pathways are inhibition of spontaneous activity, increased bladder compliance (decreased bladder tone during filling), greater distention needed to activate the micturition reflex (increased bladder capacity), and decreased afferent activity, with no effect on voiding contraction (no risk for urinary retention).

These mechanisms are distinct from those of antimuscarinic therapies used to treat OAB. Accordingly, the combination of these two types of medications is being investigated to determine whether concomitant use can result in increased efficacy with an acceptable profile of safety and tolerability. Based on results with an animal model it was concluded that the "combination of antimuscarinics and β_3 -AR agonists can result in increased efficacy and potency and supports the hypothesis that combining these compound classes in the clinic could have beneficial effects in treating urinary bladder dysfunction" (Rekik et al, 2013). In a phase II clinical study (the Symphony study) evaluating the combination of solifenacin and mirabegron in 1307 patients with OAB (Abrams et al, 2013), the patients were randomized to receive one of six combinations—mirabegron 25 or 50 mg in combination with solifenacin 2.5, 5, or 10 mg; or monotherapy with mirabegron or

solifenacin (at each of the same doses studied in the combinations); or placebo. The study duration was 12 weeks. The primary efficacy variable was change in MVV per micturition; secondary variables included change in micturition frequency and incontinence episode frequency (IEF) per 24 hours. The investigators reported that mirabegron combination therapy with solifenacin (the latter at a dose exceeding 5 mg) demonstrated greater efficacy than solifenacin 5 mg alone on MVV and micturition frequency (Abrams et al, 2013). The enhanced efficacy with the combination was of a magnitude that is probably similar to the enhanced efficacy one might expect from up-titrating the dose of the antimuscarinic. However, the combination was not associated with the adverse effects one would expect to encounter with higher doses of antimuscarinics. In this study, all six combinations appeared to be well tolerated and there appeared to be no safety concern or significant increase in adverse effects with the combination treatment compared with either monotherapy (Abrams et al, 2013).

Combined Antimuscarinics. Although antimuscarinic agents are the first choice of treatment for patients with OAB symptoms, these drugs do not always lead to the desired effect of detrusor stability and continence, especially for patients with SCI or neurologic diseases such as multiple sclerosis or meningocele. In these patients, the goal of urologic therapy is to maintain continence and to reduce intravesical pressure. When antimuscarinic treatment fails, however, invasive procedures such as the injection of botulinum neurotoxin type A (BoNTA), intravesical application of drugs, or surgery are necessary.

A combined antimuscarinic regimen was evaluated as a noninvasive alternative by Amend and colleagues (2008) for patients who had neurogenic bladder dysfunction with incontinence, reduced bladder capacity, and increased intravesical pressure. They added secondary antimuscarinics to the existing double-dose antimuscarinics for patients who previously demonstrated unsatisfactory outcomes with double-dose antimuscarinic monotherapy. The study drugs were tolterodine, oxybutynin, and trospium. After a 4-week combined regimen, incontinence episodes decreased and reflex volume, maximal bladder capacity, and detrusor compliance increased. Side effects were comparable to those seen with normal-dose antimuscarinics. Those positive findings were speculated to be the result of (1) additive or synergistic activation of different muscarinic receptors or interactions of receptors on different parts of the bladder wall, (2) undiscovered faster metabolism of antimuscarinics requiring an increased dose of different antimuscarinic drugs, and/or (3) downregulation of subdivisions of antimuscarinic receptors under monotherapy that may lead to better susceptibility of other subdivisions when treated by the second drug. The combined regimen needs further investigation to verify its efficacy as a noninvasive alternative for patients in whom antimuscarinic monotherapy fails.

Antimuscarinics and 5 α -Reductase Inhibitors. The standard first-line medical therapy for men with moderate-to-severe LUTS is an α_1 -AR antagonist, a 5 α -reductase inhibitor, or combination therapy with both. Both α_1 -AR antagonist and 5 α -reductase inhibitors alleviate LUTS in men by reducing bladder outlet resistance. α_1 -AR antagonists decrease smooth muscle tone in the prostate and bladder neck, whereas 5 α -reductase inhibitors reduce prostate volume. As mentioned, several trials have demonstrated the efficacy and safety of combination therapy with antimuscarinics and α_1 -AR antagonist for patients with OAB and coexisting BPO. However, post hoc analyses of the TIMES study (Kaplan et al, 2006) suggested that men with smaller prostates benefit more from antimuscarinic therapy than those with larger prostates (Roehrborn et al, 2008a, 2009). Chung and colleagues (2010) conducted an open-label, fixed-dose study to assess the efficacy and safety of tolterodine ER in combination with dutasteride in men with a large prostate (≥ 30 g) and persistent OAB symptoms after α_1 -AR antagonist therapy who had been unsuccessfully treated with dutasteride alone. At the start of the study, all patients had been on dutasteride 0.5 mg daily for at least 6 months and α_1 -AR antagonist therapy had failed. All patients were given 4 mg of tolterodine ER daily for 12 weeks and had discontinued α_1 -AR antagonist therapy

before the start of the study. At 12 weeks, the frequency ($-3.2/24$ hr, $P < .02$), urgency (19.2%, $P < .03$), number of severe OAB episodes (71.4%, $P < .05$), and incidence of nighttime voiding (-0.9 , $P < .003$) were found to have decreased significantly from baseline. The IPSS decreased with dutasteride treatment (from 19.3 to 14.3) and further decreased with the addition of tolterodine to 7.1 ($P < .001$). Storage symptoms decreased from 9.8 to 4.5 ($P < .001$). Dry mouth occurred in four (7.5%) patients, constipation in one (2%), and decreased sexual function in two (3.9%). PVR increased by 4.2 mL, Qmax decreased by 0.2 mL/sec, and no patients developed retention. The authors concluded that the combination of tolterodine and dutasteride was effective, safe, and well tolerated in men with large prostates with persistent OAB symptoms and LUTS secondary to BPO.

The results of this study indicate that antimuscarinics are safe and effective in selected patients with OAB and BPO when used in combination with 5 α -reductase inhibitors. Further studies are required to verify the efficacy of antimuscarinics combined with 5 α -reductase inhibitors in these patients.

α_1 -Adrenergic-Receptor Antagonists with 5 α -Reductase Inhibitors. It has been well established that the combinations of α_1 -AR antagonists with 5 α reductase inhibitors (doxazosin finasteride in Medical Therapy of Prostatic Symptoms [MTOPS] trial; dutasteride plus tamsulosin in Combination of Avodart and Tamsulosin [CombAT] study) can improve clinical outcomes and reduce the incidence of BPH and LUTS progression measured as symptom worsening, retention, or progression to surgery (McConnell et al, 2003; Roehrborn et al, 2010).

KEY POINTS: DRUGS FOR MALE LOWER URINARY TRACT SYMPTOMS

- Because male LUTS may arise from prostatic obstruction, bladder dysfunction, or both, a logical step is to combine an α_1 -adrenergic antagonist with antimuscarinics to treat such patients. There are several trials demonstrating that this combination is more effective at reducing male LUTS than just α -blockers alone in men with OAB and BPO. In these trials the PVR was unchanged. However, there is not universal agreement because other trials do not show effects. Such usage has been recorded in patients with NDO with successful results.
- Because β_3 -adrenergic agonists and antimuscarinics have different mechanisms of action, it is attractive to speculate that a combination would be more effective than either drug used alone, especially because the adverse effect profiles are different. Such trials are ongoing.
- Also under investigation is the combination of different antimuscarinic agents in patients in whom antimuscarinic monotherapy fails.
- Antimuscarinic therapy in patients with OAB symptoms and prostatic pathology is more effective in men with smaller prostates.
- It is well established that the combination of an α -adrenergic antagonist and a 5 α -reductase inhibitor will improve clinical outcomes and reduce the incidence of symptomatic progression in patients with LUTS and BPH or BPO.

Toxins

Intravesical pharmacologic therapy for LUTS stems from the fact that circumventing systemic administration of active compounds offers two potential advantages. First, high concentrations of pharmacologic agents can be given to the bladder tissue, producing enhanced local effects. Second, drugs inappropriate for systemic administration because of off-target effects can be safely used. Attractive as it may be, intravesical pharmacologic therapy should still be considered as a second-line treatment in patients refractory

to oral therapy or who do not tolerate its systemic side effects. However, this statement is based on the assumption that intervention therapy should follow oral medication. Research aiming at defining if patient subgroups will benefit from intravesical therapy as first-line treatment is clearly necessary.

Botulinum Toxin

Mechanism of Action. Botulinum toxin (BoNT) is a neurotoxin produced by *Clostridium botulinum*. Of the seven subtypes of BoNT, subtype A (BoNTA) has the longest duration of action, making it the most relevant clinically. BoNTA is available in four different commercial forms, with the proprietary names of Botox, Dysport, Xeomin, and Prosigne. Although the toxin is the same, it is wrapped by different proteins that modify the relative potency of each brand. This was the basis for the introduction of the nonproprietary names onabotulinumtoxinA (onabotA), abobotulinumtoxinA (abobotA), and incobotulinumtoxinA (incobotA) for Botox, Dysport, and Xeomin, respectively. Prosigne is the proprietary name of a BoNTA produced in China, which currently does not have a known nonproprietary name. Although potency of each one is usually expressed in units (U), the doses are not interchangeable. Clinical dose conversion studies for the LUT do not exist. Available information indicates that onabotA is roughly three times more potent than abobotA and equivalent to incobotA. Nevertheless, these equivalences should be approached with caution.

Most of the information available about intravesical application of BoNTA derives from the use of onabotA (Botox). However, in addition to subtype A, some studies have investigated the effect of detrusor injection subtype B, rimabotulinumtoxinB (proprietary names being Miobloc or Neurobloc according to countries).

BoNT consists of a heavy and a light chain linked by a disulfide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein 2 (SV2) (Dong et al, 2006) by the heavy chain before being internalized by the nerve terminal along with the recycling process of synaptic vesicles. The two chains are then cleaved and the light chain passes into the cytosol, where it cleaves the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmic membrane necessary for neurotransmitter release. Attachment proteins (SNARE [soluble N-ethylmaleimide sensitive factor attachment protein receptor]) include synaptosome-associated protein 25 kD (SNAP-25), synaptobrevin (vesicle-associated membrane protein [VAMP]), and syntaxin. BoNTA cleaves SNAP-25, rendering the SNARE complex inactive (Humeau et al, 2000; Chancellor et al, 2008a). Subtype B acts preferentially through the inactivation of VAMP (Humeau et al, 2000).

BoNTA application was extensively evaluated in striated muscle. In this tissue, paralysis occurs by prevention of ACh release from cholinergic motor nerve endings (Humeau et al, 2000). Accumulation of neurotransmitter-containing synaptic vesicles is followed by terminal axonal degeneration. Striated muscle paralysis recovers within 2 to 4 months. During this time, axons develop lateral sprouts and eventually regenerate completely (de Paiva et al, 1999).

In the human bladder, SV2 and SNAP-25 expression has been demonstrated in parasympathetic, sympathetic, and sensory fibers (Coelho et al, 2010, 2012a, 2012b). Almost all parasympathetic nerves express the two proteins (Coelho et al, 2010, 2012a). Because these nerves play a fundamental role in detrusor contraction during voiding, the blockade of ACh release is believed to play an essential role in detrusor hypocontractility or acontractility that follows BoNTA injection in the bladder. In accordance with this view, it was shown that in normal or spinal cord-injured animals, BoNTA treatment decreased the bladder contractions evoked by electrical stimulation of spinal nerves without altering intrinsic contractions (Ikeda et al, 2012). However, cholinergic axon sprouting concomitant with clinical remission could not be documented in the detrusor (Haferkamp et al, 2004).

Bladder sensory impairment is also expected to play an important role in the final effect of BoNTA bladder injection. BoNTA inhibits the spinal cord release of glutamate, substance P (SP), and calcitonin gene-related peptide (CGRP) from sensory nerves (Purkiss et al, 2000; Aoki, 2005; Meng et al, 2007) as well as the

release of neuropeptides at the peripheral extremities (Rapp et al, 2006; Lucioni et al, 2008). BoNTA has also been shown to reduce the suburothelium immunoreactivity for transient receptor potential (TRP) channel TRPV1 or P2X₃ (Apostolidis et al, 2005b). Morenilla-Palao and colleagues (2004) have shown that BoNTA impedes TRPV1 trafficking from intracellular vesicles to the neuronal membrane, a process that is also dependent on SNARE proteins. All these mechanisms may contribute to the recent observation that BoNTA reduces afferent firing from bladder afferents and antidromic release of neuropeptides (Ikeda et al, 2012). Although SV2 and SNAP-25 immunoreactivity has not been detected in urothelial cells (Coelho et al, 2010), urothelial function seems also compromised after BoNTA administration. BoNTA has been shown to inhibit ATP release from urothelium in animal models of SCI (Khera et al, 2004; Smith et al, 2008). Therefore it is not surprising that administration of BoNTA to inflamed rat bladders reduces spinal c-Fos counts at the L6 and S1 spinal cord segments (Vemulakonda et al, 2005).

Cleaved, inactive SNAP-25 appears rapidly after BoNTA injection. In the guinea pig, a robust expression of cleaved SNAP-25 could be detected already at 12 hours and maximum intensity could be detected at 24 hours with little changes afterward. In guinea pigs, cleaved SNAP-25 expression was restricted to nerve fibers. Almost all parasympathetic fibers, either preganglionic and postganglionic, were affected, whereas less than half of the sensory fibers expressed the cleaved protein (Coelho et al, 2012a, 2012b). In the human urinary bladder, cleaved SNAP-25 could be detected in NDO patients up to 11 months after BoNTA injection (Schulte-Baukloh et al, 2007). The longer duration of cleaved SNAP-25 in the detrusor smooth muscle, longer than in striated muscles, has no firm explanation at the moment. However, the longer persistence of the inactive form of SNAP-25 plus the involvement of preganglionic and postganglionic parasympathetic neurons may contribute to persistence of the BoNTA effect in the bladder.

Myofibroblasts form a syncytium through extensive coupling via the gap-junction protein connexin 43 and have close contacts with sensory nerves. These facts led to the hypothesis that myofibroblasts act as modulators of bladder behavior (Wiseman et al, 2003; Apostolidis et al, 2006). However, the expression of connexin 43 is not altered by BoNTA (Roosen et al, 2009). Hence, at the moment, firm evidence for the action of BoNTA on myofibroblasts is scant.

BoNTA may decrease the levels of neurotrophic agents in the bladder tissue. Levels of nerve growth factor (NGF) (Giannantoni et al, 2006, 2013; Liu et al, 2009) and brain-derived neurotrophic factor (BDNF) (Pinto et al, 2010) have been shown to decrease in the bladder and/or urine after BoNTA injections. Because both neurotrophins have paramount roles in growth, maintenance, and plasticity of peptidergic sensory nerves, these findings may point toward another mechanism whereby BoNTA acts on the bladder.

Clinical Use. Comprehensive reviews of the clinical use of BoNTA have been produced during the last few years, covering different aspects of this treatment (Kuo, 2005a, 2005b; Chapple and Patel, 2006; Nitti, 2006; Patel et al, 2006; Kuo, 2007; Karsenty et al, 2008; Apostolidis et al, 2009; Sahai et al, 2009; Cruz et al, 2011; Dowson et al, 2011, 2012; Duthie et al, 2011; Herschorn et al, 2011a; Mangera et al, 2011; Denys et al, 2012; Fowler et al, 2012; Andersson et al, 2013a; Tincello et al, 2014).

Efficacy. RCTs have documented the clinical effects of onabotulinumtoxinA both in NDO and IDO, wherein the drug decreases incontinence episodes, frequency, and urgency and improves QoL (Sahai et al, 2007; Dmochowski et al, 2010a; Mangera et al, 2011; Tincello et al, 2012). The drug was also shown to be effective in patients with OAB (Nitti et al, 2013b). Successful OAB treatment with BoNTA does not appear to be related to the existence of DO. No differences in outcomes were found between those with and those without baseline DO (Rovner et al, 2011; Kanagarajah et al, 2012). Nitti and colleagues (2013b) reported results of the first large (N = 557) phase III placebo-controlled trial of onabotulinumtoxinA in OAB patients. To be included, patients had three or more UI episodes in 3 days and eight or more micturitions per day. They were randomized 1:1 to receive intradetrusor injection of

onabotulinumtoxinA 100 U or placebo (saline). Coprimary end points were change from baseline in UI episodes per day and proportion of patients with a positive response on the treatment benefit scale (TBS) at week 12 after treatment. Secondary end points included other OAB symptoms and health-related QoL. OnabotulinumtoxinA significantly reduced the daily frequency of UI episodes versus placebo (−2.65 vs. −0.87; $P < .001$), and 22.9% versus 6.5% of patients became completely continent. A larger proportion of onabotulinumtoxinA-treated patients than those receiving placebo reported a positive response on the TBS (60.8% vs. 29.2%; $P < .001$). All other OAB symptoms improved versus placebo ($P \leq .05$). OnabotulinumtoxinA improved patients' health-related QoL across multiple measures ($P < .001$).

The finding that onabotulinumtoxinA 100 U was consistently effective with a twofold to fourfold improvement over placebo in all symptoms of OAB is important; an effect of this magnitude versus placebo does not seem to have been reported previously with antimuscarinics or β_3 -AR agonists.

Adverse Effects. The most frequent side effects reported after intradetrusor BoNTA injection are bladder pain and urinary infections (Del Popolo et al, 2008; Karsenty et al, 2008; Kuo et al, 2010). Hematuria may also occur, most of the times mild in nature. The most dangerous side effect, paralysis of the striated musculature caused by circulatory leakage of the toxin, has never been reported. Transient muscle weakness was, nevertheless, reported with abobotA application in several studies (Wyndaele and Van Dromme, 2002; Akbar et al, 2007; Del Popolo et al, 2008). Of 199 NDO patients followed for 8 years, 5 developed hyposthenia when injected with abobotA 1000 U (Del Popolo et al, 2008). In another study with 44 patients, 3 adults also treated with 1000 U developed muscular weakness, which subsided after 5 to 7 weeks (Akbar et al, 2007). No such cases were reported with onabotA (Karsenty et al, 2008). The reason for the lack of transient muscle weakness in BoNTA-treated patients is unclear but might be related to the larger size of its molecule, which limits diffusion into the bloodstream. Caution should be used in selecting high-risk patients for treatment, including children, patients with low pulmonary reserve, and patients with myasthenia gravis. Aminoglycosides should be avoided during BoNTA treatment because they might block motor plates and therefore enhance BoNTA effect.

The most feared complication of BoNTA application in patients with voluntary voiding is urinary retention and a transient necessity to perform CIC. It is therefore strongly recommended that in patients with spontaneous voiding BoNTA administration be preceded by a complete discussion of information regarding this risk. Caregivers should ideally teach CIC to each patient before toxin injection. In the study by Nitti and colleagues (2013a), the majority of adverse effects occurred in the first 12 weeks (15.5% with onabotA vs. 5.9% with placebo). The most frequently reported adverse effect was uncomplicated urinary tract infection with no upper urinary tract involvement. Other adverse effects were dysuria (12.2%), bacteriuria (5.0%), and urinary retention (5.4%). PVR urine volume significantly increased with onabotA versus placebo, with the highest volume at week 2 after treatment, and 8.7% of patients had an increase from baseline of 200 mL or more in PVR urine volume at any time after the initial toxin treatment (none with placebo). The proportion of patients who initiated CIC at any time during treatment cycle 1 was 6.1% versus none in the placebo group; for over half the patients who initiated CIC (10 of 17), the duration of CIC was 6 weeks or less. This value is lower than those reported in previous studies on IDO. In the study of Nitti and colleagues (2013b), discontinuation rates because of adverse effects were low in both the onabotulinumtoxinA (1.8%) and in the placebo (1.4%) groups.

Visco and colleagues (2012) performed a double-blind, double placebo-controlled, randomized trial (the ABC trial) in women with idiopathic UI. The participants were randomly assigned for a 6-month period to daily oral antimuscarinic medication (solifenacin, 5 mg initially, with possible escalation to 10 mg and, if necessary, subsequent switch to trospium ER, 60 mg) plus one intradetrusor injection of saline or one intradetrusor injection of

100 U of onabotulinumtoxinA plus daily oral placebo. The authors concluded that oral antimuscarinic therapy and onabotulinumtoxinA by injection were associated with similar reductions in the frequency of daily episodes of UI. The group receiving onabotulinumtoxinA was less likely to have dry mouth and more likely to have complete resolution of UI but had higher rates of transient urinary retention and urinary tract infections.

Capsaicin and Resiniferatoxin (Vanilloids). There is a rationale for the use of intravesical vanilloids (capsaicin and resiniferatoxin [RTX]) to suppress DO and urgency without DO. Results have not been consistent, and practical application has been a hurdle.



This subject is covered in detail on the Expert Consult website.

KEY POINTS: TOXINS FOR OVERACTIVE BLADDER

- Intradetrusor injections of onabotulinumtoxinA have been shown to be effective in the treatment of NDO and IDO as well as OAB symptoms without DO. The mechanism of action seems to be through both efferent and afferent decreases in the release of transmitter(s) substance(s). The doses used are different for neurogenic and idiopathic conditions. A potential complication in patients with voluntary voiding is urinary retention, and all such patients should be informed of this risk.
- There is a definite rationale for the use of intravesical capsaicin and RTX (vanilloids) for the treatment of patients with DO. Alcoholic capsaicin solution is extremely irritating, and RTX is much less pungent. There have been positive clinical trials with RTX, although some negative results occur as well. At the present time, this is not commonly used.

Estrogens for Urgency Urinary Incontinence and Overactive Bladder Symptoms

Estrogen has been used to treat postmenopausal urgency and urgency incontinence for many years, but there have been few controlled trials to confirm that it is of benefit (Hextall, 2000). A double-blind multicenter study of 64 postmenopausal women with "urge syndrome" failed to show efficacy (Cardozo et al, 1998). All women underwent pretreatment urodynamic investigation to ensure that they had either "sensory" urgency or DO. They were randomized to treatment with oral estriol 3 mg daily or placebo for 3 months. Compliance with therapy was confirmed by a significant improvement in the maturation index of vaginal epithelial cells in the active but not the placebo group. Estriol produced subjective and objective improvements in urinary symptoms but was not significantly better than placebo.

Another RCT from the same group using 25-mg estradiol implants confirmed the previous findings (Rufford et al, 2003), and furthermore found a high complication rate in the estradiol-treated patients (vaginal bleeding).

Symptoms of OAB increase in prevalence with increasing age, and LUTS and recurrent urinary tract infections are commonly associated with urogenital atrophy. Although the evidence supporting the use of estrogens in LUT dysfunction remains controversial, there are considerable data to support their use in urogenital atrophy, and the vaginal route of administration correlates with better symptom relief by improvement in vaginal dryness, pruritus, and dyspareunia, greater improvement in cytologic findings, and higher serum estradiol levels (Cardozo et al, 1998). Overall, vaginal estradiol has been found to be the most effective in reducing patient symptoms, although conjugated estrogens produced the most extensive cytologic change and the greatest increase in serum estradiol and estrone. The most recent meta-analysis of intravaginal estrogen treatment in the management of urogenital atrophy was reported by Suckling and colleagues (2003). Overall, 16 trials including 2129 women were analyzed,

and intravaginal estrogen was found to be superior to placebo in terms of efficacy, although there were no differences among types of formulation. Fourteen trials compared safety among the different vaginal preparations and found a higher risk of endometrial stimulation with conjugated equine estrogens (CEE) as compared with estradiol.

Thus, theoretically there could be a role for combination treatment with an antimuscarinic agent and vaginal estrogen in postmenopausal women. However, the two clinical trials that have been reported to date differ in their outcomes. Tseng and colleagues (2009) showed superior efficacy in terms of symptom improvement for OAB when tolterodine was used with vaginal estrogen cream as opposed to tolterodine alone. However, Serati and colleagues (2009) found no difference between tolterodine with or without topical estrogen in women with symptomatic DO.

Evidence Regarding Estrogens and Incontinence from Large Clinical Trials. The Heart and Estrogen/Progestin Replacement Study (HERS) included 763 postmenopausal women under the age of 80 years with CHD and intact uteri (Grady et al, 2001). It was designed to evaluate the use of estrogen in secondary prevention of cardiac events. In a secondary analysis, 1525 participants who reported at least one episode of incontinence per week at baseline were included. Participants were randomly assigned to 0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate (MPA) in one tablet ($n = 768$) or placebo ($n = 757$) and were followed for a mean of 4.1 years. Severity of incontinence was classified as improved, unchanged, or worsened. The results showed that incontinence improved in 26% of the women assigned to placebo compared with 21% assigned to hormones, whereas 27% of the placebo group worsened compared with 39% of the hormone group ($P = .001$). This difference was evident by 4 months of treatment, for both UI and SUI. The number of incontinence episodes per week increased an average of 0.7 in the hormone group and decreased by 0.1 in the placebo group ($P < .001$). The authors concluded that daily oral estrogen plus progestogen therapy was associated with worsening UI in older postmenopausal women with weekly incontinence and did not recommend this therapy for treatment of incontinence. However, it is possible that the progestogen component may have had an influence on the results of this study.

The Women's Health Initiative (WHI) was a multicenter double-blind placebo-controlled randomized clinical trial of menopause hormone therapy in 27,347 postmenopausal women aged 50 to 79 years enrolled from 1992 to 1998; UI symptoms were known in 23,296 participants at baseline and 1 year (Hendrix et al, 2005). The women were randomized based on hysterectomy status to active treatment or placebo. Those with a uterus were given 0.625 mg of conjugated equine estrogen (CEE) per day plus 2.5 mg of MPA per day (CEE + MPA), whereas those who had undergone hysterectomy received estrogen alone (CEE). At 1 year, hormone therapy was shown to increase the incidence of all types of UI in women who were continent at baseline. The risk was highest for SUI, followed by mixed UI. The combination of CEE and MPA had no significant effect on development of urge UI, but CEE alone increased the risk. For those women experiencing UI at baseline, frequency of micturition worsened in both active groups. Quantity of UI worsened at 1 year in both active groups. Those women receiving hormone therapy were more likely to report that UI limited their daily activities at 1 year. Thus, based on this secondary analysis of data from a huge study, CEE alone or in combination with MPA after 1 year of therapy was shown to increase the risk of UI in continent menopausal women and worsen UI in those incontinent at baseline.

The Nurses' Health Study (Grodstein et al, 2004) was a biennial postal questionnaire starting in 1976. In the study, 39,436 postmenopausal women aged 50 to 75 years who reported no urinary leakage at the start of the study were followed up for 4 years to identify incident cases of UI; 5060 women with occasional and 2495 with frequent incontinence were identified. The risk of developing UI was increased in postmenopausal women taking hormones compared with women who had never taken hormones.

Rationale for Intravesical Vanilloids. The rationale for intravesical vanilloid application in patients with DO is the demonstration that capsaicin, following bladder C-fiber desensitization, suppresses involuntary detrusor contractions dependent on a sacral micturition reflex (de Groat, 1997). The C-fiber micturition reflex is usually inactive, but it was shown that it is enhanced in patients with chronic spinal cord lesions above sacral segments (de Groat, 1997) in those with chronic BOO (Chai et al, 1998) and in those with IDO (Silva et al, 2002). In the bladders of NDO patients, the enhancement of the micturition reflex is accompanied by an increase in the number of suburothelial C-fibers expressing TRPV1 (Brady et al, 2004a). It is curious that NDO patients who responded better to intravesical RTX exhibited a significant decrease in the density of TRPV1 immunoreactive fibers, whereas nonresponders experienced a nonsignificant variation (Brady et al, 2004a). A decrease in TRPV1 expression in urothelial cells of NDO patients was also demonstrated after intravesical application of RTX (Apostolidis et al, 2005a, 2005b, 2006).

Changes in suburothelial C-fiber innervation expressing neuropeptides (Smet et al, 1997) or TRPV1 (Liu and Kuo, 2007) were also reported in patients with sensory urgency. In IDO patients, responders to intravesical RTX are closely associated with the overexpression of the receptor in the bladder mucosa (Liu and Kuo, 2007). In women with sensory urgency, TRPV1 mRNA expressed in trigonal mucosa was not only increased but also inversely correlated with the bladder volume at first sensation of filling during cystometry, further indicating that TRPV1 may play a role in premature bladder sensation (Liu et al, 2007).

Intravesical Capsaicin. Intravesical capsaicin for NDO was studied in six noncontrolled (Fowler et al, 1992b, 1994; Geirsson et al, 1995; Das et al, 1996; Cruz et al, 1997; De Ridder et al, 1997) and one controlled (de Sèze et al, 1998) clinical trial. Capsaicin was dissolved in 30% alcohol, and 100 to 125 mL (or half of the bladder capacity if lower than that volume) of 1- to 2-mM solutions were instilled into the bladder and left in contact with the mucosa for 30 minutes. Best clinical results were found in patients with incomplete spinal cord lesions, in whom clinical improvement could be observed in up to 70% to 90% (Fowler et al, 1994; Cruz et al, 1997; De Ridder et al, 1997). In patients with complete spinal cord lesions, the success rate was much lower (Geirsson et al, 1995).

Only one small randomized controlled study compared capsaicin against 30% ethanol, the vehicle solution. Ten patients received capsaicin; a significant regression of the incontinence and urge sensation was found. In contrast, only 1 of the 10 patients who received ethanol had clinical improvement (de Sèze et al, 1998).

The pungency of alcoholic capsaicin solutions has prevented the widespread use of this compound. In particular, the possibility of triggering autonomic dysreflexia with capsaicin, especially in patients with higher spinal cord lesions, has progressively restrained its use. The relevance of capsaicin might, however, be back, with a recent report by de Sèze and colleagues (2006), who used a new capsaicin formulation. They conducted a double-blind placebo-controlled study with a glucidic solution of capsaicin in 33 NDO patients. The glucidic capsaicin-treated group showed improvement both in symptoms and in urodynamic parameters above the comparator arm. The global tolerance of this new capsaicin formulation was excellent (de Sèze et al, 2006).

Resiniferatoxin in Neurogenic Detrusor Overactivity. RTX has the advantage over capsaicin in being much less pungent (Cruz et al, 1997). Intravesical RTX application in NDO patients was evaluated in five small open-label studies (Cruz et al, 1997; Lazzeri et al, 1997, 1998; Silva et al, 2000; Kuo, 2003). Different RTX concentrations, 10 nM, 50 nM, 100 nM, and 10 μ M, were tested. RTX brought a rapid improvement or disappearance of UI in up to 80% of the selected patients and a 30% decrease in their daily urinary frequency. Furthermore, RTX also increased the volume to FDC and maximal cystometric capacity. In general, in patients receiving 50- or 100-nM RTX, the effect was long-lasting, with a duration of more than 6

months being reported. In patients treated with 10- μ M doses, transient urinary retention sometimes occurred (Lazzeri et al, 1998).

In a placebo-controlled study, the urodynamic effects of RTX in NDO patients were specifically evaluated. Only in the RTX arm, a significant increase in FDC and maximal cystometric capacity was found (Silva et al, 2005). RTX also caused a significant improvement in urinary frequency and incontinence (Silva et al, 2005).

RTX 600 nM was compared against BoNTA (Botox, 300 U) in a study involving 25 patients with NDO from chronic SCI. Both neurotoxins were capable of significantly reducing the number of daily incontinence episodes and improving maximum bladder capacity, although BoNTA turned out to be more effective.

Resiniferatoxin in Idiopathic Detrusor Overactivity. The first study with intravesical RTX in IDO patients was designed as a proof-of-concept study and involved 13 patients. Intravesical RTX 50 nmol/L was associated with an improvement in volume to FDC from 170 \pm 109 mL to 440 \pm 153 mL at 30 days, and to 391 \pm 165 mL at 90 days. An increase in mean MCC from 291 \pm 160 mL to 472 \pm 139 mL at 30 days and to 413 \pm 153 mL at 90 days was also observed. These improvements were accompanied by a decrease in episodes of urgency incontinence and of daily frequency (Silva et al, 2002). Subsequent small open-label studies confirmed these observations using either a single high dose (50 to 100 nM) or multiple low doses (10 nM) (Kuo, 2003; Dinis et al, 2004; Kuo, 2005b).

The effect of RTX on refractory IDO was evaluated in two randomized clinical trials (Kuo et al, 2006; Rios et al, 2007). Kuo and colleagues (2006) randomized 54 patients to receive four weekly instillations of a low-concentration RTX solution (10 nmol/L) or the vehicle solution, 10% ethanol in saline. Three months after completing the four intravesical treatments, the RTX-treated group had 42.3% and 19.2% of patients feeling much better or improved, respectively. This was significantly more than in the placebo group—14.2% and 7.1%, respectively. At 6 months, treatment remained effective in 50% of patients in the RTX group but only in 11% in the placebo group (Kuo et al, 2006). Such clinical and urodynamic findings could not be reproduced in another study in which patients were randomly assigned to receive a single intravesical dose of 100 mL of either RTX 50 nM or placebo. Patients were followed for only 4 weeks. During this period a single 50-nM intravesical dose of RTX was not better than placebo for the treatment of women with IDO and urgency incontinence (Rios et al, 2007).

Resiniferatoxin and Urgency. The involvement of bladder C fibers in IDO has led some investigators to explore the role of these sensory afferents in the genesis of urgency. In a noncontrolled study involving 12 male patients with LUTS associated with BPH, mean IPSS halved after intravesical administration of RTX (50 nmol/L). The decrease in IPSS was largely the result of improvements in scores related to urgency, in addition to improvement in nocturia and frequency (Dinis et al, 2005). In another open-label study, 15 patients with intractable urgency and frequency, with or without urgency incontinence or bladder pain or discomfort, and without urodynamic evidence of DO received one single administration of 50-nM RTX solution. A trend toward an improvement of urgency was noticed (Apostolidis et al, 2006).

In a quasi-randomized study, 23 OAB patients with refractory urgency entered a 30 day run-in period in which medications influencing the bladder function were interrupted. At the end of this period, patients filled out a 7-day bladder diary. Then patients underwent instillation of 100 mL of 10% ethanol in saline (vehicle solution), and 30 days later a second 7-day diary was collected. Finally, patients underwent instillation of 100 mL of 50-nM RTX in 10% ethanol in saline, and additional bladder diaries were collected at 1 and 3 months. After vehicle instillation, the mean number of episodes of urgency per week was 56 \pm 11. At 1 and 3 months after RTX instillation, the number of episodes of urgency decreased to 39 \pm 9 (P = .002) and 37 \pm 6 (P = .02), respectively (Silva et al, 2007).

After cessation of hormone therapy, there was a decreased risk of incontinence such that 10 years after stopping hormones the risk was identical in women who had and who never had taken hormone therapy.

The most recent meta-analysis of the effect of estrogen therapy on the LUT was performed by [Cody and colleagues \(2009\)](#) and is notable because the conclusions are starkly different from those drawn from the previous review ([Moehrer et al, 2003](#)). Overall, 33 trials were identified, including 19,313 incontinent women (1262 involved in trials of local administration), of whom 9417 received estrogen therapy. **Systemic administration (of unopposed oral estrogens—synthetic equine estrogens and CEEs) resulted in worse incontinence than placebo**, although this was heavily influenced by the size of the WHI study ([Hendrix et al, 2005](#)). **With regard to combination therapy, there was a similar worsening effect on incontinence when compared with placebo. There was some evidence suggesting that the use of local estrogen therapy may improve incontinence, and overall there were one to two fewer voids in 24 hours and less frequency and urgency.**

The authors concluded that local estrogen therapy for incontinence may be beneficial, although there was little evidence of long-term effect. The evidence would suggest that systemic hormone replacement using CEEs may make incontinence worse. In addition, they reported that there are too few data to comment reliably on the dose type of estrogen and route of administration.

Estrogen has an important physiologic effect on the female LUT, and its deficiency is an etiologic factor in the pathogenesis of a number of conditions. However, the use of estrogen either alone or in combination with progestogen has yielded poor results. **The current level 1 evidence against the use of estrogen for the treatment of UI comes from studies powered to assess their benefit in the prevention of cardiovascular events**, and therefore the secondary analyses have been based only on self-reported symptoms of urinary leakage without any objective data. Despite this, all of these large RCTs show a worsening of preexisting UI, both SUI and UI, and an increased new incidence of UI with both estrogen and estrogen plus progestogen. However, the majority of subjects in all of these studies were taking combined equine estrogen, and this may not be representative of all estrogens taken by all routes of administration.

In a systematic review of the effects of estrogens for symptoms suggestive of OAB, the conclusion was that estrogen therapy may be effective in alleviating OAB symptoms, and that local administration may be the most beneficial route of administration ([Cardozo et al, 2004c](#)). It is quite possible that the reason for this is that the symptoms of urinary urgency, frequency, and urge incontinence may be a manifestation of urogenital atrophy in older postmenopausal women rather than a direct effect on the LUT ([Robinson and Cardozo, 2003](#)). Although there is good evidence that the symptoms and cytologic changes of urogenital atrophy may be reversed by low-dose (local) vaginal estrogen therapy, there is currently no evidence that estrogens with or without progestogens should be used in the treatment of UI.

KEY POINTS: HORMONES AND URINARY INCONTINENCE

- Conclusions reached in a number of studies have been that (1) daily oral estrogen plus progestogen therapy is associated with worsening UI in older postmenopausal women with weekly incontinence, and (2) CEE alone or in combination with MPA increases the risk of UI in continent menopausal women and worsens UI in those incontinent at baseline.
- There is some evidence suggesting that local (vaginal) therapy with estrogen may improve OAB symptoms in postmenopausal women, perhaps by its reversal of urogenital atrophy.

Other Hormones and Desmopressin

Progesterone and progestogens are thought to increase the risk of UI. LUTS, especially SUI, have been reported to increase in the progestogenic phase of the menstrual cycle ([Hextall et al, 2001](#)). In similar studies, progesterone has been shown to increase β -AR activity, leading to a decrease in the urethral closure pressure in female dogs ([Raz et al, 1973](#)). However, in the WHI there appeared to be no difference whether or not progestin was given in addition to estrogen ([Hendrix et al, 2005](#)).

Selective estrogen receptor modulators (SERMS) have been reported to have varying effects. Each of the SERMS has receptor ligand conformations that are unique and have both estrogenic and antiestrogenic effects. In the clinical trials of levormeloxifene, there was a fourfold increase in the incidence of incontinence, leading to cessation of the clinical trial ([Hendrix et al, 2001](#)). However, raloxifene has not been shown to have any effect at all on UI ([Waetjen et al, 2004](#)). There are no reported clinical trials evaluating the effect of androgens, and in particular testosterone, on UI in women.

Desmopressin. The endogenous hormone vasopressin (also known as *antidiuretic hormone*) has two main functions: It causes contraction of vascular smooth muscle, and it stimulates water reabsorption in the renal medulla. These functions are mediated by two specific vasopressin receptors, of which there are two major subtypes, namely the V_1 and V_2 receptors. The V_2 subtype is particularly important for the antidiuretic effects of vasopressin. A genetic or acquired defect in making and secreting vasopressin leads to central diabetes insipidus, and genetic defects in the gene encoding the V_2 receptor can cause nephrogenic diabetes insipidus ([Insel et al, 2007](#)). Accordingly, decreased vasopressin levels are believed to be important in the pathophysiology of some forms of polyuria, specifically NP, which can lead to symptoms such as nocturia ([Matthiesen et al, 1996](#); [Weiss et al, 2011a](#)). Nocturia is currently defined by the ICS as the complaint that an individual has to wake at night one or more times to void. It is, however, “an underreported, understudied, and infrequently recognized problem in adults” ([Weiss et al, 2011b](#)). Nocturia leads to decreased QoL ([Kupelian et al, 2011](#)) and has been associated with both increased morbidity and mortality ([Nakagawa et al, 2010](#); [Kupelian et al, 2012](#)). Although it remains largely unknown which fraction of patients with nocturia can indeed be explained by too little vasopressin, the presence of NP in the absence of behavioral factors explaining it (such as excessive fluid intake) is usually considered as an indication that a (relative) lack of vasopressin may exist ([Bosch and Weiss, 2010](#); [Weiss et al, 2011b](#)).

Based on these considerations, vasopressin-receptor agonists have been used to treat nocturia, both in children and in adults. Desmopressin is the most common vasopressin analogue used to treat nocturia. Desmopressin shows selectivity for antidiuretic over vasopressor effects. It has a more powerful and longer-lasting antidiuretic action than vasopressin. It is available in formulations for oral, parenteral, and nasal administration. It has a fast onset of action, with urine production decreasing within 30 minutes of oral administration ([Rittig et al, 1998](#)). Because symptomatic hyponatremia with water intoxication, which is the only serious adverse event reported in children, occurred after intranasal or intravenous administration of desmopressin ([Thumfart et al, 2005](#); [Robson et al, 2007](#); [Van de Walle et al, 2010](#)), the FDA and the European Medicines Agency (EMA) removed the indication for the treatment of primary nocturnal enuresis from all intranasal preparations of desmopressin. An oral lyophilisate formulation (MELT) requiring no concomitant fluid intake is currently available. In a recent open-label, randomized, crossover study, desmopressin MELT was shown to have similar levels of efficacy and safety at lower doses than the tablet formulation of desmopressin in children. A recent study confirmed the superior pharmacodynamic characteristics of desmopressin MELT to desmopressin tablets ([De Guchtenaere et al, 2011](#)).

The use of desmopressin in children with nocturnal enuresis was comprehensively reviewed by [Glazener and Evans in 2002](#). These authors evaluated 47 RCTs involving 3448 children, of whom 2210

received desmopressin. According to the analysis, desmopressin was effective relative to placebo in reducing bedwetting; a dose of 20 μ g resulted in a reduction of 1.34 wets per night (95% CI 1.11 to 1.57), and children were more likely to become dry with desmopressin (98%) than with placebo (81%). However, there was no difference between desmopressin and placebo after discontinuation of treatment, indicating that **desmopressin suppresses the symptom of enuresis but does not cure the underlying cause**. In addition, not all children responded sufficiently to desmopressin monotherapy. The combination of desmopressin and an enuresis alarm resulted in a greatly improved short-term success rate and decreased relapse rates (Alloussi et al, 2011). The combination of desmopressin and antimuscarinics resulted in better short- and long-term success rates as well as a lower relapse rate than desmopressin alone (Austin et al, 2008; Alloussi et al, 2009). For nonresponders to desmopressin, replacement of desmopressin with other medications such as tricyclic antidepressants or loop diuretics could be of benefit, whereas muscarinic-receptor antagonists may be ineffective in such children (De Guchtenaere et al, 2007; Neveus and Tullus, 2008).

Other studies have explored a possible treatment role for desmopressin in the treatment of nocturia in adults. A search for these studies in Medline using the terms *desmopressin* and *nocturia* was performed and limited to clinical studies of de novo nocturia, that is, those that excluded subjects in whom childhood enuresis persisted into adulthood. Several previous studies investigated the use of desmopressin for the treatment of nocturia in the context of multiple sclerosis (Eckford et al, 1994, 1995). One study with single-dose administration reported a reduction in NP, but by design did not assess nocturia (Eckford et al, 1995). Three placebo-controlled double-blind studies with small patient numbers (16 to 33 patients total per study) reported a significant reduction in nocturia (Hilton et al, 1983; Eckford et al, 1994; Valiquette et al, 1996). Other controlled studies of similar size, most with a crossover design, used micturition frequency within the first 6 hours after desmopressin administration rather than nocturia as their primary end point. These studies consistently reported that desmopressin treatment for up to 2 weeks was efficacious (Kinn and Larsson, 1990; Fredrikson, 1996; Hoverd and Fowler, 1998). Although desmopressin treatment was generally well tolerated, 4 of 17 patients in one study discontinued treatment because of asymptomatic or minimally symptomatic hyponatremia (Valiquette et al, 1996). Accordingly, **desmopressin is now registered for the treatment of nocturia in multiple sclerosis patients** (Cvetkovic and Plosker, 2005). In a small open-label study, desmopressin was also reported to reduce NP in SCI patients (Zahariou et al, 2007).

Further studies have explored the use of desmopressin in adults with nocturia in the apparent absence of neurologic damage. The recruited patient populations were based on different criteria, including having at least two nocturia episodes per night or having NP. Earlier studies mostly used a desmopressin dose of 20 μ g given either orally (Asplund et al, 1999) or intranasally (Hilton and Stanton, 1982; Cannon et al, 1999), and tended to be very small (25 or fewer patients). Later studies, as part of the NOCTUPUS program, were considerably larger, involving a total of 1003 screened patients, and higher oral doses (0.1–0.4 mg) were administered for a period of 3 weeks of double-blind treatment in adults (Mattiasson et al, 2002; Lose et al, 2004; van Kerrebroeck et al, 2007). A total of 632 patients entered the dose-titration phase and 422 patients entered the double-blind phase of the three NOCTUPUS trials. To counter the argument that the study was performed in desmopressin responders after the dose titration phase, all patients in the NOCTUPUS trials were washed out after the dose-titration phase, and to be randomized the patients were required to be returned to baseline nocturnal diuresis before inclusion in the double-blind phase. The trials showed that oral desmopressin (0.1, 0.2, or 0.4 mg) is effective in both men and women aged 18 years or older with nocturia. The number of nocturnal voids decreased from 3 to 1.7 in the desmopressin group compared with 3.2 to 2.7 in the placebo group. In women, the number of nocturnal voids in the desmopressin group decreased from 2.92 to 1.61, whereas that in the placebo group decreased from 2.91 to 2.36. When clinical response was

defined as 50% or greater reduction in nocturnal voids from baseline, 34% of men experienced clinical response with desmopressin, compared with 3% of men who received placebo. In women, 46% of desmopressin-treated patients experienced a clinical response, compared with 7% of patients on placebo.

The efficacy of desmopressin for the treatment of nocturia was confirmed in a long-term (10 to 12 months) open-label study involving 249 patients, which was an extension of the randomized studies in known desmopressin responders. However, a rebound effect was seen when treatment was withdrawn, confirming the association between continued treatment and response (Lose et al, 2004). An open-label pilot study in a nursing home setting also reported that desmopressin had beneficial effects (Johnson et al, 2006).

Around 75% of community-dwelling men and women with nocturia (two or more voids per night) have NP (Rembratt et al, 2003; Swithinbank et al, 2004). The key urologic factors most relevant to nocturia are NP and OAB in women (Irwin et al, 2008) and NP and BPH in men. About 74% of women with OAB have nocturia, and 62% of patients with OAB and nocturia have NP. Among men with nocturia, 83% have NP, 20% have NP alone, and 63% have NP in combination with another factor such as a small nocturnal bladder capacity or BOO (Chang et al, 2006). Therefore, desmopressin combination therapy with α_1 -AR antagonists and/or antimuscarinics should be considered for patients with treatment-resistant nocturia. Seventy-three percent of α_1 -AR antagonist-resistant BPH patients experienced a 50% or greater reduction in nocturnal voids with oral desmopressin (Yoong et al, 2005). A randomized, double-blind, placebo-controlled study evaluating the long-term (1, 3, 6, and 12 months) efficacy and safety of low-dose (0.1 mg) oral desmopressin in elderly (65 years or older) patients reported that low-dose oral desmopressin led to a significant reduction in the number of nocturnal voids and nocturnal urine volume in patients with BPH (Wang et al, 2011).

Because nocturia can be caused by different factors, several studies have investigated whether desmopressin may be beneficial in patients with other symptoms in addition to nocturia. In a small, nonrandomized pilot study of men believed to have BPH, desmopressin was reported not only to improve nocturia, but also to reduce the overall IPSS (Chancellor et al, 1999). An exploratory, placebo-controlled double-blind study in women with daytime UI reported that intranasal administration of 40 μ g of desmopressin increased the number of leakage-free episodes 4 hours after drug administration (Robinson et al, 2004). One double-blind, placebo-controlled pilot study in patients with OAB treated with 0.2 mg of oral desmopressin reported a reduction in voids along with an improvement in QoL (Hashim et al, 2009). Although these data indicate that desmopressin may be effective in treating LUT dysfunction not limited to nocturia, they are too sparse to allow treatment recommendations.

Desmopressin was well tolerated in all the studies and resulted in significant improvements compared with placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. There was also an improvement in QoL. However, one of the main clinically important side effects of desmopressin use is hyponatremia. Hyponatremia can lead to a variety of adverse events ranging from mild headache, anorexia, nausea, and vomiting to loss of consciousness, seizures, and death. Hyponatremia usually occurs soon after treatment is initiated. The **risk of hyponatremia appears to increase with age, cardiac disease, and increasing 24-hour urine volume** (Rembratt et al, 2006). Based on a meta-analysis, the incidence is around 7.6% (Weatherall, 2004). **Increased age and female gender are well-known risk factors** for the development of desmopressin-induced hyponatremia. Bae and colleagues (2007) assessed the effects of long-term oral desmopressin on serum sodium and baseline antidiuretic hormone secretion in 15 elderly male patients with severe nocturia (more than three voids nightly) who did not show hyponatremia within 7 days of administration of 0.2 mg desmopressin. Desmopressin (0.2 mg) was administered orally nightly for 1 year. Before and 1 month after the 1-year medication 24-hour circadian studies were performed to

monitor changes in antidiuretic hormone. Every 3 months during the 1-year medication period, serum changes and timed urine chemistry were monitored. The results showed that long-term desmopressin administration gradually decreased serum sodium and induced statistically, but not clinically significant, hyponatremia after 6 months of treatment. Administration of desmopressin for 1 year did not affect baseline antidiuretic hormone secretion. The authors recommended that for long-term desmopressin administration, serum sodium should be assessed regularly, at least every 6 months.

A recent focus has been on exploring gender differences in the antidiuretic response to desmopressin. Juul and colleagues (2011) found an increasing incidence of hyponatremia with increasing dose; and at the highest dose level of 100 µg, decreases in serum sodium were approximately twofold greater in women over 50 years of age than in men. The gender difference could not be explained by pharmacokinetic differences. They calculated an ED₅₀ ratio for men/women to be 2.7 (1.3 to 8.1). A new dose recommendation stratified by gender was suggested in the treatment of nocturia: For men, 50 to 100 µg MELT was suggested to be an efficacious and safe dose, and for women a dose of 25 µg MELT was recommended as efficacious with no observed incidences of hyponatremia. Initiation of desmopressin is currently not indicated for patients aged 65 years or older. The mechanisms behind desmopressin-induced hyponatremia are well understood, and serum sodium monitoring at baseline and early during treatment of older patients for whom treatment with desmopressin is indicated can greatly reduce their risk of developing the condition. Other advice regarding treatment administration, such as restriction of evening fluid intake and adherence to the recommended administration regimen, should be followed to minimize the risk of hyponatremia (Vande Walle et al, 2007).

Desmopressin is useful for patients with nocturia as well as for children with nocturnal enuresis. The drug has been proven to be well tolerated and effective in several randomized, placebo-controlled trials and is recommended as a first-line treatment (either as monotherapy or in combination with other agents) with proper precaution for patients who have been appropriately evaluated and whose nocturia is related to NP, whether or not this is accompanied by BPH or OAB. For assessment, see Table 79-3. A rapidly acting, quickly metabolized preparation with minimal risk of hyponatremia would obviously be useful for the treatment of nocturia in adults and could have application for “spot usage” for a limited time period in patients with OAB.

KEY POINTS: DESMOPRESSIN IN NOCTURNAL POLYURIA

- Desmopressin is an analogue of vasopressin that shows selectivity for antidiuretic effects (water reabsorption in the renal medulla) over vasopressor effects. It suppresses the symptom of nocturnal enuresis in children without curing the underlying cause. It has been used in a number of studies in patients with and without neurogenic disease for the treatment of nocturia. Results in general have been statistically significant improvements in nocturnal voids and hours of undisturbed sleep.
- The most important adverse event is hyponatremia, an increased risk of which is seen with age, female gender, cardiac disease, and increased 24-hour urine volume. Some regimen of serum sodium monitoring is indicated along with other advice designed to minimize the risk of hyponatremia.

Drug Treatment of Overactivity in Augmented or Intestinal Neobladders

With regard to the subject of overactivity in bowel augmented or intestinal neobladders, Andersson and colleagues (1992) reviewed

this subject and its pharmacologic treatment. They noted a few instances of positive results with drugs given systematically, but locally applied agents were believed to offer more promise. Pure antimuscarinic agents had produced few good results, either locally or systemically. Oxybutynin had shown some good results with local therapy but poor results with systemic therapy. The α- and β-AR agonists had shown little or no effects. Other possibilities mentioned included opioid agonists (diphenoxylate and loperamide), calcium antagonists, potassium channel openers, and NO donors. Apostolidis and colleagues (2007) reported a case of successful treatment with botulinum toxin A after failed augmentation ileocystoplasty.

Future Possibilities

Please see the Expert Consult website for this section.



Increasing Outlet Resistance

Many factors seem to be involved in the pathogenesis of SUI: urethral support, vesical neck function, and function of the nerves and musculature of the bladder, urethra, and pelvic floor (DeLancey, 1997; Mostwin et al, 2005; Koelbl et al, 2009; Chapple and Milsom, 2012). Anatomic factors cannot be treated pharmacologically. However, women with SUI have lower resting urethral pressures than age-matched continent women (Henriksson et al, 1979; Hilton et al, 1983), and because it seems likely that there is a reduced urethral closure pressure in most women with SUI, it seems logical to increase urethral pressure to improve the condition.

Factors that may contribute to urethral closure include tone of urethral smooth and striated muscle and the passive properties of the urethral lamina propria, in particular its vasculature. The relative contribution to intraurethral pressure of these factors is still subject to debate. However, there is ample pharmacologic evidence that a substantial part of urethral tone is mediated through stimulation of α-ARs in the urethral smooth muscle by released NA (Andersson, 1993; Andersson and Wein, 2004). A contributing factor to SUI, mainly in elderly women with lack of estrogen, may be lack of mucosal function. The pharmacologic treatment of SUI aims at increasing intraurethral closure forces by increasing the tone in the urethral smooth and striated muscles. Several drugs may contribute to such an increase (Andersson, 1988; Zinner et al, 2004), but relative lack of efficacy and/or side effects have limited their clinical use. For assessments, see Table 79-4.

Drugs Used for Treatment of Stress Incontinence In Women

Estrogens

Estrogens and the Continence Mechanism. The estrogen-sensitive tissues of the bladder, urethra, and pelvic floor all play an important role in the continence mechanism. For women to remain continent, the urethral pressure must exceed the intravesical pressure at all times except during micturition. The urethra has four estrogen-sensitive functional layers, all of which have a role in the maintenance of a positive urethral pressure: (1) epithelium, (2) vasculature, (3) connective tissue, and (4) muscle.

Two types of estrogen receptors (α and β) have been identified in the trigone of the bladder, urethra, and vagina, as well as in the levator ani muscles and fascia and ligaments within the pelvic floor (Smith et al, 1990; Copas et al, 2001; Gebhardt et al, 2001). After menopause, estrogen receptor α has been shown to vary depending on exogenous estrogen therapy (Fu et al, 2003). In addition, exogenous estrogens affect the remodeling of collagen in the urogenital tissues, resulting in a reduction of the total collagen concentration with a decrease in the cross-linking of collagen in both continent and incontinent women (Keane et al, 1997; Falconer et al, 1998). Studies in both animals and humans have shown that estrogens also increase vascularity in the periurethral plexus, which can be measured as vascular pulsations on urethral pressure profilometry (Versi and Cardozo, 1986; Robinson et al, 1996; Endo et al, 2000).

Peripherally Acting Drugs

Vitamin D₃-Receptor Analogues. It is well known that vitamin D affects skeletal muscle strength and functional efficiency, and vitamin D insufficiency has been associated with notable muscle weakness. The levator ani and coccygeus skeletal muscles are critical components of the pelvic floor and may be affected by vitamin D nutritional status. Weakened pelvic floor musculature is thought to be associated with the development of UI and fecal incontinence symptoms. Aging women are at increased risk for both pelvic floor dysfunction and vitamin D insufficiency; to date, only small case reports and observational studies have shown an association between insufficient vitamin D and pelvic floor dysfunction symptom severity (Parker-Autry et al, 2012). Rat and human bladders were shown to express receptors for vitamin D (Crescioli et al, 2005), which makes it conceivable that the bladder may also be a target for vitamin D. Analogues of vitamin D₃ have also been shown to inhibit BPH cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells (Crescioli et al, 2002, 2003, 2004). Experiments in rats with bladder outflow obstruction (Schröder et al, 2006) showed that one of the analogues, BXL-628, at nonhypercalcemic doses did not prevent bladder hypertrophy, but reduced the decrease in contractility of the bladder smooth muscle that occurred with increasing bladder weight (Schröder et al, 2006). The mechanism of action for the effects has not been clarified. However, elocalcitol was shown to have an inhibitory effect on the RhoA/Rho-kinase pathway (Morelli et al, 2007). Upregulation of this pathway has been associated with bladder changes associated with diabetes, outflow obstruction, and DO (Peters et al, 2006; Christ and Andersson, 2007). In rats with outflow obstruction, previous elocalcitol treatment improved the effects of tolterodine on bladder compliance (Streng et al, 2012). It was suggested that in rats, elocalcitol exerted additional beneficial actions on outflow obstruction-induced functional changes during the filling phase of micturition. If this finding is valid in humans, combined therapy with the drug would be of value.

The effect of elocalcitol on prostate volume was evaluated in patients with BPH, and it was found that elocalcitol was able to arrest prostate growth within 12 weeks in men aged 50 years or older with prostatic volume of 40 mL or greater (Colli et al, 2006). In an RCT enrolling 120 female patients with OAB in which the primary end point was an increase in the MVV, a significant increase versus placebo (22% vs. 11%) was demonstrated (Colli et al, 2007). The determination of whether or not vitamin D–receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of LUTS and OAB requires further RCTs. However, currently the development of the drug seems to be stopped (Tiwari, 2009).

Transient Receptor Potential Channel Antagonists. The TRP channel superfamily has been shown to be involved in nociception and mechanosensory transduction in various organ systems, and studies of the LUT have indicated that several TRP channels, including TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1, are expressed in the bladder and may act as sensors of stretch and/or chemical irritation (Araki et al, 2008; Everaerts et al, 2008; Andersson et al, 2010a; Araki, 2011). TRPV1 and TRPV4 channels have been found to be expressed in the urinary bladder (Tominaga et al, 1998; Birder et al, 2001; Gevaert et al, 2007). TRPV1 is present and active both in the urothelium and in the nerve fibers of several species including humans (Ji et al, 2002; Charrua et al, 2009b). TRPV4 was initially described in the urothelium of rodents and humans (Janssen et al, 2011). Coexpression of the two receptors was observed in 20% of rat urothelial cells (Kullmann et al, 2009). Recent observations indicate, however, that TRPV4 may also be expressed in bladder afferents. In fact, about 30% of L6 dorsal root ganglia neurons that project to the urinary bladder coexpress TRPV1 and TRPV4 (Cao et al, 2009). The physiologic meaning of this observation is unclear.

TRPV1 KO mice have a normal or quasi-normal phenotype. In awake animals, the only change detected in TRPV1 KO mice was a smaller volume per void when compared with wild-type (WT) controls (Birder et al, 2001). In cystometries performed under

anesthesia, the TRPV1 KO mice phenotype seems also very benign. Some studies reported that these animals have totally normal cystometric traces (Charrua et al, 2007). However, other studies showed that TRPV1 KO mice develop a few nonvoiding contractions preceding the voiding contraction (Birder et al, 2001; Frias et al, 2012). Accordingly, TRPV1 antagonists (GRC-6211) did not show any relevant effect on bladder activity of intact rodents (Charrua et al, 2009a). In contrast with TRPV1 KO mice, the micturition phenotype of TRPV4 KO animals is clearly abnormal. TRPV4 KO mice are incontinent, most probably because of incomplete bladder emptying (Gevaert et al, 2007). Cystometric studies carried out under physiologic conditions revealed that TRPV4 KO mice have a marked increase in the intercontraction interval when compared with WT littermates (Birder et al, 2002; Gevaert et al, 2007). Likewise, TRPV4 antagonists (HC-067047) decreased the frequency of bladder contractions and increased the intercontraction interval (Everaerts et al, 2010). These observations indicated that TRPV4 has a role in the control of the normal micturition reflex.

Indisputably, TRPV1 and TRPV4 have a role in the increase of micturition frequency associated with cystitis (Charrua et al, 2007; Everaerts et al, 2010). Whereas inflamed WT mice exhibit bladder hyperactivity and intense spinal Fos expression after different forms of bladder inflammation, including acetic acid or bacterial extracts, TRPV1 KO mice have normal cystometries and normal spinal c-Fos expression (Charrua et al, 2007). The same holds true for TRPV4. In fact, TRPV4 KO mice exhibit significantly lower voiding frequencies and larger voided volumes than WT after inflammation with cyclophosphamide (Everaerts et al, 2010).

The blockade of TRPV1 and TRPV4 with specific antagonist confirms the observations carried out in KO animals. As a matter of fact, the TRPV1 antagonist GRC-6211 and the TRPV4 antagonist HC-067047 both abolish the increase of micturition frequency associated with chemical cystitis (Charrua et al, 2009a; Everaerts et al, 2010). Systemic coadministration of TRPV1 and TRPV4 antagonist was more effective in treating the cystitis-induced increase of micturition frequency than the individual application of each antagonist (Avelino et al, 2013). In particular, the effect could be observed at very low doses of the TRPV1 and TRPV4 antagonists, which had no effect when given isolated. This observed effect might be the answer to overcome the eventual adverse events related to the application of some of these antagonists (Planells-Cases et al, 2011). Just to mention a few, TRPV1 antagonists are associated with hyperthermia and increased risk of cardiac ischemia (Avelino et al, 2013), and TRPV4 antagonists may eventually precipitate urinary retention and overflow incontinence (Gevaert et al, 2007).

It has long been known that TRPV1 is involved in the emergence of NDO after spinal cord transection (Avelino and Cruz, 2006). A TRPV1 antagonist, GRC-6211, has been shown to decrease reflex DO in rats after chronic spinal cord transection. With increasing doses, it was possible to obtain a total suppression of bladder activity (Santos-Silva et al, 2012).

There seem to be several links between activation of different members of the TRP superfamily and LUTS, DO, and OAB, and further exploration of the involvement of these channels in LUT function, normally and in dysfunction, may be rewarding. However, proof-of-concept studies in humans are still lacking.

Prostanoid-Receptor Agonists and Antagonists. Developments in the field of prostanoid receptors may open new possibilities for use of selective prostanoid-receptor antagonists for OAB and DO treatment (Aoki et al, 2009; Jones et al, 2009). There is evidence suggesting that PGE₂ contributes to the pathophysiology of OAB and DO: PGE₂ infused into the bladder induces DO in humans and animals and increases PGE₂ production in DO models, and there are high concentrations of PGE₂ in the urine of patients with OAB (McCafferty et al, 2008). PGE₂ is an agonist at EP receptors 1 to 4, all G protein coupled, which mediate its physiologic effects. Based on studies using KO mice and EP₁-receptor antagonists, it was suggested that the effects of PGE₂ on bladder function were mediated through EP₁ receptors (Schröder et al, 2004). EP receptors can be found on urothelium/suburothelium, in detrusor smooth muscle, and in intramural ganglia (Wang et al, 2008; Rahnama'i et al, 2010,

2011). Functionally, it has been proposed that modulation of bladder activity exerted via EP₁ receptors occurs via an afferent mechanism. Schröder and colleagues (2004) found no difference in urodynamic parameters between unobstructed EP₁ receptor KO and WT mice. However, EP₁ receptor KO mice did not respond to intravesical PGE₂ instillation, whereas WT mice developed DO. The lack of EP₁ receptor did not prevent bladder hypertrophy caused by partial bladder outflow obstruction, but after obstruction WT mice had pronounced DO, whereas this was negligible in EP₁ receptor KO mice.

Lee and colleagues (2008b) found that in normal rats a selective EP-receptor antagonist significantly increased bladder capacity, micturition volume, and micturition intervals. The antagonist significantly decreased the stimulatory effects of PGE₂ and decreased the frequency and amplitude of nonvoiding contractions in animals with BOO. It has also been shown that EP₃ receptor KO mice have a diminished response to bladder infusion of PGE₂ and demonstrate an enhanced bladder capacity under basal conditions (Jones et al, 2009). These findings suggest an important contribution for EP₃ receptors in the modulation of bladder function under physiologic conditions as well as under conditions of enhanced PGE₂ production evoking DO. Thus, EP₁ and EP₃ receptors may have a role in PGE₂-mediated DO.

It is interesting to note that activation of EP₃ receptors evoked diuresis and that EP₃-receptor antagonism was found to induce an antidiuretic effect (Jugus et al, 2009). Thus, to modulate bladder activity, it appears that the EP₃ receptor has a role in regulating urine production. Both effects may be useful for treatment of OAB and DO. It cannot be denied that EP₁ and EP₃ receptors constitute interesting and promising targets for drugs aimed at OAB and DO treatment. However, a randomized, double-blind, placebo-controlled phase II study to investigate the efficacy and safety of the EP₁-receptor antagonist ONO-8539 in patients with the OAB syndrome suggests that the role of EP₁-receptor antagonism in the management of the OAB syndrome is minimal (Chapple et al, 2014a).

Intraprostatically Injected Drugs

NX-1207. NX-1207 is a new drug under investigation for the treatment of LUTS associated with BPH. It is a new therapeutic protein of proprietary composition with selective proapoptotic properties (Shore, 2010). The drug is injected directly into the transitional zone of the prostate as a single administration to induce focal cell loss in prostate tissue through apoptosis, leading to nonregressive prostate shrinkage and both short- and long-term symptomatic improvement. Information about the drug is scarce and mostly published in abstract form and not yet in the peer-reviewed literature. Two U.S. phase II trials have been performed (Shore, 2010). One of them was a multicenter, randomized, noninferiority study involving 32 clinical sites with 85 patients and two dose ranges (2.5 and 0.125 mg) and an active open-label comparator (finasteride). Patients and investigators on NX-1207 were double-blind as to dose. The primary end point was change in American Urological Association (AUA) Symptom Index score at 90 and 180 days for a single injection of NX-1207 as compared with finasteride on a noninferiority basis. Inclusion criteria included an AUA symptom score of 15 or higher, diminished peak urine flow (<15 mL/sec), and a prostate size of 30 to 70 mg. The mean AUA symptom score improvement after 90 days in the intent-to-treat group was 9.71 points for 2.5-mg NX-1207 (n = 48) versus 4.13 points for finasteride (n = 24) (*P* = .001) and 4.29 for 0.125-mg NX-1207 (n = 7) (*P* = .034). The 180-day results also were positive (NX-1207 2.5 mg noninferior to open-label finasteride).

No significant changes in serum testosterone or serum prostate-specific antigen (PSA) levels were noted in the NX-1207 cohorts. There were no reported adverse effects on sexual function. Two U.S. multicenter, double-blind, placebo-controlled phase III studies are currently underway. The results of such studies are needed to assess whether or not this therapeutic principle is a useful addition to the current treatment alternatives.

PRX302. PRX302 is a modified form of proaerolysin, a highly toxic bacterial pore-forming protoxin that requires proteolytic processing by PSA (Singh et al, 2007). The safety and efficacy of PRX302 was

evaluated in men with moderate-to-severe BPH (Denmeade et al, 2011). The patients were refractory, intolerant, or unwilling to undergo medical therapies for BPH and had an IPSS higher than 12, a QoL score higher than 3, and prostate volumes of 30 to 80 g. Fifteen patients were enrolled in phase I studies, and 18 patients entered phase II studies. Patients received intraprostatic injection of PRX302 into the right and left transition zone via a transperineal approach in an office-based setting. Phase I subjects received increasing concentrations of PRX302 at a fixed volume; phase II subjects received increasing volumes per deposit at a fixed concentration. IPSS, QoL, prostate volume, Qmax, IIEF score, serum PSA levels, pharmacokinetics, and adverse events were recorded at 30, 60, 90, 180, 270, and 360 days after treatment. Sixty percent of men in the phase I study and 64% of men in the phase II study treated with PRX302 had greater than 30% improvement compared with baseline in IPSS out to day 360. Patients also experienced improvement in QoL and reduction in prostate volume out to day 360. Patients receiving more than 1 mL of PRX302 per deposit had the best response overall. There were no deleterious effects on erectile function. Adverse events were mild to moderate and transient in nature. The major study limitation was the small sample size.

Elhilali and colleagues (2013) conducted a phase IIb double-blind safety and efficacy evaluation of intraprostatic injection of PRX302 in 92 patients with IPSS of 15 or greater, peak urine flow of 12 mL/sec or less, and prostate volume of 30 to 100 mL. The patients were randomized 2:1 to a single ultrasound-guided intraprostatic injection of PRX302 versus vehicle (placebo). It was concluded that PRX302 produced clinically meaningful and statistically significant improvement in patient subjective (IPSS) and quantitative objective (peak urine flow) measures sustained for 12 months.

Cannabinoids. There is increasing evidence that cannabinoids can influence micturition in animals as well as in humans, both normally and in bladder dysfunction (Ruggieri, 2011). The effects of the cannabinoids are exerted via two types of well defined receptors, CB₁ and CB₂, distributed widely in the body. However, additional receptor subtypes cannot be excluded (Pertwee et al, 2010; Ruggieri, 2011). Both in the CNS and in peripheral tissues, CB₁ and CB₂ receptors have been identified; centrally CB₁ and peripherally CB₂ receptors seem to be predominant (Pertwee et al, 2010; Ruggieri, 2011). CB₁ as well as CB₂ receptors have been identified in all layers of the human bladder (Merriam et al, 2008; Gratzke et al, 2009; Tyagi et al, 2009; Walczak et al, 2009); their expression in the urothelium was found to be significantly higher than in the detrusor, and the expression of CB₁ was higher than that of CB₂ (Tyagi et al, 2009). Gratzke and colleagues (2009) found higher expression of CB₂ receptors, but not CB₁ receptors, in the mucosa than in the detrusor. Compared with the detrusor, larger amounts of CB₂ receptor-containing nerves that also expressed TRPV1 or CGRP were observed in the suburothelium. Nerve fibers containing CB₂ receptors and VACHT (cholinergic neurons) were located in the detrusor. In general, activation of CB₁ peripherally has been associated with vasodilation and motility changes via suppression of release of neurotransmitters, whereas activation of CB₂ appears to induce anti-inflammatory, antinociceptive, and immunosuppressive actions (Pertwee et al, 2010; Ruggieri, 2011). Several animal studies have suggested a modulatory role of CB₂ receptors in both afferent signaling and cholinergic nerve activity (Gratzke et al, 2009, 2010, 2011). Thus, in vivo the selective CB₂-receptor agonist, cannabimimetic, increased micturition intervals and volumes and increased threshold and flow pressures, suggesting that peripheral CB₂ receptors may be involved in sensory functions. In rats with partial urethral obstruction treated daily for 14 days with cannabimimetic, bladder weight was lower, the ability to empty the bladder was preserved, and nonvoiding contraction frequency was low compared with those in controls.

The key enzyme for the degradation of anandamide and other endogenous cannabinoids is fatty acid amide hydrolase (FAAH). FAAH was found to be expressed in rat and human urothelium and was coexpressed with CB₂ receptors. In rats, an FAAH inhibitor altered urodynamic parameters that reflect sensory functions, suggesting a role for the endocannabinoid system in bladder mechanosensory functions (Strittmatter et al, 2012).

It has not been established whether the effects of the cannabinoids are exerted in the CNS (brain, spinal cord) or peripherally. In a preliminary report, [Blyweert and colleagues \(2003\)](#) demonstrated an effect of combined CB₁/CB₂-receptor activation on DO in rats with spinal cord transection, which seemed to exclude the brain as a main site of action.

Clinical experiences with the cannabinoid treatment of micturition disturbances including LUTS are limited ([Ruggieri, 2011](#)), but both open-label and placebo-controlled studies have demonstrated that orally administered cannabinoid modulators may alleviate neurogenic OAB symptoms refractory to first-line treatment ([Brady et al, 2004b](#); [Freeman et al, 2006](#); [Kavia et al, 2010](#)). [Brady and colleagues \(2004b\)](#) evaluated the efficacy of two whole-plant extracts (Δ^9 -tetrahydrocannabinol and cannabidiol) of *Cannabis sativa* in patients with advanced MS and refractory LUTS. Urinary urgency, the number and volume of incontinence episodes, frequency, and nocturia decreased significantly after treatment. [Freeman and colleagues \(2006\)](#) tested in a subanalysis of a multicenter trial (the Cannabinoids in Multiple Sclerosis [CAMS] study) whether cannabinoids could decrease urge incontinence episodes without affecting voiding in patients with MS. The CAMS study randomized 630 patients to receive oral administration of the cannabis extract Δ^9 -tetrahydrocannabinol or matched placebo. Based on incontinence diaries, a significant decrease in incontinence episodes was demonstrated.

[Kavia and colleagues \(2010\)](#) assessed the efficacy, tolerability, and safety of Sativex (nabiximols) as an add-on therapy in alleviating bladder symptoms in patients with MS. They performed a 10-week, double-blind, randomized, placebo-controlled, parallel-group trial on 135 randomized subjects with MS and OAB. The primary end point, reduction in daily number of UI episodes from baseline to end of treatment (8 weeks), showed little difference between Sativex and placebo. However, four of seven secondary end points were significantly in favor of Sativex, including number of episodes of nocturia, number of voids per day, and number of daytime voids. The improvement in I-QoL was in favor of Sativex but did not reach statistical significance.

Systemic cannabinoids have effects on the LUT that may have therapeutic potential; local delivery (intravesical, spinal) may be possible, but more information is needed. The mechanisms of cannabinoid receptors in control of the human LUT are incompletely known, and further research is necessary for the development of novel cannabinoid drugs for treatment of LUT disorders.

Centrally Acting Drugs. Many parts of the brain seem to be activated during storage and voiding ([Griffiths, 2007](#); [Fowler et al, 2008](#); [Griffiths and Tadic, 2008](#); [Griffiths, 2011](#)), and there is increasing interest in drugs modulating the micturition reflex by a central action ([Andersson and Pehrson, 2003](#)). Several drugs used for pain treatment also affect micturition, morphine and some antiepileptic drugs being a few examples. However, central nervous mechanisms have so far not been preferred targets for drugs aimed to treat OAB, because selective actions may be difficult to achieve. [Holstege \(2005\)](#), reviewing some of the central mechanisms involved in micturition, including the periaqueductal gray (PAG) and the pontine micturition center (PMC), suggested that “the problem in OAB or urgency-incontinence is at the level of the PAG or PMC and their connections, and possible treatments for this condition should target the micturition pathways at that level.”

Gonadotropin-Releasing Hormone Antagonists. The beneficial effects of the 5 α -reductase inhibitors finasteride and dutasteride in the treatment of male LUTS are well documented. The efficacy of other hormonal treatments—for example, antiandrogens or gonadotropin-releasing hormone (GnRH; also known as luteinizing hormone-releasing hormone [LHRH]) agonists—is either poor or occurs at the expense of unacceptable side effects such as medical castration associated with hot flashes, decrease of potency and libido, and negative effects on bone density after long-term androgen ablation ([Schroeder et al, 1986](#); [Peters and Walsh, 1987](#); [Bosch et al, 1989](#); [Eri and Tveter, 1993](#)). With GnRH antagonists, submaximal noncastrating blockade of the androgen testosterone and consequently of dihydrotestosterone (DHT) can be achieved, thus

avoiding medical castration. Several GnRH antagonists, such as cetrorelix, ozarelix, and teverelix, have been tested in phase IIA/IIB clinical trials for their ability to improve LUTS in patients with BPH ([Colli and Tankó, 2010](#)).

[Debruyne and colleagues \(2008\)](#) demonstrated in a phase II RCT that the LHRH antagonist cetrorelix, given subcutaneously weekly for 20 weeks to 140 men with LUTS (IPSS ≥ 13 , peak urinary flow rates 5 to 13 mL/sec), rapidly caused a significant improvement in the mean IPSS. The peak decrease was -5.4 to -5.9 versus -2.8 for placebo. All dosage regimens tested were well tolerated, and the authors concluded that the drug offered a safe and effective treatment for male LUTS.

Because of these results, two phase III studies were conducted in the United States and Europe (\AA terna Zentaris); in the U.S. study, 637 men were randomized to receive either two doses of placebo or cetrorelix on weeks 2 and 26. The drug showed no statistically significant benefit in improving IPSS. In addition, cetrorelix did not have a significant effect on peak flow rate or prostate volume versus placebo. It is difficult to reconcile this lack of efficacy, given favorable prior results. A subsequent multicenter European trial also failed to show any treatment-related efficacy of cetrorelix. The experience with cetrorelix highlights the importance of randomized, placebo-controlled trials that are appropriately powered to show clinical benefit and safety.

Gabapentin. Gabapentin is one of the new first-generation antiepileptic drugs that expanded its use into a broad range of neurologic and psychiatric disorders ([Striano and Striano, 2008](#)). It was originally designed as an anticonvulsant GABA mimetic capable of crossing the blood-brain barrier ([Maneuf et al, 2003](#)). The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial ([Maneuf et al, 2003](#)). It has been suggested that it acts by binding to a subunit of the $\alpha_2\delta$ unit of voltage-dependent calcium channels ([Gee et al, 1996](#); [Striano and Striano, 2008](#)). Gabapentin is also widely used not only for seizures and neuropathic pain, but for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

[Carbone and colleagues \(2006\)](#) reported on the effect of gabapentin on NDO. They found a positive effect on symptoms and significant improvement in urodynamic parameters and suggested that the effects of the drug should be explored in further controlled studies in both NDO and non-neurogenic DO. [Kim and colleagues \(2004\)](#) studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinics. They found that 14 of 31 patients improved with oral gabapentin. The drug was generally well tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities have failed. It is possible that gabapentin and other α,δ ligands (e.g., pregabalin and analogues) will offer new therapeutic alternatives, but convincing RCTs are still lacking.

Tramadol. Tramadol is a well-known analgesic drug ([Grond and Sablotzski, 2004](#)). By itself, it is a weak μ -receptor agonist, but it is metabolized to several different compounds, some of them almost as effective as morphine at the μ receptor. However, the drug (metabolites) also inhibits serotonin (5-HT) and NA reuptake ([Grond and Sablotzski, 2004](#)). This profile is of particular interest, because both μ -receptor agonism and amine reuptake inhibition may be useful principles for treatment of LUTS, OAB, and DO, as shown in a placebo-controlled study with duloxetine ([Steers et al, 2007](#)).

In rats, tramadol abolished experimentally induced DO caused by cerebral infarction ([Pehrson and Andersson, 2003](#)). Tramadol also inhibited DO induced by apomorphine in rats ([Pehrson and Andersson, 2003](#))—a crude model of bladder dysfunction in Parkinson disease. [Singh and colleagues \(2008\)](#) gave tramadol epidurally and found the drug to increase bladder capacity and compliance and to delay filling sensations without adverse effects on voiding. [Safarinejad and Hosseini \(2006\)](#) evaluated in a double-blind, placebo-controlled, randomized study the efficacy and safety of tramadol in patients with IDO. A total of 76 patients 18 years or older were given 100 mg of tramadol SR every 12 hours for 12

weeks. Clinical evaluation was performed at baseline and every 2 weeks during treatment. Tramadol significantly ($P < .01$) reduced the number of incontinence periods per 24 hours from 3.2 ± 3.3 to 1.6 ± 2.8) and induced improvements in urodynamic parameters. The main adverse event was nausea. It was concluded that in patients with non-neurogenic DO, tramadol provided beneficial clinical and urodynamic effects. Even if tramadol may not be the most suitable drug for treatment of LUTS and OAB, the study suggests efficacy for modulation of micturition via the μ receptor.

NK1-Receptor Antagonists. The main endogenous tachykinins—SP, neurokinin A (NKA), and neurokinin B (NKB)—and their preferred receptors—NK₁, NK₂, and NK₃, respectively—have been demonstrated in various CNS regions, including those involved in micturition control (Lecci and Maggi, 2001; Covenas et al, 2003; Saffroy et al, 2003). NK₁ receptor-expressing neurons in the dorsal horn of the spinal cord may play an important role in DO, and tachykinin involvement via NK₁ receptors in the micturition reflex induced by bladder filling has been demonstrated (Ishizuka et al, 1994) in normal rats and, more clearly, rats with bladder hypertrophy secondary to BOO. Capsaicin-induced DO was reduced by blocking NK₁ receptor-expressing neurons in the spinal cord, using intrathecally administered SP-saponin conjugate (Seki et al, 2005). Furthermore, blockade of spinal NK₁ receptor could suppress detrusor activity induced by dopamine receptor (L-dopa) stimulation (Ishizuka et al, 1995).

In conscious rats undergoing continuous cystometry, antagonists of both NK₁ and NK₂ receptors inhibited micturition, decreasing micturition pressure and increasing bladder capacity at low doses and inducing dribbling incontinence at high doses. This was most conspicuous in animals with outflow obstruction (Gu et al, 2004). Intracerebroventricular administration of NK₁- and NK₂-receptor antagonists to awake rats suppressed detrusor activity induced by dopamine receptor (L-dopa) stimulation (Ishizuka et al, 2000). Taken together, available information suggests that spinal and supraspinal NK₁ and NK₂ receptors may be involved in micturition control.

Aprepitant, an NK₁-receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting (Massaro and Lenz, 2005), significantly improved symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence (with predominantly UII), as shown in a well-designed pilot RCT (Green et al, 2006). The primary end point was percent change from baseline in average daily micturitions assessed by a voiding diary. Secondary end points included average daily total UI and urgency incontinence episodes and urgency episodes. Aprepitant significantly ($P < .003$) decreased the average daily number of micturitions (-1.3 ± 1.9) compared with placebo (-0.4 ± 1.7) at 8 weeks. The average daily number of urgency episodes was also significantly ($P < .047$) reduced ($-23.2 \pm 32\%$) compared with placebo ($-9.3 \pm 40\%$), and so were the average daily number of urgency incontinence and total UI episodes, although the difference was not statistically significant. In general, aprepitant was well

tolerated and the incidence of side effects, including dry mouth, was low.

Since this initial proof-of-concept study suggested that NK₁-receptor antagonism holds promise as a potential treatment approach for OAB symptoms, a randomized, double-blind, multicenter trial enrolled 557 adults with OAB (eight or more average daily micturitions and one or more daily urge incontinence episodes) (Frenkl et al, 2010). After a 1-week placebo run-in, the patients were randomized to treatment with 8 weeks of daily 0.25-, 1-, or 4-mg serlopitant; 4-mg tolterodine ER; or placebo. Patients kept 7-day voiding diaries. The primary end point was change from baseline in micturitions per day. Secondary end points included urgency, total incontinence, urge incontinence episodes, and incidence of dry mouth. Of the 557 patients randomized, 476 completed the trial and had valid efficacy data for analysis. Mean change from baseline in daily micturitions was significantly greater for 0.25-mg (-1.1) and 4-mg (-1.1) serlopitant and for tolterodine (-1.5) than for placebo (-0.5), but not for 1-mg serlopitant (-0.8). No serlopitant dose response was demonstrated. Tolterodine was numerically superior to all doses of serlopitant in mean micturitions per day and secondary end points. The incidence of dry mouth on serlopitant (3.3%) was comparable to that on placebo (4.6%) and lower than tolterodine (8.8%). Serlopitant was generally well tolerated.

NK₁-receptor antagonists may have a role in the treatment of OAB, but at least the compounds tested so far do not offer advantages in efficacy compared with tolterodine.

A different approach, modulation of neuropeptide release rather than NK-receptor blockade, was tested in a pilot study with cizolirtine, which is an SP and CGRP release modulator at the spinal cord level. The modulation of SP and CGRP is probably related to the increase in extracellular levels of NA and serotonin. Cizolirtine 200 and 400 mg were compared with placebo in 79 OAB patients. Although the decrease in key OAB symptoms was significantly higher in the active arms, adverse events were reported in 68% and 81% of the patients on cizolirtine 200 and 400 mg. More commonly reported side effects were gastrointestinal in nature, including dry mouth and dizziness (Martínez-García et al, 2009).

KEY POINTS: OVERACTIVE BLADDER MECHANISMS AND TARGETS

- There are a number of possibilities, mostly based on theoretic mechanisms of action and studies in experimental animals, for drugs to favorably affect the symptoms of OAB and NDO or IDO.
- These mechanisms, at both the central and the peripheral levels, are intriguing, but with the possible exception of drugs directed at prostate bulk or internal organization, none have achieved consistent clinical success.

Estrogens for Stress Urinary Incontinence. The role of estrogen in the treatment of SUI has been controversial despite a number of reported clinical trials (Hextall, 2000). Some have given promising results, but this may have been because they were small observational studies and not randomized, blinded, or controlled. The situation is further complicated by the fact that a number of different types of estrogen have been used with varying doses, routes of administration, and durations of treatment.

Fantl and colleagues (1996) treated 83 hypoestrogenic women with urodynamic stress incontinence and/or DO with CEEs 0.625 mg and medroxyprogesterone 10 mg cyclically for 3 months. Controls received placebo tablets. At the end of the study period the clinical and QoL variables had not changed significantly in either group. Jackson and colleagues (1996) treated 57 postmenopausal women with urodynamic stress or mixed incontinence with estradiol 2 mg or placebo daily for 6 months. There was no significant change in objective outcome measures, although both the active and placebo groups reported subjective benefit.

Two meta-analyses of early data have been performed. In the first, a report by the Hormones and Urogenital Therapy (HUT) Committee, the use of estrogens to treat all causes of incontinence in postmenopausal women was examined (Fantl et al, 1994). Of 166 articles identified, which were published in English from 1969 to 1992, only 6 were controlled trials and 17 were uncontrolled series. The results showed that there was a significant subjective improvement for all patients and those with urodynamic stress incontinence. However, assessment of the objective parameters revealed that there was no change in the volume of urine lost; maximum urethral closure pressure increased significantly, but this result was influenced by only one study showing a large effect.

In the second meta-analysis, Sultana and Walters (1990) reviewed 8 controlled and 14 uncontrolled prospective trials and included all types of estrogen treatment. They also found that estrogen therapy was not an efficacious treatment for SUI but may be useful for the often associated symptoms of urgency and frequency. Estrogen when given alone therefore does not appear to be an effective treatment for SUI.

Several studies have shown that estrogen may have a role in combination with other therapies—for example, α -adrenoceptor agonists. However, phenylpropanolamine (the most widely used α -adrenoceptor agonist in clinical practice) has now been restricted or banned by the FDA.

In a randomized trial, Ishiko and colleagues (2001) compared the effects of the combination of pelvic floor exercise (PFE) and estriol (1 mg/day) in 66 patients with postmenopausal SUI. Efficacy was evaluated every 3 months based on stress scores obtained from a questionnaire. They found a significant decrease in stress score in mild and moderate stress-incontinent patients in both groups 3 months after the start of therapy and concluded that combination therapy with estriol plus PFE was effective and could be used as first-line treatment for mild SUI. Unfortunately, this has not been reproduced in other clinical trials.

Thus, even before the more recently reported secondary analyses of HERS (Grady et al, 2001) and WHI (Hendrix et al, 2005), it was already recognized that estrogen therapy had little effect in the management of urodynamic stress incontinence (Al-Badr et al, 2003; Robinson and Cardozo, 2003).

α -Adrenoceptor agonists. Several drugs with agonistic effects on peripheral α -ARs have been used in the treatment of SUI. Relatively recently, a central role of NA has been discovered in increasing the excitability of urethral rhabdosphincter motoneurons in the rat analog of the Onuf nucleus, an effect caused at least in part by α_1 -AR-dependent depolarization. This could contribute to the mechanism by which NA reuptake inhibitors improve SUI (Yashiro et al, 2010). Ephedrine and norephedrine (phenylpropanolamine [PPA]) seem to have been the most widely used (Andersson and Wein, 2012). The original AHCPR guidelines (AHCPR, 1992) reported eight RCTs with PPA, 50 mg twice daily for SUI in women. Percent cures (all figures refer to percent effect in patients on drug minus percent effect in patients on placebo) were listed as 0% to

14%; percent reduction in continence as 19% to 60%; and percent side effects and percent dropouts as 5% to 33% and 0% to 4.3%, respectively. The most recent Cochrane review on the subject (Alhasso et al, 2005, reprinted virtually unchanged in 2008) assessed randomized or quasi-randomized controlled trials in adults with SUI that included an adrenergic agonist drug in at least one arm of the trial. There were no controlled studies reported on the use of such drugs in men. Twenty-two eligible trials were identified, 11 of which were crossover trials, which included 1099 women, 673 of whom received an adrenergic drug (PPA in 11, midrodrine in 2, norepinephrine in 3, clenbuterol in 3, terbutaline in 1, eskornade in 1, and RO 115-1240 in 1). The authors concluded that “there was weak evidence to suggest that use of an adrenergic agonist was better than placebo in reducing the number of pad changes and incontinence episodes, as well as improving subjective symptoms.” There was not enough evidence to evaluate the merits of an adrenergic agonist compared with estrogen, whether used alone or in combination. Regarding adverse events, the review reported similar numbers with adrenergic, placebo, or alternative drug treatment. Over 25% of subjects reported such effects, but when these consisted of effects resulting from adrenergic stimulation, they caused discontinuation in only 4% of the total.

Ephedrine and PPA lack selectivity for urethral α -ARs and can increase blood pressure and cause sleep disturbances, headache, tremor, and palpitations (Andersson and Wein, 2012). Kernan and colleagues (2000) reported the risk of hemorrhagic stroke to be 16 times higher in women younger than 50 years who had been taking PPA as an appetite suppressant (statistically significant) and 3 times higher in women who had been taking the drug for less than 24 hours as a cold remedy (not statistically significant). There was no increased risk in men. PPA has been removed from the market in the United States. It is still allowed as a treatment for SUI in a few countries. Numerous case reports of adverse reactions caused by ephedra alkaloids exist, and some (Bent et al, 2003) suggested that sale of these compounds as a dietary supplement be restricted or banned. In December 2003, the FDA decreed such a ban, a move which has survived legal appeal.

Midrodrine and methoxamine stimulate α_1 -ARs with some degree of selectivity. According to the RCTs available, the effectiveness of these drugs is moderate at best, and the clinical usefulness seems to be limited by adverse effects (Weil et al, 1998; Radley et al, 2001; Alhasso et al, 2003).

Attempts to develop agonists with relative selectivity for the human urethra continue. Musselman and colleagues (2004) reported on a phase II randomized crossover study with Ro 115-1240, a peripherally active selective $\alpha_{1A/1L}$ -AR partial agonist (Blue et al, 2004), in 37 women with mild-to-moderate SUI. A moderate, positive effect was demonstrated, but side effects have apparently curtailed further development of the drug. PF-3774076, a CNS-penetrating partial α_{1A} -AR agonist, increased peak urethral pressure in dogs and was selective with respect to α_{1B} and α_{1D} receptors, but HR and blood pressure changes caused significant concern (Conlon et al, 2009). Furuta and colleagues (2009) reported that the α_2 -AR can inhibit the release of glutamate presynaptically in the spinal cord and proposed that α_2 -AR antagonists would be useful as a treatment for SUI. This hypothesis awaits testing.

β -Adrenoceptor Agonists

Clenbuterol. β -AR stimulation is generally conceded to decrease urethral pressure (Andersson, 1993), but β_2 -AR agonists have been reported to increase the contractility of some fast-contracting striated muscle fibers and suppress that of slow-contracting fibers of others (Fellenius et al, 1980). Some β -AR agonists also stimulate skeletal muscle hypertrophy—in fast-twitch more than slow-twitch fibers (Kim and Sainz, 1992). Clenbuterol has been reported to potentiate the field stimulation-induced contraction in rabbit isolated periurethral muscle preparations, an action that is suppressed by propranolol and greater than that produced by isoproterenol (Kishimoto et al, 1991). These authors were the first to report an increase in urethral pressure with clinical use of clenbuterol and to speculate on its potential for the treatment of SUI. Yamanishi and colleagues (1994) reported an inotropic effect of clenbuterol and

terbutaline on the fatigued striated urethral sphincter of dogs, abolished by β -AR blockade.

Yasuda and colleagues (1993) described the results of a double-blind placebo-controlled trial with this agent in 165 women with SUI. Positive statistical significance was achieved for subjective evaluation of incontinence frequency, pad use per day, and overall global assessment. Pad weight decreased from 11.7 ± 17.9 g to 6.0 ± 12.3 g for drug and from 18.3 ± 29.0 g to 12.6 ± 24.7 g for placebo, raising questions about the comparability of the two groups. The "significant" increase in maximal urethral closure pressure (MUCP) was from 46.0 ± 18.2 cm H₂O to 49.3 ± 19.1 cm H₂O, versus a change of -1.5 cm H₂O in the placebo group. Fifty-six of 77 patients in the clenbuterol group reported some degree of improvement versus 48 of 88 in the placebo group. The positive effects were suggested to be a result of an action on urethral striated muscle and/or the pelvic floor muscles. Ishiko and colleagues (2000) investigated the effects of clenbuterol on 61 female patients with stress incontinence in a 12-week randomized study, comparing drug therapy and PFEs. The frequency and volume of stress incontinence and the patient's own impression were used as the basis for the assessment of efficacy. The improvement in incontinence was 76.9%, 52.6%, and 89.5% in the respective groups. In an open study, Noguchi and colleagues (1997) reported positive results with clenbuterol (20 mg bid for 1 month) in 9 of 14 patients with mild-to-moderate stress incontinence after radical prostatectomy (RP). Further well-designed RCTs investigating effects of clenbuterol are needed to adequately assess its potential as a treatment for stress incontinence.

β -Adrenoceptor Antagonists. The theoretic basis for the use of β -AR antagonists in the treatment of stress incontinence is that blockade of urethral β -ARs may enhance the effects of NA on urethral α -ARs. Propranolol has been reported to have beneficial effects in the treatment of stress incontinence (Gleason et al, 1974; Kaisary, 1984), but there are no RCTs supporting such an action. In the study by Gleason and colleagues (1974), the beneficial effects manifest only after 4 to 10 weeks of treatment, a phenomenon that is difficult to explain. Donker and Van der Sluis (1976) reported that β -blockade did not change urethral pressure profile in normal women. Although suggested as an alternative to α -AR agonists in patients with SUI and hypertension, these agents may have major potential cardiac and pulmonary side effects of their own, related to their therapeutic β -AR blockade.

Serotonin-Noradrenaline Uptake Inhibitors

Imipramine. Imipramine, among several other pharmacologic effects, has classically been reported to inhibit the reuptake of NA and serotonin in adrenergic nerve endings. In the urethra this could theoretically be expected to enhance the contractile effects of NA on urethral smooth muscle by both a peripheral and a central action. Gilja and colleagues (1984) reported in an open study on 30 women with stress incontinence that imipramine, 75 mg daily, produced subjective continence in 21 patients and increased mean MUCP from 34 to 48 mm Hg. A 35% cure rate was reported by pad test and, in an additional 25%, a 50% or more improvement. Lin and colleagues (1999) assessed the efficacy of imipramine (25 mg of imipramine three times a day for 3 months) as a treatment for genuine stress incontinence in 40 women with genuine stress incontinence. A 20-minute pad test, uroflowmetry, filling and voiding cystometry, and stress urethral pressure profile were performed before and after treatment. The efficacy of "successful treatment" was 60% (95% CI 11.8 to 75.2). There are no RCTs on the effects of imipramine on SUI. No subsequent published reports have appeared.

It is interesting to note that Gillman (2007) reported that clomipramine had far greater 5-HT reuptake inhibition than imipramine and roughly similar NA reuptake inhibition. Desipramine and reboxetine had greater NA reuptake inhibition (desipramine superior), with lesser effect than imipramine on 5-HT uptake (desipramine superior).

Duloxetine. Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor that has been shown to significantly increase sphincteric muscle activity during the filling

and storage phase of micturition in the cat acetic acid model of irritated bladder function (Thor and Katofiasc, 1995; Katofiasc et al, 2002). Bladder capacity was also increased in this model, with both effects mediated centrally through both motor efferent and sensory afferent modulation (Fraser et al, 2003). The sphincteric effects were reversed by α_1 -adrenergic antagonism (prazosin) and 5-HT₂ serotonergic antagonism (LY-53857), whereas the bladder effects were mediated by temporal prolongation of the actions of serotonin and norepinephrine in the synaptic cleft (Fraser et al, 2003). Duloxetine is lipophilic, well absorbed, and extensively metabolized (CYP2D6). Its plasma half-life is approximately 12 hours (Sharma et al, 2000).

Thor and colleagues (2007) described the mechanisms of action and the physiologic effects of duloxetine. 5-HT (serotonin) and NA terminals are dense in spinal areas associated with LUT functioning, especially around the pudendal nerve neurons in the Onuf nucleus. These are projections from separate areas in the brainstem. Glutamate is the primary excitatory neurotransmitter in the spinal cord, activating the pudendal neurons in the Onuf nucleus, causing contraction of the urethral rhabdosphincter. The rhabdosphincter innervation is proposed as distinct from that of the levator ani (Thor and de Groat, 2010). The responsiveness of the rhabdosphincter motor neurons to glutamate is modulated (facilitated) by 5-HT (through 5-HT₂ receptors) and NA (through α_1 -ARs). 5-HT and NA, however, only modulate, and, when micturition occurs, glutamate excitation and rhabdosphincter contraction cease. Excitatory effects on urethral sphincter activity are shared to a lesser extent by receptors for 5-HT_{1A} (indirect through a supraspinal stimulation), thyrotropin-releasing hormone vasopressin, *N*-methyl-D-aspartate (NMDA), and AMPA; inhibitory effects are similarly mediated by κ_2 opioid receptors, α_1 -ARs, and GABA-A, GABA-B, and glycine receptors (Thor and de Groat, 2010). Some CNS-penetrant selective 5-HT_{2C} agonists have been found to increase urethral muscle tone and inhibit micturition reflexes in animal models, and these are additional candidates for clinical development for the treatment of SUI (Brennan et al, 2009; Andrews et al, 2011).

Several RCTs have documented the effect of duloxetine in SUI (Norton et al, 2002; Dmochowski et al, 2003a; Millard and the Asia Pacific Tolterodine Study Group, 2004; Van Kerrebroeck et al, 2004). A Cochrane review of the effects of duloxetine for SUI in women is available; the last substantive amendment is listed as May 25, 2005 (Mariappan et al, 2005). Fifteen reports were deemed eligible for analysis, 9 primary studies and 6 additional reports related to 1 or 2 of the primary references. An additional analysis "performed under the auspices of the Cochrane Incontinence Group" was performed on just the 9 primary trials comparing duloxetine and placebo, and published separately (Mariappan et al, 2005). The results can be summarized as follows. Subjective "cure" in the duloxetine 80 mg daily (40 mg bid) group was higher than in the placebo group (10.8% vs. 7.7%, overall relative risk [RR] 1.42, 95% CI 1.02 to 1.98, $P = .04$). The estimated absolute size of effect was about 3 more patients cured for every 100 treated. Objective cure data, available from only 1 trial, showed no clear difference between drug and placebo. Duloxetine showed greater improvement in I-QoL (weighted mean difference for 80 mg 4.5, 95% CI 2.83 to 6.18, $P < .00001$). Adverse effects in 6 trials were analyzed. These were reported by 71% of drug subjects and 59% of those allocated to placebo. Nausea was the most common adverse event, with an incidence that ranged from 23% to 25%, and was the main reason for discontinuation. Other side effects reported were vomiting, constipation, dry mouth, fatigue, dizziness, and insomnia—overall RR was 1.30 (95% CI 1.23 to 1.37). Across these 6 trials, 17% in the drug group withdrew, as did 4% in the placebo arm. In the 2007 article, the authors conclude by saying that further research is needed regarding whether management policies incorporating duloxetine are clinically effective and cost-effective compared with other current minimally invasive and more invasive approaches in patients with varying severity of SUI, and that "longer term experience is now a priority to determine whether there is sustained efficacy during and after duloxetine use and to rule out complications."

Hurley and colleagues (2006) characterized the safety of duloxetine for treatment of SUI in women, using an integrated database

generated from four published placebo-controlled clinical trials. The database included 1913 women randomized to duloxetine (958) or placebo (955), examining adverse events, serious adverse events, vital signs, ECGs, and laboratory analytes. Adverse events occurring initially or worsening during the double-blind treatment period were considered treatment emergent. Differences between duloxetine-treated and placebo-treated groups were compared statistically. Common treatment-emergent adverse events included nausea (23.2%), dry mouth (13.4%), fatigue (12.7%), insomnia (12.6%), constipation (11.0%), headache (9.7%), dizziness (9.5%), somnolence (6.8%), and diarrhea (5.1%). Most treatment-emergent adverse events that emerged early were mild to moderate, rarely worsened, and resolved quickly. Overall, adverse event discontinuation rates were 20.5% for duloxetine and 3.9% for placebo ($P < .001$). Most discontinuations (83%) occurred within the first month of treatment. Serious adverse events were uncommon and did not differ between treatments. Statistically significant but clinically unimportant mean increases in HR (2.4 beats/min) and systolic and diastolic blood pressure (≤ 2 mm Hg) occurred. No arrhythmogenic potential was observed, and any rare, transient, asymptomatic increases in hepatocellular enzymes were normalized. The authors concluded that duloxetine was safe and tolerable, although transient adverse events were not uncommon. Hashim and Abrams (2006) suggested that to reduce the risk of nausea, treatment should begin with a dose of 20 mg twice daily for 2 weeks, which should then be increased to the recommended 40-mg bid dose.

Ghoneim and colleagues (2005) randomized women with SUI to one of four treatment combinations: duloxetine alone (40 mg bid), pelvic floor muscle training (PFMT), combination, and placebo. Overall, drug with or without PFMT was superior to PFMT alone or placebo, whereas pad results and QoL data favored combination therapy over single treatment. Cardozo and colleagues (2004a) reported that 20% of women awaiting continence surgery changed their minds while taking duloxetine. Duckett and colleagues (2006) offered a 4-week course to women awaiting a tension-free vaginal tape operation. Thirty-seven percent (of 73) declined. Excluding women for whom concomitant prolapse surgery was planned, 8 of 33 (24%) scheduled for incontinence surgery alone came off the list. Sixteen (48%) discontinued duloxetine because of adverse events, and 9 (27%) found the drug ineffective.

Bent and colleagues (2008) reported on the effects of 12 weeks of duloxetine (40 mg bid) versus placebo in a large group of women with mixed urinary incontinence (MUI). For SUI episodes, the mean IEF per week decreased 58.9% with drug (7.69 to 3.93) versus 43.3% for placebo (8.93 to 6.05). It is interesting to note that corresponding decreases for UUI episodes were 57.7% versus 39.6%. Both sets of values are statistically significant, but the baselines are different and the absolute change for SUI amounted to -3.76 episodes per week for drug and -2.87 for placebo. Nausea was reported by 18% of patients on drug and 4.5% on placebo. Corresponding percents for other adverse events included dry mouth (12 vs. 2.8), dizziness (9.7 vs. 2.4), constipation (8.3 vs. 4.2), and fatigue (6.7 vs. 2.8). Nausea and dizziness were less common in a subgroup taking concurrent antidepressants. Women 65 years and older with SUI or stress-predominant MUI (S-MUI) were given duloxetine (40 mg bid after a 2-week start on 20 mg bid) or placebo for 12 weeks by Schagen van Leeuwen and colleagues (2008). Their report concludes that "this study supports the use of duloxetine in elderly women with SUI or S-MUI." The data show an absolute change in SUI plus S-MUI episodes of -11.7 and -6.9 incontinence per week (drug and placebo) and median percent changes of -52.5% versus -36.7% from 24-hour diaries, both significant at $P < .001$. However, the changes for SUI alone were -53% versus -42% (nonsignificant), whereas for S-MUI alone they were -51.6% versus -32.7% ($P < .001$). Nausea was less than in other trials (7.5% vs. 3.1%), perhaps because of the lower starting dose. Other adverse events included fatigue (14.2% vs. 5.4%), constipation (10.4% vs. 0.8%), dizziness (9.0% vs. 4.6%), and excess sweating (5.2% vs. 0%).

Persistence on duloxetine was studied by Vella and colleagues (2008), who found that only 31% of an original cohort of 228 were

still taking drug beyond 4 weeks, 12% at 4 months, 10% at 6 months, and 9% at 1 year. Fifty-six percent of the discontinuations were attributed to side effects, and 33% to lack of efficacy. Bump and colleagues (2008), however, reported that the positive effects of duloxetine were maintained in patients who continued treatment up to 30 months, but admitted that this subgroup was likely to include predominantly patients who had favorable responses. The number decreased from 1424 in this cohort at 3 months to 368 at 30 months.

Shaban and colleagues (2010) concluded that duloxetine is "optional second line for women not willing or unfit for surgery after warning against side effects as recommended by NICE [National Institute for Health and Care Excellence] guidelines in the UK." Similar sentiments have been expressed by Robinson and Cardozo (2010).

Duloxetine is licensed at 40 mg twice daily for the treatment of SUI in the European Union in women with moderate-to-severe incontinence (defined as 15 or more episodes per week). It was withdrawn from the FDA consideration process in the United States for the treatment of SUI but is approved for the treatment of major depressive disorder (20 to 30 mg bid initially, 60 mg once daily for maintenance), diabetic peripheral neuropathic pain (60 mg once daily), generalized anxiety disorder (60 mg once daily), fibromyalgia (30 mg once daily initially, 60 mg once daily for maintenance), and chronic musculoskeletal pain (30 mg once daily initially, 60 mg once daily for maintenance). The product information contains a black box warning of "increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder and other psychiatric disorders," noting also that "depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide" (Cymbalta prescribing information, revised September 2011). Other warnings and precautions in the prescribing information for psychiatric indications, not SUI, include hepatotoxicity (not to be used in patients with substantial alcohol use or chronic liver disease); orthostatic hypotension; serotonin syndrome (general statement regarding SSRIs and SNRIs); abrupt discontinuation (may result in dizziness, paresthesias, irritability, and headache); inhibitors of CYP1A2 (such as ciprofloxacin) and thioridazine (do not administer concomitantly); and potent inhibitors of CYP2D6 (may increase concentration). Adverse events for 6801 drug- and 4487 placebo-treated patients reported in the prescribing information for Cymbalta (treatment for the indications mentioned) are nausea (24% vs. 8%), dry mouth (13% vs. 5%), fatigue (10% vs. 5%), somnolence (10% vs. 3%), insomnia (10% vs. 6%), constipation (10% vs. 4%), and dizziness (10% vs. 5%).

Stress Urinary Incontinence in Men

Although a problem of significant magnitude, especially after RP for cancer, the pharmacologic treatment of male SUI is an area that has received relatively little attention.

Intrinsic sphincter function is the most important outlet factor maintaining continence in men. Urethral support is less important, and there is no entity similar to the hypermobility phenomenon in women. The proximal urethral sphincter extends from the bladder neck through the prostatic urethra. Its function is removed by RP. The distal urethral sphincter includes the rhabdosphincter, urethral smooth muscle, and extrinsic paraurethral skeletal muscle, extending from the prostatic urethra below the verumontanum through the membranous urethra (Koelbl et al, 2009). Tsakiris and colleagues (2008) searched for articles on drug treatment of male SUI published from 1966 to June 2007 and did a generalized database search in addition. Nine trials were identified as using α -adrenergic agonists, β_2 antagonists, or SNRIs. Only one of these included a comparison arm (Filocamo et al, 2007), 40-mg bid duloxetine plus PFE versus PFE with placebo. The results suggested a positive effect of drug but were a bit confusing. Of patients completing the 4-month trial (92 of 112) 78% of the drug-treated patients versus 52% of those in the placebo group were "dry." However, 1 month after the end of the study, the corresponding figures were 46%

versus 73%, a shift still observed 2 months later. The authors of the review article recommended further larger and well-designed studies on duloxetine for this potential use.

Cornu and colleagues (2011) reported a series of post-RP men with SUI or S-MUI randomized to duloxetine (15) and placebo (16) after a 2-week placebo run-in. Dosage was 20 mg bid for 7 days, 40 mg bid for 67 days, and 20 mg for 14 days. Subjects were at least 1 year postsurgery. Outcome measures included percent decrease in IEF, 1-hour pad test, and various QoL measures. Statistical significance for IEF percent decrease occurred only at weeks 8 and 12 ($[-]52.2\% \pm 38.6\%$ vs. $[+]19\% \pm 43.5\%$), but there was clearly a trend at 4 weeks. There was no statistical difference in 1-hour pad test weights, but there was in various QoL scores. A 50% to 100% decrease in IEF was seen at 12 weeks in over half the patients. Adverse events for drug and placebo included fatigue (50% vs. 13%), insomnia (25% vs. 7%), libido loss (19% vs. 7%), constipation (13% vs. 7%), nausea (13% vs. 7%), diarrhea (13% vs. 7%), dry mouth (6% vs. 0%), anorexia (6% vs. 0%), and sweating (25% vs. 20%). Drawbacks and concerns are the small number (the original proposed sample size was 90) and the lack of any placebo effect on IEF and QoL. There were 4 men with MUI in the drug group and 5 in the placebo group. Results for SUI and UUI were not separated.

One would logically not expect improvement to continue after drug withdrawal unless a permanent change occurred in behavior, anatomy, or neuromuscular function. In another uncontrolled use study on men with post-RP SUI, Collado Serra and colleagues (2011) reported on 68 men whose median interval from surgery was 28.8 months. The reported results are somewhat confusing, but the overall impression is that some success was achieved. Treatment was intended to last for 9 months and restarted at 3 months if UI had worsened after cessation. The follow-up examinations were performed every 3 months, evaluating the symptoms, adverse effects, number of pads used daily, and International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form (ICIQ-IU-SF) results. At the end of the first follow-up period, 39 (57%) of 68 patients had reduced the number of pads used daily. The pads per day nadir was achieved at the second follow-up visit in 29 (43%) of 68 patients, in 3 (8%) of 37 at visit 3, and 2 (12%) of 17 at visit 4. Once the nadir of success with treatment had been reached, the efficiency of duloxetine was maintained in 84% of patients and worsened in 16% despite continuing treatment. In this study, 25% of patients withdrew because of adverse events and 33% because of lack of effect.

Usage of duloxetine for SUI in men is universally off-label. A drug for this indication would be welcome. Larger, controlled, and better-designed studies are necessary to provide conclusive positive or negative data on this subject.

PHARMACOLOGIC THERAPY TO FACILITATE BLADDER EMPTYING

Increasing Intravesical Pressure and Bladder Contractility

Parasympathomimetic Agents

Because a major portion of the final common pathway in physiologic bladder contraction is stimulation of parasympathetic postganglionic muscarinic cholinergic receptor sites, agents that imitate the actions of ACh might be expected to be effective in treating patients who cannot empty the bladder because of inadequate bladder contractility. ACh, which is a quaternary amine, cannot be used for therapeutic purposes because of its action at both muscarinic and nicotinic receptors; it is rapidly hydrolyzed by acetylcholinesterase and by butyrylcholinesterase (Brown and Taylor, 2006). Many ACh-like drugs exist, but only bethanechol chloride exhibits a relatively selective in vitro action on the urinary bladder and gut with little or no nicotinic action (Brown and Taylor, 2006). Bethanechol is cholinesterase resistant and causes an in vitro contraction of smooth muscle from all areas of the bladder (see Chapter 69).

KEY POINTS: DRUGS FOR STRESS URINARY INCONTINENCE

- Pharmacologic efforts to increase outlet resistance in men and women have focused on increasing urethral tone or contractile ability at a peripheral or central level.
- The role of estrogen in the treatment of SUI has been somewhat controversial; however, the majority opinion seems to be that estrogen when given alone does not appear to be an effective treatment for SUI in the woman.
- The use of peripheral α -adrenergic agonists has largely been abandoned because of the adverse effects associated with these agents and the weak evidence of efficacy compared with placebo.
- Paradoxically, there are theoretic rationales for using both β -AR agonists and antagonists for treatment of SUI, but there are few data suggesting significant efficacy over control, and further well-designed randomized clinical trials are necessary.
- Duloxetine is a combined norepinephrine and serotonin reuptake inhibitor that increased sphincteric activity in an animal experimental model during the filling and storage phase of micturition. This compound has been widely tried in a variety of situations and using a variety of parameters. Some trials suggest statistical efficacy, more so in subjective data than objective data, and further research is needed regarding whether management policies incorporating this compound are clinically effective and cost-effective compared with other current approaches in women with varying degrees of SUI. Currently, duloxetine is licensed in the European Union for women with moderate to severe stress incontinence. It is approved in the United States for treatment of a variety of disorders, but was withdrawn from the approval process for the treatment of SUI.
- Effective pharmacologic management of SUI in men would be a welcome addition to the armamentarium, but this has received relatively little attention. There are a few clinical trials with interesting experimental designs and results, and it is obvious that larger, controlled, and better-designed studies are necessary to provide conclusive positive or negative data. The use of duloxetine for SUI in men is universally off-label.

Bethanechol, or agents similar to it, has historically been recommended for the treatment of postoperative or postpartum urinary retention, but only if the patient is awake and alert and if there is no outlet obstruction. The recommended dose has been 5 to 10 mg subcutaneously. For over 50 years, bethanechol has been recommended for the treatment of the atonic or hypotonic bladder and has been reported as effective in achieving "rehabilitation" of the chronically atonic or hypotonic detrusor (Sonda et al, 1979). Bethanechol has also been reported to stimulate or facilitate the development of reflex bladder contractions in patients in spinal shock secondary to suprasacral SCI (Perkash, 1975).

Although bethanechol has been reported to increase gastrointestinal motility and has been used in the treatment of gastroesophageal reflux, and although anecdotal success in specific patients with voiding dysfunction seems to occur, there was little or no evidence to support its success in facilitating bladder emptying in a series of patients in whom the drug was the only variable (Finkbeiner, 1985; Barendrecht et al, 2007). In one set of trials, a pharmacologically active subcutaneous dose (5 mg) did not demonstrate significant changes in flow parameters or residual urine volume in (1) a group of women with a residual urine volume greater than or equal to 20% of bladder capacity but no evidence of neurologic disease or outlet obstruction; (2) a group of 27 "normal" women of approximately the same age; or (3) a group of patients with a positive bethanechol supersensitivity test (Wein et al, 1980a, 1980b). This dose did increase cystometric filling pressure and also decreased

bladder capacity threshold, findings previously described by others (Sonda et al, 1979). Short-term studies in which the drug was the only variable have usually failed to demonstrate significant efficacy in terms of flow and residual urine volume data (Barrett, 1981). Farrell and colleagues (1990) conducted a double-blind randomized trial that looked at the effects of two catheter-management protocols and the effect of bethanechol on postoperative retention after gynecologic incontinence surgery. They concluded that bethanechol was not helpful at all in this setting. Although bethanechol is capable of eliciting an increase in bladder smooth muscle tension, as would be expected from *in vitro* studies, its ability to stimulate or facilitate a coordinated and sustained physiologic-like bladder contraction in patients with voiding dysfunction has been unimpressive (Finkbeiner, 1985; Andersson, 1988).

It is difficult to find reproducible urodynamic data that support recommendations for the use of bethanechol in any specific category of patients. Most, if not all, "long-term" reports in such patients are neither prospective nor double-blind and do not exclude the effects of other simultaneous regimens (such as treatment of urinary infection, bladder decompression, timed emptying, or other types of treatment affecting the bladder or outlet), an important observation to consider when reporting such drug studies. Whether repeated doses of bethanechol or any cholinergic agonist can achieve a clinical effect that a single dose cannot is speculative, as are suggestions that bethanechol has a different mode of action or effect on atonic or decompensated bladder muscle than on normal tissue.

Bethanechol administered subcutaneously does cause an increased awareness of a distended bladder and presumably the desire to void (Downie, 1984). This could facilitate more frequent emptying at lower volumes and thereby help to avoid overdistention, but, it would seem, only in a bladder that is capable of a contraction. O'Donnell and Hawkins (1993) administered 5 mg of bethanechol subcutaneously to 10 neurologically intact men and made the following cystometric observations: Bladder volume at first desire to void decreased (220 mL to 85 mL), maximal bladder capacity decreased (380 mL to 160 mL), first desire to void occurred at a higher pressure (5 cm H₂O vs. 28 cm H₂O), and compliance was reduced. They concluded that bethanechol affects the ability of the bladder to accommodate volume. Patients were comfortable at a resting bladder pressure of 20 cm H₂O (uncommon in their population), and the pressures at maximal bladder capacity were considerably higher than commonly seen under normal conditions. This suggested to them that either bladder pressure alone is not a significant factor in the perception of a sensation of first desire to void or that bethanechol somehow alters the threshold at which perception of desire to void occurs (because these patients showed a tolerance for increased intravesical pressure before first desire to void and at maximal bladder capacity). De Wachter and Wyndaele (2001) determined the bladder electrical threshold in healthy volunteers receiving 5 mg bethanechol subcutaneously. They found a marked decrease in the volume at which various filling sensations occurred and that the electrical threshold decreased after drug administration. De Wachter and colleagues (2003) treated 18 women with impaired detrusor contraction with subcutaneous bethanechol (5 mg four times daily) for 10 days. At the end of treatment 61% of the patients voided without a PVR volume. They also found that in these women the sensation of filling and the electrical sensitivity were significantly increased compared with before treatment. The authors suggested that patients likely to respond to bethanechol can be identified by determination of the bladder electrical perception threshold.

Riedl and colleagues (2000) performed a clinical study in 45 patients with detrusor areflexia. The patients were tested with electromotive administration of intravesical bethanechol. Bethanechol 25 mg given orally once daily was then prescribed for 15 patients, and voiding control was assessed after 6 weeks of therapy. A mean pressure increase of 34 cm H₂O during the electromotive administration of bethanechol was found in 24 of 26 patients with areflexia and neurologic disease compared with only 3 cm H₂O in 3 of 11 with a history of chronic bladder dilation. Oral bethanechol restored

spontaneous voiding in 9 of 11 patients who had had a positive response to the electromotive administration of bethanechol, whereas all 4 without a pressure increase during the electromotive administration of bethanechol did not void spontaneously. The researchers concluded that electromotive administration of intravesical bethanechol can identify patients with an atonic bladder and adequate residual detrusor muscle function who are candidates for restorative measures, such as oral bethanechol and intravesical electrostimulation. Those who do not respond to the electromotive administration of bethanechol do not benefit from oral bethanechol and are candidates for catheterization.

No agreement exists as to whether cholinergic stimulation produces an increase in urethral resistance (Wein et al, 1980a, 1980b). It would appear that pharmacologically active doses, in fact, do increase urethral closure pressure, at least in patients with NDO (Sporer et al, 1978). This would of course tend to inhibit bladder emptying. As to whether cholinergic agonists can be combined with agents to decrease outlet resistance to facilitate emptying and achieve an additive or synergistic effect, our own experience with such therapy, using even 200 mg (50 mg qid) of oral bethanechol daily, has been disappointing. Certainly, most clinicians would agree that a total divided daily dose of 50 to 100 mg rarely affects any urodynamic parameter at all. In a prospective, single-blind randomized study consisting of 119 patients with underactive detrusor, Yamanishi and colleagues (2004) studied the effect of combination of a cholinergic drug (bethanechol 60 mg daily or distigmine 15 mg daily) and an α -AR antagonist (urapidil 60 mg daily). The effectiveness of each therapy was assessed 4 weeks after initialization of the therapy using IPSS. IPSS remained unchanged after the cholinergic therapy, but was significantly lower after the α -AR antagonist treatment and the combination therapy. With regard to the total IPSS, there were significant differences between the cholinergic and the α -AR antagonist groups, and also between the cholinergic and combination groups, in favor of the latter. The average and maximum flow rates did not increase significantly after monotherapy with either the cholinergic drug or the α -AR antagonist, but they significantly increased after combination therapy compared with baseline values. PVR volume did not decrease significantly after the cholinergic drug therapy but decreased significantly after the α -AR antagonist and the combination therapies. The authors concluded that combination therapy with a cholinergic drug and an α -AR antagonist appeared to be more useful than monotherapy for the treatment of underactive detrusor.

The question of whether bethanechol may be efficacious in a particular patient can be answered by a brief uroynamically controlled trial in which institution of therapy is the only variable. In the laboratory, a functioning micturition reflex is an absolute requirement for the production of a sustained bladder contraction by a subcutaneous injection of the drug (Downie, 1984). Patients with incomplete lower motoneuron lesions constitute the most reasonable group for a trial of bethanechol (Awad, 1985), although subcutaneous administration may be required. It is generally agreed that, at least in a "denervated" bladder, an oral dose of 200 mg is required to produce the same urodynamic effects as a subcutaneous dose of 5 mg (Diokno and Lapidus, 1977).

The potential side effects of cholinomimetic drugs include flushing, nausea, vomiting, diarrhea, gastrointestinal cramps, bronchospasm, headache, salivation, sweating, and difficulty with visual accommodation (Brown and Taylor, 2006). Intramuscular and intravenous use can precipitate acute and severe side effects, resulting in acute circulatory failure and cardiac arrest, and are therefore prohibited. Contraindications to the use of this general category of drug include bronchial asthma, peptic ulcer, bowel obstruction, enteritis, recent gastrointestinal surgery, cardiac arrhythmia, hyperthyroidism, and any type of BOO.

One potential avenue of increasing bladder contractility is cholinergic enhancement or augmentation. Such an action might be useful alone or in combination with a parasympathomimetic agent. Metoclopramide is a dopamine-receptor antagonist with cholinergic properties (Pasricha et al, 2006). It has a central antiemetic effect

in the chemoreceptor trigger zone and peripherally increases the tone of the lower esophageal sphincter, promoting gastric emptying. Its effects seem to be related to its ability to antagonize the inhibitory action of dopamine, to augment ACh release, and to sensitize the muscarinic receptors of gastrointestinal smooth muscle. Some data from dogs suggest that this agent can increase detrusor contractility (Mitchell and Venable, 1985), but there are no controlled studies documenting a useful clinical effect in the treatment of detrusor underactivity.

Cisapride is a substituted piperidinyl benzamide with a number of different pharmacologic activities, including a possible direct stimulation of smooth muscle (Pasricha, 2006). Until recently it was commonly used as a prokinetic agent, particularly for gastroesophageal reflux and gastroparesis. It was also suggested that it could improve bladder contractility (Binnie et al, 1988; Carone et al, 1993; Steele et al, 2001). However, there was never any particularly convincing data that the drug improved voiding function, and it is no longer available in the United States because of its potential to induce serious and occasional cardiac arrhythmias (Pasricha, 2006). The concept, however, of cholinergic enhancement or augmentation remains attractive but awaits the development of a bladder-selective compound.

Prostaglandins

The reported use of prostaglandins to facilitate emptying is based on hypotheses that these substances contribute to the maintenance of bladder tone and bladder contractile activity (see Chapter 69 and Andersson, 1993; Zderic et al, 1995; Andersson, 1999a, 1999b, 1999c; Andersson and Wein, 2004 for a complete discussion). Prostaglandins and thromboxane A_2 (TXA_2) have been shown to be present in human bladder in the following quantitative order: $PGE_2 > PGE_1 > PGF_{2\alpha} > TXA_2$; isolated detrusor muscle is contracted by $PGF_{2\alpha}$, PGE_1 , PGE_2 , and TXA_2 (see references in Andersson and Wein, 2004). Prostanoids are synthesized locally in both bladder muscle and mucosa, with synthesis being initiated by various physiologic stimuli such as detrusor muscle stretch, mucosal injury, neural stimulation; by ATP; and by mediators of inflammation (Andersson and Wein, 2004). Prostanoids may affect bladder activity directly by effects on the smooth muscle or indirectly through effects on neurotransmission. Possible roles mentioned by Andersson (2000b) include (1) neuromodulators of efferent and afferent neurotransmission; (2) sensitization or perhaps (3) activation of certain sensory nerves; and (4) potentiation of ACh release from cholinergic nerve terminals through prejunctional prostanoid receptors. PGE_2 seems to cause a net decrease in urethral smooth muscle tone; $PGF_{2\alpha}$ causes an increase.

Bultitude and colleagues (1976) first reported that instillation of 0.5 mg of PGE_2 into the bladders of female patients with varying degrees of urinary retention resulted in acute emptying and in improvement of longer-term emptying (several months) in two thirds of the patients studied ($N = 22$). Desmond and colleagues (1980) reported results with intravesical use of 1.5 mg of this agent (diluted with 20 mL of 0.2% neomycin solution) in patients whose bladders exhibited no contractile activity or in whom bladder contractility was relatively impaired. Twenty of 36 patients showed a strongly positive immediate response, and 6 showed a weakly positive one. Fourteen patients were reported to show prolonged beneficial effects, all but 1 of whom had shown a strongly positive immediate response. Stratification of the data revealed that an intact sacral reflex arc was a prerequisite for any type of positive response. Tammela and colleagues (1987) reported that one intravesical administration of 10 mg of $PGF_{2\alpha}$ facilitated voiding in women who were in retention 3 days after surgery for SUI. The drug was administered in 50 mL of saline solution as a single dose and retained for 2 hours. However, in these "successfully" treated patients, the average maximum flow rate was 10.6 mL/sec with a mean residual urine volume of 107 mL, and the authors stated that "bladder emptying deteriorated in most patients on the day after treatment." Koonings and colleagues (1990) reported that daily intravesical

$PGF_{2\alpha}$ and intravaginal PGE_2 reduced the number of days required for catheterization after stress incontinence surgery when compared with a control group receiving intravesical saline solution.

Others, however, have reported negative results. Grignaffini and Bazzani (1998) reported on instillation of 1.5 mg of PGE_2 in 50 mL of saline solution into the bladder of 50 patients on their fourth day after vaginal hysterectomy and cystourethropepy, with a control group of 60 patients. The results are presented in an interesting fashion. After catheter removal, following the PGE_2 or control treatment, 58% of the PGE_2 -treated group voided spontaneously as compared with 48.3% of the control group. This difference was not significant. Thus 42% of the treated group and 51.7% of the control group were in retention. Of those who were in retention, the number who were in retention for less than 3 days was greater in the PGE_2 group (32%) versus the control group (25%), and this was statistically significant. Likewise, the number who remained in urinary retention for 3 days or longer after the initial treatment was 10% in the PGE_2 -treated group versus 26.7% in the control group. Stanton and colleagues (1979) and Delaere and colleagues (1981) reported on success using intravesical PGE_2 in doses similar to those reported earlier; Delaere and colleagues (1981) similarly reported no success using $PGF_{2\alpha}$ in a group of women with emptying difficulties of various causes. Wagner and colleagues (1985) used PGE_2 in doses of 0.75 to 2.25 mg and reported no effect on urinary retention in a group of patients after anterior colporrhaphy.

In a prospective randomized double-blind study, Hindley and colleagues (2004) tested the hypothesis that the combination of intravesical PGE_2 and oral bethanechol is additive or synergistic in improving bladder emptying. Nineteen patients with detrusor underactivity (17 men and 2 women) were eligible and randomized to one of two treatments. One group (9 patients) received once-weekly intravesical PGE_2 (1.5 mg in 20 mL of 0.9% saline) plus bethanechol 50 mg four times daily, for a total of 6 weeks. A second group of 10 patients received a once-weekly instillation of saline together with placebo tablets, again for 6 weeks. Although there was evidence of a pharmacologic effect, bethanechol and PGE_2 had a limited therapeutic effect compared with placebo. The authors did not recommend this treatment as routine but suggested that it may be considered for the occasional treatment of a patient with detrusor underactivity.

There has been little recent activity in this area, a fact that usually means that clinicians have lost interest or that the initial optimistic results have not been confirmed. Prostaglandins have a relatively short half-life, and it is difficult to understand how any effects after a single application can last up to several months. If such does occur, it must be the result of a "triggering effect" on some as yet unknown physiologic or metabolic mechanism. Because of the number of conflicting positive and negative reports with various intravesical preparations, double-blind, placebo-controlled studies would obviously be helpful to see whether there are circumstances in which prostaglandin use can reproducibly facilitate emptying or treat postoperative retention. Potential systemic side effects of prostaglandin use include vomiting, diarrhea, pyrexia, hypertension, and hypotension (Campbell and Halushka, 1996).

Blockers of Inhibition

de Groat and coworkers (see Chapter 69; de Groat et al, 1993, 1999; Zderic et al, 1995; de Groat, 1997) have demonstrated a sympathetic reflex during bladder filling that, at least in the cat, promotes urine storage partly by exerting an α -AR-mediated inhibitory effect on pelvic parasympathetic ganglionic transmission. Some have suggested that α -AR blockade, in addition to decreasing outlet resistance, may in fact facilitate transmission through these ganglia and thereby enhance bladder contractility. On this basis, Raz and Smith (1976) were the first to advocate a trial of an α -AR blocking agent for the treatment of nonobstructive urinary retention. A complete discussion of postoperative retention, including the use of α -AR antagonists for its treatment, is presented elsewhere (see Chapter 65).

Opioid-Receptor Antagonists

Endogenous opioids have been hypothesized to exert a tonic inhibitory effect on the micturition reflex at various levels (see Chapter 69; Zderic et al, 1995), and agents such as opioid-receptor antagonists therefore may offer possibilities for stimulating reflex bladder activity.

Thor and associates (1983) were able to stimulate a micturition contraction with naloxone, an opioid-receptor antagonist, in unanesthetized cats with chronic SCI. The effects, however, were transient, and tachyphylaxis developed. Vaidyanathan and colleagues (1981) reported that an intravenous injection of 0.4 mg of naloxone enhanced detrusor reflex activity in 5 of 7 patients with neuropathic bladder dysfunction caused by incomplete suprasacral spinal cord lesions. The maximum effect occurred within 1 to 2 minutes after intravenous injection and was gone by 5 minutes. Murray and Feneley (1982) reported that the same dose of naloxone caused, in a group of patients with IDO, an increase in detrusor pressure at zero volume and at first desire to void, a decrease in the maximum cystometric capacity, and a worsening of the degree of instability. Galeano and colleagues (1986) reported that although naloxone increased bladder contractility in cats with chronic spinal injury, it also aggravated striated sphincter dyssynergia and spasticity—a potential problem in the treatment of emptying failure. Wheeler and colleagues (1987) noted no significant cystometric changes in a group of 15 SCI patients after intravenous naloxone, whereas 11 showed decreased perineal EMG activity. Although an intriguing area, the concept of reversing an inhibitory opioid influence to stimulate reflex bladder activity is of little practical use at present.

KEY POINTS: TREATMENT OF DETRUSOR UNDERACTIVITY

- A pharmacologic agent that is effective for the treatment of detrusor underactivity or underactive bladder would be welcome. It is difficult to find reproducible urodynamic data that support a recommendation for the use of oral bethanechol chloride in any specific category of patients, despite its pharmacologic characteristics as a cholinergic agonist. It is possible that bethanechol, by increasing static intravesical pressure, may cause afferent stimulation at a lower bladder volume than usual, prompting detrusor contraction at a more favorable bladder volume. Such an action would be expected to occur only in bladders that were not truly acontractile.
- Prostaglandins could theoretically facilitate bladder activity either directly by effects on the smooth muscle or indirectly through effects on neurotransmission or increased sensitization to filling stimuli. Initial reports of the use of intravesical prostanoids producing lasting favorable clinical effects have not been confirmed. Work continues on oral agents.

Decreasing Outlet Resistance

Decreasing Outlet Resistance at a Site of Anatomic Obstruction

This topic includes the treatment of BOO secondary to BPE. A full discussion is appropriately included in Chapter 104.

Decreasing Outlet Resistance at the Level of the Smooth Sphincter

α -Adrenoceptor Antagonists. Whether or not one believes that there is significant innervation of the bladder and proximal urethral smooth musculature by postganglionic fibers of the sympathetic nervous system, one must acknowledge the existence of α - and β -AR sites. The smooth muscle of the bladder base and proximal urethra contains predominantly α -ARs, although β -ARs are present. The bladder body contains both varieties of ARs, with

β -ARs (β_3) being more common (see Chapter 69; Zderic et al, 1995; Andersson, 2000b). The human LUT contains more α_2 - than α_1 -ARs, but adrenergically induced prostatic smooth muscle contraction and human LUT smooth muscle contraction are mediated largely, if not exclusively, by α_1 -ARs. There are at least three subtypes of α_1 -ARs, designated α_{1A} , α_{1B} , and α_{1D} . Adrenergically induced smooth muscle contraction in the human LUT is mediated largely by the α_{1A} (and in the detrusor α_{1D}) subtype (Docherty, 1998; Harada and Fujimura, 2000; Andersson and Wein, 2004; Michel and Vrydag, 2006; Andersson and Gratzke, 2007; Yamada and Ito, 2011). In addition to the three cloned α_1 -ARs, there is a possible fourth, α_{1L} , although the α_{1L} -AR is probably a variant of the α_{1A} type. There is a tremendous amount of information and controversy in the literature regarding the selectivity of certain α -AR blocking agents for these respective receptor subtypes. Conclusions are drawn regarding the “best” α_1 -AR antagonist for the treatment of at least BPH on the basis of in vitro and in vivo pharmacologic selectivity, but many authors note that this does not necessarily translate into functional selectivity in a given patient (Andersson, 2002c; Djavan et al, 2004). The various α -AR antagonists are dealt with in more detail in Chapter 104.

Krane and Olsson (1973) were among the first to promote the concept of a physiologic internal sphincter partially controlled by tonic sympathetic stimulation of contraction-mediating α -ARs in the smooth musculature of the bladder neck and proximal urethra. Furthermore, they hypothesized that some obstructions at this level during bladder contraction are a result of inadequate opening of the bladder neck and/or of an inadequate decrease in resistance in the area of the proximal urethra. They also theorized and presented evidence that α -AR blockade could be useful in promoting bladder emptying in such a patient with an adequate detrusor contraction but without anatomic obstruction or detrusor striated sphincter dyssynergia. They and many others (see Wein and Barrett, 1988) have confirmed the usefulness of α -AR blockade in the treatment of what is now usually referred to as *smooth sphincter or bladder neck dyssynergia or dysfunction*. Successful results, usually defined as an increase in flow rate, a decrease in residual urine, and an improvement in upper tract appearance (where pathologic), could often be correlated with an objective decrease in urethral profile closure pressure.

One would expect success with such therapy to be most evident in patients without detrusor striated sphincter dyssynergia, as reported by Hachen (1980). Mobley (1976), however, reported a startling 86% subjective success rate in 21 patients with a reflex neurogenic bladder, with a corresponding success rate of 66% in what was called “flaccid” and 57% of what was called “autonomous” neurogenic bladder dysfunction, with success being defined as PVR urine volume consistently less than 100 mL. Scott and Morrow (1978), on the other hand, noted excellent results with phenoxybenzamine therapy in 9 of 10 patients with a flaccid bladder and a flaccid external sphincter and in a single patient with an upper motor neuron bladder with intact sympathetic innervation, but in only 8 of 21 patients with hyperreflexia and autonomic dysreflexia, and in none of 6 patients with an upper motor neuron bladder and sympathetic denervation (lesion between T10 and L2).

Although most would agree that α -AR blocking agents exert their favorable effects on voiding dysfunction by affecting the smooth muscle of the bladder neck and proximal urethra, information in the literature suggests that they may decrease striated sphincter tone as well, and other information suggests that they may exert some of their effects on at least the filling and storage symptoms of voiding dysfunction by decreasing bladder contractility (see previous discussion). Much of the confusion relative to whether α -AR blocking agents have a direct (as opposed to indirect) inhibitory effect on the striated sphincter relates to the interpretation of clinical observations and experimental data referable to their effect on urethral pressure in the region of the urogenital diaphragm and on electromyographic activity in the periurethral striated muscle of this area. One cannot tell by pressure tracings alone whether decreased resistance in this area of the urethra is secondary to a decrease in smooth or striated muscle activity. Nanninga and colleagues (1977)

found that the electromyographic activity of the external sphincter decreased after phentolamine administration in three paraplegic patients and attributed this effect to a direct inhibition of sympathetic action on the striated sphincter. [Nordling and colleagues \(1981\)](#) demonstrated that clonidine and phenoxybenzamine (both of which pass the blood-brain barrier) also decreased urethral pressure in this area and yet had no effect on EMG activity. They concluded (1) that the effect of phentolamine was from smooth muscle relaxation alone; (2) that the effect of clonidine, and possibly phenoxybenzamine, was elicited mostly through centrally induced changes in striated urethral sphincter tonus; and (3) that these agents also had an effect on the smooth muscle component of urethral pressure. None of the three drugs, however, affected the reflex rise in either urethral pressure or electromyographic activity seen during bladder filling, and none decreased the urethral pressure or electromyographic activity response to voluntary contraction of the pelvic floor striated musculature. [Gajewski and colleagues \(1984\)](#) concluded that α -AR blockers do not influence the pudendal nerve-dependent urethral response in the cat through a peripheral action but that at least prazosin can significantly inhibit this response at a central level. [Thind and colleagues \(1992\)](#) reported on the effects of prazosin on static urethral sphincter function in 10 healthy women. They found a reduction—predominantly in the midurethral area—and hypothesized that the response was caused by a decrease in both smooth and striated sphincter activity, the latter as a result of reduced somatomotor output from the CNS. Clinically, [Chancellor and colleagues \(1994\)](#) reported that terazosin, a selective α_1 -AR antagonist, had little or no effect on striated sphincter function in SCI patients and had no effect on functional obstruction caused by sphincter dyssynergia in these patients.

α -AR blocking agents have also been used to treat both bladder and outlet abnormalities in patients with so-called autonomous bladders—such as those with myelodysplasia, sacral spinal cord or infrasacral neural injury, and voiding dysfunction after radical pelvic surgery ([Wein and Barrett, 1988](#)). Decreased bladder compliance is a common clinical problem in such patients, and this, along with a fixed urethral sphincter tone, results in the paradoxical occurrence of both storage and emptying failure.

Specific α -adrenergic blocking agents are discussed fully in Chapter 104 with reference to management of BPO. A brief description can be found on the Expert Consult website.

Decreasing Outlet Resistance at the Level of the Striated Sphincter

There is no class of pharmacologic agents that will selectively relax the striated musculature of the pelvic floor. Three different

types of drugs have been used to treat voiding dysfunction secondary to outlet obstruction at the level of the striated sphincter: the benzodiazepines, dantrolene, and baclofen.

The use of these is discussed in detail on the Expert Consult website.

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The complete reference list is available online at www.expertconsult.com.

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KEY POINTS: DECREASING OUTLET RESISTANCE

- α -Adrenergic blocking agents are capable of reducing smooth muscle tone in the bladder outlet in both men and women and in the prostatic muscle. Such agents can be used with success in patients with bladder neck dysfunction and in men with BOO secondary to prostatic enlargement. Blockade of the α_{1A} -AR would theoretically exert the greatest effect, and whether there is any difference in the efficacy of the individual agents available remains a topic of controversy.
- There is no class of pharmacologic agents that will selectively relax the striated musculature of the pelvic floor. There are few references that provide any information regarding efficacy of the benzodiazepines for this purpose. Baclofen seems to be most useful when administered intrathecally; dantrolene is seldom if ever used for this purpose. Injection of botulinum toxin into the striated sphincter has been used with some clinical success, especially in patients with neurologic striated sphincter dyssynergia. The potential for spread to nearby structures is greater than with intravesical therapy, and distant effects can also occur, but these are rare.

Phenoxybenzamine. Phenoxybenzamine was the α -AR antagonist originally used for the treatment of voiding dysfunction (see Te, 2002). Phenoxybenzamine has blocking properties at both α_1 - and α_2 -AR sites. The initial adult dose of this agent is 10 mg/day, and the usual daily dose for voiding dysfunction is 10 to 20 mg. After discontinuation, the effects of administration may persist for days, because the drug irreversibly inactivates α -ARs and the duration of effect depends on the rate of receptor synthesis (Hoffman and Lefkowitz, 1996). Side effects affect approximately 30% of patients (Kirby, 1999) and include orthostatic hypotension, reflex tachycardia, nasal congestion, diarrhea, miosis, sedation, nausea, and vomiting (secondary to local irritation). It has mutagenic activity in the Ames test, and repeated administration to animals can cause peritoneal sarcomas and lung tumors (Westfall and Westfall, 2006). Although this agent has been in clinical use for some 35 years without clinically apparent oncologic associations, one must now consider the potential medicolegal ramifications of long-term therapy, especially in younger persons. A reassessment of the use of phenoxybenzamine for treatment of urinary tract disorders was made by Te (2002). It is seldom used at present.

Prazosin. Prazosin was the first potent selective α_1 -AR antagonist (see Westfall and Westfall, 2006) used to lower outlet resistance (Andersson et al, 1981). The duration of action is 4 to 6 hours; therapy is usually begun in daily divided doses of 2 to 3 mg. The dose may be very gradually increased to a maximum of 20 mg daily, although seldom has anyone used more than 9 to 10 mg daily for voiding dysfunction. The potential side effects of prazosin are consequent to its α_1 -AR blockade. Occasionally, there occurs a "first-dose phenomenon," a symptom complex of faintness, dizziness, palpitation, and, infrequently, syncope, thought to be caused by acute postural hypotension. The incidence of this can be minimized by restricting the initial dose of the drug to 1 mg and administering this at bedtime. Other side effects associated with chronic prazosin therapy are usually mild and rarely necessitate withdrawal of the drug.

Terazosin and Doxazosin. Terazosin and doxazosin are two highly selective postsynaptic α_1 -AR antagonists. They are readily absorbed with high bioavailability and a long plasma half-life, enabling their activity to be maintained over 24 hours after a single oral dose. Both of these agents have been evaluated with respect to their efficacy in patients with LUTS and decreased flow rates presumed secondary to BPH. Their efficacy in decreasing symptoms and raising flow rates has been shown to be superior to placebo and similar to that of prazosin (Kirby, 1999; Lepor et al, 2012). Their safety profiles have been well documented as a result of their widespread use over several years for the treatment of hypertension. Side effects are related to peripheral vasodilation (postural hypotension), and both drugs have to be started at a low dose and titrated to obtain an optimum balance between efficacy and tolerability. Dizziness and weakness are sometimes observed, and these are presumed secondary to CNS actions. These drugs are marketed for the treatment of hypertension as well as LUTS presumed secondary to BPH.

Alfuzosin and Tamsulosin. Alfuzosin and tamsulosin, both highly selective α_1 -AR blockers, have appeared and are marketed solely for the treatment of BPH because of some reports suggesting preferential action on prostatic rather than vascular smooth muscle (Kirby, 1999; Djavan et al, 2004; Lepor et al, 2012). Marketing claims aside, whether there is any difference in the efficacy or side effect profiles of these individual agents remains a topic of controversy. Both are able to be administered once daily and without titration. Available data suggest that retrograde ejaculation and rhinitis are more common with tamsulosin and silodosin, whereas dizziness and asthenia are more common with terazosin and doxazosin (Kirby et al, 2000; Djavan et al, 2004; Lepor et al, 2012).

Silodosin. Silodosin is a novel, highly selective α_{1A} -AR antagonist (Yoshida et al, 2007). Clinical data (Kawabe et al, 2006; Chapple et al, 2011; Novara et al, 2013) showed that silodosin showed significant improvement in LUTS associated with BPH, as well as in QoL. The improvements were observed in both voiding and storage symptoms. Long-term study revealed that the efficacy and safety were sustained for 1 year. The most common adverse event in the silodosin group was abnormal ejaculation, which occurred in 22% of patients (Kawabe et al, 2006). Adverse events associated with lowering of blood pressure were low.

Thus, agents with α -AR blocking properties at various levels of neural organization have been used in patients with very varied types of voiding dysfunction—functional outlet obstruction, urinary retention, decreased compliance, and DO. Our own experience would suggest that a trial of such an agent is certainly worthwhile, because the effect or lack of effect will become obvious in a matter of days, and any pharmacologic side effects are, of course, reversible. However, our results with such therapy for non-BPH-related voiding dysfunction have been somewhat less spectacular than those of at least some other investigators.

Nitric Oxide. In the future there may be other pharmacologic mechanisms that are explored to produce relaxation in the smooth muscle of the bladder neck, urethra, or prostatic stroma. Nitric oxide is a neurotransmitter capable of producing smooth muscle relaxation, at least in the female rabbit urethra, pig urethra, and human bladder neck (Andersson and Persson, 1993; Andersson and Wein, 2004). A selective nitrergic action on bladder neck and urethral smooth muscle is an interesting theoretic possibility. Mumtaz and colleagues (2000) suggested that a topical intraurethral NO donor could induce urethral smooth muscle relaxation without affecting bladder smooth muscle function and that this is a possible clinical avenue of exploration. Mamas and colleagues (2001, 2003) hypothesized that augmentation of external sphincter NO could be an effective pharmacologic treatment for DSD. In a functional urodynamic study, Reitz and colleagues (2004a) assessed the effect of the NO donor isosorbide dinitrate on the external urethral sphincter. Magnetic stimulation of the sacral roots was performed in eight healthy men to evoke reproducible contractions of the external urethral sphincter. Sublingual administration of isosorbide dinitrate (10 mg) could significantly reduce the resting pressure of the external urethral sphincter for at least 1 hour. The maximal contractile strength measured as the maximal urethral pressure during single pulse and continuous magnetic stimulation of the sacral roots also decreased significantly. NO did not induce a significantly faster fatigue of the external urethral sphincter during continuous magnetic stimulation of the sacral roots. The authors suggested that NO donors could offer a new pharmacologic approach to treat urinary retention caused by an overactive or non-relaxing external urethral sphincter. In a later study on 12 male SCI patients with NDO and DSD, Reitz and colleagues (2004b) found that NO significantly reduced external urethral sphincter pressures at rest ($P < .05$) and during dyssynergic contraction ($P < .05$), whereas bladder pressures at rest and during contraction as well as the reflex volume remained unchanged. In patients who used suprapubic tapping for bladder emptying, the mean post-triggering residual volume was significantly reduced ($P < .05$). The researchers concluded based on their findings that NO donors could offer a potential pharmacologic option to treat DSD in SCI patients.

The benzodiazepines are classified both as antianxiety agents (Baldessarini, 2006) and as sedative-hypnotics, muscle relaxants, and anticonvulsants (Charney et al, 2006). Dantrolene and baclofen are characterized as antispasticity agents (Standaert and Young, 2006; Taylor, 2006). Baclofen and diazepam exert their actions predominantly within the CNS, whereas dantrolene acts directly on skeletal muscle. Unfortunately, **there is no completely satisfactory form of therapy for alleviation of skeletal muscle spasticity.** Although these drugs are capable of providing variable relief in given circumstances, their efficacy is far from complete; and troublesome muscle weakness, adverse effects on gait, and a variety of other side effects minimize their overall usefulness as treatments of spasticity (Standaert and Young, 2006; Taylor, 2006).

GABA and glycine have been identified as major inhibitory transmitters in the CNS (Andersson and Wein, 2004; Bloom, 2006). GABA is the most widely distributed inhibitory neurotransmitter in the mammalian CNS. GABA receptors have been divided into three types. The GABA-A receptor directly gates a chloride ionophore and has modulatory binding sites for benzodiazepines, barbiturates, neurosteroids, and ethanol (Bloom, 2006). The GABA-B or metabotropic receptor couples to calcium and potassium channels by means of G proteins and second messenger systems. It inhibits adenylate cyclase, activates potassium channels, and reduces calcium conductance. The GABA-B receptor is activated by baclofen and is resistant to drugs that modulate GABA-A receptors. There is a third class of GABA receptors, the GABA-C receptor, which is less widely distributed than the A and B subtypes (Bloom, 2006). GABA appears to mediate the inhibitory actions of local interneurons in the brain and presynaptic inhibition within the spinal cord (Bloom, 2006). Glycine receptors are prominent in the brainstem and spinal cord and have many features analogous to the GABA-A receptor.

Benzodiazepines. Benzodiazepines potentiate the action of GABA by promoting GABA binding to the GABA-A receptor (Baldessarini, 2006; Charney et al, 2006). Benzodiazepines are extensively used for the treatment of anxiety and related disorders (Baldessarini, 2006), although pharmacologically they can also be classified as centrally acting muscle relaxants. The generalized anxiety disorder that is responsive to pharmacotherapy with these agents is characterized by unrealistic and/or excessive anxiety and worry about life circumstances (Shader and Greenblatt, 1993). Specific symptoms can be related to motor tension, autonomic hyperactivity (frequent urination can be a manifestation of this, as well as nausea, vomiting, diarrhea, and abdominal distress), and excessive vigilance. Other common uses have included treatment of insomnia, stress-related disorders, muscle spasm, and epilepsy and as preoperative sedation (Lader, 1987). Side effects include nonspecific CNS depression manifesting as sedation, lethargy, drowsiness, a feeling of slowing of thought processes, ataxia, and decreased ability to acquire or store information (Shader and Greenblatt, 1993; Baldessarini, 2006). Some believe that any muscle relaxation effect in clinically used doses is caused by the CNS depressant effects and cite a lack of clinical studies showing any advantages of these agents over placebo or aspirin in this regard (Baldessarini, 2006; Charney et al, 2006). Effective total daily doses of diazepam, the most widely used agent of this group, range from 4 to 40 mg. Other benzodiazepine anxiolytic agents include chlorthalidoxepoxide, clorazepate, prazepam, halazepam, clonazepam, lorazepam, oxazepam, and alprazolam.

Few references are available that provide evaluable data on the use of any of the benzodiazepines in the treatment of functional obstruction at the level of the striated sphincter. Opinions, however, are commonly expressed, at least with regard to diazepam. We have not found the recommended oral doses of diazepam to be effective in controlling the classic type of detrusor striated sphincter dyssynergia secondary to neurologic disease. If the cause of incomplete emptying in a neurologically normal patient is obscure and the patient has what appears to be inadequate relaxation of the pelvic floor striated musculature urodynamically (e.g., dysfunctional voiding, occult neuropathic bladder, the Hinman syndrome), a trial of such an agent may be worthwhile. The rationale for use is

either that of relaxation of the pelvic floor striated musculature during bladder contraction or that such relaxation removes an inhibitory stimulus to reflex bladder activity. Improvement under such circumstances may simply be caused, however, by the antianxiety effect of the drug, or by the intensive explanation, encouragement, and modified biofeedback therapy that usually accompanies such treatment in these patients.

Baclofen. Baclofen depresses monosynaptic and polysynaptic excitation of motoneurons and interneurons in the spinal cord by activating GABA-B receptors (Standaert and Young, 2006). Baclofen's primary site of action is in the spinal cord, but it is also reported to have activity at more rostral sites in the CNS. Baclofen has been found useful in the treatment of skeletal spasticity from a variety of causes (especially amyotrophic lateral sclerosis (Standaert and Young, 2006). Determination of the optimal dose in an individual patient requires careful titration. Treatment is started at an initial dose of 5 mg twice daily, and the dose is increased every 3 days up to a maximum daily dose of 20 mg four times a day. With reference to voiding dysfunction, Hachen and Krucker (1977) found a daily oral dose of 75 mg ineffective in patients with striated sphincter dyssynergia from traumatic paraplegia, whereas they found a daily intravenous dose of 20 mg highly effective. Florante and colleagues (1980) reported that 73% of their patients with voiding dysfunction secondary to acute and chronic SCI showed lower striated sphincter responses and decreased residual urine volumes after baclofen treatment, but only with an average daily oral dose of 120 mg. Potential side effects of baclofen include drowsiness, insomnia, rash, pruritus, dizziness, and weakness. It may impair ability to walk or stand and is not recommended for the management of spasticity caused by cerebral lesions or disease. Sudden withdrawal has been shown to provoke hallucinations, anxiety, and tachycardia; hallucinations during treatment, which have been responsive to reductions in dosage, have also been reported (Roy and Wakefield, 1986).

Drug delivery often frustrates adequate pharmacologic treatment, and baclofen is a good example of this. GABA's hydrophilic properties prevent its crossing the blood-brain barrier in sufficient amounts to make it therapeutically useful. For oral use, the more lipophilic analogue, baclofen, was developed. However, its passage through the barrier is likewise limited, and it has proved to be a generally insufficient drug when given orally to treat severe somatic spasticity and micturition disorders secondary to neurogenic dysfunction (Kums and Delhaas, 1991).

Intrathecal infusion bypasses the blood-brain barrier; CSF levels 10 times higher than those reached with oral administration are achieved with infusion amounts 100 times less than those taken orally (Penn et al, 1989). Direct administration into the subarachnoid space by an implanted infusion pump showed initially promising results for not only skeletal spasticity but also striated sphincter dyssynergia and DO.

Nanninga and colleagues (1989) reported on such administration to seven patients with intractable spasticity. All patients experienced a general decrease in spasticity, and the amount of striated sphincter activity during bladder contraction decreased; six showed an increase in bladder capacity. Four previously incontinent patients were able to stay dry with CIC. The action on DO is not unexpected, given its spinal cord mechanism of action, and this inhibition of bladder contractility when the drug is administered intrathecally may in fact prove to be its most important benefit. Laubser and colleagues (1991) studied nine SCI patients with refractory spasticity, using an external pump to initially test response. Eight showed objective improvement in functional abilities; three of seven studied urodynamically showed an increase in bladder capacity. Kums and Delhaas (1991) reported on nine paraplegic or quadriplegic men (secondary to trauma or MS) with intractable muscle spasticity treated with intrathecal baclofen. After a successful test period through an external catheter, a drug delivery system was implanted and connected to a spinal catheter. Doses per 24 hours ranged from 74 to 840 µg. Patients were studied before and 4 to 6 weeks after initiation of therapy. Mean residual urine volume fell from 224 to

110 mL ($P = .01$), mean urodynamic bladder capacity rose from 162 to 263 mL ($P = .005$), and pelvic floor spasm decreased at both baseline and at maximum bladder capacity ($P = .005$ and $P = .025$, respectively). Three subjects became continent. In addition, CIC was no longer complicated by adductor spasm. [Bushman and colleagues \(1993\)](#) reported an increase in bladder storage in three individuals with hereditary spastic paraplegia treated with intrathecal baclofen. Tolerance to intrathecal baclofen with a requirement for increasing doses may prove to be a problem with long-term chronic use, and studies are underway to investigate this. [Vaidyanathan and colleagues \(2004\)](#) reported a case with insidious development of autonomic dysreflexia and hydronephrosis resulting from dyssynergic voiding after discontinuation of intrathecal baclofen therapy. They recommended that in SCI patients in whom intrathecal baclofen therapy is terminated, close monitoring of the urologic status is needed.

Dantrolene. Dantrolene exerts its effects by a direct peripheral action on skeletal muscle ([Standaert and Young, 2006](#); [Taylor, 2006](#)). It is thought to inhibit the excitation-induced release of calcium ions from the sarcoplasmic reticulum of striated muscle fibers, thereby inhibiting excitation-contraction coupling and diminishing the mechanical force of contraction. The blockade of calcium release is not complete, however, and contraction is not completely abolished. It reduces reflex more than voluntary contraction, probably because of a preferential action on fast-type, as compared with slow-type, skeletal muscle fibers. It has been shown to have therapeutic benefits for chronic spasticity associated with CNS disorders.

The drug has been reported to improve voiding function in some patients with classic detrusor striated sphincter dyssynergia and was initially reported as being very successful in doing so ([Murdock et al, 1976](#)). Therapy in adults is recommended to begin at a dose of 25 mg daily, and this is gradually increased by increments of 25 mg every 4 to 7 days to a maximal oral dose of 400 mg given in four divided doses. [Hackler and coworkers \(1980\)](#) achieved improvement in voiding function in approximately half of their patients treated with dantrolene but found that such improvement required oral doses of 600 mg daily. Although no inhibitory effect on bladder smooth muscle seems to occur ([Harris and Benson, 1980](#)), the generalized weakness that dantrolene can induce is often significant enough to compromise its therapeutic effects. Other potential side effects include euphoria, dizziness, diarrhea, and hepatotoxicity. Fatal hepatitis has been reported in 0.1% to 0.2% of patients treated with the drug for 60 days or longer, and symptomatic hepatitis may occur in 0.5% of patients on treatment for more than 60 days, whereas chemical abnormalities of liver function are noted in up to 1%. The risk of hepatic injury is twofold greater in female patients ([Ward et al, 1986](#)).

One agreed-on use of dantrolene is to acutely manage malignant hyperthermia, a rare hereditary syndrome characterized by vigorous contraction of skeletal muscle precipitated by excess release of calcium from the sarcoplasmic reticulum, usually in response to neuromuscular blocking agents or inhalational anesthetics. Almost all hospital pharmacies stock parenteral dantrolene for this purpose. Virtually no one currently uses dantrolene for the treatment of voiding dysfunction.

Botulinum Toxin. As mentioned previously, botulinum toxin is an inhibitor of the release of ACh and other transmitters at the neuromuscular junction of somatic nerves in striated muscle, and of autonomic nerves in smooth muscle ([Simpson, 2004](#)). It is interesting that it produces enough weakness of the muscle to prevent or considerably ameliorate spasm or involuntary contraction but not to completely block voluntary control, a phenomenon hypothesized to occur because more active neuromuscular junctions are more likely than less active junctions to be blocked by the effect of the drug ([Hallett, 1999](#)). Its urologic use for the treatment of detrusor striated sphincter dyssynergia was first reported by [Dykstra and colleagues \(Dykstra and Sidi, 1990; Dykstra et al, 1998, 2003\)](#). Injections were carried out weekly for 3 weeks, achieving a duration of effect averaging 2

months. The only side effects reported in the [Dykstra](#) articles were transitory limb paresis and transitory exacerbation of autonomic hyperreflexia.

[Fowler and colleagues \(1992a\)](#) injected 6 women with difficult voiding and urinary retention secondary to what is now called the *Fowler syndrome* (manifesting with abnormal myotonus-like electromyographic activity in the striated urethral sphincter). Although voiding characteristics improved in no patient (a fact attributed to the type of repetitive discharge activity), 3 women did develop transient stress incontinence, a positive effect of sorts, indicating that the sphincter muscle had indeed been weakened. [Petit and colleagues \(1998\)](#) reported on the endoscopic injection of botulinum toxin A (Botox), 150 IU, into the striated urethral sphincter, using a four-point injection technique (the medication was diluted to 4 mL with saline solution). Seventeen patients with SCI or spinal cord disease were treated, and evaluation 1 month after treatment disclosed the following positive results: (1) a decrease in PVR by an average of 176 mL; (2) a decrease in bladder pressure during an emptying contraction by an average of 19 cm H₂O; and (3) a decrease in urethral pressure during an emptying bladder contraction by an average of 24 cm H₂O. The authors judged voiding to be improved in 10 patients. Side effects included the new appearance of stress incontinence in 2 patients and exacerbation of preexisting incontinence in 3. The duration of the effect was variable, but no less than 2 to 3 months. There were no adverse effects on striated muscle elsewhere. The authors concluded that Botox was a promising treatment for striated sphincter dyssynergia in certain patients refractory to CIC or surgery. [Gallien and colleagues \(1998\)](#) injected Botox transperineally in 5 men with traumatic quadriplegia and striated sphincter dyssynergia. Using a total initial dose of 100 U, divided into four injections of 25 U each, the authors noted what they called improved bladder function in all patients, with a significant decrease in residual urine volume (however, on examination of the figures, the mean reduction was only 14 mL, with 1 of the patients requiring a second set of injections). The maximum urethral pressure on average did not change, the maximum detrusor pressure during an emptying episode decreased 5 cm H₂O, and the functional detrusor capacity increased by an average of 89 mL. Urinary catheterization was able to be stopped in 2 patients, and autonomic hyperreflexia dramatically decreased in intensity in 4 patients. The time to improvement was 10 to 21 days and the duration was 3 to 5 months. No patient had significant side effects. [Wheeler and colleagues \(1998\)](#) reported on 3 men with SCI, all of whom had emptying problems related to striated sphincter dyssynergia. The sphincter was injected transperineally with botulinum toxin, using electromyographic control for localization. Two of the patients reported excellent results. [Schurch and colleagues \(1996\)](#) used both transurethral and transperineal injections in 24 male SCI patients with voiding dysfunction secondary to striated sphincter dyssynergia. They judged that in 21 of these patients, striated sphincter dyssynergia was significantly improved with a concomitant decrease in PVR urine volume in "most cases." Nine of 24 patients had a decreased PVR volume from 450 to 50 mL; in 7 patients, the residual urine volumes were less than 50 mL to begin with and remained unchanged; and in 8 patients, the PVR urine volumes were high and remained unchanged. The authors commented that transurethral injections appeared to be more effective, at least in reduction in maximum urethral pressure, than did transperineal injections. They noted no side effects. [de Seze and colleagues \(2002\)](#) performed a double-blind lidocaine-controlled study in 13 patients with spinal cord disease and DSD and demonstrated the superiority of botulinum toxin compared with lidocaine in improving clinical symptoms and increased urethral pressure.

A potential side effect is the spread to nearby muscles, particularly when high volumes of the toxin are injected. Distant effects can also occur, but distant weakness or generalized weakness, caused by the toxins spreading in the blood, is very rare. Botulinum toxin should be used only under close supervision in patients with already disturbed neuromuscular transmission or during treatment with aminoglycosides.

Theoretically, any agent that promotes striated sphincter relaxation in a uroselective manner could be used to decrease outlet resistance and facilitate voiding dysfunction. [Yoshiyama and colleagues \(2000\)](#) described the laboratory use of intravenous α -bungarotoxin as improving voiding in SCI rats. The drug is a toxin

extracted from the venom of a Formosan snake; it selectively blocks nicotinic receptors without influencing transmission in autonomic ganglia. Although a long way from clinical use, nicotinic receptors in the striated sphincter have been shown to be a potential target for drug therapy for striated sphincter dyssynergia.

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Conservative Management of Urinary Incontinence: Behavioral and Pelvic Floor Therapy and Urethral and Pelvic Devices

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Indications	Bladder Training and Scheduled Voiding Regimens
Assessment before Behavioral Treatments	Behavioral Treatment for Voiding and Pelvic Floor Dysfunction
Patient Education	Lifestyle Modifications
Pelvic Floor Muscle Training	Adherence to Conservative Treatment
Behavioral Training with Urge Suppression	Role of Conservative Interventions for Prevention of Urinary Incontinence
Role of Biofeedback	Mechanical Vaginal and Urethral Devices for Incontinence
Pelvic Floor Muscle Electrical Stimulation	Behavioral Treatment Model for Urology Practice

Conservative treatments for urinary incontinence (UI) include any therapy not involving surgical treatment (Moore et al, 2013). Because behavioral treatments are effective and essentially risk free, they are the mainstay of conservative treatment and are recommended as first-line therapy by several guidelines and consensus panels (Shamliyan et al, 2008; Gormley et al, 2012; Moore et al, 2013). Behavioral treatments are a group of interventions that improve lower urinary tract symptoms (LUTS) by changing patients’ behavior or environment or by teaching new skills.

Behavioral treatment programs usually comprise multiple components, and it is generally recognized that the best programs are individualized according to patient condition, needs, and environment. Components of a behavioral program may include patient education and any of the following: self-monitoring (bladder diary), pelvic floor muscle training (PFMT) and exercise, active use of pelvic floor muscles (PFMs) for urethral occlusion (“stress strategies,” the “knack”), urge prevention and suppression techniques (urge strategies), bladder training with urge control techniques (distraction, self-assertions), biofeedback (BF), electrical stimulation, fixed or incremental voiding schedules, delayed voiding, fluid management, caffeine reduction, dietary changes, weight loss, teaching normal voiding techniques, and/or other lifestyle changes. The most common behavioral interventions are depicted in Figure 80-1, and a list of LUTS to which they are potentially applicable is presented in Box 80-1. In most urologic settings, conservative treatment programs are designed and administered by advanced practice providers (nurse practitioners and physician assistants) (Newman and Wein, 2013; Newman, 2014) after a simple noninvasive assessment.

The most established behavioral treatment programs are PFMT, behavioral training (BT) with urge suppression, and bladder training. These therapies encompass two fundamental approaches to treating LUTS. One approach focuses on the bladder outlet, teaching skills for improving PFM strength and

control and techniques for urge suppression. The other approach focuses on controlling bladder function by changing voiding habits, such as with bladder training and delayed voiding, also supported with urge control techniques. These therapies are grounded in the concept that the patients with LUTS can be educated about their condition and develop skills and strategies to reduce or eliminate symptoms.

Behavioral treatments can also be categorized as patient-dependent or caregiver-dependent (Newman et al, 2014). Bladder training, PFMT, and BT are examples of patient-dependent interventions, because they rely on active patient’s participation. These therapies require adequate function, learning capability, and motivation of the individual. Caregiver-dependent interventions, such as prompted voiding, are useful in people with some functional disabilities. The success of these interventions depends largely on caregiver knowledge and motivation, rather than on the patient’s physical function and mental status.

In addition to these established primary treatment approaches that focus on improving the patient’s direct control over bladder and PFM function, there are a number of lifestyle modifications that seek to improve LUTS indirectly by changing the patient’s behavior or avoiding factors that exacerbate symptoms or make the bladder more difficult to control. These interventions include fluid management, caffeine reduction, reduction of bladder irritants, management of constipation, and weight loss.

Behavioral treatments are supported by a large body of research (Moore et al, 2013) and have been recommended as treatment for UI and non-neurogenic overactive bladder (OAB) by multiple organizations (Shamliyan et al, 2007; Gormley et al, 2012) and international guidelines (Moore et al, 2013). The International Consultation on Incontinence (ICI) Committee on Adult Conservative Management details evidence and recommendations for all conservative treatments (Tables 80-1 and 80-2) using the Oxford grading system (Table 80-3). In this chapter, we also describe devices that can prevent urine loss mechanically.

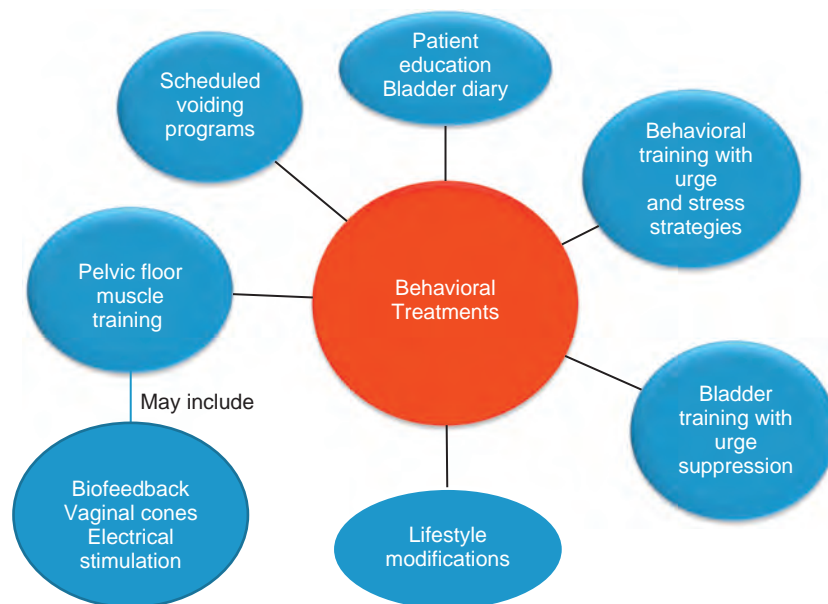


Figure 80-1. Common behavioral treatments. (From Newman DK, Wein AJ. Managing and treating urinary incontinence, 2nd ed. Baltimore: Health Professions Press; 2009.)

TABLE 80-1 Lifestyle Modifications: Levels of Evidence and Recommendations

LIFESTYLE PRACTICE	LEVELS OF EVIDENCE	RECOMMENDATIONS
Diet	Indications from epidemiologic data suggest diet may play a role in UI. Level of evidence: 3	
Fluid	Fluid intake may play a minor role in the pathogenesis of UI.	Minor decrease of fluid intake by 25% may be recommended provided baseline consumption is not <30 mL/kg/day. Grade of recommendation: B
Caffeine	Caffeine consumption may play a role in exacerbating UI. Small clinical trials do suggest that decreasing caffeine intake improves continence. Level of evidence: 2	A reduction in caffeine intake is recommended for those with incontinence symptoms. Grade of recommendation: B
Bowel function	There is some evidence to suggest that chronic straining may be a risk factor for the development of UI. Level of evidence: 3	Further research is needed to define the role of straining during defecation in the pathogenesis of UI.
Obesity	Massive weight loss (15-20 BMI points) significantly decreases UI in morbidly obese women. Level of evidence: 2 Moderate weight loss may be effective in decreasing UI especially if combined with exercise. Level of evidence: 1	Weight loss in obese and morbidly obese should be considered a first-line treatment to reduce UI prevalence. Grade of recommendation: A

BMI, body mass index; UI, urinary incontinence.

Modified from Moore K, Bradley C, Burgio B, et al. Adult conservative treatment. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence. Proceedings from the 5th International Consultation on Incontinence. Plymouth (UK): Health Publications; 2013. p. 1101-228.

TABLE 80-2 Pelvic Floor Muscle Training, Behavioral Therapy, Biofeedback, Electrical Stimulation: Levels of Evidence and Recommendations

TREATMENT	RECOMMENDATIONS
Timed voiding	Timed voiding with a 2-hour voiding interval may be beneficial as a sole intervention for women with mild UI with infrequent voiding patterns. Grade of recommendation: C
PFMT Pregnant women	HPs should carefully consider the cost/benefit of population-based approaches to HP taught antepartum or postpartum PFMT; that is, HP instruction to all pregnant or postpartum women regardless of their current or prior continence status. Grade of recommendation: B Continent, pregnant women having their first baby should be offered a supervised (including regular HP contact) and intensive strengthening antepartum PFMT program to prevent postpartum UI. Grade of recommendation: A
PFMT Postpartum	Postnatal women, immediately after delivery: Individually taught PFMT program that incorporates adherence strategies for women who had a vaginal delivery of a large baby (≥ 4000 g) or a forceps delivery. Grade of recommendation: C For postnatal women with persistent symptoms of UI 3 months after delivery: PFMT should be offered as first-line conservative therapy. Grade of recommendation: A An “intensive” PFMT program (in terms of supervision and exercise content) is likely to increase the treatment effect. Grade of recommendation: B
PFMT	Supervised PFMT should be offered as first-line conservative therapy to women with stress, urgency, or mixed UI. Grade of recommendation: A The most intensive PFMT program possible should be provided (in terms of exercise dose, HP teaching, and supervision) within service constraints; HP taught and supervised programs are better than self-directed programs; more HP contact is better than less. Grade of recommendation: A
PFMT in women with SUI	PFMT is better than electrical stimulation as first-line conservative therapy, particularly if PFMT is intensively supervised. Grade of recommendation: B PFMT is better than BT as first-line conservative therapy. Grade of recommendation: B
PFMT in women with pelvic organ prolapse	PFMT can improve prolapse symptoms and severity. Grade of recommendation: A Preoperative PFMT may help improve quality of life and urinary symptoms in women undergoing surgery for prolapse. Grade of recommendation: C
PFMT in men after prostatectomy	Some preoperative or immediate postoperative instruction in PFMT for men undergoing radical prostatectomy may be helpful. Grade of recommendation: B It is not clear whether PFMT taught by digital rectal examination offers any benefit over and above verbal or written instruction in PFMT. Grade of recommendation: B The use of BF to assist PFMT is currently a therapist/patient decision based on economics and preference. Grade of recommendation: B
PFMT + BT in women with UI or MUI	PFMT and BT are effective first-line conservative therapy. Grade of recommendation: B For women with SUI or MUI, a combination of PFMT/BT may be better than BT alone in the short term. Grade of recommendation: C

Continued

TABLE 80-2 Pelvic Floor Muscle Training, Behavioral Therapy, Biofeedback, Electrical Stimulation: Levels of Evidence and Recommendations—cont'd

TREATMENT	RECOMMENDATIONS
BT	<p>BT is an appropriate first-line treatment for UI in women.</p> <p>Grade of recommendation: A</p> <p>In a choice between BT and anticholinergic drug for women with DO or UUI, either may be effective.</p> <p>Grade of recommendation: B</p> <p>BT may be preferred by some clinicians and women because it does not produce the side effects and adverse events associated with drug therapy.</p> <p>Grade of recommendation: D</p> <p>There may be no benefit in adding brief written instruction in BT to drug therapy for incontinence, but it may improve episodes of frequency.</p> <p>Grade of recommendation: B</p> <p>A combination of PFMT/BT may be better than PFMT alone in the short-term for women with symptoms of stress UI or MUI.</p> <p>Grade of recommendation: B</p> <p>Clinicians and researchers should refer to the operant conditioning and educational literature to provide a rationale for their choice of training parameters or approach.</p> <p>Grade of recommendation: D</p> <p>HPs should provide the most intensive BT supervision that is possible within service constraints.</p> <p>Grade of recommendation: D</p>
PFMES	<p>PFMES might be better than no treatment in improving symptoms.</p> <p>Grade of recommendation: B</p> <p>For women with SUI, maximal clinic-based PFMES might be better than daily low-intensity home-based PFMES in improving symptoms.</p> <p>Grade of recommendation: B</p> <p>PFMES plus PFMT or BF-assisted PFMT program does not appear to add benefit.</p> <p>Grade of recommendation: B</p> <p>For men with postprostatectomy incontinence, there does not appear to be any benefit of adding PFMES to a PFMT program</p> <p>Grade of recommendation: B</p>
Vaginal cones	<p>For women with SUI, VCs with supervised training sessions by a trained HP can be offered as a first-line conservative therapy to those who can and are prepared to use them.</p> <p>Grade of recommendation: B</p> <p>VCs may be inappropriate in some cases because of inability to insert or retain the cone or because of side effects and discomfort. Trained HP assessment is recommended</p> <p>Grade of recommendation: D</p>

BF, biofeedback; BT, behavioral therapy; DO, detrusor overactivity; HP, health professional; MUI, mixed urinary incontinence; PFMES, pelvic floor muscle electrical stimulation; PFMT, pelvic floor muscle training; SUI, stress urinary incontinence; UI, urinary incontinence; UUI, urge urinary incontinence; VC, vaginal cone.

Modified from Moore K, Bradley C, Burgio B, et al. Adult conservative treatment. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence. Proceedings from the 5th International Consultation on Incontinence. Plymouth (UK): Health Publications; 2013. p. 1101–228.

BOX 80-1 Conditions That Have Benefited from Behavioral Treatments

- Stress urinary incontinence
- Overactive bladder (urgency, frequency)
- Urgency urinary incontinence
- Neurogenic detrusor overactivity
- Mixed urinary incontinence
- Nocturia
- Pelvic floor muscle spasm (dysfunction)
- Nonrelaxing striated sphincter

Modified from Newman DK, Wein AJ. Office-based behavioral therapy for management of incontinence and other pelvic disorders. Urol Clin North Am 2013;40:613–35; and Newman DK, Wein AJ. Managing and treating urinary incontinence, 2nd ed. Baltimore: Health Professions Press; 2009. p. 245–306.

INDICATIONS

Behavioral interventions are well established for treating stress and urgency UI and OAB. Behavioral interventions are also appropriate for voiding dysfunction, although less evidence exists for this condition. Most patients who are motivated and cooperative with behavioral treatment experience some degree of improvement. There is wide variation in outcomes, and little is known of the characteristics of patients who respond best to behavioral treatment. **Therefore, because they are virtually risk free, behavioral treatments should be offered as first-line therapy to any man or woman who is willing and able to participate.** Even patients with dementia can benefit from the appropriate, caregiver-guided behavioral treatment program.

ASSESSMENT BEFORE BEHAVIORAL TREATMENTS

Perhaps the most important step in evaluating the patient with LUTS is a **focused and detailed history**, including onset of

TABLE 80-3 Oxford Levels of Evidence and Grades of Recommendation

Any level of evidence may be positive (the therapy works) or negative (the therapy does not work). A level of evidence is given to each individual study.	
LEVEL	EVIDENCE
1	Usually involves meta-analysis of trials (RCTs) or a good-quality RCT, or “all or none” studies in which no treatment is not an option—for example, in vesicovaginal fistula.
2	Includes “low”-quality RCT (e.g., <80% follow-up) or meta-analysis (with homogeneity) of good-quality prospective “cohort studies.” These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, in which those with the condition in the first group are compared with those in the second group.
3	Includes: <ul style="list-style-type: none"> • Good quality retrospective “case-control studies” in which a group of patients who have a condition are matched appropriately (e.g., for age, sex, etc.) with control individuals who do not have the condition. • Good quality “case series” in which complete group of patients, all with the same condition/disease/therapeutic intervention, are described, without a comparison control group.
4	Includes expert opinion where the opinion is based not on evidence but on “first principles” (e.g., physiologic or anatomic) or bench research. The Delphi process can be used to give “expert opinion” greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of “options”; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made.
Uses four grades from the Oxford system. As with the levels of evidence the grades of evidence may apply either positively (do the procedure) or negatively (do not do the procedure).	
GRADE	RECOMMENDATION
A	Usually depends on consistent level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway. However, there will be occasions in which excellent evidence (level 1) does not lead to a grade A recommendation—for example, if therapy is prohibitively expensive, dangerous, or unethical. Grade A recommendation can follow from level 2 evidence. However, a grade A recommendation needs a greater body of evidence if based on anything except level 1 evidence.
B	Usually depends on consistent level 2 and/or 3 studies, or “majority evidence” from RCTs.
C	Usually depends on level 4 studies or “majority evidence” from level 2 or 3 studies or Delphi-processed expert opinion.
D	“No recommendation possible” would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

RCT, randomized controlled trial.

From Abrams P, Khoury S, Grant A. Evidence based medicine: overview of the main steps for developing and grading guideline recommendation. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence. Paris: EAU/ICUD; 2013. p. 8–9.

symptoms, duration, progression, characteristics, and situational antecedents or triggers (Newman, 2005; Newman and Wein, 2013). Understanding these factors will determine the design of a behavioral treatment program and guide its implementation.

To supplement the history, it is very useful for the patient to complete a 3- to 7-day bladder diary (Tincello et al, 2007) (see Fig. 80-2 for an example of a completed bladder diary with voided volumes, sometimes referred to as a Frequency Volume Chart). The diary is a valuable tool for the patient, as well as the provider. In the assessment phase, the diary provides information on the type and amount of fluid intake, type and frequency of symptoms, such as incontinence episodes, frequency of urination, the urgency associated with each, and the circumstances or reasons for incontinence episodes, which helps the provider plan appropriate components of behavioral intervention (Sampselle, 2003). Many providers also are interested in having the patient note the type and quantity of absorbent incontinence pads used and to quantify amount of urine leakage.


A bladder diary is also the best noninvasive tool available to objectively monitor the patient's voiding habits and the effect of treatment on symptoms, guiding the use of various treatment components. In bladder training programs, having patients record the times they void provides a foundation for determining initial and incremental voiding intervals. Voided volumes are more bur-

densome for patients to document, but they provide a practical estimate of the patient's functional bladder capacity in daily life.

In addition to guiding behavioral treatment from the provider's perspective, the self-monitoring effect of completing a diary can enhance the patient's awareness of drinking and voiding habits and helps them recognize how their LUTS, especially incontinent episodes, may be related to their activities. This increased awareness is thought to empower the patient to help in retraining more effectively (Vella et al, 2012). A review of a diary can assist patients in identifying the times they are at increased risk for a UI episode and activities that precipitate UI episodes, which helps them be prepared to implement behavioral skills.

Another approach to collecting information on bladder habits is the Questionnaire-Based Voiding Diary (QVD) for self-assessment of the type and volume of fluid intake and the type of UI (Arya et al, 2008) (Fig. 80-3). This instrument has been validated and can be completed in an initial office visit in 5 to 7 minutes (Arya et al, 2008, 2011).

In addition to a bladder diary, a urinalysis performed by dipstick or microscopic examination is recommended to check for signs of infection. A postvoid residual value is not necessary before instituting behavioral treatment, unless symptoms suggest incomplete bladder emptying.

BLADDER DIARY					
DAY 1					
Time 	Trips to bathroom How much urine did you pass (in oz)?	Did you feel a strong urge to go? (yes, no)	Urine Leakage	Circumstances of Urine Leakage	Drinks What kind and how much? 1 glass = 4 oz 1 cup = 8 oz
6:00 a.m. - awake	6 oz	yes	✓	Getting out of bed rushing to bathroom	½ glass of water
6:30 a.m.	5 oz	yes			1 ½ cups of coffee,
8:00 a.m.	5 oz	yes			1 cup of coffee
10 a.m.	7 oz	yes			½ glass of water
12 p.m.	Forgot to measure		✓	Running water, washing hands	8 oz of soda, 1 glass of milk, 1 glass of water
12:30 p.m.	4 oz	yes			
2:30 p.m.	7 oz				½ glass of water
4:30 p.m.					1 cup of tea
5 p.m.					2 glasses of water
7 p.m.	8 oz	yes	✓	exercising	1 glass of water
8 p.m.	4 oz				2 glasses of wine
10 p.m.-to bed	4 oz				
12 a.m.	5 oz	yes			
3:30 a.m.	8 oz				
5 a.m.	don't know				½ glass of water
TOTAL	10 daytime voids/ 4 nighttime voids Volume 63 oz+/1890 mLs+	7 urgency episodes	3 incontinence episodes		72 oz cups/glasses (2160 mL)

Circle the product you are using

Write the number

of products used: 2

Pantliners



Pads



Protective Underwear



Briefs or "diapers"

Comments: _____

Figure 80-2. Example of a completed bladder diary.

QUESTIONNAIRE-BASED VOIDING DIARY (QVD)

Instructions: We would like to find out about your fluid intake, urinary output and urinary symptoms. Please answer each question, thinking about your fluid consumption and the symptoms you have experienced in the last month.

A. Please fill in the bubble for the number of drinks AND the amount for each beverage. If you do not drink a certain type of beverage daily , please fill in the bubble corresponding to 0.													
Beverage	Number of drinks per day (If 1 or more drinks per day, please indicate drink size →)											Size of each drink	
A1. Water	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz
A2. Caffeinated Coffee	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz
A3. Decaffeinated Coffee	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz
A4. Caffeinated Tea	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz
A5. Decaffeinated Tea	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz
A6. Caffeinated Soda	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz
A7. Decaffeinated Soda	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz
A8. Milk	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz
A9. Fruit juice/drinks (Hi-C, Kool Aid, cranberry cocktail)	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz
A10. Alcoholic Drinks	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10	<input type="radio"/> 10+	<input type="radio"/> Less than 8 oz <input type="radio"/> 8-16 oz <input type="radio"/> 17-24 oz <input type="radio"/> More than 24 oz

B. Fluid Intake Behavior	Never	Occasionally	Sometimes	Most of the time	All of the time
B1. Do you drink large amounts of caffeinated tea or coffee?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
B2. Do you drink large amounts of carbonated drinks?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
B3. Do you drink extra fluids to lose or maintain your weight?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
B4. Do you 'make yourself' drink fluid even if you are not thirsty?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
B5. Do you restrict or cut down on your fluid intake to control your urinary symptoms?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Figure 80-3. Questionnaire-based voiding diary. (Courtesy Lily Arya, MD.)

Continued

QUESTIONNAIRE-BASED VOIDING DIARY (QVD)

C. Urinary output	Never	Occasionally	Sometimes	Most of the time	All of the time
C1. Do you urinate large amounts of urine when you first wake up in the morning?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
C2. Do you urinate large amounts of urine in the afternoon (12 noon to 5 pm)?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
C3. Do you urinate large amounts of urine in the evening (5 pm to bedtime)?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
C4. Do you urinate large amounts of urine in the night after you have fallen asleep?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

D. Urinary symptoms

- D1. How often do you urinate in the daytime?
- ☐ 1-5
 - ☐ 6-10
 - ☐ 11-15
 - ☐ 16-20
 - ☐ more than 20 times
- D2. How often do you have to get up in the night to urinate after you have fallen asleep?
- ☐ Never
 - ☐ 1
 - ☐ 2
 - ☐ 3
 - ☐ 4 or more
- D3. Do you have to rush to the toilet to urinate?
- ☐ Never
 - ☐ Occasionally
 - ☐ Sometimes
 - ☐ Most of the time
 - ☐ All of the time
- D4. Do you leak urine (even small drops) as you are rushing to the toilet?
- ☐ Never
 - ☐ Occasionally
 - ☐ Sometimes
 - ☐ Most of the time
 - ☐ All of the time
- D5. Do you leak urine when you cough or sneeze or are physically active?
- ☐ Never
 - ☐ Occasionally
 - ☐ Sometimes
 - ☐ Most of the time
 - ☐ All of the time
- D6a. How often do you experience urinary leakage?
- ☐ Less than once a month
 - ☐ A few times a month
 - ☐ A few times a week
 - ☐ Every day and/or night
- D6b. How much urine do you lose each time?
- ☐ Drops
 - ☐ Small splashes
 - ☐ More

Severity Index. This will be completed by your doctor or nurse.

☐ Slight, ☐ Moderate, ☐ Severe, ☐ Very Severe

Arya LA, Banks C, Gopal M, et al. Development and testing of a new instrument to measure fluid intake, output, and urinary symptoms: the questionnaire-based voiding diary. *Am J Obstet Gynecol* 2008;198:559.e1-559.e7.

PATIENT EDUCATION

Because behavioral treatments are based on principles of learning, an important first step in any behavioral program is to provide basic education, so that patients can understand their condition, the treatment process, and the therapeutic goals. Patient education includes an explanation of the anatomy of the bladder, urethra, vagina/prostate, pelvic floor, and rectum; how they function and are interrelated; and the causes and mechanisms of their particular condition. **It is essential for patients to understand that a behavioral program is based on changing habits and learning new skills, and that improvement is often gradual (Lukacz et al, 2011).** Further, understanding that their results will depend on active participation and daily practice facilitates adherence and realistic expectations about therapeutic outcomes.

PELVIC FLOOR MUSCLE TRAINING

PFMT and exercise, also known as pelvic floor rehabilitation (Payne, 2012), is a cornerstone of behavioral treatment for LUTS. First described by Margaret Morris in 1936, it was originally designed to teach patients how to control and exercise perivaginal muscles with the goal of strengthening the muscles and reducing stress UI. It was first popularized by Arnold Kegel, a gynecologist who proposed that stress UI was due to a lack of awareness of function and coordination of PFMs (Kegel, 1948) and who also demonstrated that women could reduce their stress UI through PFMT and exercise (Kegel, 1948, 1956). Over time, this intervention has evolved both as a nurse-directed behavior treatment and as a physical therapy, combining principles from both fields into a widely accepted conservative treatment for incontinence and other LUTS.

In women, it is postulated that a PFM contraction may raise the urethra and press it toward the symphysis pubis, prevent urethral descent, and improve structural support of the pelvic organs (Berghmans et al, 1998). PFMT may result in hypertrophy of the striated muscles, thus increasing the external mechanical pressure on the urethra. Intensive PFMT is also hypothesized to reinforce structural support of the bladder neck in women, limiting its downward movement during increases in abdominal pressure (DeLancey, 1988; Bø, 1995, 2004).

PFMT involves the patient learning how to contract and relax the PFM, performing a regular exercise regimen to improve strength and control and actively using a PFM contraction to occlude the urethra during physical activities that increase abdominal pressure and precipitate urine leakage (Miller et al, 1998). Details of training regimens vary, and few are well-described in the current evidence-based literature (Moore et al, 2013).

Assessment of Pelvic Floor Muscle Function

Before initiation of PFMT, an assessment of the PFM can provide useful baseline information about strength, coordination, and control. PFM function can be assessed by several methods, including digital palpation, visual observation, electromyography (EMG), manometry, or ultrasonography. Digital assessment is the most commonly used technique in clinical practice (Newman and Wein, 2009, 2013). The most widely used digital palpation methods are the Brink score and the Laycock PERFECT assessment scheme (Newman and Laycock, 2008). The Brink score employs a 4-point scale to assess the contraction pressure, vertical displacement, and endurance of squeeze. The Laycock PERFECT (mnemonic for: Power, Endurance, Repetitions, Fast, Every, Contraction, Timed) assessment scheme uses a 6-point scale to score strength and endurance and the number of repetitions and fast contractions.

PFM strength can be determined in women by inserting one or two fingers into the vagina to the level of the first knuckle, then palpating the muscular attachments along the pubic arch and the insertion of the levator ani and coccygeus muscles (Newman and Laycock, 2008; Newman, 2014). The levator ani can be palpated just superior to the hymeneal ring, at the 4- and 8-o'clock positions,

to determine strength, and whether palpation reproduces any discomfort or tenderness. The patient is asked to contract the PFMs around the examiner's finger with as much force and for as long as she is able. She is asked to squeeze or pull in and upward with vaginal muscles in short, fast contractions called "flicks." **It is important to realize that, when asked to contract the PFM, women may use the wrong muscles, strain down, or perform a Valsalva maneuver, or fail to activate all layers of the pelvic musculature.** The examiner notes through observation whether accessory muscles (such as gluteal, abdominal muscles) also contract.

When assessing PFM strength, three criteria should be used (Brink et al, 1989) and the results noted (Messelink et al, 2005):

- Pressure: The amount of pressure or strength of the muscle contraction, which can range from imperceptible to a firm squeeze
- Duration: The number of seconds that the examiner feels the muscle contraction
- Alteration in position: In a well-supported pelvic floor, the muscle contraction can lift the base of the examiner's finger. Use of accessory muscles should be noted (abdominal movement, gluteal lifting). If the patient has an "overactive PFM" (voluntary PFM relaxation is absent, partial or complete), the degree should be noted. Overactive PFM is defined as one that does not relax or may even contract when relaxation is functionally needed (e.g., during micturition).

Assessment of the PFM in men and women also can be performed by evaluating anal sphincter contraction and tone. This is done by having the patient relax and bear down. As the sphincter relaxes, the examiner gently inserts an index finger into the anal canal in a direction pointing toward the umbilicus. Resting sphincter tone can be noted as weak, moderate, or strong. Normally, the muscles of the anal sphincter close snugly around the entire circumference of the examiner's finger. In the rectum, the distal external sphincter is felt just inside the anal canal. The puborectalis portion of the levator ani muscle can be palpated approximately 2.5 to 4 centimeters from the anal verge. To assess the strength of the sphincter muscle, the patient is asked to tighten the rectum. The examiner should feel a gripping or "pulling in" around the entire finger circumference.

Teaching Pelvic Floor Muscle Control

- The first step in PFMT is to teach the patient how to identify the PFMs and contract and relax them reliably. This can be done using verbal feedback based on vaginal or anal palpation during the digital assessment. It can also be done using visual or auditory BF or electrical stimulation (Newman and Wein, 2009, 2013; Newman, 2014). Instructions to patients can include the following:
 - "Contract your muscles around my finger(s). Try to pull up and in."
 - "Without tensing the muscles of your legs, buttocks, or stomach, imagine trying to prevent the passing of gas or pinching off of a stool by tightening the ring of muscles around the anus. A closing and lifting sensation should be felt."
 - For men: "Imagine moving the penis up and down without moving any other part of the body."
 - For women: "You should feel your vagina and rectum pull up and in."

One problem commonly encountered in teaching PFM control is that patients tend to recruit other muscles, such as the rectus abdominis muscles or gluteal muscles, instead of or in addition to the PFMs. Contracting certain abdominal muscles can be counterproductive when it increases pressure on the bladder or pelvic floor. **Thus it is important to observe for the use of other muscles and help patients contract PFMs selectively while relaxing ancillary muscles.** Instructing patients not to hold their breath or to count out loud can be helpful to avoid bearing down. Coordinated training of transversus abdominis muscles also has been recommended by some clinicians, because it is thought that these muscles facilitate

PFM contraction. However, in a review of the literature, [Bo and colleagues \(2009\)](#) noted an absence of evidence for this type of training, and it remains controversial.

It is important to verify that patients have identified and can contract the PFMs properly before initiating an exercise regimen. Not being able to identify the PFMs or to exercise them incorrectly may be the most common reason for poor outcomes with this treatment modality. PFM control is a skill that may take time to master, but with repeated training, most patients are successful. In the past, most patients were given a pamphlet or brief verbal instructions on how to do PFM exercises and were told to “lift the pelvic floor” or to interrupt the urinary stream. Although these simple approaches may be adequate for some patients, it does not ensure that they understand which muscles to use when they begin a structured exercise program at home.

Pelvic Floor Muscle Exercise Regimens

Once patients demonstrate the ability to properly contract and relax the PFM, they are given instructions for daily practice and exercise. The purpose of daily exercise is twofold: to increase muscle strength and to enhance motor skills through practice. Specific exercise regimens vary considerably in frequency and intensity, and the ideal exercise regimen has not yet been determined. However, good results have been achieved in several trials using 45 to 60 paired contractions and relaxations per day.

We use an “exercise prescription” to prescribe the daily exercise program (sample of an exercise prescription is found in [Box 80-2](#)) ([Newman and Wein, 2013](#); [Newman, 2014](#)). One approach is to recommend a series of “quick flicks” or 1- to 2-second contractions, followed by sustained contractions (endurance contractions) of 5 seconds or longer. The patient is encouraged to aim for a high level of concentrated effort with each PFM contraction because greater contraction intensity is associated with improvement in PFM strength.

It is equally important to relax the PFM completely between each contraction. Each exercise consists of muscle contraction followed by a period of relaxation using a 1:1 or 1:2 ratio. This allows the muscles to recover between contractions and facilitates optimal strength building.

It is usually recommended that patients space the exercises across the day, typically in 2 to 5 sessions per day to avoid muscle fatigue. Exercising while in the prone position is often recommended at first, because it is the least challenging. However, it is important for patients to progress to sitting or standing positions with time, so that they become comfortable and skilled using their muscles to avoid incontinence in any position.

Use of Pelvic Floor Muscle Contraction to Prevent Stress Incontinence

The goal of behavioral treatment for stress UI is to teach patients how to prevent urine loss in daily life by occluding the urethra using active contraction of PFMs ([Miller et al, 1998](#)). Although exercise alone can improve urethral pressure and structural support and reduce incontinence, this motor skill enables patients to consciously occlude the urethra at specific times when urine loss is imminent. A careful history or examination of a bladder diary can alert the provider and patient of the circumstances during which each individual patient commonly experiences urine loss. Patients then learn to anticipate these activities and prevent leakage by contracting the PFM to occlude the urethra before and during coughing, sneezing, lifting, or any other physical activities that have precipitated urine leakage.

This skill has been referred to as the “stress strategy” ([Burgio et al, 1989](#)) and “the Knack” ([Miller et al, 1996, 2008](#)). Although using this technique requires initial vigilance on the part of the patient and a conscious effort to develop the habit of using muscles to increase urethral closure, it eventually becomes automatic. A handout with instructions for the patient is presented in [Box 80-3](#).

BOX 80-2 Sample Pelvic Floor Muscle Exercise Prescription

Please complete the following exercises every day:

SHORT QUICK EXERCISE

Contract the muscle quickly for 1 to 2 seconds and immediately relax.

LONG SUSTAINED EXERCISE

Contract the muscle, and hold the contraction for a count of ____ then immediately relax for a count of ____.

After each muscle contraction, be sure to rest your muscle for the same amount of time.

When you have completed the short quick exercise and the long sustained exercise in the lying down, sitting, and standing positions, you will have completed one session.

EXERCISE SESSION

Lying Down

Short quick exercise: Do 5 exercises holding for 1 to 2 seconds.
Long sustained exercise: Do 5 exercises holding for (5 to 10) seconds.

Sitting

Short quick exercise: Do 5 exercises holding for 1 to 2 seconds.
Long sustained exercise: Do 5 exercises holding for (5 to 10) seconds.

Standing

Short quick exercise: Do 5 exercises holding for 1 to 2 seconds.
Long sustained exercise: Do 5 exercises holding for (5 to 10) seconds.

Do two exercise sessions each day—one in the morning and one in the evening, for a total of 60 exercises.

Special Tips

- Always empty your bladder before beginning your exercise session.
- Count out loud with sustained or long exercises; remember to keep breathing!
- Keep your stomach, leg, and buttock muscles relaxed. Rest your hand on your stomach; it should not move or tense.
- If it helps, take a deep breath between each exercise to help you keep other muscles relaxed.

Modified from Newman DK, Wein AJ. Office-based behavioral therapy for management of incontinence and other pelvic disorders. *Urol Clin North Am* 2013;40:613–35; and Newman DK, Wein AJ. Managing and treating urinary incontinence, 2nd ed. Baltimore: Health Professions Press; 2009. p. 245–306.

Evidence for Pelvic Floor Muscle Training

PFMT is an established treatment supported by a large body of evidence. A Cochrane review of PFMT-based treatments concluded that these treatments were effective for both stress and mixed UI ([Dumoulin et al, 2014](#)) and can reduce urgency, but women with pure stress UI may have better outcomes ([Bo & Herbert, 2013](#)). PFMT is better than no treatment, a placebo drug, or an inactive control treatment for women with stress, urgency, and mixed UI ([Ayeleke et al, 2013](#); [Moore et al, 2013](#)). Women treated with PFMT show benefit on a number of outcomes, including cure, better quality of life, reduction in daily leakage episodes, and less urine

BOX 80-3 Handout for Teaching Stress Strategies and the “Knack”

Urine leakage occurs when the pressure pushing urine out is higher than the pressure holding it in your bladder. Any activity that increases pressure in your stomach may cause you to lose urine. Leakage can occur during coughing, sneezing, standing up, when exercising, bending, or lifting. It is possible to squeeze your pelvic floor muscles during specific activities and prevent leakage. A bladder diary will help you identify activities that cause leakage.

1. Quickly squeeze your pelvic floor muscles (like trying to hold back gas) just before and during activities that normally cause you to leak (coughing, sneezing, bending, lifting, getting up from a chair).
2. If you forget to squeeze your muscles and urine leaks out, go ahead and squeeze your muscles right then. It will not prevent that leakage, but will help link squeezing the muscles with that activity.
3. The Stress Strategy requires careful timing and practice. It may take some time for you to get the “knack” of doing it. Do not get discouraged. Eventually, it will become automatic.
4. Remember: **“Squeeze before you sneeze.”**

Modified from Burgio KL, Pearce KL, Lucco AJ. *Staying dry: a practical guide to bladder control*. Baltimore: Johns Hopkins Press; 1989. p. 67–100; and Newman DK, Wein AJ. *Managing and treating urinary incontinence*, 2nd ed. Baltimore: Health Professions Press; 2009. p. 245–306.

leakage on a pad or paper towel test immediately after treatment and long term. Cure rates for PFMT range from 16% to 27% and improvement rates from 48% to 80.7%. Evidence is lacking regarding the best approach to PFMT, but **there is consensus that supervised PFMT is more effective than unsupervised programs** (Hay-Smith et al, 2011, 2012; Moore et al, 2013), although the degree and type of supervision needed are uncertain. Moreover, the treatment effect appears to be enhanced when PFMT is based on sound muscle training principles such as specificity, overload progression, correct contraction confirmed before training, and use of the “knack” (intentional muscle contraction), a motor skill for PFM contraction.

The effect of PFMT in women with stress UI does not seem to decrease with age; in trials of older women, both primary and secondary outcome measures were comparable to those in trials focused on younger women. Thus age should not be a deterrent to PFMT (Betschart et al, 2013). Based on this evidence, supervised PFMT should be offered as a first-line conservative therapy for women of all ages with stress, urgency, or mixed UI.

Postpartum Urinary Incontinence

PFMT is recommended during pregnancy and after childbirth, both for prevention and treatment of incontinence (Neilson, 2009; Mørkved and Bø, 2013; Wesnes and Lose, 2013). Cochrane reviews of randomized or quasi-randomized controlled trials in pregnant or postnatal women included 22 trials involving 8485 women (Boyle, 2012, 2014). Postpartum women with UI who were randomized to PFMT taught and supervised by a health care professional were less likely to be incontinent 6 to 12 months after delivery, compared to no treatment or usual care. The ICI committee (Moore et al, 2013) recommends that PFMT should be offered as first-line therapy to postpartum women with UI persisting 3 months after delivery. Evidence for the value of perinatal PFMT for prevention of postpartum UI can be found in the section Role of Conservative Interventions for Prevention of Urinary Incontinence.



Figure 80-4. Example of weighted vaginal weights.

Postprostatectomy Urinary Incontinence

Stress UI is a complication of radical prostatectomy, regardless of the technique used (Resnick et al, 2013). PFMT is the primary conservative treatment for UI secondary to prostatectomy. It may be taught using digital rectal examination (DRE) with verbal feedback or with BF or electrical stimulation.

Trials of PFMT for established postprostatectomy UI have yielded mixed results but generally show that PFMT reduces UI in the first 3 months after surgery (Campbell et al, 2012; Moore et al, 2013). Less research has focused on UI that persists long term. One randomized controlled trial (RCT) compared BT (PFMT + bladder control strategies) versus no treatment in men with UI persisting 1 to 17 years after radical prostatectomy (Goode et al, 2011). After 8 weeks of treatment, men in the BT group showed 55% reduction in UI episodes, significantly greater than the 24% reduction in the control group, and improvements were sustained to 12 months.

According to Moore and colleagues (2013), it is not clear whether PFMT should be delivered in the form of hands-on therapy or verbal instruction. Current evidence suggests that the addition of PFM electrical stimulation or BF does not appear to improve continence outcomes over PFMT alone (Mariotti et al, 2009). However, BF is an effective approach and providers may prefer it over DRE.

Many studies of postprostatectomy UI involve perioperative PFMT for prevention of postprostatectomy UI. These studies are covered in the section on Role of Conservative Interventions for Prevention of Urinary Incontinence.

Vaginal Cones for Pelvic Floor Muscle Training

Weighted vaginal cones are sometimes used to help women identify and control their PFMs and to support adherence to PFMT (Herbison and Dean, 2013; Moore et al, 2013) (see Fig. 80-4 for an example of a set of graded weighted vaginal cones). When a cone is placed in the vagina while standing, it is usually necessary to contract the PFM to keep it from slipping out. The sensation of losing the cone prompts women to hold it in by tightening the PFMs. Women are instructed to insert the heaviest cone they can retain while standing, at first, and then while walking around. When successful with this first cone, they are progressed to the next heaviest cone. The goal is for women to be able to retain the cone using a PFM contraction while walking around for two sessions of 15 min/day, for 1 month or more. Some women find the cones helpful and motivating. Others find them uncomfortable, difficult to insert (because of a narrowed vaginal opening), or impossible to retain (because of a prolapse or enlarged vaginal opening).

A 2013 Cochrane review (Herbison and Dean, 2013) analyzed 23 trials involving 1806 women, of whom 717 received cones. All of the trials were small, and in many the quality was difficult to

judge. They concluded that there was some evidence that weighted vaginal cones are better than no active treatment in women with stress UI and may be of similar effectiveness to PFMT and pelvic floor electrical stimulation, but more definitive trials are needed to understand the role of weighted vaginal cones in the treatment of UI.

BEHAVIORAL TRAINING WITH URGE SUPPRESSION

BT is a stand-alone treatment that teaches patients how to use their PFMs to inhibit detrusor contraction and how to use this skill as a part of a larger urge suppression strategy that constitutes a new way of responding to urge for patients with urgency, frequency, and/or urgency UI. BT evolved out of BF-assisted BT in which bladder and anal sphincter BF were used together to teach patients to inhibit detrusor contraction during retrograde bladder filling. Originally, the focus of training was on bladder pressure feedback and learning cortical inhibition of detrusor contraction. During these BF sessions, it was observed that spontaneous anal sphincter activity appeared to affect detrusor pressures, and it was subsequently demonstrated that a well-timed, volitional contraction of the anal sphincter (reflecting PFM), guided by visual BF, could abort fully developed detrusor contractions, deter developing contractions, and suppress the sensation of urgency (Burgio et al, 1985, 1998).

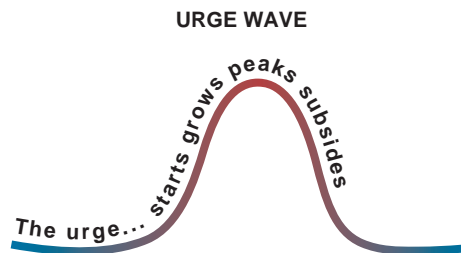
Later, it was shown that this skill could be taught without BF, using verbal feedback based on vaginal palpation instead. In a randomized trial of BT with and without BF, older women with urgency UI, taught using verbal feedback based on vaginal palpation, achieved outcomes as good as those achieved using bladder-sphincter BF when this skill was integrated into a larger strategy (Burgio et al, 2002). BT is now generally conducted using verbal feedback based on vaginal palpation, making it more widely available.

Based on these findings, although PFMT and exercise was originally designed for the treatment of stress UI, it is now used as a central element in the treatment of urgency UI and OAB. In BT, patients are taught PFM control and exercise in the same way as for stress UI. What differs is how they use their muscles to manage urgency and prevent urine loss. In addition to using PFM to occlude the urethra, patients learn to use PFM contractions as one part of a broader strategy to respond to the sensation of urge, as follows.

Patients with urgency and urgency UI often feel compelled to rush to the nearest bathroom when they feel the urge to void, believing that they are about to lose control. With BT, they learn how this natural “gotta go” response is actually counterproductive, because it increases physical pressure on the bladder, increases the feeling of fullness, exacerbates urgency, and triggers detrusor contraction. Further, as the patient approaches the toilet, visual cues can trigger urgency and incontinence. To avoid this conditioned response, patients are taught not to rush to the bathroom when they feel the urge to void. Instead, they are advised to stay away from the bathroom, so as to avoid exposure to cues that trigger urgency. They are encouraged to pause, sit down if possible, relax the entire body, and contract PFM repeatedly, without relaxing in between contractions, to diminish urgency, inhibit detrusor contraction, and prevent urine loss. They focus on inhibiting the urge sensation, giving it time to pass. Once the sensation subsides, they walk at a normal pace to the toilet. (A handout for teaching the urge suppression strategy is in Fig. 80-5.)

Once patients master the urge suppression strategy, instead of walking to the bathroom immediately after suppressing the urge, they are encouraged to delay voiding for 5 minutes to consolidate their skill. If they are voiding too frequently, this delayed voiding interval can be increased gradually until they achieve a normal voiding frequency.

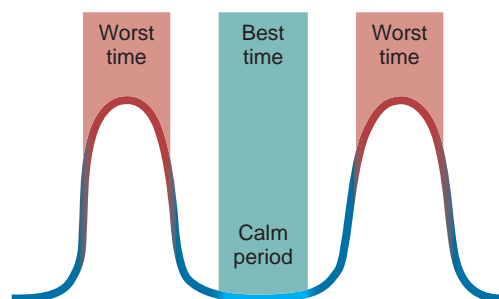
The effectiveness of BT with urge suppression as a stand-alone therapy for urgency UI has been established in several clinical series studies (Burgio et al, 1985; Baigis-Smith et al, 1989; Rose et al, 1990; McDowell et al, 1992) and in RCTs using intention-to-treat models, in which mean reductions of incontinence range from



When the urge strikes...

- Stop and stay still. **Do not** rush to the toilet.
- Sit down if you can.
- Squeeze your pelvic floor muscles quickly 3 to 5 times and repeat as needed—don't relax muscles in between.
- Relax the rest of your body. Taking several slow, deep breaths.
- Concentrate on suppressing the urgency. Once it calms down, squeeze again as you stand.
- Walk to the bathroom at a normal pace—do not rush or hurry.
- If the urge returns on the way to the bathroom, stop and squeeze away the urge again.

WHEN TO VOID



Here are some other ways you can try to control your bladder urge.

- **Distract yourself** by focusing on a mental activity: Use mind games. Turn your attention to counting backward from 100 by 7s or working on a crossword puzzle. Do a task that requires a lot of thought—for example, balance your checkbook, write a letter, do homework, or some other activity that requires a great deal of attention.
- **Use self-talk or good self-statements.** Tell yourself: “I am the boss, not my bladder.” “I am in control.” “I can beat this.” Create a statement that fits your situation and personality the best. Keep saying this statement over and over until the feeling of urgency passes.

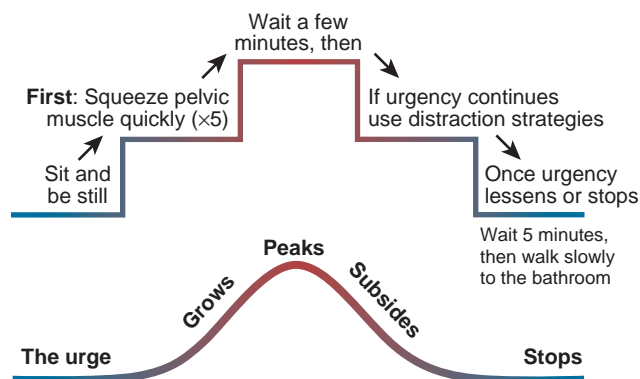


Figure 80-5. Patient handout with instructions for the urge suppression strategy. (Urge wave, from Burgio KL, Pearce KL, Lucco AJ. *Staying dry: a practical guide to bladder control*. Baltimore: Johns Hopkins Press; 1989. p. 79; When to void, from Burgio KL, Pearce KL, Lucco AJ. *Staying dry: a practical guide to bladder control*. Baltimore: Johns Hopkins Press; 1989. p. 80; Steps to controlling urgency, courtesy Diane K. Newman.)

60% to 80% (Burgio et al, 1998, 2002). In one RCT, BT reduced incontinence episodes significantly more than individually titrated drug treatment and patient perceptions of improvement and satisfaction with their progress were higher (Burgio et al, 1998).

This therapy also has been shown to reduce urgency, frequency, and nocturia in both men and women. As an example, the Male Overactive Bladder in Veterans (MOTIVE) study compared BT with urge suppression to antimuscarinic therapy (extended-release oxybutynin) in men with OAB in the absence of bladder outlet obstruction (Burgio et al, 2011). Mean 24-hour voids decreased significantly in both groups, and these reductions were statistically equivalent.

BT with urgency suppression has also been shown to reduce nocturia in both men and women (Johnson et al, 2005; Burgio et al, 2011; Johnson et al, 2013). Patients are instructed to use urge suppression techniques when they wake up at night with bladder fullness or an urge to void. If the fullness/urge subsides, they are encouraged to go back to sleep. If after a minute or two the urge to void has not subsided, they are advised to get up and void, so as not to interfere unnecessarily with their sleep. Johnson and colleagues (2005) showed that both BT and drug therapy reduced nocturia more than placebo in women, and BT was significantly more effective than drug therapy. In a study in men with nocturia (Johnson et al, 2013), both behavioral treatment (PFMT, delayed voiding and urge suppression techniques) and drug (antimuscarinic) therapy reduced nocturia in men when added to α -blocker therapy, but the addition of behavioral treatment was statistically better than the addition of antimuscarinic therapy for nocturia.

Evidence has shown that combining BT with drug therapy can improve outcomes of drug therapy for urge incontinence. In a multisite trial conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Urinary Incontinence Treatment Network, women with urge-predominant incontinence were randomized to receive extended-release tolterodine with or without BT. Women who underwent BT in addition to drug therapy reported greater improvements in patient perception of improvement, patient satisfaction, and validated measures of symptom distress and bother while on active therapy, as well as 6 months after drug therapy was discontinued (Burgio et al, 2008).

In addition to being a central element of behavioral training, the urge suppression strategy has been adopted as one of several techniques to help patients postpone voiding in bladder training or delayed voiding programs.

ROLE OF BIOFEEDBACK

BF is not a treatment in itself, but a technique for teaching patients control over physical responses. Commonly known for its role in treatment of headaches, muscle spasm, and hypertension, it is also a very effective method for teaching bladder and PFM control in the treatment of LUTS. **BF helps patients learn by giving them precise, instantaneous feedback of their physiologic responses, such as PFM contraction.** The "perineometer" developed by Dr. Kegel was a BF instrument that assisted women to learn PFM control by giving immediate feedback of efforts to contract PFMs. BF may be especially helpful in patients who are having difficulty identifying and isolating the correct muscles or who need encouragement to continue with prescribed treatment.

Most BF instruments are now computerized and display feedback visually on a monitor (Fig. 80-6). Pelvic floor muscle activity can be measured by manometry or surface electrode electromyography (EMG), using vaginal or anal probes or surface skin electrodes. Signals are enhanced through the computer, and feedback is provided on a monitor for visual feedback or via speakers for auditory feedback (Figs. 80-7 through 80-9). When patients observe the results of their attempts to control PFM activity, learning occurs by means of operant conditioning (trial and error learning).

An advantage of EMG over manometric pressure is that, provided the machinery is of sufficient sophistication with adequate filtering, EMG apparatus can use the newer types of electrodes that



Figure 80-6. Prometheus biofeedback equipment with monitors for visual feedback. (Courtesy Penn Urology, University of Pennsylvania.)



Figure 80-7. Provider teaching patient using biofeedback.

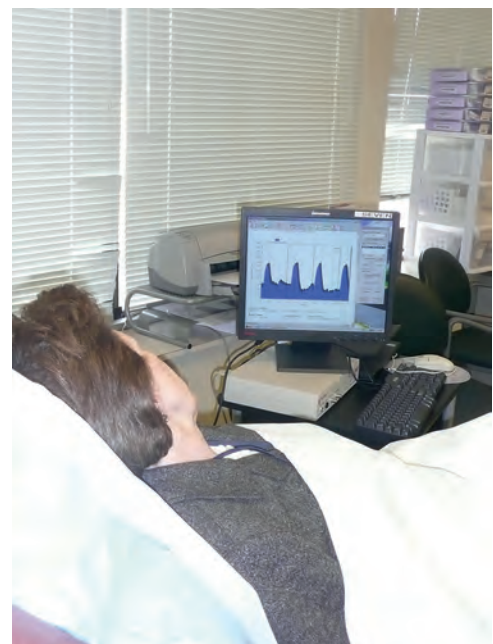


Figure 80-8. Patient viewing biofeedback tracings.

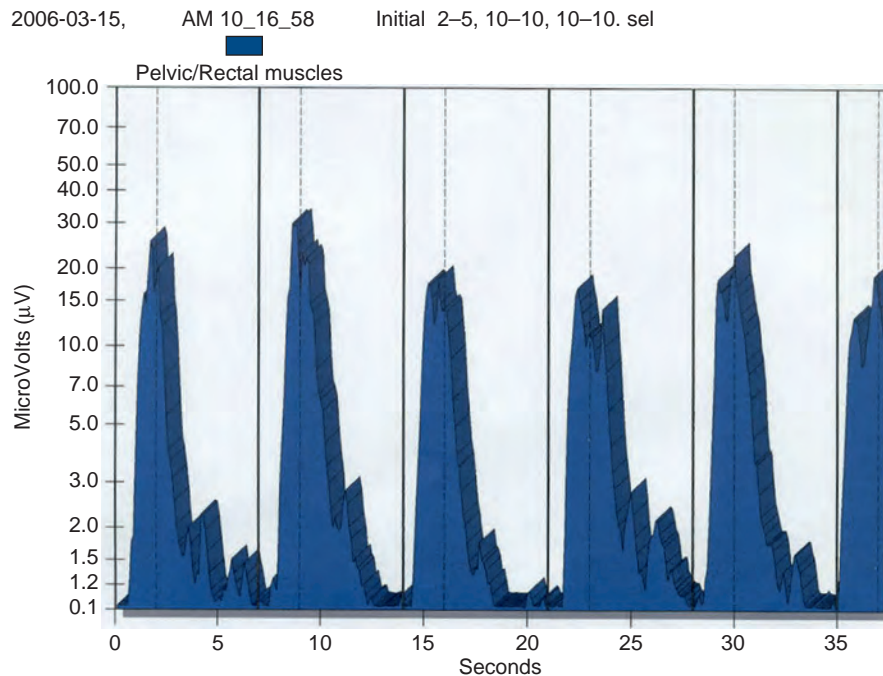


Figure 80-9. Example of a biofeedback graph.

are lightweight and designed to stay in place, hence allowing more functional positions during assessment and treatment. Like other methods, EMG can be multichannel, which allows the simultaneous display of PFM contraction and inhibition of counterproductive accessory muscle contractions (e.g., abdominal, gluteal muscle).

BF-assisted PFMT in conjunction with other conservative treatment components has been tested in several studies, producing mean reductions of UI ranging from 60% to 85% (Moore et al, 2013). BF technology is an excellent method to help patients identify and exercise PFMs, but it is not the only effective method, and it is not considered essential. The literature is inconsistent on the issue of whether BF enhances outcomes of PFMT. A 2011 Cochrane review (Herderschee et al, 2011, 2013) included 24 trials involving 1583 women and concluded that women who received PFMT with BF were significantly more likely to report cure or improvement compared to those who received PFMT alone. However, these studies should be interpreted cautiously because the treatment groups differed on parameters other than BF, such as preparation of the clinician providing the therapy, and women in the BF groups usually had more extensive contact with providers.

PELVIC FLOOR MUSCLE ELECTRICAL STIMULATION

Pelvic floor muscle electrical stimulation with a nonimplanted device involves the application of a low-grade of electrical stimulation to the PFM to stimulate contraction in patients with different types of UI or symptoms of urgency, frequency, and nocturia (Newman and Wein, 2009). Electrical stimulation has a twofold action: contraction of PFMs and inhibition of unwanted detrusor contractions (Schreiner et al, 2013). Electrical stimulation is provided by office-based machines or portable battery-powered stimulators that are used in the office or by the patient at home. These units have different combinations of current types, waveforms, frequencies, intensities, electrode types, and placements.

Pelvic floor muscle electrical stimulation is usually a component of conservative treatment in urologic practice, because clinicians use it to assist in PFM identification (Starr et al, 2013). Patients with LUTS secondary to neurologic disease (e.g., multiple sclerosis) also may benefit from this therapy. Many clinicians institute this treatment in patients who have failed other behavioral treatments and

prescribe home units for long-term treatment. There are two main types of electrical stimulation, as follows:

Long-term or chronic electrical stimulation delivered below the sensory threshold aiming at detrusor inhibition by afferent pudendal nerve stimulation. According to Fall and Lindstrom (1994), the electrically evoked activity results in reflex activation of hypogastric efferents and central inhibition of pelvic efferent mechanisms sensitive to low-frequency stimulation. The device is used for 6 to 12 hours per day for several months.

Maximal electrical stimulation, using a high-intensity stimulus (just below the pain threshold), aims to improve urethral closure by direct and reflexogenic contraction of striated periurethral musculature (Fall and Lindstrom, 1991). Detrusor inhibition by afferent pudendal nerve stimulation also has been suggested as a mechanism (Berghmans et al, 2002). This type of electrical stimulation is applied for short durations (15 to 30 minutes) several times per week (or one to two times daily using portable devices at home).

In the context of conservative therapy, electrical stimulation can be applied using surface skin electrodes, delivering transcutaneous electrical stimulation via suprapubic, sacral, or external anal surface skin electrodes or intravaginal or intrarectal sensors. Parameters for electrical stimulation include current source, pulse width and duration, current intensity (range), stimulus frequency, pulse shape, length of session, total number of sessions, and rest to work ratio, which are varied according to type of UI and type of electrical stimulation. Berghmans and colleagues (2002) reported that frequencies of 5 to 20 Hz are usually used for urgency UI, 20 to 50 Hz for stress UI (including after prostatectomy), and approximately 20 Hz or high and low frequency alternately for mixed UI. Pulse durations range from 200 to 1000 µsec. The pulse shape is generally rectangular, and biphasic pulses are preferred.

The literature on electrical stimulation in women indicates that it is effective for improving stress, urgency and mixed UI compared to sham or no treatment (Moore et al, 2013). However, it does not appear to enhance outcomes over those obtained through PFMT alone or PFMT with BF. Less work has been done examining electrical stimulation in men (Berghmans et al, 2013). Overall, there is little evidence to suggest that electrical

stimulation improves outcomes of PFMT, with or without BF, but it may hasten the recovery of continence after prostatectomy.

BLADDER TRAINING AND SCHEDULED VOIDING REGIMENS

Scheduled voiding regimens, also known as toileting programs, have for decades been a mainstay of treatment for urge UI and OAB. Scheduled voiding regimens include bladder training, timed voiding, habit training, and prompted voiding (Table 80-4). Although these regimens share the common feature of being based on a toileting schedule, they differ on the role of the patient (active vs. passive), how adjustments are made to the voiding schedule, the nature of patient education, the use of reinforcement techniques, and the nature of the patient-provider interaction (Moore et al,

2013). Bladder training is self-administered and requires the patient to resist urgency and delay voiding. Timed voiding, habit training, and prompted voiding most often rely on caregiver involvement.

Bladder Training

Bladder training is a behavioral intervention developed originally for the treatment of urgency UI. Many patients who experience urgency UI or urgency without leakage, tend to void frequently. This response provides immediate relief from the sensation of urgency, but it sets the stage for more and more frequent urination. Once frequent voiding becomes a habit, it can be difficult to change and may lead to reduced functional bladder capacity, detrusor overactivity, and, in some cases, urge UI. Detrusor overactivity produces urgency, completing a cycle of urgency and frequency that is then

TABLE 80-4 Understanding Toileting Programs

TYPE	DEFINITION	KEY COMPONENTS
Timed voiding (or scheduled toileting)	Fixed, predetermined time intervals between toileting	The following is an example of a toileting program that can be used by institutions or caregivers that includes 8 times in a 24-hr period, or every 3 hr: <ul style="list-style-type: none"> • <i>Day:</i> On awakening, after breakfast, midmorning, before lunch, and after an afternoon nap (midafternoon). • <i>Evening:</i> Before dinner and at bedtime. • <i>Night:</i> Determine if person wants to be awakened at night to void and identify times.
Habit training	Fixed voiding schedule based on identified patterns of incontinence to preempt incontinence.	Using a bladder diary, incontinence and voiding patterns are identified and an individualized toileting schedule is developed. In institutions such as nursing homes, a typical toileting schedule may be determined around daily events.
Prompted voiding	Involves prompting and assisting patients to toilet and positive reinforcement for requesting toileting assistance either spontaneously or following verbal prompts from a caregiver.	The major elements of prompted voiding are: <ul style="list-style-type: none"> • <i>Monitoring:</i> The caregiver checks on a regular basis (use toileting schedule described in scheduled toileting) and person is asked to report verbally if wet or dry. • <i>Prompting:</i> The person is asked if they need to void and assisted with voiding. • <i>Praise and encouragement:</i> The caregiver provides if the person is continent. Most successful in individuals who can ask for assistance or void when prompted.
Functional incidental training (FIT)	Combines prompted voiding with functionally oriented, low-intensity endurance and strength-training exercises.	Combine mobility and transfer training with prompted voiding,
Bladder training	Training involves establishing a voiding schedule and incrementally increasing the voiding interval.	Promotes restoration of normal bladder function through incremental voiding schedules and education regarding urge inhibition techniques. Requires person to be able and willing to participate actively. <p><i>Four primary components:</i></p> <ol style="list-style-type: none"> 1. Education program that usually combines written, visual, and verbal instruction addressing the physiology and pathophysiology of the lower urinary tract. 2. Scheduled voiding with systematic delay of voiding that requires the ability to resist or inhibit the sensation of urgency, to postpone voiding, and to urinate according to a timetable rather than according to the urinary urge. 3. Use of techniques to suppress urgency (quick pelvic floor muscle contractions, deep breathing with relaxation, distraction techniques). 4. Gradual increases in voiding interval. 5. Reinforcement through consistent encouragement and positive feedback.

Modified from Flanagan L, Roe B, Jack B, et al. Systematic review of care intervention studies for the management of incontinence and promotion of continence in older people in care homes with urinary incontinence as the primary focus (1966-2010). *Geriatr Gerontol Int* 2012;12:600-11; Newman DK, Burgio KL, Markland AD, et al. Urinary incontinence: nonsurgical treatments. In: Griebing TL. *Geriatric urology*. London: Springer-Verlag; 2014. p. 142; and Newman DK, Wein AJ. *Managing and treating urinary incontinence*. 2nd ed. Baltimore: Health Professions Press; 2009. p. 245-63.

perpetuated. This cycle can be broken using bladder training or a program of progressive delayed voiding.

The goal of bladder training is to restore normal bladder function and capacity using consistent, incremental voiding schedules. First known as bladder drill, it was an intensive intervention that was often conducted in an inpatient setting. Now the program is implemented more gradually in an outpatient setting. Bladder training is a multicomponent intervention that involves patient education regarding LUT function, setting incremental voiding schedules, and teaching urge control techniques to help patients postpone voiding and adhere to the schedule (Fantl et al, 1991; Wyman and Fantl, 1991; Wallace et al, 2009).

Usually bladder training begins with the patient completing a bladder diary to document voiding patterns and frequency. Based on the diary, an initial voiding interval is established (Moore et al 2013). Often, this is a 1-hour interval during waking hours, although a shorter interval (e.g., ≤ 30 minutes) may be necessary at first. Another method is for the clinician to select a voiding interval based on the longest time interval between voids that is comfortable for the patient. The patient is to void on waking in the morning, every time the interval has passed, and just before bedtime. The schedule is increased by 15 to 30 min/week, depending on the patient's tolerance to the schedule (i.e., fewer incontinent episodes than the previous week, minimal interruptions to the schedule, and the individual's control over urgency).

In bladder training, the patient is asked to postpone urination, which for most patients involves coping with the sensation of urgency while they wait. The approach to urgency management used in clinical practice has been to suggest various techniques for relaxation or distraction to another activity (Fantl et al, 1991; Wyman and Fantl, 1991; Wyman, 2007). Patients are encouraged to get their mind off the bladder by engaging in an activity that requires mental but not physical effort (see Fig. 80-5). Common activities include making a telephone call, reading, or making a to-do list. Distracting attention from the bladder in this way can reduce anxiety and allows time for the urge to subside. Also used are affirming self-statements such as "I am in control of my bladder," or "I can wait." Repeated rapid contraction of the PFM (termed "quick flicks") with the individual remaining posturally still and waiting for the sensation to pass has proved to be a useful adjunct to the bladder training regimen for OAB (Newman and Wein, 2009; Payne, 2012; Moore et al, 2013).

Ideally, the provider should monitor a patient's progress on a weekly basis during the training period, make individualized adjustments to the voiding interval, and provide positive reinforcement during the training period. Patient self-monitoring using voiding diaries is a useful tool to help patient and clinician evaluate adherence to the schedule, evaluate progress, and determine whether the voiding schedule should be changed.

The underlying mechanisms of how bladder training works are unknown. However, one of the most important features of bladder training is that it dissociates voiding from urgency, and it may be that voiding by the clock, rather than in response to urgency, weakens the urge-void response. Other hypotheses include improved cortical control of bladder activity and urethral closure, improved central modulation of afferent stimuli, altered behavior because of better awareness of LUT function, and increased bladder capacity.

Evidence for Bladder Training

Several systematic reviews have been published that provide synthesis and grading of evidence for bladder training in the treatment of UI or urgency UI (Berghmans et al, 2000; Roe et al, 2007; Wallace et al, 2009; Moore et al, 2013). The ICI included RCTs with participants who had UI (urge, stress, and mixed), as well as participants who had OAB without UI. Based on 17 trials involving 2462 women and five trials with 142 men, the ICI noted and described remarkable variability in bladder training protocols and concluded that there was no evidence to suggest the most effective method or specific parameters of bladder training. However, they recommend that clinicians provide the most intensive bladder

training supervision that is possible within service constraints (Moore et al, 2013).

From the few trials available of bladder training in women with urge, stress, and mixed UI, the ICI concluded that bladder training is more effective than no treatment, but there was insufficient evidence to draw conclusions on its effect in men. They also found insufficient evidence to draw conclusions on the comparative effectiveness of bladder training and current drug therapy or for their combined effectiveness for women with detrusor overactivity or urgency UI. In a comparative effectiveness review of nonsurgical treatments for UI in women, the Agency for Healthcare Research and Quality (AHRQ) (Shamiliyan et al, 2012) found that UI outcomes did not differ between bladder training and PFMT; nor were there differences between bladder training alone and bladder training combined with PFMT.

Other Scheduled Voiding Regimens

Toileting programs are the cornerstone of continence care for cognitively impaired patients. Other than BT, toileting programs are usually caregiver-dependent, defined as the need for a professional or family caregiver to assist with toileting (Newman and Wein, 2009). Scheduled voiding can be beneficial for toileting-dependent residents in nursing homes or individuals living at home who have an available and willing caregiver. Individuals who have difficulty or require human or mechanical assistance with toileting are referred to as having "toileting disability" (Talley et al, 2014). These individuals may have mobility or cognitive impairment or may need some assistance from at least one person, but are able to cooperate with toileting. The choice of timed voiding, habit training, or prompted voiding program is determined by the cognitive and functional status of the individual, the variability of the voiding pattern, and the need for reinforcement for adherence to the regimen.

Timed Voiding

Timed voiding also has been called scheduled toileting, routine toileting, and fixed toileting. The goal of timed voiding is to prevent incontinence by providing regular opportunities for bladder emptying before the bladder reaches capacity. Keeping the bladder volume below capacity may decrease leakage associated with a detrusor contraction that occurs with a full bladder, as well as decrease leakage that might occur with stress UI. No other physiologic mechanism has been determined. Timed voiding has been recommended for patients who cannot use the toilet independently. It has been used primarily in institutional settings as a passive toileting assistance program, in which a caregiver takes the patient to void every 2 to 4 hours except at night, and for patients with neurogenic bladders associated with multiple sclerosis and other neurologic diseases (Ostaszkiwicz et al, 2004b, 2005b). Ideally, the schedule for toileting is based on some objective measure, such as a bladder diary, on data collected using a bladder volume recording instrument (Newman et al, 2005), or from an electronic device used to monitor and record incontinence episodes (Colling et al, 2003).

Timed voiding is a "passive" type of toileting program, because it takes place regardless of whether patients have a sensation to void, but the schedule is usually followed only during waking hours (Ostaszkiwicz et al, 2005b). The goal is to keep the person dry, and no effort is made to motivate the person to resist the urge to urinate. Although fewer than 20% of frail elders become completely dry with timed voiding, between 30% and 50% of incontinent elders may improve, reducing the number and volume of incontinence episodes. This is probably also true in people being cared for in their homes.

Timed voiding also can be useful for cognitively intact elders who have developed bladder sensory impairment as a result of neurologic conditions. Voiding by the clock, instead of waiting for urgency, and before spontaneous bladder emptying occurs, can prevent or reduce incontinence. A brief, 2- to 3-day trial of timed

voiding can determine if it will be successful for an individual. Timed voiding is also intended to normalize frequency in a patient with infrequent voiding and/or diminished sensation (Payne, 2012).

Habit Training

Habit training is a variant of timed voiding, with the difference being that the toileting schedule is matched to the patient's voiding pattern, rather than being fixed as it is in timed voiding. Using the patient's bladder diary, a toileting schedule is assigned to fit a time interval that is shorter than the patient's normal voiding pattern and to precede the period when incontinent episodes are expected. Thus the voiding interval may be lengthened or shortened throughout the day depending on the patient's voiding pattern, with the goal to preempt incontinence. In the traditional applications of habit training, it is a caregiver-dependent toileting assistance program that is initiated and maintained by the active involvement of a professional or family caregiver (Ostaszewicz, 2004a, 2005a).

Habit retraining has primarily been used in institutional settings with cognitively and physically impaired adults; but it also has been tested with the homebound elderly population (Colling et al, 2003). Habit retraining has applicability for use in unimpaired adults who have a consistent pattern of incontinence that occurs at approximately the same time interval each day or is induced by diuretic use. The interval may be set permanently or gradually increased.

Colling and colleagues (2003) developed a habit training program called Pattern Urge-Response Toileting (PURT) and tested it with 78 caregiver-dependent homebound frail elders. Caregivers in this study were relatives, usually spouses providing care. Three weeks of voiding patterns were obtained from electronic data loggers; individualized toileting schedules were identified based on each person's voiding pattern; and caregivers were taught when and how to provide toilet assistance to the care recipient. The PURT program reduced the number of incontinence episodes over 24 hours by 18%, decreased the mean number of daily episodes from 4.9 to 4.0, and reduced the volume of UI over 24 hours by 39%.

Prompted Voiding

Prompted voiding is a toileting program that combines scheduled voiding with prompting from a caregiver. It is used to teach people with or without cognitive impairment to initiate their own toileting through requests for help and positive reinforcement from caregivers when they do so. It has been used primarily in nursing home settings with cognitively and physically impaired older adults (Schnelle et al, 1989; Burgio et al, 1994; Eustice et al, 2000).

Prompted voiding has three components: (1) regular monitoring with encouragement to report continence status, (2) prompting of resident to toilet on a scheduled basis, and (3) praise with positive feedback when the resident is continent and tries to toilet (Lekan-Rutledge, 2000; Lyons and Specht, 2000). For prompted voiding to be effective, individuals must be able to delay voiding and cooperate with toileting or have awareness of when they need to void.

A systematic review (Flanagan et al, 2012) of four RCTs from 1996 to 2010 of the management of incontinence in care homes using prompted voiding showed a decrease in incontinent episodes. Research on prompted voiding has been conducted mostly in nursing homes and has shown that between 25% and 40% of incontinent residents respond well to toileting assistance; approximately 38% cannot successfully use the toilet when necessary, even when provided help by research assistants (Ouslander et al, 1995). In one study of 191 incontinent residents in seven nursing facilities, 25% to 40% responded well to prompted voiding during the day, with incontinence episodes decreasing from three or four during the day to one or none.

Ouslander and colleagues (2005) combined prompted voiding with other activities of daily living as part of a multicomponent intervention known as Functional Incidental Training (FIT). FIT used a "designated" versus "integrated" nursing assistant role to

combine restorative care including a walking program, exercise therapy, and continence care. This intervention repeatedly has been shown to improve physical function, as well as UI in nursing facility residents (Schnelle et al, 1995; Ouslander et al, 2005). A 3-day trial of prompted voiding can demonstrate whether it is likely to be effective (Ouslander et al, 1995).

Challenges of Caregiver-Administered Voiding Schedules

The impact of a toileting regimen on caregivers can be significant (Roe et al, 2011). UI management has been rated as the third most troublesome caregiving task, behind a lack of time for their own needs and managing the care recipient's emotional and behavioral problems (Colling et al, 2003). Engberg and colleagues (2002) reported areas of caregiver strain in relation to incontinence, including odor (56%), toileting (55%), changing pads and clothing (53%), UI-related costs for pads or briefs (53%), wet clothing (50%), and changing bed linens (44%). Drennan and colleagues (2012) conducted a qualitative study of managing incontinence for people with dementia living at home and found that toilet prompting or reminding can lead to irritation and arguments, because patients perceive this as being treated like a child.

Delayed Voiding

Delayed voiding is another approach to helping patients expand the interval between voids. It differs from bladder training in that patients are not placed on a predetermined voiding schedule. When first experiencing an urge to void, patients are instructed to use their urge suppression techniques until the urge subsides (see Fig. 80-5). However, instead of going to the bathroom immediately after suppressing the urge, they postpone urination by waiting 5 minutes before voiding.

In patients who have experienced urgency UI, even a mild urge to void triggers a trip to the bathroom as soon as possible, because of the fear of leakage otherwise. However, most patients can be convinced to try a 5-minute delay, particularly in safe circumstances such as at home alone. Often, they are surprised to find that after a brief wait, the urge subsides or disappears altogether. This enhances their sense of control and helps restore confidence so that they can gradually increase the delay time to achieve a normal frequency.

BEHAVIORAL TREATMENT FOR VOIDING AND PELVIC FLOOR DYSFUNCTION

PFM dysfunction, especially PFM overactivity, is characterized by elevated resting tone (hypertonicity) and decreased relaxation capacity and manifests in such symptoms as pelvic floor tenderness/pain, pelvic pain, bladder pain syndrome, and/or voiding symptoms, including hesitancy, straining to void, and incomplete bladder emptying. Assessment includes digital palpation of the PFMs to detect tenderness and pain, resting tone, contraction strength, and ability to relax. Some women have an "overactive pelvic floor" characterized by generally high resting tone. Others may have increased muscle tension only when attempting to void.

When muscle tension or spasm is detected, behavioral treatment focuses on teaching conscious relaxation of PFM, especially in the context of voiding. The first step is to educate the patient about bladder and pelvic floor anatomy and function. Normal voiding is a coordinated process in which pelvic floor relaxation precedes and can initiate detrusor contraction and urethral relaxation. Some women habitually void by Valsalva, believing that they need to bear down to push urine out and empty the bladder. This can result in a reflex contraction of the PFMs, impeding urine flow. Patients with dysfunctional voiding need to understand that pushing is not necessary and may be counterproductive. Instead, they can facilitate voiding through voluntary PFM relaxation, which will allow the bladder to empty naturally.

PFMT focuses on developing an awareness of muscle tension as distinct from muscle relaxation. Actively contracting the muscles

demonstrates the sensations associated with muscle tension and assists patients to discriminate and contrast it with the sensations of relaxation. An active contraction also leads to a more complete subsequent relaxation. Perineal or vaginal biofeedback also can be used to bring muscle tension to a conscious level.

Using PFMT to enhance muscle relaxation in patients with high-tone PFM is referred to as *down training*. Teaching a muscle to relax is often more difficult than teaching it how to contract (*up training*). Patients being treated for pain often will benefit from BF-assisted PFMT, which enables them to coordinate PFM movement with the BF visual signal. Once able to feel the muscle release and relax, the patient can begin coordination of muscle relaxation after a contraction.

As with PFM exercises for incontinence, daily exercise involves not only contracting but also relaxing muscles fully between contractions. This is particularly important for patients with voiding dysfunction. To emphasize relaxation, these patients are taught to focus more on the relaxation phase, which is extended with a 1:4 ratio or longer as indicated.

Once the patient has learned the sensation of adequate PFM relaxation during exercise sessions, it is important to address voiding habits, so that the relaxation skills can be generalized. For many women, voiding is an activity that is rushed because of a busy lifestyle and they do not take the time needed to allow normal voiding. **With behavioral treatment, patients are encouraged to create a relaxing environment and plan adequate time for voiding.** They are instructed in good voiding technique. Specifically they are to slow down, take a deep breath, relax their body, relax their PFMs, and wait for the urine to flow. Anecdotally, some women benefit from double voiding or lingering until another detrusor contraction occurs, leading to more complete emptying. A second void can be facilitated by rising up from the toilet seat slightly, sitting back down, and relaxing the PFMs once more.

LIFESTYLE MODIFICATIONS

In addition to the behavioral interventions that improve symptoms through teaching new skills or strategies, there are a number of lifestyle modifications that change a person's habits and/or lifestyle choices to mitigate factors that may contribute to LUTS. Lifestyle modification involves a conscious choice by the individual to change a practice that is under their control and may contribute to LUTS. Lifestyle modifications are sometimes referred to as *self-care practices*. They can be used as a primary intervention in some cases, but usually they are adjunctive. Lifestyle changes include **fluid management, reduction of caffeine and other dietary irritants, addressing constipation, and weight loss.** Although there is much less evidence for lifestyle modifications, these changes can have a significant impact on overall bladder health and have become integral to conservative management (Burgio et al, 2013).

Fluid Management

Fluid intake plays a role in the prevention of several urinary system diseases, and adverse effects on the urinary system can result from insufficient hydration. Modifying the type or volume of fluids, either as a primary or an adjunctive strategy, is often recommended to optimize outcomes as part of conservative intervention for LUTS. Fluid intake modifications depend on the patients' pattern of intake, which can be assessed by having them complete a 24- to 48-hour diary of intake and output, including voided volumes when possible. Reviewing such a diary can reveal excessive fluid intake, inadequate fluid intake, and diurnal patterns of intake that may be contributing to LUTS.

Excessive Fluid Intake

Excessive fluid intake can be a problem when large volume intake triggers symptoms of urgency, frequency, or incontinence (Segal et al, 2011). Fluid intake averaging greater than 3700 mL/day has

been associated with higher voiding frequency and incidence of UI compared with an intake of approximately 2400 mL/day (Miller et al, 2011). In a study of healthy young men, those with excessive fluid intake not only had significantly increased urine volume and frequency but also had significantly elevated bladder pressure on ambulatory urodynamics (Schmidt et al, 2004). Some people increase their fluid intake deliberately in an effort to "flush" their kidneys or lose weight. In others it is simply a habit. In in-depth interviews conducted with participants in the Boston Area Community Health (BACH) study (Elstad et al, 2011), women reporting the need to increase fluid intake attributed it to popular health messages recommending daily fluid intake and that water was "good for you." Men, on the other hand, tended to describe the function of water in the body as to ward off infection, "flush out the kidneys," or "keep your system cool." **When patients consume an abnormally high volume of fluid (e.g., > 2100 mL of output per 24 hours), reducing excess fluids is often an appropriate measure and can be helpful for reducing urgency, frequency, and urge incontinence.**

Inadequate Fluid Intake

In practice, it is more common to see inadequate fluid intake, because people with bladder problems often restrict their intake in an effort to control symptoms. In the BACH study interviews (Elstad et al, 2011), men and women across all three racial/ethnic groups reported decreasing fluid intake to manage or cope with urinary symptoms. Studies of community-residing elders with LUTS also report self-care practices including self-imposed restrictions of fluids to prevent urinary urgency, frequency, and incontinence (Brink et al, 1987; Wyman and Fantl, 1991; Johnson et al, 2000; Miller et al, 2003; Diokno et al, 2004a, 2006; Wyman et al, 2009). Working women also report limiting fluid intake as strategies to avoid urinary symptoms (Nygaard and Linder, 1997; Fitzgerald et al, 2000, 2002).

In some cases, particularly in older adult women, the resulting fluid intake may be inadequate and places them at risk for dehydration. Underhydration may play a role in the development of urinary tract infections (UTIs) and constipation and decrease the functional capacity of the bladder. In a study of 791 female teachers, those who drank less than the volume they desired had more than twice the risk for UTI (Nygaard et al, 1997).

Although it may seem counterintuitive, it is usually good advice to encourage patients to consume at least six 8-oz glasses of fluid each day to maintain adequate hydration. **Fluid intake should be regulated to six 8-oz glasses or 30 mL/kg body weight per day with a 1500 mL/day minimum at designated times unless contraindicated by a medical condition.** The Institute of Medicine issued a report in 2004 with guidelines for total water intake for healthy people (Institute of Medicine and Food and Nutrition Board, 2004). That recommendation for women was 2.7 L/day, but was intended to include water consumed through both beverages and food. This food versus fluid component has been a source of confusion for the public and professionals alike, with a misperception of fluid source as only deriving from beverage intake.

A useful strategy to encourage increased fluid intake when appropriate is to point out that concentrated urine has a stronger odor than more dilute urine. Patients with incontinence are often quite sensitive about urinary odor and welcome a suggestion to decrease odor.

Timing of Fluid Intake

Although overall fluid restriction is not a good strategy, it can be very helpful to restrict fluids at particular times when toilet access will be limited, such as before a social outing. Patients using temporary fluid restriction should be encouraged to keep their total daily fluid intake optimized, by making up the missed fluids earlier or later.

Avoiding excessive fluid intake in the evening hours can also be helpful for reducing nocturia (e.g., 3 to 4 hours before bedtime).

In patients who retain fluid during the day and have nocturia because of mobilization of fluid during sleep, behavioral interventions focus on managing daytime accumulation of fluid. Patients are advised to wear support stockings to prevent accumulation of edema fluids or to elevate the lower extremities in the late afternoon to mobilize the fluid well before bedtime.

In some patients, a midafternoon to late afternoon loop diuretic is useful to complete diuresis before bedtime. For patients who are already taking a loop diuretic, nocturia often can be improved by altering the timing of the diuretic (so that most of the effect has occurred before bedtime). Loop diuretics are also known to aggravate incontinence by increasing the rate of bladder filling and producing sudden urges. Such effects sometimes can be avoided by discontinuing the diuretic, changing to a nonloop diuretic, or altering the timing of administration. An example is taking the loop diuretic *after* coming home from work so that diuresis can be accomplished during the evening, but before bedtime.

Evidence for Fluid Management

Although fluid management is widely used in clinical practice there is little scientific evidence on fluid intake related to bladder health. Two small randomized trials suggest a negative effect for increased fluid intake. In one study ($n = 24$), adults with OAB were randomized to either decrease or increase of fluids (Hashim and Abrams, 2008). When patients decreased their fluid input by 25%, there was a significant reduction in daytime frequency (23%), urgency (34%), and nocturia (7%). Increasing fluid input by 25% and 50% resulted in a worsening of daytime frequency but had no effect on urgency, nocturia, or urge incontinence. In a study of women with urodynamically confirmed idiopathic detrusor overactivity ($n = 30$), decreasing fluid intake significantly decreased voiding frequency and urgency incontinent episodes (Swithinbank et al, 2005). However, the Nurses' Health Study, which prospectively investigated the association between total fluid intake and incident UI over 4 years in 65,167 women, found no association between fluid intake and UI (including stress, urgency, and mixed UI) (Townsend et al, 2011).

Caffeine Reduction

Caffeine plays a role in symptoms of urgency, frequency, and urge incontinence partly because it is a diuretic and partly because it is a bladder irritant for many people. The consumption of caffeinated beverages, foods, and medications is easily underestimated. Caffeine is found in many foods and drinks that people consume daily, particularly coffee and tea. Caffeine is consumed regularly by more than 85% of adults in the United States (Mitchell et al, 2014). Approximately 73% of children consume caffeine on a given day and coffee and energy drinks represent a greater proportion of caffeine intake than soda intake, which has declined (Branum et al, 2014).

Urodynamic studies have shown that caffeine increases detrusor pressure (Creighton and Stanton, 1990) and is a risk factor for detrusor overactivity (Arya et al, 2000; Holroyd-Leduc and Strauss, 2004). Caffeine promotes LUTS via decreased threshold of sensation at filling phase and increased flow rate and voided volume (Jura et al, 2011; Lohsiriwat, et al, 2011). Lohsiriwat and colleagues (2011) found that caffeine, at a dose of 4.5 mg/kg, caused diuresis and decreased threshold of bladder sensation at filling phase, with an increase in flow rate and voided volume. Similarly, daily administration of oral caffeine (150 mg/kg) resulted in detrusor overactivity and increased bladder sensory signaling in the mouse (Kershen et al, 2012).

Caffeine intake also has been associated with LUTS in epidemiologic studies, in both men (Davis et al, 2013) and women (Jura et al, 2011; Townsend et al, 2012; Gleason et al, 2013). Data from the Nurses' Health Study II reported that 25% of these participants experienced frequent (at least once a week) UI with high caffeine intake (Townsend et al, 2012). The BACH study reported on beverage intake and LUTS in a large cohort ($n = 4144$) (Maserejian et al, 2013). Women who had increased coffee intake by at least two

servings per day had 64% higher odds of progression of urgency. Women who had recently increased soda intake, particularly caffeinated diet soda, had higher symptom scores, urgency, and LUTS progression.

In men, greater coffee intake (>2 cups/day vs. none) or total caffeine intake at baseline increased the odds of storage symptom progression (Maserejian et al, 2013). Davis and colleagues (2013) also found that caffeine consumption (equivalent to ~ 2 cups of coffee daily; 250 mg) was significantly associated with moderate-to-severe UI in men in the United States.

There is also evidence that reducing caffeine intake can help reduce episodes of both stress and urgency incontinence (Tomlinson et al, 1999; Gray, 2001; Bryant et al, 2002). Based on the literature, the ICI recommends decreasing caffeine intake to improve continence (Moore et al, 2013). However, the amount of caffeine reduction necessary to prevent associated LUTS is not known.

Many patients are reluctant initially to forgo their caffeinated beverages, but they may be convinced to try it for a short period, such as 3 to 5 days, to determine if they are sensitive to its effects. If they experience relief from their symptoms, they are often more willing to reduce or eliminate caffeine from their diet. To avoid symptoms of caffeine withdrawal, most notably headaches and irritability, it is recommended that caffeine reduction be approached gradually and include mixing caffeinated and decaffeinated beverages incrementally over several weeks.

Other Dietary Irritants

Although data are scarce, a number of other substances are thought to irritate the bladder, including sugar substitutes (aspartame), citrus fruits, highly spiced foods, and tomato products. There are innumerable clinical cases in which these substances appear to be aggravating urgency and incontinence, and reducing them has provided clinical improvement. However, this should not be interpreted to mean that all patients with LUTS should eliminate these foods from their diets. A diary of food and beverage intake is useful for identifying which substances are in fact irritants for individual patients; and a trial period of eliminating these substances one at a time can be used to confirm the relationship.

It also has been suggested that alcohol intake can contribute to urgency, frequency, and incontinence by means of a diuretic effect. However, there is little in the literature to support this hypothesis. In a study of alcohol consumption and UI among community-dwelling Japanese women (Hirayama and Lee, 2012), increases in risk of UI with alcohol drinking and mean ethanol intake did not reach statistical significance. Research is needed in the effect of caffeinated alcoholic beverage and LUTS because consumption is widespread among young adults in the United States (MacKillop et al, 2012).

Bowel Function

Bowel disorders, including chronic constipation (fewer than three stools per week) and straining during defecation, have been linked to LUTS (Cardozo and Robinson, 2002; Carter et al, 2012), and the ICI committee concluded there is "some evidence" to suggest that chronic straining may be a risk factor for the development of UI. The close proximity of the bladder and urethra to the rectum and their similar nerve innervations make it likely that there are reciprocal effects between them. As early as 1988, Lubowski and associates reported that denervation of the external anal sphincter and PFMs may occur in association with a history of excessive straining on defecation (Lubowski et al, 1988). Many believe that if straining is a lifetime habit, it may have a cumulative effect on pelvic floor and bladder function as well. Further, animal studies and clinical data support bladder-bowel cross-sensitization, or crosstalk between the bowel and bladder (Kaplan et al, 2013).

The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) II (Coyne et al, 2011) survey ($n = 2160$) indicated that OAB is more

likely to be reported by both men and women with chronic constipation. In a case-control study of women with LUTS ($n = 820$) and matched controls ($n = 148$), constipation and straining during defecation were significantly more common among the women with LUTS, including detrusor overactivity and urgency, than among the controls (Manning et al, 2003).

Fecal impaction and constipation have been cited as factors contributing to urinary incontinence in women, particularly in nursing home populations (Ouslander and Schnelle, 1995). Fecal impaction can be an irritating factor in OAB or obstruct normal voiding, causing incomplete bladder emptying and overflow incontinence. Disimpaction provides immediate relief for some patients, but a bowel management program is usually needed to avoid recurrence.

Self-care practices that promote bowel regularity are an integral part of any behavioral treatment plan. Initial assessment should include questions about bowel history and bowel habits. When constipation is reported, recommendations include ensuring adequate dietary fiber and fluids to ensure normal stool consistency. Sufficient fluid intake is necessary for fiber supplementation to be effective. Also helpful are regular exercise, external stimulation, and establishment of a regular time for bowel evacuation, preferably after a meal to capitalize on postprandial bowel motility.

Obesity and Weight Reduction

Obesity is an established risk factor for UI. A large amount of epidemiologic data, including several systematic reviews, demonstrates an association between body mass index (BMI) and UI, as well as other LUTS, including urgency and frequency (Dallosso et al, 2003; Subak et al, 2009a; Vaughan et al, 2012; Milsom et al, 2013; Khullar et al, 2014). Further, reductions in UI have been observed in morbidly obese women who have had dramatic weight loss after bariatric surgery (Bump et al, 1992; Burgio et al, 2007; Knoepf et al, 2013) and in women who achieved moderate weight loss through supervised behavioral weight-loss programs (Bump et al, 1992; Subak et al, 2005, 2009b; Wing et al, 2010a).

Knoepf and colleagues (2013) reported on the resolution and incidence of UI in women undergoing bariatric surgery, by examining national claims data for 3765 cases with 3 years of follow-up claims data. After surgery, 62.4% of patients (83 in 133) diagnosed with UI before their surgery no longer had a coding diagnosis of UI. In contrast, only 42.1% (56 in 133) of those in a nonbariatric surgery cohort lost their coding diagnosis of UI ($P = .0009$). Incidence of new UI did not differ significantly between the groups, however.

Even moderate weight loss has been shown to improve bladder symptoms in overweight women. In fact, loss of 5% to 10% of body weight, sustained over a 12-month period, can decrease incontinence episodes as much as 70% (Bump et al, 1992; Subak et al, 2005; Wing et al, 2010b). The most definitive of the studies is an RCT comparing the effects of an intensive 6-month, group-administered, weight loss program (including diet, exercise, and behavior modification) to a structured education control program (Subak et al, 2009b). Both groups also received a booklet describing a step-by-step self-administered behavioral program to reduce incontinence. After a mean weight loss of 8.0%, the weight loss group reported a significantly greater reduction in incontinence episodes compared to the control group with a mean weight loss of 1.6% (mean = 47% vs. 28%). Thus weight loss can be a useful component of a behavioral program for incontinence in overweight women.

Based on this evidence, more clinicians should recommend weight loss as a component of lifestyle interventions for UI in overweight women (Vissers et al, 2014). Given that BMI is a modifiable risk factor, it is plausible that UI may be prevented if women maintain their weight within suggested guidelines.

ADHERENCE TO CONSERVATIVE TREATMENT

It is widely accepted that the effectiveness of conservative treatments relies on the active participation of an involved and motivated

patient. In fact, most behavioral interventions can be conceptualized as self-management. Therefore the greatest challenge for the clinician becomes how to motivate patients to be actively involved in their care, follow their daily program consistently, and persist for long enough to experience meaningful change in their symptoms. Progress in behavioral programs is typically gradual, which makes compliance even more difficult for patients who expect immediate results. Clinicians can optimize patient adherence by making it clear that it may take weeks to months for symptom improvement, and it may be irregular, with “good” days and “bad” days. Clinicians can provide support by scheduling follow-up appointments to maintain accountability, track and reinforce progress, identify and address barriers, adjust the daily regimen, encourage persistence, and let the patient know that she is not alone.

Measurement of adherence to behavioral protocols often has been overlooked in research (Dumoulin et al, 2015). Few studies provide information about how adherent patients were with PFM exercise, behavioral strategies, voiding schedules, or other components of behavioral treatment (Bø et al, 1996, 1999; Mørkved et al, 2002; Fine et al, 2007; Borello-France et al, 2010); and the literature is sparse on methods to identify barriers and improve adherence (Alewijns et al, 2003; Borello-France et al, 2010, 2013; Hay-Smith et al, 2015).

Borello-France and colleagues (2013) reported on adherence to PFM exercise and bladder control strategies as a secondary analysis of a multisite RCT comparing three interventions for stress-predominant UI, intravaginal continence pessary versus multicomponent behavioral therapy (including PFMT and bladder control strategies), versus pessary and BT combined (Richter et al, 2007). The authors concluded that adherence to PFM exercises and bladder control strategies, when implemented by trained interventionists, can be high and sustained over time. The most common barriers to adherence were trouble remembering to exercise and difficulty finding time. To help patients overcome these barriers, clinicians can use various forms of reminders (e.g., timers), link daily exercises to environmental cues, and integrate exercises into the patient’s everyday activities.

Although most clinicians agree that adherence to maintenance protocol is necessary for long-term effectiveness, there is little work on the durability of behavioral treatments. Long-term studies have shown that women following a PFMT program tend to decrease their adherence over time (Fine et al, 2007). Bø and Hilde (2013) reported that long-term adherence to PFMT varied between 10% and 70%. The few studies of long-term outcomes are inconsistent, but promising, in that many patients are able to sustain improvements in bladder control over time (Cammu and Van Nylén, 1995; Bø and Talseth, 1996; Weinberger et al, 1999). There is clearly a need for more studies of long-term outcomes to understand the reasons for regression and learn how the effects of treatment can be maintained over a lifetime.

ROLE OF CONSERVATIVE INTERVENTIONS FOR PREVENTION OF URINARY INCONTINENCE

Primary prevention of UI using behavioral interventions, including PFMT, behavioral training, or lifestyle changes (i.e., weight loss, fluid moderation, diet modification) have been investigated in four at-risk populations: older women, childbearing women, obese women with diabetes, and men undergoing prostatectomy (Shamilyan et al, 2007; Sievert et al, 2012; Moore et al, 2013; Newman et al, 2013).

Older Women

Age is perhaps the most established risk factor for UI in men and women, yet little work has been done to study approaches to preventing UI in this population. The first prevention study was an RCT comparing a group behavior modification program to no intervention in continent, postmenopausal women, 55 years and older, to determine whether the behavioral intervention could prevent UI,

increase pelvic floor muscle strength, and decrease voiding frequency (Diokno et al, 2004b). At 12 months, the treatment group had statistically significantly better outcomes than the control group in continence status, pelvic floor muscle strength (pressure score and displacement score), improved voiding frequency, and interviod interval.

Later, a smaller study was conducted in 43 women, 65 years and older, residing in an independent-living facility to determine the feasibility of a 6-week pelvic fitness and educational program to control UI and OAB (Dugan et al, 2013). Statistically significant improvements in bladder symptoms were found after 6 weeks in the treatment group, based on visual analog scale scores for symptom bothersomeness, symptoms distress (Urogenital Distress Inventory, Short Form), and impact on quality of life (Incontinence Impact Questionnaire, Short Form).

Childbearing Women

Pregnancy and childbirth are established risk factors for UI in women. For this reason, most prenatal classes include teaching about the role of the pelvic floor and PFM exercises. There is also a growing body of evidence for the preventive value of formal PFMT. Research with primiparous women has shown that intensive antenatal PFMT, including one-on-one instruction to ensure proper muscle control and continued supervision of training, can prevent the development of UI during pregnancy (35 to 36 weeks' gestation) and short-term postpartum (6 weeks to 6 months) (Boyle et al, 2012, 2014; Moore et al, 2013; Mørkved and Bø, 2013; Pelaez et al, 2014). Less clear is the impact of PFMT for preventing UI long term and in multiparous women. Based on research to date, the ICI committee (Moore et al, 2013) recommends (1) an intervention comprising a daily home PFMT and weekly health professional-led exercise classes for 12 weeks, starting at 20 to 24 weeks' gestation for pregnant women having their first baby, and (2) an individually taught strengthening PFMT program that incorporates adherence strategies for postpartum women who have had a forceps delivery or a vaginal delivery of a large baby (≥ 4000 g).

Men Undergoing Prostatectomy

Postoperative UI is almost universal immediately after prostatectomy. Although continence status usually improves in the ensuing weeks and months, it is possible to speed the recovery of continence using behavioral interventions such as PFMT. One approach is to teach men how to control their PFM before surgery, so they will have the opportunity to practice using their muscles in advance of needing to use them more actively after surgery. In one trial, a single session of BF-assisted BT reduced the duration of UI, as well as severity of symptoms in the 6 months after radical prostatectomy (Burgio et al, 2006).

Another approach is to initiate PFMT immediately after catheter removal or early in the recovery period. Results of this approach are inconsistent, but generally show benefit for the training at least in the first 3 months. Trials that have combined preoperative and early postoperative training also indicate that severity of post-prostatectomy UI can be reduced with PFMT, in the short-term (3 months) and in some studies up to 12 months (Hirschhorn et al, 2014). According to Moore and colleagues (2013), whether PFMT should be delivered in the form of hands-on therapy or verbal instruction and support remains unclear.

Urology practices have begun to include various levels of PFMT for men undergoing radical prostatectomy (Newman et al, 2014); however, translation from research to practice has not been optimum, because most men undergoing radical prostatectomy do not receive instruction on PFMT. Some clinicians take the approach of watchful waiting and reserve treatment for men with persistent UI. However, even transient UI can be distressing for men recovering from prostatectomy and hastening the return of bladder control may be important to their activity level, social life, or general well-being.

MECHANICAL VAGINAL AND URETHRAL DEVICES FOR INCONTINENCE

Mechanical devices are of two main types: those that are placed in the vagina to support the bladder neck and urethra, and those that are placed in the urethra or at its opening to block the passage of urine. Mechanical devices are most commonly used for stress UI, but they also have been used for urge and mixed incontinence. A 2011 Cochrane review (Lipp et al, 2011) of mechanical devices noted that many have been developed over the past two to three decades, but few are available in the United States. This review noted there was not enough evidence to recommend any specific type of device or to determine whether mechanical devices are better than other forms of treatment. The ideal mechanical device is one that can adequately control urine leakage, is easy to insert, has few adverse effects, and is of low cost. This is a short review of devices currently in use.

Intravaginal Devices

Women who leak urine during physical activities may benefit from a mechanical device that provides pelvic support. When pelvic support tissues are weak, the urethra may drop to a position where increased abdominal pressure cannot be transmitted to the urethra to assist with urethral closure. Intravaginal devices aim to restore the position of the upper urethra to above the level of the pelvic floor where intra-abdominal pressure can improve its closure. This can be accomplished using an incontinence pessary (Figs. 80-10 through 80-12).

Incontinence pessaries are intended to prevent urine loss by stabilizing and supporting the bladder neck or compression of the urethra during increases in intra-abdominal pressure. Some women who have urinary urgency and frequency because of pressure from a pelvic organ prolapse also may benefit from the support of an incontinence pessary.

Pessaries are made of an inert plastic or silicone material to prevent odors and absorption of vaginal secretions. There are very few contraindications to pessary use, but a pessary should not be placed in patients with evidence of an active pelvic infection, severe ulceration, or allergy to silicone or latex or in patients who are likely to be noncompliant with maintenance care and follow-up appointments. Common side effects include vaginal discharge and odor. Serious complications from pessaries are rare; however, vesicovaginal fistula, rectovaginal fistula, erosion, and subsequent impaction have been reported (Arias et al, 2008; Penrose et al, 2014).



Figure 80-10. Incontinence dish pessary with support. (Courtesy Covidien Ltd., Mansfield, MA. All rights reserved. Used with permission of Covidien.)



Figure 80-11. Incontinence dish pessary without support. (Courtesy Covidien Ltd., Mansfield, MA. All rights reserved. Used with permission of Covidien.)



Figure 80-12. Incontinence ring pessary with and without support. (Courtesy Bioteque America, San Jose, CA.)

Difficulty with self-removal and insertion may limit more widespread use of currently available pessaries.

Research on pessary use for incontinence is limited. One device that has been studied is the Uresta (EastMed, Halifax, Nova Scotia), a bell-shaped pessary (Fig. 80-13) with a handle at its base for easy insertion and removal. Its narrow tip allows for easy insertion into the vagina, like a tampon, and it positions itself so that the wide base provides support to the urethra. Farrell and colleagues (2007) tested this pessary in 32 women. Leaking episodes decreased by 4 per week (based on 7-day diary) ($P = .028$) and pad weights by 11 g ($P = .006$). No complications were reported. At 2 weeks, 66% of women were satisfied with the pessary. After 12 months, 50% of subjects continued pessary use with statistically significant differences in number of leakage episodes, pad weight, symptom severity, and impact on quality of life.

A multisite randomized trial of a continence pessary compared to behavioral therapy was conducted by the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) Pelvic Floor Disorders Network (Richter et al, 2010). The Ambulatory Treatments for Leakage Associated with Stress-Incontinence (ATLAS) trial randomized 446 women with stress-predominant incontinence to intravaginal pessary, BT, or combined treatment. At 3 months, 40% of the pessary group and 49% of the behavioral group rated themselves as “much better” or “very much better,” but these outcomes were not statistically different. Significantly more



Figure 80-13. Uresta pessary. (Courtesy EastMed, Dartmouth, NS, Canada.)

women in the behavioral group than in the pessary group, reported having no bothersome incontinence symptoms (49% vs. 33%) and treatment satisfaction (75% vs. 63%). At 12 months, patient satisfaction remained above 50% for all treatment groups, but group differences were not sustained on any measure.

Sze and Hobbs (2014) performed a comparative retrospective parallel cohort study of women whose OAB was treated with ring pessary or multicomponent BT (BT while using PFM exercises to suppress urinary urgency as needed) over a 42-month period. Ring pessary and BT had similar cure rates (29 in 150 [19%] vs. 46 in 231 [20%], respectively).

There is also evidence that tampons, disposable vaginal guards, and an intravaginal bladder neck prosthesis can alleviate stress UI symptoms (Lipp et al, 2011). It is possible that intravaginal tampons may perform as well as more formal mechanical devices, and they are widely available and familiar to women. They are also without significant adverse effects and are a less expensive option. The most recent device available is Impressa (Kimberly-Clark, Irving, TX). It is a disposable device that anchors in the vagina using support poles to stay in place. This product is available in retail stores.

Urethral Inserts and Meatal Occlusive Devices

Intraurethral devices are also known as urinary control inserts and urethral inserts. These devices act by simply blocking the passage of urine through the urethra. The devices are thought not to be effective in patients with a fibrotic urethra, in which the fibrosis limits the transmission of pressure. Only one of these, the FemSoft Insert (Rochester Medical, Stewartville, MN) is currently in use.

The FemSoft insert is a sterile, disposable, single-use intraurethral device. It consists of a narrow, silicone tube entirely enclosed in a soft, thin, mineral oil-filled silicone sleeve. The silicone sleeve forms a balloon on the tip of the insert. As the FemSoft Insert is advanced into the urethra, fluid in the balloon is transferred toward the external retainer to facilitate passage through the urethra (Fig. 80-14). Once the tip of the insert has entered the bladder, the fluid returns to fill the balloon, forming a mechanical barrier to retain urine within the bladder.

To assist with insertion, the insert is supplied on a disposable applicator and with a lubricating gel. The device is easily removed for normal voiding and should be removed at least once every 6 hours. This product is a single-use, disposable device. It is available in three diameters (16, 18, 20 Fr) with two lengths (3.5, 4.5 cm) for each diameter, and it is important that the insert be properly sized to the woman. The FemSoft insert is a prescription device and costs less than \$2. Contraindications for use include urgency UI (as bladder contraction would expel the insert), active UTI, urethral stricture, and any anatomic or pathologic urethral condition in which passage of a catheter is not clinically advisable (Newman and Wein, 2009). Adverse events include hematuria and UTI (Sirls et al, 2002).

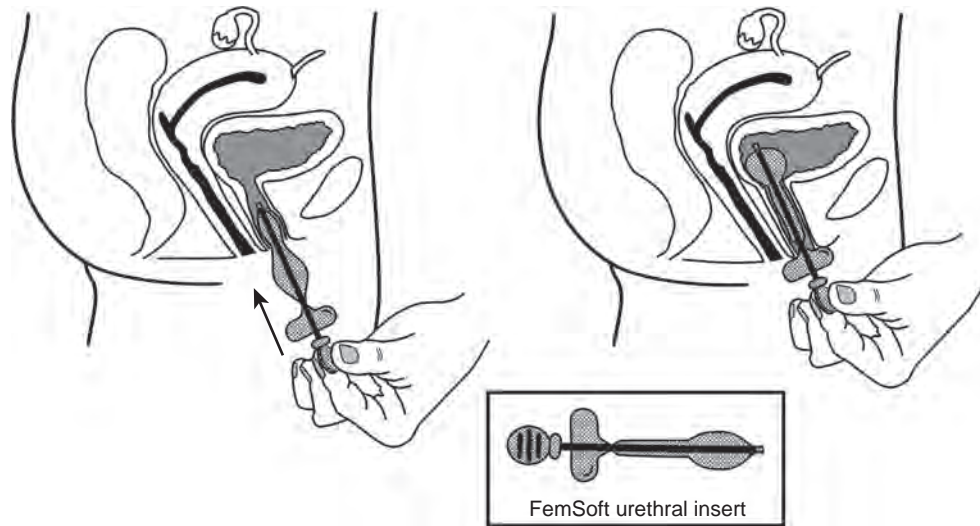


Figure 80-14. FemSoft Urethral Insert.

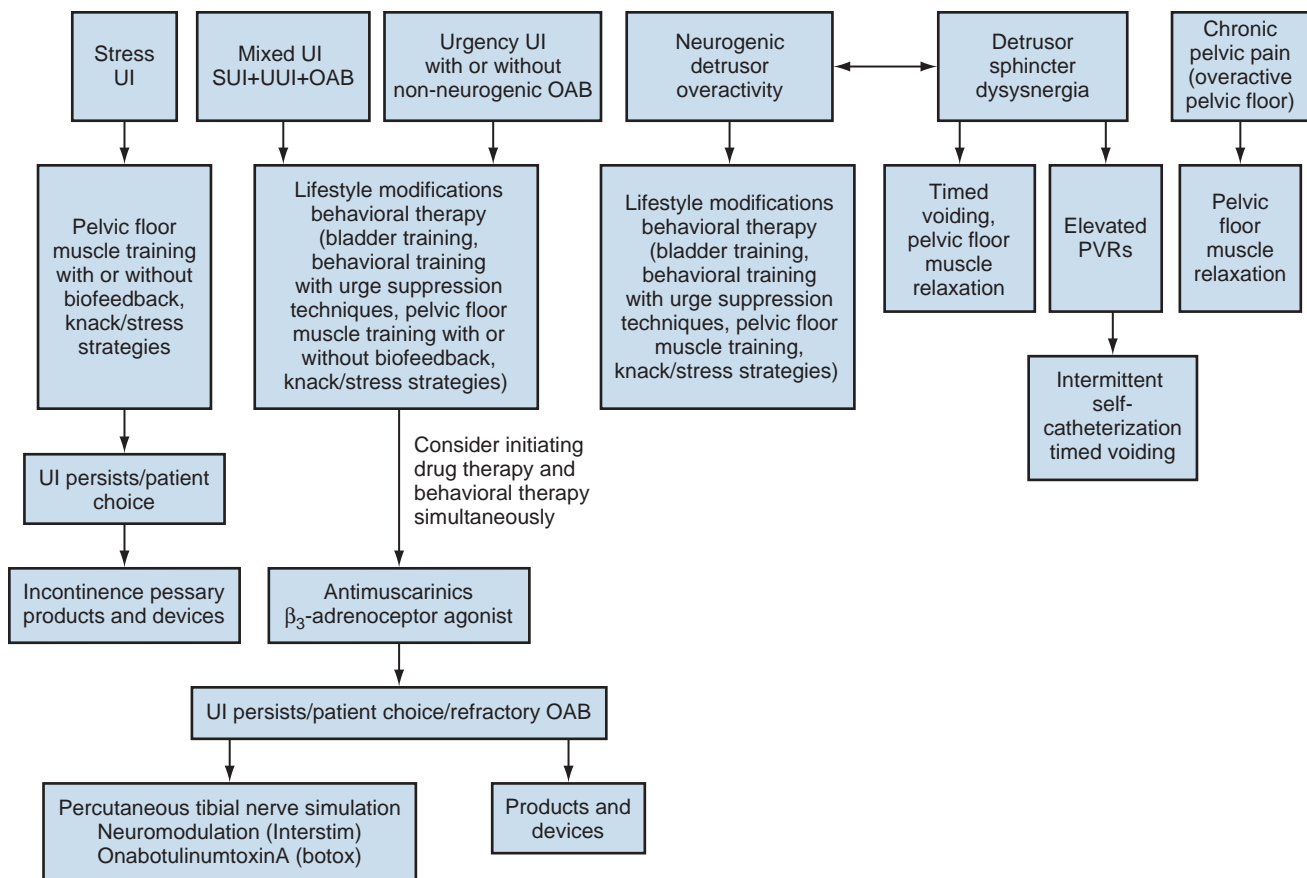


Figure 80-15. Behavioral treatment pathway for the treatment of lower urinary tract symptoms. OAB, overactive bladder; PVRs, postvoid residuals; SUI, stress urinary incontinence; UI, urinary incontinence; UUI, urge urinary incontinence. (Copyright 2013 Diane K. Newman.)

BEHAVIORAL TREATMENT MODEL FOR UROLOGY PRACTICE

Despite the evidence for the effectiveness of behavioral treatments for UI and other LUTS, and guidelines recommending them as first-line therapies, these conservative interventions are not well integrated into clinical practice in many areas. One limitation is the availability of qualified providers. However, **one successful model that has emerged in urologic practice is the integration of advanced practice providers, including continence nurse practitioners and physician assistants.** Historically, advanced practice providers have embraced behavioral treatments as a specialty practice for nonsurgical treatment of a wide range of LUT conditions. An algorithm for a behavioral treatment pathway can be found in [Figure 80-15](#).

Urology lends itself to a multidisciplinary model of a Bladder and Pelvic Floor Disorder service that provides comprehensive surgical and medical care. These centers usually offer the combined knowledge of a multidisciplinary group of experts in the field of UI, voiding, and pelvic floor dysfunction. Changes in reimbursement for nonsurgical treatments such as BF-assisted PFMT, electrical stimulation, and posterior tibial nerve stimulation have allowed urologists, to consider the expansion of current treatments (pharmacologic and surgical) to alternative multifaceted behavioral treatment programs.

KEY POINTS

- Behavioral treatments are a group of interventions that improve LUTS by changing patients' behavior or environment or by teaching new skills.
- There is strong evidence that conservative interventions are effective first-line treatments for patients with LUTS.
- The effectiveness of conservative treatments relies on the active participation of an involved and motivated patient.
- Intensive behavioral interventions that involve an experienced clinician have been shown to be more effective.

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History of Electrical Stimulation

Neurophysiology of Electrical Stimulation for Storage and Emptying Disorders

Electrical Stimulation for Storage Disorders

Electrical Stimulation for Emptying Disorders

Future Research and Conclusions

For the past century, the development of electrical neurostimulation and neuromodulation to alter physiologic processes responsible for lower urinary tract symptoms (LUTS) and lower urinary tract dysfunctions (LUTD) largely has been the result of important landmark discoveries in the clinical application of electricity and in the understanding of neuromuscular physiology. In neurostimulation the use of electrical stimuli on nerves and muscles has mainly been developed to achieve immediate clinical responses in neurogenic conditions of pelvic organ dysfunction; in neuromodulation the application of electrical stimuli to nerves has been developed to alter neurotransmission processes in non-neurogenic and neurogenic conditions. In this chapter the focus is on reviewing the application (Table 81-1) and clinical outcomes of neurostimulation and neuromodulation therapies for pelvic organ dysfunction with respect to the development of our knowledge of pelvic neuromuscular physiology and its role in translational innovations.

HISTORY OF ELECTRICAL STIMULATION

Although the field of electrical stimulation of nerves to achieve muscle contractions was not truly realized until the early 1800s, its roots can be traced into the 1700s, when inadvertent electrical impulses were found to generate strong muscle convulsions (Bell, 1811; Clarys, 1994). Magendie (1822) was one of the first to conduct physiologic investigations of the spinal nerve roots, documenting in young dogs that transection of the posterior (dorsal) segments resulted in a lack of sensation but persistence of motor function, whereas anterior (ventral) root transection yielded preservation of sensation yet abolishment of motor function. These important findings created the foundation for our understanding of basic neurophysiology of micturition and led to further discoveries on bladder function in the setting of selective rhizotomy of both the pelvic and hypogastric nerves (Giannuzzi, 1863; Langley and Anderson, 1895). Ultimately, Saxtorph in 1878 used these principles to directly stimulate the bladder in patients with urinary retention via a metal transurethral catheter (Madersbacher, 1999). His early findings allowed others to develop enthusiasm for direct stimulation of the bladder through both transurethral and direct detrusor routes (see section on direct stimulation).

Because Saxtorph had significant influence on the idea that direct bladder stimulation may lead to bladder contractility, McGuire used some of these same principles to perform direct bladder stimulation in dogs (Boyce et al, 1964). He concluded that multiple pairs of electrodes were required to achieve a more uniform pressure rise

within the bladder during the stimulated contraction. Research continued throughout the late 1900s and moved toward development of new electrodes (Susset and Boctor, 1967) and differing wire configurations (Timm and Bradley, 1969; Tscholl et al, 1971).

Direct pelvic nerve stimulation and pelvic floor muscle stimulation were not well-known or well-studied concepts until the mid-1900s because emphasis was clearly on different areas of direct stimulation (i.e., bladder). Dees (1965) studied the bladder contraction state after stimulation to the pelvic nerve. He achieved contraction of both the detrusor muscle and urethral sphincter in a cat model and produced pain and hind leg contraction as well. Others demonstrated similar findings of nonspecific contraction of the bladder and pelvic floor and other areas with direct pelvic nerve stimulation and ultimately realized that direct pelvic nerve stimulation may not be suitable for treatment of bladder dysfunction (Burgele et al, 1962; Hald et al, 1966; Holmquist and Olin, 1968). It appears that direct pelvic nerve stimulation elicits pudendal nerve activity such that outlet resistance is increased, as is pain, through simultaneous hypogastric nerve stimulation. Thus, with the limited-potential clinical utility of the pelvic nerve for stimulation, efforts focused on the pelvic floor muscles, spinal cord, and sacral roots. Caldwell and colleagues first reported experience with pelvic floor muscle stimulation with the goal of improving fecal continence and later urinary incontinence (Caldwell, 1963; Caldwell et al, 1965). Subsequently, interest increased and efforts toward external stimulation were described by anal, vaginal pessary, and direct vaginal stimulation (Hopkinson and Lightwood, 1967; Alexander and Rowan, 1968; Erlandson et al, 1977; Fall et al, 1977).

Spinal cord stimulation, by attempting to directly activate the micturition center, was thought to be a promising avenue of therapy (Nashold et al, 1971; Jonas et al, 1975; Jonas and Tanagho, 1975). Still, as in pelvic nerve stimulation, voiding was initiated; however, simultaneous sphincter activity precluded proper emptying. The subsequent series of developments pursued therapy for incomplete emptying by affecting not only bladder stimulation but, in some way, sphincter relaxation as well.

In 1972, Brindley (1972, 1974, 1977) began experimentation of sacral root stimulation that led to implantation of sacral anterior root stimulators in paraplegic patients with urinary incontinence. Evolving data showed that, for optimal bladder emptying to be achieved, sacral anterior root stimulation with posterior rhizotomies of S2, S3, and S4 would be required (Sauerwein, 1990). The posterior rhizotomy would decrease the reflex activity of the detrusor and improve bladder compliance. Tanagho and Schmidt (1982) then began further examining the sacral roots and their individual contributions to bladder and outlet function. In 1982,

TABLE 81-1 Potential Applications of Electrical Stimulation in the Treatment of Voiding Dysfunction

PURPOSE	SITES OF STIMULATION	MECHANISM
FACILITATE FILLING-STORAGE		
Inhibit detrusor contractility	V, A, SP, PT CP, SR, IV	Neuromodulation
Increase bladder capacity		
Decrease urgency and frequency		
Decrease nociception	V, A, SP, SR	Neuromodulation
Increase outlet resistance	V, A, SR	Direct stimulation (efferent nerves or roots)
FACILITATE EMPTYING		
Stimulate detrusor contraction (spinal cord–injured patient)	SAR	Direct stimulation (efferent nerves or roots)
Restore micturition reflex (idiopathic retention)	SR, IV	Neuromodulation

A, anal; CP, common peroneal; IV, intravesical; PT, posterior tibial; SAR, sacral anterior (ventral) roots; SP, suprapubic; SR, sacral roots; V, vaginal.

TABLE 81-2 Sacral Nerve Responses

SACRAL NERVE	MOTOR AND SENSORY RESPONSE
S2	<i>Motor:</i> Plantarflexion of the entire foot with lateral rotation and clamp movement of the anal sphincter <i>Sensory:</i> Sensations in the leg and buttock
S3	<i>Motor:</i> Dorsiflexion of the great toe and bellows reflex (anal wink) <i>Sensory:</i> Paresthesias or sensation of pulling in the rectum, scrotum, or vagina
S4	<i>Motor:</i> Bellows reflex only <i>Sensory:</i> Sensation of pulling in the rectum only

Tanagho and Schmidt presented initial experience in sacral root stimulation in paraplegic dogs. In this initial study they realized the design of a spiral electrode to minimize nerve damage and fixed the lead wire to the sacral lamina, thereby preventing tension on the electrode itself. They ultimately attained good bladder contraction in these dogs, with minimal sphincteric response. From these initial good results, Tanagho and coworkers then began human trials and characterized the sacral root stimulation patterns and the corresponding muscle responses (Table 81-2). In the course of the neurostimulation developments these researchers realized that sphincteric contraction abolished detrusor activity, and the role of the pudendal nerve and its modulation of bladder capacity began to evolve (Tanagho and Schmidt, 1988; Schmidt, 1989). Thus neuromodulation was introduced as a concept by which activation of the sacral roots may, in fact, modulate external sphincter function and in turn inhibit detrusor activity as a normal reflex. These early discoveries created the platform for the current and

future concepts and technologies that are used for neurostimulation and neuromodulation.

NEUROPHYSIOLOGY OF ELECTRICAL STIMULATION FOR STORAGE AND EMPTYING DISORDERS

The exact mechanisms of how neuromodulation works are not completely understood, but several plausible theories with testable hypotheses are under investigation. Most are founded on the basic neurophysiologic mechanisms that result in the normal storage and emptying functions of the bladder. Although there is an expanding amount of information on our knowledge of micturition neurophysiology, as discussed in this chapter, in this section the specifics of the micturition pathway in relation to neuromodulation are addressed.

Normal detrusor function appears to be a sacral balance under suprasacral influences of the sympathetic and parasympathetic nervous systems and their respective abilities to maintain continence. The sympathetic tone, for the most part, is dominant for the majority of time and thus provides continence or storage of urine; the parasympathetic nervous system allows detrusor contractions for emptying of the bladder. Thus the micturition reflex pathway is activated by initial bladder afferent excitation that then results in a bladder efferent excitation leading to a detrusor muscle contraction. The acquired and unique ability to void volitionally is due to either negative feedback (inhibition of voiding) or positive feed-forward (induction of voiding) influences of supraspinal inputs from the pontine micturition center on this sacral micturition reflex pathway. Any loss of either central supraspinal inhibitory influences or increased sensitization of bladder afferent signaling can lead to unmasking of involuntary voiding. Therefore this has been proved only in animals and, by deference, relates then to humans. There may be primitive reflexes that reside within the spinal cord that can be “awakened” by somatic and afferent nerve stimulation and may have something to do with the mechanism of action of neuro-modulation (de Groat, 1975, 1976; de Groat and Ryall, 1968a, 1968b). In patients with overactive bladder (OAB), some of the abnormal voiding reflex may be blocked with neuromodulation (impulse to pontine micturition center), thereby restricting involuntary detrusor contractions and restoring more normal voiding patterns. This has been shown with positron emission tomography scanning (Blok, 2006).

Bladder afferent nerve signaling sends information about pain and bladder fullness to the brain that will in turn initiate the micturition reflex. Bladder overactivity may be in part mediated by the loss of voluntary control of the voiding reflex and, furthermore, emergence of primitive voiding reflexes. In certain states of neurologic or inflammatory disease of the bladder, the previously silent C fibers may emerge and trigger the micturition reflex. Accordingly, blockade of this pathway by electrical neuro-modulation, similar to pharmacologic blockade by capsaicin (a C-fiber blocker), may suppress detrusor overactivity (DO) (Maggi and Meli, 1988; Chen et al, 1993).

Reflexes That Promote Bladder Storage

Two reflexes may play an important role in modulation of bladder function: the guarding reflex and the bladder afferent loop reflex. Both reflexes promote urine storage (guarding reflex under somatic influence and bladder loop reflex under sympathetic tone). The guarding reflex guards or prevents urine loss from times of cough or other physical stress that would normally trigger a micturition episode. Suprapontine input from the brain turns off the guarding reflex during micturition to allow efficient and complete emptying. The bladder afferent reflex works through sacral interneurons that then activate storage through pudendal nerve efferent pathways directed toward the urethral sphincter. Thus the activity has truly been realized only in cats but has been postulated to exist in humans and to function the same. Similar to the

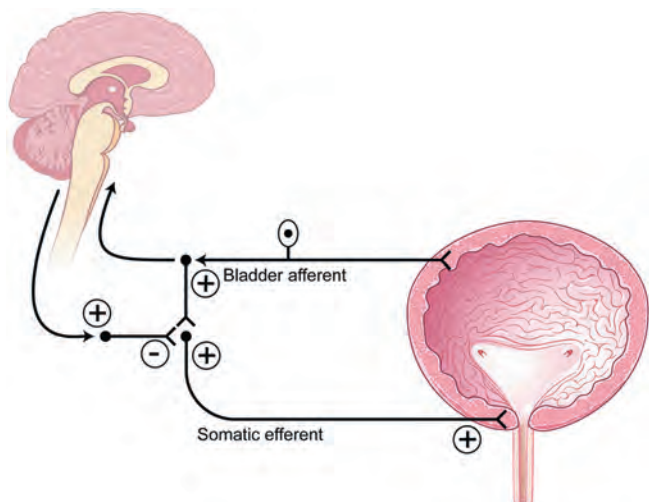


Figure 81-1. The guarding reflex promotes continence and allows the outlet to contract the urinary sphincter during periods of stress (e.g., cough). The brain can turn this reflex off during voiding. (Modified from Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. *Urol Clin North Am* 2005;32:11–8.)

guarding reflex, the bladder afferent reflex promotes continence during periods of bladder filling and is quiet during micturition (Fig. 81-1).

Reflexes That Promote Bladder Emptying

Signals from the bladder that may modulate the need to void with fullness, pain, pressure, or stretch may elicit bladder afferent activity through the A δ or even C fibers. These bladder afferent nerve fibers then synapse with both parasympathetic efferents (bladder-bladder reflex) and parasympathetic urethral efferents (bladder-urethral reflex). The urge to void may then be translated as an initial activity (inhibitory) of the bladder-urethral reflex to allow the pressure in the urethral outlet to drop immediately before a bladder contraction ensues and simultaneously permit the bladder-bladder reflex to allow a smooth bladder contraction to occur as the reflex is maintained throughout the entire void (de Groat, 1978; de Groat et al, 1981, 1996).

Putative Mechanism of Action of Sacral Neuromodulation

Although our knowledge of how neuromodulation works is evolving, two main theories exist: (1) Direct activation of efferent fibers to the striated urethral sphincter reflexively causes detrusor relaxation and (2) selective activation of afferent fibers causes inhibition at spinal and supraspinal levels. Accumulating evidence suggests that activation of somatic sacral afferent inflow at the sacral root level that in turn affects the storage and emptying reflexes in the bladder and central nervous system accounts for the positive effects of neuromodulation on both storage and emptying functions of the bladder (Yoshimura and de Groat, 1992, 1997; Leng and Chancellor, 2005). Malaguti and coworkers (2003), using detection of somatosensory evoked potentials during sacral neuromodulation, concluded that sacral neuromodulation therapy works by sacral afferent activity and concomitant activation of the somatosensory cortex. Because sacral neuromodulation has been clinically proved for both storage (urgency/frequency and urgency urinary incontinence) and emptying (nonobstructive urinary retention) dysfunctions of the bladder, isolating the mechanism of action to the micturition reflex pathway of sacral afferent and efferent pathways alone is challenging. However, by understanding the reflexes that influence the promotion of urine storage or emptying of the sacral micturition reflex pathway one begins to realize how neuro-

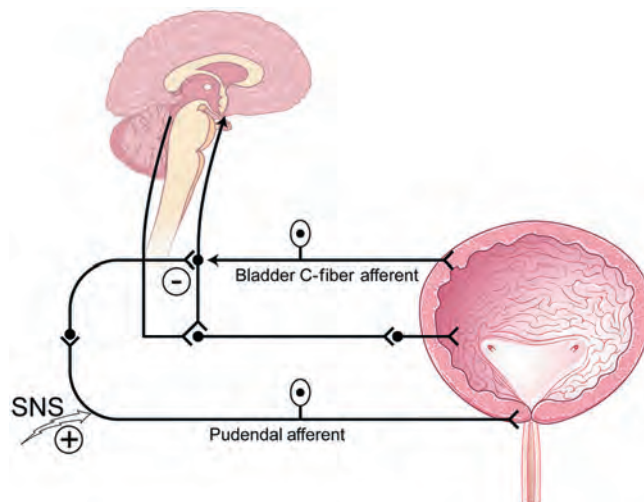


Figure 81-2. Pudendal nerve afferent firing can modulate and accordingly inhibit the bladder micturition reflex. SNS, sacral nerve stimulation. (Modified from Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. *Urol Clin North Am* 2005; 32:11–8.)

modulation may affect these reflexes and elicit symptomatic and functional improvement of voiding function (Fowler et al, 2000). Animal models of sacral neuromodulation for DO are now being developed and may shed more light on how this technology achieves its benefits (Riazimand and Mense, 2004; Vignes et al, 2009).

Putative Mechanism of Action of Sacral Neuromodulation in Overactive Bladder

The bladder storage and emptying reflexes are modulated by several centers in the brain and may be altered by neurologic injury that effectively unmasks involuntary bladder contractions. Thus sacral neuromodulation of these primitive reflexes may restore normal micturition (de Groat, 1976). Animal data exist to support the fact that somatic afferent input to the spinal cord can affect the guarding and bladder-bladder reflexes (de Groat, 1978; Chen et al, 1993). It is believed that suppression of interneuronal transmission in the bladder reflex pathway may be how sacral neuromodulation affects DO (de Groat, 1976; Kruse and de Groat, 1993; Leng and Chancellor, 2005). The inhibition by electrical neuromodulation may, in part, modulate the sensory outflow from the bladder through the ascending pathways to the pontine micturition center, thereby preventing involuntary contractions by modulating the micturition reflex circuit but allowing voluntary voiding to occur (Fig. 81-2). The preservation of voluntary voiding may be due to selective avoidance of normal sensory ascending outflow pathways of the bladder from A δ fibers to the pontine micturition center as well as initiation of the descending pathways from the pontine micturition center to sacral efferent outflow pathways. Therefore, as is seen in clinical practice, sacral neuromodulation may affect and improve the abnormal bladder sensations, involuntary voids, and detrusor contractions but still maintain normal bladder sensations and voluntary voiding patterns.

Putative Mechanism of Action of Sacral Neuromodulation in Urinary Retention

Sphincteric activity can be turned off by brain pathways to allow efficient and complete bladder emptying. If the suprasacral pathways are altered, the guarding and urethral reflexes still exist and cannot be turned off. This may cause retention, as in the spinal

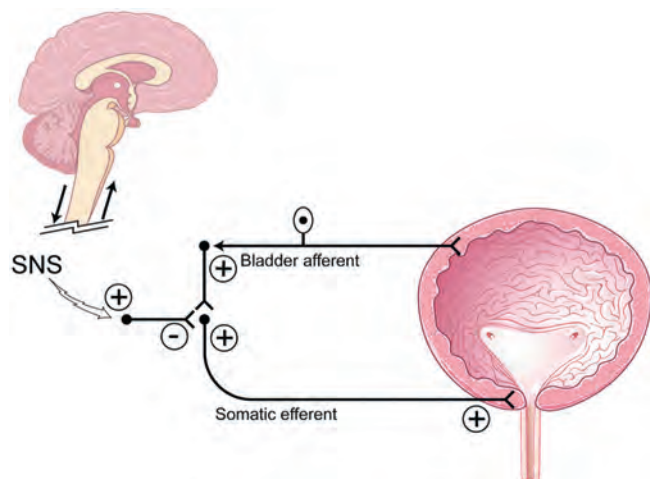


Figure 81-3. In neurologic disease the supraspinal circuitry is “disconnected” and therefore cannot turn off the spinal guarding reflex, and thus retention occurs. Sacral neuromodulation (SNS) can restore the normal voluntary pattern of micturition by inhibition of the spinal guarding reflex. (Modified from Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. *Urol Clin North Am* 2005; 32:11–8.)

cord-injured patient who in turn has detrusor-sphincter dyssynergia resulting in urinary retention. Thus inhibition of the guarding reflexes may allow urinary retention states to be improved (Fig. 81-3). Originally for urinary retention resulting from functional outlet obstruction, sacral neuromodulation was thought to directly turn off excitatory flow to the urethral outlet and facilitate bladder emptying. This may be an efferent effect of the primary afferent mechanism of sacral neuromodulation as reported by Dasgupta and colleagues (2005), who described novel neuroimaging evidence for the existence of abnormal interaction between the brainstem and cortical centers in women with urinary retention resulting from Fowler syndrome or overactive sphincteric activity. The direct therapeutic effect of sacral neuromodulation in patients with sphincter overactivity or functional outlet obstruction appears to be in the afferent restoration of a normal pattern of midbrain activity and decreased cortical activity leading to inhibition of the guarding reflexes.

ELECTRICAL STIMULATION FOR STORAGE DISORDERS

Criteria for Selection of Patients

Because many LUTS and LUTD are secondary to a neuromuscular cause, a thorough history and physical examination often will reveal the nature (acute vs. chronic) and help classify the cause (neurogenic, anatomic, postsurgical, functional, inflammatory, or idiopathic). In addition to the unique evaluation of pelvic floor muscle dysfunction (Siegel, 2005), a urinalysis is routinely performed; urine cytologic evaluation should be considered in patients who present with refractory symptoms of dysuria, urgency, or frequency of urination, because carcinoma in situ and bladder tumors may manifest as irritative bladder symptoms without hematuria. Further assessment of the bladder function, urodynamic studies including cystometrography, pressure-flow studies, and electromyography of sphincters and pelvic floor muscles are performed on a selected basis, because most non-neurogenic assessments are completed routinely with the use of a voiding diary and a focused physical examination of the pelvis. Electromyography is recommended in suspected cases of neurogenic bladder dysfunction, detrusor-sphincter dyssynergia, or Fowler syndrome and may be considered for evaluation of inappropriate pelvic floor muscle behavior (Dasgupta and Fowler, 2003). As of now, urodynamics

have not yielded adequate predictive factors that allow enhanced selection for patients undergoing sacral neuromodulation (Groenendijk et al, 2007). The characteristics of neurogenic bladders, as seen in patients with multiple sclerosis (MS) and spinal cord injury (SCI), can change with time and disease progression. Therefore re-evaluation with urodynamics and assessment of the upper urinary tracts may be needed when symptoms change despite active medical intervention.

Cystourethroscopy may yield information helpful in making a diagnosis. Anatomic lesions such as urethral stricture, bladder neck fibrosis, trabeculation, and bladder lesions have been found even in women with bladder outlet obstruction. Baseline upper tract imaging is performed in patients with neurologic disease or, if indicated, by physical or baseline studies or a patient's history.

Sacral neuromodulation is frequently attempted in patients in whom traditional conservative measures (e.g., bladder retraining, pelvic floor biofeedback, and medications) have failed and before more invasive surgical procedures (e.g., enterocystoplasty and urinary diversion). Despite all the studies done to date there are no defined preclinical factors, such as urodynamic findings, that can predict which patients will or will not respond to sacral neuromodulation.

Although most patients are considered candidates for neurostimulation and neuromodulation therapies when more conservative treatment has failed, there are some clinical considerations for excluding patients from this therapy. These include significant anatomic abnormalities in the spine or sacrum that may present challenges to gaining access; mental incapacitation of patients who cannot manage their device or judge the clinical outcome; physical limitations that prevent the patient from achieving normal pelvic organ function, such as functional urinary incontinence; and noncompliance of the patient.

Relative contraindications for patients who may be considering or who have an implantable electrical stimulation device are magnetic resonance imaging (MRI) and pregnancy. Magnetic fields produce currents in neuroelectrodes, and there is some concern that the magnetic field from MRI may damage the pulse generator, as discussed later. Many radiologists are reluctant to provide MRI services for patients with implantable electrical stimulation devices despite the anecdotal evidence that no adverse event has occurred when MRI has inadvertently or purposefully been done for emergent reasons or in small trials (Hassouna and Elkeline, 2005; Chermansky et al, 2011). For patients who have InterStim devices in place (see later), we advocate removal of the device in preparation for elective MRI based on current manufacturer recommendations. After the MRI procedure, a new neuroelectrode and generator may be placed. Anecdotal reports of patients safely undergoing the study (MRI) with the InterStim (Medtronic, Minneapolis, MN) implant in place have occurred, but patients should have the devices turned off in anticipation. Recent changes in the manufacturer recommendations do allow for head MRI to be performed with an InterStim in situ, but clearance requires several factors, including having the device turned off and use of a 1.5-Tesla magnet or lower (Medtronic models 3058 and select 3023; see manufacturer website for more information). Because of the potential for teratogenicity or abortion from the effect of electrical stimulation, it has been considered contraindicated in pregnant women with various voiding dysfunctions. However, whether electrical stimulation can cause abortion or malformation is not known. Wang and Hassouna (1999) reported no adverse effects of electrical stimulation on pregnant rats, and that termination of pregnancy is not advised for prospective mothers when electrical stimulation has been performed unknowingly in early pregnancy. Women with electrical stimulation devices for pelvic health conditions who become pregnant may simply turn off their devices during pregnancy.

Electrical Stimulation of the Bladder

Transurethral electrical bladder stimulation (TEBS) has been pursued not only for initiating sensory awareness of bladder filling and stimulating detrusor contractility (see later section) but also

for increasing bladder capacity at low pressure in pediatric patients with myelomeningocele (Kaplan et al, 1989; Decter et al, 1994). The authors in these two cited references carried on an interesting point-counterpoint discussion in publications regarding the practical benefit of TEBS (Decter, 2000; Kaplan, 2000), which remains controversial.

Both authors seem to be saying the same thing with respect to results but attach a totally different significance to the practical implications of the results. Kaplan (2000) points out that when the procedure was initiated the goal was to provide children with neurogenic bladder dysfunction, mostly secondary to spina bifida, enough sensation to detect a filling or full bladder and to have them synergistically void or catheterize in a timely manner. As the results of treatment have been evaluated over the years, the real benefit of this program, to Kaplan at least, was the potential to increase bladder capacity while maintaining or decreasing end-filling bladder pressure (in essence, improving compliance). Decter (2000) gives what seems to be a reasonable summation of the largest multi-institutional report of this therapy involving 568 patients who underwent TEBS at 11 institutions, only 335 of whom had adequate pretreatment and post-treatment urodynamics for evaluation. Bladder capacity increased by 20% or more in 56% of the 335 patients, whereas pressure at bladder capacity decreased by 25% or more in 16% of those in whom the bladder capacity increased. Decter (2000) calculated that only 30 of 335 patients had both a 20% or more increase in bladder capacity and a 25% decrease in compliance. He reports his experience with 25 patients during a 4-year period as showing that bladder capacity increased more than 20% (values referred to a comparison to age-adjusted bladder capacity) and end-filling bladder pressures showed clinically significant decreases in 29% of patients. Putting this in perspective, he believes "the practical benefits our patients derive seem limited . . . the urodynamic improvements we achieved after stimulation did not materially alter daily voiding routine (i.e., clean intermittent catheterization) of these children." Pugach and associates (2000) also reported the results of TEBS in a group of pediatric patients; only 7 of 44 (16%) had safe storage pressures with continence after treatment. Data have been limited since 2000 on this treatment modality, probably owing to targeting of other nerves with better potential.

Sacral Rhizotomy

In most cases, bilateral anterior and posterior sacral rhizotomy or conusectomy converts an overactive detrusor to an areflexic one. This alone may be inappropriate therapy because it also adversely affects the rectum, anal and urethral sphincters, sexual function, and the lower extremities. In an attempt to leave sphincter and sexual function intact, selective motor nerve section was originally introduced as a treatment to increase bladder capacity by abolishing only the motor supply responsible for involuntary contractions. The initial use of this procedure followed the observation that the third anterior (ventral) sacral root provided the dominant motor innervation of the human bladder. To enhance the clinical response and minimize side effects, differential sacral rhizotomy always should be preceded by stimulation and blockade of the individual sacral roots with cystometric and sphincterometric control.

Although technique refinements, such as percutaneous radiofrequency selective sacral rhizotomy and cryoneurolysis, have occurred, there is still controversy about the role of anterior rhizotomy procedures within a treatment plan for DO. Torrens (1985) summarized successful results in collected groups of patients that ranged from 48% for idiopathic overactivity to 81% for patients classified as having a "paraplegic bladder." However, as he astutely pointed out, the definition of success varies across series and from one patient to another. When these procedures are used, they should certainly be preceded by urodynamics and urologic evaluation of the effects of selective nerve blocks before performance, especially in patients without fixed neurologic disease or injury. Even then, unintended effects on pelvic and lower extremity sensory or

motor functions may occur with disastrous medical and legal sequelae.

Tanagho and Schmidt (1988, 1989) and Brindley and Rushton (1990) have popularized the concept of sensory deafferentation by dorsal or posterior rhizotomy to increase bladder capacity as part of their overall plan to simultaneously rehabilitate storage and emptying problems in patients with significant SCI or disease. These are patients in whom electrical stimulation also was used to alleviate emptying deficits (see section on emptying disorders). McGuire and Savastano (1984) also mentioned dorsal root gangliectomy alone in such patients to increase bladder capacity.

Gasparini and colleagues (1992) reported durability of the deafferentation response to selective dorsal sacral rhizotomy up to 64 months after section. The technique involves selecting nerve roots whose intraoperative stimulation provokes an adequate detrusor response. The dorsal and ventral components of these roots are then separated and the dorsal root or roots severed. An increase in bladder capacity of 259 to 377 mL was noted in 16 of 17 patients studied (24 in the original series), with an increase in the volume to the first contraction of 99 to 270 mL. Of the patients, 14 were cured of incontinence and 2 improved; the technique failed in 1 patient. Of 7 potent men, 2 experienced a decrease in erectile frequency but were still able to achieve penetration. Bowel and sphincter function were unaffected. Koldewijn and associates (1994) reported on the effects of intradural bilateral posterior root rhizotomies from S2 to S5 with implantation of an anterior root stimulator in a group of patients with suprasacral SCI. All showed persistent detrusor areflexia afterward, although 2 required subsequent secondary rhizotomy at the level of the conus. A majority showed decreased bladder compliance up to 5 days postoperatively, followed by a rapid increase thereafter.

Brindley (1994) summarized the advantages of bilateral posterior sacral rhizotomy in treatment of voiding dysfunction after SCI as abolishing reflex incontinence, improving compliance, and abolishing striated sphincter dyssynergia without altering resting tone. Partial or selective procedures are considered only in such patients who retain some sensation or have excellent reflex erections. Madersbacher (2000) comments that posterior sacral rhizotomy for sacral deafferentation of the bladder is best achieved by the intradural approach, which has the advantage that, in this location, motor and sensory fibers easily can be separated, whereas distal to the spinal ganglion, motor and sensory fibers are intermingled and a clear separation is no longer possible. If an intradural procedure is not possible, he believes that a deafferentation at the level of the conus medullaris is preferable to an extradural sacral approach. He mentions that he has treated 65 tetraplegic or paraplegic patients with post-SCI reflex urinary incontinence who were resistant to all other means of conservative treatment. Incontinence was abolished in 90% of these patients.

Sacral Neuromodulation

Neuromodulation is an innovative treatment of LUTS and LUTD of bladder storage secondary to neuromuscular causes. In addition to the application of evolving technologies for sacral neuromodulation therapy, expanding clinical indications such as neurogenic DO, post-sling-related voiding dysfunction, interstitial cystitis, pelvic pain, pediatric voiding dysfunction, and bowel disorders, as well as novel forms of transcutaneous and implantable neuromodulation devices for different nerve roots are under investigation.

Technique

Sacral nerve stimulation (SNS) by the InterStim procedure is performed in two stages: stage I, a clinical trial of a temporary or permanent lead for external stimulation, and stage II, implantation of a subcutaneous implantable pulse generator (IPG). Each stage can be performed with monitored anesthesia care supplemented by local anesthesia. During the initial introduction of sacral neuromodulation therapy, patients underwent a percutaneous nerve

evaluation by the placement of a unilateral percutaneous lead into the S3 foramen with use of local injectable anesthesia. The lead was connected to an external pulse generator and worn by the patient for several days. A large number of false-negative results with therapy are attributed to improper lead placement and migration. Whereas some physicians still prefer to perform the first stage by a percutaneous nerve evaluation approach, many have adopted a permanent tined lead placement for the first stage in an attempt to avoid the issues related to high false-negative results (migrated lead so as to have a suboptimal test phase) with the first stage and high false-positive results (did the lead work or is it implanted for the wrong reason with true failure) with the second stage. Changes in LUTS and postvoid residuals (PVRs) are recorded in a detailed bladder diary. If improvement is minimal or absent, revision or bilateral percutaneous lead placement may be attempted. If greater than 50% improvement in symptoms of urgency/frequency or urgency urinary incontinence is attained, a permanent IPG is implanted. The length of the trial with the external pulse generator may vary slightly from patient to patient, by the indication, and by the surgeon's practice preference. In patients with urgency/frequency and urgency urinary incontinence, a 1- to 2-week trial is generally adequate. For retention, a longer trial of 3 to 4 weeks or more may be necessary before a desired clinical response is obtained.

Previous lead placement required a more time-consuming surgical dissection of the layers above the sacral foramen and unreliable lead fixation with anchors. Recent technical advances have made implantation of the percutaneous lead easier and less prone to migration. Spinelli and colleagues (2003) were the first to present the advantages of the **tined lead** that used a percutaneous approach for placement and fixation (Fig. 81-4). Subsequent large-scale clinical experience worldwide confirms that the tined lead is less prone to migration and has decreased false-negative results with the screening trial. Furthermore, the false-positive rate of the screening trial is reduced when placement of a permanent lead with reliable fixation during the screening trial ensures that the same location of stimulation is achieved when the IPG is implanted. With a percutaneous nerve evaluation or similar temporary lead electrode during the screening trial, a different clinical outcome may occur when the permanent lead is placed at the time of the IPG implantation.

For the **first stage** of the procedure, preoperative intravenous antibiotics are given before the procedure and aseptic techniques of foreign body implants are implemented. At present, no defined antibiotic regimen is agreed upon and is left to surgeon discretion (preoperatively or postoperatively). The patient is placed in the prone position, and the buttocks are held apart by wide tape retraction so that the anus is visible during test stimulation. The anus and tape are prepared in a sterile fashion and then covered with a sepa-

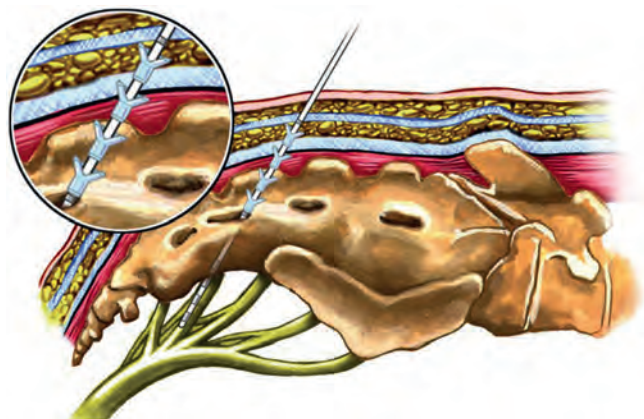


Figure 81-4. The tined lead is introduced typically into the S3 nerve foramen. The tines allow the lead to be fixed into the fascial layers above the sacrum. This lead has a quadripolar configuration (four contact points). (Courtesy Medtronic, Minneapolis, MN.)

rate plastic drape until visualization is needed during the procedure. The sterile drape covering the feet must be folded back such that the feet can be visualized during the procedure as well.

The location of the S3 foramen is approximated by measuring 9 cm cephalad to the drop-off of the sacrum and 1 to 2 cm lateral to the midline on either side. Alternatively, the site may be localized by palpating the cephalad portions of the sciatic notches bilaterally and drawing a connecting line that intersects the midline of the sacrum; one fingerbreadth on either side of the midline of the sacrum at this intersection will define the location of the S3 foramen (Fig. 81-5). The foramen needle is then inserted into the S3 foramen with a slight medial to lateral angulation to mimic the course of the nerve as it exits the foramen. The pelvic plexus and pudendal nerve run alongside the pelvis, and therefore the needle should be placed just inside the ventral foramen. The position of the needle is confirmed by fluoroscopy. The nerve is tested for the appropriate motor response, which is dorsiflexion of the great toe and bellows contraction of the perineal area, which represents contraction of the levator muscles (bellows reflex). Simultaneous sensory responses determined at the time of lead placement help optimize positioning. Although this is controversial, if one can localize the stimulation at the time of lead positioning to the vagina-rectum juncture in females and perineoscrotal area in males, this is proper localization of the device. The foramen needle stylet is then removed and

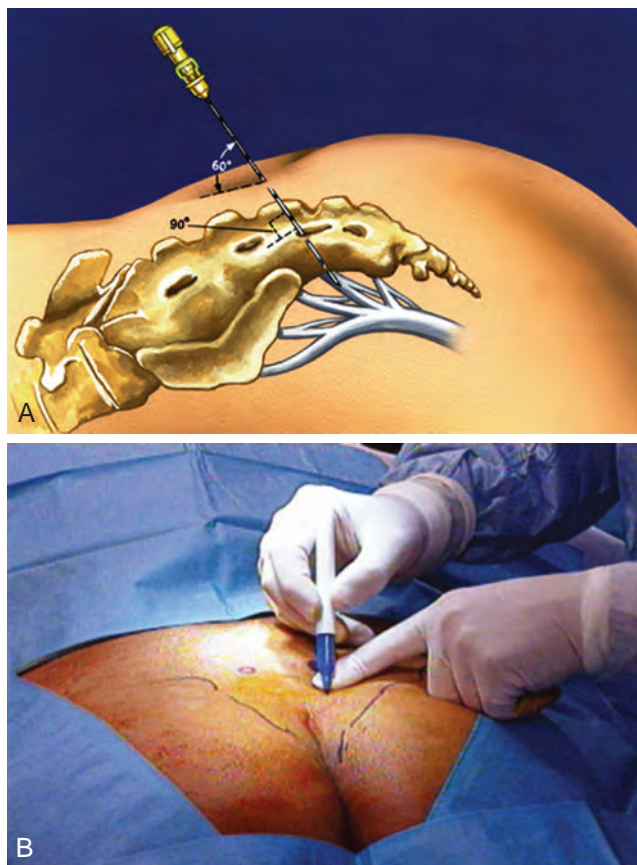


Figure 81-5. A, The percutaneous test stimulation is performed in an outpatient setting. A small lead wire is placed into S3 and connected to an external stimulator for 1 week to administer stimulation to the nerve roots. B, Measurement of the S3 nerve foramen is typically 9 cm to the coccyx and 11 cm to the anal verge. To find the rough site of the S3 nerve foramen 1 to 2 cm lateral to this mark is measured. The “cross hair” technique can be used to find the midline fluoroscopically and the lower aspect of the sacroiliac joints laterally to find the S3 nerve foramen, as well. (Courtesy Medtronic, Minneapolis, MN.)

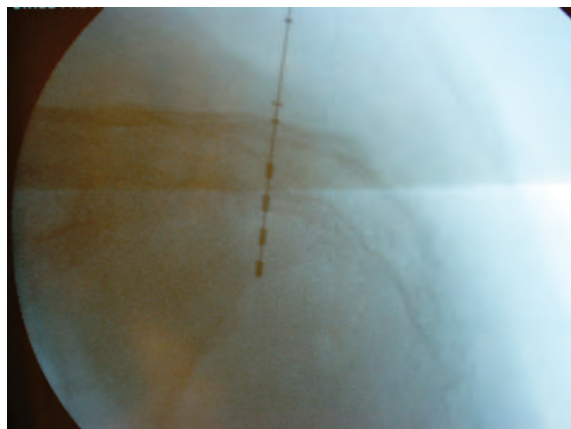


Figure 81-6. Fluoroscopy is used to confirm lead placement, typically with the lead configurations to obtain optimal muscle (bellows response and ipsilateral toe contractions) and sensory (vaginal, penile, or scrotal “pulsating” feeling) responses. The lead then may be deployed.

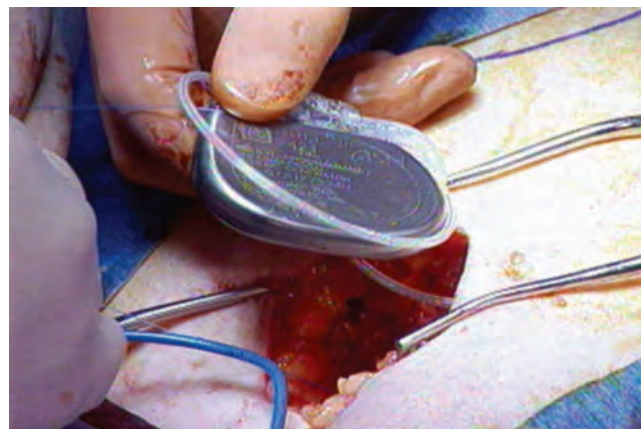


Figure 81-7. A 3- to 4-cm counterincision in the upper gluteal crease is made for a deep subcutaneous pocket to allow implantation of the implantable pulse generator.

replaced with the introducer sheath. The distal aspect of the lead consists of four electrodes numbered 0 through 3. The lead is placed into the introducer sheath as directed to expose the electrodes. Typically, electrodes are positioned such that electrodes 2 and 3 straddle the ventral surface of the sacrum (Fig. 81-6). Test stimulation is repeated on each electrode, and the responses are observed. An S3 response should be noted on at least two of the electrodes (see Table 81-2). Once the surgeon is satisfied with the position, the sheath is removed, releasing the tines that anchor the lead. If the lead is placed too deep, the tines reside within the sacral foramen and removal (if and when necessary) becomes more challenging. A sensory response, sensation of stimulation in the perineum, is not needed to confirm proper placement if the correct S3 motor response is observed, although this is debatable. However, when a motor response is absent, raising the conscious level of the patient during the procedure and detecting the correct sensory response will confirm proper localization and a clinical response may still be obtained during the screening trial period despite the absence of the motor response.

A 3- to 4-cm incision into the subcutaneous tissues in the upper lateral buttock is made below the beltline or below the level of the ischial wings for connecting the permanent lead to the percutaneous extension lead wire. If the screening trial is successful, this connection site will be the site of implantation for the IPG. With use of the tunneling device provided in the commercial kit, the permanent lead is transferred to the medial aspect of the lateral buttock incision. The lead is then connected to the extension wire, and the tunneling device is used again to transpose the extension wire from the medial aspect of the incision to an exit point on the contralateral side of the back. This transfer and long tunnel reduce the occurrence of infection from the percutaneous exit site of the wire. The extension wire is connected to the external pulse generator. Patients are able to resume their normal activities immediately but are advised to limit excessive movement-related activities, such as high-impact exercises, for the duration of the trial period.

The external generator can be flexibly programmed for the duration of the intended trial while the patient records symptoms and bladder function in a voiding diary. Initial programming should be performed to maximize patient comfort and attempt to localize sensory response to the vaginal or perineoscrotal areas with a gentle pulsating feeling. If there is more than 50% improvement in the symptoms or voiding function, a stage II procedure is performed.

A stage II procedure entails placement of the IPG. No fluoroscopy is required during stage II when a permanent neuroelectrode has been placed for the stage I procedure; however, if a percutane-

ous nerve evaluation was performed for stage I, fluoroscopic confirmation of the neuroelectrode placement is advised. The patient may be placed in the prone position or a lateral position with the site of the previous lateral incision for the lead connections placed upward (Fig. 81-7). The lateral position may improve ventilation during sedation. The previous buttock incision overlying the lead connections is opened, the percutaneous extension wire is removed, and the extension lead is secured to the permanent lead and subsequently to the IPG. Copious irrigation and antibiotic solution is often used to minimize IPG infections. A pocket is made in the subcutaneous tissue that is large enough to avoid tension on closure and at a depth to provide a covering layer of subcutaneous tissue anterior to the pulse generator to prevent erosion.

Outcomes

Urinary urgency, frequency, and urgency incontinence have a significant impact on medical health and quality of life. Neuromodulation offers an alternative to patients who may be considering irreversible surgical options when pelvic floor muscle reeducation and pharmacologic therapy have failed. Outcomes of SNS for the indications of idiopathic urgency/frequency and urgency urinary incontinence are derived from only two studies that have randomized patients to active or delayed therapy as well as reports from numerous prospective and retrospective reviews of case series and registry databases.

Schmidt and coworkers (1999) reported on SNS therapy in 76 patients with refractory urgency urinary incontinence from 16 centers worldwide randomized to active or delayed therapy (control group) during the study period of 6 months. Of the 34 patients receiving active SNS therapy compared with the delayed group, 16 (47%) were completely dry and an additional 10 (29%) demonstrated more than 50% reduction in incontinence episodes. Complications were IPG site pain in 16%, implant infections in 19%, and lead migration in 7%.

In a similar study design, Hassouna and colleagues (2000) reported the outcomes of SNS on refractory urgency/frequency conditions in 51 patients randomized from 12 centers during an initial 6-month period that was extended to 2 years. Outcomes at 6 months in the active SNS group showed improvement in the number of daily voids (16.9 ± 9.7 to 9.3 ± 5.1), volume voided (118 ± 74 mL to 226 ± 124 mL), degree of urgency (rank score of 2.2 ± 0.6 to 1.6 ± 0.9), and SF-36 quality-of-life measures. At 6 months after implantation, stimulators in the active group were turned off and urinary symptoms returned to baseline values. After reactivation of SNS, sustained efficacy was documented at 12 and 24 months.

Limited but conformational results of the earlier randomized trials have been obtained from prospective series (Shaker and Hassouna, 1998; Siegel et al, 2000; Janknegt et al, 2001; Marcelissen et al, 2010; Al-zahrani et al, 2011) and registry studies (Spinelli et al, 2001; Hedlund et al, 2002) evaluating efficacy, safety, and quality-of-life measures. The results for the registration trial that led to approval by the U.S. Food and Drug Administration (FDA) for SNS (Pettit et al, 2002) reveal that 37 of 62 patients (60%) with refractory urgency/frequency or urgency urinary incontinence achieved an improvement of 50% or more in their condition. van Kerrebroeck and coworkers (2007) reported on a 5-year prospective worldwide series for patients with the InterStim device for varying indications and for the urgency/frequency and urgency urinary incontinence populations, and good success was achieved in all groups. Of note is that the analysis included patients in the initial registration trial who then “crossed over” to the prospective 5-year trial. This study, unfortunately, was influenced by several patients who did not attend all follow-up visits and, therefore, had missing data points, a problem reflective of this challenging subgroup. Outcomes data were based on “last observation carried forward,” which is of concern for not being statistically optimal, but nonetheless these are still the longest term data available for this technology. Separate analysis with intent-to-treat models do still show these data to be conclusive of good long-term efficacy, albeit lower than the last observation carried forward. Some have tried to push the success rate or improvement percentage beyond 50% up to 70% in an attempt to get a true test and minimize any placebo phenomenon (Amend et al, 2013). This same trial also extended the stage I lead phase up to 6 weeks again to minimize placebo rates and interestingly did not show higher infection rates, although their patients were admitted to the hospital for antibiotics for longer than is done in other parts of the world.

Another impactful trial underway in the United States is prospectively evaluating sacral neuromodulation with 200 units of onabotulinumtoxinA (OBTX) in a randomized fashion in patients with idiopathic OAB. Another study compares InterStim with standard medical therapy in a randomized fashion (Siegel et al, 2015).

Special Populations

With the success of neuromodulatory therapies for refractory DO and urinary retention, it should be no surprise that indications are expanding. Despite the fact that there is no true FDA-approved indication for neuromodulation in select populations, these groups all have some component of the indicated symptom complex that includes urgency, frequency, urgency urinary incontinence, or urinary retention. The current (not FDA approved) expansion of indications for neuromodulation has developed into areas of neurogenic bladder (Parkinson disease, MS, SCI), interstitial cystitis (painful bladder syndrome), pelvic pain, and pediatric voiding dysfunction. Both fecal incontinence and bowel emptying disorders were formerly classified in this group; however, fecal incontinence is now FDA approved and represents a large growing area of implantation because of high success rates for this indication.

Neurogenic Bladder. Patients with neurogenic bladder may have several urodynamic events that lead to their symptomatic voiding dysfunction. This may include neurogenic DO, detrusor-sphincter dyssynergia, and flaccid areflexia. Whereas neuromodulation has not been well examined in cases of obvious areflexia (possibly because of the need for some end-organ response for neuromodulation to have any benefit), it has been studied in small subgroups of patients with DO and possibly detrusor-external sphincter dyssynergia, although few published reports exist.

Because the spectrum of neurologic diseases with potential bladder manifestations is wide, one must be cognizant of a few important relative contraindications before contemplating current neuromodulatory therapies, as follows: Significant bone abnormalities in the spine or sacrum that may present challenges to gaining access, mental incapacity of patients who cannot manage the device, physical limitations that prevent voiding

(functional incontinence), future need of MRI (nonbrain only), and noncompliance.

Multiple Sclerosis. MS is a chronic demyelinating disease of the central and peripheral nervous system that can cause a variety of voiding dysfunction scenarios, including neurogenic DO, detrusor-sphincter dyssynergia, areflexia, and combinations of these. Because many patients have been refractory to standard therapies, neuromodulation or neurostimulation (to be addressed later in the section on neurostimulation for retention) may be considered a part of their treatment options. In an appropriately selected patient with MS, neuromodulation truly has some promise because it may balance the function of the bladder, as well as that of the outlet (two of the main components of MS-related voiding dysfunction). This may be considered off-label use of neuromodulation because it is not approved specifically for MS-related voiding dysfunction, but approval may be based on symptoms such as urgency, frequency, or often urgency urinary incontinence and even nonobstructive urinary retention.

No prospective randomized trials exist on the use of neuromodulation in management of MS-related bladder dysfunction. Small series with encouraging results in patients with MS demonstrate that neuromodulation may have a role in treatment of MS-related voiding dysfunction (Bosch and Groen, 1996; Wallace et al, 2007; Minardi and Muzzonigro, 2012; Peeters et al, 2014). It appears that the best candidates are ones with mild, nonprogressive MS, with few functional issues, who also have DO or even retention but not areflexia. One of the major issues that arises in the patient with MS in particular is the potential change in the disease state that may be potentiated by neuromodulation. Although this may be theoretical, it was one of the factors cited by the FDA in the original sacral neuromodulation trials and precluded MS patients from being enrolled (Hassouna et al, 2000).

A secondary issue that may arise if a patient with MS is implanted with the lead and IPG system is the potential need for MRI in the future. One should maintain close contact with the patient's neurologist as to the decision to place a neuromodulatory device to prevent any future need for MRI or selection of a patient in an active phase of disease who requires routine MRI. The main concern with MRI and implantable stimulator or pacemaker-type devices is that heating of the leads has been demonstrated in vivo and in vitro (Roguin et al, 2004; Martin, 2005). Whereas some question the clinical significance of the small temperature changes with the leads, the potential exists to elicit nerve damage with heating of the lead and the magnetic field may change the generator itself (Gimbel and Kanal, 2004). As previously mentioned, the recent manufacturer change to allow head MRI has been helpful in this patient population to have InterStim placed. At present though, it is contraindicated to perform MRI of a patient with an implantable neurostimulator system, if the MRI is looking at spinal cord segments or anything below the head.

Spinal Cord Injury. Many specialists who treat neurogenic disorders resulting from SCI realize that a patient may present with a variety of clinical and urodynamic findings. Many patients have neurogenic detrusor areflexic situations, but perhaps more often and sometimes more challenging is the subset who may be incontinent from neurogenic DO with or without concomitant sphincter dyssynergia. Furthermore, the adverse sequelae of treated or untreated SCI may include infections, urolithiasis, reflux, or obstruction. The goal, then, is not only to prevent these adverse events but also to ensure a bladder that functions well, empties at a low pressure to protect the upper tracts, and maintains a good capacity and continence. Whereas it is implied that an intact reflex arc should be in place for neuromodulation to work, this has not been proved in clinical studies. Basic science data suggest that at least some communication should exist between sacral outflow and the pontine micturition center to allow processing for the reflexes that may be inhibited by the brain (de Groat et al, 1981). Thus a patient with a complete spinal cord lesion may not have the same potential benefit from neuromodulation as does one with an incomplete lesion. Again, this fact has yet to be proved clinically in patients. Shaker and colleagues (2000) described their observations

in a group of female rats that developed OAB 3 weeks after spinal cord transection, associated with an increase in neuropeptide content of the dorsal root ganglion of L6. The spinal cord transections were at level T10. Electrostimulation of S1 was carried out and abolished overactivity while still attaining the rise in neuropeptide content in the L6 dorsal root ganglion. This suggested that blockade of C-fiber afferent pathways may have been one of the mechanisms of action of neuromodulation of the sacral root. In addition, they believed the time course of the reduction in neuropeptide content may explain the long-term changes that occur with chronic neuromodulation and the time needed for DO to return toward baseline after neuromodulation is initiated.

From a clinical perspective, few studies exist in neurogenic patients alone for whom sacral neuromodulation was performed. [Andrews and Reynard \(2003\)](#) described a patient with T8 paraplegia with residual urinary urgency and urgency urinary incontinence who underwent percutaneous tibial nerve stimulation (see later section in this chapter) for his problem. This patient experienced an almost twofold increase in bladder capacity; this was repeated, and again increased cystometric capacity was demonstrated on follow-up. Patients with incomplete SCI may respond in a fashion similar to that of the remainder of the population, with fairly high success rates in motivated individuals ([Lombardi and Del Popolo, 2010](#); [Peeters et al, 2014](#)).

It is clear that this is an emerging area of interest in current techniques, and some have postulated a role for selective stimulation in neurogenic patients as a means to achieve better results. Future research will clearly need to be done in this challenging subset of patients.

Voiding Dysfunction after Prior Sling or Anti-Incontinence Surgery. It is well known that patients may develop urinary retention or some form of voiding dysfunction after vaginal sling surgery or other forms of surgical management for urinary incontinence. Whereas the mainstay of therapy is to surgically “undo” the operation, many patients who have been obstructed for some period may manifest long-term voiding difficulty. This problem may vary among urgency, frequency, urgency urinary incontinence, or continued problems with retention and incomplete emptying despite adequate urethrolysis. This patient population (when refractory symptoms continue) may be ideally suited to the placement of a sacral neuromodulation device ([Starkman et al, 2008](#)). After implantation, patients had improved quality-of-life scores, improved urgency and frequency scores, and diminished urgency urinary incontinence in a small retrospective series.

Interstitial Cystitis (Painful Bladder Syndrome). Chronic pelvic pain and interstitial cystitis are challenging and frustrating conditions for both the physician and the patient. Therapeutic options are limited and frequently ineffective. Whereas neuromodulation therapy in patients with interstitial cystitis has typically been reserved for patients considering major surgery (e.g., cystectomy and urinary diversion) when behavioral and pharmacologic therapies have failed, more innovative consideration has been given to earlier application of this therapy before chronic neuroplastic changes become irreversible.

Interstitial cystitis is not an FDA-approved indication for neuromodulation; however, the symptom complex of urinary urgency and frequency is well within the standard approved criteria. It may be realized that neuromodulation for interstitial cystitis may be best in combination with other therapies, because interstitial cystitis is thought to require a multimodal approach and neuromodulation should be considered only one part of the multimodal therapy. It is a later stage modality listed in the most recent interstitial cystitis guidelines that can be offered.

[Comiter \(2003\)](#) performed a prospective evaluation of 25 patients with refractory interstitial cystitis. Of the 25 patients, 17 demonstrated more than 50% improvement in average pain score and voiding symptoms and therefore qualified for permanent IPG placement. At a mean of 14 months of follow-up, improvements were seen in frequency, nocturia, and mean voided volume. Average pain scores decreased from 5.8 to 1.6 on a 10-point scale, and Interstitial Cystitis Symptom Index (ICSI) and Problem Index

(ICPI) scores decreased significantly. Furthermore, 94% of patients implanted had a sustained improvement in symptoms. Similar findings were noted by [Whitmore and associates \(2003\)](#) in 33 patients who had statistically improved parameters in frequency, pain, average voided volume, and maximum voided volume, as well as ICSI and ICPI scores.

[Peters and colleagues \(2003\)](#) retrospectively evaluated 21 patients with refractory interstitial cystitis with pelvic pain who underwent permanent implantation of the IPG. The patients were contacted by mail and asked to respond to a questionnaire that addressed the use of narcotic pain medication. There was an average decrease in morphine dose equivalents after implantation of 36%. In addition, patients were asked to rate their pelvic pain on a 7-point scale. Most patients reported a moderate-to-marked improvement in pain after sacral neuromodulation. Approximately one fourth of the patients were able to discontinue narcotics completely, and patients overall were satisfied with this form of therapy compared with previous ones.

[Chai and coworkers \(2000\)](#) reported that perhaps some of the effects of neuromodulation in patients with interstitial cystitis may be due to changes in antiproliferative factor. His group demonstrated that levels of antiproliferative factor and epidermal growth factor were elevated in the urine of patients with interstitial cystitis and that these levels subsequently normalized after a short trial of sacral neuromodulation.

Chronic Pelvic Pain. Pelvic pain, much like interstitial cystitis, has been investigated with therapy such as neuromodulation; again, this affects a challenging subset of patients who do not receive benefit from other treatments. [Bemelmans and associates \(1999\)](#) described the mechanism in pain inhibition as involving the gate control mechanism at the spinal segmental level. At this point, large somatic sensory fibers inhibit the activity in small A δ or unmyelinated C fibers via sacral segmental interneurons or perhaps supraspinally by way of the spinobulbospinal reflex system. The hypothesis is that sacral root stimulation for the treatment of many disorders may result from decreasing pelvic floor spasticity.

Multimodal therapy is likely to be of benefit; however, results may not be optimal in all cases. **Spinal cord stimulation at higher centers has been used by pain therapists and with moderate success; however, trial design and consistent entry criteria are debated** ([Feler, 2003](#); [Mailis-Gagnon et al, 2004](#)). Small series have looked at more selective stimulation, primarily at sacral roots. [Abouseif and colleagues \(2002\)](#) examined the effect of sacral neuromodulation on pelvic floor dysfunction in 41 of 64 patients thought to have chronic pelvic or perineal pain. Patients with chronic pelvic pain had decreased pain scores on average (5.8 to 3.7) after neuromodulation based on validated pain scales. [Siegel and associates \(2001\)](#) examined patients with intractable pelvic or genitourinary pain in the absence of neurologic or pelvic disease. Sacral neuromodulation did benefit patients, and they described a decrease in severity of pain and quality-of-life improvements. Bilateral caudal sacral stimulation may yield almost 40% improvement in pain scores in patients with mixed symptoms of voiding dysfunction and pelvic pain ([Zabihi et al, 2008](#)). Still, some form of placebo effect is likely to exist and is challenging to control in these small series.

Pediatric Voiding Dysfunction. Children often experience voiding dysfunction in fairly high rates and may in fact have refractory bladder problems that require advanced management schemes. Neuromodulation has been considered in this population because of the variety of LUTD that pediatric patients may have, including OAB, urinary retention, and non-neurogenic neurogenic bladder (the Hinman bladder syndrome). Because neuromodulation represents a minimally invasive option for refractory management, it follows that this may be an approach to be used in pediatric LUTD. Still, sacral neuromodulation is not approved by the FDA for use in pediatric patients, perhaps owing to lack of data on what the sacral lead would do with concomitant growth of the spinal cord, nerve roots, and foramina. Accordingly, efforts in the past have been centered on alternative means of delivering electrical stimulation to the bladder and pelvic floor in these patients. Few studies exist of pediatric patients and sacral

neuromodulation. [Guys and coworkers \(2004\)](#) prospectively examined 21 patients to 21 years of age with sacral neuromodulation in the setting of neurologic disease consisting predominantly of spina bifida. The neuromodulation implant group had improved compliance and bladder capacity at 6 and 9 months but not at 12 months. Of the 21 patients, 9 improved their intestinal transit times and 1 patient had complete disappearance of urinary incontinence. No patients in the control group experienced an improvement of their condition. [McGee and associates \(2009\)](#) described the use of an incisionless first- and second-stage sacral neuromodulation procedure with fairly high success rates in pediatric patients with dysfunctional elimination syndromes and had minimal complications.

Transcutaneous electrical nerve stimulation (TENS) has been used in pediatrics because it is noninvasive. Usually patch electrodes are placed on both sides of the S3 nerve foramen and connected to a pulse generator and amplifier. [Hoebeke and associates \(2001\)](#) reported on this use in 41 children. In this case series, patients had urodynamically proved DO and anticholinergic therapy had failed in all. Patients had daily therapy with the patch electrodes placed at S3, and stimulation was delivered at 2 Hz. A 76% response rate was observed, due in part to increase in bladder capacity and reduction in urgency urinary incontinence and urgency symptoms. Of 41 patients, 21 (51%) were definitively cured; the remainder experienced relapse in the ensuing 1 year of follow-up. [Bower and colleagues \(1998\)](#) reported a similar fairly high success rate with 17 children treated with S3 transcutaneous stimulation and demonstrated dryness in 73.3% of patients and improved urgency and bladder capacity based on visual analog scales and voiding diaries. A more recent study by [Malm-Buatsi and associates \(2007\)](#) also showed continued benefit in patients when 8 of 12 (75%) received statistically significant benefits when therapy was completed. Although this technology seems to have fairly good success, there has been no trial in a randomized prospective controlled fashion that may increase its acceptance.

Posterior tibial nerve stimulation (PTNS), much like TENS, has been studied in pediatric patients because of its lack of invasiveness. [DeGennaro and colleagues \(2004\)](#) reported on PTNS in children in a subset of patients with refractory non-neurogenic voiding dysfunction: 80% of patients had symptom improvement and 44% were totally dry; 62.5% had improvement in bladder capacity. Furthermore, 71% had improvement in urinary retention symptoms. No patients had significant problems from the therapy, and it was overall thought to be both safe and well tolerated. [Hoebeke and associates \(2002\)](#), in a pilot study of PTNS, demonstrated similar success with 32 children. Of the 28 children with urgency before therapy, the urgency disappeared after therapy in 7 and improved in 10. Of the 23 children with daytime incontinence before treatment, 4 became dry after stimulation and in 12 patients the incontinence decreased. Of the 19 patients who reported abnormal voiding frequency of either less than 4 or more than 8 voids per day, 16 of 19 achieved a normal frequency of 4 to 6 voids daily. [Barroso and associates \(2013\)](#) compared parasacral cutaneous neuromodulation with percutaneous tibial nerve stimulation and noted improved results with parasacral stimulation in a prospective nonrandomized study; however, despite improvements, they were not found to be statistically significant changes.

Fecal Incontinence and Bowel Disorders. Sacral neuromodulation was investigated for bowel disorders on the basis of some of the early experience in patients with bladder conditions who exhibited treatment benefits with regard to the bowel symptoms ([Pettit et al, 2002](#)). The use of sacral neuromodulation in bowel disorders has recently been approved for use in the United States and was predated for approval in many other parts of the world beforehand. The two major areas of interest with regard to neuromodulation and bowel disorders are fecal incontinence and constipation.

Fecal Incontinence. Several studies have been done to examine the utility of sacral neuromodulation in fecal incontinence ([Kenefick et al, 2002a, 2002b; Uludag et al, 2002; Melenhorst et al, 2007](#)). It appears that patients with a variety of causes of fecal incontinence seem to have benefited from sacral neuromodulation therapy in this

setting. The Cleveland Clinic scoring system allows comparisons to be made with regard to outcome measures, including incontinent episodes (solid, liquid, and flatus), pad use, and lifestyle changes. Several studies used this scoring system, and all have shown improvements in these assessed parameters ([Matzel et al, 2003; Jarrett et al, 2004](#)). Sacral stimulation has been shown to be more effective than medical management based on randomized controlled trials for fecal incontinence ([Tjandra et al, 2008](#)). The mean incontinent (fecal) episodes decreased from 9.5 per week to 3.1 ($P < .001$), and perfect continence was gained in 47.2%. Similar improvements were demonstrated in quality-of-life parameters. A recent long-term analysis demonstrated continued benefit for patients with fecal incontinence, with 89% of patients who were followed having more than 50% improvement and 36% being totally dry ([Hull et al, 2013](#)). The exact prognostic indicators for success have yet to be defined, particularly as they relate to the cause of the fecal incontinence (sphincter defect, neurologic, functional). Interestingly, even patients with 120-degree sphincter defects seem to exhibit good efficacy from this therapy. Overall, there is tremendous interest in neuromodulation for fecal incontinence. This has challenged the use of sphincteroplasty in many of these patients because the success for neuromodulation seems much higher than that of overlapping sphincter repairs.

Constipation. Constipation as such is a broad term, with the definition being in evolution. It is thought to be representative of difficult evacuation of feces and infrequent or inadequate defecation. Other refinements to the definition may include bowel frequency of fewer than three stools per week. The ROME II criteria categorize constipation into subtypes, including constipation-predominant irritable bowel syndrome, functional constipation, and pelvic floor dyssynergia ([Drossman and Corazziari, 2000](#)). Sacral neuromodulation has been examined in this regard and has had favorable results on the basis of some of the criteria listed for improvement. [Ganio and associates \(2001\)](#) described 16 patients who underwent permanent implantation of sacral leads for constipation whereby they had a more than 50% decrease in difficulty emptying the rectum and more than 80% improvement in the Cleveland Clinic constipation score that persisted during the course of 1 year of follow-up. Other series have shown similar improvements, although in smaller numbers ([Kenefick et al, 2002a, 2002b; Sharma et al, 2011](#)). Still, with the small series available, it is difficult to make any meaningful analyses. The more important parameters, perhaps, in this setting relate to quality of life; these have been assessed with SF-36 questionnaires and have proved to be beneficial at least in the study by Kenefick and associates. All of these results suggest, at least, that there is some benefit of sacral neuromodulation in refractory constipation cases. Further study is warranted to assess prognostic factors to better decide on future candidates for this therapy.

Bilateral Stimulation and Neuromodulation

The current technique for sacral neuromodulation involves a unilateral lead at the S3 nerve foramen to achieve results in cases of urgency, frequency, urgency urinary incontinence, and idiopathic nonobstructive urinary retention. Bilateral stimulation has been suggested as an alternative, particularly in failed unilateral lead placements, for potential salvage or added benefit as the bladder receives bilateral innervation ([van Kerrebroeck et al, 2005](#)). The initial consideration of bilateral stimulation was based on animal studies demonstrating that bilateral stimulation yielded a more profound effect on bladder inhibition than did unilateral stimulation ([Schultz-Lampel et al, 1998a, 1998b](#)). An animal model of unilateral versus bilateral stimulation has suggested that bilateral stimulation may be more effective overall (based on reduction of detrusor overactive contractions) than unilateral stimulation ([Kaufmann et al, 2008](#)).

There has been only one prospective clinical study to demonstrate the differences in unilateral versus bilateral stimulation ([Scheepens et al, 2002](#)). This study was a prospective randomized

crossover design in which all patients underwent unilateral as well as bilateral test stimulations to assess the benefits of bilateral stimulation. Both unilateral and bilateral test stimulation was continued for 72 hours, and the patients were randomly assigned to start with unilateral or bilateral stimulation. No significant difference was found in the unilateral versus bilateral group with regard to urgency urinary incontinence, frequency, or severity of leakage in the OAB group, although overall results were impressive in both categories. The retention group had better parameters of emptying (volume per void) in bilateral compared with unilateral stimulation. Still, the numbers were too small in the retention group for adequate conclusions to be made. **It appears that the data as presented, at least from a clinical perspective, do not suggest a large role for routine bilateral stimulation for most patients.** Perhaps there will be subgroups that may benefit more than others (e.g., retention patients), but larger scale studies with good methodology as shown in the study by [Scheepens and colleagues \(2002\)](#) will be required. Still, if the overall success rates of patients undergoing sacral neuromodulation could be increased, more patients could ultimately be helped. Accordingly, [Pham and colleagues \(2008\)](#) examined 124 patients undergoing stage I sacral neuromodulation and stratified patients into unilateral and bilateral groups, retrospectively. Successful stage I trials were noted in 58% of unilateral patients and 76% of bilateral patients. An important component that still needs to be evaluated is whether it is cost-effective to “routinely” place bilateral leads in the setting of most unilateral lead success rates approaching 70% and 80%. Perhaps the challenge lies in the fact that many consider sacral neuromodulation near end of the line therapy and accordingly try to optimize results with bilateral leads.

Selective Nerve Stimulation

Pudendal Nerve

Because the bladder afferent reflex works through sacral interneurons that then activate storage through pudendal nerve efferent pathways directed toward the urethral sphincter, the pudendal nerve is a logical target for developing neuromodulation therapies. The earliest attempts to manipulate this reflex through electrical stimulation were based on direct pelvic floor muscle stimulation by Caldwell and associates ([Caldwell, 1963](#); [Caldwell et al, 1965](#)) and others with the development of the first implantable and external pelvic floor stimulators, anal plug stimulator ([Hopkinson and Lightwood, 1966, 1967](#)), and intravaginal pessary stimulation ([Alexander and Rowan, 1968](#); [Erlandson et al, 1977](#); [Fall et al, 1977](#); [Fall, 1985](#)). To deliver optimal stimulation to the nerve directly, selective pudendal nerve stimulation was introduced by [Vodusek and coworkers \(1986\)](#) and shown to have an inhibitory effect on the micturition reflex.

Neurophysiologic studies reveal that SNS works for bladder storage disorders by a similar inhibition of the micturition reflex as a result of electrical stimulation of sensory afferent fibers, in particular by depolarization of A α and A γ somatomotor fibers that affect the pelvic floor and external sphincter and thus inhibit detrusor activity ([Hohenfellner et al, 1992](#)). Because many of the sensory afferent nerve fibers contained in the sacral spinal nerves originate in the pudendal nerve, the pudendal nerve afferents are important targets for neuromodulating the inhibitory reflex on the micturition reflex ([Peng et al, 2008](#); [Woock et al, 2008](#); [Yoo et al, 2008](#)). Furthermore, high-frequency electrical stimulation of this nerve may achieve blockade of external sphincter contractions leading to sphincter relaxation ([Gaunt and Prochazka, 2009](#)). Direct pudendal nerve neuromodulation stimulates more pudendal afferents than SNS provides and may do so without the side effects of off-target stimulation of leg and buttock muscles. Thus techniques for direct pudendal nerve stimulation at alternative locations to the sacral foramen are being developed. [Spinelli and associates \(2005\)](#) modified existing sacral neuromodulation technology and adapted it to pudendal nerve stimulation and realized the need for more sensitive neurophysiologic guidance to better guide stimulation to the pudendal nerve target. Trials using different techniques and devices

are underway for selective pudendal nerve stimulation within the ischial rectal fossa and the pure sensory afferent branch of the pudendal nerve at the level of the symphysis bone referred to as the dorsal genital nerve.

The Bion device (Boston Scientific, Natick, MA) is a minimally invasive implantable mini-stimulator with an integrated electrode for nerve neuromodulation. Early feasibility trial results of the Bion device placed at the level of the pudendal nerve exiting the Alcock canal indicate that a considerable reduction in the degree of DO incontinence can be obtained in refractory cases, including those cases of failed SNS neuromodulation ([Bosch, 2005](#)). Clinical trials of the rechargeable Bion device were halted in the United States and Europe.

External Periurethral Nerve

A relatively new way to stimulate the bladder has been investigated and is now underway with clinical trials in the use of external periurethral neuromodulation ([Nissenkorn et al, 2004, 2005](#)). This device basically entailed placement of a lead and generator apparatus in the periurethral location while the generator was in the lower abdomen subcutaneous space. The lead then stimulated the sphincter apparatus and nerves associated with this structure, presumably. Whereas their early results are fairly impressive, the device may help both urgency and stress urinary incontinence (16 patients with stress urinary incontinence were treated; 9 were dry during electrostimulation, and the remainder had a 74% reduction in pad weights). The exact positioning of the electrodes seems to be in the area proximate to the external urethral sphincter, thereby allowing for direct access to afferent nerve fibers ([Whiteside et al, 2009](#)). How this therapy benefits patients will be interesting because it has many potential uses, including stress and urgency urinary incontinence, pain syndromes, and neuromuscular disorders of the pelvic outlet.

Dorsal Genital Nerve

The dorsal genital nerves (dorsal nerve of the penis in males, clitoral nerve in females) are the terminal and most superficial branches of the pudendal nerve found at the level of the symphysis pubis. The nerves are afferent nerves that carry sensory information from the glans of the penis or clitoris. Proximally, the dorsal genital nerves form a component of the pudendal nerve and then the sacral spinal roots. As a pure sensory afferent nerve branch of the pudendal nerve, the dorsal genital nerve contributes to the pudendal-pelvic nerve reflex that has been proposed as a mechanism of bladder inhibition. Whereas squeezing the glans penis or manipulation of the clitoris is clinically known to help suppress bladder contractions as observed in behaviors of voiding avoidance, direct electrical stimulation of these organs does not produce a significant effect on the micturition reflex as measured by urodynamics during the storage phase ([Yalla et al, 1978](#); [Kondo et al, 1982](#)). However, direct dorsal genital nerve electrical stimulation in experimental and clinical studies appears promising in producing an inhibition of the micturition reflex.

Results in laboratory animals and in persons with SCI have demonstrated that electrical stimulation of the dorsal genital nerves inhibits bladder contractions ([Craggs and McFarlane, 1999](#)). In anesthetized cats ([Sundin et al, 1974](#); [Jiang and Lindstrom, 1999](#)) and in unanesthetized chronic spinal cord-injured cats, reflex bladder contractions could be inhibited by stimulation of the genital nerves ([Walter et al, 1993](#)). Conditioning stimulation of afferents in the dorsal clitoral nerves also has been shown to suppress reflex bladder contractions in anesthetized cats ([Jiang and Lindstrom, 1999](#)). Similarly, recent work in anesthetized cats has shown that low-amplitude electrical stimulation of the S1 dorsal root (which in the cat carries the dorsal genital afferents) inhibits or abolishes ongoing reflex bladder contractions ([Jezernik et al, 2001](#)), resulting in significantly shorter bladder contractions. The micturition reflex can be activated and inhibited by stimulation of these dorsal penile afferent fibers in animal models ([Woock et al, 2008](#)).

Stimulation of the dorsal penile nerve has been tested in humans to control incontinence in individuals with SCI, increase bladder volume, and reduce bladder overactivity (Wheeler et al, 1992, 1994). Penile nerve stimulation was painless, with no side effects, was effective for inhibiting DO, and may be adaptable for chronic home use as an alternative to current therapy (Wheeler et al, 1992). Similar experiments have shown that stimulation of the dorsal nerve of the penis abolishes reflexive bladder contractions and increases bladder capacity in persons with SCI (Lee and Creasey, 2002). These results demonstrate that electrical stimulation of the dorsal genital nerves can abolish DO and increase bladder capacity in individuals with neurogenic DO as a result of spinal injury. Feasibility trials with this approach have been completed and demonstrate in a small series that 81% of patients experienced a 50% or greater improvement in urgency and 47% reported a 50% or greater reduction in incontinence episodes (Goldman et al, 2008). This approach seems to have further advantages in being minimally invasive, office based, and without the need for fluoroscopy or prone positioning.

Posterior Tibial Nerve

The posterior tibial nerve is a mixed sensory and motor nerve containing fibers originating from spinal roots L4 through S3 that modulate the somatic and autonomic nerves to the pelvic floor muscles, bladder, and urinary sphincter. On the basis of translational findings of the traditional Chinese practice of using acupuncture points over the common peroneal or posterior tibial nerve to inhibit bladder activity, McGuire and associates (1983) used transcutaneous stimulation of the common peroneal or posterior tibial nerve for inhibition of DO. PTNS (Urgent PC, CystoMedix, Anoka, MN) as approved by the FDA currently consists of weekly 30-minute stimulation treatments provided by insertion of a small-gauge stimulating needle approximately 5 cm cephalad from the medial malleolus and just posterior to the margin of the tibia with the grounding electrode pad placed on the medial surface of the calcaneus (Govier et al, 2001; Cooperberg and Stoller, 2005). Increasing interest in this therapy in the United States has led to more data and similar to sacral neuromodulation experience in other conditions than OAB.

Clinical trials of PTNS have been performed in detrusor overactive conditions with and without pelvic pain (Klingler et al, 2000; van Balken et al, 2003; Vandoninck et al, 2003; Congregado Ruiz et al, 2004; Zhao et al, 2008) and urinary retention (van Balken et al, 2001; Vandoninck et al, 2003). Although clinical trials have produced variable results, PTNS is minimally invasive, demonstrates efficacy, and is easily applicable and well tolerated in all the LUT conditions studied. Peters and associates (2009b) performed a randomized trial of PTNS with tolterodine 4 mg extended release. This trial demonstrated improved global response assessments of OAB symptoms in 79.5% of PTNS patients versus 54.8% of tolterodine patients. Objective reduction in frequency, urge severity, and incontinence episodes was similar in both groups. Concern is raised about the placebo benefit of PTNS therapy and accordingly was investigated by Finazzi-Agrò and colleagues (2009) in a double-blind placebo-controlled study and 71% of patients in the PTNS group had greater than 50% improvement in OAB DO incontinence symptoms versus 0% in the placebo group. Recent outcomes have been shown in an MS subpopulation and improvements during PTNS have been demonstrated, including increases in mean first involuntary detrusor contractions and mean cystometric capacity during urodynamics (Kabay et al, 2008) and clinically long term in patients with MS (Zecca et al, 2014). One major limitation of PTNS is that there does appear to be the need for chronic treatment that may be better derived from an implantable subcutaneous stimulation device (van Balken et al, 2003) and even continuous stimulation (Oliver et al, 2003). MacDiarmid and colleagues (2010) studied the long-term effects on patients getting PTNS and global response assessments showed sustained improvements at 6 and 12 months in 94% and 96% of patients, respectively. A novel sham has been developed, and widespread study of PTNS with use of a sham

control has further validated outcomes in PTNS (Peters et al, 2009a). Still, one of the major limitations of this therapy is the need for continued and repeated sessions. This can be time-consuming yet cost comparisons (Martinson et al, 2013) suggest PTNS may be cost-effective compared with other therapies.

Transcutaneous Electrical Stimulation

Other methods of electrical stimulation have been used that seem to occupy a place midway between anal, vaginal, or perineal stimulation and sacral root stimulation. TENS devices have been used to limited degrees to achieve better tolerability to bladder filling and may have some efficacy in postponing voiding. Fall and associates (1980) described TENS use suprapubically in patients with interstitial cystitis, and subsequent studies have been done to gain wider use of this modality (Lindstrom et al, 1983; Fall and Lindstrom, 1991). The exact stimulation parameters are not agreed on because different frequencies have been used; 2 Hz may stimulate pudendal afferents, whereas 50 Hz may stimulate striated paraurethral musculature. Similarly, low-frequency TENS may have some use in abolishing detrusor contractility (Bower et al, 1998). Therefore this technology is easy to perform and apply, but it may be required for extended periods to gain treatment benefits. TENS use at S2 or S3 may make some sense, because direct stimulation transcutaneously of this area may yield better results than suprapubic stimulation. Positive results have been demonstrated on the basis of urodynamic data, with improved bladder capacity, delay in first urge to void, and reduced detrusor instability (Bower et al, 2001; Hoebeke et al, 2001). For adequate maintenance of the benefits of this therapy it must be continued for longer durations. McGuire and associates (1983) described 16 patients with involuntary bladder contractions of varying cause who were treated with common peroneal or posterior tibial nerve patch electrode stimulation: 12 patients initially were dry, 3 were improved, and 1 was "possibly improved." Ver-ecker and colleagues (1984), however, were unable to suppress hyperactivity by this method in patients with suprasacral SCI or disease. Okada and associates (1998) reported a positive experience with transcutaneous stimulation of the thigh muscle in 19 patients with DO; the maximal cystometric capacity was increased by 57% in 11 of 19 patients.

Noninvasive magnetic stimulation of the sacral roots will inhibit bladder contractions and cause effects that will persist for short times beyond the period of stimulation. This type of stimulation at present cannot be applied for prolonged periods and is currently unsuitable for long-term treatment, although it may be helpful for preliminary assessment of candidates for chronic sacral root neuromodulation. The extracorporeal magnetic stimulation provided by the "chair" has been used clinically in the past but not widely used currently for OAB, stress incontinence, and pelvic pain (Galloway et al, 2000). No other prospective data on this technology are available for OAB; furthermore, the exact mechanism of action, if effective, remains to be explained, namely, magnetic, nerve root or peripheral nerve, or intramural nerve stimulation.

Emerging Role for OnabotulinumtoxinA versus Sacral Neuromodulation in Overactive Bladder

The increasing use of OBTX in the therapy for OAB has yielded questions to how to decide whether to use OBTX or sacral neuromodulation in patients with refractory OAB. The American Urological Association Guidelines (Gormley et al, 2012) listed both therapies in the refractory setting, but clearly one must be aware of some pros and cons of each therapy to assist the patient in deciding which treatment is best for each patient subtype. Although many patients may do fine with either therapy, some scenarios may tilt the decision making in favor of one therapy over another. As mentioned, there is a large-scale randomized trial being done in the United States (200 IU OBTX vs. InterStim sacral neuromodulation) with the goal of helping answer this exact question, but until these results are available, one can only speculate as to which treatment

is better overall and which scenario portends the best outcome. At present, patients with emptying disorders or those at risk for urinary retention who do not want to catheterize would not be ideal candidates for OBTX. Furthermore, these patients need to be aware of the re-treatment intervals approximately every 6 months and this may aid in decision making. On the contrary, if someone has neurogenic conditions, is not willing to undergo an implant (permanent), or may need future MRIs, sacral neuromodulation becomes a less attractive option. The Anticholinergic vs. Botox Comparison (ABC) trial (Visco et al, 2012) sheds light on the use of 100 IU of OBTX because it may work only marginally better than higher dose anticholinergics. When more comparative data are available, the clinician will have a better understanding of the optimal place for each respective treatment.

Complications and Troubleshooting of Sacral Neuromodulation

With the widespread adoption of sacral neuromodulation, an increasing need has developed to understand the complications of this therapy and learn how to troubleshoot the devices when responses change. It appears that the introduction of the tined lead concept has changed the frequency and profile of the complications that were once only technology related while keeping the patient-related complications at the same frequency.

Published Series

The SNS study group has published several reports on the efficacy and safety of the procedure for individual indications (Siegel et al, 2000). The complications were pooled from the different studies on the basis of the fact that the protocols, devices, efficacy results, and safety profiles were identical. The studies recruited 581 patients, 219 of whom underwent implantation of the InterStim system. The complications were divided into those related to percutaneous test stimulation and those that are postimplant-related problems. Of the 914 test stimulation procedures done on the 581 patients, 181 adverse events occurred in 166 of these procedures (18.2% of the 914 procedures). Most complications were related to lead migration (108 events, 11.8% of procedures). Technical problems and pain represented 2.6% and 2.1% of the adverse events, respectively. For the 219 patients who underwent implantation of the InterStim system (lead and generator), pain at the neurostimulator site was the most commonly observed adverse effect at 12 months (15.3%). Surgical revision of the implanted neurostimulator or lead system was performed in 33.3% of cases (73 of 219 patients) to resolve an adverse event. This included relocation of the neurostimulator because of pain at the subcutaneous pocket site and revision of the lead for suspected migration. Explant of the system was performed in 10.5% for lack of efficacy. One should consider the fact that, at the time, the generator was implanted in the lower abdomen. This profile of complications has changed dramatically with use of the InterStim II generator and posterior (gluteal) pocket location.

Everaert and associates (2004) reported specifically on the complications with SNS. This was a retrospective study of 53 patients who had undergone implantation of the quadripolar electrode (Medtronic InterStim, model 3886 or 3080) and subcutaneous pulse generator in the abdominal site (Medtronic Irel 2 IPG) between 1994 and 1998. Device-related pain was the most frequent problem and occurred equally in all implantation sites (sacral, flank, and abdominal). This occurred in 18 of the 53 patients (34%) and was more frequent in patients with dysuria and retention or perineal pain. Pain responded to physiotherapy in 8 patients, and no explantation was done for pain reasons. Current-related complications occurred in 11%. They performed 15 revisions in 12 patients. Revisions for prosthesis-related pain ($n = 3$) and for late failures ($n = 6$) were not successful. Similar series have been published by White and associates (2009) and show relatively low rates (30%) of adverse events and may have been predicted by trauma, body

mass index, enrollment into a pain clinic, and history of adverse events.

A review (Hijaz and Vasavada, 2005) of the tined lead approach was performed at the Cleveland Clinic from June 2002 to June 2004 when 167 patients underwent sacral neuromodulation for indications of refractory OAB, idiopathic and neurogenic urinary retention, and interstitial cystitis. In this cohort, 180 stage I operations used the tined lead approach. After 2 to 4 weeks of test stimulation, 130 (72.2%) patients proceeded to stage II implantation of the IPG.

Stage I complications can lead to explantation or revision of the tined lead. The reasons for either fall under response related, mechanical, or infection related. In this series, 50 tined leads were explanted (27.8%). The majority of lead explantations were performed for unsatisfactory or poor clinical response (46 of 50, 92%). The rest of the explantations were done for infection (4 of 50, 8%). Explantation for response reasons is not truly considered a complication as much as it is an integral part of the procedure. Stage I revisions totaled 22 of the 180 operations (12.2%). Revisions were done for marginal response (13 of 22), frayed subcutaneous extension wire (6 of 22), lead infection (3 of 22), and improper localization of stimulus (1 of 22). Eleven (50%) of the revisions proceeded to stage II generator implantation. When the revision was done for a marginal response (13 of 22), the response was ultimately clinically satisfactory in 5 of 13 (38.5%), and patients proceeded to generator implantation. Typically, when the patient reported a marginal or equivocal response during the test stimulation in the absence of infection or mechanical problems, a lead revision was offered with intraoperative sensory testing. Because 38.5% of these revisions eventually were successful and patients proceeded to stage II, this is an option to keep in mind in motivated patients with equivocal response.

As in stage I, stage II complications can be divided into explantation (generator and lead) or revision. Explantation was performed in 16 of 130 (12.3%). Explantations were done for infection and failure to maintain response in 56.3% and 43.7%, respectively. Revisions were done for infection, mechanical (generator related), and response causes. The revision rate of stage II in this series was 20% (26 of 130).

When infection at the generator site is diagnosed, the best management is explantation of the whole system. To date, no preoperative or perioperative antibiotic regimen has been decided to be best and should otherwise be left to surgeon discretion. Antibiotic consideration should otherwise be targeted toward skin site pathogens and methicillin-resistant *Staphylococcus aureus*. At least in one trial (Amend et al, 2013), interestingly, prolonged percutaneous testing did not increase infection rates in a small series of patients.

Response-related complications necessitating revision are more common (18 of 26). The algorithm for management of a patient who presents with a decreased or absent response after a successful interval is outlined in Figure 81-8.

The outlined algorithm includes testing of impedances (Fig. 81-9). Impedance describes the resistance to the flow of electrons through a circuit. Impedance or resistance is an integral part of any functioning circuit. However, if there is too much resistance, no current will flow (open). If there is too little resistance, excessive current flow results in diminished battery longevity (short). The electrical circuit that we are referring to starts at the neurostimulator's circuitry and goes through the connectors to the extension wires, through the extension connector to the lead wires, through the lead's electrodes to the patient's tissue, and back either through another electrode and up the same path to the circuitry (bipolar) or to the neurostimulator case and into the circuitry (unipolar).

If the circuit is broken somehow, electrons cannot flow. This is called an open circuit, and impedance measurements are high. Open circuits can be caused by a fractured lead or extension wires and loose connections. Patients generally feel no stimulation if an open circuit is present. In measurement of impedances by the programmer, unipolar measurements are most useful for identifying open circuits because they take one lead wire measurement at a

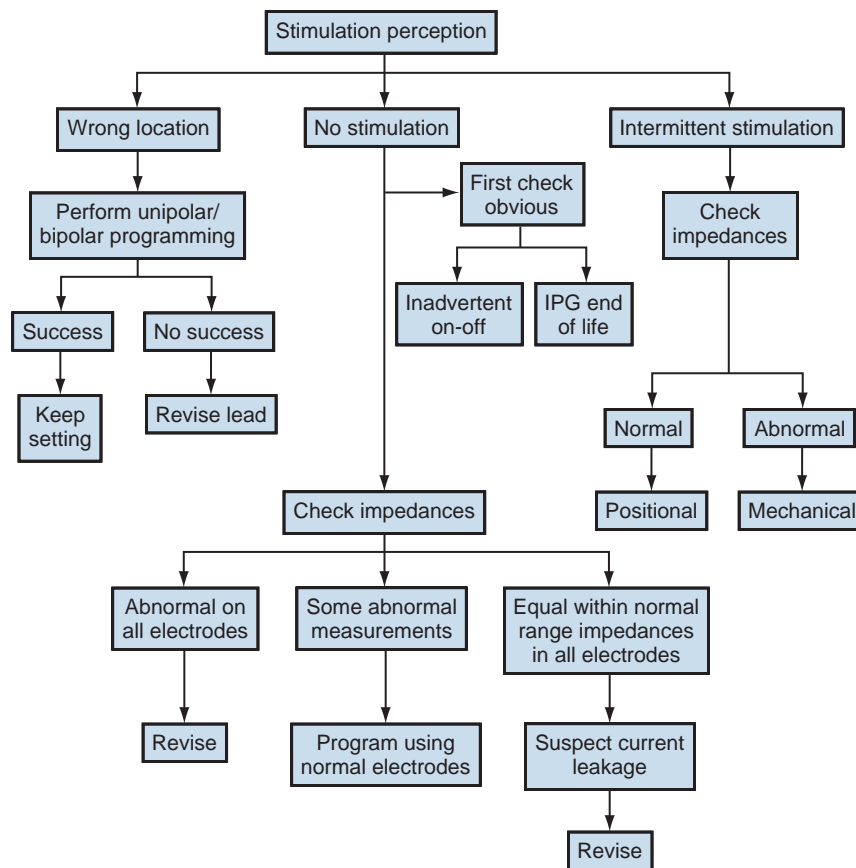


Figure 81-8. Diagnostic algorithm and troubleshooting for recurrent symptoms. IPG, implantable pulse generator.

time, immediately identifying which connection or wire has the problem.

Short circuits, which are reflected in **low impedance measurements**, can be caused by body fluid intrusion into the connectors or crushed wires that are touching each other. The electrons always will follow the path of least resistance. Patients may or may not feel stimulation, or stimulation may not be present in the correct area (i.e., the generator site) or may vary in strength (i.e., a surging sensation). In measurement of impedances by the programmer, **bipolar measurements are most useful for identifying shorts between two wires**.

Therefore impedance measurement is used as a troubleshooting tool to check the integrity of the system when a patient presents with a sudden or gradual disappearance of stimulation. Many measurements fall within the 400- to 1500-ohm range. High levels (>4000 ohms) identify open circuits, and low levels (<50 ohms) identify short circuits. Medtronic (manufacturer of the InterStim) recommends performing the impedance measurements at the time of closure of the incision; at the first programming session, to get a baseline measurement; and at any time a problem is suspected. These measurements will identify which electrodes, if any, are intact and allow the programmer to proceed with programming of only those with acceptable impedance measurements. If all electrode measurements read above 4000 ohms, a revision may be necessary.

The intraoperative algorithm for management of impedance problems includes initial testing of impedances (see Fig. 81-9). First, the tined lead is disconnected from the extension to the IPG and then dried. The connection may be irrigated with sterile water, and then the connection is dried with the 3-Fr suction device before it is reconnected again. At this stage the impedances are repeated. If they normalize, the revision can be concluded at this stage. If impedances continue to be abnormal, the 10-cm extension can be

evaluated or changed and impedances retested. If they continue to be abnormal, the lead is revised. It has been our experience that the connections to the IPG and the IPG itself seldom have anything to do with abnormal impedance values. Thus, at present, most physicians bypass much intraoperative electrodiagnostics and just change the lead to avoid any continued problems postoperatively.

Troubleshooting Algorithm

After successful completion of stage II, a number of events can occur, and the treating physician should develop an algorithm to handle these events in a timely and efficient manner. These events with their probable causes and the troubleshooting algorithm are covered in this section.

Pocket (Implantable Pulse Generator Site) Discomfort. The probable cause of pocket discomfort is pocket related or output related. Pocket-related causes of discomfort include infection, pocket location (waistline), pocket dimension (too tight, too loose), seroma, and erosion. Output-related causes include sensitivity to unipolar stimulation if this mode is used or current leak. To troubleshoot this problem the evaluating specialist is advised to do the following (Fig. 81-10):

1. Turn off the device and ask the patient if the discomfort is still present to differentiate pocket-related from output-related causes.
2. If the discomfort persists, the cause is not related to the device output. In the absence of clinical signs of infection, pocket-related causes such as pocket size, seroma, and erosion must be considered.
3. If the discomfort disappears, device output is probably causing discomfort. If the stimulation program is unipolar, switch to bipolar and see whether that eliminates discomfort. Some patients are sensitive to the unipolar mode of stimulation,

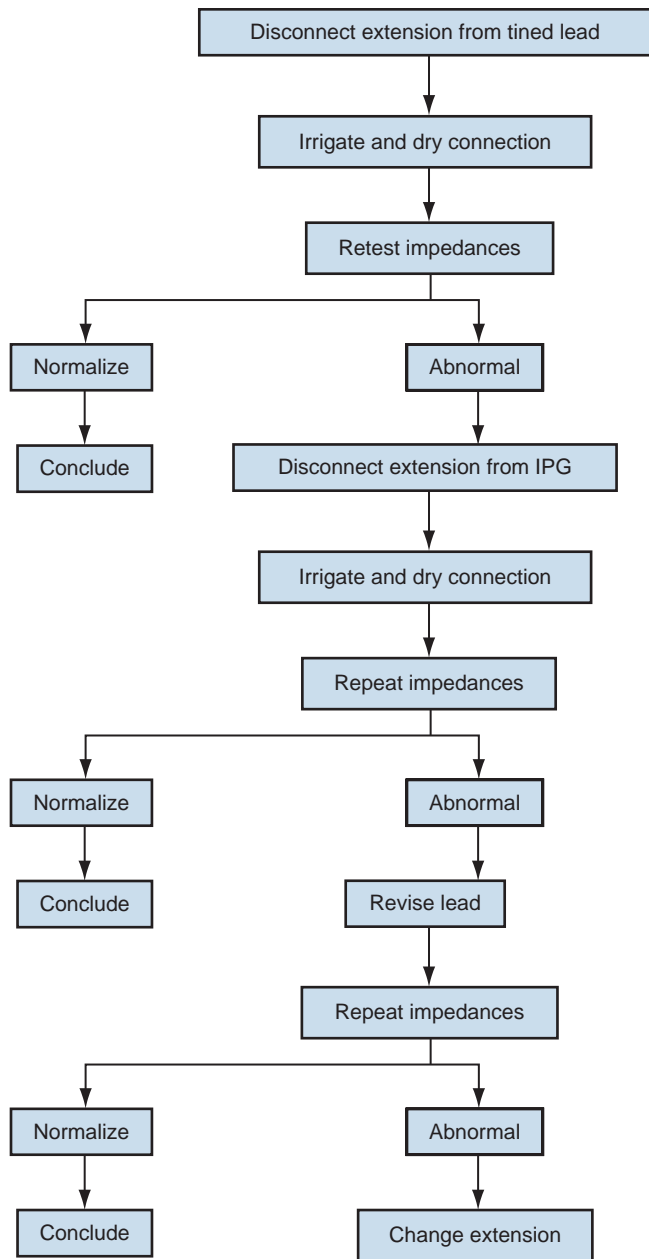


Figure 81-9. Intraoperative algorithm for impedance problem management. IPG, implantable pulse generator.

because the positive pole is the neurostimulator. Another possibility is leakage of fluid into the connector. This somehow creates a short circuit whereby the current from the device follows this fluid pathway out to the patient's tissue. Most patients report this as a burning sensation. Even though current is following this fluid out to the patient's tissue, some of the current also may be getting to the electrodes as well, so some patients feel both burning in the pocket and stimulation in the perineum. Reprogramming around this can be tried by using different electrode combinations. If reprogramming is unsuccessful, the patient is asked if the "burning" sensation is tolerable (it will not harm the patient's tissues); if it is not tolerable, a revision may be necessary to dry out the connection sites.

Recurrent Symptoms. When the patient presents with recurrent symptoms, evaluation of the stimulation perception is necessary. The possibilities are that the patient perceives the stimulation in a wrong location compared with baseline, has no stimulation, or has intermittent stimulation. Again, documentation of the exact location, amplitudes, and so on, of the best stimulation parameters

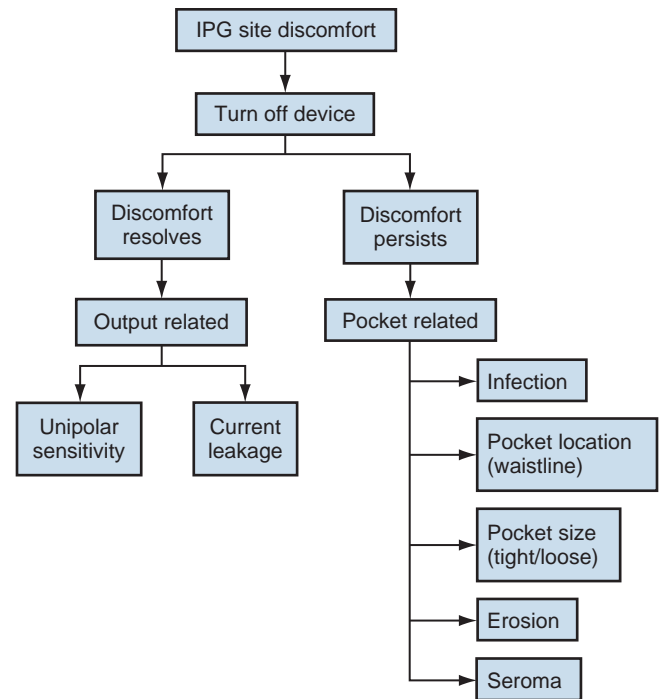


Figure 81-10. Troubleshooting algorithm for implantable pulse generator site discomfort. IPG, implantable pulse generator.

should be done early after successful implantation, to set as a baseline so when changes occur, the baseline can be noted.

Wrong Location. If the patient reports that the stimulation location or pattern has changed, it is best to go back to each unipolar setting and map where the patient feels the stimulation. The device is set to 0–, case+ and the patient is asked where she or he feels the sensation; next it is set to 1–, case+ and the patient again is asked about the sensation; next it is set to 2–, case+ and finally to 3–, case+. If these combinations do not confirm the target area, the next step is to start programming bipolar combinations. When those are exhausted, sometimes increasing the pulse width widens the stimulation area. If the programming possibilities are exhausted, revision for lead repositioning or relocation to the other side may be necessary.

No Stimulation. The obvious is checked first. The device parameters must be set high enough, an inadvertent on-off is checked (set magnet switch off to avoid inadvertent magnet activations), and whether the IPG is nearing the end of its life is checked. Next, impedance readings are performed, paying close attention to unipolar impedances. These impedances measure one lead wire with the case, so it is easy to isolate a problem. Using unipolar impedances, it is possible to tell which lead wires are still intact and which ones are not, as mentioned previously. Programming of the electrodes is then continued with acceptable impedance measurements. Bipolar measurements are checked to rule out short circuits as well (very low impedance measurements). If programming around the malfunctioning lead does not restore the stimulation, the patient will often need to undergo revision.

Intermittent Stimulation. Again, inadvertent on-off is checked. Intermittent stimulation can be caused by either a loose connection or positional sensitivity. If a loose connection is suspected, palpating the connection site and re-creating the intermittency is a good clue as to where the problem lies. Taking impedances while the patient reports the stimulation intermittently determines whether the problem is positional (acceptable impedances are still present) or mechanical (when the patient feels stimulation go off, the impedances are high). With positional sensitivity, the lead position shifts when a patient moves in a certain direction (e.g., the patient reports that the stimulation goes away on standing). The lead position may have moved farther from the nerve during standing, and

the amplitude may just need to be increased. Intermittent stimulation represents a challenging dilemma to troubleshoot.

ELECTRICAL STIMULATION FOR EMPTYING DISORDERS

There exists strong evidence to suggest that neuromodulation works through supraspinal pathways (see the section on neurophysiology of electrical stimulation). The question of how it works for refractory DO as well as for urinary retention is based on changes in supraspinal pathways and perhaps the guarding reflex. It is important to understand that before neuromodulation, neurostimulation was applied in different forms to achieve bladder emptying. Still, neurostimulation has a role today in management of disorders of bladder emptying and has evolved through many different versions before its current techniques.

Electrical Stimulation Directly to the Bladder or Spinal Cord

Clinical trials of direct electrical stimulation of the bladder to facilitate emptying originated in 1940 but have met with only partial success and intermittent enthusiasm since then (Wein and Barrett, 1988). Direct electrical stimulation was most effective in patients with hypotonic and areflexic bladders. Initial success, defined as low PVR urine volume with sterile urine, was achieved in only 50% to 60% of patients, and secondary failure often supervened, usually related to fibrosis, electrode malfunction, bladder erosion, or other equipment malfunction. The spread of current to other pelvic structures with a stimulus threshold lower than that of the bladder often resulted in abdominal, pelvic, and perineal pain; a desire to defecate or defecation; contraction of the pelvic and leg muscles; and erection and ejaculation in male patients. It was also noted that the increase in intravesical pressure was generally not coordinated with bladder neck

opening or with pelvic floor relaxation and that other measures to accomplish these ends could be necessary. Direct electrical stimulation of the sacral spinal cord was also performed as an attempt to take advantage of the remaining motor pathways to initiate micturition. Although some short-term success was noted, many of the side effects seen with direct bladder stimulation occurred as well because the stimulus applied in this way was also unphysiologic. Enthusiasm for both of these approaches has waned considerably, and resurrection seems unlikely.

Electrical Stimulation to the Nerve Roots

For the past 25 to 30 years, Brindley (1993) and the Tanagho group (Tanagho and Schmidt, 1988; Tanagho et al, 1989) pursued neurostimulation for the treatment of voiding dysfunction. The use of electrical stimulation for storage disorders and pelvic floor dysfunction has been covered. The focus of this section is on the use of anterior root electrical stimulation to facilitate emptying.

The Brindley device is the one most commonly used. Prerequisites for such use are described by Madersbacher and Fischer (Fischer et al, 1993) as (1) intact neural pathways between the sacral cord nuclei of the pelvic nerve and the bladder and (2) a bladder that is capable of contracting. The chief applications are in patients with inefficient or nonreflex micturition after SCI. Simultaneous bladder and striated sphincter stimulation is obviated by sacral posterior rhizotomy, usually complete, which eliminates reflex incontinence and improves low bladder compliance, if it is present (Brindley, 1994). The stimulation sequences and parameters themselves and their neurophysiologic consequences lead to less striated sphincter dyssynergia, even without posterior rhizotomy, than is seen in reflex micturition in a patient with SCI. Complete sacral deafferentation is usually performed, however, with the exception listed by Brindley as those patients who have genital sensation or useful reflex erections. Electrodes are applied intradurally to S2, S3, and S4 nerve roots, but the pairs can be activated independently (Fig. 81-11). The detrusor is usually

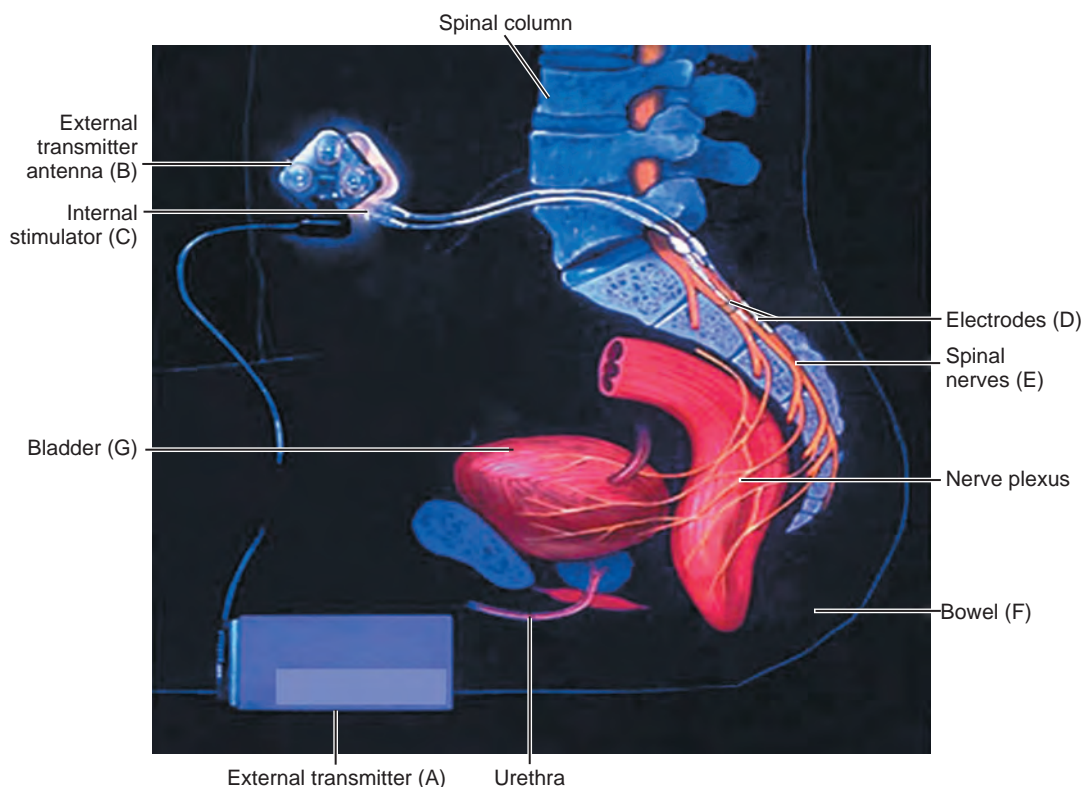


Figure 81-11. Brindley-Finotech system for sacral root stimulation. A, Transmitter to deliver current. B, External antenna. C, Internal stimulator to drive current. D, Electrodes to deliver stimulation. E, Spinal nerves. F, Bowel. G, Bladder. (Courtesy NDI Medical, Cleveland, OH.)

innervated primarily by S3 and to a smaller extent by S2 or S4. Rectal stimulation is by means of all three roots equally. Erectile stimulation is chiefly by S2, with a small contribution from S3 and none from S4. Micturition, defecation, and erection programs are possible, with stimulus patterns set specifically for each patient (Brindley, 1994). The ventral sacral roots, however, carry both parasympathetic fibers to the bladder and somatic fibers to the striated sphincter. Ventral root stimulation therefore occasionally results in detrusor–striated sphincter dyssynergia.

The current Brindley stimulator uses the principle of *post-stimulus voiding*, a term first introduced by Jonas and Tanagho (1975) to obviate this. Relaxation time of the striated sphincter after a stimulus train is shorter than the relaxation time of the detrusor smooth muscle. When interrupted pulse trains are used, voiding is achieved between the pulse trains because of the sustained high intravesical pressure. This concept and other methods that are available to overcome the stimulation-induced sphincter dyssynergia and allow low-pressure emptying are nicely reviewed by Rijkhoff and colleagues (1997). Poststimulus voiding has a few shortcomings, described in this article, because voiding occurs in spurts at above-normal bladder pressures; when the stimulus parameters are not properly adjusted the detrusor pressures can become too high, putting the upper tracts at risk; and movement of the lower limbs occurs during stimulation because the nerve roots also contain fibers innervating leg musculature, and this movement can be cumbersome for the patient.

Brindley (1994) carefully reviewed the experience in the first 500 patients treated with his prosthesis with a total follow-up, at that time, of 2033.5 years. Of the total, 2 patients were lost to follow-up and 21 died. Of the deaths, two were from septicemia (one definitely unrelated to the implant and the specifics of the other unmentioned) and one from related renal failure; the causes of five were unknown. Ninety-five reoperations were required for repair, six stimulators were removed (four infected), and two were awaiting repair. In 45 patients the stimulator was believed to be intact but not used for various reasons. In all others the stimulators were in use (411 for micturition and in most for defecation and in 13 for defecation alone) and the users were believed to be “pleased.” Upper tract deterioration was reported in only 2 of 365 patients with full deafferentation and in 10 of 135 with incomplete or no deafferentation. Two of these 10 had impaired renal function, and 1 died of this condition.

van Kerrebroeck and associates (1997) reported the results of use of the Finetech-Brindley stimulator in 52 patients. These patients were selected by screening 226 patients; complete posterior sacral root rhizotomies were performed in all. Thirty-seven of the patients had 6 months of follow-up; in these patients, complete daytime continence was achieved in 73% and night-time continence in 86%. There were significant increases in bladder capacity and bladder compliance, and residual urine was reduced significantly. Complications included cerebrospinal fluid leaks, which resolved spontaneously in 23 patients; nerve damage that resolved in 1 patient; and one implant failure caused by a cable fracture, which was successfully repaired. Sauerwein and colleagues (1999) reported in abstract form the results of sacral deafferentation and implantation of an anterior sacral root stimulator in 294 patients with SCI. Bladder spasticity was relieved in all. In 50%, micturition was achieved by stimulating S4 and S5 sacral ventral roots; in the remaining cases, it was achieved by stimulating the S2 and S3 roots. Variations in surgical approaches designed to achieve stimulation of only bladder contraction are described by Dahms and associates (2000), who also summarize overall success rates for sacral ventral root stimulation in patients with spinal cord injury at approximately 75%. Recent laparoscopic access techniques have minimized the invasiveness of this procedure and may have a role in the future in this select group of patients (Possover, 2009).

Extradural stimulation has been used by the Tanagho group (Tanagho and Schmidt, 1988; Schmidt, 1989; Tanagho et al, 1989) in the treatment of 19 patients with serious and refractory neurogenic voiding disorders. Extensive dorsal rhizotomy was performed, and a stimulator was implanted on the ventral component

of S3 or S4 with selective peripheral neurotomy (Tanagho et al, 1989). In eight patients (42%), complete success was achieved with reservoir function, continence, and low-pressure/low residual voiding with electrical stimulation. Ten patients qualified as achieving partial success, regaining reservoir function, and obtaining continence.

Electrical stimulation of the ventral sacral roots with some techniques to reduce detrusor hyperactivity and obviate striated sphincter dyssynergia has become an accepted treatment modality for LUTD in patients with SCI. Although more detailed follow-up is necessary, and further evolution will doubtless occur, these techniques have achieved remarkable improvements and success rates, which now seem to have stabilized at a high level.

Transurethral Electrical Bladder Stimulation

Intravesical electrotherapy is an old technique that has been resurrected with some interesting and promising results. The use of this technique to increase bladder capacity and compliance has been previously discussed. This section deals with the use of TEBS to facilitate bladder emptying by establishing conscious control of the initiation and completion of a micturition reflex. Fischer and colleagues (1993) describe their concept of the basis for this use as follows. In patients with incomplete central or peripheral nerve lesions—and only these patients are suitable for this method—at least some nerve pathways between the bladder and the cerebral centers are preserved but are too weak to be efficient under normal circumstances. TEBS in this situation is hypothesized to activate specific mechanoreceptors in the bladder wall. With depolarization of these receptors, activation of the intramural motor system is said to occur, resulting in small local muscle contractions that further depolarize the receptor cells. As soon as this local motor reaction reaches a certain strength, “vegetative afferentation” begins, meaning that stimuli travel along afferent pathways to the corresponding cerebral structures with the occurrence of sensation. This, in time, reinforces efferent pathways, and their stimuli create centrally induced and more coordinated and stronger detrusor contractions. Ebner and coworkers (1992) simply conceptualize the mechanism as involving an artificial activation of the normal micturition reflex and further suggest that repeated activation of this pathway may “upgrade” its performance during voluntary micturition.

Children with congenital neurogenic bladder dysfunction who have never experienced the urge to void require a biofeedback system to realize the nature and meaning of this new sensation induced by TEBS. This exteroceptive stimulation is also important for other groups of patients because it signals detrusor contractions and whether, and to what degree, voluntary detrusor control is or has become possible and, by demonstrating progress, serves as positive feedback.

This technique involves direct intraluminal monopolar electrical stimulation with a special catheter equipped with a stimulation electrode. Saline solution is used as the current-leading fluid medium in the bladder. Exteroceptive reinforcement is achieved by visual recording of detrusor contractions on a water manometer connected to the stimulation catheter. An intensive bladder training program has to be combined with TEBS and must be highly individualized. Only patients with an incomplete spinal cord lesion and with receptors still capable of reactivity and with a detrusor still capable of contractility will benefit from this technique. The achievement of conscious control requires, in addition, an intact cortex.

Fischer and colleagues (1993) used this technique in patients with incomplete SCI and other incomplete central or peripheral lesions of bladder innervation, in pediatric patients with congenital neurogenic LUTD, and in patients, especially children, with non-neurogenic dysfunctional voiding. Only patients with preserved pain sensation in sacral dermatomes S2 through S4 improved with this technique. The technique is time-consuming because stimulation must be performed on a daily basis for weeks and months, with

an individual treatment time of approximately 90 minutes. [Kaplan and Richards \(1988\)](#) reported on such therapy in myelodysplastic children, performing the treatment for 60 minutes (during a 90-minute catheterization), 3 to 5 days per week for 15 to 30 daily sessions. Of 62 patients evaluated, 42 completed at least one series of treatment. "Success" was defined differently for infants than for older children. For infants, success implied a decrease in filling pressure, an increase in the quality of bladder contraction, and a decrease in residual urine. For older children, this type of result implied a heightened awareness of detrusor contractions before and during a contraction, maintenance of low-pressure filling, effectively emptying detrusor contractions with low residual urine, and either a conscious urinary control or timely enough sensory input to allow clean intermittent catheterization for continence. Of children who initially had some detrusor contraction on initial evaluation, 80% were said to have achieved some or all of the success parameters. Of those with no initial detrusor activity, 33% achieved some success.

Other reports have been less optimistic. [Lyne and Bellinger \(1993\)](#) reported the results of TEBS treatment of 17 patients with neurologic dysfunction, 10 with myelomeningocele, and 2 with lipomeningocele. Ultimately, all patients showed detrusor contraction during therapy (12 did so initially), but results related to increased bladder capacity and improved continence were disappointing. Five patients showed minor positive changes in continence. After completion of therapy in 12 patients who had serial cystometry, 5 experienced an increase in capacity (14% to 158%) and 4 a decrease (7% to 37%). [Decter and associates \(1994\)](#) used TEBS in 25 patients with neurogenic voiding dysfunction. TEBS was correlated with an increase from 18 to 24 in the number of patients who manifested contraction on stimulation and from 3 to 12 in the number who sensed contraction during stimulation. However, cystometry showed a more than 20% increase in the age-adjusted bladder capacity in only 6 of 18 patients with serial studies and clinically significant improvements in end-filling pressures in 5 of these. A telephone questionnaire revealed that 10 of 18 patients or parents perceived an improvement in bladder function, but the authors stated that "the limited urodynamic benefits our patients achieved have not materially altered the daily voiding regimen and, because of these factors, we are not enrolling any new patients in our . . . program." This technique is certainly controversial. Some question the theoretical basis and the definitions of "success" applied to patients treated. Currently, even [Kaplan \(2000\)](#) does not seem enthusiastic about the use of this technique to attain the goal of volitional voiding, and [Decter \(2000\)](#), as previously pointed out, stated that, in his opinion, TEBS is a modality with limited clinical efficacy for facilitation of filling-storage and emptying.

Sacral Neuromodulation of Emptying Disorders

Sacral neuromodulation has been successful in patients with idiopathic nonobstructive retention, in patients with retention secondary to deafferentation of the bladder after hysterectomy, and in patients with Fowler syndrome ([Dasgupta et al, 2004; De Ridder et al, 2007](#)). Patient factors predictive of success have been sought, and increasing numbers of reports are differentiating results of sacral neurostimulation in urinary retention based on the functional disorders causing the condition, detrusor acontractility, and functional outlet obstruction. [Bross and coworkers \(2003\)](#) evaluated the predictive ability of the carbachol test and concomitant diseases in patients with an acontractile bladder. Whereas 33% of patients had a successful bilateral percutaneous nerve evaluation, a positive carbachol test result was not predictive of success. [Goh and Diokno \(2007\)](#) in a retrospective study of patients implanted for nonobstructive urinary retention found a statistically significant difference in predicting success of test stimulation for patients with a preimplantation ability to void (>50 mL) versus nonvoiders. Further evidence of the predictive role of detrusor function was reported by [Bertapelle and colleagues \(2008\)](#) in developing a detrusor contractility test using urodynamics in conjunction with sacral neurostimulation in urinary retention as exclusion criteria for sacral

neurostimulation; this test appears to be a reliable tool to rule out detrusor acontractility resulting from irreversible bladder myopathy or complete neurogenic lesion and to predict success of permanent sacral neuromodulation.

A large, prospective, randomized multicenter trial to evaluate the efficacy of SNS for urinary retention was performed by [Jonas and colleagues \(2001\)](#). After a percutaneous nerve evaluation period of 3 to 7 days, 68 patients (38% of those evaluated) with chronic urinary retention qualified for permanent implantation. Patients were randomly assigned to the treatment or control group, in which treatment was delayed for 6 months. Successful results were initially achieved in 83% of patients who received the implant, with 69% able to discontinue intermittent catheterization completely. At 18 months, 71% of patients available for follow-up had sustained improvement. These results have been corroborated by others with longer follow-up ([Datta et al, 2008; White et al, 2008](#)).

[Aboseif and coworkers \(2002\)](#) evaluated the efficacy and change in quality of life in patients with idiopathic, chronic, nonobstructive functional urinary retention. Thirty-two patients with idiopathic retention requiring intermittent catheterization underwent percutaneous nerve evaluation. Permanent implants were placed in 20 patients (17 women) who showed more than 50% improvement in symptoms. Eighteen patients were subsequently able to void and no longer required intermittent catheterization; one patient required bilateral SNS implants. Average voided volumes increased from 48 to 198 mL, and PVR volume decreased from 315 to 60 mL. Eighteen patients reported more than 50% improvement in quality of life, although the questionnaire used in the study was not described. Significant score improvements in the Beck Depression Inventory and SF-36 after sacral root neuromodulation for retention have been demonstrated by [Shaker and Hassouna \(1998\)](#). Overall success rates of the percutaneous nerve evaluation range from 33.3% to 100% ([Koldewijn et al, 1994; Scheepens et al, 2002; Spinelli et al, 2003](#)). Improvement in patients with retention may not be as rapid as in patients undergoing sacral root stimulation for other reasons. A percutaneous nerve evaluation period of at least 2 to 3 weeks and a permanent implant lead evaluation of 4 weeks or more have generally been recommended. Furthermore, bilateral or caudal SNS for urinary retention may be considered initially or for unilateral SNS trial failures, although this technique is performed infrequently and is less studied to date ([van Kerrebroeck et al, 2005; Maher et al, 2007; Pham et al, 2008](#)).

Percutaneous Tibial Nerve Stimulation for Emptying Disorders

PTNS also has been studied in the setting of nonobstructive urinary retention. At present, no randomized trials exist in this scenario; however, several case series have suggested some improvement in emptying ranging from 41% to 100% ([Vandoninck et al, 2003, 2004](#)). It is important to consider the exact definition of improvement of emptying. When one study used emptying "success" as being greater than 50% reduction in catheterized volume, success was 41%; when the definition changed to greater than 25%, success increased to 67%. Still to date, no long-term data are available for this therapy in nonobstructive retention cases.

FUTURE RESEARCH AND CONCLUSIONS

During the past century, neurostimulation and neuromodulation that originated in the 19th century have been clinically adopted. Advances in electrical innovations and our understanding of neurophysiology have provided important discoveries for the care of people with neuromuscular causes of their pelvic organ dysfunctions. To date, influencing these dysfunctions at the level of the sacral roots appears to have stood the test of time and has become generalizable to physicians worldwide. At the start of our next century of using this expanding therapy, we will need to urgently focus on developing the supportive clinical research needed to drive

further innovations and acceptance of wider clinical indications and applications. Long-term surveillance studies and randomized clinical trials to compare different techniques and nerve locations and to evaluate placebo effects are critically needed, as are more studies to elucidate modes of action to improve stimulation applications, selection of patients, and therapeutic results.

The introduction of new stimulation methods as well as application of these methods to different nerve locations will continue to provide improved treatment alternatives. In addition, these innovations will provide the ability to further develop testable hypotheses of more basic questions on electrical neurostimulation, neuromodulation, and neurophysiology of the autonomic, somatic, and central pathways that regulate pelvic organ function. Such questions need to address the observed lack of neural plasticity-induced changes with long-term neuromodulation and neurostimulation despite acute cellular changes identified in nerve signaling molecules secondary to magnetic and electrical field changes.

In OAB, the emerging use of OBTX in comparison to neuromodulation will be of much interest to the clinician and pelvic health specialist. A large-scale trial is currently underway in the United States randomizing patients with urge incontinence to 200 IU of OBTX or sacral neuromodulation (InterStim). This trial will generate much needed data on both therapies and may shed more light on ideal subjects for either modality. Thus, even without the efficacy data being available, one should be mindful about the potential for retention side effects in use of OBTX therapy, as is well known. Clearly in some patients, this is favored and may then improve overall treatment success and satisfaction.

In their present form, neurostimulation and neuromodulation work acutely through continuous electrical activity without inducing long-term neuroplastic changes. Therefore future technologies are likely to provide closed-loop conditional stimulation, much in the same manner as “on-demand” cardiac pacemakers and defibrillators do, as a means to obtain better efficacy without additional adverse electric field effects. The development of change from the present open-loop stimulation to closed-loop conditional stimulation will necessitate innovations in neurosensing of pathologic neuromuscular events of the pelvis that will lead to on-demand therapeutic electrical activity. These innovations will in turn have a profound effect on our diagnostic ability to predict clinical responses to neurostimulation and neuromodulation as we seek to maximize our benefit-risk and benefit-cost ratios in patient care.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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KEY POINTS

- Neuromodulation is a field clearly in its infancy.
- Current techniques of sacral neuromodulation are indicated for treatment of refractory urgency/frequency, urgency urinary incontinence, and nonobstructive urinary retention.
- Sacral neuromodulation has yielded successful stage I to stage II conversion rates based on 50% symptom improvement in more than 60% of patients for urgency/frequency and urgency urinary incontinence.
- The exact best nerves to stimulate have yet to be realized, but data seem to be focusing on more selective nerve stimulation, particularly in complex subgroups such as patients with neurogenic bladders. Focused research on risk factor analysis of who is the best candidate for therapy will be beneficial to selection criteria.
- Transurethral electrical stimulation has fallen out of favor for the most part.
- Transcutaneous electrical stimulation, although demonstrating good efficacy, seems to have a more limited role because of the constant need to administer the therapy, but its minimal invasiveness may allow a resurgence in interest in this therapy.
- Expanding indications for neuromodulation are likely to dominate the literature in the coming years as comfort with neuromodulation increases and more challenging subgroups are addressed.

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Therapeutic Options

Choice of Surgical Technique

Assessing Outcomes of Therapy

Indications for Retropubic Repair

General Technical Issues

Marshall-Marchetti-Krantz Procedure

Burch Colposuspension

Paravaginal Repair

Vagino-Obturator Shelf Repair

Laparoscopic Retropubic Suspension

Complications of Retropubic Repairs

Comparisons of Incontinence Procedures

Continence in women results from a complex interplay of anatomic and physiologic properties of the lower urinary tract (bladder, urethra and sphincter, and pelvic floor) acting under the coordinating control of an intact central and peripheral nervous system. The role of the pelvic floor is to provide support to both the bladder and the urethra and to facilitate normal abdominal pressure transmission to the proximal urethra, thereby maintaining continence.

Stress incontinence is a symptom, a sign, and a clinical diagnosis; the clinical symptom is that of involuntary loss of urine associated with increased intra-abdominal pressure, such as occurs during coughing and sneezing. The International Continence Society defines urodynamic stress incontinence as the involuntary loss of urine during increased intra-abdominal pressure during filling cystometry, in the absence of detrusor (bladder wall muscle) contraction (Abrams et al, 2002). Thus, urodynamic evaluation is a prerequisite for the diagnosis of urodynamic stress incontinence. Therefore, in discussing stress incontinence, this chapter refers to women with stress urinary incontinence (SUI) diagnosed on the basis of symptoms alone or urodynamically proven, so-called urodynamic stress incontinence.

Treatment options for SUI include conservative techniques and both pharmacologic and surgical interventions. In general, surgical procedures to treat SUI aim to improve the support to the urethrovaginal junction and to correct deficient urethral closure. There is a contemporary lack of consensus, however, regarding the precise mechanism by which continence is achieved in the “normal asymptomatic woman” and therefore not surprisingly in how “normality” is restored by surgical manipulation. Anti-incontinence surgery is usually used to address the failure of normal anatomic support of the bladder neck and proximal urethra, and intrinsic sphincter deficiency. Anti-incontinence surgery does not necessarily work by restoring the same mechanism of continence that was present before the onset of incontinence. Rather, it works by a compensatory approach, creating a new mechanism of continence (Jarvis, 1994a).

THERAPEUTIC OPTIONS

The surgeon’s preference, coexisting problems, and anatomic features of the patient and her general health condition influence

the choice of procedure. Numerous surgical methods have been described, but they essentially fall into seven categories (Box 82-1).

This wide variety of treatment options for stress incontinence indicates the lack of a clear consensus as to which procedure is the most effective. Several groups have reviewed the literature, often using systematic and methodical analyses of well-designed randomized controlled trials (RCTs) (Jarvis, 1994b; Black and Downs, 1996; Fantl et al, 1996; Leach et al, 1997; Moehrer et al, 2000; Lapitan et al, 2003; Moehrer et al, 2003). Most of these reviews, however, are hampered by the quality of the existing evidence base, and these reviews are based on studies of mixed quality with little standardization of the points in Box 82-2.

A review of existing literature on confounding variables affecting outcome of therapy (Smith et al, 2005) concluded the following.

1. Age may not be a contraindication to colposuspension, with success in the elderly being equivalent to success in younger patients at long-term follow-up (Gillon and Stanton, 1984; Tamussino et al, 1999), although others have reported less success with increasing age (Langer et al, 2001; Chilaka et al, 2002). Smith and associates (2009), from their review of the literature, concluded that the effect of age on outcomes is poorly defined. The effect of aging on the lower urinary tract includes a higher rate of detrusor overactivity as well as urgency incontinence and intrinsic sphincteric deficiency (ISD). In addition, older patients are more likely to have had prior interventions and may therefore have a higher rate of periurethral fibrosis and/or other abnormalities in the tissues surrounding the lower urinary tract. The presence of multiple comorbidities may also affect overall surgical outcome, including creating the possibility for increased complications and a prolonged postoperative course.
2. The influence of the level of postoperative activity has been inadequately studied, so no recommendations can be made (Smith et al, 2009).
3. There is level 4 evidence that medical comorbidity may have an impact on surgical outcomes, depending on the outcomes selected. There is level 3 evidence that psychological factors have an impact on subjective and objective outcomes in different ways (Smith et al, 2005).
4. Obesity as a confounding variable is the subject of conflicting evidence in the literature and has not been studied in a prospective fashion. Obesity has been studied only retrospectively in case series as a risk factor for success or morbidity in stress

BOX 82-1 Surgical Methods

Open retropubic colposuspension
 Laparoscopic retropubic colposuspension
 Suburethral sling procedure
 Needle suspension
 Periurethral injection
 Artificial sphincter
 Vaginal anterior repair (anterior colporrhaphy)

BOX 82-2 Standardization Needed for Studies

The patients under study (with regard to age, history of prior surgery, body mass)
 The nature of the surgical technique, taking into account the surgeon's experience
 Outcome measures and follow-up

incontinence surgery (level 4 evidence). There are no prospective, randomized trials that suggest superiority of one surgical technique over another in the obese population. Some studies have suggested increased failure rates in obese patients undergoing retropubic colposuspension (Brieger and Korda, 1992; Alcalay et al, 1995). Conversely, in a retrospective study of 198 women undergoing anti-incontinence surgery, cure rates were markedly better in those undergoing Burch colposuspension (Zivkovic et al, 1999).

5. Surgery for recurrent stress incontinence has a lower success rate. One study has reported that Burch colposuspension has an 81% success rate after one previous surgical procedure has failed, but this drops to 25% after two previous repairs and to 0% after three previous operations (Petrou and Frank, 2001). Other series report excellent results for colposuspension carried out after prior failed surgery. Maher and colleagues (1999) and Cardozo and associates (1999) have shown good objective (72% and 79%) and subjective (89% and 80%) success rates with repeated colposuspension at a mean follow-up of 9 months. Nitahara and coworkers (1999) reported a 69% subjective success at a mean follow-up of 6.9 years.
6. Berglund and associates (1996) reported that the duration of symptoms is a predictor of outcome, with a better response in those with a shorter history, which as a finding was independent of type of approach (e.g., vaginal vs. retropubic). Ward and Hilton (2002), in a randomized comparison of colposuspension and tension-free vaginal tape (TVT), found no significant impact of symptom severity on outcomes for either procedure. Tamussino and coworkers (1999), in a review of 327 women assessed a minimum of 5 years postoperatively, noted that women with moderate or severe incontinence fared worse than those with milder symptoms. In their series, only Burch colposuspension was unaffected by the severity of preoperative symptoms.
7. It has been reported that as many as 23% of women undergoing urodynamics have mixed urodynamic stress incontinence and detrusor overactivity (Clarke, 1997). In a retrospective cohort study, Colombo and associates (1996b) compared 44 women with mixed incontinence with a matched group with urodynamic stress incontinence. The cure rate was 95% in the latter group compared with 75% in the former. Other studies report a less favorable outcome of 24% to 43% in those with detrusor overactivity combined with stress incontinence (Stanton et al, 1978; Milani et al, 1985; Lose et al, 1988).

Smith and colleagues (2009) concluded that surgery for urodynamic stress incontinence should not be considered contraindicated in women with mixed symptoms of SUI and

overactive bladder syndrome or mixed urodynamic findings of urodynamic stress incontinence and detrusor overactivity (grade B recommendation). All patients undergoing surgery for SUI should be appropriately counselled to have realistic expectations of outcome; this is particularly important in those with mixed symptoms or mixed urodynamic stress incontinence (grade B recommendation).

8. The International Consultation on Incontinence (ICI), although allowing the fact that there is no consensus on the definition of intrinsic sphincter deficiency, concluded that there are limited evidence-based data to support that intrinsic sphincter deficiency influences either the outcomes of surgery or the type of surgical treatment (Smith et al, 2005, 2009). It would appear that a low leak point pressure is less predictive of outcome when compared with the presence or absence of urethral hypermobility (Smith et al, 2009).

CHOICE OF SURGICAL TECHNIQUE

Two types of stress incontinence have been suggested: one associated with a hypermobile but otherwise healthy urethra, a manifestation of weakened support of the proximal urethra, and one arising from a deficiency of the urethral sphincter mechanism itself, thereby compromising the ability of the urethra to act as a watertight outlet. Hypermobility of the bladder neck and proximal urethra results from a weakening or loss of their supporting elements (ligaments, fasciae, and muscles), which in turn may be a consequence of aging, hormonal changes, childbirth, and prior surgery. It seems likely that the majority of women with SUI will also have an element of intrinsic sphincteric weakness with a variable degree of loss of the normal anatomic support of the bladder neck and proximal urethra, resulting in hypermobility. The compelling observation that one can cite for this is that a normal individual will not have leakage however much she strains.

Differentiating Relative Contributions of Hypermobility and Intrinsic Sphincter Deficiency

The influence of urethral function defined by leak point pressure or maximum urethral closure pressure (MUCP) is difficult to define because of the large variation in outcome measures used. Furthermore, other variables such as urethral mobility are often not controlled for. Intrinsic sphincteric deficiency is usually defined as a leak point pressure below 60 or MUCP below 20. A standardized test is not available to differentiate the relative contributions of intrinsic sphincter deficiency and hypermobility, and therefore few studies have been able to accurately separate their individual contributions to the development of incontinence (Chapple et al, 2005). Retropubic procedures act to restore the bladder neck and proximal urethra to a fixed, retropubic position and are used when hypermobility is thought to be an important factor in the development of that woman's stress incontinence. This may facilitate the function of a marginally compromised intrinsic urethral sphincter mechanism, but if significant intrinsic sphincter deficiency is present, it is likely that SUI will persist despite efficient surgical repositioning of the bladder neck and proximal urethra; at present this hypothesis remains unproven. In such circumstances a sling procedure (particularly a snug fascial sling) or an artificial sphincter are most likely to be the therapy of choice.

In the normal continent woman, the bladder neck and proximal urethra are supported in a retropubic position, with the bladder base being dependent. Increases in intra-abdominal pressure are transmitted to both the bladder and the proximal urethra such that the pressure difference between the two is unchanged, promoting continence (Einhorn, 1961). A valvular effect at the bladder neck created by the transmission of abdominal pressure to the dependent bladder base may also be operative here (Penson and Raz, 1996). Furthermore, with proper bladder neck support, reflex contraction

of the pelvic floor muscles during Valsalva maneuvers and coughing acts as a backboard for urethral compression (Staskin et al, 1985).

Surgical Procedures

This chapter deals with retropubic surgical procedures, usually chosen as surgical therapy for patients with stress incontinence in which there is a significant component of hypermobility.

Open retropubic colposuspension is the surgical approach of lifting the tissues near the bladder neck and proximal urethra into the area of the pelvis behind the anterior pubic bones. When it is an open procedure, the approach is through an incision over the lower abdomen. There are four variations of open retropubic col-

posuspension: Marshall-Marchetti-Krantz (MMK), Burch, vagino-obturator shelf (VOS), and paravaginal procedures.

The term *colposuspension* was originally used to denote suspension of the urethra by the vaginal wall; however, by common usage, it now generally includes the paraurethral fascia and sometimes only this without the vagina. Retropubic colposuspension urethral repositioning can be achieved by three distinctly different procedures; these are all based on a similar underlying principle, but in a spectrum in relation to the degree of the support or elevation they achieve, and their outcomes differ somewhat in the longer term.

The **Burch colposuspension** (Fig. 82-1A) is the elevation of the anterior vaginal wall and paravesical tissues toward the iliopectineal line of the pelvic sidewall with use of two to four sutures on either

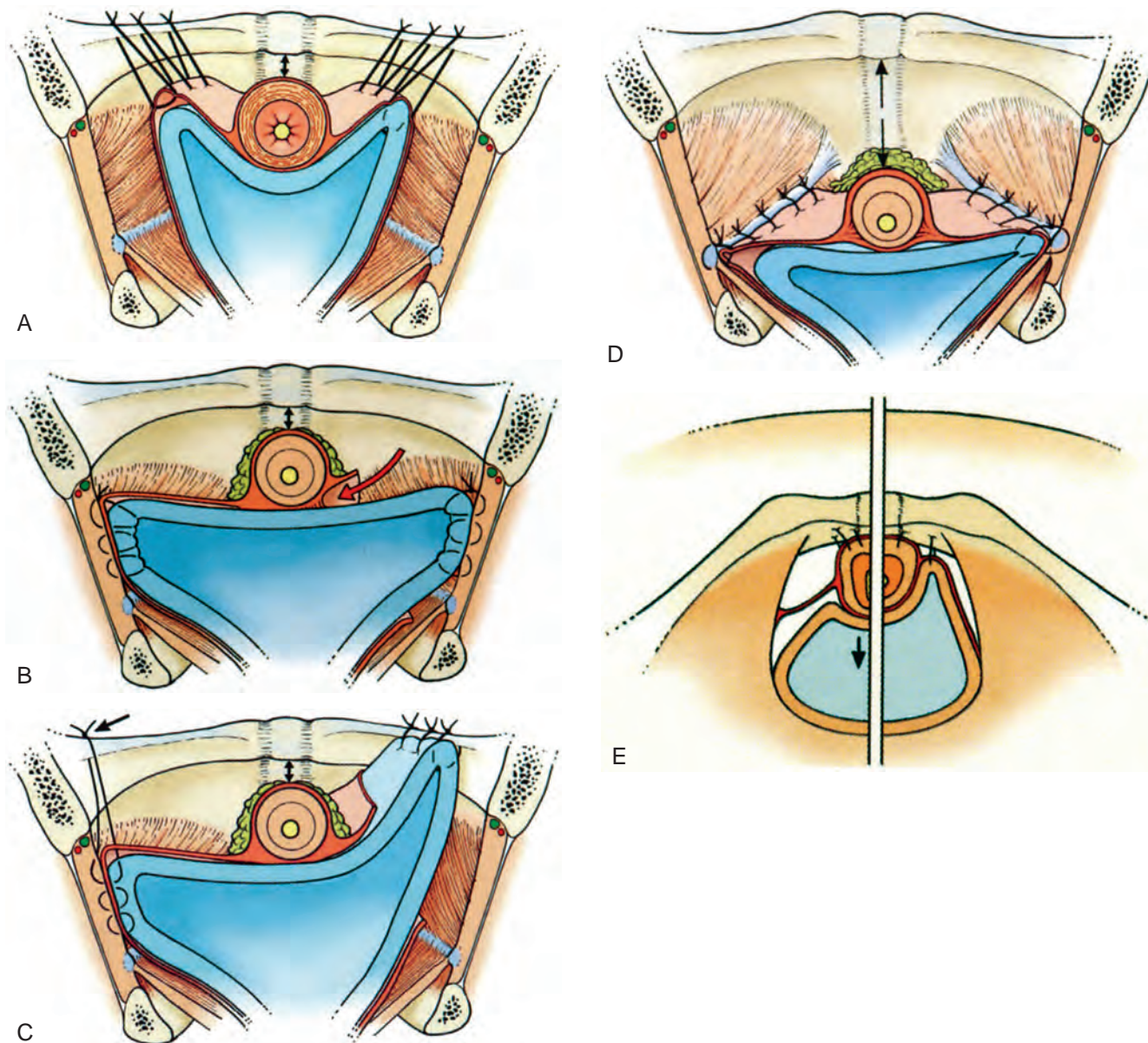


Figure 82-1. A, Coronal view, diagrammatic representation of a Burch colposuspension. B, Coronal view, diagrammatic representation of a vagino-obturator shelf procedure. C, Coronal view, diagrammatic representation of a vagino-obturator shelf procedure on the left, augmented by stitching to the iliopectineal line, and a Burch procedure on the right. D, Coronal view, diagrammatic representation of a paravaginal repair. E, Diagram demonstrating the sutures in a Marshall-Marchetti-Krantz procedure and their proximity to the urethra. (From Turner-Warwick R, Chapple CR. *Functional reconstruction of the urinary tract and gynaecology: an exposition of functional principles and surgical procedures*. Oxford [UK]: Blackwell Science; 2002.)

side (Burch, 1961). The VOS repair (Fig. 82-1B) aims to anchor the vagina to the internal obturator fascia and is a modification of a combination of the Burch and paravaginal defect repair, with placement of the sutures laterally, anchored to the internal obturator fascia rather than hitching the vagina up to the iliopectineal line (Turner-Warwick, 1986), although a more recent modification does, where appropriate, insert stitches into both the internal obturator and iliopectineal line (Fig. 82-1C). The paravaginal defect repair (Fig. 82-1D) aims to close a presumed fascial weakness laterally at the site of attachment of the pelvic fascia to the internal obturator fascia (Richardson et al, 1976). The MMK procedure (Fig. 82-1E) is the suspension of the vesicourethral junction (bladder neck) toward the periosteum of the symphysis pubis (Marshall et al, 1949) and was thought to act by buttressing the paraurethral area and bringing the vesicourethral junction into a more elevated “intra-abdominal” position.

The Degree of Urethral Elevation

The extent of the urethral elevation achieved by both the Burch (see Fig. 82-1A) and the VOS suspensions (see Fig. 82-1B and C) is higher than the arcus tendineus anchorage of the paravaginal defect repair (see Fig. 82-1D).

The Configuration of the Suspensions

A particular advantage of the horizontal urethral elevation achieved by both the VOS and the paravaginal repair suspensions is the significantly lower susceptibility to tension on the urethra and to obstructive problems than with the V-shaped configuration of the Burch suspension (see Fig. 82-1A).

Tissue Approximation

Both the VOS and the paravaginal repair suspensions are anchored by tissue-approximating sutures; thus, unlike the Burch procedure, neither the VOS nor the paravaginal repair suspension is suture-dependent in the longer term once the initial healing is complete because there is direct tissue adhesion. The VOS anchorage and suspension are significantly more robust than those of the paravaginal defect repair; the elevation this procedure achieves can be further augmented by additionally including the iliopectineal ligament in the upper sutures (see Fig. 82-1C).

Laparoscopic colposuspension is the most popular of the laparoscopic incontinence procedures that were first introduced in the early 1990s (Vancaillie and Schuessler, 1991) with the premise that, as minimally invasive procedures, they would benefit patients by avoiding the major incision of conventional open surgery and shorten the time for a return to normal activity. As in open colposuspension, sutures are inserted into the paravaginal tissues on either side of the bladder neck and then attached to the iliopectineal ligaments on the same side. There are, however, technical variations in surgery with respect to the laparoscopic approach (transperitoneal into the abdominal cavity or extraperitoneal) and in the number and types of sutures, the site of anchor, and the use of mesh and staples (Jarvis et al, 1999).

ASSESSING OUTCOMES OF THERAPY

Before the best procedure is determined, several issues regarding outcome reporting need to be addressed.

Duration of Follow-Up

It is recognized that prolonged follow-up is required to assess the true benefit of an incontinence procedure. **Short-term follow-up should be considered to have begun in all studies after participants have reached 1 year of follow-up** (Abrams et al, 2005). In the short term (2 years), most procedures are successful, and success rates among procedures are similar (Leach et al, 1997). However,

with longer follow-up (>5 years), failures manifest and the true benefit of the better procedures is realized. Most studies report outcomes after short-term follow-up, and thus results must be interpreted with caution.

The Issue of Intrinsic Sphincter Deficiency

There is no consistency in the existing literature data to support the likelihood that intrinsic sphincter deficiency can influence either the outcomes or the type of surgical treatment. The main problem is that there is no uniform consensus on the meaning of *intrinsic sphincter deficiency* and how to diagnose it (Smith et al, 2005, 2009). Nevertheless it is likely in my view (unsubstantiated by any unequivocal evidence) that although mild degrees of intrinsic sphincter deficiency coexist with hypermobility in most cases, in a situation wherein intrinsic sphincter deficiency is the predominant problem, a repositioning procedure such as a colposuspension is less likely to be successful than a tight fascial sling or artificial sphincter.

The Definition of Cure

The definition of cure varies among studies. Some authors report cure of SUI only, whereas others define cure as complete continence postoperatively, implying the absence of urge incontinence as well. The assessment of cure may vary. Some authors report subjective cure based on patient history, questionnaire, bladder diary, or medical chart review; others use more objective measures, such as pad tests, stress tests, and urodynamics.

Finally, one must question whether the goal of complete continence is reasonable, given that the condition of SUI is usually a degenerative one and corrective surgery does not replace the defective components. As well, **even in normal healthy women, urinary continence is a spectrum of dryness; approximately 40% of nulliparous 30- to 49-year-olds experience some degree of incontinence with exercise** (Nygaard et al, 1990). It seems unreasonable to expect surgery for a degenerative condition to achieve results that are better than the nondegenerative state.

The Patient's versus the Physician's Perspective

A patient's satisfaction with treatment is often based on the difference between her expectations and her experiences (Sofaer and Firminger, 2005). Thus, fulfillment of positive expectations is a key element of a patient's satisfaction (Sitzia and Wood, 1997). Because expectations vary widely, satisfaction is not a standard concept. Consequently, treatment plans must be tailored to meet a nonstandard goal. An integral step in achieving this goal is the development of a patient-physician partnership that promotes the negotiation of realistic expectations.

Logically, agreement of patient and physician with respect to treatment plan and goals should improve outcomes. When a diagnosis has been made, asking patients what they already know about the condition may give clues to expectations for treatment. The “ask-tell-ask” method may be used to mend the gaps between the physician's and the patient's expectations. The physician explains the proposed treatment plan and expectations for the outcome, then encourages the patient to ask questions. The physician provides the information requested and invites questions again, continuing the process until a mutual understanding of treatments and expectations is reached (Barrier et al, 2003). This approach may prevent “surprises” such as unexpected pain of treatment, adverse events of medication, and prolonged recovery time. Elkadry and associates (2003) emphasized this point by demonstrating a significant association between feeling unprepared for surgery and the patient's dissatisfaction after pelvic reconstruction. The same investigators also reported that achievement of patient-defined goals was more predictive of a patient's satisfaction than were objective measures of surgical success.

Clearly, one or more high-quality validated symptom and quality-of-life instruments should be chosen at the outset of a

clinical trial, representing the patient's viewpoint, accurately defining baseline symptoms as well as any other areas in which treatment may be beneficial, and assessing the objective severity and subjective impact of both. Whereas I and many others think that urodynamic studies are helpful in defining the underlying pathophysiologic process in patients with incontinence, they have not been proven to have adequate sensitivity, specificity, or predictive value (Chapple et al, 2005). The ICI meeting scientific committee concluded that although urodynamic studies, such as frequency-volume charts and pad tests, are useful, there is inadequate evidence to justify pressure-flow studies for routine testing, as either entry criteria or outcome measures in clinical trials. They recommended that most large-scale clinical trials enroll subjects by carefully defined symptom-driven criteria when the treatment will be given on an empirical basis (Abrams et al, 2005).

INDICATIONS FOR RETROPUBLIC REPAIR

The treatment of SUI in women must be tailored to the individual patient. Once evaluation has identified contributing factors, a trial of conservative therapy should be pursued and surgery considered for patients who do not respond to this. Careful assessment of the patient is essential in making an accurate diagnosis (Fig. 82-2).

The selection of technique is largely based on the surgeon's preference and prior experience; bladder base and urethral hypermobility may be surgically corrected by either a vaginal or a retropubic approach. Although it has been suggested that a retropubic colposuspension should be considered in patients who frequently generate high intra-abdominal pressure (e.g., those with chronic cough from obstructive pulmonary disease and women in strenu-

ous occupations) (Appell, 1993), it could also be argued that these patients may be better served by a pubovaginal sling as well.

Specific Indications

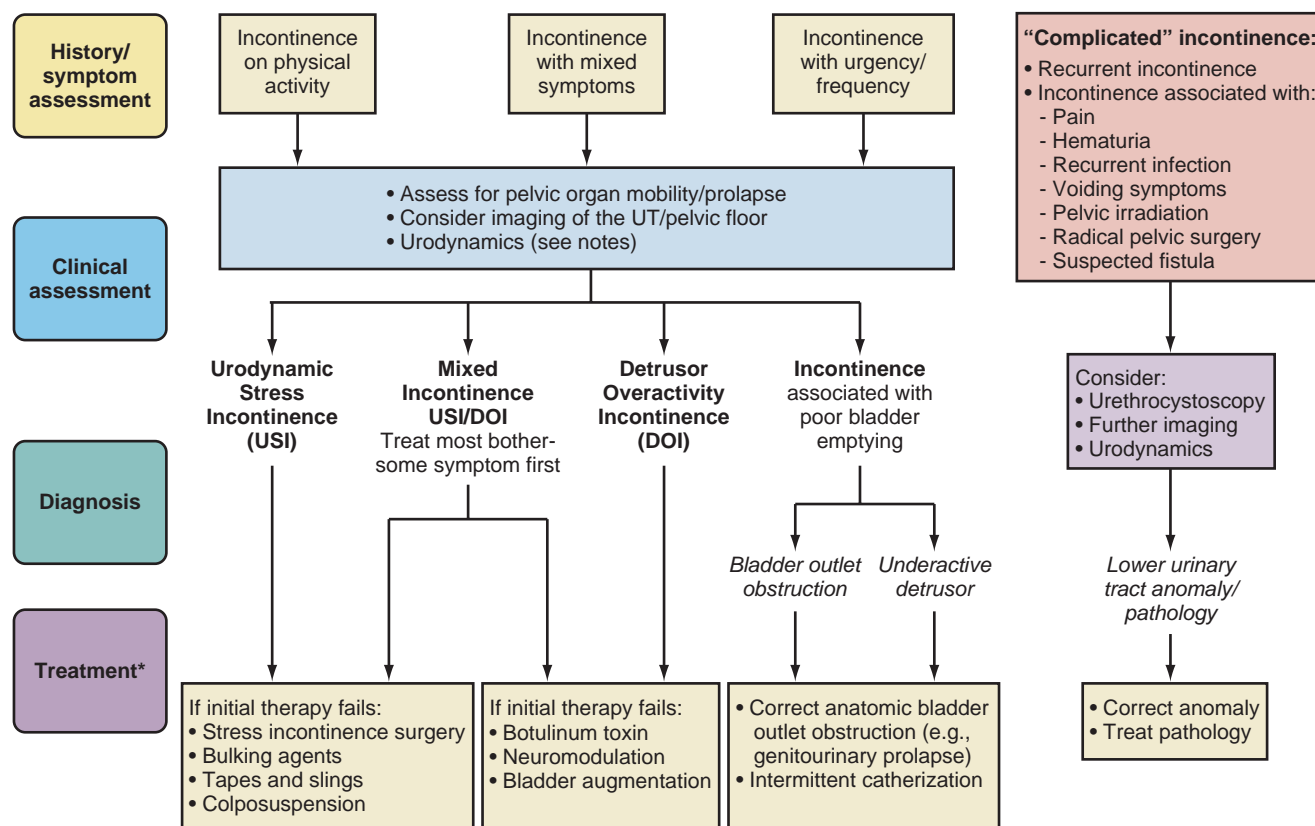
A retropubic approach for the correction of anatomic SUI is indicated (1) for a patient undergoing a laparotomy for concomitant abdominal surgery that cannot be performed vaginally and (2) where there is limited vaginal access.

Potential Contraindications

If there is a history of prior failed incontinence procedures, the existence of significant sphincteric deficiency must be suspected, even if hypermobility exists, and consideration given to performing a pubovaginal sling, although retropubic colposuspension may be successful in this scenario as well (Cardozo et al, 1999; Maher et al, 1999; Nitahara et al, 1999).

In my view, when SUI exists solely because of intrinsic sphincter deficiency (i.e., a fixed, nonfunctional proximal urethra with intrinsic urethral sphincter dysfunction), a retropubic suspension procedure is less likely to be successful because there is no hypermobility to correct and the patient is better served by a pubovaginal sling, collagen injections, or artificial sphincter (Bergman et al, 1989b). This represents a personal view that is at variance with the ICI's conclusion statement on the role of urethral occlusive forces, which states, "It would appear that a low leak point pressure is less predictive of outcome on this data when compared to the presence or absence of urethral hypermobility" (Smith et al, 2009).

In cases with a pan-pelvic floor weakness, a colposuspension should not be used in isolation but should be part of a comprehensive approach to the pelvic floor and combined as



*At any stage of the patient's care pathway, management may need to include continence products.

Figure 82-2. Algorithm for the specialized management of stress urinary incontinence in women (after the Third International Consultation on Incontinence, Monaco, 2004). UT, urinary tract.

appropriate with other alternative pelvic floor repair procedures. A retropubic colposuspension does not always adequately correct the associated vaginal prolapse that frequently coexists with bladder neck hypermobility. Although lateral defect cystocele and enterocele lend themselves to retropubic repair, a central defect cystocele, rectocele, and introital deficiency do not.

A retropubic colposuspension is contraindicated when there is an inadequate vaginal length or mobility of the vaginal tissues, for example, after prior vaginal surgery, radiotherapy, or a prior vaginal incontinence procedure (Appell, 1993). The lysis of retropubic adhesions can be performed adequately and safely by a vaginal approach in conjunction with a needle suspension procedure or pubovaginal sling.

Vaginal versus Retropubic Surgery

From a review of the literature, there is clearly a difference in the success rate of vaginal versus retropubic surgery alone with respect to correction of stress incontinence. An anterior colporrhaphy can certainly be efficacious for the correction of prolapse, with reported efficacy rates in randomized controlled studies of 42% and 57% in the management of cystoceles (Sand et al, 2001; Weber et al, 2001). For the treatment of both a cystocele and stress incontinence, an anterior colporrhaphy should be combined with a sling procedure. Goldberg and colleagues (2001), in a case-control series, demonstrated that in women with a cystocele and SUI, the addition of a pubovaginal sling to an anterior colporrhaphy significantly decreased the recurrence rate from 42% in the control group to 19% in the anterior colporrhaphy group.

Glazener and Cooper (2001) reviewed the literature on randomized or quasi-randomized trials that included anterior vaginal repair for the treatment of urinary incontinence. Nine trials were identified that included 333 women who underwent anterior vaginal repair and 599 who received comparison interventions. The researchers concluded that anterior vaginal repair was less effective than open abdominal retropubic suspension on the basis of patient-reported cure rates in eight trials, both in the medium term (failure rate within 1 to 5 years after anterior repair, 97 of 259 [37%] vs. 57 of 327 [17%], relative risk [RR] 2.29, 95% confidence interval [CI] 1.7 to 3.08) and in the long term (after 5 years, 49 of 128 [38%] vs. 31 of 145 [21%], RR 2.02, 95% CI 1.36 to 3.01). There was evidence from three of these trials that this was reflected in a need for more repeated operations for incontinence (25 of 107 [23%] versus 4 of 164 [2%], RR 8.87, 95% CI 3.28 to 23.94). These findings held irrespective of the coexistence of prolapse (pelvic relaxation), although fewer women had a prolapse after anterior repair (RR 0.24, 95% CI 0.12 to 0.47), and later prolapse operation appeared to be equally common after either a vaginal (3%) or an abdominal (4%) operation.

Long-term follow-up beyond the first year is available in only three RCTs (Bergman et al, 1989a; Liapis et al, 1996; Colombo et al, 2000). There is a low morbidity rate with anterior vaginal repair, but long-term success rates decrease with time to the extent that a 63% cure rate at 1 year fell to 37% at 5 years of follow-up (Bergman and Elia, 1995).

Based on the existing evidence, transvaginal sling procedures and open retropubic suspension procedures have similar success rates in the treatment of stress incontinence. However, with longer follow-up (and with the exception of the pubovaginal sling and loose mid-urethral tapes (see later in this chapter), patients who have retropubic procedures fare better than those undergoing vaginal repairs.

KEY POINT: RECOMMENDATION FROM THE INTERNATIONAL CONSULTATION ON INCONTINENCE COMMITTEE (SMITH ET AL, 2009)

- Anterior colporrhaphy should not be used in the management of SUI alone (grade A recommendation).

GENERAL TECHNICAL ISSUES

Retropubic Dissection

In open retropubic suspension procedures, good access to the retropubic space is crucial. This is best performed with the patient in the supine position with the legs abducted, in either a low or a modified dorsal lithotomy position with use of stirrups, allowing access to the vagina during the procedure and a perineal-abdominal progression. A urethral Foley catheter is inserted; the catheter balloon is used for subsequent identification of the urethra and bladder neck, and indeed, it is invaluable in allowing palpation of the edges of the bladder by appropriate manipulation. A Pfannenstiel or lower midline abdominal incision is made, separating the rectus muscles in the midline and sweeping the anterior peritoneal reflection off the bladder. It is essential to optimize the access to the retropubic space, and if a Pfannenstiel skin incision is made, it is advisable to use the suprapubic V modification described by Turner-Warwick and colleagues (1974). Likewise, whatever incision is made, extra valuable access to the retropubic space is obtained by extending the division of the rectus muscles down to the pubic bone and elevating the aponeurotic insertion of the rectus muscle off the upper border of the pubic bone.

The retropubic space is then developed by teasing away the retropubic fat and underlying retropubic veins from the back of the pubic bone. The bladder neck, anterior vaginal wall, and urethra are then easy to identify, often facilitated by the presence of the Foley balloon. In patients who have had previous retropubic surgery, the dissection is performed sharply, and it is important to take down all old retropubic adhesions, particularly in the face of a prior failed repair. If difficulty is encountered in the identification of the bladder neck, the bladder may be partially filled or even opened to identify its limits, and an examining finger in the vagina is invaluable in aiding the dissection (Symmonds, 1972; Gleason et al, 1976).

It is important to identify the lateral limits of the bladder as it reflects off the vaginal wall because only in this manner can one avoid inadvertent suturing of the bladder itself. Dissection over the bladder neck and urethra in the midline is to be avoided so as not to damage the intrinsic musculature. The lateral bladder wall may be "rolled off" medially and cephalad from the vaginal wall with a mounted swab and by use of countertraction with a finger in the vagina. In my experience, it is necessary to incise the endopelvic fascia. Occasional venous bleeding from the large vaginal veins is controlled by suture ligation, although it often resolves with tying of elevating sutures. To aid in the identification of the lateral margin of the bladder, it is helpful to displace the balloon of the Foley catheter into the lateral recess, where it can easily be palpated through the bladder wall.

Suture Material

Absorbable sutures were used in the original descriptions of the MMK procedure (chromic catgut), Burch procedure (chromic catgut), and VOS procedure (polyglycolic acid or polydioxanone), whereas the original paravaginal repair used nonabsorbable sutures (silicon-coated Dacron). Fibrosis during subsequent healing is likely to be the most important factor in providing continued fixation of the perivaginal fascia to the suspension sites (Tanagho, 1996); nevertheless, some surgeons believe that a nonabsorbable suture material is better because of the risk of suture dissolution before the development of adequate fibrosis (Penson and Raz, 1996). Clearly, the type of suspension suture material is a personal choice, but erosion of nonabsorbent sutures into the lumen of the bladder is a not-uncommon complication and a not-uncommon source of medical litigation (Woo et al, 1995).

Bladder Drainage

Some degree of immediate postoperative voiding difficulty can be expected after retropubic suspensions (Lose et al, 1987; Colombo et al, 1996a). Immediately postoperatively, bladder drainage may

take the form of a urethral or a suprapubic catheter, in general based on the surgeon's preference. A voiding trial is usually performed around the fifth day postoperatively. However, there is some evidence that a suprapubic catheter may be advantageous with respect to a lower incidence of asymptomatic and febrile urinary tract infection and earlier resumption of normal bladder function (Andersen et al, 1985; Bergman et al, 1987). In addition, the use of a suprapubic tube is usually more comfortable, allows the patient to participate in catheter management, and avoids the need for clean intermittent self-catheterization. Catheterization can be discontinued when efficient voiding has resumed, which is usually indicated by a postvoid residual volume either less than 100 mL or less than 30% of the functional bladder volume.

Drains

A tube drain may be placed in the retropubic space when there is concern about ongoing bleeding from perivaginal veins that may prove difficult to control with suture and electrocautery. Often, tying the suspension sutures is sufficient to stop this bleeding, but when it persists, drainage of the retropubic space is indicated. The drain is usually removed on the first to third day, when minimal output is noted.

MARSHALL-MARCHETTI-KRANTZ PROCEDURE

Technique

Marshall, Marchetti, and Krantz in 1949 described a retropubic approach for the elevation and fixation of the anterolateral aspect of the urethra to the posterior aspect of the pubic symphysis and the adjacent periosteum. Technically, the original description of the MMK procedure reported a double suture bite of the paraurethral tissue included with the vaginal wall; this may be generically entitled a cystourethropexy procedure. In 1949, Marshall and coworkers described their retropubic vesicourethral suspension in 50 patients;

38 of the patients had symptoms of SUI, and in 25 of those, prior gynecologic operations for urinary incontinence had failed. A simple suprapubic procedure was described by which the vesical outlet was suspended to the pubis (Marshall et al, 1949). In the original description, three pairs of sutures (taking double bites of tissue) were placed on each side of the urethra, incorporating full-thickness vaginal wall (excluding mucosa) and lateral urethral wall (excluding mucosa) (Marshall et al, 1949). Marchetti (1949) then modified the procedure to omit the tissue bite through the urethral wall because of concern about urethral injury. Apart from modifications in suture number and material over the years, the procedure remains the same today.

Cystourethropexy was often used as a secondary procedure for the resolution of persistent leaking after an anterior colporrhaphy. A cystourethropexy procedure does not support the posterior wall of the urethra unless the sutures include the paraurethral vaginal wall, nor does it positively reduce an anterior vaginal wall prolapse in the way that the true retropubic colposuspension procedures do. After cystourethropexy, if there is a significant urinary residual volume postcolporrhaphy with associated laxity of the anterior vagina wall, then with the descent, this applies traction to the posterior aspect of the bladder neck and tends to "tent" it open because the anterior aspect is tethered by sutures to the back of the pubis (see Fig. 82-1E). Sutures are placed on either side of the urethra (avoiding the urethral wall), taking bites through the paraurethral fascia and anterior vaginal wall (excluding mucosa). The most proximal sutures are placed at the level of the bladder neck. Each suture is then passed into an appropriate site in the cartilaginous portion of the symphysis (Fig. 82-3). However, the main technical problem relating to the MMK procedure is the difficulty of obtaining an adequately robust anchorage of the anterior wall of the urethra and the paraurethral fascia to the symphysis and the periosteum of the pubis, where the suture bites are relatively insecure. As shown in Figure 82-3, these sutures can potentially either distort the bladder neck and impair sphincter function (see Fig. 82-3A) or obstruct the bladder neck (see Fig. 82-3B). All sutures

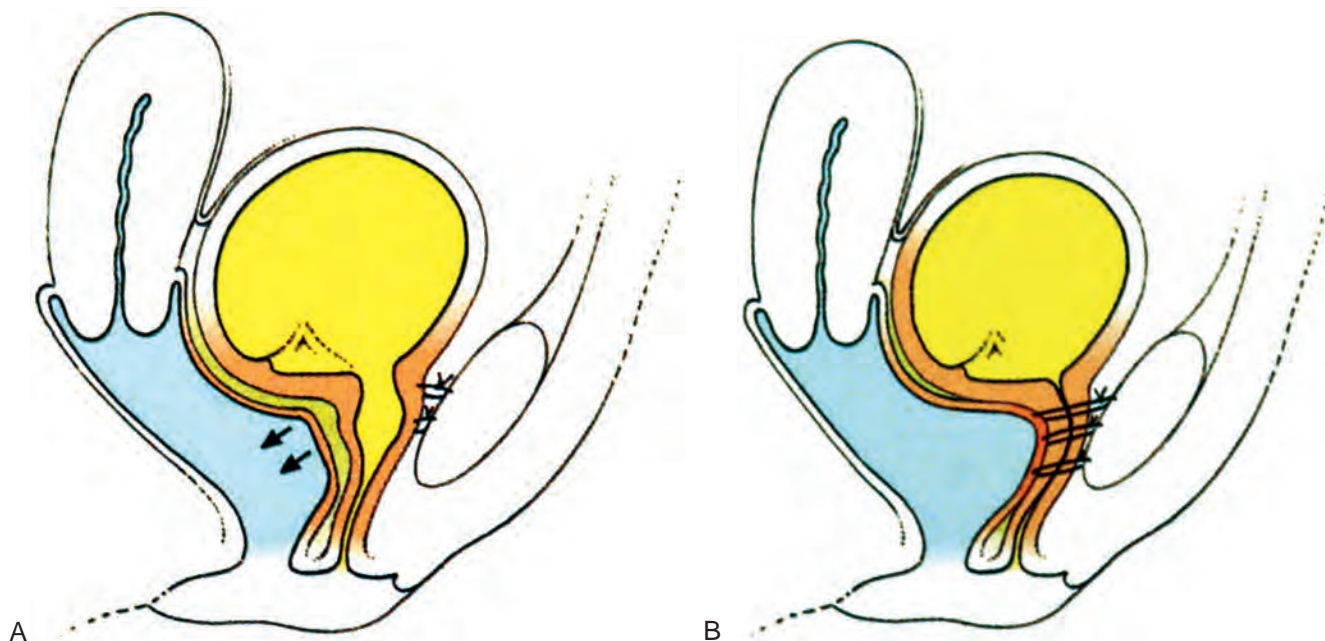


Figure 82-3. A, Potential risk of tethering the urethra with the Marshall-Marchetti-Krantz (MMK) procedure, influencing the function of the urethral sphincter mechanism. B, Potential risk of obstruction of the urethra with the paraurethral sutures of the MMK procedure. (From Turner-Warwick R, Chapple CR. *Functional reconstruction of the urinary tract and gynaeco-urology: an exposition of functional principles and surgical procedures*. Oxford [UK]: Blackwell Science; 2002.)

are inserted, and while an assistant elevates the anterior vaginal wall, each suture is individually tied, starting with the more distal pair. The proximal, or bladder neck, suture frequently needs to be passed through the insertion of the rectus abdominis muscle. Additional sutures may or may not be placed between the anterior bladder wall and the rectus muscles to pull the bladder farther anteriorly.

Results

Krantz described a personal series of 3861 cases with a follow-up of up to 31 years and a 96% subjective cure rate (Smith et al, 2005). Short- and medium-term results with the MMK procedure have been good. Mainprize and Drutz (1988) reviewed 58 articles (predominantly retrospective) published from 1951 to 1988 for treatment outcomes in 3238 cases. The cure rate, mostly based on subjective criteria, was 88%, with an improvement rate of 91%. Jarvis's meta-analysis of studies in the literature (1994b) noted subjective continence in 88.2% (range 72% to 100%) of 2460 patients with 1- to 72-month follow-up and objective continence in 89.6% (range 71% to 100%) of 384 patients with 3- to 12-month follow-up. Whether the procedure was being done primarily or secondarily affected the outcome, with subjective continence in 92% if it was done primarily versus 84.5% if it was done secondarily. Longer-term data are limited in amount. McDuffie and colleagues (1981) reported 75% success at 15 years. More recently, Clemens and coworkers (1998) noted subjective cure or improvement (SUI and urge urinary incontinence) in only 41% of patients with a mean follow-up of 17 years, and Czaplicki and colleagues (1998) noted decreasing continence rates from 77% at 1 year to 57% at 5 years to 28% at 10 years, with a mean duration of continence of 78.5 months. There are significant limitations to the data because most series are retrospective, with preoperative assessment based mainly on history and physical examination and few studies using objective data as outcome measures.

Complications occur in up to 21% of cases (Mainprize and Drutz, 1988), and the placement of sutures through the pubic symphysis incurs the risk of osteitis pubis, a potentially devastating complication of the MMK procedure that has been reported in 0.9% to 3.2% of patients (Lee et al, 1979; Mainprize and Drutz, 1988; Zorzos and Paterson, 1996). Patients usually are seen 1 to 8 weeks postoperatively with acute pubic pain radiating to the inner thighs, aggravated by moving. Physical examination reveals tenderness over the pubic symphysis, and radiography demonstrates haziness to the borders of the pubic symphysis and possibly lytic changes. Treatment is with bed rest, analgesics, and possibly corticosteroids (Lee et al, 1979). Other specific complications of the MMK procedure have included the occasional erosion of nonabsorbable cystourethropexy sutures into the bladder lumen with stone formation. Also, the positioning of sutures in the endopelvic fascia close to the bladder neck can result in a significant outlet obstruction.

Whereas the MMK procedure produces a cure rate similar to that of colposuspension, the complication of osteitis pubis means that there is little to support its use as an alternative to other colposuspension procedures. Indeed the ICI committee (Smith et al, 2009) concluded that although short-term results indicate comparable cure rates to colposuspension, there is limited evidence that the longer-term outcome is poorer after MMK (evidence level 1) and declines further over time (evidence level 3). There is no evidence to support the continued use of MMK over colposuspension.

BURCH COLPOSUSPENSION

Technique

Burch's original description of the colposuspension in 1961 followed his original procedure, which was essentially a paravaginal repair attaching the paravaginal fascia to the white line of the pelvis, the arcus tendineus. The Burch colposuspension was a novel approach to restore the urethrovesical junction to a retropubic location by approximating the periurethral fascia to the tough bands of fibrous tissue running along the superior aspect of the pubic bone (Cooper [iliopectineal] ligament) with three pairs of sutures. The original Burch retropubic colposuspension is appropriate only if the patient has adequate vaginal mobility and capacity to allow the lateral vaginal fornices to be elevated toward and approximated to the Cooper ligament on either side. This technique has been modified. Tanagho's modification (1978) approximated the vaginal wall to the lateral pelvic wall, with the sutures holding the anterior vaginal wall to the Cooper ligament being tied loosely so that two fingers could be placed between the symphysis and urethra. This achieved broad support for the urethra and bladder neck and potentially minimized the risk of postoperative voiding dysfunction. A more recent modification (Shull and Baden, 1989; Turner-Warwick and Chapple, 2002) involves a hybrid approach whereby the vaginal tissues are approximated to the internal obturator fascia with an anchoring bite to the iliopectineal ligament (see VOS repair, later).

Suture placement is facilitated by the elevation of the dissected anterolateral vaginal wall into the field by the surgeon's left vaginal-examining fingers (Fig. 82-4). The bladder is retracted to the opposite side with a mounted swab. Two to four sutures are placed on each side, each suture taking a good bite of fascia and vaginal wall, with care taken not to pass through the vaginal mucosa. Some recommend taking double bites of tissue to lessen the risk of suture pull-through (Jarvis, 1994a). The most distal suture is at the level of the bladder neck and placed no closer than 2 cm lateral to it, although some place distal sutures at the mid-urethral level (Tanagho, 1978). The suspension suture bites of the paraurethral fascia should not be positioned too close to the bladder neck and the urethra, as they are in the cystourethropexy procedures (MMK), because the unwanted effect of lateral traction-tension created by their anchorage to the iliopectineal ligaments may increase the sphincteric occlusive effect on the urethra or create a degree of obstructed voiding. Subsequent sutures are placed proximal to the level of the bladder neck, at about 1-cm intervals. The sutures are then placed into corresponding sites in the Cooper ligament, the emphasis being on a mediolateral direction for the sutures. The exact mechanism of continence of the Burch procedure is still unknown. Burch (1968) thought it to be secondary to elevation and stabilization of the bladder neck and urethra. In support of the suggestion regarding suture placement, Digesu and colleagues (2004) reviewed magnetic resonance imaging findings before and 1 year after open Burch colposuspension (OBC) in 28 women to see if this would explain the mechanism. In the 86% who were cured, the distance between the levator ani muscle and bladder neck was significantly shorter than in those in whom treatment failed. Digesu's suggestion is that insertion of sutures in a medial-lateral direction as opposed to an anterior-posterior direction may better appose the levator ani muscle and bladder neck. The highly vascular vaginal wall may bleed profusely during suture placement, and large vaginal veins often need to be oversewn, but most bleeding ceases once the sutures are tied and the vagina is suspended. To facilitate tying of the sutures, the assistant elevates the appropriate portion of the vaginal wall as each suture is tied, commencing with the more distant pair.

No attempt should be made to tie the sutures tightly. Often the vaginal wall does not approximate to the Cooper ligaments, and free suture material is seen between the vagina and the ligaments. The principle is to approximate the vaginal wall to the lateral pelvic wall, where it will heal and promote adhesion formation (Tanagho, 1978; Shull and Baden, 1989; Turner-Warwick

KEY POINT: RECOMMENDATION FROM THE INTERNATIONAL CONSULTATION ON INCONTINENCE COMMITTEE (SMITH ET AL, 2009)

- The MMK procedure is not recommended for the treatment of SUI (grade A recommendation).

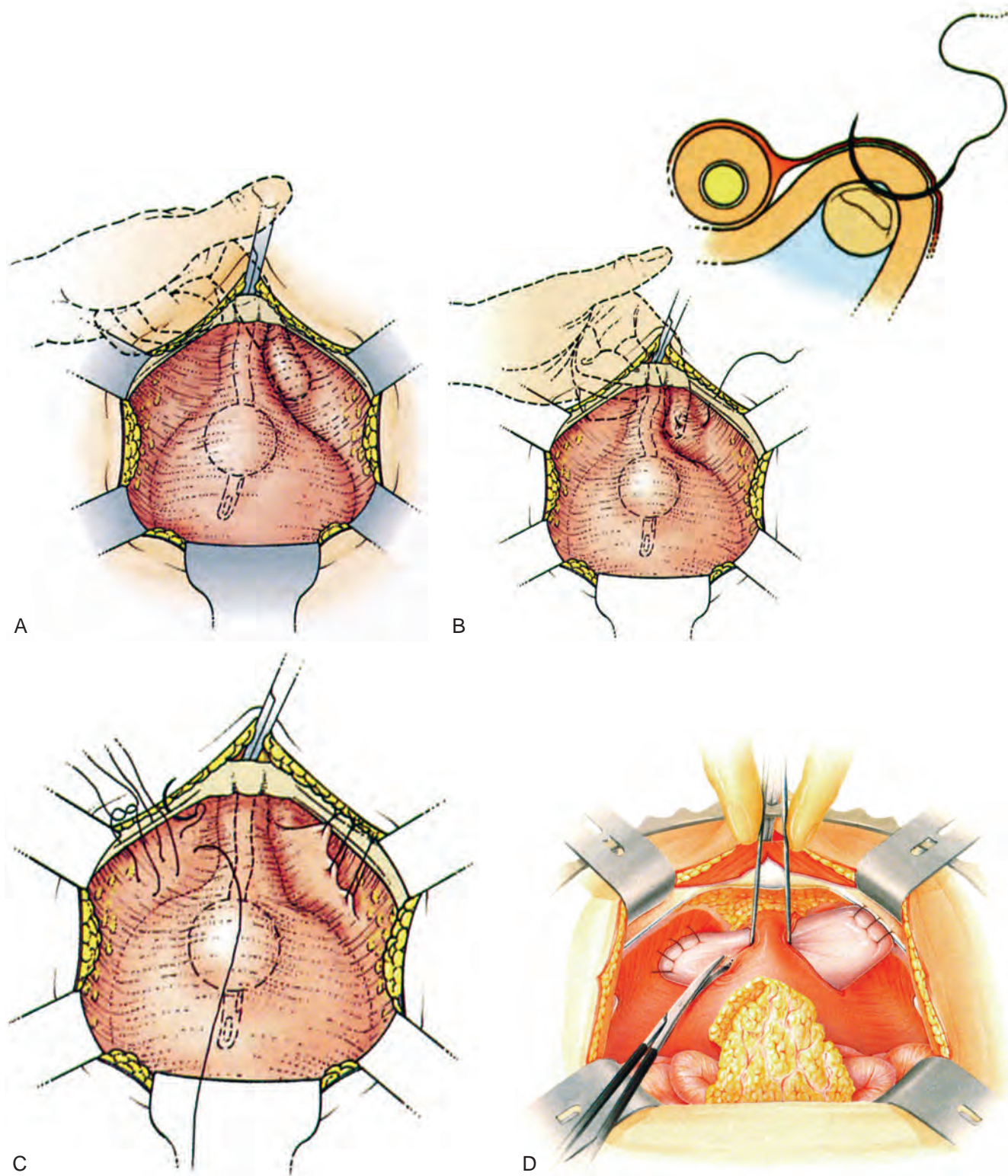


Figure 82-4. A, The use of a finger in the vagina when the pelvic tissues are dissected supero-medially off the vagina. B, Medial suture placement; note the role of the finger in steering the suture (*inset*). C, Note the mediolateral orientation of the sutures. D, Completion of a retropubic colposuspension with a vagino-obturator hitch on the left and a Burch procedure on the right. (From Turner-Warwick R, Chapple CR. Functional reconstruction of the urinary tract and gynaeco-urology: an exposition of functional principles and surgical procedures. Oxford [UK]: Blackwell Science; 2002.)

and Chapple, 2002), thereby creating a broad support for the urethra and bladder neck.

Results

As in the MMK procedure, short- and medium-term outcomes with the Burch procedure have been good. In [Jarvis's meta-analysis \(1994b\)](#), subjective continence was achieved in 91% (range 63% to 97%) of more than 1300 patients with 3 to 72 months of follow-up and objective continence in 84% of more than 1700 patients with 1 to 60 months of follow-up. [Lapitan and associates \(2003\)](#) reviewed 33 trials involving a total of 2403 women who underwent open colposuspension and found an overall cure rate of 68.9% to 88.0%, with a 1-year cure rate of approximately 85% to 90%. This decreased to 70% at 5 years. Although there may be a decline in the cure rate of only 15% to 20% beyond 5 years, [Alcalay and colleagues \(1995\)](#) noted a subjective and objective SUI cure rate of 69% with a mean follow-up of 13.8 years. [Baessler and Stanton \(2004\)](#) examined the impact of surgery on coital incontinence. Of the 30 women available for postoperative evaluation, 73% preoperatively had incontinence with penetration, 10% with orgasm only, and 17% with both. Postoperatively, 70% were cured of their coital incontinence. Moreover, in those who were subjectively cured of their stress incontinence, 87% were also cured of their coital incontinence.

[Lapitan and Cody \(2012\)](#) updated the Cochrane Collaboration review on open retropubic colposuspension for urinary incontinence in women. They reviewed 53 trials, including a total of 5244 women, and noted that the overall cure rate was 68.9% to 88.0% for open retropubic colposuspension. Two small studies suggested lower continence rates compared with conservative treatment; one trial suggested lower continence rates after open retropubic colposuspension compared with anticholinergic treatment. The evidence accrued from 6 trials showed a lower incontinence rate after open retropubic colposuspension than after anterior colporrhaphy, with these benefits being maintained over time. Evidence was obtained from 20 trials in comparison with suburethral slings, transvaginal tape, or transobturator tape, and these found no significant differences in incontinence rates in all time periods assessed. In comparison with needle suspension, there was a lower incontinence rate after colposuspension in the first year after surgery (RR 0.66, 95% CI 0.42 to 1.03), after the first year (RR 0.48, 95% CI 0.33 to 0.71), and beyond 5 years (RR 0.32, 95% CI 0.15 to 0.71). The patient-reported continence rates at short-, medium-, and long-term follow-up showed no significant difference between open and laparoscopic retropubic colposuspension, but with wide CIs. In 2 trials, incontinence was less common after Burch colposuspension than after the MMK procedure at 1- to 5-year follow-up. There were few data at any other follow-up time. The general finding was that the evidence did not show a higher morbidity or complication rate with open retropubic colposuspension compared with the other open surgical techniques, although pelvic organ prolapse (POP) was much more common than after anterior colporrhaphy and sling procedures. The authors concluded that open retropubic colposuspension is an effective treatment modality for SUI in the longer term. Within the first year of treatment the overall continence rate is approximately 85% to 90%. After 5 years approximately 70% of patients can expect to be dry. Laparoscopic colposuspension should allow speedier recovery, but its relative safety and long-term efficacy remain to be established.

Unlike with the MMK procedure, the good results with the Burch procedure appear to be durable with longer follow-up. [Lapitan and associates \(2003\)](#) reached the conclusion from a review of two trials comparing the Burch colposuspension and the MMK procedure that the Burch technique results in higher cure rates. Thus, it should be regarded as the *standard* open retropubic colposuspension procedure.

Open colposuspension is as effective as any other procedure in primary or secondary surgery at curing SUI with proven long-term success (level 1 evidence, grade A recommendation) ([Smith et al, 2005](#)).

Prophylactic Colposuspension

In 2006, the Colpopexy and Urinary Reduction Efforts (CARE) trial demonstrated that the **postoperative risk of stress incontinence in stress continent women undergoing open abdominal sacrocolpopexy could be substantially reduced by the addition of a Burch colposuspension** ([Brubaker et al, 2006](#)). Initial results at 3 months postprocedure demonstrated reduction of de novo stress incontinence from 44% in the untreated group to 24% in the Burch group, without increased rates of voiding dysfunction or urgency symptoms. Subsequent 1- and 2-year outcomes from the CARE trial showed continued benefit in patients who received the concomitant Burch procedure ([Burgio et al, 2007](#); [Brubaker et al, 2008](#)).

[Costantini and colleagues \(2012\)](#) reported on POP repair with and without concomitant Burch colposuspension in incontinent women in an RCT with at least 5 years' follow-up. This study was an update of a previously published trial on the impact of Burch colposuspension as an anti-incontinence procedure in patients with urinary incontinence and POP. Forty-seven women were randomly assigned to abdominal POP surgery and concomitant Burch colposuspension (24 patients) or POP surgery alone without any anti-incontinence surgery (23 patients). The median follow-up was 82 months (range 60 to 107). From 47 patients, 30 reached 6-year follow-up and 2 patients were lost to follow-up. In the first group, undergoing both POP and Burch colposuspension, 2 patients showed a stage 1 rectocele. In the second group, 2 patients had a stage 1 rectocele and 1 a stage 2 rectocele. In the first group, 13 out of 23 were still incontinent after surgery (56.5%) compared with 9 out of 22 (40.9%) of those who underwent only prolapse surgery. There was no significant change over time from the original assessment of this group. The authors concluded that Burch colposuspension did not improve outcomes significantly in incontinent patients when they were undergoing POP repair.

Reoperative Surgery

Poorer results are likely to occur when the procedure is performed secondarily. Scarring and fibrosis from previous surgery can prevent adequate suspension in some cases, and suture cut-through is more likely. Furthermore, after failed surgery, patients may have coexisting sphincteric weakness that places them at greater risk of recurrence after colposuspension ([Bowen et al, 1989](#); [Koonings et al, 1990](#)).

Nevertheless, [Maher and colleagues \(1999\)](#) and [Cardozo and associates \(1999\)](#) have both shown good objective (72% and 79%) and subjective (89% and 80%) success with repeated colposuspension at a mean follow-up of 9 months. [Nitahara and coworkers \(1999\)](#) reported 69% subjective success at a mean follow-up of 6.9 years. Urge incontinence and sphincteric weakness are the main causes of failure and dissatisfaction. Urge incontinence accounted for 63% (12 of 19) of failures; the remaining 7 with persistent stress incontinence in Nitahara's series demonstrated sphincteric deficiency with mean Valsalva leak point pressures of 65 cm H₂O. The low-pressure urethra has often been quoted to be an adverse risk factor for colposuspension ([Haab et al, 1996](#); [Bowen et al, 1989](#); [Koonings et al, 1990](#)), but this topic also remains controversial. Several authors have studied the urethral pressure profilometry changes after colposuspension and have noted a statistically significant increase in the postoperative pressure transmission ratio but minimal changes in the postoperative MUCP, functional urethral length, and continence area ([Faysal et al, 1981](#); [Weil et al, 1984](#); [Feyersiel et al, 1994](#)). Although a low-pressure urethra (MUCP <20 cm H₂O) is considered a contraindication to the Burch procedure, a modification of the standard Burch operation has had some success in managing SUI associated with the low-pressure urethra. [Bergman and colleagues \(1989c\)](#) combined a standard Burch procedure with the Ball procedure ([Ball, 1963](#)) wherein before the Cooper ligament suspension is performed, two or three sutures are used to plicate the anterior urethral wall at the level of the proximal and middle urethra. These researchers retrospectively noted greater

success with this technique than with a standard Burch procedure for the low-pressure urethra, and this was comparable to the success obtained with a standard Burch procedure in patients with a normal-pressure urethra (MUCP >20 cm H₂O). With longer follow-up, the Ball-Burch procedure continued to yield better results than the standard Burch procedure in patients with a low-pressure urethra, with a documented 5-year cure rate of SUI of 84% (Bergman et al, 1991; Elia and Bergman, 1995). However, there are no randomized studies addressing the issue, and whether these results can be extrapolated for the use of this technique in patients with intrinsic sphincter deficiency is debatable.

Giarenis and colleagues (2012) pose the question of what to do when a mid-urethral tape fails, emphasizing the potential role of open colposuspension as a salvage continence procedure. This was a retrospective study of 13 women who had undergone open colposuspension after a failed mid-urethral sling. The average time between insertion of the mid-urethral tape and the colposuspension was 22.6 (range 8 to 72) months. The mean operating time was 77 (range 43 to 123) minutes, including the time for the concomitant surgery. The mid-urethral tape was identified and partially excised. The authors reported a median follow-up of 12 months. Subjective and objective cure rates were 85% and 77%, respectively. Only 1 woman had severe SUI postoperatively, requiring further surgery. Three of the 8 women with preexisting urinary urgency reported postoperative improvement. Two patients reported de novo urinary urgency and urgency incontinence. Three of 10 women developed de novo detrusor overactivity that responded to anticholinergic medication. Long-term voiding difficulty was observed in only 1 patient, who performed clean intermittent catheterization for 3 months. No patients developed recurrent urinary incontinence. Three women (23%) developed symptomatic prolapse postoperatively. These patients were at stage II on the Pelvic Organ Prolapse Quantification System (POP-Q) scale involving the posterior vaginal compartment and underwent posterior repair within 22 months of colposuspension. Bearing in mind that this is a small series, nevertheless it raises the point that, allowing for the fact that there is morbidity associated with a colposuspension in this context, it is still a potential therapeutic option in these patients.

A recent Cochrane meta-analysis has looked at the evidence for the treatment of recurrent SUI after failed minimally invasive synthetic suburethral tape surgery in women (Bakali et al, 2013). Twelve studies were identified, but all were excluded because they did not meet the eligibility criteria. Six were RCTs but were not eligible because the previous incontinence surgery had not been a suburethral tape. A subset of one RCT may have been eligible for inclusion because one of the women was having repeat surgery, but the authors were unable to obtain the data according to primary surgery for this cohort from the authors of the original study. The question of how to best deal with recurrent stress incontinence after a tape procedure will depend on whether the primary problem is that of intrinsic sphincter deficiency or problems with repositioning the urethra, and the question as to whether colposuspension may have a role in this context still remains open on the basis of this review of the literature because there is no clear evidence-based conclusion available.

Conversely, Shao and colleagues (2011) reported on TVT retropubic sling for recurrent SUI after Burch colposuspension failure. In this small series of 24 women undergoing TVT procedures for recurrent stress incontinence after a previous failed Burch colposuspension, the median follow-up was 57 months (range 12 to 96 months). Preoperative and postoperative urethral mobility and urodynamics were evaluated. It was noted that preoperatively in all women there was intrinsic sphincter deficiency, and 14 had urethral hypermobility. Postoperatively, 15 patients were completely dry, and 2 had a leakage of urine less than 5 g/hr. The overall success rate was 70.8% and there was a significant postoperative increase of MUCP and a decrease of average flow rates and average hypermobility. The authors concluded that recurrent SUI after a Burch colposuspension can be successfully treated with a TVT procedure. This, however, needs to be considered cautiously as a conclusion, because in the context of intrinsic sphincter defi-

ciency, many authors in contemporary practice would express concern about putting in such a sling under any degree of tension to correct intrinsic sphincter deficiency because of the long-term potential complications with sling exposure that may occur. In this context, the potential use of an autologous sling should be carefully considered.

As with any major abdominal or pelvic surgical procedure, intra-operative and perioperative complications that may occur after a retropubic suspension include bleeding, injury to genitourinary organs (bladder, urethra, ureter), pulmonary atelectasis and infection, wound infection or dehiscence, abscess formation, and venous thrombosis or embolism. Other complications more specific to retropubic suspension procedures include postoperative voiding difficulty, detrusor overactivity, and vaginal prolapse. These are discussed in more detail along with other reported complications in a later section in this chapter.

KEY POINTS: RECOMMENDATIONS FROM THE INTERNATIONAL CONSULTATION ON INCONTINENCE COMMITTEE (SMITH ET AL, 2009)

- Open retropubic colposuspension can be recommended as an effective treatment for primary SUI, which has longevity (grade A recommendation).
- Although open colposuspension has to a large extent been superseded by the less invasive mid-urethral tapes, it should still be considered for those women in whom an open abdominal procedure is required concurrently with surgery for SUI (grade D recommendation).

PARAVAGINAL REPAIR

Technique

The origins of the paravaginal repair date to White (1912, 1997), who described the importance of the “white line” of the pelvis (arcus tendineus) as an integral structure supporting the proximal urethra and bladder base to the pelvic wall and the development of paravaginal fascial tears predisposing to cystocele formation. He performed the paravaginal repair by a vaginal approach but envisioned that it would be easier if performed abdominally (White, 1912, 1997). Later, in his original description, Burch attached the vaginal wall to the arcus tendineus in seven patients, only to realize that the attachment may not be secure, prompting him to use the Cooper ligament as an attachment site (Burch, 1961). In the 1970s, Richardson and coworkers (1976) reintroduced the concept of a lateral defect cystourethrocele as a causative factor in the genesis of SUI and popularized the paravaginal repair as a technique for management.

The patient is placed in a low lithotomy position, just as for the MMK procedure and Burch colposuspension. If there are retropubic adhesions resulting from prior surgery, they are sharply incised; the dissection is facilitated by placement of two fingers of the surgeon's left hand in the vagina. The bladder and urethra are not mobilized from the vaginal attachments. Richardson and colleagues (1981) describe an extensive reattachment of the lateral vaginal sulcus with its overlying fascia to the arcus tendineus fasciae pelvis from the back of the lower edge of the symphysis pubis to the ischial spine, using six to eight sutures placed at 1-cm intervals. The vaginal wall in the region of the bladder neck is identified, and these interrupted sutures are placed at approximately 1-cm intervals through the paravaginal fascia and vaginal wall (excluding vaginal mucosa) beginning at the urethrovaginal junction. The sutures are then passed through the adjacent obturator fascia and underlying muscle at the site of the arcus tendineus fascia (Fig. 82-5). If the arcus is

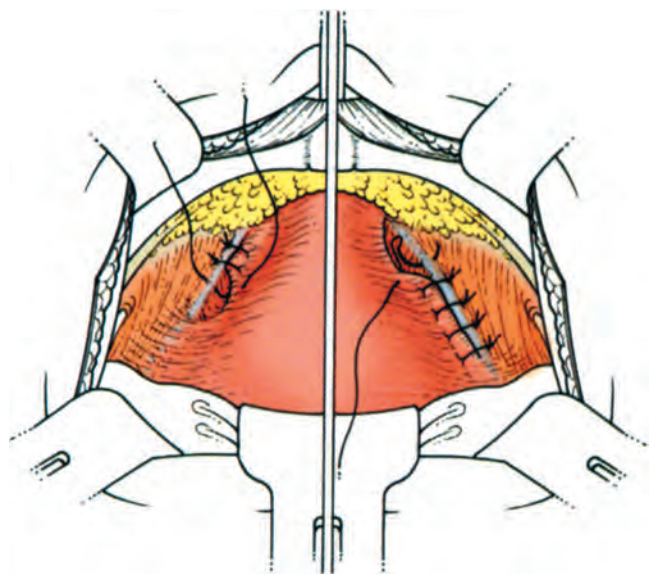


Figure 82-5. A paravaginal repair procedure.

not visible, the obturator foramen may be used as a landmark. It is situated 1.5 to 2 cm above the white line.

The end point that should be achieved is the reestablishment of the urethral axis in an anatomic position, easily allowing three fingerbreadths between the pubic symphysis and the proximal urethra but providing secure fixation and preventing rotational descent. Consequently, it has been reported that postoperative voiding difficulties are uncommon (Richardson et al, 1981).

Results

Few reports on the use of this technique have been published. With variable follow-up, cure rates greater than 90% have been reported for the paravaginal repair (Richardson et al, 1981; Shull and Baden, 1989). There is only a single randomized comparison of colposuspension with paravaginal repair including 36 patients who were randomly allocated to treatment by either colposuspension or paravaginal repair with nonabsorbable suture material. At 6 months of follow-up, there was an objective cure rate of 100% for those undergoing colposuspension and 72% for those undergoing paravaginal repair (Colombo et al, 1996a).

Small series have reported on vaginal approach to paravaginal repairs (Scotti et al, 1998; Mallipeddi et al, 2001). In particular, Mallipeddi and colleagues followed 45 patients (21 with SUI) after this approach for a mean of 1.6 years, and 57% had persistent stress incontinence; the conclusion of these researchers was that this technique had limited applicability for SUI. It can be concluded that there is level 1 or 2 evidence that abdominal paravaginal repair is less effective than colposuspension. There are limited data (level 3 or 4) on laparoscopic and vaginal paravaginal repairs, but interpretation of these data is hampered by the small numbers of patients, the short follow-up, and a combination of this procedure with other types of incontinence procedures (Smith et al, 2005).

There is limited evidence that abdominal paravaginal defect repair is less effective than open colposuspension (evidence level 2) (Smith et al, 2009).

VAGINO-OBTURATOR SHELF REPAIR

Technique

Turner-Warwick (1986; Turner-Warwick and Chapple, 2002) reported his variant of the paravaginal repair, which he called the *vagino-obturator shelf repair*. The premise for this is that there should

KEY POINT: RECOMMENDATION FROM THE INTERNATIONAL CONSULTATION ON INCONTINENCE COMMITTEE (SMITH ET AL, 2009)

- Paravaginal defect repair is not recommended for the treatment of SUI alone (grade A recommendation).

be no restriction to the intrinsic sphincteric function of the urethra by fixation or paraurethral tethering, and there should be no urethral compression (Turner-Warwick and Kirby, 1993).

Just as for other retropubic suspension procedures (Fig. 82-6), the anterior wall of the lower segment of the bladder wall is exposed and the position of the bladder neck is identified by gentle traction on a balloon catheter in the urethra. The surgeon's forefinger in the vagina elevates its anterior wall and the overlying endopelvic fascia on either side of the urethra. Lateral displacement of the catheter balloon with the finger in the vagina facilitates the identification of the inferolateral margin of the bladder, lateral to the bladder neck, and its separation from the paraurethral endopelvic fascia is achieved by simple blunt dissection with a sponge or scissor-tip retraction. This naturally exposes the surface of the obturator muscle and the arcus tendineus origin of the levator muscles deep in the sulcus below this, the site of suture placement in the paravaginal repair (which is well below the vaginal anchorage point in the VOS procedure). The obturator nerves lie superolaterally; their canals run high up in a groove under the superior pubic ramus so that once they have been identified, injury to them can be avoided. The full thickness of the vagina and its overlying layer of endopelvic fascia are elevated by the surgeon's finger in the vagina and are approximated to the internal obturator muscle and anchored to the bulk of this with absorbable 0 or No. 1 sutures mounted on robust 35- to 40-mm half-circle needles. Slight flexion of the fingertip tents the vaginal wall and facilitates the full-thickness insertion of these suture bites through it, thus avoiding inclusion of the surgical glove. Three or four successive sutures are inserted. For knot security, these are best tied continuously, head to tail, as they are inserted, rather than separating them individually. Each tied suture bite facilitates the insertion of the next (unlike in the Burch procedure, in which the sutures are not tied until they have all been inserted). A similar obturator suspension of the elevated protrusion of the vagina and its overlying endopelvic fascia is achieved on the opposite side. Some additional elevation of the lateral anchorage of the VOS by the inclusion of a bite of the iliopectineal ligament within the suture bite approximating the vagina to the obturator muscle (as in a Burch procedure) may be used to reinforce the repair (Shull and Baden, 1989). This modification is one that I favor and represents a hybrid with the Burch procedure, facilitating reattachment of the pubocervical fascia to the arcus tendineus fasciae pelvis, tissue apposition to the lateral pelvic wall, and nonobstructive elevation of the urethra and urethrovesical junction. In addition, obliteration of the pouch of Douglas (culdoplasty) may be needed to prevent enterocele (Shull and Baden, 1989; Turner-Warwick and Kirby, 1993).

Results

There are limited data available for the VOS repair, which has had reported cure rates of 60% to 86%, depending on whether the procedure was performed primarily or secondarily (Turner-Warwick, 1986; German et al, 1994). German and colleagues (1994) reported that the VOS procedure is less likely to be successful in patients who have undergone previous surgery.

Ultimately, as with all such reconstructive surgery, the surgeon should select the correct procedure for the individual patient. Although the VOS, which is a synthesis of the principles of the paravaginal repair and the Burch colposuspension, is of interest, further clinical results are necessary before definitive conclusions can be drawn.

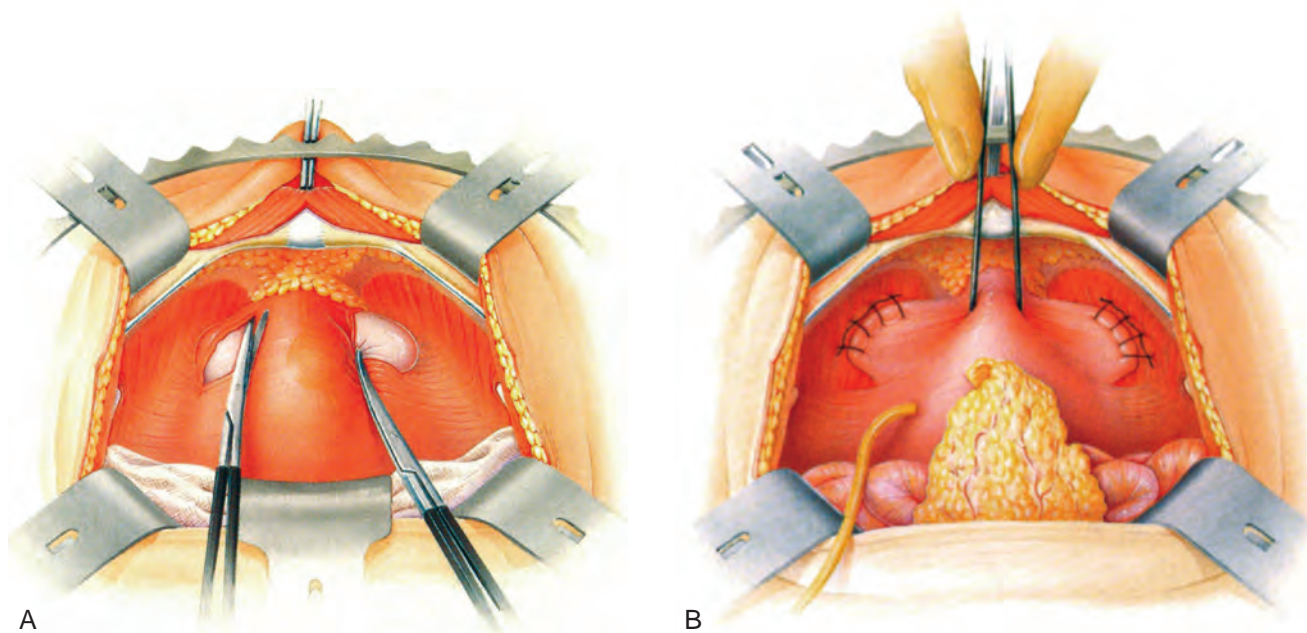


Figure 82-6. A, Mobilizing the tissues. The tissues should be stripped by blunt dissection with a mounted swab or the edge of a pair of scissors; only occasionally is sharp dissection necessary, provided the stripping action starts far laterally adjacent to the pubic bone. B, Completed vagino-obturator shelf procedure. (From Turner-Warwick R, Chapple CR. *Functional reconstruction of the urinary tract and gynaeco-urology: an exposition of functional principles and surgical procedures*. Oxford [UK]: Blackwell Science; 2002.)

LAPAROSCOPIC RETROPUBIC SUSPENSION

Laparoscopic techniques for retropubic suspension were introduced by [Vancaillie and Schuessler in 1991](#). They essentially performed an MMK urethropexy laparoscopically, and since that time, laparoscopic techniques have been applied to both the Burch procedure and the paravaginal repair. Subsequent modifications to the suspension suturing techniques have been introduced, including the use of mesh ([Ou et al, 1993](#)), staples ([Lyons, 1994](#)), and fibrin sealant ([Kiilholma et al, 1995](#)), but all adhere to the same principles of their open counterparts. Proposed advantages of the laparoscopic approach include improved intraoperative visualization, less post-operative pain, shorter hospitalization, and quicker recovery times ([Liu, 1993](#)). Disadvantages include greater technical difficulty with resultant longer operating times and higher operating costs ([Paraíso et al, 1999](#)).

The procedure may be performed extraperitoneally or transperitoneally, and each approach has its proponents. Although the extraperitoneal technique may be associated with shorter operating times, easier dissection, and fewer bladder injuries ([Frankel and Kantipong, 1993](#); [Raboy et al, 1995](#)), the transperitoneal approach provides a larger operating space and the ability to perform concomitant intraperitoneal procedures and apical prolapse repair ([Paraíso et al, 1999](#)). The specifics of the different procedures are beyond the scope of this chapter.

Short- and medium-term outcomes with the laparoscopic retropubic suspensions have become available. In their review of 13 studies of laparoscopic retropubic suspensions, [Paraíso and colleagues \(1999\)](#) found cure rates to range from 69% to 100% with follow-up of 1 to 36 months. This is comparable to outcomes of the open procedures as already noted. Both retrospective ([Polascik et al, 1995](#)) and randomized, prospective comparisons ([Summitt et al, 2000](#)) between open and laparoscopic techniques have demonstrated similar short-term success. However, with longer follow-up, laparoscopic retropubic suspensions appear to fail more frequently. [McDougall's group \(1999\)](#) retrospectively noted only 30% cure of SUI and 50% cure or improvement after a laparoscopic

Burch procedure with 45 months of follow-up, and this was no different from the results with a Raz procedure.

Five trials summarized in a Cochrane review have compared laparoscopic with open colposuspension ([Burton, 1997](#); [Su et al, 1997](#); [Burton, 1999](#); [Carey et al, 2000](#); [Summitt et al, 2000](#); [Fatthy et al, 2001](#); [Moehrer et al, 2002](#)). All had different lengths of follow-up: 6 months ([Carey et al, 2000](#)); 1 year ([Su et al, 1997](#); [Summitt et al, 2000](#)); 6 and 18 months ([Fatthy et al, 2001](#)); and 6 months, 1 year, 3 years, and 5 years ([Burton, 1997, 1999](#)). Outcome data for 6 months to 18 months were therefore available for all studies. Longer-term data are currently available only for Burton's study. The ability to synthesize data was also limited by the variable tests and definitions used to measure subjective and objective outcomes across the trials ([Moehrer et al, 2003](#)). Moehrer and colleagues, in their meta-analysis, noted that a total of 233 women received a laparoscopic and 254 women an open colposuspension, and the CIs are generally all wide as a consequence. Four trials comparing laparoscopic with open colposuspension were otherwise of good quality ([Burton, 1997, 1999](#); [Carey et al, 2000](#); [Summitt et al, 2000](#); [Fatthy et al, 2001](#)). Burton's study had the potentially confounding factors of use of absorbable sutures and of the surgeon's having carried out only a relatively small number of laparoscopic colposuspensions (<20) before commencing the trial. These factors may have influenced his results, in particular because there is believed to be a definite albeit relatively steep learning curve associated with laparoscopic colposuspensions. The fifth trial had methodologic problems with corrupted randomization and confounding factors of performance of additional surgery in some patients and the use of a different number of sutures for laparoscopic (one suture) and open (three sutures) colposuspension ([Su et al, 1997](#)). The number of sutures used appears to have a significant influence on the cure rate, with more sutures resulting in a significantly higher success rate. [Persson and Wolner-Hanssen \(2000\)](#) compared different numbers of paravaginal sutures and found a significantly higher objective 1-year cure rate (dry on "ultra-short" pad test) for women randomized to two sutures compared with one suture, with a cure rate of 83% for two sutures and 58%

for one suture. Only one trial currently has data beyond 18 months of follow-up (Burton, 1997, 1999). This suggested poorer long-term results after laparoscopic surgery. This finding should be interpreted cautiously, however, as there are concerns that the surgeon's laparoscopic performance may have been suboptimal because he had performed few laparoscopic colposuspensions when the trial started. Data from other larger trials with multiple operators are now needed to assess whether this is a real effect. All the other trials had data up to a maximum of 18 months. These show some inconsistencies. Outcome assessed by the women participating (arguably the most important outcome) appeared equally good in the two groups. Urodynamic investigations were used to assess cure objectively in all five studies. Overall, there was a significantly higher success rate after open colposuspension (RR 0.89, 95% CI 0.82 to 0.98), equivalent to an absolute difference of an additional 9% risk of failure after laparoscopic surgery. No significant differences between the two groups were observed for postoperative urgency, voiding dysfunction, or de novo detrusor overactivity. A trend was shown toward a higher complication rate, less postoperative pain, shorter hospital stay, and more rapid return to normal function for laparoscopic colposuspension. The operating time tended to be longer, the intraoperative blood loss less, and the duration of catheterization shorter for laparoscopic compared with open colposuspension (Moehrer et al, 2003).

In a review of laparoscopic colposuspension, Paraiso and colleagues (1999) noted major intraoperative and short-term complications in up to 25% of cases, with bladder injury being the most common complication and declining with experience; ureteric injury has also been reported (Aslan and Woo, 1997). The use of mesh and tacks or staples may be complicated by foreign body erosion (Arunkalaivanan and Smith, 2002; Kenton et al, 2002), and a randomized study (Ankardal et al, 2004) reported that the use of sutures was superior to the laparoscopic mesh and staple technique.

A previous Cochrane review (Moehrer et al, 2002) was dependent on small trials, recruiting a total of 487 women among them, with mostly only medium-term follow-up data (18 months) and limited evidence from other small studies and concluded that laparoscopic colposuspension had the benefit of a more rapid recovery but might have a higher complication rate, be more expensive, and possibly be less effective in the long term than open colposuspension. This highlighted the need for further well-designed clinical studies.

Carey and coworkers (2006) reported a randomized trial that recruited 200 women during 1997 and 1998, with 2-year follow-up available for 83% of participants and longer-term subjective data from a similar proportion. The primary outcome measure was objective cure (absence of urodynamic stress incontinence) at 6 months, powered to detect a difference of 20% between the two arms. Secondary measures included patient satisfaction, quality of life and general well-being, and complications. In the same year Kitchener and colleagues (2006) reported the results of the COLPO trial, which recruited 291 women in 1999 to 2001, with a 2-year follow-up rate of more than 80%. The primary outcomes were objective (dry pad test) and subjective (symptom report) cure at 24 months. Secondary outcomes included recovery time, complications, and a formal cost-benefit analysis. The trial was powered to show noninferiority of laparoscopic colposuspension to open colposuspension, assuming a cure rate of 80% for the open procedure. Both studies were well designed, well conducted, and clearly reported.

Carey and colleagues found no difference in urodynamic cure rate, incidence of detrusor overactivity, or patient satisfaction at 6 months, with an overall objective cure rate of 75%. Detrusor overactivity occurred in 12% of women, and 66% of women were urodynamically normal. If the raw data are converted to percentage scores, there was 89% satisfaction with the treatment outcomes and 88% satisfaction with the care received. The overall satisfaction was 87%. At 24 months after surgery, there were no significant differences between the two treatment groups with respect to reporting urinary stress incontinence, urgency, urgency incontinence, or sat-

isfaction score of 80 or higher. Across both treatment groups, by 24 months after surgery, 66% of women reported no stress incontinence, 38% reported no urgency, 47% reported no urgency incontinence, and 64% reported a satisfaction score of 80 or higher. Although follow-up information was available for only approximately 80% of all subjects by 24 months, a sensitivity analysis was performed assuming that all women who did not complete the 24-month follow-up had either occasional or frequent stress incontinence. With these assumptions, cure rates decreased to 61% for open colposuspension and 50% for laparoscopic colposuspension. There was no significant difference between the two treatment groups, even when adjusted for surgeon experience ($P = .08$). The study population was contacted by telephone for further follow-up at a mean of 3.7 years (range 3 to 5 years) after surgery. This follow-up was undertaken at a single point in time. A total of 162 women were contacted, 88 of whom had undergone open colposuspension and 76 of whom had undergone laparoscopic colposuspension. There were no significant differences between the two treatment groups at 3 to 5 years after surgery, and the findings were similar to the 24-month data. Mean operating time was approximately twice as long for laparoscopic colposuspension, but surgeons' estimates of blood loss and patients' estimates of immediate postoperative pain at rest were significantly less after the laparoscopic procedure, with a return to normal activities, on average, 5 days earlier ($P = .01$).

Kitchener and colleagues also found no difference in the objective cure rate (79% for laparoscopic vs. 70% for open) or subjective cure rate (55% vs. 54%) between the study arms, again showing the now well-recognized mismatch between objective and subjective outcomes. The intention-to-treat analysis indicated no significant difference in cure rates between open and laparoscopic surgery. The study was slightly underpowered based on the sample size calculations, but the analyses clearly demonstrated that laparoscopic colposuspension is not inferior to open colposuspension. The complication rate was low in both arms, with more bowel and bladder injuries in the laparoscopic arm and more wound infections in the open arm. Each demonstrated comparable improvements in generic quality-of-life scores. Other points of note included the careful selection of surgeons who had experience with both open and laparoscopic surgery and, it is interesting to note, findings that were in contrast to the Carey study and contrary to the previously held beliefs that laparoscopic surgery would be associated with longer operating times, less postoperative pain, and shorter hospital stay. For hospital stay, there was only a small advantage for laparoscopic surgery, with a median stay of 5 days compared with 6 for open surgery. The operating times were fairly similar in terms of "knife to skin" to completion of surgery—median times of 65 and 51 minutes for laparoscopic and open surgery, respectively. Postoperative pain was significantly less in the laparoscopic surgery group. There were no differences in time of return to work identified in this study. Complications of surgery were low in general, with a higher bladder injury rate for the laparoscopic procedure and a higher wound infection rate for open surgery, as would be expected. The impact of these differences was analyzed in a cost-benefit analysis accompanying this study, which suggested that a greater quality-adjusted life year total is achieved in the laparoscopic arm at both 6 and 24 months, suggesting that laparoscopic surgery may confer an additional benefit of well-being (Manca et al, 2006). However, the additional costs of laparoscopic surgery were recouped only after 24 months of follow-up, thus highlighting the need to address long-term outcomes in any surgical study.

The last major publication in this field was a meta-analysis of all of the comparative studies published from 1995 to 2006 of laparoscopic versus open colposuspension (Tan et al, 2007). End points evaluated were operative outcomes and subjective and objective cure. A random-effect model was used and sensitivity analysis performed to account for bias in patient selection. Sixteen studies matched the selection criteria, reporting on 1807 patients, of whom 861 (47.6%) underwent laparoscopic and 946 (52.4%) underwent open colposuspension. Length of hospital stay and return to

normal life were significantly reduced after laparoscopic surgery. These findings remained consistent on sensitivity analysis. Bladder injuries occurred more often in the laparoscopic group, but only with marginal statistical significance. Comparable bladder injury rates were found when studies were matched for quality, year, and randomized trials. Cure rates were similar between the two procedures at 2 years of follow-up.

The current evidence would suggest that in adequately experienced hands there is no difference in overall safety and efficacy between laparoscopic and open colposuspension. Clearly another concern is how generalizable the data on laparoscopic colposuspension are, because the majority of reported studies are from expert laparoscopists or surgeons working in specialized units. The evidence base for both laparoscopic and open colposuspension is limited by relatively short-term follow-up; robust data out to 5 years are needed. The tendency toward small numbers and poor methodology limits the interpretation of most studies, with the exception of those reported by Carey and colleagues (2006) and Kitchener and colleagues (2006). Laparoscopic colposuspension shows comparable subjective outcome but poorer objective outcome than both open colposuspension and TVT in the short to medium term; longer-term outcomes are unknown (evidence level 2). Laparoscopic colposuspension may not offer good value for money when compared with open colposuspension in the short term (i.e., first 6 months after surgery), but it could be a cost-effective alternative over 24 months (evidence level 1); other comparisons, however, suggest that minimally invasive mid-urethral tape procedures may be superior in health economic terms.

In a review article looking at the surgical management of female SUI, the question as to what is the optimal procedure is addressed (Cox et al, 2013). The traditional gold standard procedures of Burch retropubic colposuspension and pubovaginal sling are both considered to be approved treatment options for appropriate patients. RCTs, as noted in this paper, have demonstrated that synthetic mid-urethral slings are also highly effective. Cox and colleagues (2013) concluded that retropubic mid-urethral slings are associated with slightly higher success rates than transobturator slings, but at the cost of more postoperative complications. Certainly pubovaginal slings are an effective option for women with SUI in whom other procedures have failed, and in particular if there are mesh complications that require concomitant urethral surgery. The authors concluded that both retropubic and transobturator mid-urethral slings are effective for patients with mixed urinary incontinence, but the overall cure rate is lower than for patients with pure stress incontinence. They concluded that their literature review suggests that a new gold standard first-line surgical treatment for women with SUI is a synthetic mid-urethral sling inserted through a retropubic or transobturator approach. A further study looked at the cost comparison of laparoscopic Burch colposuspension, a laparoscopic two-team sling procedure, and the transobturator tape procedure for the treatment of SUI (Lo et al, 2013). This retrospective observational study of isolated minimally invasive surgical procedures reached the conclusion that a transobturator tape procedure has lower direct medical costs than a laparoscopic Burch colposuspension or a laparoscopic two-team sling procedure. This is not surprising in view of the interventions necessary. Clearly, this has been one of the main drivers that led to the lack of progression of laparoscopic colposuspension into clinical practice, despite the availability of improved laparoscopic techniques.

Barr and colleagues (2009) looked at the long-term outcome of laparoscopic colposuspension in a report from a 10-year cohort study. A consecutive series of 139 patients who had undergone laparoscopic colposuspension was reviewed and compared with 52 women who had undergone an open colposuspension in the same unit. Subjects were contacted by telephone at least 10 years postoperatively. In total, 96 patients in the laparoscopic group and 31 in the open colposuspension group were available for follow-up. The authors reached the conclusion that laparoscopic colposuspension appeared to be as effective as open colposuspension at long-term follow-up when used as treatment for stress incontinence and could be considered as an alternative surgical approach.

KEY POINTS: RECOMMENDATIONS FROM THE INTERNATIONAL CONSULTATION ON INCONTINENCE COMMITTEE (SMITH ET AL, 2009)

- Laparoscopic colposuspension is not recommended for the routine surgical treatment of SUI in women (grade A recommendation).
- Laparoscopic colposuspension might be considered for the treatment of SUI in women who also require concurrent laparoscopic surgery for other reasons (grade D recommendation).
- Laparoscopic colposuspension should be carried out only by surgeons with specific training, expertise, and appropriate workload in laparoscopic surgery and in the assessment and management of urinary incontinence in women (grade D recommendation).

COMPLICATIONS OF RETROPUBIC REPAIRS

As with any major abdominal or pelvic surgical procedure, intraoperative and perioperative complications that may occur after a retropubic suspension include bleeding, injury to genitourinary organs (bladder, urethra, ureter), pulmonary atelectasis and infection, wound infection or dehiscence, abscess formation, and venous thrombosis or embolism. Other common complications more specific to retropubic suspension procedures include postoperative voiding difficulty, detrusor overactivity, and vaginal prolapse. Potentially, it is overcorrection of the urethrovesical angle that may be a major contributory factor in the development of the long-term complications of de novo urgency, voiding dysfunction, and enterocele formation.

Nevertheless, the reported incidence of these problems is relatively low. In their meta-analysis, Leach and associates (1997) noted a 3% to 8% transfusion rate for retropubic suspensions and no significant difference in the overall medical and surgical complication rates among retropubic suspensions, needle suspensions, anterior colporrhaphy, and pubovaginal slings. Mainprize and Drutz (1988), in their review of the MMK procedure literature (2712 patients), noted an overall complication rate of 21%, with wound complications and urinary infections making up the majority (5.5% and 3.9%, respectively). Direct surgical injury to the urinary tract occurred in only 1.6%, and genitourinary tract fistulas occurred in 0.3%. Ureteral obstruction has been reported rarely after Burch colposuspension, and it usually results from ureteral kinking after elevation of the vagina and bladder base, although direct suture ligation of the ureter can occur (Applegate et al, 1987). If it is identified intraoperatively, it is best remedied by removal of the offending ligature and temporary placement of a ureteral stent. The so-called postcolposuspension syndrome, which has been described as pain in one or both groins at the site of suspension, has been noted in up to 12% of patients after a Burch procedure (Galloway et al, 1987). More recently, Demirci and colleagues (2001) reported the occurrence of groin or suprapubic pain in 15 of 220 women (6.8%) after Burch colposuspension with a follow-up of 4.5 years.

Postoperative Voiding Difficulty

Postoperative voiding difficulty after any type of retropubic suspension is not uncommon, and undoubtedly its occurrence is more likely if there is preexisting detrusor dysfunction or denervation resulting from extensive perivesical dissection. In most cases, however, it is the result of overcorrection of the urethral axis from inappropriately placed or excessively tightened sutures. If the sutures are placed too medially, they may also transfix the urethra or distort it.

Preoperatively, at-risk patients may be identified by their history of prior voiding dysfunction or episodes of urinary retention. These women should be carefully counseled preoperatively about the

potential for postoperative voiding difficulty and the possible need for self-catheterization intermittently. Their incontinence should be of sufficient magnitude that its correction offsets the risk of the need for self-catheterization.

Women with postcystourethropey voiding problems who have obstruction often do not exhibit the classic urodynamic features of obstruction. However, the history of postoperative voiding symptoms and associated new-onset bladder storage symptoms and a finding of a retropubically angulated and fixed urethra typically indicate that obstruction does exist (Carr and Webster, 1997). In such cases, revision of the retropubic suspension by releasing the urethra into a more anatomic position resolves voiding symptoms in up to 90% of patients (Webster and Kreder, 1990; Nitti and Raz, 1994; Carr and Webster, 1997).

The meta-analysis by Leach and coworkers (1997) noted that the risk of temporary urinary retention lasting more than 4 weeks postoperatively is 5% for all retropubic suspensions, and the risk for permanent retention is estimated to be less than 5%. These risks are not significantly different from those for needle suspensions or pubovaginal slings. Mainprize and Drutz's review of the literature (1988) yielded a 3.6% incidence of postoperative voiding problems after an MMK procedure, whereas the Burch procedure literature reports an incidence of postoperative voiding disorders ranging from 3% to 32% (Hilton and Stanton, 1983; Galloway et al, 1987; Eriksen et al, 1990; Alcalay et al, 1995; Colombo et al, 1996a). In more recent literature, voiding dysfunction may be persistent, as noted in 3.5% of a series of 310 women with a mean follow-up of 36 months (Viereck et al, 2004). Non-persistent voiding dysfunction has been reported in 12.5% (6% to 37.2%) after primary surgery (Smith et al, 2005). After colposuspension conducted as a secondary procedure, Bidmead and associates (2001) reported voiding difficulties requiring intermittent self-catheterization in 6% of cases.

Because the paravaginal repair aims to restore normal anatomy, there is theoretically little chance of overcorrection of the urethral axis, which should translate into a lower risk of postoperative obstruction. In Richardson and coworkers' study (1981), 80% of patients were able to void immediately after paravaginal repair, and "all patients had satisfactory bladder function at the time of discharge." However, temporary voiding difficulty has been noted in up to 17% of patients after a VOS procedure (German et al, 1994), and chronic (>2 years) voiding difficulty has been noted in up to 11% of patients after the paravaginal repair (Colombo et al, 1996a).

All patients should be counseled before surgery about the potential need for intermittent self-catheterization.

Bladder Overactivity

Bladder overactivity commonly accompanies anatomic SUI, and its incidence preoperatively has been reported to be as high as 30% in patients undergoing either first correction or repeated operations (McGuire, 1981). Provided it is considered as a diagnosis, urodynamic evaluation has been performed to show whether detrusor overactivity is present, an attempt at treatment of the related overactive bladder symptoms has been made (with or without success), and the patient has been advised that the presence of detrusor overactivity will increase the risk of continuing storage symptoms postoperatively, then preoperative bladder overactivity does not contraindicate a retropubic suspension procedure, provided that anatomic SUI has also been demonstrated. In the majority of patients, the bladder overactivity symptoms resolve after surgical repair (McGuire, 1988). Leach and coworkers' meta-analysis (1997) found the risk of urgency after a retropubic suspension to be 66% if urgency and detrusor overactivity were present preoperatively, 36% if there was urgency but no documented overactivity preoperatively, and only 11% if there was neither urgency nor overactivity preoperatively. There was no significant difference in the incidence of postoperative urgency among retropubic suspensions, needle suspensions, and pubovaginal slings. Postoperative urgency was noted in only 0.9% of MMK procedures in Mainprize and Drutz's meta-analysis of 15 series (1988),

although Parnell and associates (1982) reported that 28.5% of their patients developed postoperative storage symptoms. Jarvis's meta-analysis (1994b) of Burch procedures found the incidence of de novo bladder overactivity to be 3.4% to 18%. More recently, Smith and colleagues (2005) quoted a figure for postoperative detrusor overactivity of 6.6% for colposuspension (range 1.0% to 16.6%), whereas the incidence of postoperative urgency or urge incontinence after the paravaginal or VOS repair has been reported to be 0% to 6% (Shull and Baden, 1989; German et al, 1994; Colombo et al, 1996a).

For patients in whom postoperative storage symptoms persist, proven to be associated with detrusor overactivity and intractable to management with anticholinergic therapy and behavioral modification, surgical techniques including intravesical botulinum toxin therapy, neuromodulation, augmentation cystoplasty, or detrusor myectomy may be indicated.

Bladder storage symptoms arising de novo after retropubic suspension may be associated with bladder outlet obstruction. This premise is supported by the frequent coexistence of these symptoms with impaired voiding after suspension procedures and confirmed by the finding that urethrolisis, by freeing the urethra from an obstructed position, often resolves both storage and voiding symptoms (Raz, 1981; Webster and Kreder, 1990).

Vaginal Prolapse

Retropubic suspensions alter vaginal and bladder base anatomy, and thus postoperative vaginal prolapse is a potential complication. Genitourinary prolapse has been reported as a sequel to Burch colposuspension in 22.1% of women (range 9.5% to 38.2%) by Smith and colleagues (2005) in their review of the literature. The Burch procedure, because of lateral vaginal elevation, may aggravate posterior vaginal wall weakness, predisposing to enterocele. The incidence varies from 3% to 17% (Burch, 1961, 1968; Galloway et al, 1987; Wiskind et al, 1992); because of this, prophylactic obliteration of the cul-de-sac of Douglas is sometimes considered in performing retropubic suspensions (Shull and Baden, 1989; Turner-Warwick and Kirby, 1993). However, simultaneous hysterectomy is not recommended prophylactically because it does not enhance the outcome of a retropubic suspension and should be performed only if there is concomitant uterine disease (Milani et al, 1985; Langer et al, 1988). Although the Burch procedure and paravaginal or VOS repair both correct lateral defect cystourethroceles, recurrent cystourethroceles have been noted in 11% and 39% of Burch procedures and paravaginal repairs, respectively (Colombo et al, 1996a). In Mainprize and Drutz's review (1988), postoperative cystocele was noted in only 0.4% of patients after an MMK procedure.

Wiskind and coworkers (1992) noted that 27% of patients who had undergone a Burch colposuspension developed prolapse requiring surgery: rectocele in 22%, enterocele in 11%, uterine prolapse in 13%, and cystocele in 2%. More recently, it has been suggested that most women are asymptomatic, and less than 5% have been reported to request further surgery (Smith et al, 2005). Ward and Hilton (2004) reported that 4.8% of women needed a posterior repair, whereas Kwon and associates (2003) reported that 4.7% required subsequent pelvic reconstruction.

Auwad and colleagues (2006) reported the findings of the first prospective study to determine the prevalence of POP after colposuspension and to investigate possible preoperative and operative risk factors. Seventy-seven women who underwent colposuspension from 1996 to 1997 were investigated. POP was assessed before colposuspension using the POP-Q. Women were reassessed at 1 and 7 to 8 years (or when referred with symptomatic POP). By 7 to 8 years, of the 77 women, 29 (38%) had developed symptomatic prolapse, 29 (38%) had asymptomatic prolapse, 7 (9%) had no symptoms and no prolapse, and 12 (16%) could not be assessed. POP at 1 year was significantly associated with the presence of posterior vaginal descent before colposuspension (odds ratio 3.07, 95% CI 1.10 to 8.60, $P = .03$). No potentially predisposing variable reached statistical significance by 8 years postcolposuspension. The

results add support to the view that there is an association between colposuspension and the development of symptomatic POP (requiring surgery).

KEY POINT: COMPLICATIONS OF RETROPUBIC REPAIRS

- Because retropubic suspensions are unable to correct central defect cystoceles, patients must be carefully examined preoperatively to exclude their presence and must be counselled if undergoing a colposuspension because of the high risk of needing further surgery in the long term. Particularly, those in whom a weakness of the posterior compartment is identified preoperatively and those with a past history of hysterectomy might be at increased risk.

COMPARISONS OF INCONTINENCE PROCEDURES

Retropubic Repair versus Needle Suspension and Anterior Repair

Three articles that reviewed the literature on incontinence procedures all found retropubic suspensions to be more effective than either needle suspensions or anterior colporrhaphies (Jarvis, 1994b; Black and Downs, 1996; Leach et al, 1997). Cure rates were approximately 85% for the retropubic suspensions compared with 50% to 70% for the needle suspensions and anterior colporrhaphies. Results were more durable for the retropubic suspensions and better if the procedure was primary.

Overall therefore there is now high-level evidence indicating that needle suspension procedures are as effective as anterior colporrhaphy but less effective than colposuspension even in the short term (evidence level 1). Long-term studies indicate lack of longevity even of the initial modest results; long-term complications remain a concern (evidence level 3) (Smith et al, 2009).

KEY POINT: RECOMMENDATIONS FROM THE INTERNATIONAL CONSULTATION ON INCONTINENCE COMMITTEE (SMITH ET AL, 2009)

- Endoscopic and nonendoscopic bladder neck needle suspension procedures, with and without bone anchors, are not recommended for the treatment of SUI (grade A recommendation).

Retropubic Repair versus Pubovaginal Sling

Most studies in the historical literature have not demonstrated a significant difference in cure rates between retropubic suspensions (usually a Burch procedure) and pubovaginal slings (Jarvis, 1994b; Black and Downs, 1996; Leach et al, 1997). However, often, selection bias exists in that the pubovaginal sling is usually reserved for patients with multiple prior failed incontinence procedures, with less prolapse, and the presence of presumed intrinsic sphincter deficiency (a fixed urethra with periurethral fibrosis) is often used in clinical practice as a contraindication to a retropubic suspension. In an interesting randomized study in patients with a prior failed incontinence procedure (anterior repair) but without a low-pressure urethra (i.e., MUCP <20 cm H₂O), **Enzelsberger's group (1996)** found no significant difference in cure (subjective or objective) at 32 to 48 months between the Burch procedure and the Lyodura sling. However, they noted significantly more postoperative voiding difficulty with the pubovaginal sling (13% vs. 3%) and more vaginal prolapse (enterocele or rectocele) with the Burch procedure (13% vs. 3%).

A high-quality multicenter randomized clinical trial in women with stress incontinence compared the Burch colposuspension with a pubovaginal sling, using autologous rectus fascia (**Aldo et al, 2007**). Women were eligible for the study if they had predominant symptoms associated with the condition, a positive stress test result, and urethral hypermobility. The primary outcomes were success in terms of overall urinary-incontinence measures, which required a negative pad test result, no urinary incontinence (as recorded in a 3-day diary), a negative cough and Valsalva stress test result, no self-reported symptoms, and no retreatment for the condition, and success in terms of specific measures of stress incontinence as well as an assessment of postoperative urgency incontinence, voiding dysfunction, and adverse events. A noteworthy aspect of the study was the careful approach to standardization (using the recommendations from the standardization committees of the International Continence Society) with regard to clinical terms, urodynamic nomenclature, and methods of evaluation of patients across all sites. Key elements of the two surgical procedures were standardized among all participating surgeons and included the use of preoperative antibiotics, skin-incision length, number and type of Burch sutures, fascial-sling length and width, and cystoscopic evaluation of the bladder. A criticism that can be leveled at the study is the choice of technique for the Burch colposuspension with very medial paraurethral sutures. The techniques utilized are demonstrated in **Figure 82-7**.

Because these procedures are frequently performed in conjunction with surgery for pelvic prolapse, abdominal and vaginal approaches for both pelvic prolapse repair and hysterectomy were permitted; however, surgeons were required to declare before randomization which concomitant procedures would be performed.

A total of 655 women were randomly assigned to study groups: 326 to undergo the sling procedure and 329 to undergo the Burch procedure; 520 women (79%) completed the outcome assessment. At 24 months, success rates were higher for women who underwent the sling procedure than for those who underwent the Burch procedure, for both the overall category of success (47% vs. 38%, $P = .01$) and the category specific to stress incontinence (66% vs. 49%, $P < .001$). There was no significant difference between the sling and Burch groups in the percentage of patients who had serious adverse events (13% and 10%, respectively; $P = .20$). However, more women who underwent the sling procedure had adverse events than in the Burch group, with 415 events among 206 women in the sling group as compared with 305 events among 156 women in the Burch group. This difference was primarily the result of urinary tract infections; 157 women in the sling group (48%) had 305 events and 105 women in the Burch group (32%) had 203 events. When urinary tract infections were excluded, although the rates of adverse events were similar in the two groups, there was more difficulty voiding.

The distribution of time to return to normal voiding differed significantly between the two groups ($P < .001$). Voiding dysfunction was more common in the sling group than in the Burch group (14% vs. 2%, $P < .001$). Consequently, surgical procedures to reduce voiding symptoms or improve urinary retention were performed exclusively in the sling group, in which 19 patients underwent 20 such procedures. (63% vs. 47%, $P < .001$). Treatment-satisfaction rates for the 480 patients who answered the satisfaction question at 24 months were significantly higher in the sling group than in the Burch group (86% vs. 78%, $P = .02$).

A further analysis of this study focused on sexual activity as assessed by the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) among those sexually active at baseline and 2 years after surgery (**Brubaker et al, 2009**). This report demonstrated that sexual function improves after successful surgery and does not differ between Burch and sling procedures.

Chai and colleagues (2009) reviewed complications in women undergoing Burch colposuspension versus autologous rectus fascial sling for SUI. These authors reviewed serious adverse events in the Stress Incontinence Surgical Treatment Efficacy Trial (SISTER). The conclusion reached was that concomitant surgery and continence procedures increased the risk of complications. Sling surgery was

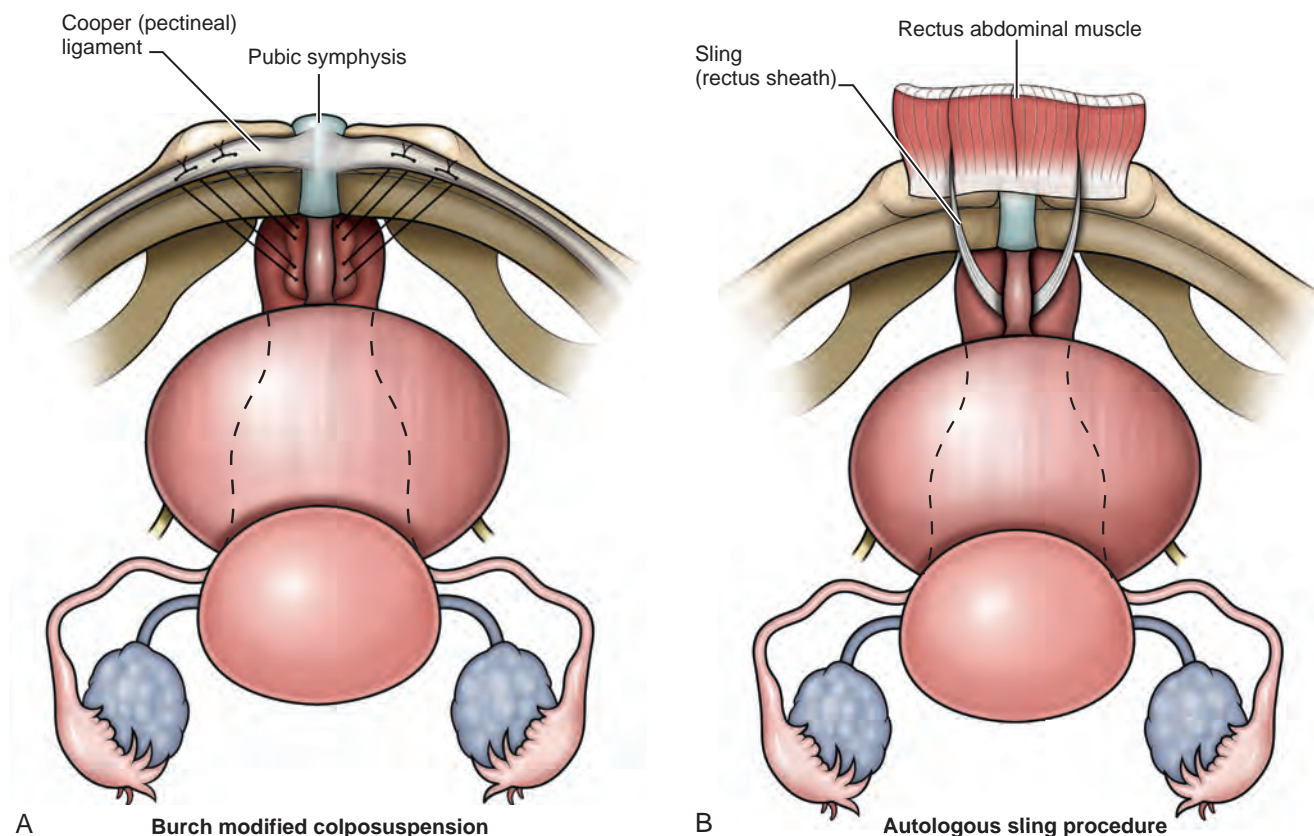


Figure 82-7. In the Burch colposuspension (A), sutures are placed in the anterior vaginal wall at the level of the bladder neck and proximal urethra and sutured to the iliopectineal ligament. In the autologous sling procedure (B), a strip of rectus fascia is harvested and permanent sutures placed at both ends. The sling is positioned beneath the urethra via a vaginal incision. The two ends of the sling are then secured to the anterior abdominal wall, either together or to the rectus fascia. (Modified from Aldo ME, Richter HE, Brubaker L, et al. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. *N Engl J Med* 2007;356:2143–55.)

associated with a higher risk of cystitis within the first 6 weeks postoperatively, and intermittent self-catheterization increased the risk of cystitis in this group. Complications were associated with surgical factors and not with patient-related factors. The authors concluded that blood loss and operative time were significantly associated with adverse events. Intermittent self-catheterization increased the cystitis rate by 17% and 23% in the Burch and sling groups, respectively.

Kraus and colleagues (2011) reported on changes in urodynamic measures 2 years after Burch colposuspension or autologous sling surgery in a report from this large study (SISTER). They noted that 655 women underwent standard urodynamic studies before and 2 years after Burch or sling surgery. The conclusion reached was that the Burch colposuspension autologous fascial sling procedure was associated with similar decreases in noninstrumental flow rates and that slings were associated with great increase in the detrusor pressure at maximum flow and bladder outlet obstruction index. They concluded that these changes suggested that both procedures were effective in part because of increasing outlet resistance; it was suggested that sling procedures might be more obstructive based on the urodynamic parameters measured.

Richter and colleagues (2012) reviewed patient-related factors associated with long-term urinary continence after Burch colposuspension and pubovaginal fascial sling surgery in a long-term follow-up of SISTER. The follow-up of patients in this study was up to 7 years after surgery. The authors concluded that urinary continence rates decreased during a period of 2 to 7 years postoperatively

from 43% to 13% in the Burch group and from 53% to 27% in the sling group. The baseline factors included in the first multivariate model were age, prior SUI surgery, menopausal state, urge index, assigned surgery, and recruiting site. All of these were independently associated with increased risk of incontinence. In the final multivariate model, included baseline and postoperative factors were Burch surgery, baseline variables of prior urinary incontinence surgery, menopausal state, and postoperative urge index. All of these were significantly associated with a greater risk of recurrent urinary incontinence. The authors concluded that preoperative and postoperative urgency incontinence symptoms, Burch urethropexy, prior SUI surgery, and menopausal status were negatively associated with long-term continence rates. More effective treatment of urgency urinary incontinence in patients who undergo SUI surgery may improve long-term overall continence rates. They concluded that in women followed for a minimum of 5 years after Burch colposuspension or pubovaginal fascial sling, prior SUI surgery, being menopausal without hormone replacement therapy, having undergone a Burch procedure, and increased postoperative urgency incontinence symptoms were significantly associated with long-term incontinence. The final conclusion was that knowledge of risk factors for surgical failure can be used to better inform patients of the likelihood of long-term continence or decreased continence rates to be experienced as a result of the surgery. The suggestion put forward is that overall continence status may be improved by proactive preoperative and postoperative assessment and effective treatment of urgency incontinence.

KEY POINT: RETROPUBIC REPAIR VERSUS PUBOVAGINAL SLING

- It can be reliably concluded that in specialist centers working in a standardized fashion, the autologous fascial sling results in a higher rate of successful treatment of stress incontinence but also greater morbidity than the Burch colposuspension.

Burch Colposuspension versus Marshall-Marchetti-Krantz Procedure versus Paravaginal Repair

In general, comparisons between the MMK and the Burch procedures have yielded similar results. [Jarvis, in his meta-analysis of the literature \(1994b\)](#), noted that overall continence rates were 89.6% and 83.9% for the MMK and the Burch procedures, respectively. When he looked at the effect of prior incontinence surgery, the continence rates were 92.1% and 94% when there was no prior surgery and 84.5% and 84% when there was a history of prior incontinence surgery for the MMK and Burch procedures, respectively. Similarly, [Black and Downs \(1996\)](#), in reviewing five studies (one randomized) that directly compared the MMK procedure with the Burch procedure, found that there was no significant difference in cure rates between the two procedures, although the Burch procedure yielded better results in general. However, they pointed out that overall the studies were of poor quality with small sample sizes.

Two randomized studies that assessed urethral sphincteric function by urethral pressure profilometry had conflicting results. [Quadri's group \(1999\)](#) compared the MMK procedure with the Burch procedure in women with a hypermobile, low-pressure urethra (MUCP <20 cm H₂O) and noted significantly higher subjective and objective 1-year cure rates with the MMK procedure. They used urethroscopy to facilitate MMK suture placement. On the other hand, [Colombo's group \(1994\)](#) excluded women with a low-pressure urethra (MUCP <30 cm H₂O) and performed a cystotomy to facilitate MMK suture placement. With 2- to 7-year follow-up (mean, 3 years), they noted higher subjective and objective cure rates with the Burch procedure, although these were not statistically significant. In addition, significantly more MMK patients had persistent postoperative voiding difficulties (28% vs. 8%).

The literature on the paravaginal repair is sparse. The only randomized study that compared the Burch procedure with a paravaginal repair found significantly greater subjective and objective cure with the Burch procedure ([Colombo et al, 1996a](#)). Until large, randomized studies with prolonged follow-up are available, the issue of which is the best procedure will remain unresolved.

Tension-Free Vaginal Tape Procedure versus Colposuspension

Since its introduction in 1996 by Ulmsten, the TVT procedure has gained widespread acceptance for treatment of SUI, given its low morbidity, short-term success rates, and ability to be performed as an outpatient procedure with use of a local or regional anesthetic ([Ulmsten et al, 1996](#)). The 7-year objective and subjective success rate for TVT is 81% ([Nilsson et al, 2004](#)). In a more recent review of this series, 77% of the initial cohort of 90 women and 89% of those alive and capable of cooperating were assessed 11.5 years after the TVT operation. Ninety percent of the women had both negative stress test and negative pad test results and were considered to be objectively cured. Subjective cure by patients' global impression was found in 77%, 20% being improved, and only 3% regarded the operation as a failure. No late-onset adverse effects of the operation were found, and no case of tape erosion was seen ([Nilsson et al, 2008](#)).

There have been a number of well-designed, prospective, randomized trials comparing the Burch colposuspension (two open and two laparoscopic) with TVT.

[Liapis and coworkers \(2002\)](#) reported a prospective randomized comparative study of Burch colposuspension (n = 35) and TVT (n = 36). They concluded that at 2-year follow-up, the TVT and Burch procedures were equally effective with an objective pad test cure rate of 84% and 86%, respectively. TVT had a shorter operative time and entailed less postoperative pain with a faster return to normal activity.

[Ward and Hilton \(2004\)](#) published a 2-year follow-up of their landmark prospective randomized trial comparing TVT and OBC. At 2 years, 74% of the initial TVT and 69% of the open colposuspension patients completed the evaluation. The objective cure rates for the TVT (81%) and colposuspension (80%) were not significantly different. However, if the missing patients were evaluated by the last observation carried forward analysis, the cure rates would favor TVT (78% vs. 68%). It is interesting that the subjective cure rates differ from the objective rates dramatically, with only 43% and 37% reporting subjective cure of stress incontinence after TVT and colposuspension, respectively. At 2 years, the colposuspension group still had significantly lower scores on mental and emotional health. The incidences of enterocele and vault prolapse were higher in the colposuspension group, requiring significantly more prolapse surgery. Likewise, the number of patients still requiring intermittent catheterization was higher in the colposuspension group. The intra-operative complications were higher in the TVT group, whereas the postoperative complications were higher in the colposuspension group. The authors' conclusion at 2 years, because of patients lost to follow-up, was unchanged from their conclusion at 6 months, namely, that TVT may be better than, worse than, or the same as colposuspension.

A Cochrane review of open colposuspension examined a total of seven trials comparing TVT with open colposuspension ([Lapitan et al, 2005](#)), although the trial by Ward and Hilton noted earlier dominated the analysis. The review concluded that TVT and open colposuspension were equally effective but that TVT carried an increased risk of complications, particularly bladder perforation. A further cost-benefit analysis based on the Ward and Hilton study showed that TVT was a cost-effective alternative to colposuspension, largely based on shorter hospital stay and rapid return to work ([Manca et al, 2003](#)).

In a further report from the Ward and Hilton study, 98 of those who had TVT and 79 of those who had colposuspension returned for 5-year follow-up; 72 in the TVT group and 49 in the colposuspension group had full subjective and objective data ([Ward et al, 2008](#)). The primary outcome in this analysis was a negative 1-hour pad test result, and this was not significantly different between the two groups: 58 of 72 (81%) women in the TVT group and 44 of 49 (90%) in the colposuspension group ($P = .021$, Fisher's exact test) at 5 years. Significantly, more women in the colposuspension group (11 [7.5%]) underwent surgery for prolapse during the follow-up period than those in the TVT group (3 [1.8%]). Tape-related complications were seen in 6 women. In the first year, one tape was divided for obstructed voiding; there was one suprapubic extrusion and one vaginal erosion. Two further vaginal erosions were detected at 5-year follow-up, and in addition, 1 woman was found to have tape within the bladder at cystoscopy after complaining of overactive bladder symptoms. There were no reported suture-related complications in the colposuspension group.

[Persson and coworkers \(2002\)](#) were one of the first groups to compare TVT and laparoscopic Burch colposuspension. At 1-year follow-up, there was no difference between objective and subjective cure rates. [Valpas and associates \(2004\)](#) conducted a prospective randomized trial comparing TVT and laparoscopic mesh colposuspension at 1-year follow-up. The objective cure rate (negative stress test result, 86% vs. 57%), satisfaction, and quality of life were statistically better for the TVT group.

[Paraiso and colleagues \(2004\)](#) prospectively randomized 72 patients into laparoscopic Burch colposuspension and TVT at a mean follow-up of 20 months, but only 17 and 16 patients were

KEY POINTS: LONG-TERM EFFICACY OF TENSION-FREE VAGINAL TAPE AND COLPOSUSPENSION

- The effect of both procedures on cure of incontinence and improvement in quality of life appears from this follow-up of a portion of the originally treated patients to be maintained in the long term out to 5 years (Ward et al, 2008). Eight-one percent of the women who had undergone TVT and 90% who had undergone colposuspension regarded themselves as satisfied or very satisfied with the results of their surgery at 5 years.
- The key messages in terms of adverse events are that vault and posterior vaginal wall prolapse are seen more commonly after colposuspension and that late tape erosion may occur several years after surgery.

available in the laparoscopic and TVT groups, respectively. Whereas objective and subjective cure rates were significantly higher in the TVT group, satisfaction of patients was equal in each group, and no difference was reported in voiding dysfunction, urgency, or symptomatic pelvic prolapse. All these laparoscopic studies require longer follow-up with greater power to demonstrate a persistent difference between TVT and Burch colposuspension.

A meta-analysis of the literature has been reported by Novara and colleagues wherein they combined the results of open and laparoscopic colposuspension (Novara et al, 2007). To date, nine RCTs have compared TVT with Burch colposuspension as primary

treatment for SUI (Liapis et al, 2002; Persson et al, 2002; Ward and Hilton, 2002; Ustün et al, 2003; Paraíso et al, 2004; Valpas et al, 2004; Ward et al, 2004; Bai et al, 2005; El-Barky et al, 2005). A further study compared Suprapubic Arc Sling (SPARC; American Medical Systems, Minnetonka, MN) with laparoscopic Burch colposuspension (Foote et al, 2006). TVT was followed by significantly higher continence rates compared with Burch colposuspension, considering success rates evaluated according to any definition of continence (OR 0.58, 95% CI OR 0.42 to 0.79, $P = .0007$), presence of negative stress test result (OR 0.38, 95% CI OR 0.25 to 0.57, $P < .0001$), and negative pad test result (OR 0.59, 95% CI OR 0.41 to 0.85, $P = .005$).

A study has contrasted direct health care costs of treatment for SUI in Sweden with four different procedures: (1) OBC; (2) laparoscopic colposuspension with sutures (LCS); (3) laparoscopic colposuspension with mesh and staples (LCM), and (4) TVT (Ankardal et al, 2007). A model was constructed representing a hospital with standardized surgical equipment, staff, and average unit costs in 2003 euros. The time used for anesthesia and surgery was calculated. Clinical data were collected from three different sources: a multicenter, randomized, prospective study comparing OBC with LCM with 1-year follow-up; a three-armed prospective study in which women were randomized to OBC, LCM, or LCS with 1-year follow-up; and a descriptive study reporting results of TVT with 5-year follow-up. Data collected from the studies and hospital cost data were put into the model to create the different cost elements. The total cost per individual showed a lower cost for TVT compared with the other alternatives. The direct costs for TVT were only 56% of the costs for OBC ($P < .001$) and 59% of the costs for LCS

KEY POINTS: RETROPUBIC SUSPENSION SURGERY FOR INCONTINENCE

- Anti-incontinence surgery does not necessarily work by restoring the same mechanism of continence that was present before the onset of incontinence. It works by a compensatory approach.
- The surgeon's preference, coexisting problems, and anatomic features of the patient and her general health condition influence the choice of procedure.
- There is lack of a clear consensus as to which surgical procedure for stress incontinence is most effective, but contemporary practice is shifting to the "loose" urethral sling being the most widely used and having largely replaced the colposuspension.
- A number of variables may influence surgical outcome: age, postoperative activity, medical comorbidity, obesity, duration of symptoms, coexistence of detrusor overactivity, prior surgery, and intrinsic sphincter deficiency.
- There is no consensus on how to differentiate the relative contributions of hypermobility and sphincteric weakness.
- There remains no consensus on how to assess the outcomes of surgery, but this requires careful assessment with adequate follow-up and use of simple objective measures as well as taking particular account of patient-perceived outcomes.
- During short-term follow-up, vaginal and open retropubic suspension procedures have similar success rates. With longer follow-up (and with the exception of the pubovaginal sling), patients who have retropubic procedures fare better.
- With the MMK procedure, placement of sutures through the pubic symphysis incurs the risk of osteitis pubis in 0.9% to 3.2% of patients.
- Burch colposuspension is as effective as any other procedure in primary or secondary surgery at curing SUI, with proven long-term success. Thus it should be regarded as the *standard* open retropubic procedure for incontinence.
- Abdominal paravaginal repair is less effective than other forms of colposuspension.
- As with any major abdominal or pelvic surgical procedure, intraoperative and perioperative complications that may occur after a retropubic suspension include bleeding, injury to genitourinary organs (bladder, urethra, ureter), pulmonary atelectasis and infection, wound infection or dehiscence, abscess formation, and venous thrombosis or embolism. Other common complications more specific to retropubic suspension procedures include postoperative voiding difficulty, detrusor overactivity, and vaginal prolapse.
- The risk of temporary urinary retention lasting more than 4 weeks postoperatively is 5% for all retropubic suspensions. The risk of permanent retention is estimated to be less than 5%. These risks are not significantly different from those of needle suspensions or pubovaginal slings.
- All patients should be counseled before surgery about the potential need for intermittent self-catheterization.
- Because retropubic suspensions are unable to correct central defect cystoceles, patients must be carefully examined preoperatively to exclude their presence. The Burch procedure, because of lateral vaginal elevation, may aggravate posterior vaginal wall weakness, predisposing to enterocele.
- Retropubic suspensions are more effective than either needle suspensions or anterior colporrhaphies.
- Laparoscopic colposuspension is not recommended as a routine surgical procedure and when performed should be carried out only by a surgeon skilled in laparoscopic surgery.
- Most studies in the literature have not demonstrated a significant difference in cure rates between retropubic suspensions (usually a Burch procedure) and pubovaginal slings.
- Comparisons between the MMK procedure and the Burch procedure have yielded similar results in general.
- The literature on the paravaginal repair is sparse. The only randomized study that compared the Burch procedure with a paravaginal repair found significantly greater subjective and objective cure rates with the Burch procedure.
- At this time, the TVT procedure appears to be at least equivalent to the Burch colposuspension, and in general is probably better.

($P < .001$). It was concluded that with use of a model and in comparing health care costs for surgical treatment of female SUI in Sweden, the TVT procedure generated a lower direct cost than both open and laparoscopic colposuspension.

The shift in practice pattern away from Burch colposuspension for the treatment of SUI to mid-urethral slings as the primary treatment of SUI shows one of the difficulties in conducting surgical RCTs, especially when the field has changed as quickly as it has in recent years in the treatment of urinary incontinence. A recent survey of urogynecology fellows found that the average third-year fellow had performed 257 mid-urethral sling procedures and only 13 Burch procedures (LeBrun et al, 2008). It would be interesting to determine if surgeon's experience with Burch colposuspension is correlated with outcomes. Indeed, the outcomes reported in the existing literature base are likely to be very different from those seen in many clinicians' clinical practices, where this has become a rare operation and where many have had very limited experience of carrying out the procedure during their training over the last decade.

A 10-year follow-up study reached the conclusion that TVT is more cost-effective than Burch colposuspension in the treatment of female SUI (Laudano et al, 2013). The conclusion reached was that both the cost and the effectiveness of TVT affected the cost-effectiveness analysis. The major criticism of any such study is that it does not take account of potential complications, which are never adequately considered in any such study, bearing in mind the potential publication bias in the literature toward best practice from specialized centers and the concern that the complications seen in real-life practice may not be reflected in the published literature. Nevertheless, this is a well-conducted study and does provide clear evidence that TVT is a cost-effective alternative.

At this time, TVT appears to be an equivalent operation to the open or laparoscopic Burch colposuspension. Although a meta-analysis (Novara et al, 2007) suggested superiority of TVT, this analysis combined open and laparoscopic procedures and studies of variable quality. It is likely that single high-quality comparative studies have greater reliability (Ward and Hilton, 2004, 2008). TVT or transobturator tape (TOT) procedures have now largely supplanted colposuspension in contemporary practice. An open colposuspension should still be considered as a surgical option in patients undergoing open surgery and still has a role when

there is associated prolapse. Laparoscopic colposuspension has been shown in the short term to have some advantages over open colposuspension in experienced hands, but as a procedure has largely been supplanted by TVT or TOT in contemporary practice. Having noted the evidence for this, there is currently considerable concern over the potential risk of "exposure" of synthetic slings noted to occur in up to 5% in the Ward and Hilton study (Jones et al, 2010). It is essential to counsel patients accordingly, and there may be a change in practice toward autologous sling material and colposuspension in the future.

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The complete reference list is available online at www.expertconsult.com.



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Surgical Anatomy of the Pelvic Floor

Site-Specific Defects by Compartment (Identification)

Preparing the Patient for Prolapse Surgery

Biologic and Synthetic Materials in Prolapse Surgery

Surgical Management of Pelvic Organ Prolapse

Surgical treatment of pelvic organ prolapse (POP) is one of the most challenging problems faced by pelvic floor surgeons. The cause is usually multifactorial; the clinical presentation and impact on the patient's quality of life (QoL) may vary considerably. Surgical correction is aimed at addressing defects in the supporting structures, which requires a comprehensive understanding of pelvic floor anatomy and function. Pelvic floor defects have been traditionally named for the prolapsing visceral organs; however, it is important to conceptualize that these disorders have less to do with the prolapsing organs and more to do with compartmental defects in the supportive tissues. Just as any hernia represents a defect in the fascia, POP represents herniations or descensus of the bladder, rectum, bowel, uterus, and urethra through defects in the pelvic floor connective tissues. Procedures must be tailored to the patient's unique presenting factors, such as comorbidities and concomitant pathology of the pelvic floor, as well as patient goals and expectations in surgical restoration of pelvic organ support. The aim of this chapter is to provide a practical overview of the surgical anatomy and discuss the vaginal and abdominal (open and laparoscopic or robotic) techniques for the treatment of POP.

Pelvic organ defects occur as compartmental defects of vaginal support. Patients may have any combination of compartmental defects, and multiple defects are very common. **The aims of surgical management include restoration of normal vaginal anatomy while maintaining and potentially restoring visceral and sexual function.** It is critical to understand the patient's goals and expectations of treatment to ensure that the prescribed treatment will meet these goals. This is the art of tailoring the appropriate treatment for each individual surgical patient.

SURGICAL ANATOMY OF THE PELVIC FLOOR

Anatomy

Supporting Structures

Bony Scaffolding. The bones of the pelvis provide the scaffold on which the soft-tissue supports (muscles, ligaments, and fascia) are anchored. It consists of paired innominate bones on both sides of the sacrum. These three bones comprise the pelvic girdle. The innominate bones are further divided into the ilium, the ischium, and the pubis. The ischial spine provides attachment for the arcus tendineus fasciae pelvis (ATFP), the sacrospinous ligament (SSL), and the coccygeus muscle (Fig. 83-1). The obturator foramen is

formed by the superior pubic ramus above, the pubic body and inferior ramus medially, and the anterior border of the ischial body below (Newell et al, 2005).

Muscular Supports of Pelvic Floor. The pelvic floor consists of all the soft tissues that essentially hold the pelvic viscera in place, including the muscular support, the fascial and ligamentous support, and the connective tissues. The pelvic floor is a three-dimensional structure that functions as a unit (Hurt, 2000). The pelvic diaphragm is composed of the levator ani muscles (which include the striated pubococcygeus and iliococcygeus muscles) and coccygeus muscles (Fig. 83-2). The coccygeus is also termed the *ischiococcygeus muscle* and is attached medially to the lateral margins of the coccyx and fifth sacral segment (Mundy, 2005) and laterally to the ischial spine. The iliococcygeus is attached to the ischial spine and the arcus tendineus levator ani laterally and the tip of the sacrum and coccyx posteriorly. The pubococcygeus is attached to the back of the pubis, and it courses lateral to the urethra (in males it is called the *pubourethralis*, and in females, because it forms a sling around the vagina, it is termed the *pubovaginalis*). In both men and women, fibers of the pubococcygeus attach to the perineal body (Mundy, 2005). The pubococcygeus compresses the visceral canals, which cross the pelvic floor. The puborectalis portion of the pubococcygeus helps to create the anorectal angle. Contraction of the puborectalis causes the rectoanal junction to move toward the pubic symphysis, which is critical in maintaining fecal continence (Rogers, 2003). **Although the muscles are referred to separately, like other structures of the pelvic floor, the boundaries are often difficult to delineate and they perform similar physiologic functions (Mundy, 2005).** The posterior levator ani group (iliococcygeus, pubococcygeus, and puborectalis muscles) fuses in the midline and attaches to the coccyx. The complex formed by this fusion is the levator plate, which serves as a supporting structure for the upper vagina and cervix. This not only serves to stabilize the upper vagina in a horizontal plane, but it also provides a protective mechanism preventing downward forces onto the perineal body (Wall and Menafee, 2002).

Beneath the pelvic diaphragm is the diamond-shaped urogenital diaphragm (Fig. 83-3). The boundaries are the pubic symphysis anteriorly, the tip of the coccyx posteriorly and laterally, and the ischiopubic rami on either side. It can be further divided anteriorly and posteriorly by imagining a line between the ischial tuberosities. This results in the urogenital triangle anteriorly and the anorectal triangle posteriorly. The deep transversus perinei muscle, also termed the *perineal membrane*, is contained by the urogenital triangle, in

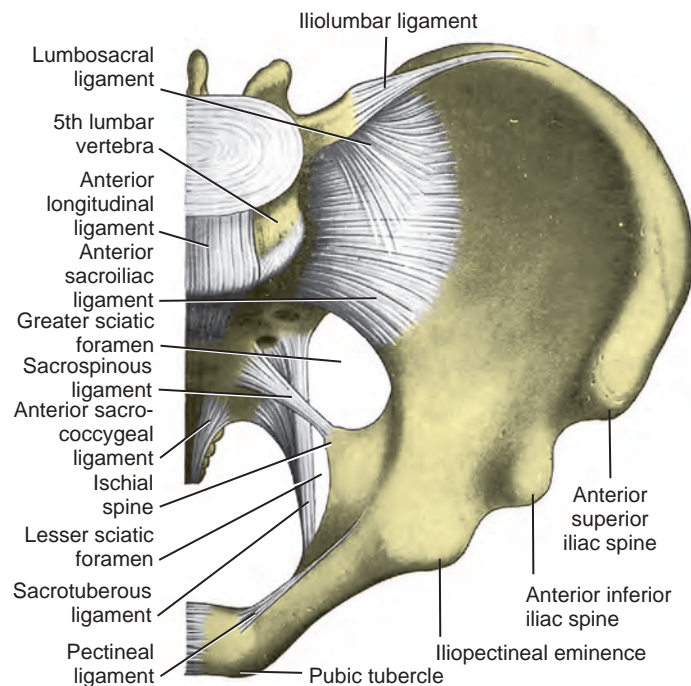


Figure 83-1. Left hemipelvis demonstrating the sacrospinous ligament, the greater sciatic foramen above, the lesser sciatic foramen below, and the sacrotuberous ligament. (From Newell R. Pelvic girdle, gluteal region and hip joint. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 39th ed. New York: Elsevier; 2005.)

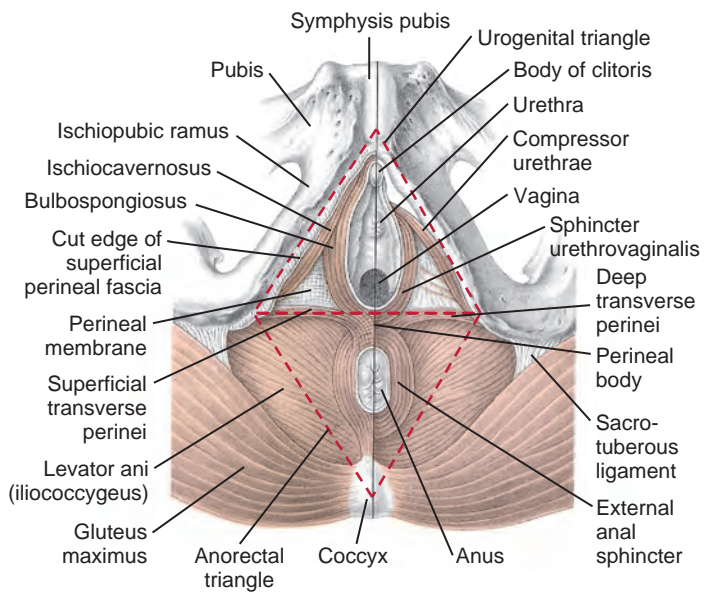


Figure 83-3. Muscles of the female perineum. The cut edge on the right side is the cut edge of the superficial fascia that has been removed. The left side depicts the deep perineal muscles (as seen without the superficial perineal muscles and overlying fascia). (From Mundy A. True pelvis, pelvic floor and perineum. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 39th ed. New York: Elsevier; 2005.)

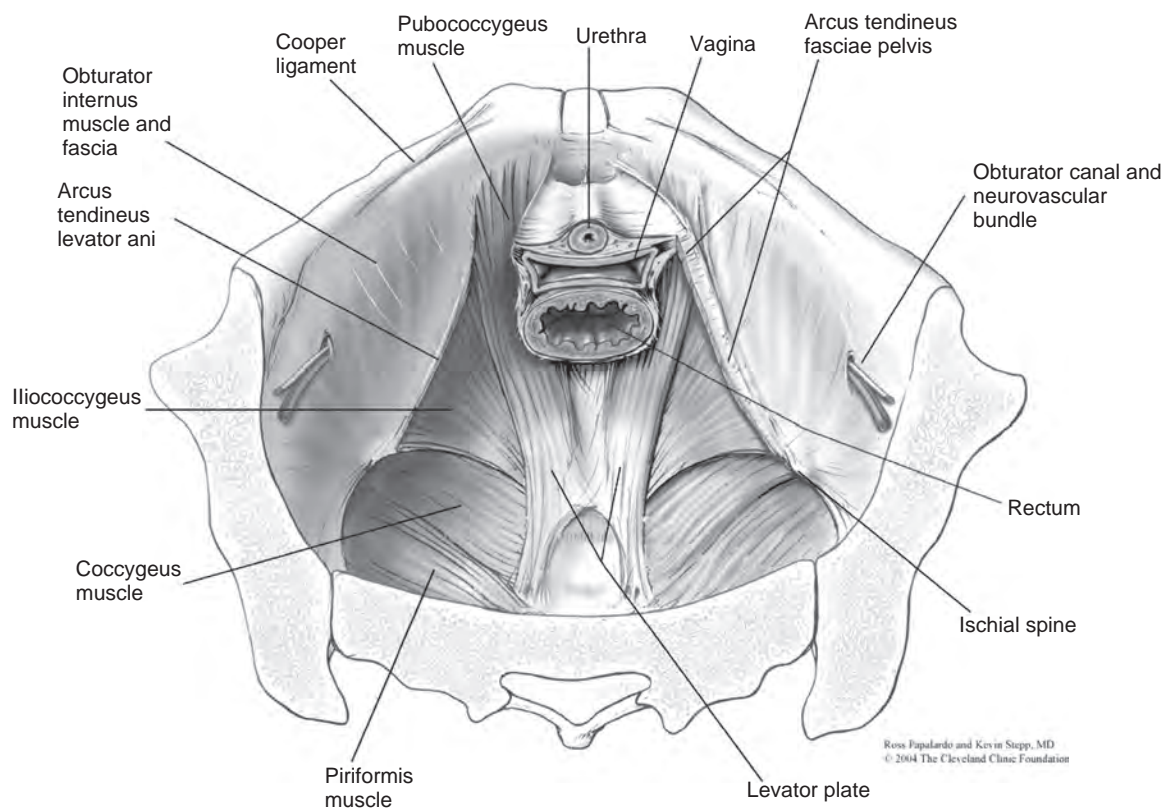


Figure 83-2. Muscles of the female pelvic diaphragm. (From Walters M, Karram M. Urogynecology and reconstructive pelvic surgery. 3rd ed. Philadelphia: Mosby; 2006.)

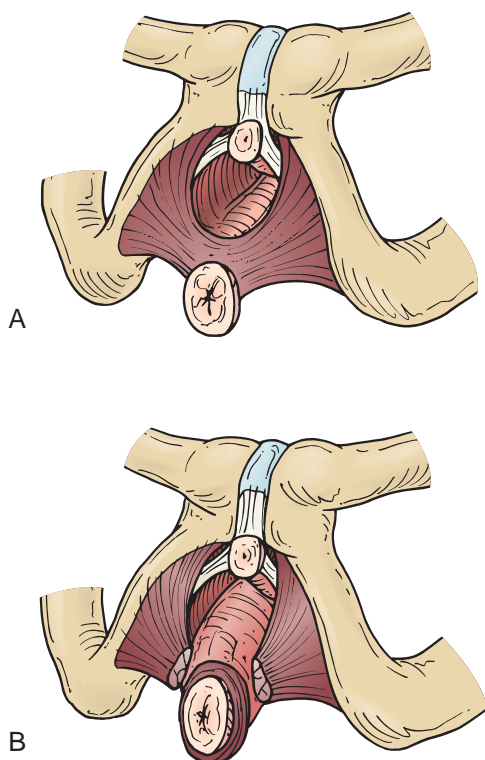


Figure 83-4. A and B, Perineal membrane. The two halves of this triangular sheet of fibromuscular connective tissue form a central tendon referred to as the *perineal body*. (Redrawn from DeLancey JO. Structural anatomy of the posterior pelvic compartment as it relates to rectocele. *Am J Obstet Gynecol* 1999;180:815–23.)

which the urethra and vagina traverse. In contrast to the perineal membrane in males, which is a sheetlike structure, the perineal membrane in females is a three-dimensional structure that has two regions, dorsal and ventral (Stein and DeLancey, 2008) (Fig. 83-4). The dorsal region is attached to the perineal body and the lateral wall of the vagina via the ischiopubic rami. The ventral region is part of a solid three-dimensional mass, which is contiguous with the paraurethral and paravaginal connective tissues. This portion contains the compressor urethrae and urethrovaginal sphincter muscles of the distal urethra (Stein and DeLancey, 2008).

The anorectal triangle contains the external anal sphincter, which attaches to the anococcygeal ligament and fuses to the superficial transversus muscle. External to the urogenital triangle are the external genital muscles, bulbospongiosus, ischiopubic rami, and superficial transversus perinei. The hymen is located just inside of the labia minora and is the fixed point of reference recommended by the International Continence Society Committee on Standardisation of Terminology, Sub-Committee on Pelvic Organ Prolapse and Pelvic Floor Dysfunction to grade prolapse (Bump et al, 1996). This is in contrast to the term *introitus*, which is ill defined.

The urogenital hiatus is the opening within the levator ani muscle through which the urethra and vagina pass. Because the rectum is attached directly to the muscles at this level, it is not within the urogenital hiatus. The hiatus is supported anteriorly by the pubic bones and levator ani muscles and posteriorly by the perineal body and external anal sphincter (Ashton-Miller and DeLancey, 2007). The urogenital hiatus elongates and descends with POP.

Endopelvic Fascia and Connective Tissue Supports. The endopelvic fascia is a network of fibromuscular tissue located between the peritoneum and the levator muscles. It surrounds and attaches the bladder, uterus, vagina, and rectum to the pelvic walls, thereby

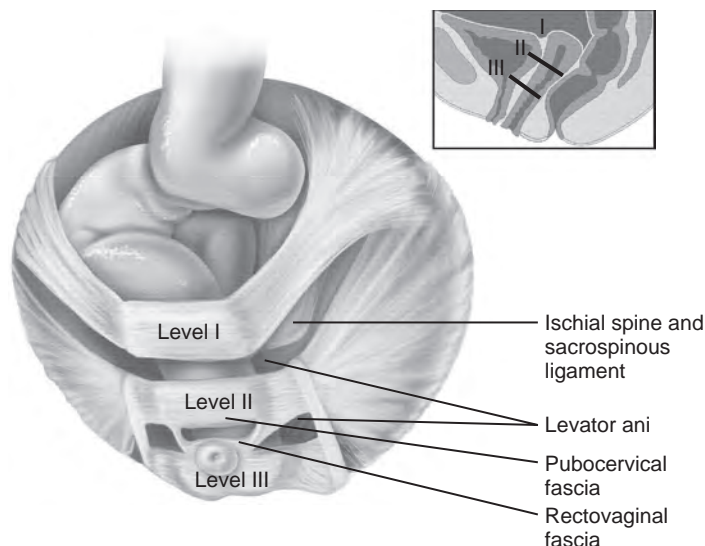


Figure 83-5. Vaginal and visceral supportive structures as defined by DeLancey. The fibers of level I support are oriented vertically and suspend the uterus and upper vagina. Level II support is more horizontal in its orientation and attached to the midvagina. Distally, level III support fuses directly into the support structures. (From DeLancey JO. Anatomic aspects of vaginal eversion after hysterectomy. *Am J Obstet Gynecol* 1992;166:1717–28.)

stabilizing the pelvic viscera. The endopelvic fascia is one continuous unit; however, distinct areas are named separately. The parametrium (broad, cardinal, and uterosacral ligaments) attach the uterus and upper vagina to the pelvic sidewall. The paracolpium (the arcus tendineus levator ani and the ATFP) attach the vagina to the pelvic sidewalls. In his landmark article, DeLancey (1992) described the supports of the vagina and conceptually divided them into three parts according to the region of vaginal support (Fig. 83-5). The structures supporting the uterus and cephalad 2 to 3 cm of the vagina comprise level I support, and these fibers originate from the greater sciatic foramen, the sacroiliac region, and lateral sacrum. The fibers are primarily vertical in their orientation and are the longest fibers of the endopelvic fascia, thereby suspending the uterus and upper vagina, and comprise the cardinal-uterosacral ligament complex. Level II support is at the midvagina. These fibers are shorter than level I support but longer than those at level III. The orientation of the attaching fibers is lateral, and they are denser than the cardinal-uterosacral complex. The endopelvic fascia splits at this level to encompass the bladder and urethra such that the abdominal leaf is still named the *endopelvic fascia* and the vaginal leaf is termed the *pubocervical* (or *perivesical*) and *periurethral fascia*. Posteriorly, the endopelvic fascia, which attaches laterally to the superior fascia of the levator ani muscles, is the *rectovaginal fascia*. Level III support of the vagina starts at the introitus and extends 2 to 3 cm above the hymenal ring. In this most distal location there is no intervening paracolpium and the vagina is fused directly to the urethra and is embedded in the connective tissue of the perineal membrane (urogenital diaphragm.) Laterally, it blends into the medial margins of the levator ani muscles, and posteriorly it blends into the perineal body.

The endopelvic fascia is a composite of tissues of fibers embedded in a matrix. The variability of this tissue matrix may lead to its inherent weakness and inconsistency in reconstructive surgery. In fact, fresh strips of pubocervical fascia have been shown to shorten 15% to 20% of their length (Richardson and DeLancey, 2000). Thus, these tissues are supportive and contractile. Histologically, this tissue is unlike abdominal wall fascia or the fascial coverings of other muscles in that they lack the organization of the fascial coverings of the skeletal muscle.

Support by Compartment

Anterior Compartment Supports. Because the urethra is fused to the anterior vaginal wall for much of its length, the supporting structures of the urethra and distal anterior vagina are one and the same. The major components are the endopelvic fascia (periurethral and pubocervical or perivesical fascia), the ATRF, and the levator ani muscles (Ashton-Miller and DeLancey, 2007). At this level, the endopelvic fascia surrounds the vagina and attaches to the ATRF bilaterally. Each ATRF stretches from the inner aspect of the ischial spine across the belly of the obturator internus muscle and terminates at the lower margin of the posterior pubic bone. This structure appears as a band closer to the pubic bone and, as it courses toward the ischial spine, fans out into a broad aponeurotic structure. Laterally it merges with the levator ani muscles at the confluence of the iliococcygeus and obturator internus muscles.

Apical (Middle) Compartment Supports. This support is provided by the cardinal-uterosacral ligament complex, level I supports as described by DeLancey (1992). They originate from fibers of the pelvic sidewall and extend to the area around the greater sciatic foramen, and to the second, third, and fourth sacral segments. From here, they fan out as they attach to the cervix and the upper vagina. The medial edge of this complex is the area of the uterosacral ligaments. The uterosacral ligaments are visible and palpable with traction of the cervix or the cuff of the vagina after hysterectomy. The fibers encircle the cervix and in aggregate are called the pericervical ring.

Posterior Compartment Supports. The rectovaginal fascia is also sometimes referred to as the *Denonvilliers fascia* in the female (Richardson and DeLancey, 2000). It has denser strands of elastin and less smooth muscle compared with the pubocervical fascia. It is stabilized in the upper vagina by the cardinal-uterosacral complex, as it is contiguous with this structure. The uterosacral ligament inserts into the rectovaginal fascia just below the attachment to the posterior cervix. Because the rectovaginal fascia is connected to the sacrum and the perineal body, it provides continuous posterior support.

The perineal body is a condensation of fibromuscular tissue and collagen, which is located in the midline between the vagina and the anus. It serves as a point of fixation for the rectovaginal fascia, the levator ani muscles, the transversus perinei muscles, and the external anal sphincter (Rosenblum et al, 2005).

Pathophysiology of Pelvic Organ Prolapse: Surgical Correlation

The levator ani muscles are composed of both type I and type II muscle fibers. Type I muscle fibers are slow-twitch fibers and provide sustained tonicity of the pelvic floor. This function serves a crucial role in providing dynamic pelvic floor support, thus taking the mechanical stress off of the endopelvic connective tissue attachments. Type II fibers are fast-twitch fibers that are mainly responsible for the reflex contractions of the pelvic floor associated with sudden increases in intra-abdominal pressure. Thus, the levator ani muscle complex fulfills multiple functions. First, the tonic contraction of the pubococcygeus muscle narrows the genital hiatus. Second, contraction of the pelvic floor leads to the elongation and elevation of the pelvic organs facilitating urinary and fecal continence. In addition, posterior levator ani tonicity elevates the upper vagina and stabilizes it into a horizontal plane near the hollow of the sacrum (Fig. 83-6) (Wall and Menafee, 2002). Direct muscular damage, neuromuscular dysfunction, and inherent tissue defects may predispose to a dysfunction of the levator ani musculature. As a result, the burden of support shifts mostly to the endopelvic connective tissues. As these structures weaken, various “breaks” occur that lead to vaginal support defects.

It is most useful to define defects by compartment while keeping in mind that many patients have multicompartments defects. In addition, some patients will have several defects within the same compartment.

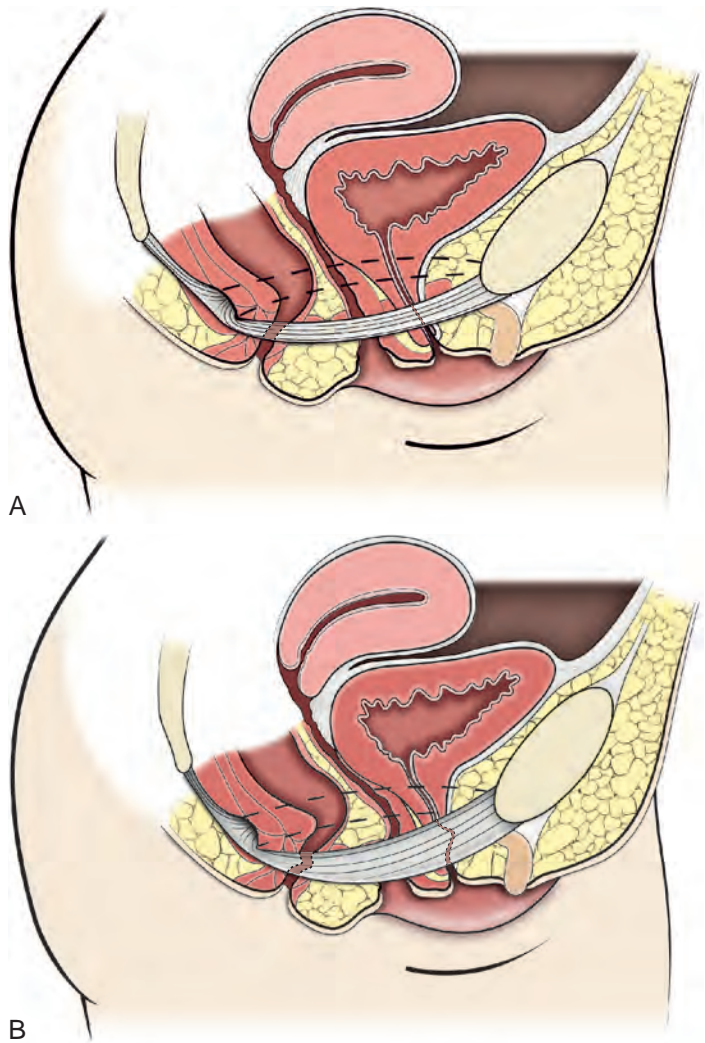


Figure 83-6. Function of the levator ani. The tonic contraction of the pubococcygeus muscle narrows the genital hiatus and leads to elongation and elevation of the pelvic organs, facilitating continence (A, at rest; B, contracted). The posterior levator ani elevates the upper vagina and stabilize it on the levator plate, which provides a supportive role to the perineal body.

SITE-SPECIFIC DEFECTS BY COMPARTMENT (IDENTIFICATION)

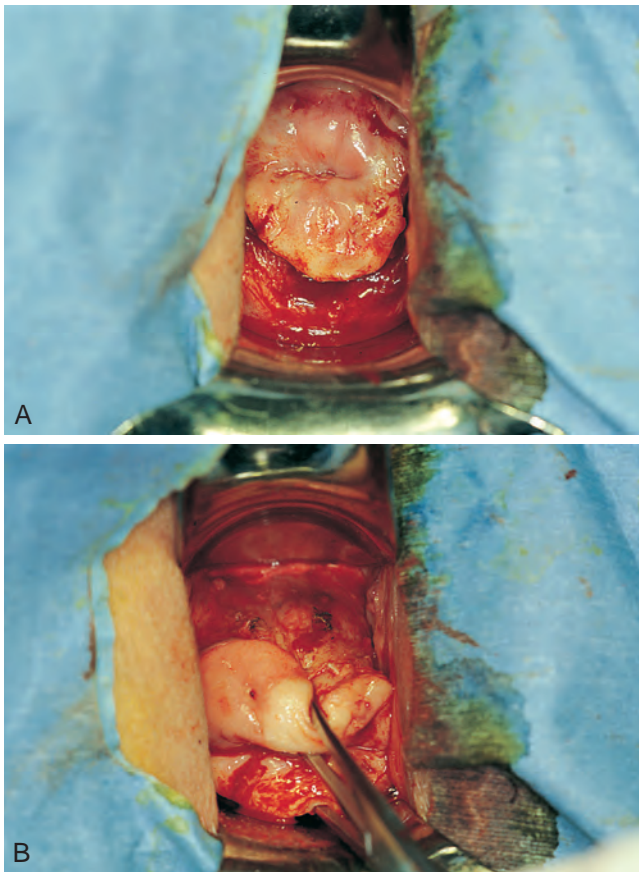
See Table 83-1.

Anterior Compartment

Within the anterior compartment, two types of defects can lead to cystoceles. The **central cystocele** results from attenuation or separation of the pubocervical fascia, resulting in a protrusion of anterior compartment structures through this defect. This protrusion results in the classic appearance of a loss of the rugae or vaginal folds of the anterior vaginal wall. Detachment of the pubocervical fascia and the pubourethral ligaments to the ATRF results in a **lateral cystocele** and can also involve the urethra. This usually results in a preservation of the rugal folds of the vaginal wall, and a “rotational” prolapse of the anterior wall (Fig. 83-7). **Urethroceles**, which are distal anterior compartment defects, usually result in urethral hypermobility (Weber and Walters, 1997).

TABLE 83-1 Compartmental Anatomy: Pelvic Organ Prolapse Quantification System (POP-Q) Sites and Organ Involvement

COMPARTMENT	POP-Q SITE	PROLAPSED ORGAN	VAGINAL WALL SITE
Anterior compartment	Aa	Urethrocele	Distal anterior vaginal wall
	Ab	Cystocele	Proximal anterior vaginal wall
Middle compartment	C	Cervix	Cervix
	D	Vaginal cuff	Vaginal cuff
		Enterocele	Uterosacral scar
Posterior compartment	Ap	Enterocele	Proximal posterior vaginal wall
	Bp	Rectocele	Distal posterior vaginal wall
		Perineal body defects	Perineal body

**Figure 83-7.** Cystoceles. Note the appearance of central and lateral defects. (From Baggish M, Karram M. *Atlas of pelvic anatomy and gynecologic surgery*. 3rd ed. Philadelphia: Saunders; 2010.)

Apical Compartment

Apical compartment defects involve a disruption in the uterosacral-cardinal ligament complex. This defect may lead to prolapse of the uterus, the vaginal cuff after hysterectomy, and the peritoneum cul-de-sac with or without bowel (enterocele). Enterocèles are most commonly associated with apical or high posterior compartment defects; however, enterocèles may rarely occur anteriorly. Enterocèles can occur with or without vaginal vault prolapse. Complete vaginal vault prolapse contains an enterocele in 75% of patients. Waters described four types of enterocèles by cause: congenital, pulsion, traction, and iatrogenic (Waters, 1956). Congenital enterocèles occur either from the failure of the peritoneum to fuse with the perineal body or from reopening of previously

fused structures. Pulsion defects occur with increased intra-abdominal pressures, and traction enterocèles occur by a pulling of the vaginal epithelium from other prolapsing organs. Iatrogenic enterocèles are created when a surgical procedure is performed that alters the normal vaginal axis or when the pubocervical fascia and the rectovaginal septum are not reapproximated after hysterectomy (Wiskind et al, 1992).

Uterine prolapse occurs with loss of support of the cardinal and uterosacral ligaments. The broad ligaments also provide uterine support and are located above insertion of the cardinal uterosacral ligaments. They are located within the leaves of the anterior and posterior peritoneum. Within this fused structure are the fallopian tubes and the round and ovarian ligaments along with their blood supply (Rosenblum et al, 2005). It is difficult to differentiate other prolapsing organs with loss of apical support high in the vagina. Accordingly, careful dissection is often needed to identify other prolapsing organs with uterine prolapse. This reinforces the concept that the endopelvic fascia is best considered as a contiguous unit that can fail together. Consequently, the bladder, small bowel, and rectum are often found prolapsing with the uterus.

Vaginal vault prolapse can occur after hysterectomy if support of the vault is not reconstituted by suspending it to the cardinal uterosacral ligament complex. Incidence of vaginal vault prolapse after hysterectomy has been reported to be as high as 18.2%, and it can contribute to prolapse in other compartments (Richter, 1982). Because of the redundancy of the support by the endopelvic fascia, failure to reattach the suspensory component does not lead to immediate vaginal eversion after hysterectomy (DeLancey, 1992). Complex vaginal eversion is vaginal eversion associated with cystocele, rectocele, or both (DeLancey, 1992). Complex vaginal eversion has been reported as high as 67% of vault prolapse (Morley and DeLancey, 1988). In this group of patients, 7% had apical prolapse and cystocele, 30% had apical prolapse with rectocele, and 30% had apical prolapse with both cystocele and rectocele.

Posterior Compartment

The posterior vaginal compartment is composed of the peritoneum of the cul-de-sac, the rectum, and the perineum. Defects in the rectovaginal fascia in the form of either attenuated fascia or site-specific tears will result in herniation of the rectum and sometimes the small bowel into the vagina. Rectocèles may be divided into low, midvaginal, or high depending on the location of loss of support, and they may occur with a combination of defects. Richardson was the first to describe site-specific defects of the rectovaginal fascia, in 1993 (Richardson, 1993) (Fig. 83-8). Defects in the cardinal-uterosacral ligament complex can result in high rectocèles and can involve enterocèles. Enterocèles are estimated to be present in 0.1% to 16% of women undergoing surgery for POP (Chou et al, 2000). Loss of support in the midvagina from the lateral attachments to the arcus tendineus fascia rectovaginalis will result in a bulging in the midportion of the posterior compartment. The



Figure 83-8. Locations where breaks in the rectovaginal septum have been observed in patients with posterior defects.

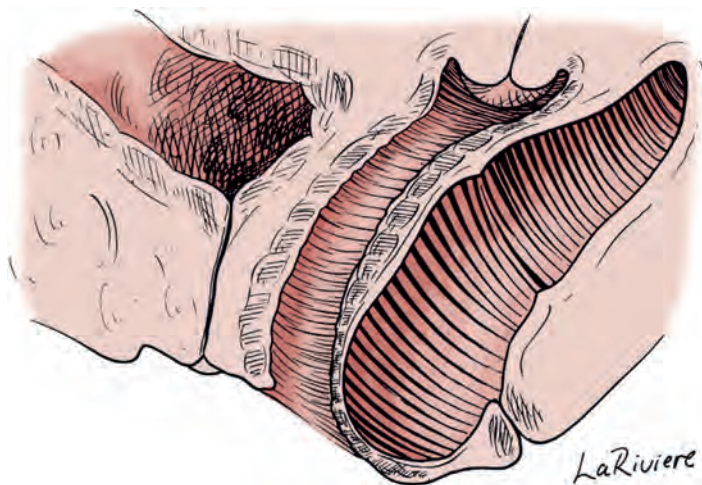


Figure 83-9. Large rectocele with perineal body defect. (From Nichols DH. Rectocele and perineal defect. In: Nichols DH, editor. *Gynecologic and obstetric surgery*. St. Louis: Mosby; 1993. p. 363–85.)

perineal body is suspended from the sacrum by the contiguous support of the uterosacral ligaments and rectovaginal septum. Any break in this support system will lead to a hypermobile perineal body, which descends with increases in intra-abdominal pressures (Richardson, 1993). Separation of the perineal body at the level of the rectovaginal fascia results in perineal descent or a low rectocele. The rectocele will be visible just inside of the hymen posteriorly (Fig. 83-9). If perineal body detachment is left untreated at the time of rectocele repair, a perineal rectocele can occur in which the rectum bulges into the perineal body, termed a *perineal rectocele* (Richardson, 1995).

PREPARING THE PATIENT FOR PROLAPSE SURGERY

Because POP is, for the most part, a QoL issue, consideration must be given to the grade of prolapse, the patient's symptoms, and the degree to which the patient's QoL is impaired (Novara and Artibani, 2005). In selecting surgical procedure(s), one must individualize management based on the unique clinical presentation of each patient, taking into account physiologic age, comorbidities, previ-

KEY POINTS: PELVIC FLOOR ANATOMY

- POP occurs as compartmental defects of vaginal support. The three compartments are anterior, apical (middle), and posterior.
- Vaginal support or attachment is provided by the endopelvic connective tissues. The cardinal and uterosacral ligaments provide level I support of the uterus and upper vagina. The endopelvic and pubocervical fasciae provide level II support of the midvagina as it attaches to the ATFP. Level III support of the distal vagina attaches to the levator ani muscles and the perineal body.
- The pelvic diaphragm consists of the coccygeus, iliococcygeus, and pubococcygeus muscles. These muscles provide an important function in maintaining continence and pelvic floor support.
- Pelvic floor defects originate from generalized weakening of endopelvic connective tissue and from breaks in sites of vaginal attachment as the pelvic floor muscles and endopelvic connective tissue weaken.

ous surgeries, and level of physical and sexual activity, as well as overall bother from POP symptoms (Flynn and Webster, 2002). Once the decision has been made to proceed with surgery, it is imperative to recall that **the best chance at restoring normal support and function is most likely associated with the first surgery** (Rogers, 2003). After the first procedure, the normal anatomic planes will no longer be present, which may add to the difficulty and complexity of subsequent surgeries. Recurrence rates increase with each attempt to surgically correct the defect(s) (Birch, 2005; Maher and Baessler, 2006a, 2006b). In addition, the pelvic floor surgeon must understand the anatomic alterations that result from each technique and how that surgery will affect the continuity and function of the endopelvic fascia and its related viscera (Rogers, 2003). A preoperative discussion is warranted to inform the patient of the anticipated risks and benefits of each surgical option so that she can choose the type of operation (if any) is best for her. Some may feel that their level of bother may not warrant the risks of prolapse surgery, and that is a reasonable informed decision.

Prolapse repairs can be defined as **restorative, compensatory, and obliterative** (Van Rooyen and Cundiff, 2008). In patients whose comorbidities preclude prolonged surgery, **obliterative procedures** may offer symptom relief with minimal morbidity. These procedures are contraindicated in patients who wish to remain sexually active; however, for the right candidate these procedures can greatly reduce symptoms with favorable risk. For those patients who have discrete defects in the fibromuscular layer of the endopelvic fascia, **restorative repairs** are an appropriate option. These repairs correct the defined defects in the native tissues by using endogenous support structures. For patients whose native tissues are particularly weak or for those who have had failed surgeries, **compensatory procedures** have been used. These procedures involve placing a graft to reinforce the repair. Grafts are made of synthetic materials and biologic and autologous tissues.

Pelvic floor reconstruction may be performed through a vaginal, open abdominal, laparoscopic, or robotic approach or any combination of these techniques. Because POP is often mixed, surgery commonly involves a combination of repairs addressing any affected compartments. In addition, an anti-incontinence procedure may be performed at the same time. **When comparing vaginal and abdominal approaches to prolapse surgery, a general consensus is that there is a benefit with the vaginal approach, which is usually associated with decreased complications and recovery time** (Weber and Richter, 2005). The operative time is typically less with the vaginal approach, as are the hospital stay and recovery time (Morley and DeLancey, 1988; Shull, 1999). These comparisons must be viewed in the context of emerging laparoscopic and robotic

approaches to POP repair. Recovery times appear improved with these techniques, making these repairs more feasible. **When evaluating outcomes, there is evidence that the abdominal approach is more durable compared with vaginal techniques (Benson et al, 1996).** It is important that all of these factors be considered when selecting the proper technique for each patient.

Preoperative Counseling of the Patient for Vaginal Pelvic Organ Prolapse Surgery

The concept of measuring success of prolapse surgery is in evolution. It is clear that success of prolapse surgery is not just objective resolution of the anatomic defects. The absence of patient symptoms, whether resolution of vaginal bulging or minimization of de novo postoperative symptoms, has the strongest correlation with the patient's assessment of overall improvement and treatment success (Barber et al, 2009b). Thus, **the concept (and definition) of success must include patient satisfaction and symptom improvement, in addition to objective measures.** This process begins before the operation, because patients' expectations and readiness to undergo surgery for POP has been shown to affect their satisfaction and how they perceive their improvement (Kenton et al, 2007). Elkadry and colleagues found that patient satisfaction after surgery for POP correlated highly with achievement of self-described goals (Elkadry et al, 2003). Thus, it is very useful to ask patients, "What are you expecting after surgery? What changes do you desire?" Furthermore, patients perceived the experience of routine postoperative events such as pain, hospital discharge with a catheter, constipation, urge incontinence, and minor effects of anesthesia as surgical complications. These perceived complications were also associated with dissatisfaction, which existed despite high cure rates. Thus a feeling of being unprepared for surgery was highly associated with a negative perception of outcome. **Negative patient perception equates largely to postoperative dissatisfaction even in the presence of high objective cure rates. It is vitally important to recognize that the absence of symptoms influences patient satisfaction to a greater degree than the elimination of anatomic prolapse.** Kenton and colleagues evaluated patients with standardized counseling, giving a three-page handout on what to expect after surgery (Kenton et al, 2007). Women who perceived they were fully prepared for surgery were more likely to be improved on the Patient Global Impression of Improvement (PGI-I) scale (Yalcin et al, 2003) and had lower postoperative scores on the Pelvic Organ Prolapse Distress Inventory (POPDI) (Barber et al, 2001) and Urinary Distress Inventory (UDI) (Shumaker et al, 1994). Also, Kenton and colleagues found that objective measures of cure did not differ by preparedness. In conclusion, **the preoperative surgeon-patient interaction is vitally important and may facilitate improved postoperative patient satisfaction.** Therefore it is recommended to have a thorough discussion while obtaining informed consent about the surgery, alternatives to surgery, the purpose of the planned surgery (what it can and cannot accomplish), the benefits of surgery (what symptoms can be improved), and the risks and complications. In addition, it is useful to review what to expect while the patient is in the hospital, what to expect at home, and strategies for coping with a catheter both in the hospital and at home if needed (Kenton et al, 2007).

BIOLOGIC AND SYNTHETIC MATERIALS IN PROLAPSE SURGERY

Pelvic surgeons have long struggled with recurrences of prolapse after surgical correction. It is estimated that 29% of women require reoperation for incontinence and prolapse (Olsen et al, 1997). The risk factors for failure of prolapse surgery include increasing age, vaginal parity, smoking, deficient tissue quality, conditions that impair wound healing (diabetes mellitus and steroid use), and conditions that stress the repair (chronic constipation, chronic obstructive pulmonary disease, and obesity.) When examining

KEY POINTS: PREOPERATIVE COUNSELING FOR PELVIC ORGAN PROLAPSE SURGERY

- The **absence** of recurrent prolapse **symptoms** influences patient satisfaction more than the elimination of anatomic prolapse.
- It is vitally important to understand the patients' goals and expectations of surgery and to carefully review the risks and benefits of each surgical approach.
- Postoperative "events" such as catheterization or urinary tract infection (UTI) are significant to the patient and negatively influence perception of outcomes.
- The discussion preceding the preoperative informed consent is a valuable time to review the patient's goals and expectations as well as to discuss the risks and benefits of each surgical option.
- It is important for the patient to be educated on what to expect throughout the perioperative course; patients may perceive perioperative events as "complications," which has a negative effect on the overall perception of the procedure.

the issue of failed prolapse surgery, there are limitations. The definition of failure is not standardized, and many studies are short term, lacking controls. However, in spite of the limitations, **it is clear that failure of prolapse surgery is not uncommon.** Some patients with POP have specific deficiencies in their tissues, which may predispose them to failure with traditional restorative procedures. Abnormal type I-to-type III collagen ratios have been identified, leading to a less organized collagen matrix (Falconer et al, 1998). Normal collagen protects fibroblasts from apoptosis, whereas abnormal fibroblasts are not protective (He et al, 2002). Decreased numbers and impaired function of fibroblasts have also been cited (Poncet et al, 2005). Overexpression of matrix metalloproteinases, which break down extracellular matrix proteins, have been demonstrated in women with prolapse (Jackson et al, 1996). These factors imply that these affected tissues may be less likely to respond to the dynamic forces placed on the female pelvic floor (Chen et al, 2004). As a result of these potential tissue disorders and inherent tissue weakness, graft interposition has been used in an effort to improve outcomes of transvaginal prolapse repairs. Although there is level 1 evidence supporting the use of synthetic graft materials for abdominal sacral colpopexy procedures (Davila et al, 2005), there is little evidence regarding the most appropriate use of transvaginal mesh (TVM) in prolapse repairs.

Classification of Graft Materials

The ideal prosthetic implant would be biocompatible, chemically inert, noncarcinogenic, mechanically strong, and sterile; would cause minimal allergic or inflammatory reaction; and would avoid shrinkage and mechanical stress (Birch, 2005). In addition, the ideal implant should be readily available and affordable. Grafts may be categorized as either synthetic or biologic, and both graft types are used in pelvic floor reconstruction. Synthetic graft materials are usually classified as absorbable or nonabsorbable (permanent). Permanent graft materials are usually classified by pore size (macroporous, microporous, submicroporous, and combined) and material structure (monofilament or multifilament). Biologic grafts are classified by source: autologous or heterologous, with the latter further categorized as allografts or xenografts (Fig. 83-10).

Basic Science: Graft-Host Interaction

Graft incorporation of the tissues involves a foreign body response. Although many materials used for synthetic grafts are reported to be chemically and physically inert and nonimmunogenic (Davila et al, 2005; Deprest et al, 2006), none are biologically inert.

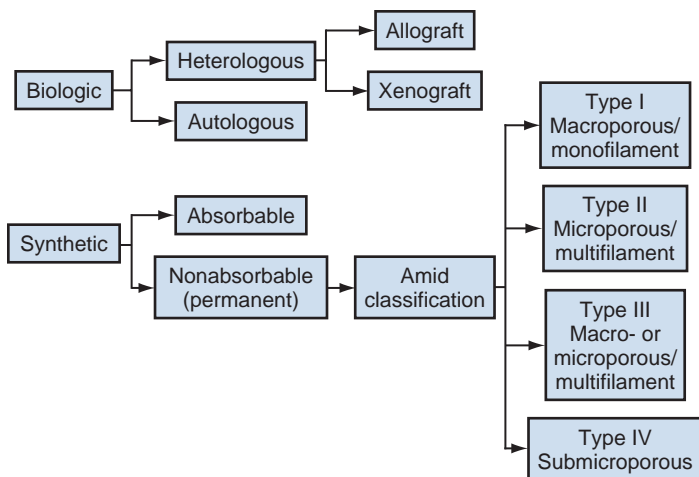


Figure 83-10. Classification of graft materials. (From Togami J, Krlin R, Winters J. Graft materials in prolapse surgery. *AUA Update Series* 2008;27:294–303.)

Regardless of the material type, wound healing with a graft follows a stepwise cascade. Initially a biofilm is produced in response to tissue injury. Low-molecular-weight protein adsorption occurs quickly at the interface and does not require a cellular response. Complex proteins such as fibrinogen, immunoglobulins, and extracellular matrix proteins follow. If bacteria are incorporated into the biofilm at this point, it can affect later wound healing (Deprest et al, 2006). These complex proteins undergo a conformational change to become more immunogenic, which leads to an inflammatory cascade by activating complement, binding antibodies, leukocytes, blood clotting, and fibrinolysis (Tang and Eaton, 1995). At this point the acute inflammatory response becomes chronic, and granulation tissue forms. This involves fibroblasts, macrophages, and giant cells and, later, neovascularization and fibrosis. At this point the implant is mechanically stable. The amount of foreign body reaction is proportional to the surface area of the material exposed to the host. **The degree of response and amount of tissue ingrowth is determined by the nature of the material, its structure, and the amount implanted for biologic grafts (Deprest et al, 2006).** Ideally, host-tissue integration into the graft takes place, leading to long-term graft function after this biologic transformation. This illustrates an important concept in that **the graft, biologic or synthetic, acts as a scaffold to provide a substrate to facilitate tissue ingrowth, rather than functioning as a permanent mechanical support (Birch, 2005).**

Once a graft has been implanted into the human host, one of four processes may occur: rejection, in which there is severe and chronic inflammatory reaction around the implant; degeneration (the result is necrosis from in situ exothermic polymerization by the host); encapsulation (minimal foreign body response in which there is fibrosis around the graft); or incorporation into the human host tissue (response in which there are inflammatory cells and giant cells leading to ingrowth of host tissues into the graft) (Williams, 1973). For long-term graft survival, it appears that **incorporation by the host through a process known as graft remodeling is necessary (Fig. 83-11).**

Pore size affects host fibroblast infiltration, flexibility, and mechanical integration of the graft (Klinge et al, 2002). Large pore size has been shown to facilitate this process by enhancing host tissue infiltration and reducing the amount of inflammatory reaction with increased fibroblast infiltration. The large pores become integrated in a loose network of perifilament granulomas filled with fat, which maintains elasticity. After ingrowth of host tissue, a process of transformation occurs to complete the process of remodeling. Solid products or products with small pores (<50 μm) induce a foreign body reaction, which fills the entire pore.

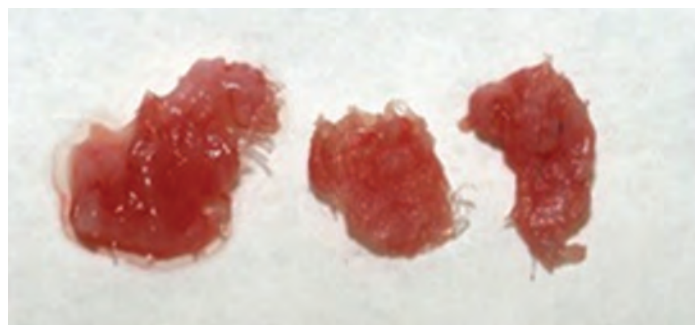


Figure 83-11. Host tissue ingrowth (process of graft remodeling) into polypropylene mesh. (From Woodruff A, Cole E, Scarpero H, et al. A histologic analysis of sling graft materials: a comparative study. *Urology* 2008;72:85–9.)

This promotes bridging of the filaments to one another, thereby predisposing to encapsulation (Beets et al, 1996).

Kaupp and colleagues described four histologic stages of the host to biologic graft implantation (Kaupp et al, 1979). Stage 1 occurs over the first 7 days. This is marked by intense inflammation around the graft, which induces capillary proliferation, formation of granular tissue, and presence of giant cells. Stage 2 encompasses the next 7 days. Granular tissues are still present, and foamy histiocytes appear. Giant cells may increase or decrease at this point. Stage 3 spans days 21 to 28, when the acute inflammation dissipates with decreased capillaries. Foamy histiocytes and giant cells increase in number. Stage 4 happens after 28 days. Giant cells are present on the surface of the implant along with dense fibrotic tissue. This initiates the process of the host-graft interaction.

Once the entire graft is infiltrated with host tissue, the transformation process is complete. If this remodeling process characterized by ingrowth and transformation occurs before the graft substrate dissolves, long-term viability of the implant may be ensured. Although synthetic mesh material is a permanent substrate, the principles of tissue incorporation are necessary to prevent infection, extrusion, or erosion. Extrusion is thought to be secondary to exposed graft, which is attributable to localized infection, inadequate closure of the wound, or poor tissue quality (decreased vascularity or thickness) (Birch, 2005).

Clinical Application of Graft Materials

Biologic Grafts

Owing to concerns regarding potential complications associated with synthetic grafts, some authors have turned to biologic grafts to circumvent these complications (Togami et al, 2008). Biologic grafts are categorized as **autologous** (patient serves as the donor), **allografts** (same species, different individual [cadaveric]), and **xenogeneic** (obtained from other species, typically pig). The advantages of biologic grafts include in vivo tissue remodeling, histologic similarity, and decreased propensity to elicit local complications (Silva et al, 2005).

The donor sites for autologous grafts include rectus fascia, fascia lata, and vaginal epithelium, with the most common being rectus fascia and fascia lata. **Autologous grafts are ideal in that they are well incorporated, pose no threat of disease transmission, and have minimal risk of encapsulation or rejection.** The major drawback is the harvesting process, with increased morbidity, time, and potential for complications at the donor site. These factors are eliminated by using allografts and xenografts (Jarvis and Fowlie, 1985). **Allografts** are obtained from cadaveric donors and include dura mater, fascia lata, and dermis. Cadaveric fascia lata and dermis are used most commonly. A major concern when using biologic materials is the potential for disease transmission. Choe and Bell

demonstrated intact DNA in freeze-dried irradiated cadaveric fascia lata and freeze-dried cadaveric dermal allograft (Choe and Bell, 2001). Fitzgerald and colleagues also examined irradiated freeze-dried or solvent dehydrated cadaveric fascia lata and found that it retained the donor human leukocyte antigen (HLA) class I and II antigens (Fitzgerald et al, 2000). Although extensive steps are taken to prevent infection exposure, risk of prion and human immunodeficiency virus (HIV) transmission is estimated to be 1 in 1.7 million (Buck et al, 1989). To date, there have not been any reports of disease transmission from grafts used for POP.

The harvesting techniques of nonautologous biologic graft materials are standardized. In their review, Chen and colleagues described the process of allograft acquisition (Chen et al, 2007). Before allografts are harvested, the donor undergoes serologic testing for hepatitis B and C, HIV, and human T-lymphotropic virus 1. Aseptic technique is used during harvest, and cultures are obtained at the time. The source animals for xenografts are specifically raised for medical purposes, with production being strictly controlled by U.S. Food and Drug Administration (FDA) guidelines (Deprest et al, 2006). Materials available are derived from porcine subintestinal mucosa, porcine dermis, bovine dermis, and bovine pericardium, although the most commonly used are from porcine sources. These function as acellular collagen-based scaffolds, to serve as a platform for host infiltration.

Allografts and xenografts must undergo tissue processing before implantation, and unlike with harvesting, there is a variance in the processing techniques of these materials. This variance may affect the biologic and biomechanical properties of the grafts. There is no consensus as to which method should be used to optimize tissue properties. In some cases, processing is carried out to affect the long-term effects of the tissue to decrease graft breakdown and increase host tissue ingrowth. Sterilization is achieved by freeze-drying, solvent dehydration, and/or gamma irradiation. Lemer and colleagues demonstrated that freeze-dried cadaveric fascia demonstrated the least desirable characteristics when compared with autologous rectus fascia, cadaveric dermis, and solvent dehydrated cadaveric fascia lata (Lemer et al, 1999). The freeze-dried cadaveric fascia demonstrated a reduced maximum load to failure and stiffness. In addition, there was greater variability in the tissue's strength and stiffness throughout its entire length.

Cross-linking is another processing technique that can affect graft performance. Cross-linking is done to delay reabsorption by collagenases (Badyalak et al, 2002). Several methods are used, including aldehyde cross-linking and hexamethylene diisocyanate (HMDI). Aldehydes are cytotoxic in high concentrations and may increase concentrations of gelatinases, which may actually increase the rate of degradation (Jorge-Herrero et al, 2001). In addition, aldehydes may cause calcification of the grafts, adversely affecting their function. Studies carried out in rats have shown no graft mineralization with HMDI cross-linked dermal implantation at 2 years in contrast to aldehydes (Oliver, 1987). Although cross-linking may be done to stabilize the implant and delay degradation, there are concerns that this process may impede host tissue infiltration and potentially lead to encapsulation. Although these concerns have never been evaluated in a definitive trial, it seems logical that these variances in processing may ultimately lead to variance in biologic graft performance.

Local complications such as encapsulation may occur after the use of porcine dermis grafts (Cole et al, 2003). Graft fenestrations have been reported to enhance ingrowth and angiogenesis (Taylor et al, 2008). They may also decrease seroma formation and local complications. Porcine small intestinal submucosa (SIS) (Surgisis, Cook Medical, Bloomington, IN) is a non-cross-linked graft processed so that the complex extracellular matrix and natural growth factors are left intact. There is histologic evidence that by 1 month the strength and histology of the graft are identical to those of native material, and at 2 years the strength of the graft exceeds the strength of native tissue—although this has not been demonstrated definitively (Konstantinovic et al, 2005).

The lack of in vivo data limits the study of many biologic and synthetic grafts. Naturally, it would be of benefit to demonstrate

how the biomechanical properties of these materials are altered or remodeled by the host. Several animal models have been used to study grafts and meshes. In the rabbit model, a free or pedicle flap of autologous rectus fascia decreased 37% in length, 63% in width, and 53% in tensile strength after implantation for 12 weeks. Neovascularization, minimal inflammation, and fibrosis were noted only along the permanent suture used to secure the graft (Fokaefs et al, 1997). In a rabbit model, freeze-dried, irradiated cadaveric fascia lata had a 90% decrease in tensile strength 12 weeks after implantation (Walter et al, 2003). There was variability in tensile strength from lot to lot and from grafts taken from different areas in the same lot. In an extensive rabbit study examining six different graft materials, tensile strength and stiffness of human cadaveric fascia and porcine xenografts decreased by 60% to 89%. Polypropylene mesh and anterior rectus fascia had no change in tensile strength from baseline (Dora et al, 2004). When comparing Gynecare TVT (Ethicon, Somerville, NJ) polypropylene sling with cadaveric fascia lata sling in the rat model, there was an advantage for the polypropylene sling in the break load and maximum average load compared with cadaveric fascia lata (Spiess et al, 2004). **There is a wide variation in the types of grafts available and the tissue processing they undergo. It is unclear how this affects the performance of the grafts because there are few data comparing them.** Before implantation, dermal allografts, solvent dehydrated fascia lata, and synthetic mesh have equal or higher tensile strength compared with autologous fascia. In some studies, freeze-dried grafts have a decreased tensile strength compared with similar grafts that have been solvent dehydrated. After implantation, autologous fascia and synthetic mesh seem to retain more of their tensile strength compared with allografts or xenografts (Chen et al, 2007).

Synthetic Grafts

Synthetic mesh is available as permanent or absorbable material. Absorbable mesh has several desirable characteristics. It promotes postoperative fibroblast activity, has less infectious disease risk, is not rejected, and has not been reported to be harmful to the viscera. One disadvantage is that the resultant scar tissue may not be as strong as the native tissue it is reinforcing (Klinge et al, 2001). **Classification of the synthetic meshes occurs by type of mesh (absorbable or nonabsorbable), pore size (macroporous or microporous), and filament type (monofilament or multifilament).** Two types of absorbable meshes are available: polyglycolic acid (Dexon, Davis and Geck, American Cyanamid, Danbury, CT) and polyglactin 910 (Vicryl, Ethicon). They differ in the duration in the tissues. Polyglactin 910 starts to hydrolyze by 21 days and loses its mechanical support by 30 days. Polyglycolic acid takes 90 days for absorption.

The most important characteristic of a synthetic mesh is its pore size. Meshes are divided into macroporous (greater than 75 microns) or microporous (less than 10 microns.) Pore size is important from the standpoint of infection because it determines whether cellular elements such as macrophages and granulocytes will be able to enter the mesh construct. In addition, it is important for tissue ingrowth with fibroblasts, blood vessels, and collagen fibrils (Amid, 1997; Deprest et al, 2006; Dwyer, 2006) (Fig. 83-12). Most bacteria are smaller than 1 μm , and granulocytes and macrophages are greater than 10 μm in diameter, but **75 μm is the key number, which allows the tissue ingrowth.** Pore size also determines the flexural rigidity. The larger the pore size, the more flexible the mesh (Dietz et al, 2003). This property may affect local tissue trauma and erosive risk (Birch, 2005).

Synthetic mesh can be monofilament or multifilament. Multifilament synthetics may have pore sizes that allow them to be classified as macroporous; however, between the fibers the size is less than 10 microns because of the way the fibers are either woven or knitted. The spaces are small enough to allow bacteria into confines less than 10 microns, which carries a greater theoretic risk than a monofilament mesh. The construct of the mesh affects pore size, and the interstitial distance is measured between the synthetic

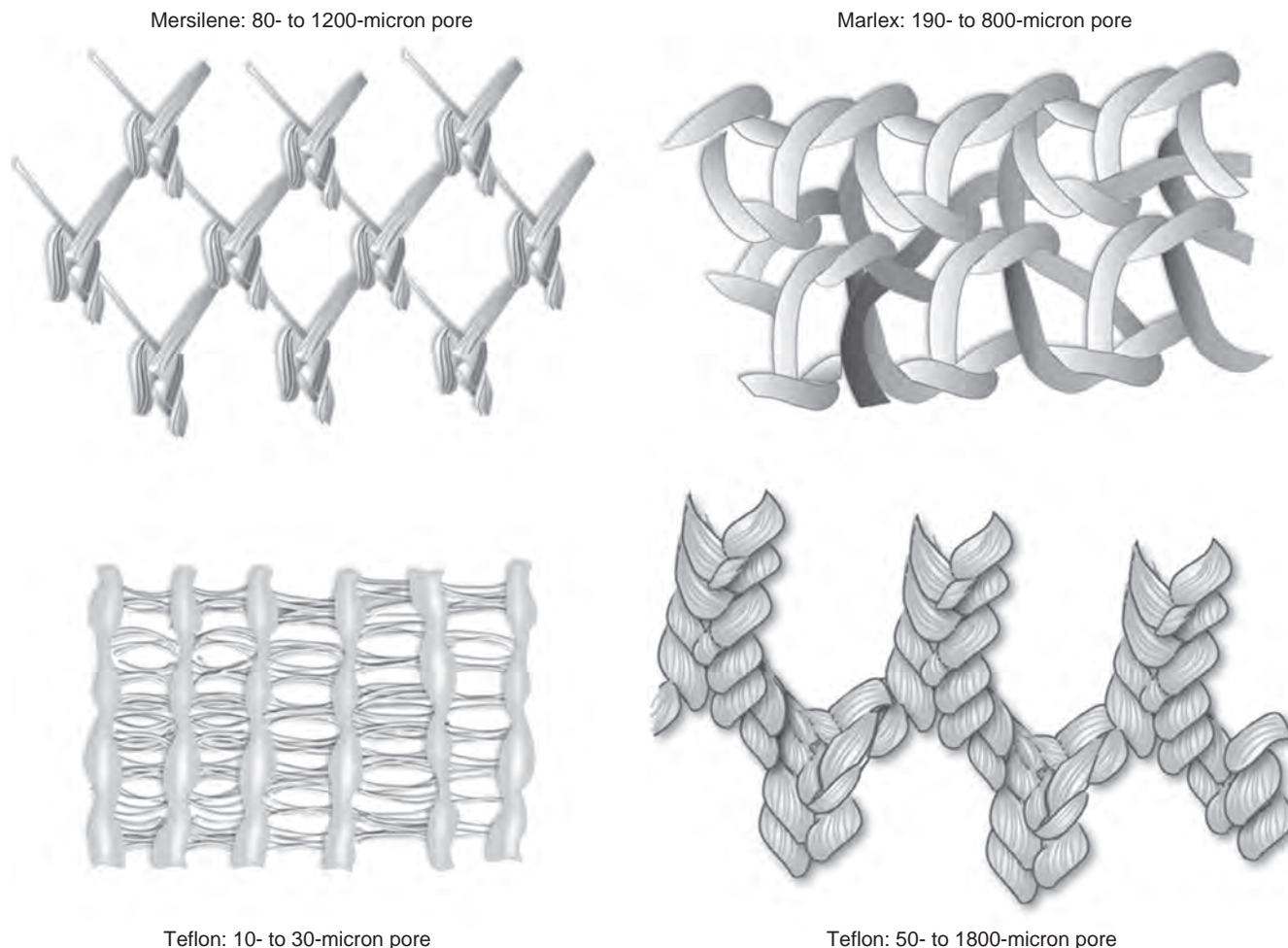


Figure 83-12. Synthetic graft pore and interstices: Note the multifilamentous nature of Mersilene, which may promote bacterial adherence. (From Togami J, Krlin R, Winters J. Graft materials in prolapse surgery. *AUA Update Series* 2008;27:294–303.)

fibers. Woven mesh has small pore size and interstices, whereas knitted materials are able to assume a macroporous configuration and are flexible with high tissue conformity.

Although there is no classification system specifically used for mesh in pelvic floor reconstruction, the Amid classification, which was originally used to describe mesh used in the treatment of abdominal wall hernias, is currently our standard (Amid, 1997). This classification emphasizes the importance of pore size and filament type (see Fig. 83-10).

Type I promotes host defenses and tissue infiltration. Type II and type III meshes result in a greater foreign body response and are associated with greater rates of erosion (Julian, 1996; Debodinance et al, 1999). The most desirable synthetic materials for pelvic floor reconstruction are lightweight, monofilament, macroporous mesh, most commonly polypropylene mesh. These meshes (of which many types are now commercially available) appear to be best tolerated in prolapse surgeries. In animal models, there is evidence that stiffness (degree of stretch when a force is applied to them) may be associated with the structural integrity of the vagina after implantation of lightweight polypropylene mesh. Implantation with stiffer polypropylene meshes resulted in increased collagenase activity and decreased collagen and elastin content. These changes resulted in deterioration of the mechanical properties of the vagina in an animal model (Feola et al, 2013; Liang et al, 2013). The clinical significance of these findings is unknown; however, further comparative studies on the various types of polypropylene meshes are warranted.

SURGICAL MANAGEMENT OF PELVIC ORGAN PROLAPSE

See Table 83-2.

Anterior Compartment

Anterior Colporrhaphy

Kelly first described his method of cystocele repair as a treatment for urinary incontinence (Kelly, 1913). He emphasized the importance of repairing the pubocervical fascia with plication sutures to repair the central defect in the anterior vaginal wall. This procedure eventually became known as the *anterior colporrhaphy* or *native tissue cystocele repair* and is now used for the treatment of anterior prolapse. Use for the treatment of incontinence diminished after the American Urological Association (AUA) Female Stress Urinary Incontinence Clinical Guidelines Panel meta-analysis found a failure of nearly 40% (Leach et al, 1997).

Anterior compartment defects are commonly combined central and lateral defects. Thus, an anterior colporrhaphy, which corrects only central compartment defects, usually must be combined with a paravaginal repair or lateral anchoring for the treatment of anterior wall prolapse. Isolated central defects are rare, and in these instances colporrhaphy alone may suffice. The early series on anterior colporrhaphy for the treatment of anterior vaginal wall prolapse reported objective success rates of 80% to 100%

TABLE 83-2 Surgical Approach to Pelvic Organ Prolapse

POP-Q SITE	VAGINAL	ABDOMINAL
Aa Urethra	Anterior repair Bladder neck suspension sling	Retropubic urethropexy
Ba Bladder	Anterior repair Paravaginal repair Colpocleisis	Wedge colectomy Paravaginal repair Abdominal sacrocolpopexy
C Cervix/cuff	Uterosacral ligament suspension Iliococcygeus suspension Sacrospinous fixation Manchester operation Hysteropexy Vaginal hysterectomy Colpocleisis	Abdominal hysterectomy Uterosacral ligament suspension Abdominal sacral colpopexy Uterine suspension
D Cul-de-sac	McCall culdoplasty	Halban culdoplasty Moschkowitz culdoplasty
Ap	Rectovaginal plication (posterior repair) Site-specific repairs	Colpoperineopexy

POP-Q, Pelvic Organ Prolapse Quantification System.

(Macer, 1978; Stanton et al, 1982; Walter et al, 1982; Porges and Smilen, 1994). In 2001, Weber and colleagues in a randomized trial of three surgical techniques reported a 70% failure rate of native tissue anterior repairs (Weber et al, 2001). Recent reanalysis of this data set using a more contemporary and agreed-on definition of failure (prolapse beyond the hymen) reported a significantly better anatomic outcome, with only 10% of patients experiencing prolapse beyond the hymen and only 5% of patients reporting symptomatic improvement (Chmielewski et al, 2011). The extreme differences in failure rates for anterior colporrhaphy seen in the literature can be primarily explained by the variability in definition of failure and the fact that in early series these procedures were performed in patients with multiple defects.

Technique (Fig. 83-13). The patient is placed in the dorsal lithotomy position with all pressure points padded and the hip and knee joints flexed approximately 90 degrees. Preparation of the surgical area and cleansing of the vaginal and perivaginal tissue are recommended. Fixed or handheld retraction can be helpful and in general depends on patient body habitus as well as availability of surgical staff for assistance. An indwelling urethral catheter is placed and the bladder is drained either continuously or intermittently throughout the procedure. Hydrodissection may be used to facilitate the dissection. A midline incision is made in the anterior vaginal wall, extending from the vaginal apex to the bladder neck. The incision should not extend to the urethra when a simultaneous mid-urethral sling is anticipated. Optimally, the sling should be placed through a separate, mid-urethral incision. However, when performing a pubo-vaginal sling, it is desirable to create one incision that extends from the vaginal apex to the mid-urethra to facilitate more precise sling positioning over the bladder neck. The vaginal wall is dissected off the pubocervical fascia starting in the midline and advancing laterally to the ATPF. This dissection should allow sufficient visualization to delineate both central and lateral defects. Allis clamps or a self-retaining ring retractor may be used to provide optimal exposure.

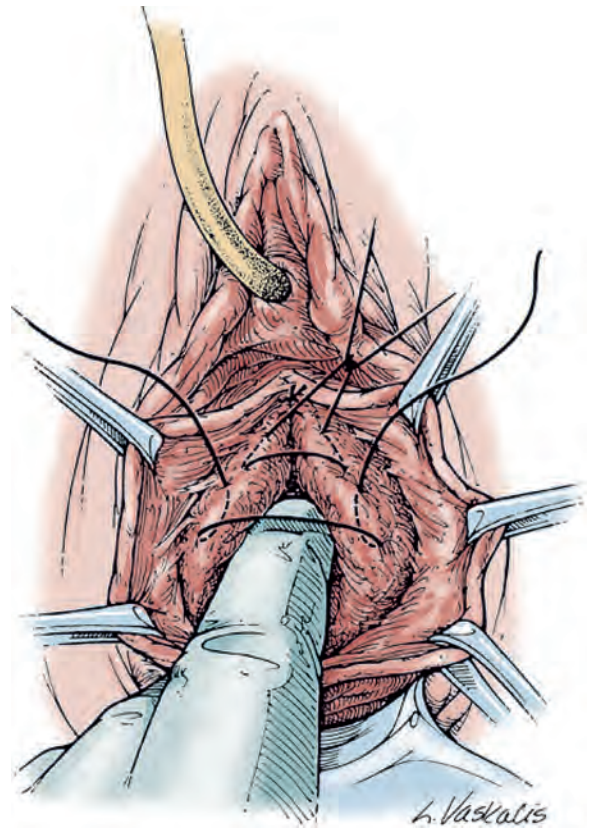


Figure 83-13. Anterior colporrhaphy. The anterior submucosal layer is imbricated with 2-0 delayed absorbable continuous or interrupted suture. (From Nicholas DH. Cystocele. In Nichols DH, editor. Gynecologic and obstetric surgery. St. Louis: Mosby; 1993. p. 334–62.)

The bladder is then reduced with a finger or instrument to facilitate lateral exposure and reapproximation of the lateral pubocervical tissues in the midline. Interrupted 2-0 or 3-0 delayed absorbable plication sutures are placed from the bladder neck to the apex in a sequential fashion. The plication sutures are then tied as the assistant reduces the prolapsed tissue. Care must be taken to avoid excessively deep suture placement that may penetrate the bladder or ureteral lumens or kink the distal ureters or intramural tunnels. Augmented repairs use allograft or mesh to reinforce the plication sutures (see the later discussion of augmented repairs). Excess anterior vaginal wall may be judiciously trimmed, and the anterior vaginal wall is closed with absorbable suture in a running fashion. After completion of the repair, indigo carmine or methylene blue is administered and cystoscopy is performed to inspect the bladder for iatrogenic injury and to visualize ureteral patency. Vaginal packing may be used to cover the surgical area and assist with hemostasis.

Results. In earlier studies, the reported cure rate of anterior colporrhaphy approached 100% (Table 83-3). In a large, retrospective study looking at 299 patients with anterior vaginal wall prolapse, Porges and Smilen reported a recurrence rate of only 3%, with a mean follow-up of 31 months (Porges and Smilen, 1994). In a prospective, randomized trial between Burch colposuspension and anterior colporrhaphy, Colombo and colleagues reported a recurrence rate again of only 3% in the 33 patients who underwent anterior colporrhaphy, with a mean follow-up of 5 years (Colombo et al, 2000). In a retrospective secondary analysis study comparing anterior colporrhaphy alone with anterior colporrhaphy plus sling, anterior prolapse was noted in 42% of those who underwent anterior colporrhaphy alone, versus 19% in those who had concomitant sling (Goldberg et al, 2001). It is interesting to note that in series comparing anterior colporrhaphy with augmented

TABLE 83-3 Results of Anterior Compartment Repair without Graft

AUTHOR	YEAR	N	FOLLOW-UP	SUCCESS RATE
ANTERIOR COLPORRHAPHY (AC)				
Stanton et al	1982	54	Up to 2 yr	85%
Macer	1978	109	5-20 yr	80%
Walter et al	1982	76	1.2 yr	100%
Porges and Smilen	1994	388	2.6 yr	97%
Colombo et al	2000	33 AC	8-17 yr	97%
		35 colposuspension	8-17 yr	66%
Sand et al	2001	70 AC	1 yr	57%
		73 AC + Vicryl mesh	1 yr	75% no mesh complications
Weber et al	2001	57 AC	23 mo	37%
		26 AC + Vicryl mesh	23 mo	42% no mesh complication
VAGINAL PARAVAGINAL REPAIR (VPVR)				
White	1909	19	Up to 3 yr	100%
Shull et al	1994	62	0.6 yr	67%
Grody et al	1995	72	0.5-3 yr	99%
Elkins et al	2000	25	0.5-3 yr	92%
Mallipeddi et al	2001	45	0.6 yr	97%
Young et al	2001	100	11 mo	78%
Morse et al	2007	27 AC + VPVR	13 mo	54%
		86 AC	24 mo	45%
ABDOMINAL PARAVAGINAL REPAIR (APR)				
Richardson	1976	60	1.7 yr	97%
Richardson	1981	213	0.5-6 yr	95%
Shull and Baden	1989	149	0.5-4 yr	95%
Bruce et al	1999	27 APR + sling	17 mo	93%
		25 APR	17 mo	76%
Scotti et al	1998	40	39 mo	97%
ANTERIOR COLPORRHAPHY WITH SLING				
Goldberg et al	2001	53 AC + sling	1 yr	81%
		90 AC	1 yr	58%

repairs, reported recurrence rates for standard anterior colporrhaphy approach 40%, significantly higher than recurrence rates noted earlier (Table 83-4). Part of this discrepancy can be accounted for by the use of alternative and composite outcome measures in these studies. Sand and colleagues reported on 161 women randomized to anterior colporrhaphy with polyglactin 910 (Vicryl) suture alone or anterior colporrhaphy with a free Vicryl mesh inlay placed under the trigone after plication of the pubocervical fascia (Sand et al, 2001). At 1 year, the women randomized to Vicryl mesh inlay had a failure rate of 25% compared with 43% in women who underwent plication with suture alone ($P = .02$). Weber and colleagues compared anterior colporrhaphy reinforced with Vicryl mesh versus traditional plication without tension using polydioxanone suture and "ultralateral" plication using both polydioxanone suture and tension (Weber et al, 2001). In this study, 114 women with symptomatic cystoceles (mostly stages 2 and 3 on the POP-Q) were randomized among the three groups. With a mean follow-up of 23 months, there was no significant difference in failure rate (defined as stage 2 or greater on the POP-Q) among the three groups. The failure rate was 30% in those who underwent tradi-

tional plication, 46% in those who underwent ultralateral plication, and 42% in those who underwent traditional plication augmented with Vicryl mesh. Unfortunately, the study did not recruit enough women to achieve statistical power to detect differences among the groups. It is interesting to note that an earlier paper by the same author stated that anterior vaginal wall prolapse recurs after standard anterior colporrhaphy in only 20% of patients (Weber and Walters, 1997). The Sand and Weber trials are not similar enough to allow meta-analysis. As noted earlier, recent re-evaluation of the Weber dataset from 2001 revealed significantly better outcomes when defining failure as recurrent prolapse beyond the hymen (Chmielewski et al, 2011). Failure rates at 1 year were 11% in the traditional plication group, 23% in the ultralateral group, and 9% in the mesh augmented group, adding up to a combined objective recurrence rate of 12% with no statistically significant difference among groups. Before the re-evaluation of these data, concern over high recurrence rates and lack of durability with anterior colporrhaphy, especially in women with moderate- or high-grade prolapse, led investigators to explore augmented repairs using biologic and nonbiologic sources.

TABLE 83-4 Outcomes of Anterior Compartment Repair with Synthetic and Biologic Graft

GRAFT TYPE	STUDY	N	MEAN FOLLOW-UP (mo)	SUCCESS RATE (%)	POSTOPERATIVE EVALUATION	COMPLICATIONS
Marlex mesh	Julian, 1996	12	24	AC alone 66.7% AC + mesh 100%	Physical examination	25% mesh exposure
	Flood et al, 1998	142	38.4	AC + mesh 100%	Physical examination	2.1% mesh exposure
	Cervigni et al, 2008	218	38	Mesh 75.7%	POP-Q	12.3% mesh exposure
Mixed fiber mesh	Migliari and Usai, 1999	15	23.4	Mesh 93.3%	Baden-Walker	0% mesh exposure
Polyglactin mesh	Weber et al, 2001	33 24 26	23.3	AC alone 30% Ultralat AC 46% AC + mesh 42%	POP-Q	1.2% mesh exposure
	Sand et al, 2001	70 73	12	AC alone 57% AC + mesh 75%	Baden-Walker	0% mesh exposure
Polypropylene mesh	Nicita, 1998	44	13.9	Mesh 100%	SEAPI QMM Scale	2.3% mesh exposure
	Migliari et al, 2000	12	20.5	Mesh 75%	Baden-Walker	0% mesh exposure
	de Tayrac et al, 2002	48	18	Mesh 97.9%	POP-Q	8.3% mesh exposure
	Dwyer and O'Reilly, 2004	81	29	Mesh 92.6%	Baden-Walker	9.0% mesh exposure
	Rodríguez et al, 2005	98	NR	AC + mesh 84%	POP-Q	0% mesh exposure
	de Tayrac et al, 2005	87	24	Mesh 91.6%	POP-Q	8.3% mesh exposure
	de Tayrac et al, 2006a	55	37	Mesh 89%	POP-Q	9.1% mesh exposure
	Jo et al, 2007	35	18	AC + mesh 94.3%	POP-Q	0% mesh exposure
	Amrute et al, 2007	76	30.7	AC + mesh 94.8%	Questionnaire	2.1% mesh exposures
	de Tayrac et al, 2007	132	13	Mesh—soft 93.2%	POP-Q	6.3% mesh exposure
	Deffieux et al, 2007	89 49	32.1 7.1	Mesh 97% Mesh—soft 92%	Baden-Walker	16% mesh exposure 24% mesh exposure
	Hiltunen et al, 2007	97 104	12	AC alone 61.5% AC + mesh—soft 93.3%	POP-Q	17.3% mesh exposure
	Altman et al, 2008	78	2	Mesh 87%	POP-Q	1.5% mesh exposure
	Nguyen and Burchette, 2008	38 37	12	AC alone 55% AC + mesh 87%	POP-Q	5% mesh exposure
	Sivaslioglu et al, 2008	42 43	12	AC alone 72% AC + mesh—light 91%	POP-Q	6.9% mesh exposure
	Carey et al, 2009	61 63	12	AC alone 65.6% AC + mesh 81%	POP-Q	5.6% mesh exposure
	Niemenen et al, 2010	97 104	36	AC alone 59% AC + mesh—light 87%	POP-Q	19% mesh exposure
	Altman et al, 2011	186 182	12	AC + mesh 60.8% AC alone 34.5%	POP-Q	3.2% mesh exposure
	Vollebregt et al, 2011	58 56	12	AC alone 41% AC + mesh 91%	POP-Q	4% mesh exposure
	Rane et al, 2012	350	24	Mesh 94.3%	POP-Q	11.1% mesh exposure

Continued

TABLE 83-4 Outcomes of Anterior Compartment Repair with Synthetic and Biologic Graft—cont'd

GRAFT TYPE	STUDY	N	MEAN FOLLOW-UP (mo)	SUCCESS RATE (%)	POSTOPERATIVE EVALUATION	COMPLICATIONS
Cadaveric fascia	Groutz et al, 2001	21	20.1	Fascia 100%	Baden-Walker	0% graft erosion
	Kobashi et al, 2002	132	12.4	Fascia 88.6%	Baden-Walker	12.9% suture exposure
	Chung et al, 2002	19	28	Fascia 89.5%	Baden-Walker	5.3% graft infection
	Clemons et al, 2003	33	18	AC + fascia 59%	POP-Q	3% anterior wall breakdown
	Powell et al, 2004	19	22.8	Autolog fascia 84.2%	POP-Q	10% graft exposure
		39	28	Fascia 79.5%		
	Gandhi et al, 2005	78 76	13	AC alone 71% AC + fascia 79%	POP-Q, Baden-Walker	0% graft exposure
	Frederick and Leach, 2005	251	60	Fascia 92.8%	Baden-Walker	9% vaginal granulation
	Ward et al, 2007	24	52	AC + fascia 41.7%	POP-Q	0% graft exposure
Porcine dermis	Gomelsky et al, 2004	70	24	Graft 87.1%	Baden-Walker	1.4% vaginal wound separation
	Leboeuf et al, 2004	19 24	15	FDR + graft 84.2% FDR 100%	SEAPI test	0% graft exposure
	Salomon et al, 2004	27	14	Graft 85.2%	POP-Q	3.7% suture exposure
	Wheeler et al, 2006	28	18.3	AC + graft 50%	POP-Q	2.8% granulation tissue
	Simsiman et al, 2006	89	24	Graft 78%	POP-Q	16.7% graft exposure
	Meschia et al, 2007	103 98	12	AC alone 81% AC + graft 93%	POP-Q	1% graft exposure
	Handel et al, 2007	18 56 25	13.5	AC alone 94% AC + graft 64% AC + mesh 96%	Baden-Walker	21% graft exposure 4% mesh exposure
	Natale et al, 2009	94 96	24	Graft 56.4% Mesh 71.8%	POP-Q	0% graft exposure 6.3% mesh exposure
	Hviid et al, 2010	26 28	12	AC alone 84.6% Graft 92.9%	POP-Q	3.6% graft exposure
	Menefee et al, 2011	24 26 28	24	AC 42% Porcine 54% Polypropylene 82%	POP-Q	4% graft exposure 14% mesh exposure
Bovine pericardium	Guerette et al, 2009	27 17	24	AC alone 63% AC + graft 76.5	POP-Q	0% graft exposure
Porcine SIS	Feldner et al, 2010	27 29	12	AC 59.3% Porcine SIS 86.2%	POP-Q	0% graft exposure

AC, anterior colporrhaphy; FDR, four defect repair; NR, not reported; POP-Q, Pelvic Organ Prolapse Quantification System; SEAPI-QMM, stress-related leak (S), emptying ability (E), anatomy (female) (A), protection (P), inhibition (I), quality of life (Q), mobility (M), and mental status (M); SIS, small intestine submucosa.

Complications. Reported complications from anterior colporrhaphy include de novo or occult stress urinary incontinence (SUI), de novo overactive bladder symptoms, postoperative urinary retention, incomplete bladder emptying, significant bleeding exceeding 350 mL, wound infection, bladder or ureteral injuries, vesicovaginal fistula, vaginal shortening, epithelial inclusion cyst, and dyspareunia. **De novo detrusor overactivity** can occur in 5% to 7% of patients after standard colporrhaphy (Raz et al, 1991). Yet, **preexisting detrusor overactivity** has been reported to resolve in up to 63% of patients after surgical repair of POP (Nguyen and Bhatia, 2001). Urinary retention usually occurs in cases during which a

concomitant anti-incontinence procedure was performed; however, retention or incomplete emptying may occur in the absence of anti-incontinence surgery and may be the result of neurologic trauma and impaired bladder contractility from the plication procedure itself. In most instances, the retention resolves after a brief period of clean intermittent catheterization (CIC). If the retention persists and the patient had a concomitant anti-incontinence procedure, sling incision or urethrolisis may be required. When impaired bladder emptying is the result of preexisting hypocontractility, the patient may require chronic CIC, neuromodulation, or as a last resort suprapubic tube drainage.

Bleeding during anterior colporrhaphy is usually caused by both the high vascularity of the vagina and the venous complex beneath the inferior pubic bone. During anterior colporrhaphy, problematic bleeding can occur if the dissection is carried out in the wrong plane. The vaginal wall should be dissected off of the pubocervical fascia directly on its white shiny surface. In patients undergoing repeat anterior colporrhaphy, scarring will often obscure the correct dissection plane. Accordingly, these patients are at higher risk for bleeding.

Bladder or ureteral injuries are rare during standard anterior colporrhaphy. Bladder injuries can occur when perforating into the retropubic space or during dissection of the vaginal flaps, especially in women with atrophic tissue. Ensuring bladder drainage before perforating the endopelvic fascia may reduce this. Should an inadvertent bladder injury occur, a two-layer closure should be performed with absorbable suture. If the patient has a history of pelvic irradiation or if the repair quality seems tenuous, a labial fat pad interposition should be considered to prevent vesicovaginal fistula formation (Kreder, 1993). Cystoscopy after the administration of indigo carmine should be routinely performed with every anterior colporrhaphy. If blue-stained urine is not seen effluxing from both ureteric orifices, ureteral catheterization, retrograde pyelography, or takedown of the plication sutures should be performed. In some cases the ureter is patent and an alternative reason including inadequate fluid resuscitation or ureteral kinking will explain the lack of efflux. Appropriate steps must be taken to ensure ureteral patency if the ureter cannot be catheterized.

Procedures for Lateral and Combined Defects

Vaginal Paravaginal Repair. In his first description of a vaginal paravaginal repair, George White described a cystocele repair that involved suturing the lateral sulci of the vagina to the white line of the pelvic fascia (White, 1909). White believed that the cause of a cystocele was weakness of the lateral vaginal attachments to the ATFP. As Kelly's anterior colporrhaphy became the primary technique of cystocele repair for the next 70 years, White's concept fell into disfavor. In 1976, Richardson reintroduced the paravaginal defect repair (PVdR), but he described the technique using an abdominal approach (Richardson et al, 1976). Regardless of the approach, the goal of a paravaginal repair is to repair a lateral compartment defect by reattaching the pubocervical fascia to the ATFP. A vaginal paravaginal repair may be combined with anterior colporrhaphy in patients with combined lateral and central defects.

Technique (Fig. 83-14). A midline vertical incision is made through the anterior vaginal wall from the bladder neck to the vaginal apex. After the vaginal wall is sharply dissected off the attenuated pubocervical fascia and bladder, the dissection is carried laterally to the pelvic sidewall. Blunt dissection can be used to facilitate this. Access to the pelvic sidewall is achieved by continued lateral dissection and perforation of the endopelvic fascia. On entry into the retropubic space, palpation is used to identify the ATFP as it courses from the ischial spine to the inferior aspect of the pubic ramus. Deep, lighted retractors may be useful to facilitate exposure. With the bladder retracted medially, five to seven interrupted nonabsorbable sutures are placed at 1-cm intervals through the ATFP. A Capiro Suture Capturing Device (Boston Scientific) needle driver may expedite placement of these sutures. These sutures are then passed through the lateral edge of the detached pubocervical fascia. No sutures should be tied until all are placed on either one side or both sides (if bilateral defects). At this point, if indicated, central defect plication sutures may be placed to complete a combined repair. As with anterior colporrhaphy, cystoscopy must be performed to confirm ureteral patency and the absence of intravesical sutures. The vaginal wall is trimmed judiciously, if needed, and closed with a 2-0 absorbable suture. Vaginal packing is placed at the end of the case.

Results (see Table 83-3). Shull and colleagues reported successful repair without any evidence of prolapse in 41 patients (73%) after a mean follow-up of 1.6 years (Shull et al, 1994). Of the 15 recur-

rences, only 4 patients developed prolapse to or through the hymen, and in these 4 the prolapse was less than what was noted preoperatively. Grody and colleagues reported a 99% success rate in 72 patients 0.5 to 3 years after vaginal paravaginal repair (Grody et al, 1995). Elkins and colleagues reported an 8% lateral cystocele recurrence rate and a 22% central cystocele recurrence rate 0.5 to 3 years after vaginal paravaginal repair in 25 patients with grade 3 or greater anterior wall vaginal prolapse (Elkins et al, 2000). Midline central defects were common, leading surgeons to perform joint repairs with an anterior colporrhaphy. Young and colleagues retrospectively evaluated 100 patients with symptomatic grade 2 to 4 combined central and lateral cystoceles (Young et al, 2001). All 100 patients underwent both vaginal paravaginal repair and concomitant anterior colporrhaphy. With a mean follow-up of 11 months, the lateral cystocele recurrence rate was only 2% and the central cystocele recurrence rate was 22%. Mallipedi and colleagues reported a 3% central cystocele recurrence 20 months after vaginal paravaginal repair in 35 patients with grade 2 to 4 anterior vaginal wall prolapse (Mallipedi et al, 2001). Of the 21 patients with concomitant SUI, 12 (57%) had persistent SUI after the paravaginal repair. The paravaginal repair, like standard anterior colporrhaphy, is ineffective in the treatment of SUI.

A retrospective analysis of patients undergoing anterior colporrhaphy alone versus anterior colporrhaphy plus PVdR reported no statistically significant differences between the groups in either subjective or objective outcome measures (Morse et al, 2007).

Although complications after vaginal paravaginal repair are infrequent, they are significant. Young reported 21 major complications, including 3 major intraoperative hemorrhagic complications (Young et al, 2001). Two patients developed lower extremity neuropathy; one was in the lithotomy position for a prolonged period of time. Elkins reported a transfusion rate of 12% (Elkins et al, 2000). Mallipedi reported 2 patients with vaginal abscesses that required drainage, 1 patient with retropubic hematoma who required re-exploration, and 1 patient with bilateral ureteral obstruction, which resolved after takedown of the repair and suture replacement (Mallipedi et al, 2001).

The vaginal paravaginal repair as described is technically more challenging than the standard anterior colporrhaphy. Complication rates are higher and usually more serious. In addition, the conventional vaginal paravaginal repair relies on suture placement through weakened pubocervical fascia. To compensate for these factors, most surgeons describe transvaginal correction of lateral defects using placement of grafts, which are attached to the pelvic sidewalls bilaterally.

Anterior Compartment Repairs Using Grafts

Technique. The incision and dissection into the retropubic space are carried out in a similar manner as in the vaginal paravaginal repair. Once access to the pelvic sidewall is achieved, the bladder is retracted medially, and two or more sutures (permanent or delayed absorbable) are placed into the ATFP and/or obturator internus fascia, which will serve as adequate lateral fixation for the graft. The graft material may also be anchored distally to the bladder neck and apically to the cervix, bladder, or vaginal wall. A Capiro Suture Capturing Device (Boston Scientific) may expedite placement of these sutures (Fig. 83-15). Before the graft is fashioned, it is useful to estimate the distance between the proximal and distal ipsilateral sutures and the distance between the sutures on each side. These measurements serve to determine the dimensions of the graft material, which is trimmed to size. At this point, central plication sutures may be performed. The previously placed pelvic sidewall sutures are then brought out to the corresponding locations on the graft. The sutures are then tied, securing the graft to the pelvic sidewall. It is useful to leave the sutures long until after cystoscopy confirms patency of the ureters. The vaginal wall is judiciously trimmed, if needed, and closed with a 2-0 absorbable suture. Vaginal packing is placed at the end of the case. Graft-augmented cystocele repairs can also be performed using a vaginal mesh kit. The technical components vary with each proprietary kit but in general involve

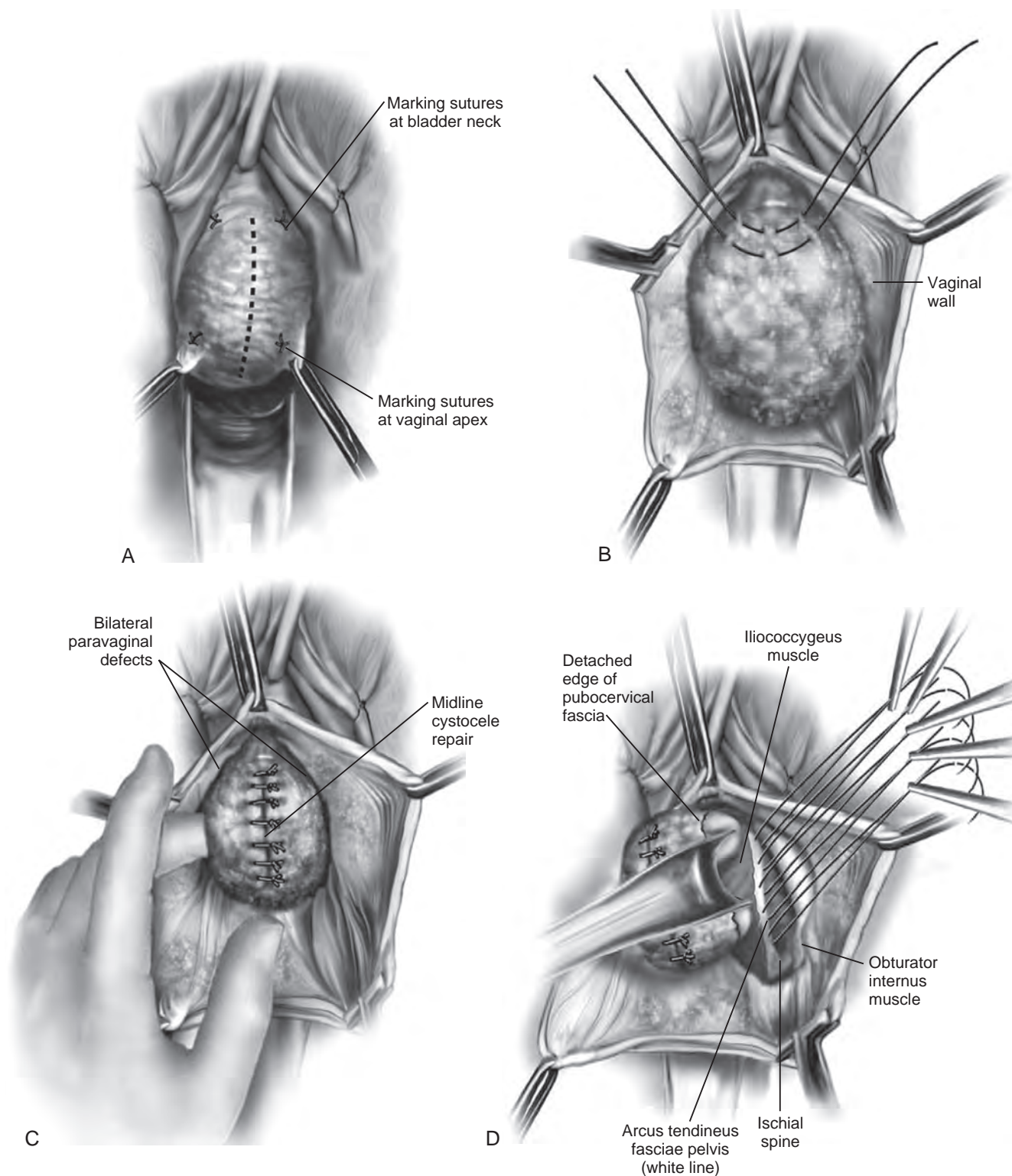


Figure 83-14. Vaginal paravaginal repair. A, Unopened anterior vaginal wall with marking sutures placed at anatomic level of bladder neck and vaginal apex. B, Anterior vaginal wall opened via a midline incision. Sutures placed for midline cystocele repair. C, Midline cystocele repair completed. Bilateral paravaginal defects identified. D, Bladder retracted medially to expose lateral pelvic sidewall. Permanent sutures have been passed through the white line.

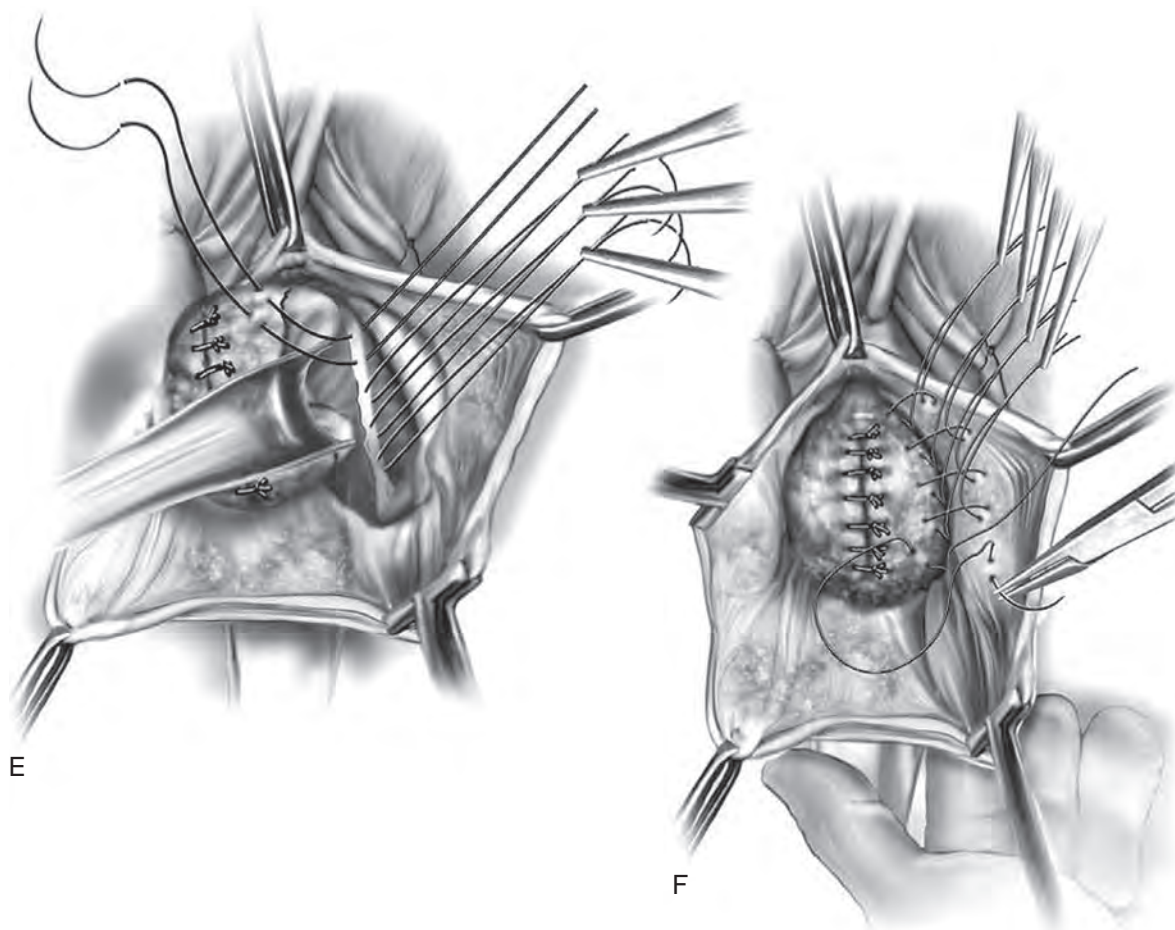


Figure 83-14, cont'd E, Top two sutures have been passed through detached edge of pubo-cervical fascia. **F,** Three-point closure is completed with all sutures passed through the pubo-cervical fascia and inside wall of the vagina. (From Baggish M, Karram M. *Atlas of pelvic anatomy and gynecologic surgery*. 3rd ed. Philadelphia: Saunders; 2010.)

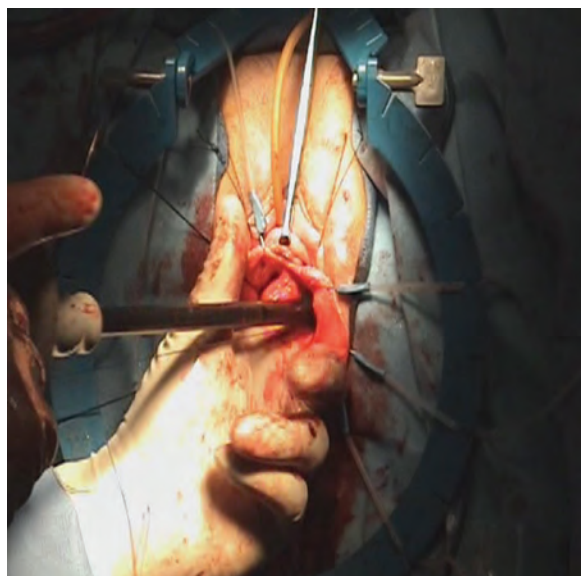


Figure 83-15. Capiro needle driver used to facilitate suture placement in the arcus tendineus fasciae pelvis. (Courtesy Victor Nitti.)

fixation of the graft to the pelvic sidewalls using different attachment mechanisms.

Results

Polypropylene Mesh (see [Table 83-4](#)). In 1996, Julian reported a prospective case-control study in which Marlex mesh overlay was found to eliminate prolapse recurrence, whereas 33% of patients who underwent anterior colporrhaphy alone experienced recurrence. Marlex mesh was associated with mesh erosion in 25% of patients ([Julian, 1996](#)). A retrospective review of Marlex mesh in 142 women with a mean follow-up of 3.2 years found no recurrence of prolapse and a 2% mesh erosion rate ([Flood et al, 1998](#)). Nicita described the use of polypropylene mesh for the treatment of anterior vaginal wall prolapse ([Nicita, 1998](#)). He sutured the mesh to the anterior aspect of the ATFP on each side using 3-0 Prolene sutures. With 2 years of follow-up, only 3 of the 44 patients (7%) had prolapse recurrence. The only patient who developed dyspareunia had vaginal mesh extrusion (exposure), and this was managed with mesh trimming and vaginal closure. Several subsequent studies using polypropylene mesh reported variable success ranging from 76% to 98% ([de Tayrac et al, 2002, 2005, 2006b; Salvatore et al, 2002; Cervigni et al, 2008; Sivaslioglu et al, 2008](#)). [De Tayrac and colleagues in 2002](#) described placement of polypropylene mesh (Gynemesh, Ethicon) into the retropubic space in a tension-free fashion without suture fixation ([de Tayrac et al, 2002](#)). The lateral extensions of the mesh were placed in contact with the ATFP and

anchored with a transobturator approach. A total of 48 women with grade 3 and 4 cystoceles underwent this procedure. After a mean follow-up of 18 months, the authors reported an anatomic success rate of 97.9%. Vaginal mesh extrusion was noted in 8.3%. In a subsequent series with 87 women and with 24 months of follow-up, de Tayrac again used Gynemesh and found that 77 women (88.5%) were cured of their symptomatic anterior vaginal wall prolapse, defined as POP-Q stage 0 or 1 (de Tayrac et al, 2005). Of the 7 patients with recurrent cystoceles, 5 were asymptomatic. Vaginal mesh extrusion was again noted in 8.3%, and the de novo dyspareunia rate was 16.7%.

In a prospective study of 98 patients with stage 3 or 4 cystoceles, Rodríguez and colleagues attached a 5- × 5-cm piece of polypropylene mesh to the obturator internus fascia using 2-0 polyglactin suture after repair of the central defect with horizontal mattress sutures of 3-0 polyglactin (Rodríguez et al, 2005) (Fig. 83-16). All patients underwent a distal urethral polypropylene sling regardless of any SUI symptoms. The researchers reported an 85% anatomic success rate, defined as stage 0 or 1. Three patients who did not report SUI before the procedure developed mild de novo SUI after the procedure. Overall QoL associated with genitourinary symptoms improved from 4.7 (unhappy) to 1 (pleased) ($P < .005$).

Carey and colleagues reported on 139 women randomized to mesh augmented anterior and posterior repair versus anterior and posterior colporrhaphy (Carey et al, 2009). No statistical difference in outcomes was noted with either objective or subjective measures. De novo dyspareunia rates were equal in the groups. Vaginal mesh exposure occurred in 5.6%.

Nguyen and colleagues used the armed Perigee device (American Medical Systems, Minnetonka, MN) in their randomized controlled trial of 76 women (Nguyen and Burchette, 2008). A marked improvement in objective anatomic outcomes at 1 year was noted compared with women who underwent anterior colporrhaphy (87% vs. 55%, $P < .05$). QoL, sexual activity, and dyspareunia rates were similar in the groups. There was a 5% mesh erosion rate and a 2% rate of transient leg pain that diminished by 8 weeks.



Figure 83-16. Anterior compartment repair with polypropylene mesh graft. Polypropylene mesh is anchored to the uterosacral ligament at the bladder base, laterally to the obturator fascia and distally to the bladder neck using 2-0 polyglactin suture. (From Rodríguez LV, Bukkapatnam R, Shah SM, et al. Transvaginal paravaginal repair of high-grade cystocele central and lateral defects with concomitant suburethral sling: report of early results, outcomes, and patient satisfaction with a new technique. *Urology* 2005;66[Suppl. 5A]:57-65.)

In a randomized controlled trial of 202 women with anterior vaginal wall prolapse, Nieminen and colleagues compared anterior colporrhaphy ($n = 97$) with the same procedure reinforced with low-weight polypropylene mesh ($n = 105$) (Hiltunen et al, 2007; Nieminen et al, 2010). After 3 years of follow-up, the addition of the polypropylene mesh to the anterior repair did statistically decrease the risk of recurrent stage 2 or greater anterior prolapse. Recurrence was noted in 14 of 105 women in the mesh group versus 40 of 97 women in the group with no graft ($P < .0001$). However, there was no statistically significant difference in symptomatic outcomes (pelvic pressure, vaginal bulge, or difficulty with bladder emptying) between the groups. Importantly, 18 patients in the mesh group (17.3%) had vaginal extrusion of the mesh; however, the use of mesh was not associated with an increase in dyspareunia.

Altman and colleagues reported on the multicenter randomized trial of the armed Gynecare Prolift device (Ethicon; not currently available in the United States) versus anterior colporrhaphy (Altman et al, 2011). According to a composite measure of both anatomic reduction and lack of bulge symptoms at 1 year, 61% of women in the Prolift group and 35% in the anterior colporrhaphy group achieved success. Subjective success was reported in 75% of the Prolift group and 62% of the anterior colporrhaphy group ($P = .008$). Prolift was associated with de novo SUI (12.3% vs. 6.0%), dyspareunia (7.3% vs. 2%), and a reoperation rate of 6% versus 0.5%. The mesh exposure rate was 11.5%.

Vollebregt and colleagues reported on a multicenter randomized trial of the armed Avaulta device (C.R. Bard, Murray Hill, NJ; not available in the United States) versus anterior colporrhaphy (Vollebregt et al, 2011). At 1 year, objective success was 91% in the Avaulta group versus 41% in the anterior colporrhaphy group. No subjective difference was noted in this study. The mesh exposure rate was only 4% and was felt to be the result of not performing a concomitant hysterectomy and/or collagen coating of the Avaulta mesh.

A 2013 Cochrane review reported that standard anterior repairs were associated with more postoperative anterior wall prolapse than polypropylene mesh repairs (relative risk [RR] 3.15; 95% confidence interval [CI] 2.50 to 3.96) and a higher rate of subjective failure (28% vs. 18%, RR 1.62, 95% CI 1.22 to 2.14) (Maher et al, 2013b). Further prolapse surgery was not more common in the anterior colporrhaphy group, and no differences in QoL data or de novo dyspareunia were identified. De novo SUI was greater in the mesh repair group (RR 1.8, 95% CI 1.0 to 3.1). The cumulative mesh erosion rate was 11.4%, and the reoperation rate to correct the erosion was 6.8%.

Alteration of the vaginal axis with compensatory prolapse in an untreated compartment has been well reported. Development of apical and/or posterior prolapse (stage 2 or greater) after an anterior repair with Prolift was seen in 46% of 150 women (Withagen et al, 2010). Pooled analysis of two studies that reported de novo prolapse after anterior repair (Nieminen et al, 2010; Vollebregt et al, 2011) showed a lower rate after anterior colporrhaphy versus anterior mesh repair (9.5% vs. 17.7%, RR 0.49, 95% CI 0.24 to 0.97).

Cadaveric Fascia (Table 83-5). Cadaveric fascia lata with or without pubovaginal sling has shown efficacy rates of 81% to 100% for the treatment of anterior vaginal wall prolapse (Kobashi et al, 2000; Groutz et al, 2001; Powell et al, 2004; Frederick and Leach, 2005). Kobashi and colleagues first described the cadaveric prolapse repair and sling procedure (CaPS) as combined treatment of both symptomatic cystocele and SUI (Kobashi et al, 2000). The procedure was performed transvaginally using a 6- × 8-cm piece of cadaveric fascia lata and bone anchors. Groutz and colleagues treated 21 women with cadaveric fascia lata anchored to the ATFP bilaterally and the cardinal and uterosacral ligaments apically (Groutz et al, 2001) (Fig. 83-17). In a larger study ($n = 251$) with a mean follow-up of 2 years after CaPS, Frederick and Leach noted a symptomatic cystocele recurrence rate of only 7% (Frederick and Leach, 2005). The cured or dry rate for SUI was only 56%, with most of the failures occurring beyond 1 year; the authors questioned the long-term efficacy of the sling portion of the procedure.

TABLE 83-5 Outcomes of Transvaginal Uterosacral Ligament Repairs

AUTHOR AND YEAR	N (COMPLETED FOLLOW-UP)	MEAN FOLLOW-UP IN MONTHS (RANGE)	SUCCESS RATE PERCENTAGE IN ALL COMPARTMENTS	METHOD OF EVALUATION	RECURRENCE RATE BY SEGMENT
Jenkins, 1997	50 (47)	33 (6-48)	96%	Physical examination	Anterior 4%
Comiter et al, 1999	104 (100)	17.3 (6.5-35)	96%	Baden-Walker	Apex 4%
Barber et al, 2000	46 (39)	15.5 (3.5-40.8)	60.6% anatomic 90% symptoms	POP-Q Symptom Assessment	Apex 5% Anterior 18% Posterior 20%
Shull et al, 2000	302 (289)	(2-38)	87%	Baden-Walker	Apex 1.3% Anterior 9% Posterior 2.7%
Karram et al, 2001	202 (168)	21.6 (6-36)	92.8% anatomic 89% symptoms	Baden-Walker Symptom Assessment	Apex 1% Ant and Post 11%
Amundsen et al, 2003	33	28 (6-43)	82%	POP-Q	Apex 6% Posterior 12%
Silva et al, 2006	72	61.2 (42-90)	84.7%	POP-Q	Apex 2.8% Anterior 4.2% Posterior 8.3%
Antovska and Dimitrov, 2006	32	24.5 (9-42)	87.50%	POP-Q	Apex 3.1% Anterior 12.4% Posterior 6.2%
Wheeler et al, 2007	35	24.3 (9-46)	100% anatomic 88.9% symptoms	POP-Q Symptom Assessment	Apex 0%
De Boer et al, 2009	156 (98)	12	50%	POP-Q	Apex 4.2% Anterior 46% Posterior 20%
Fatton et al, 2009 (extraperitoneal)	123 (110)	48 (6-60)	85.5%	POP-Q	Apex 4.6%
Doumouchsis et al, 2011	42 (39)	59.4 (40-79)	66.7%	Baden-Walker POP-Q	Apex 2.6% Anterior 30.8% Posterior 33.3%

POP-Q, Pelvic Organ Prolapse Quantification System.

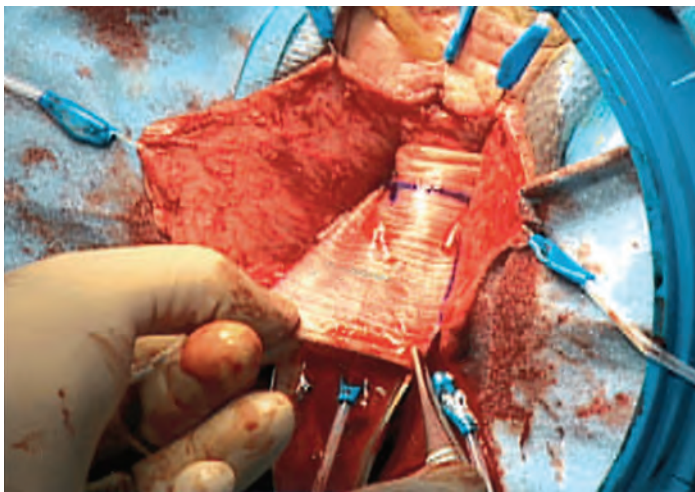


Figure 83-17. Anterior compartment repair with cadaveric fascia graft. Cadaveric fascia patch was tailored appropriately. Typically a 5- × 7-cm patch is more than adequate. (From Groutz A, Chaikin DC, Theusen E, et al. Use of cadaveric solvent-dehydrated fascia lata for cystocele repair—preliminary results. *Urology* 2001;58:179-83.)

Gandhi and colleagues published a prospective randomized controlled trial ($N = 162$) comparing ultralateral anterior colporrhaphy with 0 polyglactin suture versus the same colporrhaphy reinforced with cadaveric fascia lata in women with grade 2 or higher anterior vaginal wall prolapse (Gandhi et al, 2005). The addition of the fascia lata patch to the anterior repair did not statistically decrease the risk of recurrent prolapse ($P = .23$). Of the 39 patients with recurrent prolapse, 26 (67%) were asymptomatic. Concomitant transvaginal Cooper ligament sling was associated with a significant decrease in recurrent prolapse (odds ratio [OR] 0.015, $P < .0001$).

Cadaveric dermis has been used in the treatment of anterior compartment prolapse with efficacy of 42% to 84% at 2 years of follow-up (Chung et al, 2002; Clemons et al, 2003; Behnia-Willison et al, 2007). Chung and colleagues described anchoring the proximal portion of the 3- × 7-cm graft to the uterosacral-cardinal ligament complex, and the distal portion was used as the sling (Chung et al, 2002). Patients with lateral and paravaginal defects were excluded. Clemons and colleagues described a vaginal paravaginal repair using cadaveric dermis in 33 women with recurrent stage 2 or with primary or recurrent POP-Q stage 3 or 4 cystoceles (Clemons et al, 2003). The 3- × 7-cm graft was positioned over the bladder base and secured to the ATRP with four sutures of 2-0 braided permanent polyester bilaterally.

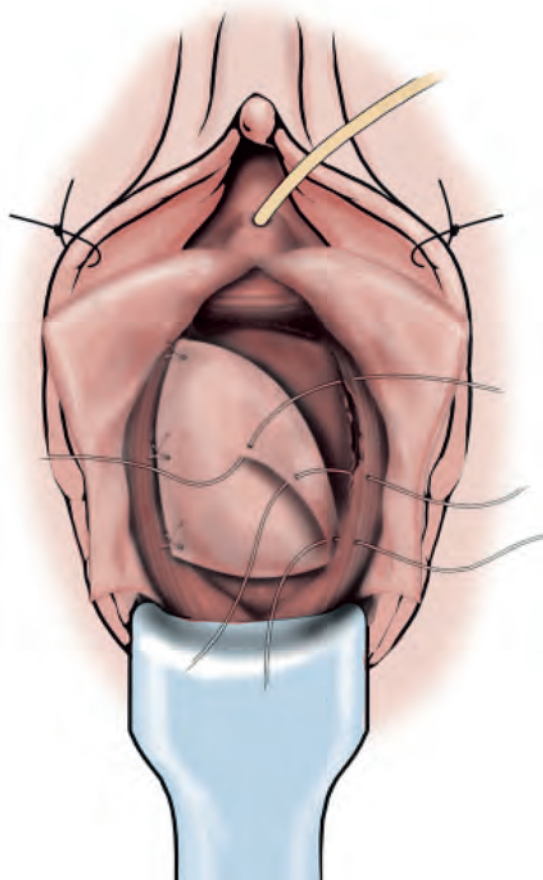


Figure 83-18. Anterior compartment repair with porcine dermis graft. Three pairs of delayed absorbable sutures are inserted into the arcus tendineus fasciae pelvis and into the porcine dermis patch. (From Gomelsky A, Rudy DC, Dmochowski RR. Porcine dermis interposition graft for repair of high grade anterior compartment defects with or without concomitant pelvic organ procedures. *J Urol* 2004;171:1581-4.)

Porcine Dermis (see Table 83-4). The majority of clinical experience in the use of xenografts for POP has been with porcine dermis. Pelvicol (C.R. Bard) is acellular cross-linked porcine dermis (Chen et al, 2007). Gomelsky and colleagues reported favorable, durable outcomes using a 6- × 8-cm piece of porcine dermis sutured laterally to the ATFP to correct high-grade cystoceles (Gomelsky et al, 2004) (Fig. 83-18). In a retrospective review of 70 patients, 61 (87%) had no cystocele recurrence after a mean follow-up of 24 months. Of the 9 patients (13%) with recurrent cystoceles, none were symptomatic. One patient had superficial vaginal wound separation, which was treated with conservative measures.

Meschia and colleagues published a prospective randomized controlled trial comparing anterior colporrhaphy with 0 polyglactin suture (n = 103) versus the same colporrhaphy reinforced with a 4- × 7-cm piece of Pelvicol (n = 98) in women with stage 2 or higher anterior vaginal wall prolapse as defined by POP-Q (Meschia et al, 2007). After 1 year of follow-up, treatment in the women randomized to receive the Pelvicol graft failed 7% of the time compared with the 19% failure rate in those women who underwent the anterior colporrhaphy alone (P = .019). One patient who received the Pelvicol graft had vaginal extrusion of the material 1 month after surgery. There were no differences between the two groups in the incidence of postoperative dyspareunia.

Handel compared two different grafts (polypropylene mesh [n = 25] and porcine dermis [n = 56]) versus traditional anterior colporrhaphy with suture alone (n = 18) (Handel et al, 2007). For

patients undergoing repair with a graft, it was anchored to the levator fascia bilaterally and to the uterosacral-cardinal ligament complex apically. With a mean follow-up of 13.5 months, there was no significant difference in failure rate (defined as grade 2 or greater) among the three groups. There was a 21% rate of vaginal extrusion of the porcine dermis.

SIS has also been compared with colporrhaphy alone in a randomized controlled trial (N = 57) (Feldner et al, 2010). The SIS group had 86.2% anatomic cure versus 59.3% in the colporrhaphy group (P = .03). Both operations significantly improved QoL without differences noted between the groups. No infections or erosion were discovered.

Biologics versus Mesh. Natale and colleagues performed a prospective randomized trial (N = 190) comparing polypropylene mesh (Gynecare) with porcine dermis (Pelvicol) in women with recurrent anterior wall prolapse (Natale et al, 2009). Objective cure was 71.9% in the mesh group and 56.4% in the porcine dermis group (P = .06). No difference in subjective cure was noted; however, a better impact of surgery on sexual function was reported in the porcine group. Mesh erosion occurred in 6.3% of the mesh group, and no erosions were seen with porcine dermis (P = .03).

Menefee and colleagues performed a randomized clinical trial comparing anterior colporrhaphy, vaginal paravaginal repair using porcine dermis, and vaginal paravaginal repair with self-styled polypropylene mesh (Menefee et al, 2011). Two-year follow-up was completed on 78 of 99 (79%) enrolled patients. Mesh repairs had the lowest anatomic failure rate (18%), followed by porcine dermis (46%, P = .015), then colporrhaphy (58%, P = .002). Subjective improvement in prolapse and voiding scores were similar, and composite failure was no different among groups (4% mesh, 12% porcine, 13% colporrhaphy). Mesh erosion was reported in 14% and porcine erosions in 4% (P = .413).

A 2013 Cochrane review concluded that objective failure rates were higher with colporrhaphy alone than with the use of biologic graft (RR 2.08, 95% CI 1.08 to 4.01) (Maher et al, 2013b). Subjective cure rates were not different between groups.

Complications. Vaginal exposure (extrusion) has been reported in anterior compartment prolapse repair with most materials. In 21 trials on mesh-augmented repairs summarized in a Cochrane review, the mean mesh erosion rate was 11.4% (64 of 563), with 6.8% (32 of 470) undergoing surgical intervention for the erosion (Maher et al, 2013b). Reoperation rates for prolapse, QoL measures, and de novo dyspareunia were no different in women undergoing native tissue repair versus mesh repair (Maher et al, 2013b). Dyspareunia has also been reported in 3.1% to 19% of patients with anterior colporrhaphy (Dwyer and O'Reilly, 2004; Yan et al, 2004; Milani et al, 2005). Blood loss (mean difference [MD] 64 mL, 95% CI 48 to 81), operating time (MD 19 min, 95% CI 16 to 21), recurrences in apical or posterior compartment (RR 1.9, 95% CI 1.0 to 3.4), and de novo SUI (RR 1.8, 95% CI 1.0 to 3.1) were significantly higher with mesh repair than with native tissue repair.

The Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) released a position statement in July 2011 in response to the FDA safety communication regarding the use of mesh for prolapse surgery. "The contemporary incorporation of mesh into surgical repair has pros and cons. Mesh may improve long-term anatomic results of surgery as compared with nonmesh repairs for some types of prolapse but is also associated with risks to the patient including vaginal extrusion, erosion, sexual dysfunction, urinary tract injury, pain, and other complications. However, it is important to recognize that many of these complications are not unique to mesh surgeries and are known to occur with non mesh procedures as well." SUFU concluded that it is not feasible "to make universal recommendations for or against the utilization of vaginal mesh based on the scientific evidence base currently available. There exists a population of patients for whom mesh has potential benefit. For these individuals, it may be appropriate to consider the implantation of transvaginal mesh if the potential risks and benefits are understood by the surgeon and the patient" (SUFU, 2011).

Other Procedures to Correct Anterior Compartment Defects

Abdominal Paravaginal Repair

Technique (Fig. 83-19). Positioning and preparation of the patient to allow both abdominal and vaginal access initiate the repair. The bladder is drained. The retropubic space is entered through either a low midline or transverse incision. In addition, this may be accomplished laparoscopically. The bladder neck, symphysis pubis, endopelvic fascia, ATRP, and obturator fascia should all be clearly identified. The site of normal vaginal attachment on the pelvic sidewall from the interior aspect of the superior pubic ramus to the ischial spine is then identified. The surgeon's nondominant hand is placed into the vagina and used to elevate the lateral superior vaginal sulcus to its site of normal attachment along the course of the ATRP. With the bladder retracted medially, four to six interrupted nonabsorbable sutures are placed at 1-cm intervals through the ATRP, extending from the ischial spine to the pubic bone. These sutures are then placed in the appropriate location in the lateral

wall of the vagina. Care is taken to avoid paravaginal veins, which commonly course through this area. Elevating the vagina to its normal anatomic position to localize suture placement site may facilitate vaginal suture placement. After the sutures are tied, cystoscopy must be performed to confirm ureteral patency and the absence of intravesical sutures. The incision is closed and the catheter is left indwelling.

Results (see Table 83-4). Richardson popularized the abdominal PVdR (Richardson et al, 1976). In a retrospective study of 233 patients with follow-up spanning 2 to 8 years, Richardson reported an anatomic cure rate of 95% (Richardson et al, 1981). Of these patients, 53 (23%) had previously undergone 1 or more anterior vaginal wall prolapse repairs. No patient required transfusion. Eighty-eight percent of the women with preoperative SUI were cured after abdominal paravaginal repair.

Other authors published the results of case series that demonstrated similar encouraging anatomic results and SUI cure rates of 85% to 97% after abdominal paravaginal repair (Baden and Walker,

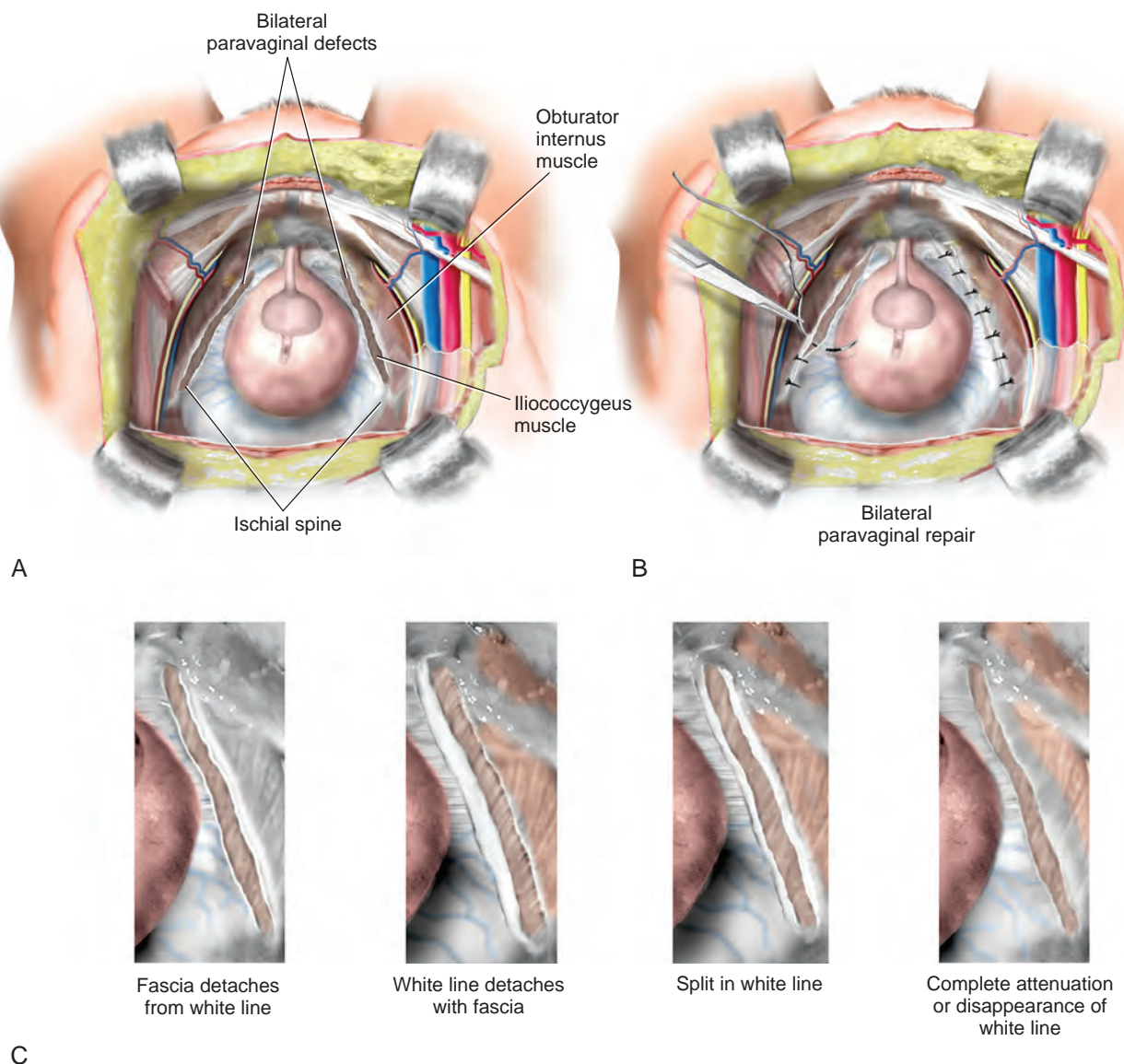


Figure 83-19. A-C, Abdominal paravaginal repair. Paravaginal defect repair as viewed from the retropubic space: approximation of the pubocervical fascia medially to the arcus tendineus fasciae pelvis laterally with 2-0 braided nonabsorbable suture. Note the vertical orientation of the vaginal vessels in relation to the transverse orientation of the bladder vessels. (From Baggish M, Karram M. Atlas of pelvic anatomy and gynecologic surgery. 3rd ed. Philadelphia: Saunders; 2010.)

1987; Shull and Baden, 1989). However, evidence over the last 15 years suggests that abdominal PVdR is not as effective as either the Burch colposuspension or suburethral sling for the treatment of SUI. In 2000, Colombo and colleagues published the results of a randomized trial comparing PVdR versus Burch colposuspension for the treatment of SUI in 18 patients (Colombo et al, 2000). With a mean follow-up of 2.2 years, the objective (urodynamic) cure rates were 100% for Burch colposuspension and 61% for abdominal PVdR. Colombo found that Burch colposuspension increased the functional urethral length and pressure-transmission ratio in the proximal urethra, whereas the abdominal paravaginal repair did not. Bruce and colleagues examined the abdominal PVdR in the treatment of women with both lateral cystocele and symptomatic SUI (Bruce et al, 1999). In this retrospective cohort of 52 patients, half underwent abdominal PVdR and half underwent abdominal PVdR with pubovaginal sling using rectus fascia. All the patients who underwent concomitant sling procedures had intrinsic sphincter deficiency (ISD). With a mean follow-up of 17 months, 4 patients (8%) had recurrent cystocele, 3 patients developed vault prolapse, and 1 patient developed an enterocele. Thus, the overall prolapse cure rate was 85%. Finally, the overall cure rate for SUI was 72% in the group that underwent PVdR alone and 85% in the group that underwent PVdR and pubovaginal sling procedures.

Anterior Compartment Repair with Sling. In patients with high-stage anterior compartment prolapse, the descent may create urethral kinking and urethral compression (Gallentine and Cespedes, 2001) (Fig. 83-20). This compression may prevent leakage of urine despite poor urethral function, thereby unmasking SUI after prolapse correction. Documenting the presence of SUI in patients with the prolapse reduced is helpful in the preoperative planning of women with high-grade anterior compartment prolapse. SUI occurring in presumably continent women after prolapse correction is known as *occult SUI*. It is essential for women with high-stage prolapse to undergo an evaluation with the prolapse reduced in order to identify those at risk for occult SUI. In three prospective studies, POP repair in clinically continent women was shown to result in postoperative SUI in 8.3% to 22% (Stanton et al, 1982; Borstad et al, 1989; Ballert et al, 2009).

To diagnose occult SUI, the prolapse may be reduced with vaginal packing, rectal swabs, a speculum blade, or a pessary. Ghoniem and colleagues used a vaginal pack (formed from two rolled 4 × 4 gauzes) to reduce large cystoceles and found occult SUI

in 69% of the women (Ghoniem et al, 1994). They found that the vaginal pack provided superior visualization of the vesicourethral angle during fluoroscopic urodynamics. Gallentine used gauze packing and a speculum blade to reduce high-stage POP and found occult SUI in at least 50% of the women with high-grade anterior compartment prolapse (Gallentine and Cespedes, 2001). Using a fitted vaginal pessary, Chaikin and colleagues detected occult SUI in 58% of the women (Chaikin et al, 2000). They also noted that none of the women had urethral obstruction after pessary placement. Multiple techniques are used to reduce prolapse, and these methods are not standardized. This has led to variance in the reported incidence of occult SUI (Haessler et al, 2005). Veronikis and colleagues compared prolapse reduction with rectal swabs, a Gellhorn pessary, and a Graves speculum blade (Veronikis et al, 1997). Because prolapse reduction with rectal swabs revealed a significantly lower mid-urethral closure pressure, these authors concluded that the rectal swabs were superior. **Sensitivity and specificity data are lacking with all of the methods used to reduce POP.** Accordingly, no method for prolapse reduction has been proven to be superior.

Performing a concomitant sling procedure at the time of anterior vaginal wall prolapse repair in women without symptoms of SUI or occult SUI remains controversial. Twiss and colleagues recommended a simultaneous anti-incontinence procedure at the time of high-grade POP repair because they contend there is no correlation between the preoperative position of the urethra with any method of cystocele reduction and the ultimate position of the urethra after surgery (Twiss et al, 2007). Thus, they contend that the diagnosis of occult SUI is inconsistent and not reproducible. Consequently, occult SUI could be missed. Other authors argue that potential complications from the placement of a concomitant sling equal the risk of occult SUI and therefore it should be offered as a second-stage procedure in those whose incontinence cannot be demonstrated preoperatively (Ballert et al, 2009). Ballert and colleagues evaluated a protocol to assess the concomitant placement of mid-urethral slings at the time of vaginal prolapse surgery (Ballert et al, 2009). They performed urodynamic testing on 140 women with POP; if SUI was seen, they recommended concomitant sling with prolapse surgery. If no SUI was seen, they repeated the testing with prolapse reduction using a pessary. Again, if occult SUI was demonstrated, they recommended a sling with prolapse surgery. Using this protocol they found an equal risk of intervention as a

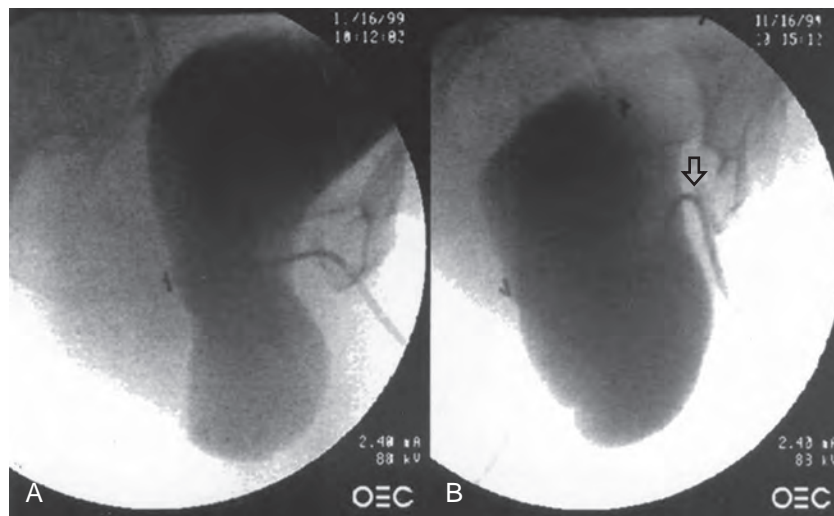


Figure 83-20. Urethral kinking caused by large cystocele. Fluorourodynamic study shows a large cystocele before (A) and after (B) Valsalva maneuver was performed. The urethra (arrow) clearly can be seen to “kink off” during the Valsalva maneuver. The patient did demonstrate severe stress urinary incontinence after prolapse reduction. (From Gallentine ML, Cespedes RD. Occult stress urinary incontinence and the effect of vaginal vault prolapsed on abdominal leak point pressures. *Urology* 2001;57:40–4.)

result of obstruction from a mid-urethral sling (8.5%) and intervention for postoperative SUI in a patient without clinical, urodynamic, or occult SUI who did not undergo a concomitant sling procedure (8.3%). Therefore, the risk of intervention resulting from sling obstruction was equal to the risk of intervention resulting from postoperative SUI when no clinical, urodynamic, or occult SUI was present preoperatively and no mid-urethral sling was placed. Because the need to intervene for complications resulting from mid-urethral sling equaled the risk of having to perform a secondary sling procedure, the necessity for secondary surgery in women without SUI after repair of anterior vaginal wall prolapse is not decreased. The risk of intervention in those with clinical symptoms of SUI but no urodynamic or occult SUI was 30%.

It has also been reported that a concomitant suburethral sling may contribute to the long-term success of anterior compartment repairs. Goldberg and colleagues demonstrated a 55% reduction in postoperative cystocele recurrence in patients who underwent a suburethral sling procedure at the time of prolapse repair (Goldberg et al, 2001). Also, Cross and colleagues reported that the support created by the simultaneous placement of a pubovaginal sling in grades 3 and 4 cystoceles was improved (Cross et al, 1997).

The Colpopexy and Urinary Reduction Efforts (CARE) trial was the first large, randomized, controlled trial evaluating a simultaneous anti-incontinence procedure with POP repair (Brubaker et al, 2006). The investigators evaluated 322 patients with stage 2 to 4 POP who underwent abdominal sacrocolpopexy (ASC), of whom 157 were randomized to concomitant Burch colposuspension and 165 were randomized to ASC alone. The addition of a Burch colposuspension to ASC decreased postoperative SUI from 44.1% to 23.6% at 3 months postoperatively. In a subsequent study examining 2-year outcomes in the same group of patients, the authors found that 32% of patients who underwent concomitant Burch colposuspension were incontinent versus 45% of patients who underwent ASC alone (Brubaker et al, 2008). Approximately one third of the women after the Burch procedure still had SUI. The Extended CARE (E-CARE) trial enrolled 213 of the original 322 participants, with 181 completing 5 years of follow-up and 121 completing 7 years (Nygaard et al, 2013). By year 7, the estimated probability of SUI in the urethropepy group was 62%, and 77% in the nonurethropepy group. The time to treatment failure for SUI was longer in the urethropepy group.

Wei and colleagues for the Pelvic Floor Disorders Network reported on 337 women enrolled in the Outcomes Following Vaginal Prolapse Repair and Mid-Urethral Sling (OPUS) trial. Women with stage 2 or higher POP without symptoms of SUI underwent randomization for a concomitant mid-urethral sling or sham at the time of vaginal prolapse surgery. At 12 months, urinary incontinence was present in 27% of sling patients and 43% of sham patients ($P = .002$). Higher rates of adverse events were seen in the sling group (bladder perforation, UTI, bleeding, incomplete bladder emptying; $P \leq .05$ for all). There was no difference noted between groups in patient-reported pelvic floor symptoms (Wei et al, 2012).

In summary, there is no standardization of testing for occult SUI. However, it is clear that all women with advanced-stage anterior compartment prolapse should be screened for the presence of SUI with the prolapse reduced, and consideration should be given to a concomitant anti-incontinence procedure. All women with preoperative symptoms of SUI, occult SUI, or urodynamically proven SUI are at elevated risk of postoperative SUI and should consider a simultaneous anti-incontinence procedure. The risks and benefits of a prophylactic anti-incontinence procedure on continent women should be reviewed with each patient. The current literature supports selective use of an anti-incontinence procedure at the time of POP repair.

Apical Vaginal Compartment

Middle compartment defects involve the vaginal apex. The organs involved in defects of the middle compartment include the uterus, bowel or omentum, and depending on the size, bladder and rectum. The apex remains the cornerstone of vaginal support, and failure

KEY POINTS: ANTERIOR COMPARTMENT REPAIR

- Anterior compartment defects can be central, lateral, or combined. A central defect results from midline separation or attenuation of the pubocervical (perivesical) fascia. A lateral defect results when the pubocervical fascia detaches from the ATFP.
- Most anterior compartment defects have concomitant lateral and/or apical defects; isolated anterior colporrhaphy is not recommended when additional defects are present.
- Anterior compartment prolapse repair does not suspend the vaginal apex. Patients with anterior compartment and apical prolapse need concomitant repairs that address each defect.
- Anatomic results after anterior repair are improved by the addition of both biologic and synthetic grafts. However, graft complications may occur. Subjective results appear unchanged with the addition of biologic grafts but are improved with the addition of synthetic grafts. QoL measures, reoperation for prolapse, and dyspareunia rates are unchanged by the addition of synthetic mesh. The risk-benefit ratio of graft use needs to be thoroughly discussed with the patient.
- Anterior colporrhaphy and paravaginal repairs are both ineffective alone in the treatment of SUI.
- All women with advanced-stage anterior compartment prolapse should be screened for occult SUI with prolapse reduction, and the risks and benefits of a concomitant anti-incontinence procedure should be discussed with the patient.

to ensure apical support at the time of prolapse correction will undoubtedly increase the risk of recurrence exponentially.

McCall highlighted this importance when he described his technique of posterior culdoplasty (McCall, 1957). This technique closed the peritoneal cul-de-sac posteriorly, thereby preventing enterocele formation, and emphasized the importance of apical fixation. In this landmark paper, he described the following technique: "The posterior culdeplasty is a simple procedure which obliterates the redundant cul-de-sac of Douglas by a series of continuous sutures so as to suspend it by the uterosacral ligaments which then are brought together in the midline.... The first suture picks up the left uterosacral ligament about 2 cm above its cut edge. Several bites of redundant sac are then taken at 1-2 cm intervals until the right uterosacral ligament is reached and picked up.... Three external through-and-through sutures of this type are usually inserted, each one higher than the last, so as to be placed through the uterosacral ligaments at intervals between the internal sutures. The highest of these is placed just at the top of the newly supported vagina. It is this suture, which brings the new vaginal vault to the highest possible level thus insuring that the vagina will be as long as possible in each instance. The internal sutures are now tied and the previously herniated cul-de-sac obliterated into a firm, shelflike structure. The external sutures are then tied and the vaginal mucosa snugged against this shelf."

Apical Vaginal Prolapse Repairs

The uterosacral vault suspension preserves the orientation of the vaginal axis in its natural position, thus potentially preventing recurrence of prolapse in other segments (Silva et al, 2006). Several authors have reported breakage of the uterosacral ligaments at specific points rather than an attenuation of the uterosacral-cardinal ligament complex, thus allowing for a more site-specific repair (Jenkins, 1997; Barber et al, 2000; Shull et al, 2000). These findings are in contrast to a histologic assessment of the uterosacral ligaments that calls into question the integrity of this structure for long-term apical support (Cole et al, 2006).

Surgical Anatomy of the Uterosacral Ligaments. The ligament is attached broadly to S1 to S3, variably to S4 (Buller et al, 2001) (Figs. 83-21 and 83-22). It proceeds in a fanlike manner anterolaterally to the cervical os and also onto the proximal portion of the posterior vagina. The ligament can be divided into three portions: the sacral, intermediate, and cervical portions. Beneath the sacral portion of the ligament runs the superior gluteal vein. Although there is great variability in the location of the ureter relative to the ischial spine (Karram et al, 2001), the ureter has been reported to be near the anterior margin of the uterosacral ligament near the cervix. As the ureter courses distally, the distance between the uterosacral ligament and ureter decreases from 4 cm near the sacrum to 0.9 cm near the cervix (Buller et al, 2001). Because of the fibrous tissues of the ureteral sheath, the ureter is subject to kinking from

traction caused by sutures placed in the adjacent tissue (Dwyer and Fattou, 2008). If sutures are placed close to the sacrum, there is a risk of entrapping fibers of the sacral plexus trunk of S1 to S4 (Siddique et al, 2006; Wieslander et al, 2007). This can result in buttock pain, which radiates to the posterior thigh and popliteal fossa. Placing sutures in the intermediate portion of the uterosacral ligament appears to be the optimal site; there are fewer structures to be potentially affected, and it provides a stable point of fixation. There is decreased chance of traction affecting the ureter at this point, because it is farther away from the ureter and its sheath. Placing the sutures from lateral to medial will also minimize accidentally catching either the ureter or its attachments in the stitch (Shull et al, 2000). The intermediate segment can be located 1 cm posterior along the palpable uterosacral ligament at the level of the ischial spine with the uterosacral ligament placed on tension (Buller et al, 2001). An advantage of suspension to the uterosacral ligament is that it minimizes injury to the pudendal and gluteal vessels relative to sacrospinous ligament fixation (SSLF) (Barber et al, 2000).

Technique

High Uterosacral Vaginal Vault Suspension. This procedure starts intraperitoneally (Karram et al, 2001). After hysterectomy, the apex is identified on the vaginal cuff at the 3 and 9 o'clock positions, which represent the attachments of the cardinal and uterosacral ligaments (Shull et al, 1993). It is useful to place stay sutures at these dimples before incision. The vaginal epithelium is dissected away from the peritoneum of the hernia sac. Once the dissection has mobilized the hernia sac from the epithelium to the neck of the sac, it is entered and the sac excised (Fig. 83-23). Laparotomy pads are placed to pack the bowel away. Ischial spines can then be palpated transperitoneally. The uterosacral ligaments will be located posteriorly and medially to the ischial spines. By placing traction to the stay sutures or by placing an Allis clamp at the 5 o'clock and 7 o'clock positions of the apex, the uterosacral ligament will tent and two to four nonabsorbable sutures can be placed through the uterosacral-cardinal ligament complex (Fig. 83-24). The ureters should be located lateral to the uterosacral ligaments; however, it should be noted that depending on the degree of the prolapse, there can be significant variability in their location relative to the edge of the uterosacral ligament (Silva et al, 2006). If there is any question as to their location, temporary stents may be placed to facilitate their palpation. In placing the needles through the uterosacral ligaments, it is important to pass them lateral to medial, exiting away from the ureter to avoid inadvertent inclusion into the tie (Shull et al, 2000). To ensure the proper depth, the suture should be

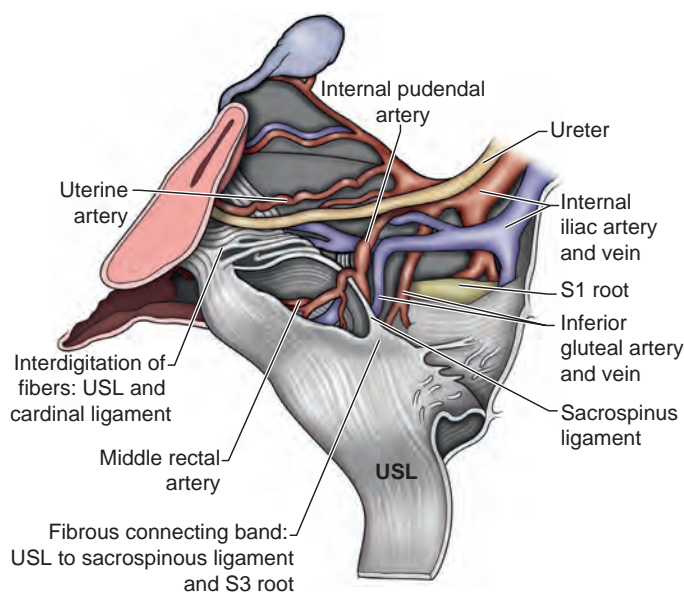


Figure 83-21. Right hemipelvis: sagittal view. The uterosacral ligament (USL) has been reflected to show subjacent anatomy. (From Buller JL, Thompson JR, Cundiff GW, et al. Uterosacral ligament: description of anatomic relationships to optimize surgical safety. *Obstet Gynecol* 2001;97:873-9.)

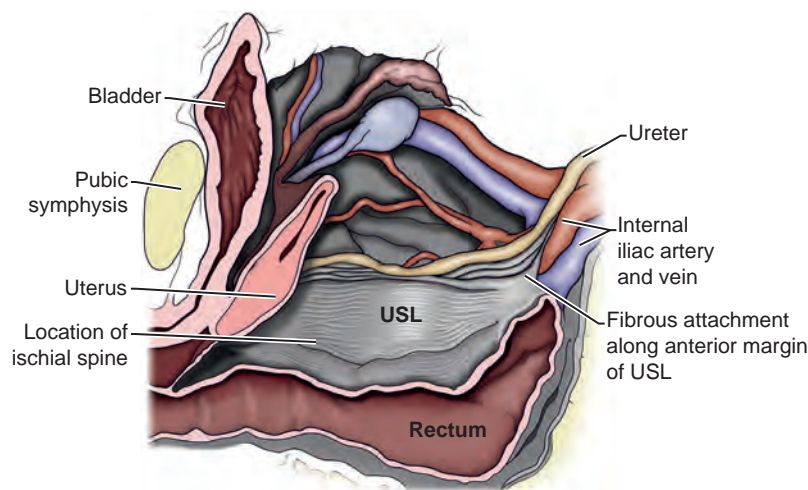


Figure 83-22. Right hemipelvis: sagittal view. The peritoneum has been removed and the uterosacral ligament (USL) was left intact to show the proximity of the ureter in this specimen. (From Buller JL, Thompson JR, Cundiff GW, et al. Uterosacral ligament: description of anatomic relationships to optimize surgical safety. *Obstet Gynecol* 2001;97:873-9.)

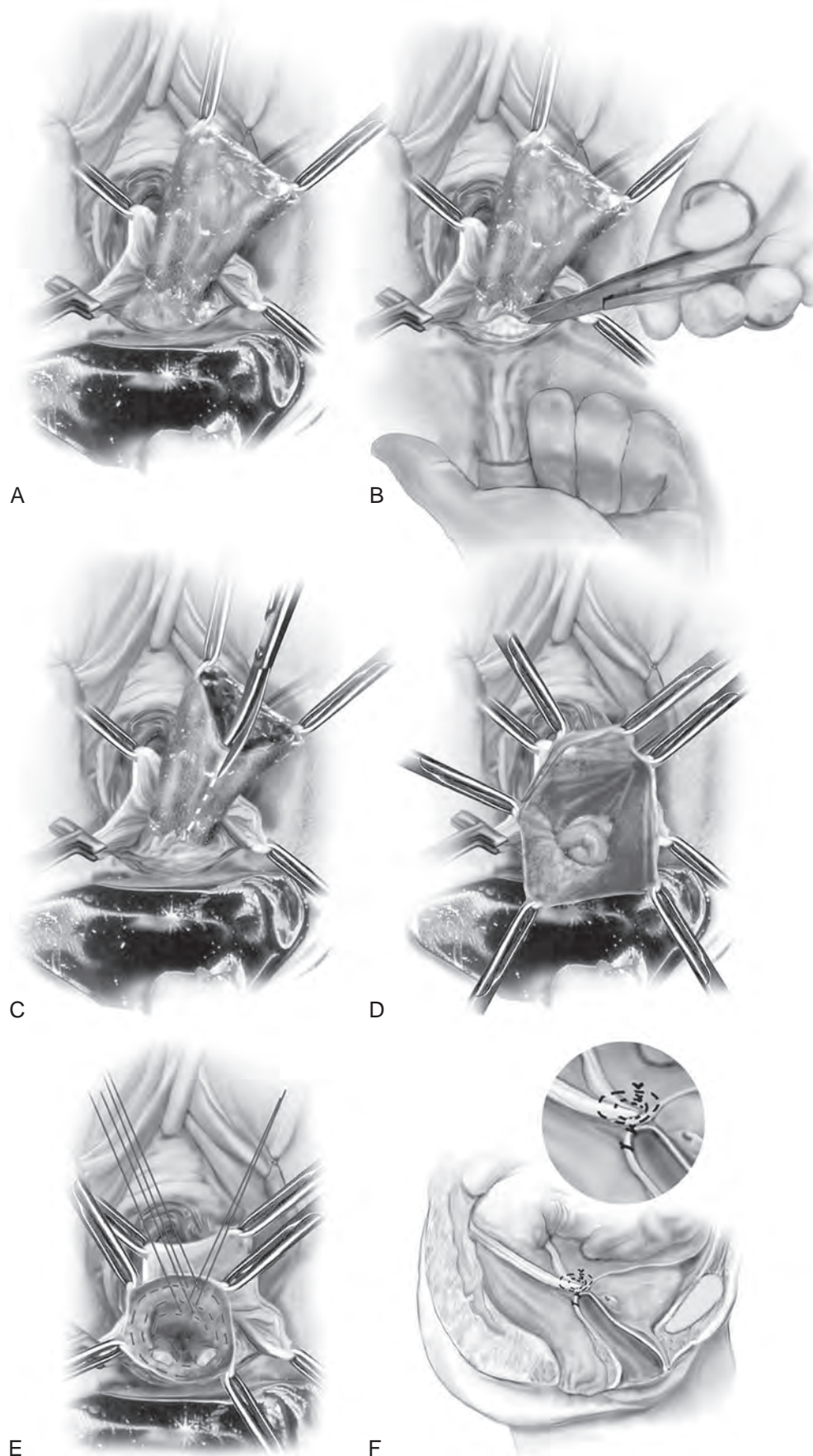


Figure 83-23. Vaginal enterocele repair. Enterocele sac is identified and opened to reduce its contents. It is then tied in a purse-string suture and the excess is excised. Before closure of the enterocele sac, the peritoneal cavity is entered to access the uterosacral ligament. (From Walters M, Karram M. *Urogynecology and reconstructive pelvic surgery*. 3rd ed. Philadelphia: Mosby; 2006.)

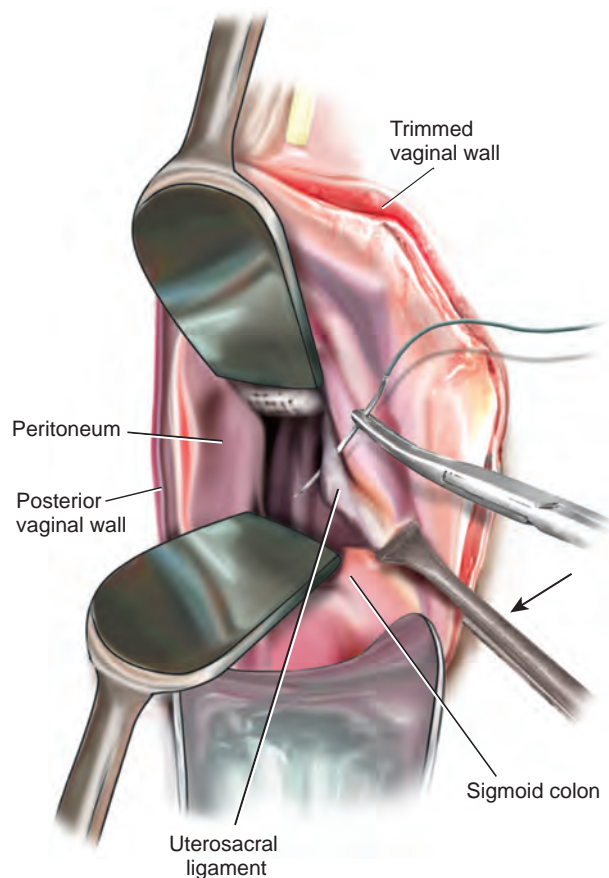


Figure 83-24. To identify the uterosacral ligament, an Allis clamp is placed on the vaginal epithelium at the right apex and pulled straight upward. With the right uterosacral ligament on tension, the uterosacral ligament is visible in the pelvis. A long Allis clamp (arrow) is used to grasp the right uterosacral ligament. (From Baggish M, Karram M. *Atlas of pelvic anatomy and gynecologic surgery*. 3rd ed. Philadelphia: Saunders; 2010.)

passed at the level of the ischial spines. Subsequent sutures are placed proximal to the last. If an anterior colporrhaphy or sling is planned, it may be done at this point. Suspensory sutures in the uterosacral ligaments are then placed in the most apical portions of the pubocervical and rectovaginal fascia. The highest sutures are then sewn to the most medial portions of the pubocervical and rectovaginal fascia. The more distal sutures are placed most laterally in the pubocervical and rectovaginal fascia and passed out of the vaginal epithelium on each side (Fig. 83-25). Cystoscopy with indigo carmine is an essential step after this procedure to confirm ureteral patency, and should be performed before trimming the suture because this will facilitate identification of the sutures if they need to be removed owing to obstruction. If no efflux of urine is seen, the sutures should be removed starting with the most lateral suture of the ipsilateral side. In addition, it is important to perform the cystoscopy after the suture is tied, not just placed (Yazdany et al, 2008). As one ties these suspending sutures, the rectovaginal fascia and pubocervical fascia are brought together at the uterosacral ligament complex, thus resuspending the apex of the vagina and closing the cul-de-sac (Fig. 83-26).

An extraperitoneal approach has also been described (Dwyer and Fatton, 2008). A midline incision is made, depending on concomitant prolapse. The vaginal epithelium is then dissected away from the endopelvic fascia, and the enterocele sac is identified and dissected free of the vault. Dissection is continued laterally until the uterosacral-cardinal ligament complex is identified posterior and medial to the ischial spine. Palpation to tent the uterosacral-cardinal ligament complex is facilitated by placing tension on the

vagina. Use of the Breisky-Navratil retractor to retract the bladder and ureters anteriorly has prevented ureteral obstruction through traction or injury (Fatton et al, 2009). Once the ligaments are identified, the sutures are placed in a similar fashion to the intraperitoneal approach. Cystoscopy and vaginal closure are performed as described previously.

Abdominal Approach to the Uterosacral Ligaments. The uterosacral ligaments may be accessed transabdominally (Lowenstein et al, 2009). This technique begins by elevating the uterus at the time of abdominal hysterectomy. Three permanent sutures are placed in each of the uterosacral ligaments proximal and medial to the ischial spine. They are numbered in the manner described by Shull (Shull et al, 2000) (Fig. 83-27). Once the hysterectomy has been performed and the cuff has been closed, the sutures are placed sequentially through the anterior and posterior leaves of the endopelvic fascia. By reapproximating the anterior and posterior muscularis of the vagina, any potential enterocele defects are closed and the cuff is elevated toward the sacrum, recreating the normal vaginal axis. Cystoscopy is performed after tying the sutures, which are left uncut until efflux of urine is demonstrated. If no urine is seen, the most lateral ipsilateral suture is removed and subsequent sutures are taken down in sequence.

Results. Transvaginal uterosacral ligament suspension has been evaluated primarily through uncontrolled retrospective case series. Table 83-5 summarizes the available literature with a mean objective success of 85% and a range of 48% to 96%. Mean reoperation rate for prolapse from the data in Table 83-5 is 5.8%. In 2010, Margulies and colleagues performed a meta-analysis and documented success based on POP-Q stage in the anterior (81.2%), apical (98.3%), and posterior (87.4%) compartments (Margulies et al, 2010). Less than half the studies in the pooled analysis reported postoperative prolapse symptoms. In those that did, 82% to 100% of patients reported relief. Ureteral kinking or injury was reported in 1% to 11% of cases. Shull and colleagues had the largest reported series of patients who underwent uterosacral ligament suspension (Shull et al, 2000). Of 289 patients who were followed, a majority (87%) had no recurrence of support defect at any site on any postoperative examination. Only 5% of the patients had grade 2 prolapse or greater. The most common site was the anterior compartment, in which 10 patients had grade 2 or 3 defects. One patient required ureteroneocystostomy. Two patients required removal of suspensory sutures. Karram and colleagues reported on 168 patients who underwent uterosacral vaginal vault suspension (Karram et al, 2001). Eighty-nine percent reported satisfaction with the results of the procedure. Ten women (5.5%) underwent subsequent surgery for recurrent prolapse. Seven women experienced a major intraoperative complication, 5 (2.4%) ureteral injuries, 1 small bowel injury, and 1 pelvic abscess requiring diverting colostomy. Silva and colleagues evaluated long-term (5.1 years) anatomic and functional outcomes of high uterosacral vaginal vault suspension (Silva et al, 2006). Surgical failure in one or more compartments occurred in 11 (15.3%) patients; apical recurrence occurred in 2 of 78 patients. Seven patients had de novo postoperative dyspareunia. Patient-reported outcomes indicated improvement in irritative voiding, obstructive voiding, stress incontinence, and overall urinary symptoms compared with preoperative scores.

A randomized controlled trial sponsored by the Pelvic Floor Disorders Network comparing uterosacral ligament suspension versus SSLF has completed enrollment of nearly 400 patients (Barber et al, 2009a). The 2-year follow-up data are not yet available. At the time this was written there were no published results, but the study aims to assess whether pelvic muscle exercises and behavioral changes around the time of apical prolapse surgery affect bladder and bowel symptoms after surgery and the success of the prolapse repair.

Fatton and colleagues examined the results of performing an extraperitoneal bilateral uterosacral vaginal vault suspension ($n = 110$) with a mean follow-up of 2 years (Fatton et al, 2009). Concurrent procedures included anterior colporrhaphy (20%), anterior mesh reinforcement (49%), posterior colporrhaphy (56%), and sling (29%). Recurrence at the apex was noted in 4.6% of patients. Global

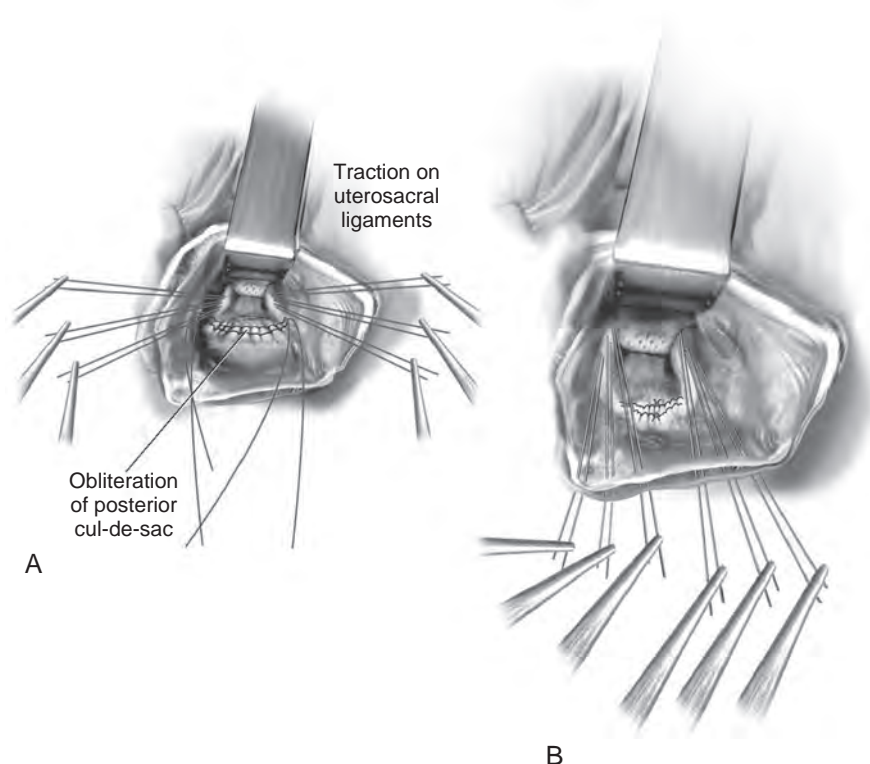


Figure 83-25. High uterosacral ligament vaginal vault suspension. Three sutures are placed from lateral to medial in each uterosacral ligament. The sutures are brought through the vaginal muscularis anteriorly (pubocervical fascia) and posteriorly (rectovaginal fascia). (From Walters M, Karram M. *Urogynecology and reconstructive pelvic surgery*. 3rd ed. Philadelphia: Mosby; 2006.)



Figure 83-26. Completed uterosacral vaginal vault suspension with anterior colporrhaphy. (From Walters M, Karram M. *Urogynecology and reconstructive pelvic surgery*. 3rd ed. Philadelphia: Mosby; 2006.)

anatomic success was reported in 85.5%. Mesh exposure occurred in 19.3%, was diagnosed within 6 months in the majority of the patients, and required conservative or minor interventions. The authors concluded that this procedure is effective at restoring apical support while avoiding the morbidity of an intraperitoneal operation.

Sacrospinous Ligament Fixation

SSLF was first described by Richter in 1942 but was not widely used until Nichols reported on the technique (Nichols, 1982). SSLF has been shown to be an effective method to correct apical prolapse

(Cruikshank et al, 2003). This technique is appealing because of its extraperitoneal approach and consistency as a strong structure on which to anchor the apex. Access to the spine was originally achieved from the posterior approach, although dissection from the anterior approach may also be performed via the paravaginal space (Cespedes, 2000; Winkler et al, 2000). The advantages of SSL suspension are success rates comparable to those of abdominal procedures (Brown et al, 1989; Imparato et al, 1992), ability to repair concomitant pelvic floor defects, absence of a laparotomy (Morley and DeLancey, 1988), shorter hospital stay (Brown et al, 1989), preservation of vaginal length and function (Morley and DeLancey, 1988; Brown et al, 1989), and cost-effectiveness (Brown et al, 1989). These reported advantages have not been fully re-evaluated in this era of laparoscopic and robotic prolapse repairs. The structures at risk with this technique include the pudendal or inferior gluteal vessels and the sciatic or pudendal nerves. Pudendal nerve entrapment results in posterior buttock pain, which may radiate down the back of the thigh. A disadvantage of this approach is the alteration in vaginal axis, which results in apical displacement posteriorly and to the right side when unilateral fixation is used. This posterior displacement can result in anterior compartment recurrence even when an anterior repair is performed (Morley and DeLancey, 1988; Shull et al, 1992; Sauer and Klutke, 1995).

Sacrospinous fixation may be performed unilaterally or bilaterally (Pohl and Frattarelli, 1997). With the unilateral suspension, right-sided placement is generally preferred. Technically, it is easier to place the sutures on the right ligament for a right-handed surgeon (Sauer and Klutke, 1995). Cespedes reported success using the bilateral anterior support and noted the advantage of a more midline location of the vaginal apex (Cespedes, 2000). Although bilateral placement has been advocated (Nichols, 1996), there is little to support the advantage of bilateral fixation over unilateral fixation when examining outcomes (Morley and DeLancey, 1988).

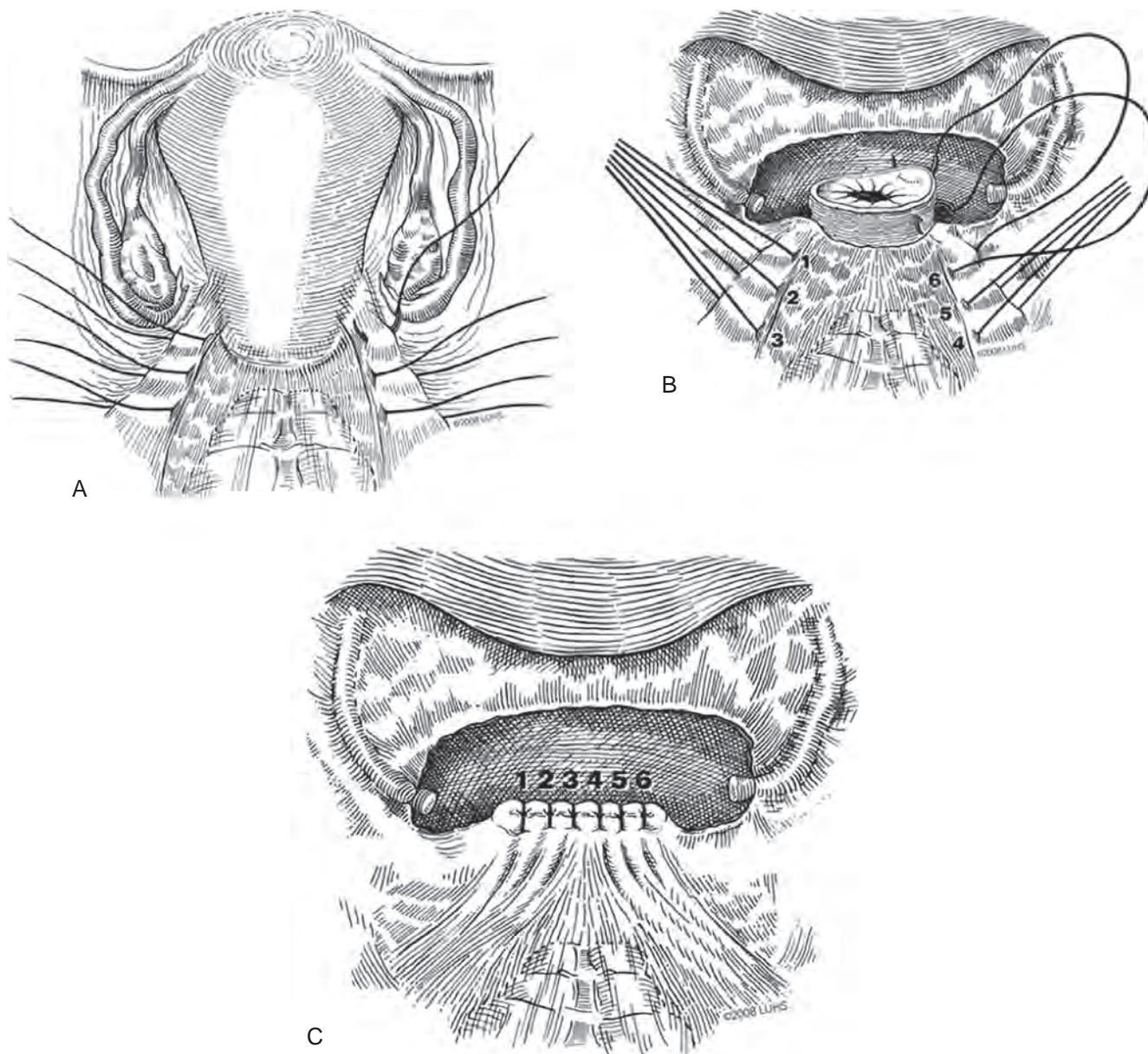


Figure 83-27. A, Three permanent sutures are placed in each of the uterosacral ligaments medial to the ischial spine. B, One end of each of the six sutures is placed serially across the vaginal apex through the anterior endopelvic fascia, and the other end is placed through the posterior endopelvic fascia. C, All sutures are tied to reapproximate the anterior and posterior vaginal muscularis, to close any potential enterocele defect, and to elevate the vaginal apex toward the sacrum. (© 2008 Loyola University Health System. Used with permission from Mary Pat Fitzgerald, MD.)

Surgical Anatomy of Sacrospinous Ligament Fixation. The SSL is approximately 7 to 8 cm in length (Morley and DeLancey, 1988) and extends from the ischial spine laterally, coursing medially under the coccygeus muscle, and inserts into the sacrum. The pudendal nerves and vessels are in close proximity to the ligament, just proximal to their course around the ischial spine (Fig. 83-28). In addition, the hypogastric plexus of veins is located superiorly and the hemorrhoidal vessels are located medially to the SSL (Morley and DeLancey, 1988); thus retraction should be carried out carefully in these areas. To avoid the gluteal vessels, the suture should be placed into the ligament and not behind it (Kettel et al, 1989). Pudendal nerve entrapment may result in pain, which localizes to the buttocks or perineum. This may be avoided by placing sutures medial to the ischial spine, about 1.5 cm (Sauer and Klutke, 1995; Alevizon and Finan, 1996). Thus the optimal position of the

suture placement is 1.5 to 2.0 cm medial to the ischial spine, directly into the SSL. Placing it too far medially may risk failure of the repair because the SSL fans and thins as it inserts into the sacrum (Sauer and Klutke, 1995). In addition, there is a higher concentration of sacral nerves in this medial location. Barksdale performed a cadaveric study to assess the histology of the SSL, taking segments near the ischial spine and middle and sacral portions of the ligament (Barksdale et al, 1997). The highest concentration of nerves was found in the sacral portion of the SSL, with the lowest being near the spine. Although it was postulated that the nerves embedded in the SSL were a potential source of neuropathic pain, no clinical correlation could be made in this cadaveric study. Lantzsch and colleagues concluded that localization and depth of the suture can also influence the occurrence and intensity of sciatic neuralgia (Lantzsch et al, 2001).

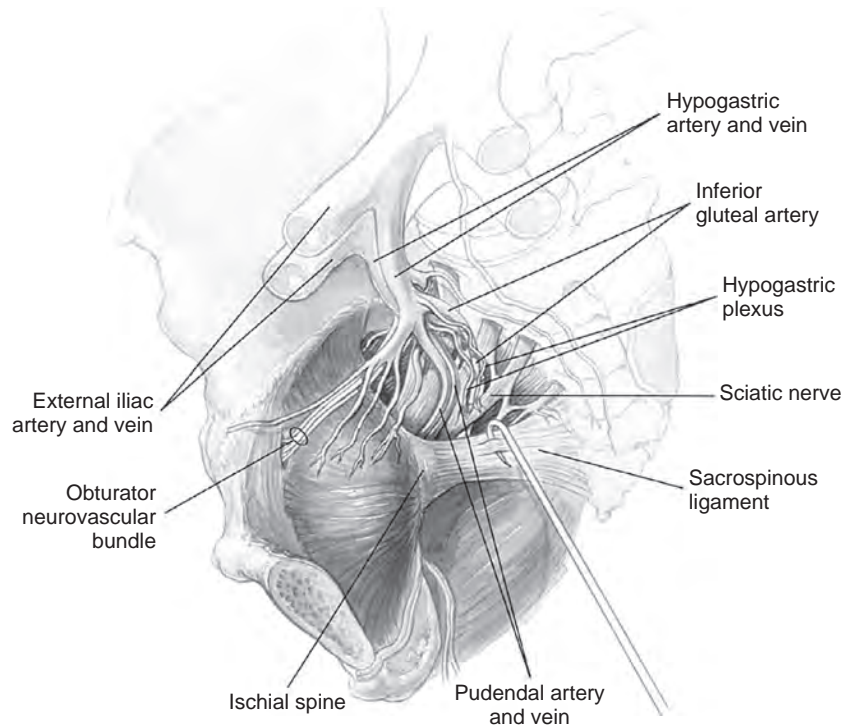


Figure 83-28. Anatomy of the sacrospinous ligament and surrounding structures. Close proximity of the pudendal vessels, hypogastric plexus, inferior gluteal vessels, and sciatic nerve should be noted. (From Walters M, Karram M. *Urogynecology and reconstructive pelvic surgery*. 3rd ed. Philadelphia: Mosby; 2006.)

Technique. The procedure starts by marking the apex of the vagina. The vaginal apex is then reduced to the SSL(s) intended to be used. This site of attachment is then tagged (or marked) for later fixation. Depending on concomitant compartmental defects, the SSL can be approached either anteriorly or posteriorly. A standard midline vaginal incision is made and the vaginal epithelium is separated from the rectovaginal septum posteriorly or the pubocervical fascia anteriorly. If an anterior compartment repair will be performed, the SSL may be approached anteriorly, exposing the paravesical space. The tissue attachments overlying the spine and ligament are swept medially. Alternatively, if the posterior approach is used, one must enter the perirectal space by bluntly mobilizing the rectum medially. On entrance to the perirectal space, the ischial spine is identified. With further dorsal and medial blunt dissection, the SSL is palpated. Blunt dissection is continued to ensure that the rectum is retracted medially, and the ligament is adequately exposed. At this point Heaney or Breisky-Navratil retractors are very useful to visualize the ligament and facilitate suture placement. In addition, lighted retractors can provide added visualization. The SSL is then palpated. The suture is placed approximately one to two fingerbreadths medial from the spine to avoid damage to the structures in the Alcock canal. Several different methods have been used to fix the suture to the sacral spinous ligament. The Capiro Suture Capturing Device or the Capiro "Thin" Suturing Device (Boston Scientific) enables the suture to be placed by palpation. Alternatively, the Miya Hook (CooperSurgical, Trumbull, CT) (Miyazaki, 1987), the Auto-suture Endo Stitch suturing device (Covidien, Norwalk, CT) (Schlesinger, 1997), a Deschamps ligature carrier, or freehand needle driver passage may be used to place the sutures under direct vision. Two sutures are most commonly placed. In cases of bilateral SSLE, one suture may be placed on each ligament. In the case of unilateral SSLE, the placement of the sutures on the ligament 2 cm apart will prevent constriction of the vaginal apex. Additional repairs may be performed at this point. Following this, the previously placed SSL sutures are brought out of the vagina to the previously marked vaginal apex (Fig. 83-29). If a permanent suture is

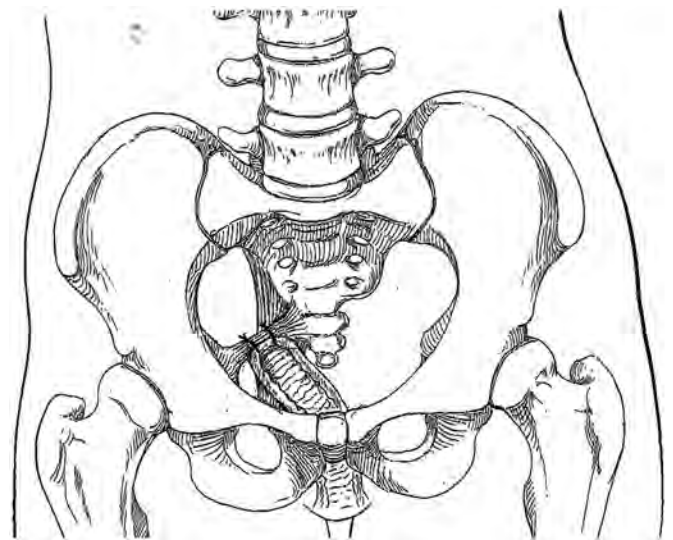


Figure 83-29. Sacrospinous ligament fixation. With a unilateral suspension, the vagina is deflected to the right side and caudally. (From Richter K, Albright W. Long-term results following fixation of the vagina on the sacrospinous ligament by the vaginal route [vaginaefixatio sacrospinialis vaginalis]. *Am J Obstet Gynecol* 1981;141: 811-6.)

used for SSLE, a pulley-stitch configuration, which ensures that the knot of the suture will remain internal, is needed. To create a pulley stitch, a knot is tied onto the fibromuscular portion on the visceral side of the vagina to create a fixed point. The free end of the suture is then pulled, thus suspending the apex to the SSL; this is then secured by tying a secure knot. Importantly, this resultant knot

remains internal and is not within the vaginal canal. Closure of the vaginal wall halfway before the sutures are tied down is useful, because the suspended apex may be quite difficult to reach. The sutures should be tied such that the vaginal apex is firmly attached to the coccygeal SSL complex with no intervening suture material bridging a gap (Morley and DeLancey, 1988; Sze and Karram, 1997). Palpation of the suture behind the vaginal cuff will ensure that the suture is tied securely. It is useful to leave the secured suture untrimmed until the cystoscopy is performed in case the suture needs to be removed. Once the efflux is visualized bilaterally, the anchoring suture is trimmed, and the remainder of the vaginal incision is closed.

Results (Table 83-6). Nichols reported outcomes of SSLF in 163 patients, some with “massive” vaginal eversion and procidentia. There were no reported recurrences of vaginal vault prolapse; however, 9 patients reported that the vagina was “too narrow” postoperatively (Nichols, 1982). This outcome was also observed in a study by Richter, who reported excellent patient satisfaction, although 8 patients were reluctant to resume sexual relations because of a perception of vaginal narrowing (Richter and Albrich, 1981). Morley and DeLancey reported on 100 patients who underwent SSLF, 33 of whom underwent isolated apical treatment, and 67 had concomitant prolapse repairs (Morley and DeLancey, 1988). Apical success was noted in 95.7%, 90.1% globally, with 4 patients having prolapse in the anterior compartment. The researchers noted that the long-term results were acceptable with minimal adverse effects.

Bilateral SSL suspension was compared with ASC in a prospective randomized study (Benson et al, 1996). Time to failure was shorter in the SSL group compared with the abdominal group (11 months vs. 22 months), with the vaginal group having 12 cystoceles requiring reoperation versus 4 cystoceles in the abdominal group. Sauer and Klutke reported on 24 patients with a mean follow up of 13.8 months (Sauer and Klutke, 1995). Blood loss was minimal and no transfusions were needed, but mild postoperative buttock pain was noted that resolved by 3 months. In 21 of 24 patients there was no recurrence of prolapse at the apex, but 1 patient underwent repeat operation for a significant cystocele. Meschia and colleagues reported on 103 patients who underwent SSLF and found excellent results for the posterior and apical compartments but disappointing results for the anterior compartment, with 16% having grade 2 or greater prolapse (Meschia et al, 1999).

The anterior compartment has been reported as a particularly vulnerable site for developing a defect after sacrospinous vaginal vault suspension. Recurrent cystoceles have been reported in 7.6% to 92% of patients after surgery (Richter and Albrich, 1981; Morley and DeLancey, 1988; Pasley, 1995). This has been attributed to vaginal retroversion (posterior displacement). This is noted not only postoperatively, but intraoperatively, although many who develop anterior defects remain asymptomatic and do not undergo subsequent surgery to correct the anterior compartment defect (Paraiso et al, 1996).

Several authors have demonstrated the feasibility and efficacy of an anterior approach to the SSL vaginal vault suspension (Cespedes, 2000; Winkler et al, 2000). Winkler reported that the anterior compartment recurrence rate after an anterior SSLF and anterior repair was 9%, in contrast to 24% after SSLF with posterior repair (Winkler et al, 2000). Cespedes reported on the bilateral anterior approach and noted no recurrences. Some of the theoretic advantages of the anterior approach include improved ability of the vagina to withstand increased intra-abdominal pressures (Pohl and Frattarelli, 1997) and less likelihood of rectal injury (Sauer and Klutke, 1995). Again, a low incidence of anterior compartment recurrence was noted, at 7% (Cespedes, 2000).

Successful healing in the short term may predict long-term success of the SSL suspension. Shull and colleagues (1992) reported on 81 women undergoing SSL suspension; 72% had previous pelvic surgery. Those who showed absence of any compartment defect at 6-week follow-up had only a 3% likelihood of requiring additional reconstructive surgery within 2 to 5 years.

Complications. Cruikshank reported that 15% of patients experienced gluteal pain after SSLF on the ipsilateral side (Cruikshank et al, 2003). In general, this pain has shown spontaneous resolution within 2 to 3 months when delayed absorbable sutures are used (Maher et al, 2001). Postoperative neuropathic pain can be managed with observation, and patients should be counseled that duration may be as long as 3 months (Sauer and Klutke, 1995). Injection of the nerve with local anesthetic has been used for treatment (Lantzsich et al, 2001). Rectal perforation has also been reported with this procedure; when recognized at the time of surgery and repaired primarily, no sequelae were observed (Richter and Albrich, 1981; Sauer and Klutke, 1995). In addition, injury to the pudendal nerve and internal pudendal vessels may occur with sutures placed too near the ischial spine.

Iliococcygeus Suspension

The iliococcygeus suspension has the advantage of maintaining the vagina in a more normal axis and is useful when the uterosacral ligaments are insufficient for attachment or cannot be identified. With this technique, the vaginal vault is attached to the fascia of the iliococcygeus muscle as the anchoring site in contrast to the uterosacral ligaments or SSLs.

Technique and Results. The iliococcygeus suspension approach is similar to that of uterosacral ligament suspension and SSLF and is usually extraperitoneal. The fascia of the iliococcygeus muscle is identified lateral to the rectum and distal to the ischial spine (Shull et al, 1993). The point of suture fixation is placed 1 cm distal to the ischial spine, near the insertion of the ATFP. This suture is then passed through the condensation of connective tissue at the apex of the vagina anteriorly through the pubocervical fascia and posteriorly through the rectovaginal fascia (Fig. 83-30). Another suture is placed on the contralateral side in a similar manner. It is recommended that bilateral suture fixation be performed to achieve

TABLE 83-6 Results of Sacrospinous Ligament Fixation

AUTHOR AND YEAR	STUDY DESIGN*	N	MEAN FOLLOW-UP IN MONTHS (RANGE)	DEFINITION OF ANATOMIC SUCCESS†	ANATOMIC SUCCESS—ALL SEGMENTS	ANATOMIC FAILURE BY SEGMENT	REOPERATION FOR PROLAPSE
Morley and DeLancey, 1988	Retrospective	92	51.6 (1-132)	Not defined	90%	Apex 4% Anterior 6%	4 (5%)
Imparato et al, 1992	Retrospective	155	Not stated	Not defined	90.3%	Not reported	None reported
Shull et al, 1992	Retrospective	81	24-60	Grade 0-1	82%	Apex 4% Anterior 12% Posterior 1%	4 (5%)

TABLE 83-6 Results of Sacrospinous Ligament Fixation—cont'd

AUTHOR AND YEAR	STUDY DESIGN*	N	MEAN FOLLOW-UP IN MONTHS (RANGE)	DEFINITION OF ANATOMIC SUCCESS†	ANATOMIC SUCCESS—ALL SEGMENTS	ANATOMIC FAILURE BY SEGMENT	REOPERATION FOR PROLAPSE
Pasley, 1995	Retrospective	144	35 (6-83)	Asymptomatic and above hymen	85.4%	Apex 5.6% Anterior 7.6% Posterior 1.4%	2 (1.3%)
Benson et al, 1996	RCT SSLF vs. ASC	42	30 (12-66)	Vaginal walls above hymen or apical descent less than 50% vaginal length	67%	Apex 12% Anterior 28.5% Posterior 2.3%	14 (37%)
Paraiso et al, 1996	Retrospective	243	76 (1-190)	Grade 0 or asymptomatic grade 1	79.7% at 5 years	Apex 4.9% Anterior 15.9% Posterior 4.9%	11 (4.5%)
Penalver et al, 1998	Retrospective	160	40 (18-78)	Any symptomatic descent	85%	Apex 6% Anterior 6% Posterior 2.5%	11 (6.8%)
Colombo and Milani, 1998	Retrospective	62	83 (48-108)	Grade 0-1	74%	Apex 8% Anterior 14% Posterior 3%	0 (0%)
Meschia et al, 1999	Retrospective	91	43 (12-86)	Grade 0-1	85%	Apex 4% Anterior 13% Posterior 9%	NR
Sze and Karam, 1997	Retrospective	75	24 (3-72)	Above hymen	71%	Anterior 21% Other 8%	7 (12.9%)
Lantzsch et al, 2001	Retrospective	123	58 (6-108)	Not defined	87%	Apex 3.5% Anterior 8% Posterior 1.6%	2 (1.6%)
Lovatsis and Drutz, 2002	Retrospective	293	(12-30)	At or beyond the introitus	97%	Apex 3% Anterior NR Posterior NR	3%
Cruikshank and Muniz, 2003	Prospective cohort	695	43 (6-60)	Reoperation for recurrence	89.4%	Apex 5.1%	105 (15%)
Nieminen et al, 2003	Retrospective	138	24	POP-Q stage 2 or greater	78.7%	Apex 4.9% Anterior 11.5% Posterior NR	NR
Maher et al, 2004	RCT SSLS vs. ASC	48	22 (6-58)	Grade 0-1	69%	Apex 19% Anterior 14% Posterior 7%	3 (6.3%)
Hefni and El-Toukhy, 2006	Prospective	305	57 (24-84)	Vaginal vault at least 6 cm distal to hymen	96%	Apex 4% Anterior 13% Posterior 0%	NR
Toglia and Fagan, 2008	Retrospective	64	26.5 (1-72)	Apex above introitus and no reoperation	78%	Apex 9% Anterior 17% Posterior 0%	2 (3%)
Aigmueller et al, 2008	Prospective	55	84 (24-180)	Above the hymen	64%	Apex 7% Anterior 29% Posterior 5%	5 (9%)
Chou et al, 2010	Retrospective	76	36 (12-60)	Grade 0	91%	Apex 5.3% Anterior 3.7% Posterior NR	4 (5.3%)

*Prospective and retrospective cohorts with N >50 published since 1985 and SSLS arms of three RCTs comparing SSLS with ASC.

†POP staging systems, if used, are indicated as grade for Baden-Walker (Baden and Walker, 1972) or stage for POP-Q (Bump et al, 1996).

ASC, abdominal sacrocolpopexy; NR, not reported; POP-Q, Pelvic Organ Prolapse Quantification System; RCT, randomized controlled trial; SSLF, sacrospinous ligament fixation; SSLS, sacrospinous ligament suspension.

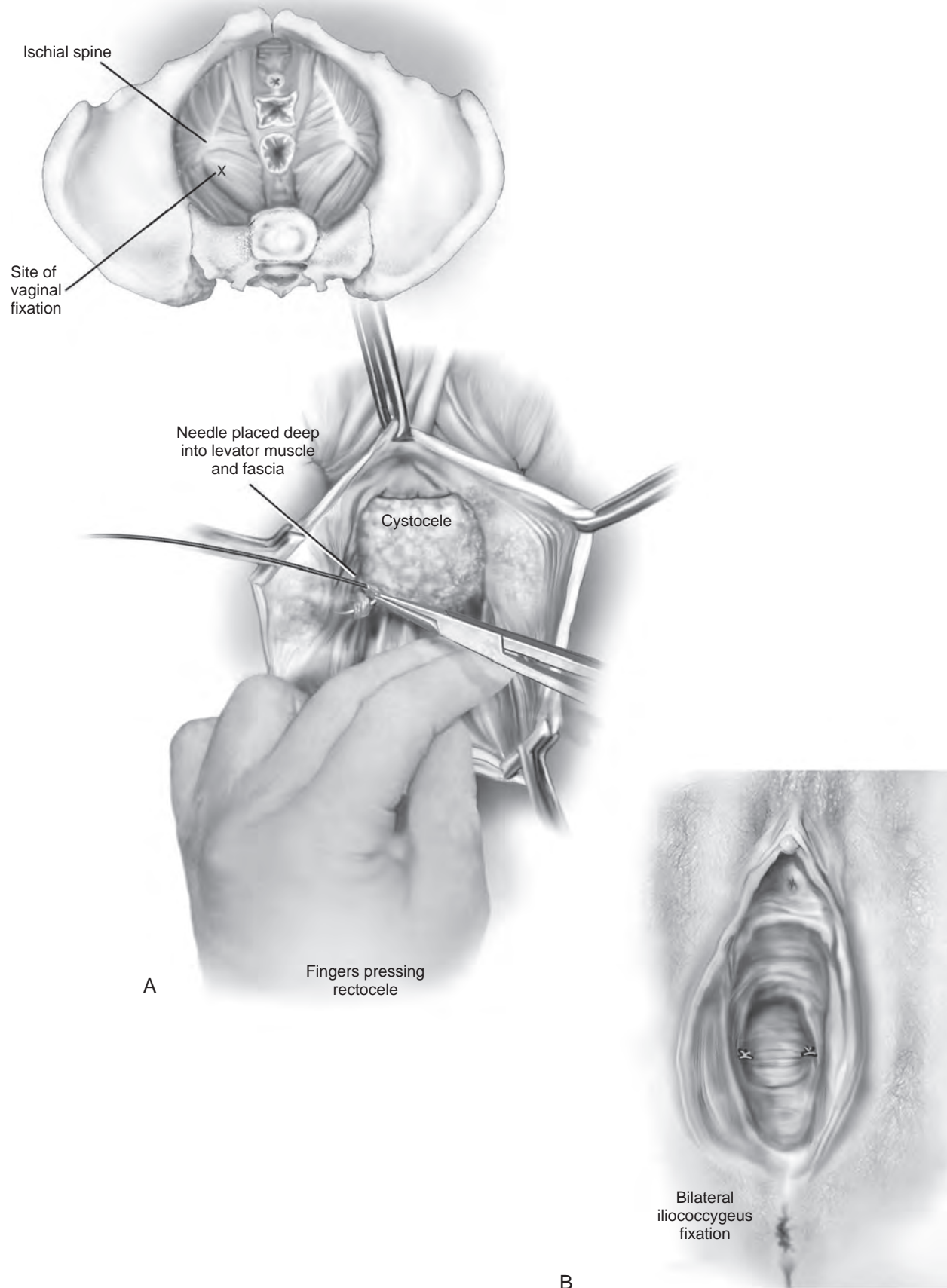


Figure 83-30. A and B, Iliococcygeus fascia suspension. (From Walters M, Karram M. Urogynecology and reconstructive pelvic surgery. 3rd ed. Philadelphia: Mosby; 2006.)

optimal results. Once the sutures are tied securely, the vagina will be suspended bilaterally. As in SSLF, the sutures may be placed through an anterior or posterior approach. Special needle drivers and lighted retraction are useful to facilitate suture placement. In cases using permanent suture, a pulley-stitch technique is applied, with the knot tied internally.

Shull reported on bilateral attachment of the vaginal cuff to the iliococcygeus fascia in 42 patients (Shull et al, 1993). Nine patients experienced pelvic support loss postoperatively, 3 in the middle (apical) compartment, 2 in the posterior compartment, and 4 in the anterior compartment. Six patients required additional surgery. Meeks and colleagues reported an anatomic cure rate of 96% in 110 patients (Meeks et al, 1994). Intraoperative complications included rectal and bladder laceration and hemorrhage requiring transfusion. Postoperative complications included vaginal cuff abscess, fever, and transient femoral neuropathy. Maher and colleagues reported a 53% cure rate in 50 patients; 19% of the patients experienced buttock pain (Maher et al, 2001).

Abdominal Sacrocolpopexy

ASC should be considered a treatment option in the following clinical scenarios: failed previous vaginal repair, isolated uterine prolapse and/or enterocele, younger women, women with a highly active lifestyle, women who are sexually active, and women who desire one of the consistently most durable repairs at the expense of a potentially more invasive approach. In these patients, ASC is an excellent choice because it maximizes functional vaginal length without significant distortion of the anatomic vaginal axis. As discussed earlier, other pelvic floor defects and SUI can be addressed at the same time. In addition to open surgery, robotic assisted laparoscopic and pure laparoscopic approaches have been described and are commonly used today (Sundaram et al, 2004; Rozet et al, 2005; Daneshgari et al, 2006; Elliott et al, 2006). The principles of the operation remain the same regardless of the approach.

Technique. The critical elements of the operation include the use of permanent mesh (type I macroporous, monofilament) as graft material, secure fixation of the graft to the sacral promontory and vaginal cuff, and reduction of a concomitant enterocele.

The patients are positioned in the low lithotomy position, providing both transvaginal and transabdominal access. A Pfannenstiel or low midline abdominal incision may be used, or a laparoscopic or robotic-assisted approach. On entry into the peritoneal cavity, it is important to achieve exposure of true pelvis by careful packing of the small intestine and sigmoid colon. This is accomplished by releasing all adhesions in the pelvis and packing the bowel above the level of the sacral promontory and displacing the sigmoid to the left, exposing the sacral promontory and posterior peritoneum. An incision is made in the posterior peritoneum over the sacral promontory, extending inferiorly along the right lateral aspect of the rectum toward the cul-de-sac. Electrocautery is used when dividing the fatty tissue over the promontory to minimize bleeding and improve visualization. Careful dissection in this area is essential to avoid shearing of presacral veins because severe bleeding may occur. The middle sacral vessel traverses over the promontory and should also be avoided. As the fatty tissue is dissected free, the anterior surface of the sacral promontory is visualized, usually by identification of the anterior longitudinal ligament. Two or three interrupted nonabsorbable sutures are placed in the anterior longitudinal ligament, with care taken to avoid perforation of the midline sacral vessels. In general, sutures are placed under the vessels and tied down over the top of the vessels. Alternatively, if vessels overlie the ligament, bipolar energy can be used on the vessels to prevent bleeding before the sutures are placed. These sutures are safely tagged for later placement into the mesh graft (Fig. 83-31). Alternatively, commercially available tacking devices may be used for securing the graft to the sacral promontory, although minimal data exist to confirm comparable efficacy.

After placement of an obturator (end-to-end anastomosis [EEA] sizer or commercially available vaginal paddle) in the vagina, the

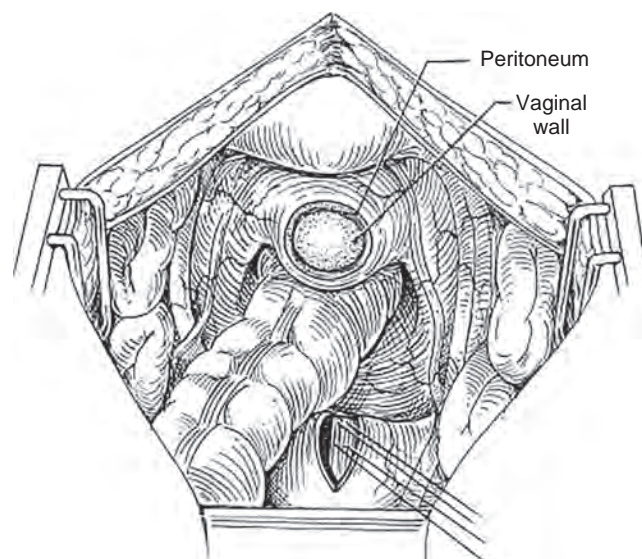


Figure 83-31. Abdominal sacrocolpopexy. Note the incision in the peritoneal cuff overlying the vagina, which exposes the vaginal cuff. Two permanent sutures are then placed in the sacral promontory to secure the graft material. (From Winters JC, Cespedes RD, Vanlangendonck R. Abdominal sacral colopexy and abdominal enterocele repair on the management of vaginal vault prolapse. *Urology* 2000; 56[6 Suppl 1]:55-63.)

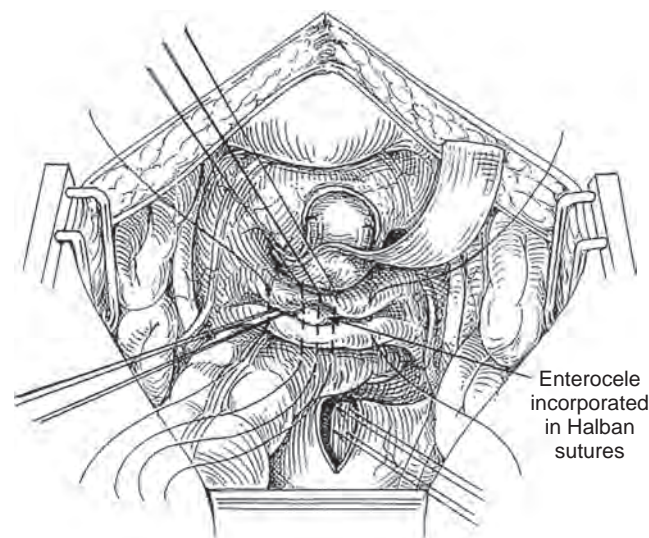


Figure 83-32. Abdominal sacrocolpopexy. Synthetic graft material is sutured securely to the vaginal cuff using multiple interrupted permanent sutures. The peritoneal cul-de-sac is closed using linearly placed sutures to obliterate this potential space. (From Winters J, Cespedes R, Vanlangendonck R. Abdominal sacrocolpopexy and abdominal enterocele repair in the treatment of vaginal vault prolapse. *Urology* 2000;56[6 Suppl 1]:55-63.)

enterocele sac, if present, is identified and secured with an Allis clamp. If the enterocele is large, a Halban culdoplasty can be performed by placing linear permanent (or delayed absorbable) sutures through the posterior peritoneum and on the outer surface of rectum up to the vaginal cuff (Geomini et al, 2001). Upward retraction of the sizer will assist in exposing the cul-de-sac. Usually four to six sutures are used to complete adequate cul-de-sac closure. This technique of closure (Fig. 83-32) is in contrast to the Moschowitz

procedure, which involves purse-string closure and may predispose to ureteral angulation and obstruction. Alternatively, if an aggressive posterior vaginal dissection to the perineum is to be performed (see later) for placement of an extended piece of posterior mesh with subsequent retroperitonealization of the mesh, the culdoplasty is usually not needed.

The peritoneum over the vaginal cuff is incised, and the peritoneum is dissected off the cuff of the vagina (see Fig. 83-32). There is significant variability in the amount of vaginal dissection reported. Some perform minimal dissection of the peritoneum and bladder attached to the vagina—enough to fix the mesh for 4 to 5 cm on each side—whereas others describe more extensive dissection that involves lifting the posterior bladder wall and trigone off the underlying vagina as well as dissecting all the way to the perineal body. With the advent of robotic techniques, it seems that more extensive dissections are being carried out with longer mesh segments attached to the bladder, although there are no controlled studies to identify the optimal technique of graft placement to the vagina. Several mesh options exist for ASC, including ready-made Y-shaped soft polypropylene mesh and sheets of soft polypropylene mesh that can be cut and fashioned to the surgeon's preference. A polypropylene, macroporous, monofilament, nonabsorbable mesh is recommended. In general, a 2.0-cm-wide by roughly 6.0-cm-long anterior segment of mesh is sutured to the exposed anterior vaginal wall using six to eight permanent sutures (commonly Prolene, Gore-Tex, Ethibond, or Ti-Cron) (Fig. 83-33). Care is taken to identify the border of the bladder to avoid suturing the graft to the bladder and to secure the most lateral portions of the mesh to prevent folding. An obturator in the vagina is useful to facilitate suture placement and secure the mesh to the vagina. The graft is secured to the vagina by folding over the cuff of the vagina and allowing the long end of the graft to exit posteriorly and extend to the sacrum. (Alternatively, a T-shaped configuration of the graft may be created. The short arm of the T is placed on the top of the vagina, and the long arm of the T is secured to the lower end of the vagina.) The posterior peritoneum is dissected off the posterior wall of the

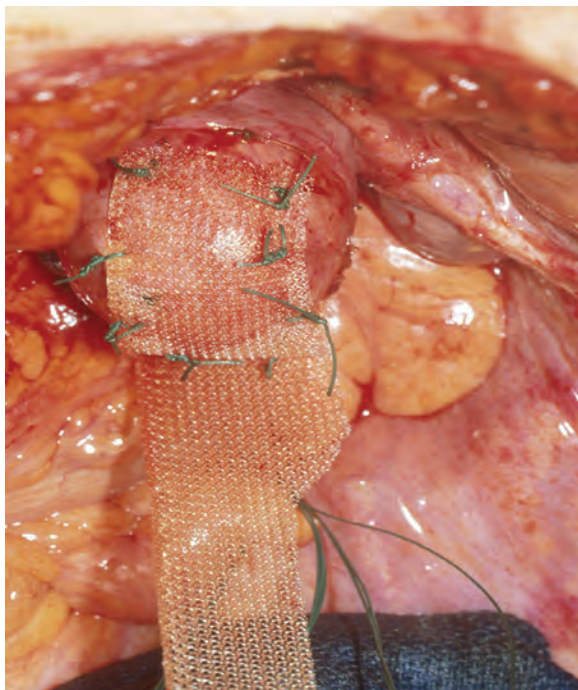


Figure 83-33. Abdominal sacrocolpopexy: intraoperative view. Permanent mesh material sutured to vaginal cuff. End-to-end anastomosis sizer was used to provide exposure of vaginal cuff. (From Scarpero H, Cespedes R, Winters J. Abdominal approach to the repair of vaginal vault prolapse. *Tech Urol* 2001;7:139–45.)

vagina entering the space between the rectum and vagina. This dissection may be extended to the perineum to allow mesh attachment to the perineal body, a procedure termed *colpoperineopexy* (Cundiff et al, 1997). The posterior segment of the mesh is then attached to the posterior vaginal wall with six to eight interrupted nonabsorbable sutures. At this step, the central sutures from the culdoplasty are placed through the long arm of the mesh if desired.

The graft is then secured to the sacral promontory. Care must be taken to avoid excessive tension. Placing the obturator all the way into the vagina but not pushing the vagina upward establishes the proper length for the graft. The graft is placed along the right lateral aspect of the rectum in the space previously developed by extending the opening of the peritoneum from the sacrum. A space of two fingers' width between the graft and the rectum prevents compression of the rectum over the graft (Fig. 83-34). Tensioning in this fashion is not feasible with a robotic or laparoscopic approach. It requires a visual cue of the mesh attachment while extending the vagina cephalad with an EEA sizer to its maximal length without actively stretching it. The promontory sutures are then brought through the mesh and tied down securely. Any excess mesh is trimmed after fixation to the sacrum. Last, the graft is positioned in the retroperitoneal space by closing the posterior peritoneum over the graft, and covering the graft on the vagina with the superior edge of the anterior peritoneum and bladder flap. Stress incontinence procedures (if indicated) are then performed. Indigo carmine is administered to ensure patency of the ureters. The patient is then examined to determine if any ancillary transvaginal prolapse repairs are needed.

ASC maintains a functional vagina and restores maximal vaginal length and support. In a comparative study, vaginal length was longer after ASC compared with sacrospinous fixation (Given et al, 1993). A nonabsorbable monofilament synthetic mesh should be used during ASC. In a study by Culligan and colleagues, patients undergoing ASC were randomized to either absorbable cadaveric fascia lata graft (Tutoplast) or nonabsorbable monofilament polypropylene. The objective failure rate for recurrence at any other vaginal site was 14 of 44 in the fascial group and 4 of 45 in the mesh group (Culligan et al, 2005).

Numerous reports by multiple authors confirm the success of ASC using mesh, and multiple authors have reported success rates greater than 90% (Snyder et al, 1991; Addison and Timmons, 1993; Webb et al, 1998; Menefee et al, 1999). In addition, there are several randomized, prospective trials comparing SSLF with ASC. In a comparative study between ASC versus vaginal repair, Benson and colleagues reported a lower success rate with vaginal repair, and an equivalent hospital stay between the two groups (Benson et al, 1996). Lo and Wang reported on their results of ASC versus SSLF at a duration of 2.1 years—94.2% success in ASC compared with 80% in SSLF (Lo and Wang, 1998). Maher and colleagues reported on a comparative study between ASC and SSLF. At 2 years' follow-up, symptoms and anatomic success were equivalent but asymptomatic failures to the introitus and recurrent cystoceles were less after ASC (Maher et al, 2004). Overall, vaginal (SSLF) procedures have a higher rate of recurrent anterior defects even when performed in the setting of a concomitant anterior repair (colporrhaphy) (Holley et al, 1995). After an isolated abdominal repair of vaginal vault prolapse without addressing concomitant pelvic floor defects, recurrent distal defects such as cystocele and rectocele may occur up to one third of the time. This may predispose to decreased patient satisfaction and the possibility of secondary vaginal repair (Blanchard et al, 2006). Although most remain asymptomatic, secondary repair of these defects may be required (Blanchard et al, 2006). It is important to counsel patients preoperatively about the possibility of distal anterior or posterior defects after ASC, and the need for secondary vaginal repair, which can occur up to 20% of the time (Blanchard et al, 2006). Recent results from the E-CARE trial show that at 7 years after ASC, the recurrence rate of POP progressively increases. The anatomic treatment failure rates ($C > TVL-2$ or $Ba/Bp > +1$) for ASC with and without Burch urethropexy were 0.27 and 0.22, respectively. It is interesting to note that half of these were asymptomatic. The symptomatic failure

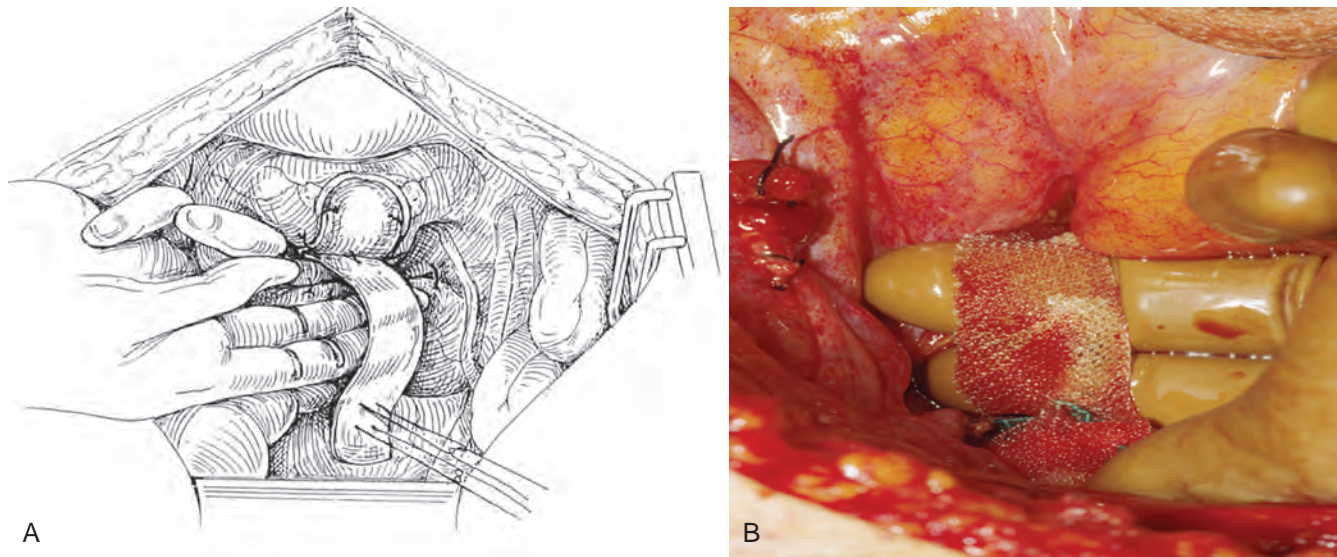


Figure 83-34. Abdominal sacral colpopexy. A, Graft is secured without tension to sacral promontory. B, Intraoperative view. (A, From Winters J, Cespedes R, Vanlangendonck R. Abdominal sacrocolpopexy and abdominal enterocele repair in the treatment of vaginal vault prolapse. *Urology* 2000;56[6 Suppl 1]:55–63; B, from Scarpero H, Cespedes R, Winters J. Abdominal approach to the repair of vaginal vault prolapse. *Tech Urol* 2001;7:139–45.)

(positive response to one or more questionnaire items or re-treatment of POP) rates with and without Burch urethropexy were 29% and 24%, respectively. However, half of these patients were not re-treated. When the researchers looked at the composite failure (met criteria for anatomic or symptomatic failure) rates for ASC with and without Burch urethropexy, they found 0.48 and 0.34 estimated probabilities of treatment failure, respectively (Nygaard et al, 2013).

Laparoscopic sacrocolpopexy has shown equivalent efficacy to open ASC in several retrospective analyses (Paraiso et al, 2005; Hsiao et al, 2007; Klauschie et al, 2009). To date, no randomized trial has compared laparoscopic sacrocolpopexy with ASC. Laparoscopic surgery appears to result in shorter hospital stay, less blood loss, and conflicting data on operative time. The generalizability of this procedure performed in a pure laparoscopic approach has been limited to those with advanced laparoscopic skill sets, because the dissections, suturing, and knot tying have a steep learning curve. Claerhout and colleagues examined the learning curve for this procedure in a laparoscopic approach and found that adequate learning occurred after 60 cases (Claerhout et al, 2009). The advent of robotic-assisted surgery has augmented the adaptation by many surgeons of a minimally invasive approach to ASC. No studies have outlined the learning curve for this approach, but expert opinion would suggest it to be shorter than the laparoscopic approach. Outcome studies are limited, but one retrospective study with short-term follow-up shows similar anatomic outcomes with less blood loss and shorter hospital stay (Geller et al, 2008). Another retrospective review of 95 robotic-assisted sacrocolpopexies with 34-month follow-up had an anatomic success rate of 95.8%. Only one mesh erosion was reported in the postoperative follow-up (Ploumidis et al, 2014). Meta-analysis of seven smaller studies (N = 315) of robotic sacrocolpopexy suggest equivalence to the laparoscopic and open approaches (Maher et al, 2013b). Anatomic success rates ranged from 60% to 100% with a mean of 93%, and subjective success ranged from 91% to 94%. The mean mesh erosion rate in these studies was 5%. In a randomized study of robotic (n = 40) versus laparoscopic (n = 38) sacrocolpopexy, Paraiso and colleagues demonstrated significant improvement in vaginal support and functional outcomes 1 year after surgery, with no differences between groups (Paraiso et al, 2011). Khan and colleagues performed a Medicare database study looking at the

outcomes of open ASC versus laparoscopic (including robotic) sacrocolpopexy. Of the 794 ASC and the 176 laparoscopic cases, apical anatomic success rates were similar, but reoperations for anterior recurrences were higher in the laparoscopic group (3.4% vs. 1.0%, $P = .018$) (Khan et al, 2013).

In a comprehensive review by Nygaard and colleagues, intraoperative complications of sacrocolpopexy included hemorrhage or transfusion (4.4%), cystotomy (3.1%), enterotomy (1.6%), and ureteral injury (1.0%). Postoperative complications included UTI (10.9%), wound infection (4.6%), ileus (3.6%), deep venous thrombosis or pulmonary embolism (3.3%), and small bowel obstruction (1.1%) (Nygaard et al, 2004). Significant hemorrhage may occur from disruption of the presacral vessels, and the occurrence of this complication may be reduced when fixation of the graft is performed higher on the sacral promontory. This bleeding risk has been reported to range from 1.6% to 4.4% and may be controlled with the use of stainless steel thumbtacks in an open ASC (Timmons et al, 1991). Fulgurating these vessels preemptively with bipolar energy, especially during a minimally invasive approach, may preclude this complication. The CARE trial data reveal that the rate of reoperation for gastrointestinal complications with this procedure is 1.2% (Whitehead et al, 2007). Vaginal exposure of mesh is another complication and is heralded by persistent pain, discharge, or infections, and clinicians must be vigilant in follow-up (Karlovsky et al, 2005). In meta-analysis, rates of mesh exposure into the vagina have been reported as 3.4% to 5.4% and may vary with the type of mesh used (Brizzolara and Pillai-Allen, 2003; Nygaard et al, 2004). Exposures occur more often with Teflon or Gore-Tex type materials and are rarer with macroporous, monofilament meshes. Surgeons performing these procedures should be aware of the recently reported 9.9% mesh exposure rate from the extended follow-up of the multicenter CARE trial (Nygaard et al, 2013). Several authors have suggested that hysterectomy at the time of colpopexy increases the rate of mesh extrusion, although these findings are not uniform (Nygaard et al, 2004; Marinkovic, 2008) and no randomized trials have addressed this issue (Nygaard et al, 2004). In 60 patients undergoing concomitant hysterectomy using a two-layer closure of the vaginal cuff followed by ASC with synthetic nonabsorbable monofilament mesh, the exposure rate was 0.8% compared with 0% in the 64 patients with a prior hysterectomy (Wu et al, 2006). In

patients undergoing a combined operation, supracervical hysterectomy or a meticulous two-layer closure of the cuff should be performed to decrease the incidence of mesh exposure. **Surgeons must be aware that the incidence of mesh exposure after ASC is higher after complete hysterectomy. In patients needing hysterectomy, the feasibility of a supracervical hysterectomy should be strongly examined. In this scenario, a supracervical hysterectomy in conjunction with the ASC is preferred. These patients should also be informed that for uterine prolapse, a vaginal hysterectomy with vaginal vault suspension is an effective option as well.** Options for the management of exposed mesh after colpopexy may include TVM excision with or without partial colpocleisis (Quiroz et al, 2008) and abdominal mesh excision.

Colpocleisis

Colpocleisis is an obliterative procedure used in the treatment of posthysterectomy vaginal vault prolapse or significant uterovaginal prolapse. In properly counseled, older patients who do not desire a functional vagina for sexual activity, colpocleisis may be an appropriate, noninvasive procedure. The total colpocleisis is performed in patients who have undergone hysterectomy and refers to removal of the vaginal epithelium to approximately 2 to 3 cm from the urethral meatus with complete closure. A partial colpocleisis is used in cases of uterovaginal prolapse; this procedure involves creating lateral channels to allow potential uterine drainage. Advantages of the colpocleisis procedures are shorter operative time, ability to use regional anesthesia or local anesthesia with sedation, minimal complications, minimal recurrence, and decreased recuperative time (Cespedes et al, 2001; Fitzgerald et al, 2008). In those whose uterus is to be left in situ, preoperative evaluation should include a Papanicolaou smear, pelvic sonogram, and endometrial biopsy if indicated. Performance of hysterectomy at the time of colpocleisis eliminates the risk of developing cervical or endometrial cancer and eliminates the risk of developing pyometra, which is a serious complication of partial colpocleisis when the channels become obstructed (Shayya et al, 2009). However, most patients selected for colpocleisis are older with significant comorbidities that make a concomitant hysterectomy undesirable.

Technique

Partial Colpocleisis. The patient is placed in standard lithotomy position. A Foley catheter is placed into the bladder. If an anti-incontinence procedure is needed, it may be performed first. The cervix is grasped with a tenaculum, and a rectangular segment of vaginal epithelium is marked anteriorly and posteriorly. The excision of the vaginal epithelium will extend 3 cm from the urethral meatus to 3 cm from the cervix (Cespedes et al, 2001). It is important to leave sufficient vaginal epithelium laterally to allow creation of the lateral channels to facilitate drainage. The epithelium is then excised. It is optional to place a 14-Fr red Robinson catheter along the vaginal sidewalls to assist in forming the channels. Then, starting at the leading edge of the prolapse, one places successive layers of 2-0 delayed absorbable sutures, which plicate and reduce the prolapse until the prolapsed tissues are above the levator plate (Fig. 83-35A). The sutures are placed in transverse rows consisting of linear sutures through the pubocervical fascia anteriorly and rectovaginal fascia posteriorly. As these sutures are tied, the apical prolapse is reduced proximally (Fig. 83-35B). Successive rows of sutures are placed until the apical prolapse is completely reduced. A high perineorrhaphy is performed by removing a triangular segment of the vaginal epithelium. The fibromuscular tissues of the perineal body are approximated in the midline with absorbable sutures to narrow the introitus. Figure 83-36 shows the completed procedures. Indigo carmine is administered and a cystoscopy is carried out to confirm ureteral patency.

Total Colpocleisis (Fig. 83-37). Total colpocleisis differs from partial colpocleisis in that the lateral channels are not left in place, but rather, the entire prolapsed vagina is denuded of its epithelium from the apex to 3 cm proximal to the urethral meatus. The dissection is carried laterally and continued to the posterior lateral sulcus. The prolapse sac is dissected away from the vaginal epithelium.

Usually the enterocele reduces easily, and no further treatment is necessary (Cespedes et al, 2001). At this point, the colpocleisis is carried out starting at the leading edge of the prolapse. Purse-string sutures of 2-0 absorbable suture are placed circumferentially around the prolapse including pubocervical and prerectal (rectovaginal) fascia (Fig. 83-37A). As each progressive suture is tied, the prolapse is reduced proximally (Fig. 83-37B). These progressive purse-string sutures are carried out until the prolapse is adequately reduced. Alternatively, the prolapse may be reduced as described for the partial colpocleisis by placing transverse rows of interrupted sutures (see Fig. 83-37C). As these rows are tied, the prolapse is reduced proximally. Successive rows of sutures are placed until the prolapse is fully reduced. The remainder of the procedure is carried out as described for the partial colpocleisis. After the prolapse is reduced, the posterior vaginal wall and perineum are repaired. A high perineorrhaphy (levator myorrhaphy) is important to narrow the introitus and prevent recurrence. Cystoscopy to ensure patency of the ureters is recommended. For both techniques, success depends on the amount of vaginal tissue sutured together. This creates a septum of support, which is enhanced by bringing the levator muscles together along with the perineorrhaphy.

Several authors have reported that it is unnecessary to open the enterocele sac if one is present, because the repair will close the potential space in which the bowel might protrude (DeLancey and Morley, 1997; Glavind and Kempf, 2005). If the enterocele sac cannot be reduced, then purse-string absorbable sutures incorporating the sac and the uterosacral remnants can be used to reduce the sac (Cespedes et al, 2001).

Results

Colpocleisis. DeLancey reported on 33 women who underwent colpocleisis over a 20-year period (DeLancey and Morley, 1997). In this study, opening of the enterocele sac was avoided. One vaginal eversion recurrence was noted. The patient was treated with repeat colpocleisis and had a good response 1 year after the second colpocleisis. All but 1 patient expressly denied regret over the decision to have an operation that precluded the ability to have intercourse; however, 1 "accepted" her sexual inactivity. Many indicated relief of the discomfort associated with the prolapse and were positive about the outcome of the operation. Cespedes reported on 38 patients who underwent a mean of 24 months' follow-up (Cespedes et al, 2001). There was no recurrent prolapse. Three patients who had a Kelly plication for incontinence had mild SUI, and two were treated successfully with collagen. All were satisfied with the procedure, and no complications were noted. Von Pechmann reported on a large study of 92 patients who underwent colpocleisis (von Pechmann et al, 2003). Patients were followed by examination and phone survey, which appraised satisfaction and regret. Regret over the loss of coital ability was expressed in 12.9% or 8 patients. In a multicenter, prospective study designed to study the effect of colpocleisis on pelvic support, symptoms, QoL, morbidity, and postoperative satisfaction, Fitzgerald and colleagues reported on 152 patients with 1-year follow-up (FitzGerald et al, 2006). Eighty-four percent stated they were either very satisfied or satisfied about the decision for vaginal closure. One patient was dissatisfied, and one was very dissatisfied. One patient underwent repeat colpocleisis for recurrence. Most patients did not experience worsening of their body image. Koski and colleagues reported on 53 patients undergoing colpocleisis; 74% had a total colpocleisis; 91% described the procedure as successful on the PGI-I scale, and examinations correlated with these findings. Urinary frequency and urgency were the most bothersome symptoms reported in 33% of patients (Koski et al, 2012).

Partial Colpocleisis. Goldman and colleagues reported on 118 patients who underwent Le Fort colpocleisis (Goldman et al, 1981). Good anatomic results were noted in 107 patients, with 101 reporting a relief of symptoms. There were 3 recurrences but none of the patients underwent further operative therapy. Immediate postoperative complications included one pulmonary embolus, fever, and UTI. Langmade and Oliver reported on 102 patients (Langmade and Oliver, 1986). There were no recurrences and no de novo stress incontinence; 16 patients had transient postoperative urinary

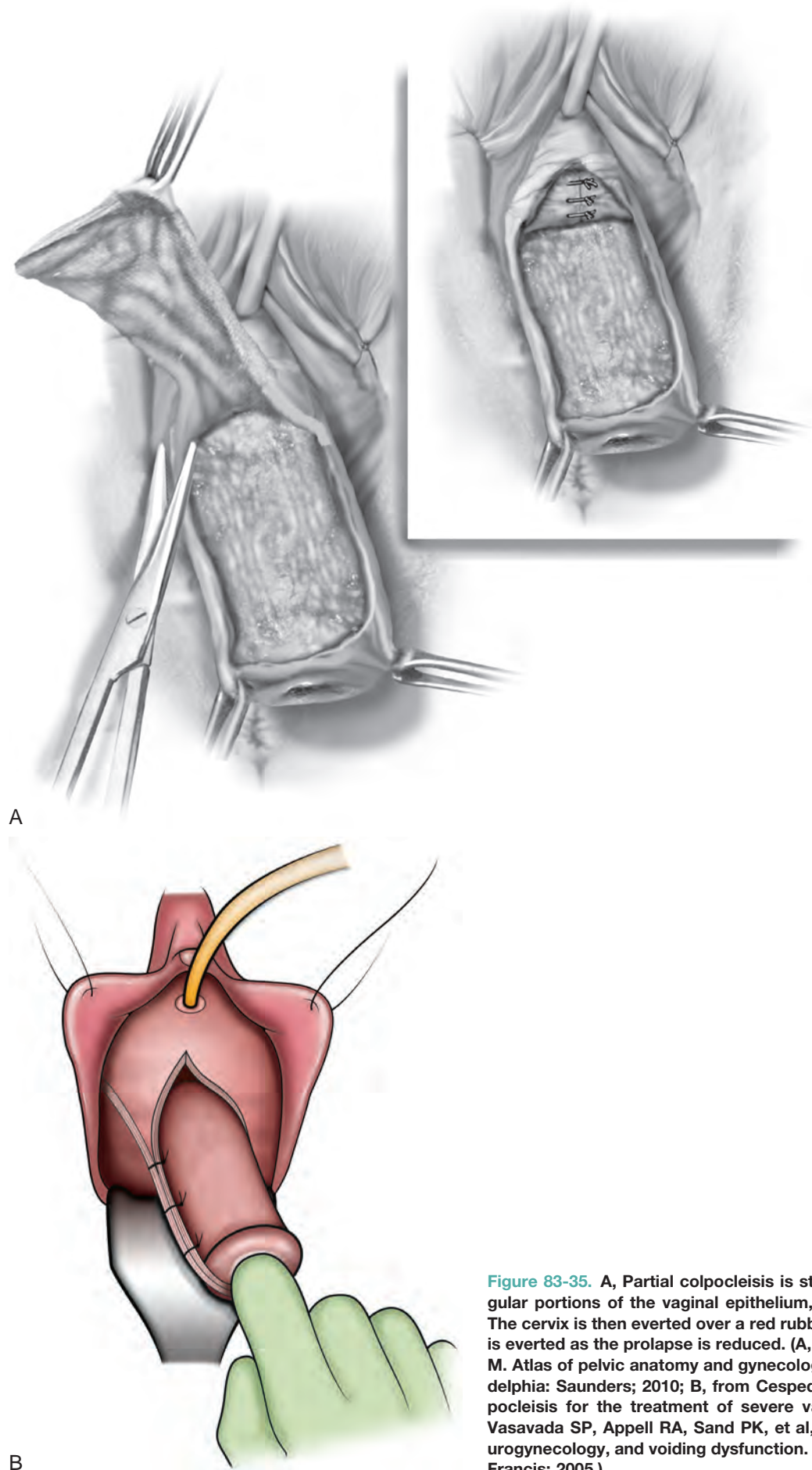


Figure 83-35. A, Partial colpocleisis is started by excising rectangular portions of the vaginal epithelium, leaving lateral channels. The cervix is then everted over a red rubber catheter. B, The cervix is everted as the prolapse is reduced. (A, From Baggish M, Karram M. *Atlas of pelvic anatomy and gynecologic surgery*. 3rd ed. Philadelphia: Saunders; 2010; B, from Cespedes RD, Winters CW. *Colpocleisis for the treatment of severe vaginal vault prolapse*. In: Vasavada SP, Appell RA, Sand PK, et al, editors. *Female urology, urogynecology, and voiding dysfunction*. Boca Raton [FL]: Taylor & Francis; 2005.)

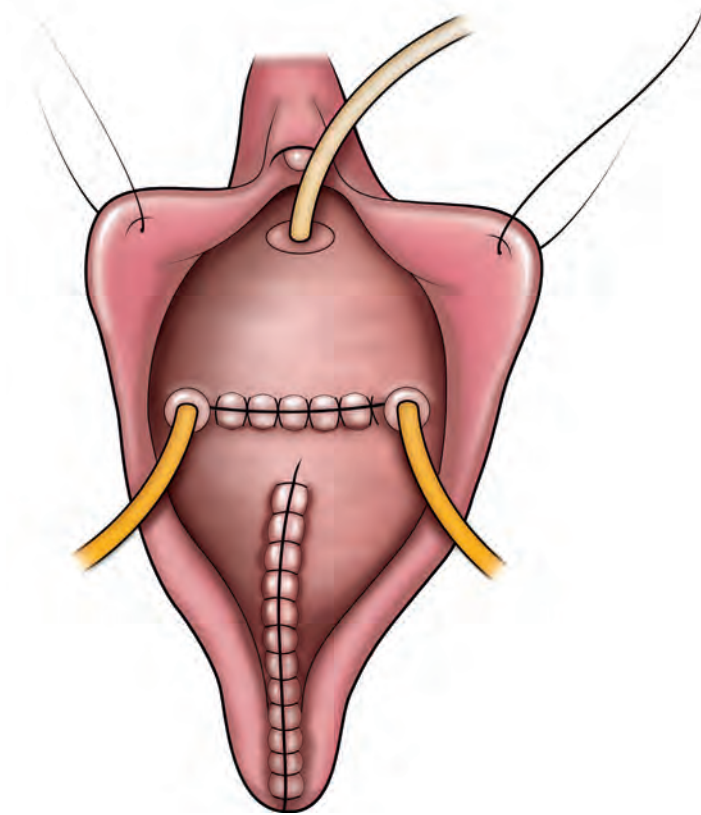


Figure 83-36. The partial colpocleisis is completed along with peri-neorrhaphy. (From Cespedes RD, Winters CW. Colpocleisis for the treatment of severe vaginal vault prolapse. In: Vasavada SP, Appell RA, Sand PK, et al, editors. *Female urology, urogynecology, and voiding dysfunction*. Boca Raton [FL]: Taylor & Francis; 2005.)

retention. There was no reported regret regarding the ability to engage in sexual intercourse. In a retrospective series of over 300 women, the anatomic success rate was 98.1%, with a patient satisfaction rate of 92.9%. These authors concluded that colpocleisis is an effective and low-risk procedure for the appropriate elderly patient with advanced POP (Zebede et al, 2013).

Crisp and colleagues reported on body image, regret, and satisfaction after Le Fort and total colpocleisis. This multicenter trial confirmed the results of earlier studies, which demonstrated improved body image, improved pelvic floor symptoms, low levels of regret, and high levels of satisfaction (Crisp et al, 2013). Urinary incontinence after colpocleisis may occur and has been attributed to several mechanisms. Occult stress incontinence may be unmasked with reduction of the urethrovesical angle as described earlier. An alternative mechanism, secondary to traction on the urethra when it is approximated with the posterior vaginal muscularis, has been proposed (FitzGerald et al, 2006). Thus it is recommended to avoid colpectomy of at least 1.5 cm of the distal anterior vaginal wall adjacent to the urethral meatus (FitzGerald et al, 2006). As with other prolapse cases, the recommendation of a concomitant anti-incontinence procedure in an asymptomatic patient is controversial and remains to be substantiated by prospective studies. However, it is clear that these women may develop SUI postoperatively. Thus all women before undergoing colpocleisis should be screened for the presence of occult SUI, and anti-incontinence procedures should be offered concomitantly in women with symptoms of SUI or occult SUI. In addition, in frail, elderly patients there is concern for urinary retention, frequently the result of impaired contractility (which may be appreciated preoperatively) and other perioperative factors. This may be more difficult to

manage because these patients are more likely to be unable to perform intermittent catheterization. These possibilities must be discussed with patients in advance of surgery. Patients considered at significant risk for retention should be offered a suprapubic tube to assist in bladder management postoperatively.

Uterine Prolapse

POP was the indication for 16.3% of all hysterectomies performed from 1988 to 1990 (Owings and Kozak, 1998). Although the majority of hysterectomies are performed transabdominally, the vaginal approach offers the advantages of less invasive surgery and the ability to repair concomitant pelvic floor defects (Eilber et al, 2004).

The uterus is suspended in the pelvis by the cardinal-uterosacral complex. The body of the uterus is enveloped between the two leaves of the broad ligament, which also surrounds the fallopian tube, round ligament, and ovarian ligament along with the uterine and ovarian vessels. The broad ligament does not provide significant support (Eilber et al, 2004). Therefore the defect prompting uterine prolapse is in the form of attenuated ligaments or specific breaks in the continuity of the cardinal-uterosacral complex. Contraindications for the vaginal approach are endometriosis of unknown extent, obliteration of the cul-de-sac, large fibroids (size disproportion to the introitus), pelvic tumor, adnexal tumor, and malignancy of the uterus or ovaries (Eilber et al, 2005).

Transvaginal Hysterectomy

Technique. The patient is placed in the dorsal lithotomy position. A catheter is placed to drain the bladder. Retraction of the labia with a ring retractor and stays is useful. Two Lahey clamps are placed on the cervix. Care must be taken to place it on the most distal portion of the cervix, as the bladder may descend fairly low on the anterior vaginal wall. The incision is made full thickness through the vaginal epithelium around the cervix approximately 1 cm from the cervical os. The posterior peritoneal fold is exposed by applying traction to the tenaculum and using a right-angle retractor to apply counter-traction to the vagina. Once the posterior peritoneal fold is identified, it is opened sharply to enter the cul-de-sac. Once the cul-de-sac is entered, the uterus and adnexa can be palpated to check for pathology. The anterior dissection is performed on the glistening white surface of the uterus, which confirms the correct plane of dissection. Traction on the cervix with countertraction applied anteriorly will facilitate the dissection of the vesicouterine space. The peritoneum is identified anteriorly and entered. The uterosacral ligament can then be identified for suspension to restore the vaginal cuff once the uterus has been removed.

The cardinal and uterosacral ligaments are isolated, divided, and suture-ligated with delayed absorbable suture. The uterine arteries are identified and ligated. If the ovaries and adnexa are to be left in situ, the utero-ovarian ligament, Fallopian tube, and round ligaments are divided and suture-ligated. The remainder of the broad ligament is divided bilaterally and the uterus removed. It is not unusual to have an elongated cervix with prolapse, which can make visualization of the fundus of the uterus challenging. All pedicles are examined for hemostasis.

Vaginal vault suspension is crucial because the hysterectomy alone will not restore the anatomy of the vaginal vault. This can be accomplished by placing sutures through the apex of the vaginal wall and into the uterosacral or sacrospinous ligaments. These sutures are not tied down until after the culdoplasty is performed and the cuff is closed. Purse-string sutures of 0 Vicryl are placed to close the cul-de-sac. These sutures incorporate the pubocervical fascia, cardinal-uterosacral ligament complex, broad ligaments, and perirectal fascia. Care is taken to avoid ureteral injury, which can occur if sutures are placed too laterally on the pubocervical fascia. The vaginal cuff is closed in a continuous locking or interrupted fashion. The vault suspension sutures are tied, suspending the vaginal vault and restoring vaginal depth. Cystoscopy is then performed to ensure ureteral patency and absence of bladder injury.

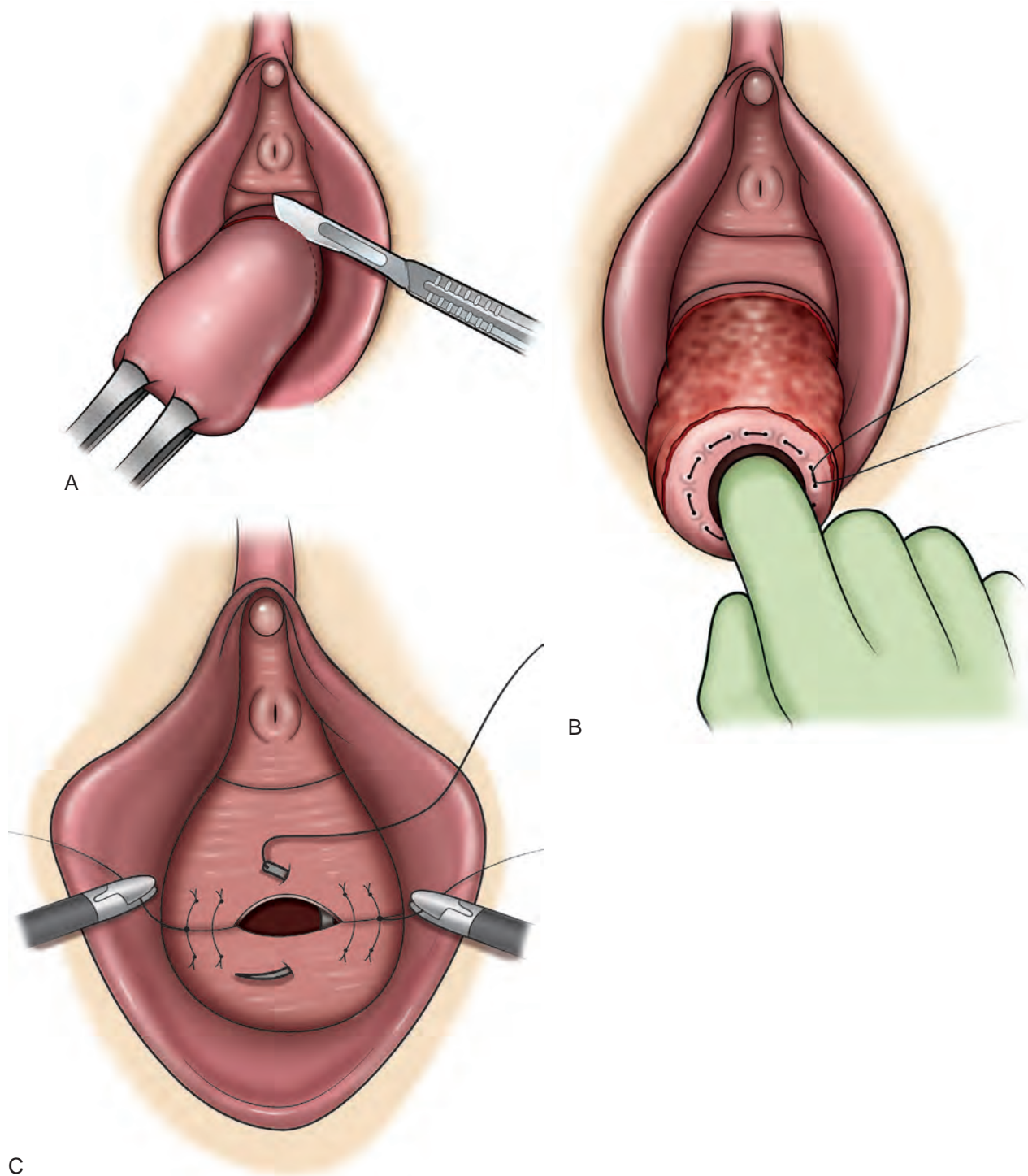


Figure 83-37. Total colpocleisis. A, A circumferential incision is created at the base of the prolapse. B, Purse-string sutures are placed in the prolapsed tissues to reduce it. C, The vaginal epithelium is closed transversely. (From DeLancey JO, Morley GW. Total colpocleisis for vaginal eversion. *Am J Obstet Gynecol* 1997;176:1228–35.)

Uterine Preservation

Traditionally, surgical repairs to restore pelvic floor support in the setting of uterine prolapse included hysterectomy. Recently, however, there has been great interest in preservation of the uterus with use of prolapse surgery to maintain future fertility, decrease surgical risk associated with the hysterectomy, and satisfy women who wish to

retain their uterus and who feel concerned about sexual function with the loss of their uterus (Maher et al, 2013b). Uterine preservation is considered safe in select groups of women but is contraindicated in those with abnormal uterine and cervical pathology, abnormal menstrual bleeding, postmenopausal bleeding, familial cancer with *BRAC1* and *BRAC2*, hereditary nonpolyposis colon cancer, tamoxifen therapy, and poor compliance with

routine gynecologic care. Frick and colleagues demonstrated a 13% risk of endometrial cancer or hyperplasia in women with postmenopausal bleeding and prior negative evaluation (Frick et al, 2010).

Vaginal Hysteropexy

Vaginal hysteropexy can be performed with and without the use of mesh. The Manchester procedure may be used for this indication, but its main use currently appears to be for the treatment of cervical elongation. It involves amputation of the cervix with reattachment of the cardinal ligaments. The sacrospinous hysteropexy attaches the cervix or uterosacral ligaments to the SSL. In 2010, Dietz and colleagues randomized 37 women to sacrospinous hysteropexy and 34 to vaginal hysterectomy with uterosacral ligament suspension and demonstrated a 21% risk of apical recurrence in the hysteropexy group versus 3% in the hysterectomy group ($P = .03$) (Dietz et al, 2010). Both groups had a high rate of postoperative anterior wall prolapse (50% hysteropexy, 65% hysterectomy, $P = .2$). No difference in functional outcome or QoL was reported. Hysteropexy was associated with a shorter length of hospital stay, earlier return to work, and longer total vaginal length (8.8 cm vs. 7.3 cm, $P < .01$). Meta-analysis of 428 women who underwent sacrospinous hysteropexy and 262 who underwent transvaginal hysterectomy with a variety of suspension procedures revealed an 87% anatomic success rate in the hysteropexy group versus 93% in the hysterectomy group ($P = .054$) (Maher et al, 2013a). Failures tend to occur in those with severe advanced prolapse; high-risk women should consider concomitant hysterectomy to achieve a durable response.

Vaginal mesh hysteropexy typically involves the use of trocars or a Capio device to facilitate the passage of mesh arms through the SSL. The mesh is positioned on the proximal anterior wall to support the cervix and reinforces the anterior plication for reduction of the cystocele. There are a few retrospective cohort studies reporting efficacy of vaginal mesh hysteropexy. McDermott and colleagues used Total Prolift (Ethicon) with ($n = 65$) and without ($n = 24$) concomitant hysterectomy in a nonrandomized fashion (McDermott et al, 2011). Mean follow-up was 10.8 months; hysterectomy patients were found to have a significantly higher POP-Q point C measurement (7.9 cm vs. 6.8 cm; $P = .05$) and longer genital hiatus (3.8 cm vs. 3.3 cm; $P = .03$) than patients who underwent hysteropexy. The clinical significance of this difference is likely meaningless and may simply represent the presence of the cervix occupying the apical portion of the vagina. There were no significant differences for other POP-Q measurements, mesh erosion rates (8% vs. 13%; $P = .7$), or patient-reported outcome measures. Meta-analysis of 316 cases of mesh hysteropexy reported a success rate of 86%, with a mesh exposure rate of 8.8%. A large multicenter trial is underway comparing vaginal mesh hysteropexy using Uphold LITE (Boston Scientific) versus vaginal hysterectomy with uterosacral ligament suspension (NICHD Pelvic Floor Disorders Network, 2014).

Abdominal Hysteropexy

Early reports of abdominal hysteropexy described suturing of the uterus directly to the sacral promontory (anterior longitudinal ligament) or attaching a strip of autologous fascia between the cervix and the promontory. Additional techniques have used a variety of grafts to harness support, commonly the use of polypropylene mesh secured posteriorly to the cervix and posterior vaginal wall with an anterior segment that is passed through the broad ligament to support the anterior cervix and anterior vaginal wall. Meta-analysis of the available data suggests a 63% to 100% (mean 91%) anatomic success rate and a 1.5% mesh exposure rate (Maher et al, 2013b).

Uterosacral hysteropexy is performed by plicating the uterosacral ligaments and anchoring the cervix with or without the addition of a culdoplasty. Minimal high-quality data exist comparing this technique with the others mentioned earlier or with hysterectomy. Meta-analysis of 176 laparoscopic uterosacral hysteropexy reports an 83% success rate (Wei et al, 2012).

KEY POINTS: APICAL COMPARTMENT REPAIR

- The apical compartment is the cornerstone of vaginal support. Failure to ensure apical support at the time of prolapse correction will undoubtedly increase the risk of recurrence.
- Suture placement into the intermediate segment of the uterosacral ligament provides a stable fixation point and decreases the chance of ureteral injury.
- SSLF may result in posterior displacement of the vaginal apex and increase the risk of anterior compartment prolapse.
- Abdominal sacral colpopexy should be performed with permanent graft material and is an excellent option for correction of middle compartment defects. Minimally invasive techniques using laparoscopy and robotic-assisted surgery show similar efficacy.
- Women with uterine prolapse who undergo hysterectomy should have a concomitant vaginal vault suspension to prevent recurrent prolapse.
- Hysteropexy may offer women with less severe prolapse a uterine-sparing option.

Posterior Compartment Repair

Symptoms attributable to posterior compartment prolapse can be divided conceptually as herniation symptoms, defecatory dysfunction, and sexual dysfunction (Cundiff et al, 2004). Herniation symptoms include vaginal bulging and bleeding of the epithelium from excoriation. Defecatory dysfunction includes stool trapping requiring vaginal splinting or manual digitations, defecatory urgency, and constipation. It is important to differentiate among outlet obstruction (including defects in the support of the posterior compartment, perineum, and rectum), motility disorders, and anismus (Cundiff et al, 2004). Anismus is the failure of the puborectalis to relax during defecation. Motility disorders, which usually involve impaired transit of the rectum and anus, are treated with dietary modifications and medication. Anismus responds to biofeedback, and pelvic floor support defects are treated surgically. In combined disorders, it is recommended that nonsurgical treatment for anismus or slow-transit constipation (the most common disorder of motility) be treated before embarking on surgical intervention. Sexual dysfunction is thought to be secondary to dyspareunia, although decreased desire and anorgasmia may also be contributing factors (Handa et al, 2004). Several authors have sought to identify patient factors that would predict who might benefit most from rectocele repair (Murthy et al, 1996; Watson, 1996). These include sensation of vaginal mass or bulge, need for digitalization (splinting) to complete rectal evacuation, nonemptying or partial emptying on defecography, and presence of a large rectocele. Sensation of incomplete emptying and constipation are not specific to rectoceles and may be associated with other disorders including irritable rectum and slow-transit constipation. **Patients should be counseled that surgical repair of the posterior compartment may likely reduce vaginal protrusion symptoms and decrease or eliminate the need for vaginal splinting. However, some patients may have persistence of constipation, because motility disorders and anismus can independently coexist with prolapse and persist after a seemingly successful repair.**

Rectoceles can be approached transanally or transvaginally. Nieminen and colleagues randomized 30 patients to rectovaginal fascia plication or transanal repair (Nieminen et al, 2004). Both approaches resulted in a high rate of symptom resolution (93% for the vaginal approach vs. 73% for the transanal approach.) However, the vaginal approach had better objective findings and a lower rate of prolapse recurrence (7% vs. 66%). The traditional posterior colporrhaphy was devised in the 19th century to treat perineal tears,

which occurred during vaginal delivery. The original description involved plicating the pubococcygeus muscles and the posterior vaginal wall and reconstruction of the perineal body, which was termed *posterior colpoperineorrhaphy* (Cundiff et al, 2004). This resulted in a rigid inferior shelf, which reduced the herniation of the posterior wall and prevented descensus of the vaginal vault or uterus. In 1961, Francis and Jeffcoate reported a high incidence of dyspareunia after colporrhaphy with levator plication (Francis et al, 1961). In their series of 243 women, 50% developed postoperative dyspareunia. In addition, there is evidence to suggest that the traditional posterior colporrhaphy with levator plication may worsen defecatory symptoms. Khan and Stanton reported increased symptoms of fecal incontinence, constipation, incomplete evacuation, and dyspareunia postoperatively (Khan and Stanton, 1997). Because of the increase in dyspareunia postoperatively, plication of the levator ani muscles has largely been abandoned. Site-specific repairs and midline fascial plication without levator ani plication have emerged as the predominant surgical treatments of rectocele. It is important to remember that level 1 and 2 evidence supports the superior objective outcomes of midline posterior plication without levatorplasty compared with site-specific repairs.

Posterior Colporrhaphy

Technique (Fig. 83-38). The patient is placed into dorsal lithotomy position. If a patient requires an anterior or middle compartment repair, it is performed first (Rovner and Ginsberg, 2001). The anterior wall can be retracted with a Heaney retractor to improve visualization. Hydrodissection may be accomplished by injecting saline or a local anesthetic. A midline incision is made on the posterior vaginal epithelium. For a high rectocele the incision may be as high as the vaginal apex; for smaller rectoceles the incision is started at the most caudal position. The rectovaginal fascia (muscularis) is separated from the vaginal epithelium with Metzenbaum scissors. The tips of the scissors should be pointed toward the vaginal epithelium to avoid rectal injury. The dissection proceeds laterally until the pararectal attachments to the pelvic sidewall are visualized. In cases of large posterior defects, a purse-string suture of 2-0 or 3-0 absorbable suture may be placed at the base of the rectal herniation to reduce it; however, care should be taken to avoid foreshortening the posterior wall cephalad to caudad. In addition, this acts to bring the attenuated rectovaginal tissue together to aid in its reapproximation. The rectovaginal tissue is then plicated in the midline with either interrupted or continuous 2-0 absorbable suture. Care is taken to avoid excessively lateral placement or wide spacing of these sutures, which could result in painful ridges along the posterior vaginal wall. Suture placement is continued distally and incorporated into a perineal body reapproximation. The excess vaginal epithelium is trimmed and closed with an absorbable 2-0 suture. A perineorrhaphy may also be performed before the vaginal epithelium is closed.

Site-Specific Repair. To minimize complications associated with posterior colporrhaphy, a site-specific defect repair was described. Richardson described discrete defects in the rectovaginal fascia found in both patients undergoing posterior colporrhaphy and cadaveric dissections (Richardson, 1993). He found that the most common defect was the transverse configuration, separating the vaginal septum from the perineal body (Fig. 83-39). This essentially results in a separation of the rectovaginal tissues from the perineal body. The goal of the site-specific repair is to restore the anatomy by closing these discrete defects.

A midline incision is made on the posterior vaginal epithelium. For a high rectocele the incision may be as high as the vaginal apex; for smaller rectoceles the incision is started at the most caudal position. The rectovaginal fascia (muscularis) is separated through a virtually bloodless plane from the vaginal epithelium. The index finger of the nondominant hand is then inserted into the rectum to facilitate identification of the fascial defect. The defect is closed with absorbable interrupted sutures. The excess vaginal epithelium is trimmed and the vaginal epithelium is closed with interrupted sutures.

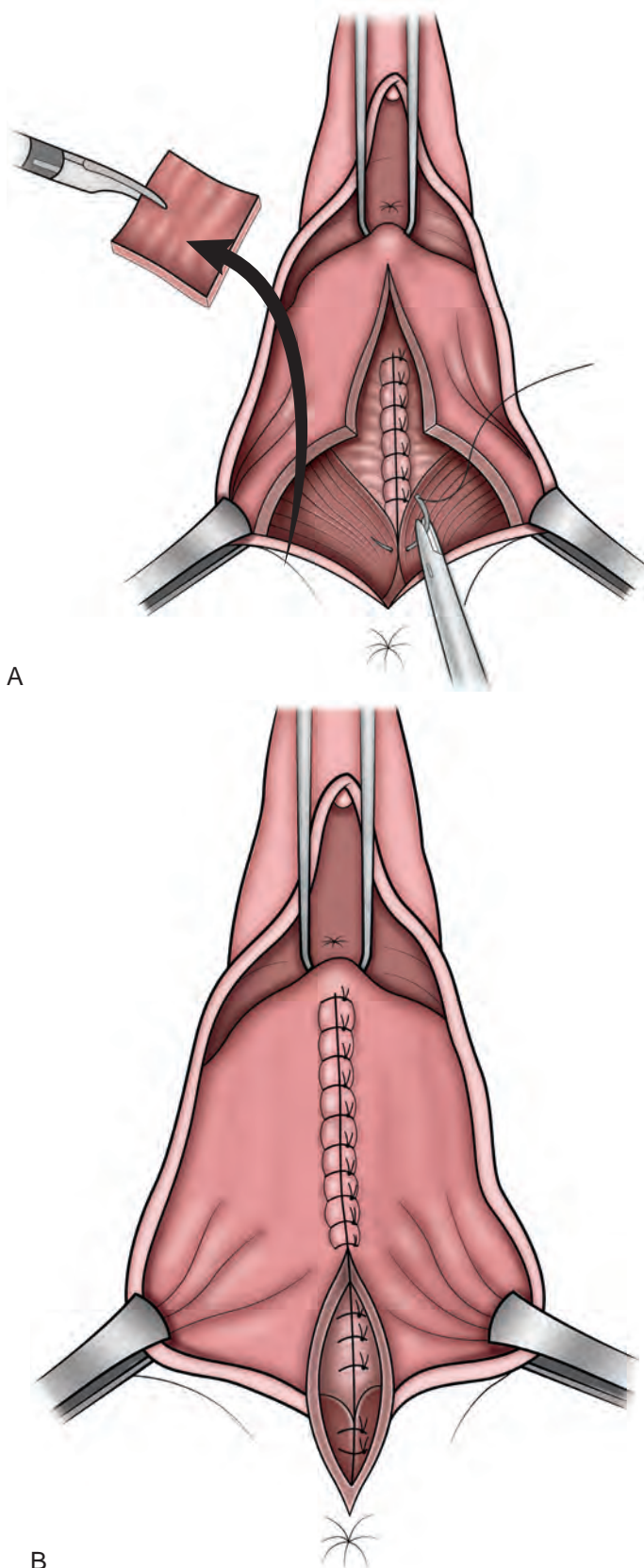


Figure 83-38. A and B, Technique of posterior colporrhaphy with rectovaginal tissue plication. (From Ginsberg D. Treatment of vaginal wall prolapse. In: Goldman H, Vasabada S, editors. Female urology: a practical clinical guide. Totowa [NJ]: Humana Press; 2007. p. 281–96.)

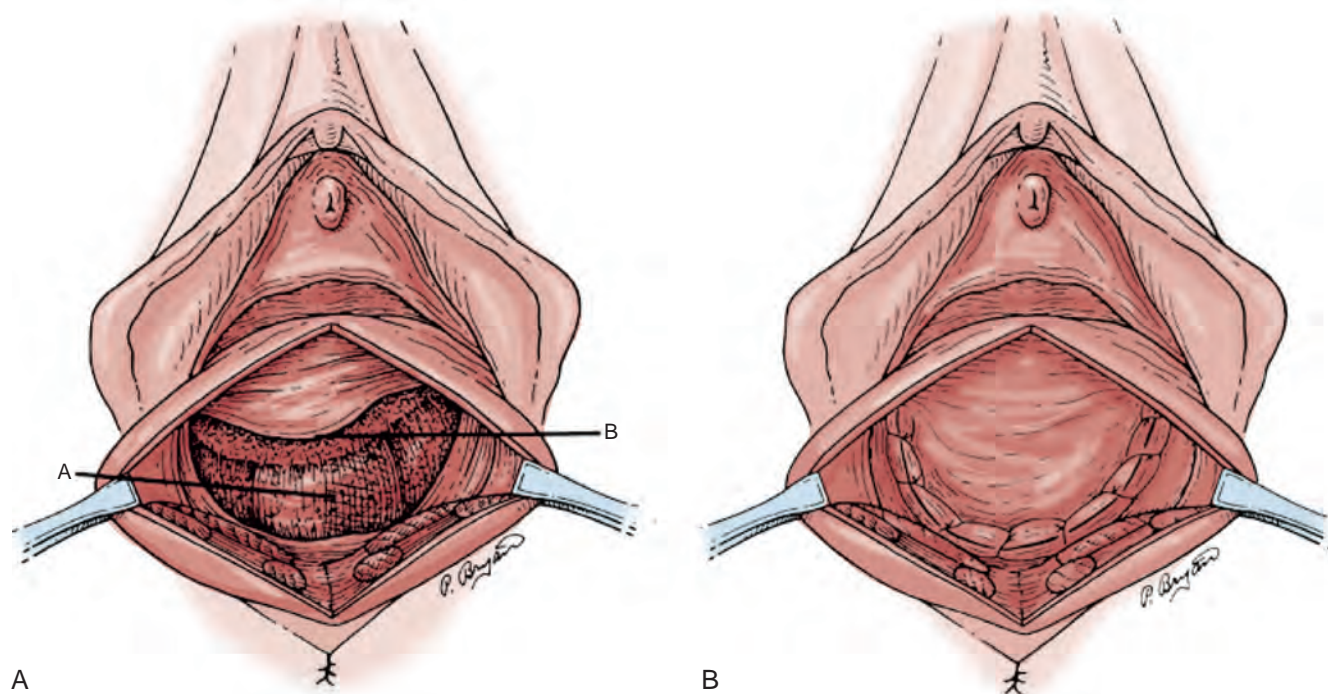


Figure 83-39. A and B, Site-specific rectocele repair. A low transverse defect is identified and repaired primarily. (From Richardson AC. The rectovaginal septum revisited: its relationship to rectocele and its importance in rectocele repair. *Clin Obstet Gynecol* 1993;36:976–83.)

Perineorrhaphy. A triangular incision at the mucocutaneous junction is made (Rovner and Ginsberg, 2001). The triangular island of posterior vaginal wall is sharply removed from the prerectal levator fascia. Horizontal mattress sutures are used to approximate the attenuated perineal body fibromuscular tissue. Once these are brought together, the muscles of the urogenital diaphragm are reconstituted and support is restored to the central tendon. It is important that a smooth contour be created along the suture line, because ridges may cause dyspareunia. A vaginal packing moistened with saline, antibiotic solution, cream, or gel is then placed.

Results (Table 83-7). Kahn and Lopez reported on the anatomic and functional results of posterior repair using levator plication. Both reported anatomic success; however, many patients complained of bowel symptoms and dyspareunia postoperatively (Khan and Stanton, 1997). Because of these adverse events associated with levator plication, this technique has been largely abandoned.

Paraiso and colleagues randomized patients prospectively to posterior colporrhaphy (rectovaginal fascial plication), site-specific repair, or site-specific repair with porcine SIS graft (Paraiso et al, 2006). They found that posterior colporrhaphy and site-specific rectocele repair had similar functional and anatomic outcomes. The addition of the porcine-derived graft did not improve anatomic outcomes. Rates of dyspareunia did not differ when comparing all three groups. In a follow-up study of these same patients specifically looking at bowel symptoms, Gustilo-Ashby found that anatomic cure was associated with a reduced risk of postoperative straining and sensation of incomplete bowel evacuation, but not with other bowel symptoms (Gustilo-Ashby et al, 2007). They found that bowel symptoms, including feeling of incomplete emptying, straining to defecate, splinting to defecate, and fecal incontinence, improved significantly after rectocele repair. Abramov and colleagues retrospectively studied patients with advanced posterior vaginal prolapse and compared patients who underwent posterior repair with those who underwent site-specific repair (Abramov et al, 2005). They found that the recurrence of posterior defects was higher in the site-specific group compared with the midline plication of the rectovaginal fascia: 33% versus 14% for second degree,

and 11% versus 4% for third degree. In addition, recurrence of symptomatic rectocele was greater in the site-specific group (11% vs. 4%). Rates of de novo dyspareunia and postoperative bowel symptoms were the same in both groups. Maher and colleagues prospectively studied the efficacy of posterior repair with plication of the rectovaginal fascia (Maher et al, 2004). They found that improved anatomic outcome correlated with improved functional outcomes. Eighty-seven percent no longer experienced obstructive defecation postoperatively. Significant improvements were seen in awareness of prolapse, obstructive defecation, straining to defecate, hard stools, dyspareunia, and digitations. Dyspareunia decreased from 37% to 5%. Singh and colleagues reported on a prospective study of 42 women evaluated for bowel, sexual, urinary, and prolapse symptoms as well as anatomic outcomes after fascial plication technique (Singh et al, 2003). At 6-week follow-up, 87% noted the relief of vaginal symptoms to be 73% to 92%. Sixty-five percent had improvement of the defecatory symptoms, and 38% had improvement of sexual discomfort. None of the patients reported de novo dyspareunia or bowel symptoms.

In contrast to the generalized repair of midline plication of the rectovaginal fascia, several authors have reported their experience with site-specific repair. Glavind and Madsen prospectively studied 67 patients who underwent a discrete repair (Glavind and Madsen, 2000). Of the 67 patients, 64 were found to have a discrete defect, which was repaired, and in 3 there was an attenuation of the tissue. At 3-month follow-up, 85% of those who reported bowel symptoms preoperatively reported resolution of symptoms. Two patients (3%) had de novo dyspareunia. Porter and colleagues examined anatomic, functional, and QoL aspects of posterior colporrhaphy in a retrospective study (Porter et al, 1999). Improvement or cure was noted for pain or pressure, vaginal mass, splinting, and difficulty with defecation. Constipation did not significantly change. Preoperative dyspareunia improved in 73% of patients, worsened in 19%, and occurred de novo in 3 patients. Emotional health also improved, specifically thoughts of embarrassment and frustration. Kenton and colleagues reported on 66 patients who underwent

TABLE 83-7 Results of Posterior Compartment Repair

TECHNIQUE	STUDY	NUMBER	REVIEW (mo)	ANATOMIC CURE (%)	VAGINAL BULGE (%)	VAGINAL DIGITATION (%)	DEFECATORY DYSFUNCTION (%)	DYS-PAREUNIA (%)	
Midline fascial plication	Paraiso et al (2006)	Preop							
		Postop	24	24/28 (86)			80 9/28 (32)	56 13/28 (46)	
	Abramov et al (2005)	Preop	183		150/183 (82)	100		17	8
		Postop	183	>12		4		33/183 (18)	31/183 (17)
	Maher et al (2004)	Preop							
		Postop	38	12	33/38 (87)	100	100	3 6/38 (16)	37 2/38 (5)
	Singh et al (2003)	Preop	42						
		Postop	26	18	24/26 (92)	78 2/26 (8)		76 5/26 (19)	33 5/26 (19)
Site-specific repair	Sung et al (2012)	Preop							
		Postop	80 70	12	63/70 (90)	4/58 (7)	9/58 (15.5)	12/57 (21)	4/57 (7)
	Paraiso et al (2006)	Preop	37						
		Postop	27	17.5	21/23 (91)		58 6/27 (22)		48 8/27 (30)
	Abramov et al (2005)	Preop							
		Postop	124 124	>12	69/124 (56)	100		15 24/124 (19)	8 20/124 (16)
	Glavind and Madsen (2000)	Preop	67						
		Postop	67	3	67/67 (100)				12 2/67 (3)
	Porter et al (1999)	Preop							
		Postop	125 72	6	73/89 (82)	27/72 (38) 10/72 (14)	17/72 (24) 10/72 (14)	44/72 (61) 32/72 (44)	26/39 (67) 18/39 (46)
	Kenton et al (1999)	Preop	66						
		Postop	46	12	41/46 (89)	86 4/46 (9)	30 7/46 (15)	53 20/46 (43)	28 4/46 (9)
	Cundiff et al (1998)	Preop							
		Postop	69 61	12	50/61 (82)	100 11/61 (18)	39 11/61 (18)	13 5/61 (8)	29 6/61 (10)
	Augmented repairs								
	Small intestine submucosa (SIS)	Paraiso et al (2006)	Preop						
Postop			31 26	17.5	14/26 (54)		29 (97) 5 (21)	15 (51) 2 (7)	0 (0) 1 (6)
Cadaveric fascia lata	Kobashi et al (2005)	Preop							
		Postop	73 62	13.7		6/50 (12)	38/62 (61) 4/62 (6.5)	53/62 (85.5) 9/62 (14.5)	14/39 (35.9) 9/39 (23.1)
Cadaveric dermis	Kohli and Miklos (2003)	Preop							
		Postop	43 30	12.9	28/30 (93)				

site-specific repair; all patients had reattachment of the rectovaginal septum to the perineal body. Statistically significant symptom relief was noted in the realms of protrusion, manual evacuation, difficult defecation, and dyspareunia. Constipation was unchanged. Three patients developed de novo dyspareunia, and 1 had de novo constipation. At 1 year, 7 of 11 patients who had used manual evacuation preoperatively returned to doing so. The authors commented that this might have been the result of a functional decompensation of the rectum, which is not corrected surgically. Finally, Cundiff reported on the anatomic and functional aspects of discrete fascial defect repair of the posterior compartment (Cundiff et al, 1998). At 12-month follow-up, 86% were noted to have stage 1 or less. Splinting was eliminated in 63% of patients who reported this symptom preoperatively. The mean satisfaction score was 8.6 (10 highest). **The mean improvement did not correlate to the anatomic correction but did correlate with alleviation of defecatory symptoms, stressing the importance of symptom relief being of priority to the patient over anatomic correction.**

Interposition Graft Repairs of the Posterior Compartment

Both synthetic mesh and biologic grafts have been used in posterior repairs, though data are lacking regarding routine use. Also, several authors caution against the use of synthetic materials in the posterior compartment owing to the potential for dyspareunia and visceral erosion, favoring the use of biologic grafts (Chen et al, 2007). Kohli and Miklos reported anatomic outcomes in 43 patients who underwent a site-specific repair with cadaveric dermis; 30 were available for evaluation at an average of 12.9 months. The graft was fixed proximally to the vaginal apex, laterally to the levator ani muscles, and distally to the perineal body. They reported a 93% success rate using the POP-Q grading system (Kohli and Miklos, 2003). Kobashi and colleagues reported using cadaveric fascia lata in 73 patients. With a mean follow-up of 13.7 months, there was an 83% to 89% improvement in symptoms. Ninety percent of those examined had a grade 0 rectocele by the Baden-Walker classification (Kobashi et al, 2005). Dell and O'Kelley used Pelvisoft, a fenestrated, porcine dermal acellular matrix, and reported no wound complications (Dell and O'Kelley, 2005). Contrary to these encouraging results, Altman reported on 29 patients using collagen mesh for symptomatic rectocele (Altman et al, 2005). Twenty-three were available at 3-year follow-up; 41% had recurrence of stage 2 or greater, and 12 of 23 patients reported incomplete rectal evacuation. The researchers advocated further study before recommending the routine use of graft-augmented tissue repair.

A number of authors have used permanent mesh materials via a posterior approach. Using permanent materials, multicompartmental repairs are more commonly performed extending from the SSL to the perineal body. De Tayrac reported on 26 patients with 2-year follow-up (de Tayrac et al, 2006b). Objective and subjective cure rates of 92.3% and 88%, respectively, were observed. Dwyer used a technique whereby Atrium mesh was attached to the SSL bilaterally and to the perineal body (Dwyer and O'Reilly, 2004). Fifty patients underwent posterior repair, 17 of whom had both anterior and posterior repair. No rectocele recurrence was seen at 13 months. Lim and colleagues reported using a composite Vicryl-Prolene mesh (Vypro II, Ethicon) for correction of isolated rectoceles. In this descriptive study, 90 patients underwent loose placement of an interposition graft in the posterior compartment with no primary repair. Success was noted in 27 of 31 (87%) at minimum 6-month follow-up. Five patients with recurrence of the rectocele did not have prolapse in other compartments (Lim et al, 2005). Mercer-Jones and colleagues reported 22 patients who underwent transperineal placement of either Vypro II or Prolene mesh; 77% reported moderate, good, or excellent results after mesh repair (Mercer-Jones et al, 2004).

When deciding on treatment options for the posterior compartment, both the surgeon and the patient should be aware that graft extrusion rates of 1.3% to 12% have been reported (Kobashi et al, 2005; Lim et al, 2005; de Tayrac et al, 2006b, 2007), as well as dyspareunia rates as high as 60% (Milani et al, 2005).

KEY POINTS: POSTERIOR COMPARTMENT REPAIR

- Because motility disorders often coexist with posterior compartment prolapse, patients should be counseled that constipation may persist despite successful anatomic correction.
- Levator ani muscle plication should not be performed during rectocele repair because of the high risk of dyspareunia postoperatively.
- Despite the high cure rates seen with the use of mesh in the posterior compartment, dyspareunia and vaginal extrusion may be significant.
- Repair of the perineal body is often performed at the time of rectocele repair to recreate approximation of the rectovaginal connective tissues to the central tendon of the perineum.

Vaginal Kits

Synthetic TVM kits have been introduced to provide a graft-augmented durable repair. The proposed advantages of kits are a "less invasive" procedure, standardization of technique, standardization of mesh, and the ability to repair multiple compartments through a vaginal approach. The presence of the mesh at the level of the vaginal apex with fixation is in contrast to the traditional colporrhaphy and may provide correction to multiple compartments, thus making comparisons with traditional prolapse repairs challenging. Currently there are a number of vaginal prolapse repair kits on the market. Because of concerns regarding the use of TVM in the treatment of POP, some companies have voluntarily withdrawn their kit products from the market; Prolift (Ethicon), Proxima (Ethicon), and Avaulta (C.R. Bard) are among the most notable. Implanting surgeons must realize that these procedures are using a significantly higher volume of mesh than conventional mid-urethral slings, and some procedures involve placing trocars into the deep pelvic musculature. **Thus, pelvic surgeons must make an informed decision with the patient, which weighs the apparent advantage in anatomic efficacy, decreased invasiveness, and potential durability against the potential morbidity associated with mesh erosion and the possibility of more significant complications unique to these procedures.**

Technique

Trocar-Based Anterior Compartment Repairs. The anterior prolapse repair follows many of the same basic steps for all of the kit procedures. A midline incision is created in the anterior vaginal wall. Hydrodissection may facilitate a deep, full-thickness vaginal dissection. The full-thickness dissection is important to minimize the occurrence of vaginal exposure of mesh. The dissection progresses laterally to the level of the endopelvic fascia, which is entered by sharp or blunt dissection. The pelvic sidewalls are developed until the ischial spines and ATFP are palpated. Stab incisions are made overlying the obturator foramen. The distal incisions are placed in the anteromedial edge of the obturator foramen at the level of the clitoris, and the proximal incisions are placed 2 cm below and 1 cm lateral to the distal incision. The trocars are used to position the arms of the mesh patch along the ATFP. The distal trocars are placed approximately 2 cm from the distal aspect of the pubic bone, and the proximal trocars are advanced along the ATFP, exiting 1 cm distal to the ischial spine. It should be noted that the proximal trocars in the Perigee system are different from the distal needles, which facilitates a deep passage of the proximal devices to the ischial spine. The mesh arms are used to position the mesh appropriately without tension. Sutures are used to fix the mesh both proximally at the level of the vaginal cuff (preferably delayed absorbable or permanent sutures) and distally proximal to the bladder neck with absorbable sutures. Before mesh placement, anterior colporrhaphy may be performed to correct a central defect if present. Cystoscopy is performed to confirm lower urinary tract

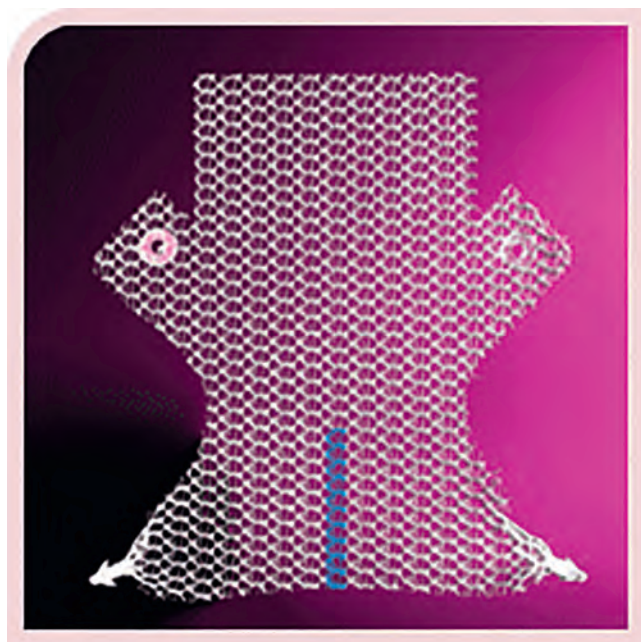


Figure 83-40. Transvaginal kits: Elevate transvaginal mesh. (Courtesy American Medical Systems.)

integrity. Care is taken to confirm the absence of excessive tension on each of the mesh arms (or points of attachment) (Fig. 83-40). The vagina is then closed without trimming the vaginal wall to minimize the occurrence of vaginal mesh extrusion. A loosely interrupted vertical mattress closure may be used to create a virtual two-layer closure of the vaginal epithelium.

Apical and Posterior Trocar-Based Repairs. The posterior and apical approach to kit placement does vary among kit devices. The Prolift device used proximal attachment through the SSL, while the Apogee device is fixed proximally 1 cm distal to the ischial spine. For all procedures, the dissection begins with a posterior vaginal incision, which is full thickness. The dissection proceeds laterally and proximally to expose the ischial spine (Apogee). Two stab incisions are made 3 cm lateral and below the anus. With a hand in the vagina retracting the rectum, the trocars are advanced through the ischiorectal fossa. The Apogee trocars exit 1 cm distal to the ischial spine. The mesh is trimmed so that it does not extend to within 1 cm of the perineal body. This avoids mesh complications in the perineum. The mesh is fixed laterally with absorbable sutures. The mesh is fixed with permanent or delayed absorbable suture proximally to the vaginal apex or posterior lip of the cervix. As with the anterior compartment, no trimming of the epithelium is recommended, and closure is completed with absorbable suture.

Non-Trocar-Based Repairs. There are new kits that do not use trocars for mesh placement. After dissection and exposure similar to the trocar-based procedures, the Uphold device (Boston Scientific) uses a Cadio needle driver system to pass the arms of the mesh through the SSL proximally and the ATRP and obturator internus fascia distally to provide anterior support. It may also be deployed posteriorly using the Cadio device as well. The Elevate (American Medical Systems) has a unique “tacking” device, which anchors the graft in the SSL as well as ATRP. The surgical approach and dissection required are similar to those of the aforementioned procedure; however, a tacking device uses fixation to the SSL proximally and the ATRP and obturator internus fascia distally. There is a special tool that facilitates adjustment of mesh tension after the tacking mechanism has been deployed proximally. An advantage of these devices is that there are no trocar passes required through the deep pelvic musculature.

Results. As with all prolapse procedures, there is a paucity of peer-review data to guide the most appropriate usage of transvaginal kits. Much of the literature regarding kits is from the experience with the

Prolift device, not currently available in the United States. Gauruder-Burmester and colleagues reported on a retrospective analysis of 121 women undergoing procedures with Apogee or Perigee mesh. Success rates of 93% were achieved (Gauruder-Burmester et al, 2007). Seventy-seven women were followed prospectively after placement of Perigee mesh for anterior POP. With an 18-month mean follow-up, an objective cure rate of 93% was achieved. Two women had recurrent prolapse symptoms, and 1 required subsequent surgery. Five mesh exposures occurred, and there were no other significant complications (Moore and Miklos, 2009). Rane and colleagues reported on a 5-year prospective experience with the Perigee system for anterior repair. The primary outcome was POP-Q stage 1 or less anterior vaginal wall prolapse, and secondary evaluation included questionnaire and review of clinical database. In 350 patients followed for a minimum of 2 years, a 94.3% anatomic success rate was achieved. Twenty patients (5.7%) had either recurrent prolapse symptoms or stage 2 prolapse. Five required repeat prolapse surgery, 2 having hysterectomy for stage 3 uterine prolapse. Thirty-nine (11.1%) of women had mesh exposure, of whom 34 required mesh excision under anesthesia. Four patients had 16 surgeries for recurrent mesh exposure. Two patients had hematoma—one requiring evacuation and another a transfusion (Rane et al, 2012). In women with SUI and anterior compartment prolapse, the Perigee system was compared with anterior repair in women who underwent a concomitant TVT-O (Ethicon) procedure. With a minimum of 1-year follow-up in all patients, the authors concluded that the anatomic outcomes were significantly better after the Perigee procedure for the anterior defect. Similar cure rates of SUI were seen, although there appeared to be less frequency in the Perigee group. The mesh erosion rate overall was 4.5%, with 2% attributed to the Perigee mesh. The incidence of dyspareunia was similar between groups (Lau et al, 2011). A prospective multicenter trial evaluated Elevate anterior and apical compartment repair. Of the 128 patients, 112 completed 12-month follow-up. The anatomic success rate was 87.7% for the anterior compartment and 95.9% for the apical compartment. The incidence of mesh exposure was 6.3%. A small percentage of patients experienced transient buttock pain (3.9%), de novo stress incontinence (3.9%), retention (3.9%), dyspareunia (3.2%), and hematoma (2.3%). Three of the mesh excision patients required in-office revision, and 3 required revision under anesthesia (Stanford et al, 2013). Rapp and colleagues evaluated the Elevate procedure prospectively in 40 patients for a minimum of 2 years (mean 34 months). These authors also noted that 36 patients experienced anatomic success, with only 4 having recurrent prolapse, of whom 2 were symptomatic. Two patients had mesh exposure, and 1 had transient leg pain. There were significant improvements in the QoL questionnaire assessments, leading these authors to conclude that the Elevate is a safe and effective system for prolapse correction (Rapp et al, 2014). Feiner and colleagues performed a meta-analysis of the peer-reviewed literature and select peer-reviewed gynecologic abstracts to evaluate outcomes and complications following transvaginal synthetic apical suspension procedures. After the Apogee procedure, 525 women had a mean follow-up of 26 weeks (range 10 to 56 weeks). Mean objective success was 95% (range 81% to 100%). In the same meta-analysis, posterior or total Prolift was performed in 1295 women with mean follow-up time of 30 weeks (range 12 to 52 weeks), and the mean objective success rate was 87% (range 75% to 94%) (Feiner et al, 2009). Although these early data demonstrate successful outcomes, it is important to note that serious complications, some unique to these procedures, are being reported. These concerns have prompted comments regarding new procedures and materials for the treatment of incontinence and prolapse, warning that there are insufficient data supporting the routine use of these devices (Ostergard, 2007). In a Cochrane review of POP surgery, Maher and colleagues concluded that “the advantages of a permanent polypropylene mesh must be weighed against disadvantages including longer operating time, greater blood loss, prolapse in other areas of the vagina, new-onset urinary stress incontinence, and the mesh becoming exposed in the vagina in 11% of women. In general, there is a lack of evidence to support TVM operations used in apical or posterior

compartment surgery” (Maher et al, 2013b). In light of this, it is incumbent on physicians to openly discuss these issues with patients. (See overview of mesh controversy, later.)

Complications. Mesh complications are most commonly in the form of mesh exposure or “extrusion.” Extrusion rates of approximately 10% can be expected (Gauruder-Burmester et al, 2007; Feiner et al, 2009). The exposures seem to occur more frequently on the anterior wall, and a concomitant hysterectomy significantly increases the risk (de Tayrac et al, 2007; Gauruder-Burmester et al, 2007). Measures to minimize the occurrence of vaginal mesh exposure are minimizing excessive vaginal wall trimming and closing without tension. Some advocate closing with a vertical mattress technique to separate the graft from the wound (de Tayrac et al, 2006a). Symptoms of mesh extrusion include vaginal discharge, persistent bleeding, pain, dyspareunia, partner pain, dysuria, and recurrent UTIs. Examination by palpation as well as visualization is important to detect this complication. Although some patients can be managed with either observation or local treatment, most will require excision with primary vaginal closure (de Tayrac et al, 2006a). Infected vaginal mesh can lead to sinus formation, abscess, and enterovaginal fistula formation. One case of necrotizing fasciitis with *Staphylococcus aureus* requiring extensive perineal debridement and colostomy has been reported after a kit procedure (Abdel-Fattah et al, 2008).

Unfortunately, significant lower urinary tract erosion into the bladder or urethra has also been reported, with significant consequences (Yamada et al, 2006). Including transvaginal kits systems, the incidences of visceral (including urethra) injuries have been reported from 2.7% to 4.4% (Altman and Falconer, 2007; de Tayrac et al, 2007). The rates of bladder perforation vary from 0.9% to 2.8% (Altman and Falconer, 2007; de Tayrac et al, 2007; Fatton et al, 2007). Bladder perforation after retropubic mid-urethral sling procedures is not uncommon and appears to be a benign event in the presence of adequate bladder drainage (Kuuva and Nilsson, 2002). The fate of bladder injury at the time of mesh prolapse repairs is much less certain. **If the bladder is injured, it is our opinion that the procedure should be completed without a mesh interposition of the anterior compartment, as placing mesh in the setting of a bladder laceration would prohibitively increase the risk of erosion.** Extensive erosions into the bladder necessitating partial cystectomy have been reported (Abdel-Fattah et al, 2008). With urethral injury, the defect should be repaired primarily, and again, mesh or graft placement should not be performed.

Rectal perforation is reported in 0.7% to 2.8% of cases (Altman and Falconer, 2007; de Tayrac et al, 2007). If rectal injury is recognized intraoperatively, synthetic mesh should not be placed (Mercer-Jones et al, 2004; de Tayrac et al, 2006b). Rectal erosion of synthetic mesh may necessitate both rectal and vaginal excision (Hurtado et al, 2007). From these outcomes, it is clear that **if the rectum is perforated, a multilayer closure should be performed; povidone-iodine distention of the rectum should follow to ensure the integrity of the repair, and the procedure should be abandoned.**

The trocars are passed through the pelvic muscular complex for both anterior and posterior kit repairs. The trocars pass near the ischial spine, and significant intraoperative bleeding may occur. This would usually emanate from the pudendal neurovascular bundle, and embolization of the source of bleeding has been reported (Mokrzycki and Hampton, 2007). Multiple authors have reported pelvic hematomas following transvaginal kit procedures (Ignjatovic and Stosic, 2007; LaSala and Schimpf, 2007; Abdel-Fattah et al, 2008). Abdel-Fattah described concerning vascular complications after Prolift and Apogee or Perigee procedures, including arterial injury. Hematomas have also been reported with these procedures (Ignjatovic et al, 2007). Commonly, patients will report unusually more pelvic pain than typically encountered. Computed tomography (CT) is an excellent method to detect hematomas. Thus, if excessive postoperative pain occurs after the procedure, one should consider an evaluation with CT to look for a hematoma. If present, observation with serial hematocrit levels is the appropriate initial evaluation; however, surgical drainage may

be required for expanding hematomas, decreasing hematocrits, refractory pain, or infection.

Local complications such as pelvic pain, defecatory pain, and dyspareunia have been reported after kit procedures (Altman and Falconer, 2007; de Tayrac et al, 2007). When examining these patients, one must carefully look for areas of impaired healing, banding or tenting of the mesh, “trigger points” that elicit pain, and signs of focal inflammation. If these abnormal areas are identified, release of the arms or the site of mesh tension may alleviate these areas of discomfort. When performing the mesh release, one should excise as much offending mesh material as possible before vaginal closure. In cases of infection, granulomas, or persistent draining sinuses, all mesh involved in the infected areas must be removed. If no local incriminating factors are found, a period of conservative therapy consisting of physical therapy, trigger point injections, and other adjunctive techniques should be attempted first.

KEY POINTS: TRANSVAGINAL KITS

- When considering a transvaginal kit for POP repair, one must weigh the increased anatomic efficacy and decreased invasiveness against the potential morbidity of mesh erosion, mesh extrusion, and visceral organ injury.
- To minimize vaginal mesh extrusion, the trimming of the vaginal wall should be minimized and the incision should be closed without tension.
- If either the bladder or rectum is injured during POP repair, mesh interposition should not proceed because the risk of erosion is high in these situations.
- Prompted by over 1000 reports of mesh complications, the FDA in October 2008 issued a warning to both surgeons and patients regarding the transvaginal use of mesh.

The Use of Mesh in Vaginal Surgery: The Current Controversy

The high failure rates of POP and SUI surgery have long been recognized (Olsen et al, 1997). Owing to inherent connective tissue defects that contribute to SUI and POP, surgeons have long sought materials that could augment repairs and result in more durable outcomes. Biologic materials have been used, but unfortunately have had inconsistent results owing to variability of graft function. When mesh is used as a graft in prolapse surgery, there are differences in volume of mesh, sites of mesh implantation, amounts of vaginal dissection, and surgical expertise required to perform these procedures competently when compared with mesh for SUI. Based on the enormous success of the mid-urethral sling, the FDA granted more than 100 510(k) exemptions for mesh “kits” to be used in the surgical management of POP (U.S. Food and Drug Administration, 2013). With use of the initial technique of transobturator access, the trocars and mesh grafts were modified to facilitate multicompartiment POP repair. This resulted in larger grafts being inserted or tunneled to the SSL, iliococcygeus fascia, arcus tendineus, obturator internus, levator ani, and perineal body. To accomplish this, considerably more vaginal dissection through wider incisions is required. Wider vaginal flaps can be more prone to “breakdown,” resulting in mesh exposure. Fluid accumulation or bleeding from deep dissection as well as tension or buckling of the mesh sheets may adversely affect graft incorporation, leading to an exposure, erosion, or pain. Tacking or tunneling of larger volumes of mesh into the deep pelvic musculature may lead to neuromuscular dysfunction of the levator ani complex and subsequent pelvic floor dysfunction. Lastly, some surgeons who were not performing transvaginal tissue-based prolapse repairs may have started performing these procedures as an “extension” of the transobturator technique. It is very clear that much more advanced dissection skills and techniques are required when performing a mesh-based prolapse repair

versus a mid-urethral sling. There is no doubt that a number of high-volume accomplished vaginal surgeons are performing mesh-based prolapse repairs safely on their patients (Murphy et al, 2012). But it is not all just about experience of the surgeon. There should be little dispute that the volume, techniques of dissection, and location of the mesh for POP repairs are associated with a risk profile that is much greater than that of the mid-urethral sling and that these procedures are vastly different—even with the same type of mesh.

Outcomes data comparisons also reveal disparity between these two procedures. With the first-generation mid-urethral sling, the efficacy and safety have been demonstrated worldwide through multiple studies with little dispute (U.S. Food and Drug Administration, 2013). Thus, these procedures are a clear (and often preferred) option in the surgical treatment of SUI. The same cannot be said for POP repairs. Most would agree that anatomic outcomes appear better in the anterior compartment (Maher et al, 2013a). However, the data are less compelling in the posterior compartment and apex. When subjective outcomes and reoperation rates are included, the data regarding mesh for prolapse are less clear—distinctly opposite from the first-generation mid-urethral sling (U.S. Food and Drug Administration, 2013). Thus the precise indications for TVM for prolapse are much less clear. A Public Health Notification is an important message from the FDA Center for Devices and Radiological Health to the health care community (Schultz, 2008). This message describes a risk associated with the use of a medical device and provides recommendations to avoid or reduce the risk. In October 2008, the FDA released a public health statement that “serious complications are associated with transvaginal placement of surgical mesh in repair of pelvic organ prolapse and stress urinary incontinence.” This report was designed to alert health care practitioners of complications associated with transvaginal placement of surgical mesh to treat POP and SUI. This report stated that over 3 years the FDA received more than 1000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI. As a result, a number of recommendations were made to physicians, which included obtaining specialized training for each mesh placement technique and informing patients that implantation of surgical mesh is permanent. It was also recommended to inform patients about the potential for serious complications and their adverse effect on QoL. As part of this notification, the FDA embarked on additional investigations into mid-urethral sling and POP procedures using mesh, which resulted in an update of the Public Health Notification in 2011 (U.S. Food and Drug Administration, 2011b). This update was to inform the public once again regarding serious complications related to the use of TVM in POP. **Of note, the 2011 notification was regarding POP only, and did not include SUI.** In 2013, the FDA released additional findings regarding the use of mesh for SUI and POP (U.S. Food and Drug Administration, 2013). In the area of mesh for SUI, the FDA concluded that the “safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to 1 year. Longer follow-up data is available in the literature, but there are fewer of these long-term studies compared to studies with one-year follow-up.” The FDA also concluded that mesh “sling surgeries for SUI have been reported to be successful in approximately 70 to 80 percent of women at one year, based on women’s reports and physical exams ... and that the vaginal exposure of mesh occurred in 2% of cases.”

This is distinctly different from the conclusions regarding the use of TVM for POP, wherein the FDA concluded that “complications are not rare ... and are of serious concern ... and that there is no clear benefit to using mesh in the transvaginal correction of POP.” These conclusions led the FDA to recommend changing the classification of TVM to Class III devices and to require extensive premarket testing on any new mesh kits for prolapse, and lastly to require 522 postmarket surveillance studies comparing TVM with tissue-based repairs to demonstrate safety and efficacy of TVM for prolapse. During this period, any prolapse kits using mesh currently available will still be able to be used by surgeons. In contrast, the FDA did not reclassify TVM for the sling in the treatment of SUI.

No premarket data or postmarket 522 data will be required for the first-generation mid-urethral sling procedures (retropubic and obturator) (U.S. Food and Drug Administration, 2011a). **Based on these observations, it is clear that the FDA concluded that the benefit-risk ratio of the first-generation mid-urethral slings was clearly favorable and did not recommend any alteration in their use.** To be clear, the FDA did require postmarket 522 studies of the second-generation mini-slings because of concerns that these procedures have inferior efficacy compared with retropubic or transobturator slings (U.S. Food and Drug Administration, 2013).

Subsequently, a plethora of legal actions has occurred based on the FDA activity regarding vaginal mesh. Multiple class action lawsuits have been organized against the manufacturers of mesh used for the treatment of SUI and POP. Millions of dollars have already been awarded, and this figure will likely rise exponentially. Several large companies have decided to withdraw their mesh products for POP from the market place. There is an infiltration of the media regarding class action lawsuits against mesh manufacturers, which has resulted in a global negative bias regarding mesh for the treatment of SUI and POP. Some of these advertisements contend that the mesh is “defective” and has been “recalled.” These claims are not congruent with the FDA findings and have also created concern in many women who have been successfully implanted with vaginal mesh—seeking removal of the “defective mesh.”

To date, there has been no recall or clinical evidence of defective mesh. In fact, the FDA action of allowing continued use of these products while postmarket surveillance is ongoing demonstrates that the FDA did not conclude that these products are defective. Also, the continued inclusion of the mid-urethral sling in these advertisements is in direct opposition to the FDA findings and level I evidence from NIH-sponsored clinical trials, which demonstrate that mid-urethral sling procedures are safe and effective.

So, where does this leave clinicians of today? We are in an environment of having to deal with the realities of POP and SUI QoL disturbances and recurrences after native tissue repair in our patients who are now anxious and likely have a very negative bias against mesh. These realities exist with almost nonexistent high-quality, comparative evidence in the area of POP. What can we do to appropriately counsel and guide our patients regarding surgical procedures that are best for them? It is clear that these answers do not exist, and comparative trials as well as registries are desperately needed to guide us through this process.

In an effort to aid surgeons, the following recommendations are offered with the goal of safe, judicious, and effective use of vaginal mesh for SUI and POP.

- **Patients should be counseled extensively regarding the mesh procedure(s) recommended.** They should be informed that they are getting mesh (and why it is best for them), that there are nonmesh alternatives, and that there are complications that do occur that are unique to mesh. They should be informed that these complications may be permanent and may require more than one operation, which may or may not correct the problem. Patients should also be informed that the most common complication unique to mesh is mesh exposure, which may be asymptomatic or may require a surgical revision, which may address the problem.
- **Clinicians should refer patients to the manufacturer’s website regarding the specific procedure for them.** They should be encouraged to learn more about their procedure in advance of the surgery. **Clinicians should refer patients to the FDA website regarding the FDA vaginal mesh communication** and also to the websites of subspecialty societies (AUA, SUFU) that contain consensus statements and other links regarding vaginal mesh.
- **Clinicians should maintain the strong distinction between mid-urethral sling procedures (retropubic and obturator) and TVM procedures for POP.** Patients should be informed of the FDA actions, which were vastly different between the two procedures, and that there is prospective NIH research demonstrating the safety and efficacy of the mid-urethral sling. Although the litigation involves all procedures, patients should be informed that the currently available evidence demonstrates the safety and

efficacy of the mid-urethral sling, making it the standard surgical treatment for SUI.

- **Widespread, routine use of TVM—particularly for primary procedures—should be discouraged in patients with POP.** Because the current evidence of TVM for POP is much more limited and the indications far less clear, the American College of Obstetricians and Gynecologists (ACOG) and American Urogynecologic Society (AUGS) position statement reflects a balanced use of mesh for POP that should be considered by all surgeons. This statement recommends reserving the use of vaginal mesh in the surgical repair of POP to women at high risk “in whom the benefit of mesh placement may justify the risk.” These women include those with recurrent prolapse—particularly of the anterior compartment—and those with medical comorbidities that “preclude more invasive and lengthier open and endoscopic procedures” (*Committee on Gynecologic Practice, 2011*).
- **Surgeons performing TVM procedures should be proficient in reconstructive pelvic surgery using native tissue techniques and should have a thorough understanding of pelvic floor anatomy as well as the complications that can occur after pelvic floor surgery.** Mesh techniques are an adjunct to perform pelvic floor procedures in properly selected patients. Mesh procedures are not “new procedures” to treat POP and SUI. In other words, if a pelvic surgeon has not performed SSL dissections and/or fixation, he or she should not be performing mesh kit procedures requiring similar dissection. Obtaining proficiency in these surgical skills should precede any introduction of apical mesh kit procedures. Institutions should be cautious to grant privileges to surgeons performing TVM procedures for prolapse who do not have preexisting credentials to do pelvic floor surgery.
- **Surgeons should be vigilant in assessing patient complaints.** Patients must be reassured that any postoperative concern is not dismissed. Surgeons should directly address these concerns and offer assistance in second-opinion referrals in the absence of an explanation. With the current uncertainty and negative perceptions of mesh, patients need reassurance that their concerns are adequately addressed and that reasonable attempts are being made to address them.
- **Surgeons should endorse and participate in prospective, comparative clinical trials as well as registries to advance the knowledge of and identify best practices of TVM usage.**

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▶ Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The Evolution of Slings

Preoperative Assessment

Alternative Treatment Options

Pubovaginal Slings

Midurethral Slings

Regulatory and Legal Issues Related to Sling Mesh Complications

THE EVOLUTION OF SLINGS

Urethral slings are currently the procedure of choice for the surgical correction of female stress urinary incontinence (SUI). A variety of materials (autologous, allograft, xenograft, and synthetic) and techniques have been pursued for sling placement. The concept of slings for urethral support was first introduced in 1907 by D. Von [Giordano \(1907\)](#) as a gracilis muscle graft wrapping around the urethra ([Aldridge, 1942](#)). Later, German surgeons used slings fashioned from muscle and fascia in children with incontinence ([Goebell, 1910](#)). The rectus abdominis muscle and fascia were first used to treat SUI by [Frangenheim in 1914](#) and then later modified by Albert [Aldridge in 1942](#) ([Frangenheim, 1914](#); [Aldridge, 1942](#)). It was Aldridge who first theorized that the abdominal muscles' response to increased intra-abdominal pressure could be used anatomically to compress the urethra. In his operation, Aldridge used a 1.5- × 6-cm strip of rectus fascia that was left attached to the aponeurosis of the rectus abdominis muscle in the midline (only the two ends were mobilized) and then passed under the urethra, where the free ends of the sling were then sutured together. Aldridge left the sling attached to the rectus fascia in the midline because he theorized that this would allow the sling to compress the urethra when the abdominal muscles responded to increases in intra-abdominal pressure. Aldridge stated that he came up with this "fundamental principle" by reading a case report of a surgery performed by Phillip [Price in 1933](#), who used a fascia lata sling passed around the urethra and attached to the rectus muscle to cure the incontinence of a woman with congenital absence of the sacrum and coccyx ([Price, 1933](#)). In this article, Price stated that by attaching the sling to the rectus muscle he was able to take full advantage of changes in the patient's posture and position to tighten or relax the sling at times when incontinence is most likely to occur. Although the technique described by Price was very similar to modern autologous pubovaginal sling (PVS) surgery, we now know that with healing and incorporation, the sling becomes fixed and immobile in the retropubic space and continence is not related to the fact that it is secured over the rectus abdominis muscle fascia. Anecdotally, this is proven by the fact that cutting these securing sutures in a patient with an obstructive sling months after surgery will not release tension.

In 1956, [Jeffcoate](#) used Aldridge's technique on 40 women and reported an 86% cure rate. However, it was McGuire's modifications and subsequent use of the PVS in patients in whom prior retropubic suspensions and anterior colporrhaphies had failed, with a cure rate of 91% that reintroduced and popularized the procedure ([McGuire and Lytton, 1978](#)). Then in 1988, [Blaivas and Olsson \(1988\)](#) used McGuire's technique in their description of the modern PVS placed at the bladder neck, in an effort to correct urethral hypermobility

and modify the pressure transmission invoked by intra-abdominal pressure changes.

Later theories regarding the causes of incontinence focused on urethral hypermobility as the primary cause of SUI. In this model the abnormally low location of the bladder neck in patients with SUI resulted in unequal intra-abdominal pressure transmission to the bladder and urethra. In 1994, [DeLancey](#) published a revised model that made a significant contribution to the current understanding of the continence mechanism. [DeLancey's proposal](#) was that in healthy individuals, a "suburethral hammock" attached laterally supports the urethra, but that in patients with SUI there is a deficiency of this supporting layer that is evidenced by hypermobility of the bladder neck and urethra ([DeLancey, 1994](#)). It was theorized that descent of these structures inferiorly allowed for unequal pressure transmission and subsequent SUI. Therefore a PVS placed at the bladder neck is able to improve SUI by providing a layer of tissue that compresses the urethra during times of increased intra-abdominal pressure. This and similar theories emphasize that urethral support is derived from attachments to the arcus tendineus fasciae pelvis (ATFP) and levator ani muscles.

From 1991 to 1998 the PVS had surpassed needle-type suspensions and anterior urethropexies to become the predominant invasive surgical method for the treatment of SUI in the United States ([Anger et al, 2009](#)). Then in 1998 the U.S. Food and Drug Administration (FDA) approved the first midurethral sling (MUS) for use in patients with SUI, and the rate of sling surgery increased by more than threefold (78.3 to 237.4 per 100,000 person-years) ([Jonsson et al, 2012](#)). Unfortunately, as with most national databases, Medicare data are limited by the fact that the Common Procedural Terminology (CPT) codes do not reveal the exact type of sling that is placed. However, many authors have speculated and inferred that the dramatic acceleration in sling surgeries is most likely a result of the increased popularity of the MUS ([Oliphant et al, 2009](#); [Wu et al, 2011](#)).

Unlike the PVS, the MUS should be placed loosely at the midportion of the urethra. Placement of the MUS at this location is partially based on the theories initially espoused by Ingelman-Sundberg (1953). These researchers noted that the pubococcygeal muscles insert at the level of the midurethra just outside the vaginal epithelial wall and play a vital role in the midurethral continence mechanism. They further propounded that this anatomic finding is important when considering methods to correct urinary incontinence. Decades later, Westby and colleagues (1982) and [Asmussen and Ulmsten \(1983\)](#) demonstrated that in women who are continent, maximum urethral closure pressures (MUCPs) occur at the midurethra and that this phenomenon is most likely caused by the confluence of anatomic structures in that area.

Based on the aforementioned theories and other published experiments, in 1990 **Petros and Ulmsten** proposed a unifying concept called the *integral theory*. They stated that the most important factors to preserve continence were adequate function of the pubourethral ligaments, the suburethral vaginal hammock, and the pubococcygeus muscle. They postulated that injury to any of these three components from surgery, parturition, aging, or hormonal deprivation could lead to impaired midurethral function and subsequently urinary incontinence. **Ulmsten and colleagues** published one of numerous studies used as the basis for the integral theory in 1987. In that paper, the researchers performed biopsy of the skin and round ligament of eight continent women and seven incontinent women and found that the tissues of incontinent women contained 40% less collagen. From this information, the authors concluded that weakness of the connective tissue supporting the urethra secondary to the loss of collagen might contribute to incontinence.

In 1995, **Ulmsten and Petros (1995)** applied the integral theory to the development of the first retropubic synthetic MUS, which they termed an *intravaginal slingplasty*. In this initial paper, Ulmsten and Petros reported that they completely cured incontinence in 39 of 50 (78%) women who underwent the intravaginal slingplasty and that there were no complications. In 1998, **Ulmsten and colleagues** had changed the name of the procedure to *tension-free vaginal tape (TVT)* and reported the results of a prospective multicenter study looking at this surgical technique's safety and efficacy. In that study, 119 of 131 (91%) patients were cured of their incontinence. In terms of complications, 2 patients developed transient urinary retention, 2 patients developed hematomas, 1 patient developed persistent urinary retention that required "a small adjustment" via a vaginal incision, 1 patient experienced mesh perforation of the bladder that was recognized at the time of surgery (mesh was replaced), and, although it is unclear if there was vaginal mesh exposure, 1 patient developed a wound infection that required a minor surgical procedure and vaginal estrogen. It is interesting to note that this first multicenter trial of MUS surgery may have also been the first to report two of the now well-known unique and troublesome complications of MUS surgery: mesh perforation of the urinary tract and mesh exposure.

For several years the retropubic approach was the only published method of placing a tension-free MUS, but in 2001, **Delorme** described the first transobturator approach. In that study, 39 of 40 patients were cured of their incontinence and only 1 patient experienced a complication. The authors commented that unlike the retropubic MUS, this new approach did not violate this surgical plane that lies in close proximity to the bladder and therefore decreased the risk of bladder or bowel injury. Initially, many proponents of the transobturator sling believed that there was no need to perform a cystoscopy after trocar passage; however, the American Urological Association (AUA) guideline states that a cystoscopy can be performed to minimize the risk of mesh urinary tract perforation (**Appell et al, 2009**). Ten years after the introduction of the MUS, **Richter and colleagues (2010)** published a study demonstrating that retropubic and transobturator MUSs were equally efficacious and generally safe.

The most recent step in the evolution of the sling came in 2006 with the FDA approval of the first single-incision MUS (TVT Secur, Ethicon Endo-Surgery, Somerville, NJ) (**Abdel-Fattah et al, 2011**). Data are less robust for the single-incision slings (mini-slings) and this will be discussed later in the chapter. Similar to transobturator slings, the risk of bladder or bowel injury is low with single-incision slings; however, cystoscopy is recommended in general to rule out bladder or urethral injury.

Over the past 10 years, numerous studies have continued to demonstrate the efficacy and safety of all different types of sling procedures for the treatment of SUI. However, recently, regulatory and professional organizations have raised concerns about mesh exposure and perforation complications unique to synthetic mesh materials, biologic grafts, and the specialized tools used to place them (**Novara et al, 2008**), prompting initial warnings from the FDA. Most of these concerns are related to graft materials used in

transvaginal pelvic organ prolapse surgery, although suburethral slings were implicated by technical similarities. In 2010, the International Urogynecological Association (IUGA) and the International Continence Society (ICS) released a report clarifying and standardizing the terminology related to complications from insertion of synthetic and biologic materials during female pelvic surgery (**Haylen et al, 2011**). According to that report, synthetic mesh is termed a *prosthesis* and a biologic implant is termed a *graft*. Mesh located in the lower urinary tract is termed a *perforation*, and extrusion of mesh through the skin or vagina is termed *exposure*. This topic is of great importance to pelvic surgeons and their patients and will be discussed in further detail later in this chapter.

KEY POINTS: EVOLUTION OF SLINGS

- Early theories regarding the cause of stress incontinence were focused on the unequal transmission of pressure to the bladder and urethra, urethral hypermobility, and the abnormal inferior location of the urethra.
- Later theories emphasized the importance of three separate components that support the proximal and midurethra (pubourethral ligaments, the suburethral vaginal hammock, and the pubococcygeus muscle).
- Based on these theories, PVSs are placed under mild tension at the bladder neck to reestablish the suburethral hammock, and MUSs are placed loosely at the midurethra to prevent movement of the posterior urethral wall.

PREOPERATIVE ASSESSMENT

The AUA guideline for the surgical management of female SUI states that the goal of a diagnostic evaluation in a woman with incontinence is to characterize the type of incontinence, assess underlying comorbid medical conditions, elucidate the differential diagnoses, and discover prognostic information that will aid in the selection of treatment (**Appell et al, 2009**). The evaluation of urinary incontinence begins with a thorough history focused on the onset, frequency, character, and severity of the incontinence and other voiding symptoms. Some clinicians may find that a validated questionnaire and a voiding diary best accomplish this step. It is also important to reveal factors that worsen the patient's incontinence such as sexual intercourse. It is also critical to accurately assess the degree of a patient's urgency because this symptom has been shown to correlate with worse outcomes after sling surgery (**Richter et al, 2008**). The rest of the history should be dedicated to evaluation of other factors that can affect bladder and urethral function such as neurologic diseases, medications, and prior surgeries. Also, it is important to query the patient about problems related to fecal incontinence or defecation. Knowledge of prior radiation is also useful because radiation may compromise the quality of a rectus fascial graft.

A focused neurourologic examination and pelvic examination should be performed on any patient with complaints of urinary incontinence. Uncovering physical findings of a neurologic or musculoskeletal disorder may aid in the treatment of a patient's incontinence symptoms. The pelvic examination should be performed to evaluate for any correctable anatomic abnormalities that can contribute to incontinence such as a vesicovaginal fistula and any abnormalities that are the result of urinary incontinence such as vaginal epithelial irritation. Using both resting state and provocative maneuvers (i.e., Valsalva and coughing) the examination should evaluate vaginal anatomy, including the urethral meatus and vaginal support (i.e., pelvic organ prolapse); quality of vaginal tissues, including the presence of tissue atrophy and irritation; the presence of urinary incontinence, including the degree of urethrovesical hypermobility; and any other associated findings, such as the presence of fistulae, foreign materials, or other anatomic abnormalities. During the examination, the patient should also be asked to perform

Valsalva maneuvers to reveal pelvic organ prolapse, urethral hypermobility, and stress incontinence. Although the usefulness of this test is controversial, a Q-tip test can also be performed to assess abnormal mobility of the urethra. With this test a patient is considered to have urethral hypermobility if a Q-tip inserted into the urethra moves more than 30 degrees during abdominal straining (Bergman and Bhatia, 1987). Lastly, if a supine stress test with a full bladder does not demonstrate urinary incontinence, then a standing stress test is imperative.

Based on AUA guidelines, a urinalysis and measurement of postvoid residual (PVR) volume should be performed on all patients, but more extensive imaging is not part of the routine evaluation of urinary incontinence. However, in some patients abnormal findings in the history, physical examination, or urinalysis may warrant this type of further evaluation. For example, the initial presentation of undiagnosed neurologic conditions such as multiple sclerosis or central nervous system tumors may manifest with urologic symptoms; therefore, in these patients, magnetic resonance imaging (MRI) of the head, spine, and pelvis for spinal cord or brain lesions could prove beneficial.

Although the value of urodynamics in predicting outcomes after sling surgery is debatable (Nager et al, 2008, 2011), according to the AUA guideline for SUI surgery, urodynamics and cystoscopy are indicated in any patient in whom a definitive diagnosis of stress incontinence is unclear or when there are concomitant overactive bladder (OAB) symptoms, a history of prior lower urinary tract surgery, the possibility of neurogenic bladder, a negative stress test result, an unexplained abnormality on urinalysis, a high PVR volume, grade 3 or greater prolapse, and evidence of dysfunctional voiding (Appell et al, 2009). Obviously this step of evaluation is dependent on the willingness of the patient to undergo the studies and the impact that further evaluation will have on treatment options. Of note, urodynamic testing should be performed with and without a pessary if significant prolapse is present.

In the incontinent patient, the goal of urodynamics is to evaluate urethral and bladder function. In general, in patients with SUI, the abdominal leak point pressure (ALPP) and the MUCP are often used as indicators of urethral dysfunction. In 1981, McGuire looked at the urodynamic properties of patients in whom SUI operations had failed and determined that MUCP below 20 cm H₂O was indicative of type III SUI (now known as *intrinsic sphincter deficiency* [ISD]) (McGuire, 1981). Several years later, Sand and colleagues (1987) performed urodynamic studies on 86 women undergoing modified Burch colposuspensions and determined that women with MUCP of 20 cm H₂O or lower had a significantly higher failure rate (54% vs. 18%) than women with MUCP above 20 cm H₂O. Other authors have also used MUCP of 20 cm H₂O or lower to characterize a patient with severe urethral dysfunction (Clemons and La Sala, 2007; Fritel et al, 2008).

In addition to MUCP, ALPP can also give the clinician a general sense of the severity of SUI. ALPP has been used as an indicator of urethral dysfunction since this relationship was first described by McGuire and colleagues (1993). In this initial study, the authors performed urodynamic studies on 125 women with SUI and determined that ALPP below 60 cm H₂O signified ISD, and ALPP above 90 cm H₂O signified no or very little ISD. The definition of ISD has evolved from one based on strict urodynamic criteria to a clinical diagnosis. In understanding surgical treatment, it is essential to appreciate that all women with stress incontinence have some component of ISD.

In addition to the evaluation of the urethra during urodynamic studies, assessment of bladder pressure during filling and emptying yields valuable prognostic information about bladder function. Most important, the discovery of detrusor overactivity (DO) during evaluation of incontinence may have an impact on deciding the appropriate treatment options. Although it has been theorized that both the stress leakage of urine into the urethra (Kuru, 1965) and the traction on pelvic nerves that occurs when increased abdominal pressure is applied to weakened pelvic supportive tissue (Serels et al, 2000) can induce DO, other treatment options should be considered before proceeding with sling surgery in patients with

DO because stress-induced DO may be difficult to treat with a sling alone. Abnormally small bladder capacity and decreased compliance may also negatively affect the outcomes of sling surgery, and these factors should also be considered.

KEY POINTS: PREOPERATIVE ASSESSMENT

- At minimum, women being evaluated for urinary incontinence should undergo a focused history and physical examination characterizing the patient's symptoms, confirming SUI, and excluding complicating factors. In addition, basic clinical tests such as urinalysis and a PVR volume measurement should be performed.
- Urodynamic studies are not needed in all patients before SUI treatment; however, such studies may prove useful if the diagnosis of stress incontinence is unclear or when there are complicating factors, such as concomitant bladder storage and voiding symptoms, prior lower urinary tract surgery, the possibility of neurogenic bladder, a negative stress test result, an unexplained abnormality on urinalysis, or significant pelvic organ prolapse.
- Although slings are an effective treatment for both genuine stress urinary incontinence (GSI or genuine SUI) and mixed urinary incontinence (MUI), a thorough understanding of preoperative symptomatology will help guide counseling and treatment decisions.

ALTERNATIVE TREATMENT OPTIONS

In most cases of incontinence, surgery should not be considered until more conservative management has failed. Initial conservative therapy includes patient self-awareness and education, dietary modification, fluid restriction, weight loss, and pelvic floor muscle training (Dalloso et al, 2003). There is significant evidence in the literature to support these methods of treatment (Osborn et al, 2013). A 2009 study by Subak and colleagues of 338 obese women randomized to one of two different weight loss programs highlighted the importance of weight loss. After 6 months, the two programs showed an average 8- and 1.6-kg weight loss with a corresponding significant 58% and 33% reduction in SUI. Another conservative treatment option is pelvic floor muscle training (Kegel exercises). These are theorized to help with pelvic floor muscle strength and coordination. A Cochrane Database systematic review by Dumoulin and Hay-Smith (2008) of 13 randomized and quasi-randomized trials of pelvic floor muscle training in patients with SUI concluded that pelvic floor muscle training should be recommended to most patients with SUI before surgical treatment. In addition to lifestyle modification and pelvic floor muscle training, pessaries and other devices have been shown to help with SUI in select individuals (Staskin et al, 1998; Robert and Mainprize, 2002).

The submucosal injection of periurethral bulking agents through a cystoscope into the urethra is a minimally invasive, mildly successful treatment for SUI. The recent discontinuation of bovine-derived cross-linked collagen by its manufacturer has led to the increased use of several newer synthetic agents. However, both a Cochrane review (Kirchin et al, 2012) and a review by the Fourth International Consultation on Urinary Incontinence (Abrams et al, 2010) of periurethral bulking agents concluded that there was limited evidence for the benefit of these agents. Nevertheless, because of the low risk of side effects, periurethral bulking agents are still a good option for many patients who are not ready to undergo a more invasive surgical procedure.

PUBOVAGINAL SLINGS

PVSs (slings at the bladder neck as distinct from MUSs) are highly versatile for the treatment of uncomplicated and complicated

urinary stress incontinence. PVSs are indicated for treatment of incontinence associated with a deficiency in a portion of the midurethral complex, hypermobility, ISD, MUI, concomitant cystoceles (Cross et al, 1997; Serels et al, 1999), urethral diverticula, and neurologic conditions (Austin et al, 2001). More specifically, in neuropathic patients, such as those with myelodysplasia, PVSs are indicated for the SUI that may occur between clean intermittent catheterizations (CICs) (once a thorough urodynamic evaluation of compliance and bladder capacity is completed). PVSs also aid in the reconstruction of the urethra after damage secondary to trauma, synthetic mesh (or graft) perforation, and iatrogenic hypospadias, or they can be used for interposition during urethral repairs of urethrovaginal fistulae or urethral diverticula (Gormley et al, 1994; McGuire and O'Connell, 1995; Blaivas and Heritz, 1996; Leng and McGuire, 1998). PVSs are also indicated for recurrent SUI after failed retropubic suspensions or MUS placement (Beck et al, 1988; Petrou and Frank, 2001). Although many different sling materials and techniques have been developed, the PVS using autologous fascia is the gold standard for management of ALL forms of SUI.

Anatomy and Mechanics of a Pubovaginal Sling

Female SUI is caused by a combination of damage to the midurethral complex and ISD. Urethral hypermobility is a physical indication that the midurethral complex is not working properly. The female urethra lies under the pubic symphysis, and the pubourethral ligaments suspend the anterior urethral wall to the pubic arch. In cases of urethral hypermobility, Valsalva or other stress maneuvers cause the posterior wall of the urethra to slide away from the anterior urethral wall and in turn open the bladder neck and proximal urethra. Uneven pressure transmission combined with the opening of the bladder neck (funneling) cause a loss of urine with stress maneuvers. ISD arises from defects within the urethra proper, so that the urethral sphincter is unable to coapt and generate enough resting urethral closing pressure to maintain continence.

The female urethra is composed of four separate tissue layers that assist in keeping it closed. Compression from the middle muscular layer helps to maintain the resting urethral closure mechanism, and the outer seromuscular layer augments this closing pressure. In normal circumstances, the resting urethral closing pressure of the internal sphincter exceeds the resting or Valsalva pressure exerted by the bladder. In addition, fast-twitch fibers of the external sphincter are responsible for a sudden voluntary contraction and slow-twitch fibers provide continuous passive control by the involuntary guarding reflex during bladder filling. In addition to these structures, the integrity of the pelvic diaphragm is also dependent on the levator ani for continence control. Lastly, the urethropelvic ligament and pubocervical fascia provide support to the bladder neck and undersurface of the bladder, respectively, to prevent SUI (Vasavada and Rackley, 2009).

The PVS is positioned at the bladder neck to provide urethral compression without obstruction during times of increased intra-abdominal pressure. The ultimate goal is to provide adequate urethral coaptation and increase urethral responsiveness to abdominal pressure. This must be balanced against the risks of ischemia, retention, and erosion from unnecessary tension. Aldridge's (1942) earliest anatomic descriptions left the sling attached to the rectus fascia in the midline. This limits sling mobility and provides no method for avoiding excess tension, often resulting in outlet obstruction. In addition, the sling is often too short to completely pass under the urethra. McGuire and Lytton (1978) modified this technique with a longer, 12-cm strip of rectus fascia that remained attached to the rest of the rectus fascia laterally on one side. Again, this technique was limited because with one side attached there was also no way to adjust the tension. The present concept of the PVS comes from Blaivas and Olsson (1988), who modified McGuire's technique by using a shorter free graft of rectus fascia whose tension could be adjusted. It is the incorporation of the sling into the endopelvic fascia and subsequent fibrosis, and not entry into the retropubic space, that prevents SUI. Incorporation of the sling into the endopelvic fascia and eventual fixation of the sling in the retropubic

space prevents it from responding to changes related to the abdominal musculature, contrary to the theory earlier described by Aldridge and previous surgeons. The width (2 to 3 cm) of the PVS ensures that there is sufficient support to provide the needed urethral compression and a cross-sectional area adequate to avoid the formation of a narrow constricting band. The ideal PVS material requires longevity and durability to allow for strong sling scaffolding, and the material should be incorporated and remain intact, with limited tissue reaction.

Pubovaginal Sling Materials

Autologous, allograft, xenograft, and synthetic materials have been used for the construction of a PVS. The ideal material provides long-lasting suburethral support with minimal complications. Ideally, implanted materials should be incorporated into the host with minimal tissue reaction. In reality, most materials promote organized fibrosis and reinforce the sphincteric mechanism through improved suburethral support. Theoretically, a greater degree of fibrosis leads to better clinical results (Bidmead and Cardozo, 2000; Woodruff et al, 2008). Yet, inflammatory infiltration can lead to rapid sling material degradation and possible tissue destruction with erosion (Bidmead and Cardozo, 2000). Although there is complete biocompatibility of the autologous sling and negligible urethral perforation, biologic graft and synthetic prosthetic materials have been increasingly used to decrease operative time, morbidity, pain, and hospital stay (Niknejad et al, 2002).

Pubovaginal Sling Autologous Graft Materials

The most commonly used autologous materials are rectus abdominis fascia harvested from the abdominal wall and fascia lata harvested from the lateral thigh. Fitzgerald and colleagues (2000) reported that after sling placement, rectus fascial grafts undergo extensive remodeling and have abundant fibroblasts and connective tissue on biopsy specimens. Other authors have published similar findings. In 2008, Woodruff and colleagues performed a histologic comparison of PVS materials (10 synthetic, 5 autologous, 5 allograft, and 4 xenograft) and noted that the greatest degree of host fibroblast infiltration and neovascularization with minimal inflammatory or foreign body reaction was in autologous materials. Analysis of explanted specimens up to 65 months after placement revealed that the autologous fascial grafts were consistently intact and displayed grossly only a small amount of degradation. In addition to the value of minimal tissue inflammation, autologous tissue is also beneficial because of the negligible risk of urethral erosion (Webster and Gerritzen, 2003). However, disadvantages include increased operative time, hospital stay, postoperative pain, risk of suprapubic wound seroma, and risk of incisional hernia (Gomelsky and Dmochowski, 2003).

It is important to note that even if the rectus fascia harvest site is scarred and thickened from prior operations, this does not compromise its usefulness for PVS placement. Nevertheless, there are some instances, such as a prior ventral hernia repair, in which fascia lata is the preferred autologous material for PVSs. This fascia is harvested from the thigh and has similar properties to rectus fascia (Beck et al, 1988; Latini et al, 2004). Like rectus fascia, fascia lata is completely biocompatible and is associated with minimal tissue reaction. Unlike rectus fascia, the recovery time is less and there is no risk of future abdominal hernia formation. However, it does require repositioning of the patient, increased operative time, and operating in an area unfamiliar to most pelvic surgeons (Govier et al, 1997). In 1997, Wheatcroft and colleagues reported that 67% of their patients had pain on walking for 1 week after fascia lata harvest surgery (Wheatcroft et al, 1997). Latini and coworkers (2004) reported that only 7% of patients complained of pain at incision site 1 week after surgery in their series using a Crawford fascial stripper. Thigh muscle herniation has also been reported in the literature, but this appears to only occur when large strips of fascia are removed (Dubiel and Wigren, 1974; Wheatcroft et al, 1997). In these studies the rate of thigh herniation was 51%

(20 of 39) with a 10- × 20-cm fascial graft and 0% (0 of 24) with a 1.5- × 12- to 15-cm fascial graft.

Vaginal epithelium has also been used as an autologous tissue. [Raz and colleagues \(1989\)](#) described use of in situ vaginal wall for autologous sling material. However, this tissue may lack sufficient tensile strength, and there is a risk of epithelial inclusion cyst formation and vaginal shortening. Also a lack of retropubic space dissection may militate against overall efficacy of this procedural variety ([Raz et al, 1989](#); [Ghoniem and Hassouna, 1998](#); [Loughlin, 1998](#); [Appell, 2000](#)).

Pubovaginal Sling Allograft Materials

Biologic and synthetic graft materials have been increasingly used to decrease operative time, morbidity, pain, and hospital stay. Cadaveric allografts used in many nonurologic surgical arenas (e.g., orthopedics, neurosurgery) were eventually adopted for SUI. **Allograft slings are currently derived from either cadaveric fascia lata or acellular human dermis.** After harvest, the allografts are processed by solvent dehydration or by lyophilization (freeze-drying) to remove genetic material and to prevent the transmission of infectious agents. Secondary sterilization may also be achieved by gamma radiation ([Gomelsky et al, 2003](#)). Unlike with autologous material, histologic analysis reveals that cadaveric dermis has minimal host fibroblast infiltration and neovascularity, particularly in central aspects of the graft ([Woodruff et al, 2008](#)). In addition, gross examination revealed disruption of the sling scaffold and significant thinning and degradation of the graft.

In general, **allografts are pliable, easy to use, and available in a variety of sizes.** Furthermore, **no specific allograft has shown a clinical advantage in use;** however, acellular dermis rehydrates in 0.9% saline more quickly than does cadaveric fascia lata (5 minutes vs. 15 to 30 minutes) ([Gomelsky et al, 2003](#)). In addition, biomechanical studies have shown that solvent-dehydrated cadaveric fascia lata and acellular dermis have a higher maximal load failure than freeze-dried cadaveric fascia lata ([Hinton et al, 1992](#); [Lemer et al, 1999](#)). More specifically, [Lemer and colleagues \(1999\)](#) prospectively studied the maximum load failure and stiffness of autologous rectus fascia versus freeze-dried fascia versus solvent-dehydrated fascia and cadaveric dermal grafts. The mean values for maximum load to failure, maximum load graft width, and stiffness were all significantly lower for the freeze-dried fascia lata group compared with the autologous, solvent-dehydrated, and dermal graft groups. Lemer and colleagues theorized that ice crystal formation produced by tissue freezing disrupts the collagen matrices and causes decreased tissue integrity and durability. Dermal grafts differ from fascial allografts because they are derived from skin that is processed to eliminate the epidermis and all immunogenic cellular elements. Dermal grafts provide a protein matrix that serves as a collagen scaffold for the host's own cellular matrix.

Because they are harvested from cadavers, allografts raise the concern of potentially transmitting illnesses such as the human immunodeficiency virus (HIV), hepatitis, and Creutzfeldt-Jakob prion disease (CJD). Since the onset of screening in 1985, there has been one documented case of HIV transmission from a tissue transplant. The estimated risk of acquiring tissue from a properly screened donor infected with HIV is 1 per 1,667,600 ([Gallantini and Cespedes, 2002](#)). A few cases of CJD have been reported after transplantation of cadaveric dura or corneas; however, skin obtained from animals infected with these prions has demonstrated no detectable infectious particles. Currently, the theoretic risk of developing CJD from non-neural allograft is 1 in 3.5 million. No cases of hepatitis or CJD have ever been attributed to the use of processed cadaveric fascia or dermis ([Amundsen et al, 2000b](#); [Gallantini and Cespedes, 2002](#)). Although the theoretic risk of developing hepatitis from allograft graft material is unknown, within the musculoskeletal tissue transplantation literature, two cases of hepatitis transmission have been reported. One of those was a tissue donor (cancellous chips) who transmitted HIV, hepatitis B virus, and human T-lymphotropic virus. These transmissions all occurred before the implementation of extensive donor screening for viruses and bac-

teria and the availability of serologic tests (or both) ([Shutkin, 1954](#)). In June 2002, the Centers for Disease Control and Prevention (CDC) reported a case of hepatitis C virus (HCV) transmission from minimally processed, cryopreserved patellar tendon allograft. In this case, donor screening was performed during the window period for HCV testing. Retest of the donor sample with HCV RNA testing confirmed the donor as the source once the recipient reported HCV infection 1 year after transplantation ([CDC, 2003](#); [Vangsness et al, 2006](#)). Despite the low risk of disease transmission, human DNA has been detected in various allograft materials ([Choe and Bell, 2001](#); [Hathaway and Choe, 2002](#)). The clinical significance of this is unknown.

Pubovaginal Sling Xenograft Materials

Xenografts have been used since the 1980s ([Descurtins and Buchmann, 1982](#); [Iosif, 1987](#)) because of their immediate accessibility and use with minimal morbidity. Porcine and bovine xenografts have been used as sling materials with decreasing popularity in recent years. The forms of xenograft used are **porcine dermis, porcine small intestinal submucosa (SIS), and bovine pericardium.** Modern processing techniques using diisocyanate to remove genetic material have made porcine grafts both safer and more pliable; however, in a 12-week rabbit model, there was significant loss of tensile strength after implantation ([Dora et al, 2004](#)). It is interesting to note that histopathologic analysis has shown porcine SIS to contain growth factors that may reduce host-graft immunologic reaction and lessen tissue scarring ([Wiedemann and Otto, 2004](#)). Although most data support SIS as nonimmunogenic, animal studies by [Thiel and colleagues \(2005b\)](#) suggested that an intense inflammatory reaction occurs 30 to 90 days after subcutaneous implantation. In a report by [Kalota \(2004\)](#), 6 of 18 (33%) patients experienced postoperative inflammation after an SIS PVS procedure. [Konig and colleagues \(2004\)](#) reported a single case of postoperative inflammation with abscess formation with SIS use. [Ho and colleagues \(2004\)](#) reported a similar reaction in 6 of 10 patients. In a series by [John and colleagues \(2008\)](#), all of the patients had pain and erythema at the abdominal incision, and 2 developed abscesses. Of note, 5 of the 6 patients with inflammatory responses were continent. Five patients were treated conservatively and 1 patient required abscess drainage. The exact cause of these problems is unknown but is likely related to a foreign body reaction from the multilayered (eight-ply) SIS material, a reactive manufacturing ingredient, or the tendency for suprapubic fat to produce an inflammatory reaction.

In 2001, [Kubricht and colleagues](#) showed that porcine SIS has less tensile strength than cadaveric fascia lata. Bovine pericardium is available in a preparation cross-linked with glutaraldehyde or as a non-cross-linked acellular matrix ([Gomelsky et al, 2003](#)). Histopathologic comparison of sling materials by [Woodruff and colleagues](#) revealed xenograft (porcine dermis) to have no host fibroblast infiltration, no inflammatory reaction, and no foreign body reaction ([Woodruff et al, 2008](#)). This study also showed that xenograft had the highest propensity to encapsulate. The researchers found that a capsule formed around the porcine dermis specimens, isolating the graft from the periurethral tissue. The grafts were described as appearing similar to their original appearance at time of implantation.

Pubovaginal Sling Synthetic Prosthetic Materials

In 1959, [Francis Usher](#) introduced the first synthetic biomaterial, polyethylene mesh for use in hernia surgery. In the decades since, other synthetic materials have been introduced and there has been a transition to **polypropylene** ([Amid, 1997](#)). The first synthetic sling, made of nylon, was introduced in 1953 ([Kraatz, 1953](#)). The addition of synthetic material for use in PVS surgery brought the advantages of an almost unlimited supply of artificial graft material in various sizes and shapes, consistency in quality, the elimination of harvest site complications, and decreased operative time. **Compared with biologic grafts, synthetic materials are more uniform,**

more consistent, and more durable. In addition, synthetic prosthetic materials are sterile, biocompatible, and noncarcinogenic (Niknejad et al, 2002). On histopathologic comparison, synthetic materials demonstrate the least amount of degradation or disruption and the greatest amount of fibroblast ingrowth and tissue ingrowth into the specimen (Woodruff et al, 2008). Microscopically, synthetic materials are associated with significant fibroblast infiltration and a foreign body reaction characterized by giant cells and occasional microcalcifications. This foreign body reaction is not visible grossly, and no graft disruption or adverse effects to the host occur.

Artificial graft materials do have potential drawbacks, including graft infection, urinary tract perforation, and vaginal exposure. The chemical and physical properties of each artificial material and patient characteristics determine how the sling is incorporated into the surrounding tissue and its susceptibility to infection or exposure. The susceptibility to infection in multifilament fibers is proportional to the porosity and the pore size of the materials (Amid, 1997; Niknejad et al, 2002). Tightly woven mesh provides a safe harbor for small bacteria, excluding macrophages and polymorphonuclear leukocytes. Loosely woven mesh allows tissue ingrowth and neovascularization without limiting cellular access. Tissue bonding to the mesh strengthens and supports the repair. A tightly woven and large-diameter filament mesh will tend to exhibit increased stiffness or decreased pliability, which may contribute to exposure. The classification by Amid (1997) used for synthetic materials in hernia surgery may be practically applied to urology as well (Table 84-1). The most frequently used materials are grouped into four types. Type I are totally macroporous prostheses (Trelex Natural Mesh [Boston Scientific, Natick, MA]; Marlex [C.R. Bard, Murray Hill, NJ]; Prolene [Ethicon]) containing pores larger than 75 microns, which is the pore size for admission of macrophages, fibroblasts, blood vessels, and collagen fibers (White et al, 1981; Bobyn et al, 1982; White, 1988). Type II includes totally micropo-

rous prostheses (Gore-Tex, Surgical Membrane, and Dualmesh, which are all expanded polytetrafluoroethylene [ePTFE] and manufactured by W.L. Gore and Associates, Newark, DE) containing pores less than 10 microns in at least one of their dimensions. Type III includes macroporous prostheses with multifilamentous or microporous components (polytetrafluoroethylene [PTFE]—Teflon [DuPont USA, Wilmington, DE]; braided Dacron mesh—Mersilene [Ethicon]; braided polypropylene mesh—Surgipro [US Surgical, Norwalk CT]; and perforated MycroMesh patch [W.L. Gore and Associates]). Last, type IV includes biomaterials with submicronic pore size (Silastic, Celgard [polypropylene sheeting]) (Amid et al, 1992) (Table 84-2). Amid (1997) proposed that the risk of infection and seroma formation was decreased by use of type I mesh.

The most commonly used synthetic material for PVSs is polypropylene mesh. It is composed of loosely woven strands of polypropylene and has a pore size greater than 80 μ m, permitting passage of macrophages and excellent host tissue ingrowth (Kobashi et al, 2002). This represents type I in the Amid classification. Historically, sling techniques have changed to limit the associated morbid complications. For example, synthetic material is rarely used in PVSs to pull the bladder neck into a high retropubic position because of high perforation rates (discussed later in chapter). Instead, newer approaches position sling loosely at the midurethra (discussed later in chapter) (Niknejad et al, 2002).

Pubovaginal Sling Operative Procedure

Pubovaginal Sling Patient Counseling

In addition to the normal preoperative counseling, if a synthetic prosthetic or biologic graft material is being used, surgeons should thoroughly counsel their patients about the permanent nature of these products and the unique and sometimes serious complications related to their use. In our opinion, this step is vitally

TABLE 84-1 Amid Classification for Synthetic Materials

TYPE	DESCRIPTION	BRANDS
I	Pores >75 μ m; macroporous	Trelex Natural Mesh, Marlex, Prolene
II	Pores <10 μ m; microporous	Gore-Tex, Surgical Membrane, Dualmesh (all three are ePTFE)
III	Macroporous with multifilamentous or microporous components	Teflon (PTFE), Surgipro (braided polypropylene mesh), Gore-Tex MycroMesh (perforated ePTFE patch), Mersilene (braided Dacron* mesh)
IV	Submicronic pore size	Silastic†, Celgard‡ (polypropylene Silastic laminated sheeting)

*Dacron is polyethylene terephthalate (polyester) and is manufactured by DuPont USA.
†Silastic is a silicone polymer manufactured by Dow Corning Corporation in Midland, MI.
‡Celgard is manufactured by Celgard LLC in Charlotte, NC.
ePTFE, expanded polytetrafluoroethylene.

Modified from Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. *Hernia* 1997;1:15–21.

TABLE 84-2 Synthetic Pubovaginal Sling Materials

TRADE NAME	COMPOSITION	DETAILS
Mersilene	Polyethylene terephthalate	Multifilament fibers, very porous, becomes firmly embedded in native tissues
Teflon	Polytetrafluoroethylene	Multifilament
Gore-Tex	Expanded polytetrafluoroethylene	Very flexible
Silastic	Silicone plus woven polyethylene terephthalate	Minimal tissue reaction, which facilitates removal or revision if necessary
ProteGen	Synthetic mesh impregnated with collagen matrix	Removed from market secondary to high rate of vaginal extrusion
Marlex, Prolene	Polypropylene	Monofilament with open weave pattern

Modified from Niknejad K, Plzak LS, Staskin DR, et al. Autologous and synthetic urethral slings for female incontinence. *Urol Clin North Am* 2002;29:597–611.

KEY POINTS: PUBOVAGINAL SLING MATERIALS

- The ideal material for the construction of a PVS is sterile, biocompatible, noncarcinogenic, and consistent in quality.
- The implanted material should be incorporated into the host with minimal tissue reaction and provide long-lasting suburethral support with minimal complications.
- Autologous materials remain the gold standard and are associated with no tissue reaction and negligible urethral perforation. To decrease operative time, hospital stay, and postoperative recovery, other biomaterials are used.
- In addition, tissue-processing techniques for allografts may disrupt the microstructure and affect their strength properties.
- Xenografts have less tensile strength than allograft in situ and have the highest propensity to encapsulate.
- Synthetic materials are characterized by significant inflammatory and foreign body reactions and are associated with higher rates of graft infection and perforation.

important secondary to the increased awareness of patients and their families regarding the **potential dangers of synthetic mesh**. Patients should also be counseled about the risk of **transient and permanent voiding dysfunction after surgery**. This should include a discussion of postoperative difficulty emptying the bladder and de novo urgency and frequency. Of note, teaching patients how to perform CIC preoperatively may decrease trips to the emergency room and the need for an indwelling catheter.

Pubovaginal Sling Anesthesia, Patient Positioning, and Preparation

PVSs may be performed using spinal or general anesthesia, but the choice of anesthesia is typically based on patient, surgeon, and anesthesia provider preference. An AUA Best Practice Policy Statement from 2008 recommends the preoperative administration of a single dose of a first- or second-generation cephalosporin, aztreonam (in cases of renal insufficiency), or an aminoglycoside plus metronidazole or clindamycin (Wolf et al, 2008). We routinely place bilateral lower extremity intermittent pneumatic compression (IPC) devices before administration of anesthesia. The AUA Best

Practice Policy Statement for the Prevention of Deep Venous Thrombosis in Patients Undergoing Urologic Surgery states that for incontinence surgery, the use of IPC devices, low-dose unfractionated heparin, or low-molecular-weight heparin should be based on individual patient and procedural risk factors (Forrest et al, 2008). The patient is placed in the dorsal lithotomy position, and the abdomen (from umbilicus down) and vagina are prepared and draped in sterile fashion. In the United States, povidone-iodine is the most commonly used antiseptic for vaginal preparation; however, in other countries this is not the case (American College of Obstetricians and Gynecologists [ACOG], 2013). In September 2013, ACOG released a committee opinion that chlorhexidine gluconate solutions containing 4% alcohol or less were both safe and effective for vaginal preparation (off-label use).

Next a weighted speculum is placed in the vagina and an 18-Fr Foley catheter is inserted into the urethra. The patient should be placed in moderate Trendelenburg position; for optimal visualization during vaginal dissection, the surgeon may benefit from a headlight. A vaginal ring retractor is used initially for retracting the labia majora and later to retract the incision to further improve visualization and ease of dissection.

In the case of fascia lata harvesting, the IPC device is placed below the patient's patella on the harvest side. The knee is elevated and supported with a 1-L bag of intravenous fluid or an appropriate cushion or pad. The involved extremity is internally rotated at the hip and secured to the table using 3-inch tape, below the operative site. The thigh is prepared and draped to expose its anterolateral aspect from the greater trochanter to the patella distally. The greater trochanter and lateral femoral condyle of the femur are identified and marked. These landmarks denote the proximal and distal attachments of the fascia lata (Dwyer and Kreder, 2008).

Graft Harvest for Autologous Pubovaginal Sling

A 6- to 7-cm Pfannenstiel incision is made approximately 2 cm above the pubic symphysis and carried down to the rectus fascia. A 2-cm × 8-cm graft is then marked out on the rectus fascia in a transverse or longitudinal direction. The premarked graft is harvested out of the rectus fascia using a scalpel or electrocautery (Fig. 84-1A). If a transverse fascial incision is used, maintaining a 2-cm or greater distance away from the pubic symphysis will help ensure a tension-free fascial closure. Freeing the edges of the fascia away from the underlying rectus muscle with a scalpel or electrocautery may also aid in a tension-free closure but could theoretically weaken the fascia. The fascia is closed with a running No. 1 polydioxanone

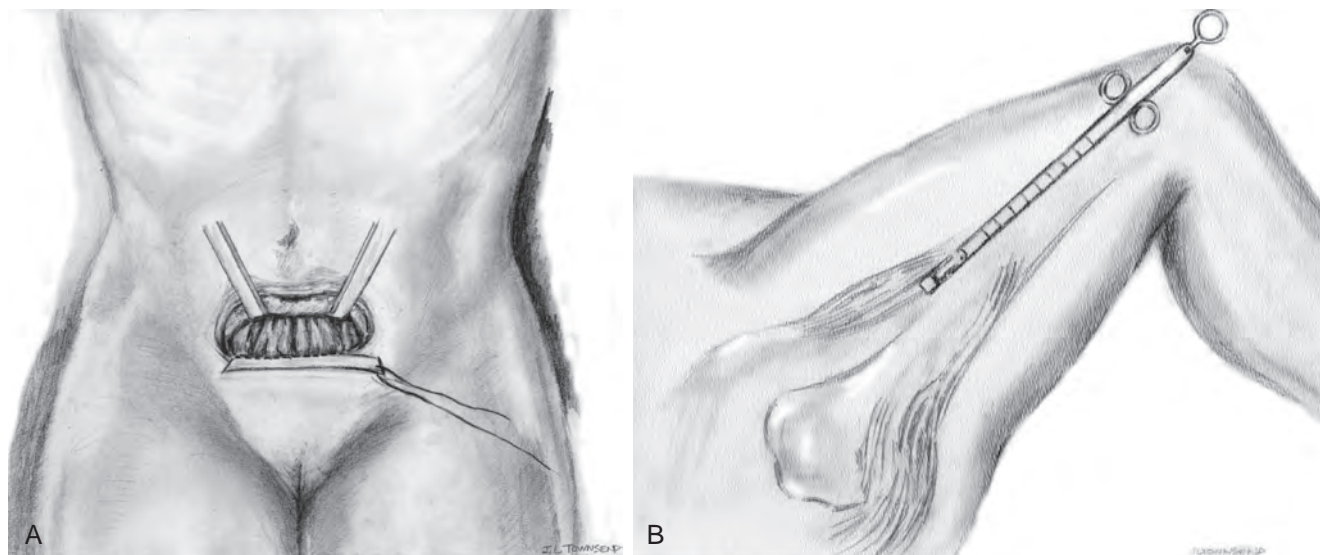


Figure 84-1. A, Rectus fascial graft harvest. B, Autologous fascia lata harvest.

(PDS) or similar suture. If the fascia cannot be closed adequately, it may be necessary to place an interposing segment of synthetic mesh or biologic graft.

After harvest, the autologous graft is placed in a 0.9% normal saline solution. On a sterile side table, the overlying fat and per fascial tissue are cleaned off of the graft and a separate No. 1 PDS or 1-0 polypropylene suture is secured to each end of the graft. Each suture should be placed perpendicular to the sling fibers (transverse harvest only), run across each end of the graft, and tied down. Sutures are left long, and the graft is again placed in the 0.9% normal saline until needed.

For fascia lata harvest, a 3-cm longitudinal incision is marked beginning just above the patella over the iliotibial band (Fig. 84-1B). Dissection is carried down to the level of the fascia lata, where two parallel, longitudinal, incisions 2 cm apart are made. The graft is bluntly lifted off the underlying muscle and clamped as far distally as possible with a right-angle clamp (3 to 4 cm) and transected, allowing one free end. The free end is secured with a No. 1 PDS suture, and the proximal fascia lata is lifted off the muscle belly with a thin, malleable retractor. The fascia lata is separated from both the adipose tissue and muscle fibers by passing the retractor superficial and deep to the fascia lata. With the free distal end under tension, a Crawford fascial stripper is used to extend the fascial incision proximally and divide it before removal. Classically, the fascial strip was 20 × 2 cm in dimension; however, now shorter lengths (8 cm) are used (Karram and Bhatia, 1990). Another No. 1 PDS suture is secured to the other free end of the graft and the sling is placed in 0.9% normal saline until needed. Immediate compression is applied to the thigh to constrict perforating vessels. The area is carefully evaluated for arterial bleeders before closure. The wound is irrigated and closed in three layers without closing the fascia lata. Once the thigh closure is complete, a compressive wrap is applied to the thigh, and the IPC device is replaced. The compressive bandage should remain in place for 8 hours postoperatively, and early ambulation should be encouraged (Dwyer and Kreder, 2008).

Pubovaginal Sling Vaginal Approach

Initially, 0.9% sterile normal saline is injected into the vaginal epithelium, surrounding the urethra to provide hydrodistention and aid in tissue dissection. We prefer an inverted U-shaped incision because it provides excellent exposure of the urethra to the level of the bladder neck and direct access to the endopelvic fascia and subsequently retropubic space (Fig. 84-2). The top of the incision is made approximately 2 cm below the urethral meatus (an Allis clamp placed immediately below the meatus improves visualization), and the arms of the U should extend to the level of the bladder neck (determined by palpation of the Foley balloon). A

15-blade knife is used to carry this incision down through the vaginal epithelium, with care to stay above the periurethral and pubocervical fascia (to avoid bleeding and injury to the urethra and bladder). With an Allis clamp and Metzenbaum scissors, thick vaginal epithelial flaps are created. The flaps are retracted with help of the vaginal ring retractor.

Once adequate lateral flaps have been created, the ischiopubic rami should be easily palpable, and it is now appropriate to perforate the endopelvic fascia. To prevent inadvertent bladder perforation, it is imperative that the bladder be adequately drained before this maneuver and before the later passage of Stamey needles or larger clamps. With the Metzenbaum scissors angled toward the ipsilateral shoulder and the tips pointed upward, the endopelvic fascia is perforated by remaining directly medial and immediately under the ischiopubic ramus at the superior margin of dissection (Fig. 84-3). Perforation occurs in a superolateral direction, and the Metzenbaum scissors are spread widely to aid in the next step of dissection. Using blunt finger dissection, the retropubic space is dissected bilaterally (Fig. 84-4). With this dissection, the infrapubic and retropubic dissection planes are now connected. During this step, it is important to ensure that the retropubic space is fully opened. The posterior surface of the pubic symphysis should be easily palpable with very little intervening tissue. Intraoperatively, this allows for free movement of the sling and easy tensioning.



Figure 84-3. Perforation of endopelvic fascia.



Figure 84-2. Inverted-U incision.



Figure 84-4. Blunt dissection of retropubic space.



Figure 84-5. Passage of Stamey needles behind pubis.

Even though the abdominal fascia is closed, simultaneous finger palpation through the abdominal and vaginal incisions should be possible, while gently palpating the bladder medially. Aggressive medial mobilization should not be attempted because it may result in bladder injury. Hemostasis should be achieved with bipolar cautery. In the case of women who have undergone prior urethral suspension or sling procedures, more aggressive sharp dissection may be required. In difficult cases, the safest dissection plane into the retropubic space should be immediately adjacent to the periosteum of the pubis, and dissection should be performed sharply as much as possible to minimize the risk of injury to the pelvic viscera.

Pubovaginal Sling Placement and Fixation

Stamey needles are passed from above, through the abdominal incision by careful guidance behind the pubis. The needles are in contact with the pubis until they are brought out lateral to the bladder into the vaginal incision (Fig. 84-5). Alternatively, large surgical instruments such as tonsil clamps may also be used instead of the Stamey needles (McGuire and Lytton, 1978; Blaivas and Olsson, 1988). Again it is important to emphasize that the bladder must be completely drained before passage of the Stamey needles to avoid inadvertent bladder injury. Cystoscopy should be performed with a 70-degree lens after passage of needles to confirm integrity of the bladder, by following the course of needles (while an assistant moves the needles downward and medially toward the bladder). Except when there is hematuria visible or other cause for suspicion, all urologists do not perform cystoscopy after needle passage (Niknejad et al, 2002; Seung-June et al, 2007). It is our belief that cystoscopy is an essential step that eliminates the serious complication of sling perforation of the bladder. In the case of a small bladder injury or inadvertent passage of Stamey needles through the bladder, the needles are removed and passed again and the procedure is completed. Once extravasical passage is confirmed, the Foley catheter is replaced and an ampule of indigo carmine is given to confirm ureteral efflux during final cystoscopy for sling tensioning.

The ends of graft suture are passed through the Stamey needle eyelets. After marking the center of the graft with a clamp, the Stamey needles are removed and the ends of the suture are brought out through the abdominal incision and tagged with hemostat clamps (Fig. 84-6). The distal aspect of the graft is sutured to the periurethral tissue with two simple 4-0 polyglactin 910 sutures. After adequate hemostasis is achieved, the vaginal incision is closed with a watertight, running 2-0 polyglactin 910 suture. Before final tensioning of the sling, the vagina should be closed and weighted speculum removed to eliminate distortion that can affect the final tension. In addition, any additional procedures, such as transvaginal pelvic prolapse repair, should be completed before sling tensioning. The PDS sutures are tied down above the rectus

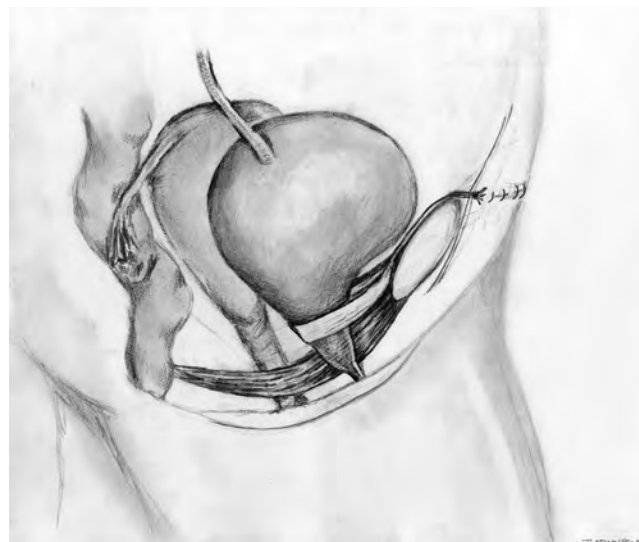


Figure 84-6. Sagittal view of pubovaginal sling position at bladder neck in retropubic position.



Figure 84-7. Passage of and tying of sling through abdominal incision.

fascia (Fig. 84-7) while cystoscopy with a 30-degree lens is performed to visualize adequate coaptation of the proximal urethra. In most cases the sling should be tensioned with a two-fingerbreadth width distance between the rectus fascia and the PDS knot. The amount of tension may vary owing to the mobility of the urethra or desire to create permanent retention in an individual who will do permanent catheterization. The abdominal incision is closed with a subcuticular 4-0 polyglactin 910 suture. The Foley catheter is left to straight drainage and a conjugated estrogen-covered vaginal packing is placed.

Pubovaginal Sling Postoperative Care

The vaginal packing is removed on postoperative day 1 and the Foley is removed once the patient is out of bed and ambulating (postoperative day 1). If the patient voids adequately (on PVR confirmation), she is discharged home. If she is unable to urinate or has an elevated PVR volume, she is discharged home with a Foley catheter. She will return within 5 days for a repeat trial of void. Patients are instructed to avoid heavy lifting (more than 5 pounds) and sexual intercourse for 6 weeks after surgery. Sexual intercourse should be resumed only after a physical examination and confirmation by the surgeon, but no sooner than 6 weeks after surgery.

KEY POINTS: PUBOVAGINAL SLING OPERATIVE PROCEDURE

- Closure of the rectus fascia without tension is sometimes problematic. To prevent this difficulty, it is important to maintain a distance of 2 cm or more from the pubic symphysis.
- If undermining the fascial edges does not adequately mobilize the fascia, then interposition of a segment of synthetic mesh or graft may be necessary.
- It is important to ensure that the bladder is empty before dissection in the retropubic space or passage of needles.
- It is recommended to perform a cystoscopy after trocar passage to ensure integrity of the bladder and at the time of sling tensioning to visualize the bladder neck.

Outcomes of Pubovaginal Slings for Predominantly Stress Urinary Incontinence

Autologous Pubovaginal Slings

Since McGuire's reintroduction of the autologous PVS in 1978 with an 80% overall success rate (McGuire and Lytton, 1978), even with long-term follow-up continence rates have been reproducibly satisfactory after this surgery (Table 84-3). The earliest series (McGuire et al, 1987; Blaivas and Jacobs, 1991) with rectus fascial slings included a diverse and complex patient population: pelvic radiation, diabetes, spinal cord injury, and pelvic trauma. In the McGuire study, even the 34% of patients with "proximal urethral function loss" documented by urodynamics (MUCP <4 cm H₂O per the article) had a high 82% cure rate (McGuire et al, 1987). In addition, the majority of the patients who required CIC postoperatively had a neurogenic bladder and were counseled to expect urinary retention.

In a retrospective study of 63 women with ISD from 1996, Mason and Roach (1996) confirmed the success of a smaller (4 × 2 cm) modified rectus fascial sling with an average 12-month follow-up. Postoperatively, 12 (19%) patients had urgency and 10 (15.9%) had frank urge urinary incontinence (UUI). However, by 6 months these symptoms had resolved in all but 3 (4.8%), who remained on anticholinergic medication.

Cross and colleagues (1997) found that in patients with grade 3 or 4 cystoceles and SUI, an anterior colporrhaphy in conjunction with a PVS yielded excellent results. In their study, 33 (92%) of the cystoceles were cured on physical examination a median 20.4 months after surgery. Thirty-two patients (89%) were cured of their urinary incontinence based on the results of a urinary system questionnaire. However, they also reported a 19% rate of postoperative de novo urgency and urgency incontinence. Yet only 3% had persistent urgency incontinence requiring treatment. Lastly, 2.8% underwent further urethrolisis to resolve voiding difficulties related to obstruction.

One year later, the same authors published their results of a retrospective analysis of 150 patients who underwent PVS for urinary incontinence (Cross et al, 1998b). In that study, 98% of the patients had predominantly SUI and 93% of all patients were cured of their incontinence based on the results of in-office questionnaires and telephone interviews. Also in 1998, Chaikin and colleagues presented the results of a retrospective analysis of 251 women who underwent autologous PVS procedures. The authors reported an overall 92% cured or improved rate. It is interesting to note that in that study the authors also compared the correlation of different methods of assessing outcomes after surgery. The authors found that there was excellent agreement among a validated questionnaire, pad test, voiding diary, and subjective physician assessment (kappa coefficient greater than 0.9).

Hassouna and Ghoniem (1999) reported long-term outcomes of a modified rectus fascial pubovaginal sling (MPVS) in 112

patients with an 89% rate of primarily SUI symptoms. Ghoniem first described the MPVS in 1991 as a modification of the free rectus fascial strip technique popularized by McGuire. The MPVS involves the fixation of a 7- × 2.5-cm graft to the pubocervical and periurethral ligaments in a four-quadrant manner. In 1991, Ghoniem reported a 95% success rate; however, the more recent study by Hassouna and Ghoniem (1999) assessed outcomes using a quality-of-life (QoL) questionnaire and found a lower 80.8% rate of success. In this later study, all 15 of the patients with documented failure had urgency incontinence or severe irritative symptoms. The additional QoL assessment highlights the impact that urgency incontinence, frequency, nocturia, and pain can have on patient satisfaction.

In 2000, Morgan and colleagues published the results of a retrospective study of 247 women who underwent a PVS procedure with a long mean follow-up of 51 months. In this study, 56% of patients had genuine SUI symptoms, and outcomes focused on QoL were measured using the Urogenital Distress Inventory (UDI) short form. The authors reported an 85% cure rate at 5 years; however, for this level of cure to be achieved, 14 patients (5.7%) had secondary procedures. This included 6 periurethral collagen injections and 3 repeat PVSs. In addition, 5 patients had obstructive symptoms that required urethrolisis. Four of these 5 women had a subsequent return to normal voiding. Important to note, this study shows that when stress incontinence has resolved for more than 1 year after an autologous PVS, the long-term risk of recurrent stress incontinence is low.

A 2001 study by Groutz and colleagues of 67 patients is noteworthy because it reported outcomes based on whether the PVS was for primary (57%) or recurrent incontinence (43%). The latter group had undergone one to three prior unsuccessful anti-incontinence procedures for recurrent incontinence. In terms of the prior procedures, the rates of needle suspension, retropubic suspension, and PVS were 31%, 28%, and 10%, respectively. The cure rate was significantly higher in patients with primary incontinence than in those with recurrent incontinence (74% vs. 59%, $P = .006$). Yet there were no surgical failures in either group. All of the patients were either cured or improved based on their outcome scores that incorporated 24-hour voiding diary, 24-hour pad test, and patient satisfaction.

In a retrospective review and telephone interview of 57 patients who had undergone a PVS procedure for incontinence, Richter and colleagues (2001) assessed long-term QoL. Like the study by Groutz and colleagues, this study also included a significant number of patients who were treated with a PVS for recurrent incontinence after a previous retropubic suspension (46%) or needle suspension (24%). Also, with a rate of postoperative voiding dysfunction comparable to that of patients undergoing their first anti-incontinence surgery, this study again showed that a PVS is effective treatment for recurrent SUI. Overall, telephone interviews that focused on QoL revealed that 88% of patients felt the sling improved their QoL, and 82% stated that they would undergo the surgery again. Remarkably, in 87% of patients, the initial postoperative voiding trial failed, and 11.8% required long-term CIC. The telephone interviews revealed that 5.8% of the patients had to use adaptive positions to facilitate voiding, but, it is interesting to note, all of these patients were satisfied because of freedom from urinary incontinence and did not elect urethrolisis. This satisfaction may relate to an emphasis during preoperative counseling in conveying the possibility of long-term voiding dysfunction after a PVS procedure.

Petrou and Frank (2001) also looked at recurrent urinary incontinence but focused on the safety and efficacy of a repeat PVS procedure after failed suburethral slings in 14 women (5 cadaveric bone-anchored suburethral slings, 3 autologous PVSs, 3 cadaveric bone-anchored PVSs, and 3 vaginal patch slings). Overall, 86% of the patients considered themselves cured or improved after surgery. Postoperative complications included a pelvic abscess related to a prior cadaveric sling, osteomyelitis pubis related to the prior bone-anchored sling, and 1 case of long-term urinary retention.

A 2006 study by Howden and colleagues is worth discussing because of its long 7.1-year mean follow-up and relatively large

TABLE 84-3 Outcomes of Autologous Pubovaginal Slings

STUDY	N	TYPE	AGE (MEAN OR MEDIAN YEARS)	GSI	FOLLOW- UP (MEAN OR MEDIAN MONTHS)	CURED, IMPROVED, OR FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY OR UUI	PERSISTENT URINARY RETENTION
McGuire et al, 1987	81*	R	14-83	NA	36	82% cured 18% failed	NA	NA	2.5%
Beck et al, 1988	170	FL	56.7	NA	1.5-120	92.4% cured 7.6% failed	Stress test	1%	2.9%
Blaivas and Jacobs, 1991	67	R	54	50%	42	82% cured 9% improved 9% failed	CR	1%	9%†
Zaragoza, 1996	60	R	56.6	42%	25	95% cured 5% failed	CR	12%	0%
Mason and Roach, 1996	63	R	56	100%	11.7	85.7% cured or improved 14.3% failed	VQ	NR	3.2%
Govier et al, 1997	32	FL	61	66%	14	<i>Subjective:</i> 87.5% cured 9.4% improved 3.1% failed <i>Objective:</i> 70% cured 20% improved 10% failed	CR; telephone interview; stress test	9.4%	0%
Haab et al, 1997	40	R	65.7	33%	48.2	73% cured 17% improved 10% failed	VQ	10.8%	7.5%
Cross et al, 1998b	150	R	57	68%	22	93% cured	CR; telephone interview	19%	2.8%
Chaikin et al, 1998	251	R	56	25%	36	<i>Overall:</i> 73% cured 19% improved 8% failed <i>Patient:</i> 67% cured 26% improved 7% failed <i>Physician:</i> 46% cured 49% improved 5% failed <i>Pad test:</i> 74% cured 20% improved 6% failed <i>VD:</i> 72% cured 7% improved 21% failed	VQ, stress test, VD, pad test	3%	1.6%
Wright et al, 1998	33	NA	56	55%	16	94% cured or improved	CR	10%	4%
Hassouna and Ghonheim, 1999	112	R	55.5	49%	42	80.8% cured or improved 19.2% failed	VQ; pad test	20.8%	0%

Continued

TABLE 84-3 Outcomes of Autologous Pubovaginal Slings—cont'd

STUDY	N	TYPE	AGE (MEAN OR MEDIAN YEARS)	GSI	FOLLOW- UP (MEAN OR MEDIAN MONTHS)	CURED, IMPROVED, OR FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY OR UUI	PERSISTENT URINARY RETENTION
Brown and Govier, 2000	46	FL	62	35%	44	73% cured 27% improved 0% failed	VQ	NR	6.5%
Morgan et al, 2000	247	R	54.5	56%	51	85% cured	CR	7%	2%
Groutz et al, 2001	67	R	56	100%	33.9	67% cured 33% improved	CR, stress test, VD, pad test	10%	0%
Richter et al, 2001	57	R or FL	18-84	NR	42	97% cured	Telephone interview; UDS	0%	7%
Flynn and Yap, 2002	71	R or FL	53	36.6%	44	77% cured 13% improved 10% failed	CR	5%	1.4%
Chou and Flisser, 2003	131	R	66	48.5%	36	SUI: 97% cured MUI: 93% cured	VD; pad test; VQ	NR	0.8%
Latini et al, 2004	100	FL	NR	NR	52.8	85% cured or improved	VQ	NR	0%
Almeida et al, 2004	30	R	53.4	NR	33	70% cured 20% improved 10% failed	CR	NR	NR
Howden et al, 2006	153	R	62.7	NR	85.2	71.7% cured 28.3% failed	VQ; stress test	NR	NR
Albo et al, 2007	326	R	51.6	76%	24	66% cured or improved	Pad test; stress test; VD	3%	6%
Mitsui et al, 2007	29	R	64	21%	25	80% cured 10% improved 10% failed	VQ; UDS	3.4%	28%
Onur et al, 2008	25	R	57	NR	18	84% cured or improved	VQ	8%	0%
Athanasopoulos et al, 2011	264	R	53	80%	27.8	76% cured 9% improved 15% failed	Pad test	18.5%	1.9%
Welk and Herschorn, 2012	33	R	57	NR	16	62% cured or improved	VQ	33%	3%
Lee et al, 2015	84	R or FL	61	44%	89	63% cured or improved	VQ	19%	3%

*One of 82 was a male patient and excluded.

†Four of 6 patients had neurogenic bladders and planned on CIC postoperatively.

CIC, clean intermittent catheterization; CR, chart review; FL, fascia lata; GSI, genuine stress urinary incontinence; MUI, mixed urinary incontinence; NR, not recorded; R, rectus fascia; SUI, stress urinary incontinence; UDS, urodynamic studies; UUI, urge urinary incontinence; VD, voiding diary; VQ, validated questionnaire.

153-patient sample size. The authors retrospectively assessed outcomes using four different validated questionnaires and found that 71.7% of patients were continent and only 3.3% required reoperation because of SUI.

The Stress Incontinence Surgical Treatment Efficacy Trial (SISTER) (Albo et al, 2007), a multicenter, randomized clinical trial, compared the rectus fascial autologous sling (326 women) with Burch colposuspension (329 women). The two primary outcomes were composite measures of success in terms of overall urinary incontinence (no self-reported symptoms of incontinence, increase of <15 g in pad weight during a 24-hour pad test, and no medical or surgical treatment for incontinence) and in terms of stress incontinence (no self-reported symptoms of stress incontinence and negative stress test result). The authors found that whereas the PVS was more effective at curing SUI (47% vs. 38%, $P < .001$), it was associated with a significantly higher rate of postoperative voiding dysfunction and cystitis. Of note, all of the surgical procedures for bladder outlet obstruction (20) occurred in the sling group, and 2 patients in the Burch colposuspension group experienced ureteral injuries.

A 2011 study by Athanasopoulos and colleagues was one of the earliest and largest studies to describe the outcomes of the PVS in patients in whom treatment with a MUS had failed. In this study of 264 patients, 29.9% had a prior history of MUS and all of the patients underwent partial sling removal at the time of PVS placement. The authors reported an overall success rate in terms of markedly improved or cured incontinence of 84.7%, and a history of previous incontinence surgery did not affect this outcome.

The study with one of the longest follow-up periods after PVS sling surgery in the literature is a 2013 retrospective study by Lee and colleagues (2015) of 84 patients with a median follow-up of 89 months. The overall improved or cured rate measured by validated questionnaires was 63%. The authors focused their analysis on comparing patients with previous incontinence surgery versus patients undergoing what they called primary PVS surgery and, similar to earlier studies, found no difference in outcomes. Of note, in their first table the authors reported that they included the 4 patients with a prior history of MUS in the primary PVS group, but this appears to be an error.

Rectus fascia is the most commonly used autologous material. However, intermediate and long-term results of fascia lata PVSs are comparable to those of rectus fascia (Beck et al, 1988; Govier et al, 1997). In a retrospective study of 170 patients with recurrent stress incontinence, Beck and colleagues (1988) noted an impressive 92.4% cure rate measured by absence of leakage on a postoperative cough test (full bladder, standing and sitting). It is interesting to note that the authors tested intraoperative urethral pressure to ensure that the slings could create pressures of 80 to 90 cm H₂O. A 1997 study by Govier and colleagues using fascia lata grafts is particularly noteworthy because the authors compared outcomes of a chart review with responses to a questionnaire and found that the latter yielded worse but likely more accurate outcomes (87.5% vs. 70%, respectively). This patient satisfaction–derived cure rate was similar to the questionnaire-based outcomes noted by Brown and Govier (2000). In addition, in this study, all of the patients had thigh pain at 1 to 2 weeks, and 11% described persistent thigh pain at 6 weeks. Latini and colleagues (2004) used the Crawford fascial stripper to obtain fascia lata. They also reported that 1-week postoperatively, 20% of patients had localized numbness at the harvest site, 7% had harvest site pain, and 5% had tendinitis in harvest site leg. Despite this, 83% of respondents indicated that the procedure had had a positive effect on their life, 82% would recommend the surgery to a friend, and 83% would undergo the procedure again.

In summary, over the past 15 years the continence rate after PVS has ranged from 61% to 97%, although the measurement of outcomes is varied. In general, there is no direct correlation between universally accepted objective and subjective measures of improvement or cure for anti-incontinence procedures (Padmanabhan and Nitti, 2006). The most commonly cited reason for failure relates to urgency symptoms, and urgency incontinence at follow-up

is a common reason for patient dissatisfaction. Postoperative de novo or urgency incontinence rates range from 2% to 20.8% (Mason and Roach, 1996; Zaragoza, 1996; Haab et al, 1997; Chaikin et al, 1998; Cross et al, 1998b; Hassouna and Ghoniem, 1999; Morgan et al, 2000; Groutz et al, 2001; Flynn and Yap, 2002; Albo et al, 2007; Mitsui et al, 2007; Onur et al, 2008).

Allograft Pubovaginal Slings

The autologous fascial PVS remains the gold standard treatment for SUI with efficacious and durable outcomes. However, in an effort to reduce overall morbidity, operative time, and pain related to graft procurement, cadaveric allograft slings were introduced (Table 84-4). In general, there are limited outcome data, and the efficacy and durability of these slings are questionable. Early literature used cadaveric frozen or freeze-dried fascia lata with a variety of methods to secure the sling, such as suture fixation and bone anchors (Handa et al, 1996; Wright et al, 1998; Fitzgerald and colleagues, 1999; Amundsen et al, 2000b; Brown and Govier, 2000; Carbone et al, 2001; Flynn and Yap, 2002; O'Reilly and Govier, 2002; Walsh et al, 2002; Richter et al, 2003; Almeida et al, 2004; Howden et al, 2006). Experience has shown that these tissue-processing techniques can have deleterious effects on cadaveric sling outcomes (Nazemi et al, 2008). Failure rates for frozen or freeze-dried grafts range from 6% to 37.6% (Handa et al, 1996; Wright et al, 1998; Fitzgerald et al, 1999; Brown and Govier, 2000; Carbone et al, 2001; Flynn and Yap, 2002; O'Reilly and Govier, 2002; Walsh et al, 2002; Amundsen et al, 2003; Richter et al, 2003; Almeida et al, 2004; Howden et al, 2006).

Handa and colleagues (1996) reported on some of the earliest short-term outcomes for cadaveric fresh-frozen and freeze-dried fascia lata, with promising cure rates. Two of their patients (12%) developed abdominal wound infections, which resolved with local care, including drainage. They reported de novo urgency in 36% of the patients. Two of the 3 patients who had stress incontinence recurrence were continent after undergoing a synthetic MUS procedure.

Fitzgerald and colleagues (1999) reported on 35 patients undergoing cadaveric irradiated fascia lata sling placement with a high failure rate of 17%. Symptom recurrence was seen very early (1 week to 5 months). Histopathologic analyses of the retrieved material indicated the following ongoing processes in the failed graft: disorganized remodeling, areas of graft degeneration, and evidence of immune reaction. These findings led the researchers to conclude that freeze-dried, irradiated donor fascia lata grafts should not be used for urogynecologic procedures owing to the high material failure rate.

Two studies of patients with predominantly SUI symptoms (Walsh et al, 2002; Richter et al, 2003) documented good results without significant adverse outcomes using freeze-dried fascia lata. Walsh and colleagues (2002) prospectively evaluated 31 women with promising short-term follow-up. There was complete resolution of SUI in 94% at both 4 months and 1 year. There was also an improvement in the presence and severity of urgency and urgency incontinence after surgery, reflected in the declining use of anticholinergic medications from before surgery to 4 months and 1 year postoperatively (55% to 32% to 26%). Richter and colleagues (2003) conducted a prospective long-term study using validated questionnaires for a follow-up of 48 months. Difficulty emptying the bladder was described by 58.2% of patients at 12-month follow-up, with 34.2% describing it as slight. By 48 months, 50% of patients continued to have difficulty emptying their bladders. Patients reported a 90.2% satisfaction rate at 12 months' follow-up and continued to be satisfied at 48 months' follow-up (85.7%).

Two groups documented high failure rates with freeze-dried allograft (Carbone et al, 2001; O'Reilly and Govier, 2002). Carbone and colleagues (2001) used cadaveric fascia with titanium bone anchors for placement bilaterally in the pubic symphysis. They reported a 38% failure rate and 17% reoperation rate, at a short-term follow-up of 11 months. Average time to reoperation was 9 months (3 to 15 months). Intraoperative findings at reoperation

TABLE 84-4 Outcomes of Allograft Pubovaginal Slings

STUDY	N	TISSUE	AGE (MEAN OR MEDIAN YEARS)	GSI	FOLLOW- UP (MEAN OR MEDIAN MONTHS)	CURED, IMPROVED, OR FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY OR UUI	PERSISTENT URINARY RETENTION
Handa et al, 1996	16	FF or FD	52-83	NR	6.2-11.8	<i>Subjective:</i> 86% cured <i>Objective:</i> 79% cured	CR; stress test	36%	6.3
Wright et al, 1998	59	FD	60	52%	9.6	98% cured	CR	10%	2.5%
Fitzgerald et al, 1999	35	FD	NR	NR	0.2-9	82.8% cured	CR; stress test	NR	NR
Amundsen et al, 2000b	104	FD	61.7	35%	19.4	54% cured 21% improved 25% failed	VQ; pad test	15%	1%
Brown and Govier, 2000	121	FD	62	50%	12	74% cured 19% improved 7% failed	Mailed VQ	NR	1.7%
Huang et al, 2001	18	SD	51.7	61%	9.2	72.2% cured or improved 27.8% failed	Mailed VQ	NR	NR
Carbone et al, 2001	154	FD	60	NR	10.6	62.4% cured or improved 37.6% failed	VQ; telephone interview	3.2%	0%
Flynn and Yap, 2002	63	FD	54	4.8%	29	71% cured 13% improved 16% failed	CR	28%	0%
O'Reilly and Govier, 2002	121	120 FF and 1 SD	62	100%	6.5	86.4% cured 13.6% failed	Mailed VQ	NR	NR
Walsh et al, 2002	31	FD	63	26%	13.5	94% cured 6% failed	VD; VQ	NR	3.2%
Richter et al, 2003	102	FD	63.1	NR	35	75% cured or improved 25% failed	VQ	NR	NR
Carey and Leach, 2004	265	SD	<80 yr: 61.2 >80 yr: 82.8	<80 yr: 44% >80 yr: 32%	<80 yr: 24.3 >80 yr: 21.4	<80 yr: 61% cured or improved 24% failed >80 yr: 55% cured or improved 32% failed	VQ	<80 yr: 13% >80 yr: 10%	0%
Almeida et al, 2004	30	FD	53.4	NR	36	40% cured 28% improved 22% failed	CR	NR	NR
Owens and Winters, 2004	25	DG	62	72%	14.8	32% cured 36% improved 32% failed	CR; telephone interview	NR	12%*
Crivellaro et al, 2004	253	DG	58.3	38.3%	18	53% cured 25% improved 22% failed	VQ; VD	5%	2%
Onur and Singla, 2005	25	SD	62	60%	12	80% cured 20% failed	VQ	12%	0%

TABLE 84-4 Outcomes of Allograft Pubovaginal Slings—cont'd

STUDY	N	TISSUE	AGE (MEAN OR MEDIAN YEARS)	GSI	FOLLOW- UP (MEAN OR MEDIAN MONTHS)	CURED, IMPROVED, OR FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY OR UUI	PERSISTENT URINARY RETENTION
Frederick and Leach, 2005	251	SD	66	61%	24	76% cured or improved 24% failed	VQ	8.5%	1.2%
Howden et al, 2006	150	FD	63	NR	43.2	60.4% cured or improved 39.6% failed	VQ; stress test	NR	NR
Pianezza et al, 2007	37	NR	60.2	54%	45.6	75.8 mean UDI score	VQ	NR	8.1%
Nazemi et al, 2008	358	SD	38-97	NR	24-60	34% cured 48% improved 18% failed	VQ	2.8%	1%
Onur et al, 2008	25	SD	61	NR	13	79% cured or improved 21% failed	VQ	12.4%	0%

*Retention defined as catheter longer than 2 weeks.

CR, chart review; DG, dermal graft; FD, freeze dried; FF, fresh frozen; GSI, genuine stress urinary incontinence; NR, not recorded; SD, solvent dehydrated; UDI, Urogenital Distress Inventory; UUI, urge urinary incontinence; VD, voiding diary; VQ, validated questionnaire.

revealed the titanium anchors to be in position, the polypropylene sutures to be intact, and retropubic fibrosis and scarring of the urethropelvic ligament suggesting appropriate placement of the sling. However, all of the allogenic fascia appeared to be fragmented, attenuated, or simply absent. These authors have subsequently abandoned the use of cadaveric fascia allografts in all PVSs at their institution. O'Reilly and Govier (2002) reported high intermediate failure rates in 121 women. Eight patients had recurrent stress incontinence at a mean of 6.5 months (4 to 13 months). Seven of the 8 women had previous incontinence surgery and had multiple comorbidities including neurologic disease, diabetes, previous pelvic irradiation, and previous pelvic surgery. Based on these results and findings by Lemer and colleagues (1999), this group also discontinued the use of fresh-frozen grafts and switched to solvent-dehydrated cadaveric fascia and dermal grafts.

Huang and colleagues (2001) were the earliest group to report unfavorable experiences using solvent-dehydrated allografts in 18 women with short-term follow-up. They reported a 27.8% failure rate with full recurrence of incontinence and subsequently stopped using all allograft as a sling material. On reoperation with an autologous PVS for recurrent SUI, the allograft remained only rudimentary and was very friable. Histologic examination of the retrieved allograft revealed wavy collagen fibers with loosely packed fibroblasts and focal areas of degeneration.

In 2005, Frederick and Leach reported prospective, intermediate-term results of a surgery that used a solvent-dehydrated cadaveric prolapse repair and sling (CaPS) anchored to the pubic symphysis to correct both anterior compartment prolapse and incontinence, with cured, improved, and failure rates of 56%, 26%, and 17.5%, respectively. There was one case of osteitis pubis related to use of transvaginal bone anchors that resolved with conservative management. It is interesting to note that 56% of the failures occurred after 12 months of follow-up. Overall, 80% of the women were satisfied and 77% stated that they would undergo the CaPS procedure again. In another study using validated questionnaires (i.e., UDI-6, Incontinence Impact Questionnaire [IIQ-7]) after cadaveric fascia lata PVS surgeries, Pianezza and colleagues (2007) reported on similar levels of long-term patient satisfaction. They found that patients with preoperative mixed incontinence were at the greatest risk

for postoperative dissatisfaction. Nazemi and colleagues (2008) described durable improvements in incontinence episodes, patient satisfaction, and validated QoL end points in both a CaPS and a CaTS (cadaveric transvaginal sling placement alone) cohort. Yet there was a reduction in dry rates with extended follow-up (24 months, 48 months, and 60 months), especially in the CaTS group (23%, 18%, and 9%, respectively). Lastly, 4% of patients developed sling extrusion, and 4% required sling incision and urethrolisis.

Because of early and intermediate graft failure with cadaveric fascia lata, surgeons were impelled to use alternative materials such as cadaveric dermal grafts. Crivellaro and colleagues (2004) presented their prospective series of patients treated with bone-anchored Repliform cadaveric human dermal allograft (LifeCell, The Woodlands, TX) PVS. There was a 22% failure rate, and average incontinence improvement rate at 9 months was 85% and at 18 months was 80%. The two patients requiring long-term intermittent catheterization had neurogenic bladders. Owens and Winters (2004) assessed outcome and patient satisfaction with Duraderm allograft (C.R. Bard). Initial results were promising with a dry rate of 68% and improved rate of 24%. At intermediate follow-up, only 32% of the patients were dry and 36% noted improvement. Two of the eight patients experiencing failure underwent periurethral bulking agent injections with significant improvement, and one is dry after an autologous sling procedure. Surgical re-exploration revealed almost complete absence of graft material, without evidence of infection or excessive inflammatory response.

Six studies have compared the outcomes of women undergoing PVS procedures using either autologous or cadaveric allograft fascia (Wright et al, 1998; Brown and Govier, 2000; Flynn and Yap, 2002; Almeida et al, 2004; Howden et al, 2006; Onur et al, 2008). Four groups found the outcomes comparable with equally high success rates and no negligible difference in complications. They concluded that allograft fascia lata may be used as an alternative to autologous fascia for PVS, to reduce operative time and decrease postoperative pain and disability (Wright et al, 1998; Brown and Govier, 2000; Flynn and Yap, 2002; Onur et al, 2008). With long-term follow-up, two groups noted superior continence outcomes in the autologous group (Almeida et al, 2004; Howden et al, 2006). Almeida and colleagues (2004) did not report adverse outcomes in either group.

TABLE 84-5 Outcomes with Xenograft Pubovaginal Slings

STUDY	N	TYPE	AGE	GSI	FOLLOW-UP (MONTHS)	CURED, IMPROVED, OR FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY	PERSISTENT URINARY RETENTION
Rutner et al, 2003	152	SIS	NR	49%	27.6	93.4% cured 2% improved 4.6% failed	CR	NR	0%
Abdel-Fattah et al, 2004	74	Pelvicol	53	NR	36	77.8% cured 9.7% improved 12.5% failed	Mailed VQ	17.6%	0%
Giri et al, 2006	51	Pelvicol	46	NR	36	31% cured 23% improved 46% failed	Mailed VQ; telephone interview	2%	2%
Wilson et al, 2008	37	Xenform Matrix*	67.7	NR	19.5	83.8% SUI cured 54.1 global cured	Stress test; VQ	NR	NR

*Xenform Matrix is an acellular bovine dermis.

CR, chart review; GSI, genuine stress urinary incontinence; NR, not recorded; SIS, single-incision sling; SUI, stress urinary incontinence; VQ, validated questionnaire.

Howden and colleagues (2006) found that recurrent symptoms occurred in a higher proportion in the cadaveric group (39.6%) compared with the autologous group (28.3%) ($P = .04$). The reoperation rate was also higher for the allograft group (12.7% vs. 3.3%, $P = .003$).

Some studies support the efficacy of solvent-dehydrated fascial slings (Frederick and Leach, 2005; Onur and Singla, 2005; Pianezza et al, 2007; Nazemi et al, 2008), yet previously reported failures coupled with the consistent success and rapid adoption of synthetic MUSs has led to abandonment of all types of cadaveric allograft at most centers. Thus there is a paucity of data to assess long-term outcomes and define sling outcomes after solvent-dehydration techniques (Nazemi et al, 2008).

Synthetic Material Pubovaginal Slings

There are few randomized studies looking at outcomes after placement of a synthetic PVS. One of those studies is a prospective randomized trial comparing the synthetic PVS procedure with the Burch colposuspension (Sand et al, 2000). In this study 17 women were randomized to receive the sling. The authors concluded that the synthetic suburethral sling placed at the bladder neck under tension had equivalent results to the modified Burch procedure after a short 3 months of follow-up. The sling material used was ePTFE. It is interesting to note that although the authors reported no problems with exposure or perforation, they state in their discussion section that they stopped using this type of sling because of complications reported by Weinberger and Ostergard (1995).

In that study by Weinberger and Ostergard (1995), 108 women were treated with an ePTFE PVS for SUI; 40% developed a wound complication and 21% required complete or partial sling removal (10 with sinus tract formation, 4 with persistent vaginal granulation, 3 with prosthetic exposure, and 1 with groin pain). Clearly because of its material properties (small pores), ePTFE is not an ideal synthetic sling material. Likewise, there have also been problems with other synthetic sling materials (polyethylene and polypropylene) with less-than-ideal physical properties placed under tension at the bladder neck (Drutz et al, 1990; Young et al, 2001; Wohlrab et al, 2009).

Xenograft Pubovaginal Slings

Because of the morbidity of autologous fascial harvest, high failure rates of allograft materials, and high exposure and perforation rates

with synthetic PVSs, xenografts are an attractive option. In general, they are associated with a low rate of infection, exposure, and perforation owing to their incorporation into host tissue (Rutner et al, 2003). The majority of studies in the literature have used gamma-sterilized porcine dermis (Pelvicol, C.R. Bard), porcine SIS, and bovine dermis as xenografts for use in PVSs (Arunkalaivanan and Barrington, 2003; Rutner et al, 2003; Abdel-Fattah et al, 2004; Wiedemann and Otto, 2004; Giri et al, 2006; Wilson et al, 2008) (Table 84-5).

Rutner and colleagues (2003) were the first to describe the use of porcine SIS as a bone-anchored PVS in 152 patients with long-term follow-up. They reported cure rates comparable to those of the autologous sling. Among the 7 failures (4.6%), 5 patients had recurrent SUI within 3 months of surgery, and the other 2 had recurrences at 9 and 11 months postoperatively. Two of the failures were related to the bone anchors. One patient had repeat porcine SIS PVS, with continued failure to relieve incontinence, and 1 patient became dry after carbon bead periurethral bulking injections. One patient achieved continence with urethrolisis 2 years after the initial surgery. At reoperation, grossly no evidence of the implanted SIS material was found. However, biopsies of the periurethral tissue did reveal fibrosis and muscular tissue with a few remnants of SIS. Wiedemann and Otto (2004) performed the first extensive histopathologic examination of porcine SIS in a series of 15 women with SIS PVSs. Three reoperations (20%) were necessary because of recurrent SUI at a mean of 12.7 months. All 3 patients underwent reoperation with implantation of a polypropylene mesh sling and achieved immediate continence. Biopsy specimens from the SIS band under the vaginal mucosa of those 3 patients revealed only focal residues of SIS without any evidence of tissue reaction. There was also no evidence of a significant immunologic or chronic inflammatory reaction. These authors concluded that the advanced incorporation of the implant would lend to good biocompatibility.

Arunkalaivanan and Barrington (2003) first reported on Pelvicol PVSs in a randomized, short-term trial comparing Pelvicol PVS with TVT. Questionnaire-based cure rates were comparable between the two: 85% in the TVT group and 89% in the Pelvicol implant group. Abdel-Fattah and colleagues (2004) presented the 3-year follow-up data for this prospective trial. Cure rates remained high and comparable between the two groups: 79.1% for the TVT group and 77.8% for the Pelvicol group. There was no statistical difference with regard to complication rates or postoperative pad score. Giri and colleagues (2006) compared the 3-year efficacy of Pelvicol

versus autologous rectus fascia in 101 consecutive, nonrandomized patients. Although porcine dermis reduced the associated surgical morbidity, there were significantly inferior long-term cure rates compared with the autologous PVS. Treatment failure occurred by 9 months in the autologous group and by 24 months with the Pelvicol sling. Repeat urodynamic studies indicated stress incontinence as the cause of treatment failure in 18 of 20 (90%) treated with porcine dermis, but in only 3 of 8 (37.5%) with a rectus fascial sling. These authors concluded that Pelvicol should not be used as a substitute for rectus fascia.

Bovine dermis is the most recently reported material used for a xenograft PVS (Wilson et al, 2008). Women with a high risk for sling failure (advanced age, previous surgical failure, and ISD) underwent either a bovine dermis or autologous rectus fascia PVS procedure with short-term follow-up. Global cure rates and SUI cure rates were not statistically different between the two groups. Four women (8.3%) in the autologous group underwent reoperation with periurethral bulking agent injections, repeat autologous PVS, and anterior colporrhaphy with interposition graft. Two women (5.4%) in the bovine dermis group underwent additional interventions: periurethral bulking agent injections and a repeat autologous PVS. Biopsies of the bovine dermis sling material during reoperation (for SUI recurrence at 3 months) revealed that the sling had been replaced by fibrosis, hemorrhage, and mild chronic inflammatory infiltrate, with no acellular component. Tissue breakdown, represented by intermittent areas of myxoid degeneration, were present and may have indicated evidence of early graft failure.

Outcomes of Autologous Pubovaginal Slings for Mixed Urinary Incontinence

The treatment of patients with mixed urgency and SUI is complicated and often involves a combination of anticholinergic therapy and surgery. Medical therapy for MUI is associated with significant resolution of the urgency component in only two thirds of patients (Nordling et al, 1979; Stephenson and Mundy, 1994). Anticholinergic therapy alone does not address the bladder outlet and would not be expected to achieve complete dryness. However, anti-incontinence surgery may cure or aggravate urgency symptoms or lead to de novo urgency. This aspect of anti-incontinence surgery is unpredictable and a major cause of patient dissatisfaction.

In 1999, Fulford and colleagues were the first group to use video-urodynamics in the assessment of how a PVS affects MUI. In that study, 69% (59 of 85) of the women had MUI. Despite the fact that 97% of all the women were continent, only 66 (78%) were satisfied with the surgical result, because of the persistence of urgency symptoms or de novo urgency in 27 women. Among these 27 women, 41% had an open bladder neck at rest compared with only 8% of the women without postoperative UUI ($P < .01$). The storage symptoms eventually resolved in 69% (32) of the patients, almost all of whom had a closed bladder neck at rest. Of note, the postoperative urgency symptoms were not significantly associated with any preoperative clinical or urodynamic variables.

Schrepferman and colleagues (2000) attempted to predict urinary urgency resolution after a PVS procedure with preoperative video-urodynamics. Sixty-nine women with MUI were divided into two groups: a sensory urgency group (28 women with one or more episodes of subjective symptoms without DO) and a motor urgency group (41 patients with one or more episodes of subjective urgency symptoms correlating with DO). They concluded that there was a significantly greater resolution of urinary urgency symptoms in those with low-pressure DO than in those with high-pressure DO or no DO. Overall, the urgency resolution rate in patients with mixed incontinence was 51%. Also in 2000, Serels and colleagues reviewed the records of 36 patients with stress-induced DO. In that study, 75% of patients had resolution of urgency incontinence and 92% achieved a cure. However, again, ALPPs measured during urodynamic studies did not correlate with outcomes.

Osman (2003) evaluated the outcomes of PVS and Burch colposuspension in patients with MUI (no DO) compared with a control group of patients with genuine SUI. The ALPP on preoperative urodynamic studies was used to determine whether patients underwent a PVS or a Burch colposuspension. The Burch arm consisted of 24 (8 genuine SUI and 16 MUI) patients with an ALPP exceeding 90 cm H₂O, and the PVS arm consisted of 26 (12 genuine SUI and 14 MUI) patients with an ALPP below 90 cm H₂O. In the PVS groups, the incidence of persistent UUI in the MUI patients was 12% and the incidence of de novo UUI in the genuine SUI patients was 20%. The incidence of residual urgency was not significantly higher than that of de novo urgency in those with genuine SUI.

Chou and Flisser (2003) used a validated questionnaire, voiding diary, and pad testing to report the outcomes of PVSs for MUI and genuine SUI. Among 98 patients, 46 (46.9%) had genuine SUI and 52 (53.1%) had MUI (26% with DO). The cure or improvement rates were 97% in the SUI group and 93% in the MUI group ($P = .33$). Increasing episodes of urgency and urgency incontinence on preoperative voiding diary correlated directly with surgical failure, whereas voiding frequency was associated with cure. The authors postulated that these patients might have adopted this frequent voiding preoperatively to avoid incontinence.

Stoffel and colleagues (2008) found no difference in preoperative video-urodynamics between women with MUI and DO and those without DO. However, MUI patients with DO had less improvement in UDI-6 scores than MUI patients without DO, despite similar reduction in pad use. The authors concluded that the presence of preoperative DO on urodynamic findings may relate to decreased QoL and decreased urgency resolution rates after a PVS procedure.

There are to date no consistent video-urodynamic parameters in patients with MUI that relate to outcomes with a PVS. However, the presence of residual urgency is similar to de novo urgency with a PVS. Also, increasing episodes of urgency and urgency incontinence may correlate with surgical failure. Overall, the PVS remains an effective treatment option for MUI with cure rates similar to those of simple SUI.

Outcomes of Autologous Pubovaginal Slings for Urethral Reconstruction

Autologous PVSs serve an important role in the reconstruction of the urethra after anatomic damage (tissue loss) ranging from the relatively mild deformity of urethrocuteaneous fistulae and urethral diverticula to the more severe, traumatic absence of the urethra or bladder neck. The causes of damage also include protracted obstetric deliveries, anti-incontinence surgeries, aggressive transurethral resections of the bladder neck, long-term indwelling urethral catheters, pelvic trauma, tumors, and radiation (Blaivas and Jacobs, 1991). The goals of surgical repair are to restore function and anatomy while fashioning an unobstructed, continent urethra (Blaivas and Heritz, 1996).

Swierzewski and McGuire (1993) reviewed the records of 14 women who underwent urethral diverticulectomy during a 3-year period. Eight patients (57%) had symptoms of SUI preoperatively, and 7 of these women had SUI documented on preoperative urodynamic studies. Only these 7 women underwent a combined urethral diverticulectomy and autologous PVS procedure. All 14 women were cured of their SUI with a mean follow-up of 17 months (3 to 21 months). The authors concluded that the presence of a urethral diverticulum does not compromise the successful cure of SUI by a PVS.

Chancellor and colleagues (1994) performed PVS procedures in 14 women with destroyed urethras secondary to long-term indwelling Foley catheter management of neurogenic bladder dysfunction. In these patients significant tension was applied to the sling suspension to achieve urethral closure. Ten patients had simultaneous intestinal augmentations or diversions and 2 had concurrent suprapubic tube placement. The other 2 had adequate preoperative bladder capacity and compliance. All of the patients achieved

continence after a mean follow-up of 24 months. The authors concluded that the PVS is simpler and avoids the risk of fistula formation associated with bladder neck closure, which has historically been used in the aforementioned patient population.

Blaivas and Heritz (1996) performed a retrospective study of 49 women who underwent a one-stage urethral reconstruction to repair extensive damage to the urethra or bladder neck (45% from prior urethral diverticulectomy) with 4 years' average follow-up. Forty-one of these women had a concomitant PVS placed for management of preoperative SUI. After PVS placement, none of the patients had postoperative SUI and only 1 patient experienced obstruction and urgency symptoms requiring incision and was subsequently continent at last follow-up. On the other hand, 3 of the 5 women who had Pereyra repairs developed postoperative SUI and required secondary PVSs (all 3 were continent at last follow-up). **This study illustrates the fact that the PVS in the setting of urethral reconstruction has excellent results when compared with other surgeries for incontinence.**

Faerber (1998) reported on 16 women who had simultaneous PVS and diverticula repairs after urodynamic evaluation. All of the women were either significantly improved (12%) or cured (88%) of incontinence, and only 2 patients developed de novo urgency. The average time for complete bladder emptying was 5 weeks. For the initial 2 weeks, a Foley catheter was left in place for urethral healing.

Rovner and Wein (2003) reported on the circumferential urethral diverticulum repair in nine patients who received either end-to-end urethroplasties or dorsal urethroplasties. Based on preoperative SUI status or evidence of an open bladder neck on preoperative cystography, eight patients were recommended to undergo concurrent PVS placement. All patients had a rectus fascial PVS sling placed, except one who requested a porcine PVS and one who refused to have a PVS. All patients were continent postoperatively, except for the one patient who refused PVS surgery and developed de novo SUI.

Flisser and Blaivas (2003) evaluated the results of 74 women with urethral pathology who required vaginal flap reconstructions. A majority of the women had required reconstruction for a diverticulum or urethral fistula secondary to iatrogenic causes. Fifty-six of these women underwent a concomitant PVS procedure. The authors found that 73% (54) of the women considered themselves cured postoperatively. In addition, in 3 of the 4 patients who had persistent SUI, a modified Pereyra procedure had failed, but these patients were cured at reoperation. One patient was continent after operative revision of PVS for obstruction and significant urgency incontinence.

KEY POINTS: PUBOVAGINAL SLING OUTCOMES

- The autologous PVS is associated with cure rates of 46% to 97% with variable measurements of outcome used. De novo urgency and urgency incontinence rates are also variable.
- There are no risk factors that consistently predict outcomes after a PVS.
- The reported cure rate of PVS surgery for recurrent SUI is excellent. In randomized trials, porcine dermis was associated with significantly inferior long-term cure rates compared with the autologous PVS.
- Treatment of patients with MUI is complicated and involves a combination of anticholinergic therapy and surgery.
- The PVS is an effective treatment option for stress-induced DO with cure rates similar to those of simple PVS. The presence of preoperative DO may relate to decreased QoL and decreased urgency resolution rates after a PVS procedure.
- Autologous PVSs serve an important role for providing continence and robust tissue coverage in urethral reconstruction (urethral fistula, urethral diverticulum, destroyed urethra).

Voiding Dysfunction Secondary to Bladder Outlet Obstruction after Pubovaginal Sling Surgery

The voiding dysfunction that develops from the iatrogenic bladder outlet obstruction by a PVS is often also related to DO and impaired detrusor contractility. The incidence of voiding dysfunction after PVS surgery varies widely in the literature, from 2.5% to 35% (**Foster and McGuire, 1993; Carr and Webster, 1997; Cross et al, 1998b; Chaliha and Stanton, 1999**). The traditional PVS is known to have higher rates of voiding dysfunction than the Burch colposuspension (**Stanton et al, 1983**). In the SISTER trial comparing the autologous rectus fascia PVS and the Burch colposuspension, success rates were higher for women who underwent the sling procedure, but these patients experienced significantly greater voiding dysfunction (63% vs. 47%, $P < .001$), urinary tract infections (UTIs), difficulty voiding, and postoperative urgency incontinence (**Albo et al, 2007**). A meta-analysis by the AUA Stress Urinary Incontinence Clinical Guidelines Panel reported that the incidence of urinary retention more than 4 weeks after PVS placement was 8% and the risk of permanent retention "generally does not exceed 5%" (**Leach et al, 1997**). In a series of 252 women at 4 years' follow-up, **Morgan and colleagues (2000)** reported a prolonged urinary retention rate of only 2.4%.

The presentation of patients with obstruction is variable and the symptoms range from complete urinary retention and urgency incontinence to the less obvious irritative symptoms. Obstruction may also cause recurrent UTIs, prolonged suprapubic pain, and painful voiding, even if emptying is completed. Nitti and colleagues found that 16% of patients who required PVS lysis did not have obstructive symptoms or retention (**Nitti et al, 2002**). Some studies report persistent postoperative urgency incontinence and urgency as more common presenting symptoms (8% to 25%) than frank retention, after PVS surgery (**Cross et al, 1998b**). The risk of iatrogenic obstruction usually relates to technical factors—that is, placement and tension of sutures or sling material. During surgery, if the sling is too loose, there is an inadequately supported bladder neck (proximal urethra) and there is potential for continued SUI. However, if the sling is tied too tightly, there is excessive elevation of the bladder neck toward the pubic bone, causing hypersuspension or overcorrection of the urethrovesical angle and the potential for obstruction.

It has been shown that preoperative voiding dysfunction affects a patient's ability to empty after anti-incontinence surgery. Subclinical preoperative impaired detrusor contractility may manifest symptomatically with a relative obstruction when urethral resistance is increased by anti-incontinence surgery. Dysfunctional voiding or failure of relaxation of the external (striated) urethral sphincter may also affect emptying after surgery (**Fitzgerald and Brubaker, 2001**). Also, a patient who habitually voids by abdominal straining may have difficulty emptying after incontinence surgery. Because of the variability of presenting symptoms after PVS surgery, it is important to ascertain the predominant symptom with a thorough history.

If a patient has postoperative urethral obstruction, physical examination may reveal an abnormal urethral angulation, a fore-shortened nonpliable vagina, or a nonmobile urethra. However, hypersuspension is usually not evident on physical examination. The PVR volume is very important in the evaluation of voiding dysfunction, although no clear cutoff values for obstruction exist (**Siddighi and Karram, 2007**). Cystoscopy is useful to rule out bladder pathology, sling perforation, and a hypersuspended urethra. Video-urodynamics are useful in selected cases at the physician's discretion. **However, the most important criterion for a sling incision or urethrolisis remains the temporal relationship between the symptoms and the surgical procedure.**

There are no well-established risk factors for patients who are likely to experience voiding dysfunction after PVS surgery. However, several studies have investigated multiple factors that may be predictive. In 1996, Weinberger and Ostergard (1996) studied 108 women receiving synthetic PVSs and found that impaired detrusor contractility predicted postoperative urinary retention. Similarly, in 2003, **Miller and colleagues (2003)** noted that women

receiving an allograft PVS who voided with no or minimal detrusor pressure (19%) had a significantly increased risk of postoperative retention. In contrast, no patient with a normal detrusor contraction developed retention postoperatively. However, other researchers have not confirmed this association between impaired detrusor contractility and subsequent voiding dysfunction after PVS surgery (McLennan et al, 1998). Although urodynamic studies are useful in understanding the voiding dynamics of incontinent women, low detrusor pressure and Valsalva voiding preoperatively should not exclude patients from having an anti-incontinence procedure.

Mitsui and colleagues (2007) further analyzed the risk factors for postoperative voiding dysfunction after PVS surgery. The authors found that patients with a PVR greater than 100 mL ($P = .05$) or Qmax less than or equal to 20 mL/sec ($P = .09$) during preoperative urodynamic studies were more likely to require prolonged intermittent self-catheterization. In this group, 28% needed prolonged intermittent self-catheterization (range 4 to 40 months). Lemack and colleagues (2008) examined the preoperative and postoperative urodynamic data for patients enrolled in the SISTEr trial (prospective, randomized clinical trial comparing PVS with Burch) to predict voiding dysfunction after surgery. Urodynamic findings did not predict postoperative voiding dysfunction or the risk of surgical revision in the pubovaginal group. In general, although postoperative urgency and urgency incontinence (voiding dysfunction) are strongly related to failure, there are no preoperative risk factors that consistently predict these outcomes after PVS surgery.

A key factor in assessing voiding dysfunction is the presence of prolapse that was either uncorrected at time of surgery or that occurred postoperatively. Prolapse of sufficient size may kink or angulate and externally compress the urethra. After surgery, apical, anterior, and posterior prolapse must be ruled out as a cause of the urethral obstruction. In 2000, Kobashi and colleagues reported on a technique of combined cystocele repair and PVS using a single piece of cadaveric fascia. After an average 12.4 months of follow-up, only 1 patient of 132 developed persistent obstruction that required urethrolisis (Kobashi et al, 2002). In 2002, Barnes and colleagues reported on 38 women with grade 3 or 4 pelvic prolapse and occult stress incontinence who underwent concurrent PVS with prolapse repair (Barnes et al, 2002). No patient developed permanent urinary retention. Two (5.3%) of the women developed de novo urgency incontinence. Existing urgency incontinence resolved in 45%. They concluded that concurrent surgery had little negative effect on postoperative bladder emptying. In general, there is a paucity of literature on the effects of concurrent PVS and prolapse repair on postoperative emptying and voiding symptoms.

Surgical Management of Voiding Dysfunction after Pubovaginal Sling Surgery

Although transient urinary retention is common, most patients return to spontaneous voiding within the first 10 days (Zaragoza, 1996; Cross et al, 1998b). Obstruction after an autologous PVS procedure usually improves or resolves with time. This is the reason that most physicians historically prefer waiting 3 months before considering surgical intervention after PVS surgery. (It may not be suitable to wait this long after MUS procedures.) **It is appropriate and effective to initially treat persistent voiding dysfunction conservatively.** This includes temporary catheter drainage, CIC, timed voiding, double voiding, biofeedback, pelvic floor muscle training, and anticholinergic therapy.

In the first 6 weeks after autologous PVS surgery, we have had success with loosening the sling in the operating room using spinal or general anesthesia. This is done by first inserting a cystoscope into the bladder and then gently applying caudal pressure to the urethra. **This procedure is not advised with synthetic slings.** Other anecdotal evidence also shows improvement in obstruction with urethral dilation and downward traction after autologous PVS surgery. These results may vary from temporary relief to worsening of the urethral rigidity secondary to periurethral fibrosis (Zimmern et al, 1987; Beck et al, 1988). Transurethral resection or incision of

the bladder neck is likely to fail because the sling is extraluminal and transurethral resection may cause damage to the sphincter, damage to the bladder neck, or periurethral fibrosis, leading to worsened incontinence or even a bladder neck contracture (Ghoniem and Elgamasy, 1995). After 6 weeks or when conservative measures fail, a formal urethrolisis or sling incision is indicated.

Surgical management of bladder outlet obstruction after a PVS procedure traditionally involves complete urethrolisis by a retropubic, transvaginal, or suprimeatal approach, with success rates of 65% to 93% (Foster and McGuire, 1993; Carr and Webster, 1997; Cross et al, 1998a; Goldman et al, 1999; Petrou et al, 1999). Most of these series include patients with obstruction after different anti-incontinence procedures. Only two groups stratified their results specifically for PVSs (Foster and McGuire, 1993; Petrou et al, 1999). Foster and McGuire (1993) reported that transvaginal urethrolisis was successful in 50% of PVS obstructions, which was less than both needle suspensions (75%) and retropubic urethropexy (63%). Their conclusion was that transvaginal lateral dissection is insufficient in relieving the direct suburethral compressive force of the sling. Petrou and colleagues (1999) reported that the suprimeatal approach is superior to the transvaginal approach because the former allows access and division of the lateral wings of the sling. In their series, 8 of 12 patients had successful results. In another series of 12 women, Petrou and Young (2002) reported resolution of obstruction in 10 patients after retropubic urethrolisis. Of note, 2 of the 10 women with resolution of obstruction developed SUI. Carr and Webster (1997) reported complete or significant resolution of symptoms in 86% of patients after retropubic urethrolisis. Overall, recurrent stress incontinence after formal urethrolisis is reported as 0% to 19%. See Table 84-6.

Sling incision has comparable success rates (84% to 100%) and shorter operative time and less morbidity than formal urethrolisis (McLennan and Bent, 1997; Amundsen et al, 2000a; Shenassa et al, 2000; Kusuda, 2001; Nitti et al, 2002; Goldman, 2003; Thiel et al, 2005a). Most series report the results of simply a single incision of the PVS; however, incision of the sling in conjunction with the interposition of autologous graft material between the cut ends of the sling has been proposed to prevent recurrent incontinence. Ghoniem and Elgamasy (1995) were the first to report on the successful use of sling incision and interposition of a free graft of vaginal wall for obstruction. However, others have found that this technique does not live up to this expectation. Shenassa and colleagues (2000) and McLennan and Bent (1997) used vaginal wall interposition in 12 and 4 women, respectively. The success rates were 92% and 100%, but stress incontinence recurred in 25% of patients in each series.

Several authors have reported on successful midline or lateral sling incision without graft interposition. In 2000, Defreitas and Herschorn (2000) had a 94% success rate in 16 women after lateral sling incision, with a 34% rate of recurrent stress incontinence. Lateral incision is beneficial to avoid urethral injury in cases when the sling is identified, but the dissection plane between the urethra and sling is difficult. Amundsen and colleagues (2000a) used midline incision of a PVS in 10 of 32 patients, in whom the sling was easily identified. In the rest, formal urethrolisis with entrance into the retropubic space was performed. The overall success rate was 84%, but the results were not stratified between sling incision and formal urethrolisis. Of note, in 9 of 12 of the obstructing autologous slings in this study, the sling material could not be identified and was replaced by dense fibrosis. Kusuda (2001) reported successful outcomes for 5 patients who underwent lateral sling incision. Nitti and colleagues (2002) reported on 19 women who underwent PVS lysis for obstruction. The success rate was 84% and the recurrent stress incontinence rate was 17%. Two of the 3 women with failure underwent subsequent successful retropubic urethrolisis. This allowed for complete release of all retropubic space scarring that likely contributed to the failure of the suburethral sling release. Goldman (2003) performed simple sling incision in 14 women with iatrogenic urethral obstruction. This included 3 patients with a midurethral polypropylene mesh sling. In this study, 13 of 14 (93%) patients had complete or significant

TABLE 84-6 Result of Therapy for Bladder Outlet Obstruction after Pubovaginal Sling Surgery

STUDY	N	MANAGEMENT	MEAN TIME TO TREATMENT (MONTHS)	SUCCESS RATE	RECURRENT SUI	SUBSEQUENT TREATMENT
Foster and McGuire, 1993	10	Transvaginal urethrolisis	25.9	50%	0%	NR
Carr and Webster, 1997	51	Retropubic, vaginal, or infrapubic urethrolisis	15	Retropubic, 86% Vaginal, 73% Infrapubic, 25%	13.7%	NR
Cross et al, 1998a	15	Transvaginal urethrolisis	16	72%	6.7%	PVS
Goldman et al, 1999	11	Transvaginal urethrolisis	14	84%	19%	NR
Petrou et al, 1999	12	Suprameatal transvaginal urethrolisis	18	66.7%	0%	NR
Defreitas and Herschorn, 2000	16	Lateral sling lysis	NR	94%	34%	NR
Amundsen et al, 2000a	32	Transvaginal urethrolisis, 22 Sling lysis, 10	9.8	84%	12.5%	Contigen, 1
Kusuda, 2001	5	Sling lysis	1.5-24	100%	0%	NR
Nitti et al, 2002	19	Sling lysis	10.6	84%	17%	Contigen, 2 PVS, 1
Goldman, 2003	14	Sling lysis	8.6	93%	21%	MUS, 1
Thiel et al, 2005a	13	Sling lysis	2.2	45% cured 45% improved	7.7%	None

MUS, midurethral sling; NR, not recorded; PVS, pubovaginal sling; SUI, stress urinary incontinence.

improvement of voiding dysfunction and 1 (7%) required subsequent urethrolisis. Also, 21% (3 patients) developed recurrent SUI; however, only 1 required treatment (repeat mesh midurethral sling). Long-term results after simple sling incision were reported by Thiel and colleagues (2005a) for 13 women with catheter-dependent urinary retention after PVS surgery. At 5 years' follow-up, patients reported 45% cure and 45% improvement. Also, 7.7% of the women noted recurrent stress incontinence, but chose not to pursue further therapy.

There are no preoperative or urodynamic parameters that consistently predict success or failure of urethrolisis. Foster and McGuire (1993) found that patients with detrusor instability had a higher rate of failure, but later studies contradicted this. Carr and Webster (1997) found that the only parameter predictive of success was no prior urethrolisis. Nitti and Raz (1994) found that as the PVR volume increased, so did the failure; however, others have not confirmed this.

Failure of urethrolisis may be caused by persistent or recurrent obstruction, DO, impaired detrusor contractility, or learned voiding dysfunction. Recurrent obstruction may result from periurethral fibrosis and scarring or intrinsic damage to the urethra that has occurred from the prior urethrolisis surgery. The most common reason for failure is likely insufficient dissection and lysis of the urethra. Scarpero and colleagues (2003) reported on the value of repeat urethrolisis after failed urethrolisis in 24 women. Both transvaginal and retropubic approaches were chosen depending on the clinical situation. Obstruction was cured in 92%, but storage symptoms resolved in only 12%. Even though they were improved, 69% continued to require anticholinergic therapy. SUI recurred in 18% of the women. This supports the use of repeat urethrolisis in the face of initial failure or in cases wherein the aggressiveness of the initial dissection is unknown. In addition, after an aggressive transvaginal urethrolisis, a retropubic urethrolisis may also be considered.

Refractory storage symptoms after urethrolisis can be challenging to treat. OAB symptoms are refractory in more than 50%,

and this affects patient satisfaction and QoL (Starkman et al, 2008a). There are no predictors of this outcome after urethrolisis, yet DO preoperatively may suggest an increased likelihood of refractory OAB. Also, there are no established guidelines for management. In 2007, Starkman and colleagues examined 25 women with urinary urgency incontinence after urogynecologic surgery (19 PVS, 3 retropubic suspension, and 3 transperitoneal vesicovaginal fistula repair; 4 required further urethrolisis) who were subsequently treated with sacral neuromodulation (SNM). The authors found that SNM was effective (80% reported >50% improvement and 6 were continent) and there were no significant differences in response based on age, duration of symptoms, type of surgery, and urodynamic parameters. One year later, Starkman and colleagues (2008b) evaluated the value of SNM in the management of 8 women who had undergone at least one urethrolisis. Six patients had a favorable response during test stimulation and underwent implantation of an implantable pulse generator (IPG). All 6 of these patients were significantly improved. In summary, in addition to anticholinergics, SNM should be considered as an option for de novo or refractory urgency and urgency incontinence after urethrolisis.

Complications of Pubovaginal Slings

Pubovaginal Sling Perforation and Exposure

The incidence of PVS perforation and exposure is partially dependent on the composition of sling material. Synthetic slings perforate 15 times more often into the urethra and are exposed 14 times more often in the vagina than autologous, allograft, and xenograft slings (Blaivas and Sandhu, 2004). This is based on a meta-analysis of peer-reviewed literature in 1997 (287 articles) (Leach et al, 1997). In this study the urethral perforation rate was 0.02% and the vaginal exposure rate was 0.007% in 1515 patients who received synthetic slings. This is compared with a urethral perforation incidence of 0.003% and a vaginal exposure incidence of 0.0001% in 1715 patients undergoing autologous and allograft

TABLE 84-7 Pubovaginal Sling Perforation and Exposure

STUDY	NUMBER AND TYPE	LOCATION	MEAN TIME TO TREATMENT (MONTHS)	MANAGEMENT	RECURRENT SUI	SUBSEQUENT TREATMENT
Myers and LaSala, 1998	7 Mersilene	7 Vagina*	4.1	7 Transvaginal partial excision	0%	NR
Kobashi et al, 1999	34 ProteGen	17 Vagina 7 Urethra 4 Vagina + urethra 6 UV fistula	7.9	34 Transvaginal complete excision and bone anchor removal	74%	6 PVS 2 Contigen†
Ducket and Constantine, 2000	5 Silicone	5 Abdominal sinus 1 Abdominal + vaginal sinus	8.6	Transvaginal complete excision	20%	NR
Clemens et al, 2000	10 ProteGen 1 Gore-Tex 2 Autologous 1 Allograft	6 Vagina 2 Bladder 6 Vagina + urethra	11.2	12 Transvaginal 2 Retropubic complete excision	50%	1 PVS 2 PVS and Contigen
Golomb et al, 2001	1 Autologous	Urethra	48	Transvaginal partial excision	0%	NR
Amundsen et al, 2003	2 ProteGen 1 Polypropylene 5 Allograft 1 Autologous	9 Urethra	9	Transvaginal complete excision	22%	1 PVS 1 Contigen
Bradley et al, 2003	2 Allograft	2 Vagina	2.5-5	1 Partial 1 Complete transvaginal excision	50%	NR
Wohlrab et al, 2009§	62 Mersilene	6 Bladder 56 Vagina	24	NR	NR	NR

*One patient was seen again 3 months after excision with further vaginal exposure.

†Contigen is a bovine-derived cross-linked collagen periurethral bulking agent.

§Total of 762 patients (perforation 0.7%, vaginal exposure 7.3%).

NR, not recorded; PVS, pubovaginal sling; SUI, stress urinary incontinence; UV, urethrovaginal.

KEY POINTS: VOIDING DYSFUNCTION AFTER PUBOVAGINAL SLING

- Obstruction, DO, and impaired detrusor contractility are manifestations of voiding dysfunction from iatrogenic outlet obstruction by a PVS.
- The incidence of permanent retention is usually 5% or less.
- Persistent urgency incontinence and urgency (8% to 25%) are more common presenting symptoms in bladder outlet obstruction after a PVS procedure than frank retention.
- A key to diagnosis is the temporal relationship between the anti-incontinence surgery and the onset of voiding symptoms. Urodynamic studies are essential in these cases to diagnose and make an appropriate treatment plan.
- Transient urinary retention usually resolves within 10 days, and obstruction from a PVS may improve or resolve with time; therefore most surgical interventions should be avoided until at least 6 months after surgery.
- Reported success rates of the surgical management of bladder outlet obstruction after a PVS procedure are 65% to 93%. There is a 0% to 19% recurrent SUI rate after urethrolisis.
- There are no preoperative variables that predict success or failure of urethrolisis. OAB symptoms are refractory in 50% of affected patients after urethrolisis and contribute to a significant portion of the reported failures.

sling procedures. In subsequent studies, most perforations and exposures were associated with synthetic slings, particularly woven polyester slings (Summit et al, 1992; Bent et al, 1993; Chin and Stanton, 1995; Weinberger and Ostergard, 1995; Myers and LaSala, 1998; Kobashi et al, 1999; Clemens et al, 2000; Duckett and Constantine, 2000; Amundsen et al, 2003). More recently, there have been a few reported cases of autologous and allograft sling perforations and exposures (Handa et al, 1999; Golomb et al, 2001; Amundsen et al, 2003; Bradley et al, 2003; Blaivas and Sandhu, 2004). See Table 84-7.

Most urethral perforations are diagnosed 1 to 18 months after the original surgery, with a mean presentation time of approximately 9 months (Blaivas and Sandhu, 2004). Presenting symptoms often include urinary retention, urgency, and mixed incontinence. In addition, synthetic sling perforations and exposures are also associated with vaginal discharge, vaginal pain, suprapubic pain, and recurrent UTIs. The etiology of these symptoms is usually multifactorial. One category of causes is local tissue factors—that is, postsurgical scarring, urethral atrophy, estrogen deficiency, and radiation-induced ischemia. The other category is surgical techniques—that is, excessive tension, dissection too near urethra, or perforation of the urethra or bladder.

Urinary tract perforation by an autologous PVS is rare. There are only four cases of perforation documented in the peer-reviewed literature. Handa and colleagues (1999) and Golomb and colleagues (2001) each reported an individual case of an autologous

sling eroding through the midurethra. **Colomb and colleagues (2001)** reported that the autologous sling eroded into midurethra after traumatic urethral catheterization for prolonged urinary retention. Other possible causative factors include misplacement or incorrect technique in sling passage or positioning, excessive tension, or traumatic urethral instrumentation after placement of a PVS (e.g., for hematuria clot evacuation or surveillance cystoscopy). In two of the aforementioned cases, the perforated portion of the sling was excised and the urethra was closed. **Clemens and colleagues (2000)** described two cases of bladder dome perforation by an autologous rectus fascial sling. The patients had recurrent UTIs, dysuria, and urgency incontinence. One of these patients had a bladder calculus on the sling material visible on cystoscopy. The other woman had edema and suture at the dome. In both cases, adequate cystoscopy with 30- and 70-degree lenses after Stamey needle passage may have avoided these complications. Both cases were successfully managed with endoscopic removal of stitches and treatment of the stone. No further treatments were necessary.

Management of autologous and allograft sling urethral perforation usually involves incision or excision of the part of the sling that has perforated and simple closure of the urethra (**Blaivas and Sandhu, 2004**). Rarely are additional coverage measures (e.g., Martius flap) required. **Because urinary tract perforation and vaginal exposure of synthetic PVSs are more common and associated with significant morbidity, synthetic material is no longer used for bladder neck slings.** In fact, the ProteGen sling (Boston Scientific) was withdrawn from the market in January 1999 possibly because of the high urinary tract perforation rates (**Clemens et al, 2000**). Some authors believe that synthetic PVS sling perforation into the urinary tract necessitates complete removal of the sling and all other foreign materials (sutures, bone anchors, screws) whenever present (**Blaivas and Sandhu, 2004**). However, we believe that as long as the synthetic material is no longer under tension and excised far away from the bladder, it is not necessary to remove all of the foreign material (except in cases of infection or severe pain). The technique for this removal is discussed in the MUS section.

The incidence of SUI after synthetic PVS removal for urethral perforation is 44% to 100%, and treatment often involves a secondary PVS (**Kobashi et al, 1999; Clemens et al, 2000; Amundsen et al, 2003**). In 2003, **Flisser and Blaivas** reported an 87% continence rate when perforations were managed with concurrent placement of a new PVS. In 2004, **Blaivas and Sandhu (2004)** also noted that secondary procedures such as periurethral bulking agents and PVSs are successful in a majority of patients. However, if the bladder neck is involved with the perforation, **Blaivas and Sandhu** noted a much lower overall continence rate, even with the use of concomitant autologous slings at the time of reconstruction.

Pubovaginal Sling Nonurologic Complications

The most common complications of the PVS are related to the urinary tract; however, there are significant nonurologic complications. The authors of the 2009 update of the AUA guideline for SUI surgery performed an extensive meta-analysis of the literature that included nonurologic complications (**Appell et al, 2009**). They found that the most common nonurologic complications were pulmonary, cardiovascular, neurologic, and gastrointestinal (bowel injury). In addition, the panel estimated a death rate of approximately 3 per 10,000 procedures, combining all SUI procedures (retropubic suspension, transvaginal suspensions, anterior repairs, and PVSs).

In 2007, **Anger and colleagues** analyzed Medicare claims data for short-term complications after sling surgery (mostly MUSs) among female beneficiaries aged 65 years and older (**Anger et al, 2007a**). From 1999 to 2001 a total of 1356 sling procedures were performed. In the 3 months after the procedure, 12.5% of women developed surgical or urologic complications, and 33.6% were diagnosed with UTIs. At 1 year after surgery, the following nonurologic complications were reported: bowel injury or obstruction (6.6%), cardiac complications (9.1%), thromboemboli complications (2.6%), pulmonary complications (15.3%), and other (22.1%). Multivariate analysis revealed that nonwhite patients were more

likely to experience urologic and nonurologic postoperative complications. In addition, women aged 65 to 69 years were significantly less likely to experience nonurologic complications or undergo treatment for outlet obstruction or re-treatment for incontinence than women older than 75 years.

More specific information about the type of complications can be gleaned by reviewing the literature. In the previously mentioned randomized controlled trial by **Albo and colleagues (2007)**, 326 women underwent autologous PVS procedures. In this population, rates of serious adverse events for the autologous PVS and Burch colposuspension groups were 13% and 10%, respectively. In the sling group, deep venous thrombosis (DVT) and serious bleeding both had an incidence of 0.3%. Although the authors did not describe the specific type of complication, there was also a 3.4% incidence of serious wound complications. The most common wound complications after autologous PVS surgery are wound infection, seroma, and incisional hernia. In their experience with over 500 patients, **Blaivas and Chaikin (2011)** reported a 1% rate of wound infections and a 1% rate of incisional hernias. In another retrospective study of 247 women from 2000, the rate of incisional hernias was a similar 0.8% (**Morgan et al, 2000**). Although rare, incisional hernias related to harvesting the rectus fascia are an unfortunate serious complication of autologous PVSs that usually require surgical correction.

KEY POINTS: COMPLICATIONS OF PUBOVAGINAL SLINGS

- The incidence of perforation is dependent on the sling material, with synthetic slings perforating 15 times more often into the urethra and exposing 14 times more often into the vagina than other materials. For this reason, the synthetic PVS is no longer used for support at the bladder neck.
- Synthetic sling vaginal exposures typically manifest with vaginal discharge, pain, suprapubic pain, and recurrent UTIs and require nearly complete removal.
- The incidence of recurrent SUI after synthetic PVS urethral perforation is 44% to 100%, and treatment often involves a second PVS.
- The perforation or exposure of autologous PVSs is rare.

MIDURETHRAL SLINGS

Mechanics, Anatomy, and Materials of Midurethral Slings

Mechanics of the Midurethral Sling

According to the integral theory, the most important factors in preserving continence are adequate function of the pubourethral ligaments, the suburethral vaginal hammock, and the pubococcygeus muscle (**Petros and Ulmsten, 1990**). An injury to any of these three components from surgery, parturition, aging, or hormonal deprivation can lead to impaired midurethral function and subsequently urinary incontinence. Urethral hypermobility is a symptom of damage to these normal supporting structures of the urethra and not a cause of SUI.

Preoperative ultrasonographic and MRI have demonstrated that the proximal urethra in patients with SUI is often open at rest and that regardless of urethral mobility, movement of the anterior and posterior walls of the urethra during stress most likely contributes to a shearing affect that opens the urethra and results in incontinence (**Sanders et al, 1994; Huang and Yang, 2003; Dietz and Wilson, 2004; Masata et al, 2006; Kociszewski et al, 2008**). Based on these observations, it appears that a MUS works by impeding the movement of the posterior urethral wall above the sling, directing its motion in an anteroinferior or anterior direction. In addition, inward movement of the posterior urethral wall after placement of a MUS results in urethral lumen narrowing (compression). This securing of the posterior wall of the urethra (with

or without compression during stress maneuvers) is one theory of how MUSs achieve continence.

In addition to this support of the urethra, some authors have proposed that MUSs work through a mechanism of dynamic urethral kinking during stress events. [Lo and colleagues \(2001\)](#) used ultrasonographic imaging to document evidence of urethral kinking during stress maneuvers.

Ideally, a retropubic or transobturator MUS is placed loosely at the midurethra. Its function does not require it to be tight. The sling is anchored in the endopelvic fascia for retropubic-directed slings and in the obturator internus and externus muscle and fascia for transobturator-directed slings. Over time the synthetic mesh sling becomes fixed in either of these two locations and provides support along its entire course inferior to the pubic symphysis and ischiopubic rami and not just at the midline area posterior to the urethra. This broad support might be the reason why in studies with more than 30 patients by [Laurikainen and Killholma \(2006\)](#), [Gamé and colleagues \(2006\)](#), [Clifton and colleagues \(2014\)](#) and [Klutke and colleagues \(2001\)](#), 50%, 70%, 79%, and 93% of women, respectively, remained continent after MUS incision for obstruction.

Several authors have found that for retropubic and transobturator MUSs, the lack of urethral mobility is a negative prognostic factor for a worse outcome in terms of cure of incontinence and that decreased urethral mobility postoperatively is associated with persistent incontinence ([Minaglia et al, 2005, 2009](#); [Haliloglu et al, 2010](#)). Also, the persistence of urethral hypermobility postoperatively is not associated with a worse outcome. It appears that lack of urethral mobility is an indication that the patient has a fixed urethra and ISD. Overall, patients without urethral hypermobility do not respond as well to MUS surgery. A loosely placed MUS combined with a mobile urethra may allow the sling to compress the urethra during times of Valsalva and stress while remaining nonobstructive when the urethra is at rest.

Despite the fact that transobturator and retropubic MUSs are placed without tension, there is controversy about whether tension or resistance is directed at the bladder outlet. In one study of 404 retropubic MUS procedures, urodynamic studies before and after surgery showed an increase in voiding time but no difference in flow rate, urethral closure pressure, or urethral functional length after MUS surgery ([Meschia et al, 2001](#)). A study by [Lo and colleagues \(2001\)](#) also showed no statistical difference in several urodynamic parameters (average flow, Qmax, PVR, MUCP, and functional urethral length) in 82 patients before and after retropubic MUS surgery.

In contrast, [Gateau and colleagues \(2003\)](#) analyzed pre- and post-retropubic MUS urodynamics in 112 patients and showed consistent decreases in Qmax, increased mean PdetQmax, increased mean urethral resistance, and elevated PVR urine. They concluded from their data that retropubic MUS leads to obstructive changes in the bladder outlet. [Sander and colleagues \(2002\)](#) evaluated the voiding phase before and 1 year after the retropubic MUS procedure. They found both subjective and objective changes in the voiding phase, with 78% of patients experiencing more difficult voiding and significant decreases in Qmax, corrected Qmax, and average flow. PVR urine was also significantly increased, although not greater than 25% capacity.

Unlike retropubic and transobturator MUSs, for single-incision MUSs it appears that restriction of urethral mobility after surgery is associated with a better outcome ([Martan et al, 2009](#)). [Martan and colleagues \(2009\)](#) analyzed 85 patients after a single-incision sling procedure with perineal ultrasonography. Efficacy was evaluated with a cough test and validated questionnaires. Objectively, 62% had a negative cough test result. The sling was noted to restrict urethral mobility, and a higher degree of restriction was associated with a higher likelihood of cure. This restrictive effect was noted to weaken within the first 3 months after surgery. A study of 57 patients who underwent single-incision MUS surgery from 2013 also showed that outcomes were worse in patients who had persistent urethral hypermobility after surgery ([Spelzini et al, 2013](#)). It is possible that the efficacy of single-incision slings is related to their restriction of urethral mobility and that this restriction is required to secure the posterior urethral wall, is required for adequate urethral kinking, or

results in compression of the urethral lumen. Of note, the authors have found that single-incision slings need to be placed tighter than other MUSs to achieve the desired effect.

Anatomy of the Retropubic Midurethral Sling

For a retropubic MUS, the trocars must pass through the retropubic space, which is also known as the *space of Retzius* or *prevesical space*. This space is bounded anteriorly by rectus abdominis muscles and the bony pelvis (pubic symphysis and ischiopubic rami). The lateral borders of the space are the bony pelvis and the obturator internus muscle. The bladder and proximal portion of the urethra lie posterior to this space. The endopelvic fascia (paravaginal connective tissue or pubocervical fascia) forms the inferior-lateral boundary of the prevesical space and is attached medially to the levator ani muscles at the bladder neck and inferior portion of the pubic symphysis. The endopelvic fascia is attached laterally to the ATPF and the ischiopubic rami. The endopelvic fascia separates the prevesical space from the vesicovaginal space. The prevesical space mainly contains loose connective tissue and adipose tissue. Obese patients may have more adipose tissue in this space, and this might contribute to the lower rate of trocar-related bladder injuries seen in this patient population ([Stav et al, 2010b](#)).

The left and right dorsal nerves of the clitoris (DNCs) run along the inferior surface of the ischiopubic rami and cross under the pubic bone approximately 1.4 cm from the midline ([Achtari et al, 2006](#)). After placing retropubic MUSs in 10 cadavers [Achtari and colleagues](#) found that the sling was an average 1.1 cm from the DNC at its closest point. The fact that the superior incisions for a retropubic MUS are typically made at least 2 cm from the midline should help ensure that a DNC is not injured by a trocar or sling. At a distance of 3.2 cm (laterally), the obturator vessels are the closest major vascular structures to a retropubic MUS ([Muir et al, 2003](#)).

The vesicovaginal space is the initial plane of dissection for a retropubic MUS. This space is bounded by the posterior wall of the bladder and the anterior wall of the vagina ([Corton, 2013](#)). The space extends to the proximal and middle urethra. Below this location, the posterior wall of the urethra and the anterior vaginal wall are fairly fused. A relatively thick periurethral fascia covers the posterior urethra. The female urethra is approximately 3 cm in length (therefore an incision 1.5 cm from the meatus is the midurethra).

Anatomy of the Transobturator Midurethral Sling

Like the retropubic MUS, transobturator MUS surgery begins with dissection in the vesicovaginal space. This dissection is carried out lateral to the urethra until the inferior border of the ischiopubic rami and pubic symphysis can be easily palpated. A trocar must traverse the obturator internus muscle, obturator membrane, and obturator externus muscle as it goes through the obturator foramen. Lateral to the obturator foramen are the adductor muscles (gracilis and adductor brevis muscles) of the thigh ([Corton, 2013](#)). The obturator nerve and vessels are located in the obturator canal at the superior aspect of the obturator foramen.

Several authors have performed cadaveric dissections to better understand the anatomic relationships of the transobturator MUS. [Delmas and colleagues \(2003\)](#) used the out-to-in approach on 10 female cadavers to detail the relevant pelvic anatomy in relationship to the sling insertion path. In this study, dissection demonstrated that the sling consistently passed 4 cm anterior and caudal to the obturator canal, confirming the relative safety of neurovascular structures. They also demonstrated that the sling traverses a plane between the perineal and levator ani musculature above the pudendal neurovascular pedicle.

In 2005, [Bonnet and colleagues](#) performed the in-to-out trans-obturator technique as described by [de Leval \(2003\)](#) in 13 cadavers to determine the sling path and proximity to surrounding structures. The authors noted that the sling never penetrated the adductor longus muscle and was a safe distance from neurovascular structures. However, in approximately 70% of studied cases, the implanted material did traverse the adductor magnus, adductor brevis, and gracilis muscles during its path into the pelvis. At the

level of the obturator foramen, the sling traverses the obturator externus and internus muscles as well as the obturator membrane. The distance between an inserted sling and the obturator nerve and vessels at the level of the obturator foramen ranged from 2.2 to 3 cm (mean 2.62 ± 0.2 cm). The authors stated that hyperflexion of the hip and the rotational trajectory of the helical passer help to ensure this separation. Also, the anterior branches of the obturator artery and vein are protected from injury by the bony architecture of the inferior pubic rami. Medially, the transobturator sling enters the anterior compartment of the ischiorectal fascia, in the area of the levator ani membrane and obturator internus muscle. A properly placed sling remains outside the pelvic space and does not penetrate the levator ani muscular group. Lastly, slings remain above the perineal membrane at all times and the DNC is found caudal to the perineal membrane and thus is protected from injury during trocar passage.

A study by Whiteside and Walters (2004) further evaluated the obturator anatomy in relationship to sling insertion in six female cadavers. These authors found that the mesh, on average, passed 2.4 cm inferior and medial to the obturator canal and that both divisions of the obturator nerve (anterior and posterior) were 3.4 cm and 2.8 cm, respectively, separated from the path of the trocar. However, they also noted that the trocar passed within, on average, 1.1 cm proximity to the most medial and anterior branches of the obturator vessels (the vessels described by Bonnet and colleagues behind the inferior pubic rami). These authors concluded that a risk of injury does exist and appropriate caution should be exercised.

The anatomic variation between the in-to-out and out-to-in transobturator MUS approaches has been compared, especially with regard to their association with adverse outcomes. Cadaver dissections after an in-to-out transobturator MUS placement noted that the mean distance from the vaginal incision to the obturator membrane was 4.0 cm, and from the vaginal incision to the obturator neurovascular bundle was 6.75 cm (Rogers et al, 2005). At the obturator membrane, the closest point of the passer is only a mean distance of 2 cm from the obturator neurovascular bundle. This is the reason the curved passer is directed away from these structures and advanced. Also, an anterior branch of the obturator artery coursed medially along the exterior edge of the obturator foramen in 60% of the cadavers. However, similar to Bonnet and colleagues (2005), Rogers and coworkers felt that the exterior bony rim of the obturator foramen protected this artery during an in-to-out pass, but they also postulated that this vessel could be potentially injured in an out-to-in approach.

Anatomy of the Single-Incision Midurethral Slings

For single-incision slings the plane of dissection is only in the vesicovaginal space. Although the trocars are much shorter, they are passed into the retropubic space or through the obturator foramen. As with the other MUSs, cadaveric dissection aids in the anatomic localization of the single-incision sling. Using 14 embalmed and 5 fresh-frozen female bodies, Hubka and colleagues (2009) placed single-incision MUS trocars bilaterally. After dissection, they measured the distances from the obturator bundle (obturator nerve and vessels) and found that the mean distances of the sling from the obturator nerve and vessels were 3.05 cm and 3.07 cm, respectively. Perforation of the fascia of obturator internus muscle occurred in 4.4%, and they felt that because of this, injury to variable vessels could theoretically occur. The position of the single-incision MUS was not found to change with repositioning of the legs.

Midurethral Sling Materials

In their initial description of the MUS from 1995, Ulmsten and Petros used Mersilene, Gore-Tex, Teflon, and Lyodura (cadaveric dura mater graft, linked to CJD transmission). However, because of complications related to other synthetic materials in the general surgery hernia literature, Ulmsten and colleagues (1998) eventually settled on a polypropylene multifilamentous woven mesh that they

termed the *intravaginal slingplasty* (IVS, Tyco Healthcare, Mansfield, MA) (1996). Currently, a soft, loosely woven, polypropylene monofilament mesh with a pore size exceeding $75 \mu\text{m}$ is the most commonly used material. As previously discussed, this material allows for optimal migration of host inflammatory components (leukocytes and macrophages) into the mesh for purposes of infectious surveillance and host wound healing (imbibition and inosculation). It was found that this material was also optimal for inciting fibrous tissue ingrowth. This type of mesh is known as a type I mesh (Amid classification) and has previously been described in the general surgical literature as being favorable from the standpoints of its mechanical properties (stretch and elasticity) (Dietz et al, 2001, 2003).

UraTape (Mentor-Porgés, Le Plessis-Robinson, France) was the first transobturator MUS, and outcomes related to its use were first reported by Delorme and colleagues in 2003. UraTape is a polypropylene microporous sling with a central silicone core. UraTape was eventually replaced by ObTape (Mentor-Porgés) because of a high rate of vaginal exposure, probably related to the silicone core. However, possibly because of its semi-microporous ($<50 \mu\text{m}$) properties, vaginal exposure problems have also been reported with ObTape (Siegel, 2005; Yamada et al, 2006). A second-generation transobturator sling developed by Mentor-Porgés is known as the Aris transobturator tape; it has a larger $200\text{-}\mu\text{m}$ pore size that allows improved tissue ingrowth with less encapsulation. A unique transobturator mesh is the BioArc, which has a biologic (porcine dermis, InteXen) graft material that is sutured on either end to the polypropylene mesh. The biologic material actually occupies a suburethral position (de Leval, 2003; Delorme et al, 2003). Table 84-8 displays the most commonly available MUS materials.

KEY POINTS: MECHANICS, ANATOMY, AND MATERIALS OF MIDURETHRAL SLINGS

- The integral theory states that the most important factors to preserve continence are adequate function of the pubourethral ligaments, the suburethral vaginal hammock, and the pubococcygeus muscle. An injury to any of these three components from surgery, parturition, aging, or hormonal deprivation can lead to impaired midurethral function and subsequently urinary incontinence.
- Urethral hypermobility is a symptom of damage to the normal supporting structures of the urethra and not a cause of SUI.
- The initial MUSs were made of materials with smaller pore sizes. Currently the majority of MUSs are made of loosely woven polypropylene.

Midurethral Sling Operative Procedures

Midurethral Sling Patient Counseling

Because MUS surgery involves the implantation of a synthetic, prosthetic material, surgeons should thoroughly counsel their patients about the permanent nature of these products and the unique and sometimes serious complications related to their use. Also, similar to the PVS, patients should also be counseled about the risk of transient and permanent voiding dysfunction after surgery. This should include a discussion of postoperative difficulty emptying the bladder and de novo urgency and frequency.

Midurethral Sling Anesthesia, Patient Positioning, and Preparation

MUS surgery can be performed using local (with or without sedation), spinal, or general anesthesia, but the final choice of

TABLE 84-8 Midurethral Sling Material Characteristics

MANUFACTURER	BRAND NAME	COMPOSITION	STRUCTURE	AMID TYPE	PORE SIZE (μm)	INSERTION METHOD
AMS ^a	SPARC	Polypropylene	Monofilament	Type I	>100	Retropubic
	Monarc	Polypropylene	Knitted monofilament	Type I	>100	Transobturator
	BioArc SP or TO	Polypropylene and biologic graft	Monofilament	Type I	>100	Retropubic or transobturator
	MiniArc Precise	Polypropylene	Monofilament	Type I	>100	Single incision
Boston Scientific	Obtryx	Polypropylene ^b	Monofilament	Type I	>100	Transobturator
	Advantage Fit	Polypropylene ^b	Monofilament	Type I	>100	Retropubic
	Lynx	Polypropylene ^b	Monofilament	Type I	>100	Retropubic
	Prefyx PPS	Polypropylene ^b	Monofilament	Type I	>100	Retropubic, transobturator, or prepubic
	Solyx	Polypropylene ^b	Monofilament	Type I	>100	Single incision
C.R. Bard	Uretex SUP	Polypropylene	Monofilament	Type I	>100	Retropubic
	Align US or TO	Polypropylene	Monofilament	Type I	>100	Retropubic or transobturator
	Ajust Helical	Polypropylene	Monofilament	Type I	>100	Single incision
Gynecare (Ethicon)	Gynecare TVT	Polypropylene	Monofilament	Type I	>100	Retropubic
	Gynecare TVT-O	Polypropylene	Monofilament	Type I	>100	Transobturator
	TVT Secur (TVT-S)	Polypropylene	Monofilament	Type I	>100	Single incision
Tyco Healthcare	IVS	Polypropylene	Multifilament	Type III	<75	Retropubic
	IVS-02	Polypropylene	Multifilament	Type III	<75	Retropubic
	IVS-04	Polypropylene	Multifilament	Type III	<75	Transobturator
Mentor-Porgés	Aris	Polypropylene	Monofilament	Type I	>100	Retropubic or transobturator
	ObTape	Polypropylene	Thermoannealed	Type III	50	Transobturator
C.L. Medical ^c	I-Stop	Polypropylene	Monofilament	Type I	>100	Single incision, retropubic, or transobturator
TFS Surgical ^d	TFS (tissue fixation sling)	Polypropylene	Monofilament	Type I	>100	Single-incision
Promedon SA ^e	Safyre VS or T	Polypropylene, silicone ^f	Multifilament	Type III	<75	Retropubic or transobturator

^aAMS, American Medical Systems, Minnetonka, MN (parent company is Endo International).

^bDetangled suburethral component.

^cC.L. Medical is located in Sainte Foy-Lès-Lyon, France.

^dTFS Surgical is located in Adelaide, South Australia, Australia.

^ePromedon SA is located in Cordoba, Argentina.

^fThe suburethral component is polypropylene mesh, and the arms (columns) of the sling are made of polydimethylsiloxane polymer.

anesthesia is typically based on patient, surgeon, and anesthesia provider preference. In the original description of the MUS, local anesthesia was used so that the patient would be able to perform an intraoperative cough as a method of adjusting sling tension. It was believed that this would minimize the incidence of obstruction. However, multiple studies have failed to show a difference in the efficacy or safety of MUS performed with local versus spinal anesthesia (Wang and Chen, 2001; Adamiak et al, 2002). In one of those studies of 103 women who underwent MUS procedures, a comparison of local and spinal anesthesia was made; 67 women underwent the procedure with local and 36 with spinal anesthetic (Adamiak et al, 2002). In the postoperative evaluation there was no difference

in the success rate of the MUS surgery performed; there was also no difference in the rate of complications between the groups. However, there was a difference in the patients' ability to perform a cough test effectively during the procedure in the spinal anesthesia group, but this did not result in an increase in the rate of postoperative obstruction. It appears that tensioning the sling by cough stress test is not necessary.

As for the PVS, the AUA guidelines and Best Practice Policy Statements pertaining to antibiotic and DVT prophylaxis should be followed. Also, povidone-iodine or chlorhexidine gluconate solutions containing 4% or less alcohol (off-label) are both safe and effective for vaginal preparation. The MUS procedure is typically performed

with the patient positioned in the dorsal lithotomy position with a significant degree of flexion (70 degrees or more) of the thighs.

Surgical Approach for Retropubic Midurethral Slings

The device consists of two specially curved 5-mm diameter (size varies by manufacturer) insertion trocars that are attached to a 40-cm segment of polypropylene mesh that is 1.1 cm wide (size varies by manufacturer). The sling is typically covered with a clear plastic sheath, which protects the mesh from contamination and allows easy passage through host tissues. For the down-to-up technique, a rigid catheter guide is typically placed in the urethra with an 18-Fr Foley catheter to help deflect the bladder away from the path of trocar insertion. An ergonomic handle is attached to the trocar to aid in its manipulation. **Figure 84-8** shows some of the various types of slings and trocars.

For retropubic MUS insertion under local anesthesia with or without sedation, approximately 5 mL of local anesthetic is injected into the vaginal area as well as into the planned suprapubic insertion skin sites. In addition, another 20 mL of local anesthetic agent is injected into the area along the posterior aspect of the pubic bone to the level of the urogenital diaphragm to anesthetize the retropubic space. Additional vaginal infiltration includes 10 mL injected on either side of the urethra to the level of the urogenital diaphragm.

After appropriate anesthesia, two small suprapubic stab incisions are created just above the level of the symphysis pubis, approximately 2 cm lateral to the midline. A third midline vaginal incision approximately 1.5 cm long is created 1.5 cm from the external meatus of the urethra. After the vaginal incision is created, minimal dissection is performed using Metzenbaum scissors under the vaginal flaps on either side to elevate the vaginal epithelium from the underlying periurethral tissue to the level of the pubocervical (endopelvic) fascia, which is not perforated. For the down-to-up technique, the trocar is then placed in the dissection tunnel immediately beneath the vaginal epithelium on one side of the urethra with the trocar tip situated in close proximity to the lower rim of the pubic ramus. With controlled pressure, the trocar is elevated through the endopelvic fascia, into the space of Retzius, through the rectus muscles, and through the previously created suprapubic skin incision. During this maneuver, the trocar is kept in close contact with the inferior surface of the pubic bone to avoid perforation of the lower urinary tract and also to avoid intraperitoneal entry. Tactile contact with the bone and slow graded pressure during trocar advancement ensure direct apposition of metal to bone and avoidance of bladder injuries. The technique for up-to-down trocar passage is very similar; however, a catheter guide (Foley in urethra) is typically not used and the tip of the trocar is guided onto the index finger of the opposite hand and out of the vaginal incision lateral to the urethra.

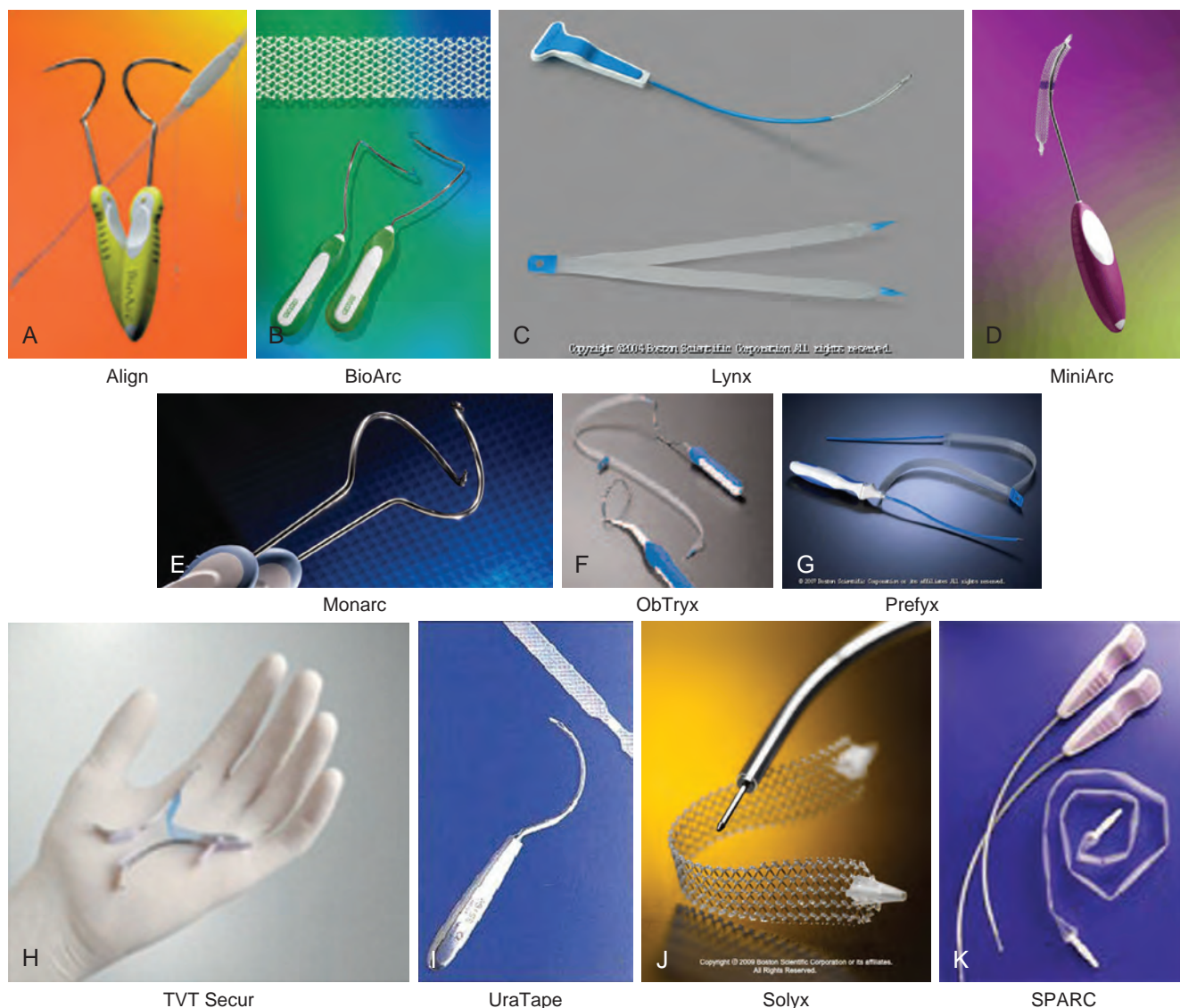


Figure 84-8. A-K, Midurethral sling trocars and prosthetics.

Simultaneous deflection of the lower urinary tract is accomplished during insertion using the catheter guide and catheter with pelvic viscera deflected away from the site of needle insertion. The same maneuver is performed contralaterally so that each trocar exits through the appropriate skin incision. **Cystoscopy is performed to exclude trocar penetration of the lower urinary tract.** The use of a 70-degree lens is essential, as is complete distention of the bladder with irrigant to exclude subtle tangential injury. **If perforation is noted, the trocar is withdrawn and passed once more with an effort to avoid further perforation.** Once cystoscopy has demonstrated no evidence of bladder injury, the mesh is brought through the incisions and tension adjustment of the sling is performed. Tension adjustment is commonly performed by inserting a surgical instrument (clamp) or metallic sound between the sling and urethra while the covering plastic sheath is removed from the field. **In general, a MUS should be placed loosely at the midurethra because its function is not primarily related to compression.** Redundant mesh is then excised at the level of the suprapubic skin incisions and all incisions are closed (Fig. 84-9).

Surgical Approach for Transobturator out-to-in Slings

The patient is placed in the dorsal lithotomy position with legs in hyperflexion (120 degrees). A small 1.5-cm midline vaginal incision is created 1.5 cm from the meatus as with the retropubic MUS, and dissection is carried out laterally to the ischiopubic ramus. A puncture incision is made in the obturator foramen at the level of the clitoris in the leg using the trocar; the obturator membrane is perforated, at which point resistance is noted by the operative surgeon. Using the nondominant index finger and identifying the landmarks of ramus and the obturator internus muscle, the trocar is turned in a medial orientation and advanced on the tip of the index finger and brought out through the vaginal incision. Inspection is carried out at this point to exclude inadvertent penetration of the vaginal fornix or associated urinary structures. The synthetic material is then attached to the trocar and brought out through the inner thigh stab wound. The procedure is then repeated on the contralateral side. Cystoscopy to rule out urethral and bladder injury is recommended

after trocar passage. **It is important not to neglect a careful examination of the urethra.** Tension is set on the sling by passing a clamp between the sling and urethra such that a surgical clamp can be passed easily between these two structures. Excess material is then cut at the skin puncture site and the incisions are closed according to the surgeon's preference.

Surgical Approach for Transobturator in-to-out Slings

The vaginal component of the procedure is the same as in the out-to-in technique. Stab incisions are created approximately 2 cm superior to the horizontal line level with the urethra and 2 cm lateral to the labial folds, which will be the exit point for the helical passer. Once the device is inserted through the urethra and the upper part of the ischiopubic ramus is reached with the device, the obturator membrane is perforated sharply with scissors. The introducer is then passed at a 45-degree angle relative to the midline sagittal plane until it reaches and perforates the obturator membrane. The open side of the introducer is passed out facing the surgeon. The more distal end of the tubing is then mounted on the spiral segment of the helical passer and slipped along the open gutter of the introducer. The passer is aligned parallel to the sagittal axis and rotated so that the tip of the tubing exits the inter-thigh stab incision. The tubing is then removed from the passer until the first few centimeters of the mesh become externalized, and the procedure is repeated on the contralateral side. Next, cystoscopy is performed to ensure no injury to the bladder or urethra. All plastic covering sheaths are then removed simultaneously from the sling while maintaining no tension on the sling itself, using the technique previously described. Operative technique varies with insertion method. Various procedures using similar insertion methods represent relatively similar technique (Fig. 84-10).

Surgical Approach for Single-Incision Slings

Each of the single-incision slings has a proprietary method of placement that varies by the manufacturer. In general, the sling devices consist of a short segment of loosely woven polypropylene mesh

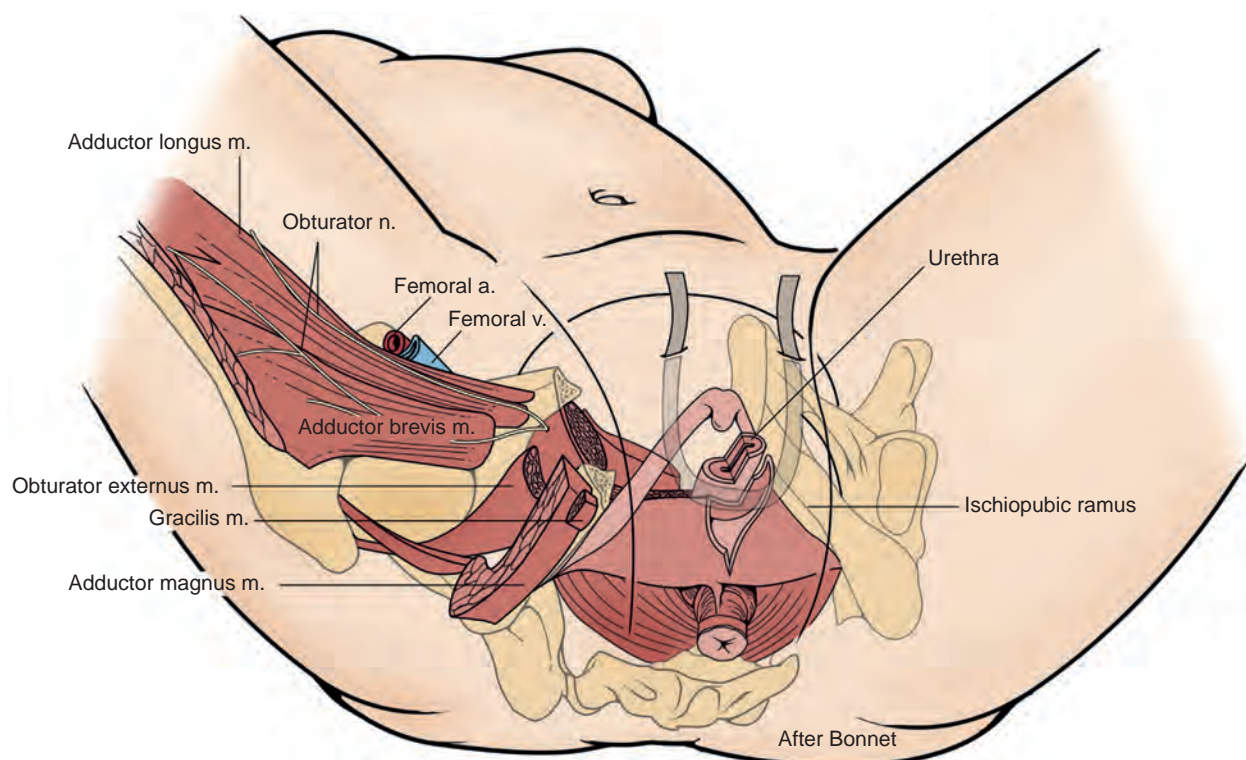


Figure 84-9. Midurethral sling as placed via the retropubic approach.

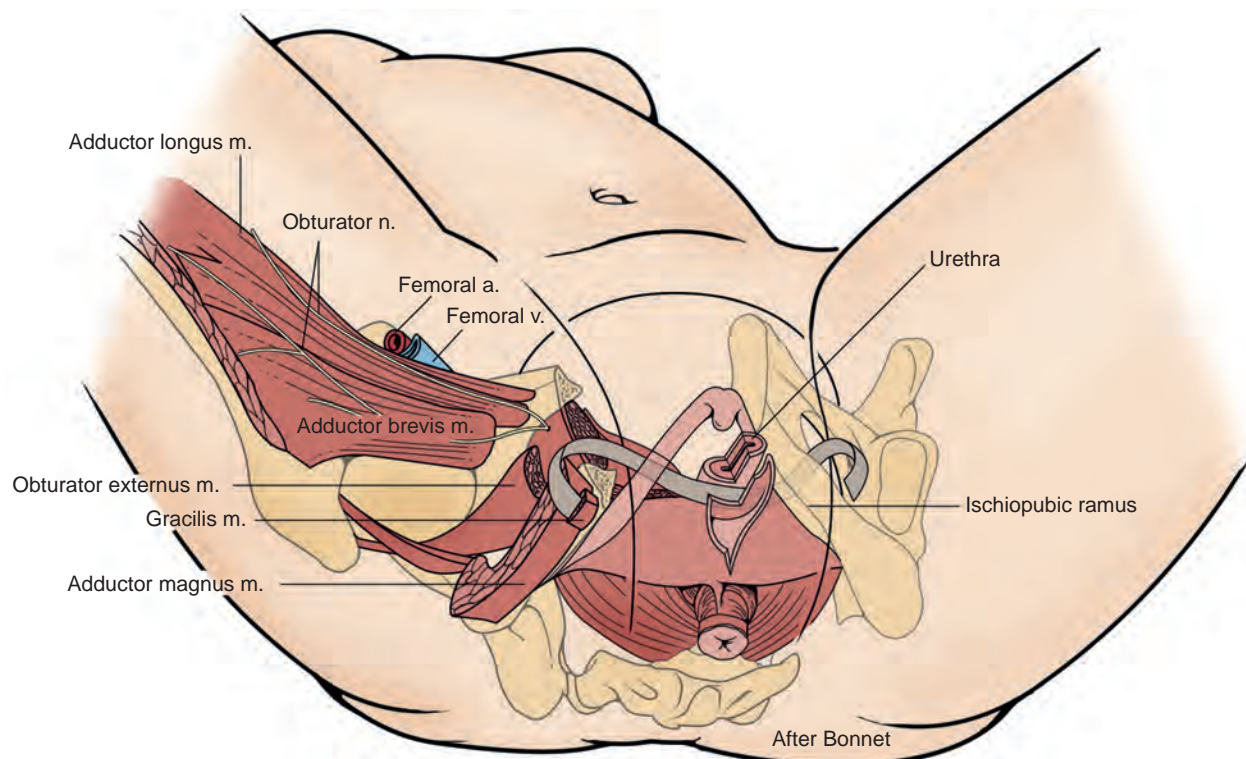


Figure 84-10. Midurethral sling as placed via the transobturator approach.

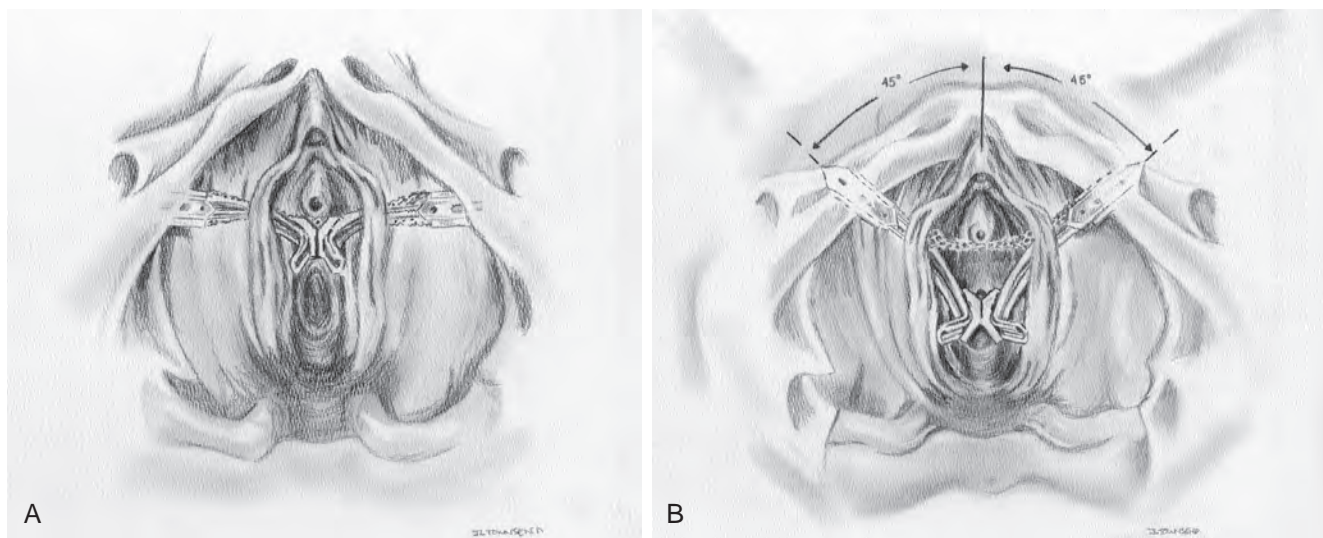


Figure 84-11. Midurethral sling as placed via a single-incision approach. **A**, Hammock style. **B**, U position.

with two harder pointed ends that allow it to anchor in place. A curved stainless steel trocar or other type of applicator device is used to push the ends of the sling into a secure position. The sling is placed under the midurethra and can be fixed in the hammock position (Fig. 84-11A) into the obturator internus muscle or in the U-shaped position (Fig. 84-11B) into the connective tissue of the urogenital diaphragm (endopelvic fascia) behind the pubic bone (Meschia et al, 2009).

The procedure is performed with the patient in the dorsal lithotomy position (with sequential compression devices in place) with a significant degree of flexion (70 degrees or more) of the thighs. A Foley catheter is placed before the procedure to ensure the bladder

is fully decompressed before passage of the device. As heretofore described, the patient has received parenteral sedation, and approximately 5 mL of 0.9% normal saline is used to hydrodistend the anterior vagina. After the vaginal incision is created, minimal dissection is performed using Metzenbaum scissors under the vaginal flaps on either side to elevate the vaginal epithelium from the underlying periurethral tissue to the level of the pubocervical fascia, which is not perforated. One trocar of the device is placed in the right dissection tunnel immediately beneath the vaginal epithelium and advanced up to the ischiopubic bone and into the obturator internus muscle, where the trocar holder anchors the sling edges. The left side is introduced in the same way, creating a

hammock-shaped sling. The definitive sling tension is achieved when the tip of a hemostat is easily passed between the urethra and the sling. Cystoscopy with a 30-degree rigid cystoscope should be performed before completion of the procedure. This step is essential to avoid the future morbidity of repeat surgery for intravesical or urethral mesh. Efflux of both ureteric orifices is confirmed. **Our experience suggests that the tension of single-incision MUSs should be tighter than the classic retropubic or transobturator MUS surgeries to achieve the same result.**

Outcomes of Midurethral Slings for Predominantly Stress Urinary Incontinence

In reviewing the extensive outcomes for the MUS, several caveats must be entertained. Outcomes are reported in varying fashions using different tools, lengths of follow-up, and overall definitions of success and failure. These factors should be kept in mind when attempting to compare different groups and procedural nuances.

Outcomes for Retropubic Midurethral Slings in Patients with Predominantly Stress Urinary Incontinence

The initial study of the retropubic MUS technique reported an 80% (author-defined) success rate (Ulmsten et al, 1996). A subsequent prospective multicenter trial that included 130 women with genuine stress incontinence who were observed for 1 year revealed success, improvement, and failure rates of 91%, 7%, and 2%, respectively (Ulmsten et al, 1998). In this first multicenter study, complication rates were low but did include one bladder mesh perforation and one wound infection (possibly mesh exposure). The rate of voiding dysfunction was also relatively low, with only 1 patient experiencing retention for 12 days, which resolved spontaneously, and 3 patients with less than 3 days of voiding dysfunction that required short-term catheterization.

In 2001, Nilsson and Kuuva (2001) evaluated 161 consecutive retropubic MUS operations (28% of patients had failed prior incontinence surgery, 11% had ISD, and 37% had mixed incontinence). At 16 months' mean follow-up the overall objective cure rate was 87%, with 7% of patients significantly improved and another 5% of procedures considered failures. The trocar bladder injury rate at the time of insertion was 3.7%, and 4.3% of women experienced short-term de novo voiding dysfunction. Urgency symptoms arising after surgery occurred in 3% of women, yet 80% of the women who had preoperative urgency symptoms had relief of those symptoms at their 16-month visit. No serious complications were noted.

Long-term results mirror the short-term experience with this procedure. Success rates ranging from 81% to 90% have been reported at more than 3 years. Ulmsten and colleagues (1999) reported an 86% success rate in 50 women at 3 years. Olsson and Kroon (1999) reported 90% success in 51 women at 3 years. Doo and colleagues (2006) evaluated the long-term efficacy and safety of this procedure among 134 Korean women. The overall 5-year success rate was 94.9%, with an 86.6% patient satisfaction rate. Although success rates between 1 and 5 years were similar (97.7% and 94.9%), the cure rate decreased from 90.1% to 76.9%. Nilsson and colleagues (2001) reported success rates of 84.7% at 5 years and 81.3% at 7 years (Nilsson et al, 2004) in a cohort of 90 women. Liapis and colleagues prospectively assessed the efficacy of the MUS in 65 women. At 5-year follow-up, the objective cure rate was 53% and the failure rate was 9.4%, whereas at 7-year follow-up the objective cure rate was 80% and the failure rate was 13.5% (Liapis et al, 2008). Song and coworkers (2009) reported on the second longest follow-up (>7 years) in 306 women, with a cure rate of 84.6%. They reported on 6 patients who developed mesh exposure.

As a continuation of their earlier work, Nilsson and colleagues (2008) provided the longest (11 years) prospective observational cohort study of 90 women with primary stress incontinence. Ninety percent of these women were objectively cured, and 77% of the

patients reported subjective cure. No late-onset adverse effects or cases of mesh erosion were seen. The Austrian Urogynecology Working Group (Tamussino et al, 2001) published their data compiled within the Austrian central registry, beginning in 1998. There were no serious complications and no mortality within the registry. It is interesting to note that 363 (45%) of the patients in the registry had a MUS in combination with other procedures (prolapse repair). All of these long-term studies attempted to evaluate risk factors for declining effectiveness, and in general there does appear to be a tendency for higher failure rates in older patients and patients with diminished urethral function (ISD).

Over a dozen randomized clinical trials have compared the retropubic MUS with traditional incontinence procedures in published peer-reviewed journals. This includes five comparing MUS with open colposuspension (Ward and Hilton 2002, 2004; Bai et al, 2005; El-Barky et al, 2005; Ward and Hilton, 2008), four comparing retropubic MUS with laparoscopic colposuspension (Persson et al, 2002; Ustun et al, 2003; Paraiso et al, 2004; Valpas et al, 2004), two comparing retropubic MUS with a fascial sling (Bai et al, 2005; Wadie et al, 2005), and one comparing retropubic MUS with no treatment (Campeau et al, 2007). Table 84-9 displays the outcomes of retropubic MUS surgeries from randomized controlled trials.

Among the retropubic MUS versus Burch comparisons, the trials by Ward and Hilton (2002) and Valpas and colleagues (2004) enrolled the greatest number of patients. The Ward and Hilton trial that compared retropubic with open colposuspension published data at short-term (Ward and Hilton, 2002), intermediate-term (Ward and Hilton, 2004), and long-term (Ward and Hilton, 2008) follow-up. At 6 months' follow-up, the 344 women randomized to retropubic MUS (175 patients) and Burch arms (169 patients) demonstrated no significant difference in cure rates. The MUS was associated with more operative complications (i.e., bladder trocar injury), and the colposuspension was associated with more postoperative complications and longer recovery. At 2 years' follow-up, the overall cure rates noted were relatively low, with 63% of the MUS surgery patients and 51% of colposuspension patients being cured (Ward and Hilton, 2004). Also, there were significantly more patients in the colposuspension group needing intermittent self-catheterization (<0.0045) and surgery for pelvic organ prolapse (<0.0042) than in the MUS group. At long-term follow-up (5 years), there was no difference in cure rates. Consistent with earlier studies, prolapse was seen more commonly in Burch group. Two mesh exposures were found in the retropubic MUS group. Unlike earlier reports of high (27%) rates of de novo urgency and urgency incontinence in the literature (Jarvis, 1994) after colposuspension, Ward and Hilton reported that less than 2% of patients after MUS and less than 5% of patients after colposuspension experienced this problem (Ward and Hilton, 2008). Ward and Hilton (2002) and El-Barky and colleagues (2005) (another study of retropubic MUS vs. Burch colposuspension) found operation time, hospital stay, and time until return to normal activity significantly shorter in the MUS groups. El-Barky and coworkers (2005) reported two bladder trocar injuries in the MUS group, whereas wound infections were significantly more common among the Burch patients.

Bai and colleagues (2005) compared MUS surgery with open colposuspension and autologous PVS. At 3- and 6-month follow-up, there were no differences in cure rates among the operations, but at 12 months the PVS had significantly higher cure rates (92.8%) than the colposuspension (87.8%) or MUS (87.0%). In a 2005 comparison of the MUS and the PVS, Wadie and colleagues (2005) found the PVS and MUS to be equally effective. Lastly, the MUS may be more cost-effective and superior in terms of impact on health care spending compared with open colposuspension (Manca et al, 2003).

Four randomized trials (Persson et al, 2002; Ustun et al, 2003; Paraiso et al, 2004; Valpas et al, 2004) have been performed comparing retropubic MUS surgery with laparoscopic colposuspension. Valpas and colleagues and Persson and colleagues reported results after 12 months of follow-up, and Paraiso and colleagues reported outcomes at 18 months. The results of these trials revealed MUS cure rates ranging from 86% to 97% and colposuspension cure rates

TABLE 84-9 Outcomes with Retropubic Midurethral Slings (Randomized Controlled Trials)

STUDY	N	TYPE	FOLLOW-UP (MONTHS)	CURED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY	ANY URINARY RETENTION
Liapis et al, 2002	36	Gynecare TVT	24	84%	Pad test	22%	0%
Persson et al, 2002	38	Gynecare TVT	12	89%	UDS	3%	0%
Ward and Hilton, 2002	175	Gynecare TVT	6	66%	Pad test	NR	0%
Ustun et al, 2003	23	Gynecare TVT	24	82.6%	UDS	NR	0%
Rechberger et al, 2003	50	Gynecare TVT	(13.5)	88%	Stress test	16%	20%
	50	IVS		80%		8%	4%
Abdel-Fattah et al, 2004	60	Gynecare TVT	36	85%	VQ	15%	3.3%
Paraíso et al, 2004	36	Gynecare TVT	18	96.8%	UDS	NR	NR
Valpas et al, 2004	70	Gynecare TVT	18	85.7%	Stress test	NR	NR
Bai et al, 2005	31	Gynecare TVT	12	87%	VQ	0%	12.9%
El-Barky et al, 2005	25	Gynecare TVT	6	72%	VQ	8%	20%
Lim et al, 2005	61	Gynecare TVT	3	78.7%	UDS	6.6%	NR
	61	SPARC		75%		10%	
	60	IVS		78.3%		1.7%	
Andonian et al, 2005	43	Gynecare TVT	12	95%	Pad test	NR	5%
	41	SPARC		83%			5%
Wadie et al, 2005	28	Gynecare TVT	6	92%	UDS	0%	10.7%
Tseng et al, 2005	31	Gynecare TVT	24	87.1%	UDS	NR	NR
	31	SPARC		80.7%			
Foote et al, 2006	31	SPARC	24	77.4%	VQ	15.9%	NR
Meschia et al, 2006	92	Gynecare TVT	24	85%	Pad test	9%	2.2%
	87	IVS		72%		11%	1.1%
Lord et al, 2006	147	Gynecare TVT	1.5	97.3%	Stress test	40.5%	4.1%
	154	SPARC		97.4%		42.4%	7.8%
Wang et al, 2006	29	SPARC	6	NR	Pad test	10.3%	NR
Zullo et al, 2007	35	Gynecare TVT	12	91%	UDS	9%	2.9%
Porena et al, 2007	70	Gynecare TVT	(32)	71.4%	VQ	14%	NR
Lee et al, 2007b	60	Gynecare TVT	12	86.8%	VQ	6.6%	0%
Schierlitz et al, 2008	67	Gynecare TVT	6	79%	UDS	21%	11%
Rinne et al, 2008	134	Gynecare TVT	12	95.5%	Stress test and pad test	1.5%	0.7%
Jelovsek et al, 2008	36	Gynecare TVT	(65)	52%	VQ	NR	NR
Rechberger et al, 2009	201	IVS-02	18	59.7%	UDS	8.6%	3.5%
Basu and Duckett, 2010	33	Gynecare TVT	6	93.3%	UDS	6.1%	6.1%
Richter et al, 2010	291	Gynecare TVT	12	80.8%	Stress test and pad test	NR	3.7%
Tincello et al, 2011	437	Gynecare TVT	12	87.2%	Stress test	3%	2.1%
Teo et al, 2011	41	Gynecare TVT	12	50%	Pad test	5.1%	4.5%
Basu and Duckett, 2013	33	Advantage Fit	36	81%	VQ	NR	NR

Parentheses connote mean or median values.

NR, not recorded; UDS, urodynamic studies; VQ, validated questionnaire.

ranging from 57% to 100% (variable methods of reporting). There was no apparent difference between the two procedures in the Persson and colleagues trial, but Paraíso and colleagues and Valpas and colleagues noted that the MUS surgery resulted in significantly higher rates of success in terms of urinary incontinence. These trials noted no other apparent differences between techniques other than that the MUS group recovered more rapidly and had a lower need for subsequent urogenital prolapse procedures than the colposuspension group. However, [Dean and colleagues \(2006\)](#) reviewed seven randomized trials comparing MUS and laparoscopic colposuspension and found no statistically significant difference in reported subjective cure rates within 18 months, but the overall objective cure rate was significantly higher for retropubic MUSs.

[Novara and colleagues \(2008\)](#) performed a meta-analysis of 33 randomized controlled trials comparing retropubic MUSs with other anti-incontinence procedures. Complications were similar

between MUS and Burch colposuspension, with exception of bladder trocar injury (higher in MUS group) and reoperation rate (higher in Burch arm). Retropubic MUSs and PVSs were found to be equally effective, with better cure rates than the Burch colposuspension ([Novara et al, 2008](#)).

A number of randomized studies exist comparing different types of retropubic MUSs. Three trials compared the Gynecare TVT with the Suprapubic Arc Sling (SPARC), a polypropylene mesh material approaching the midurethra from the abdominal incision ([Andonian et al, 2005](#); [Tseng et al, 2005](#); [Lord et al, 2006](#)). [Tseng and colleagues \(2005\)](#) found the Gynecare TVT and SPARC to be equally effective. The SPARC group had a greater number (12.9%) of bladder trocar injuries than the Gynecare TVT group (0%). Although this was not statistically significant, the authors felt it was clinically significant. In 2005, [Andonian and colleagues \(2005\)](#) randomized 84 patients to either arm and found no statistically

significant difference between SPARC and Gynecare TVT in terms of objective cure rates at 12 months' follow-up. Mesh exposure, infected pelvic hematoma, and UTI were found postoperatively only in the SPARC group, but there were no differences in other perioperative complications (bladder trocar injury, blood loss, hospital stay, urinary retention, postoperative analgesia). [Lord and colleagues \(2006\)](#) found the Gynecare TVT group to have a lower rate of vaginal exposure (4.8% vs. 10.5%) and a statistically significantly higher subjective cure rate (87.1% vs. 76.5%) than the SPARC group. In addition, the authors found the SPARC to be more difficult to adjust correctly, and a statistically significant number of patients required loosening of the sling ($P = .002$).

[Arunkalaivanan and Barrington \(2003\)](#) compared the Gynecare TVT with allogenic acellular porcine collagen, Pelvicol (C.R. Bard), in a questionnaire-based study. They reported on both 12-month and 36-month results and found no difference in subjective cure rates. Gynecare TVT was compared in three studies with IVS, a multifilament, microporous polypropylene mesh material, which is passed similarly to a SPARC. [Rechberger and colleagues \(2003\)](#) reported no differences in cure rates at 13 months' follow-up with 50 patients in each group. With exception of postoperative acute urinary retention occurring significantly more commonly among the Gynecare TVT patients, complications were similar. [Meschia and colleagues \(2006\)](#) compared the TVT and IVS with intermediate follow-up and reported subjective cure rates of 80% (Gynecare TVT) and 78% (IVS) and objective cure rates of 85% (Gynecare TVT) and 72% (IVS). Eight (9%) of the IVS patients experienced vaginal erosion, with none found in the Gynecare TVT group. The TVT was compared with the IVS and SPARC by [Lim and colleagues \(2005\)](#) in the SUSPEND trial. There was no significant difference between the cure rates: 87.9% (Gynecare TVT) versus 81.5% (IVS) and 71.4% (SPARC). There was a significantly greater rate of mesh exposure in the SPARC group. [Balakrishnan and colleagues \(2007\)](#) followed a subgroup of IVS patients from the [Lim group \(2005\)](#) for up to 30 months and found 13% with sling erosions, requiring removal. Of the 29 patients (47%) from this initial IVS group seen 12 to 34 months postoperatively, 24% experienced sling erosion with associated sinus formation, requiring sling removal. In the [Novara and](#)

[colleagues \(2007\)](#) meta-analysis, the Gynecare TVT was found to be more efficacious than the IVS and SPARC.

Outcomes for Transobturator Midurethral Slings in Patients with Predominantly Stress Urinary Incontinence

Subsequent to the development of the retropubic MUS, it was recognized that the transobturator MUS approach was also a viable method for correction of SUI. Since the initial description of the transobturator MUS by [Delorme in 2001](#), continence rates have been reproducibly satisfactory ([Table 84-10](#)). Reported continence rates range from 40% to 97% on the basis of a variety of subjective (questionnaire and QoL single-item assessment) and objective (cough stress test, uroflowmetry, physical examination) measures. Overall, the outcomes of transobturator MUS procedures in patients with predominantly SUI are similar to those of the retropubic MUS.

Many prospective randomized studies have compared transobturator with retropubic MUS procedures, ranging in follow-up from 6 to 31 months ([Lee et al, 2007b](#); [Porena et al, 2007](#); [Zullo et al, 2007](#); [Rinne et al, 2008](#); [Schierlitz et al, 2008](#); [Rechberger et al, 2009](#); [Richter et al, 2010](#)). Between the two groups there were a significantly greater number of bladder trocar injuries in the retropubic versus the transobturator patients: 6.5% versus 0% ([Rechberger et al, 2009](#)) and 7.3% versus 0% ([Schierlitz et al, 2008](#)). Both of these groups also found the retropubic MUS to be more effective than the transobturator MUS in patients with ISD. Schierlitz and colleagues observed that at 6-month follow-up, 13% of the transobturator patients with ISD required further surgery, whereas 0% of the retropubic MUS patients with ISD required reoperation for SUI ([Schierlitz et al, 2008](#)). Porena and colleagues noted that incontinence was significantly improved in the transobturator MUS group (still present in 24%) but persisted in 44% of the retropubic MUS group ([Porena et al, 2007](#)). A few key points are consistent between these studies: these techniques were safe, there were no long-term complications in either group, cure rates were equal (with the exception of the ISD group), and patients were equally satisfied.

TABLE 84-10 Outcomes with Transobturator Midurethral Slings (Randomized Controlled Trials)

STUDY	N	TYPE	FOLLOW-UP (MONTHS)	CURED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY	ANY URINARY RETENTION
Wang et al, 2006	31	Monarc	6	NR	Pad test	9.7%	NR
Zullo et al, 2007	37	Gynecare TVT-O	12	89%	UDS	0%	0%
Porena et al, 2007	75	ObTape	(31)	77.3%	VQ	11%	NR
Lee et al, 2007b	60	Gynecare TVT-O	12	86.8%	VQ	0%	0%
Schierlitz et al, 2008	71	Gynecare TVT-O	6	55%	UDS	10%	4.9%
Rinne et al, 2008	131	Gynecare TVT-O	12	93.1%	Stress test and pad test	2.3%	1.5%
Rechberger et al, 2009	197	IVS-04	18	61.4%	UDS	5.0%	5.0%
Richter et al, 2010	137	Gynecare TVT-O	12	77.6%	Stress test and pad test	NR	0.7%
	161	Monarc		77.4%			
Hinoul et al, 2011	85	Gynecare TVT-O	12	97.6%	Stress test	NR	4%
Teo et al, 2011	29	Gynecare TVT-O	12	41%	Pad test	11.3%	1.6%
Tincello et al, 2011	238	Gynecare TVT-O	12	96.4%	Stress test	0%	0.8%
Sivaslioglu et al, 2012	36	I-Stop TOS	(64)	75%	Stress test	NR	5.5%
Bianchi-Ferraro et al, 2013	54	Gynecare TVT-O	12	87%	Stress test, pad test, and UDS	3.5%	3.5%
Mostafa et al, 2013	68	Gynecare TVT-O	12	82.3%	Stress test	6.5%	11.8%
Abdel-Fattah et al, 2014*	35	Aris	36	67.6%	VQ	NR	NR
Abdel-Fattah et al, 2014*	31	Gynecare TVT-O	36	50%	VQ	NR	NR

*All patients with mixed urinary incontinence.
 Parentheses connote mean or median values.
 NR, not recorded; UDS, urodynamic studies; VQ, validated questionnaire.

In 2010, [Richter and colleagues](#), published results of the prospective randomized trial comparing the retropubic MUS with the transobturator MUS with 12 months of follow-up. In this study, 298 women underwent a retropubic sling procedure and 299 underwent a transobturator sling procedure. The objective cure rates in terms of a negative stress test, pad test, and no re-treatment for the retropubic and transobturator groups were 80.8% and 77.7%, respectively (no statistically significant difference). The rate of voiding dysfunction requiring surgery was significantly higher in the retropubic group (2.7% vs. 0%).

Outcomes for Single-Incision Midurethral Slings in Patients with Predominantly Stress Urinary Incontinence

Surgical treatment of SUI has expanded to include single-incision slings. This technology was first approved (Gynecare, TVT Secur) by the FDA in 2006. There are fewer data available regarding the safety and efficacy of this new generation of slings compared with the retropubic and transobturator MUSs.

[Neuman \(2008\)](#) performed a prospective observational study of 100 consecutive women with a hammock-style single-incision sling. The perioperative and 12-month postoperative data were compared between the first 50 patients and the last 50 patients. The objective failure rate went down from 20% to 8% between the two groups, with the sling being placed closer to the urethra. Four (8%) patients in the first group had vaginal perforation with the inserter. This was avoided in the second group by widening the submucosal tunnel. The mesh exposure rate decreased from 12% to 8% by the creation of deeper submucosal tunnels. There was one case of a paravesical self-remitting hematoma. Otherwise, the authors reported no cases of bladder or urethral perforation, UTI, wound infection, or intraoperative bleeding. At 12-month follow-up, the objective cure rates between the two groups were 88.6% and 93.5%.

In 2009, [Dmochowski and colleagues](#) reported preliminary results on one of the largest trials of the single-incisions MUS, with 29 sites in 8 countries. Effectiveness was measured by a standing cough stress test and an Incontinence Quality-of-Life instrument (I-QOL). In this study, 642 women were studied; 64.5% had a hammock (fixed into the obturator internus muscle) placement and 35.5% had the U (fixed into the endopelvic fascia toward the retropubic space) placement of the sling. Also, 65.3% had genuine SUI and 34.7% had MUI with predominantly stress symptoms. Intraoperative complications noted included 1 bladder perforation (0.2%) and 3 cases of bleeding exceeding 200 mL (0.5%). Postoperatively, there was 1 reported case of retention (0.2%), 10 UTIs (1.6%), 6 cases of voiding dysfunction (0.9%), and 15 cases of de novo urgency (2.3%). There were 5 cases of mesh erosion (0.8%). Improvements in QoL at 3 months were sustained at 12 months. Objective incontinence rate with the cough test was 11% at 6 months and 12.5% at 12 months, giving an objective cure rate of 87.5%.

Also in 2009, [Pickens and colleagues](#) presented their initial experience with 120 MiniArc cases at 13-month follow-up. Success was defined as using no pads, with subjective outcomes assessed with the IIQ-7 and UDI-6 questionnaires. Thirty-five percent had concurrent UUI. At 13 months, 94% had complete resolution of SUI and 6 reported significant improvement; 1 patient had a treatment failure. Twenty-four percent reported resolution of their UUI. Three (0.4%) intraoperative bladder perforations were reported. Two patients experienced retention postoperatively; in 1 the condition resolved, and the other patient underwent urethrolisis because of persistent retention.

[Krofta and colleagues \(2009\)](#) analyzed the efficacy and safety of the TVT Secur sling in 82 women through use of a cough stress test and validated questionnaires. There were no major perioperative complications or cases of urinary retention reported. Two patients had UTI (2.9%) and 4 wound infections (5.8%) within the first week after surgery. Mesh erosion occurred in 4 patients (6%). Subjective outcomes were cure of 58.2%, 23.9% improvement, and 17.9% failure. Objective cure rate was 51.5%. A second anti-

incontinence procedure was performed in 8 patients (6 retropubic MUS, 2 Burch colposuspension). These authors felt that the single-incision MUS was inferior to other MUS procedures.

In a prospective, multicenter study of 154 women with single-incision slings, [Debodinance and colleagues \(2009\)](#) reported cure rates of 70.3%, improvement in 11%, and failure in 18.7% at 1-year follow-up; 31.8% had MUI. Perioperative complications included 5 hemorrhages, 1 bladder injury, 1 vaginal wound, 21 cases of elevated PVR volume, and 1 case of persistent groin pain. Two patients returned with vaginal exposure of mesh and 1 with a granuloma; 61.1% reported cure of their urgency, and 12.3% reported de novo urgency. The overall cure rate did not change between 2 months and 1 year.

[Meschia and colleagues \(2009\)](#) used multiple validated questionnaires and cough test to assess 91 women at 1-year follow-up after placement of a single-incision sling. Fifty-five patients had a sling placed in the hammock position and 40 patients in the U position. The researchers reported subjective and objective cure rates of 78% and 81%, respectively. No bladder perforations were encountered. Two patients had intraoperative hemorrhage greater than 500 mL. Postoperative complications included 7 women with voiding difficulty (8%), 9 with recurrent UTI (10%), 9 with de novo urgency (10%), and 2 vaginal exposures. Among the 20 failures, 8 patients went on to have a second anti-incontinence procedure (5 retropubic MUS, 2 transobturator MUS, 1 Reemex implant).

Several studies have compared single-incision slings with standard MUSs (retropubic or transobturator). The largest of these is a 2011 study by [Tincello and colleagues](#) using the TVT Worldwide Observational Registry. This study compared 12-month outcomes of the different sling types (TVT Secur, Gynecare TVT, and the TVT Obturator System) in 1334 women. The primary outcome measures were the standing cough stress test, the I-QOL questionnaire, and the EQ-5D. The baseline characteristics including proportions of MUI were similar. Single-incision sling patients returned to normal activities quicker than those who received either the retropubic or transobturator MUS. Satisfaction rates were similar among the three groups. Objective cure rates were as follows: 84.2% for single-incision sling, 87.2% for retropubic MUS, and 96.4% for transobturator MUS. With regard to complications, all three techniques were similar.

[Basu and Duckett \(2010\)](#) performed a prospective, randomized controlled trial of the retropubic MUS versus the MiniArc single-incision sling in 70 women with 6 months' follow-up. The MiniArc group had statistically lower subjective cure rates and urodynamics stress incontinence cure rates than the retropubic MUS group (63.3% vs. 100% and 45% vs. 93%). At 6-month follow-up, 50% of the MiniArc patients had urodynamic SUI versus 7% in the retropubic group.

In 2010, [Hinoul and colleagues](#) performed one of the first randomized controlled trials comparing the transobturator MUS versus the single-incision sling. In this 12-month study, data were available for 160 randomized women (85 TVT-O and 75 TVT Secur); QoL and subjective outcomes were reported using validated questionnaires. One bladder perforation occurred in the transobturator MUS group. The objective cure rates for the transobturator MUS were significantly higher than for the TVT Secur (97.6% vs. 83.6%, $P < .05$); however, the TVT Secur surgery was associated with less pain in the first week postoperatively. This pain difference disappeared within 2 weeks.

Also in 2011, [Abdel-Fattah and colleagues](#) performed a meta-analysis to examine the effectiveness and safety of single-incision versus other MUS surgeries. The authors found nine randomized controlled trials comparing these two operations that included a total of 758 women with a mean follow-up of 9.5 months. The authors found that single-incision slings were associated with significantly lower subjective and objective cure rates than other MUS surgeries. The authors concluded that this form of therapy was inferior to the standard MUSs.

There is evidence in the literature that single-incision slings have decreasing efficacy with longer follow-up. In a 2012 study

TABLE 84-11 Outcomes with Single-Incision Midurethral Slings (Randomized Controlled Trials)

STUDY	N	TYPE	FOLLOW-UP (MONTHS)	CURED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY	ANY URINARY RETENTION
Basu and Duckett, 2010	37	MiniArc	6	64.9%	UDS	5.4%	5.4%
Tincello et al, 2011	659	TVT Secur	12	84.2%	Stress test	2.2%	0.3%
Hinoul et al, 2011	75	TVT Secur	12	83.6%	Stress test	NR	3%
Sivaslioglu et al, 2012	36	TFS Sling	(64)	83%	Stress test	NR	0%
Basu and Duckett, 2013	38	MiniArc	36	47.4%	VQ	NR	NR
Mostafa et al, 2013	69	Ajust Helical	12	81.2%	Stress test	8.7%	4.3%
Bianchi-Ferraro et al, 2013	63	TVT Secur	12	84.1%	Stress test, pad test, and UDS	1.5%	3.0%

Parentheses connote mean or median values.

NR, not recorded; UDS, urodynamic studies; VQ, validated questionnaire.

by Han and colleagues of 96 women prospectively followed after TVT Secur surgery, a significant decrease in subjective cure rate was seen between years 1 and 3 (85.4% to 72.9%). In another study from 2012 by Masata and colleagues with 2 years of follow-up, 197 women were randomized to receive single-incision sling surgery or transobturator MUS surgery. The authors found that the single-incision sling had significantly lower objective and subjective cure rates (objective 69.0% vs. 92.6%; subjective 75.2% vs. 89.7%). Table 84-11 displays the outcomes of single-incision sling surgeries from randomized controlled trials.

Outcomes of Midurethral Slings for Mixed Urinary Incontinence

Evidence suggests that MUSs are successful for women with mixed urinary symptoms as well. However, interpretation of these studies should be judicious because many outcomes are reported on the basis of symptoms only, with no urodynamic substantiation. In a retrospective analysis of 112 consecutive women with SUI and mixed incontinence by Jeffry and colleagues from 2002, the objective cure rate measured by clinical and urodynamic examination was 89.3% at a mean follow-up of 25 months. Objective cure was defined as no evidence of stress incontinence, a negative stress test result, and no urinary retention or PVR volume greater than 150 mL. No difference was found in the objective cure rate between patients with SUI and those with mixed incontinence. The overall subjective cure rate determined by the Contilife questionnaire was 66%. Subjective cure was lower than objective cure in both SUI patients and patients with mixed incontinence—69.3% and 54.2%, respectively. The type of incontinence did not alter the incidence of postoperative voiding difficulty. Ten of the 24 patients with mixed incontinence had persistence of the urgency component.

Holmgren and colleagues (2005) evaluated the outcome of the retropubic MUS in women with stress and mixed incontinence with mailed questionnaires 2 to 8 years postoperatively. This was a large cohort of 970 women, and the 78% response rate was remarkable; 580 women with stress incontinence and 112 women with mixed incontinence were eligible for analysis. However, urodynamic studies were not performed in these women, and therefore categorization of their incontinence was based only on a positive stress test result and a history of leakage immediately preceded by urgency. Specific questions regarding stress and urgency incontinence were posed, and respondents selected options including worsened, unchanged, improved, almost cured, and cured. For analysis, the women were grouped into cohorts by the number of years since they had undergone retropubic MUS surgery. The mean age of women with mixed incontinence was significantly greater than the mean age of women with stress incontinence (67 years vs. 61.2 years). Adjustment for age was made in the analysis. In addition,

women with mixed incontinence had a statistically significant higher body mass index (BMI), rate of cesarean delivery, history of radiation, and prevalence of urinary frequency than those with stress incontinence. The 580 women with genuine SUI had a durable 85% subjective cure rate after 3 and 8 years of follow-up. However, only 60% of the 112 women with mixed incontinence were cured 3 years after surgery, and outcomes declined steadily thereafter. By 6 to 8 years postoperatively, the cure rate in women with mixed incontinence was only 30%. In addition, urgency and episodes of urgency incontinence increased with time after the MUS. In the final analysis, the lower cure rate in the patients with mixed incontinence may be a result of the other variables in this population such as age, cesarean section, radiation, and higher BMI. These differences in the populations confound the ability to assess outcome and highlight the limitations of this study design. Overall, despite the population variables, early outcomes of MUS are good and equal in women with stress incontinence and those with urgency incontinence. The diminishment of results over time needs to be confirmed by a prospective study (Holmgren et al, 2005).

In a similar Finnish study, 191 women who had undergone MUS were evaluated by examination or telephone interview for outcome at a mean follow-up of 17 months (Laurikainen and Killholma, 2003). Sixty-four (34%) of these women had preoperative MUI. None of the women had preoperative urodynamic evaluation; instead, the preoperative diagnosis was based on symptoms. Cure after MUS was judged as self-report of being completely dry in any stress situation. At latest follow-up, 164 of the 191 patients were completely cured, for a cure rate of 87.7%. The cure rate in women with mixed incontinence was 69% compared with a cure rate of 97% in the women with genuine stress incontinence. This outcome difference was statistically significant. No difference in cure rate was found between women who had undergone concomitant surgery or MUS alone. Sixty percent of the women with mixed incontinence considered themselves improved from an urgency incontinence perspective as well. The lower cure rate in the mixed incontinent patients is not fully known. No description of the preoperative physical examination is given, and it is not known how many of them were among the 149 (78%) who had urethral hypermobility. The authors suggested that on the basis of these results, preoperative urodynamic studies should be performed in women with mixed incontinence before anti-incontinence surgery.

Segal and colleagues (2004) evaluated 98 women after MUS explicitly to answer the question of what happens to urinary urgency incontinence. The outcome of MUS procedures in women with mixed incontinence or significant stress incontinence with associated frequency and urgency was assessed retrospectively by a variety of methods: subjectively by patients' symptoms, by the rate of anticholinergic use before and after MUS, and by before and after QoL questionnaires. One strength of this study is that patients with concomitant surgery were excluded to minimize the confounding

effect of other causes on urinary urgency incontinence or frequency and urgency. Sixty-five women were identified as having urgency incontinence, and follow-up occurred at 3 months and 1 year. Several preoperative factors were looked at for risk of postoperative frequency, urgency, or urgency incontinence requiring anticholinergics. On the basis of preoperative subjective symptoms, the urgency component was found to be resolved in 63.1% after MUS. Two patients with complaints of urgency incontinence only but stress incontinence identified on urodynamic studies had persistent urinary urgency incontinence requiring anticholinergic drug treatment. Seventy-five patients had preoperative urinary frequency and urgency, which resolved in 57.3% after MUS. It is interesting to note that 30 (57.7%) of the 52 patients requiring anticholinergic medications preoperatively no longer needed medication after surgery. Only 4 (4.1%) patients needed anticholinergics for the first time after MUS. Of all the variables assessed as possible risk factors for postoperative OAB requiring an anticholinergic, only a history of prior anti-incontinence surgery was statistically significant. Patients with prior surgery were eight times more likely to have postoperative OAB requiring use of anticholinergics. Overall, the resolution of preoperative urgency incontinence was 63% and resolution of preoperative urinary frequency and urgency was 57.3%. Resolution based on no longer needing anticholinergic medication postoperatively was 57.7%. MUS surgery resulted in statistically significant improvement in QoL scores postoperatively in women with stress-predominant mixed incontinence and stress incontinence with urinary frequency and urgency (Segal et al, 2004).

Rezapour and Ulmsten (2001) reported their 5-year data on the efficacy and safety of MUS in women with mixed incontinence. In all of these women the urgency component was sensory, and no woman had urodynamic evidence of DO. Eighty women were evaluated and reported in a retrospective fashion. All had undergone urodynamic evaluation preoperatively and all were found to have stress incontinence as well as motor detrusor contractions during filling. At follow-up, 85% were reported as cured and an additional 4% had improved symptoms on the basis of pad testing and symptom questionnaire. The researchers concluded that urodynamic studies were essential before surgery to analyze presenting symptoms. Only one patient had prolonged retention (6 weeks), but 8% were found to have small hematomas and one patient required exploration for bleeding.

In 2008, Paick and colleagues reported short-term outcomes of retropubic and transobturator MUS surgeries in women with MUI. There was no significant difference in cure rates for SUI. Preoperative DO was an independent risk factor for treatment failure of the urgency incontinence component. Athanasiou and colleagues (2009) compared the efficacy of retropubic and transobturator MUSs for treatment of urinary incontinence in women with MUI and idiopathic DO. There were no subjective differences in outcome, yet women undergoing retropubic MUSs were less likely to have persistent DO postoperatively.

Kulseng-Hanssen and colleagues (2008) evaluated outcomes of retropubic MUS procedures in 1113 women with MUI based on the patient's predominant bothersome concern—that is, stress incontinence, urgency incontinence, or stress and urgency incontinence equally. There were no differences in cure rates among the three groups. Predominant stress incontinence had significantly better results at 7 and 38 months than the other two groups, especially the patients reporting mainly UII. Eleven percent of women had an increase in urgency incontinence 38 months after the sling procedure. The authors concluded that patients with predominant urgency incontinence have poorer results than those with predominant stress incontinence.

In a retrospective evaluation of long-term effects of retropubic MUS on OAB and urodynamic SUI, Leron and colleagues (2009) noted 88.7% cure and 9% improvement with 62.2% improvement in OAB symptoms. There was no change in severity of symptoms in a third of the patients. De novo OAB symptoms developed in 6.2%.

Using the AUA Symptom Index for measurement of outcomes, Ballert and colleagues (2008) found no difference in storage,

voiding, or total score between patients with SUI and those with MUI or those undergoing retropubic versus transobturator MUS. Sinha and colleagues (2008) used the Medical, Epidemiologic, and Social Aspects of Ageing (MESA) questionnaire and other outcome measures used by the British Society of Urogynaecology (BSUG) database for short-term evaluation of the retropubic MUS in women with MUI. Stress and urgency incontinence were either cured or improved in 78% and 75% of women, respectively. The postoperative global impression of outcome noted great or moderate improvement in 75% of patients and reduction in mean MESA scores of 69% ($P < .001$).

Duckett and colleagues (2008) used perineal ultrasonography in 77 women with DO and urodynamic stress incontinence to determine whether the position of a retropubic MUS has any effect on the resolution of irritative symptoms. They found that placement of the sling on any part of the urethra is not more likely to resolve irritative bladder symptoms.

Three studies have attempted to correlate preoperative variables with outcomes of retropubic MUS procedures in women with MUI (Duckett and Basu, 2007; Gamble and colleagues, 2008; Panayi et al, 2009). Duckett and Basu (2007) reported on correlation between preoperative pressure-flow studies and resolution of DO and OAB symptoms after placement of a sling. Pressure-flow studies were compared before and after the placement of the sling. Women with a Qmax significantly decreased after the sling surgery were more likely to have persistent OAB symptoms. The flow rate was significantly higher in women before the sling placement with an objective cure of DO after surgery than in those with persistent DO. The researchers felt that this supported an obstructive cause in women with persistent DO.

In 2008, Gamble and colleagues found that age, nocturia, maximum capacity, and choice of sling procedure (lowest rate of DO with transobturator MUSs, followed by retropubic MUSs and then PVSs) affected the persistence of DO and UII. Panayi et al (2009) found higher median preoperative opening detrusor pressure in women with DO postoperatively (33 cm H₂O vs. 26 cm H₂O, $P < .05$) after MUS surgery.

Four groups have discussed treatment of MUI with a transobturator sling (Botros et al, 2007; Paick et al, 2008; Tahseen and Reid, 2009; Abdel-Fattah et al, 2014). Botros and colleagues (2007) compared the resolution of DO, UII, and de novo urgency among the Monarc (125), Gynecare TVT (99), and SPARC (52) procedures. De novo urgency was significantly lower in the Monarc group (8% vs. 33% with the Gynecare TVT and 17% with the SPARC, $P = .04$), yet rates of resolution of DO, UII, and de novo DO did not differ among the three groups. Paick and colleagues (2008) placed 72 Gynecare TVT, 22 SPARC, and 50 transobturator slings in women with MUI. There were no significant differences in SUI cure rates or general urinary incontinence cure rates among the three slings. The presence of DO during preoperative urodynamic studies was associated with a high treatment failure of UII in all three groups. Tahseen and Reid (2009) performed a transobturator MUS procedure in 58 women and found a 77% SUI cure rate and 19% SUI improvement rate. In addition, UII was cured in 43% and improved in 36% of women with MUI. Twenty-one percent had persistent UII.

Overall, although most studies have reported that patients with genuine SUI have a higher cure rate than patients with MUI, MUSs do appear to be an effective treatment for incontinence. In addition, several studies have demonstrated improvement in OAB symptoms and less need for anticholinergic medications in patients with MUI after MUS surgery.

Outcomes of Midurethral Slings for Intrinsic Sphincteric Deficiency

A deficient sphincter mechanism is an important risk factor for failure of conventional anti-incontinence procedures. It is difficult to evaluate the efficacy of surgical treatment for ISD because no universally accepted definition presently exists. However, as previously stated in the PVS section, ISD is often defined uroynamically

as a leak point pressure less than 60 cm H₂O or an MUCP less than 20 cm H₂O. What is clear from the current literature is that the success of MUSs is lower in patients with a fixed urethra (no urethral mobility) and low leak point pressures. In addition, a preoperatively fixed urethra seems to be more predictive of a worse outcome (no cure) than a low leak point pressure. Patients with fixed urethras have poor outcomes after MUS surgery regardless of leak point pressure.

In 2001, [Rezapour and colleagues](#) published a prospective 4-year follow-up study of 49 women with ISD who underwent retropubic MUS procedures. Forty-one of these women had hypermobility of the urethra; the other 8 had immobile urethras. Postoperatively, 36 (74%) of patients were cured and 12% were improved; in 7 patients (14%) the procedure failed. It is important to note that none of the women with fixed urethras were cured; only 3 improved, and in 5 the procedure failed. Other studies support lower cure rates of retropubic MUS in women with low leak point pressures when rates of urethral hypermobility (fixed vs. nonfixed urethras) are not statistically different ([Paick et al, 2004](#)). Urethral mobility before MUS procedures has been shown to be predictive of success. The more the proximal urethra moves during Valsalva maneuvers, the better the cure rate for incontinence ([Fritel et al, 2002](#)). Leak point pressures alone have not been shown to predict outcome after a MUS procedure ([Gutierrez Banos et al, 2004](#); [Rodriguez et al, 2004](#)); therefore, **low leak point pressures are not necessarily a contraindication to retropubic MUS surgery**. Leak point pressures in the era of the MUS should be correlated with the patient's physical examination and used to counsel patients about their risk for a reduced chance of success.

A few more recent studies have also been performed to assess the clinical effectiveness of the retropubic MUS procedure in women with ISD ([Ghezzi et al, 2006](#); [O'Connor et al, 2006](#); [Bai et al, 2007](#); [Rechberger et al, 2009](#)). In all of these studies, patients were included with urodynamic stress incontinence from ISD, based on a Valsalva leak point pressure (VLPP) below 60 cm H₂O. Ghezzi and colleagues (2006) prospectively studied 35 patients and noted a 93.7% cure rate at 12.5 months' follow-up. Two of the three patients in whom the procedure failed were noted to have a fixed urethra preoperatively. In a retrospective study, Bai compared the treatment outcomes of the retropubic MUSs in patients with ISD (31 patients) and non-ISD (80 patients) SUI after 1-year follow-up. Whereas the 1-month follow-up found significant difference in cure rates between the ISD (87%) and non-ISD patients (100%), by 1 year after surgery there was no significant difference ([Bai et al, 2007](#)). [Rechberger and colleagues \(2009\)](#) conducted a prospective, randomized trial with a follow-up of 18 months comparing the clinical effectiveness of retropubic and transobturator MUSs. Although the efficacy of both techniques was comparable, the retropubic route was more efficient in the ISD group ([Rechberger et al, 2009](#)).

For transobturator MUSs, [Delorme \(2001\)](#) noted that 15.6% of his patients had ISD, and [Mellier and colleagues \(2004\)](#) diagnosed 28% of their patients with ISD. Despite these diverse populations of patients, relatively similar results were obtained. O'Connor and colleagues were the first group to examine the early outcomes of the transobturator approach for SUI in women with variable VLPP. Patients were divided into high (>60 cm H₂O) and low (<60 cm H₂O) categories based on VLPP. The odds of continued SUI after transobturator MUS surgery were 12 times greater for women with VLPP below 60 cm H₂O compared with those with VLPP above 60 cm H₂O ([O'Connor et al, 2006](#)). In general, no preoperative predictors of outcomes using either clinical or urodynamic parameters have been established to determine overall results of MUS procedures.

Even though the 2010 [Richter and colleagues](#) study comparing retropubic and transobturator slings was not designed to look at ISD, all the patients underwent preoperative urodynamic studies. The authors found that VLPP and MUCP had no effect on the outcomes of the sling surgeries. However, the authors did not look at the effect of urethral hypermobility on outcomes.

Overall, clinical experience with the MUS operation suggests that it is beneficial in the management of stress incontinence in

patients with ISD as long as there is preoperative urethral mobility. In addition, the absolute reported rates of cure and improvement for patients with ISD are within the range of reported results experienced with other types of procedures.

Outcomes of Midurethral Slings for Recurrent Stress Urinary Incontinence

There are limited data specifically addressing the efficacy of MUS procedures as secondary surgery in women with recurrent incontinence. Several small studies with relatively short follow-up could be found addressing the issue ([Azam et al, 2001](#); [Rezapour and Ulmsten, 2001](#); [Kuuva and Nilsson, 2002](#); [Lo et al, 2002](#); [Rardin et al, 2002a](#); [Kuuva and Nilsson, 2003](#)). Comparison of these studies is hampered by differences in the definitions used for cure, improvement, and failure and the methods of evaluating outcomes (objective, subjective, or both). Also, the population of patients in most studies of recurrent SUI may be biased by the inclusion of women in whom bulking agents had failed. Despite these limitations, cure rates of MUS surgery after prior failed anti-incontinence surgery range from 81% to 89.6%. With further review of these articles, several trends emerge. The procedure can be performed in the same way as it is performed for primary SUI. The complication rate is similar to that of retropubic MUSs done for primary SUI, but the risk of bladder perforation appears to be higher in women who have had one or more prior retropubic suspensions. Also, as is the case with primary surgery, the failure rate is higher in women with immobile urethras.

One of the longest follow-ups of women who underwent retropubic MUS procedures for recurrent incontinence is 4 years in a study by [Rezapour and Ulmsten \(2001\)](#). The 34 women studied had undergone 64 different anti-incontinence surgeries. Any patient with significant prolapse, DO, or ISD defined as MUCP of less than 20 cm H₂O was excluded. By physical examination, 24 women had a hypermobile urethra. Ten had a less mobile urethra, but none had a fixed urethra. The procedure was performed using the standard MUS technique, and only one bladder perforation occurred in a patient with a prior Marshall-Marchetti-Krantz (MMK) urethroplasty. No significant complications were encountered. Twenty-eight (82%) were cured by objective and subjective parameters; 3 (9%) were improved based on failure to achieve more than 90% improvement in QoL; and in 3 the procedures were failures. Postoperative voiding dysfunction was negligible with no change in PVR urine after 8 weeks. Long-term catheterization was not necessary in any patient. These results were durable up to 5 years.

Only a few small series present the outcomes of patients treated with a repeat MUS for recurrent SUI ([Riachi et al, 2002](#); [Villet et al, 2002](#); [Lee et al, 2007a](#); [Tsivian et al, 2007](#); [Biggs et al, 2009](#)). In these studies, the cure rates for patients with recurrent SUI are higher for retropubic slings than for transobturator slings. Tsivian found that in 12 patients with repeat MUS surgeries, the only procedure that failed was the transobturator MUS placement ([Tsivian et al, 2007](#)). Similarly, Lee found that the cure rate for the repeat transobturator approach was 62.5% as compared with 92.3% for the repeat retropubic sling procedure ([Lee et al, 2007a](#)). A possible explanation for this difference is the angle of the sling; specifically, the retropubic sling has a U shape, which may be more supportive and obstructive than the transobturator MUS. In addition, the out-to-in approach to the transobturator procedure may require wider dissection of the periurethral area, leading to future migration of the sling. Salvage procedures are performed in some women in whom the initial MUS failed because of underlying ISD or who now have a fixed urethra from the initial surgery. This is consistent with the evidence of high success with retropubic slings for patients with a component of ISD.

In 2010, [Stav and colleagues](#) reported the results of a retrospective analysis of outcomes in 1035 women after primary MUS surgery and 75 women after repeat MUS surgery ([Stav et al, 2010a](#)). The authors found that repeat MUS surgery was significantly less effective at curing incontinence than a primary sling (62% vs. 86%,

$P < .001$). The rates of complications were similar between the two groups; however, the repeat group had a significantly higher rate of de novo urgency and de novo urgency incontinence. All of the patients underwent preoperative urodynamic studies, and the rate of preoperative MUI was similar between the two groups. It is interesting to note that the rate of ISD was significantly higher in the repeat group preoperatively (31% vs. 13%, $P < .001$).

In 2013, [Agur and colleagues](#) performed a meta-analysis of the 10 randomized, controlled trials of MUSs that addressed recurrent SUI. The review included 350 women with a mean follow-up of 18.1 months. The authors found no significant difference in subjective cure rates in patients after retropubic versus transobturator MUS surgery.

KEY POINTS: MIDURETHRAL SLINGS FOR RECURRENT STRESS URINARY INCONTINENCE

- A repeat midurethral synthetic sling procedure for persistent or recurrent SUI is a viable option for select patients in whom the initial procedure has failed.
- Some studies show cure rates to be higher for retropubic slings than for transobturator slings. This may be the result of unequal rates of ISD in different study populations.

Outcomes of Midurethral Slings in Patients with Pelvic Organ Prolapse

A large proportion of women with stress incontinence have associated pelvic organ prolapse. Many studies have explored the outcomes of MUS surgery with concomitant pelvic organ prolapse surgery. The advantage of using a synthetic sling concomitantly with pelvic organ prolapse repair is that operative time is reduced and blood loss from the MUS portion is minimal compared with placement of autologous slings or retropubic suspensions. **Some of the theoretic risks of MUSs with concomitant transvaginal surgery are that the increased dissection will increase exposure of the graft, leading to greater rates of infection, perforation, or vaginal exposure, or that increased blood loss or anatomic distortion from the concomitant procedures could increase the rate of sling migration and postoperative voiding dysfunction or obstruction.**

Although most studies tend to be small and have short follow-up, **results suggest that the MUS can be added to prolapse surgery with minimal morbidity.** Success rates in combined MUS and prolapse repair vary from 72.7% to 93% ([Jomaa, 2001](#); [Huang et al, 2003](#); [Meltomaa et al, 2004](#); [Wei et al, 2012](#)). Even in questionnaire-based assessments 3 years after surgery, the data do not show a statistical difference in the cure rate of SUI and incidence of urgency symptoms after MUS surgery alone or in combination with other vaginal surgery ([Meltomaa et al, 2004](#)). However, transient urinary retention occurred more often in patients undergoing concomitant vaginal surgery, but urethrolysis rates were low and not statistically different between groups. Interpretations of rates of postoperative urinary retention are limited by variation in the definition of retention, and therefore caution must be exercised when reviewing outcomes.

[Gordon and colleagues \(2005\)](#) examined retropubic MUS surgery as a prophylactic procedure for stress incontinence in prolapse repairs. None of the patients had undergone prior incontinence surgery. With a mean follow-up of 14 months, no patient developed symptomatic stress incontinence, but 3 had a positive stress test result urodynamically. Six of 9 patients with preoperative urgency had persistent symptoms, and 4 (13.3%) developed de novo urgency without evidence of obstruction. No woman had urinary retention lasting more than 2 weeks.

Five-year data from a prospective analysis of a large group of women undergoing MUS surgery for occult stress incontinence combined with transvaginal repair of second- or third-degree prolapse showed a low incidence of complications ([Groutz et al, 2004](#)). The authors reported that 1 case of bladder perforation was managed conservatively without consequence. Two patients experienced extended voiding difficulty requiring catheterization for more than 7 days, but urethrolysis was not necessary in any case. Three cases of vaginal erosion were documented. Two patients developed recurrent symptomatic stress incontinence, and another 15 patients were found to have asymptomatic, urodynamically confirmed stress incontinence. Eight patients developed de novo urgency incontinence, and 72% of the 18 patients with preoperative urgency incontinence had postoperative persistent incontinence. The Cochrane Incontinence Group reviewed 22 randomized trials of surgical prolapse repair including 2368 women. They concluded that the addition of a retropubic MUS to endopelvic fascial plication, Burch colposuspension, and abdominal sacrocolpopexy may reduce the incidence of postoperative SUI, but issues of cost and associated adverse effects were unclear ([Maher et al, 2008](#)).

Although concurrent surgery does not appear to alter success of MUS, whether concurrent surgery alters the time to efficient voiding or incidence of urinary retention was examined separately in a retrospective study of 267 women (66% having concurrent prolapse repair) by [Sokol and colleagues \(2005\)](#). The authors noted that there was no significant difference in median days to voiding and rate of urinary retention based on prolapse repair status. However, increasing age, decreasing BMI, and postoperative UTI were independent predictors of time to adequate voiding. Only a previous history of incontinence surgery was an independent predictor of urinary retention. No statistically significant difference in the rate of urethrolysis between MUS alone and MUS with prolapse repair was found.

Unlike most other authors, [Partoll \(2002\)](#) claimed that urinary retention is far more common after combined procedures than MUS placement alone. Results showed a 94% cure rate at 11 months and an alarming 43% rate of urinary retention after concurrent anterior or posterior repair. However, in her study, urinary retention was defined as not meeting the criteria for catheter removal on postoperative day 2. The expectation of voiding efficiently within 48 hours of surgery, rather than the more lenient expectations in other studies, probably accounts for the higher rate of retention found in her study. Using Medicare claims data on a 5% national random sample of female beneficiaries who underwent sling procedures, [Anger and colleagues \(2008\)](#) reviewed 1356 sling cases. Of these, 467 (34.4%) included concomitant prolapse repairs. Women who underwent prolapse repair at the time of the sling surgery were significantly more likely to be diagnosed with postoperative outlet obstruction (9.4% vs. 5.5%, $P < .007$), but less likely to undergo a repeat procedure for stress incontinence or reoperation for prolapse within 1 year after sling surgery.

When MUSs are placed for urodynamic or occult SUI at time of prolapse repair, the risk of intervention because of obstruction is equivalent to the risk of intervention for SUI if no MUS was placed (8.5% and 8.3%, respectively) ([Ballert et al, 2009](#)). Also, the risk of intervention for stress incontinence in patients with clinical stress incontinence but no urodynamic or occult SUI and no MUS was 30%.

MUSs placed with either transvaginal or laparoscopic-assisted vaginal hysterectomy and anterior or posterior colporrhaphy have been shown to have success rates similar to those in published series of MUS surgery alone ([Huang et al, 2005](#)). Complication rates are also in accordance with other MUS series, with 2% bladder trocar injury, 11% postoperative urgency, and 11% postoperative voiding difficulty. A study specifically looking at the complications and cure rates of MUS performed with or without vaginal hysterectomy found that there was no overall difference ([Darai et al, 2002](#)). The MUS-hysterectomy group did have a trend toward more bladder perforation and lower postoperative urinary flow rates, but it was not statistically significant. Objective and subjective cures for this

group were 92.5% and 75%, respectively, which was not significantly different from the MUS-alone group.

In 2007, [Anger and colleagues](#) evaluated the relationship between provider specialty and outcomes of sling surgery, specifically related to concurrent prolapse management ([Anger et al, 2007b](#)). Using 1999 to 2000 Medicare data, the researchers found that 1063 sling procedures were performed by urologists, and gynecologists performed 246. Urologists performed concomitant prolapse repairs in 29.1% of cases versus 55.7% among gynecologists ($P < .0001$). Postoperatively, urologists were more likely to perform a repeat incontinence procedure (9.3% vs. 4.9%, $P = .024$) and prolapse repair (26.0% vs. 12.2%, $P < .0001$). These findings suggest that urologists should identify and manage prolapse at the time of evaluation of urinary incontinence to avoid the morbidity and cost of repeat surgery.

In 2012, Wei and colleagues presented their results of the Outcomes Following Vaginal Prolapse Repair and Midurethral Sling (OPUS) trial. This trial attempted to determine whether the use of a concomitant prophylactic anti-incontinence procedure (retropubic MUS) prevents the development of SUI in women undergoing prolapse surgery, and to evaluate the cost-effectiveness of this prophylactic approach. A sham incision was used in the control arm. A total of 327 women (no preoperative incontinence) completed follow-up at 1 year; the rate of patients with objective or subjective urinary incontinence was significantly higher in the sham group versus the MUS group (43.0% vs. 27.3%). The rates of trocar bladder injury, UTI, and bleeding, although low, were all significantly higher in the MUS group. It is our opinion that placement of a prophylactic MUS at the time of prolapse surgery should be performed only after thorough preoperative counseling regarding patient expectations and goals.

Outcomes of Midurethral Slings in Elderly Patients

Although there is a large body of literature that demonstrates the efficacy and low morbidity of MUSs, there is a paucity of data evaluating the effect of advanced age on outcomes. Aging affects the lower urinary tract both anatomically and functionally. The aging lower urinary tract has a higher rate of DO, urgency incontinence, and ISD. Emptying abnormalities related to impaired contractility are also more common in elderly persons. Older women are more likely to have had prior procedures for incontinence and therefore may have higher rates of urethral fixation. More severe vaginal atrophy related to long-standing lack of salubrious estrogen support of the vaginal tissues in the older woman could pose a greater risk of poor healing and exposure after vaginal incontinence surgery. In addition, older patients are generally considered poorer surgical candidates because of medical comorbidities that could complicate the surgery, the surgical outcome, or the postoperative course.

A few studies with relatively small numbers of patients have examined the safety and efficacy of MUSs in older women. In all these studies, "old" was defined as 70 years and older. The most robust of the studies was a prospective comparison of 460 consecutive women who underwent MUS surgery with a mean follow-up of 26 months by [Gordon and colleagues \(2005\)](#). In that study, 157 (34%) were elderly, and all women underwent urodynamic evaluations preoperatively and 3 months postoperatively. Preoperatively, a statistically significant greater prevalence of mixed incontinence was noted in the older (31%) versus younger (23%) patients. Intraoperative complications were infrequent, although there were significantly fewer bladder trocar injuries in the elderly population. The incidence of postoperative fever, UTI, wound infection, and hematoma formation was similar in the two groups. Older patients did experience some age-related morbidities such as pulmonary embolism (2), cardiac arrhythmia (2), DVT (1), and pneumonia (1), whereas younger patients had only 1 case of cardiac arrhythmia. Older women experienced no increased risk of vaginal exposure. The rates of postoperative voiding dysfunction necessitating catheterization for more than 1 week were low and similar between groups. Cure rates were similar between the elderly and

young patients (93% and 94%, respectively). Rates of urgency incontinence were similar between groups, but the rate of de novo urgency incontinence was significantly greater in the older patients (18% vs. 4%).

A similar rate of postoperative de novo urgency incontinence (18.4%) in elderly women undergoing MUS surgery was documented in a smaller study of 76 women ([Sevestre et al, 2003](#)). One strength of this study is that a description of the degree of urethral hypermobility was given. Of these women, 53% had urethral hypermobility defined by Q-tip test greater than 30 degrees, 28.9% had undergone prior incontinence procedures, and 4 (5.3%) showed urodynamic evidence of DO. At a mean follow-up of 24.6 months, 67% of the patients were cured as determined by questionnaire and examination. Ten procedures (13.2%) failed, and all of these patients had negative Q-tip tests preoperatively. Satisfaction with the procedure was 82%, and rates of dissatisfaction were higher in those with de novo urgency incontinence. For the older women with a negative Q-tip test, the cure rate was 71%, compared with 100% in women with a positive Q-tip test. The rate of immediate urinary retention was 26.3%, but only 1 patient had urinary retention for more than 1 week.

[Liapis and colleagues \(2006\)](#) also correlated the degree of urethral hypermobility and outcomes of MUS surgery in women aged 65 to 85 years. An overall cure rate of 76% was reported, with positive correlation to bladder neck mobility. In patients in whom the angle of displacement on the Q-tip test was less than 30 degrees, 42% became continent, whereas 90% were continent among those with an angle greater than 30 degrees. Among those in whom the angle was less than 10 degrees, 80% remained incontinent.

The success rates and complications after Burch colposuspension and MUS were compared in women over 70 years versus younger women ([Pugsley et al, 2005](#)). The cure rates were similar between the age groups. There was an increased incidence of UTI in the elderly Burch colposuspension and MUS patients. Women over 70 years required more long-term self-catheterization in the Burch colposuspension group.

The cure rates in older women with urethral hypermobility are comparable to those in younger women. Complication rates vary, with some studies citing a higher rate of age-related morbidities but no apparent increase in intraoperative complications. [Jha and colleagues \(2009\)](#) evaluated factors influencing outcome with retropubic MUSs and found that age did not significantly affect outcomes for stress incontinence reduction or improvement in QoL. Postoperative voiding dysfunction or increased de novo urgency do seem to be complications of greater incidence and significant impact in older women. Postoperative urgency symptoms in as many as 60% of women older than 70 years have been reported ([Allahdin et al, 2004](#)), and 44% developed the symptom de novo. [Bafghi and colleagues \(2005\)](#) noted cure rates among patients younger than 70 years of 97.5% versus 78.5% among patients older than 70 years ($P = .001$). The satisfaction among the younger group was also higher than in the older group: 92.6% and 66.7%, respectively. This difference was attributed to higher rates of de novo and persistent urgency incontinence in the over-75 years age group.

Another important measure of the success of the MUS in elderly patients is QoL assessments. The outcome of MUS surgery was assessed prospectively in older women at a mean follow-up of 22 months by a validated health-related QoL instrument, the King's Health Questionnaire ([Walsh et al, 2004](#)). The improvement in stress incontinence was greater in the age group younger than 70, which is not clearly attributed to any preoperative factor. Rates of preoperative DO were 24% versus 9% in older and younger women, respectively. Older women had a history of prior surgery more often than younger women (67% vs. 28%) and lower leak point pressures, but no specific comment on their physical examination findings and degree of urethral hypermobility was made. Although the outcome of MUS surgery was successful, the hospital course may be longer, as found by [Walsh and colleagues \(2004\)](#). The mean hospital stay in their series was 6 days, indicating that the postoperative morbidity in this age group was significant. The reasons for

the longer hospital stays were not given in this study. [Campeau and colleagues \(2007\)](#) compared elderly women who either underwent a Gynecare TVT procedure or had to wait 6 months for surgery, using QoL questionnaires. The women who underwent surgery had a significantly higher QoL ($P < .0001$), yet 22.6% experienced bladder perforation and 12.9% urinary retention.

[Hellberg and colleagues \(2007\)](#) used a mailed questionnaire for 970 consecutive MUS procedures performed from 1995 to 2001, to compare outcomes between women older than 75 years and younger women at a mean follow-up of 5.7 years. The older women were significantly more often on hormone replacement therapy, had lower education, and had a history of recurrent urinary infections, previous vaginal repair, and previous incontinence surgery. The elderly patients more commonly had mixed incontinence and required longer hospitalization postoperatively. The unfavorable cure rate among the older women (55.7% vs. 79.7%, $P = .0001$) was a result of a higher failure rate for stress incontinence rather than for urgency symptoms.

A multicenter, prospective randomized clinical trial was performed to compare MUS surgery versus no treatment in elderly women with SUI ([Campeau et al, 2007](#)). Campeau studied 69 women over the age of 70 years who consented to be randomized to undergo immediate MUS surgery or wait for 6 months before submitting to the same surgery (control group). The main outcomes measured included the I-QOL questionnaire, the Patient Satisfaction Questionnaire, and the Urinary Problems Self-Assessment Questionnaire. At 6 months after randomization, the group of elderly women who underwent immediate MUS surgery had significant improvement in QoL and patient satisfaction and fewer urinary concerns compared with the group of women waiting for the same surgery. It is important to note that no age-related morbidity was observed in the immediate surgery group.

Possibly because of preoperative factors such as MUI or even decreased urethral hypermobility, the rate of persistent SUI after retropubic or transobturator MUS procedures appears higher in the elderly population. In addition, the elderly population has a higher incidence of de novo urgency and urgency incontinence after MUS surgery. Also, although there may be some initial increase in perioperative morbidity in the elderly population, MUS surgery does appear to be safe. Lastly, while the literature is insufficient to support one anti-incontinence surgical procedure over another for the elderly woman, it can be concluded that **elderly women should not be excluded from potentially curative MUS surgery based on their age alone.**

Outcomes of Midurethral Slings in Obese Patients

Whether obesity affects surgical outcome with MUSs is controversial. Several studies have examined the safety and efficacy of MUS surgery in this population. In a prospective study of 242 women with SUI, women were stratified into three groups on the basis of BMI ([Mukherjee and Constantine, 2001](#)). The cure rate in obese women was 90% versus 95% in women with a BMI of 25 to 29 and 85% in those with a BMI less than 25. No women experienced a wound infection, and there was no higher rate of retropubic hematoma in obese women. In addition, obese patients undergoing MUS surgery did not demonstrate a statistically significant difference in the incidence of voiding dysfunction (de novo urgency symptoms, urgency incontinence, or voiding disorders).

Although few in number, studies with 6 to 12 months of follow-up support equal efficacy and no difference in postoperative complication rates. [Skriapas and colleagues \(2006\)](#) matched 31 women with BMI above 40 with 52 women with BMI below 30 and reported on their 18.5-month follow-up after MUS surgery. The continence rates among the morbidly obese group were not significantly different from the control group, 87% and 92% ($P = .0103$), respectively. The early postoperative complications were significantly higher among the morbidly obese patients. [Killingsworth and colleagues \(2009\)](#) reported on 127 overweight to obese women and concluded that success rates, patient satisfaction, and complications were not significantly different with increasing BMI. [Meschia](#)

[and colleagues \(2007\)](#) had similar findings to [Mukherjee and Constantine \(2001\)](#) and [Killingsworth and colleagues \(2009\)](#), with no differences in BMI of successes and failure, suggesting that MUS surgery could be confidently used in overweight women. [Muller and colleagues \(2007\)](#) reviewed randomized and retrospective clinical trials in the English MUS surgery literature from 1998 to 2006. Neither age over 70 years nor morbid obesity was a risk factor for failure of the MUS; however, there was an increase in de novo urgency among the elderly women and those with a BMI over 35.

[Hellberg and colleagues \(2007\)](#) conducted a questionnaire-based study including 970 consecutive MUS procedures performed from 1995 to 2001 to compare outcomes between women with a BMI above 35 ($n = 61$) and those who had normal weight at a mean follow-up of 5.7 years. There was a sharp decline in long-term cure rates between women with BMI below 25 and those above 35: 81.2% and 52.1%, $P < .001$. The obese women were significantly older, had a higher parity, were less educated, and more often had diabetes and chronic bronchitis. The women with normal weight had higher mean PVR volume postoperatively and required more adjustments of sling. The increased failure rate among the obese population was a result of low cure rates of both stress and urgency components.

Contrary to the findings of earlier studies by [Lovatsis and colleagues \(2003\)](#) and [Rafi and colleagues \(2003\)](#), [Stav and colleagues \(2010b\)](#) and [Greer and colleagues \(2008\)](#) found a higher rate of bladder trocar injury in nonobese patients during MUS surgery. **Overall, the rate of complications appears to be similar in obese versus nonobese patients undergoing MUS surgery.** In a review of the literature, only a retrospective study of 742 women (247 obese) undergoing vaginal surgery (55% MUS surgery) by [Chen and colleagues \(2007\)](#) showed a significantly higher rate of complications in obese patients (operative site wound infection: 7% vs. 2%, $P = .01$).

In further assessing the literature, most studies have consistently shown a lower cure rate in obese patients after MUS surgery, but only 3 of 16 studies showed a statistically significant worse outcome in obese patients. All 3 of those studies defined outcomes subjectively only. The largest of those series was a retrospective study by [Stav and colleagues \(2010b\)](#) of 741 obese (BMI above 25) and 371 nonobese women. The cure rate measured by validated questionnaires was significantly lower in the obese population (80% vs. 90%) at a mean follow-up of 50 months. Overall, although there is no definitive prospective randomized trial, it does appear that there is a consistently lower cure rate in obese women. However, MUSs are still an effective treatment in this patient population with relatively low morbidity. [Table 84-12](#) contains a review of the current literature.

KEY POINTS: MIDURETHRAL SLING SURGERY OUTCOMES IN PATIENTS WITH CONCOMITANT PROLAPSE REPAIR AND IN ELDERLY AND OBESE PATIENTS

- The literature supports the use of MUSs in a variety of special populations of patients. Efficacy and safety of MUSs are not compromised in the elderly, the obese, or those undergoing concomitant vaginal surgery.
- A few small studies suggest that concomitant vaginal surgery places a patient at higher risk for delayed return to normal voiding and urinary retention. However, limitations in the studies prevent comparison of the data.
- It is difficult to analyze the current sling data because of the lack of standard definitions of cure and improvement and lack of standard outcome measures.
- Absolute conclusions about the use of MUSs in special populations should not be made until larger prospective multicenter studies have been performed.

TABLE 84-12 Outcomes after Midurethral Sling Surgery in the Obese Population

AUTHOR	FOLLOW-UP (MONTHS)	PROCEDURE	BMI	N	CURE RATE	
					SUBJECTIVE	OBJECTIVE
Mukherjee and Constantine, 2001	6	RPS	<25	58	85%	
			25-29	98	95%	
			>30	87	89%	
Chung and Chung, 2002	12	RPS	<30	31	100%	
			>30	60	100%	
Rafii et al, 2003	(27)	RPS	20-25	86	74%	93%
			26-30	62	72%	89%
			>30	39	72%	82%
Lovatsis et al, 2003	6	RPS	>35	35	89%	
			<30	35	91%	
Skriapas et al, 2006	(18)	RPS	<30	52	92%	90%
			>40	31	87%	90%
Ku et al, 2006	(10)	RPS	18.5-23	81	93%	
			23-27.5	159	91%	
			>27.5	45	84%	
Hellberg et al, 2007	(68)	RPS	19-24	291	81%	
			>35	61	52% (s)	
Killingsworth et al, 2009	12	RPS	<25	68	81%	
			25-29.9	65	86%	
			≥30	62	82%	
Rechberger et al, 2009	18	RPS	<25	41	81%	
			25-29.9	80	80%	
			>30	80	68%	
		TOS	<25	43	86%	
			25-29.9	81	72%	
			>30	73	70%	
Stav et al, 2010b	(50)	RPS and TOS	<25	371	94%	
			>25	741	80% (s)	
Esin et al, 2011	12	TOS	<25	42	96%	92%
			>30	46	91%	91%
Haverkorn et al, 2011	(23)	TOS	<30	161	92%	
			>30	117	81% (s)	
Mohamad Al-Ali et al, 2013	12	RPS	<25	25	60%	76%
			25-30	33	61%	76%
			>30	35	49%	40%
Hwang et al, 2012	12	RPS	<22.9	90	94%	94%
			23-27.5	153	96%	97%
			>27.6	31	97%	97%
		TOS	<22.9	13	92%	100%
			23-27.5	33	94%	91%
			>27.6	3	67%	67%
Heinonen et al, 2013	(66)	TOS	<30	100	85%	
			>30	34	84%	
Moore et al, 2013	24	SS	<30	126		86%
			>30	62		81%

Parentheses connote mean or median values.

BMI, body mass index; RPS, retropubic midurethral sling; (s), statistically significant relationship with $P < .05$; SS, single-incision midurethral sling; TOS, transobturator midurethral sling.

Modified from Osborn DJ, Strain M, Gomelsky A, et al. Obesity and female stress urinary incontinence. *Urology* 2013;82:759–63.

Complications of Retropubic, Transobturator and Single-Incision Midurethral Slings

Over the past 10 years there has been a 27% increase in the rate of surgery for SUI, and a large portion of that increase is a result of the growing popularity of the MUS (Jonsson et al, 2012). However, in 2010 the FDA released a revised statement alerting the public to safety concerns regarding the use of synthetic mesh for pelvic organ prolapse and SUI surgery (U.S. Food and Drug Administration, 2010). The FDA became aware of problems related to synthetic mesh because of information contained in the Manufacturer and User Facility Device Experience (MAUDE) database. According to MAUDE data, from 2008 to 2010 there were 1371 voluntary and involuntary self-reported medical device reports of complications related to MUSs, and a significant portion of those were mesh perforation and exposure (U.S. Food and Drug Administration, 2011).

In general, complications associated with retropubic, transobturator, and single-incision MUSs appear to be within the acceptable range for incontinence procedures. However, it is important to remember that QoL is affected not only by the outcome of the incontinence surgery from the standpoint of cure or improvement but also by the appearance of voiding difficulties, UTIs, and other adverse consequences of the surgical procedure itself. The Finnish MUS registry demonstrated a pronounced learning curve for surgeons adopting the new MUS technology (Kuuva and Nilsson, 2003). This registry is unique in that all of the nation's MUS procedures are recorded in this data bank and therefore the results are reflective of the entire national experience with this new procedure. Another registry is also maintained in Austria and includes over 5000 cases, but it does not involve all surgeons in the country (Tamussino et al, 2001). Overall, the rate of complications associated with the MUS procedure is relatively low. The rates of bladder trocar injury in the two aforementioned national registries were 2.7% and 3.8%. The rates of voiding dysfunction and wound healing problems were 7.6% and 1%, respectively. A more comprehensive look at complications in randomized prospective trials and large retrospective studies is presented in Table 84-13 on the Expert Consult website.

As previously mentioned, the term *perforation* means that the polypropylene mesh has either entered the urinary tract (urethra, bladder, or ureters) or has penetrated bowel. The term *exposure* of mesh refers to the occurrence of visible or palpable mesh in the vagina or skin that is not covered by overlying tissue. For the purposes of this discussion, *trocar injury* refers to the passage of the trocar into the urethra or bladder at the time of sling placement.

The exact cause of these complications is debatable, but they likely arise from a combination of patient and technical factors. These factors include patient body habitus, subclinical infection, poor tissue ingrowth into the sling, disturbed wound healing, rolling or twisting of the sling, excessive friction between host tissue and the sling, sling material properties, and iatrogenic injury and surgeon technical error (Kobashi and Govier, 2003; Domingo et al, 2005; Stav et al, 2010b). Biomechanical properties of the sling material have also been shown to play a major role in the incidence of complications related to mesh exposure. Although various materials have been historically used for sling implants, there has been a trend in the contemporary literature toward the use of macroporous polypropylene slings. The increased pore size of these materials allows for excellent tissue ingrowth, promotes integration with the surrounding host tissues, and decreases encapsulation and infection (Dietz et al, 2001, 2003; Slack et al, 2005). Adherence to meticulous surgical technique and use of polypropylene mesh with favorable biomechanical properties should help the surgeon minimize complications.

Midurethral Sling Mesh Exposure

Vaginal mesh exposure is a rare complication after the MUS procedure (Fig. 84-12). In a review of prospective trials and large retrospective studies of MUS outcomes, the rate of vaginal mesh exposure was 0.5% to 8.1% (see Table 84-13 on the Expert Consult

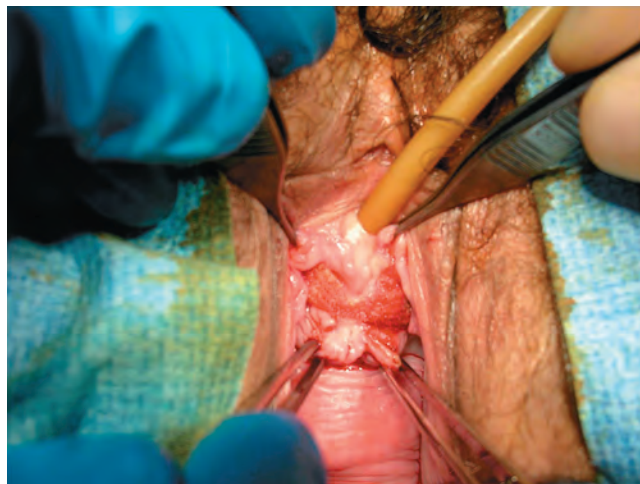


Figure 84-12. Vaginal mesh exposure.

website). Most cases of vaginal mesh exposure manifest within a few weeks to a few months after the MUS procedure. Symptoms of vaginal exposure include vaginal discharge (with variable constituents and different amounts of blood and inflammatory components), a palpable rough surface in the vagina, sexual discomfort (including partner related), pelvic pain, inguinal discomfort, and lower urinary tract symptoms (urgency, frequency, persistent incontinence, hematuria). Symptoms are often nonspecific, and therefore a high index of suspicion is required. In cases of mesh exposure, careful vaginal examination usually identifies an area on the anterior vaginal wall with separated epithelial edges and visible mesh. The management of this complication is not standardized, and there are various reports claiming successful outcomes with observation, partial sling excision, complete sling excision, and reapproximation of the vaginal mucosa over the exposed mesh (Table 84-14).

It appears that the material composition of mesh is particularly important in the event of mesh exposure. Domingo and colleagues (2005) reported a relatively high incidence of vaginal exposure in their series using either the ObTape or UraTape. They attributed their exposure rate to the characteristics of the particular mesh that they used, with the reduced pore size and other mechanical properties of that particular material. They noted a slightly increased risk of exposure with the ObTape, 19% versus 12% compared with the UraTape, and they felt that this was most likely because of reduction in pore size and a higher degree of encapsulation. They also concluded that synthetic mesh with larger pore sizes facilitates vascular and tissue ingrowth, optimizing mesh incorporation. In this series, sling exposure was usually managed by removal through the transvaginal approach alone or combined with the transobturator approach. They noted continence rates of 78% (despite mesh removal in their series). Other authors have also reported a high rate of vaginal exposure of up to 15% after ObTape or UraTape MUS surgery (Babalola et al, 2005; Domingo et al, 2005; Deval et al, 2006; Al-Singary et al, 2007; Dobson et al, 2007; Giberti et al, 2007; Juma and Brito, 2007; Karsenty et al, 2007).

Australasian data on exposures presented by Hammad and colleagues (2005) included 17 vaginal exposures. Thirty-five percent of the exposures were asymptomatic and identified by vaginal examination. Symptomatic patients reported palpable mesh, vaginal discharge, local pain, UTI, and dyspareunia.

Newer, macroporous polypropylene slings have a much lower incidence of exposure and infectious complications (Neuman, 2007; Waltregny et al, 2008; Lee et al, 2009; Rechberger et al, 2009). Of the 197 women who underwent placement of multifilament transobturator slings by Rechberger and colleagues (2009), 2.5% developed vaginal exposures. Two groups reported no evidence of mesh exposure at 1-year (Lee et al, 2009) and 3-year (Waltregny et al, 2008) follow-up. Waltregny and colleagues (2008) reported 1

TABLE 84-13 Review of Randomized Prospective Trials and Large Retrospective Studies for Midurethral Sling Complications

REFERENCE	PATIENTS	HEMATOMA OR SIGNIFICANT HEMORRHAGE	BLADDER OR URETHRA TROCAR INJURY	VAGINAL MESH EXPOSURE	MESH PERFORATION OF THE URETHRA	MESH PERFORATION OF THE BLADDER
Tamussino et al, 2001 ^a	RPS 2795	2.3%	2.7%	NR	NR	NR
Persson et al, 2002	RPS 38	5.3%	NR	2.6%	NR	NR
Ward and Hilton, 2002	RPS 175	2.3%	8.8%	2.3%	0%	0.6%
Liapis et al, 2002	RPS 36	0%	11.1%	NR	NR	NR
Kuuva and Nilsson, 2002 ^b	RPS 1455	2.4%	3.8%	0.7%	0%	0.5% ^c
Rechberger et al, 2003	RPS 100	4%	6%	0%	0%	0%
Levin et al, 2004	RPS 313	1.3%	5.1%	1.3%	0%	0.6%
Paraiso et al, 2004	RPS 33	5.5%	6.1%	3%	NR	NR
Abdel-Fattah et al, 2004	RPS 68	2.9%	0%	0%	0%	0%
David-Montefiore et al, 2006	RPS 42 TOS 46	4.8% 0%	9.5% 0%	NR	NR	NR
Lim et al, 2005	RPS 181	NR	5.5%	6.1%	NR	NR
Andonian et al, 2005	RPS 84	1.2%	23.8%	1.2%	NR	NR
Hammad et al, 2005 ^d	RPS 1459	NR	NR	1.2%	0.6% ^e	0%
Tseng et al, 2005	RPS 62	12.9% ^f	6.4%	8.1%	NR	NR
Foote et al, 2006	RPS 49	NR	10.2%	NR	NR	NR
Meschia et al, 2006	RPS 179	2.1%	3.2%	4.2%	NR	NR
Lord et al, 2006	RPS 301	3.3%	7.6%	NR	NR	NR
Wang et al, 2006	RPS 29 TOS 31	3.4% 0%	3.4% 0%	3.4% 0%	NR	NR
Tamussino et al, 2007	TOS 2543	3.3%	0.5%	0.4%	NR	NR
Zullo et al, 2007	RPS 35 TOS 37	2.8% 0%	5.7% 0%	0% 0%	NR	NR
Lee et al, 2007 ^b	RPS 60 TOS 60	0% 0%	3.3% 0%	0% 0%	0% 0%	0% 0%
Porena et al, 2007	RPS 73 TOS 75	1.4% 0%	2.7% 1.3%	1.4% 4%	0%	0%
Rinne et al, 2008	RPS 134 TOS 131	NR	NR	0% 0.8%	0%	0%
Rechberger et al, 2009	RPS 201 TOS 197	2.0 % 0%	6.5% 0%	2.0% 2.5%	0%	0%
Basu and Duckett, 2010	RPS 33 SS 37	NR	0% 2.7%	0% 5.4%	0%	0%
Richter et al, 2010	RPS 298 TOS 299	0.3% 0%	5.4% 0%	4% 1.3%	0% 0%	0% 0%
Hinoul et al, 2011	TOS 85 SS 75	1% 0%	0% 0%	1% 7%	0% 0%	0% 0%
Tincello et al, 2011	RPS 437 TOS 238 SS 659	2.1% 0.4% 0.1%	0.4% 0.4% 0.7%	1.5% 0.4% 1.2%	0%	0%

Continued

TABLE 84-13 Review of Randomized Prospective Trials and Large Retrospective Studies for Midurethral Sling Complications—cont'd

REFERENCE	PATIENTS	HEMATOMA OR SIGNIFICANT HEMORRHAGE	BLADDER OR URETHRA TROCAR INJURY	VAGINAL MESH EXPOSURE	MESH PERFORATION OF THE URETHRA	MESH PERFORATION OF THE BLADDER
Pushkar et al, 2011	RPS 187	9.1%	5.4%	0.5%	0%	0%
	TOS 537	1.5%	0.6%	1.5%		
Teo et al, 2011	RPS 66	1.5%	0%	5.3%	0%	0%
	TOS 61	1.6%	0%	2%		
Bianchi-Ferraro et al, 2013	TOS 54	0%	2.7%	0.5%	0%	0%
	SS 63	1.5%	3.0%	1.5%		

^aRetrospective study of gynecologists in Austria (one bowel perforation).

^bRetrospective survey of pelvic surgeons in Finland.

^cEight patients (nine patients had intravesical mesh recognized and removed at the time of sling surgery).

^dRetrospective survey of pelvic surgeons in Australia and New Zealand.

^eNine patients.

^fPostoperative suprapubic ultrasonography performed on all patients.

NR, no record or authors did not comment on this complication; RPS, retropubic sling; SS, single-incision sling; TOS, transobturator sling.

Modified from Osborn DJ, Kaufman MR, Dmochowski RR. Complications after surgery for stress urinary incontinence. Urologické Listy 2013;4: 39–44.

TABLE 84-14 Management of Vaginal Mesh Exposure

	TOTAL PATIENTS	CONSERVATIVE MANAGEMENT	FINAL MANAGEMENT	SYMPTOM RESOLUTION*	CONTINENT
Meschia et al, 2001	2	0%	2 resutured vagina	100%	100%
Kuuva and Nilsson, 2002	10	30%	4 resutured vagina 3 observation 2 partial mesh excision 1 unknown	NR	NR
Volkmer et al, 2003	1	0%	1 partial mesh excision	100%	0%
Karram et al, 2003	3	33%	1 partial mesh excision 1 vaginal advancement flap 1 antibiotics	100%	67%
Kobashi and Govier, 2003	4	100%	4 observation	NR	100%
Tsivian et al, 2004	5	20%	4 partial mesh excision 1 observation	100%	80%
Levin et al, 2004	4	0%	4 partial mesh excision	NR	NR
Sharma and Oligobo, 2004	3	0%	3 partial mesh excision	100%	NR
Huang et al, 2005	6	0%	6 partial mesh excision	100%	100%
Hammad et al, 2005	17	0%	17 partial mesh excision	65%	NR
Starkman et al, 2006	11	0%	11 partial mesh excision	100%	NR
Giri et al, 2007	5	0%	5 resutured vagina	100%	NR
Ordorica et al, 2008	11	0%	11 complete mesh excision	100%	82%
Lapouge et al, 2009	12	0%	12 partial mesh excision	83%	33%
Al-Wadi and Al-Badr, 2009	1	0%	1 partial mesh excision and Martius flap	100%	100%
Hinoul et al, 2011	7	0%	7 resutured vagina	100%	NR
Teo et al, 2011	3	0%	2 resutured vagina 1 partial mesh excision (failed resuturing twice)	100%	NR
Bianchi-Ferraro et al, 2013	3	33%	1 resutured vagina 1 partial mesh excision 1 topical conjugated estrogen	100%	NR

*Most common presenting symptoms were vaginal pain, dyspareunia, palpable mesh, urinary tract infection, and vaginal discharge. NR, not recorded.

intraoperative vaginal sulcus laceration, which was closed uneventfully. Lee and colleagues (2009) proposed that a modified canal transobturator sling (creating a suburethral tunnel between two oblique lateral incisions in the anterior vaginal wall) decreases the incidence of vaginal exposure compared with the classic single midline incision. The value of this technique needs to be confirmed by a randomized control trial.

Chen and colleagues (2008) analyzed risk factors associated with vaginal exposure (6 of 239 patients, 2.5%) after synthetic sling placement. Women with diabetes were 8.3 times more at risk of developing vaginal exposure after synthetic sling placement. The vaginal exposure-free rate during the 24-month follow-up increased significantly in women with diabetes and type III multifilamentous polypropylene slings (intravaginal slingplasty). These authors encourage counseling women with diabetes of the risk of exposure.

Management of Midurethral Sling Mesh Exposure. Management of mesh exposure is within the scope of practice of most pelvic surgeons; however, mesh perforation of the bladder or urethra may require a tertiary referral. Some authors propose observing any exposure of mesh that is less than 1 cm because the area may heal spontaneously with mixed results (Kobashi and Govier, 2003; Tijdink et al, 2011). In the Kobashi and Govier study,

one Gynecare TVT and three SPARC patients with vaginal exposure were treated in a conservative fashion. All patients were observed with serial physical examinations and all patients had spontaneous re-epithelialization of the mesh at 3 months. The authors attributed their success to the macroporous characteristics of the polypropylene mesh, which facilitated excellent tissue ingrowth. Conservative management is less likely to be successful with older, less used sling materials such as Gore-Tex, polyethylene terephthalate, and silicone (Kobashi et al, 1999). In general, small areas of mesh exposure should be treated with sequentially increasing invasiveness. The first treatment should involve observation and then the addition of conjugated estrogen and possibly antibiotic creams. The next step should be limited excision and trimming with vaginal closure. If these options fail, excision of most of the mesh from a transvaginal approach should be pursued in most cases. Table 84-14 reviews the management of mesh exposure in the literature.

In a review by Huang and colleagues (2005), six vaginal exposures and one bladder perforation after polypropylene synthetic sling placement were initially expectantly managed. In four patients with vaginal mesh exposure of less than 1 cm, conservative management was initiated for a 3-month period. One of these patients was observed for 24 months without adverse sequelae. In contrast with the results seen by Kobashi and Govier (2003), none of the patients

in this review had vaginal epithelialization over the area of exposure. Therefore, all six patients underwent transvaginal mesh excision in conjunction with an excision of all fibrotic vaginal tissue. Symptoms resolved in all patients, and all patients were continent at their last follow-up. Although all patients ultimately required surgical intervention, the authors felt that a trial of conservative management in appropriately selected patients (i.e., exposure less than 1 cm) was reasonable, and that if no epithelialization occurs at 3 months of follow-up, the mesh should be surgically removed.

Depending on the preference of the surgeon and the size of the exposure, if conservative measures fail, the next step for intervention should be operative management. In the series reported on by [Tijdkink and colleagues \(2011\)](#), of 48 patients with mesh exposure, only 6 had persistent exposure after partial mesh excision. **Operative management typically involves excision of the exposed mesh, thorough irrigation with antibiotic solution, and closure of vaginal flaps.** The addition of topical antibiotics and conjugated estrogen cream may theoretically improve tissue quality before surgical intervention.

In a review of mesh-related complications in a series of 200 patients, [Tsivian and coworkers \(2004\)](#) observed five vaginal sling exposures. Four patients required surgical excision of the exposed mesh, and one asymptomatic patient was being observed conservatively without adverse outcomes. Exposure resolved in all patients after partial mesh excision and judicious vaginal debridement.

In the Finish nationwide review of 1455 MUS procedures, 10 patients were identified with vaginal polypropylene sling exposure. Three of these patients were managed without surgical intervention with good results and maintenance of continence ([Kuuva and Nilsson, 2002](#)). Four patients had the vaginal mucosa resutured over the exposed mesh, and two patients required partial mesh excision. One patient was lost to follow-up and management was unknown at the time of their report. According to this national registry, continence was maintained in all patients, regardless of the management.

Among 166 MUS surgeries performed by [Giri and colleagues \(2007\)](#), 5 patients (3%) developed vaginal exposure 4 to 40 months postoperatively. Patients reported vaginal discharge, pain, bleeding, and dyspareunia. In the operating room, the eroded margin of vaginal mucosa was trimmed and closed over the mesh. All of the patients were subsequently symptom free at 12-month follow-up.

[Ordorica and colleagues \(2008\)](#) reported on 11 vaginal exposures after nonautologous sling placement (33 retropubic, 2 bone anchors, 3 transobturator tape). In all cases, involved sling and suture were excised. The bone anchors were unable to be removed. An autologous sling was placed in the same setting if the patient complained of SUI at presentation. Two patients had recurrent or persistent SUI, 2 had de novo urgency or frequency, and 1 developed osteitis pubis.

The sexual function of women after correction of exposure from a MUS was determined using a validated questionnaire (Female Sexual Function Index [FSFI]) by [Kuhn and colleagues \(2009b\)](#). Among 21 exposures, 3 healed with topical estrogen and 18 patients with larger defects required operative intervention. Initially, vaginal closure was attempted, but 2 patients had recurrent exposure. One patient had repeat vaginal closure, and the other had partial sling excision and vaginal closure. The domains of desire, arousal, lubrication, satisfaction, and pain improved significantly. Orgasm remained unchanged.

Midurethral Sling Trocar Injury to the Urinary Tract

In most studies in the literature, results listed for perforation (or injury) of the bladder or urethra refer to trocar passage into the urinary tract at the time of surgery. In these studies, the trocar injury is recognized at the time of surgery and the trocar is passed again and the surgical case is continued. Trocar injury is generally thought of as a benign condition, and no study has shown a link between trocar injury and perioperative hemorrhage, hematomas, or subsequent mesh perforation of the bladder or urethra. Because of the nature of trocar passage, the rate of trocar injury is

KEY POINTS: MIDURETHRAL SLING MESH EXPOSURE

- Conservative management seems to be a plausible option in well-selected patients who are relatively asymptomatic and have small-caliber exposures (<1 cm). Good results have also been observed in selected patients with vaginal advancement flaps and suture approximation of the debrided vaginal mucosa over the exposed mesh.
- Even with partial excision of the mesh, continence is maintained in the majority of patients.
- Observation should never be considered when there is urethral or intravesical perforation. More data supporting specific management strategies are necessary before a given approach can be advocated for patients with this complication.
- We recommend initial judicious observation for small vaginal exposures (with use of topical conjugated estrogen cream when appropriate). Excision should be reserved for failure of conservative therapy or when local symptoms mitigate against observational management (e.g., bothersome dyspareunia).

generally lower with transobturator versus retropubic MUSs. The rate of bladder or urethral trocar injury at the time of retropubic MUS surgery in randomized trials falls between 2.7% and 23.8% ([Andonian et al, 2005](#); [Porena et al, 2007](#)).

Although initial reports described the risk with the transobturator MUS approach as being negligible, the rate of bladder or urethral trocar injury at the time of transobturator MUS surgery in randomized studies falls between 0% and 1.3% ([Porena et al, 2007](#); [Richter et al, 2010](#)) (see [Table 84-13](#) on the Expert Consult website). In 2004, [Minaglia and colleagues \(2004\)](#) reported three cases of intraoperative bladder injury while performing the transobturator insertion method. They identified all injuries intraoperatively because of their use of cystoscopy as an adjunct to all insertion procedures. All injuries were managed with catheter placement for 1 week postoperatively, and these authors noted no complications after sling removal and reinsertion at that same setting. It is possible that bladder trocar injuries are more likely to occur with out-to-in transobturator slings. With 10 of 11 bladder injuries occurring with the out-to-in technique in their study, [Tamussino and colleagues \(2007\)](#) concluded that trocar injury was more likely with this method.

Midurethral Sling Mesh Perforation of the Urethra

Urethral mesh perforation is defined as presence of sling material within the urethral lumen ([Fig. 84-13](#)). The incidence of urethral

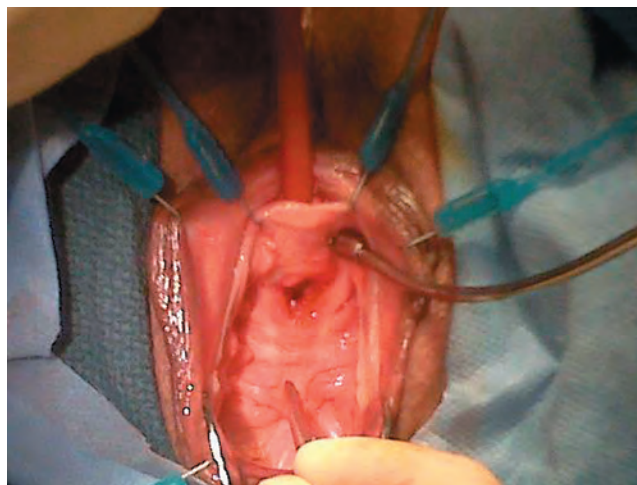


Figure 84-13. Urethral mesh perforation and urethrovaginal fistula.

perforation following MUS (transobturator and retropubic) surgery was 0% to 0.6% in a review of randomized prospective and large retrospective studies (see Table 84-13 on the Expert Consult website). Factors thought to contribute to urethral perforation include compromised urethral blood supply (e.g., from radiation therapy or estrogen deficiency), excessive sling tension, extensive dissection too close to the urethra with subsequent urethral devascularization, iatrogenic urethral injury (at time of device insertion), and traumatic urethral dilation. Furthermore, twisting or rolling of the sling can create a ridge that leads to pressure necrosis and perforation through the urethra (Dell and O'Kelley, 2005). Management of this complication is extremely challenging with the possibility of significant morbidity, because access to the sling is traditionally gained by incising the urethra, although endoscopic management has been attempted.

Presenting symptoms are variable. In almost all published cases, voiding dysfunction is predominant, with typical symptoms including urgency, urgency incontinence, obstructive voiding, urinary retention, history of self-catheterization, urethral dilations, recurrent UTI, and persistent urinary incontinence (Haferkamp et al, 2002; Madjar et al, 2002; Pit, 2002; Sweat et al, 2002; Lieb and Das, 2003; Vassallo et al, 2003; Glavind and Sander, 2004; McLennan, 2004; Tsivian et al, 2004; Wai et al, 2004). Diagnosis is often delayed in these patients for an extended period of time. In a review by Amundsen and colleagues (2003), the average time from placement of the initial PVS to diagnosis of urethral perforation was 9 months.

Confirming the presence of the mesh within the urethral lumen during cystoscopy makes diagnosis. Voiding cystourethrography has also been useful adjunctively by documenting a dilated proximal urethra related to high-grade obstruction caused by the eroded sling (Lieb and Das, 2003). A review of urethral perforation management is presented in Table 84-15.

Nine urethral perforations (0.6%) were reported in the Australasian data presented by Hammad and colleagues (2005). Thirty percent of these perforations manifested more than 1 year after surgery, and 89% were symptomatic. Presenting symptoms included urinary retention, bleeding, and local pain. One case was discovered incidentally on cystoscopy. Unlike the reported vaginal exposures, 33% of the urethral perforations occurred when the polypropylene sling procedure followed another anti-incontinence procedure. Four (44%) were managed conservatively (two patients were too frail to undergo operative intervention). Five patients (56%) had transvaginal excision. All five who underwent excision were cured and dry.

Management of Midurethral Sling Mesh Perforation of the Urethra. Multiple studies have reported the successful treatment of urethral mesh perforation endoscopically (see Table 84-15). Although we prefer transvaginal surgical excision as a first-line treatment, endoscopic management of small areas of mesh perforation appears to be a reasonable initial option based on a review of the literature. If endoscopic treatment fails, the next step in management of urethral mesh perforation typically involves transvaginal urethrotomy and excision of the perforated mesh. An autologous fascial sling or a Martius labial fat pad graft can be used at the discretion of the surgeon.

For endoscopic management, McLennan successfully managed a MUS urethral perforation endoscopically (2004). Hysteroscopic scissors were used to transect the mesh flush with the urethral mucosa. Catheter drainage was continued postoperatively for 72 hours. The patient remained symptom free and continent at 10 months of follow-up. Wijffels and colleagues (2009) used an endoscopic transurethral approach successfully in three cases of urethral perforation. The visible mesh was grasped with forceps and cut while on traction with scissors. This was performed on both sides of the urethra. One patient had recurrent SUI and had another MUS placed. Baracat and colleagues (2005) successfully used a similar approach for five urethral perforations.

In our opinion, although it is easy to ablate or remove a small portion of perforated mesh endoscopically with the aid of a holmium laser or endoscopic scissors, these patients are likely

to experience recurrence and need further surgeries. Endoscopic excision does not release the tension on the mesh that may be contributing to the perforation and does not provide any interposing tissue. For surgical excision, we will often remove the mesh so that it is no longer in close proximity to the bladder and no longer under tension. The approach and type of incision depend on the location of the perforation.

Other authors have described transvaginal excision of perforated mesh. In 2002, Pit described the management of two cases of urethral perforation. In both these cases the urethra was incised and the mesh was cut at the level of the mucosa. The mesh was then dissected on its medial edge toward the inferior ischiopubic ramus and cut bilaterally, which allowed the mesh to be removed from the periurethral fascia. A Martius graft was placed over the urethra in one case and a cadaveric fascia lata graft was used in the second case. A second MUS was then placed over the tissue bolsters without complication.

Glavind and Sander (2004) reported a urethrovaginal fistula caused by urethral perforation of the polypropylene mesh. Transvaginal mesh excision failed to resolve the fistula, and the patient required two transabdominal fistula repairs until closure was achieved and symptom resolution occurred. Persistent stress incontinence was managed by conservative means with satisfactory results. Sokol and Urban (2008) reported use of the internal urinary sphincter for covering the defect after sling resection. They suggested that this may reduce the risk of fistula formation and be a less morbid option than a Martius flap. Four other additional case reports reported excellent results with use of a midline transvaginal approach with partial mesh excision and closure of the urethra (Haferkamp et al, 2002; Madjar et al, 2002; Lieb and Das, 2003; Wai et al, 2004). The postoperative results reported by each of these investigators were excellent, with all patients achieving symptom resolution after surgical intervention. In two patients, mild recurrent stress incontinence was successfully managed with biofeedback (Glavind and Sander, 2004; Wai et al, 2004). In two patients, continence was achieved with an intraoperative fascial sling, and in a single case, a postoperative fascial sling resulted in satisfactory continence (Vassallo et al, 2003; Wai et al, 2004).

For slings that perforate into the urethra, we prefer an inverted-U incision because this allows for exposure of the proximal urethra, bladder neck, and endopelvic fascia as well as providing a vaginal epithelial flap that avoids overlapping suture lines, theoretically decreasing the risk of a fistula. The distal portion of the inverted U should be distal to the site of the urethral perforation, and the proximal portions of the U incision should extend to the level of the bladder neck in most cases. We will often use a Martius labial fat pad flap to further prevent fistula formation. A PVS is routinely placed if dissection of the sling out of the urethra creates a large defect or a defunctionalized urethra. Mesh excision is typically carried out to the level of the pubic bone or ischiopubic rami. This type of excision leaves behind the arms of the mesh that tunnel into the retropubic space or obturator fossa. It is typically not necessary to enter these spaces because the mesh at this location is no longer under tension and is far from the urethra. We typically leave a Foley catheter for 3 weeks after repair of the urethra.

Midurethral Sling Mesh Perforation of the Bladder

The finding of synthetic mesh within the lumen of the urinary bladder is another particularly distressing complication (Fig. 84-14). This complication is rare after the MUS procedure and, based on a review of the literature (see Table 84-13 on the Expert Consult website), when this complication is reported the incidence falls between 0.5% and 0.6% (Kuuvva and Nilsson, 2002; Ward and Hilton, 2002). The majority of intravesical mesh perforations are most likely the result of an unrecognized cystotomy or placement of the mesh within the urinary bladder at the time of surgery. True migration of the mesh across the seromuscular wall of the bladder into the lumen is much less likely. Thus, performing a complete and thorough cystoscopic examination of the bladder

TABLE 84-15 Management of Mesh Urethral Perforation

	TOTAL PATIENTS	CONSERVATIVE MANAGEMENT	FINAL MANAGEMENT	SYMPTOM RESOLUTION*	CONTINENT
Pit, 2002	2	0%	2 transvaginal partial mesh excision, reconstruction, Martius flap, and MUS	100%	100%
Haferkamp et al, 2002	1	0%	1 transvaginal partial mesh excision and reconstruction	100%	100%
Sweat et al, 2002	2	0%	1 transvaginal near-complete mesh excision and reconstruction and Martius flap 1 transvaginal retropubic near-complete mesh excision and reconstruction	NR	100%
Madjar et al, 2002	1	0%	1 transvaginal partial mesh excision and reconstruction	100%	100%
Lieb and Das, 2003	1	0%	1 transvaginal partial mesh excision and reconstruction	NR	0%
Vassallo et al, 2003	1	0%	1 transvaginal partial mesh excision and reconstruction	100%	100%
Wai et al, 2004	1	0%	1 endoscopic and transvaginal partial mesh excision and reconstruction.	100%	0%
Glavind and Sander, 2004	1	0%	1 transvaginal partial mesh excision and reconstruction	0%	0%
Baracat et al, 2005	5	0%	5 endoscopic partial mesh excision	100%	100%
Hammad et al, 2005	9	44%	5 transvaginal partial mesh excision and reconstruction 4 observation	NR	NR
Starkman et al, 2006	5	0%	3 transvaginal partial mesh excision, reconstruction, and PVS 2 transvaginal partial mesh excision and reconstruction	100%	100%
Powers et al, 2006	2	0%	2 transvaginal partial mesh excision and reconstruction	50%	100%
Mesens et al, 2007	1	0%	1 transvaginal partial mesh excision and reconstruction	100%	100%
Sokol and Urban, 2008	1	0%	1 transvaginal partial mesh excision and reconstruction	100%	100%
Velemir et al, 2008	8	12%	2 transvaginal partial mesh excision and reconstruction 4 endoscopic partial mesh excision 1 endoscopic and transvaginal partial mesh excision and reconstruction 1 observation	88%	50%
Wijffels et al, 2009	3	0%	3 endoscopic partial mesh excision	100%	67%
Jo et al, 2011	3	0%	2 endoscopic partial mesh excision 1 endoscopic and transvaginal partial mesh excision and reconstruction	100%	67%
Shah et al, 2013	14	0%	8 transvaginal and retropubic complete mesh excision and reconstruction 6 transvaginal partial mesh excision and reconstruction	100%	72%

*Most common presenting symptoms were urinary tract infection, urethral obstruction, urge urinary incontinence, pain, incontinence, urgency, dysuria, and hematuria.

MUS, midurethral sling; NR, not recorded; PVS, pubovaginal sling.

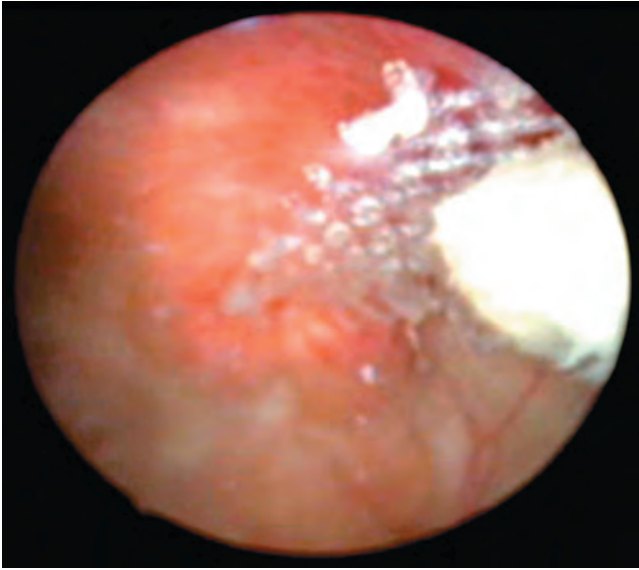


Figure 84-14. Cystoscopic view of intravesical retropubic sling perforation.

with adequate hydrodistention is critical to minimize this complication. We have found that the trocar may sometimes telescope the bladder wall during insertion and obscure visible bladder perforation. A review of urethral perforation management is presented in Table 84-16.

Patients typically report a variety of symptoms after their MU procedure. A review of seven reported cases in the literature by [Negoro and colleagues \(2005\)](#) found that the typical symptoms are lower abdominal pain, intermittent gross hematuria, recurrent UTI, urgency, frequency, dysuria, and urinary incontinence. Diagnosis is made by cystoscopic examination of the bladder. Imaging modalities such as computed tomography scans and cystography may help in difficult cases but are not a substitute for cystoscopic examination.

Theoretically, transobturator slings should have a lower rate of mesh perforation into the bladder than retropubic slings. However, [Parekh and colleagues \(2006\)](#) reported a case of intravesical mesh perforation after transobturator sling placement and cystocele repair. The patient did not undergo cystoscopy intraoperatively. She initially had mesh on the left side of the bladder, then 6 months later had sling material on the right side of the bladder. She underwent a successful transurethral, transvaginal, and suprapubic mesh resection.

Management of Midurethral Sling Mesh Perforation of the Bladder. Observational treatment is not recommended for mesh perforation of the bladder because the mesh often becomes encrusted, leading to stone formation, persistent lower urinary tract storage and voiding symptoms, recurrent UTI, and intermittent gross hematuria. Different techniques and surgical approaches have been advocated with varying levels of invasiveness, complexity, and success.

For small areas of mesh perforation, the literature supports endoscopic excision with scissors or ablation with the holmium laser as an appropriate initial step. [Oh and Ryu \(2009\)](#) evaluated the efficacy of transurethral resection in 14 patients with intravesical mesh. The intravesical mesh was resected deep into the perivesical fat. The patients had dysuria, hematuria, pelvic pain, and urgency. Six patients had stone encasing the mesh at the time of transurethral excision. With a mean follow-up of 18 months, 13 (92.9%) patients had their mesh completely removed endoscopically with no recurrence. One patient had recurrent bladder stones. One patient had mild SUI and UII, which were controlled with anticholinergics. No further treatment for SUI was performed.

In a case report, [Jorion \(2002\)](#) excised the mesh endoscopically using an offset nephroscope transurethrally and a 5-mm laparoscopic trocar placed suprapubically. Laparoscopic grasping forceps were used to grasp the mesh, and endoscopic shears excised the mesh flush with the bladder mucosa, allowing the mesh to be easily removed. Cystoscopy at 1 month revealed healed mucosa, and the patient was continent and symptom free. In another report by [Tsivian and coworkers \(2004\)](#), the mesh was initially cut endoscopically, but because of an adherent calculus, the mesh could not be extracted endoscopically. Therefore a suprapubic approach was required to remove the stone and intravesical mesh.

Holmium:yttrium-aluminum-garnet (Ho:YAG) laser excision (or vaporization) of encrusted intravesical MUS has been successful in numerous cases ([Hodroff et al, 2004](#); [Barakat et al, 2005](#); [Giri et al, 2005](#); [Lane et al, 2005](#); [Huwyler et al, 2008](#); [Shrotri et al, 2010](#)). Patients often have bladder stones that have formed on the intravesical portions of the sling. For this problem, [Irer and colleagues \(2005\)](#) and [Mahmoud and Wadie \(2007\)](#) described successful endoscopic laser lithotripsy of the calculi and transurethral resection of the sling material. We reserve endoscopic (holmium laser) management of intravesical mesh perforation for very small areas of perforation in select patients.

After endoscopic excision fails or as an initial treatment, mesh perforated into the bladder can be removed from a transvaginal or retropubic approach. For slings that perforate into the bladder at or below the trigone, we prefer an inverted-U incision similar to the aforementioned management of urethral perforation because this allows for exposure of the proximal urethra, bladder neck, and endopelvic fascia as well as providing a vaginal epithelial flap that avoids overlapping suture lines, theoretically decreasing the risk of a fistula. Similar to the management of urethral perforations, we do not excise the entire sling as long as it is no longer under tension and is far from the bladder.

For slings that perforate the bladder dome or other areas of the bladder not accessible from a transvaginal approach, we remove the mesh transabdominally. The sling can usually easily be seen entering the bladder in the retropubic space. Although not always necessary, opening the bladder in the midline usually aids with closure and identification of the exact area of bladder perforation. In general, reconstruction should involve nonoverlapping suture lines and interposition of tissue such as a labial fat pad, greater omentum, or autologous fascial sling.

In a report by [Negoro and colleagues \(2005\)](#), a retropubic approach was used to resect the intravesical portion of the mesh. The bladder was closed with absorbable suture, and catheter drainage was maintained postoperatively. The patient was symptom free and continent at 10-month follow-up. [Volkmer and colleagues \(2003\)](#), [Sweat and colleagues \(2002\)](#), and [Huang and colleagues \(2005\)](#) used a combined transvaginal and abdominal approach to remove the sling in its entirety. One patient had residual urgency and frequency treated with anticholinergics; the other patients had resolution of symptoms but recurrent stress incontinence managed with collagen in one and pelvic floor muscle training and estrogen in the remaining two.

There are several reported cases of successful laparoscopic removal of intravesical mesh after retropubic sling placement. One of these cases used a three-port intraperitoneal approach ([Siow et al, 2005](#)), and the other two used a three-port extraperitoneal approach ([Rehman et al, 2008](#)). All the patients were symptom free and dry after the mesh removal.

Infection and Pain after Midurethral Sling Surgery

Groin and suprapubic pain are potential problems after MUS placement. Thigh and groin pain appear to be more commonly associated with the transobturator approach. A randomized controlled study from Finland ([Laurikainen et al, 2007](#)) revealed that 16% of women in the transobturator (in-to-out) group had groin pain compared with only 1.5% of those in the retropubic MUS arm. In addition, it appears that groin pain persists longer after the transobturator MUSs ([Daneshgari et al, 2008](#)). [Long and colleagues](#)

TABLE 84-16 Management of Mesh Bladder Perforation

	TOTAL PATIENTS	CONSERVATIVE MANAGEMENT	FINAL MANAGEMENT	SYMPTOM RESOLUTION*	CONTINENT
Wyczolkowski et al, 2001	1	0%	1 retropubic partial mesh excision	100%	100%
Sweat et al, 2002	1	0%	1 transvaginal and retropubic partial mesh excision and reconstruction	100%	0%
Jorion, 2002	1	0%	1 endoscopic partial mesh excision	100%	100%
Volkmer et al, 2003	2	0%	2 complete transvaginal mesh excision and reconstruction	100%	0%
Levin et al, 2004	2	0%	2 endoscopic partial mesh excision	NR	NR
Tsivian et al, 2004	1	0%	1 endoscopic and retropubic partial mesh excision and reconstruction	100%	100%
Huang et al, 2005	1	0%	1 transvaginal and retropubic complete mesh excision and reconstruction	100%	0%
Negoro et al, 2005	1	0%	1 retropubic partial mesh excision and reconstruction	0%	0%
Irer et al, 2005	1	0%	1 endoscopic partial mesh excision	100%	100%
Giri et al, 2005	3	0%	3 endoscopic partial mesh excision	100%	100%
Baracat et al, 2005	6	0%	6 endoscopic partial mesh excision	100%	100%
Siow et al, 2005	1	0%	1 transabdominal laparoscopic partial mesh excision and reconstruction	50%	100%
Starkman et al, 2006	7	0%	7 transvaginal and retropubic partial mesh excision and reconstruction	NR	NR
Mustafa and Wadie, 2007	1	0%	1 endoscopic partial mesh excision	100%	100%
Ordorica et al, 2008	2	0%	1 retropubic partial mesh excision and reconstruction (extravesical) 1 retropubic partial mesh excision and reconstruction	100%	NR
Huwyler et al, 2008	5	0%	5 endoscopic partial mesh excision	100%	100%
Rehman et al, 2008	2	0%	2 extraperitoneal laparoscopic partial mesh excision and reconstruction	100%	100%
Shrotri et al, 2010	1	0%	1 endoscopic partial mesh excision	100%	100%
Oh and Ryu, 2009	14	0%	14 endoscopic partial mesh excision	100%	93%
Foley et al, 2010†	9	0%	7 endoscopic partial mesh excision 2 endoscopic and retropubic partial mesh excision	100%	33%
Zivanovic et al, 2013‡	3	0%	2 endoscopic and transvaginal partial mesh excision 1 endoscopic partial mesh excision	100%	100%
Shah et al, 2013	7	0%	7 transvaginal and retropubic complete mesh excision and reconstruction	100%	100%

*Most common presenting symptoms were urinary tract infection, urge urinary incontinence, pain, incontinence, urgency, hematuria, bladder stone, and dysuria.

†Includes one patient who had an I-Stop out-to-in transobturator midurethral sling.

‡All were TVT Secur slings.

NR, not recorded.

KEY POINTS: MIDURETHRAL SLING MESH PERFORATION OF THE URETHRA AND BLADDER

- Overall, the incidence of urethral and bladder mesh sling perforation is extremely low in the reported MUS literature.
- As the number of synthetic MUS surgeries continues to increase, physicians need to be mindful of the potential complications, have a high index of suspicion, and be aware of the management options available to treat the patient.
- Conservative observational treatment is not an option for urethral and bladder mesh perforation.
- Currently, for urethral and bladder perforations, transvaginal (or transabdominal) excision of the mesh with closure of the urethrotomy or bladder is our preferred first-line method of treatment in most cases.
- If the repair is tenuous, a vascularized Martius labial fat pad graft can bolster the repair. Furthermore, an autologous fascial sling can be placed at the time of surgery to augment the repair or in a delayed fashion to treat recurrent SUI.

(2009) and Wang and colleagues (2009) also both found the transobturator group to have significantly more postoperative groin and thigh pain. Doo and colleagues (2006) noted persistent suprapubic pain in three (2.2%) women at 5-year follow-up after a retropubic MUS.

De Leval (2003) reported that 15.9% of patients after transobturator MUS surgery had temporary groin pain that resolved after the second postoperative day. Similarly, Krauth and colleagues (2005) reported 14 cases (2.3%) of patients with postoperative perineal groin pain after transobturator MUS surgery. They also noted it to be transient and responding to nonsteroidal anti-inflammatories in all but one case. They hypothesized that the cause of the pain was either subclinical hematoma or a transient neuropathic phenomenon. In 2011, a randomized controlled trial by Teo and colleagues comparing the retropubic and transobturator MUSs was aborted because of a 26.4% incidence of leg pain in the transobturator sling group (1.7% in retropubic MUS group).

Fortunately, chronic groin and leg pain is an uncommon complication after MUS surgery. Roth (2007) found that in three women with persistent groin pain 3 months postoperatively, steroids and local anesthetic were effective for pain relief and had no side effects. Wolter and colleagues published a case report on recalcitrant medial thigh pain after transobturator MUS placement, which ultimately required medial thigh and transobturator exploration by orthopedic surgery and sling excision (Wolter et al, 2008).

Wound-related complications include **minor superficial cutaneous infections and pelvic abscesses**. In their randomized controlled trial from 2002, Ward and Hilton found a 2% rate of vaginal wound infection after retropubic MUS surgery. In 2010, Richter and colleagues found a 0.7% rate of vaginal wound infection in both the retropubic and transobturator MUS arms. In 2004, a case of necrotizing fasciitis was reported in an obese, diabetic patient (Connolly, 2004). This resolved after intensive resuscitation. It is interesting to note that a review of necrotizing fasciitis in gynecologic surgery found that obesity (88%), hypertension (65%), and diabetes (47%) were all factors associated with the development of fasciitis after surgery (Gallup et al, 2002).

Fortunately, severe infection is a rare complication after MUS surgery, and the diagnosis of this complication is variable and can take as long as several years (Choi et al, 2011; Yenilmez et al, 2013). In 2006, Mahajan and colleague reported one case of failed sling and vaginal exposure that was associated with severe groin pain, fever, and chills 10 days postoperatively. The sling was easily removed through a vaginal incision, and mesh cultures were positive for *Bacteroides fragilis*. Complete symptom resolution occurred within 1 week of mesh removal. Abscesses and adductor myositis

have also been reported, manifesting as leg pain, difficulty ambulating, and cellulitis (Goldman, 2006; DeSouza et al, 2007; Karsenty et al, 2007; Leanza et al, 2008; Zumbé et al, 2008). In 2004, Gamé and colleagues (2004) reported an infected obturator hematoma after placement of an ObTape sling that required exploration and drainage. ObTape is no longer available for implantation. In general, severe infectious complications appear to be more common with the older, non-loosely woven polypropylene slings (Babalola et al, 2005).

Management of Midurethral Sling Severe Infection or Pain. In most cases, postoperative groin or leg pain after MUS surgery can be managed with nonsteroidal anti-inflammatory medications, rest, and even physical therapy. Duckett and Jain (2005) reviewed different strategies for managing groin pain after a retropubic MUS placement or similar midurethral sling procedures in 5 (1%) women. Initial conservative management was successful in most patients. Four patients with persistent or severe pain were given a combination of steroid and local anesthetic injections. Two women developed recurrent pain and had the sling excised, with significant pain relief. Medial thigh pain is a common problem after transobturator MUS surgery and, as with retropubic MUSs, can usually be managed conservatively. A prospective study of 100 women who underwent transobturator MUS surgery showed a high 24.4% incidence of groin pain (Lim et al, 2006). Of importance, with conservative treatment the incidence of persistent groin pain 12 months after surgery was only 3.7%.

In instances of chronic mesh pain and severe infection when nonoperative therapy has failed, it may be necessary to attempt a complete mesh excision from both sides of the bone. In the case of retropubic mesh this involves an abdominal and vaginal incision, and in the case of transobturator mesh this involves a medial thigh and vaginal incision. For the complete excision of transobturator mesh we typically consult an orthopedic surgeon to aid with lateral dissection of the sling. In 2012, Reynolds and colleagues published their results of a series of eight patients with chronic groin pain after transobturator MUSs that necessitated mesh excision from the obturator foramen. Five of the eight patients were cured of their pain after a median 8 months of follow-up.

Voiding Dysfunction after Midurethral Sling Surgery

Voiding dysfunction is a common problem after MUS surgery. These voiding symptoms are typically the result of obstruction from the sling as a consequence of the sling being placed too tightly or in the wrong location (too proximally) or associated with pelvic organ prolapse (unrecognized preoperatively or de novo); however, some patients may have voiding dysfunction without evidence of obstruction. Based on anecdotal experience removing hundreds of chronically obstructing slings, we have found that obstructive slings are most likely to be found close to the bladder neck. In addition, we have found that progression of anterior and apical prolapse can cause a nonobstructive sling to become obstructive 10 years or more after placement of the sling. If the diagnosis of sling obstruction is in doubt, urodynamics can be performed to provide confirmation (Volkmer et al, 2003; Levin et al, 2004). Again, whereas most voiding dysfunction after MUS surgery is the result of sling obstruction, not all patients will have obstruction on urodynamic evaluation. Table 84-17 displays a literature review of the management of voiding dysfunction after MUS surgery.

Tables 84-9, 84-10, and 84-11 contain information about rates of voiding dysfunction with MUSs. In general, the rates of de novo urgency and perioperative urinary retention are similar among the different types of MUSs. The most common symptoms of obstruction are an inability to void (urinary retention), incomplete emptying, and de novo urgency and frequency. Over several weeks to a month, the irritative voiding symptoms (urgency, frequency, and pain) become more prevalent as the bladder attempts to adjust to the obstruction.

The optimal evaluation for patients with postoperative voiding dysfunction is poorly defined in the literature. The decision to

TABLE 84-17 Management of Voiding Dysfunction from Obstruction after Midurethral Sling Surgery

	TOTAL PATIENTS IN SERIES	PATIENTS WITH RETENTION OR SYMPTOMS OF OBSTRUCTION	FINAL MANAGEMENT	TIME TO SURGERY (MEAN OR MEDIAN)	RESOLUTION OF RETENTION AFTER SURGICAL MANAGEMENT	CONTINENT AFTER SURGICAL MANAGEMENT
Klutke et al, 2001	600	17 (2.8%)	17 transvaginal loosening or midline sling transection	64 days	100%	94%
Meschia et al, 2001	404	17 (4.0%)	15 observation or CIC 2 midline sling transection	NR	100%	NR
Rardin et al, 2002b	1175	23 (2.0%)	17 midline sling transection 2 urethrolisis 4 segmental resection	121 days	100%	82%
Kuuva and Nilsson, 2002	1455	34 (2.3%)	33 observation or CIC 1 midline sling transection	90 days	100%	100%
Hong et al, 2003	375	32 (8.5%)	28 observation or CIC 4 midline sling transection	90 days	100%	100%
Karram et al, 2003	350	17 (4.9%)	11 CIC 6 midline sling transection	42 days	100%	67%
Volkmer et al, 2003	—	3	2 midline sling transection 1 segmental resection	214 days	100%	67%
Long et al, 2004	71	7 (9.9%)	7 right-sided lateral transection (J-sling)	28 days	86%	71%
Levin et al, 2004	313	8 (2.6%)	7 catheter 1 segmental resection and urethrolisis	60 days	100%	100%
Tsivian et al, 2004	—	8	5 midline sling transection 3 segmental resection	420 days	100%	75%
Zubke et al, 2004	—	3	3 midline sling transection and mesh lengthening	NR	100%	100%
Abouassaly et al, 2004	241	47 (19.5%)	37 CIC 7 midline sling transection 3 segmental resection	NR	100%	60%
Hammad et al, 2005	1459	95 (6.5%)	62 CIC or catheter 19 midline sling transection 7 urethrolisis 7 transvaginal loosening	NR	NR	NR
Sokol et al, 2005	267	29 (10.9%)	13 urethrolisis 11 CIC or catheter 5 urethral dilation	42 days	NR	NR
Nguyen, 2005	163	10 (6%)	10 transvaginal loosening	5 days	100%	100%

TABLE 84-17 Management of Voiding Dysfunction from Obstruction after Midurethral Sling Surgery—cont'd

	TOTAL PATIENTS IN SERIES	PATIENTS WITH RETENTION OR SYMPTOMS OF OBSTRUCTION	FINAL MANAGEMENT	TIME TO SURGERY (MEAN OR MEDIAN)	RESOLUTION OF RETENTION AFTER SURGICAL MANAGEMENT	CONTINENT AFTER SURGICAL MANAGEMENT
Laurikainen and Killholma, 2006	9040	50 (0.6%)	50 midline sling transection or bilateral transection	197 days	88%	49%
Gamé et al, 2006	—	30	30 lateral sling transection	381 days	70%	91%
Glavind and Glavind, 2007	143	10 (7%)	5 transvaginal loosening 3 CIC 2 midline sling transection	92 days	100%	71%
Hinoul et al, 2011	98	2 (2%)	2 midline sling transection	NR	100%	NR
Bianchi-Ferraro et al, 2013	117	4 (3.4%)	4 CIC	NR	100%	NR

CIC, clean intermittent catheterization; NR, not recorded.

perform urethrolisis is usually based on a clear temporal relationship between onset of symptoms and the surgical procedure. Urodynamic studies can be useful in selected cases at the physician's discretion. However, it appears that the temporal relationship correlating symptoms with an antecedent surgical procedure should be the primary criterion in selecting patients for urethrolisis and sling release procedures. Cystoscopy is useful to rule out bladder pathology, urethral mesh perforation, and a hypersuspended bladder neck.

In older nonrandomized studies there did not appear to be a significant difference in postoperative voiding dysfunction between retropubic and transobturator MUS surgeries (Mansoor et al, 2003; de Tayrac et al, 2004). However, in a more recent randomized controlled trial by Richter and colleagues (2010), there was a significantly higher rate of voiding dysfunction necessitating surgery (or permanent catheter) after a retropubic MUS compared with a transobturator sling procedure (2.7% vs. 0%). In addition, the rate of urinary retention (catheter for longer than 6 weeks) was also higher in the retropubic MUS group (3.7% vs. 0.7%).

When selecting patients for the retropubic MUS procedure, it might be helpful to identify preoperative factors predictive of voiding dysfunction and urinary retention after surgery. In a study by Hong and colleagues (2003), 375 patients were analyzed to see which factors predicted urinary retention after the retropubic MUS procedure. Urinary retention, defined as the need to catheterize for 72 hours or longer after surgery, was identified in 32 patients. Twenty-eight patients resumed normal voiding within 3 months, and 4 patients required a transvaginal sling release procedure. On multivariate analysis, only peak flow rate predicted urinary retention. In 2004, a small study of 14 patients showed that low PdetQ-max on a preoperative pressure-flow study correlated with elevated PVR urine in 3 patients who had undergone retropubic MUS surgery (Kawashima et al, 2004).

Tsivian and colleagues (2009) assessed the effect of concomitant vaginal surgery on the outcomes of transobturator sling placement. The group without concurrent vaginal surgery had no voiding dysfunction postoperatively, whereas seven (11%) in the group of patients who had undergone additional pelvic surgery experienced voiding dysfunction. However, Sokol and colleagues (2005), who

looked at factors related to delayed normal voiding in patients with and without concurrent prolapse repair at the time of their retropubic MUS surgery, did not find this same trend. The median days to voiding (8 days vs. 5 days) and rate of urinary retention were similar between patients with and without prolapse repair. However, increasing age, decreasing BMI, and postoperative UTI were independent predictors of increased time to adequate voiding. Previous history of incontinence surgery was the only independent variable predictive of urinary retention. In summary, there does not appear to be a consensus in the literature regarding preoperative factors that contribute to voiding dysfunction after MUS surgery.

Management of Voiding Dysfunction after Midurethral Sling Surgery. Urinary obstruction after MUS surgery is usually transient and can be managed with short-term intermittent catheterization, although occasionally symptoms mandate sling release. Long-term retention after retropubic MUS surgery is a rare complication. In these cases, removal or incision of the sling usually improves the patient's symptoms.

In most cases, postoperative voiding dysfunction can be successfully treated conservatively. In the literature, temporary catheter drainage, CIC, timed voiding, biofeedback, pelvic floor muscle training, and selective medical therapy have all been successful to some degree in managing postoperative voiding dysfunction. In the Kuuva and Nilsson analysis of the Finnish database (2002), 20 of 34 patients with urinary retention resumed a normal voiding pattern after only 1 day to 2 weeks of conservative management. However, 2 patients took a longer 5 and 6 weeks to return to normal voiding. Only 1 of the 34 patients required midline sling lysis, and normal voiding resumed. Also, in that study there were 111 patients with voiding dysfunction but no retention. Thirteen of these patients had voiding dysfunction that lasted up to 4 months, and 2 patients required surgical transection of the sling to achieve a normal voiding pattern (Kuuva and Nilsson, 2002, 2003).

Several reports have shown some benefit of urethral dilation or loosening the sling under anesthesia (Hong et al, 2003; Ozel et al, 2004; Mishra et al, 2005). Mishra and colleagues (2005) performed urethral dilation on 3 of 52 women who had retention 3 months after MUS surgery. Two of the 3 patients voided effectively after urethral dilation. In this series, the postoperative retention rate was significantly higher (23%) than in other published data. It is

our opinion that urethral dilation is of limited usefulness and, if used too aggressively, may be detrimental. There are concerns about the potentially traumatic nature of dilation, which could induce scarring of the urethra or lead to mesh perforation.

Cutting the MUS in the midline through a single vertical vaginal incision is the preferred method to manage persistent voiding dysfunction that results from an obstructive sling within the first 3 months after surgery. In our opinion, after 3 months the sling is fixed along its entire course, and midline sling incision may not achieve enough sling relaxation to resolve voiding dysfunction. In these cases, we perform a more formal sling excision and urethrolisis similar to that described earlier for sling excision after perforation.

Reassuringly, studies by Laurikainen and Killholma (2006), Gamé and colleagues (2006), Clifton and colleagues (2014), and Klutke and colleagues (2001) found that 50%, 70%, 79%, and 94% of patients, respectively, remained continent after sling lysis. In the large review by Klutke and colleagues (2001), 17 of 600 patients (2.8%) required reoperation secondary to urinary retention and persistent obstructive symptoms after retropubic MUS surgery. In their series, sling release was performed at mean of 64 days after MUS surgery. The sling was identified and either released with downward traction for 1 cm or cut in the midline. There was one urethral injury, which was repaired without sequelae. Symptoms resolved in all patients after sling release, all patients voided to completion, and 16 patients remained continent. In 2006, Laurikainen and Killholma performed a nationwide retrospective review of 9040 patients who had undergone MUS surgery. In that study, approximately 50% of the 48 patients who required sling lysis were cured of their voiding dysfunction and remained continent. However, 4 (8.3%) continued to have retention after lysis. There was no difference in continence rate among patients based on interval between MUS placement and sling lysis. Repeat sling lysis or urethrolisis was used to treat refractory retention. Lastly, Gamé and colleagues (2006) presented results of 30 women who required sling lysis with a lateral sling incision over a 4-year period. Of importance, 70% were continent after intervention.

Zubke and colleagues (2004) managed three patients with urethral obstruction after MUS surgery by using a novel surgical technique. They cut the sling in the midline with a transvaginal approach and sutured the edges of the sling to a polypropylene mesh, thus lengthening the sling. All three patients were continent and resumed normal voiding after intervention.

The exact timing of sling incision in the literature is variable; however, most authors recommend waiting at least 2 weeks (Long et al, 2004; Glavind and Glavind, 2007) before sling incision in cases of sling obstruction. Even though Kuuva and Nilsson (2002) reported return to normal voiding after 6 weeks of conservative management, the majority of studies do not support waiting more than 4 weeks. In our opinion, in cases of significant obstruction or retention, the sling should be incised within 4 weeks of surgery. Also, in our experience, even though some patients may return to “normal voiding” with conservative management, they often have persistent urgency and frequency.

Sexual Dysfunction after Midurethral Sling Surgery

Varying degrees of sexual impairment have been reported after MUS surgery. The rate of sexual impairment after MUS sling surgery is as high as 20% (Mazouni et al, 2004). In the study by Mazouni and colleagues (2004), 71 women were prospectively followed after they underwent retropubic MUS surgery. In that study, 55 women had no sexual impairment before surgery, and 14.5% of the women developed dyspareunia and 5.4% experienced decreased libido after surgery. However, in a more recent study of 1112 women by Stav and colleagues (2010b) not designed to specifically look at sexual dysfunction, the rate of de novo dyspareunia after MUS surgery was only 3%.

Marszalek and colleagues (2007) performed a cross-sectional analysis and noted that a 14.3% deterioration in sexual function was significantly associated with de novo urgency, dyspareunia, and

KEY POINTS: MIDURETHRAL SLING VOIDING DYSFUNCTION

- Based on the available data, it appears that long-term urinary retention and obstructive voiding dysfunction are rare after the MUS procedure.
- Although definitions of urinary retention and indications for management vary in the reported literature, most patients are initially managed conservatively.
- Anecdotal cases have shown modest benefit from urethral dilation.
- For patients with persistently elevated residual urine and bothersome symptoms refractory to conservative management, transvaginal sling release procedures consistently provide resolution of symptoms with maintenance of continence in the majority of patients. We recommend a waiting period of at least 2 to 4 weeks before sling release.
- Sling release should be attempted through a small midline vaginal incision using minimal dissection.

the sensation of incomplete emptying. In 2008, Demirkesen and colleagues compared sexual satisfaction after MUS surgery and Burch colposuspension. In that study, 54% expressed a negative change, with most reporting dyspareunia. The MUS appeared to more adversely affect sexual satisfaction, but the difference was not significant. Kuhn and colleagues (2009a) reviewed the impact of sling removal on postoperative female de novo dyspareunia and found that the pain improved significantly.

There is also evidence that treatment of urinary incontinence can improve sexual function after surgery. In the randomized controlled trial by Ward and Hilton (2008), the rate of dyspareunia actually decreased from 34% preoperatively to 13% 5 years after sling surgery. In 2009, Bekker and colleagues published the results of a retrospective evaluation of sexual function in 136 women after MUS surgery. The authors found that 21.3% of women reported improved sexual intercourse after surgery and 5.9% reported worsened sexual intercourse. The authors mostly attributed the improved sexual function to a significant decrease in coital incontinence.

Other Complications after Midurethral Sling Surgery

A diverse group of complications have been reported with the MUS, in addition to those mentioned previously. These include infection, bleeding, vascular injury, bowel perforation, and death. UTI is probably the most common and easily treatable complication of MUS surgery. Rates of UTI after MUS surgery range from 22% to 31% in large randomized controlled trials (Ward and Hilton, 2002; Richter et al, 2010).

Another less common complication is intraoperative and postoperative bleeding. This complication is usually variably and subjectively reported in the literature. A review of the literature reveals that severe bleeding or hematoma occurs in approximately 2% to 3% of patients and can usually be managed with observation or local compression (see Table 84-13 on the Expert Consult website). Table 84-13 also shows that in 8 of 10 studies reviewed comparing different MUS surgeries, bleeding complications occurred more commonly after retropubic MUS surgery. In their study, Wei and colleagues (2012) found the average estimated blood loss after MUS surgery to be 156 mL. In 2004, Flock and colleagues (2004) reported that 4.1% of 249 patients experienced a hemorrhage of 300 mL or more and required surgical intervention after retropubic MUS surgery. Tseng and colleagues (2005) performed ultrasonography on all 62 women after MUS surgery and found that 8 (12.9%) patients had significant retropubic hematomas greater than 5 cm on the day after surgery. Only 1 patient required hematoma evacuation, and in the rest, repeat ultrasonographic examinations 1 month after surgery revealed the

hematomas had resolved. Of interest, this study revealed that a postoperative hematoma may be a relatively common asymptomatic event after trocar passage.

Serious complications such as vascular perforation, intestinal perforation, or even death remain extremely rare. The rate of serious vascular complications in the Finnish registry was 0.07% (Kuuva and Nilsson, 2002). Comparably, the Austrian registry reported a bowel perforation rate of 0.04% (Tamussino et al, 2001). In 2007, Deng and colleagues (2007) reviewed the complications reported to the FDA MAUDE database. The authors found that of 928 reported complications, 161 were considered major. The major complications included 39 vascular injuries, 38 bowel injuries, and 10 deaths.

REGULATORY AND LEGAL ISSUES RELATED TO SLING MESH COMPLICATIONS


The FDA approved the first MUS for use through the 510(k) approval process in 1998. It is interesting to note that all subsequent MUSs have also been approved for use through this process (Secunda, 2011). The 510(k) approval process for Class II products (mesh products fall into this class) allows medical device manufacturers to bypass the normal premarket approval procedure as long as the new device is substantially equivalent to an existing product (U.S. Food and Drug Administration, 2013a, 2013b). Once the FDA determines that a product is substantially equivalent to an existing product, the company receives a letter of approval to market the new device.

The success of MUSs for incontinence led to the development of mesh products for pelvic organ prolapse repair. Subsequently, the FDA determined that these products were substantially equivalent to existing mesh products already approved, and in turn FDA's 510(k) approval process led to the rapid approval of these products also. The FDA and many physicians believe that the 510(k) approval process is a necessary and important practice that allows for medical device advances to occur more rapidly. Of note, through the Freedom of Information Act (5 U.S.C. § 552(a)(2) (Title 5 United States Code section 552 subsection a2)), all FDA letter communications to manufacturers are available online.


However, while the use of mesh during pelvic organ prolapse repairs has increased, so too have complications related to its use. In October 2008, the FDA released a public health notification (PHN) alerting the public about "rare" complications and problems related to transvaginal mesh products used for pelvic organ prolapse. In 2011, the FDA modified this alert by removing the term "rare" and stating that surgical mesh for pelvic organ prolapse repair does not conclusively improve outcomes over traditional nonmesh or native tissue repairs and is associated with unique potentially serious adverse outcomes (U.S. Food and Drug Administration, 2011).

If a product approved by the FDA through the 510(k) process is found to have potential serious adverse health consequences, the FDA can require the manufacturer to perform costly 522 postmarket surveillance studies. In the case of mesh for pelvic surgery, the FDA was alerted to potential serious adverse events through the MAUDE database and reports in the urologic and gynecologic literature. In January 2012, the FDA mandated that all manufacturers of synthetic prosthetic mesh and biologic graft materials marketed for pelvic organ prolapse repair and single-incision sling products perform 522 postmarket surveillance studies. MUS products (except single-incision slings) were excluded from this mandate because in September 2011 an FDA advisory panel deemed existing MUS products "safe and effective" and recommended that these products not undergo 522 postmarket surveillance. For future MUS products, the FDA determined that the 510(k) approval process is still applicable as long as well-designed bench or animal studies are included with the 510(k) application. However, premarket clinical studies for new SUI products may be required if the FDA determines that there is a need for clinical information to demonstrate substantial equivalence to an existing product (Baxley, 2011).

Even though the FDA has determined that existing MUS products are safe and effective, this unfortunately does not prevent MUSs from being caught up in the fervor of litigation related to products used for pelvic organ prolapse repair. In June 2010, a settlement was reached to halt the first class-action lawsuit against the manufacturer of ObTape (Mentor-Porgés) (Chapple et al, 2013). To date, AMS (parent company Endo Pharmaceuticals), Ethicon (Gynecare, parent company Johnson & Johnson), Boston Scientific, and C.R. Bard have all been targeted by multidistrict federal litigation for complications related to their MUS products. C.R. Bard and Ethicon have already discontinued their mesh products, and as litigation increases, other manufacturers may decide to follow suit. Currently, most litigation is directed at device manufacturers; however, this could change. It is important for pelvic surgeons to continue to thoroughly counsel their patients about the permanent nature of mesh products and the potentially serious complications related to their use.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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Pelvic Reconstructive Surgery

Complications of Mesh in Pelvic Reconstructive Surgery

Evaluation of Mesh Complications

Treatment of Mesh Complications

Conclusion

Urologists most often use mesh for the surgical treatment of urinary incontinence and pelvic organ prolapse. This topic becomes increasingly important to surgical training as the number of patients undergoing such procedures rises annually secondary to the increasing number of women at risk and the refinement of surgical technique into more minimally invasive outpatient approaches (Jones et al, 2010; Bradley et al, 2011). Augmentation of traditional native tissue repairs with nonabsorbable synthetic mesh products demonstrated great promise in short-term outcome studies; however, longer term evaluation revealed a 19% erosion rate and a 28% incidence of dyspareunia (Committee on Gynecologic Practice, 2011). Urologists worldwide must now balance the higher anatomic success rates of mesh repair against the longer term risks of erosion and other complications, some of which cannot be completely reversed.

The trend toward dominance of mesh-augmented over native tissue repairs for the treatment of incontinence and prolapse was most pronounced from 2000 to 2006, after which overall mesh use declined for prolapse and incontinence procedures (Wu et al, 2009; Rogo-Gupta, 2013). The exact reasons for the shift are unknown; however, many authors suspect multifactorial influences. Professional organizations began questioning the benefits of mesh over nonmesh options in 2004; in 2008, the U.S. Food and Drug Administration (FDA) released its first in a series of public communications regarding the safety of mesh in pelvic surgery (Sung et al, 2008; Maher et al, 2011; Walter et al, 2011).

Although individual synthetic products in pelvic surgery have been placed under particular scrutiny, concerns have been raised regarding multiple aspects of these procedures, including material type and location and method of placement. The Society of Gynecologic Surgery questioned the appropriateness of mesh for posterior compartment prolapse, a concern that was echoed by the Cochrane Collaboration (Sung et al, 2008; Maher et al, 2011). Others publicly questioned method of placement. In 2011, the Society of Obstetricians and Gynaecologists of Canada stated that trocar-guided placement devices should be considered novel techniques and were associated with adverse sequelae (Walter et al, 2011). A summary of available data on mesh-related complications was devised in a collaborative effort between the American College of Obstetricians and Gynecologists and the American Urogynecologic Society in 2011 (Committee on Gynecologic Practice, 2011). The Committee on Gynecologic Practice recommended counseling patients regarding the risk of mesh exposure (range 1% to 19%); buttock, groin, or pelvic pain (range 0% to 18%); de novo dyspareunia (range 2% to 28%); and reoperation (range 1% to 22%).

The increasing incidence of mesh complications in urologic surgery suggests that a re-evaluation of their use in practice is warranted. Complications range from mild and self-limited to chronic and irreversible (Committee on Gynecologic Practice, 2011). For example, anatomic obstruction of the urinary tract may resolve with removal of the implant; however, chronic pain may persist for years. Although there is no international consensus regarding standard practice of mesh in incontinence and prolapse surgery, guidelines exist for surgical planning, patient counseling, and obtaining appropriate informed consent (Committee on Gynecologic Practice, 2011).

Prolapse and incontinence surgery is generally considered safe and minimally invasive, and all patients, whether they undergo mesh or nonmesh surgery, are at risk for complications, including infections, urinary urgency and urge incontinence, pelvic organ prolapse, and outlet obstruction. In this chapter, we discuss etiology, evaluation, and treatment of mesh complications in pelvic reconstructive surgery. Our primary focus is female patients with pelvic organ prolapse and urinary incontinence; however, comparable complications may be seen in men undergoing pelvic surgery (Bauer et al, 2010; Weinberger et al, 2013).

KEY POINTS: INTRODUCTION

- Higher anatomic success rate of mesh repair must be balanced against complication risk.
- Complications include exposure (1% to 19%); buttock, groin, or pelvic pain (0% to 18%); de novo dyspareunia (2% to 28%); and reoperation (1% to 22%).

PELVIC RECONSTRUCTIVE SURGERY

Epidemiology

The number of women in the United States with pelvic floor disorders is projected to increase rapidly in the coming decades from 28 to 44 million between 2010 and 2050 (Wu et al, 2009). Historically, at least 11% of these women undergo at least one surgical procedure during treatment (Maher et al, 2011); this is likely to translate to a potentially overwhelming number of patients seeking care in an already overburdened health care system. These increased demands on the health care system in the wake of health care reform may

place added pressure on urologic surgeons as the future of health care delivery is unclear. Urologic surgeons must feel confident in their repair techniques and be prepared to offer cost-effective, reliable treatments with acceptable long-term outcomes. Urologic surgeons must feel comfortable in regard to the outcomes of mesh repair techniques and their ability to identify and address mesh-related complications.

Risk factors for incontinence differ by gender. In women who often also experience pelvic organ prolapse, risk factors include age, parity, obesity, menopause, genetic predisposition, and chronic pelvic strain. In general, tissue damage from mechanical trauma and hormone effects combined with genetic predisposition and lifelong behavioral patterns culminate in the pattern of symptoms that brings patients to physician offices. Treatment aims at addressing multiple components of pelvic floor dysfunction.

Urinary incontinence treatment is recommended for symptomatic patients (Dmochowski et al, 2010). Over the past three decades, the most commonly performed surgery for stress urinary incontinence has shifted from needle suspensions to mid-urethral slings, which are recommended by the American Urological Association as the most durable treatment option for stress incontinence. Alternatives that are less commonly performed, but still a part of the urologist's armamentarium, include slings of non-synthetic material, needle suspensions, urethral bulking agents, and artificial urinary sphincters. Prolapse repair is offered to symptomatic patients who have failed conservative management. Symptoms range from vaginal bulge to obstructive urination or defecation to dyspareunia. Experts also recommend treatment for patients with end-organ damage from prolapse such as hydronephrosis, vaginal ulcerations, urinary retention, or cystoscopic findings of urinary obstruction. For the treatment of prolapse of the pelvic organs, the current standard of surgical repair is a mesh suspension of the prolapse to the sacral promontory (sacrocolpopexy). Mesh also can be placed vaginally to repair isolated or multiple compartment prolapse.

Historically, native tissue prolapse repair was reported to have a 30% failure rate; however, more recent reviews highlight much higher subjective success rates (Lee et al, 2012). Mesh was adopted to augment native tissue repair to improve objective outcomes as measured using the Pelvic Organ Prolapse Quantification or Baden-Walker systems. Perfect support is defined as stage 0; however, 75% of asymptomatic women have greater than stage 1 findings. As a result, many patients who were satisfied with their surgical outcomes were categorized as failures if their objective measures did not meet criteria for success. This demonstrates the discrepancy between objective prolapse and subjective symptoms, which is of utmost importance when considering surgical intervention to improve quality of life. Pelvic reconstructive surgeons correct anatomy to restore function and improve quality of life. Surgical outcome should be evaluated not only by anatomic improvement but also by symptomatic improvement and demonstrable impact on overall quality of life. We should strive to minimize complication rates for procedures.

For surgeons, expertise with traditional and mesh-augmented pelvic reconstructive surgery is recommended. Surgeons should counsel patients on the risks and benefits of all options, while providing recommendations and obtaining informed consent. Counseling should include the risk of late-onset complications that are difficult to predict. Factors affecting complications that may present years after placement include vaginal atrophy, low-grade infection, tissue aging, or a dynamic host-graft response not completely understood. The fact that many of these risk factors are nonmodifiable makes prevention of these complications challenging.

Materials

Synthetic mesh is one of many materials used in pelvic reconstructive surgery and was introduced into prolapse repair to improve long-term durability compared with repairs using native tissue, fascia autografts, allografts, or xenografts. Synthetic material has

many advantages, including easy placement, broad coverage, and tension-free placement. Designed to replace damaged support structures, mesh products may be hand-cut and customized to each individual patient or purchased in premade kits. Kits are available for the correction of urethral hypermobility and prolapse of the anterior, apical, and posterior vaginal compartments and range in their mechanisms of placement and fixation (Washington, 2011). Examples of vaginally placed mesh techniques include trocar-guided placement, tine or suture fixation, and implants that are adjustable after implantation. When anterior compartment repair uses trocars, the arms traverse the adductor and obturator muscles bilaterally. In procedures without trocars or single-incision procedures, the implant does not traverse the adductor or obturator muscles; rather, it is fixed to fascia or ligaments themselves. Trocar-guided apical and posterior repair kits pass mesh through the sacrospinous ligaments and exit the skin in the gluteal area. Mesh also can be placed abdominally for prolapse correction to suspend the uterus, cervix, or vaginal cuff to the sacrum. Despite the popularity of mesh kits, the most commonly used mesh product in gynecologic surgery is a free mesh hand-cut by the surgeon.

Mesh graft composition has evolved since its initial introduction into pelvic surgery. The most widely used products are made of polypropylene because this material has demonstrated significantly fewer morbid complications compared with prior material. Polypropylene, categorized as a type I macroporous monofilament mesh, has been implicated in long-term complications only more recently; it remains unclear whether these complications are due to the material itself, host response, surgical factors, or a process not yet identified. Other products have been largely abandoned because of associations with infection, graft rejection, and pain, as was seen with Mersilene mesh (Ethicon, Somerville, NJ) and silicone slings used in the 1960s and 1980s, respectively (Williams and Telinde, 1962; Stanton et al, 1985; Duckett and Constantine, 2000).

The process of mesh degradation and tissue incorporation begins at insertion (Clave et al, 2010). Local inflammation and granular tissue creation converts to dense fibrous tissue over approximately 2 to 3 months, incorporating the graft into the surrounding tissue. Concurrently, mesh shrinkage occurs wherein there is a 30% to 60% decrease in graft size (Garcia-Urena et al, 2007).

The increasing number of mesh products approved and marketed makes thorough evaluation of any single product increasingly challenging. This dilemma is not unique to urologic surgery and has been described in other surgical specialties including orthopedics: A hip replacement device was implanted in more than 100,000 patients before it was recalled in 2010 because of a 49% 6-year revision rate (Curfman and Redberg, 2011). In 2011, the FDA called for nationwide randomized controlled trials to evaluate the use of mesh in pelvic reconstructive surgery after their determination that existing literature was insufficient to form proper conclusions (U.S. Food and Drug Administration, 2011). Similar concerns have been raised in other countries.

Although the future of mesh in pelvic reconstruction is unclear, it will likely continue to be used by experienced surgeons in carefully selected patients in whom the benefits outweigh the risks. Surgeons must be aware of the factors that contribute to mesh complications and obtain proper informed consent before mesh placement for any indication.

KEY POINTS: PELVIC RECONSTRUCTIVE SURGERY

- A discrepancy exists between objective findings and subjective success for prolapse and incontinence repair.
- Complications may be due to synthetic material, host response, surgical factors, or a process not yet identified.
- In 2011, the FDA called for nationwide randomized controlled trials to evaluate the use of mesh in pelvic reconstructive surgery.

COMPLICATIONS OF MESH IN PELVIC RECONSTRUCTIVE SURGERY

Complications related to mesh use have gained international attention more recently. More than two decades after the widespread incorporation of polypropylene mesh into pelvic reconstructive procedures, new data suggest 10% of patients experience serious complications, including some that cannot be completely reversed (Committee on Gynecologic Practice, 2011). Some complications are minimally morbid and can be managed conservatively in outpatient settings (Niro et al, 2010). This includes vaginal mesh exposure, a finding that resulted in the discontinuation of much research that may have revealed the more serious long-term complications had the trials continued. Additional complications include bleeding, infection, fistula, pain, dyspareunia, organ perforation, obstruction, and dysfunction. The details of each are discussed later in this chapter. Although the exact etiology of many complications is unknown, we discuss existing opinion regarding the factors contributing to mesh complications.

Etiology of Complications

Complications of mesh insertion occur secondary to modifiable and nonmodifiable factors. For example, when mesh is placed superficially, patients may experience bleeding, pain, dyspareunia, or infections from local ulceration and necrosis. Surrounding tissue may be predisposed to such reaction in cases of extensive local dissection, previous surgery, radiation, immunosuppression, or other local trauma. Sutures also must be selected and placed with care because wound separation would undoubtedly lead to mesh exposure. Hemostasis is essential when using mesh. Anemia may contribute to poor tissue healing, and hematomas may become infected, place pressure on suture lines, and contribute to wound separation. Large hematomas, which may cause pain, cause urinary obstruction, or require drainage if they do not spontaneously resolve, are seen less often.

Mesh is subject to bacterial contamination that may not be entirely prevented by sterile surgical technique (Culligan et al, 2003). This process is not unique to urologic surgery as demonstrated in examinations of implants used in other types of surgery (Gristina et al, 1985). Strategies to decrease contamination including hair removal, preoperative antiseptic washes, and antibiotics have been hypothesized to decrease implant contamination (Darouiche et al, 2010). Some products have protective sheaths for placement to avoid direct contact with the skin edge because this is likely a source of bacteria even after standard surgical preparation. In microscopic examinations of explanted mesh, bacterial contamination is followed by biofilm formation manifesting clinically as drainage or with nonspecific symptoms such as fatigue, fever, and chills. This process of low-grade infection may continue for a long time or escalate into cellulitis, wound separation, pain, bleeding, discharge, and erosion or organ infection.

The integrity of surrounding tissue affects surgical outcomes. Metabolism initiates foreign body degradation, and neovascularization assists in tissue incorporation. These processes are intrinsic to the patient and not modifiable by the surgeon. Sensitivity of the urethra and vagina to local estrogen effects suggests that postmenopausal women may be more subject to bleeding, infection, or poor wound healing. As a result, some surgeons chose to administer preoperative estrogen, which has been demonstrated to alter vaginal cytology in women with atrophic vaginitis (Vaccaro et al, 2013).

Placement method has an impact on some complications of mesh insertion. Location of fixation and trocar placement largely contribute to pain complications of mesh in urologic surgery and may vary significantly (Hinoul et al, 2007). Retropubic sling arms can incorporate urethra, bladder muscularis, levator musculature, and obturator muscle when a trocar is passed close to the pubic bone, rectus muscle, or lumbar nerve branches in their trajectory. Arms also may densely adhere to the retropubic periosteum. Trans-

obturator slings similarly may adhere to urethra, bladder, and levator before traversing the obturator muscles and adductor musculature responsible for hip flexion and adduction (Fig. 85-1). Nerve damage from trocar passage or implant placement may manifest immediately as sharp, focused pain. Nerve injuries that manifest late are typically subtle. Women may report decreased or lack of sensation to the labia, clitoris, or perineum.

Complications of the perioperative period range in severity. Mild complications such as voiding dysfunction or discomfort often resolve spontaneously with minimal intervention, and careful monitoring of these patients is recommended. When complications persist past the perioperative period or do not resolve with conservative management, they may require medication or intervention. Such complications include prolonged voiding dysfunction, urinary obstruction, vaginal pain or dyspareunia, erosion into an organ or exposure through the vaginal wall, and defecatory dysfunction (Fig. 85-2). Long-term complications may manifest months or years after insertion.

Anatomy of Complications

Complications may be related to neurologic, musculoskeletal, or organ injury. Understanding of the innervation and organs surrounding the area of mesh placement is recommended for all surgeons who place mesh for reconstruction. This knowledge is essential for proper mesh placement and thorough evaluation of complications postoperatively.

Genitourinary Tract and Surrounding Structures

Complications of mesh placed for support of the bladder or urethra range in severity. Lower urinary tract symptoms are the most commonly reported, and pain may occur at any point in bladder filling or emptying. Spasmlike pain, pain with position change, or activity-related pain may indicate involvement of the levator ani, obturator muscles, or fascia. Implanted mesh in the bladder wall is often associated with urgency and urge incontinence, whereas urethral damage may cause dysuria and urethral pain. Mesh can penetrate partially or completely through the bladder wall and can be found penetrating the mucosa, under the mucosa, or in the muscularis. Mucosal involvement is associated with complications of exposure such as hematuria and stone formation, whereas mesh in the muscularis rarely causes such complications (Fig. 85-3). Complete obstruction from mesh placement typically manifests with urgency, frequency, inadequate emptying, or elevated postvoid residuals. Incomplete obstruction has a similar presentation. Vaginal intercourse can be painful when mesh is placed in the vaginal muscularis superficially.

Mesh penetration into the urethra or bladder typically manifests with hematuria, urinary tract infections, or pain. Retropubic sling arms may damage the ilioinguinal nerve (L1) and the genital branches of the genitofemoral nerve causing sharp localized pain, whereas obturator arms may damage the posterior branches of the femorocutaneous, posterior cutaneous (L2-S3), pudendal, perineal, inferior anal, or obturator nerves (L5-S1) (Fisher and Lotze, 2011).

Mesh also may become fixated to the bony pelvis causing osteomyelitis or pain from traction as mesh shrinkage occurs between tensioned arms. Mild periosteal damage or inflammation is self-limited; however, severe localized pain may warrant diagnostic imaging (Grimes et al, 2012). Tenderness to palpation of the pelvis may be seen during this process or when implants adhere to the inferior pubic rami. Retropubic hematomas occur in 25% of sling placements (Giri et al, 2005). Trauma to the anterior rectus muscle following retropubic sling is often positional, is relieved with rest, and resolves with time. Trocar-guided transobturator mesh may be associated with myositis, hip and thigh pain from muscles innervated by the obturator (L2-L4) and sciatic (L4-S3) nerves. Such pain occurs with abduction, adduction, lateral thigh rotation, walking, and prolonged sitting. When these complaints occur immediately postoperatively, they are often associated with intraoperative

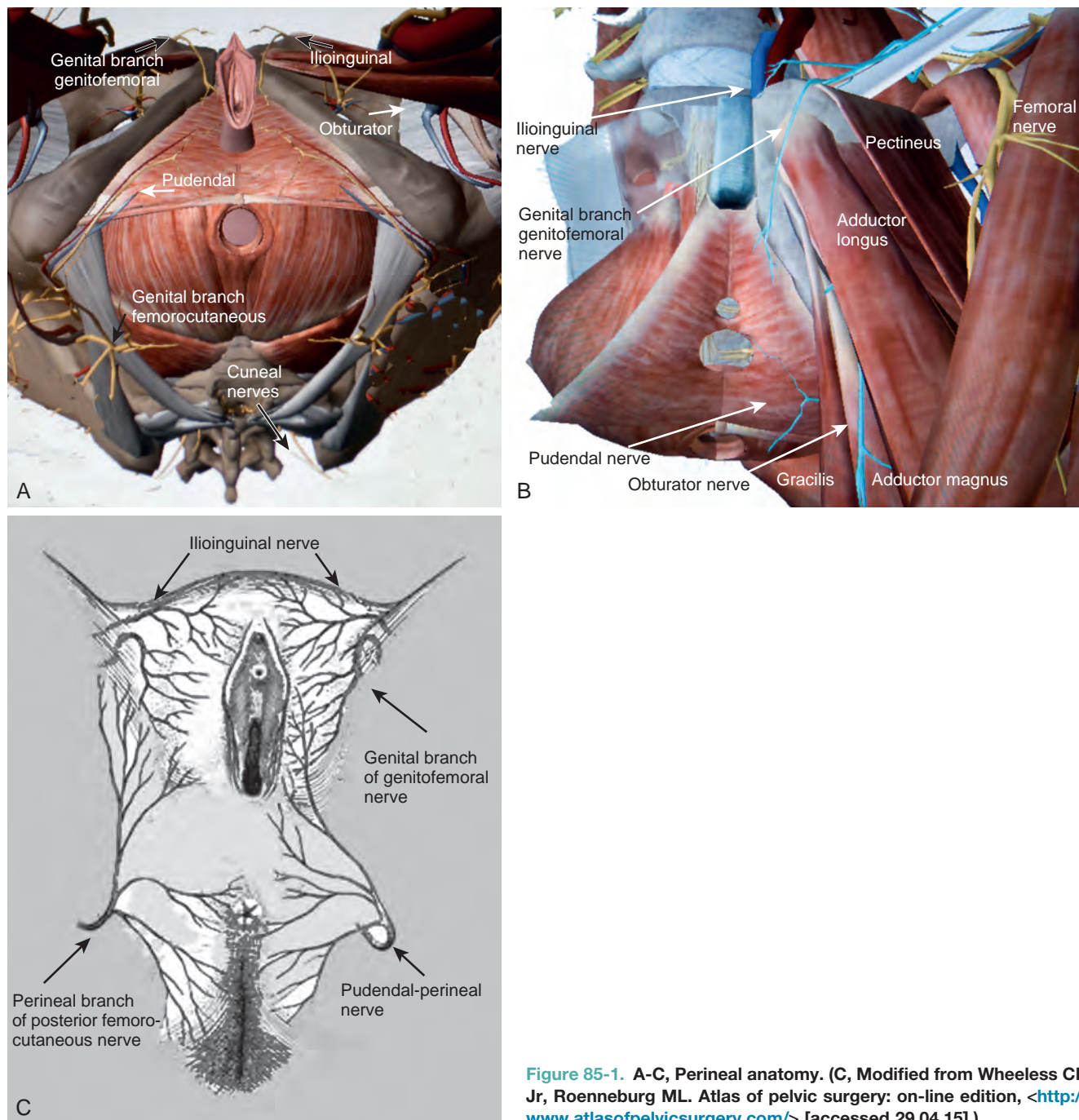


Figure 85-1. A-C, Perineal anatomy. (C, Modified from Wheless CR Jr, Roenneburg ML. *Atlas of pelvic surgery: on-line edition*, <<http://www.atlasofpelvicsurgery.com/>> [accessed 29.04.15].)

positioning; with severe or prolonged pain of this type, the surgeon should consider mesh complication in the differential diagnosis.

Vagina and Pelvic Floor

Musculoskeletal complications of mesh placed vaginally for prolapse are similar to complications described for the bladder and urethra. Mesh placed for apical prolapse correction may additionally affect the coccygeus muscle overlying the sacrospinous ligament or nearby piriformis muscle, innervated by the piriformis nerve (L5-S2). In such cases, patients report pelvic floor spasms, dyspareunia, and prolonged pelvic pain. Pain may radiate from the gluteus, innervated by inferior gluteal nerve (S1), to the vagina. Spasms may cause incontinence or obstruction of urination or defecation, which can be particularly troubling for patients.

Mesh placed for sacral suspension also has been associated with complications including sacral pain, osteomyelitis, and nerve root entrapment and disk damage. Such rare complications occur when the sutures are placed below the sacral promontory at the S1, S2, or S3 foramina. When the uterus or cervix is left in situ, mesh erosion into these organs may manifest as bleeding, cramping, drainage, or pain. Damage to lateral vasculature including obturator, uterine, and vaginal arteries also has been reported. Nerve injury to the lumbosacral plexus may occur during dissection and mesh fixation.

Gastrointestinal Tract and Surrounding Structures

Mesh placed for repair of rectocele may cause muscular pain. Damage to the levator or gluteus maximus can occur with

trocarguided mesh, whereas damage to the anal sphincters may occur from fixation or local dissection. Both techniques have been associated with dyspareunia and defecatory dysfunction. Sharp focal pain results from injury to the sciatic or pudendal nerves and typically manifests immediately after insertion.

KEY POINTS: COMPLICATIONS OF MESH IN PELVIC RECONSTRUCTIVE SURGERY

- Complications occur in 10% of patients, and some cannot be completely reversed.
- Neurologic, musculoskeletal, and organ injury range in severity and time of presentation.

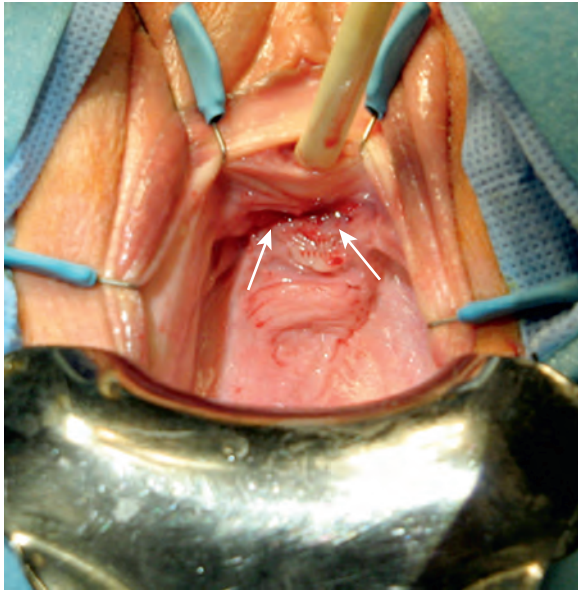


Figure 85-2. Vaginal exposure (arrows).

EVALUATION OF MESH COMPLICATIONS

History

Evaluation of mesh complications begins with a careful, detailed history (Fig. 85-4). In cases of patient referral, operative and progress notes should be reviewed for complications or issues or to corroborate the patient's recollection of events. Concomitant procedures, planned procedures that were aborted, or intraoperative consultations by specialists warrant special attention. Next, a timeline of presenting symptoms should be obtained in relation to time since surgery. Lastly, details of each symptom should be described, including quality, severity, and relieving and exacerbating factors. The absence of significant findings on initial examination does not reliably rule out future complications, and patients should be counseled regarding the possible need for repeat evaluations and long-term complications.

Obstruction of urination or defecation after surgery may manifest as complete or incomplete obstruction. Symptoms include urgency, frequency, and need to strain or change positions while emptying. Patients with urinary obstruction may have high or normal postvoid residuals and the presence or absence of inadequate emptying symptoms because they may have adopted compensatory strategies to achieve bladder emptying. The overall incidence of urinary obstruction requiring intervention in patients after mid-urethral sling procedures is approximately 8% (Dmochowski et al, 2010). Etiologies include penetration of sling material into the bladder or urethra, complete urethral fixation, sling excessively tight, periurethral fibrosis, or secondary bladder prolapse.

In patients who present with pain, noting the severity, timing of onset, and relieving and exacerbating factors provides necessary information in determining the etiology. Routine postoperative pain is self-limited and resolves with medical management and within the perioperative period, although the exact duration is variable. The concurrent processes of tissue healing and mesh shrinkage also may contribute to pain, which is typically described as constant, dull, and worsened with activity or increases in intra-abdominal pressure. Local (i.e., warm water, ice, topical medications) and systemic (i.e., pain control, bladder relaxants, stool softeners)

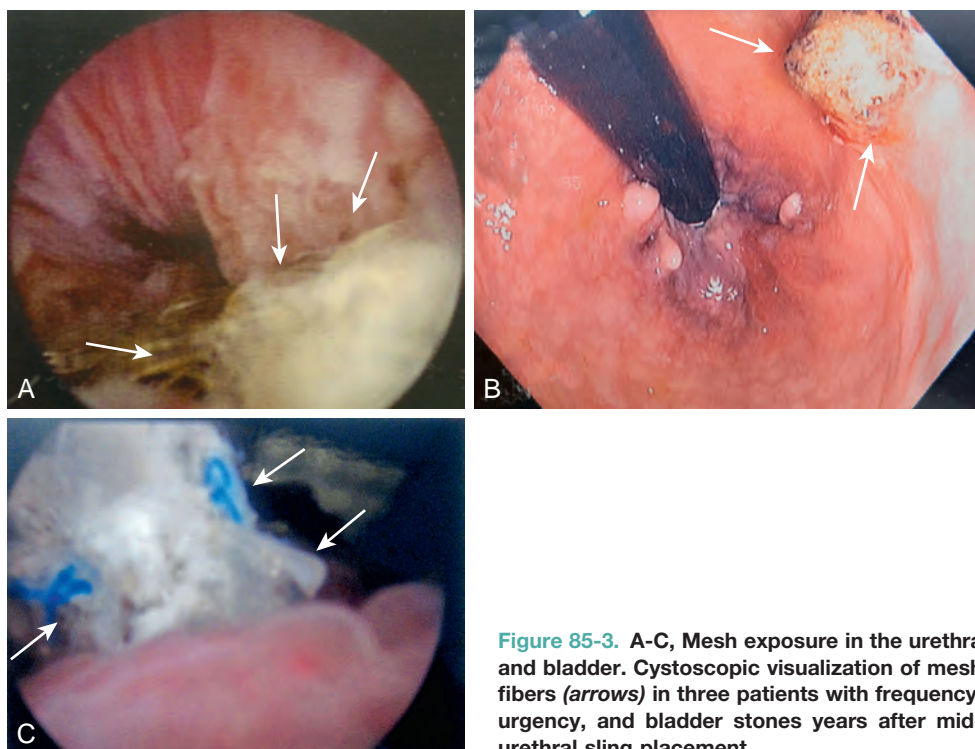


Figure 85-3. A-C, Mesh exposure in the urethra and bladder. Cystoscopic visualization of mesh fibers (arrows) in three patients with frequency, urgency, and bladder stones years after mid-urethral sling placement.

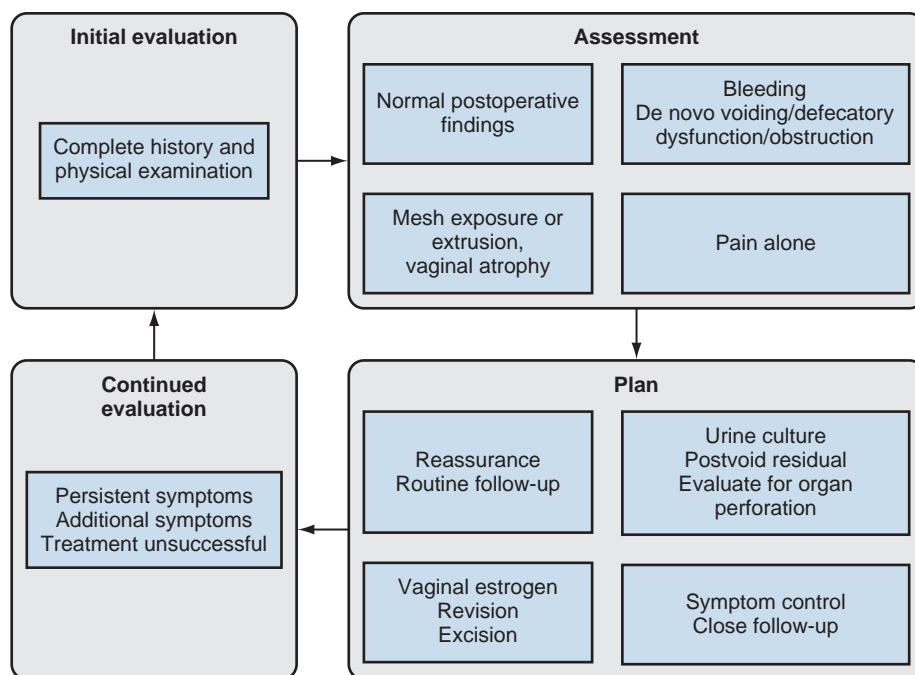


Figure 85-4. Treatment algorithm for patients presenting with possible mesh complications.

treatments may be appropriate. Close follow-up and repeat examinations are recommended to monitor for improvement. A history of prolonged pain and bleeding of the bladder or rectum suggests mesh penetration and should be evaluated further. Fatigue has been reported in patients with chronic infection.

Some patients may report pain out of proportion to examination findings or experience pain despite local and systemic treatments. These patients warrant further evaluation as detailed subsequently because pain in susceptible patients may trigger the development of symptoms similar to those seen in patients with chronic pelvic pain. Obtaining a history of patient experience after prior surgeries; episodes of prolonged or severe pain; or pain syndromes such as interstitial cystitis/painful bladder syndrome, fibromyalgia, or chronic pelvic pain may help greatly in the management of these patients.

Evaluation for complications should occur at each office visit, even in patients without a history of mesh-related complications. Some complications, such as mesh exposure and dyspareunia, may manifest 8 to 10 years after insertion because they are increased with vaginal atrophy. The surgeon should consider following all patients with prior mesh implantation.

Physical Examination

Physical examination in patients presenting with mesh complications should focus on abnormalities whose treatment would relieve the symptoms. For example, **extrusion of mesh or permanent suture material into the vagina or through skin incisions, wound separation, hematoma, or abscesses can be addressed immediately and likely be completely reversed.** Physical examination greatly aids diagnosis of urinary obstruction after mid-urethral sling. The presence of urethral mobility suggests symptoms will resolve after a course of self-catheterization, whereas a highly suspended and fixed urethra suggests placement under tension and may require revision. This is in contrast to pain complications, which sometimes cannot be reversed, even with complete removal of mesh. Findings of alterations in pain processing such as allodynia or hyperalgesia should trigger immediate treatment or referral if all options have been exhausted.

Exposure is not a necessary component of mesh complications; complications can occur even in the absence of exposure and should be treated as separate issues in most cases. Mesh may be

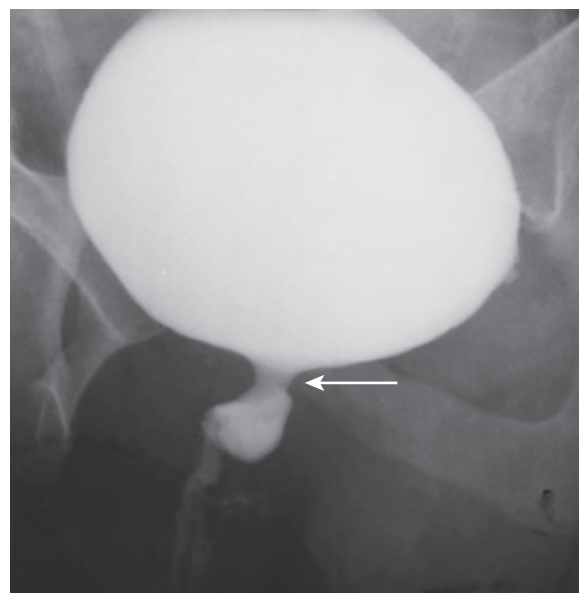


Figure 85-5. Voiding cystourethrogram demonstrates narrowing (arrow) in a patient with lower urinary tract symptoms after mid-urethral sling placement.

palpable without exposure in cases of folding or shrinkage beneath the vaginal surface that can be identified on physical examination as palpation of tense cords or bands. Infiltration of mesh into the vaginal epithelium may appear indurated and tender to palpation. This finding should trigger repeated examinations because it may represent the beginning stages of erosion or exposure.

Diagnostic Studies

Additional imaging studies or diagnostic procedures may be warranted based on physical examination findings. Cystoscopy, vaginography, or colonoscopy can be used to identify mesh extrusion in the urethra or bladder, vagina, or colon. A voiding cystourethrogram can identify the location of anatomic obstruction (Fig. 85-5).

Video-urodynamics can aid in diagnosing patients presenting with urinary incontinence and voiding dysfunction by providing information on the level of obstruction, storage dysfunction, and the presence of stress incontinence. Ultrasonography, computed tomography, and magnetic resonance imaging may be used to identify collections such as hematoma or abscesses (Fig. 85-6). Stone formation in the lower urinary tract should raise suspicion for underlying mesh penetration.

Ultrasound is a useful tool to identify mesh location and depth of penetration (Fig. 85-7). It is sometimes necessary to identify mesh location preoperatively in cases where patients present without prior operative records, the procedure type is unknown, or multiple prior revisions are present. Preoperative evaluation can assist greatly in surgical planning and patient counseling in these cases. Similarly, ultrasonography can clearly demonstrate mesh penetration through the periurethral fascia under the urethral mucosa, a finding that cannot be appreciated by cystoscopy.

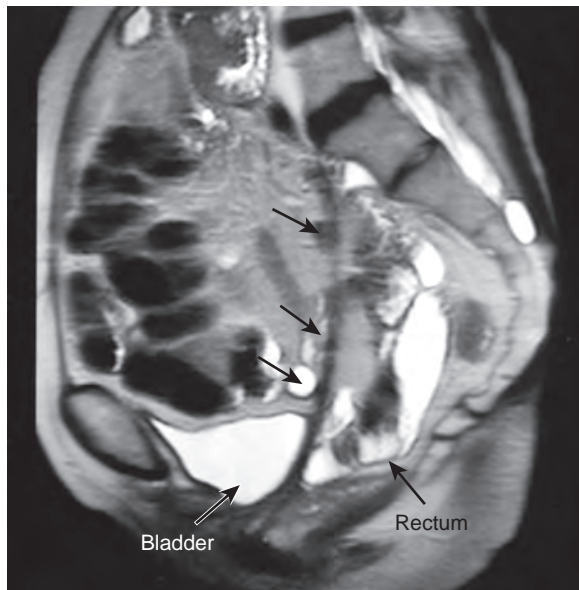


Figure 85-6. Magnetic resonance imaging identifies mesh (arrows) in a patient with pain after sacrocolpopexy.

Diagnosis

The use of standardized nomenclature has been encouraged for evaluation of mesh exposure (Skala et al, 2011). Clear documentation facilitates monitoring of symptoms over time as well as communication between physicians in cases of referral (Table 85-1) (Haylen et al, 2011). The International Continence Society and the International Urogynecologic Association recommend documenting complications by time of presentation, symptom severity, and presence of associated symptoms.

TREATMENT OF MESH COMPLICATIONS

Expectant Management and Counseling

There is a place for expectant management of mesh complications. The decision to proceed with expectant management should take into consideration the time since mesh placement, degree of symptoms, organ systems affected, and patient satisfaction. Patients who elect for expectant management must be appropriately counseled regarding treatment options and offered realistic expectations regarding anticipated improvement. A patient with asymptomatic mesh exposure without pain or pelvic organ dysfunction is an

TABLE 85-1 Suggested Terminology for Complications Related to the Use of Mesh

TERMINOLOGY	DEFINITION
Complication	Morbid process not part of original surgery
Contraction	Size reduction
Prominence	Parts project beyond a surface
Penetration	Enters
Separation	Physically disconnected
Exposure	Displaying or revealing
Extrusion	Gradual passage out of body
Perforation	Abnormal opening into hollow organ
Dehiscence	Gaping along natural or sutured lines

Modified from Haylen BT, Freeman RM, Swift SE, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prosthesis (meshes, implants, tapes) and grafts in female pelvic floor surgery. *Int Urogynecol J Pelvic Floor Dysfunct* 2011;22:3–15.

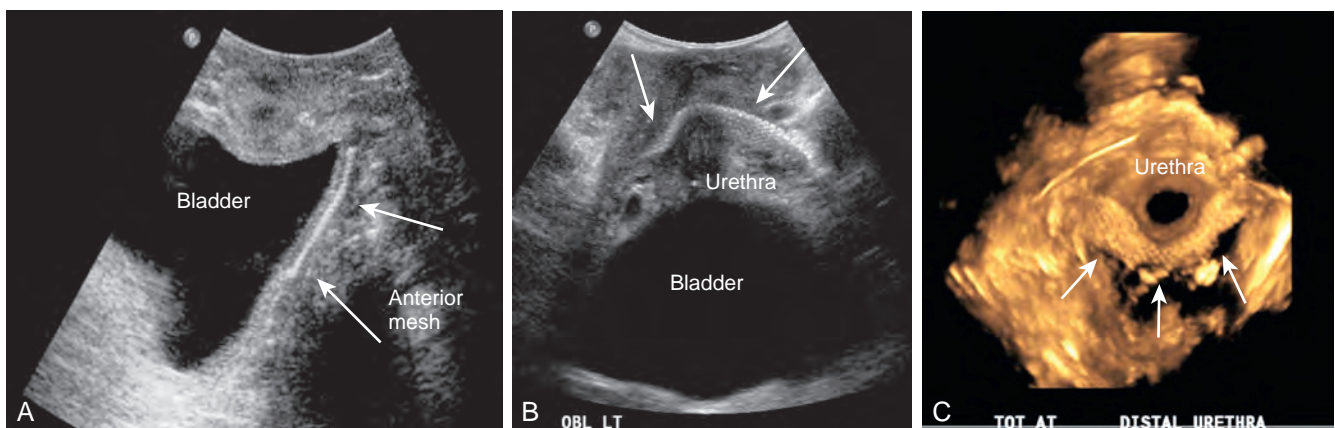


Figure 85-7. Translabial ultrasonography. A, Anterior vaginal synthetic graft (arrows), two-dimensional sagittal view. B, Mid-urethral synthetic sling (arrows), two-dimensional oblique view. C, Mid-urethral synthetic sling, no penetration of periurethral fascia (arrows), three-dimensional reconstruction.

example of an appropriate candidate for expectant management. These patients may present at any time from the immediate to delayed postoperative period, including decades later. However, the etiology of exposure and contributing factors depend significantly on time since placement. Immediate exposure suggests wound separation directly, whereas late presentation suggests a chronic process. In contrast, patients may present in the delayed postoperative period during which time weakened vaginal epithelium, inflammation, mesh shrinkage, and improper placement all may contribute to new diagnosis of exposure. This diagnosis can be particularly frustrating for physicians and patients who were reassured by lack of exposure at the first postoperative visit.

Medical Management

If an infectious component of mesh exposure is suspected, treatment with antibiotics is reasonable, with the expectation that persistent infection and exposure resistant to medications may require surgical excision of exposed portions, or more, to prevent further deterioration. Clindamycin and metronidazole are commonly used antibiotics for vaginal exposure. **If tissue atrophy is suspected, initiating vaginal estrogen can combat this process** and has been successful in reversing some atrophic findings (Vaccaro et al, 2013).

Medical management of pain symptoms is appropriate in select cases. Etiologies of pain such as urinary or fecal obstruction, hematoma, and abscess should be ruled out or treated appropriately. Drainage may be required for abscesses that do not respond to antibiotic therapy (Rafii et al, 2006; Ugurlucan et al, 2013). Residual pain may be treated with consultation with a pain specialist as needed. Pain out of proportion to physical examination, pain that fails medical management, or pain that persists past the postoperative period should be addressed promptly, and surgeons should be prepared to discuss additional treatment options. Pelvic floor physical therapy is appropriate for patients with pain, multicompartiment organ dysfunction, scar tissue, or preexisting pain syndromes. **Surgical removal of mesh in cases of severe refractory pain may improve symptoms in most patients** (Tijdink et al, 2011).

Surgical Management

Patients with persistent urinary retention may be offered surgical urethrolisis. This procedure can be performed through vaginal incisions, where the urethra is circumferentially freed from the anterior vaginal wall and pubic bone. Interposition with tissue flaps such as Martius labial flaps can be used to decrease recurrence. Outcome is difficult to predict, and voiding pressure/flow studies may be unnecessary before discussing intervention for obstruction (Winters et al, 2012). Improvement in obstruction can be achieved in 80% of patients after urethrolisis (Nitti and Raz, 1994), although many have residual urgency symptoms (Starkman et al, 2008).

Patients with pelvic organ dysfunction in the absence of pain or infection are candidates for partial mesh excision. This strategy is also an option for carefully selected patients with recurrent exposures who have failed conservative management. These patients must be aware that infection in this setting may not be limited to exposed segments alone, and they remain at risk for exposure of remaining mesh. The decision to proceed with complete excision is a difficult one, especially in patients whose prolapse and incontinence symptoms have been relieved. For this reason, we encourage careful patient selection, thorough counseling, and expectant management. Early removal may completely reverse symptoms (El-Nashar et al, 2013). Multiple failed attempts at partial excisions can be frustrating for the patient and the surgeon and contribute to low patient satisfaction. The surgeon also must consider that complete removal is more challenging when a patient has undergone prior partial excisions.

Complete excision of pelvic reconstruction mesh has been described (Fig. 85-8). In cases where mesh extends to suprapubic or thigh skin, marking puncture sites preoperatively at the location of patient discomfort may facilitate identification while the patient

is under anesthesia. Mesh size can be significantly smaller than when initially placed, making intraoperative identification difficult without external markings. **Armed products are among the most surgically challenging because of mesh quantity and the anatomic structures traversed, and referral to a surgeon with extensive experience with these procedures is recommended.** Removal of mid-urethral slings should begin with inspection and palpation of the anterior vaginal wall.

For **removal of retropubic slings**, an incision is made horizontally across the sling, with care not to incise the sling completely. The central incision should be carried to the sulci laterally where bilateral vertical incisions are made to facilitate entry into the retropubic space. Alternatively, lateral incisions can be made in the anterior vaginal wall. The sling is isolated from the vaginal wall and marked with a permanent suture. This is repeated on the contralateral side. A transverse incision is made in the anterior vaginal wall across the sling, with care not to incise the sling. When the midportion of the sling is visualized, it can be transected in the midline, and the lateral portions can be held with clamps or sutures for countertraction during dissection. Infiltrated or eroded vaginal wall should be excised. Starting with the central free portion, the sling arm can be dissected laterally until the retropubic space is reached. Using a curved scissor, the retropubic endopelvic fascia is sharply entered at the location of the sling arm. At this juncture, the medial portion must be dissected from the perivesical tissue, and the anterior portion must be dissected from the posterior pubic symphysis. This portion of the dissection is often very challenging and may require sharp tools for complete removal such as periosteal elevators used in orthopedic surgery. When the mesh arm is released from the bone and perivesical tissues, gentle traction should reveal the location of attachment to the anterior abdominal wall (presumably at or near the site of preoperative marking). A skin incision is made, and the subcutaneous tissue is incised to reveal the mesh, which is grasped with a clamp for retraction. The fascia is perforated sharply where the mesh traverses it. The entire sling arm should be free and can be removed. The same procedure is repeated for the opposite arm.

Removal of mid-urethral slings with transobturator arms begins similarly (Reynolds et al, 2012). When the midportion of the sling is released to the lateral incisions, the obturator fascia and obturator internus must be perforated and the mesh freed from its attachments circumferentially. The mesh must be dissected off the pubic bone, obturator membrane, and obturator externus. Gentle traction should reveal the location of the mesh as it traverses the adductor fossa toward the lateral labial or medial thigh exit site. The skin can be incised to reveal the adductor fascia and the gracilis and adductor longus muscles beneath. The mesh is transferred through the adductor fossa and subsequently removed. These steps are repeated on the opposite side.

Removal of vaginal prolapse mesh requires dissection of a larger portion of vaginal wall. Incision planning depends on the location and size of mesh, location and number of vaginal exposures, and plans for reconstruction after mesh removal. For removal of armed anterior vaginal mesh, a vertical incision is made in the anterior vaginal wall. Dissection is carried out laterally to the perivesical space to isolate the anterior mesh arms. The posterior arms are carefully dissected to the sacrospinous ligament attachments. During the process of mesh dissection from the sacrospinous ligament, care should be taken not to injure branches of the uterine artery because this can result in significant blood loss that is difficult to control. The pudendal nerve and lumbosacral nerve plexus also may be in the area of dissection in these cases and are at risk for injury. If anterior vaginal mesh is to be removed concurrently with a mid-urethral sling, an inverted-U incision is creased after removal of the mid-urethral sling, and the lateral incisions are carried to the vaginal cuff or uterus. This technique allows mobilization of the flaps for a tension-free closure. Using gentle traction, the vaginal wall and bladder can be separated from the underlying mesh.

Removal of isolated arms in patients with prior revisions is significantly more challenging because no central intact portion can be tractioned to identify the location of lateral arms. Large defects

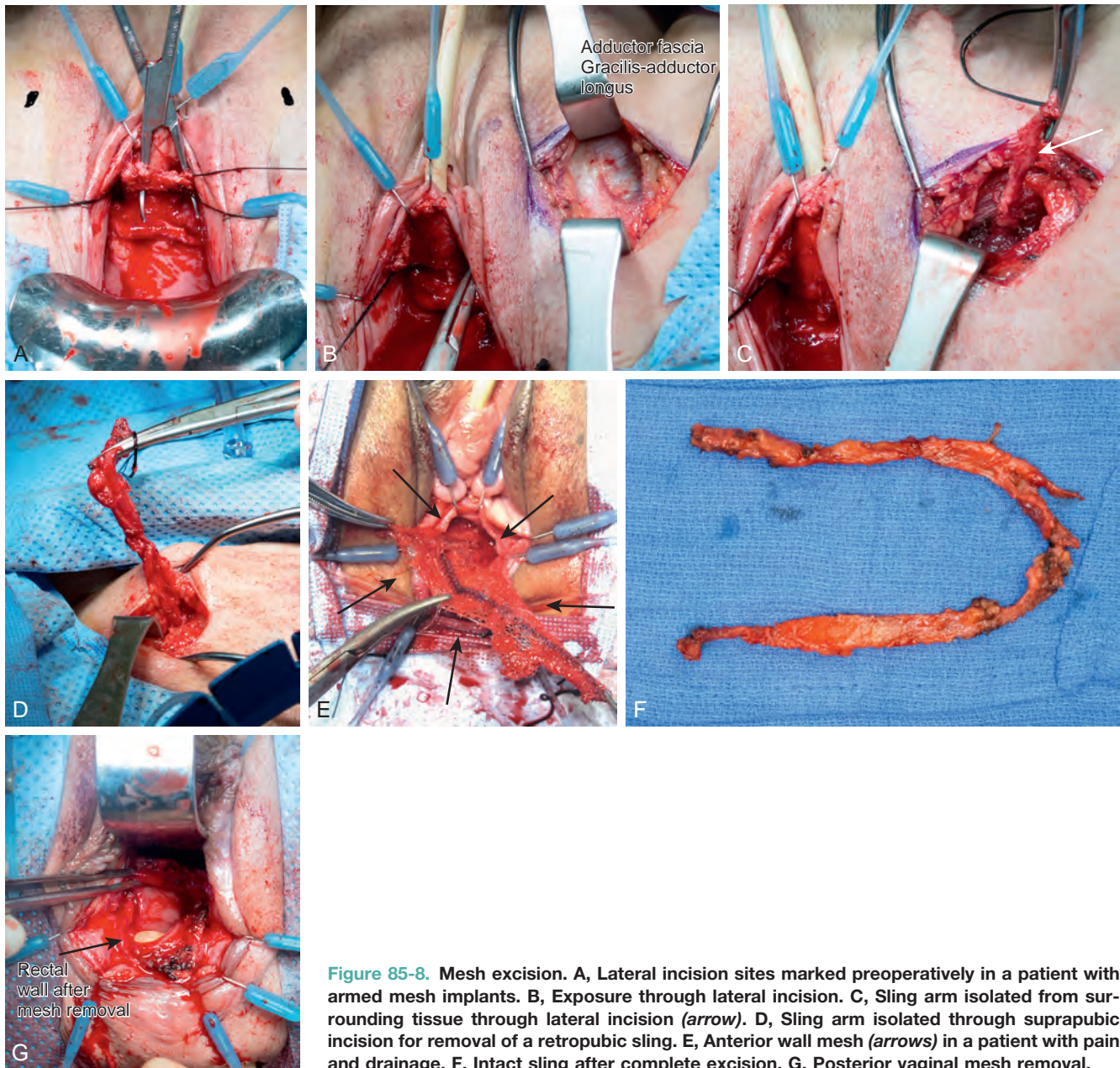


Figure 85-8. Mesh excision. A, Lateral incision sites marked preoperatively in a patient with armed mesh implants. B, Exposure through lateral incision. C, Sling arm isolated from surrounding tissue through lateral incision (arrow). D, Sling arm isolated through suprapubic incision for removal of a retropubic sling. E, Anterior wall mesh (arrows) in a patient with pain and drainage. F, Intact sling after complete excision. G, Posterior vaginal mesh removal.

may remain after mesh removal, especially after excision of exposed anterior vaginal mesh. These cases may require tissue flaps from the vaginal cuff or labia or other advanced pelvic reconstruction to repair defects without resultant vaginal stenosis. Pubovaginal slings of nonsynthetic tissue may be used for recurrent stress urinary incontinence (Shah et al, 2013).

Alternative Therapy

Alternative management strategies may be appropriate for patients with complications of mesh procedures. Acupuncture, botulinum toxin, and pelvic floor physical therapy have been used in the management of pelvic floor dysfunction and may be used in patients with a history of pelvic reconstructive surgery (Herderschee et al, 2013). Concurrent management with chronic pain specialists, gastroenterologists, or other specialists may assist with symptom control and patient satisfaction while the surgeon pursues evaluation and treatment.

Evaluation of recurrent prolapse or incontinence symptoms should not be undertaken until all complications have been addressed. Excision of mesh used in pelvic reconstructive surgery should not be delayed for fear of recurrent symptoms. Large series demonstrate a 30% to 50% incontinence risk after sling excision, and short-term data suggest only 20% of anterior compartment prolapse recurs after mesh removal (Marcus-Braun and von Theobald, 2010; Nakamura et al, 2013). The suggested explanation is that fibrotic tissue is at least as durable as traditional colporrhaphy alone.


CONCLUSION

Surgeons who perform mesh placement should strive to be competent with treatment of mesh complications and surgical removal. Complications of mesh used in the treatment of incontinence and prolapse are greater in frequency and morbidity than previously

described. Although some of these are mild and easily treated, some are not completely reversible. Estimates of frequency of complications are likely to increase as more patients undergo mesh-augmented surgery and longer term outcomes are reported.

The future is not a world without mesh; there remains a place for mesh-augmented incontinence and prolapse repair. Such procedures remain viable options for patients with poor tissue quality, patients who have failed prior nonaugmented repairs, and patients who have been appropriately counseled regarding the trade-off of possibly improved anatomic outcome against increased complication rates. Also, **current FDA investigation is focused on mesh placed vaginally for repair of anterior, posterior, or apical prolapse and not mesh placed abdominally for prolapse or mesh slings placed for urinary incontinence.** Urologic associations agree with this statement and continue to support mesh use for mid-urethral slings for the treatment of stress urinary incontinence (Dmochowski et al, 2010; American Urogynecologic Society and Society of Urodynamics, 2014). However, surgeons who are unfa-

miliar with removal of such devices and have limited experience in placement should be cautioned regarding their use and encouraged to refer to more experienced physicians when indicated.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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Use of Injectable Agents in Female Stress Urinary Incontinence

Pathophysiology of Postprostatectomy Incontinence and the Use of Injectable Agents for Male Stress Urinary Incontinence

The quest for injectable agents for urinary incontinence started at the end of the 19th century when R. Gersuny (Gersuny, 1900) from Vienna suggested periurethral paraffin injection for urethral compression. In 1914, Howard Kelly (Kelly and Dumm, 1914) warned about the dangers of embolism after injection and pointed out that this treatment showed only temporary improvement of symptoms. In 1938, Murless first reported the injection of morrhuate sodium, a sclerosing agent synthesized from cod liver oil, into the anterior vaginal wall for treatment of stress urinary incontinence (SUI) (Murless, 1938). Of the 20 patients treated, 17 were cured or improved for at least 12 months. Sloughing of a segment of the anterior vaginal wall was seen in 12 patients, and of these, 75% were cured. Murless postulated that success was the result of contraction of the resulting scar of the anterior vaginal wall. Quackels (1955) reported on the injection of paraffin for incontinence after prostatectomy in 1955, and Sachse (1963), based on previous reports, injected a mineral oil preparation, granugenol oil, or Dondren, another sclerosing agent. He reported cures in 12 of 24 men who had undergone prostatectomy and 4 of 7 women. However, significant complications of pulmonary emboli and urethral sloughing were seen. With the last case report of distal ureteral stenosis after periurethral injection, it was recommended not to use sclerosing agents for incontinence (Bubanz et al, 1980).

Polytetrafluoroethylene (Teflon) paste was first introduced by Berg (1973) and then popularized by Politano and colleagues (1973). Shortliffe and coworkers (1989) published the first report on glutaraldehyde cross-linked (GAX) collagen, and Santarosa and Blaivas (1994) described the use of autologous fat in women with SUI. More recently, newer synthetic materials have been described that theoretically should improve efficacy, durability, and safety.

The ideal injectable agent should be easily injectable and should conserve its volume over time. It should also be biocompatible, nonantigenic, noncarcinogenic, and nonmigratory and should cause little or no inflammatory reaction (Kershen and Atala, 1999) or fibrotic ingrowth (Dmochowski and Appell, 2000). The components of the bulking agent should not separate or dissociate on injection, and, if the agent contains microcrystalline or micropolymeric components, they should be reasonably uniform spheres of particle sizes above 110 μm that are nonfragile and adhere to host tissue (Dmochowski and Appell, 2000). If unsuccessful, the treatment should not interfere with subsequent surgical intervention. To date, no substance has met all of these requirements.

Over the past 35 years there has been an evolution of injectable agents, and diverse types have been tested. In the late 1990s, injection therapy was the most commonly performed anti-incontinence procedure in women with SUI, at a rate of 3649 procedures per 100,000 women (Nygaard et al, 2004). By 2007 the rate had fallen to 2236 procedures per 100,000 (Rogo-Gupta et al, 2013). Reasons

Use of Injectables for Incontinence after Urinary Diversion

for the decline in numbers may be the less-than-optimal results, especially in the long term, and the availability of other minimally invasive options (Kong and Vasavada, 2009). Box 86-1 lists the agents that are discussed in this chapter. Most are bulking agents, but recently the injection of autologous stem cells for sphincter enhancement and implantable balloons that compress the urethra have been introduced.

The evidence for and the clinical use of injectable agents for SUI in women and men are reviewed in this chapter.

USE OF INJECTABLE AGENTS IN FEMALE STRESS URINARY INCONTINENCE

Pathophysiology of Stress Urinary Incontinence and the Role of Injectable Agents

The goal of injectables is to augment or restore urethral mucosal coaptation and its “hermetic seal effect” contribution to the continence mechanism (Appell and Winters, 2007) and to maintain coaptation during periods of increased abdominal pressure (Reynolds and Dmochowski, 2012). It is generally thought that these agents improve intrinsic sphincter function, although the exact mechanism has not been defined (Smith et al, 2009). Bulking agents such as collagen have been reported (McGuire and Appell, 1994; Monga et al, 1995) to augment urethral mucosa and improve coaptation and intrinsic sphincter function, as evidenced by an increase in post-treatment abdominal leak pressure (Herschorn et al, 1992; Richardson et al, 1995; Winters and Appell, 1995). Bulking agents do not usually obstruct voiding after the initial post-treatment period (Monga et al, 1995). Monga and coworkers (1995) showed that successfully treated patients have an increased area and pressure transmission ratio in the first quarter of the urethra. They suggested that placement of the injectable at the bladder neck or proximal urethra prevents bladder neck opening under stress, although this is controversial. Proper placement of the injectable, possibly just below the bladder neck, rather than actual quantity of the agent (Khullar et al, 1997) improves intrinsic sphincter dysfunction (ISD).

Patient Selection, Indications, and Contraindications

Injectable agents are one of the many treatment options for SUI. Although initially it was thought that these agents would be most effective in patients with ISD alone, multiple reports have shown clinical efficacy in patients with hypermobility (Herschorn et al, 1996; Steele et al, 2000; Bent et al, 2001a; Lose et al, 2010). Injectable agents may provide a rapid response for some patients and are an option for those who do not wish to undergo more

BOX 86-1 Types of Injectable Agents for Stress Urinary Incontinence**BIOLOGIC AGENTS****Bulking Agents**

No longer used: Homologous: bovine collagen (Contigen), porcine collagen (Permacol)

No longer used: Autologous fat

Cell-Based Therapy

Autologous muscle-derived stem cells (MDSCs), adipose tissue-derived stem cells (ADSCs)

Minced autologous striated muscle

SYNTHETIC AGENTS

Currently used: Carbon-coated zirconium beads (Durasphere), polydimethylsiloxane (Macroplastique), dextranomer hyaluronic acid (Deflux), polyacrylamide hydrogel (Bulkamid), calcium hydroxylapatite (Coaptite)

No longer used: Polytetrafluoroethylene (Teflon), ethylene vinyl alcohol (Tegress)

BALLOONS

Currently used: Adjustable balloons (ACT, ProACT)

No longer used: Microballoons (UroVive)

invasive procedures. However, the patient must understand that efficacy and duration are inferior to surgery and that follow-up injections may be required. Other possible indications include elderly patients, those with high anesthetic risk, or those willing to accept an improvement rather than cure of their SUI symptoms (Appell et al, 2012). Other considerations may include patients who cannot stop anticoagulation, desire nonsurgical therapy using only local anesthesia, desire more children, have mild persistent SUI after an SUI procedure, have SUI and poor bladder emptying, or have mild SUI associated with exercise (Cespedes and Serkin, 2009).

Detrusor overactivity should be treated before injection because results may be compromised (Herschorn et al, 1996). Severe urethral scarring from radiation or surgery may affect mucosal pliability by preventing bulking and retention of the injectable in the urethra.

Contraindications include active urinary infection and hypersensitivity to the injectable material.

Workup

Patients who may be candidates for injectable agents should undergo a diagnostic evaluation to confirm the diagnosis in a similar fashion to other patients with SUI. A focused history to characterize the chief complaint including the frequency, severity, and degree of bother should be done. An assessment of other urinary symptoms should be completed and the desire for treatment should be ascertained. Helpful tools include various validated symptom and quality-of-life questionnaires and frequency-volume charts (Appell et al, 2012; Staskin et al, 2013).

Physical Examination

The physical examination should provide information about the cause of the lower urinary tract symptoms and suggest additional management options. The general examination should include an abdominal examination to evaluate the skin, surgical incisions, and the presence of any hernias or abdominal masses, including a full bladder. Pelvic and perineal examination should be performed.

Pelvic Examination

The patient is placed in the lithotomy position. The external genitalia should be examined for dermatologic lesions and inflammatory conditions. The internal genitalia should be examined for estrogen deficiency, urine or abnormal vaginal discharge, pelvic organ prolapse, and abnormal pelvic masses. The poorly estrogenized vaginal wall has a thinned epithelium with loss of transverse rugae, which are normally present in its lower two thirds (Fantl et al, 1994). The patient should be examined with a comfortably full bladder to assess stress leakage and, if necessary, with an empty bladder to assess other pelvic organ prolapse and masses.

Because incontinence (or pelvic organ prolapse) may not be evident, or its full extent demonstrated, in the dorsal lithotomy position, it has been recommended that the patient be examined in the semiupright or even upright position (Walters and Karram, 1992). A systematic examination of the vaginal walls and perineum should also be done. (For details, please refer to the chapter on pelvic organ prolapse.)

Urethral mobility can be observed with the patient straining or by the cotton-swab or Q-tip test (Crystle et al, 1971). The angles of deflection of the Q-tip at rest and with straining are measured with a goniometer. Hypermobility is defined as a maximum strain axis of more than 30 degrees from the horizontal. Urethral axis testing does not diagnose any form of incontinence because continent women may demonstrate rotational descent of the urethra (Fantl et al, 1986) and incontinent women may have no descent. Although this method has been shown to be reproducible (Fantl et al, 1986), it has not been compared with other radiologic methods. However, it may be helpful in assessing the degree of hypermobility.

If the patient has a fixed nonmobile urethra, especially if there has been previous SUI surgery, and leaks occur with coughing and/or straining, most likely the patient has ISD as the predominant cause of the SUI. However, if hypermobility is present, the relative contribution of the causes (ISD vs. anatomic support) cannot be ascertained clinically.

Additional Testing

The initial evaluation of urinary incontinence in women includes a history, physical examination, urinalysis, and measurement of post-void residual (PVR) urine (Abrams et al, 2010). The basic evaluation may be satisfactory for proceeding with treatment, including surgery, for patients with straightforward stress incontinence associated with hypermobility with normal PVR volume (Fantl et al, 1996). The indications for additional testing include an inability to make a definitive diagnosis based on symptoms and the initial evaluation; concomitant overactive bladder symptoms; prior lower urinary tract surgery (including failed anti-incontinence procedures); known or suspected neurologic disease affecting the bladder; negative stress test result; abnormal urinalysis findings such as hematuria or pyuria; abnormal PVR urine; beyond hymen and symptomatic pelvic prolapse; and dysfunctional voiding (Appell et al, 2012). Additional testing can include pad testing and/or voiding diary, urodynamic studies, cystoscopy, and imaging. The evaluation can be tailored to elucidate the patient's problem.

Urodynamic Studies

In the evaluation of the patient with SUI, urodynamic studies before interventional treatment are helpful in specific circumstances. These studies are used to confirm the diagnosis if the symptoms are confusing or complex and other problems are suspected, such as detrusor overactivity, urethral obstruction or voiding dysfunction, low bladder compliance, and/or impaired or absent detrusor contractility (Appell et al, 2012; National Institute for Health and Care Excellence [NICE], 2013). Urodynamic studies have also been recommended if there has been previous surgery for SUI or anterior compartment prolapse (NICE, 2013). Multichannel urodynamic studies are not recommended in patients with pure SUI diagnosed on history and physical examination (NICE, 2013; Lucas et al,

2014). There is also evidence that women with uncomplicated clinically demonstrable SUI whose surgery is determined by office evaluation alone have similar postoperative outcomes to patients who undergo office evaluation plus urodynamic studies (Nager et al, 2012). Similarly, in a randomized controlled trial (RCT) comparing SUI patients who had urodynamic findings discordant with symptoms, there were similar postoperative outcomes whether the patients had immediate surgery versus other tailored intervention determined by the urodynamic findings (van Leijssen et al, 2013). However, urodynamic testing was recommended before surgical intervention in all patients at the Fifth International Consultation on Incontinence (Rosier et al, 2013).

Because injectable agents are indicated for the ISD component of SUI, can urodynamic studies assess ISD? Two measures of urethral function have been used: maximum urethral closure pressure (MUCP) and abdominal leak point pressure (ALPP). MUCP of 20 cm H₂O or lower has been suggested as indicating clinically significant urethral weakness, but there is controversy regarding the diagnostic and predictive value of urethral pressure profilometry in characterizing ISD (Weber, 2001). Similarly an ALPP of 60 cm H₂O or lower was identified as an indicator of severe ISD (McGuire et al, 1993), but many studies have not confirmed the test's value in quantifying the degree of ISD (Koelbl et al, 2009). Previously, ALPP measurements of initially 65 cm H₂O or lower and then 100 cm H₂O or lower were used as indicators of ISD to justify the use of injectable agents (Appell and Winters, 2007). However, because ISD may be present in many patients with SUI with or without urethral hypermobility (Koelbl et al, 2009, 2013), the specific value of either MUCP or ALPP may be of no importance in the clinical decision about the use of injectables. As with other patients with SUI who opt for interventional therapy, urodynamic studies may be helpful for the aforementioned reasons.

Cystoscopy

Routine cystoscopy is not recommended for the evaluation of SUI. However, it is indicated for the evaluation of incontinent patients

who have sterile hematuria or pyuria; urgency incontinence to rule out other pathologies (e.g., bladder tumor, interstitial cystitis); recurrent or iatrogenic incontinence when surgery is indicated or planned; or vesicovaginal fistula or extraurethral incontinence (Tubaro et al, 2009), or when urodynamic studies fail to duplicate symptoms of incontinence (Fantl et al, 1996). Furthermore, **preinjection cystoscopy is helpful to make sure that there are no adverse factors or unexpected findings that may prevent or compromise the injection procedure such as extensive urethral scarring from previous surgery, radiation, trauma, foreign bodies, or urethral diverticula.**

Injection Techniques

The materials can be administered using local anesthesia with cystoscopic control as an outpatient procedure. Both the **periurethral** and **transurethral** methods have been done to implant the agent within the urethral wall, preferably into the submucosa or lamina propria. It is thought that the implant should be positioned at the bladder neck or proximal urethra. Different sites can be chosen, such as the 3 and 9 o'clock or 4 and 8 o'clock positions. The needle size depends on the viscosity of the injectable. Preoperative and postoperative antibiotics are frequently administered. The technique for injection is shown in Figures 86-1 and 86-2. Additional bilateral periurethral infiltration of 2 to 3 mL of 1% or 2% aqueous lidocaine injected lateral to the urethra may improve patient comfort. The goal with current injectables is to create mucosal apposition at the end of treatment.

Periurethral Technique

The patient is placed in the lithotomy position and prepared and draped in the usual sterile fashion. Topical 2% urethral lidocaine jelly is instilled into the meatus. Perimeatal blebs are raised with 1% or 2% aqueous lidocaine at the 3 and 9 or 4 and 8 o'clock positions approximately 3 to 4 mm lateral to the urethral meatus with a 25-gauge needle. A 20-Fr urethroscope with a 30-degree telescope is inserted into the urethra. The periurethral needle is

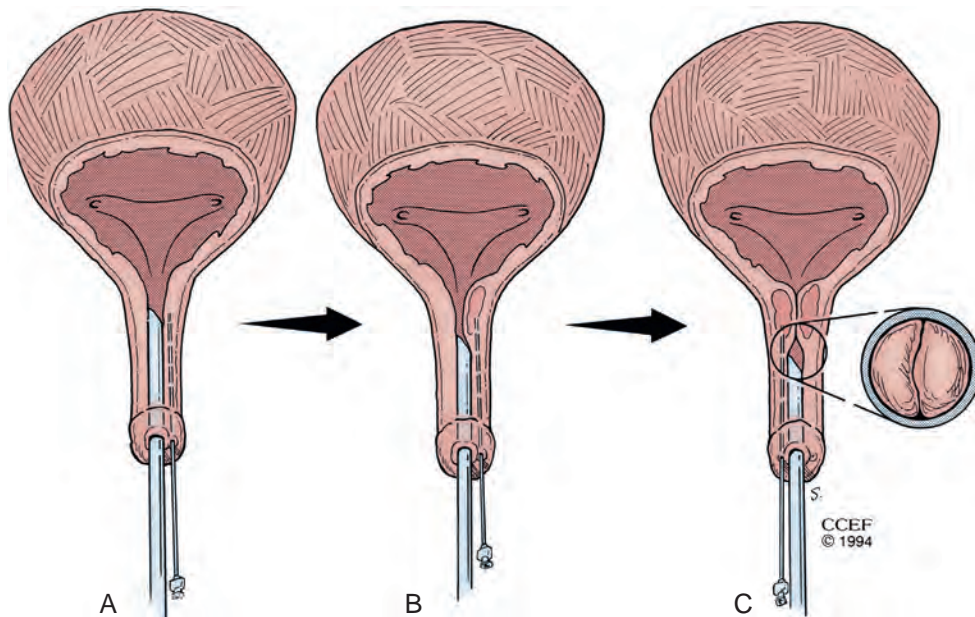


Figure 86-1. Periurethral collagen injection. The 20-Fr cystoscope with a 30-degree lens is positioned in the urethra while the substance is injected into the bladder neck region. A, Appearance of the urethra before treatment. B, Periurethral needle positioned in the proximal urethra below the bladder neck. C, Appearance of the urethra after injection. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1994-2011. All rights reserved.)

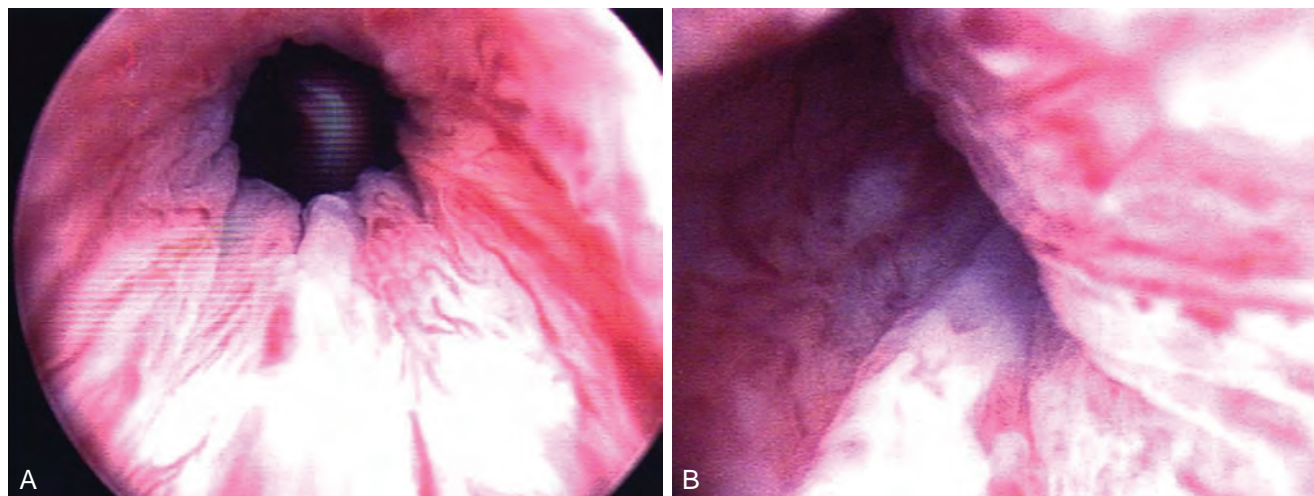


Figure 86-2. A, Cystoscopic view of the open bladder neck region before injection. B, Collagen has been injected via the periurethral route on the patient's left side. Note the intraluminal bulking effect of the bulking agent.

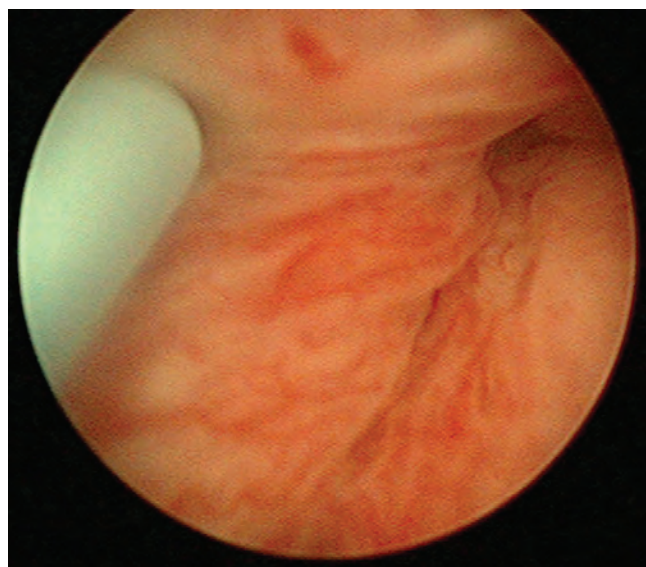


Figure 86-3. Appearance of urethra after injection of collagen with a transurethral needle, shown on the left. Both sides of the urethra have been injected, giving the appearance of an occlusive prostate.

introduced and advanced parallel to the endoscope sheath until its position can be seen cystoscopically just below the bladder neck within the mucosa. The surgeon can hold the cystoscope in one hand and advance the needle with the other. Care must be taken to prevent the needle from getting too close to or entering the urethral lumen because rupture of the mucosa and extravasation will occur. Rocking the needle will confirm the position of the tip. If penetration of the mucosa occurs, the needle should be removed and repositioned. The substance is injected either unilaterally or bilaterally to create the appearance of “prostatic” lobes (Fig. 86-3). Transvaginal injection with the needle placed through the biopsy port of an ultrasound probe has also been described (Appell, 1996).

An 18-gauge bent-tipped needle has been designed for the periurethral approach for placement of Durasphere beads within the proper plane (Appell and Winters, 2007).

Transurethral Techniques

With Cystoscopic Monitoring. The implant can also be injected transurethral through the cystoscope with specially designed injection needles or with other devices that do not necessitate cystoscopy. In this approach a 0-, 12-, or 30-degree lens may be used. Various cystoscope sheaths are available, but one with a flat rather than a beaked end will prevent the needle from penetrating the urethra proximal to the view from the lens. Endoscopic instrument companies have an array of equipment designed for transurethral injections. The material can be injected through a semirigid needle that is advanced through a working element or a flexible needle that is advanced by the surgeon. Both have 22-gauge tips that are about 1 cm long.

The patient is prepared in the same fashion as for the periurethral approach. Topical urethral lidocaine jelly as well as aqueous lidocaine injected periurethrally can be used. The injection needle is inserted into the urethra at a 30- to 45-degree angle and advanced proximally in the submucosal region under the surface of the mucosa. The point of penetration of the urethra has to be at a distance below the bladder neck of more than the length of the needle to prevent extravasation of the substance into the bladder. Injections can be given at the 3-, 6-, and 9-o'clock positions until mucosal apposition is achieved. The cystoscope should not be advanced through the bulked up urethra and bladder neck to avoid compressing or causing extravasation of the injected material.

Because of the high viscosity of Macroplastique, injections of this material require the use of a ratcheted injection gun (Fig. 86-4). The injection needle is 7 Fr with a 10-mm 18-gauge needle tip.

Polyacrylamide hydrogel (PAHG; Bulkamid) is provided in 1-mL syringes with a 12-cm 23-gauge needle and is injected via a short 0-degree urethroscope and plastic sheath (Fig. 86-5).

The periurethral and transurethral approaches for collagen were compared first by Faerber and colleagues (1998), who reported no significant difference in success rates and numbers of injections required in 24 patients with transurethral treatment versus 21 with a periurethral approach. However, significantly more collagen was required for the periurethral approach. Schulz and coworkers (2004) reported similar findings in 40 women randomly assigned to either technique. There was no difference in short-term success rate, but the 20 women assigned to the periurethral approach required more collagen than those assigned to the transurethral approach. Furthermore, the Cochrane review

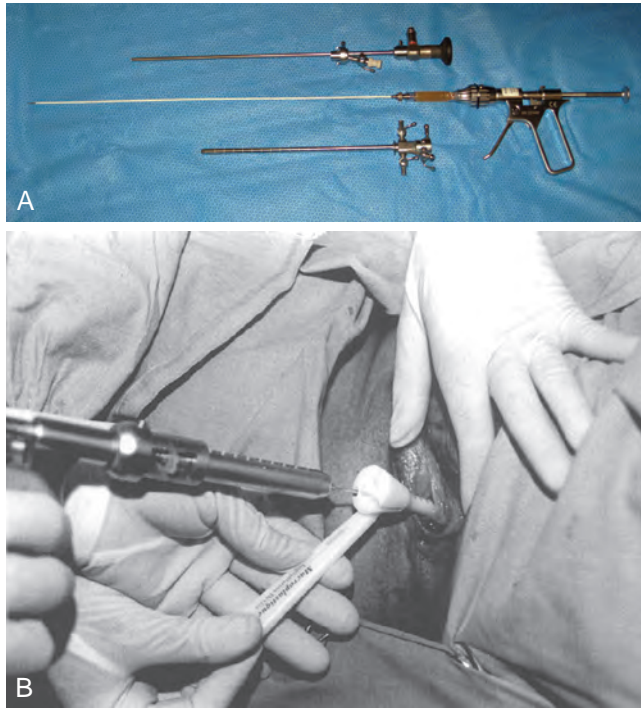


Figure 86-4. A, Silicone macroparticle injection gun. The injection needle is 7 Fr with a 10-mm, 18-gauge needle tip. B, The implantation procedure. The bulking agent is injected through the device using the injection gun and a rigid needle. (From Tamanini JT, D'Ancona CA, Netto NR Jr. Treatment of intrinsic sphincter deficiency using the Macroplastique Implantation System: two-year follow-up. *J Endourol* 2004;18[9]:906–11.)

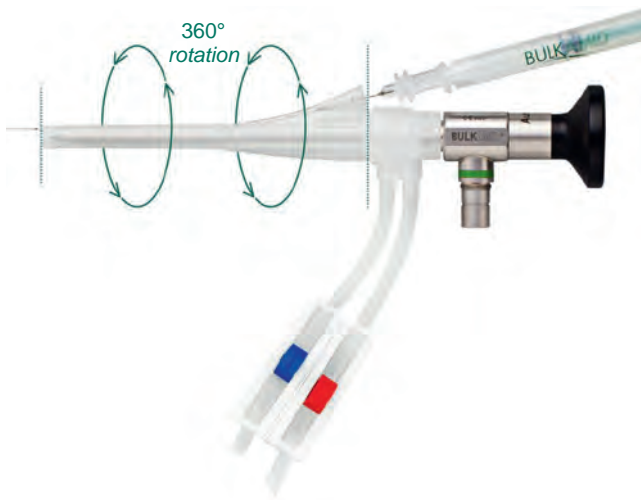


Figure 86-5. Bulkamid urethral injection system. Bulkamid is injected transurethraly with a short 0-degree telescope through a plastic sheath. The sheath with injection needle port rotates to allow injection of the agent at different sites. (From Sokol ER, Karram MM, Dmochowski R. Efficacy and safety of polyacrylamide hydrogel for the treatment of female stress incontinence: a randomized, prospective, multicenter North American study. *J Urol* 192[3]:843–9.)

concluded that there are insufficient data to determine whether the transurethral is superior to the periurethral approach and whether mid-urethral injection offers any benefit over bladder neck injection (Kirchin et al, 2012). The transurethral approach is now more commonly reported than the periurethral approach.

Regarding the distribution of the injected agent, circumferential dispersal around the urethra appears to correlate with a better outcome as determined in studies using three-dimensional ultrasound (Radley et al, 2001; Defreitas et al, 2003; Poon et al, 2005; Hegde et al, 2013).

Without Cystoscopic Monitoring. A handheld device that allows the operator to inject Macroplastique transurethraly without cystoscopy was introduced by Henalla and colleagues (2000) in a multicenter trial of 40 patients (see Fig. 86-4B). Device efficacy and acceptability were rated highly by the surgeons at 92.5% and 95%, respectively, and at 3 months 74.3% of patients had a good outcome. Twelve-month outcomes in a cohort of 21 patients who had Macroplastique injections administered with this device were reported by Tamanini and coworkers (2003); 57.1% of patients considered themselves cured, 19% improved, and 23.8% failed. Two-years outcomes showed some deterioration in results, with 47% cured, 14.3% improved, and 38.1% failed (Tamanini et al, 2004).

Periprocedure Care

Although randomized trials have not been done, prophylactic antibiotics with a fluoroquinolone or trimethoprim-sulfamethoxazole (TMP-SMX) for 24 hours or less can be recommended (Wolf et al, 2008). An additional 2 to 3 days has also been suggested (Appell and Winters, 2007).

After the injection the patient is asked to cough or strain in the supine and then the upright position. If leakage still occurs, more agent may be given. If no leakage is seen, the procedure may be terminated. The patient then voids and can be discharged. Urinary retention can be treated by insertion of a fine Foley catheter (12 to 14 Fr or smaller) overnight or intermittent catheterization. Although not specifically reported, an indwelling Foley catheter may cause molding of the agent and lead to early failure, so long-term catheterization should be avoided.

Reinjections

The minimum timing for reinjections is variable and depends on the agent. Although bovine GAX collagen (Contigen) could be reinjected within 7 days, most clinicians have waited 4 weeks or longer to assess response of the urethra and the need for reinjection (Appell and Winters, 2007). Silicone microimplant (Macroplastique) injections can be repeated after 12 weeks (see <http://www.uroplasty.com/Uroplasty/view/files/pdf/4171.pdf>). Carbon-coated zirconium beads (Durasphere) can be reinjected after a minimum of 7 days (Lightner et al, 2001) and calcium hydroxylapatite (CaHA; Coaptite) after 1 month or less (Mayer et al, 2007). PAHG (Bulkamid) has been reinjected at 1 to 2 months (Tooze-Hobson et al, 2012; Sokol et al, 2014).

Pitfalls in Reported Study Results of Durability

A number of pitfalls in reporting of injectable studies can lead to inflated success rates. Because injectable agents can be repeated if the treatment is not a success, authors should specify whether the time point of reporting is after all treatments have been completed or whether it is from baseline. If durability is reported after all injections have been administered, then an accurate picture of duration of efficacy can be conveyed. A Kaplan-Meier curve of efficacy has been useful in showing what happens to patients' continence outcome over time (Herschorn and Radomski, 1997; Lightner et al, 2001). Nevertheless, some studies report duration of results from initial treatment (Richardson et al, 1995) or do not specify (Monga et al, 1995). This may result in overestimation of success because failed treatments are repeated and counted as successes within the follow-up period. Another pitfall is reporting success rates for cohorts of patients followed for the long term rather than on all patients treated from the start (Stenberg et al, 2003). If the patients in whom treatment has failed and those who have been lost to follow-up are not included in the denominator, the success rate will be higher.

TABLE 86-1 Stamey Incontinence Grading System

GRADE	DESCRIPTION
0	Continent
1	Patient loses urine with sudden increases in abdominal pressure but not when supine
2	Patient loses urine with physical stress (walking; changing from a reclining to a standing position; sitting up in bed)
3	Patient has total incontinence; urine loss unrelated to physical activity and/or position

Another problem encountered in clinical studies, especially longer-term studies, is accounting for missing data from patients who dropped out. One way of handling this is to impute or assign a value based on a previous result. A standard method is last observation carried forward (LOCF). Although this may solve the problem of missing data, it may bias the study in favor of a good outcome. For example, in the 2-year follow-up study of Bulkamid, [Tooze-Hobson and coworkers \(2012\)](#) reported a responder rate of 64% in 116 women. However, there were 135 women treated at the beginning of the study and only 86 were available for the 24-month follow-up. If one calculates the number of responders in the 86 evaluable patients using the 64% responder rate and then uses that number to calculate the percentage in the 135 patients, the success rate then becomes 41%, substantially less than that reported. In view of this potential bias, other, more robust methods than LOCF are available to provide for missing data ([Siddiqui et al, 2009](#)).

Outcome Assessment in Bulking Agent Clinical Trials by the U.S. Food and Drug Administration

The Stamey grading system (0 to 3) ([Stamey, 1979](#)) ([Table 86-1](#)) for SUI has been recommended as the primary outcome measure by the U.S. Food and Drug Administration (FDA) since the original U.S. collagen trial ([McGuire and Appell, 1994](#)). Although the scale has been used extensively, there is little evidence that it is as valid or reliable as other measures such as voiding diaries, pad tests, and leak point measurements ([Payne et al, 2009](#)).

Systematic Reviews and Clinical Practice Guidelines on the Use of Injectable Agents for Women with Stress Urinary Incontinence

The Cochrane Database of Systematic Reviews published an update review of injectable agents in women in 2012 ([Kirchin et al, 2012](#)). The authors reviewed the findings of 14 trials including 2004 women and concluded that the lack of long-term follow-up and health economic data means that at present, injection therapy cannot be recommended as an alternative therapy for women fit for other surgical procedures. The evidence does not support the usefulness of injection therapy as a first-line option. However, it may be a useful option for short-term symptomatic relief for women with comorbidities that preclude anesthesia, at least for a 12-month period. Two or three injections are likely to be required for achievement of a satisfactory result.

Injection therapy was also reviewed at the Fifth International Consultation on Urinary Incontinence ([Dmochowski et al, 2013](#)). The authors concluded that bulking agents provide an option in the management of women with stress incontinence. Although efficacy may diminish over time and may be inferior to that of surgical treatment, the overall complication rate is relatively low.

The American Urological Association (AUA) clinical practice guidelines support the use of injectable agents for patients who

do not wish to undergo more invasive surgery and who understand that both efficacy and duration are inferior to those after surgery. Other groups include the elderly, those who are at high anesthetic risk, and those willing to accept an improvement in their incontinence without necessarily achieving dryness ([Appell et al, 2012](#)). The European Association of Urology guidelines also mention that bulking agents may provide short-term improvement and require repeat injections. They are less effective than surgical options but have fewer adverse effects ([Lucas et al, 2014](#)).

KEY POINTS: USE OF INJECTABLES IN FEMALE STRESS URINARY INCONTINENCE

- The ideal injectable that is biocompatible, nonantigenic, noncarcinogenic, and nonmigratory; causes little or no inflammatory reaction or fibrotic ingrowth; and retains efficacy over time has not yet been found.
- The goal of injectables is to augment or restore urethral mucosal coaptation and its hermetic seal effect and to maintain coaptation during periods of increased abdominal pressure.
- Although initially it was thought that these agents would be most effective in patients with nonhypermobile ISD alone, multiple reports have shown clinical efficacy in patients with hypermobility.
- Injectable agents may provide a rapid response for some patients and are an option for those who do not wish to undergo more invasive procedures. The efficacy and duration are inferior to those after surgery, and reinjections are frequently required. Other possible indications include elderly patients, those with high anesthetic risk, and those willing to accept an improvement in rather than cure of their SUI symptoms.
- The workup includes history and physical examination. Urodynamic studies may be helpful. Cystoscopy is helpful to rule out adverse factors such as scarring, foreign bodies, and diverticula that may prevent or compromise injections.
- Injectables are indicated for the ISD component of SUI. However, because ISD may be present in many patients with SUI with or without urethral hypermobility, the specific value of either the MUCP or ALPP may be of little importance in the clinical decision about the use of injectables.
- The results of periurethral and transurethral techniques are similar. Most reports now involve use of the transurethral technique.
- Perioperative antibiotics for 24 hours or less can be recommended.

Glutaraldehyde Cross-linked Bovine Collagen (Contigen)

Bovine collagen production was discontinued in 2010 with the development of biocompatible hyaluronic acid (HA) fillers for cosmetic soft-tissue augmentation ([Schwanke, 2010](#)). The HA is cross-linked chemically to prevent degradation and has tissue bulking properties ([Park et al, 2014](#)).

Until it was discontinued, GAX collagen was the most widely used and best-studied urethral injectable agent. It was the standard against which all new injectables were compared.

GAX collagen is a highly purified suspension of bovine collagen in normal saline containing at least 95% type I collagen and 1% to 5% type III collagen ([Remacle et al, 1990](#)). This cross-linking makes the GAX collagen resistant to the fibroblast-secreted collagenase. As a result of this, the GAX collagen is only very slightly resorbed. The implant causes little inflammatory reaction or granuloma formation and is colonized by host fibroblasts and blood vessels. It is not known to migrate. However, it does degrade over time with volume loss via absorption of the carrier medium ([Kershen and Atala, 1999](#)) and may be replaced by host collagen, to explain its persistence

(Keefe et al, 1992). For its antigenicity to be decreased, the GAX collagen is prepared by selective hydrolysis of the nonhelical amino- and carboxy-terminal groups (telopeptides) of the collagen molecule, which are the antigenic parts of the molecule (Remacle and Delaye, 1988).

All patients had to undergo a skin test into the volar aspect of the forearm 30 days before treatment. Approximately 3% of patients had a positive skin test reaction, with 70% showing the reaction within 3 days, indicating a preexisting sensitivity to bovine dermal collagen through dietary exposure. The remaining 30% did not respond until later, so a 4-week period was required (Keefe et al, 1992). A negative skin test result did not preclude development of a hypersensitivity reaction to subsequent treatment and, although infrequently used, a second skin test was recommended (Elson, 1989; Stothers and Goldenberg, 1998). Positive responders were excluded.

GAX collagen was injected transurethraly or periurethraly through a 22-gauge needle. It was supplied in syringes, which contained about 3 mL of collagen. Ordinarily one to three syringes were injected during each treatment.

Because more is known about this agent than any other to date, the results are outlined in the following section.

GAX Collagen Results. The results are shown in Table 86-2. The use of GAX collagen was first reported by Shortliffe and colleagues (1989), and since then numerous reports of its efficacy, safety, ease of administration, and relative lack of morbidity have appeared. Our original report, with short-term follow-up of 32 patients for 6 months (Herschorn et al, 1992), showed a cure and improvement rate of 90.3%. For longer-term results of more than 1 to 2 years, cure and improvement rates vary from 57% (Khullar et al, 1997) to 94% (Cross et al, 1998). Most patients need one or two treatment sessions with a mean of 5.6 to 15 mL of collagen. Winters and Appell (1995) reported a 50% rate of complete continence in a multicenter trial after 2 years. Corcos and Fournier (1999) reported 4-year follow-up with 40% improvement and 30% cure. The longest follow-up reported to date is from Gorton and coworkers (1999). They reported on 53 patients with at least 5 years after their last collagen injection. Only 14 (26%) had persistent improvement, and of these, 1 (2%) was completely dry. Because patients in any series are treated at different times and because durations of follow-up vary, a Kaplan-Meier curve is useful to display the persistence of a good result (Herschorn and Radomski, 1997). Figure 86-6 shows that the probability of remaining dry after the last collagen injection was 72% at 1 year, 57% at 2 years, and 45% at 3 years. A similar deterioration over time was reported by Gorton and coworkers (1999).

Multiple factors that may influence outcome have been reported. Previous incontinence surgery was identified by Eckford and Abrams (1991) as a favorable factor, but this was not supported by others (Herschorn et al, 1996). Preoperative detrusor overactivity may be an adverse factor (Herschorn et al, 1996; Smith et al, 1997). The degree of mucosal coaptation after injection as judged on cystoscopy was not found to correlate with long-term improvement (Kim et al, 1997). Elia and Bergman (1996) used perineal ultrasound to measure the location of the collagen deposit 3 months after the procedure. They reported that a positive outcome was more likely if collagen was located at a distance of 6 mm or less from the bladder neck. Defreitas and coworkers (2003) correlated a good outcome with circumferential distribution of collagen around the urethra. They performed three-dimensional transvaginal ultrasound in 46 patients at a median follow-up of 14 months and found that the 21 satisfied patients had a higher rate of circumferential distribution compared with the 25 unsatisfied patients. Regarding the technique and site of injection, the Cochrane review concluded that there are insufficient data to determine whether transurethral is superior to periurethral injection and whether mid-urethral offers any benefit over bladder neck injection (Kirchin et al, 2012).

Collagen and Hypermobility. The use of collagen for patients with hypermobility has been reported extensively. Moore and colleagues (1995) included patients with hypermobility. Faerber (1996) treated elderly patients with type 1 abnormality. In the

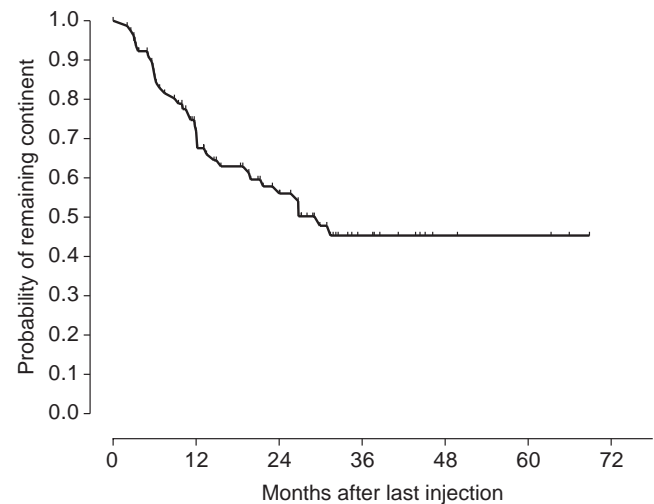


Figure 86-6. Durability: Kaplan-Meier curve showing durability of cure of incontinence after the last collagen injection in 78 patients. (From Herschorn S, Radomski SB. Collagen injections for genuine stress urinary incontinence: patient selection and durability. *Int Urogynecol J Pelvic Floor Dysfunct* 1997;8[1]:18-24.)

report by McGuire and Appell (1994), the results at longer than 1 year in women with ISD were similar to those in women with hypermobility, although there were far more women with ISD. Monga and coworkers (1995) included patients with hypermobility and found that cure rates were not reduced for women with up to 2.5 cm of movement. In our series of 181 patients there was no significant difference in outcome in patients with or without hypermobility (Herschorn and Radomski, 1997). Corcos and Fournier (1999) found no difference between patients with and without bladder neck hypermobility in their 4-year follow-up on 40 patients. Steele and colleagues (2000) found that urethral mobility did not significantly affect the success rate. Furthermore, 4 of 6 patients with urethral hypermobility were dry at the 6-month follow-up examination, whereas of the 19 women without hypermobility, only 32% remained dry. Bent and colleagues reported a 44% cure and improvement rate for 12 months in a cohort of 90 women with SUI and hypermobility (Bent et al, 2001a). They concluded, as have others, that collagen injection therapy is appropriate in women with hypermobility.

Collagen versus Surgery. Berman and Kreder (1997) found that after an average follow-up of 14.9 months after sling cystourethropexy, 71.4% of the patients were continent versus 26.7% of patients with collagen after 21.3 months. They analyzed associated costs and concluded that surgery was more cost-effective than collagen. In a multicenter prospective randomized trial, Corcos and colleagues (2005) reported a lower success rate of 53.1% in the collagen-treated patients versus 72.2% in the surgery group. However, general and disease-specific quality-of-life scores were similar, satisfaction was slightly higher in the surgery group, but complications were less frequent and severe with collagen. They concluded that collagen was a reasonable alternative to surgery. The follow-up was relatively short, and the study was done before the era of mid-urethral slings.

Collagen Complications. Treatment-related morbidity has been minimal. Common complications include transient urinary retention, which ranges in incidence from 1% to 21% (Herschorn et al, 1992; Winters and Appell, 1995; Appell and Winters, 2007) and can be managed with intermittent catheterization or short-term use of a Foley catheter. Urinary tract infection (UTI) occurs in 1% to 25% (Herschorn et al, 1992; Winters and Appell, 1995; Appell and Winters, 2007). De novo detrusor overactivity was reported in 11 of 28 elderly women (39%) treated by Khullar and coworkers (Khullar et al, 1997). Stothers and colleagues reported de novo urgency with urgency incontinence in 43 of 337 patients (12.8%), 21% of whom did not respond to anticholinergics

TABLE 86-2 Comparison of Collagen Parameters and Results

STUDY	NO. OF PATIENTS	TYPE OF INCONTINENCE	FOLLOW-UP (mo)	NO. OF PATIENTS WHO BECAME DRY (%)	NO. OF PATIENTS WHOSE CONDITION IMPROVED (%)	NO. OF PATIENTS IN WHOM TREATMENT FAILED (%)
Eckford and Abrams (1991)	25	Not specified	3	16 (64)	4 (16)	5 (20)
Kieswetter et al (1992)	16	Not specified	9	7 (44)	7 (44)	2 (13)
Stricker and Haylen (1993)	50	ISD	Mean: 11 Range: 1-21	21 (42)	20 (40)	7 (14)
McGuire and Appell (1994)	17	Mobile	>12	8 (47)	3 (18)	6 (35)
	137	ISD	>12	63 (46)	47 (34)	21 (19)
O'Connell et al (1995)	44	42 with ISD 2 hypermobile	1-2 (longest 7 of the whole group)	20 (45)	8 (18)	16 (37)
Moore et al (1995)	11	Types 1 and 3	2	1 (9)	7 (64)	2 (18)
Winters and Appell (1995)	50	ISD	>12	48 (96) dry or socially continent	2 (4)	
Monga et al (1995)	60	Some hypermobile	3 (n = 59)	27 (46)	24 (41)	
			12 (n = 54)	22 (41)	20 (37)	
			24 (n = 29)	14 (48)	6 (21)	
Richardson et al (1995)	42	ISD	46 (10-66 after first injection)	17 (40)	18 (43)	7 (17)
Homma et al (1996)	60	Hypermobile	24	4 (7)	39 (65)	17 (28)
Faerber (1996)	12	Type 1	10.3 (range 3-24)	10 (83)	2 (17)	0
Herschorn et al (1996)	181	Type 1 (54)	Mean 22 (range 4-69)	42 (23)	94 (52)	45 (25)
		Type 2 (67)	≥24 (n = 62)	27 (43.5)	29 (46.8)	6 (9.7)
		Type 3 (60)	≥36 (n = 25)	13 (52)	8 (32)	4 (16)
Smith et al (1997)	94	Type 3	Median: 14	36 (38.3)	27 (28.7)	31 (33)
Khullar et al (1997)	21	Not specified	24 (minimum)	10 (48)	2 (10)	9 (43)
Swami et al (1997)	107	Some hypermobile	24 (minimum)	27 (25)	43 (40)	37 (35)
Cross et al (1998)	139	Type 3	Median 18 (range 6-36)	Substantially improved 103 (74)	29 (21)	7 (5)
Corcos and Fournier (1999)	40	Type 1 (8) Type 2 (20) Type 3 (12)	Average 52 47-55 (range)	12 (30%)	16 (40%)	12 (30%)
Gorton et al (1999)	53	Hypermobile	60 (minimum)	1 (2)	13 (25)	39 (74)
Groutz et al (2000a)	63	Type 3	Mean 6.4 ± 4.9	13%	10% good 17% fair 42% poor	18%
Steele et al (2000)	40	9 hypermobile 31 without	8.4	71%	29%	
			8.2	32%	68%	
Bent et al (2001a)	90	Types 1 and 2	12	19 (21%)	19 (21%)	62 (58%)
Mohr et al (2013)	312	Not specified	12	73.2% (includes an additional 212 patients with other injectables)		26.8%

ISD, intrinsic sphincter deficiency.

(Stothers et al, 1998). Hematuria can occur in 2% of patients (Appell and Winters, 2007). Extravasation resolves quickly with flushing away of the dilute collagen suspension and sealing over of the small needle site.

Rare complications include periurethral abscess formation (Sweat and Lightner, 1999). Another is a reaction in the previously negative skin test site after a urethral collagen injection (Stothers and Goldenberg, 1998). This occurred in three patients (1.9%) and was associated with arthralgias in two. Mohr and colleagues (2013) reported a late-onset allergic reaction in two women at 3 and 6 weeks after treatment. Both required steroids, and one was hospitalized for 34 days. Hypersensitivity reactions have been reported before in dermatology (Elson, 1989), and two negative pretreatment skin tests have been suggested for prevention of such a reaction. The potential for hypersensitivity reactions is present because antibody production is stimulated by collagen injection (McClelland and Delustro, 1996).

Vesicovaginal fistula occurring after collagen injections for SUI in two women after cystectomy and neobladder was described by Pruthi and colleagues (2000). Carlin and Klutke (2000) reported a urethrovaginal fistula in a woman whose warfarin was not completely reversed. She had a postinjection hematoma, and ultimately a fistula to the vagina developed.

Currently Used Injectable Agents

Carbon-Coated Zirconium Beads (Durasphere and Durasphere EXP)

Durasphere consists of nonabsorbable pyrolytic carbon-coated zirconium beads suspended in a water-based polysaccharide carrier gel of 2.8% β -glucan (Lightner et al, 2001). Pyrolytic carbon has been used in medical devices such as heart valves. The bead size ranges from 212 to 500 μ m, which is larger than the threshold for particle size migration of 80 μ m (Malizia et al, 1984). It is nonantigenic, and no skin testing is required. The agent can be delivered through an 18-gauge needle via the transurethral or periurethral approach with cystoscopic monitoring. It is more viscous than collagen, so greater pressure is required for delivery into the tissues.

As a result of reported difficulty of injecting the agent, the beads were modified and made smaller. The bead sizes of Durasphere EXP now range from 90 to 212 μ m, still larger than the 80- μ m threshold for migration (Malizia et al, 1984).

Results. Published results for use of Durasphere are shown in Table 86-3. In the original multicenter randomized 235-patient clinical trial of Durasphere versus collagen, Lightner and colleagues (2001) reported a 12-month continence grade improvement rate of 76 of 115 (66.1%) in the Durasphere group versus 79 of 120 (65.8%) in the collagen group ($P = 1.000$). They also reported that at 1 year after their last treatment, 49 of 61 (80.3%) in the Durasphere group versus 47 of 68 (69.1%) in the collagen group had a

continence grade improvement ($P = .162$). Both injectables performed similarly. There was also no difference in the number of injections or pad weight test result. However, the injected initial and repeat injection volumes of Durasphere were significantly less than those of collagen. It is notable that in the 12-month result after the last injection, 45% (106 of 235) of the study patients were not accounted for.

In another randomized prospective trial of Durasphere versus collagen, Andersen (2002) reported that 80% (20 of 25) of Durasphere patients versus 61.9% (13 of 21) of collagen patients had a continence grade improvement ($P = .205$) after a mean of 2.6 and 2.8 years, respectively, after initial treatment. This is similar to the study of Lightner and colleagues (2001).

In a series of 13 women, Pannek and colleagues (2001) reported a decline in success from 76.9% at 6 months to 33% at 12 months. In contrast to Lightner and colleagues (2001), they demonstrated particle migration locally and to distant sites on follow-up plain radiographs. As a result of reported injection difficulties, Madjar and coworkers (2003) modified the technique by injecting local anesthetic into the mucosa to raise a circumferential bleb into which the Durasphere was injected. They reported results from 46 of 70 (65.7%) of patients. At a mean of 9.4 months, 65.2% of patients considered themselves to be cured or improved.

In a longer-term follow-up matched cohort study, Chrouser and colleagues (2004) reported initial success of 63% in both groups. With longer follow-up of 24 and 36 months, Durasphere was effective in 33% and 21%, whereas collagen was effective in 19% and 9%, respectively. The results in both groups were not significantly different. Sokol and coworkers (2008) tried to improve on the results of transurethral collagen by injecting additional periurethral Durasphere. However, they failed to show any benefit. After 6 months there was no difference in cure rates—33.3% in the combined versus 29.4% in the collagen alone group.

No study with Durasphere has shown a benefit over collagen.

Complications. In the multicenter randomized trial of Durasphere versus collagen, the adverse event profiles were similar with both agents (Lightner et al, 2001). However, more women had significantly more post-treatment urgency and acute retention with Durasphere versus collagen—24.7% and 16.9% versus 11.9% and 3.4%, respectively. Pelvic radiographs taken 1 and 2 years after injection showed stability of the bulking agents at the injection site. Pannek and associates (2001) did report particle migration. This was subsequently attributed to the high pressure necessary to inject the viscous material with large particles, resulting in material displacement into vascular or lymphatic spaces (Appell et al, 2006). Durasphere EXP with smaller particles is less likely to lead to this.

Other reported adverse events include urethral mucosal prolapse (Ghoniem and Khater, 2006), periurethral sterile abscess formation in 2.9% of a series of 135 patients (Madjar et al, 2006), or rarely a pseudoabscess found 5 years after injection (Berger and Morgan, 2012).

TABLE 86-3 Carbon-Coated Zirconium Beads (Durasphere) Results for Female Stress Incontinence

STUDY	NO. OF PATIENTS	FOLLOW-UP (mo)	NO. OF PATIENTS WHO BECAME DRY (%)	NO. OF PATIENTS WHOSE CONDITION IMPROVED (%)	NO. OF PATIENTS IN WHOM TREATMENT FAILED (%)
Lightner et al (2001)	61 Durasphere 68 Collagen	12	49 (80.3) 47 (69.1)		12 (19.7) 21 (30.9)
Andersen (2002)	26 Durasphere 26 Collagen	31.2 (25 patients) 33.6 (21 patients)	10 (40) 3 (14)	10 (40) 10 (48)	5 (20) 8 (38)
Pannek et al (2001)	9	12	—	3 (33.3)	6 (66.7)
Madjar et al (2003)	46	9.4	6 (13)	24 (52.2)	16 (34.8)
Chrouser et al (2004)	43 Durasphere 43 Collagen	24, 36 24, 36	(33), (21) (19), (9)		(67), (79) (81), (91)

TABLE 86-4 Results of Silicone Microimplant (Macroplastique) Injections for Female Stress Urinary Incontinence

STUDY	NO. OF PATIENTS	FOLLOW-UP (yr)	NO. OF PATIENTS WHO BECAME DRY (%)	NO. OF PATIENTS WHOSE CONDITION IMPROVED (%)	NO. OF PATIENTS IN WHOM TREATMENT FAILED (%)
Harriss et al (1996)	40	3	16 (40)	7 (18)	17 (43)
Sheriff et al (1997)	34	2		16 (47)	18 (53)
Koelbl et al (1998)	32	1		19 (59)	13 (41)
Usman and Henalla (1998)	102	0.25		69 (68)	—
Barranger et al (2000)	21	2.5	4 (19)	8 (38)	9 (43)
Radley et al (2001)	60	1.5	12 (20)	25 (42)	23 (38)
Soliman and Evans (2001)	68	1.6	24 (35)	18 (26.5)	26 (38.2)
Peeker et al (2002)	22	≥2	14 (63.6)	3 (13.6)	5 (22.7)
Grdal et al (2002)	29	2	13 (45)	4 (14)	12 (41)
Tamanini et al (2003)	21	1	12 (57)	4 (19)	5 (24)
Tamanini et al (2004)	21	2	10 (48)	3 (14)	8 (38)
Zullo et al (2005)	61	5	11 (18)	24 (39)	26 (43)
Plotti et al (2009)	24	1	10 (42)	10 (42)	4 (17)
ter Meulen et al (2009)	24	1	6 (25)	8 (33)	8 (33) Data missing 2 (8)
Ghoniem et al (2009)	122 Macroplastique 125 Collagen	1	45 (36.9) 31 (24.8)	30 (24.6) 29 (23.2)	47 (38.5) 65 (52)
Hegde et al (2013)	100	Approximately 18-19 wk (median)		72 (72)	28 (28)

Silicone Microimplants (Macroplastique)

Silicone microimplants (Harriss et al, 1996) are solid polydimethylsiloxane (silicone rubber) particles suspended in a nonsilicone carrier gel that is absorbed by the reticuloendothelial system and excreted unchanged in the urine. Because 99% of the particles are between 100 μ m and 450 μ m in diameter, the likelihood of migration is low. Henly and coworkers (1995) demonstrated distant migration of small particles, less than 70 μ m, but no migration of particles greater than 100 μ m in diameter. Although there was a typical histiocytic and giant cell reaction within the injection site, there was no granuloma formation in response to the larger particles. Because the substance is quite viscous, it must be injected with an injection gun and a 16-gauge-tip transurethral needle. The vials contain 2.5 mL of silicone macroparticles (Macroplastique).

Results. The results are shown in Table 86-4. Harriss and colleagues (1996) reported on 40 patients followed for a minimum of 3 years, at which time 16 (40%) were dry and 7 (18%) were improved; in 17 (43%), treatment had failed. Twelve of the 16 required one injection and 4 needed two injections to become dry. Sheriff and coworkers (1997) reported an overall success of 48% in 34 patients after unsuccessful stress incontinence surgery, and Koelbl and colleagues (1998) reported a 60% success rate in 32 women after 12 months but noted a time-dependent decrease in success. Radley and coworkers (2001) reported a success rate of 61% (19.6% cured and 41.1% improved) in 60 women after a mean of 19 months. Barranger and coworkers (2000) in a group of 21 patients reported a dry rate of 19%, improved rate of 38%, and failure rate of 52% at a median follow-up of 31 months. It is interesting to note that they did not observe a time-dependent decrease in results. Tamanini and coworkers reported 1- and 2-year results in 21 patients with the use of a handheld noncystoscopic injector

system (see Fig. 86-4B) (Tamanini et al, 2003, 2004). There was a decrease in continence outcome after 2 years.

Zullo and coworkers followed 61 women for a minimum of 60 months and reported a cure rate of 18%, improvement rate of 39%, and failure rate of 43%. They selected patients without hypermobility (Zullo et al, 2005). Plotti and colleagues reported 84% cure and improvement rates in a series of 24 women with de novo SUI after radical hysterectomy (Plotti et al, 2009). In a randomized study in patients with SUI and urethral hypermobility, ter Meulen and colleagues compared Macroplastique, administered by the noncystoscopic injector system, with pelvic floor exercises. After 3 months, significantly more patients in the injection group were dry or improved. Eighteen of the 24 Macroplastique patients were followed for 12 months, and of these, 14 considered themselves to be cured or markedly improved (ter Meulen et al, 2009).

Ghoniem and colleagues reported results of a North American multicenter randomized trial of Macroplastique versus collagen (Ghoniem et al, 2009). After 1 year, 61.5% (75 of 122) with Macroplastique and 48% (60 of 125) with collagen had an improvement of at least 1 Stamey grade. This indicated that Macroplastique was noninferior to collagen ($P < .001$). The proportion of the patients who were dry was higher in the Macroplastique group at 36.9% versus 24.8% ($P < .05$). However, there were no significant differences in pad weight testing, quality-of-life scale, or adverse events. The same authors subsequently reported the 2-year results in the Macroplastique group (Ghoniem et al, 2010). Of those who had a benefit at 12 months, 84% maintained that level of cure or improvement to 24 months. That means that of the original 122 patients, 51.7% had a good outcome at 2 years.

Hegde and colleagues (2013) recently reported on parameters that may determine short-term success. Of 100 patients injected, 72 had a good clinical outcome and 28 were either not improved or

worsened. The groups were followed for a median of 19.3 and 17.8 weeks, respectively. The authors found that proximally located and circumferentially distributed Macroplastique was associated with the best clinical outcomes.

A systematic review and meta-analysis of Macroplastique series from 1990 to 2010 was reported by Ghoniem and Miller (2013). The authors included 24 published articles with a total of 958 patients. Short-term (<6 months) cure and improvement rates were 43% and 75%, respectively. Medium-term (6 to 18 months) rates were 37% and 73%. Long-term (>18 months) rates were 36% and 64%. The median reinjection rate was 30%, and higher reinjection rates resulted in improved long-term outcomes.

Complications. Self-limited side effects of UTI, hematuria, dysuria, urgency, frequency, voiding difficulty, and urinary retention have been reported (Ghoniem et al, 2009). Rarely erosion of the injectable occurs. The lack of a granulomatous reaction and migration of the large silicone particles may provide some benefit over smaller-particle injectable agents such as previously used Teflon. In their systematic review, Ghoniem and Miller noted a median adverse event rate of 7% for temporary urinary retention, 7% for urgency incontinence, 3% for UTI, 50% for temporary dysuria, and 45% for transient hematuria. They noted the absence of any serious reported adverse events over the 20 years of global experience (Ghoniem and Miller, 2013).

Polyacrylamide Hydrogel (Bulkamid)

PAHG is a nontoxic, nonresorbable sterile aqueous gel consisting of 2.5% cross-linked polyacrylamide and 97.5% nonpyrogenic water. It is homogeneous, stable, and nonbiodegradable and has tissue-like viscosity and elasticity. According to Lose and colleagues (2010), the acrylamide monomers are bound covalently by strong single bonds, and the linear chain structure of the polymer has been folded into a three-dimensional configuration that forms a large and very stable molecule. The total amount of residual acrylamide monomer in the PAHG is less than 1 µg/mL of the product, less than the normal daily intake of acrylamide in food and water. This means that the hazardous nature of the acrylamide monomer is not an issue.

It was originally used in plastic surgery for tissue augmentation (Breiting et al, 2004) and in the production of soft contact lenses and for intraocular applications (Lloyd et al, 2001).

As mentioned earlier, PAHG (Bulkamid) is provided in 1-mL syringes with a 12-cm 23-gauge needle and is injected via a short 0-degree urethroscope and plastic sheath (see Fig. 86-5). The kit contains two 1-mL syringes, and circumferential injection is recommended.

Results. The results are shown in Table 86-5. Lose and colleagues (2006) reported a pilot study with 25 women followed for 1 year after their last injection. Of the 21 who completed the study, 8 were dry and 9 were improved; in 4 the treatment failed. The authors noted that 11 women (44%) underwent a reinjection after 3 months because of lack of effect. In a larger European multicenter study involving 135 women, 98 of whom completed the 12-month study, Lose and coworkers (2010) reported a responder (cured or improved) rate of 66% and a dry rate of 24%; 19 patients did not respond. Using the authors' percentage of responders at 66%, the nonresponders must have comprised 34%. Therefore the results are given for a total of only 56 patients. The authors did not account for the discrepancy and it may be a pitfall in the reporting, as mentioned earlier. Efficacy was similar with either SUI or mixed incontinence. Reinjection was necessary in 35% of patients, and the responder rate was significantly lower in this group. Tooze-Hobson and colleagues (2012) reported the 2-year outcomes of the same cohort of 135 patients. Although only 86 patients were available for the 24-month follow-up, the authors used the LOCF method and presented outcomes for 124 patients at 12 months and 116 patients at 24 months. Responder rates were 67% at 12 months and 64% at 24 months. As mentioned previously, the LOCF and imputation method may overestimate the actual success rate. However, there appears to be persistence of response to 2 years. The responder rate of the group requiring reinjection was thus not significantly different from the single-treatment group.

In a 12-month study involving 29 patients (Leone Roberti Maggiore et al, 2012), 26 (89.7%) had subjective success and 23 (79.3%) had objective success. Nine patients (31%) needed reinjection 3 to 6 months after the first injection. The authors reported on sexual function using the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12 (PISQ-12). Twenty-three patients

TABLE 86-5 Results of Polyacrylamide Hydrogel (PAHG; Bulkamid) Injection for Female Stress Urinary Incontinence

STUDY	NO. OF PATIENTS	FOLLOW-UP (yr)	ACTUAL NO. REPORTED AT FOLLOW-UP	NO. OF PATIENTS CURED (%)	NO. OF PATIENTS WHOSE CONDITION IMPROVED (%)	NO. OF PATIENTS IN WHOM TREATMENT FAILED (%)
Lose et al (2006)	25	1	21	8 (38)	9 (43)	4 (19)
Lose et al (2010)	135	1	56	13 (23)	24 (43)	19 (34)
Tooze-Hobson et al (2012)	135	2	86 LOCF 116	20 (17)	54 (47)	42 (36)
Leone Roberti Maggiore et al (2012)	29	1	29	23 (79.3)		6 (20.7)
Vecchioli-Scaldazza et al (2014)	20	2	18	Not reported		
Martan et al (2014)	52	Mean 22 mo	51	8 (15.7)	15 (29.4)	28 (54.9)
Sokol et al (2014)	229 PAHG 116 collagen	1	201 102	24-hr pad test 44/183 (24) 22/90 (24.4)	Cure or improved 145/188 (77.1) 70/100 (70)	No change or worse 43/188 (22.9) 30/100 (30)

LOCF, last observation carried forward.

maintained sexual function and 6 resumed sexual function after treatment. The outcome of Bulkamid injection in women aged 80 and older was reported recently (Vecchioli-Scaldazza et al, 2014). Eighteen of 20 patients were followed for 2 years. The authors tracked pad numbers, stress testing, urodynamic parameters, quality of life assessed with the Incontinence Impact Questionnaire (IIQ-7), and patient satisfaction with the visual analog scale and Patient Global Impression of Improvement questionnaire. They noted persistence of improvement in the group parameters at 24 months but did not report the number or percentage of responders. Martan and colleagues reported the results in a complex group of 52 patients, 40 with previous unsuccessful surgery and 12 with ISD (Martan et al, 2014). All but 1 patient, who died, were followed for at least 6 months after their last treatment. The reinjection rate was 10%. After a mean of 22 months, 10 of 51 (19.6%) had a negative cough stress test result, and on subjective assessment with the International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form (ICIQ-UI-SF), 8 of 51 (15.7%) reported being completely dry and 23 of 51 (45.1%) were dry or improved.

PAHG (Bulkamid) was compared with collagen in a multicenter North American randomized trial (Sokol et al, 2014). Of the 345 women, 229 received PAHG and 116 received collagen. At 1 year, 53.2% of the PAHG group and 55.4% of the collagen group showed a 50% or greater decrease in leakage and incontinence episodes. In the collagen group at 1 year, 50% reported zero SUI episodes and 70% considered themselves cured or improved, whereas in the PAHG group 47.2% reported zero SUI episodes and 77.1% considered themselves cured or improved. The results confirmed that PAHG is noninferior to collagen. The PAHG reinjection rate of 77.3% receiving two injections and 35.8% receiving three injections was higher in this study than in previous studies. The mean total volume of 3.3 mL in this study was more than twice the mean total volume of 1.53 mL in the European multicenter PAHG study, which reported a 1-year responder rate of 67% (Tooze-Hobson et al, 2012). The required volume of agent and the numbers of procedures determine cost. The commercial kit contains a total of 2 mL of PAHG, so two or more kits and procedures may be required to achieve a 77% responder rate.

Complications. In the large multicenter RCT, 381 adverse events were seen in 136 women, 59.4% of the total number treated with PAHG (Sokol et al, 2014). The most common procedure- or injectable-related complications were UTI (12.3%), transient pain at implant site (48.1%), and urinary retention after the procedure (17.3%). Other complications were hematuria (3.7%), nocturia (3.7%), de novo urgency (2.5%), and urgency urinary incontinence (2.5%). Rare problems are vaginal discomfort and worsening incontinence. No serious complications have been reported.

Calcium Hydroxylapatite (Coaptite)

CaHA, which is a normal constituent of bone, can be manufactured into particles of a spheric mean diameter of 100 μ m (75 to 125 μ m) suspended in a carboxymethylcellulose gel carrier. Exogenous CaHA has been used in orthopedic and dental applications (Bucholz, 2002), as well as soft-tissue augmentation of vocal cords (Belafsky and Postma, 2004), face (Tzikas, 2004), and the ureteral orifice for reflux (Mevorach et al, 2006). Animal experiments have demonstrated safety and biocompatibility. It stimulates fibroblast infiltration when placed into soft tissue, which may explain its long-term bulking effect after degradation of the carrier gel (Mayer et al, 2007).

The implant is currently supplied in 1-mL syringes and can be injected via a transurethral approach through a 21-gauge needle.

Results. Mayer and colleagues (2001) reported initial results in 10 women with ISD and limited hypermobility. After 1 year, 7 reported substantial improvement, 2 improved, and 1 had no change. No significant complications were reported. In a randomized prospective trial of CaHA versus collagen, Mayer and coworkers (2007) reported results in 231 women. Up to five injections were performed in the first 6 months of the trial. At 12 months, 83 (63.4%) of 131 CaHA patients showed improvement of one Stamey grade or more

versus 57 (57%) of 100 collagen patients ($P = .34$). There was no difference in cure (39% CaHA vs. 37% collagen) or improvement (50% CaHA vs. 46% collagen) rates. More CaHA patients required only one injection, and the total average injected volume was lower (4.0 mL vs. 6.6 mL respectively; $P < .0001$).

Complications. Minor adverse events such as transient retention (41%), UTI, and urgency incontinence (5.7%) were reported (Mayer et al, 2007). Serious adverse events were vaginal wall erosion of the implant and dissection of the material beneath the trigone. Because the injectable has a greater particle density than collagen, it is thought to have the potential to cause more local tissue pressure effects. Rare complications are urethral mucosal prolapse (Palma et al, 2006; Lai et al, 2008) and injection site granulomas (Gafni-Kane and Sand, 2011).

Porcine Dermal Collagen

Porcine dermal collagen implants have been used in hernia repairs and pelvic floor reconstruction (Harper, 2001; Dench et al, 2006). It is maintained in its original three-dimensional forms and is close to human dermis in architecture (Meyer et al, 1978). It is biocompatible, and patients do not have to be skin tested as with bovine collagen.

Bano and colleagues (2005) reported early results of a randomized trial of porcine dermal collagen versus Macroplastique. There were 25 patients in each arm. The porcine collagen was injected periurethraly in 21 patients. At 6 months, 15 (60%) of 25 in the collagen group were dry, and 10 were unchanged or worse (40%). In the Macroplastique group, 9 (36%) were dry, 1 (4%) improved, and 14 (56%) were unchanged or worse. There were no significant differences between the groups. Minor complications of transient retention and urgency incontinence were seen in both groups and were similar.

Autologous Chondrocytes

A bulking agent composed of autologous chondrocytes has been used to treat children with vesicoureteral reflux (Diamond and Caldamone, 1999). Animal studies of the implant demonstrated stability and lack of migration over time (Atala et al, 1994; Cozzolino et al, 1999). The injectable material consists of autologous chondrocytes in a calcium alginate gel administered endoscopically through a 22-gauge needle. The chondrocytes obtained from biopsy of the external pinna of the patient's ear are expanded in tissue culture and combined with a carrier gel that degrades after injection.

Bent and coworkers (2001b) reported 12-month results in 32 women after a single outpatient injection in a multicenter trial. Incontinence grading indicated 16 patients dry and 10 improved for a total of 26 (81.3%). Side effects were minimal.

Adjustable Continence Therapy

The Adjustable Continence Therapy (ACT) device was developed as an alternative to bulking agents that would not migrate (Kocjancic et al, 2008). It consists of two inflatable silicone balloons attached to silicone tubing with a titanium and silicone port (Fig. 86-7). The procedure can be done using local, regional, or general anesthesia. The balloons are placed into the periurethral space at the bladder neck with introducer devices inserted through two 1-cm incisions in the labial sulci at the level of the vaginal introitus. The procedure is carried out under fluoroscopic guidance with a contrast-filled Foley balloon positioned at the bladder neck. After the correct position is ascertained, the device balloons are inflated with 1 to 1.5 mL of an isotonic solution (sterile water and contrast material). The aim is to increase urethral resistance and support the bladder neck with the inflated balloons (Stecco et al, 2006). The ports are buried in the subcutaneous tissue of the labia to enable postoperative reinjection of the balloons if necessary (Kocjancic et al, 2008). Beginning at 6 weeks, additional fluid, usually with volumes of 2 mL, can be added to the balloons by percutaneous injection

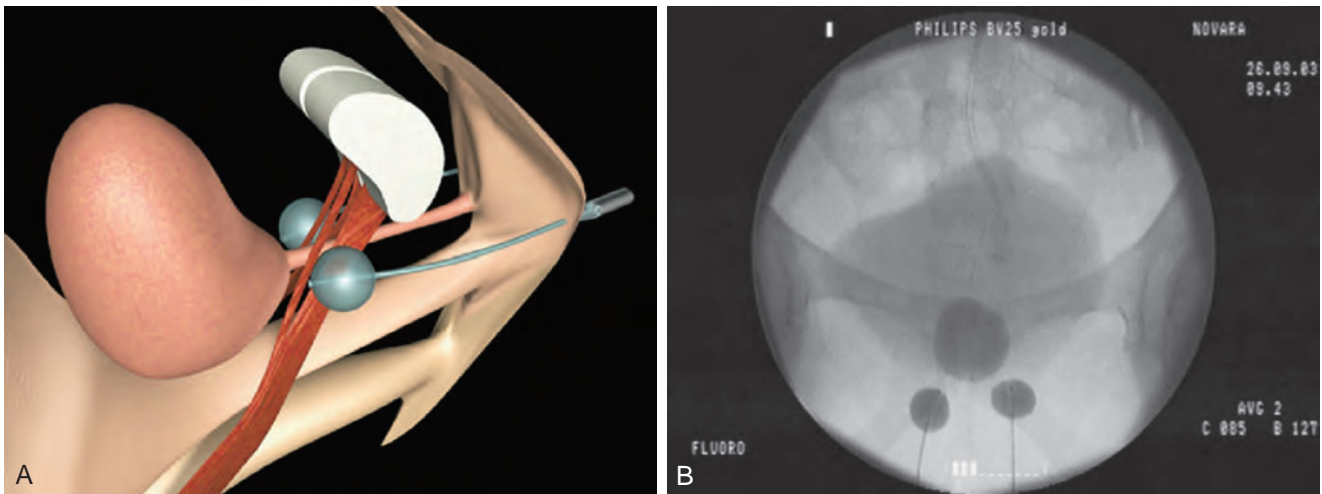


Figure 86-7. Illustration of Adjustable Continence Therapy balloon device for women. **A**, Schematic diagram showing percutaneous placement of the balloons on both sides of the bladder neck. **B**, Fluoroscopic picture showing contrast agent in the bladder, Foley catheter, and balloons. (From Aboseif SR, Franke EI, Nash SD, et al. The Adjustable Continence Therapy system for recurrent female stress urinary incontinence: 1-year results of the North America Clinical Study Group. *J Urol* 2009;181[5]:2187–91.)

through the port sites, if necessary. Each balloon has a volume of 8 mL.

Results. Chartier-Kastler and colleagues (2007) reported on a series of 68 women. Of the 29 women followed for a mean of 2 years, 87% were dry or improved. However, 26 patients underwent explantation, and 13 records were incomplete or were missing data. Kocjancic and colleagues (2008) performed implantation in 49 patients, of whom 38 were followed for more than 1 year. Of these, 26 of 38 (68%) were dry, 6 of 38 (16%) improved, and in 6 of 38 (16%) the procedure failed. In 62%, one to five fluid additions were necessary throughout the follow-up period. Wachter and coworkers (2008) reported a series of 41 women. The dry rate was 44%, marked improvement was seen in 15%, and 41% had slight improvement or no change. Device adjustment was needed in 70% of patients. Aboseif and coworkers (2009) reported a North American study consisting of 162 patients, of whom 84% had undergone at least one unsuccessful surgical procedure for SUI. Of those followed for 1 year or longer, 107 of 140 (76.4%) improved by 1 or more Stamey grades, 67 of 130 (52%) had less than 2 g on pad weight testing, and 102 of 126 (81%) had a greater than 50% reduction in provocative pad weight. Within 9 months of implantation, a mean of 2.3 balloon readjustments were required.

In a subsequent series, Kocjancic and colleagues (2010), reported 6-year outcomes on 29 of 57 patients. On the Patient Global Impression of Improvement questionnaire, 64% of patients rated their symptoms as very much improved, 23% as much improved, and 13% as minimally improved or unchanged. In a second report from the North American multicenter study, Aboseif and coworkers (2011) reported on 1-year outcomes in 77 of 89 patients. With an intention-to-treat analysis, 39.3% were dry (<2 g on provocative pad weight test) or 77.5% improved (≥50% reduction on pad weight test).

Because volume adjustments were done during the follow-up periods in all series, there are no data available on continence outcome long after cessation of fluid addition.

Complications. Complications have occurred in 24% (Aboseif et al, 2009) to 39% (Wachter et al, 2008) of patients, with most classified as mild to moderate. Intraoperative urethral or bladder perforation has been reported in 3% to 17% of patients. Recent intraoperative perforation rates are 3.7% to 45% (Phe et al, 2014). During the first year postoperatively, complications reported are balloon migration (6.5% to 17.5%) or dysfunction (0.6% to 8.9%). Others include urethral erosion (2% to 15%), cutaneous

erosion of the port (3% to 75%), device infection (0.6% to 6%), treatment failure or worsening of incontinence (2.5% to 11.7%), dysuria or retention (1.5% to 6.8%), and de novo urgency (10.5%) (Phe et al, 2014).

The explantation rate is 15% to 30.8%. The reimplantation rate is up to 50% in various studies (Phe et al, 2014).

Overall, the procedure may be more suited to patients after surgical failures. To date, 38% to 100% of patients in reported series have had previous unsuccessful SUI surgery (Phe et al, 2014). Long-term durability still has to be established.

Cell-Based Therapy

Cell-based therapy for SUI aims at repairing deficient anatomic components of the urethral continence mechanism. Because there is still debate about the mechanism for SUI, it is not specifically known which components—the urethral mucosa, anatomic supports, smooth or striated muscle—play a distinct role in the patient (Delancey, 2010). However, cell-based therapies have demonstrated experimentally an increase in most or all of the components of the sphincter mechanism.

Cells Used in Cell-based Therapies for Stress Urinary Incontinence. Embryonic stem cells (ESCs), derived from the inner cell mass of the blastocyst, possess a vast proliferation potential and can transform into any cell type in the body (Gras and Lose, 2011). Because of the potential risk of tumor formation and immunologic and ethical concerns, potential use of these cells is limited. In contrast to ESCs, adult stem cells (ASCs), or tissue-specific stem cells, are involved in normal growth, cell turnover, and maintenance and repair processes (Gras and Lose, 2011). Their limitations of mortality and limited differentiation potential also may make them safer (Staack and Rodriguez, 2011). Mesenchymal-derived stem cells (MSCs) (connective tissue from the embryonic mesoderm) have been investigated for use in SUI. Examples of MSCs are those isolated from bone marrow (bone marrow stem cells [BMSCs]) or adipose tissue (adipose-derived stem cells [ADSCs]) and hematopoietic stem cells from blood or umbilical cord (umbilical cord blood stem cells [UCBSCs]). The cells can be expanded before transplantation in a culture medium and can release paracrine factors to stimulate surrounding tissue regeneration. Large numbers of progenitor cells with a specialized phenotype can be obtained by in vitro growth. Examples of these are chondrocytes

from cartilage and skeletal muscle–derived stem cells (MDSCs) that can form myoblasts (Staack and Rodriguez, 2011). Autologous cells are preferred (Gras and Lose, 2011).

Animal Studies. Although BMSCs have been used widely in other sites, their use in the lower urinary tract is limited to experimental studies owing to difficulties in harvesting the cells (Aref-Adib et al, 2013). A relatively large number of animal studies have demonstrated that injection of cells isolated from skeletal muscle (MDSCs) can repair urethral injury or denervation. The cells survive and a normal repair process occurs with formation of new innervated myofibers, smooth muscle cells, loose interstitial tissue, and vessels. These observations have been confirmed by histologic and immunohistochemical tests. Functional testing on isolated urethral tissue and urodynamic tests on whole animals also have supported the results (Gras and Lose, 2011). ADSCs can differentiate into fibroblasts, myoblasts, smooth muscle cells, endothelial cells, or skeletal muscle and promote nerve regeneration (Staack and Rodriguez, 2011). Experimental studies have demonstrated immunohistochemical evidence of repair and improved urethral function in incontinent rat models. Furthermore, the abundance of donor tissue and easy isolation may allow for use of freshly isolated rather than cultured cells (Roche et al, 2010). Although animal studies are promising, most are small with short follow-up. They involve young animals that may not reflect an older human population (Aref-Adib et al, 2013).

Human Studies. The first study involved injecting autologous ear chondrocytes as a urethral bulking agent in 32 women (Bent et al, 2001b). After 1 year, 81% were improved and 50% were dry. No long-term follow-up has been published.

Mitterberger and coworkers (2007) reported on 123 women with SUI who underwent transurethral ultrasound-guided injection of autologous fibroblast injection into the urethral submucosal and myoblast injection into the rhabdosphincter. The cells were cultured from skeletal muscle biceps biopsies. One year after therapy, 94 women (76%) were cured, 16 (13%) were substantially improved, 9 (7%) were slightly improved, and 4 were lost to follow-up. No complications were reported. However, Strasser and coworkers, from the same group in Innsbruck, Austria (Strasser et al, 2007), published results of a randomized trial of autologous myoblast versus collagen injection, and the article was subsequently retracted by *The Lancet* owing to irregularities in the conducting of the clinical trial (Kleinert and Horton, 2008). This retraction has left us with relatively small, short-term, or early-phase studies in the literature to date.

The outcome of injection of autologous MDSCs via a transurethral ultrasound device followed by 5 weeks of self-administered transvaginal functional electrical stimulation was reported in 39 women (Blaganje and Lukanovic, 2013). At 6 months, 23.7% of the patients considered their SUI cured, and 52.6% reported improvement. Cornu and coworkers (2014) reported the long-term outcome of use of autologous MDSCs in 12 women, 11 of whom had undergone multiple previous SUI procedures. Of the 2 patients who were dry at 1 year, both were still dry at 6 years. Of the 5 who were considered improved at 1 year, all worsened, but 3 remained satisfied. There were 5 failures.

Stangel-Wojcikiewicz and coworkers (2014) reported 2-year outcomes of transurethral sphincter injections of autologous MDSCs harvested from the deltoid in 16 women with SUI. After 2 years, 8 were dry and 4 were improved; in 4 the treatment failed. The authors noted that the mean time for initial improvement was 4.7 months, and improvement continued for 8 months. They also noted that success was seen with a relatively small number of cells. Peters and colleagues (2014) reported the safety and 12-month efficacy outcomes of two pooled phase II studies of autologous MDSC injections in 72 of the 80 study patients. The investigators used four increasing doses of intrasphincteric injections (10^4 , 50×10^4 , 100×10^4 , and 200×10^4) of MDSCs obtained by quadriceps biopsy. They found that higher-dose groups tended to have greater percentages of patients with at least a 50% reduction in stress leaks and pad weight. All groups had statistically significant improvements in Urogenital Distress Inventory (UDI-6) and IIQ-7 scores.

Lee and coworkers (2010) reported the outcome of transurethral injection of a 2-mL suspension of umbilical cord blood stem cells in 36 of 39 women. After 12 months, 26 (72.2%) were cured or 50% or more improved, and in 10 (27.8%) the procedure failed.

To avoid the need for expensive cell preparation technology, Gras and colleagues tested the effect of transurethral injection of minced autologous striated muscle harvested and prepared for use at the time of urethral injection (Gras et al, 2014). Periurethral injections were done with urethral visualization with a vaginal ultrasound probe in 20 women with uncomplicated and 15 with complicated SUI. After 12 months, cure and improvement were noted in 25% and 63% of the uncomplicated group and 7% and 57% of the complicated group, respectively. The results appear similar to reports with harvested stem cells.

Most adverse events have been minor and easily managed. Peters and colleagues (2014) reported that biopsy-related adverse events occurred in 4 patients and included wound hematoma (2), procedural dizziness and associated responses (2), postoperative bleeding requiring sutures (1), and joint swelling (1). Injection procedure-related adverse events occurred in 18% (14 of 80), and included dysuria (7), pelvic or abdominal pain (4), vulvovaginal pruritus (3), urinary urgency (2), and transient hematuria (2).

The technology looks promising and may provide advantages over bulking agents. However, there are no large or comparative studies, and no long-term data are available yet. Furthermore, the ultimate cost of the technology will determine whether it becomes a feasible alternative.

Autologous Fat

Autologous fat has been used for esthetic and defect reconstruction since the 1980s (Billings and May, 1989). Although fat is biocompatible and readily available, 50% to 90% of the transferred adipose tissue graft may not survive (Horl et al, 1991). Graft survival depends on minimal handling, low suction pressure during liposuction, and the use of large-bore needles. Smaller grafts survive better than larger ones (Bircoll and Novack, 1987).

The procedure involves harvesting abdominal wall fat by liposuction with use of either local (Trockman and Leach, 1995) or general anesthesia (Su et al, 1998). The injection is usually carried out via the periurethral route with a 16- or 18-gauge needle. Post-procedure care may involve intermittent catheterization or even a suprapubic tube (Su et al, 1998).

Results. A number of reports of urethral fat injections have been published and appear in Table 86-6. Most of the series report short-term results, with success apparently lower than that with other injectables, apart from the study of Su and colleagues (1998) with a follow-up of more than 12 months. Palma and coworkers (1997) showed that repeat injections improved the cure rate from 31% to 64%. Haab and colleagues (1997) reported a comparative study with collagen. After a mean of 7 months, 13% of the women with fat injection were cured versus 24% of the women with collagen injections. The subjective improvement rate was also higher with the collagen. Lee and colleagues reported a randomized double-blind study of autologous fat versus saline injection (Lee et al, 2001). At 3 months, 6 of 27 (22.2%) and 6 of 29 (20.7%) women were cured or improved in the fat and saline groups, respectively. In this study, periurethral fat injection did not appear to be more efficacious than placebo in treating stress urinary incontinence.

Since the publication of the randomized trial of Lee and colleagues (2001) showing that fat was no more efficacious than saline, no further publications have appeared in the literature. Furthermore, the report of a death from fat embolism (Currie et al, 1997) most likely discouraged additional studies. However, experimental work on the use of ADSCs to help improve function after urethral injury has progressed in the rat model (Lin et al, 2010) and in a pilot study with five women with SUI (Kuismanen et al, 2014).

Complications. Reported complications are similar to those of other injectables and include UTI, retention, hematuria, and extravasation. Additional problems with the donor site, the abdominal wall, such as pain, hematomas, and infection, may also be seen.

TABLE 86-6 Results of Autologous Fat Injection

STUDY	NO. OF PATIENTS	FOLLOW-UP (mo)	NO. OF PATIENTS WHO BECAME DRY (%)	NO. OF PATIENTS WHOSE CONDITION IMPROVED (%)	NO. OF PATIENTS IN WHOM TREATMENT FAILED (%)
Cervigni et al (1994)	11	22.6	6 (54.5)	2 (18)	3 (27.3)
Santarosa and Blaivas (1994)	12	11		7 (58)	5 (42)
Trockman and Leach (1995)	32	6	4 (13)	14 (44)	14 (44)
Haab et al (1997)	45	7	6 (13)	13 (29)	26 (58)
Palma et al (1997)	30	12	1 injection: 4/13 (31) 2 injections: 11/17 (65)	—	—
Su et al (1998)	26	Mean 17.4 (range 12-30)	13 (50)	4 (15)	9 (35)

Other noteworthy complications are urethral pseudolipoma (Palma et al, 1996) and fat embolism (Sweat and Lightner, 1999), one of which was fatal (Currie et al, 1997).

Dextranomer Hyaluronic Acid Copolymer (Deflux, Zuidex)

Dextranomer hyaluronic acid (DHA) copolymer consists of dextranomer microspheres (80 to 250 μ m) in a carrier gel of non-animal-stabilized HA. The gel is a biocompatible, biodegradable material free of animal products, has no immunogenic properties, and has been shown not to migrate to different organs after submucosal injection (Stenberg et al, 1999). Stenberg and colleagues first reported the use of this substance in 20 women. They injected it transurethraally through a cystoscope. After 6 months, 9 patients were cured and 7 improved; in 3, the treatment failed. Six to 7 years later, 5 remained dry and 4 were still improved. Overall, 9 of the original 20 had a long-term response.

Subsequently the procedure was modified by injection of the DHA copolymer through a system consisting of a handle (Implacer) through which four needles with attached syringes are mounted. A plastic protector is pushed forward to sheathe the needles. The device is inserted into the urethra and positioned below the bladder neck by measurement of the distance from the meatus. The barrel is slid backward to unsheath the four needles, and a total of 2.8 mL of DHA is injected blindly into the urethra, 0.7 mL into each quadrant. Van Kerrebroeck and colleagues (2004) reported early results in 42 women. Thirty-two (76%) had improvement in leakage at 3 and 12 months. Chapple and colleagues (2005) reported the results of 142 patients treated in a European multicenter trial. The protocol consisted of an initial injection followed by another at 8 weeks if required. A total of 61 patients (43%) underwent the second injection. At month 12, 77% of the patients demonstrated a positive response—a 50% or greater decrease in leakage on provocative testing.

Lightner and colleagues (2009) reported 12-month outcomes of a North American prospective 2:1 randomized trial of Zuidex-Implacer versus collagen injected cystoscopically in 344 women. The study failed to demonstrate that Zuidex was noninferior to collagen. A 50% reduction in urinary leakage on provocation testing, the primary outcome, was achieved in 84% of collagen-treated women versus 65% of Zuidex-treated women. There was also a 15% incidence of pseudoabscess formation. This negative trial prompted the company to withdraw the Zuidex product.

To determine whether the relatively poor success and high rate of pseudoabscess formation was related to the material or the Implacer, Lightner and coworkers (2010) did a study with cystoscopically guided injections of DHA copolymer. Of the 35 treated women with ISD, 23 returned their post-treatment questionnaires.

At an average of 16 months after the last injection, 47% were cured or markedly improved; however, 6 of 13 without pretreatment urgency also developed de novo urgency incontinence. Pseudoabscesses developed in 4 patients (11%). The authors concluded that the injectable itself is associated with the poor outcomes and further study is not warranted. A similar product, Deflux, approved for vesicoureteral reflux, is still available and can be used without the Implacer.

Complications. The reported side effects were similar to those of other injectables, apart from injection site infections and pseudocyst or pseudoabscess formation requiring drainage or excision (Chapple et al, 2005; Petrou et al, 2006; Abdelwahab and Ghoniem, 2007; Lightner et al, 2010). Urethrovaginal fistula after sterile abscess has also been reported (Hilton, 2009).

KEY POINTS: OUTCOMES OF INJECTABLE AGENTS FOR FEMALE STRESS URINARY INCONTINENCE

- Until it was discontinued in 2010, collagen was the most widely used and reported injectable agent.
- Results of injectables may be optimized if there is circumferential distribution of the injection material in the proximal urethra.
- In two separate randomized clinical trials versus collagen, both carbon-coated zirconium beads (Durasphere) and CaHA (Coaptite) showed similar results to collagen after a 1-year follow-up.
- In a randomized clinical trial comparing silicone microparticles (Macroplastique) with collagen, silicone microparticles were shown to be noninferior to collagen after 1-year follow-up.
- PAHG (Bulkamid) was also shown to be noninferior to collagen in a North American 1-year multicenter randomized trial.
- Complications of currently used injectables are usually mild and may be self-limited. Common ones include transient retention, urinary infection, de novo urgency and urgency incontinence, and hematuria.
- ACT silicone balloons were devised as a nonmigrating injectable alternative. No comparative studies have been done, and long-term durability has not been demonstrated.
- Cell-based therapies are in the investigational stages. Clinical reports are few and have included autologous ear chondrocytes, MDSCs and UCBSs.

PATHOPHYSIOLOGY OF POSTPROSTATECTOMY INCONTINENCE AND THE USE OF INJECTABLE AGENTS FOR MALE STRESS URINARY INCONTINENCE

Postprostatectomy incontinence (PPI) may be caused by bladder dysfunction, sphincter dysfunction, or a combination of the two. Urodynamic investigations can be helpful to rule out bladder outlet obstruction or significant bladder dysfunction. In addition to incontinence symptoms, storage and voiding symptoms may be associated (Gray et al, 1999; Hollenbeck et al, 2002). Urodynamic studies have demonstrated that sphincter incompetence occurs as the sole cause in more than two thirds of patients, whereas isolated bladder dysfunction (detrusor overactivity, poor compliance, detrusor underactivity during voiding) is uncommon, occurring in less than 10% of patients (Ficazzola and Nitti, 1998; Groutz et al, 2000b). However, sphincter and bladder dysfunction can coexist in at least one third of incontinent patients. Decreased sphincter resistance may be caused by tissue scarring in some cases and is reflected by a low urethral compliance; however, this parameter is difficult to measure (Groutz et al, 2000b). Scarring may lead to an anastomotic stricture evidenced by endoscopy or urethrography and may be clinically suspected when both incontinence and decreased force of stream coexist.

The preoperative length of the membranous urethra determined on magnetic resonance imaging (MRI) has been shown to be related to time to postoperative continence (Coakley et al, 2002). Urodynamic studies have revealed that a reduced functional urethral length was predictive of incontinence (Hammerer and Huland, 1997; Van Kampen et al, 1998; Wei et al, 2000). Cameron and coworkers (2015) showed in a pilot study that patients with PPI were less able to increase urethral pressure during a Kegel maneuver and had shorter anatomic urethral sphincter length on MRI than continent controls. The state of a patient's pelvic floor may also influence continence or return to continence after radical prostatectomy. Physiotherapy and pelvic floor rehabilitation have been shown to improve or enhance continence (decreased time to final continence level) in the postoperative period in two randomized studies, but only if such measures are instituted before or immediately after catheter removal (Van Kampen et al, 2000; Parekh et al, 2003). Maximum difference between physiotherapy and no treatment is achieved at 3 months, with almost no difference at 12 months. A randomized study in which randomization occurred 6 weeks after surgery showed no difference in continence at 6 months (Wille et al, 2003).

Urethral bulking theoretically works by adding bulk and increasing coaptation at the level of the bladder neck and proximal urethra. Several agents have been used including bovine collagen (Contigen) and silicone microparticles (Macroplastique). All agents share similar problems including the need for multiple injections, deterioration of effect over time, and low cure rates. An alternative technology with implanted adjustable volume balloons (ProACT) will be discussed.

Workup

Basic evaluation includes history, physical examination, urinalysis, and PVR urine. A frequency-volume chart (Griffiths et al, 1993) or bladder diary is also helpful. A pad test quantifies the severity of incontinence. The 24-hour home test is the most accurate pad test for quantification and diagnosis and the most reproducible (Mouritsen et al, 1989). The 1-hour pad test is widely used because it is more easily done and standardized. PVR urine is a good estimation of voiding efficiency (Diokno et al, 1988; Starer and Libow, 1988).

Blood testing (blood urea nitrogen [BUN], creatinine, glucose) is recommended if compromised renal function is suspected or documented (Fantl et al, 1996).

Uroflowmetry may be helpful to assess voiding function.

Cystourethroscopy is done to verify integrity of the urethral wall and bladder neck and the status of the bladder (e.g., trabeculation, stones, diverticula). Injectables are not effective with

scarred supramembranous urethras because the tissues cannot expand with the agent. The status of the urethra should be assessed preoperatively.

Invasive urodynamic studies may be useful to assess bladder and urethral function before interventional therapy (Herschorn et al, 2013). Detrusor overactivity or decreased bladder compliance demonstrated on multichannel testing may be contributing to symptoms and may merit alternative treatment. Sphincter weakness can be documented by Valsalva maneuver (McGuire et al, 1993) or cough (Schick, 1985) ALPP, but its reproducibility has been studied in women and not men. Although ALPP may be helpful, it has been shown to be a poor predictor of incontinence severity after radical prostatectomy (Twiss et al, 2005). Furthermore, in male patients, ALPP measurement may be better accomplished via a rectal catheter because a urethral catheter may occlude a scarred urethra (Flood et al, 1996). The evidence supporting the use of various urodynamic tests in the diagnosis of PPI was recently reported in a consensus publication from the International Consultation on Incontinence–Research Society (ICI-RS) (Rosier et al, 2014). Flow, PVR volume, cystometry, and pressure-flow study results have level 4 evidence, and urethral pressure profile, video-urodynamics, surface electromyography (EMG), and ambulatory urodynamic studies have no evidence. Furthermore, evidence supporting the predictive value of urodynamic studies is also lacking. Invasive urodynamic studies are therefore an optional test.

Injection Techniques

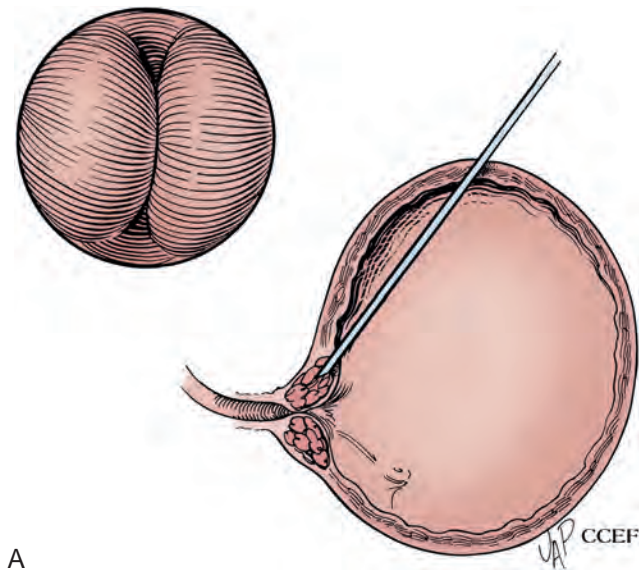
Retrograde Injection

Male patients are placed in the lithotomy position, and the surgical field is prepared in the usual sterile fashion (Fig. 86-8A). The procedure can be performed using local, regional, or general anesthesia. If local anesthesia is used, 2% topical urethral lidocaine jelly can be inserted 10 minutes before instrumentation. In some patients, preoperative sedation may also be of benefit. A 20- or 22-Fr cystoscopic sheath is used with a 0-degree or 30-degree lens. GAX collagen is provided in a 3.0-mL Luer-Lok syringe containing 2.5 mL of injectable material. The syringe attaches to a 5-Fr injection catheter containing a 1.5-cm 20-gauge needle at the tip. Most men are injected transurethally under cystoscopic vision.

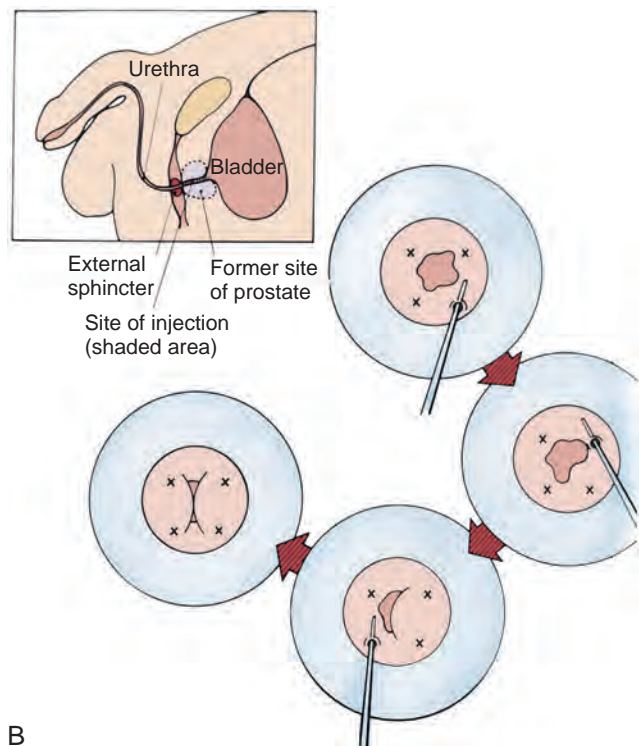
The postprostatectomy urethra is frequently scarred and not very pliable; thus, several needle insertions are frequently needed to deposit sufficient material to produce urethral coaptation. The injection is completed in up to four quadrants after localization of the appropriate level in the proximal urethra. The needle is advanced under the urethral mucosa with the beveled portion of the needle facing the urethral lumen to allow for layering of the material. The injectable material is then delivered, creating a bleb under the urethral mucosa that protrudes into the urethral lumen. This is performed in a circumferential manner in four quadrants, creating a bleb in each quadrant. After completion, the urethral mucosa should be completely coapted, creating the appearance of an obstructed urethra. Extrusion of the injectable agent into the urethral lumen as the needle is withdrawn may occur. This may be prevented in most cases by leaving the needle in place for at least 30 seconds after the injection is completed or by flushing the material with saline. The loss of additional material is diminished by preventing advancement of the cystoscope proximal to the injection sites. If material extravasation occurs in all quadrants during injection, the procedure should be terminated and rescheduled (Appell and Winters, 2007).

Antegrade Injection

Because of less-than-optimal results, an alternative method of injecting collagen in men was introduced, involving a suprapubic antegrade approach. The antegrade approach has the advantage of direct visualization of the bladder neck and the injection of material into more supple, less scarred urethra (see Fig. 86-8B). The patient is placed in the lithotomy position and flexible cystoscopy is carried



A



B

Figure 86-8. A, Retrograde urethral injection technique in men. Schematic representation of transurethral circumferential injection in a male after prostatectomy. B, Antegrade urethral technique injection in the male after radical prostatectomy. (A, Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1994-2011. All rights reserved.)

out, simultaneously filling the bladder. A percutaneous suprapubic puncture allows placement of two guidewires into the bladder. The site is dilated to 16 Fr with Amplatz dilators. A sheath may be used, but commonly the cystoscope (flexible or rigid pediatric) can be advanced over one of the guidewires into the bladder. A small red rubber catheter or the flexible cystoscope can be used to assist in localization of the bladder neck. The needle is placed just under the urethral mucosa at the level of the bladder neck and advanced proximally, meaning it is pulled back toward the bladder. The bladder neck closes off completely as the material is injected. Injection stops after the bladder neck closes off, with the two sides meeting in

apposition near the midline. A small suprapubic tube can be placed to avoid the possible necessity of urethral catheterization.

Periprocedure Care

Prophylactic antibiotics with a fluoroquinolone or TMP-SMX for 24 hours or less can be recommended (Wolf et al, 2008). An additional 2 to 3 days has also been suggested (Appell and Winters, 2007).

The patient then voids and can be discharged. Urinary retention can be treated by insertion of a fine Foley catheter (12 to 14 Fr or smaller) overnight or intermittent catheterization. Although not specifically reported, an indwelling Foley catheter may cause molding of the agent and lead to early failure, so long-term catheterization should be avoided.

Reinjections

The same schedule applies as in female patients.

Glutaraldehyde Cross-linked Bovine Collagen (Contigen)

As mentioned earlier, GAX collagen was discontinued in 2010. Its use is presented here because there is still more experience with this injectable than with all others to date.

GAX collagen was injected transurethral with cystoscopic monitoring into the supramembranous urethra. It has also been injected percutaneously through a suprapubic approach in an antegrade manner. The published results for both techniques are shown in Tables 86-7 and 86-8.

For collagen, success rates for PPI range from 36% to 69%, with 4% to 20% of patients reporting being dry (McGuire and Appell, 1994; Aboseif et al, 1996; Cummings et al, 1996; Sanchez-Ortiz et al, 1997; Smith et al, 1998a; Cespedes et al, 1999; Klutke et al, 1999; Tiguert et al, 1999). Unfortunately, the end points in most of these studies are subjectively based, making comparisons difficult; however, it is clear that cure rates (total dryness) are low, and multiple injections are required to achieve modest rates of subjective improvement. There is no advantage of delivery technique (retrograde vs. antegrade). Several authors have identified factors that negatively affect results, including extensive scarring or stricture formation, previous radiation, and high-grade stress incontinence and low ALPP (Aboseif et al, 1996; Sanchez-Ortiz et al, 1997; Smith et al, 1998a; Cespedes et al, 1999). One study reported more favorable results for collagen in treating incontinence after transurethral prostatectomy as opposed to radical prostatectomy (35.2% social continence vs. 62.5%) (Smith et al, 1998a). Westney and coworkers (2005) reported long-term results in 322 men followed for a mean of 40.1 months. Overall, 55 patients (17%) were dry for a mean of 11.1 months and required 3.8 injections with a total volume of 29.3 mL. Their mean duration of response was 11.1 months. In those who experienced any improvement, the mean duration of response was 6.3 months. These authors concluded that collagen was of some benefit but the duration of response was limited.

Collagen injection does not adversely affect outcomes of artificial sphincter implantation and does not increase the complication rate (Gomes et al, 2000), nor does collagen injection adversely affect the outcome of the bone-anchored male sling (Comiter, 2002; Onur and Singla, 2006). The cost-efficacy of injections remains to be determined.

Complications. In addition to the complications reported in the section on female patients, worsening of incontinence symptoms may occur in 1.5% of male patients (Westney et al, 2005).

Currently Used Injectable Agents

Silicone Microimplants (Macroplastique)

Colombo and colleagues (1997) reported on 6 men with PPI followed for a mean of 15.5 months. Of 6 patients, 5 became dry and 1 was substantially improved. Although initial success has been

TABLE 86-7 Results of Retrograde Transurethral Collagen Injection Therapy for Postprostatectomy Incontinence

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	MEAN NO. OF INJECTIONS	MEAN VOLUME (mL)	NO. OF PATIENTS WHO BECAME DRY (%)	NO. OF PATIENTS WHOSE CONDITION IMPROVED (%)	NO. OF PATIENTS IN WHOM TREATMENT FAILED (%)
Shortliffe et al (1989)	14	19-23	1.6	28.4	3 (21)	5 (36)	6 (43)
Herschorn et al (1992)	10	6	4.7	51.8	2 (20)	5 (50)	3 (30)
Bevan-Thomas et al (1999)	257	28	4.4	36.6	52 (20)	101 (39)	104 (40)
Smith et al (1998a)	54	29	4	20	—	19 (35)	35 (65)
Cespedes et al (1999)	110	7	4.2	28.4	58 (53)	10 (9)	42 (38)
Aboseif et al (1996)	88	10	2.8	31	42 (48)	33 (38)	13 (15)
Martins et al (1997)	46	26	2.8	31	11 (24)	21 (46)	14 (30)
Faerber and Richardson (1997)	68	38	5	36	7 (10)	7 (10)	54 (79)
Griebing et al (1997)	25	13.3	2.6	35.5	0 (0)	10 (40)	15 (60)
Cummings et al (1996)	19	10.4	1.8	13.8	4 (21)	7 (37)	8 (42)
Elsergany and Ghoniem (1998)	35	17.6	2	10	7 (20)	11 (31)	17 (49)
Tiguert et al (1999)	21	12.5	2.9	18.2	1 (5)	12 (57)	8 (38)
Westney et al (2005)	322	40.1	4.37	36	55 (17)	87 (27)	180 (56)

TABLE 86-8 Results of Antegrade Injection Collagen Injection Therapy for Postprostatectomy Incontinence

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	MEAN NO. OF INJECTIONS	MEAN VOLUME (mL)	NO. OF PATIENTS CURED (%)	NO. OF PATIENTS WHOSE CONDITION IMPROVED (%)	NO. OF PATIENTS IN WHOM TREATMENT FAILED (%)
Wainstein and Klutke (1997)	48	8.5	—	14.5	12 (25)	22 (46)	14 (29)
Appell et al (1996)	24	12	1	7.1	9 (37.5)	15 (62.5)	—
Klutke et al (1999)	20	28	1	14.5	2 (10)	7 (35)	11 (55)

demonstrated with silicone microimplants, results deteriorate over time. Bugel and coworkers treated 15 patients. They noted rapid deterioration after initial improvements with success rates of 40%, 71%, 33%, and 26% at 1, 3, 6, and 12 months, respectively (Bugel et al, 1999). They also noted that a urethral closure pressure of at least 30 cm H₂O was essential for success. Kymala and colleagues (2003) studied 50 patients with mild-to-moderate SUI (average 48 mL on 1-hour pad test); 12% achieved short-term continence after one injection, and an additional 20%, 18%, and 10% achieved continence with 2, 3, or 4 injections, respectively. Follow-up, however, was limited to 3 months. In a series of 14 men with spinal injuries and SUI, Hamid and coworkers (2003) reported that 5 (36%) were dry, 3 (21%) were improved, and in 6 (43%) the procedure had failed after a mean follow-up of 35 months. Longer-term deterioration of outcome was also reported by Lee and coworkers (2014). In a group of 30 incontinent men, the cure and improvement rate at 1 month was 43% (13 of 30), but at 6 months only 6 of 19 evaluable patients had a successful result (1 dry, 5 improved).

In a randomized trial of the Artificial Urinary Sphincter (AUS) versus Macroplastique injection in patients with minimal SUI (the vast majority had SUI after benign prostatic hyperplasia [BPH] surgery, with more than one third of the cohort having SUI after open radical prostatectomy), Imamoglu and colleagues (2005) demonstrated no difference in success with AUS versus Macroplastique in men with mild incontinence. However, in patients with

more severe incontinence, the AUS was superior, with minimal improvement seen after transurethral Macroplastique.

Complications. Side effects in men are similar to those reported in women.

Adjustable Balloons (ProACT)

The adjustable balloon procedure is based on the concept of passive compression and uses balloons located on either side of the urethra. Balloons may be progressively inflated until there is optimal coaptation, thereby achieving continence. The biomaterial ACT was originally developed for female SUI and subsequently was applied to male incontinence. The male ProACT device was first reported in 2000 (Hubner, 2000).

The device consists of a silicone elastomer balloon attached to an injectable titanium port with a silicone tube (Fig. 86-9). A balloon is implanted on either side of the urethra, either under the bladder neck for post-radical prostatectomy incontinence, or under the verumontanum for post-transurethral resection of the prostate (TURP) incontinence. The ports are positioned subcutaneously in the scrotum, allowing simple access for percutaneous adjustment of the balloon volume. The implantation is performed with the patient under general or spinal anesthesia through a short perineal incision. A trocar covered with a U-shaped sheath is inserted up to the site of implantation, and then the balloon is pushed along

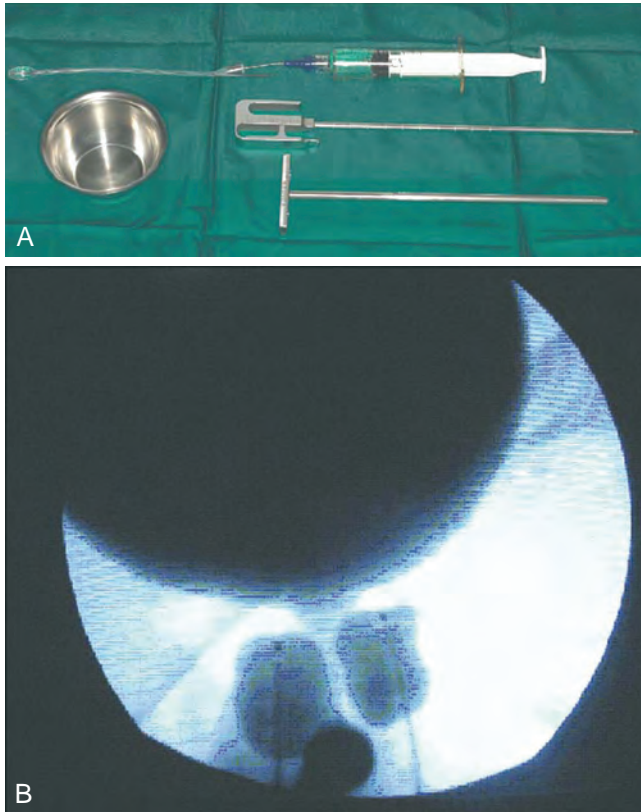


Figure 86-9. Illustration of Adjustable Continence Therapy balloon device for men. A, Balloon, trocar, and U-shaped insertion device are shown. Syringe with contrast agent is connected to balloon port. B, Fluoroscopic picture showing contrast agent in the bladder and urethra with balloons near the bladder neck. (From Trigo-Rocha F, Gomes CM, Pompeo AC, et al. Prospective study evaluating efficacy and safety of Adjustable Continence Therapy [ProACT] for post radical prostatectomy urinary incontinence. *Urology* 2006;67[5]: 965–69.)

inside the sheath. Fluoroscopic and urethroscopic guidance are used for the procedure. Transrectal ultrasound-guided implantation (Gregori et al, 2006, 2010) is a possible option. The balloons are filled with 2 mL of isotonic sterile water and contrast medium during the initial procedure. After approximately 1 month, the balloons are refilled with 1 mL of this solution at each period (maximum filling is 8 mL) until continence is achieved. The adjustments of the filling are volume limited and are carried out step by step to obtain a pseudocapsule surrounding the balloons to minimize the risk of urethral erosion or migration.

Results from 11 studies are shown in Table 86-9. The duration of follow-up was variable, and not all patients undergoing implantation had their follow-up documented. The percentage of successfully treated patients was frequently based on the number of patients still in the study at the follow-up point in time and not on the total number entering the study. This raises the success rates because the failures, or patients lost to follow-up, were dropped from the denominator. The reported pad-free rate varied from 14% (Cansino Alcaide et al, 2007) to 67% (Kocjancic et al, 2007). The percentage of patients using 0 or 1 pad per day ranged from 44% (Kjaer et al, 2012) to 81% (Gilling et al, 2008). The mean procedure time ranged from 19 minutes (Kocjancic et al, 2007) to 53 minutes (Roupret et al, 2011). Along with improvements in pad use, there were parallel improvements in Incontinence Quality-of-Life instrument (I-QOL) score (Hubner and Schlarp, 2005; Trigo-Rocha et al, 2006; Lebret et al, 2008). The mean number of postoperative

adjustments of the balloon was 3 to 5, with some patients requiring up to 15.

In a simultaneously treated cohort study from two centers, Crivellaro and colleagues (2008) reported no difference in outcome for the adjustable balloons versus bone-anchored male sling. At a mean follow-up of 19 months, 30 of 44 men (68%) who had undergone adjustable balloon procedures were dry and 7 (16%) were improved versus 23 of 36 (64%) and 8 (22%) after bone-anchored male sling placement, respectively, after a mean of 33 months ($P > .05$).

Complications. The most common perioperative complication is urethral or bladder perforation, necessitating termination of the implant on the perforated side. However, contralateral implantation was not adversely affected, and repeat ipsilateral implantation was invariably achieved after healing of the urethral or bladder wall. Lebret and coworkers (2008) reported a perforation rate of 10%, and Hubner and Schlarp (2007) reported a rate of 18% early in their series, but a lower urethral perforation rate in more recent cases—illustrating a relatively short learning curve for optimal balloon placement near the urethral-bladder wall. The rate of temporary urinary retention was reported to be 5% (Hubner and Schlarp, 2007). Voiding was restored by removing fluid from the balloon.

Device explantation is related to balloon failure, infection, erosion, or migration. The explantation rate ranged from 10% to 58% (see Table 86-9) but decreased with experience (Hubner and Schlarp, 2007). Device removal is straightforward, because a deflated balloon can be explanted transperineally. Reported risk factors for failure and complications were prior external beam radiotherapy (Lebret et al, 2008; Gregori et al, 2010) and severe preoperative incontinence (Gregori et al, 2010). Kocjancic and colleagues (2007) reported a continence rate of 67% in nonirradiated patients compared with 36% in radiated patients.

Conclusion. The adjustable balloon (ProACT) technique appears to be a feasible procedure to improve continence in the short and medium term. Appropriate candidates include those with mild-to-moderate leakage and no previous radiation. The benefit of an adjustable system should be weighed against the need for multiple sessions to refill the balloons and with reported rates of perioperative and postoperative complications necessitating removal. Furthermore, the follow-up period in many studies includes adjustments, so long-term durability is not yet known.

The technology appears to have better results than injectable agents in men. Additional studies comparing this technology with slings and the artificial sphincter are required. The device is not commercially available in the United States.

KEY POINTS: USE OF INJECTABLES IN MALE STRESS URINARY INCONTINENCE

- The workup includes history and physical examination, urinalysis, uroflowmetry, and assessment of PVR urine. Urodynamic studies may be helpful. Cystoscopy is done to verify the status of the urethra because scarring may prevent the tissues from expanding with the bulking agent.
- Both transurethral retrograde and percutaneous antegrade techniques are feasible, with no differences in outcomes reported.
- Commonly reported injectables have included collagen and silicone microparticles. These agents show initial good results, the need for multiple treatment sessions, and deterioration of outcome over time. Reports of injectables in male patients are far few than those in female patients.
- The use of implanted adjustable silicone (ProACT) balloons appears to be a feasible technique. However, randomized trials have yet to be done, multiple sessions are needed to fill the balloons, and long-term durability is not known.

TABLE 86-9 Results and Complications of Adjustable Balloons (ProAct) in Postprostatectomy Urinary Incontinence

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	NO. OF ADJUSTMENTS (BALLOON REFILLING)	POSTOPERATIVE COMPLICATIONS WITH EXPLANTATION (UNILATERAL OR BILATERAL)	CONTINENCE—0 OR 1 PAD/DAY	COMPLETE CONTINENCE
Hubner and Schlarp (2005)	117	13	3 (1-15)	46%	67% (42/63)	35% (22/63) (same at 1 and 2 years)
Trigo-Rocha et al (2006)	23	22	5 (1-6)	17%	65% (15/23)	
Hubner and Schlarp (2007)	50 first 50 last	20 23	5 4	58% 24%	52% 60%	
Cansino Alcaide et al (2007)	69	22	2	12%	70%	14%
Kocjancic et al (2007)	64	20	3 (0-8)	17%		67%
Gilling et al (2008)	37	24	3.3 (0-7)	11%	81% (of 34 patients)	62% (of 34 patients)
Lebret et al (2008)	62	6	4	31%	71%	30%
Gregori et al (2010)	62	25	3.6 (0-14)	11%		61%
Roupret et al (2011)	128	56		18%	68%	66%
Kjaer et al (2012)	114	58	Median 4 (0-14)	20%	44%	25%
Utomo et al (2013)	49	—	—	10%	Overall 75.5% 93% (14/15 with mild UI) 83% (15/18 with moderate) 50% (8/16 with severe)	

UI, urinary incontinence.

USE OF INJECTABLES FOR INCONTINENCE AFTER URINARY DIVERSION

There are increasing numbers of reports in the literature about the use of injectables after diversion. *Izes and colleagues (1997)* demonstrated in a canine study that GAX collagen injected circumferentially into the lumen of the ileocecal valve can increase the leak point pressure for up to 1 month after injection. Subsequently, *Smith and colleagues (1998b)* reported results of collagen use in four women and two men with leaking Indiana pouches. These authors injected a mean of 16 mL circumferentially into the ileocecal junction to obtain visual closure of the bowel lumen. After a mean follow-up of 26 months, five of the six patients remained dry.

Guys and colleagues (2002) reported on the use of Macroplastique for other leaking continent catheterizable channels. They injected 6 patients (4 appendix and 2 ileum) with a mean of 6 (3 to 8) mL. One had a second injection after 3 months. Four of 6 were continent after a mean of 11 (8 to 18) months. *Halachmi and colleagues (2004)* reported cure in 3, improvement in 1, and no change in 1 of 5 patients with stoma leakage. *Prieto and colleagues (2006)* treated 14 patients with leaking stomas with 2 to 6 mL (mean 3.7 mL) of DHA. With a mean follow-up of 1 year, 10 were dry after one injection, 1 was dry after two injections, and in 3 the treatment failed. *Welk and coworkers (2008)* achieved success in 2 of 4 patients with DHA injections. *Kass-Ilya and colleagues (2015)* reported a 50% success rate in 24 patients after a mean of 30

months with use of Macroplastique. Three were dry and 9 were improved. Five of the 9 improved patients went on to surgery at a mean of 41 months. Injectable agents appear to be a benefit in more than 50% of reported patients and may obviate or delay surgical revision.

Injectables have been rarely reported in women after neobladder construction. *Tchetgen and colleagues (2001)* reported on 3 women with SUI after cystectomy and orthotopic neobladder. An average of two injections were given, with a cure in 1 patient, improvement in 1, and no change in 1. *Wilson and colleagues (2004)* administered transurethral collagen to 11 patients and pyrolytic carbon-coated zirconium beads to 1 patient with SUI after cystectomy and neobladder. After a mean of 22.5 months, 2 patients (16.7%) were dry, although they continued to have urinary frequency. Four patients (33.3%) were improved and 6 were unchanged. The authors concluded that the treatment response was not optimal or durable.

New-onset vesicovaginal fistula was reported in two patients who had undergone collagen injection for SUI after cystectomy and neobladder (*Pruthi et al, 2000*). Both patients underwent transvaginal fistula repair with pubovaginal sling.

To date, the success of injectables for neobladder urethral incontinence is limited.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Additional Therapies for Storage Failure at the Bladder Level

Additional Therapies for Storage Failure at the Bladder Outlet

Additional Therapies for Emptying

Catheterization

Increasing Intravesical Pressure or Facilitating Bladder Contractility

Additional Therapies for Storage and Emptying Failure: Circumventing the Problem

Summary

Disorders of the storage and emptying phases of micturition result in voiding dysfunction and often lead to bothersome urinary symptoms. The location of the storage or emptying failure may occur at the bladder, the bladder outlet, or a combination of both. Storage failure originating from the bladder results from poor bladder compliance, decreased capacity, detrusor overactivity (DO), and/or altered bladder sensation. Failure of the bladder outlet to store urine is due to an incompetent closure mechanism. Emptying disorders can similarly be classified by location. At the bladder level, impaired or absent detrusor contractility leads to emptying failure. At the bladder outlet, emptying difficulties are caused by anatomic obstruction or sphincter dyssynergia/dysfunction. In previous chapters, numerous therapies for bladder storage and emptying failure have already been discussed, illustrating the complexities of voiding dysfunction management. A comprehensive summary of these treatment options can be found in Boxes 70-3 and 70-4 in Chapter 70.

This chapter will cover additional therapies to improve bladder storage and emptying, including contemporary augmentation cystoplasty techniques for adults, surgical and nonsurgical management of the incompetent bladder outlet, modified cystoplasty incorporating a catheterizable channel and catheterization.

ADDITIONAL THERAPIES FOR STORAGE FAILURE AT THE BLADDER LEVEL

Failure of the filling/storage phase of micturition often results in urinary symptoms of frequency, urgency, and/or incontinence. Additionally, poor bladder compliance and reduced capacity may lead to renal function deterioration. The goals of therapy for storage failure are urine accommodation in the bladder at low pressures, improved bladder capacity, decreased incontinence related to DO, and preservation of renal function.

Augmentation Cystoplasty

Augmentation cystoplasty is a well-established technique that typically involves adding an enteric segment to the bladder to increase its size. This can improve bladder compliance and capacity, preserve renal function, and minimize incontinence resulting from severe DO. Augmentation cystoplasty is performed in patients who have failed or who are not candidates for more conservative forms of intervention such as anticholinergics, intravesical instillation of medication, intravesical injection of botulinum toxin, and/or

clean intermittent catheterization (CIC). The contemporary indications for augmentation cystoplasty are narrowing with the rising efficacy of these conservative therapies, especially botulinum toxin, and their ability to improve bladder compliance and capacity (Karsenty et al, 2008). However, augmentation cystoplasty plays an important role in the management of refractory patients. In the appropriate patient, augmentation cystoplasty is an excellent treatment option that can enhance bladder function and improve patients' quality of life.

Historical Perspective

First reported in canines by Tizzoni and Foggi in 1888 (Tizzoni and Foggi, 1888), augmentation ileocystoplasty was performed in humans one year later by von Mikulicz (1889). After 1972, with the introduction of CIC and the wider use of enteric segments in urologic procedures, the technique of augmentation cystoplasty gained popularity (Biers et al, 2012). In 1982, Bramble's technique of clam cystoplasty (1982), further popularized by Mundy and Stephenson (1985), established the use of augmentation cystoplasty in the urologic community.

More recently, the number of augmentation cystoplasty procedures being performed has declined. Data from the United Kingdom show a 38% reduction in augmentation cystoplasty operations from 2000 to 2010. This reduction appears to coincide with a dramatic increase in the use of intravesical botulinum toxin (Biers et al, 2012). The decline also may be related to increasing concern for complications associated with augmentation cystoplasty, including malignancy, spontaneous bladder perforation, and metabolic changes (Schlomer et al, 2013).

Indications for Augmentation Cystoplasty

Although augmentation cystoplasty is performed less frequently today, it is still a mainstay for several important reasons in the management of patients who have failed or who are not candidates for other conservative therapies. The key indications for augmentation cystoplasty arising from storage failure at the bladder level are poor bladder compliance, reduced bladder capacity, and significant DO.

Bladder Compliance

Compliance is defined as the relationship between change in bladder volume and change in detrusor pressure. Ideally, as the

bladder fills the detrusor pressure should remain low, with little to no change as volume increases. Impaired bladder compliance can be a result of changes in the viscoelastic properties of the bladder, as seen in disease processes that increase collagen deposition in the bladder wall. These disease states include radiation cystitis or chronic inflammatory and infectious processes (i.e., genitourinary tuberculosis or schistosomiasis). Bladder compliance also can be negatively affected by neurologic diseases such as myelodysplasia and multiple sclerosis, as well as spinal cord injury (SCI). In these neurologic conditions, increases in afferent input and changes in sympathetic facilitation of bladder filling contribute to decreased compliance. Additionally, patients with lesions below the sacral cord may develop compliance issues as a result of decentralization (Reyblat and Ginsberg, 2008). It is well known that patients with poor bladder compliance and/or subsequent increases in detrusor pressures of greater than 40 cm H₂O without leakage during bladder filling are at risk for vesicoureteral reflux and upper tract deterioration (McGuire et al, 1981). Patients with poor compliance require intervention to reduce storage pressures, thereby preserving renal function. Multiple studies show that augmentation cystoplasty successfully reduces detrusor pressures and improves bladder compliance. In the literature, there is a reported 65% to 82% reduction in mean maximum detrusor pressure after augmentation cystoplasty (Khastgir et al, 2003; Quek and Ginsberg, 2003; Gurung et al, 2012). Additionally, long-term data with 6 to 14 years of postoperative follow-up show this improvement in compliance to be sustained over time (Khastgir et al, 2003; Quek and Ginsberg, 2003; Gurung et al, 2012). After augmentation cystoplasty, resolution or marked improvement in vesicoureteral reflux is also reported (Khastgir et al, 2003).

Capacity

Reduced bladder capacity, found in conjunction with poor bladder compliance and/or severe DO, is another indication for augmentation cystoplasty. Patients with significantly reduced bladder capacities are bothered by incontinence, frequent urination, and/or the frequent need to perform CIC to avoid leakage. These bothersome lower urinary tract symptoms (LUTS) negatively affect patients' social, psychological, and physical quality of life (Ku, 2006; Liu et al, 2010). Patients who have undergone augmentation cystoplasty have improvements in bladder capacity with an increase in mean cystometric capacity from 200 mL to over 500 mL postoperatively (Khastgir et al, 2003; Quek and Ginsberg, 2003; Gurung et al, 2012; Khavari et al, 2012). Additionally, after augmentation cystoplasty, patients have significant improvement in their quality of life and a 93% to 96% satisfaction rate (Khastgir et al, 2003; Gurung et al, 2012).

Detrusor Overactivity

Augmentation cystoplasty is also indicated in patients with severe DO who are refractory to anticholinergics, intravesical injection of botulinum toxin, and/or neuromodulation. DO is a urodynamic finding characterized by involuntary detrusor contractions during filling cystometry. These involuntary detrusor contractions may be solitary, phasic, or terminal and can occur in neurogenic and non-neurogenic patients. DO can result in significant urinary urgency, frequency, and/or incontinence. Patients may ultimately require augmentation cystoplasty to alleviate these symptoms. A systematic review of the literature demonstrated that patients with neurogenic DO incontinence scored lower on various health-related quality-of-life instruments measuring physical, emotional, and psychological parameters when compared to their continent counterparts (Tapia et al, 2013). Not surprisingly, urinary incontinence from neurogenic DO also negatively affects patients' sexual function (Valtonen et al, 2006). As mentioned previously, augmentation cystoplasty improves patients' quality of life substantially and has a high satisfaction rate of 93% to 96% (Khastgir et al, 2003; Gurung et al, 2012). Overall continence rates in patients with neurogenic DO also improve after augmentation cystoplasty and

range from 80% to 100% (Biers et al, 2012). Although augmentation cystoplasty is not commonly performed for idiopathic DO, data show similar continence and satisfaction rates of 78% to 90% in this population (Edlund et al, 2001).

Augmentation Cystoplasty Techniques

Many gastrointestinal tract segments have been used for bladder augmentation. These segments include ileum, sigmoid colon, cecum, and stomach. Each is associated with its own advantages and disadvantages. A more detailed discussion of various augmentation techniques and complications is addressed in Chapter 145.

Ileocystoplasty is the most common type of augmentation cystoplasty, because of the reconstructive urologist's familiarity with ileum and the ileum's ability to easily reach to the pelvis. Although hyperchloremic metabolic acidosis can occur after using ileum or colon for bladder substitution, the use of ileum for augmentation seems to result in less significant metabolic disturbances. Patients with SCI followed for over 10 years after ileocystoplasty had no evidence of metabolic abnormalities (Gurung et al, 2012). Normal electrolyte and arterial blood gas levels were also found after long-term follow-up of 25 pediatric patients with ileocystoplasty. However, 12% of these patients had mild osteopenia, which is a potential sequela of chronic acidosis (Hafez et al, 2003). Although patients may develop metabolic acidosis after ileocystoplasty or colcystoplasty, this acidosis is often clinically insignificant and only 16% require oral bicarbonate therapy (Biers et al, 2012).

Colon has also been successfully used for augmentation cystoplasty. The sigmoid can be redundant in chronically constipated neurogenic patients, is easy to position on the bladder, and has a large lumen and abundant mesenteric blood supply. One advantage of using cecum, or the ileoceccocystoplasty technique, is the ability to use the ileocecal valve along with terminal ileum to create a continent catheterizable channel (Sarosdy, 1992; Sutton et al, 1998). Disadvantages of using large bowel instead of small bowel for augmentation include more significant metabolic disturbances (Vaida et al, 2003), increased mucus production, and a theoretic heightened risk for malignancy. Before proceeding with augmentation cystoplasty, colonoscopy is recommended in all patients in whom colon will be used. Using the terminal ileum for ileoceccocystoplasty also puts patients at risk for vitamin B₁₂ deficiency. Thus, levels must be monitored over the long term.

When small or large bowel is unavailable or metabolic acidosis is present, stomach is an option for use in bladder augmentation. The advantages of gastrocystoplasty are decreased mucus production and less bacterial colonization. The popularity of gastrocystoplasty has waned with increasing awareness of associated complications. Hematuria-dysuria syndrome occurs in up to 70% of patients with gastrocystoplasty and is characterized by suprapubic pain, dysuria, bladder spasms, and hematuria. However, only 4% of patients with this syndrome will require chronic treatment with histamine-2 blockers or proton pump inhibitors (Leonard et al, 2000). Other complications include peptic ulcers in the bladder, augment perforation, hyperchloremic hyponatremic alkalosis, increased gastrin production, and malignancy (Biers et al, 2012).

Contraindications to Augmentation Cystoplasty

Augmentation cystoplasty is contraindicated in patients who have diseases of the bowel (i.e., inflammatory bowel disease, irradiated bowel, short gut syndrome) or bladder pathologic conditions that would preclude using the bladder (Sajadi and Goldman, 2012). Patients or caregivers also must be willing and able to perform CIC for the long term. A patient with a progressive neurologic disease, such as multiple sclerosis, may not have the ability to perform CIC in the future. Noncompliance with CIC puts the patient at risk for life-threatening spontaneous bladder perforation. Renal disease also may be a relative contraindication to augmentation cystoplasty. Baseline renal insufficiency can worsen with

the absorption and electrolyte changes that result from exposure of bowel to urine. However, if augmentation cystoplasty is indicated for renal impairment, renal function is expected to stabilize or improve. The series by [Ivancić and colleagues \(2010\)](#) of pediatric patients with chronic renal insufficiency undergoing augmentation cystoplasty showed either improvement or no change in renal function after surgery.

KEY POINTS: ADDITIONAL THERAPIES FOR STORAGE FAILURE AT THE BLADDER LEVEL—AUGMENTATION CYSTOPLASTY

- The goals of therapy for storage failure are urine accommodation in the bladder at low pressures, improved bladder capacity, decreased incontinence related to DO, and preservation of renal function.
- Augmentation cystoplasty is performed in patients who have failed or who are not candidates for more conservative forms of intervention such as anticholinergics, intravesical instillation of medication, intravesical injection of botulinum toxin, and/or CIC.
- Studies show that augmentation cystoplasty reduces the mean maximum detrusor pressure by 65% to 82% and this reduction is sustained over time.
- Although augmentation cystoplasty is a more invasive treatment, it can increase bladder capacity up to 500 mL and improve patients' quality of life substantially with a high satisfaction rate of over 90%.
- Although hyperchloremic metabolic acidosis can occur after using ileum or colon for bladder substitution, the use of ileum for augmentation seems to result in less significant metabolic disturbances.
- Disadvantages of using large bowel instead of small bowel for augmentation include more significant metabolic disturbances, increased mucus production, and a theoretic heightened risk for malignancy.
- For patients undergoing augmentation cystoplasty with colon, a colonoscopy is recommended in all patients preoperatively. Vitamin B₁₂ levels must also be monitored long term.
- Augmentation cystoplasty is contraindicated in patients who have diseases of the bowel (i.e., inflammatory bowel disease, irradiated bowel, short gut syndrome) or bladder pathologic conditions that would preclude using the bladder.

ADDITIONAL THERAPIES FOR STORAGE FAILURE AT THE BLADDER OUTLET

The inability to store urine can be the result of an incompetent bladder outlet arising from hypermobility of the urethrovesical junction, intrinsic sphincteric deficiency, denervation of the sphincteric musculature, or frank urethral loss because of various causes such as urethral erosion in women after prolonged urethral catheter use, radiation, or refractory urethral fistulae. When severe, this urinary incontinence can significantly affect patient's quality of life, leading to embarrassment and avoidance of social activities. The following sections will discuss alternative treatments for urine storage failure at the bladder outlet that have not been covered in depth in other chapters in this text.

Myoplasty for Storage Failure

Severe urinary incontinence from sphincteric damage after surgery or a congenital neurologic disorder is often managed by a sling procedure, artificial urinary sphincter, or urethral closure. The use of an autologous muscle transfer to form a neosphincter around the urethra has been reported in a few small clinical series. Case

reports describe transposition of the gracilis muscle to the urethra or bladder neck by transection of the distal muscle at the tibial tuberosity with preservation of the proximal neurovascular pedicle. The gracilis muscle is wrapped around either the bladder neck or the bulbous urethra and attached to itself (bulbous urethra) or the back of the os pubis (bladder neck) ensuring circumferential pressure on the urethra with electrical stimulation of the myoplasty. [Janknegt and colleagues \(1992\)](#) performed the first gracilis myoplasty in three patients with severe incontinence from trauma, in those with congenital epispadias, and after transurethral resection of the prostate. Working from both the lower abdomen and the perineum, the gracilis muscle was mobilized and transferred around the bladder neck with anchoring sutures placed in the pubic periosteum. Six weeks later a small incision in the thigh, near the proximal gracilis muscle, allowed placement of intramuscular electrode leads for electrical stimulation of the myoplasty. With follow-up of 5 to 9 months, two of three men had significantly improved continence with the stimulated myoplasty and were able to void to completion. In 1997, another small case report of three men with postprostatectomy incontinence underwent gracilis myoplasty with placement around the bulbous urethra ([Chancellor et al, 1997a](#)). Six weeks later the electrodes were implanted, with 75% subjective improvement in continence 6 months after electrical stimulation of the urethral neosphincter. There were no significant complications reported in either study. Eleven men with severe stress urinary incontinence were treated in a multi-institutional study with "dynamic" gracilis myoplasty followed by electrode implantation, with only one patient not showing some improvement in continence ([Chancellor et al, 1997b](#)). The authors emphasized the importance of muscle training through continuous electrical stimulation whereby muscle type conversion from fast-twitch to slow-twitch fibers is accomplished, providing resting tone for urethral closure. Despite these early reports showing promise for gracilis myoplasty for the treatment of sphincteric deficiency causing storage failure, no further studies have been undertaken to advance this procedure.

Urethral Compression Devices for Male Urinary Incontinence

The concept of urethral compression to manage male sphincteric incontinence was first reported in [Heister's 1750](#) surgical textbook, *Institutiones Chirurgicae*. He described the Heister penile clamp, a metal clamp worn across the base of the penis to control male urinary leakage ([Heister, 1750](#)). This closely resembles the Cunningham clamp, which is a well-known external fixed urethral compression device used today ([Fig. 87-1](#)). In 1961, [Berry's \(1961\)](#) implantable prosthetic device marked a new era of internal fixed urethral compression devices. This acrylic prosthesis, available in various configurations and sizes, was implanted via a perineal



Figure 87-1. The Cunningham clamp. (Bard Medical Division, Covington, GA.)

approach immobilizing the urethra up against the urogenital diaphragm with four steel wires. Berry's prosthetic did not gain wide usage because of issues with pain, displacement, and infection (Madjar et al, 2001). Kaufman, another pioneer in the field of post-prostatectomy incontinence treatment, described in several articles an evolution of the Kaufman internal fixed urethral compression procedure. The Kaufman I and II procedures relied on compression of the bulbar urethra using cavernous crural crossover or approximation, respectively (Kaufman, 1970, 1972). The Kaufman III procedure involved implanting a silicone gel prosthesis via a perineal approach to compress the bulbar urethra (Kaufman, 1973). Although initial results were promising, these procedures were eventually replaced with the evolution of the bulbourethral male sling and Scott's development of the implantable artificial urinary sphincter device (Scott et al, 1974), the AMS 721 (American Medical Systems, Minnetonka, MN). A thorough discussion of these contemporary surgical treatments for male sphincteric incontinence can be found in Chapter 91.

In certain male patients with urinary incontinence, external fixed urethral compression devices still play a role in management. In most cases, continence is achieved by wearing an external device around the penis that compresses the urethra between foam pads. The amount of compression can be adjusted by the patient to achieve dryness and minimize pressure-related injuries to the penis. Penile clamps are indicated for patients with sphincteric incontinence, often resulting from prostate surgery. These patients may have medical conditions that preclude them from other surgical options, or they are in the early postprostatectomy recovery period when surgical intervention is deferred. Patients should have normal bladder capacity and compliance. Additionally, external penile compression devices should be avoided in patients with impaired sensation or cognition, because these patients are more prone to pressure-related injuries to the penis. Obstruction to penile blood flow can be minimized by removing the device every 3 to 4 hours and by avoiding usage while sleeping or while having an erection. Moore and colleagues (2004) reported efficacy, comfort, and patient satisfaction with three penile compression devices: the Cunningham clamp (Bard Urological, Covington, GA), the C3 (Timms Medical Technologies, White Bear Lake, MN), and the U-Tex (Laborie Medical Technologies, Williston, VT). The study population included 12 men with postprostatectomy incontinence requiring continuous pad protection. Over 4 consecutive days, patients were randomly assigned to use either one of the three devices or pads alone as a control group. Each group wore the device or pads continuously for 4 hours (maximum time recommended for continuous usage), and pad weights were obtained before and after the study period to quantify leakage. Additionally, patients were asked to complete a questionnaire at the conclusion of the study. Urine leakage was significantly reduced by all three devices evaluated; however, the Cunningham clamp was the most effective of the three devices tested, reducing urine leakage by nearly 85%. The Cunningham clamp was also noted to reduce cavernosal blood flow significantly more than the other devices. Overall, patients rated the Cunningham clamp the most acceptable and preferable of the devices evaluated.

Female Urethral Occlusive Devices

Several female urethral meatal occlusive devices have been developed to address female stress urinary incontinence, including the CapSure (Bard Urological), FemAssist (Insight Medical, Boston, MA), and Impress (UroMed, Needham, MA) devices. These products either form a seal over the urethral meatus or create a negative pressure that increases urethral resistance, permitting urethral wall coaptation (Bellin et al, 1998). Unfortunately, due to the anatomy of the female urethra and the location of the meatus, these devices were difficult to apply and keep secured in place. Local tissue irritation and pain were also factors. Ultimately, these products did not gain widespread popularity and were pulled from the market. The future remains unclear for innovations in this type of occlusive urethral application for women.

Female urethral inserts or plugs are available and work by passively occluding the urethral outlet. They must be removed each time a patient voids and require a patient to feel comfortable with inserting such a device into the urethra itself. The first urethral insert to be approved for marketing by the U.S. Food and Drug Administration, the Reliance (UroMed) has been withdrawn from the market. The second-generation FemSoft stent (Rochester Medical Corporation, Stewartville, MN) (see Fig. 80-14 in Chapter 80) was FDA approved in 1997 and is currently available. Very little is published in the literature regarding the results of urethral inserts. However, one study by Sirls and colleagues (2002) reported the results of a 5-year, multicenter trial of 150 women with a 15-month follow-up using the FemSoft insert (2002). Pad weight testing and voiding diaries demonstrated efficacy of the insert, and patients reported overall satisfaction. Adverse events were common, but minor, and included symptomatic urinary tract infections (UTIs) in 31.3%, mild trauma with insertion in 6.7%, hematuria in 3.3%, and migration in 1.3% of women. Although widely applicable to women with stress urinary incontinence, it seems that there is a potential barrier in finding patients who are willing to instrument the urethra. Certainly, women who experience leakage only during certain predictable activities such as sports or who are not ready or interested in surgical intervention may be more willing to use a urethral insert to stay dry.

Intravaginal Incontinence Devices

The use of a mechanical device to treat female urinary incontinence dates back to Egyptian times (Edwards, 1970). Although today there are safe and effective surgical treatments for stress urinary incontinence, some women may still choose a nonsurgical treatment option for medical or personal reasons. There are numerous intravaginal devices designed to support the anterior vaginal wall and urethrovesical junction, thus improving urethral closure and resistance to increases in intra-abdominal pressure (Bhatia and Bergman, 1985; Komesu et al, 2008). These devices include tampons, contraceptive diaphragms, pessaries, and pessary-like devices. In the literature, there is a paucity of robust clinical data describing the efficacy of pessaries for treatment of stress urinary incontinence. Most of the studies available are limited by small numbers and short-term follow-up (Nygaard, 1995; Donnelly et al, 2004; Farrell et al, 2007).

More recently, Richter and associates (2010) published the results of the Ambulatory Treatments for Leakage Associated with Stress Incontinence (ATLAS) trial, a multicenter, randomized control trial of 446 women with 12 months of follow-up. The objective of the study was to compare the efficacy of a continence pessary to evidence-based behavioral therapy or combination therapy in treating women with stress incontinence. Outcomes were based on responses to the Patient Global Impression of Improvement and the stress incontinence subscale of the Pelvic Floor Distress Inventory. Patients had greater satisfaction (75% vs. 63%, $P = .02$) and less bothersome incontinence symptoms (49% vs. 33%, $P = .006$) in the behavioral therapy group compared to the pessary group at 3 months. Combination therapy was better than pessary alone, but not behavioral therapy alone. However, these group differences were not sustained at the 12-month mark, although all treatment groups continued to report greater than 50% satisfaction rates.

In general, the advantages of a continence pessary or comparable intravaginal device are the applicability to a broad spectrum of patients with stress or mixed urinary incontinence, the ease of device fitting in the office without cumbersome or invasive testing, the flexibility of wearing the device for predictable activities that bring on incontinence, the mild side-effect profile, and the ability of the device to manage bothersome prolapse symptoms in addition to incontinence. The disadvantages of a continence pessary can be difficulty with insertion and removal of the device for periodic cleaning, vaginal discharge, odor and/or irritation, dislodgement, and the inability of the device to address intrinsic sphincter deficiency or appropriately transmit pressure to a fibrotic urethra.

Bladder Outlet Closure: Functional and Complete

In certain instances, when other surgical interventions have failed, urethral or bladder neck closure is necessary to treat refractory incontinence. These neurogenic and non-neurogenic patients are those with urethral erosion, severe stress incontinence, bladder neck incompetence, or difficult urethral fistulae. One familiar clinical scenario is that of a neurogenic female patient managed with a long-term indwelling urethral catheter. Over time, the catheter balloon causes pressure necrosis and urethral/bladder neck destruction. The patient is left with a very patulous, incompetent outlet and suffers with severe urinary incontinence. [Chancellor and associates \(1994c\)](#) reported their results with **functional bladder neck closure using an obstructing autologous pubovaginal sling** in 14 female patients with neurogenic, end-stage bladders and a destroyed bladder outlet from chronic indwelling Foley use. All women had an intact bladder neck and at least 1 cm of viable proximal urethra. With a mean follow-up of 24 months, all patients had success with minimal incontinence and a low rate of complications. **This type of functional bladder neck closure avoids complete closure of the urinary system, providing a “pop-off” valve for leakage at higher pressures and allows access for possible future instrumentation.** In this type of scenario, in which the sling is meant to obstruct the bladder outlet, autologous or cadaveric slings are superior to mesh slings, which would be much more likely to erode into the urethra. However, several studies have described using mesh slings in a “spiral” fashion to wrap the urethra circumferentially for refractory patients with stress urinary incontinence ([Rutman et al, 2006](#); [Mourtzinou et al, 2008](#); [Rodriguez et al, 2010](#)). This tech-

nique, first described by [Rutman and associates \(2006\)](#), involves a transvaginal urethrolisis to gain access to the urethra circumferentially. A polypropylene mesh sling with sutures attached to each of the ends is completely wrapped around the urethra, crossing at the ventral urethra, and then the ends are passed retropubically and tied above the fascia. Success of 72% to 87%, or overall improvement in symptoms, was reported in these small series with few complications noted ([Rutman et al, 2006](#); [Mourtzinou et al, 2008](#); [Rodriguez et al, 2010](#)). Further discussion regarding sling procedures can be found in Chapter 84.

When preservation of a functional bladder outlet is not a viable option, transvaginal, transabdominal, or combined bladder neck closure along with LUT reconstruction to the abdominal wall is indicated. **It should be noted that closure of the bladder neck is more challenging than a simple cystorrhaphy. The bladder neck is hyperactive in neurogenic patients, and stress is placed on the bladder neck closure with every voiding reflex.** It is imperative to have a multilayer, watertight closure and use postoperative drains to avoid fistula formation ([Fig. 87-2](#)). Additionally, an adequate time of continuous bladder drainage and use of anticholinergics will limit the stress on the bladder neck suture line.

[Levy and colleagues \(1994\)](#) reported a 40% success rate using a transvaginal bladder neck closure. They subsequently modified the approach, using a combined transvaginal-transabdominal approach, and reported a 100% success rate at a mean 16-month follow-up for the subsequent 10 patients. [Shpall and Ginsberg \(2004\)](#) reported on 39 patients who underwent a combined transabdominal bladder neck closure and various continent and incontinent diversions. At a mean of 37 months, 6 patients (15%) developed fistulae; however,

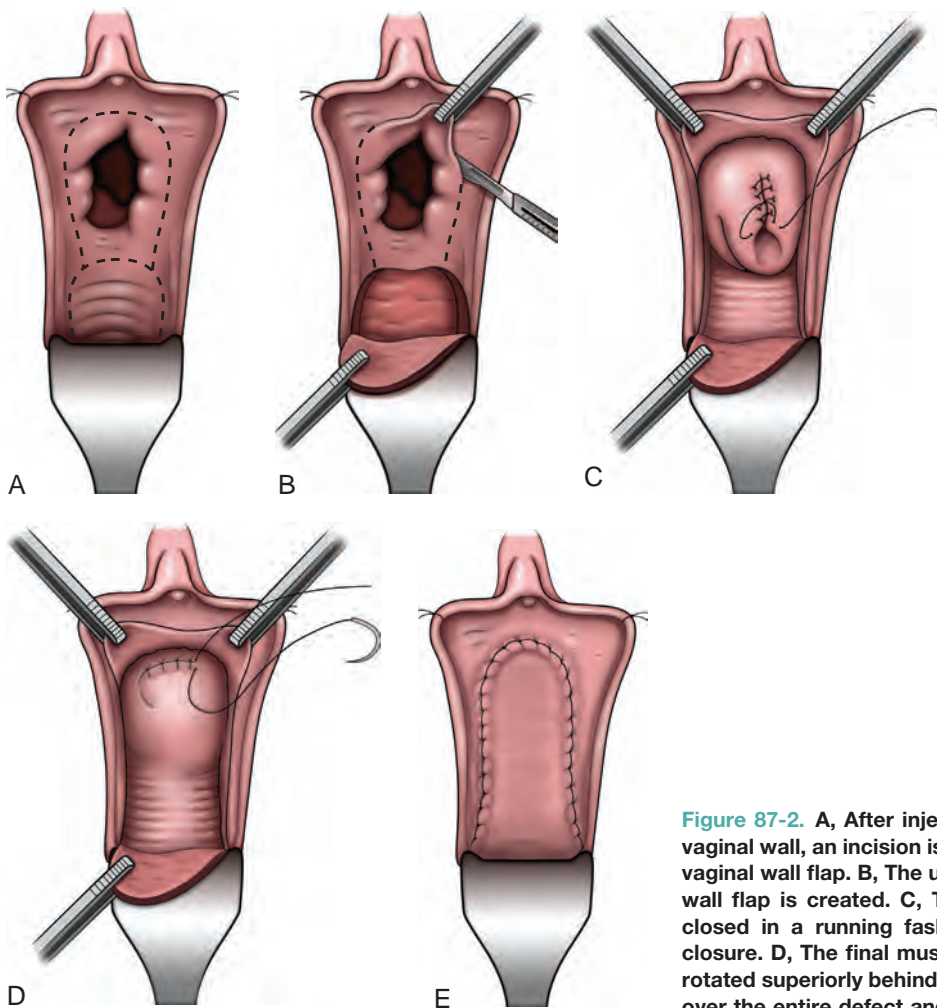


Figure 87-2. A, After injection of normal saline solution into the anterior vaginal wall, an incision is made around the urethral opening to create the vaginal wall flap. B, The urethral meatus is dissected free, and the vaginal wall flap is created. C, The bladder neck wall musculature is vertically closed in a running fashion after the mucosal layer has a watertight closure. D, The final muscular layer is closed in a horizontal fashion and rotated superiorly behind the pubis. E, The vaginal epithelium is advanced over the entire defect and closed with a running suture.

4 patients underwent successful repair, for an overall 95% cure rate. Additionally, O'Connor and colleagues (2005) reported on 35 patients with a mean 79-month follow-up who underwent a transabdominal bladder neck closure for refractory incontinence. They were initially successful in 28 (83%) patients, with an overall 94% cure rate after one revision. Most recently, Kavanagh and associates (2012) reported with a median follow-up of 69 months on 28 pediatric or adolescent patients who underwent concomitant transabdominal bladder neck closure with enterocystoplasty and Mitrofanoff diversion. Bladder neck closure was successful in 96.4% of patients with only one requiring repair of a postoperative vesicovaginal fistula. In addition, there was no evidence of progressive or new hydronephrosis in their cohort. **Ultimately, closure of the bladder outlet with simultaneous LUT reconstruction is often required and can be highly successful in certain refractory patients who have failed other surgical treatments for their destroyed bladder outlet.** Bladder neck closure is definitive, and patients need to understand the importance of adhering to bladder drainage, such as CIC via their catheterizable channel, to avoid the complication of spontaneous bladder perforation. Although rare, concerns also arise over the potential difficulty in accessing the bladder acutely because of an emergency situation or possible stomal stenosis; reported rates of stenosis are 6% to 19.5% (Welk et al, 2008; Leslie et al, 2011; Ardelt et al, 2012). One group discusses equipping all their patients with MedicAlert bracelets and instructing them on how to decompress their bladder if need be via percutaneous needle aspiration (Kavanagh et al, 2012).

KEY POINTS: ADDITIONAL THERAPIES FOR STORAGE FAILURE AT THE BLADDER OUTLET

- The use of a stimulated autologous muscle transfer to form a neosphincter around the urethra, a gracilis myoplasty, has been reported in a few small clinical series. Despite early reports showing promise for the treatment of sphincteric deficiency causing storage failure, no further studies have been undertaken to advance this procedure.
- Penile clamps are indicated for patients with sphincteric incontinence, often resulting from prostate surgery. These patients may have medical conditions that preclude them from other surgical options, or they are in the early post-prostatectomy recovery period when surgical intervention is often deferred. Normal bladder capacity and compliance are relative requirements, and use of these devices should be avoided in patients with impaired sensation or cognition, because these patients are more prone to pressure-related injuries to the penis.
- Female occlusive urethral devices have been developed, but because of the female urethral anatomy may be difficult to apply, insert, or maintain. The ideal occlusive urethral device for women does not exist.
- Numerous intravaginal devices exist that support the anterior vaginal wall and urethrovaginal junction, thus treating stress urinary incontinence by improving urethral closure and resistance to increases in intra-abdominal pressure.
- In certain instances, bladder outlet closure is necessary to treat refractory urinary incontinence. Functional urethral closure with an autologous pubovaginal sling avoids complete closure of the urinary system providing a pop-off valve for leakage at higher pressures and allows access for future transurethral instrumentation.
- Closure of the bladder neck is more challenging than a simple cystorrhaphy. The bladder neck is hyperactive in neurogenic patients and stress is placed on the bladder neck closure with every voiding reflex leading to the most common complication, fistula formation.

ADDITIONAL THERAPIES FOR EMPTYING

Continent Catheterizable Channels

Some neurogenic patients require CIC to empty but have difficulty accessing the native urethra. This can be the case in patients with limited upper extremity dexterity or in female patients who are wheelchair-bound and find it troublesome to position themselves for CIC. Often, these patients depend on caregivers to assist them with CIC, have impaired self-esteem and body image, and ultimately desire more independence. Walsh and colleagues (2004) studied quadriplegic female patients who underwent surgery for creation of continent catheterizable channels. The authors show that these patients had significant improvements in quality of life measures and had increased efficiency in catheterizing (decrease in time to catheterize from 27 (range 10 to 40) to 7.8 (range 1 to 15) minutes). Another study by Zommick and associates (2003) reviewed outcomes of continent LUT reconstruction in 21 patients with cervical-level SCIs and varying degrees of upper extremity dexterity. These patients, who all underwent creation of a continent urinary stoma, reported improvements in quality of life because of eradication of urinary drainage bags, increased continence, more freedom, and improved body image. In addition, a majority (95%) were able to maintain CIC long-term by themselves or with the help of a caregiver.

Urethral loss also can necessitate creation of a continent catheterizable channel to maintain bladder access and continence. In addition to neurogenic patients, patients with non-neurogenic benign disease processes such as recalcitrant bladder neck contracture, urethral loss from stricture or radiation damage, and refractory urethral fistulae are candidates for continent LUT reconstruction. Finally, neurogenic patients undergoing augmentation cystoplasty who also have severe incontinence from various causes, including urethral erosion, severe stress incontinence, or bladder neck incompetence, will need concomitant bladder outlet surgery at the time of augmentation cystoplasty and formation of a continent catheterizable channel.

Various techniques, many using the flap-valve mechanism for continence, have been described: the Mitrofanoff appendicovesicostomy (Mitrofanoff, 1980); a transverse ileal tube (Yang-Monti) (Yang, 1993; Monti et al, 1997); tapered ileum implanted into a serous-lined extramural tunnel (Abol-Enein and Ghoneim, 1999); and the ileocecostoplasty, which uses the ileocecal valve to provide continence (Sarosdy, 1992; Sutton et al, 1998) (Fig. 87-3). These channels are not free of complications, and long-term issues with catheterization, incontinence, and stomal stenosis can occur. A large retrospective study by Leslie and associates (2011) analyzed the long-term outcomes of 169 pediatric patients who had either undergone a Mitrofanoff appendicovesicostomy or a transverse ileal, or Monti, tube. The authors report a 39% revision rate (8% stricture, 4% prolapse, 10% incontinence, and 17% stomal stenosis at skin level). Despite revisions, 96% of channels were still functional at last follow-up. A comprehensive review of the literature on continent catheterizable channel techniques using the flap-valve mechanism shows comparable mean complication rates of 13.3% incontinence and 19.5% stomal stenosis (Ardelt et al, 2012). The choice of continent channel technique is often influenced by the patient's anatomy and the surgeon's preference.

CATHETERIZATION

Catheterization, in its many forms, is an effective method of bladder emptying and is a useful adjunct when efforts to increase intravesical pressure and/or decrease outlet resistance have been unsuccessful. In addition, for those patients who have filling/storage failure caused by bladder overactivity and/or sphincteric incontinence, catheterization also may be used if the dysfunction can be converted solely or primarily to one of emptying by non-surgical or surgical means (Wein and Barrett, 1988). The common goals, irrespective of the mode of catheterization, are to provide

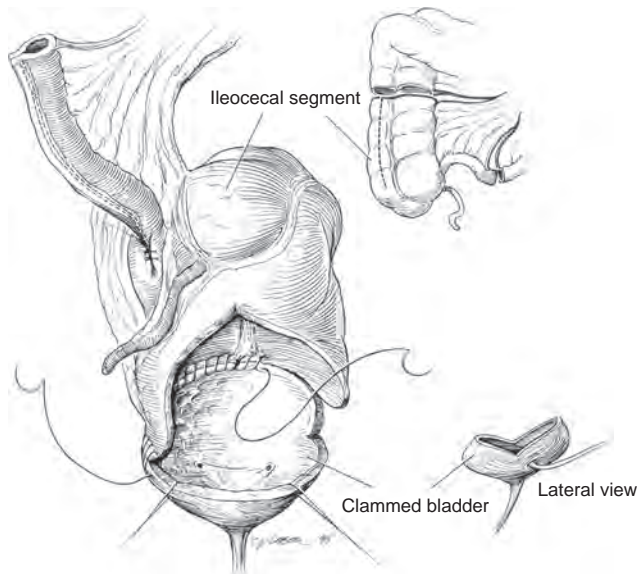


Figure 87-3. Diagram of the continent ileocecal augmentation cystoplasty with the bowel segment used (right cecum and distal ileum) in the upper right corner and a view of the bivalved bladder in the lower right corner. (From Sutton MA, Hinson JL, Nickell KG, et al. Continent ileocecal augmentation cystoplasty. *Spinal Cord* 1998;36:246–51.)

KEY POINTS: ADDITIONAL THERAPIES FOR EMPTYING—CONTINENT CATHETERIZABLE CHANNELS

- Indications for creation of a continent catheterizable channel include difficulty with catheterizing per urethra (i.e., diminished upper extremity dexterity, inability to easily access the urethra), urethral loss from scarring, radiation, or fistula formation; and urethral incompetence and severe leakage in patients requiring bladder outlet closure.
- These continent catheterizable channels are not free of complications and long-term issues with catheterization, incontinence, and stomal stenosis can occur.

low-pressure storage, preserve continence, avoid renal deterioration, minimize complications, and maintain quality of life.

Indwelling urethral catheters are generally used for short-term bladder drainage, and careful use of a small-bore catheter for a short time is unlikely to adversely affect the ultimate outcome, especially if used in the initial bladder management in SCI (Lloyd et al, 1986). Long-term bladder drainage may be obtained by intermittent catheterizations or by an indwelling suprapubic or urethral catheter. Historically, the most appropriate form of bladder drainage in patients requiring prolonged bladder management has been debated. Most studies evaluating the different forms of long-term bladder management have been retrospective and in patients with SCI, because they represent the majority of patients requiring long-term catheterization. The main area of controversy concerns whether long-term indwelling catheterization in neurologically impaired patients is associated with an inferior outcome compared to CIC, specifically regarding urinary tract complications or quality of life.

Although CIC is currently the preferred management for patients requiring prolonged bladder drainage, it is a recent innovation. Intermittent catheterization was first introduced as a sterile procedure in 1949 by Guttman and, at the time, challenged the beliefs of most urologists (Guttman, 1949; Guttman and Frankel, 1966).

It was not until Lapidès and colleagues (1972) introduced the concept of clean intermittent catheterization that widespread usage became more common. As the popularity of CIC grew, long-term indwelling catheterization was condemned, based on both infectious risks and a perceived increased risk for other urologic complications. Jacobs and Kaufman (1978) reported that there were more renal and other urologic complications with long-term (>10 years) catheterization use than with short-term use. Hackler (1982) also reported accelerated renal deterioration in patients with SCI managed with long-term suprapubic catheterization. McGuire and Savastano (1984) reported a poorer outcome in women with an indwelling urethral catheter than in those on CIC after 2 to 12 years. Of 13 in the catheter group, 54% had adverse changes on intravenous pyelography, as opposed to 0% in the CIC group. Other urologic complications were also more frequent and severe in the catheter group.

Conversely, more recent investigations have suggested the complications from chronic indwelling catheters may be lower than previously thought. Sekar and coworkers (1997) reported on the effect of different bladder management methods in 1114 patients with SCI using total and individual kidney–effective renal plasma flow as the primary outcome measure. Follow-up was relatively long with 51.3% followed for 0 to 3 years, 40% for 5 years, and 20% for at least 10 years. Unfortunately, many issues such as unclear methods of urinary management at discharge, incomplete data on approximately 200 patients, and the fact that most men who were discharged using CIC later changed to condom catheter drainage, weaken the authors' conclusions that there was very little change in renal function over time in patients using different bladder management methods. Dewire and associates (1992) reviewed the course of 32 quadriplegic patients managed with, and 25 without, an indwelling catheter. The groups were roughly comparable, and follow-up was for 10 years or longer. The incidences of upper and LUT complications and renal deterioration were not significantly different. Chao and coworkers (1993) did a similar review on 32 patients with SCI with an indwelling urethral (14 patients) or suprapubic catheter (18 patients) versus 41 patients without. Follow-up was 20 years or longer. Although the catheterized group had a higher prevalence of upper tract scarring and caliectasis, no significant differences were found in other indices of renal function or in the prevalence of other urologic complications. Jackson and DeVivo (1992) reported on the results of indwelling catheterization in 108 women (with SCI) followed for 2 to 5 years (56 women), 6 to 9 years (31 women), and 10 or more years (21 women) after injury. Compared with the male population, the majority of which were being managed by condom drainage, there was no difference in upper or lower tract complications. MacDiarmid and colleagues (1995) reported on suprapubic catheterization in 44 patients with SCI, with follow-up ranging from 12 to 150 months (mean 58 months). They reported that no patient had renal deterioration or vesicoureteral reflux and that the incidences of incontinence, infection, and calculi were acceptable. Of the patients, 11% had leakage, 100% had bacteriuria, 41% developed bladder calculi, 7% developed renal calculi, 36% developed episodes of catheter blockage, and only 5% had gross hematuria requiring hospitalization and bladder irrigation.

Upper tract and infectious complications often occur regardless of whether intermittent or indwelling catheterization is used. Although bacteriuria is common in all forms of bladder catheterization, symptomatic infection is not. The presence of asymptomatic bacteriuria does not usually require treatment and should be distinguished from an invasive, symptomatic UTI. Treatment of asymptomatic bacteriuria has not proved beneficial, and the use of continuous prophylactic antibiotics is rarely indicated (Gribble and Puterman, 1993). Nevertheless, infectious complications are the most common complications associated with prolonged catheterization, and procedures such as frequent catheter changes should be considered to reduce these complications (Weld and Dmochowski, 2000; Wyndaele, 2002). Much interest has recently been generated with catheter-associated infections in hospitalized patients. Under new rules by the Centers for Medicare and Medicaid

Services, hospitals will not be compensated for catheter-associated UTIs, causing many hospitals to intensify their efforts in implementing preventive measures (Saint et al, 2009). For more information regarding bacteriuria and catheter-associated UTI see Chapter 12.

More recent studies have shown the superiority of CIC over long-term indwelling catheter drainage. Weld and Dmochowski (2000) reported a retrospective review of 316 patients with SCI with a mean follow-up of 18.3 years. Bladder management methods included chronic urethral catheterization in 114 patients, CIC in 92, spontaneous voiding in 74, and suprapubic catheterization in 36. Complications were recorded in terms of infectious complications (epididymitis and pyelonephritis), renal and bladder calculi, urethral complications (stricture and periurethral abscess), and radiographic abnormalities (vesicoureteral reflux and abnormal urographic findings). Overall, there were 398 complications recorded, of which 236 developed in 61 patients (53.5%) on chronic urethral catheterization, 48 in 16 patients (44.4%) on suprapubic catheterization, 57 in 24 patients (32.4%) who voided spontaneously, and 57 in 25 patients (27.2%) on CIC. Separate bar graphs for each type of complication seem to confirm the overall superiority of CIC as the least problematic long-term form of bladder management (Fig. 87-4).

The exact cause of upper tract deterioration in patients with long-term indwelling catheters is unclear because the bladder should be well drained by a catheter; however, it is likely related to chronic "occult" or subclinical DO in the face of sphincteric dyssynergy providing a functional obstruction. Regardless of the cause, it is clinically heralded by the development of poor detrusor compliance demonstrated on urodynamic studies. Weld and colleagues (2000) reported the effects of bladder management (CIC, spontaneous voiding, or chronic indwelling urethral catheterization) on bladder compliance and changes in compliance with time in patients with SCI. Logistical regression analysis of compliance versus bladder management and interval since injury revealed that CIC and spontaneous voiding were more associated with normal compliance than indwelling urethral catheterization. Poor compliance was statistically associated with vesicoureteral reflux, radiographic upper tract abnormalities, clinical pyelonephritis, and upper tract calculi. The authors concluded that CIC protects bladder compliance in patients with SCI and helps prevent poor compliance and upper tract complications with time. Jamil and associates (1999) reported on ambulatory urodynamics in 30 patients with SCI whose bladders were managed with an indwelling urethral catheter. They found that freely draining indwelling catheters did not guarantee consistently low intravesical pressure. Of 30 patients, 11 demonstrated intermittent detrusor contractions causing intravesical pressure increases greater than 40 cm H₂O for up to 4.5 minutes. These patients had used an indwelling catheter for a mean of 14.3 years (range, 4 to 36 years). Renal scarring was observed in 9 patients, and, of these, 6 were in the group with the abnormal bladder contractions, whereas only 5 of 21 patients with normal kidneys had such pressure rises. The clinical correlate emphasized by the authors was their belief that maintenance of a compliant bladder and suppression of high-pressure contractions in chronically catheterized patients may play a role in the prevention of renal deterioration. Kim and associates (1997) demonstrated in a retrospective analysis that anticholinergic medications can reduce the incidence of hydronephrosis, improve bladder compliance, and decrease leak point pressures in patients with chronic catheters. The role of anticholinergics with various forms of prolonged bladder management and in the prevention of upper tract complications has not yet been clarified (Feifer and Corcos, 2008).

There is certainly some controversy about the classic teaching that long-term continuous bladder catheterization in patients with neurogenic bladder dysfunction should be avoided at all costs. There are clearly some situations in which such management is desirable and necessary. Studies that purport to compare methods of management regarding lower and upper tract complications are often flawed and prevent total acceptance of their conclusions. In

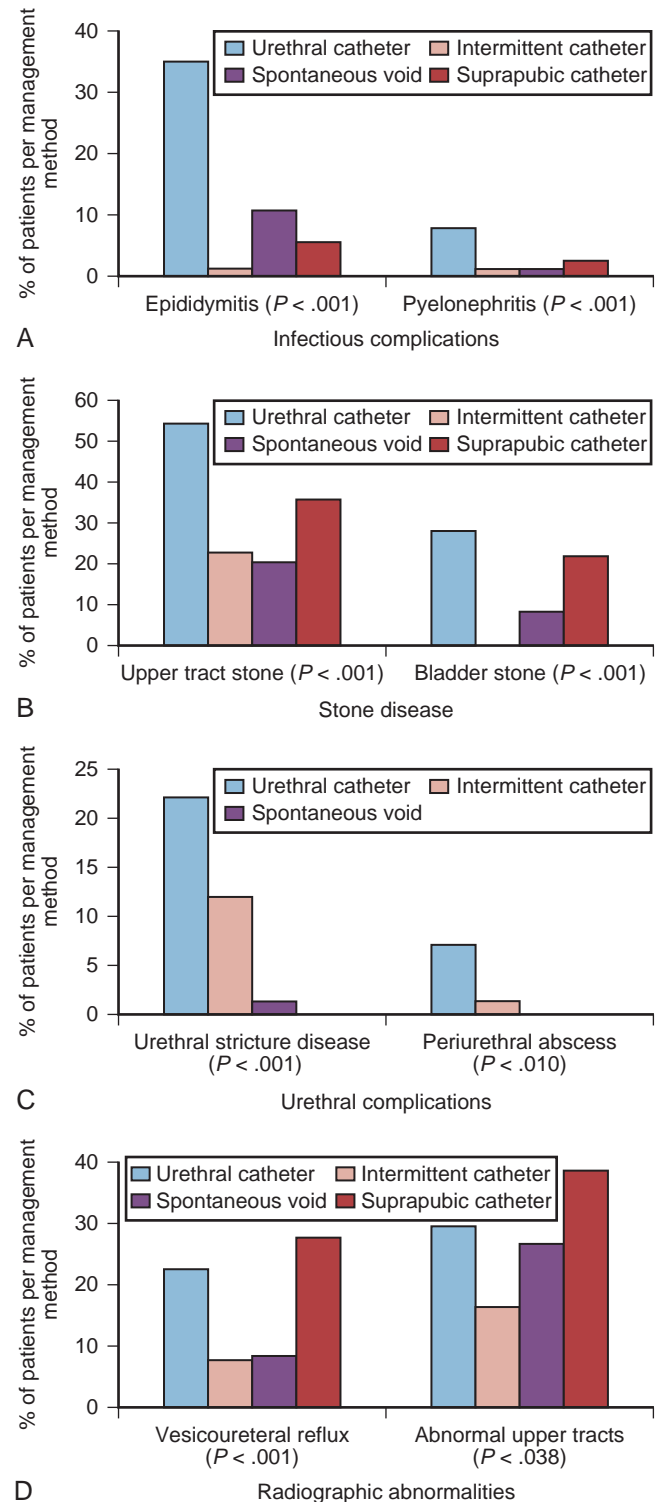


Figure 87-4. Complications related to specific bladder management methods: infectious (A); stone disease (B); urethral (C); radiographic abnormalities (D). (Modified from Weld KJ, Dmochowski RR. Effect of bladder management on urological complications in spinal cord injured patients. *J Urol* 2000;163:768–72.)

the absence of a prospective, randomized study or acceptable retrospective data, patient and family comfort, convenience, and quality of life must be strongly considered in the decision of which method of catheterization will be employed. Regardless of which method is used, periodic upper and lower tract evaluation using renal ultrasonography and cystoscopy should be considered in all patients who require prolonged bladder management. Finally, the use of

urodynamics to monitor the bladder in neurologically impaired individuals is controversial. At a minimum, we believe that urodynamics should be performed after the initial neurologic injury is stable and whenever any significant changes in continence or voiding function occur. The initial urodynamics is useful to direct early bladder management, while subsequent urodynamics evaluations are performed to determine if LUT changes, such as the development of dyssynergia, have occurred.

Clean Intermittent Catheterization

CIC has proved to be the most effective and practical means of attaining a catheter-free state in the majority of patients who are unable to empty their bladders spontaneously. CIC has revolutionized the treatment of difficult cases of neuromuscular dysfunction of the LUT by providing a safe and effective method that preserves the independence of the patient to empty the LUT in cases in which continence has been achieved pharmacologically or surgically, producing total or partial urinary retention. For example, without CIC, the successful outcomes achieved using augmentation cystoplasty or continent urinary diversion would have never been achieved. CIC is based on a theory proposed by Lapides that high intravesical pressure or bladder overdistention is primarily responsible for the development of UTI, not the bacteriuria itself. Theoretically, reduced blood flow to the bladder can lead to increased host susceptibility to bacterial invasion and UTI. Bacteria introduced by CIC would be neutralized by the host, and relatively sterile urine would be maintained as long as bladder distention and high intraluminal pressures were avoided. The long-term efficacy and safety of such a program has been demonstrated by Lapides and others (Weld and Dmochowski, 2000).

Whereas indwelling catheter drainage requires little input from the patient, a cooperative, well-motivated patient or family is a requirement for CIC. The patient must have adequate hand control, or a family member must be willing to perform the catheterization. In addition, there must be adequate urethral exposure. Graham (1989) reported on the factors required to successfully develop a catheterization program for patients with functional limitations, which commonly exists in patients with neurogenic bladder dysfunction. It is advantageous to have a dedicated nurse who instructs the patients and families in the catheterization regimen; provides them with understandable written instructions to refresh their memory regarding technique, precautions, and danger signals; and provides continuing support for patients and families who call with questions or problems regarding their regimen. Many patients are initially reluctant to perform any procedure on their own genitalia. Patients need a thorough explanation of the advantages of CIC along with assurances that it is simple and that it will not tie them to their houses or to an absolute time schedule. Additionally, proper selection of equipment for the patient's intelligence and financial level will increase patient acceptance of and compliance with a self-catheterization program. Patients who are reticent initially are continually amazed by the ease with which such a regimen is established. Successful CIC is intimately associated with patient compliance, and therefore patients should be monitored periodically to ensure catheterization is performed properly. Of note, CIC should be used cautiously in patients known to have autonomic dysreflexia.

Intermittent catheterization may be performed by clean, aseptic, or sterile techniques (Hudson and Murahata, 2005). CIC often includes reusing a catheter several times before disposal. It is washed, generally with soap and water, and allowed to air-dry before storage. When reusing catheters, some have advocated boiling or microwaving for sterilization (Douglas et al, 1990). In April 2008, in an attempt to decrease the incidence of UTIs in patients performing intermittent catheterization, Medicare policy regarding intermittent catheterization changed. Any patient requiring intermittent catheterization may obtain up to 200 sterile catheters per month for one-time use. This change in policy has negated the need for reusing catheters in most patients, but it still may be necessary in patients without insurance coverage or other financial limitations. For adult patients, catheterization is

typically performed at a minimum of every 4 to 6 hours to minimize bacterial dwell time. CIC may need to be more frequent if large volumes of fluid are ingested. In most cases, catheterizations should be timed to maintain bladder volumes below the normal 400- to 500-mL capacity to minimize bladder wall pressure. Even smaller volumes may be required if they have poor detrusor compliance. Catheter choice is variable, but a 12- to 16-Fr soft catheter may be used for males and a short (6-inch "female") 12- to 16-Fr catheter for females. Note that rigid catheters have the potential to injure the urethra in insensate males because they may not "make the bend" at the prostate, causing a false passage such that CIC may be quite difficult or impossible. Larger catheters may be required in patients with a prior bowel augmentation or those who require bladder irrigation. In men, hydrophilic coated catheters have been found to reduce the incidence of UTI and hematuria and have higher patient satisfaction rates than conventional plastic catheters (Vapnek et al, 2003; De Ridder et al, 2005). Patients with recurrent UTIs, despite the use of single-use sterile catheters, may obtain sterile catheter kits for sterile intermittent catheterization. Anticholinergic medication should be considered when urine leakage occurs between catheterization intervals or if high storage pressures develop. Wyndaele (2002) reported that trauma from catheterization occurs frequently, but effects are usually not long-standing, and urethral stricture and false passages are more common the longer that CIC is employed.

Continuous Catheterization

Long-term indwelling catheters should be considered when anatomic, functional, or familial limitations prohibit performance of intermittent catheterization. Continuous catheterization also may be indicated in patients with complications from persistent incontinence or autonomic dysreflexia, despite therapy or when a small bladder capacity prohibits effective CIC. Long-term catheterization may be accomplished by either a urethral or suprapubic catheter. The basics of urethral catheterization, including the technique of suprapubic tube (SPT) insertion are covered in Chapter 6.

In males, the benefits of an indwelling SPT over urethral catheterization include a lower incidence of epididymitis and urethral stricture disease (Weld and Dmochowski, 2000) and preserved sexual function (Rutkowski et al, 1995) (see Fig. 87-4). Overall, suprapubic catheters have been associated with high rates of patient satisfaction. Barnes and associates (1993) concluded that long-term suprapubic catheters were well tolerated by patients with neuropathic bladders. Based on the replies of 32 patients who expressed an opinion, 84% were satisfied; however, the follow-up was short (mean 23 months), and in 2 of 12 patients assessable at over 2 years, creatinine levels increased. Other problems occurred, including recurrent catheter blockage in 38%, recurrent symptomatic urinary infections in 23%, and displaced catheters requiring reinsertion in the operating room in 15%. Urethral leakage occurred in 8 of 14 females with a suprapubic catheter alone and in 6 of 16 males. Patients using a suprapubic catheter must be warned that urinary incontinence may commence or worsen in the setting of sphincteric incontinence or reflex DO, because active opening of the sphincteric unit will occur in the absence of dyssynergia. Sheriff and associates (1998) discussed the clinical outcomes in a satisfaction survey of 185 patients with neuropathic bladder dysfunction treated with long-term suprapubic catheterization (follow-up, 3 to 68 months; mean, 24 months). The authors reported an 82% satisfaction rate; however, the main reason for this SPT procedure was failed CIC from poor hand function. In addition, only 103 of the 185 patients filled out the satisfaction questionnaire, and only 8 patients had a suprapubic catheter for longer than 2 years. Complications in this group included 5 patients with a small bowel injury during insertion, 2 with significant hemorrhage, 2 requiring catheter repositioning, 1 requiring reinsertion because of dislodgement, 8 with persistent incontinence, and 18% with recurrent catheter blockage. Bacteriuria existed in 98% of the patients, but recurrent symptomatic infection occurred in only 4%. More recently, Ahluwalia and colleagues (2006) reported a

satisfaction rating of 71% among 219 patients having indwelling suprapubic catheters for greater than 50 months.

A controversial issue, common to all long-term indwelling catheters, is the development of bladder cancer. The long-term risk of carcinoma in the patient with SCI with a chronic catheter has been estimated to be 8% to 10% (Locke et al, 1985; Delnay et al, 1999). Kaufman and colleagues (1977) were among the first to recognize that patients with SCI and chronic indwelling catheters had an increased incidence of bladder cancer, particularly squamous cell carcinoma (SCC). Several others reported similar findings (Chao et al, 1993; Stonehill et al, 1996). Since these reports, the association between chronic indwelling catheterization and the development of bladder carcinoma has been debated. **No associations with intermittent catheterization have been identified.** Chronic inflammation is the most likely causative factor and may be caused by the indwelling catheter itself, bladder calculi, and/or recurrent infections. It is not clear whether earlier treatment of these conditions or better follow-up will lessen the risk for bladder carcinoma. A mechanism for the development of bladder carcinoma secondary to long-term inflammation was described by Wall and colleagues, (2001). According to their report, inducible nitric oxide synthase expressed by inflammatory macrophages in areas of chronic inflammation may lead to the formation of potentially carcinogenic nitrosamines in the bladder. For more on the development of carcinoma and the associations with SCI and chronic catheterization, see Chapter 75.

When SCC is identified in patients with SCI, it is often advanced and commonly fatal; however, routine screening cystoscopy for at-risk patients with SCI is controversial. Although some authors suggest that screening cystoscopy conveys a survival advantage by identifying bladder cancer at an earlier stage (Navon et al, 1997), others have found no advantage for screening (Yang and Clowers 1999; Hamid et al, 2003). Cytologic examination, although commonly performed, is not useful for detecting SCC (Bejany et al, 1987). Additionally, SCC may not always be cystoscopically detectable (Kaufman et al, 1977). For this reason, routine random biopsies have been advocated by some (Stonehill et al, 1996). Despite the lack of data in patients without SCI, most urologists recommend all patients with chronic catheters undergo annual screening, generally starting after 8 years (Stonehill et al, 1996). Gross hematuria has been reported by several investigators as the most common manifesting symptom for patients eventually diagnosed with bladder cancer (Hess et al, 2003). Despite the disparate opinions regarding screening, certainly all would agree that patients with new-onset gross hematuria should be evaluated with upper tract imaging, urinary cytologic studies, cystoscopy, and perhaps random biopsies. Other patients to consider for close surveillance should include patients with known risk factors for the development of carcinoma, such as recurrent UTIs or recurrent bladder stones.

INCREASING INTRAVESICAL PRESSURE OR FACILITATING BLADDER CONTRACTILITY

External Compression (Credé) and Valsalva Maneuver

The Credé maneuver (manual compression of the bladder) is most effective in patients with decreased bladder tone who can generate an intravesical pressure greater than 50 cm H₂O and have decreased bladder outlet resistance (Wein and Barrett, 1988). The technique of voiding by the open-handed Credé method involves placement of the thumbs of each hand over the area of the anterior superior iliac spines and the digits over the suprapubic area, with slight overlap at the fingertips. The slightly overlapped digits are pressed into the lower abdomen and when they are located behind the symphysis are pressed downward to compress the fundus of the bladder. For some patients, this maneuver can be accomplished more efficiently by using a closed fist of one hand or a rolled-up towel. Straining as the Credé maneuver is applied is generally counterproductive because this increases intra-abdominal pressure and causes bulging of the abdominal wall, which then tends to lift the compressing hands off the fundus of the bladder.

KEY POINTS: ADDITIONAL THERAPIES FOR EMPTYING—CATHETERIZATION

- Catheterization is an effective tool in promoting bladder emptying and also may assist patients with filling/storage failure resulting from overactivity and/or sphincteric incontinence, especially if the bladder can be converted solely or primarily into a storage organ using either medical or surgical means.
- Whether long-term indwelling catheterization is inferior to CIC remains a main area of controversy, specifically regarding urinary tract complications and quality of life.
- Asymptomatic bacteriuria is common in catheterized patients and does not require treatment unless the patient becomes symptomatic.
- Periodic surveillance should be considered in patients with chronic catheters, because elevated bladder pressures, poor bladder compliance, and upper tract deterioration may develop despite seemingly adequate bladder drainage by CIC or an indwelling catheter.
- Maintenance of low intravesical pressure and avoidance of bladder overdistention is essential to successful CIC.
- The most common complications associated with catheter use include infectious (epididymitis, periurethral abscess, pyelonephritis), renal and bladder calculi, urethral stricture, and vesicoureteral reflux.
- The exact cause of upper tract deterioration in patients with long-term indwelling catheters is unclear; however, it is likely related to chronic “occult” or subclinical DO in the face of sphincteric dyssynergy providing a functional obstruction.
- Poor compliance is associated with vesicoureteral reflux, radiographic upper tract abnormalities, clinical pyelonephritis, and upper tract calculi.
- In patients with SCI, urodynamics should be performed after the initial neurologic injury is stable and whenever any significant changes in continence or voiding function occur. Periodic upper and lower tract evaluation using renal ultrasonography and cystoscopy should also be considered in all patients who require prolonged bladder management.
- CIC should be used cautiously in patients known to have autonomic dysreflexia.
- Intermittent catheterization may be performed by clean, aseptic, or sterile techniques.
- Any patient requiring intermittent catheterization may obtain up to 200 sterile catheters per month for one-time use.
- In most patients, catheterizations should be timed to maintain bladder volumes below the normal 400- to 500-mL capacity.
- Long-term indwelling catheters should be considered when anatomic, functional, or familial limitations prohibit performance of intermittent catheterization.
- In males, the benefits of an indwelling SPT over urethral catheterization include a lower incidence of epididymitis and urethral stricture disease with preservation of sexual function.
- The long-term risk for carcinoma in the patient with SCI with a chronic catheter has been estimated to be 8% to 10%. This association has not been identified in patients performing intermittent catheterization.
- The development of gross hematuria in patients with a chronic indwelling catheter should prompt further evaluation, including upper tract imaging, urine cytology, cystoscopy, and consideration of bladder biopsy.

If the guarding reflex arc is intact, this also may produce a striated sphincter contraction. The Credé maneuver is much easier in a patient with a lax, lean abdominal wall than in one with a taut or obese one, and it is more readily performed in a child than an adult.

A similar increase in intravesical pressure may be achieved by abdominal straining (Valsalva maneuver). The proper technique involves sitting and letting the abdomen protrude forward on the thighs. During straining in this position, hugging of the knees and legs may be advantageous to prevent any bulging of the abdomen. To increase intravesical pressure in this manner requires voluntary control of the abdominal wall and diaphragmatic muscles.

“Voiding” by the Credé or Valsalva maneuver is generally discouraged, because it is nonphysiologic and is resisted by the same forces that normally resist stress incontinence. Reflex sphincteric opening of the bladder outlet does not occur with external compression maneuvers of any kind, and, in many cases, an increase in outlet resistance may occur reflexively. If adequate emptying does not occur in the properly selected patient, other types of therapy to decrease outlet resistance may be considered; however, these treatments may adversely affect urinary continence.

The best chance for success with this mode of therapy (some would say it should never be used) is in the patient with an areflexic bladder and some degree of outlet denervation. This is most commonly seen in the patient with an autonomic neurogenic bladder (Lapides classification), T11 through L2 SCI in whom the sympathetic nervous supply is damaged, or after outlet resistance is decreased surgically or by botulinum toxin injection. Most of these patients already have stress incontinence, and the Credé or Valsalva maneuver simply helps the patient overcome outlet resistance to empty the bladder at a convenient time. These techniques also may be useful to decompress a neobladder when the outlet resistance is low either by volitional sphincteric relaxation or when surgically induced.

Vesicoureteral reflux is a relative contraindication to external compression or the Valsalva maneuver, especially in patients capable of generating a high intravesical pressure. The most flagrant misuse of this form of management is in the patient with a neurogenic bladder and poor detrusor compliance, because the increased storage pressures can cause upper tract deterioration with minimal filling. External compression or Valsalva maneuvers will only further aggravate this already dangerous situation.

Even when the patient has a flaccid bladder and/or low detrusor leak point pressures, close follow-up and periodic evaluation are necessary to avoid upper tract deterioration. Chang and colleagues (2000) reported the long-term urologic complications and residual volumes of 74 SCI patients with flaccid bladders who routinely performed the Credé maneuver as their primary form of bladder management for more than 20 years. Residual urine volume was greater than 100 mL in 93% of patients, and 50% were greater than 300 mL. The authors also reported that 59.5% developed ureteral dilation, 35.1% developed hydronephrosis, and 16.2% suffered renal deterioration. Males were significantly more likely to develop these complications than females, probably because of increased outlet resistance. Other complications included recurrent UTIs, pyuria, urinary lithiasis, epididymo-orchitis, genital-rectal prolapse, and hemorrhoids (Chang et al, 2000; Wyndaele, 2008).

Promotion or Initiation of Reflex Contractions

In patients with SCI and an intact sacral spinal cord, voiding can be elicited by exploiting existing spinal reflexes. The sacral micturition reflex occurs when tension receptors within the bladder wall are stimulated by bladder filling and activate sensory afferent neurons. Motor efferents from the spinal cord respond by generating a reflexive bladder contraction and, when of adequate magnitude, will result in voiding. Bladder contractions obtained in this manner are often involuntary and sporadic. In some cases, patients with SCI may be able to trigger this reflex voluntarily by manual stimulation of areas within the sacral or lumbar dermatomes. According to the classic reference by Glahn (1974), the most effective method of initiating a reflex contraction is rhythmic

suprapubic manual pressure (seven or eight pushes every 3 seconds). Quick repetitive stimulation in this manner is thought to produce a summation effect on the tension receptors in the bladder wall, resulting in activation of the bladder reflex arc. Ideally, the elicited contraction would be of sufficient magnitude and duration to empty the bladder. Other commonly used maneuvers to induce reflex detrusor contraction include pulling the skin or hair of the pubis, scrotum, or thigh; squeezing the clitoris; or digital rectal stimulation (Wein and Barrett, 1988). Patients able to void in such a way are encouraged to find their own optimal trigger points and position for urination. If induced emptying can be carried out frequently enough to keep bladder volume and pressure below the threshold for activation of the involuntary micturition reflex and below pressures that might cause upper tract deterioration, incontinence can be controlled, similar to timed voiding in normal individuals. Reflex voiding depends on the ability to stimulate detrusor contractions and may be most suitable for patients with SCI or conditions characterized by DO. To void reflexively, patients require manual dexterity and the ability to transfer to a commode, or at least the ability to use and maintain an external collecting device. For this reason, reflex voiding may not be suitable for many female patients. Surgical procedures to reduce outlet resistance should be considered if significant obstruction or sphincter dyssynergia are present. Complications with this voiding technique are most often related to the use of external collection devices or from the development of high-pressure storage resulting in upper tract deterioration. To ensure compliance, periodic surveillance should be performed with consideration of regular urodynamic evaluation.

Some clinicians believe that the micturition reflex can be “trained” by maintaining a copious fluid intake and periodically clamping an indwelling catheter or by CIC at regular intervals. This cyclic pattern of filling and emptying may promote storage, and emptying in a more physiologic manner focuses attention on the urinary tract and ensures an adequate fluid intake. It is true that balanced LUT function can be achieved while using this program (Opitz, 1984; Menon and Tan, 1992), but whether this is a cause-and-effect relationship is unknown and difficult to prove.

One fascinating set of experiments that relates to the concept of establishing or promoting a reflex pathway for micturition is that reported by Xiao and de Groat (1999). They created a reflex pathway from the skin to the central nervous system in cats by intradural microanastomosis of the left L7 ventral root to the S1 ventral root, leaving the L7 dorsal root intact to conduct cutaneous afferent signals. A detrusor contraction, without striated sphincter dyssynergia, could be initiated by scratching the skin or by percutaneous electrical stimulation in the L7 dermatome. The pathway was found to be mediated by cholinergic transmission at both ganglionic and peripheral levels. **The importance of this experimental model is that somatic motor axons were able to innervate parasympathetic bladder ganglion cells and therefore transfer somatic reflex activity to the LUT.** Xiao and colleagues (2003) reported on the first human clinical trial, in which 15 males with neurogenic overactivity and detrusor-external sphincter dyssynergia (DESD) secondary to complete suprasacral SCI underwent a ventral root microanastomosis between the L5 and the S2 and/or S3 ventral root. With a mean follow-up of 3 years, recovery in bladder storage and emptying function was reported in 10 (67%) patients. Average residual urine decreased from 332 mL to 31 mL, with resolution of UTIs and overflow incontinence. Postoperative urodynamics demonstrated the resolution of DO and DESD to near-normal storage pressures, with synergic voiding and without DESD. Improvement in bowel function also was noted. Xiao and colleagues (2005) subsequently reported on 20 children with neurogenic bladder from spina bifida, among whom 17 of 20 (71.4%) demonstrated urodynamic improvements after surgery. Partial loss of L4 or L5 motor function, ranging from slight muscular weakness to visible foot drop, was reported in 5 of 20 patients. Xiao (2006) recently reviewed the initial human trials to date, and although encouraging results have been reported, experiences from other centers are needed to confirm these findings.

Stimulated Myoplasty for Bladder Emptying

Few treatment options are available for patients with detrusor underactivity except for self-intermittent catheterization. Restoration of bladder contractility remains an elusive goal for most patients with this condition. The first animal feasibility studies to augment bladder contractility used a unilateral rectus abdominis muscle wrap over the bladder to facilitate bladder emptying (Chancellor et al, 1994a). The rectus muscle, with intact neurovascular pedicle, was dissected free at one end and wrapped over the bladder, where it was reattached to itself and created a spherical configuration housing the bladder. Evaluation of the transposed muscle showed no damage to the blood supply or innervation of the rectus muscle, and the underlying bladder retained its volume despite neurogenically induced underactivity. This model was touted as the precursor for a clinical trial wherein the patient would learn to contract his rectus muscle voluntarily and create sufficient extrinsic pressure to void. The first case report using the rectus myoplasty involved a 33-year-old man with an L4 SCI from a gunshot wound 10 years before enterocystoplasty covered by the left rectus muscle transposed over the bladder (Chancellor et al, 1994b). One month later the patient could void by contracting his rectus muscle generating 50 cm H₂O detrusor pressure as recorded by video-urodynamic testing. This ability persisted for 11 months until the case was reported in the literature. Initial experience with the rectus abdominis was limited to this single case despite the relative ease of the technique when compared to the complexity of the latissimus dorsi free flap requiring neurovascular reanastomosis. Latissimus dorsi cardiomyoplasty was being used for heart failure in selective cases during this period (Blanc et al, 1993), and the concept for a similar application for detrusor underactivity was embraced by groups in San Francisco and Germany. Von Heyden and associates (1998) experimented with dogs and pigs using the rectus muscle with its segmental intercostal nerve innervation and they abandoned the muscle because of the lack of suitable motor nerves for muscular control of the flap. Free latissimus dorsi muscle flaps were harvested and transferred over the bladder in dogs; revascularization and electrical stimulation of the thoracodorsal nerve successfully induced pressures sufficient for partial evacuation of the bladder. The advantage of a singular nerve supply with ample geometry provided by the latissimus dorsi free flap led to the first clinical application in 1998 by Stenzl and colleagues (1998). Three patients with bladder acontractility, dependent on catheterization, were treated with latissimus dorsi myoplasty and all three were able to void by abdominal straining and avoid catheterization. A larger clinical study followed using the free transfer of the latissimus dorsi muscle to restore voluntary voiding, with 14 of 20 patients able to void spontaneously with postvoid residual volumes of less than 100 mL (Ninkovic et al, 2003). The largest latissimus dorsi detrusor myoplasty experience was reported by Gakis and colleagues (2011) in 24 patients with detrusor underactivity and a mean follow-up of 46 months. Preoperatively, all patients required intermittent catheterization 4 to 7 times daily. This multi-institutional study from 2001 to 2008 resulted in complete voluntary voiding in 71% of patients with a 91% reduction in UTIs. Three patients reduced the frequency of catheterization by 50%, and 4 patients failed to show improvement.

ADDITIONAL THERAPIES FOR STORAGE AND EMPTYING FAILURE: CIRCUMVENTING THE PROBLEM

Patients with urinary incontinence may choose to wear an external collecting device or absorbent pad to manage leakage. For some, their incontinence is minimal or they are unwilling or unable to undergo more definitive treatment. However, in some instances, patients have failed multiple anti-incontinence procedures and external collecting devices or pads are the only management options available.

KEY POINTS: ADDITIONAL THERAPIES FOR EMPTYING—INCREASING INTRAVESICAL PRESSURE OR FACILITATING BLADDER CONTRACTILITY

- The Credé maneuver is most effective in patients with decreased bladder tone who can generate an intravesical pressure greater than 50 cm H₂O and have decreased bladder outlet resistance.
- Both the Credé and Valsalva maneuvers may elevate intravesical pressure sufficiently to cause upper tract deterioration, especially if performed in the setting of poor detrusor compliance. Even when the patient has a flaccid bladder and/or low detrusor leak point pressures, close follow-up and periodic evaluation are warranted.
- In patients with SCI with an intact sacral spinal cord, reflex voiding can be initiated through activation of the sacral micturition reflex. Voiding can be elicited by rhythmic suprapubic manual pressure; pulling the skin or hair of the pubis, scrotum, or thigh; squeezing the clitoris; or digital rectal stimulation.
- Reflex voiding depends on the ability to stimulate detrusor contractions and may be most suitable for patients with SCI or conditions characterized by neurogenic DO.
- Stimulated myoplasty for bladder emptying failure has been accomplished, but requires further investigation.

External Collecting Devices

To date no external urinary collecting device for females has been successful or effective. The female urethral meatal anatomy has made it difficult to design a leak-proof apparatus that is easy to apply and maintain. However, external collecting devices for men—the condom catheter, penile sheath, or Texas catheter—are generally effective in urine collection. For male patients who are unable to perform CIC because of cognitive impairment, quadriplegia, or lack of reliable assistance from a caregiver, the condom catheter may be preferable over an indwelling urethral catheter. A study by Saint and colleagues (2006) reported the results of a randomized controlled trial of 75 hospitalized male veterans in which 41 men were randomized to wear an indwelling urethral catheter and 34 men wore a condom catheter. The median hospital stay was 3 days. Condom catheters were associated with a lower incidence of bacteriuria, symptomatic UTIs, and death compared to the use of an indwelling urethral catheter. Patients also reported that external urinary collection devices were more comfortable and less restrictive on daily activities than indwelling catheters. It should be emphasized that despite the reduced incidence of adverse outcomes, the use of external collection devices and absorbent products is associated with a higher risk for UTIs compared with cases in which no appliances are used (Sturmann et al, 1989). It is generally recommended that condom catheters be changed daily, because the risk for UTI is increased when catheters are changed less frequently (Waites et al, 1993; Zimakoff et al, 1996). The use of a condom catheter is not free of complications. It can cause allergic reactions, skin maceration, and/or penile edema. Furthermore, the penile skin and glans should be examined at every catheter change to ensure no skin breakdown or contact reactions have occurred (Newman, 1999). These devices have the potential to cause pressure necrosis of the penis and, when severe, may even damage the urethra (Golji, 1981). Pressure-related complications are more likely to occur in patients with impaired sensation, such as those with neurogenic LUT dysfunction (Golji, 1981). External urine collecting devices also are prone to dislodge or fall off, especially if the patient is wearing an inappropriate size. Additionally, patients with SCI may have reflex penile retraction and paralysis associated with pelvic bending, making it difficult to maintain the device. Van Arsdalen and colleagues (1981) reported on the

use of a noninflatable penile prosthesis in this type of patient to facilitate applying and maintaining a condom catheter. Zermann and associates (2006) describe the long-term results of penile prosthetic surgery for urinary incontinence and/or erectile dysfunction in neurologically impaired patients. At a mean follow-up of 7.2 years, 90.3% of urinary management problems were resolved. The overall infection rate was 5%, and the rate of explantation was 7.7%, which is comparable to the explantation rate in non-neurogenic patients.

Absorbent Products

Urinary incontinence can be a socially debilitating problem leading to fear of odor, discovery, and embarrassment. Many patients with urinary incontinence purchase and wear some type of absorbent product, which may include pads, shields, drip collectors, guards, undergarments, briefs, diapers, or underpads. Consumers spend billions of dollars on these products (Getliffe et al, 2007; Erikson et al, 2008) and for the majority, selection is often based on trial and error, cost, convenience, and manufacturers' claims (Baker and Norton, 1996; Fantl et al, 1996). Recently, the National Association for Continence (NAFC) formed a Council of experts with the goal of establishing national, independent quality performance standards for disposable adult absorbent products. The full recommendations of the NAFC Council include nine performance assessment parameters: "rewet rate (a measure of a product's ability to withstand multiple incontinent episodes between changes), rate of acquisition (a measure of the speed at which urine is drawn away from the skin by a product), product retention capacity (a measure of a product's capacity to hold fluid without rewetting the skin), sizing options, absorbency levels, product safety, closure technology, breathable zones (a measure of the air permeability across a textile-like fabric at a controlled differential pressure), and elasticity" (Muller and McInnis, 2013). More research is needed to evaluate the impact of these parameters on cost and quality of care.

Often recognized as the authority in the management of the incontinent patient, urologists should acknowledge the basic nursing principles and skin care recommendations that may significantly contribute to patient care. Absorbent products should be changed frequently to help avoid buildup of odor and limit the exposure of the skin to urine. Prolonged exposure of the skin to a wet environment may lead to supersaturation and disruption of the skin's protective barriers, promoting skin maceration, dermatitis, and possibly infection. **Incontinence-associated dermatitis (IAD) can be defined as inflammation of the surface of the skin with redness, edema, and, in some cases, bullae containing clear exudate (Gray et al, 2007). IAD predominately occurs in skin folds and may promote candidiasis or bacterial skin infections. Gray and associates (2007) published an excellent review of the epidemiology, pathophysiology, and management of IAD with recommendations for prevention and treatment.**

Further information regarding the types of absorbent products available for males and females, including a review of skin care management, external collection, and urethral compression devices

can be found in the book by Newman and Wein (2009) and the comprehensive resource guide available from the NAFC (2008) (<http://www.nafc.org>).

KEY POINTS: CIRCUMVENTING THE PROBLEM

- No reliable external urine collecting device exists for females; however, these devices, or condom catheters, can be used successfully in men who are unable to perform CIC.
- Condom catheter use is associated with a lower incidence of bacteriuria, symptomatic UTIs, and death compared to the use of an indwelling urethral catheter. They are also perceived to be more comfortable and less restrictive on daily activities than indwelling catheters.
- Pressure-related complications from condom catheter use are more likely to occur in patients with impaired sensation or cognition.
- IAD can be defined as inflammation of the surface of the skin with redness, edema, and, in some cases, bullae containing clear exudate. IAD predominately occurs in skin folds and may promote candidiasis or bacterial skin infections.

SUMMARY

Disorders of the storage and emptying phases of micturition have various causes and can be classified by the location of the dysfunction, either at the bladder level or the bladder outlet. Treatment strategies are numerous and often combine medical and surgical management. Continued research is warranted to further our understanding of the pathophysiology of storage and emptying failure so we may continue to improve patients' quality of life.

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The complete reference list is available online at www.expertconsult.com.



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Biology and Principles of Aging

Demographics of Aging

Clinical Evaluation of the Geriatric Urology Patient

Major Geriatric Syndromes and Urology

End-of-Life Care and Urology

Summary

Aging is a universal process that affects all living organisms. Alterations in anatomy and physiology associated with the normal aging process lead to functional changes in all aspects of human medicine including the genitourinary system. This chapter will focus on human aging and the associated alterations in structure and function that affect urologic care for older adults.

Dr. Ignatz Leo Nacher was the first to use *geriatrics* as a clinical term in a scientific publication (Nacher, 1909). That article highlighted early concepts about considering care for older adults as a distinct branch of medicine. More than a century later, geriatrics is not only a recognized and respected distinct specialty within general medicine, but in multiple other health care disciplines including nursing, pharmacy, physical and occupational therapy, social work, and others. More recently, the growing need for geriatrics expertise in all of the medical and surgical specialties including urology has been recognized (Drach and Griebling, 2003; Bell et al, 2011). Research efforts and educational materials have been developed and have helped to expand knowledge about the unique aspects of medical needs and care delivery for older adults with urologic health problems (Webb and Duthie, 2008; Griebling, 2009b; Guzzo et al, 2013; Griebling, 2014; Reuben et al, 2014).

In clinical medicine, the term *geriatrics* is most commonly used to refer to care of patients 65 years of age or older. In part, this is a social construct because this is the age when Medicare and Social Security benefits have traditionally started for people in the United States. The World Health Organization (WHO) actually classifies people older than age 60 as being “elderly,” because life expectancy is still shorter in many parts of the developing world. With continuing advances in medical care and extended longevity in many developed countries, many would argue that clinical geriatrics now encompasses an even older population, often focused on those 70 years and older. However, in many circumstances, **chronologic age may be a much less important factor than physiologic or functional age.**

One of the basic principles in geriatric medicine is a focus on **patient-centered care**. This places the goals of care for patients, their caregivers, and other loved ones at the core of clinical evaluation and treatment. In some cases the goal may be treatment with curative intent. However, in many instances this may not be possible. In all cases there should be an **emphasis on quality of life (QoL), and stabilization or improvement in functional status.** This frequently includes a goal to maintain independence for as long as possible and to reduce the need for assistance or care from others to the extent possible. Promotion of urinary continence and improved bladder function is a good example of this type of care within the scope of urologic practice. Improvement in independent

toileting and continence status can reduce the need for caregiver assistance and may in turn decrease the risk of need for nursing home placement (Andel et al, 2007).

BIOLOGY AND PRINCIPLES OF AGING

There are several plausible theories about why people age and experience changes over time. The **Hayflick limit** describes the phenomenon of limitations in the number of cellular replication cycles inherent to most cell types (Hayflick and Moorhead, 1961). This may result from a variety of factors. **Telomere shortening** has been identified as a common cellular change seen with aging. **Activation of various tumor suppressor genes** or other genetic pathways may also serve to either promote or suppress cellular senescence. **Release of free radicals and other types of oxidative stress increase** with aging and can lead to mitochondrial damage and other intracellular changes. Some cell types exhibit **apoptosis or programmed cell death**. Numerous inflammatory biomarkers have been shown to increase with age and could potentially accelerate the aging process. **These accumulated changes can lead to the alterations in tissue and organ function commonly seen with advancing age.** These types of changes can influence clinical outcomes including tissue and wound healing, restoration of function, and outcomes of reconstructive urologic surgical procedures (Griebling, 2009a).

Physiologic Aging

Changes in function with increasing age can be seen in essentially all organ systems. Generalized changes can be exacerbated by specific disease progression. A number of these different processes have direct impact on genitourinary health, urologic function, and clinical decision making relative to urologic care.

Renal blood flow decreases with aging. This can be caused by atherosclerotic plaque formation in the renal arteries and other vascular diseases. Kidney mass also decreases progressively after 65 years of age. This leads to a **concomitant decrease in the glomerular filtration rate (GFR) of approximately 10 mL/min per decade**, reaching about 50% by age 80. Approximately 26% of all adults older than age 70 have some degree of chronic renal impairment. **This can have substantial impact on dosage of medications cleared by renal metabolism** (Hanlon et al, 2009). In many cases, lower doses will be adequate to achieve clinical effects, and doses typically used in younger patients may lead to toxicity or untoward side effects. Renal concentrating ability is also reduced, and older adults tend to make a larger volume of more dilute urine (Sands, 2003).

Accurate estimation of renal function in older adults can be challenging. **Serum creatinine levels alone may not reflect actual renal function**, particularly in frail older adults or those with reduced lean body mass. In these patients, serum creatinine measurements will tend to overestimate function and underestimate the degree of renal impairment (Giannelli et al, 2007). Measures that calculate estimated GFRs including the Cockcroft-Gault equation will tend to be more accurate in this elderly population (Scrutinio et al, 2009). Routine assessment and reporting of estimated GFR can help to improve prescribing accuracy for drugs that require renal metabolism (Kurtal et al, 2009).

The diurnal pattern of water consumption and urine production also changes with aging. Total water intake appears to decrease among older adults with aging, with population studies indicating that only 19% to 27% of geriatric patients actually reach the daily recommended levels of fluid consumption (Zizza et al, 2009). Endogenous secretion of arginine vasopressin decreases with age. Because of this, older adults tend to excrete the majority of their fluid output at night, which can lead to symptomatic nocturia (Tani et al, 2008). This relative nocturnal polyuria can be a major contributing factor to clinically bothersome symptoms (Natsume et al, 2009).

Cardiac compliance and elasticity decrease with aging, which leads to decreased cardiac output and stroke volume. This can have important implications, particularly when considering older adults as candidates for urologic surgery. Hypertension is also a common condition seen with aging and can negatively influence functional reserve capacity. Hypertension in older adults can be caused by myriad factors, including renovascular conditions.

The **respiratory system** undergoes substantial changes with aging. Pulmonary surface area for oxygen diffusion decreases, leading to changes in ventilation-perfusion ratio. Chest wall elasticity and respiratory muscle strength both decrease, and there is decreased maximal expansion. Pulmonary fibrosis and chronic obstructive pulmonary disease (COPD) are common conditions seen with aging and can also negatively influence respiratory function. Cigarette smoking increases these risks and exacerbates age-related changes. Increased cough may worsen symptoms among patients with concomitant stress urinary incontinence (UI). As with cardiovascular disease, alterations in pulmonary function play a major role in consideration for surgical therapy in older adults. **Although most deaths in the perioperative period in geriatric patients are caused by cardiovascular events** such as myocardial infarction and stroke, **most prolonged hospitalizations are the result of pulmonary problems** such as pulmonary embolism, pneumonia, and respiratory failure and difficulty weaning from ventilator support (Somme et al, 2003).

Hepatic function also declines with time. Loss of hepatocytes leads to **decreased metabolic efficiency for drugs cleared by hepatic metabolism**. Alterations in the cytochrome P450 mechanism are common and can be influenced by a variety of medications. This can alter hepatic metabolism and may necessitate dose adjustment of medications cleared by the liver. It is also important to consider drug-drug interactions that may be influenced by changes in the cytochrome P450 pathway. Certain foods, particularly grapefruit, can also interfere with the cytochrome P450 pathway and potentially impair drug metabolism.

Immunologic function, particularly T cell-mediated immunity, tends to slowly decline with age. This leads to a generalized increase in the risk of infections among older adults including a greater risk for both upper and lower urinary tract infections (UTIs) and pneumonia.

Gastroenterologic changes include a generalized slowing of bowel motility, which can lead to alterations in stool frequency and consistency. **Altered water reabsorption from the colon can increase risk for constipation**. This can be particularly affected by anticholinergic and other medications that may slow bowel motility. This in turn increases the risk for constipation and fecal impaction with aging. These conditions can be exacerbated by medications used in the treatment of some urologic conditions such as antimuscarinics prescribed for overactive bladder (OAB), urinary urgency and frequency, and urgency UI (Kim et al, 2014b).

Vascular changes are common with aging. These include changes in peripheral vasculature, cardiac and central nervous system vascular anatomy, and renal perfusion. Hypertension, tobacco use, and diabetes all contribute to vascular disorders seen more commonly with aging. Plaque formation and atherosclerotic disease may limit circulation to the kidneys, bladder, penis, and other genitourinary organs. Decreased penile blood flow can lead to erectile dysfunction in elderly men (Justo et al, 2010). Pelvic ischemia has also been linked to the subsequent development of lower urinary tract symptoms (LUTS) in older adults (Pinggera et al, 2008; Kim et al, 2010a). Color Doppler ultrasound demonstrates diminished arterial blood flow, which is associated with pelvic ischemia and higher rates of LUTS. Animal models show that pelvic ischemia is associated with increased levels of proinflammatory cytokines and other biomarkers suggesting that oxidative stress plays a role in this process (Nomiya et al, 2012). Free radical release and oxidative stress may cause ultrastructural damage that can lead to neurodegeneration and other anatomic and functional abnormalities (Azadzo et al, 2007, 2010, 2011; Tyagi et al, 2014b). Early research suggests that melatonin and other compounds such as free radical scavengers could be potential agents to prevent urologic sequelae from this type of ischemia (Nomiya et al, 2013).

Metabolic changes are common with aging. Rates of both the metabolic syndrome and type 2 diabetes mellitus increase substantially with advancing age. These conditions can contribute to multiple clinical conditions including vascular insufficiency, erectile dysfunction, renal impairment, and bladder dysfunction (Park et al, 2008). With aging, there is a **relative increase in adipose tissue and a loss of lean body mass and muscle**. This influences fluid distribution and drug metabolism and increases the rate of accumulation of lipophilic metabolites. **Because of this, many lipophilic drugs need to be dose titrated in older adults**. Obesity and overweight have reached epidemic proportions in the United States and are associated with increased rates of associated medical conditions including diabetes and metabolic syndrome.

Aging and the Lower Urinary System

Many of the common genitourinary conditions occur with higher incidence and prevalence rates in older adults, but these should not necessarily be considered a normal or inevitable part of the aging process. Examples include UTIs, UI, erectile and sexual dysfunction, and many of the urologic malignancies. Various changes commonly occur in the genitourinary tract as a result of the normal aging process. One of the greatest challenges in geriatric urology is to differentiate between normal aging and pathologic processes that can affect the genitourinary system and lead to associated symptoms.

Several structural changes that occur in the bladder with aging have been linked to functional changes that can cause specific clinical symptoms (DuBeau, 2006). The ratio of smooth muscle to collagen in the wall of the bladder decreases, which may lead to decreased contractile strength. Studies using electron microscopy and other structural imaging modalities have demonstrated these changes as well as development of "dense bands" and loss of caveolae (Elbadawi et al, 1993; Lowalekar et al, 2012). These alterations have been linked to increased involuntary detrusor contractions and changes in contraction strength and velocity. Functional bladder innervation also appears to diminish over time with chronic obstruction or overactivity (Fry et al, 2011). Changes in detrusor anatomy can also lead to a decrease in elasticity and compliance, defined as the change in bladder volume related to bladder pressure. These alterations can lead to changes in both urine storage and bladder emptying (Elbadawi et al, 1997). Sensory changes may be caused by alterations in the epithelium and associated receptors and neurotransmitters. Oxidative stress damage may also occur as a result of the aging process and may be associated with symptomatic bladder dysfunction (Aybek et al, 2011). Bladder capacity tends to remain relatively stable or to decrease only slightly with advancing age (Pfisterer et al, 2006a, 2006b).

Progressive anatomic changes in pelvic floor support and muscle strength can also occur with aging. Cadaveric studies using biopsy

specimens of the urogenital diaphragm have documented that striated muscle tissue is substantially reduced or absent in many older women relative to connective tissue (Betschart et al, 2008). However, aging may not be the sole risk factor, and other variables including parity and history of vaginal delivery should be considered (Weemhoff et al, 2010). Bony structural support in the pelvis may also contribute to these changes and can potentially be influenced by geriatric skeletal disorders such as osteopenia or osteoporosis (Richter et al, 2013). Pelvic floor muscle dysfunction is common among elderly women, and research indicates many of them may not be able to generate voluntary muscle contractions on initial examination (Talaszy et al, 2012). Some of this observed change in pelvic floor support may be a result of apoptotic cellular changes in these tissues (Saatli et al, 2014).

Decreased striated muscle density in the rhabdosphincter can lead to an increased propensity for stress UI, particularly in elderly women. These anatomic changes may be caused, at least in part, by apoptosis associated with aging (Strasser et al, 1999, 2000). This can subsequently lead to a loss of the normal circumferential anatomy and appropriate urethral resistance and closure pressures (Klauser et al, 2004; Kurihara et al, 2004).

DEMOGRAPHICS OF AGING

Aging and Population Trends

The overall population of the United States and of many other developed countries is aging at a very rapid pace. This is the result of a number of factors including improved longevity, decreased overall birth rates, and enhanced medical technology that makes effective treatment for many conditions possible. Older adults, defined as those 65 years of age and older, currently account for approximately 13% of the total U.S. population. However, it is estimated that this will increase to at least 20% by the year 2030 (Fig. 88-1). The fact of the matter is that those older than age 85 represent the fastest growing segment of the U.S. population. The aging of the “baby boom” generation including those born between 1946 and 1964 is also contributing to this demographic trend. Approximately 10,000 people per day now turn 65 years of age in the United States. This is a global phenomenon and is occurring in almost all portions of the world with the exception of sub-Saharan Africa, where mean life expectancy is still relatively shorter. Worldwide, approximately 420 million people were older than age 65 in 2000, and it is estimated that this will increase to more than 973 million by 2030 (Centers for Disease Control and Prevention [CDC], 2014). Remaining life expectancy for those already age 65 continues to steadily increase in the United States and in many developed countries worldwide.

The vast majority of older adults continue to live in the community, with only a minority requiring residential long-term care in nursing homes or other types of facilities. The need for nursing home services does increase with advancing age, with approximately 15% of those older than 85 years living in long-term care facilities. (Federal Interagency Forum on Aging-Related Statistics, 2012).

Global Implications for Urologic Health Care

As the population ages, there will be an increased need for health care providers with specific knowledge and skills to evaluate and treat clinical conditions in this heterogeneous and complex patient population. In many ways, urology is by its very nature a geriatric specialty. Except for those who exclusively practice pediatric or adolescent urology, most urologists in general practice have a majority of patients in their practice who are older than 65 years. Urology consistently ranks among the top three specialties in the United States in terms of the total volume of older adults seen in clinical practice. Only ophthalmology and cardiology outrank urology in terms of the total volume of geriatric care provided in the specialty (Drach and Griebing, 2003).

Epidemiologic studies have consistently shown that incidence and prevalence rates for the most common urologic conditions

tend to increase substantially with advancing age. This includes UI and lower urinary tract dysfunction, pelvic organ prolapse (POP), UTI, bladder outlet obstruction (BOO), and benign prostatic hyperplasia (BPH). With the exception of testicular cancers, all of the urologic malignancies have a predilection to occur in older adults. Sexual health problems are more common among older men and women compared with younger patients. **Increased population growth among older adults will mean that more elderly patients will develop urologic disorders**, which in turn will likely translate into increased rates of surgical care among geriatric patients (Takao et al, 2008). All these factors contribute to the expanding need for expertise in geriatric urology (Drach and Griebing, 2003).

CLINICAL EVALUATION OF THE GERIATRIC UROLOGY PATIENT

Older adults frequently have more complex health needs compared with younger patients. This is in part because of changes associated with aging, and also the increase in comorbidity seen in elderly patients. **Physiologic alterations associated with aging can lead to loss of functional reserve capacity**, which in turn leads to impaired response to stressors such as infection, surgery, chemotherapy or other urologic conditions or treatments (Fig. 88-2). The concept of the body trying to restore or remain in balance in response to internal or external stressors has been termed *homeostasis*. In geriatrics, the decline in functional reserve capacity associated with aging is sometimes described using the term *homeostenosis*, a reference to the narrowing of arteries that occurs with atherosclerosis. For a given stressor, older adults with lower baseline functional reserve capacity may not be able to respond as well or may actually have a more exaggerated response compared with younger patients with more reserve. An example would be the development and progression of postoperative pneumonia. In a healthier younger patient, this may be relatively indolent and self-limited and may promptly resolve with appropriate antibiotic therapy. However, in a more debilitated older adult with less functional reserve capacity, the same level of pneumonia could result in a much more profound illness that could require more intense treatment and time to resolve. It could also have a higher likelihood of progression to more serious disease.

One of the most commonly used measures of comorbidity is the **Charlson Comorbidity Index (CCI)**. This was initially developed to identify underlying disease conditions that could help to predict subsequent mortality risk (Charlson et al, 1987). The instrument assigns points to each chronic condition, with a sum score indicating level of risk based on comorbidity. The CCI has been used extensively and has been validated for use in surgical patients. It has been applied recently to some urologic conditions such as kidney cancer to help make clinical decisions between surveillance and surgery in elderly patients (O'Connor et al, 2009). Self-reported health is an important predictive factor among geriatric patients. **Poor self-reported health among older adults has been linked to increased overall and disease-specific mortality and has in some cases been found to be a stronger negative predictor than physician-rated health status** (Giltay et al, 2012).

Because of this, older adults often require more involved clinical evaluation in relation to their urologic treatment. This includes a number of specific areas that are somewhat unique to geriatrics but that influence overall care for the patient. Development of comorbid chronic health conditions is common with aging. **The majority of adults older than 65 years have at least one chronic medical condition, and more than 50% have at least two** (Wolff et al, 2002).

Functional Assessment

Functional assessment in geriatrics includes a number of components designed to evaluate reserve capacity and levels of dependence or independence. This includes evaluation of an older adult's ability to independently perform specific tasks. **A clear understanding of an individual patient's baseline functional status is vital to his**

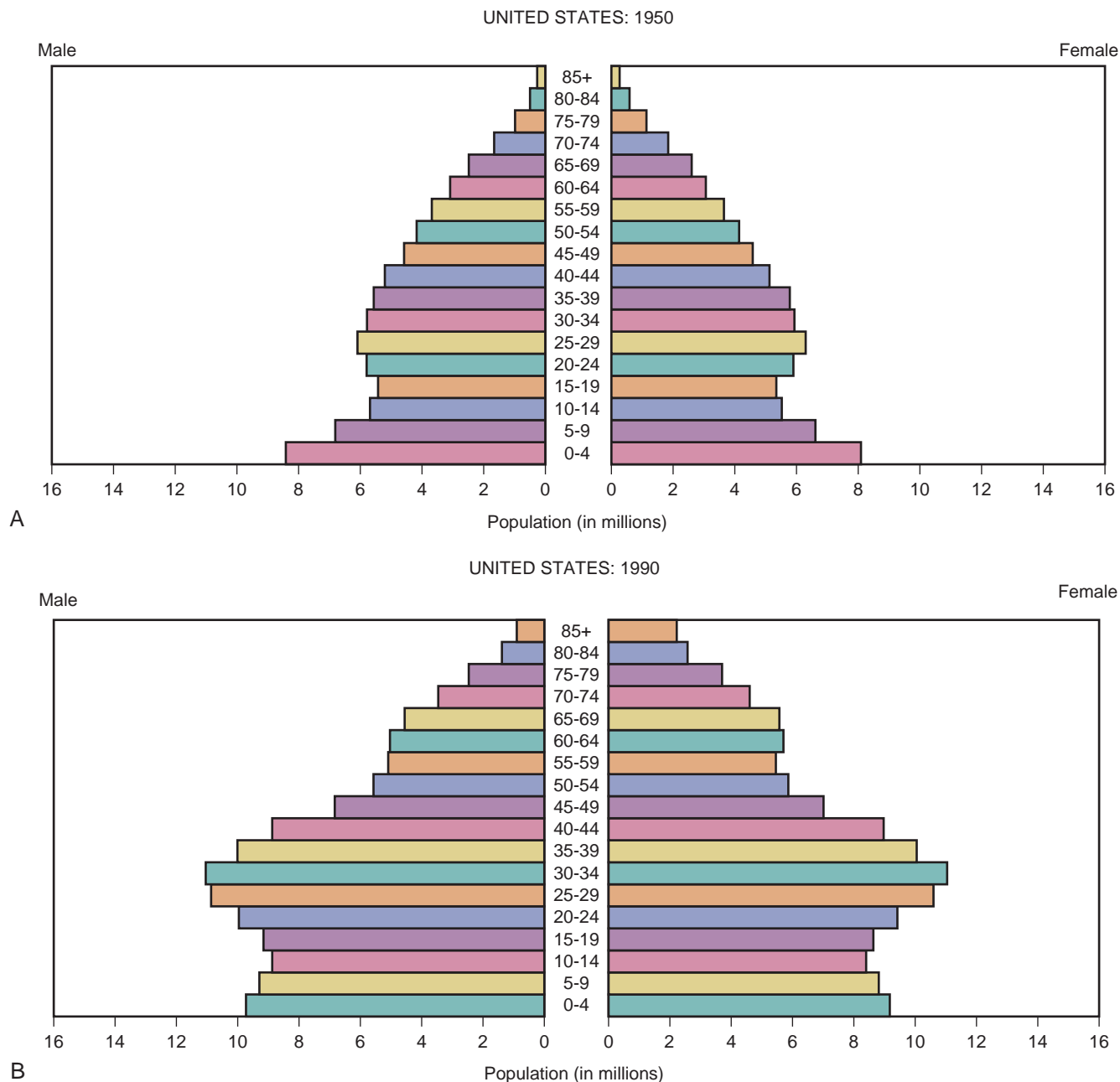


Figure 88-1. Age-sex population pyramids based on U.S. census data. A, 1950 census. B, 1990 census.

or her care (Dunlop et al, 2002). This provides a framework to better understand subsequent changes associated with surgery or other treatments. **Baseline functional status has been shown to be predictive of other health care outcomes** including remaining life expectancy, morbidity, and mortality (Lubitz et al, 2003). There is wide heterogeneity among older adults, and this is not specifically related to chronologic age. Progression of clinical disorders and response to treatments can both lead to changes in functional status, and the clinician needs to be able to identify these alterations compared with baseline function. The following components form the basic parts of functional assessment in geriatric patients.

Activities of Daily Living

The **activities of daily living (ADLs)** include basic tasks people need to do to function and interact in the world. These include bathing, dressing, grooming, using the toilet, feeding, and perform-

ing physical ambulation. Each of these factors is evaluated on a scale ranging from complete independence to needing full assistance (Lawton and Brody, 1969). Alterations in ADLs are among the most predictive factors for need of caregiving assistance with aging. Although there can be variations in the pattern of progressive need for help with ADLs, bathing is typically the one for which people first need assistance. Feeding tends to be preserved the longest, even in people who are otherwise quite debilitated. A simple way to determine if people are beginning to need assistance with their ADLs is to ask if someone is able to shower or bathe independently. This can be an early sign of alterations in overall status that may be predictive of future change.

Instrumental Activities of Daily Living

The **instrumental activities of daily living (IADLs)** add a higher cognitive and executive function component to the basic ADLs.

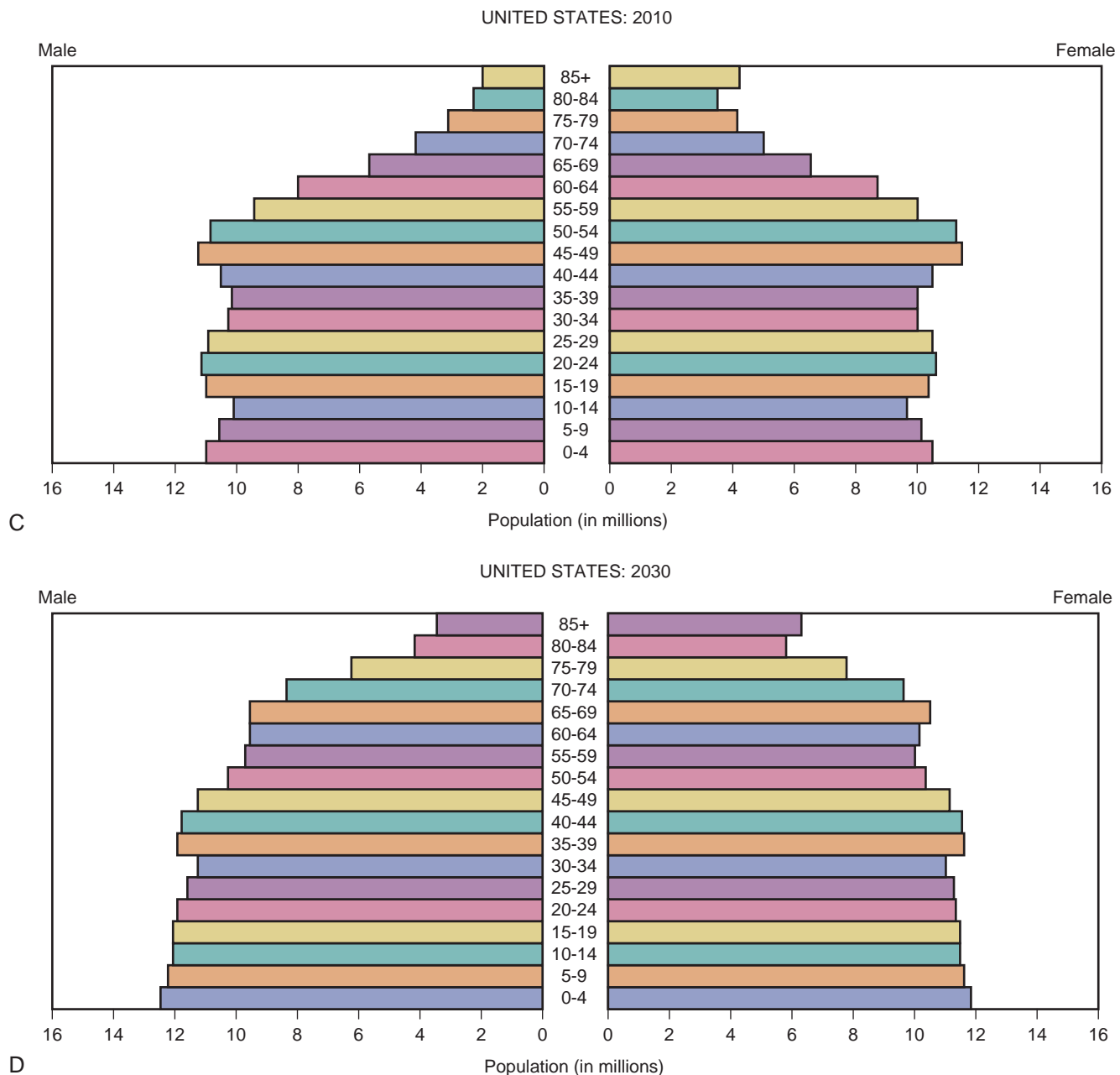


Figure 88-1, cont'd C, 2010 census. D, 2030 (projected). Note the sizeable increase in total population and the progressive change over time from a pyramid shape, in which the majority of the total population is relatively young, to a rectangular shape, in which a substantially larger portion of the population is older than 65 years. The pronounced bulge in the graphs for 1990 and 2010 represents the “baby boom” generation. (From U.S. Census Bureau, www.census.gov.)

These include shopping, preparing food, performing housekeeping tasks, doing laundry, managing finances, using the telephone or other communication devices, managing medications, and using transportation. As people age, it is common for them to need some assistance with the IADLs before they need help with ADLs, although there can be quite a bit of variation in these change patterns. Many community and home-based services are available to help with both ADL and IADL needs as people age.

Both ADL and IADL function can be predictive of overall health status and future health variables. Using data from the Medicare Current Beneficiary Survey from 1992 to 1998, Lubitz and colleagues examined nearly 17,000 people aged 70 at the time of enrollment and studied longitudinal outcomes stratified by functional status (Lubitz et al, 2003). Those who were independent in all ADL and IADL variables had an estimated remaining life

expectancy of 14.3 years and annual health care costs of \$4600 (in 1998 dollars). Loss of independence in one IADL reduced expected remaining life expectancy to 12.4 years and increased annual health care expenditures to \$8500. Needing assistance with at least one of the basic ADLs led to a reduction of remaining life expectancy to 11.6 years and increased annual health care expenditures to \$14,000. These data clearly demonstrate that loss of functional independence is linked to reduced life expectancy and increased health care costs. Understanding baseline ADL and IADL function also helps clinicians to monitor changes in status over time and with treatments.

Mobility

Limitations in mobility can have a substantial impact on overall functional status for older adults. **Mobility impairment is**

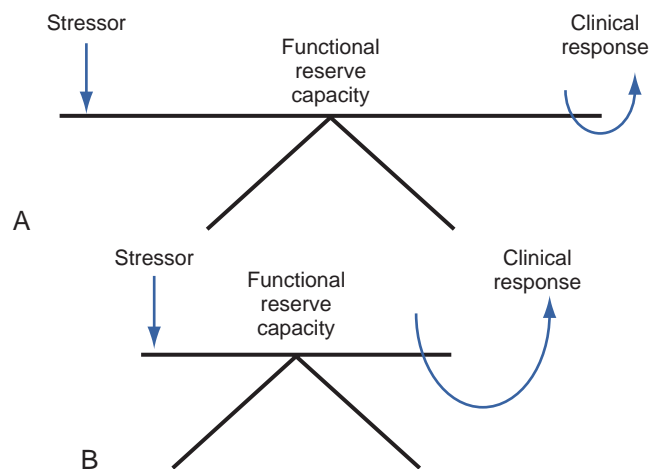


Figure 88-2. Changes in functional reserve capacity with aging. With aging, there is a progressive decline in functional reserve capacity. This diagram demonstrates the conceptual model of *homeostasis* (A) wherein the body tries to maintain balance in response to various stressors such as disease or clinical treatment. Progression to *homeostenosis* (B) is caused by relative decline in functional reserve capacity. In this case, response to identical stressors may be more difficult or complications more pronounced owing to loss of functional reserve capacity.

frequently associated with urologic issues including the development of what is termed *functional incontinence*. In these patients, UI is a result of factors other than those related to the bladder, such as impaired mobility or cognition. Improvement in the underlying factors such as return of independent mobility could help to improve or resolve the UI.

One of the most commonly used and well validated clinical assessments for mobility is the **Timed Up and Go (TUG) test** (Podsiadlo and Richardson, 1991). To perform this test, the patient is seated in a stationary, hard-backed chair with arms. He or she is asked to stand, walk 3 meters, turn, return to the chair, and sit down. If the patient normally uses an assistive device such as a walker or cane for ambulation, he or she is allowed to use it during the test. Most older adults without mobility limitations can complete this task in 10 seconds or less. Frailer older adults who still maintain good mobility independence can complete this in 20 seconds or less. Inability to complete the test or needing more than 20 seconds to do so indicates a higher level of dependence for mobility. Although it seems quite simple, the TUG test measures a number of complex components associated with independent mobility. These include the ability to follow directions, quadriceps strength in standing from the seated position, gait, balance, and coordination. Diminished quadriceps strength is recognized as an early sign of decreased overall muscle function.

One of the newer conceptual models that expands on the complexity of the concept of mobility is the **Life Space Assessment** (Baker et al, 2003). This examines the degree to which a person is able to independently interact with his or her world. Measurements range from the extremes of being confined to one's bedroom to being fully able to travel and go out independently into the greater community and world at large. This can have important implications for urologic function. For example, someone who is limited to his or her bedroom may require complete assistance for toileting. An understanding of baseline life space capabilities also helps to better evaluate postoperative function in people undergoing surgery (Stewart et al, 2009).

Slower gait speed in elderly patients has been closely linked to reductions in remaining life expectancy, chronic disability, nursing home placement, and injurious falls (Hardy et al, 2007; Rothman et al, 2008). It has been shown to be one of the strongest predictors of mortality and other negative health outcomes among older

adults (Seino et al, 2013). It is likely that this represents a marker condition that includes changes in other functional status components including muscle strength and sarcopenia, nutritional status, and baseline levels of activity. Fatigue and easy exhaustion with physical activity are also associated with increased risk of mortality in elderly patients (Hardy and Studenski, 2008). These factors, including diminished levels of physical activity, a sense of easy exhaustion, and reduced gait speed, are all clinical components of the frailty phenotype (Fried et al, 2001).

Cognition

Cognitive changes in older adults are quite common and can be acute or chronic. An appreciation of baseline cognitive status for an individual patient is important, particularly in relation to changes that can be observed longitudinally over time or directly related to various therapies. Alterations in cognitive status may be associated with delirium or dementia, and recognition of these factors is important for correct diagnosis and subsequent treatment.

Various methods can be used to assess cognitive status. The most commonly used validated instruments include the **Folstein Mini-Mental State Examination (MMSE)** and the **Mini-Cog** (Folstein et al, 1975; Borson et al, 2000). Both instruments provide valuable information on the cognitive status of patients. The MMSE provides a brief cognitive assessment in several domains including orientation, ability to follow directions, visual-spatial capacity, and short-term memory. It can be influenced by educational status, with more highly educated individuals tending to score higher at baseline. The instrument is graded on a scale from 0 to 30, with scores of 24 or lower generally considered positive for dementia.

The Mini-Cog assesses ability to follow directions, visual-spatial cognition, and short-term memory and executive function. It is less influenced by educational level than the MMSE. Advantages of the Mini-Cog include ease of administration and shorter time required to complete assessment. It can usually be done within about 3 minutes and includes two components: a three-item short term repetition with recall, and a clock-drawing test. Subjects are asked to repeat and remember three words. These should be unrelated items and should not include abstract ideas, emotions, colors, or terms that modify or describe one another. Examples of words often used in testing are *apple*, *penny*, and *table*. These are also somewhat more complex because they all have two syllables. After the patient attempts to repeat the words, he or she is asked to draw the face of a clock including all 12 numbers, and to set the hands to a specified time (usually 11 : 10). The patient may be provided with a paper that already includes the circle, or he or she may draw the circle and complete the clock (Fig. 88-3). After the patient has finished drawing the clock, he or she is asked to repeat the three previously presented and repeated words. This concludes the test. Zero to three points are assigned for short-term recall, one for each correctly repeated word. Either zero or two points are assigned for the clock drawing, depending on whether all components were correctly completed. A total score of 0 to 2 is positive for possible dementia, and a score of 3 to 5 is considered negative. The Mini-Cog has been validated in a variety of settings, does not require specialized equipment, is relatively quick and easy to administer, and is less influenced by language and educational status than are other available tests.

Understanding preoperative cognitive function is important for several reasons. It can help gauge the capacity of patients to provide informed consent for treatment and can serve as a comparison for later observed cognitive status. **Advance directives and informed decision making regarding health care are important parts of geriatric practice.** Reduced baseline cognitive function has been associated with worse postoperative outcomes in elderly surgical patients. Examples include a higher incidence of delirium (78% vs. 37%, $P < .001$), longer hospital stays (15 ± 14 vs. 9 ± 9 days, $P = .008$), higher rate of discharge institutionalization (42% vs. 18%; $P = .001$), and higher 6-month mortality (13% vs. 5%; $P = .040$) (Robinson et al, 2012).

Potentially reversible causes of memory loss in patients should be considered and addressed if appropriate. Conditions commonly

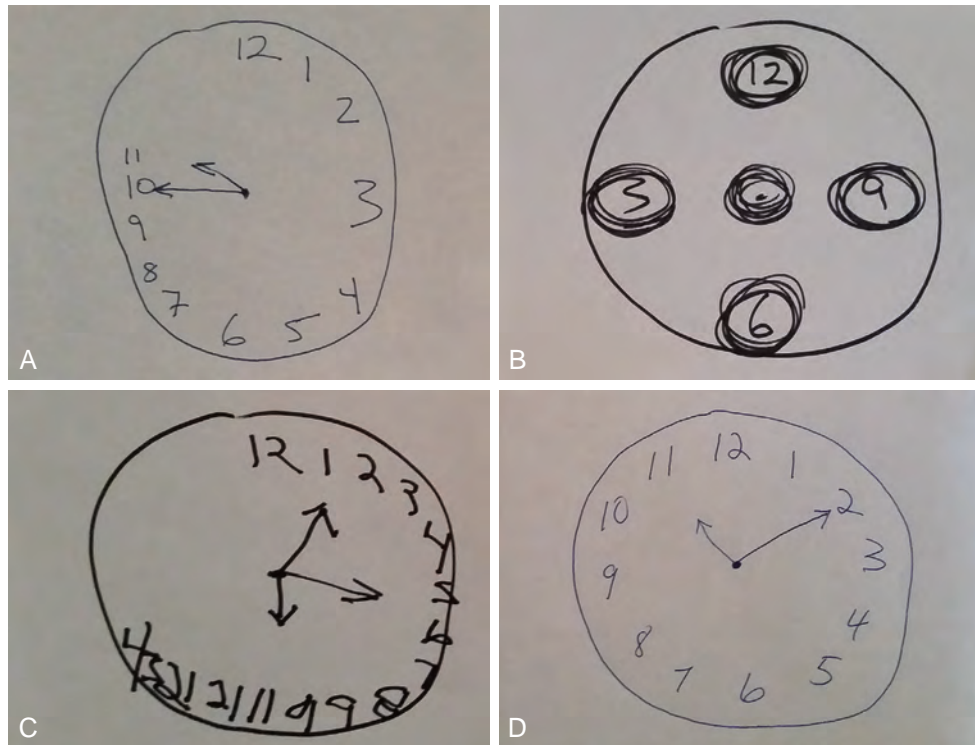


Figure 88-3. Mini-Cog clock drawing test results (abnormal and normal). Examples of the clock drawing test from the Mini-Cog assessment. **A, Abnormal.** Note the incorrect spatial orientation of the numbers and placement of the hands. **B, Abnormal.** Only four numbers are included and no hands are drawn to show time. Note the perseveration on drawing the circles around the numbers. **C, Abnormal.** Note the incorrect spatial orientation of the numbers, repetition of part of the numerical sequence, and incorrect number and placement of hands. **D, Normal.** Note the correct spatial orientation of the numbers and placement of the hands to indicate time per the instructions.

seen in urologic practice include vitamin B₁₂ deficiency, hypothyroidism, and medication side effects. Patients with a history of urinary diversion using small intestine can be at particular risk for vitamin B₁₂ deficiency, and replacement therapy may be necessary. Although not necessarily reversible, tertiary neurosyphilis can be associated with both memory loss and neurogenic bladder and voiding dysfunction.

Depression

Depression is a very common condition among older adults. As with other conditions, the incidence and prevalence both increase with advancing age, but depression should not be considered a normal or expected part of the aging process. A number of urologic health conditions have been associated with increased rates of depression, including UI and various genitourinary malignancies. The Geriatric Depression Scale (GDS) is a short, validated screening tool to assess for possible depression in older adults (Sheikh and Yesavage, 1986). The instrument consists of 15 items with yes-or-no responses. A score of 0 to 2 points is considered normal. If someone scores 3 or more points, the screening test is considered positive for possible depression. This could alert the provider to the potential need for additional evaluation. Input from the patient's primary care provider or consultation with either a geriatrician or a geriatric psychiatrist may be indicated.

Examples of urologic conditions that occur at higher rates in geriatric patients and that tend to be associated with risk for depression include UI, POP, prostate cancer, and sexual dysfunction (Kafri et al, 2013; Kahn et al, 2013; McCabe and Althof, 2014; Ravi et al, 2014). UI has been shown to be undertreated in the general older adult population and has substantial negative effects on multiple

health domains (Chang et al, 2008). Additional research is needed to identify the role of treatment of urologic conditions on mental health outcomes.

Surgical Risk and Medical Optimization

Surgical therapy remains one of the mainstays of urologic treatment for many of the clinical conditions that affect geriatric patients. Unfortunately, many clinicians and patients seem to have an inherent bias against surgical therapy for older adults. However, with careful planning, surgical therapy may be an appropriate option for treatment of many urologic conditions seen in older adults. The development of minimally invasive surgical techniques has opened up a new avenue for potential therapy for many patients. Age by itself should not be a limiting factor, and in most cases clinical comorbidity is a much more influential issue. However, even in these cases, careful preoperative planning and medical optimization can potentially reduce risk of complications after urologic surgery (Takao et al, 2008).

One of the primary tasks of the urologic surgeon planning operative care for a geriatric patient is to identify potential risks and benefits associated with surgery. Preoperative optimization should be carefully considered. Although it is technically not possible to "clear" someone for surgery, a wide variety of steps can be taken to optimize health status in different realms before surgery. The American College of Surgeons and the American Geriatrics Society (AGS) collaborated on a project to help outline evaluations that should be used before surgery in older adults (Chow et al, 2012). These recommendations are grounded on evidence-based data regarding evaluation of each organ system and various functional components. The goals of these evidence-based recommendations are to

BOX 88-1 Preoperative Assessment Recommendations for Older Adults

- Assess cognitive ability and capacity
- Screen for depression
- Identify risk factors for delirium
- Screen for alcohol and other substance use
- Perform cardiac evaluation (American College of Cardiology or American Heart Association)
- Conduct pulmonary risk assessment
- Document functional status and risk of falls
- Determine baseline frailty score
- Assess baseline nutritional status (consider preoperative replacement or supplementation)
- Obtain detailed medication history and monitor for polypharmacy
- Determine patient's treatment goals and expectations
- Determine familial and social support systems
- Order appropriate diagnostic tests and laboratory tests as clinically indicated

Modified from Chow WB, Rosenthal RA, Merkow RP, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J Am Coll Surg* 2012;215:453–66.

help identify risks and improve status before surgical intervention. This includes several targeted components in addition to the basic functional assessment with ADLs, IADLs, cognitive status, and mobility that have been previously described (Box 88-1) (Chow et al, 2012). Data obtained from the National Surgical Quality Improvement Program (NSQIP) were used to construct recommendations highlighted in this document.

Chronologic age is usually not identified as an independent risk factor in most research examining morbidity and mortality outcomes from surgery. However, extensive surgical time and poor baseline American Society of Anesthesiologists (ASA) classification status have been linked to worse outcomes in elderly urologic surgical patients (Peled et al, 2009). In addition, compared with elective cases, urgent and emergent surgical procedures have been shown to be associated with greater overall morbidity and mortality among geriatric patients undergoing urologic surgery (Peled et al, 2009).

Nutritional assessment is important for overall health and wound healing. One problem is that no single measure has proven adequate for complete preoperative assessment (Griebing, 2004). Different questionnaires and various biomarkers have been used. Albumin and prealbumin measure protein nutrition and are the most commonly used serum markers. Data on preoperative nutrition supplementation in geriatric patients have been variable (Evans et al, 2014). One question is whether improved nutrition can help contribute to pressure ulcer prevention (Hill-Brown, 2011). Although nutrition is a contributor to this condition, other factors such as tissue pressure and shear forces may play a stronger role. Good nutrition does appear to influence wound healing (Rosenthal, 2004; Jaul, 2010). Postoperative wound infections are a common and often preventable complication of surgery in older adults. They tend to increase both length of hospital stay and associated costs. Elderly surgical patients who experience a surgical site infection have been found to have a 3.5-times greater risk of mortality than those who do not develop this type of infection (Kaye et al, 2009). The Centers for Medicare and Medicaid Services (CMS) have included surgical site infections as one of the “never events” for which hospitals will not be reimbursed. Diminished functional status has been shown to be associated with an increased risk of

surgical wound infections (Chen et al, 2010). This is likely because of a reduction in overall functional reserve capacity, which is associated with changes in immunity and other organ system response.

Postoperative urinary retention is another very common problem that occurs frequently in geriatric patients. A wide variety of factors can increase the risk for postoperative urinary retention, including medication effects, opioid narcotics, decreased mobility, delirium, cognitive impairment, and a history of preexisting lower urinary tract anatomic and functional issues. Correction of the underlying cause will often lead to resolution of the problem, and time is an important factor in many cases (Darrah et al, 2009; Johansson and Christensson, 2010).

Anesthesia

Anesthetic considerations are important in planning for surgical interventions in geriatric urologic patients. Patients often ask if regional anesthesia would be a safer alternative than general anesthesia. Most studies to date have not shown significant differences in either morbidity or mortality among older adults undergoing surgery using regional blocks versus general anesthesia (Mason et al, 2010; Tognoni et al, 2011).

Other important anesthetic considerations include thermoregulation during surgery, fluid balance, and patient positioning. **Hypothermia during noncardiac surgery increases risk for cardiovascular and thromboembolic events** including myocardial infarction, deep vein thrombosis, and stroke. Intraoperative hypothermia has also been associated with risk of postoperative wound infection (Leeds et al, 2014). Maintenance of appropriate intraoperative patient temperatures has been identified as an essential goal and is one of the variables that is tracked for quality of hospital care in the United States. Proper fluid balance is also important, and care must be taken to avoid fluid overadministration, which can induce pulmonary edema or congestive heart failure (CHF) in older adults. Patient positioning requires careful attention to padding pressure points to prevent neuropathy, and adjusting to limitations in joint flexibility in patients with arthritis (Rozet and Valilala, 2007; Akhavan et al, 2010). Positioning patients awake before induction of anesthesia can be useful in these circumstances to prevent injury.

Cognitive changes are frequently seen immediately after anesthesia in geriatric patients. Reported rates can be as high as 56%, with 25% still having some change compared with baseline at 3 months after general anesthesia (Price et al, 2008). Although this usually resolves, in some cases cognitive changes can be more prolonged. Among older adults undergoing noncardiac surgery, advancing age, history of stroke, and lower baseline educational levels have all been associated with postoperative cognitive decline (Monk et al, 2008).

Prehabilitation

Recent research has examined the potential usefulness of preoperative conditioning and strength-building exercise in older adults. Termed *prehabilitation*, these efforts focus on improving overall conditioning, stamina, and endurance for activity. This may help to improve or at least slow the decline in functional reserve capacity. Nutritional interventions typically focus on improving protein reserves before surgical intervention. **General assessments or “eyeballing” the patient to determine level of frailty may not be adequate, and more precise measures are useful for preoperative evaluation of risk** (Hubbard and Story, 2014). Preoperative interventions have shown mixed results, and additional research will be necessary to identify optimal targets for intervention and appropriate candidates for these types of treatments.

Comprehensive Geriatric Assessment

Comprehensive geriatric assessment (CGA) is a structured method of complete health care analysis for older adults. This type of evaluation is usually conducted by a geriatrician who specializes in the primary care of older adults in conjunction with other

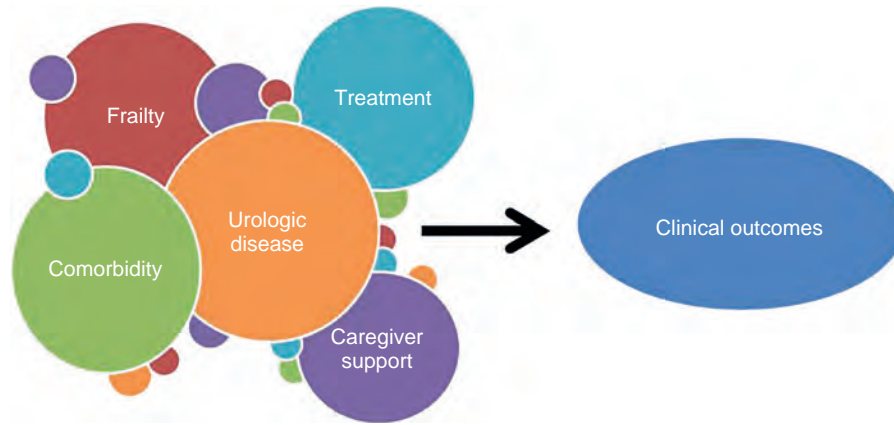


Figure 88-4. Conceptual model of health complexity and clinical outcomes in geriatrics. This schematic highlights the interrelated nature of urologic disease, comorbidity, frailty, treatment, caregiver support, and other variables. Note that these are related and influence one another but are distinct entities that do not completely overlap. Numerous other factors can contribute to and interact with these variables to influence overall clinical outcomes.

multidisciplinary health care providers including nurses, pharmacists, social workers, physical and occupational therapists, and others. Some primary care practitioners may offer CGA as part of their clinical care for geriatric patients. **Consultation and partnering with a geriatrician** in care of older adults with complex medical problems can help facilitate what can sometimes be a complex process. Similarly, **working with anesthesiology colleagues** for preoperative assessment can help to clarify clinical needs and choices of anesthetic technique in an attempt to optimize care.

There is great interest in the role of expanded assessment of geriatric patients undergoing major surgery and influence on subsequent outcomes. One study of 62 elderly women undergoing pelvic floor reconstructive surgery showed no statistically significant difference in multiple outcomes between those randomized to an enhanced CGA and those who underwent routine preoperative evaluation (Richter et al, 2005). However, the researchers noted that this may have been a result of the overall high functional and health status of women in this study. Studies with frailer and more functionally impaired older adults may yield different results. Information gleaned from CGA has been shown to be predictive of both morbidity and mortality risk after surgery (Kim et al, 2013). Geriatric patients undergoing radical cystectomy have been found to have increased complications and length of hospital stay related to underlying comorbidity and functional limitations that can be identified on careful preoperative assessment (Prentis et al, 2013). Additional research on this topic will help to elucidate the most important factors that should be included in these types of evaluations to help optimize outcomes in geriatric surgical patients.

MAJOR GERIATRIC SYNDROMES AND UROLOGY

Geriatric syndromes are defined as conditions that are complex in nature, tend to occur more commonly among older adults, are typically multifactorial, and can have substantial clinical or other outcomes for affected patients. Successful prevention or treatment often requires a multicomponent approach. Examples of geriatric syndromes include frailty, falls, pressure ulcers, polypharmacy, delirium, and UI. Different syndromes can interact and influence one another. For example, frailty is linked to falls, and both conditions are closely associated with UI. Each of these syndromes can have direct and indirect effects on urologic health in older adults (McRae et al, 2014). Data from the Health and Retirement Study on more than 11,000 older adults living in the community and nursing homes demonstrated that 49.9% had at least one geriatric syn-

drome, and presence of multiple geriatric syndromes was common (Cigolle et al, 2007). Geriatric syndromes strongly increased risk of dependency on others for completion of ADLs even after controlling for demographic factors and chronic diseases. One geriatric syndrome led to an adjusted risk ratio of 2.1 (95% confidence interval [CI] 1.9 to 2.4); for two syndromes this increased to 3.6 (95% CI 3.1 to 4.1), and for three or more syndromes to 5.6 (95% CI 5.6 to 7.6). In a cross-sectional analysis of 12,480 older adults, prevalence of geriatric syndromes among those with cancer was 60.3% compared with 53.2% in those without a history of cancer ($P < .001$) (Mohile et al, 2011). This highlights the complexity of these conditions and overlap with other health issues associated with aging.

Frailty

Frailty is a complex condition frequently seen in elderly patients that is becoming better understood with ongoing research. It is not age dependent and can also occur in younger people, although incidence and prevalence both increase with advancing age. **It overlaps with but is not completely identical to the concepts of comorbidity or disability (Fig. 88-4).** *Comorbidity* refers to presence of other health states or conditions. Examples would include diabetes or hypertension. *Disability* refers to need for assistance from others to accomplish various tasks. An example would be the need to have someone help with bathing, dressing, or using the toilet. Potential relationships between preoperative frailty and postoperative outcomes have recently garnered increased research attention (Revenig et al, 2013).

Several different definitions and conceptual models of frailty exist, and these differ somewhat based on theoretic components they include. One causation theory is an accumulated deficits model. In this conceptual framework, multisystem deterioration is combined with reduced functional reserve capacity. Accumulated deficits can be counted numerically, and increased summative scores indicate a higher degree of frailty. In this model, frailty tends to progress with cyclic deterioration over time and with more added deficits. The Deficit Accumulation Index (DAI) has been used in an attempt to identify preoperative levels of frailty and predict subsequent outcomes (Braden and Bergstrom, 1994; Cohen et al, 2012). However, the DAI was not found to be statistically predictive of outcomes in this study. This indicates that a simple numerical scoring of deficits may not be adequate, and interactions among components are more complex.

Although different operational definitions of frailty have been proposed, one of the more commonly used is the conceptual model

developed by Fried and colleagues, which includes measureable changes for five different components (Fried et al, 2001). This frailty phenotype includes unintentional weight loss of more than 10 pounds or more than 5% of total body weight in 1 year, reduced grip strength, slowing of gait speed and mobility, decreased overall levels of activity, and a sense of easy exhaustion with activity. Individuals with three or more components are considered “frail,” those with one or two components are classified as “pre-frail,” and those with none of the components are “non-frail.”

The predictive value of frailty assessment in older urologic patients, particularly those being considered for surgery, has been the subject of recent research. Frailty evaluation can be accomplished relatively easily in outpatient clinical settings, and results can be predictive of both morbidity and mortality outcomes in elderly surgical patients (Ravaglia et al, 2008; Makary et al, 2010; Kim et al, 2014a). Data derived from electronic medical records can be used, although these may not provide complete information in all cases (Amrock et al, 2014). Inclusion of cognitive changes in addition to physical assessment has been shown to improve predictive value for clinical outcomes among hospitalized older adults (Wou et al, 2013).

Translational research studies have attempted to identify a relationship between various inflammatory biomarkers and the frailty phenotype. Increased levels of interleukin-6 (IL-6), D-dimer, C-reactive protein, white blood cell count, and others have been described in correlation with increased frailty (Chang et al, 2012c; Fontana et al, 2013). There is some debate over whether low levels of inflammatory response may actually be beneficial, particularly for wound healing, but that higher levels may be destructive because of oxidative stress.

Falls

Older adults are at an increased risk for falls and associated injuries including long bone and hip fractures. UI and use of indwelling urinary catheters have both been identified as risk factors for potentially injurious falls (Brown et al, 2000; Chiarelli et al, 2009; Foley et al, 2012). Similarly, LUTS including OAB have been shown to increase fall risk in community-dwelling older adults and those requiring home care services (Hunter et al, 2013; Kurita et al, 2013). In long-term care facilities, UI and behavioral changes associated with cognitive decline and dementia have been identified as independent risk factors for falls in older adults (Hasegawa et al, 2010). Nocturia can also play a role (Galizia et al, 2012). Contributing clinical and environmental factors include orthostatic or postural hypotension, vertigo, gait and balance problems, poor lighting, physical obstacles, or long distance between the bed and toilet. Urinary urgency is a common risk factor for falls as a result of nocturia or urgency UI. When older adults attempt to rush to the toilet, fall risks increase. Slipping on wet floors caused by urine leakage can also occur. Additional identified risk factors for falls include visual and other sensory impairments, alterations in cognitive status, and delirium.

Urinary catheters have been shown to increase risk of falls in older adults. Similarly, other **physical restraints** have been associated not only with increased falls but other potentially dangerous injuries including strangulation and accidental death. **Physical restraints should be avoided if at all possible**, and efforts targeted at reducing their use have been quite beneficial in nursing home and other care settings. Other interventions designed to improve overall care in long-term care facilities have also been shown to improve outcomes and decrease risk of falls associated with UI in this setting (Min et al, 2011).

Elderly men on androgen deprivation therapy (ADT) are at particularly increased risk for fractures and other injuries associated with falls (Bylow et al, 2008). Hormonal manipulation with androgen deprivation is associated with decreases in bone mineral density and an increased risk of development of osteopenia and osteoporosis. This causes bones to be more brittle and increases risk of fracture during falls. Elderly men with associated LUTS resulting from BPH or other conditions have been shown to have higher rates

of falls and fractures than men without these urologic conditions (Parsons et al, 2009).

Pressure Ulcers

Pressure ulcers are areas of localized tissue necrosis that typically occur over bony prominences as a result of prolonged pressure against a hard surface. Tissue shearing can also occur with movement and transfers. Changes in skin anatomy and integrity occur as a part of the general aging process, with a decrease in the amount of elastic tissue and alterations in collagen and other connective tissue quality. In addition, older adults often have decreased sensation in cutaneous tissues and may be prone to increased rates of underlying skin infections. These factors all increase the risk of pressure ulcer formation in older adults. **UI is another common factor that increases pressure ulcer risk in older adults.** Maceration of tissues from chronic moisture can lead to progressive tissue loss, particularly when combined with physical pressure or shearing forces.

Positioning and transfers during surgery in older adults are especially important. Care must be taken to adequately pad all pressure points during surgery, and efforts made to eliminate shearing effects during transfers between beds and transport carts. Many older adults have arthritis, and this can make positioning for surgery challenging, particularly in the dorsal lithotomy position. In these cases, positioning the patient while awake before induction of anesthesia can be quite useful to help confirm a comfortable position and prevent injury.

Early mobilization and physical activity after surgery are important for many reasons, including reducing the risk of pneumonia, deep vein thrombosis, pulmonary embolus, and pressure ulcers. Even among healthy younger people, extended bed rest is associated with substantial loss of mobility, aerobic capacity, and lower extremity strength (Kortebein et al, 2008). These negative effects are compounded in older adults, who may start at diminished baseline functional levels. Frequent turning of patients who are in bed or using a wheelchair is another important prevention method. Use of specialized air mattresses or other pressure reduction methods also helps reduce risk.

Pressure ulcers are staged based on clinical characteristics. Stage I ulcers include nonblanching erythema of intact skin. Stage II ulcers include partial thickness skin loss but do not involve muscle or other deeper tissues. These can appear as an abrasion, blister, or shallow crater. Stage III ulcers involve full-thickness skin loss that may extend to but not through the underlying fascia. Stage IV ulcers are characterized by extension into deeper tissues, including muscle or bone, with possible exposure of supporting structures such as tendons.

It is important to carefully document skin integrity in older adults being admitted to hospital care. CMS has designated new pressure ulcer formation as one of the “never events” that is considered preventable in essentially all cases. Accordingly, they will not reimburse facilities or providers for care for new pressure ulcers.

The prevalence of pressure ulcers among hospitalized elderly patients has been reported to be as high as 8.9% (Barrois et al, 2008). **Urinary, fecal, and dual incontinence have been identified among the strongest risk factors for the development of pressure ulcers in the elderly population.** Clinicians should have a high index of suspicion for the risk of pressure ulcers, and careful examination should be performed as part of the routine physical examination in older adults with bladder and bowel incontinence. Among hospitalized older adults, increased length of time waiting in the emergency room, immobilizing procedures or medications, and intensive care unit stays have all been identified to increase the risk of developing pressure ulcers (Baumgarten et al, 2008).

Polypharmacy and Medication Optimization

Polypharmacy is a highly prevalent and complex geriatric syndrome that has been defined in a number of different ways. The simplest definition is the use of multiple medications. More recent

definitions include the concepts of increased regimen complexity and use of potentially inappropriate medications (PIMs). More complex medical regimens may be difficult for older adults to follow correctly and can lead to poorer compliance with prescribed therapy. Risk of drug interactions increases exponentially with increased numbers of medications. Use of inappropriate medications can lead to untoward side effects and other negative outcomes (O'Connor et al, 2012). Rates of PIM prescription among older adults are high, with approximately 25% of more than 272,000 patients in one study being on PIMs in the perioperative period (Finlayson et al, 2011). The ultimate goal is to optimize pharmacotherapy and minimize risk in older adults using medications. **The practice of medication reconciliation during hospitalization and clinical evaluation has become a common practice and is an important step in helping to reduce or eliminate polypharmacy in geriatric patients.** During this process, all medications including prescription and nonprescription medications are assessed. Clinical indications for each medicine are verified, and response determined. Ideally, medications without a clear clinical indication should be discontinued. PIMs should also be identified, and safer agents substituted if possible. In addition, medication underuse can occur with elderly patients, and it is important to recognize when medications might be clinically indicated based on guidelines or other evidence-based practice.

In 1993, the late Dr. Mark Beers convened a consensus panel to develop a listing of potentially inappropriate medications for use in older adults in nursing home settings. This original listing has been updated and expanded over time to include all older adults and is no longer limited by location or type of clinical care. **The AGS has recently published a revised version of the Beers Criteria (AGS Beers Criteria Update Expert Panel, 2012).** This is a highly evidence-based document that categorizes medications into different groups based on characteristics and considerations for use in older adults. The most recent version includes information on level of evidence used to make recommendations, and overall strength of the recommendation from the expert panel. The plan is that this document will be regularly updated as new data on medications become available.

Some medications are considered always inappropriate for elderly patients and should be avoided in all cases. An example of such a medication often used in urologic practice is meperidine (Demerol). This drug was included because of the significant potential risks for delirium and other adverse events caused by accumulation of a toxic metabolite, poor overall efficacy, and availability of other more clinically useful alternatives. Other urologic medications are included in portions of the AGS Beers Criteria document. For example, antimuscarinic agents used in treatment of OAB and

urgency UI are included in a group of medications to avoid with specific comorbid conditions; these medications should be avoided or used with caution in older adults with a history of chronic constipation or cognitive impairment. Nitrofurantoin is included as a medication to avoid in older adults with impaired renal function (GFR below 60 mL/min) or for chronic prophylaxis because of the potential risk of pulmonary fibrosis. It is acceptable for treatment of acute UTIs and other short-term indications in patients with adequate renal function. A summary of medications commonly used in urologic practice included in the 2012 AGS Beers Criteria is presented in Table 88-1.

Medications with anticholinergic effects deserve special mention. There are a large number of different medications that can have potential anticholinergic effects in older adults. This is in part because of cross-reactivity among different types of receptors located in different organs including salivary gland, bowel, and bladder. Common anticholinergic effects in older adults include dry mouth, constipation, dry eye, and confusion. Several studies have examined the concept of total anticholinergic burden in older adults. Increased anticholinergic burden can worsen underlying cognitive function, memory, and associated comorbid conditions such as Alzheimer disease (Han et al, 2008; Fox et al, 2011a, 2011b). Serum studies have shown that total anticholinergic burden can be measured, although listings of medications must be used in conjunction with this to improve diagnostic accuracy (Lampela et al, 2013). Attempts should be made to reduce or eliminate use of anticholinergics to the greatest extent possible. Reductions in overall anticholinergic burden have been associated with improvements in behavioral and cognitive outcomes in affected elderly patients (Kersten et al, 2013). When these medications are used for a clinically indicated purpose, response should be closely monitored to determine if an appropriate effect is achieved, and the medication discontinued or changed if warranted.

A basic principle for prescribing medications in the geriatric patient population is to "start low and go slow." This refers to the fact that lower medication doses may be effective in older adults compared with younger patients, and that high initial doses can often have adverse effects. Starting with lower doses and gradually increasing medication dosage with time can help to alleviate some of these potential problems. **One caveat that needs to be considered is that medication dose may need to be increased to reach the point of clinical efficacy.** Therefore care should be taken to avoid keeping doses of medications so low that they are not actually effective for symptoms they are prescribed to treat. Dose escalation should be continued until a clinically effective end point, maximum dose for a particular medication, or intolerable side effects are reached.

TABLE 88-1 Select Medications Commonly Used in Urology Included in the 2012 Beers Criteria

MEDICATION	RECOMMENDATION	RATIONALE	QUALITY OF EVIDENCE	STRENGTH OF RECOMMENDATION
α_1 -Blockers <ul style="list-style-type: none"> • Doxazosin • Prazosin • Terazosin 	Avoid use as an antihypertensive (all patients) Avoid use in women with stress UI	Not recommended as routine treatment for hypertension; alternative agents have superior risk-benefit profile; high risk of orthostatic hypotension; may aggravate stress UI in women.	Moderate	Strong
Nitrofurantoin	Avoid for long-term suppression Avoid in patients with CrCl below 60 mL/min	Safer alternatives available; potential for pulmonary toxicity; lack of efficacy in patients with CrCl below 60 mL/min because of inadequate drug concentration in urine.	Moderate	Strong

Continued

TABLE 88-1 Select Medications Commonly Used in Urology Included in the 2012 Beers Criteria—cont'd

MEDICATION	RECOMMENDATION	RATIONALE	QUALITY OF EVIDENCE	STRENGTH OF RECOMMENDATION
Tertiary tricyclic antidepressants, alone or in combination <ul style="list-style-type: none"> Amitriptyline Imipramine 	Avoid	Highly anticholinergic and sedating and cause orthostatic hypotension.	High	Strong
First-generation antihistamines (as single agent or as part of combination products) <ul style="list-style-type: none"> Diphenhydramine (oral) Hydroxyzine Promethazine 	Avoid	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as a hypnotic; anticholinergic effects and toxicity. Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate.	High: hydroxyzine and promethazine Moderate: diphenhydramine	Strong
Androgens <ul style="list-style-type: none"> Methyltestosterone Testosterone 	Avoid unless indicated for moderate to severe hypogonadism	Potential for cardiac problems and contraindicated in men with prostate cancer.	Moderate	Weak
Estrogens with or without progestins	Avoid oral or topical patch; topical vaginal cream acceptable use for management of dyspareunia, lower urinary tract infections, and other vaginal symptoms	Evidence of carcinogenic potential (breast and endometrium) and aggravation of UI for oral or transdermal; lack of cardioprotective effect and cognition protection in older women. Evidence that vaginal estrogens for treatment of vaginal dryness are safe and effective in women with breast cancer, especially at doses of estradiol below 25 µg twice weekly.	High: oral and patch Moderate: topical	Strong: oral and patch Weak: topical
Anticholinergics Benzodiazepines Meperidine	Avoid in patients with or at high risk of delirium	Can induce or worsen delirium.	Moderate	Strong
Anticholinergics Benzodiazepines	Avoid in patients with dementia or cognitive impairment	Can cause adverse central nervous system side effects.	High	Strong
Meperidine	Avoid as an analgesic	Not an effective oral analgesic in commonly used doses; may cause neurotoxicity; safer alternatives available.	High	Strong
Oral antimuscarinics for UI <ul style="list-style-type: none"> Darifenacin Fesoterodine Oxybutynin (oral) Solifenacin Tolterodine Trospium 	Avoid in patients with chronic constipation (unless no other alternatives are available)	Can worsen constipation; antimuscarinics overall differ in incidence of constipation; response variable; consider alternative agent if constipation develops.	High	Weak
Inhaled anticholinergic agents	Avoid in men with LUTS and/or BPH	May decrease urinary flow and cause urinary retention.	Moderate	Strong

Note: This is *not* a complete listing of all medications included in the 2012 Beers Criteria.

BPH, benign prostatic hyperplasia; CrCl, creatinine clearance; LUTS, lower urinary tract symptoms; UI, urinary incontinence.

Modified from American Geriatrics Society (AGS) Beers Criteria Update Expert Panel: American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Amer Geriatr Soc 2012;60:616–31. Please see this citation for detailed information.

It is also important for clinicians to avoid the “prescribing cascade.” In this situation a patient is prescribed a medication for a clinical problem. Because of side effects from this medication, the patient develops new symptoms that are attributed to a different cause, leading to prescription of a second medication to treat the side effects. To avoid this problem, clinicians should consider whether a new symptom might be the result of a medication side effect rather than another cause. The American Geriatrics Society has included the concept that a medication review should be performed any time a new prescription is given as part of their Choosing Wisely list (AGS Choosing Wisely Workgroup, 2014).

Delirium

Delirium is an extremely important geriatric syndrome to consider in older urologic patients. Delirium is defined as an acute confusional state characterized by fluctuations in mental status and inattention. In addition, patients must exhibit either disorganized thinking or an altered level of consciousness. This most commonly manifests in the form of agitation; however, a hypoactive form can also occur. Patients may experience hallucinations or delusions. These symptoms can be quite disturbing to patients, loved ones, and clinical care providers. Agitated patients tend to act out physically or emotionally, and the behavior can usually be easily recognized. The hypoactive form of delirium can be much more subtle and difficult to diagnose. However, there are data to suggest that hypoactive delirium actually may be more dangerous in terms of negative sequelae including risk for mortality (DeCrane et al, 2011).

Delirium is highly prevalent and is associated with substantial negative outcomes. However, the condition is often under-recognized in this population (Vollmer et al, 2010). Rates of developing postoperative delirium range from 10% to 15% after noncardiac surgery and increase in cases of either urgent or emergency surgical procedures (Demeure et al, 2006). Patients who develop delirium postoperatively have a twofold to threefold increase in the risk of mortality within the first year after surgery (McCusker et al, 2002; Ely et al, 2004). There is also an increased risk of progressive cognitive decline and potential need for placement in nursing home care at the time of hospital discharge in patients who develop an episode of delirium (Rudolph et al, 2008; Popejoy et al, 2013).

There are multiple risk factors for development of delirium in geriatric patients. Examples include electrolyte abnormalities, pain, sensory impairment, immobility, dehydration, sleep deprivation, pneumonia or other infections, and alcohol withdrawal. Having had a prior episode of delirium is also a strong risk factor for future delirium. Patients with underlying dementia are also at higher risk. Acute UTIs in older adults may be a cause for delirium, and urinary samples including cultures should be checked as part of the evaluation if this is suspected (Eriksson et al, 2010). In a study of urologic surgical patients, poorer baseline functional status and older age were identified as risk factors for delirium, but type of anesthesia (regional vs. general) and mode of surgery (open vs. endoscopic) were not (Tognoni et al, 2011). Some medications, including statins, have been identified as another potential risk factor in surgical patients (Redelmeier et al, 2008).

Inouye and colleagues developed and validated the Confusion Assessment Method (CAM) as a way to identify and diagnose delirium (Inouye et al, 1990). These diagnostic criteria require that patients exhibit an acute change in mental status with a fluctuating course and inattention. In addition, they must also exhibit either disorganized thinking or an altered level of consciousness. The CAM has been used in numerous clinical settings and has been shown to be easy to use and interpret. Using these criteria, delirium can be diagnosed with 94% to 100% sensitivity and 90% to 95% specificity (Inouye, 2006).

Several studies have examined the effects of delirium on clinical outcomes in older adults including those developing the condition after surgery. In one study of 49 geriatric patients undergoing radical cystectomy, the incidence of postoperative delirium was 29%, and readmission and reoperation rates were both higher in those who

developed delirium compared with those who did not (Large et al, 2013).

Prevention of delirium is key, and clinicians should have a high index of suspicion for diagnosis in patients who exhibit signs or symptoms of the condition. Some medications are known to substantially increase risk of delirium in older adults, including sedative hypnotics, anticholinergics, and opioid narcotics. Care must be taken to control pain but also to avoid inducing delirium caused by medications. Pain itself is a risk factor for development of delirium, and this must be carefully assessed and managed. In patients with underlying cognitive impairment such as dementia, pain can be difficult to assess accurately (Horgas et al, 2009). Patient-controlled analgesia (PCA) offers the potential benefit of avoiding overdosage of medication, provided only the patient is pushing the administration button on the device. However, proper use of PCA requires a cognitively intact patient who understands the therapy and is able to self-administer medication when needed to control pain.

Treatment for delirium includes methods to reduce disruption and improve sensory interaction with the patient and his or her surroundings. This includes maintaining proper sleep-wake cycles, minimizing distractions including alarms and other loud noises, having family or other loved ones at the bedside to help reorient the patient, making sure a patient's hearing aids and glasses are provided, and assisting with mobility. Underlying fluid and electrolyte imbalances should be corrected. In patients who present a physical danger to themselves or care workers, temporary physical or chemical restraint may be necessary. **The preferred medication treatment is haloperidol administered intravenously in small doses, usually starting at 0.25 or 0.5 mg.** Doses may be repeated at approximately 15-minute intervals until the patient is calm. A total dose of 1 to 2 mg or more may be required, but it is safer to administer this in progressive small quantities and monitor for response rather than giving a large bolus dose, which could be too sedating. Other benzodiazepines or sedative hypnotics should be avoided in general because of potential adverse effects including worsening of delirium, severe sedation, or an increase in associated delusions or hallucinations. Physical restraints should be used only with extreme caution and for short time periods and are indicated only if the patient is in imminent danger of harming himself or herself or others.

Costs associated with postoperative delirium in geriatric surgical patients are quite high. Development of delirium, even subsyndromal delirium, is associated with increased rates of hospital readmission, reoperation, caregiver requirements, and need for institutionalization (Cole et al, 2008; Large et al, 2013). Economic analysis has shown an approximately 2.5-fold increase in costs for elderly patients who experience an episode of delirium while in the hospital compared with those who do not develop delirium (Leslie et al, 2008).

Urinary Incontinence

The International Continence Society (ICS) defines *urinary incontinence* as the involuntary loss of urine (Abrams et al, 2002). **From a clinical perspective, UI can be considered both a specific diagnosis and a geriatric syndrome.** This is particularly true among frail older adults, who may have multiple chronic conditions and geriatric syndromes (Fonda et al, 2005; DuBeau et al, 2010; Wagg et al, 2013b). Urologists and gynecologists tend to view UI as a clinical diagnosis, in contrast to geriatricians who conceptualize it more as a geriatric syndrome. As previously described, geriatric syndromes are defined as common conditions seen in older adults that are complex in nature, are usually multifactorial, and can have substantial clinical or other negative health outcomes for affected patients.

The incidence and prevalence of UI both increase in older adults. However, incontinence should not be considered a normal or inevitable part of the aging process. Just because someone is elderly or frail does not mean that they should experience UI. This is a common myth among both health care providers and patients that

needs to be dispelled. UI is more commonly associated with underlying medical conditions or other factors rather than chronologic age itself.

Negative Impacts of Urinary Incontinence

UI can have substantial negative health outcomes in older adults (Dugan et al, 2000). The condition is associated with social isolation, depression, stigmatization, and embarrassment for many affected patients. Many people discontinue activities that they enjoy because of urinary leakage. They may stop going out to the theater or to movies, stop attending church or temple, or stop visiting friends because of the condition. Incontinence can also have important negative physical effects. Chronic incontinence can be associated with skin irritation and breakdown, development or worsening of pressure ulcers, UTIs, and falls and fractures. UI also has effects on mental health, including increased rates of depression among affected older adults (Laganà et al, 2014). Research has shown that UI has a stronger negative influence on overall levels of happiness than many other common chronic conditions in older adults, including diabetes, hypertension, arthritis, and osteoporosis (Angner et al, 2009). Only chronic debilitating pain has been shown to be a stronger negative predictor of diminished happiness.

Costs of Incontinence

The direct and indirect financial costs of UI are staggering. Medicare expenditure data showed that costs of care for UI nearly doubled from \$128 million in 1992 to \$234 million in 1998 (Anger et al, 2006). This represents a 15% per capita increase in treatment costs once adjusted for inflation. Other economic analysis has shown an estimated national cost of evaluation and care for OAB with urgency UI of \$65.9 billion in 2007 with projected increases to \$76.2 billion in 2015 and \$82.6 in 2020 (Coyne et al, 2014). It must be noted that this includes care for patients of all ages, not just older adults. Recent analysis has shown increasing rates of office visits, hospitalization, and other resource utilization for UI, which also tend to drive up associated costs (Thom et al, 2005). The estimated annualized cost in 2000 for nursing home admissions as a result of UI was \$6.0 billion (Morrison and Levy, 2006). In addition, there are substantial environmental costs associated with use of absorbent pads and products going into landfills.

UI can have substantial negative effects on both general and health-related QoL in older adults. It limits the ability of people to participate in leisure activities and engage with others in the community (Kwong et al, 2010). Many older adults will stop participating in activities they enjoy owing to fear or embarrassment about urinary leakage. The associated psychosocial effects can be substantial and include problems with depression and social isolation (Pintarelli et al, 2011; Chung et al, 2013; Lee et al, 2013b; Yip et al, 2013; Sahin-Onat et al, 2014). Depression can be particularly problematic among older adults and can cause issues in other facets of life including mental health domains, nutrition and eating, sleep quality, and happiness (Angner et al, 2009; Sexton et al, 2011).

UI can cause significant psychological distress for elderly patients, often because of their reduction in other activities (deVries et al, 2012). Many older adults require assistance with toileting and other ADLs. Levels of caregiver burden can also be substantially higher among those with associated UI, particularly if other ADL impairments are present (Gotoh et al, 2009; Miu et al, 2010; Tamanini et al, 2011). The type of UI may influence outcomes related to QoL, particularly for those with mixed symptoms (Frick et al, 2009). However, other epidemiologic studies in older adults have shown that the degree of incontinence as measured by severity appears to be more influential on health-related QoL outcomes than type of UI (Aguilar-Navarro et al, 2012; Barentsen et al, 2012).

Among older adults living in nursing homes, UI has been shown to have negative impact on a number of important QoL parameters including dignity, autonomy, and mood (Xu and Kane, 2013). Successful treatment of UI has been shown to substantially improve health-related QoL outcomes (Fonda et al, 1995).

Transient Urinary Incontinence

UI in older adults is frequently transient in nature. In fact, studies indicate that up to 30% of UI in community-dwelling older adults and nearly 50% of UI in elderly patients admitted to acute care hospitals may be caused by transient conditions (Resnick et al, 1988; Herzog and Fultz, 1990). The identification of transient incontinence among elderly patients is important because it highlights the interplay between various organ systems and genitourinary function. For example, if a patient develops worsening peripheral edema because of an exacerbation of CHF, this could increase nocturnal urinary production and associated nocturia or nocturnal enuresis. Similarly, temporary mobility impairment from lower extremity cellulitis in a patient with detrusor overactivity (DO) and urinary urgency may lead to development of urgency UI. Although no direct changes occurred in bladder function in either example, changes in fluid volume or mobility status led to urinary leakage. Treatment of underlying causative conditions could result in improvement or complete resolution of UI. Prospective evaluation and treatment for these conditions in elderly patients have been shown to be effective (Resnick, 1989).

A wide variety of conditions can lead to associated transient UI. Patients with sudden or new onset of UI symptoms should be screened for possible associated causative conditions. However, even patients with longstanding UI can be affected if these underlying conditions have been present but untreated over time. Multiple causes are frequently involved in geriatric patients.

Detailed information on specific causes of transient UI in older adults is included on the Expert Consult website.



Established Urinary Incontinence

Established or chronic UI is an extremely common problem in geriatric patients. Recent epidemiologic data show that of all people over 65 years of age, 43.8% report a history of any urinary leakage (Gorina et al, 2014). Among community-dwelling elderly women, 12% report severe or very severe UI. More than half of community-dwelling women and about a quarter of men report experiencing UI. Overall, 36.6% of those in residential care facilities, not including nursing homes, experienced UI, and women were 1.2 times as likely to report this as men (95% CI 1.03 to 1.4). Similarly, of those older adults receiving home care services, 40.2% reported problems with bladder control, and women were 1.7 times more likely to experience this than men (95% CI 1.3 to 2.1) (Gorina et al, 2014). **Types of Established Urinary Incontinence.** The major categories of established UI in older adults are similar to those in younger people, although there are some important clinical caveats that must be noted (Diokno, 1990).

Urge UI is the most common form of established incontinence among elderly people. This is typically associated with symptoms of urinary urgency and frequency. DO is often seen on urodynamic evaluation and is a common cause among older adults (Griebling, 2013b). The ICS defines *urge incontinence* as the complaint of involuntary leakage accompanied by or immediately preceded by urgency and *detrusor overactivity* as a urodynamic observation characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked (Abrams et al, 2002). Although the exact cause of DO is unclear, a number of different theories and mechanisms associated with aging have been explored. These include bladder and pelvic organ ischemia, free radical release and tissue damage from oxidative stress, inflammatory effects, changes in both central and peripheral neural control, and cellular dysfunction (Smith, 2010; Young et al, 2013; Chancellor, 2014; Tyagi et al, 2014a).

Normal urine storage and voiding are complex processes that require synchronous interaction between the bladder and peripheral and central nervous systems. Interaction between brain activity and bladder function in older adults has been the subject of research interest (Griffiths et al, 2005, 2007). Studies have used both static and functional magnetic resonance imaging (MRI), sometimes done in conjunction with urodynamic studies, to assess these

UTI causes an inflammatory reaction in the urothelium, which can lead to increased sensations of bladder filling. This causes urinary frequency and in some cases urinary UI. This should be considered symptomatic and should be evaluated and treated appropriately. In contrast, true asymptomatic bacteriuria does not by itself cause UI and does not require antibiotic therapy. Atrophic vaginitis or urethritis is common in elderly women and may be associated with dysuria or a burning sensation with voiding. Physical examination reveals thinning and loss of rugation of vaginal mucosa, although inflammatory changes with erythema and mucosal hemorrhage may also be seen in a minority of patients. In elderly women who are sexually active, atrophic vaginitis can lead to dyspareunia. Treatment with vaginal estrogens can help ameliorate symptoms of this condition and may help improve continence status in affected individuals. It also helps reduce incidence of symptomatic UTIs in postmenopausal women (Goldstein et al, 2013).

Fecal impaction is frequently seen in older adults. This can be caused by slow transit time through the gut or increased water reuptake in the colon. Fecal incontinence (FI) and diarrhea may be presenting symptoms because liquid stool proximal to the impaction moves around the impacted stool bolus. Disimpaction often results in resolution of both urinary and fecal symptoms. Chronic constipation is a common problem in older adults. Treatment and prevention with a bowel regimen can help. This typically involves multiple modalities including stool softeners, an increase in dietary or supplemental fiber, increased fluid intake, and judicious use of products such as polyethylene glycol (MiraLax) (Schnelle et al, 2010).

Numerous different medications can cause transient incontinence in older adults including psychotropics, diuretics, benzodiazepines, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, tricyclic antidepressants, methylxanthines, α -blockers, narcotic analgesics, and others (Landi et al, 2002; Tsakiris et al, 2008; Kashyap et al, 2013). Polypharmacy is a common problem in older adults that has also been linked to increased risk of UI (Talas and Lechleitner, 2012). Diuretics are commonly prescribed for treatment of hypertension or peripheral edema but cause an increase in urinary production that can overwhelm the bladder and cause urinary urgency, frequency, and urgency UI (Peron et al, 2012). If taken at night, diuretics can potentially induce nocturia and nocturnal enuresis. ACE inhibitors, also used to treat hypertension, can induce cough and worsen stress UI, particularly in older women. Combinations of these medications for treatment of hypertension have been shown to have synergistic effects in worsening UI in older adults (Peron et al, 2012). Opioids and narcotic analgesics tend to decrease detrusor contractility and can cause urinary retention with associated incontinence. Cholinesterase inhibitors prescribed to help slow progression of memory loss in Alzheimer dementia can increase detrusor contractility, leading to symptomatic UI (Hashimoto et al, 2000). Tricyclic antidepressants can exert a strong anticholinergic effect and decrease detrusor contractility, leading to difficulty voiding or urinary retention. The α -adrenergic receptor antagonists cause smooth muscle relaxation and can worsen stress UI, particularly in women.

Data from the Women's Health Initiative study demonstrated that systemic administration of estrogen was actually associated with increased rates of UI (Hendrix et al, 2005). It is one reason that systemic estrogen is usually not encouraged in elderly women. The most recent update of the AGS Beers Criteria also includes a recommendation to avoid systemic estrogens in elderly women because of this increased risk of UI (AGS Beers Criteria Update Expert Panel, 2012). Alcohol and other substance abuse should also be considered as a potential cause of UI. Anticholinergic medica-

tions can worsen UI by exacerbating urinary retention and incomplete bladder emptying. This in turn can lead to greater urinary frequency as the bladder reaches capacity quickly even after voiding. In addition, older adults may have decreased salivary secretions, which can be worsened by anticholinergic medications. Increased fluid intake in response to this dry mouth can worsen incontinence symptoms. Over-the-counter decongestant medications used to treat colds and flu often have strong anticholinergic properties. These can worsen urinary retention, particularly in men with underlying BPH and some degree of BOO.

Psychological or behavioral factors including depression or anxiety can lead to changes in continence status (Steers and Lee, 2001). Successful treatment of underlying psychological issues may help reduce or resolve UI. Similarly, delirium or dementia can cause incontinence as a result of cognitive changes. In delirium, these are typically associated with acute confusion and fluctuation in status and inattention. Dementia tends to be more long-standing and progressive over time but can also be associated with substantial cognitive change and inattention to voiding (Lee et al, 2014). Although dementia may not be reversible, acute delirium is typically treatable and UI may resolve with abatement of acute cognitive changes.

Mobility impairment can cause problems with UI (Kim et al, 2015). This can result from either acute or chronic conditions. Hip and long bone fractures, arthritis, joint deformities, spinal stenosis, and claudication can significantly limit mobility. Other gait and balance problems include disequilibrium, vertigo, orthostatic or other forms of hypotension, generalized deconditioning, and muscle weakness. Visual impairment and other sensory limitations can increase fear of falling and result in reduction of mobility. Stroke often leads to mobility impairment, which may or may not improve with time and rehabilitation.

Normal pressure hydrocephalus is a condition seen more commonly in older than in younger adults. The condition is characterized by a triad of symptoms including ataxic gait, cognitive dysfunction, and UI. Ventriculoperitoneal (VP) shunt placement is the main therapy for normal pressure hydrocephalus and may lead to complete resolution of symptoms, particularly if patients are treated relatively early after onset of symptoms (Akiguchi et al, 2008). Other neurologic disorders can lead to problems with UI in elderly patients. Parkinson disease is often associated with sleep disorders and may increase nocturia (Vaughan et al, 2013). It also increases risk of urinary urgency and DO. UI is particularly common in older adults with Alzheimer disease, Lewy body dementia, and vascular dementia (Sakakibara et al, 2005; Ransmayr et al, 2008).

Excess urinary output, polyuria, can also lead to transient UI. In addition to diuretics, other potential causes include metabolic derangements, CHF, pulmonary edema, venous insufficiency, malnutrition with hypoalbuminemia, diabetes insipidus, syndrome of inappropriate antidiuretic hormone production (SIADH), or excessive fluid intake as a result of psychogenic polydipsia or other factors. Peripheral edema can cause increased urine production when the patient moves to a recumbent position and tissue fluid recirculates, leading to increased urinary production. Affected patients may benefit from elevating their legs above heart level late in the afternoon to off-load some of this excess fluid before retiring to bed, thus reducing nocturia. Numerous medications can also exacerbate the development of peripheral edema including thiazolidinediones or glitazone medications used to treat diabetes, amantadine used to treat Parkinson disease, β -blockers, calcium channel blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs).

relationships (Krhut et al, 2012; Tadic et al, 2012; Morris, 2013). Normative data examining continent younger and elderly women have been obtained using functional MRI scanning during bladder filling and voiding (Griffiths et al, 2009). These include data on both motor and sensory changes in control patients associated with small filling volumes, often associated with urgency in symptomatic patients (Tadic et al, 2013). In contrast to asymptomatic controls, patients with a history of urinary urgency, frequency, and UI tend to have an increase in white matter hyperintensities on brain MRI (Kuchel et al, 2009; Wehrberger et al, 2013). These findings support the hypothesis that alterations in brain anatomy and physiology may play a crucial role in urinary control in older adults. Additional research will help to further elucidate these complex processes and may identify future targets for therapy.

UI is particularly common after stroke. Approximately 70% of stroke survivors will experience problems with bladder control (Marinkovic and Badlani, 2001). Stroke severity is closely linked with development of UI, and those with more severe stroke tend to have more severe incontinence problems. Both ischemic and hemorrhagic stroke can cause subsequent incontinence. Continued UI in those who were previously dry is a marker condition for increased morbidity and mortality after stroke (Patel et al, 2001). Stroke laterality and hemispheric dominance have generally not been found to be associated with differences in UI patterns or severity (Gupta et al, 2009; Kim et al, 2010b). However, brainstem strokes that affect the pontine micturition center tend to cause worse incontinence. DO is the predominant urodynamic finding in patients with poststroke incontinence and is typically associated with urinary urgency, frequency, and urge UI. However, some patients will experience poor detrusor contractions and chronic urinary retention with associated incontinence. Continued UI after stroke is associated with greater levels of functional dependence and higher overall care needs (Mizrahi et al, 2011). Poststroke incontinence has been linked to poorer overall QoL and alterations in sense of well-being (Tibaek et al, 2011). FI is also a common finding in patients with poststroke UI because of overlap in neural control mechanisms (Brittain et al, 2006; Kovindha et al, 2009). Interaction between cognitive and mobility impairment after stroke and associated UI and voiding dysfunction is complex. Among those with mobility impairment, decreased mobility velocity has been linked to worse LUTS severity (Tibaek et al, 2009).

The term *precipitancy* has been used to describe the symptom that occurs with DO in older adults (Resnick, 1990). In patients with no sensation of warning, precipitant leakage may be experienced as an unconscious or reflex episode of incontinence. In contrast, in those with a warning sensation, precipitancy is the abrupt sensation of imminent leakage, regardless of time interval or the amount of urine loss (Resnick, 1990).

DO may exist with or without other comorbid disease. Underlying neurologic disorders such as Parkinson disease, Alzheimer disease, multiple sclerosis, spinal stenosis, or prior stroke tend to be associated with DO and related urinary dysfunction. However, in many cases, no specific cause for DO can be identified. This makes evaluation and targeted treatment of DO in older adults more challenging.

The term *overactive bladder* is used to describe the symptom complex experienced by patients. This includes “urgency, with or without urge incontinence, usually with frequency and nocturia” (Wein and Rovner, 2002). This can be further subdivided into OAB-dry, in which patients experience urinary urgency and frequency symptoms but do not actually leak urine, and OAB-wet, in which urgency UI also occurs.

One form of bladder dysfunction that is unique in the geriatric population is detrusor hyperactivity with impaired contractility (DHIC) (Resnick and Yalla, 1987). In this condition the patient experiences DO with bladder filling, which is associated with the typical symptoms of urinary urgency, frequency, and potentially urgency UI. However, during the voiding effort the bladder does not contract efficiently or with sufficient force to completely empty. In some ways, this represents a functional combination of both OAB and underactive bladder (UAB). Brain imaging studies have shown

hypoperfusion abnormalities that localize to the frontal and global cortical areas and that are often associated with cognitive impairment (Griffiths et al, 2002). In some cases, detrusor contraction strength may actually be increased, particularly in the presence of urge UI. Monotherapy with antimuscarinic medications or other bladder relaxants can worsen urinary retention and promote development of chronic urinary retention with associated incontinence. Successful treatment often requires multimodal therapy including behavioral interventions and medications to inhibit DO and clean intermittent catheterization (CIC) to empty the bladder. Intentional induction of urinary retention with antimuscarinic medications to control hyperactivity, combined with CIC performed on a regular schedule to empty the bladder, can be a successful method for clinical management in some patients. Future research will be needed to help develop more optimal forms of management for this complex condition (Taylor and Kuchel, 2006; Smith et al, 2014b).

Stress UI is common in older people and may occur in both men and women. **In women, stress UI is usually caused by either urethral hypermobility or intrinsic sphincter deficiency (ISD).** Both pelvic floor support and urethral closure pressure tend to decrease with advancing age, and this increases risk of both urethral hypermobility and ISD in elderly women. Urethral atrophy associated with decreased tissue estrogenization and other age-related factors can exacerbate ISD and stress UI in this population. Stress UI in men is often related to prior surgical therapy for either BPH or prostate cancer. Both transurethral resection of the prostate (TURP) and radical prostatectomy have been associated with increased risk of stress UI in men. Enhancements in surgical technique and targeted therapy with pelvic floor muscle exercise (PFME) and other behavioral interventions may potentially reduce overall incidence and prevalence of postprostatectomy UI in older men (Goode et al, 2011; Mirza et al, 2011; Kojima et al, 2013).

Detrusor underactivity, sometimes called underactive bladder, can be caused by a wide variety of conditions. Often the cause is idiopathic, but recent research has led to emerging data on this condition (Griebeling, 2013a; Chancellor, 2014; Griebeling et al, 2014). Poorly controlled diabetes can lead to impairment of bladder contractility and a diabetic cystopathy. Patients can develop impairments in bladder sensation, leading to behavioral changes and a prolongation of the intervoiding interval. This cyclic but chronic bladder overdistention may be associated with subclinical bladder ischemia, which leads to progressive muscle dysfunction. Pelvic atherosclerosis is associated with diminished arterial blood flow to the bladder, which could cause ischemic changes. This in turn can promote development and release of free radicals and accumulation of oxidative stress, causing damage to cells and tissues.

Untreated chronic BOO can lead to detrusor dysfunction and chronic urinary retention in men, although this is less common with early detection and targeted interventions. Anatomic urethral obstruction in women is uncommon and most typically caused by prior urethral trauma. Large POP can cause functional obstruction with urethral kinking or angulation. Many of these women describe having to manually reduce prolapse with a finger in the vagina to void to completion. Use of a pessary or surgical prolapse repair can help treat this type of voiding dysfunction. Iatrogenic urinary retention can occur after surgical therapy for stress UI and may require surgical revision of the prior repair (Anger et al, 2007a, 2007b).

The term *functional incontinence* is sometimes used to describe urinary leakage caused primarily by factors other than the bladder itself. The ICS does not specifically define or recognize this term, but it is commonly used in research and clinical practice. **The most common factors associated with functional incontinence in geriatric patients include mobility limitations and cognitive impairments.** Care must be exercised to consider potentially reversible causes of transient UI other than restricted mobility and cognitive changes because these can coexist in patients felt to have functional incontinence. The identification of a functional component should also not presume that underlying lower urinary tract function is normal. Indeed, older adults with mobility or cognitive impairment and functional incontinence may have other underlying urologic pathology that predisposes them to UI. **Neither cognitive**

impairment nor immobility mean that UI will be an inevitable outcome. In fact, the majority of older adults with both mobility limitation and cognitive impairments are actually continent. In one study of nursing home residents, 17% with severe dementia were continent, and if they were able to transfer between the bed and a chair, half were continent (Resnick et al, 1988). It is also important to consider these functional limitations because although they may not directly cause UI, they can certainly contribute to the condition in otherwise susceptible individuals. Even multiple small improvements in various functional components can substantially improve or resolve UI and associated clinical problems.

Urinary Incontinence Risk Factors Specific to Geriatrics

Several etiologic factors for UI and other forms of voiding dysfunction are unique to older adults and deserve special consideration. **Impairments in functional status, including dependence on others for ADLs, have been closely linked to increased prevalence of UI** (Jenkins and Fultz, 2005; Huang et al, 2007; Khatutsky et al, 2013). Mobility impairment with diminished walking speed and balance may be important contributors to declines in ADL function and risk of UI (Fritel et al, 2013). Alterations in IADLs appear to have less influence on continence status compared with ADLs (Omli et al, 2013). Older adults are more likely to have multiple comorbidities that increase risk of developing UI. These include diabetes, metabolic syndrome, hypertension, and heart disease (Smith et al, 2010; Khatutsky et al, 2013). Risk factors for UI in elderly men and women can differ as a result of multiple factors including anatomic differences, prior medical and surgical history, and lifestyle variables (Tikkinen et al, 2013).

Modifiable risk factors including smoking and alcohol use have been identified as risk factors for UI in geriatric cohort studies (Hirayama et al, 2009; Ikeda et al, 2011). Obesity and overweight are also linked to risk of UI in older adults. This may be a result of increased intra-abdominal pressure and mobility impairments associated with morbid obesity. Both high body mass index (BMI) and increased waist circumference have been associated with UI in elderly patients (Byles et al, 2009; Krause et al, 2010).

Cognitive impairment, particularly after stroke or from underlying dementia, presents a substantial risk for development of UI among older adults (Hatta et al, 2011). Among geriatric patients with dementia living at home, reported prevalence of UI ranges from 1% to 38%, and those with more severe symptoms require more specialized home care services (Drennan et al, 2013). Alzheimer dementia tends to be associated with loss of short-term memory, which can impair ability of affected older adults to recognize sensations associated with a full bladder and need to void, accurately identify the toilet, and be able to adjust clothing or perform other tasks needed to maintain continence. Vascular dementia has been linked to diminished inhibitory control, which may influence continence status (Haruta et al, 2013).

CHF can cause UI for several reasons. Affected patients tend to make more atrial natriuretic peptide, which in turn leads to increased urine production. They also tend to have more problems with peripheral edema, which can increase urine output, particularly at night. **Increased CHF severity has been linked to increased UI severity in clinical studies** (Palmer et al, 2009; Chiu et al, 2012). Diuretics are frequently used in management of CHF, and these can worsen UI as a result of increased urine output. Decreased pulmonary status with reductions in functional lung capacity have been associated with worse UI (Hirayama et al, 2009). Common neurologic disorders in older adults such as Parkinson disease can cause DO and associated urge UI (Araki et al, 2000; Winge and Nielsen, 2012).

The term *aging in place* has been used to describe what is often considered an ideal paradigm in geriatrics. The goal is to help keep older adults living in their own homes as long as possible with as much independence as is feasible. Changes in ADL status including development of UI can be limiting factors in some cases. Older adults with UI and other ADL impairment may have greater needs for home health services compared with continent and more func-

tionally independent elders (Du Moulin et al, 2009). Those living in residential care facilities have also been shown to have increased UI prevalence and care needs compared with community-dwelling older adults (De Gagne et al, 2013). In settings where public health resources are limited, older adults simply may not have access to these types of services (Burti et al, 2012).

Incontinence in the Nursing Home Setting. UI is one of the most common conditions found in older adults living in nursing homes and other long-term care settings. Based on national data, reported prevalence of bladder incontinence is 46.1% for short-term nursing home residents and 75.8% for long-term care residents (Gorina et al, 2014). Similar rates have been observed in other countries, with more than 50% of nursing home residents experiencing chronic incontinence (Jerez-Roig et al, 2014). UI is often considered one of the primary factors that necessitates facility placement among older adults. Using national data, the calculated attributable fraction of nursing home admissions resulting from UI is approximately 0.10 (95% CI 0.08 to 0.13) for men and 0.06 (95% CI 0.05 to 0.09) for women (Thom et al, 1997; Morrison and Levy, 2006). However, **new-onset UI is also a common finding among nursing home residents after admission to care facilities** (Palmer et al, 1991; Ouslander et al, 1993). Efforts have helped to substantially reduce use of indwelling urinary catheters in nursing homes, and most facilities now report relatively low rates of 7.3% among long-term residents and 13.9% in short-term residents (Gorina et al, 2014). Short-term urinary catheters can be quite useful, particularly in older adults with associated clinical problems such as mobility limitation from lower extremity or pelvic fractures. However, even in these circumstances, rates of catheter-associated infections of more than 30% have been reported (Kamdar et al, 2009).

All nursing home residents undergo a comprehensive evaluation, including an assessment of urinary control and continence status, at the time of admission. Additional assessments are performed at least quarterly and more frequently if clinically indicated. Completion of the Minimum Data Set (MDS), a comprehensive multidimensional clinical assessment and documentation tool, is required for every nursing home resident in facilities that receive reimbursement from Medicare and/or Medicaid. It is completed within the first 2 weeks of admission, and at least annually. A short form is completed quarterly and in cases of substantial clinical change. Nursing homes in the United States are under strict regulatory control, and frequent inspections are required. F-Tag 315 is the national quality measure that examines UI and catheter use in nursing homes (Johnson and Ouslander, 2006). It is used to help facility surveyors assess care for UI and catheter use in long-term care facilities. In a survey study of nursing home staff and state surveyors, there were substantial differences in knowledge about UI and attitudes toward this federal regulation (DuBeau et al, 2007). Other research has shown similar variation in levels of understanding and attitudes about UI of nursing home staff (Saxer et al, 2009). **Organizational factors can be as important as clinical medicine and nursing issues in this setting** (Yoon et al, 2012). This highlights the need to include nursing home staff and administrators in quality improvement. Process change in nursing home settings can be challenging, and ongoing research seeks to improve these methods (Grabowski et al, 2014).

Catheters are usually not used for UI management in this setting. Rather, they are used for treatment of chronic urinary retention, particularly among older adults who cannot tolerate CIC because of physical or cognitive issues or in cases of significant caregiver burden (Jonsson et al, 2011b; Lin et al, 2011). **Continued use of indwelling catheters in nursing home residents is subject to intense scrutiny and must be clinically justified in each specific case** (Gammack, 2003). Management of UI and other voiding dysfunction among morbidly obese nursing home residents can be particularly problematic. These individuals often have multiple comorbid conditions, and mobility and transfers may be severely limited (Bradway et al, 2010). Catheter use may be considered in select cases.

The need for continued Foley catheter drainage among older adults discharged from acute care hospitalization has been

associated with substantially increased rates of both short-term mortality and need for institutional placement at time of discharge (Bootsma et al, 2013). However, caution must be used to balance risk and benefit. Bacterial colonization is common, with 98% of indwelling catheters among geriatric nursing home residents affected (Jonsson et al, 2011a).

Absorbent pads and products are often used as part of a “check-and-change” approach to management of UI in geriatric nursing home residents, particularly in cases where more active forms of therapy might not be feasible because of cognitive or other functional impairments. Although many nursing home residents prefer scheduled toileting and active interventions, use of pads and products can be effective in select cases (Pfisterer et al, 2007). Research has shown, however, that pad-per-day use does not necessarily correlate well with actual UI volumes or severity (Omli et al, 2010).

Urologic consultation in nursing home settings can be useful for evaluation and management of complex genitourinary conditions or to supplement ongoing therapies administered by nursing home staff (Watson et al, 2010). This can obviate the need to transport older adults from their place of residence to outpatient clinics or hospital settings. However, in the current national model of physician reimbursement, this type of on-site consultation service can be difficult to maintain over time because of administrative and cost barriers.

Targeted protocols to treat UI in long-term care settings have proven quite successful. Prompted toileting can be used with residents who have adequate mobility and cognitive function to use toilet facilities independently. Patients are prompted by caregivers or staff to use the toilet on a regular schedule. Timing is adjusted based on specific individual needs. In those older adults with mobility and/or cognitive impairment, assisted toileting procedures may be necessary. These involve having staff physically assist older adults to the toilet and guiding them through the process of adjusting clothing, using the toilet, and cleaning after voiding and/or defecation. Individually devised plans may be needed for each resident depending on his or her condition. Use of bladder scan ultrasound may be useful in this process to help identify when subjects need to use the toilet (Iwatsubo et al, 2014). The use of assistive toileting devices such as handheld urinals or bedside commodes may be necessary depending on functional status. Functional incidental training (FIT) has been used as a successful model of assisted toileting with older nursing home residents. In the FIT model, residents combine physical activity and mobility training with scheduled and assisted toileting (Schnelle et al, 1995).

Clinical Evaluation of Incontinence

Clinical evaluation of UI in older adults requires special consideration of associated health factors and can differ substantially from standard evaluation in younger and healthier patients. In particular, careful attention must be paid to potential contributions of comorbidity, either as a causative factor or an effect from UI. Evaluation should seek to identify any of the previously described reversible transient causes of incontinence. It should also assess caregiver and social support and the environmental setting where the older adult resides. The evaluation could also identify other serious urologic conditions that can be associated with UI including bladder cancer, benign or malignant prostate disease, neurologic disorders, or stone disease.

Additional details about the evaluation of UI in geriatric patients including history, physical examination, assessment of postvoid residual (PVR) volume, voiding diaries, laboratory testing, and urodynamic studies can be found on the Expert Consult website.

Treatment of Incontinence

Treatment of UI must be carefully tailored to the individual patient. This is particularly true among geriatric patients because there can be substantial heterogeneity among individuals based on comorbidities, functional status, and goals of care. Because causes of established UI in geriatric patients are multifactorial, treatment

also frequently requires multiple components and approaches. **In many cases the actual target of therapy may be outside of the lower urinary tract to address contributions from comorbidities and other contributing clinical conditions.** Behavioral therapies are a mainstay of treatment of UI in geriatrics, although medications and surgeries can also be used successfully in this population.

Additional information regarding specific geriatric considerations for treatment of incontinence with behavioral therapies, pharmacotherapies, and surgeries, including bulking agents, sling procedures, artificial urinary sphincter (AUS) placement, neuromodulation, chemodenervation, urinary diversion and indwelling urethral or suprapubic catheters, and use of urine containment and absorbent products, is included on the Expert Consult website.

Other Lower Urinary Tract Dysfunction, Pelvic Floor Conditions, and Genitourinary Trauma

A wide variety of other lower urinary tract and pelvic floor conditions can affect older adults and require special considerations for geriatric patients.

Details on BOO, UAB and urinary retention, nocturia, FI, continence promotion and advocacy, POP, UTIs and asymptomatic bacteriuria, hematuria, and genitourinary trauma are included on the Expert Consult website.

Genitourinary Malignancies

Almost all of the genitourinary cancers occur with greater incidence and prevalence in geriatric patients than in their younger counterparts. The one exception is testis cancer, wherein lymphoma is the most common histology seen in geriatric men.

Detailed information on specific geriatric considerations for Prostate cancer, bladder cancer, kidney cancer, and testis cancer are included on the Expert Consult website.

Sexual Health in Elderly Women and Men

Sexual health is an important part of life for most adults, even at advanced age. **Many older adults wish to remain sexually active throughout their life (Hyde et al, 2010).** Data from the National Survey of Sexual Health and Behavior (NSSHB) in 2009 demonstrated that 20% to 30% of all older adult men and women remained sexually active well into their 80s (Schick et al, 2010). **A common myth is that older adults are not able or interested in participating in sexual activity.** Forms of sexual expression may change with time over the life span (Lindau et al, 2007). Lack of a partner is a limiting factor for many older adults. Penetrative sexual activity may become less important for some older adults, and there may be an increased emphasis on intimacy and other types of erotic interaction. Masturbation may become an important form of sexual expression for many older adults.

Comorbidity plays an important role in sexual health for many older adults. Those with better overall health tend to be more sexually active than those with poorer functional health status (Lindau and Gavrilova, 2010; Bach et al, 2013). **Changes in sexual health may be a sign or symptom of underlying systemic disorders.** Multiple studies have linked obesity, diabetes, cardiovascular disease, and neurologic disorders such as Parkinson disease and stroke to erectile dysfunction in elderly men (Marinkovic and Badlani, 2001; Seftel, 2003; Riedner et al, 2006; Justo et al, 2010; Garimella et al, 2013). Alterations in sex hormones and testis function have been shown to influence erectile function and cardiovascular health in elderly men (Rastrelli et al, 2013). UI and other LUTS can negatively influence sexual health for many older adults (Griebing, 2006; Tannenbaum et al, 2006). Frailty affects multiple physical and psychosocial domains and has been shown to be linked to worse sexual health status (Lee et al, 2013a). Other physical health issues may influence the ability to engage in sexual activity. Severe arthritis may make some positions for intercourse painful or impossible. Atrophic vaginitis can cause dyspareunia in

Evaluation should be individually tailored to the clinical needs and goals of the patient and his or her caregivers. In some cases, complete resolution of UI may not be feasible, but even small improvements in the condition can yield substantial functional results. For example, improvement in volume or frequency of urinary leaking may allow someone who was previously confined to the home the ability to get out and interact in social settings more easily. Simple interventions can sometime have substantial positive effects. In most clinical guidelines, these form the cornerstone of initial therapies. However, a comprehensive approach is often the most effective when addressing the complex topic of UI in older adults.

History. A detailed history is essential to proper diagnosis and selection of therapy for UI in older adults. The characteristics of incontinence including duration, frequency, and volume should be determined. Any exacerbating factors such as physical activity, coughing, laughing, sneezing, or other factors should be assessed. A review of medical records can be extremely valuable. This would include any prior treatments that have been attempted and prior surgical records if available. Some patients will be unable to provide their own historical information, and portions of or in some cases the entire history may need to be obtained from caregivers or surrogates. A telephone call to the patient's geriatrician or primary care provider can be quite valuable for obtaining historical information. For those older adults who reside in long-term care facilities, a call to the nursing staff member most familiar with the patient can help put clinical questions into better context. This can also help clarify goals of evaluation and treatment.

In some cases, a careful history will allow the clinician to determine the type(s) of UI a given patient experiences. However, this is not always true, particularly for elderly patients who may have more complex voiding dysfunction. The symptom of urinary urgency is extremely common but is neither particularly sensitive nor specific for DO. This may or may not be accompanied by actual urinary leakage. Similarly, urinary frequency is a common complaint that must be placed in clinical context. This may be caused by true DO, sensory changes that result in frequency of urination, or incomplete urination leading to rapid refilling of the bladder. In some cases this is a learned behavior or purposeful technique to avoid UI that might occur near bladder capacity. Voiding diaries can be helpful in gaining more insight into these clinical complaints.

Identifying the most bothersome component or characteristics of UI is particularly important in older adults. This can help to target treatments that can yield clinically meaningful improvements even if urinary leakage cannot be completely eliminated and is one of the main components of patient-centered therapy.

Physical Examination. The physical examination is a crucial part of overall assessment of older adults with UI. In addition to routine aspects of physical examination including pelvic examination in women and genital and rectal examination in men, several unique components are also included for older adults with incontinence. The general physical examination should include identification of conditions associated with fluid overload and associated incontinence including peripheral edema, CHF, and pulmonary edema.

Neurologic examination includes gait and balance, mobility, and ability to transfer between positions. This includes ability to get on and off a chair, which can be similar to getting on and off the toilet. Clinical signs associated with common rheumatologic and neurologic disorders in older adults should also be evaluated. These include changes from arthritis and joint disorders, Parkinson disease, multiple sclerosis, prior stroke, spinal stenosis, cord compression, vertebral disk herniation, acute or chronic back pain, dementia, and delirium.

Perineal sensation should be tested, and may be diminished or asymmetric, particularly in those with a history of underlying neurologic disease. For example, patients with a history of stroke and associated hemiparesis may have asymmetric perineal sensation. Tissue quality should be assessed including presence or lack of rugation of the vaginal mucosa. Atrophic vaginitis is common in postmenopausal women and is usually caused by lack of estrogen.

This can also lead to fusion or "agglutination" of the labia minora or labia majora. In some cases this can cause voiding dysfunction and BOO (Chang et al, 2012a). Vaginal narrowing or stenosis is another common finding on pelvic examination in elderly women. This is sometimes associated with a prior history of pelvic radiation therapy.

Pelvic examination in women should be performed with the bladder moderately full to evaluate for stress UI. Many older women wish to void before pelvic examination because it makes this more comfortable, and they may be used to doing so before routine gynecologic examinations. In some cases, women want to void before examination to avoid potential embarrassment with urine leakage in front of the clinician. However, if the patient voids to completion before the examination, determination of stress leakage with cough or Valsalva will be severely limited. Gentle reassurance of the importance of doing the examination with urine in the bladder and objective identification of stress leakage can be very useful and can help put the patient at ease.

Rectal examination may reveal signs associated with chronic constipation or fecal impaction. The bulbocavernosus reflex may be absent in older adults, although this change may or may not be associated with underlying neurologic pathology. Prostate enlargement or nodularity may be palpable, although prostate size on rectal examination does not necessarily correlate with symptoms. Rectal cancers are more common among older adults, and the majority of lesions are palpable on digital rectal examination. Stool guaiac testing should also be considered and can help to identify otherwise silent pathology in some patients (Goetzl et al, 2008).

Having the patient void as part of the physical examination can be particularly useful in geriatric patients. This may include actually taking the patient to the toilet to observe his or her behaviors and level of need for assistance. Is the patient able to recognize the toilet? Is he or she able to identify the sensations provided by a full bladder and respond appropriately to these signals? Is the patient able to adjust clothing independently to allow use of the toilet? This can provide insight into potential issues of cognitive or physical functional impairment that could change the course of recommended therapy.

Assessment of Postvoid Residual Volume. Many older adults do not completely empty the bladder with voiding. Elevation of the PVR volume is common in older adults. However, no specific volume is considered pathologic and there is a great deal of controversy surrounding the importance of elevated PVR volume in older adult patients. (Huang et al, 2011; Shimoni et al, 2015).

Measurement of PVR volume can be accomplished with either ultrasound scan or bladder catheterization. Ultrasound is convenient and eliminates the need for urethral instrumentation. However, the device is expensive and not all clinics will have this equipment available. Some nursing homes, outpatient clinics, emergency rooms, and other facilities that provide care for older adults have invested in this type of technology (Omli et al, 2008).

Measurement should ideally be completed immediately after a voluntary void rather than after an incontinent episode. However, in some patients, particularly those with cognitive impairment, this may not be feasible. Measurement of PVR volume after an incontinent leakage episode can be useful, particularly if the volume is low because this indicates complete bladder evacuation.

Voiding Diaries. The use of voiding diaries can be particularly helpful in assessing UI and other forms of voiding dysfunction in older adults. They can help identify patterns of voiding in terms of time and associated factors. This can be useful to differentiate the type of UI in some cases. It can also be helpful in identifying cases of daytime or nocturnal polyuria. Research has shown that diaries completed over 3 days can be valid for analysis, and this eliminates need for extended 7-day or longer diaries (Dmochowski et al, 2005). Most diaries are completed using paper forms, although electronic diaries are also available and are frequently used in clinical research trials. If clinicians are going to use voiding diaries with older adult patients, care should be used to make sure the font is large and easily readable and that adequate instructions are provided for proper completion.

Findings from the voiding diary can be very useful in helping to guide treatment for UI in older adults. The voiding diary can help identify voiding patterns and provides an objective tool to validate subjective symptoms. It can be particularly helpful in patients with nocturia to differentiate nocturnal polyuria from some of the other causes of the condition (Weiss and Blaivas, 2000; Udo et al, 2009). In some cases, recording fluid intake may be useful, but this increases the complexity of the data the older adult is asked to collect. Information on fluid intake is particularly useful to identify polydipsia or fluid restriction, which could be causing voiding problems.

Laboratory Testing. Geriatric patients need some special considerations for laboratory testing related to urologic health. Urinalysis and urine cultures should be obtained when clinically indicated and can help to identify underlying comorbidity. **The American Urological Association (AUA) guidelines recommend checking a urinalysis as part of the initial evaluation for UI** (Dmochowski et al, 2010; Gormley et al, 2012). Gross or persistent microhematuria warrants additional evaluation, including in older adults who are on anticoagulation therapy (Davis et al, 2012). Urine cultures are important to help diagnose the cause of UTIs and guide therapeutic choices. Persistent sterile pyuria should raise suspicion for possible genitourinary tuberculosis in older adults, who can harbor this infection without other signs or symptoms (Kulchavenya et al, 2013).

Measurement of serum creatinine alone frequently does not adequately reflect true renal function in geriatric patients. This is because of natural loss of muscle mass with aging, which influences observed serum creatinine levels. Several options have been developed to correct for this measurement disparity (Aucella et al, 2010). A 24-hour urine collection will provide the most accurate information but may be difficult to obtain for many patients, particularly those with substantial UI. The most commonly used estimation equations include the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) models. Correction factors for age and body habitus can help improve accuracy of these estimates of GFR (Schaeffner et al, 2012; Van Pottelbergh et al, 2014; Zhu et al, 2014).

Serum electrolytes should be checked in patients with delirium because this can be a causative and potentially reversible factor in some cases. Glucose measurement is useful in diagnosing underlying diabetes, which could be associated with renal, lower urinary tract, and sexual health disorders.

Urodynamic Studies. Urodynamic studies can be useful in the evaluation of select elderly patients with UI and other forms of voiding dysfunction (Diokno, 1990). The AUA has published guidelines regarding the use of urodynamic studies for assessment of voiding dysfunction (Winters et al, 2012). **Primary indications for urodynamic studies, particularly in older adults, include failed prior therapy, underlying neurologic or other comorbid conditions that could influence voiding function, and planned genitourinary reconstruction.** It is important to consider if and how findings from urodynamic testing might change treatments. If different urodynamic results would not alter therapy, then testing would not be warranted. However, if different treatment options would be considered based on the observed results from the testing, then it would be justified. Pressure-flow urodynamic testing can be particularly helpful to differentiate between functional obstruction and UAB with poor contractility and incomplete bladder emptying.

Several factors must be specifically considered for geriatric patients who may undergo urodynamic testing. Although minimally invasive, the study is in some ways an interventional procedure and must be conducted in this context. The test is quite interactive, and patients need to be able to follow directions and describe what they are feeling at various points. They need to be able to be positioned adequately and undergo catheter placement. Older adults with cognitive or mobility limitations may have difficulty participating in urodynamic testing, which could compromise the quality of the findings. **Ideally, the symptoms being targeted for analysis and treatment should be reproduced during urodynamic testing.** This can be difficult to achieve in the urodynamic laboratory, but a variety of techniques can be used to help with standardization of methodology. The importance of good urodynamic technique and testing quality cannot be overemphasized (Schäfer et al, 2002). Most urodynamic testing is conducted in hospital or clinic-based facilities, although portable and ambulatory urodynamic evaluation can be performed in select cases. The role of urodynamic testing in the nursing home and other care settings is relatively limited and should be reserved for specific cases where results of the testing would substantially influence treatment considerations. Staffing and reimbursement may also be a limiting factor for studies done in mobile settings such as nursing homes.

In a large cohort study of urodynamic findings in 100 community-dwelling elderly women, the most common clinical conditions identified include DO and DHIC (Valentini et al, 2010). These tended to be strongly correlated with patient symptoms. However, other studies have contradicted this finding and suggest that in some older adults the observed correlation between clinical symptoms and urodynamic findings may be lower (Bromage et al, 2010). This likely reflects alterations in anatomy or physiology and overall heterogeneity of changes seen with advancing age among older adults.

Behavioral Therapies. Behavioral therapies are considered the mainstay of therapy for treatment of UI in older adults. They offer the advantage of good clinical efficacy while avoiding potential side effects often associated with medications or surgery.

Some older adults choose to limit fluid intake in an attempt to reduce urge incontinence or urinary urgency or frequency episodes (Miller et al, 2011; Segal et al, 2011). Although this can be useful in select cases, particularly at night in those with symptomatic nocturia, care must be taken to avoid dehydration. **Reduced fluid consumption can exacerbate both UI and constipation.** In addition, restriction of fluids can lead to production of a stronger and more concentrated urine, which is actually more irritating to the epithelium. Although total urine volume is reduced, increased urinary concentration can actually worsen urge symptoms. Other common dietary recommendations include avoidance of foods or beverages that tend to trigger urinary urgency and frequency symptoms. These include caffeine, carbonated beverages, alcohol, and spicy or acidic foods (Gleason et al, 2013).

Timed or scheduled toileting can be quite useful in some patients with urinary urgency and frequency. Many older adults have worse symptoms near bladder capacity. **Voiding on a more regular schedule before reaching capacity may help to limit urge sensations and associated leaking.** Bladder retraining, a series of steps to increase the intervoiding interval, can also be useful in select cases. This can help to slowly increase functional bladder capacity and response to sensations of bladder filling. One clinical trial demonstrated a mean reduction of 57% for urge incontinence frequency in elderly women (Fantl et al, 1991). Delayed voiding is similar except that patients do not follow a predetermined time interval, but instead base their schedule on sensations as they experience them (Burgio et al, 2011). Biofeedback training is sometime used in combination with this type of intervention (Newman, 2014). Urge suppression methods are frequently combined with other types of therapy as a form of habit retraining to improve UI symptoms (Ostaszewicz et al, 2004).

PFME is one of the primary forms of behavioral therapy used to treat UI in older adults. Numerous studies have shown that both men and women with various types of UI can benefit. However, simply telling people to do Kegel or pelvic muscle exercises is unlikely to be successful. **Most older adults require specific training for these methods to work.** Cognitive impairment may limit practicality of this therapy in some patients. It requires a motivated patient who is willing to do the exercises and is able to follow guided instruction. In a study of hospitalized older women (mean age 78.2 ± 6.3 years), the vast majority (74.5%) were unable to voluntarily contract their pelvic floor muscles (Talaszi et al, 2012). With proper instruction, PFME has been shown to improve UI more than just bladder training and timed voiding alone (Sherburn et al, 2011). PFME is often used in combination with other forms of behavioral or pharmacologic therapies, and effects may be additive or synergistic (Burgio et al, 2000; Ghoniem et al, 2005). In some cases, patients may be able to decrease or discontinue medications for UI, depending on success of PFME and behavioral treatments (Burgio et al, 2008). It has also been shown to be effective in men with a history of postprostatectomy incontinence and in patients with symptomatic nocturia (Johnson et al, 2005; Goode et al, 2011).

PFME appears to have a direct effect on pelvic anatomy and physiology. It has been shown to improve both pelvic floor muscle morphology and dynamic function over time (Dumoulin et al, 2007; Madill et al, 2013). A variety of teaching methods have been developed and advocated for PFME instruction in older adults. These have been used successfully in nursing home settings (Engel et al, 1990; Vinsnes et al, 2012). Group instruction is feasible and has been shown to have good outcomes (Sampselle et al, 2005; Lajiness et al, 2007). This may be particularly useful for older adult patients, who may benefit not only from direct instruction but also from interaction and support of the group learning PFME together. It may also be a more efficient and cost-effective way to disseminate this type of clinical education for multiple patients. This was shown to be effective in a nursing home setting where participants also experienced improvements in overall functional status (Tak et al,

2012). Online instruction with Internet-based teaching and interactive support forums has been shown to be successful in early trials (Sjöström et al, 2013).

Vaginal cones can be used to augment pelvic floor exercise and may help patients to identify the muscles used in this technique. However, randomized controlled trials have not shown statistically significant differences in continence outcomes with or without cones (Pereira et al, 2012, 2013). Electrical stimulation of pelvic floor muscles can also be used, but results of this treatment compared with PFMEs alone have been mixed (Castro et al, 2008; Correia et al, 2014). Weight loss has been shown to be effective at improving stress UI and FI in elderly women with obesity (Subak et al, 2009; Markland et al, 2011).

Pharmacotherapies. Medications are widely used in treatment of UI. The specific drug selected is typically based on the type and cause of UI experienced by the patient. Unfortunately, there are currently no pharmacologic agents available in the United States that are particularly effective for treatment of stress UI in older adults. Medications with α -agonist properties such as pseudoephedrine have been tried but tend to have substantial side effects and limited clinical efficacy in geriatric patients. The older medication phenylpropanolamine was removed from the market by the U.S. Food and Drug Administration (FDA) because of increased risk of serious side effects including hemorrhagic stroke and other thromboembolic events (Meadows, 2001). Duloxetine, a balanced serotonin and noradrenaline reuptake inhibitor, also has α -adrenergic properties and has been considered as a possible treatment option for stress UI (Basu and Duckett, 2009). Although it is used in some parts of the world, it is not approved by the FDA for this purpose.

The majority of medications have been designed to treat OAB including urinary urgency, frequency, and urge UI. These are mostly antimuscarinic, anticholinergic medications that act by blocking muscarinic receptors in the bladder which in turn decreases detrusor contractions. The classic medication in this group is oxybutynin. Although it can be quite effective for management of bladder symptoms, it has strong anticholinergic properties that can cause problematic side effects in older adults. The most common include dry mouth and constipation, although dry eye, headache, confusion, and other anticholinergic effects may also occur (Pagoria et al, 2011; Moga et al, 2013). A variety of newer anticholinergic medications have been developed with the goal of reducing DO and associated OAB symptoms but minimizing potential side effects. These medications can be used in men and women, and all have been shown to have relatively similar efficacy (Madhuvrata et al, 2012).

Several of the newer medications have theoretic advantages for use in older adults. In some cases these may have a real physiologic effect, but to some extent the primary purpose has been differentiation in marketing for various drugs. Differences among medications have been based on a variety of factors including lipophilicity, molecular size, selective affinity for various muscarinic receptor subtypes, drug half-life, and other metabolic effects. For example, trospium is a quaternary amine, unlike the other agents, which are tertiary amines. Animal studies have shown that trospium may be less likely to cross the blood-brain barrier, which may therefore decrease the potential cognitive side effects from this medication (Kranz et al, 2013). However, changes in the blood-brain barrier with aging increase permeability and may alter drug efflux in older adults (Chancellor et al, 2012). Studies of these types of medications in older adults need to examine cognitive side effects (Kay et al, 2006; Paquette et al, 2011). Improved selectivity of muscarinic receptor binding is another focus in drug development. The goal is to target the bladder (M_2 and M_3) but avoid the salivary gland and bowel (both M_3), which may help reduce the risk of dry mouth and constipation (Abrams and Andersson, 2007).

The route of administration and type of drug delivery system are also important considerations for several of these medications. These can influence pharmacokinetics and pharmacodynamics of these preparations. Immediate-release drugs offer quick onset of action, but long-acting or timed-release agents may have a benefit of a more stable steady state of circulating medication. Transdermal preparations avoid the first pass effect through the liver and may be

useful in patients with hepatic insufficiency. They are also useful in patients with swallowing difficulties that can prevent effective use of oral tablet or capsule formulations. Liquid oxybutynin is available and can be administered through feeding or gastric tubes in patients unable to swallow liquids or other formulations.

One of the challenges is that older adults are frequently excluded from clinical trials used to approve medications and other treatments because of their underlying comorbidity and heterogeneity (Briggs et al, 2012; Beers et al, 2014). However, the reality is that these drugs are widely prescribed in this patient population in routine clinical practice (Kraus et al, 2010). This means that potential side effects and interactions among medications and underlying comorbidity have been studied in less detail, which makes clinical decisions and prediction of outcomes more difficult. Several studies have examined use of antimuscarinic medications specifically in older adult cohorts. Fesoterodine was demonstrated to have good clinical efficacy in a 12-week randomized, placebo-controlled trial in a group of 562 elderly patients with a mean age of 75, and with 50.4% of patients being 75 years of age or older (DuBeau et al, 2014). This group had high baseline rates of comorbidity, polypharmacy, and functional impairment, which mirrors real-world prescribing challenges. The medication was well tolerated in general, and overall adverse event rates were similar to those seen in younger patient populations. These results were also demonstrated in a similar trial of fesoterodine conducted with geriatric patients in Europe (Wagg et al, 2014b). Studies on older adults have also shown relatively good efficacy and tolerability for tolterodine, solifenacin, darifenacin, and trospium (Lipton et al, 2005; Wagg et al, 2006; Chapple et al, 2007; Griebeling et al, 2009; Sand et al, 2011; Wagg et al, 2013a). One study of fixed low-dose, extended-release oxybutynin in cognitively impaired older adults living in nursing homes did not seem to worsen cognition and decreased the number of wet pad checks by 38%, but failed to show a significant benefit for UI overall (Lackner et al, 2011). An earlier study had also shown relatively good tolerability with no increase in rates of delirium in a cohort of cognitively impaired nursing home residents (Lackner et al, 2008).

Most of these medications undergo either hepatic or renal metabolism, and care needs to be used in patients with liver or kidney impairment. Use of the lowest clinically effective dose is usually recommended. Drug-drug interactions tend to occur with other drugs that undergo hepatic metabolism. Drug-food interactions have also been identified, particularly with alcohol and grapefruit, which can lead to inhibition of the cytochrome P450 pathway. **Use of the antimuscarinic and anticholinergic medications is also contraindicated in patients with closed-angle (narrow) glaucoma.** Consultation with a patient's ophthalmologist or optometrist may be needed in these cases before prescribing these medications. Open-angle glaucoma is much more common, and this by itself is not a contraindication to use of the antimuscarinic anticholinergic medications for treatment of urinary symptoms.

Adverse effects of antimuscarinic medications are one of the primary limiting factors for ongoing use, particularly among older adults (Sears et al, 2010; Wagg et al, 2012). Discontinuation of medication is common, and several different medications may need to be tried to find one that is acceptable for an individual patient. Urinary retention is a theoretic risk with all of these medications, although this is not commonly seen in clinical practice. Monitoring of PVR volumes after initiation of therapy might be considered.

A new class of agents for treatment of OAB is the β_3 -adrenoceptor agonists. Mirabegron is the only agent in this class currently approved in the United States and is available in 25-mg and 50-mg doses taken once daily. This acts on detrusor smooth muscle to decrease contractility and reduce symptoms associated with overactivity. Studies in older adults have demonstrated good clinical efficacy with relatively few side effects (Wagg et al, 2014a). This class of medications offers the potential advantage of reducing bladder symptoms without the risk of anticholinergic side effects.

Regimen compliance and continuation can be problematic with the antimuscarinic medications, particularly among older adults. Discontinuation rates are relatively high, ranging up to 50% to 86%

at 1 year (Wagg et al, 2012; Mauseth et al, 2013; Sicras-Mainar et al, 2014). Although all of the available medications have been shown to be effective in clinical trials, the response of an individual patient to a specific medication is difficult if not impossible to predict. Patient perception of the degree of improvement is very important in the patient's decision to continue or stop pharmacotherapy (Basra et al, 2008). Older adults frequently discontinue these types of medications because of either lack of perceived efficacy or development of adverse effects such as dry mouth, constipation, or confusion.

Cost is also an important consideration when using pharmacotherapy for UI in older adults (Perimenis et al, 2006; Armstrong et al, 2012). Many geriatric patients are on a fixed income, and they may or may not have insurance coverage for prescription medications. Coverage varies widely among different policies and different drugs. Even under the Medicare Part D benefit, older adults may have a substantial out-of-pocket expense, particularly if they are on multiple medications and have used the extent of their available benefits. Different medications may have different preferred formulary status with different coverage plans. Patients often need help navigating these complexities with their insurance providers and pharmacies.

Use of antimuscarinic medications in patients with underlying cognitive impairment or dual use in those on cholinesterase inhibitors requires special consideration. These drugs theoretically act in pharmacologic opposition and may influence symptoms of the other disease process. There have been anecdotal reports of patients developing UI after initiation of a cholinesterase inhibitor, and, conversely, cognitive decline has been reported in some patients after initiation of an anticholinergic medication for treatment of urinary symptoms (Hashimoto et al, 2000; Siegler and Reidenberg, 2004; Starr, 2007). This can be associated with an increased risk of polypharmacy in these older adults (Modi et al, 2009). In fact, initiation of one medication may lead to symptoms that prompt subsequent prescription of the other class of medications, an example of the prescribing cascade (Jonnell and Fastbom, 2008; Boudreau et al, 2011). Larger observational studies have shown that combined use of these medications can lead to progressive cognitive decline in some older adults (Sink et al, 2008). In these cases, it can be helpful to consult directly with the treating geriatrician or neurologist to determine which medication should take priority based on the overall clinical situation. Risks and benefits of medications must be balanced with observed outcomes with regard to both urologic and neurocognitive function. Risks of cognitive change or confusion with anticholinergic medications are real, although overall reported incidence is relatively small. Discontinuation of medication usually results in resolution of the cognitive side effects.

Potential cardiac risks are also a consideration with specific antimuscarinic agents. For example, high doses of tolterodine may cause QT prolongation, which can lead to symptomatic bradycardia and even torsades de pointes. The maximum dose for specific medications should be carefully considered and should not be exceeded (Rosa et al, 2013). Anticholinergic medications also have a potential risk of inducing tachycardia, although this has not been reported as a common clinical adverse event of currently available medications. The β_3 -adrenoceptor agonist mirabegron has been associated with slight increases in blood pressure and should be used carefully in older adults with a history of hypertension (Sanford, 2013). Underlying cardiovascular disease plays an important role in these cases and should be considered when prescribing medications for treatment of OAB.

Surgical Therapies. A number of different forms of surgical therapy are used for treatment of UI in older adults. These include surgical procedures for both stress and urge UI. Many older adults want to avoid surgery as a possible treatment option for UI, POP, or other urologic conditions. Similarly, many clinicians may not consider surgical options for geriatric patients because of concerns about potential risks and complications related to age (Griebeling, 2011). However, there is a growing body of evidence that indicates surgery may be safe and effective for carefully selected older adults with UI and other genitourinary disorders. Age alone is

rarely a significant risk factor for postoperative outcomes, which tend to be more closely related to comorbidity and functional status. In fact, considering surgery earlier in the treatment algorithm may be appropriate in some cases. For example, prolapse repair performed earlier after menopause in older women has been shown to have improved outcomes compared with surgery that is substantially delayed (Ahn et al, 2010). Development of newer, less invasive effective surgical procedures has made some surgical options more viable for use in elderly patients (Atiemo et al, 2006). In addition, efforts to better optimize older adults medically before surgery may help to improve outcomes (Chow et al, 2012).

Bulking agent injections have been used to treat stress UI in older women (Lightner et al, 2002; Keegan et al, 2007). They offer the advantage of a minimally invasive technique with relatively good success rates. However, overall success is somewhat more limited compared with other surgical techniques owing to longevity of the effect and need to repeat the procedure. Conversely, the ability to repeat treatment can also be seen as a clinical advantage to bulking agent injections. A variety of materials have been used for this purpose including cross-linked bovine collagen, synthetic gels, and microbeads (Khullar et al, 1997; Winters et al, 2000; Lightner et al, 2001; Vecchioli-Scaldazza et al, 2014). **Bulking agent injection therapy may be particularly appealing in elderly women with stress UI who may not be candidates for more involved surgical therapy.** The use of bulking agents in men has shown substantially less overall success compared with efficacy in women (Griebing et al, 1997).

Sling procedures are used for treatment of stress UI. Slings for treatment in women include both pubovaginal and midurethral procedures. Various graft materials have been used for this purpose including autologous fascial grafts, other biologic grafts using either cadaveric fascia or xenografts, and synthetic mesh. Slings have also been developed for treatment of stress UI in men. A number of published studies have examined safety and efficacy of sling procedures for treatment of stress UI in geriatric patients. These have shown good outcomes in general, with no significant difference in complication rates compared with younger patients (Stav et al, 2010; Jun et al, 2012; Serati et al, 2013). However, other clinical reports suggest older women may be at increased risk for perioperative UTIs and other complications (Groutz et al, 2011). Continence outcomes may also differ, with one study reporting inferior rates of improvement in elderly women compared with younger patients after midurethral mesh sling (Kim et al, 2011a). In this study, elderly women had higher rates of parity, hysterectomy, and prior anti-incontinence or prolapse surgery. This could have influenced observed results. An analysis of Medicare beneficiary data demonstrated that elderly women appear to have a higher risk of urinary retention, urinary urgency, and other complications after sling surgery compared with younger women (Anger et al, 2007a, 2007b). Some surgeons may avoid using mesh specifically in elderly women because of potentially increased risks of erosion or other complications after this type of surgery (Reynolds et al, 2013).

AUS implantation is often used for treatment of stress UI in men. AUS devices are not commonly used in women any longer owing to advances in sling procedures, bulking agent injections, and other minimally invasive surgical options. Cognitive status and manual dexterity must be carefully considered in elderly men being considered for AUS placement because they will need to operate the device several times daily to effectively manage incontinence and void. In select patients this therapy can be quite effective (O'Connor et al, 2007). Sling procedures for treatment of UI in men have been developed, but to date there are no clinical data examining outcomes specifically in geriatric patients.

Neuromodulation uses electrical stimulation of the nerves that control detrusor contractility to treat voiding dysfunction. Two forms of neuromodulation are currently available: sacral neuromodulation with implantable electrodes (InterStim, Medtronic), and peripheral tibial nerve stimulation (Urgent PC, Uroplasty). Both have shown good success in research trials and clinical practice. Studies on use of these therapies in geriatric patients have been somewhat limited; however, reported results are promising (White

et al, 2009; Schreiner et al, 2010; Griebing, 2010). Success rates up to 83.3% at 1 year have been reported in geriatric patients who went on to generator placement (Angioli et al, 2013). Reported complication rates are quite low, even in elderly patients with multiple comorbidities (Chughtai et al, 2015). Age by itself does not appear to substantially influence overall success of therapy (Peters et al, 2013). Posterior tibial nerve stimulation has been used successfully for older adults in a residential care setting, and in patients with a history of voiding dysfunction related to prior stroke (Booth et al, 2013; Monteiro et al, 2014). Successful use of neuromodulation therapy requires that the patient be able to identify characteristics of his or her symptoms and participate in ongoing programming and adjustment of the device as needed. In some cases, if the patient is unable to do this himself or herself, assistance from a caregiver may be required.

Chemodenervation of the detrusor muscle is used to treat urinary urgency, frequency, and urgency UI. This has typically been reserved for use in cases that are refractory to other forms of therapy including behavioral or pharmacologic interventions. The most commonly used agent for this purpose is onabotulinumtoxinA. Studies in older adults have been relatively limited but have shown clinical efficacy and overall safety (White et al, 2008). The major concern of this particular therapy is the risk of urinary retention, which could necessitate CIC or indwelling catheter drainage at least temporarily.

Urinary diversion is another possible option for treatment of intractable UI in highly selected older adults. In some elderly patients, use of a urinary conduit with management of a stomal appliance is preferable to UI. **Care must be taken to evaluate potential risks of surgery and to balance this with the potential benefits of independent urinary control provided by urinary diversion (Osborn et al, 2014).** In select patients, creation of a continent catheterizable diversion may also be an option (Gowda et al, 2008).

Use of indwelling catheters is usually avoided in older adults because of the associated risks of UTI, catheter colonization, urinary tract stones, or tissue erosion (Ouslander et al, 1987; Drinka, 2006; Leuck et al, 2012). Chronic use of indwelling catheters after discharge from acute hospitalization in older adults has been linked to negative outcomes including an increased risk of mortality (Holroyd-Leduc et al, 2007). Catheters should be removed as soon as feasible to help prevent these negative outcomes. Indwelling catheters are also not particularly helpful in management of DO because they tend to exacerbate bladder contractions and can make symptoms worse. They should also be avoided for simple convenience or fluid monitoring in most patients in acute care settings.

However, use of indwelling catheters can be useful in highly select cases. These include patients with chronic urinary retention and incomplete bladder emptying who are unable to undergo CIC for various reasons. Other examples include those with morbid obesity, severe extremity contractures, or other body habitus changes that prevent catheterization. Older adults with dementia or severe cognitive impairment, severe urethral stricture disease not amenable to surgical correction, or other anatomic changes may not tolerate CIC. In such patients, use of an indwelling catheter may be more appropriate. Patients with sacral pressure ulcers or other skin breakdown may also benefit from temporary indwelling catheter drainage to keep the affected area dry and allow for tissue healing. Temporary urinary catheter drainage can also be useful after flap placement or other reconstructive surgery to keep the surgical site dry during the healing process.

When chronic catheterization is necessary, placement of a suprapubic catheter is usually preferred over urethral catheterization. This helps prevent bladder neck erosion and urethritis in all patients, and decreases rates of epididymitis and prostatitis in men. Once the tract is healed, the suprapubic tube may be easier for staff to change and may also be more comfortable for the patient. This also positions the catheter out of the urethra and genital tract and allows patients to be sexually active if so desired. The catheter should be changed at least monthly or more often if necessary based on individual clinical variables (Wilde et al, 2013). In general, cystoscopy

is recommended on at least an annual basis, particularly after the first several years of use, to evaluate for any mucosal changes such as squamous metaplasia or development of stones. If patients have problems with urinary leakage around the catheter or from the urethra, treatment should be focused on reducing bladder contractions with antimuscarinic or other agents, and assuring adequate catheter drainage. It is strongly recommended that providers *not* increase the caliber of the tube. Increasing the diameter of the catheter will not solve the underlying cause of the urinary leakage and will serve only to dilate the suprapubic tract or urethra. This can lead to severe problems with erosion and catheter extrusion. Catheters of 16 or 18 Fr are typically adequate for use as a suprapubic tube.

Urine Containment and Absorbent Products. A variety of devices and products are available to help manage urinary leakage. Although these should not be considered a curative treatment option, they can be quite useful for management of symptomatic urine loss. In some cases, use of these types of products can allow affected individuals the opportunity to participate in social activities they would otherwise avoid because of embarrassment or other factors associated with UI.

Absorbent pads and products come in a wide array of designs. These range from small pads to extra absorbent briefs and can be used for both light and heavier volumes of urinary leakage (Fader et al, 2007, 2008). There are some differences in products available for men and women with designs specific for leakage target zones based on anatomy. Advances in technology have continued to improve products including better management of odor and absorbency (White, 2003). Gel-based products may offer better odor control and have good overall absorbency, although they may not be able to control large volume leakage as well as products using wood pulp or fiber. Pads may be particularly effective in helping to reduce associated dermatologic complications such as urea derma-

titis of the perineum (Sugama et al, 2012). Pads and absorbent products are frequently used in the UI management scheme of nursing home residents and can be a useful adjunct in this setting (Pfisterer et al, 2007). Use in acute care settings should be relatively limited if possible and has been shown to potentially increase rates of UI (Zisberg et al, 2011).

Condom catheters, also known as urinary sheaths, can be a useful adjunct for management of urinary leakage in men. These disposable devices surround the penis and are connected to a urinary drainage collection bag. Some men use these in selective settings such as when they go out of their home or participate in social activities. They can also be used at night to help control urinary leakage and decrease bother from nocturia, particularly in men with mobility limitations that make traveling to the toilet difficult or dangerous. Proper sizing of condom catheters and good skin hygiene are essential for successful use. Skin breakdown or necrosis can occur if the device is not properly maintained or if the condom is too small or placed too tightly around the penile shaft.

Urethral clamps and plugs are available in a wide variety of styles. Cunningham and other types of penile clamps should be used only during the daytime and need to be moved to different locations on the penile shaft every few hours to prevent tissue injury or necrosis. Men need to have adequate hand dexterity and cognitive function to use these types of devices successfully. Urethral caps and plugs have been developed for use in women. These offer the advantage of a nonsurgical option but can be difficult to use because of the disposable design, which requires removal and replacement with every void and associated costs. They also require adequate hand dexterity for routine use. These types of devices may be most useful when used selectively to prevent urinary leakage during exercise or other physical activities, or when leaving the home environment.

Bladder Outlet Obstruction

BOO, particularly resulting from BPH or urethral stricture disease, is more common in elderly than in younger patients. Incidence and prevalence rates for BPH, UI, and other forms of voiding dysfunction in men increase with advancing age (Griebing, 2008; Parsons et al, 2008; Irwin et al, 2011). Evidence-based guidelines for evaluation and management have been developed (McVary et al, 2011). However there still appears to be quite a bit of variation in initial evaluation and management among different practices (Strope et al, 2011; Erickson et al, 2014).

The spectrum of both medical and surgical therapies should be considered, and decisions based on each patient's unique situation. In many cases, men want to start with medications before considering surgical therapy. Recent research has led to an increased use of combination therapy with α -blockers and other forms of medication including phosphodiesterase type (PDE5) inhibitors, antimuscarinic agents, and 5 α -reductase inhibitors (Chung et al, 2011; Regadas et al, 2013).

Tissue ischemia caused by oxidative stress and diminished blood flow to the pelvic organs and prostate is a factor that theoretically could worsen BOO symptoms. Animal studies have suggested that an antioxidant diet may help to reduce the negative effects of this condition (Bisogni et al, 2012). There is great interest in whether similar results might be possible in humans.

Surgical therapies can be very useful, particularly in men with a history of acute urinary retention caused by BOO or in those who have not experienced sufficient improvement on pharmacotherapies. In addition to traditional transurethral resection, laser surgery and other minimally invasive forms of therapy have been used successfully in elderly men with BPH (Kuntz et al, 2008; Elshal et al, 2013). Bipolar plasmakinetic TURP has been used to reduce bleeding during surgery in elderly men with larger prostate glands (Coskuner et al, 2014).

Care must be taken when considering treatment of elderly men with BPH, particularly those with associated neurologic conditions such as Parkinson disease, Shy-Drager syndrome, multiple sclerosis, or other underlying disorders. These can exacerbate bladder storage and voiding problems and may increase risk for UI and other negative outcomes. Even after relief of BOO, DO may not completely resolve. This can be frustrating to patients and may continue to require therapy to control bothersome symptoms. TURP has traditionally been avoided in men with combined BOO and detrusor underactivity, although newer data have been challenging this long-held concept (Ou et al, 2012).

In select patients who are not good surgical candidates, urethral stents may be considered as an option (Milroy and Allen, 1996). Complications of urethral stents include technical issues and difficulty with tissue overgrowth and urethral strictures. However, in select men who might otherwise be dependent on indwelling catheter drainage, urethral stents may offer a viable treatment alternative (Gesenberg and Sintermann, 1998; Bozkurt et al, 2013). Urethral reconstruction may be feasible in select elderly men, and good outcomes have been reported using dorsal onlay skin grafts among other techniques (Schwettner et al, 2010).

Ophthalmic side effects of medications used to treat BOO need to be considered carefully in elderly men. The floppy iris syndrome is a condition that causes billowing of the iris during surgical cataract extraction and lens implantation (Bell et al, 2009; Friedman, 2009). It is important that elderly men on tamsulosin and other medications for treatment of BOO inform their eye surgeon before any procedure. These medications may need to be discontinued for at least a week before planned cataract surgery.

Underactive Bladder and Urinary Retention

UAB is a condition characterized by poor bladder emptying that is not necessarily caused by BOO. It likely encompasses multiple causes and clinical conditions (Taylor and Kuchel, 2006). This may be related to both a failure of the detrusor muscles to contract and a failure of the neural pathways to properly stimulate the bladder

(Smith, 2010). The ICS defines the term *detrusor underactivity* as "a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete emptying within a normal time span" (Abrams et al, 2002). The specific term *underactive bladder* has not yet been defined by the ICS.

Research on UAB is relatively new, and there are few epidemiologic studies on the condition. (Griebing, 2013a). In a population-based survey, 23% of 633 respondents indicated they had difficulty emptying the bladder (Valente et al, 2014). In a similar study of older adults who had undergone urodynamic testing for voiding dysfunction, 40.2% of men and 13.3% of women were diagnosed with detrusor underactivity (Jeong et al, 2012). **Both structural and functional changes appear to lead to development of UAB.** Ultrastructural studies have demonstrated that aging is associated with an increased deposition of collagen and a reduction in the ratio of smooth muscle to connective tissue (Elbadawi et al, 1993, 1997).

Progression of prior OAB or BOO may be involved in this process (Chancellor, 2014). Alterations in both active contraction and passive muscle stretch appear to play an important role as well (Young et al, 2013). Bladder ischemia has been linked to subsequent development of detrusor dysfunction and UAB. Studies using color flow Doppler ultrasound have shown that there is a quantifiable decrease in pelvic arterial blood flow in some elderly patients with LUTS. This may be a result of atherosclerosis or other vascular insufficiency (Pinggera et al, 2008; Kim et al, 2010a). The development of animal models of UAB will help advance future research on this topic (Tyagi et al, 2014a).

Several different forms of UAB have been identified in geriatric patients, and this can manifest in several different ways. Detrusor failure can be caused by sacral nerve injury with development of cauda equina syndrome. Patients typically experience lower extremity weakness and problems with gait and mobility. Some may develop frank paraplegia. In these patients the bladder typically has a low pressure during filling and does not contract well to void.

Acute urinary retention can be caused by BOO or detrusor failure. Decompression with an indwelling urinary catheter is usually required initially, with careful monitoring for postobstructive diuresis and electrolyte fluctuations. Evaluation for renal insufficiency or hydronephrosis is also warranted. **Catheter clamping before removal should be avoided, because this has not been shown to be of any clinical benefit and will serve only to induce discomfort.** In men with a history of BOO from BPH, initiation of medical therapy with α -blockers or 5 α -reductase inhibitors can be considered.

DHIC is one of the more common conditions seen in geriatric practice (Resnick and Yalla, 1987; Yalla et al, 2007). This condition is characterized by urinary urgency and frequency resulting from DO during bladder filling and storage. However, during the voiding effort, the bladder contracts poorly and does not empty well. Because of this, patients experience both urinary urgency and frequency but incomplete voiding and urinary retention.

Adequate treatment of UAB can be complex. In many patients it may require intermittent bladder catheterization. However, in some patients this may be difficult or impossible because of comorbidity such as severe hand arthritis or cognitive impairment. Augmented voiding techniques including the Credé maneuver or bladder tapping may be used by some patients (Ersoz et al, 2013). Care should be taken to monitor the upper urinary tract in these patients for development of hydronephrosis or other evidence of clinical deterioration.

Unfortunately, there is currently no effective pharmacologic therapy that improves bladder emptying in UAB. Theoretically, the cholinergic medications should lead to improved smooth muscle contraction in the urinary bladder, but **medications such as bethanechol have failed to demonstrate clinical efficacy.** A recent Cochrane review concluded that this medication should not be used for the treatment of urinary retention or UAB (Lapitan et al, 2013). Increased research and education on UAB will help advance our understanding of the clinical condition in geriatric patients (Griebing et al, 2014).

Nocturia

Nocturia is one of the most common and bothersome urinary conditions that occurs in elderly patients (Weiss and Blaivas, 2000; Wehrberger et al, 2012). The ICS defines *nocturia* as “getting up from sleep in order to void” (Abrams et al, 2002). This is usually preceded and followed by additional episodes of sleep. Polysomnography studies have documented that a majority of episodes of nocturia occur during superficial rapid eye movement (REM) sleep (Krystal et al, 2010; Bal et al, 2012). However, waking to urinate can also lead to difficulty getting back to sleep, with 46% of older adults in one survey reporting this as a substantial clinical problem (Endeshaw, 2009). Affected older adults also report worse disease burden, poor overall sleep quality, and an increased rate of falls compared with those who fall back to sleep more easily. Sleep duration is often decreased in older adults, and this has been identified as an independent risk factor for nocturia in elderly patients (Udo et al, 2009). Several biochemical processes appear to influence both nocturia and nocturnal polyuria. Obstructive sleep apnea results in decreased antidiuretic hormone (ADH) secretion and increased brain natriuretic peptide (BNP), which can lead to nocturnal polyuria (Hoshiyama et al, 2014). Nighttime melatonin secretion is inversely proportional to nocturia in older adults (Obayashi et al, 2014). Worse nocturia severity has also been linked to progression of underlying neurologic disorders such as Parkinson disease (Vaughan et al, 2013). Improved understanding of these complex associations between comorbid conditions and nocturia may help to improve future options for diagnosis and treatment.

The epidemiology of nocturia is complex and is linked to underlying risk factors associated with the condition. There appear to be some underlying differences in nocturia between men and women as a result of a variety of anatomic and physiologic factors (Tikkinen et al, 2006; Bing et al, 2007, 2008). An epidemiologic survey of 6000 people in Finland revealed multiple associated conditions including urinary urgency, snoring, BPH in men, and overweight and obesity (Tikkinen et al, 2009). At an individual level, urinary urgency appears to be one of the strongest correlated conditions. However, none of the conditions studied accounted for more than 50% of cases, even in age-adjusted risk analysis. Some modifiable behavioral factors have also been associated with nocturia, including alcohol consumption and cigarette smoking (Lee et al, 2012).

Nocturia can have a substantial negative impact on QoL. In general, one episode of nocturia per night is well tolerated by most people and is usually considered normal. However, two or more episodes of nocturia nightly have been linked to diminished sleep quality, reduced overall and health-related QoL, depression, and other detrimental clinical outcomes (Tikkinen et al, 2010). Increased rates of morbidity and mortality have both been linked to nocturia (van Doorn et al, 2012). Worse nocturia severity has been directly correlated with increased rates of complications including falls, fractures, and other negative clinical outcomes (Bing et al, 2007, 2008). This association appears to be independent of age and is more associated with severity of nocturia (Temml et al, 2009). This is true both in community-dwelling older adults and in those living in nursing home and other facilities (Galizia et al, 2012). Falls are associated with increased rates of both hip and long bone fractures, which in turn increase the risk for immobility and mortality (Nakagawa et al, 2010). Fat embolization from bone fractures can cause stroke and pulmonary embolus. Falls associated with nocturia can be caused by a number of factors including problems with balance and gait, attempting to travel to the toilet in the dark, navigating obstacles that may be in the path to the bathroom, and other factors.

Even in younger people, increased rates of nocturia have been associated with increased mortality (Fitzgerald et al, 2007; Nakagawa et al, 2010; Kupelian et al, 2011). This is likely a result of the fact that nocturia may be a marker condition of other comorbid diseases including cardiovascular and pulmonary diseases.

A careful history is useful in helping to identify potential causes of nocturia. Multiple different conditions can contribute to noctu-

ria. These include nocturnal polyuria, medications that increase urine production or disrupt sleep, diabetes insipidus, SIADH, hypertension, CHF, pulmonary or peripheral edema, obstructive sleep apnea, and other sleep-related disorders (Guilleminault et al, 2004; Burgio et al, 2010). A fluid intake and output diary can be helpful in differentiating causes of nocturia in many older patients.

Successful treatment of nocturia in elderly patients can be challenging and complex. Because the cause of nocturia is typically multifactorial, single therapies provided in isolation are often ineffective, and multimodal therapy targeting different causes may be required. Behavioral therapies and medications have been shown to be more effective in combination and should be focused on the underlying mechanisms of nocturia (Vaughan et al, 2009). Behavioral strategies that have shown promise include limitation of evening fluid consumption, PFME training, delayed voiding methods, and urge suppression techniques (Johnson et al, 2013). Use of diuretics during the earlier portions of the day may help to off-load excess fluid. Patients with peripheral edema may benefit from lying in a recumbent position earlier in the day to create a postural diuresis and off-load some of this excess fluid before retiring to bed for the night. Use of pressure gradient stockings may also be helpful.

Obstructive sleep apnea is often treated with continuous positive airway pressure (CPAP) ventilation support. In patients with incomplete bladder emptying and nocturia, CIC performed at bedtime may permit better sleep by improving functional bladder capacity at night, thus allowing the bladder more time to fill during sleep. Use of assistive devices such as bedside commodes or handheld urinals can help to reduce difficulties associated with nocturia in older adults. This can be particularly useful in those with mobility limitations or a strong risk for falls during nighttime toileting.

Desmopressin has been advocated as a potential pharmacologic treatment for nocturia caused by nocturnal polyuria. However, substantial caution should be exercised when using this medication, particularly in geriatric patients. Older adults tend to have less capacity for compensatory regulation of electrolyte imbalance. Hyponatremia is one of the major risks associated with use of desmopressin in elderly patients (Weatherall, 2004; Rembratt et al, 2006). Development of clinically significant hyponatremia can occur even several months after starting medication (Bae et al, 2007). In addition to potential hyponatremia, there are multiple other potential contraindications for use of vasopressin in older adults. These include risk of exacerbation of underlying heart failure, renal insufficiency, alterations in potassium and calcium excretion, and other electrolyte disturbances.

The primary risk is hyponatremia, which can be profound in some cases and can lead to negative outcomes including agitation, confusion, or coma. Staggered administration of desmopressin and furosemide has been shown in short-term research to improve outcomes and possibly reduce associated risks of electrolyte abnormalities (Fu et al, 2011). Newer formulations with rapidly dissolving oral preparations or “melts” that do not require water consumption for administration may be associated with lower rates of complications. Low-dose therapy (<0.2 mg) appears to be effective in most cases (Song et al, 2014). Dosage requirements may differ in men and women because of underlying physiologic differences, with older women appearing to require lower baseline doses (Yamaguchi et al, 2013). Clinical trials of desmopressin for treatment of nocturia in elderly patients are still ongoing, and this medication is not currently approved in the United States for this purpose.

Fecal Incontinence

Older adults commonly experience difficulty with bowel function. This can be caused by changes in motility, absorption, and other physiologic alterations associated with the aging process. Fecal impaction can actually manifest as diarrhea as a result of liquid material oozing around a stool bolus leading to FI, particularly in those with low anal closure pressures. Elderly patients often

experience dual bowel and bladder incontinence because the same neural pathway controls both of these processes. **FI can be particularly problematic in older adults** (Quander et al, 2005; Hayden and Weiss, 2011). Health care providers must specifically ask about bowel function during clinical assessment. Older patients may not voluntarily provide information on bowel problems because of embarrassment or other personal reasons.

Reported prevalence rates of FI range from 17% of community-dwelling women older than age 85 to 43% of elderly women residing in nursing home facilities (Townsend et al, 2013). More recent data confirm these prevalence rates, with 17.3% of community-dwelling older adults reporting having experienced accidental bowel leakage (Gorina et al, 2014). Among those receiving home health care services, FI was reported by 13.1% of those aged 65 to 74 years and 20.8% of those aged 85 years and older. Patients in hospice care have reported prevalence of UI of 9.9%, FI of 24.0%, and dual incontinence of 28.0% (Gorina et al, 2014). **UI is highly correlated with FI, and older adults with one condition are at increased risk for developing the other problem.** Rectal hypersensitivity and anatomic defects of the anal sphincter muscle complex have been identified as additional risk factors for development of FI (Lewicky-Gaupp et al, 2009).

Both constipation and FI are highly prevalent among nursing home residents. In one study, 81.1% of elderly nursing home residents had an average of three bowel movements every 5 days, and only 29% were classified as continent (Schnelle et al, 2009). These rates improved substantially to 74% continent after use of relatively simple targeted therapies including prompted toileting. Multimodal therapy may also be quite useful in older adults with UI and FI and has been shown to substantially reduce problems with constipation (Schnelle et al, 2010).

Continence Promotion and Advocacy

Education of patients and providers is a critical aspect of continence promotion for older adults (Newman et al, 2013). There are a number of common myths about UI in geriatrics that hamper appropriate evaluation and treatment in many cases. **UI should never be considered a normal or inevitable part of the aging process.** Patients and providers need to be aware that there are often treatments that can substantially improve and in some cases completely eliminate incontinence. Many of these successful therapies involve nonsurgical methods. Surgery may be an appropriate and successful treatment option for some select patients with specific clinical indications.

Enhanced public awareness may improve access to and use of care services. An analysis of data from more than 82,000 elderly Medicare beneficiaries demonstrated a 37% prevalence of UI, but only 41% of those who experienced UI had spoken with a health care professional about their symptoms (Chang et al, 2008). Some have argued that systematic screening for UI may be beneficial among older women (Visser et al, 2013). In a survey study, elderly women indicated that they did not seek help because they did not feel their symptoms were severe enough to justify treatment (73.4%), they had already found a way to cope with symptoms (57.3%), they thought UI was a normal part of aging (46.9%), they thought there was no cure or effective treatment available (23.8%), or their general practitioner did not ask about UI (20.3%) (Visser et al, 2012). These findings demonstrate that there is a role for improved public and professional education and a need for advocacy on this topic.

Targeted continence promotion programs for older adults have been successful in the community setting. These can increase knowledge among patients with incontinence and have been shown to encourage help-seeking and self-treatment behaviors (Tannenbaum et al, 2010). Evidence-based self-management tools have been developed and can be useful in this process for motivated patients (Holroyd-Leduc et al, 2011). Future research will help improve understanding of the best methods for dissemination of this type of information among older adults with UI and other urologic conditions.

Pelvic Organ Prolapse

POP is a common clinical condition seen in elderly women. Incidence and prevalence of POP both increase with advancing age, but like other conditions it should not be considered an expected or normal part of the aging process. **Risk factors for POP in elderly women include history of prior pregnancy and vaginal delivery, prior pelvic trauma, and changes in tissue quality and structure.** Biopsy studies have shown that with advancing age there is a progressive loss of smooth and striated muscle and an increase in collagen and other connective tissues in the urogenital diaphragm (Betschart et al, 2008). Apoptotic changes in pelvic floor tissues also occur that can predispose to prolapse (Saatli et al, 2014). These changes lead to laxity of pelvic floor architecture and subsequent loss of support.

Evaluation of POP in elderly women requires careful history and physical examination. Many older women describe the sensation of a vaginal bulge. This is often worse after physical activity or in the late afternoon or evening after the patient has been up and about during the day. **Severe prolapse can be associated with difficulties with urination or defecation as a result of urethral angulation or anatomic changes in rectal configuration.** Some women, particularly with a large prolapse, will describe a need to manually reduce the bulge with their fingers to void or defecate. The clinician should attempt to reduce the prolapse during pelvic examination. The position of the uterus, if present, and the vaginal cuff should be assessed. Prolapse of the vaginal apex may require specific surgical fixation to either the sacrospinous or uterosacral ligaments.

Pessaries can be quite useful in treatment of POP in elderly women. These come in a wide variety of shapes and sizes and need to be individually fitted to the patient. When correctly sized, the patient is usually unable to feel the pessary in the vagina. If the pessary is too small, it will tend to fall out with physical activity or straining. If it is too large, the pessary will tend to be uncomfortable and may cause tissue irritation or erosion over time. Pessaries should be removed and cleaned periodically, and the tissue integrity checked (Khaja and Freeman, 2014). In patients with limited hand dexterity or cognitive impairment, this might require assistance from a care provider. Visiting nurse services can sometime help with pessary management. It is important that the pessary be routinely checked to avoid complications associated with neglect including erosion into surrounding structures or vaginal infections. Concomitant use of vaginal estrogen can be useful to help prevent some of these complications.

Pessaries offer potential advantages of avoiding surgery and allowing patients self-control over the clinical situation. Many older women do very well with pessaries and continue to use them over time. Factors associated with increased long-term success include age 72 years or older, careful fitting, and provision of clear instructions for use (Friedman et al, 2010). Successful pessary use has been associated with improved overall and health-related QoL, and improved body image in elderly women with POP (Patel et al, 2010). However, some older women do not like using pessaries or do not want to be bothered with having to remove and replace the device on a regular basis. If the pessary improves genitourinary symptoms but the patient does not like using the device, this may indicate that she could experience a good functional outcome with surgery.

Surgical repairs for POP are feasible even in elderly women. These procedures can be done using vaginal, laparoscopic, robotic, or open surgical techniques. A variety of both native tissue repairs and procedures using biologic or mesh grafts can be used. Several studies have shown that mesh repairs can be successful for treatment of POP even in elderly women (Shah et al, 2004; Gabriel et al, 2010). However, as with any surgical treatment, patients do need to be very carefully counseled about use of mesh grafts and potential risks and benefits associated with this technique (Mohammed et al, 2013; Reynolds et al, 2013). Surgical repair with native tissue grafts such as autologous or cadaveric fascia has also been successfully used in elderly women with POP and UI (Carey and Leach, 2004). Many older women may choose to avoid or delay surgery for POP.

However, in those who do eventually undergo surgical repair, there is evidence to suggest that increased time between development of symptoms, particularly after menopause, and subsequent surgery is associated with poorer subjective postoperative improvements (Ahn et al, 2010).

One surgical option that can be considered for select older women with POP is colpopcleisis with perineoplasty. This procedure essentially reduces the prolapse and closes the vaginal introitus. This should be considered a permanent and nonreversible procedure. Two different surgical techniques are used. In women who still have their uterus, the procedure is usually performed leaving lateral channels on each side of the vaginal vault to permit uterine drainage. Total colpopcleisis is used in women after hysterectomy and consists of a denudation of the vaginal mucosa and subsequent reduction and conical closure of the prolapse. Perineoplasty is performed to reduce the size of the vaginal introitus and prevent recurrence of bulging from the outlet. Women need to be expressly counseled that penetrative sexual activity will not be possible after this type of surgery. However, it does not preclude other forms of erotic or sexual activity. Reported success rates with colpopcleisis have been quite high, and rates of subsequent regret after having the procedure are quite low (Koski et al, 2012; Vij et al, 2014). Colpopcleisis has been shown to improve both bladder and bowel symptoms in women with a history of significant prolapse (Gutman et al, 2010; Vij et al, 2014).

Urethral caruncle is a protrusion of tissue from the urethra and is seen more commonly in elderly than in younger women. In most cases these are painless and benign. Unless they are quite large, they often do not affect voiding function. (Ozkurkcugil et al, 2010). Topical estrogen therapy is useful and often leads to tissue contraction and involution of the caruncle. Surgical excision is not typically necessary. However, if surgery is performed, care must be taken to avoid damage to the external urethral sphincter, which could lead to stress UI.

Urinary Tract Infections and Asymptomatic Bacteriuria

UTI is one of the most common clinical conditions seen in older adults, and particularly in elderly women. **It is important to distinguish between symptomatic UTIs and asymptomatic bacteriuria.** Symptomatic infections require evaluation and treatment, usually with antibiotic therapy. **Urinary cultures are strongly recommended to verify the infection, determine the associated bacterial organism, and identify antibiotic susceptibility or resistance patterns.** Empiric treatment with antibiotics may need to be modified depending on the results of the urine culture and drug susceptibility panels. If older adults have difficulty providing a clean-catch urine specimen, a catheterized urine sample should be obtained to help with accurate diagnosis (Gordon et al, 2013).

Symptoms of acute UTI may include urinary urgency and frequency, cloudy or foul-smelling urine, fever, bladder pain, and dysuria. However, many older adults may not show these symptoms as a result of alterations in the immunologic or other systems (Arinzon et al, 2012). Instead, **elderly patients may experience what have been called "atypical" symptoms in other populations.** These include confusion, agitation, lethargy, and anorexia, among others (Juthani-Mehta et al, 2009). Acute UTIs in older adults can lead to clinically symptomatic delirium (Eriksson et al, 2011). Urine cultures should be checked to determine if an associated UTI is present, and appropriate antibiotic therapy initiated if indicated.

More complex UTIs such as pyelonephritis are often associated with underlying comorbidity including diabetes, anemia, and urolithiasis (Kang et al, 2008). Antibiotic therapy should be instituted in most cases and should be based on culture and drug susceptibility results. **Urosepsis in elderly patients can be quite serious, and increased mortality is seen in this population.** Associated factors that increase the risk of mortality from bacteremia in geriatric patients include advanced age (≥ 85 years), chronic renal disease, severe cognitive impairment, and hypothermia (Rebelo et al, 2011). Hospital-acquired UTIs also appear to carry a greater risk for mortal-

ity than community-acquired infections, at least among older adults in acute hospital settings (Chin et al, 2011). Treatment of these serious infections typically requires directed antibiotic therapy and fluid resuscitation. Fungal UTIs occur more commonly with advanced age, and particularly in patients with reduced immune status, including those with a history of transplant, advanced human immunodeficiency virus (HIV) disease or acquired immunodeficiency syndrome (AIDS), or poorly controlled diabetes. Treatment with antifungal agents such as fluconazole can be effective in many cases (Fraissee et al, 2011).

In contrast, asymptomatic bacteriuria is very common in older adults and in general does not require therapy. Approximately 10% to 20% of all older women living in the community will have bacteria in their urine on routine analysis, and rates are typically higher in long-term care and other institutional settings (Varli et al, 2012). Although less common than in women, rates of asymptomatic bacteriuria still approach about 10% in community-dwelling elderly men (Juthani-Mehta, 2007). Asymptomatic bacteriuria has been associated with increased serum and urinary inflammatory cytokines, but this does not necessitate antibiotic therapy (Chang et al, 2012b). Dipstick urinalysis can be useful in diagnosis, particularly in long-term care settings, with a goal of correctly differentiating symptomatic UTI and asymptomatic bacteriuria and reducing overuse of antibiotics when not clinically indicated (Bonnal et al, 2008; Sundvall and Gunnarsson, 2009). The AGS has included avoidance of antimicrobial therapy for asymptomatic bacteriuria as one of their original five things to avoid or question as part of the Choosing Wisely campaign (AGS Choosing Wisely Workgroup, 2013).

A variety of clinical factors increase risk of UTIs in older adults. Catheter-associated UTIs are one of the most prevalent types of infection seen in acute care hospitals and other inpatient settings (Daniels et al, 2014). CIC can reduce infection rates in patients with chronic urinary retention, although one study of elderly stroke survivors did show a trend toward increased infection rates (Stott et al, 2009). However, this association disappeared after controlling for stroke severity. BMI has been linked to UTI in older adults, with both obese and significantly underweight elderly patients having higher rates of infection (Dorner et al, 2010).

Administration of vaginal estrogens can be quite useful in reducing rates of symptomatic UTIs in elderly women. After menopause, there is loss of the natural acidification of vaginal fluid. This increased alkalinity prevents growth of *Lactobacillus* species, the natural flora in the vaginal vault. *Lactobacillus* is an important part of the natural host-defense mechanism to prevent UTI. **Addition of topical vaginal estrogens can help reacidify vaginal fluid, which permits growth of *Lactobacillus* species.** This in turn helps to kill off pathogenic bacteria that cause symptomatic UTI. The medication comes in several different forms including vaginal creams, vaginal tablets or suppositories, and a small ring-shaped device that releases estrogen continuously over several months. If using creams, a small amount with fingertip application in the vagina is usually sufficient if administered three times weekly at bedtime. Vaginal estrogens are in general contraindicated in women with a personal history of either breast or uterine cancer. However, emerging data suggest that women with known estrogen receptor negative (ER-) breast cancers may be able to safely use this type of therapy. The amount of estrogen absorbed systemically is usually low. Patients with this type of history should consult with their oncologist before starting therapy.

The use of cranberry juice or other cranberry supplements is popular with many people as a form of UTI prophylaxis. This works by interaction between fructose and proanthocyanidins in cranberry and bacterial cell walls, which leads to inhibition of adherence to the urothelium. Although many people describe clinical efficacy, results in scientific studies have been mixed. Recent data from a randomized, double-blind, placebo-controlled trial in nursing home residents showed there were reductions in infection rates, but these were limited to those patients with a previously high rate of infections (Caljouw et al, 2014). The overall cost-effectiveness of cranberry therapy also appears to be limited based on observed

clinical outcomes and economic analysis, which demonstrated an estimated cost exceeding \$5200 annually to prevent one clinically significant UTI (van den Hout et al, 2014).

Chronic antibiotic use for UTI prophylaxis should be avoided, unless no other options are available, because of an increased risk of development of resistant organisms. The choice of antibiotics is also important. Although it can be useful for short treatment of acute infections, nitrofurantoin should be avoided for chronic prophylaxis because of risks of pulmonary fibrosis and associated complications in older adults. In addition, it should be avoided in those with impaired renal function, defined as creatinine clearance (CrCl) below 60 mL/min (Leung et al, 2007; AGS Beers Criteria Update Expert Panel, 2012).

Evaluation and management of UTIs in nursing home and assisted care settings require special consideration. Overuse of antibiotics is very common in these locations, which may be a result of the substantial challenge of correctly diagnosing symptomatic UTIs in older nursing home residents who may have subtle or atypical symptoms (Juthani-Mehta et al, 2007; D'Agata et al, 2013; Kistler et al, 2013). In addition to avoiding treatment of asymptomatic bacteriuria, careful antibiotic selection is important. **Use of antibiotics based on local prevalence of specific organisms can help guide therapy.** Guidelines from professional organizations can also help to reduce overuse of specific antibiotics that may increase the risk of developing drug-resistant infection in given locations (Daneman et al, 2011; Fagan et al, 2012). As with acute care hospitals, there are data to suggest that environmental contamination in nursing homes may increase the risk of some types of infections including methicillin-resistant *Staphylococcus aureus* (Murphy et al, 2012). Strict hand washing and other infection-prevention methods can help to substantially reduce this risk.

The costs associated with evaluation and treatment of UTIs in the United States are staggering and surpass those for almost all of the other major genitourinary disorders (Griebing, 2005a, 2005b). This is a result of multiple factors including a high incidence and prevalence of UTIs, but also excess evaluation and overtreatment of conditions that may not require therapy including asymptomatic bacteriuria. A sizeable volume of clinical care for UTIs is provided in emergency room settings, which exponentially increases associated costs.

Hematuria

Hematuria is a common clinical condition seen in elderly patients, particularly those on anticoagulants. Patients with gross or persistent microhematuria should undergo clinical evaluation (Davis et al, 2012). The use of anticoagulation is common in older adults, particularly for prevention of stroke in those with atrial fibrillation and other arrhythmias, deep vein thrombosis, and other hematologic disorders. Supratherapeutic anticoagulation, particularly with warfarin, has been associated with an increased risk of developing acute kidney injury (AKI). (Lim and Campbell, 2013).

Genitourinary Trauma

Evaluation and management of genitourinary trauma in elderly patients requires some special considerations. Compared with younger adults, elderly patients are more likely to experience blunt rather than penetrating traumatic injuries. Underlying comorbidity and clinical conditions associated with the aging process put geriatric patients at higher risk for poor outcomes. For example, falls are one of the leading causes of traumatic injuries among older adults, with more than 2.3 million emergency room visits for this annually in the United States (CDC, 2010). The rate of genitourinary injuries caused by falls in geriatric patients is 26.5% compared with 8.4% in younger adults ($P < .0001$) (Bjurlin et al, 2011).

The basic principles of management of genitourinary trauma do not differ considerably based solely on age. The decision for conservative versus more aggressive therapy should be based primarily on the nature of the injury. However, careful consideration of associated comorbidity with medical optimization of these other conditions is essential for successful management. For example, **older adults with osteoporosis may be at higher risk for pelvic fracture resulting from falls compared with those without this associated comorbidity.** Treatment in these patients may require different techniques including greater use of embolization therapy than in younger or healthier patients (Kimbrell et al, 2004). **Men on ADT are at higher risk for hip and long bone fractures because of changes in bone mineral density associated with hormonal therapy** (James et al, 2014). Treatment with agents such as alendronate or zoledronic acid may decrease this fracture risk in these patients (Planas et al, 2009; Campbell et al, 2010).

Older adults are also more likely to require discharge to either a rehabilitation facility or nursing home (13.6% and 18.5%, respectively) compared with younger adults (8.6% and 3.1%, respectively) after acute management for genitourinary trauma (both, $P < .0001$) (Bjurlin et al, 2011). Geriatric trauma is a relatively new scientific field, and additional work will be needed to better identify specific protocols for this population. Early research has shown that inclusion of data on chronic comorbidities in geriatric trauma patients may be superior to traditional measures of vital signs and injury pattern alone in decision making and clinical outcomes (Brooks et al, 2014). In addition, there is interest in creating and validating an index of frailty specific for elderly trauma patients to see if this may influence evaluation, treatment, and outcomes (Joseph et al, 2014).

Prostate Cancer

The evaluation and treatment of prostate cancer in elderly men differs somewhat from the general population. The U.S. Preventive Services Task Force recommendation does not support routine screening for prostate cancer in any group, although this is highly controversial (U.S. Preventive Services Task Force, 2008; Moyer et al, 2012). When prostate cancer screening is performed, it is generally recommended that this be discontinued in men once they reach 70 to 75 years of age. This is because definitive therapy for prostate cancer is typically reserved for men with an estimated remaining life expectancy of 10 or more years (Hoffman et al, 2010). Because the mean life expectancy for men in the United States is approximately 82 to 84 years, most clinicians would argue to limit use of definitive therapy with radical prostatectomy or radiation therapy to those aged 75 years or younger. It is interesting to note that in survey research, about a third of older adults indicate that they would rather not know either their predicted life expectancy or survival probability (Clarke et al, 2008). This can be problematic in relation to discussions about clinical decisions in this population.

Recent research has examined factors that can be associated with recommendations to stop screening, including PSA velocity and genetics, and risk factor group profiles (Tang et al, 2010, 2011). Despite these recommendations, many older men choose to continue screening for various personal reasons (Caire et al, 2010; von Wagner et al, 2013). There is also some variation among practitioners in terms of following these guidelines for discontinuing screening in geriatric men (Hudson et al, 2009; Bynum et al, 2010; Whittle, 2010). In contrast to routine screening, targeted diagnosis in select patients at risk for prostate cancer can help to guide therapy, even if it is not done with curative intent (Paterson et al, 2013). This can help in the overall care and management of disease in older men.

There are a number of caveats that must be considered based on the overall clinical situation for each man. The AUA has published guidelines on treatment of clinically localized prostate cancer that include considerations related to overall health, comorbidity, and age (Thompson et al, 2007). The International Society of Geriatric Oncology recently published results of a study indicating the importance of including assessment of ADL and IADL function in the care decisions for elderly men with prostate cancer (Droz et al, 2010). The combination of functional status and disease burden combined with predicted longevity and other parameters may help with this complex decision process.

Although prostate cancer in elderly men is often an indolent, slow-growing disease, some patients have more aggressive cancers (Scosyrev et al, 2012; Kunz et al, 2013). Various factors may predispose to more advanced prostate cancer in elderly men, including a history of hypertriglyceridemia (Hayashi et al, 2012). However, other studies continue to show that most elderly men die of other diseases including cardiovascular and pulmonary disorders (Jeong et al, 2009; Ketchandji et al, 2009).

Several studies have shown that elderly men who undergo radical prostatectomy can have good clinical outcomes that in many cases are equivalent to those seen in younger men (Greco et al, 2009; Namiki et al, 2010; Pierorazio et al, 2010). However, other studies have demonstrated that elderly men are at higher risk for negative clinical outcomes including upgrading and upstaging of their disease, greater risk for biochemical recurrence, and surgical complications (Richstone et al, 2008; Trinh et al, 2012; Ko et al, 2013). Radiation therapy is often used in elderly prostate cancer patients because it is considered to be less invasive. It has been associated with acceptable clinical outcomes including health-related QoL, although as with any treatment there are risks for incontinence and erectile dysfunction, among others (Namiki et al, 2010; Mirza et al, 2011). UI can be particularly bothersome in elderly men treated for prostate cancer. This can have substantial negative effects on activity, mood, and QoL (Park et al, 2012; Kopp et al, 2013). Cryotherapy has been advocated as a possible treatment for elderly men with

organ-confined prostate cancer who may not be candidates for more invasive forms of therapy (Dhar et al, 2011).

In elderly men with metastatic prostate cancer, hormonal therapy or chemotherapy may be used to reduce disease progression. Docetaxel has been shown to improve overall survival in early trials (Miyake et al, 2012). ADT can certainly be useful in select patients but is also associated with potential adverse effects, particularly in elderly men. ADT has been shown to increase the risk of cardiovascular disease, myocardial infarction, and diabetes in elderly men (Keating et al, 2013). Changes in bone mineral density are associated with increased risk of fractures as a result of osteoporosis and osteopenia (Shao et al, 2013). These effects can be tempered by the use of agents such as alendronate and zoledronic acid (Planas et al, 2009; Campbell et al, 2010). Other negative side effects include decreased libido, gynecomastia, hot flashes, and sexual dysfunction. ADT has also been linked to development of sarcopenia in elderly men (Reis et al, 2009). Finally, the cost of ADT may be a barrier to ongoing therapy for some patients (Krahn et al, 2011).

Bladder Cancer

Bladder cancer is one of the most common urologic malignancies seen in the geriatric population, and incidence and prevalence both increase substantially with advancing age. Owing to the long latency of carcinogen exposure, age is one of the most important independent risk factors for development of bladder cancer, with a median age at diagnosis above 70 years (Shariat et al, 2010b). In general, diagnosis is similar in elderly and younger patients. Diagnosis of bladder cancer is associated with negative effects on overall and health-related QoL, with reductions in both physical and mental health domains (Fung et al, 2014).

Guidelines have been developed for evaluation and management of bladder cancer, and an audit study showed that these are generally followed (88.8%) in elderly patients (Bolenz et al, 2010). The role of tumor restaging with repeat resection has been demonstrated in elderly patients, although rates have been shown to be quite low among Medicare beneficiaries (Skolarus et al, 2011). This can be very useful to help identify muscle-invasive disease, which may require different treatment. It is interesting to note that bacille Calmette-Guérin (BCG) therapy has shown decreased efficacy in elderly patients with non-muscle-invasive bladder cancer compared with younger patients (Margel et al, 2011). This may result from an age-related decrease in the immune system and reduced ability to mount an immune response to therapy in geriatric patients.

Treatment for muscle-invasive bladder cancer has usually focused on surgical extirpation with radical cystectomy and urinary diversion. From a surgical standpoint, this is one of the most invasive and potentially morbid surgeries done in the field of urology. In addition, many of these patients have substantial underlying comorbidity. For example, the condition is strongly linked to a history of smoking, which can predispose to lung disorders such as COPD and restrictive airway disease. These increase the risk of anesthetic complications in this already vulnerable population.

Multiple studies have demonstrated that with careful preoperative planning and intraoperative and postoperative management, radical cystectomy can be accomplished safely even in elderly patients (May et al, 2007; Guillotreau et al, 2012). This appears to convey a potential survival advantage in many patients (Tyritzis et al, 2012). However, this needs to be evaluated within the context of overall health and comorbidity. Many patients with bladder cancer may die of other competing conditions, and this must be considered when making treatment decisions for elderly patients with muscle-invasive bladder cancer (Fisher et al, 2009; Resorlu et al, 2009; Donat et al, 2010). Some studies have shown an increased rate of perioperative and postoperative complications in elderly patients undergoing radical cystectomy, likely as a result of other chronic disease and functional status (Lund et al, 2010; Liberman et al, 2011). Sarcopenia, a key component of the frailty phenotype, appears to be a predictor of postoperative complications

in elderly women undergoing radical cystectomy (Smith et al, 2014a). Diminished performance status has been shown to be a negative predictor of outcomes among geriatric patients treated for muscle-invasive bladder cancer (Weizer et al, 2007).

Bladder-sparing therapies with endoscopic resection and adjuvant chemotherapy or radiation have been used in research in geriatric patients with muscle-invasive bladder cancer. Some studies have shown similar survival rates for more conservative therapy compared with radical cystectomy (Martini et al, 2013). However, overall time in the hospital is often longer for those treated with bladder-sparing therapies, and this can have a negative effect on remaining QoL (Wehrberger et al, 2010). Other data suggest that very elderly patients and those with greater clinical comorbidity have poorer outcomes in terms of both overall and cancer-specific survival (Tran et al, 2009; Kohjimoto et al, 2010). Radiation therapy has been used mostly for palliation of significant bleeding in patients who are otherwise not suitable surgical candidates (Kouloulis et al, 2013). This therapy appears to be well tolerated in these select patients.

Kidney Cancer

Kidney cancer is often diagnosed as an incidental finding in geriatric patients undergoing abdominal imaging for other conditions. Over the past 30 years, there has been a steady increase of 2% to 3% annually in the incidence of kidney cancer diagnoses (Chow et al, 1999). Although increased rates of kidney cancer have been seen in all age groups, the largest have been identified in those in the seventh and eighth decades of life (Katz et al, 1994). In elderly patients with small tumors, surveillance is feasible and may preclude the need for invasive surgery (O'Malley et al, 2010). Advanced age above 75 years has been identified as a risk for more advanced disease, and older adults may need to be watched with greater caution. It is important to consider overall health and comorbidity when making treatment decisions. Use of measures such as the CCI can be useful in this regard and can help identify those who may be at substantially higher risk with treatment (Charlson et al, 1987; O'Connor et al, 2009).

Older adults have been shown to tolerate both radical and partial nephrectomy. In general, complication rates do not appear to be substantially influenced by chronologic age, but more by comorbidity (Roos et al, 2008; Sun et al, 2012). Laparoscopic and robotic procedures for partial nephrectomy appear to be well tolerated by older adults with similar clinical outcomes and complication rates compared with younger patients (Guzzo et al, 2009; Thomas et al, 2009; Hillyer et al, 2012). However, rates of use of partial nephrectomy in elderly patients still lag behind younger cohorts (Kates et al, 2011). The reasons for this are unclear but may be based on concern over underlying clinical conditions and ability to perform surgery in frailer older adults.

In patients with more advanced disease, cytoreductive nephrectomy has been used successfully in elderly individuals, although some complications including need for transfusion are higher in geriatric patients (Kader et al, 2007; Sun et al, 2012). Subsequent immunotherapy may be difficult in some patients, particularly if they have functional impairments and decreased overall performance status. Radical nephroureterectomy has been described in geriatric patients with upper tract urothelial cancers, although reported cancer-specific survival has been lower in those older than 80 years compared with younger patients (Shariat et al, 2010a).

Testis Cancer

Although testis cancer can occur at any age, most germ cell tumors occur in young men aged 15 to 35. **In geriatric men, the most common testicular malignancy is lymphoma (Shih et al, 2014).** This should be evaluated and treated as a systemic condition because isolated testicular involvement is rare. When germ cell tumors of the testis do occur in elderly men, evaluation and general treatment principles should follow those of younger men. One important caveat is that doses of chemotherapeutic agents may need to be adjusted based on comorbidity that affects renal, hepatic, or pulmonary function. This highlights the need for a thorough geriatric assessment in these patients. With successful treatment, life expectancy approaches that of other elderly men without testis cancer (Wheater et al, 2011).

elderly women. Use of water-based lubricants and vaginal estrogen replacement therapy may be useful in these cases. Many chronic diseases that affect sexual health tend to be under-reported and underdiagnosed among older adults. For example, hypogonadism, erectile dysfunction, and osteoporosis are conditions that influence sexuality and overall health but that frequently remain undiagnosed in elderly men (Frost et al, 2012).

Sexual health has also been closely linked to mental health in older adults, with higher rates of depression noted in those with erectile or sexual dysfunction (Cheng et al, 2007; Korfage et al, 2009). Body image is an important factor with regard to sexual satisfaction and mental health regarding sexuality (Carr et al, 2013). This can be affected by a number of factors including weight, BMI, and history of prior genitourinary cancer surgery or stoma formation. In longitudinal studies of men, regular sexual activity has been identified as a protective factor in continued sexual health and is associated with lower rates of subsequent erectile dysfunction (Koskimäki et al, 2008).

There are important differences in human sexuality between men and women. In comparison to the plethora of data on evaluation and treatment of erectile dysfunction in men, there has been much less research conducted examining sexual response and health needs in elderly women. **Population-based research does show that many elderly women remain interested in sex and have sexual health care concerns that deserve clinical attention** (Huang et al, 2009; Schick et al, 2010). As with men, comorbid disease such as metabolic syndrome and diabetes can have a negative influence on sexual health (Kim et al, 2011b). Older women have been found to place strong emphasis on relationships and psychosocial aspects of sexuality including intimacy (Kim and Jeon, 2013). Improved sexual function has been linked to better self-rated health and life satisfaction in cohort studies of geriatric women (Woloski-Wruble et al, 2010; Thompson et al, 2011). In women who have undergone prior treatment for urologic or gynecologic disease, treatment of the underlying pathology can have a substantial impact on sexual health, and this must be considered in evaluation and treatment (Ratner et al, 2011).

Environmental factors can influence sexual health for many older adults. In some cases, elderly persons may live with extended family or be in situations where privacy for sexual activity may be an issue. **Sexual health in nursing home residents deserves special consideration.** There has been an increased awareness and understanding of this in recent years, and many nursing homes work to accommodate this for residents (Mroczek et al, 2013). This may include allowing couples to live in the same room and share a bed, providing privacy and time free from interruptions or medical care, and offering specific medical and nursing care for sexual health needs. Recent research has worked to develop and validate an assessment instrument specific for sexual health in nursing home residents (Bauer et al, 2014). **In patients with dementia and other cognitive impairment, inappropriate displays of sexual behavior may occur and can be problematic. Specific evaluation and treatment tailored to these issues can be useful in these cases** (Bardell et al, 2011).

Treatment of sexual health problems should be designed to address the needs of each individual patient. This must be done in the context of overall health and comorbidity. For example, elderly men with heart disease may not be candidates for PDE5 inhibitors if they have a history of chest pain and use nitrates or take medications that contradict use of this treatment. Some elderly men may have physical or cognitive impairments that limit the use of other therapies such as penile injections or vacuum erection devices. Surgery with placement of a penile prosthesis may be an option for some patients but could be limited in those who are poor surgical candidates. Some men do well with this, and advanced age alone should not be the deciding factor for selection for surgery (Al-Najar et al, 2009).

Some adults may engage in relatively high-risk sexual behaviors, and this can put them at risk for transmission of sexually transmitted diseases including HIV. Condom use in this age group has been reported to be relatively low overall and may increase risk for some

people (Schick et al, 2010; Choe et al, 2011). This generation was never really targeted in public health campaigns about safer sex, and specific counseling about this is warranted. Some health care providers may lack awareness or expertise about geriatric sexuality. **Clinicians need to appreciate their own level of comfort and knowledge in providing sexual health care in the geriatric population and should seek additional information or consultation with others if needed.**

Sexual orientation is an important factor to consider in sexual health care. To date there has been relatively little research on the specific sexual health needs or goals of elderly lesbian, gay, or bisexual persons. Additional work in this field will help to increase understanding to improve quality of care. Transgendered older adults may also have unique urologic needs including hormonal replacement and care after reconstructive surgery (Gooren and Lips, 2014). Cultural and religious views play an important role in human sexuality and should be considered and respected in the evaluation and treatment of sexual health in the older adult population. **The goal should be to provide sexual health care that is respectful of each patient's needs, desires, and goals of therapy.**

Discharge Planning and Care Coordination

Successful management of geriatric urology patients, particularly those undergoing surgical therapy, requires careful coordination and planning. Within this context, discharge planning is vitally important. **Many older adults admitted to the hospital or who undergo surgery will lose independence of at least one of the ADLs at least temporarily.** This may necessitate assistance from caregivers or transition to another place for care. A variety of options are available after discharge from the acute care hospital, including home health nursing or other care services, inpatient or outpatient rehabilitation, and placement in a skilled care facility. Nearly \$40 billion dollars are spent annually on this type of postdischarge care, which represents about 10% of the total Medicare budget (Robinson et al, 2011). Full recovery to prehospitalization baseline levels can occur but is less common than some level of continued impairment (Gill et al, 2009).

High-quality communication between acute care discharging hospital staff and receiving staff at long-term care facilities can greatly facilitate these transitions (King et al, 2013). Goals of care must be carefully considered, and needs and abilities of family or other loved ones to assist in the process must be assessed. Cost is an important factor, and options may be determined in part by coverage available to individual patients. **Ideally, discharge planning should begin as early as possible when treatment determinations are being made.** If the patient is to return to his or her home in the community, what is the environment like and how will this influence function? Are there stairs in the home, and is the patient able to maneuver them safely? What are the toilet facilities like in the home, and are modifications such as grab bars, a bedside commode, or other accommodations needed? Input from professionals in multiple health care disciplines including urology, nursing, physical and occupational therapy, social services, and others can be extremely helpful. The psychological and emotional needs of the patient and caregivers should also be considered (Farage et al, 2008; Gotoh et al, 2009). Development of UI can be particularly stressful for older adults who may already have substantial other requirements (deVries et al, 2012). Particularly with patients whose care needs are significant or require extensive time, caregiver burden must be considered (Tamanini et al, 2011).

Elder Mistreatment

Mistreatment of older adults is an unfortunate but common problem that requires vigilance and a high index of suspicion for optimal diagnosis and intervention. **Screening for elder mistreatment is a responsibility of all health care providers.** In the United States and many other countries, health care providers are mandatory reporters for suspected abuse or neglect. Clinicians who report suspected elder mistreatment in good faith are typically

protected from liability or retaliation. Increasingly, urologists and other urologic health care providers are seeing older adults on an ongoing basis for treatment of chronic conditions. Therefore these clinicians may be in an excellent position to identify potential abuse and neglect among elderly patients. **A variety of types of elderly mistreatment must be considered, including physical abuse, emotional and psychological abuse, sexual abuse, financial exploitation, and neglect by caregivers or self-neglect.**

A careful history and physical examination are essential to diagnose and document suspected elder mistreatment. Ideally, the interview and examination should be conducted privately with the older adult, but this can be difficult, particularly if the patient has impairments in cognition, vision, speech, or hearing. **Providers need to be alert to potential signs of abuse or neglect** including overall appearance; poor hygiene; distractions or nervous interactions, particularly with accompanying caregivers; or social withdrawal and avoidance of questions. Other physical signs of abuse and neglect include bruises, abrasions or lacerations, or physical findings that are out of proportion to the described mechanism of injury. A careful genitourinary and pelvic examination should be performed in cases of suspected sexual abuse, and screening for sexually transmitted infections should be considered.

Identification of sexual mistreatment of older adults is particularly in the realm of urologic care. It is defined by the National Center on Elder Abuse as “nonconsensual sexual contact of any kind” (U.S. Department of Health and Human Services, 2014). Clinicians should be alert for signs and symptoms of sexual abuse including genital lacerations or other injuries, unusual or unexpected infection patterns including sexually transmitted infections, and avoidance behavior or fear on the part of the patient. Changes from prior observed behavior may be particularly noticeable if the clinician has been following an older adult patient longitudinally over time.

UI has been identified as a risk factor for increased rates of psychosocial abuse against elderly people (Garre-Olmo et al, 2009). Increased rates were also noted in those with depression and social isolation, conditions that are often associated with incontinence. **UI has been identified as a risk factor for neglect of older**

adults by their caregivers (Heath et al, 2005). Self-neglect by older adults is also a common but frequently undiagnosed problem. **Increased rates of self-neglect have been associated with higher levels of self-reported disability and impairments in baseline physical function (Dong et al, 2009).** The question of whether successful treatment of UI among older adult patients will help prevent or reduce rates of associated abuse and neglect deserves additional research attention.

END-OF-LIFE CARE AND UROLOGY

Palliative and end-of-life care is an important part of urologic health for many older adults. Some of the urologic malignancies may progress to a point where palliative care is appropriate. **When cure of the condition is no longer possible, treatment can shift to a palliative care mode. This does not mean that all treatment is withdrawn or that it is less focused or intense than curative therapy. Indeed, aggressive symptom management is one of the hallmark goals of palliative care** for most patients. Urologists and other urologic health care providers play a key role in the care of patients at the end of life who have genitourinary disorders.

Important aspects of high-quality palliative care include pain and symptom management, realization of personal goals for the patient and family, and coordination of care (Agar et al, 2009). Surgical therapy may play a role in select cases where cytoreductive therapy for a large tumor burden or removal of tumor for intractable bleeding or pain may help to relieve symptoms. In some cases, urinary or bowel diversion may be indicated for this purpose. Selective radiation therapy for painful bone metastases may be useful. Treatment is highly selective and tailored specifically to the needs of each individual patient. Integrated health care delivery models that include providers from multiple disciplines are feasible and can help to improve the delivery of care in these circumstances (Bergman et al, 2014). Among older adults in assisted living facilities, use of hospice services has been shown to reduce need for nursing home or other institutional placement (Dobbs et al, 2012). This can allow patients to remain living at home as long as possible

KEY POINTS

- Patient-centered care is a main focus in geriatrics, and evaluation and treatment should be tailored to meet the needs and goals of each individual. This includes consideration of family and caregiver needs.
- Multiple biologic processes contribute to the phenomenon of normal aging.
- Human aging affects the structure and function of all organ systems, including the genitourinary system.
- The elderly population is growing at a very rapid pace both in the United States and in most developed countries worldwide.
- Decreased functional reserve capacity and increased comorbidity are common with aging and strongly influence clinical outcomes.
- In addition to considering overall health status, functional assessment in geriatric patients includes evaluation of ADLs, IADLs, mobility, cognition, and other health domains.
- Comorbidity and changes in functional status tend to be stronger predictors of clinical outcomes in older adults compared with chronologic age.
- Careful optimization of medical conditions before surgery or other treatment may help improve clinical outcomes and reduce complications in geriatric urology patients.
- Geriatric syndromes are complex, multifactorial conditions that can negatively affect elderly patients. Examples include frailty, falls, pressure ulcers, polypharmacy, delirium, and UI.
- Transient UI is common in older adult patients and can be caused by many different factors. Successful treatment of the underlying condition will often help to improve or resolve the incontinence.
- Established UI is associated with substantial negative effects in elderly patients such as depression, limitation of activities, and social isolation. Evaluation and treatment plans should be individualized and can help to improve or resolve symptoms in many cases.
- Lower urinary tract and bowel dysfunction including BOO, UAB, urinary retention, nocturia, and FI are common in geriatric patients.
- POP can be successfully treated in many elderly women through use of both surgical and nonsurgical methods.
- Asymptomatic bacteriuria in geriatric patients does not usually require antibiotic therapy and needs to be differentiated from symptomatic UTI.
- Almost all of the genitourinary malignancies have higher incidence and prevalence with advancing age.
- Sexuality remains an important part of overall and health-related QoL for most older adults. Symptoms of sexual dysfunction may be signs of other underlying comorbidity such as heart disease, diabetes, or neurologic conditions.
- Urologists and urologic health care providers can play a key role in identifying elder mistreatment and neglect.
- High-quality palliative and end-of-life care is an important part of geriatric urology practice.

and can increase QoL outcomes in this setting. Consultation with trained, dedicated palliative care specialists can be extremely helpful in providing necessary care for older adults near the end of life.

SUMMARY

The aging process can have substantial effects on the genitourinary system in both men and women. Care for older adult patients needs to be tailored to their specific requirements based on a careful assessment and understanding of overall health and comorbid conditions. **Many clinical conditions seen in the specialty of urology occur with greater incidence and prevalence in elderly patients. In some ways, this makes urology by definition a geriatric specialty.** Some facets of urologic care differ significantly between elderly and younger patients. **Clinical principles of geriatrics are not always intuitive, and the body of evidence related to care for elderly patients is growing rapidly.** Additional research and education on these topics will help enhance our ability to provide high-quality care for the older adults whom we serve.

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The complete reference list is available online at www.expertconsult.com.

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General Considerations

Urogynecologic Fistulae

Uroenteric Fistulae

Urovascular Fistulae

Other Urinary Fistulae

A fistula represents an extra-anatomic communication between two or more epithelial- or mesothelial-lined body cavities or the skin surface. Although most fistulae in the industrialized world are iatrogenic, they may also occur as a result of congenital anomalies, malignancy, inflammation and infection, radiation therapy, iatrogenic (surgical) or external tissue trauma, ischemia, parturition, and a variety of other processes. The potential exists for fistula formation between a portion of the urinary tract (i.e., kidney, ureters, bladder, and urethra) and virtually any other body cavity, including the chest (pleural cavity), gastrointestinal (GI) tract, lymphatics, vascular system, genitalia, skin, and reproductive organs. Classification is generally based on the organ of origin in the urinary tract and the termination point of the fistula (e.g., vagina, skin, GI tract). The presenting symptoms and signs are variable and depend to a large degree on the involved organs, the presence of underlying urinary obstruction or infection, the size of the fistula, and associated medical conditions such as malignancy.

GENERAL CONSIDERATIONS

Acquired urinary fistulae in the industrialized world are almost universally unexpected and may result in a great deal of inconvenience, discomfort, and physical disability for the affected individual. They are most often acquired as a result of a medical or surgical intervention for an unrelated problem, and, consequently, considerable emotional and psychologic distress often accompanies the diagnosis and subsequent treatment. As a result, not infrequently, the medicolegal aspects of these cases can be very disturbing to the treating health care practitioner, with an increasing proportion of these cases being adjudicated in court (Thomas and Williams, 2000). Nevertheless, minimizing patient discomfort, maintaining a positive and honest patient-physician relationship while providing constant reassurance, and, finally and perhaps most important, pursuing expeditious and successful treatment of the fistula will most often result in a satisfactory, nonconfrontational, mutually satisfying long-term outcome.

Notably, after the initial diagnosis of a urinary fistula, which results in external urinary leakage, immediate management or control of the urinary leakage is vital. Addressing this quickly will reduce skin breakdown and related complications, as well as alleviate much of the psychologic distress on the part of the affected individual. The judicious use of catheters, pads, and appliances can be very helpful in this regard. Skin care and odor control products are also adjunctive measures in minimizing patient-related distress until definitive therapy and repair of the fistula can be undertaken. These simple measures can often deflect or assuage the anger of an

otherwise very disaffected patient, thereby reducing the potential for further aggravating an already difficult medical and, possibly, litigious situation.

The principles of repair of urinary fistulae are outlined in Box 89-1 and can be applied to virtually any type of fistula involving the urinary tract. Prevention of urinary fistulae is, of course, paramount; however, nutrition, infection, and malignancy are important considerations not only when assessing a patient for the risk of creation of a fistula during any given intervention, but also during an evaluation for the repair of an existing urinary fistula. Although the vast majority of urinary fistulae in the industrialized world occur in healthy, well-nourished individuals, a nutritional assessment may be an important factor in some patients with fistulae, such as those patients with malignancies. Ensuring adequate nutrition is integral to surgical healing in general, but is especially important in the setting of a urinary fistula. Not uncommonly, the catabolic processes contributing to the lack of healing, which may have been a contributing factor in the initial fistula formation, are often ongoing. This is especially relevant in fistulae related to radiation therapy or in debilitated patients.

Although some types of urinary fistulae will heal with conservative management, surgery often assumes a role in the definitive repair. Repair and reconstruction of urinary fistulae are sometimes complex. These should be approached on a case-by-case basis, because repair may involve some innovative and even improvisational maneuvers in the operating room. The surgeon should be familiar with a variety of approaches and techniques, because one approach will not be optimal for all patients with a given type of urinary fistula. Principles of surgical management of urinary fistulae are outlined in Box 89-2. The finding of a persistent fistula after presumably definitive treatment may suggest the existence of other contributing host factors, such as malignancy, nutritional issues, the possibility of an unrecognized foreign body, tissue ischemia, or surgical factors such as inadequate postoperative urinary drainage, persistent distal urinary obstruction, or technical problems with the surgery.

KEY POINTS: PRESENTATION

- Urinary fistulae are often associated with considerable physical and psychologic distress for the patient and can have medicolegal consequences.
- Nutrition, infection, malignancy, urinary obstruction, and the presence of a foreign body are all important factors to consider in the initial approach to urinary fistula and in those patients in whom primary therapy has failed.

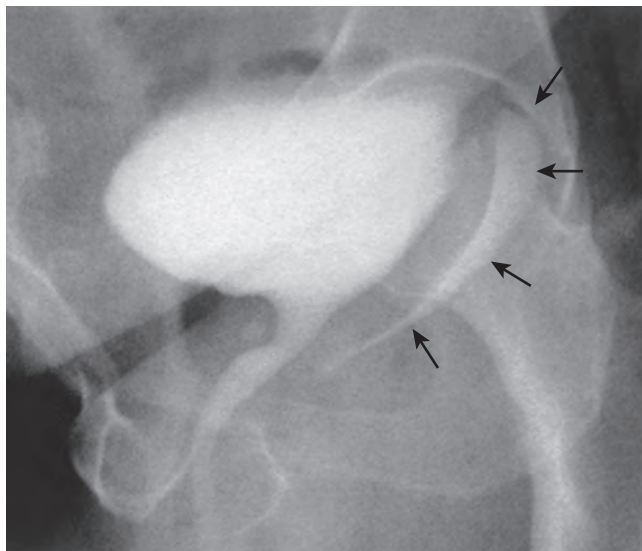


Figure 89-1. Voiding cystourethrogram demonstrates filling of the vagina (arrows) with voiding as a result of a posthysterectomy vesicovaginal fistula.

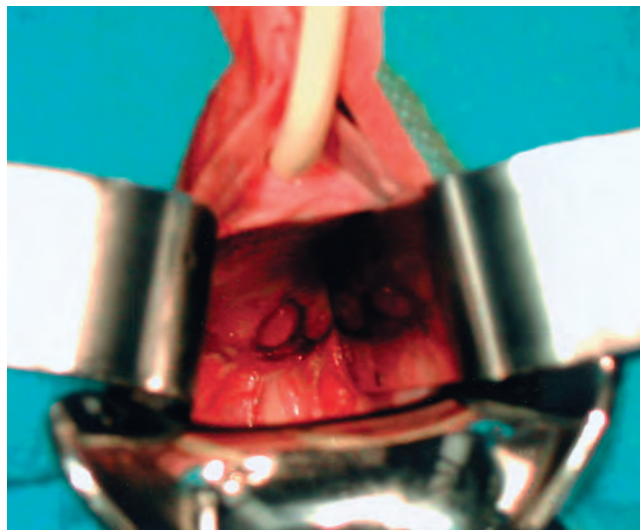


Figure 89-2. Posthysterectomy vesicovaginal fistula (VVF). Retraction with a weighted speculum and Heaney right-angled retractors to provide lateral retraction are needed to visualize this posthysterectomy VVF in a nulliparous woman.

BOX 89-1 Principles of Urinary Fistula Management

- Ensure adequate nutrition.
- Eliminate infection.
- Achieve unobstructed urinary drainage and/or stenting.
- Remove or bypass distal urinary obstruction.
- Beware of malignant cause of fistula.

BOX 89-2 Principles of Surgical Repair of Urinary Fistula

- Adequate exposure of the fistula tract with debridement of devitalized and ischemic tissue
- Removal of involved foreign bodies or synthetic materials from region of fistula, if applicable
- Careful dissection and/or anatomic separation of the involved organ cavities
- Watertight closure
- Use of well-vascularized, healthy tissue flaps for repair (atraumatic handling of tissue)
- Multiple-layer closure
- Tension-free, nonoverlapping suture lines
- Adequate urinary tract drainage and/or stenting after repair
- Treatment and prevention of infection (appropriate use of antimicrobials)
- Maintenance of hemostasis

Etiology and Prevalence

The etiology of VVF differs in various parts of the world. In the developing world, VVF is the most common fistula (>75%) (Tebeu et al, 2012) and occurs mainly from obstetric complications. In the industrialized world, the most common cause (>75%) of VVF is injury to the bladder at the time of gynecologic, urologic, or other pelvic surgery (Symmonds, 1984; Lee et al, 1988; Tancer, 1992). Surgical injury to the lower urinary tract most commonly occurs in the setting of hysterectomy (Fig. 89-2), whereas most of the remainder are related to general surgical procedures in the pelvis, anterior colporrhaphy or cystocele repair, anti-incontinence surgery, or other urologic procedures (Armenakas et al, 2004). At the Zekai Tahir Burak center in Turkey, 25,998 gynecologic and obstetric operations were performed over a 3-year period. The bladder was the most frequently injured organ. Urinary tract injury rates were reported to be 0.49% for the bladder and 0.24% for the ureter in gynecologic operations, and 0.18% for the bladder and 0.01% for the ureter in obstetric operations (Ozdemir et al, 2011). Of 207 VVFs repaired at the University of California–Los Angeles (UCLA) over a 10-year period ending in 2001, Eilber and colleagues (2003) reported the cause as abdominal hysterectomy in 83%, vaginal hysterectomy in 8%, radiation in 4%, and miscellaneous in 5%. In 1964, other causes of VVF in the industrialized world include malignancy, pelvic radiation, and obstetric trauma (including forceps lacerations and uterine rupture) (Everett and Mattingly, 1956; Gerber and Schoenberg, 1993). The use of vaginal mesh for prolapse repair may also result in VVF (Margulies et al, 2008; Ridgeway et al, 2008). Although fortunately uncommon during labor, approximately 22% of uterine ruptures are associated with a bladder injury (Raghavaiah and Devi, 1975). However, obstructed labor and obstetric trauma, in general, now account for very few VVFs in industrialized nations, probably because of the widespread availability of excellent prenatal and perinatal obstetric care.

The rate of iatrogenic bladder injury during abdominal hysterectomy is estimated to be between 0.5% and 1.0% (Keettel et al, 1978). Mathevet and colleagues (2001) reported the incidence of bladder injury during vaginal hysterectomy to be 1.7% in 3076 cases, with all injuries being recognized and repaired intraoperatively. Despite the immediate intraoperative repair reported in this series, there were four VVFs noted, giving a crude VVF rate during vaginal hysterectomy of 0.13%. The reported incidence of intraoperative bladder injury varies considerably in the literature,

UROGYNECOLOGIC FISTULAE

Vesicovaginal Fistula

Vesicovaginal fistula (VVF) is the most common acquired fistula of the urinary tract (Gerber and Schoenberg, 1993) and has been known since ancient times (Fig. 89-1).

Please see the Expert Consult website for further details.



However, it was not until 1663 that Hendrik von Roonhuyse first described surgical repair of VVF by denuding the fistula margins and then reapproximating them with sharpened stiff swan quills (Margolis and Mercer, 1994). Johann Fatio is generally credited with the first successful VVF repair, in 1675, using von Roonhuyse's technique (Falk and Tancer, 1954). In 1838, using leaden suture, John Peter Mettauer was the first U.S. surgeon to claim a successful VVF closure (Kight, 1967). In 1852, James Marion Sims published his now famous surgical series describing his method of surgical treatment of VVF using silver wire in a transvaginal approach (Sims, 1852). Of note, it was not until his 30th attempt at closure of VVF that he achieved success. However, **Sims remains the subject of considerable debate regarding his ethics** (Richardson, 1994; Sartin, 2004), because it is unknown whether the patients in his surgical series were willing and consenting participants (all were African-American slaves in pre-Civil War America). He was later to become one of the great figures in the history of operative gynecology. **The first successful transabdominal approach to VVF repair was reported by Trendelenburg in 1888, and the concept of an interpositional flap was first proposed and reported in 1928 by Martius, who used a labial fat pad.** Before 1900, the most common cause of VVF in the United States was obstructed labor (Stothers et al, 1996).

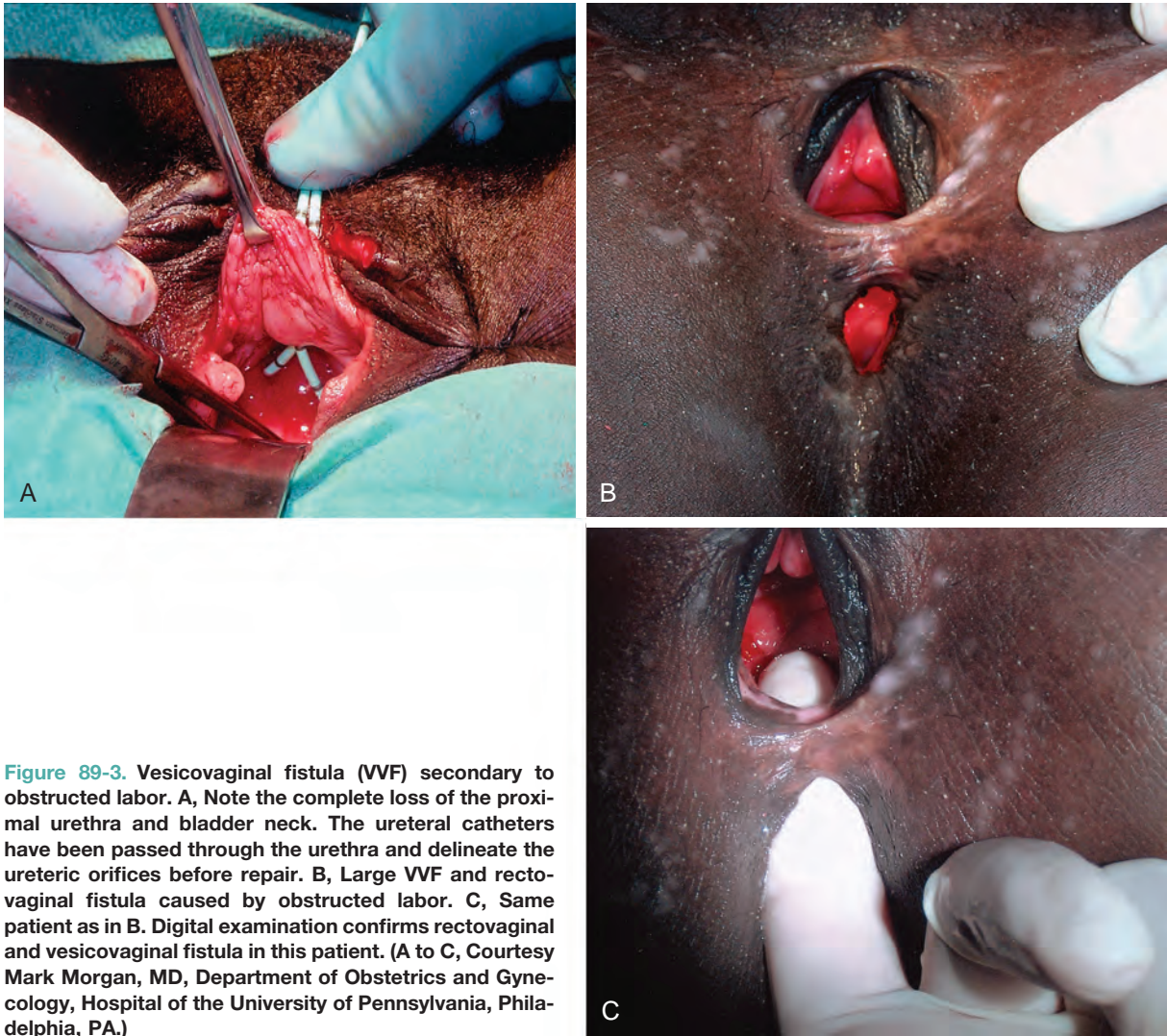


Figure 89-3. Vesicovaginal fistula (VVF) secondary to obstructed labor. **A**, Note the complete loss of the proximal urethra and bladder neck. The ureteral catheters have been passed through the urethra and delineate the ureteric orifices before repair. **B**, Large VVF and rectovaginal fistula caused by obstructed labor. **C**, Same patient as in **B**. Digital examination confirms rectovaginal and vesicovaginal fistula in this patient. (A to C, Courtesy Mark Morgan, MD, Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, PA.)

depending on whether routine cystoscopy was performed. In series in which cystoscopy was not performed, the overall rate of bladder injury was reported to be approximately 2.6 per 1000 cases, whereas in series in which cystoscopy was routinely performed, the overall rate of bladder injury was approximately 10.4 per 1000 cases (Gilmour et al, 1999). The incidence of fistula after hysterectomy is estimated to be approximately 0.1% to 0.2% (Harris, 1995). There are approximately 140 to 150 VVF repairs annually in England and Wales (Hilton, 1997).

Posthysterectomy VVFs are thought to result most commonly from an incidental unrecognized iatrogenic cystotomy near the vaginal cuff (Kursh et al, 1988). If unrecognized intraoperatively, a pelvic urinoma may develop and ultimately drain out through the vaginal cuff. Ongoing urinary drainage along this tract results in a fistula. Other potential mechanisms for posthysterectomy VVF include tissue necrosis from cautery, a suture placed through both the bladder and vaginal wall during closure of the vaginal cuff, or an attempt to control pelvic bleeding by suture ligation. Tissue ischemia and then necrosis promotes fibrosis and induration, finally resulting in an epithelial or mucosal lining of the tract and the development of a fistula tract. Possibly, factors other than an isolated suture placed through the bladder and vagina are necessary for posthysterectomy VVF formation because, at least in an animal model, deliberate suture fixation of the bladder to the vagina does not invariably result in VVF in the absence of infection, urinary extravasation, or other complicating factors (Meeks et al, 1997).

In the developing world, where routine perinatal obstetric care may be limited, VVF most commonly occurs as a result of prolonged obstructed labor resulting from cephalopelvic disproportion, with resulting pressure necrosis to the anterior vaginal wall, bladder, bladder neck, and proximal urethra from the baby (Arrowsmith et al, 1996) (Fig. 89-3). The constellation of problems resulting from obstructed labor is not limited to VVF and has been termed the *obstructed labor injury complex* and includes varying degrees of each of the following: urethral loss, stress incontinence, hydroureteronephrosis, renal failure, rectovaginal fistula, rectal atresia, anal sphincter incompetence, cervical destruction, amenorrhea, pelvic inflammatory disease, secondary infertility, vaginal stenosis, osteitis pubis, and foot drop (Arrowsmith et al, 1996). The obstructed labor injury complex occurs largely in developing countries in certain cultures as a result of several factors, including (1) marriage and conception at a very young age, which results in childbearing in a relatively small and immature pelvis, (2) poor nutrition resulting in stunted skeletal (e.g., pelvic) growth in the mother, and (3) relative absence of qualified prenatal and obstetric care (Margolis and Mercer, 1994). Patients may experience obstructed labor for days in a rural environment, eventually traveling to a distant health care facility only to have a stillborn fetus and a VVF. In direct contradistinction to the epidemiology of VVF in the industrialized world, 96.5% of 932 VVFs seen at a single hospital in Nigeria over a 7-year period were temporally associated with labor and delivery (Wall et al, 2004). In a large study in Ethiopia, a total of 14,070 women of reproductive

age were included in a survey. Among women who had ever given birth (9713), some 103 experienced obstetric fistula in their lifetime, which means 10.6 per 1000 women who ever gave birth. It is estimated that in Ethiopia nearly 142,387 patients with obstetric fistula exist. Those women who are circumcised had higher odds of reporting the condition. Women who gave birth 10 or more times had higher odds of developing obstetric fistula than women with 1 to 4 children (Biadgilign et al, 2013). The incidence of obstetric fistula in developing countries has been estimated at approximately 0.3% to 0.4% of deliveries (Margolis et al, 1994), or 1 to 4 per 1000 vaginal deliveries (Margolis et al, 1994; Danso et al, 1996). In sub-Saharan Africa the incidence rate has been estimated at 10.3 per 100,000 deliveries (Vangeenderhuysen et al, 2001). An estimate of up to 500,000 new cases of obstetric fistula occur throughout the world annually (Hilton, 2003), although the total morbidity from obstructed maternal labor has been estimated to be in excess of 5 million individuals annually (Kelly, 1991). Risk factors include young or old maternal age and primigravid status (Danso et al, 1996).

Obstetric fistulae tend to be larger and located distally in the vagina and may involve large portions of the bladder neck and proximal urethra. Even in experienced hands, these are often very difficult to repair because of the extensive soft-tissue loss, as well as the ischemia and fibrosis of adjacent tissues (Arrowsmith, 1994; Elkins, 1994). Obstetric fistulae are devastating injuries in the developing world, with significant socioeconomic ramifications (Donnay and Weil, 2004; Wall et al, 2004). The affected individuals, commonly young teens, are often ostracized and shunned by family and friends and become permanent outcasts in society. Only rarely are these individuals able to get adequate care and repair because of the lack of organized health care in many countries in the developing world. Major efforts are under way to improve education, the socioeconomic status of women, and access to health care in these regions (Tahzib, 1983, 1989; Kelly, 1991; Wall, 1996; Donnay and Weil, 2004; Kelly, 2004). With improvements in the delivery of prenatal care in some areas of the developing world, it appears that the incidence of VVF from obstetric causes may be decreasing as a subset of all VVF, with a proportional increase in the rate of iatrogenic gynecologic fistulae approaching that in industrialized nations (Ayhan et al, 1995; Obi et al, 2008). Another important cause of VVF in some parts of the world is traditional folk treatments such as "gishiri cutting," which may account for up to 13% of VVFs in some series (Tahzib, 1983). This ritual practice involves using a knife to incise the anterior vagina as a treatment for a variety of conditions, including infertility, dyspareunia, dysuria, and back pain.

Other causes of VVF include urologic or gynecologic instrumentation, including percutaneous procedures (Ramsay et al, 1992; Pruthi et al, 2000); retroperitoneal, vascular, or pelvic surgery; infectious and inflammatory diseases (Borjas and Rodriguez Diaz, 1949; Bland and Gelfand, 1970; Ba-Thike et al, 1992; Monteiro et al, 1995); foreign bodies (including neglected pessaries) (Binstock et al, 1990; Goldstein et al, 1990; Grody et al, 1999); congenital VVF (Rousseau et al, 1996); sexual trauma (Roy et al, 2002); vaginal laser procedures (Colombel et al, 1995); and external violence (Box 89-3). The three most common locally advanced malignancies that result in VVF include cervical, vaginal, and endometrial carcinoma, which in aggregate account for approximately 3% to 5% of VVFs in the industrialized world. Treatment of vaginal cancer is associated with a high complication rate; up to 30% of patients develop significant complications including rectovaginal fistula or VVF, grade III to IV proctitis, cystitis, and vaginal stricture (Gunderson et al, 2013).

VVFs caused by radiation therapy deserve special mention. These VVFs may occur several decades after completion of the radiation (Zoubek et al, 1989). The incidence of urinary fistula after radiation therapy varies with the type, dose, and location of the radiation. Both external beam and interstitial (Aristizabal et al, 1983) radiation therapy may result in VVF. An incidence of 1.6% of any type of urinary fistula was noted in one series of more than 2200 patients treated with a variety of different radiation modalities

BOX 89-3 Etiology of Vesicovaginal Fistula

Traumatic

Postsurgical

- Abdominal hysterectomy
- Vaginal hysterectomy
- Anti-incontinence surgery
- Anterior vaginal wall prolapse surgery (e.g., colporrhaphy)
- Vaginal biopsy
- Bladder biopsy, endoscopic resection, laser therapy
- Other pelvic surgery (e.g., vascular, rectal)
- External trauma (e.g., penetrating, pelvic fracture, sexual)

Radiation therapy

- Advanced pelvic malignancy
- Infectious or inflammatory cause

Foreign body

Obstetric

- Obstructed labor
- Forceps laceration
- Uterine rupture
- Cesarean section injury to bladder

Congenital

for cervical carcinoma (Alert et al, 1980). In a series of 10,709 women treated by telebrachytherapy (67.5 Gy) for a range of gynecologic cancers in one center over a 22-year period, 133 (1.2%) developed urologic complications, of whom 35 (0.3%) developed fistulae (Maier et al, 1997). Perez reported a 0.6% to 2.0% incidence of VVF formation in 1456 patients undergoing combined external beam radiotherapy and brachytherapy for stages I to III cervical cancer (Perez et al, 1999). In a series of 2096 patients undergoing therapy for cervical cancer, there was an overall genital fistula rate of 1.8%, including rectovaginal fistulae. All patients diagnosed with fistula had received radiation therapy, and the median interval from completion of radiation to presentation of VVF was 8.7 months (Emmert and Kohler, 1996). Higher radiation doses seem to correlate with a greater risk for overall morbidity, as well as fistula formation (Perez et al, 1984, 1999). The endarteritis resulting from the radiation therapy may involve the surrounding tissues, limiting reconstructive options. An important consideration in any fistula after radiation therapy for malignancy is the possibility that the fistula represents a recurrence of the malignancy. Therefore biopsy of the fistula tract should be strongly considered before considering definitive repair in these patients.

Intraoperative Risk Factors for Iatrogenic Vesicovaginal Fistula

Clearly, intraoperative injury to the urinary bladder is a primary risk factor for subsequent development of a postoperative VVF. Other risk factors for postoperative VVF formation include prior uterine surgery (cesarean section), endometriosis, infection, diabetes, arteriosclerosis, pelvic inflammatory disease, and prior radiation therapy (Blandy et al, 1991; Likic et al, 2008). The American Association for the Surgery of Trauma (AAST) grade of the bladder trauma is the strongest predictor of subsequent VVF formation. Two of 3 patients developing a VVF had a grade V injury, compared with only 1 of 48 who did not develop a VVF. A grade V bladder injury as defined by the AAST involves injury to the trigone. It postulated that the proximity of the injury to the vaginal cuff serves as an avenue for VVF formation because the site of the bladder injury comes in direct contact with the healing cuff (Duong et al, 2011). The operative approach to hysterectomy is an important factor, because bladder injuries are at least three times more

common during abdominal hysterectomy compared with vaginal hysterectomy. Intraoperative recognition and repair of bladder injury are paramount in prevention of VVF; however, despite intraoperative repair, VVF may still occur in a substantial number of patients. In 1969, Hutch emphasized five factors in the prevention of VVF during gynecologic surgery: (1) immediate detection of bladder injury using vital dyes if necessary; (2) watertight closure of the bladder; (3) satisfactory extravesical drain placement; (4) avoidance of a vaginal incision, if possible, after recognition of the bladder injury; and (5) prolonged, uninterrupted postoperative bladder drainage (Hutch and Noll, 1970).

Clinical Features

Evaluation and Diagnosis. VVF must be distinguished from urinary incontinence from other causes, including stress (urethral) incontinence, urge (bladder) incontinence, and overflow incontinence, as well as ureterovaginal fistula.

Presentation. The most common complaint in patients with VVF is constant urinary drainage per vagina. The amount of urinary leakage can vary considerably from patient to patient and may be proportional to the size of the fistula tract. Patients may void a variable amount, depending on the size of the fistula and the volume of urinary leakage. For example, when a large VVF is present, patients may not void at all and simply have continuous leakage of urine into the vagina. Small, pinpoint fistulae may cause intermittent wetness, which is positional in nature. In the supine position, when sleeping, the amount of leakage reported by the patient may be minimal, but on rising to a seated or standing position the amount of leakage may increase precipitously. Patients may also report recurrent cystitis, perineal skin irritation from constant wetness, vaginal fungal infections, or rarely pelvic pain. In fact, pain is an uncommon finding in patients with VVF unless there is considerable skin irritation or the VVF occurred as a result of radiation therapy.

VVF after hysterectomy or other surgical procedures may manifest after removal of the urethral catheter, or VVF may be seen 1 to 3 weeks later with urinary drainage per vagina. It may be possible to identify some patients at high risk for VVF in the immediate postoperative period. Kursh and colleagues (1988) noted that patients who developed VVF after hysterectomy more commonly had postoperative ileus, hematuria, bladder irritability, and elevated white blood cell count compared with a cohort of patients who did not develop VVF. Occasionally, posthysterectomy VVF may go undiagnosed for an extended period of time, because postoperative clear or serosanguineous vaginal discharge is often attributed to the surgery itself.

As noted previously, VVF resulting from radiation therapy may not manifest for months to years after completion of radiation. These VVFs tend to represent very challenging reconstructive cases owing to the size and complexity of the fistula, the poor quality of the surrounding tissues, and the associated voiding dysfunction resulting from the radiation effects on the urinary bladder.

Physical Examination. A pelvic examination with a speculum should always be performed in the evaluation of VVF. The bivalved speculum examination usually provides a precise assessment of VVF including the location, size, and number of fistulae. Vaginoscopy has been suggested as an adjunct measure, in some cases, using a modified endoscope to precisely visualize the fistula tract (Redman, 1990). Today vaginoscopy using a flexible cystoscope makes it easier to visualize the fistula, particularly with a dye in the bladder. Most commonly, VVFs after hysterectomy are located along the anterior vaginal wall at the level of the vaginal cuff (Fig. 89-4). A visual and manual assessment of inflammation surrounding the fistula is necessary, because it may affect timing of the repair. Significant inflammation, infection, or induration around the fistula may mitigate against immediate repair. Relevant vaginal anatomy, including depth, associated prolapse, atrophy, and introital size are carefully recorded, because these may affect the surgical approach to repair. Anatomically, fistulae located high in the vagina, at the level of the hysterectomy cuff in a deep narrow

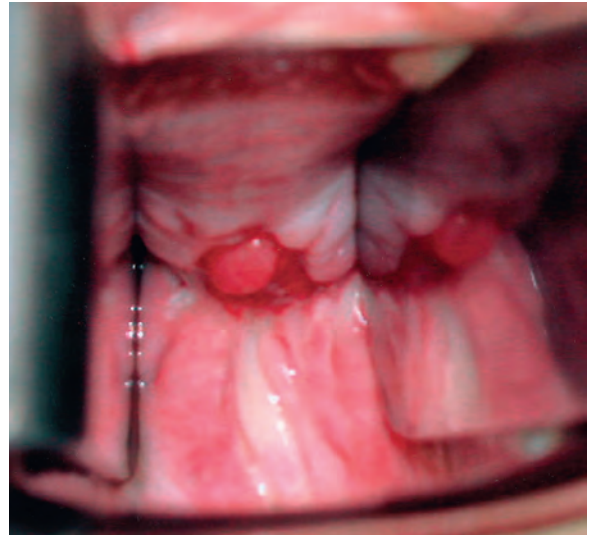


Figure 89-4. Vesicovaginal fistula (VVF) on physical examination. A large VVF is seen at the apex of the vagina after hysterectomy. The VVF in this image is seen as reddish pink bladder mucosa prolapsing into the vagina. Handheld Heaney right-angled retractors provide lateral retraction in this image.

vagina, may be best approached by some surgeons abdominally because a vaginal approach in these patients can be challenging. This may be especially relevant in nulliparous females in whom there is usually very limited pelvic floor laxity or vaginal prolapse. Postmenopausal vaginal atrophy may be treated with preoperative topical estrogen replacement, thereby optimizing the health and vascularity of potential reconstructive flaps. Palpation for masses or other pelvic pathology, which may require attention at the time of fistula repair, is also performed. Notation of prior incisions in the perineum, lower abdomen, and thigh is necessary because these tissues may be required for flap reconstruction when definitive repair is undertaken.

The presence of a VVF may be confirmed by instilling a vital blue dye into the bladder per urethra and observing whether vaginal drainage is discolored. Small or occult fistulae may be identified in this fashion (Drutz and Mainprize, 1988). A colored solution, such as methylene blue or indigo carmine, is mixed into solution and infused into the bladder. The vagina may be packed with gauze or directly inspected for blue-tinged leakage. If blue-tinged leakage is not apparent and the diagnosis of VVF is in doubt, the sensitivity of this test may be improved by placing a vaginal packing and ambulating the patient for a short period of time. Staining at the introital (distal) end of the packing suggests urinary incontinence or a urethrovaginal fistula, whereas proximal staining suggests a VVF. If the vaginal packing remains dye-free with this maneuver, then the possibility of a ureterovaginal fistula can be investigated with the use of clean vaginal packing, intravenous indigo carmine (or other vital dye), and a repeat pad test. Blue staining at the proximal end of the pad after this maneuver suggests the presence of a ureterovaginal fistula.

A double dye or tampon test may confirm the diagnosis of urinary fistula, as well as suggesting the possibility of an associated ureterovaginal or urethrovaginal fistula (Moir, 1973; Raghavaiah, 1974). In one variation of the double dye test, a tampon is placed per vagina. Oral phenazopyridine is administered, and vital blue dye is instilled into the bladder. If the tampon is discolored yellow-orange at the top, it is suggestive of a ureterovaginal fistula. Blue discoloration in the midportion of the tampon suggests VVF; whereas blue staining at the bottom suggests a urethrovaginal fistula.

Clear vaginal discharge after hysterectomy does not invariably represent a urinary fistula or incontinence. Other than normal

vaginal secretions, less common causes include a peritoneovaginal fistula (Ginsberg et al, 1998), lymphatic fistula (Lau and Wong, 1994), vaginitis, and fallopian tube fluid (Leach et al, 1987). Incontinence after cesarean section, in which a VVF has been excluded, may suggest the possibility of a ureterovaginal or vesicouterine fistula.

Cystoscopy. An endoscopic examination should be performed in patients for whom a suspicion of VVF is present (Fig. 89-5). Immature fistulae may appear as areas of localized bullous edema without distinct ostia. Mature fistulae may have smooth margins with variably sized ostia. In some cases, multiple pits and cavities along an area of the traumatized posterior bladder wall, in the setting of a small VVF, may make it difficult to identify the exact fistula tract. In these cases, a guidewire or ureteral catheter may be placed through the working channel of the cystoscope and into the fistula tract (Fig. 89-6). Visualization of the wire in the vagina confirms the exact location of the VVF on both the bladder and genital sides. Cystourethroscopy can confirm the presence of the fistula but also may reveal the size of the tract, the presence of collateral fistulae, and the location of the ureteric orifices in relation to the fistula.

Small fistulae, usually less than 3 to 4 mm in diameter, may be amenable to simple fulguration, which can be performed at the time of cystoscopy (see later discussion) (Stovsky et al, 1994). Of importance, in the setting of a prior history of pelvic malignancy, a biopsy of the fistula is often done to evaluate for the possibility of a recurrent malignancy. Fistulae located near or at the ureteric orifice may require ureteral reimplantation at the time of VVF repair. This type of requirement would usually mitigate against a completely transvaginal attempt at repair.

Imaging. A cystogram and/or voiding cystourethrogram (VCUG) and an upper tract study should be performed in patients being evaluated for a VVF. The cystogram may objectively determine the presence and location of the fistula. On filling of the bladder, contrast often begins to opacify the vagina, almost immediately confirming the presence of a VVF. VVFs are often best seen in the lateral projection (Fig. 89-7) in which the bladder and vagina are not superimposed. Often, the actual VVF tract may be visible in the

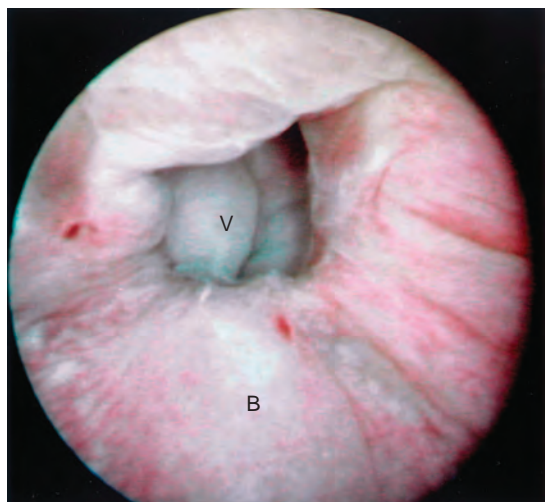


Figure 89-5. Endoscopic view of vesicovaginal fistula (VVF). This is the same patient as in Figure 89-4. The fistula is now seen from the bladder side. This VVF is large enough to allow one to see directly into the vagina (V) through the bladder (B).

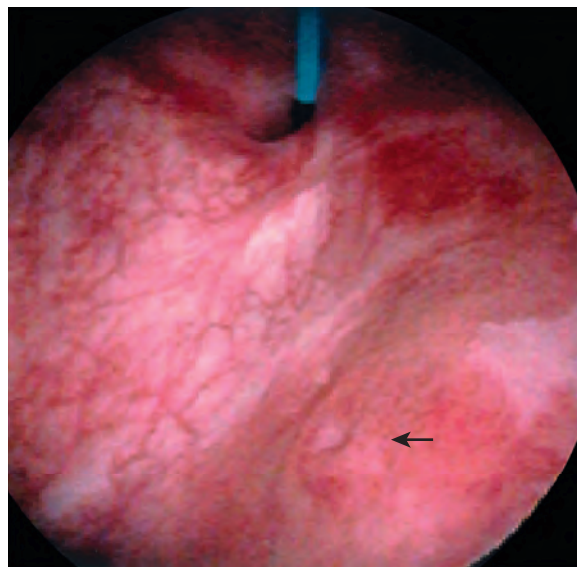


Figure 89-6. Confirmation of a vesicovaginal fistula (VVF). A 4-Fr ureteral catheter traverses the fistula tract in this endoscopic photograph. The VVF is high on the posterior bladder wall, the typical location for a posthysterectomy VVF. The right ureter can be seen (arrow).

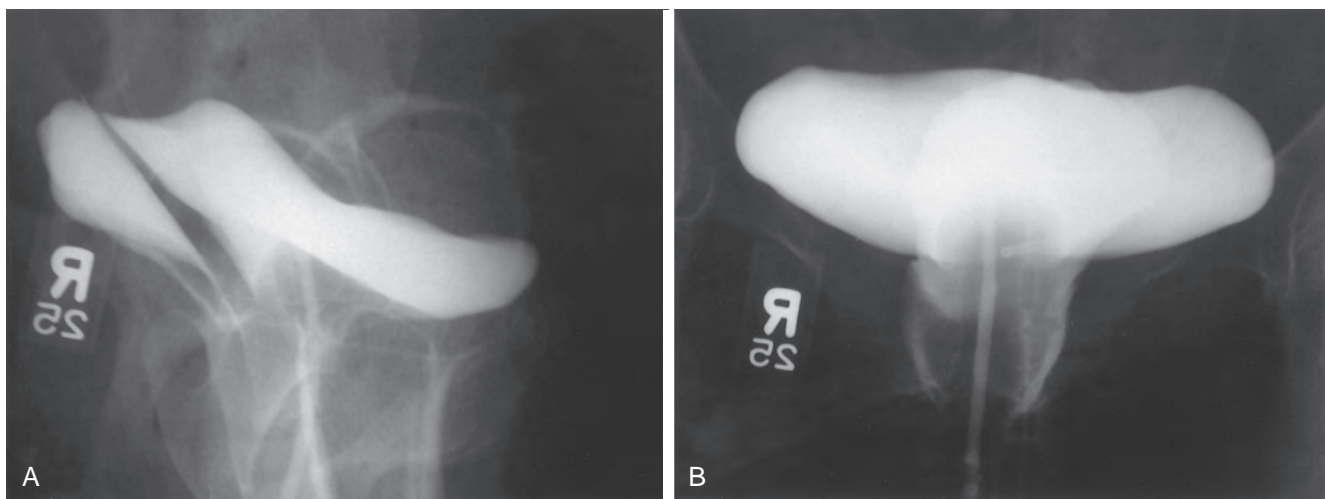


Figure 89-7. Cystogram demonstrating a vesicovaginal fistula (VVF). A, Lateral image demonstrates a posthysterectomy VVF. B, Anteroposterior view. The contrast agent is seen opacifying and outlining the vagina, superimposed on the bladder.

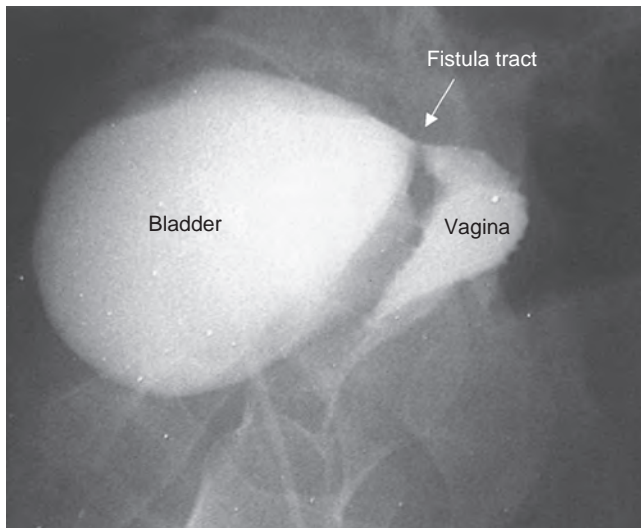


Figure 89-8. Lateral image during cystography demonstrates the vesicovaginal fistula tract.

lateral projection (Fig. 89-8). However, voiding images may be necessary in some patients with small fistulae to demonstrate the VVF. The slight increase in intravesical pressure that accompanies micturition is usually adequate to demonstrate even very small fistulae. It is important to note that a cystogram that fails to demonstrate a suspected VVF but lacks voiding images or post-void images should be considered nondiagnostic. During voiding, care should be taken to exclude vaginal voiding or reflux of contrast from the introital region cephalad into the vagina, which would produce a falsely positive image. An involuntary bladder contraction can be provoked with rapid filling during cystography, and if the intravesical pressure rises sufficiently, this may also be sufficient to demonstrate a VVF when the filling images of the cystogram failed to demonstrate it. In some instances, a cystogram can also permit an assessment of bladder capacity (important in the setting of prior radiotherapy), cystocele, bladder neck competence, and vesicoureteral reflux, any of which may have an impact on operative repair.

Up to 12% of postsurgical VVFs have an associated ureteral injury or ureterovaginal fistula (Goodwin and Scardino, 1980); thus, upper urinary tract evaluation is important. Intravenous urography (IVU) (Gerber and Schoenberg, 1993), or, more recently, computed tomography (CT) urography is usually sufficient for this purpose. In one series of 216 consecutive patients with VVF caused by obstructed labor, almost 50% of patients were diagnosed with an upper tract abnormality on IVU. Caliectasis was found in 71% of those affected; however, almost 10% were found to have a non-functioning renal unit (Lagundoye et al, 1976). If there is suspicion for a ureterovaginal fistula or if the distal ureter is not well seen on IVU, retrograde pyelography may be performed (Blandy et al, 1991) (Fig. 89-9).

In addition to contrast cystography and VCUG, CT, ultrasonography, and magnetic resonance imaging (MRI) have been used in the evaluation of VVF (Kuhlman and Fishman, 1990; Outwater and Schiebler, 1993; Yang et al, 1994). Delayed CT visualization of contrast within the vagina is considered highly suspicious for VVF in the majority of cases (Kuhlman and Fishman, 1990) (Fig. 89-10). In cases of suspected VVF, CT should be performed with only intravenous contrast, or, alternatively, a CT cystogram can be performed to isolate the bladder. A vaginal tampon placed per vagina during IVU or CT scan may improve the sensitivity for finding small or occult VVF in patients with an otherwise negative evaluation (Wesolowski and Meaney, 1977). Cross-sectional imaging may also be helpful in assessing for recurrent malignant disease in those with such a history.

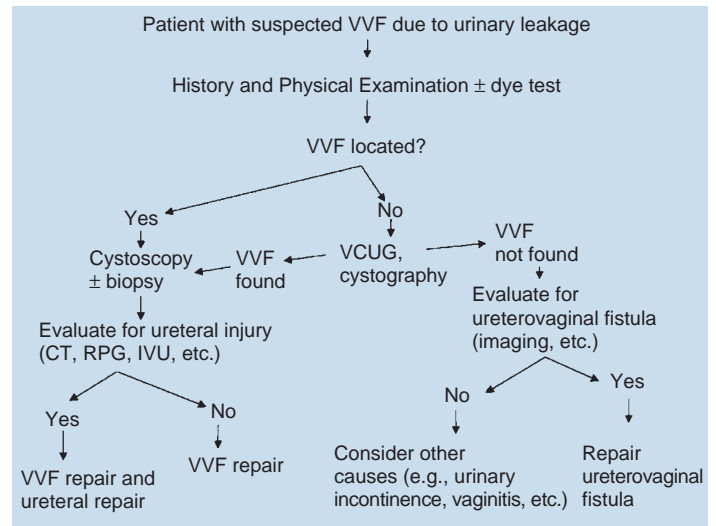


Figure 89-9. Algorithm for the diagnosis of vesicovaginal fistula (VVF). CT, computed tomography; IVU, intravenous urography; RPG, retrograde pyelography; VCUG, voiding cystourethrogram.

Other Studies. Appropriate urine studies including culture, and cytology when indicated, are performed. Urine may extravasate externally or internally. Creatinine levels in the urine are higher than serum levels. Therefore, in the setting of a suspected fistula, testing the creatinine level in either the extravasated fluid or the accumulated ascites and comparing this value to the the serum creatinine levels will confirm urinary leakage but not the location of the fistula. Likewise, testing potassium levels will show higher levels compared with serum levels (Kruger and Whiteside, 2003). When infection is detected, appropriate antibiotic coverage is initiated. Urodynamics, including video-urodynamics, are generally not necessary in the evaluation of routine posthysterectomy VVF. However, in the setting of a prior history of radiation or radical pelvic surgery (e.g., radical hysterectomy) or in those with preexisting neurogenic vesicourethral dysfunction, a urodynamic evaluation can be used to evaluate for significant detrusor dysfunction, including impaired bladder compliance.

Treatment

Conservative and Minimally Invasive Therapy. The goal of treatment of VVF is the rapid cessation of urinary leakage with return of normal and complete urinary and genital function. As noted previously, the physical and psychologic impact of constant urinary incontinence from a VVF can be overwhelming because of the burden of continual wetness, undesirable odor, vaginal and bladder infections, and their related discomfort. Bladder catheterization may temporize some of these effects until definitive repair is undertaken but often will not completely eradicate leakage, especially in those with a large fistula or those with significant detrusor overactivity. Furthermore, catheterization may provoke additional irritation and pelvic pain and is a constant reminder to the patient of an iatrogenic insult.

Regardless of the aforementioned limitations and drawbacks, a trial of indwelling catheterization and anticholinergic medication for at least 2 to 3 weeks may be warranted in selected patients with newly diagnosed VVF, because spontaneous healing may result (Davits and Miranda, 1991). The characteristic of fistulae most widely accepted for favorable outcome with conservative management is size less than 2 to 3 mm. An analysis of pooled data on 348 fistulae showed a spontaneous closure rate with catheterization of 13% ± 23% (De Ridder et al, 2013). Simple injuries to the bladder that do not involve devascularization or thermal injury spread that result in interrupted blood supply to the area have a good chance of healing conservatively. Drainage of the

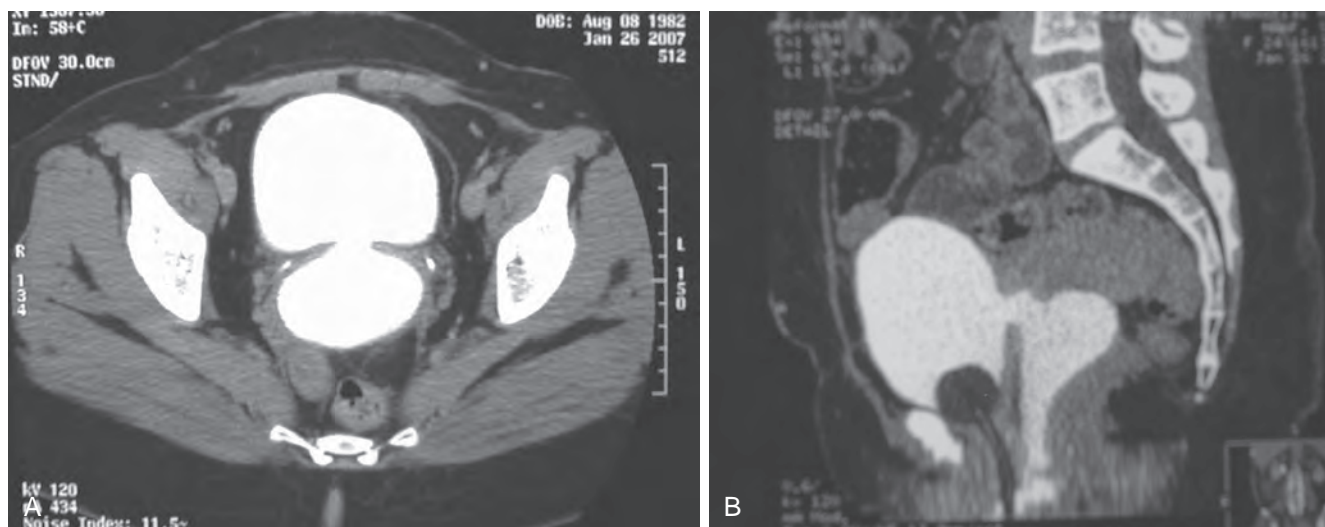


Figure 89-10. Computed tomography (CT) scan of vesicovaginal fistula (VVF). A, After intravenous administration of the contrast agent, there is high-density material in both the bladder and vagina consistent with a VVF. The fistulous connection is between the bladder anteriorly and the vagina posteriorly. B, Sagittal CT reconstruction demonstrating VVF.

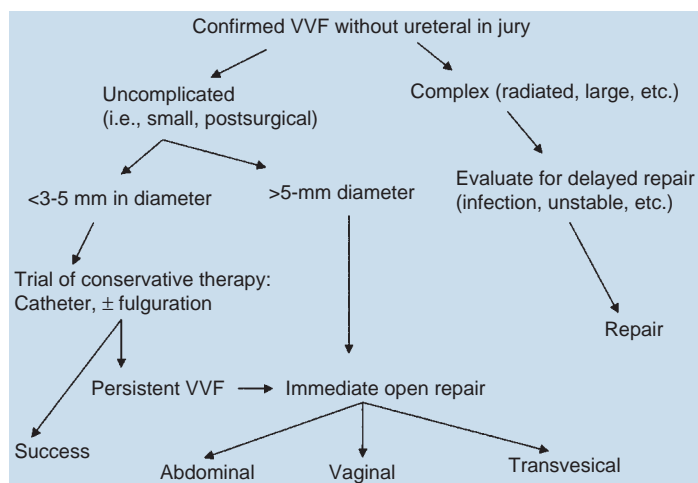


Figure 89-11. Algorithm for management of vesicovaginal fistula (VVF).

bladder should start immediately to prevent epithelialization of the fistula tract. When considering management of iatrogenic VVF, attention should be paid not only to the size of the defect, but also the period between the injury and initiation of therapy, the mechanism of injury, and patient factors such as pelvic anatomy and overall health. Patients should be counseled that conservative management may take up to several months (Wild et al, 2012). Fistulous tracts that remain open 3 or more weeks after adequate Foley drainage are unlikely to resolve without further intervention, especially those that appear completely epithelialized on examination.

Patients with small epithelialized fistulae may benefit from a minimally invasive treatment involving disruption of the epithelial layer of the fistula tract (Fig. 89-11). Catheterization may be combined with minimally invasive electrocoagulation of the fistula tract. In this approach, a small cautery electrode is passed into the fistula tract endoscopically as far as possible. The electrode is slowly withdrawn from the tract with the electrode set on coagulation. The edges of the fistula tract should blanch. This approach was advocated by O'Connor as far back as 1938 for small, highly situated

fistulae (O'Connor and Sokol, 1951) and has been reported in several small case series. Endoscopic transvesical VVF fulguration may be a safe and effective procedure for small VVFs on a day care basis, with decreased morbidity, improved cosmesis, and decreased hospital stay (Shah, 2010). Also, laser welding has been tried with success in a small series of women with fistula smaller than 3 mm (Dogra and Saini, 2011). All successfully treated patients had VVF less than 3 mm in diameter; in two patients with 6-mm VVF this approach failed. **Of importance, in patients with a thin vesicovaginal septum, large VVF, a nonoblique fistula tract, or significant inflammation around the fistula tract, fulguration risks failure and the possibility of enlarging the size of the fistula.** This approach may also devitalize adjacent tissues, thereby compromising their future use as flaps. Fibrin sealant has been used as an adjunctive measure to treat VVF (Pettersson et al, 1979; Hedelin et al, 1982). The fibrin sealant may be injected directly into the fistula tract after fulguration as described earlier. The bladder is then drained for several weeks. Presumably, the gel-like nature of the fibrin sealant plugs the hole until tissue ingrowth occurs from the edges of the fistula. Fibrin sealant has been used successfully in combination with (Morita and Tokue, 1999) and without (Evans et al, 2003b) bovine collagen as an additional "plug." **In general, these conservative measures are useful for small, oblique fistulae (usually less than 2 to 3 mm in diameter), in patients who are agreeable to this course of therapy.**

Case reports of other minimally invasive VVF repair techniques have been reported, including laser tissue welding with a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (Dogra and Nabi, 2001), as well as transurethral endoscopic suturing (Okamura et al, 1997; McKay, 2001).

Surgical Repair. It has been stated that the best opportunity to achieve successful repair of VVF is with the initial operation (Weed, 1978; Elkins, 1994). Previous failed attempts at repair produce scarring and anatomic distortion and may compromise potential reconstructive flaps. Therefore careful preoperative planning is essential to maximize the chances for a successful result. **There is no "best" approach for all patients with VVF.**

Timing: Immediate versus Delayed Repair. The timing of VVF repair is somewhat controversial. Repair of VVF should be as expeditious as possible to minimize patient suffering; however, optimal timing for repair should allow consideration of certain medical and surgical factors as well. It is generally accepted that VVF resulting from obstructed labor should be associated with a

3- to 6-month delay before definitive repair (Wein et al, 1980a; Arrowsmith, 1994; Waaldijk, 1994) to allow maximum demarcation of ischemic tissue and resolution of the associated edema and inflammatory reaction. Longer periods of time, up to 6 to 12 months, have been advocated for radiation-induced fistulae (Wein et al, 1980a), which are often associated with severe obliterative endarteritis and reduced tissue vascularity.

In the classical teaching of VVF, a minimal waiting period of several months is suggested—from the inciting event before the definitive repair attempt—to allow reduced tissue edema and inflammation, and optimal pliability of the tissues (Persky and Rabin, 1973; Lawson, 1978; O'Connor, 1980; Wein et al, 1980a). O'Connor recommended a waiting period of 3 to 6 months for suprapubic VVF repairs (O'Connor et al, 1973). In this setting, reduced inflammation and edema permit easier identification of tissue planes (and therefore flap development), less bleeding, and less tension on the reapproximated suture lines. **There is no consensus in the literature as to the definition of "early" in this context, with different studies either failing to specify at all, or giving a broad range of definition. Although some studies have used the terms "immediate" (Lee et al, 2010), "less than 2 weeks" (Shelbaia and Hashish, 2007), or "less than 30 days" (Soong and Lim, 1997), most reports have considered either less than 6 weeks (Badenoch et al, 1987; Blandy et al, 1991; Kam et al, 2003) or less than 3 months (Wang and Hadley, 1990; Moriel et al, 1993; Shelbaia and Hashish, 2007; Radoja et al, 2010) as their definition of early intervention. Although relatively few studies have reported their outcomes for both early and late approaches to management, overall the results do not appear to be significantly different. The overall results for early management are estimated at 91% \pm 6% and for later management (where provided) 90% \pm 27% ($P = 1.00$; Fisher's exact test). The enthusiasm for delayed management has waned, and, in general, uncomplicated postgynecologic urinary fistulae may be repaired as soon as they are identified and confirmed, thereby minimizing patient discomfort and anguish (Collins et al, 1971; Persky et al, 1979; Fourie, 1983; Badenoch et al, 1987; Cruikshank, 1988; Wang and Hadley, 1990; Blandy et al, 1991; Blaivas et al, 1995; Kostakopoulos et al, 1998). This is especially true when they occur as a result of clean surgical trauma (Wang and Hadley, 1990). Nondelayed closure has also been applied to obstetric fistulae with good results (Waaldijk, 1994, 2004). Nevertheless, in some cases, the timing of a VVF repair is best tailored to the individual patient (Blaivas et al, 1995). Raz and colleagues (1993) suggested that uncomplicated VVF after**

abdominal hysterectomy could and should be repaired as expeditiously as possible transvaginally; however, a 2- to 3-month waiting period may be warranted for some VVFs after vaginal hysterectomy. Conversely, if an abdominal approach is being considered after a particularly difficult or complicated abdominal surgery that resulted in the VVF (e.g., complicated by abscess, urinoma), then a delay may be warranted to allow resolution of active inflammation. Another potential reason to delay repair is to treat ongoing infection or inflammation at the level of the vaginal cuff. Periodic reexamination of the vaginal tissues can be performed every 1 to 2 weeks, and definitive repair scheduled when suitable pliability is noted (Carr and Webster, 1996).

A vaginal approach can be attempted as soon as 2 to 3 weeks after the initial injury, if conservative therapy fails (i.e., the patient remains wet when a Foley catheter is in place to provide adequate drainage of the bladder) and the patient is in good general health. The vaginal tissues are usually relatively undisturbed from the prior causative surgery, especially if the surgery was transabdominal. Wide healthy vaginal flaps can usually be obtained. In the rare circumstance in which a VVF is seen within the first 24 to 48 hours postoperatively, an immediate repair can be attempted (Margolis and Mercer, 1994); however, it is possible that these VVFs, especially if small in diameter, may heal spontaneously with catheterization over the course of several weeks. It is well documented that similar outcomes can be achieved with early versus delayed abdominal and vaginal repair (Collins et al, 1960; Persky et al, 1979; Zimmern et al, 1985; Badenoch et al, 1987; Wang and Hadley, 1990; Blandy et al, 1991), with success rates in excess of 90% for uncomplicated VVF.

Approach: Abdominal versus Vaginal. VVF may be repaired through a transvaginal or transabdominal (transvesical) approach. Each approach has merits depending on the particular circumstances of the fistula, and excellent outcomes can be expected with both approaches (Table 89-1). Although factors such as size, location, and the need for adjunctive procedures often influence the choice of approach, the most important factor is the experience of the operating surgeon. Thus there is no preferred approach for all fistulae, and the "optimal" approach to the uncomplicated postgynecologic VVF is usually the one that is most successful in the individual surgeon's hands (Gerber and Schoenberg, 1993; Akman et al, 1999). There are no randomized studies comparing abdominal and vaginal approaches; given that surgeons undertaking both routes for repair would usually see specific indications for the two, such a comparison is most unlikely ever to be seen

TABLE 89-1 Abdominal versus Transvaginal Repair of Vesicovaginal Fistula

	ABDOMINAL	TRANSVAGINAL
Incision	Abdominal incision	Vaginal incision(s) can be done immediately in the absence of infection or other complications.
Timing of repair (elapsed time from fistula creation)	Often delayed 3-6 months.	
Exposure	Fistula located low on the trigone or near the bladder neck may be difficult to expose transabdominally.	Fistula located high at the vaginal cuff may be difficult to expose transvaginally.
Location of ureters relative to fistula tract	Fistula located near ureteric orifice may necessitate reimplantation.	Reimplantation may not be necessary even if fistula tract is located near ureteric orifice.
Sexual function	No change in vaginal depth.	Risk of vaginal shortening (e.g., Latzko technique).
Use of adjunctive flaps	Omentum, peritoneal flap, rectus abdominis flap.	Labial fat pad (Martius fat pad), peritoneal flap, gluteal skin or gracilis myocutaneous flap.
Relative indications	Large fistulae, location high in a deep narrow vagina, radiation fistulae, failed transvaginal approach, small-capacity bladder requiring augmentation, need for ureteral reimplantation, inability to place patient in the lithotomy position.	Uncomplicated fistulae, low fistulae.

as feasible, ethical, or appropriate. We have identified nine nonrandomized cohort studies reporting results from both abdominal and vaginal procedures (Demirel et al, 1993; Langkilde et al, 1999; Kam et al, 2003; Ou et al, 2004; Catanzaro et al, 2005; Ayed et al, 2006; Hadzi-Djokic et al, 2009; Ockrim et al, 2009; Hilton, 2012). In all, these series included 388 vaginal repairs and 345 abdominal repairs with overall closure rates at first operation of 89% and 87%, respectively ($P = .367$; Fisher's exact test). The same reports included 255 transvesical repairs with a 93% cure rate and 399 transperitoneal repairs with an 89% success rate ($P = 0.130$; Fisher's exact test) (De Ridder et al, 2013). Although it has been a long-held belief that gynecologists prefer to fix VVF transvaginally and urologists prefer a transabdominal approach because of their respective training and experience (Edwards, 1982; Gerber and Schoenberg, 1993), this difference is becoming increasingly blurred as urologists gain more experience and comfort operating transvaginally for a variety of disparate indications.

The vast majority of VVFs in the industrialized world are amenable to a transvaginal repair (Turner-Warwick, 1972; Margolis and Mercer, 1994). The relative advantages of a transvaginal approach compared with an abdominal approach are outlined in Box 89-4 on the Expert Consult website and include shorter operative times, briefer hospital stay, and less blood loss (Goodwin and Scardino, 1979). The principal disadvantages of the transvaginal approach include the relative lack of familiarity of the vaginal cuff anatomy to many urologists; the potential for vaginal shortening, especially with the Latzko approach; and, finally, the difficulty in exposing high or retracted fistulae located near the vaginal cuff, especially in deep, narrow vaginas, or in those without any apical prolapse, such as that found in nulliparous females (see Fig. 89-2). Patients who are unable to get into the high-lithotomy position because of musculoskeletal conditions are not candidates for a transvaginal approach.

The abdominal approach to VVF repair is advantageous in several circumstances. If the VVF is associated with other intra-abdominal pathology requiring repair—including an associated ureteral injury (i.e., ureterovaginal fistula), or a complex fistula, including those involving another intra-abdominal organ—then a transabdominal approach is indicated to address the problems simultaneously. If the VVF is located adjacent to the ureteric orifice, some authors have suggested that this is an indication for an abdominal approach (Carr and Webster, 1996), whereas others have not so advocated (Dupont and Raz, 1996). In patients with a small-capacity or poorly compliant bladder (often secondary to radiation) requiring augmentation cystoplasty, an abdominal approach is indicated, because both procedures can be performed using the same incision. Complicated fistulae, including those associated with multiple prior failed attempts at repair (Kristensen and Lose, 1994) or those that are quite large (>5 cm), might be best approached abdominally as well. Nevertheless, a prior failed attempt at repair is not necessarily a contraindication to a transvaginal approach because excellent results can be achieved in this setting (Eilber et al, 2003).

Combined transabdominal-transvaginal approaches to VVF have been described (Clark and Holland, 1975; Taylor et al, 1980; Henriksson et al, 1982). This approach may be applicable selectively in the setting of large, complex, or recurrent VVF after prior attempts at repair. Laparoscopic or robotic-assisted repair (detailed later) of fistulae located above the trigone is gaining increasing popularity because these procedures have a potential to decrease the morbidity of the open abdominal approach (Nabi and Hemal, 2001).

Handling of Fistula Tract: Excision versus No Excision. A long-held tenet for successful fistula closure, dating back to the original description by Sims in 1852, involves complete excision of the fistulous scar tissue and tract (Fearl and Keizur, 1969; Persky et al, 1979; Wein et al, 1980a; Fourie, 1983). This approach ensures clean, well-vascularized viable edges to be approximated for the initial layer of repair. Simple excision of the scar in an inverted "funnel" shape with careful reapproximation of the defective edges has been shown to be an effective repair of VVF (Iselin et al, 1998; Flynn et al, 2004). However, excision of the fistula tract itself is

not always necessary and may even compromise the repair in some patients (Zimmern et al, 1985; Cruikshank, 1988; Tancer, 1992; Raz et al, 1993; Margolis and Mercer, 1994). There is only a single randomized trial comparing aspects of surgical technique; Shaker and colleagues reported a randomized controlled trial (RCT) comparing trimming of the fistula edge with no trimming (Shaker et al, 2011). Although there was no statistical difference in success rates between the two groups, in patients in whom repair was unsuccessful and trimming had been undertaken, the fistula tended to become larger, whereas fistulae wherein there was no trimming were more likely to be smaller on recurrence. There are several potential disadvantages of excision of the fistula tract. First, this creates a larger soft-tissue defect to be repaired. Excision of the fibrous tract may lead to bleeding, which, if cautery is used, may result in tissue necrosis and impede healing (Eilber et al, 2003). If the VVF is adjacent to the ureter, then excision of the tract may mandate reimplantation of the ureter. Alternatively, if the tract is left in situ, the ureter may be catheterized for the repair and then left undisturbed during a transvaginal operation, obviating the need for reimplantation. In addition, in chronic fistulae, a strong fibrous ring forms outside the epithelialized tract, which maintains some strength through the repair if this layer is incorporated into the closure. This can be an important consideration in patients with significant detrusor overactivity postoperatively from either the repair itself or the indwelling drainage catheters.

Use of Adjuvant Flaps or Grafts: Type and Application. Before embarking on surgical repair, the surgeon should be familiar with a variety of adjuvant flaps and grafts that allow for the interposition of healthy tissue during VVF repair. It is often not possible to predict which patients will require these procedures. The indications for tissue interposition are not well defined, but these measures are most commonly used in the setting of irradiated tissues, obstetric fistulae, failed prior repairs, large fistulae, and patients with tenuous repairs. The various types of flaps are discussed in more detail later in the chapter.

Other Considerations. Preoperative estrogen supplementation may be beneficial in the postmenopausal patient with vaginal atrophy and VVF (Massee et al, 1964). There exist few data in the literature, beyond expert opinion, to support its use. However, topical estrogen preparations may improve vascularity (Margolis and Mercer, 1994) and local tissue quality (Carr and Webster, 1996). Therefore a trial of topical estrogens in individuals with postmenopausal vaginal atrophy and a posthysterectomy VVF may be warranted, provided that there are no contraindications to their use.

Perioperative intravenous antibiotics are often administered, although their usefulness in posthysterectomy VVF repair is questionable in the absence of infection. Whether antibiotics should be administered prophylactically before surgical repair is controversial, but at least one study suggests that preoperative antibiotics do not improve outcomes when administered before the repair of obstetric fistula (Tomlinson and Thornton, 1998). Treatment of existing infection based on preoperative urine culture is potentially beneficial in preventing bacteremia during surgery. However, prolonged use of broad-spectrum antibiotics postoperatively after repair may result in bacterial resistance and possibly fungal vaginal infections that may compromise suture lines.

Sexual activity should be documented preoperatively. Patients should be specifically queried regarding sexual function and dyspareunia occurring before the onset of the event that resulted in the fistula. Although this information is subject to recall bias, it may play an important role in the choice of surgical approach, as well as having medicolegal implications postoperatively. Some types of vaginal procedures for the repair of VVF, including the Latzko partial colpocleisis, may result in vaginal shortening and postoperative dyspareunia. Preoperative documentation of this preexisting condition can be invaluable. Furthermore, adjuvant procedures that may alter vaginal appearance or function, such as the harvesting of a Martius fibrofatty labial flap or an episiotomy, should be carefully discussed with the patient in advance, especially regarding sexual function.

BOX 89-4 Potential Advantages of a Transvaginal Approach for Posthysterectomy Vesicovaginal Fistula

Avoidance of a laparotomy and its associated morbidity
Short operative time
Brief inpatient stay
Quick convalescence and return to normal activities
Minimal postoperative pain
Minimal blood loss
Absence of the need for wide opening or bivalving of the bladder
Approach not compromised by multiple prior abdominal and/or pelvic surgeries
Concomitant anti-incontinence or prolapse surgery may be performed
Local interpositional flaps are adjacent (e.g., Martius, peritoneal)
A three- or four-layer closure is possible
If failure occurs, subsequent abdominal approach is not compromised

Finally, postoperative drainage after VVF repair can be maintained by single or dual catheters. Some authors suggest that a urethral catheter alone provides satisfactory drainage (Collins et al, 1960; Fearl and Keizur, 1968; Tancer, 1980; Leng et al, 1998). Others advocate a suprapubic catheter alone (Blaivas et al, 1995; Carr and Webster, 1996; Iselin et al, 1998) to minimize bladder spasms and trauma to the surgical repair. Most commonly, both urethral and suprapubic drainage catheters (O'Connor et al, 1973; Wein et al, 1980a; Dupont and Raz, 1996; Eilber et al, 2003) are left postoperatively. The disadvantage to single-catheter drainage is principally that the catheter will malfunction, clog, or kink, resulting in bladder filling, eventual overdistention, and disruption of the suture line.

Preoperative Counseling and Indications for Surgery. Surgical repair of a VVF is indicated after confirmation of the diagnosis. As noted previously, a trial of conservative management may be warranted in selected cases, especially in those with a newly diagnosed, small, uncomplicated fistula in which the vaginal leakage significantly improves or resolves with catheter drainage. When conservative measures fail or if after adequate counseling the patient requests repair before a trial of conservative management, surgical treatment is pursued. Before surgery, patients should be counseled that VVFs in the industrialized world are repaired on the first attempt in more than 90% of cases; however, prolonged postoperative urinary catheter drainage is necessary after surgery. Postoperative urinary urgency and frequency are common for a period of time after removal of the catheter but are usually self-limited. Finally, the patient should be aware that it may be necessary to alter the surgical plan intraoperatively as a result of a variety of factors encountered during the operation, and that interpositional flaps or grafts may be used.

Vaginal Techniques. Common vaginal approaches to the repair of uncomplicated VVF are described. The merits of the vaginal approach are reviewed in Table 89-1 and Box 89-4 on the Expert Consult website.

Vaginal Flap or Flap-Splitting Technique. The vaginal flap or flap-splitting approach popularized by Raz and colleagues (Zimmern et al, 1985; Raz et al, 1993; Stothers et al, 1996; Eilber et al, 2003) results in a three-layer closure without the use of an adjuvant flap, and a four-layer closure if a flap is used (Fig. 89-12). It can be performed as an outpatient procedure and is applicable to most simple, uncomplicated VVFs (Fig. 89-13).

Please see the Expert Consult website for further details.

Complications. Proper surgical technique is critical in avoiding complications. Dissection in the proper surgical planes assures minimal bleeding. When significant bleeding is encountered during the dissection, it is possible that an improper plane of dissection was entered. Careful intraoperative inspection and reevaluation of the surgical planes are warranted. Furthermore, excessive use of cautery may compromise the vascular supply of the tissue flaps used for repair. This may become evident only in the postoperative period with ischemic flaps and recurrence of the fistula. Intraoperative bleeding should be controlled with fine absorbable suture whenever possible. **The possibility of ureteral injury is a concern, if the VVF is located adjacent to the insertion of the ureter.** If there is doubt regarding a ureteral injury, then cystoscopy should be performed after the intravenous administration of indigo carmine. Blue efflux from the ureteric orifice confirms ureteral patency.

Long-term complications from transvaginal VVF repair include vaginal shortening and stenosis. Careful attention to flap mobilization and reconstruction will minimize this complication. In addition, excessive resection of the vaginal wall should be avoided during reconstruction to avoid vaginal shortening or scarring.

The most important complication of VVF repair is recurrence of the fistula. A repeat transvaginal approach can be attempted with satisfactory success. A careful review of potential factors leading to failure of the initial repair is undertaken, and any remediable factors (e.g., inadequate nutrition, vaginal atrophy, excessive postoperative bladder spasms) are addressed. Strong consideration should be given to the use of adjuvant flaps in repeat VVF repairs, in which tissue quality may be suboptimal.

Other Transvaginal Techniques. There are multiple variations to transvaginal fistula repair, including those originally described by Latzko in 1914. The Latzko high-partial colpocleisis is a very popular approach among some reconstructive surgeons, with reported success rates in excess of 90% (Kaser, 1977; Tancer, 1980). This approach may not be as successful as the vaginal flap technique for large obstetric fistulae (Elkins et al, 1988). In this procedure, the fistula tract is isolated, and the tissue surrounding the VVF tract is denuded of vaginal "epithelium" circumferentially for a distance of 1 to 2 cm. Care is taken to avoid deeply "denuding" the vaginal tissues to avoid entry into the bladder or perivesical fascia. The denuded areas are then reapproximated over the fistula tract with a series of interrupted absorbable sutures. Sutures are not placed into the bladder wall or vesical mucosa. The edges of the vaginal wall are then reapproximated as a second layer, creating a partial colpocleisis in some patients. Advantages of the Latzko procedure include minimal blood loss, no need for ureteral reimplantation (even for a fistula adjacent to the ureter, because sutures are not placed through the bladder), and a short convalescence. Potential disadvantages include the possibility of vaginal shortening (Enzelsberger and Gitsch, 1991), as well as the creation of directly overlapping suture lines.

Webster and colleagues reported excellent results with a transvaginal approach to VVF by vaginal cuff excision (Iselin et al, 1998; Flynn et al, 2004). In this approach, the fistula tract is isolated, and the entire epithelialized portion of the tract is excised in the fashion of a wide inverted cone, leaving a funnel-shaped defect from the vesical to the vaginal side of the fistula. The defect is then closed in three or four layers using absorbable suture. The principal advantages of this technique are that mobilization of vaginal flaps is not required, and vaginal shortening is minimal.

Abdominal Techniques. VVF may be repaired transabdominally, and this is the preferred approach in those cases requiring augmentation cystoplasty or ureteral reimplantation. Compared with the vaginal approach, the abdominal approach to VVF repair is associated with a longer recovery time and in-patient hospitalization, greater blood loss, more cosmetic deformity, and, in general, greater morbidity. Abdominal repair of VVF may be performed intraperitoneally or extraperitoneally, as well as transvesically.

Suprapubic Intraoperative or Extraperitoneal Approach. The patient is positioned in a low lithotomy position with access to the vagina in the sterile operative field. Ureteral catheters may be placed preoperatively or intraoperatively to assist in identification of the ureters, especially if the VVF is in close proximity to the ureteric orifices. A lower midline incision is carried out. As classically described by O'Connor and colleagues (O'Connor and Sokol, 1951; O'Connor et al, 1973), the bladder is approached extraperitoneally; however, in some cases, the peritoneum will be entered. The bladder is opened vertically, and the cystostomy is extended down to the opening of the VVF (Fig. 89-14). As the dissection proceeds distally, stay sutures placed on the bladder edges greatly assist in retraction. In addition, a curved sponge stick placed per vagina with gentle upward traction can provide excellent exposure of the VVF. With the bladder having been bivalved down to the level of the VVF, the VVF tract is excised, and the dissection is continued beyond the fistula tract to develop the vesicovaginal space (Fig. 89-15). The vagina is carefully dissected and separated from the bladder for a distance of 2 to 3 cm beyond the VVF. **The key to the operation is the mobilization of the bladder from the vagina caudal to (beyond) the VVF tract.** After wide mobilization from the bladder, the vagina is closed with a running absorbable suture. At this point, if an interpositional flap of greater omentum is to be used, it is mobilized and then secured 1 to 2 cm distally beyond the excised VVF tract (see later discussion) (Wein et al, 1980a). The bladder is then closed in several layers. A suprapubic tube and urethral catheter are usually left for postoperative drainage. Anticholinergic agents are used liberally in the postoperative period to minimize bladder irritability, which may be problematic.

Bladder augmentation or ureteral reimplantation, if necessary, can be incorporated into the suprapubic approach before closure

Step 1: Positioning, Preparation, and Retraction. The patient is placed in the dorsal lithotomy position; rectal packing is placed (to aid in identification of the rectum); and the lower abdomen and perineum are prepared with a standard surgical preparation solution. Appropriate exposure is maintained with use of a vaginal weighted speculum, silk labial retraction sutures, and a ring retractor with hooks. A suprapubic tube is placed, cystoscopy with reassessment of the VVF location is performed, and ureteral catheters are placed if the fistula tract is adjacent to or involves the ureteric orifices. A posterolateral episiotomy may be performed to improve exposure in patients with a narrow introitus. A urethral catheter is placed in addition to the suprapubic tube, maximizing postoperative urinary drainage (see Fig. 89-13A). **Any concomitant anti-incontinence or other vaginal surgery that is to be performed simultaneously with VVF repair should be done before reconstruction to avoid disturbing the repair once completed.**

Step 2: Incision. The fistula tract is cannulated with a small Foley catheter (10 to 12 Fr) and, after inflation of the balloon, gentle downward traction is placed on the Foley catheter, pulling the VVF toward the introitus. Occasionally a small VVF requires dilation with metal sounds to place the Foley catheter. To facilitate dilation of the fistula tract in these cases, a guidewire may be placed through the fistula tract endoscopically, and sequential dilation performed using Goodwin sounds. The gentle traction on the VVF provided by the Foley catheter greatly enhances exposure (see Fig. 89-8). The vaginal flaps are marked (see Fig. 89-13B). Saline is then injected into the anterior vaginal wall surrounding the fistula tract and along the lines of the vaginal flaps. The fistula tract is carefully circumscribed. An inverted J-shaped or U-shaped incision that circumscribes the fistula tract is made with the limbs of the J or U extending to the apex of the vagina. The circumscribed fistula is incorporated into the curved portion of the incision. The nature of this incision allows creation of a vaginal wall flap that can be advanced and rotated over the fistula repair. This helps avoid vaginal shortening and overlapping of suture lines during reconstruction. However, some surgeons have recommended that the long end of the incision be extended along the anterior vaginal wall toward the introitus (Wang and Hadley, 1990).

Step 3: Creation of Vaginal Wall Flaps. The vaginal wall flaps are created by dissecting in a proximal, distal, and lateral direction away from the fistula tract (see Fig. 89-13C). Initially, dissection may be difficult because of scarring from the insult that resulted in the VVF. It is important to remain in the correct surgical plane while developing the vaginal wall flaps, so as not to compromise their vascularity. Adequate mobilization of the vaginal wall distal to the VVF is especially important, because it will be necessary to advance the proximal vaginal wall flap beyond the fistula as the final layer of closure. Each flap is mobilized 2 to 4 cm from the fistula tract, exposing the underlying perivesical fascia. The ring of vaginal wall tissue, where the initial incision circumscribed the fistula opening, is left intact; thus, flap creation is done in healthy tissue, avoiding dissection of the actual fistula tract. This technique facilitates dissection in proper tissue planes, avoids bleeding edges at the resected fistula tract, ensures that closure of the fistula is done with healthy tissue (vaginal wall flaps), and decreases the risk of potential bladder perforation. Wide mobilization of the vagina off the perivesical fascia for a distance of several centimeters of bladder allows creation of a tension-free closure.

Step 4: Fistula Closure. Closure of the fistulous opening is now done. The catheter in the fistula tract is removed, and the first layer of the repair is performed. Interrupted 3-0 or 4-0 absorbable sutures are placed in a transverse or vertical fashion across the fistula. These sutures incorporate bladder wall and the fistulous tract itself, starting in healthy tissue approximately 0.5 cm away from the margin of the fistula (see Fig. 89-13D). Inclusion of the fistula tract in the repair (and not resecting the fistula) provides a strong anchor of supporting tissue for the first layer of the repair. The use of a double-armed suture, with both sides thrown from within the fistula tract outward, facilitates incorporation of good-quality tissue. The Foley catheter can be taken off traction while these sutures are placed to avoid puncturing the balloon. The second layer of the repair is placed with interrupted 2-0 or 3-0 absorbable sutures. These sutures are placed to invert the previous layer by imbricating the perivesical fascia and the deep musculature of the bladder over the first layer and fistula tract (see Fig. 89-13E). The sutures should be applied at least 3 to 5 mm from the prior suture line, free of tension, and at a 90-degree angle from the first suture line to minimize overlapping of the two lines of repair. The integrity of the repair is confirmed by filling the bladder with 200 to 300 mL of saline mixed with indigo carmine and observing for vaginal staining. At this point, if desired, an interpositional peritoneal or Martius flap may be mobilized and secured over the existing suture line (Raz et al, 1993; Eilber et al, 2003).

Step 5: Advancement and Closure of Vaginal Wall Flap. The final and third layer of closure is done with the vaginal wall flaps that were previously created. The redundant, excess anterior (distal) vaginal flap is excised, and the posterior (proximal) vaginal flap is advanced beyond the fistula closure. This covers the fistula site with fresh, healthy vaginal tissue, which helps avoid overlapping of suture lines.

Step 6: Closure of the Vaginal Wall. The flap is advanced at least 2 to 3 cm beyond the fistula closure, and the vaginal wall is closed with a running, locking, absorbable 2-0 suture. An antibiotic-impregnated vaginal packing is placed for 24 hours postoperatively. The urethral Foley and suprapubic catheters are left to drain for 10 to 14 days.

Postoperative urinary drainage is essential, and the draining catheter(s) are left in all patients postoperatively until cystography confirms successful repair of the fistula. In general, imaging is obtained 10 to 21 days from the time of repair. If a persistent leak is noted, ongoing catheterization and repeat imaging at a 2- to 3-week interval may demonstrate eventual resolution (Schwab and Rovner, 2003). Anticholinergic agents are given to decrease bladder irritability. A cystogram is done before catheter removal to document integrity of the repair. Sexual intercourse is avoided for 2 to 3 months postoperatively.

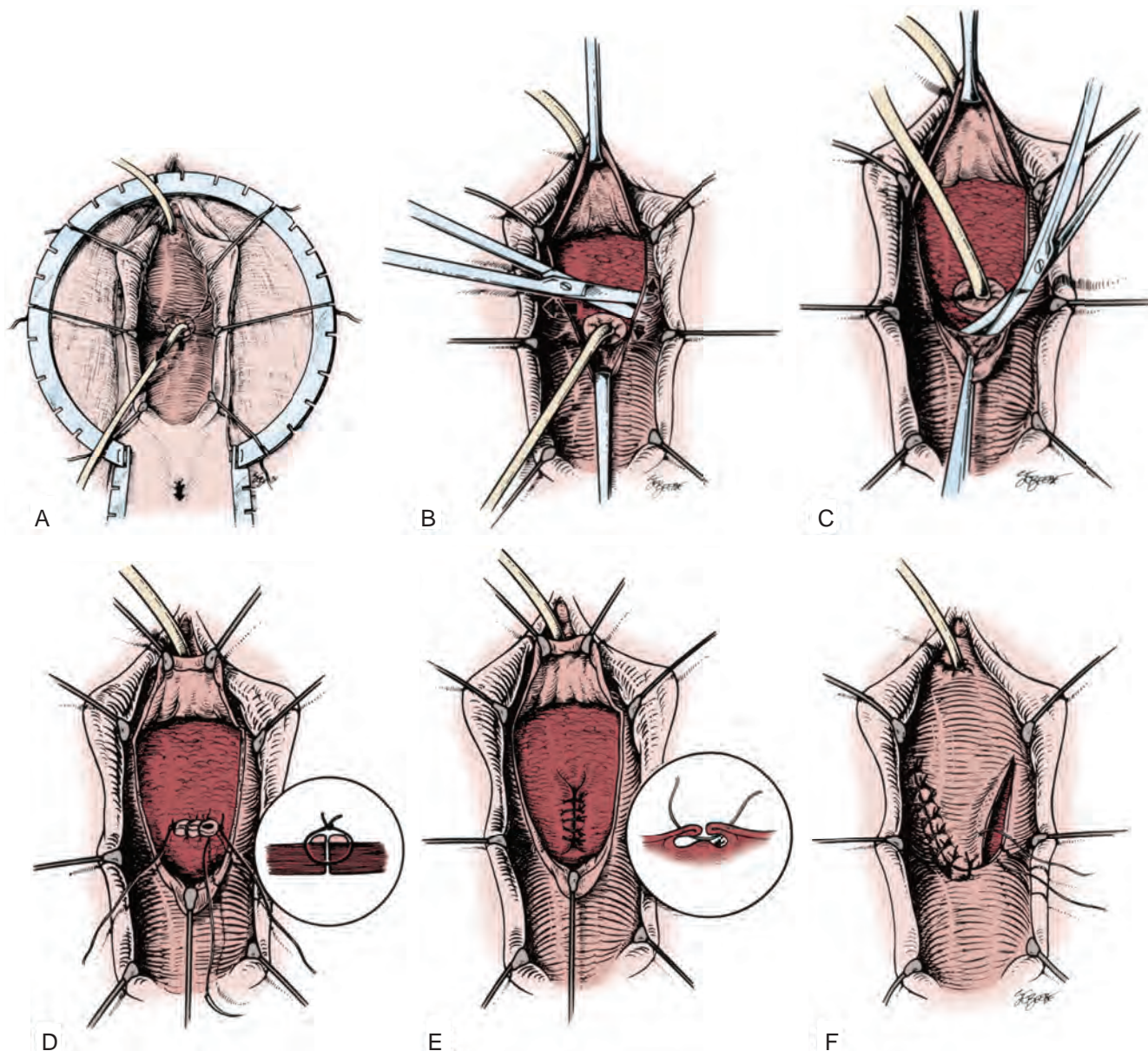


Figure 89-12. Technique of vaginal repair of a posthysterectomy vesicovaginal fistula (VVF). A, Retraction including ring retractor, vaginal speculum, and Foley catheter in the VVF tract. A Foley catheter is seen in the VVF tract providing traction on the vaginal cuff. B, Mobilization of anterior vaginal wall flap. Lateral flaps are developed as well, thereby isolating the VVF tract. C, Mobilization of posterior vaginal wall flap. D, Initial layer of closure is performed without excising the edges of the fistula tract. E, The perivesical fascia is closed with Lembert-type sutures. This line of closure is perpendicular to the initial suture line. F, The vaginal wall flaps are advanced to avoid overlapping suture lines. (From Ganabathi K, Sirls L, Zimmern P, et al. *Vesicovaginal fistulae: reconstructive techniques*. In: McAninch J, editor. *Traumatic and reconstructive urology*. Philadelphia: Saunders; 1996. p. 317.)

of the bladder. Large or small bowel may be used for augmentation cystoplasty, depending on the clinical circumstances.

Transvesical. A suprapubic transvesical approach to VVF repair has also been described (Landes, 1979; Cetin et al, 1988; Gil-Vernet et al, 1989). In this approach, the bladder is opened through a vertical cystotomy but is not bivalved down to the VVF tract. From a transvesical approach, the VVF tract is circumscribed and excised transvesically. The vaginal edges are then carefully mobilized from the bladder. The vagina and bladder are closed sequentially. A V-shaped flap of adjacent posterior bladder wall may be brought down as a flap to close a large gap or to minimize overlapping

suture lines (Gil-Vernet et al, 1989). This approach has been successful in both simple and complex fistula (Gil-Vernet et al, 1989; Leng et al, 1998), and modifications have been described incorporating an omental flap (Hellenthal et al, 2007).

Laparoscopic and Robotic Approaches. Laparoscopic VVF repair is an alternative to the classical open approach described previously. Compared with the O'Connor transabdominal approach, laparoscopic repair is reported to be associated with less surgical trauma, shorter convalescence, and lower morbidity (Nezhat et al, 1994; von Theobald et al, 1998; Miklos et al, 1999; Ou et al, 2004). Laparoscopic VVF repair is most useful in the same scenarios as the

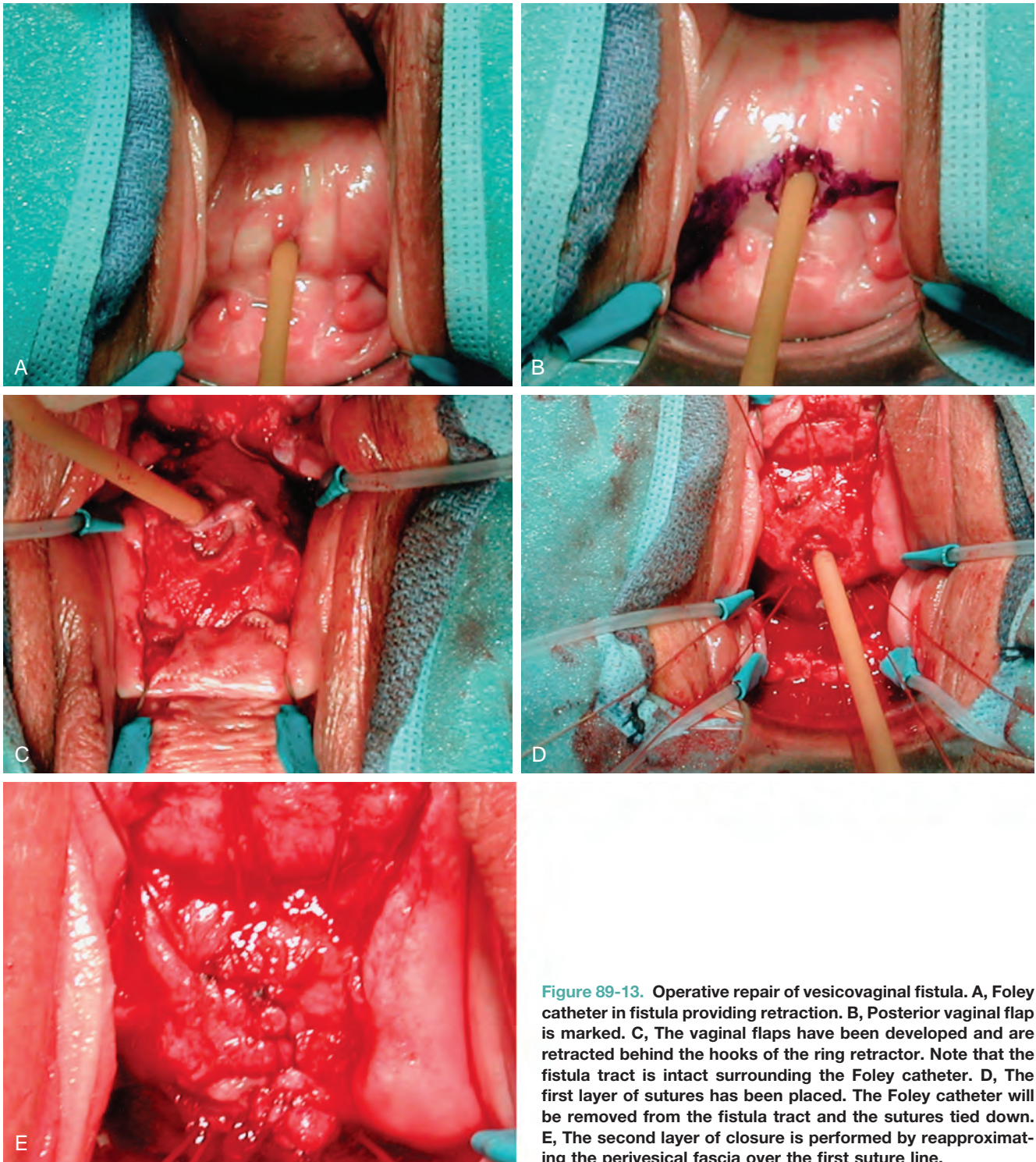


Figure 89-13. Operative repair of vesicovaginal fistula. A, Foley catheter in fistula providing retraction. B, Posterior vaginal flap is marked. C, The vaginal flaps have been developed and are retracted behind the hooks of the ring retractor. Note that the fistula tract is intact surrounding the Foley catheter. D, The first layer of sutures has been placed. The Foley catheter will be removed from the fistula tract and the sutures tied down. E, The second layer of closure is performed by reapproximating the perivesical fascia over the first suture line.

transabdominal repair, such as in the setting of a high VVF in which a vaginal operation would be anatomically challenging. Dense pelvic adhesions and/or inflammation from prior abdominal surgery can make this approach less desirable in some patients. Furthermore, intracorporeal laparoscopic suturing, a requirement for VVF repair, is an advanced skill many surgeons lack. Because of these limitations, the laparoscopic VVF repair has not been widely adopted.

Successful robotic VVF repair was first reported in 2005 (Melamud et al, 2005), and several small case series have been subsequently reported (Sundaram et al, 2006; Hemal et al, 2008). A five-port

technique has been described using a vaginal pack to maintain pneumoperitoneum throughout the case (Sundaram et al, 2006; Hemal et al, 2008). Removal of the vaginal packing without loss of pneumoperitoneum confirms successful closure. Advantages to the robotic technique include three-dimensional visualization, wristed instrumentation reducing the severe angulation required for laparoscopic VVF repair, and technically simpler intracorporeal knot tying.

Although there have been no direct comparisons among the classical transabdominal VVF repair, transvaginal VVF repair, and the minimally invasive robotic and laparoscopic techniques, it is

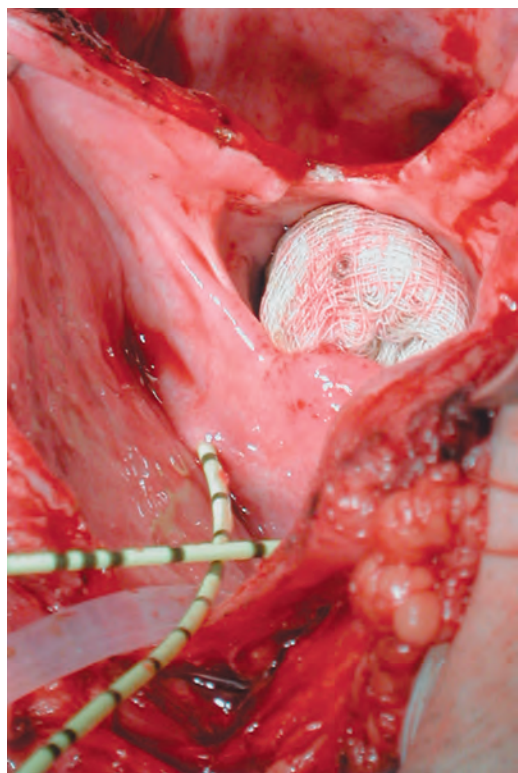


Figure 89-14. Intraoperative photograph from a suprapubic vesicovaginal fistula (VVF) repair. The bladder has been opened anteriorly and bivalved in the midline down to the level of a very large VVF. The gauze packing lies in the vagina. The ureteral catheters were placed to identify the ureters intraoperatively.

doubtful that a single procedure will emerge as the optimal surgery for all patients with VVF, given the variability in the nature of the condition, the patients in whom it occurs, and the expertise of individual surgeons.

Steps of Transabdominal Transvesical Laparoscopic Repair of Vesicovaginal Fistula. Please see the Expert Consult website.

Robotic Repair of Vesicovaginal Fistula. Please see the Expert Consult website.

Postoperative Care and Follow-Up. Please see the Expert Consult website.

Complications. Please see the Expert Consult website.

Special Considerations for Laparoscopic and Robotic Repair. Please see the Expert Consult website.

Conclusions on Vesicovaginal Fistula Repair. Please see the Expert Consult website.

Adjuvant Procedures in the Repair of Vesicovaginal Fistula: Tissue Interposition. The interposition of a healthy, well-vascularized tissue flap during VVF repair may be beneficial under certain circumstances. Tissue flaps are especially helpful in the setting of complex fistulae, such as those that have recurred after a prior attempt at repair, those related to previous radiotherapy, ischemic or obstetric fistulae, large fistulae, and, finally, those associated with a difficult or tenuous closure because of poor tissue quality. For VVFs repaired transvaginally, a labial fat pad (Martius flap) or a peritoneal flap is most commonly used. From a transabdominal approach, omentum or peritoneum is often used as an interpositional flap (Eisen et al, 1974).

Martius Flap. For low or distal fistulae, a Martius fibrofatty labial flap is a reliable source of tissue. The fibrofatty labial flap was first described by Heinrich Martius in 1928. This flap consists of adipose tissue and connective tissue and is the preferential tissue for fistulae involving the trigone, bladder neck, and urethra (Zimmern et al, 1986; Rangnekar et al, 2000). The blood supply

to the flap derives inferiorly from the posterior labial vessels (off the internal pudendal artery), superiorly from the external pudendal artery, and laterally from the obturator artery. The lateral blood supply is sacrificed during mobilization of the flap; the flap may be divided at either its most superior or inferior margin (basing the blood supply on the inferior or superior vascular pedicle, respectively), depending on where the flap will be transferred (Figs. 89-31 and 89-32).

Please see the Expert Consult website for further details.

Rangnekar and colleagues (2000) reported on the usefulness of the Martius flap in both urethrovaginal fistulae and VVFs, the majority of which (32 of 46) were a result of obstetric trauma. Of the VVF repairs, 4 of 21 repairs without a Martius flap failed, compared with none of the 13 procedures that included an adjuvant Martius flap. Eilber and colleagues (2003) reported that 33 of 34 (97%) patients undergoing repair of a distal VVF with a Martius flap were cured after the first operation.

For posthysterectomy fistulae, the distance from the labial harvesting site of the Martius flap to the fistula at the apex of the vagina may be considerable. Mobilizing and then tunneling the Martius flap to reach this location may compromise its blood supply and viability. In these cases, a peritoneal flap is preferred (Raz et al, 1993).

Peritoneal Flap. The use of a peritoneal flap during transvaginal repair of a complex VVF is a simple procedure that does not require extravaginal harvesting of the flap. This technique is primarily used in conjunction with repair of a high-lying posthysterectomy VVF (Raz et al, 1993; Eilber et al, 2003). Notably, peritoneal flaps may also be used as an adjunctive measure during transabdominal repair of VVF, although the approach and technique are vastly different (Eisen et al, 1974).

After a two-layer closure as described previously, the peritoneum is identified posteriorly. The peritoneum and preperitoneal fat are identified, isolated, and mobilized from the caudal origin of the vaginal wall flap using sharp dissection. Usually, dissection just beyond the posterior wall of the bladder will expose the edge of the peritoneum in the anterior cul-de-sac (Raz et al, 1993). The peritoneum is identified as a distinct layer from the bladder. The peritoneum is not opened but is mobilized and then advanced over the fistula repair and secured with interrupted absorbable sutures in a tension-free manner (Fig. 89-33). If a peritoneotomy is made during dissection or mobilization, the peritoneal defect can be closed as the flap is secured to the perivesical fascia over the fistula repair. The vaginal flap is then advanced and closed as previously described.

Raz initially reported success in 9 of 11 patients with high VVF undergoing peritoneal flap placement (Raz et al, 1993). A later study from the same institution reported on the use of peritoneal flaps in 83 patients, of whom 80 were cured after the first operation (Eilber et al, 2003). Two of the 3 patients with failed procedures underwent successful repair with a repeat transvaginal repair and peritoneal flap; the 1 remaining patient required a transabdominal repair with omental interposition.

Greater Omentum. The omentum is a particularly useful structure in the repair of VVF. Although most commonly used as an adjunct during transabdominal VVF repair (an interpositional layer between the bladder and vagina), it has occasional usefulness in transvaginal VVF repair, if it had been brought down into the pelvis during a prior surgical procedure. Favorable properties of the omentum include its ability to be mobilized on a well-vascularized pedicle into the deep pelvis without tension, its inherent lymphatic properties, its ability to contribute to healing even in the presence of infection, and the ease with which epithelialization occurs on its surface (Turner-Warwick, 1976; Wein et al, 1980b).

Please see the Expert Consult website for further details.

Evans and colleagues (2001) reported retrospectively on the use of an omental interpositional flap in 37 patients undergoing transabdominal VVF. Of the 29 patients with a benign cause of VVF, all 10 patients in whom an omental flap was used were cured, compared with only 12 of 19 (63%) in whom an omental flap was not used. Orford and Theron (1985) reported a 93% cure rate with the use of an omental pedicle graft in 52 patients undergoing VVF

TABLE 89-2 Instrumentation for Robotic Repair of Vesicovaginal Fistula

SURGEON INSTRUMENTATION			
RIGHT ARM	LEFT ARM	THIRD ARM	ASSISTANT INSTRUMENTATION
Hot Shears (monopolar curved scissors) or Needle driver	Plasma kinetic forceps or Maryland bipolar grasper SutureCut needle driver	Not necessary; if used, ProGrasp forceps	A 5-mm suction-irrigator Blunt-tipped grasper Laparoscopic needle driver Laparoscopic scissors if SutureCut needle driver is not used

Courtesy Dr. Ashok K. Hemal, Wake Forest University.

BOX 89-5 Equipment for Robotic Repair of Vesicovaginal Fistula

ROBOTIC EQUIPMENT

da Vinci Robotic System*
Three 8-mm trocars
A 0-degree and 30-degree three-dimensional (3D) laparoscope
Hot Shears* (monopolar curved scissors)
Maryland bipolar forceps
Plasma kinetic forceps
One large needle driver and one SutureCut† needle driver
ProGrasp* forceps

LAPAROSCOPIC EQUIPMENT

One trocar (12 mm)
One 5-mm trocar for the bedside assistant
A 5-mm suction cannula
A 5-mm laparoscopic grasper
A 5-mm endoscopic needle driver

SUTURE MATERIALS

3-0 Poliglecaprone monofilament synthetic absorbable suture with RB-1 needle
3-0 Barbed suture (composed of absorbable copolymer of glycolic acid and trimethylene carbonate (polyglyconate))

*Intuitive Surgical, Sunnyvale, CA.

†SutureCut, Lexington, KY.

Courtesy Dr. Ashok K. Hemal, Wake Forest University.

See Table 89-2 and Box 89-5.

Step 1: Patient's Position, Bimanual Examination, and Cystoscopy. Under general anesthesia, the patient is placed in the lithotomy position, and a bimanual as well as a speculum examination is performed. Cystoscopy and insertion of ureteral catheters helps identify and protect the ureters during surgical dissection. When feasible, ureteral catheter of a different color or a Glidewire (Terumo Interventional Systems, Somerset, NJ) should be placed across the fistula emerging from the vagina. An indwelling urethral Foley catheter is placed. Gentle traction is applied on the Foley catheter to mechanically block the bladder neck and prevent CO₂ leakage. However, if this is not sufficient, a sponge is inserted into the vagina up to the vaginal apex to prevent CO₂ leakage.

Step 2: Port Placement. The pneumoperitoneum is established, and a three-port transabdominal approach is used. A primary 10-mm port is inserted in the midline supraumbilically. The laparoscope is introduced, and two 5-mm ports are placed lateral to the rectus muscle between ipsilateral spinoumbilical line. Additional ports are created in both iliac fossae under laparoscopic vision as per requirements and difficulty in surgery.

Step 3: Adhesiolysis and Dissection. Often, adhesions are present in these cases and require lysis from the posterior surface of the urinary bladder. Once this has been completed, dissection is started around the fistulous site. The peritoneum between the bladder and vagina is incised. The posterior bladder wall is incised vertically in the proximity of the fistula with cold scissors or an ultrasound scalpel, and dissection is continued until the catheter going across the fistula can be seen. The incision is carried downward as far as the fistula tract. This cystotomy requires wide dissection of the interveticovaginal plane so that the bladder can be easily separated from the vagina, to encircle the fistula. With use of laparoscopic scissors with gentle traction and countertraction, a plane is developed precisely between the bladder and vagina.

Step 4: Excision and Freshening Edges of the Fistula. The goal is to excise the fistulous tract all around until viable tissue margins in both the bladder and vagina are created. However, if this is difficult, then edges are freshened on either side of opening. The bladder wall is further separated from the vagina around the catheter to ensure adequate mobilization, and the vesicovaginal space is extended laterally to allow for tension-free suturing. Traction on the urethral catheter balloon helps facilitate sharp dissection of the plane between bladder and vagina. A sponge retractor in the vagina helps to elevate the vaginal fornices to guide the dissection.

Step 5: Reconstruction. Basic VVF repair is done in three layers. Vaginal closure is initiated at the apex of the incision with viable tissue in one layer using a continuous transverse 2-0 synthetic absorbable suture (Vicryl, Ethicon) or more recently barbed suture is commonly used for this step. Closure of the vagina is followed by interposition of the omentum or pericolic or mesenteric fat over the vaginal suture line. A suture is then placed at the anterior vaginal wall, distal to the vaginal closure. This suture is then used to anchor part of the omental flap, which can be harvested from the nearest anatomic location. Bladder closure is subsequently performed in two layers: first, mucosal closure with continuous 3-0 synthetic absorbable suture, then the seromuscular closure with interrupted 2-0 synthetic absorbable suture.

Step 6: Checking of Watertight Closure, Drain Placement, and Removal of Ureteric Catheters. The bladder is filled with 150 mL of water to assess the watertight closure. Bladder drainage is usually accomplished by a 20-Fr urethral Foley catheter. Usually a suprapubic cystostomy is not required. A drain is placed into the pelvic cavity. Bilateral ureteral catheters are removed sequentially if present.

Patient's Preparation. Mechanical and antibacterial bowel preparation the day before surgery is not done routinely except in cases of complicated VVF. A prophylactic dose of weight-adjusted low-molecular-weight heparin can be given the evening before surgery and every 24 hours thereafter until ambulation. Antibiotic is given within an hour of incision.

Patient's Position. General endotracheal anesthesia is administered.

During cystoscopy the patient is placed in lithotomy position with the operating table positioned horizontally, taking great care to facilitate the movement of the C-arm between the kidney and bladder area. This is for the placement of the ureteral catheters as well as a catheter through the fistula site if possible.

The patient in the dorsolithotomy position is secured to the table, with care taken to pad all pressure points, and her arms are tucked. Shoulder bolsters (TrenStop [Steris, Mentor, OH]) are applied to prevent cranial slide. Position is tested by placing the patient in steep Trendelenburg position. The patient is finally placed into a low lithotomy position to allow complete access to the vagina and bladder. A sterile field is created by preparing the perineum and proximal thighs and infraxiphoid abdomen using chlorhexidine gluconate after clipper shaving. A Foley catheter is placed per urethra to straight drain, and the ureteral catheters and catheter traversing through the fistulous opening are kept in the sterile area.

Finally, for commencement of the omentum mobilization for tissue interposition, the patient is placed back in an almost horizontal position, parallel with the floor (0 to 15 degrees), thus contributing to the performance of tension-free fixation of the omentum and helping to keep the small bowel contents in the epigastrium. In addition, the hips and the knees are only slightly flexed to reduce the distance between the mesentery root and os pubis, facilitating a tension-free approximation of omentum to the VVF area.

Port Placement (Fig. 89-16). Next, a high-flow, low-pressure pneumoperitoneum is obtained using a Veress technique in the supra-umbilical midline after the aspiration and drop test is passed. Next, a 12-mm camera port is placed 5 cm above the umbilicus. Inspection of the peritoneal cavity is performed to look for adhesions. Two additional ports are placed as follows: a left paramedian 8-mm robotic port, a left far lateral 8-mm robotic port, a right paramedian 8-mm robotic port, and a 5-mm port for suction and assistance or AirSeal system (SurgiQuest, Milford, CT). The robot is placed between the patient's legs and docked to the ports. Alternatively, side docking can be done, because this may allow more room for vaginal manipulation if needed.

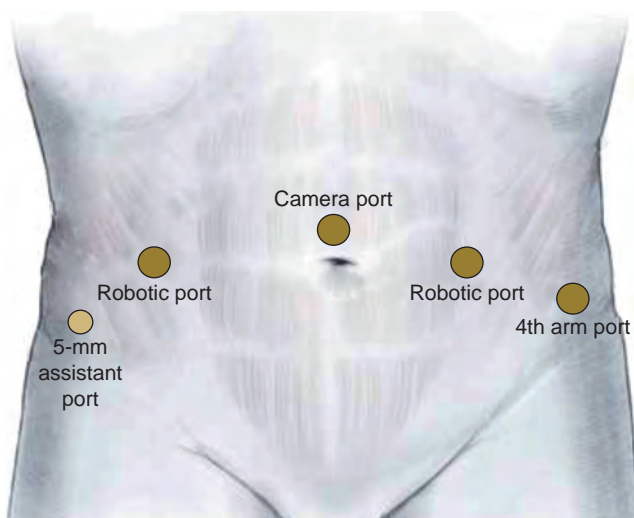


Figure 89-16. Sites for port placement for robotic repair of vesicovaginal fistula. (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

Any da Vinci system can be used, but the new Si system with four arms is preferred. With use of the new system, the trocars can be placed relatively independent of the patient's body habitus and higher, which is very important in cases with difficult mobilization of the omentum.

Surgical Steps of Robotic-Assisted Laparoscopic Vesicovaginal Fistula Repair

Bimanual examination and cystoscopy. Bimanual examination and cystoscopy are performed as in the laparoscopic approach.

Adhesiolysis. In a patient with prior abdominal procedures, the first trocar can be inserted preferably using the Hasson technique. After inspection of the peritoneal cavity, a meticulous adhesiolysis of the omentum and bowel is performed from the surrounding structures, especially in the pouch of Douglas. With a combination of sharp and blunt dissection with plasma kinetic or Maryland fenestrated bipolar forceps and monopolar curved scissors, adhesiolysis is carried out to delineate the anterior surface of the uterus (if present) and the superior aspect of the bladder. The small bowel loops and/or the sigmoid colon usually requires careful dissection off the bladder in posthysterectomy patients. Trendelenburg tilt allows the intestinal contents to fall cranially. Sometimes release of the adhesions close to the port sites is necessary laparoscopically before placement of all ports for the robotic device.

Techniques of localization and exposure of fistula. The bladder is identified by moving or traction on the Foley catheter. There are three ways to approach the fistula to avoid O'Connor's technique of bivalving the bladder.

1. Posterior cystotomy. (Figs. 89-17 to 89-25 illustrate posterior cystotomy technique for robotic repair of VVF.) In direct proximity and superior to the VVF, the posterior bladder wall is incised vertically with the monopolar robotic scissors. The cystotomy is continued in the direction of the catheter that defines the fistula, completely opening the posterior bladder wall and encircling the fistulous opening. If the fistulous tract is relatively small and visible through the cystotomy, the vaginally placed ureteral catheter, which was used as a marker for the fistula, is cut and removed.
2. Vaginal incision with cystotomy. In this approach the incision can be made from the normal part of vagina starting on the anterior surface. The incision is carried vertically downward, encircling the fistula. The ureteric or Foley catheter that runs along the fistulous tract is manipulated by the bedside assistant and identified from the movement of bladder wall, which allows the creation of minimal cystotomy.

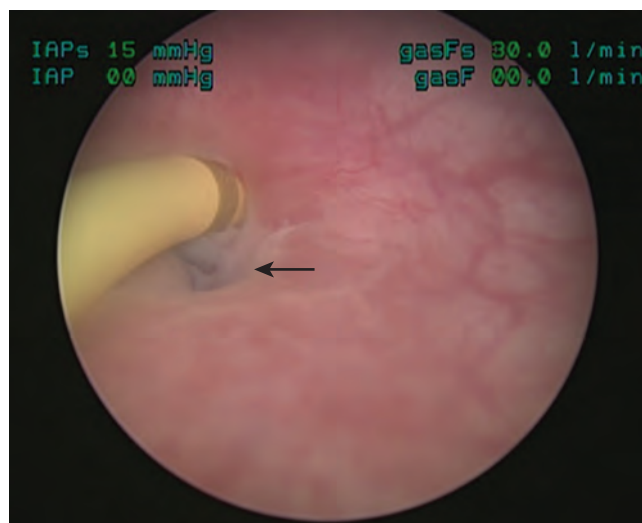


Figure 89-17. Cystoscopic view of vesicovaginal fistulous opening; the ureteral catheter (arrow) is going through it. (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

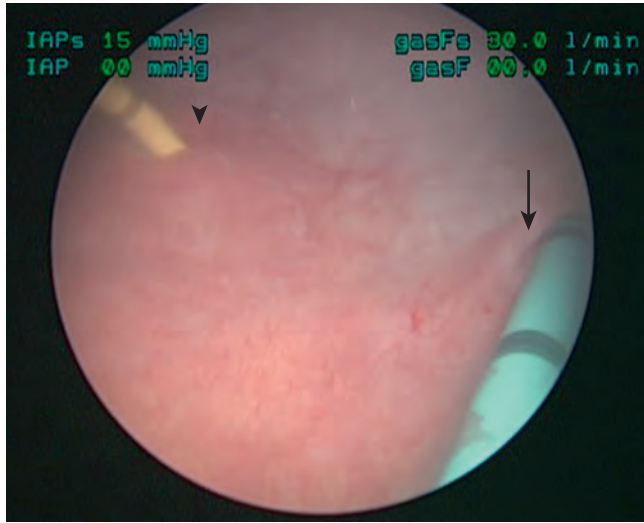


Figure 89-18. Cystoscopic view of vesicovaginal fistulous opening; the yellow ureteral catheter can be seen across the fistula (arrowhead) and blue ureteral catheter going through the normal ureteric orifice (arrow). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

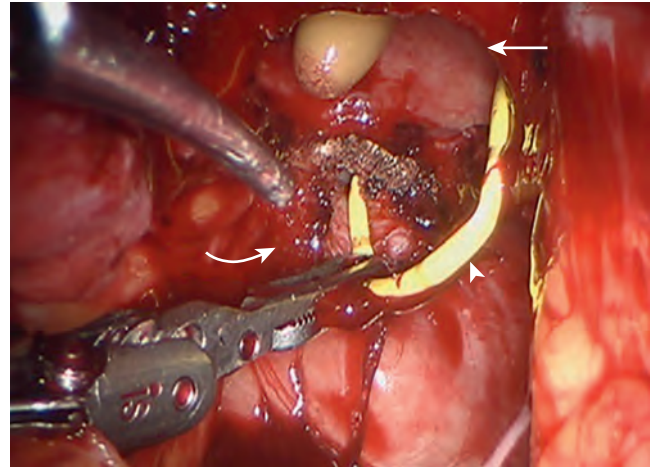


Figure 89-19. The exposed bladder (arrow) and tip of the yellow Foley catheter can be seen. The vaginal fistulous opening (curved arrow) and ureteral catheter can be seen across the fistulous opening (arrowhead). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

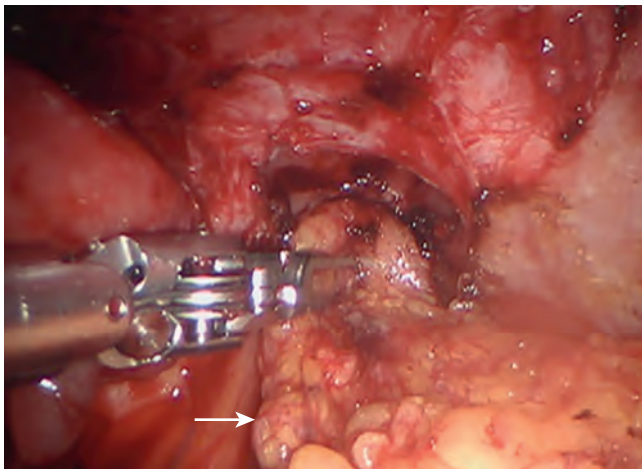


Figure 89-20. Previously mobilized omentum is checked for easy interposition after the fistula repair (arrow). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

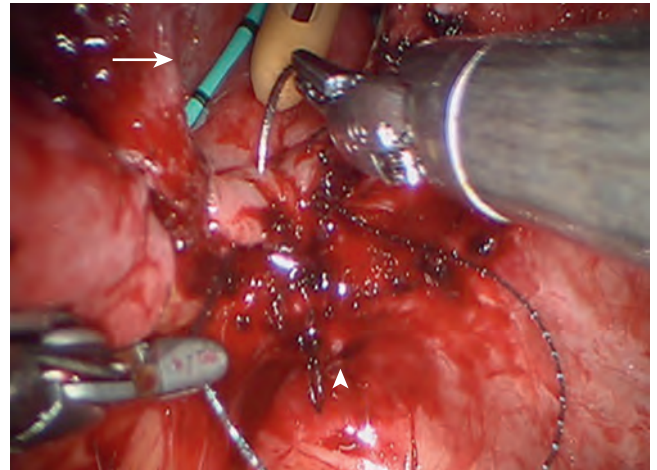


Figure 89-21. Completion of vaginal wall closure using 3-0 barbed suture after refreshing the edges of the fistulous site (arrowhead); cystotomy edge (arrow). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

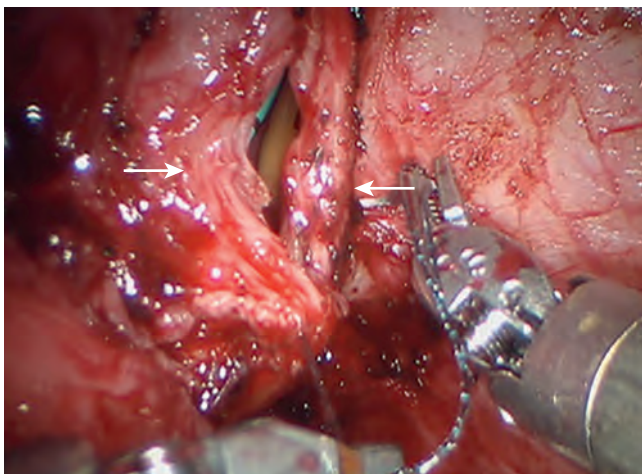


Figure 89-22. Cystotomy is being closed using barbed suture (arrow). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

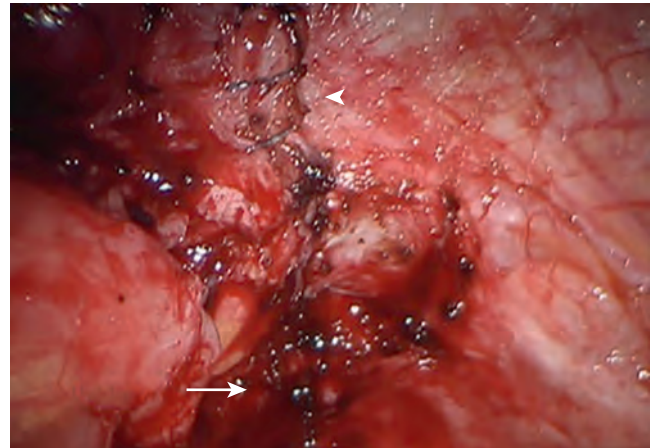


Figure 89-23. Complete reconstruction of bladder (arrowhead) and vagina (arrow). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

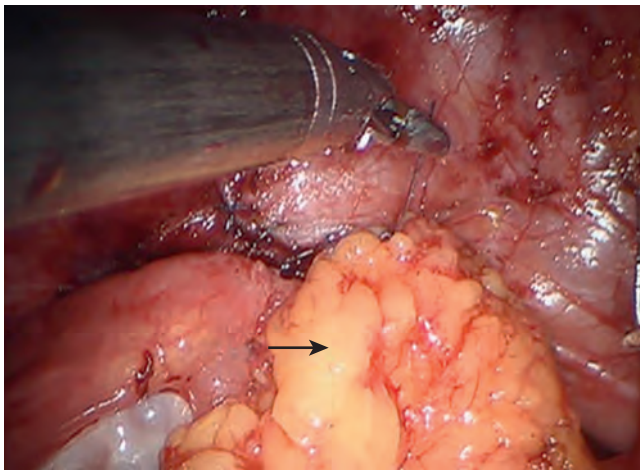


Figure 89-24. Omentum is interposed between vagina and bladder repair (arrow). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

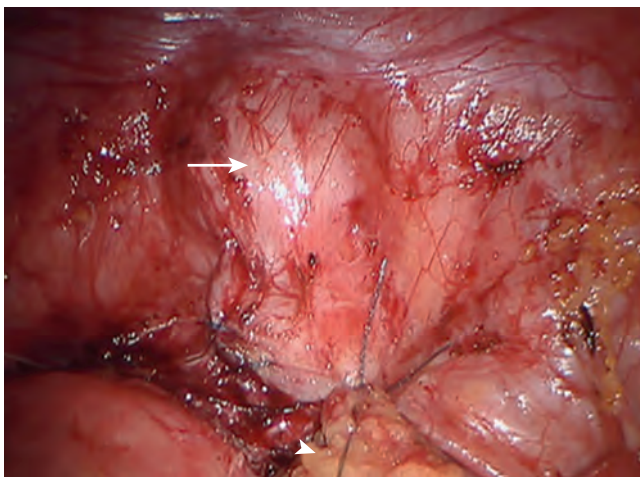


Figure 89-25. Reconstruction is checked with instillation of 150 mL of water (arrow); interposed omentum (arrowhead). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

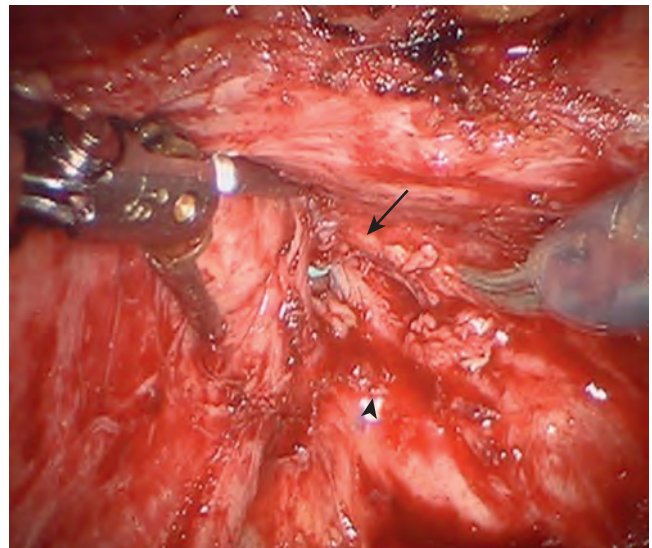


Figure 89-26. Minimal cystotomy to expose the fistulous site; dissection of bladder (arrow) and vagina (arrowhead). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

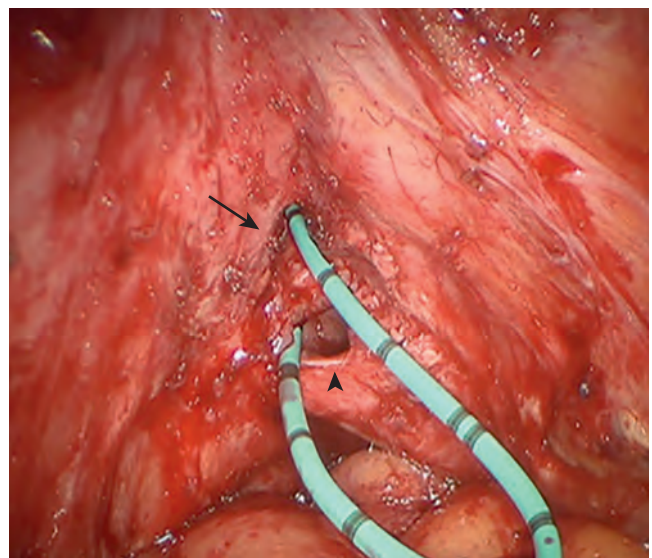


Figure 89-27. Dissected bladder (arrow) and vaginal (arrowhead) site of fistula with a catheter across. (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

3. Minimal dissection technique. (Figs. 89-26 to 89-30 illustrate the minimal dissection technique for robotic repair of VVF in a different case.) Under three-dimensional stereoscopic vision, a gentle drawing on the ureteral catheter, which was passed through the VVF, is usually helpful for the location of the approximate site of the fistula. The dissection is commenced in this area, and once the area has been identified by manipulation of the catheter, then a small cystotomy is created to identify the catheter across the fistula. Subsequently the incision is extended on either side as per requirement.

Excision of fistulous tract and refreshing of edges of fistula on bladder and vaginal site. The margins of resection of the fistulous tract are further dissected using monopolar robotic scissors. If the fistula is large and/or not completely identified, then the vaginally placed Foley catheter is pulled intra-abdominally through the cystotomy and is used as a retractor for the anterior bladder wall to splint open the cystotomy, thus allowing better visualization of the fistula and the stented ureteric orifices. There is no need to excise the borders of the fistulous tract widely as long as a lateral margin of viable tissue is visible. This is another advantage of magnification available with a minimally invasive approach. Occasionally, a wide excision may be necessary to expose the communication between the bladder and vagina. The excised tissue is sent for histologic examination.

Mobilization of the bladder and vaginal flap for tension-free reconstruction. The bladder and vaginal flaps are created to provide tension-free closure using cold scissors and with sparing use of plasmakinetic forceps for hemostasis if there is bleeding. Use of a fourth arm helps in providing traction and countertraction. Once the bladder wall is fully mobilized off the anterior aspect of the vagina, the preplaced ureteral catheters are helpful in identifying the ureteric orifices and preventing inadvertent injury to the ureters. Further mobilization and separation of the posterior wall of the bladder from the anterior vaginal wall allows a tension-free closure. Because the trigone and ureteric orifices invariably lie in close proximity to the fistulous edges, it is important to avoid uncontrolled blunt and wide excision, which may hamper subsequent closure. It is preferable to do a slow and careful sharp dissection of the fistulous edges, which must be freshened.

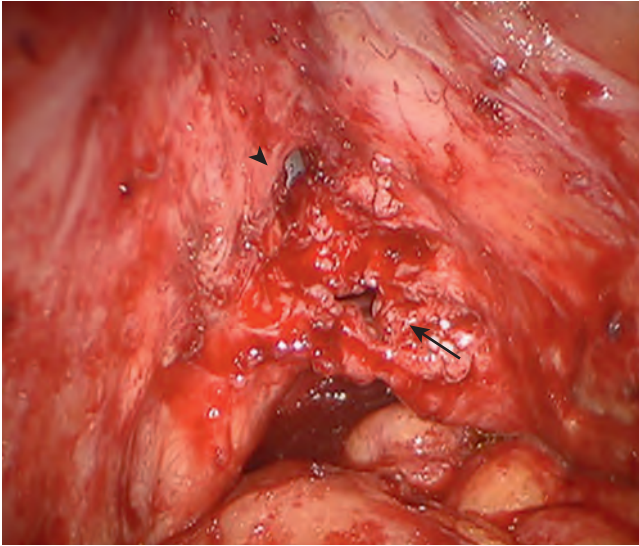


Figure 89-28. Dissected and freshened edges of vaginal site (arrow) and bladder site (arrowhead). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

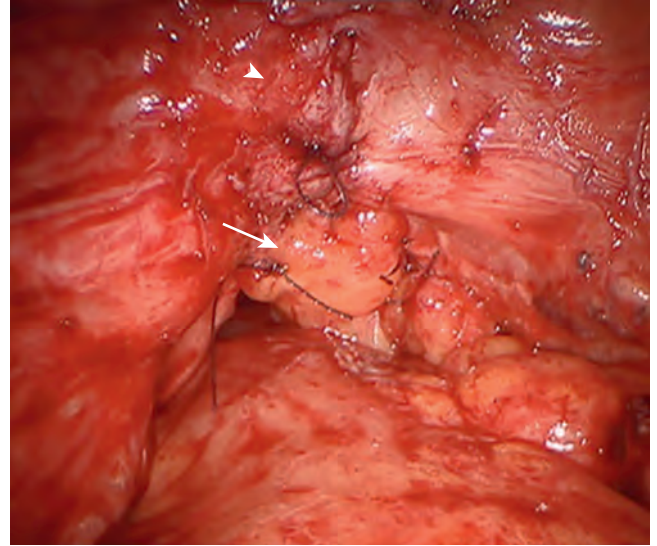


Figure 89-30. Omentum is tacked over vaginal repair (arrow); repaired bladder in two layers (arrowhead). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

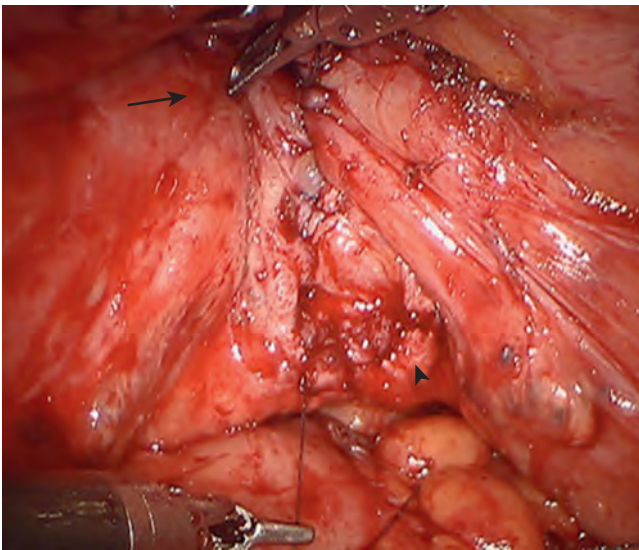


Figure 89-29. Reconstruction of vagina in two layers (arrowhead); bladder wall repaired in two layers (arrow). (Courtesy Dr. Ashok K. Hemal, Wake Forest University.)

Reconstruction of vagina and bladder. The closure of vagina is performed using 3-0 barbed suture, which is placed transversely for tension-free closure as a running watertight suture. If the size and the orientation of the vaginal gap allow less tension on the closure line, a vertically placed suture line could be acceptable.

Reconstruction of the bladder. The bladder is usually closed in a vertical manner to minimize the contact surface of suture lines. However, it depends on the size of the fistula. Also, after dissection, sometimes these can have a dog ear-shaped deformity. Bladder closure is initiated at the caudal part or close to the trigone area or at the most distal part of cystotomy near the ureteric orifices. If single-layer closure is performed, then 3-0 barbed suture is a good choice. If two-layer closure is contemplated, then the first layer includes mucosa and a portion of detrusor muscle layer using a 4-0 monofilament absorbable suture in a running continuous fashion. The second layer of detrusor muscle is then done. If the cystotomy is quite long, the bladder closure can be started from the proximal

open bladder edge until the superoposterior part of the bladder is closed. Then, with new suture, the most distal segment of the cystotomy is closed until the two are securely knotted together approximately in the middle of the cystotomy line. In so doing, the proximal suture can be used as traction to provide better exposure and subsequently improved visualization for the critical part of the cystotomy closure near the ureteric orifices. In addition, using two separate sutures for cystotomy closure avoids possible laxity of the single suture line. Second-layer bladder closure can be performed using 3-0 barbed suture. Watertight closure is confirmed by filling the bladder with 150 mL of water.

Interposition of the tissue. Tissue interposition between the bladder and vaginal suture lines is performed, preferably using a well-vascularized pedicle of omentum. To reduce tension on the vascular pedicle of omentum and better mobilize this in the lower abdomen, the patient is placed in an almost horizontal position. In case the omentum is completely retracted in the upper abdomen, it can be mobilized in the beginning and can be tagged to pelvis. Whenever omentum is easily available, it is the best choice and should always be used for interposition between the suture lines. If omentum is unavailable or cannot be adequately mobilized, the epiploic appendices of the sigmoid colon or a peritoneal flap from the nearest anatomic location is used as tissue for interposition.

Fixation of interpositional tissue. At the anterior vaginal wall distal to the vaginal closure, a 3-0 barbed suture is placed, which is used as a fixation to anchor the interpositional tissue. To avoid any contact between both suture lines and provide stability on fixation, the interpositional tissue is anchored with a suture on the resilient vaginal wall and distally to the end of the vaginal closure line. To prevent laxity on fixation, the interpositional tissue is also fixed left and right on the peritoneal edges of the cystotomy. Thus the interpositional tissue completely covers the suture line of the vagina, forming a triangle; each point is fixed on elastic and well-vascularized tissue.

Catheter and drain. A 20-Fr indwelling catheter is placed. No suprapubic cystostomy tube is placed. A 15-Fr Jackson-Pratt is introduced into the pelvis through left robotic port and secured to the skin with a silk suture.

Exiting cannula and closure. Reducing the pressure of pneumoperitoneum under 10 mm Hg, the robotic and assistant trocar sites are removed under endoscopic guidance to make sure there is no bleeding from vessels of the abdominal wall. At the end, the fascia of the 12-mm camera port is closed with monofilament absorbable suture. The skin is closed with 4-0 Monocryl subcuticular sutures.

Postoperative care after robotic VVF repair is different from that of the open procedure and may include the following.

1. The drain is typically removed within 24 hours postoperatively or when drainage fluid is less than 50 mL. Typically patients go home within 24 to 48 hours with an indwelling urethral catheter, which ensures continuous drainage of the bladder and proper healing. Typically, suprapubic cystostomy tube is not placed. If required, anticholinergics are used to prevent bladder spasms.
2. Normally the urethral catheter is removed on postoperative day 7 to 14, depending on the quality of reconstruction and the surgeon's preference. A retrograde cystogram may be performed before removal of the bladder catheter to confirm fistula closure but is not always mandatory. Patients are warned to avoid the use of tampons and refrain from sexual activity for at least 8 weeks postoperatively.
3. Appropriate prophylactic antibiotics are generally given as per protocol. The patient typically starts antibiotics a day before catheter removal.
4. Early mobilization and ambulation are encouraged using the principles of fast-track postoperative care: no nasogastric tube, with mobilization starting 6 hours after the end of the procedure. The patient is started on a liquid diet same evening and is progressed to a normal diet the next day.

Robotic-assisted laparoscopic repair has led to higher success rates over pure laparoscopy, which is technically more difficult. Conversion to open surgery may be required based on nonprogression of surgery, severe inflammation, severe adhesions, or difficulty in suturing or if there is a requirement for simultaneous bladder augmentation.

Major complications have been reported, including compartment syndrome in lower extremities, enterocutaneous fistula, and inferior epigastric artery injury, with the overall major complication rate being 2.3%.

Laparoscopic Repair of Vesicovaginal Fistula. The first laparoscopic repair of VVF was reported by [Nezhat and colleagues \(1994\)](#). Later [Nabi and Hemal \(2001\)](#) reported a modified technique of laparoscopic repair of VVF and right nephrectomy for a nonfunctioning kidney in a single session. Sotelo and colleagues reported an expeditious approach, intentionally opening first the bladder, leading accurately to the fistulous tract without the need for additional vaginal incisions or further dissection of the vesicovaginal space. Several series involving laparoscopic repair of VVF have been reported. Important series have been summarized in [Table 89-3](#). The operation time varies from 70 minutes to 390 minutes in different studies. Hospital stay depends on the practice policies in different countries. A few studies reported that patients were discharged with a urethral catheter and drain on the first postoperative day, whereas other centers kept their patients in the hospital while the urethral catheter and drain were kept in place for up to 2 weeks. In the available data the recurrence rate of the fistula is about 6.5% and the overall success rate is about 93.5%. Laparoscopy allows fistula repair with a limited bladder incision, unlike in an open procedure, with all the advantages of minimally invasive procedures such as a magnified view of the operative field, hemostasis, decreased hospital stay, and shorter convalescence.

Robotic-Assisted Laparoscopic Repair of Vesicovaginal Fistula. See [Table 89-4](#).

The first case series of robotic-assisted laparoscopic repair of VVF with step-by-step technique was reported by Hemal and associates in 2006 ([Sundaram et al, 2006](#)). This series included six patients with advantages of shorter hospital stay, faster recovery, and less morbidity. Later, other authors reported their experience with use of robotic assistance.

Hemal and colleagues also reported the first series of complex VVF robotic repairs, reporting their experience in seven cases of recurrent supratrigonal fistulae in which they first intentionally incised the bladder ([Gupta et al, 2010](#)).

The success rate reported for robotic-assisted repair was close to 100% in most of these small series, with the potential advantage that the robotic device allows more surgeons to use this minimally invasive approach.

Laparoscopic versus Robotic versus Open Approach. There is no level 1 evidence to prove superiority of one approach over another. Outcomes depend on the surgeon's experience and practice. Minimally invasive series demonstrate efficacy in primary VVF repair with acceptable success rates. Two retrospective studies described transition from open to laparoscopic repair and found that the latter was minimally invasive with similar success ([Ou et al, 2004](#)). In another retrospective case-matched study of 32 patients, Gupta and colleagues evaluated robotic-assisted laparoscopic versus open repair for recurrent VVF without any significant statistical difference in success rate (100% vs. 90%), mean operative time, complication rate, use of interpositional flap (omental vs. peritoneum), or complications (0% vs. 10%). The most significant difference between the two groups was shorter average hospitalization (3.1 vs. 5 days) favoring the robotic-assisted group, with decreased morbidity as opposed to open surgery ([Gupta et al, 2010](#)).

TABLE 89-3 Data on Laparoscopic Repair of Vesicovaginal Fistula

AUTHOR	NO. OF PATIENTS	TRANSVESICAL VERSUS EXTRAVESICAL	AVERAGE OPERATION TIME (min)	AVERAGE BLOOD LOSS (mL)	SUCCESS RATE	AVERAGE DURATION OF URETHRAL CATHETER (DAYS)	AVERAGE LENGTH OF HOSPITAL STAY (DAYS)	COMPLICATIONS
Miklos and Moore, 2015	41	Extravesical	NA	70	40/41	NA	NA	None
Zhang et al, 2013	18	Transvesical	135	NA	18/18	15	NA	None
Sirithanaphol et al, 2012	5	NA	220	NA	5/5	24.4	4.4 days	None
Utrera et al, 2012	8	Transvesical	150	NA	8/8	NA	4.7	1 patient UTI
Simforoosh et al, 2012	5	O’Conor	134	300	4/5	NA	4	None
Abdel-Karim et al, 2011	15	Extravesical	171	110	15/15	21	4	None
Shah, 2009	25	Transvesical	145	NA	19/22	14	4.5	Conversion to open 3

NA, not available; UTI, urinary tract infection.

TABLE 89-4 Data on Robotic Repair of Vesicovaginal Fistula

AUTHOR	NO. OF PATIENTS	TRANSVESICAL VERSUS EXTRAVESICAL	AVERAGE OPERATING TIME (min)	BLOOD LOSS (mL)	DURATION OF URETHRAL CATHETERIZATION (DAYS)	AVERAGE LENGTH OF HOSPITAL STAY (DAYS)	SUCCESS RATE	COMPLICATIONS
Dutto and O'Reilly, 2013	1	NA		NA	10	2	1/1	None
Rogers et al, 2012	2	Extravesical	NA	NA	12	3	2/2	None
Kurz et al, 2012	3	Extravesical		NA	14	5	3/3	None
Abdel-Karim et al, 2011	5	Extravesical	198	90	21	2	5/5	None
Hemal et al, 2008	7	Transvesical	141	90	14	3	7/7	None
Schimpf et al, 2007	1	Extravesical	270	NA	NA	2	1/1	None
Sundaram et al, 2006	5	Transvesical	233	70	10 days	5	5/5	None

NA, not available.
Courtesy Dr. Ashok K. Hemal, Wake Forest University.

The key points of surgery include vaginoscopy and cystoscopy to assess the fistula and placement of ureteral catheters through the fistula and normal ureters. One of the important steps to be considered is the transvaginal catheterization of the VVF. This is achieved by placement of a ureteral catheter from the bladder, cystoscopically, cannulating the fistula and retrieving it from the vagina. Occasionally a reverse “railroading” is needed owing to the angulation of the fistulous tract, wherein the guidewire is placed transvaginally and retrieved from the bladder transurethrally. If the fistula is large, a Foley catheter can be directly placed transvaginally into the bladder. Tugging the catheter aids in locating the approximate site of the fistula as seen from within the abdominal cavity, allowing the placement of a minimal cystotomy near the area of interest, close to the midline. However, a Foley catheter placed transvaginally through the fistula into the bladder allows better appreciation of the movement and location in the transperitoneal endoscopic view.

Steps to avoid complications. Ureteral catheterization is an important step to prevent inadvertent ureteral injury during dissection as well as during reconstruction. It allows visualization of the ureteric orifices within the bladder, preventing the surgeon from taking a stitch too close to them during bladder reconstruction. It also keeps the operating field relatively dry, and ureteral catheters can be removed at the end of the procedure.

Adequate adhesiolysis is mandatory before a vesicotomy is performed. The primary causative procedure will invariably lead to intraperitoneal adhesion. Such adhesions could be parietal in nature, wherein adhesiolysis may be necessary to allow appropriate port placement, or could be visceral wherein bowel loops may obscure the area of interest in the pelvis. Gentle and sharp dissection to aid the bowel to fall away is imperative to prevent a bowel injury during fistula dissection and to allow tension-free closure of the vagina and bladder.

The modified technique prevents bivalving of the bladder and extensive dissection. Posterior cystotomy or limited dissection to quickly access the fistulous site and subsequent meticulous dissection and freshening of edges or, if needed, excision of fibrous edge are necessary. “Stay midline” is probably the safest dictum to prevent ureteral injury during dissection.

It is important to mobilize well-vascularized flaps to allow tension-free closure. An interposing tissue is useful for the success of repair.

If available, omentum is preferred, especially when repairing recurrent fistula, because it helps in rapid absorption of the inflammatory exudates owing to abundant lymph supply, and it significantly decreases the chance of failure.

The optimal approach for VVF repair depends on surgeon expertise. Transvaginal repair remains a minimally invasive approach with little morbidity and convalescence in the hands of a skilled and experienced surgeon. For patients requiring an open abdominal approach or flap interposition, laparoscopic or robotic-assisted approaches offer decreased morbidity and convalescence compared with traditional open techniques. The surgeon's experience and skill set guide the selection of surgical approach, taking into account the cause, localization, size, time of presentation, and complexity of the fistula. If available, use of robotic assistance in laparoscopy is the preferred approach for minimally invasive surgeons.

The flap is harvested after the first two layers of closure of the VVF but before advancing the final vaginal wall flap over the repair (see earlier discussion). To harvest the flap, a vertical incision is made over the labia majora. The borders of dissection include the labio-crural fold laterally, the labia minora and the bulbocavernosus muscle medially, and Colles fascia covering the urogenital diaphragm posteriorly. Flap harvest is accomplished in a lateral to medial fashion. Dissecting down to the adductor muscles laterally before coming around the width of the Martius flap facilitates the harvest of a thick, fatty segment for flap placement. Before final division of the flap inferiorly or superiorly, mobilization may be facilitated by gentle downward traction using a Penrose drain, incorporating the entire thickness of the fibrofatty flap. For a posterior-based flap, the main vascular supply to the flap is located at the base of the labia majora. The anterior segment is clamped and transected anterior to the pubic symphysis (see [Fig. 89-31](#)).

With the flap having been mobilized, a tunnel is created from the labial incision to the site of the fistula repair (see [Fig. 89-32](#)). A hemostat is used to transfer the fibrofatty flap from the harvest site, through the tunnel, to the level of the fistula repair. The flap is placed over the fistula repair and secured with interrupted absorbable sutures in a tension-free manner. The vaginal wall flap is advanced over the Martius flap and closed as previously described. A small Jackson-Pratt or Penrose drain may be left in the labial incision in the operative bed. The labial incision is closed, and a pressure dressing may be applied to the labial skin incision.

The blood supply of the greater omentum derives principally from the right and left gastroepiploic arteries, as well as the distal branches of the gastroduodenal and splenic arteries, respectively. The right and left gastroepiploic arteries join along the greater curvature of the stomach to form the gastroepiploic arch. The arterial anatomy within the greater omentum is variable but usually consists of a right and left omental artery, and occasionally a middle omental artery, all of which run perpendicular to their origin off the gastroepiploic arch. The caliber of the right gastroepiploic artery is usually larger than the left one, which generally favors a pedicle based on this artery; however, in practice, a pedicle based on either artery may be used (Kiricuta and Goldstein, 1972; Bissada and Bissada, 1992). In addition, anatomically, the origin of the right gastroepiploic artery is somewhat caudal compared with the left one, allowing a slight advantage in reaching into the deep pelvis. In some cases, the free distal end of the greater omentum is long enough to reach into the deep pelvis in a tension-free manner without any further mobilization. In either situation, the omental flap is secured with absorbable suture to healthy tissue at a location distal to and beyond the closed VVF tract, between the vagina and bladder. Securing the omental flap beyond and between the suture lines of the closed viscera prevents overlying or apposed suture lines.

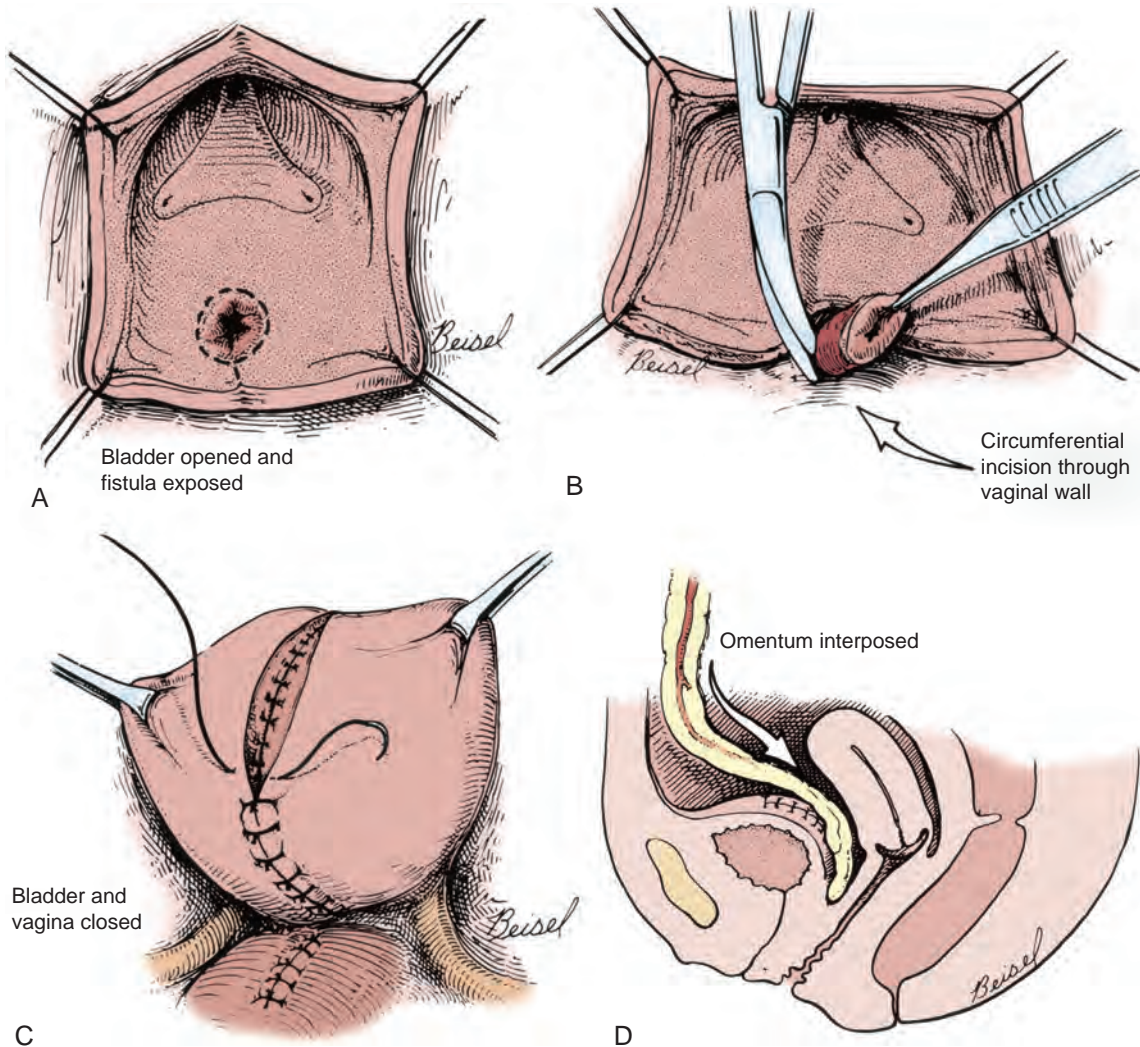


Figure 89-15. Diagrams of suprapubic repair of vesicovaginal fistula (VVF). A, The bladder opened and bivalved down to the level of the VVF. B, The VVF tract is excised. C, After closure of the vagina, the bladder is closed in multiple layers. D, Omentum is interposed between the bladder and vaginal closures. (From Ganabathi K, Sirls L, Zimmer P, et al. Vesicovaginal fistulae: reconstructive techniques. In: McAninch J, editor. *Traumatic and reconstructive urology*. Philadelphia: Saunders; 1996. p. 315.)

repair. In addition to its use in routine posthysterectomy VVF, the omentum is reported to be a useful adjunct in complicated or complex cases, such as those associated with large VVFs (Kiricuta and Goldstein, 1972; Bissada and McDonald, 1983), obstetric VVFs (Baines et al, 1976; Sharma et al, 1980), and VVFs associated with radiation therapy (Bissada and Bissada, 1992; Evans et al, 2001).

Other Flap and Graft Techniques. A variety of flaps including gracilis muscle flaps (Izes et al, 1992), labial myocutaneous flaps (Symmonds and Hill, 1978), seromuscular intestinal flaps (Mraz and Sutory, 1994), and rectus abdominis flaps (Menchaca et al, 1990; Viennas et al, 1995; Reynolds et al, 2008) have been used as adjunctive measures in the repair of complex VVF. Obstetric fistulae associated with significant urethral loss may be repaired, in part, with the use of anterior or posterior bladder flaps (Hanash and Sieck, 1983; Elkins et al, 1992; Khanna, 1992). The gracilis muscle in the medial thigh is a convenient adjunct to repair large soft-tissue defects, especially those associated with radiation therapy (Obrink and Bunne, 1978; Heckler, 1980). The gracilis muscle is in close proximity to the vagina and has a reliable blood supply. The muscle is mobilized through a thigh incision from its distal attachment on the tibial condyle, with care taken to preserve its blood supply. It is

tunneled cephalad into the vagina subcutaneously and secured over the fistula. Bilateral gracilis muscle flaps can be used for total vaginal reconstruction.

Bladder mucosa as a free graft has been used for repair of VVF (Brandt et al, 1998; Ostad et al, 1998; Sharifi-Aghdas et al, 2002). The bladder is approached extraperitoneally and a small cystotomy is performed. The fistula tract is identified and denuded of mucosa circumferentially for approximately 1 cm. A free graft of bladder mucosa is harvested from the edge of the cystotomy and placed over the denuded VVF tract and secured in place with absorbable suture. Brandt and colleagues (1998) reported a 96.3% success rate in 80 patients. Ostad and colleagues (1998) reported on 6 patients with complex, high, irradiated, large or recurrent VVF, all of whom were cured by this technique.

Outcomes of Vesicovaginal Fistula Repair. The success rate reported for a simple VVF repair in the modern era, whether through an abdominal or vaginal approach, is in excess of 90% (Table 89-5 on the Expert Consult website). Long-term follow-up suggests that the majority of patients are greatly improved, although minimally bothersome symptoms may persist in a minority of patients over the long term, causing little impact on quality of life (Dolan et al,

TABLE 89-5 Outcomes for Vesicovaginal Fistula Repair

AUTHOR (DATE)	NO. OF PATIENTS	SUCCESS (%)	APPROACH	COMMENTS
Eisen et al (1974)	29	90	Abdominal	Peritoneal flap
Kaser (1977)	38	92	Vaginal	Latzko
Persky et al (1979)	7	86	6 abdominal 1 vaginal	
Tancer (1980)	45	93	43 vaginal 1 abdominal 1 spontaneous closure	Latzko vaginal approach
O'Connor (1980)	42	88	Abdominal	
Wein et al (1980a)	34	88	Abdominal	
Keettel et al (1978)	168	94	156 vaginal 6 abdominal 6 combined	
Lee et al (1988)	182	98	145 vaginal 37 abdominal	100% success with abdominal approach
Gil-Vernet et al (1989)	42	100	Abdominal	Transvesical
Wang and Hadley (1990)	16	94	Vaginal	
Blandy et al (1991)	25	100	Abdominal	
Motiwalla et al (1991)	68	94	Abdominal	58 transvesical 10 transabdominal with omental flap
Raz et al (1993)	11	82	Vaginal	Peritoneal flap
Arrowsmith (1994)	98	96 (81% success after first attempt)	Multiple	All obstetric fistulae
Elkins (1994)	82	95 (88% success after first attempt at VVF)		All obstetric fistulae
Kristensen and Lose (1994)	18	94	Abdominal	5 ureteral reimplants required
Blaivas et al (1995)	24	96	15 vaginal 8 abdominal 1 spontaneous closure	
Ayhan et al (1995)	70	93	66 vaginal 4 abdominal	
Brandt et al (1998)	80	96	Abdominal	Bladder mucosa autograft
Iselin et al (1998)	20	100	Vaginal	Vaginal cuff excision
Evans et al (2001)	37	76	Abdominal	Includes 8 malignant fistulae
Eilber et al (2003)	207	97	Vaginal	

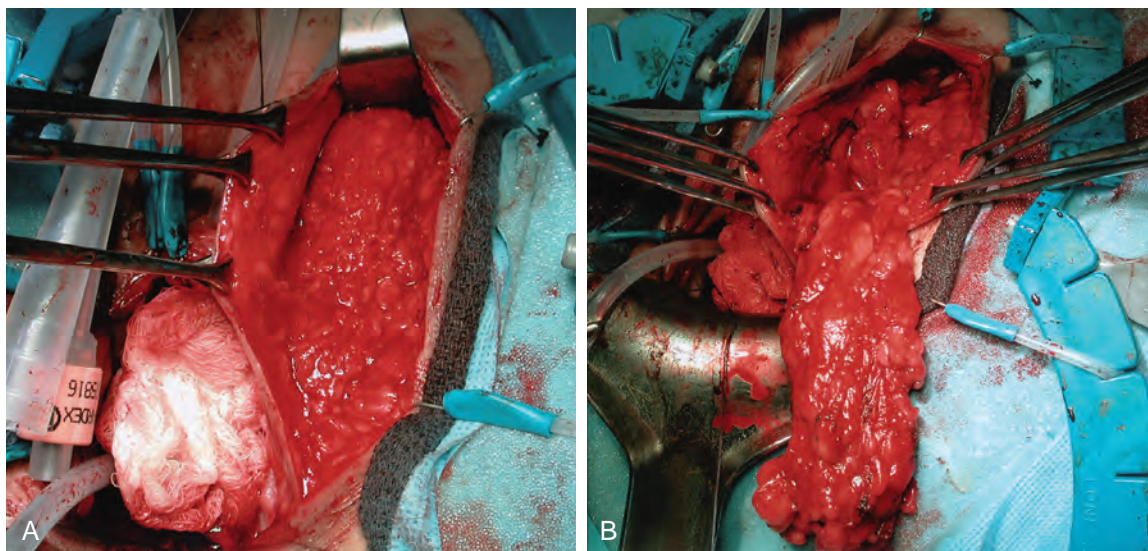


Figure 89-31. Harvesting of a Martius flap. A, The incision is made in the labia. B, A large flap may be obtained.

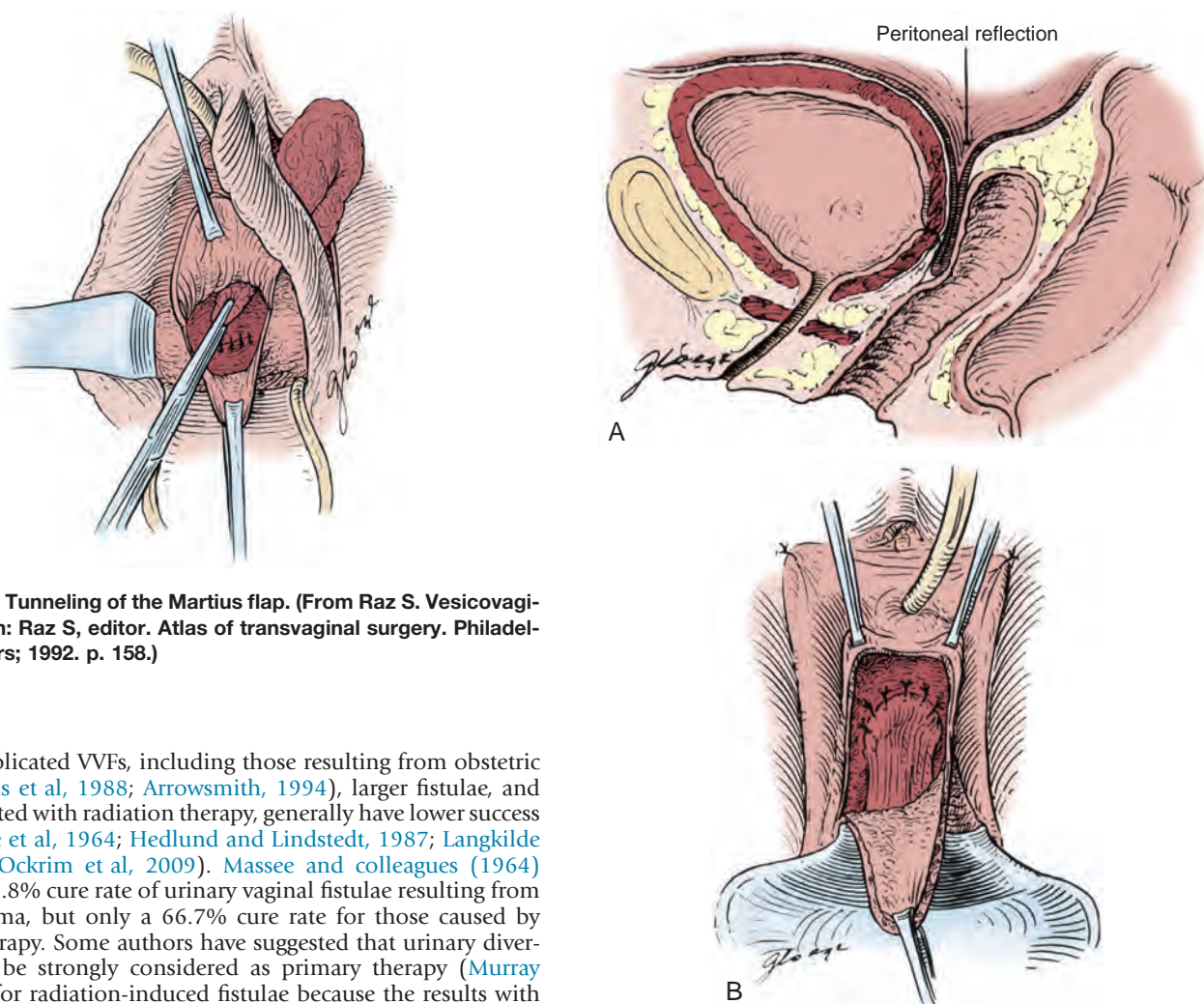


Figure 89-32. Tunneling of the Martius flap. (From Raz S. Vesicovaginal fistulae. In: Raz S, editor. Atlas of transvaginal surgery. Philadelphia: Saunders; 1992. p. 158.)

2008). Complicated VVFs, including those resulting from obstetric causes (Elkins et al, 1988; Arrowsmith, 1994), larger fistulae, and those associated with radiation therapy, generally have lower success rates (Massee et al, 1964; Hedlund and Lindstedt, 1987; Langkilde et al, 1999; Ockrim et al, 2009). Massee and colleagues (1964) reported a 93.8% cure rate of urinary vaginal fistulae resulting from surgical trauma, but only a 66.7% cure rate for those caused by radiation therapy. Some authors have suggested that urinary diversion should be strongly considered as primary therapy (Murray et al, 2002) for radiation-induced fistulae because the results with surgical repair in this group are less than optimal (Langkilde et al, 1999). In patients with obstetric fistulae associated with loss of the bladder neck and proximal urethra, relatively high rates of persistent severe sphincteric incontinence are noted despite successful repair of the VVF (Murray et al, 2002; Browning, 2004), and this type of fistula is involved in the majority of treatment failures (Kelly, 1992). Thus despite a technically successful VVF

Figure 89-33. Peritoneal flap. A, Diagrammatic representation of the location of the peritoneal flap during vesicovaginal fistula repair. B, Diagram of peritoneal flap advanced over fistula repair. (A and B, From Raz S. Fistulae: transvaginal repair of vesicovaginal and urethrovaginal fistulae. In: Raz S, editor. Atlas of transvaginal surgery. 2nd ed. Philadelphia: Saunders; 2002. p. 242.)

repair, functionally, from the patient's perspective, some of these individuals may not be significantly improved after the repair owing to severe stress urinary incontinence (SUI). Pubovaginal slings and periurethral injectable agents are often beneficial in these patients, once the VVF has been surgically closed (Arrowsmith, 1994). In the developing world, access to synthetic mid-urethral slings is limited. Furthermore, the safety of using such materials in the setting of extensive reconstruction, such as that after repair of an obstetric fistula, is not established.

Vesicovaginal Fistula and Urinary Diversion. In some patients, repair of VVF is not possible or multiple surgical attempts have failed. This is probably most commonly associated with existing pelvic malignancy, severe radiation damage, and/or large soft-tissue loss, especially in the setting of obstetric fistula. However, some patients may simply not be candidates for repair owing to coexistent medical morbidities, making them a prohibitive surgical risk. In the former group, urinary diversion in the form of either a urinary conduit (Kisner and Kesner, 1987) or a continent reservoir can be considered. Fistulae in patients who are not candidates for surgical intervention may be managed by percutaneous ureteral occlusion and permanent nephrostomy (Kinn et al, 1986; Stern et al, 1987; Hubner et al, 1992; Farrell et al, 1997; Amsellem-Ouazana et al, 2006; Natarajan et al, 2007; Shindel et al, 2007).

In the developing world, where catheters and ostomy appliances are either too expensive or completely unavailable, continent urinary diversion or incontinent urostomies are often not practical, which presents ethical issues with the alternative treatments (Wall et al, 2008). In these situations, internal urinary diversion with ureterosigmoidostomy has some application in patients with unreconstructable lower urinary tracts (Attah and Ozumba, 1993). It should be recognized that this is clearly a last-resort operation owing to its significant metabolic and neoplastic potential.

KEY POINTS: VESICOVAGINAL FISTULAE

- VVF is the most common acquired fistula of the urinary tract.
- In the industrialized world, surgical injury to the bladder is the most common cause of VVF, most commonly seen after hysterectomy. In the developing world, VVF is most commonly related to complications from obstructed labor.
- VVFs caused by radiation therapy are usually complex.
- VVF occurring in the setting of a history of pelvic malignancy should undergo biopsy before repair to exclude recurrent malignancy as a cause of the fistula.
- Diagnosis of VVF can be confirmed on VCUG. Voiding images should be obtained if the fistula was not demonstrated on the filling images of the cystogram.
- Upper tract imaging is obtained after a diagnosis of VVF to exclude injury to the ureter(s).
- Small, oblique fistulae may respond to conservative therapy, including prolonged urinary catheterization with or without fulguration of the fistula tract.
- There is no optimal method for the surgical repair of all VVFs. In the properly selected patient, transabdominal and transvaginal approaches to fistula repair have similar success rates. Laparoscopic and robotic approaches for VVF repair are advancing the field. Adjuvant tissue flaps may be useful to prevent surgical failure in the setting of complex or recurrent fistula, radiation fistula, obstetric fistula, and fistulae with tenuous repairs.

Ureterovaginal Fistula

Ureteral fistulae to the genital tract in the female most often connect with the vagina but have also been reported to connect with other

BOX 89-6 Etiology of Ureterovaginal Fistula

GYNECOLOGIC SURGERY

Abdominal hysterectomy
Vaginal hysterectomy
Radical hysterectomy
Cesarean section
Anterior colporrhaphy (cystocele repair)

OTHER PELVIC SURGICAL PROCEDURES

Vascular surgery
Urologic surgery including retropubic bladder neck suspensions
Colon surgery

OTHER CAUSES

Locally advanced malignancy
Radiation therapy
Pelvic trauma
Chronic inflammatory diseases (e.g., actinomycosis)

genital structures, including the fallopian tube (Crochet et al, 2008) or uterus (Billmeyer et al, 2001). Risk factors for the development of ureterovaginal fistulae include endometriosis, obesity, pelvic inflammatory disease (Symmonds, 1976), and radiation therapy and pelvic malignancy. Nevertheless, Symmonds has noted that the patient with a ureteral injury after gynecologic surgery is typically one who had an uncomplicated, technically easy hysterectomy for minimal disease (Symmonds, 1976). Thus, except for those oncologic cases wherein a segment of ureter is deliberately excised, many ureteral injuries are likely the result of technical or iatrogenic factors.

Etiology and Presentation

The most common cause of ureterovaginal fistulae is surgical injury to the distal ureter, with gynecologic procedures being by far the most common (Symmonds, 1976; Dowling et al, 1986; Badenoch et al, 1987; Lee et al, 1988; Blandy et al, 1991) (Box 89-6). The incidence of iatrogenic ureteral injury during major gynecologic surgery is estimated to be about 0.5% to 2.5% (Symmonds, 1976; Payne, 1996; Gilmour et al, 1999). A large prospective case series from Finland found an incidence of ureteral injury associated with hysterectomy for benign pathology of 0.2% (10 of 5279), with the lowest rate associated with vaginal hysterectomy and no difference between open and laparoscopic abdominal hysterectomy (Brunner et al, 2011). The incidences of immediate and delayed ureteral injury during radical hysterectomy were found to be 1.3% (7 of 536) and 2.4% (13 of 536), respectively, in a series from Serbia; injuries appeared more common after prolonged surgery and in patients with diabetes, obesity, or wound infection (Likic et al, 2008). A registry study from the United States found an overall incidence of ureteral injury during radical hysterectomy of 0.8% (Frankman, 2010). Case series from referral centers in India, Pakistan, and Egypt showed that the proportion of urinary tract injuries resulting from obstetric or gynecologic surgical trauma that primarily affected the ureter varied from 1% to 23% (Kumar et al, 2009; Sachdev et al, 2009; Nawaz et al, 2010; El-Tabey et al, 2011).

The mechanism of injury resulting in iatrogenic postoperative ureterovaginal fistulae includes ureteral laceration or transection, blunt avulsion, crush injury, partial or complete suture ligation, and, finally, ischemia caused by operative devitalization of the ureteral vascular supply and/or cautery injury. Overall, the ureter is most commonly injured during gynecologic surgery in the distal one third or pelvic portion, which is, accordingly, the only location at which a ureteral injury may result in a

ureterovaginal fistula. Not uncommonly this occurs inadvertently during an attempt by the surgeon to control active bleeding using clamps or suture ligation of large tissue segments in the deep pelvis.

The pelvic ureter is intimately related to the female genital tract throughout its course. **In the deep pelvis, the ureter passes at the lateral edge of the uterosacral ligament and ventral to the uterine artery, and then passes just lateral to the cervix and fornix of the vagina.** In close apposition to these structures, the ureter must be carefully avoided during any gynecologic procedure in the deep pelvis. **Any injury to the ureter that exposes the ureteral lumen (i.e., laceration) or results in delayed necrosis of a portion of the ureter (i.e., suture ligation) and subsequent urinary extravasation may lead to a fistula.** A ureterovaginal fistula may result from a sequence of events, including urinary extravasation from the ureteral injury, urinoma formation, subsequent extension along non-anatomic planes created during surgery, and eventual drainage through the vaginal incision or an ischemic area of the vaginal cuff. Infection, prior radiation therapy, or other factors that may impede healing probably promote the development of ureterovaginal fistulae under these circumstances.

The most common presenting symptom is the onset of constant urinary incontinence 1 to 4 weeks after surgery (Mandal et al, 1990). This may have been preceded by several days of flank or abdominal pain, nausea, and low-grade fever, presumably as a result of urinoma and/or obstruction of the kidney (Lee et al, 1988). Flank pain will often be masked in the postoperative period because of the use of postoperative narcotic analgesics. **Of importance, and in direct contrast to VVF, in the setting of continuous urine leakage from a ureterovaginal fistula, patients will continue to report normal voiding habits because bladder filling is maintained from the contralateral, presumably undamaged, upper urinary tract.**

Prevention

Ureterovaginal fistula occurring in the early postoperative phase predominantly after hysterectomy is the most frequent presentation to urologists of upper urinary tract fistula. A randomized study involving 3141 women undergoing open or laparoscopic gynecologic surgery lasting for longer than 30 minutes found that the

incidence of ureteral injury after prophylactic insertion of ureteral stents (1.2% [19 of 1583]) was similar to controls (1.1% [17 of 1558]) (Chou et al, 2009). A previous cost analysis from the U.S. perspective suggested that stenting was worthwhile only if the risk of injury was higher than 3.2% (Schimpf et al, 2008). If injury does occur, many cases, even those involving bilateral injury, can be managed by endoscopic techniques (Shaw et al, 2008).

Diagnosis and Management

Unfortunately, intraoperative diagnosis of a genitourinary (GU) or GI injury is made in only about half of the cases that result in fistula (Ostrzenski and Ostrzenska, 1998). In one study, 36% of VVFs were found within 1 week of a laparoscopic hysterectomy and 50% in the second week. Most patients who had undergone transabdominal hysterectomies had leakage in the second week (90%) (Kochakarn and Pummangura, 2007).

Diagnosis and confirmation of a ureterovaginal fistula can usually be accomplished with a combination of a relevant history, physical examination, and appropriate radiologic studies, including cross-sectional imaging (such as a CT urogram), IVU, and retrograde pyelography (Mandal et al, 1990) (Fig. 89-34). Urine may extravasate externally or internally. Creatinine levels in the urine are higher than serum levels. Therefore, in the setting of a suspected fistula, testing the creatinine level in either the extravasated fluid or the accumulated ascites and comparing this value to the the serum creatinine levels will confirm urinary leakage but not the location of the fistula. Likewise, testing potassium levels will show higher levels compared with serum levels (Kruger and Whiteside, 2003).

A double dye test may be of some value in differentiating between a ureterovaginal fistula and VVF as a cause of ongoing urinary leakage (Raghavaiah, 1974). Suspicion of a ureterovaginal fistula should prompt upper tract imaging (Badenoch et al, 1987). The IVU or CT urogram most commonly will demonstrate some degree of ureteral obstruction and associated caliectasis or ureteral dilation (Selzman et al, 1995). These findings in the presence of constant vaginal drainage strongly suggest a ureterovaginal fistula. Alternatively, if the fistula is mature and large, the upper urinary tract may appear completely unremarkable; however, urine will be seen opacifying the vagina before the postvoid image

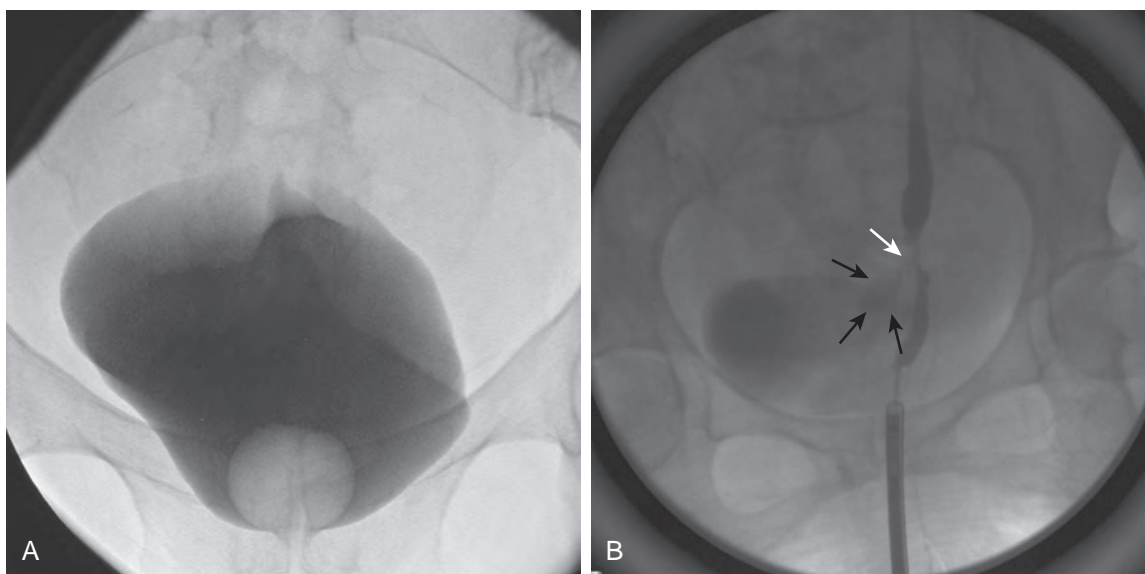


Figure 89-34. Diagnosis of ureterovaginal fistula. A, Normal cystogram in a woman with constant urinary drainage after undergoing an abdominal hysterectomy. B, Retrograde pyelogram demonstrates a distal ureteral stricture with a small fistula tract (white arrow) with contrast in the vagina (black arrows) superimposed on contrast in the bladder from the contralateral retrograde ureterogram.

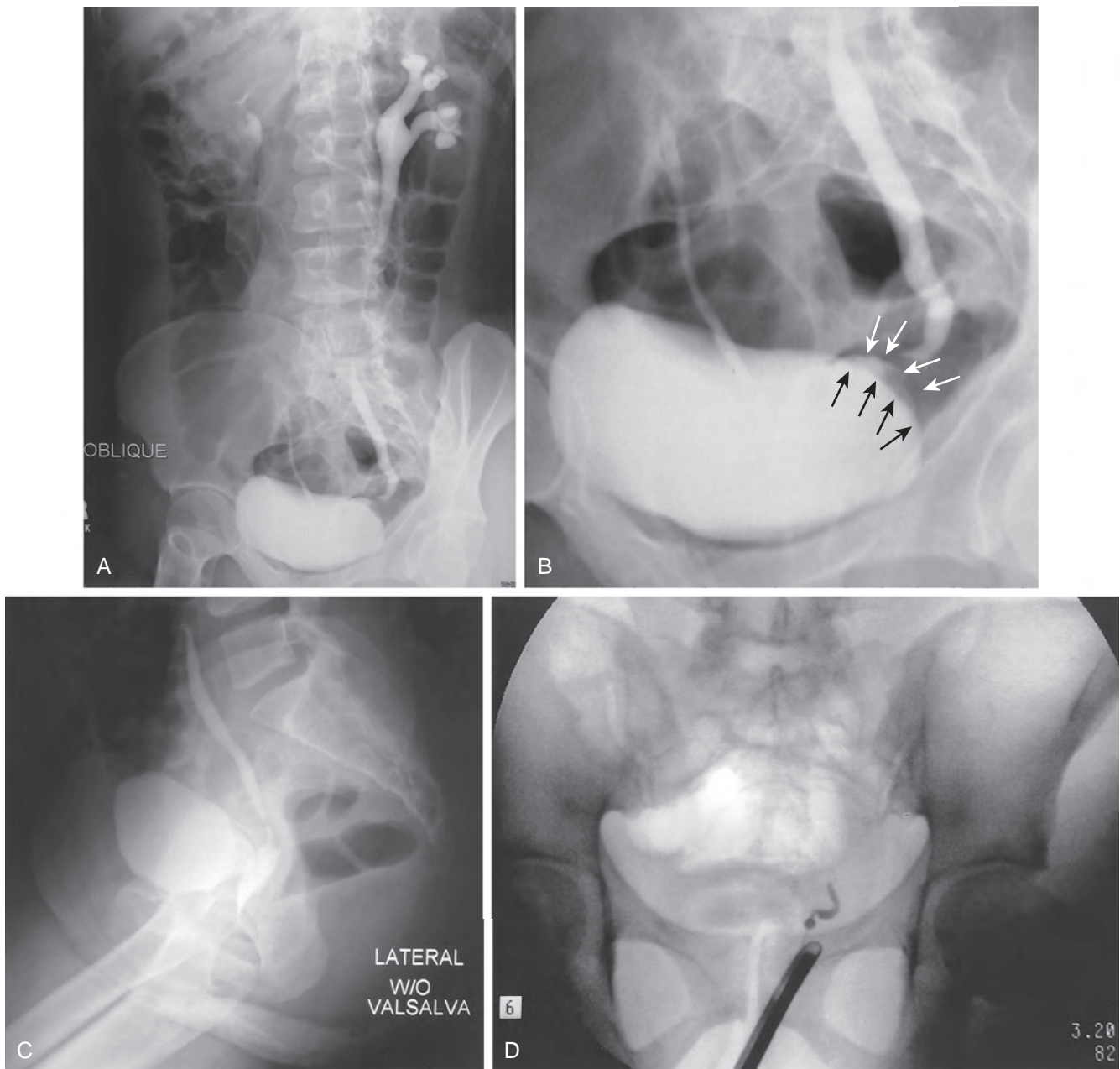


Figure 89-35. Ureterovaginal fistula. A, Oblique view on intravenous urography shows mild left-sided hydroureteronephrosis associated with a distal tapering of the ureter. B, Faint and subtle opacification of the vagina (white arrows) is somewhat obscured by bladder filling (bladder edge indicated by black arrows) on this oblique image. C, Lateral view demonstrates the ureter clearly entering the vagina. D, Retrograde pyelogram demonstrates abrupt termination of the distal ureter.

(Fig. 89-35). Antegrade pyelography after nephrostomy tube decompression of a partially obstructed ureter may be associated with similar findings (Fig. 89-36). A high oblique or lateral film may be necessary to differentiate the contrast in the bladder from that in the vagina. A retrograde pyelogram may show the ureter and fistula well or may demonstrate an abrupt termination of the ureter 2 to 4 cm from the ureteric orifice. If retrograde pyelography demonstrates the fistula, as well as ureteral continuity, then an attempt at stenting is warranted. Cystography is performed primarily to exclude a coexistent VVF. A cystogram will not demonstrate the ureterovaginal fistula unless there is preexisting vesicoureteral reflux. Ureterovaginal fistulae may be seen on CT urography or MRI (Fig. 89-37); however, an additional role for such

cross-sectional imaging is to evaluate for an associated pelvic abscess or undrained urinoma. An unstructured review by Narayanan and colleagues suggested that MRI, particularly with T2 weighting, provided optimal diagnostic information regarding fistula associated with pelvic malignancy, with contrast-enhanced CT with late excretory phase an acceptable alternative (Narayanan et al, 2009). These newer modalities were considered to be superior to other x-ray contrast techniques and ultrasonography. MRI is also used more widely (Abou-El-Ghar et al, 2012).

The goal of therapy is the expeditious resolution of urinary leakage, avoidance of urosepsis, and preservation of renal function. Once the diagnosis is made, prompt drainage of the affected upper urinary tract is essential (Gerber and Schoenberg, 1993),

because partial ureteral obstruction is often present. An attempt at ureteral stenting or percutaneous nephrostomy tube decompression is warranted as soon as possible (Dowling et al, 1986; Kostakopoulos et al, 1998) if direct open surgical repair is not immediately considered. Occasionally, conservative, nonoperative management alone will result in fistula closure in patients with ureteral continuity and a normal-appearing ureter beyond the fistula (Alonso et al, 1986), although this is unusual. Endoscopic management, including ureteral stenting, may be sufficient to promote closure of the fistula in some cases. Dowling and colleagues (1986) reported that 11 of 23 patients with ureteral injuries recognized postoperatively

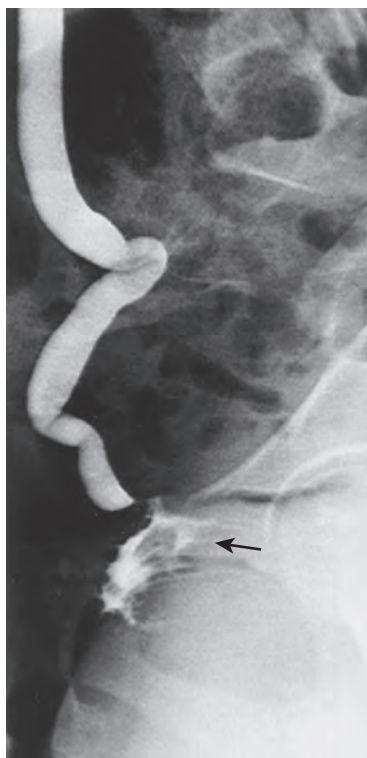


Figure 89-36. Ureterovaginal fistula. Antegrade nephrostogram demonstrates mild ureterectasis with opacification of the vagina (arrow).

were successfully managed with nephrostomy tube drainage and/or ureteral stenting. Selzman and coworkers (1995) reported successful management of 7 of 20 ureterovaginal fistulae with internal ureteral stenting alone. None of the 7 patients in whom a ureteral stent was successfully placed required open surgery. In general, if ureteral continuity can be demonstrated on imaging, retrograde placement of a stent is often possible. In some cases, an antegrade stent placement will be successful where a retrograde attempt had failed. The use of ureteral stenting in patients with ureterovaginal fistulae was reported in 11 studies, including 126 patients in total (Andriole et al, 1984; Lang, 1984; Dowling et al, 1986; Mandal et al, 1990; Barton et al, 1992; Koonings et al, 1992; Campbell et al, 1993; Lingeman et al, 1995; Beaghtler et al, 1997; Narang et al, 2007; Ustunsoz et al, 2008); this resulted in closure in 63 cases altogether. Success rates were 6% to 100%, although the overall closure rate across all series is calculated at $50\% \pm 18\%$.

If ureteral stenting is unsuccessful owing to complete ureteral occlusion or if prolonged leakage persists despite stenting, then formal surgical repair is indicated (Fig. 89-38). Timing of the repair of ureterovaginal fistulae is controversial. Some authors advocate early repair (Talbert et al, 1965; Flynn et al, 1979; Badenoch et al, 1987; Blandy et al, 1991; Selzman et al, 1995), whereas others recommend a delay of 4 to 8 weeks (Hulse et al, 1968; Lee and Symmonds, 1971). More recent literature suggests that early repair is preferred and is not associated with an increase in morbidity or higher failure rates (Payne, 1996).

As noted previously, ureterovaginal fistulae most commonly result from injury to the distal one third of the ureter below the level of the iliac vessels. The usual site of the injury is in the very distal ureter and the surrounding fibrosis and inflammation usually preclude primary repair of the fistula. Therefore open surgical repair most commonly involves ureteroneocystostomy. The ureter is located and dissected as distally as possible in the pelvis. Care is taken to preserve the periureteral adventitial layer to prevent ureteral ischemia. The ureter is divided distally, and a ureteroneocystostomy is performed with or without a psoas hitch. It is not important to create a tunneled anastomosis. Occasionally a Boari flap or replacement with bowel segments (with or without reconfiguration) may be necessary because of extensive ureteral injury. Robotic and laparoscopic repairs using the same principles as open repair have been reported (Modi et al, 2005; Laungani et al, 2008; Modi et al, 2008; Patil et al, 2008), with the potential benefits of shorter hospitalization and quicker convalescence. Recent case series suggest that this standard surgery can be performed safely and with reasonable operative times using laparoscopic or robotic techniques if

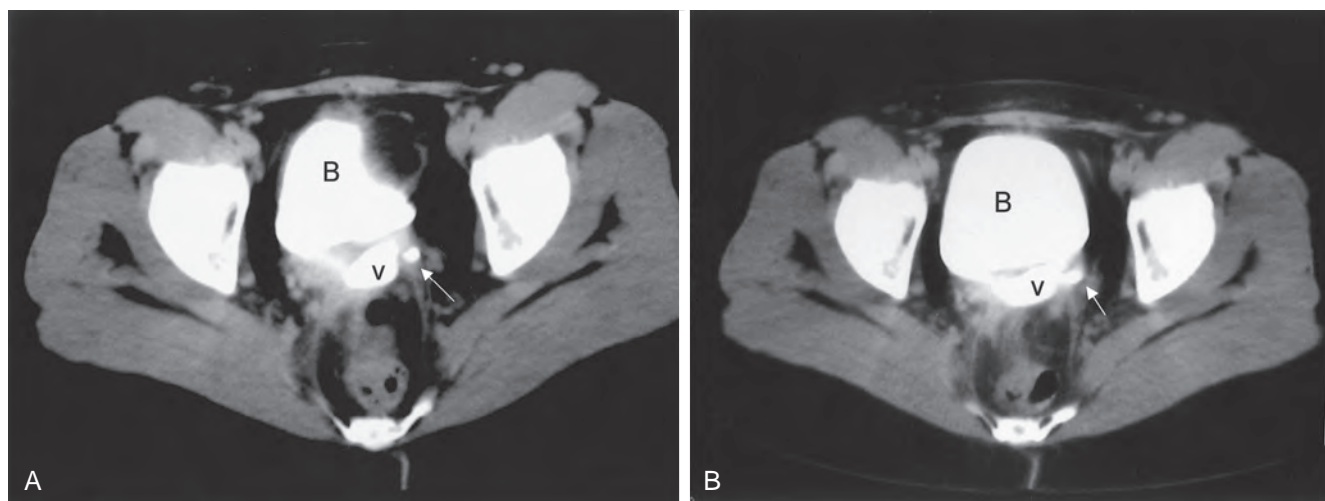


Figure 89-37. Computed tomography (CT) scan of ureterovaginal fistula. A, CT scan demonstrates contrast material within the bladder (B) and vagina (v). The ureter is visible (arrow) adjacent to the vagina. B, This image shows the ureter (arrow) entering the vagina.

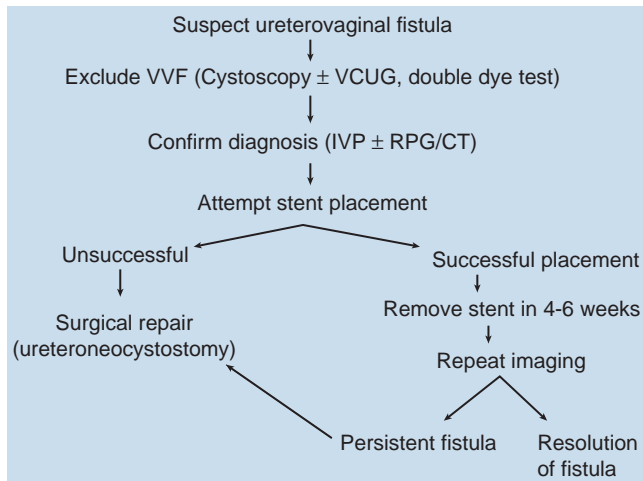


Figure 89-38. Algorithm for diagnosis and management of ureterovaginal fistula. CT, computed tomography; IVP, intravenous pyelography; RPG, retrograde pyelography; VCUG, voiding cystourethrography; VVF, vesicovaginal fistula.

surgeons with the relevant skills and appropriate facilities are available (Puntambekar et al, 2006; Laungani et al, 2008; Modi et al, 2008). A case report has suggested that open repair through the vagina is possible if abdominal access is problematic (Chen et al, 2007). Rarely, transureteroureterostomy, ileal substitution of the ureter, or renal autotransplantation is required. In patients with a normal contralateral kidney in whom there is extensive renal damage because of obstruction or infection, nephrectomy may be the most expeditious method of management.

Successful repair of ureterovaginal fistulae is expected in more than 90% of cases. Blandy and colleagues reported on early repair of iatrogenic injury to the ureter in 43 cases including 30 ureterovaginal fistulae. All patients were cured using a combination of techniques including the Boari flap (Blandy et al, 1991). Others have reported similar results (Lee and Symmonds, 1971; Flynn et al, 1979; Mandal et al, 1990).

Ureteral fistulae to other gynecologic organs have been reported. Ureterouterine fistulae may occur as a result of cesarean section, uterine malignancy, and elective abortion (Keegan and Forkowitz, 1982; Lazarevski and Badiev, 1996; Wang and Hung, 1997; Sheen et al, 1998). Uretero-fallopian tube fistulae have also been reported as a consequence of laparoscopic fulguration of endometriosis (Steckel et al, 1993).

KEY POINTS: URETEROVAGINAL FISTULAE

- Ureterovaginal fistulae occur more commonly after benign hysterectomy than after radical hysterectomy.
- Patients have constant urinary leakage but usually a normal voiding pattern.
- In the setting of ureteral patency, a trial of an indwelling ureteral stent may result in resolution of the fistula.
- If conservative management fails or if there is complete obstruction of the distal ureter, then ureteral reimplantation with or without a psoas hitch is usually curative.

Vesicouterine Fistula

Etiology and Presentation

Vesicouterine fistulae are among the least common urogynecologic fistulae. Less than 100 cases were reported in the world literature from 1908 to 1986, with no series having more than 4 patients

(Tancer, 1986). However, the incidence of this condition is increasing in parallel with the rising numbers of low-segment cesarean sections being done worldwide (Porcaro et al, 2002). Cesarean section is by far the most common cause of this unusual fistula (Tancer, 1986; Miklos et al, 1995; Vu et al, 1995). Tancer related that of the 74 cases of vesicouterine fistulae reported from 1947 to 1986, 57 followed low-segment cesarean section, 7 followed vaginal operative delivery, and the remaining cases were related to a variety of disparate scenarios, including induced abortion, hysterectomy, and dilation and curettage (D&C) (Tancer, 1986). Jozwik and colleagues (1997) reported that 21 of 24 vesicouterine fistulae treated over a 12-year period occurred after cesarean section, the majority of which were repeat cesarean sections. Those undergoing vaginal birth after prior cesarean section (VBAC) are also at risk for vesicouterine fistula (Gil and Sultana, 2001). Vesicouterine fistulae may occur spontaneously as a result of a ruptured uterus during obstructed labor. In these cases, the posterior bladder wall may tear along the uterine rupture line creating the potential for a fistula. Bladder wall invasion by chorionic villi penetrating beyond the uterine serosa, placenta percreta, may also create a vesicouterine fistula (Krysiewicz et al, 1988). A foreign body such as an intrauterine device (IUD) (Schwartzwald et al, 1986), uterine artery embolization (Sultana et al, 2002), brachytherapy (Memon et al, 1998), and traumatic bladder catheterization (Futter and Baker, 1995) have all been reported to cause vesicouterine fistula. In most cases, simultaneous injury to the bladder and uterus is the inciting event. An unrecognized and unrepaired (occult) bladder injury, or incorporation of a portion of the bladder during closure of the uterus during any number of operations, may result in a vesicouterine fistula. Anatomically, the most common location of the fistula is along the posterior bladder wall in the midline, or from the genital side, just cephalad to the internal cervical os.

Unlike other types of urogynecologic fistulae, vesicouterine fistulae may or may not manifest with constant urinary incontinence because of the sphincter-like activity of the cervix; the exception is in the setting of an incompetent cervix wherein urinary leakage is constant. In this clinical setting, which typically occurs after vaginal delivery, urine flows from the bladder through the fistula into the uterine cavity and then into the vagina through an incompetent cervical os. Tancer (1986) described 12 such patients, with urinary incontinence as the presenting symptom, out of 15 patients with vesicouterine fistulae after vaginal operative delivery. However, in the setting of a relevant clinical history, vesicouterine fistulae will also manifest with menouria and cyclic hematuria in the setting of urinary continence. Youssef syndrome describes the presenting symptom complex of vesicouterine fistula: menouria, cyclic hematuria with associated apparent amenorrhea, infertility, and urinary continence (Youssef, 1957; Tancer, 1986) in a patient who has undergone prior low-segment cesarean section. Endometriosis of the bladder, in which cyclic hematuria may be present, must be differentiated from this condition.

Diagnosis and Management

Diagnosis of vesicouterine fistula can be made by a combination of cystoscopy and radiographic studies, although a high degree of suspicion is necessary to pursue the diagnosis if initial radiographic studies prove negative (Smayra et al, 2005). Cystoscopy may demonstrate a midline lesion along the posterior bladder wall (Fig. 89-39). Urine cytology may reveal endothelial cells. Instillation of contrast material into the bladder (cystogram) will outline the uterine cavity (Fig. 89-40), whereas a hysterosalpingogram will demonstrate filling of the bladder. MRI, CT (Fig. 89-41), and ultrasonography have been used in the diagnosis and evaluation of vesicouterine fistulae as well (Mercader et al, 1995; Huang et al, 1996; Murphy et al, 1999). IVU or contrast-enhanced CT can be used to exclude concomitant ureteral injury.

Several different approaches have been advocated for the treatment of vesicouterine fistulae. Spontaneous resolution may occur, and Graziotti and colleagues (1978) noted that only five such cases,

including theirs, had previously been reported in the literature. Therefore these authors recommend against a “precocious” surgical repair of these lesions because time may allow some fistulae to resolve without surgery. Prolonged indwelling bladder catheterization or fulguration of the fistula tract followed by bladder drainage may be successful in select cases, especially in patients with small, immature fistulae (Graziotti et al, 1978; Molina et al, 1989; Ravi et al, 2003; Novi et al, 2004). Hormonal induction of menopause will induce involution of the puerperal uterus, and this principle has been used with some success in treating this condition as well (Hemal et al, 1994; Jozwik and Jozwik, 1999; Ravi et al, 2003). Jozwik and Jozwik (1999) reported successful treatment in eight of nine patients with use of hormonal manipulation.

Surgical therapy for vesicouterine fistulae is often contingent on the specific reproductive wishes of the patient (Smayra et al, 2005), as well as other surgical factors, but is considered definitive

therapy (DiMarco et al, 2006; Rao et al, 2006). If there is no further desire for childbearing, then transabdominal hysterectomy and bladder closure should be considered. Ureteral stents can be placed to facilitate identification of the ureters intraoperatively. After performance of the hysterectomy, the fistula tract on the posterior bladder wall is excised and the bladder is closed primarily. An omental flap can be placed into the deep pelvis to buttress the bladder closure and separate the bladder closure from the vaginal closure to reduce the possibility of a postoperative VVF. For the patient who desires preservation of fertility, uterine-sparing surgery can be considered. In a manner similar to an O’Conor transabdominal VVF repair, the bladder is opened and bivalved down to the fistula tract. Careful dissection allows separation of the bladder from the uterus beyond the fistula tract. The fistula tract is excised from both structures, the uterus and bladder are closed individually, and an interpositional flap, usually omentum, is secured between the two organs. Fertility is possible after repair of vesicouterine fistula. Lotocki and colleagues (1996) reported five pregnancies with four full-term deliveries in a cohort of 16 patients who had undergone uterine-sparing surgery for vesicouterine fistulae. Minimally invasive laparoscopic and robotic surgical approaches to the repair of vesicouterine fistulae have been reported (Miklos, 1999; Tarhan et al, 2007; Ramalingam et al, 2008).

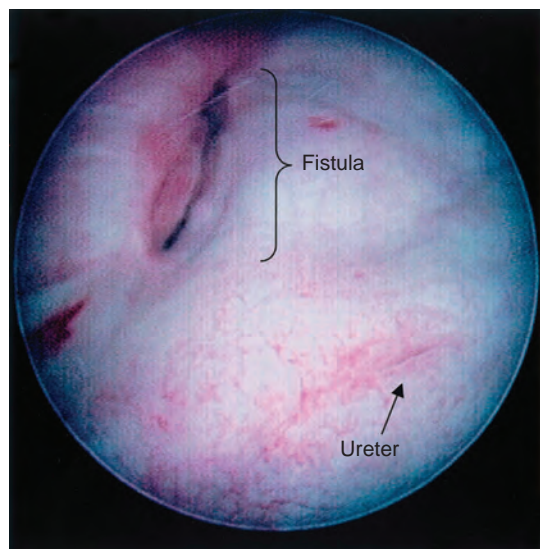


Figure 89-39. Cystoscopic view of vesicouterine fistula before repair.

KEY POINTS: VESICOUTERINE FISTULAE

- The most common cause of vesicouterine fistulae is low-segment caesarean section.
- Vesicouterine fistulae do not always manifest with urinary incontinence.
- Nonsurgical management of vesicouterine fistulae is possible by hormonally inducing involution of the uterus with maintenance of urinary drainage.
- Management of vesicouterine fistulae is contingent on the reproductive wishes of the patient. Hysterectomy followed by repair of the bladder is indicated for the individual who no longer desires fertility. Uterine-sparing procedures can be used, and successful pregnancy is possible after vesicouterine fistula repair.

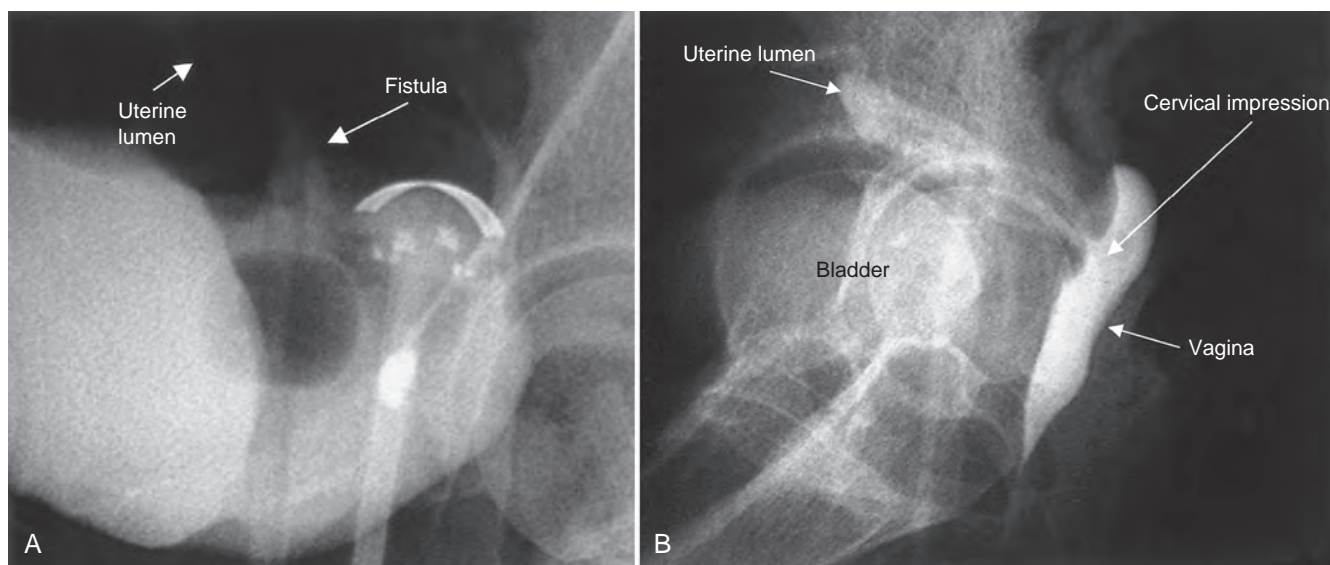


Figure 89-40. Cystogram demonstrating vesicouterine fistula in a postpartum woman. A, Filling of the bladder demonstrates a small amount of contrast material cephalad to the tip of the Foley catheter. The uterine cavity is faintly seen. B, Postvoid image demonstrates filling of the uterine cavity and cervical canal. The bladder is not well demonstrated. This patient's status is immediately postpartum. Contrast material in the vagina outlines the incompetent cervical canal and os.

Urethrovaginal Fistula

Etiology and Presentation

In the developing world, urethrovaginal fistula may occur as a result of obstructed labor with or without associated VVF. In industrialized countries, urethrovaginal fistulae in adults mostly have an iatrogenic cause.

In feminizing genital reconstructions in children with ambiguous genitalia and surgical repairs of cloacal malformations, urethrovaginal fistulae can occur as early or late complications (Dhabalia et al, 2009; Oguzkurt et al, 2009; Levitt and Pena, 2010; Levitt et al, 2011; Park et al, 2011). Also in transsexual adults undergoing female-to-male reconstruction, urethrovaginal fistulae have been reported (Hage et al, 1993).

In the surgical treatment of stress incontinence in women with bulking agents (Carlin and Klutke, 2000; Hilton, 2009) or synthetic slings, several cases of urethrovaginal fistula have been reported (Glavind and Larsen, 2001; Reisenauer et al, 2007; Morton and

Hilton, 2009; Estevez et al, 2010). Even conservative treatment of prolapse with pessaries can lead to the formation of fistula if these pessaries are neglected for an extended period of time, although fistula formation after only 2 weeks of pessary use has been described (Walker et al, 2011; Hilton and Cromwell, 2012).

Trauma—including inappropriate catheterization—and foreign bodies are obvious causes of fistula (Parkhurst et al, 1981; Holland et al, 2001; Blaivas and Purohit, 2008; Liu et al, 2008; Cameron and Atiemo, 2009; Kobayashi et al, 2010; Thrumurthy et al, 2010).

Urethral diverticula and their surgical repair may also lead to urethrovaginal fistula (Ganabathi et al, 1994; Ben Amna et al, 2002; Porgiglia et al, 2002).

Urethrovaginal fistula has also been described in some Behçet patients with vasculitis and local necrosis of the urethrovaginal septum (Waidelich et al, 1994; Chung et al, 2005).

Complications of radiation therapy for pelvic malignancy can also result in the formation of urethrovaginal fistula (Flottorp and Inversen, 1960) (Figs. 89-42 and 89-43). Other causes of urethrovaginal fistulae include trauma (including pelvic fracture) and vaginal neoplasms. Another important cause in the long-term-care setting is urethral catheter erosion (Trop and Bennett, 1992; Andrews and Shah, 1998). In patients with poor sensation, especially the cognitively or otherwise neurologically impaired patient, pressure necrosis from a chronically indwelling catheter may result in traumatic hypospadias and urethrovaginal fistula. If the condition is not recognized, over time the catheter may erode to the level of the bladder neck and beyond, effectively creating a bivalved urethra and a urethrovesicovaginal fistula (Fig. 89-44).

Symptoms of urethrovaginal fistulae are largely dependent on the size and location of the fistula along the urethral lumen. A small fistula may produce only minimal leakage, whereas a large urethrovaginal fistula can cause continuous urine drainage. Proximal fistulae can be associated with stress incontinence, or, if they are located at the bladder neck, continuous incontinence may result, similar to that associated with VVF. Distal fistulae beyond the sphincteric mechanism may be completely asymptomatic or may be associated with a splayed urinary stream. Occasionally, distal fistulae are associated with vaginal voiding and pseudoincontinence, so called because the patient reports urinary incontinence that occurs only when rising from a seated position after voiding. This occurs as a result of urine accumulation in the vagina during voiding, with emptying occurring on standing—so-called vaginal voiding (Fig. 89-45).



Figure 89-41. Computed tomography scan with contrast enhancement demonstrating a vesicouterine fistula. Contrast material is layering in the partially filled urinary bladder; contrast opacification of the uterine canal (arrow) suggests a vesicouterine fistula.

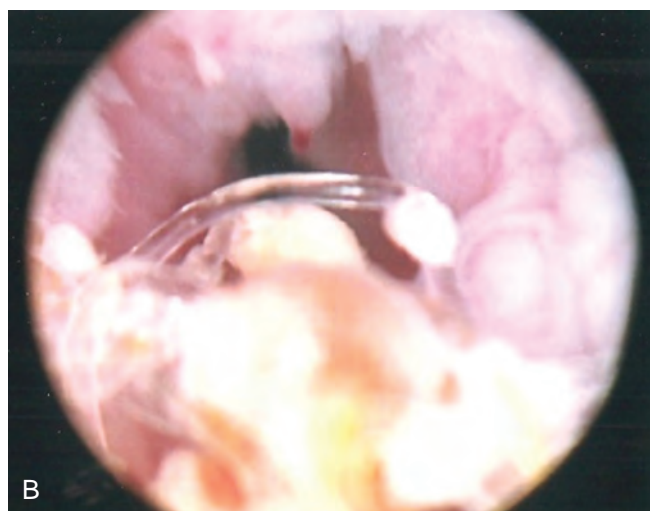
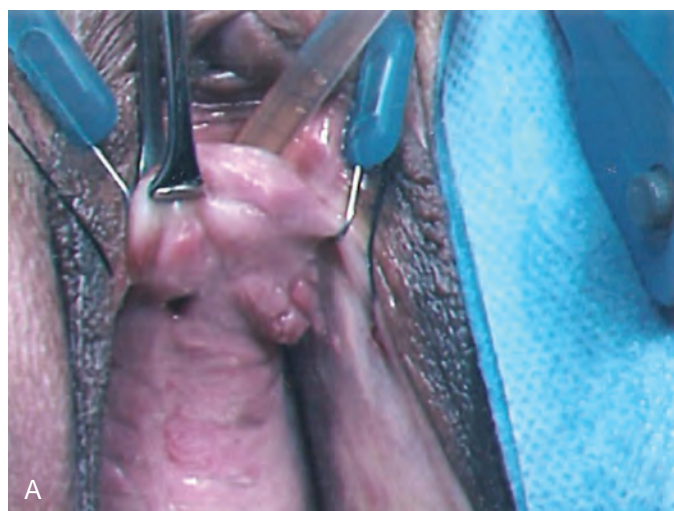


Figure 89-42. Urethrovaginal fistula after mid-urethral synthetic sling procedure. A, Intraoperative view demonstrating a urethrovaginal fistula at the bladder neck after a mid-urethral sling procedure. B, Cystoscopy demonstrates intraurethral sling material with calcified material.



Figure 89-43. Urethrovaginal fistula at the bladder neck from obstructed labor. A hemostat is shown entering the urethral meatus. (Courtesy Mark Morgan, MD, Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, PA.)

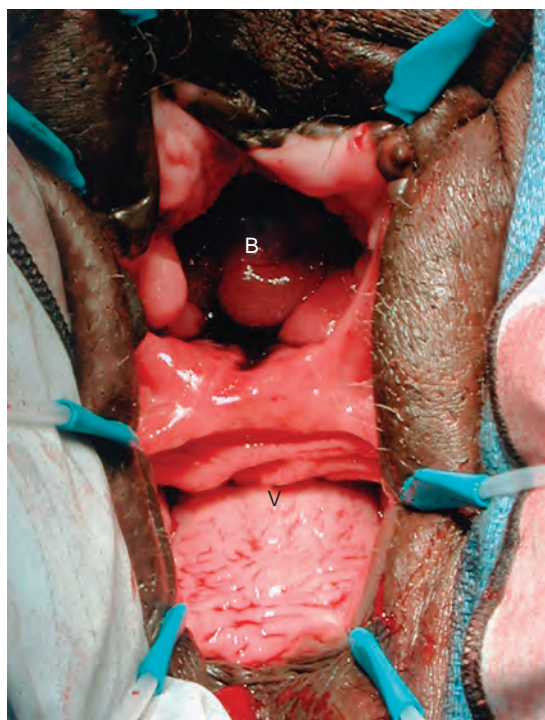


Figure 89-44. Severe complete erosion of the urethra secondary to chronic indwelling urinary catheter. This patient with advanced multiple sclerosis underwent surgical bladder neck closure and ileovesicostomy (ileal chimney). B, bladder; v, vagina.

Diagnosis and Management

The diagnosis of urethrovaginal fistula can often be made on physical examination and cystourethroscopy; however, voiding cystourethrography is most useful (Fig. 89-46), especially in complex cases. Small fistulae may be very difficult to locate on

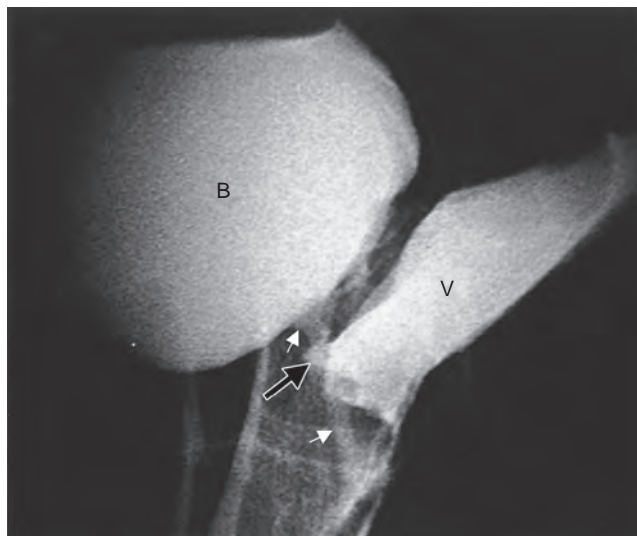


Figure 89-45. Urethrovaginal fistula on lateral voiding image from voiding cystourethrography demonstrates fistula (black arrow) in this patient with a primary symptom of vaginal voiding. The urethra proximal and distal to the fistula is well opacified (white arrows). B, bladder; V, vagina.

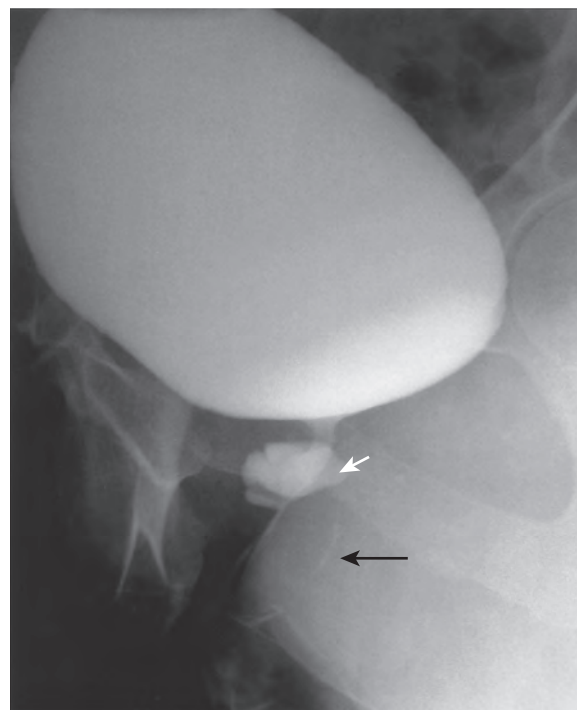


Figure 89-46. This patient was referred for the evaluation of persistent incontinence after urethral diverticulectomy. A voiding cystourethrogram demonstrates incomplete resection of the urethral diverticulum (white arrow) with a pinpoint postoperative urethrovaginal fistula (black arrow shows a small amount of contrast material faintly outlining the anterior vaginal wall). Resection of the residual diverticulum with repair of the fistula by a Martius flap was curative.

physical examination, even with a speculum, owing to the surrounding vaginal rugation (Fig. 89-47). It is important to note that an associated VVF will be found in up to 20% of cases, and therefore a thorough evaluation of the entire lower urinary tract is warranted (Lee et al, 1988).

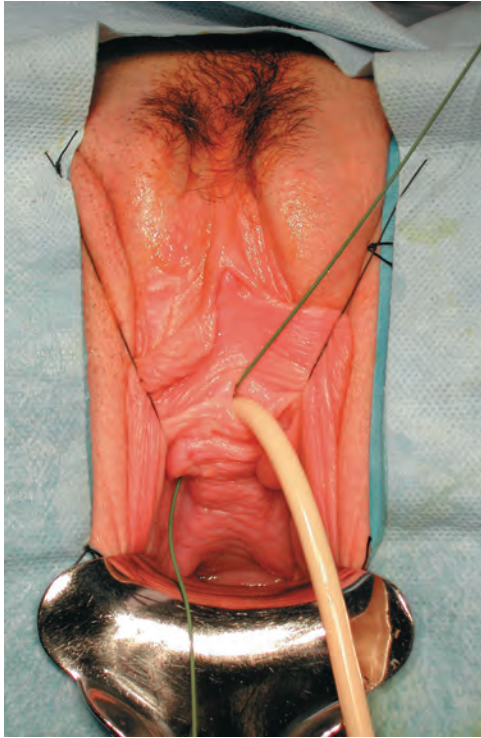


Figure 89-47. Urethrovaginal fistula. Identification of the exact fistula tract can be difficult in redo cases. Passage of a flexible wire endoscopically from the urethral lumen into the vagina can aid in locating the fistula tract.

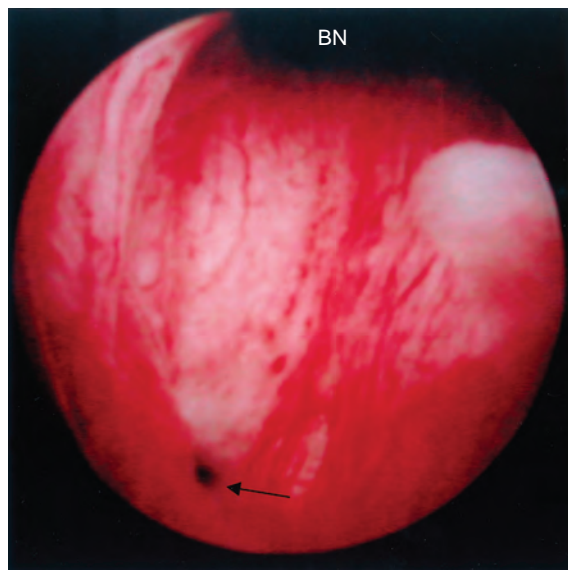


Figure 89-48. Endoscopic view of a urethrovaginal fistula (arrow). This patient reported ongoing urinary incontinence for 10 years after an endoscopic bladder neck suspension. BN, bladder neck.

Endoscopic examination of the urethra should be performed. However, because of its short length, the female urethra may be difficult to fully examine with a standard rigid cystoscope, because the irrigation fluid is discharged 1 to 2 cm proximal to the lens. A flexible cystoscope or a specially designed female cystoscope with a short beak is very helpful in visualizing the entire urethral lumen, because the irrigation fluid is discharged next to the lens, distending the adjacent urethral lumen (Fig. 89-48). Once the diagnosis is

made on cystoscopy, the bladder is examined for additional fistulae. Video-urodynamics may accurately characterize any associated incontinence, including that associated with detrusor dysfunction, although this will not often influence the decision of closing the fistula. This study also allows assessment of the anatomic relationship of the fistula to the bladder neck and urethra, as well as examination for associated VVF.

The surgical repair of urethrovaginal fistulae is challenging and can often be more difficult than repair of VVF. This is a result of several factors, including extensive soft-tissue defects as well as the lack of local viable tissue for a multilayer repair (Keettel et al, 1978). Repair of urethrovaginal fistulae usually involves the use of rotational vaginal wall flaps, but anterior-based (Elkins et al, 1992) and posterior-based (Khanna, 1992) bladder flap tubes have been used as well.

A number of factors should be considered before repair. If the fistula is the result of a foreign body, such as a synthetic sling (Reisenauer et al, 2007), the foreign material should be excised as widely as possible from the margins of the fistula, debridement performed on the associated devitalized or inflamed tissue, and then the fistula closed with healthy tissues and flaps, if necessary. Small fistulae may be managed by a multilayered closure, usually with an interpositional graft such as a Martius flap (Webster et al, 1984; Leach, 1991). Larger fistulae, including those resulting from obstructed labor, may require extensive surgery, including urethral reconstruction (Tehan et al, 1980; Elkins et al, 1992; Wang and Hadley, 1993). Distal fistulae without associated voiding symptoms or incontinence may be observed or, alternatively, can be managed with an extended meatotomy (Lamensdorf et al, 1977). The quality of the vaginal tissues should be optimized before operative repair, which may include the use of antibiotics to treat associated infection, or topical estrogen treatment in patients with significant atrophic vaginitis. Similar to VVF, timing of repair is controversial. Some authors have suggested that a waiting time of 2 to 6 months is advisable in most patients, with a waiting period of up to 1 year in those with radiation fistulae (Webster et al, 1984; Zimmern et al, 1986). Other authors have advocated immediate repair as soon as the vaginal tissues are free of infection and inflammation (Blaivas, 1989; Blaivas et al, 1995).

Operative Technique. The repair of urethrovaginal fistulae is conceptually very similar to the vaginal flap repair of VVF described previously. The patient is positioned in the dorsal lithotomy position, and urethral and suprapubic catheters are placed. A ring retractor is helpful for exposure. Allis clamps are used to reflect the vaginal wall cephalad, exposing the fistula. In some patients an episiotomy may facilitate exposure of the fistula, improving visualization for repair (Webster et al, 1984). However, because of the distal (with respect to the vagina) location of these lesions, this is not usually necessary.

After infiltration of the fistula margins with injectable saline, the fistula tract is circumscribed through the vaginal wall (Fig. 89-49). The fistula tract and immediate surrounding epithelium are not typically excised, because this will create a larger defect in the urethra that will be more difficult to close without undue tension. However, the vaginal wall is dissected several millimeters from the edge of the circumscribed fistula tract in a radial orientation. An inverted U- or J-shaped incision is marked along the anterior vaginal wall, with the base of the U or J at the margin of the circumscribed fistula tract. This is infiltrated with injectable saline, and the anterior vaginal wall flap is developed, exposing the underlying periurethral fascia to the level of the bladder neck or beyond, depending on the size and location of the fistula. If a concomitant anti-incontinence procedure is planned, dissection may be carried out laterally from the edges of the flap at the level of the bladder neck and the retropubic space entered.

The edges of the circumscribed tract are reflected over the fistula and apposed with absorbable suture to create the first layer of closure. The periurethral fascia is then reapproximated in a perpendicular suture to the first layer of closure, thereby minimizing overlap. At this point, a Martius flap or other adjuvant flap can be secured over the periurethral fascia. Finally, the anterior vaginal wall

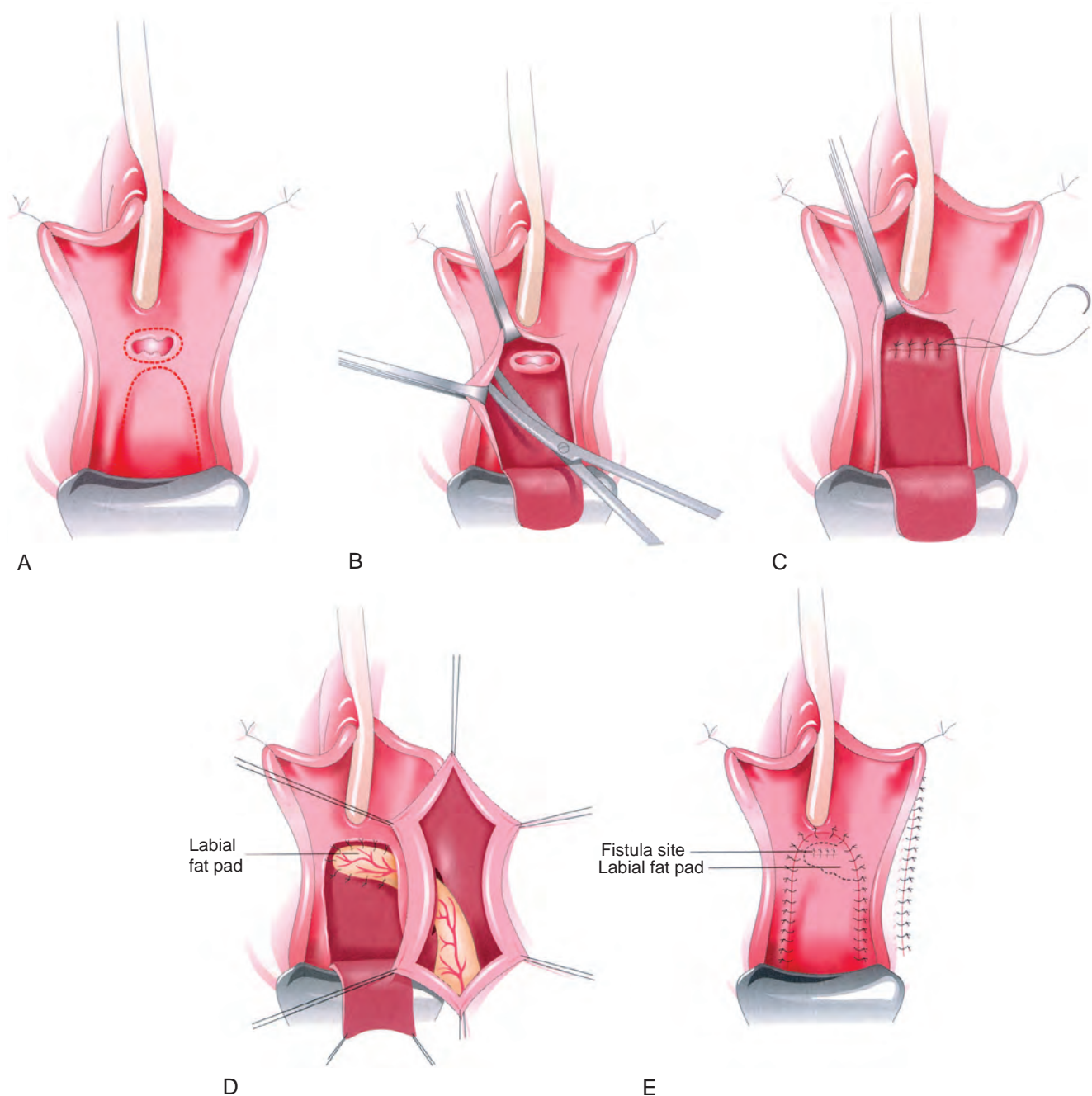


Figure 89-49. Operative diagram of urethrovaginal fistula repair. A, Inverted U incision is made in the anterior vaginal wall with the base of the U at the proximal margin of the fistula. The fistula is circumscribed. B, The anterior vaginal wall flap is mobilized, exposing the periurethral fascia. Dissection is also carried out laterally and distally from the margins of the fistula. The edges of the fistula tract are not excised. C, The epithelialized margins of the fistula tract are reapproximated with absorbable suture for the initial layer of closure. The periurethral fascia may be closed as a second layer, imbricating the initial layer of closure (not shown). D, A Martius flap may be harvested from the labia majora and tunneled as an additional layer of closure. E, The anterior vaginal wall flap is advanced over the closure and secured with absorbable suture. (From Leach GE, Kobashi KC. Urethral diverticulum and fistula. In: Cardozo L, Staskin D, editors. Textbook of female urology and urogynecology. London: Isis Medical Media; 2001. p. 721–45.)

flap is brought over the repair, including a Martius flap if used, and secured beyond the original fistula tract.

Adjuvant Flaps and Procedures in the Repair of Urethrovaginal Fistula. Various types of soft-tissue flaps are often an important component of a successful urethrovaginal fistula repair

because fistula excision and vaginal flap advancement have been historically associated with a high rate of failure (Birkhoff et al, 1977; Keettel et al, 1978; Davis et al, 1980; Patil et al, 1980; Leach, 1991; Fall, 1995; Bruce et al, 2000; Rangnekar et al, 2000). A variety of adjuvant procedures have been used in the repair of

urethrovaginal fistulae, including, most commonly, a Martius labial fat flap, but also gracilis and rectus abdominis muscle, myocutaneous flaps, vaginal wall flaps, fibrin glue, and free labial skin grafts (Keettel et al, 1978; McKinney, 1979; Tolle et al, 1981; Webster et al, 1984; Krogh et al, 1989; Leach, 1991; Izes et al, 1992; Candi-ani et al, 1993; Fall, 1995; Rangnekar et al, 2000). Whereas in obstetric fistula repair it was not found to have any benefit in a large retrospective study in 440 women, the labial bulbocavernosus muscle and fat flap by Martius is still considered by some to be an important adjunctive measure in the treatment of GU fistula wherein additional bulking with well-vascularized tissue is needed (Browning, 2006). Rangnekar and colleagues reported on 12 patients with urethrovaginal fistula, of whom 8 were treated with a Martius flap and 4 with a conventional repair. Only 1 of the 8 had a fistula recurrence, whereas 3 of the 4 conventional repairs broke down; it should be noted, however, that these cases were not randomized between surgical techniques (Rangnekar et al, 2000). Puneekar and colleagues described 15 patients with complex and recurrent fistula; these authors used the skin island flap modification with excellent results (Puneekar et al, 1999). Radopoulos published the findings of a small series of 5 recurrent and complex urethrovaginal fistulae that all healed with use of a Martius flap (Radopoulos et al, 2008). The series involving fistulae of nonobstetric causes are small, and all of them are retrospective. There are no prospective data, nor randomized studies (Birkhoff et al, 1977; Baskin et al, 2005). The indications for Martius flap in the repair of all types of fistula remain unclear.

Webster and colleagues (1984) reported on 11 patients with urethrovaginal fistulae, of whom 10 underwent surgical repair. Three of the 10 had recurrence of the fistula, all of whom were salvaged with a subsequent repair combined with a Martius labial fat pad interposition. Two patients had primary repair with a Martius flap (see prior discussion under VVF for a more complete discussion of the Martius flap), and both were cured. These authors recommended a Martius flap for all patients undergoing urethrovaginal fistula repair. Bruce and colleagues (2000) reported on the use of a pedicled rectus abdominis muscle flap based on the inferior epigastric artery for complex and refractory urethrovaginal fistulae in 6 patients. In all patients, at least one attempt at repair with a Martius flap had failed. Six of 6 patients remained successfully closed at a mean follow-up of 23 months. One of 6 patients had persistent urge incontinence postoperatively. The authors concluded that the rectus abdominis flap is a useful adjunct in the repair of complex or refractory urethrovaginal fistulae.

Suprapubic as opposed to urethral catheterization postoperatively for at least 14 days to allow adequate healing has been suggested (Tehan et al, 1980; Webster et al, 1984), although the use of only a single drainage catheter postoperatively is not universally agreed on. Other authors use both a suprapubic and a urethral catheter (Leach, 1991). Anticholinergics are administered liberally to reduce bladder irritability. Usually a VCUG with contrast administered through the suprapubic tube is obtained to document resolution of the fistula.

SUI may persist after repair of urethrovaginal fistulae. Whether repair of SUI should be done concomitantly with the fistula surgery or should be deferred until after repair of the fistula is controversial. Blaivas and colleagues (1989) argued that sphincteric incontinence should be repaired at the time of fistula surgery, with a Martius flap interposed between the fistula repair and a pubovaginal fascial sling. Webster and colleagues (1984) suggested that SUI associated with a proximal or mid-urethral urethrovaginal fistula should not be corrected until the fistula is closed and the patient reassessed for persistent incontinence. These authors suggest, however, that SUI associated with distal urethrovaginal fistula can be repaired concomitantly.

Overall, the success rate of urethrovaginal fistula repair is variable but is not generally considered to be as high as that for VVF repair (Gerber and Schoenberg, 1993). Not uncommonly, two or more procedures may be necessary to achieve a satisfactory result (Webster et al, 1984).

KEY POINTS: URETHROVAGINAL FISTULAE

- Distal urethrovaginal fistulae are often asymptomatic, whereas proximal fistulae may cause intermittent or constant urinary leakage.
- Urethrovaginal fistulae caused by surgical trauma may be difficult to visualize on physical examination or cystoscopy.
- Diagnosis of a urethrovaginal fistula is best made with VCUG.
- Repair of urethrovaginal fistulae can be challenging and often involves an interpositional tissue flap because of the relative lack of surrounding connective tissue in the mid-urethra and distal urethra.

UROENTERIC FISTULAE

Vesicoenteric Fistula

Etiology and Presentation

Vesicoenteric fistulae commonly occur in the setting of bowel disease, such as diverticulitis, colorectal carcinoma, and Crohn disease. Less common causes include radiation, infection, and trauma—external penetrating trauma, as well as iatrogenic surgical trauma. Diverticulitis is the most common cause of colovesical fistulae in most series, accounting for approximately 70% of cases (Mileski et al, 1987; Pollard et al, 1987; Walker et al, 2002; Najjar et al, 2004) (Table 89-6). The second most common cause of vesicoenteric fistulae is cancer, followed by Crohn disease. The peak incidence of vesicoenteric fistula occurs at 55 to 65 years of age, although fistulae from Crohn disease manifest much earlier (Badlani et al, 1980). Approximately 2% of patients with diverticulitis may experience a colovesical fistula as a complication of their disease (Hafner et al, 1962). In a multi-institutional retrospective review of 400 patients with Crohn disease over a 10-year period, 8 patients (2%) were found to have enterovesical fistulae (Gruner et al, 2002). The underlying GI tract disease strongly influences the type of fistula; ileovesical fistulae are more common in Crohn disease than in cancer, and colovesical fistulae are usually a result of diverticulitis.

Symptoms of vesicoenteric fistulae may originate from the urinary or GI tract; however, in general, lower urinary tract symptoms are more common at presentation (Morse and Dretler, 1974; Ray et al, 1976). In the early stages, symptoms are nonspecific and relate to lower urinary tract dysfunction. Lower urinary tract symptoms include pneumaturia, frequency, urgency, suprapubic pain, recurrent urinary tract infections (UTIs), and hematuria (Table 89-7). Pneumaturia is considered the most common presenting symptom noted in 50% to 70% of cases (Morse and Dretler, 1974; Pontari et al, 1992; Jarrett and Vaughan, 1995; Solem et al, 2002). GI symptoms may include fecaluria and tenesmus. The classic presentation of vesicoenteric fistula is described as Gouverneur syndrome and consists of suprapubic pain, urinary frequency, dysuria, and tenesmus (Sans et al, 1986). Recurrent UTIs or cystitis refractory to antibiotic therapy may suggest a colovesical fistula (Rao et al, 1987). Although it is rare for enterovesical fistulae to have sepsis as the presenting sign (Woods et al, 1988), patients with

TABLE 89-6 Causes of Vesicoenteric Fistulae*

Diverticulitis	65%-75%
Malignancy	10%-15%
Crohn disease	5%-6%
Other (trauma, appendiceal abscess, foreign body)	<5%

*See Morse and Dretler, 1974; Amendola et al, 1984; Pollard et al, 1987; Schofield, 1988; Walker et al, 2002.



Figure 89-50. Cystoscopic view of a chronic long-standing colovesical fistula. Unlike the majority of these fistulae, there is minimal inflammation around the fistula tract.



Figure 89-51. Computed tomography scan of colovesical fistula. Note the air in the bladder with the thickened posterior bladder wall.

TABLE 89-7 Presenting Symptoms of Vesicoenteric Fistula*

Pneumaturia	52%-77%
Fecaluria	36%-51%
Urinary tract infection symptoms (frequency, urgency, dysuria)	44%-45%
Fever and chills	41%
Abdominal pain	25%
Nonspecific gastrointestinal symptoms	25%
Hematuria	5%-22%
Orchitis	10%
Urine per rectum	5%

*See Morse and Dretler, 1974; Pontari et al, 1992; Najjar et al, 2004.

sepsis are found to have urinary obstruction in approximately 70% of cases (Mileski et al, 1987).

Diagnosis

Many studies exist for the diagnosis of enterovesical fistulae; however, there are significant problems with both false negatives and false positives among the diagnostic modalities, and thus the diagnosis is often made on clinical grounds. Cystoscopy has the highest yield in identifying a potential lesion, with some type of abnormality noted on endoscopic examination in more than 90% of cases (Morse and Dretler, 1974) (Fig. 89-50). However, the findings on cystoscopy are often nonspecific and include localized erythema, papillary, or bullous change; a definitive diagnosis using cystoscopy can be made in only 35% to 46% of cases (Woods et al, 1988; Pontari et al, 1992). Cystoscopy and biopsy of abnormal-appearing tissue or an established fistula tract in the setting of a history of malignancy are indicated to evaluate for the possibility of a malignant fistula.

Cross-sectional imaging, especially CT scanning, has become the imaging modality of choice (Goldman et al, 1984, 1985; Jarrett and Vaughan, 1995; Gruner et al, 2002). CT or MRI (Haggett et al, 1995) may localize the fistula tract, as well as the involved segment of bowel. The triad of findings on CT that are suspicious for colovesical fistulae consist of (1) bladder wall thickening

adjacent to a loop of thickened colon, (2) air in the bladder (in the absence of previous lower urinary manipulation), and (3) the presence of colonic diverticula (Labs et al, 1988). Labs and colleagues (1988) correctly diagnosed colovesical fistulae on CT in 11 of 12 patients with surgically confirmed lesions. CT is now generally considered to be the most sensitive and specific modality for the diagnosis of colovesical fistulae in suspect patients (Najjar et al, 2004), with diagnostic accuracy as high as 90% to 100% (Goldman et al, 1985; Jarrett and Vaughan, 1995). The high diagnostic accuracy of CT in detecting enterovesical fistulae relates to its ability to detect even a very small amount of air in the bladder (Fig. 89-51). Although air in the bladder on diagnostic imaging is very suggestive of colovesical fistulae, false positives may be created by recent instrumentation (catheterization, cystoscopy) or an active UTI with a gas-forming organism. CT scanning should be done after the administration of oral contrast but before the administration of intravenous contrast to permit detection of barium within the bladder. Ultrasonography has also been reported to be useful in the diagnosis of colovesical fistulae. A characteristic “beak” sign may be noted; however, this study is not usually performed in the routine evaluation of the patient with a suspected enterovesical fistula (Chen et al, 1990).

Although commonly used, cystography and transrectal contrast studies (e.g., barium enema) are in general less likely to demonstrate the fistula. Rao and colleagues (1987) reported that 14 of 24 barium enemas either demonstrated or were suspicious for colovesical fistulae in a series of surgically treated patients. Barium enemas and/or colonoscopy may be valuable adjunctive studies in evaluating for colonic disease, such as malignancy, as a cause of the fistula; the preoperative knowledge of such a condition can considerably alter management decisions. Nevertheless, barium enemas have limited use in the diagnosis of enterovesical fistulae owing to low sensitivity (Amendola et al, 1984). The Bourne test, however, can be a useful adjunctive study in the evaluation of colovesical fistulae (Bourne, 1964). As described, the Bourne test is performed after a nondiagnostic barium enema. The first voided urine after the barium enema is immediately centrifuged and then examined radiographically. Radiodense particles in the urine are considered a positive test result and evidence for a vesicoenteric fistula. Amendola and colleagues (1984) reported a positive Bourne test in 9 of 10 patients with colovesical fistulae; the Bourne test was the only evidence for a colovesical fistula in 7 such patients who had an otherwise negative evaluation with a combination of other diagnostic studies.

The diagnosis of vesicoenteric fistulae may be confirmed by the oral administration of activated charcoal, which, in the

setting of a fistula, will appear in the urine as black particles (Geier et al, 1972). This test provides no anatomic information regarding the location of the fistula but is useful in confirming the diagnosis in suspect cases. Intrarectal administration of vital dyes has been advocated for the diagnosis of occult colovesical fistula; however, the dye may be absorbed and then excreted in the urine, giving a false-positive test result (Deshmukh et al, 1977). Accepting the limitations of small case series in this regard, a number of studies have investigated the value of a range of investigative techniques in the detection and evaluation of enterovesical or colovesical fistulae (Amendola et al, 1984; Pollard et al, 1987; Kuhlman and Fishman, 1990; McBeath et al, 1994; Jarrett and Vaughan, 1995; Liu et al, 1999; Bernstine et al, 2002; Kavanagh et al, 2005; Garcea et al, 2006). Because in each study the authors have presented only results from patients known to have fistulae, sensitivity may be estimated; however, specificity, positive predictive value, and negative predictive value cannot. No test was shown to have consistent reliability; excluding those investigations for which only a single report was identified, CT (53%), cystoscopy (48%), and, in the case of colovesical fistula, barium enema (38%) were perhaps the most useful; IVU and sigmoidoscopy or colonoscopy appear to have limited usefulness in the diagnosis of GI fistula (De Ridder et al, 2013).

Management

Nonoperative management is a viable option in selected patients with vesicoenteric fistula. Amin and colleagues (1984) reported on 4 of 30 patients with colovesical fistulae secondary to diverticulitis who were observed without active intervention for 3 to 14 years. There were no significant long-term sequelae in this select patient population. In nontoxic, minimally symptomatic patients with nonmalignant causes of enterovesical fistulae, a trial of medical therapy including intravenous total parenteral nutrition (Dudrick et al, 1999), bowel rest, and antibiotics may be warranted. This may be the preferred initial approach, especially in patients with Crohn disease, in whom the notion of immediate exploratory laparotomy and bowel resection is often discouraged because of the chronic relapsing nature of the disease (Evans et al, 2003a). There is also the potential for successful medical management of other fistulae resulting from inflammatory bowel disease (Mahadevan et al, 2003; Parsi et al, 2004). Ileovesical fistula in Crohn disease may be managed with antibiotics, nutritional support, often including total parenteral nutrition, and various combinations of immunomodulatory agents. In a nonsystematic review of the management of internal fistulae in Crohn disease, Levy and Tremaine described the drugs that have been reported to close internal fistulae partially or completely, including azathioprine, 6-mercaptopurine, mycophenolate mofetil, cyclosporine A, tacrolimus, and infliximab (Levy and Tremaine, 2002).

One case series of 500 patients with Crohn disease included 17 with enterovesical fistulae; all received sulfasalazine, most were treated with corticosteroids and antibiotics intermittently, and 8 in addition received 6-mercaptopurine. Although it is not clear that their fistulae closed completely, 6 continued on medical treatment alone for several years (Margolin and Korelitz, 1989).

Present and colleagues reported a placebo-controlled randomized trial of the tumor necrosis factor- α (TNF- α) neutralizing agent infliximab, a murine-human chimeric monoclonal antibody that binds both the soluble subunit and the membrane-bound precursor of TNF- α , in patients with externally draining fistulae associated with Crohn disease (Present et al, 1999). Adverse events were very common, but complete resolution of all fistulae was achieved in 55%, and 50% reduction in fistulous drainage was achieved in 68% of patients on 5-mg infliximab. This study did not include ileovesical fistulae, although a case of successful use of infliximab in an ileovesical fistula has been reported (Game et al, 2003).

The goal of operative management is to separate and close the involved organs with minimal anatomic disruption and normal long-term function of both systems. Unfortunately, enterovesical fistulae may be complicated by intense pelvic inflammation, pelvic

abscess, and phlegmon formation (in some cases), requiring complex staged reconstructions (Shackley et al, 2000). Bowel resection and/or partial cystectomy may be necessary to obtain viable tissue margins to ensure adequate, watertight closure of the involved viscera. An interpositional flap of greater omentum is often placed between the repaired bowel and urinary bladder to prevent overlapping suture lines and provide a well-vascularized surface for healing.

Both single and multistage procedures have been advocated, depending on the clinical circumstances (Morse and Dretler, 1974; Castro, 1975; Ray et al, 1976; Morrison and Addison, 1983; Mileski et al, 1987; Pollard et al, 1987; Rao et al, 1987; Shackley et al, 2000; Walker et al, 2002; Najjar et al, 2004). A one-stage procedure involves removal of the fistula, closure of the involved organs, and primary reanastomosis of the bowel after resection of the involved bowel segment. A two-stage approach advocates removal of the fistula, closure of the involved organs, and creation of a temporary proximal diverting colostomy, with a later return to the operating room for colostomy takedown once the fistula tract has been demonstrated to be closed. The choice of whether to proceed with a one-stage or two-stage repair is influenced by the location and cause of the fistula, the patient's general condition, the presence of a pelvic abscess, and the presence of colonic obstruction (McConnell et al, 1980). Patients with an inflammatory cause of the fistula but without gross contamination can be treated with a one-stage procedure, whereas those with an unprepared bowel, gross contamination, or abscess may require a multistage procedure (Mileski et al, 1987; Shackley et al, 2000). As noted previously, most patients with colovesical fistulae present themselves electively with lower urinary tract symptoms, not emergently in extremis with sepsis (Mileski et al, 1987). Therefore adequate preoperative support, including bowel preparation, nutritional supplementation, and appropriate antibiotics, can be used in the majority of patients, allowing an elective one-stage approach. The authors of many case series have advocated a one-stage approach in the majority of cases but have indicated that this should be limited to patients whose nutritional state is good and in whom there is no evidence of severe inflammation, radiation injury, advanced malignancy, intestinal obstruction, major medical problem, or advanced age (McConnell et al, 1980; Mileski et al, 1987; Pollard et al, 1987; Pontari et al, 1992; McBeath et al, 1994; Hsieh et al, 1997). More recent series have tended to imply a greater advocacy of the one-stage approach; Garcea and colleagues in a series of 90 patients with colovesical fistula reported primary anastomosis in 61 of 65 (94%) cases wherein left colon resection was undertaken (Garcea et al, 2006). Balaguera and colleagues argued against diverting colostomy or Hartmann procedure as being unnecessary, and possibly bringing additional morbidity (Balaguera et al, 2006).

In addition to the aforementioned criteria, it is intuitive that the more complex a fistula tract, the more relevant a phased approach to treatment becomes. Shackley and colleagues described a series of 10 patients with highly complex fistulae involving three to six separate organs and surfaces (Shackley et al, 2000). They advocate a three-stage multidisciplinary management package, involving (1) an acute stage involving proximal defunctioning and distal drainage of both the GI and urinary tracts to isolate the fistula, together with the eradication of sepsis; (2) a recovery stage consisting of total parenteral nutrition, organ support, radiologic planning of surgical reconstruction, and intensive nursing; (3) joint urologic and GI reconstructive surgery when the patient was stable and nutritionally replenished and the sepsis was controlled. The mean time to reconstruction was 5 (1 to 20) months; the fistulae were treated successfully in all patients, with functional restoration in 4 and/or diversion of the GI and urologic tracts in 6 (Shackley et al, 2000).

Laparoscopic management of colovesical fistulae has been reported, albeit with a relatively high rate of conversion to open repair (Joo et al, 1997). Several reports have described a laparoscopic approach to one-stage treatment of colovesical fistulae, including a total of 30 patients (Serizawa et al, 1996; Menenakos et al, 2003; Pokala et al, 2005; Tsivian et al, 2006). The overall conversion rate was seen to be higher for fistulae involving the

duodenum, vagina, and sigmoid colon than for those involving the bladder (10%), although a low threshold for conversion to open surgery was advocated in one series (Pokala et al, 2005).

KEY POINTS: VESICOENTERIC FISTULAE

- The most common cause of vesicoenteric fistulae is diverticulitis.
- Presenting symptoms are usually urinary, most commonly pneumaturia.
- Diagnosis is generally made with a combination of cystoscopy and cross-sectional imaging, including a CT scan.
- Repair of colovesical fistulae involves a single-stage or multistage procedure, depending on a number of clinical factors, including the presence of gross fecal contamination and infection.

Ureteroenteric Fistula

Fistulae between the ureter and the bowel are most likely to occur in the setting of inflammatory bowel disease such as Crohn disease. The segment of bowel most likely to be involved is the terminal ileum (Banner, 1987), and thus the vast majority of ureteroenteric fistulae are unilateral and right sided (Sigel et al, 1977). Rarely, diverticulitis (Ney et al, 1986; Cirocco et al, 1994; Maeda et al, 1998) or ulcerative colitis will lead to a left-sided ureteroenteric fistula (Sigel et al, 1977). Involvement of the ureter is usually at the level of the sacral promontory (Sigel et al, 1977). Other causes of ureteroenteric fistulae include calculous disease, tuberculosis (TB), external and iatrogenic (surgical) trauma, radiation therapy, and transitional cell carcinoma (Javadpour et al, 1973; Sankaran et al, 1974; McElwee et al, 1983; Sumiya et al, 1985; Flood et al, 1992; Goetz et al, 1992; Toporoff et al, 1992; Oh et al, 2002). Unlike vesicoenteric fistulae, ureteroenteric fistulae are more likely to manifest with bowel rather than urinary symptoms. Pain may also be reported in the hip, flank, or anterior thigh.

The diagnosis can be made by retrograde pyelography, although CT and MRI are more useful. Barium contrast studies of the small bowel will often show a diseased segment of bowel but will only rarely demonstrate the fistula. Treatment involves ureterolysis and possible bowel resection. Ureteral resection is not necessary if it can be separated from the involved bowel segment and stented. Unfortunately, in many of these cases, significant renal damage has occurred before the definitive diagnosis, and thus nephrectomy may be necessary for definitive management (Sigel et al, 1977).

Pyeloenteric Fistulae

Pyelointestinal fistulae represent an epithelialized connection between the renal pelvis or collecting system of the kidney and the GI tract. Chronic inflammatory disease, such as xanthogranulomatous pyelonephritis or other infectious diseases involving the kidney or bowel, historically has been the most common cause of this condition (Schwartz et al, 1970; Greene et al, 1975; Bhargava et al, 1982; Cheate et al, 1985; Desmond et al, 1989; Yildiz et al, 1993; Majeed et al, 1997). However, iatrogenic surgical trauma, especially that related to percutaneous renal surgery and percutaneous nephrolithotomy (PCNL), has been associated with an increasing number of such fistulae (LeRoy et al, 1985; Culkin et al, 1990) (Fig. 89-52). Penetrating external trauma, malignancy, ulcer disease, ingested foreign bodies, and complex calculous disease may also result in pyeloenteric fistulae (Brust and Morgan, 1974; Mooreville et al, 1988; Blatstein and Ginsberg, 1996; Ginsberg et al, 1996; Chen et al, 2002). Right-sided pyeloenteric fistulae most often involve the duodenum owing to their close anatomic relationship, whereas left-sided pyeloenteric fistulae most commonly involve the descending colon.

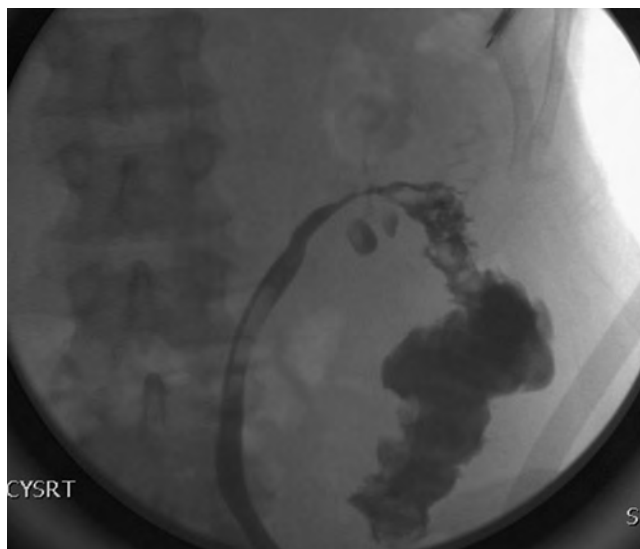


Figure 89-52. Pyelocolonic fistula after cryosurgical ablation of a renal tumor. Retrograde pyeloureterogram demonstrates contrast extravasation into the colon.

The majority of patients have nonspecific symptoms, including malaise, nonspecific GI symptoms, urinary frequency, flank mass, or tenderness. Approximately 60% to 70% of patients have flank pain, fever, and pyuria (Desmond et al, 1989). Iatrogenic fistulae as a result of endourologic procedures may cause minimal symptoms. In some cases, they are noted only incidentally on postoperative nephrostogram (Culkin et al, 1990). Diagnosis can be made with a combination of urography, retrograde pyelography, and nephrostogram. The GI tract may be studied with a barium swallow or enema.

Historically, pyeloenteric fistulae were treated by nephrectomy and closure of the GI tract (Greene et al, 1975); however, given the changing nature of the cause of these lesions, in many cases the fistula may be initially treated conservatively, especially if associated with a normally functioning kidney. A large nephrostomy tube, enteric suction or bowel rest, antibiotics, and removal of any foreign body (e.g., a stone) may be attempted. Internal stenting of the urinary tract may be pursued for maximal drainage (Desmond et al, 1989). Fistulae associated with a poorly functioning kidney are best treated by primary closure of the bowel and nephrectomy. Case reports of ureterocolic fistulae occurring after renal cryotherapy and gunshot trauma all resolved with insertion of a ureteral stent (Vanderbrink et al, 2007; Ould Ismail et al, 2010). This is in line with previous accounts of this complication after PCNL (El-Nahas et al, 2006).

Urethrorectal (Rectourethral or Prostatorectal) Fistula

Acquired rectourethral fistula (RUF) may occur in the male under a variety of clinical circumstances, including those related to prostatectomy for benign or malignant disease, cryotherapy, pelvic radiotherapy, anorectal surgery, external penetrating trauma (Bukowski et al, 1995; al-Ali and Kashmoula, 1997), urethral instrumentation (Thompson and Marx, 1990), locally advanced prostatic or rectal malignancy, infection (e.g., TB) (Okanya et al, 1988), ruptured prostatic abscess, or inflammatory disease (e.g., Crohn disease) (Stamler et al, 1985; Fazio et al, 1987). Congenital RUF associated with imperforate anus is covered in Chapter 128.

Etiology and Presentation

The incidence of RUF after radical retropubic prostatectomy (RRP) is low, but owing to the frequency with which the

operation is performed, it is the most common cause of RUF in most modern series (Stephenson and Middleton, 1996; Nyam and Pemberton, 1999; Renschler and Middleton, 2003). Rectal injury during radical prostatectomy occurs in less than 1% to 2% of patients (Igel et al, 1987; Borland and Walsh, 1992; McLaren et al, 1993; Guillonnet et al, 2003). In a Mayo RRP series, there were 27 documented rectal injuries in 2212 patients (McLaren et al, 1993). In this series, 26 of 27 injuries were recognized intraoperatively and repaired. Six patients underwent temporary colostomy, and 4 patients developed RUF. In a community-based practice, Harpster and colleagues (1995) reported rectal injuries in 7 of 516 patients undergoing RRP (1.4%) and in 1 of 17 patients undergoing radical perineal prostatectomy (Harpster et al, 1995). Five rectal injuries were recognized and repaired intraoperatively. There were 3 RUFs reported in this series; none closed with conservative management, and all required formal repair. Rassweiler and colleagues (2003) reported 1 RUF in a series of 219 patients undergoing RRP but 7 RUFs in 538 patients undergoing laparoscopic radical prostatectomy. All operations were performed by the same surgical team. Guillonnet and colleagues (2003) reported a 1.3% incidence of rectal injury in 1000 consecutive patients undergoing laparoscopic radical prostatectomy. Eleven of 13 injuries were recognized and repaired intraoperatively with a two-layer closure. One of these patients subsequently underwent temporary colostomy for complications related to the injury. Both patients with rectal injuries that were recognized postoperatively underwent colostomy. One of the 2 patients with a lately recognized rectal injury developed an RUF requiring a primary surgical closure.

In the setting of radical prostatectomy, a prior history of pelvic radiation therapy, rectal surgery, or transurethral resection of the prostate (TURP) is associated with an increased risk of RUF (Thompson and Marx, 1990; McLaren et al, 1993). RUF that occurs after radical prostatectomy is usually seen at the vesicourethral anastomosis and is often caused by an unrecognized rectal injury at the time of surgery. However, when a rectal injury is recognized and repaired intraoperatively, RUF is extremely uncommon. Borland and Walsh reported 10 rectal injuries in 1000 nonirradiated patients undergoing radical prostatectomy at Johns Hopkins Hospital; however, no patient developed a RUF (Borland and Walsh, 1992). Nine of 10 patients had a two-layer closure performed with an omental interpositional flap at the time of injury. One patient underwent a temporary diverting colostomy; the rectal injury was diagnosed and repaired on postoperative day 2. Anal sphincter dilation was performed on all patients, and they received 7 to 14 days of postoperative antibiotics.

The reported incidence of RUF after cryosurgical ablation as primary therapy for localized carcinoma of the prostate is 0.5% to 2% (Zippe, 1996; Long et al, 2001), whereas the rate of RUF after cryotherapy as salvage therapy for prostate cancer is somewhat higher at approximately 3.3% (Chin et al, 2001). The incidence of RUF after brachytherapy for prostate cancer as reported by Theodorescu and colleagues (2000) is 0.4%. RUFs have also been reported to follow high-intensity focused ultrasound (HIFU) treatment (Uchida et al, 2002; Blana et al, 2004), HIFU combined with external beam radiotherapy (6% incidence) (Gelet et al, 2004), laparoscopic radical prostatectomy (Guillonnet et al, 2003; Katz et al, 2003; Rassweiler et al, 2003; Dafnis et al, 2004), and transurethral thermotherapy for benign prostatic hyperplasia (BPH) (Norby and Frimodt-Moller, 2000). The incidence of RUF in Crohn disease is estimated to be approximately 0.3% (Stamler et al, 1985) (Fig. 89-53). Fistulae caused by Crohn disease are complex, and management should be individualized (Stamler et al, 1985; Fazio et al, 1987; Santoro et al, 1995; Cools et al, 1996; Rius et al, 2000).

The presentation of RUF is variable. Symptoms may include fecaluria, hematuria, UTI, nausea, vomiting, and fever. Peritonitis and sepsis may occur as well. Digital rectal examination often permits palpation of the fistula tract along the anterior rectal wall. Cystoscopy and sigmoidoscopy (Shin et al, 2000) visualize the fistula tract in the vast majority of cases and provide a mechanism for biopsy. In patients with a history of pelvic malignancy, biopsy of the fistula is suggested to evaluate for a local recurrence



Figure 89-53. Rectourethral fistula caused by Crohn disease. Contrast material is seen posterior to the bladder on this voiding image from voiding cystourethrogram. (Courtesy Nancy Curry, MD, Department of Radiology, Medical University of South Carolina, Charleston, SC.)



Figure 89-54. Rectourethral fistula after brachytherapy for carcinoma of the prostate. A retrograde urethrogram demonstrates filling of the rectum in this patient who was seen several years after brachytherapy with fecaluria. The bladder is not opacified. The brachytherapy seeds can be seen in the area of the prostate.

of the tumor (Shin et al, 2000). A VCUG or retrograde urethrogram (RUG) usually provides a definitive diagnosis of RUF (Fig. 89-54). The exact anatomic location and size of the fistula are also usually well delineated on the VCUG or RUG, providing important information in surgical planning. Lateral projections may be necessary to visualize small fistulae, because contrast in the rectum or urethra can sometimes obscure extremely thin fistulous tracts. Upper tract imaging should be performed in patients with RUF to exclude a

related ureteral injury. It is important to make an assessment of continence and sphincteric function in patients with RUF after radical prostatectomy. Given the location of most RUFs at or near the vesicourethral anastomosis and the membranous urethra, there is a risk for persistent severe stress incontinence postoperatively after RUF repair (Ghoniem et al, 2008). In many patients with RUF and severe stress incontinence, closure of the RUF may not be sufficient to bring about continence. Additional procedures may be needed to bring about a satisfactory result in these patients; this is an important issue to discuss in preoperative patient counseling.

Management

Most RUFs will require surgical repair (Bukowski et al, 1995; Stephenson and Middleton, 1996), although it is clear that some will close with conservative management. RUF that follows open or laparoscopic prostatectomy may heal spontaneously with catheter drainage, bowel rest, and intravenous hyperalimentation. In some cases, fecal diversion is necessary. Rassweiler and colleagues (2003) reported that 6 of 8 RUF patients were treated successfully in such a manner. Two patients required a temporary colostomy. Noldus and colleagues (1999) reported closure with conservative management in 7 of 13 patients with RUF after radical prostatectomy or cystoprostatectomy. Successful closure in 6 patients eventually was accomplished with a transanal Latzko procedure (see later). Successful minimally invasive management has been reported, as well, with use of endoscopic suturing, fulguration of the fistula tract, and the application of fibrin glue (Wilbert et al, 1996).

Surgical repair of RUF can be challenging, and the basic tenets of operative fistula repair are especially relevant in these cases (see Box 89-2). Several surgical approaches have been advocated and are outlined later. **Single and staged repairs have been described for the repair of RUF.** The controversy surrounding the staged repair centers on the issue of whether or not to perform fecal diversion at all, or whether to perform it before or at the time of repair of the urinary tract. Some authors have advocated fecal diversion and staged repair of all RUFs (Shin et al, 2000). This is considered the standard conservative approach and, in combination with an indwelling urethral catheter, permits a trial of spontaneous healing of the fistula without open manipulation of the urinary tract. In support of the single-stage repair, a successful one-stage approach limits the potential morbidity and cost of multiple procedures that, by design, accompany the staged repair. **Suggested guidelines for cases in which a one-stage approach might be appropriate include surgically induced, small RUFs not associated with infection, an abscess, or a poor bowel preparation (Wood and Middleton, 1990; Nunoo-Mensah et al, 2008).** Staged repairs might be considered in cases of large fistulae, those associated with radiation therapy, uncontrolled local or systemic infection, immunocompromised states, or inadequate bowel preparation at the time of definitive repair (Stephenson and Middleton, 1996; Nunoo-Mensah et al, 2008).

Transrectal approaches with and without division of the anal sphincter have been described for the operative repair of RUF. The York-Mason procedure is a transrectal, transsphincteric approach that has been found to be effective and to have low morbidity (Henderson et al, 1981; Prasad et al, 1983; Wood and Middleton, 1990; Stephenson and Middleton, 1996; Fengler and Abcarian, 1997; Renschler and Middleton, 2003). Classically, this is a staged repair with fecal diversion performed before repair of the RUF. However, in patients with small, nonirradiated fistulae, a single-stage approach can be used, provided that a vigorous bowel preparation and broad-spectrum antibiotics are used (Renschler and Middleton, 2003). For repair of the urinary tract, the patient is placed prone on the operating room table in the jackknife position. A full-thickness incision through the posterior anus and dorsal rectal wall is performed and deepened down to the level of the coccyx through the external anal sphincter (Fig. 89-55). Care is taken to mark or tag each layer of the anal sphincter as it is divided. Later in the procedure during closure, careful anatomic

reapproximation of the layers of the external anal sphincter is necessary to avoid the devastating complication of anal incontinence postoperatively. The anorectal incision as described provides excellent exposure of the fistula in the anterior rectal wall. The fistula tract is excised, and the anterior rectal wall is mobilized circumferentially around the fistula margins. The urethra is closed, and then the anterior rectal wall is closed. Finally, the rectal mucosa is reapproximated, providing a three-layer closure. Alternatively, after excision of the RUF, an anterior rectal wall flap can be developed and advanced over the fistula (al-Ali and Kashmoula, 1997), similar to the transvaginal repair of VVF using the vaginal wall (see previous discussion under VVF repair). Closure of the incision is performed by reapproximating the posterior rectal wall and then sequentially closing the layers of the anal sphincter in an anatomic fashion. Results with the York-Mason procedure have been excellent. In the largest series of patients undergoing the York-Mason procedure, Renschler and Middleton (2003) reported a successful repair in 22 of 24 patients. One of the two failures was subsequently repaired with another York-Mason procedure. No serious complications were reported, and no patient developed anal incontinence or anal stenosis. Similar excellent results have been noted by other authors (Prasad et al, 1983; Bukowski et al, 1995; Fengler and Abcarian, 1997).

In contrast to the transrectal, transsphincteric approach, the **transanal approach** to RUF repair does not involve division of the anal sphincter. Exposure of the fistula is provided by dilation of the anus and fixed retraction. The Latzko procedure is one such approach (Noldus et al, 1999; Hata et al, 2002). Similar to the Latzko method described previously for transvaginal VVF repair (see prior discussion), the fistula tract and surrounding rectal mucosa are denuded in all four quadrants. The fistula is then closed in three layers. The major disadvantage to this approach is the relatively poor exposure and lack of maneuverability within the operative field. Rectal advancement flaps have also been used to successfully treat RUF through a transanal approach (Fazio et al, 1987; Dreznik et al, 2003; Garofalo et al, 2003).

A **perineal approach** to RUF has been advocated by some authors in selected cases of RUF (Bukowski et al, 1995; Nyam and Pemberton, 1999; Youssef et al, 1999; Zmora et al, 2003). Anatomically, this is a familiar approach for many urologists and has the added advantage of local access to a variety of potential interpositional flaps. Excellent results have been obtained with the perineal approach in combination with an interpositional flap, including gracilis muscle (Ryan et al, 1979; Rius et al, 2000; Zmora et al, 2003; Ghoniem et al, 2008; Gupta et al, 2008), pedicled Dartos muscle (Venable, 1989; Youssef et al, 1999; Yamazaki et al, 2001; Varma et al, 2007), penile skin (Morgan, 1975), levator muscle (Goodwin et al, 1958), and bladder (Kokotas and Kontogeorgos, 1983). Transabdominal approaches to RUF have been described with limited success (Bukowski et al, 1995; Nyam and Pemberton, 1999; Shin et al, 2000). The principal advantage of this technique is the availability of greater omentum for an interpositional flap. Potential disadvantages include the morbidity and prolonged postoperative convalescence associated with a laparotomy incision, poor exposure of the operative field (with limited maneuverability in the deep pelvis), and the risk of urinary and fecal incontinence.

The repair of RUF after external beam radiotherapy (Chrouser et al, 2005), combined radiotherapy (Marguet et al, 2007), brachytherapy (Lane et al, 2006), or cryosurgical ablation of the prostate can be especially difficult (Izawa et al, 2000; Elliott et al, 2006). These fistulae may be large and are associated with considerable induration, fibrosis, and ischemia for a variable distance around the fistula, limiting reconstructive options. Urinary reconstruction may not be possible in some of these cases, necessitating urinary diversion. Moreira and colleagues (2004) reported on 11 cases of RUF after brachytherapy for the treatment of prostate cancer; all of these patients underwent diverting colostomy. Three patients with satisfactory baseline continence underwent primary repair by a York-Mason approach with a gracilis flap; 7 patients underwent urinary diversion combined with radical pelvic surgery (6 cystoprostatectomy, 1 prostatectomy); and 1 refused repair. Izawa and colleagues

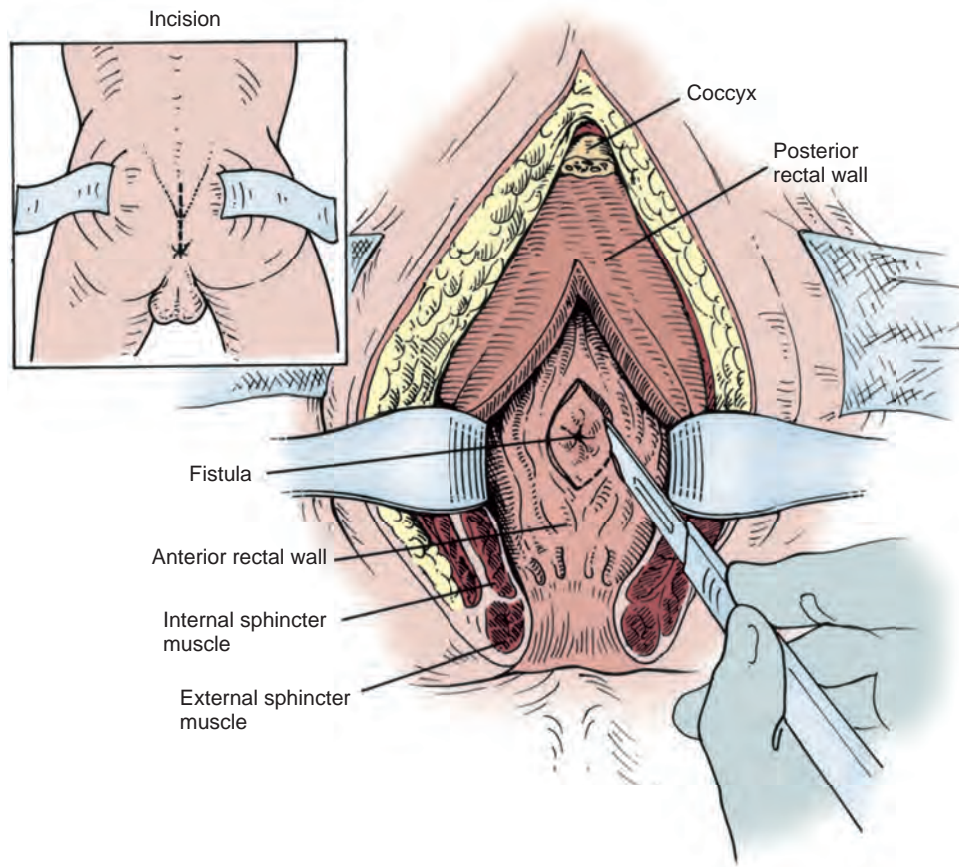


Figure 89-55. Diagram of York-Mason approach to the repair of rectourethral fistula. (From Middleton RG. Rectourethral fistula repair. In: Krane RJ, Siroky MB, Fitzpatrick JM, editors. *Operative urology*. Philadelphia: Churchill Livingstone; 2000. p. 286.)

(2000) reported on the management of severe complications of cryosurgical ablation of the prostate, including two cases of prostatopubic fistulae and one RUF. Two of these patients underwent cystoprostatectomy, and one had a bladder neck closure and continent reconstruction.

KEY POINTS: RECTOURETHRAL FISTULA

- Rectourethral fistula is an uncommon outcome that results most commonly from the surgical treatment of localized prostate cancer.
- Diagnosis of RUF can be confirmed with VCUG.
- Treatment of RUF most commonly involves surgical repair; however, select patients may respond to conservative therapy, including Foley catheter drainage.

UROVASCULAR FISTULAE

Fistulae between the urinary tract and the vascular system are rare but have increased in frequency with the rapid integration of minimally invasive interventions in the upper urinary tract, such as percutaneous access procedures (Clayman et al, 1984; Segura et al, 1985) and indwelling ureteral stents (Kar et al, 1984; Smith, 1984; Teuton et al, 1987; Sacks and Miller, 1988; Cass and Odland, 1990). These fistulae include communications between the upper urinary tract, including the collecting system or ureter, and an artery or vein.

Renovascular and Pyelovascular Fistulae

The most common causes of renovascular or pyelovascular fistulae are procedures in which percutaneous renal access is required, such as PCNL (Clayman et al, 1984; Segura et al, 1985; Lang, 1987; Lee et al, 1987). Typically, these fistulae are created through puncture of an intrarenal vascular structure during creation or dilation of the nephrostomy tract. The damaged vessel may bleed on puncture or may not hemorrhage immediately owing to external compression and tamponade from the catheter in the nephrostomy tract. However, on removal of the catheter, brisk bleeding may be noted into the relatively lower-pressure renal collecting system (Patterson et al, 1985). Alternatively, a long-term indwelling nephrostomy tube may lead to pyelovascular fistula formation. In this setting, a chronic indwelling large-bore nephrostomy tube may result in erosion into an adjacent renal vessel with resulting hemorrhage on removal of the tube. Lee and colleagues (1987) reported an 11.2% incidence of bleeding requiring transfusion and 1.2% incidence of bleeding requiring surgical or angiographic intervention after PCNL in 582 patients. Patterson and colleagues (1985) reported a vascular injury in 0.9% of 1032 patients undergoing percutaneous renal stone surgery. Segura and colleagues (1985) reported a 3% transfusion rate in 1000 patients undergoing PCNL. Other causes of renovascular fistula include external penetrating and blunt trauma (Stower et al, 1989), infection, and open renal surgery, including partial nephrectomy.

Patients with renovascular fistulae may have life-threatening hemorrhage and hypovolemic shock, or intermittent gross hematuria. After PCNL these fistulae may appear on removal of the nephrostomy tube with brisk bleeding out of the flank from the

nephrostomy tube tract in combination with brisk hematuria, or they may manifest several days to weeks later with only hematuria (Clayman et al, 1984; Patterson et al, 1985).

Treatment of renovascular fistulae is contingent on the presentation, cause, and hemodynamic stability of the patient. Patients with severe hemorrhage on removal of the nephrostomy tube can be temporized in some instances by replacing the tube, or, in large mature tracts, by placing a Foley catheter to tamponade the bleeding. In patients with ongoing bleeding, transcatheter angiographic embolization of the lacerated vessel is recommended (Clayman et al, 1984; Patterson et al, 1985). Occasionally, flank exploration is necessary with partial or simple nephrectomy to control hemorrhage.

Uterovascular Fistula

Rarely reported before the advent of indwelling ureteral stents, uterovascular fistulae are becoming increasingly common. Most reported uterovascular fistulae are ureteroiliac artery fistulae, although ureteroiliac vein fistulae have been reported as well (Teuton et al, 1987). Ureteroarterial fistulae are extremely rare, with few cases reported in the literature (Holmes et al, 1998; Georgopoulos et al, 2003).

Most cases of ureteroarterial fistulae are reported in patients with a prior history of vascular disease, radiation therapy, and/or pelvic surgery, especially in the setting of indwelling ureteral stents. In fact, ureteroarterial fistulae are highly associated with indwelling stents (Nelson and Fried, 1981; Kar et al, 1984; Smith, 1984; Bhargava and Yusuf, 1987; Sacks and Miller, 1988; Cass and Odland, 1990; Batter et al, 1996; Bergqvist et al, 2001). Of the 37 cases of ureteroarterial fistula before 1996 reported in the literature by Batter and colleagues (1996), 24 were associated with a ureteral stent (Table 89-8 on the Expert Consult website). All patients in this review had at least one of the risk factors listed in Table 89-8 on the Expert Consult website. Pressure necrosis from a chronic, relatively inflexible indwelling stent against a pulsatile iliac artery may be an important factor in the development of ureteroarterial fistulae in some cases (Batter et al, 1996). Fistula formation occurs between the high-pressure vascular lumen and the low-pressure ureter with the development of gross hematuria. A history of radiation therapy or prior pelvic surgery may exacerbate the already compromised and stented ureter, thus increasing the risk of fistula formation (Toolin et al, 1984). Ureteroarterial fistulae are also highly associated with vascular pathology such as iliac artery aneurysms. Atherosclerotic aneurysms may produce perivascular inflammation and fibrosis that entraps the overlying ureter, especially in the region of the iliac vessels. The ureter may become fixed and obstructed and in such a position may be subject to chronic pulsations from the underlying abnormal vessel. Placement of a ureteral stent to relieve the obstruction may further compromise the ureteral wall where it crosses over the vessel, resulting in pressure necrosis and eventual fistula formation (Sacks and Miller, 1988; Cass and Odland, 1990). Ureteroarterial fistulae have been reported after balloon dilation of ureteral strictures (Sacks and Miller, 1988; Quillin et al, 1994). Ureteroarterial fistulae may also occur in the setting of ileal conduit reconstruction, pelvic malignancy, prior ureterolithotomy, external penetrating trauma, and pregnancy (Reiner et al, 1975; Cass and Odland, 1990; Dervanian et al, 1992; Puppo et al, 1992; Wampler et al, 1992; Batter et al, 1996; DePasquale et al, 2001; Siablis et al, 2002; Takahashi et al, 2004).

Uterovascular fistulae may manifest with microscopic hematuria, intermittent gross hematuria, or life-threatening exsanguinating hemorrhage. The key to the diagnosis of ureteroarterial fistulae is a high index of suspicion in an at-risk patient with gross hematuria (Smith, 1984; Dervanian et al, 1992; Batter et al, 1996). These fistulae are rarely considered in the initial differential diagnosis of gross hematuria. Intermittent gross hematuria or the sudden onset of massive hematuria in a patient with an indwelling stent and a history of previous iliac artery surgery or radiation should raise the suspicion of a ureteroarterial fistula (Cass and Odland, 1990).

The routine urologic and radiologic evaluation of hematuria will not generally provide evidence of ureterovascular fistula (Quillin et al, 1994). Even in suspected or proven cases, preoperative radiologic investigations, including nonselective arteriography and pyelography, are often nondiagnostic (Cass and Odland, 1990; Batter et al, 1996). This is especially true in patients with intermittent hematuria in whom there is no active bleeding at the time of the radiographic investigation, presumably because of thrombus over the site of the fistula. Selective or subselective arteriography of the iliac vessels may be more revealing in suspected cases, and provocative maneuvers, such as stent removal, or mechanical friction of the ureteral lumen by manipulation of the stent may be necessary to demonstrate the fistulous connection in patients without active bleeding who are undergoing angiography (Keller et al, 1990; Quillin et al, 1994). However, these adjuvant maneuvers should be performed only with extreme caution in an appropriate setting where immediate angiographic or surgical intervention is possible. In the review by Batter and colleagues (1996), retrograde pyelography was diagnostic for only 6 of 10 patients in whom it was performed, and arteriography was diagnostic for a ureterovascular fistula in only 4 of 14 cases. Indirect evidence of a ureteroarterial fistula can be found on CT, but findings are usually nonspecific and only suspicious in retrospect after a confirmed diagnosis achieved by other means (Baum et al, 1987; Jafri et al, 1987). Nevertheless, in a stable patient with a suspected ureterovascular fistula, a full radiographic evaluation may be pursued, not only for diagnostic purposes but also to evaluate potential reconstructive options (Batter et al, 1996) and, in select cases, to perform therapeutic angiographic embolization procedures.

Because these patients may be in extremis with hypotension and severe hemorrhage, surgical intervention must be considered early, especially because radiographic evaluation may be nondiagnostic (Dervanian et al, 1992). In cases in which angiography is pursued for diagnosis, an endovascular stent graft may be placed (Bergqvist et al, 2001; Sherif et al, 2002; Krambeck et al, 2005; Meester et al, 2006; Muraoka et al, 2006; Ishibashi et al, 2007; Araki et al, 2008).

Eventual management of these fistulae must address both the vascular and the urinary sides of the fistula. Successful management of the vascular side may involve embolization, endovascular stent graft placement, primary repair (Kar et al, 1984), or even ligation with or without extra-anatomic vascular bypass. Limb salvage is an important consideration in iliac artery fistulae, and therefore vascular surgery consultation is necessary in most cases. Ultimate management of the vascular side of the fistula is dependent on several factors, including the presence of infection or abscess, presence of aneurysm or occlusive disease in the iliac artery, and the availability of collateral circulation to the ipsilateral lower extremity (Batter et al, 1996). Often, vascular occlusion, either angiographically or surgically, is followed by vascular bypass procedures in these cases. A systematic literature review found reports of 139 cases of ureteroarterial fistula published from 1899 to 2008 (van den Bergh et al, 2009). All patients had hematuria, with 25% also having other urinary symptoms or back pain. Virtually all patients had a relevant past surgical history, particularly pelvic cancer surgery (54%) and arterial surgery with graft insertion (31%), and 61% had a ureteric stent in situ. The great majority affected the iliac segment, and preoperative imaging was not always diagnostic. A total of 18 (13%) patients died as a result of the fistula. Many vascular and urologic interventions were used either alone or in combination. Later cases suggested that endovascular repair of the arterial defect gave the best results with lower mortality. Another, more recent case series of 20 patients also showed a high mortality of 10% to 20% but did not find any difference in outcome between open or endovascular graft insertion techniques (Fox et al, 2009).

Repair and reconstruction of the urinary tract is complicated in these patients, who often have a history of pelvic irradiation, malignancy, vascular disease, and/or prior surgery. Preservation of nephrons is a priority in functioning renal units. Urinary

TABLE 89-8 Predisposing Risk Factors in 37 Patients with Ureteroarterial Fistulae

Prior genitourinary or pelvic surgery	68%
Ureteral stenting	65%
Radiation therapy	46%
Prior vascular surgery	19%
Vascular pathology	19%

From Batter SJ, McGovern FJ, Cambria RP. Ureteroarterial fistula: case report and review of the literature. *Urology* 1996;48:481–9.

reconstruction can be performed by ureteroureterostomy, trans-ureteroureterostomy, cutaneous ureterostomy, or percutaneous nephrostomy with ureteral ligation (Nelson and Fried, 1981; Kar et al, 1984; Smith, 1984; Batter et al, 1996; Gibbons et al, 1998). Nephrectomy is usually reserved for poorly functioning kidneys or for patients unfit for urinary reconstruction.

General recommendations to prevent ureteroarterial fistulae include the use of the smallest, softest, and most flexible ureteral stents for the shortest time interval possible in patients at risk for ureterovascular fistula (Cass and Odland, 1990; Puppo et al, 1992).

KEY POINTS: UROVASCULAR FISTULAE

- Pyelovascular fistulae most commonly result from percutaneous interventional procedures to the upper urinary tract.
- Patients with suspected ureteroarterial fistulae usually have one or more risk factors including a history of pelvic radiotherapy, indwelling ureteral stents, prior pelvic surgery, and/or vascular disease.
- Ureteroarterial fistulae are difficult to diagnose radiographically with standard imaging, including CT scan and retrograde pyelography.
- Patients suspected of having a ureteroarterial fistula based on history and the presence of significant risk factors should be treated expeditiously and aggressively on presentation.

OTHER URINARY FISTULAE

Urinary fistulae have been reported between the kidneys and thoracic cavity with a number of causes, including infection, trauma, and stone disease. Infectious causes include xanthogranulomatous pyelonephritis, TB, and renal abscess (Arida and Verderame, 1977; Blight, 1980; Kyriakopoulos et al, 1991; Haney et al, 1992; Alifano et al, 1999). Fortunately, nephropleural and nephrobronchial fistulae are uncommon. Of importance, percutaneous access to the kidney for endourologic procedures may be complicated by nephropleural fistula. Lallas and colleagues (2004) reported a 1% incidence of nephropleural fistulae in 375 patients undergoing percutaneous access procedures. All of the affected patients had a supracostal access tract performed; none of the patients with a subcostal access tract developed this complication. Presenting symptoms may include cough, a urine-like taste in the mouth, fever, and flank pain. Rarely, recurrent lung abscess may be a manifestation of an occult nephropleural fistula (Caberwal et al, 1977; O'Brien and Ettinger, 1995).

Treatment of nephropleural or nephrobronchial fistulae typically involves percutaneous drainage of any associated abscess (if present), treatment of associated infection, and/or urinary obstruction, and surgical exploration with interposition of healthy tissue. Iatrogenic fistulae resulting from percutaneous access procedures can be managed nonoperatively in some cases (Lallas et al, 2004). For patients undergoing surgical exploration, a double-lumen endotracheal tube may be useful during surgery to isolate the affected lung and pleural cavity and prevent contamination of the contralateral side (Rao et al, 1981). Nephrectomy is indicated in poorly functioning renal units.

Cutaneous fistulae from the urinary tract may arise from the kidney, ureter, bladder, or urethra. Renocutaneous fistulae may occur as a result of chronic infection, especially in the setting of calculous disease (Haney et al, 1992). Often the associated renal unit is poorly functioning, and thus definitive treatment is provided by nephrectomy. External trauma or iatrogenic surgical trauma, such as percutaneous renal surgery or partial nephrectomy, may also result in a renocutaneous fistula. Prompt treatment with internal ureteral stenting is usually successful by providing unobstructed antegrade urinary drainage. Most ureterocutaneous and vesicocuta-

neous fistulae are iatrogenic or otherwise purposefully surgically created to facilitate urinary drainage. Other uncommon causes include external penetrating trauma, malignancy, and chronic infection.

For newly diagnosed urocutaneous fistulae, it is imperative to evaluate for distal urinary obstruction. If present, the obstruction should be treated, if possible, or bypassed. Individuals with non-healing urocutaneous fistulae caused by chronic infection not only should be evaluated for an occult source of the infection, but also should undergo a nutritional evaluation because these individuals may be catabolic, immunosuppressed, and unable to mobilize adequate metabolic reserves to initiate wound closure. Other considerations in individuals with nonhealing urocutaneous fistulae include occult malignancy or an undiscovered foreign body.

Urethrocuteaneous fistulae in the male most commonly are seen as sequelae of hypospadias repair and are covered in Chapter 130.

Urinary Leak after Renal Preservation Surgery

A large case series identified urinary fistula, defined as urinary drainage from a drain site more than 14 days postoperatively, in 4% (45 of 1118) of patients undergoing partial nephrectomy (Kundu et al, 2010). This was associated with larger tumors, greater blood loss, and longer ischemia time, but not the mode of surgery (laparoscopic vs. open). The majority resolved without intervention, but 30% required ureteral stent insertion or percutaneous drainage. A poor-quality quasi-randomized study involving 16 patients with persistent leakage after pelvic cystectomy despite stenting found that use of intranasal desmopressin 40 µg daily resulted in a shorter time to resolution of leak compared with controls (Razzaghi et al, 2009).

Urinary Leak after Renal Transplantation

A case series from Brazil observed a fistula rate of 3.0% (31 of 1046) at a mean of 28 (1 to 131) days after transplantation, predominantly as a result of distal ureteral necrosis and with most cases requiring open repair (Mazzucchi et al, 2006). Fistula occurred more commonly in patients with diabetes and was associated with lower graft survival and 2 deaths from sepsis. A case series from China observed fistula development in 3.5% (43 of 1223) of patients at a mean of 6 (range 3 to 20) days after transplantation, again primarily a result of necrosis of the distal transplanted ureter (Nie et al, 2009). Open intervention with reimplantation of the ureter into the bladder or native ureter was required in 34 patients, with 1 other patient requiring transplant nephrectomy. The occurrence of a fistula did not appear to prejudice graft or patient survival. Initial implantation of the transplant ureter into the native ureter appeared to result in a lower rate of fistula. A further case series from Serbia found a fistula rate after renal transplantation of 2.2% (5 of 224), and all required open repair (Basić et al, 2011).

Radiation Fistula

Injury to the GI or urinary tract may arise after therapeutic radiation, with the incidence of complications increasing when the dose exceeds 50 Gy. The obliterative endarteritis associated with ionizing radiation in therapeutic doses may proceed over many years and may result in fistula formation long after the primary malignancy has been treated (Zoubek et al, 1989; Hilton, 2012). The associated devascularization in the adjacent tissues means that conventional surgical repair has a high likelihood of failure and may also result in re-presentation with several fistulae over a period of many years. If abdominal repair surgery or urinary diversions are undertaken, a high risk of GI anastomotic leak and progressive sepsis has been reported, perhaps related either to inadequate resection of irradiated bowel or to damage to other organs at operation (Cochrane et al, 1981). All these factors often make the management of post-radiation fistulae more challenging than that of postsurgical or even obstetric fistulae. Modified surgical techniques are often required, and indeed, where the same techniques have been applied to both

surgical and postradiation fistulae, the results from the latter have been consistently poorer (Hedlund and Lindstedt, 1987; Langkilde et al, 1999; Jovanovic et al, 2010). Spontaneous healing seems rarely if ever to occur (Ralph et al, 1990; Hilton, 2012) and only one case report was identified, of presentation of a radiation fistula 22 years after initial treatment, in which healing occurred after cauterization (for biopsy) and prolonged catheter drainage (Madjar and Gousse, 2001).

Diversion Procedures

Because of the wide field abnormality surrounding many radiotherapy-associated fistulae, several authors have suggested that urinary and/or fecal diversion should be seen as the treatment of choice in such cases (Jones et al, 1984; Krause et al, 1987; Emmert and Kohler, 1996; Langkilde et al, 1999). Others have employed a routine policy of preliminary urinary and fecal diversion, with later undiversion in selected cases (Vanni et al, 2010). In a nonrandomized cohort of rectourethral fistula repairs, Vanni and colleagues reported 100% closure at first operation in 35 nonirradiated patients, compared with 84% in 39 irradiated patients (Vanni et al, 2010). In addition, 97% of the nonirradiated patients subsequently underwent undiversion, whereas 31% of the irradiated patients required permanent fecal diversion because of a noncompliant rectum or severe sphincter dysfunction (Vanni et al, 2010).

Some authors have emphasized the place of repair in carefully selected cases of radiotherapy-associated fistulae (Hilton, 2012). Of 36 radiation-associated or malignant fistulae in the series reported by Hilton, although 11 patients declined surgery or died before treatment and 6 underwent primary diversion, of the 19 (53%) who underwent repair, closure was achieved in 18 (95%) at first operation (Hilton, 2012). Finally, some authors seem to take the view that diversion has little or no place in the management of radiation-induced VVF in particular (Pushkar et al, 2009). Of 216 radiation-induced fistulae managed over a 47-year period by Pushkar and colleagues, 210 patients underwent a vaginal and 6 an abdominal repair procedure (it should be noted that this is a retrospective case series, and although not stated in the paper, it is possible that other patients not included in this review actually underwent diversion) (Pushkar et al, 2009). It should be noted, however, that with this almost exclusive use of the vaginal repair procedure, although a cumulative closure rate of 80% was eventually achieved after four or more operations, closure was achieved in only 48% after first repair, in 40% after a second operation, in 52% after a third operation, and in 35% after a fourth operation.

In view of the anastomotic problems associated with radiation-induced fistula, the transverse colon has often been favored over ileum as a conduit in this context, to avoid the risk of employing irradiated bowel and distal ureter (Schmidt et al, 1975; Kisner and Kesner, 1987; Ravi et al, 1994). Although these benefits seem clear, it should be noted that high perioperative morbidity (37%) and reoperation rates (20%) have been reported from this procedure (Ravi et al, 1994).

As an alternative to the latter operation, wherein both urinary and fecal diversion are proposed, Hampson and colleagues described the technique of left colic urinary diversion with distal transverse end colostomy (Hampson et al, 1994). This technique allows a shorter operative time and avoids the necessity for an intestinal anastomosis. In patients wishing to remain sexually active after such procedures, the residual bladder or rectal wall may be used to augment the vagina (Leissner et al, 2000). Where VVF coexists with significant bladder contracture after surgery or radiation, an abdominal (transperitoneal) repair might be considered, along with simultaneous ileocystoplasty (Hsu et al, 2002; Tabakov and Slavchev, 2004) or colocystoplasty (Kulkarni and Gulla, 1998). Fistula repair performed concurrently with vaginal reconstruction using sigmoidovaginoplasty has also been described by Verbaeys and colleagues (2007). Although one might anticipate very high operative and postoperative morbidity from such complex multiple procedures, the outcome in the very small numbers reported appears to have been good.

Repair Techniques

Several different techniques for the vaginal repair of fistulae have been reported, although the methods of flap-splitting or dissection and repair in layers (variously attributed to Hayward, Collis, and Lawson Tait) (Wall, 2005) and partial colpocleisis (Latzko, 1942) have been the most widely advocated in radiation-associated fistulae. When patients do not wish to maintain sexual function, complete colpocleisis may be used to good effect (Hilton, 2012). In a nonrandomized cohort study, Hilton reported anatomic closure by colpocleisis in 94.7% of patients with radiation-associated fistulae, compared with 96.1% for a range of repair procedures in fistulae of surgical cause (Hilton, 2012).

The technique of sigmoid exclusion or isolation has been described for the management of radiation-associated colovesical or enterovesical and colovaginal or enterovaginal fistulae (Aitken and Elliot, 1985; Levenback et al, 1994). Although the results have generally been good, with the avoidance of a permanent urinary or fecal stoma, Levenback and colleagues reported poorer results than after resection of the affected bowel, largely related to bleeding from the isolated segment and bacterial infection (Levenback et al, 1994).

The interpositional grafts mentioned earlier are particularly useful in radiation-induced fistula.

Please see the Expert Consult website for further details.



Other Management Approaches

In patients with intractable urinary incontinence from radiation-associated fistula, percutaneous nephrostomy or ureterostomy might be considered (Krause et al, 1987). This may in some cases extend life perhaps inappropriately, and where life expectancy is deemed to be very short, ureteral occlusion might be more appropriate. Several methods have been described, including the insertion of coils (Amsellem-Ouazana et al, 2006), coils with gelatin sponge (Farrell et al, 1997; Gaylord and Johnsrude, 1989), clips (Farrell et al, 1997), nylon plugs with injection of polidocanol (Kinn et al, 1986), isobutyl-2-cyanoacrylate (Schild et al, 1994), and balloons (Papanicolaou et al, 1985; Sanchez et al, 1988; Schild et al, 1994; Horenblas et al, 2000). These were reviewed by Avritscher and colleagues with success rates ranging from 50% to 100% for the different methods, and with an overall success rate of 77% in 150 cases from nine papers reviewed (Avritscher et al, 2004).

Recommendations

Although diversion is used more widely in radiation-associated fistulae of all types as compared with nonirradiated fistulae, there is low-level evidence that repair procedures can achieve successful fistula closure and continence in appropriately selected cases.

Where urinary and/or fecal diversions are required, attempts should be made to avoid using irradiated tissues whenever possible and to minimize the potential for anastomotic complications.

There is low-level evidence to support the use of interpositional grafts when repair of radiation-associated fistula is undertaken.

In patients with intractable urinary incontinence from radiation-associated fistula in whom life expectancy is very short, ureteral occlusion might be considered; there is insufficient evidence to recommend any particular technique.

KEY POINTS: OTHER FISTULAE

- Nephropleural or nephrobronchial fistulae are uncommon and may occur secondary to percutaneous access procedures to the upper urinary tract.
- Urocutaneous fistulae may originate from multiple locations within the urinary tract.

Several techniques have been described to reinforce fistula repair in different sites depending on the type of repair undertaken. These include the Martius bulbocavernosus muscle and labial fat graft, a gracilis muscle or myocutaneous graft, omental pedicle grafts, and peritoneal flaps. Although there is no high-level evidence to support the use of these techniques, the interposed tissue has been presumed to help by creating an additional layer in the repair, to fill in “dead space” and reduce the risk of hematoma formation beneath the repair, to bring in a new blood supply into the area, and to reduce scarring. For each of these hypotheses, interpositional grafts might be considered to have their greatest benefit in the repair of radiation-associated fistulae.

At abdominal repair of vesicovaginal or rectovaginal fistulae, the use of a pedicled omental graft has been widely advocated (Kiricuta and Goldstein, 1972; Turner-Warwick, 1976). The omentum is dissected from the greater curve of the stomach and rotated down into the pelvis on either the right or left gastroepiploic artery; this technique may be used for any transperitoneal procedure but has its greatest potential advantage in radiation-associated fistulae.


The role of interpositional flaps in transabdominal repair procedures was reviewed by Evans and colleagues (2001). They reported 37 patients with fistulae of largely surgical cause, of whom 12 of 12 treated with an omental or peritoneal interpositional flap were cured, compared with 16 of 25 managed without interposition (64%); this finding was consistent for fistulae of both benign and malignant etiology. Although their cases were not randomized and the authors acknowledge that their overall cure rate (75%) was rather lower than in many series, nevertheless they concluded that an interpositional flap should be recommended when a transabdominal repair is undertaken, particularly when the repair is performed by a less experienced surgeon.

Although the Martius graft was widely employed in the context of obstetric fistula repair in the past, there is no high-level evidence to support its use in this context, and there seems to be a general move away from it among obstetric fistula surgeons. One small nonrandomized cohort study reported benefit in patients with multiple or recurrent fistulae, based on a univariate analysis (Rangnekar et al, 2000); another reported no advantage to the experienced obstetric fistula surgeon (Browning, 2006). In the series of fistulae of all causes from the United Kingdom reported by Hilton, the fistula closure rate was not significantly different between procedures in which an interpositional graft (omental or labial) was (92.0%) or was not (96.1%) used in the repair ($P = .264$; Fisher's exact test) (Hilton, 2012).

In the situation of vaginal repair of radiation-associated fistula, Pushkar and colleagues strongly advocated the use of the labial fat graft interposed at fistula repair (Pushkar et al, 2009). Hilton advocated its use to fill dead space in the lower vagina at complete colpocleisis (Hilton, 2011). With the former technique, closure at first operation was 48% (Pushkar et al, 2009); with the latter, 95% closure at first operation has been described (Hilton, 2012).

Labial skin grafts have also been employed in the repair of radiation-associated fistulae, either interpositional tissue or as a replacement for sloughed or indurated vaginal skin. Labia minora flaps with the outer surface de-epithelialized (Bizic et al, 2010) and labia majora flaps (Lai and Chang, 1999; Stanojevic et al, 2010) have both been described in this context.

Muscle and myocutaneous grafts have also been employed as interpositional tissue in fistula repair. These tend to be very bulky grafts and are perhaps best used, therefore, in circumstances of extreme tissue loss. The technique of rectus abdominis flap interposition was described in one series of 10 patients, although none of these cases were radiotherapy related (Tran et al, 1999). Viennas and colleagues reported one case of a radiation-induced VVF repair by this technique (Viennas et al, 1995). Gracilis muscle along with selective use of a buccal mucosal overlay graft has been used in rectourethral fistulae, with 84% cure in radiation-associated cases (Vanni et al, 2010).

 Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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Bladder Diverticula

BLADDER DIVERTICULA

The term *bladder diverticulum* is usually reserved for the finding of a subjectively large herniation of the bladder urothelium through the muscularis propria of the bladder wall. This results in a thin-walled, urine-filled structure adjacent to and connecting with the bladder lumen through a variably sized neck, or ostium. Histologically the diverticulum wall is composed of mucosa, subepithelial connective tissue or lamina propria, some scattered thin muscle fibers, and an adventitial layer (Fig. 90-1) (Peterson et al, 1973; Gil-Vernet, 1998). A fibrous capsule or pseudocapsule outer shell is often present and may be a useful surgical plane for excision (see later discussion). The outside wall of the bladder diverticulum often contains some residual scattered strands or bundles of smooth muscle; however, these are disorganized and nonfunctional. Therefore bladder diverticula generally empty poorly during micturition, leaving a large postvoid residual urine volume that results in the characteristic findings on presentation and imaging.

Classification, Pathophysiology, and Etiology

Bladder diverticula may occur in both adults and children but overall approximately 90% of bladder diverticula occur in adults (Psutka and Cendron, 2013). In addition, these lesions are far more common in males than females, with a ratio of approximately 9:1 in both the adult and pediatric age groups (Idrees et al, 2013).

Bladder diverticula may be classified as either congenital or acquired. Pathophysiology, presentation, clinical implications, and imaging may differentiate these two types. Congenital diverticula usually present during childhood, with a peak incidence in those less than 10 years old (Boechat and Lebowitz, 1978). These are usually solitary, occur most commonly in males (Stage and Tank, 1992; Sarihan and Abes, 1998; Evangelidis et al, 2005; Garat et al, 2007; Idrees et al, 2013), and are located lateral and posterior to the ureteral orifice, often in association with vesicoureteral reflux (Evangelidis et al, 2005; Garat et al, 2007; Psutka and Cendron, 2013). In contrast to adults, in whom coexistent lower urinary tract neurogenic dysfunction or obstruction is almost always present, the primary causation in the pediatric age group is generally thought to be a congenital weakness of the detrusor muscle, most often at the level of the ureterovesical junction with or without coexistent lower urinary tract abnormalities (Johnston, 1960; Hutch, 1961; Hutch et al, 1961; Stephens, 1979; Psutka and Cendron, 2013). Approximately 90% of pediatric or congenital bladder diverticula occur in the vicinity of the ureterovesical junction (Psutka and Cendron, 2013). Congenital bladder diverticula may occur in the presence of normal voiding dynamics in the absence of bladder outlet obstruction (Cendron and Alain, 1972; Barrett et al, 1976; Blane et al, 1994); however, up to 60% of congenital bladder diverticula may be associated with an underlying syndrome, neuropathic voiding dysfunction, or outlet obstruction

Female Urethral Diverticula

(Blane et al, 1994). Blane and colleagues (1994) reported the incidence of bladder diverticula in children to be approximately 1.7% in a pediatric genitourinary database of more than 5000 cases. Congenital bladder diverticula are usually relatively larger in comparison with those associated with obstruction or neurogenic bladder dysfunction (Gearhart, 2002).

The most common presentation of congenital bladder diverticula is acute urinary tract infection (UTI) resulting from stasis (Bauer and Retik, 1974; Pieretti and Pieretti-Vanmarcke, 1999; Evangelidis et al, 2005; Garat et al, 2007). Less common presentations include enuresis, pyelonephritis, acute retention, and stones. Notably, secondary bladder outlet obstruction may occur when the diverticulum extends distally toward the bladder neck (Taylor et al, 1979; Epstein et al, 1982; Verghese and Belman, 1984; Oge et al, 2002). Typically, congenital bladder diverticula are found in smooth-walled bladders and are not associated with significant trabeculation on cystoscopic examination (Hutch, 1961). In patients with prune-belly syndrome or posterior urethral valves, bladder diverticula may be located at the dome and be associated with aberrant voiding dynamics and/or anatomy. These are to be distinguished from the urachal diverticula seen in some pediatric urologic conditions. Importantly, unlike secondary or adult bladder diverticula, there is virtually no increased association with malignancy in congenital diverticula (Tamas et al, 2009; Alexander et al, 2012; Idrees et al, 2013).

Congenital bladder diverticula have been noted in association with a number of congenital syndromes, including Menkes syndrome (kinky hair or copper deficiency syndrome) (Harcke et al, 1977; Daly and Rabinovitch, 1981), Williams syndrome (Babbitt et al, 1979; Blane et al, 1994; Schulman et al, 1996), Ehlers-Danlos syndrome (Breivik et al, 1985; Levard et al, 1989; Schippers and Dittler, 1989; Rabin et al, 1991; Bade et al, 1994; Cuckow et al, 1994; Burrows et al, 1998), and fetal alcohol syndrome (Lewis and Woods, 1994). Whether there is a genetic predisposition to the formation of bladder diverticula in individuals without congenital syndromes is unclear, although congenital bladder diverticula have been reported in twins (Beall and Berger, 1978) and possibly as an autosomal dominant trait in a family (Hofmann et al, 1984). Because of the association of congenital bladder diverticula with genetic syndromes, it has been suggested that chromosomal testing should be pursued in such patients (Blane et al, 1994); however, this testing is generally not recommended in children with a single simple lesion (Psutka and Cendron, 2013).

Acquired (also termed "secondary") diverticula occur most commonly in the setting of bladder outlet obstruction or neurogenic vesicourethral dysfunction. Similar to the congenital type, these diverticula are located most commonly at the ureterovesical hiatus (Van Arsdalen and Wein, 1992) but also occur elsewhere in the bladder. Acquired diverticula in males usually occur after age 60, which corresponds to the age of the development of prostatic enlargement (Fig. 90-2). Bladder outlet obstruction (including that

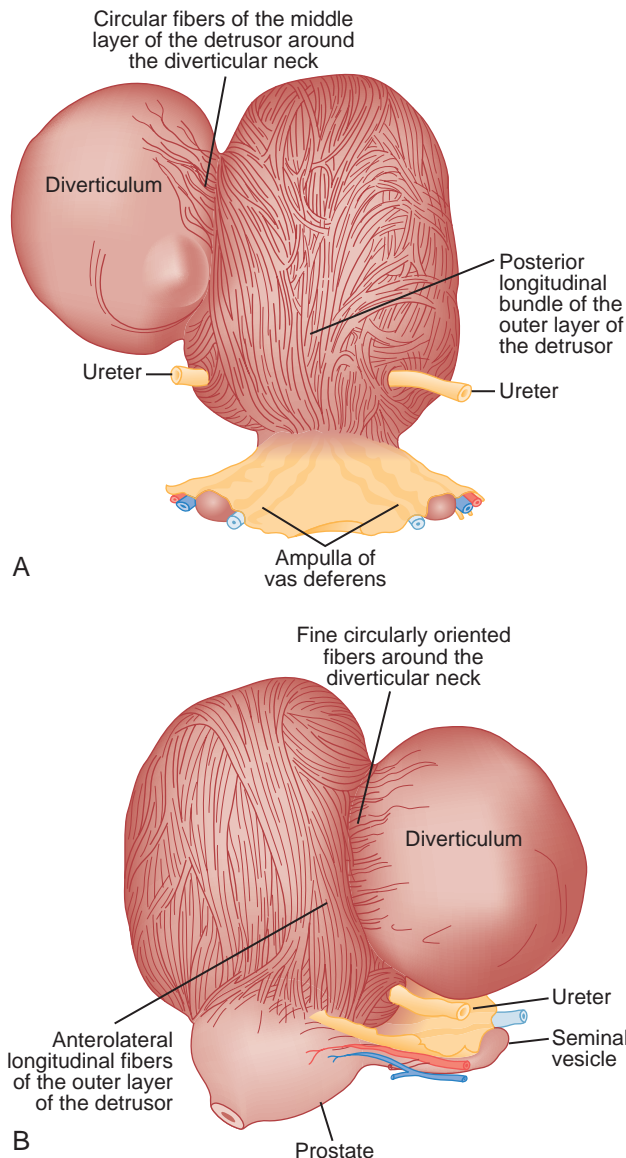


Figure 90-1. Drawing of bladder diverticulum. A, Posterior view. B, Lateral view.

resulting from benign and malignant disease of the prostate), bladder neck obstruction (bladder neck hypertrophy, bladder neck contracture, etc.), and urethral stricture are commonly associated factors in adults, although obstruction is not considered to be present in all cases (Blacklock et al, 1983). Approximately 70% of bladder diverticula are associated with benign prostatic hyperplasia (Gerridzen and Futter, 1982). Historically, the reported prevalence of moderate- to large-sized bladder diverticula in association with “prostatism” is approximately 1% to 6% (Burns, 1944). Acquired diverticula are often multiple, typically found in association with significant bladder trabeculation (Wesselhoef et al, 1963), and much more common in males than females (Senger et al, 1952; Pool and Hacker, 1966). Bladder diverticula in females are relatively uncommon and often associated with bladder outlet obstruction (Gillon et al, 1988). When found in the female, careful evaluation of the bladder outlet will often reveal a cause for obstruction such as dysfunctional voiding, vaginal prolapse, bladder neck hypertrophy, urethral stricture, or iatrogenic obstruction resulting from anti-incontinence surgery (Safir et al, 1998) (Fig. 90-3). It is important to note that acquired bladder diverticula may also be found in children and young adults secondary to a number of conditions, including bladder neck dysfunction, posterior urethral valves, and neurogenic vesicourethral dysfunction. If the diverticu-

lum is located superolateral to the ureteral orifice, without involving the trigone in the setting of a neuropathic bladder and vesicoureteral reflux, it is termed a “Hutch” diverticulum, named after the individual who described this finding in a series of paraplegic individuals (Hutch, 1952). These diverticula may also occur in the setting of dysfunctional voiding.

Bladder diverticula may also be iatrogenic (Hernández et al, 1997; Suzuki et al, 2002; Chertin and Prat, 2008). Inadequate closure of the muscular layers of the bladder wall following a cystotomy for any indication may result in formation of a bladder diverticulum at a weak point of the suture line. “Iatrogenic” bladder diverticula may also occur following ureteral reimplantation surgery at the ureteroneocystostomy site (Ahmed and Tan, 1982; Sheu et al, 1998).

Diagnosis

Presentation and Evaluation

Acquired bladder diverticula do not typically produce specific symptoms and are most often found incidentally in the evaluation of other signs and symptoms, especially UTI. Because large bladder diverticula empty poorly or incompletely during voiding, symptoms and signs, if present, are usually attributed to urinary stasis within the diverticulum or, alternatively, to its mass effect in the lower abdomen and pelvis. Retrospectively, when queried, patient symptoms such as incomplete bladder emptying, lower abdominal fullness, and double voiding may be attributed to some large bladder diverticula. These symptoms, however, are nonspecific and can be due to prostatic enlargement, obstruction, or a number of other lower urinary tract conditions. Most bladder diverticula are found during the investigation of nonspecific lower urinary symptoms, hematuria, or infection—or, alternatively, noted incidentally during radiographic or endoscopic investigation of these conditions. As noted previously, congenital bladder diverticula most often present with UTI (Bauer and Retik, 1974; Pieretti and Pieretti-Vanmarcke, 1999; Evangelidis et al, 2005; Garat et al, 2007), but hematuria, abdominal pain, or an abdominal mass may be present as well. Inguinal hernias containing bladder diverticula have also been reported (Scardino and Upson, 1953; Bolton and Joyce, 1994; Buchholz et al, 1998; Schewe et al, 2000).

UTI in the male has been associated with bladder diverticula, because it is often an infection in a male that provides the impetus for further clinical investigation uncovering a diverticulum. A bladder diverticulum and subsequent urinary stasis may result in a predisposition for UTI and may also confer an increased difficulty in eradicating an existing infection (Shah, 1979; Taylor et al, 1979).

The initial evaluation of a bladder diverticulum includes a thorough history and physical examination, including digital rectal examination. In the male, prostate-specific antigen testing is pursued where appropriate. The history should quantitate lower urinary tract symptoms, query potential occult sources of neurogenic vesicourethral dysfunction (spinal surgery, etc.), and properly characterize any prior lower urinary tract surgery.

Urine analysis and urine culture as well as urine cytology should be considered in most patients with bladder diverticula, especially when nonoperative management is being considered. Abnormalities of the urine sediment are common in patients with bladder diverticula. Pyuria and hematuria are often present. In fact, relapsing or persistent pyuria unresponsive to antibiotic therapy may be an indication for bladder diverticulectomy in an otherwise asymptomatic patient. The finding of a bladder diverticulum in an adult should prompt further evaluation for bladder outlet obstruction, as well as endoscopic examination and imaging of the lower and upper urinary tract.

Imaging

The diagnosis of bladder diverticula relies on radiographic and endoscopic findings. Bladder diverticula are part of the radiologic

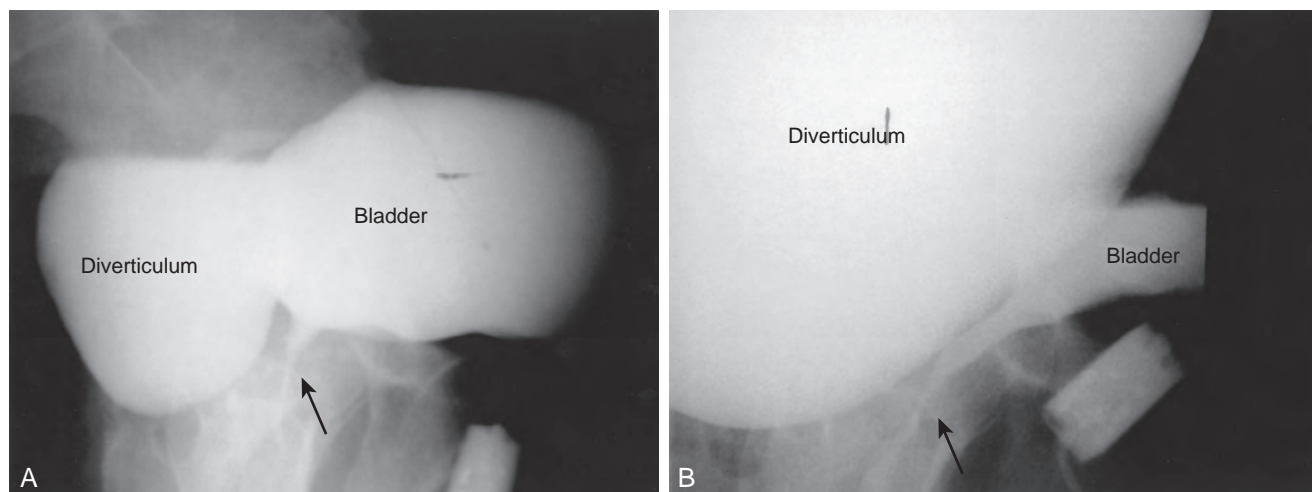


Figure 90-2. Voiding cystourethrogram (VCUG) demonstrating a bladder diverticulum in a male. **A**, The diverticulum is seen posterior to the bladder on this lateral voiding image (arrow points to urethra). There is a fluid-fluid level within the diverticulum representing the relatively denser contrast media settling below the urine. **B**, Later image from the VCUG demonstrates near emptying of the bladder with enlargement of the diverticulum.

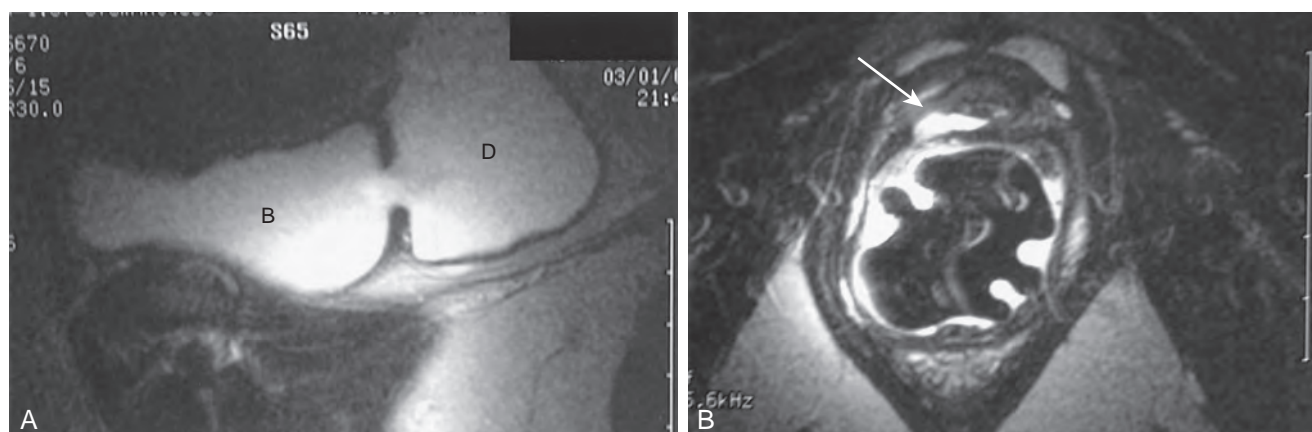


Figure 90-3. Bladder and urethral diverticula in a female. **A**, Magnetic resonance imaging (MRI) of a bladder (B) diverticulum (D). **B**, Endoluminal MRI demonstrating urethral diverticulum (arrow points to urethral diverticulum).

continuum that includes cellules and saccules. Cellules, saccules, and bladder diverticula are thought to represent increasingly larger and therefore more severe manifestations of the same pathologic process involving elevated intravesical voiding pressure (Talner et al, 2000). Cellules and saccules represent small outpouchings between hypertrophied bands of bladder muscle, with saccules generally being larger than cellules. However, there are no universally agreed upon minimum size requirements that distinguish cellules, saccules, and bladder diverticula, and the differentiation among these three entities is often subjective and arbitrary (Talner et al, 2000).

As noted previously, bladder diverticula are often found incidentally in the radiographic investigation of recurrent UTIs or other nonspecific lower urinary tract symptoms or signs. The differential diagnosis of a fluid-filled structure adjacent to the bladder is lengthy and includes müllerian cysts; uterine, ovarian, and fallopian tube abnormalities; urachal cysts; ectopic ureter or ureterocele; and post-surgical changes, including lymphocele.

Fluoroscopically monitored voiding cystourethrography (VCUG) is an excellent study to detect bladder diverticula; however, false negatives are possible (Hernanz-Schulman and Lebowitz, 1985). A

VCUG with anterior-posterior, oblique, and lateral images provides information regarding anatomy, location, and size and also associated vesicoureteral reflux and, importantly, emptying of the bladder diverticulum with voiding. Vesicoureteral reflux may be found in up to 13% of patients with congenital bladder diverticula (Barrett et al, 1976). The finding of vesicoureteral reflux associated with bladder diverticula in the pediatric population has historically prompted ureteroneocystostomy in all cases; however, recently authors have pursued a more selective approach, reimplanting only those ureters associated with complicating factors such as renal scarring or progressive renal function deterioration (Afshar et al, 2005). Anomalous voiding into the diverticulum during a detrusor contraction may result in paradoxical enlargement of the bladder diverticulum during micturition (Wesselhoft et al, 1963) (see Fig. 90-2). Presumably, this occurs during the detrusor contraction as the contrast flows from an area of relatively high pressure in the bladder into the diverticulum, which represents an area of low pressure. In some instances the bladder may empty partly into the diverticulum and partly through the urethra. Often, with continued observation under fluoroscopy following the cessation of voiding, the empty bladder will start to refill as the

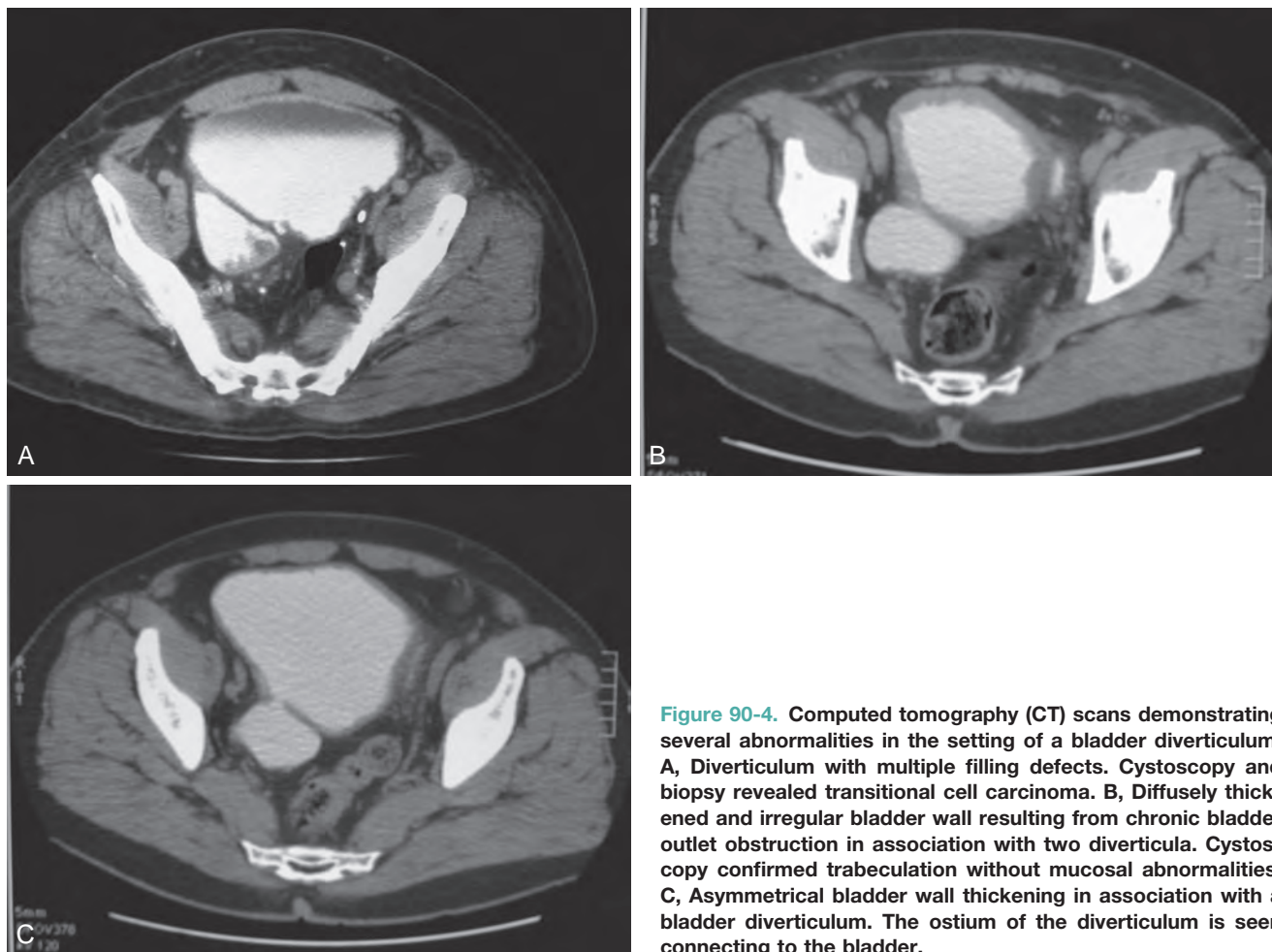


Figure 90-4. Computed tomography (CT) scans demonstrating several abnormalities in the setting of a bladder diverticulum. **A,** Diverticulum with multiple filling defects. Cystoscopy and biopsy revealed transitional cell carcinoma. **B,** Diffusely thickened and irregular bladder wall resulting from chronic bladder outlet obstruction in association with two diverticula. Cystoscopy confirmed trabeculation without mucosal abnormalities. **C,** Asymmetrical bladder wall thickening in association with a bladder diverticulum. The ostium of the diverticulum is seen connecting to the bladder.

diverticulum discharges back into the bladder. The amount of post-void residual urine in the bladder diverticulum and bladder should be noted.

Cross-sectional imaging of the lower urinary tract may provide useful information regarding bladder diverticula and critical information regarding the surrounding anatomy. **Review of the radiographic films should accurately characterize the number, anatomy, and location of the diverticula as well as assess for masses within the diverticulum.** Filling defects within the diverticula or other bladder abnormalities should prompt further investigation (Fig. 90-4). If the neck of the diverticulum is obstructed from a tumor or otherwise not patent, cross-sectional imaging may be required for diagnosis (Dondalski et al, 1993). Finally, cross-sectional imaging will provide surgically relevant information, including the location of the ureters and surrounding structures (rectum, etc.), which can be quite distorted owing to the space-occupying nature of some large bladder diverticula.

Imaging of the upper urinary tract may include intravenous pyelography, ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI). **In the absence of hematuria or a known or suspected urinary tract malignancy, the goal of upper tract imaging in the adult is to evaluate for asymptomatic or silent hydroureteronephrosis related to the diverticulum** (Lebowitz et al, 1979; Sharma et al, 1997) which has been reported to be present in up to almost 7% of cases in one series (Fox et al, 1962). In children with bladder diverticula the reported incidence of upper tract abnormalities, including renal scarring, dysplasia, and hydronephrosis, has been reported to be as high as 30% (Tokunaka et al, 1980; Gotoh et al, 1987). Hydronephrosis may be related to obstruction of the ureter (Livne and Gonzales, 1985;

Kwan and Lowe, 1992), an underlying urodynamic abnormality that resulted in the formation of the diverticulum, vesicoureteral reflux in association with the diverticulum, and inflammation (Bellinger et al, 1985), or may be completely unrelated to the bladder diverticulum. A multichannel urodynamic study in combination with a VCUG or, alternatively, a video-urodynamic study is useful in this setting to differentiate upper from lower urinary tract causes of the hydronephrosis.

A bladder diverticulum may cause deviation with or without compression of the ipsilateral ureter. **Medial deviation of the pelvic ureter is most commonly seen; however, lateral deviation may also occur** (Talner et al, 2000) (Fig. 90-5). Such information is important in determining surgical approach and whether or not to place ureteric stents preoperatively. Furthermore, a bladder diverticulum that encompasses the ureteral orifice may create a functionally shortened intramural ureteral segment and result in vesicoureteric reflux (see later discussion).

Urodynamics

In the adult, bladder outlet obstruction and/or neurogenic voiding dysfunction may result in the formation of bladder diverticula. Therefore a video-urodynamic study can be very helpful in the investigation of these patients (Adot Zurbarano et al, 2005). The role of urodynamics in the evaluation of congenital bladder diverticula is less well defined (Psutka and Cendron, 2013). However, **failure to identify and treat an existing underlying urodynamic abnormality prior to or concomitantly with definitive surgical therapy for bladder diverticula may result in a high risk of recurrent diverticula or other problems following surgery.** Furthermore,

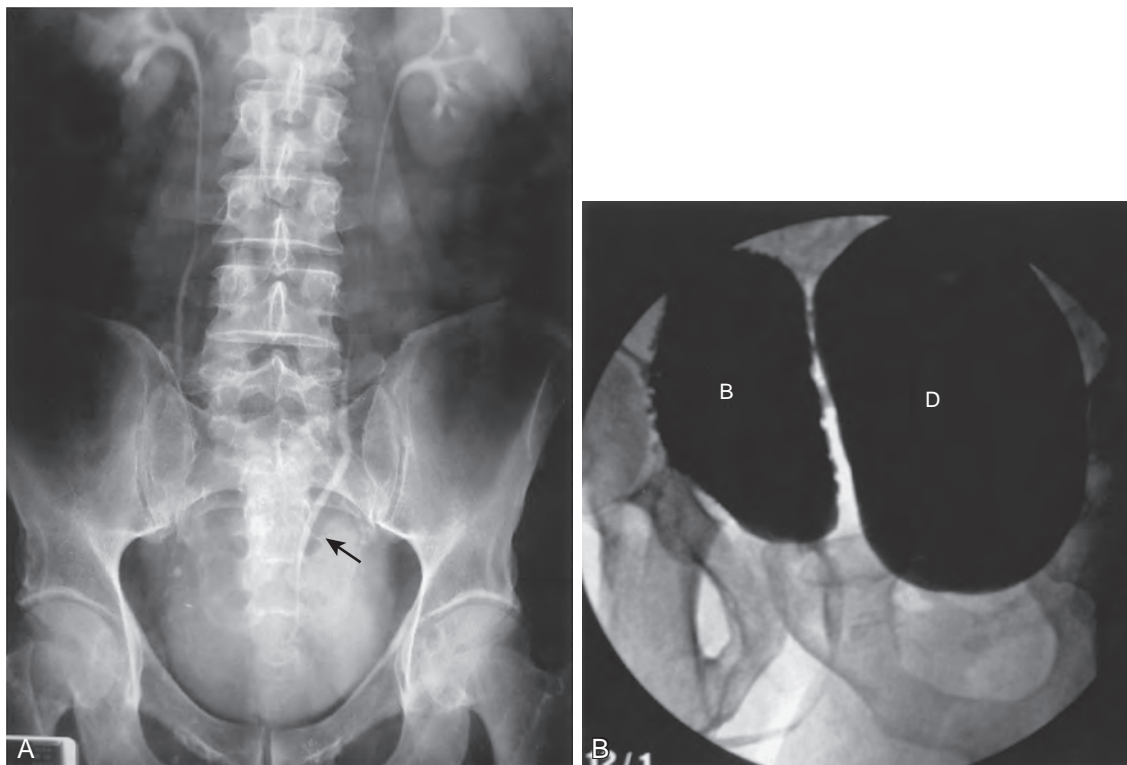


Figure 90-5. Bladder diverticulum with deviation of the ureter. This patient had a long history of recurrent urinary tract infections as a result of presumed prostatitis. **A**, Image from 10-minute intravenous urogram demonstrating medial deviation of the pelvic ureter (arrow). **B**, Voiding image from the voiding cystourethrogram revealed a large, smooth-walled bladder diverticulum (**D**) emanating from the trabeculated bladder (**B**).

successful treatment of the urodynamic abnormality may improve bladder emptying and potentially result in resolution of the symptoms and/or complications without the need for bladder diverticulectomy.

Bladder outlet obstruction, impaired contractility, elevated post-void residual urine, and detrusor overactivity are some of the urodynamic findings associated with bladder diverticula. Importantly, **bladder contractility may appear to be diminished on urodynamics because of the “pressure sink” effect of the bladder diverticulum.** This artifact occurs as the detrusor contracts and the intravesical contents are decompressed through the path of least resistance into the bladder diverticulum as opposed to the urethra (Wilson and Klufio, 1985). Nevertheless, when carefully measured, bladder contractility is not significantly different from that in individuals with benign prostatic hyperplasia without bladder diverticula (Adot Zurbano et al, 2005). In addition, elevated postvoid residual urine may be present as a result of retained urine in the diverticulum regardless of the presence or absence of impaired bladder contractility or bladder outlet obstruction.

Endoscopic Examination

Endoscopically, the entire interior of each bladder diverticulum should be thoroughly inspected for stones or abnormal-appearing epithelium. Flexible cystoscopy is often required to examine the entire interior of some diverticula. The location of the diverticula relative to the ureters and bladder outlet is noted, and the size of each diverticulum is carefully recorded (Fig. 90-6). Ideally, urine cytology should be obtained from the diverticulum during endoscopic examination. Any abnormal-appearing epithelium or lesions within the diverticulum are carefully biopsied. Extreme care must be taken during the biopsy to prevent perforation, because the wall of the diverticulum is very thin owing to the lack of a muscularis propria layer. All epithelial lesions under

consideration for biopsy should be considered malignant until proven otherwise. Perforation of the diverticular wall during biopsy risks tumor seeding into the perivesical fat with potential adverse prognostic implications.

Patients who elect nonoperative management of bladder diverticula are usually followed closely with periodic endoscopic examinations and cytology. The natural history of untreated bladder diverticula is unknown, but the possibility of malignant transformation over time because of urinary stasis within the diverticulum should be considered.

Associated Conditions

Bladder Outlet Obstruction

Acquired bladder diverticula are commonly found to exist in the setting of bladder outlet obstruction. Common causes of bladder outlet obstruction in the male include benign and malignant disease of the prostate and urethral stricture disease. Less common causes include bladder neck hypertrophy (primary bladder neck obstruction), vesicourethral anastomotic stricture following prostatectomy, and functional obstruction as a result of neurogenic vesicourethral dysfunction (bladder neck and/or striated sphincter dyssynergia). Strong consideration should be given toward management of bladder outlet obstruction prior to or concomitant with treatment of the bladder diverticulum. Whether such procedures should be done concomitantly or staged is controversial (Powell and Kreder, 2009). In some patients, especially those with small diverticula, treatment of bladder outlet obstruction alone may subsequently allow low pressure and complete emptying of the bladder diverticulum with micturition, thus reducing the potential for complications associated with these lesions and possibly avoiding the need for future operative intervention in the form of surgical diverticulectomy.

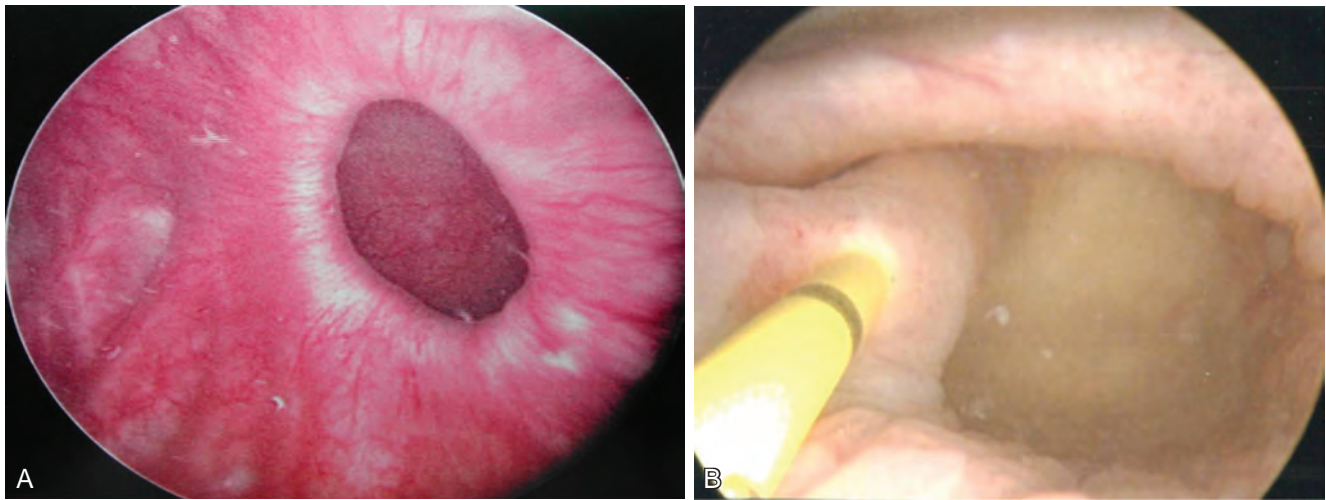


Figure 90-6. Endoscopic views of bladder diverticula. **A**, Lateral wall diverticulum in a male with bladder outlet obstruction. **B**, Paraureteral diverticulum in an adult female with vesicoureteral reflux and urinary tract infections. The right ureter is intubated with a catheter.

Malignancy

Much has been written about the association of bladder diverticula and malignancy. Historically, the risk of malignancy in bladder diverticula has been reported to be elevated. This increased risk of bladder cancer in diverticula has been attributed to urinary stasis and to chronic inflammation that is often found on pathologic examination of bladder diverticulum tissue (Kelalis and McLean, 1967; Idrees et al, 2013). Forty-five percent to 80% of bladder diverticulectomy specimens will harbor inflammatory changes to the urothelium (Gerridzen and Futter, 1982; Idrees et al, 2013). The overall prevalence of malignant tumors within a bladder diverticulum has been reported as ranging from 0.8% to 10% (Montague and Boltuch, 1976; Mičić and Ilić, 1983; Melekos et al, 1987; Baniel and Vishna, 1997; Golijanin et al, 2003). However, it is likely that the prevalence of bladder diverticula overall is under-reported and, as such, the prevalence of tumors within diverticula is probably considerably smaller than that noted here. Nevertheless, the most common histologic type of malignancy seen within bladder diverticula is transitional cell carcinoma in approximately 70% to 80% of cases, followed by squamous cell carcinoma in 20% to 25% of cases (Montague and Boltuch, 1976; Redman et al, 1976; Mičić and Ilić, 1983; Van Arsdalen and Wein, 1992; Yu et al, 1993; Baniel and Vishna, 1997; Golijanin et al, 2003). Tumors in bladder diverticula occur almost exclusively in adults, with a peak occurrence between ages 65 and 75 (Ostroff et al, 1973).

In addition to the potentially increased risk of bladder cancer, the finding of a neoplasm within a bladder diverticulum has particularly important diagnostic and therapeutic considerations because the bladder diverticulum wall lacks a well-developed muscularis propria layer. Therefore such a finding may portend a poorer prognosis because of the potential for rapid transmural involvement of invasive bladder cancer and extravesical extension. In addition, the lack of a defined muscular wall risks early dissemination of tumor cells into an extravesical location during transurethral resection of these lesions and makes precise pathologic staging difficult (Idrees et al, 2013).

The prognosis for patients with these tumors has been historically reported as poor (Faysal and Freiha, 1981; Mičić and Ilić, 1983; Das and Amar, 1986; Melekos et al, 1987), although some reports may suggest otherwise in selected patients (Montague and Boltuch, 1976; Baniel and Vishna, 1997). The poor prognosis has been attributed to delayed diagnosis and advanced stage at presentation

(Ostroff et al, 1973; Fellows, 1978; Faysal and Freiha, 1981; Mičić and Ilić, 1983). Historically, this has supported the prophylactic surgical treatment of all bladder diverticula, including asymptomatic and minimally symptomatic lesions (Kelalis and McLean, 1967). However, more recently it has been suggested that such management is not warranted, and observation with careful follow-up and periodic endoscopic surveillance is acceptable in asymptomatic individuals without evidence of dysplastic or malignant changes (Fellows, 1978).

Accurate identification of tumors within bladder diverticula has been demonstrated using a variety of radiographic techniques, including CT, MRI, and ultrasonography (Dragsted and Nilsson, 1985; Saez et al, 1985; Williams and Gooding, 1985; Lowe et al, 1989; Dondalski et al, 1993; Durfee et al, 1997; Mallampati and Siegelman, 2004) (see Fig. 90-4). Whether these modalities can reliably predict extravesical invasion and therefore affect staging and prognosis is not clear. It has been suggested that clinical stage at presentation is the most important prognostic factor for patients with tumors in bladder diverticula, with 5-year actuarial survival ranging from 83% \pm 9% in patients with superficial disease to 45% \pm 14% in those presenting with extradiverticular disease (Golijanin et al, 2003). One small series suggests that aggressive individualized multimodal therapy in these patients, including surgery, chemotherapy, and radiation therapy, may improve prognosis (Garzotto et al, 1996). Because pathologic staging following transurethral resection is difficult and often inaccurate, some authors have suggested a very aggressive approach to these tumors. This surgical staging approach involves an open exploration and partial or radical cystectomy without a prior transurethral resection (Redman et al, 1976). Others have advocated a selective individualized approach, taking into account the clinical stage and pathologic grade of the tumor (Golijanin et al, 2003).

Low-grade, low-stage tumors may be successfully treated with diverticulectomy alone (Baniel and Vishna, 1997; Sulaiman et al, 1998); however, it is important to recognize that the ability to reliably predict stage and grade preoperatively is limited, and therefore this approach should be undertaken only with caution in select cases, with adequate counseling and follow-up.

The role for less invasive treatment strategies of low-grade bladder tumors found in bladder diverticula is not well defined. As noted earlier, the potential risk of perforation with transurethral resection is higher with these tumors because of the lack of a defined muscularis propria layer. However, whether these patients can be safely treated with biopsy and fulguration with or without

intravesical chemotherapy/immunotherapy and interval cystoscopic surveillance for low-grade tumors, is unclear.

Other Associated Conditions

The location of many bladder diverticula at the level of the ureterovesical junction may explain the high incidence of associated ipsilateral ureteral abnormalities. For a ureter found within a diverticulum, the lack of a muscular backing to the diverticulum results in a functionally shortened intramural tunnel (see Fig. 90-6B). A very high prevalence of ipsilateral vesicoureteral reflux has been noted in association with congenital bladder diverticula (Amar, 1972; Barrett et al, 1976). Other considerations in the evaluation and management of bladder diverticula include the potential development of stones within the diverticulum, ureteral obstruction (Lebowitz et al, 1979; Bellinger et al, 1985; Kwan and Lowe, 1992; Khan et al, 1994; Sharma et al, 1997), and even the potential for the rare but life-threatening complication of perforation and/or rupture of the bladder diverticulum (Mitchell and Hamilton, 1971; Keeler and Sant, 1990; Itoh and Kounami, 1994; Jorion and Michel, 1999).

KEY POINTS: BLADDER DIVERTICULA—DIAGNOSIS

- Bladder diverticula do not contain a defined functional muscularis propria layer and therefore larger ones generally empty poorly with micturition.
- In the adult, bladder diverticula are often associated with bladder outlet obstruction or neurogenic vesicourethral dysfunction.
- Many bladder diverticula are found in a paraureteric location.
- Bladder diverticula are most often diagnosed incidentally in the evaluation of nonspecific lower urinary tract symptoms or infection.
- Patients with bladder diverticula should be evaluated for bladder outlet obstruction, and, if this is present, it should be addressed in advance of or concomitantly with definitive treatment of the bladder diverticulum.
- Malignancy can occur within a bladder diverticulum, and consideration should be given to the possibility of early extravesical disease extension owing to the lack of a defined muscularis propria.

Management

In general, if the etiology of the bladder diverticulum is believed to be consistent with bladder outlet obstruction and there are no other complicating factors, definitive treatment of the bladder outlet is indicated prior to formal diverticulectomy. This approach allows reassessment of the diverticulum following relief of outlet obstruction and, if bladder emptying is satisfactory and symptoms resolve, then the diverticulum may not require surgical excision. However, simultaneous open bladder diverticulectomy/open prostatectomy as well as simultaneous bladder diverticulectomy/transurethral prostatectomy can be performed (Porpiglia et al, 2004). If treatment of the obstruction is pursued initially and results in satisfactory emptying of the diverticulum postoperatively, and complicating factors such as reflux, infection, malignancy, or stones are absent, then ongoing surveillance of the diverticulum may be all that is required. Emptying of the diverticulum following relief of outlet obstruction may be assessed on VCUG, video-urodynamics, or cross-sectional imaging such as ultrasound.

Management options in the treatment of bladder diverticula include observation, endoscopic management, and surgical excision; however, there are many factors to consider during the evaluation of these lesions prior to deciding on appropriate therapy (Fig. 90-7).

Observation and Nonsurgical Management

Adult patients with minimal symptoms and no complicating factors may opt for observation with surveillance. These patients should be counseled regarding the potentially increased risk of malignancy and the need for periodic reassessment as well as the unpredictable course and potentially aggressive nature of malignancy if subsequently found in this setting. They should also be counseled regarding the symptoms and signs that indicate progression, including increasing lower urinary tract symptoms, hematuria, and UTI. The optimal schedule and type of surveillance for those individuals choosing observation is not well defined but consists of a periodic reassessment of symptoms, urine studies (including cytology), and endoscopic examination of the lower urinary tract (Yu et al, 1993).

Patients who have poor bladder emptying following relief of obstruction and remain symptomatic, or those who are unable or unwilling to undergo surgical excision of the bladder diverticulum, may be effectively treated with clean intermittent catheterization (CIC) or an indwelling catheter. In this setting, and in the absence of future complicating factors, ongoing CIC and periodic surveillance of the bladder diverticulum may be acceptable.

Indications for bladder diverticulectomy in children are similar to those in adults. However, in children with multiple bladder diverticula associated with a chromosomal syndrome, observation and medical management are usually preferred because of the inherent connective tissue disorders found in these patients, which impair postoperative wound healing, increase perioperative surgical risk, and predispose to recurrence (Psutka and Cendron, 2013).

Indications for Intervention

Many patients with incidentally found congenital or acquired bladder diverticula are managed expectantly and with periodic surveillance. Bladder diverticula can vary tremendously in size and, in some instances, are larger than the bladder itself. The size of the diverticulum does not appear to correlate with symptoms or complications and therefore cannot be used as an absolute indication to proceed with surgery. Bladder diverticulectomy is indicated for the treatment of lower urinary tract symptoms related to the diverticulum that are not otherwise responsive to medical therapy, or for the major complications directly related to it: persistent symptoms, chronic relapsing UTI, stones within the diverticulum, carcinoma or premalignant change, and upper urinary tract deterioration as a result of obstruction or reflux. Symptoms or complications related to bladder diverticula are most often due to poor emptying of the diverticulum and urinary stasis. Therefore excision of the diverticula would be expected to improve emptying of the lower urinary tract, provided that the primary problem that resulted in the formation of the bladder diverticulum (i.e., obstruction) has been adequately addressed.

Excision of bladder diverticula is most commonly elective. The relative merits of surgical excision versus surveillance should be carefully considered and discussed with each patient individually. The patient should be in relatively good health and be a reasonable surgical risk prior to considering the procedure. Preoperative medical status should be assessed and reversible risk factors (nutritional, renal, cardiac, pulmonary, etc.) corrected and/or optimized. Preoperative UTI should be treated. Patients who are prohibitive surgical risks because of concurrent medical illness or other factors should not undergo surgical excision but may be candidates for CIC or endoscopic treatment.

Endoscopic Management

Endoscopic management of bladder diverticulum may be considered in patients who are aged or somewhat debilitated, those who are not good candidates for an open operative approach, or those undergoing transurethral resection of the prostate in whom there exists an associated poorly draining diverticulum (Orandi, 1977; Vitale and Woodside, 1979). Transurethral

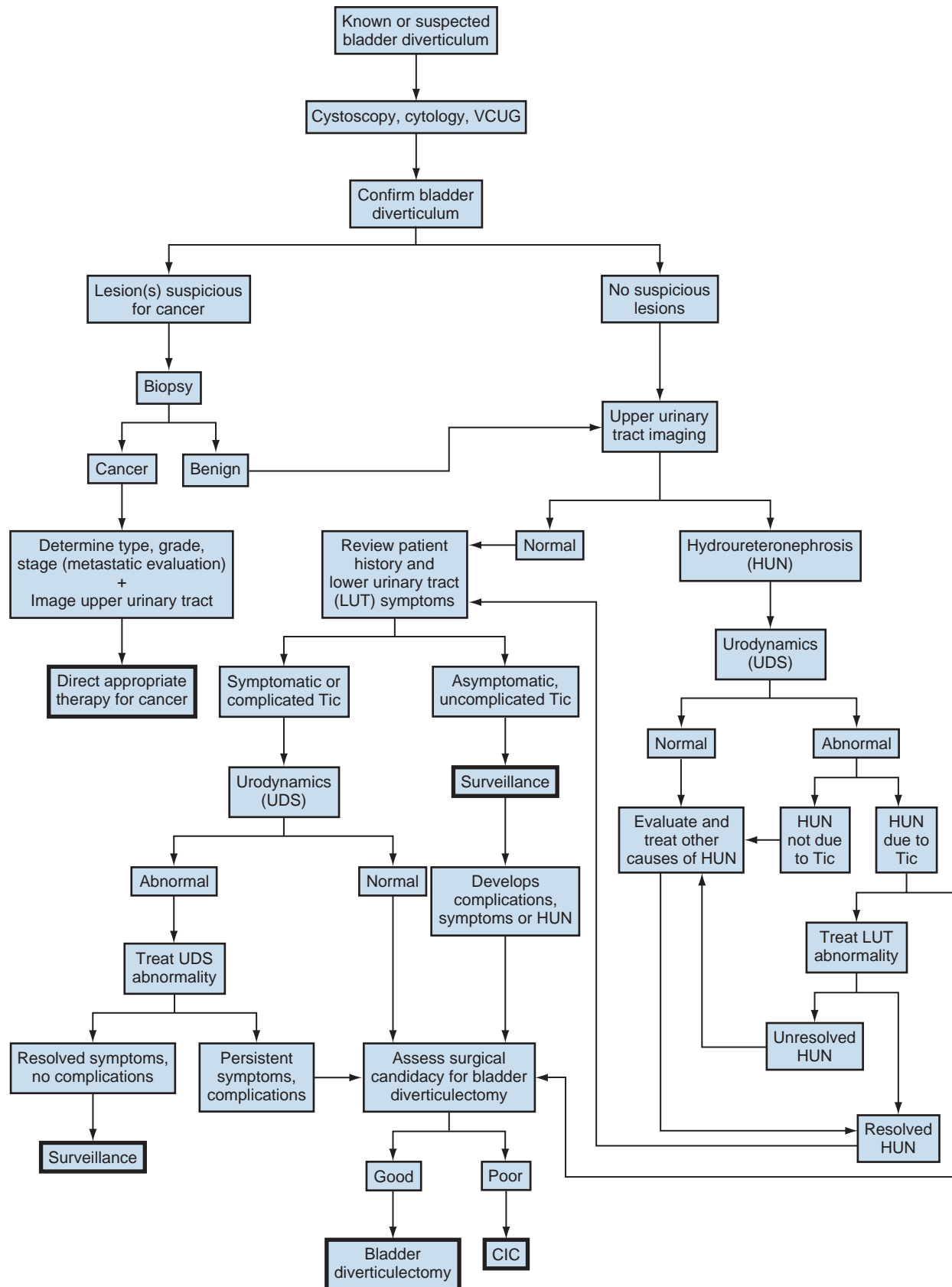


Figure 90-7. Algorithm for the evaluation and therapy of bladder diverticula. Bold-outlined boxes are potential endpoints in the algorithm. CIC, clean intermittent catheterization; Tic, bladder diverticulum; VCUG, voiding cystourethrogram. (Modified from Rovner ES, Wein AJ. Bladder diverticula in adults. In: Resnick M, Elder JA, Spinnak JP, editors. Decision making in urology. 3rd ed. Hamilton [Ontario]: B.C. Decker; 2004. p. 260–3.)

resection of the diverticular neck has been reported to be successful in select cases (Vitale and Woodside, 1979). This technique is usually performed with a standard resectoscope. The neck of the diverticulum is incised using the resectoscope loop or Collins knife. Incisions are carried down to the muscular fibers of the bladder at the level of the ostium of the diverticulum. Circumferential resection of the entire neck may be performed. When successful, this procedure enlarges the neck of the diverticulum, disrupting the narrow sphincteric-like properties of its connection to the bladder lumen and thereby permitting improved emptying of the diverticulum during micturition. Although generally safe and well tolerated, this technique has resulted in urinary retention because of a reversal of flow during micturition and “venting” of the bladder contents into the diverticulum postoperatively (Schulze and Hald, 1983). This technique has been reported to be less successful in those individuals with large diverticula (Orandi, 1977; Vitale and Woodside, 1979). Transurethral resection of the diverticular neck may be combined with fulguration of the entire urothelial lining of the diverticulum (Clayman et al, 1984; Adachi et al, 1991a, 1991b; Yamaguchi et al, 1992). Fulguration of the lining of the diverticulum should result in obliteration of the diverticulum or a considerable reduction in its size.

Open Surgical Management

Open excision is usually performed through a transvesical approach, although extravesical and combined approaches have been described. In cases of marked prostatic enlargement and obstruction, open suprapubic prostatectomy and transvesical bladder diverticulectomy may be performed concomitantly. Adequate preoperative imaging and endoscopic evaluation should provide information regarding the size, number, and location of all bladder diverticula. Furthermore, the relationship of the adjacent anatomic structures, including the major pelvic vessels, ureters, and bowel, should be noted. Surgically, the bladder is most commonly approached extraperitoneally through a low midline or transverse incision. The retropubic space is entered and developed. Regardless of the technique used, careful dissection is required during excision of the diverticulum to avoid ureteral injury, because many bladder diverticula are located adjacent to the ureter or may be adherent to it. Ureteral stents are often placed preoperatively or intraoperatively to facilitate dissection and avoid ureteric injury. Often, several bladder diverticula are noted preoperatively. Simultaneous resection of all existing bladder diverticula should be performed to optimize postoperative bladder emptying (Gil-Vernet, 1998).

Transvesical Bladder Diverticulectomy. The transvesical approach to bladder diverticulectomy was first reported by Hugh Hampton Young in 1906 (Gil-Vernet, 1998). The bladder is opened along the anterior wall and suitable retraction is placed in order to visualize the neck of the diverticulum. For the excision of small diverticula, saccules, or cellules, a locking instrument such as an Allis-type clamp is passed through the neck of the diverticulum and the base or bottom of the diverticulum is grasped, pulled, and everted back into the bladder. In the absence of extravesical adhesions or inflammation, a small diverticulum can be completely everted into the bladder and exposed in this manner. The urothelium of the diverticulum at the level of the neck is incised circumferentially, and the diverticulum is removed. The defect in the bladder wall is closed with absorbable suture in two layers. Care must be taken when performing this technique to avoid injuring structures adherent or adjacent to the external surface of the diverticulum, because they may be blindly pulled into the bladder with the diverticulum wall and inadvertently injured during resection.

If eversion of the diverticulum is not possible because of adhesions or inflammation, or the diverticulum is too large to permit complete exposure during eversion, submucosal excision of the diverticulum may be performed. An anterior cystotomy is performed, the bladder is opened, and suitable retraction is placed to visualize the neck of the diverticulum within the bladder. The neck of the diverticulum is then identified and mobilized initially,

similar to the technique used for the first part of the dissection of the ureter during ureteroneocystostomy. The diverticular neck is circumscribed sharply with scissors or electrocautery, and the plane between the wall of the diverticulum and the surrounding fibrous capsule is defined (Fig. 90-8). Traction is placed on the edges of the neck of the diverticulum with Allis clamps (Scanlan International, St. Paul, MN) circumferentially, and the neck and then the exterior walls of the diverticulum are carefully mobilized from the surrounding tissues and delivered into the bladder lumen. Sharp and blunt dissection on the exterior wall of the diverticulum is performed in a well-defined periadventitial plane between the diverticulum wall and the fibrous pseudocapsule. Packing of the diverticulum with gauze may facilitate dissection and provide some countertraction (Fig. 90-9). The diverticulum is completely freed from its fibrous pseudocapsule and removed. The bladder wall defect is repaired in two layers with absorbable sutures. Drainage of the potential space left by the pseudocapsule is usually not necessary (Firstater and Farkas, 1977).

Combined Intravesical-Extravesical Approach. For individuals with large diverticula and/or considerable peridiverticular inflammation, a purely transvesical approach may not be feasible. In addition, involvement of the ureter within the diverticulum or severe peridiverticular inflammation encompassing the ureter may have altered the usual course of the ureter and may incur a prohibitive risk of injuring the ureter with a transvesical approach. Therefore a combined intravesical and extravesical approach may be warranted. Ureteral catheters are usually placed to prevent ureteral injury. The bladder is opened as if for a transvesical diverticulectomy. The diverticular neck is incised circumferentially. The surgeon's finger is then inserted into the diverticulum to identify the location of the rest of the diverticulum (Fig. 90-10). The diverticulum may be packed with gauze as well. If the neck of the diverticulum is sufficiently mobile, the anterior aspect of the neck is brought up into the operative field outside the bladder using the surgeon's finger. The overlying tissue is dissected free, and the anterior portion of the neck of the diverticulum is exposed and incised extravesically. The neck is circumferentially mobilized and then transected. The diverticular wall is then mobilized and dissected free of its attachments as described previously. In some cases, anterior reflection of the surgeon's finger allows opening of the diverticulum itself, and dissection can be carried out in the plane between the pseudocapsule and the urothelium in a completely extravesical fashion. In some cases, it may be necessary to divide the ipsilateral superior vesical pedicle to facilitate exposure and delivery of the diverticulum. If additional difficulty is encountered in exposing the diverticulum, the original cystotomy incision can be extended or enlarged in a “T” fashion over to the neck of the diverticulum. This procedure generally removes the entire diverticulum, including the mucosa and fibrous pseudocapsule. In cases in which considerable inflammation is encountered and the diverticulum is closely adhering to adjacent vital structures, it may be necessary to leave portions of the fibrous pseudocapsule in situ. The bladder is closed as described previously.

Laparoscopic and Robotic Diverticulectomy. Minimally invasive techniques, such as laparoscopy and robotics (Myer and Wagner, 2007), have been applied to surgical diverticulectomy (Das, 1992; Parra et al, 1992; Jarrett et al, 1995; Faramarzi-Roques et al, 2004; Abdel-Hakim et al, 2007; Macejko et al, 2008). As compared to open surgery the potential advantages of this approach include smaller incisions, less postoperative pain, shorter hospital stay, and a shorter convalescence. The principles of such minimally invasive techniques parallel those of the open surgical approach: (1) mobilization of the diverticular sac, including the neck; (2) excision of the sac; and (3) closure of the bladder. Transvesical as well as intra- and extraperitoneal approaches have been reported. The transvesical approach uses trocars inserted extraperitoneally directly into the bladder, thereby minimizing the risk to intraperitoneal contents (Pansadoro et al, 2009). Transperitoneal (Stolzenburg et al, 2011) and transvesical (Roslan et al, 2012) laparoendoscopic single-site surgery techniques have also been described that purport to even further minimize the risk to intra-abdominal structures.

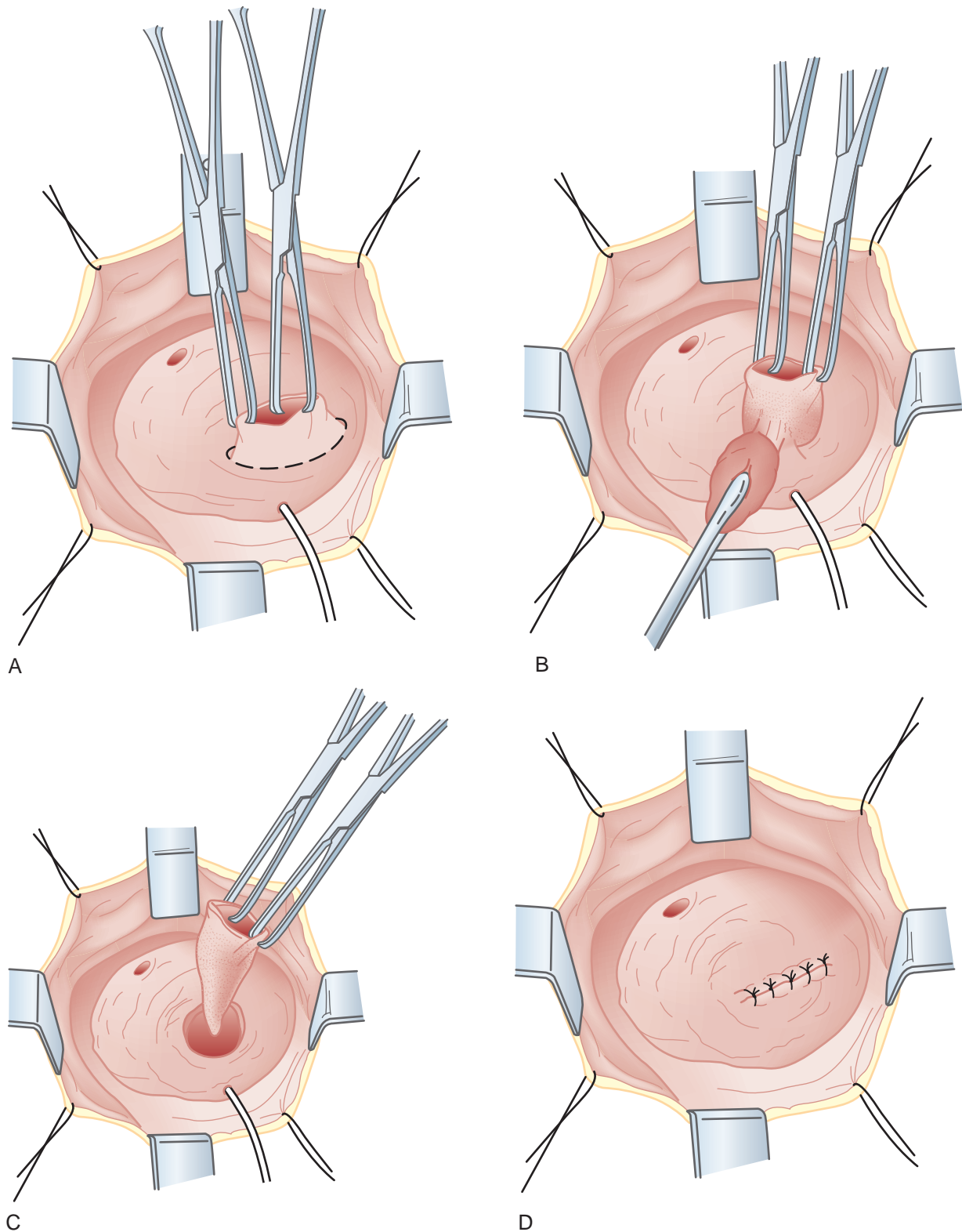


Figure 90-8. Intravesical submucosal bladder diverticulectomy. A, The neck of the diverticulum is grasped and circumscribed sharply. B, The adventitial tissue is dissected free from the diverticulum wall. C, The diverticulum is completely removed. D, The bladder is repaired.

Small nonrandomized, noncomparative case series suggest that outcomes using minimally invasive techniques, especially robotics, are similar to those with established open techniques (Eyraud et al, 2013). One small study compared laparoscopic versus open bladder diverticulectomy in 25 patients (Porpiglia et al, 2004). Outcomes

were similar, but notably blood loss and hospital stay were significantly lower in the laparoscopic group whereas operative time was almost twice as long (240 vs. 136 minutes). A review of 13 published series of robotic diverticulectomies involving a total of 44 patients revealed a mean operative time of 186 ± 68 minutes

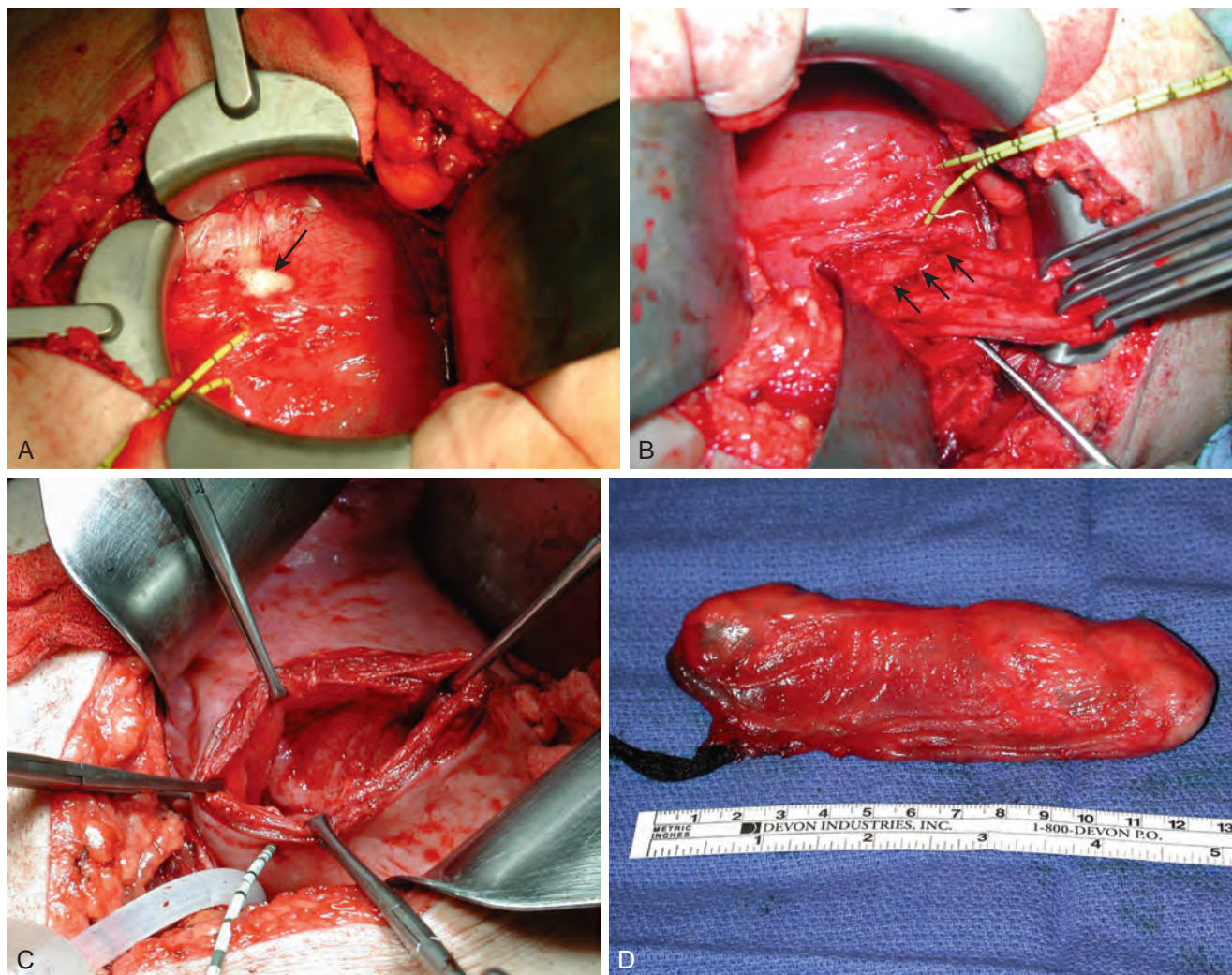


Figure 90-9. Transvesical submucosal bladder diverticulectomy. A, Intraoperative packing of the diverticulum (arrow) with gauze may facilitate dissection. Ureteric catheters demonstrate the proximity of the diverticulum to the right ureter. B, Allis clamps are seen on the edge of the neck of the diverticulum providing traction. The arrows show the plane of dissection along the pseudocapsule of the diverticulum as it is dissected free from the retroperitoneal tissues. C, View into the retroperitoneal space through the bladder wall defect created by removal of the diverticulum. D, Intact diverticulum specimen packed with gauze.

(Eyraud et al, 2013). Potential advantages of the robotic approach as compared to the laparoscopic approach include improved surgical access and maneuverability in the deep pelvis as well as increased precision, dexterity, and visualization in complex reconstructive cases; however, this is somewhat counterbalanced by the increased cost of robotic equipment (Eyraud et al, 2013).

Complications

The most troubling potential complication during bladder diverticulectomy is ureteral injury. Fortunately, this is rare and can be avoided by careful attention to technique. Placement of a ureteral catheter perioperatively can be very helpful in identifying the ureter during surgery. If a ureteric injury is identified intraoperatively, a partial transection may be repaired primarily and stented. Complete transection usually mandates ureteral reimplantation into the bladder with or without a psoas hitch. Other complications include UTI, bleeding, prolonged urinary extravasation postoperatively, and urinary fistula. Vascular, bowel, or rectal injury may occur during bladder diverticulectomy owing to the proximity of these adjacent

structures to the diverticulum. Prompt recognition and repair are imperative. Good surgical technique, retraction, and maintenance of countertraction during extensive dissection will avoid many of these injuries. Fortunately rectal injuries are rare, though the location of many posterior bladder diverticula put the rectum at risk.

KEY POINTS: BLADDER DIVERTICULA—MANAGEMENT

- Bladder diverticulectomy is not indicated in all cases. Surgical treatment should be reserved for the treatment of symptoms related to the diverticulum, chronic relapsing UTI, stones within the diverticulum, carcinoma or premalignant change, and upper urinary tract deterioration as a result of obstruction or reflux.
- Surgical diverticulectomy can be performed with a variety of approaches, including minimally invasive techniques.

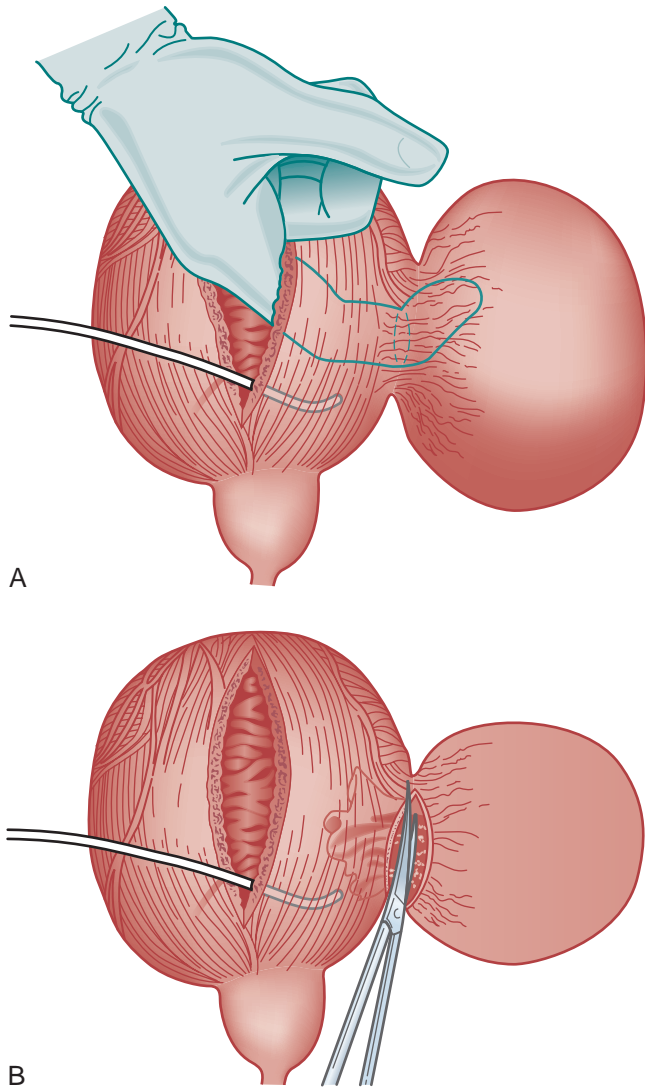


Figure 90-10. Combined intravesical-extravesical bladder diverticulectomy. **A,** The surgeon's finger is inserted into the diverticulum through a cystostomy, allowing identification of the diverticular neck. **B,** The diverticular neck is divided and the remaining portion of the diverticulum is dissected free from the surrounding tissues.

FEMALE URETHRAL DIVERTICULA

A urethral diverticulum (UD) in the female is a variably sized urine-filled periurethral cystic structure adjacent to the urethra within the confines of the pelvic fascia, connected to the urethra via an ostium. Such lesions represent some of the most challenging diagnostic and reconstructive problems in female urology. Urethral diverticula (UD) are notable for a bewildering array of clinical presentations ranging from completely asymptomatic, incidentally noted lesions on physical examination or imaging to very debilitating, painful vaginal masses associated with incontinence, stones, severe dyspareunia, and/or tumors. Anatomic variations between patients and in the location, size, and complexity of these lesions ensure that each case is unique.

Although described as early as the 19th century (Hey, 1805), the modern era of female UD began in the 1950s with the advent of positive-pressure urethrography (PPU) by Davis and Cian (1956). Over the next several years, there was a dramatic increase in number of cases of UD reported in the literature. A published series of 121 cases by Davis and TeLinde (1958) approximately doubled the number of cases reported during the previous 60 years. Development of adjuvant imaging techniques such as ultrasonography and

surface coil/endoluminal MRI have contributed greatly to further understanding of UD (Fig. 90-11).

Anatomy of the Female Urethra

The normal female urethra is a musculofascial tube approximately 3 to 4 cm in length, extending from the bladder neck to the external urethral meatus, suspended from the pelvic sidewall and pelvic fascia (tendinous arc of the obturator muscle) by a sheet of connective tissue known as the urethropelvic ligament. The urethropelvic ligament is composed of two layers of fused pelvic fascia that extend toward the pelvic sidewall bilaterally (Fig. 90-12). This structure can be considered to have an abdominal side (the endopelvic fascia) and a vaginal side (the periurethral fascia). Within and between these two leaves of fascia lie the urethra and the location of most UD.

The urethral lumen is lined by a urothelial layer proximally and a nonkeratinized stratified squamous cell type distally. The urethra may be conceptualized as a rich, vascular, spongy cylinder surrounded by an envelope consisting of smooth and skeletal muscle and fibroelastic tissue (Young et al, 1996). Within the thick, vascular lamina propria/submucosal layer are the periurethral glands (Fig. 90-13). These tubuloalveolar glands exist over the entire length of the urethra posterolaterally; however, they are most prominent over the distal two thirds, with the majority of the glands draining into the distal one third of the urethra. The Skene glands are the largest and most distal of these glands. These glands drain outside the urethral lumen, lateral to the urethral meatus. It is from pathologic processes involving the periurethral glands that most acquired female UD are thought to originate.

The urethra has several muscular layers: an internal longitudinal smooth muscle layer, an outer circular smooth muscle layer, and a skeletal muscle layer. The skeletal muscle component spans much of the length of the urethra but is more prominent in the middle third. It has a U-shaped configuration, being deficient dorsally. Ventral to the urethra, but separated from it by the periurethral fascia, lies the anterior vaginal wall (see Fig. 90-12). The location and competence of the urethral sphincters have important implications when considering surgical repair of UD because of the anatomic overlap of these two entities.

Arterial inflow to the urethra derives from two sources. The proximal urethra has a blood supply similar to the adjacent bladder, whereas the distal urethra derives its blood supply from the terminal branches of the inferior vesical artery through the vaginal artery that runs along the superior lateral aspect of the vagina (Hinman, 1993). Lymphatic drainage of the female urethra is to the external and internal iliac nodes from the proximal urethra, and to the superficial and deep inguinal lymph nodes from the distal urethra. Innervation to the female urethra is from the pudendal nerve (S2 to S4), and afferents from the urethra travel through the pelvic splanchnic nerves.

Urethral Diverticula

Pathophysiology and Etiology

As conceptualized by Young and colleagues (1996), UD represent a cavity dissecting within the confines of the fascia of the urethropelvic ligament. This defect is often an isolated cystlike appendage with a single discreet connection to the urethral lumen known as the neck, or ostium (Fig. 90-14). However, complicated anatomic patterns may exist, and in certain cases the UD may extend partially (saddlebag UD) around the urethra, anterior to the urethra (Vakili et al, 2003), or circumferentially around the entire urethra (Rovner and Wein, 2003) (Fig. 90-15).

The exact origin of UD is still unproven. A major debate in the early part of the 20th century focused on whether UD were congenital or acquired lesions (Johnson, 1938; Gilbert and Rivera Cintron, 1954; Pinkerton, 1963). Although this condition exists in children, the diagnosis may represent a different clinical entity from adult female UD. Scattered reports of congenital UD in female

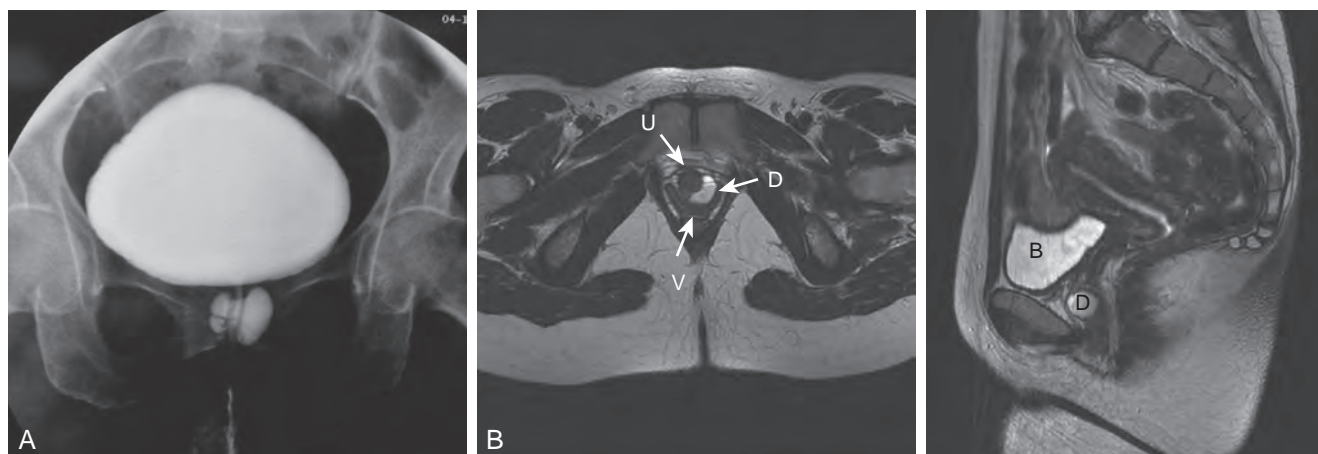


Figure 90-11. Imaging of urethral diverticula. A, Anterior-posterior view from a voiding cystourethrogram demonstrating a collection of contrast below the bladder, suggesting a urethral diverticulum. B, Surface coil magnetic resonance image with both sagittal (left) and axial (right) T2 images demonstrating the relevant anatomy of a patient with a urethral diverticulum (D). B, bladder; U, urethra; V, vagina.

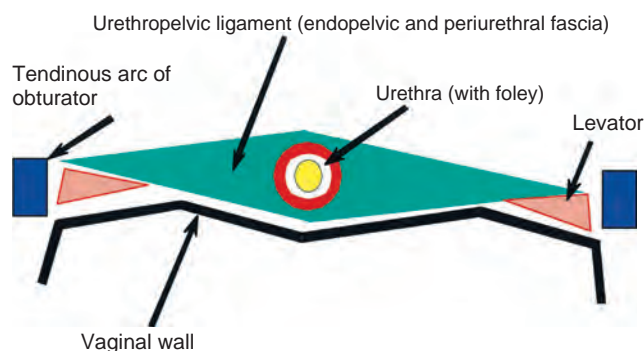


Figure 90-12. Schematic diagram of the anatomy of the mid-urethra in the coronal plane.

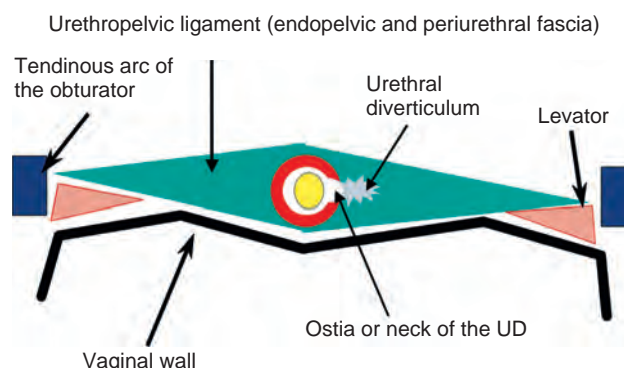


Figure 90-14. Diagram of urethral diverticulum (UD), which forms within and between the layers of the urethropelvic ligament.

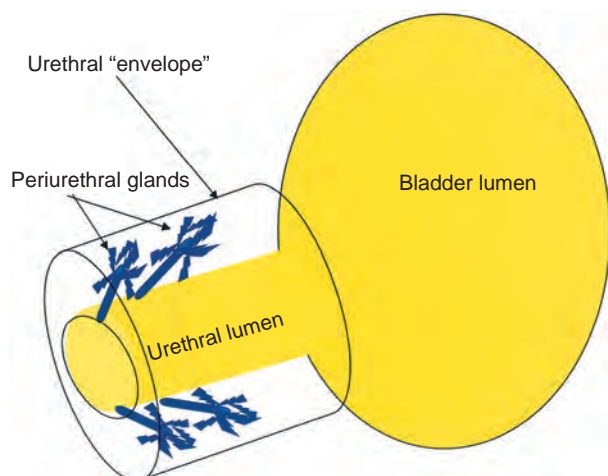


Figure 90-13. Periurethral glands are located within the submucosa of the urethra deep to the muscular envelope, draining distally but arborizing proximally.

infants have been described (Glassman et al, 1975). Marshall (1981) reported five cases of UD in young females, of whom three underwent spontaneous regression. Congenital anterior UD is a well-described entity in boys (Kirks and Grossman, 1981; Lau and Ong, 1981; Kaneti et al, 1984), but this is considered to be an

entirely different clinical entity from UD in the female. Congenital Skene gland cysts have been reported (Kimbrough and Vaughan, 1977; Lee and Kim, 1992) but are considered extremely rare. Diverticula in the pediatric population have been attributed to a number of congenital anomalies, including an ectopic ureter draining into a Gartner duct cyst and a forme fruste of urethral duplication (Silk and Lebowitz, 1969; Vanhoutte, 1970; Boyd and Raz, 1993). The vast majority of UD, however, are classified as acquired and are diagnosed in adult females. In two large series of UD, there were no patients reported who were younger than 10 years of age (Davis and TeLinde, 1958; Davis and Robinson, 1970), arguing against a congenital etiology for these lesions. Although it is possible that there exists a congenital defect in patients that results in or represents a precursor to UD, which then only becomes symptomatic later in life, it is still unproven.

There are multiple theories regarding the formation of acquired UD. For many years, acquired UD were believed to be most likely due to trauma from vaginal childbirth (McNally, 1935). It was postulated that mechanical trauma during vaginal delivery resulted in herniation of the urethral mucosa through the muscular layers of the urethra with the subsequent development of a UD. However, up to 20% to 30% of patients in some UD series are nulliparous (Lee, 1984; Ganabathi et al, 1994), which may significantly discount parity as a risk factor. Trauma with forceps delivery, however, has been reported to cause UD (Kłyszczko et al, 1985), and the radiographic appearance of periurethral injectable agents,

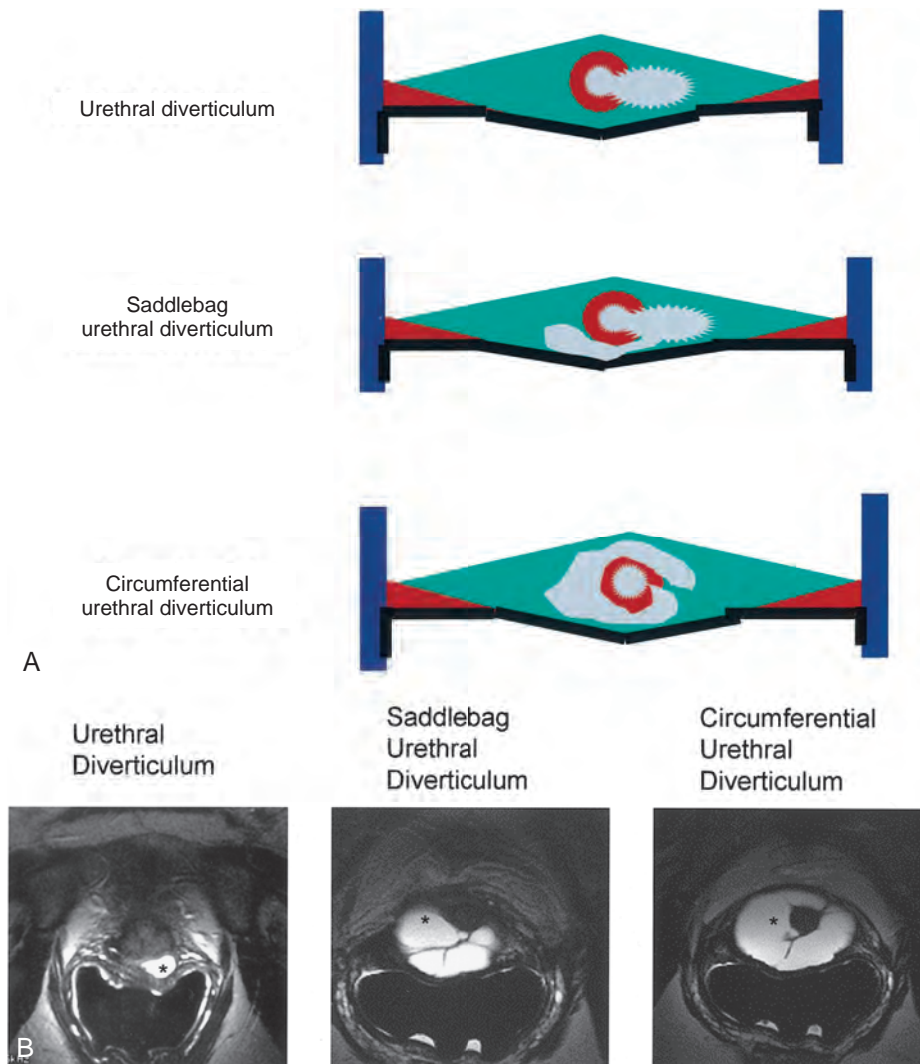


Figure 90-15. Multiple different morphologies of urethral diverticulum (UD) may exist. A, Schematic diagrams representing three different morphologies of UD. B, Endoluminal magnetic resonance images corresponding to each of the configurations in three different patients (asterisk indicates UD).

including collagen (Clemens and Bushman, 2001; Bridges et al, 2005) and other injectable agents (Castillo-Vico et al, 2007), can simulate a UD.

The periurethral glands are thought to be the probable site of origin of acquired UD (Young et al, 1996). Huffman's anatomic work with wax models of the female urethra was critical to the early theories regarding the pathophysiology of UD and the involvement of the periurethral glands (Huffman, 1948). By reviewing 10- μ m transverse sections, he refuted earlier anatomic descriptions of the glandular anatomy of the female. He characterized the periurethral glands as located primarily dorsolateral to the urethra, arborizing proximally along the urethra, and yet draining into ducts located in the distal one third of the urethra (see Fig. 90-13). Furthermore, he noted that periductal and interductal inflammation was found commonly. In support of these observations and an infectious (acquired) etiology of UD, in over 90% of UD cases the ostium is located posterolaterally in the mid- or distal urethra, which corresponds to the anatomic location of the periurethral glands (Lang and Davis, 1959; MacKinnon et al, 1959).

Although there are probably other unknown factors that may facilitate the initiation, formation, or propagation of UD, infection of the periurethral glands seems to be the most generally accepted common etiologic factor in most cases. Peters and

Vaughan (1976) found a strong association with concurrent or previous infection with *Neisseria gonorrhoeae* and UD. However, the initial infection and, especially, subsequent reinfections may originate from a variety of sources, including *Escherichia coli* and other coliform bacteria as well as vaginal flora. Nevertheless, UD have been attributed historically to recurrent infection of the periurethral glands, with obstruction, suburethral abscess formation, and subsequent rupture of these infected glands into the urethral lumen. Continual filling and pooling of urine in the resultant cavity may lead to stasis, recurrent infection, and eventual epithelialization of the cavity, forming a permanent UD. This concept was first popularized by Routh (1890) over a century ago and has now become the most widely accepted theory regarding the formation of female UD. Reinfection, inflammation, and recurrent obstruction of the neck of the cavity are theorized to result in patient symptoms and enlargement of the diverticulum. It should be noted that Daneshgari and colleagues (1999) have reported non-communicating UD diagnosed by MRI. Whether this lesion represents a forme fruste of UD or simply a UD with an obstructed ostium is unclear.

Young and colleagues (1996) have formulated a modern hypothesis regarding the pathogenesis of UD through extensive clinical experience with this entity, including the diagnosis, imaging, and

surgical repair of UD. These authors have proposed that acquired UD results from infection and obstruction of the periurethral glands. These glands are normally found in the submucosal layer of the spongy tissue of the distal two thirds of the urethra. Repeated infection and abscess formation in these obstructed glands eventually result in enlargement and expansion. Initially the expanding mass displaces the spongy tissue of the urethral wall and then enlarges to disrupt the muscular envelope of the urethra. This results in herniation into the periurethral fascia. The enlarging cavity can then expand and dissect within the leaves of the periurethral fascia and urethropelvic ligament. This expansion occurs most commonly ventrally, resulting in the classic anterior vaginal wall mass palpated on physical examination in some patients with UD. However, it is important to note that these may also expand laterally, or even dorsally, about the urethra. Eventually, the abscess cavity ruptures into the urethral lumen, resulting in the communication between the UD and the urethral lumen.

This proposed pathophysiology appears to adequately explain the anatomic location and configuration of many UD and is supported by the work of Huffman noted previously. However, it is not without critics. Some have argued that UD represent one form in the continuum of periurethral cysts (Tsivian et al, 2009). In addition, about one third of UD occur in the proximal portion of the urethra (Thomas et al, 2008), which is not consistent with the location of the majority of the drainage ducts for the periurethral glands. Finally, if this proposed pathophysiology were true, the finding of periurethral abscesses as a result of infection and enlargement of the periurethral glands should be at least as common as UD, but such lesions are indeed rarely seen clinically.

Prevalence

Moore (1952) stated that UD as an entity is “found in direct proportion to the avidity with which it is sought.” Although it is not considered a rare lesion today, less than 100 cases of UD had been reported in the literature prior to 1950. With the development of sophisticated imaging techniques, including PPU in the 1950s, the diagnosis of UD became increasingly common.

The true prevalence of female UD, however, is not known; it is reported to occur in up to 1% to 6% of adult females in some series. Determining the true prevalence of UD would require appropriate screening and imaging of a large number of symptomatic and asymptomatic adult female subjects in a primary care setting, which, to date, has not been done. Bruning (1959) found UD in 3 of 500 female autopsy specimens. In 1967, Andersen reported the results of PPU done for 300 women with cervical cancer but without lower urinary tract symptoms and found UD in 3%. Aldridge and colleagues (1978) reported a prevalence of UD of 1.4% in women presenting with incontinence and related symptoms. Stewart and associates (1981) found UD in 16 of 40 highly symptomatic females investigated with PPU. Endorectal coil MRI was performed on 140 consecutive female patients with lower urinary tract symptoms, and the incidence of UD was approximately 10% (Lorenzo et al, 2003). However, this represented a series of symptomatic females at a tertiary referral center and therefore probably is not reflective of the general population. Burrows and colleagues (2004) reviewed U.S. hospital and ambulatory surgery databases and concluded that the rate of urethral diverticulectomy surgery from 1994 to 1996 was approximately 6.7 per 1 million females. However, this is well below the historical prevalence figures cited previously. Further complicating an accurate assessment of the epidemiology of UD is that the condition can be asymptomatic and is often misdiagnosed or overlooked.

Some series have suggested a racial predilection, with African-Americans being as much as six times as likely to develop UD as their Caucasian counterparts (Davis and Robinson, 1970). This distribution was historically believed to be attributed to an urban bias because most of the clinical series of these cases were reported from academic medical centers in large cities. However, a recent retrospective series from the Cleveland Clinic revealed that approximately two thirds of urethral diverticulectomies performed at that

institution over a 26-year period were in Caucasians. Nevertheless, inpatient surgery for UD in the United States occurred threefold more commonly in African-Americans than in whites from 1979 to 1997 (Burrows et al, 2004).

Diverticular Anatomy and Histology

The interior surface of UD may be urothelial, squamous, columnar, or cuboidal epithelium, or mixed (Tsivian et al, 2009). In some cases, the epithelium is absent and the wall of the UD consists of only fibrous tissue. Two thirds of resected UD demonstrate inflammatory changes (Thomas et al, 2008).

Most UD demonstrate benign histopathology but premalignant and malignant changes can be seen. Approximately 10% of urethral diverticulectomy specimens may demonstrate significant histopathologic abnormalities, including metaplasia, dysplasia, or frank carcinoma, that require long-term follow-up or additional therapy (Thomas et al, 2008). Fewer than 100 cases of carcinoma within UD have been reported in the English-language literature (Rajan et al, 1993). The most common malignant pathology in UD is adenocarcinoma, followed by transitional cell and squamous cell carcinomas (Rajan et al, 1993; Thomas et al, 2008). This is in direct contrast to primary urethral carcinoma, in which the primary histologic type is squamous cell carcinoma. Some authors have suggested that UD is associated with the development of urethral adenocarcinoma in the female (Oliva and Young, 1996). If this is true, then observational management or nonexcisional therapy of UD, such as marsupialization or endoscopic incision, should always be combined with a biopsy to rule out malignancy (McLoughlin, 1975). There is no consensus on proper treatment in these cases, and recurrence rates are high with local treatment alone (Rajan et al, 1993). The incidental finding of malignancy in these cases can be particularly troubling when found intraoperatively, or even more disturbing on the postoperative pathology report. Although it is interesting to speculate, it has not been conclusively demonstrated that any particular preoperative imaging modality, such as ultrasonography or MRI (Chung et al, 2010), can reliably and prospectively diagnose a small malignancy arising in a UD. When considering curative therapy, it is unclear whether extensive surgery, including cystourethrectomy with or without adjuvant external beam radiotherapy, is superior to local excision followed by radiotherapy (Patanaphan et al, 1983).

Multiple benign lesions, including both nephrogenic adenoma and endometriosis, have been described within UD (Palagiri, 1978; Peterson and Matsumoto, 1978; Piazza et al, 1987; Paik and Lee, 1997). Pathologically, nephrogenic adenoma can be difficult to differentiate from adenocarcinoma.

Calculi within UD are not uncommon and may be diagnosed in 4% to 10% of cases (Ward et al, 1967; Ginesin et al, 1988; Romanzi et al, 2000) and are most likely due to urinary stasis and/or infection (Fig. 90-16). They may be suspected by physical examination findings or noted incidentally on imaging evaluation. The presence of a stone will not significantly alter the evaluation or surgical approach and can be considered an incidental finding. The stone is removed with the UD specimen at the time of surgery.

UD are found within the periurethral fascia bordered by the anterior vaginal wall ventrally. The size of the lesion may vary from only a few millimeters to several centimeters. In addition, the size may vary over time as a result of inflammation, intermittent obstruction of the ostium, and subsequent drainage into the urethral lumen. In the sagittal plane, UD are most often located and centered at the level of the middle third of the urethra, with the luminal connection, or ostium, located posterolaterally. They may extend distally along the vaginal wall almost to the urethral meatus, or proximally up to and beyond the bladder neck underneath the trigone of the bladder (Fig. 90-17). A bewildering array of configurations can be noted on imaging and at surgical exploration (Table 90-1). In the axial plane, the UD cavity may extend laterally along the urethral wall and, in some cases, around to the dorsal side of the urethra or may wrap circumferentially around the entire urethra.

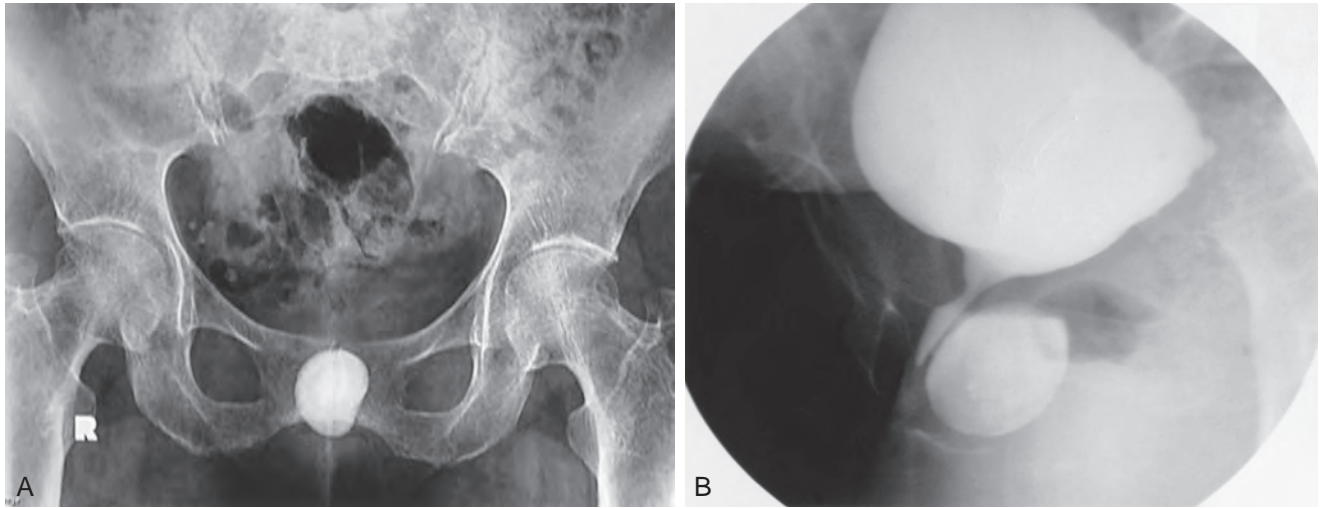


Figure 90-16. Calculi within a urethral diverticulum. A, Scout film shows a calcified density overlying the symphysis pubis. B, Voiding image from a voiding cystourethrogram demonstrates that the density seen on the scout film represents a stone within a urethral diverticulum.

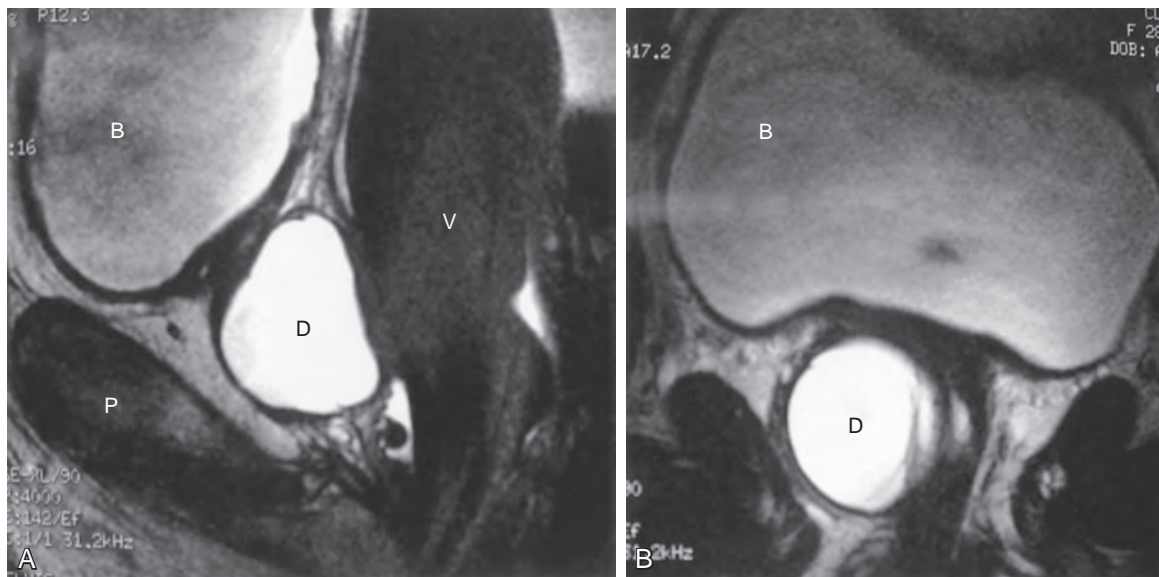


Figure 90-17. T2 MRI demonstrating a large urethral diverticulum (D) extending to the trigone of the bladder (B) in the sagittal (A) and coronal (B) planes. P, symphysis pubis; V, vagina.

UD may be bilobed (dumbbell shaped), extending across the midline in a so-called saddlebag configuration (see Fig. 90-15). Multiple loculations are not uncommon, and approximately 6% of patients have multiple UD at presentation (Thomas et al, 2008). Varying degrees of sphincteric compromise may exist because of the location of diverticulum relative to the proximal and distal urinary sphincter mechanisms, or sphincteric compromise may coexist with UD as a result of other factors. This is important to note when considering surgical repair, as discussed later.

Presentation

The majority of patients with UD present between the third and seventh decades of life (Johnson, 1938; Moore, 1952; Pathak and House, 1970; Ginsburg and Genadry, 1983; Ganabathi et al, 1994). The presenting symptoms and signs in patients with UD are protean (Box 90-1). The classic presentation of UD has been described

historically as the “three Ds”—dysuria, dyspareunia, and dribbling (postvoid)—but this presentation is only infrequently seen. Such a designation is of historical interest only because it was coined in the period before extensive radiologic imaging was available (Lee and Fynes, 2005). However, individually or collectively, these symptoms are neither sensitive nor specific for UD. Although presentation is highly variable, the most common symptoms are irritative (frequency, urgency, etc.) lower urinary tract symptoms, pain, and infection (Davis and TeLinde, 1958; Davis and Robinson, 1970; Peters and Vaughan, 1976; Leach et al, 1986). Dyspareunia will be noted by 12% to 24% of patients (Davis and TeLinde, 1958; Davis and Robinson, 1970). Approximately 5% to 32% of patients will complain of postvoid dribbling (Davis and Robinson, 1970; Ganabathi et al, 1994) and one third will have associated incontinence (Ganabathi et al, 1994). Recurrent cystitis or UTI is also a frequent presentation, seen in one third of subjects (Davis and Robinson, 1970; Ganabathi et al, 1994), probably as a

TABLE 90-1 Diverticular Morphology and Characteristics

SERIES	NUMBER OF PATIENTS	SIZE RANGE (cm)	AXIAL LOCATION (%)			NUMBER (%)		CORONAL LOCATION (%)		
			ANTERIOR	LATERAL	POSTERIOR	SINGLE	MULTIPLE	PROXIMAL	MID	DISTAL
Lang and Davis (1959)	108	N/A	N/A	N/A	N/A	N/A	N/A	11(10)	50(46)	47(44)
Hoffman and Adams (1965)	60	0.5-5.0	N/A	N/A	N/A	N/A	N/A	4(7)	29(48)	23(38)
Pavlica et al (1988)	47	0.5-6.0	3(6)	6(13)	38(81)	41(87)	6(13)	3(6)	39(83)	5(11)
Kim et al (1993)	16	0.9-4.5	5(31)*	N/A	11(69)	N/A	N/A	4(25)	10(63)	2(12)
Leach et al (1993)	61	0.02-5.0	N/A	N/A	N/A	55(90)	6(10)	15(25)	37(60)	9(15)

*Anterior and lateral.
Modified from Westney OL, Leng WW, McGuire EJ. The diagnosis and treatment of female urethral diverticulum [lesson 37]. AUA Update Series 2001;20:291.

BOX 90-1 Signs and Symptoms of Urethral Diverticula**SYMPTOMS**

Vaginal or pelvic mass
 Pelvic pain
 Urethral pain
 Dysuria
 Urinary frequency
 Postvoid dribbling
 Dyspareunia
 Urinary urgency
 Incontinence
 Urinary hesitancy
 Vaginal or urethral discharge
 Double voiding
 Sense of incomplete emptying

SIGNS

Recurrent urinary tract infection
 Hematuria
 Vaginal or perineal tenderness
 Urinary retention
 Vaginal mass
 Urethral discharge with stripping of anterior vaginal wall

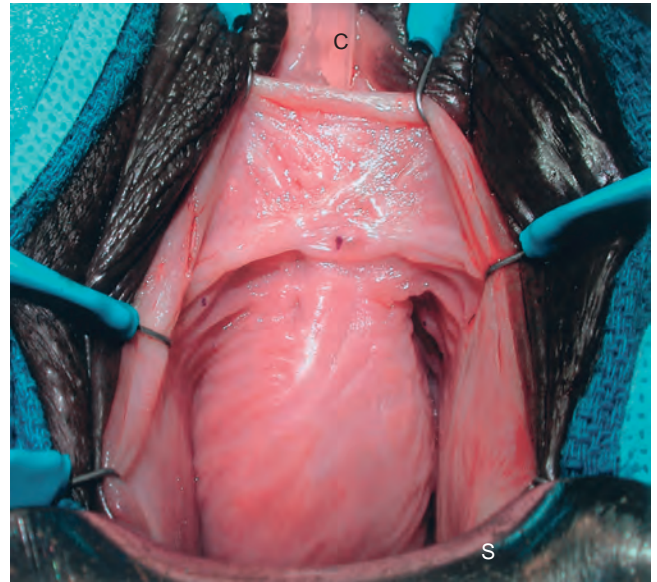


Figure 90-18. Large anterior vaginal wall mass. The urethral catheter (C) is seen superiorly, and a weighted vaginal speculum (S) is seen inferiorly. Scott retractor hooks are seen exposing the anterior vaginal wall in this intraoperative photograph.

result of urinary stasis in the UD. Multiple bouts of recurrent cystitis should alert the clinician to the possibility of a UD. Other complaints include pain, a vaginal mass, hematuria, vaginal discharge, obstructive symptoms or urinary retention, and incontinence (stress or urge). Patients may present with complaints of a tender or nontender anterior vaginal wall mass, which upon gentle compression may reveal retained urine or purulent discharge per the urethral meatus. Although spontaneous rupture of these lesions is extremely rare, urethrovaginal fistula may result under these circumstances (Nielsen et al, 1987). Notably, up to 20% of patients diagnosed with UD may be completely asymptomatic, having the lesions diagnosed incidentally on imaging or physical examination.

It is important to note that the size of the UD does not correlate with symptoms. In some cases, very large UD may result in minimal symptoms, and, conversely, some UD that are nonpalpable may result in considerable patient discomfort and distress. Finally, symptoms may wax and wane and even resolve for long periods of time. The reasons for these exacerbations and remissions are poorly understood but may be related to periodic and repeated episodes of infection and inflammation.

Because many of the symptoms associated with UD are nonspecific, patients may often be misdiagnosed and treated for years for a number of unrelated conditions before the diagnosis of UD is made. This may include therapies for interstitial cystitis, recurrent cystitis, vulvodynia, endometriosis, and vulvovestibulitis. In one series of 46 consecutively examined women eventually diagnosed with UD, the mean interval from onset of symptoms to diagnosis was 5.2 years (Romanzi et al, 2000). In this series, women consulted with an average of nine physicians prior to the definitive diagnosis being made, despite the fact that 52% of women had a palpable mass on examination. This underscores the importance of a baseline level of suspicion and a thorough pelvic examination in female patients complaining of lower urinary tract symptoms or other symptoms that may be associated with UD.

UD has also been reported to present during pregnancy. Moran and colleagues (1998) reported four cases of UD diagnosed during pregnancy. Conservative treatment included antibiotics and aspiration or incision and drainage. Two women delivered vaginally and the other two delivered by cesarean section for unrelated reasons.

In one patient, drainage was performed during labor to facilitate delivery. Three of the four women had definitive repair performed after delivery. It is not known if pregnancy is associated with formation of UD, although patients may be more likely to become symptomatic during this period. Usually, conservative management with antibiotics may be desirable until after delivery to avoid precipitating premature labor, although successful surgical treatment during pregnancy has been reported (Wittich, 1997).

Evaluation and Diagnosis

The diagnosis of UD can be made with a combination of a thorough history, physical examination, appropriate urine studies (including urine culture and analysis), endoscopic examination of the bladder and urethra, and selected radiologic imaging. A urodynamic study may also be helpful in completing the evaluation in selected cases.

History and Physical Examination. A thorough history is essential in patients presenting with a diagnosis of UD as well as those without an established diagnosis. Though the presenting symptoms and signs are nonspecific for UD, a thorough accounting of lower urinary tract symptoms, signs (hematuria, etc.), prior diagnostic studies, and response to therapy is critical. Such an approach will permit appropriate counseling regarding improvement or resolution of symptoms in those individuals with a diagnosis of UD and may suggest such a diagnosis in those presenting as diagnostic dilemmas. Important historical data include prior pelvic surgery, especially incontinence procedures; bulking agents may present as UD on imaging (Kumar et al, 2011) and prior sling surgery may present difficulties in accessing and surgically repairing the UD. The presence or absence of urinary incontinence and pad usage, as well as the type of incontinence (urge vs. stress vs. postvoid dribbling, etc.) should be recorded. Sexual function and dyspareunia should be documented as well because vaginal reconstructive surgery may have adverse (or favorable) effects on these individuals.

During physical examination, the anterior vaginal wall should be carefully palpated for masses and tenderness. The location, size, and consistency of any suspected UD should be recorded. Most UD are located ventrally over the middle and proximal portions of the urethra, corresponding to the area of the anterior vaginal wall 1 to 3 cm inside the introitus (Fig. 90-18). More distal lesions

near the urethral meatus or distorting the urethral meatus are likely Skene gland cysts or abscesses. Only about one third of UD present with a tender anterior vaginal wall mass (Ganabathi et al, 1994). However, UD may also be located anterior to the urethra or extend partially or completely around the urethral lumen. UD may also extend proximally toward the bladder neck. These UD may produce distortion of the bladder outlet and trigone of the bladder on cystoscopy or on radiographic imaging. Special care should be taken during surgical excision and reconstruction owing to concerns for intraoperative bladder and ureteral injury, as well as the potential development of postoperative voiding dysfunction and urinary incontinence.

Distal vaginal masses or perimeatal masses may represent other lesions, including abnormalities of Skene glands (see later discussion). The differentiation between these lesions sometimes cannot be made on the basis of a physical examination alone and may require additional radiologic imaging. A particularly hard anterior vaginal wall mass may indicate a calculus or malignancy within the UD and mandates further investigation. During physical examination, the urethra may be gently “stripped” or “milked” distally in an attempt to express purulent material or urine from within the UD cavity. Although often described for the evaluation of UD, this maneuver is not successful in producing the characteristic discharge per urethral meatus in the majority of patients (Leach and Bavendam, 1987).

The vaginal walls are assessed for atrophy, rugation, and elasticity. Poorly estrogenized, atrophic tissues are important to note if surgery is being considered for definitive treatment. These tissues are mobilized intraoperatively and may be used for flaps during excision and reconstruction. Topical estrogens may be administered preoperatively in such cases to improve the quality of the tissues. The distal vagina and vaginal introitus are also assessed for capacity. These factors may have an impact on surgical planning, because a narrow introitus can make surgical exposure difficult and may mandate an episiotomy or other measures. Finally, during physical examination a provocative maneuver to elicit stress incontinence should be performed, as well as an assessment of the presence or absence of any vaginal prolapse.

Urine Studies. Urine analysis and culture should be performed. The most common organism isolated in patients with UD is *E. coli*. However, other gram-negative enteric flora, as well as *N. gonorrhoeae*, *Chlamydia*, streptococci, and staphylococci, are often present (Davis and TeLinde, 1958; Hoffman and Adams, 1965). A sterile urine culture does not exclude infection, because these patients are often on antibiotic therapy at presentation. In patients with irritative symptoms or in whom a malignancy is suspected, urine cytology can be performed.

Cystourethroscopy. Cystourethroscopy is performed in an attempt to visualize the UD ostium as well as to evaluate for other causes for the patient’s lower urinary tract symptoms. A flexible fiberoptic cystoscope or specially designed rigid female cystoscope can be extremely helpful in evaluating the female urethra. The short beak of the female cystoscope and the lack of a beak on a flexible cystoscope maintain the discharge of the irrigation solution immediately adjacent to the lens and thus aid in distention of the relatively short (as compared to the male) urethra, permitting improved visualization. It may also be advantageous to compress the bladder neck while an assistant simultaneously applies pressure to the diverticular sac with a finger. Luminal discharge of purulent material can often be seen with this maneuver or with simple digital compression of the UD during urethroscopy. The UD ostium is most often located posterolaterally at the 4 and 8 o’clock positions at level of the mid-urethra but can be very difficult to identify in some patients (Fig. 90-19). The success in identifying a diverticular ostium on cystourethroscopy is highly variable and is reported to range from 15% to 89% (Davis and Robinson, 1970; Leach and Bavendam, 1987; Ganabathi et al, 1994). As a note of caution, patients with UD are often highly symptomatic, and endoscopic examination can be very difficult to initiate or complete without anesthesia. Notably, a positive examination may help in

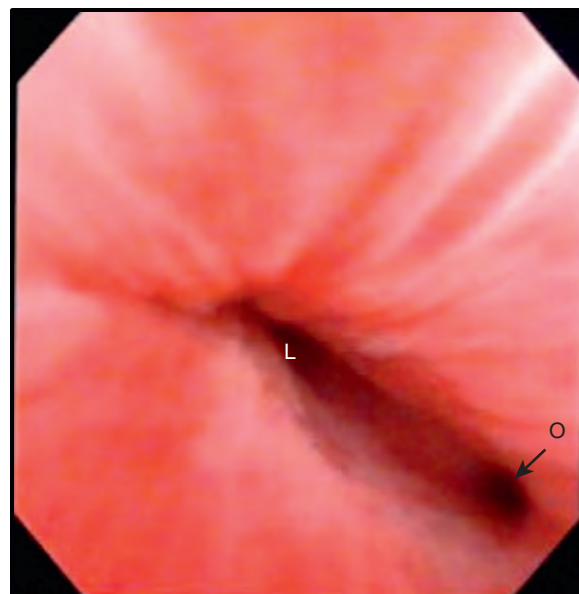


Figure 90-19. Cystoscopic view of the ostium (O) of a UD, which is often difficult to visualize endoscopically. L, lumen of the urethra.

surgical planning; however, the failure to locate an ostium on cystourethroscopy should not influence the decision to proceed with further investigations or surgical repair.

Urodynamics. For patients with UD and urinary incontinence or significant voiding dysfunction, a urodynamic study may be helpful in accurately characterizing these symptoms (Bhatia et al, 1981; Reid et al, 1986; Summitt and Stovall, 1992). Urodynamics may document the presence or absence of stress urinary incontinence (SUI) prior to repair. Approximately one third of women will present with symptoms of urinary incontinence and approximately 50% of women with UD will demonstrate SUI on urodynamic evaluation (Bass and Leach, 1991; Ganabathi et al, 1994). A video-urodynamic study is optimal as it combines both a VCUG and a urodynamic study, thus consolidating the diagnostic evaluation and decreasing the number of required urethral catheterizations during the patient’s clinical workup. For patients undergoing surgery for UD who have coexistent symptomatic SUI demonstrated on physical examination or urodynamically demonstrable SUI, or in those found to have an open bladder neck on preoperative evaluation, a concomitant anti-incontinence surgery can be offered. Multiple authors have described successful repair of UD and stress incontinence in the same operative setting (Bass and Leach, 1991; Swierzewski and McGuire, 1993; Ganabathi et al, 1994; Faerber, 1998). Synthetic materials (e.g., mid-urethral polypropylene mesh) should not be used in an anti-incontinence procedure synchronously with UD surgery because of the potentially increased risk of urethral erosion and infection (Dmochowski et al, 2010). Whether such material can be safely used months or years following successful UD surgery in patients with de novo or persistent SUI is unknown. Alternatively, a small number of patients may have evidence of bladder outlet obstruction on urodynamic evaluation because of the obstructive or mass effects of the UD on the urethra. It should be noted that SUI may coexist with obstruction (Bradley and Rovner, 2004) but, nevertheless, both conditions can be treated successfully with a carefully planned and executed operation. For patients with mild nonbothersome SUI, it is reasonable to perform urethral diverticulectomy and then re-evaluate for the development of postoperative SUI.

Urethral pressure profilometry has also been used by some authors to assess and/or diagnose patients with UD, noting a biphasic pattern or pressure drop at the level of the lesion during

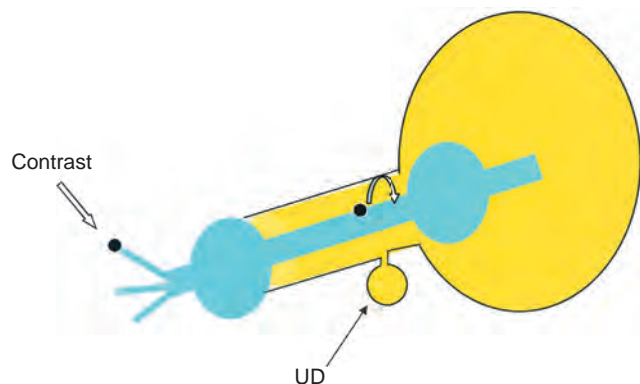


Figure 90-20. Schematic diagram of a double-balloon catheter. The curved white arrow represents flow of the contrast as it enters the urethral lumen. UD, urethral diverticulum.

the study (Bhatia et al, 1981; Wagner et al, 1986; Summitt and Stovall, 1992).

Imaging

High-quality preoperative imaging is important in the diagnosis and therapy of female UD. Aside from its utility as a diagnostic entity, radiologic imaging should also provide an accurate reflection of the relevant anatomy of the UD, including its relationship to the proximal urethra and bladder neck.

Diagnostic Contrast Radiography. A number of imaging techniques have been applied to the study of female UD, and no single study can be considered the gold standard or optimal imaging study for the evaluation of UD. Each technique has relative advantages and disadvantages, and the ultimate choice of diagnostic study in many centers often depends on several factors, including local availability, cost, and the experience and expertise of the radiologist. Currently available techniques for the evaluation of UD include double-balloon PPU, VCUG, intravenous urography, ultrasonography, and MRI with or without an endoluminal coil.

Historically, double-balloon PPU had been considered to be the optimal study for the diagnosis and assessment of female UD (Davis and Cian, 1956; Davis and TeLinde, 1958; Greenberg et al, 1981; Ganabathi et al, 1994). In this technique, a highly specialized catheter (Trattner catheter) with two balloons separated by several centimeters is inserted into the female urethra (Fig. 90-20). This catheter contains a channel that exits through a side hole between the two balloons. One balloon is positioned adjacent to the external urethral meatus, and the other balloon is situated at the bladder neck. Both balloons are inflated, creating a seal about the urethral lumen. Contrast is then infused through the channel under slight pressure, distending the urethral lumen between the two balloons and forcing contrast into the UD, thereby opacifying the cavity. This highly specialized study provides outstanding images of the urethra and UD and importantly, unlike VCUG, is not dependent on the patient successfully voiding during the study. However, PPU is not widely performed clinically and the specialized Trattner catheter is only variably available.

As an alternative to PPU, VCUG may provide excellent imaging of UD (Fig. 90-21). It is widely available and is a familiar diagnostic technique to most radiologists. Sensitivity for UD with this technique varies from 44% to 95% (Ganabathi et al, 1994; Jacoby and Rowbotham, 1999). Patients often will have difficulty in initiating micturition in the radiology suite because of the pain associated with urethral catheterization, psychogenic inhibition attributable to voiding in the presence of others, or other factors. In the absence of voiding, the UD will often not be seen. Therefore a VCUG that does not demonstrate a UD but did not contain voiding images or postvoid images is nondiagnostic. If the patient is unable to

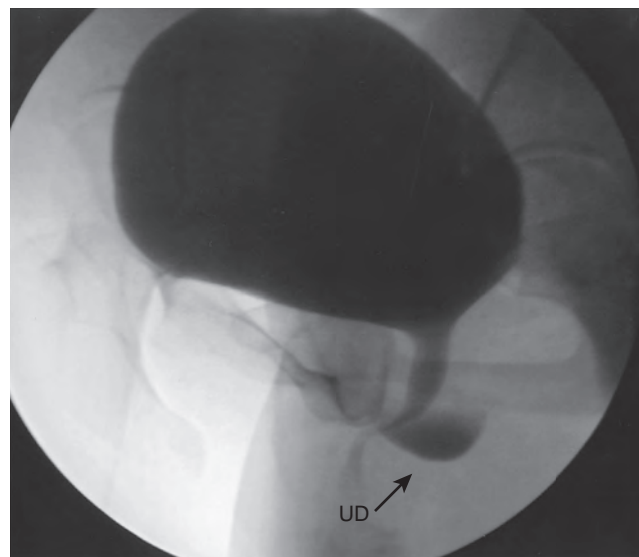


Figure 90-21. Voiding image from a voiding cystourethrogram demonstrating a urethral diverticulum (UD).

void under fluoroscopy during the VCUG, an attempt should be made to void in the privacy of an adjacent bathroom. If voiding in private was successful, a postvoid film taken under these circumstances will likely show a collection of contrast inferior to the bladder demonstrating the UD. Unfortunately, an inability to generate an adequate flow rate during the VCUG will result in suboptimal filling of the UD and an underestimation of its size and complexity (Fig. 90-22). Three-dimensional CT VCUG with reconstructions is a novel imaging technique for UD but is not yet widely available clinically (Kim et al, 2005).

Intravenous urography may be considered in patients in whom it is necessary to delineate the upper urinary tract or to evaluate for the possibility of a congenital ectopic ureteral anomaly as the cause of an anterior vaginal wall mass (Blacklock et al, 1982). The postvoid film of the urogram can be helpful for the diagnosis of UD in some patients (Stern and Patel, 1976; Goldfarb et al, 1981).

Ultrasonography. This study has been advocated for the preoperative assessment of vaginal masses and UD by multiple authors (Lee and Keller, 1977; Wexler and McGovern, 1980; Baert et al, 1992; Mårtensson and Duchek, 1994; Chancellor et al, 1995; Vargas-Serrano et al, 1997; Dmochowski, 2001; Fortunato et al, 2001; Lee et al, 2001; Gerrard et al, 2003). Abdominal, transvaginal, translabial, and transurethral techniques have been described. Transvaginal imaging often provides information regarding the size and location of UD. On ultrasonographic imaging, the UD appears as an anechoic or hypoechoic area with enhanced through-transmission. Ultrasonography is relatively noninvasive and does not expose the patient to radiation. Another significant advantage of ultrasonography is that successful imaging of UD does not require voiding. However, ultrasonography may not produce detailed high-resolution images that demonstrate precise surgical anatomy.

Magnetic Resonance Imaging. As an alternative to the radiologic investigations noted previously, MRI permits relatively noninvasive, high-resolution, multiplanar imaging of UD. UD appear as areas of decreased signal intensity on T1 images compared with the surrounding soft tissues, and have high signal intensity on T2 images. A distinct advantage of MRI compared with VCUG is that successful imaging of UD is wholly independent of voiding and that it is free from ionizing radiation. Surface coil (Hricak et al, 1991; Kim et al, 1993) (Fig. 90-23) and endoluminal (Siegelman et al, 1997; Wang and Wang, 2000; Blander et al, 2001; Lorenzo et al, 2003) techniques have been described. Endoluminal magnetic resonance imaging (eMRI) places the magnetic coil into a body

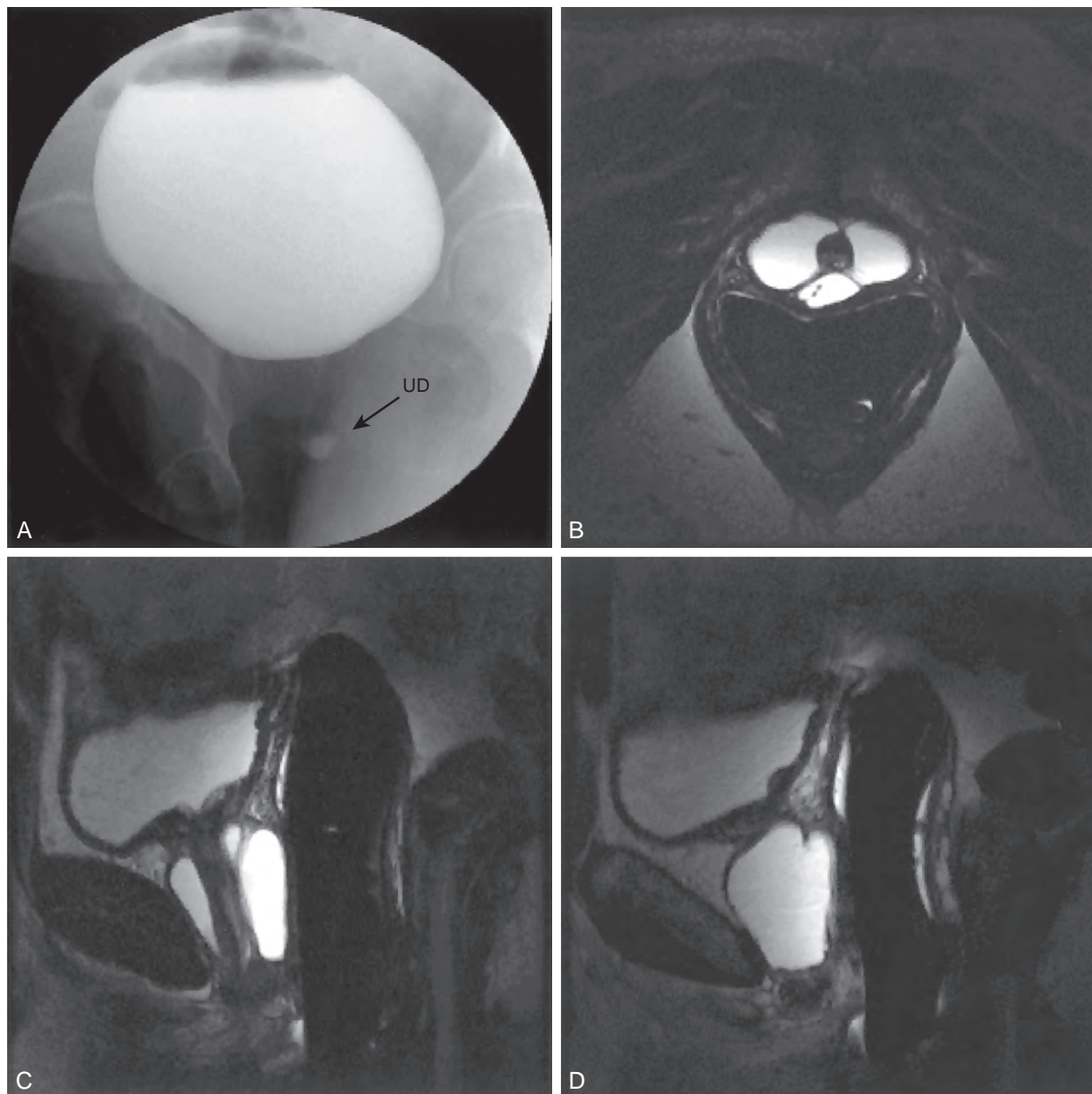


Figure 90-22. Voiding cystourethrogram (VCUG) and magnetic resonance image (MRI) from a patient with a large circumferential urethral diverticulum (UD). A, The voiding image from the VCUG shows poor opacification of the proximal urethra with suboptimal distention of the UD as a result of a poor voiding effort. B to D, The endoluminal MRI demonstrates the full extent and complexity of the lesion on the T2 axial (B), midline sagittal (C), and parasagittal (D) images.

cavity adjacent to the area of interest. This location produces an improved signal-to-noise ratio and high-resolution imaging of these areas (Siegelman et al, 1997; Blander et al, 2001) with excellent sensitivity and specificity for the diagnosis of UD (Dwarkasing et al, 2011). For the evaluation of UD, the eMRI coil is placed intravaginally or intrarectally. Both surface coil MRI and eMRI appear to be superior to VCUG and/or PPU in the evaluation of UD (Kim et al, 1993; Neitlich et al, 1998; Blander et al, 2001), but the technology is expensive and not widely available. Notably, there are several lesions, including periurethral bulking agents, that can be misdiagnosed as UD on MRI, and this imaging technique may be inadequate in the diagnosis of malignancy within UD, a rare but important finding (Chung et al, 2010).

Contraindications to MRI for UD are few; these include metallic foreign body fragments, claustrophobia, and an inability to tolerate the endoluminal probe.

Differential Diagnosis: Periurethral Masses Other Than Urethral Diverticula

Periurethral masses other than UD comprise a wide spectrum of conditions that must be differentiated from each other and UD. It may often be possible to make a definitive diagnosis based on history and physical examination alone; in other cases, judicious use of radiographic and cystoscopic studies will be necessary to exclude UD.

Vaginal Leiomyoma. Vaginal leiomyomata are benign mesenchymal tumors of the vaginal wall that arise from smooth muscle elements. They commonly present as a smooth, firm, round mass on the anterior vaginal wall (Fig. 90-24). Vaginal leiomyoma is an uncommon lesion, with approximately 300 cases reported in the literature (Young et al, 1991). In a recent series of 79 patients with periurethral masses, 4 (5%) were found to have vaginal leiomyoma

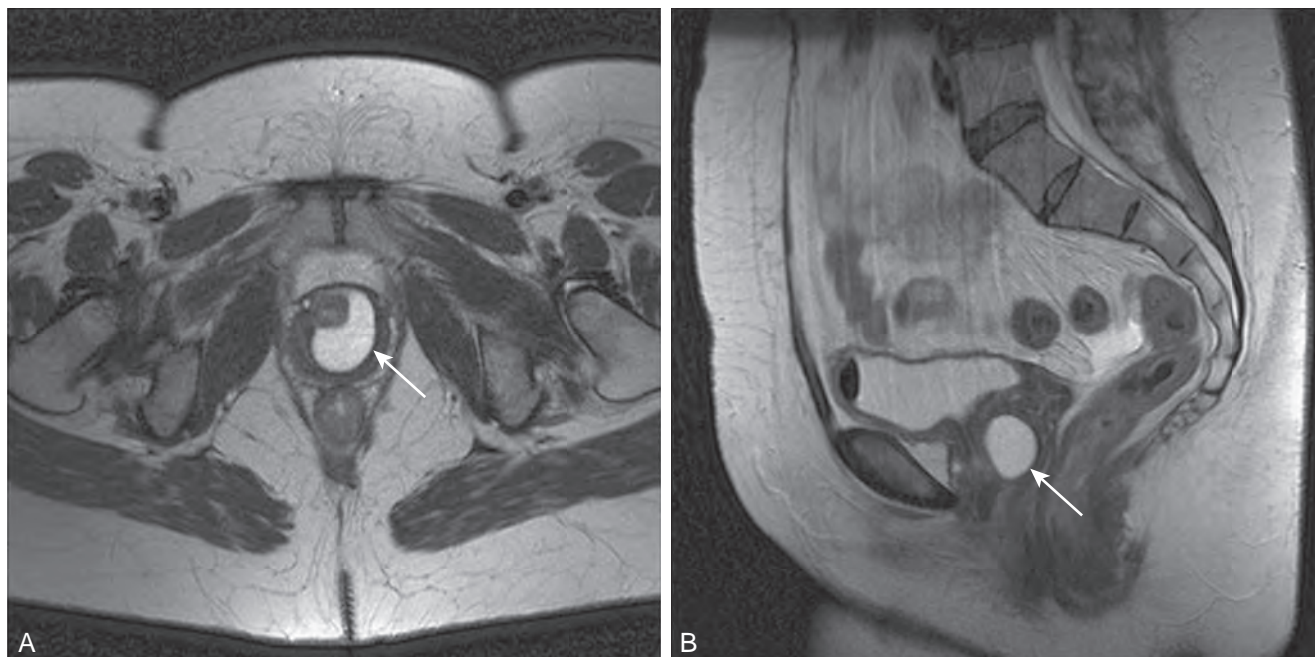


Figure 90-23. Surface coil T2 magnetic resonance image demonstrating a urethral diverticulum (arrows) in the sagittal (A) and axial (B) planes.

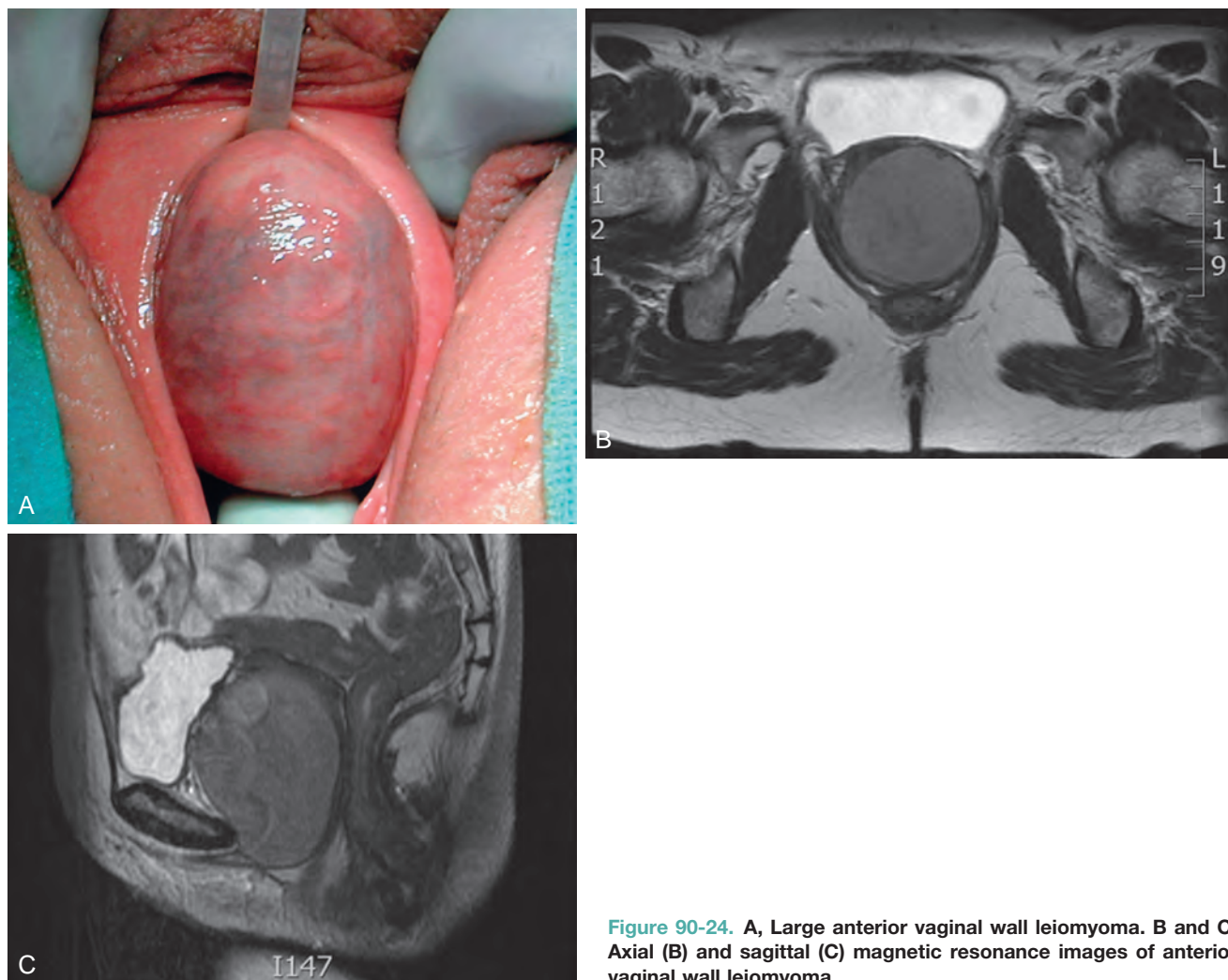


Figure 90-24. A, Large anterior vaginal wall leiomyoma. B and C, Axial (B) and sagittal (C) magnetic resonance images of anterior vaginal wall leiomyoma.

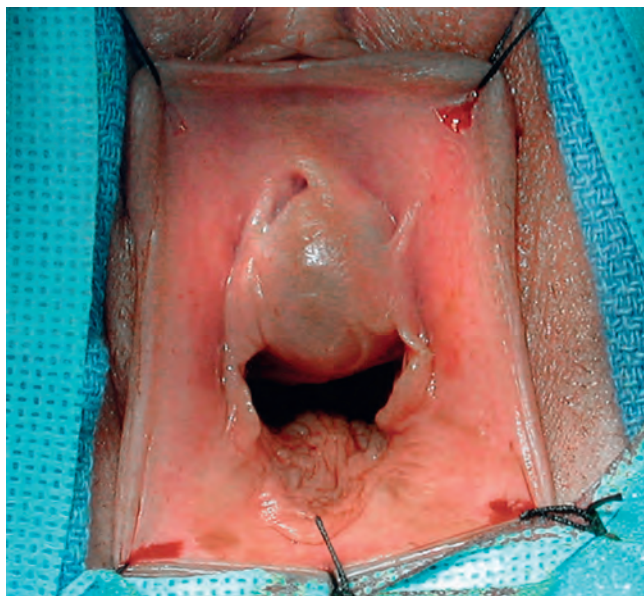


Figure 90-25. Skene gland cyst in a 19-year-old female. Note the large periurethral mass with displacement of the urethral meatus.



Figure 90-26. Upper pole ectopic ureter in a 39-year-old female being evaluated for lifelong urinary incontinence and recurrent pyelonephritis. A tubelike structure (arrow) representing the turgid, debris-filled ectopic ureter is seen on the anterior vaginal wall.

(Blaivas et al, 2004). These masses were all apparent on physical examination as freely mobile, firm, nontender masses on the anterior vaginal wall. They may be misdiagnosed as UD (Shirvani and Winters, 2000). Symptoms, if they exist, are usually related to the size of the lesion and include a mass effect, obstruction, pain, and dyspareunia. They commonly present in the fourth to fifth decade. Similar to uterine leiomyoma, these lesions are usually estrogen dependent and have been demonstrated to regress during menopause (Liu, 1988). Excision or enucleation (Young et al, 1991) through a vaginal approach is often curative and is recommended to confirm the diagnosis, to exclude malignant histology, and also to alleviate symptoms.

Skene Gland Abnormalities. Skene gland cysts and abscesses are similar lesions that are differentiated based on clinical findings (Fig. 90-25). Both lesions generally present as small, cystic masses just lateral or inferolateral to the urethral meatus. They may be lined with transitional or stratified squamous epithelium. Abscesses may be extremely tender and inflamed, and, in some cases, purulent fluid can be expressed from the ductular orifice. **Classically, in contrast to UD, these lesions do not communicate with the urethral lumen.** Skene gland cysts are not uncommonly noted in neonatal girls and young to middle-age female patients (Lee and Kim, 1992). Symptoms may include dysuria, dyspareunia, obstruction, and pain. **Differentiation from UD can often be made on physical examination, because these lesions are located relatively distally on the urethra, often distorting the urethral meatus, as compared with UD, which most commonly occur over the mid- and proximal urethra.** Various treatments for Skene gland abnormalities have been described, including aspiration, marsupialization, incision and drainage, and simple excision. Surgical excision is curative.

Adenocarcinoma arising in Skene glands has been reported. Because of homology with the prostate, these patients may demonstrate elevated prostate-specific antigen levels that normalize with treatment (Dodson et al, 1994).

Gartner Duct Abnormalities. Gartner duct cysts represent mesonephric remnants and are found on the anterolateral vaginal wall from the cervix to the introitus. Because these are mesonephric remnants, they may drain ectopic ureters from poorly functioning or nonfunctioning upper pole moieties in duplicated systems (Fig. 90-26). They have also been reported with single-system ectopia, although this is much less common in females (Gadbois

and Duckett, 1974; Currarino, 1982). It is not clear what proportion of patients with Gartner duct cysts will have ipsilateral renal abnormalities, but upper tract evaluation is recommended. In contrast, approximately 6% of subjects with unilateral renal agenesis will have a Gartner duct cyst (Eilber and Raz, 2003). Up to 50% of patients with Gartner duct cysts and renal dysplasia may also have ipsilateral müllerian duct obstruction (Sheih et al, 1998).

Treatment depends on symptoms and association with ectopic ureters. If the lesions are asymptomatic and are associated with a nonfunctioning renal moiety, they can be observed. Aspiration followed by sclerotherapy has been successful (Abd-Rabbo and Atta, 1991). Simple excision or marsupialization has also been recommended for symptomatic lesions. If the cyst is associated with a functioning renal moiety, treatment must be individualized.

Vaginal Wall Cysts. Vaginal wall cysts usually present as small asymptomatic masses on the anterior vaginal wall (Deppisch, 1975) but may enlarge to cause lower urinary tract symptoms or dyspareunia (Fig. 90-27). They may arise from multiple cell types: mesonephric (Gartner duct cysts), paramesonephric (müllerian), endometriotic, urothelial, or epidermoid (inclusion cyst). A specific diagnosis cannot be reliably made until the specimen is removed and examined by a pathologist. The histologic subtype is usually of little consequence, although epidermoid cysts are usually associated with previous trauma or vaginal surgery. Pradhan and Tobon (1986) described the pathologic characteristics of 43 vaginal cysts removed over a 10-year period from 41 women. The derivation of the cyst was müllerian in 44%, epidermoid in 23%, and mesonephric in 11%. The remainder were a Bartholin gland type, endometriotic, and indeterminate. As with other periurethral masses, they must be differentiated from UD. Treatment is usually by simple excision in symptomatic patients.

Urethral Mucosal Prolapse. Urethral prolapse presents as a circumferential herniation or eversion of the urethral mucosa at the urethral meatus. The prolapsed mucosa commonly appears as a beefy red doughnut-shaped lesion that completely surrounds the urethral meatus. It may be asymptomatic or present with bleeding, spotting, pain, or urinary symptoms. It is commonly noted in two separate populations: postmenopausal women and prepubertal



Figure 90-27. Anterior vaginal wall cyst prior to planned excision. This mass was misdiagnosed as a cystocele and followed for many years in this patient with considerable lower urinary tract symptoms. A midline incision has been marked out prior to operative repair.

girls. Although thought to be more common in young African-American girls, more recent series do not confirm this predilection (Fernandes et al, 1993; Rudin et al, 1997). In children, it is often causally related to Valsalva voiding or constipation. Eversion of the mucosa may then occur as a result of a pathologically loose attachment between smooth muscle layers of the urethra (Lowe et al, 1986). Etiology is much less clear for postmenopausal women, although it has been epidemiologically linked to estrogen deficiency. Treatment may be medical or surgical. Medical treatment involves topical creams (estrogen, anti-inflammatory) and/or sitz baths. Various surgical techniques have been described, including cauterization, ligation around a Foley catheter, and complete circumferential excision. Circumferential excision with suture reapproximation of the remaining urethral mucosa to the vaginal wall can be performed with few complications. Rudin and colleagues (1997) reported outcomes in 58 girls with urethral prolapse. Medical treatment was initially successful in 20 patients among whom there were 5 recurrences. The remaining 38 patients failed initial conservative management and underwent surgical excision with 4 complications, including urethral stenosis in 2 patients. Jerkins and colleagues (1984) found superior results in surgically treated patients when compared with medical management or catheter ligation.

Urethral Caruncle. Urethral caruncle is an inflammatory lesion of the distal urethra that is most commonly diagnosed in postmenopausal women. It usually appears as a reddish exophytic mass at the urethral meatus, which is covered with mucosa. These lesions are often symptomatic and noted incidentally on gynecologic examination. When irritated, they may cause underwear spotting or become painful. Less commonly they may cause voiding symptoms. Rarely, these lesions may thrombose, resulting in a discolored periurethral mass (Fig. 90-28). Etiologically, they are related to mucosal prolapse. Chronic irritation contributes to hemorrhage, necrosis, and inflammatory growth of the tissue that corresponds to the histology of excised lesions. If the lesion is atypical in appearance or behavior, excision may be warranted to exclude other entities. Intestinal metaplasia, tuberculosis, melanoma, and lymphoma have all been reported to either coexist with or mimic urethral

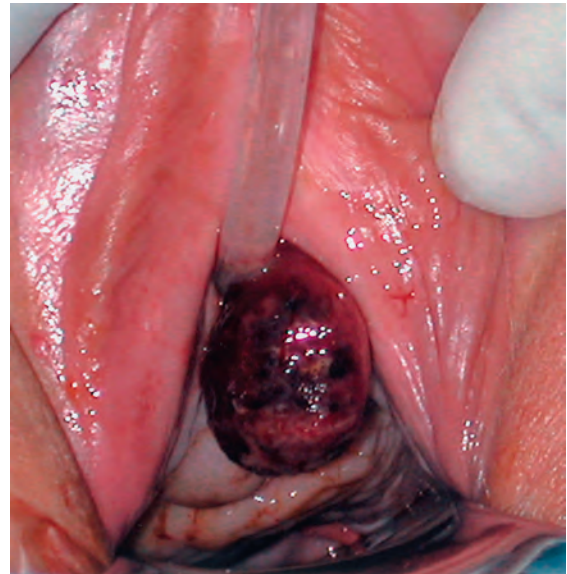


Figure 90-28. Thrombosed urethral caruncle in a postmenopausal female. The Foley catheter is seen in the urethra. Simple excision was curative.

caruncles (Willett and Lack, 1990; Indudhara et al, 1992; Khatib et al, 1993; Lopez et al, 1993; Atalay et al, 1998).

There is a paucity of literature regarding optimal treatment of urethral caruncle. Most authors recommend initial conservative management with topical estrogen or anti-inflammatory creams and sitz baths. Large or refractory lesions may be managed with simple excision. The tip of the lesions should be grasped and traction employed to fully expose the base of the caruncle. The lesion can then easily be excised. If a large defect remains, the mucosa may be reapproximated with absorbable suture. In most instances, the urethral mucosa will heal around a Foley catheter, which may be left in place for several days.

Periurethral Bulking Agents. The transurethral or periurethral injection of bulking agents for the treatment of stress incontinence may result in an anterior vaginal wall mass that appears cystic on imaging, consistent with a UD (Clemens and Bushman, 2001; Bridges et al, 2005; Castillo-Vico et al, 2007). A careful history will elicit this possibility. Typically, these lesions do not communicate with the urethra and are largely asymptomatic. Symptomatic lesions may be surgically excised transvaginally (Kumar et al, 2011).

Classification of Urethral Diverticula

Although not yet widely adopted, a classification system for UD has been proposed by Leach and colleagues (1993). This staging system for UD, termed the L/N/S/C3 classification system, is similar to that used for cancer staging and is based on several characteristics of UD, including location, number, size, anatomic configuration, site of communication to the urethral lumen, and continence status of the patient. This system attempts to standardize description of UD, but currently it has not been prospectively applied or validated by other authors. Another proposed classification scheme uses the location of the UD as the primary determinant of surgical approach, with distal lesions undergoing marsupialization and more proximal lesions undergoing excision and reconstruction (Ginsburg and Genadry, 1983).

Finally, a classification system proposed by Leng and McGuire (1998) divides UD into two categories based on the presence or absence of a preserved periurethral fascial layer. In some patients with UD who have undergone prior vaginal or urethral surgery, the periurethral fascial layer may be deficient, resulting in a pseudodiverticulum. These authors suggest that the recognition of this anatomic configuration has important implications for surgical

reconstruction. These patients may require additional reconstruction or interposition of a tissue flap or graft for reconstruction.

KEY POINTS: FEMALE URETHRAL DIVERTICULA—DIAGNOSIS

- Female UD are often diagnosed in the evaluation of nonspecific lower urinary tract symptoms, including dysuria, pelvic pain, vaginal mass, dyspareunia, and recurrent UTIs.
- Multiple imaging modalities may be used in the diagnosis and evaluation of female UD, including PPU, VCUG, ultrasonography, and MRI; each of these techniques has inherent advantages and disadvantages.
- The differential diagnosis of periurethral vaginal masses is extensive. A careful history, physical examination, and appropriate diagnostic studies will usually be adequate to provide a definitive preoperative diagnosis.

Surgical Repair of Female Urethral Diverticula

Indications for Repair

Although often highly symptomatic, not all UD mandate surgical excision. Some patients may be asymptomatic at presentation, with the lesion incidentally diagnosed on imaging for another condition

or, perhaps, incidentally noted on routine physical examination. Other patients may be unwilling or medically unable to undergo surgical removal. Very little is known regarding the natural history of untreated UD. Whether these lesions will progress in size, symptomatology, or complexity with time is unknown. For these reasons, and because of the lack of symptoms in selected cases, some patients may not desire surgical therapy. However, it should be noted that there are multiple reports in the literature of carcinomas arising in UD (Marshall and Hirsch, 1977; Prudente de Toledo et al, 1978; Tesluk, 1981; Tines et al, 1982; Patanaphan et al, 1983; Gonzalez et al, 1985; Thomas and Maguire, 1991; Rajan et al, 1993; Seballos and Rich, 1995; Hickey et al, 2000), and it is possible that certain carcinomas arising in UD are asymptomatic and may not be initially or prospectively identified on radiologic imaging (Chung et al, 2010). Thus patient counseling is necessary with patients who elect primary nonoperative management. Patients electing nonoperative management can be treated with low-dose antibacterial suppressants and digital stripping of the anterior vaginal wall following micturition to prevent postvoid dribbling and reduce the risk of UTI resulting from stasis in the UD. Whether long-term surveillance is required in these patients, with periodic physical examinations, radiographic imaging, or endoscopic examination, is unknown.

Symptomatic patients, including those with dysuria, refractory bothersome postvoid dribbling, recurrent UTIs, dyspareunia, and pelvic pain, may be offered surgical excision. Those with UD and symptomatic SUI can be considered for a concomitant anti-incontinence procedure at the time of UD excision (see later discussion) (Fig. 90-29).

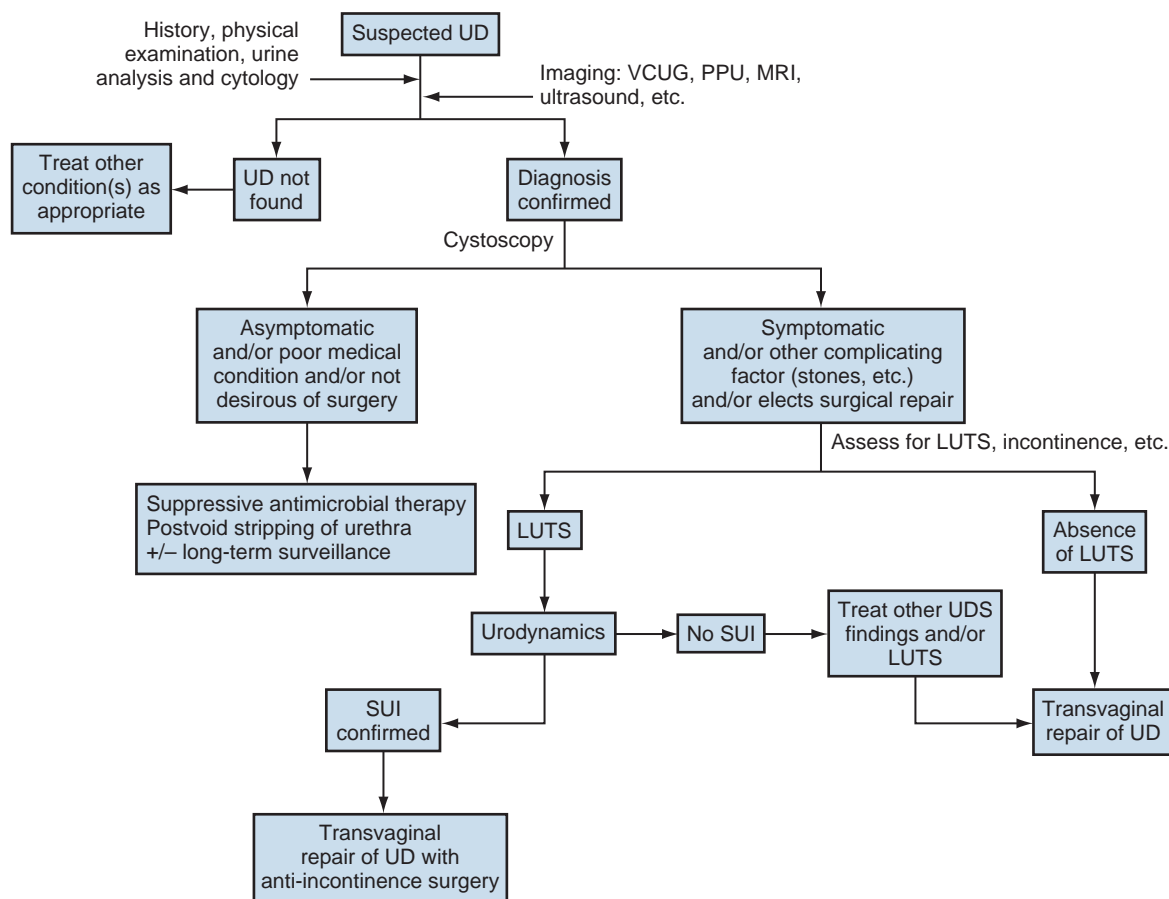


Figure 90-29. Algorithm for treatment of urethral diverticula. LUTS, lower urinary tract symptoms; MRI, magnetic resonance imaging; PPU, positive-pressure urethrography; SUI, stress urinary incontinence; UD, urethral diverticulum; UDS, urodynamics; VCUG, voiding cystourethrography.

Techniques for Repair

Alternative Techniques. A variety of surgical interventions for UD have been reported since 1805 when Hey described transvaginal incision of the UD and packing the resulting cavity with lint. Approaches have included transurethral (Davis and Robinson, 1970) and open (Spence and Duckett, 1970; Roehrborn, 1988) marsupialization, endoscopic unroofing (Lapides, 1978; Spencer and Stroom, 1987), fulguration (Saito, 2000), incision and obliteration with oxidized cellulose (Ellick, 1957) or polytetrafluoroethylene (Mizrahi and Bitterman, 1988), coagulation (Mizrahi and Bitterman, 1988), and excision with reconstruction. **Most commonly, a complete excision and reconstruction is performed as described below.** However, for distal lesions, a transvaginal marsupialization as described by Spence and Duckett may reduce operative time, blood loss, and recurrence rate (Spence and Duckett, 1969, 1970; Roehrborn, 1988). During this procedure, care must be taken to avoid aggressively extending the incision proximally, which could result in vaginal voiding or potentially damage the proximal and distal sphincteric mechanism, resulting in SUI. Another potentially significant complication with the Spence-Duckett procedure is that, in sexually active women, a pseudoseptum may be created by the marsupialization of the urethra with respect to the anterior vaginal wall, which may result in dyspareunia. Therefore this approach is probably only applicable to UD in very select cases involving the distal one third of the urethra. It is not commonly performed.

Excision and Reconstruction. Excision and reconstruction is probably the most common surgical approach to UD in the modern era. The principles of the urethral diverticulectomy operation have been well described (Box 90-2). There are only a few minor issues about which some surgeons may disagree, including the type of vaginal incision (inverted “U” vs. inverted “T”), whether it is necessary to remove the entire mucosalized portion of the lesion, and, finally, the optimal type of postoperative catheter drainage (urethra only vs. urethra and suprapubic).

Complex urethral reconstructive techniques for the repair of UD have been described. Fall (1995) described the use of a bipedicle vaginal wall flap for urethral reconstruction in patients with UD and urethrovaginal fistula. Laterally based vaginal flaps have also been used as an initial approach to UD (Woodhouse et al, 1980; Appell and Suarez, 1982). Complex anatomic configurations may exist, and many novel approaches have been described for complicated anteriorly located or circumferential lesions (Clyne and Flood, 2002; Rovner and Wein, 2003; Vakili et al, 2003).

The technique described herein is similar to that described by Leach and Raz (Leach et al, 1986), based on earlier work by Benjamin and colleagues (1974) and Busch and Carter (1973).

Preoperative Preparation. The urine should be sterile preoperatively. Surgery should not proceed in the setting of an acute UTI. Prophylactic antibiotics are often used preoperatively to ensure sterile urine at the time of surgery. Patients can also be encouraged to strip the anterior vaginal wall following voiding, thereby consistently emptying the UD and preventing urinary stasis and recurrent

UTIs. This may not be possible in those with noncommunicating UD or in those who have significant pain related to the UD. In some patients with postmenopausal atrophic vaginitis, application of topical estrogen creams for several weeks prior to surgery may be beneficial in improving the overall quality of the tissues with respect to planned operative dissection and mobilization. Preoperative parenteral antibiotics are administered especially for those with recurrent or persistent UTIs.

Urethral diverticulectomy surgery is complex and sometimes quite technically challenging. Further complicating these cases are the associated preoperative symptoms, such as pain, dyspareunia, voiding dysfunction, UTIs, and urinary incontinence. These associated symptoms are often, but not always, improved or eliminated with surgical repair despite even a technically successful surgery. Therefore the importance of appropriate preoperative patient counseling regarding surgery and postoperative expectations of cure cannot be overemphasized.

Patients with symptomatic SUI can be offered simultaneous anti-incontinence surgery. Preoperative video-urodynamics may be helpful in evaluating the anatomy of the UD, assessing the competence of the bladder neck, and confirming the diagnosis of SUI. Video-urodynamics can often accurately differentiate and characterize true SUI from postvoid dribbling, vaginal voiding, and false incontinence resulting from urine discharge from a urine-filled UD.

In patients with SUI and UD, Ganabathi and others have described satisfactory short-term results with concomitant needle bladder neck suspension in these complex patients (Lockhart et al, 1990; Ganabathi et al, 1994). More recently, pubovaginal fascial slings have been used in patients with UD and SUI with satisfactory outcomes (Swierzewski and McGuire, 1993; Faerber, 1998; Romanzi et al, 2000). As noted previously, synthetic slings should not be placed concomitantly at the time of urethral diverticulectomy (Dmochowski et al, 2010). Placement of synthetic material adjacent to a fresh suture line following diverticulectomy in the setting of potentially inflamed tissues and infected urine may increase the risk of complications, such as urethral erosion and vaginal exposure of the sling material, as well as urethrovaginal fistula formation.

Procedure. The patient is placed in the lithotomy position with all pressure points well padded. The use of padded adjustable stirrups for the lower extremities greatly enhances operative access to the female perineum. A standard vaginal antiseptic preparation is applied. A weighted vaginal speculum and Scott retractor with hooks aid in exposure. A posterolateral episiotomy may be beneficial in some patients for additional exposure, although the mid-urethral (and therefore somewhat distal in the vaginal canal) location of most UD usually precludes the need for this type of adjunctive procedure. A Foley catheter is placed per urethra. If desired, a suprapubic tube is placed at the start of the procedure, either using the Lowsley retractor or proceeding percutaneously under direct transurethral cystoscopic visual guidance. Placement of the suprapubic tube at the end of the case is not advisable because this will require traversing the fresh urethral suture line and risk disruption of the repair.

An inverted U is marked along the anterior vaginal wall with the base of the U at the level of the distal urethra and the limbs extending to the bladder neck or beyond (Fig. 90-30A). Care is taken to ensure that the limbs of the U are progressively wider proximally (toward the bladder neck) to ensure adequate vascularity at the distal lateral margins of the anterior vaginal wall flap. Compared with the inverted T incision, the inverted U incision provides excellent exposure laterally at the level of the midvagina and can be extended proximally as needed for lesions that extend beyond the bladder neck. Injectable saline can be infused along the lines of the incision to facilitate dissection. An anterior vaginal wall flap is created by careful dissection in the potential space between the vaginal wall and the periurethral fascia. The use of sufficient countertraction during this portion of the procedure is important in maintaining the proper plane of dissection. Care is taken to preserve the periurethral fascia and avoid inadvertent entry into the UD.

BOX 90-2 Principles of Transvaginal Urethral Diverticulectomy (UD)

- Mobilization of a well-vascularized anterior vaginal wall flap(s)
- Preservation of the periurethral fascia
- Identification and excision of the neck, or ostium, of the UD
- Removal of entire UD wall or sac (mucosa)
- Watertight urethral closure
- Multilayered, nonoverlapping closure with absorbable suture
- Closure of dead space
- Preservation or creation of continence

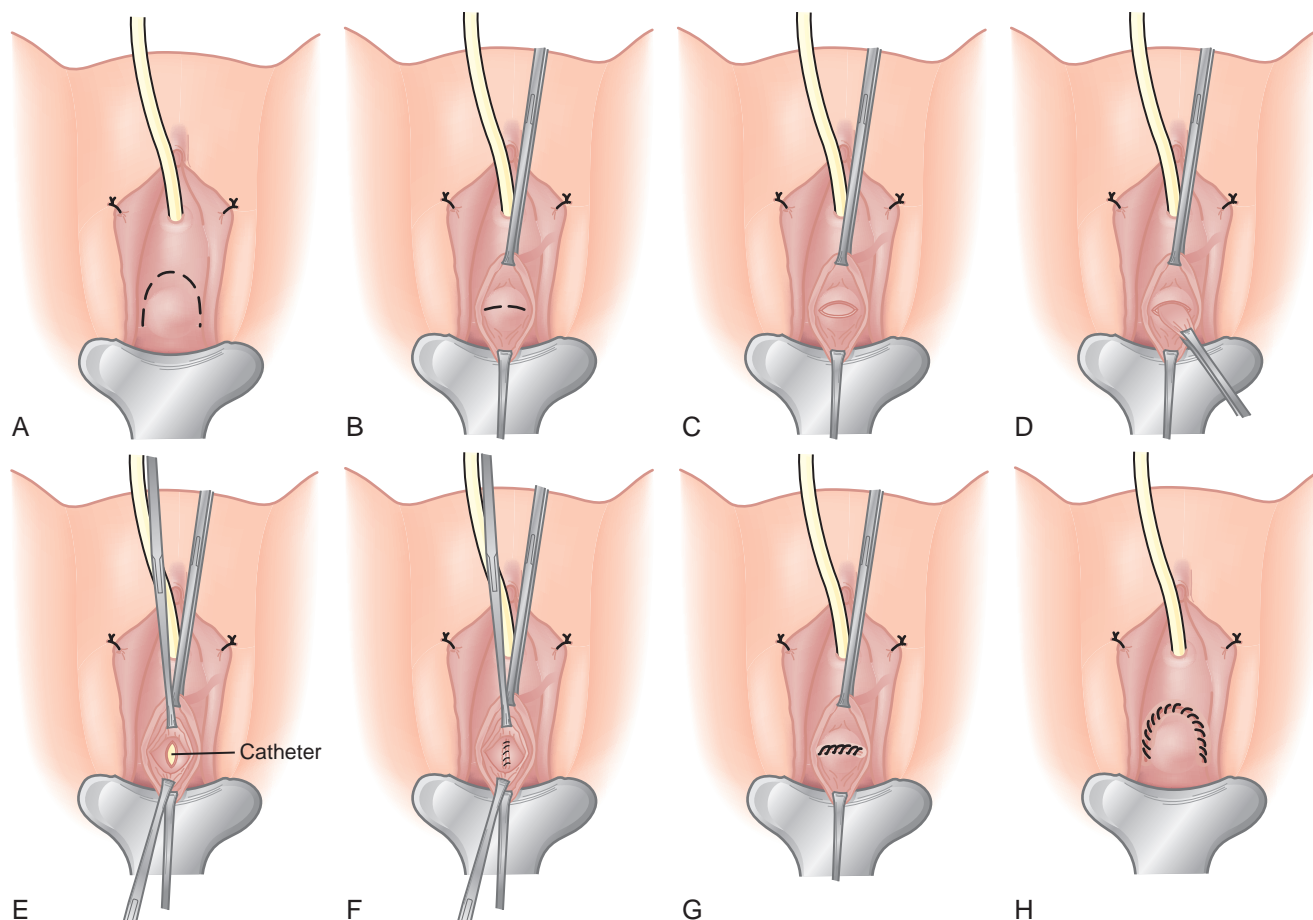


Figure 90-30. A, An inverted U incision is marked on the anterior vaginal wall. Retraction is aided by the use of Allis clamps and a ring retractor with hooks. B, After reflection of the anterior vaginal wall, a transverse incision is made in the periurethral fascia. The dotted line represents the intended incision line. C, The periurethral fascia is incised and dissected from the underlying urethral diverticulum. D, The diverticular sac is freed from the periurethral fascia. E, The urethral catheter is seen after complete excision of the diverticular sac. F, The urethra is closed with absorbable suture. G, The periurethral fascia is closed with care to obliterate any dead space. H, The anterior vaginal wall flap is advanced over the periurethral suture line and secured with running interlocking absorbable suture.

A distinct layer of periurethral fascia is usually interposed between the vaginal wall and the UD. Preservation and later reconstruction of this layer is of paramount importance to prevent recurrence, close dead space, and avoid urethrovaginal fistula formation postoperatively. Pseudodiverticula have been described wherein this layer of tissue is considerably attenuated or even absent (Leng and McGuire, 1998). In these patients, an interpositional flap or graft, such as a pubovaginal sling, may be used for reconstruction.

The periurethral fascia is incised transversely (Fig. 90-30B). Proximal and distal layers of periurethral fascia are carefully developed, avoiding entrance into the UD. The UD is then grasped and dissected back to its origin on the urethra within the leaves of the periurethral fascia (Fig. 90-30C). In many cases, it is necessary to open the UD to facilitate dissection from the surrounding tissues. The ostium or connection to the urethra is identified and the walls of the UD are completely removed. Every effort should be made to remove the entire mucosalized surface of the UD to prevent recurrence (Ganabathi et al, 1994; Fortunato et al, 2001). This may involve removing small adherent or inflamed portions of the urethral wall, especially in the area of the ostium (Fig. 90-30D). All abnormal tissue in the area of the ostium should be removed, if possible, to ensure that no mucosal elements of the UD wall remain,

which could result in postoperative urine leakage and recurrence. Elaborate methods of identifying the full extent of the UD cavity have been described, including catheterization of the UD with urinary (Moore, 1952; Kohorn and Glickman, 1992) and Fogarty (Wear, 1976) catheters, packing the UD with gauze (Hyams and Hyams, 1939), infusing and staining the UD with methylene blue (Gilbert and Rivera Cintron, 1954), and the use of silicone (Hirschhorn, 1964) or cryoprecipitate (Feldstein, 1981) to create a solid mass and ease dissection. However, these measures are mostly of historical interest only and are usually not necessary in modern UD surgery (Leach and Bavendam, 1987; Ganabathi et al, 1994).

The Foley catheter is often seen transvaginally through the operative site following complete excision of UD (Fig. 90-30E). The urethra can be reconstructed over as small as a 12-Fr Foley catheter without long-term risk of urethral stricture (Young et al, 1996) and should be closed in a watertight fashion with absorbable suture (Fig. 90-30F). The closure should be tension free. Uncommonly, a UD may extend circumferentially around the urethra and require segmental resection of the involved portion of the urethra and complex reconstruction (Tamada et al, 2000; Rovner and Wein, 2003).

The periurethral fascial flaps are reapproximated with absorbable suture in a perpendicular orientation to the urethral closure

TABLE 90-2 Complications of Transvaginal Urethral Diverticulectomy

COMPLICATION	% RANGE OF REPORTED INCIDENCE
Urinary incontinence	1.7%-16.1%
Urethrovaginal fistula	0.9%-8.3%
Urethral stricture	0%-5.2%
Recurrent urethral diverticula	10%-20%
Recurrent urinary tract infection	0%-31.3%
Other:	
Hypospadias/distal urethral necrosis	Not available
Bladder or ureteral injury	Not available
Vaginal scarring or narrowing: dyspareunia, etc.	Not available

Modified from Dmochowski R. Surgery for vesicovaginal fistula, urethrovaginal fistula, and urethral diverticulum. In: Walsh PC, Retik AB, Vaughan ED Jr, et al, editors. *Campbell's urology*. 8th ed. Philadelphia: Saunders; 2002.

line to minimize overlap and the risk of postoperative urethrovaginal fistula formation (Fig. 90-30G). Care is taken to secure the periurethral fascial flaps so that all dead space is closed.

If desired, a fibrofatty labial (Martius) flap can be harvested at this point and placed over the periurethral fascia as an additional layer of closure (Dmochowski, 2001). Indications for such a flap are not universally agreed upon. However, in those patients with poor-quality tissues, with attenuated periurethral fascia, or in whom significant inflammation is encountered intraoperatively, a well-vascularized adjuvant flap (e.g., Martius flap) may reduce the risk of wound breakdown and subsequent complications such as urethrovaginal fistula.

The anterior vaginal wall flap is then repositioned and reapproximated with absorbable suture (Fig. 90-30H). This completes a three-layer closure (four layers if a Martius flap is used). An antibiotic-impregnated vaginal pack is placed.

Postoperative Care. Antibiotics are continued for 24 hours postoperatively. The vaginal packing is removed and the patient discharged home with closed urinary drainage. Antispasmodics are used liberally to reduce bladder spasms. A pericatheter VCUG is obtained at 14 to 21 days postoperatively. If there is no extravasation, the catheters are removed. If extravasation is seen, then repeat pericatheter VCUGs are performed weekly until resolution is noted. In the vast majority of cases, extravasation will resolve in several weeks with this type of conservative management (Schwab and Rovner, 2003).

Complications. Careful adherence to the principles of transvaginal urethral diverticulectomy should minimize postoperative complications. Nevertheless, complications may arise (Table 90-2). One small series suggested that large diverticula (>4 cm) or those associated with a lateral or horseshoe configuration may be associated with a greater likelihood of postoperative complications (Porgiglia et al, 2002). Common complications include recurrent UTIs, urinary incontinence, or recurrent UD. Urethrovaginal fistula is an uncommon but distressing complication of urethral diverticulectomy and deserves special mention. A urethrovaginal fistula located beyond the sphincteric mechanism should not be associated with symptoms other than perhaps a split urinary stream and/or vaginal voiding. Therefore an asymptomatic distal urethrovaginal fistula may not require repair, although some patients may request repair. Conversely, a proximal fistula located at the bladder neck or at the mid-urethra in patients with an incompetent bladder neck will likely result in considerable symptomatic urinary leakage. These patients should undergo repair with consideration for the use of an adjuvant tissue flap, such as a Martius flap, to provide a well-

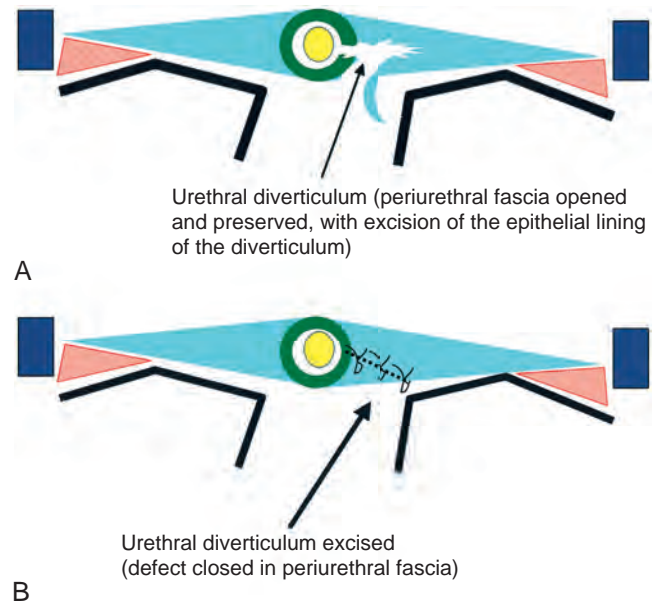


Figure 90-31. Diagrams demonstrating the importance of preserving and reconstructing the periurethral fascia. A, The periurethral fascia has been opened and the urethral diverticulum has been excised. B, The periurethral fascia has been closed.

vascularized additional tissue layer. The actual timing of the repair relative to the initial procedure is controversial. Meticulous attention to surgical technique, good hemostasis, avoidance of infection, preservation of the periurethral fascia (Fig. 90-31), a well-vascularized anterior vaginal wall flap, and a multilayered closure with nonoverlapping suture lines should minimize the potential for postoperative urethrovaginal fistula formation.


Significant postoperative de novo SUI may occur in 7% to 16% of individuals undergoing urethral diverticulectomy surgery without a concomitant anti-incontinence surgery (Han et al, 2007; Ljungqvist et al, 2007; Stav et al, 2008). However, Lee and colleagues (2008) noted some degree of de novo SUI in 49% of patients following urethral diverticulectomy, the majority of which was minor and did not require additional therapy. Only 10% of these individuals underwent a subsequent SUI operation. Risk factors for de novo SUI may include the size of the diverticulum (>30 mm) and more proximal location (Stav et al, 2008).

Persistence of Symptoms Following Urethral Diverticulectomy. Some patients will have persistence or recurrence of their preoperative symptoms postoperatively. The finding of a UD following a presumably successful urethral diverticulectomy may occur as a result of a new UD, or, alternatively, as a result of recurrence of the original lesion. Recurrence of UD may be due to incomplete removal of the UD, inadequate closure of the urethra or residual dead space, or other technical factors. The risk of long-term recurrence is approximately 10% to 20% (Lee, 1983; Han et al, 2007; Ljungqvist et al, 2007; Ingber et al, 2011). Lee (1983) noted recurrent UD in 8 of 85 patients at follow-up of 2 to 15 years from the initial UD resection, while Ljungqvist and colleagues (2007) reported recurrence in 11 of 68 patients during a 26-year follow-up. The risk of recurrence of UD following transvaginal excision may be related to the complexity of the anatomic configuration and location. Han and colleagues (2007) reported no recurrent UD in 17 patients with simple UD, but of the 10 patients with circumferential UD, recurrence was noted in 6 (60%). Notably in this series, secondary procedures were not as successful in completely removing the UD. Ockrim and colleagues (2009) similarly cured all 19 patients presenting with simple UD on the first attempt, but the 11 patients with complex anatomic configurations required a total of 17 procedures for success. Proximal location and multiple UD at presentation are also potential risk factors for recurrence (Ingber et al, 2011).

Repeat urethral diverticulectomy surgery can be challenging because of altered anatomy, scarring, and the difficulty in identifying the proper anatomic planes. Complications such as fistula and recurrence of the UD are more common in reoperative cases (Ljungqvist et al, 2007).

KEY POINTS: FEMALE URETHRAL DIVERTICULA—MANAGEMENT

- Concomitant urinary incontinence symptoms should be thoroughly investigated preoperatively, and strong consideration should be given toward surgical treatment of SUI at the time of urethral diverticulectomy.
- Transvaginal excision and urethral reconstruction is the most common approach to the treatment of UD in the female.

 Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.



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Surgical Procedures for Sphincteric Incontinence in the Male: The Artificial Urinary Sphincter and Perineal Sling Procedures

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Classification, Pathophysiology, and Cause

History and Development of Devices

Mechanisms of Device Action

Evaluation and Diagnosis

Indications for Surgery

Technique of Implantation

Artificial Urinary Sphincter Complications

Sling Complications

Long-Term Results of Artificial Urinary Sphincter and Slings

Summary

Urinary incontinence (UI), the complaint of any involuntary leakage of urine (Abrams et al, 2002), may be the result of congenital anomalies, injury, genitourinary surgery, and other conditions. The most common cause of sphincteric UI in men is radical prostatectomy, with the primary mechanism being failure to store urine secondary to inadequate resistance of the outlet sphincter. Despite improvements in surgical technique that have reduced the rate of postprostatectomy UI, the burden of disease in the United States remains high and is expected to rise because of continued large numbers of radical prostatectomy performed annually (Kowalczyk et al, 2012).

UI significantly compromises health-related quality of life in men (Coyne et al, 2003, 2012) and can be improved by surgical treatment, including transurethral bulking agents, bulbar urethral slings, and the artificial urinary sphincter (AUS). These procedures prevent involuntary urinary loss by increasing outlet resistance. Although bulking agents have been used in the past as first-line treatment for male sphincteric UI, the severity of incontinence and postsurgical scarring in the vesicourethral region after prostatectomy have made surgical correction first-line treatment for the majority of cases.

After a number of generations, several bulbar urethral slings have emerged as viable treatment options for male UI. Long-term follow-up is now available for these slings, allowing patients to make more informed decisions about treatment, particularly for mild-to-moderate incontinence. However, the AUS remains the gold standard for the treatment of UI in males because of its long-term durability and effectiveness across the spectrum of moderate and severe degrees of urinary loss.

CLASSIFICATION, PATHOPHYSIOLOGY, AND CAUSE

Urinary continence in the male depends on a compliant and contractile bladder body, functional posterior urethra including the bladder neck and prostate (internal sphincter), and an intact rhabdosphincter (external sphincter). Thus stress UI develops only in men with concomitant internal and external sphincter impairment. Internal sphincter incompetence results from pelvic surgery, bladder neck injury, specific sympathetic neuropathic dysfunction,

or embryologic disruption. Incompetence of the external sphincter occurs most frequently after radical prostatectomy, but also can result from pelvic fracture urethral injuries, traumatic and acquired myelopathy, and congenital disorders such as spinal dysraphism, sacral agenesis, and the exstrophy/epispadias complex. Table 91-1 shows conditions in which the bladder neck and rhabdosphincter may be dysfunctional or compromised. Associated bladder dysfunction including decreased compliance or detrusor overactivity (DO) may complicate or confound the diagnosis and management of male UI and requires careful evaluation (see later).

Male incontinence is rare in the general population, affecting only 5% of older men (Bortolotti et al, 2000). The incidence of UI in men parallels the rate of various surgical procedures and urologic conditions listed in Table 91-1. Incontinence after transurethral resection of the prostate (TURP) may reflect persistent bladder overactivity but rarely results from damage to the external sphincter during transurethral resection. In a large Veterans Affairs Cooperative Study (Wasson et al, 1995) the rate of de novo UI after TURP was no different from that in the watchful waiting group. The historical incidence of incontinence after radical prostatectomy varies from 2.5% to 87% (Foote et al, 1991). Progressive improvement in urinary control has been reported to occur for as long as 2 years after surgery; in one study the percentage of men who used one pad or fewer after radical prostatectomy was 71%, 87%, 92%, and 98.5% at 3, 6, 12, and 24 months, respectively (Lepor and Kaci, 2004). Nerve-sparing techniques pioneered by Walsh (Eggleston and Walsh, 1985) have been associated with a reduced incidence of postoperative UI (Wei et al, 2000a). Although the mechanism of this effect remains debated, sensory and motor pudendal innervation of the rhabdosphincter is generally preserved after radical prostatectomy; in contrast, autonomic afferent denervation and impaired membranous urethral sensitivity seems to be associated with UI after radical prostatectomy (Catarin et al, 2008). Modifications to the posterior reconstruction of the rhabdosphincter during radical prostatectomy have been proposed to accelerate return to continence, but are not associated with improved long-term continence (Rocco et al, 2012). Bladder neck stenosis is associated with a reduced continence rate after radical prostatectomy, likely as a result of secondary surgical intervention (Park et al, 2001).

TABLE 91-1 Common Causes and Mechanisms of Male Sphincteric Urinary Incontinence

CONDITION	BN/PU DYSFUNCTION	RHABDOSPHINCTER DYSFUNCTION	OVERALL RISK FOR SUI
Radical prostatectomy	Present	Significant risk	Moderate
TURP	Present	Minimal risk	Low
Pelvic fracture/urethral injury	Rare	Significant risk	Low
Myelomeningocele	At risk	At risk	Moderate
Exstrophy/epispadias	At risk	At risk	Moderate

BN/PU, bladder neck/proximal urethra; SUI, sphincteric urinary incontinence; TURP, transurethral resection of the prostate.

Contemporary series demonstrate improved continence after prostatectomy when compared to historical rates, but wide variation in reported outcomes reflect patient-specific and surgeon-specific factors as well as methodology of data collection (Flynn and Webster, 2004). Validated disease-specific questionnaires such as the UCLA Prostate Cancer Index (Litwin et al, 1998) or the Expanded Prostate Cancer Index Composite (Wei et al, 2000b) that capture symptoms of stress and urge incontinence are recommended. Rates of incontinence are higher when calculated from such self-report instruments compared to chart review or physician recorded outcomes (Carlson and Nitti, 2001; Flynn and Webster, 2004). For example, Litwin and colleagues (1995) reported that up to 40% of patients in a large cohort study complain of persistent long-term UI after radical prostatectomy. Although most patients reported mild UI, 4% complained of significant lifestyle-compromising leakage.

HISTORY AND DEVELOPMENT OF DEVICES

Devices to control UI in men have been described since antiquity (Schultheiss et al, 2000). One of the first modern prosthetic devices to treat incontinence in men was reported by Berry and associates in 1961 (Engel and Wade, 1969). This acrylic prosthesis was designed to kink and compress the bulbar urethra but poor results, pain, and fistula formation led to its abandonment (Engel and Wade, 1969). In 1970, Kaufman reported the first of several procedures to provide continence by compressing the urethra with the Kaufman I procedure. This was modified by incorporating a tetrafluoroethylene mesh tape in the Kaufman II and a silicone gel-filled hemispherical prosthesis in the Kaufman III, giving a success rate of 70%.

Slings to treat SUI in men were introduced in 1975 by Kishev, who described the placement of a pliable prosthetic “wad” under the bulbar urethra. Schaeffer and associates (1998) then described a bulbourethral sling that used bolsters suspended from the rectus fascia. Another report documented results with a composite graft of polypropylene and porcine skin collagen placed suburethrally (John, 2004). Male bulbourethral slings have continued to evolve with the development of bone screws for stable fixation of synthetic mesh to the inferior pubic ramus (InVance, American Medical Systems, Minnetonka, MN), transobturator fixation (AdVance, American Medical Systems), and a combined prepubic and transobturator sling (Virtue, Coloplast, Minneapolis, MN). The bone-anchored sling is no longer commercially available in the United States, which reduces options for complex cases involving failure of transobturator sling or AUS.

In 1976, Rosen designed the first model of an AUS, but hydraulic failure and fistula formation approached 100% and this device was abandoned (Fowler and Auld, 1985). Scott presented his initial report with the AMS 721 (American Medical Systems, Minnetonka, MN), noting a 79% success rate (Timm et al, 1976; Scott, 1978). Over the next 10 years, further developments in design of the AUS were made. The AMS 742 allowed automatic cuff closure after cuff decompression. The AMS 791 and 792 used a silicone rubber cuff and a deactivation button (Scott, 1989). The AMS 800 included the

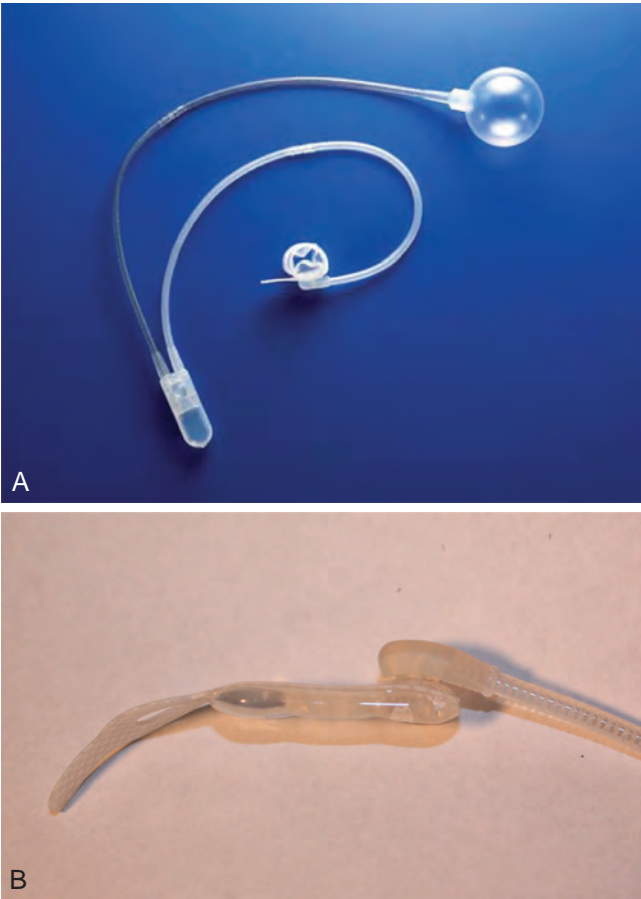


Figure 91-1. AMS 800 (American Medical Systems, Inc.) narrow-backed artificial urinary sphincter (A); close-up view of a 3.5-cm cuff (B). Note the subtle folds of the three-cushion design unique to the 3.5-cm cuff.

deactivation button within the control pump; and in 1987, the narrow-backed cuff was introduced (Fig. 91-1A), which, by improving pressure transmission from the cuff pressure to the underlying tissue, has greatly decreased the incidence of urethral erosion and tissue atrophy (Light and Reynolds, 1992). The most recent AUS modification is the addition of the 3.5-cm cuff to the size options for the device. This has allowed placement in cases with atrophy of the urethra and revision cases necessitating placement of the cuff distally, where the urethra is naturally much smaller in diameter. The 3.5-cm cuff has very specific design characteristics (see Fig. 91-1B) that were needed to achieve a concentric compression of the urethra in this small diameter (see later). Other strategies developed to address bulbar atrophy include fascial wrapping and transcorpo-real cuff placement.

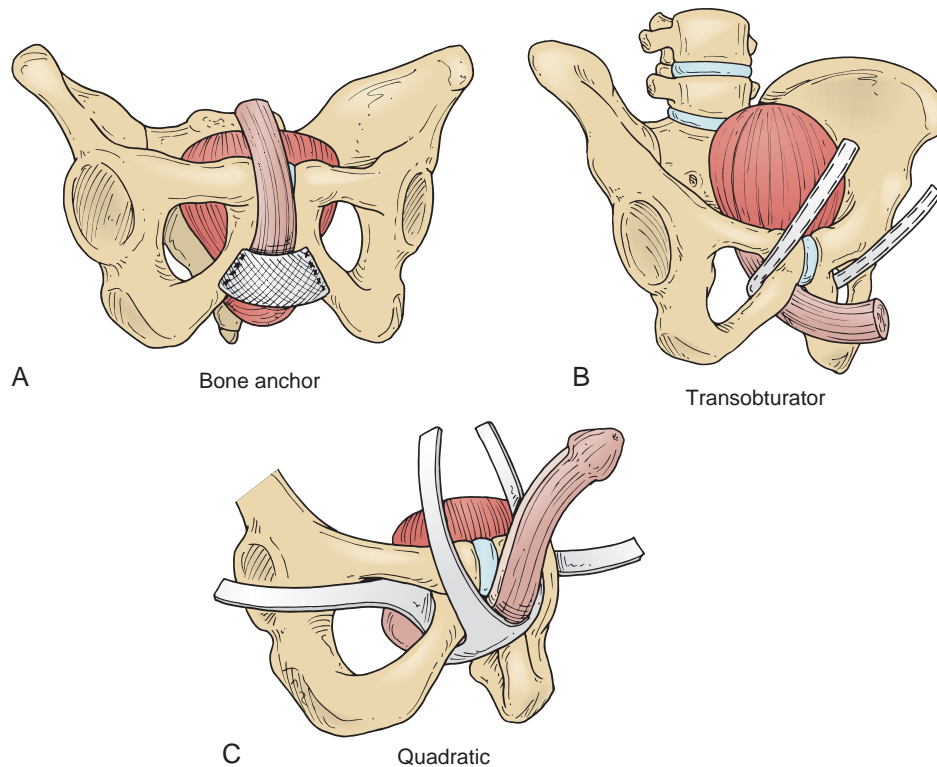


Figure 91-2. Illustrations demonstrating proposed mechanism of three major slings. A, Bone-anchored. B, Transobturator. C, Quadratic fixation.

MECHANISMS OF DEVICE ACTION

Slings have evolved from simple obstructive foreign bodies to sophisticated devices that rely on interaction with the bony pelvis to compress or reposition the male urethra (Fig. 91-2). The mechanism of continence with the bone-anchored sling was thought to be from compression of the urethra, as demonstrated by an increase in fixed resistance of the urethra (Ullrich and Comiter, 2004). Further support for this proposed mechanism was the development of techniques to optimize tensioning of the sling, which also reduce the risk for urinary retention (Comiter, 2002).

Transobturator slings are hypothesized to enhance rhabdosphincter function without significant compression. Urodynamic studies show an increase in abdominal leak point pressure without other urodynamic evidence of obstruction (Davies et al, 2009; Soljanik et al, 2011). The mechanism of action is by repositioning and lengthening the membranous urethra. Evidence for this comes from fluoroscopic studies and magnetic resonance imaging (Firoozi and Vasavada, 2009; Soljanik et al, 2013). The latter studies demonstrate an increase in membranous urethral length and elevation of the bladder neck, posterior bladder wall, and rhabdosphincter (Soljanik et al, 2013).

The Virtue sling, now commercially available in the United States, is a four-armed mesh device (quadratic fixation) that provides a long segment of urethral compression against the urogenital diaphragm and a separate elevation component because of the prepubic and transobturator arms, respectively (Comiter et al, 2012).

The AUS (AMS 800) consists of a fluid-filled cuff placed around the bladder neck or bulbar urethra, which provides a 2-cm zone of circumferential compression. The degree of compression is determined by the compliance of the pressure-regulating balloon (PRB), with the pressure selected based on patient tissue characteristics and location of the cuff. The standard PRB for bulbar AUS—61 to 70 cm H₂O—optimally balances the need for occlusion with the risk for erosion. Lower pressures provide reduced continence rates but may be advisable if risk for erosion is considered excessive. The degree

of occlusion provided by standard 61 to 70 cm H₂O is similar in magnitude to that measured in successful male sling surgery. However, when the cuff is opened, urethral resistance drops to negligible levels, thus allowing men without significant detrusor contractility to empty via straining or Credé maneuver. Interestingly, the amount of urethral lengthening achieved with the AdVance male sling, 1.2-cm post-tensioning, is significantly less compared to the 2-cm zone of compression with AUS.

EVALUATION AND DIAGNOSIS

The initial evaluation of a man with UI requires a detailed history, physical examination, and urinalysis. Complex cases of sphincteric UI also will require cystoscopy and pressure-flow urodynamics to evaluate potential bladder neck stenosis and bladder storage function, respectively. Figure 91-3 shows the overall management algorithm.

History

The medical history should focus on the type, degree, and severity of UI; previous surgical procedures; and symptoms of neurologic disease. Specific evaluation of the failed AUS will be considered at the end of this section. Differentiation between stress and urge UI is important and can be aided by the voiding diary and pad test—simple inexpensive assessments of UI that are recommended before proceeding with invasive testing (Flynn and Webster, 2004). The 2- to 7-day voiding diary reliably assesses the number of incontinence episodes and may uncover significant urgency and urge incontinence (Groutz et al, 2000). Self-reported daily pad usage varies considerably with only moderate concordance with UI volume (Dylewski et al, 2007). Thus, the 24-hour home pad weight test, which objectively measures the magnitude of the incontinence, may be helpful in directing appropriate therapy. However, because the effectiveness of current surgical therapies has not been stratified according to severity of UI, the most important

MALE SPHINCTERIC URINARY INCONTINENCE (UI)

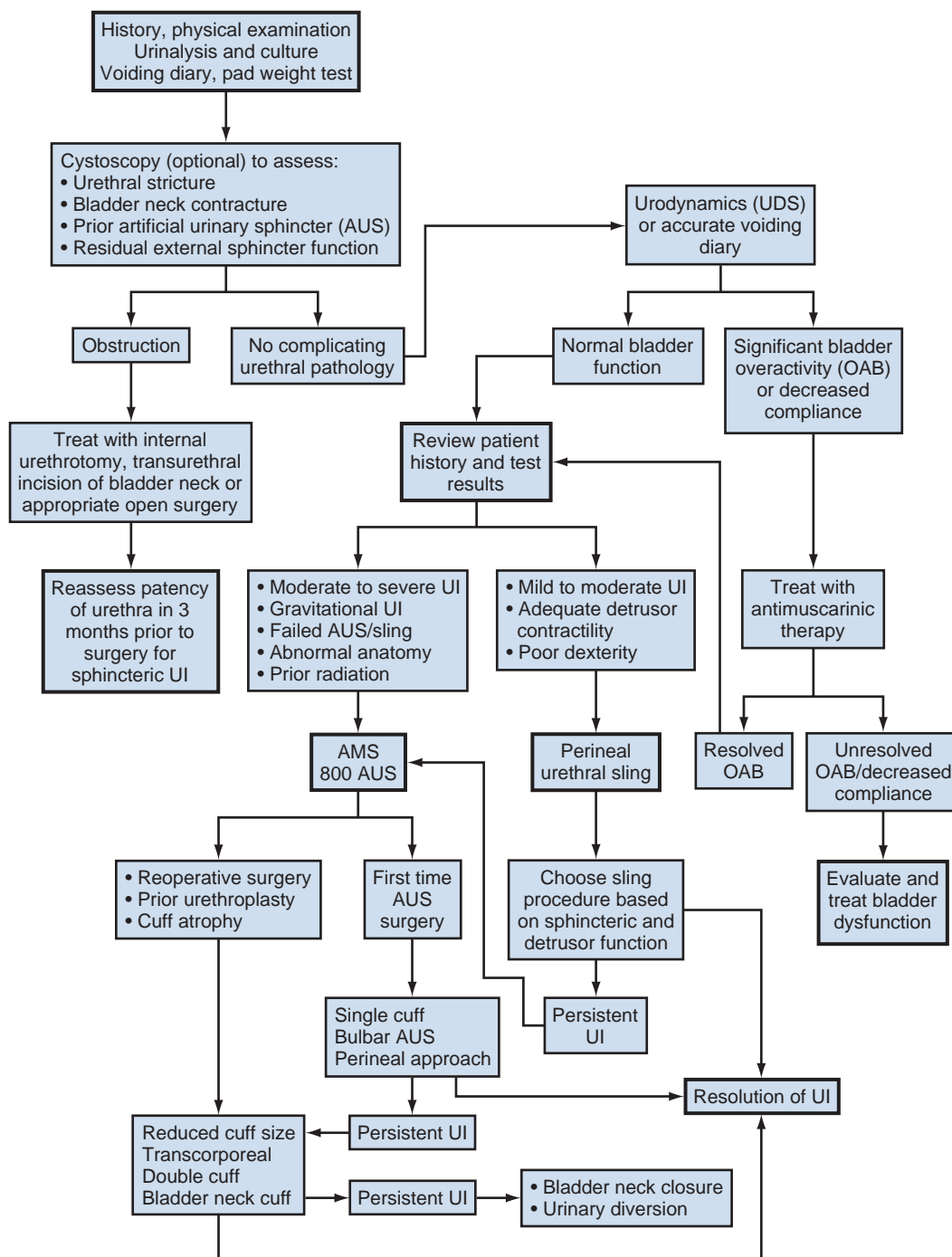


Figure 91-3. Algorithm for the evaluation and management of sphincteric urinary incontinence. OAB, overactive bladder; UI, urinary incontinence.

current use for the pad test may be as an outcome measure postoperatively. Efforts to design patient reported outcome measures that more closely correlate with pad weight and patient bother from UI will be important future directions for the field of male incontinence.

Physical Examination

A complete examination of the abdomen, back, genitalia, perineum, rectum, and neurologic system is essential to identify conditions associated with specific causes of UI. The skin should be inspected for signs of breakdown or secondary fungal or bacterial infection,

which need to be treated before surgery. Previous surgical incisions should be noted when planning AUS PRB placement. Likewise, inguinal hernias should be identified, and, if contralateral PRB placement is not possible, concomitant repair is advisable. Scrotal examination will detect pathologic processes that may influence pump placement such as hydrocele, hernias, and scrotal masses.

Laboratory

Urine analysis and culture are required before surgical correction of male UI, and all abnormalities need complete investigation.

UTI must be appropriately evaluated and eradicated. Serum creatinine and prostate-specific antigen should be obtained to assess renal function and cancer status after radical prostatectomy. Renal insufficiency requires careful evaluation before proceeding with surgical intervention.

Cystoscopy

Detection of vesicourethral anastomotic stricture, bladder neck stenosis, and bulbar urethral stricture before planned surgery may be achieved by history or uroflowmetry in most cases (Yurkanin et al, 2001). Because unrecognized urethral pathologic processes can significantly complicate all surgical approaches, endoscopic evaluation should be considered before surgical correction of UI after radical prostatectomy or TURP if there is any suspicion of bladder neck stenosis, which is rare (Wasson et al, 1995; Erickson et al, 2009; Krambeck et al, 2009). Cystoscopic evaluation of the degree of residual function of the external sphincter may help identify appropriate candidates for transobturator sling procedures (see later and Fig. 91-4). Furthermore, in patients with recurrent incontinence after AUS implantation, cystoscopy may aid in differentiating mechanical failure from other causes such as urethral atrophy. Finally, when an AUS or sling (Harris et al, 2009) has been removed because of infection or erosion, repeat evaluation of the urethra before reimplantation is recommended to identify stricture, diverticulum, and other urethral complications.

Urodynamics

Assessment of bladder capacity, compliance, and contractility is required before considering surgical correction of UI. A careful history and voiding diary may be sufficient to assess the adequacy of bladder function; noninvasive studies with uroflowmetry and postvoid residual urine volume, when normal, serve to confirm bladder capacity, completeness of bladder emptying, and the absence of bladder neck stenosis. When more comprehensive evaluation is required, however, pressure-flow urodynamics permits an accurate determination of bladder function and incontinence type and severity (Thiel et al, 2007). Intrinsic sphincteric dysfunction will be identified in almost all cases. Although 40% to 45% of men

with UI after radical prostatectomy have bladder dysfunction, it is the sole cause of incontinence in a very small percent (Leach et al, 1996; Ficazzola and Nitti, 1998). Filling cystometry can be difficult in men with severe incontinence, and occlusion of the bladder neck with a balloon catheter may be required to assess compliance and overactivity. Decreased bladder capacity was a predictor of worse outcomes from male sling surgery in one series (Warner et al, 2012). DO, although not a contraindication to surgery for UI if discovered, requires realistic counseling regarding the likelihood of successful outcome. Reduced bladder compliance presents a more serious concern, because prolonged storage at high pressures may lead to deteriorating renal function. Notably, such urodynamic findings do not reliably predict worse post-AUS continence (Trigo-Rocha et al, 2008; Lai et al, 2009). This effectiveness in spite of adverse urodynamic findings could portend silent upper tract deterioration. Conversely, detrusor hypocontractility on pressure-flow urodynamics may indicate the need for AUS if adequate detrusor function does not exist to overcome the fixed resistance of a compressive sling (Comiter, 2007).

In 2012, the American Urological Association (AUA) released guidelines on the use of urodynamics in the clinical evaluation of the patient with voiding dysfunction (Winters et al, 2012). Specific recommendations for the patient with stress incontinence include at minimum that surgeons considering invasive therapy in patients with SUI should assess the postvoid residual (PVR) urine volume. Furthermore, clinicians may perform multichannel urodynamics in patients with both symptoms and physical findings of stress incontinence who are considering invasive, potentially morbid or irreversible treatments, which include placement of the male sling or AUS.

Evaluation of Persistent Incontinence after Artificial Urinary Sphincter

The diagnostic evaluation of recurrent UI after AUS must differentiate among inadvertent deactivation, insufficient urethral compression (oversizing of cuff), mechanical failure with fluid loss, cuff erosion, bladder storage failure, urethral or bladder neck atrophy under the cuff, as well as rare causes such as a plugged delay-fill resistor or kinked tubing (Montague and Angermeier, 2001). The evaluation includes the same general approach described for de novo UI in Figure 91-3. A history of sudden loss of continence suggests deactivation or mechanical failure. Active cycling of the device excludes inadvertent deactivation. If the pump is deactivated with inadequate fluid to cycle, passive filling can be achieved by squeezing the pump on its lateral edges or by pushing on the pump with a cotton-tipped applicator opposite the deactivation button. Fluid loss from the device implies mechanical failure and leak. Plain radiography (for contrast-filled systems) or ultrasonography (for saline-filled systems) of the PRB during cycling can help differentiate fluid loss from cuff atrophy. If the PRB size changes with cycling and refills passively, mechanical failure is less likely and thus suggests cuff atrophy (Taylor and Lebowitz, 1985; Lorentzen et al, 1987). Cystoscopy, in addition to excluding erosion, can be used to visualize the cuff during cycling and give insight into the likelihood of atrophy. Urodynamics should be performed when bladder storage failure is suspected.

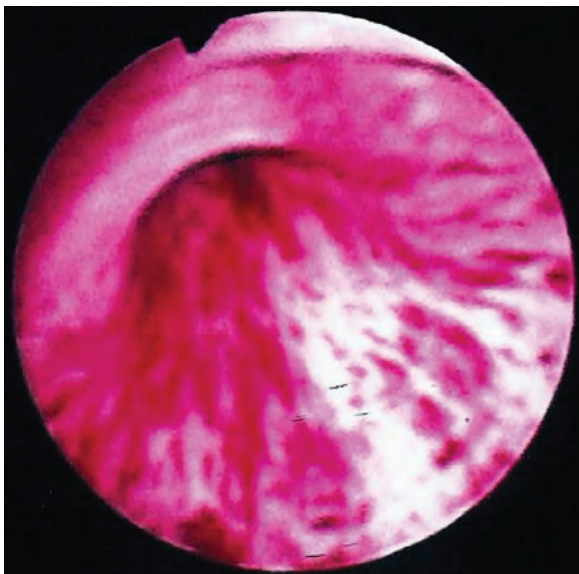


Figure 91-4. Appearance of external sphincter of a man with post-prostatectomy urinary incontinence showing incomplete circumferential coaptation. Such a patient would not be an ideal candidate for the transobturator sling, which relies on repositioning of a functional external sphincter unit.

KEY POINTS: INITIAL EVALUATION

- A careful history and voiding diary characterize the type and severity of UI in most men.
- Urinalysis (and culture if indicated) is required before surgical treatment.
- Suspected outlet obstruction, significant bladder overactivity, or impaired bladder contractility should prompt cystoscopy and/or urodynamic studies.

INDICATIONS FOR SURGERY

Surgical correction of UI is indicated in male patients with irreversible sphincter incompetence and bothersome involuntary leakage of urine. Although all men should complete a course of pelvic floor exercise, evidence to support the value of extensive or one-to-one pelvic floor muscle training after radical prostatectomy or TURP is lacking (Campbell et al, 2012). Because progressive improvement in continence occurs after radical prostatectomy, some authors recommend a 1-year observation period (Peyromaure et al, 2002; Flynn and Webster, 2004). However, it is unnecessary to delay intervention for patients with severe or gravitational UI who show no improvement beyond 6 months, particularly if cystoscopy shows a significant external sphincter defect. Because of limited efficacy, submucosal bulking agents are not part of the treatment algorithm for UI after radical prostatectomy (Kuznetsov et al, 2000; Montague and Angermeier, 2000; Abrams et al, 2009; Herschorn et al, 2010). Thus, the AUS and slings should be considered as first-line surgical therapy for sphincteric incontinence in most men, although a trial of a bulking agent may be appropriate in cases of neurogenic male stress UI.

Once the diagnostic evaluation has been completed (see Fig. 91-3), the best option for a given patient can be selected. Factors to consider include the severity of UI and associated bother; patient characteristics, including body mass index, prior surgical procedures, adjuvant radiation therapy, bladder function, and cystoscopic findings; manual dexterity and cognitive function; efficacy of the various implants; long-term risk for complications and reoperation; and patient preference. Absolute contraindications to surgical correction of male UI are few and include bladder disorders that jeopardize renal function, such as diminished vesical compliance and vesicoureteral reflux at low intravesical pressure. Inadequate tissue integrity at the bladder neck or urethra to accommodate a sling or AUS may require bladder neck closure or urinary diversion. Additionally, urinary tract abnormalities that require future transurethral management, such as bladder cancer or refractory vesicourethral anastomotic strictures, should be considered relative contraindications to surgery. In such cases, an AUS or sling procedure could impair transurethral access and repeated instrumentation may put the devices at risk for infection or erosion. Although metastatic prostate cancer is not a contraindication to surgical correction of UI, improvements in quality of life must be balanced against performance status and life expectancy.

The AUS remains the established device for treatment of moderate-to-severe UI, supported by numerous publications documenting its benefits. Advantages include reproducible and reliable outcomes, ability of patients to empty the bladder without detrusor contraction, and proved efficacy after pelvic irradiation. A national study using validated questions from the UCLA Prostate Cancer Index provides useful data on AUS results (Dalkin et al, 2003). After AUS, few men have severe degrees of incontinence (9%) but many continue to use pads and report a moderately high urinary bother. There is accumulating data that men who are completely dry after radical prostatectomy have significantly better health-related quality of life compared to those who wear one pad daily (Cooperberg et al, 2003). Whether this is also the case after AUS remains unknown. Long-term durability of the AUS is well established, although a revision rate of 16% and 28% at 2 and 5 years, respectively, highlights the limitations of the devices (Dalkin et al, 2003) and is consistent within a large single-institution series in which 72% had the original sphincter in place and functioning at a mean follow-up of 69 months (Elliott and Barrett, 1998).

Perineal slings have emerged as an alternative to AUS for mild-to-moderate male stress UI. A transobturator sling introduced by AMS (AdVance) has been shown to be effective in short-term to intermediate-term follow-up of well-characterized case series (two). In these selected populations, approximately 75% of patients are cured or significantly improved, with results persisting at 12 to 36 months. Thus, male sling procedures represent a significant addi-

tion to the surgical armamentarium for UI by providing an alternative to AUS for mild-to-moderate UI.

Slings can be seen as alternatives for those who refuse AUS from fear of infection, erosion, or mechanical failure, as well as those with limited physical or cognitive capacity. Comiter (2007) notes that the techniques differ in their indications, relative success rates, and complication rates for patients with varying degrees of incontinence. The trade-off between risk and efficacy must be considered, with most authors recommending AUS for more severe UI. For mild UI, bulbar sling procedures become viable alternatives, whereas AUS may represent therapeutic overkill. Thus, the bone-anchored and transobturator slings primarily should be used in cases with mild-to-moderate incontinence, which can be defined as a 24-hour pad weight of less than 150 g for mild UI (Flynn and Webster, 2004) and less than 400 g for moderate UI (Fischer et al, 2007; Collado Serra et al, 2013). A sling procedure should not be offered to those with prior radiation therapy or urethral erosion as the degree of urine loss that exists in this group usually exceeds the limits of the procedure (Schaeffer et al, 1998; Dikranian et al, 2004; Castle et al, 2005; Giberti et al, 2009; Torrey et al, 2013).

When deciding between the two devices (AUS vs. the male sling), men will follow surgeon recommendations. However, when given the choice, men will most often choose the sling, to avoid the perceived risks for mechanical malfunction, revision surgeries, and device-associated problems (Kumar et al, 2009). This tendency may lead to a higher rate of failure with slings. In light of these choices made by patients and clinicians, a subset of patients will require reoperation after placement of a transobturator male sling because of inadequate treatment of incontinence.

KEY POINTS: IMPLANT SELECTION

- Surgical intervention is indicated for stress UI resulting from intrinsic sphincteric dysfunction that fails to improve with conservative management.
- Implant selection depends on the severity of UI, prior surgical procedures, bladder function, cystoscopic findings, manual dexterity and cognitive function, long-term risk for complications and reoperation, and patient preference.
- Slings should not be used in cases of radiation and severe gravitational UI.
- AUS should not be used in cases of poor manual dexterity, cognitive disability, poor urethral tissue integrity, or severely reduced bladder compliance

TECHNIQUE OF IMPLANTATION

Operative Preparation

The entire operative site is shaved and an antiseptic skin preparation is performed, including the lower abdomen, genitals, and perineum. Surgery is conducted under general or spinal anesthesia with the patient in the low lithotomy position. Intravenous antibiotics including an aminoglycoside (gentamicin or tobramycin 5 mg/kg) and a first- or second-generation cephalosporin or vancomycin are administered within 60 minutes before skin incision according to AUA Guidelines on antimicrobial prophylaxis (Wolf et al, 2008). A chlorhexidine scrub for 10 minutes followed by iodine povacrylex (0.7% available iodine) and isopropyl alcohol, 74% weight to weight (DuraPrep, PPG Industries, Pittsburgh, PA), was shown in one recent study to reduce postpreparation bacterial skin culture rates compared to povidone-iodine, although clinical implant infection rates were similar between groups (Yeung et al, 2013). The patient is then carefully draped; a urethral catheter may be placed to drain the bladder and facilitate identification and dissection of the urethra.

Artificial Urinary Sphincter

The AUS cuff is most commonly placed around the bulbar urethra via a perineal incision. The aim is to place the cuff as proximal on the bulbar urethra as possible, proximal to the fusion of the two corporeal bodies (Fig. 91-5A). This location allows safe circumferential dissection of the urethra, provides protection of the cuff from

activation while sitting, and exposes the largest diameter of corpus spongiosum for placement of the cuff. A transscrotal approach was popularized by Wilson and associates (2003) but demonstrated suboptimal results for the control of incontinence and required modification (see later).

After incision of the skin, Colles fascia, and bulbospongiosus muscle, the Buck fascia is incised as it reflects off the bulbar urethra

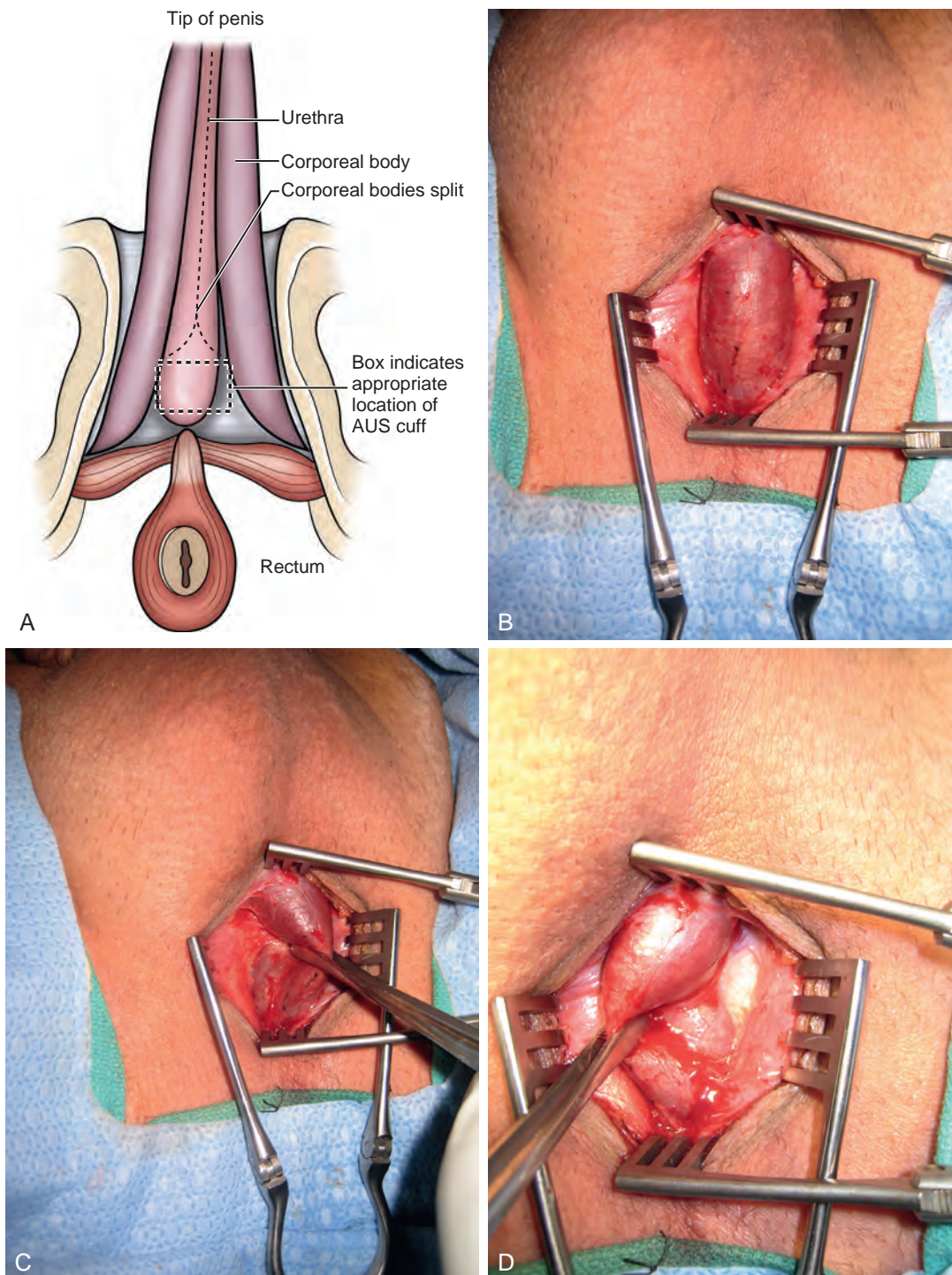


Figure 91-5. Perineal anatomy and bulbar urethral dissection. A, Preferred location for first-time bulbar cuff proximal to convergence of corpora cavernosa. Note box indicating ideal cuff placement. B, Exposure of the corpus spongiosum after division of the bulbospongiosus muscle. C, Dissection at interface between spongiosum and right crus of the cavernosum. D, Dissection at interface between spongiosum and left crus of the cavernosum. AUS, artificial urinary sphincter.

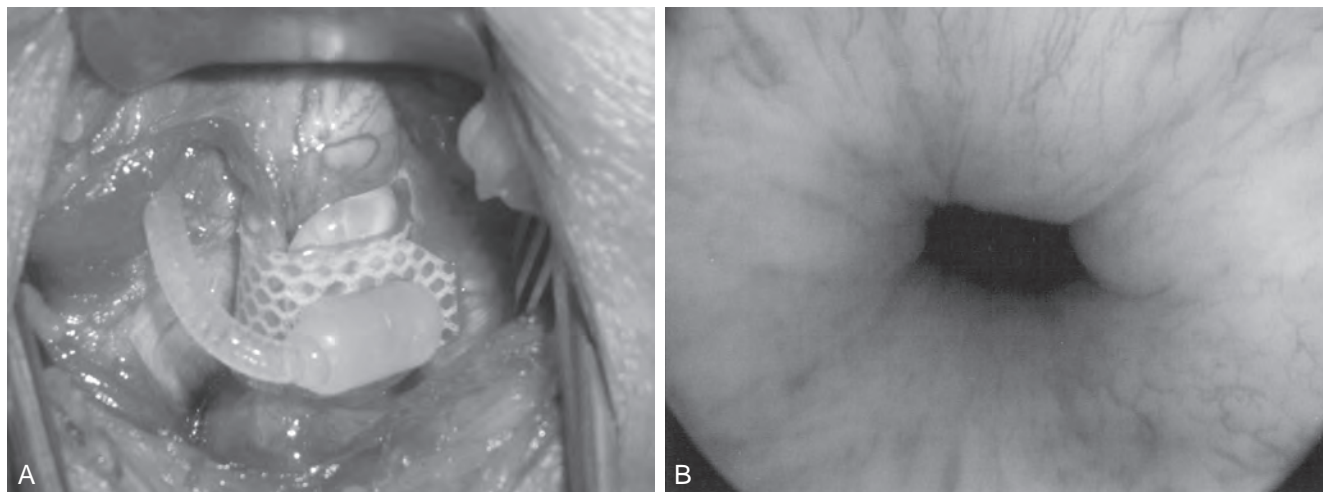


Figure 91-6. Appropriate appearance of cuff. **A,** Perineal placement encircling the bulbar urethra. **B,** Endoscopic appearance with cuff activated.

onto the diverging corporeal bodies (see Fig. 91-5B to D). A 2-cm-wide tunnel is created under direct vision using sharp dissection, dorsal to the Buck fascia over the roof of the urethra. A right-angle clamp is then passed through this tunnel. Blunt spreading dissection is discouraged in this area because it risks injury to the urethra, especially in reoperative cases. **The circumference of the urethra is measured around the corpus spongiosum to guide selection of cuff size, most commonly 4 or 4.5 cm.** The urethral catheter should be removed before measurement. Although some authors advocate selecting a cuff size 0.5 to 1 cm smaller than the measured circumference of the urethra to compensate for postoperative sub-cuff atrophy of the spongiosum, the best test of cuff fit is the visual and endoscopic appearance after it has been placed around the urethra (Fig. 91-6). If the cuff size is obviously incorrect, the appropriate next size should be selected. The tubing from the AUS cuff is passed through the overlying bulbospongiosus muscle into the deep perineal space beneath the Colles fascia.

The cuffs are available in various sizes starting at 3.5 cm and range up to 11 cm (3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11 cm). The larger sizes are reserved for bladder neck implantation. The 3.5-cm cuff allows the surgeon to further downsize devices to obtain better urethral coaptation in patients with significant urethral atrophy from radiation or prior AUS placement and those needing very distal placement of cuffs because of multiple revisions. Use of this new smaller size has resulted in similar outcomes with minimal additive complications such as erosions and pain (Hudak and Morey, 2011).

Pressure-Regulating Balloon

The placement of the PRB may be achieved through a scrotal, perineal, or abdominal incision, depending on prior surgical incisions, body habitus, and surgeon preference. Implanters should be familiar with each approach. For abdominal placement, a horizontal lower quadrant incision is made in the abdomen ipsilateral to pump placement. The rectus or external oblique fascia is incised, allowing the surgeon to split the underlying muscle and access the preperitoneal or intraperitoneal space. Digital dissection creates the space required for the PRB, which is small. **We place a 61- to 70-cm H₂O PRB in all bulbar AUS and reserve the 71- to 80-cm H₂O PRB for bladder neck cuff placement.** The abdominal wall fascia is closed around the tubing.

Alternatively, the PRB can be placed via the external inguinal ring, using techniques adapted from penile implant surgery. Using either a transverse scrotal or perineal incision, the external ring is identified and used to provide access to the retropubic space by penetrating through the floor of the inguinal canal with a fingertip

or instrument. No sutures are required because the transversalis fascia provides a natural barrier to PRB extrusion. Contraindications to this approach include mesh hernia repairs, radical cystectomy, and other extensive abdominal surgery. In such cases, the abdominal approach reduces the risk for bladder or intestinal injury.

The PRB is filled with 23 mL of sterile normal saline or contrast material, unless a bladder neck cuff is used, which requires additional fluid volume according to manufacturer instructions. Filling solutions include 0.9% normal saline, Cysto-Conray (Mallinckrodt Pharmaceuticals, St. Louis, MO) 60 mL of contrast diluted with 15 mL of sterile water, or Hypaque (GE Healthcare, Wauwatosa, WI) 25% 50 mL contrast diluted with 60 mL of sterile water. To provide an isotonic solution, contrast solutions always should be diluted with sterile water. Contrast media are contraindicated if the patient has an iodine or contrast allergy.

Control Pump Placement

The pump assembly is placed into the anterior scrotum from the inguinal, scrotal, or perineal incision. When the PRB has been placed abdominally, dissection proceeds inferiorly to the scrotum above the abdominal wall fascia accessing the anterior scrotum deep to the Scarpa fascia. A finger placed outside the dependent portion of the scrotum then invaginates this skin upward into the inguinal incision, allowing the fascial layers to be stripped off the dartos layer with an instrument, creating a small pocket for the pump (Fig. 91-7). The pump is then placed into that position with the tubing held loosely with a Babcock clamp. For the single-incision approaches, a small sub-dartos pouch is created directly from the scrotal or perineal incision, orienting the pump accordingly toward the foot (scrotal) or head (perineal), respectively.

Making the Connections

Connections typically are made in the abdominal incision, when used, protecting the connections from excess wear and allowing easy exploration at a later date. **The quick connectors supplied by the manufacturer provide excellent, secure, and watertight connections for newly implanted devices.** However, they cannot be used for revision surgeries because a biofilm on the tubing interferes with watertight connection. Therefore one must use hand-tie connectors in revision cases in which the entire device is not being replaced. After completing the connections, the device is cycled several times through the activation and deactivation states. We verify adequate coaptation of the urethra via urethroscopy. The closed cuff should cause slight blanching of the urethral tissue, indicating adequate urethral coaptation, filling, and connection of



Figure 91-7. Placement of the pump beneath the skin in a sub-dartos pocket.

the device (see Fig. 91-6B). Conversely, the deactivated cuff should not cause complete coaptation. If coaptation is deemed excessive in this circumstance, replacement with a larger diameter cuff should be considered.

Tandem Cuff Artificial Urinary Sphincter

Up to 11% of men may have significant incontinence after single-cuff AUS placement, despite significant improvements in AMS 800 design and implantation techniques (Montague and Angermeier, 2000). In such patients, when the cause of persistent UI is incomplete urethral occlusion, the addition of a second cuff around the bulbar urethra (Fig. 91-8A and C) can yield satisfactory continence (Brito et al, 1993; Kabalin, 1996; DiMarco and Elliott, 2003; O'Connor et al, 2003). Indiscriminate use of the tandem cuff approach as first-line surgical treatment should be tempered by higher rates of erosion associated with the distal cuff in several series (Kowalczyk et al, 1996a; Bell and Mulcahy, 2000).

Placement of the second cuff can be accomplished via the perineal incision. After circumferentially dissecting around the distal bulbar urethra, at least 1.5 to 2 cm distal to the primary cuff, a new

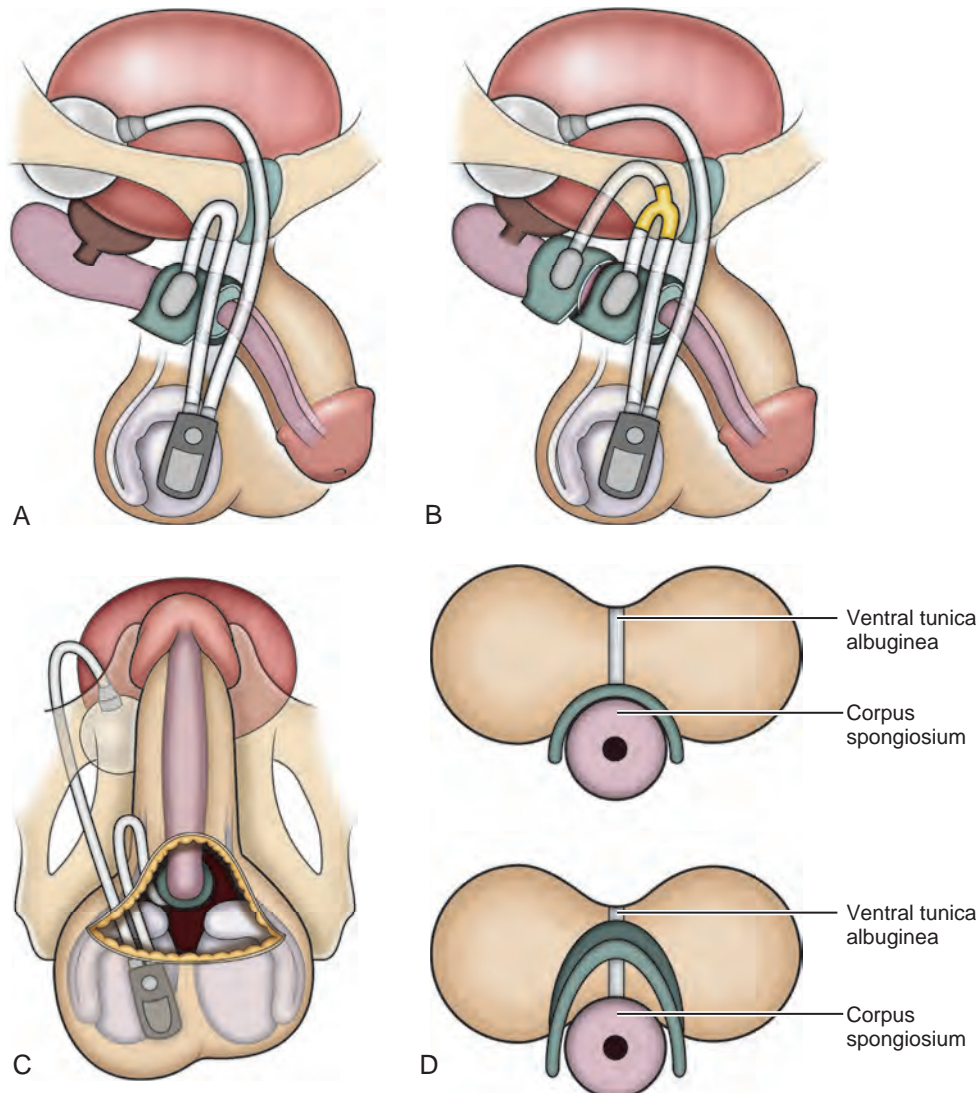


Figure 91-8. Diagram of the artificial urinary sphincter (AUS), including perineal (A), scrotal (B), tandem (C), and transcorporeal (D) approaches. Note the incorporation of the ventral tunica albuginea with the corpus spongiosum in the transcorporeal approach.

cuff, usually 4.0 cm, is placed. **Connection to the existing device requires division of the existing cuff tubing and use of a metal Y connector.** An additional 3 mL of fluid must be added to the system. When adding a new cuff to an existing system, the tubing must be connected with hand-ties, as described earlier. The entire device is left deactivated for 6 weeks postoperatively.

Transcorporeal Artificial Urinary Sphincter Cuff

The transcorporeal placement of the AUS provides another approach to difficult initial or revision surgery (Guralnick et al, 2002). Rather than dissecting between the corpus spongiosum and the ventral cavernosa, parallel longitudinal incisions in the tunica albuginea of the corpora cavernosa, near the interface with the corpus spongiosum, allow the plane of dissection to pass through the septum of the corpora from one side to the other. This technique leaves the ventral tunica albuginea attached to the dorsum of the spongiosum (Fig. 91-8D). The lateral edges of the tunica albuginea may need to be imbricated *behind* the cuff; preplacement of sutures to accomplish this is advisable. **Advantages of the transcorporeal approach include reduced risk for urethral injury during reoperation after prior erosion or urethra injury; better cuff fit because of the increased bulk of the urethra; and potential reduction in erosion risk** (see Fig. 91-8). The technique is particularly useful when proximal cuff atrophy occurs under a narrow (e.g., 4.0 cm) cuff. Transcorporeal placement 2 to 3 cm distally, leaving an intervening segment of normal urethra, may yield AUS continence results similar to those in Table 91-2. Webster and associates reported a cure and improvement rate of 84% without intraoperative urethral injuries or postoperative urethral erosions at a mean follow-up of 17 months (Guralnick et al, 2002). An operative video in the AUA video series details the technique. Literature on the effectiveness of this approach remains sparse (Smith et al, 2013).

Transscrotal Artificial Urinary Sphincter

Wilson and associates (2003) described a technique in which all components of the AUS are placed through a transverse scrotal incision. Originally developed for reoperative surgery because of urethral atrophy, it allowed placement of a more distal cuff in tandem or with the transcorporeal technique (see Fig. 91-8B). Although the initial report was favorable in terms of continence outcomes, several reports suggest that the transscrotal technique yields inferior continence results (Stone et al, 2003; Henry et al, 2008). One possible explanation is that it does not allow equivalent placement of the cuff around the proximal, larger diameter bulbar urethra when compared to the perineal approach. Corroborative evidence comes from data on implanted cuff size. In the Mayo Clinic experience, 267 of the 272 perineal cuffs measured 4.5 cm and the remaining cuffs were 5.0 cm (Elliott and Barrett, 1998). Conversely, in the transscrotal series 32 of the 37 cuffs measured 4.0 cm and the remaining cuffs were 4.5 cm (Wilson et al, 2003). A modified version of the transscrotal approach, using enhanced exposure (Wilson et al, 2010), has allowed the use of larger cuff sizes around

the proximal bulbar urethra and may address the concerns raised in the literature.

Bladder Neck Artificial Urinary Sphincter

Bladder neck AUS remains an optional, although more invasive, method of cuff placement in men with sphincteric UI in whom the prostate is without external surgical or traumatic disruption. Thus, for causes of myelomeningocele and other neuropathic disorders, it should be considered as an alternative to bulbar AUS (Herndon et al, 2003). Its use is contraindicated after radical prostatectomy. Advantages include lower likelihood of erosion and cuff atrophy. Placement of the cuff is more complex, requiring a lower abdominal incision, exposure of the bladder base, and circumferential dissection of the vesicoprostatic junction. Opening the endopelvic fascia helps develop the plane of dissection; a catheter placed in the urethra and another in the rectum helps in identifying these structures. If necessary, cystostomy with placement of a finger in the lumen of the bladder neck also may assist the dissection. The bladder neck in adults requires a much larger cuff implant (usually ≥ 8 cm), higher PRB pressure (usually 71 to 80 cm H₂O), and a larger fluid volume in the system. Manufacturer packaging includes details relevant to implantation. In children, cuff and PRB characteristics may need to be altered significantly (Ruiz et al, 2006).

KEY POINTS: IMPLANTATION OF ARTIFICIAL URINARY SPHINCTER

- Standard implantation of the bulbar AUS places the cuff around the corpus spongiosum proximal to the convergence of the corporeal bodies.
- PRB of 61 to 70 cm H₂O is advised for all bulbar urethral cuffs; placement may be via abdominal, scrotal, or perineal approach.
- Postoperative deactivation of the cuff for 4 to 6 weeks is essential for proper healing without erosion.
- Prolonged urinary retention requires suprapubic cystostomy drainage.
- Revision surgery for nonmechanical causes may require modified cuff placement using 3.5-cm cuff, tandem cuff, or transcorporeal placement.

Transobturator Bulbourethral Sling

Rehder and Gozzi (2007) described a male transobturator sling that provides an alternative surgical technique for suburethral placement. Its use has been primarily for UI after radical prostatectomy. **Transobturator male slings are designed to reposition and lengthen the membranous urethra.** After exposing the corpus

TABLE 91-2 Outcomes and Complication Rates of Surgical Therapy for Mild-to-Moderate Male Sphincteric Urinary Incontinence

DEVICE	OUTCOMES (%)			
	CURED OR IMPROVED	CURED	IMPROVED	FAILED
Artificial urinary sphincter	82-89	73-76*	13-16	18-25
Bone-anchored sling	67-92	37-67†	12-37	8-33
Transobturator sling	70-84	40-80	13-30	16-30

*Defined as 0-1 pad.

†Defined as no pads. Not included are results from series that included higher proportion of men with history of adjuvant radiotherapy.

spongiosum in a manner identical to that in the AUS described earlier, the space between the corpus spongiosum and corpora cavernosa is developed on each side. The corpus spongiosum is dissected along its ventral surface proximally to the level of the perineal body, which is marked to facilitate later sling positioning. The corpus spongiosum is released from the bulbospongiosus muscle to allow appropriate repositioning with tensioning of the sling. Using the inferior margin of the adductor longus muscle as a landmark, a small stab wound is made approximately 1 fingerbreadth below the muscle on each side. A spinal needle locates the obturator foramen immediately lateral to the pubic ramus. Then, using an outside-inside direction, the appropriate left- or right-sided helical passing device is inserted from the thigh through the obturator foramen and out of the perineal wound medial to the ipsilateral corporeal body. This needle should be brought out as close as possible to the superior aspect of the triangle formed by the corpus spongiosum and the pubic ramus. Once this has been completed bilaterally, the polypropylene mesh is loosely positioned in the perineum, attached to the passing devices, and pulled out of the obturator foramen to the medial thigh without tension. **The mid-portion is placed on the corpus spongiosum (Fig. 91-9A), fixed to the corpus spongiosum with four to six permanent or absorbable sutures, and the arms of the sling are pulled up to tension the device. With tensioning, the perineal body and proximal bulbar urethra should move proximally and cephalad 3 to 4 cm to achieve appropriate positioning (see Fig. 91-9B). The maneuver is performed during cystoscopic visualization of the external sphinc-**

ter region to confirm the repositioning of the urethra (see Fig. 91-9C and D). Once in position, final tensioning is achieved after removing the plastic covering of the sling arms. The tail ends of the sling are tunneled by pulling the device ends into the main perineal incision without trimming excess length. The perineal incision is closed in layers including the bulbospongiosus muscle, Colles fascia, and skin. Overnight catheter drainage is usually sufficient for decompression of the bladder.

Bone Anchor Bulbourethral Sling

The bone-anchored perineal sling popularized using the AMS InVance implant is a synthetic mesh device placed outside the bulbospongiosus muscle and attached to the pubic rami. A vertical perineal incision centered over the bulbar urethra exposes the bulbospongiosus muscle and the medial aspect of each inferior pubic ramus (Fig. 91-10A). Three titanium bone screws preloaded with a pair of 1-0 polypropylene sutures are inserted in the antero-medial aspect of each descending pubic ramus using a bone drill (see Fig. 91-10B). The proximal bone screws are placed just beneath the junction of the descending ramus and pubic symphysis, and the distal screws are inserted approximately 3 cm caudally, at the level of the bulbar urethra. **Comiter and associates (1997) described retrograde leak point pressure (RLPP) to tension the device.**

A 4- by 7-cm sling composed of synthetic or organic material is secured to the bone-anchored sutures by passing the sutures through the sling with the aid of an 18-gauge needle, 0.5 cm from the right

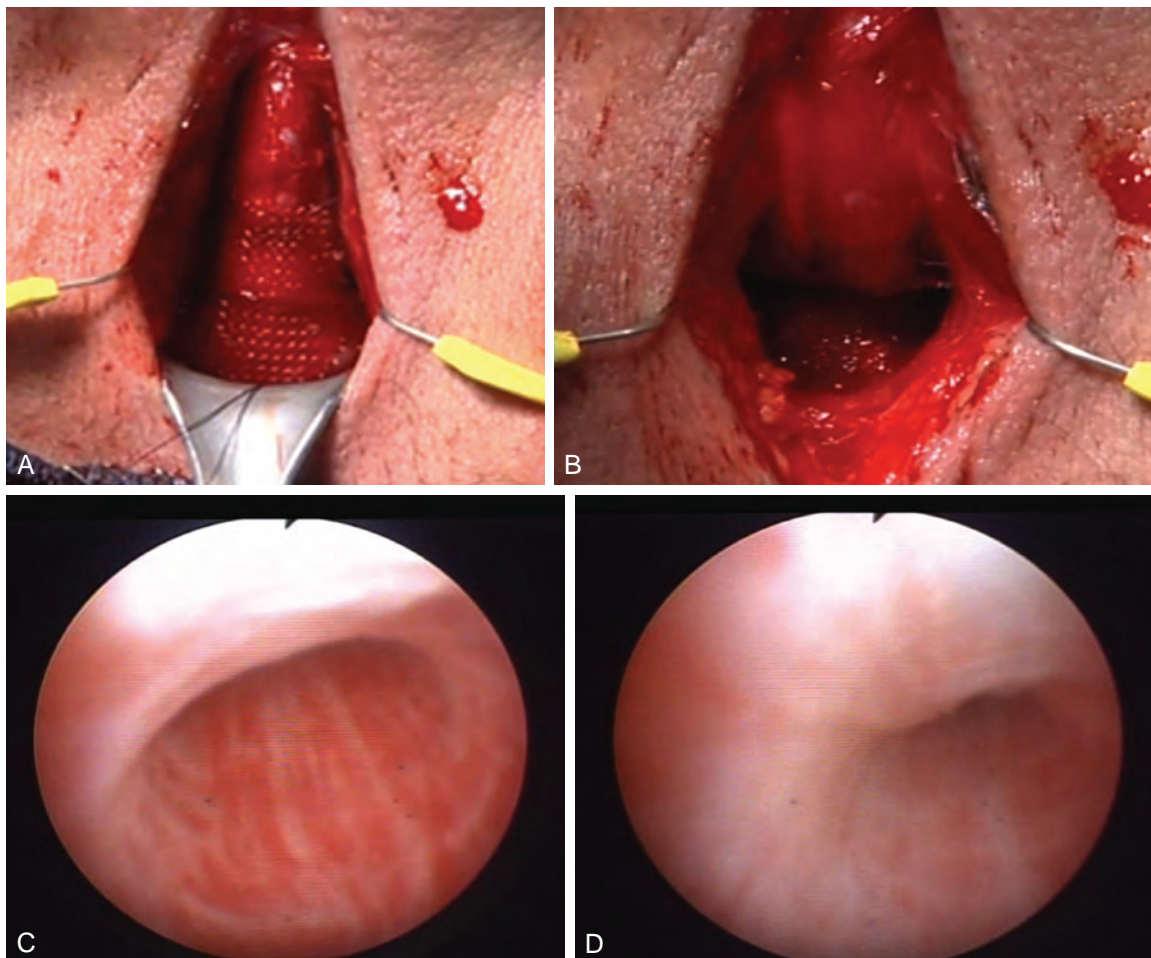


Figure 91-9. Transobturator sling. A, Perineal appearance of sling in place on corpus spongiosum before tensioning. B, Perineal appearance of sling after tensioning. C, Endoscopic appearance before tensioning. D, Endoscopic appearance after tensioning.

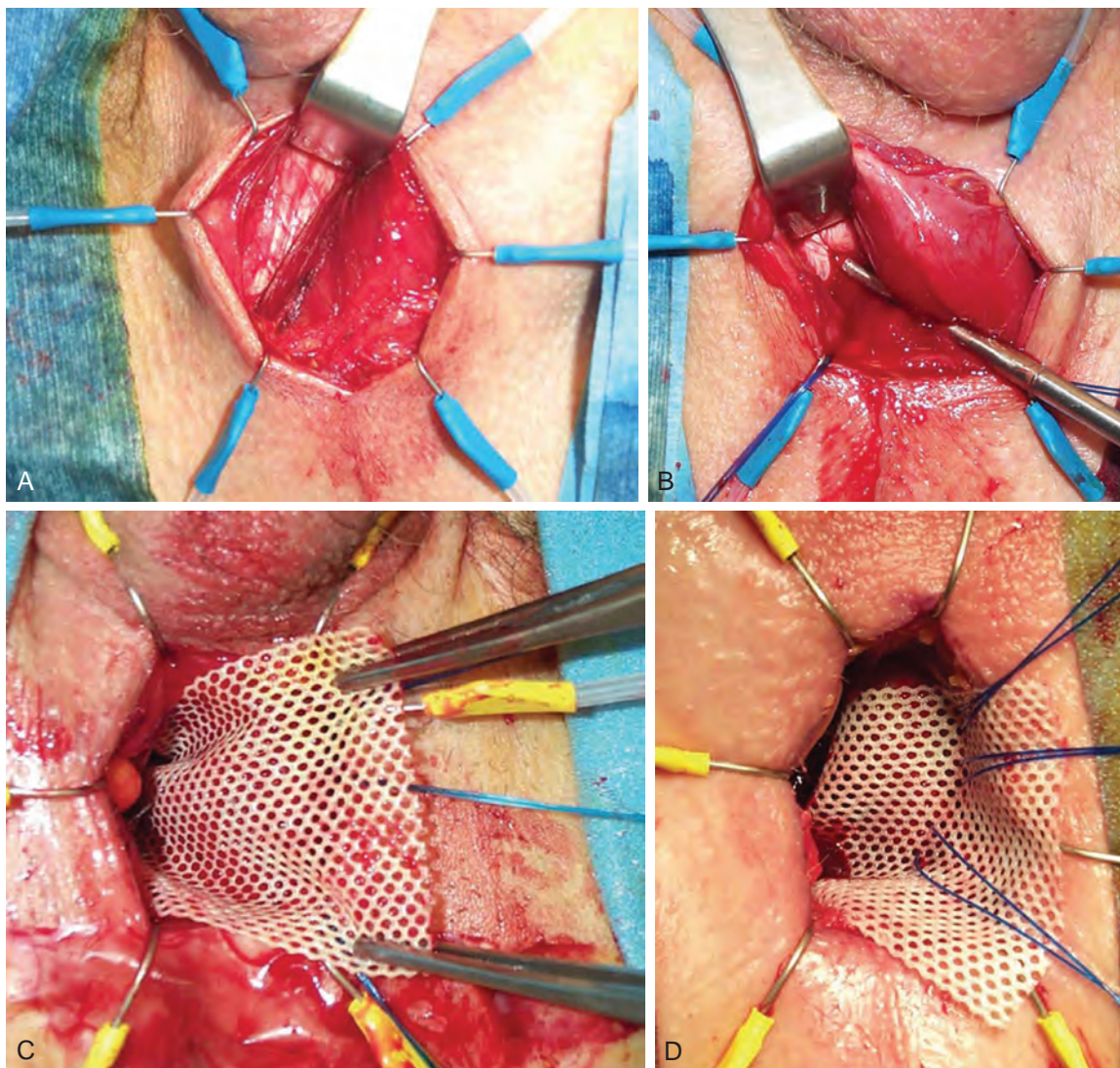


Figure 91-10. Bone-anchored sling insertion. **A**, Exposure of the right crus of the corpus cavernosum with bulbospongiosus muscle retracted medially. **B**, Screw insertion into inferior pubic ramus. **C**, Placement of the right side of the synthetic mesh device. **D**, Initial tensioning with sutures on the left side of the sling.

edge, equally spaced along the width of the sling. The right-sided sutures are then tied down to the bone (see Fig. 91-10C). With the sling positioned over the bulbospongiosus muscle, the contralateral sutures are passed through the left side of the sling and secured with a single throw of the suture over a silk safety tie. RLPP is repeated, allowing sling tension to be adjusted by moving the left-sided sutures more medially (tighter) or laterally (looser) until a RLPP of 60 cm H₂O is achieved (see Fig. 91-10D). The wound is irrigated and closed in two layers. The catheter is removed in the recovery room or the following morning for a trial of voiding.

Determining the appropriate tension of the sling is the most critical portion of the operation. Although the original choice of 60 cm H₂O was based on the pressure range of the AUS PRB, subsequent studies have demonstrated that patients who achieve an RLPP of 60 cm have better outcomes than those who demonstrate a lower compression pressure (Ullrich and Comiter, 2004). Alternative methods of sling tensioning have been described, such as an intraoperative cough test to determine sling tensioning (Madjar et al, 2001; Rajpurkar et al, 2005). When used as a salvage procedure after failed prior AUS or other sling, or in cases in which more severe incontinence is treated by inducing urinary retention, the sling is tightened as much as possible without regard to RLPP.

Other Devices

A sling with emerging clinical data, Virtue has two lateral strips for transobturator urethral elevation in addition to two prepubic arms designed to provide concomitant compression (see Fig. 91-2). This quadratic fixation has yielded acceptable early results (Comiter, 2007). The device has been approved by the U.S. Food and Drug Administration (FDA) and is marketed by Coloplast (Comiter et al, 2012). Its role in the treatment armamentarium has not been clearly defined, but because of its compressive mechanism the device potentially can be used for more severe cases of UI in a wider spectrum of causes in addition to radical prostatectomy.

The Prostate Adjustable Continence Therapy device (ProACT; Uromedica, Plymouth, MN) consists of two balloons, placed on both sides of the bladder neck to increase outlet resistance. Percutaneous adjustment of the pressure applied to the bladder neck is performed through titanium ports within the scrotum. Hübner and Schlarp showed significantly improved continence as they used this device over time, which stimulated the use of the ProACT device in centers in Europe (Hübner and Schlarp 2005; Trigo-Rocha et al, 2006). A trial in the United States has been registered with the FDA, but its recruitment status is unknown (ClinicalTrials.gov, accessed 13.11.26).

KEY POINTS: SLING INDICATIONS AND MECHANISMS

- Male bulbar urethral slings are indicated in men with mild-to-moderate sphincteric UI, intact bladder contractility, and well-vascularized urethral anatomy.
- Transobturator slings reposition and elongate the membranous urethra and depend on the intact external sphincter.
- Bone-anchored slings provide a compressive mechanism of continence and require specific protocols for tensioning.
- Quadratic fixation provides an alternative to the two-arm devices, with limited data on efficacy and durability.

ARTIFICIAL URINARY SPHINCTER COMPLICATIONS**Urinary Retention**

Urinary retention after AUS is rare, but is more frequent with transcorporeal and 3.5-cm cuffs compared to larger cuffs (Smith et al, 2013); in the immediate postoperative period it should be managed by transurethral bladder drainage with a small (10 or 12 Fr) catheter for 24 to 48 hours. Cuff deactivation must be confirmed before catheterization. If the patient fails a voiding trial at 48 hours, suprapubic cystostomy drainage is recommended to reduce the risk for urethral erosion. Ultrasound or fluoroscopic guidance is recommended to prevent puncture or potential contamination of the PRB. Retention persisting beyond several weeks implies undersizing of the cuff; in such cases, reoperation and cuff replacement may be required. Correlation with preoperative urodynamic findings is advised in such cases. Late-onset urinary retention mandates endoscopic and urodynamic evaluation to rule out proximal urethral obstruction, erosion, or detrusor failure.

Artificial Urinary Sphincter Infection

Infection remains a serious and devastating complication of any implant surgery. The rate of infection with initial AUS surgery is 1% to 3% (Gundian et al, 1989; Marks and Light, 1989; Litwiller et al, 1996; Montague and Angermeier, 2000) but may be as high as 10% in patients who have undergone pelvic radiation and in reoperations (Montague, 1992). Skin pathogens are the most commonly cultured organism, usually from *Staphylococcus epidermidis* and *Staphylococcus aureus* (Licht et al, 1995; Magera and Elliott, 2008). The introduction of the InhibiZone (American Medical Systems) surface treatment combining rifampin and minocycline hydrochloride to the AUS cuff and pump was postulated to lead to a reduction in postoperative infection rates, although the reduced infection rate seen with penile implants (Carson, 2004) has not been replicated in the AUS literature (de Cógáin and Elliott, 2013). Late infections (>4 months) may represent indolent organisms introduced at the time of infection or by hematogenous spread. Therefore, in men with AUS, antibiotics should be considered before urinary tract manipulation in accordance with AUA Guidelines (Wolf et al, 2008).

The initial presentation of an early postoperative AUS infection is usually scrotal pain, although erythema, edema, and frank purulence will commonly accompany this symptom. Because implant infections are not amenable to antibiotic therapy, AUS infection will almost always require explantation. Traditional management includes device removal followed by a waiting period of several months with delayed reimplantation.

Immediate salvage of infected, noneroded AUS can be accomplished with complete device removal, antiseptic irrigation, and immediate reimplantation (Kowalczyk et al, 1996b; Bryan et al, 2002). This procedure includes an irrigation regimen used in penile prosthesis salvage protocols (Mulcahy et al, 1995). Mulcahy and associates used this approach to salvage seven of eight patients with infected noneroded AUS in a total of nine operations (Bryan et al, 2002). In all cases the entire AUS was removed and the wounds were copiously irrigated according to a seven-solution protocol before a new system was implanted. Contraindications to prosthesis

salvage include sepsis, ketoacidosis, necrotizing infection, immunosuppression, and the finding of gross purulent material at the time of explantation.

Urethral Erosion

Urethral erosion is reported in up to 5% of AUS implantations (Gundian et al, 1989; Marks and Light, 1989; Litwiller et al, 1996; Singh and Thomas, 1996; Montague and Angermeier, 2000). Furlow and Barrett (1985) introduced the concept of postoperative deactivation during the healing process to decrease pressure-induced ischemia and necrosis. Delayed deactivation has lowered the risk for urethral erosion, especially in cases of reimplantation. Motley and Barrett (1990) saw a decrease in secondary urethral erosion from 18% to 1.3% with this technique. In an analysis of their 13-year experience in patients with urethral erosions, Webster and associates (Raj et al, 2006) determined that patients with hypertension, coronary artery disease, prior radiation therapy, and prior AUS revisions were more than twice as likely to suffer secondary urethral erosions.

Immediate removal of all the components of the AUS is imperative in cases of erosion, because they are assumed to be infected. The urethral injury is managed with urethral catheter drainage and/or suprapubic cystostomy (Kowalczyk et al, 1996b; Flynn and Webster, 2004). Perineal wounds are considered infected and loosely approximated or allowed to close by secondary intention. Reimplantation is considered only after urethral healing is confirmed by urethrography and a delay of 3 to 6 months is observed.

Urethral patency must be confirmed by cystoscopy or retrograde urethrogram before attempted device replacement (Motley and Barrett, 1990; Kowalczyk et al, 1996b; Frank et al, 2000). A new cuff should be placed either proximal or distal to the previous site. Significant scarring as well as a compromised vascular supply makes replacement of the cuff at the erosion site difficult and risky (Motley and Barrett, 1990; Kowalczyk et al, 1996b). Frank and colleagues (Frank et al, 2000) reported a successful outcome in 87% of de novo reimplantations after erosion or infection, with recurrent urethral erosion in 8.7%. The authors recommended nightly deactivation of the AUS in cases of reimplantation for prior erosion. More recently, in a series of 46 patients with prior AUS erosion who underwent reimplantation, 35% suffered another erosion within an average of 6.7 months (Raj et al, 2006). Use of the transcorporeal approach in such cases may reduce the risk for urethral injury during the secondary surgery as well as potentially provide greater protection against subsequent erosion.

Urethral Atrophy

Urethral atrophy results from the chronic compression of the spongy tissue under the occlusive cuff. This is the most common reason for revision of the AUS. Treatment options include cuff downsizing, movement of the cuff to a more proximal or distal location where the urethra may be thicker, or placement of a second cuff in tandem. Simple replacement of the PRB with a higher pressure reservoir to overcome urethral atrophy is no longer recommended because of the risk for erosion (Raj et al, 2005).

Our approach is to downsize the cuff in the same location when possible. If the existing cuff is 4.0 cm, the option to use a 3.5-cm cuff is now available. Alternatively, we reposition the cuff more proximally, when feasible, or distally using the transcorporeal technique if necessary, and measure the appropriate cuff size. Saffarian and associates (2003) reported a significant improvement in daily pad usage from 3.9 to 0.5 in 17 patients with urethral atrophy. In a large series of secondary AUS surgery, the cuff was replaced in 142 cases, of which 33% of cuffs were placed distal to the original location, 11% were placed proximal, and 52% were placed at the original cuff location (Raj et al, 2005). The cuffs were downsized in 56% of cases, unchanged in 30%, and upsized in 13%, reflecting the new locations. In cases of urethral atrophy, several prominent centers have successfully added a second cuff in tandem to salvage continence (Brito et al, 1993; DiMarco and Elliott, 2003).

Mechanical Failure

The historical incidence of mechanical failure has diminished substantially after introduction of the narrow-backed cuff. [Elliott and Barrett \(1998\)](#) reviewed the long-term durability of the AMS 800 in 323 patients who underwent implantation at the Mayo Clinic between 1983 and 1994. The change in design resulted in a decrease in nonmechanical failure from 17% to 9%, primarily because of a reduction in urethral atrophy. A decrease in mechanical failure from 21% to 7.6% was primarily the result of a reduction in cuff leak, along with improvements in the synthetic material that lessened the risk for fracture or kinking of the device. **Patients can generally expect a 7- to 10-year device life for the AUS. In the absence of infection or erosion, replacement of an isolated malfunctioning component may be feasible if the revision occurs within 3 years of implantation. However, a slow leak from the PRB may be difficult to diagnose intraoperatively, and, if in doubt, total device replacement is prudent. Devices greater than 3 years old should be replaced in toto.**

Special Circumstances

The management of **urethral and vesicourethral anastomotic stricture** encountered after AUS implantation proposes a unique challenge. Stricture at the site of the AUS cuff may result from compression or ischemia and may indicate impending urethral erosion. One such bulbar urethral stricture was successfully managed with periodic filiform and follower dilation ([Debell and Wessells, 2001](#)). Others have successfully treated strictures proximal to an AUS with balloon dilation ([Westney et al, 1999](#)) or holmium laser through a flexible ureteroscope ([Anger et al, 2005](#)). In the event significant endoscopic manipulation is required proximal to the cuff site, our practice is to surgically uncouple the cuff for the duration of the endoscopic procedure.

SLING COMPLICATIONS

The most commonly reported complications of male slings include perineal pain, urinary retention, infection, anchoring complications from bone anchors, and rare cases of erosion. **Perineal pain may be reported in up to 74% of patients after bone-anchored slings, but most resolve within 3 months ([Comiter, 2005](#)).** Retention is short lived and resolves within several weeks. Isolated cases have required release of the sling. The infection/erosion rate for both types of slings ranges from 2% to 15% and the need for revision (secondary to bone-anchor dislodgement) has been reported from 2% to 4.2%. Larger series with longer term follow-up suggest low rates of erosion and infection ([Bauer et al, 2010](#)). Patients should be counseled as to the possibility of persistent pain and osteitis pubis after slings, although such complications are extremely rare.

KEY POINTS: COMPLICATIONS

- Device infection requires total explantation and salvage antibiotic regimens.
- Device erosion requires total explantation and catheter drainage.
- Troubleshooting of recurrent UI after AUS requires a systematic and exhaustive evaluation.
- Cuff atrophy requires downsizing, repositioning, tandem cuff, or transcorporeal surgery.

LONG-TERM RESULTS OF ARTIFICIAL URINARY SPHINCTER AND SLINGS

Outcomes of surgical correction of male UI depend on patient and device characteristics. First in importance is the severity of UI. Many

urologic surgeons reserve sling surgery for mild-to-moderate degrees of incontinence, but severity is poorly characterized by pad number (see earlier). A difference in baseline incontinence between studies introduces unmeasured bias and makes comparisons of case series difficult. We have summarized available data in [Table 91-2](#).

[Montague and Angermeier \(2000\)](#) reviewed the results of the AUS in 286 patients from five centers. They noted that on average 76% of patients were dry (dry zero or one pad per day) and 13% were improved, for an overall success rate of 89% at a mean follow-up of 18 to 44 months. Revision of the device occurred due to urethral erosion in 5%, AUS infection in 3%, and mechanical failure in 15%. Other studies have confirmed these results ([Hajivasiliou, 1999](#); [Venn et al, 2000](#)). Although many patients still need minor protection with urinary pads, most are satisfied with the long-term outcome of the AUS ([Haab et al, 1997](#); [Montague et al, 2001](#); [Dalkin et al, 2003](#)). Success rates for revision surgery compare favorably with initial surgery, although infection and erosion rates are higher ([Raj et al, 2005](#)). Differences among centers may be related to surgical volume, inclusion of secondary implants, and the sensitivity and accuracy of outcome measures. The long-term fate of patients implanted with transcorporeal cuffs and the newly introduced 3.5-cm cuff remains to be determined. Initial results from one center are promising ([Hudak and Morey, 2011](#)), although outcomes from other centers presented in abstract form ([Voelzke, 2013](#)) raise a note of caution regarding infection and erosion, likely a result of the complexity of cases in which the urethra is narrowed as a result of prior surgery, erosion, radiation, or other causes ([Lai and Boone, 2012](#)).

Results with the bone-anchored and transobturator sling appear similar to those with AUS (see [Table 91-2](#)). Initial success rates with both devices were very high, although subsequent series show greater variability of outcomes ([Guimaraes et al, 2009](#)). One surgeon did not identify a learning curve in adoption of the transobturator male sling ([Zuckerman et al, 2013](#)), but other centers with less extensive experience with male urethral surgery, AUS, or female sling surgery may note greater variation in outcomes with initial cases.

The role of the transobturator AdVance sling in the armamentarium has been firmly established. Early promising results ([Bauer et al, 2009](#); [Soljanik et al, 2012](#)) have been confirmed by other centers, and a persistent benefit with only modest deterioration of outcome at 2 to 3 years of follow-up has been reported ([Bale, 2011](#); [Bauer et al, 2011](#); [Li et al, 2012](#); [Rehder et al, 2012](#); [Kowalik et al, 2015](#)). Patient selection criteria are evolving, particularly with regard to cutoffs based on incontinence severity (e.g., pad number or weight) for consideration of AUS. The poorer prognosis for patients having undergone prior adjuvant radiotherapy has been replicated in additional series ([Torrey et al, 2013](#)).

The approach to failure of the male sling is also evolving. Reoperation and implantation of AUS has been shown to be safe and effective after a prior male sling, having similar outcomes as in surgically naive patients ([Lentz et al, 2012](#); [Linder et al, 2013](#)). Repeat male sling surgery was effective in one study, with the caveat that selection criteria must be carefully considered ([Soljanik et al, 2010](#)).

The inconsistent outcomes with male perineal sling surgery likely also reflect variability in rhabdosphincter function. In the future, quantitative assessment of residual rhabdosphincter function may be important in selection of patients for sling surgery or AUS. Finally, sling implantation inherently introduces greater variability in technique. Many factors are at play, including location of sling placement along the bulbar urethra, pelvic bony anatomy, degree of tension placed on the device, and other unmeasured influences. In contrast, the AUS occludes the bulbar urethra with a very high degree of reproducibility and mechanical reliability, allowing consistent results regardless of the degree of incontinence or experience of the surgeon.

SUMMARY


The continued high rate of surgery for localized prostate cancer portends that male sphincteric UI will remain prevalent and require

KEY POINTS: LONG-TERM RESULTS OF ARTIFICIAL URINARY SPHINCTER AND SLINGS


- AUS continues to provide a reliable solution to male UI of all degrees of severity across the range of first-time implantation to complex reoperative and high-risk patients.
- Transobturator slings such as Advance and newer devices provide long-term durable outcomes for mild-to-moderate male UI after radical prostatectomy.
- Bone-anchored sling demonstrates high rates of success, but the most commonly used InVance sling is no longer commercially available in the United States.

surgical treatment to improve symptoms and quality of life. The initial evaluation must include a focused history and physical examination, voiding diary, pad weight test, and, in selected cases, cystoscopy and pressure-flow urodynamics. The AUS remains the gold standard treatment for moderate-to-severe male UI, especially in complex cases, with excellent overall success and acceptable complication rates. For mild-to-moderate UI in the absence of prior urethral surgery, radiation therapy, or detrusor acontractility, male slings provide efficacious alternatives. The outcomes after AUS and male sling cannot be fully compared because of differences in baseline incontinence severity, end points, follow-up, and patient numbers. Nevertheless, **regardless of severity, nearly 90% of men with sphincteric UI will have minimal leakage and acceptable quality of life related to urinary symptoms after surgical treatment.** Similar cured and improved rates for UI after radical prostatectomy have been reported with both the bone-anchored and transobturator slings. However, several caveats exist. Results of slings in radiated patients are inferior. The appropriateness of standard transobturator slings for incontinence of other causes (e.g., TURP, neurogenic, post-traumatic) has not been demonstrated. No sling has been compared to AUS in a controlled clinical trial. It is

likely that selection bias regarding UI severity and other factors exists in choosing a sling versus AUS at most institutions. Furthermore, **perineal sling implantation depends on subtle technical maneuvers relating to positioning and tensioning.** Conversely, **once the urethra has been circumferentially mobilized and measured, the effectiveness of AUS is largely independent of technique.** Thus, the occasional implanter will be more likely to achieve success with AUS versus sling procedures, although the potential for erosion and mechanical failure will continue to drive the need for alternative solutions.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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92

Tumors of the Bladder

David P. Wood, Jr., MD

Benign Tumors of the Bladder

Urothelial Cancer

The urothelium of the bladder is traditionally considered to be lined by transitional cells, which, as suggested by the name, can transform into a variety of benign and malignant tumors. In this chapter we will discuss the epidemiology, etiology, pathology, staging, origin, recurrence, dissemination, molecular biology, detection, and prevention of the more common benign and malignant tumors of the bladder, with an emphasis on urothelial cancer.

BENIGN TUMORS OF THE BLADDER

There are numerous benign tumors of the bladder, but the more common ones include epithelial metaplasia, leukoplakia, inverted papilloma, nephrogenic adenoma, leiomyoma, cystitis cystica, and cystitis glandularis.

Epithelial Metaplasia

Epithelial metaplasia is focal areas of transformed urothelium with normal nuclear and cellular architecture surrounded by normal urothelium usually located on the trigone and composed of squamous (squamous metaplasia) or glandular (glandular metaplasia) cells. Squamous metaplasia often has a knobby appearance and is covered by white, flaky, easily disrupted material lying on the trigone. Glandular metaplasia appears as clumps of raised red areas that appear inflammatory and are often confused for cancer. Approximately 40% of women and 5% of men have squamous metaplasia of the bladder, which is usually related to infection, trauma, or surgery (Ozbey et al, 1999). Spinal cord injury is associated with squamous metaplasia, most likely from catheter trauma and urinary tract infections (Vaidyanathan et al, 2003). Glandular metaplasia can extensively involve the bladder, particularly the trigone, but biopsy is not required. Treatment is unnecessary, and a preventive agent has not been identified.

Leukoplakia

Leukoplakia of the bladder is similar to squamous metaplasia with the addition of keratin deposition that appears as a white flaky substance floating in the bladder (Staack et al, 2006). Leukoplakia occurs in other organs that are covered by squamous epithelium and is often premalignant (Zhang et al, 2009). However, cytogenetic studies on bladder leukoplakia are consistent with a benign lesion, and no treatment is necessary (Staack et al, 2006).

Nonurothelial Malignancies

Inverted Papilloma

An inverted papilloma is a benign proliferative lesion that is associated with chronic inflammation or bladder outlet obstruction and can be located throughout the bladder but most commonly on the trigone, comprising less than 1% of all bladder tumors (Jones et al, 2007; Kilciler et al, 2008; Picozzi et al, 2012). Inverted papillomas demonstrate an inverted growth pattern composed of anastomosing islands of histologically and cytologically normal urothelial cells invaginating from the surface urothelium into the lamina propria but not into the muscularis propria (Fig. 92-1) (Picozzi et al, 2012). When diagnosed according to strictly defined criteria (e.g., lack of cytologic atypia), inverted papillomas behave in a benign fashion with only a 1% incidence of tumor recurrence (Kilciler et al, 2008; Picozzi et al, 2012). The use of fluorescence in situ hybridization (FISH) to evaluate chromosomal changes can distinguish between an inverted papilloma and a urothelial cancer with an inverted growth pattern (Jones et al, 2007). Transurethral resection is the treatment of choice.

Papilloma

Urothelial papilloma is a benign proliferative growth in the bladder that is composed of delicate stalks lined by normal-appearing urothelium (see Fig 92-1) (Montironi and Lopez-Beltran, 2005). Papillomas had previously been categorized as grade 1 Ta tumors of the bladder until the World Health Organization (WHO) changed the classification of noninvasive bladder cancer in 1998 (Epstein et al, 1998). Papillomas rarely have mitotic figures and lack markers of aggressive growth such as TP53 or RB mutations, but 75% of these tumors have mutations in fibroblast growth factor receptor-3 (FGFR-3) (van Rhijn et al, 2004). Papillomas may recur, but they do not progress or invade.

Nephrogenic Adenoma

Nephrogenic adenoma is a rare tumor caused by chronic irritation of the urothelium; it arises from a variety of sources, including trauma, previous surgery, renal transplantation, intravesical chemotherapy, stones, catheters, and infection (Wood et al, 1988; Pavlidakey et al, 2010). Nephrogenic adenoma is composed of glandular-appearing tubules similar to renal tubules that involve the mucosa and submucosa of the bladder. The lesion may be vascular, which explains the presence of gross hematuria in most cases (Franke et al, 2011). There is no racial or gender association with the entity. The constant theme of chronic inflammation

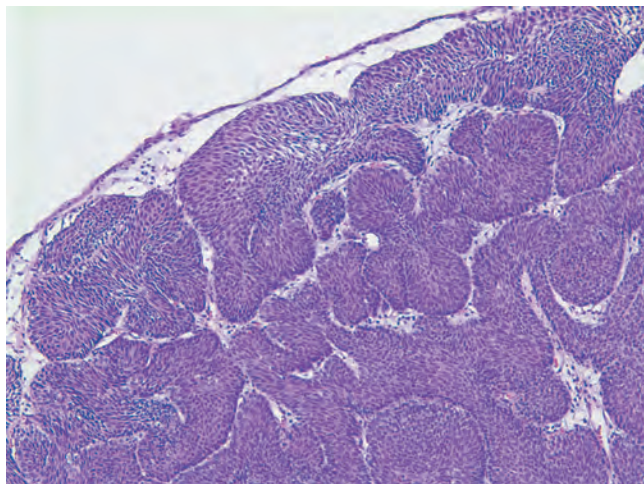


Figure 92-1. Papilloma.

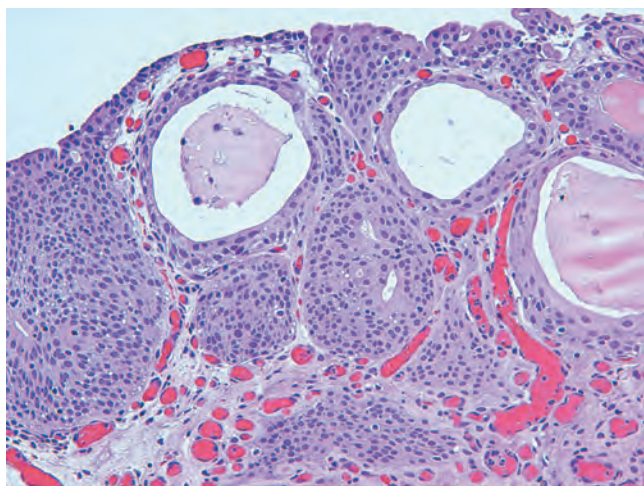


Figure 92-2. Cystitis glandularis.

suggests that metaplastic changes to the urothelium lead to nephrogenic adenoma, although some authors have proposed a theory that nephrogenic adenoma arises from nests of displaced mesonephric tissue in the urothelium that is activated with mucosal injury (Franke et al, 2011). The most frequent presenting sign is gross hematuria, often in conjunction with a urinary tract infection. Treatment consists of transurethral resection and elimination of the chronic irritation.

Cystitis Cystica and Glandularis

Cystitis cystica and/or glandularis is a common finding in normal bladders, usually associated with inflammation or chronic obstruction (Semins and Schoenberg, 2007). These benign tumors represent cystic nests that are lined by columnar or cuboidal cells and are typically associated with proliferation of von Brunn nests (Fig. 92-2). Cystitis glandularis can be associated with pelvic lipomatosis and may occupy the majority of the bladder (Buckley et al, 2007). There have been a few case reports of cystitis cystica or glandularis transforming into adenocarcinoma, and therefore regular endoscopic evaluation of patients with these entities is recommended (Smith et al, 2008). The most common presenting feature of cystitis cystica or glandularis is irritative voiding symptoms and hematuria. Treatment is transurethral resection and relief of the obstruction or inflammatory condition.

Leiomyoma

Leiomyomas are the most common nonepithelial benign tumor of the bladder composed of benign smooth muscle. Several hundred cases have been reported, but this may under-represent the true prevalence. These tumors occur most commonly in women of child-bearing age and are histologically similar to leiomyomas of the uterus (Goel and Thupili, 2013). Leiomyomas appear as smooth indentations of the bladder and can be confused with a bladder tumor except for the normal urothelium overlying the tumor (Fasih et al, 2008). Imaging, especially magnetic resonance imaging (MRI), can confirm the diagnosis and spare invasive procedures (Fasih et al, 2008). Surgical resection is required if the leiomyoma is large or painful.

UROTHELIAL CANCER

Epidemiology

The incidence rate of a cancer is defined as the number of new cancers diagnosed per 100,000 persons per year. The prevalence rate is the total number of cancers per 100,000 persons per year, not just new cases. Because urothelial cancer is a cancer of the environment and age, the incidence and prevalence rates increase with age, peaking in the eighth decade of life, and there is a strong association between environmental toxins and urothelial cancer formation (Parkin, 2008; Siegel et al, 2013). The incidence rate of urothelial cancer has been rising over the last 60 to 70 years, but the rate of rise has recently decreased significantly and in some geographic areas has leveled off (Parkin, 2008). Unfortunately, the incidence rate is rising the fastest in underdeveloped countries where industrialization has led to carcinogenic exposure.

According to the latest American Cancer Society statistics, there were 72,570 total cases diagnosed in the United States in 2013 involving 54,610 men and 17,960 women and accounting for 7% of all cancers (Siegel et al, 2013). Bladder cancer is a lethal disease, with 15,210 deaths recorded in 2013, including 10,820 men and 4390 women, and accounts for 3% of all cancer deaths (Siegel et al, 2013). Bladder cancer contributes to 0.7% of the absolute decrease in the cancer death rate seen during this time, when all cancers are considered (Siegel et al, 2013). Globally, the incidence rate of bladder cancer has been increasing, but because of smoking cessation programs, at a slower rate over the last decade (Parkin, 2008). The mortality rate from bladder cancer has decreased significantly from 1990 to 2004, with both men and women achieving an 18.4% decrease in mortality rate (Fig. 92-3). This decrease in mortality rate is more striking in men than women because of the earlier peak when men began to smoke, which occurred approximately 20 years before women. Because of the latency period with urothelial cancer-causing agents in tobacco, we should see a commensurate decrease in the mortality rate in women in 15 to 20 years as their smoking cessation programs become more widespread.

Gender, Racial, and Age Differences

Males are 3 to 4 times more likely to develop bladder cancer than females, presumably because of an increased prevalence of smoking and exposure to environmental toxins (Parkin, 2008; Siegel et al, 2013). African-American males have a 19% higher incidence rate than white males for all cancers and a 37% higher death rate. However, for urothelial cancer, white males have a higher incidence and death rate than African-Americans (Parkin, 2008; Siegel et al, 2013). African-American women have a 6% lower incidence but a 17% higher death rate than white women for all cancers (Siegel et al, 2013). However, bladder cancer is roughly 1.5 times more common in white women than in African-American women. A white male has a 3.7% chance of developing urothelial cancer in his lifetime, which is roughly 3 times the probability for white females or African-American males and more than 4.5 times the probability for African-American females (Hayat et al, 2007; Siegel et al, 2013). The risk of developing invasive bladder cancer

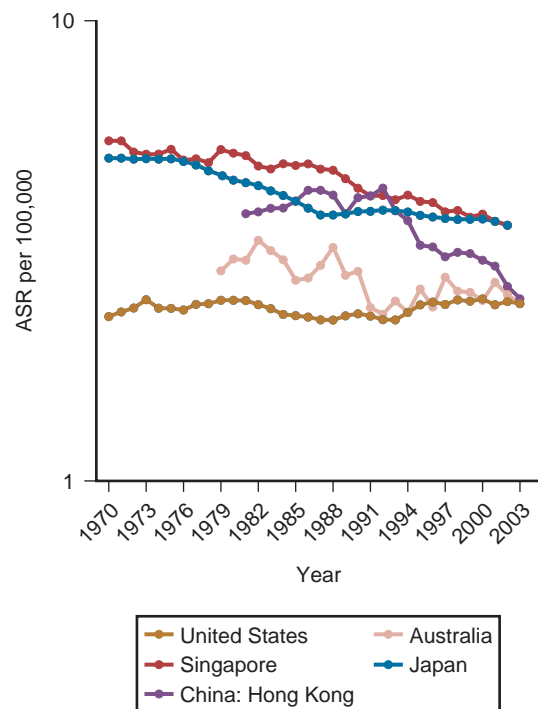


Figure 92-3. Age-standardized rate (ASR) of global mortality from bladder cancer. (From Parkin DM. The global burden of urinary bladder cancer. *Scand J Urol Nephrol Suppl* 2008;218:12–20.)

is age dependent (Siegel et al, 2013). For men from birth to age 39 years, the incidence rate of invasive bladder cancer is 0.02%; ages 40 to 59 years, 0.41%; ages 60 to 69 years, 0.96%; ages 70 years and older, 3.5%; and from birth to death, 3.7%. The bladder cancer incidence for women from birth to age 39 years is 0.1%; ages 40 to 59 years, 0.13%; ages 60 to 69 years, 0.26%; ages 70 years and older, 0.99%; and from birth to death, 1.17%. In general, adolescents and young adults (younger than 40 years) tend to develop well-differentiated noninvasive, rather than invasive, bladder cancer (Linn et al, 1998). Unlike many other cancers in which younger patients tend to develop more aggressive disease, the opposite appears to be true in bladder cancer, because these patients more frequently have noninvasive low-grade tumors at presentation (Wang et al, 2012b).

Global Burden of Bladder Cancer

There is a geographic difference in bladder cancer incidence rates across the world, with the highest occurring in Southern and Eastern Europe, parts of Africa, the Middle East, and North America, and the lowest occurring in Asia and underdeveloped areas in Africa (Jemal et al, 2010). Bladder cancer is the 9th most common cancer worldwide, with 357,000 cases recorded in 2002 (Parkin, 2008). Bladder cancer is the 13th most common cause of death, accounting for 145,000 deaths worldwide (Parkin, 2008; Jemal et al, 2010). The incidence rate of bladder cancer has been rising in Asia and Russia because of an increased prevalence of smoking. Sixty-three percent of all bladder cancer cases occur in developed countries, with 55% from North America and Europe. In the United States, the highest bladder cancer incidence rate is in Rhode Island and the lowest is in the District of Columbia (Siegel et al, 2013). The histologic cell type of bladder cancer is very geographically dependent, but urothelial cancer is the most common. In North America and Europe, 95% to 97% of cases are urothelial carcinoma; in Africa 60% to 90% are urothelial and 10% to 40% are squamous cell; and Egypt has the highest rate of squamous cell carcinoma because of the endemic infections with *Schistosoma* species (Parkin, 2008).

Mortality

The mortality rate from bladder cancer in Egypt is three times higher than in Europe and eight times higher than in North America because of the aggressive nature of squamous cell carcinoma that is highly prevalent in Egypt (Parekh et al, 2002). In the United States, death rates for all cancer sites combined decreased by 2.6% per year in males and by 1.8% in females from 2002 to 2004 compared with 1.5% and 0.8% per year in males and females, respectively, from 1992 to 2002 (Siegel et al, 2013). The mortality rate for bladder cancer has decreased by 5% during this period primarily because of smoking cessation, changes in environmental carcinogens, and healthier lifestyles. Better chemotherapy has improved the survival rate in patients with metastatic bladder cancer, and changes in physician practices related to more timely care and more aggressive treatment in healthy patients could lead to improvement in overall survival as well. Lee and colleagues (2006) reported that a delay of more than 12 weeks from the diagnosis of bladder cancer to cystectomy treatment was associated with a decrease in overall and cancer-specific survival. However, more intensive treatment (intravesical chemotherapy and cystoscopy) for patients with noninvasive bladder cancer did not correlate with better survival or reduced need for invasive treatment (Hollenbeck et al, 2009; Morris et al, 2009).

KEY POINTS: EPIDEMIOLOGY

- Bladder cancer is related to age and exposure to environmental carcinogens, primarily smoking.
- The median age of bladder cancer diagnosis is 70 years for men and women, and the incidence of and mortality from the disease increase with age.
- Bladder cancer is less common in African-Americans than in whites; however, the death rate from bladder cancer is higher in African-Americans than in whites.
- The incidence rate of bladder cancer is decreasing faster in men than in women because of the recent decrease in the percent of men smoking compared with women.

Etiology

Bladder cancer is caused by genetic abnormalities and external risk factors, including carcinogen exposure, nutritional factors, fluid intake, alcohol, inflammation, infection, chemotherapy, radiation, and possibly artificial sweeteners.

Genetic Factors

The higher incidence of bladder cancer in white compared with African-American males is probably not genetic but environmental, or it may be related to differential susceptibility to carcinogens (Bouchardy et al, 1995; Wanner et al, 1995; Bouchardy et al, 1996). There are several polymorphisms that seem to be related to the formation of bladder cancer, in particular the susceptibility to environmental carcinogens. *N*-acetyltransferase (NAT) detoxifies nitrosamines, a known bladder carcinogen. Specifically, NAT-2 regulates the rate of acetylation of compounds such as caffeine, which are related to bladder cancer formation. The slow NAT-2 polymorphism is related to bladder cancer with an odds ratio of 1.4 compared with the fast polymorphism (Garcia-Closas et al, 2005). Glutathione-S-transferase (GSTM1) conjugates several reactive chemicals, including arylamines and nitrosamines. The null GSTM1 polymorphism is associated with an increased bladder risk with a relative risk of 1.5 (Garcia-Closas et al, 2005). Null GSTM1 and slow NAT-2 lead to high levels of 3-aminobiphenyl and higher risk of bladder cancer. These polymorphisms are present in 27% of white, 15% of African-American, and 3% of Asian males, thus partially explaining the different bladder cancer incidence rates across ethnic groups.

Heredity. First-degree relatives of patients with bladder cancer have a twofold increased risk of developing urothelial cancer themselves, but high-risk urothelial cancer families are relatively rare (Aben et al, 2002; Murta-Nascimento et al, 2007; Kiemeny, 2008). The hereditary risk seems to be higher for women and non-smokers, but it is not related to secondhand exposure to smoking in families. The inherited risk of bladder cancer formation appears to affect all stages of urothelial carcinoma and is not associated with bladder cancer formation at an earlier age. Unfortunately, there are no clear mendelian inheritance patterns, making classic linkage studies impossible. Most likely, there are a variety of low-penetrance genes that can be inherited to make a person more susceptible to carcinogenic exposure, thus increasing the risk of bladder cancer formation.

External Risk Factors

In addition to the skin and lungs, the bladder is the main internal organ affected by occupational carcinogens. The primary culprits are the aromatic amines that bind to DNA (Deldos and Lerner, 2008; Reulen et al, 2008). Twenty percent to 27% of all bladder cancers are associated with industrial exposure of some type, primarily in areas with a heavy concentration of chemical industries (Case and Hosker, 1954; Blot and Fraumeni 1978; Reulen et al, 2008). Among the first chemical agents implicated in the formation of bladder cancer in dye and rubber workers were benzidine and β -naphthylamine (Case and Hosker, 1954). Other industrial agents implicated in bladder cancer formation include polycyclic aromatic hydrocarbons (PAHs), diesel exhaust, and paint substances (Zeegers et al, 2001).

Environmental carcinogens can enter the system and cause bladder cancer from inhalation or through skin absorption. In general, there is a long latency period of 10 to 20 years between the industrial exposure and the formation of the bladder cancer; thus, proving definitive causative relationships is difficult (Dryson et al, 2008). However, there are a variety of occupations statistically associated with bladder cancer formation, and all are industrial in nature. The overall increased risk of bladder cancer formation in industrial workers is 30%, with agriculture workers having the lowest and rubber workers the highest risk of bladder cancer formation.

Smoking. Tobacco is the main known cause for urothelial cancer formation, particularly cigarette smoking, and accounts for 60% and 30% of all urothelial cancers in males and females, respectively (Brennan et al, 2001; Boffetta, 2008; Gandini et al, 2008; Freedman et al, 2011). The relative risk of developing urothelial cancer from smoking is 2.8 and 2.73 in men and women, respectively (Gandini et al, 2008). Overall there is a two to six times greater chance of developing urothelial cancer with smoking, and the intensity and duration of smoking are linearly related to the increased risk, with no clear plateau level (IARC Working Group, 2004; Boffetta, 2008; Freedman et al, 2011). If a person smokes 1 to 9 cigarettes versus more than 21 cigarettes per day, the relative risk of bladder cancer is 1.5 versus 5.4, respectively (Weir and Dunn, 1970). If a person smokes for 1 to 10 years versus more than 40 years, the relative risk of bladder cancer is 1.2 versus 3.0, respectively (Burns and Swanson, 1991). If a person smokes for more than 60 years, he or she has a sixfold increased risk of developing urothelial cancer compared with a nonsmoker (Burch et al, 1989). Cigars and pipes are probably associated with bladder cancer formation, but there are too few studies evaluating only cigar and pipe smokers because of the high probability that these subjects also smoke cigarettes. The risk of secondhand smoke in bladder cancer formation is low and not statistically different from that for nonsmokers (Zeegers et al, 2002). It is important to note that smoking cessation does make a difference in urothelial cancer formation. Smokers who have stopped for 1 to 3 years have a 2.6 relative risk, and those who have stopped for more than 15 years have a 1.1 relative risk of bladder cancer formation (Wynder and Goldsmith 1977; IARC Working Group, 2004). Smoking is responsible for 30% of all deaths from bladder cancer in males and accounts for 46% of all

bladder cancer deaths in high-income countries and 28% in low- to middle-income countries (Brennan et al, 2000; Parkin, 2008).

Nutritional Factors. Most nutrients or other metabolites are excreted in the urine and have prolonged contact with the urothelium, particularly in the bladder; therefore nutrition plays a role in urothelial cancer formation (Steinmaus et al, 2000; Brinkman and Zeegers, 2008). However, there are inconsistent reports regarding the exact fruits and vegetables that are beneficial in preventing urothelial cancer, suggesting that epidemiologic factors are at play. In general, a Mediterranean diet leads to the lowest urothelial cancer risk. In a case-control study, there were fewer cases of urothelial cancer in the group given a Mediterranean diet versus a standard Western diet, probably because of the increased ingestion of fruits and vegetables (de Lorgeril et al, 1998). Both fruits and vegetables—specifically citrus fruits, apples, berries, tomatoes, carrots, and cruciferous vegetables—contain several active compounds that are important in detoxification. Micronutrients associated with a preventive effect on urothelial cancer formation are mainly antioxidants, including vitamins A, C, and E; selenium; and zinc (Michaud et al, 2000; Zeegers et al, 2002; Schabath et al, 2005; Brinkman and Zeegers, 2008). Fish, rice, and cereal do not seem to have a protective or detrimental effect with regard to urothelial cancer formation (Radosavljevic et al, 2005). Nutritional factors that have been associated with causing or promoting the formation of urothelial cancer include salted and barbecued meat, pork, total fat, pickled vegetables, soy, and spices (Balbi et al, 2001).

Occurrence of urothelial cancer is moderately higher in coffee and tea drinkers, but this may be compounded by smoking or other dietary factors associated with people who drink coffee or tea (Pelucchi et al, 2008). There is no apparent intensity or duration association of coffee and tea ingestion, suggesting an indirect causative effect, unlike for smoking. In conclusion, there are inconsistencies regarding nutritional factors related to urothelial cancer formation, in part because of confounding effects and associations, including coffee ingestion and smoking, ingestion of fruits and vegetables without involvement of smoking, and epidemiologic factors. However, even if not directly causative, there is a very clear association between a healthy diet and a decreased risk of urothelial cancer formation.

Artificial Sweeteners. Some animal studies have shown that large doses of saccharin or cyclamates may influence the development of bladder cancer (Allen et al, 1957; Sontag 1980). These studies are controversial because of the high doses of saccharin and cyclamates provided to the animals and the altered composition of these compounds, which may have influenced the carcinogenic activity found in animal studies (Cohen et al, 1995). Epidemiologic studies in humans have shown no evidence of an increased risk of bladder cancer in consumers of artificial sweeteners (Armstrong and Doll 1975; Morrison et al, 1982).

Analgesic Abuse. Acetaminophen is the active metabolite of phenacetin, a commonly used antipyretic and analgesic. Consumptions of large quantities of acetaminophen or phenacetin (5 to 15 kg during a 10-year period) have been associated with an increased risk of renal cancer and, perhaps, bladder cancer (Piper et al, 1985). However, these studies relied on interviews and questionnaires to ascertain drug exposure rather than actual determination of analgesic use. Kaye and colleagues (2001) performed a nested matched case-control study and found no association between acetaminophen or other nonsteroidal anti-inflammatory drug ingestion and bladder cancer.

Inflammation and Infection. Infection is clearly a contributor to the formation of squamous cell carcinoma in patients chronically infected with *Schistosoma haematobium* and will be covered in the section on squamous cell carcinoma of the bladder (Abol-Enein, 2008). There is a possible link between human papillomavirus (HPV) and urothelial cancer formation. HPV encodes two oncoproteins, E6 and E7. E6 interacts with TP53, which has a role in bladder cancer progression and formation (Westenend et al, 2001). A meta-analysis supports a possible association between HPV infection and bladder cancer, reporting a 2.3 relative risk with confidence intervals (CIs) of 1.3 to 4.1 (Gutierrez et al, 2006). However, the

association between HPV and bladder cancer depends significantly on the method of analysis, the statistical evaluation of the data, proved infection status, and recall bias by the individual. The BK virus is oncogenic in newborn hamsters and can immortalize mammalian cells in vitro (Newton et al, 2005). BK virus can cause severe hemorrhagic cystitis in bone marrow transplant recipients; however, there is no consistent link between BK virus infection and urothelial carcinoma.

Bacterial. Several investigators have suggested that chronic bacterial infections may play a role in bladder cancer formation (Davis et al, 1991). Clinically, chronic catheter use, stones, and infections are associated with bladder carcinoma, but the mechanism of neoplastic formation is not well understood (Abol-Enein, 2008). The mechanism of action may be related to the production of carcinogens such as nitrosamines that can be produced with chronic urinary tract infections (Radomski et al, 1978). In an animal model, rats with a urinary tract infection produce increased urinary levels of N1 N-dimethylnitrosamine over a 24-week period, and this was associated with urothelial hyperplasia and early neoplastic changes in the urothelium. The potential carcinogens were produced primarily with infections caused by *Escherichia coli* and *Pseudomonas*. A retrospective review of published literature suggests that chronic urinary tract infections are associated with bladder cancer, reporting a 1.4 to 1.6 relative risk of developing bladder cancer for any history of urinary tract infection versus none (Abol-Enein, 2008). However, there has been no prospective study examining the association between urinary tract infections and bladder cancer risk. It remains possible that the positive association between infection and urothelial cancer is driven by detection bias or preferential recall between cases and controls. Finally, a large case-control study from the United States based on data from the National Bladder Cancer Study Group reported a relative risk of bladder cancer formation of 4.8 (95% CI 1.9 to 11.5) for subjects with three or more urinary tract infections versus none (Kantor et al, 1984).

Radiation. The potential association between radiation exposure and bladder cancer formation is primarily based on atomic bomb survivors during World War II (Ron et al, 1994; Thompson et al, 1994; Pierce et al, 1996; Hall, 2008). Since 1950, 86,572 people who were exposed to atomic bomb radiation have been followed. Seventy-three percent had a low dose of exposure (less than 50 mSv), and 6% had exposure to very high doses of radiation (more than 500 mSv). There is a significant increased risk of dying from any cancer if a person is exposed to more than 50 mSv. For urothelial cancer, the relative risk of urothelial cancer formation is 1.63 in men and 1.74 in women. It is interesting to note that urothelial cancer formation after radiation is not age related, but the latency period is 15 to 30 years. Further support that radiation can cause bladder cancer is an increased risk of urothelial cancer in patients with prostate or cervical cancer who were treated with radiation therapy (Boice et al, 1988; Neugut et al, 1997; Brenner et al, 2000).

Chemotherapy. Chemotherapy destroys malignant cells by causing significant DNA and cellular damage but can also have a profound effect on rapidly dividing normal epithelium such as in the bladder. The only chemotherapeutic agent that has been proven to cause bladder cancer is cyclophosphamide (Travis et al, 1995; Nilsson and Ullen, 2008). The risk of bladder cancer formation is linearly related to the duration and intensity of cyclophosphamide treatment, supporting a causative role. Phosphoramidate mustard is the primary mutagenic metabolite that causes bladder cancer in patients exposed to cyclophosphamide.

KEY POINTS: EXTERNAL RISK FACTORS

- Bladder cancer is caused by genetic abnormalities and external risk factors.
- Smoking is the most common cause of urothelial cancer.
- A diet rich in fruits and vegetables is protective against bladder cancer formation.

Pathology

Histologically, 90% of bladder cancers are of urothelial origin, 5% are squamous cell carcinomas, and less than 2% are adenocarcinoma or other variants (Lopez-Beltran, 2008). **Urothelial carcinoma is the most common malignancy of the urinary tract and is the second most common cause of death among genitourinary tumors.** At initial presentation, 80% of urothelial tumors are non-muscle invasive. There are multiple growth patterns of urothelial cancer, including flat carcinoma in situ (CIS), papillary tumors that can be low or high grade, and sessile tumors with a solid growth pattern. Non-muscle-invasive cancers can be very large because of lack of genetic alterations required for invasion. Likewise, invasive tumors can be quite small if early genetic changes occur within the tumor cell, allowing for an invasive phenotype.

In 2004, WHO adopted the International Society of Urological Pathology (ISUP)-recommended staging system, which is the standard histologic nomenclature for urothelial carcinoma (Sauter et al, 2004). The clinical pattern of presentation is related to the cytologic and architectural alterations that occur within the tumor. Table 92-1 lists the histologic changes that occur from normal epithelium to high-grade muscle-invasive disease. Box 92-1 lists the neoplasms that can occur in the bladder.

Precursor Lesions to Urothelial Cancer

Normal bladder urothelium is multilayered and less than seven cells thick (Epstein et al, 1998; Montironi and Lopez-Beltran, 2005). The cells mature from the basement membrane to the surface cells in an orderly fashion. The surface has large umbrella cells that may have nuclear atypia and form asymmetrical units. Their membrane is composed of uroplakin proteins and is rigid. These umbrella cells are part of the urine bladder barrier that prevents toxins within the urine from transforming urothelial cells.

Precursor lesions are a continuum from hyperplasia to atypia to dysplasia and finally cancer. Hyperplasia is characterized by markedly thicker mucosa with or without atypia. The urothelium is more than seven cells thick, and there is some disorganization of the cellular architecture. Hyperplasia is often adjacent to low-grade tumors and thought to be a precursor lesion (Epstein et al, 1998). **Loss of parts of chromosome 9 can occur in hyperplasia, particularly if adjacent to low-grade tumors** (Hartmann et al, 1999).

Urothelial dysplasia has abnormal cytologic and nuclear changes that are preneoplastic but are not sufficient to be characterized as CIS (Sauter et al, 2004). Dysplasia is characterized by cohesive cells with mildly abnormal nuclear changes. There is nuclear crowding with prominent nucleoli, and abnormal mitotic figures may be present. Allelic loss of chromosome 9 and occasional TP53 abnormalities in urothelial dysplasia are found (Hartmann et al, 1999; Li et al, 2010). However, dysplasia is a good indication of urothelial instability and a marker of recurrence and progression in those with known urothelial cancer. Isolated dysplasia progressing to CIS occurs in approximately 19% of cases, but dysplasia in the face of previous history of urothelial cancer will form CIS in approximately 60% of cases (Cheng et al, 1999).

Urothelial Cancer Histology

Non-muscle-invasive bladder cancer (NMIBC) includes CIS, papillary urothelial neoplasia of low malignant potential (PUNLMP), and low- and high-grade urothelial cancer that previously had been called *superficial bladder cancer*, which is a misnomer. The clinical significance of the WHO grading classification is shown in Table 92-2. The grade distribution of NMIBC is 25% PUNLMP, 50% low grade, and 25% high grade (including CIS) (Holmang et al, 2001; Samarasinghe et al, 2002). CIS is characterized as non-papillary, flat, high-grade tumors in which the surface epithelium contains cancer cells (Sauter et al, 2004). The cells are large, pleomorphic, and chromatin clumping, and abnormal mitotic figures are common. Loss of umbrella cells is a characteristic, separating CIS from dysplasia. All CIS is high grade by definition. **The genetic**

TABLE 92-1 Histologic Characteristics of Noninvasive Papillary Urothelial Tumors of the Bladder According to the World Health Organization 2004 Classification

PAPILLOMA		PAPILLARY NEOPLASM OF LOW MALIGNANT POTENTIAL	LOW-GRADE PAPILLARY CARCINOMA	HIGH-GRADE PAPILLARY CARCINOMA
ARCHITECTURAL FEATURES				
Papillae	Delicate	Delicate, occasionally fused, not branching	Fused, branching	Fused, branching
Organization of cells	Identical to normal urothelium	Ordered Polarity identical to normal urothelium, any thickness, cohesive	Predominantly ordered, minimal crowding, and minimal loss of polarity; any thickness, cohesive	Predominantly disordered with frequent loss of polarity, variable thickness, discohesive
CYTOLOGIC FEATURES				
Nuclear size	Identical to normal urothelium	May be enlarged but uniform	Enlarged with variation in size	Enlarged with variation in size readily visible
Nuclear shape	Identical to normal urothelium	Elongated, round to oval, uniform	Round to oval, slight variation in shape and contour	Moderate to marked pleomorphism
Nuclear chromatin	Fine	Fine	Mild variation	Moderate to marked variation, hyperchromasia
Nucleoli	Absent	Absent to inconspicuous	Usually inconspicuous	Multiple prominent nucleoli may be present
Mitoses	Absent	Rare, basal	Occasionally at any level	Usually frequent, at any level
Umbrella cells	Uniformly present	Present	Usually present	Usually absent

From Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: a summary and commentary. *Int J Surg Pathol* 2005;13(2):143–53.

BOX 92-1 Histologic Type of Tumors of the Urinary Bladder According to the World Health Organization 2004 Classification

Urothelial neoplasia	Pseudosarcomatous stroma
Benign	Stromal osseous or cartilaginous metaplasia
Urothelial papilloma	Osteoclast-type giant cells
Inverted papilloma	With prominent lymphoid infiltrate
Papillary urothelial neoplasia of low malignant potential	Squamous cell carcinoma
Malignant papillary	Usual type
Papillary carcinoma, low grade	Variant
Papillary carcinoma, high grade	Verrucous
Papillary carcinoma with squamous or glandular differentiation	Basaloid
Malignant nonpapillary	With sarcomatoid features
Flat carcinoma in situ	Adenocarcinoma (from bladder mucosa, urachal, with exstrophy)
Invasive carcinoma	Usual intestinal type
Variants of invasive carcinoma	Mucinous (including colloid)
Nested pattern	Signet ring cell
Small tubular pattern	Clear cell
Microcystic pattern	Hepatoid
Inverted pattern	Mixture of aforementioned patterns
Squamous differentiation	Adenocarcinoma NOS
Glandular differentiation	Tumors of mixed cell types
Micropapillary	Undifferentiated carcinomas*
Sarcomatoid carcinoma	Small cell carcinoma
Clear cell urothelial carcinoma	Large cell neuroendocrine carcinoma
Plasmacytoid	Lymphoepithelioma-like carcinoma
With syncytiotrophoblasts	Giant cell carcinoma
With unusual stromal reactions	Undifferentiated carcinoma NOS
	Metastatic carcinoma

*Refers to tumors that are undifferentiated by light microscopy.

NOS, not otherwise specified.

Modified from Lopez-Beltran A. Bladder cancer: clinical and pathological profile. *Scand J Urol Nephrol Suppl* 2008;218:95–109.

TABLE 92-2 Clinical Significance of Different Non–Muscle-Invasive Urothelial Cancer Categories in the World Health Organization 2004 Grading System

	PAPILLOMA	PAPILLARY NEOPLASM OF LOW MALIGNANT POTENTIAL	LOW-GRADE PAPILLARY CARCINOMA	HIGH-GRADE CARCINOMA (PAPILLARY AND CIS)
Recurrence (%)	0-8	27-47	48-71	55-58
Grade progression (%)	2	11	7	N/A
Stage progression (%)	0	0-4	2-12	27-61
Survival (%)	100	93-100	82-96	74-90

CIS, carcinoma in situ; N/A, not applicable.
From Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: a summary and commentary. *Int J Surg Pathol* 2005;13(2):143–53.

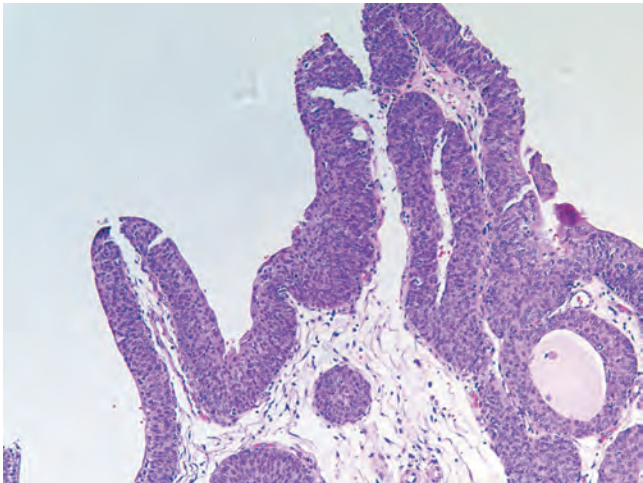


Figure 92-4. Papillary urothelial neoplasm of low malignant potential.

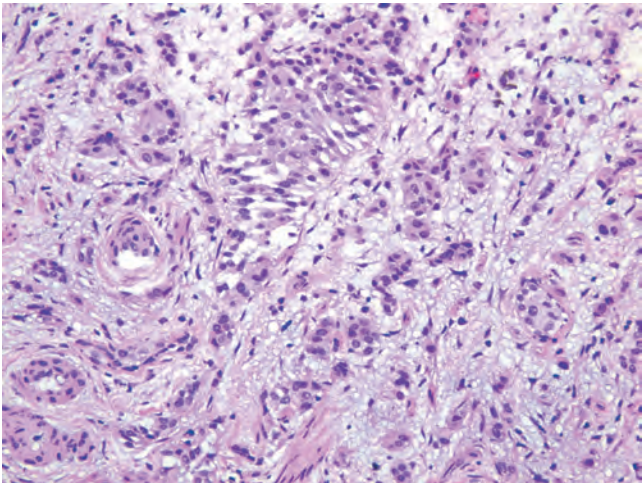


Figure 92-5. High-grade urothelial cancer invading the lamina propria.

abnormalities associated with CIS include alterations to the *RB*, *TP53*, and *PTEN* genes (Cordon-Cardo et al, 2000; Cordon-Cardo, 2008; Lopez-Beltran, 2008). CIS is immunoreactive for cytokeratin 20, and NMP22 is present in the cells. CIS is a precursor lesion for invasive cancer and can spread to the distal ureters and prostatic urethra on the surface or in a pagetoid manner, undermining normal adjacent urothelium (Lopez-Beltran et al, 2002). Endoscopically, CIS is reddish with heaped-up mucosa and can be mistaken for inflammatory changes or radiation cystitis. CIS in association with invasive tumors has a worse prognosis, with a 45% to 65% 5-year death rate (Lopez-Beltran et al, 2002).

PUNLMP is a papillary growth with minimal cytologic atypia that is more than seven cells thick and is usually solitary and located on the trigone (Fig. 92-4) (Holmang et al, 2001; Sauter et al, 2004). PUNLMP is composed of thin papillary stalks, where the polarity of the cells is maintained and the nuclei are minimally enlarged. PUNLMP has a low proliferation rate and is not associated with invasion or metastases, but almost 80% involve loss of chromosome 9 (Cheng et al, 2004). PUNLMP is different from a benign papilloma in that a PUNLMP has a thicker cell layer and large nuclei with occasionally mitotic figures. PUNLMP recurs within the bladder in 35% of patients, but progression is rare, occurring in less than 4% (Oosterhuis et al, 2002).

Low-grade urothelial carcinoma is typically papillary in nature with a fibrovascular stalk and frequent papillary branching with increased cellular size, some nuclear atypia (more than in PUNLMP), and occasional mitotic figures (Epstein et al, 1998). Genetic abnormalities associated with low-grade cancer include deletion of 9q and alterations in *FGFR-3*, *HRAS*, and *PI3K* (Holmang et al, 2001; Cordon-Cardo, 2008). The architectural and histologic changes that

separate low-grade urothelial carcinoma from a PUNLMP include multiple stalks, more cytologic atypia, and the multifocal nature of low-grade carcinomas compared with the solitary PUNLMP.

High-grade papillary urothelial cancer is composed of fused papillary stalks with high-grade cancer in the urothelial layer. A disordered growth pattern, numerous mitotic figures, and pleomorphic cells with exaggerated nuclei are present. Over 80% of high-grade cancers will invade the underlying stroma if left untreated. Genetic abnormalities include deletions of 2q, 5q, 10q, and 18q and gains of 5q and 20q (Knowles, 2008a). Alterations of *TP21* and *TP27* along with *TP53* have been reported.

There are key genetic and phenotypic changes that occur in cancer cells, thus providing the ability to invade the underlying stroma. Invasive urothelial carcinoma is divided into two groups: lamina propria and deep muscle invasion. Lamina propria invasive tumors are high-grade cancers that can be in clusters or in single cells, with single-cell invasion having a worse prognosis (Fig. 92-5). Rarely, low-grade cancers can invade the lamina propria. Vascular invasion can occur within the lamina propria because of the large vascular network within this tissue layer; however, it is frequently overcalled because of retraction artifact around tumor nests. There is a subdivision of lamina propria invasion into T1a (invasion above muscularis mucosa) and T1b (invasion below the muscularis mucosa).

Staging

The American Joint Committee on Cancer (AJCC) in combination with the Union for International Cancer Control meets on a regular basis to determine the tumor, nodes, and metastases (TNM) staging

TABLE 92-3 Definition of TNM

PRIMARY TUMOR (T)

TX

Primary tumor cannot be assessed

T0

No evidence of primary tumor

Ta

Noninvasive papillary carcinoma

Tis

Carcinoma in situ: “flat tumor”

T1

Tumor invades subepithelial connective tissue

T2

Tumor invades muscularis propria

pT2a

Tumor invades superficial muscularis propria (inner half)

pT2b

Tumor invades deep muscularis propria (outer half)

T3

Tumor invades perivesical tissue:

pT3a

Microscopically

pT3b

Macroscopically (extravesical mass)

T4

Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall

T4a

Tumor invades prostatic stroma, uterus, vagina

T4b

Tumor invades pelvic wall, abdominal wall

REGIONAL LYMPH NODES (N)

Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

NX

Lymph nodes cannot be assessed

N0

No lymph node metastasis

N1

Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)

N2

Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)

N3

Lymph node metastasis to the common iliac lymph nodes

DISTANT METASTASIS (M)

M0

No distant metastasis

M1

Distant metastasis

ANATOMIC STAGE AND PROGNOSTIC GROUPS

GROUP	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

Required for staging

None

Clinically significant

Presence or absence of extranodal extension

Size of the largest tumor deposit in the lymph nodes

World Health Organization/International Society of Urologic Pathology grade

From Edge SB, Byrd DR, Compton CC, et al, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.

classifications. The 2009 staging system is shown in [Table 92-3](#) (Edge and Compton, 2010). Ta and CIS disease have no invasion of the basement membrane, but endophytic growth of low-grade tumors into the lamina propria is possible, and cancer can occur in von Brunn nests (Jones et al, 2007; Picozzi et al, 2012). T1 disease, as mentioned earlier, can be divided into T1a and T1b disease (Smits et al, 1998). The subdivision is based on the muscularis mucosa, which comprises thin wavy vesicles of muscle within

the lamina propria that are associated with large vessels and lymphatics. The prognostic significance of T1a and T1b disease is inconsistent because of the lack of muscularis mucosa in many bladder biopsy specimens. Essentially, the T1a and T1b stratifications suggest that the deeper the tumor invades the lamina propria, the worse the survival.

Muscle-invasive disease is subdivided into T2a and T2b. T2a includes invasion into the inner half of the muscularis propria,

whereas T2b is deeper into the outer half. Analysis of the AJCC data would suggest that there is a disease-free survival difference between T2a and T2b disease (Edge and Compton, 2010). T3 disease constitutes invasion outside the bladder proper into the periadipose tissue. T3a disease involves microscopic extension, whereas T3b involves macroscopic extension. Clinically, T3a disease is identified by a palpable mass at the time of examination under anesthesia during the initial transurethral resection and subsequently is non-palpable after the tumor is resected. T3b disease has a persistent palpable mass after transurethral resection of the tumor. Pathologically, T3a disease is microscopic extension into the periadipose tissue, whereas T3b disease is macroscopic extension. T4a disease is invasion of the prostatic stroma, uterus, or vagina, and T4b disease is invasion of the pelvic wall or abdominal wall. **Extension of the tumor into the prostatic urethra without stromal invasion is currently classified under the prostatic urethral section and does not carry an adverse prognosis for patients with known bladder cancer (Pagano et al, 1996; Edge and Compton, 2010).** Prostatic stromal invasion, however, particularly if it is a direct extension from the bladder through the muscle into the prostate, does have a poor prognostic factor, with a 5-year overall survival of less than 25% (Esrig et al, 1996; Pagano et al, 1996).

A major problem in bladder cancer is understaging, occurring in 34% to 64% of patients. Chang and colleagues (2001) reported that 27% of T1 tumors were upstaged after radical cystectomy, and 49% of T2 tumors were upstaged to T3. **Because of this understaging, the American Urological Association (AUA) guidelines call for a repeat transurethral resection in patients with T1 tumors to assess for muscle invasive disease even if muscle was present in the specimen (Hall et al, 2007).**

KEY POINTS: HISTORY AND STAGING

- The WHO 2004 grading scheme should be used routinely.
- The delineation of PUNLMP describes bladder lesions that can recur but rarely invade.
- Low-grade papillary lesions are likely to recur in up to 60% of patients but invade in less than 10% of cases. High-grade lesions also recur; however, invasion and subsequent stage progression can occur in 50% of tumors.
- *Superficial bladder cancer* is a misnomer and should be replaced by NMIBC, which includes PUNLMP, CIS, Ta, and T1 tumors.
- Muscle-invasive bladder cancer leads to death in a significant proportion of patients despite aggressive therapy.

Origin, Recurrence, and Dissemination of Urothelial Cancer

Primary Tumors

The formation of primary urothelial carcinoma is a combination of environmental, genetic, and epigenetic causes. The main environmental factor associated with primary urothelial cancer is cigarette smoking, which is present in one third to one half of all bladder cancers in men and in 30% in women (Brennan et al, 2001; Boffetta, 2008). Smokers have a 2.77 relative risk of developing bladder cancer compared to nonsmokers (Gandini et al, 2008). Other external risk factors are listed above in the section on etiology. These external environmental factors then cause genetic and epigenetic instability that ultimately results in the formation of urothelial carcinoma. **The deletion of parts or all of chromosome 9 is most likely the earliest mutation seen in low-malignant potential NMIBC (Obermann et al, 2003).** There is a known tumor suppressor gene at 9p21 that is a negative regulator of *RB* (Berggren et al, 2003). Another genetic abnormality mutated in 75% of low-malignant potential NMIBC is *FGFR-3* (Billerey et al, 2001; Gomez-Roman et al, 2005). High-malignant potential NMIBC is more likely associated with deletions

of tumor suppressor genes such as *TP53* and *RB* (Chatterjee, 2004a; George et al, 2007; Sanchez-Carbayo et al, 2007). There are a large number of genes associated with stage progression because of the general genetic instability seen in high-grade tumors. It is the accumulation of these multiple genetic alterations, most often caused by external risk factors, that leads to the formation of urothelial cancer.

Recurrent Tumors

A hallmark of urothelial cancer is the high recurrence rate, which approaches 80% for high-malignant potential NMIBC. The two primary theories for recurrent tumor formation are field change effects within the bladder and tumor implantation. **With use of a cDNA expression library, genetic abnormalities seen in CIS can be found in endoscopically normal-appearing urothelium away from the primary tumor (Dyrskjot et al, 2012a).** Similarly, alterations in certain urine markers that are associated with bladder cancer can be found in biopsy-negative bladders from patients with a history of urothelial carcinoma, suggesting that normal-appearing urothelium has the capacity to produce these various tumor markers (Keese et al, 1996; Black et al, 2006). **Multifocality and rapidly recurring tumors are strong prognostic factors associated with finding histologically abnormal urothelium in endoscopically normal-appearing bladder tissue.** In addition, the effectiveness of maintenance bacillus Calmette-Guérin (BCG) therapy in preventing tumor recurrence compared with an induction course only is supportive of field-change effects in the normal-appearing urothelium (Lamm et al, 2000). This suggests that treating the “nonvisible” tumors can prevent or delay the formation of visible cancer.

Tumor implantation during a transurethral resection of the bladder tumor has been suggested as a possible cause for recurrent tumor formation (Soloway and Masters 1980; Pode et al, 1986). The immediate introduction of intravesical therapy, after the tumor inoculation and cauterization, significantly reduced the implantation rate in patients with low-grade urothelial cancer, thus supporting the concept of tumor implantation as a cause of recurrent tumors (Kurth et al, 2000; Sylvester et al, 2004).

Angiolymphatic Invasion

The key phenotypic change that occurs in urothelial cancer that is destined to metastasize is the ability to invade the angiolymphatic system, which is seen in approximately 25% of invasive urothelial carcinoma (Kunju et al, 2008). **Angiolymphatic invasion is a poor prognostic sign with a 40% risk of nodal disease and is an independent predictor of overall and cancer-specific survival (Abdel-Latif et al, 2004; Lotan et al, 2005).** A transurethral resection of the bladder tumor can detect angiolymphatic invasion that is subsequently found in the radical cystectomy specimen 65% of the time. It is critical to use CD-31 and CD-34 monoclonal antibodies with immunohistochemistry to accurately identify the blood vessels in contrast to tumor retraction artifacts (Lotan et al, 2005; Kunju et al, 2008).

Pagetoid Spread

Pagetoid spread occurs when cancer cells grow underneath a layer of normal-appearing surface urothelium (Lopez-Beltran et al, 2002) (Fig. 92-6). Pagetoid spread is primarily seen in urothelial CIS and was first described by Melicow and Hollowell in 1952. Detection of pagetoid spread is difficult because it occurs in approximately 15% of bladders that contain CIS and decreases to 11% in patients with papillary high-malignant potential NMIBC (Orozco et al, 1993; McKenney et al, 2001). Pagetoid spread of urothelial cancer can occur into the prostatic urethra and distal ureters. This is more common after repeated doses of intravesical therapies, and therefore biopsies of normal-appearing prostatic urothelium are needed in the evaluation of patients with positive urine cytology and yet endoscopically normal bladder (Wood et al, 1989a, 1989b).

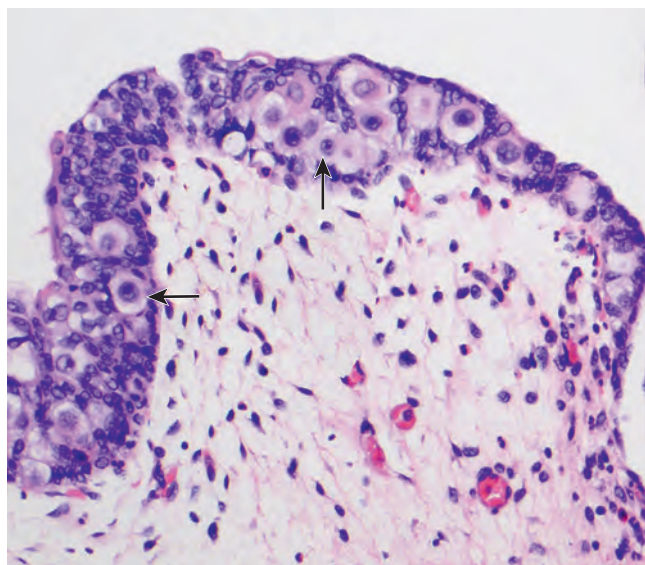


Figure 92-6. Pagetoid spread of carcinoma in situ (CIS). Large, paler-appearing malignant cells of urothelial CIS (arrows) are spreading as single cells within or undermining the normal urothelium.

Direct Extension

Direct extension of tumors into the basal lamina, connective tissue, and, ultimately, the angiolymphatic system is caused by genetic and epigenetic changes that produce substances capable of invading these tissues. These substances include collagenases, motility and growth factors, and cell adhesion molecules.

There are numerous motility and growth factors present within the extracellular matrix that increase tumor growth. Proepithelin may play a critical role as an autocrine growth factor in the establishment and progression of bladder cancer, and studies suggest that proepithelin may be a novel biomarker for the diagnosis and prognosis of bladder neoplasms (Lovat et al, 2009). The ability of cancer cells to migrate and invade through the extracellular matrix is a critical step for tumor metastasis. Other growth factors associated with bladder cancer invasion include epidermal growth factors (EGFs), transforming growth factor- α , heparin-binding growth factor, and insulin-like growth factor (IGF) (Theodorescu et al, 1998). Cell adhesion molecules are critical for integrity of cell-cell junctions and the inhibition of cell growth. Cell adhesion molecules associated with invasive urothelial carcinoma include E-cadherin, integrins, CD-44, and NCD-44 (Kashibuchi et al, 2007).

Prognostic Factors

There are genetic, pathologic, and phenotypic changes in bladder cancer that are characteristic of poor cancer-specific survival. Overall genetic instability is the hallmark of invasive urothelial cancer, but specifically alterations of *TP53*, *RB*, and *PTEN* carry a very poor prognosis (Chatterjee et al, 2004b). Wang and colleagues (2009) developed a gene expression signature that could accurately segregate poor- and good-risk noninvasive and invasive bladder cancers. They were able to make the segregation even within similar pathologically staged tumors. However, despite the major advances in understanding the genetics of urothelial carcinoma, the stage and grade of the primary tumor is still the strongest predictor of survival. Grade is indicative of the growth potential of the cell, and stage describes the extent of the cancer and the ability to invade. The ability of high-grade tumors to invade and thus metastasize is a result of micrometastatic disease from angiolymphatic invasion. Proliferation markers, such as MIB-1 and PCNA, are found in high-grade tumors and are associated with a worse prognosis (Lopez-Beltran and Cheng, 2003). Alteration in cell cycle regulators, such as cyclins, *TP53*, and *TP27*, leads to increased proliferation as seen

by MIB-1 staining. Ultimately, it will be the integration of stage, grade, and molecular markers that will greatly improve the prognostic determination of urothelial carcinomas and, it is hoped, provide new therapeutic targets.

KEY POINTS: ORIGIN, RECURRENCE, AND INVASION

- Primary urothelial cancer is an environmentally caused tumor that recurs because of persistent genetic changes within the normal-appearing urothelium.
- Recurrent urothelial tumors occur by activation of nascent normal cells that have some genetic instability by environmental factors and tumor seeding during transurethral tumor resection.
- Accumulation of genetic changes leads to cellular proliferation, loss of cell-cell adhesion, and invasion.
- The depth of invasion and grade of the tumor are the best prognostic determinants of urothelial cancer, but molecular assays are likely to be incorporated into future staging schemas.

Molecular Biology

Somatic mutations are more common than germline mutations, and if germline mutations occur, they are associated with a specific type of cancer such as von Hippel-Lindau disease. These somatic and germline genetic changes result in an altered phenotype that can be enhanced or at times be caused by epigenetic alterations, such as promoter methylation or protein degradation, that suppress gene function involved in bladder cancer formation (Wolff et al, 2005).

Specific genetic changes occur between each stage of urothelial tumor development (Cordon-Cardo et al, 2000; Simon, 2004; Cordon-Cardo, 2008). Traditionally, there are two pathways in urothelial cancer formation: normal urothelium to low-grade noninvasive disease, and normal urothelium to CIS and subsequent muscle-invasive disease. A proposed third pathway involves normal urothelium to hyperplasia or dysplasia to high-grade papillary carcinoma and subsequent muscle-invasive disease (Fig. 92-7). Low-grade papillary carcinoma with additional genetic alterations can develop into high-grade papillary disease and subsequent muscle-invasive disease, but it is rare for high-grade tumors to mutate into low-grade cancers. In general, low-grade papillary tumors have genomic stability that allows tumor recurrence but rarely progression. High-grade papillary cancer and CIS have unstable genomes that more readily allow additional genetic alterations needed for muscle-invasive or metastatic disease (Spruck et al, 1994; Knowles, 2006; Lindgren et al, 2006).

The genetic alterations that are the hallmark of low-grade non-muscle-invasive disease are alterations in *FGFR-3* and deletions of chromosome regions 9p and 9q. High-grade invasive disease has infrequent *FGFR-3* mutations but a high rate of *TP53* mutations that approaches 60%. Noninvasive tumors that have both *FGFR-3* and *TP53* mutations are rare and constitute the third pathway to the formation of invasive disease by forming papillary rather than sessile T1 cancer that is derived from CIS (Knowles, 2006; van der Kwast, 2008). Genetic changes that occur in noninvasive and invasive bladder cancers are listed in Tables 92-4 and 92-5, respectively.

Normal urothelium transforms into low-grade papillary cancer through activation of proto-oncogenes, resulting in phenotypic changes that are histologically named *papilloma*, *PUNLMP*, *hyperplasia*, and *low-grade urothelial cancer*. Papillomas lack genetic alterations and have no *FGFR-3* mutations, thus distinguishing this growth pattern from low-grade urothelial carcinoma, and therefore are probably not a precursor lesion to cancer (Knowles, 2006). Conversely, PUNLMP does contain the same genetic abnormalities seen in low-grade urothelial carcinoma, has a proliferation rate

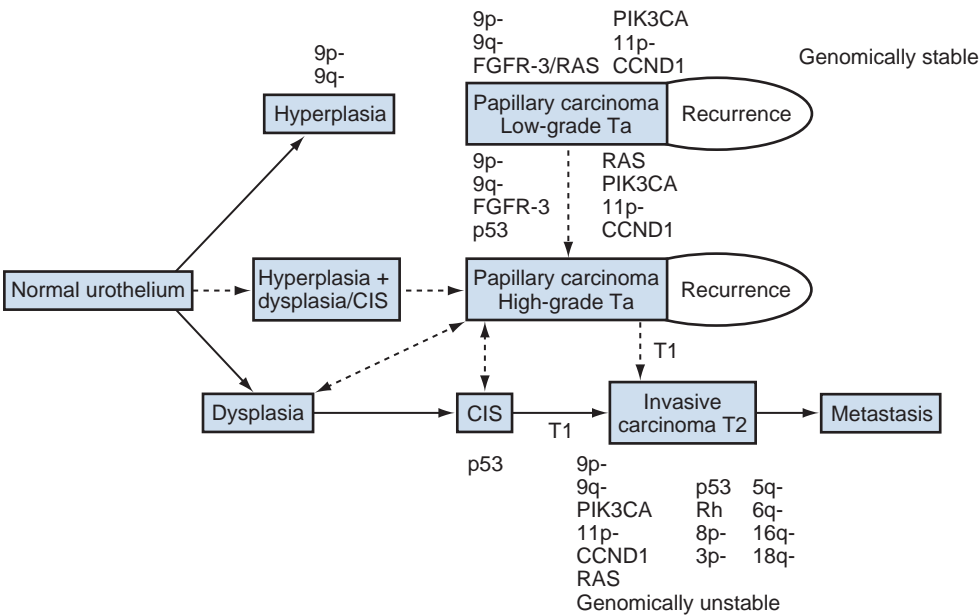


Figure 92-7. Pathogenesis of urothelial cancer formation. CIS, carcinoma in situ. (From Knowles MA. Bladder cancer subtypes defined by genomic alterations. Scand J Urol Nephrol Suppl 2008;218:116–30.)

TABLE 92-4 Genetic Changes Identified in Ta Bladder Tumors

GENE (CYTOGENETIC LOCATION)	ALTERATION	FREQUENCY
ONCOGENES		
<i>HRAS</i> (11p15)/ <i>NRAS</i> (1p13)/ <i>KRAS2</i> (12p12)	Activating mutations	15%
<i>FGFR-3</i> (4p16)	Activating mutations	60%-80%
<i>CCND1</i> (11q13)	Amplification, overexpression	10%-20%
<i>PIK3CA</i> (3q26)	Activating mutations	25% PUNLMP; 16% Ta
<i>MDM2</i> (12q13)	Overexpression	Approximately 30% overexpression
TUMOR SUPPRESSOR GENES		
<i>CDKN2A</i> (9P21)	Homozygous deletion, methylation, mutation	HD 20%-30%; LOH approximately 60%
<i>PTCH</i> (9q22)	Deletion, mutation	LOH approximately 60%; mutation frequency low
<i>DBCI</i> (9q32-33)	Deletion, methylation	LOH approximately 60%
<i>TSCI</i> (9q34)	Deletion, mutation	LOH approximately 60%; mutation approximately 12%
DNA COPY NUMBER CHANGES; TARGET GENE(S) UNKNOWN*		
2q	Deletion	10%
8p	Deletion	16%
9p	Deletion	36%-47%
9q	Deletion	44%-66%
10p	Deletion	20%
10q	Deletion	20%
11p	Deletion, LOH	10%-24%
13q	Deletion	17%
17q	Deletion	15%
18q	Deletion	13%
Y	Deletion	24%-28%
1q	Gain	11%-14%
17q	Gain	14%
20q	Gain	13%-17%
8p12	Amplification	Occasional
11q13 (including <i>CCND1</i>)	Amplification	Occasional

*Comparative genomic hybridization analyses.
HD, homozygously deleted; LOH, loss of heterozygosity; PUNLMP, papillary urothelial neoplasm of low malignant potential.
From Knowles MA. Bladder cancer subtypes defined by genomic alterations. Scand J Urol Nephrol Suppl 2008;218:116–30.

TABLE 92-5 Genetic Changes Found in Invasive (T2 or Higher) Bladder Tumors

GENE (CYTOGENETIC LOCATION)	ALTERATION	FREQUENCY
ONCOGENES		
<i>HRAS</i> (11p15)/ <i>NRAS</i> (1p13)/ <i>KRAS2</i> (12p12)	Activating mutations	10%-15%
<i>FGFR-3</i> (4p16)	Activating mutations	0%-34%
<i>ERBB2</i> (17q)	Amplification, overexpression	10%-14% amplification
<i>CCND1</i> (11q13)	Amplification, overexpression	10%-20%
<i>MDM2</i> (12q13)	Amplification, overexpression	4% amplification
<i>E2F3</i> (6p22)	Amplification, overexpression	9%-11% amplification in $\geq T1$
TUMOR SUPPRESSOR GENES		
<i>CDKN2A</i> (9p21)	Homozygous deletion, methylation, mutation	HD 20%-30%; LOH approximately 60%
<i>PTCH</i> (9q22)	Deletion, mutation	LOH approximately 60%; mutation frequency low
<i>DBCI</i> (9q32-33)	Deletion, methylation	LOH approximately 60%
<i>TSCI</i> (9q34)	Deletion, mutation	LOH approximately 60%; mutation approximately 12%
<i>PTEN</i> (10q23)	Homozygous deletion, mutation	LOH 30%-35%; mutation 17%
<i>RB1</i> (13q14)	Deletion	37%
<i>TP53</i> (17p13)	Deletion, mutation	70%
DNA COPY NUMBER CHANGES; TARGET GENE(S) UNKNOWN*		
2q	Deletion	12%
5q	Deletion	15%-24%
6q	Deletion	15%-28%
8p	Deletion	29%-34%
9p	Deletion	21%-30%
9q	Deletion	17%
10q	Deletion	16%-21%
11p	Deletion	18%-24%
11q	Deletion	22%
13q	Deletion	19%
15q	Deletion	13%
16q	Deletion	15%
17q	Deletion	17%-24%
18q	Deletion	16%-17%
Y	Deletion	21%
1q	Gain	17%-33%
3q	Gain	18%
5p	Gain	24%-37%
7p	Gain	20%
8q	Gain	23%-34%
10p	Gain	12%
17q	Gain	30%
20p	Gain	21%
20q	Gain	26%-28%
1q22	Amplification	<5%
3p24	Amplification	<5%
6p22	Amplification	5%-10%
8p12	Amplification	<5%
8q21-22 and q24	Amplification	<5%
10p13-14	Amplification	<5%
12q15	Amplification	<5%
17q21	Amplification	<5%
20q13	Amplification	<5%

*Comparative genomic hybridization analyses.

HD, homozygously deleted; LOH, loss of heterozygosity.

From Knowles MA. Bladder cancer subtypes defined by genomic alterations. Scand J Urol Nephrol Suppl 2008;218:116-30.

similar to low-grade carcinoma, and is likely to be a precursor to low-grade bladder cancer. Thus there are no clear DNA markers that can distinguish PUNLMP from low-grade cancer (Dyrskjot et al, 2012a). Urothelial hyperplasia is considered a precursor of low-grade carcinoma, and the most frequent genetic deletion is of chromosome 9—most likely the earliest mutation seen in low-grade urothelial cancer formation (Obermann et al, 2003). A variety of tumor suppressor genes are present on both regions 9p and 9q. At 9p21, *CDKN2A* codes for TP16 (INK4A), which is a negative regulator of *RB*, and *TP14ARF*, which is a negative regulator of *TP53* (Berggren et al, 2003). In addition, *CDKN2B* is located at 9p21 and codes for TP15. It is less clear which genes located on 9q are deleted. *PTCH* is located at 9q22, and *DBC1* and *TSC1* are located on 9q33-34 (Aboulkassim et al, 2003; Adachi et al, 2003). The multiple gene losses on chromosome 9 cumulatively lead to the formation of low-grade urothelial neoplasia. It is rare in low-grade papillary cancers to have markers of aggressiveness, such as loss of chromosome 17p, 2q, 4, or 11p (Cordon-Cardo, 2008).

FGFR-3 is related to epidermal growth factor receptor (EGFR), which is not mutated in low-grade cancers but can be overexpressed in low- or high-grade urothelial cancer. FGFR-3 is a tyrosine kinase that causes enhanced growth of bladder cells and is altered in up to 75% of noninvasive low-grade tumors (Gomez-Roman et al, 2005). Altered FGFR-3 can be found in CIS and muscle-invasive disease, although to a much lesser extent, supporting the overlapping nature of tumor formation with multiple genetic changes destined to make either noninvasive or invasive disease. It is interesting to note that *FGFR-3* mutations are also found in seborrheic keratosis, which is a benign papillary skin wart that can be multiple, can recur, but does not invade (Logie et al, 2005). FGFR-3 mRNA is overexpressed eightfold in noninvasive disease and up to fourfold in muscle-invasive disease. Normal urothelium does not produce the FGFR-3 protein, but more than 71% of noninvasive bladder cancers will be immunopositive for the FGFR-3 receptor (Billerey et al, 2001). Because of the differential FGFR-3 expression between normal and cancerous tissue, it could be a therapeutic target (Knowles, 2008b). *FGFR-3* and *HRAS* mutations are mutually exclusive because they are in the same *RAS-MEK-ERK* pathway. Mutations of *FGFR-3* cause constitutive activation of the FGFR-3 receptor and thus signaling through the *MAPK* pathway (Cordon-Cardo, 2008; Knowles, 2008b). *FGFR-3* and *TP53* mutations are virtually mutually exclusive as well, but not because of a common signaling pathway. It is unclear why these two mutations are mutually exclusive, but it does highlight the different pathways in the formation of urothelial carcinoma (Bakkar et al, 2003).

RAS genes are from a family of transforming oncogenes that were originally identified in T24 bladder cancer cell lines (McBride et al, 1982). The most frequent site of *HRAS* activations are mutations in codons 12, 13, 59, and 61 that result in increased enzymatic activity. *HRAS* mutations occur in 40% of urothelial carcinoma, and mutations in codon 12 are the most common (Czerniak et al, 1992). Point mutations in *PIK3CA* are found in 10% of noninvasive bladder cancer and are critical in the *PTEN* pathway (Cairns et al, 1998). *FGFR-3* and *PIK3CA* work together in a similar pathway, and thus both mutations are often seen in the same tumor. Deletions on 9q activate the tumor suppressor genes *TSC1*, *PTCH*, and *DBC1* (Hornigold et al, 1999; Louhelainen et al, 2006).

The transformation of normal urothelium to high-grade invasive bladder cancer is a continuum from dysplasia to CIS and then invasive disease. The conversion of normal urothelium to dysplasia is associated with chromosome 9 deletions in 75% of cases, abnormal TP53 accumulation in 50%, and increased cellular growth in all cases (Mallofre et al, 2003). The subsequent genetic changes to CIS are most likely deletions of tumor suppressor genes rather than activation of oncogenes, and alterations of *TP53* are the main hallmark of high-grade disease (George et al, 2007; Sanchez-Carbayo et al, 2007). *TP53* is located on chromosome 17p and controls the expression of multiple apoptosis-related genes. The presence of *TP53* nuclear protein overexpression and *TP53* gene mutations occur in approximately 80% of high-grade tumors, including CIS. Primary CIS, which is defined as CIS not

associated with a papillary or invasive lesion, has *TP53* overexpression but lacks deletion of chromosome 9. This is in contrast to secondary CIS, which is associated with papillary lesions, can display alterations in chromosome 9, and has molecular expression profiles similar to the adjacent papillary tumor, thus highlighting the overlapping pathways to invasive disease from flat CIS or the hyperplasia to papillary high-grade disease, and then subsequent muscle-invasive disease (Hopman et al, 2002). Also, the same expression signature that exists for secondary CIS can be found in biopsy specimens of morphologically normal urothelium in the same bladder (Dyrskjot et al, 2004). The retinoblastoma gene (*RB*) encodes for a 110-kD nuclear phosphoprotein that functions as a negative cell cycle regulator (Chatterjee et al, 2004a, 2004b). Undetectable levels of the *RB* protein are associated with poor prognoses and increased tumor growth, presumably by affecting the *E2F* gene pathway. Decreased *PTEN* expression is seen in advanced urothelial cancers and CIS. *PTEN* genetic alterations are an independent predictor of survival in advanced cancer, and altered *PTEN* and *TP53* mutations are associated with aggressive tumor growth (Puzio-Kuter et al, 2009).

The genetic changes that occur between noninvasive and invasive high-grade lesions are essentially in genes needed to invade rather than to grow. The earliest changes seen in T1 disease are deletions of 3p, 5q, 6q, 11p, 16q, and 18q (Cordon-Cardo, 2008). Alterations in the *TP53*, *RB*, and *PTEN* pathways are hallmarks of invasive disease, and the combined alterations of all three pathways carry a much worse prognosis (Chatterjee et al, 2004a, 2004b). Finally, the general genetic instability seen in muscle-invasive disease to metastatic disease makes identification of specific genes associated with this progression difficult to clearly delineate (Knowles, 2008a).

Many investigators are using the genetic changes identified in urothelial cancer to determine the malignant potential of small noninvasive cancers by using molecular staging (van der Kwast, 2008). Through the formation of cDNA expression libraries, 80% of Ta urothelial cancers are correctly staged by their genetic profile. Of the 20% of Ta tumors that were wrongly classified as T1 or T2 by genetic profiling, most had a significantly worse prognosis than the correctly staged Ta tumors (Dyrskjot et al, 2003; Blaveri et al, 2005; Dyrskjot et al, 2012b). A 16-gene expression chip of CIS has been developed to discriminate CIS from normal bladder urothelium, with an 80% sensitivity and a 68% specificity. Unfortunately, gene abnormalities for CIS can be found in normal urothelium, confirming the field-chain effect seen in bladder cancer (Dyrskjot et al, 2012b). The main genetic changes that separate noninvasive from invasive disease, as mentioned earlier, include high *FGFR-3* and low *TP53* mutation rates and general genetic stability. T1 disease has low *FGFR-3* and high *TP53* mutation rates and loss of 17p, 13q, and 8p (Knowles, 2008a). Many of these genetic changes are not necessarily related to invasive potential but instead reflect the different grade of tumor seen in Ta and T1 disease. The separation of T1 and T2 disease by genetic analysis is more difficult because of the overall worsening genetic instability and because both are high-grade tumors. However, T2 tumors have more frequent allelic imbalance of chromosomes 6, 10p, and 22 (Koed et al, 2005). Finally, response to chemotherapy in T2 tumors may be predicted by cDNA profiling of the extracellular matrix metalloproteinase inducer (*EMMPRIN*) and survivin genes, although further prospective studies are required (Als et al, 2007). The accumulation of genetic changes in cell cycle regulation (*TP53*), angiogenesis (*NRP2*), and metastasis suppressors (*RhoGDI2*) eventually leads to the highly malignant phenotype of high-grade urothelial cancer (Aaboe et al, 2006). On the horizon, these genetic signatures of aggressive disease will be used for prognostic and therapeutic intent. Wang and colleagues (2009) developed a multiplex quantitative polymerase chain reaction (PCR) assay that accurately segregated Ta, T1, and T2 bladder cancer into high- and low-risk groups. Using a 57-gene mRNA expression profile, at 2 years the high-risk groups had greater stage progression in each pathologic group. A prospective multi-institutional study is needed to confirm these results but may herald a new staging method.

Detection of Urothelial Carcinoma

Gross, painless hematuria is the primary symptom in 85% of patients with a newly diagnosed bladder tumor, and microscopic hematuria occurs in virtually all patients (Khadra et al, 2000; Alishahi et al, 2002; Wallard et al, 2006). The hematuria is usually intermittent and can be related to Valsalva maneuvers; therefore any episode of gross hematuria should be evaluated even if subsequent urinalysis is negative. Fifty percent of patients with gross hematuria will have a demonstrable cause, 20% will have a urologic malignancy, and 12% will have a bladder tumor (Khadra et al, 2000). The risk of malignancy in patients with recurrent gross or microscopic hematuria who had a full, negative evaluation is nearly zero within the first 6 years (Khadra et al, 2000). This should be considered when recommending repeat evaluations for patients with recurrent hematuria.

A full hematuria evaluation for bladder cancer includes cystoscopy, urine cytology, upper-tract imaging (primarily a computed tomography [CT] scan of the abdomen and pelvis), and a prostate-specific antigen (PSA) blood test. A PSA blood test is recommended because 10% of patients with recurrent gross hematuria will have prostate cancer (Mishriki et al, 2008). Microscopic hematuria is typically asymptomatic and carries a 5.4% risk of urologic malignancy and a 4.1% risk of bladder cancer (Mishriki et al, 2008). For patients with a negative microscopic hematuria evaluation, 84.5% never had a recurrence, and of those with repeat microscopic hematuria, none had a urologic malignancy with a 13-year follow-up (Mishriki et al, 2008). The AUA guidelines for evaluation include cystoscopy, upper tract imaging, and urine cytology (Grossfeld et al, 2001). The guidelines recommend consideration for re-evaluation of low-risk patients with microscopic hematuria, but repeat evaluation every 6 months with urinalysis, cytology, and blood pressure (to detect renal disease) is recommended for high-risk patients.

The main diagnostic tests for bladder cancer are cystoscopy and biopsy. White light cystoscopy (WLC) is the gold standard; flexible office cystoscopy is as reliable as rigid endoscopy (Grossfeld et al, 2001) and has excellent sensitivity and specificity for papillary tumors but is relatively poor for CIS. Cystoscopy with porphyrin dye (commonly referred to as *blue light cystoscopy*) may be more sensitive in the detection of CIS (Fradet et al, 2007; Grossman et al, 2007). Porphyrin-induced fluorescence cystoscopy uses photoactive porphyrins, such as hexaminolevulinate, that accumulate preferentially in neoplastic tissue and emit red fluorescence under blue-wavelength light. This may improve the detection of small papillary lesions and CIS. A phase 3 trial evaluating WLC and blue light cystoscopy in patients with known or suspected tumors was completed (Grossman et al, 2007). Blue light cystoscopy detected 58% of CIS compared with 15% for WLC. However, at the patient level, the sensitivity of blue light was 87% and was 83% for white light. Blue light cystoscopy has a false-positive rate of 39% (Fradet et al, 2007). The true impact of blue light cystoscopy on the detection of bladder cancer is unclear, and further studies are required to determine its exact clinical role.

Narrow-band imaging (NBI) is an endoscopic optical image enhancement technique that enhances the contrast between mucosal surfaces and microvascular structures without the use of dyes. The depth of light penetration into the bladder wall increases with increasing wavelength. NBI illuminates the mucosal surface with light of a narrow bandwidth in the blue (415 nm) and green (540 nm) light spectrum, which are strongly absorbed by hemoglobin. Consequently, the vascular structures appear dark brown or green against a pink or white mucosal background. Commercially available systems have integrated NBI and WLC, allowing activation of the NBI wavelengths with the push of a button. Herr and Donat (2008) performed white light and NBI cystoscopy in 427 consecutive patients with a history of NMIBC. Of the 103 patients with a tumor recurrence, 56% had additional tumors identified with NBI compared with use of WLC, and in 12% of patients, the recurrent tumor was found only with NBI. For WLC and NBI cystoscopy, the overall sensitivities were 87% and 100% and the

overall specificities were 85% and 82%, respectively. A recent study suggests that NBI more accurately detects tumor recurrence after BCG therapy than do urine cytology or WLC, and NBI can obviate the need for random bladder biopsies in post-BCG bladders (Herr and Donat, 2008). NBI detected tumor recurrence in 21 of 22 patients with tumor recurrence after BCG, but another 10 patients had a false-positive NBI, resulting in unnecessary biopsies. Because the NBI and WLC are performed by the same urologist, observation bias may skew these results.

Random bladder biopsies are recommended to detect unsuspected CIS or small papillary tumors in endoscopically normal urothelium. Overall, there is a 2.5% detection rate of CIS or small papillary tumors in specimens from random biopsies of patients with known or suspected bladder tumors (Fradet et al, 2007). For patients with concurrent bladder tumors, a random biopsy will detect dysplasia or CIS in up to 23% of cases (Mufti and Singh, 1992). It is reasonable to perform random biopsies in high-risk individuals, such as those given postintra-vesical therapy or those with a positive cytology and an endoscopically negative bladder. Urine cytology, first introduced by Papanicolaou in 1945, evaluates the morphologic changes associated with bladder cancer and is the gold standard urinary marker against which other markers are held (Papanicolaou and Marshall, 1945). Overall, the sensitivity and specificity of cytology in detecting bladder cancer are 40% to 62% and 94% to 100%, respectively (van Rhijn et al, 2005; Volpe et al, 2008). Positive urine cytology is virtually diagnostic of a bladder tumor, although there are cases in which the tumor is not endoscopically visible. The sensitivity and specificity of urine cytology are dependent on the cytopathologist, the number of samples evaluated, and the stage and grade of the tumor (Volpe et al, 2008). Instrumented urine during cystoscopy has improved sensitivity and specificity, but an invasive procedure is required (Badalament et al, 1987). Fifteen percent of patients with atypical cytology that is not diagnostic of cancer have an underlying malignancy (Novicki et al, 1998). Thus patients with atypical cytology need more frequent evaluation or repeat random bladder biopsies.

Urine Markers for Urothelial Cancer

Van Rhijn and colleagues (2005) conducted a systematic literature review evaluating urine marker studies for surveillance only and included markers that had been evaluated in at least two studies published from two separate institutions (Table 92-6). We will discuss the markers that had at least 70% sensitivity and specificity plus novel markers that may be important in the future. The sensitivity and specificity of these tests are lower in patients undergoing surveillance evaluations with no active tumor or those with low-grade cancers (van Rhijn et al, 2005; Zwarthoff, 2008).

NMP-22 is a nuclear matrix protein that is used to form the cell nuclei. NMP-22 is shed into the urine and has a 20-times higher concentration in the urine of bladder cancer patients than in non-cancer controls (Keese et al, 1996). There are a variety of NMP-22 cutoff levels for bladder cancer detection, but typically a level of 10 units/mL is used to identify patients with or without cancer (Soloway, 1996; Grossman et al, 2006). A lower cutoff level of 5 units/mL improves the sensitivity but significantly worsens the specificity. The cutoff level does not appear to be related to stage or grade of the disease. False positives with NMP-22 can occur from patients with an active urinary tract infection or significant hematuria (Atsu et al, 2002). Grossman and colleagues (2006) reported a large multi-institutional study evaluating the efficacy of using NMP-22 as a marker. With use of a cutoff level of 10 units/mL, the overall sensitivity and specificity for detecting urothelial cancer were 49% and 87%, respectively. The sensitivity for Ta, T1, and T2 tumors was 36%, 65%, and 88%, respectively. A combination of cystoscopy and NMP-22 detected all but one of the 103 tumors seen in this study. NMP-22 picked up eight of the nine tumors missed by WLC. NMP-22 appears to be an adjunct to WLC in approximately 10% of patients.

The Lewis blood group antigen X is usually absent from urothelial cells in adults except for occasional umbrella cells (Sheinfeld

TABLE 92-6 Sensitivity and Specificity of Urinary Markers in the Detection of Urothelial Cancer

MARKER	MEDIAN SENSITIVITY (%)	RANGE (MINIMUM %–MAXIMUM %)	MEDIAN SPECIFICITY (%)	RANGE (MINIMUM %–MAXIMUM %)
BTA stat	70	24-89	75	52-93
BTA TRAK	69	57-79	65	48-95
NMP22	73	47-100	80	56-95
FDP	61	52-81	79	75-96
ImmunoCyt	83	50-100	80	69-90
Cytometry	60	45-83	80	36-87
Quanticyt	59	45-69	79	70-93
Hb-dipstick	52	41-95	82	68-93
Lewis X	83	80-89	85	80-86
FISH	84	73-92	95	92-100
Telomerase	75	7-100	86	24-93
Microsatellite	91	83-95	94	89-100
CYFRA 21.1	94	74-99	86	67-100
UBC	78	66-87	91	80-97
Cytokeratin 20	91	82-96	84	67-97
BTA	50	28-80	86	66-95
TPS	72	64-88	78	55-95
Cytology	48	31-100	94	62-100

From van Rhijn BW, van der Poel HG, van der Kwast TH. Urine markers for bladder cancer surveillance: a systematic review. *Eur Urol* 2005;47(6):736–48.

et al, 1990). There is increased Lewis X expression in bladder cancers, and it is independent of secretor status, grade, and stage. The sensitivity and specificity for the detection of bladder cancer are 75% and 85%, respectively. There is no commercially available test to date. CK 20 and CYFRA 21.1 are fragments of cytoskeletal proteins that can be detected in the urine of bladder cancer patients by either protein or mRNA detection (Ramos et al, 2003). CK 20 has a sensitivity and specificity of 85% and 76%, respectively. A recent multicenter study of 446 patients evaluating the role of CYFRA 21.1, with a cutoff value of 4 ng/mL, found a sensitivity and specificity of 43% and 68%, respectively (Fernandez-Gonzalez et al, 2008). Unfortunately, none of the Ta tumors were identified at the 4-ng/mL cutoff. Decreasing the CYFRA 21.1 cutoff to 1.5 ng/mL increased Ta detection to 33%, but the specificity dropped to an unacceptable 43%. Therefore it is not felt to be a useful marker in the current form, or at least not for low-grade disease.

FISH identifies fluorescently labeled DNA probes that bind to intranuclear chromosomes. The current commercially available probes evaluate aneuploidy for chromosomes 3, 7, and 17 and homozygous loss of 9p 21 (Zwarthoff, 2008). The median sensitivity and specificity of FISH analysis are 79% and 70%, respectively (van Rhijn et al, 2005). A recent prospective study of 250 patients evaluated the role of FISH analysis for identifying recurrent urothelial cancer (Yoder et al, 2007). FISH detected 25 of 39 concurrent tumors, and 35 tumors occurred later in 56 patients who initially had a positive FISH test result. The authors suggested that this was an anticipatory finding. Another study, by Moonen and colleagues (2007), evaluated 105 patients with urothelial cancer. The sensitivity for Ta, T1, and T2 tumors was 26.7%, 60%, and 50%, respectively. These lower sensitivity findings were confirmed (Gudjonsson et al, 2008). It appears that FISH analysis is moderately useful for high-grade disease and may be anticipatory of new tumor formation; however, because of the recurrent nature of noninvasive bladder cancer, it is difficult to tell whether the FISH test was identifying chromosomal abnormalities present in normal-appearing urothelium or if it yielded false-positive results. Multiple markers are available to identify short DNA repeats present throughout the chromosomes that are lost in some tumor cells. Microsatellite analysis amplifies these repeats in the genome that are highly polymorphic, and PCR amplification can detect tumor-associated loss of heterozygosity by comparing the peak ratio of

the two alleles in tumor DNA in the urine sample with the presence of the alleles in a blood sample from the same individual (Wang et al, 1997). The sensitivity and specificity of microsatellite analysis for the detection of urothelial carcinoma range from 72% to 97% and 80% to 100%, respectively (Wang et al, 1997). A European study evaluated microsatellite analysis in voided urine samples for the detection of low-malignant potential non-muscle-invasive urothelial carcinoma (van der Aa et al, 2009). They report sensitivity and specificity of 58% and 72%, respectively. Microsatellite analysis missed only one T1 high-grade urothelial cancer. It is interesting to note that if the microsatellite analysis was persistently positive, there was an 83% 2-year recurrence rate, but if the analysis was persistently negative, only 22% of patients had recurrent tumors. It is hoped that standardization of the test will allow analysis without a blood sample, and this will significantly improve the patient's acceptance.

CpG dinucleotide islands cluster around promoters in an unmethylated state to allow gene expression (Knowles, 2007). Methylation of the CpG islands shuts down the promoter, and, if the promoter in question is part of a tumor suppressor gene, then cancer can form. Examples of promoter methylation of CpG islands causing epigenetic changes in urothelial cancer include the *P16/CDKN2A* gene (Gonzalez-Zulueta et al, 1995). The sensitivity of gene methylation for the detection of bladder cancer is 75%; however, methylated CpG islands can be found in the normal urothelial cells of older patients (Yates et al, 2006). *FGFR-3* point mutations are found in 75% of NMIBC, particularly in Ta tumors (van Rhijn et al, 2004; Wolff et al, 2005). Unfortunately, there are more than 11 different point mutation sites within this gene, and therefore identification of all possible mutations is difficult in a single urine sample. Single-strand conformational polymorphism can detect these point mutations, and a snapshot assay has been produced that holds the possibility for rapid identification of *FGFR-3* mutations (van Oers et al, 2005). Surface-enhanced laser desorption/ionization (SELDI) mass spectroscopy of urine samples has a sensitivity and specificity for detecting bladder cancer of 50% to 90% and 60% to 90%, respectively (Vlahou et al, 2001). Tumor grade, patient age, and type of analysis are confounders of SELDI analysis, and a multi-institutional trial is needed to determine its effectiveness in identifying urothelial carcinoma. Survivin is an anti-apoptotic protein that has a high expression in urothelial cancer

(Smith et al, 2001). Survivin is found in 10% to 30% of bladder cancers and is readily shed into the urine. The sensitivity and specificity of survivin in the detection of urothelial tumors are 64% to 100% and 87% to 93%, respectively (Smith et al, 2001; Shariat et al, 2004). This test may be useful in predicting which patients will respond to intravesical therapy (Hausladen et al, 2003). Survivin was relatively poor at detecting advanced-stage or high-grade tumors, with a sensitivity of 71% for stage T2 tumors and 80% for high-grade cancers (Shariat et al, 2004). Hyaluronic acid controls intercellular communications and cell replication. Urothelial cancer induces hyaluronic acid production from fibroblasts, and the amount correlates with the stage of the disease. The sensitivity and specificity of hyaluronic acid for detection of bladder cancer are 91% to 100% and 84% to 90%, respectively (Pham et al, 1997; Lokeshwar et al, 2002). The sensitivity and specificity for discriminating between low-grade and high-grade lesions are unclear. Telomerase resides at the terminal ends of the chromosomes and duplicates random DNA repeats to prevent cell death (Rhyu, 1995). Telomerase activity is measured via telomeric repeat amplification protocol (TRAP) and is detected in 80% of urine from patients with bladder cancer with no grade differential. The sensitivity and specificity are 90% and 88%, respectively (Sanchini et al, 2005). The ImmunoCyt test (DiagnoCure, Quebec, Canada) detects mucin-based antigens that are present on most bladder cancer cells. The sensitivity and specificity are 61% to 92% and 71% to 90%, respectively (Halling et al, 2000; Pfister et al, 2003).

Virtually all patients report pain and discomfort with office cystoscopy. Urine marker studies could obviate this pain in select situations as described earlier. However, patients reported that a urine marker study would need 90% sensitivity to replace office cystoscopy (Vriesema et al, 2000). The primary concern is missing tumor cells by relying on the urinary marker. None of the currently available urinary markers meet this 90% sensitivity on a reliable basis, and therefore a combination of cystoscopy with urine markers, in select situations, is appropriate for surveillance of patients with NMIBC.

KEY POINTS: DETECTION OF UROTHELIAL CANCER

- Painless gross hematuria occurs in 85% of patients with bladder cancer and requires a complete evaluation that includes cystoscopy, urine cytology, CT scan, and a PSA blood test.
- Patients with microscopic hematuria require a full evaluation, but low-risk patients do not require repeat evaluations. High-risk individuals primarily are those with a smoking history and should be evaluated every 6 months.
- WLC with random bladder biopsies is the gold standard for tumor detection, but blue light cystoscopy may be an adjunct.
- There are various urine markers that can be used to evaluate secreted proteins or shed cells in the hope of noninvasively detecting bladder cancer. To date, none of these markers has a high enough sensitivity or specificity to replace office cystoscopy.

Prevention of and Complementary Medicine Treatments for Urothelial Cancer

Bladder cancer is primarily caused by urothelial exposure to carcinogens in the environment. The long lag time between carcinogenic exposure and subsequent bladder cancer formation makes testing of preventive measures difficult. Prevention of urothelial cancer is a high priority because it is the most expensive cancer to treat for several reasons, including that most urothelial cancer patients do not die from the disease, there is a high recurrence rate, and the primary mode of cancer control is repeated surgical procedures (Botteman et al, 2003; Siegel et al, 2013). There are three

avenues to cancer prevention: primary prevention or avoidance, prevention of malignant transformation of premalignant lesions, and prevention of tumor recurrence. Because there are no well-defined premalignant lesions in bladder cancer formation, most research has centered on primary tumor prevention and prevention of recurrent tumor.

Smoking cessation is the primary mode to prevent urothelial carcinoma. Smoking is responsible for 30% to 50% of all bladder cancers in males, and smokers have a twofold to sixfold higher chance of getting bladder cancer than nonsmokers (Boffetta, 2008; Freedman et al, 2011). Smoking cessation will decrease the risk of eventual urothelial cancer formation in a linear fashion. After 15 years of not smoking, the risk of cancer formation is the same as for someone who never smoked (IARC Working Group, 2004). The strong influence of smoking in bladder cancer formation prevents accurate determination of other less significant dietary, micronutrient, or lifestyle changes that may alter bladder cancer formation. There have been several animal studies that show calorie restriction prolongs life and prevents cancer (Kuska, 2000). The mechanism is unclear but may be mediated through IGF-1, because calorie-restricted mice given IGF-1 had cancer formation similar to that in normal-calorie mice but more than in calorie-restricted mice without IGF-1 supplementation (Dunn et al, 1997). However, it is difficult to translate these calorie-restriction animal studies to the human setting, because exercise level cannot be controlled. The key seems to be lower caloric intake rather than total body weight, although the two are indirectly related. A randomized breast cancer study evaluated low- versus normal-fat diets in women with recently resected breast cancer. Women on the low-fat diet with aggressive breast cancer had a significantly lower risk of recurrence. This could be the result of a variety of factors, including weight loss, lower caloric intake, and lower insulin levels (Chlebowski et al, 2006). Fruit and vegetable ingestion has been postulated to prevent a variety of cancers, including urothelial cancer. There have been many prospective and case-control studies evaluating fruit and vegetable intake. Most show equivocal results, although one showed a statistically significant difference in bladder cancer rates only in male subjects (Michaud et al, 2000). Citrus fruits, apples, berries, and tomatoes have been shown in some but not all studies to result in a lower risk of urothelial cancer (Brinkman and Zeegers, 2008). Carrots and cruciferous vegetables, particularly cabbage, cauliflower, and kale, have also been implicated as having an inverse relationship with bladder cancer formation. None of these studies has been a randomized trial; therefore whether ingestion of fruits and vegetables leads to a healthier lifestyle that is associated with lower urothelial cancer formation or whether these particular agents have a direct effect on urothelial cancer formation is unclear.

Several studies have evaluated the role of vitamin ingestion in bladder cancer formation. None of the large vitamin trials have shown a decreased risk with regard to primary urothelial cancer prevention (Grossman et al, 2008). A randomized trial of patients with urothelial cancer did show that BCG plus high-dose vitamins significantly prolonged the time of recurrence (Lamm et al, 1994). In this randomized trial of active urothelial cancer patients, all received intravesical BCG plus the recommended dietary-allowed vitamin doses, and half were randomly assigned to high-dose vitamins that included 4000 units of vitamin A, 100 mg of vitamin B₆, 2000 mg of vitamin C, 400 international units of vitamin E, and 90 mg of zinc daily. The high-dose vitamin group had a significantly prolonged time to urothelial cancer recurrence, with a 5-year disease survival rate of 91% compared with 41% in the standard-dose vitamin group ($P = .0014$). To date, follow-up trials have not been conducted to corroborate these results. Micronutrient ingestion has been suggested to decrease the bladder cancer risk.

The urogenesis theory suggests that high fluid intake leads to more micturition and lower concentrations of potential carcinogens in the urine and thus a lower risk of urothelial cancer (Braver et al, 1987). There are conflicting results showing an inverse relationship between fluid intake and urothelial cancer formation, but it is

strongest in women (Michaud et al, 2007). The health professional follow-up study of 48,000 participants found that total fluid intake was inversely related to urothelial cancer formation but only in comparing the highest quintile (>2500 mL) and lowest quintile (<1300 mL) groups (Michaud et al, 2007). Green tea contains polyphenolic compounds that are potent antioxidants—specifically, epigallocatechin-3 gallate, which inhibits urothelial cell growth in vitro (Qin et al, 2007). A large Japanese study of 49,566 men and 54,874 women evaluated the effect of smoking, caffeine, and green tea on urothelial cancer formation during a 15-year period (Kurahashi et al, 2009). As expected, smoking was strongly associated with urothelial cancer formation. Caffeine, in the form of either coffee or green tea, may be associated with urothelial cancer formation, and this effect was strongest in women. Caffeine is a known risk factor for urothelial cancer formation, and the carcinogenic effect of caffeine on urothelial cancer cells may be stronger than the antioxidant effect found in green tea (Pelucchi et al, 2008).

KEY POINTS: PREVENTION

- Stopping or never starting smoking is the best prevention for bladder cancer.
- There are no clear dietary or micronutrient programs to prevent primary bladder cancer.
- BCG plus high-dose vitamins may prevent recurrent bladder cancer.

Histologic Variants of Urothelial Cancer

Urothelial carcinoma of the bladder had previously been labeled transitional cell carcinoma of the bladder because of its known propensity for cellular differentiation into other tumor types, such as squamous cell carcinoma, adenocarcinoma, and clear cell carcinoma. Recently the wider spectrum of histologic variance of urothelial cancer has been identified to include distinct growth patterns of urothelial carcinoma, altered cellular differentiation of urothelial carcinoma, mixed cellular growth patterns, and unusual stromal reactions combined with urothelial cancer growth (Lopez-Beltran, 2008). The more common histologic variants will be discussed. It has been suspected that variants of urothelial cancer may not respond to systemic chemotherapy in a similar manner as traditional urothelial cancer. Although the regimens may be different, especially for small cell disease, the response rate of variants of urothelial cancer is similar to that of traditional urothelial cancer (Xylinas et al, 2012).

Micropapillary Urothelial Carcinoma

Micropapillary urothelial carcinoma was first described in the early 1990s as a tumor growth pattern that occurs in many organs, including bladder, breast, lung, and ovary, usually manifesting at an advanced stage (Amin et al, 1994; Samaratunga and Khoo, 2004). The incidence of micropapillary urothelial carcinoma is 0.7% to 2.2% of all urothelial tumors, with a male-to-female ratio of 10:1 and an average age at diagnosis of 65 years (Amin et al, 1994). Because of the advanced stage at diagnosis, the 5- and 10-year overall survival rate of patients with micropapillary urothelial carcinoma is 51% and 24%, respectively (Kamat et al, 2007). The cancer-specific and overall survival rates are similar, suggesting that most patients died from their cancer (Kamat et al, 2007). The histologic characteristics of micropapillary urothelial carcinoma are similar to papillary serous carcinoma of the ovary that develops delicate filiform processes with infiltrating clusters of micropapillary tumors lacking vascular stalks (Fig. 92-8). Micropapillary urothelial carcinoma is associated with conventional urothelial carcinoma in 80% of cases (Lopez-Beltran and Cheng, 2006). Angiolymphatic invasion is common even in non-muscle-invasive disease, high-

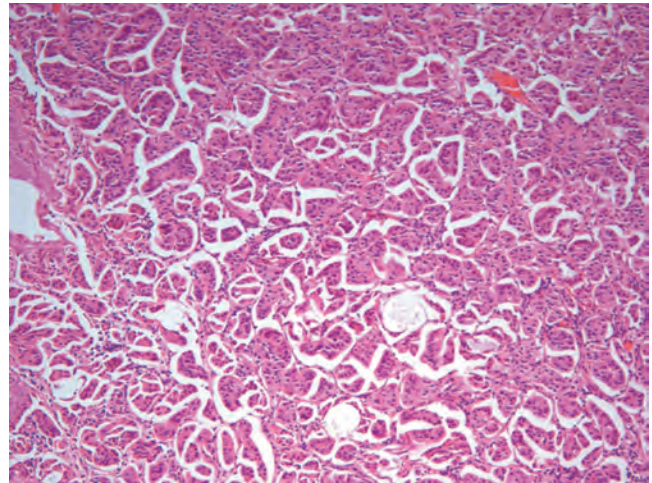


Figure 92-8. Micropapillary urothelial cancer.

lighting the aggressive nature of this cancer. There is a high progression rate from NMIBC to muscle-invasive bladder cancer approaching 70%, with a high subsequent metastatic rate despite treatment (Johansson et al, 1999; Kamat et al, 2007). The most effective treatment for all stages of micropapillary urothelial carcinoma is surgical resection. Treatment with transurethral resection and BCG therapy is ineffective unless the tumor is completely resected (Kamat et al, 2007). As with ovarian cancer, neoadjuvant chemotherapy does not appear effective in micropapillary urothelial carcinoma (Bristow et al, 2002; Kamat et al, 2007). Neoadjuvant chemotherapy may actually worsen survival by delaying therapy when compared with immediate cystectomy. Even in the best of situations, immediate cystectomy for non-muscle-invasive micropapillary bladder cancer has a cancer-specific survival rate of 72% compared with 60% for those treated with transurethral resection of the bladder tumor and BCG followed by cystectomy at the time of progression (Kamat et al, 2007). The best outcomes occurred in those patients who had no residual micropapillary tumor at the time of cystectomy, suggesting that complete resection of the tumor is the key procedure. Patients with locally advanced disease do poorly despite aggressive chemotherapy and surgical resection, with a cancer-specific survival rate of less than 22% at 4 years. There are no specific molecular markers associated with micropapillary urothelial carcinoma; however, these tumors are immunoreactive for epithelial membrane antigen and cytokeratins 7, 20, and 34 (Samaratunga and Khoo, 2004). Micropapillary urothelial carcinoma manifests at an advanced stage, with less than 9% of patients having noninvasive disease and more than 50% having muscle-invasive, nodal, or metastatic disease (Kamat et al, 2007).

Nested Variant of Urothelial Carcinoma

The nested variant of urothelial carcinoma is a rare but aggressive cancer that has a male-to-female ratio of 6:1 and can be confused with benign lesions such as von Brunn nests that are in the lamina propria, cystitis cystica, and inverted papillomas (Holmang et al, 2001). There is little nuclear atypia in the nested variant of urothelial carcinoma, but the tumor cells will often contain areas with large nuclei and mitotic figures (Fig. 92-9). Despite aggressive therapy, the mortality rate from the nested variant urothelial carcinoma is significant, with 70% of patients dying of their disease within 3 years (Terada, 2012).

Clear Cell Variant of Urothelial Carcinoma

Seventy percent of urothelial cancer will have foci of clear cells within the tumor (Lopez-Beltran and Cheng, 2006). These clear cells contain glycogen-rich vacuoles and may be confused with metastatic clear cell carcinoma of the kidney; however, the clear

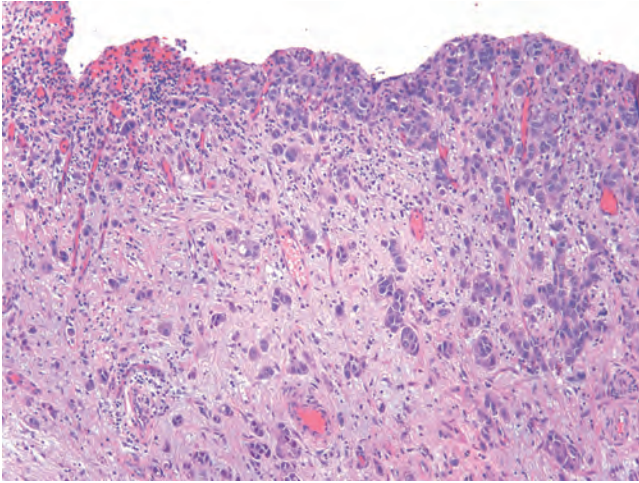


Figure 92-9. Nested variant of urothelial cancer.

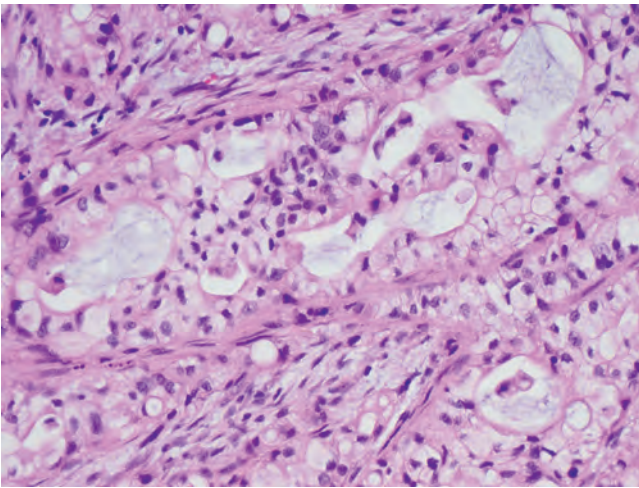


Figure 92-10. Clear cell adenocarcinoma of the bladder. Infiltrating adenocarcinoma, showing acini, nests, and infiltrating single cells composed predominantly of cells with clear cytoplasm.

cell variant does not portend a significantly worse prognosis for urothelial cancers (Fig. 92-10).

Glandular or Adenocarcinoma Differentiation

Mixed tumor differentiation is most common with squamous cell cancer, but glandular differentiation occurs in only 6% of urothelial cancer cases (Lopez-Beltran and Cheng, 2006). Glandular differentiation is defined as the presence of two glandular spaces within the tumor (Fig. 92-11). It is important that these glandular spaces not be confused with lymphatic invasion or with processing artifacts. Mucin production can occur, and tumor cells seem to be floating in the mucin. Adjuvant chemotherapy plus radical cystectomy is the best method of treatment for glandular-differentiated urothelial cancer. Previous data have suggested that neoadjuvant chemotherapy was relatively ineffective against glandular and squamous differentiation for muscle-invasive disease. A recent secondary analysis of the Southwest Oncology Group Trial 8710 of neoadjuvant muscle methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by cystectomy versus cystectomy alone for muscle-invasive bladder cancer evaluated the effect of neoadjuvant therapy on mixed cellular differentiation of urothelial cancer. Among the patients with mixed tumors, the survival benefit from chemotherapy appeared to be greater in magnitude

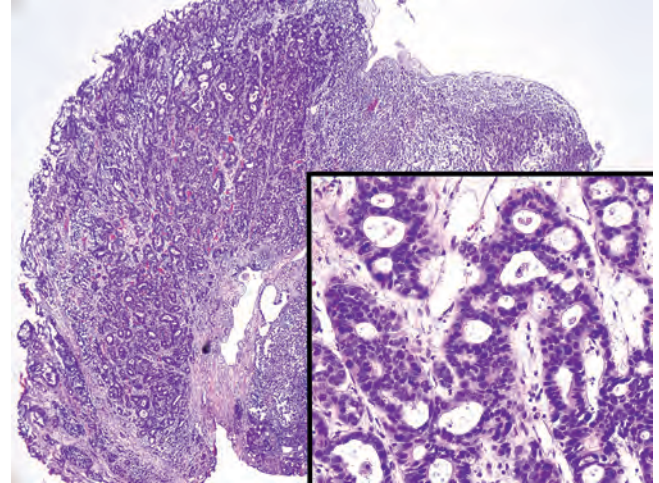


Figure 92-11. Adenocarcinoma of the bladder. Transurethral resection of the prostate fragment showing extensive involvement by primary bladder adenocarcinoma. Note presence of cribriform and glandular architecture of tumor (inset).

(hazard ratio [HR] 0.46, $P = .02$) than among patients with pure urothelial carcinoma (HR 0.9, $P = .48$) compared with immediate cystectomy (Scosyrev et al, 2010). This suggests that neoadjuvant chemotherapy is an appropriate treatment before radical cystectomy for patients with invasive mixed differentiation urothelial cancer.

Plasmacytoid Tumor

A plasmacytoid tumor is a variant of urothelial carcinoma that has been recognized by the WHO classification system since approximately 2011. This variant is characterized by plasmacytoid cells with the centric nuclei that often invade through the bladder wall and into the perivesical adipose tissue at the time of diagnosis (Keck et al, 2013). These tumors are usually diagnosed at an advanced stage in part because the onset of hematuria is delayed as a result of the sessile and nonpapillary tumor growth pattern (Wang et al, 2012a). These tumors responded very poorly to systemic chemotherapy, with a survival rate shorter than 27 months on average from time of diagnosis (Keck et al, 2013).

NONUROTHELIAL MALIGNANCIES

Sarcomas

Sarcomas are the most common mesenchymal tumor of the bladder but constitute less than 1% of all bladder cancers (Berkmen and Celebioglu, 1997; Parekh et al, 2002; Dotan et al, 2006). Subclassification of sarcoma is based on histologic variations, depending on the specific malignant cell type (Parekh et al, 2002; Spiess et al, 2007). Leiomyosarcoma is the most common histologic subtype, followed by rhabdomyosarcoma and then, rarely, angiosarcoma, osteosarcoma, and carcinosarcoma. The male-to-female ratio is 2:1, and the average age at presentation is in the sixth decade of life. There are no clear agents that cause bladder sarcomas, although there is an association with pelvic radiation and systemic chemotherapy for other malignancies (Spiess et al, 2007). It is important to note that bladder sarcomas are not smoking related. Genetic abnormalities of leiomyosarcoma are inconsistent and not used in staging or identification. The majority of sarcomas are high grade, and more than 75% are confined to bladder muscle (Rosser et al, 2003; Dotan et al, 2006). The most common presenting symptom is gross painless hematuria in 79%, followed by local irritative symptoms in 16%. Transurethral resection of the tumor, which may appear to have normal overlying urothelium, is necessary for diagnosis along with abdominal and chest imaging. The grade of the

sarcoma is the primary prognostic factor and is incorporated into the overall sarcoma staging system (Dotan et al, 2006). Treatment for localized disease includes radical cystectomy, with a premium on obtaining negative surgical margins because the local recurrence rate is 2.4 times higher in patients with a positive surgical margin (Dotan et al, 2006). The overall 5-year disease-free survival rate for leiomyosarcoma of the bladder is 52% to 62% (Rosser et al, 2003). Other poor prognostic factors associated with sarcomas include angiolymphatic invasion and metastatic disease at the time of presentation. **Active chemotherapeutic regimens are lacking for bladder sarcomas, but doxorubicin, ifosfamide, and cisplatin are the most effective agents** (Dotan et al, 2006; Spiess et al, 2007). The most common site for metastatic disease is the lung, followed by bone, liver, and, rarely, soft-tissue organs. Rhabdomyosarcomas may occur at any age, but in young children, they produce polyploid lesions at the base of the bladder, described as *botryoides tumors*. Multimodality therapy combining chemotherapy with surgical resection and radiation is used in the treatment of pediatric rhabdomyosarcomas (Zanetta et al, 1999).

Signet Ring Cell Carcinoma

Primary signet ring cell carcinoma of the bladder is extremely rare, constituting less than 1% of all epithelial bladder neoplasms (Morelli et al, 2006) (Fig. 92-12). Signet ring cell carcinoma can be of urachal origin and directly extend into the bladder. **In general, these tumors are high-grade, high-stage tumors at presentation and have a uniformly poor prognosis.** The primary treatment is radical cystectomy; however, in the majority of patients there are regional or distant metastases at the time of presentation, and the mean survival time is less than 20 months (Torenbeek et al, 1996). There are reports of elevated carcinoembryonic antigen (CEA) in patients with signet ring cell carcinoma. The prognostic significance of this elevated serum marker is unclear (Morelli et al, 2006). Understaging is very common in signet ring cell carcinoma, with peritoneal studding common at the time of surgical exploration.

Small Cell Carcinoma

Small cell carcinoma primarily arises in the lung but can occur in extrapulmonary sites, including the bladder, prostate, and colon (Thota et al, 2013) (Fig. 92-13). **Small cell carcinoma of the bladder should be considered and treated as metastatic disease,**

even if there is no radiologic evidence of disease outside the bladder. Small cell carcinoma of the bladder accounts for much less than 1% of all primary bladder tumors. In general, small cell carcinoma of the bladder is very chemosensitive, and the primary mode of therapy is chemoradiation therapy. The tumor affects men older than 70 years, and there is a slightly higher prevalence in smokers (Choong et al, 2005). The origin of extrapulmonary small cell carcinoma is unclear, but may be related to multipotential stem cells that can develop into small cell carcinoma within extrapulmonary organs (Thota et al, 2013). The most common presenting symptom is painless gross hematuria; however, local irritation and pain are relatively frequent. At transurethral resection the mass is indistinguishable from urothelial carcinoma, and resection is required to make a histologic diagnosis. Histologically, the common cellular pattern is diffuse sheets of dark blue cells with necrosis and mitosis. Chromogranin A staining is the primary method to distinguish high-grade urothelial carcinoma from small cell cancer of the bladder (Iczkowski et al, 1999). A variety of chemotherapeutic regimens have been used, but therapy with carboplatin or cisplatin and etoposide is the current treatment of choice (Choong et al, 2005). It is common to have a complete response from initial chemotherapy; however, clinical relapse occurs in more than 80% of patients. It is not uncommon to see small cell carcinoma admixed with other histologic types of bladder cancer, including urothelial, adenocarcinoma, and squamous cell cancer (Choong et al, 2005). This supports the stem cell theory of histogenesis, with multipotential undifferentiated stem cells producing small cell carcinoma and other histologic types of bladder cancer. Identical patterns of allelic loss in small cell carcinoma and coexisting urothelial cancers suggest a common clonal origin. Small cell carcinoma of the bladder exhibits both epithelial and neuroendocrine differentiation. Neuron-specific enolase, chromogranin A, and synaptophysin markers help differentiate small cell from urothelial carcinoma (Mukesh et al, 2009). Although chemoradiation therapy is the primary treatment for small cell carcinoma of the bladder, experience combining chemotherapy with radical cystectomy for primary small cell cancers of the bladder has shown equal, or perhaps better, local control and disease-free survival than found with chemoradiation (Quek et al, 2005). However, with 5-year cancer-specific survival rates of 16% to 18% with chemoradiation or chemotherapy and radical cystectomy, respectively, the primary method to improve survival will be more effective systemic therapy.

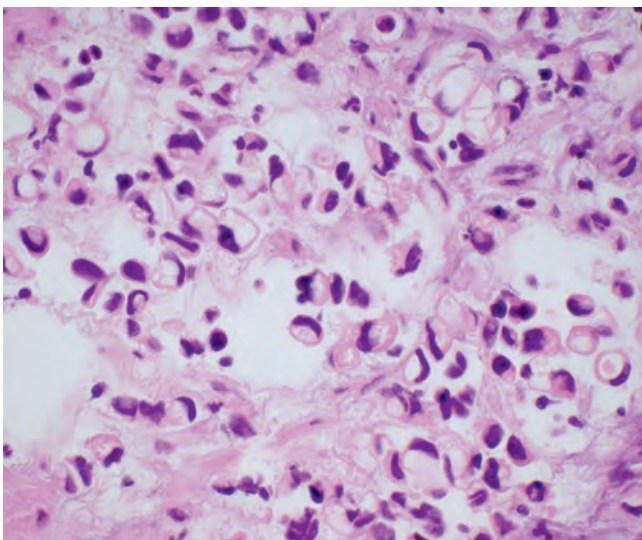


Figure 92-12. Signet ring cell cancer of the bladder. Infiltrating single tumor cells possess large amounts of pale to clear cytoplasm, with the nucleus being stretched and pushed to the periphery (signet ring appearance).

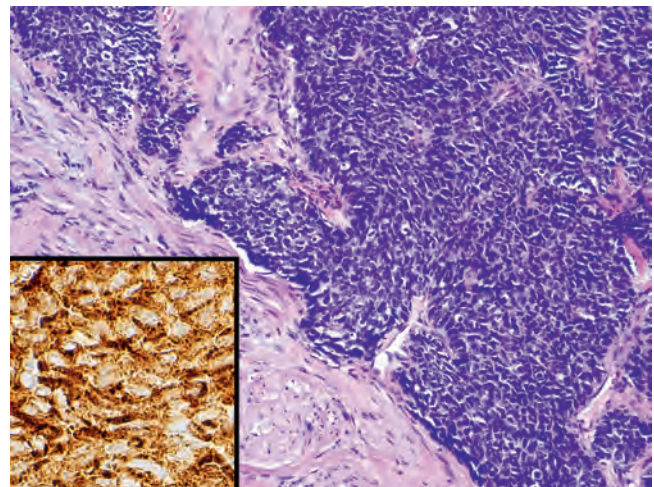


Figure 92-13. Small cell carcinoma of the bladder. Tumor composed of sheets and nests of basophilic appearing tumor cells with high nucleocytoplasmic ratio. Histologic features resemble small cell carcinoma seen in the lung. Tumor cells stain and show diffuse and strong immunoreactivity with neuroendocrine markers chromogranin (inset) and synaptophysin.

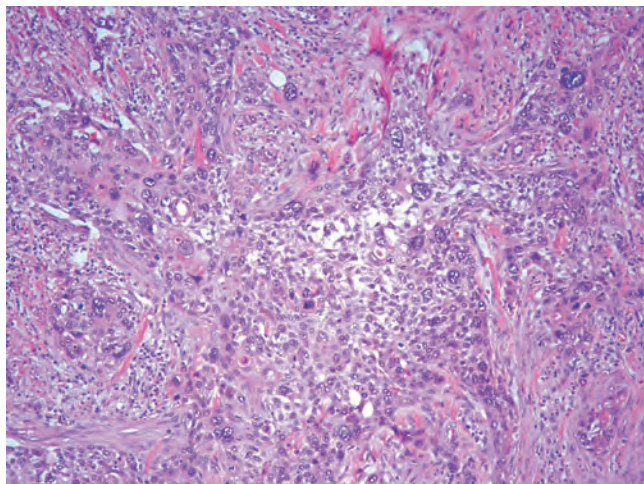


Figure 92-14. Squamous cell cancer with associated urothelial cancer.

Squamous Cell Cancer

Chronic infection with *S. haematobium* or, to a lesser degree, other bacteria leads to squamous cell formation of the bladder (Abol-Enein, 2008). The *Schistosoma* ova are deposited in the wall of the bladder and produce chronic inflammation that converts the urothelium to a squamous cell epithelium. Squamous cell epithelium has a much greater proliferation rate, and, with the presence of chronic inflammation, over time this greater proliferation rate leads to cancer formation. The exact mechanism by which *Schistosoma* ova can cause squamous cell carcinoma is unclear, but two factors are suspected. One is the increased proliferation rate, and the second is the chronic inflammation and exposure to environmental agents. The increased proliferation of the squamous epithelium leads to a higher risk of spontaneous genetic alterations that can cause cancer (Cohen and Ellwein, 1990). A chronic inflammatory process and exposure to environmental agents can combine to generate genotoxic substances in the urine, such as *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine. This substance is generated in very high levels in the urine of patients chronically infected with *Schistosoma* organisms and is a known bladder cancer carcinogen in bladder cancer models (Abol-Enein, 2008). In addition, chronic infection with *S. haematobium* converts nitrates to nitrites and subsequently to nitrosamines, which are known bladder carcinogens. Chronic schistosomiasis leads predominantly to squamous cell carcinoma rather than urothelial carcinoma, with 70% of infected patients who develop bladder cancer having squamous cell carcinoma, although many will have both urothelial and squamous cell cancer (Cohen and Johansson, 1992) (Fig. 92-14). Spinal cord-injured patients are also at risk for developing squamous cell carcinoma, most likely because of chronic catheter irritation and infection. Older studies have suggested a 2.5% to 10% incidence of squamous cell carcinoma in the spinal cord-injured population, with a mean delay of 17 years after the spinal cord injury (Kaufman et al, 1977). More recent analysis of the association of spinal cord injury and bladder cancer formation has shown a remarkably lower risk of bladder cancer formation of 0.38%, most likely because of better catheter care (Bickel et al, 1991). This supports the concept that chronic infection and foreign bodies can lead to bladder cancer formation.

Prostatic Urethral Cancer

Ortega was the first to describe urothelial carcinoma involving the prostatic urethra (Ortega et al, 1953) (Fig. 92-15). Prostatic urethral cancer is associated with urothelial cancer in 90% of patients, primarily CIS, and most will have multifocal bladder tumors. However, the incidence of prostatic urethral disease in patients with primary

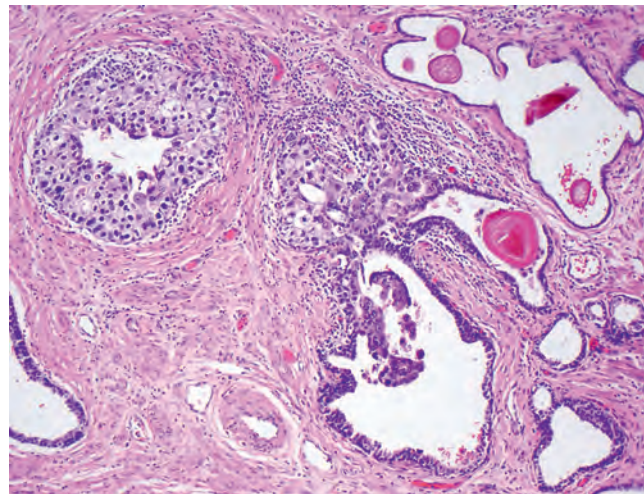


Figure 92-15. Urothelial carcinoma in situ (CIS) of the prostate. Urothelial CIS is growing within benign prostatic acini. The size and contour of the prostatic acini are still maintained, with replacement of inner lining of columnar epithelium of prostate by multilayered epithelium of urothelial CIS.

KEY POINTS: HISTOLOGIC VARIANTS

- Eighty percent of urothelial carcinomas will contain some mixed differentiation, most commonly squamous cell.
- Altered growth patterns, particularly micropapillary and nested variants, carry a poor prognosis, even for non-muscle-invasive disease.
- Neoadjuvant chemotherapy appears to be active in mixed tumors containing adenocarcinoma or squamous cell cancer but not against altered growth patterns such as in micropapillary and nested urothelial cancer.
- Small cell carcinoma of the bladder should be treated as metastatic disease with institution of chemotherapy followed by either radiation therapy or surgery for elimination of the local disease.
- Signet ring carcinoma is uniformly understaged and invariably is at local, regional, or metastatic stage at presentation.

urothelial cancer is only 3% (Rikken et al, 1987). Secondary prostatic urethral involvement in patients with a history of urothelial cancer is approximately 15% at 5 years and 30% at 15 years, almost uniformly associated with extensive intravesical therapy (Herr and Donat, 1999). For patients undergoing radical cystectomy for urothelial cancer, the risk of identifying prostatic urethral disease is 40%. Risk factors for prostatic urethral involvement are CIS of the bladder neck and a history of intravesical chemotherapy (Wood et al, 1989a). Most patients with prostatic urethral disease will have direct extension of the bladder cancer into the prostatic urethra; however, some patients will have pagetoid spread underneath normal-appearing urothelium at the bladder neck.

Transurethral resection of the prostatic urethra is the primary method for detecting prostatic urethral carcinoma, with a sensitivity and specificity of greater than 90% (Wood et al, 1989a; Donat et al, 2001a, 2001b). Transurethral resection of the prostatic urethra should be performed on all patients with positive urine cytology but a negative bladder biopsy, or on those with recurrent bladder cancer after multiple courses of intravesical chemotherapy. For patients with noninvasive prostatic urethral cancer, transurethral resection of the prostate with BCG therapy is appropriate (Palou et al, 2007). For patients with prostatic ductal disease, complete transurethral resection of the prostate is warranted, plus BCG

therapy. The current 2009 bladder cancer staging system now excludes noninvasive prostatic urethral disease from the T4 category. These tumors have a relatively good prognosis not consistent with T4 staging status. Prostatic urethral cancer is now staged in a prostatic urethral category in the AJCC staging manual (Edge and Compton, 2010). Only patients with prostatic stromal invasion, either direct or indirect, are considered to have T4a-staged disease. Prostatic stromal invasion occurs in 7.6% to 25% of patients with prostatic urethral cancer (Wood et al, 1989b; Herr and Donat, 1999). Ninety percent of these cases are associated with previous bladder tumors, and almost all patients have had previous BCG therapy. Transurethral biopsy of the prostate is recommended; however, if patients have direct extension of the tumor through the bladder wall into the prostate, a prostate needle biopsy may be warranted (Donat et al, 2001b). Patients with prostatic stromal disease are staged at T4a, and a better prognosis is associated with those who have stromal invasion through the prostatic urethra compared with invasion directly through the bladder wall into the prostate (Esrig et al, 1996). Multimodal therapy combining chemotherapy with radical cystectomy is the appropriate treatment (Palou et al, 2007).

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The complete reference list is available online at www.expertconsult.com.

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Pathology: Grading and Staging

Endoscopic Surgical Management

Perioperative Intravesical Therapy to Prevent Tumor Implantation

Immunotherapy

Intravesical Chemotherapy

Refractory High-Grade Disease

Role of “Early” Cystectomy

Surveillance and Prevention

Secondary Prevention Strategies

Traditionally known as *superficial bladder cancer*, **malignant urothelial tumors that have not invaded the detrusor are more appropriately termed *non–muscle-invasive* cancers** (Epstein et al, 1998; Smith et al, 1999). The former term suggested that all such tumors shared the relatively benign course of low-grade papillary tumors, giving misleading reassurance to patients with the highly malignant subcategories of carcinoma in situ (CIS) and high-grade Ta and T1 lesions. **Approximately 70% are non–muscle invasive at presentation. Of these, 70% present as stage Ta, 20% as T1, and 10% as CIS (Fig. 93-1) (Ro et al, 1992).**

The presence of bladder cancer is usually suspected when hematuria occurs. Patients with macroscopic (gross) hematuria have reported rates of bladder cancer of 13% to 34.5% (Lee and Davis, 1953; Varkarakis et al, 1974). Microscopic hematuria is associated with a 0.5% to 10.5% rate of bladder cancer (Golin and Howard, 1980; Mohr et al, 1986; Sultana et al, 1996; Khadra et al, 2000). The presence of irritative voiding symptoms may double that risk, especially for CIS (5% vs. 10.5%) (Mohr et al, 1986). For example, the Mayo Clinic reported that 80% of patients with CIS had irritative symptoms on presentation (Zincke et al, 1985). In a review of 600 patients diagnosed with interstitial cystitis, 1% of the patients had a missed diagnosis of urothelial carcinoma. Of note, two thirds of these patients did not have hematuria (Tissot et al, 2004). Thus cystoscopy and upper tract imaging are indicated in patients with hematuria and/or unexplained irritative symptoms (Grossfeld et al, 2001; Davis et al, 2012).

Recurrence is common in all patients with non–muscle-invasive urothelial cancer (UC) but can often be controlled successfully with transurethral surgery, intravesical therapy, or a combination. In contrast to recurrence, patients can be divided into low or high risk for progression, which is the true concern. Low-grade Ta lesions are low risk, whereas all high-grade lesions (including CIS) have a high risk of progressing. The frequency of progression and death is shown in Table 93-1.

PATHOLOGY: GRADING AND STAGING

Pathologic Grading

Although the World Health Organization (WHO) has determined that the term *urothelial cancer* is preferable to the term *transitional cell cancer* (TCC), the latter remains in widespread use. However, the WHO recommendation to move away from the traditional

grading system (1 to 3, from low grade to high grade) is now accepted by most urologists and pathologists. The WHO recommends that **malignant tumors be classified as low grade or high grade, regardless of invasion status.**

By contrast, essentially benign papillary tumors with orderly cellular arrangement, minimal architectural abnormalities, and minimal nuclear atypia are distinct from those two grades and are designated papillary urothelial neoplasm of low malignant potential (PUNLMP). Such tumors would have been labeled either papillomas or grade 1 TCC in older systems but are now regarded as so unlikely to progress that they are considered benign. However, on the basis of this low risk, the WHO recommends that such pathology reports contain the note, “Patients with these tumors are at risk of developing new bladder tumors (‘recurrence’), usually of similar histology. However, occasionally these subsequent lesions manifest as UC, such that follow-up of the patient is warranted” (Epstein et al, 1998). Papillomas are truly benign and not associated with risk of progression (Figs. 93-2 through 93-5; also see Fig. 93-1).

Pathologic Staging

The bladder has three main histologic layers: (1) urothelium, (2) suburothelial loose connective tissue called *lamina propria*, and (3) detrusor or muscularis propria (which is absent beneath the urothelium of diverticula). Stage Ta denotes a papillary tumor confined to the urothelium, regardless of grade. CIS (also termed *Tis*) is a flat, high-grade lesion confined to the same layer, and T1 is a tumor invading lamina propria. The TNM grading system is illustrated in Figure 93-1.

The demarcation between “superficial” and “invasive” has sometimes been errantly considered between T1 and T2. However, **T1 tumors invade the lamina propria by definition, so they cannot be accurately characterized as noninvasive.** Unlike the urothelium, which is devoid of vessels or lymphatics, the lamina propria is rich in both, providing opportunity for metastasis. These tumors sometimes invade the wispy and discontinuous muscularis mucosae of the lamina propria, which can be confused for muscularis propria (detrusor) during pathologic interpretation. **Imprecise verbiage on the pathology report can lead the urologist to misinterpret invasion of muscularis mucosae to be muscle invasive, risking an overstaging error.** Direct communication between urologist and pathologist is essential when this occurs.

TABLE 93-1 Estimates of Disease Progression in Non-Muscle-Invasive Bladder Cancer: World Health Organization/International Society of Urologic Pathology Consensus Classification

TUMOR TYPE	RELATIVE FREQUENCY (%)	PROGRESSION (%)	DEATHS (%)
NONINVASIVE			
Papilloma	10	0-1	0
Papillary urothelial neoplasm of low malignant potential	20	3	0-1
Papillary cancer, low grade (TaG1)	20	5-10	1-5
Papillary cancer, high grade (TaG3)	30	15-40	10-25
INVASIVE			
Papillary cancer (T1G3)	20	30-50	33
CARCINOMA IN SITU			
Primary	10	>50	—
Secondary	90	—	—

From Donat SM. Evaluation and follow-up strategies for superficial bladder cancer. Urol Clin North Am 2003;30:765–6.

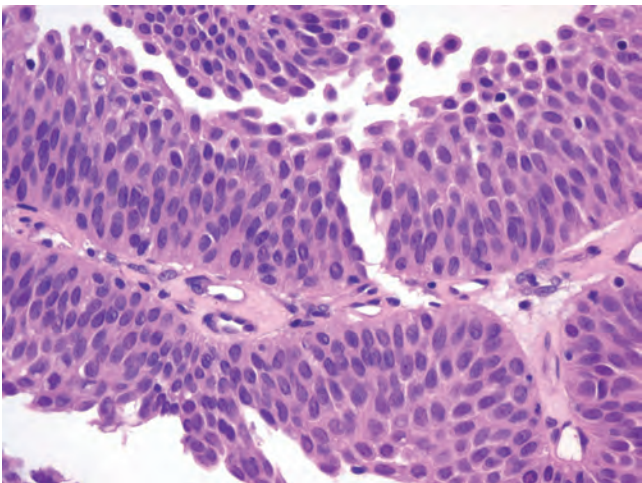
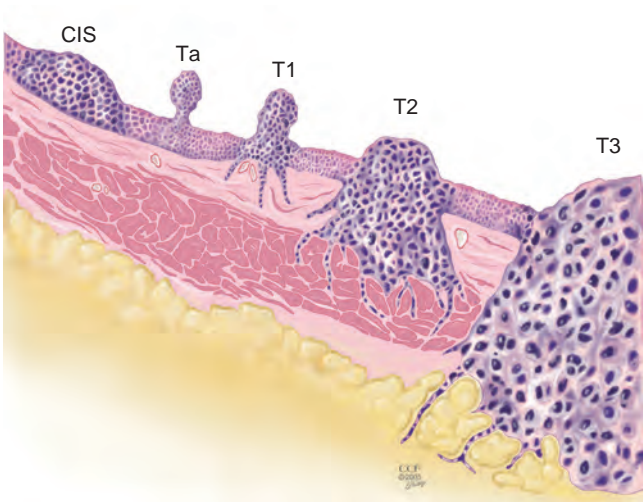


Figure 93-1. Carcinoma in situ is a high-grade, flat malignancy confined to the urothelium. Papillary tumors confined to the urothelium are Ta, whereas papillary tumors invading lamina propria are T1. The T1 tumor here intertwines with the wispy fibers of the muscularis propria but by definition does not invade the smooth muscle fibers of the detrusor. T2 tumors invade the detrusor muscle, and T3 tumors are in extravesical fat as shown.

Figure 93-2. The urothelium is thickened, but cells and nuclei are normal in papillary urothelial neoplasm of low malignant potential (×40).

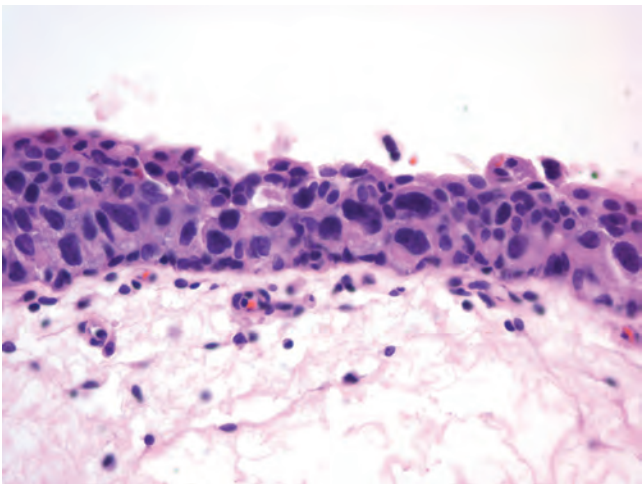
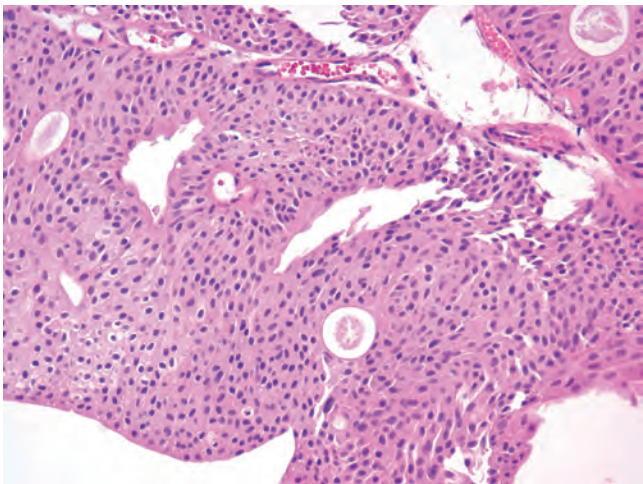


Figure 93-3. Ta low-grade tumor (×40). Cells are relatively normal but exhibit irregularity and some nuclear differentiation.

Figure 93-4. Carcinoma in situ (×40) exhibits severe irregularity of cellular structure and nuclear pleomorphism, but there is no invasion of lamina propria.

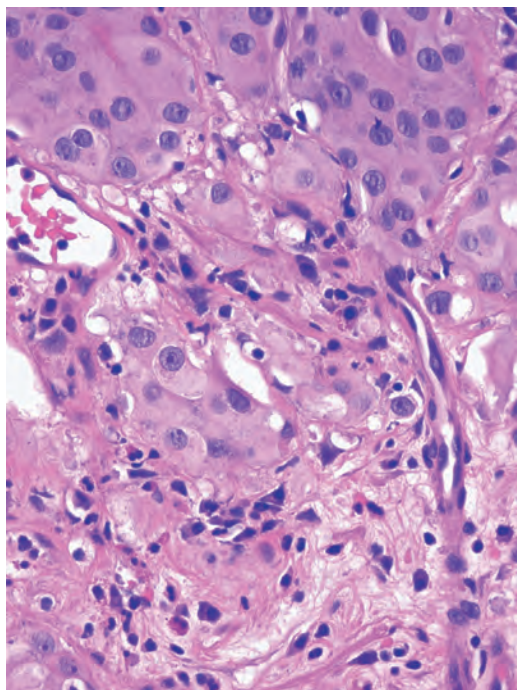


Figure 93-5. T1 ($\times 40$) high-grade tumor exhibits nesting of abnormal cells and mitotic figures. Tumor cells can be seen invading the lamina propria in the lower one third of the photomicrograph.

Deep lamina propria invasion carries a substantially more serious prognosis in some reports, and some have proposed these be subcategorized as T1b (Younes et al, 1990). However, the value of substaging has not been validated in other studies (Platz et al, 1996), so the 1998 Bladder Cancer Consensus Conference Committee rejected the concept (Epstein et al, 1998).

Tumor Biology

Low-grade tumors rarely invade the lamina propria or detrusor, so invasive tumors may be almost equated with high-grade histology. However, tumors of all grades and degrees of potential aggressiveness can be identified before invasion, so no such grading assumption can be made about these lesions.

Low-grade Ta lesions recur at a rate of 50% to 70% and progress in approximately 5% of cases. In contrast, high-grade T1 lesions recur in more than 80% of cases and progress in 50% of patients within 3 years. This behavior is primarily grade, rather than stage, dependent, because high-grade tumors progressed with similar frequency regardless of whether they were invasive (T1) or noninvasive (Ta) (Herr, 2000b). Prognosis also correlates with tumor size, multiplicity, papillary versus sessile configuration, presence or absence of lymphovascular invasion, and status of the remaining urothelium (Althausen et al, 1976; Lutzeyer et al, 1982; Heney et al, 1983a, 1983b; Kunju et al, 2008).

The variance in biologic behavior for low-grade versus high-grade lesions correlates with the known dual molecular lines of genetic development for these two pathways and supports the concept that high-grade and low-grade cancers may be considered as essentially different diseases (Hasui et al, 1994; Droller, 2005). Chromosomal alterations caused by oxidative DNA damage create two separate genetic pathways to the development of UC (Spruck et al, 1994; Richter et al, 1997; Cote and Chatterjee, 1999). The first and more common (low grade) leads to noninvasive, papillary tumors. These usually follow an indolent course unless they convert to or are associated with a tumor of the second pathway (Kiemeny et al, 1993).

The second pathway leads to the development of high-grade cancer including CIS, T1, and, ultimately, muscle-invasive carcinoma. Such genetic alterations can be evaluated using karyotyping, microsatellite analysis for allelic imbalance (Mao et al, 1996), comparative genomic hybridization (Kallioniemi et al, 1995), DNA ploidy analysis by flow cytometry (Bittard et al, 1996), and fluorescence in situ hybridization (FISH) (Degtyar et al, 2004). These evaluations can show that low-grade papillary tumors tend to exhibit relatively few chromosomal abnormalities, primarily involving loss of all or part of chromosome 9 (particularly the q arm, which holds tumor-suppressing loci). In contrast, high-grade tumors tend to have numerous and greatly variable chromosomal gains and losses. In addition to their relatively predictable aneuploidy, high-grade tumors can also lose all or part of chromosome 9 (Richter et al, 1997). Although almost any chromosome can be affected, aneuploidy of chromosomes 7, 9, and 17 is associated with especially aggressive tumors (Olumi et al, 1990; Waldman et al, 1991; Degtyar et al, 2004).

Because of these differing genetic imprints, it has been suggested that papillary pTa tumors could almost be considered benign and might be a completely separate disease entity in contrast to high-grade tumors (Sauter and Mihatsch, 1998; Harnden, 2007). Nevertheless, high-grade and low-grade lesions are known to coexist. UC is traditionally considered a field change disease, with tumors arising at different times and sites. Rarely, patients who initially have low-grade tumors will subsequently develop high-grade tumors, often years after the original tumors, so long-term surveillance is usually appropriate (Holmäng and Ströck, 2012).

Pathologic Characteristics by Stage and Implications for Clinical Management

Stage Ta tumors are usually low grade. Although recurrence is common, especially in the setting of multiplicity, progression is rare. However, 2.9% to 18% of Ta tumors are high grade, with an average of 6.9% (Sylvester et al, 2005). The most important risk factor for progression is grade, not stage (Millán-Rodríguez et al, 2000; Sylvester et al, 2005).

CIS is occasionally mischaracterized as “preinvasive” (Sylvester et al, 2005), but it is actually a flat, noninvasive UC that is high grade by definition and is regarded as a precursor to the development of invasive high-grade cancer.

CIS lesions are composed of severely dysplastic urothelium. Microscopically, the slide will demonstrate disorderly histology with nuclear atypia characteristic of high-grade malignancy; denudement of some or all of the mucosa as a result of loss of cellular cohesion sometimes complicates interpretation. A pathology report read as dysplasia or atypia can create confusion. Most pathologists consider mild examples of these entities to be benign. However, lesions interpreted as severe dysplasia or severe atypia are regarded as being the same entity as CIS (Epstein et al, 1998). Again, unambiguous communication between pathologist and urologist can minimize the risk for misinterpretation.

From 40% to 83% of patients with CIS will develop muscle invasion if untreated, especially if associated with papillary tumors (Althausen et al, 1976). Among patients thought to have CIS alone, up to 20% who are treated with cystectomy are found to actually contain invasion on final pathology (Farrow et al, 1976). The presence of CIS in specimens from cystectomy performed for presumed T1 tumors was associated with upstaging in 55% of patients in one series, compared with 6% upstaging in patients without CIS (Masood et al, 2004). In a series of 1500 patients, CIS was the second most important prognostic factor after grade (Millán-Rodríguez et al, 2000). Multicentricity presents another ominous characteristic of CIS (Koch and Smith, 1996). The presence of irritative voiding symptoms has been associated with diffuse disease, invasion, and a compromised prognosis, but there is no consensus on this finding in the literature (Smith et al, 1999; Sylvester et al, 2005).

TABLE 93-2 Risk of Understaging When Cystectomy Is Performed for Presumed Non–Muscle-Invasive Disease

STUDY	INSTITUTION	RISK (%) OF UNDERSTAGING
Stein et al, 2001	Southern California	39
Dutta et al, 2001	Vanderbilt University	40
Bianco et al, 2004	Wayne State University	27
Bayraktar et al, 2004	Vakif Gureba Hospital, Aksaray-Istanbul, Turkey	50
Huguet et al, 2005	Servicio de Urologia, Fundació Puigvert, Barcelona	27
Ficarra et al, 2005	University of Verona, Italy	43

T1 tumors are usually papillary and often have a narrow stalk; a nodular or sessile appearance suggests deeper invasion. Deep penetration into the lamina propria, especially if involving muscularis mucosae, increases the risk of recurrence and progression in some reports. Lymphovascular invasion (Lotan et al, 2005), pyuria (Azuma et al, 2013), and bladder neck involvement (Kobayashi et al, 2014) also increase this risk. Hydronephrosis usually indicates muscle invasion.

There is significant potential for understaging in patients with high-grade, apparently non–muscle-invasive tumors, especially those that appear to be stage T1. Many tumors are found to be more extensive than the transurethral resection (TUR) specimen indicated when patients undergo cystectomy. Stein reported that one third of patients believed to have non–muscle-invasive disease at the time of cystectomy were found to actually have muscle invasion; only half of these cases were organ confined. Metastases were already present in 8% of these patients (Freeman et al, 1995). His subsequent review noted that understaging errors from 34% to 62% have been reported (Stein et al, 2001), and a study from the Mayo Clinic before widespread use of intravesical therapy showed that 78% of patients with clinical T1 disease who underwent cystectomy had muscle invasion, with 62% having extravesical disease. Studies addressing the risk of understaging of T1 tumors are shown in Table 93-2.

Although it is likely that the patients who underwent cystectomy had more serious risk factors than those who did not, these data offer compelling evidence that the term *superficial* to describe all such lesions is misleading and would ideally be eliminated from urologic practice and the literature.

KEY POINTS: PATHOLOGY

- Malignant tumors are now classified as low grade or high grade, regardless of invasion.
- High-grade and low-grade cancers may be regarded as essentially separate diseases from genetic development, biologic behavior, and management standpoints.
- The most important risk factor for progression is grade, not stage.
- CIS is a precursor as well as a risk factor for progression, invasion, and metastasis.
- Papillary tumors with orderly cellular arrangement, minimal architectural abnormalities, and minimal nuclear atypia are designated papillary urothelial neoplasm of low malignant potential (PUNLMP).

ENDOSCOPIC SURGICAL MANAGEMENT

Procedures

When bladder cancer is identified during office-based cystoscopy, the location, number, and morphology of tumors are recorded, as is involvement of areas likely to reflect extravesical extension such as the ureteral orifices and bladder neck or prostatic urethra. Urinary cytology is obtained as a baseline and to establish the likelihood of high-grade disease. Positivity will encourage random bladder biopsy at the time of TUR, as discussed later.

Upper tract imaging is usually performed before TUR both to identify other sources of hematuria and to assess the extravesical urothelium because of the “field change” nature of UC, which can affect such tissue throughout the urinary tract. Retrograde pyelography or ureteroscopy can be planned for any upper tract abnormalities identified. Expert consensus is that patients with solitary or limited low-grade Ta lesions do not need imaging unless they have concomitant hematuria, owing to the very low risk of extravesical disease (Goessl et al, 1997; Davis et al, 2012).

Transurethral resection of bladder tumor (TURBT) under regional or general anesthesia is the initial treatment for visible lesions and is performed to (1) remove all visible tumors and (2) provide specimens for pathologic examination to accurately determine stage and grade. Bimanual examination of the bladder is often performed with the patient under anesthesia before preparation and draping unless the tumor is clearly small and noninvasive, and is repeated after resection. Fixation or persistence of a palpable mass after resection suggests locally advanced disease, although the additional value of this maneuver in the era of modern imaging appears limited and may even be misleading (Ploeg et al, 2012). An increase in abdominal girth or fullness after resection suggests intraperitoneal perforation.

Complete visualization to plan the resection is facilitated by either the flexible cystoscope or preferably the 70-degree rigid rod lens, which allows maintenance of the anatomic relationships. Resection is performed using a 12- or 30-degree lens placed through a resectoscope sheath because this deflection allows visualization of the loop placed at this location. Continuous irrigation with the bladder filled only enough to visualize its contents minimizes bladder wall movement and lessens thinning of the detrusor through overdistention, which should reduce the risk of perforation (Koch and Smith, 1996). Video TUR allows magnification, facilitates resident teaching, allows documentation of findings, and reduces the risk of body fluid exposure to the surgeon (Manoharan and Soloway, 2005; Nieder et al, 2005). Resection is performed piecemeal, delaying transection of any stalk until most tumor has been resected, to maintain countertraction. Friable, low-grade tumors can often be removed without the use of electrical energy because the nonpowered cutting loop will break off many low-grade tumors. This minimizes the chance of bladder perforation and unnecessary cautery damage or loss of specimens. Higher-grade, more solid tumors and the base of all tumors require the use of cutting current; cautery yields hemostasis once the entire tumor has been resected. Lifting the tumor edge away from detrusor lessens the chance of perforation (Holzbeierlein and Smith, 2000). Repeated slow fulguration may complicate the ability of the pathologist to determine grade or invasion status. There appears to be variability in completeness of resection among surgeons. In patients with multiple tumors who had adjuvant treatment, recurrence rates varied from 7.4% to 45.8% depending on the surgeon (Brausi et al, 2002).

After all visible tumor has been resected, an additional pass of the cutting loop or a cold-cup biopsy can be obtained to send to pathology separately to determine the presence of muscle invasion of the tumor base. A chip evacuator gathers the specimen. Final confirmation of hemostasis in the presence of minimal irrigation after all chips have been removed through vigorous irrigation is helpful.

Traditionally, TUR has been performed in sterile water because saline solutions conduct electricity and disperse energy from the

monopolar cautery cutting loop. Glycine is more expensive, and there is no evidence of its benefit in this setting compared with water (Holzbeierlein and Smith, 2000). Introduction of bipolar electroresection is reported to allow TUR in saline and to minimize the risk of the obturator reflex, which can predispose to bladder perforation (Shiozawa et al, 2002; Miki et al, 2003). The use of general anesthesia with muscle-paralyzing agents also prevents obturator reflex, although I find this rarely necessary. This can also be accomplished by direct injection of 20 to 30 mL of local anesthetic (lidocaine) into the obturator nerve and its canal, but few centers have experience with this (Khorrami et al, 2010).

Resection of diverticular tumors presents significant risk of bladder wall perforation, and accurate staging is difficult to achieve in this circumstance because the underlying detrusor is absent. Invasion beyond the diverticular lamina propria immediately involves perivesical fat (stage T3a by definition). Resection in diverticula almost inevitably leads to perforation. **Low-grade diverticular tumors are best treated with a combination of resection and fulguration of the base.** Conservative resection can be followed with subsequent repeat resection if the final pathologic interpretation is high grade. High-grade tumors require adequate sampling of the tumor base, often including perivesical fat, despite the near certainty of bladder perforation. An indwelling catheter usually allows healing within a few days. **Partial or radical cystectomy should be strongly considered for high-grade diverticular lesions.**

Anterior wall tumors and tumors at the dome in patients with large bladders can be difficult to reach. Minimal bladder filling combined with manual compression of the lower abdominal wall to bring the tumor toward the resectoscope facilitates removal. Modern resectoscopes are long enough to reach the entirety of most bladders; creation of a temporary perineal urethrostomy offers deeper access but is rarely necessary except in the obese patient with an inaccessible tumor. Digital manipulation through the rectum or vagina can occasionally facilitate resection.

Care must be taken during resection near the ureteral orifice to prevent obstruction from scarring after fulguration. **Pure cutting current causes minimal scarring and may be safely performed, including resection of the orifice if necessary.** Resection of the intramural ureter can sometimes lead to complete eradication of the tumor but risks reflux of malignant cells. The clinical implications of this are unclear (Palou et al, 1992).

Alternatively, **small tumors may be resected using the cold-cup biopsy forceps alone.** This is especially helpful in elderly women, who are predisposed to perforation owing to their thin-walled bladders. If perforation occurs, the cup causes a smaller hole than does the cutting loop. A Bugbee electrode facilitates hemostasis. **A successful cauterization method involves placing the Bugbee electrode inside the biopsy site with the bladder under minimal distention.** When the electrode touches the cut surface of the biopsy crater, the electrical energy will cause the mucosa to contract around the electrode unless the bladder is full. Light irrigation clears the area of blood and vaporization bubbles created during fulguration. Visualizing a small (1 to 2 mm) ring of white coagulation confirms hemostasis and yields less damage to the bladder than that occurring when the biopsy area is "painted" with cautery. Removing the electrode from the site before discontinuing the energy current lessens the chance of pulling the fresh clot off as the Bugbee electrode separates from the urothelium.

If a tumor appears to be muscle invasive, biopsies of the borders and base to establish invasion may be performed in lieu of complete resection, because cystectomy will likely follow based on confirmatory biopsies. Failure to demonstrate invasion necessitates repeat resection unless the decision is made to proceed to cystectomy based on factors other than muscle invasion.

The necessity of obtaining detrusor muscle in the surgical specimen is widely taught but not established in benefit. For example, the potential for muscle invasion for low-grade disease is essentially nonexistent, so a transmural biopsy offers little potential benefit compared with the risk of bladder perforation incurred. If a grading miscalculation occurs, a repeat TUR with intentional procurement

of underlying detrusor is routine practice as described later and is included in American Urological Association (AUA) guidelines (Hall et al, 2007).

Complications of Transurethral Resection of Bladder Tumor and Bladder Biopsy

Minor bleeding and irritative symptoms are common side effects in the immediate postoperative period. The major complications of uncontrolled hematuria and clinical bladder perforation occur in fewer than 5% of cases, although a majority of patients will exhibit contrast agent extravasation indicative of minor perforation if cystography is performed. The incidence of perforation can be reduced by attention to technical details, avoiding overdistention of the bladder, and using anesthetic paralysis during the resection of significant lateral wall lesions to lessen an obturator reflex response. Moreover, large, bulky tumors and those that appear to be muscle invasive are often best resected in a staged manner because it is believed that repeat resection can more safely remove residual tumor if indicated.

The vast majority of perforations are extraperitoneal, but intraperitoneal rupture is possible when tumors are resected at the dome (Collado et al, 2000). The risk of tumor seeding from perforation appears to be low (Balbay et al, 2005). Anecdotal reports have identified extravesical recurrences after perforation, theoretically caused by seeding (Mydlo et al, 1999). It has been suggested that the risk of tumor seeding is higher in patients who undergo surgical repair, but this may be related to patient selection because only serious intraperitoneal perforations are likely to be managed in this manner (Mydlo et al, 1999; Skolarikos et al, 2005).

Management of extraperitoneal perforation by prolonged urethral catheter drainage is usually possible. Intraperitoneal perforation is less likely to close spontaneously and usually requires open or laparoscopic surgical repair. Decisions for surgical correction should be made on the basis of the extent of the perforation and the clinical status of the patient.

TUR syndrome from fluid absorption is uncommon and managed in the same manner as during transurethral resection of the prostate (TURP).

As long as resection of the ureteral orifice is performed with pure cutting current, scarring is minimal and obstruction unlikely. Cystoscopy to visualize efflux, which is occasionally aided by intravenous administration of indigo carmine or methylene blue or retrograde ureteropyelography, can determine presence or absence of obstruction. If fluorescence cystoscopy is in use as described later, the urine jet will fluoresce brightly as well. If the orifice is resected or cautery is used nearby, renal ultrasonography in the postoperative period can identify asymptomatic obstruction. Balloon dilation of the orifice or endoscopic incision can relieve obstruction, but failure to respond will rarely necessitate reimplantation (Chang et al, 1989).

Repeat Transurethral Resection of Bladder Tumor

Complete tumor removal is not always possible, whether as a result of excessive tumor volume, anatomic inaccessibility, medical instability requiring premature cessation, or risk of perforation. However, even in the absence of these circumstances **repeat TUR is often indicated if high-grade tumor is identified.** When repeat TUR is performed within several days to several weeks of the original resection, residual tumor is identified at the site of the initial resection at least 40% of the time (Klan et al, 1991; Mersdorf et al, 1998; Vogeli et al, 1998). In a review, Miladi and coworkers (2003) found that a second TURBT detected residual tumor in 26% to 83% of patients and corrected clinical staging errors in half of those patients. The potential for understaging high-risk disease ranged from 18% to 37% (Amling et al, 1994).

Repeat TURBT is usually appropriate in the evaluation of T1 tumors because a repeat TUR can demonstrate worse prognostic findings in up to 25% of specimens (Schwaibold et al, 2000). This

is especially likely if no muscle is identified on initial pathology, which can occur in almost half of cases. The Vanderbilt University group reported a 64% risk of understaging T1 lesions when muscle was absent, compared with 30% when muscle was present in the specimen (Dutta et al, 2001). Herr (1999) reported that a second resection changed treatment in one third of patients. It is important to note that survival was 63% in patients who underwent a second TURBT versus 40% for those who did not in a German observational study (Grimm et al, 2003), and recurrences appear to be lower after repeat TUR (Sfakianos et al, 2014). The efficacy of bacille Calmette-Guérin (BCG) in preventing progression appears to be higher in patients with high-grade papillary tumors and CIS if a restaging TURBT was performed before instillation of BCG (Herr, 2005).

Repeat resection is helpful in the setting of a second opinion unless clear evidence of muscle invasion is identified on the initial resection, especially if the outside pathology slides are not available for review. Alternatively, subspecialty pathologic reinterpretation at the time of second opinion can yield information potentially leading to a change in management in almost one third of patients (Lee et al, 2010).

The consensus is that patients with pT1 and many high-grade Ta tumors merit repeat resection. There is no consensus on timing, but most authors recommend 1 to 6 weeks after the initial resection (Nieder et al, 2005).

Role of Random or Additional Biopsies

Biopsies of any suspicious areas are an important part of a complete evaluation. Cold-cup biopsies may not provide as much information regarding muscular invasion but provide tissue sampling without cautery artifact that can interfere with pathologic interpretation (Soloway et al, 1978; Smith, 1986).

The use of random biopsies to identify CIS in otherwise normal-appearing mucosa remains controversial. May and colleagues (2003) performed random biopsies in high-risk patients and found that the results were positive in 12.4% and altered treatment in 7%, including 14 of 1033 patients in whom the only positive tissue was in the random biopsy specimen, not the primary resected tumor. However, even when velvety red patches were sampled, only 11.9% of biopsy specimens were positive in one report (Swinin et al, 2004). A European Organisation for Research and Treatment of Cancer (EORTC) retrospective review found that 10% of random biopsy specimens were positive (3.5% CIS) and concluded that such biopsies were not warranted (van der Meijden et al, 1999). Fujimoto and colleagues (2003) prospectively evaluated the role of random biopsies of normal-appearing urothelium and found cancer in only 8 of 100 biopsy samples, 5 of which were CIS. They concluded that random biopsies are indicated only in the setting of multiple tumors or positive cytology. The current consensus is that random biopsies are not indicated in low-risk patients (i.e., those with low-grade papillary tumors and negative cytology), but there remains no consensus with regard to patients with high-grade disease, and most urologists perform random biopsies in this setting.

Prostatic urethral biopsy using the cutting loop may be performed, especially if neobladder creation is anticipated for high-risk disease, but bleeding may be more common (Holzbeierlein and Smith, 2000). The additional value of the information obtained from cold-cup and urethral biopsies must be weighed against the theoretic risk that biopsies provide an exposed bed to aid tumor implantation (Kiemeneij et al, 1994; Yamada et al, 1996). Traditional teaching is that TURP and TURBT of a low-grade bladder tumor may be performed at the same setting but that resection of a high-grade bladder tumor should not be performed coincident to TURP to avoid tumor seeding and possible intravasation of tumor cells likely to metastasize. Despite anecdotal reports of low-grade tumors implanting in the prostatic urethra after simultaneous resection, this risk appears to be small (Tsivian et al, 2003).

Laser Therapy

Laser coagulation allows minimally invasive ablation of tumors up to 2.5 cm in size. The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has the best properties for use in bladder cancer. Lesions can be coagulated until nonviable through protein denaturation using a straight or 90-degree noncontact "free beam" laser using power output of up to 60 W. The most significant complication of laser therapy is forward scatter of laser energy to adjacent structures, resulting in perforation of a hollow, viscous organ such as overlying bowel. This is rare but most commonly occurs with the Nd:YAG laser because of its deeper tissue penetration than with holmium(Ho):YAG and potassium titanyl phosphate (KTP) lasers (Smith, 1986). Unless higher energy is necessary for a very large tumor, limiting energy to 35 W precludes exceeding 60°C on the outer bladder wall, minimizing the risk of perforation (Hofstetter et al, 1994). The most efficient delivery appears to be an end-fire noncontact fiber with a 5- to 15-degree angle of divergence, which allows variable penetration depth up to 5 mm (Smith and Landau, 1989; Holzbeierlein and Smith, 2000). Treatment should be under direct visualization and should discontinue as soon as protein denaturation is evident by the white appearance of the treated tissue. Persistence after this occurs risks extravesical injury.

Laser therapy can be more expensive than resection owing to the cost of laser fibers, but bleeding is negligible and there is no risk of obturator reflex. Small lesions can be treated easily using intravesical anesthesia. Because there is no tissue available for pathologic inspection, the optimal candidate for laser therapy is the patient with recurrent, low-grade lesions whose biology is already known. Additional information regarding tumor grade may be obtained with a cold-cup biopsy if necessary. Some reports suggest lower recurrence rates using laser compared with TURBT, but this remains inconclusive (Smith et al, 1983; Malloy et al, 1984; Beisland and Seland, 1986; Smith, 1986; Beer et al, 1989).

Office-Based Endoscopic Management

Many patients with small (typically <0.5 mL, but up to 1 cm diameter in experienced hands), low-grade recurrences can be managed safely in the office setting with use of diathermy or laser ablation (Donat et al, 2004). Instillation of viscous or injectable 1% to 2% lidocaine through a catheter and a dwelling time of 15 to 30 minutes yields satisfactory mucosal analgesia, although pain with fulguration of 1- to 5-mm tumors is often acceptable without analgesia. A prior tissue diagnosis and a negative cytology for the initial tumor occurrence are mandatory to determine whether the tumor is of high or low grade.

In addition, many small, low-grade tumors can be safely observed until they exhibit significant growth because of the minimal risk of progression (Soloway et al, 2003; Pruthi et al, 2008).

Fluorescence Cystoscopy and Narrow Band Imaging

Endoscopically, urologists can suspect malignancy only on the basis of the presence of visible changes such as tumors or "red spots." As noted, random biopsy of normal-appearing areas occasionally detects unsuspected malignancy, usually CIS. Conversely, a multicenter study found that 37% of the biopsies performed on the basis of suspicious endoscopic findings resulted in a false-negative biopsy, emphasizing the subjectivity and attendant false-positive and false-negative rates of cystoscopy (Riedl et al, 2001). The imperfect sensitivity of cystoscopy potentially explains the high rate of cancer recurrence soon after complete removal of all visible tumors (tumor cell implantation also contributing, as described earlier). It is likely that cancer was already present but not visible at the time of resection and simply became visible at follow-up when it became morphologically abnormal enough to differentiate from adjacent normal urothelium.

Photoactive porphyrins accumulate preferentially in neoplastic tissue. Under blue light they emit red fluorescence, which can help in the diagnosis of indiscernible malignant lesions. Intravesical application of 5-aminolevulinic acid (5-ALA), a precursor of photoactive porphyrin, avoids residual systemic photosensitization (Lange et al, 1999).

When this technology is used, both small papillary tumors and almost one third more cases of CIS overlooked on cystoscopy are identified (Jichlinski et al, 2003; Schmidbauer et al, 2004; Fradet et al, 2007). Of all tumors, 96% were detected with hexaminolevulinate (HAL) imaging compared with 77% with standard cystoscopy. Detection was improved for CIS (95% vs. 68%), and papillary tumors (96% vs. 85%) (Jocham et al, 2005). The clinical impact of improved tumor detection seems intuitive, and prospective evidence has shown that this decreases recurrence rates in patients who undergo HAL fluorescence cystoscopy compared with controls (Filbeck et al, 2003; Denzinger et al, 2007; Grossman, 2007; Rink et al, 2013). This impact appears to persist for at least 4 years. There may be an impact on progression, although the study was underpowered to prove this trend (Stenzl et al, 2010) (Figs. 93-6 and 93-7).

Narrow band imaging (NBI) is an optical image enhancement technology intended to improve the visibility of blood vessels

inherent to neoplastic processes. NBI light is composed of two specific wavelengths that are absorbed by hemoglobin; 415-nm light penetrates only the superficial mucosal layers, whereas 540-nm light penetrates more deeply. The combination allows improved visualization of tumors. The clinical impact of this remains under investigation, and no studies have been performed to date regarding recurrence or progression (Liu et al, 2012).

KEY POINTS: ENDOSCOPIC SURGICAL MANAGEMENT

- TURBT is performed both to remove all visible tumors and to provide specimens for pathologic examination to determine stage and grade.
- Repeat resection within 1 to 6 weeks is usually indicated in patients with high-grade disease, especially if no muscle was present in the initial TURBT.
- All suspicious lesions should be sampled, but random biopsies are not required in low-risk patients.
- Office-based fulguration and observation may be applied to certain low-risk patients.
- Fluorescence cystoscopy with 5-ALA derivatives improves the ability to visualize inconspicuous tumors and reduces recurrence rates after TUR.

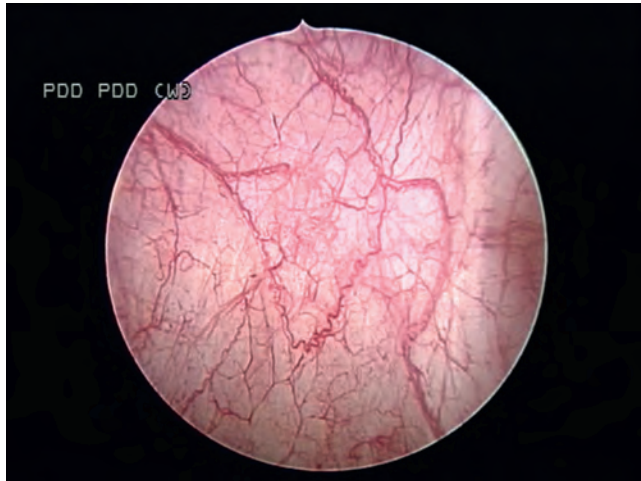


Figure 93-6. White light microscopy reveals normal-appearing mucosa. (Courtesy H. Barton Grossman, MD.)

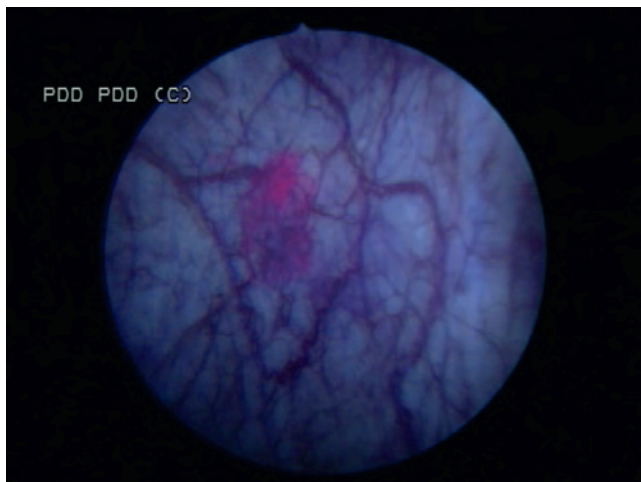


Figure 93-7. Blue light microscopy reveals accumulation of hexaminolevulinate in the same area proven subsequently to contain a small focus of carcinoma in situ. (Courtesy H. Barton Grossman, MD.)

PERIOPERATIVE INTRAVESICAL THERAPY TO PREVENT TUMOR IMPLANTATION

It is believed that tumor cell implantation immediately after resection is responsible for many early recurrences, and this has been used to explain the observation that initial tumors are most commonly found on the floor and lower sidewalls of the bladder, whereas recurrences are often located near the dome as a result of “flotation” (Heney et al, 1981). Thus, intravesical chemotherapy to kill such cells before implantation has been used for decades (Zincke et al, 1983; Klan et al, 1991).

Mitomycin C (MMC) appears to be the most effective adjuvant intravesical chemotherapeutic agent perioperatively, although epirubicin is used in Europe and direct comparative studies are lacking (Witjes and Hendricksen, 2008). Consistent with its proposed mechanism of action to prevent tumor cell implantation, a single dose administered within 6 hours lessens recurrence rates, whereas a dose 24 hours later does not (Isaka et al, 1992; Oosterlinck et al, 1993; Sekine et al, 1994; Solsona et al, 1999; Duque and Loughlin, 2000), and maintenance therapy does not reduce the risk further (Bouffieux et al, 1995; Tolley et al, 1996). Nevertheless, level 1 data demonstrate clearly that single-dose MMC or epirubicin immediately after resection reduces tumor recurrence, particularly for the initial presentation of a solitary papillary low-grade tumor (Box 93-1).

A meta-analysis found that low-risk patients at a median follow-up of 3.4 years experience a drop in the odds of recurrence from 48.4% to 36.7%. Patients with multiple tumors experience a 56% reduction in the odds of recurrence. MMC, epirubicin, and pirarubicin all significantly lessened the recurrence of both single and multiple tumors. Thiotepa did not show the same benefit, but data were limited and some studies used dilute strengths (Sylvester et al, 2004). The number needed to treat (NNT) to prevent one recurrence in the meta-analysis was 8.5, so some authors have suggested that intravesical chemotherapy reduces overall cost of care by reducing the need for secondary resections. However, subsequent studies have shown that the tumors prevented are primarily smaller tumors that are often treated in the office or ambulatory surgery setting (Berrum-Svennung et al, 2008). In addition, the benefit appears limited to patients with low risk of recurrence (Gudjonsson et al, 2009), so the economic impact regarding recurrences remains controversial if recurrences are treated in any manner other than inpatient care (Rao and Jones, 2009; Lee et al, 2012).

BOX 93-1 Successful Perioperative Administration of Intravesical Chemotherapy

1. Include intent to administer perioperative chemotherapy (and agent) on actual operative schedule.
2. Contact pharmacy before surgery to have medication available. A written prescription may be required.
3. After resection, confirm absence of clinical perforation. Place three-way catheter into bladder while patient is still in operating room. Attach inflow port to saline infusion bag and clamp inflow.
4. Administer chemotherapeutic agent through catheter outflow port in recovery room within 6 hours of operation, and clamp outflow tubing with hemostat to allow retention.
5. Give order for outflow tubing to be opened 1 hour after administration and for irrigation, to be opened to gravity drainage for next 30 to 60 minutes.
6. Remove Foley catheter and discard in biohazard container.
7. Wear gloves.

Modified from O'Donnell MA. Practical applications of intravesical chemotherapy and immunotherapy in high-risk patients with superficial bladder cancer. *Urol Clin North Am* 2005;32:121–31.

The use of perioperative intravesical therapy is widespread in Europe but has achieved limited adoption in the United States (Madeb et al, 2009) potentially because of the cost, complexity, and potential for side effects, combined with the fact that it has not been shown to have adequate impact for recurrent, multiple, or high-grade tumors (Sylvester et al, 2004).

Although local irritative symptoms are the most common complications of postoperative instillation, serious sequelae and rare deaths have occurred, especially in patients with perforation during resection (Oddens et al, 2004). Other reported conditions associated with intravesical chemotherapy (with perioperative or multidose regimens) include chemical cystitis, cutaneous desquamation, decreased bladder capacity as a result of contractures, calcified eschars, and complications or added difficulty of subsequent cystectomy (Doherty et al, 1999; Cliff et al, 2000; Nieuwenhuijzen et al, 2003; Oddens et al, 2004; Shapiro et al, 2006). Chemotherapy should be withheld in patients with extensive resection or when there is concern about perforation.

BCG can never be safely administered immediately after TUR because the risk of bacterial sepsis and death is high.

KEY POINTS: PERIOPERATIVE INTRAVESICAL THERAPY TO PREVENT TUMOR IMPLANTATION

- Single-dose intravesical chemotherapy administered within 6 hours of resection reduces recurrence of low-risk tumors, with significant impact in the setting of initial presentation of solitary low-grade papillary tumors.
- The incremental benefit in patients with recurrent or multiple tumors is limited.
- No benefit has been found in patients with high-grade disease.

IMMUNOTHERAPY**Bacille Calmette-Guérin**

BCG is an attenuated mycobacterium developed as a vaccine for tuberculosis that has demonstrated antitumor activity in several

different cancers including UC (Morales et al, 1976). The original regimen described by Morales included a percutaneous dose, which was discontinued after success with a similar intravesical regimen by Brosman (1982).

BCG powdered vaccine is reconstituted with 50 mL of saline and should be administered through a urethral catheter under gravity. Treatments are typically begun 2 to 4 weeks after tumor resection, allowing time for re-epithelialization, which minimizes the potential for intravasation of live bacteria (Lamm et al, 1992). For the same reason, a urinalysis is usually performed immediately before instillation to further confirm absence of infection or significant bleeding to decrease the likelihood of systemic uptake of BCG. In the event of a traumatic catheterization, the treatment should be delayed for several days to 1 week, depending on the extent of injury. Active urinary tract infection is often considered an indication to delay treatment until it has been managed, but recent publications question the need to avoid BCG in the presence of asymptomatic bacteriuria (Herr, 2012). After instillation, the patient should retain the solution for at least 2 hours. Some clinicians have advocated that the patient turn from side to side to bathe the entire urothelium, but there is no scientific support for this practice. Fluid, diuretic, and caffeine restriction before instillation limits dilution of the agent by urine and facilitates adequate retention of the agent for 2 hours (Lamm et al, 2000b). Patients are usually instructed to clean the toilet with bleach, although there is no demonstrable risk of close contact infection.

Mechanism of Action

Intravesical immunotherapy results in a massive local immune response characterized by induced expression of cytokines in the urine and bladder wall and by an influx of granulocytes and mononuclear and dendritic cells (Shen et al, 2008). The initial step appears to be direct binding to fibronectin within the bladder wall, subsequently leading to direct stimulation of cell-based immunologic response and an antiangiogenic state. Numerous cytokines involved in the initiation or maintenance of inflammatory processes including tumor necrosis factor- α (TNF- α), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon- γ (IFN- γ), and interleukin-1 (IL-1), IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, and IL-18 have been detected in the urine of patients treated with intravesical BCG and other immunostimulatory agents. The observed pattern of cytokine induction with preferential upregulation of IFN- γ , IL-2, and IL-12 reflects induction of a T-helper type-1 (Th1) response. This immunologic response activates cell-mediated cytotoxic mechanisms that are believed to underlie the efficacy of BCG and other agents in the prevention of recurrence and progression (Bohle and Brandau, 2003). BCG may concomitantly stimulate IL-10, resulting in the suppressive Th2 response. Overall, response to intravesical immunotherapy may be limited if a patient has an immunosuppressive disease or by advanced age (Joudi et al, 2006a, 2006b).

Bacille Calmette-Guérin Treatment of Carcinoma in Situ

American urologists use BCG by a 2:1 margin compared with intravesical adjuvant or maintenance chemotherapy (e.g., doxorubicin hydrochloride [Adriamycin], gemcitabine, thiotepa), whereas European urologists favor chemotherapy. BCG is approved for this indication by the U.S. Food and Drug Administration (FDA). Before the adoption of BCG intravesical therapy, CIS reportedly progressed at an average rate of 7% per year (Zinke et al, 1985). The initial tumor-free response rate is as high as 84% (Brosman, 1982; De Jager et al, 1991; Hudson and Herr, 1995; Lamm et al, 2000a, 2000b, 2000c). Approximately 50% of patients experience a durable response for a median period of 4 years. Over a 10-year period, approximately 30% of patients remain free of tumor progression or recurrence, so close follow-up is mandatory. The majority of these occur within the first 5 years (Herr et al, 1992). Herr and coworkers (1989) reported progression in

19% of initial responders at 5 years but found the rate to be 95% in nonresponders—findings confirmed by other investigators (Coplen et al, 1990; Harland et al, 1992). The AUA guidelines panel supported BCG as the preferred initial treatment option for CIS (Hall et al, 2007).

BCG has gained a preeminent role in North America on the basis of higher efficacy reports compared with intravesical chemotherapy, despite greater morbidity than chemotherapy (O'Donnell, 2007). In more than 600 patients, there was a 68% complete response rate to BCG and a 49% complete response rate to chemotherapy. In responders, 68% of patients treated with BCG remained free of disease as compared with 47% of patients receiving chemotherapy, on the basis of a median follow-up of 3.75 years. The overall disease-free rates were 51% and 27%, respectively (Sylvester et al, 2005).

Bacille Calmette-Guérin Treatment of Residual Tumor

Intravesical BCG can effectively treat residual papillary lesions but should not be used as a substitute for surgical resection. Investigators have demonstrated a nearly 60% response by residual tumor with intravesical BCG alone (Brosman, 1982; Schellhammer et al, 1986; Coplen et al, 1990).

Carcinoma of the mucosa or the superficial ducts of the prostate can be adequately treated by BCG with a 50% tumor-free rate. A limited TURP or fulguration can be effective in decreasing tumor burden and facilitating exposure of the prostate surface to BCG administration (Bretton et al, 1990; Schellhammer et al, 1995).

Bacille Calmette-Guérin Prophylaxis to Prevent Recurrence

Early single-center studies demonstrated an advantage in decreased tumor recurrence of approximately 30% when a 6-week course of BCG was administered after recovery from TURBT (Brosman, 1982; Morales et al, 1992). In several larger series, tumor recurrence after TURBT was reduced by 20% to 65%, for an average of approximately 40% (Pagano et al, 1991a, 1991b; Herr et al, 1992; Melekos et al, 1993; Krege et al, 1996). A meta-analysis of 2000 patients with Ta, T1, and/or CIS disease found that patients receiving maintenance BCG had a statistically decreased rate of recurrence compared with those receiving induction therapy alone (Han and Pan, 2006). A subsequent reevaluation of the published data concluded that 3 years of maintenance therapy was supported by the literature but that patients with intermediate-risk disease may be equally managed with 1 year of maintenance (Ehdaie et al, 2013).

The efficacy of BCG after TURBT for high-risk papillary disease has been demonstrated in several series of T1 lesions, with recurrence rates of 16% to 40% and progression rates of 4.4% to 40%, a substantial improvement compared with TUR alone (Cookson and Sarosdy, 1992; Pansadoro et al, 1995; Herr, 1997; Jimenez-Cruz et al, 1997; Gohji et al, 1999; Hurler et al, 1999a, 1999b). Tumor multiplicity and associated CIS were associated with increased risk of progression. Substaging lesions on the basis of the presence or absence of muscularis mucosae invasion in a series of 49 patients did not improve prediction of recurrence (69% vs. 65%) or progression (22% vs. 29%) after BCG therapy (Kondylis et al, 2000).

Impact of Bacille Calmette-Guérin on Progression

Although reports of the impact of BCG on tumor recurrence are compelling, the greater need is the potential for impact on progression. In 403 patients with CIS, BCG reduced the risk of progression by 35% compared with intravesical chemotherapy (Sylvester et al, 2002).

In a randomized trial of 86 patients with high-risk superficial disease, Herr and colleagues (1988) demonstrated a greater delay in interval progression for BCG patients versus TUR controls. In addition, the cystectomy rate was significantly decreased for CIS patients treated with BCG (11% vs. 55% for controls), as was the time to cystectomy. However, only 27% of patients were alive with

an intact functioning bladder after follow-up over 10 to 15 years, so this apparent advantage is temporary in many cases (Cookson et al, 1997). Available data suggest that BCG can delay progression of high-risk bladder cancer, yet the long-term survival advantage is not fully defined.

Nevertheless, two meta-analyses have concluded that BCG reduces the risk of progression. Progression at 2.5 years' median follow-up was reduced by 27% (9.8% for BCG vs. 13.8% for non-BCG) in one (Sylvester et al, 2002) and by 23% (7.7% for BCG vs. 9.4% for MMC) at 26-month median follow-up in another analysis (Bohle and Bock, 2004). In both cases the superior results with BCG were seen only in trials using BCG maintenance therapy. In contrast, no chemotherapy trials have achieved a significant reduction in progression (Grossman et al, 2008).

The AUA guidelines panel concluded that BCG appeared likely to reduce progression (Hall et al, 2007).

Determining Optimum Bacille Calmette-Guérin Treatment Schedule

The optimal treatment schedule and dose for BCG have not been established (Herr et al, 2011). Morales wrote in the reply to an editorial comment to his landmark article, "This regimen is arbitrary, and may be modified in the future as additional data become available" (Morales et al, 1976). In reality, several studies suggest that a 6-week induction course alone is insufficient to obtain an optimal response in many patients and that maintenance therapy is requisite (Lamm et al, 2000a, 2000b, 2000c; Palou et al, 2001).

One of the enduring urban myths in urology is the story of the initial work of Dr. Alvaro Morales with BCG. Although the rumor is usually stated that he chose the dosage regimen based on the fact that the drug is shipped in a "six-pack," he relates that there is more to the story: "A contemporary abstract had indicated that BCG was ineffective for bladder cancer. However, from our experience and that of others, we knew that at least a 3-week period of immunizations was needed for mounting a delayed hypersensitivity reaction. The intradermal administration provided not only assurance of an enhanced systemic recognition, but also an inexpensive and readily available marker of immune competence. To this day, I remain convinced that eliminating the simultaneous transdermal administration is very convenient for patients and physicians but is not as effective. It was our impression that the skin reactions reached by weeks 4 to 5 were not further enhanced by more BCG. The Frappier labs provided us with boxes of six vials. We thus—for better or worse—decided to stop treatment at 6 weeks, assuming that what was seen on the skin was occurring on the bladder mucosa. Fortunately, that turned out to be true. Bohle and others reported years later that 6 weeks were ideal for maximum response to BCG, although we now know that maintenance dosing enhances response even further."

The average additional response to a second induction course is 25% in those patients treated for prophylaxis and 30% in CIS patients (Haaff et al, 1986; Kavoussi et al, 1988; Bretton et al, 1990; Coplen et al, 1990; Sylvester et al, 2002; Bohle and Bock, 2004). However, additional courses of BCG to treat refractory patients after a second 6-week course are accompanied by a significant risk of tumor progression in 20% to 50% of patients (Nadler et al, 1994). Catalona and colleagues (1987) reported roughly a 7% actuarial risk of progression with every additional course of BCG therapy. Response to BCG at 6 months can be used as a predictor of prognosis, with the number of patients developing progressive disease being significantly higher among nonresponders (Orsola et al, 1998).

The Southwest Oncology Group (SWOG) reported the most significant impact of maintenance therapy. Patients received a 6-week induction course followed by three weekly instillations at 3 and 6 months and every 6 months thereafter for 3 years. Estimated median recurrence-free survival was 76.8 months in the maintenance arm and 35.7 months in the control arm ($P = .0001$). Average recurrence-free survival was 111.5 months in the

control arm and was not able to be estimated in the maintenance arm ($P = .04$). Overall 5-year survival was 78% in the control arm and 83% in the maintenance arm. No toxicities above grade 3 were observed, yet **only 16% of patients tolerated the full dose-schedule regimen**. Two thirds of the patients who stopped BCG because of side effects did so in the first 6 months, suggesting that the side effects do not increase appreciably with additional time on therapy. An interpretation that the intended full course of maintenance therapy cannot be accomplished in most patients because of side effects is misleading. **Owing to the fact that the treatment group fared better despite most patients having failed to complete the full course of therapy, the maximum benefit may have been achieved earlier. Shorter maintenance schedules and reduced dosages may accomplish the same results with less toxicity** (Lamm et al, 2000a).

For high-grade T1 lesions or CIS, maintenance therapy has proven superior in multiple studies (Palou et al, 2001). **The determination of whether the optimal treatment schedule should be as described in the SWOG study, monthly, or on some other schedule remains undefined, and optimal duration of a monthly maintenance schedule, if chosen, is unknown** (Lamm et al, 2000a, 2000b, 2000c; O'Donnell, 2005).

Several investigators have evaluated the potential for BCG dose reduction (Morales et al, 1992; Melekos et al, 1993; Martinez-Pineiro et al, 1995; Pagano et al, 1995). In general, a decrease in toxicity with no statistical difference in efficacy has been noted in small series (Pagano et al, 1991b; Mack and Frick, 1995; Hurler et al, 1996), although multifocal and high-grade tumors may respond better to full dosage (Martinez-Pineiro et al, 2002). Some studies have shown an upregulation of the Th1 response with a lower dose of BCG. Lengthening of the instillation interval may decrease side effects without loss of efficacy (Bassi et al, 2000). Studies in Europe, where BCG inoculation for tuberculosis is more common than in North America, suggest that the dose may be safely reduced by half (Martinez-Pineiro et al, 2002). The difference in response to doing so in immunologically naive North Americans is unknown, but Morales and colleagues (1992) found a significant decrease in response rates (67% vs. 37%), especially for patients with CIS in combination with papillary tumors treated with the reduced dose.

Antibiotic therapy may have a beneficial effect in treating or preventing systemic side effects of BCG therapy, yet it may also inhibit the effectiveness of BCG therapy if it is given routinely for urinary tract prophylaxis during a course of BCG therapy (Durek et al, 1999a, 1999b). **Quinolones in particular may affect the viability of BCG and should be avoided if possible during the course of BCG treatments** (Durek et al, 1999b) (Boxes 93-2 and 93-3).

Interferon

IFNs are glycoproteins produced in response to antigenic stimuli. These agents have multiple antitumor activities including inhibition of nucleotide synthesis; upregulation of tumor antigens, anti-angiogenic properties; and stimulation of cytokine release with enhanced T- and B-cell activation, as well as enhanced natural killer cell activity (Naitoh et al, 1999). Among several subtypes, IFN- α has been the most extensively studied. It is most active in doses of at least 100 million units, although optimal dose and administration schedule have yet to be determined (Torti et al, 1988; Belldgrun et al, 1998).

IFN as a solitary agent is more expensive and less effective than BCG or intravesical chemotherapy in eradicating residual disease, preventing recurrence of papillary disease, and treating CIS (20% to 43% complete response). Its long-term efficacy for CIS is less than 15% (Belldgrun et al, 1998). A randomized trial demonstrated CIS responses from 5% at low doses (10 million units) to as high as 43% at high doses (100 million units) (Torti et al, 1988). As a prophylactic agent, IFN alone demonstrated recurrence rates that were inferior in general to those of BCG alone (from 60% to 16%) (Glashan, 1990; Kalble et al, 1994). It has demonstrated limited

BOX 93-2 Contraindications to Bacillus Calmette-Guérin (BCG) Therapy

ABSOLUTE CONTRAINDICATIONS

Immunosuppressed and immunocompromised patients*
Immediately after transurethral resection on the basis of the risk of intravasation and septic death
Personal history of BCG sepsis
Gross hematuria (intravasation risk)
Traumatic catheterization (intravasation risk)
Total incontinence (patient will not retain agent)

RELATIVE CONTRAINDICATIONS

Urinary tract infection (intravasation risk)
Liver disease (precludes treatment with isoniazid if sepsis occurs)
Personal history of tuberculosis (risk theorized but unknown)
Poor overall performance status
Advanced age

NO OR INSUFFICIENT DATA ON POTENTIAL CONTRAINDICATIONS

Patients with prosthetic materials have not been shown to have increased risk of infectious or other complications in limited literature (Rosevear et al, 2010)
Ureteral reflux
Anti-tumor necrosis factor medications (theoretically predispose to BCG sepsis)

*Recent small series suggest this may not be an absolute contraindication (Herr, 2012).

From Ehlers S. Why does tumor necrosis factor targeted therapy reactivate tuberculosis? *J Rheumatol* (Suppl) 2005;74:35-9.

activity against T1 tumors (Malmstrom, 2001). However, it can occasionally be effective in patients in whom BCG has failed (15% to 20% complete response; see later).

IFN- α has also been studied in a combination treatment regimen with either chemotherapy or BCG (Bercovich et al, 1995; Stricker et al, 1996). There appeared to be additive effects with either epirubicin or MMC. Several trials investigated the combination of BCG and IFN and suggested the potential superiority of the combination or the possibility of decreasing the dose of BCG, which may reduce side effects. Initial pioneering work by O'Donnell and colleagues (1999) reported a 63% disease-free rate at 12 months and 53% at 24 months with use of combination therapy. In a larger trial of 1000 patients, 231 patients with CIS were evaluated. In those CIS patients in whom an induction course of BCG failed, the combination of low-dose BCG and IFN produced a 45% durable response at 2 years. However, in those patients who had CIS and were BCG naive, the BCG and IFN combination treatment resulted in 59% disease-free status at 24 months (Joudi et al, 2006a). Overall, patients in whom BCG alone failed within 12 months had a poor response to combination therapy. Of the non-responders to combination BCG and IFN, the majority of patients who experienced treatment failure with recurrence did so within 4 months of initial treatment (Grossman et al, 2008).

Investigational Immunotherapeutic Agents

A number of novel agents have shown potential, but none has reached clinical practice. Keyhole limpet hemocyanin (KLH) from the hemolymph of the mollusk *Megathura crenulata* is a nonspecific immune stimulant whose potential effectiveness in UC was identified serendipitously (Olsson et al, 1974; Jurincic et al, 1989). Recent work suggests continued promise for this agent, but no

BOX 93-3 Cleveland Clinic Approach to Management of Bacillus Calmette-Guérin (BCG) Toxicity**GRADE 1: MODERATE SYMPTOMS <48 HOURS**

Mild or moderate irritative voiding symptoms, mild hematuria, fever <38.5°C.

Assessment

Possible urine culture to rule out bacterial urinary tract infection.

Symptom Management

Anticholinergics, topical antispasmodics (phenazopyridine), analgesics, nonsteroidal anti-inflammatory drugs.

(Asymptomatic prostatic granulomas that occur after BCG therapy can occasionally mimic prostate cancer clinically and/or radiographically. There is no evidence to support treatment in this setting [Suzuki et al, 2013].)

GRADE 2: SEVERE SYMPTOMS AND/OR >48 HOURS

Severe irritative voiding symptoms, hematuria, or symptoms lasting >48 hr

All maneuvers for grade 1, plus the following:

Assessment

Urine culture, chest radiograph, liver function tests.

Management

Consult immediately with physician experienced in management of mycobacterial infections and complications.

Consider dose reduction to one half to one third of dose when instillations resume.

Treat culture results as appropriate.

Antimicrobial Agents

Administer isoniazid and rifampin, 300 mg/day and 600 mg/day, orally until symptom resolution.

Do not use monotherapy.

Observe for rifampin drug-drug interactions (e.g., warfarin).

GRADE 3: SERIOUS COMPLICATIONS (HEMODYNAMIC CHANGES, PERSISTENT HIGH-GRADE FEVER)**Allergic Reactions (Joint Pain, Rash)**

Perform all maneuvers described for grades 1 and 2, plus the following:

Isoniazid, 300 mg/day, and rifampin, 600 mg/day, for 3-6 mo depending on response.

Solid Organ Involvement (Epididymis, Liver, Lung, Kidney, Bone, Joint, Prostate)

Isoniazid, 300 mg/day; rifampin, 600 mg/day; ethambutol, 15 mg/kg/day single daily dose for 3-6 mo.

Cycloserine often causes severe psychiatric symptoms and is to be strongly discouraged.

BCG is almost uniformly resistant to pyrazinamide, so this drug has no role.

Consider prednisone, 40 mg/day, when response is inadequate or for septic shock (never given without effective antibacterial therapy).

From Walton Tomford, MD, Cleveland Clinic.

clear superiority to available agents (Lammers, 2012). Mycobacterial cell wall DNA extract contains a mixture of immunostimulatory DNA attached to antigenic cell wall. Phase II trial results indicate success rates less than those achieved with BCG, but with good tolerability; however, no agent is commercially available (Morales et al, 2001, 2009).

IL-2 is highly expressed after BCG stimulation and is a key component of the Th1 immune response. Preclinical data suggest a potential benefit and little toxicity (Horinaga et al, 2005). Multiple studies have documented the potential use of either intravesical IL-2 alone, with BCG, or with BCG and IFN (Shapiro et al, 2007). Preclinical data identifying the efficacy of liposome-mediated intravesical IL-2 with biologic response modifiers have elucidated long-term T-cell memory against muscle-invasive bladder cancer and non-muscle-invasive bladder cancer (NMIBC) (Horiguchi et al, 2000; Larchian et al, 2000).

KEY POINTS: IMMUNOTHERAPY

- Intravesical BCG has higher efficacy and side effects compared to intravesical chemotherapy.
- BCG should be used cautiously for patients with low-risk disease because of concern about side effects.
- Management of infectious complications of BCG is shown in Box 93-3.
- BCG is the only agent shown to delay or reduce high-grade tumor progression.
- The optimum dose and the treatment schedule for BCG are undetermined, but results are better with maintenance therapy, if tolerated.
- BCG is contraindicated in the setting of a disrupted urothelium because of the risk of intravasation and septic death.
- IFN- α has not been shown to have benefit compared with BCG for primary treatment but appears to work well in combination with low-dose BCG, especially for salvage.

INTRAVESICAL CHEMOTHERAPY

Induction therapy using chemotherapeutic agents instilled within 6 hours of TURBT has demonstrated a clear impact on recurrence rates, as described earlier. However, the role of chemotherapy in the adjuvant setting is less clear compared with the efficacy of BCG. A SWOG comparison of doxorubicin and BCG showed a 15% progression rate in BCG patients compared with a 37% progression rate in chemotherapy patients (Lamm et al, 1991). Nevertheless, the risk of BCG infectious complications is nonexistent with chemotherapy, leading many in the European community to favor this approach.

The agents are summarized in Table 93-3.

Mitomycin C

MMC is an alkylating agent that inhibits DNA synthesis. The drug is usually instilled weekly for 6 to 8 weeks at dose ranges from 20 to 60 mg. A meta-analysis of nine clinical trials compared its efficacy on progression with that of BCG. Within median follow-up of 26 months, 7.67% of the patients in the BCG group and 9.44% of the patients in the MMC group developed tumor progression (Bohle and Bock, 2004). Another review found a 38% reduction in tumor recurrence with MMC. This was not as effective as BCG but was considered in most studies to make MMC a viable option for reduction in recurrence (but not for progression) in light of its lesser side effects, particularly the low but real risk of BCG sepsis (Huncharek et al, 2001).

Optimization of MMC delivery can result in halving of the recurrence rate in some studies. This can be achieved by eliminating residual urine volume, fasting overnight, using sodium bicarbonate to reduce drug degradation, and increasing concentration to 40 mg in 20 mL (Au et al, 2001). The use of local microwave therapy in

TABLE 93-3 Comparisons among Intravesical Agents

AGENT	PERIOPERATIVE USE	RISK GROUP	CYSTITIS (%)	OTHER TOXICITY	DROPOUT (%)	CONCENTRATION AND DOSE
Doxorubicin (Adriamycin)	Yes	Low to intermediate	20-40	Fever, allergy, contracted bladder, 5%	2-16	50 mg/50 mL
Epirubicin	Yes	Low to intermediate	10-30	Contracted bladder rare	3-6	50 mg/50 mL
Thiotepa	Yes	Low to intermediate	10-30	Myelosuppression 8%-19%	2-11	30 mg/30 mL
Mitomycin	Yes	Low to intermediate	30-40	Rash 8%-19%, contracted bladder 5%	2-14	40 mg/20-40 mL
BCG	No	Intermediate to high	60-80	Serious infection, 5%	5-10	1 vial/50 mL
Interferon	No	Salvage	<5	Flulike symptoms 20%	Rare	50-100 MU/50 mL
Gemcitabine	Yes	Salvage	Mild	Occasional nausea	<10	1-2 g/50-100 mL

BCG, bacille Calmette-Guérin.

Modified from O'Donnell MA. Practical applications of intravesical chemotherapy and immunotherapy in high-risk patients with superficial bladder cancer. *Urol Clin North Am* 2005;32:121-31.

conjunction with MMC, 20 mg/50 mL, reduced recurrence rates from 57.5% to 17.1% in a multicenter trial. A study using microwave therapy with higher doses of 40 to 80 mg for 6 to 8 weeks in high-grade bladder cancer found a recurrence-free rate of 75% at 2 years (Gofrit et al, 2004; van der Heijden et al, 2004).

Electromotive intravesical MMC appears to improve drug delivery into bladder tissue (Di Stasi and Riedl, 2009). This treatment reported reduction in recurrence rates with MMC from 58% to 31%, whereas patients in the BCG control arm had a 64% recurrence rate (Di Stasi et al, 2003). Peak plasma MMC was significantly higher in the electromotive group, supporting its reputed mechanism of action. Electromotive intravesical MMC remains unavailable in the United States.

Doxorubicin and Its Derivatives

Doxorubicin (Adriamycin) is anthracycline antibiotic that acts by binding DNA base pairs, inhibiting topoisomerase II, and inhibiting protein synthesis. In a review, doxorubicin demonstrated a 13% to 17% improvement over TUR in preventing recurrence but no advantage in preventing tumor progression (15.2% vs. 12.6%) (Kurth et al, 1997). The principal side effect of intravesical doxorubicin is chemical cystitis, which can occur in up to half of patients. Reduced bladder capacity has been reported in several series (Thrasher and Crawford, 1992).

The doxorubicin derivative epirubicin decreases recurrence compared with TUR alone by 12% to 15% (Oosterlinck et al, 1993). This was demonstrated with a single, immediate, perioperative dose, as well as in full 8-week courses of intravesical therapy. Epirubicin is available for UC in Europe and is FDA approved but is unavailable for treatment of UC in the United States.

Valrubicin is a semisynthetic analog of doxorubicin that was approved by the FDA for treatment of BCG-refractory CIS in patients who cannot tolerate cystectomy; the drug became available in 2009 in the United States (Sweatman et al, 1991; Greenberg et al, 1997; Grossman et al, 2008). In a cohort of 90 patients with BCG-refractory CIS, only 21% demonstrated a complete response (Steinberg et al, 2000), so its use is not widespread.

Thiotepa

Thiotepa (triethylenethiophosphoramidate) is the only chemotherapeutic agent approved by the FDA specifically for the intravesical treatment of papillary bladder cancer. It is an alkylating agent and is not cell cycle specific. In controlled clinical trials (N = 950 patients), it has been shown to significantly decrease tumor recurrence

in 6 of 11 studies by up to 41% (mean decrease, 16%). Systemic side effects can be seen owing to its low molecular weight, resulting in up to half of administered doses being absorbed, risking hematopoietic toxicity (Thrasher and Crawford, 1992). Nevertheless, most centers have substituted its use with BCG or the aforementioned chemotherapeutic agents.

Novel Agents

Gemcitabine and the taxanes paclitaxel and docetaxel have demonstrated activity against metastatic bladder cancer (Calabro and Sternberg, 2002). Intravesical gemcitabine can be safely administered either weekly or twice weekly for six to eight treatments. Minimal systemic absorption occurs through the bladder. Several small phase I and phase II studies have demonstrated reduction of recurrence of 39% to 70% including modest efficacy in heavily pretreated BCG-refractory patients (Maymi et al, 2004; O'Donnell, 2005). Taxanes have been formulated into an active intravesical treatment, but current published data are limited to preclinical studies (Lu et al, 2004).

Combination Therapy

Combining mechanisms of different agents is a logical and often successful approach to improve response rates for systemic therapy. However, studies have not identified clear benefit to doing so in intravesical therapy. For instance, in the study by Fukui and coworkers (1992), MMC (20 mg) was administered on day 1 and doxorubicin (40 mg) on day 2 once a week for 5 weeks in 101 patients. Fifty-one patients demonstrated a complete response and were further randomized to maintenance or no maintenance. Local side effects were significant in 50% of patients. Patients with CIS had fewer recurrences with maintenance therapy. Other studies demonstrated similar outcomes, with a general theme of increased local side effects with modest outcome improvement (Isaka et al, 1992; Sekine et al, 1994).

A combination of chemotherapy and BCG was evaluated in prospective trials by several investigators. The EORTC reported a 46% complete response rate when a solitary marker tumor was intentionally not resected and patients were subsequently given sequential MMC and BCG (van der Meijden et al, 1996). In a study of 188 patients with Ta and T1 lesions, no difference was seen with regard to recurrence, progression, or side effects in those patients treated with BCG and MMC compared with those treated with MMC alone. There was actually a significantly longer disease-free interval in the BCG monotherapy arm (55%) compared with the

same combination arm (45%) in another study of 314 patients (Malmstrom et al, 1999; Solsona et al, 2002). Thus no clear advantage is obtained with sequential therapy, combination chemotherapy, or chemotherapy and BCG regimens using any of the combinations explored to date (Rintala et al, 1995, 1996; Witjes et al, 1998; Nieder et al, 2005).

KEY POINTS: INTRAVESICAL CHEMOTHERAPY

- Intravesical chemotherapy has a clear impact on tumor recurrence when immediately instilled after TURBT and in the adjuvant setting. There is no clear evidence of an impact on progression.
- Combinations of various chemotherapeutic agents and chemotherapy combined with BCG have not demonstrated major benefit combined with single-agent treatment, with the exception of IFN.
- In general, side effects of chemotherapy tend to be less common and less severe than those for BCG, but BCG is more efficacious.

REFRACTORY HIGH-GRADE DISEASE

Recurrent or persistent disease after an initial 6-week course of BCG has been traditionally referred to as *BCG failure*, although this term has been poorly defined in the past. Current consensus is that persistent disease after BCG therapy can be categorized as BCG refractory (nonimproving or worsening disease despite BCG), BCG resistant (recurrence or persistence of lesser degree, stage, or grade after an initial course, which then resolves with further BCG), or BCG relapsing (recurrence after initial resolution with BCG). BCG-refractory patients in particular are an especially high-risk group and should be strongly considered for immediate cystectomy if young and in generally good health (Herr and Dalbagni, 2003). Intravesical treatment should be reserved for patients who refuse or are too ill to undergo cystectomy or on defined investigational protocols.

The necessity of biopsy to determine BCG response is unclear, although it should be strongly considered in high-risk patients to determine disease status at this key point in time. Urine cytology can be useful in this setting. Dalbagni and colleagues (1999) reported minimal usefulness of routine biopsy after BCG if cystoscopy and urinary cytology were both negative. Whereas 5 of 11 patients with erythematous bladder mucosa and positive cytology had positive bladder biopsies, none of 37 with erythematous lesions and negative cytology were positive, and only 1 in 13 patients with a normal mucosa had a positive biopsy (Dalbagni et al, 1999). Other studies have suggested that the value of routine post-BCG biopsy is limited (Dalbagni et al, 1999). UroVysion FISH (Abbott Molecular, Chicago, IL) conversion from positive to negative has been shown to correlate with BCG response in single-center studies (Kipp et al, 2005; Whitson et al, 2009).

Declaring failure may take up to 6 months because the response rate for patients with high-grade bladder cancer treated with BCG rose from 57% to 80% 3 to 6 months after therapy. Clearly, the tumoricidal activity continued for some period after cessation of therapy. This has obvious implications not only for declaring BCG failure and the need for subsequent therapy but also for interpretation of success rates of salvage protocols if administered soon after therapy (Herr and Dalbagni, 2003).

Management of Refractory High-Grade Disease

Although most urologists will administer an initial 6-week course of intravesical therapy for high-risk patients (most likely involving BCG in North America and chemotherapy in Europe), management of patients with persistent disease after the first course is more complex. Such patients are at increased risk of progression,

which is particularly likely in the event of early recurrence, progression while on therapy, or multiple recurrences.

If the initial treatment was chemotherapy, a course of BCG should be considered. BCG has demonstrated superiority to repeat courses of chemotherapy in this setting because the latter will lead to only an approximately 20% disease-free survival (Malmstrom et al, 1999; Steinberg et al, 2000). For patients who have failed BCG, a second course still gives a 30% to 50% response (Pansadoro and De Paula, 1987; Brake et al, 2000). Patients who cannot tolerate BCG for any reason may be considered for salvage chemotherapy, but the risk of failure and progression is high.

Further courses of BCG or chemotherapy beyond two are not recommended because they will fail 80% of the time, although recent studies suggest some potential for newer agents (Skinner et al, 2013). Rapid disease progression is common in such patients, so salvage chemotherapy, investigational protocols, and IFN alone or in combination with reduced doses of BCG may be appropriate only for patients who are unwilling or unable to undergo surgery even after being informed of their risks (Catalona et al, 1987).

The combination of IFN- α with BCG is expensive and has not been shown superior to BCG alone in primary therapy, so it has been used mostly for BCG failures. Small single-institution studies using low-dose BCG (typically one-third dose) plus 50 to 100 million units of IFN- α have demonstrated 1- to 2-year success rates of 50% to 60%, with better results with a second reinduction option and three sets of 3-week miniseries maintenance treatments 3, 9, and 15 months later (O'Donnell et al, 2001; Lam et al, 2003; Punnen et al, 2003). A large national multicenter phase II trial of combination BCG plus IFN- α in BCG-naïve and BCG-failure patients revealed similar findings (O'Donnell et al, 2004). Estimates for freedom from disease at 2 years were 57% for BCG-naïve patients and 42% for BCG-failure patients. Progression was seen in only 8% of patients in each group, suggesting that this combination has a potential role regardless of prior BCG response.

Role of Alternative Options for Refractory Disease

Photodynamic therapy (PDT) is performed by administering a photosensitizing agent such as porfimer sodium (Photofrin) systemically or HAL intravesically. Two to 3 days after the substance has cleared from the normal tissue (for Photofrin), the patient is given an intravesical treatment with red laser light (630 nm) for 12 to 20 minutes. Intravesical intralipid allows for more uniform distribution of laser light (Manyak et al, 1990). After excitation by light, the photosensitizer reacts with molecular oxygen to form free radicals and reactive singlet oxygen, which are cytotoxic.

The response rate in CIS patients from combined series is 66%, with a duration of 37 to 84 months (Jocham et al, 1989; Nseyo et al, 1997, 1998; Walther, 2000). For patients with papillary disease, an overall response rate of 51% has been achieved with a median time to recurrence of 24 to 48 months (Naito et al, 1991; Nseyo et al, 1997, 1998; Walther, 2000). PDT has been limited by significant side effects such as bladder contracture or irritability (50%) and dermal sensitivity (19%) (Naito et al, 1991; Uchibayashi et al, 1995; Nseyo et al, 1997, 1998).

Research efforts have been directed at development of improved photosensitizers and modifications in laser dosimetry (Kriegmair et al, 1996a; Nseyo et al, 1997, 1998). HAL, a more lipophilic ester of 5-ALA, generates a sensitizer called *protoporphyrin IX* that appears more tumor specific, although clinical data are limited (Datta et al, 1998). Preclinical studies using hypericin have shown promise (Kamuhabwa et al, 2004). Radachlorin is composed of three chlorins and appears promising, at least in the setting of BCG-refractory high-grade disease (Lee et al, 2013).

Radiation therapy in the treatment of NMIBC is typically restricted to individuals who refuse cystectomy after the failure of intravesical therapy or who are unsuitable for major surgery (Kim et al, 2000). A complete response to radiation therapy and TUR is attainable in 50% to 75% of patients, but the additional benefit of radiation to TUR remains unclear (De Neve et al, 1992; Rozan et al,

1992; Jansson et al, 1998). Five-year response rates are 44% to 60%. There is no significant effect on CIS. Owing to reports that up to 50% of patients will develop progression and a high likelihood of death (Rödel, 2001), there is a limited role for radiation therapy other than for palliative purposes in this population. Combinations of radiation and chemotherapy have shown promise but have not reached widespread use (Gray et al, 2013).

KEY POINTS: MANAGEMENT OF REFRACTORY DISEASE

- Patients who experience failure of an initial course of intravesical therapy after TURBT are at high risk of recurrence or progression.
- Failure of initial chemotherapy or BCG is most appropriately treated with a subsequent course of BCG because its efficacy in this setting is significantly greater than that of chemotherapy.

ROLE OF “EARLY” CYSTECTOMY

Despite local therapy, many cases of high-grade NMIBC will progress to invasion and risk of cancer death. Although the initial response rate to BCG therapy in CIS patients can be above 80%, patients in whom treatment fails will have a 50% chance of disease progression and potential for disease-specific mortality (Catalona et al, 1987; Nadler et al, 1994). Early (3-month) failure for T1 tumors after BCG is associated with an 82% progression rate, compared with a 25% progression rate in patients who do not experience treatment failure at 3 months (Herr et al, 1997; Herr, 2000a). Up to 20% of patients with CIS will die of UC within 10 years (Herr et al, 1989); each occurrence of T1 tumors is associated with a 5% to 10% chance of metastasis (Herr and Sogani, 2001), and residual tumor found on repeat resection in these patients is associated with an 82% chance of development of muscle invasion (Herr et al, 1997). These data offer compelling evidence of the potential to underestimate disease status in high-risk patients.

Cookson and coworkers (1997) reported that 27% of high-risk patients treated initially with aggressive intravesical therapy did well and died of other causes, and the same low number survived with an intact, functioning bladder 15 years after diagnosis. However, approximately half of patients experienced progression, and one third died of their disease. In contrast, patients who undergo immediate cystectomy for clinical T1 tumors benefit from more accurate pathologic staging in addition to a 10-year disease-free survival of 92%, compared with 64% of those with clinical T1 tumors who were found to actually have muscle invasion at the time of cystectomy (Bianco et al, 2004).

Despite the benign connotation of the term *superficial* formerly applied, up to 50% of patients with presumed non-muscle-invasive high-grade disease who undergo cystectomy will actually be found to have muscle-invasive disease. Such procedures have traditionally been termed *early cystectomy* on the basis of the fact that they are performed before the traditional surgical indication of documented muscle invasion. Considering that up to 15% will already have micrometastases (Chang and Cookson, 2005) and that a delay in cystectomy of even 12 weeks is associated with poorer survival, some of these procedures do not seem to be early enough (Sanchez-Ortiz et al, 2003; Chamie, 2013).

The risk of progression must be weighed against the risk, morbidity, and impact on quality of life for cystectomy. Thus a reasonable goal might be, as termed by Chang and Cookson (2005), “timely” cystectomy for patients at risk.

Ten-year survival after cystectomy for non-muscle-invasive cancer can range from 67% to 92% (Amling et al, 1994; Freeman et al, 1995). However, despite the bias that substantial progression can be averted with the benefit of early detection and close surveillance in patients whose tumors are identified before

muscle invasion, it appears that such patients who progress to having muscle invasion may have a poorer prognosis than do those who have muscle-invasive disease on initial presentation (Schrier, 2004; Lee et al, 2007). Thus overconfidence in disease control status with high-risk patients on surveillance creates a false sense of security.

The AUA guidelines panel listed cystectomy as the first option for patients with refractory high-grade disease after an initial course of intravesical therapy (see later). Nevertheless, fewer than one in five American urologists surveyed stated that they would recommend cystectomy for their patients with CIS refractory to two courses of intravesical BCG, a group with an 80% risk of failure or progression (Joudi et al, 2006a). Cystectomy in that setting, or for persistent high-grade papillary disease after two courses of intravesical therapy, is the standard of care and should not be considered “early.”

Some series suggest that tumor markers such as p53 and RB may be useful for stratifying high-risk patients for such decisions in the future. High-risk p53 lesions have a 75% progression rate, compared with 25% in p53-negative lesions. Survival is 60% at 10 years in patients with p53-positive lesions, whereas it is 88% in patients with p53-negative lesions (Sarkis et al, 1993). Grossman and colleagues (1998) found that for T1 lesions evaluated for p53 and RB, progression at 5 years was 30% if either marker was positive and 47% if both markers were positive. No progression was noted in lesions that were wild type for both markers (Grossman et al, 1998). Although p53 positivity did not predict response for BCG-treated patients in another study, post-BCG p53-positive expression was a marker of tumor progression (p53 positive, 82% progression and 41% mortality; p53 negative, 13% progression and 7% mortality) (Lacome et al, 1996). Other studies have refuted these findings, so the role of p53 for the prediction of tumor behavior and response to therapy remains under debate (Peyromaure et al, 2002).

The role of surgical approaches involving potential oncologic concessions such as seminal and nerve-sparing cystectomy in such patients theoretically at lower risk of recurrence compared with patients with muscle invasion remains unknown (Hautmann and Stein, 2005). The availability of neobladder for less disfiguring urinary diversion has been reported to decrease the delay in treatment of such patients, potentially leading to significantly improved disease-free survival (Hautmann, 1998). The impact on disease outcomes is unproven.

Critical evaluation of partial cystectomy for NMIBC is limited, although the practice is common (up to 20% of patients treated with extirpative therapy in the United States) even in patients with muscle invasion (Hollenbeck et al, 2005). Holzbeierlein and colleagues (2004) reported that 6.9% of the patients at Memorial Sloan-Kettering Cancer Center for surgical management of bladder cancer underwent partial cystectomy (29% of whom did so for clinical non-muscle-invasive disease). Five-year survival was 69%, and two thirds of patients were alive with an intact, functioning bladder. CIS was the most significant predictor of progression.

Partial cystectomy provides more accurate pathologic staging than does TURBT and allows lymphadenectomy. Appropriate candidates with non-muscle-invasive tumors would logically be the same as those for invasive cancer—those with solitary tumors at the dome or well away from the trigone and no CIS.

Cystectomy should also be considered in patients whose cancer cannot be reasonably controlled through resection: bulky tumors, inaccessible because of a large bladder or urethral stricture disease, or otherwise not amenable to safe removal endoscopically.

In summary, radical cystectomy offers the most accurate pathologic staging option and should be strongly considered for patients with NMIBCs that are high grade and invading deeply into lamina propria, exhibit lymphovascular invasion, are associated with diffuse CIS, are in diverticula, substantially involve the distal ureters or prostatic urethra, are refractory to initial therapy, or are too large or anatomically inaccessible to be removed in their entirety endoscopically. It can also be used in patients who understand the risks and benefits of bladder preservation versus cystectomy and request definitive therapy (Stein, 2003). Partial

cystectomy has limited data but might be a promising bladder preservation option situated between the extremes of TURBT combined with intravesical therapy and radical cystectomy.

KEY POINTS: EARLY CYSTECTOMY

- Patients at high risk for progression should be considered for cystectomy.
- Failure to respond to an initial course of intravesical therapy is occasion to reconsider cystectomy.
- Failure to respond to a second course is an indication for immediate cystectomy unless contraindicated or the patient chooses to pursue clinical trials or newer proven intravesical options if evidence builds for their use.

SURVEILLANCE AND PREVENTION

Although bladder cancer is less common than prostate cancer, expenditures are almost twice as high for bladder cancer because of its chronic nature and the need for long-term surveillance. According to the Agency for Healthcare Research and Quality, annual expenditures were \$2.2 billion in 2003 for bladder cancer versus \$1.4 billion for prostate cancer (Donat, 2003). A significant portion of this cost is associated with surveillance (Hedelin et al, 2002).

Surveillance strategies for UC recurrence have historically relied on the diagnostic combination of cystoscopy and urinary cytology. In clinical practice, only 40% of patients actually comply with a standard surveillance protocol (Schrage et al, 2003). Most protocols include this combination every 3 months for 18 to 24 months after the initial diagnosis, then every 6 months for the following 2 years, and then annually, resetting the clock with each newly identified tumor (Fitzpatrick, 1993). Although the accuracy of both tests relies on subjective and operator-dependent interpretation of visible findings, their traditional presumed status as the gold standard has been widely accepted (Brown, 2000).

Cystoscopic Surveillance

Office-based cystoscopy offers rapid, relatively painless visual access to the urothelium. Papillary tumors arising from the smooth bladder surface are readily identified. CIS is classically described as a velvety red mucosal patch, although the reliability of such findings has been called into question.

The role of cystoscopy as a gold standard in cancer detection has come under scrutiny with the emergence of tumor markers and the development of newer endoscopic technology including fluorescence cystoscopy as described previously (Kriegmair et al, 1996a, 1996b; Filbeck et al, 1999; Kriegmair et al, 1999). Nevertheless, for office-based diagnosis it allows identification of the site and characteristics of most tumors. There is a high positive predictive value with cystoscopy because most lesions believed to be malignant are proven so pathologically. The endoscopic appearance cannot reliably predict tumor stage or grade, although sessile morphology and/or the presence of necrosis suggests high-grade disease likely to be invasive.

Cystoscopy is usually performed in the outpatient setting. Rigid rod-lens systems offer accurate visualization of the bladder. Flexible fiberoptic cystoscopes are almost as sensitive and are markedly more comfortable for men, although there is no clear advantage to their use in women because of the short, straight female urethra. Newer digital chip cystoscopes offer similar tolerability but markedly better visualization owing to clarity and magnification on video monitors. Complete visualization of the bladder mucosa is possible in a matter of seconds in most patients. Their high-resolution imaging obviates the only potential advantage of rigid cystoscopy (slightly better optics than fiberoptic flexible scopes). Thus, flexible cystoscopy has essentially replaced rigid cystoscopy for surveillance in men in North America and may do so in women.

Using the same technology for flexible cystoscopy as described earlier for HAL fluorescence rigid cystoscopy, phase II studies have had mixed results but suggest that office-based fluorescence cystoscopy can improve the detection of CIS and papillary tumors (Loidl et al, 2005; Witjes et al, 2005).

The vast majority of both men and women tolerate office-based cystoscopy with minimal discomfort. Intraurethral injection of local anesthetics is almost universal among urologists despite a paucity of data to support the practice. Most studies and a meta-analysis (Patel et al, 2008b) have failed to identify benefit (Palit et al, 2003; Rodriguez-Rubio et al, 2004), and two recent studies actually found that pain experience was higher with the use of local anesthetics than in patients cystoscoped using aqueous lubricant alone (Ho et al, 2003; Chen et al, 2005). Considering the fact that anesthetic agents can partially cloud visualization, this ubiquitous practice should be reconsidered. Use of a video monitor allows the patient to see and understand the findings, theoretically distracting them from any discomfort. Men who are able to do so tolerate the procedure with approximately 50% less pain (visual analog scale 2.21 vs. 1.31, $P < .01$) than those who cannot see their findings on the monitor (Patel et al, 2007). This has not been found to be of significant benefit in women, probably because of the straighter urethra (Patel et al, 2008a).

The bladder should be evacuated before cystoscopy. This removes concentrated amorphous detritus and radiographic contrast if studies were performed earlier in the day. Aspiration with use of a 60-mL syringe attached to the irrigant port is occasionally necessary during the procedure. This can further lessen clouding. A systematic approach is mandatory to ensure that all urothelium is visualized.

Attempts have been made to modify the previously described surveillance schedule with use of decision analysis tools (Kent et al, 1989; Abel, 1993). Several authors recommend termination of surveillance at 5 or more years for low-risk patients (Haukaas et al, 1999). However, the actual cost of surveillance cystoscopy was responsible for only 13% of the expenditures for bladder cancer care in one study, so the financial opportunity may be limited for such efforts (Schoenberg et al, 2000; Hedelin et al, 2002). In addition, the risk of recurrence and potential for progression exists beyond this period. Reports of late recurrences of high-grade cancer years after the original tumor temper some authors' enthusiasm for terminating surveillance at any point (Thompson et al, 1993; Morris et al, 1995; Leblanc et al, 1999; Zieger et al, 2000). Thus there is no consensus on such programs.

Other investigators have examined the predictive impact of early or multiple recurrences and how this might affect surveillance (Parmar et al, 1989; Holmäng et al, 1995; Reading et al, 1995). Tumor recurrence on initial 3-month cystoscopy and number of tumors on initial resection (single or multiple) provides the most predictive information with regard to recurrence in several studies. Absence of recurrence on the 3-month surveillance cystoscopy in patients with Ta low-grade tumors is associated with recurrence rates so low that annual cystoscopy appears safe even at that point (beginning 12 months after the initial resection (Fitzpatrick et al, 1986; Olsen and Genster, 1995; Frydenberg et al, 2005). Finally, patients with a negative cystoscopy and a negative UroVysion assay (see later) are at low risk of recurrence in the following 6 to 12 months, creating opportunity to individualize the surveillance schedule (Sarosdy et al, 2002).

Urine Cytology

Cytology involves microscopic evaluation of stained cellular smears from the urine. Unlike tumor markers, urinary cytology is not a laboratory test—it is a pathologist's interpretation of the morphologic features of shed urothelial cells. Poor cellular cohesion in high-grade tumors, especially CIS, enhances the yield.

Its high specificity is the most important feature of cytology because a positive reading regardless of cystoscopic or radiographic findings suggests the existence of malignancy in the vast majority of patients. Even in the setting of UC, of patients with a

negative workup (cystoscopy and upper tract imaging) with a persistently positive cytology, 40% were found to have genitourinary cancer within 24 months (Nabi et al, 2004).

Bladder irrigation or barbotage increases the cellularity available for evaluation compared with voided urine. Nevertheless, Murphy and colleagues (1981) showed that urine collected cystoscopically before a bladder wash was obtained provided additional diagnostic information. Bladder washings had a higher yield, but 13.1% of cancers would have been missed in bladder washings alone. Moreover, mechanical trauma has the potential to create cellular alterations that might interfere with interpretation. Radiographic contrast media have also been implicated in creating cellular shrinkage, nuclear pyknosis, fragmentation, and cytoplasmic vacuolization that might lead to a false-positive reading, especially when injected for retrograde ureteropyelography (McClennan et al, 1978). This may not be a concern when low osmolar, ionic and nonionic, contrast media are used (Andriole et al, 1989).

Although cytology has traditionally been believed to have high sensitivity for high-grade cancer, recent studies do not support this. Mayo Clinic researchers observed that only 58% of bladder tumors were identified using cytology. Its sensitivity was not limited to low-grade tumors because only 71% of high-grade cancers were identified. Because this was lower than expected, they subsequently reviewed the literature and found that cumulative data from series published after 1990 reported that cytology actually identified (using the older grading system) 11% of grade 1, 31% of grade 2, and only 60% of grade 3 tumors (Halling et al, 2000). In contrast, they observed that these recent findings were well below those reported before 1990, when the sensitivity of cytology was 94% for grade 3 tumors, but could find no explanation for this deterioration. These findings are supported by numerous other studies and emphasized by a recent multicenter study involving several institutions noted for bladder cancer expertise that found cytology had an overall sensitivity of 15.8%, and 37.5% for patients with high-grade tumors (Grossman et al, 2005).

Thus cytology has high specificity but low sensitivity for both high-grade and low-grade tumors including CIS in recently published reports.

Tumor Markers

Many attempts have been made to develop a UC biomarker test to complement or replace urinary cytology. Most of these have had adequate sensitivity but poor specificity, resulting in substantial false-positive readings, creating the need for further diagnostic testing. Current urinary markers have been developed to detect tumor-associated antigens, blood group antigens, growth factors, cell cycle and apoptosis, and extracellular matrix proteins. The most significant issue limiting widespread adoption of tumor markers is the lack of prospective data to support their impact on prognosis or disease management (Lokeshwar et al, 2005).

The qualitative point-of-care test **BTA stat** (Polymedco, Cortlandt Manor, NY) and the quantitative **BTA TRAK** (Polymedco) assay detect human complement factor H-related protein. The overall sensitivity of these tests ranges from 50% to 80%, whereas the specificity is between 50% and 75%. These tests are more sensitive than cytology, but their results can be falsely positive in patients with inflammation, infection, or hematuria (Liou, 2006).

ImmunoCyt (DiagnoCure, Saint Foy, Canada) is a hybrid of cytology and an immunofluorescence assay. Three fluorescent-labeled monoclonal antibodies are targeted at a UC variant of carcinoembryonic antigen and two bladder mucins. Sensitivity and specificity are reported to be 86% and 79%, respectively. The assay has not been shown to be affected by benign conditions, but interpretation is complex and operator dependent (Toma, 2004; Têtu, 2005).

The **NMP22 BladderChek Test** (MatriTech, Newton, MA) is based on the detection of nuclear matrix protein 22, part of the mitotic apparatus released from urothelial nuclei on cellular apoptosis. The protein is elevated in UC, but it is also released from dead and dying urothelial cells. Benign conditions of the urinary tract such as stones, infection, inflammation, hematuria, and cystoscopy

can cause a false-positive reading. Both a laboratory-based, quantitative immunoassay and a qualitative point-of-care test are available. The sensitivities and specificities range from 68.5% to 88.5% for sensitivity and from 65.2% to 91.3% for specificity (Liou, 2006). A multi-institutional trial involving 1331 patients showed that, overall, the NMP22 was more sensitive than cytology but less specific. Sensitivities were 50% and 90% for noninvasive and invasive cancer, respectively, with an overall sensitivity of 55.7%. Overall specificity was higher for cytology at 99.2% compared with NMP22 at 85.7%. The sensitivity of cystoscopy in this study was 88.6%, but when combined with NMP22, this increased to 93.7% (Grossman et al, 2005).

UroVysion (Abbott Molecular, Chicago, IL) is a cytology-based test that uses FISH of DNA probes or labels specifically chosen to identify certain chromosomal foci. Probes to identify aneuploidy of chromosomes 3, 7, and 17 are combined with a probe to the 9p21 locus. Probes can be developed to identify essentially any locus, but this combination has the best sensitivity and specificity (Halling et al, 2000). Cumulative data from comparative studies show sensitivity for cytology compared with FISH of 19% versus 58% for grade 1, 50% versus 77% for grade 2, and 71% versus 96% for grade 3. Similar findings occurred by stage, wherein cytology compared with FISH sensitivity was 35% versus 64% for Ta, 66% versus 83% for T1, and 76% versus 94% for muscle-invasive carcinoma (Jones et al, 2006).

Notably, cytology detected only 67% of patients with CIS versus 100% detection by FISH in comparative studies. **UroVysion has the highest specificity of the available tumor markers.** It will, however, detect chromosomal changes before the development of phenotypic expression of malignancy, so it leads to an “anticipatory positive” reading in some patients. Such readings are often not false positives and will lead to identification of clinical tumors within 3 to 15 months in the majority of cases (Sarosdy et al, 2002). Moreover, patients testing negative are unlikely to experience tumor recurrence in less than 1 year (Yoder et al, 2007). This may allow identification of patients at risk of recurrence versus those unlikely to develop recurrence, to individualize surveillance protocols.

UroVysion has also been shown to clarify equivocal findings in patients with atypical or negative cytology (Skacel et al, 2003). It is not affected by hematuria, inflammation, or other factors that can cause false-positive readings with some tumor markers, so it appears to be useful as a marker of BCG response (Kipp et al, 2005; Whitson et al, 2009). “Nondiagnostic” UroVysion reports identifying limited cellularity or positive cells at numbers below defined standards can be regarded as negative and are not associated with increased risk of bladder cancer recurrence in the future compared with expectations with “normal” readings (Nguyen et al, 2009).

A retrospective study suggests that a multiplex of eight biomarkers in combination may improve performance compared with currently available markers if validated in further studies (Rosser et al, 2013).

The usefulness of tumor markers and the choice of which one to use is not clear at this time. For example, if indication for biopsy in the operating room is the end point, then high specificity is desired to limit the number of negative biopsies. On the other hand, if increasing the interval of cystoscopic surveillance is the end point, then high sensitivity, particularly for high-grade tumors, is desired. Defining that a patient has a low likelihood of recurrence within the following year can allow individualization of surveillance protocols (Fig. 93-8) (Grossman et al, 2006).

Extravesical Surveillance

The proportion of patients developing upper tract UC after treatment of non-muscle-invasive disease has been reported as 0.002% to 2.4% over intervals of 5 to 13 years (Shinka et al, 1988; Oldbring et al, 1989; Holmäng et al, 1995; Sadek et al, 1999), although the risk increases substantially over time to as high as 18% in very high-risk populations (Herr et al, 1997). Synchronous tumors were detected in no patients (0%) with grade 1 (using the prior grading system) tumors, 1.1% with grade 2, and 1.3% with grade 3, as well as 0% for low-grade Ta and 7% for T1 (Herranz-Amo et al,

TABLE 93-4 Suggested Surveillance Strategies

RISK	TUMOR STATUS	CYSTOSCOPY SCHEDULE	UPPER TRACT IMAGING
Low	Solitary Ta low grade	3 mo after initial resection Annually beginning 9 mo after initial surveillance if no recurrence Consider cessation at 5 or more yr Consider cytology or tumor markers	Not necessary unless hematuria present
Intermediate	Multiple Ta low grade Large tumor Recurrence at 3 mo	Every 3 mo for 1-2 yr Semiannually or annually after 2 yr Consider cytology or tumor markers Restart clock with each recurrence	Consider imaging, especially for recurrence Imaging for hematuria
High	Any high grade (including CIS)	Every 3 mo for 2 yr Semiannually for 2 yr Annually for lifetime Cytology at same schedule Consider tumor markers Restart clock with each recurrence	Imaging annually for 2 yr, then consider lengthening interval

CIS, carcinoma in situ.

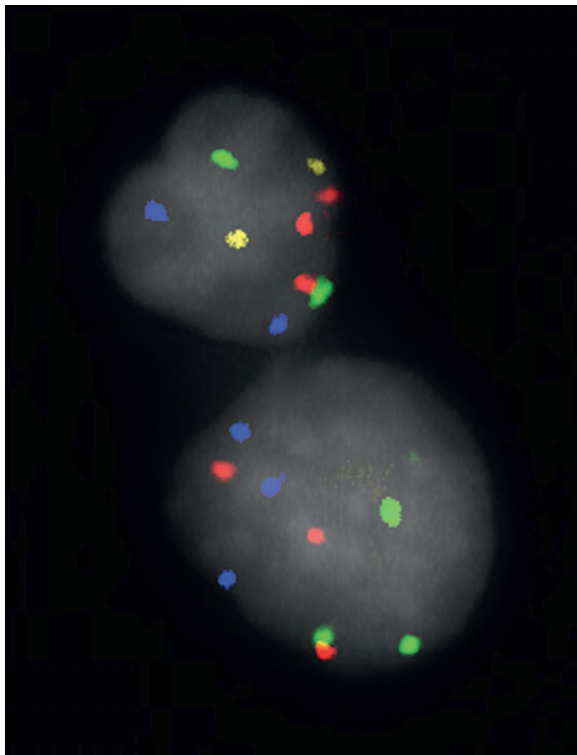


Figure 93-8. An abnormal enlarged cell (lower right) demonstrates three copies of chromosome 3 (red), chromosome 7 (green), and chromosome 17 (aqua) on use of fluorescence in situ hybridization. Homozygous deletion of band 9p21 locus (yellow) is also present. (Courtesy Raymond Tubbs, MD, Department of Laboratory Pathology, Cleveland Clinic Foundation.)

1999). The Surveillance, Epidemiology, and End Results (SEER) database showed that only 0.8% of bladder cancer patients develop subsequent upper tract tumors, so surveillance is of limited value unless the patient has hematuria or a high-grade tumor, especially if it is near the ureteral orifice (Wright et al, 2009). In a review of 591 patients with median follow-up of 86 months, upper tract recurrence was 0.9% in low-risk patients (solitary, low-grade, low-stage Ta/T1), 2.2% in patients at intermediate risk (recurrent or multifocal disease), and 9.8% in high-risk patients including intravesical chemotherapy failures (Hurle et al, 1998). Most reviews have concluded that patients who have high-grade

or multiple tumors should undergo upper tract imaging on the basis of the risk of upper tract disease, but those with low-grade tumors probably do not benefit from imaging unless performed for hematuria.

The proper study to evaluate the upper tract is debatable. Excretory urography is the traditional choice but gives limited information about renal parenchyma and can miss small tumors. Retrograde ureteropyelography requires instrumentation, but this is often not a problem because these patients require removal of the primary bladder tumor, so the procedures can be combined. Multiphasic computed tomography (CT) urography has become the preferred technology for the evaluation of hematuria, but its role in the evaluation of patients with NMIBC has not been extensively reported (Herts, 2003; Davis et al, 2012).

Although infrequent, the appearance of upper tract disease is associated with mortality rates of 40% to 70%. Patients with high-risk disease treated with BCG experience upper tract recurrence risk of 13% to 18% (Miller et al, 1993; Herr et al, 1997). The risk for recurrence in this population appears greatest over the first 5 years after treatment (median time to detection, 56 months) yet persists at least 15 years.

Selective cytology of the upper tract may increase the yield of upper tract lesions detected, but, in the presence of a bladder tumor, selective upper tract cytology may be falsely positive and is not recommended for most patients (Zincke et al, 1983; Sadek et al, 1999).

Secondary tumor involvement of the prostatic urethra and ducts by UC may be detected in 10% to 15% of patients with high-risk non-muscle-invasive disease within 5 years and in 20% to 40% within 10 years (Donat, 2003). Patients who have refractory disease are at risk for extravesical recurrence in the prostatic fossa in approximately one third of cases, 44% of which are fatal (Herr et al, 1988). Involvement of the prostatic ducts by low-grade UC should usually be managed by complete TURP for disease eradication and to facilitate contact of intravesical therapy to the prostatic urethra. Involvement of the ducts by high-grade disease is best managed by radical cystoprostatectomy, and consideration of urethrectomy should be made, especially if tumor is present near or at the surgical margin (Liedberg et al, 2007).

In summary, surveillance strategies should be individualized on the basis of the risk of recurrence in the bladder and extravesical sites (Table 93-4).

SECONDARY PREVENTION STRATEGIES

Both lifestyle changes and chemoprevention could potentially reduce the risk of recurrence and have been considered in the management of patients with non-muscle-invasive disease.

BOX 93-4 American Urological Association 2007 Guidelines for Non-Muscle-Invasive Bladder Cancer**INDEX PATIENT NO. 1: ABNORMAL UROTHELIAL GROWTH BUT NOT PROVEN CANCER**

Standard: Obtain biopsy to confirm grade for all index patients.

If possible, eradicate all visible tumors.

If cancer, periodic cystoscopy.

Option: Single dose of postoperative intravesical chemotherapy.

INDEX PATIENT NO. 2: SMALL-VOLUME, LOW-GRADE Ta

Recommendation: Single dose of postoperative intravesical chemotherapy.

INDEX PATIENT NO. 3: MULTIFOCAL OR LARGE LOW-GRADE Ta, OR RECURRENT LOW-GRADE Ta

Recommendation: Intravesical BCG or MMC—goal to prevent/delay recurrence.

Option: Maintenance BCG or MMC.

INDEX PATIENT NO. 4: HIGH-GRADE Ta, T1, OR CIS

Standard: If T1 disease, but no muscularis in specimen, repeat resection.

Recommendation: Intravesical BCG with maintenance therapy.

Option: Consider cystectomy for select patients.

INDEX PATIENT NO. 5: HIGH-GRADE Ta, T1, AND/OR CIS AFTER PRIOR INTRAVESICAL THERAPY

Standard: T1 disease but no muscularis in specimen, repeat resection.

Recommendation: Consider cystectomy as therapeutic alternative.

Option: Further intravesical therapy may be considered.

BCG, bacille Calmette-Guérin; CIS, carcinoma in situ; MMC, mitomycin C.

From Hall MC, Chang SS, Dalbagni G, et al. Guideline for the management of non-muscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol* 2007;178(6):2314–30.

Lifestyle changes are particularly important because UC is directly linked to environmental factors in the majority of cases. **Smoking cessation, increased fluid intake, and a low-fat diet may all reduce the risk of recurrence**, with the former being of paramount importance. **Increased hydration reduces the concentration and dwell time of carcinogens** and thereby reduces the risk of malignant transformation within the urothelium (Jiang, 2008). The Physician Health Study showed an inverse correlation between fluid intake and the incidence of UC on longitudinal follow-up, but this simple measure may also be of benefit for secondary prevention for patients who already have a history of UC (Michaud et al, 1999). **High fat and cholesterol intake are now firmly established as risk factors** for many cancers, although the mechanisms are not as well defined as for other malignancies (Steineck et al, 1990).

A variety of agents have been investigated for chemoprevention strategies for patients with UC, including retinoids (i.e., vitamin A and its analogs) (Sporn et al, 1977; Becci et al, 1978; Eichholzer et al, 1996; Steinmaus et al, 2000), pyridoxine (vitamin B₆) (Byar and Blackard, 1977; Newling et al, 1995), α -tocopherol (Virtamo, 2000; Lotan et al, 2012), and difluoromethylornithine (DFMO) (Messing et al, 2005). However, none of these agents has proven useful in rigorous trials. Isoflavones were studied for the same purpose, but the studies were abandoned owing to higher bladder cancer risk in the patients consuming greater amounts of soy products (Sun, 2004).

The most promising data for secondary chemoprevention of UC relate to the use of high doses of multivitamins. One small study randomized 65 patients with noninvasive UC to either a recommended daily allowance (RDA) multivitamin or megadose vitamins with augmented levels of vitamins A, B₆, C, and E (Lamm et al, 1994). Comparison of the two regimens revealed no difference in recurrence rates in the first year; however, there was a statistically significant advantage for the megadose group when the 5-year recurrence rates were calculated. At that point, 80% of patients in the RDA group had experienced recurrence compared with only 40% in the megadose group. These findings suggest that the beneficial effect of megadose vitamins is related to their suppressive effect on partially transformed cells within the urothelium rather than inhibition of early recurrences, which are typically caused by tumor cell implantation or incomplete resection. Confirmation of these findings by larger prospective trials is necessary.

KEY POINTS: SURVEILLANCE AND PREVENTION

- Cystoscopy is the hallmark of surveillance. The optimum schedule is undefined but may be individualized on the basis of risk.
- Table 93-4 demonstrates reasonable surveillance protocols based on clinical scenarios. Guidelines for management are shown in Box 93-4.
- A number of tumor markers have shown the ability to improve the sensitivity of cytology, but specificity is lower for most.
- Increased fluids, smoking cessation, and a low-fat diet are recommended.

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The complete reference list is available online at www.expertconsult.com.

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Clinical Presentation, Diagnosis, and Evaluation

Radical Cystectomy and Pelvic Lymph Node Dissection for Muscle-Invasive Bladder Cancer

Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer

Adjuvant Chemotherapy for Muscle-Invasive Bladder Cancer

Bladder Preservation

Prognostic Nomograms for Muscle-Invasive Bladder Cancer

Conclusions

CLINICAL PRESENTATION, DIAGNOSIS, AND EVALUATION

Bladder cancer has the fifth highest incidence of all malignancies in the United States, with an estimated 74,690 new cases and 15,580 deaths in 2014 (Siegel et al, 2014). Twenty percent to 30% of patients will present with muscle-invasive bladder cancer at the time of initial presentation. Despite aggressive therapy, a significant proportion of patients ultimately will experience recurrence and will die of their disease. Clinical understaging is not uncommon at the time of initial diagnosis with muscle-invasive disease, and therefore a multimodal therapeutic approach is often necessary to improve survival. A multidisciplinary approach is paramount to integrate appropriate therapy to individual patients, including surgery, systemic chemotherapy, and radiation therapy. This chapter reviews the evaluation and treatment of patients with muscle-invasive and metastatic bladder cancer.

Natural History

The majority of patients present with muscle-invasive disease at the time of initial presentation. A smaller subset (approximately 20%) will progress to muscle-invasive disease after an initial diagnosis of non-muscle-invasive bladder cancer. Muscle-invasive bladder cancer is a highly lethal entity and if left untreated will result in mortality within 2 years of diagnosis in 85% of cases (Prout et al, 1956). Additionally, some studies have shown worse outcomes for patients who progress from non-muscle-invasive disease; however, this is likely related to understaging of presumed noninvasive disease (Guzzo et al, 2009). Bladder cancer death after appropriate local therapy is typically the result of systemic disease; the majority of deaths occur within 2 years of initial treatment. Non-local-regional relapses are reflective of the presence of micrometastatic disease at the time of diagnosis and treatment and they continue to hamper long-term survival rates for patients with muscle-invasive disease. The significant risk of micrometastatic disease and our current inability to stage and to identify accurately patients with non-organ-confined disease before definitive local therapy continue to hamper pretreatment decisions and argue for a multidisciplinary treatment approach.

Histology

The majority of primary bladder cancers are urothelial carcinomas, representing more than 90% of all bladder tumors. Although squamous cell carcinoma comprises only approximately 5% of all bladder cancers in the Western world, it is more common in parts

of the Middle East and Africa secondary to endemic infection with schistosomal parasites, and it accounts for a significant percentage of bladder cancer histology in these regions (el-Mekresh et al, 2009). Squamous cell carcinoma histology in Western countries is more commonly associated with chronic urinary tract inflammation including patients with chronic indwelling catheters. Even rarer, adenocarcinomas represent roughly 2% of bladder cancers and can originate from either the urothelium or the urachus. Patients with bladder exstrophy are classically at an increased risk for bladder adenocarcinoma. Before definitive treatment it is important to rule out other more common sites of adenocarcinoma such as breast and colorectal sources. Standard treatment regardless of histologic subtype is radical cystectomy; however, timing of neoadjuvant chemotherapy and/or radiation therapy can vary by histologic subtype (Willis et al, 2013). Pure neuroendocrine variants of bladder cancer are relatively rare but highly aggressive, and they typically present at high pathologic stages or with metastatic disease (Mazzucchelli et al, 2009). Neuroendocrine features can also be seen with other histologic variants. Standard treatment for neuroendocrine bladder tumors includes neoadjuvant chemotherapy and radical cystectomy (Siefker-Radtke et al, 2004). Neuroendocrine tumors can be associated with paraneoplastic syndromes including ectopic adrenocorticotrophic hormone production, hypercalcemia, and hypophosphatemia. Carcinoid tumors, a type of neuroendocrine tumor, can also originate in the bladder. Large cell neuroendocrine tumors have also been reported and have a similar disease biology to that of small cell tumors (Akamatsu et al, 2008). Other rare histologic entities include rhabdomyosarcoma, leiomyosarcoma, and primary lymphoma.

Variant histologies of urothelial carcinoma also exist, including micropapillary, sarcomatoid, squamous, and glandular differentiation. Micropapillary tumors are aggressive and resemble papillary serous carcinoma of the ovary. There are conflicting reports regarding the responsiveness of micropapillary disease to neoadjuvant chemotherapy (Kamat et al, 2007; Ghoneim et al, 2011; Meeks et al, 2013). There is scant evidence to support treatment guidelines for many variant urothelial histologies; however, many of these subtypes are aggressive, and early definitive therapy should be considered. It is important to recognize variant histology to avoid diagnostic misinterpretations that could delay definitive care.

Clinical Staging

Clinical staging for bladder cancer is the assessment of disease extent before definitive treatment, whereas pathologic stage is determined by microscopic analysis of radical cystectomy and pelvic

TABLE 94-1 Incidence of Pathologic Pelvic Node Metastasis (%) at Radical Cystectomy in Selected Contemporary Series (2000-2012)

	NO. OF PATIENTS	P1	P2A	P2	P2B	P3A	P3	P3B	P4A	P4	P4B
Stein et al, 2001	1054	7		18		26		46	42		
Leissner et al, 2004	290	2	11		22	46		40	40		80
Vazina et al, 2004	176	4		16			40			50	
Steven et al, 2007	263	5	14		24	40		33	42		
Ghoneim et al, 2008	2720	2	8		19		39			36	
Tarin et al, 2012	591	6		18				40		60	

lymphadenectomy specimens. Clinical staging for bladder cancer is determined by pathologic analysis of the depth of the invasion of the tumor on the transurethral resection (TUR) specimen, bimanual examination of the patient under anesthesia, liver function tests, chest radiography, and contrast-enhanced cross-sectional imaging of the abdomen and pelvis with upper tract imaging. Clinical understaging is not uncommon and contemporary cystectomy series demonstrate pathologic upstaging rates to be as high as 50% for patients with clinical T2 stage tumors (Table 94-1) (Svatek et al, 2011).

TUR is the gold standard method for establishing the diagnosis of muscle-invasive bladder cancer. In addition to pathologic staging, TUR also can provide valuable information on histologic variants that may direct therapeutic decision making. Although data are limited, a complete resection of macroscopic tumor is advisable when it is safe and feasible. Complete resection decreases local tumor burden and may optimize the response to neoadjuvant chemotherapy, or for patients undergoing chemoradiotherapy it may improve bladder preservation. Additionally, prospective randomized neoadjuvant chemotherapy trials have clearly demonstrated a significant survival benefit in patients who are pT0 at the time of radical cystectomy. This survival benefit (pT0 status) occurred regardless of whether neoadjuvant chemotherapy was administered, suggesting a potential benefit of aggressive TUR (Grossman et al, 2003b; Lavery et al, 2014). The status of the bladder neck in women and the prostatic urethra in men should also be carefully evaluated at the time of initial resection, as it can impact clinical decision making with regard to neoadjuvant chemotherapy (prostatic stromal invasion), surgical management of the urethra, and choice of urinary diversion at the time of radical cystectomy. Biopsies of the prostatic urethra may provide useful information in advance of radical cystectomy (Lerner et al, 2008). Using a resectoscope, a full loop of tissue is taken from the midprostate (or bladder neck in shorter prostates) to the mid- to distal verumontanum and 5 and 7 o'clock adjacent to the verumontanum. This is the site of the highest concentration of prostatic ducts and the area where carcinoma in situ (CIS) is most likely to be found (Sakamoto et al, 1993). The full-thickness prostatic resection allows the pathologist to evaluate the interface between the urethral mucosa, prostatic ducts, and stroma, which allows for accurate staging of the prostatic urethra (Wood et al, 1989). Negative prostatic urethral biopsies are associated with negative apical urethral margins and can replace the need for intraoperative frozen section at the time of radical cystectomy (Lerner and Shen, 2008). In women, bladder neck biopsies are an accurate surrogate for urethral biopsy when orthotopic urinary diversion is under consideration.

Bimanual examination under anesthesia remains an important aspect of primary tumor assessment. The examination is performed typically by placing the dominant hand on the suprapubic region and one or two fingers from the nondominant hand in the rectum (males) or vagina. Bimanual examination can be performed at the time of initial tumor resection and should be done before and after resection. The bimanual examination should be performed with the bladder drained and without a Foley catheter in place to maximize palpation of the bladder. Findings described originally by Marshall

are T2a: nonpalpable; T2b: induration but no three-dimensional mass; T3a: three-dimensional mass that is mobile; T4a: invading adjacent structures such as the prostate, vagina, or rectum; T4b: fixed to pelvic sidewall and not mobile (Marshall, 1952). Bimanual examination is not 100% accurate in predicting final tumor pathology, with an 11% clinical overstaging and a 31% clinical understaging rate reported (Ploeg et al, 2012).

Cross-sectional imaging plays an important adjuvant role to TUR and physical examination in the assessment and staging of the primary bladder tumor in patients with muscle-invasive disease. Abdominal and pelvic cross-sectional imaging are recommended by the National Comprehensive Cancer Network (NCCN) when muscle-invasive disease is suspected before TUR (NCCN guidelines Version 1, 2014). Studies vary widely on the overall sensitivity and specificity of computed tomography (CT) imaging with regard to final pathologic tumor stage at the time of radical cystectomy. Studies using multidetector CT scanners have reported the best results, with sensitivities ranging from 89% to 91% and specificities of 92% to 95% for local staging (Kim et al, 2004; Koplay et al, 2010). The timing of imaging is also important to note relative to TUR. Although it is optimal to obtain cross-sectional imaging before TUR, if imaging is obtained subsequently, it should be delayed approximately 7 days post-procedure to minimize inflammatory artifact, which can be mistaken for T3 disease (Kim et al, 2004). A high suspicion for extravesical disease is warranted when hydronephrosis is noted on cross-sectional imaging. The presence of hydronephrosis on staging CT is associated with an increased risk of extravesical disease (27.8% vs. 17.3%) at the time of cystectomy (Bartsch et al, 2007; Canter et al, 2008). The reported sensitivity and specificity of CT in detecting nodal metastasis ranges from 31% to 50% and 68% to 100%, respectively (Picchio et al, 2006; Baltaci et al, 2008; Lodde et al, 2010).

Magnetic resonance imaging (MRI) is generally considered to be more accurate than CT in detecting local tumor stage; however, reports vary in the literature. Rajesh and colleagues (2011) reported on 100 consecutive patients who underwent a 1.5-T MRI with gadolinium. The authors reported that the sensitivity and specificity of MRI in differentiating between organ-confined and non-organ-confined disease was 90.5% and 60%, respectively (Rajesh et al, 2011). Other studies have reported staging sensitivity ranging from 68% to 80% and specificity of 90% to 93%. MRI does appear to show an advantage over CT in predicting tumor stage, but is not particularly more accurate in detecting lymph node metastasis. Additionally, MRI has been reported as useful in predicting tumor grade and tumor chemosensitivity (Tuncbilek et al, 2009; Yoshida et al, 2012).

The usefulness of positron emission tomography and CT (PET/CT) in local staging of bladder cancer is limited as a result of the excretion of standard PET (^{18}F -fluorodeoxyglucose) into the urine. Although PET/CT has not proven of superior benefit to that of CT alone for local staging, some studies have demonstrated its superiority with regard to nodal staging. The reported sensitivity and specificity of PET/CT in detecting nodal metastasis ranges from 57% to 81% and 88% to 100%, respectively (Drieskens et al, 2005; Kibel et al, 2009; Apolo et al, 2010; Lodde et al, 2010).

Pathologic Staging

The American Joint Committee on Cancer (AJCC) tumor, node, metastases (TNM) system is the most commonly used method for staging bladder cancer (Table 94-2) and can be used for staging

TABLE 94-2 Tumor Node Metastasis Staging System for Bladder Cancer

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: “flat tumor”
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

REGIONAL LYMPH NODES (N)*

Nx	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvic (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

Note: cTNM is the clinical classification, and pTNM is the pathologic classification.

*Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

From Edge SB, Byrd DR, Compton CC, et al, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.

patients clinically and pathologically. T staging follows a stepwise fashion based on depth of tumor penetration. As with other tumors, N and M stages refer to the presence of regional nodal and distant metastasis, respectively. The prognostic value of T2 and T3 substaging has been widely debated and reported. A multicenter series of 565 radical cystectomy patients with pT2, node-negative disease demonstrated improved recurrence-free (73.2% vs. 58.7%) and cancer-specific survival (78.0% vs. 65.1%) for pT2a and pT2b disease, validating this subgrouping (Tilki et al, 2010a). The prognostic usefulness of the pT3 subgrouping was also reported in the same cohort of radical cystectomy patients. Of the 356 pT3N0 patients, pT3b substaging was associated with worse recurrence-free (60.7% vs. 47.9%) and cancer-specific survival (64.4% vs. 55.0%) at 5 years (Tilki et al, 2010b). The T4a prostate designation requires established stromal invasion, which can occur via the urethra or as a direct extension via the bladder neck or posteriorly into the seminal vesicles or periprostatic ducts. CIS in the prostatic urethra or ducts does not represent upstaging because outcome is determined by the primary bladder cancer stage (Esrig et al, 1996; Pagano et al, 1996). Lymph node staging is illustrated in Table 94-2; positive nodes above the common iliac artery are considered N+M1 disease. Pathologically, organ-confined bladder cancer is considered to be pT2bN0M0 or less at the time of cystectomy (Soloway et al, 2012).

RADICAL CYSTECTOMY AND PELVIC LYMPH NODE DISSECTION FOR MUSCLE-INVASIVE BLADDER CANCER

For patients with clinical T2-T4a, N0, M0 disease, radical cystectomy and bilateral pelvic lymph node dissection remains the gold standard therapy by which all other treatment modalities should be compared. Radical cystectomy provides excellent local control with pelvic recurrence rates as low as 4% in patients with node-negative disease (Morris et al, 2009). Randomized trial data have demonstrated superior outcomes with neoadjuvant systemic chemotherapy, which will be further discussed in subsequent sections.

Time from initial diagnosis of muscle invasion to cystectomy likely impacts oncologic outcomes, particularly if there is a delay of greater than 12 weeks. Sanchez-Ortiz and colleagues (2003) initially published this observation in their cohort of 290 cystectomy patients noting a higher proportion of extravesical tumors, nodal metastasis, and worse survival in patients in which cystectomy was delayed more than 12 weeks. Since that observation was published, multiple studies have demonstrated similar results (Chang et al, 2003; Lee et al, 2006b; Gore et al, 2009). Lee and associates (2006b) reported worse disease-specific and overall survival rates for patients with muscle-invasive disease who underwent radical cystectomy more than 3 months after initial diagnosis. Administrative data sets have also provided similar findings. Of 441 patients who underwent radical cystectomy from 1992 to 2001 in the Surveillance, Epidemiology, and End Results (SEER) database, a delay in surgery of more than 12 weeks and 24 weeks resulted in a twofold increase in disease-specific and overall mortality compared to more timely surgical intervention (Gore et al, 2009). Similar results have been noted in other radical cystectomy cohorts (Ayres et al, 2008; Fahmy et al, 2008; Kulkarni et al, 2009). Although it is difficult to say with certainty, based on retrospective surgical cohorts, exactly how expeditiously surgery should be performed, a significant delay does appear to be detrimental to oncologic outcomes.

In men, radical cystectomy includes excision of the surrounding perivesical soft tissue, prostate, and seminal vesicles, and, in women, it includes the ovaries, uterus with cervix, and anterior vagina. Since the mid-2000s, greater emphasis has been placed on urinary and sexual quality of life following cystectomy. This has led to a greater interest in organ preservation in both men and women. In men, preservation of the neurovascular bundles, some or all of the prostate, and the seminal vesicles have been reported in an attempt to

improve postoperative quality of life. The majority of reports is limited to small retrospective cohorts and must be analyzed within the context of such limitations. It is also important for the surgeon to weigh the oncologic risk of organ preservation relative to that of cancer recurrence. For instance, prostate cancer can be present in upward of 23% to 54% of radical cystoprostatectomy specimens with up to a third having clinically significant disease (Abdelhady et al, 2007; Pettus et al, 2008). Additionally, the significant incidence of urothelial carcinoma involving the prostate (17% to 75%) noted on complete radical cystoprostatectomy specimens is an obvious oncologic limitation with this technique (Ayyathurai et al, 2007; Pettus et al, 2008; Revelo et al, 2008; Richards et al, 2010; Arce et al, 2011; Tabibi et al, 2011). If prostatic preservation is considered, transurethral sampling of the prostatic urethra and bladder neck is advisable to maximize appropriate patient selection. Other reported preoperative features associated with prostatic urethral involvement include the presence of tumor at the bladder neck (Pettus et al, 2008; Richards et al, 2010; Abdelsalam et al, 2011; Arce et al, 2011), tumor multifocality (Nixon et al, 2002; Kefer et al, 2008), and the presence of CIS (Kefer et al, 2008; Richards et al, 2010; Arce et al, 2011). Functional outcomes following prostate preservation tend to be directly associated with the amount of tissue spared at the time of surgery. Davila and coworkers (2007) reported on a small number of patients undergoing either apical ($n = 15$) or total prostate-sparing cystectomy ($n = 6$). Using the erectile function domain score of the International Index of Erectile Function (IIEF) questionnaire, the authors reported mild erectile dysfunction in the apical-sparing group. Also using an apical-sparing technique, Wunderlich and associates reported a 94% day and nighttime continence rate with 87% of patients achieving baseline erectile function following surgery (Wunderlich et al, 2006). Posterior sparing (posterior prostate and seminal vesicles) was also reported by several authors with limited numbers of patients. Using this technique, excellent outcomes with regard to continence and erectile function have been reported (Spitz et al, 1999; Girgin et al, 2006). Finally, total prostate sparing has also been described in several series of patients. Nieuwenhuijzen and coworkers (2008) reported outcomes of 41 patients who underwent total prostate sparing at the time of radical cystectomy and they noted 95% and 74% day and nighttime continence rates, respectively. However, 12 patients did require long-term clean intermittent catheterization because of an inability to empty volitionally. Erectile function was maintained in 78% of patients who were functioning preoperatively. Although organ preservation has the potential to improve overall quality of life, radical cystoprostatectomy remains the gold standard.

Preservation of the uterus, ovaries, and vagina has also been explored in women at the time of radical cystectomy. Although an anterior exenteration has classically been advocated in women at the time of radical cystectomy, urothelial carcinoma rarely involves the gynecologic organs with an overall incidence of approximately 5% of cases (Chang et al, 2002). Unless there is tumor involvement of the bladder neck, a complete urethrectomy can be omitted at the time of cystectomy allowing for orthotopic bladder substitution in women. Additionally, carefully selected patients can also forgo removal of the uterus and anterior vagina, which potentially allows for better anatomic support for a neobladder and preserves the autonomous nerves.

Bilateral Pelvic Lymph Node Dissection

A meticulous pelvic lymph node dissection is an essential component of radical cystectomy. It is well established that approximately 25% of patients will have pathologic lymph node metastases at the time of cystectomy (Lerner et al, 1993), and lymph node status is the most powerful surrogate for long-term recurrence-free and overall survival following radical cystectomy (Poulsen et al, 1998; Stein et al, 2001). The value of a meticulous pelvic lymph node dissection was first reported by Skinner and coworkers (1982), demonstrating better local control rates, potential for cure, and acceptable morbidity in patients undergoing radical cystectomy. Since that initial report, multiple surgical series have demonstrated

the profound impact of nodal involvement at the time of radical cystectomy with approximately 70% to 80% of patients with lymph node metastasis ultimately experiencing disease recurrence in contrast to approximately 30% of patients with a negative pelvic lymph node dissection (Shariat et al, 2006b; Stamatakis et al, 2012). The extent of lymph node dissection at the time of cystectomy has been shown as an independent predictor of survival and local recurrence even when chemotherapy status and other pathologic factors are controlled (Herr et al, 2004). Whereas the importance of a lymph node dissection seems undebatable, what actually constitutes an adequate lymph node dissection and its exact therapeutic benefit remains less clear.

Anatomic Extent of Pelvic Lymph Node Dissection and Landing Zones

The primary lymphatic drainage site for bladder cancer includes the internal iliac, external iliac, obturator, and presacral lymph nodes. Secondary drainage sites include higher echelon nodes, including the common iliac, para-aortic, interaortocaval, and paracaval lymph nodes (Abol-Enein et al, 2004; Leissner et al, 2004; Vazina et al, 2004). Although multiple studies have demonstrated that an extended pelvic lymph node dissection offers improved prognostic staging, the exact anatomic extent of dissection remains somewhat controversial. The cranial extent of an adequate lymph node dissection varies across cystectomy series ranging from the crossing of the ureter at the level of the common iliac vessels to as high as above the aortic bifurcation at the level of the inferior mesenteric artery (Poulsen et al, 1998; Mills et al, 2001; Abol-Enein et al, 2004; Leissner et al, 2004).

Multiple surgical series have evaluated the anatomic extent and distribution of nodal metastasis at the time of cystectomy. Abol-Enein and colleagues in Mansoura, Egypt, evaluated the extent and distribution of positive lymph nodes in 200 consecutive patients who underwent radical cystectomy at a single institution over a 4-year period (Abol-Enein et al, 2004). The anatomic extent of the lymph node dissection was the inferior mesenteric artery superiorly in all patients. Twenty-four percent of patients exhibited nodal disease, with a mean number of eight positive lymph nodes. In 22 patients only a single lymph node was positive, of which 21 were located in the endopelvis. Metastasis outside of the true pelvis was only found in multinodal disease and was associated with involvement of the obturator and/or iliac nodes in all cases. The authors found no evidence of "skip" metastasis in patients with positive nodes. The authors suggested that the obturator and internal iliac nodes represent the sentinel lymphatic drainage areas and that if lymphadenectomy proved to be negative on frozen-section analysis at the time of surgery, a more superior dissection was not warranted. Similarly, the Memorial Sloan Kettering Cancer Center (MSKCC) group has reported on the anatomic extent and spread of lymph node metastasis (Bochner et al, 2004). The authors reported on 144 patients who underwent either a standard or extended pelvic lymph node dissection at the time of radical cystectomy. A standard pelvic lymph node dissection was defined superiorly by the iliac bifurcation and included the external iliac, hypogastric, and obturator lymph node packets. An extended dissection also included the nodal packets to the level of the aortic bifurcation to no more than 2 cm proximal to the bifurcation. The common iliac and presacral nodes were also included in the extended dissection template. As one would expect, the absolute number of positive nodes was significantly higher in the extended lymph node dissection group (22.5 vs. 8). However, there was not a staging advantage noted in the extended lymph node group, with both dissections yielding the same percentage of patients with positive lymph nodes (21%). Four percent of patients presented with positive lymph nodes identified within the para-aortic packets, all of which also showed positive lymph nodes in lower dissection packets. The authors did note four patients with micrometastatic disease to the common iliac vessels only, concluding that this area should be considered part of the standard lymph node dissection.

Although “skip” metastasis appears to be a relatively rare event in bladder cancer, it has been reported in the literature. A prospective multicenter study of 290 patients undergoing radical cystectomy with extended pelvic lymphadenectomy reported nodal metastasis in 27.9% of patients (Leissner et al, 2004). The authors reported lymph node metastasis based on three defined anatomic regions. Level 1 included lymph nodes below the common iliac bifurcation, level 2 included lymph nodes above the common iliac bifurcation but below the aortic bifurcation, and level 3 included lymph nodes to the level of the inferior mesenteric artery. Although no skip lesions were noted above the level of the aortic bifurcation, 6.9% of patients had nodal metastasis in level 2. Tarin and colleagues (2012) reported their lymph node dissection findings in 591 patients undergoing a radical cystectomy during a 10-year period, of which 19% exhibited positive nodes. The authors reported 6% of patients with skip lesions above the common iliac bifurcation with no positive nodes in the true pelvis. Finally, Vazina and associates (2004) also reported one patient with lymph node metastases at or above the aortic bifurcation or common iliac region without nodal involvement of more distal sites in their series of 176 radical cystectomy patients.

The anatomic extent of the pelvic lymph node dissection has also been evaluated in multiple series with regard to oncologic outcome. Dhar and colleagues (2008) reported on two consecutive series of patients from the Cleveland Clinic and the University of Bern, totaling 658 patients who either underwent a limited or an extended pelvic lymph node dissection. The limited node dissection included the pelvic sidewall between the genitofemoral and obturator nerves, and the bifurcation of the iliac vessels to the circumflex iliac vein. The extended dissection extended cephalad to the crossing of the ureters with the common iliac arteries and removal of all tissue along the lateral and medial portion of the internal iliac vessels. The overall proportion of lymph node positive patients in the extended versus limited cohorts was 26% and 13%, respectively. The 5-year recurrence-free survival of patients with lymph node positive disease was 7% for limited and 35% for extended node dissection. The 5-year recurrence-free survival for pT2pN0 cases was 67% and 77% for limited and extended dissections, respectively, and 23% and 57% for pT3N0 cases, respectively. The 5-year recurrence-free survival for pT2pN0-2 cases was 63% and 71%, respectively, for limited and extended lymph node dissections and 19% and 49%, respectively, for pT3pN0-2 patients. This study, in a large cohort of patients, confirms the value of an extended pelvic lymph node dissection with regard to staging accuracy and prognosis.

Based on the anatomic mapping studies described previously, it is recommended that an adequate pelvic lymph node dissection for bladder cancer at a minimum includes all lymphatic tissue around the common iliac, intercommon iliac, internal iliac, and obturator packets bilaterally. It has also been suggested that frozen-section analysis be performed for the lymph nodes in the true pelvis, and if metastasis is not identified, a more superior dissection can be omitted.

Number of Lymph Nodes Removed at the Time of Cystectomy

Multiple retrospective surgical series have attempted to quantify the minimum number of lymph nodes that constitutes an adequate pelvic lymph node dissection (Leissner et al, 2000; Bochner et al, 2001; Herr, 2003; Stein et al, 2003). Although controversy remains regarding the actual number of nodes that constitutes an adequate dissection, the absolute number of nodes removed has been shown to provide important prognostic information and staging accuracy both in lymph node positive and lymph node negative patients.

As one would expect, increasing nodal yield at the time of pelvic lymph node dissection improves the sensitivity of detecting nodal metastasis. Using a multi-institutional cohort, Capitanio and colleagues (2009) evaluated the probability of finding lymph node positive disease at the time of cystectomy based on the total number

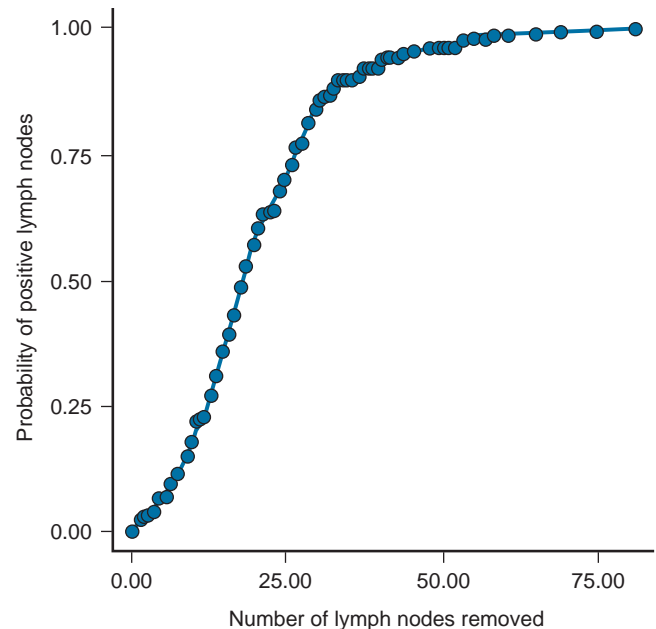


Figure 94-1. A plot describing the relationship between the number of lymph nodes removed and the probability of detecting lymph node metastasis. (From Capitanio U, Suardi N, Shariat SF, et al. Assessing the minimum number of lymph nodes needed at radical cystectomy in patients with bladder cancer. *BJU Int* 2009;103:1359–62.)

of lymph nodes removed. Of the 731 patients included in this study, 23.8% had positive nodes. Using receiver operating characteristic curves, the authors predicted a 75% chance of identifying one or more lymph node metastases if 25 nodes were removed. This probability improved to 90% with 45 nodes and decreased to 50% if 15 to 25 nodes were removed, suggesting a 25-node minimum as a reasonable cut-off to adequately stage and detect lymph node metastasis (Fig. 94-1).

In addition to staging, lymph node count has been reported to improve therapeutic efficacy; however, prospective data to substantiate such a benefit are currently lacking. Leissner and colleagues (2000) retrospectively analyzed outcomes in 447 cystectomy patients in Mainz, Germany. Using a 16-node threshold, there were significant differences in cancer-specific and disease-free survival among patients with 16 or more lymph nodes removed compared to those with fewer nodes removed. For their survival analysis, a 16 lymph node threshold was used because the correlation between the total number of lymph nodes removed and the percentage of positive nodes was strongest at this count. There is no general consensus in the literature regarding the exact threshold of nodes at which a survival benefit can be predicted, with most studies reporting numbers in the 9 to 16 range (Leissner et al, 2000; Herr et al, 2002; Herr, 2003; Konety et al, 2003; Stein et al, 2003; Hollenbeck et al, 2008; May et al, 2011). Koppie and colleagues (2006) from the MSKCC group reported a study designed to determine if there is a minimum number of lymph nodes analyzed, above which there is no improvement in survival. The study included 1121 patients who underwent radical cystectomy during a 14-year period. The authors were unable to find a plateau in the dose-response curve with an increasing number of nodes up to 23; however, few patients had more than 24 nodes removed. Limitations of this study include the fact that 13% of patients had no nodes identified on the pathology report and the percent of patients who underwent an extended node dissection was not reported.

Although the studies in the last two sections have demonstrated the prognostic and therapeutic value of a thorough pelvic lymph node dissection at the time of radical cystectomy, it must be remembered that they are all either retrospective or nonrandomized

reports. There are inherent biases that need to be accounted for when considering the actual value and extent of a pelvic lymph node dissection when one considers it from a nonprospective, non-randomized approach. Surgical and nonsurgical factors, including anatomic extent of the template and pathologic processing, including the number of packets submitted to pathology, can greatly influence nodal counts (Bochner et al, 2001; Stein et al, 2007a; Ather et al, 2008; Kulkarni et al, 2008; Fang et al, 2010). More definitive studies are currently underway to address this issue better, including two randomized controlled trials, one in the United States and one in Europe, with the goal of determining the importance and extent of lymph node dissection at the time of radical cystectomy.

Lymph Node Density and Extracapsular Nodal Extension

Lymph node density refers to the percentage of positive nodes relative to the total number of nodes removed (Kassouf et al, 2008). Studies regarding the impact of lymph node density on prognosis have been mixed. Stein and colleagues (2003) first described the concept of lymph node density in bladder cancer. In their study of node-positive bladder cancer patients, they identified a lymph node density of 20% to carry prognostic value. Herr (2003) and colleagues have also demonstrated the 20% lymph node density value to confer prognostic value. In their study of 162 patients with lymph node positive bladder cancer patients who had a lymph node density of less than 20%, these patients experienced a significantly better 5-year disease-specific survival following radical cystectomy. Similarly, Guzzo and colleagues (2010) reported the outcomes of 85 node-positive patients following radical cystectomy, and they found that lymph node density less than 20% predicted a more favorable response to adjuvant chemotherapy. Conversely, Tarin and colleagues (2012) could not demonstrate an association between lymph node density compared to that of lymph node status alone in 591 radical cystectomy patients who underwent extended lymphadenectomy. A similar study by Jensen and colleagues of 167 radical cystectomy patients echoed these findings (Jensen et al, 2012). The current lymph node density studies reported in the literature are retrospective surgical series, and they report varying lymph node counts and templates of dissection, in turn limiting comparisons between studies.

Several small retrospective series have reported the potential prognostic significance of extranodal extension. Fajkovic and colleagues (2013) evaluated extranodal extension in 748 node-positive bladder cancer cases treated with cystectomy at several centers. A total of 375 (50%) presented with extranodal extension. Using a multivariable model, including pT stage, tumor grade, age, gender, lymphovascular invasion, surgical margin status, lymph node density, total lymph nodes, number of positive nodes, and adjuvant therapy, extranodal extension was significantly associated with both disease recurrence and cancer-specific mortality. Similarly, Seiler and colleagues (2011) reported an extranodal extension to be an independent predictor of overall survival and disease-specific survival in a smaller cohort (n = 162) of lymph node positive patients.

Intraoperative Decision Making

Grossly Positive Nodes and T4b Disease

The management of patients with grossly involved lymph nodes includes treatment of systemic micrometastatic disease and locoregional disease. If disease is recognized on preoperative imaging and outside the true pelvis, a CT-guided biopsy can be performed to confirm histology. If it is positive, then chemotherapy should be initiated followed by radical cystectomy. If adenopathy is encountered at the time of cystectomy, a frozen section should be taken to confirm metastasis, and an extended lymph node dissection and radical cystectomy should be completed when feasible. Cystectomy is not performed when lymph node metastases are unresectable because of bulk, when there is evidence of extensive periureteral disease, when the bladder is fixed to the pelvic sidewall, or when

the tumor is invading the rectosigmoid colon. Not surprisingly, if radical cystectomy is aborted, patient prognosis is poor. The Johns Hopkins group published their outcomes of 35 patients who had an aborted cystectomy because of intraoperative findings of metastatic disease (Guzzo et al, 2008). Sixty percent of patients in the study cohort died from disease progression at a median time of 26 months. Similarly, Yafi and colleagues (2011) reported outcomes on 31 patients in which cystectomy was aborted for unresectable disease. The 2-year and 5-year overall survival in this cohort of patients was 41% and 0%, respectively.

Intraoperative Frozen Sections of the Ureter

The incidence of involvement of the distal ureter with tumor on final pathology at the time of radical cystectomy was 6% to 8% (Sharma et al, 1970; Gakis et al, 2011). There is not a definitive recommendation for the precise length of the distal ureter that should be removed at the time of surgery. Final ureteral margin status has proven to be an independent predictor of upper tract recurrence following cystectomy (Tran et al, 2008; Volkmer et al, 2009). However, the overall incidence of upper tract recurrence following cystectomy is a relatively rare event ranging from 2% to 8% (Schumacher et al, 2006; Tran et al, 2008; Giannarini et al, 2010; Gakis et al, 2011). There are several risk factors for upper tract recurrence following cystectomy including bladder CIS, distal ureteral involvement with tumor, and high-grade pTa-T1 disease (Volkmer et al, 2009). Upper tract recurrences have been reported to recur most commonly between 2 and 4 years postcystectomy (Meissner et al, 2007; Sanderson et al, 2007; Wagner et al, 2008). Unfortunately, when upper tract recurrences do occur they are often locally advanced and can be associated with worse outcomes than de novo upper tract disease (Balaji et al, 1999; Sved et al, 2004; Sanderson et al, 2007). The risk of upper urinary tract recurrence appears to be a stable event with time (Tran et al, 2008).

The role of intraoperative frozen-section analysis of the ureters at the time of cystectomy remains somewhat controversial. Although it would seem intuitive that achieving a negative ureteral margin is necessary, the literature has not always demonstrated improved outcomes with this approach (Schoenberg et al, 1996; Silver et al, 1997; Lee et al, 2006a; Osman et al, 2007). Contemporary studies report frozen-section analysis of the distal ureteral margins to have a 74% to 75% sensitivity, a 98% to 99% specificity, and a positive predictive value of 98% (Raj et al, 2006; Gakis et al, 2011). Whether or not sequential resection for positive frozen ureteral margins confers an absolute benefit remains questionable. An analysis of 1397 cystectomy patients who underwent frozen-section analysis of the distal ureters demonstrated an initial positive margin rate of 12.7% (Tollefson et al, 2010). In those with initial positive margins, 83% were subsequently converted to a negative margin with further resection. Interestingly, those with an initial positive margin but negative final margin still were at higher risk for upper tract recurrence (hazard ratio [HR] = 4.88, 95% confidence interval [CI] 3.02 to 7.90, $P < .001$) compared to those with initial negative margins. This risk was intermediate to that of those with positive final margins (HR = 7.37, 95% CI 4.3 to 16.44, $P < .001$). These findings suggest patients with ureteral disease at the time of cystectomy experience an increased risk of upper tract recurrence regardless of margin status, but this risk can be at least partially mitigated by achieving a negative margin. The impact of ureteral skip lesions has also been reported. Investigators from the University of Texas MD Anderson Cancer Center evaluated 660 radical cystectomy patients who had both a distal frozen and final proximal ureteral margin (Hoang et al, 2014). Ureteric skip lesions (negative distal frozen, positive proximal permanent margin) were identified in 4.8% of patients with CIS, which is the most common skip lesion (55.9% of cases). Skip lesions were associated with lower median overall survival in patients with pT0 or pTa disease.

Given the findings outlined earlier, it appears logical to attempt to clear the distal ureter when feasible at the time of radical cystectomy. When frank tumor is encountered, it should be resected to a negative margin. When CIS only is encountered, maximal resection

without compromising ureteral length for urinary diversion is advocated, as it is debatable whether a negative CIS margin reduces upper tract recurrence or is definitively associated with a worse outcome (Lee et al, 2006a; Raj et al, 2006). In patients who are at high risk for an upper tract recurrence, ureteropyeloscopy, when feasible, is the most sensitive means for detecting upper tract recurrences.

Prostatic Urothelial Carcinoma and Management of the Distal Urethra

The absolute risk of urethral recurrence following cystectomy ranges from 4% to 8% in men (Nieder et al, 2004; Varol et al, 2004; Stein et al, 2005; Huguet et al, 2008; Nelles et al, 2008; Cho et al, 2009). The majority of urethral recurrences are symptomatic, but in patients who are deemed at high risk for such events, periodic cytology can be useful for detection of recurrences (Clark et al, 2004; Huguet et al, 2008). Risk factors for urethral recurrence include non-muscle-invasive disease on final pathology and prostatic urethral involvement (Stein et al, 2005; Huguet et al, 2008). The extent of prostatic involvement is also predictive of urethral recurrence. Prostatic stromal invasion is associated with the highest risk (as high as 30%) compared to that of prostatic urethral CIS and ductal or acinar involvement (Hardeman, 1990). Urethrectomy should be considered in men with diffuse CIS of the prostatic urethra or ducts or if there is prostatic stromal invasion. Preoperative evaluation of the prostatic urethra via biopsy can be performed to characterize further the risk of urethral recurrence and help dictate intraoperative management of the distal urethra and choice of urinary diversion. The sensitivity and specificity of transurethral prostatic urethral biopsy is moderate with a relatively low positive predicate value compared to final cystoprostatectomy specimens (Donat et al, 2001). Given the modest value of preoperative urethral biopsy, some experts advocate for urethrectomy only in the setting of a positive apical urethral margin (Donat et al, 2001; Stein et al, 2005). Small low-grade papillary tumors of the urethra can be resected before cystectomy and the urethra retained if there is no other indication for urethrectomy. Of note, several retrospective surgical series have reported a decreased risk of urethral recurrence in patients with orthotopic urinary diversions (Hassan et al, 2004; Nieder et al, 2004; Stein et al, 2005). Whereas some have hypothesized that this decrease may be related to a protective effect of exposing the urethra to urine, it is more likely a result of selection bias.

Managing the Female Urethra

Before female orthotopic bladder substitution became more commonplace, complete removal of the female urethra at the time of radical cystectomy was routine. T4 tumors involving the urethra and/or vagina mandate complete urethrectomy, and these patients should not be offered urethral preservation. Concomitant involvement of the urethra in women with bladder cancer ranges from 2% to 12% (Stenzl et al, 1995; Stein et al, 2007b). Clinical features associated with an increased risk of distal urethral tumor

involvement include primary tumor location at the bladder neck, vaginal involvement, or inguinal lymphadenopathy (Stein et al, 1995; Maralani et al, 1997; Stein et al, 1998). Although tumor presence at the bladder neck is significantly associated with urethral involvement, approximately 60% of patients with tumors in this location will not have a tumor in the urethra on final pathology and therefore controversy exists with regard to an absolute need for complete urethrectomy in this setting. Frozen-section analysis of the distal urethra has demonstrated high correlation with final urethral margin and should be performed in all women in which orthotopic bladder substitution is being considered (Stein et al, 1998; Akkad et al, 2006). Isolated urethral recurrence following orthotopic bladder substitution occurs in approximately 1% of cases (Ali-El-Dein et al, 2009; Stein et al, 2009).

Oncologic Outcomes following Radical Cystectomy

Table 94-3 illustrates the reported oncologic outcomes of large surgical series. Pathologic tumor stage and presence of nodal metastasis are the strongest predictors of recurrence and survival following cystectomy (Frazier et al, 1993; Stein et al, 2001; Madersbacher et al, 2003; Hautmann et al, 2006; Shariat et al, 2006b; Ghoneim et al, 2008; Manoharan et al, 2009). Patients who are pT0 or who have residual noninvasive disease on final pathology have excellent outcomes with 5-year cancer-specific survival rates approaching 90% (Stein et al, 2001; Ghoneim et al, 2008). Patients with pT2 tumors have 5-year disease-specific survival rates ranging from 70% to 81%. Pathologic T2 substratification has been shown in multiple studies to confer prognostic value with regard to recurrence-free and disease-specific survival (Bastian et al, 2008; Ghoneim et al, 2008; Tilki et al, 2010a). The presence of non-organ-confined disease (>pT2) is a strong predictor of outcome. Pathologic T3 patients fare significantly worse with 5-year disease-specific survival rates ranging from 40% to 52%. The prognostic value of pT3 substaging has been debated in the literature. Two large multicenter surgical series have reported a prognostic discrimination between pT3a and pT3b, with node-negative patients reporting an improved recurrence-free and disease-specific survival advantage in pT3a patients (Tilki et al, 2010b; Sonpavde et al, 2011). However, pT3 substaging has not demonstrated improved stratification in node-positive patients (Quek et al, 2004). Lymph node status appears to be the single greatest predictor of disease outcome. Node-positive disease confers a poor prognosis with 5-year disease-specific survival rates ranging from 21% to 35%. However, long-term survival has been reported in patients with low-volume lymph node metastasis (Steven et al, 2007; Dhar et al, 2008; Bruins et al, 2009; Rink et al, 2013).

Margin status is also an important predictor of recurrence following radical cystectomy (Dotan et al, 2007; Novara et al, 2010). A multicenter, retrospective study of 4410 radical cystectomy patients reported an overall soft tissue positive margin rate of 6.3% (Novara et al, 2010). A positive soft tissue margin was associated with a significantly increased risk of disease recurrence (HR = 1.52, $P < .001$) and cancer-specific mortality (HR = 1.51, $P < .001$). Additional variables that were reported to possess prognostic value following radical cystectomy include the presence of lymphovascular invasion (Lotan et al, 2005; Herrmann et al, 2008; Shariat et al, 2010),

TABLE 94-3 Percentage of 5-Year Disease-Specific Survival (DSS) by Pathologic Stage after Radical Cystectomy with and without Pelvic Lymph Node Metastasis: Selected Series Reporting DSS (2000-2012)

SELECTED SERIES	NO. OF PATIENTS	≤P1	P2A	P2	P2B	P3A	P3	P3B	P4A,B	N NEG	N+
Stein et al, 2001	1054	88		81		68		47	44	78	35
Madersbacher et al, 2003	507	76		74			52		36	—	33
Hautmann et al, 2006	788	90		72			43		28	75	21
Shariat et al, 2006b	888	81		72			44		28	80	35
Ghoneim et al, 2008	2720	82	75		53		40		29	62	27
Manoharan et al, 2009	432	81		70			44		16	72	29

molecular markers (Youssef et al, 2011; Shariat et al, 2014), surgical expertise and hospital volume (Konety et al, 2005), body mass index (Bagrodia et al, 2009), and age (Hollenbeck et al, 2004; Nielsen et al, 2007). Despite aggressive surgical therapy, approximately 50% of cystectomy patients will ultimately die of disease. Recurrence of disease often occurs within the first 2 years following surgery, with median recurrence times of 7 to 18 months reported in large series.

NEOADJUVANT CHEMOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER

Nearly 50% of patients with muscle-invasive bladder cancer treated with cystectomy alone will progress to metastatic disease (Stein et al, 2001; Ghoneim et al, 2008). Clearly, surgery alone is not sufficient therapy in a large number of patients with invasive bladder cancer. Systemic therapy with cisplatin-based chemotherapy has been shown to provide response rates in multiple bladder cancer studies since the mid-1980s (Sternberg et al, 1985; Stenzl et al, 2009). Since the initial reports of its usefulness in muscle-invasive bladder cancer, there have been multiple randomized controlled studies undertaken to define further the effectiveness of neoadjuvant cisplatin-based chemotherapy in advance of cystectomy. Unfortunately, many of these studies have been hampered by inadequate power and a lack of standardization of surgical approaches to demonstrate clearly a survival advantage with neoadjuvant chemotherapy in most of these studies when they are evaluated individually.

There are several arguments for cisplatin-based chemotherapy in the neoadjuvant setting for patients with muscle-invasive bladder cancer. First, systemic chemotherapy is often better tolerated before surgery, rather than after surgery when patients may experience a delay in chemotherapy administration because of complications or debilitation. Second, patients who present with micrometastatic disease will receive therapy in a more timely fashion when their burden of disease is potentially low. Third, neoadjuvant chemotherapy has the potential to downstage bulky and locally advanced tumors, allowing for a higher likelihood for negative surgical margins that are a known predictor of local recurrence following cystectomy. Finally, neoadjuvant chemotherapy allows the clinician to assess each individual's response to therapy. A disadvantage of neoadjuvant chemotherapy is a delay in definitive local therapy for patients who do not respond to chemotherapy and thus experience disease progression.

The European Organization for Research and Treatment of Cancer (EORTC) and the Medical Research Council (MRC) performed the largest neoadjuvant chemotherapy trial in bladder cancer. This study evaluated the benefit of 3 cycles of neoadjuvant cisplatin, methotrexate, and vinblastine in 976 patients before radiation or cystectomy (International Collaboration of Trialists, 1999). The study was designed to detect an absolute improvement in survival of 10% with a power of 90% and a type 1 error of 5%. Eighty percent of the 491 patients who were assigned to the chemotherapy arm completed 3 cycles. The study was performed at 106 centers and the decision as to whether patients received radiation or cystectomy was at the discretion of the investigators. Chemotherapy-related mortality was reported to be 1%. At the time of the initial analysis there was a trend noted toward improved survival in the neoadjuvant chemotherapy arm (HR = 0.85, 95% CI 0.71 to 1.02; $P = .075$) with a median follow-up of 4 years. This translated into a nonsignificant absolute difference in survival of 5.5% at 3 years with survival rates of 50% for those who did not receive chemotherapy compared to 55.5% for those who did. The results of this trial were updated in 2011, with a median patient follow-up of 8 years (Hall, 2002). The updated survival results were notable for a statistically significant 16% reduction in the risk of death for patients in the chemotherapy arm (HR = 0.84, 95% CI 0.72 to 0.99; $P = .37$). The estimated 10-year survival in the chemotherapy arm was 36% compared to 30% in the control arm, translating to a 6% absolute survival benefit (Griffiths et al, 2011). Limitations of the

EORTC/MRC trial when compared to current clinical practice include the fact that cisplatin, methotrexate, and vinblastine is not considered a standard of care for muscle-invasive bladder cancer and has not been compared directly to methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC). Additionally, approximately 40% of patients in both the chemotherapy arm and local therapy arm received radiation and not radical cystectomy.

The intergroup trial (Southwest Oncology Group [SWOG] 8710) randomized 317 patients to 3 cycles of neoadjuvant MVAC versus cystectomy alone for CT2-T4aN0M0 bladder cancer (Grossman et al, 2003a). Eighty-two percent of patients randomized to chemotherapy ultimately underwent a cystectomy with a mean time to surgery of 115 days. Thirty-eight percent of the chemotherapy patients achieved pT0 status at the time of cystectomy compared to 15% of the controls ($P < .001$). The median overall survival time in the chemotherapy group was 77 months compared to 46 months in the cystectomy-only group. The 5-year overall survival rates were 57% and 43% in the chemotherapy and cystectomy-only arms, respectively. However, the survival results failed to reach statistical significance ($P = .06$). Notably, patients who were downstaged to pT0 achieved excellent outcomes with 80% alive at 5 years compared to 40% of patients with residual disease. A secondary analysis of the SWOG 8710 data compared subgroup outcomes for patients with pure urothelial carcinoma versus mixed histologic subtypes (Scosyrev et al, 2011). The authors reported a survival advantage in the mixed histology subgroup that received neoadjuvant chemotherapy. Given the fact that this was a secondary subgroup analysis, it is difficult to draw definitive conclusions; however, this analysis does suggest that patients with mixed histology should be considered for neoadjuvant chemotherapy. Other randomized trials of neoadjuvant chemotherapy for bladder cancer are summarized in Table 94-4.

Most of the trials reported in the literature have failed to demonstrate a statistically significant survival advantage for those patients who received neoadjuvant chemotherapy. Contributing to these findings are inherent limitations to the trial designs including small sample sizes, varying and sometimes suboptimal chemotherapy protocols, premature closure, and inadequate follow-up (Sylvester and Sternberg, 2000). In an attempt to clarify further the precise benefit of neoadjuvant chemotherapy, several investigators have performed meta-analyses of the current chemotherapy trials. The Advanced Bladder Cancer (ABC) Meta-analysis Collaboration (2005a, 2005b) undertook the largest meta-analysis. This report was an update to the group's previous meta-analysis in 2003, now including the SWOG 8710 trial data for a total of 11 randomized neoadjuvant chemotherapy trials. Individual patient data were analyzed from 3005 patients making up 98% of patients from all known eligible trials. The trials were grouped based on the use of single agent platinum or platinum-based combination chemotherapy. There was a significant benefit in favor of platinum-based combination chemotherapy with regard to overall survival (HR = 0.86, 95% CI 0.77 to 0.95, $P = .003$). This resulted in an absolute survival benefit of 5%, improving overall survival from 45% to 50% at 5 years. Disease-free survival data were available on 2846 patients from 10 trials. There was a significant benefit in the platinum-based combination chemotherapy group (HR = 0.78, 95% CI 0.71 to 0.86, $P < .0001$). The 5% survival benefit was consistent across patient subgroups including age, sex, clinical stage, and performance status.

The Cancer Care Ontario Program in Evidence-based Care Practice Guidelines Initiative also reported a neoadjuvant chemotherapy meta-analysis (Winkvist et al, 2004). The authors reviewed 16 randomized-controlled trials (3315 patients) and identified 11 (2605 patients) with suitable data. The pooled HR was 0.90 (95% CI 0.78 to 0.96, $P = .02$) in favor of neoadjuvant chemotherapy. When the eight trials using cisplatin-based combination chemotherapy were analyzed, the pooled HR was 0.87 (95% CI 0.78 to 0.96, $P = .006$), consistent with an overall survival benefit of 6.5% (95% CI 2 to 11).

Based on the randomized trial results and subsequent meta-analyses, cisplatin-based neoadjuvant chemotherapy is associated with an overall survival advantage of 5% to 6% and a pathologic

TABLE 94-4 Randomized Trials of Neoadjuvant Chemotherapy

STUDY	NO. OF PATIENTS	NEOADJUVANT ARM	CONTROL ARM	STAGE	SURVIVAL RATE
EORTC/MRC (<i>International Collaboration of Trialists, 1999</i>)	976	CMV + RC/RT	RC/RT	T2-4aNxM0	10-yr OS: 36% vs. 30% ($P = .037$)
Nordic I (<i>Malmstrom et al, 1996</i>)	325	CA + RT + RC	RT + RC	T1-4aNxM0	5-yr OS: 59% vs. 51% ($P = .1$)
Nordic II (<i>Sherif et al, 2002</i>)	317	CM + RC	RC	T2-4aNxM0	5-yr OS: 53% vs. 46% ($P = .24$)
SWOG (<i>Grossman et al, 2003a, 2003b</i>)	317	MVAC + RC	RC	T2-4aN0M0	5-yr OS: 57% vs. 43% ($P = .06$)
WMURG/ABCSG (<i>Wallace et al, 1991</i>)	255	Cis + RT	RT	T2-4aNxMx	No difference
GUONE (<i>Bassi et al, 1998</i>)	206	MVAC + RC	RC	T2-4aN0M0	5-yr OS: 55% vs. 54% ($P = \text{NS}$)
Abol-Enein et al, 1997	196	CarboMV + RC	RC	T2NxMx	5-yr OS: 62% vs. 42% ($P = .013$)
GISTV (<i>Italian Bladder Cancer Study Group, 1996</i>)	171	MVEC + RC	RC	T2-4N0M0	Median OS: NR vs. 5.5 yr ($P = \text{NS}$)
CUETO (<i>Martinez Piñeiro et al, 1995</i>)	122	Cis + RC	RC	T2-4aNx-2M0	6.5-yr OS: 35% vs. 37% ($P = .95$)
Daveca 89-02 (<i>Sengelov et al, 2002</i>)	120	CM + RT	RT	T2-4bNx-3M0	5-yr OS: 19% vs. 24% ($P = .98$)
Coppin et al, 1996	99	Cis + RT/RC	RT + RC	T2-4bN0-3M0	3-yr OS: 47% vs. 33% ($P = .34$)

CA, cisplatin and doxorubicin; CarboMV, carboplatin, methotrexate, and vinblastine; Cis, cisplatin; CM, cisplatin and methotrexate; CMV, cisplatin, methotrexate, and vinblastine; CUETO, Spanish Oncology Group; EORTC/MRC, European Organization for Research and Treatment of Cancer/Medical Research Council; GISTV, Gruppo Italiano per lo Studio dei Tumori della Viscica (Italian Bladder Cancer Study Group); GUONE, Gruppo Uro-Oncologico del Nord-Est (North-Eastern Uro-Oncological Group, Italy); MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; MVEC, methotrexate, vinblastine, epirubicin, and cisplatin; OS, overall survival; RC, radical cystectomy; RT, radiation therapy; SWOG, Southwest Oncology Group; WMURG/ABCSG, West Midlands Urological Research Group/Australian Bladder Cancer Study Group.

complete response rate of 30% to 40%. Currently the NCCN guidelines recommend clinicians strongly consider neoadjuvant cisplatin-based chemotherapy for cT2N0M0 patients and recommends neoadjuvant cisplatin-based chemotherapy for cT3-T4aN0M0 patients. The European Association of Urology guidelines currently recommend neoadjuvant chemotherapy for T2-T4aN0M0 patients and also note that it should always be a cisplatin-based combination regimen. Despite the evidence supporting neoadjuvant chemotherapy, it continues to be underused. An analysis of 7161 patients with stage III bladder cancer within the National Bladder Cancer Database noted that only 11.6% of patients received perioperative chemotherapy, of which 1.2% were in the neoadjuvant setting (*David et al, 2007*). SEER-Medicare data have also demonstrated a lack of penetrance of neoadjuvant chemotherapy in the setting of muscle-invasive disease (*Porter et al, 2011*).

ADJUVANT CHEMOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER

Patients with pT3-T4 or node-positive disease are known to be at high risk for failure following cystectomy. Adjuvant chemotherapy has been used in this population in an attempt to treat micrometastatic disease and to improve survival. The rationale for systemic chemotherapy following cystectomy includes the fact that it allows for immediate local treatment with cystectomy and avoids any delay in treatment in patients with chemotherapy-resistant tumors (*Sternberg and Sylvester, 2014*). The availability of final pathology also allows clinicians to select patients at the highest risk for failure who are most likely to benefit, while sparing those who are less likely to progress from the side effects of systemic chemotherapy. Additionally, the role of molecular markers to predict disease aggressiveness and therapeutic response is likely to expand in the future. Cystectomy in this case would provide adequate tissue to direct individualized therapy based on molecular and genomic analysis.

A major limitation of adjuvant chemotherapy is that it is often difficult or impossible for patients to undergo systemic

therapy following cystectomy secondary to surgical deconditioning, deteriorating renal function, or perioperative complications (*Hall et al, 1996; Donat et al, 2009*). For example, in a randomized trial evaluating adjuvant chemotherapy for pT3-4/N+ disease, 25% of patients randomized to the chemotherapy arm did not receive such therapy (*Skinner et al, 1991*). Adjuvant chemotherapy trials have been hampered by small overall numbers and difficult patient accrual, which has limited the ability to draw definitive conclusions regarding the overall effectiveness of this approach.

Randomized Trials of Adjuvant Chemotherapy

There have been multiple randomized trials set forth to define the role of adjuvant chemotherapy (*Table 94-5*). Unfortunately these trials have not provided sufficient evidence to support adjuvant chemotherapy, and this is because of low numbers, difficulty with patient accrual, early termination of the trials, and flawed statistical design. The first prospective, randomized trial to demonstrate a survival benefit with adjuvant chemotherapy was reported by the University of Southern California (USC) group (*Skinner et al, 1991*). A total of 91 patients with pT3/T4 or N+ disease following cystectomy were randomized to cisplatin-based chemotherapy versus observation. Three-year time to progression was significantly better in the chemotherapy group with 70% of patients free of disease compared to 46% assigned to observation. Median survival was also significantly improved in the chemotherapy arm (4.3 years vs. 2.4 years; $P = .0062$). Although this trial did demonstrate an advantage in favor of adjuvant chemotherapy, it has been criticized for several reasons. First, the overall number of patients is small, which limits statistical power. Additionally, chemotherapy regimens were not standardized and included cisplatin, cyclophosphamide, and doxorubicin (Adriamycin) (CISCA)-like regimen, single-agent cisplatin, and chemotherapy regimens selected by clonal assays. This trial also highlighted the difficulty of administering chemotherapy after cystectomy with 25% of patients who were assigned to receive chemotherapy and who were not receiving therapy.

TABLE 94-5 Adjuvant Chemotherapy Trials Following Cystectomy

INVESTIGATOR	NO. OF PATIENTS	REGIMEN	CHEMO	NO CHEMO	RESULTS/SHORTCOMINGS
Logothetis et al, 1988	133	CISCA	62	71	Benefit; not randomized
Skinner et al, 1991	91	CAP	47	44	Benefit DFS 4.3 vs. 2.4 yr; few patients received therapy
Stockle et al, 1992, 1995	49	MVAC/MVEC	23	26	Benefit DSS (71.8 vs. 20.4 mo); no chemotherapy at relapse in control arm
Studer et al, 1994	77	DDP	40	37	No benefit
Bono et al, 1997	83	CM	48	35	No benefit for N0
Freiha et al, 1996	50	CMV	25	25	Benefit TTP (37 vs. 12 mo); early closure, no overall survival benefit
Otto et al, 2001	108	MVEC	55	53	No benefit
Cognetti et al, 2012	194	GC	102	92	No benefit for N0 or N+

CAP, cisplatin, cyclophosphamide, and doxorubicin; CISCA, cisplatin, cyclophosphamide, and doxorubicin (Adriamycin); CM, cisplatin and methotrexate; CMV, cisplatin, methotrexate, and vinblastine; DDP, diamminedichloroplatinum (cisplatin); GC, gemcitabine and cisplatin; MVAC, methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin; MVEC, methotrexate, vinblastine, epirubicin, and cisplatin; TTP, time to progression.

A German trial randomized 49 patients with pT3b/T4a and/or N+ disease to receive 3 cycles of MVAC or MVEC (methotrexate, vinblastine, epirubicin, and cisplatin) (Stockle et al, 1992, 1995). A total of 26 patients were randomized to chemotherapy, and 69% received it. Three-year disease-free survival was significantly improved in the chemotherapy arm (63% vs. 13%, $P = .002$), and based on these results the study stopped early. This study was updated with a total of 83 patients (38 received chemotherapy after the close of the trial based on the interim analysis). Ten-year follow-up data maintained an advantage in the chemotherapy group with regard to progression-free survival (44% vs. 13%, $P = .02$) and disease-specific survival (42% vs. 17%, $P = .007$). Although there was a trend toward an overall survival benefit in the adjuvant chemotherapy arm, this was not statistically significant (27% vs. 17%, $P = .07$). Ultimately, 92% of patients in the observation arm showed evidence of tumor progression compared to 27% who received chemotherapy. Much like the USC trial, this trial has also been widely criticized. Overall, the number of patients is small because of early closure of the trial after interim analysis. Many patients in the observation group were not offered chemotherapy at the time of disease progression and, as one would expect, not all patients randomized to chemotherapy ultimately received such therapy.

Since the mid-2000s there have been several attempts at large-scale adjuvant chemotherapy trials, most of which have been presented in abstract form. Unfortunately, the majority of these studies have been hampered by poor accrual. The results of an Italian adjuvant chemotherapy, multicenter, randomized phase III trial have been published (Cognetti et al, 2012). This study randomized 194 patients with pT2G3, pT3-4, N0-2 urothelial carcinoma to observation ($n = 92$) versus four cycles of chemotherapy ($n = 102$). The chemotherapy cohort was randomly assigned to one of two regimens; either gemcitabine 1000 mg/m² days 1, 8, and 15 and cisplatin 70 mg/m² day 2 or the same gemcitabine schedule plus cisplatin 70 mg/m² day 15, every 28 days. With a median follow-up of 35 months, the 5-year overall survival was 48.5% with no difference between the chemotherapy and observation arm ($P = .24$). There was also no statistical difference in disease-free survival in the observation (42.3%) and chemotherapy arms (37.2%). Only 62% of patients received the planned course of chemotherapy, however. The initial study was designed to randomize 610 patients in a 1:1 fashion, but was closed early because of poor accrual. The smaller sample size resulted in significant underpowering of the study in detecting a significant difference between adjuvant chemotherapy and observation.

The Cancer and Leukemia Group B (CALGB) trial randomized patients following cystectomy with acceptable renal function to either a rapid cycling regimen of chemotherapy with 4 cycles of

doxorubicin-gemcitabine administered at 14-day intervals with granulocyte colony-stimulating factor (G-CSF) support followed by 4 cycles of paclitaxel-cisplatin provided at 21-day intervals compared to adjuvant gemcitabine with cisplatin in a 4-week cycle (Bajorin, 2001). The accrual goal in this trial was 800 patients; however, the study was terminated for poor accrual, and ultimately fewer than 100 patients enrolled. Similarly, the EORTC-30994 trial randomized patients with pT3-4 and/or N+ disease with acceptable renal function to either 4 cycles of either gemcitabine/cisplatin, MVAC, or High Dose Intensity (HD) MVAC versus observation. The accrual goal for this trial was 660 patients, but it closed as a result of poor accrual enrolling a total of 278 patients (Sternberg et al, 2001c). The USC/SWOG International trial randomized 114 patients with pT1-2, N0, p53-positive tumors to 3 cycles of adjuvant MVAC or observation (Stadler et al, 2009). A total of 114 patients were randomized, but further accrual was halted after interim analysis showed no difference in recurrence-free survival. Additionally, 67% of those randomized to MVAC received all 3 cycles and 12% received none. The Spanish Oncology Genitourinary Group (SOGUG) 99/01 trial randomized patients with pT3-4 or node-positive disease to 4 cycles of paclitaxel, gemcitabine, and cisplatin versus observation. At a median follow-up of 51 months, a 5-year overall survival advantage was noted with chemotherapy (60% vs. 31%, $P < .0009$); however, the trial was stopped prematurely because of poor accrual after 7 years after randomizing 142 patients, which was well below the target of 340.

Similar to the neoadjuvant chemotherapy, the Advanced Bladder Cancer (ABC) Meta-analysis Collaboration (2005a, 2005b) evaluated the effect of adjuvant chemotherapy reviewing 11 randomized trials and ultimately including 6 trials with a total of 491 patients. The overall HR for survival from this meta-analysis was 0.75 (95% CI 0.60 to 0.96, $P = .019$) suggesting a 25% relative reduction in the risk of death in favor of adjuvant chemotherapy compared to controls. This translated to a 9% absolute survival benefit at 3 years. Despite the positive findings, the authors of the meta-analysis point out that insufficient evidence remains to base treatment decisions reliably. Notably, there were major deficiencies in the trials included in the meta-analysis such as small sample sizes, early closure of trials, limitations in statistical analysis, and differences in the way disease-free survival was defined (Sternberg and Collette, 2006a).

Despite the efforts of the trials outlined previously, the evidence for adjuvant chemotherapy is lacking. An updated meta-analysis including 945 patients noted that adjuvant chemotherapy seems to be most beneficial to patients with node-positive disease; however, this meta-analysis was limited by many of the same issues outlined earlier (Leow et al, 2014). The available evidence suggests perioperative chemotherapy does confer a survival benefit for bladder

cancer patients, with stronger evidence available in the neoadjuvant approach. The optimal approach and benefit to systemic chemotherapy in the adjuvant setting remains incompletely defined, and based on the difficulty with patient accrual in past trials it may remain unanswered. Currently the NCCN guidelines favor neoadjuvant chemotherapy instead of adjuvant chemotherapy based on higher-level evidence data; however, the guidelines do suggest considering adjuvant chemotherapy in the setting of pT3-4 or node-positive disease based on the available data. The EUA guidelines currently recommend adjuvant chemotherapy within clinical trials but not as a routine therapeutic option, as randomized trials and meta-analyses have not provided sufficient evidence to support routine use.

BLADDER PRESERVATION

Although radical cystectomy remains the standard of care for patients with muscle-invasive bladder cancer, it is a major operative procedure with significant risk of perioperative morbidity and mortality (Shabsigh et al, 2009). Data from Medicare claims have shown radical cystectomy to have the second highest 30-day readmission rate compared to other urologic and nonurologic procedures (Goodney et al, 2003). The high incidence of perioperative complications, coupled with a classically older patient population with multiple medical comorbidities, has led patients and clinicians to seek alternatives to cystectomy. Bladder preservation should be undertaken with the goal of curative therapy and to maintain a functionally intact bladder.

Historical series have demonstrated inferior results with single modality therapy (radical TUR, chemotherapy alone, or radiation alone) compared to that of radical cystectomy. With this in mind, successful bladder preservation should be viewed as a multimodal therapy involving aggressive TUR, systemic chemotherapy, and radiation therapy. Appropriate patient selection is also extremely important to optimize response to bladder-sparing protocols. Each patient should be thoroughly evaluated regarding perioperative risk before undergoing radical cystectomy. Patients who are medically unfit for surgery or who refuse surgery can be considered for bladder preservation. Patients who are deemed “medically fit” to undergo cystectomy should be offered cystectomy as the standard of care; however, bladder preservation is a reasonable option for those who are highly selected and counseled appropriately. Patients with hydronephrosis, obvious T3 disease on imaging, presence of CIS, multifocal tumors, and/or incomplete macroscopic tumor resection are suboptimal candidates for bladder preservation.

Single Modality Treatment

Radical Transurethral Resection

Primary support for radical TUR as a single modality therapy for patients with T2 disease is largely based on the finding of p0 disease in approximately 10% of patients treated with radical cystectomy alone. A major limitation of radical TUR monotherapy is the significant risk of occult extravesical disease noted in patients with clinical T2 disease. Pathologic T3 and pT4 disease has been noted in cT2 cystectomy specimens in up to 40% and 9% of patients, respectively (Karakiewicz et al, 2006b). Additionally, multiple radical cystectomy series have consistently shown an approximately 25% risk of occult nodal metastasis at the time of surgery (Stein et al, 2001). Therefore, TUR monotherapy in upwards of 50% of patients presenting with muscle-invasive bladder cancer would be undertreatment. In highly selected patients, however, several authors have reported reasonable long-term results with this approach.

In a series of 133 patients and a minimum of 15-year follow-up, radical TUR was reported to have a disease-specific survival of 82%, 80%, and 77% and progression-free survival of 76%, 65%, and 58% at 5, 10, and 15 years, respectively (Solsona et al, 2010). Patients were excluded from this approach if they presented with tumors greater than 3 cm or hydronephrosis. Patients with CIS at the time

of TUR were treated with intravesical therapy. Wide resection of the TUR site was also performed at 3 and 6 months, and the patients underwent intensive endoscopic surveillance every 3 months for 2 years, every 6 months for 3 years, and annually thereafter. Long-term results with TUR monotherapy (≥ 10 years) have also been reported by the MSKCC group (Herr, 2001). This cohort of 99 patients with muscle-invasive disease all underwent a restaging TUR that demonstrated either no tumor (74%) or residual non-muscle-invasive disease (26%) before enrolling in a bladder-preservation protocol. The 5- and 10-year disease-specific survival rates were 82% and 76% with actual bladder preservation rates of 67% and 57%, respectively. Patients with cT0 disease at the time of restaging TUR achieved the best long-term responses with a 10-year disease-specific survival of 82% compared to 57% for those with residual non-muscle-invasive disease. A third of the patients ultimately developed muscle-invasive bladder cancer, of which nearly half (47%) died of disease. The MD Anderson group has also reported on a smaller cohort of patients treated with TUR monotherapy and a median follow-up of 2.5 years (Leibovici et al, 2007). Criteria for TUR monotherapy in this cohort included no residual tumor at the resection site on repeat TUR, normal examination under anesthesia, normal upper urinary tract evaluation, and no urethral involvement. Of the 327 patients who presented with muscle-invasive bladder cancer during a 6-year period, 35 (11%) met entry criteria and 27 elected for bladder preservation. With a median follow-up of 2.5 years, 44% remained free of disease, whereas 56% experienced a recurrence. Of the 15 patients who had a subsequent recurrence, one presented with lymph node positive disease. Eight patients ultimately underwent cystectomy, of which five showed extravesical disease on final pathology.

Although specifically selected individuals can achieve a durable response with radical TUR, most patients presenting with muscle-invasive bladder cancer are not appropriate candidates and will not be cured with TUR monotherapy. If a patient is going to elect TUR monotherapy, that patient should be properly informed regarding risk of recurrent disease and should be appropriately selected based on clinical criteria including a negative restaging TUR, no hydronephrosis, no evidence of adenopathy, tumor size less than 3 cm, and lack of multifocal disease.

Partial Cystectomy

Compared to radical TUR, partial cystectomy offers two distinct advantages. First, a full pelvic lymphadenectomy can be performed that allows for complete staging. Second, the full thickness of bladder wall and associated perivesical fat can be removed. Historically, partial cystectomy was associated with poor outcomes including 5-year overall survival rates as low as 24% (Kassouf et al, 2006) and high rates of local recurrence and wound recurrences. However, with more stringent selection criteria, partial cystectomy can be associated with acceptable oncologic outcomes.

Ideal candidates for partial cystectomy include those with small, solitary tumors amenable to wide resection with 2-cm margins. Ideally the tumor should be away from the ureteral orifices to avoid reimplantation. It is imperative that the tumor is in a location that allows for complete resection while maintaining adequate functional bladder capacity. Partial cystectomy is also the treatment of choice for urachal adenocarcinoma; however, these lesions are distinct pathologic entities from urothelial carcinoma and the studies that follow are specific to urothelial carcinoma. The presence of CIS is considered by most to be a contraindication to partial cystectomy, and random bladder biopsies can be performed preoperatively. The MSKCC group has also recommended the routine use of intraoperative frozen sections and proceeding with radical cystectomy if a negative margin cannot be achieved (Holzbeierlein et al, 2004). Using strict selection criteria, long-term oncologic results can approach that of radical cystectomy (Holzbeierlein et al, 2004; Kassouf et al, 2006).

Contemporary series demonstrate non-muscle-invasive recurrences in 12% to 50%, muscle-invasive recurrences in 17% to 57%, and metastatic recurrence in 14% to 52% of cases, respectively

(Holzbeierlein et al, 2004; Kassouf et al, 2006; Smaldone et al, 2008). The 5-year overall, recurrence-free and disease-specific survival in the same series were 67% to 70%, 39% to 62%, and 84% to 87%, respectively. Bladder intact rates and bladder intact without evidence of disease rates were reported by the MSKCC and the MD Anderson groups as 65% to 74% and 49% to 67%, respectively. Salvage cystectomy may be necessary in up to a quarter of patients and can be associated with a cure in 75% of cases. It is important to note the presence of late recurrence of muscle-invasive disease in 3 patients (41, 44, and 138 months) in the MD Anderson experience, highlighting the need for long-term follow-up in such patients. There are risk factors for recurrence after partial cystectomy.

Partial cystectomy has also been reported in combination with neoadjuvant chemoradiation therapy. Koga and colleagues have reported on 46 patients with muscle-invasive bladder cancer who were treated with this approach (Koga et al, 2012). Selection criteria included a solitary tumor comprising less than 25% of the total bladder area, no involvement of the bladder neck or trigone, and a complete TUR. Treatment consisted of 40 Gy of external beam radiation concurrently with two cycles of cisplatin (20 mg/day for 5 days). Only 3 patients (7%) showed residual muscle-invasive disease at the time of partial cystectomy. At a median follow-up of 45 months, the 5-year overall and cancer-specific survival were both 100%. Whereas radical cystectomy remains the gold-standard therapy following neoadjuvant chemotherapy, resection of the primary tumor site with partial cystectomy has been used in partial and complete responders (Herr et al, 1998; Sternberg et al, 2003). Adjuvant chemotherapy has been reported to improve progression-free survival in patients with adverse pathologic features at the time of partial cystectomy (Kassouf et al, 2006); however, absolute numbers are small, warranting further studies to define the role of adjuvant therapy partial cystectomy.

Radiation Monotherapy

Radiation therapy has been used to treat muscle-invasive bladder cancer since before the mid-1980s. For clarity of presentation in this section, the term radiation monotherapy will also be used to describe studies in which debulking TUR was performed before radiation. The rationale for this terminology is that it is often difficult to ascertain exactly how complete the debulking TUR was that was performed across various series, which likely varies from institution to institution. Radiation therapy is typically administered in a 1.5- to 2.0-Gy dose per fractions, although higher doses have been reported in Europe. Total dose is generally between 55 and 65 Gy. Higher doses have been shown to improve local response rates, but these come at the cost of increased toxicity.

Five-year overall survival rates have been reported from 26% to 50%; however, local failures can be seen in more than 30% of cases when radiation is used as monotherapy. Rodel and colleagues (2002) reported on 126 patients treated with radiation monotherapy. The authors reported 5- and 10-year overall survival rates of 40% and 19%, respectively, which were inferior to results obtained with a chemoradiation regimen. As with cystectomy series, response to radiation monotherapy is largely dependent on the stage of disease. Local control rates have been reported to be as low as 27% for patients with T3 disease (Pollack et al, 1996). A more recent multicenter study demonstrated more favorable results for radiation monotherapy (2-year disease-free survival of 54% and 5-year overall survival of 35%); however, improved survival was noted in patients treated with combined chemoradiation therapy (James et al, 2012). Prognostic factors for local failure after radiation monotherapy are similar to those of radical TUR, including tumor multifocality, presence of hydronephrosis, and higher clinical T stage.

Combined external beam radiation and brachytherapy have also been explored as possible bladder preservation techniques. Using a technique of 30 Gy of external beam radiation followed by 40 Gy of brachytherapy, Nieuwenhuijzen and colleagues (2005) reported 5- and 10-year overall survival rates of 62% and 50%, with 5- and 10-year disease-specific survival rates of 73% and 67%, respectively. The local control rate at 5 years was 73%. Survival

results were similar to radical cystectomy patients at the same institution during that time period; however, this was not a prospective, randomized trial and therefore definitive conclusions compared to radical cystectomy outcomes are not valid. Additionally, patients with high-grade T1 bladder cancer were also included in this analysis, limiting its generalizability to a population of strictly muscle-invasive patients.

Radiation monotherapy currently should be considered inferior to that of combined chemoradiation therapy, but it can be considered in the palliative setting or for patients who are otherwise unfit and unwilling to undergo any other form of therapy (chemotherapy or surgery).

Primary Chemotherapy

The primary role for systemic chemotherapy in the treatment of muscle-invasive bladder cancer has been in the neoadjuvant or adjuvant setting in combination with radical cystectomy. Similar to radiation monotherapy, it is generally accepted that combination chemoradiation therapy is superior to chemotherapy alone. It is well established that an increased proportion of patients who receive neoadjuvant chemotherapy will have p0 disease at the time of cystectomy. Radical cystectomy remains the standard of care in patients who have had a complete response to neoadjuvant therapy; however, patients have refused cystectomy in this setting. The MSKCC group has reported outcomes for 63 patients who declined cystectomy after achieving a complete response with neoadjuvant chemotherapy (Herr, 2008). At a minimum of 5 years of follow-up, 64% of patients were alive and 54% exhibited an intact bladder. Thirty-six percent of the cohort ultimately died of bladder cancer, of which the majority relapsed with invasive disease in the bladder. Predictors of prolonged survival with chemotherapy alone in this group included small solitary tumors and low-stage, completely resected tumors. Sternberg and colleagues have also reported on the use of systemic MVAC and TUR with the intention of bladder preservation (Sternberg et al, 2003) in 104 patients. Following completion of chemotherapy, patients underwent a repeat TUR and 49% were noted to have a complete response. Sixty percent of patients were alive at a median follow-up of 56 months without further therapy. Patients downstaged to pT0 or to non-muscle-invasive disease exhibited superior survivals compared to those with persistent muscle-invasive disease. These data suggest that some patients with low-risk muscle-invasive tumors can be cured with TUR and chemotherapy alone. However, the results presented earlier were obtained at specialized centers and it is unknown whether they can be applied to other practice settings.

Trimodal Therapy

Although radical cystectomy with neoadjuvant chemotherapy remains the gold standard by which all other treatments for muscle-invasive bladder cancer should be measured, several studies have shown bladder preservation to be a reasonable option in highly selected patients. Ideal candidates for bladder preservation should have good baseline bladder function, have a complete resection of all visible tumors endoscopically, have small solitary tumors with limited CIS, and have no evidence of hydronephrosis. If held to strict criteria, approximately 6% to 19% of patients presenting with muscle-invasive bladder cancer could be considered as candidates for such an approach (Smith et al, 2013). The major chemoradiation bladder preservation trials are summarized in Table 94-6.

Two basic strategies for trimodal bladder preservation exist: split-course and continuous-course therapy. Split-course therapy is based on the premise of midtreatment restaging. Patients are administered induction chemoradiation therapy to approximately 40 Gy, which is followed by restaging with cross-sectional imaging and endoscopic evaluation. If persistent invasive disease is noted, radical cystectomy is recommended. Those without persistent invasive disease undergo consolidative chemoradiotherapy to approximately 64 Gy. As the name implies, continuous-course treatment involves a full course of chemoradiation therapy followed by an endoscopic

TABLE 94-6 Major Prospective Trimodal Bladder Preservation Studies

STUDY	NO. OF PATIENTS	STAGE	CHEMOTHERAPY	RT	CR RATE	SALVAGE CYSTECTOMY RATE	SURVIVAL
Housset et al, 1993	54	T2-4N0-1Mx	Cisplatin + 5-FU × 4	44 Gy	74%	NA	3-yr CSS 62%, OS 59%
Shipley et al, 1998	62	T2-4aN0Mx	Cisplatin × 3	64.8 Gy	60%	25.8%	5-yr OS 49%
Tunio et al, 2012	200	T2-4N0Mx	Cisplatin weekly	65 Gy	93%		5-yr OS 52%
James et al, 2012	182	T2-4aN0Mx	5-FU, MMC × 2	55 or 64 Gy		11.4%	5-yr OS 48%
Gogna et al, 2006	113	T2-4N0Mx	Weekly cisplatin	64 Gy	70%	13%	5-yr OS 50%
Kaufman et al, 2009a, 2009b	50	T2-4aN0Mx	Weekly cisplatin + paclitaxel	64.3 Gy	87%		5-yr OS 56%, 5-yr CSS 71%

CR, complete response; CSS, cause-specific survival; 5-FU, 5-fluorouracil; MMC, mitomycin C; OS, overall survival.

restaging examination 6 months after therapy to allow time for an adequate response to therapy. Regardless of approach, maximal tumor debulking before trimodal therapy is critical to optimize therapeutic results. Studies have demonstrated improved 5- and 10-year overall survival rates for patients with complete TURs (57% and 39%) compared to those without complete resection (43% and 29%) before trimodal therapy. Additionally, the rates of radical cystectomy for visibly complete resections are lower (11%) compared to incomplete resections (42%) (Efsthathiou et al, 2012).

The split-course approach has largely been developed within the Radiation Therapy Oncology Group (RTOG). The RTOG has completed six prospective protocols using slightly different techniques to evaluate the efficacy of trimodal therapy for muscle-invasive disease. In total, 415 patients were entered into these trials. The 5-year overall survival rate was approximately 50% for the entire cohort with 75% of patients achieving a “cure” while maintaining an intact bladder (Shipley et al, 2003). The most recent RTOG protocol randomized 93 patients with cT2-T4, N0 disease to cisplatin/paclitaxel or cisplatin/5-fluorouracil (5-FU) with induction and consolidation radiotherapy followed by adjuvant gemcitabine/paclitaxel/cisplatin. Induction dose radiotherapy was 40.3 Gy, with a consolidation dose of 24 Gy. If T1 or higher disease was found after induction therapy, salvage radical cystectomy with adjuvant chemotherapy was performed. With a median follow-up of 3 years, the complete response rate was 72% and 62% for cisplatin/paclitaxel and cisplatin/5-FU, respectively. The bladder-intact survival rates at 4 years were 73% and 69%, respectively. Late grade toxicity greater than or equal to 3 was noted in 9% and 4% of patients, respectively. The Massachusetts General Hospital has reported the largest institutional experience with split-course trimodal therapy. They have published long-term results regarding their 348-patient cohort with 5-, 10-, and 15-year overall survival rates of 52%, 35%, and 22%, respectively. As expected, the overall survival rates are best for those with cT2 disease at 61%, 43%, and 28% compared to 41%, 27%, and 16% for those with T3/T4 tumors. The 5-, 10-, and 15-year disease-specific survival rates were 64%, 59%, and 57%, respectively, with bladder-intact rates of 60%, 45%, and 36%, respectively (Efsthathiou et al, 2012).

Continuous-course trimodal therapy has also been reported in long-term institutional series as well as prospective trials. A multicenter, phase 3 trial randomized 360 patients to continuous-course chemoradiation therapy compared to radiation therapy alone. Patients in the chemoradiation cohort received mitomycin followed by 5-FU in conjunction with radiation. The primary end point was locoregional disease-free survival. The secondary end points were overall survival and toxicity. At 2 years, the locoregional disease-free survival in the chemoradiation therapy group was 67%. The 5-year overall survival rate was 48%, and there was no significant increase in toxicity compared to the radiation-only group (James et al,

2012). Another large series of continuous-course chemoradiation therapy has been reported in Germany, in which the majority of patients received cisplatin-based chemotherapy. In this series of 331 patients, the 5-, 10-, and 15-year overall survival rates were 54%, 36%, and 24%, respectively. Stratifying patients by T2/T3 disease yielded overall survival rates of 45%, 26%, and 16%; whereas patients with T4 disease fared far worse. The overall 5-year bladder-intact survival was 40% to 54% (Rodel et al, 2002; Krause et al, 2011).

Direct comparisons between bladder preservation and radical cystectomy series cannot be made. Prospective trials are needed to compare the efficacy of trimodal therapy to that of radical cystectomy; however, it is worth noting that reported outcomes from trimodal therapy series are comparable to those of surgical series. Following trimodal therapy, although there is no universally accepted follow-up regimen, close surveillance with cross-sectional imaging and cystoscopy are necessary.

PROGNOSTIC NOMOGRAMS FOR MUSCLE-INVASIVE BLADDER CANCER

As detailed in previous sections, the TNM staging system provides valuable prognostic information following radical cystectomy. Despite its usefulness, there is often wide variation between patients with regard to absolute risk of recurrence as a result of the heterogeneity of tumor biology and patient characteristics. Better understanding and prediction of disease outcome is important to deliver appropriately the adjuvant therapy and to counsel patients with regard to the risk of disease recurrence. The use of standard pathologic data to predict outcomes was discussed in previous sections. Nomograms have been developed in an effort to predict better the prognosis in patients with muscle-invasive disease (Bochner et al, 2006; Karakiewicz et al, 2006a; Shariat et al, 2006a). In addition to standard pathologic features, molecular markers are now being incorporated into predictive models not only to improve prognostic accuracy, but also to provide the potential to predict response to therapy (Karam et al, 2007; Shariat et al, 2008; Youssef et al, 2009; Shariat et al, 2010).

Nomograms incorporating clinical, pathologic, and molecular data have been developed as predictive tools in the muscle-invasive setting (Fig. 94-2). Two consortia have published easy-to-use nomograms for predicting recurrence following radical cystectomy. The International Bladder Cancer Consortium (IBCC) collected data on 9064 patients from 12 centers of excellence (Bochner et al, 2006). Significant variables in the nomogram included age, grade, pathologic stage, histologic subtype, lymph node metastasis, and timing of surgery. The final nomogram was significantly superior to standard prediction models in predicting disease-free survival following

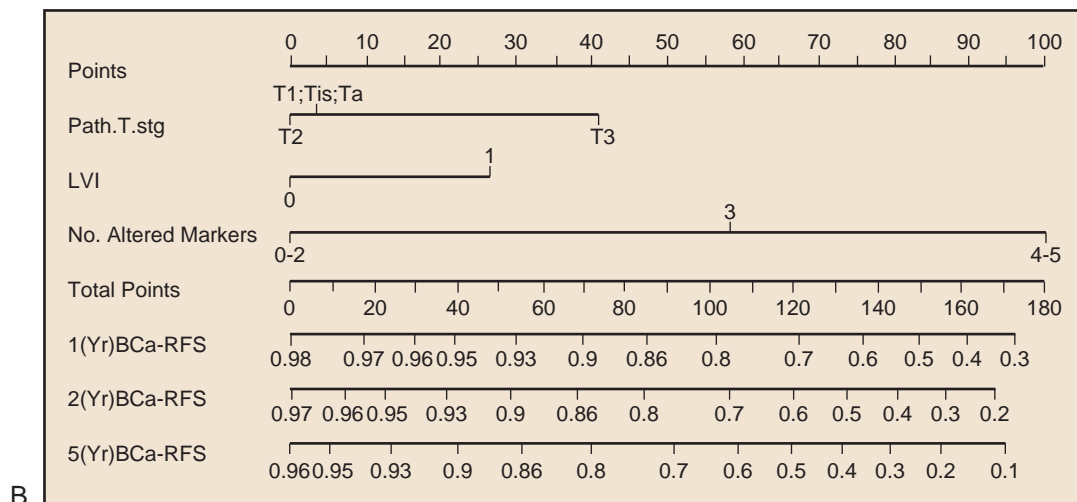
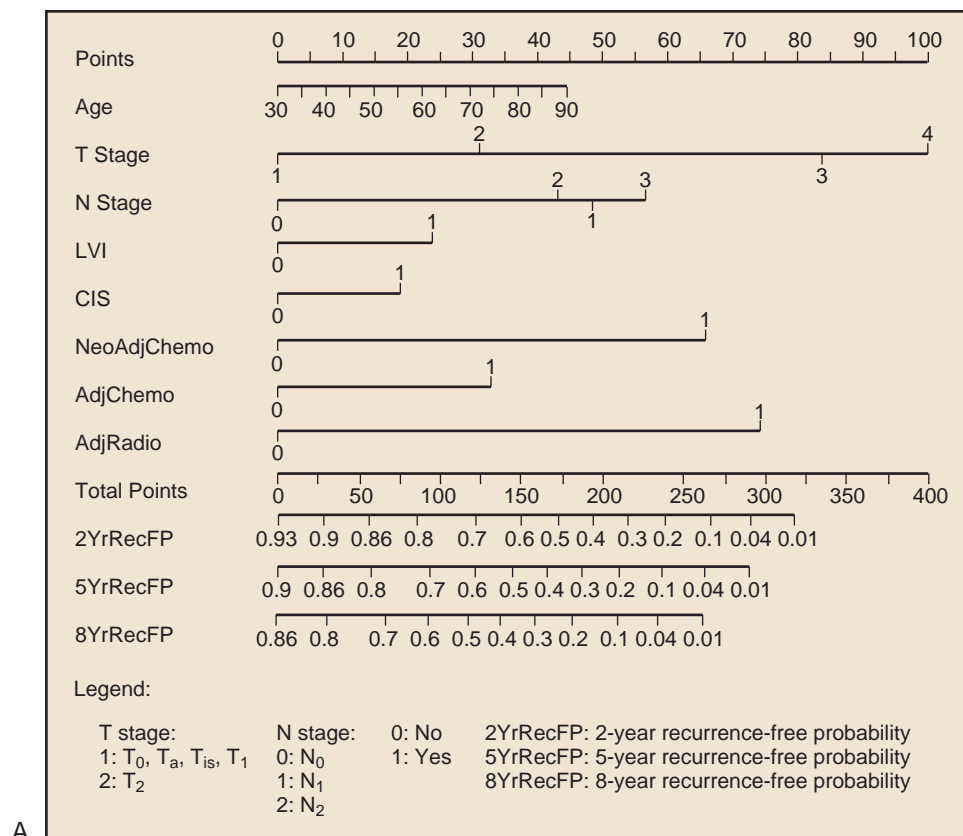


Figure 94-2. To obtain nomogram-predicted probability of recurrence, locate patient values at each axis. Draw a vertical line to the “Point” axis to determine how many points are attributed for each variable value. Sum the points for all variables. Locate the sum on the “Total Points” line. Draw a vertical line toward the 2YrRecFP, 5YrRecFP, and 8YrRecFP axes to respectively determine the 2-year recurrence-free probability, 5-year recurrence-free probability, and 8-year recurrence-free probability. RFS, recurrence-free survival. **A**, Postoperative nomogram for predicting recurrence after radical cystectomy. **B**, Postoperative nomogram for predicting recurrence after radical cystectomy incorporating tissue biomarkers. CIS, carcinoma in situ; LVI, lymphovascular invasion. (A, From Karakiewicz PI, Shariat SF, Palapattu GS, et al. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. *J Urol* 2006;176(4):1354–62; B, from Shariat SF, Karakiewicz PI, Ashfaq R, et al. Multiple biomarkers improve prediction of bladder cancer recurrence and mortality in patients undergoing cystectomy. *Cancer* 2008;112(2):315–25.)

cystectomy (CI 0.75) compared to TNM stage (CI 0.68) or standard pathologic grouping models (CI 0.62). The authors modeled several lymph node variables including total number removed, number of positive nodes, and lymph node density, but found binary node status (positive vs. negative) to be the best predictor. The Bladder Cancer Research Consortium (BCRC) has also published a postcystectomy nomogram based on 728 patients from 3 centers (Karakiewicz et al, 2006a). As opposed to the IBCC nomogram, all patients in the BCRC had urothelial histology. Multivariate predictors of disease recurrence, cancer-specific mortality, and all-cause mortality at 2, 5, and 8 years postcystectomy included pT stage, nodal status, lymphovascular invasion, perioperative chemotherapy administration, and adjuvant radiation therapy. The nomogram improved predictive accuracy in favor of that of the AJCC staging system by 3.2% (0.748 vs. 0.780). Both nomograms have been validated in other patient cohorts (Zaak et al, 2010).

Although postcystectomy nomograms provided enhanced prognostic value following treatment, precystectomy nomograms may include a greater impact in directing definitive therapy including neoadjuvant chemotherapy decisions. Using the same multicenter cystectomy cohort, Karakiewicz and colleagues (2006b) evaluated 726 patients and developed a nomogram incorporating age, TUR stage, tumor grade, and the presence of CIS. The multivariate nomogram was 75.7% accurate versus TUR stage (71.4%) in predicting non-organ-confined disease (pT3 or 4). The nomogram was also more accurate (63.1% vs. 61%) in predicting lymph node metastasis on final pathology. Although the overall performance characteristics of this nomogram did not dramatically improve the ability to predict non-organ-confined disease, it does demonstrate the usefulness and future potential of multivariable nomograms in the predictive setting. A nomogram has also been published to predict response rates to trimodal bladder preservation therapy (Coen et al, 2013). A cohort of 325 patients who underwent bladder preservation at a single institution was used in this evaluation. The final nomogram incorporated clinical T stage, presence of hydronephrosis, completeness of TUR, age, gender, and tumor grade. The ROC (receiver operating characteristic) curve for a complete response to therapy using this nomogram was 0.69, and for bladder-intact disease-free survival it was 0.61.

Although nomograms appear to improve predictive accuracy over standard pathologic criteria, the addition of molecular markers has the potential to aid diagnostic accuracy further. Molecular markers are important in cell-cycle signaling and angiogenesis pathways, and their expression can be quantified by immunohistochemical staining. Inclusion of single biomarkers into prognostic nomograms is unlikely to enhance significantly the prognostic capability owing to the complex tumor heterogeneity and biology. Shariat and associates (2008) studied the use of adding the molecular markers p53, pRB, p21, p27, and cyclin E1 into a nomogram. By adding the molecular markers, the nomogram improved predic-

tive accuracy for recurrence and cancer-specific survival by 10.9% and 8.6%, respectively, for patients with pTa-3N0M0 bladder cancer following radical cystectomy. Shariat and colleagues (2012) have also evaluated p53, p27, p21, and pRB in 272 cystectomy patients and in an external testing cohort of 52 patients with chemotherapy-naïve pT1-2N0M0 urothelial carcinoma. Overall, 80% of patients showed expression of at least one marker. The addition of the number of altered markers increased the accuracy of the base model for disease recurrence and cancer-specific mortality by 15.6% and 14.8%, respectively.

Nomograms, particularly those using novel molecular markers, have demonstrated improved predictive accuracy in favor of standard TNM factors alone. To date, these studies have been performed in retrospective cystectomy and bladder-sparing cohorts and require further validation in the prospective setting. Such nomograms provide the potential to aid clinicians in direct treatment both before definitive treatment (neoadjuvant chemotherapy vs. surgery) and after treatment (adjuvant therapy vs. surveillance).

MANAGEMENT OF METASTATIC BLADDER CANCER

Systemic cisplatin-based combination chemotherapy is the standard of care for patients with metastatic urothelial bladder cancer. First-line systemic regimens include MVAC, HD-MVAC, and gemcitabine/cisplatin (Sternberg et al, 1989; Loehrer et al, 1992; Saxman et al, 1997; von der Maase et al, 2005; Sternberg et al, 2006b). Although the majority of patients with metastatic disease (40% to 70%) will experience an initial response to chemotherapy, most will ultimately progress with a median survival of 14 months and overall 5-year survival rates of 5% to 20% (Table 94-7) (Saxman et al, 1997; von der Maase et al, 2005; Sternberg et al, 2006b; Bellmunt et al, 2012). Despite the initial effectiveness of systemic cisplatin-based chemotherapy, there are several barriers to optimal delivery of chemotherapy in the bladder cancer population. Renal insufficiency is not uncommon in this population, limiting the use of cisplatin. Additionally, poor performance status, medical comorbidity, and frailty are often preexisting conditions that can limit a patient's ability to tolerate systemic therapy. A working group of medical oncologists have published criteria to define patients who are not cisplatin candidates, including any of the following: a World Health Organization or Eastern Cooperative Oncology Group performance status greater than 2, creatinine clearance less than 60 mL/min, grade 2 or above audiometric hearing loss, grade 2 or above peripheral neuropathy, or a New York Heart Association Class III or higher heart failure (Galsky et al, 2011). When cisplatin therapy is contraindicated, carboplatin has been substituted with the benefit of improved tolerability but with the cost of decreased efficacy (Petrioli et al, 1996; Bellmunt et al, 1997; Dogliotti et al, 2007). Although carboplatin is a reasonable choice for patients in whom

TABLE 94-7 Randomized Trials of Frontline Chemotherapy for Metastatic Urothelial Cancer

GROUP	NO. OF PATIENTS	TREATMENT/CONTROL ARM	RELATIVE RISK (%)	MEDIAN SURVIVAL (MO)	P VALUE
Intergroup (Loehrer et al, 1992)	269	MVAC/Cis	39 vs. 12	12.5 vs. 8.2	.0001
MDAH (Logothetis et al, 1990)	110	MVAC/CISCA	65 vs. 46	11.1 vs. 8.3	.0003
EORTC (Sternberg et al, 2006b)	263	HD-MVAC/MVAC	72 vs. 58	14.9 vs. 15.1	.0417
Lilly (von der Maase et al, 2005)	405	GC/MVAC	49 vs. 46	14.0 vs. 15.2	.66
Greece (Bamias et al, 2004)	220	DC/MVAC	37 vs. 54	9.3 vs. 14.2	.026
EORTC (Bellmunt et al, 2012)	626	GC/PCG	46 vs. 57	12.7 vs. 15.8	.03
Dreicer et al, 2004	85	CaP/MVAC	28 vs. 36	13.8 vs. 15.4	.65

CaP, carboplatin and paclitaxel; Cis, cisplatin; CISCA, cisplatin, cyclophosphamide, and doxorubicin (Adriamycin); DC, docetaxel and cisplatin; EORTC, European Organization for Research and Treatment of Cancer; GC, gemcitabine and cisplatin; HD-MVAC, high-dose MVAC; MDAH, MD Anderson Hospital; MVAC, methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin; N, number of patients; NR, not reported; OS, overall survival; PCG, paclitaxel, cisplatin, and gemcitabine.

cisplatin is contraindicated, it should not be considered a first-line therapy for those who are cisplatin candidates.

Poor performance status and the presence of visceral metastasis predict a poor response to chemotherapy for patients with locally advanced or metastatic urothelial carcinoma. The MSKCC group has published their data on 203 patients with unresectable or metastatic bladder cancer treated with MVAC (Bajorin et al, 1999). They found a Karnofsky performance status of less than 80% and visceral (lung, liver, bone) metastasis to be independent predictors of poor outcome. Median survival times for patients who had zero, one, or two risk factors were 33, 13.4, and 9.3 months, respectively.

Randomized Trials in Metastatic Bladder Cancer

A phase III Intergroup randomized trial examined the effectiveness of MVAC therapy to that of single-agent cisplatin in patients with metastatic or locally advanced bladder cancer (Loehrer et al, 1992). A total of 269 patients were randomized, and those patients in the MVAC arm were noted to have significantly higher response rates (39% vs. 12%) and overall survival rates (12.5 vs. 8.2 months). Although superior in efficacy, the MVAC arm was more toxic with regard to leukopenia, mucositis, granulocytopenic fever, and drug-related mortality (3% to 4%). MVAC has also been compared to CISCA in patients with advanced urothelial carcinoma (Logothetis et al, 1990). In this study, 110 patients (86 bladder, 23 upper tract, 1 prostatic urethra) were randomized, with the MVAC regimen demonstrating improved response rates (65% vs. 46%) and overall survival (11.2 vs. 8.4 weeks) compared to CISCA.

Although most patients with metastatic urothelial carcinoma experience some response (complete or partial) to MVAC, the long-term survival rates are dismal (Saxman et al, 1997; Bajorin et al, 1999). In an effort to improve these results, Sternberg and coworkers (2001b) investigated whether increasing the dose intensity of MVAC with G-CSF could improve complete response rates and survival. In this study, 263 patients with chemotherapy-naïve metastatic or advanced urothelial carcinoma were randomized to HD-MVAC (MVAC + G-CSF; 2-week cycle) versus standard MVAC (4-week cycle). The HD-MVAC arm did achieve higher complete response rates (21% vs. 9%) and improved progression-free survival (9.1 vs. 8.2 months); however overall survival was not significantly different between the two groups. Seven years later, additional follow-up was reported in this same cohort (Sternberg et al, 2006b). In the updated analysis, HD-MVAC was reported to have a statistically significant relative reduction in the risk of progression and death compared to that of MVAC (HR = 0.76; 95% CI 0.58 to 0.99; $P = .042$).

Although MVAC has demonstrated efficacy in treating urothelial carcinoma, it has significant toxicity. The toxicity of MVAC led to trials of alternative less-toxic chemotherapy regimens. Most notably, a phase III randomized trial comparing gemcitabine/cisplatin to MVAC was conducted in 405 patients (von der Maase et al, 2000,

2005). There was no difference in response rates (49% vs. 46%), time to progression (7.4 vs. 7.4 months), and overall survival rates (13.8 vs. 14.8 months) between the two study arms. The updated study analysis confirmed equivalence of the two regimens (HR: 1.09, 95% CI 0.88 to 1.34; $P = .66$). The gemcitabine/cisplatin regimen was better tolerated with only 37% of patients in that arm requiring dose modifications compared to 63% in the MVAC arm. Patients in the gemcitabine/cisplatin arm also experienced less grade 3/4 neutropenia, neutropenic fever, neutropenic sepsis, and mucositis. The toxicity-related death rate was also lower in the gemcitabine/cisplatin group (1% vs. 3%). Owing to its equivalent efficacy and better tolerability, gemcitabine/cisplatin is the most widely used chemotherapeutic regimen for muscle-invasive and metastatic bladder cancer.

Randomized trials have also assessed the usefulness of adding additional drugs to standard chemotherapy regimens (Bellmunt et al, 2000; von der Maase et al, 2006). The largest such trial was a phase III study that compared paclitaxel, gemcitabine, and cisplatin (PGC) to standard gemcitabine/cisplatin in 626 patients with locally advanced or metastatic urothelial cancer (Bellmunt et al, 2012). Overall response rates were significantly higher in the PGC arm (55.5% vs. 43.6%, $P = .0031$); however there was not a significant improvement in overall survival (15.8 vs. 12.7 months; HR = 0.85; 95% CI 0.72 to 1.02, $P = .075$). There was also significantly more grade 3 and 4 neutropenia and thrombocytopenia in the PGC arm. A summary of the major chemotherapy trials for metastatic bladder cancer is presented in Table 94-7.

Second-Line Chemotherapy

There is no clear standard second-line chemotherapy for patients who progress or do not respond to first-line therapy. Patients who fail first-line chemotherapy have a dismal prognosis. Salvage chemotherapy in this setting with conventional agents typically has a suboptimal response rate (Dreicer et al, 1996; McCaffrey et al, 1997; Lorusso et al, 1998; Albers et al, 2002; Vaughn et al, 2002) (Table 94-8).

Single-Agent Second-Line Chemotherapy

Multiple novel single agents have been evaluated in patients with advanced bladder cancer, typically with modest response rates of less than 20%.

Vinflunine is a novel antitubulin agent obtained from a vinca alkaloid (Culine, 2006). Bellmunt and coworkers (2009) compared vinflunine plus best supportive care (BSC) versus BSC alone in patients with metastatic urothelial carcinoma previously treated with first-line platinum chemotherapy. Overall, 370 patients were randomized with a 9% response rate in the vinflunine arm. At the time of initial publication, the results of the study met the 2.3-month improvement in overall survival (6.9 vs. 4.6 months),

TABLE 94-8 Salvage Chemotherapy for Metastatic Urothelial Cancer

DRUG	AUTHOR (REFERENCE)	N	ELIGIBILITY	RR (%)	MEDIAN PFS (mo)	MEDIAN OS (mo)
Paclitaxel (24 hr)	Dreicer et al, 1996	9	1 Prior regimen	56	—	—
Paclitaxel (weekly)	Vaughn et al, 2002	31	1 Prior regimen for advanced disease, prior adjuvant chemotherapy and taxanes allowed	10	2.2	7.2
Docetaxel (every 3 wk)	McCaffrey et al, 1997	30	1 Prior cisplatin regimen, prior taxanes not allowed	13	—	9.0
Gemcitabine	Lorusso et al, 1998	35	1 Prior platinum regimen	22.5	—	5.0
Gemcitabine	Albers et al, 2002	30	1 Prior cisplatin regimen	11	4.9	8.7
Gemcitabine-paclitaxel	Sternberg et al, 2001a	41	1 Prior cisplatin regimen including perioperative therapy	60	—	14.4

N, number of patients; OS, overall survival; PFS, progression-free survival; RR, response rate.

TABLE 94-9 Salvage Trials with Single-Agent Chemotherapeutic and Novel Agents for Metastatic Urothelial Cancer

AGENT	AUTHOR	N	PRIOR	RR (%)	MEDIAN PFS (mo)	MEDIAN OS (mo)
Gemcitabine	Lorusso et al, 1998	35	1 Prior platinum regimen	23	3.8	5
Gemcitabine	Albers et al, 2002	30	1 Prior cisplatin regimen	11	4.9	8.7
Paclitaxel	Vaughn et al, 2002	31	1 Prior regimen for advanced disease, prior adjuvant chemotherapy and taxanes allowed	10	2.2	7.2
Ifosphamide	Witte et al, 1997	56	1 Prior cytotoxic regimen	20	2.5	5.5
Docetaxel	McCaffrey et al, 1997	30	1 Prior cisplatin regimen, prior taxanes not allowed	13		9
Nab-Paclitaxel	Ko et al, 2013	48	1 Prior platinum regimen	32	6	10.8
Abraxane	Sridhar et al, 2011	47	1 Prior platinum regimen	32	6	10.8
Eribulin	Quinn et al, 2010	40	1 Prior platinum regimen	38	3.9	9.4
Vinflunine	Culine et al, 2006	51	1 Prior platinum regimen	18	3.0	6.6
Vinflunine	Bellmunt et al, 2013	370	1 Prior platinum regimen	28		6.9
Pemetrexed	Sweeney et al, 2006	47	1 Prior regimen including perioperative therapy within 12 mo	27.7	2.9	9.6
Pemetrexed	Galsky et al, 2007	12	1 Prior regimen	8	—	—
Ixabepilone	Dreicer et al, 2007	42	1 Prior platinum regimen, prior taxane allowed	11.9	2.7	8.0
Oxaliplatin	Winquist et al, 2005	18	1 Prior regimen for advanced disease, prior adjuvant chemotherapy >6 mo earlier not counted	6	—	—

N, number of patients; OS, overall survival; PFS, progression-free survival; RR, response rate.

however this did not achieve statistical significance. The authors published updated survival results in 2013, at which time overall survival had reached statistical significance in favor of the vinflunine arm (HR = 0.719; 95% CI 0.570 to 0.906, $P = .0052$) (Bellmunt et al, 2013). Vinflunine is currently approved in Europe as a second-line agent for metastatic bladder cancer. A phase III clinical trial (NCT00389155) is currently underway in cisplatin-ineligible patients with advanced urothelial carcinoma combining vinflunine and gemcitabine compared to gemcitabine alone.

Paclitaxel has been evaluated in several small phase II studies with modest results. In a study of 31 patients with advanced or progressing urothelial cancer, who had previously been treated with at least one systemic chemotherapy, the patients were treated with a 1-hour weekly infusion of 80 mg/m² of paclitaxel. The median number of cycles delivered was three (1 cycle = 4 weeks). Ten percent achieved a response with a median overall survival time of 7.2 months (Vaughn et al, 2002). Two other phase II trials did not replicate the response rates (5% to 7%) with median survival times in the 6-month range (Papamichael et al, 1997; Joly et al, 2009). Docetaxel has also been used in a similar setting as a second-line agent. This regimen demonstrated modest response rates of 13% and median overall survival times of 9 months; however, 60% of patients developed myelosuppression requiring a dose reduction (McCaffrey et al, 1997).

Pemetrexed is a multitargeted antifolate agent. Initial phase II trials were promising, using 500 mg/m² of pemetrexed intravenously every 21 days and noting complete and partial response rates of 6.4% and 21%, respectively, in 47 patients. The median time to disease progression was 2.9 months and median survival was 9.6 months (Sweeney et al, 2006). Grade 3 and 4 hematologic events were thrombocytopenia (8.5%, 0%), neutropenia (4.3%, 4.3%), and anemia (2.1%, 2.1%). However, a phase II trial using the same dose of pemetrexed showed less promising results in 13 patients with advanced disease who had previously received chemotherapy. In this cohort, only one (8%) patient had an objective response. Piritrexim is a synthetic antifolate agent that has also been investigated as a second-line agent. In a phase II trial of 27 patients with advanced, previously treated, urothelial carcinoma, piritrexim showed a 7% objective response rate. Toxicity was not insignificant with dose-limiting myelosuppression in 29% (Roth et al, 2002). Lassiter and associates (2008) obtained similar results in 23 previously treated patients in whom no objective responses were observed, and 2 patients had disease stabilization after 2 to 4 cycles.

Epothilones are nontaxane tubulin polymerization agents derived from fermentation of the myxobacteria *Sorangium cellulosum*. Ixabepilone is a semisynthetic analogue of natural epothilone B. In a phase II trial involving 45 patients with advanced urothelial carcinoma previously treated with either cisplatin or carboplatin-based chemotherapy, ixabepilone was reported to have an overall response rate of 12% and median overall survival of 8 months. Unfortunately, the toxicity profile of this drug was significant, with 27% in the trial experiencing grade 4 toxicity in addition to 1 treatment-related death (Dreicer et al, 2007). Table 94-9 illustrates published single-agent studies in patients with relapsing or progressive disease following first-line chemotherapy.

Multiaгент Second-Line Chemotherapy

For patients who progress following treatment with gemcitabine/cisplatin, second-line MVAC may be an option for select patients. Han and colleagues (2008) reported on a small cohort ($n = 30$) of patients who were treated with MVAC after failing initial therapy with gemcitabine/cisplatin. The overall response rate was 30%, and 6.7% of patients achieved a complete response. Patients who previously had a response to gemcitabine/cisplatin had a 44% response rate compared to a 14% response rate in patients who had not responded to initial therapy.

Multiple studies have investigated the effectiveness of paclitaxel and gemcitabine as a second-line agent. The published response rates of these trials vary widely from 0% to 60%, likely reflecting different dosing and administration schedules (Meluch et al, 2001; Sternberg et al, 2001a; Kanai et al, 2008; Albers et al, 2011). The largest of these trials randomized 102 patients to a temporary 6-cycle course of paclitaxel and gemcitabine compared to prolonged treatment with gemcitabine/paclitaxel. Although there was not a significant difference in overall or progression-free survival between the two groups, the objective response rates were 37.5% and 41.5%, respectively (Albers et al, 2011).

Larotaxel is a next-generation semisynthetic taxane that includes a mechanism of action similar to that of docetaxel and paclitaxel. Larotaxel has been postulated to have advantages beyond other taxanes including activating taxane-resistant tumor cell and the ability to cross the blood-brain barrier (Sessa et al, 2002; Metzger-Filho et al, 2009). In a phase III randomized trial, larotaxel/cisplatin combination therapy was compared to gemcitabine/cisplatin as first-line treatment for locally advanced or metastatic urothelial

carcinoma in 337 patients (Sternberg et al, 2013). The trial was closed early as a result of the sponsor's decision to stop clinical development of larotaxel. At the time of analysis, there was no difference in overall survival between the two study arms, and progression-free survival was worse with larotaxel/cisplatin (5.6 vs. 7.6 months), suggesting that this regimen does not improve outcomes compared to standard gemcitabine/cisplatin.

There is no general consensus regarding the optimal second-line multiagent therapy for patients with progressing and/or metastatic urothelial carcinoma.

Targeted Therapy

Vascular Endothelial Growth Factor Inhibitor Therapy

Vascular endothelial growth factor (VEGF) receptors are expressed in urothelial carcinomas (von Hardenberg et al, 2014). It is well established that VEGF recruits circulating endothelial progenitors, which are critical for angiogenesis, which is essential for tumor growth and metastatic spread (Carmeliet et al, 2000). VEGF expression in both the urine and the blood has been shown to correlate with metastatic potential and disease recurrence (Crew et al, 1999; Fauconnet et al, 2009). Bevacizumab is a humanized monoclonal antibody of VEGF. Bevacizumab has been evaluated in patients with advanced urothelial carcinoma. In a phase II trial by the Hossier Oncology Group, 43 chemotherapy-naïve patients with either metastatic or unresectable urothelial carcinoma received bevacizumab in combination with gemcitabine/cisplatin (Hahn et al, 2011). The overall response rate in this cohort was 72% (19% complete, 53% partial). With a median follow-up of 27 months, median progression-free survival was 8.2 months and median overall survival was 19.1 months. Of note, grade 3 to 4 hematologic toxicity was not insignificant, with neutropenia in 35%, thrombocytopenia in 12%, anemia in 12%, and neutropenic fever in 2%. Three treatment-related deaths were also reported. A phase 3 intergroup study is currently in progress, which aims to define further the role of bevacizumab in combination with gemcitabine/cisplatin in patients with advanced urothelial carcinoma.

Sunitinib is an oral inhibitor of multiple tyrosine kinases, including VEGF receptors. Sunitinib has demonstrated antitumor activity in human bladder cancer models (Sonpavde et al, 2009; Yoon et al, 2011). Sunitinib was reported as demonstrating a partial response in 8% and disease stabilization in 54% of 37 cisplatin-ineligible patients with advanced urothelial carcinoma (Bellmunt et al, 2011). The median progression-free survival was 5.9 months. Much like bevacizumab, sunitinib has been trialed in combination with gemcitabine/cisplatin, but the side-effect profile was unsatisfactory (Galsky et al, 2013). Sunitinib was also studied in a randomized, phase II trial of maintenance therapy following an initial response to standard chemotherapy compared to placebo (Grivas et al, 2014). The study did not achieve the predefined power as a result of poor accrual and premature closure, however the maintenance sunitinib arm did not improve 6-month progression-free survival rates (2.9 vs. 2.7 months, respectively). Sorafenib, a similar multikinase inhibitor, has been studied in combination with gemcitabine/cisplatin but did not demonstrate superiority compared to chemotherapy alone (Krege et al, 2014).

Epidermal Growth Factor Receptor Therapy

Epidermal growth factor receptor (EGFR) has demonstrated overexpression in bladder tumors and the extent of expression has also correlated with stage and grade of tumors (Neal et al, 1990). Cetuximab is a monoclonal antibody to EGFR and it has been approved for colorectal carcinoma. Cetuximab has been studied in the phase II setting in patients with metastatic urothelial cancer who received previous chemotherapy (Wong et al, 2012). A total of 39 patients were randomized to cetuximab with or without paclitaxel. The single-agent cetuximab arm closed after 9 of 11 patients progressed by 8 weeks. Cetuximab did appear to augment the activity of the paclitaxel arm, with an overall response rate of 28.5% and a median

progression-free survival of 115 days. Cetuximab has also been evaluated in combination with gemcitabine/cisplatin in the phase II setting, but did not improve overall survival (Pea, 2012). The oral tyrosine kinase inhibitor (TKI) gefitinib has produced disappointing results today in urothelial carcinoma trials. In a phase II trial of 31 patients with metastatic urothelial carcinoma, gefitinib was largely ineffective, with a median progression-free survival of 2 months; only two patients survived with no disease progression past 6 months (Petrylak et al, 2010). Gefitinib has also been evaluated in combination with gemcitabine/cisplatin and did not improve response rate compared to that of historical controls (Philips et al, 2009). Gefitinib is also being evaluated as maintenance therapy following systemic chemotherapy; however, the results from such studies have not been reported.

Trastuzumab, an anti-Her-2 monoclonal antibody, has been evaluated in several studies. Human epidermal growth factor receptor 2 (HER2)/neu expression in urothelial cancers is variable and may predict a more aggressive phenotype. In 44 patients with HER2/neu-positive tumors, the overall response rate was 70% when combined with paclitaxel, gemcitabine, and carboplatin (Hussain et al, 2007). Trials using trastuzumab either as a single agent in advanced urothelial carcinoma or as a combination agent with concurrent radiation therapy in the bladder-sparing setting are currently underway. Lapatinib is an oral TKI that targets both EGFR and HER2. A phase II trial of lapatinib in 59 patients whose disease progressed on platinum-based chemotherapy demonstrated disease stabilization in 31% of evaluable patients (Wülfing et al, 2009). The median time to disease progression and overall survival was 8.6 weeks and 17.9 weeks, respectively. The median survival was significantly improved in patients whose tumors expressed EGFR and/or HER2. Only one of six patients was able to receive full dosing of lapatinib in combination with paclitaxel because of grade 2/3 gastrointestinal toxicity (Culine et al, 2012). The U.S. Oncology Research network is conducting a randomized discontinuation trial that evaluates salvage therapy with lapatinib in HER2 expressing metastatic urothelial carcinoma. The EORTC is also evaluating lapatinib in combination with gemcitabine/cisplatin in a phase I dose escalation trial. Finally, erlotinib, a TKI to HER1 and HER2 has been evaluated in a neoadjuvant setting before cystectomy in patients with muscle-invasive bladder cancer (Pruthi et al, 2010). Twenty patients were included in this study, of which 25% were pT0 and 35% were downstaged at the time of cystectomy.

Novel Pathways for Targeted Therapy

Multiple alternative pathways have been investigated as potential therapeutic targets in the bladder cancer population including MET, phosphatidylinositol-3 kinases (PI3K), heat shock proteins, cytotoxic T-lymphocyte antigen 4 (CTLA-4), and prostate stem cell antigen (PSCA) (Ghosh et al, 2014). Carbazantinib is an oral chemotherapy agent that targets MET and VEGFR2 and prevents angiogenesis by inhibition of hepatocyte growth factor-induced MET signaling in urothelial cell lines (Cecchi et al, 2012). A phase II trial of carbazantinib is currently underway in patients with metastatic urothelial carcinoma. Ipilimumab is an inhibitor of CTLA-4 (Ghosh et al, 2014). Ipilimumab interrupts CTLA-4 inhibition of T cells and thus allows for cytotoxic T-lymphocyte destruction of tumor cells (Page et al, 2013). A phase II trial of ipilimumab with gemcitabine and cisplatin is currently underway in patients with metastatic urothelial carcinoma. As our understanding of bladder cancer genetics and molecular pathways increases, targeted therapeutics have the potential to take on a greater role in metastatic bladder cancer treatment in the future.

CONCLUSIONS

Optimal treatment of muscle-invasive bladder cancer requires a multidisciplinary approach incorporating urologic oncologists, medical oncologists, and radiation oncologists. Current clinical staging modalities lack the sensitivity and specificity to predict

accurately the final disease stage, which is currently a major limitation to pretreatment decision making. The gold standard therapy for organ-confined muscle-invasive bladder cancer is radical cystectomy with neoadjuvant cisplatin-based chemotherapy. Bladder preservation with chemoradiation therapy has become an increasingly popular option in the muscle-invasive setting and has demonstrated outcomes comparable to those of radical cystectomy in highly selected patients. Despite aggressive surgical therapy, approximately 50% of cystectomy patients will ultimately die of disease.

Meta-analysis from systemic cisplatin-based neoadjuvant chemotherapy trials has demonstrated a modest but statistically significant survival advantage. The evidence for adjuvant chemotherapy is less robust secondary to inadequately powered trials and methodological flaws. Initial response rates with cisplatin-based chemotherapy in the metastatic setting are good; however, durable responses are rare and outcomes for this patient population are dismal. Multiple new second-line chemotherapy trials have been completed or are underway with varying response rates. Newer biologic agents hold promise; however, evidence is currently lacking and more studies are warranted.

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The complete reference list is available online at www.expertconsult.com.

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Transurethral Resection of Bladder Tumors

Patient Preparation

Surgical Technique

Pelvic Lymphadenectomy

Radical Cystectomy: Male

Radical Cystectomy: Female

Partial Cystectomy

Postoperative Care

According to data available from the American Cancer Society, there was expected in 2015 to be an estimated 74,000 new cases and 16,000 deaths from bladder cancer in the United States (Siegel et al, 2013). This ranks bladder cancer as one of the most common noncutaneous malignancies and accounts for 6% of cancers among men. Without appropriate surgical therapy the disease can be deadly and can impart significant health care costs. Surgical therapy, whether for non-muscle-invasive or muscle-invasive disease requires careful attention to technique, oncologic principles, and a firm understanding of disease pathogenesis.

During the initial evaluation, transurethral resection (TUR) serves to not only establish the pathologic diagnosis and the local extent of the disease, but it should also be viewed as a complete oncologic procedure, especially in the setting of low-grade and non-muscle-invasive tumors. However, in the setting of a muscle-invasive tumor, to achieve adequate local control and to maximize the chance for cure, radical cystectomy with a regional lymph node dissection is necessary.

The history of both TUR and also surgical removal of the bladder dates to the 1800s. Bardenheuer of Germany is credited with performing the first cystectomy in 1887 in a patient with an advanced tumor of the bladder (Stenzl et al, 2005). Around that same time the first modern endoscope was invented through collaboration between Maximilian Carl-Friedrich Nitze and Joseph Leiter. Nitze, another German urologist, and Leiter, an instrument maker, created a tool that throughout the following decades would evolve into the modern instrumentation used today.

The first modern technique for radical cystectomy appeared in 1956 from Paquin and Marshall. In their early description, radical cystectomy in men began with a perineal exploration and dissection of the rectum from the bladder and prostate under direct visualization. Additionally they favored cutaneous ureterostomies for urinary diversion (Paquin and Marshall, 1956). The initial report by Whitmore and Marshall (1956) of surgical outcomes in 100 patients in that same year demonstrated significant morbidity and 17 (17%) postoperative deaths. Refinements during the years have resulted in substantial improvements in both oncologic outcomes and surgical morbidity. A more contemporary analysis of 1142 patients demonstrated only a 0.9% inpatient mortality rate and a 2.7% 90-day mortality rate following radical cystectomy (Shabsigh et al, 2009).

Oncologic outcomes have similarly improved from the 21% to 49% 5-year survival rate reported by Whitmore and colleagues in 1962 (Whitmore and Marshall, 1962) to a 59% 5-year survival rate in a study of 507 patients (Madersbacher et al, 2003) and 66% in the largest report to date of 1054 patients treated at the University of Southern California. In addition to improvements in surgical

technique, the administration of neoadjuvant chemotherapy has been demonstrated to improve survival from a median of 46 months to 77 months (Grossman et al, 2003) and should be considered in all patients with muscle-invasive tumors who are scheduled to undergo radical cystectomy.

TRANSURETHRAL RESECTION OF BLADDER TUMORS

Advances in operative instrumentation have greatly enhanced the ability of urologists to identify, treat, and follow patients with bladder tumors. The approach to a new patient with a bladder tumor mirrors that of any new patient visit, with particular attention paid to those factors most likely to have contributed to the development of bladder cancer. A detailed history and physical examination should be performed. Care should be taken to identify known risk factors including but not limited to tobacco exposure, previous cyclophosphamide chemotherapy, aromatic amines, and phenacetin use. Information regarding surgical implants and valvular heart disease may influence antibiotic prophylaxis and should be obtained and compared to current guidelines. Additionally all patients should be queried regarding either a personal or a family history of bleeding with procedures and the use of anticoagulants, as these questions will be relevant in preparation for surgery. The authors have not observed significant bleeding difficulty in patients who are on aspirin and it is not our routine to stop aspirin therapy; however, we advise caution in patients taking other anticoagulants (e.g., warfarin, heparin, clopidogrel) as these pose a higher bleeding risk.

Physical examination should be thorough and should include palpation of abdomen and suprapubic region noting any palpable mass. A digital rectal examination (DRE) in men can be informative and can raise suspicion of prostatic involvement. Likewise a bimanual examination in women can elucidate anterior vaginal involvement. Routine laboratory studies should be obtained and should include a complete blood count, metabolic panel, coagulation panel, and urinalysis with culture. In the setting of active infection, resection should be delayed until clearance of bacteria with appropriate therapy.

Upper tract imaging should be obtained to complete the diagnostic evaluation and this can include renal ultrasound in conjunction with retrograde pyelogram, computed tomography (CT) urogram (CTU), magnetic resonance imaging (MRI), and rarely intravenous pyelogram. Care should be taken to ensure adequate renal function (glomerular filtration rate [GFR] >60 mL/min) if intravenous iodinated contrast is being considered.

As an alternative, MRI contrast agents can be administered for GFR greater than 30 mL/min but these are contraindicated for those less than 30 mL/min. In the case of muscle-invasive tumors, formal staging evaluation should be obtained inclusive of the chest, abdomen, and pelvis.

Patients will routinely have first undergone cystoscopy in the office with a flexible cystoscopy, allowing for visual confirmation of a mucosal tumor and aiding in surgical planning. At the time of diagnostic cystoscopy, care should be taken to note the location and extent of tumor burden.

Although experienced clinicians have been shown to predict accurately the stage and grade of tumors on follow-up cystoscopy (Herr et al, 2002), adequate tissue sampling must be obtained at baseline even when a low-grade tumor is suspected. In the setting of tumors overlying a ureteral orifice, clinicians should be prepared to perform additional interventions including ureteroscopy, and they may require the use of fluoroscopy at the time of TUR.

TUR of bladder tumors is performed with the aid of a rigid cystoscope. To ensure adequate maneuverability the patient should be positioned in dorsal lithotomy. Based largely on an extrapolation from a randomized study examining antibiotic prophylaxis for TUR of the prostate in 400 patients, which showed a reduction in postoperative bacteriuria (Wagenlehner et al, 2005), the American Urologic Association recommends the routine use of antibiotic prophylaxis for patients undergoing TUR of bladder tumors, and it should be administered within one hour of the procedure.

A thorough visual inspection is then performed using the 30-degree lens to examine the urethra in its entirety and then to perform a preliminary evaluation of the bladder mucosa and ureteral orifices. A visual obturator should be used to minimize trauma

to the urethra during this phase. After initial inspection, a 70-degree lens should be used to completely evaluate the bladder again with particular attention paid to the bladder neck, dome, and anterior wall. If necessary a more acute lens such as a 120-degree can be used if full visualization is not possible otherwise. The location and extent of tumors should be noted.

Resection can then be performed with either monopolar or bipolar electrocautery. Irrigation fluid can either be sterile water or 1.5% glycine in the case of monopolar electrocautery or 0.9% sodium chloride if bipolar current is used. This has the added benefit of lowering the risk of postoperative electrolyte abnormalities as well as mitigating an obturator reflex if the tumor is overlying the lateral walls of the bladder.

The goal of any resection should be the visual eradication of any tumor burden and the assurance of an adequate depth of resection. Utilizing cutting current, a loop electrode is used to resect the tumor inclusive of muscularis propria (Fig. 95-1). Histologically, bladder tumors frequently exhibit growth beyond the visible edge and, as such, resection should include an approximate 2-cm margin of normal-appearing tissue. Wide resection of tumors will ensure completeness whether the tumor has a broad base or a tentacular growth pattern (Fig. 95-2). After resection to visual completion, the bladder should be emptied and a bimanual examination under anesthesia (EUA) should be performed. Accordingly, any palpable lesion should be noted and staged clinically (cT3b).

Tumors may pose specific challenges, and a proper understanding of technique will help mitigate the risk of complications. When tumors are encountered on the lateral wall, there is the risk of an obturator reflex whereby the cautery current stimulates the obturator nerve, causing the ipsilateral leg to adduct. This can lead to

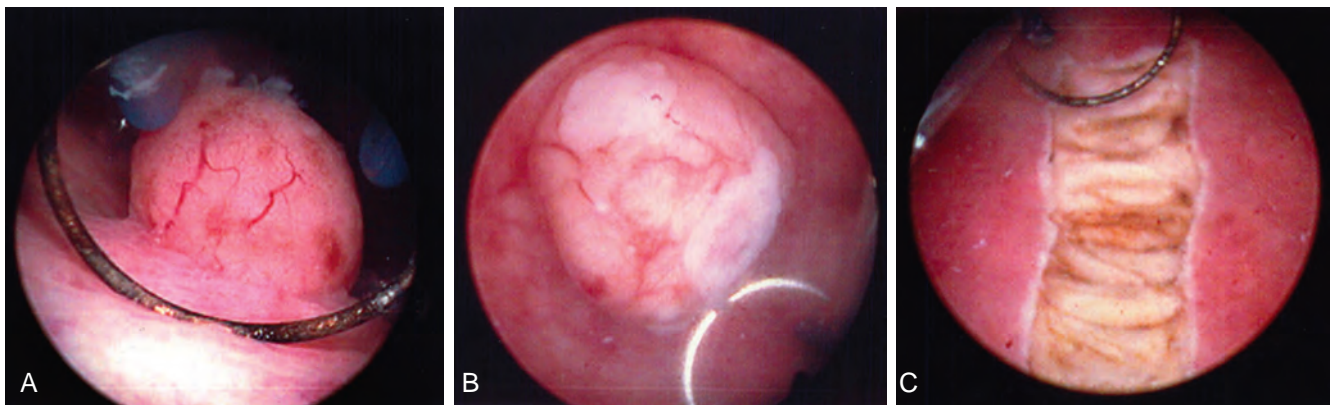


Figure 95-1. A, Broad-based papillary lesion. B, Resection of lesion with loop electrocautery. C, Depth of resection to detrusor muscle.

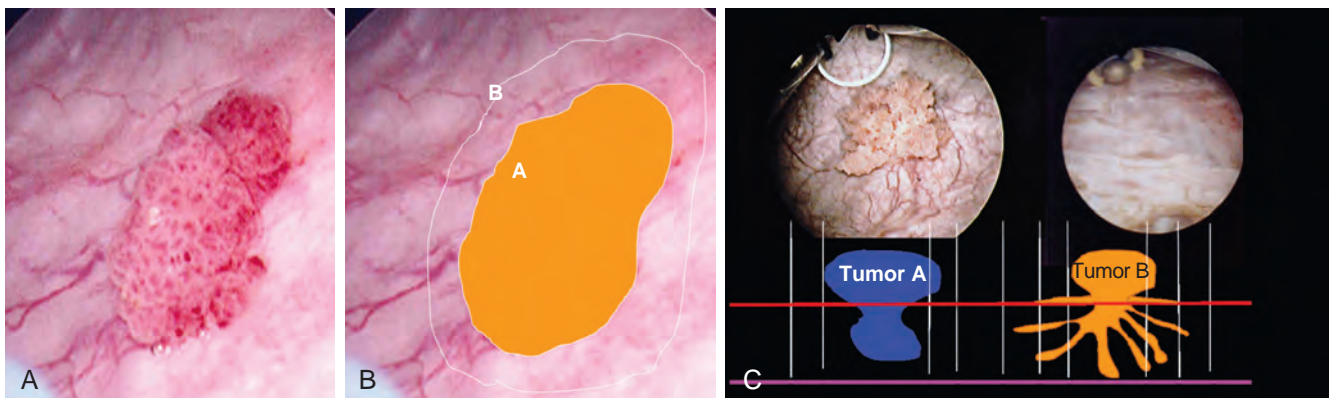


Figure 95-2. A, Papillary bladder lesion. B, Visual boundary of tumor (A) and margin of resection to optimize tumor destruction (B). C, Deep invasion of tumor in broad-based and tentacular pattern.

inadvertent deflection of the instrument laterally and can cause perforation. To lessen this risk, we recommend the following techniques. First, minimize distention of the bladder to the minimum needed to perform the resection. Second, check whether available bipolar cautery may mitigate or eliminate the reflex. Last, if the patient is under a general anesthetic, muscle relaxant can be administered thereby lessening any movement resulting from obturator nerve stimulation. Tumors overlying a ureteral orifice pose another challenge. In this setting, only cutting current should be used and resection strokes should be as quick as possible to minimize the possibility of cauterizing the ureteral orifice closed. **Data suggest routine stenting is not necessary following ureteral orifice resection.** Mano and colleagues found that of 79 patients in whom a ureteral orifice was resected, only 3 (4%) developed hydronephrosis (Mano et al, 2012). Although this retrospective study would suggest stenting is not needed in the case of large resections and extensive cautery, we would suggest that stenting might be useful in the short term, although it may not affect ultimate stricture rates. Finally, tumors located at the dome of the bladder may be difficult to resect because of angulation, distance, and concern for intraperitoneal perforation. The challenges are multifactorial and in some cases difficult to overcome. Minimizing bladder distention and suprapubic pressure, either with your nondominant hand or with that of an assistant, can help maneuver the bladder tumor into a location more amenable to resection. Care should be observed to avoid prolonged cautery, as transmission of heat/energy could potentially occur to adjacent bowel viscera even in the absence of bladder perforation.

Perforation of the bladder may be the natural result of an adequate resection, especially in the setting of advanced tumors (Fig. 95-3). Whereas posterior tumors and those of the dome may result in an intraperitoneal perforation (see Fig. 95-3B), resections elsewhere in the bladder are more likely to result in an extraperitoneal perforation (see Fig. 95-3A). In the event of an extraperitoneal perforation, treatment consists of Foley catheter drainage and observation. However, **large intraperitoneal perforations, although rare, with an incidence of 0.36% in a study of 4144 TURs (Golan et al, 2010), can lead to significant morbidity.** Findings during resection suggestive of an intraperitoneal rupture include loss of

bladder distention, visualization of a defect posteriorly or at the dome, and palpable distention of the abdomen. When suspected, confirmation can be obtained with a cystogram at the same setting. In the presence of an intraperitoneal rupture, treatment consists of abdominal exploration, meticulous inspection of the bowel, and repair of the injury with both a Foley catheter and abdominal drainage.

Although data would suggest little to no effect on progression rates, adjuvant intravesical chemotherapy has demonstrated efficacy in reducing recurrences (Kurth et al, 1997). A meta-analysis of 18 randomized controlled trials for a pooled cohort of 3103 patients showed that a single dose of intravesical chemotherapy (e.g., Mitomycin-C, epirubicin) within 24 hours following TUR of non-muscle-invasive bladder tumor resulted in a 13% absolute reduction in tumor recurrence from 50% to 37% yielding a number needed to treat of 7.2 (Abern et al, 2013). Caution should be applied, however, and adjuvant therapy should only be administered in the absence of perforation. In the setting of high-grade non-muscle-invasive disease, bacille Calmette-Guérin therapy remains the most active agent but should not be administered in the immediate postoperative setting. Rather, a waiting period of 2 to 4 weeks should be observed and a lack of gross hematuria should be confirmed before administration.

PATIENT PREPARATION

In advance of surgical therapy for bladder cancer, appropriate pre-operative staging and medical evaluation should be performed. **Patients with adequate renal function and an absence of allergy to iodinated contrast can be staged with CT of the chest, abdomen, and pelvis.** In instances where renal function is impaired, MRI can be substituted. This allows for assessment of distant and regional disease spread and can guide the use of neoadjuvant chemotherapy. Although studies have been conducted examining novel agents for the detection of lymph node metastasis (Birkhäuser et al, 2013) and comparing MRI and CT accuracy (Vargas et al, 2012), CT currently remains the most common modality for staging. A retrospective analysis of 100 patients by Baltaci and colleagues (2013)

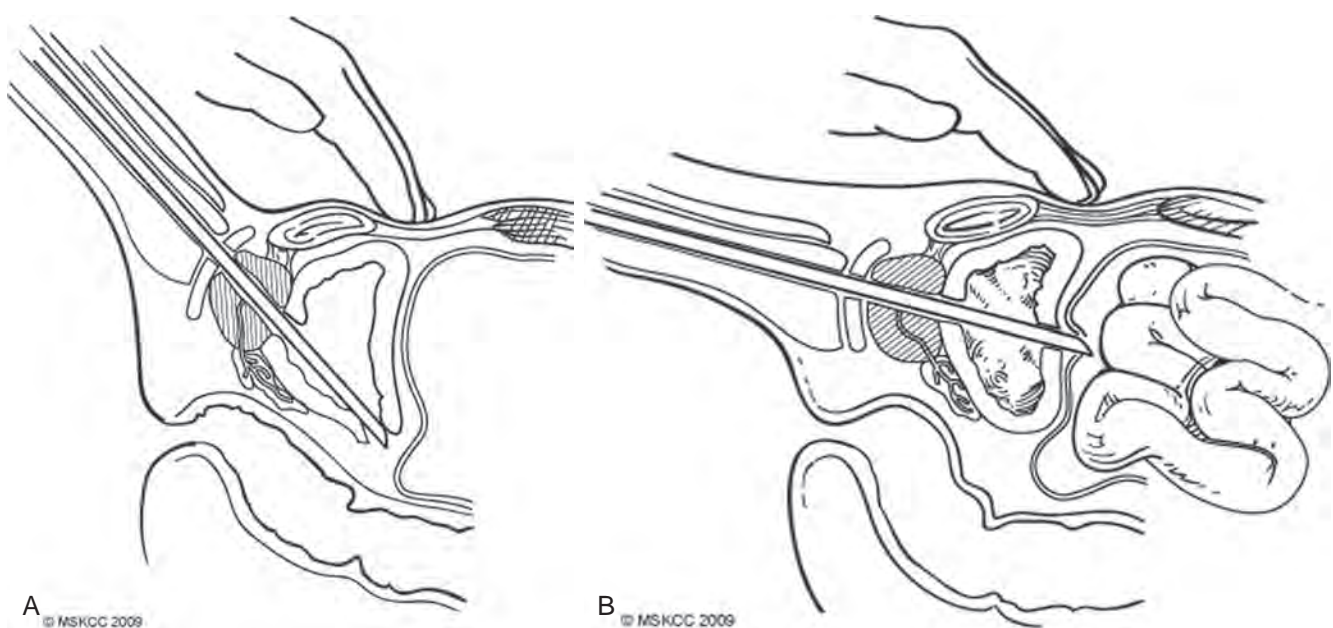


Figure 95-3. A, Extraperitoneal bladder rupture during transurethral resection (TUR) of a bladder tumor. B, Intraperitoneal bladder rupture during TUR of a bladder tumor with subsequent intraperitoneal leakage of irrigant and urine. (A and B, © 2009 Memorial Sloan Kettering Cancer Center.)

demonstrated an accuracy of 72% and 86% for the detection of perivesical invasion and lymph node metastasis, respectively. In a smaller study of 16 patients comparing MRI to CT imaging accuracy in determining final T stage, CT was correct in 63%, overstaged in 31%, and understaged in 6% (Vargas et al, 2012).

After confirmation before surgery of localized disease, patients should undergo routine medical evaluation to maximize health status. Comorbidities such as coronary artery disease, smoking-related lung disease, and peripheral vascular disease will commonly be encountered. After medical optimization, regardless of preferred urinary diversion, enterostomal therapy should be used for stoma marking. Although rare, patients should be made aware of the possibility of an ileal conduit urinary diversion even in the case of a planned continent diversion. Careful marking of the ostomy site to avoid interference, both in a standing and in a seated position, is performed to maximize appliance fit and to minimize stomal irritation. If stomal therapists are not available, the surgeon should be familiar with marking strategies and should perform these while the patient is awake and wearing typical clothing.

Mechanical bowel preparation was historically used in the hope of mitigated anastomotic leak, abdominal, and wound infection rates in patients undergoing bowel surgery. However, the results of two large randomized trials in colorectal surgery have brought into question this assumption. Ren and colleagues found, in their study of an enhanced recovery pathway following colorectal surgery, that those who did not undergo a bowel preparation, among other modifications, were no more likely to experience a complication (9.4% vs. 9.7%) and had similar rates of anastomotic leak (Ren et al, 2011). Another large study of 380 patients who underwent colorectal surgery with or without mechanical bowel preparation showed that wound infection rates (prep vs. no prep 6.4% vs. 5.7%), anastomotic leak (prep vs. no prep 3.7% vs. 2.1%), and abdominal abscess (prep vs. no prep 1.1% vs. 1%) were similar (Zmora et al, 2003). Further study in radical cystectomy patients undergoing ileal conduit urinary diversion demonstrated similar findings (Xu et al, 2010). Additionally a study of 40 patients undergoing radical cystectomy with ileal urinary diversion randomized to either 3-day bowel preparation or overnight fasting showed a lower incidence in prolonged ileus (10% vs. 5%) if bowel preparation was not used (Hashad et al, 2012). For this reason we advise against routine bowel preparation for patients undergoing radical cystectomy with urinary diversion, especially if only ileal segments are to be used.

To enhance further the return to bowel function, the μ opioid receptor antagonist alvimopan should be administered 30 to 90 minutes before surgery, as it has been studied and it demonstrates a benefit in both functional bowel recovery and length of hospitalization. The results of a phase III multicenter trial of alvimopan administered 30 to 90 minutes before bowel resection and twice daily thereafter indicated that those who received this drug exhibited lower rates of postoperative ileus (7.3% vs. 15.7%) and a time decrease of 6.2 to 5.2 days for a written discharge order to be pro-

vided (Ludwig et al, 2008). A phase IV study examining the same drug in radical cystectomy patients demonstrated a 2.63-day reduction in hospital stays, lower rates of total parenteral nutrition for postoperative ileus (10% vs. 25%), and a cost savings of \$2340 to \$2640 per patient (Kauf et al, 2014).

Although we do not advise on the routine use of oral antibiotic prophylaxis as an adjunct to mechanical bowel preparation, **intravenous antibiotics should be administered within 1 hour of surgical incision.** The choice of antibiotic should be customized to local bacterial susceptibility patterns and should include both gram-positive coverage (skin flora) and gram-negative aerobes and anaerobes (distal small bowel and large bowel flora). Generally a broad-spectrum cephalosporin such as cefoxitin will provide adequate coverage. Last, in the absence of significant bleeding, high-risk patients should undergo both mechanical thromboembolic prophylaxis (stockings and pneumatic compression) and pharmacologic prophylaxis before the induction of general or spinal anesthesia. Extended prophylaxis in the postoperative period has also been shown to decrease thromboembolic events. A prospective study of 703 patients randomized to either 8 days or 28 days of pharmacologic prophylaxis after abdominal or pelvic surgery showed that those treated for 4 weeks had an 82.4% reduction in the incidence of major venous thromboembolism (0.8% vs. 4.6%) without an increase in bleeding complications (Kakkar et al, 2010).

Patient positioning is vital to provide adequate exposure and to minimize the risk of related complications. Male patients should be placed supine with the flexion point of the table at the level of the anterior superior iliac spine (Fig. 95-4A). Flexion to 15 degrees is usually adequate and can be lessened as necessary if there is a history of spinal fusion or lumbar injury. In women, a low lithotomy position with the aid of stirrups or the use of spreader bars provides access to the vagina. In female patients, table flexion is generally not possible. The operative field should be inclusive of the abdomen from the level of the xiphoid to the upper portion of the thighs. The genital organs, including the vagina in women, and the perineum should be prepared as well. A solution containing 10% povidone-iodine is recommended, as preparations containing chlorhexidine gluconate should be avoided when used on genital skin.

SURGICAL TECHNIQUE

A lower midline incision is made sharply extending distally from the level of the symphysis pubis to the umbilicus superiorly. Frequently an infraumbilical incision provides adequate exposure but can be extended cephalad as needed (Fig. 95-4B). Ensuring incision of the abdominal fascia in the midline aids in both fascial closure and in helping to prevent inadvertent release of the rectus abdominis from its tendinous insertion at the level of the pubis. Upward retraction of the umbilicus (toward the ceiling) aids in the identification of the linea alba. After the midline is identified, the fascia

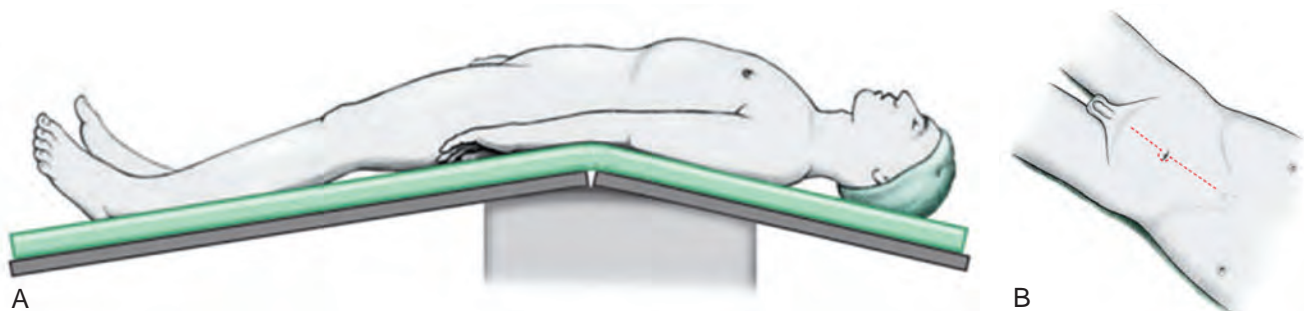


Figure 95-4. Positioning of the patient in the supine position with the bed flexed to 15 degrees (A). An incision is made in the midline from 2 cm above the umbilicus to just above the level of the pubis (B).

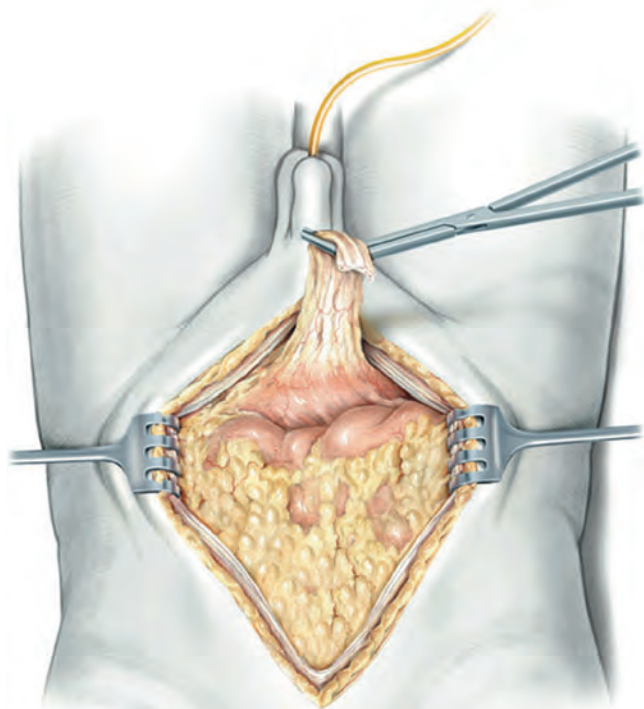


Figure 95-5. Mobilization and division of the umbilicus.

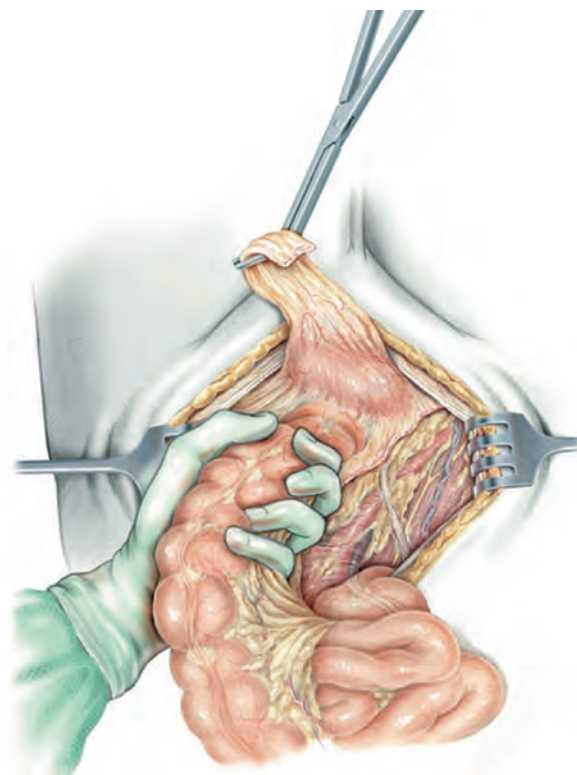


Figure 95-6. Mobilization of the root of the small bowel mesentery and the left colon.

is divided and the space of Retzius is entered. Blunt dissection is performed to release the bladder from the pelvic sidewall attachments bilaterally. This is carried in a cephalad direction to the level of the vas deferens in men and the round ligament in women. At this point a peritoneotomy is made lateral to either medial umbilical ligament and the urachus is controlled and divided (Fig. 95-5). The peritoneum is incised lateral to the medial umbilical ligaments bilaterally to the level of the internal inguinal rings at which point the vas deferens in men and the round ligaments in women will be identified and are divided.

Attention is then turned to the bowel mobilization to achieve adequate exposure of the great vessels and the ureters. On the right side the white line of Toldt is incised and carried around the cecum where then the posterior peritoneum is incised to allow mobilization of the root of the small bowel mesentery. On the left side the white line of Toldt is likewise incised, and a window is created below the sigmoid colon mesentery to communicate with the right-sided posterior peritoneotomy. This space will later be used to transpose the left ureter to the right lower quadrant for urinary diversion (Fig. 95-6).

With the aid of a self-retaining retractor such as a Bookwalter, exposure is maximized and the bowel retracted cephalad. Communication with the anesthesiologist at this point is vital to ensure that inadvertent compression of the vena cava has not resulted. A moistened laparotomy pad or pads should be placed behind retractor blades to protect the abdominal contents. After adequate exposure is achieved, the bilateral ureters are dissected free from their attachments beginning a few centimeters above where they cross the iliac arteries to the level of the detrusor hiatus. Care should be used to ensure that adequate ureteral adventitia is maintained. The superior vesical artery should be ligated and divided before completing the ureteral dissection as this aids in maximizing ureteral length. The ureter is then controlled with either suture ties or suture ligature and is divided.

Although controversial, the distal ureteral margin can be sent for frozen section analysis to evaluate for the presence of urothelial carcinoma. Although studies have shown a correlation between

findings of carcinoma in the ureteral margin and subsequent upper tract recurrence (Schumacher et al, 2006), an impact on survival has not been well established (Raj et al, 2006). Additionally the study by Raj and colleagues indicated that despite sequential resection to achieve a negative margin in 48 instances of an initial positive ureteral margin, upper tract recurrence was not eliminated (Raj et al, 2006). According to surgeon preference, temporary ureteral catheters directed off the surgical field can be used to maintain urinary flow during the remainder of the procedure, or the ureters can be temporarily ligated to avoid spillage of urine into the operative field.

PELVIC LYMPHADENECTOMY

Pelvic lymphadenectomy can be performed at this time or after removal of the bladder specimen according to surgeon preference. The anatomic boundaries of a standard template dissection consist of the genitofemoral nerves laterally, the internal iliac artery medially, Cooper ligament inferiorly, and the point at which the ureter crosses the common iliac artery superiorly (Fig. 95-7A). In cases of advanced disease, an extended dissection inclusive of the entire common iliac lymph node packet and the presacral lymph node packet can be obtained (Fig. 95-7B). Although further extension cephalad to include the para-aortic packet to the level of the inferior mesenteric artery has been studied in bladder cancer, none have demonstrated any additional staging information beyond a dissection from the common iliac arteries distally (Bochner et al, 2004, Bruins et al, 2014). Care should be taken during lymphadenectomy to avoid injury to the obturator nerve and to ensure control of lymphatics at the caudal and cephalad extremes (Fig. 95-7C) and when complete to confirm that no residual lymphoid tissue remains in the operative field (Fig. 95-7D). Surgical quality as measured by nodal yield has demonstrated a survival benefit in bladder cancer. Herr (2004) and colleagues found that in patients in whom at least 10 lymph nodes were removed, 5-year survival improved from 44% to 61%. Later an examination of 1260 patients

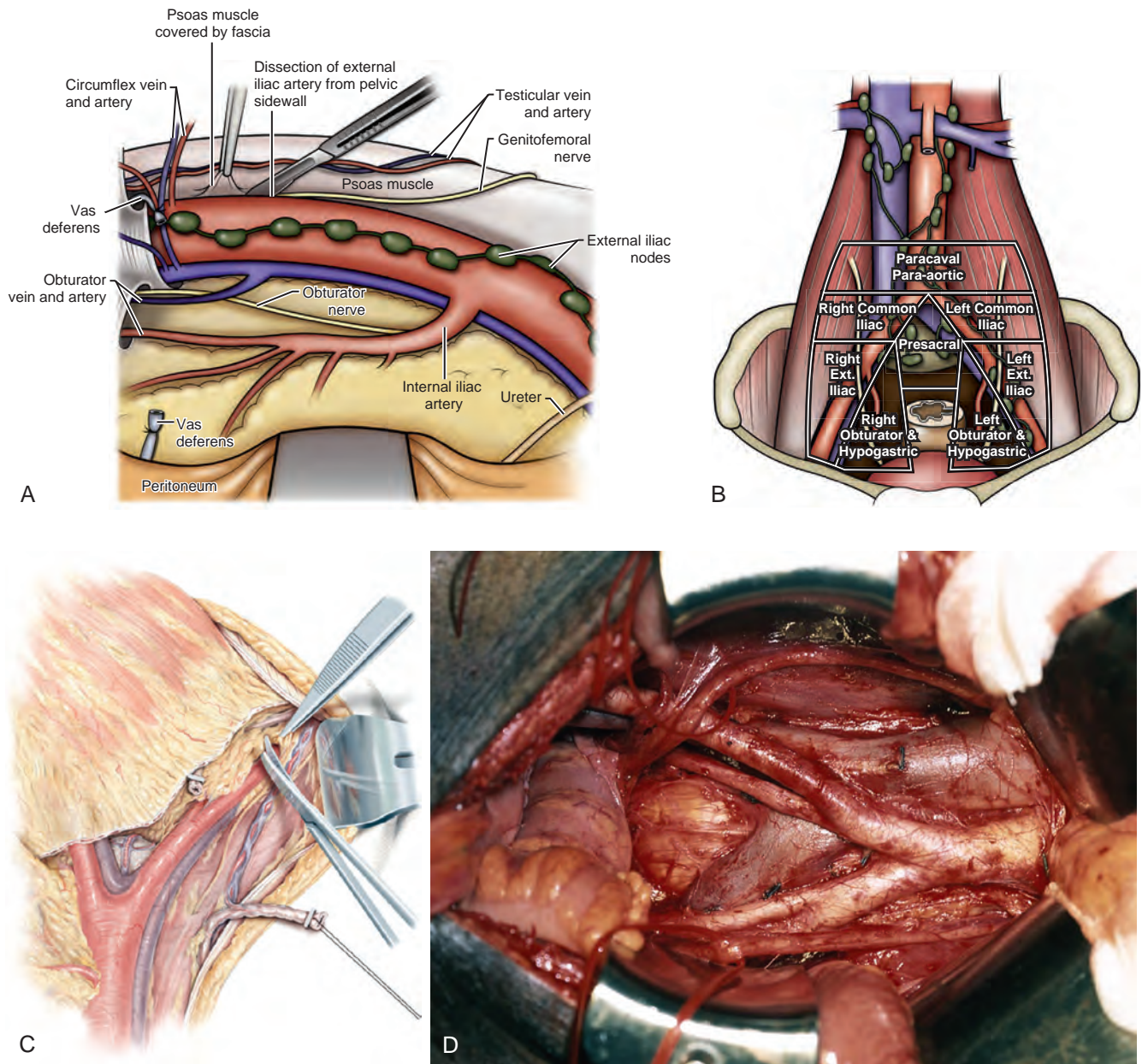


Figure 95-7. A, Standard pelvic lymph node dissection. B, Distributions of the eight node packets from an extended pelvic and retroperitoneal lymph node dissection. C, Meticulous pelvic lymph node dissection. D, Completed extended pelvic lymph node dissection.

in the Surveillance, Epidemiology, and End Results data set with lymph node metastatic bladder cancer showed that for those who had more than 10 lymph nodes removed, overall survival also improved from a median of 13 months if 1 to 5 nodes were removed to 23 months if 10 or more were removed (Wright et al, 2008).

Completion of the pelvic lymphadenectomy aids in the exposure and identification of the vascular pedicles to the bladder (Fig. 95-8). Control of the main branches to the bladder, including the superior, middle, and inferior vesical arteries, can be achieved with the aid of a vascular stapler (see Fig. 95-8B), surgical clips (see Fig. 95-8A), or vascular sealing instruments.

RADICAL CYSTECTOMY: MALE

After completely ligating the lateral vascular pedicles, attention is turned to the posterior dissection. The rectal cul-de-sac is identified and the peritoneum is incised where it overlies the seminal vesicles

(Fig. 95-9A and B). If there is a large tumor at the base of the bladder, care must be observed to ensure an adequate margin of resection at this point. The rectum is dissected free with either blunt dissection or sharp dissection in the midline and is carried to the level of the prostate, at which point Denonvilliers fascia is encountered and incised. In cases of advanced disease, previous pelvic radiation, or reactive fibrosis from previous resection or intravesical chemotherapy, difficulty in developing this plane may be encountered. In such instances blunt dissection should not be performed, as this may cause inadvertent injury to the rectum. Instead, under direct visualization, sharp dissection should be performed with care taken to maintain rectal integrity. If a rectal injury is encountered, primary repair with or without flap coverage and/or bowel diversion should be performed (Kozminski et al, 1989). After release of the rectum in the midline, dissection is carried laterally and the posterior vesical pedicles are identified (Fig. 95-10A). Similar to the lateral pedicles, they can be controlled with surgical clips, ties, vascular staplers, or sealing instruments (Fig. 95-10B). Care should be

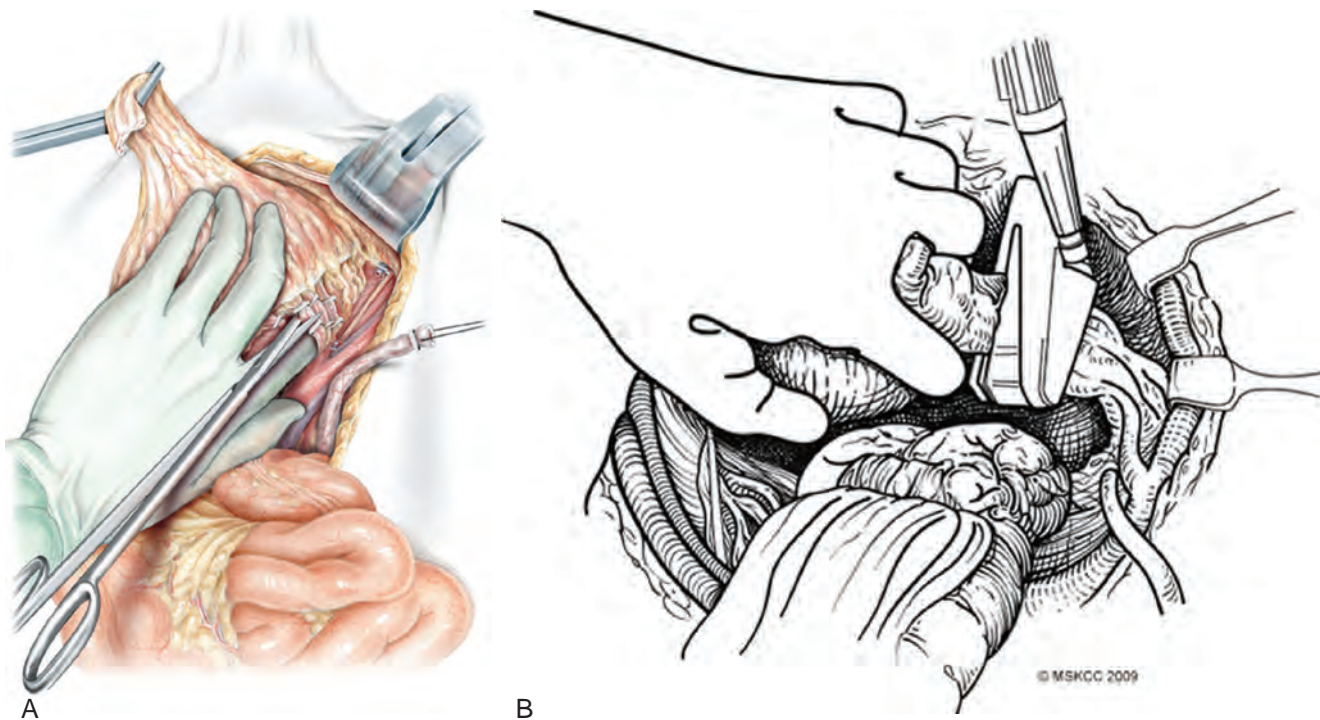


Figure 95-8. A, Application of clips to the lateral vascular pedicle of the bladder. B, Application of an endovascular stapler to the lateral vascular pedicle of the bladder. (B, © 2009 Memorial Sloan Kettering Cancer Center.)

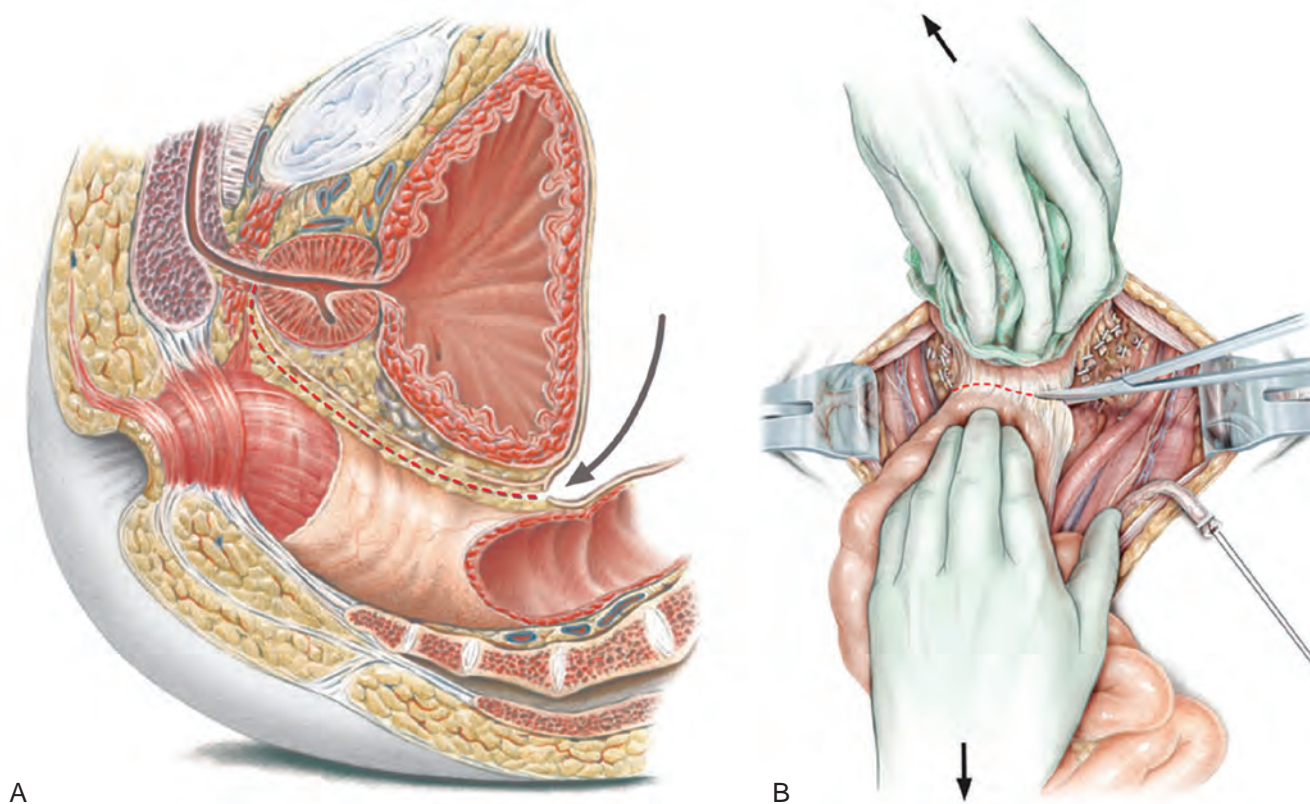


Figure 95-9. A, The posterior plane beyond the cul-de-sac, which separates the bladder and prostate from the rectum. B, Division of the peritoneum overlying the rectum in the cul-de-sac.

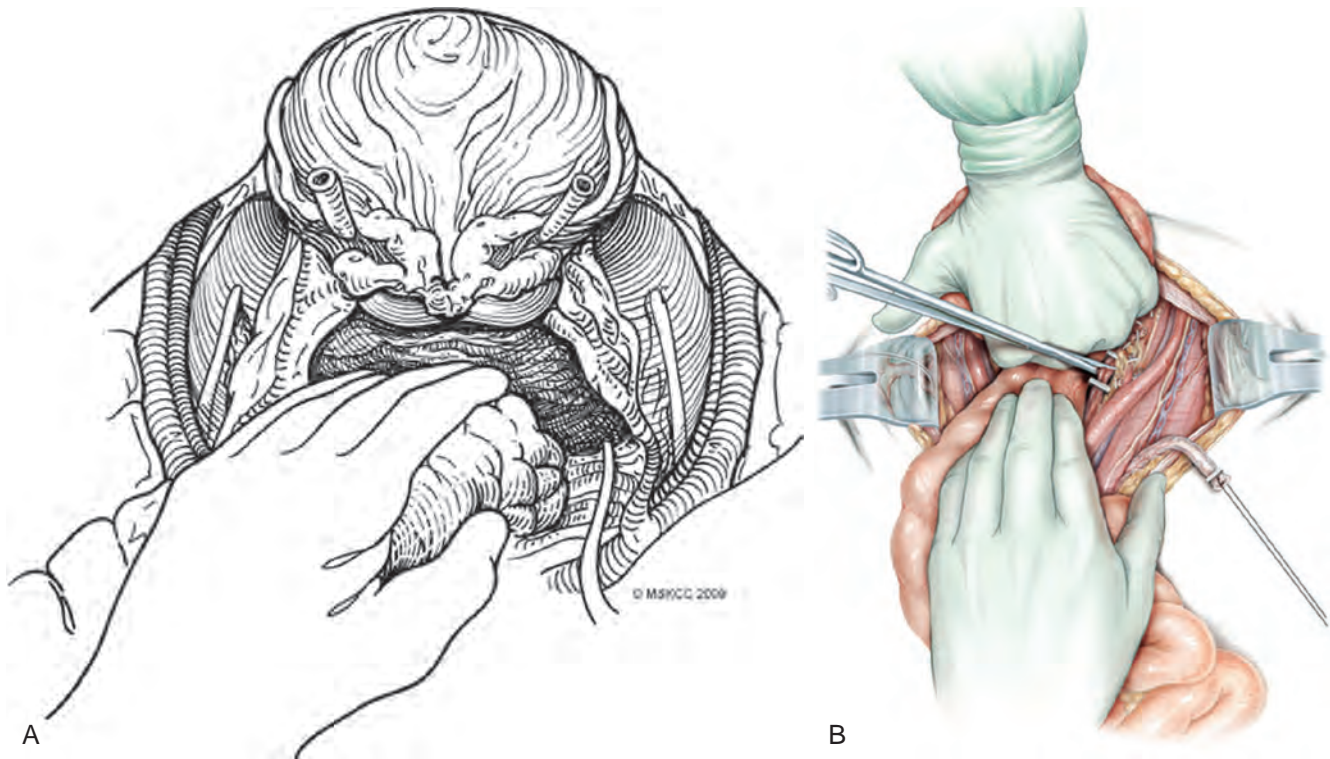


Figure 95-10. A, Exposure of the posterior vascular pedicle of the bladder for ligation. B, Ligation and division of the posterior pedicle. (A, © 2009 Memorial Sloan Kettering Cancer Center.)

taken, however, if sealing instruments are used, as the heat they generate can transmit and may injure the rectum if in close proximity. With a gloved finger surgeons should shield the rectum from the tips of such instruments while in use.

After completion of the posterior dissection, the urethra should be palpable and at this point attention can be turned to the anterior dissection in a fashion similar to a radical prostatectomy. The endopelvic fascia overlying the levator muscles is incised sharply, allowing for identification of the confluence between the urethra and the dorsal venous complex. Ligation and division of the dorsal venous complex (Fig. 95-11) allows for visualization of the anterior urethra, which is then incised.

If continent ileal neobladder urinary diversion is planned, adequate urethral length must be maintained and a frozen section analysis of the urethral margin performed. In a study of 436 patients who underwent eight cutaneous or orthotopic diversions, urethral recurrence occurred in 7.9% of patients at 5 years and at a median of 1.6 years following radical cystectomy (Freeman et al, 1996). Additionally the study demonstrated that patients with an orthotopic diversion were at lower risk of urethral recurrence (4% vs. 10%), although the reason is unclear. In another study of 118 male patients following radical cystectomy, no patients with a negative intraoperative urethral frozen section had a urethral recurrence at 10 years of follow-up (Lebet et al, 1998). A large study examining the usefulness of preoperative prostatic urethral biopsy in predicting final urethral margin status demonstrated poor correlation (68%), but very high negative predictive value (100%) if the intraoperative frozen section was negative (Kassouf et al, 2008). We therefore recommend that in the presence of a positive urethral margin, orthotopic neobladder should not be performed and the patient should be made aware of this possibility during preoperative counseling.

The role of preservation of the neurovascular bundles, unlike in radical prostatectomy, remains controversial in radical cystectomy. A technique analogous to radical prostatectomy (Fig. 95-12A and B) can be applied; however, the functional outcomes remain

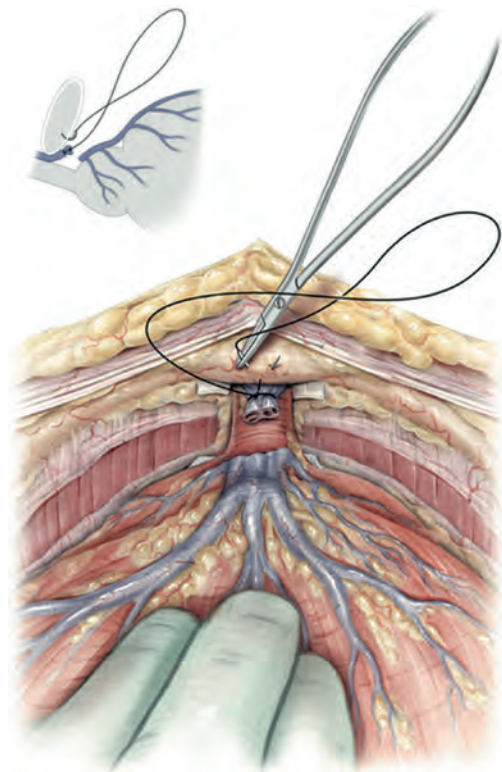


Figure 95-11. Division of the dorsal venous complex.

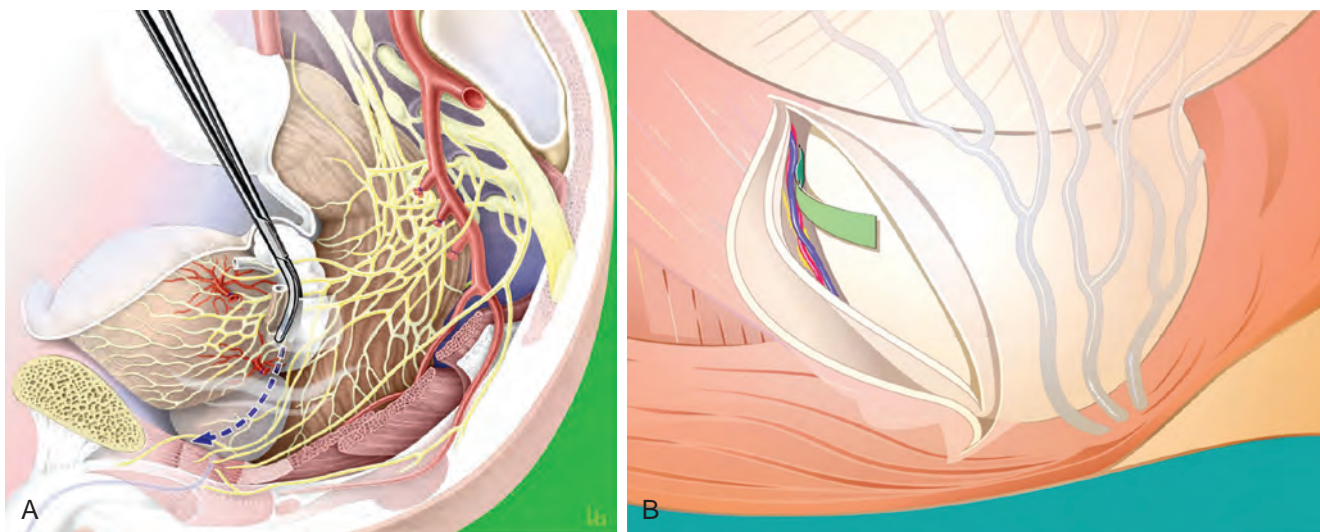


Figure 95-12. A, Nerve-sparing radical cystectomy in the male patient. B, Separation of the plane between the prostatic capsule and the neurovascular bundle.

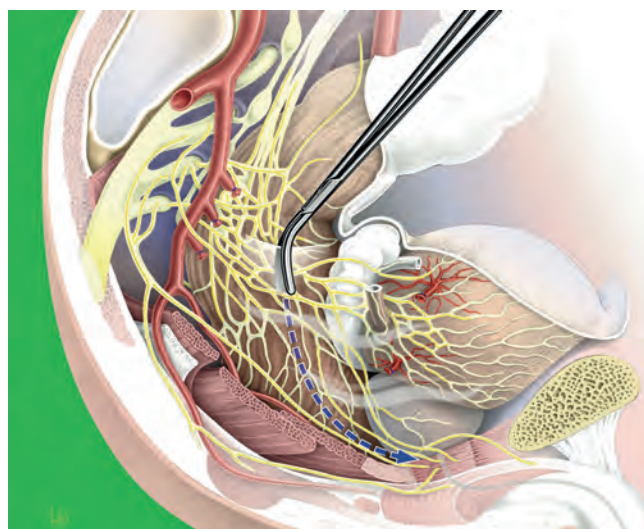


Figure 95-13. Non-nerve-sparing radical cystectomy in the male.

significantly worse. In a report of erectile dysfunction in sexually active men treated with radical cystectomy, [Zippe and colleagues \(2004\)](#) found in their series of 49 men that only 6 of 16 (38%) who underwent nerve-sparing surgery were naturally potent after surgery, and only 7 of 49 (14%) were potent when including all patients (nerve-sparing and non-nerve-sparing). These results do not differ significantly from reports of men who underwent non-nerve-sparing cystectomy as reported by [Asgari and colleagues \(2013\)](#). In that study of 81 sexually active men, they found that at 1 year only 9.8% (ileal conduit) to 35% (neobladder) regained function sufficient for vaginal penetration and maintenance of erection until the completion of intercourse ([Asgari et al, 2013](#)). Among men who underwent nerve sparing, age, similar to the radical prostatectomy series, is a strong predictor of functional recovery with a drop from 62% potency for men aged 40 to 49 years to 20% for those 70 to 79 years ([Schoenberg et al, 1996](#)). Additionally, in their report of 101 patients only 5 (5%) suffered a local recurrence; however, caution should be noted as one was a patient with pT2 disease. The risks and benefits of nerve sparing should be judged according to preoperative sexual function and disease burden. **Non-nerve sparing (Fig. 95-13)** is the preferred choice in advanced disease and in patients with preexisting erectile dysfunction.

Additional efforts have been used to improve sexual functional outcomes including subtotal resection of the prostate. Described techniques include leaving the prostate in its entirety or sparing the prostatic capsule and/or the seminal vesicles. These approaches have largely been studied in the context of orthotopic neobladder urinary diversion. In the setting of nonurothelial cancers, Spitz and colleagues showed that both erectile and ejaculatory function could be maintained in 3 of 4 patients ([Spitz et al, 1999](#)). In another report, Colombo and colleagues showed excellent erectile function outcomes in all of the 27 patients and no instances of local recurrence; however, follow-up was limited to only 32 months ([Colombo et al, 2004](#)). There is, however, concern because of the high rate of occult prostate cancers in radical cystectomy specimens. This has been shown to be as high as 41% in larger series ([Revelo et al, 2004](#)). Despite this, in highly selected patients excellent local control can be maintained. In a study of 100 patients without evidence of prostate cancer preoperatively and negative frozen section at surgery, only 5 (5%) developed local recurrence, although distant metastasis did develop in 31 patients ([Vallancien et al, 2002](#)). To achieve such outcomes, however, proper patient selection is paramount. Preoperative evaluation should include DRE, prostate specific antigen (PSA) testing, transurethral prostatic resection, and intraoperative frozen section analysis. In the setting of PSA or DRE abnormality prostate biopsy should be done in advance of surgery.

RADICAL CYSTECTOMY: FEMALE

Radical cystectomy in the female patient historically included total anterior pelvic exenteration inclusive of the bladder, urethra, anterior vagina, uterus, and cervix. This allows for adequate resection and is vital in the presence of a positive EUA or if there is concern for anterior vaginal wall invasion (cT4a). It should also be noted that compared to men, women present with more advanced disease ([Kluth et al, 2013; Mitra et al, 2014](#)). Additionally, in the study by Kluth and colleagues of more than 8000 patients, in multivariable analysis female gender was an independent risk factor for death from disease (hazard ratio = 1.17 [range 1.05 to 1.31], $P = .005$) ([Kluth et al, 2013](#)). For this reason, anterior pelvic exenteration remains the gold standard of therapy. As discussed later, however, in patients with low-stage disease (cT1 and cT2) where orthotopic neobladder is considered, vaginal and urethral sparing is necessary.

As described earlier, the initial steps for bowel mobilization, anterior bladder mobilization, and ureteral dissection are the same in men and in women with the exception of the gonadal vessels. In female patients the ovarian vessels should be identified during the

bowel mobilization and ligated with a 2-0 silk suture distally, and both a 2-0 silk suture ligature and a tie proximally, and then divided. Anterior pelvic exenteration begins with identification of the posterior cervical fornix (Fig. 95-14A), and the vaginal cuff is incised at this position (Fig. 95-14B). After gaining entry to the vaginal canal, the lateral and posterior vascular pedicles to the bladder can be controlled easily. According to surgeon preference, vascular staplers, sealing devices, or clips are applied and the specimen can be dissected free inclusive of the uterus, cervix, anterior vaginal cuff, and bladder. The urethral meatus is then incised, either antegrade from the pelvis or externally from the vaginal introitus, and the specimen is removed (Fig. 95-15A and B). Care should be taken to ensure that sufficient vaginal mucosa is maintained above the urethral meatus to allow for closure of the vaginal defect in subsequent steps. Because of the vascular nature of the female pelvis and the sinusoidal nature of the vascular pedicles as they pass over the lateral vaginal wall, care is needed to ensure hemostasis. To com-

plete the vaginal closure with a 2-0 polyglactin suture, the posterior vaginal wall must be released from the rectum (Fig. 95-15C). The posterior vaginal flap is then closed to the corresponding mucosae of the introitus in a clamshell fashion to maintain vaginal girth at the cost of some vaginal length. **Bothersome drainage of peritoneal fluid will result if the vaginal closure is not watertight, and an interrupted closure is preferred.** A vaginal packing is then placed with the dual purpose of distending the vagina and tamponading any residual vaginal wall hemorrhage (particularly useful if vaginal sparing is performed; discussed later) and aids in the identification of unrecognized defect in the closure. This packing should be removed within two postoperative days.

In the absence of bladder neck involvement and the presence of low-stage disease ($\leq T2$), orthotopic neobladder can be considered. This necessitates urethral sparing with adequate length proximal to the striated sphincter and anterior vaginal wall sparing to provide support to the neobladder. As described previously, the

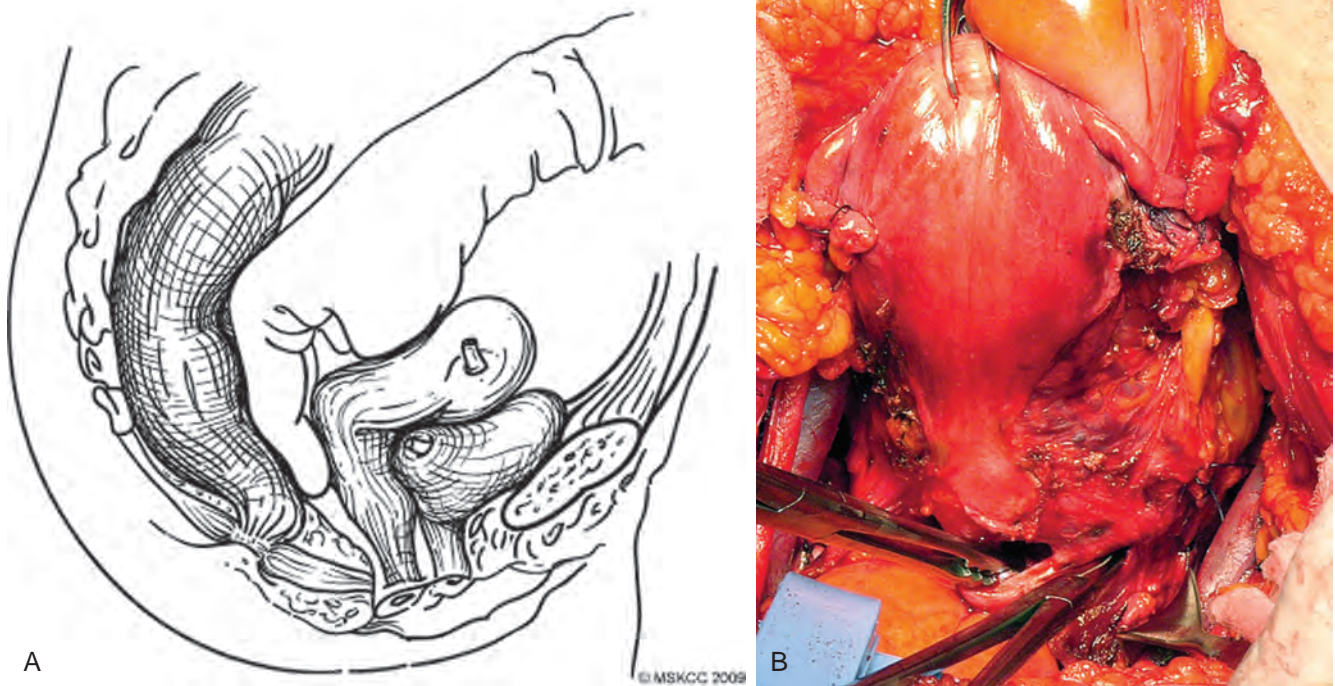


Figure 95-14. A, Identification of the vaginal cuff posterior to the cervix. B, Incision of the posterior vaginal cuff. (A, © 2009 Memorial Sloan Kettering Cancer Center.)

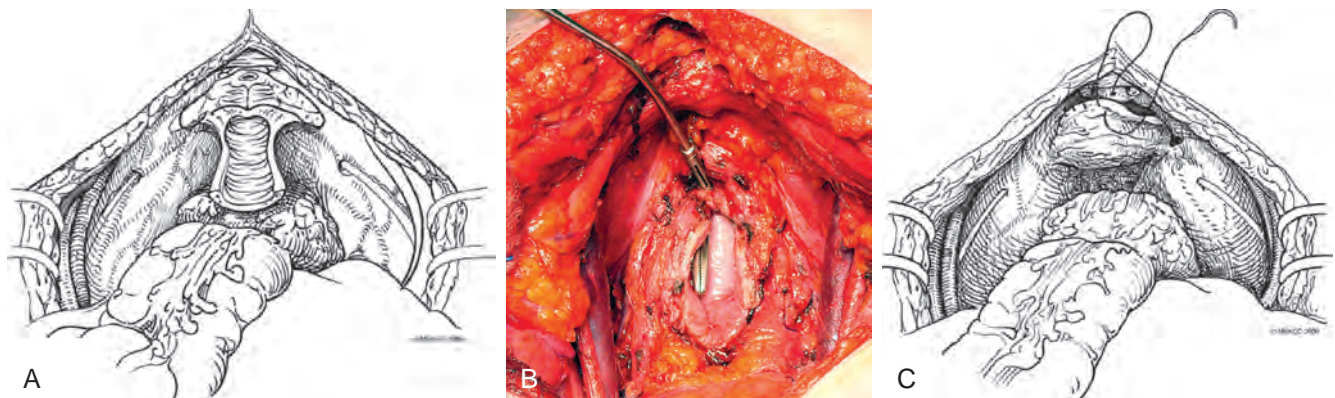


Figure 95-15. A, Posterior vaginal wall and defect at the level of the introitus after en bloc removal of the bladder in an anterior pelvic exenteration in the female patient. B, Intraoperative photograph of the introital defect. C, Coverage of the introital defect with a flap made from the posterior vaginal wall.

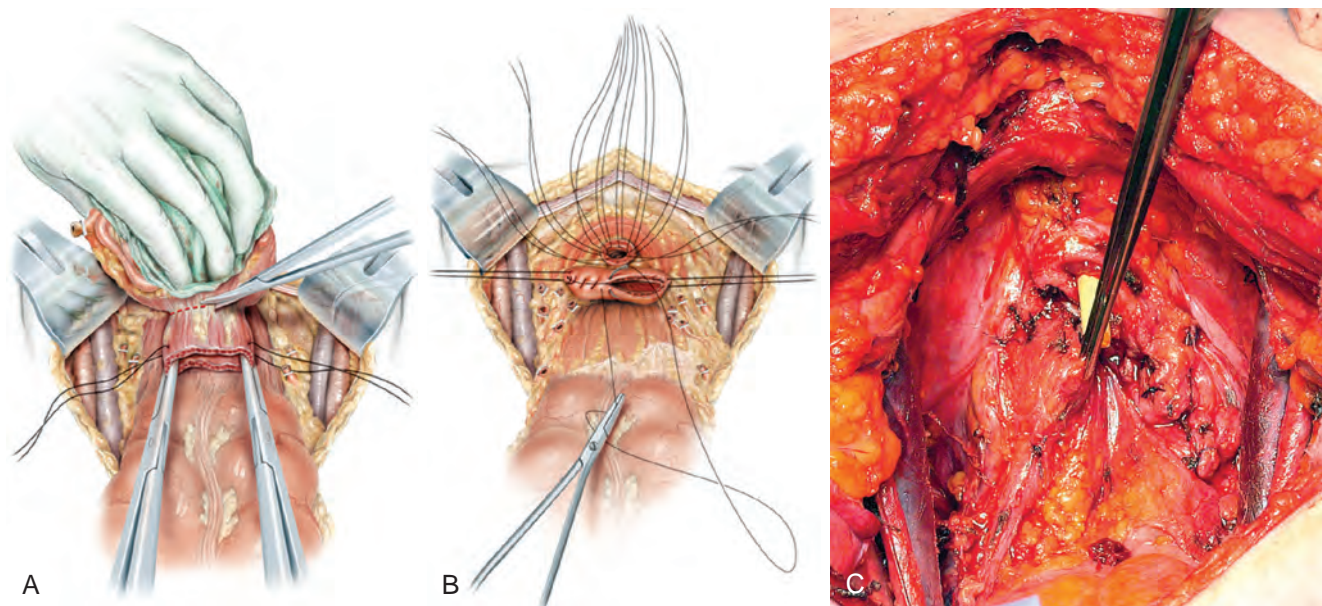


Figure 95-16. A, Circumferential division of the vaginal cuff from the attachments to the cervix. B, Closure of the vaginal cuff and placement of the urethral anastomotic sutures. C, Intraoperative photograph of the completed repair.

lateral vascular pedicles are intimate with the lateral wall of the vagina and to control these vessels properly they must be separated from the vagina before ligation. This can be achieved either after removal of the cervix and uterus at the level of the cervical fornix (Fig. 95-16A) or while they are still in place. A vaginal packing during this step can aid in defining the plane of separation between the bladder and the anterior vaginal wall in the midline. After development this space is extended laterally, separating the lateral vascular pedicles from the lateral vaginal wall. To ensure that an adequate bladder margin is maintained, the vessels should not be divided until the midpoint of the lateral vaginal wall, in the anterior posterior plane, has been reached. This dissection is carried to the level of the bladder neck, which can easily be identified by use of the Foley catheter balloon as a guide. Maintaining the integrity of the striated sphincter, the specimen is removed at this level (Fig. 95-16B) and a frozen section of the urethral margin is sent and managed in the same fashion as in male neobladder candidates. Again, if the urethral margin analysis demonstrated malignancy, orthotopic diversion is contraindicated. The vaginal apex is closed with 2-0 polyglactin sutures and urethral anastomotic sutures placed (see Fig. 95-16B and C).

PARTIAL CYSTECTOMY

Consideration for bladder-sparing surgery in the setting of muscle-invasive urothelial carcinoma requires proper patient selection. For those with solitary lesions of small size and who lack concurrent carcinoma in situ (CIS), results from partial cystectomy are similar to those of radical cystectomy. In an analysis of 37 such patients treated at the MD Anderson Cancer Center, nine (24%) developed either a muscle-invasive and/or metastatic recurrence; however, the 5-year overall and the disease-specific survival rates were 67% and 87%, respectively (Kassouf et al, 2006). In a population-based matched cohort study examining partial versus radical cystectomy when matched for surgical quality (number of lymph nodes removed) and clinicopathologic features, partial cystectomy was equivalent in terms of overall and cancer-specific survival (Capitanio et al, 2009). Patients initially treated with partial cystectomy can be salvaged with radical cystectomy; however, survival is significantly worse for locally advanced disease at the time of salvage. In patients with organ-confined disease, 5-year

survival is 60% whereas it is only 7% for extravesical disease (Bruins et al, 2012).

In the select patients who are candidates for partial cystectomy, preoperative preparation includes counseling regarding the possibility of radical cystectomy and the discussion of urinary diversion, as it is possible that an adequate margin will not be possible or extravesical disease will be encountered. Partial surgical removal includes pelvic lymphadenectomy, as described earlier, as well as anterior bladder mobilization. Cystostomy is performed in an area away from the tumor. The tumor is then excised including the underlying bladder wall and perivesical fat with a mucosal margin of 1 to 2 cm and confirmation of resection adequacy with frozen section analysis. If necessary, the ureteral orifice or intramural ureter can be excised and a reimplantation performed. After excision of the tumor the cystostomy is closed with 2-0 polyglactin suture in 2 or 3 layers, and an instillation of fluid via a Foley catheter is performed to ensure a watertight closure. Copious warm water irrigation of the surgical field is performed to minimize the possibility of pelvic seeding. A closed suction drain should be placed and the cystostomy closure interrogated with a cystogram on postoperative day 7 before removal of the Foley catheter.

Although rare, primary adenocarcinoma arising from the urachus requires additional resection. These tumors are most commonly confined to the dome of the bladder although they may grow by direct extension to involve other areas. A circumferential incision around the umbilicus is made and extended toward the pubis. Complete excision includes the umbilicus, the urachus, and the dome of the bladder with a visual margin free from tumor (Fig. 95-17). Again this is confirmed with frozen section analysis, and additional resection may be necessary. Bladder augmentation with the use of an intestinal segment can be performed if bladder capacity is significantly reduced.

POSTOPERATIVE CARE

Radical cystectomy is a complex procedure involving not only the genitourinary but also the gastrointestinal tract because of urinary diversion. In addition to this complexity, patients are frequently elderly and present with significant comorbidities. Although major complications are infrequent (13%) any complication remains common (64%) with the most frequent being gastrointestinal

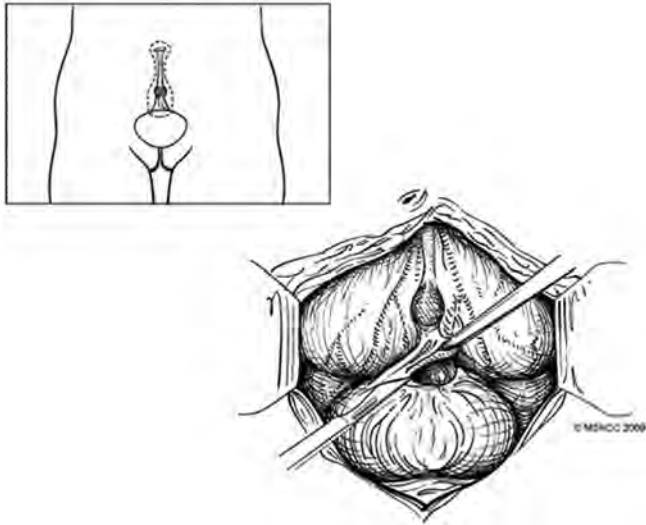


Figure 95-17. Resection of an adenocarcinoma of the urachus. (© 2009 Memorial Sloan Kettering Cancer Center.)

(29%) or infectious (25%) (Shabsigh et al, 2009). Postoperative efforts are necessarily directed at minimizing the possibility of complications and maximizing the return of normal physiology. Immediately after surgery, laboratory results including cell count, electrolytes, and renal function are assessed and fluid dynamics are monitored. Frequently patients will require initial observation in intensive care or stepdown units. Routine nasogastric suction is not needed; however, it is considered in compromised mentation or known issues with airway protection. As discussed earlier, thromboembolic prophylaxis should be continued in the postoperative setting in the absence of hemorrhage. In addition to pharmacologic measures, early ambulation should be used and pulmonary exercise (incentive spirometry) with deep breathing and coughing should be encouraged.

Delayed return of bowel function frequently prolongs hospitalization after radical cystectomy. Medications such as alvimopan can be used, which has been shown to improve return of bowel function and to shorten hospital stays. Additional postoperative steps to enhance recovery include neostigmine (with telemetry monitoring) to encourage further the return of bowel function, promotility suppositories, stress ulcer prophylaxis, antiemetics, early enteral feeding in the absence of nausea and/or emesis, and avoidance of narcotic pain medication (ketorolac and acetaminophen unless contraindicated) (Djaladat and Daneshmand, 2013).

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KEY POINTS

- Bladder cancer is a common cancer associated with high cost and frequent fatality.
- Radical cystectomy offers excellent survival for organ-confined disease.
- TUR is both diagnostic and therapeutic, especially for low-grade tumors.
- Perioperative intravesical chemotherapy decreases recurrence rates by 13%.
- A standard template pelvic lymphadenectomy includes the genitofemoral nerves laterally, the internal iliac artery medially, Cooper ligament inferiorly, and the point at which the ureter crosses the common iliac artery superiorly.
- Ureteral margin frozen section aids in predicting upper tract recurrence but sequential resection to a negative margin might have no impact.
- Nerve-sparing radical cystectomy aids in the preservation of sexual function and is performed in a manner analogous to radical prostatectomy.
- Subtotal prostatic resection can further enhance return of sexual function but should only be offered in select patients in whom the risk of occult prostate cancer is low.
- Vaginal sparing is appropriate in the absence of locally advanced tumors and allows for orthotopic urinary diversion.
- Partial cystectomy can be considered in rare, solitary urothelial tumors without concomitant CIS.
- Urachal adenocarcinomas are treated with en bloc resection of the umbilicus and dome of the bladder.
- Enhanced recovery protocols can aid in the recovery of normal physiology after radical cystectomy and can shorten hospital stays.

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Bladder Diverticulectomy

Ureteral Reimplantation

Psoas Hitch and Bladder Advancement Flaps

Enterocystoplasty

Vesicovaginal and Ureterovaginal Fistula

Urachal Surgery and Partial Cystectomy

Robotic Radical Cystectomy

Female Robotic Cystectomy

Simple/Supratrigonal Cystectomy

Transvesical Foreign Body and Stone Extraction

Surgery of the urinary bladder and distal ureter often involves significant extirpative as well as reconstructive techniques, demanding skill and experience from the urologic surgeon. As a result of these technical challenges, bladder surgery is associated with significant complication rates. In an attempt to minimize the morbidity of open surgery, minimally invasive techniques for surgery of the urinary bladder have been introduced and refined. Procedures that previously required large open incisions now can be performed through a limited number of keyhole incisions.

Laparoscopic and robotic techniques can be used for essentially every bladder operation. In most cases, improved cosmetic results are accompanied by reductions in associated pain, duration of hospitalization, and recovery times. Technology continues to drive the field forward, and natural orifice transluminal endoscopic surgery and laparoendoscopic single-site surgery (LESS) techniques have been employed to reduce further the incisions and morbidity associated with surgery of the urinary bladder. This chapter describes conventional laparoscopic, robotic, and LESS approaches to surgery of the distal ureter and the bladder, focusing on indications, techniques, complications, and outcomes (Box 96-1).

BLADDER DIVERTICULECTOMY

Diverticula of the urinary bladder can be congenital, acquired, or, rarely, iatrogenic in nature. Bladder diverticula are characterized by a herniation of the urinary mucosa through a weakness or absence of the detrusor muscle. Bladder diverticula have scattered and/or nonfunctional residual muscle fibers, which can impair emptying and contribute to urinary stasis. Congenital bladder diverticula include periureteral diverticula, also referred to as Hutch diverticula, which can be associated with vesicoureteral reflux (VUR). Posterior urethral valves and neurogenic bladder are also commonly associated with diverticula. Various conditions, including Williams syndrome, Menkes disease, and prune-belly syndrome, can include multiple diverticula in the absence of outlet obstruction. Acquired diverticula are most commonly associated with bladder outlet obstruction (BOO), with resultant high-pressure voiding and subsequent diverticula formation. Traditionally, diverticulectomy has been approached through an open low midline incision. However, with the evolution of minimally invasive techniques, complex and multiple bladder diverticula can be managed laparoscopically or robotically (Fig. 96-1). In combination with endoscopic manage-

ment of BOO and bladder calculi, these techniques often result in reduced morbidity to the patient.

Evaluation and Surgical Indications

The first step in evaluation of a bladder diverticulum involves the determination of the underlying cause responsible for the diverticulum. Most often, this involves confirmation of BOO and may involve determination of urinary flow rate, postvoid residual urine volume, and urodynamic studies. Underlying BOO must be identified and addressed, typically at the time of diverticulectomy. Cystoscopy is an essential component of the evaluation of bladder diverticula. Diverticula size, number, and location are recorded, and proximity to the ureteral orifices is noted. The bladder outlet is evaluated for evidence of prostatic hypertrophy, presence of an intravesical component, bladder neck contracture, or stricture. Ultrasound scan of the prostate can be useful to assess prostate volume, which can aid in determining the appropriate outlet procedure, when indicated. In conjunction with urinary cytology, thorough inspection of all diverticula is mandatory to rule out malignancy. Small diverticula can be managed with cystoscopic fulguration. Voiding cystourethrography defines the location, size, and number of diverticula and can diagnose concomitant reflux or urinary stasis. Upper tract imaging with intravenous urography (IVU) or computed tomography (CT) urogram is useful to evaluate the relationship of the ureter to the diverticulum to prevent injury during surgery as well as identify any hydronephrosis resulting from obstruction. Urinalysis and culture is essential before surgical intervention.

Small, asymptomatic bladder diverticula without associated complications can be observed. Diverticulectomy is indicated for large diverticula with incomplete emptying, chronic or repeated urinary tract infection, bladder calculi, or pain. Occasionally, a bladder diverticulum can result in ureteral reflux or obstruction, requiring diverticulectomy and ureteral reimplantation. Transitional cell carcinoma within a bladder diverticulum is an indication for partial cystectomy. Any BOO must be addressed either before or at the time of diverticulectomy.

Surgical Approach

Since Czerny's first description of diverticulectomy in 1897 (Knappenberger et al, 1960), the surgical treatment of bladder diverticula

BOX 96-1 Minimally Invasive Surgery of the Bladder and Distal Ureter

Bladder diverticulectomy
 Ureteral reimplantation
 Boari and bladder advancement flaps
 Enterocystoplasty
 Mitrofanoff and Monti tube
 Vesicovaginal and ureterovaginal fistula
 Partial cystectomy and urachal surgery
 Radical cystoprostatectomy and extended lymphadenectomy
 Female radical cystectomy
 Simple/supratrigonal cystectomy
 Bladder stone and foreign body removal

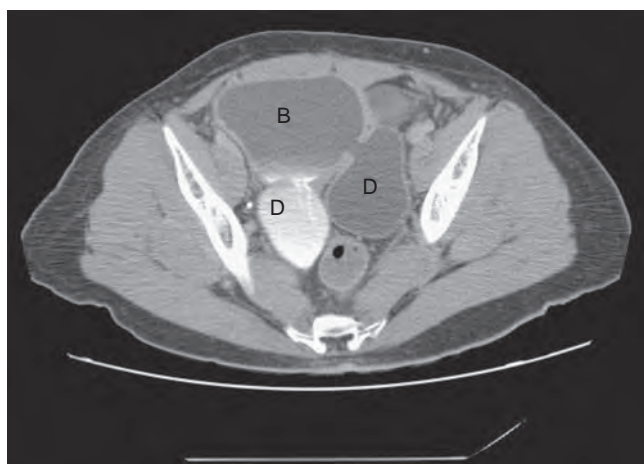


Figure 96-1. Computed tomography urogram of the abdomen/pelvis of a patient with Williams syndrome and four bladder diverticula. Laparoscopic bladder diverticulectomy of diverticula can be performed in a single setting in experienced hands. Contiguity between true bladder (B) and two posterior bladder diverticula (D) is demonstrated.

has evolved from open surgery, to endoscopic procedures, to laparoscopic and robotic techniques. Transperitoneal laparoscopic bladder diverticulectomy (LBD) was first introduced in 1992 (Das, 1992; Parra et al, 1992) and later in the pediatric setting (Kok et al, 2000). Numerous subsequent reports demonstrated the reproducibility of the technique via a transvesical as well as extravesical approach (Nadler et al, 1995). Extraperitoneal laparoscopy may limit the risk of visceral injury and intra-abdominal urine leak. The transperitoneal approach provides a wide and generous working space and superior access for posterior diverticula. LBD has also been described for tumor within a diverticulum (Tai et al, 2007; Thwaini et al, 2008; Wang et al, 2008) and is described in more detail in the section on laparoscopic and robotic partial cystectomy.

Similarly, robotic bladder diverticulectomy (RBD) has been described in adults and children as an effective minimally invasive alternative providing similar benefits (Myer and Wagner, 2007; Rao et al, 2007; Macejko et al, 2008; Tareen et al, 2008; Meeks et al, 2009). The robotic approach mimics the laparoscopic technique, aids the surgeon without extensive laparoscopic experience, and provides a comfortable ergonomic platform for working in the deep pelvis. The choice of surgical approach for bladder diverticulectomy depends on numerous factors, including the number and location of diverticula, proximity of the diverticulum to the ureter, and the

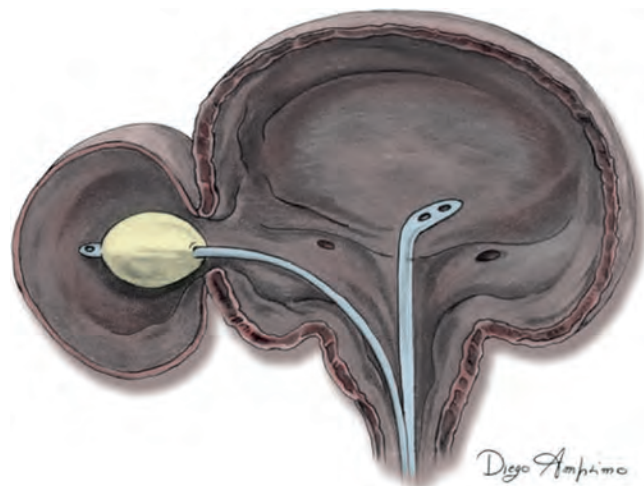


Figure 96-2. Selective catheterization of the bladder diverticulum with a Council tip catheter. A Foley catheter in the bladder permits selective distention of the diverticulum to aid in diverticular identification and dissection. Ureteral catheterization aids in ureteral identification to avoid injury. (Modified from Porpiglia F, Tarabuzzi R, Cossu M, et al. Sequential transurethral resection of the prostate and laparoscopic bladder diverticulectomy: comparison with open surgery. *Urology* 2002;60:1045.)

need for concomitant ureteral or bladder outlet surgery. Complex and multiple diverticula requiring concomitant ureteral reimplantation can be handled via a laparoscopic or robotic approach, provided that the surgeon has sufficient experience and skill.

Various alternative approaches to laparoscopic diverticulectomy have been described in attempts to minimize morbidity further. Transvesical pneumovesicoscopic diverticulectomy has been described involving the cystoscopic establishment of carbon dioxide pneumovesicum, with subsequent transabdominal trocar placement directly into the bladder (Badawy et al, 2008; Marte et al, 2010). LESS has been employed to address bladder diverticula as well via a transabdominal (Stolzenburg et al, 2011) as well as a transvesical approach (Roslan et al, 2012).

Technique

Before port placement, flexible cystoscopy can be performed for ureteral catheterization if necessary. Selective catheterization of the diverticulum can be performed by placing a Council tip catheter over a guidewire into the diverticulum and a separate Foley catheter into the bladder proper for selective filling and intraoperative identification of bladder diverticula (Nadler et al, 1995; Porpiglia et al, 2002; Khonsari et al, 2004), as seen in Figure 96-2.

Alternatively, real-time illumination of the diverticulum with a flexible cystoscope is a useful aid in identifying the diverticulum, as described later (Parra et al, 1992; Jarrett et al, 1995; Nadler et al, 1995). In our experience, this is particularly valuable in patients with multiple diverticula, in which separate catheterization of each diverticulum is not practical. Intravesical methylene blue also has been described as an aid to identify the bladder neck during robotic diverticulectomy (Moore et al, 2012). After pneumoperitoneum is established by a closed or open technique, trocars for RBD and LBD are positioned as depicted in Figure 96-3.

If approached transperitoneally, LBD or RBD begins with an incision of the peritoneum overlying the diverticulum. For complex, large, or multiple diverticula, the bladder can be mobilized: The peritoneum is incised medial to the obliterated umbilical ligament bilaterally, the urachus is divided, and the bladder is “dropped” posteriorly allowing for entry into the space of Retzius. The 10-mm LigaSure device (ValleyLab, Boulder CO) can be used during LBD,

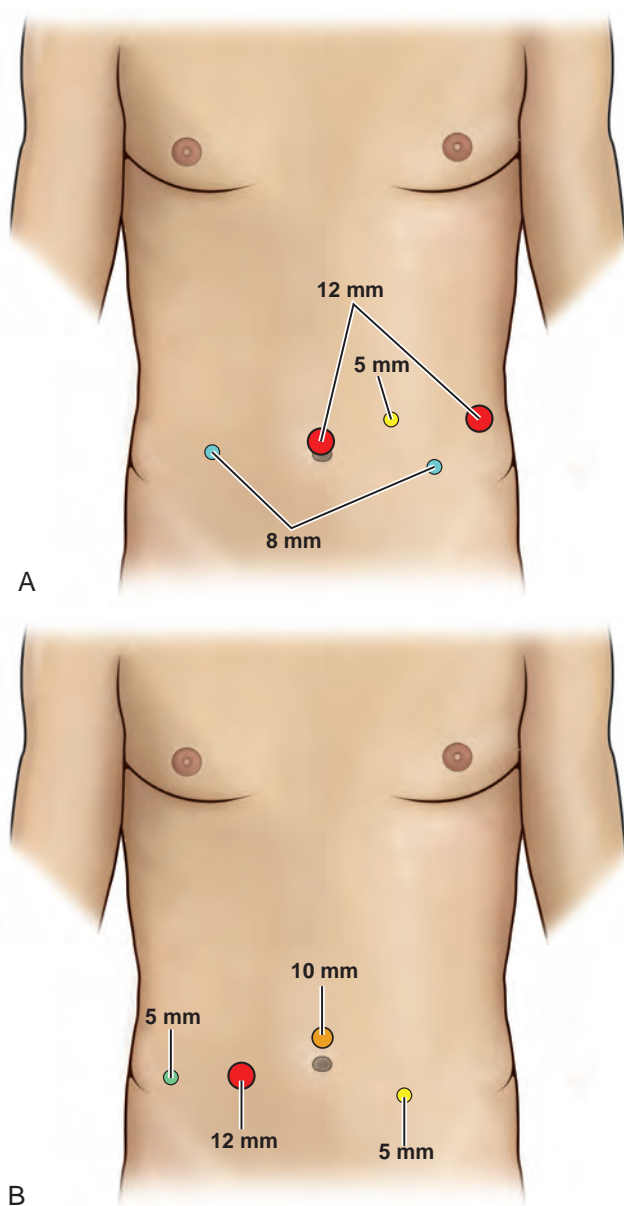


Figure 96-3. A, Robotic bladder diverticulectomy. A 12-mm port at the umbilicus is employed for the endoscope. Two 8-mm robotic trocars are placed 10 cm inferolaterally at the pararectus location. At the surgeon's discretion, assistant ports are placed as needed; options include a 5-mm trocar (placed halfway in between the camera and robotic trocar) and/or a 12-mm trocar (two fingerbreadths above the anterior superior iliac spine). If needed, an additional 8-mm trocar can be used for the fourth arm of the robot two fingerbreadths above the contralateral anterior superior iliac spine. B, Laparoscopic bladder diverticulectomy. A 10-mm port at the umbilicus is employed for the endoscope. For a right-handed surgeon, working ports include a 12-mm and 5-mm trocar, at the right and left pararectus location, respectively. An optional 5-mm trocar can be placed approximately 2 cm cephalad and medial to the anterior superior iliac spine (depicted in green).

and a combination of monopolar and bipolar cautery instrumentation is employed during RBD. With the aid of either selective catheterization and filling or cystoscopic transillumination, the diverticulum is identified (Fig. 96-4). Peridiverticular adhesions are transected, and the mouth of the diverticulum is circumscribed and excised. Constant vigilance is required to prevent injury to the ureter or ureteral orifice. If necessary, a transvesical approach can be

employed. The bladder is opened, and the diverticulum is pulled into the bladder, circumscribed, and excised. In either approach, the bladder is closed anatomically in two layers with absorbable suture. During LBD, freehand intracorporeal suturing can be employed. Alternatively, an Endo Stitch device (Covidien, Mansfield, MA) can be used as a suturing aid. An Endo GIA (Covidien) stapling device can also be used for excision; however, this carries with it the theoretical risk of bladder stone formation (Kerbl et al, 1993). The bladder is filled to ensure watertight closure. A Jackson-Pratt drain is placed via one of the trocar sites to avoid an unnecessary additional incision. If needed, ureteral reimplantation secondary to reflux, obstruction, or iatrogenic injury is performed as described in the following section.

LESS has been demonstrated as an approach to diverticulectomy with excellent cosmetic outcomes (Roslan et al, 2012). After single-site access in the transabdominal approach, the operation follows the same basic steps as described earlier. During transvesical single-site diverticulectomy, the procedure begins with cystoscopy-guided placement of a single port access device transvesically, followed by the establishment of pneumovesicum (Roslan et al, 2013). The diverticular neck is circumscribed with a monopolar scissors or hook, and the diverticulum is excised. Retraction can be aided by transurethral and/or cystoscopic instrumentation. The defect is subsequently closed, and the specimen is extracted (Roslan et al, 2013).

Surgical management for BOO can be performed concomitantly, either immediately before or after bladder diverticulectomy. Surgical management includes transurethral resection of the prostate (TURP), potassium titanyl phosphate laser vaporization, holmium laser enucleation, and photoselective vaporization (Iselin et al, 1996; Grönlund et al, 1998; Porphiglia et al, 2002; Faramarzi-Roques et al, 2004; Shah et al, 2006; Kural et al, 2009). If endoscopic management is performed after diverticulectomy, a suprapubic catheter should be placed to avoid perforation at the bladder-closure suture lines. Similarly, laparoscopic or robotic simple prostatectomy can be performed at the time of LBD or RBD (Magera et al, 2008).

Postoperative care involves Jackson-Pratt drain removal, typically 48 hours postoperatively. Cystography is performed to rule out a bladder leak before Foley catheter removal, at approximately 1 week after surgery.

Outcomes and Complications

Minimally invasive techniques are effective in treating bladder diverticula. LBD is effective in reducing postvoid residual to normal values (<50 mL) (Fig. 96-5). LBD has been demonstrated to be effective even in patients with complex pathology, including multiple diverticula and giant diverticula measuring 30 cm (Khonsari et al, 2004). RBD has been demonstrated to be effective with excellent perioperative outcomes and average hospital stays of approximately 2 to 3 days (Altunrende et al, 2011; Eyraud et al, 2013).

Minimally invasive management of a bladder diverticulum and BOO with concomitant LBD and TURP has been demonstrated to be superior compared with open bladder diverticulectomy and transvesical prostatectomy. Laparoscopic BD and TURP is associated with reduced blood loss, analgesic requirements, and shorter hospital stay, but longer OR times (Porphiglia et al, 2002, 2004). No complications were noted with either approach, and postoperative urinary flow rates were equivalent. In a series of 13 patients undergoing extravesical LBD without concurrent management of BOO, Abdel-Hakim and colleagues (2007) experienced only one complication in the form of extravasation from the suture line that resolved with conservative management. Sequential holmium laser enucleation of the prostate and laparoscopic extraperitoneal bladder diverticulectomy has been performed with good outcomes (Shah et al, 2006). RBD and concomitant photoselective vaporization of the prostate also has been described with excellent outcomes and limited morbidity (Kural et al, 2009). Complications of minimally invasive bladder diverticulectomy are similar to complications encountered during open bladder diverticulectomy and include ureteral injury, infection, urinary extravasation, urinary fistula, wound infection, and bowel injury.

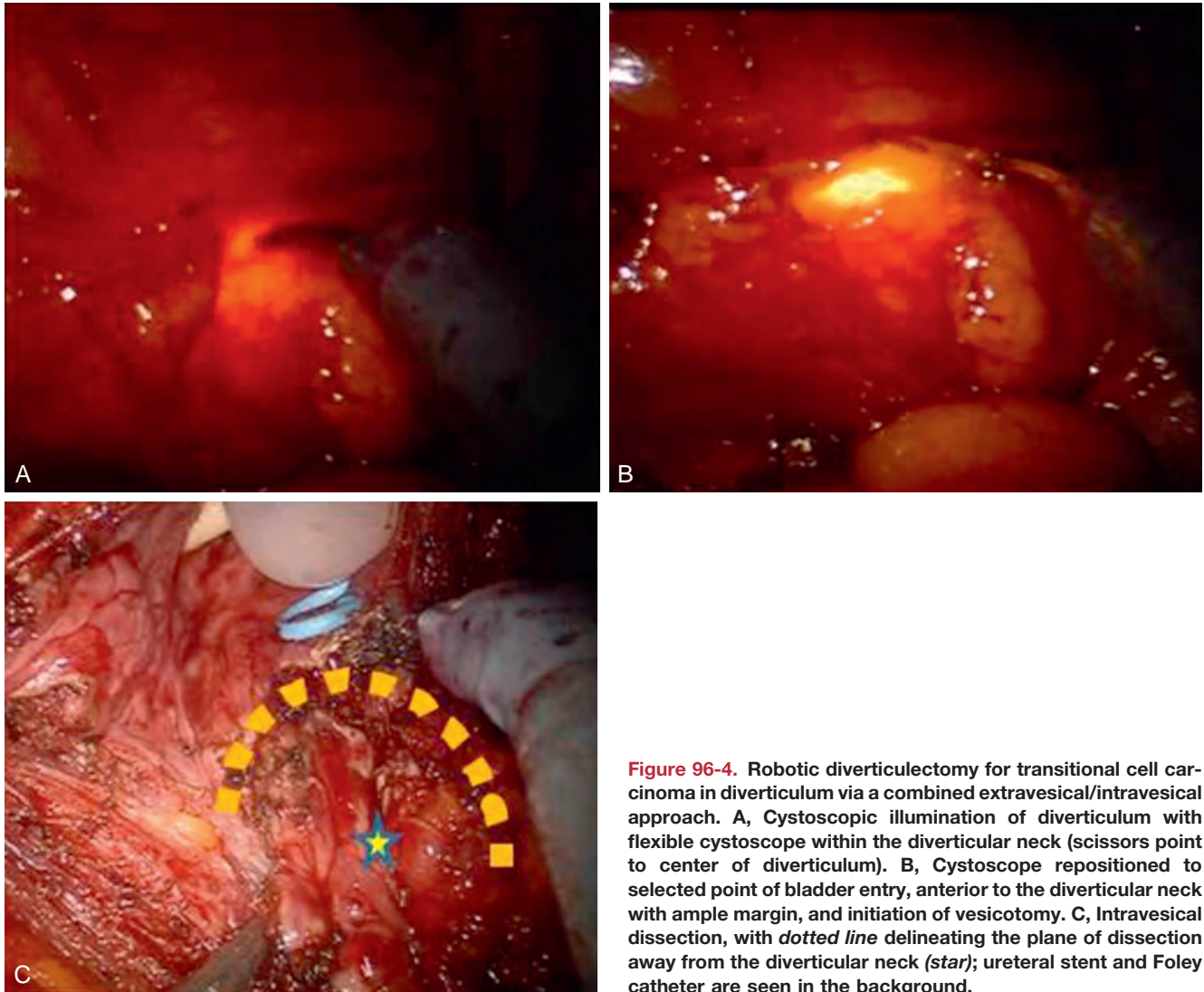


Figure 96-4. Robotic diverticulectomy for transitional cell carcinoma in diverticulum via a combined extravesical/intravesical approach. A, Cystoscopic illumination of diverticulum with flexible cystoscope within the diverticular neck (scissors point to center of diverticulum). B, Cystoscope repositioned to selected point of bladder entry, anterior to the diverticular neck with ample margin, and initiation of vesicotomy. C, Intravesical dissection, with *dotted line* delineating the plane of dissection away from the diverticular neck (*star*); ureteral stent and Foley catheter are seen in the background.

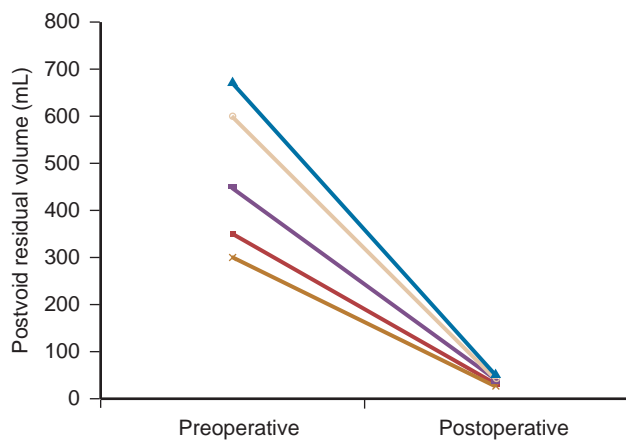


Figure 96-5. Significant reductions in postvoid residual urinary volumes document the efficacy of laparoscopic bladder diverticulectomy for complex bladder diverticula. (Data from Richstone and Kavoussi, unpublished data, 2007.)

Conclusions

LBD and RBD are effective approaches for complex diverticula. Bladder outlet or ureteral surgery can be managed in the same setting using endoscopic and/or laparoscopic techniques. Transvesical and LESS approaches are feasible and may speed recovery and improve cosmetic results.

KEY POINTS: BLADDER DIVERTICULECTOMY

- Laparoscopic and robotic bladder diverticulectomy is an effective approach for even complex diverticula.
- Bladder outlet or ureteral surgery can be managed in the same setting using endoscopic and/or laparoscopic techniques.

URETERAL REIMPLANTATION

Ureteral reimplantation is traditionally performed via an open low midline or Pfannenstiel incision. Laparoscopic ureteroneocystostomy is a well-described and effective alternative, but it requires significant laparoscopic experience and intracorporeal suturing skills. In a drive to limit scar number and size, LESS ureteral reimplantation may offer cosmetic benefits, albeit with even greater technical demands on the surgeon. In contrast, the robotic-assisted laparoscopic approach offers simplified suturing and reconstructive

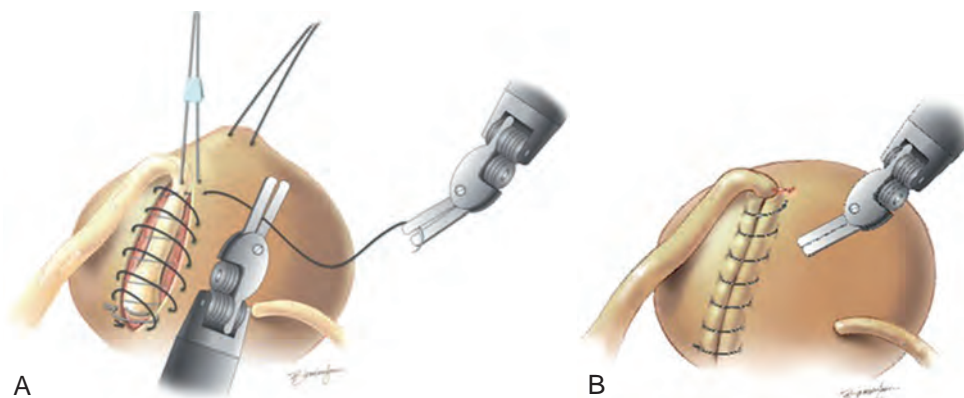


Figure 96-6. Robotic extravesical ureteral reimplantation. A tunnel is made in the detrusor muscle for the ureter, completing the antirefluxing mechanism. A, After anastomosis of the spatulated ureter to the bladder mucosa, detrusorrhaphy is initiated. B, Completed extravesical reimplantation. (From Gundeti MS, Kojima Y, Haga N, et al. Robotic-assisted laparoscopic reconstructive surgery in the lower urinary tract. *Curr Urol Rep* 2013;14:333.)

aspects of this procedure, while offering the cosmetic and recovery benefits of minimally invasive surgery.

Evaluation and Surgical Indications

Indications for ureteroneocystostomy include VUR, ureteral obstruction, and transection. The specific indications for ureteral reimplantation in the setting of VUR are beyond the scope of this chapter and are discussed elsewhere in this text. Ureteral obstruction can be secondary to stone disease and inflammatory, infectious, iatrogenic, and traumatic etiologies as well as benign or malignant mass lesions. When medical and/or endoscopic approaches fail or are deemed insufficient for the given pathology, ureteral reimplantation is indicated.

VUR is evaluated and graded with voiding cystourethrography. In the setting of ureteral obstruction, stricture length can be evaluated with a combination of excretory and retrograde urography. An estimation of the length of the diseased segment is critical in determining whether ureteral length would allow for a ureteroneocystostomy or warrant more complex reconstruction. In addition, the anatomic location of the strictured segment needs to be assessed because upper ureteral strictures require more complex reimplantation techniques. A retrograde pyelogram can be useful to define strictured segments anatomically or locate the position of ureteral tumors. Nuclear renography is useful to document obstruction and, when necessary, to evaluate function when there is a history of longstanding or severe obstruction or reflux. In appropriate patients, it is critical to consider and rule out malignancy with urinary cytology, endoscopy, and appropriate imaging.

Technique

Laparoscopic and robotic ureteral reimplantation can be performed via an extravesical or intravesical approach. Refluxing or nonrefluxing reimplantation techniques have been described. The approach should be tailored to patient age, pathology, anatomy, and surgeon preference.

Nonrefluxing Ureteral Reimplantation

Several investigators demonstrated the feasibility of laparoscopic correction of VUR in animal studies (Atala et al, 1993; Schimberg et al, 1994; McDougall et al, 1995). Laparoscopic extravesical Lich-Gregoir ureteral reimplantation in humans followed shortly thereafter (Ehrlich et al, 1994; Reddy and Evans, 1994; Janetschek et al, 1995). Typical port site placement is similar to that employed for bladder diverticulectomy (see Fig. 96-3).

The extravesical Lich-Gregoir technique can be performed via a conventional laparoscopic or robotic-assisted approach. The ureter is identified medial to the obliterated umbilical ligament, and the

overlying peritoneum is incised. The ureter is mobilized to the ureterovesical junction, preserving periureteric tissue to ensure adequate vascular supply. The location of the proposed tunnel is determined with the bladder filled with saline and care taken to avoid creating a “kinking” tunnel. A 5:1 tunnel-to-ureteral diameter is maintained. Taking care to avoid perforation of the bladder mucosa, the detrusor muscle is incised to create a sufficient trough. The ureter is placed within the trough, and the detrusor is closed over it, using a series of interrupted 3-0 absorbable sutures (Fig. 96-6) (Reddy and Evans, 1994; Hedican et al, 1999; Lakshmanan and Fung, 2000; Gundeti et al, 2008).

The transvesical Cohen cross-trigonal approach has been employed by several authors using the pure laparoscopic and the robotic technique (Gill et al, 2001; Peters and Woo, 2005; Yeung et al, 2005; Kutikov et al, 2006). By avoiding the peritoneal cavity, the transvesical approach has the potential to limit complications associated with the transabdominal approach. A three-trocar configuration accommodates either the pure laparoscopic or the robotic technique.

As originally described by Gill and colleagues (2001), the procedure is performed with two 5-mm transvesical trocars, glycine irrigation within the bladder, and visualization throughout the procedure with a transurethral 24-Fr resectoscope. An electrosurgical Collins knife is used to incise the bladder mucosa and create the cross-trigonal trough, and the detrusor is then sewn over the ureter laparoscopically. This procedure was modified by Yeung and colleagues (2005) using carbon dioxide insufflation of the bladder and a midline trocar for laparoscopic, rather than cystoscopic, visualization of the procedure. In pediatric patients, two 3-mm trocars can be used for working ports, a 5-mm midline trocar can be used for the camera, and an 8-Fr pediatric feeding tube can be placed in the urethra for intermittent suctioning (Kutikov et al, 2006). Similarly, a three-trocar robotic transvesical approach to cross-trigonal reimplantation has been described (Peters and Woo, 2005). After circumferential incision around the ureteral orifice, the ureter is mobilized by incising periureteral attachments. The native hiatus is reduced with 4-0 absorbable suture, and a cross-trigonal submucosal tunnel and new mucosa hiatus are created. The ureter is advanced and anchored with several interrupted 4-0 absorbable sutures, and the periureteral mucosa is sutured to the bladder mucosa with 5-0 absorbable stitches (Fig. 96-7).

Refluxing Ureteral Reimplantation

Laparoscopic or robotic ureteral reimplantation for benign ureteral stricture disease or select cases of ureteral malignancy is commonly performed in a refluxing manner (Seideman et al, 2009). We routinely perform laparoscopic ureteral reimplantation using a three-trocar approach (Fig. 96-8).

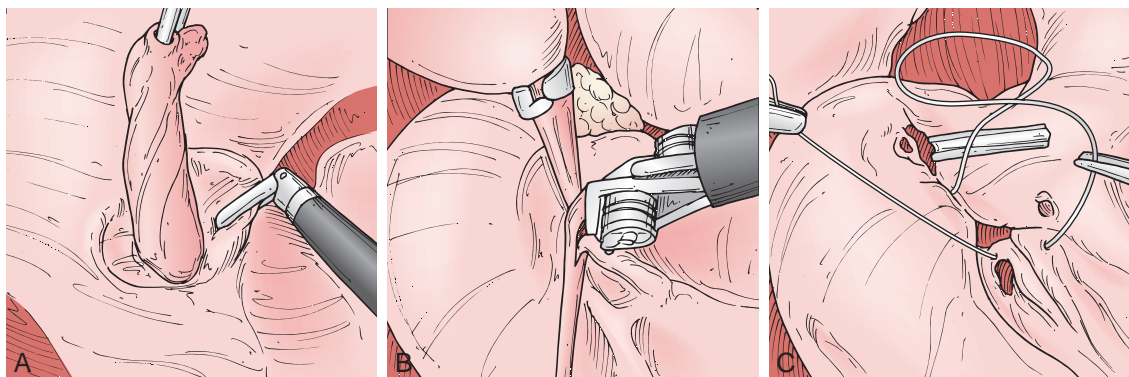


Figure 96-7. A-C, Robotic transvesical cross-trigonal ureteral reimplantation.

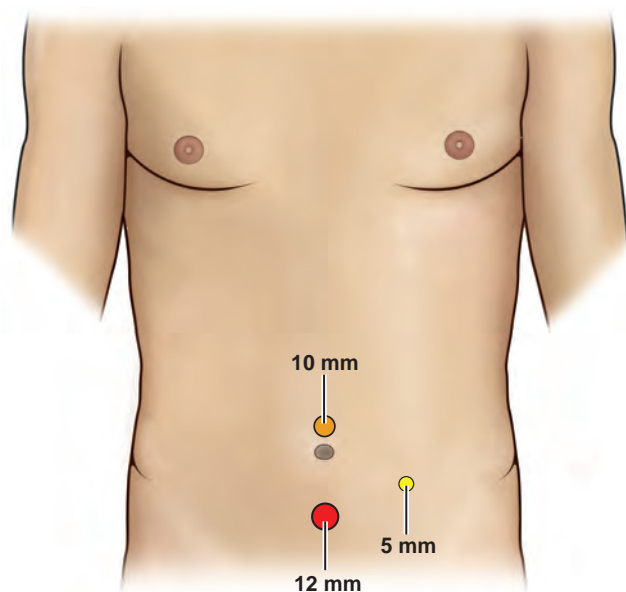


Figure 96-8. Ureteral reimplantation. Trocar placement for left ureteral reimplantation includes a 10-mm umbilical camera port and a 12-mm working port placed halfway between the umbilicus and the symphysis pubis. A 5-mm working port is placed at the lateral edge of the rectus muscle at the level of the umbilicus on the ipsilateral side of the procedure.

The distal ureter is dissected, and the diseased segment is excised. In cases of transitional cell carcinoma, it is important to excise the entire distal ureter including the ureteral orifice. To this end, we recommend taking a “formal bladder cuff,” which can be performed entirely laparoscopically or robotically. The bladder is opened at the dome, and the ureteral hiatus and distal ureter are formally excised from within the bladder. The hiatus is sutured closed with 2-0 Vicryl sutures, and the anterior cystostomy is similarly closed. A Foley catheter is left in place for 7 days postoperatively. A new ureteral hiatus is created at the dome of the bladder, and the spatulated ureter is reimplanted with 4-0 absorbable sutures in a running or interrupted fashion (Reddy and Evans, 1994; Fugita and Kavoussi, 2001). The posterior wall of the bladder can be sutured to the psoas tendon (psoas hitch) with 2-0 Prolene sutures to take any tension off of the ureteral reimplantation. Minimally invasive management of longer ureteral defects is discussed in the next section on psoas hitch and bladder advancement flaps.

Outcomes and Complications

Clinical experience with laparoscopic and robotic ureteroneocystostomy continues to evolve. Small feasibility studies prevail; however,

a few larger studies with intermediate-term follow-up data support the efficacy of the approach.

Lakshmanan and Fung (2000) described 71 extravesical ureteral reimplantations in 47 patients for management of VUR. No patients experienced subsequent obstruction or recurrent reflux. Complications were minimal and included three ureteral injuries, two of which required open reimplantation. Yeung and colleagues (2005) performed 30 laparoscopic transvesical cross-trigonal reimplantations in 16 patients. The mean operative time was 112 minutes for unilateral cases and 178 minutes for bilateral cases. Two patients had subcutaneous and scrotal emphysema that resolved spontaneously. The radiographic success rate was 96%.

In the largest reported series in adult patients, Seidman and colleagues (2009) reported on 45 patients undergoing laparoscopic ureteral reimplantation for benign and malignant pathology. The median hospital stay was 3 days, and estimated blood loss was 150 mL. Minimal complications were experienced, including urinary extravasation at the anastomotic site in three patients, which was conservatively managed. With a mean follow-up time of 2 years, the authors reported a 96% success rate.

Rassweiler and colleagues (2007) compared 10 patients undergoing laparoscopic ureteral reimplantation with 10 patients treated by open techniques. In this small series, the laparoscopic approach was associated with less blood loss, lower analgesic requirements, less time to oral intake, shorter hospital stay, and shorter convalescence time. Similarly, Simmons and colleagues (2007) retrospectively compared 12 laparoscopic versus 34 open ureteral reimplantation procedures, demonstrating a reduced blood loss and shorter hospitalization associated with laparoscopy. Complication rates and ureteral patency rates were equivalent at a mean follow-up of nearly 2 years. Several authors have documented the feasibility of robotic-assisted ureteral reimplantation (Yohannes et al, 2003; Uberoi et al, 2007; Patil et al, 2008). The robotic technique recapitulates the laparoscopic technique and may facilitate the learning curve for reconstructive procedures requiring intracorporeal suturing.

More recently, LESS surgery has emerged as a technique with the potential for improved cosmetic outcomes and perhaps reduced pain and convalescence. LESS ureteroneocystostomy has been reported, but larger series are needed to validate the efficacy and safety of the approach (Desai et al, 2009). Roslan and colleagues (2012) reported a case of a LESS ureteroneocystostomy. Khanna and associates (2012) reported on three cases of LESS ureteral reimplantation. With a median follow-up of 29 months, none of the three patients required revision or had recurrent stricture disease. There are clear technical challenges, and most surgeons reporting on LESS ureteral reimplantations have had broader experiences in LESS nephrectomy and other types of LESS reconstructive surgeries.

Conclusions

Laparoscopic and robotic ureteroneocystostomy are viable alternatives to open surgery. Extravesical and transvesical approaches can

be employed to perform refluxing or nonrefluxing ureteral reimplantation. Evolving data support the efficacy of this approach for VUR and ureteral obstruction or transection. In the future, LESS may provide an even less invasive approach to ureteroneocystostomy, possibly reducing disfigurement and morbidity.

KEY POINTS: URETERAL REIMPLANTATION

- Laparoscopic and robotic ureteroneocystostomy are viable alternatives to open surgery.
- Extravesical and transvesical approaches can be employed to perform refluxing or nonrefluxing ureteral reimplantation.
- Evolving data support the efficacy of this approach for VUR, as well as ureteral obstruction or transection.
- In the future, LESS surgery may provide an even less invasive approach to ureteroneocystostomy, possibly reducing disfigurement and morbidity.

PSOAS HITCH AND BLADDER ADVANCEMENT FLAPS

When faced with minimal distal ureteral loss, simple ureteroneocystostomy is sufficient to reestablish urinary continuity. However, more extensive gaps require more complex reconstructive techniques. The Boari bladder flap was introduced for bridging larger gaps between the ureter and bladder in 1894 in a canine model and in humans in 1947 (Fugita and Kavoussi, 2001). Laparoscopic Boari flap was first performed in a porcine model and in humans in 2001 (Fergany et al, 2001; Fugita and Kavoussi, 2001). This procedure can be performed with or without a psoas hitch to anchor the bladder to gain additional length and avoid anastomotic tension. Defects of the distal third ureter are routinely bridged with this technique. The robotic approach can ease the technical burdens of extensive intracorporeal suturing required for Boari flap creation (Schimpf and Wagner, 2008; Allaparthi et al, 2010). More recent literature has documented the feasibility of laparoscopic Boari flap to reach the proximal ureter and/or renal pelvis in select cases. When this approach is insufficient, ureteroureterostomy, transureteroureterostomy, autotransplantation, or ileal ureteral substitution can be considered.

Evaluation and Surgical Indications

Laparoscopic or robotic Boari flap with or without psoas hitch is indicated when the degree of ureteral loss precludes simple ureteroureterostomy or ureteroneocystostomy. Preoperative evaluation of ureteral obstruction includes antegrade and/or retrograde urography to estimate the extent of disease and aid in planning for the surgical approach. Ultimately, intraoperative findings dictate the need for Boari flap and/or psoas hitch. Nuclear renography is indicated if impaired renal function is suspected. Cystoscopy, urinalysis, and urinary cytology is performed to rule out malignancy.

Technique

Laparoscopic or Robotic Boari Flap

Laparoscopic Boari flap was first described in humans by Fugita and Kavoussi (2001) in a series of three patients with distal ureteral obstruction. The robotic-assisted laparoscopic approach was first reported several years later (Schimpf and Wagner, 2008). Trocar placement for laparoscopic reimplantation and Boari flap or advancement flap is depicted in Figure 96-8. Trocar placement for the robotic approach is identical to that used for diverticulectomy, as seen in Figure 96-3. With either approach, the procedure begins by incising the ipsilateral white line of Toldt and identifying the ureter as it crosses the iliac vessels. The ureter is mobilized distally, and the diseased segment is excised, ensuring that the distal margin is well vascularized and healthy. If indicated, a distal margin is sent for frozen section, and the ureter is spatulated. The bladder is filled

with 200 mL of normal saline and mobilized by incising the peritoneum medial to the obliterated umbilical ligaments bilaterally and transecting the urachus. Blunt dissection allows the bladder to “drop” posteriorly, and the space of Retzius is entered. Ligation of the contralateral bladder pedicle with an Endo GIA stapling device and psoas hitch using 2-0 absorbable suture often can provide enough mobilization to perform a ureteroneocystostomy (Modi et al, 2005; Schimpf and Wagner, 2008). If this maneuver does not suffice, a Boari flap or bladder advancement flap is performed. Using electrosurgical scissors or a 10-mm LigaSure device, an anterior bladder flap is created beginning approximately 2 cm from the bladder neck and extending to the ipsilateral bladder dome; the apex of the flap is approximately 2 cm, and the base of the flap is approximately 4 cm (Fig. 96-9) (Fugita and Kavoussi, 2001). Care should be taken to confirm that the base of the flap is wide enough to ensure adequate vascularity. The spatulated ureter is anastomosed to the apex of the flap with interrupted 4-0 absorbable suture. After placement of a 7-Fr double-pigtail catheter over a guidewire, the flap is closed in a running fashion in two layers with 4-0 and 2-0 absorbable suture or with the assistance of an EndoStitch device. The bladder is filled to 300 mL to identify any sites of anastomotic leakage, and a Jackson-Pratt drain is placed through the 5-mm trocar site. The Jackson-Pratt drain is typically removed in 48 hours, and the Foley catheter is removed in 1 week after cystography confirms no urinary leakage. The ureteral stent is removed in 4 weeks.

Laparoscopic or Robotic Bladder Advancement Flap

Laparoscopic bladder advancement flap was first described by Lima and colleagues (2005) as a simplified alternative to a Boari flap. The bladder is opened with a transverse incision, placed one third of the distance from the dome to the bladder neck (Fig. 96-10). The spatulated ureter is anastomosed to the bladder flap in a fashion similar to a Boari flap, described previously.

Laparoscopic “Mega-Boari” Flap

Proximal ureteral strictures generally have required ureteral substitution or autotransplantation. We have had success with “mega-Boari” flap formation, successfully mobilizing a bladder flap to the level of the proximal ureter or renal pelvis, in six patients (Richstone and Kavoussi, unpublished data, 2007). The kidney is mobilized completely, and, when necessary, descensus and nephropexy is performed to gain length. The ureter or renal pelvis is divided at the proximal aspect of the diseased segment. The bladder is mobilized by incising the peritoneum bilaterally, medial to the obliterated umbilical ligaments. The posterior peritoneum is incised to free the posterior wall of the bladder. The contralateral ureter is identified and protected. The urachus is then divided, and the contralateral bladder pedicle is divided. The bladder flap is created with a transverse cystotomy incision along the lateral and posterior bladder wall above the trigone (Fig. 96-11). Extreme care is taken to avoid injury to the contralateral ureteral orifice. A 2.5-cm flap is developed from the posterior surface of the bladder extending toward the anterior aspect. The free edge of the flap is transposed superiorly toward the kidney. To gain length for the flap, several stepwise 1-cm incisions are made along both of the edges of the bladder flap. In this fashion, the “mega-Boari” flap can reach the level of the spatulated renal pelvis without tension. Anastomosis is performed with running 4-0 Vicryl suture, and the posterior bladder tube is closed with running 2-0 absorbable suture over a 7-Fr × 28-cm double-J ureteral stent. The remaining bladder defect was closed with running 2-0 absorbable suture.

Laparoscopic Single-Site Surgery Boari Flap

LESS Boari flap has been described and may improve cosmetic results. Either a homemade or a manufactured multichannel LESS port is used. Alternatively, multiple standard trocars can be introduced through a single site, typically the umbilicus. Robotic-assisted

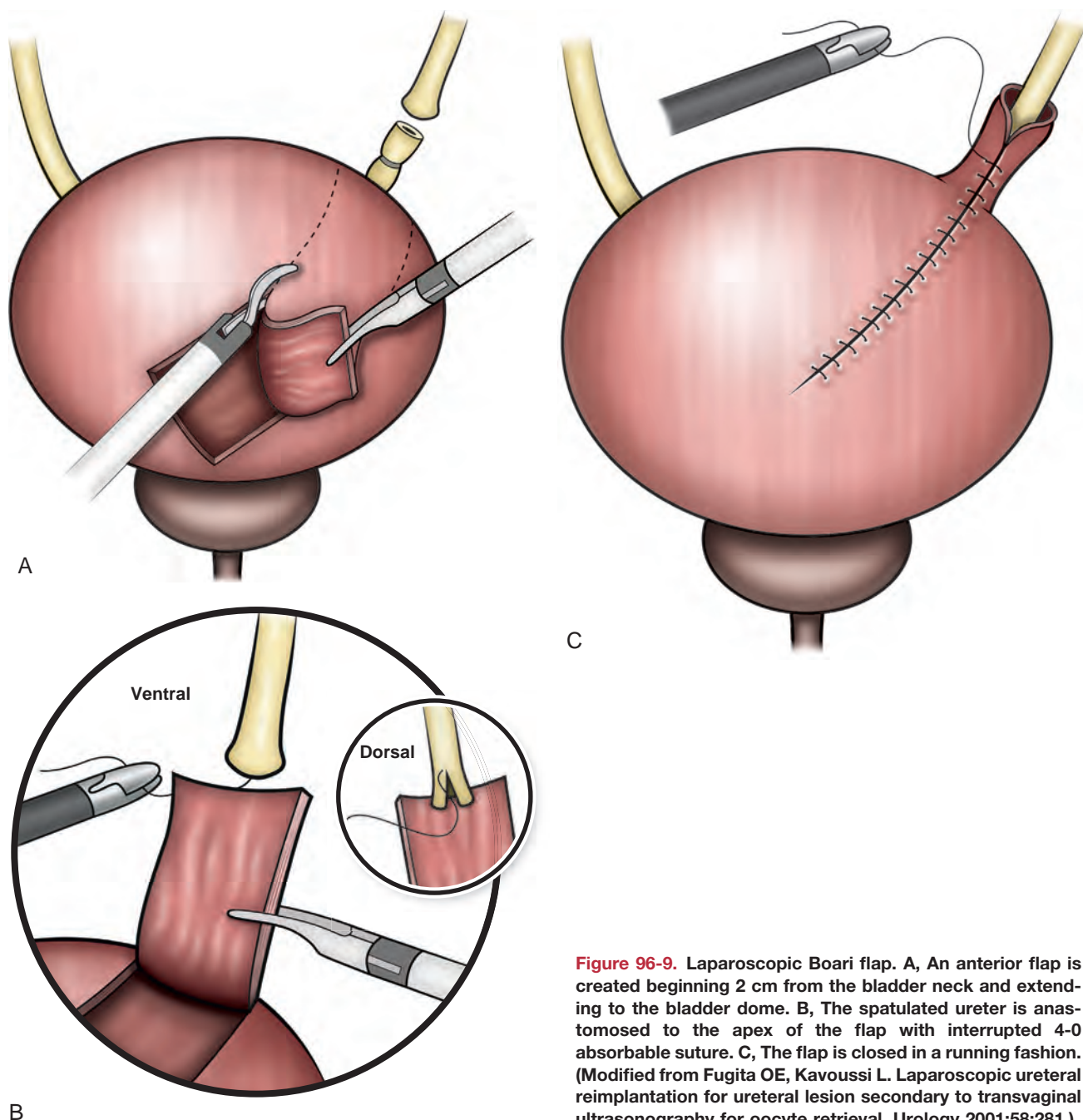


Figure 96-9. Laparoscopic Boari flap. A, An anterior flap is created beginning 2 cm from the bladder neck and extending to the bladder dome. B, The spatulated ureter is anastomosed to the apex of the flap with interrupted 4-0 absorbable suture. C, The flap is closed in a running fashion. (Modified from Fugita OE, Kavoussi L. Laparoscopic ureteral reimplantation for ureteral lesion secondary to transvaginal ultrasonography for oocyte retrieval. *Urology* 2001;58:281.)

LESS approach also can be used. After access is obtained, the procedure is performed identically to laparoscopic and robotic flap creation (Khoder et al, 2011).

Outcomes and Complications

The first clinical series of laparoscopic ureteral reimplantation with Boari flap was reported in 2001 and involved three patients (Fugita and Kavoussi, 2001). The approach was demonstrated to be feasible with a mean operative time of 220 minutes and estimated blood loss ranging from 400 to 600 mL. With a mean follow-up period of 11 months, all patients had resolution of obstruction. Castillo and colleagues (2005) reported a slightly larger series of laparoscopic Boari flap in eight patients. Operative times (mean 157

minutes), blood loss (mean 124 mL), and hospital stay (mean 3 days) further validated the feasibility of the technique. Two complications occurred, including one pulmonary embolism and one episode of urinary leakage at the anastomosis requiring laparoscopic repair. With a mean follow-up of 18 months, all patients had resolution of obstruction. Seideman and colleagues (2009) reported the largest single-center series of laparoscopic Boari flap in 21 of 45 patients undergoing laparoscopic ureteral reimplantation with significant follow-up (mean 24 months). Two patients underwent distal ureterectomy for transitional cell carcinoma. Median length of stay was 3 days, and median estimated blood loss was 150 mL. Complications included small bowel obstruction in one patient, *Clostridium difficile* colitis and respiratory distress in one patient, and urinary leakage in two patients that was managed conservatively in

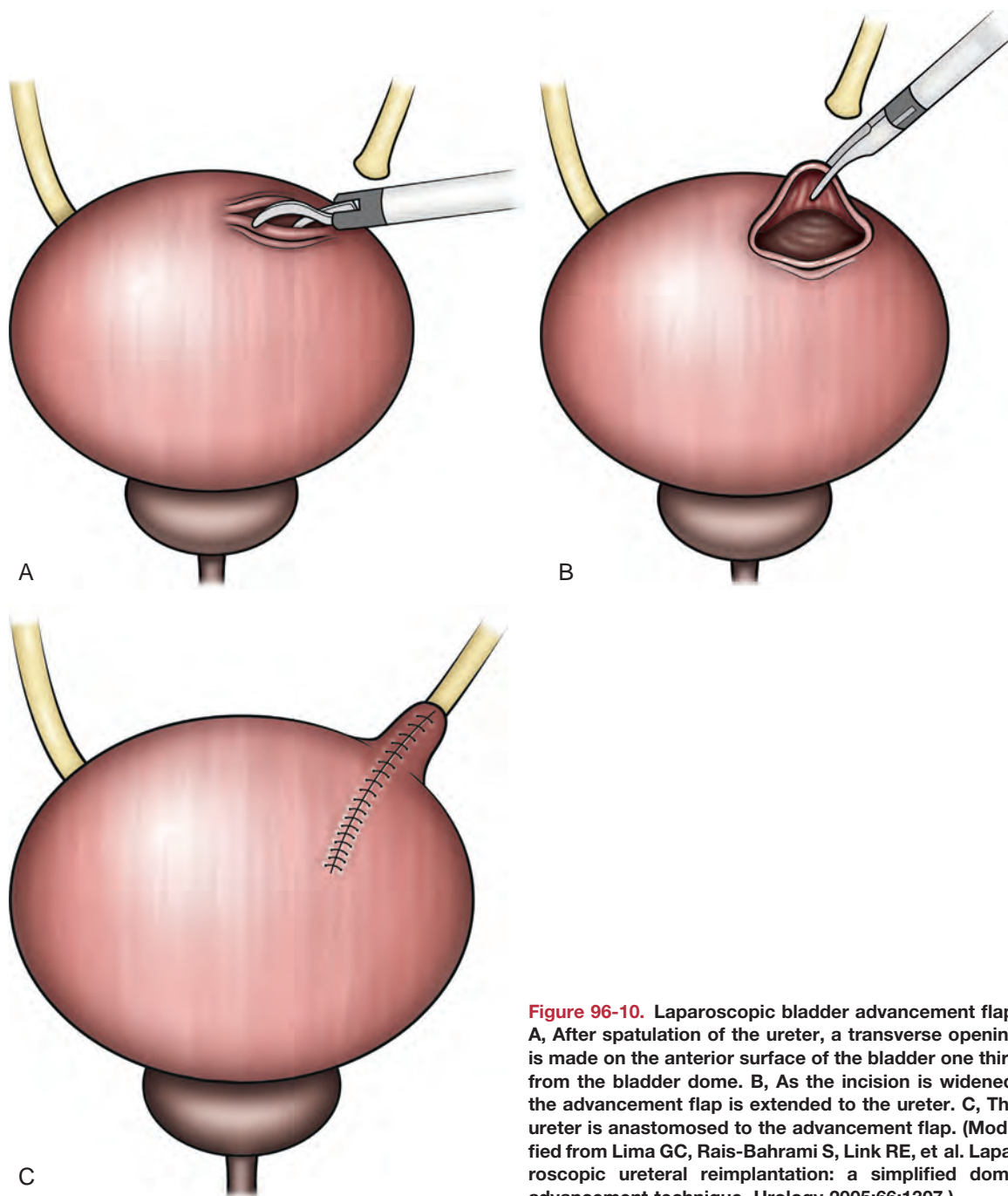


Figure 96-10. Laparoscopic bladder advancement flap. A, After spatulation of the ureter, a transverse opening is made on the anterior surface of the bladder one third from the bladder dome. B, As the incision is widened, the advancement flap is extended to the ureter. C, The ureter is anastomosed to the advancement flap. (Modified from Lima GC, Rais-Bahrami S, Link RE, et al. Laparoscopic ureteral reimplantation: a simplified dome advancement technique. *Urology* 2005;66:1307.)

both cases. In a multi-institutional series of 30 patients undergoing laparoscopic Boari flap, excellent outcomes were achieved (Castillo et al, 2013). In that series, mean operating room time was 161 minutes, and mean estimated blood loss was 123 mL with no intraoperative complications or conversion to open surgery. Post-operative complications occurred in 17% of patients, with a success rate of 97% at a mean follow-up of 32 months. Similarly, excellent results have been reported with a robotic approach, albeit with smaller series to date (Allaparthi et al, 2010; Musch et al, 2013).

Conclusions

Laparoscopic and robotic approaches to psoas hitch, Boari flap, and bladder advancement flap for patients with moderate distal ureter loss have been demonstrated to be an effective alternative to open

surgical techniques. Outcomes appear favorable compared with open series.

KEY POINTS: PSOAS HITCH AND BLADDER ADVANCEMENT FLAPS

- Laparoscopic and robotic approaches to psoas hitch, Boari flap, and bladder advancement flap for patients with moderate distal ureter loss have been demonstrated to be an effective alternative to open surgical techniques.
- Outcomes appear favorable when compared with open series.

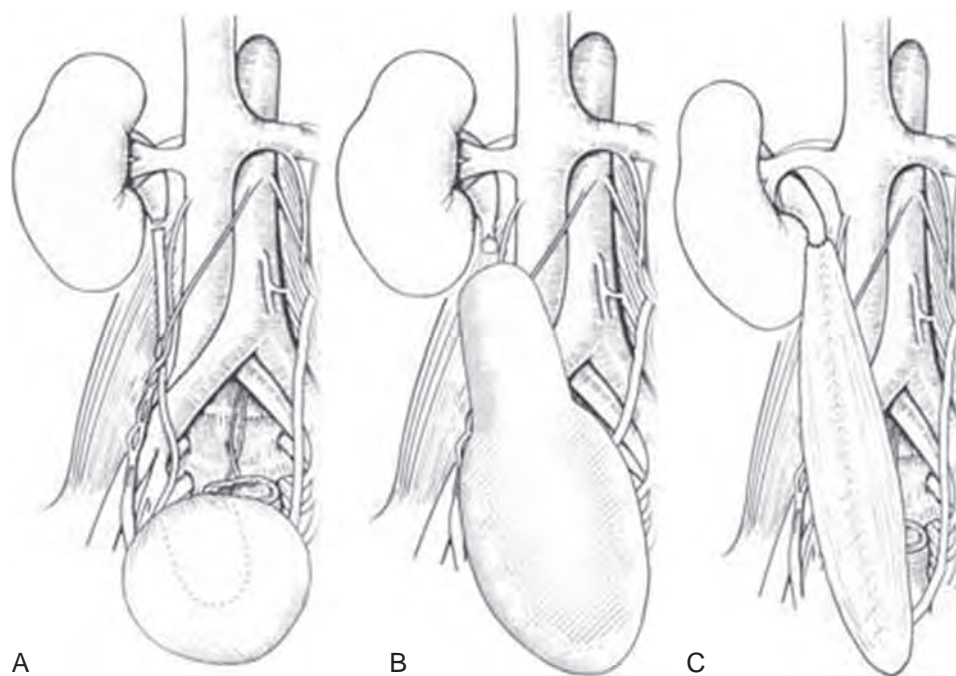


Figure 96-11. Laparoscopic mega-Boari flap for proximal ureteral stricture. After renal mobilization and transection of the ureter at the level of obstruction, the posterior bladder is scored for incision on the outer posterior aspect of the bladder (A). Viewed anteriorly, the flap is mobilized; *dashed lines and translucency* indicate incision and flap on the outer posterior aspect of the bladder (B). The anastomosis is created and the posterior aspect of the bladder flap is closed (C). (Data from Richstone and Kavoussi, unpublished data, 2014.)

ENTEROCYSTOPLASTY

Augmentation cystoplasty is a well-established surgical option for a patient with a poorly compliant bladder with a small capacity who has failed conservative management. [Docimo and colleagues \(1995\)](#) were the first to perform a purely laparoscopic gastrocystoplasty in a single patient. Although the procedure took almost 11 hours and involved a 13-day hospital course, the feasibility of the technique was demonstrated. Subsequently, [Gill and associates \(2000\)](#) described laparoscopic ileocystoplasty, sigmoidocystoplasty, and cecocoloplasty with bowel anastomosis done extracorporeally. Over the past decade, ileocystoplasty has emerged as the most widely employed technique. Reports of laparoscopic, robotic, and LESS bladder augmentation have documented the reproducibility of these techniques by purely intracorporeal and partly extracorporeal approaches.

Evaluation and Surgical Indications

Candidates for augmentation cystoplasty include patients with poorly compliant bladders with small capacity who are capable of self-catheterization ([Elliott et al, 2002](#)). Most commonly, these patients have a neurogenic bladder secondary to spinal dysraphism or other anatomic abnormalities. All patients should undergo video-urodynamics before augmentation. An ultrasound scan should be obtained to rule out hydronephrosis, which should be evaluated before surgery. All patients must be physically and psychologically competent and willing to perform self-catheterization. Contraindications to either open or minimally invasive augmentation include renal insufficiency, renal tubular acidosis, and gastrointestinal disease including short gut syndrome, inflammatory bowel disease, and liver failure ([Elliott et al, 2002](#)).

Technique

The procedure begins with cystoscopic evaluation and placement of bilateral open-ended or single-J ureteral catheters, which are secured

to a urethral catheter. Pneumoperitoneum is established. Laparoscopic or robotic enterocystoplasty is performed using three to five trocars depending on the surgeon's experience and preference. The bladder is fully mobilized by incising the peritoneum medial to the obliterated umbilical ligament bilaterally, and the urachus is divided to "drop" the bladder posteriorly and enter the space of Retzius. An appropriate 15- to 20-cm segment of bowel is chosen taking care to ensure an adequate vascular pedicle and that the segment will reach to the bladder neck. The bowel work can be completed via a purely laparoscopic approach ([Meng et al, 2002](#)) or extracorporeally by extending the length of the umbilical incision ([Gill et al, 2000](#)) as described subsequently. In either approach, the segment is harvested using an Endo GIA stapler. The mesentery can be divided with additional reloads of the Endo GIA or with a 10-mm LigaSure device. Bowel continuity is reestablished with a side-to-side anastomosis using the Endo GIA device. The anastomosis is completed using a TA stapler (Covidien) if performed extracorporeally and with a series of Lembert sutures if performed using intracorporeal suturing ([Fig. 96-12](#)). The mesenteric window, or "trap," is closed to prevent internal herniation.

The bowel segment is irrigated copiously, the staple lines are excised on each end, and the segment is then opened along the antimesenteric border. During ileal augmentation, the sides of the bowel segment are approximated to form a U-shaped segment with running 2-0 polyglactin 910 suture. At this time, the bladder is filled with saline and bivalved at the midsagittal line. The segment is brought down to the pelvis without tension or torsion of the mesenteric pedicle. With the bowel segment oriented so that the apex of the U is positioned anteriorly at the bladder neck, the patch is sutured to the bladder in a running continuous fashion with 2-0 polyglactin 910 suture, beginning posteriorly and ending anteriorly ([Gill et al, 2000](#); [Elliott et al, 2002](#); [Meng et al, 2002](#)). The integrity of the completed augmentation is confirmed by irrigating the bladder via the Foley catheter, and finally a pelvic drain is positioned. Laparoscopic and robotic ileocystoplasty and cecocoloplasty with creation of a catheterizable stoma also have been

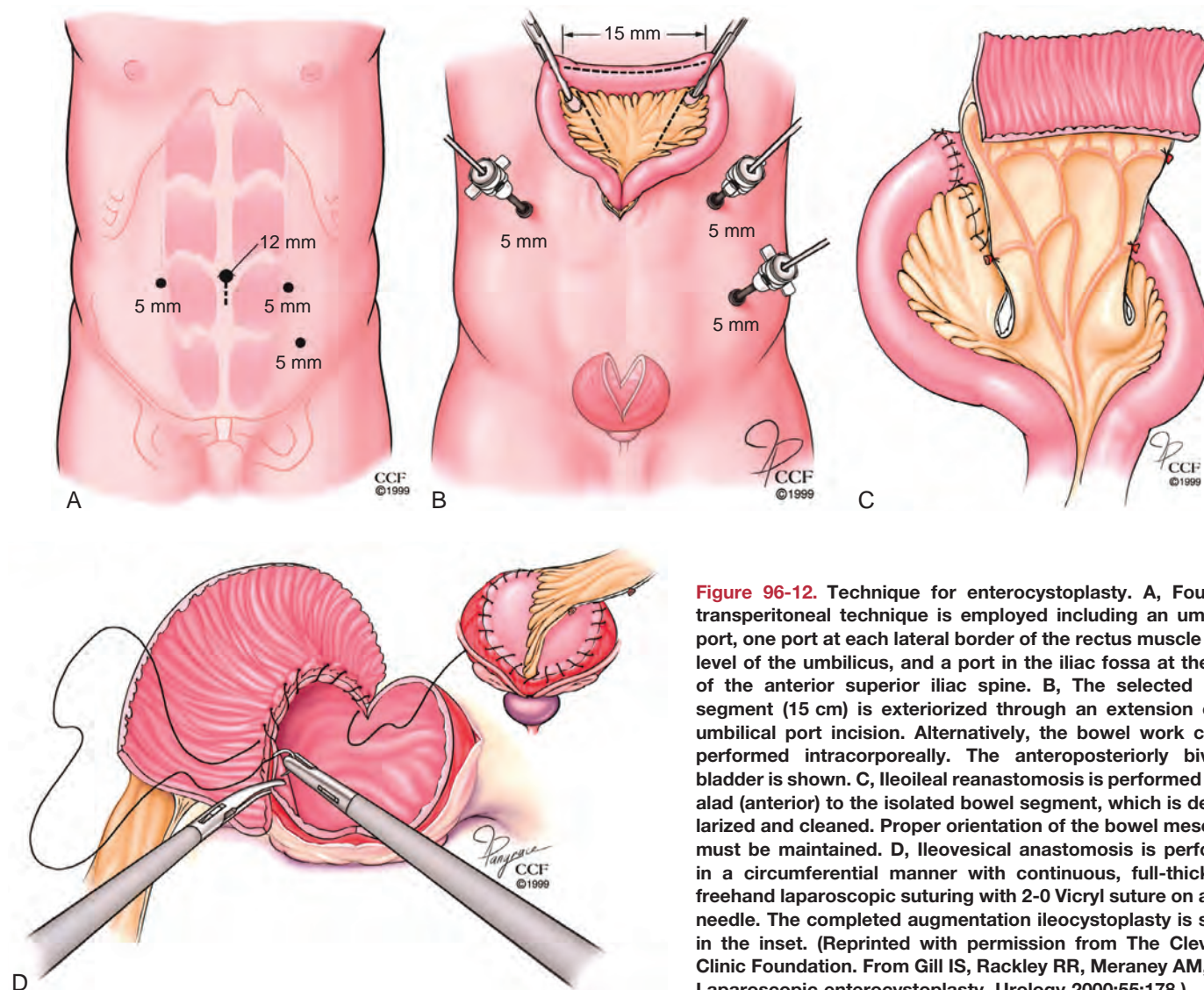


Figure 96-12. Technique for enterocystoplasty. **A**, Four-port transperitoneal technique is employed including an umbilical port, one port at each lateral border of the rectus muscle at the level of the umbilicus, and a port in the iliac fossa at the level of the anterior superior iliac spine. **B**, The selected bowel segment (15 cm) is exteriorized through an extension of the umbilical port incision. Alternatively, the bowel work can be performed intracorporeally. The anteroposteriorly bivalved bladder is shown. **C**, Ileoileal reanastomosis is performed cephalad (anterior) to the isolated bowel segment, which is detubularized and cleaned. Proper orientation of the bowel mesentery must be maintained. **D**, Ileovesical anastomosis is performed in a circumferential manner with continuous, full-thickness, freehand laparoscopic suturing with 2-0 Vicryl suture on a CT-1 needle. The completed augmentation ileocystoplasty is shown in the inset. (Reprinted with permission from The Cleveland Clinic Foundation. From Gill IS, Rackley RR, Meraney AM, et al. Laparoscopic enterocystoplasty. *Urology* 2000;55:178.)

described (Gill et al, 2000; Gundeti et al, 2008). For patients with concomitant refractory constipation, the Malone antegrade continence enema procedure can be performed concurrently (Shadpour et al, 2005). As an alternative to vesicoplasty for select patients, appendicovesicostomy has been performed laparoscopically (Hsu and Shortliffe, 2004; Lorenzo et al, 2007) and with a robotic-assisted laparoscopic approach (Lendvay et al, 2008). More recently, LESS enterocystoplasty has been reported, but larger series are needed to validate the efficacy and safety of the approach (Desai et al, 2009).

Outcomes and Complications

Complications of laparoscopic and robotic bladder augmentation are similar to complications encountered during open surgery and include infection, metabolic derangements, stones, perforation, mucus production, and malignancy. Intracorporeal bowel segment irrigation and detubularization may increase the risk of infectious complications.

Docimo and colleagues (1995) performed the first pure laparoscopic gastrocystoplasty in a patient with a five-port technique. The procedure involved almost 11 hours of operating time and a 13-day hospitalization. A laparoscopic-assisted approach, in which the laparoscopic work was largely limited to bowel mobilization, followed (Hedican et al, 1999; Chung et al, 2004). Gill and colleagues (2000) reported the first laparoscopic ileocystoplasty,

sigmoidocystoplasty, and cecocoloplasty. Bowel harvest and anastomotic work was done extracorporeally with a four-port approach. In this small series of three patients, operative times of 5 to 8 hours and blood loss of 50 to 200 mL were reported. A rectus sheath hematoma was the only complication that occurred. The first purely laparoscopic ileocystoplasty in a human was reported in 2002 (Elliott et al, 2002; Meng et al, 2002). The patient underwent a 9-hour procedure and required a 13-day hospitalization secondary to prolonged ileus. The largest published series of minimally invasive cystoplasty comprises six patients who underwent pure laparoscopic ileocystoplasty and an antegrade continence enema procedure (Shadpour et al, 2005). Operative times were 5 to 8.5 hours, with a median hospitalization of 5 days. Complications included one ileal anastomotic leak that resolved conservatively and one appendiceal stomal stenosis requiring revision. With intermediate-term follow-up (13 to 16 months), all patients were continent of urine between catheterizations, and nearly all had perfect fecal continence. Purely intracorporeal robotic augmentation ileocystoplasty with and without Mitrofanoff appendicovesicostomy also has been described (Al-Othman et al, 2008; Gundeti et al, 2008). The technique is essentially identical to the laparoscopic approach, but it may facilitate the learning curve for intracorporeal suturing. Famakinwa and associates (2013) updated this series and reported their experience of 18 children who underwent robotic-assisted laparoscopic Mitrofanoff appendicovesicostomy. With a median follow-up of 24.2 months, results were quite promising. The appendix was

anastomosed to the posterior wall of the bladder intravesically when concomitant enterocystoplasty was performed. It was done extravesically on patients who did not require an enterocystoplasty. Results and complications were in line with standard open techniques with a median operative time of 494 minutes (Famakinwa et al, 2013).

In a continuing attempt to improve cosmesis and possibly other outcome measures, LESS enterocystoplasty has been reported (Noguera et al, 2009). This technique is an exact replication of the technique described by Gill and colleagues (2000) with extracorporeal bowel work. The operating time was 300 minutes, estimated blood loss was less than 100 mL, and there were no intraoperative or postoperative complications.

Conclusions

Small feasibility studies documented that bladder augmentation cystoplasty can be performed laparoscopically, robotically, and, more recently, with a LESS approach. The principles of open cystoplasty can be replicated by experienced laparoscopic and robotic surgeons, despite the technical rigors associated with bowel work and extensive reconstruction. Although cosmetic outcomes are likely improved, further study is necessary to determine what additional benefits these approaches may confer to this patient population.

KEY POINTS: ENTEROCYSTOPLASTY

- Small feasibility studies document that bladder augmentation cystoplasty can be performed laparoscopically, robotically, and more recently with a LESS approach.
- The principles of open cystoplasty can be replicated by experienced laparoscopic and robotic surgeons, despite the technical rigors associated with bowel work and extensive reconstruction.
- Although cosmetic outcomes are likely improved, further study is necessary to determine what additional benefits these approaches may confer to this patient population.

VESICOVAGINAL AND URETEROVAGINAL FISTULA

Vesicovaginal fistula (VVF) is a distressing condition that often leads to significant psychological and medical morbidity. In the underdeveloped world, birth trauma is the most common etiology of VVF. Prolonged, obstructed labor leads to bladder ischemia and subsequent VVF formation (Miller and Webster, 2001). In developed nations, urogynecologic surgery is the most common cause of VVF, particularly as a complication of abdominal hysterectomy. VVF is estimated to occur after 1 in 1800 abdominal hysterectomies (Miller and Webster, 2001). Less common etiologies of VVF include trauma, foreign body erosion, pelvic irradiation, and other urogynecologic operations (Miller and Webster, 2001). Ureterovaginal fistulae (UVF) are also typically the result of ureteral injury during urogynecologic surgery, most often hysterectomy.

Evaluation and Surgical Indications

Patients with VVF/UVF after hysterectomy classically present with continuous urinary incontinence 10 to 14 days after surgery (Miller and Webster, 2001). A complete evaluation of upper and lower tract is necessary to identify the source of leakage as a VVF, urethrovaginal fistula, or UVF. Vesicouterine fistulae also can occur. All patients should undergo a thorough pelvic examination, cystoscopy, and vaginoscopy. A “double dye” tampon test with oral phenazopyridine and intravesical methylene blue is a useful office-based test. Appropriate imaging includes cystography and IVU to identify VVF and UVF, respectively. Retrograde ureterography is indicated if IVU is inconclusive for ureteral fistula (Miller and Webster, 2001).

Conservative management of VVF includes bladder drainage with a Foley catheter and/or endoscopic fulguration; however, success rates are low (7% to 12.5%) (Sotelo et al, 2005). Most fistulae ultimately require surgical repair, which can be done with an abdominal, vaginal, or combined approach. Controversy exists regarding the ideal approach for fistula repair, and surgeon preference and experience most often dictate the approach (Miller and Webster, 2001). It has been argued that large fistulae, fistulae in close proximity to the ureteral orifices, and recurrent fistulae after failed transvaginal repair are particularly well suited for an abdominal approach (Hemal et al, 2008). Similarly, controversy exists over the ideal timing of fistula repair. Although traditional management has favored delayed intervention, the literature supports early repair in select cases (Blandy et al, 1991; Blaivas et al, 1995; Langkilde et al, 1999; Miller and Webster, 2001).

Technique

Transabdominal VVF and UVF repair has been demonstrated to be feasible and effective using a pure laparoscopic or robotic-assisted laparoscopic approach. Core principles of open surgical fistula repair can and must be followed via minimally invasive approaches, including (1) wide exposure and complete excision of the fistulous tract; (2) optimal tissue health (adequate vascularity, freedom from infection, inflammation, and malignancy); (3) a tension-free, watertight, multilayered closure with nonoverlapping suture lines; (4) interposition of omentum, a peritoneal or bladder flap, or sigmoid epiploicae in between the bladder and vaginal suture lines; and (5) adequate postoperative bladder drainage (Sotelo et al, 2005; Wong et al, 2006).

After induction of anesthesia, cystoscopy is performed, and bilateral ureteral catheters are placed for ureteral identification and protection. To aid in identification and dissection of the fistulous tract, an additional ureteral catheter is passed from the bladder through the fistula and out the vaginal introitus. A Foley catheter can be used in lieu of a catheter for a large fistula. A sponge stick is placed in the vaginal vault to manipulate the vagina.

Pneumoperitoneum is established, and four or five trocars are placed, similar to bladder diverticulectomy (see Fig. 96-3). Two or three robotic arms can be employed, depending on the surgeon's preference. A transperitoneal approach is commonly employed. The patient is placed in the steep Trendelenburg position, and the robot is docked if a robotic-assisted approach is used. Cystoscopic illumination of the bladder allows for ready identification of the fistula location. Replicating the open technique described by O'Connor (1980), a vertical cystotomy incision is made from the dome to the fistula (Chibber et al, 2005). Sotelo and colleagues (2005) described a limited cystotomy in the vicinity of the fistulous tract to limit bladder dissection. Using this approach, dissection of the prevesical space and extensive bivalving of the bladder is avoided. Dissection is continued posteriorly until the catheter in the fistulous tract is identified. Alternatively, direct dissection in the vesicovaginal space can be performed. To prevent loss of pneumoperitoneum, a clamped Foley catheter with an inflated balloon and moist sponge pack can be placed in the bladder and vagina, respectively. The vesicovaginal space is dissected to separate the bladder from the vagina. The fistulous tract is excised completely, ensuring viable edges of bladder and vagina (Fig. 96-13).

The surgeon must remain cognizant of the ureteral orifices at all times to avoid injury. The bladder is closed vertically using 2-0 or 3-0 polyglactin 910 suture in two layers. The vagina is closed transversely to allow for nonoverlapping suture lines. Omental tissue can be interposed between the suture lines and anchored to the anterior vaginal wall with interrupted absorbable sutures (Sotelo et al, 2005). Alternatively, a peritoneal flap (Hemal et al, 2008; Gozen et al, 2009) or pericolic or mesenteric fat (Chibber et al, 2005) can be used for interposition. The bladder is filled with sterile saline to ensure a watertight closure. The ureteral catheters are removed. A Foley catheter in the bladder and closed suction pelvic drain are placed. The drain is removed within 24 to 48 hours. Cystography is performed 10 to 14 days after surgery, and the Foley catheter is removed.

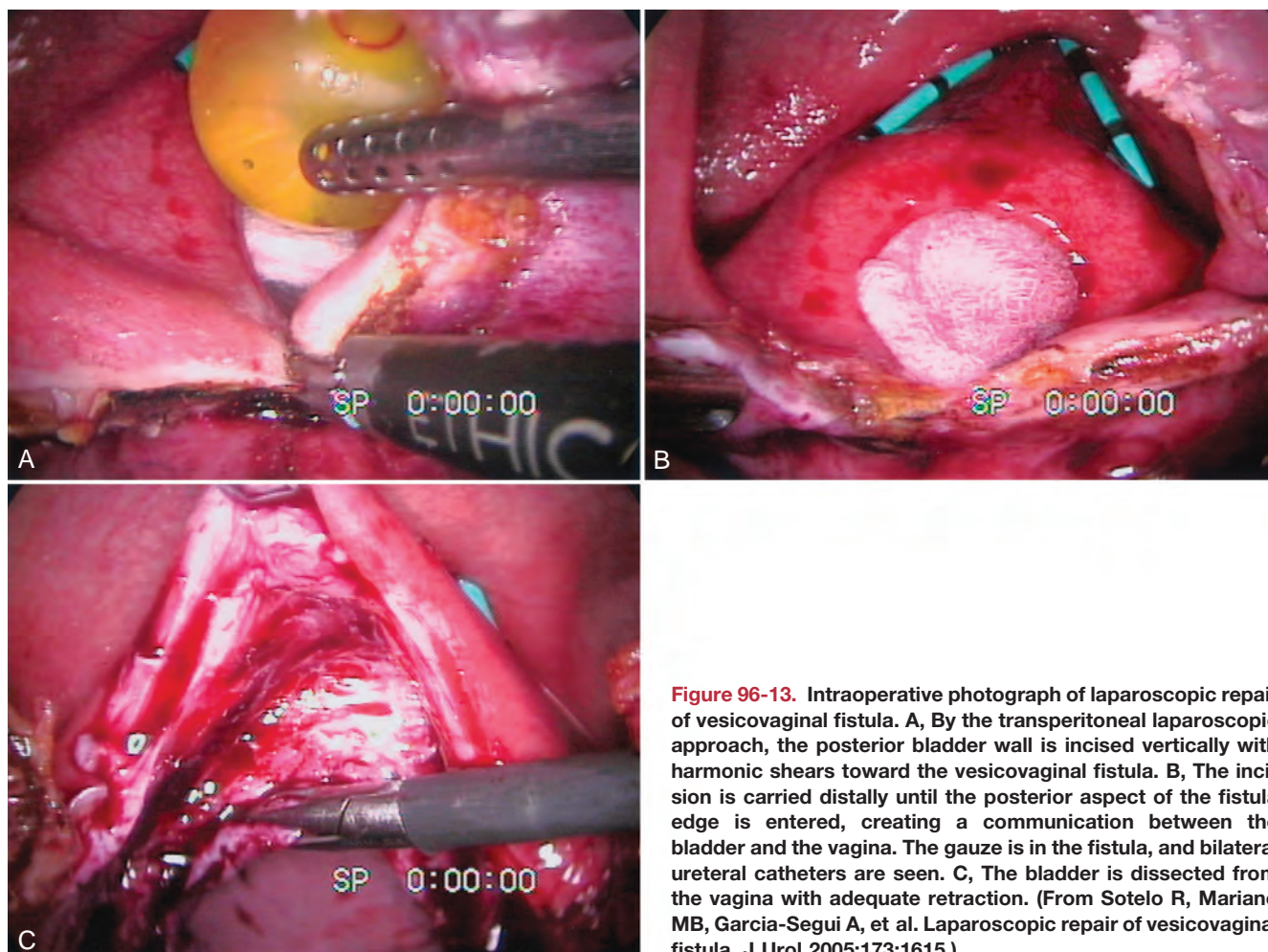


Figure 96-13. Intraoperative photograph of laparoscopic repair of vesicovaginal fistula. **A**, By the transperitoneal laparoscopic approach, the posterior bladder wall is incised vertically with harmonic shears toward the vesicovaginal fistula. **B**, The incision is carried distally until the posterior aspect of the fistula edge is entered, creating a communication between the bladder and the vagina. The gauze is in the fistula, and bilateral ureteral catheters are seen. **C**, The bladder is dissected from the vagina with adequate retraction. (From Sotelo R, Mariano MB, Garcia-Segui A, et al. Laparoscopic repair of vesicovaginal fistula. *J Urol* 2005;173:1615.)

Outcomes and Complications

Laparoscopic and robotic VVF repair were first performed in 1994 (Nezhat et al, 1994) and 2005 (Melamud et al, 2005), respectively. The reproducibility of laparoscopic VVF repair has been demonstrated with 49 patients reported in 12 published series (Sotelo et al, 2005; Gozen et al, 2009). In the largest reported series, Sotelo and colleagues (2005) reported success in 14 of 15 patients with a mean follow-up time of 26.2 months. Two complications occurred: one enterotomy and subsequent fistula and one epigastric arterial bleed requiring a return to the operating room. In a series of 11 patients with VVF and 1 patient with vesicouterine fistula, Das Mahapatra and Bhattacharyya (2007) had one failure with 12 to 36 months of follow-up. Chibber and colleagues (2005) reported on eight patients undergoing VVF or vesicouterine fistula repair with a 100% success rate at 3 to 40 months and no complications. Otsuka and colleagues (2008) successfully performed laparoscopic VVF on seven patients with no recurrences and two complications, including one urinary tract infection and an inferior limb compartment syndrome. Several authors also documented the feasibility and success of laparoscopic VVF for recurrent fistulae (Miklos et al, 1999; Nabi and Hemal, 2001; Otsuka et al, 2008).

Similarly, robotic-assisted laparoscopic VVF repair has been demonstrated as feasible in several series (Melamud et al, 2005; Sundaram et al, 2006; Schimpf et al, 2007; Sears et al, 2007; Hemal et al, 2008). With short-term follow-up, no failures and no complications have been reported to date. Successful laparoscopic and robotic-assisted laparoscopic ureterovaginal fistula repair also has

been reported (Ramalingam et al, 2005; Laungani et al, 2008). Similarly, laparoscopic and robotic rectourethral fistula repair and laparoscopic cervicovesical fistula repair have been reported (Hemal et al, 2001; Sotelo et al, 2007, 2008). Transvesical LESS VVF repair has been reported as well. The largest series in the literature included five patients (Abdel-Karim et al, 2011). In this series, VVF repair was performed using a TriPort (Olympus, Tokyo, Japan), bent instruments, and an EndoEYE camera (Olympus). An additional 5-mm port was added for triangulation and to aid with suturing. All repairs were done through an extravesical approach, but a cystostomy was made to excise the fistula tract, and an omental pedicle was interposed between the vagina and bladder at conclusion. The vaginal closure was performed with a one-layer closure using 3-0 polyglactin 910, and the bladder was closed in two layers using similar suture. Surgical times ranged from 170 to 240 minutes. All patients stayed in the hospital for 2 days. Mean follow-up was 8 months, and there have been no recurrences to date (Abdel-Karim et al, 2011).

Conclusions

Laparoscopic and robotic-assisted laparoscopic repair of VVF has been demonstrated to be reproducible and effective in small series. Larger series and randomized studies are necessary to determine what advantages may be conferred to patients compared with transabdominal and transvaginal approaches. In the future, LESS VVF repair may confer advantages of laparoscopy with optimal cosmetic outcomes.

KEY POINTS: VESICOVAGINAL AND URETEROVAGINAL FISTULA

- Laparoscopic and robotic-assisted laparoscopic repair of vesicovaginal fistula has been demonstrated to be reproducible and effective in small series.
- Larger series and randomized studies are necessary to determine what advantages may be conferred to patients compared with transabdominal and transvaginal approaches.
- In the future, LESS VVF repair may confer advantages of laparoscopy with optimal cosmetic outcomes.

URACHAL SURGERY AND PARTIAL CYSTECTOMY

The urachus is the embryologic remnant of the allantois and provides ligamentous support from the dome of the bladder to the umbilicus. Benign and malignant processes can affect the urachus. Benign conditions include urachal cysts and inflammatory and infectious processes. Urachal adenocarcinoma is rare and typically manifests as a tumor at the dome of the bladder, but it has been reported in the urachus alone without any bladder manifestations. Partial cystectomy can be performed for urachal adenocarcinoma and select cases of transitional cell carcinoma. Partial cystectomy is also indicated for other bladder pathology, including pheochromocytoma, lymphangioma, bladder sarcoma, and infiltrative endometriosis.

Evaluation and Surgical Indications

Most patients with urachal adenocarcinoma present with microscopic or gross hematuria. Occasionally, a mucinous adenocarcinoma may manifest with mucoid discharge or pyuria. Infected or inflamed urachal cysts may manifest with bloody discharge from the umbilicus or an indurated and fluctuant umbilicus. Diagnostic evaluation includes cystoscopy and CT. Cystoscopically, a lesion at the dome of the bladder is the hallmark finding. Imaging reveals a dome lesion in the bladder. Staging is critical to rule out lymphadenopathy or distant metastatic disease. For benign or infectious lesions of the urachus, CT may reveal a periumbilical cyst or abscess.

Treatment is indicated for symptomatic or infected urachal cysts. Although studies are limited, there is no clear evidence to suggest that urachal cysts will transform into urachal malignancies, and treatment should be limited to symptomatic patients. In the setting of inflammation or infection, patients should be treated with oral or intravenous antibiotics. Swab culture of the umbilicus and urine cultures should be sent before initiating antibiotics. Anti-inflammatory medications may be used for relief of symptoms. In the setting of a fluctuant umbilicus, local incision and drainage can be performed. If the infection resolves with complete relief of symptoms, no further intervention is required. In the setting of recurrent infected urachal cyst, surgical excision is indicated. The entire urachus should be excised including a small area on the dome of the bladder. If proper incision and drainage of any subcutaneous fluid has been performed, it is unnecessary to remove the umbilicus in the absence of malignancy.

Urachal carcinoma mandates a formal excision of the entire urachus, including a partial or radical cystectomy, depending on the extent of bladder involvement. Because these lesions often involve only the dome of the bladder, a partial cystectomy may be sufficient and has been demonstrated to provide equal oncologic efficacy (Herr et al, 2007). In this setting, the entire urachus is removed en bloc with the dome of the bladder inferiorly and the umbilicus superiorly. In addition, wide peritoneal wings are taken to ensure adequate margins. An extended pelvic lymphadenectomy is performed for adequate staging.

Patients with solitary transitional cell carcinomas at the bladder dome or within a bladder diverticulum are potential candidates for

partial cystectomy. Patients with multifocal disease are not candidates, mandating thorough cystoscopic evaluation with mapping bladder and prostatic urethral biopsies. Patients with bladder pheochromocytoma are managed medically to ensure medical optimization and avoidance of intraoperative hypertensive crises.

Technique***Patient Positioning and Port Site Placement***

Patients undergoing laparoscopic or robotic partial cystectomy are positioned in the dorsal lithotomy position. The patient is placed in the steep Trendelenburg position to allow the small bowel contents to migrate out of the pelvis for better visualization. Port configurations for laparoscopic and robotic partial cystectomy are similar to those used for diverticulectomy (see Fig. 96-3). When performing partial cystectomy for urachal carcinoma with removal of the umbilicus, the 12-mm camera port is inserted at least 5 cm above and 2 cm to the left of the umbilicus.

Cystoscopic Evaluation

When the patient is positioned and the ports are placed, the operating surgeon should begin with flexible or rigid cystoscopy. The robotic/laparoscopic intraperitoneal light is turned down so that the surgeon can see the illuminated bladder from inside the abdominal cavity; this allows the surgeon to delineate the involved area of the bladder from an intraperitoneal perspective and ensure adequate margins of resection (see Fig. 96-4). Electrocautery can be used to outline the area of resection on the outside of the bladder. When electrocautery is complete, the cystoscope is removed, and a Foley catheter is placed.

Surgical Technique

In contrast to conventional open surgery, when performing partial cystectomy for urachal cancer, the urachus is dissected out last. The laparoscopic/robotic surgeon should leave the bladder attached to the anterior abdominal wall during the initial dissection to maximize visualization and exposure. The bladder can be filled with approximately 200 to 300 mL of sterile water to define the anatomy better. Using an electrocautery, the bladder segment to be resected is scored, and dissection proceeds through all layers of the bladder with the exception of the bladder mucosa. Before dividing the bladder mucosa, the bladder should be emptied to avoid any spillage of bladder contents into the abdominal cavity. Before dividing the bladder mucosa, the entire urachus with wide peritoneal wings is dissected all the way to the level of the umbilicus. The urachus is divided at this level, and the umbilicus can be removed at the end of the case if necessary. When the entire urachus is dissected free, the bladder is opened, and the entire bladder lesion is excised circumferentially. The specimen is immediately placed in a 10- or 15-cm Endo Catch bag (Covidien). A frozen section analysis is performed on the bladder margin to ensure complete resection. If negative margins cannot be obtained, a radical cystoprostatectomy is performed. If margins are adequate, the bladder is closed in two layers using absorbable suture. A Foley catheter is left in place for 7 days and removed after negative cystography. An extended pelvic lymph node dissection is carried out as described subsequently. The specimen bag is retrieved at the time of umbilical resection through the resultant defect. All port sites are closed, and a pelvic drain is left in place for 24 hours. For partial cystectomy for transitional cell carcinoma or nonurachal pathology, the urachus can be taken down early in the dissection. After identification of the bladder pathology, a laparoscopic/robotic partial cystectomy can be performed via a combined extravesical and intravesical approach. In this technique, the bladder is opened anterior/superior to the pathology, allowing for an adequate margin, and the lateral and inferior borders are addressed for a circumferential dissection via an intravesical perspective (Fig. 96-14).

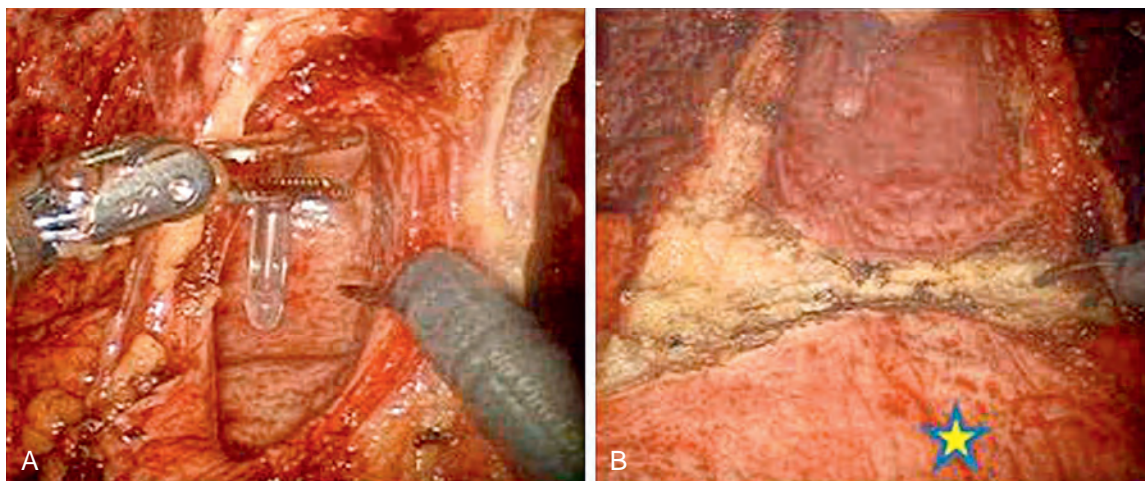


Figure 96-14. Robotic partial cystectomy for transitional cell carcinoma of the bladder. This muscle-invasive bladder tumor was addressed via a combined extravesical and intravesical approach. A, After illumination of the prior resection site, the bladder is entered superior to the tumor site. B, Once the bladder is entered, the dissection is completed by an intravesical approach circumferentially around the prior resection scar (star).

Outcomes and Complications

Multiple series have demonstrated the feasibility of laparoscopic and robotic partial cystectomy for a variety of bladder pathologies, including pheochromocytoma (Nayyar et al, 2010; Pandey et al, 2010; Kang et al, 2011), lymphangioma (Seyam et al, 2012), and endometriosis (Sener et al, 2006; Chammas et al, 2008). In several series on urachal and transitional cell carcinoma, hospital stay ranged from 2.5 to 4 days (Wadhwa et al, 2006; Colombo et al, 2008; Park et al, 2008); however, in our experience, patients can often be discharged on postoperative day 1 with the Foley catheter in place. With no recurrences at a mean follow-up of up to 28.5 months, preliminary data suggest these techniques to be oncologically sound with minimal complications reported (Wadhwa et al, 2006; Colombo et al, 2008; Park et al, 2008).

Conclusions

Laparoscopic/robotic partial cystectomy is technically feasible with limited morbidity. Available data are limited by short-term oncologic follow-up. With the growing popularity of robotic surgery, reported cohorts in the literature will likely grow, and confidence in the procedure will increase.

KEY POINTS: PARTIAL CYSTECTOMY

- Laparoscopic/robotic partial cystectomy is technically feasible.
- Morbidity is limited.
- The urologic literature is scant in reported series, and oncologic follow-up is short.
- This remains an untested technology in the treatment of urachal or transitional cell carcinoma.
- With the growing popularity of robotic surgery, reported cohorts in the literature will likely grow and confidence in the procedure will increase.

ROBOTIC RADICAL CYSTECTOMY

Given the significant complication rate associated with radical cystectomy, minimally invasive techniques have been employed in an attempt to reduce the morbidity of what has traditionally been one of the most invasive of urologic operations. Laparoscopic radical cystectomy (LRC) for the treatment of bladder cancer has proven feasible and reproducible. More recently, robotic-assisted radical cystectomy (RARC) has grown in popularity and has largely supplanted the laparoscopic approach. Ongoing research is helping to elucidate the degree of benefit offered by minimally invasive radical cystectomy and to demonstrate long-term oncologic outcomes.

Technique

Surgical Positioning and Port Placement

Operative setup is dictated in many cases by the specific characteristics of the operating room and the number of available assistants. We prefer to use the robotic fourth arm, positioned on the patient's right side two fingerbreadths above the right anterior superior iliac spine. The single bedside assistant is positioned on the patient's left. With this configuration, when the fourth arm grasper is employed, it can be used opposite the grasper that is typically in the surgeon's left hand. The result is two-handed grasping and manipulation. Operative setup for RARC when two bedside assistants are used is depicted in Figure 96-15. At least three monitors are needed in this setting. The scrub nurse should be positioned on the side of the assistant using the 15-mm port to facilitate exchange of clip applicators, sutures, and Endo Catch retrieval bags. The console surgeon must have easy access to the operative table to scrub into the procedure at a moment's notice.

The patient is placed in the dorsal lithotomy position using standard operative stirrups (Fig. 96-16). With the table flat, plastic sleds are used to tuck the patient's arms. All pressure points are protected using standard egg crate foam padding. The patient is secured to the operating table using a cross-shoulder harness made by four strips of egg crate foam padding. Each strip is 6 inches × 24 inches, and two strips are used on each side of the patient creating an "X" configuration across the patient's chest. The pads are secured to the operating table using cloth tape. Care must be taken not to

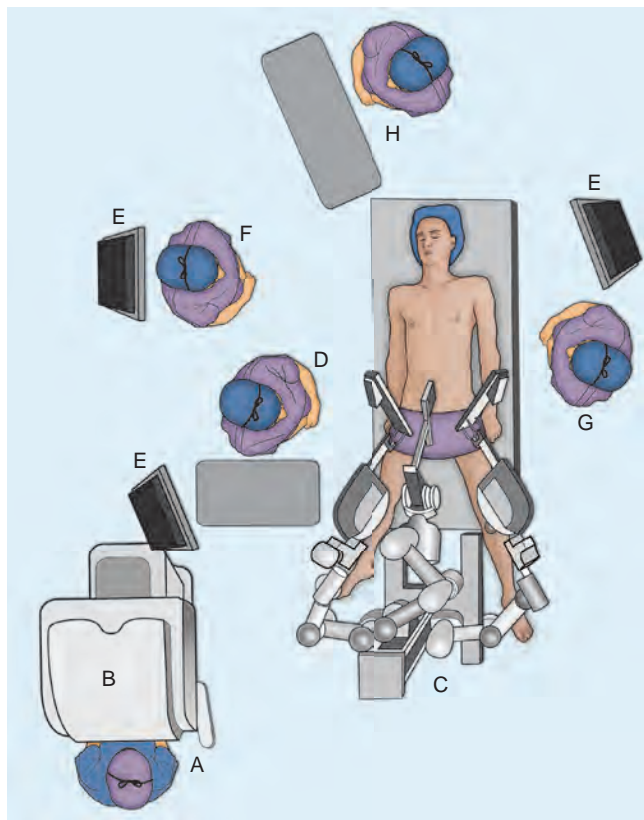


Figure 96-15. Operating room setup for robotic cystoprostatectomy. A, Surgeon; B, console; C, da Vinci system; D, scrub nurse; E and J, high-definition monitors; F, right assistant; G, left assistant; H, anesthesia. If using a robotic fourth arm, we prefer the solitary bedside assistant to be positioned on the patient's left, with a grasper employed via the fourth robotic arm positioned two fingerbreadths above the right anterior superior iliac spine. When the fourth arm grasper is employed, it can be used opposite the grasper typically in the surgeon's left hand to aim in two-handed grasping and manipulation.

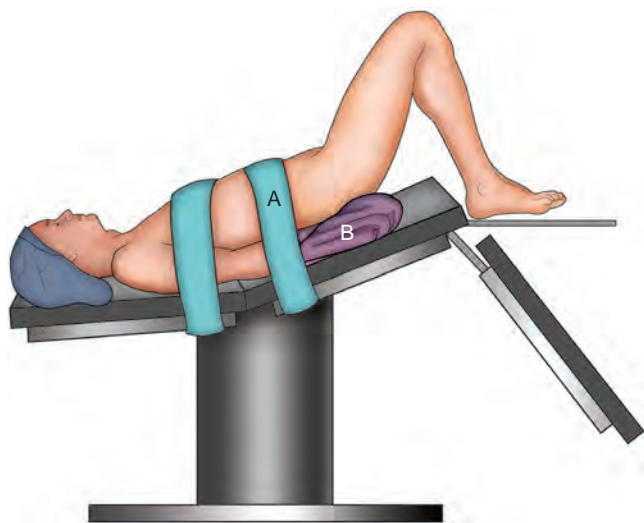


Figure 96-16. Patient positioning. The patient is placed in the dorsal lithotomy position using standard operative stirrups. All pressure points are protected using standard egg crate foam padding. A, Cross-shoulder harness made by four strips of egg crate foam padding. Each strip is 6 × 24 inches, and two strips are used on each side of the patient creating an "X" configuration across the patient's chest. The pads are secured to the operating table using cloth tape. B, Plastic sleds are used to tuck the patient's arms.

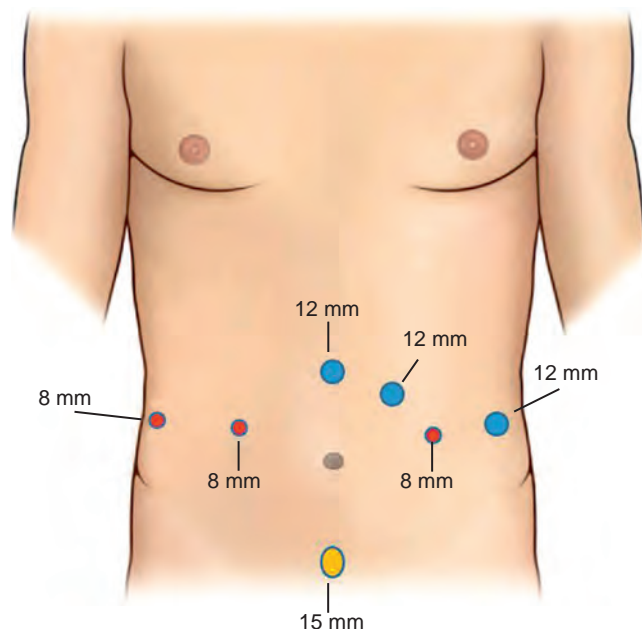


Figure 96-17. Port site placement for robotic cystoprostatectomy with intracorporeal diversion. After insufflations, a 10- to 12-mm, bladed disposable trocar is placed superior to the umbilicus; the cephalad placement is important to reach the aortic bifurcation during extended lymphadenectomy and for intracorporeal bowel work. All remaining trocars are placed under direct vision. Left and right 8-mm robotic ports are placed 10 cm lateral to and 4 cm inferior to the camera port. A 12-mm trocar is placed for the bedside assistant port two fingerbreadths above the left anterior superior iliac spine; the fourth robotic arm is used with an 8-mm robotic trocar two fingerbreadths above the right anterior superior iliac spine. An additional 12-mm assistant trocar is placed midway between the camera port 8-mm robotic port on the ipsilateral side as the primary bedside assistant; this accommodates either a 10-mm LigaSure or a GIA stapling device to aid in transection of the bladder pedicles. Lastly, a 15-mm suprapubic trocar is used when performing intracorporeal urinary diversion, which aids in placement of the Endo GIA for side-to-side ileal anastomosis.

secure the lower portion of the pads below the costal margin because this may interfere with subsequent lateral port placement. Once the patient is secured to the table, the leg attachment is lowered, and the patient is placed in 30-degree steep Trendelenburg position. The anesthesia team places an orogastric tube to low wall suction for the duration of the case, and foam padding is placed over the patient's face to prevent injury from the camera, particularly when the 30-degree down lens is being used. A Foley catheter is placed on the operative field.

When performing intracorporeal urinary diversion, a 6- to 8-cm Pfannenstiel incision can be marked; a midline laparotomy incision is marked for specimen extraction and extracorporeal bowel work if preferred. For extended lymphadenectomy and the ability to visualize the aortic bifurcation adequately as well as maximal cranial dissection of the ureter, the camera trocar is best positioned approximately 25 cm from the pubic symphysis, or approximately 5 cm cephalad to the umbilicus. Initial access and insufflation of the abdominal cavity is performed using a Veress needle to 15 mm Hg. In obese patients, communication with the anesthesia team is imperative because pneumoperitoneum can result in unacceptably high inspiratory pressure necessitating a lower abdominal insufflation pressure. A six-trocar approach is employed (with an additional seventh trocar when performing intracorporeal diversion), as seen in [Figure 96-17](#).

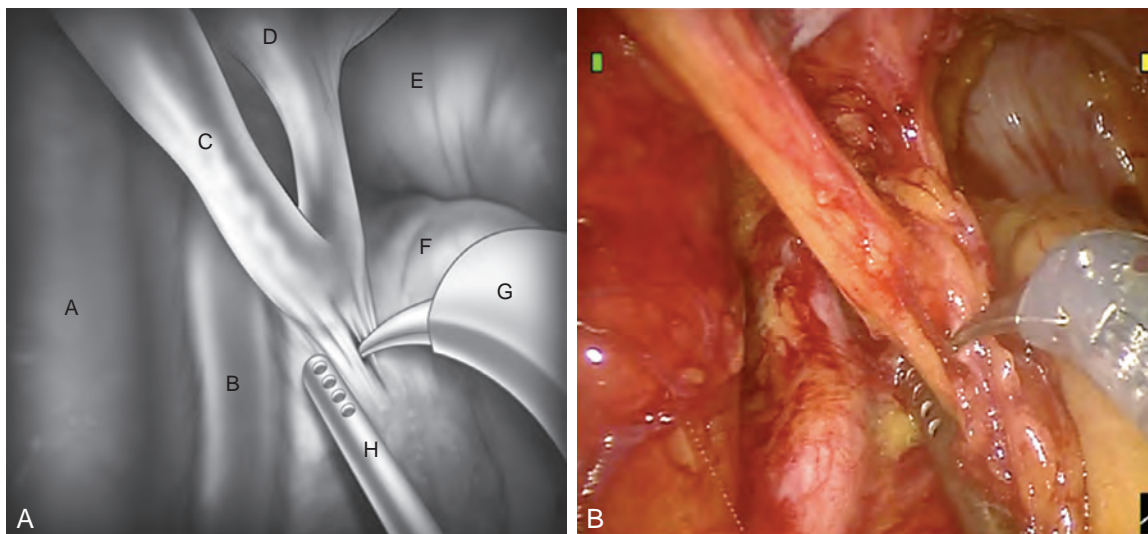


Figure 96-18. A and B, Dissection of the ureter. Identification of the ureter, shown here on the patient's left side, begins with retraction of the sigmoid colon by the right bedside assistant (using a MicroFrance grasper) or robotic fourth arm (using a ProGrasp; Intuitive Surgical, Sunnyvale, CA). *A*, Pelvic sidewall and external iliac artery; *B*, hypogastric artery; *C*, ureter, retracted anteriorly by left robotic arm; *D*, bladder and ureteral hiatus; *E*, rectum; *F*, sigmoid colon; *G*, right robotic arm; *H*, suction-irrigator. The surgeon incises the posterior peritoneum overlying the external iliac artery, where the ureter is most easily identified. The ureter should not be directly grasped by the surgeon or the assistants, and effective ureteral retraction can be accomplished by placing the left robotic grasper beneath the ureter. The ureter is dissected proximally as high as possible to the level of the upper common iliac artery. Distal dissection is performed to the level of the ureteral hiatus.

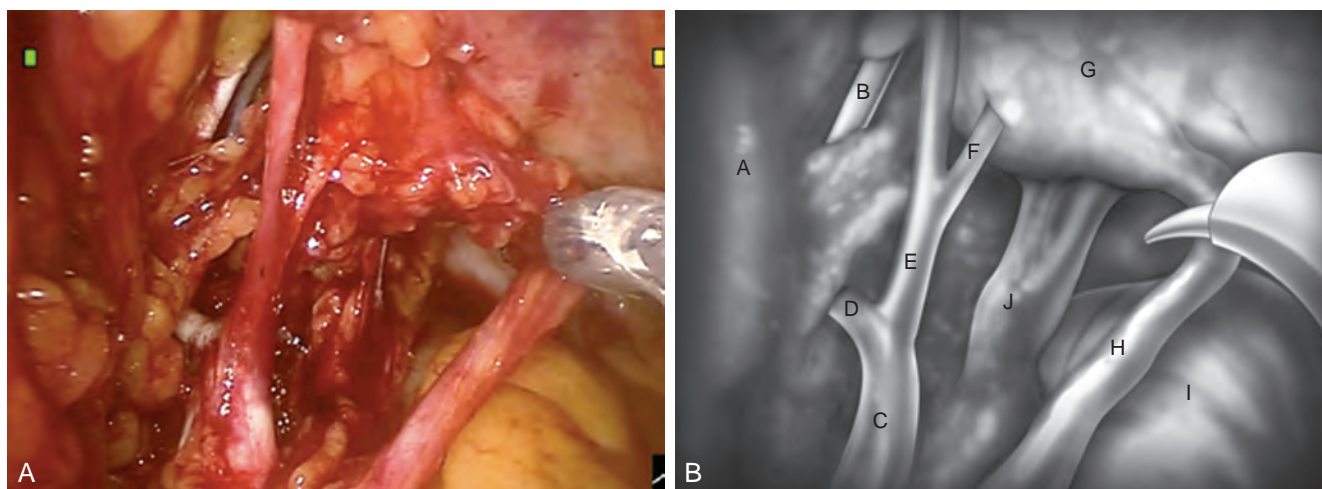


Figure 96-19. A and B, Development of the anterior pedicle, shown here on the patient's left side, begins with identifying the avascular plane located between the pelvic sidewall and the bladder. *A*, Pelvic side wall; *B*, obturator nerve; *C*, internal iliac (hypogastric) artery; *D*, obturator artery; *E*, superior vesical artery; *F*, branch off of superior vesical artery; *G*, bladder; *H*, ureter; *I*, rectum; *J*, posterior pedicle to bladder.

Ureteral Identification and Transection

The technique for robotic cystectomy is described further on; laparoscopic cystectomy follows essentially the same procedure with differing instrumentation. Dissection is initiated by incising the avascular white line of Toldt on the patient's left; this allows the descending colon to be reflected medially exposing the retroperitoneal space beneath. This incision should be carried out as cranially as possible to allow for maximal left ureteral mobilization. The

ureter is identified and dissected proximally and distally. An identical dissection is performed on the right side (Fig. 96-18).

Division of the Anterior Pedicle

When each ureter is dissected as caudally as possible, the anterior pedicle to the bladder, including the superior vesical artery, is identified (Fig. 96-19). Identification is facilitated by developing the avascular plane between the external iliac vessels and the lateral aspect

of the bladder. At the most posterior aspect of this plane is the superior vesical artery. This vessel can be clipped and divided. In a non-nerve-sparing operation, the remaining anterior pedicle is divided using a 10-mm LigaSure device. In a nerve-sparing operation, surgical clips are employed to avoid the use of electrocautery near the neurovascular bundles. When the anterior pedicle is divided, this allows for identification of the ureteral hiatus into the bladder. At this point, each ureter is clipped and divided. The proximal clip has a long suture attached to it for identification at a later time in the case. At this point, both vasa deferentia can be divided as well.

Development of the Posterior Plane

After both ureters are divided, attention is paid to separating the bladder off of the rectum (Fig. 96-20). From left to right, the posterior peritoneal reflection between the bladder and the rectum is divided. The surgeon should be certain to get beneath the posterior leaflet of Denonvilliers fascia to ensure an adequate posterior margin. This plan of dissection is carried out as distally as possible, preferably to the level of the prostatic apex. This maneuver allows for identification of the posterior pedicles of the bladder. At this point, the bladder has not yet been released from its attachments on the anterior abdominal wall.

Division of the Posterior Bladder and Prostatic Pedicles

Using a 10-mm LigaSure device or reticulating laparoscopic stapler with 2.5-mm vascular staple loads, the bedside assistant divides the posterior pedicles of the bladder bilaterally (Fig. 96-21). This is carried out as distally as possible. In a nerve-sparing operation, clips and staples are used instead of thermal energy. Once the bladder pedicles are completely divided, the endopelvic fascia is divided on each side. This allows for identification of the prostatic pedicles, which are divided in a similar fashion (Fig. 96-22). This division should proceed as caudally as possible because the posterior plane will be difficult to visualize once the bladder is "dropped" posteriorly.

Dropping of the Bladder

When the pedicles are completely divided, the bladder can be released from its anterior abdominal wall attachments (Fig. 96-23). The urachus is first divided just below the level of the umbilicus.

Wide peritoneal wings are taken downward, and the median umbilical ligaments are divided. The space of Retzius is completely dissected. Any remaining endopelvic fascia is opened at this point. If a nonorthotopic urinary diversion is going to be performed, the puboprosthetic ligaments are divided. In an orthotopic urinary diversion, the puboprosthetic ligaments are preserved.

Division of Dorsal Vein Complex

A 0-0 polyglactin 910 suture on a CT-1 needle is passed underneath the dorsal vein complex, distal to the apex of the prostate (Fig. 96-24). Because urothelial cell carcinoma can involve the prostatic urethra, prostate-sparing cystectomy is not recommended, and the entire prostate is removed en bloc with the bladder. Once the DVC is secured, it is divided; this exposes the underlying urethra. The urethra is divided distal to the prostatic apex. The Foley catheter is lifted upward, and a Hem-o-lok clip is placed over it to prevent any urinary spillage into the operative field. The catheter is divided distal to the clip, leaving the balloon inflated acting as a ball valve to prevent spillage, and the assistant pulls the cut catheter in a cranial direction. The posterior urethra is divided, and any remaining attachments are released. The bladder, prostate, and seminal vesicles are placed into a 15-cm Endo Catch bag. At this point, an extended pelvic lymphadenectomy is performed.

Extended Pelvic Lymph Node Dissection

Pelvic lymphadenectomy is an essential component of radical cystectomy performed for malignancy (Fig. 96-25). Lymphadenectomy is essential for accurate staging, allowing the practitioner to counsel patients regarding prognosis and to make decisions regarding adjuvant treatment. The extent of lymphadenectomy has been correlated with improved oncologic outcomes, even in the setting of limited lymph node metastases. However, even when radical cystectomy is performed via an open approach, pelvic lymph node dissection is often limited or not performed at all. Over the last decade, there has been extensive literature documenting that an extended lymph node dissection can be performed via laparoscopic/robotic surgery. Several large series, including multicenter international consortia, have demonstrated high lymph node yields that demonstrate feasibility and reproducibility. With sufficient experience, an extended lymph node dissection can be performed robotically in approximately 45 to 60 minutes of operative time.

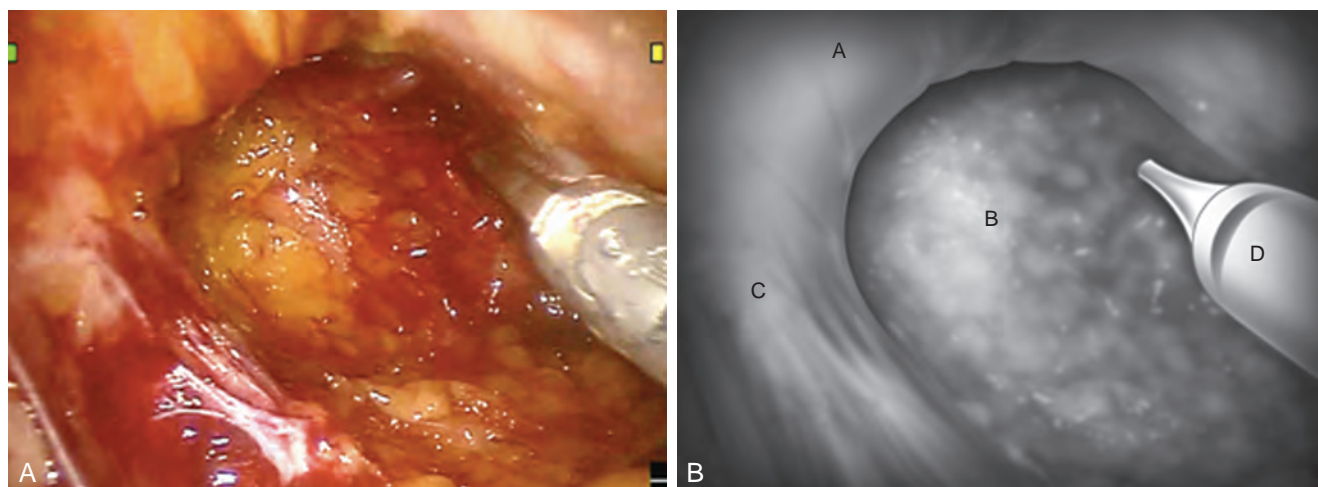


Figure 96-20. A and B, Once the anterior pedicles are divided, the posterior peritoneal reflection is incised separating the bladder and rectum in the midline. A, Bladder; B, rectum; C, left posterior pedicle; D, right robotic arm with monopolar scissors. The left assistant lifts the bladder anteriorly, and the right assistant retracts the posterior peritoneal edge. Using a combination of broad, sweeping motions and electrocautery with the monopolar scissors, one can develop the posterior plane between the bladder and the rectum beneath the posterior leaflet of Denonvilliers fascia. This dissection is carried as distally as possible and well beyond the vasa deferentia and seminal vesicles toward the prostatic apex.

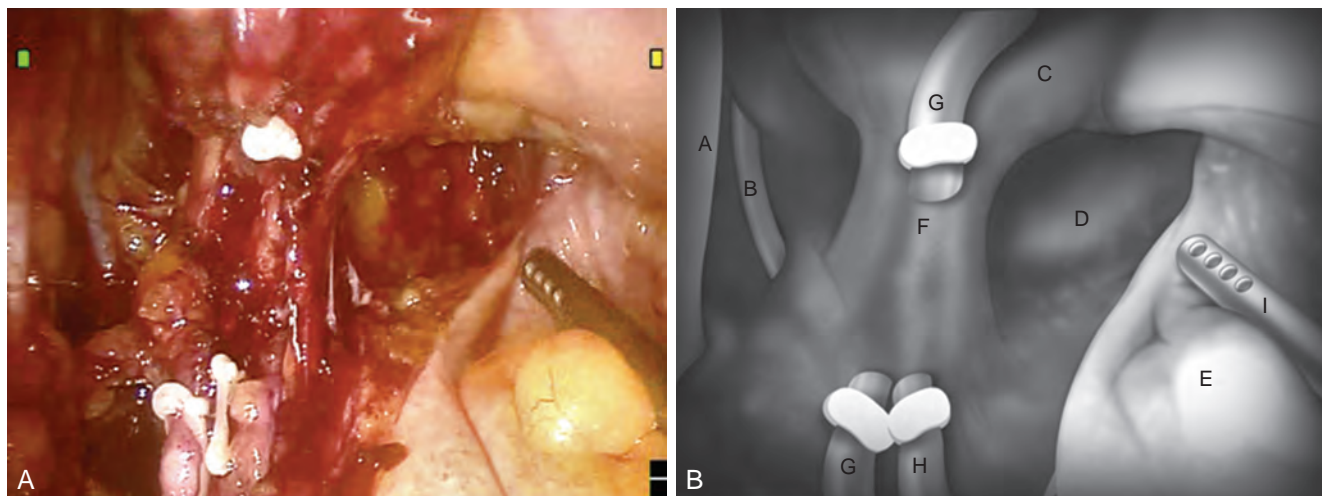


Figure 96-21. A and B, Development of the plane between the bladder and the rectum reveals the posterior pedicle, shown here on the patient's left side. *A*, External iliac vein; *B*, obturator vein; *C*, bladder; *D*, rectum; *E*, sigmoid colon; *F*, posterior pedicle; *G*, superior vesical artery, cut; *H*, branch of superior vesical artery, cut; *I*, suction-irrigator. The posterior pedicle is located just distal to the previously divided anterior pedicle. Exposure of the left posterior pedicle is facilitated by the bedside assistant (or fourth robotic arm) providing superior and medial traction on the bladder, while the remaining assistant provides posterior retraction of the rectum. Division of the posterior pedicle is complete when the endopelvic fascia is encountered.

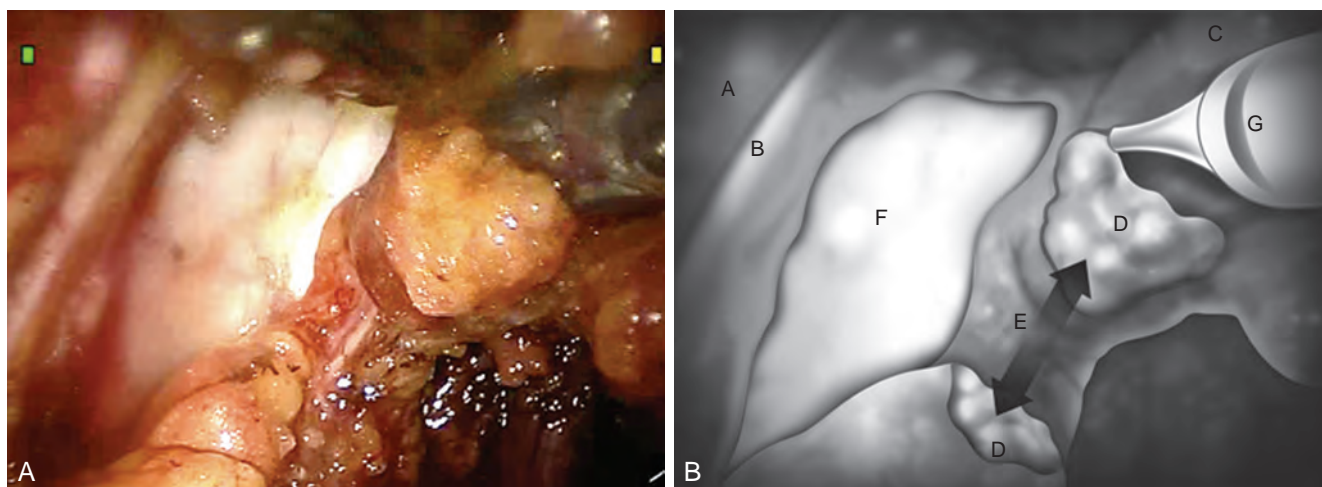


Figure 96-22. A and B, Adipose tissue overlying the endopelvic fascia, shown here on the patient's left side, is removed by the robotic instruments using sweeping motions. *A*, Pubic bone; *B*, pectineal line; *C*, bladder; *D*, posterior pedicle, cut; *E*, beginning of prostate pedicle; *F*, endopelvic fascia; *G*, right robotic arm. The endopelvic fascia is sharply incised using the robotic scissors. This exposes the prostate pedicles, which are secured and divided using the LigaSure device in a non-nerve-sparing operation or Hem-o-lok clips in a nerve-sparing procedure. To avoid injury to the rectum, the right assistant should retract the rectum posteriorly using either the suction or the grasper. It is important to carry this dissection as distally as possible because once the bladder is released from its anterior attachments, visualization of the posterior prostatic apex is quite limited.

We begin the dissection with a “split and roll” technique, beginning at the level of the external iliac artery. All lymph nodes are removed circumferentially around the artery. Dissection proceeds distally to Cooper ligament, with the lateral border being the genitofemoral nerve. The external iliac vein is identified, and all nodes are removed circumferentially around the vein, below the vein with the pelvic sidewall as the lateral border, and to the obturator nerve. All nodes around and below the obturator nerve and vessels are retrieved. The dissection continues proximally up

the common iliac artery, to the bifurcation of the aorta, and at least to the level of the inferior mesenteric artery. The hypogastric artery is identified and skeletonized. Presacral nodes are removed. The dissection continues to the contralateral side, where an equivalent dissection is performed, removing all lymph nodes from above the bifurcation down to the common, external, and internal iliac vessels distally to Cooper ligament. Lymph node packets are placed separately in entrapment bags to maximize lymph node counts.

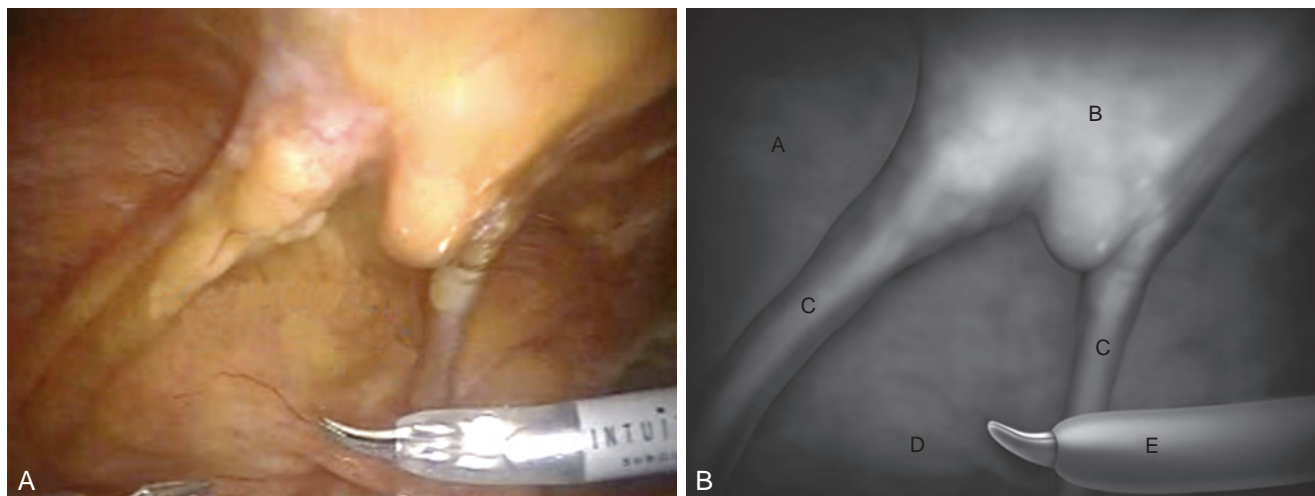


Figure 96-23. A and B, Dropping the bladder from the anterior abdominal wall. Oncologic principles dictate removal of the urachus with the bladder en bloc with wide peritoneal wings. A, Anterior abdominal wall; B, urachus; C, medial umbilical ligaments; D, bladder; E, right robotic arm. The importance of placing the camera port several centimeters superior to the umbilicus at the beginning of the procedure is revealed. If the camera port is not placed superiorly enough, complete excision of the urachus is compromised as well as the proximal extent of the subsequent pelvic lymphadenectomy. The medial umbilical ligament on each side is grasped by the contralateral assistant and/or robotic fourth arm. Providing medial retraction, the monopolar scissors are used to incise the anterior peritoneum. The peritoneum is incised widely in an inferior direction until the pubic bone is exposed.

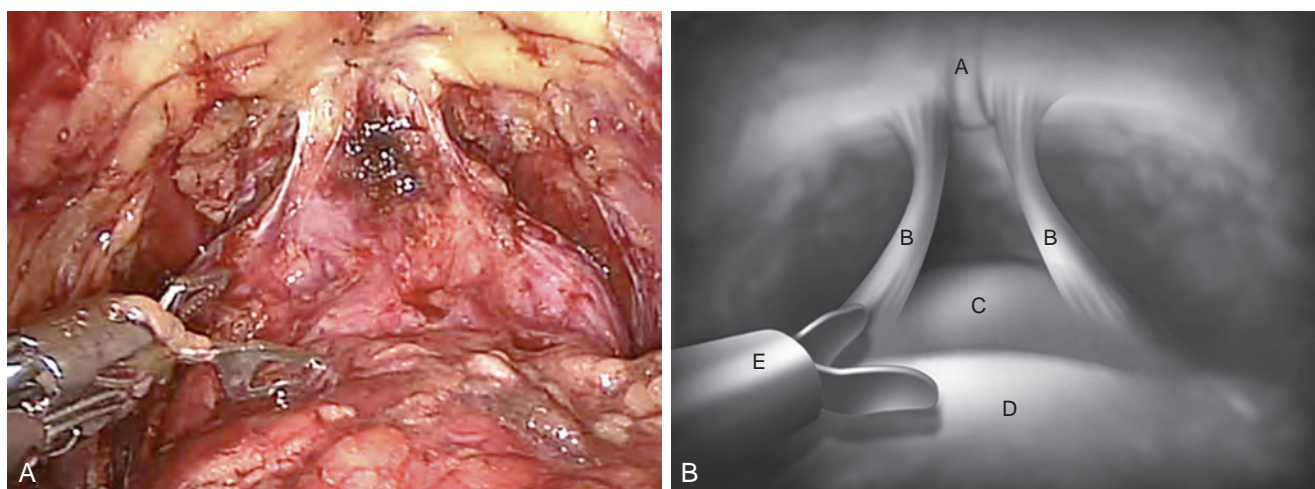


Figure 96-24. A and B, Transection of the dorsal vein complex. A, Pubic bone; B, puboprostic ligaments; C, prostate; D, bladder; E, left robotic arm. The puboprostic ligaments are preserved for orthotopic urinary diversion. For nonorthotopic diversion, the urethra is not preserved, and the puboprostic ligaments are divided for optimal distal dissection. A 0-0 polyglactin 910 suture is placed to secure the dorsal vein complex. In a non-nerve-sparing cystoprostatectomy, the dorsal vein complex can be divided with thermal modalities; in nerve-sparing procedures, electrocautery is avoided. The urethra is also divided without electrocautery for patients undergoing orthotopic neobladder construction. With superior traction on the bladder, the anterior half of the urethra is divided, and the Foley catheter is pulled into the patient. The catheter is secured with a large Hem-o-lok clip and divided, preventing possible tumor spillage. The left assistant provides superior retraction on the prostate and bladder by grasping the cut end of the Foley catheter. Remaining apical attachments are divided, and the bladder, prostate, and seminal vesicles are placed in a 15-mm Endo Catch bag (Covidien, Mansfield, MA).

Transposition of Left Ureter to Right Side

A separate plane is developed just anterior to the great vessels underneath the sigmoid colon (Figs. 96-26 and 96-27). A grasping instrument is placed from the right side under the sigmoid

mesentery to the left side. The suture on the end of the left ureter is grasped, and the left ureter is brought under the sigmoid colon to the right side. At this point, the extirpative portion of the operation is complete, and the surgeon proceeds to intracorporeal or extracorporeal urinary diversion and specimen extraction.

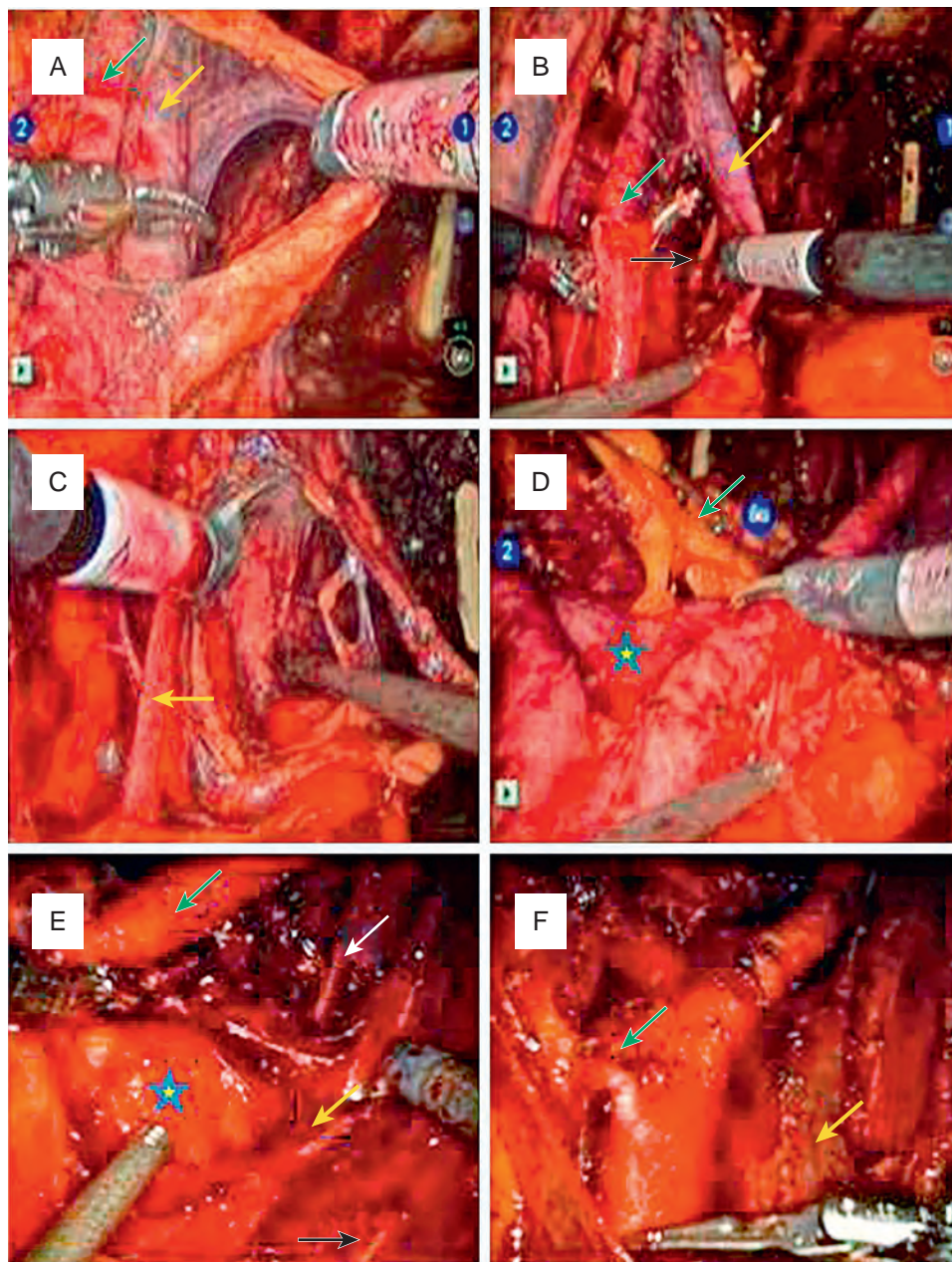


Figure 96-25. Extended lymphadenectomy. Borders of the dissection include inferior mesenteric artery/aortic bifurcation proximally, Cooper ligament inferiorly, genitofemoral nerve laterally, and sacral promontory medially. All presacral, hypogastric, external iliac, obturator, and common iliac lymph node packets are removed en bloc. A, After split and roll over the left common and external iliac artery (green arrow) and vein (yellow arrow), the lymph node packet is medialized and clipped distally at the level of Cooper ligament. B, All lymph node tissue is excised circumferentially around the common and external iliac arterial (green arrow) and venous (yellow arrow) systems. C, Nodes above and below the obturator nerve (yellow arrow) are removed. D, The presacral node packet (green arrow) is removed, and the sacrum is visualized (star). E, The right common iliac artery is medialized, with all nodes between the artery (green arrow) and vein (yellow arrow) removed, with the lateral border visualized (genitofemoral nerve) (black arrow). The sacrum is indicated by the star. F, Dissection is completed above the inferior mesenteric artery (green arrow).

Urinary Diversion. Urinary diversion is performed via an extracorporeal or a completely intracorporeal approach. Conventional options for diversion, including ileal conduit, continent cutaneous diversion, or orthotopic neobladder, can be performed using either approach, as described in a separate chapter. For extracorporeal diversion, a midline infraumbilical vertical incision is typically used, through which the specimens are extracted. When performing

intracorporeal diversion, a vertical or horizontal extraction incision (6 to 8 cm) is used (Fig. 96-28).

Female Robotic Cystectomy

Radical cystectomy in a female patient can be performed using laparoscopic and robotic approaches. Typically, this procedure involves

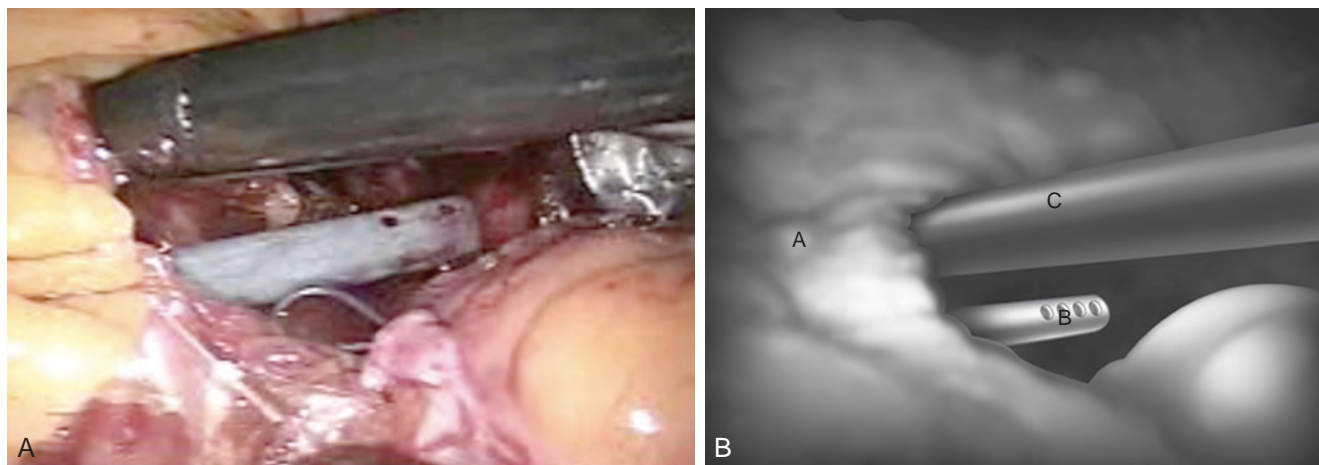


Figure 96-26. A and B, Transposition of the left ureter under the sigmoid colon. The left assistant places the suction-irrigator device through the left 5-mm port. With the right assistant retracting the sigmoid colon with a grasper, the surgeon defines a plane posterior to the sigmoid mesentery and superior to the aortic bifurcation just anterior to the great vessels. The suction device is passed from left to right along this plane. Further dissection is often necessary on the right side of the sigmoid mesentery to identify the tip of the suction device. A, Sigmoid colon; B, suction-irrigator, passed posterior to the sigmoid mesentery from the patient's left to right side; C, right robotic arm, elevating sigmoid colon. The right assistant passes a laparoscopic Maryland dissector through the 5-mm to 15-mm port, and the tips of the Maryland dissector are placed firmly into the suction device. The right assistant directs the instrument toward the patient's left side such that the tips of the Maryland dissector can be found posterior to the sigmoid mesentery on the patient's left side. The 0-0 tie attached to the left ureter is placed in the Maryland grasper, and the left ureter is brought behind the sigmoid mesentery to the patient's right side.

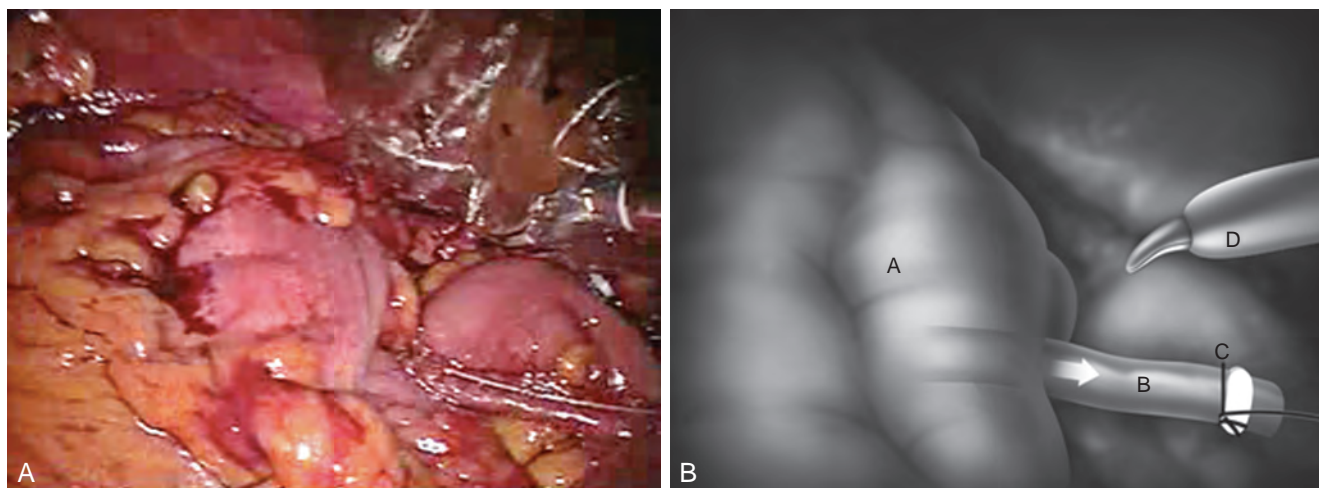


Figure 96-27. A and B, Completed transposition of the left ureter. A, Sigmoid colon; B, left ureter, passed posterior to the sigmoid mesentery and delivered to the patient's right side; C, Hem-o-lok clip with 0-Vicryl tie attached to the cut end of the left ureter; D, right robotic arm.

concomitant hysterectomy, bilateral salpingo-oophorectomy, and resection of the anterior vaginal wall. In appropriately selected patients, the gynecologic organs and vaginal wall can be spared.

Technique. After ureteral mobilization, the superior and inferior vesical arteries and the uterine and ovarian vessels are ligated. The round ligaments are transected, and the uterus, fallopian tubes, and ovaries are sutured to the obliterated umbilical ligaments to facilitate visualization of the posterior dissection. The peritoneum is incised in the pouch of Douglas. With the aid of a sponge stick in the vagina, the fundus is opened at the posterior fornix, just below

the level of the insertion of the cervix. The dissection proceeds distally to the level of the bladder neck. After identification of the bladder neck, the specimen is transected and excised approximately 0.5 cm distal to the bladder neck. The vaginal wall is closed either longitudinally or transversely with absorbable suture. In appropriately selected patients, the gynecologic organs and anterior vaginal wall can be spared (Fig. 96-29). After ureteral mobilization and transection, the peritoneum is incised in the uterovesical pouch. Dissection begins in the plane between the posterior bladder wall and anterior vaginal wall and continues distally to the level of the

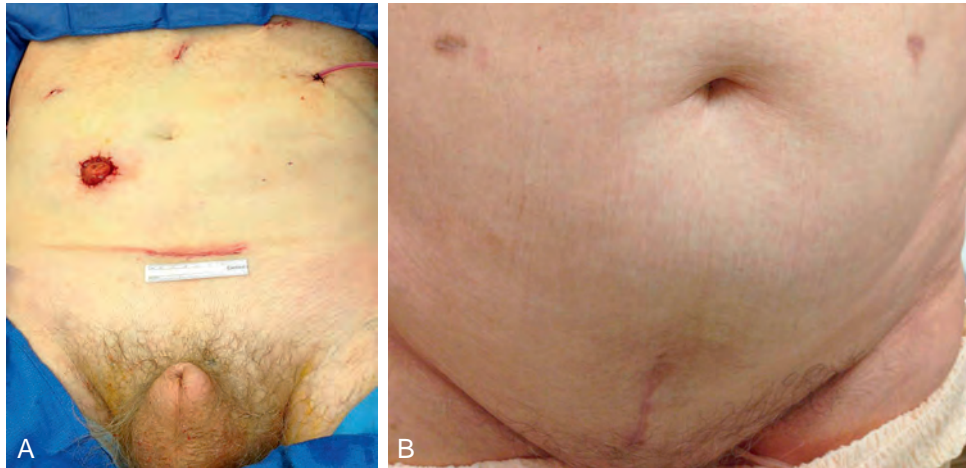


Figure 96-28. Cosmetic results after robotic cystectomy and diversion. A, Robotic cystectomy with intracorporeal ileal conduit and 8-cm Pfannenstiel extraction incision. B, Robotic cystectomy with intracorporeal neobladder formation using 6-cm vertical extraction incision.

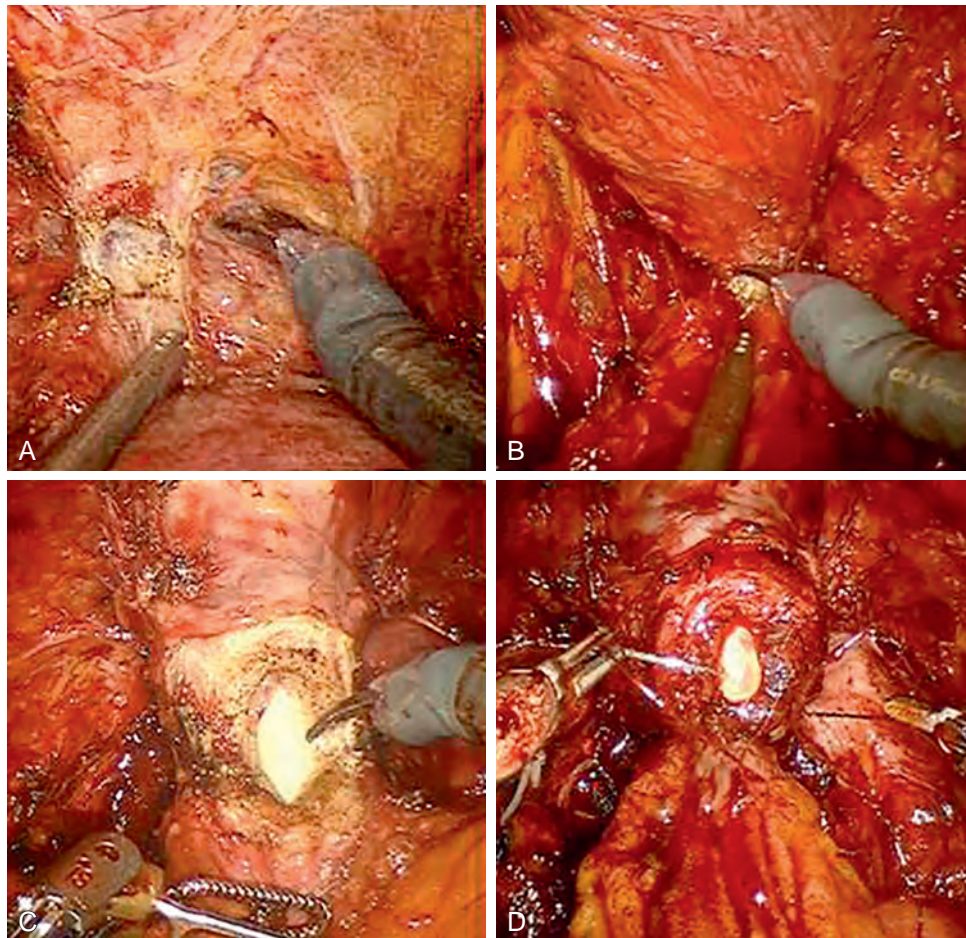


Figure 96-29. Organ-sparing female robotic radical cystectomy. The peritoneum is incised in the uterovesical pouch (A). Dissection begins in the plane between the posterior bladder wall and anterior vaginal wall and continues distally to the level of the bladder neck (B). The bladder neck is dissected circumferentially and transected (C). The urethral anastomosis is completed in this example of intracorporeal orthotopic neobladder construction (D).

bladder neck. The bladder neck is dissected circumferentially and transected, and the specimen is immediately placed in an entrapment sac (Table 96-1).

Outcomes and Complications

Robotic radical cystectomy is a challenging procedure that requires significant robotic surgical skills. The learning curve has been described by several groups, including the International Robotic Cystectomy Consortium (IRCC). The IRCC analysis suggested that after approximately 20 patients, it is possible to reach an acceptable operative time, and 30 cases were required to reach lymph node yields greater than 20 (Hayn et al, 2010a, 2010b). The same group explored the impact of prior robotic prostatectomy experience on RARC outcomes, demonstrating that previous prostatectomy case volume may improve operative time, blood loss, and lymph node yield at RARC; however, it did not appear to affect positive surgical margin rates.

Perioperative outcomes after LRC and RARC have been well characterized and compared with open surgical techniques. Retrospective comparative studies demonstrated that RARC is associated with reduced estimated blood loss and transfusion rates and shorter hospitalization, but longer operative times compared with open surgery (Wang et al, 2008; Kader et al, 2013). Randomized prospective trials demonstrated that RARC was associated with decreased estimated blood loss compared with open cystectomy and “trended” toward a decreased rate of excessive length of stay and fewer transfusions, with no difference in operative times (Parekh et al, 2013). In another randomized prospective trial, RARC was associated with reduced estimated blood loss, time to flatus and bowel movement, and in-hospital anesthesia, but longer operative times compared with open surgery (Nix et al, 2010).

Data regarding oncologic outcomes associated with LRC and RARC continue to accumulate. In an analysis of 513 patients, the IRCC demonstrated an overall positive margin rate of 6.8%, ranging from 1.5% for pT2 or less, to 8.8% for pT3, and to 39% for pT4 disease (Hellenthal et al, 2010). When comparing RARC with open cystectomy, retrospective series demonstrated no differences in pathologic outcomes such as lymph node yields or positive margin rates (Kader et al, 2013). Similarly, small randomized prospective trials demonstrated no differences in positive surgical margin rates or lymph node yields (Nix et al, 2010; Parekh et al, 2013). Additional studies have documented the feasibility of robotic extended node dissection and its equivalency to open surgery (Abaza et al, 2012; Desai et al, 2012). It has been demonstrated that high-volume institutions and high-volume surgeons are more likely to perform extended robotic node dissection, with higher node counts (Marshall et al, 2013). Few studies have documented long-term follow-up data, given the relative infancy of LRC/RARC compared with open surgery. For example, in a small set of patients with more than 5 years of follow-up, patients undergoing RARC experienced an overall survival of 64%, disease-specific survival of 75%, and disease-free survival of 50%, results that are comparable to open series (Khan et al, 2013). A series of 121 patients who underwent LRC or RARC provides the longest follow-up data available to date, with a median follow-up of 5.5 years. In this study, the actuarial overall survival, cancer-specific survival, and recurrence-free survival were 55%, 73%, and 71% at 3 years; 48%, 71%, and 65% at 5 years; and 35%, 63%, and 54% at 10 years (Snow-Lisy et al, 2014).

Complication rates associated with RARC have been reported and are generally comparable to open series. Within a large multi-institutional study of 939 patients (IRCC) with greater than 90 days of follow-up, 41% and 48% of patients experienced a complication within 30 and 90 days of surgery, respectively (Johar et al, 2013). Serious complications (high grade 3 to 5) occurred in 19% of patients. Gastrointestinal, infectious, and genitourinary complications were most common. Receipt of blood transfusion was associated with high-grade complications. Mortality was 1.3% at 30 days and 4.2% at 90 days. With standardized reporting, complication rates have been reported to be 80%, with 35% of these being major complications within 90 days (Yuh et al, 2012). In this series of

241 patients, the most common complications were infectious, gastrointestinal, and procedural complications. Several factors were associated with major complications, including comorbidity, preoperative hematocrit, and orthotopic diversion.

Retrospective and prospective randomized studies have compared complication rates between RARC and open cystectomy. In a retrospective study of 100 open versus 100 robotic cystectomies, the overall and major complication rates were lower for robotic versus open surgery (35% vs. 57% and 10% vs. 22%, respectively) (Kader et al, 2013). In a U.S. Nationwide Inpatient Sample comparing 1444 open with 224 robotic cystectomies, patients undergoing RARC experienced fewer inpatient complications (49.1% and 63.8%, $P = .035$) and fewer deaths (0% and 2.5%, $P < .001$) (Yu et al, 2012). In a randomized prospective trial of 41 patients, there was no significant difference in overall complication rates (Nix et al, 2010). Similarly, in the only other randomized trial to date, no difference was seen in the rate of complications of grade 2 or higher (Parekh et al, 2013).

The issue of cost-effectiveness also has been explored, comparing minimally invasive cystectomy with the open approach. Smith and colleagues (2010) demonstrated that robotic cystectomy is associated with a higher financial cost than open surgery. This higher cost was corroborated by Yu and colleagues (2012) comparing 1444 open and 224 robotic radical cystectomies. However, other authors have demonstrated that robotic cystectomy can be cost-effective compared with open surgery, particularly for ileal conduit reconstruction, where shorter length of stay and reduced complications can drive down comparative cost of the robotic approach (Lee et al, 2011a, 2011b).

Conclusions

Minimally invasive surgical techniques for radical cystectomy represent an evolving field in urology. Surrogates of oncologic efficacy and emerging long-term data suggest oncologic equivalency. Although studies suggest some perioperative benefits, at the expense of longer operating room times, further study is needed to elucidate exact benefits.

KEY POINTS: ROBOTIC RADICAL CYSTECTOMY

- Robotic-assisted radical cystectomy represents an evolving field in urology.
- It is certainly one tool that can be used in the treatment of invasive bladder cancer.
- Morbidity is limited, operative time is comparable, and long-term oncologic outcomes are awaited.

SIMPLE/SUPRATRIGONAL CYSTECTOMY

Evaluation and Surgical Indications

Nonradical cystectomy, also known as simple cystectomy or supratrigonal/prostate-sparing cystectomy, can be used as a last resort in many patients with unrelenting symptoms or persistent infections. Such circumstances may include intractable interstitial cystitis, radiation cystitis, hemorrhagic cystitis, intractable bleeding, postradiation fistulae, or postradiation urgency nonresponsive to medical/conservative therapy, among others. Surgical excision of the bladder, robotic or otherwise, should be considered only as a last-resort procedure after all other medical and more conservative therapies have failed. A formal discussion of urinary diversion options should be undertaken with the patient and family before surgery.

Technique

Robotic or laparoscopic simple cystectomy can be performed with a similar setup to radical cystectomy as described earlier. The ureters

TABLE 96-1 Clinicopathological Outcomes of Robotic Assisted Radical Cystoprostatectomy

INSTITUTION	NO. PTS.	TECHNIQUE	OR TIME (hr) (MEDIAN)	EBL (mL) (MEDIAN)	COMP. RATE	MEDIAN LOS	% ILEAL CONDUIT	% + MARGIN	LN YIELD
University of Texas (Parekh et al, 2013)	20	RARC	300	400	25%	6	N/A	5%	11 (median)
University of North Carolina (Nix et al, 2010)	21	RARC	252	200	33%	4	50%	0%	19 (mean)
Washington University (Nepple et al, 2013)	36	RARC	410 (mean)	675 (mean)		7.9 (mean)	56%	14%	17 (median)
University of Alabama (Knox et al, 2013)	58	RARC	468 (mean)	276 (mean)	43%	6.3 (mean)	91%	7%	21 (mean)
Weill Cornell (Ng et al, 2010)	83	RARC	365 (mean)	460 (mean)	48%	5.5	56%	7%	16 (median)
Weill Cornell (Kauffman et al, 2011)	85	RARC	360 (median)	400			71%	6%	17 (median)
Wake Forest (Kader et al, 2013)	100	RARC	451 (mean)	423 (mean)	35%	6	97%	11%	18 (mean)
University of North Carolina (Pruthi et al, 2010)	100	RARC	258 (median)	250	8% (> grade 3)	4.9 (mean)	61%	0%	19 (mean)
Roswell Park (Guru et al, 2009)	100	RARC	343 (mean)	598 (mean)	38%		93%	3%	17-26 (mean)
City of Hope (Yu et al, 2012)	196	RARC	432 (median)	400 (median)	80% (30% major)	9 (median)	32%	4.1%	28 (median)

COMP., complications; EBL, estimated blood loss; LN, lymph node; LOS, length of stay; OR, operating room; RARC, robotic-assisted radical cystectomy.

are first isolated and transected at the level of the bladder. Posterior dissection is initiated by incising the posterior peritoneal reflection. The superior vesical artery and anterior pedicle to the bladder are divided. Posterior dissection is carried out to the level of the base of the prostate, just beyond the seminal vesicles. When the posterior dissection is complete, the bladder is dropped off of the anterior abdominal wall attachments. Once this is done, the anterior bladder is incised at the level just proximal to the prostate. The trigone is left intact. The posterior bladder wall is incised, and the bladder is placed in an Endo Catch bag for the remainder of the case. The trigone can serve as a point of attachment for a urethrovaginal anastomosis in the setting of an orthotopic urinary diversion. When a simple cystectomy is performed for postradiation fistulae, the prostatic fossa should be debrided of underlying necrotic tissue because this is a potential area of persistent postoperative infection and abscess formation. Consideration should be given to bringing in a vascular pedicle flap in this setting to allow for healthy tissue in growth and proper wound healing.

Outcomes and Complications

There have been no long-term studies of laparoscopic or robotic simple cystectomy. Most data are from case reports and personal reporting of single surgeon experiences. Complications are similar to complications reported in radical cystectomy series. Cases are highly selective, and each one must be considered on an individual basis.

TRANSVESICAL FOREIGN BODY AND STONE EXTRACTION

Indications

Transabdominal cystolithotomy is indicated in patients with very large and/or multiple bladder stones or when transurethral approaches are deemed inefficient (e.g., excessive stone burden, failed prior endoscopic treatment). This procedure is particularly indicated in patients with large prostates in whom minimally invasive suprapubic or retropubic prostatectomy is being performed concomitantly via laparoscopic or robotic approaches. In addition, foreign bodies within the bladder can be removed laparoscopically, via a transperitoneal or transvesical LESS approach, or robotically. Procedures for removal of foreign bodies have been described for objects including surgical materials and mesh (Maher and Feiner, 2011; Yoshizawa et al, 2011; Kim et al, 2012; Macedo et al, 2013; Roslan et al, 2013), migrated intrauterine devices, broken sewing needles (Lee et al, 2010), and electrical wires (Ko et al, 2010).

Technique

Various techniques can be employed for laparoscopic/robotic foreign body excision. A laparoscopic or robotic transperitoneal approach is the most straightforward technique. After standard abdominal insufflation, transperitoneal trocars are employed (Maher et al, 2011; Macedo et al, 2013). An anterior vesicotomy is performed, and the foreign body is visualized. Ureteral catheterization is performed if needed, and the foreign body is removed or excised. The bladder is closed with absorbable suture (Fig. 96-30).

The abdominal cavity can be avoided by using a transvesical approach, which can be performed with multiple trocars (Fig. 96-31) (Yoshizawa et al, 2011; Kim et al, 2012). After cystoscopy and saline instillation into the bladder, a 5-mm trocar is placed into the bladder under direct vision, the bladder is drained, and pneumovesicum is established at 8 to 12 mm Hg. Two additional trocars are placed, and foreign body excision is performed.

Transvesical excision of foreign bodies and/or mesh also can be performed via a transvesical single-site method (Fig. 96-32) (Ingber et al, 2009; Roslan et al, 2013). After cystoscopy and saline instillation, a single-site device is deployed, and the foreign body is identified and excised followed by bladder closure. To aid in retraction, a grasper can be placed transurethrally (Roslan et al, 2013).



Figure 96-30. Transperitoneal laparoscopic mesh excision. After establishment of pneumoperitoneum, transabdominal trocars are placed via traditional techniques. The bladder is opened and mesh, stones, or foreign bodies are removed. The bladder is closed in two layers with absorbable sutures. An intravesical mesh is shown with associated large bladder calculi.

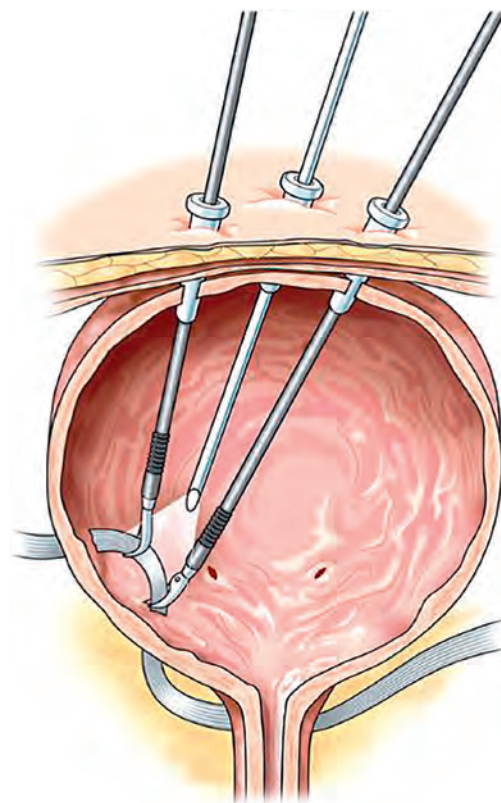


Figure 96-31. Transvesical laparoscopic mesh excision. After cystoscopy, transvesical trocars are placed directly into the bladder. Pneumovesicum is established and maintained. Mesh or other foreign bodies are excised, and the bladder is closed with absorbable suture. (From Yoshizawa T, Yamaguchi K, Obinata D, et al. Laparoscopic transvesical removal of erosive mesh after transobturator tape procedure. *Int J Urol* 2011;18:861.)

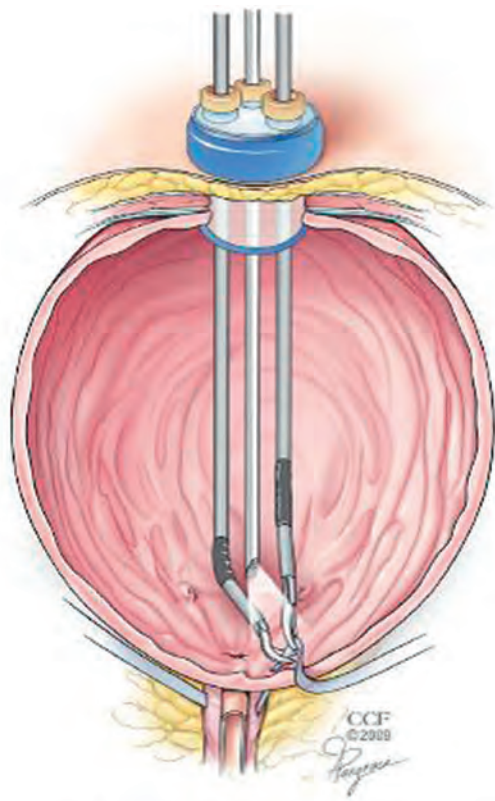


Figure 96-32. Transvesical single-site mesh excision. After cystoscopy, the bladder is distended with saline. A single-site access port is placed directly in the bladder, and pneumovesicum is established. Transvesical single-site mesh excision is performed, and the bladder is closed. (From Ingber MS, Stein RJ, Rackley RR, et al. Single-port transvesical excision of foreign body in the bladder. *Urology* 2009; 74:1347.)

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Surgical Anatomy

Selecting the Segment of Intestine

Bowel Preparation

Intestinal Anastomoses

Ureterointestinal Anastomoses

Renal Deterioration

Urinary Diversion

Metabolic and Neuromechanical Problems of Urinary Intestinal Diversion

Summary

Reconstructive urologic surgery frequently requires use of bowel for ureteral substitution, bladder augmentation, or bladder replacement. In rare cases, gastrointestinal segments may also function as urethral or vaginal substitutes. The stomach, jejunum, ileum, and colon all have a role in urinary tract reconstruction. Successful use of intestinal segments requires a thorough knowledge of their surgical anatomy. The surgeon must know the methods of preparing the intestine for an operation and the techniques for isolating segments of intestine and reconstituting continuity of the enteric tract. Crucial to success is an understanding of the technical procedures and potential complications of incorporating the intestine into the urinary tract. With this knowledge, reconstruction of the urinary tract may be performed with the proper segment of intestine in the least morbid way. This chapter reviews the technical aspects involved in the use of intestinal segments in urologic surgery that pertain to all types of reconstructive procedures and describes the important potential acute and long-term difficulties and complications of the use of intestinal segments.

SURGICAL ANATOMY

 Please see the Expert Consult website for this section, including [Figures 97-1 and 97-2](#).

SELECTING THE SEGMENT OF INTESTINE

 Please see the Expert Consult website for this section.

BOWEL PREPARATION

It has been a long-held tenet of elective intestinal surgery that **bowel preparation is beneficial**. The bacterial population in the stomach is relatively low, but in the remaining segments of the bowel including the jejunum, ileum, and colon, there are high bacterial counts. Early studies suggested that bowel anastomoses in patients whose intestinal tract had not been prepared before surgery had increased wound infection rates, increased intraperitoneal abscesses, and an anastomotic dehiscence rate greater than in patients who received proper bowel preparation before surgery ([Irvin and Goligher, 1973](#); [Dion et al, 1980](#)). Other studies showed that mechanical preparation resulted in collapsed bowel at the time

of surgery, which was shown to reduce the incidence of anastomotic leaks ([Christensen and Kronborg, 1981](#)). Studies have recently begun to question the widely held belief that bowel preparation is mandatory. In meta-analyses of randomized clinical trials of anastomotic leakage during colon and rectal surgery, researchers found that there was no support for the conclusion that mechanical bowel preparation reduces anastomotic leak rates and other complications in elective open colon surgery ([Guenaga et al, 2011](#)). A randomized study in a small group of patients undergoing ileal loop diversion showed no difference in outcomes between the groups of patients who received bowel preparation and those who did not ([Hashad et al, 2012](#)).

In experimental animals, it has been shown that an anastomosis with vascular compromise at the anastomotic line, which would normally result in perforation, heals if the bowel has been properly prepared with antibiotics. Also, solid feces may place strain on the anastomosis in the early phase of healing and result in ischemia with subsequent perforation. **Complications that result from bacterial contamination are a major cause of morbidity and mortality in patients undergoing urologic procedures.** Infectious complications after radical cystectomy that are a direct result of fecal contamination may occur in 18% to 20% of patients who undergo radical cystectomy and include wound infections, peritonitis, intra-abdominal abscesses, wound dehiscence, anastomotic dehiscence, and systemic sepsis ([Bracken et al, 1981](#)). More recent series suggest that current management practices appear to have made a substantial improvement, with perioperative infectious complications of 7% ([Stein et al, 2004](#)). In another contemporary series of radical cystectomy with continent or ileal loop urinary diversion in 167 patients, there was an infection complication rate of 7.2% ([Mansson et al, 2003](#)). Another large series of 359 patients found infectious complications in 11.1% ([Berneking et al, 2013](#)).

There are two aspects to bowel preparation: **mechanical and antibiotic**. Both methods attempt to reduce the complication rate from intestinal surgery. **Mechanical preparation reduces the amount of feces, whereas antibiotic preparation reduces the bacterial count.** The bacterial flora in the bowel consists of aerobic organisms, the most common of which are *Escherichia coli* and *Enterococcus faecalis*, and anaerobic organisms, the most common of which are *Bacteroides* species and *Clostridium* species. The bacterial concentration ranges from 10 to 10⁵ organisms per gram of fecal content in the jejunum, 10⁵ to 10⁷ in the distal ileum, 10⁶ to 10⁸ in the ascending colon, and 10¹⁰ to 10¹² in the descending colon.

The segments of bowel urologists use most frequently are the ileum, colon, and rectum. The jejunum and stomach are also used, although less commonly, in reconstructive procedures. Successfully performing surgical mobilization of these structures and constructing them into their new role require a thorough knowledge of the surgical anatomy of the vascular supply and metabolic function of each portion of the intestinal tract.

Stomach

The stomach is a vascular organ that receives its blood supply primarily from the celiac trunk (Fig. 97-1). Three branches of the celiac axis give rise to the majority of the arterial supply of the stomach.

1. The **left gastric (coronary) artery** arises directly from the celiac axis and supplies the lesser curvature.
2. The **hepatic artery**, after arising from the celiac axis, **gives off the right gastric artery**, which also supplies the lesser curve of the stomach, and the **gastroduodenal artery**, which supplies the antrum and duodenum before giving off the **right gastroepiploic artery**.
3. The **splenic artery** originates from the celiac axis and gives off the **vasa brevia (short gastrics)**, which supply the fundus and cardia, and the **left gastroepiploic artery**.

The right gastroepiploic artery meets with the left gastroepiploic artery; thus both supply collateral flow to the greater curve of the stomach. By use of the gastroepiploic vessels, a pedicle of stomach may be mobilized as far as the pelvis. The pedicle may consist of the entire antrum pylori or a wedge of the fundus.

The blood supply for these segments is based on either the left or right gastroepiploic artery, depending on the portion of stomach used. On occasion, the left gastroepiploic artery is atretic at some point in its course and does not provide an adequate blood supply. Under these circumstances, the right gastroepiploic artery must be used. When a wedge of fundus is used, it should not include a significant portion of the antrum and should never extend to the pylorus or all the way to the lesser curve of the stomach. When the blood supply is based on the left gastroepiploic artery, the short gastric vessels that course from the gastroepiploic artery to the stomach are ligated along the greater curve proximal to the pedicle to the origin of the gastroepiploic artery. The omentum is left attached to the gastroepiploic vessels and helps secure and support them. It may be necessary for proper pedicle mobility to detach the omentum from the colon along the avascular plane located at the point of its attachment to the transverse colon. If an antrectomy is performed, a Billroth I anastomosis reconstitutes gastrointestinal continuity. The stomach has a thick seromuscular layer that can be easily separated from the mucosa should a submucosal ureteral reimplantation be necessary.

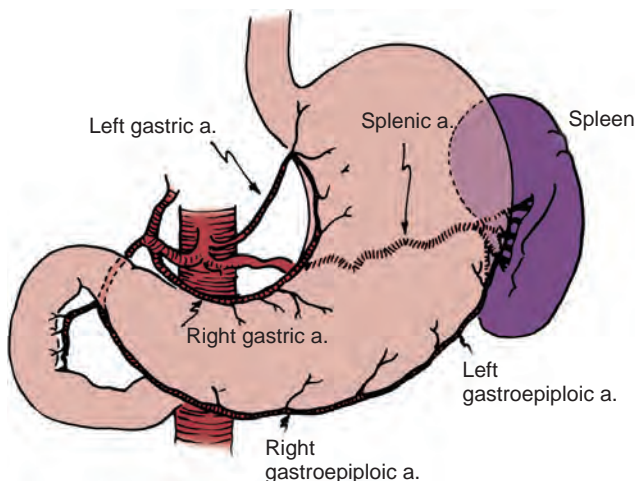


Figure 97-1. Arterial supply of the stomach.

Small Bowel

The small bowel is about 22 feet long; however, it may vary from 15 to 30 feet in length. Its largest diameter is in the duodenum; the lumen becomes smaller in the more distal portions, reaching its smallest diameter in the ileum, approximately 12 inches from the ileocecal valve. **About two fifths of the small bowel is jejunum, whereas the distal three fifths is ileum.** There is no definite demarcation between the two; however, each possesses several unique properties that allow the surgeon to distinguish one from the other intraoperatively. **The ileum, being more distal in location, has a smaller diameter. It has multiple arterial arcades, and the vessels in the arcades are smaller than those in the jejunum. The ileal mesentery is also thicker than the jejunal mesentery. In contrast, the jejunal diameter is larger, the arterial arcades are usually single, and the vessels composing them are larger in diameter.** The arcades anastomose one with another and give off straight vessels, which enter the bowel and form an anastomotic network within the bowel wall. **It has been shown experimentally that up to 15 cm of small bowel can survive laterally to a straight vessel.** Thus theoretically, the mesentery could be cleaned from the small bowel for a length of 15 cm without necrosis of the end. **In general, however, it is unwise to assume that more than 8 cm of small bowel will survive away from a straight vessel.** The arcades receive their blood from the superior mesenteric artery. When segments of jejunum or ileum are isolated, the mesentery should be transected in such a way that the isolated intestinal segment receives its blood supply from an arcade supplied by a palpable artery of substance that courses through the base of the mesenteric pedicle.

Two portions of the small bowel may lie within the confines of the pelvis and, as such, may be exposed to pelvic irradiation and pelvic disease: the last 2 inches of the terminal ileum, which is often fixed in the pelvis by ligamentous attachments, and the 5 feet of small bowel beginning approximately 6 feet from the ligament of Treitz, the mesentery of which is the longest of the entire small bowel. As such, this portion of the small bowel can descend into the pelvis. **In a postirradiated patient, one should try to avoid use of these two segments of the small intestine in any reconstructive procedure.**

Colon

The large bowel is divided into the cecum, ascending colon, transverse colon, left colon, sigmoid colon, and rectum. Portions of the large bowel are fixed or retroperitoneal, and other segments lie free within the peritoneal cavity. The cecum, on rare occasion, may lie free within the abdominal cavity and therefore may have great mobility. In general, however, it is fixed in the right lower quadrant. Two accessory peritoneal bands bind the cecum and distal ileum to the retroperitoneum and lateral abdominal wall. One band arises from the distal ileum, attaches to the cecum, and is fixed to the retroperitoneum. A second band arises from the cecum and fixes the cecum to the posterior abdominal wall laterally. The remainder of the ascending colon is fixed to the right posterior abdominal wall to the level of the hepatic flexure, at which point the hepatocolic ligament secures this portion of the colon to the liver. The transverse colon lies free within the abdominal cavity and is fixed in the left upper quadrant at the splenic flexure by the phrenocolic ligament. The transverse colon is attached to the stomach by the gastocolic omentum. The descending colon is fixed to the lateral abdominal wall; however, the sigmoid colon may or may not lie free within the abdominal cavity. The rectosigmoid colon's most cephalad portion is intraperitoneal, and at its distal, more caudad, portions it becomes retroperitoneal, and finally subperitoneal.

The colon receives its blood supply from the superior mesenteric artery, inferior mesenteric artery, and internal iliac arteries (Fig. 97-2). The major arteries supplying the colon and rectum include the ileocolic, right colic, middle colic, left colic, sigmoid, superior hemorrhoidal, middle hemorrhoidal, and inferior hemorrhoidal arteries. These arteries anastomose with one another to form the arc of Drummond and allow considerable leeway in

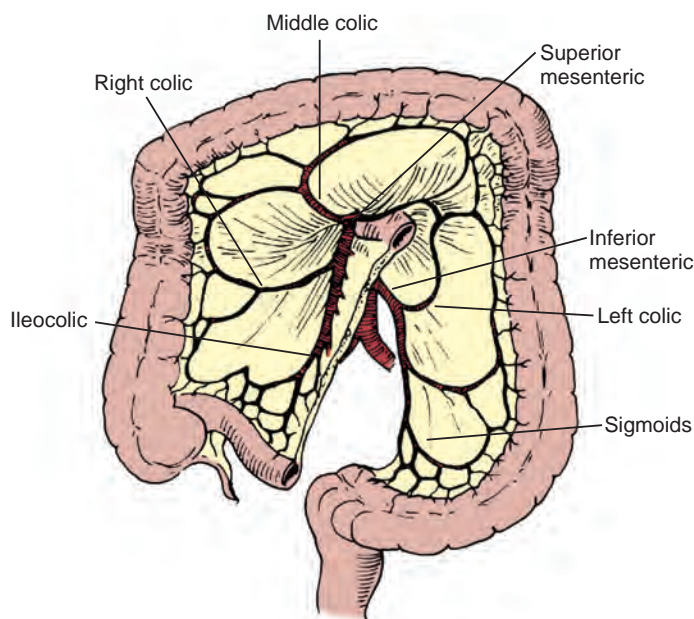


Figure 97-2. Arterial supply to the small bowel and colon.

mobilizing the colon. The middle colic artery arises from the first portion of the superior mesenteric artery and typically ascends the transverse mesocolon to the right of midline. The right colic artery usually arises just below the middle colic artery from the superior mesenteric artery and courses to the right colon. In some cases, the right colic may arise from the ileocolic artery or directly from the middle colic artery. If the right colic arises from the ileocolic artery, mobilization of a distal ascending colon segment is more likely to be brought easily into the deep pelvis. On occasion—particularly if the right colic artery originates from the middle colic artery—it is necessary to divide the right colic artery at its origin to mobilize the

distal portion of the ascending colon to the pelvis. The ileocolic artery is the terminal portion of the superior mesenteric artery and supplies the last 6 inches of ileum and ascending colon. The left colic artery arises from the inferior mesenteric artery, and then the inferior mesenteric artery gives off four to six sigmoid branches, the last of which becomes the superior hemorrhoidal artery. This anastomoses with the middle hemorrhoidal artery, a branch of the internal iliac artery, which in turn anastomoses with the inferior hemorrhoidal artery, the terminal branch of the internal pudendal artery. The middle sacral artery, which originates directly from the aorta, may supply the posterior aspect of the rectum.

Three weak points involving the vascular supply to the colon have been described. The **Sudeck critical point**, which is located between the junction of the **sigmoid and superior hemorrhoidal arteries**, was thought to be a particularly tenuous anastomotic area such that if the colon were transected in this region, the anastomosis would heal with difficulty because the blood supply might be compromised. Similarly, the **midpoints between the middle colic and right colic arteries and between the middle colic and left colic arteries also have somewhat tenuous anastomotic communications**. Although anastomoses in these areas usually heal well, provided the principles of proper technique are followed, it is usually wise to select an area for the anastomosis to one side of these points.

The ascending colon is mobilized first by transecting the cecal and distal ileal fibrous attachments to the lateral abdominal wall and retroperitoneum as described previously and then by detaching it from the lateral abdominal wall along the avascular line of Toldt. This is a bloodless plane, provided the colonic mesentery is not violated. The transverse colon is mobilized by dividing the gastocolic omentum (along the avascular plane of its attachment to the colon), the hepatocolic ligament (which may have some small vessels coursing through it), and the phrenocolic ligament. The descending colon is mobilized, much like the right colon, by incision of the avascular line of Toldt lateral to the colon. With these attachments taken down, there is considerable mobility of the colon. Further mobility is gained by isolating a pedicle of the intestinal segment on the basis of one of the major arterial vessels described earlier.

The stomach, jejunum, ileum, and colon have unique properties, each of which has special advantages and disadvantages. The selection of the proper intestinal segment should be based on the patient's condition, renal function, history of previous abdominal procedures, and type of diversion or substitution required. The stomach has been used as a replacement for bladder, for augmentation cystoplasty, as a conduit, and for continent diversions (Abdel-Azim and Abdel-Hakim, 2003; DeFoor et al, 2003; Bissada et al, 2004; Castellan et al, 2012). The advantages of the stomach over other intestinal segments for urinary intestinal diversion are that it is less permeable to urinary solutes, it has a net excretion of chloride and protons rather than a net absorption of them, and it produces less mucus. Urodynamically, it behaves as other intestinal segments do. When it is used in urinary reconstruction, electrolyte imbalance rarely ensues in patients with normal renal function, although a hypochloremic metabolic alkalosis has been described. The incidence of bacteriuria has been reported to be as low as 25%, much less than the 60% to 80% incidence reported for ileal and colon segments. However, more recent data suggest that there is no difference in bacteriuria among any of the segments. The urine, which usually has a pH of 6 to 7, does not typically result in an increased incidence of peristomal skin problems. Authors have also noted that in bladder augmentation patients, there is little difference in urinary pH between gastric and ileal augmentations. Serum gastrin levels are usually normal or minimally elevated, depending on what portion of the stomach is used and how much (Leong, 1978; Adams et al, 1988). Although exclusion of the antrum from the gastrointestinal tract has not resulted in elevated serum gastrin levels and an ulcer diathesis clinically (Lim et al, 1983), antral exclusion experimentally results in elevated circulating gastrin levels, which may cause major intestinal ulcerative problems in the postoperative period (Tiffany et al, 1986).

Rarely, severe ulcerative complications have occurred in cases in which stomach has been used for urinary reconstruction (Reinberg et al, 1992; Tainio et al, 2000). Long-term histamine (H_2) or proton-pump inhibition should be considered for these patients. When the antral portion of the stomach is used, reconstitution is generally by a Billroth I anastomosis. Complications with Billroth I gastroduodenostomy are well documented. The antrum should not be used if the fundus is available. Early complications of the use of portions of the stomach for reconstruction include gastric retention caused by atony of the stomach or edema of the anastomosis; hemorrhage, most commonly originating from the anastomotic site; hiccups secondary to gastric distention; pancreatitis as a consequence of intraoperative injury; and duodenal leakage. Delayed complications include dumping syndrome, steatorrhea, small stomach syndrome, increased intestinal transit time, bilious vomiting, afferent loop syndrome, hypoproteinemia, and megaloblastic or iron deficiency anemia. Postoperative bowel obstruction occurs with an incidence of 10% (2 of 21 patients) (Leong, 1978). Gastroduodenal and gastroureteral leaks have also been reported, occasionally resulting in a fatal outcome (Leong, 1978).

The use of stomach for urinary intestinal diversion may be considered when the use of other intestinal segments in a patient with a decreased amount of intestine would result in serious nutritional problems. One advantage of using stomach segments in the patient with severe abdominal adhesions is that the area of the stomach is, in general, adhesion free and easily mobilized. **Complications specific to the use of stomach include the hematuria-dysuria syndrome and severe metabolic alkalosis associated with respiratory distress in some patients (see the discussion of metabolic complications, later).**

The jejunum is usually not used for reconstruction of the urinary system because it may result in severe electrolyte imbalance. In general, diseases that would make the ileum inappropriate for use also make the jejunum inappropriate for use. Rarely, it is the only segment available. Under these circumstances, as distal a segment of jejunum as possible should be used to minimize the electrolyte problems.

The ileum and colon are used most often for urinary tract reconstruction and have been used in all types of reconstructive procedures. The ileum is mobile and of small diameter, has a constant blood supply, and serves well for ureteral replacement and the formation of conduits. **Loss of significant portions of the ileum results in nutritional problems because of lack of vitamin B_{12} absorption, diarrhea because of lack of bile salt reabsorption, and fat malabsorption.** On occasion, the mesenteric fat is excessive, making mobility and anastomosis difficult. Also, the mesentery may be so short that it is difficult to mobilize the ileum into the deep pelvis. **Postoperative bowel obstruction occurs in up to 10% of patients who have segments isolated from the ileum for urinary tract reconstruction (Varkarakis et al, 2006).** As many as half of the obstructions occur in the early postoperative period (Schwarz and Jeffs, 1975).

The colon requires mobilization from its fixed positions to give it the mobility necessary for use in urinary reconstruction. It has a larger diameter than the ileum and is usually easily mobilized into any area of the abdomen or pelvis. In patients who have received pelvic irradiation, portions of the right, transverse, and descending colon may be used confidently with the knowledge that they have not been exposed to the radiation therapy. Removal of segments of colon from the enteric tract results in fewer nutritional problems than does removal of segments of ileum, provided the ileocecal valve is not violated. Should the ileocecal valve be used, diarrhea, excessive bacterial colonization of the ileum with malabsorption, and fluid and bicarbonate loss may occur. **The incidence of postoperative bowel obstruction with colon is 4%, less than that occurring with ileum.** Both ileal and colon segments result in the same type of electrolyte imbalance with similar frequencies. **An antireflux ureterointestinal anastomosis by the submucosal tunnel technique is easier to perform with use of the colon.** In general, ileum and colon are comparable and have few differences, which does not argue strongly for the selection of one over the other except under special circumstances.

Mechanical Bowel Preparation

Mechanical bowel preparation reduces the total number of bacteria but not their concentration. Thus the same number of organisms is present per gram of fecal content (Nichols et al, 1972). Therefore spilling enteric contents during the procedure may be less likely with the mechanically prepared bowel because there is less of it to spill; however, once spilled, cubic centimeter for cubic centimeter, the inoculum is the same as if the bowel had not been prepared. Recent analysis has suggested, however, that there may in fact be an increase in bacterial contamination in patients who have undergone bowel preparation (Fa-Si-Oen et al, 2005).

Conventional bowel preparations commonly used in the past tended to exhaust the patient and exacerbate nutritional depletion because they typically required a 3-day preparation period of insufficient calorie intake (Table 97-1). The use of elemental diets has been advocated to clean the colon of feces while not compromising the nutritional status of the patient. Unfortunately, they have not proved useful because the elemental diets do not empty the colon of feces, and they do not reduce the bacterial flora (Arabi et al, 1978). In an attempt to reduce the time required for intestinal preparation and to obviate low-calorie intakes, whole-gut irrigation has been used. Originally, whole-gut irrigation was performed by placement of a nasogastric tube (NGT) into the stomach and infusion of 9 to 12 L of lactated Ringer solution or normal saline during a several-hour period. These fluids were subsequently replaced with 10% mannitol, which was equally successful in ridding the bowel of its fecal content; however, the mannitol served as a bacterial nutrient and thereby facilitated microbial growth (Hares and Alexander-Williams, 1982). These solutions have largely been replaced by a polyethylene glycol (PEG)–electrolyte solution. Whole-gut irrigation may be exhausting to the patient and may, in fact, result in a fluid gain, particularly when either saline or mannitol is used. Whole-gut irrigation is contraindicated in patients with an unstable cardiovascular system, patients with cirrhosis, patients with severe renal disease, patients with congestive heart failure, and those with an obstructed bowel. Whole-gut irrigation has been found to be no more effective than conventional preparations in reducing wound infections and septic complications (Christensen and Kronborg, 1981), even though there is a reduction of aerobic flora compared with the conventional preparations (van den Bogaard et al, 1981). The advantages of the whole-gut irrigation are that it gives the patient dietary freedom, there is a short preparation time, and it eliminates an enema. Its disadvantages are that it may result in the patient’s exhaustion, it is rather rigorous, and it does result on occasion in fluid overload.

The PEG-electrolyte lavage solutions (e.g., GoLYTELY or the more palatable NuLYTELY) are effective lavage agents in preparing the gut for elective colon and rectal surgery, as well as for urologic surgery in which bowel is used. For the adult, 20 to 30 mL/min or approximately 1 to 1.5 L/hr for 3 hours is given either orally or through a small-caliber NGT placed into the stomach. If it is taken by mouth, it is better tolerated if the solution is chilled. The administration of PEG lavage is stopped when the rectal effluent is clear and there is no particulate matter in it or when 4 L of fluid has been given. The septic complications with its use are approximately 4%. An inadequate preparation occurs in 5% of the patients using this

modality (Wolff et al, 1988). For children, even those younger than 1 year, PEG lavage may be used at a rate of 20 to 40 mL/kg/hr and given until the rectal effluent is clear and free of particulate matter (Tuggle et al, 1987). Metoclopramide, 10 mg in adults, is often given simultaneously to control nausea.

Oral cathartic bowel preparation is another acceptable strategy for reducing fecal burden before intestinal surgery. Oral solutions of magnesium citrate or sodium phosphate are both effective in cleansing the intestinal tract (Borden et al, 2010). The volume of fluid the patient must consume is substantially lower (148 mL MagCitra[®] and 45 mL NaPhosphate), and the preparations are typically well tolerated in healthy patients.

Bowel preparation can increase metabolic complications and cause electrolyte disturbances, which could affect surgical care. Caution must be exercised in elderly and debilitated patients receiving sodium phosphate preparation; the sodium phosphate preparation has been shown to cause significant derangements in potassium, calcium, and phosphorus levels in frail individuals (Beloosesky et al, 2003). Phosphate nephropathy has been recognized as a serious complication of oral sodium phosphate (OSP) bowel preparation (Markowitz et al, 2005). Caution should be used in prescribing OSP to patients with underlying renal insufficiency or being treated with nephrotoxic medications. In the United States, OSP was recently changed to prescription only by the U.S. Food and Drug Administration (FDA). OSP should rarely be used. The only study in postsurgical complications comparing sodium phosphate with PEG found no significant difference in complication rates (Oliveira et al, 1997). One study suggested that PEG is better tolerated by elderly patients and causes less disruption in potassium and sodium levels (Seinela et al, 2003). Oral electrolyte solution rehydration may prevent some of the complications of bowel preparation (Tjandra and Tagkalidis, 2004).

A number of studies have questioned the efficacy of mechanical bowel preparation. Some have suggested that a limited mechanical bowel preparation is all that is necessary; others have questioned even the need for a mechanical bowel preparation. In one study, 2 L of PEG plus metoclopramide was compared with the administration of 4 L of PEG solution. There was no difference in surgical complication rate or the extent to which the bowel was clean (Grundel et al, 1997). In another study, when 4 L of PEG was compared with 90 mL of sodium phosphate, there was no significant difference in surgical complication rate (Oliveira et al, 1997). Two meta-analyses have found that there is an increased anastomotic dehiscence rate with preoperative mechanical bowel preparation (Wille-Jørgensen et al, 2003; Bucher et al, 2005). PEG may be the agent responsible for the increased rate of complications, but other preparation strategies have not been adequately analyzed (Slim et al, 2004). A meta-analysis of randomized trials comparing mechanical bowel preparation with no bowel prep before elective colorectal surgery found no difference between the groups for anastomotic leakage, abdominal abscess, or wound sepsis (Slim et al, 2009). No study has adequately addressed the issue of the need for debulking of the intestine before laparoscopic approaches to intestinal surgery. It is extremely important to note that in these studies, the administration of intravenous antibiotics was crucial in keeping the complication rate low. Moreover, it is important to note that in these studies there was limited exposure of the

TABLE 97-1 Mechanical Bowel Preparation

PREOPERATIVE		CONVENTIONAL	POLYETHYLENE GLYCOL–ELECTROLYTE SOLUTIONS	
DAY	DIET	CATHARTIC	DIET	POLYETHYLENE GLYCOL
3	Low residue plus supplements	10 oz citrate of magnesia over 2 hr at 1 PM	Regular plus supplements	2–4 L (adults) or 25 mL/kg/hr × 2 hr (do not exceed 2 L) (children)
2	Low residue plus supplements		Low residue plus supplements	
1	Clear liquids		Clear liquids	

intestine because the patients underwent elective bowel resections, unlike urologic procedures in which long segments of the intestine are opened or interposed in a urinary tract that is normally free of fecal contents. No studies have carefully looked at the safety of omitting mechanical bowel preparation in urologic reconstructive surgery (Large et al, 2012).

Antibiotic Bowel Preparation

There has been considerable recent controversy as to whether the addition of oral antibiotics in elective colon and small bowel surgery reduces mortality and morbidity significantly. The long-held practice of mechanical and oral antibiotic bowel preparation dates to the 1970s. In one study, the septic complication rate was reduced from 68% in the control group to 8% in the antibiotic group (Washington et al, 1974). Most series, however, report a lesser incidence of reduction in wound infection, in general from 35% without antibiotics to 9% with their use (Clarke et al, 1977). Others have suggested that the mortality rate drops from 9% to 3% with the use of antibiotics (Baum et al, 1981). It is clear that the use of antibiotics protects vulnerable bowel in that it may allow the tenuous anastomosis to survive. Other studies, however, have shown that without the use of oral antibiotics in mechanically prepared bowel in elective surgery, the septic complication rate is comparable with that in those studies using antibiotics, and the rate of *Clostridium difficile* colitis was lower without oral antibiotics (Wren et al, 2005). In the presence of a bowel obstruction, however, oral antibiotics are of little value because they do little good in sterilizing the bowel. The disadvantages of antibiotics may include postoperative increase in the incidence of diarrhea; pseudomembranous enterocolitis; theoretically increased incidence of tumor implantation at the suture line that is not germane to urologic surgery; monilial overgrowth resulting in stomatitis, thrush, and diarrhea; and, with prolonged use, malabsorption of protein, carbohydrate, and fat. The antibiotics most commonly used for bowel preparation include kanamycin, which is the best single agent; neomycin and erythromycin base; and neomycin and metronidazole (Table 97-2). With an appropriate antibiotic preparation, enteric organisms are reduced to 10^2 per gram of feces (Nichols et al, 1972). A contemporary randomized trial of patients undergoing elective colonic surgery found the lowest fecal bacterial concentrations when patients had preoperative mechanical bowel preparation, oral neomycin, and supplemental "synbiotic" treatment (to provide benign flora to the intestine). No difference in clinical infections was seen between patients prepared with or without oral antibiotic bowel preparation (Reddy et al, 2007). A large series of 2475 patients from Michigan undergoing colon surgery showed lower infection (5.0% vs. 9.7%) and less *C. difficile* colitis (0.5% vs. 1.8%) with mechanical and oral antibiotic bowel preparation (Kim et al, 2014).

Perioperative intravenous antibiotics appear to be the most important means of preventing infectious complications of intestinal surgery. Systemic antibiotics must be given before the operative event if they are to be effective. Ideally, antibiotics should be given between 1 and 2 hours before the start of surgery (Classen et al, 1992). They appear to be most effective against the anaerobic flora and apparently reduce the complications caused by these

organisms (Dion et al, 1980). Perioperative systemic antibiotics, when added to the oral regimen, reduced the septic complication rate from 15% to 20% to half that rate in several series (Hares and Alexander-Williams, 1982; Gottrup et al, 1985). Other studies, however, have shown no effect of systemic cephalosporin, for example, in reducing septic complications (Wolff et al, 1988). If perioperative antibiotics are given, they should be effective against anaerobes because it is complications from these organisms against which perioperative antibiotics appear to be particularly effective. Third-generation cephalosporins have been advocated as an appropriate systemic antibiotic. Other recent studies support the use of both oral and systemic antibiotic prophylaxis before intestinal surgery (Kim et al, 2014). It is clear that preoperative antibiotics reduce postoperative complications. Most agree that preoperative intravenous antibiotics are important, and many advocate discontinuing the use of oral antibiotics because the incidence of *C. difficile* diarrhea may be increased and there appears to be no advantage, provided preoperative intravenous antibiotics are given within an hour of the operative event (Wren et al, 2005).

It is my preference to perform both a mechanical and an antibiotic bowel preparation. The patient is allowed a normal diet until 1 day preoperatively, at which time a clear liquid diet is begun and citrate of magnesia is taken as a cathartic. Oral antibiotic bowel preparation with neomycin and erythromycin base is also prescribed. On the day of surgery, the patient is given intravenous antibiotics 1 hour before the incision.

Diarrhea and Pseudomembranous Enterocolitis

Bowel preparations may result in diarrhea and pseudomembranous enterocolitis. Pseudomembranous enterocolitis is the more severe form of a spectrum of diarrhea. Clinically, this occurs after a bowel preparation in the postoperative period and is heralded by abdominal pain and diarrhea usually in the absence of fever or chills. As the symptoms and infection become more severe, systemic toxicity supervenes. These patients can develop a toxic megacolon, and if this occurs, the mortality may exceed 15% to 20%. Historically, pseudomembranous enterocolitis was thought to be caused by *Staphylococcus*, but there was, in fact, little evidence to support that organism as the causative agent. It is now clear that *C. difficile* plays a significant role in the majority of cases. *C. difficile* elaborates at least two toxins that cause diarrhea and enterocolitis. *C. difficile* does not invade the bowel, and it is not normally a significant inhabitant of the fecal flora. It is held in check by other bacteria that inhibit its growth. Thus antibiotics destroy the bacteria that inhibit the growth of *C. difficile* and thereby allow it to flourish. The toxin produces a diffuse inflammatory response with cream-colored plaque formation, erythema, and edema of the bowel wall. On microscopic examination, the villi appear to be intact and there is a polymorphonuclear leukocyte infiltrate of the submucosa (Bartlett, 2002).

As the disease progresses, large areas of mucosa may slough and areas of the bowel are denuded of their mucosa. The lesions may involve the colon, in which case it is called *pseudomembranous enterocolitis*, or the small bowel, in which case it is called *pseudomembranous enteritis*, or they may involve both. The diagnosis may be suspected from the symptoms or endoscopy and is confirmed by

TABLE 97-2 Antibiotic Bowel Preparation

PREOPERATIVE DAY	KANAMYCIN	NEOMYCIN PLUS ERYTHROMYCIN BASE	NEOMYCIN PLUS METRONIDAZOLE
3	1 g kanamycin orally every 1 hr × 4, then 4 times/day	—	—
2	1 g kanamycin orally 4 times/day	—	1 g neomycin 4 times/day plus 750 mg metronidazole 4 times/day
1	1 g kanamycin orally 4 times/day	1 g erythromycin base plus 1 g neomycin at 1 PM, 2 PM, and 11 PM	1 g neomycin 4 times/day plus 750 mg metronidazole 4 times/day

culture of the organism or identification of its toxin. Because culture takes a prolonged time, it is more expeditious and therefore clinically useful to confirm the diagnosis by identifying the toxin produced by *C. difficile*. Once the diagnosis has been made, treatment involves the administration of vancomycin or metronidazole and discontinuance of other antibiotics that the patient is receiving. Vancomycin or metronidazole is effective in most cases. Rarely, toxic megacolon supervenes, necessitating subtotal colectomy as a lifesaving procedure (Chang, 1985). Newer therapy with antibodies to the toxin hold promise in reducing the morbidity of the disease (Lowy et al, 2010).

INTESTINAL ANASTOMOSES

Regardless of the type of anastomosis or the methods used to perform it, certain fundamental principles must be observed to minimize morbidity and mortality from intestinal surgery. **In urologic procedures in which gut is used, the most common cause of mortality and morbidity within the immediate postoperative period relates to complications involving the bowel,** either with the enteroenterostomy or with the segment interposed in the urinary tract. Therefore it cannot be overemphasized that great care must be taken and proper techniques used in handling bowel in urologic procedures. Unfortunately, the portion of the procedure that involves mobilization of the intestine and reanastomosis often follows a rather lengthy extirpative endeavor and is performed when the surgical team is not fresh. Therefore the following principles should be so firmly ingrained in the surgeon that they are performed without the need to recall each one specifically.

The first principle of proper technique for intestinal anastomoses is adequate exposure. The intestine should be mobilized sufficiently that the anastomosis may be performed without struggling for exposure. If possible, it is preferable to mobilize the intestine sufficiently so that the anastomosis can be performed on the anterior abdominal wall. The area of the anastomosis should be walled off from the rest of the abdominal cavity with Mikulicz pads. This is important so that any inadvertent enteric spills are not distributed throughout the abdominal cavity. The mesentery must be cleared from the bowel segments to be anastomosed for a suitable distance (usually 0.5 cm) from the intestinal clamps or staple line at the severed ends so that good serosal apposition may be achieved without interposed mesentery. Sufficient serosa must be exposed so that the seromuscular sutures or staples can be placed directly in the serosa without traversing the mesentery.

The second principle of performing a proper anastomosis is to maintain a good blood supply to the severed ends of the bowel. The blood supply may be compromised by construction of an anastomosis under tension, excessive dissection or mobilization of the bowel, excessive use of the electrocautery, and tying of the sutures so tightly that the intervening tissue is strangulated. A cut margin of bowel that is pink and bleeds freely suggests that the blood supply has not been compromised; however, hemostasis must be ensured before beginning the anastomosis. The site of transection is selected at a point where the blood supply is adequate to both segments. The mesentery should be transilluminated so that the blood supply may be defined before transection of the bowel segment. In urologic surgery, the location of the transection is elective so that an area may be selected in which excellent arcades supply both sections of the transected segment. The area must be selected with an eye to how deep the mesenteric transection must be for proper segment mobility. After location of the appropriate area where the mesentery is to be transected, it is cleaned from the serosa, severed between mosquito clamps, and tied with 4-0 silk sutures. Alternatively, the mesentery may be transected with the LDS staple device (Covidien Surgical, Mansfield, MA), a bipolar cautery device, or ultrasonic shears.

The third principle involves prevention of local spillage of enteric contents. The best way of preventing spills is to operate on bowel properly prepared (i.e., devoid of feces and collapsed). Stripping of the enteric contents between the fingers both cephalad

and caudad from the proposed transection site and application of a noncrushing occlusive clamp across the bowel make a spill even less likely. The clamp should prevent enteric contents from exiting the cut ends of the bowel without interference with the mesenteric blood supply. After linen-shod clamps are applied and the area is walled off, Allen clamps are applied to the bowel and the bowel is transected between the Allen clamps. An anastomotic staple device may be used to transect the bowel at this point in place of Allen clamps (see later). Local spills and local sepsis have an adverse effect on the healing anastomosis, and it is for this reason that noncrushing occlusion clamps, in addition to an adequate bowel preparation, are advisable. If a spill does occur, it should be caught in the Mikulicz pads if the bowel has been properly walled off as described previously. The isolated segment that is to be used in the reconstructive procedure should be irrigated thoroughly with copious amounts of normal saline. The segment should be walled off. The irrigant is placed in one end of the segment and caught in a kidney basin as it exits the other end. This should be continued until the efflux is clear. This procedure prevents local spills during the ureterointestinal anastomosis and other aspects of reconstruction.

The fourth principle, germane to all intestinal anastomoses, is that there should be an accurate apposition of serosa to serosa of the two segments of bowel to be anastomosed. The anastomosis should be watertight and performed without tension. The bowel must be handled gently with the use of noncrushing forceps. The anastomotic line should be inverted and not everted. There is considerable controversy about this issue in that an everted anastomosis has been shown to heal with few complications. It is clear that when marginal conditions occur, an inverted anastomosis is more likely to remain intact than is the everted anastomosis.

The fifth principle is not to tie the sutures so tightly that the tissue is strangulated. Obviously, the sutures must bring the serosa of the two segments firmly together. Nonabsorbable sutures used for the anastomosis result in a stronger anastomotic line in the early healing phase compared with absorbable sutures, but the difference is minimal and probably not particularly significant.

The final principle involves realignment of the mesentery of the two segments of bowel to be joined. These should be parallel to each other; the surgeon should ensure that there is no twist on completion of the anastomosis.

Factors that significantly contribute to anastomotic breakdown include poor blood supply, local sepsis induced by fecal spillage, drains placed on an intra-abdominal anastomosis, and anastomosis performed in irradiated bowel. Poor blood supply and local sepsis cause ischemia. Drains placed on the anastomosis increase the likelihood of an anastomotic leak, and an anastomosis performed in irradiated bowel is more likely to result in an anastomotic failure than one performed in nonirradiated tissue. The importance of careful technique and adherence to these principles is emphasized by the fact that in one series of urinary intestinal diversion, 75% of the lethal complications that occurred in the postoperative period were related to the bowel. Eighty percent of these patients had received radiation before the intestinal surgery (Mansson et al, 1979). Prior radiation significantly increases the likelihood of serious complications after radical cystectomy (Eswara et al, 2012).

Types of Anastomoses

Intestinal anastomoses may be performed with use of sutures or staples. Properly performed, both have similar complication rates (Catena et al, 2004). In selected circumstances, however, one method may have advantages over the other. **Because there is a high rate of stones that form on surgical staples (Woodhouse and Robertson, 2004), absorbable suture should be used for intestinal segments that are exposed to urine (e.g., suturing intestine to renal pelvis or bladder, closing the proximal end of a conduit [Costello and Johnson, 1984], and forming an intestinal pouch for urine).**

Enteroenterostomy by a Two-Layer Suture Anastomosis

A 3-0 silk holding suture is placed on the mesenteric border just beneath the Allen clamps traversing both segments to be anastomosed, and a second suture is placed on the antimesenteric border similarly just beneath the Allen clamps (Fig. 97-3). It is important that the mesentery be cleaned sufficiently that these sutures can be placed in the serosa under direct vision. A row of silk sutures is placed 2 mm apart between the two holding sutures. This is accomplished by rotating the two Allen clamps away from each other, thus apposing the serosal surfaces. Sutures must traverse the muscularis but should not traverse the full thickness of the bowel. After all sutures have been placed, each is tied and the tails of all the sutures are cut, except those at each end; these are used as holding sutures. The Allen clamps are removed, and hemostasis is achieved, if necessary, with the light application of electrocautery. A 3-0 double-ended chromic intestinal suture is placed in the posterior suture line through all layers and tied to itself. Each end of the suture is then run in a locking fashion away from the midpoint until the mesenteric and antimesenteric borders are approached. As the lateral aspects of the bowel are approached, the suture is converted to a Connell suture (Fig. 97-4), which proceeds onto the anterior

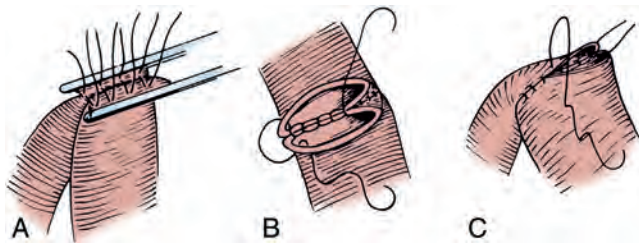


Figure 97-3. Two-layer suture anastomosis. A, Two holding sutures of 3-0 silk have been placed at the mesenteric and antimesenteric border, and the posterior wall is approximated with seromuscular sutures of 3-0 silk. B, A 3-0 intestinal chromic suture is placed through the full thickness of the bowel posteriorly, tied to itself, and run to the lateral borders with a continuous locking suture. At the lateral borders, it is converted to a Connell suture. C, The Connell suture brings the anterior margins together, inverting the suture line. The anastomosis is completed by placement of horizontal mattress seromuscular sutures of 3-0 silk over the anterior suture line (not depicted).

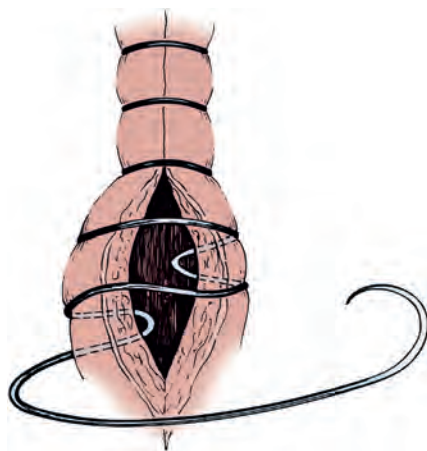


Figure 97-4. Connell suture. The suture traverses the bowel from serosa to mucosa and then from mucosa to serosa on the same side of the anastomosis. The suture is then placed on the opposite side of the anastomosis “outside in–inside out.” The sequence is repeated until the two segments are approximated.

bowel wall. The sutures meet anteriorly in the midline and are tied together. The anterior serosa is then apposed with interrupted 3-0 silk sutures. The noncrushing occlusive clamps are removed, and the mesentery is closed with interrupted 3-0 silk sutures.

Patency of the anastomosis is ensured by palpating the anastomosis with the thumb and forefinger and feeling an annulus of tissue around the fingers. This anastomotic technique is used when the antrum pylorus is removed and intestinal continuity is restored by a Billroth I procedure. It is also the most secure of all the anastomoses and should be used when one is forced to do an anastomosis under less than ideal circumstances.

Enteroenterostomy by a Single-Layer Suture Anastomosis

The single-layer anastomosis for reapproximating bowel is an excellent technique with a low complication rate, that is, a 0.2% anastomotic leakage rate compared with an 8.4% anastomotic leakage rate for a stapled anastomosis in one large series (Leslie and Steele, 2003).

The mesenteries of the two segments of bowel to be anastomosed are aligned, and a 3-0 silk suture is passed through the seromuscular layers of both segments on the mesenteric side; a second suture is similarly placed on the antimesenteric side. The mesenteric suture is tied, and the antimesenteric suture is left untied. The Allen clamps are removed, and hemostasis is achieved with light electrocautery. The critical point of the anastomosis, where most leaks occur, is at the mesenteric border. Leaking usually occurs because the sutures are placed carelessly or the serosa has not been cleaned of mesentery sufficiently that the sutures can be placed through it under direct vision. Because this mesenteric border is the critical area, it is approached first. Two 3-0 silk sutures are placed through the full thickness of the bowel on either side of the mesenteric holding suture. These sutures are placed in such a way as to include more serosa than mucosa, thus causing inversion of the suture line (Fig. 97-5A). Some prefer to use a Gambee stitch at this point, which involves placing the suture through the full thickness of the bowel followed by traversing a small segment of mucosa of each segment of bowel before exiting through the full thickness of the bowel of the other segment (Fig. 97-5B). The two bowel sutures on the mesenteric border are tied, with care taken to invert the suture line, thus apposing serosa. Then 3-0 silk sutures are placed 2 mm apart, both on the anterior and posterior walls, inverting the suture line, thus apposing the serosa of the two bowel segments to each other. On approaching the antimesenteric holding suture, several sutures are placed before all are tied. A patent

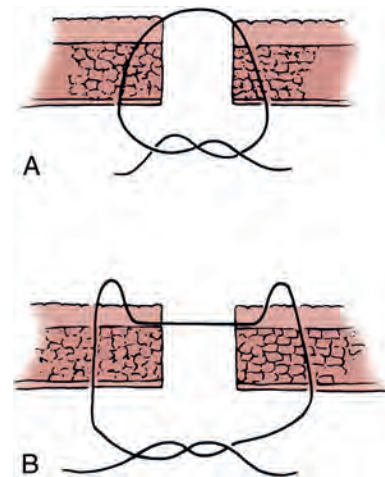


Figure 97-5. A, When it is properly placed, the suture through the intestine should include more serosa than mucosa. B, The Gambee stitch. The suture is placed through the full thickness of the bowel, the mucosa is traversed, and then the mirror image procedure is performed on the segment to be anastomosed.

anastomosis is confirmed by feeling the annulus with the thumb and forefinger as described previously.

End-to-Side Ileocolic Sutured Anastomosis

The transected end of the colon is closed in the following manner (Fig. 97-6). A 3-0 silk suture is placed beneath the Allen clamp on the mesenteric border, and a second suture is placed on the antimesenteric border. These are tied. A 3-0 chromic suture is placed beneath the clamp in a horizontal mattress fashion. Beginning at the mesenteric border, it is tied to itself and the horizontal mattress suture is placed until the antimesenteric border is reached, at which point the suture is again tied to itself. The clamp is removed, and an over-and-over suture is performed with the same chromic suture throughout the full thickness of the bowel until returning to the point of origin (i.e., the mesenteric border is approached). At this point, the suture is again tied to itself. The suture line is buried by approximating the serosa on each side with interrupted 3-0 silk sutures placed 2 mm apart. Our preference is to close the end of the colon similarly to the way one closes the proximal end of a conduit. After a 3-0 silk suture is placed through the serosa on the antimesenteric and mesenteric sides, the clamp is removed and a 3-0 chromic suture is placed through all layers at the mesenteric and antimesenteric end. A Connell suture is used—the two chromic sutures meet in the middle and are tied together. Seromuscular sutures of 3-0 silk are placed to appose the serosal margins.

The mesenteries are aligned, and the ileal serosa is sutured with interrupted 3-0 silk sutures to the colonic serosa 2 mm below a taenia (Fig. 97-7). The taenia is incised the length of the diameter of the ileum adjacent to it. As described earlier for the two-layer anastomosis, a 3-0 double-ended intestinal chromic suture is placed through all layers of the colon and ileum in the midpoint of the posterior wall and run in a locking fashion laterally to either side of the incision in the taenia. At the most lateral border, the suture is converted to a Connell suture and the anterior wall is closed. Seromuscular sutures of 3-0 silk placed from ileum to colon bury the anterior suture line. The mesentery is reapproximated.

Ileocolonic End-to-End Sutured Anastomosis with Discrepant Bowel Sizes

A 3-0 silk suture is placed on the mesenteric border of the ileum and colon (Fig. 97-8). A second 3-0 silk suture is placed on the antimesenteric border of the colon immediately beneath the Allen clamp. The other end of the suture is placed on the antimesenteric border of the ileum at a distance proximal to the Allen clamp so that the serosal lengths between the two sutures of both ileal and colon segment are equal. Thus an equal amount of ileal serosa is applied to the length of colonic serosa bordering the severed end

of bowel. In the seromuscular layers of ileum and colon, 3-0 silk sutures are placed 2 mm apart, thus apposing the serosa of the ileum to the colon. The Allen clamps are removed. Hemostasis is achieved, and the antimesenteric border of the ileum is incised to the level of the most proximal suture in the ileum. Thus the bowel lumens are now of identical size. With a 3-0 chromic double-ended intestinal suture, the posterior row is run in a locking fashion, laterally converting to a Connell suture, and the anterior row is completed. Seromuscular sutures of 3-0 silk bury the anterior suture line.

Stapled Anastomoses

The theoretical benefits of a stapled anastomosis are that it provides for a better blood supply to the healing margin, there is

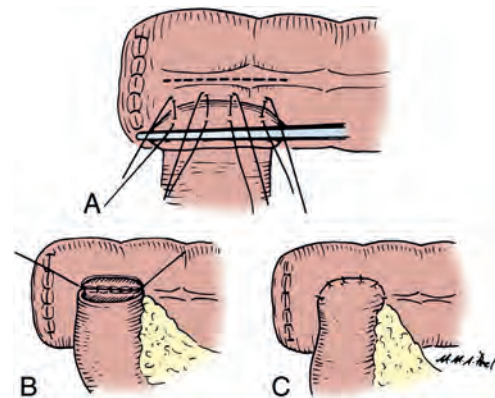


Figure 97-7. End-to-side anastomosis. A, The serosa of the ileum is sutured to the serosa of the colon 2 to 3 mm below a taenia. B, The taenia is opened for a distance sufficient to accommodate the diameter of the ileum. A 3-0 chromic suture is placed through all layers on the posterior wall, tied to itself, run in a locking fashion to both borders, and converted to a Connell suture laterally, thus completing the inversion anteriorly. C, The anterior margin of serosa is reapproximated with interrupted horizontal mattress sutures of 3-0 silk.

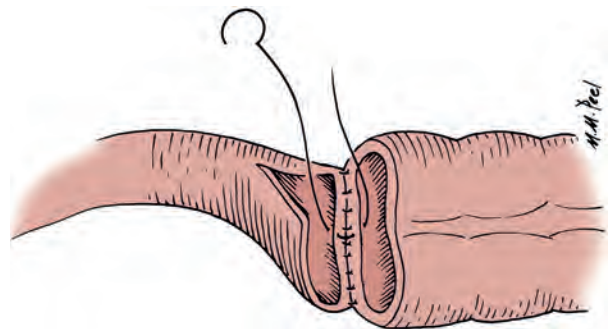


Figure 97-8. Anastomosis of discrepant-sized bowel. A seromuscular suture of 3-0 silk is placed adjacent to each end of the lumen on the mesenteric side. A second 3-0 silk seromuscular suture is placed adjacent to the lumen on the colon and on the antimesenteric border proximal to the cut end of the small bowel at a distance sufficient that when the antimesenteric border is incised, the lumens are the same size. Interrupted seromuscular sutures of 3-0 silk are then placed at 2-mm intervals between the two holding sutures. The small bowel is opened on its antimesenteric border until the opening in the small bowel is the same size as the opening in the colon. A 3-0 chromic suture is placed through all layers, tied to itself, and run laterally in a running locking fashion. At the borders, it is converted to a Connell suture, thus inverting the anterior margin. The anastomosis is completed with interrupted horizontal mattress 3-0 silk sutures that bring the seromuscular layers together anteriorly. This is similar to the closure depicted in Figure 97-3.

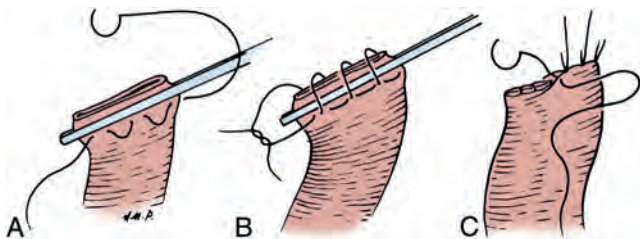


Figure 97-6. Closure of the proximal end of the intestine. A, A 3-0 chromic suture is tied to itself at the antimesenteric border and placed beyond the intestinal clamp in a horizontal mattress fashion until the mesenteric border is reached. The suture is then tied to itself at this point. B, The intestinal clamp is removed, and an over-and-over suture through the full thickness of the bowel returns the chromic suture to its point of origin, where it is again tied to itself. C, Interrupted horizontal mattress seromuscular sutures of 3-0 silk invert the chromic suture line.

reduced tissue manipulation, there is minimal edema with uniformity of suture placement, a wider lumen is constructed, there is greater ease and less time involved in performing the anastomosis, and the length of postoperative paralytic ileus is reduced. When they are placed in intestine through which urine traverses, however, stapled anastomoses using nonabsorbable staples frequently cause stone formation and should be avoided (Costello and Johnson, 1984; Woodhouse and Robertson, 2004).

The TA (transverse anastomosis) stapled anastomosis everts the suture line. Because staples close in a B configuration and do not crush the tissue, theoretically they prevent ischemia at the suture line. This may be obvious when a staple line is used to transect the bowel and bleeding continues to occur. The bleeding points may be lightly electrocoagulated or tied off with fine absorbable suture. Stapled bowel anastomoses have been shown to be as efficacious as hand-sewn anastomoses because both have similar complication rates. **They usually require less time to perform when the techniques are properly learned, but for prolonged procedures they save little if any time when the length of time for the whole procedure is taken into account.** In a large prospective, randomized trial in which a two-layer closure was compared with a staple closure, it was found that the complication rate was the same, but the time required to complete the stapled anastomosis was 10 minutes less than that for the hand-sewn anastomosis; when the total operative time was compared between the two, it was the same (Didolkar et al, 1986). **A comparison of complications between sutured and stapled anastomoses reveals a leak and fistula rate of 2.8% for stapled and 3% for sutured anastomoses (Chassin et al, 1978).** The clinically significant leak rate, however, is only 0.9% (Fazio et al, 1985). A 4.5% incidence of stapled anastomotic leakage has been reported during ileal conduit construction (Costello and Johnson, 1984).

Thus the use of staples or sutured anastomosis is at the discretion of the surgeon. A stapled anastomosis appears to be superior to a hand-sewn anastomosis in an esophageal-intestinal anastomosis and a low rectal anastomosis. In these two areas, the circular stapler allows a more precise anastomosis than is often possible with hand-sewing techniques. Because these are not problems of urologic surgery, staples are used if that is the preference of the surgeon. The one area in urology where I believe the stapling device is superior is in the ileocolonic end-to-side anastomosis. With use of the circular stapling device, a widely patent anastomosis can be achieved expeditiously.

Three staple instruments are commonly used in intestinal reconstruction: the linear stapler, the anastomotic stapler, and the circular stapler. The linear stapler places a double or triple row of staggered staples in a straight line. Depending on the cartridge and instrument chosen, various lengths of staple lines and heights of the closed staples may be chosen. The length is selected according to how long one wants the staple line to be. **The height of staple is selected according to the tissue to be stapled.** Vascular and pulmonary tissues require staples with a closed height of 1 mm (open height of 2.5 mm). Most intestinal anastomoses are performed with medium staples, which have a closed height of approximately 1.5 mm (open height of 3.5 mm). On occasion, for thick tissues, large staples are required that have a closed height of 2 mm (open height of 4.8 mm). If there is any doubt in selecting the staple size, the tissue thickness may be measured with a special instrument used for this purpose. In general, tissues less than 1 mm or more than 3 mm in thickness are not amenable to the use of staples. Recently, staplers with a variety of staple heights within the same cartridge have been introduced and should provide more safety in varying tissue thicknesses.

The anastomotic stapler places two linear double rows of staggered staples. When the knife is advanced, the staple line is divided. The height of the staples is also chosen according to the tissue to be transected.

The circular stapler places two concentric, staggered circular staple rows and cuts the tissue within the circle completely from the surrounding tissue. It may be selected in various diameters and with various heights of staples. The diameter and height are selected

according to the tissue to be anastomosed. The diameter to be selected is determined by sizing the diameter of the tissue to be stapled. Special sizers are available for this maneuver. In most intestinal anastomoses in urology, the height of the closed staple is 1.5 to 2 mm. The following is a description of various types of stapled anastomoses.

Ileocolonic Anastomosis with the Circular Stapling Device

The mesenteric borders are cleared for a distance of 1.5 cm from the cut end of both the colon and the ileum (Fig. 97-9). Holding sutures of 3-0 silk are placed on the mesenteric and antimesenteric border of the colon. Two other holding sutures are placed on the medial and lateral walls of the colon, midway between the mesenteric and antimesenteric sutures. A purse-string suture of 2-0 polypropylene (Prolene) is placed around the ileum no more than 2 mm from the cut end. It is important to take small bites of mucosa to avoid bunching of tissue. Sutures must be placed evenly to avoid a gap. A purse-string instrument can be used for this step, if preferred. The ileal diameter is determined with sizers so that the correct circular stapler diameter instrument may be chosen—usually 25 mm. A purse-string suture is also placed in a circle, 1 cm in diameter, through which a taenia traverses on the medial aspect of the colon. A stab wound is made in the center of the colonic purse-string suture. The distal anvil of the circular stapler is removed, and the instrument is placed through the open end of the colon with its post passed out the stab wound made in the center of the purse-string on the medial wall of the colon. The purse-string is tied tight. The top anvil is then secured to the post, and the ileum is placed over it. The ileal purse-string is tied.

Care must be taken to align the mesenteries at this point. The instrument is approximated with a staple gap of 1.5 to 2 mm. Care must be taken not to catch fat or mesentery in the gap. The instrument is fired and removed by rotatory movement from the colon. Two doughnuts of tissue should be identified on the instrument, and they should have their complete circumference intact with no gaps. With a finger in the open end of the colon and through the anastomosis, seromuscular sutures of 3-0 silk are placed 3 to 4 mm apart around the circumference of the anastomotic line.

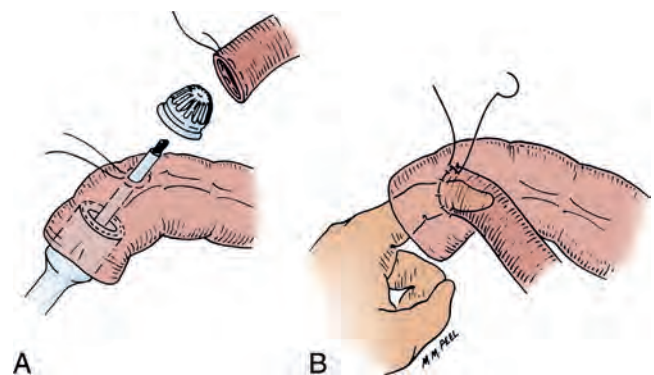


Figure 97-9. Stapled circular anastomosis. A, A purse-string suture of 2-0 polypropylene (Prolene) is placed around the circumference of the small bowel, and a second purse-string suture 1 cm in diameter is placed on a medial taenia 5 to 6 cm from the open end of the colon. The anvil is removed. A stab wound is made in the center of the purse-string suture in the colon, and the circular stapler is introduced through the end of the colon, with its post thrust through the stab wound. B, The anvil is placed on the post and introduced into the end of the small bowel, the purse-string sutures in the small bowel and colon are tied snugly around the post, and the circular stapler is approximated with a gap of 1.5 to 2 mm, with care taken not to include any mesentery in the gap. The anastomosis is completed by placement of interrupted silk sutures around the circumference of the anastomosis.

The transected end of the colon may be closed by the suture technique or by the use of staples. If the end is to be closed with sutures, one 3-0 chromic suture is brought out the mesenteric border and another out the antimesenteric border, and both are tied to themselves with the knots on the inside of the bowel. The two sutures are run toward each other with a Connell stitch until they meet, and then they are tied to each other. The suture line is inverted by placement of a second row of 3-0 silk seromuscular sutures. If staples are preferred, the holding sutures are held up and a linear stapler is applied across the open end. Excess tissue is trimmed and the stapler removed. By holding the holding sutures up, one is secure in applying the staple line to the serosa and mucosa circumferentially around the bowel. Some invert the staple line with seromuscular sutures of 3-0 silk. This is not necessary, however. The mesentery between the two segments is now approximated with interrupted 3-0 silk sutures.

End-to-End Stapled Anastomosis: Ileal-Ileal or Ileocolonic Anastomosis

The antimesenteric border of the two bowel segments to be joined is approximated with a 3-0 silk suture 5 to 6 cm from the cut ends of the bowel (Fig. 97-10). A holding suture is placed through both

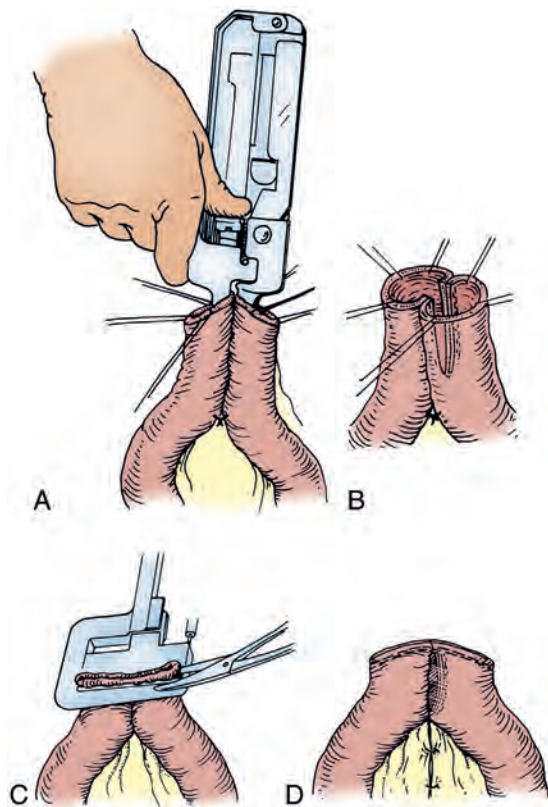


Figure 97-10. Stapled end-to-end anastomosis. A, A 3-0 silk suture is placed 5 to 6 cm from the cut ends of the intestine on the antimesenteric borders of both intestinal segments and tied. Holding sutures are placed around the circumference of both intestinal lumens, one suture securing together the antimesenteric borders of both intestinal segments. The linear anastomotic stapler is placed into the lumens, secured and locked in place, and fired. The knife is advanced. B, The appearance of the intestinal anastomosis after firing of the stapler device. C, The open end of the two intestinal segments is closed with a linear stapler by elevation of the holding sutures while the linear stapler is applied so that the circumferences of the mucosa and serosa are incorporated in the staple margin. D, The anastomosis is completed by closure of the mesentery with interrupted 3-0 silk sutures.

segments of bowel at their cut ends at the midpoint of the antimesenteric borders. Stay sutures are placed at the mesenteric border of each bowel segment, and two other sutures midway between the mesenteric and antimesenteric border on the lateral aspects of the bowel are also placed. The anastomotic stapler is positioned in the lumens of both segments of bowel along the antimesenteric border. The antimesenteric holding suture is pulled up adjacent to the stapler. The anastomotic stapler is locked in place, the staples are fired, and the knife is advanced. The staple lines are inspected for bleeders, which if persistent should be suture ligated with an absorbable suture. It is important for several 3-0 silk sutures to be placed at the apex of the stapled and cut antimesenteric incision. At this point, slight tension on the anastomotic line can place undue stress on the staple margin and cause a leak. The holding sutures are held up, and a linear stapler is placed across the open end of bowel and fired. Care must be taken so that the staples include the serosa in its entire circumference. Excess bowel tissue is excised flush with the instrument before it is disengaged. The mesentery is then reapproximated.

Laparoscopic and Robotic Anastomoses

Laparoscopic and robotic approaches to cystectomy and augmentation cystoplasty have been reported (Guilliotreau et al, 2009; Goh et al, 2012). In these procedures of urinary diversion with continent neobladder or ileal ureter substitution, a purely laparoscopic or robotic technique is possible for bowel resection with the use of endoscopic stapling devices. Proper placement of the trocars is dependent on the need to mobilize the bowel and the procedure for which the bowel is to be used. Trocar placement for mobilization of the distal ileum is illustrated in Figure 97-11. The technique primarily involves the use of endoscopic linear cutting and stapling devices, which can be used to divide small bowel and its mesentery (Figs. 97-12 and 97-13). Reanastomosis purely intracorporeally can be accomplished with the same endo-GIA stapler to reconstitute bowel continuity with a side-to-side functional end-to-end anastomosis (Gill et al, 2000; Potter et al, 2000). An endoscopic TA stapler may be used to complete the bowel closure.

A laparoscopic or robotic ileal conduit can be performed with these techniques. The ureterointestinal anastomosis is performed with freehand laparoscopic suturing. One of the abdominal trocar sites is used to draw the bowel segment through the abdominal wall for stoma construction. Completely laparoscopic orthotopic ileal neobladder has been reported (Gill et al, 2002). The neobladder is constructed by freehand running suture with use of laparoscopic techniques (Fig. 97-14). The results of laparoscopic bowel anastomoses suggest that these anastomoses are safe, but no large series

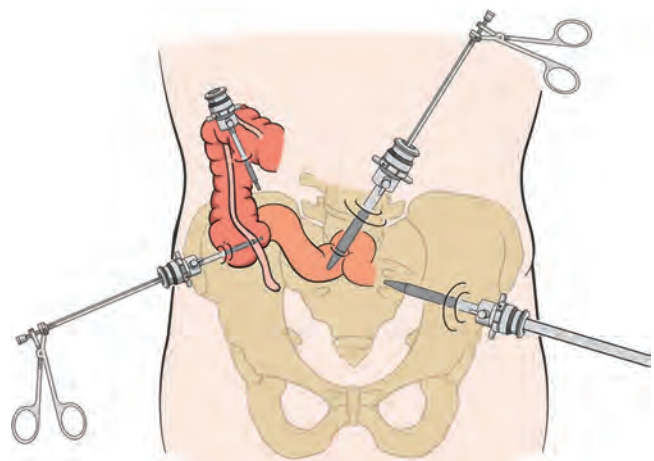


Figure 97-11. Trocar placement for laparoscopic mobilization of the distal ileum.

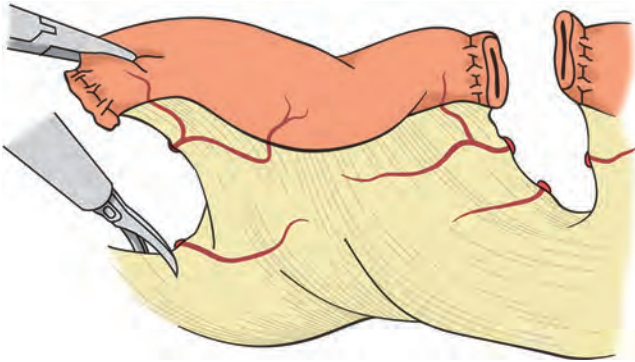


Figure 97-12. Laparoscopic mobilization of a small bowel segment for use in reconstruction. The visceral peritoneum is divided sharply; then the mesenteric vessels are ligated and divided. Staplers, ultrasonic shears, or bipolar cautery devices may be used to divide the mesenteric vessels.

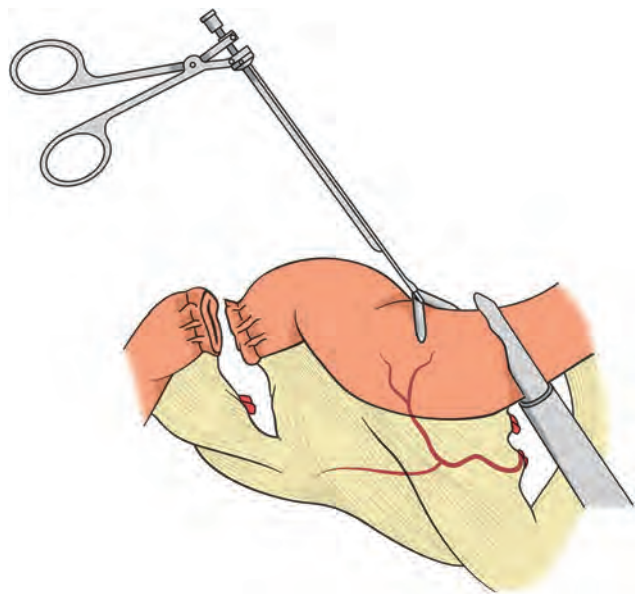


Figure 97-13. The endoscopic gastrointestinal stapler divides the intestinal segment. The staple line must be excised from the segment intended for use in the urinary reconstruction.

that compares open with laparoscopic approaches for bowel anastomosis has been published (Canin-Endres et al, 1999; Rothenberg, 2002). Robotic surgical approaches to radical cystectomy and urinary diversion have become increasingly reported. A barbed monofilament suture may facilitate suturing of the neo-bladder (Tyrizis et al, 2013).

Other approaches to laparoscopic or robotic intestinal surgery include laparoscopic mobilization of the bowel segment and exteriorization of the segment; the anastomosis of the bowel and ureteral anastomoses are then performed in an open fashion through a small laparotomy incision (Fig. 97-15). This is now the preferred approach for many performing laparoscopic or robotic cystoprostatectomy. Purely laparoscopic intestinal anastomoses in radical cystectomy are associated with a much higher complication rate from intestinal and ureteral anastomotic leaks than an exteriorized approach (Stephenson and Gillis, 2008). In radical cystectomy, a small incision is already required for intact specimen removal. An open approach therefore allows direct tactile assessment of the anastomoses.

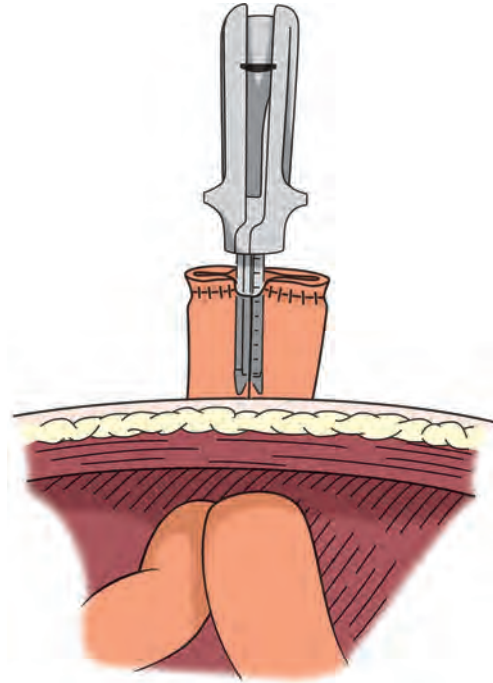


Figure 97-14. Many urologic procedures in which intestinal segments are used for reconstruction involve extirpative surgery in which a small laparotomy is used for specimen removal. In this case the small laparotomy is used to deliver the bowel segment outside the abdomen. Any form of anastomosis may be used by this technique, which also reduces the chance of spillage of intestinal contents.

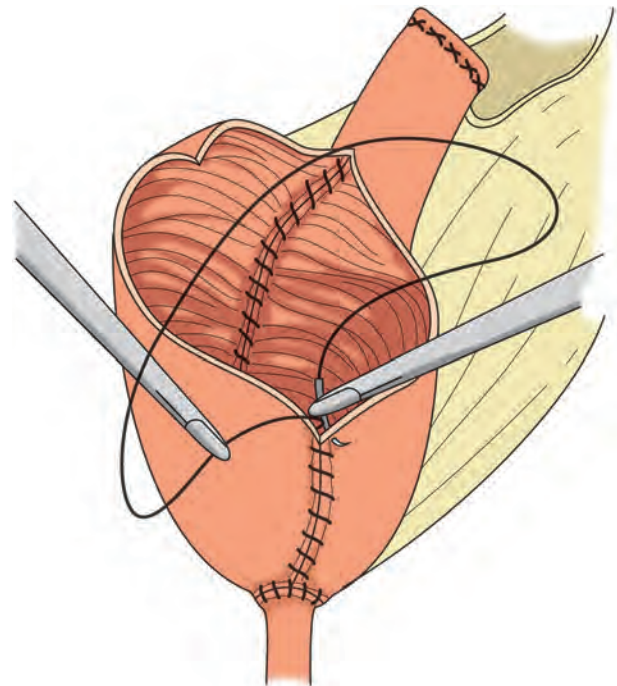


Figure 97-15. Completely intracorporeal laparoscopic construction of a small intestinal neobladder; 2-0 polyglycolic acid suture is used in a running closure of the pouch.

Compression Anastomoses and the Biofragmentable Ring

There is a long history of experimental work on compression anastomoses. These technologies may facilitate natural orifice and minimally invasive surgery. With the most clinical evidence, the biofragmentable ring has proven safe, effective, and time efficient.

Several studies have shown that these intestinal anastomoses are as safe as hand-sewn or stapled anastomoses (Ghitulescu et al, 2003). Other compression devices have been devised but have not gained in popularity (Kaidar-Persno et al, 2008).

Postoperative Care

The patient should not be allowed to begin oral alimentation until bowel function returns after surgery. Coordinated small bowel activity begins within hours after the operative event, and stomach activity may return as early as 24 hours postoperatively. Clear liquids may be begun when the paralytic ileus resolves and bowel activity resumes. If clear liquids are tolerated, the diet may be advanced. This sequence of events generally takes 1 to 4 days. **If the nutritional condition of the patient is impaired preoperatively, a postoperative complication delays oral feeding, or the paralytic ileus is still present on the fifth postoperative day, the patient should receive intravenous nutrition that supplies the total calorie requirement (hyperalimentation). It is preferable to begin the hyperalimentation the day after surgery if any of these complications are anticipated.** Once started, it is discontinued only when oral intake is sufficient to satisfy the body's calorie requirements. Some have advocated the use of a jejunal feeding tube for the early institution of intestinal feeding (Maffezzini et al, 2008).

The use of nasogastric or gastrostomy decompression during the postoperative period of ileus is somewhat controversial. In a prospective study of elective intestinal anastomoses in which 274 patients had postoperative gastric decompression and 261 patients were given nothing by mouth until bowel activity resumed, there was no significant difference in major intestinal complications between the two groups; however, those who did not have gastric decompression showed a much greater incidence of abdominal distention, nausea, and vomiting. It must be understood that only healthy patients with no complications were entered into the study. Sixty percent of the patients initially entered were excluded. Specific exclusion criteria included emergency surgery with peritonitis, extensive fibrous adhesions, enterotomies, previous pelvic irradiation, intra-abdominal infection, pancreatitis, chronic obstruction, prolonged operating time, and difficult endotracheal intubation (Wolff et al, 1988). Meta-analysis of randomized studies of postoperative nasogastric decompression suggests that bowel function returns earlier without a tube. In this study, nonsignificant trends were seen toward fewer pulmonary complications but more wound complications when an NGT was not used (Nelson et al, 2005).

Because of the limitations in the available studies, it is still recommended to use nasogastric decompression in all but the most medically fit patients. Vomiting in the postoperative period increases the risk of aspiration and morbidity in the compromised patient. Moreover, tube decompression allows the administration of ice chips by mouth before enteric activity resumes, thus enhancing the patient's comfort. If the patient has severe pulmonary disease, decompression by placement of a gastrostomy tube at the time of surgery facilitates pulmonary toilet and enhances comfort. In patients who have significant comorbid conditions such as sepsis, consideration should be given to administration of an H₂ blocker and an antacid via the stomach tube every 2 hours as needed to keep the gastric pH above 5 during the period of ileus. By keeping the gastric contents alkaline in these critically ill patients in the postoperative period, the incidence of gastric stress ulceration is markedly reduced.

Because many studies have shown that the absence of an NGT in the postoperative period after intestinal surgery does not increase intestinal anastomotic complications compared with patients in whom NGTs are used, there is a trend to reduce the length of time the NGT is in place. In patients who underwent a radical cystectomy and who were given metoclopramide 10 mg intravenously every 6 hours, until taking fluids orally, Donat and colleagues (1999) found that three quarters of the NGTs could be removed in less than a day. Compared with the standard regimen of NGT drainage, the group given metoclopramide had a much earlier return of bowel function

(Donat et al, 1999). More recent studies also support the safety of early NGT removal (Park et al, 2005).

Complications of Intestinal Anastomoses

The complications that follow anastomoses include leakage of fecal contents, sepsis, wound infections, abdominal abscesses, hemorrhage, anastomotic stenosis, pseudo-obstruction of the colon (Ogilvie syndrome), and intestinal obstruction. These untoward events increase morbidity and are frequently major contributors to mortality (Hautmann et al, 2010). The complication rates for elective colocolonic and ileocolonic anastomoses performed in prepared bowel with contemporary technique are intestinal leak, 2%; hemorrhage, 1%; and stenosis or obstruction, 4%. These complications require reoperations in 1% of the patients and result in death in 0.2% of patients (Jex et al, 1987). The mean time to diagnose an anastomotic leak is 12 days postoperatively; some have occurred even after 30 days (Hyman et al, 2007). Many of the complications of radical cystectomy are attributable to the use of intestinal segments for urinary diversion (Takada et al, 2012).

Fistulas

Fistulas in the postoperative period are of two types, fecal and urinary. These generally occur within the first several weeks after the operative event. They frequently result in sepsis and markedly increase morbidity and mortality. Fecal fistulas occur in 4% to 5% of patients (Sullivan et al, 1980; Beckley et al, 1982). Sepsis is a common complication of these untoward events and carries with it a mortality of 2% (1 of 47 patients) (Hill and Ransley, 1983). In long-term evaluation, approximately 10% of urinary diversion patients will suffer from fistulas (Gilbert et al, 2013).

Sepsis and Other Infectious Complications

Wound infections, pelvic abscesses, and wound dehiscences may complicate the immediate postoperative period. Although wound dehiscences and pelvic abscesses are rare complications, morbid wound infections occur with an incidence of 5% (3 of 62 patients) (Loening et al, 1982). Many of these complications may be averted by operating on a properly prepared bowel, by walling off the intestine with Mikulicz pads while the anastomosis is being completed, and by irrigating the intestinal segment to be used in the reconstruction until it is free of any residual enteric contents before it is manipulated and its contents are spilled in the abdomen and pelvis. The overall septicemia rate after radical cystectomy is currently 3.6%, with a 17% mortality rate (Davies et al, 2009). When assessed for cumulative incidence of infectious complications, nearly 45% of patients after urinary diversion will require treatment (Gilbert et al, 2013).

Bowel Obstruction

The incidence of intestinal obstruction after abdominal procedures for urinary intestinal diversion differs according to whether the stomach, ileum, or colon is used for the diversion. In patients who have had a segment of stomach or ileum removed for the diversion, there is a 10% incidence of postoperative bowel obstruction requiring treatment. When the colon is used, the incidence of postoperative obstruction requiring an operation is 5% (Table 97-3). Half of the bowel obstructions occur in the early postoperative period. In one series, after radical cystectomy and ileal conduit, 15% of the patients had a mild obstruction in the first 6 months that responded to conservative management, whereas 3% required an operation to relieve the obstruction during this period. The occurrence of obstruction after this 6-month period was much less frequent (Sullivan et al, 1980). More recently, a 10.5% incidence of reoperation for bowel obstruction was noted in a large series of radical cystectomy patients (Varkarakis et al, 2006). Bowel obstruction can be a morbid event: A significant number of patients who develop obstruction after an ileal conduit and require an

TABLE 97-3 Complications of Urinary Intestinal Diversion*

COMPLICATION	TYPE OF DIVERSION	NO. OF PATIENTS (COMPLICATION/TOTAL NO.)	INCIDENCE (%)
Bowel obstruction	Ileal conduit	124/1289	10
	Colon conduit	9/230	4
	Gastric conduit	2/21	10
	Continent diversion	2/250	0.8
Ureteral-intestinal obstruction	Ileal conduit	90/1142	8
	Antireflux colon conduit	25/122	20
	Colon conduit	8/92	9
	Continent diversion	16/461	4
Urine leak	Ileal conduit	23/886	3
	Colon conduit	6/130	5
	Continent diversion		
	Ileum	104/629	17
	Colon	5/123	4
Stomal stenosis, hernia	Ileal conduit	196/806	24
	Colon conduit	45/227	20
	Continent diversion	28/310	9
Renal calculi	Ileal conduit	70/964	7
	Antireflux colon conduit	5/94	5
Pouch calculi	Continent diversion	42/317	13
Acidosis requiring treatment	Ileal conduit	46/296	16
	Antireflux colon conduit	5/94	5
	Gastric conduit	0/21	0
	Continent diversion		
	Ileum	21/263	8
	Colon/colon-ileum	17/63	27
Pyelonephritis	Ileal conduit	132/1142	12
	Antireflux colon conduit	13/96	13
	Continent diversion	15/296	5
Renal deterioration	Ileal conduit	146/808	18
	Antireflux colon conduit	15/103	15

*Composite from the literature. Follow-up averages 5 years for ileal conduits, 3 years for colon conduits, 2 years for gastric conduits, and 2 years for continent diversions.

Data is from the following sources, which can be found in this chapter's reference list on the Expert Consult website: Jaffe et al, 1968; Castro and Ram, 1970; Malek et al, 1971; Smith, 1972; Schmidt et al, 1973; Richie, 1974; Flanigan et al, 1975; Schwarz and Jeffs, 1975; Shapiro et al, 1975; Middleton and Hendren, 1976; Althausen et al, 1978; Elder et al, 1979; Hagen-Cook and Althausen, 1979; Pitts and Muecke, 1979; Sullivan et al, 1980; Beckley et al, 1982; Loening et al, 1982; Adams et al, 1988; Boyd et al, 1989; Madersbacher et al, 2003; Studer et al, 2006; Nieuwenhuijzen et al, 2008.

operation die. The most common cause of the obstruction is adhesions, followed by recurrent cancer. These two causes account for the great majority of the cases. Volvulus and internal hernia account for far fewer cases (Jaffe et al, 1968). Rarely, severe stenosis or obstruction at the anastomotic suture line occurs. Stenosis is a result of edema, poor technique, or performing the anastomosis on ischemic bowel (Fig. 97-16); obstruction is a result of improper technique.

The incidence of postoperative bowel obstruction may be reduced by using nonirradiated bowel, performing the anastomosis on well-vascularized bowel, closing all apertures, reperitonealizing the isolated segment, decompressing the gastrointestinal tract for an adequate time, placing omentum over the anastomosis, and reconstituting the pelvic floor after exenterative surgery. Orthotopic neobladders appear to result in fewer bowel obstructions than ileal conduits or cutaneous reservoirs (Van Hemelrijck et al, 2013). The isolated segment is reperitonealized by tacking its antimesenteric border to the lateral abdominal sidewall peritoneum. The proximal mesenteric border should be tacked to the posterior parietal peritoneum because failure to obliterate this potential space has resulted in entrapment of bowel, causing a bowel obstruction. Placing the sigmoid colon in the area may close

the pelvic space left after an anterior exenteration. This effectively prevents small bowel from herniating into the raw pelvis. Omentum may also be mobilized and used to fill any space the sigmoid colon does not fill. In a total exenteration, sufficient sigmoid colon is not available and the omentum is often not bulky enough to fill the pelvis and thus prevent small bowel from filling the denuded pelvis. This situation is of particular concern in patients who must receive postoperative pelvic irradiation. The bowel may be kept out of the pelvis in these patients by reconstructing the pelvic floor with polyglactin mesh. The mesh is sutured along the posterior pelvic brim to the sacral promontory and presacral fascia and laterally to the adventitia of the iliac vessels. Laterally and anteriorly, it is sewn to the peritoneum two thirds of the distance between the pubis and umbilicus. Omentum is then brought down, placed over the mesh, and sutured in position. This effectively excludes the bowel from the pelvis for 4 to 6 weeks while postoperative irradiation is being administered (Sener et al, 1989).

Hemorrhage

Hemorrhage is a rare complication of intestinal anastomoses. It is much more likely to occur when stomach is used and a Billroth I



Figure 97-16. Upper gastrointestinal tract series illustrates a small bowel stricture (arrow) at the ileoileostomy after ileal conduit urinary diversion. At the time of the initial ileoileostomy, the anastomotic suture line appeared bluish. At subsequent exploration, a bowel lumen of only 2 mm was found. The serosa at the anastomotic site was fibrotic.

anastomosis is constructed. It is usually caused by failure to secure bleeding at the time of anastomosis or anastomotic ulcers that develop on the suture line.

Intestinal Stenosis

Intestinal stenosis occurs at two distinct times: in the immediate postoperative period and during the long term. Intestinal stenosis in the immediate postoperative period is caused by technical mishaps or edema. Edema resolves by continuing the intestinal decompression, whereas technical mishap requires a reoperation. During the long term, it is likely caused by ischemia or perienteric infection. [Figure 97-16](#) shows an upper gastrointestinal tract series of a severe intestinal stenosis caused by ischemia. At the time of the ileoileostomy, the suture line was blue. Chronic symptoms of partial small bowel obstruction occurred in the postoperative period.

Pseudo-Obstruction

Pseudo-obstruction of the colon, or Ogilvie syndrome, on rare occasion may complicate the early postoperative period. Its cause is not understood. **Pseudo-obstruction usually occurs within the first 3 days postoperatively in patients with multiple medical illnesses.** The patient develops severe abdominal pain, and a radiograph of the abdomen reveals a dilated cecum. A gentle water-soluble contrast enema eliminates the possibility of a mechanical obstruction. In the presence of a rising leukocyte count or cecum that is increasing in size and exceeds 12 to 15 cm in diameter, rupture may be imminent. Under these circumstances, an emergency cecostomy should be performed ([Clayman et al, 1981](#)). In less acute circumstances, endoscopic decompression may be attempted ([DeGiorgio and Knowles, 2009](#)).

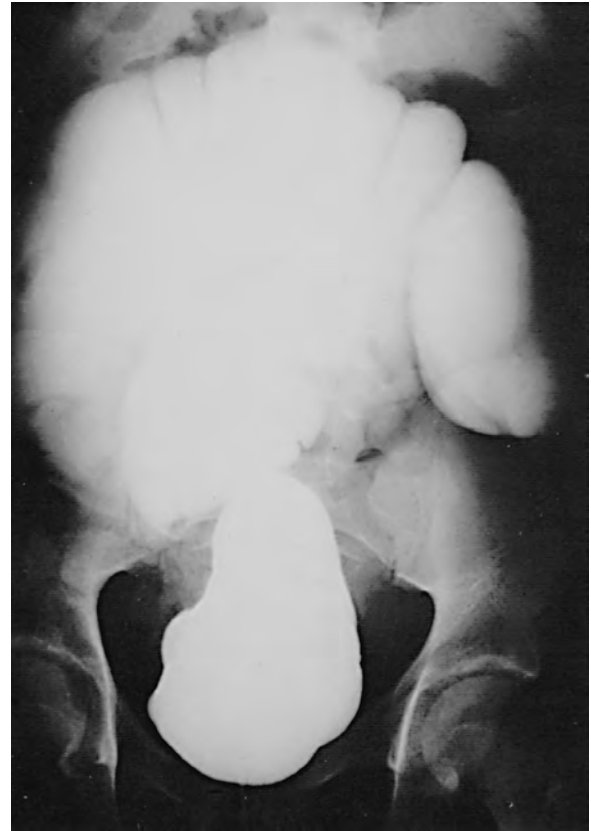


Figure 97-17. Volvulus of an orthotopic right colon bladder. This segment enlarged markedly because of the patient's lack of adherence to a regimen of frequent intermittent catheterization.

Complications of the Isolated Intestinal Segment

Intestinal Stricture

Strictures of intestinal segments are usually late complications primarily occurring in conduits, although they have been described in ileal ureters as well. **The stricture is thought to be a consequence of lymphoid depletion of the intestine exposed to urine.** The lymphoid depletion contributes to persistent infection, which may result in midloop stricture, bacterial seeding of the upper tracts, and renal deterioration ([Tapper and Folkman, 1976](#)). Because of the persistent infection and lack of intestinal resistance to the detrimental action of bacteria, submucosal edema with fibrosis and stricture formation occurs. The intestinal segment may also be blocked by encroachment of hypertrophied mesenteric lymph nodes. **Hypertrophied mesenteric lymph nodes, submucosal lymphoid depletion, edema, and fibrosis are commonly found when intestinal segments that have been chronically exposed to urine are examined pathologically.**

Elongation of the Segment

Another complication of the intestinal segment is elongation, occasionally resulting in massive enlargement. When this occurs in conduits or ureteral substitutes, there is usually a distal obstruction. In continent diversions, it may signal failure to catheterize the pouch frequently enough. If allowed to persist, the increased pressure may result in deterioration of renal function. Enlargement and elongation of the intestine may also result in a volvulus of the segment ([Fig. 97-17](#)).

Abdominal Stomas

Two types of stomas may be made on the anterior abdominal wall: those that are flush with the skin and those that protrude. The flush

stoma is preferable for the continent type of diversion in which intermittent catheterization is carried out and over which a small dressing is placed. The stoma that protrudes is preferable when a collection device is worn. **A properly protruding stoma worn with an appliance results in a lesser incidence of stomal stenosis and a better appliance fit with fewer peristomal skin problems. There are two types of protruding stomas: the end stoma and the loop end ileostomy. Most complications of stomas are the result of technical errors in their construction. Therefore to minimize such complications, specific technical points must be rigidly followed.**

The site of the stoma should be selected preoperatively. This is done by marking the stomal site with the patient in the sitting position, as well as in the supine position; care is taken to place it over the rectus muscle at least 5 cm away from the planned incision line. The point chosen should be well away from skin creases, scars, the umbilicus, belt lines, and bone prominences. A site in which radiotherapy has previously injured the area should be avoided. **All stomas should be placed through the belly of the rectus muscle and be located at the peak of the infraumbilical fat roll.** If the stoma is placed lateral to the rectus sheath, a parastomal hernia is likely to occur. The bowel should traverse the abdominal wall perpendicular to the peritoneal lining (i.e., it should come straight out). One should avoid trimming fat or epiploic appendages from around the margin of the stoma, and the appliances should be applied in the operating room.

The stoma should be brought through a circular incision made at the predetermined site. A perfectly circular opening in the skin may be made by placing the finger hole of a Kelly clamp at the desired point and grasping the skin in the center of the hole with a Kocher clamp. Pulling up on the Kocher clamp and pushing the handle of the Kelly clamp against the abdominal wall allows for a small button of skin to be removed with a single pass of the knife. This makes a perfectly circular opening in the skin. However, the tendency to remove too much skin is great, resulting in a circular opening that is too large. To avoid this complication, one should not cut the skin flush with the Kelly clamp but rather immediately beneath the Kocher clamp. The subcutaneous tissue is left intact. This is spread, not excising any fat, because the fat falls back adjacent to the bowel and eliminates any dead space. Kocher clamps are placed on the fascia in the incision and pulled medially so that when the fascia and peritoneum are incised, they are incised directly over the skin line and thus do not result in angulation of the gut when the abdominal incision is closed. The fascia is incised in a cruciate manner, and the rectus muscles are spread. The peritoneum is incised. The opening should accommodate two fingers snugly.

Nipple Stoma: "Rosebud"

A Babcock clamp is placed through the opening, and the bowel is grasped and brought out for a distance of 5 to 6 cm to make a nipple of about 2 to 3 cm in length (Fig. 97-18). Two 3-0 chromic sutures are placed through the seromuscular layer of the bowel and

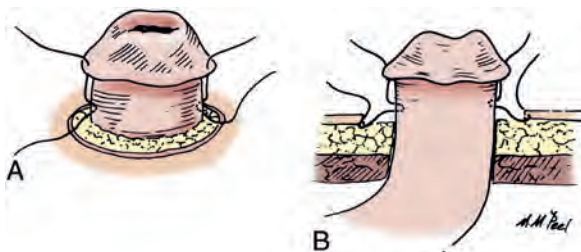


Figure 97-18. A and B, Nipple stoma. Five to 6 cm of intestine are brought through the abdominal wall. The serosa is scarified, and quadrant 3-0 chromic sutures are placed through the full thickness of the distal end of the intestine. Each suture is placed in the seromuscular layer 3 cm proximal and then secured to the dermis before it is tied.

the peritoneum on the anterior abdominal wall. Alternatively, the serosa may be sutured to the fascia with two 2-0 chromic sutures. The mesentery is aligned in its normal anatomic direction before the serosa is sutured to the peritoneal wall. The ileum is usually curved in a concave manner toward the mesentery. If the curvature is severe, the mesentery may be partially incised 1 cm from the bowel wall (Fig. 97-19). Thus a portion of mesentery is preserved along the entire length of the bowel. This should straighten the curve in the bowel significantly if not completely. Four 3-0 chromic sutures are placed in quadrants through the full thickness of the bowel edge and through the seromuscular layer of the bowel 3 to 4 cm from the cut edge and then through the subcuticular skin layer. Sutures should not traverse the full thickness of the skin but should be placed through the subcuticular and subdermal layers only.

When the sutures are tied, the bowel is everted and forms a nipple. A more secure nipple may be made by performing multiple myotomies through the seromuscular layer of the bowel above the skin line before construction of the nipple. The myotomies adhere serosa to serosa and reduce the risk of stomal retraction. This is particularly appropriate for patients who are obese.

Flush Stoma

Quadrant sutures of 3-0 chromic are placed through the full thickness of the bowel and subsequently passed through the subdermal layer of the skin and tied. Several sutures are placed between the quadrant sutures from bowel to subdermal skin. This constructs a flush stoma that has a 1-mm raised margin.

Loop End Ileostomy

Obese patients have a thick abdominal wall and often a thick, short ileal mesentery. This makes construction of an end ileal stoma extremely difficult. **The loop end ileostomy obviates some of these problems and is usually easier to perform than the ileal end stoma in the patient who is obese (Fig. 97-20).** To construct this type of stoma, the distal end of the ileum is closed as described previously for closing the proximal end of an intestinal segment, and a loop is brought up through the belly of the rectus muscle and onto the anterior abdominal wall. This avoids bringing the mesenteric border onto the abdominal wall and prevents one side of the ileostomy from being involved with mesentery. A slightly larger skin opening is required than for the end stoma. A 3-cm disk of skin is

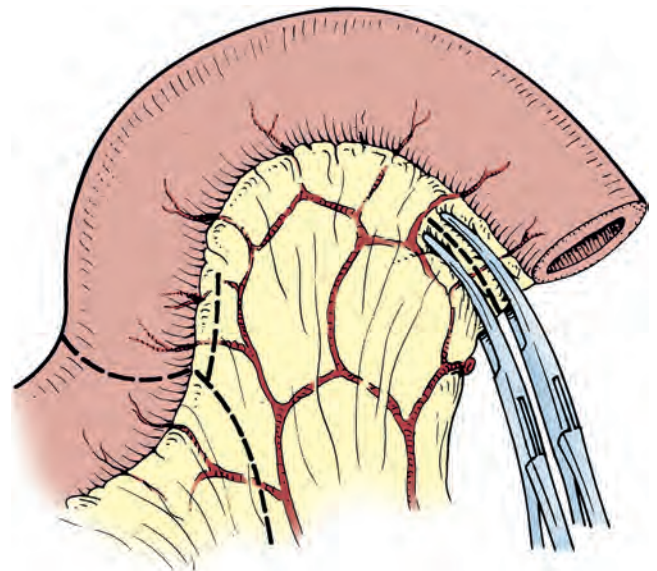


Figure 97-19. If it is tethered by the mesentery, the bowel may be straightened by incising the mesentery several centimeters away from the serosa and parallel to the bowel.

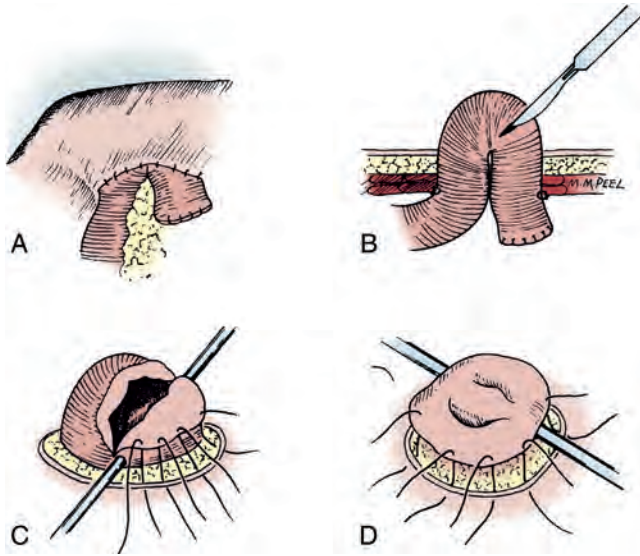


Figure 97-20. Loop end ileostomy. A, After the distal end of the loop is closed and the bowel is drawn through the rent in the abdominal wall, the bowel is held in place by a rod passed through the mesentery. The mesentery is realigned, and the peritoneum is sutured to the serosa of the bowel circumferentially. B, A transverse incision is made in the bowel four fifths of the loop distance cephalad. C, The cephalad portion of the stoma is simply sutured to the dermal layer of skin with interrupted 3-0 chromic sutures. D, On the inferior aspect of the incision, 3-0 chromic sutures are placed through the full thickness of the cut edge, then through the seromuscular layer, and then through the dermis. This everts the caudal portion of the stoma.

removed. The subcutaneous tissue is spread, the fascia incised, the rectus spread, and the peritoneum incised as described earlier. The opening should admit two fingers comfortably. The loop may be pulled through the opening in the abdominal wall by passing an umbilical tape through a small opening in the mesentery at a distance from the distal end that is sufficient to leave that end in the abdomen when the loop has been pulled through the abdominal wall. By gentle traction on the umbilical tape, the loop is brought onto the abdomen.

The distal portion of the bowel is brought through the opening such that the closed end lies cephalad to the body of the segment. When a sufficient amount of loop protrudes beyond the skin edge, a small rod is placed through the hole in the mesentery at the apex of the loop and holds the bowel on the anterior abdominal wall during suturing. If the rent in the rectus muscle is too large, it may be closed with interrupted 0 chromic sutures from within the abdomen. The serosa is sutured to the peritoneum on the anterior abdominal wall. The bowel wall is opened in a transverse direction at a point four fifths of the distance cephalad to the most caudal portion of the loop. With 3-0 chromic sutures, the full thickness of the caudal incision in the bowel is sutured back to itself (serosa) and then to the dermis as in the rosebud technique. The cephalad nonfunctional opening is sutured directly to the dermis. The rod is sutured to the skin and left in place for 7 days.

The Turnbull loop stoma results in a lesser incidence of stoma stenosis but a higher incidence of parastomal hernias (Emmott et al, 1985). Overall, the two types of stoma are functionally equivalent over time (Chechile et al, 1992). Stomas for the colon may be constructed in much the same way as end stomas for the ileum. Their suturing, however, is usually more flush than everted.

Complications of Intestinal Stomas

Complications of the abdominal stoma are the single most common problem encountered in the postoperative period after urinary intestinal diversion. Early complications of abdominal

stomas include bowel necrosis, bleeding, dermatitis, parastomal hernia, prolapse, obstruction, stomal retraction, and stomal stenosis. At some point, virtually every patient has one of these complications. Many of these complications can be reduced by proper construction of the stoma. If periodic visits to the enterostomal therapist are made, products for skin care are appropriately used, nonirritative stomal adhesives are used, the urine in the collection device is maintained acidic, and properly fitting collection devices are used, most stomal complications can be significantly reduced and many eliminated.

Parastomal skin lesions may be classified as irritative, which are manifested by hypopigmentation, hyperpigmentation, and skin atrophy; erythematous erosive lesions, which appear as macular lesions, scaling of the skin, and loss of the epidermis; and pseudoverrucous, which are wartlike lesions (Borglund et al, 1988).

Stomal stenosis has been reported, on average, in 20% to 24% of patients with ileal conduits and 10% to 20% of patients with colon conduits (see Table 97-3). This incidence has been considerably reduced by better attention to stomal care and better-fitting appliances (Eisenberg et al, 2014). Stomal stenosis is less for loop stomas than for end stomas. Parastomal hernias occur rarely (1% to 4%) with end stomas but are more likely to occur with loop stomas, with reported incidences ranging from 4% to 20%. Incidence of stenosis of catheterizable stomas is high, reaching more than 50% in children (Barqawi et al, 2004). Stoma-related complications appear to be more common in an umbilically placed stoma versus one in the abdominal wall (De Ganck et al, 2002). Others have reported excellent long-term results with few complications in the concealed umbilical stoma (Glassman and Docimo, 2001).

Bleeding, stomal stenosis, and dermatitis can be markedly reduced by attention to parastomal skin care and by the use of a properly fitting appliance around a protruding stoma. The other complications are minimized by proper surgical technique.

Parastomal hernia occurs frequently after ileal loop urinary diversion, with an incidence of 2% to 6.6% (Gilbert et al, 2013). It can be effectively treated with open repair (Franks and Hrebinko, 2001; Ho and Fawcett, 2004). Laparoscopic approaches have also been reported with mixed results. One series reported a 56% failure rate within 6 months of laparoscopic parastomal hernia repair with Gore-Tex mesh (Safadi, 2004). This contrasts with the high success rate reported in another small series (Kozlowski et al, 2001).

Massive bleeding from the conduit occasionally occurs, usually as a result of varices. There have been several interesting reports of patients who have developed ileal conduit varices generally as a result of hepatic dysfunction and portal hypertension. Treatment by transhepatic portal-systemic shunt and transhepatic angiography and embolization is a relatively minimally invasive technique that has promise, and its use is worthwhile in these difficult patients (Lashley et al, 1997; Medina et al, 1998).

URETEROINTESTINAL ANASTOMOSES

The ureter may be anastomosed to the colon or small bowel in a refluxing or nonrefluxing anastomosis. There is considerable controversy as to whether a nonrefluxing or refluxing anastomosis is desirable in urinary tract reconstruction. Regardless of type of diversion, renal failure has been seen in 12.5% of patients over the long term (Gilbert et al, 2013). Deterioration of the upper tracts for ileal and colon conduits has been reported in 10% to 60% of the patients (Koch et al, 1992; Samuel et al, 2006). In one series, 49% of the upper tracts showed changes after conduit diversion, 16% of which had an increase of the blood urea nitrogen of 10 mg/dL or more (Schwarz and Jeffs, 1975). Deterioration of the upper tracts is usually a consequence of lack of ureteral motility, infection, or stones and less commonly caused by obstruction at the ureteral-intestinal anastomosis. Because bacteriuria occurs in almost all conduits and because the intestine certainly does not inhibit and may, in fact, promote bacterial colonization, many have suggested that a nonrefluxing anastomosis would minimize the incidence of renal deterioration.

The evidence that suggests a nonrefluxing system in urinary intestinal diversions is desirable comes from several observations. In a group of patients who had nonrefluxing colon conduits constructed, those whose anastomoses remained nonrefluxing had a lesser incidence of renal deterioration than did those in whom the antireflux anastomosis failed. Follow-up for 9 to 20 years revealed that 79% (22 of 28 patients) of the refluxing renal units deteriorated, whereas only 22% (11 of 51 patients) of the nonrefluxing units deteriorated (Elder et al, 1979; Husmann et al, 1989). Others have reported that in continent diversions, the majority of patients who experience reflux show upper tract dilation and deterioration, whereas few show upper tract deterioration when a nonrefluxing anastomosis is present (Kock et al, 1978). Similar findings have been reported in experimental animals.

If a nonrefluxing ureteral-colonic conduit diversion is constructed, only 7% of the renal units show evidence of pyelonephritic scarring after 3 months. If a refluxing anastomosis is constructed, 83% of the renal units show scarring. Half of the conduits in both groups have significant bacteriuria (Richie and Skinner, 1975). Others have not found the same high incidence of renal deterioration associated with ureteral-intestinal reflux. One group of investigators studying colon conduits noted no difference in the incidence of renal deterioration regardless of whether the colon conduit demonstrated reflux; 17% (5 of 29) of nonrefluxing renal units showed deterioration compared with 18% (5 of 27) of refluxing units (Hill and Ransley, 1983). In another series, only 3 of 135 renal units with refluxing ureteral-intestinal anastomoses that were unobstructed showed evidence of renal deterioration (Shapiro et al, 1975). A more recent study compared refluxing and nonrefluxing ureteral-intestinal anastomoses in 58 patients with conduit diversions; 56 renal units were refluxing and 60 renal units were nonrefluxing. There was no difference in renal deterioration or in pyelonephritis between the two groups. Ureteral-intestinal stricture formation occurred in 2% of refluxing units as opposed to 13% of nonrefluxing units (Pantuck et al, 2000). A high-capacity, low-pressure reservoir may not require antirefluxing anastomoses (Hohenfellner et al, 2002).

It does not appear that conduit pressures are transmitted to the renal pelvis. The pressure within the renal pelvis in refluxing conduit diversions is not elevated above normal, and it is not dependent on the segment of bowel used (i.e., ileum or colon) (Magnus, 1977; Kamizaki and Cass, 1978; Hayashi et al, 1986). Peristaltic ureteral contractions apparently dampen pressure transmission from intestine to renal pelvis, attesting to the importance of normal ureters. When bowel is substituted for the ureter, it does not appear that it makes any difference whether there is reflux at the bladder. The voiding pressure is blunted by the distensible bowel segment. Indeed, in one study of continent diversions in which a segment of ileum formed the pouch to which the ureters were anastomosed, radionuclide voiding cystography failed to detect reflux to the kidneys (Waidelich et al, 1998). Moreover, there is no difference in ileal and colon conduits between those who experience reflux and those who do not in renal function measured 2 to 5 years postoperatively (Mansson et al, 1984). Also, the successful construction of an antirefluxing anastomosis does not prevent bacterial colonization of the renal pelvis. In six of eight patients with nonrefluxing enterocystoplasties and one patient with a nonrefluxing colon conduit in whom the absence of reflux was documented by loopogram, percutaneous renal pelvic aspiration revealed positive cultures (Gonzalez and Reinberg, 1987). One stated advantage of a refluxing anastomosis in patients who have urothelia and are prone to malignant change is that the upper tracts may be observed by periodic introduction of contrast material into the conduit. From these studies, it appears that reflux associated with impaired ureteral peristalsis in the presence of bacteriuria or obstruction results in renal deterioration, but it has not been established for either conduit or continent diversions that reflux associated with the normal ureter in the absence of obstruction is detrimental to the adult kidney.

Although many techniques have been described to make the various types of ureterointestinal anastomoses, certain basic surgical principles are germane to all the anastomoses regardless of type. Only as much ureter as needed should be mobilized so that there is no redundancy or tension on the anastomosis. Mobilization should not strip the ureter of its periadventitial tissue because it is in this tissue that the ureter's blood supply courses. The ureter should be cleaned of its adventitial tissue only for 2 to 3 mm at its most distal portion where the ureter-intestinal mucosa anastomosis is to be performed. The ureterointestinal anastomosis must be performed with fine absorbable sutures, which are placed so that a watertight mucosa-to-mucosa apposition is constructed. The bowel should be brought to the ureter and not vice versa (i.e., the ureter should not be extensively mobilized so that it can be brought into the wound to the bowel lying on the anterior abdominal wall). At the completion of the anastomosis, the bowel should be fixed to the abdominal cavity, preferably adjacent to the site of the ureterointestinal anastomosis. If possible, the anastomosis should be retroperitonealized or a pedicle flap of peritoneum should be placed over the anastomosis.

In those diversions in which the intestinal stoma is brought to the abdomen and the proximal end of the bowel fixed to the retroperitoneum, there are two places where the bowel may be conveniently fixed to the retroperitoneum without jeopardizing mesenteric blood supply. The most convenient point of fixation is below the root of the small bowel mesentery at the level of the pelvic brim. The ureterointestinal anastomosis may be retroperitonealized at the level of the pelvic brim, thus fixing the bowel segment to the posterior body wall. In situations in which the ureters are short, a more cephalad fixation to the posterior peritoneum may be accomplished by placing the proximal end in the right upper quadrant cephalad to the takeoff of the right colic artery and immediately below the duodenum. This is a relatively avascular area and places the intestine fairly close to the right and left kidneys, thus reducing the length of ureter required to reach the intestinal segment.

Perhaps one of the most difficult complications of ureterointestinal anastomoses to manage is a stricture. In general, strictures are caused by ischemia, a urine leak, radiation, or infection. The incidence of urine leak for all types of ureterointestinal anastomoses is 3% to 5% (see Table 97-3). This incidence of leak can be reduced nearly to zero if soft Silastic stents are used. In one series of ureterointestinal anastomoses done at the same institution, the nonstented group had a 2% anastomotic leak and a 4% stricture rate. When non-Silastic rigid stents were used, there was a 10% incidence of stricture. When a soft Silastic stent was used, however, there were no strictures or leaks (Regan and Barrett, 1985). In a similar series in which colon conduits were constructed after gynecologic exenterative operations, the nonstented group had an 18% leak rate and an 18% stricture rate, whereas those who had been stented had a 3% leak rate and an 8% stricture rate (Beddoe et al, 1987). Early postoperative metabolic complications were reduced in a randomized study of stented versus nonstented anastomoses (Mattei et al, 2008). Thus the evidence indicates that modern soft Silastic stents are effective in reducing the leak rate, subsequent stricture formation, and postoperative complications. Better technique and better suture materials have also reduced the incidence of stricture in nonrefluxing anastomoses. In a series of nonrefluxing ureterocolonic anastomoses, researchers reported an 8% incidence of stricture formation (Stein et al, 1996b).

In constructing a submucosal tunnel in those procedures in which a nonrefluxing anastomosis is made, it is often helpful to inject saline with a 25-gauge needle submucosally to raise the mucosa away from the seromuscular layer. This makes dissection considerably easier (Menon et al, 1982).

These principles of surgical technique are common to all ureterointestinal anastomoses. Each type of ureterointestinal anastomosis, however, has specific technical points unique to its construction. Techniques involving ureterocolonic anastomoses are discussed first, followed by ureter-small bowel anastomoses.

Ureterocolonic Anastomoses

Combined Technique of Leadbetter and Clarke

The combined technique of Leadbetter and Clarke establishes a nonrefluxing ureterocolonic anastomosis by using a submucosal tunnel. The technique combines the ureterocolonic anastomosis of Nesbit, which is a refluxing elliptical anastomosis to the intestine, with the tunneled technique of Coffey (Fig. 97-21) (Leadbetter and Clarke, 1954).

The anterior taenia is incised obliquely for 2.5 to 3 cm as close to the mesenteric border as possible. The mucosa is dissected off

the muscularis for the entire length of the incision. At the distal end of the incision in the taenia, the mucosa is picked up with a fine Adson forceps, and a small button is excised. The ureter is spatulated for 5 to 7 mm such that an elliptical anastomosis may be made. The ureter is sewn mucosa to mucosa with 5-0 polydioxanone sutures (PDS) by either interrupted sutures with the knots tied on the outside or a running suture. If the suture line is to be run, it is wise to begin the anastomosis at the apex of the ureter. This suture is tied, and the posterior row is run to the most distal portion of the ureter, which is subsequently tied. A second running suture completes the anterior aspect. The seromuscular layer is then reapproximated loosely over the ureter in such a way as to allow “the ureter [to] lie in the bowel as a hammock without being compressed” (Leadbetter and Clarke, 1954). The bowel should be fixed to the peritoneum so that there is no tension on the ureters.

The complications reported with this procedure include a leak rate of 2.5%; deterioration of the upper tracts, which varies from 4.3% to 25%; and a stricture rate that varies from 8% to 14% (Table 97-4).

Transcolonic Technique of Goodwin

The transcolonic technique of Goodwin establishes a nonrefluxing ureterocolonic anastomosis by construction of a submucosal tunnel (Fig. 97-22). By this technique, the anastomosis is performed from within the bowel (Goodwin et al, 1953). If it is performed in bowel in continuity with the gastrointestinal tract, a noncrushing occlusive clamp is applied across the bowel cephalad to the desired point of the ureterointestinal anastomosis. This clamp is placed loosely about the bowel so as not to occlude the arterial supply in the mesentery.

A vertical incision is made in the bowel anteriorly, and the desired point of entrance of the ureter into the bowel is identified. A 0.5-cm incision is made in the posterior mucosa, and with use of a curved hemostat the mucosa is dissected from the submucosal layer in an oblique fashion coursing from medial to lateral. The hemostat is passed beneath the mucosa for a distance of approximately 3 to 4 cm and then brought through the serosa. A traction suture that has been placed on the ureter is then grasped with the hemostat, and the ureter brought into the colon. Both ureters should be brought into the bowel before they are sutured to the mucosa. The ureters should lie without tension or angulation. A No. 5 feeding tube is passed through the ureter to be sure that there is no kinking as it passes through the bowel wall. The redundant ureter is excised, and its end is spatulated and sewn with interrupted 5-0 PDS to the mucosa, with care taken to include with the mucosa some muscularis so that the ureter is securely fixed in place. A Silastic stent is placed up both ureters. As the ureters come through

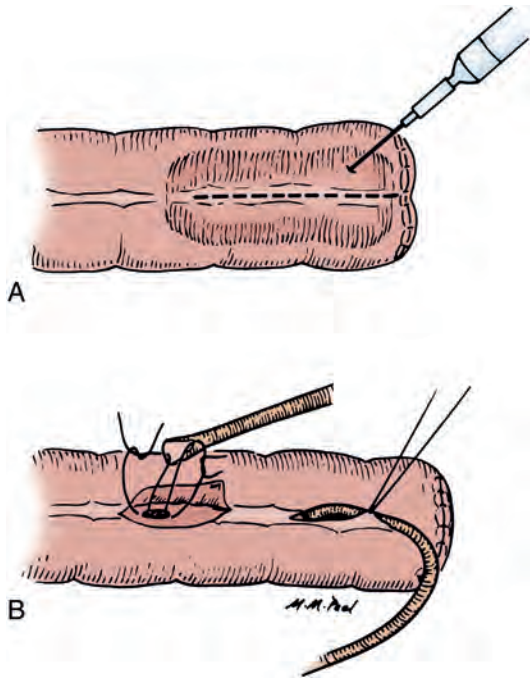


Figure 97-21. Leadbetter-Clarke ureterointestinal anastomosis. **A**, Injection of the submucosal tissues with saline facilitates the dissection. **B**, A linear incision is made in the taenia, the taenia is raised, and the mucosa is identified. A small button of mucosa is removed, and the ureter is spatulated and then sutured to the mucosa with 5-0 polydioxanone sutures. The seromuscular layer is sutured over the ureter, with care taken not to compromise or occlude the ureter.

TABLE 97-4 Complications of Ureterointestinal Anastomoses

PROCEDURE	NO. OF PATIENTS	STRICTURE (%)	LEAKAGE (%)	REFLUX (%)
COLON				
Leadbetter-Clarke ¹⁻⁴	127	14	3	4
Strickler ⁵	28	14	—	—
Pagano ⁶	63	7	—	6
SMALL BOWEL				
Bricker ^{7,8,18,19}	1809	7	4	—
Wallace-Y ^{9-11,17,19}	129	3	2	—
Nipple ⁸	37	8	—	17
Serosal tunnel ¹²	10	10	—	0
Le Duc ¹³⁻¹⁷	82	18	2	13

The following sources can be found in this chapter’s reference list on the Expert Consult website:
¹Hagen-Cook and Althausen, 1979; ²Leadbetter and Clarke, 1954; ³Hill and Ransley, 1983; ⁴King, 1987; ⁵Jacobs and Young, 1980; ⁶Pagano et al, 1984; ⁷Clark, 1979; ⁸Patil et al, 1976; ⁹Clark, 1979; ¹⁰Beckley et al, 1982; ¹¹Wendel et al, 1969; ¹²Starr et al, 1975; ¹³Hautmann et al, 1988; ¹⁴Le Duc et al, 1987; ¹⁵Klein et al, 1986; ¹⁶Lockhart and Bejany, 1987; ¹⁷Palascak et al, 2001; ¹⁸Studer et al, 2006; ¹⁹Kouba et al, 2007.

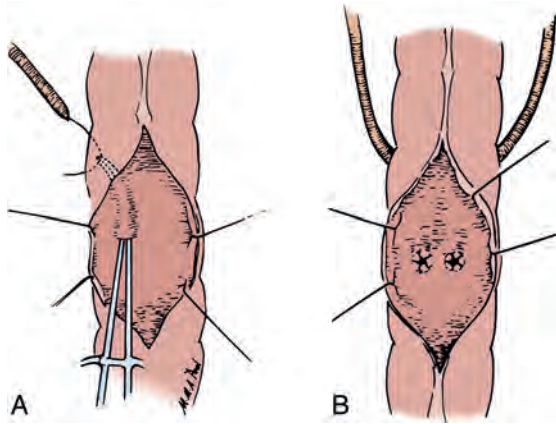


Figure 97-22. Transcolonic technique of Goodwin. **A**, The bowel is opened on its anterior surface; a small rent in the mucosa is made; and with a mosquito hemostat, the mucosa is raised from the submucosa extending laterally. A 3- to 4-cm tunnel is made before the clamp exits the serosal wall. The ureter is grasped and pulled into the submucosal tunnel. **B**, Both ureters have been drawn into the bowel through their submucosal tunnels before each is spatulated and circumferentially sutured to the mucosa. These sutures should also incorporate a portion of the muscularis for security. Where the ureter enters the colonic sidewall adjacent to the mesentery, the adventitia of the ureter is secured to the colonic serosa with interrupted 5-0 polydioxanone sutures.

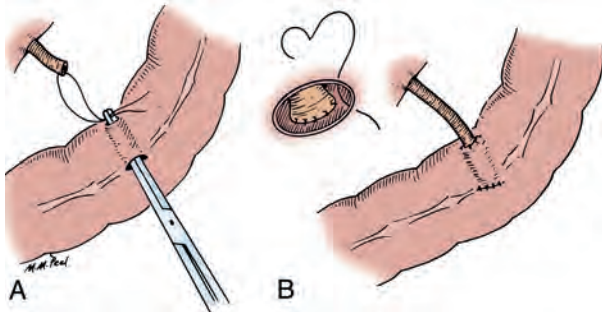


Figure 97-23. Strickler ureterointestinal anastomosis. **A**, A small linear incision is made in the taenia, and the submucosa is dissected from the mucosa laterally. After a distance of 3 to 4 cm has been achieved, a small hole is made in the serosa and the ureter is drawn through. **B**, A button of mucosa is excised, and the ureter is spatulated and sutured to the mucosa with 5-0 polydioxanone sutures. The rent in the taenia is closed with interrupted sutures, and an adventitial suture at the ureter's entrance point into the colon secures it to the serosa of the colon.

the serosa from without the bowel, the adventitia of the ureter is sutured to the serosa of the colon with two 4-0 PDS sutures. The anterior bowel wall is closed in two layers.

The reported results with this technique appear to be satisfactory. However, specific reliable data on the complication rate are not available.

Strickler Technique

The Strickler technique establishes a nonrefluxing ureterocolonic anastomosis by construction of a submucosal tunnel (Fig. 97-23) (Strickler, 1965; Jacobs and Young, 1980). A 1-cm incision is made on the margin of the taenia. The technique originally described removal of a 2-mm button of seromuscular tissue. A 2-cm tunnel is formed laterally beneath the seromuscular layer

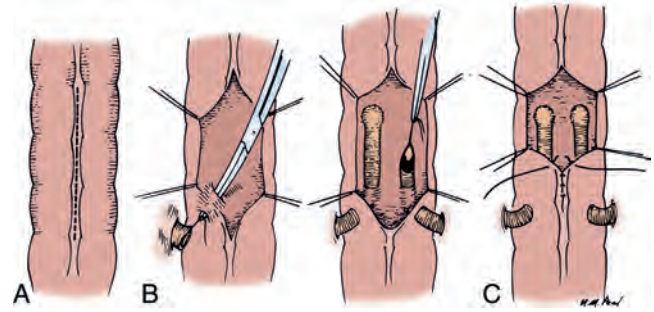


Figure 97-24. Pagano ureterointestinal anastomosis. **A**, A linear incision is made in the taenia between 4 and 5 cm in length. **B**, The submucosa is dissected from the mucosa laterally on both sides to the level of the mesentery. The ureters are drawn into the submucosal tunnel distally and sutured to the mucosa with 5-0 polydioxanone sutures proximally. **C**, The serosa is reapproximated, with incorporation of the mucosa in the midline.

with a hemostat. The seromuscular layer is incised, with care taken not to tent up the mucosa and inadvertently incise it. The holding suture in the ureter is grasped and drawn throughout the submucosal tunnel. The ureter is spatulated for 0.5 cm. A button of mucosa is removed, and the full thickness of the ureter is sewn to the mucosa of the bowel with either interrupted or running 5-0 PDS. The serosa is reapproximated over the ureter with 4-0 silk sutures. The serosal suture line is perpendicular to the course of the ureter. Where the ureters enter the serosa, they are also fixed with interrupted 4-0 PDS sutures. A lateral peritoneal flap is placed over the anastomosis.

The advantage of this anastomosis is that because the taeniae do not need to be aligned, one can form the tunnel according to the normal course of the ureter and avoid angulation. This technique reliably prevents reflux but results in a stricture rate of approximately 14% (see Table 97-4).

Pagano Technique

The Pagano technique establishes a nonrefluxing ureterointestinal anastomosis by construction of a submucosal tunnel (Fig. 97-24) (Pagano, 1980). The taenia is incised for a length of 4 to 5 cm, and the seromuscular layer is separated from the mucosa on both sides of the taenia laterally as far as the mesenteric border. The ureter is brought in one end (i.e., the distal end) laterally and laid in the 4- to 5-cm tunnel paralleling the mesenteric border. A button of mucosa is excised, and the ureters are spatulated and sutured to the mucosa with either interrupted or running 5-0 PDS. The seromuscular layer is then closed loosely with silk sutures in the midline. Each suture includes the seromuscular layer of the taenia and the mucosa in the midline.

This technique has a reported low complication rate. The leakage rate is approximately 3%, the stricture rate is 6%, and the reflux rate is approximately 6% (see Table 97-4) (Pagano et al, 1984).

Cordonnier and Nesbit Techniques

The Cordonnier and Nesbit techniques use no tunnel and are direct refluxing anastomoses of the ureter to the colon (Nesbit, 1949; Cordonnier, 1950). They are not desirable for ureterosigmoidostomies. They are performed in much the same way as a Bricker anastomosis would be performed for the small bowel (see later).

Small Bowel Anastomoses

There is a variety of ureter–small bowel anastomoses, which are of two basic types: end to side, and end to end. The end-to-side anastomoses may be constructed in a refluxing or nonrefluxing manner.

Bricker Anastomosis

The Bricker anastomosis is a refluxing end-to-side ureter–small bowel anastomosis that is simple to perform and has a low complication rate (Fig. 97-25) (Bricker, 1950). Although originally described for the small bowel, it may be used in any suitable intestinal segment.

In the original description, the adventitia of the ureter was sutured with interrupted silk sutures to the serosa of the bowel. The mucosa and serosa were incised; a small mucosa plug was removed; and with fine absorbable chromic sutures, the full thickness of the ureter was sewn to the mucosa of the bowel. The anterior layer of ureteral adventitia was then sewn with interrupted silk sutures to the serosa of the bowel. A less cumbersome method of performing this anastomosis is to excise a small button of seromuscular tissue and mucosa, spatulate the ureter for 0.5 cm, and suture the full thickness of the ureter to the full thickness of the bowel (i.e., mucosa and seromuscular layer to ureteral wall) with either interrupted or running 5-0 PDS. The anastomosis is stented with a soft Silastic catheter.

The stricture rate for this anastomosis varies from 4% to 22% (average of 6%). The leak rate is approximately 3% in the absence of stents (see Table 97-4). Open and robotic approaches have a comparable stricture rate (Anderson et al, 2013).

Wallace Technique

A frequently used anastomotic technique is that of Wallace, in which the end of the intestine is sutured to the end of the ureter (Fig. 97-26) (Wallace, 1970; Albert and Persky, 1971). This is a refluxing anastomosis. The intestinal segment used may be either small bowel or colon. There are three basic types of anastomoses:

1. The end of one ureter is sutured to the end of the other ureter, and this composite anastomosis is sutured to the end of the bowel.
2. A Y anastomosis of the ureters is constructed and sutured to the end of the bowel.
3. A head-to-tail ureteroureteral anastomosis is formed, which is then sutured to the end of the bowel.

The ureters are spatulated for 1.5 to 2 cm, and fine 5-0 PDS sutures are used for each anastomosis.

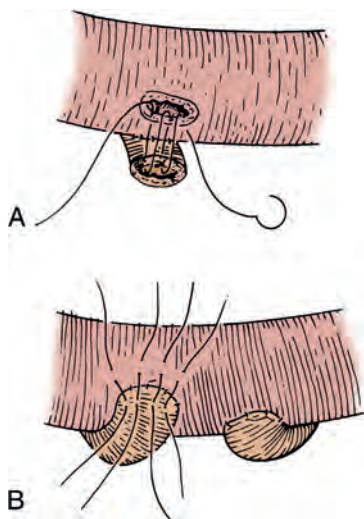


Figure 97-25. Bricker ureterointestinal anastomosis. A, The adventitia of the ureter is sutured to the serosa of the bowel. A small full-thickness serosal and mucosal plug is removed. Interrupted 5-0 polydioxanone sutures approximate the ureter to the full thickness of the mucosa and serosa. B, The anterior layer is completed by interrupted sutures placed through the adventitia of the ureter and the serosa of the small bowel.

For the first anastomosis, a fine suture is placed at the apex of each ureter with the knot tied to the outside. The posterior medial ureteral walls are sutured together, and the anterior lateral walls are sutured directly to the bowel with interrupted 5-0 PDS. Where the suture line of the end of the ureters comes to the bowel, a horizontal mattress suture is placed to make the anastomosis watertight. If a Y type of anastomosis is desired, after the posterior ureteral walls have been sutured together as described previously, the anterior walls of the ureters are sutured together, and the end of the composite anastomosis is sutured to the bowel. Again, where the suture lines meet the bowel, a horizontal mattress suture is placed so that the anastomosis is watertight. The head-to-tail anastomosis involves suturing the end of one ureter to the apex of the other. The posterior medial walls of the two ureters are approximated. The anterior lateral walls are sutured to the bowel.

The Wallace anastomosis has the lowest complication rate of any of the ureterointestinal anastomotic techniques. Incidence of stricture formation is approximately 3%, of deterioration of the upper tracts is about 4%, and of leakage is about 2% (see Table 97-4). The Wallace technique is not recommended for patients who have extensive carcinoma in situ or who have a high likelihood of recurrent tumor in the ureter. A recurrence of tumor at the anastomotic line in one ureter would block both ureters, causing uremia from bilateral obstruction.

Tunneled Small Bowel Anastomosis

The tunneled small bowel anastomosis method attempts to establish a nonrefluxing anastomosis by construction of a submucosal tunnel (Fig. 97-27) (Starr et al, 1975). Two 0.5-cm incisions are

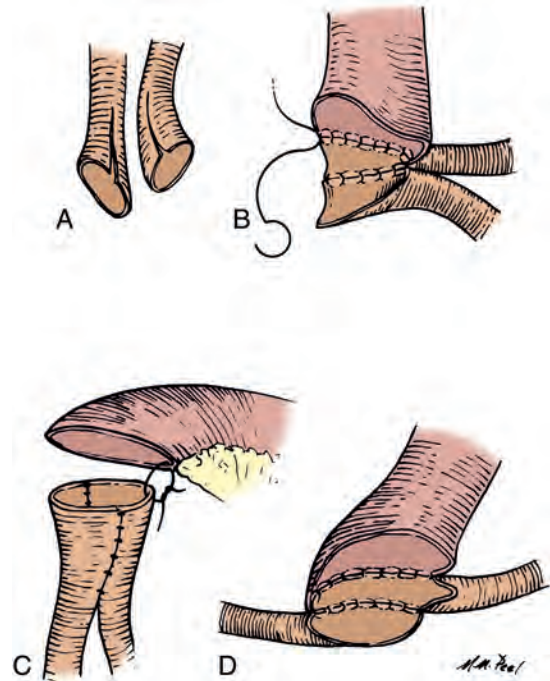


Figure 97-26. Wallace ureterointestinal anastomosis. A, Both ureters are spatulated and laid adjacent to each other. B, The apex of one ureter is sutured to the apex of the other ureter with 5-0 polydioxanone sutures (PDS). The posterior medial walls of both ureters are then sutured together with interrupted or running 5-0 PDS, the knots tied to the outside. The lateral ureteral walls are then sutured to the intestine. C, A Y-type anastomosis is formed by completing the anterior row of the anterior lateral ureteral walls of the ureters as shown in B and then suturing the ends of the ureters directly to the intestine. D, The head-to-tail anastomosis involves suturing the apex of one ureter to the end of the other. The posterior medial walls are sewn together, and then the ends and lateral walls are sewn to the intestine.

made in the serosa on the antimesenteric border 2.5 cm apart at right angles to the long axis of the bowel. The seromuscular layer is then gently separated from the mucosa with a blunt hemostat. The ureter is pulled through one incision, a button of mucosa is removed over the other incision, and the ureter is spatulated and sutured to the mucosa with interrupted 5-0 PDS. The serosa is then closed with interrupted 4-0 silk, and the adventitia of the ureter is sutured at its entrance through the serosa of the bowel to the serosa.

Good results have been reported, but this technique has not been widely used. Therefore long-term follow-up is not available (Osman et al, 2004).

Split-Nipple Technique

The split-nipple technique attempts to establish a nonrefluxing anastomosis by using a nipple mechanism. It may be applied to either the small or large bowel. This technique was described by Griffiths and involves formation of a nipple in the ureter and implantation into the small bowel (Fig. 97-28) (Turner-Warwick and Ashken, 1967). A 0.5-cm longitudinal incision in the ureter is made, and the ureteral wall is turned back on itself, constructing a nipple at least twice as long as its width. The cuff is stabilized at the corners with sutures. A button of seromuscular and mucosal tissue is removed, and the ureter is then placed into the bowel such that it protrudes through the mucosa. The adventitia just proximal to

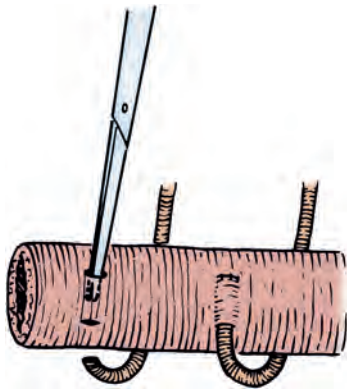


Figure 97-27. Tunneled small bowel anastomosis. A small transverse incision is made in the small bowel, and a second transverse incision 3 cm lateral to it is also made. The submucosal tunnel is made, a button of mucosa is removed, and the ureter is drawn through the tunnel and sutured directly to the mucosa. The rent in the serosa is closed, and an adventitial ureteral suture is placed and secured to the serosa at the ureter's entrance to the small bowel.

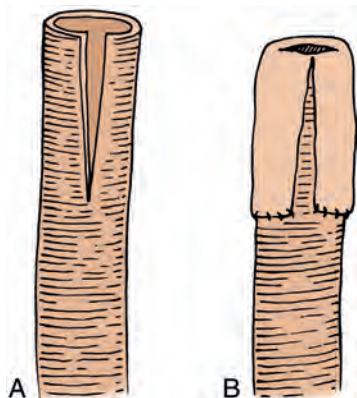


Figure 97-28. A and B, Split-nipple technique. The ureter is spatulated and turned back on itself, and the end of the ureter is secured to the adventitia of the ureter with interrupted 5-0 polydioxanone sutures.

the point where the ureter has been sewn to itself is sutured to the full thickness of the bowel wall with interrupted 5-0 PDS. The anastomosis is stented.

In one series, this type of anastomosis prevented reflux in more than 50% of the patients. In subsequent series, approximately 80% of patients had a nonrefluxing anastomosis with an acceptably low incidence of stenosis (see Table 97-4). There is a stricture rate of about 7% (De Carli et al, 1997).

Le Duc Technique

The Le Duc method establishes a nonrefluxing anastomosis by laying the ureter onto the interior of the bowel wall, eventually resulting in a submucosal tunnel when it is re-epithelialized (Fig. 97-29) (Le Duc et al, 1987). This technique has been used to prevent reflux in the ureter–small intestine anastomosis. Excellent exposure is required, and therefore the small bowel needs to be opened along its antimesenteric border for a length of approximately 5 cm. The mucosa is incised for a length of 3 cm beginning 2 cm proximal to the cut edge of the bowel. It is important to begin the mucosal tunnel away from the cut edge of the bowel to allow enough distal bowel for closure without jeopardizing the entrance point of the ureter. The ureter is then brought through the serosa at the most distal portion of the mucosal sulcus, laid in the trough, spatulated, and sutured to the proximal end of the sulcus with interrupted 5-0 PDS using the full thickness of ureteral wall and anchored to the muscularis and mucosal layers of the bowel. The mucosa of the sulcus of the bowel is then sutured to the adventitia of the ureter. The mucosa of the bowel should not be sutured over the ureter but rather to its lateral aspect. The idea is that the mucosa eventually grows over the top of the ureter. Where the ureter enters the small bowel, its adventitia is sutured to the bowel serosa with 4-0 silk sutures. Stents are placed in the ureter, and their passage must be unimpeded to ensure that there is no angulation. The bowel should be fixed to the body wall near the site of the ureteral implantation so that the ureters do not angulate.

The complication rate for this technique is relatively low, although the follow-up is also relatively short. Initial reports suggested that it carried with it an 87% incidence of maintaining an antireflux valve with a 5% incidence of stricture and a 2% incidence of leak (Schwaibold et al, 1998). A modification of the Le Duc technique was prompted by a 15% incidence of stricture when longer follow-up was available. With the modified technique, the stricture rate was 3% with 2½ years of follow-up. The technique involves construction of a 3-cm mucosal sulcus to the submucosa.

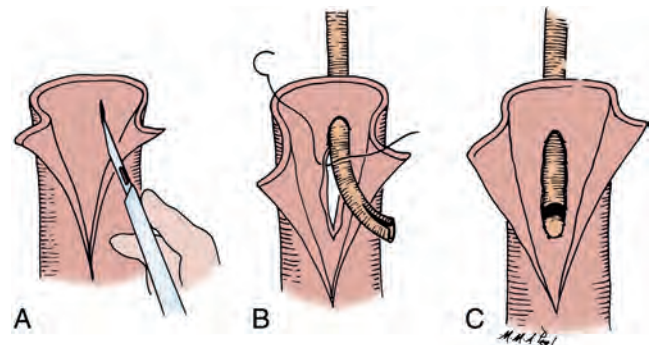


Figure 97-29. Le Duc ureterointestinal anastomosis. A, The small bowel is opened for approximately 4 to 5 cm. A longitudinal rent in the mucosa is made and the mucosa raised. B, At the distal end of the mucosal rent, a hole is made in the serosa, and the ureter is then drawn through. The entrance of the ureter through the serosa should be at least 2 cm proximal to the cut end of the bowel to allow sufficient bowel length to close the end. C, The ureter is spatulated and sutured to the mucosa and muscle layers. The mucosa is not reapproximated over the top of the ureter but rather sutured to the side of it.

The ureter is brought in the proximal sulcus transmurally and anchored to the serosa externally. The ureter is spatulated for 1.5 cm, and only the spatulated portion is sewn to the muscularis of the bowel. The proximal intraluminal ureter is not fixed to the bowel (see [Table 97-4](#)).

Hammock Anastomosis

The hammock anastomosis involves conjoining the ureters and implanting them into the small bowel in a nonrefluxing manner. The small bowel is closed at its proximal end, and three 10-cm longitudinal incisions separated by 1 to 2 mm are made through the seromuscular layer to the mucosa. These incisions are cross-hatched by multiple incisions. This serves as a hammock. The ureters are conjoined as in the Wallace technique and sutured to the intestinal mucosa. The ureters are buried by closing the intestinal wall over the top of them with seromuscular sutures of 3-0 polyglycolic acid suture ([Hirdes et al, 1988](#)).

With this technique, there is a 6% incidence of ureteroileal stenosis and approximately a 20% incidence of reflux. Follow-up, however, is relatively short.

Ureteral Dipping Technique

Described in 640 patients who underwent continent urinary diversion, the dipping technique is relatively simple to perform and has excellent success ([Wishahi et al, 2013](#)). Wishahi and colleagues form the neobladder, then make a small opening in the small bowel wall. The ureter is “dipped” approximately 1 cm into the bladder cavity, then secured to the seromuscular portion of the bowel. No mucosal anastomosis is performed, but the long-term success of renal preservation reported deserves further investigation.

Ureter–Small Bowel Anastomosis Using Serosal Compression of the Extramural Ureter as an Antireflux Mechanism

Primarily applicable to a continent diversion in which detubularized small bowel is used and an antireflux ureterointestinal anastomosis is desired, ureter–small bowel anastomosis involving serosal compression of the extramural ureter requires two segments of small bowel to be juxtaposed. The ureter is laid between the two small bowel serosal surfaces, which are sutured posterior and anterior to the extramural portion of the ureter. The technique is as follows.

The posterior wall of the extramural tunnel is composed of the two segments of small bowel sutured together with 3-0 silk ([Fig. 97-30A and B](#)). The two segments of small bowel are opened along their antimesenteric borders. The ureter is spatulated and sutured to the mucosal-seromuscular layer with 5-0 absorbable sutures. The edges of the opened small bowel are then reapproximated over the anterior ureter with absorbable sutures ([Fig. 97-30C](#)), thus making a serosal tunnel 4 cm in length. When the bowel is distended, it then applies pressure to the extramural ureter, thus preventing reflux ([Abol-Enein and Ghoneim, 1994](#)).

With an average of 3 years of follow-up, the anastomotic stricture rate is 4% and the rate of failure of the antireflux mechanism is 3% ([Abol-Enein and Ghoneim, 2001](#); [Turkolmez et al, 2004](#)).

Intestinal Antireflux Valves

Another technique for preventing reflux into the ureter involves construction of an antireflux mechanism with bowel distal to the ureterointestinal anastomosis. The ureter is sutured by the technique of either Bricker or Wallace (as described earlier) to the end of the bowel, and the bowel is used to make a one-way valve. Unlike with individual ureterointestinal antirefluxing anastomosis, when these valves fail or stenose, both kidneys are affected. Three basic types of antireflux mechanisms commonly used with the bowel are ileocecal intussusception, ileoileal intussusception, and ileal nipple valve placed into colon.

Intussuscepted Ileocecal Valve

The mesentery is cleaned from the ileum for a length of 8 cm beginning at the cecum and coursing proximally ([Fig. 97-31](#)). At least 5 cm of ileum proximal to the detached mesentery must be intact to ensure intestinal viability. Thus the ileum should not be transected less than 13 cm from the ileocecal junction. A No. 22 catheter is placed through the ileum into the cecum. The ileal serosa is scarified either by multiple cross-incisions with a knife or with the electrocautery unit. The 8-cm segment is intussuscepted over the catheter into the cecum. The intussuscepted ileum is secured to the cecal wall with 3-0 silk sutures placed circumferentially 2 mm apart.

The valve has a moderate tendency to fail because the intussusception has a significant chance of reduction. In one series, the antireflux mechanism remained intact in 55% of the patients during the long term ([Hensle and Burbige, 1985](#)). The intussusception may be made more secure by using a modification described by King. The mesentery is cleaned as described before. The cecum is opened along a taenia, and the ileum is intussuscepted over the catheter under direct vision. Where the intussusception lies adjacent to the cecal wall, mucosa of the intussuscepted ileum and the cecal mucosa adjacent to it are incised down to muscle. The muscles are sewn together with interrupted 3-0 chromic suture. Long-term follow-up in eight patients reveals maintenance of the antireflux valve in seven with the modified technique ([King, 1987](#); [Friedman et al, 1992](#)). The Mainz group advocates stapling the intussuscepted ileum to the ileocecal valve to prevent reduction. In their series, 82% of patients maintained valve competence; however, there was a 20% incidence of stone formation ([Wiesner et al, 2006](#)).

Intussuscepted Ileal Valve

The mesentery is cleaned from an 8-cm segment of ileal serosa ([Fig. 97-32](#)). There must be 5 cm of ileal mesentery proximal and distal to the cleared segment to ensure proper blood supply. The ureters are sewn to the proximal end of ileum. The distal end of ileum is opened along its antimesenteric border to within 2 to 3 cm of the cleared mesentery to provide adequate exposure and direct visualization of the intussuscepted segment. A Babcock clamp is placed into the lumen of the bowel, and a portion of bowel wall is grasped by invaginating it into the clamp with a finger. The ileal segment is intussuscepted by pulling on the Babcock clamp with gentle constant traction. If there is resistance, the mesentery is usually too bulky, and it must be defatted carefully before another attempt to intussuscept the segment. A 5-cm intussuscepted segment should protrude. The gastrointestinal stapler without the knife or the linear stapler, from which the distal five to eight staples have been removed, is used to secure the intussusception in place; three rows with the gastrointestinal stapler or four rows with the linear stapler are placed in quadrants. The staple size should be 4.8 mm. The proximal staples are important in securing the intussusception and preventing its reduction, whereas the distal staples are less effective and more likely to be exposed to urine and thus facilitate stone formation. It is for this reason that the distal staples are removed from the staple cartridge before it is placed in the stapler and before the intussusception is stapled. With the cautery unit, the mucosa of the intussusception is incised along its length. Adjacent to this incision, another is made in the mucosa of the ileum. The muscularis of both is exposed and sewn together with interrupted 3-0 chromic suture. The distal serosa is then sutured proximally to the serosa of the intussuscepted segment circumferentially with 3-0 nonabsorbable sutures. This is meant to secure the intussusception and to prevent its reduction with failure of the antireflux mechanism. The valve is successful in preventing reflux 90% of the time ([Kock et al, 1982](#); [Skinner et al, 1989](#)).

Because the intussuscepted nipple valve as an antireflux mechanism has resulted in a 10% complication rate (5% stone formation on the exposed staples, 4% stenosis, and 1% prolapse [[Stein et al, 1996a](#)]), modifications have been developed in an attempt to

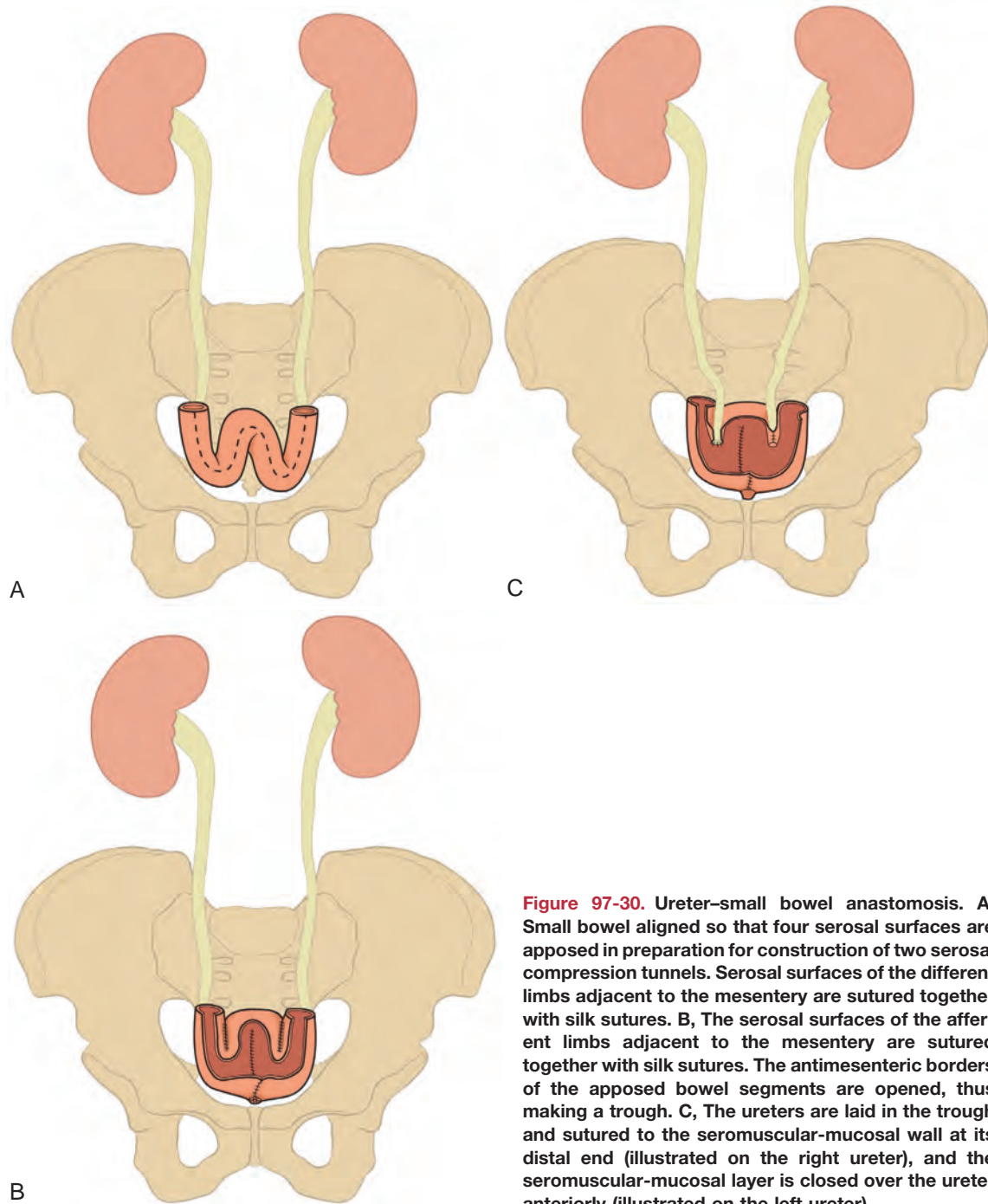


Figure 97-30. Ureter–small bowel anastomosis. **A,** Small bowel aligned so that four serosal surfaces are apposed in preparation for construction of two serosal compression tunnels. Serosal surfaces of the different limbs adjacent to the mesentery are sutured together with silk sutures. **B,** The serosal surfaces of the afferent limbs adjacent to the mesentery are sutured together with silk sutures. The antimesenteric borders of the apposed bowel segments are opened, thus making a trough. **C,** The ureters are laid in the trough and sutured to the seromuscular-mucosal wall at its distal end (illustrated on the right ureter), and the seromuscular-mucosal layer is closed over the ureter anteriorly (illustrated on the left ureter).

reduce these untoward outcomes. One such modification has been described by the University of Southern California group. An 8- to 10-cm isolated segment of ileum is tapered distally and laid between two segments of small bowel in which their serosal walls adjacent to the mesentery are sutured together. This serves as the posterior support for the isolated segment. The apposed bowel is opened along its antimesenteric border; lateral flaps are constructed adjacent to the segment and closed over its anterior aspect, thus making a serosal trough in which 4 cm of the segment of tapered ileum is positioned (Stein and Skinner, 2003). When the pouch is closed, a nipple valve is constructed. The concept is that as pressure in the pouch increases, the walls of the tapered nipple valve are compressed, thus preventing reflux. The authors call their modification a *T pouch*.

Nipple Valve

The simplest intestinal antireflux valve to make is the nipple valve with use of ileum (Fig. 97-33). The mesentery is cleared from the last 8 cm of the cut end of the ileum. The distal 6 cm of serosa is scarified by multiple cross-striations and then turned back on itself to form a nipple. The nipple should be at least 4 to 4.5 cm in length. The end of the inverted ileum is then sutured to itself with interrupted 4-0 PDS. An incision on the taenia large enough to accommodate the segment is made. A No. 22 catheter is placed through the segment, and its serosa is sutured to the colon serosa circumferentially with interrupted 3-0 silk sutures placed 2 mm apart. The long-term success rate for this type of valve is unknown but is comparable to tunneled anastomoses (Osman et al, 2004).

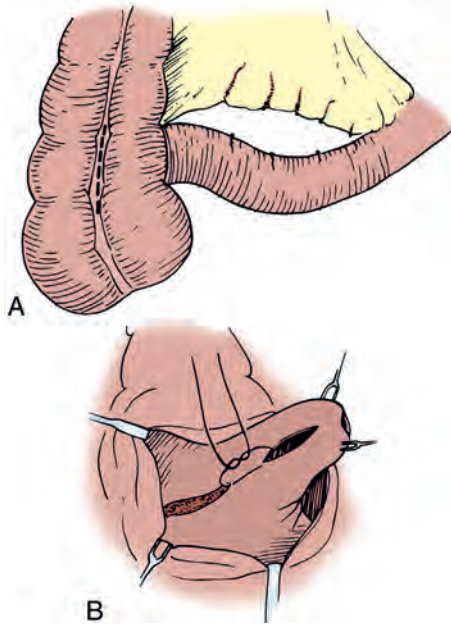


Figure 97-31. Ileocecal intussusception. A, An 8-cm segment of ileal mesentery is cleaned from the serosa beginning at the ileocecal junction. At least 5 cm of mesentery remains attached to the proximal ileum. An incision is made along a taenia at the level of the ileocecal valve. B, The ileum is intussuscepted over a 22-Fr catheter into the cecum under direct vision. The mucosa of the intussuscepted segment is incised, and the mucosa of the cecum adjacent to it is also incised. The muscle coats of both segments are sutured together. The serosa of the ileum is secured to the serosa of the cecum with interrupted 3-0 silk sutures placed circumferentially (not depicted).

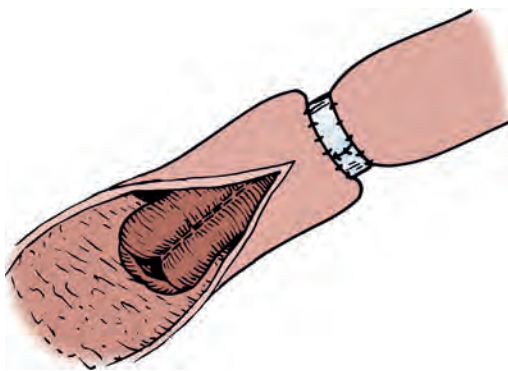


Figure 97-32. Intussuscepted ileal nipple valve. An 8-cm length of ileal mesentery is cleaned from the serosa. The ileum distally is opened within 2 to 3 cm of the rent in the mesentery; a 5-cm length of ileum is intussuscepted and secured by placement of staples in quadrants. The ileal mucosa is incised adjacent to an incision in the intussuscepted segment, and the two muscle coats are sutured together with interrupted 3-0 chromic suture. The serosa of the intussuscepted segment is sutured circumferentially to the base of the ileum, into which the proximal segment is intussuscepted with interrupted silk suture.

Complications of Ureterointestinal Anastomoses

The complications that occur with ureterointestinal anastomoses include leakage, stricture, reflux in those anastomoses that were performed to prevent reflux, and pyelonephritis. In a review of the various types of procedures, it appears that of the colonic antirefluxing procedures, the Pagano technique offers the lowest incidence of stricture with an acceptable incidence of reflux. With

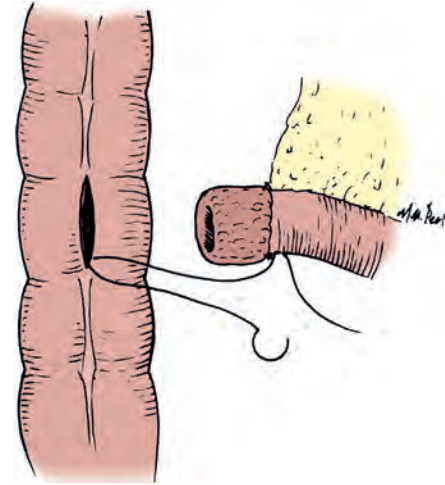


Figure 97-33. Nipple valve. Approximately 8 cm of mesentery are cleaned from the distal end of the ileum, and the serosa is scarified and then turned back on itself to form a nipple of approximately 4 cm in length. The end of the ileum is sutured to itself with interrupted 4-0 polydioxanone sutures (PDS). A rent is made in the colon through a taenia, and the nipple valve is placed through the rent and secured with circumferential interrupted 4-0 PDS through the full thickness of the colon and the seromuscular layer of the ileum.

respect to small bowel antireflux procedures, the Le Duc procedure and the ureterointestinal serosal apposition procedure seem to offer the lowest incidence of stricture with the highest success rates in preventing reflux. With respect to stricture formation and leakage, it appears the Wallace technique has the best results. In a comparison of the Bricker, the Wallace, and the nipple valve, however, in one series there was no difference in complication rate among any of the procedures. In another contemporary series the Wallace technique had the lowest incidence of stricture (Kouba et al, 2007). All had an incidence of approximately 29% of some form of obstruction in the long term (Mansson et al, 1979). In a more recent study, there appeared to be no difference between rate of reflux and stricture when a Bricker anastomosis was compared with a split-cuff nipple. The incidence of stricture was 7% for both types (De Carli et al, 1997).

Urinary Fistula

Urinary fistulas typically occur within the first 7 to 10 days postoperatively with an incidence of 3% to 9% (see Table 97-4) (De Nunzio et al, 2013; Loening et al, 1982). The incidence of urinary intestinal leak is markedly reduced by the use of soft Silastic stents (Mattei et al, 2008). A urinary intestinal leak may cause peri-ureteral fibrosis and scarring with subsequent stricture formation.

Stricture

In general, the antirefluxing techniques have a higher incidence of stricture. Patients are at risk for ureterointestinal strictures for the life of the anastomosis and must be observed on a scheduled periodic basis. A stricture has been reported to develop 13 years after the procedure (Shapiro et al, 1975). Ureteral strictures also occur away from the ureterointestinal anastomosis. This stricture is most common in the left ureter and is usually found as the ureter crosses over the aorta beneath the inferior mesenteric artery. It has been suggested that this occurs because of overly aggressive stripping of adventitia and angulation of the ureter at the inferior mesenteric artery.

Once a stricture has developed, various techniques may be used to rectify the situation. The most successful is re-exploration, with removal of the stenotic segment and reanastomosis of the ureter to the bowel by one of the aforementioned techniques. A number of

studies have compared open surgical correction of ureterointestinal anastomotic strictures with endourologic methods. In general, open repair has a success rate of approximately 75% at 3 years versus 15% for balloon dilation with similar follow-up (DiMarco et al, 2001). Open surgical methods may be morbid and difficult procedures. Endourologic procedures using balloon dilation have not proved to be durable, and therefore many surgeons have used either cold knife incisions or laser incisions. When several series involving use of endourologic methods are combined, there is a 50% to 60% success rate with 2 years of follow-up. Strictures occurring in less than 1 year from the original procedure, strictures 1.5 cm or longer, and left-sided strictures have less favorable outcomes with endourologic methods (Kramolowsky et al, 1987, 1988; Cornud et al, 1996; Laven et al, 2001; Poulakis et al, 2003). These data must be viewed with caution because longer follow-up usually results in additional recurrences. In selected patients, metallic stents have been used, which might be a reasonable approach in a patient with a limited life expectancy, thus avoiding a major open operation (Barbalias et al, 1998). In a study in which nonmalignant ureterointestinal strictures were stented, researchers reported that all patients were successfully treated with 2 years of follow-up; one patient developed a stone on the stent (Palascak et al, 2001).

Pyelonephritis

Acute pyelonephritis occurs both in the early postoperative period and during the long term. Its incidence is approximately 10% to 20% in patients diverted with ileal conduits and 9% in those diverted with antirefluxing colon conduits (see Table 97-3). These complications cause considerable morbidity and in fact are associated with significant mortality. In one series of intestinal segments in the urinary tract, 8 of 178 patients died of sepsis (Schmidt et al, 1973). That these complications may result in delayed mortality is indicated by the fact that 2 of 115 children and 3 of 127 adults died of septic complications 5 to 14 years after intestinal diversion (Pitts and Muecke, 1979). When sepsis is associated with decreasing renal function and uremia, the morbidity and mortality are markedly increased.

Table 97-4 summarizes the complications and success rates for the various types of anastomoses. The table is derived from composite reports in the literature in which specific anastomoses were described and from which the data could be accurately analyzed. Because of these two requirements, it is not possible to comment, for example, on the incidences of reflux or leakage among various anastomotic types inclusively. These complications can be minimized by adherence to the principles of ureterointestinal surgery discussed earlier.

RENAL DETERIORATION

The incidence of renal deterioration after conduit urinary intestinal diversion has varied from 10% to 74% (Madersbacher et al, 2003; Gilbert et al, 2013; Eisenberg et al, 2014). This variance is perhaps a result of the fact that many reports include both renal units that were abnormal and those that were normal before diversion. In analyzing abnormal renal units before diversion and documenting progressive disease, it is difficult to be sure whether the urinary diversion caused the progression or whether progression is caused by the intrinsic abnormality for which the diversion was constructed. When the incidence of renal deterioration is determined by comparing renal units that were normal before diversion and then deteriorated postoperatively, 18% of patients who have ileal conduits show progressive deterioration versus 13% who have nonrefluxing colon conduits (see Table 97-3). Twenty percent of patients with nonrefluxing continent ileocecal bladders show some evidence of deterioration of the upper tracts when they are observed during the long term (Benchekroun, 1987). This deterioration leads to a 10% incidence of azotemia in children with ileal conduits (Schwarz and Jeffs, 1975) and a 12% (5 of 41 patients) incidence of renal failure in patients with colon conduits

constructed for benign disease (Elder et al, 1979). There is significant and progressive deterioration in renal function in the majority of patients independent of the type of urinary diversion (Eisenberg et al, 2014).

The incidence rates for both sepsis and renal failure are greater in patients with ureterosigmoidostomy than in those with conduits. Sepsis and renal failure may occur either in the immediate postoperative period or many years later. The most common cause of death in patients who have had a ureterosigmoidostomy for more than 15 years is acquired renal disease (i.e., sepsis or renal failure). In this group of patients, approximately 10% to 22% die of these disorders (Zabbo and Kay, 1986), some as late as 27 years after diversion (Mesrobian et al, 1988). In patients with ileal conduits, about 6% ultimately die of renal failure (Richie, 1974).

Renal Function Necessary for Urinary Intestinal Diversion

The amount of renal function required to effectively blunt the reabsorption of urinary solutes by the intestinal segment and to prevent serious metabolic side effects depends on the type of urinary intestinal diversion constructed (i.e., the amount of bowel to be used and the length of time the urine is exposed to the intestinal mucosa). Thus a greater degree of renal function is necessary for retentive (continent) diversions than for short conduit diversions. In general, patients who have a glomerular filtration rate (GFR) on average above 40 mL/min tolerate a continent diversion reasonably well. Indeed, in one study, two groups of patients were analyzed: those with GFRs around 100 mL/min (range, 91 to 112) and those with GFRs around 55 mL/min (range, 36 to 69). Both seemed to tolerate the metabolic load well with a minimal development of metabolic acidosis. There was a slightly increased incidence of metabolic acidosis in the group with low GFR, as would be expected; however, in this group, distal tubule function was excellently maintained as demonstrated by ammonium chloride loading. This observation points out that GFR is not the sole determining factor that allows the body to manage intestinal diversion. Indeed, GFR is but one factor. Just as important is distal tubule function. This article confirms that when distal tubule function is normal and the GFR is above 40 mL/min, patients do extremely well (Kristjansson et al, 1997).

There are five components of renal function: renal blood flow, glomerular filtration, tubule transport, concentration and dilution, and glomerular permeability. Aspects of renal function that must be specifically addressed are GFR, best measured by inulin clearance; ability of the tubule to acidify, determined by ammonium chloride loading; concentrating ability, determined by water deprivation; and glomerular permeability, reflected by urine protein concentrations. In general, patients with normal urine protein content who have a serum creatinine concentration below 2.0 mg/dL do well with intestine interposed in the urinary tract. Serum cystatin C is a promising serum protein that reflects GFR more accurately than creatinine; however, its usefulness in urinary intestinal diversion has not yet been determined (Herget-Rosenthal et al, 2012; Inker et al, 2012). At a level of serum creatinine below 2 mg/dL, renal blood flow, GFR, tubule transport, and concentrating and diluting ability are relatively well preserved. In patients whose serum creatinine concentration exceeds 2 mg/dL and who are being considered for retentive diversion or in whom long segments of intestine will be used, a more detailed analysis of renal function is necessary. If the patient can achieve a urine pH of 5.8 or less after an ammonium chloride load, has a urine osmolality of 600 mOsm/kg or higher in response to water deprivation, has a GFR that exceeds 35 mL/min, and has minimal protein in the urine, the patient may be considered for a retentive diversion.

URINARY DIVERSION

This section deals with specific types of conduit urinary diversions. Fundamentally, there are two types of conduits: (1) those using the

small bowel, which includes the jejunum or ileum, and (2) those in which a portion of large bowel is used. Conduits made of stomach have been described but are rarely indicated and may carry with them difficult problems of stomal maintenance. Their construction is not discussed here. Each type of conduit has specific indications and advantages, and for each there are specific complications. Some complications, however, are similar among all types. The indications for a conduit are the need for urinary diversion: after a cystectomy; because of a diseased bladder; before transplantation in a patient who has a bladder that cannot adequately receive the transplant ureter; and for dysfunctional bladders that result in persistent bleeding, obstructed ureters, poor compliance with upper tract deterioration, and inadequate storage with total urinary incontinence.

Preparation

Regardless of whether small or large bowel is used for the conduit, although subject to debate as noted previously, it is my preference that all patients have a bowel preparation as outlined earlier. The reason for this is that large segments of bowel are exposed to the urinary tract and in many cases require detubularization, thus exposing the abdominal cavity to a large amount of solid fecal material if the bowel is unprepared. The specific types of ureteroileointestinal anastomosis and stomal construction and their complications are also described in previous sections. This section describes features that are unique to the construction of the conduit. The complications cited for each conduit also depend on the length of follow-up and the concomitant procedure performed.

Ileal Conduit

In the ileal conduit procedure, a portion of distal ileum is chosen. It is the simplest type of conduit diversion to perform and is associated with the fewest intraoperative and immediate postoperative complications. It is not advisable to use ileum for a conduit in patients with a short bowel syndrome, in patients with inflammatory small bowel disease, and in those whose ileum has received extensive irradiation, often as a consequence of prior radiation therapy for a pelvic malignant neoplasm.

Procedure

A segment 10 to 15 cm in length is selected 10 to 15 cm from the ileocecal valve. The cecum and ileal appendage (i.e., that portion of the distal ileum fixed to the retroperitoneum) are mobilized. The ileal mesentery is transilluminated, and a major arcade to the segment selected identified. With a mosquito clamp, the mesentery immediately beneath the bowel is penetrated, and the bowel is encircled with a vessel loop. An area at the base of the mesentery that is to one side of the feeding vessel is selected, and a second vessel loop is placed through the mesentery. At this juncture, the peritoneum overlying both sides of the mesentery is incised from bowel vessel loop to the base of mesentery vessel loop. With mosquito clamps, the tissue is clamped, severed, and tied with 4-0 silk. A portion of mesentery 2 cm in length is cleaned away from the bowel beneath the mesenteric incision. This procedure is repeated at the other end of the selected segment. The base of the mesentery should be as wide as possible and the mesenteric windows not excessive (in general about 5 cm in length) to prevent ischemia of the segment. Allen clamps are placed across the bowel in an angled fashion such that the antimesenteric portion is shorter than the mesenteric portion. (Some prefer to transect the bowel with an anastomotic stapler.) Thus a triangular piece of bowel is removed and discarded.

The isolated ileal segment is placed caudad, and an ileoileostomy is performed as described earlier (Fig. 97-34). The mesenteric window of the ileoileostomy is closed with interrupted 3-0 silk sutures. The isolated segment is then flushed with copious amounts of saline until the irrigant is clear, at which point the ureters are brought out the retroperitoneum in the right lower quadrant. To

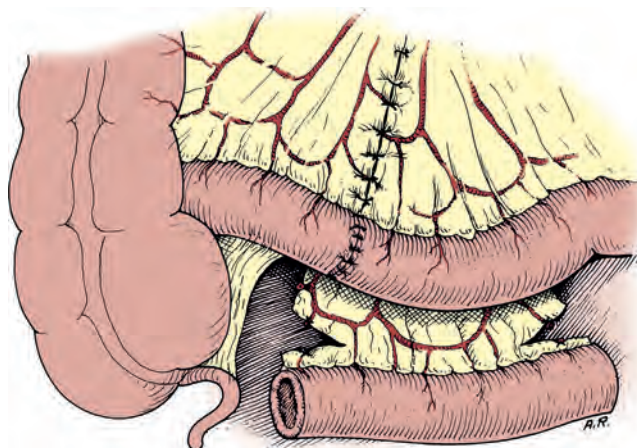


Figure 97-34. The isolated segment of ileum is placed caudal to the ileoileostomy. An incision on the mesentery of the isolated segment 1 cm from the bowel wall straightens the end. In general, this is not necessary unless the mesentery is excessively bulky.

accomplish this, the left ureter must be brought over the great vessels and posterior to the sigmoid mesentery to the rent in the posterior peritoneum. This may be done by mobilizing the cecum cephalad to identify the right ureter. The left ureter may be identified by incising the line of Toldt of the left descending colon (Fig. 97-35). This dissection allows anastomosis of the ileal segment as proximally as needed to the ureter. Indeed, the ileum may be anastomosed directly to the renal pelvis on both sides if necessary (see Fig. 97-35C). After a cystectomy, the ureters are identified caudad to the iliac vessels and may be conveniently traced cephalad similar to the previous description. The ureteroileal anastomoses are performed as described previously. These anastomoses are stented.

A convenient method of introducing the stent through the loop to the opening in the bowel is illustrated in Figure 97-36. The base of the conduit is fixed to the retroperitoneum in the right lower quadrant by suturing the posterior peritoneum to the conduit, thus effectively retroperitonealizing the ureteroileal anastomosis. The stoma is made as described previously. I prefer to suture the loop segment to the lateral peritoneal wall, thus obviating any chance of herniating small bowel lateral to the conduit. Many prefer to bring the segment directly to the anterior abdominal wall, however, thus allowing bowel to descend caudad on either side of the loop.

Robotic surgical approaches have been described but should be attempted only by the most experienced surgeons (Tyrizis et al, 2012).

Complications

Early and late postoperative complications are listed in Table 97-5. It is difficult to clearly ascribe these complications solely to construction of the conduit because many are reported in patients undergoing a cystectomy as well. These incidences in Table 97-5 are therefore expected to reflect the high end of the spectrum. Bleeding may occur from either the stoma or the conduit itself. Approximately 10% of patients have stomal bleeding. In 4%, it originates from the loop beneath the fascia (Delgado and Muecke, 1973). Bleeding that is extremely difficult to manage may be a result of cirrhosis and varices. In this situation, life-threatening bleeding from the conduit may occur. To stop the bleeding, portal decompression may be required (Chavez et al, 1994). A less morbid method involves percutaneous transhepatic portal shunt or transhepatic angiography with embolization (Lashley et al, 1997; Medina et al, 1998). Indeed, this has been successful in several reported cases. Complications not listed include hypertension, renal failure, decreased renal function, and death. These complications

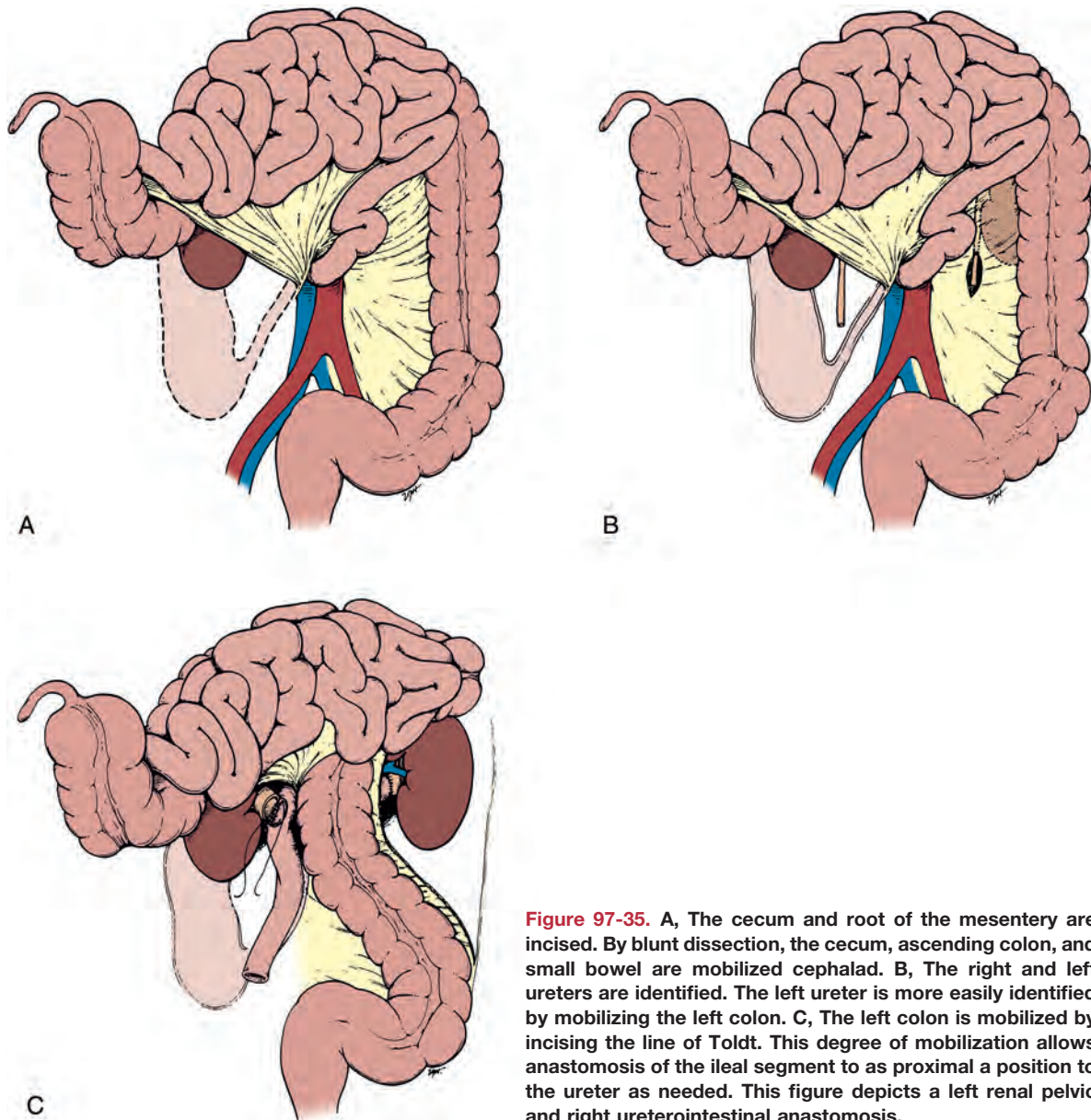


Figure 97-35. A, The cecum and root of the mesentery are incised. By blunt dissection, the cecum, ascending colon, and small bowel are mobilized cephalad. B, The right and left ureters are identified. The left ureter is more easily identified by mobilizing the left colon. C, The left colon is mobilized by incising the line of Toldt. This degree of mobilization allows anastomosis of the ileal segment to as proximal a position to the ureter as needed. This figure depicts a left renal pelvic and right ureterointestinal anastomosis.

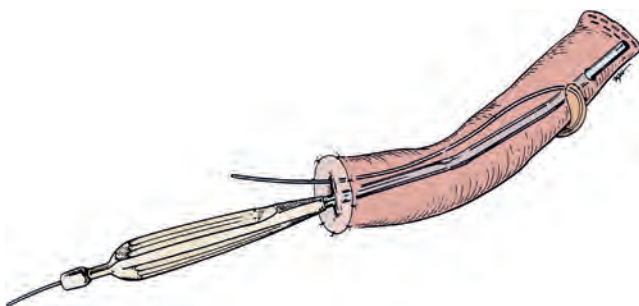


Figure 97-36. The ureterointestinal anastomoses should be stented with soft Silastic stents. These stents may be conveniently introduced with a Yankauer suction instrument from which the tip has been removed. The suction instrument is introduced by way of the distal end of the segment to the desired location of the ureteral anastomosis. When one cuts down on the Yankauer tip, its end protrudes through the bowel at the desired site. The stent is threaded through the suction instrument, and the instrument is removed.

in large part depend on the concomitant procedure performed, the length of follow-up, and the status of the kidneys before diversion. During the long term (20 years), 7% of patients have renal failure requiring dialysis, and 60% show deterioration of the upper tracts (Koch et al, 1992). After salvage cystectomy, complications are increased so that approximately one third of patients have one of the early complications (Abratt et al, 1993). Also, the complication rate is increased in patients in whom an intestinal segment is used who require renal transplantation (Nguyen et al, 1990).

One should be cautious in identifying duplex ureters. A failure to identify a second ureter on one side results in intraperitoneal urine leak and can cause excessive morbidity (Evans et al, 1994). The duplex ureters may be dealt with by implanting them separately if they are of sufficient caliber, or they may be spatulated, sewn together, and then implanted into the ileal conduit as a single unit (Fig. 97-37).

Jejunal Conduit

The jejunum has the largest diameter of the small bowel and the longest mesentery. In general, jejunal conduits have not had a high

TABLE 97-5 Complications: Ileal Conduit*

	EARLY	LATE
Urine leak	2% (9/356)	
Bowel leak		
Sepsis	3% (7/230)	3% (4/142)
Acute pyelonephritis	3% (21/700)	18% (133/726)
Wound infection	7% (17/230)	2% (4/178)
Wound dehiscence	3% (11/326)	
Gastrointestinal bleeding	2% (2/90)	
Abscess	2% (3/168)	
Prolonged ileus	6% (14/230)	
Conduit bleeding	2% (3/178)	10% (18/178)
Intestinal obstruction	3% (18/610)	5% (42/878)
Ureteral obstruction	2% (14/610)	6% (56/878)
Parastomal hernia		2% (9/454)
Stomal stenosis		3% (143/486)
Stone formation		7% (59/822)
Excessive conduit length		9% (26/276)
Metabolic acidosis		13% (27/206)
Conduit infarction		2% (2/90)
Volvulus		0.7% (2/268)
Conduit stenosis		3% (11/320)
Conduit-enteric fistula		<1%

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

TABLE 97-6 Complications: Jejunum Conduit*

	EARLY	LATE
Urine leak	14% (3/21)	
Wound dehiscence	5% (1/21)	
Acute pyelonephritis		10% (2/21)
Gastrointestinal bleeding	4% (1/27)	
Electrolyte abnormalities		27% (17/62)
Stomal stenosis		7% (2/27)
Bowel obstruction		7% (2/27)
Ureteral stricture		12% (5/41)
Enteric fistula	2% (4/140)	

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

rate of acceptance because of perceived electrolyte abnormalities. A more recent report of patients, most of whom were observed for more than 5 years, has shown that the bulk of electrolyte problems are minor; only about 4% in that series had severe hyponatremic metabolic acidosis. Renal calculi (12%), parastomal hernia (6%), and pyelonephritis (4%) constituted the majority of the remaining complications (Fontaine et al, 1997). The advantage of using the jejunum is that it avoids irradiated bowel and ureter. It is difficult to make a case for the jejunal conduit except in circumstances in which it is inadvisable to use either colon or ileum. However, this series does point out that when necessary, one can successfully use jejunum as a conduit. This might occur in patients who have extensive irradiation that involves the ileum, those with severe adhesions of the ileum and absence of the large bowel, and those who have an absent colon with inflammatory disease of the distal small bowel. **The contraindications to its use are severe bowel nutritional disorders and the presence of another acceptable segment.**

Procedure

The procedure is similar to that for an ileal conduit. A 10- to 15-cm segment of jejunum is isolated 15 to 25 cm from the ligament of Treitz as described for the ileal conduit. One should plan for the stoma to be in the upper quadrant, typically the left upper quadrant. The remainder of the technique is as described for the ileal conduit.

Complications

The early and long-term complications are similar to those listed for ileal conduit except that the electrolyte abnormality is a hyperkalemic, hyponatremic metabolic acidosis instead of the hyperchloremic metabolic acidosis of ileal diversion (Table 97-6). The treatment of the jejunal syndrome consists of administration of sodium chloride and sodium bicarbonate. Thiazide diuretics may also be used and are helpful in allaying the hyperkalemia (Hasan et al, 1994).

Colon Conduit

Three types of colon conduits are commonly used: transverse, sigmoid, and ileocecal. Each has specific indications with advantages and disadvantages.

The transverse colon is used when one wants to be sure that the segment of conduit used has not been irradiated in individuals who have received extensive pelvic irradiation. It is also an excellent segment when an intestinal pyelostomy needs to be performed. The sigmoid conduit is a good choice in patients undergoing a pelvic exenteration who will have a colostomy. Thus no bowel anastomosis needs to be made. It also allows non-refluxing submucosal reimplantation and provides for an easily placed left-sided stoma when that is desirable.



Figure 97-37. Intravenous urogram 6 days postoperatively in a patient who had bilateral duplex ureters. The ureters on each side were spatulated, sewn together, and anastomosed to the ileum.

The use of sigmoid colon is contraindicated with disease of this segment or when the hypogastric arteries have been ligated and the rectum has been left in situ. The latter circumstance may result in sloughing of the rectum or its mucosa because its blood supply of necessity is interrupted. It is also unwise to use this segment in individuals with extensive pelvic irradiation because it has probably been included in the radiation fields.

An ileocecal conduit has the advantage of providing a long segment of ileum when long segments of ureter need replacement, as well as the advantage of providing colon for the stoma. It is also used in situations in which free reflux of urine from the conduit to the upper tracts is thought to be undesirable. Contraindications to the use of transverse, sigmoid, and ileocecal conduits include the presence of inflammatory large bowel disease and severe chronic diarrhea.

Procedure

Transverse Colon. The segment may be isolated on the right or middle colic arteries, most commonly the latter (Fig. 97-38). The gastrocolic ligament is taken down, and the omentum is dissected from the portion of colon that is to be isolated. The splenic and hepatic flexures should be mobilized next. The proper length of segment is determined by taking into consideration the desired location of the stoma and the length of available ureters. In general, a length of 15 cm is sufficient. It is important not to isolate a segment that is too short and therefore incapable of reaching the retroperitoneum in such a position that a tension-free ureterocolonic anastomosis may be performed and retroperitonealized. The segment is isolated between bowel clamps, and a two-layer colocolostomy or stapled anastomosis is performed as outlined earlier. The segment is placed caudad to the anastomosis. If a colopyelostomy is to be performed, the segment should be placed cephalad to the bowel anastomosis. The isolated segment is irrigated with copious amounts of saline until the effluent is clear. The proximal end is closed with a running Connell suture of 3-0 chromic and a second layer of Lambert sutures of 3-0 silk. The ureterocolic anastomoses are then performed (see earlier), and the end is anchored to the retroperitoneum close to the midline. The stoma is usually placed in the right upper quadrant but may be placed anywhere in the abdomen if indicated.

Sigmoid Colon. The sigmoid colon is mobilized by incising its peritoneal attachments and the line of Toldt along the descending colon. The segment is isolated on the sigmoid vessels and placed lateral to the sigmoid colon (Fig. 97-39). The anastomosis of the sigmoid colon and ureterocolic anastomosis are as described for the transverse colon.

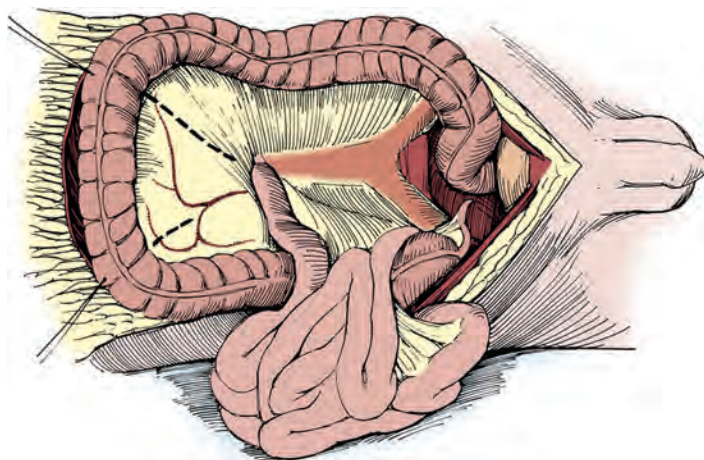


Figure 97-38. Transverse colon conduit may be based on right colic or middle colic arteries (depicted). (From Hinman F Jr. *Atlas of urologic surgery*. Philadelphia: Saunders; 1989.)

Ileocecal Conduit. The ileocecal conduit is based on the terminal branches of the superior mesenteric artery (i.e., ileocecal artery). The segment is placed caudad, and an ileum–ascending colon anastomosis is performed as described previously. The stoma is placed in the right lower quadrant. The ileocecal valve may be reinforced to ensure prevention of reflux. This is described earlier (see Fig. 97-31). For the ureterointestinal anastomoses, also see the earlier description.

Complications

Early and late complications after a transverse colon (Beckley et al, 1982; Schmidt et al, 1985; Ravi et al, 1994), sigmoid, or ileocecal conduit are listed in Tables 97-7 to 97-9. As is true for the small bowel, complications not listed including death, renal failure, and renal deterioration depend on the concomitant procedure performed and the length of follow-up. It is interesting to note that early reports suggested a lower incidence of renal deterioration with colon conduits, but some recent series suggest that the incidence of these complications is about the same. However, there continue to be proponents of the colon conduit because in the long term the apparent incidence of pyelonephritis is 7.6% and of preservation of the upper tracts is 78% (Stein et al, 1996b).

Complications of the ileocecal conduit in one reported series occurred in 21% of patients (Matsuura et al, 1991). In this series, complications of the ileal conduit were compared with those of the ileocecal conduit, and there appeared to be no difference in the frequency of early and late postoperative complications. Early complications included urinary leakage, bowel obstruction, fecal leakage, acute renal failure, fulminant hepatitis, pneumonia, gastrointestinal bleeding, hemorrhage, perforation of ileum, heart failure, and wound dehiscence. Late complications included stomal prolapse, acute pyelonephritis, bowel obstruction, urinary stones, parastomal hernia, incisional hernia, stomal stenosis, and fecal leakage. There was no difference in the incidence of deterioration of the upper tracts with either form of diversion. Of some note is that at high pressures, a large portion of the ileocecal conduits experienced reflux. At low pressures, however, there was minimal or no reflux. Whenever a portion of colon is used for a conduit, chronic diarrhea may be a consequence.

Ileal Vesicostomy

An ileal vesicostomy uses spatulated ileum and a generous transverse cystostomy to decompress the bladder and to allow an appliance to be used on the abdomen. This procedure is particularly well suited to spinal cord injury patients or those with significant neurologic disease. The concept is that patients with a neurogenic bladder have an easier job of caring for themselves with an abdominal stoma. Patients who are particularly good candidates are those with significant detrusor–external sphincter dyssynergia. Those who have detrusor hyperreflexia, particularly women, may have an increased incidence of incontinence. The complications of the procedure include urethral incontinence requiring closure of the urethra in 20% of patients, stomal stenosis, and bladder and renal calculi.

The procedure is performed by spatulating an ileal segment and performing a generous transverse cystostomy. The spatulated ileum is sutured to the bladder with absorbable suture, and the distal segment is brought to the abdominal wall by fashioning a rosebud stoma. This results theoretically in a low-pressure reservoir. Its appeal is that if indicated at a later date, the patient's anatomy can be converted back to normal (Mutchnik et al, 1997; Atan et al, 1999).

Management Common to All Conduits

All anastomoses are stented with Silastic stents. A convenient method for introducing the stents through the conduit and into the ureter is illustrated in Figure 97-36. They are removed individually on the fourth to sixth postoperative days. If there is no

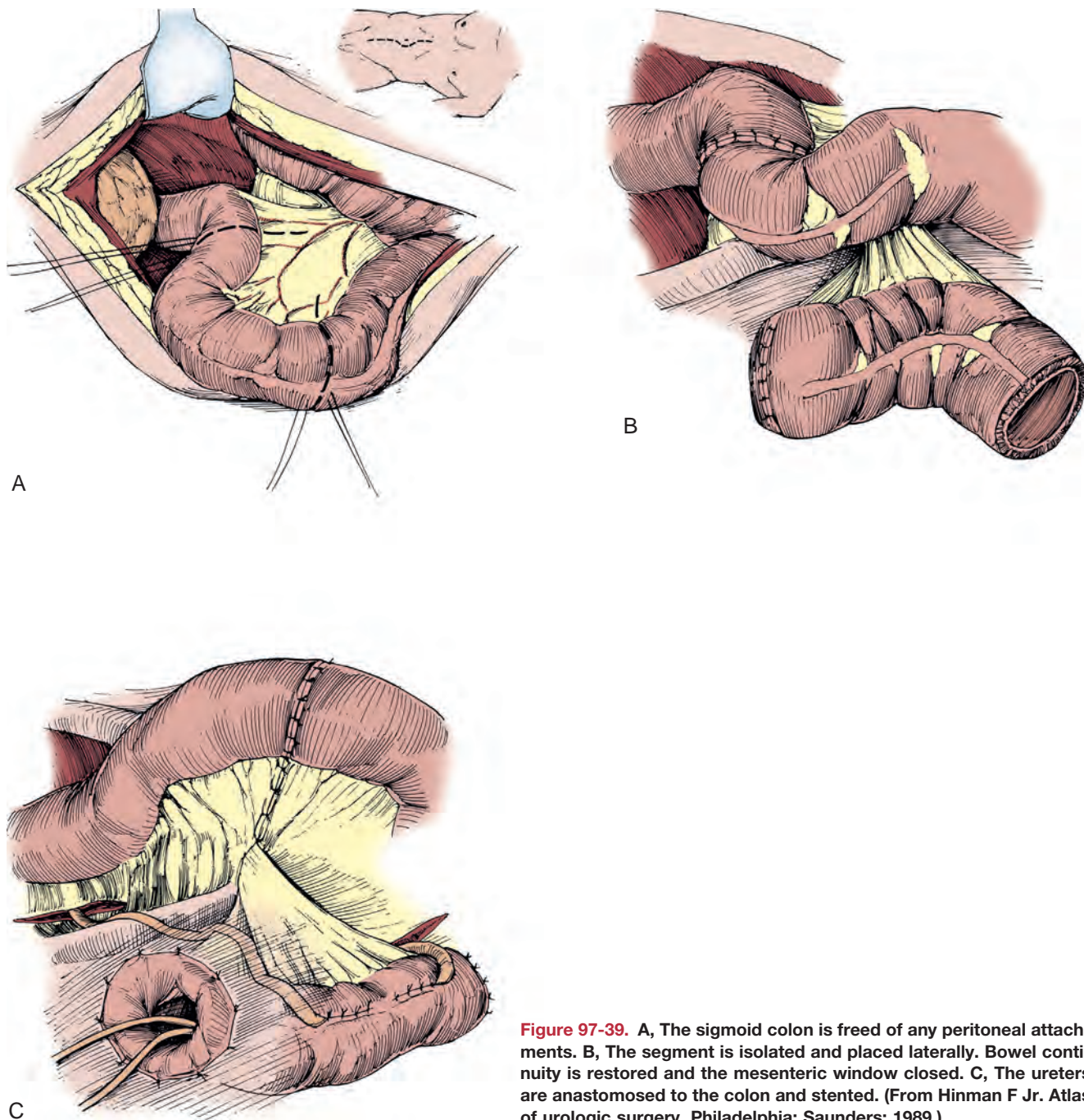


Figure 97-39. A, The sigmoid colon is freed of any peritoneal attachments. B, The segment is isolated and placed laterally. Bowel continuity is restored and the mesenteric window closed. C, The ureters are anastomosed to the colon and stented. (From Hinman F Jr. *Atlas of urologic surgery*. Philadelphia: Saunders; 1989.)

increase in drainage, the Jackson-Pratt closed-suction drain is removed. **All conduits are retroperitonealized**, with the uretero-intestinal anastomosis being placed in the retroperitoneum. This may be accomplished by suturing the posterior peritoneum to the serosa of the conduit above the ureterointestinal anastomosis. A drain may then be laid into the retroperitoneum. I prefer to drain the ureterointestinal anastomosis with a Jackson-Pratt or Blake closed-suction drain laid in the retroperitoneum 3 to 4 cm away from the anastomosis. The peritoneal cavity should not be drained.

All patients are given nothing by mouth until bowel function has returned. A progressive diet is instituted after confirmation of bowel activity. It has been my practice to use NGT decompression in all patients having a bowel anastomosis. In reported surgical series, it is clear that there are advantages and disadvantages of NGT decompression after intestinal surgery. Without its use, vomiting is more common. With its use, pulmonary complications are more

frequent. For patients with severe respiratory disease, consideration should be given to performing a gastrostomy. All patients have sequential compression boots applied as prophylaxis for pulmonary embolus. I have not used heparin or warfarin prophylaxis in this group of patients.

METABOLIC AND NEUROMECHANICAL PROBLEMS OF URINARY INTESTINAL DIVERSION

Problems that result from interposition of intestine in the urinary tract may be conveniently divided into three areas for the purposes of discussion: metabolic, neuromechanical, and technical-surgical. Metabolic complications are the result of altered solute reabsorption by the intestine of the urine that it contains. Neuromechanical aspects involve the configuration of the gut, which affects storage volume and contraction of the intestine that may lead to difficulties

TABLE 97-7 Complications: Transverse Colon Conduit*

	EARLY	LATE
Urine leak	8% (11/137)	8% (2/25)
Acute pyelonephritis		11% (8/75)
Wound infection	5% (5/92)	
Wound dehiscence	7% (8/109)	
Abscess		5% (3/62)
Prolonged ileus	6% (2/30)	
Ureteral stricture	6% (5/84)	17% (37/215)
Bowel obstruction	3% (1/30)	2% (2/109)
Parastomal hernia		4% (5/114)
Stones		11% (11/98)
Enterocutaneous fistula		2% (1/62)
Stomal stenosis		2% (1/62)
Stomal prolapse		11% (6/56)
Metabolic acidosis		12% (3/26)

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

TABLE 97-8 Complications: Sigmoid Conduit*

	EARLY	LATE
Urine leak	1% (1/70)	
Wound infection	1% (1/70)	
Wound dehiscence	1% (1/70)	
Acute pyelonephritis		7% (5/70)
Bowel obstruction		6% (4/70)
Ureteral stricture		9% (6/70)
Stones		4% (3/70)
Parastomal hernia		3% (2/70)
Stomal stenosis		3% (2/70)

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

TABLE 97-9 Complications: Ileocecal Conduit*

	EARLY	LATE
Urine leak	6% (9/147)	
Bowel leak	3% (5/147)	
Gastrointestinal bleeding	1% (1/147)	
Wound dehiscence	7% (11/147)	
Acute pyelonephritis		14% (20/147)
Bowel obstruction	3% (5/147)	10% (14/147)
Stomal prolapse		16% (24/147)
Parastomal hernia		5% (7/147)
Stomal stenosis		2% (3/147)
Stones		5% (8/147)
Fecal fistula		2% (3/147)

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

in storage. Finally, technical-surgical complications involve aspects of the procedure that result in surgical morbidity; these have been discussed after each section on the technical aspects of urinary intestinal diversion. The following is a discussion of metabolic and neuromechanical problems.

Metabolic Complications

Metabolic complications include electrolyte abnormalities, altered sensorium, abnormal drug metabolism, osteomalacia, growth retardation, persistent and recurrent infections, formation of renal and reservoir calculi, problems ensuing from removal of portions of the gut from the intestinal tract, and development of urothelial or intestinal cancer. Many of these complications are a consequence of altered solute absorption across the intestinal segment. The factors that influence the amount of solute and type of absorption are the segment of bowel used, the surface area of the bowel, the amount of time the urine is exposed to the bowel, the concentration of solutes in the urine, the renal function, and the pH of the fluid.

Electrolyte Abnormalities

Serum electrolyte complications and the type of electrolyte abnormalities that occur are different, depending on the segment of bowel used. If stomach is used, a hypochloremic metabolic alkalosis may occur. If jejunum is the segment used, hyponatremia, hyperkalemia, and metabolic acidosis occur. If the ileum or colon is used, a hyperchloremic metabolic acidosis ensues. Other electrolyte abnormalities that have been described include hypokalemia, hypomagnesemia, hypocalcemia, hyperammonemia, and elevated blood urea nitrogen and creatinine. Specific abnormalities for each segment of intestine are detailed.

When stomach is used, a hypochloremic, hypokalemic metabolic alkalosis may ensue. In general, this is not a significant problem unless the patient has concomitant renal failure, in which case there is a significant impairment of bicarbonate excretion or the patient is significantly dehydrated (Kurztrock et al, 1998). The metabolic alkalosis on occasion can be severe and life-threatening (syndrome of severe metabolic alkalosis) (Table 97-10). This syndrome has been reported in patients with normal renal function. When it is fully manifested, lethargy, respiratory insufficiency, seizures, and ventricular arrhythmias may occur (Gosalbez et al, 1993). These symptoms are usually preceded by vomiting resulting in dehydration. A pronounced hypochloremic, hypokalemic metabolic alkalosis ensues. Patients are usually successfully treated with an H₂ blocker to reduce proton secretion by the gastric segment and rehydration. In life-threatening circumstances, arginine hydrochloride infusion has been used to rapidly restore acid-base balance. On occasion, when H₂ blockers are ineffective, the proton pump blocker omeprazole has been successfully used. Rarely, omeprazole is ineffective, and if the life-threatening metabolic alkalosis persists, the gastric segment must be removed (Gosalbez et al, 1993).

The role of the serum concentration of gastrin appears pivotal in the syndrome. In the severe cases that have been reported, there is typically an elevated serum gastrin level. Serum gastrin levels are significantly correlated with systemic bicarbonate concentration in gastrectomy patients; the greater the gastrin level, the more severe the metabolic alkalosis (Tanrikut and McDougal, 2004). When volume depletion, hypochloremia, and hypokalemia result from vomiting in those who normally have elevated circulating gastrin levels and a persisting long-standing metabolic alkalosis, the patient is at greater risk for development of the syndrome of severe metabolic alkalosis and manifestation of the symptoms outlined previously. Thus, persistent loss of protons from the gastric-augmented bladder with net addition of bicarbonate to the systemic circulation, alteration of normal homeostatic mechanisms for acute changes in acid-base balance, and impaired ability of even a normal kidney to excrete bicarbonate in the face of hypochloremia, hypokalemia, and increased circulating aldosterone levels (because of the dehydration) create a vicious circle in which normal homeostatic mechanisms are circumvented. Indeed, elevated aldosterone levels have been reported in this syndrome (Gosalbez et al, 1993). Hypokalemia, hypochloremia, and increased aldosterone levels impair the kidney's ability to excrete excess bicarbonate. These perturbations coupled with a continued addition of bicarbonate from

TABLE 97-10 Syndromes of Electrolyte Disturbances in Patients in Whom Bowel Is Interposed in the Urinary Tract

SYNDROME	SEGMENT	SYMPTOMS	ASSOCIATED ABNORMALITIES
Syndrome of severe metabolic alkalosis	Stomach	Lethargy, muscle weakness, respiratory insufficiency, seizures, ventricular arrhythmia	Elevated aldosterone, hypochloremia, hypokalemia
Syndrome of hyperkalemia, hypochloremia, metabolic acidosis	Jejunum	Lethargy, nausea, vomiting, dehydration, muscle weakness	Elevated renin, angiotensin
Syndrome of hyperchloremia, metabolic acidosis	Ileum, colon	Fatigue, anorexia, lethargy, weakness	Total-body potassium depletion, hypocalcemia

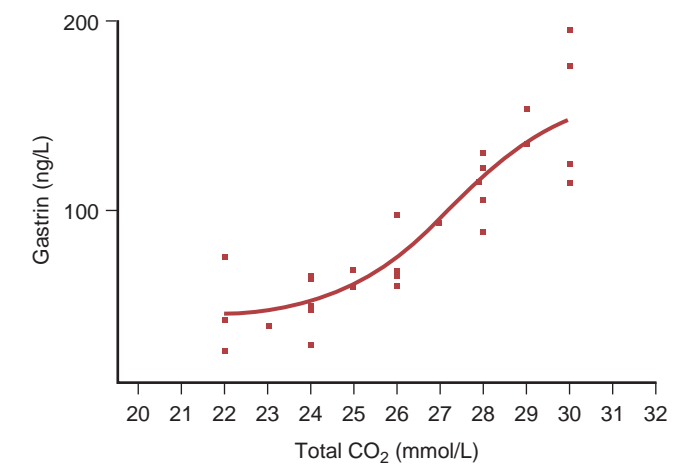


Figure 97-40. Sigmoid relationship of serum gastrin level to serum bicarbonate. Notice that over the physiologic range of normal gastrin levels, 10 to 120 ng/L, there is little change in serum bicarbonate. However, at levels of serum gastrin in excess of 120 ng/L, small changes in serum gastrin levels result in large changes in serum bicarbonate.

the gastric segment produce the extreme electrolyte abnormalities noted in the patients described. In view of the sigmoid correlation of serum bicarbonate to gastrin levels in patients with gastric segments in the urinary tract, patients at greatest risk for development of the syndrome of severe metabolic alkalosis are those whose serum gastrin concentrations exceed 120 ng/L because on this portion of the curve, small additional increments in gastrin concentration result in large increases in serum bicarbonate (Fig. 97-40). On the other hand, patients with serum gastrin concentrations below 100 ng/L can have significant increases in gastrin levels with little change in serum bicarbonate. Failure to properly empty the diversion with overdistention of the gastric segment would be expected to increase the serum gastrin level because stretch is a stimulus for gastrin release. For those who have either an elevated resting gastrin level in excess of 120 ng/L or impaired renal function, both patient and physician should be made aware of the consequences of dehydration and distention of the segment.

Electrolyte disorders that occur when jejunum is used for urinary intestinal diversion, particularly when proximal jejunum is used, include hyponatremia, hypochloremia, hyperkalemia, azotemia, and acidosis (see Table 97-10). These disorders result from an increased secretion of sodium and chloride with an increased reabsorption of potassium and hydrogen ions. This excessive loss of sodium chloride carries with it water, and thus the patient becomes dehydrated. The dehydration results in hypovolemia, which increases renin secretion and thereby aldosterone production (Golimbu and Morales, 1975). Aldosterone production may also be stimulated by hyperkalemia. The high levels of renin-aldosterone facilitate sodium reabsorption by the kidney and

potassium loss, which produce a urine low in sodium content and high in potassium. This, when presented to the jejunum, results in a favorable concentration gradient for loss of sodium by the jejunum and increased reabsorption of potassium, thus perpetuating the abnormalities.

These electrolyte abnormalities result in lethargy, nausea, vomiting, dehydration, muscle weakness, and elevated temperature. If the abnormalities are allowed to persist, the patient may become moribund and finally die. This syndrome may be exacerbated by administration of hyperalimentation solutions. The mechanism by which hyperalimentation solutions exacerbate this syndrome in patients with jejunal intestine interposed in the urinary tract is unclear (Bonnheim et al, 1984). The severity of the syndrome depends on the location of the segment of jejunum that is used. The more proximal the segment, the more likely the syndrome is to develop. Its incidence varies from a low of 25% (Klein et al, 1986) to the majority of patients demonstrating significant abnormalities. Severe abnormalities may occur in as few as 4% when short segments are used (Fontaine et al, 1997). Treatment of the disorder is rehydration with sodium chloride and correction of the acidosis with sodium bicarbonate. Provided that renal function is normal, the hyperkalemia is corrected by renal secretion. On occasion, a diuretic may be helpful to correct the hyperkalemia. After restoration of normal electrolyte balance, long-term therapy involves oral supplements with sodium chloride. A thiazide diuretic has also been useful in selected patients to control hyperkalemia in the long term (Hasan et al, 1994).

The electrolyte abnormality that occurs with the ileum and colon is hyperchloremic metabolic acidosis (see Table 97-10). This acidosis occurs to some degree in most patients who have ileum or colon interposed in the urinary tract but is usually of a minor degree. Its clinical significance when it is of a minor degree at this time is unknown. Hyperchloremic acidosis has been reported with a frequency of 68% of patients (19 of 28 patients; 10 of the 19 cases were severe enough to require treatment) with ileal conduits (Castro and Ram, 1970). In another study, 70% of patients with ileal conduits observed for 4 years or longer had a decreased serum bicarbonate concentration (Malek et al, 1971). A more current study places the incidence at about 25% (Nieuwenhuijzen et al, 2008) with about 4% requiring hospitalization for correction (Studer et al, 2006). Severe electrolyte disturbances occur to a much lesser degree. It has been reported to be a major problem in 18% of patients (8 of 45) with intestinal cystoplasties (Whitmore and Gittes, 1983), in 10% of patients (17 of 178) with ileal conduits (Schmidt et al, 1973), and in 80% of patients (112 of 141) with ureterosigmoidostomies (Ferris and Odel, 1950). In continent diversions involving either ileum and cecum or cecum alone, most patients have an elevated serum chloride and depressed serum bicarbonate (Ashken, 1987; McDougal et al, 1989). Sixty-five percent of patients with Mainz pouches require alkali therapy to maintain a normal acid-base balance (Thuroff et al, 1987). Early reports of patients with continent diversions made of ileum note a much lower incidence of electrolyte problems, in the range of 10% to 15% (see Table 97-3) (Allen et al, 1985; Boyd et al, 1989). Symptoms in those in whom the syndrome is severe include easy fatigability, anorexia, weight loss, polydipsia, and lethargy.

Those with ureterosigmoidostomies also have an exacerbation of diarrhea.

These electrolyte abnormalities, if significant and allowed to persist, result in major metabolic abnormalities, to be discussed subsequently. In and of themselves, however, they may be lethal because severe electrolyte abnormalities have contributed to death of patients (Heidler et al, 1979).

The mechanism of hyperchloremic metabolic acidosis is a result of the ionized transport of ammonium. Ammonium substitutes for sodium in the $\text{Na}^+\text{-H}^+$ antiport. The exchange of the weak acid NH_4 for a proton is coupled with the exchange of bicarbonate for chloride. Thus ammonium chloride is absorbed across the lumen into the blood in exchange for carbonic acid (i.e., CO_2 and water). Ammonium may also gain entry to the blood from bowel lumen through potassium channels (McDougal et al, 1995).

The treatment of hyperchloremic metabolic acidosis involves administration of alkalinizing agents or blockers of chloride transport. Alkalinization with oral sodium bicarbonate is effective in restoring normal acid-base balance. Oral administration of bicarbonate may not be tolerated particularly well, however, because it can produce considerable intestinal gas. An effective alternative is sodium citrate and citric acid solution (Bicitra or Shohl solution) used together; however, many patients do not care for the taste. Potassium citrate, sodium citrate, and citric acid solution (Polycitra) may be used instead if excessive sodium administration is a problem because of cardiac or renal disease and if potassium supplementation is desirable or at least not harmful. In patients in whom persistent hyperchloremic metabolic acidosis occurs and in whom excessive sodium loads are undesirable, chlorpromazine or nicotinic acid may be used to limit the degree of the acidosis. These agents used alone do not correct the acidosis in humans, but they limit its development and thus reduce the need for alkalinizing agents. Chlorpromazine and nicotinic acid inhibit cyclic adenosine monophosphate and thereby impede chloride transport. Chlorpromazine may be given at a dose of 25 mg three times a day. On occasion, as much as 50 mg three times a day may be necessary, but at such doses, side effects are not uncommon. Chlorpromazine should be used with care in adults because there are many untoward side effects including tardive dyskinesia. Nicotinic acid may be given at a dose of 400 mg three or four times a day. The drug should not be used in patients with peptic ulcer disease or significant hepatic insufficiency. Side effects that may be observed include exacerbation of liver dysfunction, exacerbation of peptic ulcer disease, headaches, and double vision. Flushing and dermatitis are not uncommon and generally disappear as the patient becomes adapted to the drug.

Hypokalemia and total-body depletion of potassium may occur in patients with urinary intestinal diversion. This is more common in patients with ureterosigmoidostomies than it is in patients who have other types of urinary intestinal diversion (Geist and Ansell, 1961). In one study, patients with ureterocolonic diversions had a 30% reduction in total body potassium, whereas those with ileal conduits had, as a group, no significant alteration in total body potassium; individually, however, some had as much as a 14% reduction in total body potassium (Williams et al, 1967). Patients with continent diversions have also been noted to have a decrease in total body potassium. The patients most susceptible to total body potassium depletion are those with long-standing uncorrected metabolic acidosis (Stein et al, 1998). The potassium depletion is probably caused by renal potassium wasting as a consequence of renal damage, osmotic diuresis, and gut loss through intestinal secretion. The last-mentioned (probably quantitatively) plays a relatively minor role. Indeed, it has been shown that ileal segments exposed to high concentrations of potassium in the urine reabsorb some of the potassium, whereas colon is less likely to do so (Koch et al, 1990). Thus those with ileum interposed in the urinary tract likely blunt the potassium loss by the kidney, whereas those with colon do not, which explains why patients with ureterosigmoidostomies and ureterocolonic diversions are more likely to have total body potassium depletion.

When the depletion is severe, the patient may develop a flaccid paralysis. In treating these patients, one must remember that if the hypokalemia is associated with severe hyperchloremic metabolic acidosis, treatment must involve both replacement of potassium and correction of the acidosis with bicarbonate. If the acidosis is corrected without attention to potassium replacement, severe hypokalemia may occur, marked flaccid paralysis may develop, and significant morbidity may ensue (Koff, 1975).

Because the bowel transports solutes and because its membrane is not particularly watertight, osmolality generally re-equilibrates across the bowel wall. Thus attempts to deprive a patient of water and determine osmolality as a reflection of renal function are inappropriate because the bowel alters the osmotic content. The bowel also makes the contents more alkaline, and therefore it is impossible to determine the ability of the kidney to acidify simply by measuring urinary pH in patients with urinary intestinal diversion. Finally, because urea and creatinine are reabsorbed by both the ileum and the colon, serum concentrations of urea and creatinine do not necessarily accurately reflect renal function (Koch and McDougal, 1985; McDougal and Koch, 1986).

Histologic alterations of the intestine may occur over time when urine is chronically exposed to the mucosa. Villous atrophy and the formation of pseudocrypts may occur, particularly in the ileum. These changes are patchy because there is normal ileal mucosa interspersed between these abnormalities. Submucosal inflammatory infiltrates may also be observed. There appear to be fewer changes in the colonic mucosa during the long term. In the colon, a decrease in the size of goblet cells has been described. In time, some transport processes may be altered, with some solutes less actively transported, whereas other processes of solute transport remain active (Philipson et al, 1983). The ability to establish a hyperchloremic metabolic acidosis, however, appears to be retained by most segments of ileum and colon over time. In an experimental study, chronic exposure of intestine to urine resulted in a decreased number of transporters, but those that remained were perfectly functional (Grocela and McDougal, 1999).

Altered Sensorium

Alteration of the sensorium may occur as a consequence of magnesium deficiency, drug intoxication, or abnormalities in ammonia metabolism. Patients who develop magnesium deficiency do so either secondary to nutritional depletion or in relation to magnesium wasting by the kidney in much the same way that calcium wasting occurs (see later). Alterations in the sensorium have also occurred because of diabetic hyperglycemia; however, this is not a consequence of the intestinal diversion. In such patients, reabsorption of urinary glucose can result in hyperglycemia without demonstrable glucosuria (Onwubalili, 1982). Perhaps the more common cause of an altered sensorium is altered ammonia metabolism. Ammoniogenic coma in patients with urinary intestinal diversion has been reported in those with cirrhosis (Silberman, 1958), those with altered liver function without underlying chronic liver disease (McDermott, 1957), and those with normal hepatic function as determined by serum enzyme activities (Mounger and Branson, 1972; Kaufman, 1984; Perez-Fidalgo et al, 2007). The syndrome is most commonly associated with decreased liver function, however, and even in patients in whom normal liver function has been reported, the crude methods by which it was assessed in those reports have made it impossible to confirm the absence of subtle alterations in liver function. The syndrome is most commonly found in patients with ureterosigmoidostomies but has been reported in those with ileal conduits as well (McDermott, 1957).

The treatment of ammoniogenic coma involves draining the urinary intestinal diversion, either with a rectal tube in patients with ureterosigmoidostomy or with a Foley catheter in those with a continent diversion so that the urine does not remain exposed to the intestine for extended periods. Neomycin is administered orally to reduce the ammonia load from the enteric tract, and

protein consumption is curtailed, thus limiting the nitrogen load to the patient until serum ammonium levels have returned to normal. In severe circumstances, arginine glutamate, 50 g in 1000 mL of 5% dextrose in water, may be given intravenously. This complexes the ammonia by providing substrate for the formation of glutamine (Silberman, 1958). Lactulose may be given orally or by rectum (Edwards, 1984). This complexes the ammonia in the gut and prevents its absorption. Consult the hospital pharmacist for dosages and schedules of these therapies.

Abnormal Drug Absorption

Drug intoxication has been reported in patients with urinary intestinal diversion. **Drugs more likely to be problematic are those absorbed by the gastrointestinal tract and excreted unchanged by the kidney.** Thus the excreted drug is re-exposed to the intestinal segment, which then reabsorbs it, and toxic serum levels develop. This has been reported with phenytoin (Dilantin) (Savarirayan and Dixey, 1969) and with certain antibiotics that are excreted unchanged. Although chemotherapy is usually well tolerated by patients with conduits, methotrexate toxicity has been documented in a patient with an ileal conduit (Bowyer and Davies, 1986).

A more recent study suggests that in patients with normal renal function, both those with and those without continent diversions tolerate chemotherapy well. The authors studied 23 patients with continent diversions and 19 with ileal conduits who received cisplatin, methotrexate, and vinblastine. The authors concluded that there was no difference in toxicity in patients without diversions, those with ileal conduits, and those with continent diversions. Indeed, the patients with continent diversions did not have a Foley catheter placed during the chemotherapy infusion. However, if one looks carefully at the data, it is clear that there is in fact an increased toxicity in the continent diversion group, although it did not achieve statistical significance (Srinivas et al, 1998). In patients receiving antimetabolites, it is prudent to carefully monitor the patient for toxic products that are excreted in the urine and capable of intestinal absorption, lest lethal toxic serum levels develop. **Moreover, in patients with continent diversions who are receiving chemotherapy, consideration should be given to draining the pouch while the toxic drugs are being administered.**

Osteomalacia

Osteomalacia or renal rickets occurs when mineralized bone is reduced and the osteoid component becomes excessive. Osteomalacia has been reported in patients with colocolostomy (Hassain, 1970), ileal ureters (Salahudeen et al, 1984), colon and ileal conduits, and, most commonly, ureterosigmoidostomies (Harrison, 1958; Specht, 1967). **The cause of osteomalacia may be multifactorial but commonly involves acidosis.** With persistent acidosis, the excess protons are buffered by the bone with release of bone calcium. With its release, it is excreted by the kidney. Support for the theory that chronic acidosis is causative in osteomalacia comes from those patients in whom correction of the acidosis results in remineralization of the bone (Richards et al, 1972; Siklos et al, 1980). It has also been shown, however, that major alterations in serum bicarbonate are not necessary for the development of the syndrome (Koch and McDougal, 1988; McDougal et al, 1988). Moreover, some patients with osteomalacia secondary to urinary intestinal diversion do not have bone demineralization corrected with restoration of normal acid-base balance. **These patients have been found to manifest vitamin D resistance that is independent of the acidosis.** It is likely that this resistance is of renal origin. Resistance can be overcome by supplying 1 α -hydroxycholecalciferol, a vitamin D metabolite that is much more potent than vitamin D₂. When this substrate is provided in excess amount, remineralization of bone occurs (Perry et al, 1977). Also, it has been shown that reabsorption of urinary solutes may play a role in increasing calcium excretion by the kidney. Sulfate filtered by the kidney inhibits calcium reabsorption and results in both calcium and magnesium loss by the kidney. Thus if the gut increases its sulfate reabsorption

and requires the kidney to increase sulfate excretion, this results in hypercalciuria and hypermagnesuria (McDougal and Koch, 1989). Finally, there is some evidence to indicate that the calcium-to-parathormone ratio is altered, suggesting that a resistance to parathormones develops during the long term (Tanrikut and McDougal, 2004). **Osteomalacia in urinary intestinal diversion may be caused by persistent acidosis, vitamin D resistance, and excessive calcium loss by the kidney.** It appears that the degree to which each of these contributes to the syndrome may vary from patient to patient.

It is clear that a number of metabolic problems have been obviated when meticulous attention is paid to correction of the abnormalities prospectively. If a base deficit of more than 2.5 mEq/L is corrected, some investigators have found no evidence of bone mineral density abnormalities (Stein et al, 1998). Indeed, the type of diversion does not seem to make a difference when the acidosis is taken into account and corrected (Kawakita et al, 1996). Others suggest that there is no difference in continent diversions and ileal conduits (Campanello et al, 1996); however, in such selected series, the distribution of acidosis across both groups is typically identical. It is clear that if the groups are large enough and not preselected, there is an increased incidence of acidosis in continent diversion patients. Indeed, if patients are followed long enough, some will develop bone mineral density abnormalities, particularly those who are acidotic over the long term (Incel et al, 2006). The take-home message is that if one pays meticulous attention to correction of the acidosis, bone mineral density abnormalities will probably not become a problem.

In general, patients who develop osteomalacia report lethargy; joint pain, especially in the weight-bearing joints; and proximal myopathy. Analysis of serum chemistries reveals that the calcium concentration is either low or normal. The alkaline phosphatase level is elevated, and the phosphate level is low or normal (Harrison, 1958). The treatment as indicated earlier involves correction of the acidosis and dietary supplementation of calcium. If this does not result in remineralization of the bone, the active form of vitamin D may be administered. If this is not successful, the more active metabolite of vitamin D₃, 1 α -hydroxycholecalciferol, should be administered.

Growth and Development

Considerable evidence suggests that urinary intestinal diversion has a detrimental effect on growth and development. In a study of 93 myelodysplasia patients observed for 17 to 23 years, significant aberrations in growth were noted when morphometric parameters were analyzed. Anthropometric measurements in those with urinary intestinal diversion showed a decrease in linear growth in all indices measured, with a statistically significant decrease in biacromial span and elbow-hand length (Koch et al, 1992).

Patients with long-term urinary diversions are more susceptible to fractures and to complications after orthopedic procedures. When myelodysplastic patients with ileal conduits were compared with a similar group of patients who retained their bladder and were on intermittent catheterization, the patients with an ileal conduit had an increased number of fractures, as well as malunions and nonunions after orthopedic procedures (Koch et al, 1992). It was found that more patients with urinary intestinal diversion fell below the tenth percentile than did patients who were treated with intermittent catheterization. There was, in fact, no difference in height and weight between the two groups studied (Koch et al, 1992; McDougal, 1992).

There is also experimental evidence for impaired linear growth in urinary intestinal diversion. Rats with unilateral ureterosigmoidostomies observed long term demonstrated significantly decreased femoral bone length compared with nondiverted controls (Koch and McDougal, 1988). Thus it appears clear that although obvious alterations in growth and development do not occur, when carefully studied, patients who have urinary intestinal diversions constructed in childhood and who maintain these diversions for more than 10 years have significant changes in linear growth.

Infection

An increased incidence of bacteriuria, bacteremia, and septic episodes occurs in patients with bowel interposition. A significant number of patients with intestinal cystoplasty develop pyelonephritis, and 13% have septic and major infectious complications (Kuss et al, 1970). The episodes are more frequent after colocolostomy than ileocolostomy (Kuss et al, 1970). In a contemporary series, 4% of patients were admitted to a hospital for sepsis (Studer et al, 2006). Acute pyelonephritis occurs in 10% to 17% of patients with colon and ileal conduits (Schmidt et al, 1973; Schwarz and Jeffs, 1975; Hagen-Cook and Althausen, 1979). Approximately 4% of patients (8 of 178) with ileal conduits die of sepsis (Schmidt et al, 1973).

Patients with conduits have a high incidence of bacteriuria. Indeed, approximately three quarters of ileal conduit urine specimens are infected (Guinan et al, 1972; Middleton and Hendren, 1976; Elder et al, 1979). It is clear that some patients are merely colonized at the distal end of the conduit because the incidence of positive cultures can be markedly diminished by culture of the proximal portion of the loop by a double-catheter technique (Smith, 1972). Many of these patients, however, show no untoward effects and seem to do well with chronic bacteriuria. Deterioration of the upper tracts is more likely when the culture becomes dominant for *Proteus* or *Pseudomonas*. Thus patients with relatively pure cultures of *Proteus* or *Pseudomonas* should be treated, whereas those with mixed cultures may, in general, be observed, provided they are not symptomatic. Patients with continent diversions also have a significant incidence of bacteriuria and septic episodes (McDougal, 1986). Indeed, two thirds of patients with Kock continent diversions have positive cultures (Kock, 1987). The reasons for the increased incidence of bacteriuria and sepsis are unclear, but it is likely that the intestine is incapable of inhibiting bacterial proliferation, in contrast to the urothelium. Thus intestine that normally lives symbiotically with bacteria when interposed in the urinary tract serves as a source for ascending infection and septic complications. Moreover, the intestine may make the urine less bacteriostatic and thereby promote the growth of bacteria. Distention of the intestinal segment may aid in translocation of bacteria across the intestine and into the blood. Studies have shown some changes in intestinal mucosal immunologic bacterial defense mechanisms; however, for the most part they seem to be preserved (Wullt et al, 2004).

Stones

One of the consequences of persistent infection is the development of magnesium ammonium phosphate stones. Indeed, the great majority of stones formed in patients with urinary intestinal diversions are composed of calcium, magnesium, and ammonium phosphate. Those most susceptible to development of renal calculi are patients who have hyperchloremic metabolic acidosis, preexisting pyelonephritis, and urinary tract infection with a urea-splitting organism (Dretler, 1973). The incidence of renal stones is 3% to 4% in patients with colon conduits (Althausen et al, 1978; Hagen-Cook and Althausen, 1979) and 10% to 12% in those with ileal conduits (Schmidt et al, 1973). In those with continent cecal reservoirs, there is a 20% incidence of calculi within the reservoir (Ashken, 1987). The stones may be a result of persistent infection with alkalization of the urine, persistent hypercalciuria for reasons described previously, and alterations of urinary excretion products by the intestine. A major cause of calculus formation in conduits and pouches is a foreign body such as a staple or nonabsorbable suture, on which concretions form. In intestinal reservoirs, alterations in bowel mucosa may also serve as a nidus for stone formation. Finally, alterations in intestinal mucus, particularly in the presence of infection or obstruction, may serve as a nidus or, more important, may interfere with emptying and thereby exacerbate infection and stone formation (N'Dow et al, 2004).

Intestinal Motility, Short Bowel, and Nutritional Problems

Many nutritional problems may occur from the loss of significant intestinal absorptive surface resulting from removal of substantial portions of the gut for construction of a urinary intestinal diversion. In patients with a significant loss of ileum, vitamin B₁₂ malabsorption has been reported and results in anemia and neurologic abnormalities. Vitamin B₁₂ deficiency has been shown to occur in 10 of 41 patients who received preoperative radiotherapy before radical cystectomy and ileal ureterostomy (Kinn and Lantz, 1984), and 21% of children who have undergone ileocolostomy have low serum levels of vitamin B₁₂ (Rosenbaum et al, 2008). Loss of significant portions of ileum also results in malabsorption of bile salts. Because the ileum is the major site of bile salt reabsorption, the lack of reabsorption allows bile salts entry into the colon, which causes mucosal irritation and diarrhea. Also, loss of the ileum results in the loss of the "ileal break." The ileal break is a mechanism whereby gut motility is reduced when lipids come in contact with the ileal mucosa so that increased absorption can occur. With the loss of ileum, the lipid does not result in decreased motility and is presented unmetabolized to the colon, which may cause fatty diarrhea.

It has been difficult to demonstrate untoward effects of low serum vitamin B₁₂ levels in these patients. The liver stores enough vitamin B₁₂ to supply the body's requirement for 3 to 5 years without oral intake. Thus pathologic problems would not be expected to manifest themselves for many years and have rarely been reported. Moreover, low serum levels of vitamin B₁₂ do not necessarily correlate with metabolic deficiency. To assess whether or not there is a metabolic impact, it is necessary to measure serum levels of homocysteine and/or methylmalonic acid. Because vitamin B₁₂ serves as a coenzyme in the metabolic pathways of homocysteine and methylmalonic acid, their measurement is a sensitive indicator of whether the low vitamin B₁₂ level is significant. These measurements have not been done in this group of patients, and thus it is unclear at this time as to the importance of vitamin B₁₂ measurements in these patients. Many physicians, however, empirically give parenteral vitamin B₁₂ as a precaution to patients who have had intestinal diversions of ileum in place for more than 5 to 7 years.

Loss of the ileocecal valve may have a number of untoward effects. Because of the loss of the valve, reflux of large concentrations of bacteria into the ileum may occur, resulting in small intestinal bacterial overgrowth. This may result in nutritional abnormalities that involve interference with fatty acid reabsorption and bile salt interaction. With the lack of absorption of fats and bile salts, these are presented to the colon and result in diarrhea. Moreover, reflux of bacteria into the small bowel may result in bile salt deficiency. Also, the lack of fat absorption may result in deficiencies of the fat-soluble vitamin A, osteomalacia caused by lack of vitamin D, and complexing of calcium with the fats to form soaps, thus preventing its absorption. The ileocecal valve also serves as a break, and an intact valve prolongs transit time of the small bowel and enhances absorption. Thus its loss may contribute to nutritional abnormalities. Some have advocated reconstruction of the valve mechanism between ileum and colon when the ileocecal segment is used for reconstruction.

Loss of a significant portion of jejunum may result in malabsorption of fat, calcium, and folic acid; however, significant portions of jejunum are rarely used for urologic reconstructive procedures. Loss of the colon may result in diarrhea because of lack of fluid and electrolyte absorption, loss of bicarbonate because of its increased secretion in the ileum and lack of reabsorption, and dehydration because of the loss of fluids.

Of concern when intestinal segments are used in urinary reconstruction is the effect removal of a segment of intestine from the alimentary tract might have on intrinsic bowel function. Indeed, removal of major segments from the alimentary tract may cause nocturnal bowel movements, fecal urgency, fecal incontinence, diarrhea, and nutritional deficiencies (Riddick et al, 2004). A study compared patients with ileal conduits with those who had segments

used for clam cystoplasty and, not surprising, found that those with clam cystoplasty had a 40% incidence of significant bowel problems. It is known that there is an association between detrusor instability and irritable bowel, perhaps accounting for the incidence of untoward disorders of bowel function in this series (N'Dow et al, 1998). Thus there is a need for heightened awareness of bowel dysfunction in patients with detrusor instability in whom bowel segments are to be used. A recent report of patients who had an ileocystoplasty noted that 7% had significant diarrhea (Blaivas et al, 2005). One should warn patients who will have major portions of the intestinal tract used in the reconstruction that bowel problems may ensue.

Cancer

The incidence of cancer development in patients with ureterosigmoidostomy varies between 6% and 29%, with a mean of 11% (Schipper and Decter, 1981; Stewart et al, 1982; Zabbo and Kay, 1986). In general, there is a 10- to 20-year delay before the cancer manifests. **On histologic examination, the tumors include adenocarcinoma, adenomatous polyps, sarcomas, and transitional cell carcinoma.** Case reports of tumors developing in patients with ileal conduits, colon conduits, bladder augmentations, rectal bladder, neobladders, and ileal ureters have been described (Austen and Kalble, 2004). Anaplastic carcinomas and adenomatous polyps have been reported in patients with ileal conduits. Adenocarcinoma has developed in patients with colon conduits; adenocarcinoma, undifferentiated carcinoma, sarcomas, and transitional cell carcinomas have developed in patients with bladder augmentations with both ileum and colon (Filmer, 1986).

The causative mechanism of the development of the carcinoma is not understood. Whether the tumor arises from transitional epithelium or colonic epithelium is unclear. Because most of the tumors are adenocarcinomas, it has been assumed that the tumor arises from the intestinal epithelium. Adenocarcinomas have been shown to arise from transitional cell epithelium exposed to the fecal stream in experimental animals (Aaronson et al, 1989). Furthermore, studies show that the ureters in ureterosigmoidostomy patients have an exceedingly high incidence of dysplasia (Aaronson and Sinclair-Smith, 1984). Moreover, if the transitional epithelium is removed from the enteric tract, adenocarcinomas do not develop. **If the urothelium is left in contact with the intestinal mucosa, however, even though the diversion is defunctionalized and the area is not bathed in urine, adenocarcinoma may still develop.** This is illustrated by a case report in which a patient who had a ureterosigmoidostomy that was defunctionalized with a conduit subsequently developed cancer 9 months later. The distal ureters at the sigmoid were left in situ. Twenty-two years later, the patient developed cancer at the site of the ureterointestinal anastomosis (Schipper and Decter, 1981). This suggests that **when ureterointestinal anastomoses are defunctionalized, they should be excised rather than merely ligated and left in situ.** Other evidence including cell staining techniques suggests that the colon is the primary organ of origin (Mundy, personal communication, 1991). Whether the urothelium or intestine is the primary site of origin, it seems likely that tumors can arise from both tissues.

The highest incidence of cancer occurs when the transitional epithelium is juxtaposed to the colonic epithelium and both are bathed by feces (Shands et al, 1989). Nitrosamines, known mutagens, are produced in rats with ureterosigmoidostomy (Cohen et al, 1987), but there appears at least at this juncture no convincing evidence to support a primary role for them in the genesis of the tumor. An abnormal pattern of colonic mucin secretion has been demonstrated in patients with ureterosigmoidostomy, but its significance is unclear (Iannoni et al, 1986). Induction of specific enzymes associated with carcinoma has also been demonstrated. Ornithine decarboxylase, an enzyme that has been found to be elevated in malignant colonic mucosa, is also elevated in experimental animals with vesicosigmoidostomy (Weber et al, 1988). The role of epidermal growth factor and other growth factors is currently being investigated. Evidence suggests that these may at least play a

role in development, if not in induction. At this time, the cause of the genesis of cancer in urinary intestinal diversion is not known. **Because its incidence is significant in patients with ureterosigmoidostomies, they should have routine colonoscopies on a scheduled periodic basis.**

Neuromechanical Aspects of Intestinal Segments

Both small bowel and colon contract to propel luminal contents in an aboral direction. The ability to propel luminal contents is a consequence of muscle activity, as well as coordinated nerve activity. Both the small bowel and the colon have an outer longitudinal layer of muscle and an inner circular layer. There is also a muscularis mucosa, which is immediately beneath the mucosa and may extend into the villi. The outer and inner layers of muscle, however, play the major role in peristalsis. In the colon, the outer longitudinal layer of muscle condenses to form three taeniae coli. The bowel receives its parasympathetic innervation from the vagus. It is also innervated by the sympathetic nervous system. The nerves lie between the circular and longitudinal layers of muscle. The enteric nervous system operates autonomously, and therefore one can denervate the intestine and not affect the coordinated contractions. These contractions are termed *activity fronts* and may be stimulated by feeding, or they may be inhibited by exposure of the lumen to various substances (e.g., lipid in the ileum decreases ileal motility). Two aspects of neuromechanical properties are particularly germane to urinary intestinal diversion: volume-pressure relationships and motor activity.

Volume-Pressure Considerations

The volume-pressure relationships depend on the configuration of the bowel. If one splits the bowel segment and turns it back on itself, the volume may be doubled if the ends are not closed (Fig. 97-41). In reconstruction of intestinal segments for the urinary tract, however, one must close the ends. Thus the limit of doubling the volume is never quite reached. Indeed, the greater the ratio of length to diameter, the greater the volume change when the ends are closed. If the ends are closed when a ratio of diameter to length of 1:3.5 is reached, splitting the segment no longer increases the volume. By splitting most segments, one is, in fact, increasing the volume by about 50%. The goal in reconfiguring the bowel is to achieve a spheric storage vessel. This

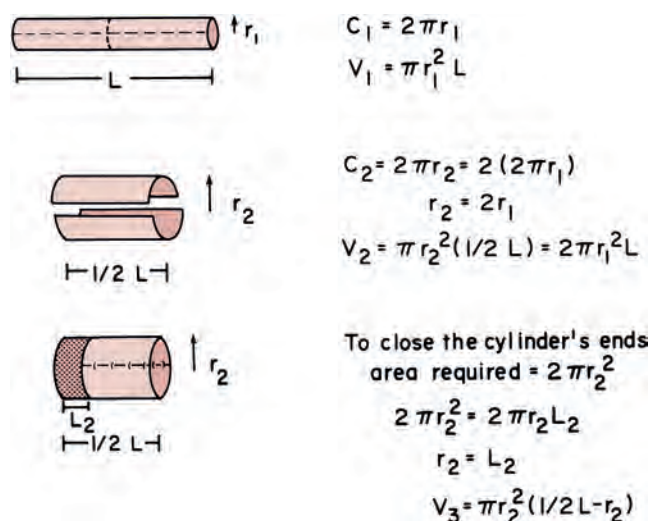


Figure 97-41. Effect of "detubularization." The bowel is split on its antimesenteric border and divided in two. When the two segments are placed together, the circumference is doubled, thus doubling the volume. Closing the ends of the cylinder requires a reduction in its length equal to the radius of the end. This limits the increase in volume that occurs by reconfiguration.

configuration has the most volume for the least surface area. By increasing the volume, it has been suggested that pressure relationships within the confines of the intestine are reduced. This is based on Laplace's law, which states that for a sphere, the tension of its wall is proportional to the product of the radius and pressure. Thus theoretically, for a given wall tension, the greater the radius, the smaller the generated pressure. This is desirable in an attempt to prevent deterioration of the upper tracts or incontinence. This relationship (Laplace's law), however, may not be accurately reflected for intestinal segments because they are not perfectly spheric, and the intestinal wall does not conform to Hooke's law but rather demonstrates viscoelastic properties, which tend to distort the relationship between pressure applied at the wall and tension generated in it. In any event, it seems desirable to attempt to construct as spheric a container as possible if one is attempting to make a reservoir.

Over time, the volume capacity of segments increases. This occurs only if they are frequently filled. Their volume decreases with time if they are nonfunctional (Kock et al, 1978). Over time, it can be demonstrated that there is a marked accommodation in volume of pouches made from intestine. For ileal pouches, it has been shown that the capacity increases sevenfold after 1 year (Berglund et al, 1987). As the reservoirs increase in volume, there is a significant increase in smooth muscle thickness of the bowel wall (Philipson et al, 1983).

Motor Activity

It has been suggested that splitting the bowel on its antimesenteric border discoordinates motor activity and thereby causes a lesser intraluminal pressure. Clearly, the ideal situation is to provide the patient with a spheric vessel that has few or ineffective contractions of its walls. It can be demonstrated in experimental animals that after the bowel wall has been split on its antimesenteric border and reconfigured, acutely there is a marked interruption of coordinated activity fronts, which over a period of 3 months return to their normal coordinated state (Concepcion et al, 1988). This has also been demonstrated clinically: Initially after reconfiguration of the bowel (detubularization), coordinated activity fronts have been shown to decrease. During extended periods, however, many of the peristaltic waves (activity fronts) reappear and can be readily demonstrated (Fig. 97-42).

The literature is contradictory with respect to the effect of detubularization on segments of ileum and colon used to construct storage vessels for continent diversions. Pressure within the lumen of bowel that has both ends closed may be increased by adding volume or reducing the size of the bowel through contractions of its wall. Because the bowel wall is freely permeable to water, the higher osmotic content of urine obligates movement of water into the bowel lumen. Most patients with continent diversions excrete 2 to 4 L/day (McDougal, 1986). In evaluating whether motor activity is the primary determinant of intravesical pressure, one must be cognizant of fluid volume changes. Also, as indicated previously, early reports of detubularized segments would be

expected to differ from later reports when coordinated activity fronts in these segments return.

These facts are often forgotten, and because pressure measurements are used to infer motor activity, rather than its direct measurement as reflected by changes in bowel wall tension, it is not difficult to understand why there are so many contradictions reported in the literature. Detubularization of ileal segments has been reported by some to decrease motor activity at a year compared with immediately postoperatively (Berglund et al, 1987), whereas others have noted increased motor activity at 1 year. Involuntary pressure waves occur in 25% of patients with Kock pouches. Maximum intravesical pressures average 41 cm H₂O in these pouches (Chen et al, 1989). Ileum has also been shown to have fewer activity fronts per unit of time than cecum (Berglund et al, 1986). Cecum has been observed to have the same number of activity fronts 1 year postoperatively, but the amplitude of the pressure waves has been observed to decrease over time (Hedlund et al, 1984). Maximum pressures in normal cecum have been shown to range from 18 to 100 cm H₂O (Jakobsen et al, 1987), whereas detubularized cecum has been shown to have pressures that range from 5 to 25 cm H₂O 1 year postoperatively (Hedlund et al, 1984). Others, comparing ileum to cecum, find no difference in pressure generated after a year (Hedlund et al, 1984). The Mainz pouch, which uses both ileum and cecum, has an average pressure at capacity of 39 cm H₂O with a maximum pressure of 63 cm H₂O (Thuroff

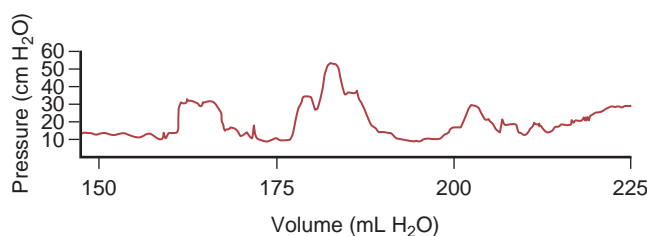


Figure 97-42. Pressure waves recorded 1 year postoperatively in a patient with a continent diversion constructed from detubularized ileum and right colon. Notice that the coordinated pressure waves are of magnitude and frequency similar to those found in a normal colonic or ileal segment.

KEY POINTS

- Although 15 cm of small bowel can survive beyond the last vessel, it is unwise to assume that more than 8 cm of small bowel will survive beyond a straight vessel.
- The bacterial concentration ranges from 10^4 to 10^5 in the jejunum, 10^5 to 10^7 in the distal ileum, 10^6 to 10^8 in the ascending colon, and 10^{10} to 10^{12} in the descending colon.
- A mechanical bowel preparation reduces the total number of bacteria, not their concentration.
- The guiding principles of a proper intestinal anastomosis include adequate exposure, good blood supply, prevention of spillage of enteric contents, accurate apposition of the serosa of the two segments of bowel, proper tension of the sutures, and realignment of the mesentery of the two segments.
- After a ureteral anastomosis, deterioration of the upper tracts in the long term is usually caused by a lack of ureteral motility, infection, or stones and less commonly by a stricture at the anastomotic site.
- Antirefluxing ureteral-intestinal anastomoses have a higher rate of stricture than refluxing anastomoses.
- Limited segments of bowel should be used in patients who have an inability to acidify the urine to less than 5.8, an inability to concentrate greater than 600 mOsm/kg, or a GFR less than 35 mL/min.
- Metabolic complications of intestine interposed in the urinary tract include electrolyte abnormalities, altered sensorium, abnormal drug metabolism, osteomalacia, growth retardation, persistent and recurrent urinary tract infection, formation of calculi, short gut, and development of urothelial or intestinal cancers.
- Those gastrectomy patients most at risk for the development of the syndrome of severe metabolic alkalosis are those with high resting levels of serum gastrin who overdistend their pouches and are dehydrated.
- The electrolyte abnormality that occurs with ileum and colon is a hyperchloremic metabolic acidosis.
- Patients receiving chemotherapy who have intestine interposed in the urinary tract have increased toxic effects of chemotherapeutic agents compared with patients with normal urinary tracts.

et al, 1987). Thus, reconfiguring bowel usually increases the volume, but its long-term effect on motor activity and wall tension is unclear at this time. It has been my observation that some patients with orthotopic bladders after a number of years of spontaneous voiding require intermittent catheterization. In these patients the bowel segment has become flaccid, and the ability of the patient to generate intraluminal pressure by a Valsalva maneuver is limited.

SUMMARY

This chapter has addressed complications both independent of and dependent on the specific type of urinary intestinal diversion. Each unique type of diversion has its own set of individual complications. Moreover, the procedure preceding the urinary intestinal diversion also has a set of complications that must be added to those described previously. It is clear that with current modalities of urinary intestinal diversion, long-term complications significantly contribute to mortality and morbidity. Many patients who have intestinal diversion after an extirpative procedure for cancer, however, die of the cancer rather than of these long-term complications. Those for whom a urinary intestinal diversion has been constructed for benign disease and those who are cured of cancer are most likely to experience long-term morbid complications. The knowledge of the frequency of these complications and the correct performance of preoperative preparation, surgical technique, and postoperative care, as outlined in this chapter, should provide the best chance for the least mortality and morbidity in patients undergoing urinary intestinal diversion.

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General Considerations

Continent Urinary Diversion

Quality-of-Life Assessments

Variations in Operative Technique

Summary

GENERAL CONSIDERATIONS

Continent urinary diversion is widely accepted by both urologist and patient alike as an acceptable form of urinary reconstruction after cystectomy. Orthotopic urethral anastomotic procedures and continent catheterizable stomal reservoirs have stood the test of time, and both procedures should be considered for all appropriate patients. Orthotopic continent diversion and the metabolic consequences of continent urinary diversion are covered in separate chapters and are not discussed in detail here. This chapter focuses on the most common continent cutaneous diversion surgeries associated with the highest success rates. Over the past 35 years the design of the reservoir has not substantially changed. However, an evolution has occurred in the techniques used to create anti-reflux and continence mechanisms to make them more effective and reliable. In addition, attention will be given to the long-term quality-of-life outcomes of continent cutaneous reservoirs, as well as to the newer laparoscopic and robotic approaches used to create such reservoirs.

Despite the considerable enthusiasm for continent urinary diversion operations, those procedures requiring the use of external urinary collecting appliances remain more common. Although continent urinary diversion is certainly appropriate in selected patients, the procedures are technically more challenging and are associated with higher short-term and long-term complication rates than those that use external collecting devices. However, the operating time associated with these more complex procedures has been significantly reduced by the widespread use of absorbable and metal staples in the construction of the reservoirs and limbs. These techniques are discussed in detail later. Also, as experience with continent urinary diversion has grown, complication rates have decreased. As a result, the use of continent diversions has increased in some centers.

Patient Selection

Because the ability to self-catheterize is essential to the patient undergoing continent diversion, the patient must be assessed for the ability to care for himself or herself. Consultation between an enterostomal therapist and the patient is extremely helpful in this regard, because the patient may be at greater ease with the therapist and more willing to express any concerns. Certain patients may not be able to comprehend the strict flushing and catheterization regimens that must be followed after continent urinary diversion or may lack the motor skills to independently perform self-care. **Patients with multiple sclerosis, quadriplegic individuals, and very frail or mentally impaired patients will at some point in their lives require family or visiting nurses for basic care and are therefore viewed as poor candidates for any form of continent diversion.** Indeed, these patients may also require assistance with external appliances, but the degree of time and expertise required

is much less burdensome on the care provider and the health care system. On the contrary, continent catheterizable diversion requires continuous attention and may limit patient and family options when determining long-term care needs.

Patient Preparation

All patients undergoing anticipated continent urinary diversion should be prepared for the possibility that a traditional ileal conduit procedure might be performed. Although it is rare to abandon a continent diversion owing to intraoperative findings, this always remains a possibility. Therefore before the operation is started, the site for an external stoma should be selected with care. In general, the location must be free from fat creases in both the standing and sitting positions and it should not be close to prior abdominal scars that may interfere with proper adherence of an external appliance. Here again, the aid of an enterostomal therapist is helpful. In general, the stoma should be brought through the right (or left) lower quadrant of the abdomen on a line extending from the umbilicus to the anterior superior iliac spine. The stoma should be as far lateral from the midline as possible, but the site selected should ensure that the bowel segment comprising the stoma traverses the rectus muscle. Failure to adhere to this rule increases the risk of parastomal hernias. The selected site for the stoma should be marked with an X scratched onto the anterior abdominal wall. Marking the stoma site with ink should be avoided because it may be washed away during the antiseptic preparation of the skin.

The surgeon undertaking continent urinary diversion should be familiar with more than one type of continent diversion technique. Although it is uncommon to have to abandon a given bowel segment for the reservoir, it is not uncommon to have to modify the antireflux or continence mechanism. In these circumstances, it is essential that the surgeon be able to select an alternate form of continent diversion from what was originally intended.

Renal and hepatic function must be reviewed carefully in the patient selected for continent diversion (Mills and Studer, 1999). The reabsorption and recirculation of urinary constituents and other metabolites require that liver function be normal. Renal function should be determined preoperatively, and if borderline, creatinine clearance should be measured. A minimal level of 60 mL/min should be documented before the patient is deemed an appropriate candidate for continent diversion. In patients with bilateral hydro-nephrosis in whom renal functional improvement might be anticipated on relief of the ureteral obstruction, the upper urinary tract should first be decompressed with either ureteral stenting or percutaneous nephrostomy (or nephrostomies), with subsequent reevaluation of renal function before consideration for a continent diversion.

Procedures that will require the use of the colon should always be preceded by a colonoscopic assessment of the entire large intestine. Performing only a sigmoidoscopy for a procedure that will use

only this segment of the large bowel is insufficient because disease proximal to the resected segment may leave the patient with short colon syndrome. The preoperative assessment of the colon is not necessary if continent urinary diversion using small intestine is planned.

Healthy patients undergoing radical cystectomy can be admitted to the hospital on the day of surgery. In most institutions a mechanical bowel preparation is employed on the day before surgery, in addition to oral metronidazole (500 mg) the night before. However, in addition to general surgery literature, several nonrandomized urologic studies have called into question the usefulness of the preoperative bowel preparation (Large et al, 2012; Raynor et al, 2013). Intraoperative antibiotics (e.g., cefoxitin 1 to 2 g) should be administered within 1 hour of skin incision.

Cystectomy

All operations described require a midline incision, skirting the umbilicus to the side opposite the selected stoma site. The incision for a right colon pouch usually extends from the pubis to a point midway between the umbilicus and the xiphoid. The cranial extent of the incision is governed by the hepatic flexure, which must be divided to obtain sufficient colonic length and to allow for the right colon to easily fold on itself. On some occasions the incision will be extended to the xiphoid. The incision for procedures using only the ileum should extend to just below the umbilicus. The cystectomy procedure is covered elsewhere in this text, and only those points germane to continent diversion are covered here.

After abdominal exploration, the ureters are isolated, transected, and transposed to an appropriate place for subsequent diversion. The right retroperitoneum is first opened over the iliac artery to expose the right ureter. In the typical circumstance of conduit diversion, the right ureter is transected below the common iliac artery. For all continent diversions, both ureters are transected as low as possible and shortened to the appropriate length once the final anatomy has been determined. The sigmoid colon is freed from its lateral peritoneal attachments by incising along the line of Toldt. A wide tunnel is created by blunt finger dissection ventral to the aorta and common iliac arteries and caudal to the inferior mesenteric artery. This affords left ureteral access to the previously exposed right retroperitoneum. In cases of uroepithelial malignancy, it is prudent to evaluate the margin status of the most distal portion of both ureters using frozen-section analysis. In situations in which substantial ureteral length is removed to obtain negative surgical margins, extension of the afferent limb mechanism may be necessary to allow tension-free ureteral intestinal anastomoses.

All sutures used in the urinary tract should be absorbable. The individual surgeon's preference will dictate the caliber and type of suture material used. In carrying out bowel surgery for continent urinary diversions, stapling is the preferred method for division of the bowel segment as well as for reconstruction of bowel continuity. This technique shortens operative times greatly and affords safe and reliable bowel anastomosis. Suturing is not necessary with the exception of placing two silk Lembert sutures at the apex of side-to-side stapled bowel anastomoses to prevent tension on the staple line. To avoid stone formation on the stapled proximal bowel segments, oversewing the stapled end of the conduit with absorbable material isolates the metal staple line from urinary contact within the lumen.

In constructing a nonappendiceal continent urinary diversion stoma, a skin button matching the diameter of the structure to be used in the diversion is resected. Cutaneous tissues are separated down to the level of the anterior rectus fascia, where a circle of similar diameter is excised from this fascia, or alternatively the fascia is incised in a cruciate fashion. In carrying out this maneuver, it is essential that the fascia and skin are properly aligned to avoid angulation. Rectus muscle fibers are separated bluntly and an instrument is passed through the posterior fascia and peritoneum. For appendiceal stomas, we prefer to perform a Y-shaped cutaneous incision that allows for a YV-type plasty

incision between the appendiceal limb and the skin (Fig. 98-1). This will decrease the likelihood of subsequent stomal stenosis. Alternatively, the appendix lends itself to an umbilical stoma (Bissada, 1993; Gerharz et al, 1997). Favorable results with this appendiceal YV plasty technique to the umbilical site have been reported (Bissada, 1998).

It is standard procedure to use long, end-hole single J-type diverting stents in all continent cutaneous urinary diversions. These stents drain urine externally, ensuring that urine is safely diverted beyond any anastomotic site during the early healing period. They can also be safely manipulated or exchanged if necessary. The end hole allows for the passage of a straight wire through the stent, which decreases the likelihood of anastomotic trauma at the time of stent removal.

We advocate the use of closed suction drains in all cases of urinary diversion. Soft silicone Jackson-Pratt closed suction drains are preferred because they have less potential for tissue damage or migration into pouches.

Abdominal closure is performed according to the surgeon's preference. A single-layer closure with No. 2 nylon, Surgilene, or Prolene taken through all layers of fascia and muscle usually provides a rapid and secure abdominal closure in the majority of patients. In obese patients, those with tissues of poor quality, or nutritionally depleted patients, through-and-through stay sutures are also used. Ureteral stents are always brought through separate abdominal stab wounds, sutured to the anterior abdominal wall, and directed into separate drainage bags for monitoring of urine output. Even at this early stage it is important to ensure adequate drainage of the reservoir to prevent pouch rupture should the ureteral stents be displaced. In the case of limited pouch access such as with an appendiceal stoma, a Malecot tube should be placed directly into the reservoir and secured to the skin. The reservoir is sutured to the abdominal wall to prevent urine leakage into the peritoneal cavity when the tube is removed. This maneuver also helps to prevent migration and angulation of the reservoir, which could result in incontinence or catheterization difficulties.

Postoperative Care and Comments

Paralytic ileus is a common complication after urinary diversion procedures. Gastric decompression should be maintained until extubation. This can be achieved in the majority of patients by means of nasogastric intubation. However, certain patients may best be managed by formal gastrostomy decompression inserted intraoperatively. These individuals include those with multiple prior abdominal procedures in whom prolonged ileus is more likely. If the patient is nutritionally depleted preoperatively, hyperalimentation has been suggested to be of value if initiated during the preoperative interval (Hensle, 1983; Askanazi et al, 1985). However, in a recent randomized controlled trial, postoperative total parenteral nutrition was found to increase infectious complications in nutritionally noncompromised patients (Roth et al, 2013).

Ureteral stents are usually removed 1 week after surgery. Before any manipulation, a urine sample from each stent should be sent for culture and sensitivity testing. Before stent removal, radiographs of the pouch may be obtained to ensure that the pouch is intact. Radiologic contrast studies are performed to ensure against ureteral anastomotic leakage. Each stent is injected with contrast agent in a search for extravasation; if none is seen, guidewires are advanced to each kidney and the stents are removed. If there is any question of extravasation, stents can be advanced over the wires, positioned fluoroscopically, and left in situ for reevaluation after additional healing time.

Late malignancy has been reported in all bowel segments exposed to the urinary stream, whether or not there is a commingling with feces (Filmer and Spencer, 1990; Shokeir et al, 1995). A study by Gitlin and colleagues (1999) suggests that the malignancy may develop from the urothelial component and not as a result of urine affecting intestinal mucosa. As a result, urinary cytology should be performed for all patients undergoing a

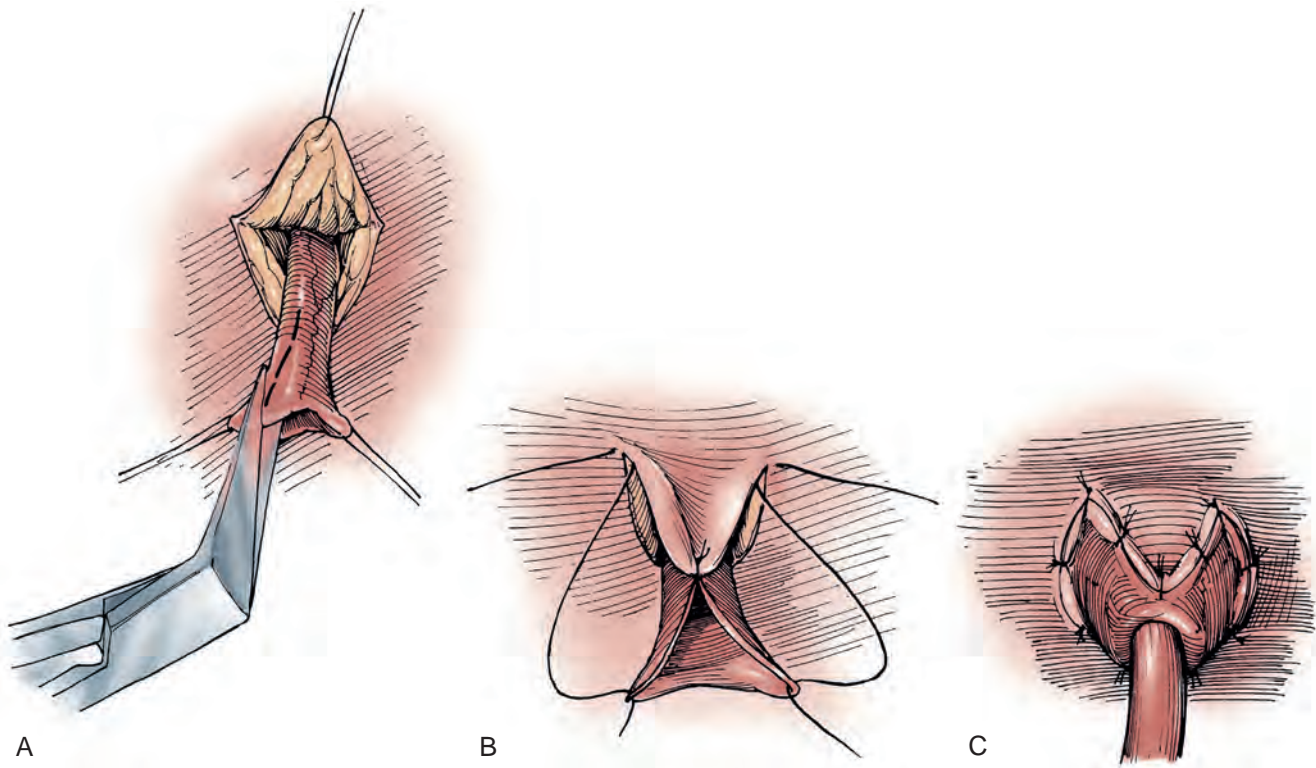


Figure 98-1. A to C, A V-flap is incised in the skin, and a similar-length incision is made on the adjacent appendiceal surface. This is similar to the technique used to mature a cutaneous ureterostomy. For an appendiceal stoma, no eversion is required. (From Hinman F Jr: *Atlas of urologic surgery*. Philadelphia: Saunders; 1989.)

continent urinary diversion, whether or not the diversion was performed secondary to a urothelial malignancy. When the ureters are directed into the fecal stream, routine colonoscopy should also be performed. Latency periods as short as 5 years have been reported; therefore all patients developing gross or microscopic hematuria should be fully evaluated (Golomb et al, 1989). If an anastomotic transitional cell cancer is discovered, the patient should be fully evaluated with upper tract imaging and ureteroscopy if possible. Antegrade ureteropyeloscopy can be employed if necessary. For an isolated anastomotic recurrence, distal ureterectomy and reimplantation may be appropriate. If nephroureterectomy is necessary, some patients may require removal of their continent diversion because of resulting renal insufficiency.

CONTINENT URINARY DIVERSION

Continent, nonorthotopic urinary diversion can be divided into two major categories. First, the variations of ureterosigmoidostomy such as ileocecal sigmoidostomy, rectal bladder, and the sigmoid hemi-Kock operation with proximal colonic intussusception allow for excretion of urine by means of evacuation. Second is the large category of continent diversions requiring clean intermittent catheterization of the constructed pouch for urine drainage at standard intervals.

The concept of refashioning bowel so that it serves as a urinary reservoir rather than a conduit has become universally accepted. This concept is based on original pioneering observations by Goodwin and others in the development of the cystoplasty augmentation procedure (Goodwin et al, 1958). The destruction of peristaltic integrity and refashioning of bowel has led to the development of many innovative urinary reservoirs constructed from bowel. Several procedures have been developed to prevent or reduce

damage to the upper urinary tract from sepsis or increased pressure from ureteral reflux, and other techniques have evolved to achieve and maintain urinary continence.

Because numerous variants of continent urinary diversion are used worldwide, a complete review of all operative techniques is beyond the scope of this or any chapter. However, many of these procedures are simple modifications of parent operations. In this chapter we describe in detail each parent operation as well as major modifications. The very fact that there are many continent urinary diversion procedures reveals an obvious corresponding fact: the “best” continent diversion has yet to be devised. There is, to date, no consensus that would indicate that one continent cutaneous diversion is superior to another, but it is becoming apparent that certain procedures are associated with lower early and late complication rates. Points of controversy include (1) which bowel segment is most appropriate for fashioning into a urinary reservoir, (2) the best techniques for achieving urinary continence, and (3) the best method for preventing urinary reflux into the upper tracts. There are now various continence mechanisms that appear reliable. In our experience, procedures using a right colon reservoir with some form of appendiceal continence mechanism are the fastest and easiest to perform.

It should be reemphasized that all continent diversions will allow for substantial reabsorption of urinary constituents that will place an increased workload on the kidneys (Mills and Studer, 1999). No patient with substantial renal impairment should be considered for any of these procedures. The long-term sequelae of continent urinary diversion are well understood and, unfortunately, commonly involve significant renal damage. Although it has been suggested that the absence of reflux into the upper urinary tracts in catheterizable pouches may reduce the long-term impact of continent diversion procedures on renal function, it should be cautioned that long-term 15-year data are available and that in some instances antireflux procedures are associated with a higher risk of

obstruction caused by anastomotic stricture (Kristjansson et al, 1995; Hohenfellner et al, 2002). In addition to increased stricture rates, it is not clear whether antirefluxing mechanisms actually result in improved preservation of the upper tracts (Pantuck et al, 2000).

The process of patient counseling that we employ always refers to ileal conduit diversion as the gold standard against which the newer, more complex operations must be compared. The patient should be advised that continent diversion is, all other considerations being equal, associated with a longer hospital stay, as well as higher complication rates and greater potential for requiring reoperative surgery. Nieuwenhuijzen and colleagues (2008) reported on 281 consecutive radical cystectomies with urinary diversion using ileal conduit, orthotopic neobladder, or Indiana pouch. There were no significant differences in early complications among the three techniques. The incidence of late complications, including metabolic disturbances and ureteroileal anastomotic strictures, were similar between the two continent diversions but more frequent compared with patients with an ileal conduit. An extensive review from our institution has demonstrated no statistically significant difference in reoperations, mortality, or hospital stay in patients undergoing continent diversion versus conduit diversion by the same three surgeons over a 3-year period (Benson et al, 1992). Analysis of the two patient groups, on the other hand, showed that those selected for continent diversion were significantly younger and four times less likely to have significant concurrent illness. What this review suggests is that, with proper patient selection, continent diversion operations can be safely conducted with results similar to those for conduit diversion. To determine if continent diversion could be safely performed in selected elderly patients, Navon and colleagues (1995) compared the clinical course of 25 patients over the age of 75 years undergoing a modified Indiana reservoir with results in a cohort of 25 randomly selected patients younger than 75. The mean age of the first group was 78.5 years, and the mean age of the second was 59.3 years. The complication rates between the two groups were acceptably low and surprisingly similar. Navon and colleagues concluded that age alone should not be a contraindication to continent diversion and that the Indiana reservoir procedure can be successfully performed in elderly patients.

Rectal Bladder Urinary Diversion

Various innovative surgical techniques have been advocated for separating the fecal and urinary streams while still employing the principles of ureterosigmoidostomy. In general, these operations can be discussed together as rectal bladder urinary diversions. In each of these operations the ureters are transplanted into the rectal stump. The proximal sigmoid colon is managed by terminal sigmoid colostomy or, more commonly, by bringing the sigmoid to the perineum, thereby using the anal sphincter to achieve both bowel and urinary control. Although these operations continue to be commonly performed, they have never been well accepted in the United States. The principal reason is the potential for the calamitous complication of combined urinary and fecal incontinence, presumably occurring as a consequence of damage to the anal sphincter mechanism during the dissection processes (Culp, 1984).

If the urologist selects one of these procedures, the preoperative evaluation should include all of the caveats of ureterosigmoidostomy. Dilated ureters are not acceptable. Patients with extensive pelvic irradiation are not candidates, and neither are those with existing renal insufficiency. Anal sphincteric tone must be judged competent before these operations are selected. Our preference has been to use a 400- to 500-mL thin mixture of oatmeal and water that the patient is asked to retain for 1 hour in the upright position (Spimak and Caldamone, 1986). Finally, colonoscopy must be carried out before the procedure to rule out preexisting colorectal disease, and surveillance must be ensured to guard against subsequent development of colon cancer. Procedures that separate the fecal and urinary streams but drain both through the rectal sphincter are not described

here. Those seeking detailed descriptions of these procedures can find them in prior editions of this chapter. The following is a brief description of more modern surgical procedures that use the intact anal sphincter for urinary and fecal continence. However, the surgical techniques for these procedures are likewise not discussed in this edition.

Folded Rectosigmoid Bladder

A modification of the ureterointestinal anastomosis was described by a group from Mansoura, Egypt (Hafez et al, 1995; El-Mekresh et al, 1997). This procedure creates a folded rectosigmoid bladder with anastomosis of the ureters via serosa-lined tunnels rather than into the taenia coli. This procedure has the advantage of a larger sigmoid reservoir, as well as the prevention of reflux by creating the aforementioned serous-lined tunnel for the anastomosis. This reimplantation technique was first described by Abol-Enein and Ghoneim (1993) and appears to have a lower complication rate than direct taenial implantation (Hafez et al, 1995).

Postoperative Care and Comments. Patients undergoing this procedure must be closely monitored for the development of hyperchloremic acidosis. This will occur in the majority of patients, and it is wise to initiate a bicarbonate replacement program after the operation. Because hypokalemia is also a feature of ureterosigmoidostomy, replacement of potassium along with bicarbonate may be achieved with oral potassium citrate. Routine nightly insertion of a rectal tube is advocated in the long-term care of the patient. However, many patients will reject this practice as uncomfortable and unappealing. Nighttime urinary drainage should be mandated for any patient who cannot maintain electrolyte homeostasis with oral medication. Bissada and associates (1995) reported that 30 of 61 patients were able to stay dry during the night without awakening. The other 31 required two or more awakenings to remain dry overnight. Hyperchloremic acidosis was reported in 4 of 61 non-compliant patients.

In 1997, El-Mekresh and associates (1997) reported on 64 patients (32 women, 20 men, and 12 children) who underwent their rectosigmoid bladder procedure from 1992 to 1995. Follow-up ranged from 6 to 36 months. Functional results were assessable in 57 patients: 1 died of a postoperative pulmonary embolism and 6 died from their disease. All patients were continent during the day with two to four emptyings, and all but 4 remained dry at night with zero to two emptyings. Four children experienced enuresis that responded to 25 mg of imipramine at bedtime. It is important to note that upper urinary tract function was maintained or improved in 95% of patients. However, six renal units (5.3%) developed obstructive hydronephrosis secondary to ureterocolic anastomotic strictures. Two were remedied by antegrade dilation, one was repaired by open revision, and one nonfunctioning renal unit was removed. The fate of the remaining two units was not specified. No patient in this series developed postoperative metabolic acidosis. However, all patients were maintained on prophylactic oral alkalinization.

Obviously, all patients undergoing these procedures have exposure of the urinary tract to fecal flora. Most authors would advocate chronic administration of an antibacterial agent to all patients (Duckett and Gazak, 1983; Spimak and Caldamone, 1986). Ureteral strictures require reoperative surgery and are experienced in 26% to 35% of patients over time (Williams et al, 1969; Duckett and Gazak, 1983).

Because of the concern for development of rectal cancer anywhere from 5 to 50 years (average 21 years) after ureterosigmoidostomy (Ambrose, 1983), it is suggested that patients with long-term ureterosigmoidostomy undergo annual colonoscopy (Filmer and Spencer, 1990). Barium enemas are relatively contraindicated because reflux of this material into the kidneys (if the antireflux procedure fails) can result in dire consequences (Williams, 1984). Additional methods for colon carcinoma screening in this population are the evaluation of stool for blood and the attempted cytologic examination of the mixed urine and feces specimen (Filmer and Spencer, 1990).

Augmented Valved Rectum

Kock developed the augmented valved rectum technique to be used in locales where stoma appliances were not readily available (Kock et al, 1988). This operation is similar to standard ureterosigmoidostomy except that a proximal intussusception of the sigmoid colon confines the urine to a smaller surface area, thus minimizing the problems of electrolyte imbalance. In addition, the rectum is patched with ileum to improve the urodynamic properties of the rectum as a urinary reservoir. Preoperative evaluation is similar to that used in ureterosigmoidostomy. The large bowel must be studied for preexisting disease, and anal sphincteric integrity must be tested before surgery.

Hemi-Kock and T Pouch Procedures with Valved Rectum

In his description of the augmented valved rectum procedure, Kock described the use of a foreshortened hemi-Kock pouch to be used as a rectal patch when the ureters were too dilated to bring down between the leaves of the intussuscepted sigmoid (Kock et al, 1988). Skinner then modified this procedure by using an entire hemi-Kock segment to augment the rectum after sigmoid intussusception (Skinner et al, 1989).

After extensive experience with the Kock ileal reservoir, the group at the University of Southern California has attempted to improve on the intussuscepted Kock continence mechanism. The result has been the modification of the T pouch to serve as an ileal anal reservoir (Stein et al, 1999a). The technique consists of the construction of a hemi-Kock or T pouch employing doubly folded, marsupialized ileum and a proximal continence mechanism to prevent pouch-ureteral reflux. This pouch is then anastomosed to the rectum directly as a patch. Contact of urine with the proximal colon can be avoided by the intussusception of the sigmoid colon proximal to the anastomotic site (Fig. 98-2).

Postoperative Care and Comments. Postoperative management and complications associated with this operation are very similar

to those that might be experienced after any procedure that directs the urinary stream into the rectum. Radiologic studies of the stents are carried out on the seventh postoperative day. Before tent studies are conducted, a Gastrografin enema may be performed through the rectal tube to ensure that the region of ureterocolonic anastomosis is intact. Follow-up films are taken to ensure prompt drainage of the upper urinary tracts into the rectosigmoid region. The rectal tube may be removed at this point, but some believe that it is advisable to have it reinserted for evening drainage over the forthcoming week. The patient is instructed to empty the colon at intervals of no more than every 2 hours, particularly in the early postoperative period.

When the rectal tube is removed, as in other situations when the urinary tract is diverted to the rectum, the patient must be closely monitored for the development of hyperchloremic acidosis. Because hypokalemic metabolic acidosis often occurs after ureterosigmoidostomy, bicarbonate replacement with oral potassium citrate should begin in the immediate postoperative setting. Long-term care should include nightly insertion of a rectal tube despite the uncomfortable and unappealing nature of the process. In addition, nighttime urinary drainage is necessary in patients who cannot maintain electrolyte homeostasis with oral medication.

The hemi-T procedure with valved rectum has one theoretic advantage over the valved rectum operation itself: because transitional ureteral epithelium is not in contact with colonic epithelium, there may be a reduced risk of development of colonic malignancy. As in the augmented valved rectum, the proximal colonic intussusception used in this procedure decreases the contact between urine and colonic epithelium, thereby potentially decreasing the risk of hyperchloremic acidosis. Nevertheless, attention should be paid to electrolyte levels after removal of stents and rectal tubes.

Skinner and colleagues reported on the results of the hemi-Kock procedure in 15 patients from 1987 to 1991 (Simoneau and Skinner, 1995). Four patients had prior bladder exstrophy and were converted to an ileoanal reservoir, and 11 patients underwent the procedure as a form of primary diversion after cystectomy. At the time

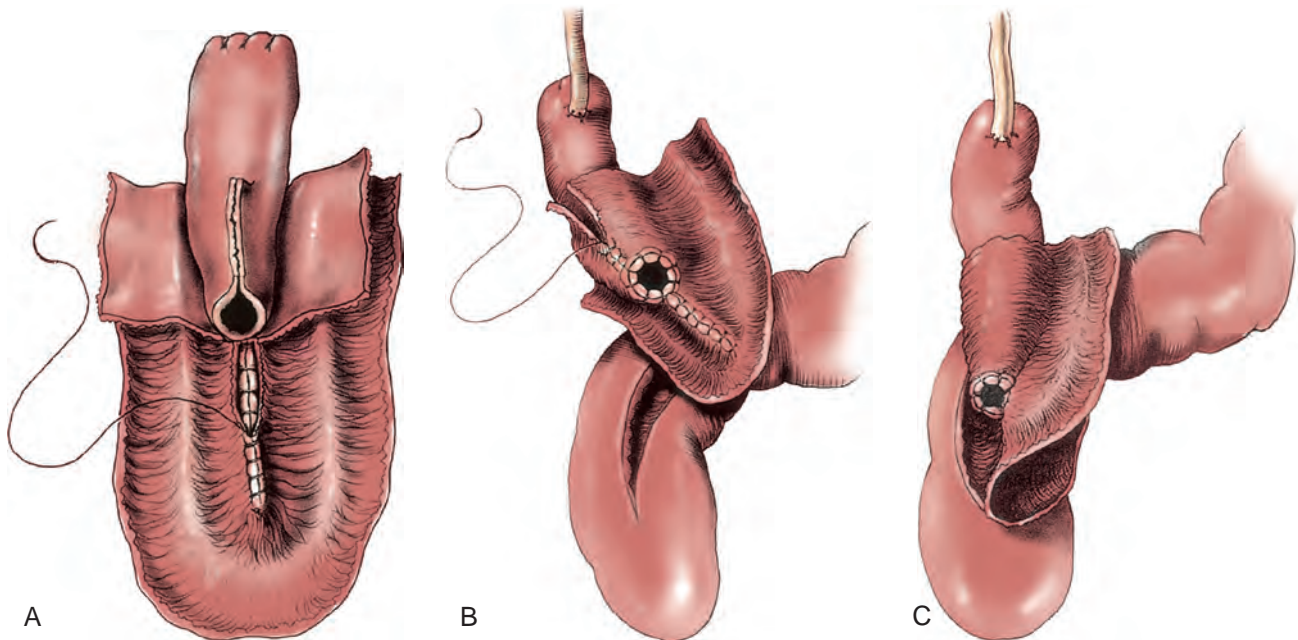


Figure 98-2. A, A 30-cm segment of ileum is selected, the first 10 cm for the T implant and the distal 20 cm for the patch. The 20-cm segment is folded into a U and opened as shown. The medial borders are closed with running absorbable sutures. B, The ostium of the T is secured to the walls of the ileum with interrupted absorbable sutures. The wall of the ileum is closed over the T mechanism with a running absorbable suture. C, The ureters are anastomosed to the top of the T in the usual end-to-side fashion. The T patch is then secured to the 15-cm proctotomy with a two-layer closure. (From Stein JP, Buscarini M, DeFilippo RE, Skinner DG. Application of the T pouch as an ileo-anal reservoir. *J Urol* 1999b;162:2052-3.)

of the report 10 patients were still alive and could be evaluated. Early postoperative complications occurred in 3 patients (20%): a colcutaneous fistula in 2 patients, urine leak in 1, and deep venous thrombosis in another. Late complications included partial small bowel obstruction in 4 patients (with 2 requiring surgery), urinary retention requiring surgery in 2 patients, and metabolic acidosis in 5 patients. Two of the 11 patients undergoing primary construction never achieved continence; both were older than 68 years. The authors summarized their experience by concluding that the operation is best suited for the younger exstrophy patient and that it is essential to avoid colonic redundancy distal to the reservoir. The use of the T pouch as an ileoanal reservoir has been reported in 1 former exstrophy patient (Stein et al, 1999a), with no reported postoperative complications.

Sigma-Rectum Pouch, Mainz II

A variation of ureterosigmoidostomy was described by Fisch and Hohenfellner in 1991 and updated in 1996 (Fisch and Hohenfellner, 1991; Fisch et al, 1996). This operation, which they termed the *sigma-rectum* or the *Mainz II pouch*, creates a low-pressure rectosigmoid reservoir of increased capacity. They viewed the simplicity and reproducibility of the operation as two of its major advantages.

Postoperative Care and Comments. The rectal tube is removed on the 3rd to 5th postoperative day, and the ureteral stents are removed around the 8th day. On the 15th postoperative day the Mainz group performs an intravenous pyelogram to assess the upper tracts and the sigma-rectum pouch construction. Radiography of the pouch is performed on the 17th postoperative day.

The results of the Mainz II pouch were reported by Fisch and associates in 1996. From 1990 to 1993, 73 patients (59 adults and 14 children) underwent the Mainz II pouch procedure. Early complications were encountered in 5 of 73 patients (6.9%). These included single examples of a dislodged ureteral stent, pneumonia, pulmonary embolism, wound dehiscence, and ileus necessitating surgical intervention. There were eight (11%) late complications that required surgery: ureteral stenosis occurred in 5 patients (6.9%); 1 patient with nephrolithiasis was treated with extracorporeal shockwave lithotripsy; 1 patient with rupture of the anterior suture line required temporary colostomy; and 1 patient experienced perianal bleeding after chemotherapy that required endoscopic coagulation. Six patients had pyelonephritis (8.2%) and were treated with antibiotics. Daytime and nighttime continence rates were reported as 94.5% and 98.6%, respectively. Oral alkalinization to prevent metabolic acidosis was used in 49 of 73 patients (67.1%). Two patients who refused any oral medication developed metabolic acidosis. The Mainz group concluded that the overall complication rate was low and comparable to that of other techniques of continent urinary diversion.

Woodhouse and Christofides (1998) reported on their experience with the Mainz II pouch in 15 primary cystectomy patients and 4 patients with prior standard ureterosigmoidostomy who were incontinent. They reported excellent results: 14 of 15 (93.3%) of the primary patients achieved documented daytime and nighttime urinary control, and the remaining patient refused follow-up but reported continence. The 4 patients undergoing a salvage procedure fared less well. Only 2 patients became continent, and the remaining 2 were found to be in chronic retention. Their failed continence was believed to be secondary to inadequate pouch emptying. Similarly excellent results have been achieved by Venn and Mundy (1999). They reported full daytime and nighttime urinary continence in 14 of 14 patients and no major postoperative complications.

Bastian and coworkers (2004) have reported on the health-related quality of life in 83 patients undergoing Mainz II urinary diversion. They found that quality of life was similar to that of age-matched controls except for diarrhea symptoms, with 100% daytime continence.

There appears to be no metabolic advantage to this procedure, because the need for oral alkalinization is similar to that with standard ureterosigmoidostomy. In fact, the only difference between

this operation and standard ureterosigmoidostomy is the partial reconfiguration of the rectosigmoid junction. It does appear that the reduced intracolonic pressures that result from the partial reconfiguration increase the sigmoid capacity and result in better daytime and nighttime continence. Whether the increased capacity and lower pressure of this pouch will decrease the incidence of upper tract complications remains to be determined by longer follow-up.

Continent Catheterizing Pouches

Numerous operative techniques have been developed for continent diversion wherein urine is emptied at intervals by clean intermittent self-catheterization. Many of these operations are described in this chapter, although certain pioneering procedures that used intact bowel—such as those of Gilchrist and associates (1950), Ashken (1987), Mansson and colleagues (Mansson et al, 1984; Mansson, 1987), Benckroun (1987), and others—are not. This is not to discredit the pioneers in the field but simply to allow this chapter to focus on those pouches that incorporate modern principles that attempt to achieve a spheric configuration and disruption of peristalsis.

In continent urinary diversion, the two favorite sites for stomal location are (1) at the umbilicus and (2) in the lower quadrant of the abdomen, through the rectus bulge and below the “bikini line.” This location is often preferred because it affords both men and women the opportunity to conceal the stoma. The umbilicus is a preferred location for the individual confined to a wheelchair and has been reported to have a lower incidence of stomal stenosis, especially when an appendiceal stoma is fashioned. The umbilical location is also far easier for the paraplegic individual to catheterize without the need for chair transfer and disrobing. In individuals with a recessed umbilicus, the umbilical location of a stoma is barely perceptible from a normal umbilical dimple. In general, the stoma site is covered with a gauze pad or square bandage to avoid mucous soiling of clothing. Patients undergoing continent urinary diversion to an umbilical location should be advised to wear a medical alert bracelet that informs the examiner of the umbilical stoma.

Before the extension of orthotopic neobladder construction to women, there was some enthusiasm for the orthotopic placement of a catheterizing portal. This procedure has been carried out in certain female patients with success. The construction of a neourethra to the introitus is attractive, provided there is no substantial difficulty in the catheterizing process. Because it can be difficult to direct a catheter through the “chimney” of an intussuscepted nipple valve, those continent diversions employing nipple valves are not particularly adaptable to orthotopic location, although they have been performed with success in a small number of patients (Olsson, 1987). In contrast, the imbricated and tapered ileal segment leading to an Indiana pouch is relatively easier to catheterize and can be used for orthotopic catheterizing diversion (Rowland et al, 1987). However, it may be difficult to obtain sufficient mesenteric length in some patients. The appendix can also be used as a neourethra, in which case mesenteric length should become less of a problem (Hubner and Pfluger, 1995).

Four general techniques have been employed to create a dependable, catheterizable continence zone. For right colon pouches, appendiceal tunneling procedures are the simplest of all to perform, because they use established surgical techniques already present in the urologic armamentarium. The in situ or transposed appendix is tunneled into the cecal taenia in a fashion similar to ureterocolonic anastomosis. Appendiceal continence mechanisms have been criticized for three general reasons. First, the appendix may be unavailable in some patients because of prior appendectomy. For those individuals, techniques have been developed that allow for the construction of a similar tube fashioned from ileum (Woodhouse and MacNeily, 1994) or from the wall of the right colon (Lampel et al, 1995a). Second, the appendiceal stump may be too short to reach the anterior abdominal wall or umbilicus while sufficient length is still maintained for tunneling. This criticism has been addressed by an operative variation described

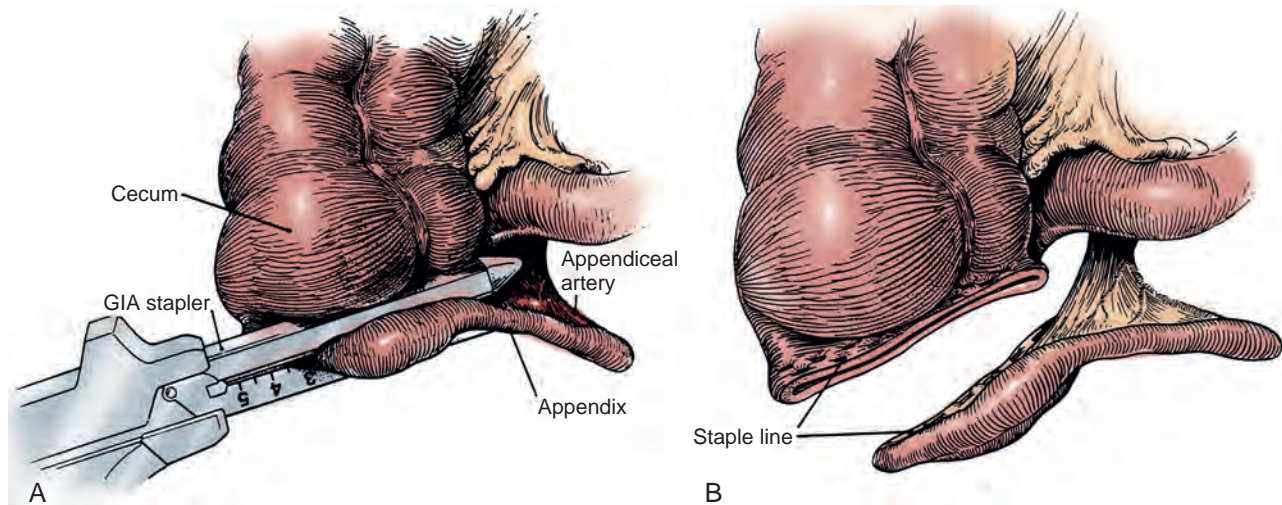


Figure 98-3. A, The appendiceal stump is lengthened by the inclusion of a tubular portion of proximal cecum by the application of the gastrointestinal anastomosis (GIA) stapler to the terminal cecum. A window is made in the mesoappendix, and the blade of the GIA stapler is advanced through the window. This maneuver ensures that the blood supply is not inadvertently damaged. B, The added length is demonstrated. The appendix is rotated and implanted into the taenia; the cecal tube serves as the stoma. (From Burns MW, Mitchell ME. Tips on constructing the Mitrofanoff appendiceal stoma. *Contemp Urol* 1990;2:10-2.)

by Mitchell, in which the appendiceal stump can be lengthened by the inclusion of a tubular portion of proximal cecum (Burns and Mitchell, 1990) (Fig. 98-3). This lengthening procedure has the added advantage of allowing for a slightly larger stoma made of cecum that is less prone to stomal stenosis. Appendiceal continence mechanisms share the feature of allowing only small-diameter (14- to 16-Fr) catheters to be used for intermittent catheterization; the large amount of mucus produced by an intestinal reservoir is more easily emptied or irrigated with use of a 20- to 22-Fr catheter. We believe that these criticisms are more theoretic and that the appendiceal or pseudoappendiceal continence mechanism remains a very attractive and reliable continence mechanism.

The second major type of continence mechanism used in right colon pouches is the tapered and/or imbricated terminal ileum and ileocecal valve. Here again the technology is rather simple, with imbrication or plication of the ileocecal valve region along with tapering of the more proximal ileum in the fashion of a neourethra (Rowland et al, 1985; Lockhart, 1987; Bejany and Politano, 1988). These techniques afford a reliable continence mechanism.

One feature of right colon pouches that has been criticized is the loss of the ileocecal valve. Although this does result in an increased frequency of bowel movements for some patients in the short term, the majority will experience bowel regularity either through intestinal adaptation or with the use of pharmacologic therapy. However, some patients have developed rather striking diarrhea or steatorrhea after the loss of the ileocecal valve. This may be particularly true in pediatric patients in whom there is neurogenic bowel dysfunction (e.g., myelomeningocele).

The third surgical principle in constructing the continence mechanism is the use of the intussuscepted nipple valve or the flap valve, which avoids the need for intussusception. The creation of nipple valves is by far the most technologically demanding of all the continence mechanisms, and it is associated with the highest complication and reoperation rates. There exists a significant learning curve before the surgeon achieves reproducible and dependable results. For this reason, nipple valve construction should probably not be chosen by the surgeon carrying out occasional construction of continent pouches. Furthermore, it should be noted that in the past two decades we have seen the introduction of numerous modifications of the original technique of Kock for construction of a stable nipple valve. The singular reason for all of

these modifications is the rather disappointing long-term stability of the nipple valve in some patients. As a result, the group at the University of Southern California has developed the T pouch, which uses a flap valve (Stein et al, 1998). This procedure, which appears much simpler than the intussuscepted nipple valve, has been used to create both a continence and an antireflux mechanism. Nipple valve failure from slippage or valve effacement can be anticipated in 10% to 15% of cases even in the hands of the very best and experienced surgeons. In addition to slippage, nipple valves are subject to ischemic atrophy. When this occurs, a new nipple valve must be fashioned from a new bowel segment.

A final feature of stapled nipple valves is the potential for stone formation on exposed staples. This was greatly lessened by the omission of staples at the tip of the intussuscepted nipple valve, as suggested by Skinner and associates (1984). However, more proximal staples occasionally erode into the pouch and serve as a nidus for stone formation. These stones are usually manageable endoscopically with forceps extraction, or else with electrohydraulic or ultrasonic disintegration of the stone with subsequent forceps extraction of the staple. Although exposed staples may serve as a nidus for stone formation, continent urinary diversion in and of itself results in more urinary excretion of calcium, magnesium, and phosphate as compared with ileal conduit diversion (Terai et al, 1995). Thus, all patients undergoing continent diversion are at an increased risk for the formation of reservoir stones.

The fourth major technique of continence mechanism construction is the provision of a hydraulic valve, as in the Benchekroun nipple (Benchekroun, 1987). In this procedure a small bowel segment is isolated, with subsequent reversed intussusception that effectively apposes the mucosal surfaces of the segment. Tacking sutures are placed on a portion of the circumference of the intussuscepted segment to stabilize the nipple valve while allowing urine to flow freely between the leaves of apposed ileal mucosa. As the pouch fills, hydraulic pressure closes the leaves, thereby ensuring continence. The premise of this technique is that as the reservoir fills, the pressure within the valve would also increase, resulting in continence. Concerns regarding stomal stenosis, especially in children, and nipple destabilization have resulted in this procedure being largely abandoned (Sanda et al, 1996). As a result, it will not be discussed in this chapter.

General Procedural Methodology

During construction of the pouch, intraoperative testing for pouch integrity should always be performed. The continence mechanism is also tested for ease of catheterization as well as continence after the pouch construction has been completed. The pouch is filled with saline, the continence mechanism catheter is removed, and the pouch is compressed lightly to look for points of leakage as well as to test the continence mechanism for its ability to contain urine. **Thereafter the continence mechanism is catheterized to ensure ease of catheter passage. This is an extremely important and crucial maneuver because the inability to catheterize is a serious complication that will often result in the need for reoperation.** In general, all redundancy should be removed from the continence mechanism. It is often useful to secure the reservoir to the anterior abdominal wall in a manner that prevents the reservoir from migrating. This can prevent the development of a false passage or a kink, thereby facilitating catheterization.

Postoperatively, the larger-bore catheter used for drainage of the pouch should be irrigated at frequent intervals to prevent mucous obstruction. This can be performed at 4-hour intervals by simple irrigation with 45 to 50 mL of saline. Less frequent intervals of irrigation can be employed when the urine is totally diverted from the kidneys by means of long indwelling stents. It is essential that as soon as possible the patient be taught how to self-irrigate and that he or she understand the required regimen. This not only familiarizes the patients with the catheterization process, but also reduces the work burden on the nursing staff and allows for earlier discharge.

On the seventh postoperative day, a contrast study may be performed to ensure pouch integrity. If no leaks are noted, ureteral stents can be removed. When it has been ascertained that the ureteral anastomoses and pouch are intact, the suction drain is removed. The suprapubic tube (if employed) can also be removed at this time, or it can be left in place until the patient is confident with self-catheterization. The patient is taught to irrigate the tube traversing the continence mechanism at 4-hour intervals and whenever any episode of intra-abdominal pressure or discomfort is experienced. Once these procedures have been mastered and the patient is tolerating a regular diet, the patient can be discharged, usually at hospital days 6 to 8.

The following represents a summary of common patient questions and everyday solutions:

- *What kind of catheter do I use?* For nipple valves, a straight-ended 22- to 24-Fr tube; for ileocecal plication, a 20- to 22-Fr coudé-tipped catheter; and for appendiceal sphincters, a 14- to 16-Fr coudé-tipped catheter.
- *How do I carry my catheter?* In a zipper-locked bag that can be placed in a woman's purse or a man's coat pocket.
- *How do I clean the stoma before catheterizing in a public facility?* With a topical antiseptic wipe (e.g., with benzalkonium chloride), which can be purchased in individual foil-wrapped packets.
- *How do I lubricate the catheter?* By tearing off the end of an individual-use foil pack of water-soluble lubricant and inserting the tip of the catheter into the pack.
- *What do I do with the stoma after catheterizing?* Cover it with a bandage.
- *How do I clean my catheter after draining my pouch?* By rinsing with ordinary tap water through the inside channel and over the outside surface before replacing the catheter in its zipper-locked bag.

In the case of ileal pouches, pouch capacity will initially be low (150 mL). Therefore the frequency of catheterization will have to be significantly different in these individuals compared with those with right colon pouches in which initial comfortable capacities will be in excess of 300 mL. To ensure restful sleep, the smaller-capacity pouches may best be managed with indwelling catheterization during sleeping hours.

General Care

Because all patients with catheterized pouches will have chronic bacteriuria, the problem of antibiotic management should be discussed. Most authors would suggest that bacteriuria in the absence of symptomatology does not warrant antibiotic treatment (Skinner et al, 1987). The construction of an effective antireflux mechanism in these pouches may help protect against clinical episodes of pyelonephritis, in contrast to patients with freely refluxing conduits. Obviously, if clinical pyelonephritis does occur, antibiotic treatment should be instituted. Episodes of recurrent pyelonephritis should be evaluated with radiography of the pouch to diagnose failure of the antireflux mechanism or upper tract stone formation.

A condition termed "pouchitis" has been described that manifests with pain in the region of the pouch along with increased pouch contractility. It should be mentioned that this condition, although infrequent, may result in temporary failure of the continence mechanism because of the hypercontractility of the bowel segment employed for construction of the pouch. The patient typically has a history of sudden explosive discharge of urine through the continence mechanism (rather than dribbling incontinence), along with discomfort in the region of the pouch. Appropriate antibiotic therapy will usually result in resolution of these symptoms. It has been our experience that short courses of antibiotics are not usually successful in treating pouch infections. This may be because of the larger amount of foreign material in the form of mucus and sediment within intestinal pouches as opposed to the bladder. Intestinal crypts may also serve as bacterial sanctuaries. Therefore whenever a pouch infection is diagnosed, antibiotic therapy should be continued for at least 10 days. Pyelonephritis will, of course, require longer courses of therapy.

Urinary retention is an infrequent but serious occurrence in catheterizable pouches. It is most commonly seen with pouches whose continence mechanism consists of a nipple valve. In these circumstances, when the chimney of the nipple valve is not near the abdominal surface, the catheter may be misdirected into folds of bowel rather than into the nipple valve proper, resulting in urinary retention. **Pouch urinary retention represents a true emergency and the patient must seek immediate attention so that catheterization and drainage by experienced personnel can be achieved promptly.** The use of a coudé-tipped catheter may be helpful. Rarely, use of a flexible cystoscope will be necessary. After the immediate problem has been resolved by emptying the pouch, a catheter should be left indwelling for 3 to 5 days to allow the edema and trauma to the catheterization portal to resolve. Before discharge, the patient should be observed to successfully self-catheterize on multiple occasions. The appropriate angle of entry, which is highly individualized, should be taught to the patient until they are comfortable with the use of the new catheter. In fact, we prefer to routinely use coudé catheters with non-nipple valve pouches.

Intraperitoneal rupture of catheterizable pouches has been reported (Kristiansen et al, 1991; Thompson and Kursh, 1992; Watanabe et al, 1994). In general, these episodes are more common in the neurologic patient in whom sensation of pouch fullness may be less distinct (Hensle, personal communication, 1993; Mitchell, personal communication, 1993). Ruptures may also be associated with mild abdominal trauma, such as a fall. In general, these patients require immediate pouch decompression and radiographic pouch studies. For patients with large defects, surgical exploration and pouch repair are required. If the amount of urinary extravasation is small and the patient does not have evidence of peritonitis, catheter drainage and antibiotic administration may suffice in treating an intraperitoneal rupture. Patients managed with this conservative approach require careful monitoring. If there is any sign of progressive peritonitis, surgical exploration and repair are imperative. We have successfully employed this nonoperative approach on patients with ruptured right colon pouches.

Continent Ileal Reservoir (Kock Pouch)

This operation was first reported for use in urinary diversion by Kock and associates in 1982 (Kock et al, 1982). This report was singularly responsible for the renewed interest in continent diversion procedures at that time. An outgrowth of the Kock procedure for continent ileostomy (Kock, 1971), the Kock pouch combined reasonably dependable techniques for ensuring urinary continence and preventing reflux to the upper urinary tracts (nipple valves) with carefully refashioned bowel that provided a low-pressure urinary reservoir. This procedure and the similarly constructed T pouch are the only catheterizable continent diversions that preserve the ileocecal valve. Skinner and his coworkers (Skinner et al, 1989; Skinner, 1992) have carefully studied and improved the technique over the years while amassing prodigious experience with the operation and its variants. The high complication rate and the technical difficulties involved with constructing this reservoir have resulted in the procedure being abandoned by most individuals. As a result, this procedure is not discussed further in this edition. Those interested in a more detailed description should refer to our chapter in previous editions of this text. However, the construction of a Kock limb remains an important procedure for use in repairing failed continence or reflux mechanisms, and as such is described in more detail. It is Skinner's operative description that is followed closely in this chapter.

Procedure. A 15- to 20-cm length of ileum is selected for creating the intussuscepted nipple valve. The proximal 10 cm serves as the valve, and the distal 5 to 10 cm serves as the patch (Fig. 98-4A). The distal length is chosen based on the volume lost after resection of the failed mechanism. Only 5 cm is necessary for the patch, but on some occasions the reservoir itself may require augmentation. The middle 6 to 8 cm of the 10-cm segment is denuded of mesentery by electrocoagulation. An Allis or Babcock clamp is advanced into the ileal terminus, grasping the full thickness of the intussusceptum and inverting the ileum into the pouch (Fig. 98-4B). Using the TA-55 stapler, three rows of 4.8-mm staples are applied to the intussuscepted nipple valve (Fig. 98-4C). The distal six staples from each cartridge are removed before staple application to ensure that the tip of the valve is free of staples. Most authors suggest that the pin of the stapling instrument should always be kept in place so that staple misalignment does not occur. This will result in a pinhole puncture site at the base of the nipple valve that should be oversewn with absorbable suture material to prevent fistula formation after staple application is complete. The nipple valve is then fixed to the back wall of the patch by one of two stapling techniques (Skinner et al, 1984). A small buttonhole may be made in the back wall of the ileal plate so that the anvil of the stapler can be passed through the buttonhole and advanced into the nipple valve before application of the fourth row of staples (Fig. 98-4D). If this is carried out, the buttonhole is oversewn afterward with absorbable material. Alternatively, the anvil of the stapler can be directed between the two leaves of the intussusciens and the fourth row of staples used to fix the inner leaf of the nipple valve to the pouch wall (Fig. 98-4E).

Some authors, including Skinner and coworkers (1989), suggest the use of an absorbable mesh collar to anchor the base of the nipple valve. If a collar is used, a 2.5-cm wide strip of absorbable mesh is placed through an additional window of Deaver at the base of the nipple valve. The mesh strip is fashioned into a collar and sewn to the base of the patch with seromuscular sutures of absorbable material (Fig. 98-4F and G). The patch is then sewn to the reservoir.

Double T Pouch

As indicated earlier, many surgeons have abandoned the Kock pouch owing largely to the technical difficulties of creating the continence and antireflux mechanisms and the high complication rates associated with them. This should not be viewed as a condemnation of the pioneering work of Kock and his associates. Without

their initial efforts, many of the procedures described in this chapter would never have come into being. Rather, this represents the natural evolution of surgical techniques.

The group at the University of Southern California modified a technique described by Abol-Enein and Ghoneim (1993, 1994) to create a novel continence mechanism created entirely from ileum (Bochner et al, 1988). Abol-Enein and Ghoneim described a technique that created an extramural serosal tunnel into which the ureters were implanted. This extramural trough created a pseudo-tunnel that prevents reflux but in theory is associated with a lower risk of obstruction than the Goodwin (1958), Leadbetter and Leadbetter (1961), or LeDuc and colleagues (1987) techniques of direct transmural ureteral implantation. Stein and colleagues (1998) first reported on the use in a neobladder of a tapered ileal segment implanted into a serosal trough as the antireflux mechanism. In 1999 they reported on their adaptation of the technique to the ileal-anal reservoir. Also in 1999 they presented their early experience with a double T pouch as a replacement for the Kock pouch at the meeting of the American Urological Association (Stein et al, 1999a), and they published their findings in 2001 (Stein and Skinner, 2001). It is their technique that is presented in this section.

Procedure. A 70-cm segment of terminal ileum is isolated 15 to 20 cm from the ileocecal valve at the line of Treves. The proximal isoperistaltic 10- to 12-cm segment is isolated and will serve as the antireflux mechanism. The distal 12- to 15-cm segment is isolated and rotated in an antiperistaltic fashion and will create the cutaneous continence mechanism (Fig. 98-5A and B). A short 2- to 3-cm mesenteric incision is made to isolate the proximal limb, and a 4-cm incision is made for the distal limb, thereby preserving the major vascular arches. The proximal and distal segments can vary in length, depending on ureteral length and the thickness of the anterior abdominal wall. The middle 44 cm of ileum is folded in a W with each limb measuring 11 cm.

The afferent antireflux mechanism is created by opening the windows of Deaver between the vascular arcades along the distal 3 to 4 cm. The efferent continence mechanism is created by opening the proximal 7 to 8 cm of vascular arcades (antiperistaltic) (Fig. 98-5C). One-fourth-inch Penrose drains are then placed in each window of Deaver to facilitate the passage of the 3-0 silk horizontal mattress sutures that are used to approximate the serosa of the corresponding 11-cm limbs of the W (Fig. 98-5D). The 3- to 4-cm anchored portion of the proximal limb is then tapered over a 30-Fr catheter, and the 7- to 8-cm anchored portion of the efferent limb is tapered over a 16-Fr catheter. In both instances, tapering is performed with a gastrointestinal anastomosis (GIA) stapler (the staples will not be in contact with urine). Care must be taken in the efferent limb to create a gradual taper so that the catheter does not hit a false cul-de-sac (Fig. 98-5E). The portions of the 11-cm W limbs not forming the troughs are then sutured together with a running 3-0 polyglycolic acid (PGA) suture. The bowel is now incised along its antimesenteric border in the portion where the serosal trough exists and in close proximity to the medial PGA suture lines when beyond the two limbs (Fig. 98-5F). The incised mucosa is then closed in two layers with a running suture of 3-0 PGA. The incised intestinal flaps (antimesenteric incision) are then sutured to each ostium with interrupted sutures of 3-0 PGA, and the two ileal flaps are sutured over each segment with a running suture of 3-0 PGA (Fig. 98-5G). The reservoir is then closed side to side in two layers with 3-0 PGA, thereby completing its construction (Fig. 98-5H and I). The ureters are anastomosed end to side over stents to the proximal limb, which has been closed with a running absorbable Parker-Kerr suture. The efferent limb is then brought to the abdominal wall stoma site, and redundant ileum is resected. The stoma is then matured with the reservoir lying immediately adjacent to the anterior abdominal wall.

Postoperative Care and Comments. Postoperative care is similar to that for any continent reservoir. Stein and colleagues initially reported on 9 patients, 7 of whom could be evaluated for continence and long-term complications and 2 of whom died of disease during follow-up (Stein et al, 1999b). All 7 patients achieved

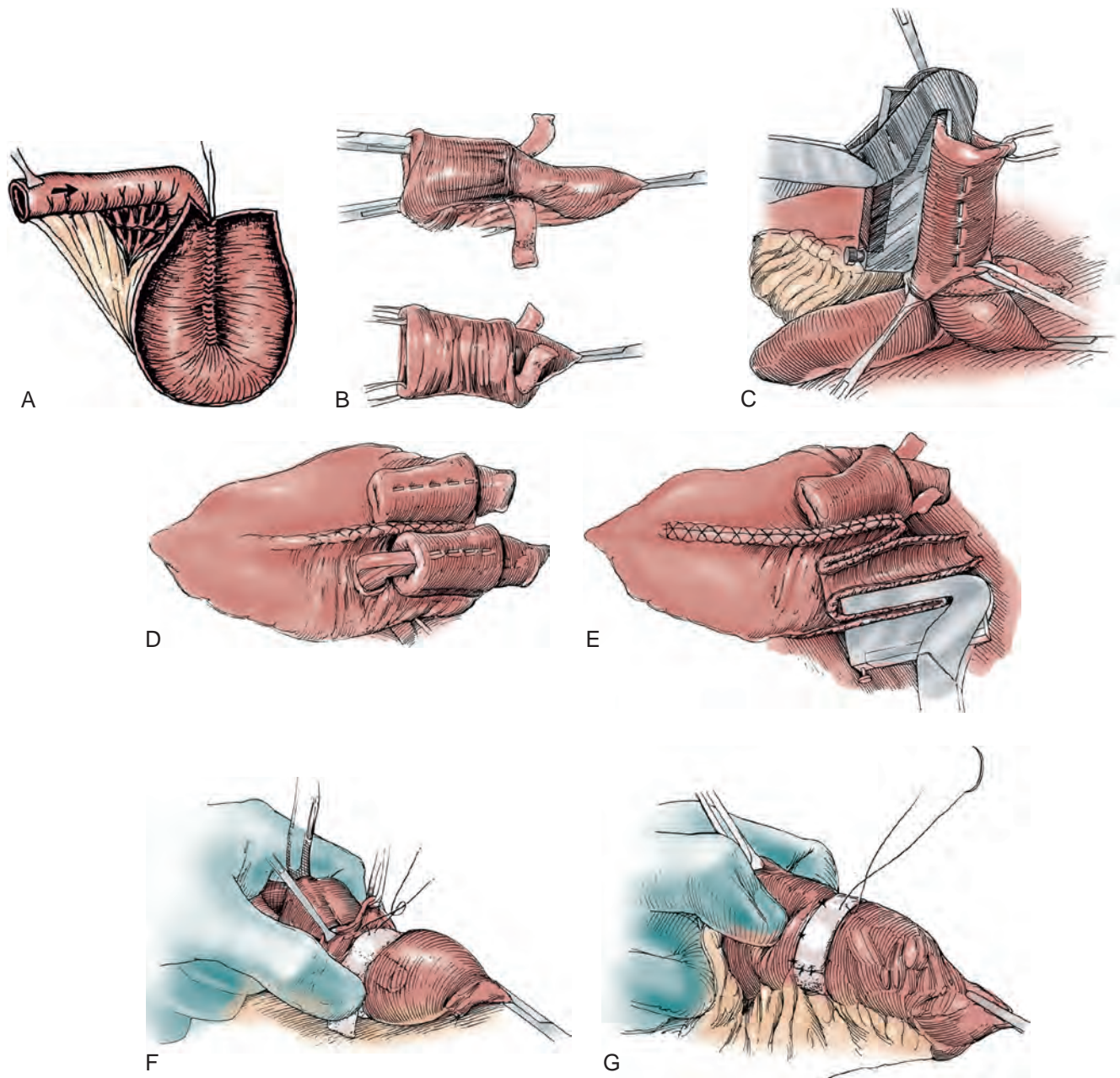


Figure 98-4. A, A 15-cm segment of terminal ileum is isolated and opened along its antimesenteric wall. The proximal 10 cm will serve as the continent intussusception, and the distal 5 to 10 cm as the patch. The size of the patch will vary according to the size of the excised segment. B, An Allis or Babcock clamp is advanced into the ileal terminus; the full thickness of the intussusciens is grasped, and it is prolapsed into the pouch. C, Three rows of 4.8-mm staples are applied to the intussuscepted nipple valve using the TA-55 stapler. D, A small buttonhole is made in the back wall of the ileal plate to allow the anvil of the TA-55 stapler to be passed through and advanced into the nipple valve. A fourth row of staples is applied. The figure shows two valve mechanisms, but in this instance there would be only one. E, The anvil of the stapler can be directed between the two leaves of the intussusciens and the fourth row of staples applied in this manner. Two valve mechanisms are shown but in this instance there would be only one. F, A 2.5-cm wide strip of absorbable mesh is placed through additional windows of Deaver at the base of each nipple valve. The mesh strips are fashioned into collars. G, The collars are sewn to the base of the pouch as well as to the ileal terminus with seromuscular sutures. (A, From Ghoneim MA, Lock NG, Lycke G, El-Din AB. An appliance-free, sphincter-controlled bladder substitute. *J Urol* 1987;138:1150–4. B to G, From Hinman F Jr: *Atlas of urologic surgery*. Philadelphia: Saunders; 1989.)

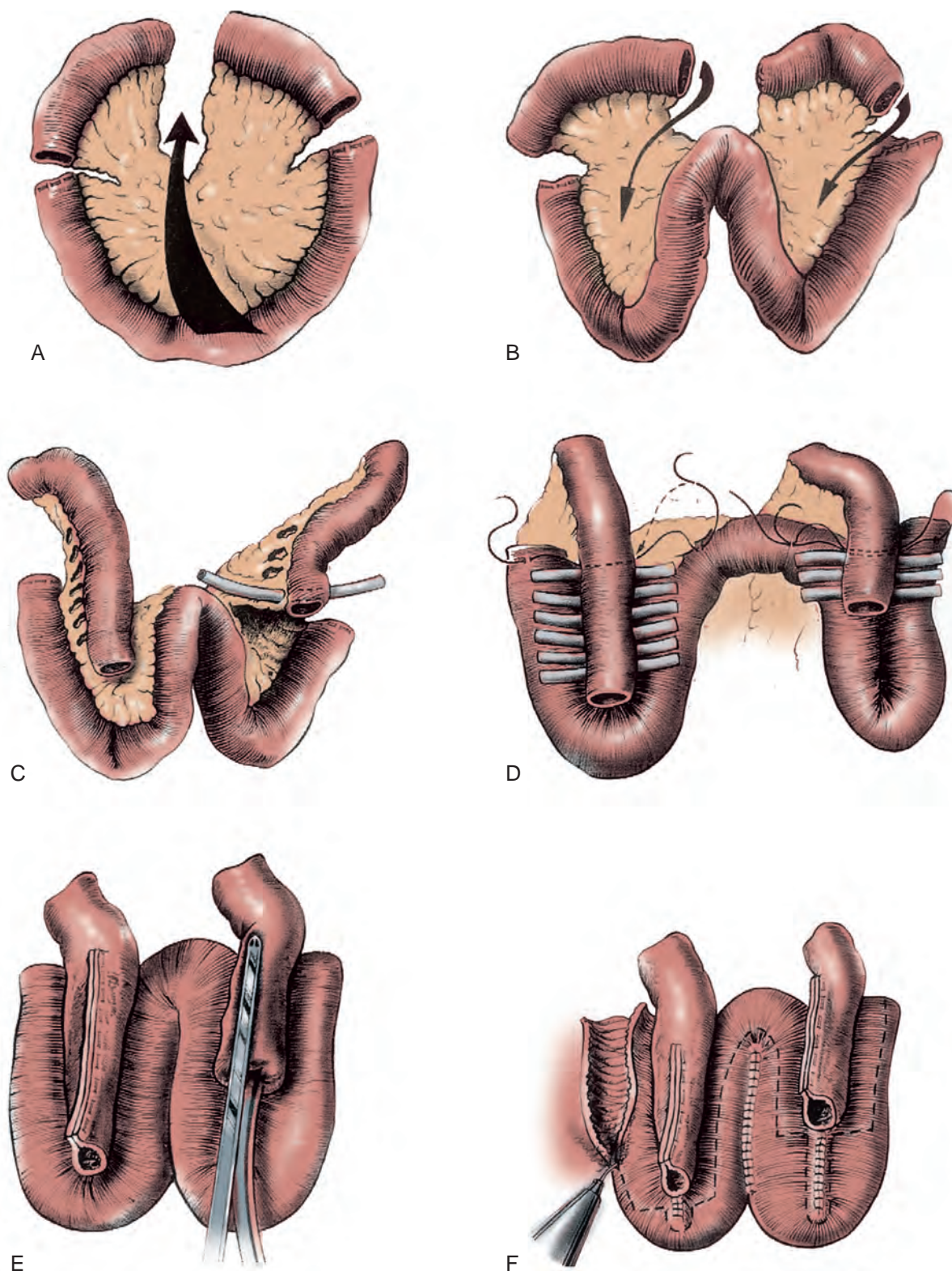


Figure 98-5. A, A 70-cm segment of terminal ileum is isolated 15 to 20 cm from the ileal cecal valve. B, A proximal 10-cm segment is isolated and rotated toward what will become the reservoir in an isoperistaltic direction. The distal 12 to 15 cm is rotated toward the reservoir in an antiperistaltic direction. C, The windows of Deaver are opened to allow the walls of the W reservoir to be apposed behind the valve mechanisms. Penrose drains are passed to guide suture passage. D, Horizontal mattress sutures of 3-0 silk are passed through each window. The distal continence mechanism is longer than the proximal antireflux mechanism. E, The proximal and distal mechanisms are tapered with a metal gastrointestinal anastomosis stapler. F, The bowel is incised along its antimesenteric border where it will overlie the two Ts. Distal to the Ts, the bowel is incised close to the approximated limbs of the reservoir.

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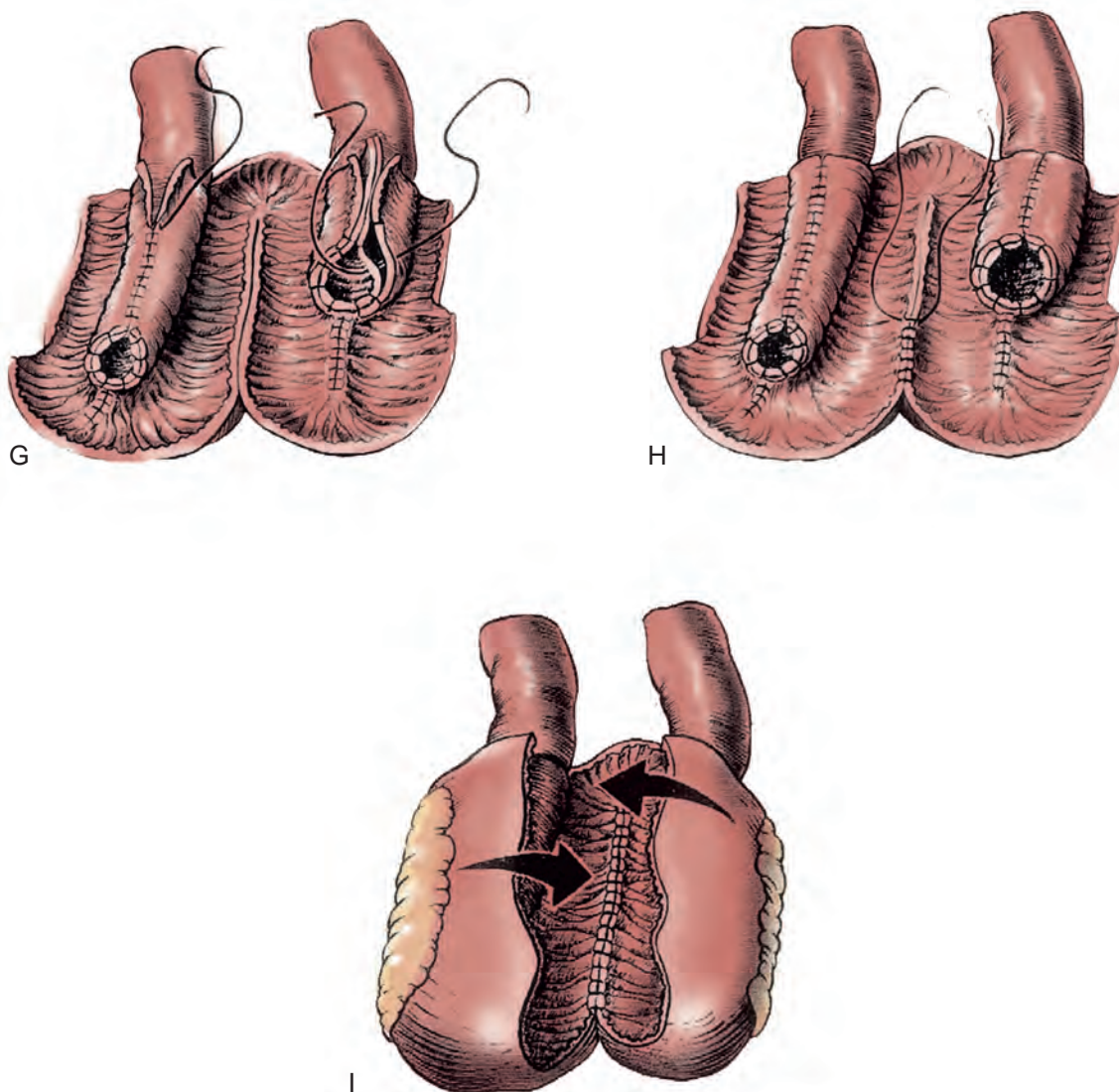


Figure 98-5, cont'd G, The ostia of the valves are secured to the bowel wall with interrupted absorbable sutures. The two flaps of ileum are closed over the Ts with running absorbable sutures. H, The back wall of the reservoir is closed with running absorbable sutures. I, The lateral walls are folded medially and the construction is completed with running absorbable sutures. (From Stein JP, Buscarini M, DeFilippo RE, Skinner DG. Application of the T pouch as an ileo-anal reservoir. *J Urol* 1999;162:2052-3.)

immediate continence on catheter removal. However, 2 patients later became incontinent, with 1 requiring surgical revision. None of the 9 patients experienced an early postoperative complication. One patient developed a reservoir stone 9 months after surgery that was removed endoscopically without sequelae. Pouch capacity was excellent: 400 to 700 mL (average 500 mL). There was no radiographic evidence of reflux in any patient, and there was no upper tract deterioration. This operative procedure appears to have many advantages over the Kock pouch, and good long-term continence results have been reported. Marino and colleagues (2002) reported on 18 patients with 1-year follow-up with 100% daytime and nighttime continence and no delayed complications. Seifert and colleagues (2008) recently published their results on 19 patients who underwent ileal double T pouch construction between 1998 and 2006. Five patients (26%) had complications related to the diversion, some of which required surgical revision. Three patients (16%), all of whom had a body mass index exceeding 30, developed necrosis of the efferent loop and subsequent cutaneous fistulae. Sixteen (84%) eventually developed both daytime and nighttime continence. Although mild acidosis was common in this group, no

urinary reflux was detected, and no patients had significant upper tract deterioration or pyelonephritis.

Mainz Pouch I

The catheterizable Mainz pouch has undergone considerable modification over the years (Thüroff et al, 1985, 1988; Stein et al, 1995; Lampel et al, 1996; Gerharz et al, 1997; Thüroff et al, 2010). The main impetus for these changes has been the difficulty encountered with the nipple valve mechanism. The operative technique has now been modified to use the intact ileocecal valve as a means of further stabilizing the intussusception (Thüroff et al, 1988). This procedure is described here without further reference to earlier prototypes.

Procedure. The catheterizable Mainz pouch varies somewhat from the orthotopic, voiding Mainz pouch. First, a longer segment of bowel is used. A 10- to 15-cm portion of cecum and ascending colon is isolated along with two separate, equally sized limbs of distal ileum and an additional portion of ileum measuring 20 cm (Fig. 98-6A). The entire colon and distal segments of ileum are

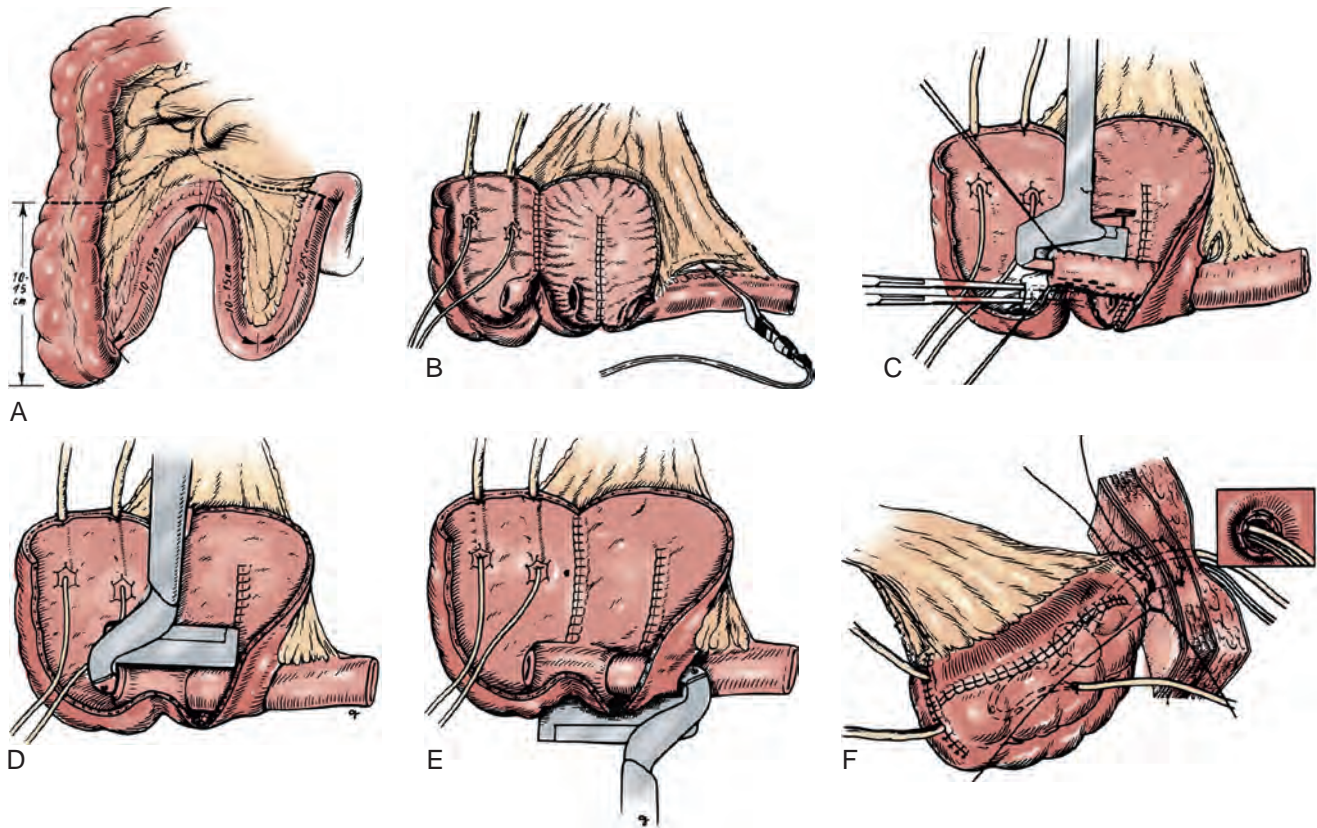


Figure 98-6. A, A 10- to 15-cm portion of cecum and ascending colon is isolated along with two separate equal-sized limbs of distal ileum and an additional portion of ileum measuring 20 cm. B, A portion of the intact proximal ileal terminus is freed of its mesentery for a distance of 6 to 8 cm. C, The intact ileum is intussuscepted, and two rows of staples are taken on the intussusciens itself. D, The intussusciens is led through the intact ileocecal valve, and a third row of staples is taken to stabilize the nipple valve to the ileocecal valve. E, A fourth row of staples is taken inferiorly, securing the inner leaf of the intussusception to the ileal wall. F, A button of skin is removed from the depth of the umbilical funnel, and the ileal terminus is directed through this buttonhole. Excess ileal length is resected and ileum is sutured at the depth of the umbilical funnel. (A, From Thüroff JW, Alken P, Hohenfellner R. The Mainz pouch [mixed augmentation with ileum 'n' cecum] for bladder augmentation and continent diversion. In: King LR, Stone AR, Webster GD, editors. *Bladder reconstruction and continent urinary diversion*. Chicago: Year Book; 1987. p. 252; B to F, From Thüroff JW, Alken P, Riedmiller H, et al. 100 cases of Mainz pouch: continuing experience and evolution. *J Urol* 1988;140:283-8.)

spatulated, taking care to preserve the ileocecal valve. These three bowel segments are folded in the form of an incomplete W, and their posterior aspects are sutured to one another to form a broad posterior plate (Fig. 98-6B). A portion of the intact proximal ileal terminus is freed of its mesentery for a distance of 6 to 8 cm, and intussusception of the segment is achieved. Two rows of staples are applied on the intussusceptum itself (Fig. 98-6C). Thereafter, the intussusciens is led through the intact ileocecal valve and a third row of staples is applied to stabilize the nipple valve to the ileocecal valve (Fig. 98-6D). Finally, a fourth row of staples is applied inferiorly, securing the inner leaf of the intussusception to the ileal wall (Fig. 98-6E).

Ureterocolonic anastomoses are created at the apex of the reservoir, which is then folded on itself in a side-to-side fashion to complete pouch construction. The entire pouch is rotated cephalad so as to bring the ileal terminus to the region of the umbilicus. A small button of skin is removed from the depth of the umbilical funnel, and the ileal terminus is directed through this buttonhole (Fig. 98-6F). The pouch is secured to the posterior fascia with interrupted absorbable sutures, and the ileal terminus is sewn similarly to anterior fascia. Excess ileal length is resected, and the ileum is sutured at the depth of the umbilical funnel with interrupted absorbable sutures.

Postoperative Care and Comments. No specific differences in postoperative care or complications associated with the Mainz pouch need to be addressed. Initial pouch capacities are higher than with the Kock or T pouch. Final mean capacity averaging over 600 mL has been reported. Pouch pressures are 23 cm H₂O at half capacity and 31 cm H₂O when the pouch is full. Contraction waves beginning at 50% pouch fullness can be recorded at an amplitude of 12 cm H₂O. Thus, this pouch seems to produce a reasonably low-pressure urinary reservoir, although the pressures are not as low as those achieved with the use of small bowel alone.

The 10- and 12-year experiences with the Mainz pouch and the variations created by its developers have been described (Stein et al, 1995; Lampel et al, 1996). From 1983 to 1994, 440 patients underwent a Mainz I operation in two urology departments, Mainz and Wuppertal. Continence mechanisms varied: In 146 patients the appendix was used as the continence mechanism; in 270 patients the intussuscepted nipple was used as the continent stoma; in 14 patients a submucosal, seromuscular bowel flap was used; and in 10 patients a submucosal full-thickness bowel flap was used. The early complication rate was 12% and included mechanical ileus requiring open revision in 9 patients (1.6%), pouch leakage requiring revision in 5 patients (0.9%), wound dehiscence in 4 patients (0.7%), and fatal pulmonary emboli in 4 patients (0.7%).

The late complication rate was 37% and was predominantly attributable to the pouch. Stomal failure requiring open revision occurred in 45 patients (8%) and was directly related to the continence mechanism. Only 2 of 146 patients (1.4%) with an appendiceal continence mechanism were incontinent, but stomal stenosis occurred in 21%. The developers of this procedure were innovative in their attempts to bring the incontinence rate down to an acceptable level. To this end they tried multiple techniques, with variable success: an alloplastic stoma (4 of 4 incontinent); sutured intussusception (8 of 8 incontinent); stapled intussusception (5 of 22, 23% incontinent); and stapled ileocecal intussusception (10 of 204, 4.9% incontinent). The stapled ileocecal intussusception described previously is the current recommendation, and the long-term incontinence rate among the patients undergoing the stapled nipple valves was reduced to 10%. Other late complications included the need for ureteral reimplantation in 28 patients (4.9%), and stomal stenosis in 29 patients with an ileal nipple (11.7%) and in 17 patients with an appendiceal stoma (14.7%).

Calculus formation in the pouch occurred in 38 patients (6.8%), resulting in 36 percutaneous procedures. Despite the loss of the terminal ileum, no significant decrease in serum vitamin B₁₂ levels has been reported, and no patient has developed macrocytic anemia or neurologic symptoms. However, 25% of patients are on oral alkalinization to avoid metabolic acidosis.

Since the inception of this procedure, the overall complication rate has been considered high (31%). However, as [Stein and associates \(1995\)](#) pointed out, 50% of the complications were manageable with percutaneous techniques. In addition, since 1988 the incontinence rate has been only 3.2%, and less than 2% in patients with an appendiceal mechanism.

[Gerharz and associates \(1997\)](#) from Marburg, Germany, reported their single-institution experience with the Mainz I ileocecal pouch. From 1990 to 1996, 202 consecutive patients underwent continent diversion, 96 with a submucosally embedded in situ appendix and 106 with an intussuscepted ileal nipple. All patients had an umbilical stoma. In 172 of 200 patients (86%), no stomal complications occurred. In 17 of 96 patients (18%) with an appendiceal stoma, 23 revisions were performed for stomal stenosis. In contrast, only 13 of 106 patients (12%) with an intussuscepted ileal nipple developed problems with their stoma. However, these patients required more invasive, major procedures for correction, whereas those with an appendiceal stenosis could usually undergo repair with a minor

procedure. Three patients with an ileal nipple (3%) developed pouch calculi, whereas none of the patients with an appendiceal continence mechanism developed stones. As a result, [Gerharz and colleagues \(1997\)](#) concluded that the appendix, when available, should be the intestinal continence mechanism of choice.

We share the enthusiasm for the use of the appendix as a continence mechanism. In our experience this technique has also been reliable and easy to perform. It has been our tendency in constructing right colon pouches involving an appendiceal continence mechanism to use the entire right colon inclusive of the hepatic flexure to form the reservoir, thereby preserving more terminal ileum. This has the theoretic advantage of fewer metabolic complications, but the Mainz group has not reported significant metabolic problems.

The introduction of the more reliable appendiceal continence mechanism has greatly increased the acceptance of the Mainz I procedure. The Mainz group has also developed two new techniques for construction of a Mitrofanoff, or appendiceal, type of tube for use in patients whose appendix is either unsuitable or absent ([Lampel et al, 1995a, 1995b; Lampel and Thüroff, 1998](#)). Both techniques use a small-caliber conduit fashioned from the large intestine in the region of the cecum. One technique uses a full-thickness tube lined by mucosa ([Fig. 98-7](#)) and the other a seromuscular tube lined by serosa ([Fig. 98-8](#)). Both techniques appear to be successful, although the full-thickness tube was associated with a lower complication rate and a higher success rate in the initial report ([Lampel et al, 1995b](#)). With longer follow-up, [Lampel and coworkers \(1995b\)](#) have observed similar success rates with both tubes; 93% of the patients with a seromuscular tube (25 of 27) and 92% of the patients with a bowel wall tube (22 of 24) were continent day and night ([Lampel and Thüroff, 1998](#)). The authors believed that either tube was reliable and that each had its own unique advantages and disadvantages. In general, the full-thickness bowel wall tube was more adaptable owing to the ability to create a longer tube. However, this came at the expense of a more tenuous blood supply. The decreased distal blood supply might be improved by creating a wider base on the tube. This could, however, make taenial implantation more difficult. The seromuscular tube was equally reliable but could be anastomosed only to the umbilicus, owing to the short adit tube. Either tube was believed to be indicated as a continence mechanism in the Mainz I pouch when the appendix was not available or as a continence mechanism for reservoirs created from other large intestinal segments. Either

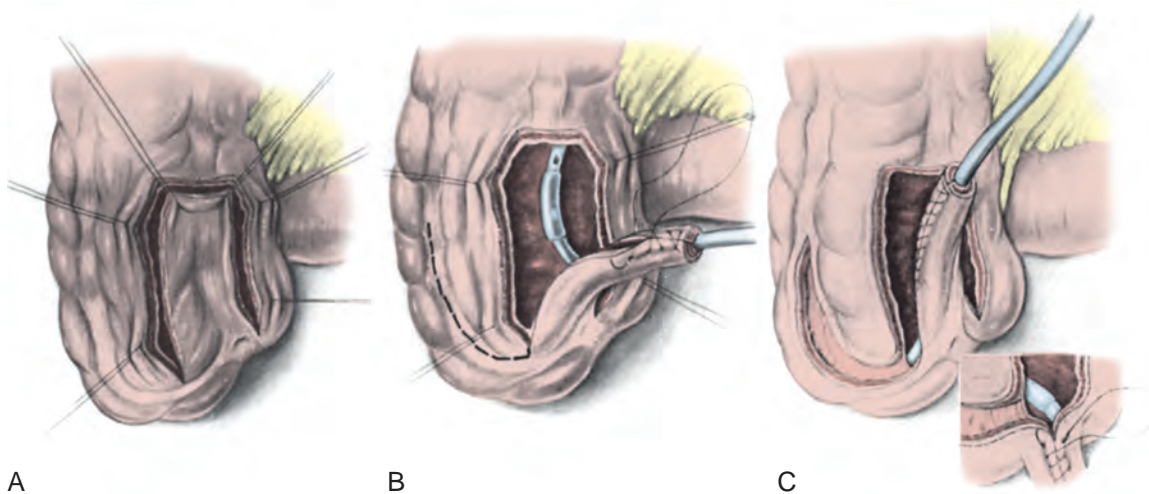


Figure 98-7. A to C, A full-thickness tube lined by mucosa is fashioned over an 18-Fr Foley catheter for tunneled reimplantation. The tube is closed with a running 3-0 absorbable suture. For longer tubes, we would advise a wider base to prevent distal ischemia. The continence mechanism is created by placing the tube into the adjacent taenial trough. (From [Lampel A, Hohenfellner M, Schultz-Lampel D, Thüroff JW. In-situ tunneled bowel flap tubes: 2 new techniques of a continent outlet for Mainz pouch cutaneous diversion. J Urol 1995;153:308-15.](#))

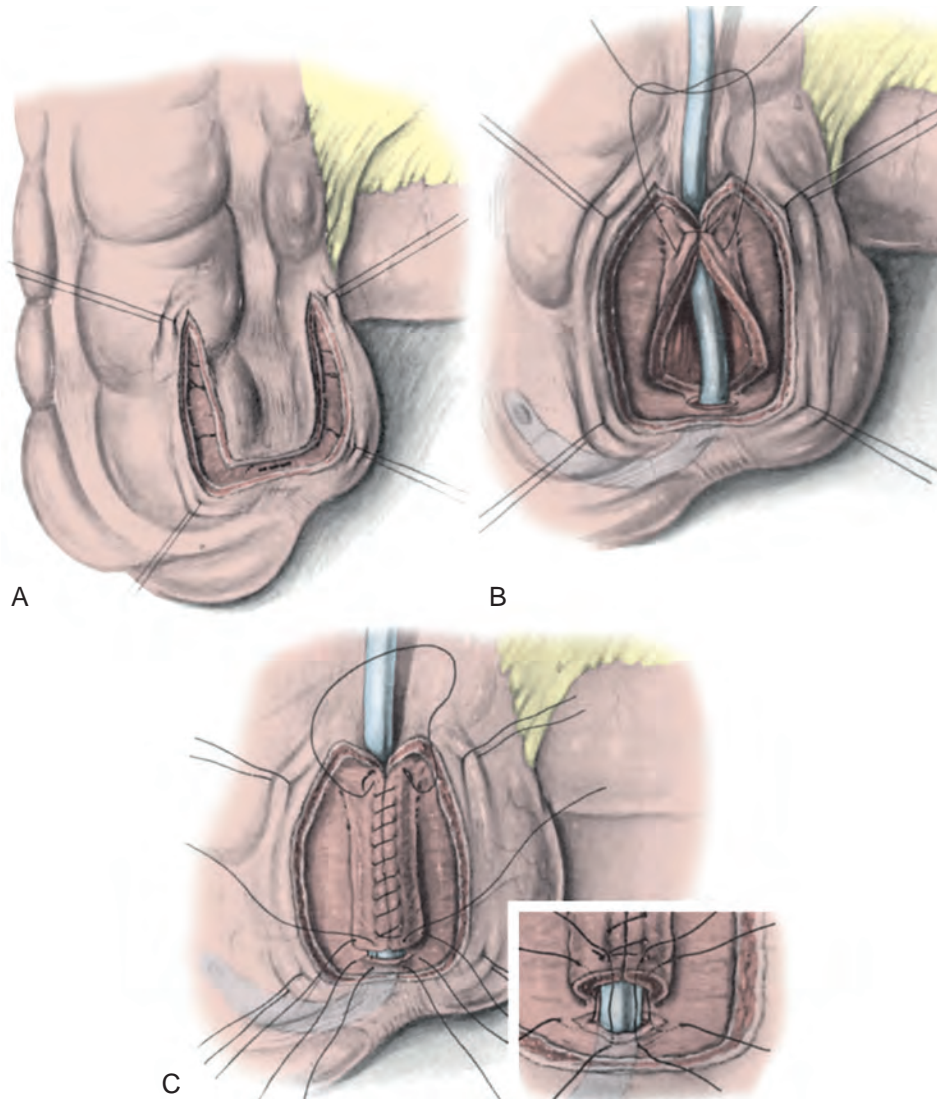


Figure 98-8. A to C, A 3- to 5-cm seromuscular tube denuded of mucosa and lined by serosa is fashioned for tunneled reimplantation. The tube is rolled over an 18-Fr Foley catheter. A mucosal window is opened at the base of the U, and the tube sutured to the mucosa with interrupted sutures. (From Lampel A, Hohenfellner M, Schultz-Lampel D, Thüroff JW. In situ tunneled bowel flap tubes: 2 new techniques of a continent outlet for Mainz pouch cutaneous diversion. *J Urol* 1995;153:308–15.)

technique could be used as a salvage procedure when another primary continence mechanism had failed.

Another novel [Mitrofanoff continence mechanism was described by Montie \(1997\)](#), who conceived of a procedure in which a 2- to 3-cm segment of terminal ileum is isolated on its blood supply ([Fig. 98-9A](#)). The width of the segment was chosen to correspond to the circumference of the tube to be created. Once isolated, the segment is opened near one of its mesenteric junctions to create a longitudinal reconfiguration ([Fig. 98-9B and C](#)). The tube is then closed with a running 3-0 absorbable suture ([Fig. 98-9D](#)). It can now be used for a Mitrofanoff implant. When longer tubes are necessary, two adjacent segments can be isolated, reconfigured, and joined together ([Fig. 98-9E and F](#)). Although the technique was originally described in dogs, [Montie \(1997\)](#) has used it in humans without complication. [Montie \(1997\)](#) reported on a high rate of stomal stenosis in dogs, but this may have been secondary to infrequent catheterizations. Stomal stenosis has not occurred in our limited series of patients. Other groups have used tapered ileum to create a tunneled access into the right colon ([Fig. 98-10](#)) ([Woodhouse and MacNeily, 1994](#); [Hampel](#)

[et al, 1995](#)). Using tapered ileum for this purpose has the advantage of a blood supply independent of the reservoir and no length restrictions while having the disadvantage of further limiting intestinal absorptive surface.

[Wiesner and colleagues \(2007\)](#) recently compared their long-term results in 458 patients who underwent Mainz I pouch construction. The anastomosis was made using a submucosal tunnel in 809 renal-ureteric units, and using a serosa-lined extramural tunnel in 74 units. At 17 months postoperatively they found a significantly higher occurrence of anastomotic obstruction in the submucosal tunnel group compared with the extramural group (7.3% vs. 4.1%, respectively). It is important to note that they found a much higher rate of obstruction in patients with previously dilated upper tracts (14%) or with a history of neurogenic bladder (17%). No significant deterioration of the upper tracts was identified.

In another comparison of patients with a Mainz I pouch, [Wiesner and colleagues \(2006\)](#) reported on 800 patients with almost 8 years of follow-up. Overall continence was approximately 93%. Stomal stenosis occurred in 23.5% of patients with a submucosally embedded in situ appendix, whereas stenosis was

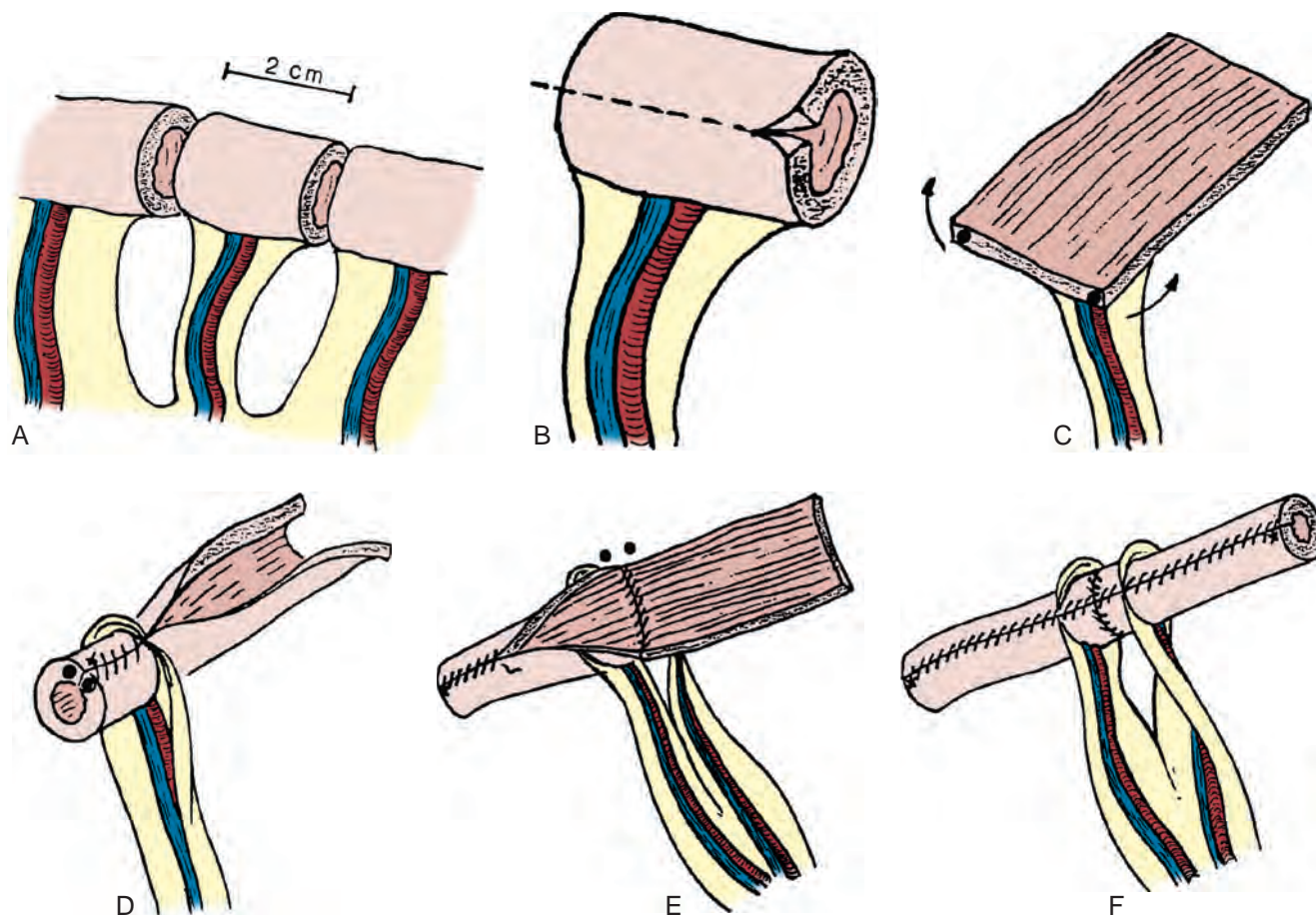


Figure 98-9. A, A 2- to 3-cm segment of terminal ileum is isolated on its own blood supply. B and C, The tubular segment is opened approximately one fourth of the way up one side. This results in a well-vascularized rectangular plate. D, The rectangular tube is now closed over a catheter with a running absorbable suture. E and F, Two adjacent segments can be joined together to create one long tube. (From Monti PR, Lara RC, Dutra MA, et al. New techniques for construction of efferent conduits based on the Mitrofanoff principle. *Urology* 1997;49:112-5.)

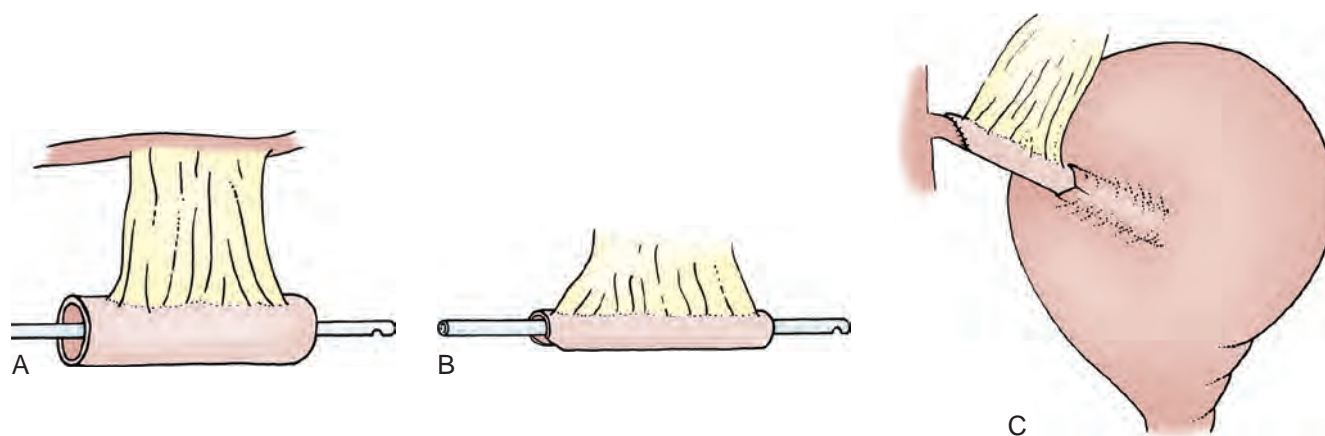


Figure 98-10. A to C, Woodhouse tapered ileum. (From Woodhouse CR, MacNeily AE. The Mitrofanoff principle: expanding upon a versatile technique. *Br J Urol* 1994;74:447-53.)

reported in 15.3% of patients with an intussuscepted ileal nipple valve. Rates of calculi formation were the reverse: 10.8% incidence in patients with an ileal nipple valve but in only 5.6% of patients with an appendix stoma. Ischemic degeneration of the continence mechanism occurred almost three times more often in the appendiceal group.

Right Colon Pouches with Intussuscepted Terminal Ileum

Additional pouches using nipple valve technology for the continence mechanism include those right colon pouches in which intussusception of the terminal ileum and ileal cecal valve is employed. These are variations on the continent cecal reservoir

initially described by [Mansson \(1987\)](#) that employ an intact cecal segment. These three pouches are the UCLA pouch ([Raz, personal communication, 1989](#)), the Duke pouch ([Webster and King, 1987](#)), and Le Bag ([Light and Scardino, 1986](#)). These surgeries differ from one another by only a few features, mainly related to the technique employed for stabilizing the nipple valve. Unless the appendix is being used as a continence mechanism, appendectomy should be performed in all cases because an in situ appendix would serve as a nidus for infection and abscess formation.

These operations are described in detail in the prior edition of this text. Since that edition was published, no new modifications to these procedures have been reported, and they are not further described here. The reader is referred to the prior edition of this text for an in-depth description of these operations.

Indiana Pouch

The concept of using the buttressed ileocecal valve as a dependable continence mechanism that can withstand the trauma of intermittent catheterization was first reported by [Rowland and colleagues \(1987\)](#) from Indiana University. This operation, which involved the partial spatulation of the cecal segment and attachment of an ileal patch, represented major contributions to the original ileocecal reservoir as described by [Gilchrist and associates \(1950\)](#), in which the intact bowel reservoir was employed and no attempt was made to strengthen the ileocecal valve. Originally, strengthening the ileocecal valve consisted of making a double row of imbricating sutures to the entire ileal segment ([Rowland et al, 1985, 1987](#)). It soon became apparent that this was necessary only in the region of the ileocecal valve. "Neourethral" pressure profiles showed that the continence zone was confined to the region of the reconfigured ileocecal valve ([Bejany and Politano, 1988](#)). The remaining "neourethra" could be tapered and brought through an abdominal or perineal stoma. At Indiana University as well as other institutions it became clear that the concept of marsupializing only a portion of the ascending colon segment left enough peristaltic integrity in the cecal region to generate pressures sufficiently high to overcome the continence mechanism in some patients. A number of groups contributed to the concept of using the entire right colon or more, marsupializing the entire structure and refashioning it in a Heineke-Mikulicz configuration ([Lockhart, 1987](#); [Bejany and Politano, 1988](#); [Benson et al, 1988](#); [Rowland, personal communication, 1989](#)). These variations have been entitled the Florida pouch ([Lockhart, 1987](#)) and the University of Miami pouch ([Bejany and Politano, 1988](#)). However, they represent relatively minor variations on the theme of the Indiana pouch.

Procedure. The Indiana pouch in its present form involves isolating a segment of terminal ileum approximately 10 cm in length along with the entire right colon to the junction of the right and middle colic artery blood supplies ([Fig. 98-11A](#)). After bowel continuity is reestablished, appendectomy is performed and the appendiceal fat pad obscuring the inferior margin of the ileocecal junction is removed by cautery ([Fig. 98-11B](#)). The entire right colon is opened along its antimesenteric border, and ureteral-taenial implants are fashioned ([Fig. 98-11C](#)). The ileocecal junction is buttressed according to various reported techniques. With nonabsorbable sutures, interrupted Lembert sutures are taken over a distance of 3 to 4 cm in two rows for the double imbrication of the ileocecal valve as described at Indiana University ([Fig. 98-11D](#)). The second row of sutures should attempt to bring the opposite mesenteric edges of ileum together, usually over a 12- to 14-Fr catheter. These two rows of sutures should be placed approximately 8 mm from one another, and the initial suture in each row may be taken in a purse-string fashion around the cecal margin as well. Alternatively, the University of Miami group suggests placing purse-string sutures in the same ileal region ([Bejany and Politano, 1988](#)). Finally, the Tampa group suggests placement of apposing Lembert sutures on each side of the terminal ileum ([Fig. 98-11E](#)). The remaining ileum can be tapered over the catheter and excess ileum removed with a stapling technique ([Fig. 98-11F](#)).

It is important to carry out the imbrication while the cecal reservoir is still open ([Rowland, 1996](#)) so that the gradual closure of the ileocecal valve can be closely observed. The pouch is then closed in a Heineke-Mikulicz configuration with a running absorbable suture. Ureteral stents and a suprapubic tube are taken through a stab wound in the pouch and led through the right lower abdominal quadrant. The pouch is rotated so as to bring the ileal neourethra as close as possible to the selected stoma site. A fingerbreadth-wide skin button is transected along with a similar button from the anterior and posterior fascia. The ileal neourethra is advanced between bundles of the rectus muscle through the stoma and excess ileum is transected. The ileal edges are sewn to skin with interrupted sutures so as to create a flush stoma.

In addition to the differences in the technique of ileocecal valve imbrication, both the University of Miami and the Florida pouches differ in the amount of colon used. The entire ascending colon and the right third or half of the transverse colon is isolated along with 10 to 12 cm of ileum. The entire upper extremity of the large bowel is mobilized laterally in the fashion of an inverted U ([Fig. 98-12A](#)). The medial limbs of the U are sutured to each other after the bowel has been spatulated ([Fig. 98-12B](#)). The bowel plate is then closed side to side ([Fig. 98-12C](#)). This inverted-U closure, however, is exactly the same as a Heineke-Mikulicz reconfiguration.

There have been recent modifications to the Indiana reservoir that allow for more rapid construction and a lower complication rate ([Rowland, 1996](#)). The modifications incorporate the use of metal staples to create the efferent limb and absorbable staples to fashion the reservoir. The concept of using a metal GIA stapler to fashion the efferent limb was first introduced by [Bejany and Politano \(1988\)](#). [Carroll and Presti \(1992\)](#) reported on the urodynamic features of the stapled and plicated terminal ileum and found that the stapled limb performed equally well and was easier to construct. The use of absorbable staples to create this and other types of reservoirs is described later in the chapter.

Postoperative Care and Comments. The postoperative care of the patient with an Indiana pouch or its variants is not substantially different from that used in patients with other right colon catheterizable diversions. In early reports, Rowland recommended discharging the patient with the suprapubic tube in place until readmission to the hospital 3 weeks later for tube removal and instruction in self-catheterization. In the current medical climate, which places a premium on outpatient procedures, tube removal and catheterization instruction are now ambulatory procedures at most institutions, including Indiana University ([Bihrlé, 1997](#)).

Average pouch capacities of 400 to 500 mL have been reported by the Indiana group ([Rowland et al, 1987](#)). Combining the partially and totally spatulated bowel procedures, this group reports a reoperation rate of 26%. Overall continence rates of 93% have been achieved. Very elegant urodynamic studies were conducted in Indiana pouch variants by [Carroll and colleagues \(1989\)](#). They found only 86% of patients totally continent in a small series. However, their pouch capacities exceeded 650 mL, and peak contractions of 47 cm H₂O were recorded at capacity.

The last 81 patients operated on by Rowland underwent construction of a stapled efferent limb, and in the last 20 the reservoir was created with absorbable staples ([Rowland, 1996](#)). The results in this group of patients were extremely favorable. Early pouch-related complications occurred in only 3 patients (3.7%). Two patients experienced a pouch leak that was managed conservatively, and 1 patient required open revision of the efferent limb owing to difficulty with catheterization. Early complications not directly attributable to the pouch occurred in 7 patients (8.6%). Transient small bowel obstruction was the most common complication, occurring in 4 patients (4.9%). One patient developed a superficial wound infection, and 1 patient developed an abdominal abscess requiring surgery (1.2%). Late complications associated with the reservoir occurred in 23 patients (28.4%). Incontinence occurred in 6 patients (7.4%): in 5 patients it occurred secondary to high pouch pressures, and in the remaining patient it was caused by failure of the efferent limb. One of the former and the latter patient

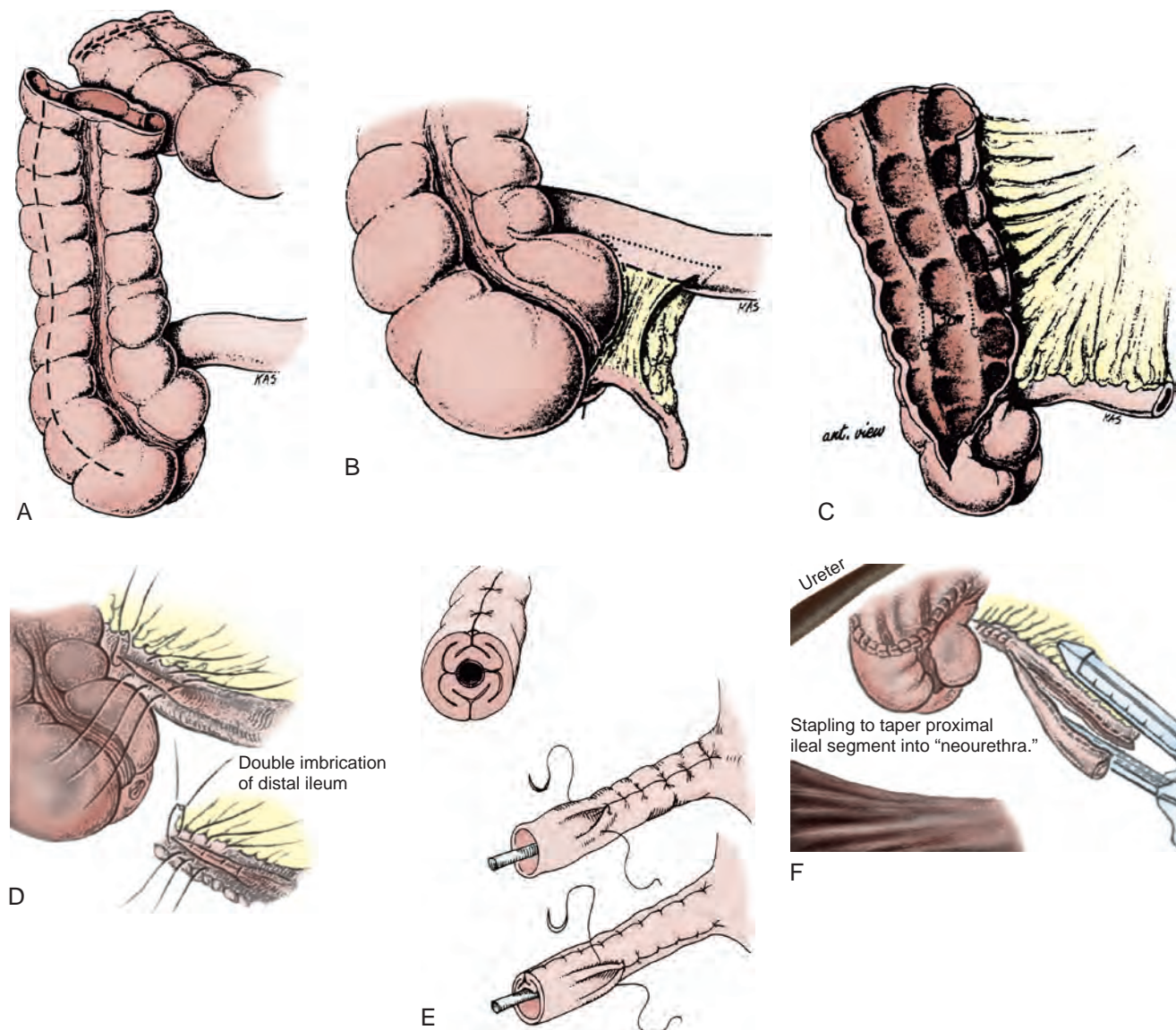


Figure 98-11. A, A segment of terminal ileum approximately 10 cm in length along with the entire right colon is isolated. B, Appendectomy is performed and the appendiceal fat pad obscuring the inferior margin of the ileocecal junction is removed by cautery. C, The entire right colon is opened along its antimesenteric border. D, Interrupted Lembert sutures are taken over a short distance (3 to 4 cm) in two rows for the double imbrication of the ileocecal valve as described at Indiana. E, Application of apposing Lembert sutures on each side of the terminal ileum. F, Excess ileum can be tapered by stapling technique. (A to C, From Benson MC, Sawczuk IS, Hensle TW, et al. Modified Indiana University continent diversion. *Curr Surg Tech Urol* 1988;1:1–8. D and F, From Olsson CA. *Contemp Urol* 62–8, September 1989. E, From Lockhart J. Remodeled right colon: an alternative urinary reservoir. *J Urol* 1987;138:730–4.)

underwent reoperation. Three patients (3.7%) developed stomal stenosis, and 3 had parastomal hernias; all 6 underwent surgery. Pouch stones occurred in 3 patients: 1 underwent open removal, and 2 had endoscopic extraction. Acute pyelonephritis was seen in 4 patients (4.9%). The most common late complication not related to the pouch was small bowel obstruction; this was seen in 6 patients and was managed conservatively in 5. In summary, the early reoperation rate was 2.5% and the late reoperation rate 14.8%. At 1 year, daytime and nighttime dry intervals of 4 hours or longer were achieved in 98% of patients. Eighty-four percent of patients stated that they slept through the night without the need to awake for catheterization. Similarly excellent results in the last 150 patients, 50 with at least 2.5-year follow-up, were reported by Bihrlé (1997).

The Florida pouch has been performed in over 190 patients (Helal et al, 1993). In 165 patients and 326 ureters, no attempt was made to create a tunneled reimplantation. This approach was adopted owing to the high incidence of ureteral obstruction encountered in the first 30 ureters that were tunneled into a Florida pouch (43 patients, 13.3%). In the last 165 patients, 16 of 326 ureters (4.9%) developed primary obstruction and were treated by percutaneous balloon dilation, nephrectomy, or observation. Although no attempt was made to create an antirefluxing anastomosis, only 7.1% of the ureters implanted demonstrated reflux. All patients are being followed conservatively, and no renal deterioration has been demonstrated. In the initial 100 patients, a 7.2% reoperation rate was reported (Lockhart, 1987). Although hyperchloremia was noted in 70% of patients, only 4 patients (including those who had

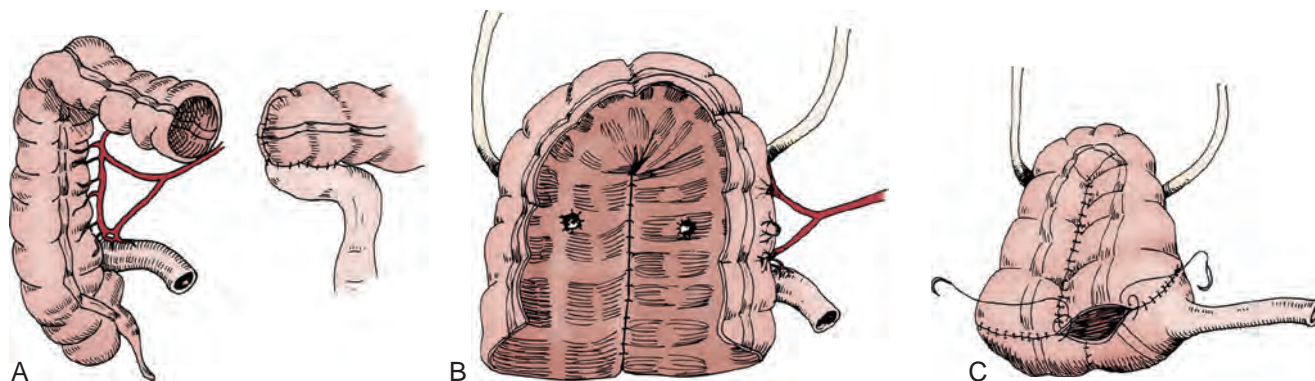


Figure 98-12. A, The entire ascending colon and the right third or half of the transverse colon is isolated along with 10 to 12 cm of ileum. B, The entire upper extremity of the large bowel is mobilized laterally in the fashion of an inverted U. The medial limbs of the U are sutured after the bowel has been spatulated. C, The bowel plate is then closed side to side. (From Lockhart J. Remodeled right colon: an alternative urinary reservoir. *J Urol* 1987;138:730–4.)

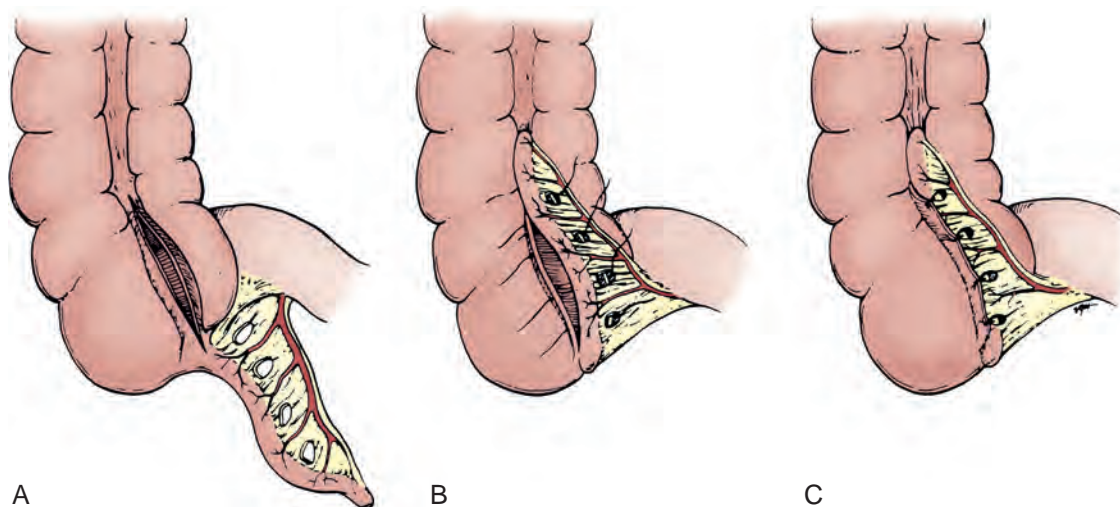


Figure 98-13. A, The appendix is left attached to the cecum and buried into the adjacent cecal taenia by rolling it back onto itself. A wide tunnel is created that extends 5 to 6 cm from the base of the appendix. Windows are created in the mesoappendix between blood vessels. The appendix is folded cephalad into the tunnel (B), and seromuscular sutures are placed through the mesoappendix (C).

preexisting renal disease) required treatment. Reservoir capacities ranged from 400 to 1200 mL, and maximal reservoir pressures at capacity ranged from 18 to 55 cm H₂O (Lockhart, 1987). The reason why these authors experienced such a high incidence of ureteral obstruction with both nontunneled and tunneled ureteral colonic anastomoses is not clear. It is also surprising that only 23 of 326 ureters that were anastomosed end to side had reflux.

The University of Miami group has reported on its results in 75 patients. Early complications occurred in 19 patients (25%). Sixteen patients (21%) experienced late complications. The success rate of the ureterocolonic anastomosis was 90%, and total continence occurred in 98.6% of patients. Average pouch capacities were 750 mL or higher, and end filling pressures of 20 cm H₂O were reported. No patient required alkali therapy.

The Indiana pouch remains one of the most reliable of all catheterizable reservoirs. It is among the easiest to construct, and it has very low rates of short-term and intermediate-term (<2 years) complications (Rowland and Kropp, 1994; Navon et al, 1995). However, there is evidence that the rate of long-term complications, mainly involving the efferent limb in a modified version of the Indiana Pouch, may be higher (Holmes et al, 2002).

Penn Pouch

The Penn pouch was the first continent diversion employing the Mitrofanoff (1980) principle, in which the appendix served as the continence mechanism. As mentioned earlier, this operation enjoys the singular feature of affording a catheterizable continent diversion that can be performed using techniques already present in the urologic armamentarium.

Procedure. Two techniques of appendiceal continence mechanisms have been reported. Mitrofanoff reported excising the appendix with a button of cecum and reversing it on itself before tunneled reimplantation (Mitrofanoff, 1980; Duckett and Snyder, 1986). Alternatively, Riedmiller and coworkers (1990) left the appendix attached to the cecum and buried it into the adjacent taenia by rolling it back onto itself. A wide tunnel is created in the taenia extending 5 to 6 cm from the base of the appendix (Fig. 98-13). Windows are created in the mesoappendix between blood vessels. The appendix is folded cephalad into the tunnel, and seromuscular sutures are placed through the mesoappendix windows to complete the tunneling. The tip of the appendix is amputated and brought to the selected stoma site.

As described by Duckett and Snyder (1986), an ileocecal pouch is created by isolating a segment of cecum up to the junction of the ileocolic and middle colic blood supplies along with a similar length of terminal ileum. These two structures are marsupialized on the antimesenteric borders and sutured to one another in the form of a neotubularized pouch. The superior margin of the pouch is sutured in a transverse fashion (all sutures being of absorbable material). A button of cecum surrounding the origin of the appendix is circumcised, and the resulting cecal aperture is closed with running absorbable suture. The mesentery of the appendix is dissected carefully from the base of the cecum, thereby preserving its blood supply. The appendix is then reversed on itself so that the cecal button can reach the anterior abdominal wall and the tail of the appendix can be directed to the taenia of the colon (Fig. 98-14). The appendiceal tip is obliquely transected and may be spatulated, then a tunneled appendiceal-taenial implantation is carried out. If additional appendiceal length is required, the variation proposed by Burns and Mitchell (1990) of creating a tube from the base of the cecum can be employed (see Fig. 98-3). Instead of simple removal of the appendix with a button of cecum before preparing it for tunneling, the entire base of the cecum leading to the appendix can be resected in continuity with the appendix by the application of the GIA stapler. We have found it helpful to spatulate the distal tip of the appendix until it accommodates a catheter at least 12 to 14 Fr in diameter.

Postoperative Care and Comments. Although not shown in Duckett's surgical drawings, we suggest that a large-bore suprapubic tube be used to drain the pouch in the early postoperative interval. The size of the catheter admitted by the appendiceal stump is insufficient to allow for the passage of ureteral stents along with the 12- to 14-Fr catheter. In addition, safe irrigation of mucous debris is best managed by a larger-bore catheter.

Many groups have used the Mitrofanoff principle owing to the simplicity and reliability of the continence mechanism (Burger

et al, 1992; Bissada, 1993; Sumfest et al, 1993; Woodhouse and MacNeily, 1994; Hampel et al, 1995). Woodhouse and MacNeily (1994) reported on a series of 100 patients who underwent surgery from 1985 to 1993. Seven different catheterizable conduits into six different types of reservoir were used. Although these researchers found the Mitrofanoff principle to be versatile and associated with a high success rate (91% continence), the reoperation rate for tube complications was 33%.

Sumfest and associates (1993) affirmed the use of the appendix as the Mitrofanoff segment of choice. They reported a continence rate of 96%. In their hands, late complications included difficulty with catheterization in 10.6% and stomal stenosis in 19.1%.

Urodynamic properties and pouch capacities will be a function of the reservoir constructed. Most often, the appendix is used in situ (Burger et al, 1992), and the right colon, either alone or with associated terminal ileum (Mainz), serves as the reservoir. We have used the in situ appendix with a detubularized right colon reservoir and the native ileocecal valve as an antireflux mechanism (refluxing ureters implanted end to side into terminal ileum). In our hands this has resulted in an excellent success rate with no upper tract problems. The adequacy of the ileocecal valve as an antireflux mechanism was also reported by Alcini and associates (1994). In their series, however, the reservoir was not always detubularized and, as expected, upper tract complications ensued owing to high reservoir pressures. This procedure is uniquely capable of affording continent cutaneous diversion to the patient with short ureters because the terminal ileum can be left long enough to reach high into the retroperitoneum.

Gastric Pouches

Pioneering animal experimentation demonstrated the feasibility of employing stomach as a bladder patch or urinary reservoir (Sinaiko, 1956; Rudick et al, 1977; Leong, 1978). The use of the stomach to create a urinary reservoir has theoretic as well as real advantages (Adams et al, 1988). First, electrolyte reabsorption would be greatly diminished by use of this bowel segment in the reservoir. This would potentially make the stomach the selected reservoir for individuals with preexisting metabolic acidosis or renal insufficiency. Hyperchloremic acidosis would not be an anticipated problem; in fact, in addition to presenting a barrier against the absorption of chloride and ammonium, the gastric mucosa secretes chloride ions (Piser et al, 1987). Furthermore, in patients in whom shortening of the bowel may be expected to lead to some degree of malabsorption, the use of stomach is an attractive alternative. The acid pH of the urine may also reduce the risk of bacterial colonization. Finally, when the entire lower bowel has been irradiated, stomach tissue may provide healthy nonirradiated tissue for use in performing continent diversion. Given these theoretic advantages, a number of groups have initiated trials with gastric pouches and composite reservoirs in both pediatric (Adams et al, 1988) and adult (Lockhart et al, 1993; Austin et al, 1997) populations.

Procedure. A wedge-shaped segment of stomach with maximal width of 7 to 10 cm is fashioned from the greater curvature. Care is taken not to extend the wedge through to the lesser curvature to preserve vagal innervation and normal gastric emptying. The left gastroepiploic artery is preferentially used as the blood supply for the isolated gastric wedge, dividing the short gastric vessels from the more proximal artery up to the gastric fundus. Alternatively, if there is a problem with the left artery, the right gastroepiploic vessel may be employed, dividing the short gastric vessels to the level of the pylorus (Fig. 98-15A and B). The stomach is then closed according to the surgeon's preference. Neither gastroduodenostomy nor gastrojejunostomy is mandatory unless the antrum of the stomach has been used. The isolated wedge is refashioned into nearly a sphere by folding it back on itself and suturing the edges together with running absorbable material. Before pouch closure, one ureter is tunneled into the reservoir according to the surgeon's preferred antireflux technique. Contralaterally, proximal transureteroureterostomy is performed. The contralateral distal ureter is used to create

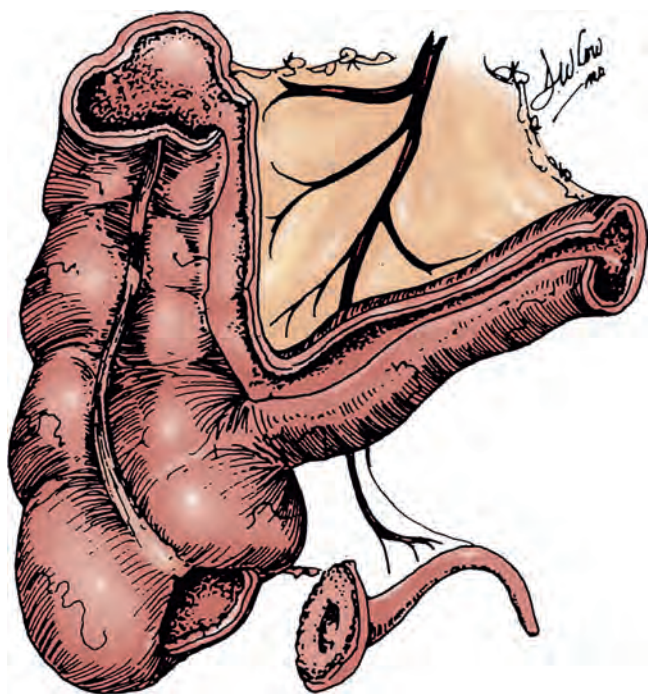


Figure 98-14. A segment of cecum up to the junction of the ileocolic and middle colic blood supplies along with a similar length of terminal ileum is isolated and marsupialized on the antimesenteric borders. A button of cecum surrounding the origin of the appendix is circumcised. The mesentery of the appendix is dissected carefully from the base of the cecum, preserving its blood supply. (From Duckett JW, Snyder HM 3rd. The Mitrofanoff principle in continent urinary reservoirs. *Semin Urol* 1987;5:55-62.)

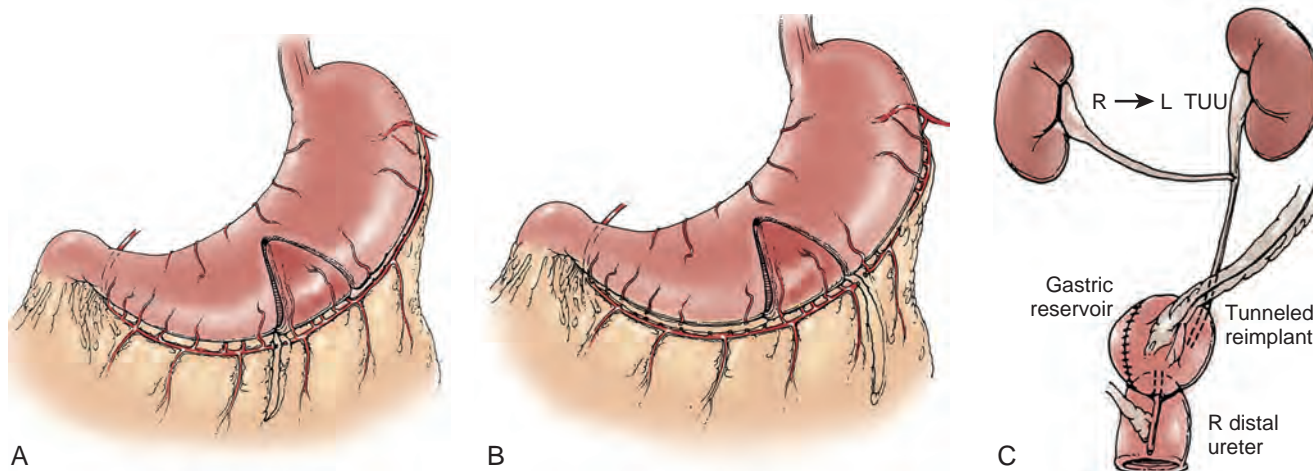


Figure 98-15. A and B, A wedge-shaped segment of stomach whose greatest width is 7 to 10 cm is fashioned from the greater curvature. The left gastroepiploic artery is preferentially used as the blood supply for the isolated gastric wedge, by dividing the short gastric vessels up to the gastric fundus. Alternatively, if there is a problem with the left artery, the right gastroepiploic vessel may be employed. C, The isolated wedge is refashioned into nearly a sphere by folding it back on itself and suturing the edges together with running absorbable material. One ureter is tunneled into the reservoir. A proximal transureteroureterostomy is performed. The ipsilateral distal ureter is tunneled into the reservoir with its distal extent brought to the introitus to serve as a catheterization portal. R → L TUU, right-to-left transureteroureterostomy. (From Adams MC, Mitchell ME, Rink RC. Gastrocystoplasty: an alternative solution to the problem of urological reconstruction in the severely compromised patient. *J Urol* 1988;140:1152-6.)

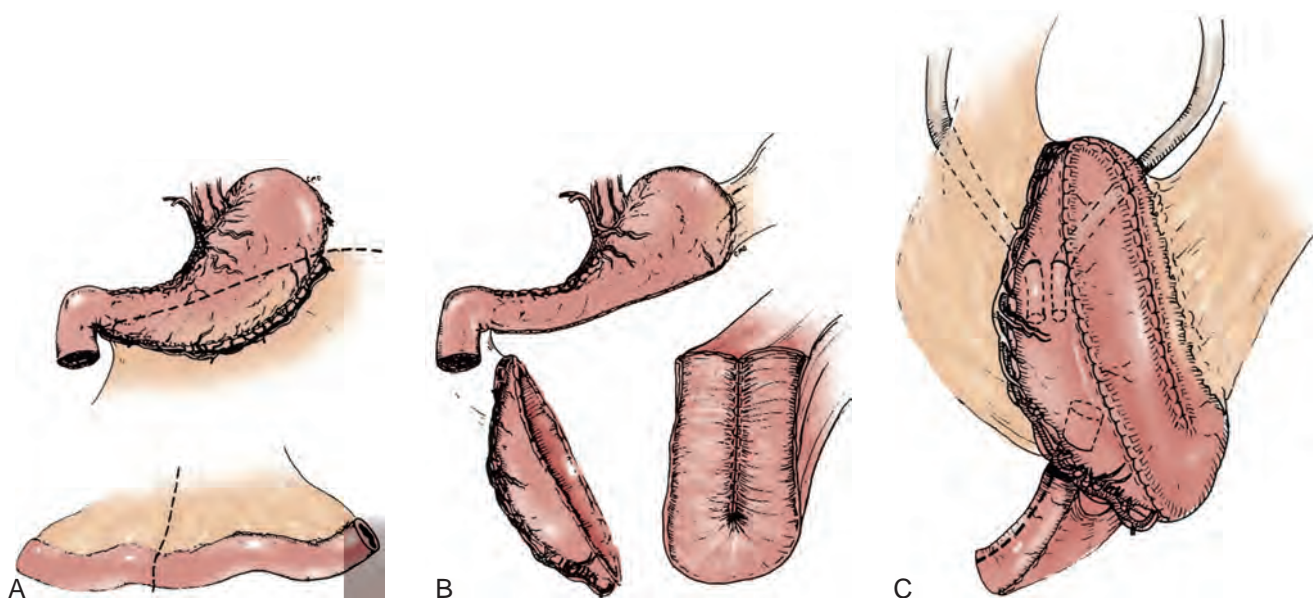


Figure 98-16. A, An 11-cm segment of stomach is isolated on the right gastroepiploic blood supply using a GIA-90 stapler. Usually, two staplers are required. B, A 22-cm segment of ileum is then isolated, opened along its antimesenteric border, and refashioned in a U shape. C, The edges of the stomach are then sutured to edges of the ileum with a running absorbable suture of 2-0 polyglycolic acid. This completes the reservoir. The ureters are tunneled into the stomach, and a Mitrofanoff continence mechanism is created with a tapered segment of ileum. (From Lockhart JL, Davies R, Cox C, et al. The gastroileal pouch: an alternative continent urinary reservoir for patients with short bowel, acidosis and/or extensive pelvic radiation. *J Urol* 1993;150:46-51.)

the continence mechanism. The distal ureter is tunneled into the reservoir in a fashion similar to an appendiceal implant. The free portion of the ureter can then be brought to the skin or to the introitus (or urethral stump in males) to serve as a catheterization portal (Fig. 98-15C). Alternatively, the wedge of stomach can be

incorporated into a reservoir composed of detubularized ileum (Lockhart et al, 1993). In this procedure, an 11-cm segment of stomach is isolated on the right gastroepiploic blood supply (Fig. 98-16A). A 22-cm segment of ileum is then isolated, opened along its antimesenteric border, and refashioned in a U shape

(Fig. 98-16B). The edges of the stomach are then sutured to edges of the ileum with a running absorbable suture of 2-0 PGA. This completes the reservoir. The ureters are tunneled into the stomach, and a Mitrofanoff continence mechanism is created according to the preference of the surgeon. For example, the group from the University of South Florida employs a tapered segment of ileum (Fig. 98-16C).

Postoperative Care and Comments. Adams and associates (1988) reported mean pouch capacities of 245 mL and end filling pressures averaging 35 cm H₂O in a small patient sample. Combining their experience of gastric continent diversion and gastrocystoplasty, they reported minimal mucus production: only 3 of 13 patients required any irrigations, and the majority maintained sterile urine. Urine pH ranged from 4 to 7, but no introital ulceration from acid urine was reported. Three patients had minor elevations of serum gastrin, and none of the continent diversions required reoperation. Leong (1978) used similar concepts in gastric pouch construction and alluded to the creation of a voiding pouch created from stomach as well.

The construction of reservoirs entirely from stomach has not seen widespread acceptance. Rather, there has been greater use of stomach segments either for bladder augmentation or as a portion of a reservoir (composite) either alone or with an in situ catheterizable tube fashioned from a portion of the stomach (Gosalbez et al, 1994; Carr and Mitchell, 1996).

Gosalbez and colleagues (1994) reported on 15 patients who received a gastric tube as part of a composite gastric patch. Complications associated with the gastric patch and in situ tube included one each of early traumatic perforation of the tube, distal tube stenosis, and mucosal redundancy. Two of these patients required reoperation. Peristomal skin irritation from acid secretion occurred in 2 patients but was not considered severe. This is a more frequent complication in other reports and has resulted in skin breakdown in some instances.

Over a 10-year period from January 1985 to June 1995, Carr and Mitchell (1996) reported on the use of stomach in 12 patients. Seven had urinary reservoirs totally constructed from stomach, whereas 5 had composite reservoirs. They reported continence in all patients but that the continence mechanisms often required revision. Average bladder capacity was 309 mL, and average compliance was 12.9 mL/cm H₂O. When stomach is used as a bladder augment or as a portion of a neobladder, a dysuria and hematuria syndrome has been reported (Nguyen et al, 1993).

Austin and associates (1997) reported on nine adult patients with a mean follow-up of 54 months who underwent construction of a continent composite reservoir that was gastroileal in seven and gastrocolonic in two. All nine patients had either preexisting metabolic acidosis or a short bowel syndrome. All nine patients achieved electrolyte neutrality, and postoperative serum pH was significantly improved ($P < .01$). Three patients had a short-term serum gastrin elevation; the level returned to normal during follow-up. One patient developed skin ulceration at the stoma site.

The use of stomach has particular appeal in the pediatric population, in which the stomach's unique acid-base properties can be used not only to reconstruct but also to help correct the metabolic problems that are often associated with the need for pediatric urinary reconstruction (Carr and Mitchell, 1996). Although experience with use of the stomach remains small, its various unique intrinsic properties as a reservoir suggest that its use will continue in selected clinical situations.

QUALITY-OF-LIFE ASSESSMENTS

Extraordinarily few well-designed, prospectively conducted studies using validated instruments exist to assess quality of life after continent cutaneous urinary diversion. Multiple international studies have suggested an improved psychosocial adjustment of the patient undergoing continent urinary and fecal diversion compared with those patients with diversions requiring collecting appliances (Salter, 1992a, 1992b; Bjerre et al, 1995; Filipas et al, 1997; Hart

et al, 1999; McGuire et al, 2000). Although this may indeed be true, as exemplified by individuals with a conduit who desire conversion to a continent procedure, it is also true that many patients adjust well to wearing external appliances. The sense of body image is a remarkably personal and subjective parameter that varies greatly from patient to patient, and in fact quality of life after a conduit procedure appears to remain quite good (Gerharz et al, 2005). However, no randomized prospective trial has ever compared the quality of life after continent cutaneous diversion with that after either orthotopic continent diversion or incontinent urostomy, and there is no definitive conclusion that one form of urinary diversion is superior to any other (Porter and Penson, 2005). Of those studies performed, there appear to be common flaws in the study design and methods used that make any direct comparisons between continent and incontinent diversions difficult (Gerharz et al, 2005).

In general, most quality-of-life studies show similar results between patients undergoing ileal conduit and cutaneous continent diversion, with the latter being associated with improvements in stomal and urinary quality-of-life scores. In one of the few prospective studies to compare quality of life after continent cutaneous and ileal conduit diversion, Hardt and coworkers (2000) followed patients from the preoperative setting until 1 year after surgery. Using validated instruments tested for reliability, they found life satisfaction improved over time in patients with continent cutaneous diversion, whereas it worsened during the first year after ileal conduit construction. Using the Beck Depression Inventory and Profile of Mood States in adults, Boyd and colleagues (1987) found that patients choosing ileal conduit diversion had the lowest expectations of their quality of life. It is interesting to note that Boyd and colleagues found the highest overall satisfaction among patients undergoing conversion from ileal conduit to Kock cutaneous pouch diversion.

Mansson and associates (2002) found no difference in overall quality of life in men undergoing continent cutaneous diversion when compared with orthotopic neobladder using the Functional Assessment of Cancer Therapy (FACT)-Bladder and Hospital Anxiety and Depression Scale. In specific questions concerning intestinal, urinary, and sexual function, patients with cutaneous reservoirs experienced less difficulty with incontinence and emptied less frequently. Sexual function appeared better in patients undergoing orthotopic bladder substitution, likely because of urethral preservation. Large and colleagues (2010) used the validated FACT-Vanderbilt Cystectomy Index to compare quality of life measures in 92 women who underwent orthotopic neobladder compared with diversion with an Indiana pouch. With a median follow-up of at least 2 years, no significant difference was found in the physical, emotional, functional, or social measures of quality of life included in the instrument.

VARIATIONS IN OPERATIVE TECHNIQUE

Minimally Invasive Continent Cutaneous Diversion

With improvements in both laparoscopic- and robotic-assisted techniques, radical cystectomy is now commonly performed in many centers using these minimally invasive techniques. Many of the centers performing minimally invasive radical cystectomy have also reported performing orthotopic ileal neobladder procedures without converting to open techniques. However, there are very few reports of continent cutaneous diversions performed using minimally invasive techniques. Given the surgical complexity of these types of diversions, the vast majority of centers perform continent cutaneous diversions via standard open techniques. Türk and colleagues (2001) reported on an initial series of five patients who underwent radical cystectomy with bilateral pelvic lymphadenectomy and continent urinary diversion with use of a rectosigmoid pouch performed with an intracorporeal laparoscopic technique. Bilateral stented antireflux uterine reimplantation was used, and laparotomy was not performed. Operative time was 7.4 hours with minimal blood loss and a mean hospital stay of 10 days. No

intraoperative or postoperative complications were encountered. Intermediate-term oncologic and functional outcomes were reportedly similar to those achieved with an open approach (DeGer et al, 2004).

The complex nature of minimally invasive reconstructive surgery necessary in continent cutaneous diversion has limited these procedures to select centers. In addition, because of the prolonged time for return of postoperative bowel function, the benefits in hospital stay seen in other oncologic surgeries (e.g., laparoscopic nephrectomy) do not seem to exist when urinary diversion is performed.

Conduit Conversion to a Continent Reservoir

The major indication for conversion of a functioning conduit to a continent urinary reservoir is the patient's desire for improved quality of life. Pow-Sang and coworkers (1992) reported on conversion in 20 patients. Fifteen were converted from an ileal conduit, and 1 each from a cecal conduit, ureterosigmoidostomy, cutaneous ureterostomy, sigmoid conduit, and a suprapubic tube. In 14 of the 20 patients the conduit was discarded or used only as a patch to a colonic reservoir. It was observed that renal units that were obstructed preoperatively were associated with a 71% failure rate. Metabolic acidosis was seen in 15 (75%) but was believed to be mild. Pouch-related complications are, in general, a function of the reconstruction selected, and complication rates should not necessarily be higher in this setting. However, patient selection is very important in determining appropriate candidates for conversion.

We prefer to use the conduit in some form whenever possible. This strategy was supported in a report on two patients by Oesterling and Gearhart (1990). The use of an existing bowel segment has the potential to diminish metabolic sequelae and may result in a lower complication rate. The form of continent reconstruction chosen will have to depend on intraoperative findings, and no one procedure is more amenable than another. Before conversion is undertaken, the patient should be fully evaluated for disease recurrence, renal functional status, urinary anatomy, hydronephrosis, intestinal length, and intestinal health.

Pahernik and colleagues (2004) have described the long-term outcomes of conversion of 39 patients from conduit diversion to Mainz I pouch diversion. With a mean follow-up of 102 months the most common complications were stomal stenosis and pouch calculi. Long-term continence was achieved in 95% of patients.

Absorbable Stapling Techniques in Continent Urinary Diversion

The principle of bowel detubularization to increase reservoir capacity and diminish the effects of peristalsis is a fundamental principle of all contemporary continent urinary diversions. The process of detubularization and refashioning of the spatulated bowel segment consumes at least 1 hour of operating time and is by far the most time-consuming and tedious aspect of pouch construction. **The use of absorbable staples has substantially reduced the time required to fashion bowel reservoirs and has demonstrated short-term and long-term reliability with respect to reservoir integrity and volume.**

Bonney and Robinson (1990) first demonstrated the potential use of absorbable staplers to substitute for conventional suturing of bowel reservoirs. These authors used a bulky absorbable stapler (Polysorb staples in a TA Premium 55 stapler [U.S. Surgical Corp., Norwalk, CT]) to construct an S-pouch configuration in a canine ileal urinary pouch model. Although the same stapler was used in humans by Bonney and Robinson in 1992 and by Cummings in 1995, its clinical use was never widely adopted because the bulky staple configuration destroyed a significant portion of the bowel diameter, particularly when applied to the small intestine. The fact that up to 20 costly staple cartridges were required to complete the closure of a bowel reservoir further reduced the potential benefits of absorbable pouch construction.

A 75-mm GIA instrument (PolyGIA [U.S. Surgical Corp., Norwalk, CT]) that incorporates substantially smaller absorbable staples was made available for clinical use in 1992. The stapler delivers four rows of absorbable polylactic acid and PGA blend copolymer staples, dividing the bowel between the second and third rows. Thus, each staple line of the pouch has a double, staggered, stapled closure. This device has enabled both the refashioning and closure of bowel pouches to be performed with fewer staple applications and is strong and watertight. Finally, the width of bowel sacrificed with the new instrument is appreciably less than that with the older staple device. Several investigators have subsequently used the new "absorbable" GIA stapler to construct catheterizable pouches and neobladders (Olsson et al, 1993; Montie et al, 1994, 1995; Olsson and Kirsch, 1995). However, it is very important to note that the absorbable PolyGIA staples must not overlap because this will result in the failure of the staples to lock together. This is in direct contrast to metal staples, which are meant to overlap to create anastomotic integrity. As a result of the need to prevent overlap of absorbable staples, the reservoir construction procedures must be varied when such staples are used, as described later.

Surgical Techniques

Right Colon Pouch

In 1993, Olsson and colleagues described a technique using the absorbable GIA staplers to fully detubularize and refashion large bowel (Olsson et al, 1993). The technique of colon pouch construction described here incorporates the principles of bowel detubularization and refashioning using absorbable staplers in a simple "one-step" process.

The right colon and 10 cm of terminal ileum are mobilized by incising the peritoneum along the white line of Toldt and along the base of the mesentery and are isolated using metal GIA staplers (Fig. 98-17A). After bowel continuity has been restored with standard metal GIA and thoracoabdominal (TA) staplers, the distal staple line of the right colon is excised and the bowel lumen is irrigated to remove residual enteric contents. Using electrocautery, a small opening (2 cm) is created on the antimesenteric border of the cecum to fit the absorbable stapler. The distal open end of the colon is aligned with the cecostomy by folding the right colon on itself, as depicted in Figure 98-17B. The limbs of the absorbable GIA stapler are inserted into the distal open end and into the cecostomy, and the stapler is fired along the antimesenteric line of the apposed folded bowel (Fig. 98-17C). It is necessary to evert the bowel to continue subsequent staple applications. This may be achieved by placing Babcock clamps on each side of the distal staple line (Fig. 98-17D). A small incision at the junction of each staple line is made to prevent overlap of the absorbable staple rows and to allow for the next staple application. Because of this incision, there is often a short unstapled area at the junction between each application of the stapler, requiring one or two simple figure-of-eight sutures of 2-0 absorbable material at each of these points. The last staple application traverses the apex of the fold of bowel. In adults, three to four applications of the stapling device have been required to construct the right colon pouch, whereas in children two or three staple applications suffice. The appearance of the nearly completed pouch is illustrated in Figure 98-17E.

Once the generic right pouch has been fashioned, several options exist for ureteral anastomosis and formation of a sphincter mechanism. These maneuvers may be approached through the coalesced distal colon opening and cecostomy, which accesses the interior of the pouch (see Fig. 98-17E). The opening permits appropriate stent placement or inspection of a buttressed ileocecal valve. Any of the Mitrofanoff techniques described in conjunction with the Mainz I procedure can be employed. Likewise, the terminal ileum can be either stapled or pliated to create a continence mechanism. Once construction of a continence mechanism and ureteral anastomoses have been performed, the opening can be closed with a running 2-0 absorbable suture or the application of an absorbable TA stapler of appropriate length.

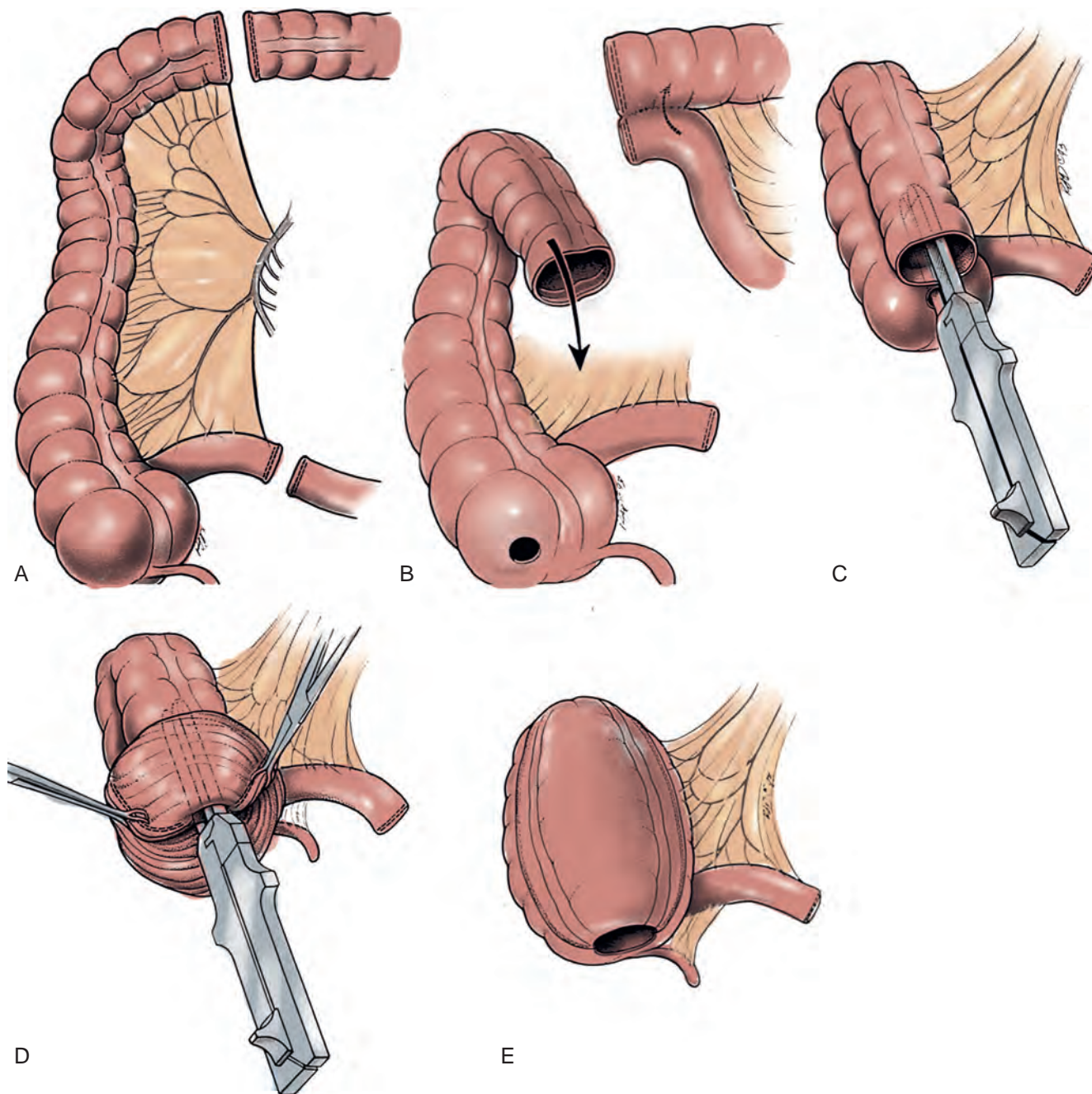


Figure 98-17. A, Isolation of colon and blood supply using metal gastrointestinal anastomosis staplers. B, Opening created in cecum and open end of colon to fit absorbable stapler. Bowel continuity restored between colon and ileum. C, Stapler activated along antimesenteric line and folded bowel. D, Inversion of bowel required to continue staple applications. E, Pouch inversion is complete. (From Olsson CA, Kirsch AJ, Whang MIS. Rapid construction of right colon pouch. *Curr Surg Tech Urol* 1993;6:1-8.)

Continent diversion procedures commonly employ the right colon or the cecum and terminal ileum. The array of right colon pouches that can be facilitated by this technique include all of the reservoirs described previously. Reservoirs using terminal ileum and cecum such as the Penn pouch and the Mainz pouch can also be fashioned in this manner.

Stapled Sigmoid Reservoir

The same stapling maneuvers can be applied to create a reservoir constructed from the sigmoid colon (Olsson and Kirsch, 1995). A portion of the sigmoid and descending colon measuring

approximately 35 cm is mobilized by incising the peritoneum along the white line of Toldt. Once mesenteric windows have been created, the segment of colon is isolated using metal GIA staplers (Fig. 98-18A). Restoration of bowel continuity is achieved with GIA, TA, or end-to-end anastomosis (EEA) staple devices.

Each of the metal stapled ends of the isolated colon are excised, and the bowel lumen is irrigated. The isolated sigmoid is folded on itself in a U configuration, aligning both open ends (Fig. 98-18B). The absorbable GIA stapler is inserted into the open bowel ends and fired along the antimesenteric line of the folded bowel (Fig. 98-18C). Following the procedure for bowel eversion as described earlier completes the reservoir. Again, usually two or three

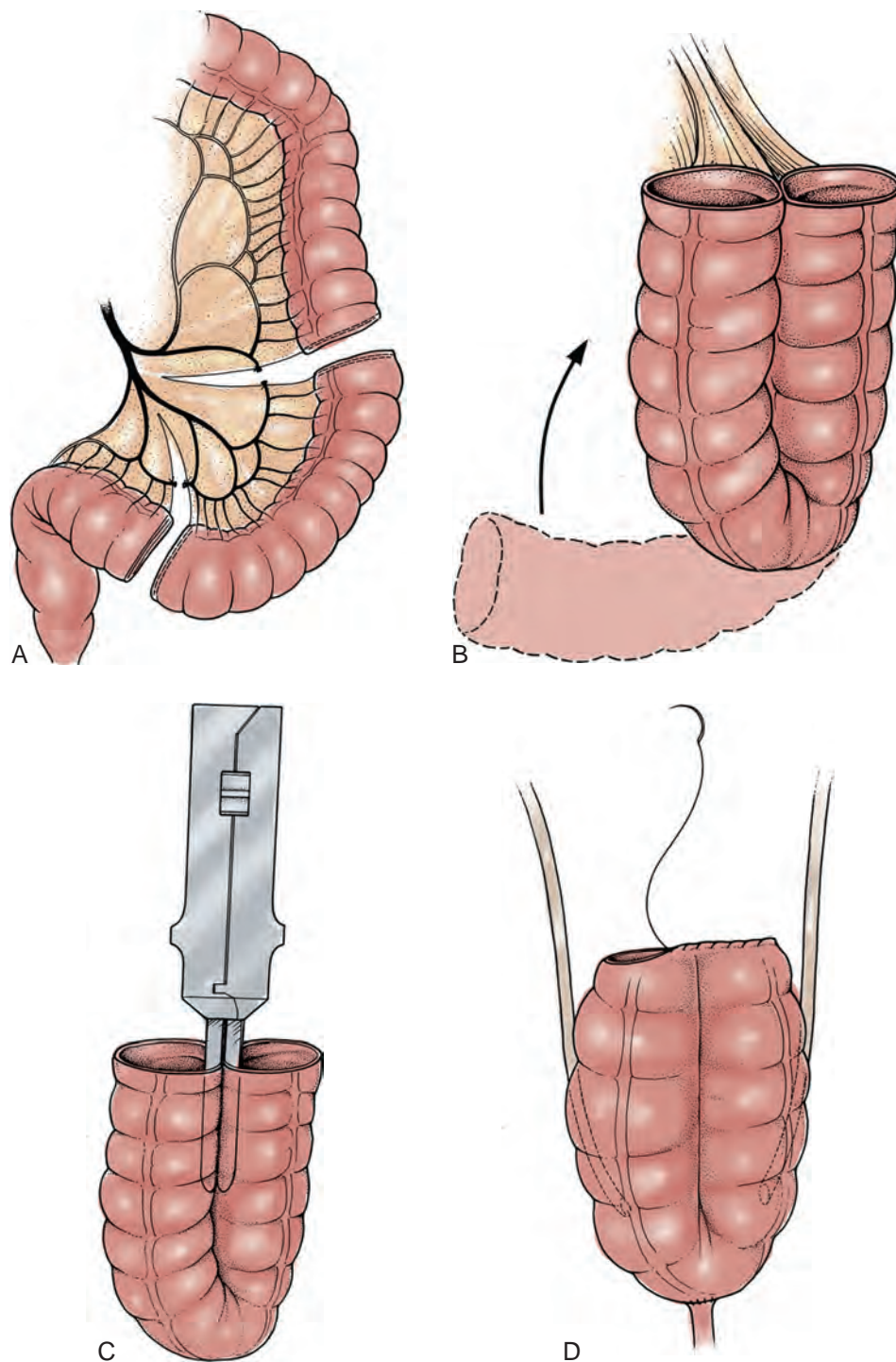


Figure 98-18. A, Isolation of colon and blood supply using metal gastrointestinal anastomosis staplers. B, Sigmoid bowel folded in U shape. C, Stapler fired along antimesenteric border of folded sigmoid. D, Oversewing of superior open end completes pouch construction. (From Olsson CA, Kirsch AJ, Whang MIS. Rapid construction of right colon pouch. *Curr Surg Tech Urol* 1993;6:1-8.)

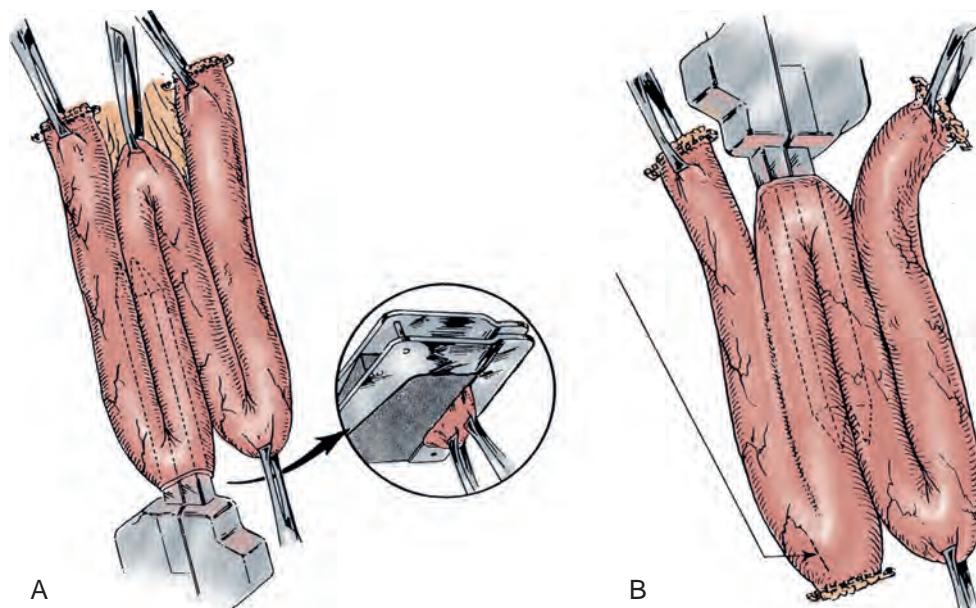


Figure 98-19. A, After closure of butt ends of reservoir with TA-55 stapler, enterotomy is made in dependent portion of first limb of W. Absorbable stapler is inserted through enterotomy and fired, creating common lumen between two adjacent limbs. Arrow indicates close-up of closure of enterotomy with TA-55 stapler. B, In middle limb of W, stapler is placed through enterotomy at apex and again common lumen is created. Staple lines are not directly apposing for their entire distance to avoid ischemia between adjacent staple lines. Arrow indicates site of enterotomy where urethroileal anastomosis will be performed. (From Pontes JE. *Genitourinary oncologic pelvic surgery*. New York: John Wiley; 1993.)

applications of the stapler are required to complete the pouch, cutting each staple line tip to avoid staple overlap.

After bowel reinversion, ureteral implants into the taenia can be carried out, using the residual colon opening to facilitate stent passage. These stents and a suprapubic tube are led through a separate stab wound in the pouch and brought through a lower abdominal wall stab incision. A continence mechanism employing one of the Mitrofanoff variations is then performed.

W-Stapled Reservoir

Montie and coworkers (1994) used the absorbable GIA stapler to construct ileal neobladders in patients undergoing cystoprostatectomy. A segment of ileum measuring 50 cm is divided with a standard metal GIA stapler 20 cm from the ileocecal valve. The terminal ends of each limb of the isolated ileal segment are closed with an absorbable TA-55 stapler, and the metal staple line is resected. The bowel is aligned in a W configuration, and an enterotomy is made 10 cm from each end (Fig. 98-19A). To facilitate closure of the enterotomy with a TA instrument (Fig. 98-19, inset), the enterotomy must be made midway between the mesentery and antimesenteric border. The absorbable GIA device is inserted through the enterotomy and is activated. This maneuver adjoins the two adjacent bowel segments. The enterotomy may be closed with the absorbable TA-55 instrument or running absorbable suture, completing the distal segment of the W. The middle and proximal segments are constructed similarly (Fig. 98-19B). Montie stresses that the segments of the W must be offset to avoid staple lines that overlap each other. Exceeding a 3- to 6-cm overlap may result in bowel ischemia.

Postoperative Care and Comments

In the first 50 adult patients to undergo our absorbable stapling technique in right colon pouch construction, with at least 7 years of follow-up there have been no complications attributable to absorbable staples. Similar results have been reported by Rowland

(1996). In the pediatric population, we have applied the absorbable stapler to continent urinary diversion, as well as to bladder augmentation (Hensle et al, 1995). In the first 18 children observed for up to 3 years, there have been no instances of pouch perforation or inadequate pouch capacity, and to date only one of the patients has developed a reservoir calculus.

Montie and colleagues (1994) used absorbable staplers to create W-stapled ileal neobladders in 25 patients. Ileal pouch construction was performed in approximately 20 minutes, and functional aspects were comparable to those of bowel reservoirs constructed by conventional suturing. Urodynamic evaluation at 6 months, however, documented a small-capacity reservoir requiring augmentation enterocystoplasty in 3 of 25 patients (12%). Montie and colleagues attributed this complication to either the size of the staples or reservoir fibrosis secondary to foreign body reaction. It is conceivable that a similar situation would arise when constructing a W-stapled T pouch.


We have used the absorbable stapler to construct both large and small bowel reservoirs. In our experience, colonic pouches appear better suited for construction with the absorbable stapler because of their relatively larger lumen. The introduction of stapling devices delivering still smaller staples and automatic staple line sealing devices may prevent the problems that occur when ileal pouches are constructed with current technology.

SUMMARY

In summary, continent urinary diversion is now an accepted part of the urologic surgical armamentarium. A wide array of surgical techniques exist to accomplish the desired goal of creating a continent, stomal free, nonrefluxing pouch. A paucity of long-term quality-of-life studies exists to compare outcomes between continent cutaneous urinary diversion and ileal conduit urinary diversion. Surgeons contemplating these forms of urinary diversion should familiarize themselves with several of the techniques and the management of the most common complications.

KEY POINTS

- Because the ability to self-catheterize is essential to the patient undergoing continent diversion, the patient must be assessed for the ability to care for himself or herself.
- Patients with multiple sclerosis, quadriplegic individuals, and very frail or mentally impaired patients will at some point in their lives require the care of members of the family or a visiting nurse, and such patients are viewed as poor candidates for any form of continent diversion.
- Renal and hepatic function must be reviewed carefully in the patient selected for continent diversion. The reabsorption and recirculation of urinary constituents and other metabolites require that liver function be normal and that serum creatinine levels be in the normal range, certainly below the level of 1.8 mg/dL.
- When the ureters are directed into the fecal stream, routine colonoscopy should also be performed. There have been isolated reports of malignancy developing earlier, and all patients developing gross or microscopic hematuria should be fully evaluated.
- Many studies from throughout the world have suggested an improved psychosocial adjustment of the patient undergoing continent urinary and fecal diversion compared with those patients with diversions requiring collecting appliances.
- Four general techniques have been employed to create a dependable, catheterizable continence zone. For right colon pouches, appendiceal techniques, pseudoappendiceal tubes fashioned from ileum or right colon, and ileocecal valve plication are adaptable. Appendiceal tunneling techniques are the simplest of all to perform in that they use established surgical techniques that are already in the urologic armamentarium.
- The second major type of continence mechanism used in right colon pouches is the tapered and/or imbricated terminal ileum and ileocecal valve. However, some patients have developed rather striking diarrhea and steatorrhea after the loss of the ileocecal valve. This may be particularly true in the pediatric patient.
- The third surgical principle used in constructing the continence mechanism is the use of the intussuscepted nipple valve or, more recently, the flap valve, which avoids the need for intussusception. The creation of nipple valves is the most technologically demanding of all the continence mechanisms and is associated with the highest complication rate.
- The fourth major technique of continence mechanism construction is the provision of a hydraulic valve, as in the Benckroun nipple. In this procedure, a small bowel segment is isolated and a reversed intussusception is used to appose the surfaces of the small bowel.
- Pouch urinary retention represents a true emergency, and the patient must seek immediate attention so that catheterization and drainage by experienced personnel can be achieved promptly.
- Because all patients with catheterized pouches will have chronic bacteriuria, the problem of antibiotic management should be discussed. Most authors would suggest that bacteriuria in the absence of symptomatology does not warrant antibiotic treatment.
- The concept of using the buttressed ileocecal valve as a dependable continence mechanism that can withstand the trauma of intermittent catheterization was first reported from Indiana University by Rowland and Mitchell (Rowland et al, 1987).
- The Indiana pouch remains one of the most reliable of all catheterizable reservoirs. It is among the easiest to construct, and it has very low short-term and long-term complications.
- The use of absorbable staplers has substantially reduced the time required to fashion bowel reservoirs and has demonstrated short-term and long-term reliability with respect to reservoir integrity and volume.
- It is anticipated that in the near future technologic advances in minimally invasive surgery will allow for the laparoscopic (robotic) construction of these reservoirs. These technologic advances will likely include automated suturing devices and biosealants.

 Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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 The complete reference list is available online at www.expertconsult.com.

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History of Orthotopic Urinary Diversion

Basic Principles of Continent Orthotopic Urinary Diversion

Patient Selection

Continence Mechanism in Patients Undergoing Orthotopic Diversion

Surgical Techniques for Continence Preservation during Radical Cystectomy

Techniques for Orthotopic Bladder Substitution

Results and Complications of Orthotopic Urinary Diversion

HISTORY OF ORTHOTOPIC URINARY DIVERSION

Since the early 1900s, innovative surgeons have sought the best method to replace the original bladder when it must be removed because of either benign or malignant disease. The objective of bladder substitution is to allow volitional voiding through the urethra while eliminating the need for a cutaneous urinary stoma or intermittent catheterization.

Ureterosigmoidostomy is the oldest form of urinary diversion. The first reported urinary diversion into a segment of bowel was by [Simon in 1852](#). He attempted a ureterosigmoidostomy in an exstrophy patient by bringing the ureters into the rectum with the use of needles and suture to create a fistula. Although the patient died of sepsis 12 months later, this marked the first reported attempt at some form of urinary diversion ([Simon, 1852](#)). Over the following 100 years the evolution of urinary diversion was marked by a continued search for better methods and techniques to reconstruct the lower urinary tract. A number of technical modifications of the ureterosigmoidostomy ensued, particularly related to the ureteral implantation technique ([Hinman and Weyrauch, 1936](#)). The rates of obstruction and ascending pyelonephritis in patients with ureterosigmoidostomy were significantly reduced after introduction of an antireflux tunneled anastomosis of the ureter into the sigmoid colon ([Leadbetter, 1951](#); [Goodwin et al, 1953](#)).

Ureterosigmoidostomy remained the diversion of choice until the late 1950s, but long-term electrolyte imbalance, upper tract obstruction and infection, and secondary malignant neoplasms arising at the ureteral implantation site were observed ([Clarke and Leadbetter, 1955](#); [Wear and Barquin, 1973](#)). In 1950 [Bricker refined and popularized the ileal conduit form of urinary diversion, building on an original description by Zaayer in 1911 \(Zaayer, 1911; Bricker, 1950\)](#). The ileal conduit is a technically simple, reliable form of urinary diversion that became widely accepted and became the gold standard to which other types of urinary diversion were compared until the 1980s. It continues to be by far the most common form of urinary diversion performed throughout the world today for patients undergoing cystectomy.

Long-term complications with the Bricker ileal conduit started to come to light in the 1970s. Although problems with hyperchloremic metabolic acidosis and pyelonephritis were substantially less common than in patients with ureterosigmoidostomy, **late complications with the ileal conduit such as peristomal hernia, stomal stenosis, pyelonephritis, kidney stones, ureteral obstruction, and renal deterioration became more apparent with longer follow-up** ([Butcher et al, 1962](#); [Shapiro et al, 1975](#); [Middleton and Hendren, 1976](#); [Pitts and Muecke, 1979](#); [Sullivan et al, 1980](#); [Kouba et al, 2007](#); [Shimko et al, 2011](#)). These clinical sequelae

were thought to be related to the high-pressure reflux of infected urine or obstruction of the upper urinary tract. It was postulated that the addition of an antireflux technique to a conduit form of diversion could help diminish the problems of reflux and renal deterioration in these patients. In fact, animal experiments provided evidence to support the advantage of nonrefluxing colonic conduits over ileal conduits ([Richie et al, 1974](#)). Unfortunately, with longer follow-up, similar complications with nonrefluxing colon conduits were observed ([Morales and Golimbu, 1975](#); [Althausen et al, 1978](#); [Elder et al, 1979](#)).

One of the earliest continent cutaneous diversions in humans was described by [Gilchrist and colleagues in 1950](#). This form of urinary reconstruction incorporated a cecal reservoir with the ileocecal valve as the continence mechanism and the distal ileum as a catheterizable stoma ([Gilchrist et al, 1950](#)). However, this innovation attracted little attention at the time. The concept of a continent cutaneous diversion was subsequently reintroduced by [Kock and colleagues in 1982](#) with a technique that was originally developed for a continent ileostomy after colectomy for inflammatory bowel disease. It incorporated an intussuscepted nipple valve to maintain continence and avoid reflux. In animal experiments and then in humans, **Kock demonstrated the importance of complete detubularization of the bowel segment and the double-folding technique that creates the most spheric shape possible** ([Eckman et al, 1964](#); [Kock et al, 1982](#)). These concepts are the cornerstone of current cutaneous and orthotopic reservoirs. After Kock described his results in his initial 12 patients, Skinner began performing this diversion in adults undergoing cystectomy for bladder cancer in 1982. Although this form of urinary diversion required catheterization of an abdominal stoma, it eliminated the need for an external urostomy appliance. It was a popular concept for patients and referring physicians alike, and Skinner quickly amassed a large clinical experience with this type of continent cutaneous diversion ([Skinner et al, 1984, 1988](#)).

The biggest challenge in the development of continent cutaneous diversion has been the design of a reliable, durable, efferent continence mechanism that is easily catheterizable. A number of techniques have been described using large and small bowel and even stomach, with many ingenious continence mechanisms. However, stones, difficulty in catheterizing, peristomal hernias, and the development of leakage are potential problems with all of them, often necessitating open surgical revision ([Lieskovsky et al, 1987](#); [Rowland, 1995](#)). Today, several different reliable techniques are available to create a continent cutaneous urinary diversion, including the Indiana pouch and various other forms of right colon pouches. These forms of diversion can potentially offer an advantage to patients over an ileal conduit, but these operations remain technically challenging and are not widely used.

The concept of orthotopic diversion began even before Kock's continent cutaneous diversion. Tizzoni and Poggi were the first to experiment in a dog, transplanting the ureters into an isolated loop of ileum interposed between the ureters and the urethra. The dog was reportedly continent and subsequently underwent three successful pregnancies before dying 30 months postoperatively (Tizzoni and Poggi, 1888). Lemoine is credited with performing the first orthotopic reconstruction in a human subject. This patient initially underwent a cystectomy with ureterosigmoidostomy. Complications related to recurrent pyelonephritis led to undiversion in this patient; the rectal segment was isolated, transected, and anastomosed to the urethra, and the sigmoid colon was brought down and anastomosed to the anus (Lemoine, 1913).

In 1979, Camey and Le Duc reported their pioneering clinical experience with orthotopic substitution to the native urethra in male bladder cancer patients (Camey and Le Duc, 1979). The initial Camey diversion used an intact segment of ileum, resulting in a high-pressure reservoir. Subsequently the Camey II detubularized reservoir (Camey, 1990); Hautmann W-neobladder (Hautmann et al, 1988); "hemi-Kock" neobladder (Skinner et al, 1991); Studer pouch (Studer et al, 1989); extraserosal-lined ureteral tunnel (Abol-Enein and Ghoneim, 1993); T pouch (Stein et al, 1998b); stomach neobladder (Hauri, 1998); cecal and ileocecal neobladders (Light and Engelmann, 1986; Mansson and Colleen, 1990); and sigmoid reservoir (Reddy and Lange, 1987) have all been described. Many of these now have a large clinical experience with long-term follow-up demonstrating good renal preservation and continence results. Orthotopic diversion quickly surpassed continent cutaneous diversion in popularity for both patients and physicians, because it allows natural voiding, is simpler to construct, and is less likely to require revision surgery at a later date.

Initially these techniques were applied only to male patients because continence in women was believed to be dependent on an intact bladder neck and there was concern about higher local recurrence with the retained urethra. In the mid 1990s it was discovered through anatomic dissections and initial clinical experience that

women could remain continent with a low-pressure reservoir and preservation of only the urethra itself (Stein et al, 1994b; Borirakchanyavat et al, 1997; Colleselli et al, 1998). In addition, there were several careful pathologic studies of female cystectomy specimens showing that preservation of the urethra did not compromise oncologic efficacy provided the urethral margin was negative on intraoperative frozen section (Stein et al, 1995; Stenzl et al, 1995b; Maralani et al, 1997; Stein et al, 1998a).

Although the ideal bladder substitute remains to be developed, the orthotopic neobladder most closely resembles the original bladder in both location and function. This form of lower urinary tract reconstruction relies on the intact external rhabdosphincter continence mechanism, seldom requires intermittent catheterization, and avoids the difficulties associated with the efferent continence mechanism of continent cutaneous reservoirs. Voiding is accomplished by relaxation of the pelvic floor musculature (as in normal voiding) along with a concomitant increase in intra-abdominal pressure (Valsalva maneuver).

Orthotopic reconstruction has replaced the ileal conduit as the standard form of reconstruction in many centers of excellence worldwide. Hautmann and Paiss attempted to determine whether the option of a neobladder substitute stimulated the decisions of patient and physician toward an earlier cystectomy in patients with bladder cancer. They reported on a total of 213 men undergoing cystectomy for bladder malignant neoplasm, 135 patients with an ileal neobladder, and 78 with an ileal conduit diversion. The interval from the primary diagnosis was 11.8 months in the neobladder and 16.7 months in the conduit group. Five-year survival rates were significantly higher for all disease stages in the neobladder group than in the conduit group, and the authors concluded that the availability of ileal neobladder may decrease the physician's reluctance to perform cystectomy early in the disease process (Hautmann and Paiss, 1998).

The experience of urinary diversion at the Keck School of Medicine of the University of Southern California demonstrates the evolution of urinary diversion at that institution (Fig. 99-1).

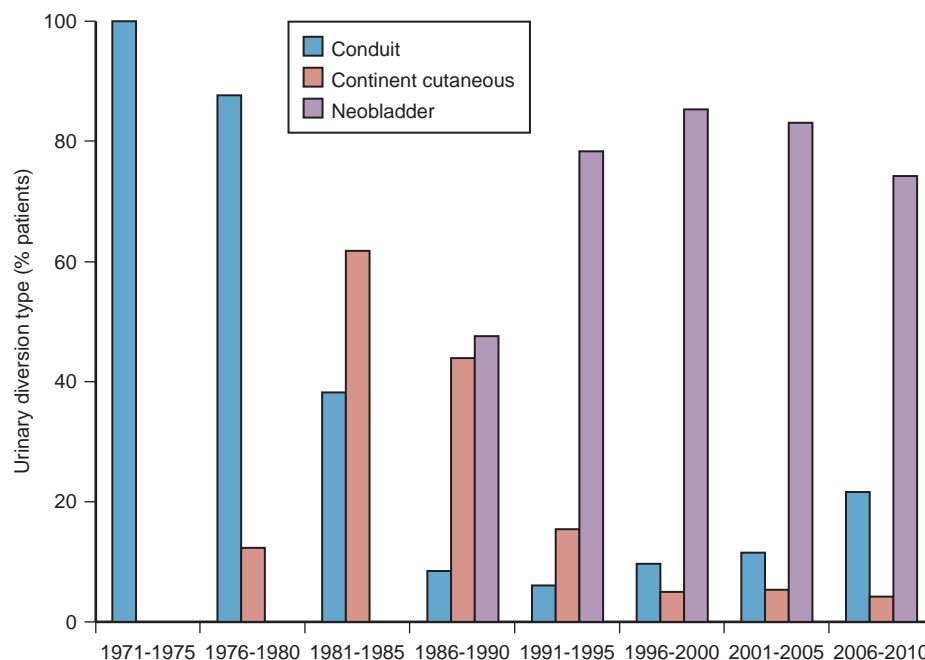


Figure 99-1. Evolution of urinary diversion at the University of Southern California from 1971 to 2010. Orthotopic reconstruction was first applied to men in 1986 and to women in 1990, with a steady increase in the number of bladder substitutes since that time and a decline in the number of conduit forms of diversion during the same period. Recent increases in the percentage of older patients with more comorbidities have resulted in a slight increase in ileal conduit diversion.

Beginning in 1986, the number of orthotopic bladder substitutions performed dramatically increased to more than 75% of cystectomies, while the number of conduits and continent cutaneous diversions declined. Similar results occurred in Ulm, Germany and many other sites that embraced continent diversion as an alternative to ileal conduit. In eight other academic centers internationally, each with a large cystectomy experience, there is a very wide range in the rate of neobladder diversion in recent years, ranging from 6% to 51% (Hautmann et al, 2013). In a population-based study in the United States using the Nationwide Inpatient Sample database from 2001 to 2008, only 8% of cystectomy patients underwent continent urinary diversion, a rate that increased only to 20% even for patients under age 55 (Kim et al, 2013). In Sweden the national rate was 14% for all patients from 2003 to 2008 (Hautmann et al, 2013). In one high-volume academic center in the United States the rate of neobladder dropped dramatically from 47% to 21% over only a 5-year period from 2000 to 2005 (Lowrance et al, 2009).

The reasons behind this very wide variability are complex. Although surgeons point to differences in patient populations (e.g., increasing age, comorbidity, socioeconomic challenges), it is much more likely that which diversion is offered and/or recommended by specific physicians and institutions is heavily influenced by differences in surgeon philosophy and training, as well as misconceptions regarding results. Chang and colleagues have pointed out that trainees in most residency programs are exposed to few if any of these procedures (Chang et al, 2006). In addition, many cystectomies in the United States are performed by surgeons who do only a few such cases per year (Barbieri et al, 2007). In the United States there is also a lack of any economic incentive for the surgeon to learn or perform a potentially more complex operation (Skinner, 2011); in fact, a longer procedure is counterproductive from a financial perspective. The adoption of robotic techniques may be further aggravating this situation.

It is estimated that approximately 80% to 90% of male patients and 75% of female patients undergoing cystectomy are potential candidates for neobladder construction from a purely medical standpoint. In the series from Ulm, Germany, only 16% of the patients undergoing cystectomy had medical contraindications to orthotopic diversion, and another 2% refused (Hautmann et al, 2010). In another study examining the choice of urinary diversion in the context of a standardized preoperative counseling program, only 6% of patients who were eligible for a continent urinary diversion chose to undergo an ileal conduit for personal reasons (Ashley and Daneshmand, 2010). It is incumbent on the surgeon who is going to offer orthotopic diversion to understand the indications, surgical techniques, and principles of perioperative management to optimize outcomes.

KEY POINTS: HISTORIC EVOLUTION OF ORTHOTOPIC URINARY DIVERSION

- Historically, urinary diversion has developed along three paths: a conduit form of diversion, continent cutaneous diversion, and most recently orthotopic diversion.
- Long-term complications of the ileal and colon conduits include stomal stenosis, peristomal hernia, pyelonephritis, calculus formation, ureteral obstruction, and renal deterioration.
- The major long-term problems with continent cutaneous diversion relate to malfunction of the efferent continence mechanism, and open surgical revision is often required.
- The orthotopic neobladder relies on the rhabdosphincter for continence; most patients are continent and able to void to completion without the need for intermittent catheterization.
- Female patients with an intact functioning urethra are also potential candidates for orthotopic diversion.

BASIC PRINCIPLES OF CONTINENT ORTHOTOPIC URINARY DIVERSION

Many methods for construction of an orthotopic neobladder using intestinal segments exist, but three basic principles must be satisfied for a successful outcome.

First, the patient must have an adequate external sphincter mechanism and nonobstructed urethra. This aspect is discussed in more detail later in the sections on patient selection and description of the anatomy of the external sphincter and surgical techniques for continence preservation.

Second, the reservoir must be sufficiently compliant to maintain a low pressure throughout the filling phase. This is best achieved by opening the bowel segment longitudinally to completely detubularize it and folding it to create a spheric shape. This concept was described by Goodwin and colleagues and further developed by Kock in elegant animal experiments (Goodwin et al, 1959; Eckman et al, 1964). The sphere has the greatest internal volume for a given surface area and thus the greatest capacity according to Laplace's law. The compliance of the wall relates to the physical characteristics of the bowel wall itself and is greater in small bowel compared with large bowel. The double-folded technique of Kock and S- and W-shaped reservoirs all effectively eliminate the coordinated high-pressure contractions of the bowel wall, allowing the reservoir to maintain low internal pressure throughout the filling phase (Kock et al, 1982; Hinman, 1988). All current continent diversion techniques use detubularized bowel to construct the reservoir.

Third, the reservoir must have adequate volume to allow for reasonable voiding intervals. In general, this should be at least 300 to 500 mL once the pouch is mature. All bowel segments effectively stretch over time if there is adequate outflow resistance. The standard 44-cm length of ileum formed into a double-folding reservoir by the Kock technique (also used for both the Studer and T pouch neobladders) has an initial capacity of less than 200 mL but within the first year stretches to hold 500 to 600 mL at low pressure (Studer et al, 1996). Figure 99-2 shows a computed tomography (CT) scan of a mature spheric pouch at 1 year. When used for a continent cutaneous pouch with high outflow resistance, this same configuration routinely stretches over time to hold more than 1000 mL at low pressure. This emphasizes that large initial volumes are not necessary to ultimately achieve an adequate voiding volume. Colonic segments do not stretch up as easily, and a larger initial volume is necessary for pouches constructed out of colon. In

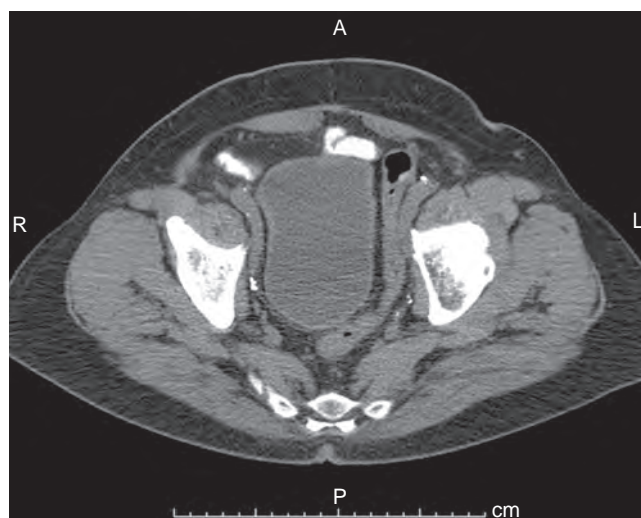


Figure 99-2. Computed tomography scan of the pelvis after construction of an ileal neobladder (Studer pouch) showing the spheric shape achieved by 1 year.

general, small bowel, when available, has advantages over colon in terms of wall compliance and ability to stretch, as well as reduced mucous formation (Khafagy et al, 2006).

KEY POINTS: THREE BASIC PRINCIPLES OF ORTHOTOPIC NEOBLADDER CONSTRUCTION

- Patient must have a healthy urethra and adequate external sphincter function to maintain continence.
- Bowel segment should be detubularized and reconstructed into a spheric shape.
- Ultimate storage volume should be at least 300 to 500 mL at low pressure.

PATIENT SELECTION

Nearly all patients who undergo radical cystectomy may be considered at least potential candidates for orthotopic urinary diversion. There are few absolute contraindications. However, a number of factors should be considered in counseling the individual patient as to the best diversion for him or her, and these can be divided into cancer-related factors and patient factors.

Oncologic Factors

Risk of Urethral Recurrence in Men

The primary oncologic contraindication for orthotopic diversion is the presence of urothelial carcinoma at the urethral margin on intraoperative frozen section at the time of cystectomy. In the male patient involvement of the prostatic urethra is associated with a higher risk of subsequent urethral recurrence. Ashworth first reported on 7 patients with urethral recurrence, and noted that 5 of them had prostatic urethral involvement on the cystectomy specimen (Ashworth, 1956). Other series have subsequently confirmed this finding (Raz et al, 1978; Faysal, 1980; Hardeman and Soloway, 1990; Levinson et al, 1990; Tobisu et al, 1991; Nieder et al, 2004). Freeman and colleagues reviewed six studies in which 31 of 122 patients (25%) with evidence of prostatic urethral involvement developed an anterior urethral tumor after radical cystectomy for bladder cancer (Freeman et al, 1996). In a large, comprehensive, pooled analysis of 25 series, Stenzl and colleagues reported a total of 256 anterior urethral tumor recurrences in 3165 patients (8.1%) undergoing cystectomy for bladder cancer (Stenzl et al, 1995b).

A retrospective review of 768 men who underwent cystectomy without urethrectomy at the University of Southern California with 13 years' median follow-up found that the overall risk of urethral recurrence was approximately 7% at 5 years and 9% at 10 years. Recurrences were observed at a median of 2 years after cystectomy (range 0.2 to 13 years). The risk was only 5% at 5 years in the 639 patients without any prostate tumor involvement compared with 11% in the 129 men with any prostate involvement (Stein et al, 2005). The extent of prostatic tumor involvement correlated with the risk of subsequent urethral recurrence. The 5-year estimated probability of urethral recurrence for superficial carcinoma in situ (CIS) or mucosa and ductal prostatic urethral involvement without stromal invasion was 12%, compared with 18% with invasion into the stroma. In a multivariate analysis, any prostate tumor involvement (superficial or invasive) remained an independent and significant predictor of a urethral tumor recurrence. CIS in the bladder and tumor multifocality were not individually associated with a significant risk for anterior urethral recurrence (Stein et al, 2005).

Isolated prostatic stromal involvement is fairly unusual in the absence of nodal disease. In an updated study of 1226 male patients from the same institution, Djaladat and colleagues (2013) found only 33 patients who had prostatic stromal invasion without nodal involvement on final pathology. The urethral recurrence rate was

6% in this group, with a median time to recurrence of 2.4 years. None of these patients had a local pelvic recurrence (Djaladat et al, 2013).

A number of authors have evaluated other tumor characteristics to determine if histopathologic parameters other than prostatic urethral involvement can identify patients at increased risk for urethral recurrence after cystectomy. Various pathologic risk factors have been examined including the presence of papillary tumors, tumor multifocality, trigone or bladder neck tumor involvement, and associated CIS in the bladder or upper tracts (Freeman et al, 1996). Several investigators have evaluated the presence of CIS in the bladder as a risk factor for urethral recurrence with variable results (Hardeman and Soloway, 1990; Levinson et al, 1990; Tobisu et al, 1991; Stein et al, 2005). Boorjian and colleagues reviewed over 1500 patients (1230 males) with 13.5 years' median follow-up. They found that tumor multifocality was a significant risk factor for urethral recurrence in addition to prostatic urethral involvement but not CIS (Boorjian et al, 2011).

Some evidence indicates that orthotopic diversion itself may provide some protection against urethral recurrence. Stein reported on 397 patients who underwent neobladder diversion compared with 371 who did not. Median follow-up of both groups was long—10 years and 19 years—and patients were excluded if they underwent prophylactic urethrectomy. In patients without prostatic involvement (85% of the neobladder patients vs. 81% of the cutaneous diversion patients), the risk of urethral recurrence at 5 years was 3% versus 8%, respectively. In patients with prostatic stromal invasion, the 5-year risk of recurrence was 11% versus 24% for those with cutaneous diversion (Stein et al, 2005). Boorjian found a similar protective effect of neobladder reconstruction in the Mayo Clinic series of over 1200 male patients with long follow-up. Both these studies found this effect persisted when other pathologic variables were controlled for (Boorjian et al, 2011). The reason for this observation is unclear, although there has been speculation that continued flow of urine, perhaps with changes in urinary characteristics caused by the interposed bowel, might be responsible (Stein et al, 2005).

There is some controversy about the importance of attempting to identify prostatic urethral involvement preoperatively, as well as what to recommend for those patients in whom prostatic involvement is identified. At the time of transurethral resection (TUR) of the primary bladder tumor, the surgeon may perform deep TUR biopsies of the prostate, preferably at the 5- and 7-o'clock positions lateral to the verumontanum. This should certainly be done if the mucosa of the prostate looks suspicious. Some authors have recommended that this should be done routinely and have advocated repeat TUR before cystectomy in patients in whom it was omitted (Wood et al, 1989; Sakamoto et al, 1993; Lerner and Shen, 2008). However, the reliability of preoperative transurethral prostatic biopsies has been challenged by others. In a prospective series of 118 patients, Lebret and colleagues examined the usefulness of preoperative prostatic biopsies compared with intraoperative frozen-section analysis of the prostatic urethral margin at the time of cystectomy in predicting urethral recurrence. They found that intraoperative frozen-section analysis was more accurate than any preoperative parameter including preoperative prostate biopsies in predicting urethral recurrence (Lebret et al, 1998). In another series of 246 men who underwent preoperative transurethral loop biopsy of the prostate, Donat and colleagues reported that this preoperative pathologic evaluation did not accurately determine prostatic tumor involvement—both false-negative and false-positive results were observed. Forty-three percent of patients with prostatic involvement on final pathology were missed on the TUR biopsy, and 12 of 36 patients with prostatic stromal invasion identified on TUR specimen had no residual prostatic involvement on the final cystectomy specimen (Donat et al, 2001). In light of this, it is questionable whether the risk of the additional anesthetic and the potential delay to definitive surgery warrant the additional information garnered by a repeat TUR with prostatic urethral biopsy. We have not routinely recommended repeat TUR solely to rule out prostatic involvement before cystectomy. Other centers have adopted a similar

philosophy with comparable clinical outcomes (Iselin et al, 1997; Hautmann, 2003).

It has been our practice to counsel patients with documented prostatic mucosal, ductal, or stromal invasion about the increased risk of urethral recurrence if the urethra is left in situ, and to help them weigh that risk against any perceived advantage of an orthotopic diversion. In general, those with prostatic stromal invasion are counseled to undergo neoadjuvant chemotherapy. In those who are not candidates for neoadjuvant chemotherapy or who have persistent prostatic urethral involvement, at surgery a concomitant urethrectomy and cutaneous form of diversion are recommended. Close surveillance of the urethra is mandatory if a neobladder procedure is performed, with periodic urethral wash cytology and urethroscopy as indicated.

Risk of Urethral Recurrence in Women

In the past, urethrectomy was routinely performed at the time of radical cystectomy in women. With the acceptance of continent neobladder in men, a number of investigators began evaluating the feasibility of preservation of the urethra in women. This was initially attempted in women with non-transitional cell carcinoma in whom there was little concern about possible urethral recurrence, with excellent functional results (Stein et al, 1994b). Before this it was generally believed that the bladder neck was the primary continence mechanism in women, but initial clinical experience proved that one could achieve excellent continence by dividing the urethra distal to the bladder neck (Tanagho et al, 1966; Stein et al, 1994b).

Two important pathologic studies were critical to the ultimate decision to expand urethral-preserving cystectomy to women with urothelial carcinoma. Stein and colleagues retrospectively evaluated a series of archival cystectomy specimens from 67 female patients undergoing cystectomy with urethrectomy for bladder cancer with re-evaluation of the primary pathology specimen. Seventeen of these women (25%) had involvement of the bladder neck, and 9 (13%) of them had urethral involvement. All female patients with an uninvolved bladder neck also had an uninvolved urethra (no skip lesions), whereas approximately 50% of patients with a bladder neck tumor had concomitant urethral tumor involvement. Risk factors for urethral involvement in this study included increased grade, stage, and lymph node involvement, but the presence of CIS did not predict urethral involvement. Vaginal wall involvement was also a major risk factor for urethral involvement. Although vaginal wall invasion was a relatively rare event (1%), all of these patients also had bladder neck involvement and 50% had urethral extension (Stein et al, 1995). The presence of vaginal wall invasion is best evaluated with bimanual examination under anesthesia, either at TUR or cystectomy.

Stenzl and colleagues also studied the risk of synchronous or secondary urethral tumors with long-term follow-up in 356 women with bladder cancer of all stages. They found urethral involvement in only 2% of the patients, and it was always associated with bladder neck involvement. Of the patients with cT2 to T4 localized disease, only 1% had urethral involvement.

No correlation between urethral tumors and other pathologic factors such as CIS or tumor multifocality was found. The researchers concluded that the urethra can be safely preserved in selected female cystectomy patients provided that neither preoperative biopsy specimens of the bladder neck nor intraoperative frozen-section specimens of the proximal urethra demonstrate any tumor or atypia (Stenzl et al, 1995b).

Maralani and colleagues similarly evaluated specimens from 43 female patients who underwent cystectomy for bladder cancer. They reported a 16% incidence of urethral tumor involvement, and vaginal involvement in this study was the most significant risk factor for urethral tumor involvement (Maralani et al, 1997). Chen and colleagues also retrospectively reviewed the risk of urethral, vaginal, and cervical involvement by transitional cell carcinoma in 115 women undergoing radical cystectomy. They found an overall 8%

incidence of tumor of the urethra, and confirmed an association between urethral tumor and tumor at the bladder neck or invading the vagina or cervix. They did find 2 patients with urethral tumor who did not have bladder neck involvement, though the researchers did not do pathologic review of the specimens. These studies and others confirmed that the most significant risk factor for urethral tumor involvement is tumor at the bladder neck (De Paepe et al, 1990; Coloby et al, 1994; Chen et al, 1997).

Stein and colleagues (1998a) embarked on a prospective study to evaluate and confirm the previously established pathologic risk factors in women undergoing cystectomy for bladder cancer to determine if these criteria safely identify appropriate female candidates for orthotopic diversion. Final pathologic analysis of the bladder neck and proximal urethra was performed and compared with the intraoperative frozen-section analysis of the proximal urethral margin. Tumor involvement at the bladder neck and proximal urethra was found in 14 (19%) and 5 (7%) cystectomy specimens, respectively. All patients with urethral tumors also demonstrated concomitant bladder neck tumors. Bladder neck tumor involvement was again found to be the most significant risk factor for tumor involving the urethra, confirming the findings from retrospective series. However, approximately half of patients with bladder neck tumors had a normal (tumor-free) proximal urethra. Furthermore, no patient with a normal bladder neck demonstrated tumor involvement of the urethra. In all cases, intraoperative frozen-section analysis of the proximal urethra correlated with and was correctly confirmed by final permanent section (Stein et al, 1998a). These results suggest that one may depend on the intraoperative frozen section to determine the feasibility of orthotopic diversion. Stenzl and colleagues reported similar results (Stenzl et al, 1998).

Clinical follow-up data from the first 88 women who underwent orthotopic diversion at University of Southern California showed that no urethral recurrences were observed with a median follow-up of 30 months in this group (Stein et al, 2002). Ali-El-Dein and colleagues (2004) prospectively evaluated 145 women undergoing cystectomy and orthotopic diversion. Two patients developed urethral recurrence. One had a primary squamous cell cancer of the bladder, and the other had urothelial carcinoma with CIS of the trigone (Ali-El-Dein et al, 2004). This series was updated with 180 patients and median follow-up of 57 months, with still only 2 documented urethral recurrences. There were no isolated vaginal wall recurrences. In this series the researchers found uterine or cervical involvement in only 1% of patients, which was suspected preoperatively in all patients based on imaging (Ali-El-Dein, 2009).

Locally Advanced Tumor Stage

Many urologists are hesitant to perform continent orthotopic diversion in patients with locally extensive disease. This is based on two factors: (1) concern about the possible impact of local recurrence on the neobladder itself and (2) a belief that these patients are doomed to suffer distant recurrence and have a shortened life expectancy and will not benefit from the neobladder.

Radical cystectomy with bilateral pelvic or iliac lymphadenectomy provides excellent local (pelvic) control for the treatment of invasive bladder cancer. Stein and colleagues reported the clinical outcomes for 1054 patients who underwent radical cystectomy for bladder cancer with a median follow-up of more than 10 years. In this series, an overall local pelvic recurrence rate of 7% was observed for the entire group of patients. The risk of pelvic recurrence ranged from 6% with organ-confined, node-negative disease to 13% for patients with extravesical or node-positive disease. Nearly 50% of patients with extravesical tumor extension and 30% of patients with lymph node positive disease were still alive without evidence of disease 5 years after cystectomy. These results suggest that local recurrence even for patients demonstrating locally advanced or lymph node positive disease is relatively infrequent and that a significant proportion of these patients will be long-term survivors and may benefit from continent diversion (Stein et al, 2001a). In an update review of 1817 patients from the same institution and a

median follow-up of 11.7 years, only 81 (4.5%) of patients had pelvic recurrence without distant metastases (Mitra et al, unpublished data).

If local tumor recurrence does develop in patients with an orthotopic diversion, only a minority will develop problems related to the urinary diversion itself. Hautmann and colleagues evaluated this issue in 43 of 357 men who underwent radical cystectomy and ileal neobladder and developed local recurrence. Most of them (84%) had advanced disease (stage pT3a or higher) on final pathology at the time of cystectomy. A total of 17 patients (43%) had concomitant distant metastasis at the time of diagnosis of the local recurrence. Local recurrence interfered with the upper urinary tract in 24 patients, the neobladder in 10 (23%), and the intestinal tract in 7; only 1 patient required removal of the neobladder because of an intestinal fistula. The authors concluded that **most patients could anticipate normal neobladder function even in the presence of locally recurrent disease** (Hautmann and Simon, 1999). Similarly, Tefilli and colleagues found that 1 of 11 patients with orthotopic diversion and local recurrence required conversion to an ileal conduit because of invasion of the neobladder (Tefilli et al, 1999).

Questions were initially raised about whether a planned neobladder reconstruction would result in the surgeon inadvertently compromising the extent of dissection and thus the cancer cure rate. To evaluate this, Yossepowitch and colleagues retrospectively evaluated 214 patients who underwent radical cystectomy and orthotopic reconstruction and compared them with 269 patients treated with a cystectomy and ileal conduit diversion. Adjusting for pathologic stage, there was no cancer-specific survival difference between the two diversion groups. Patterns of relapse in 62 of the 214 patients (29%) with an orthotopic neobladder included local recurrence in 11%, distant recurrence in 9%, and combined local and distant recurrence in 18%. Only one patient in this series required the neobladder to be converted to an ileal conduit secondary to a relapse at the ureteroenteric anastomosis and expanding into the pouch. These authors also concluded that **the low risk of local recurrence showed that in this cohort of patients the oncologic efficacy of the operation was not compromised** (Yossepowitch et al, 2003).

KEY POINTS: ONCOLOGIC FACTORS IN PATIENT SELECTION

- The presence of CIS, multifocal tumor, or extravesical disease should not preclude orthotopic diversion if frozen section of the urethral margin is negative at surgery.
- The most significant risk factor for a urethral tumor recurrence in men after orthotopic diversion is the presence of prostatic stromal invasion on final pathology.
- The most important risk factor in women for urethral tumor involvement is bladder neck or anterior vaginal wall involvement with cancer. The latter is best evaluated on bimanual examination under anesthesia at the time of transurethral resection of the bladder tumor or cystectomy.
- Intraoperative frozen-section analysis of the urethral margin in men and women provides an accurate assessment of the urethra and appropriately determines candidacy for orthotopic diversion. Preoperative biopsy of the prostatic urethra or bladder neck is not mandatory.
- Local pelvic recurrence should occur in less than 10% of patients undergoing an appropriate cystectomy and pelvic lymphadenectomy for bladder cancer and rarely interferes with the function of the neobladder. The risk of recurrence is not increased by careful preservation of the urethra during the cystectomy.

Patient-Related Factors

A number of patient-related factors need to be considered when advising a patient about the best form of urinary diversion. These

include the patient's general health and social circumstances, baseline renal function, presence of a healthy urethra and functioning sphincter muscle, manual dexterity, and previous treatments including pelvic radiation, prostate surgery, or bowel resection. Perhaps equally important is the patient's personal preference and attitudes about the risk of incontinence, potential need to self-catheterize, and management of an external appliance. The relative importance of each of these factors in determining how to counsel an individual patient must be decided on a case-by-case basis. The patient and his or her family must have a realistic understanding of the pros and cons of each type of diversion before making a decision. There is a natural inclination for most patients to opt for an orthotopic reconstruction because it is the most "natural." They must gain the understanding that problems can occur with each type of diversion, although the specific types of problems differ. An honest, informed discussion should take place, with the physician carefully explaining the various options along with the short- and long-term risks and benefits of each form of urinary diversion. It may also be helpful to have the patient talk with other patients who have undergone the various forms of urinary reconstruction. In general, patients with poor general health, the frail elderly, and patients with high surgical risks, difficult social circumstances, or poor cognitive function are probably best managed with an ileal conduit.

Age

Many authors have evaluated the success of continent diversion in elderly patients (Lance et al, 2001; Clark et al, 2005; Sogni et al, 2008). Although elderly patients undergoing orthotopic diversion may take longer to regain continence and have a higher rate of mild stress incontinence, ultimately older patients achieve daytime and nighttime continence rates similar to those for younger patients (Elmajian et al, 1996; Steven and Poulsen, 2000). **The clear consensus is that chronologic age alone is not a contraindication for continent diversion and that options should be considered for each patient on the basis of other factors** (Hautmann et al, 2013). Medical comorbidities; renal, cardiac, pulmonary, and cognitive function; and manual dexterity are all important factors that should be considered in the elderly, along with the patient's social support situation. A conduit may be easier for a caregiver to manage than an orthotopic diversion with the risk of incontinence and possible need for catheterization. However, an active, generally healthy, independent elderly patient may certainly be considered a reasonable candidate for orthotopic diversion depending on his or her wishes.

Renal Function

One of the most important contraindications for continent neobladder reconstruction is compromised renal function. Urinary electrolytes including urea, potassium, and chloride are reabsorbed from the small bowel mucosa with excretion of sodium and bicarbonate, resulting in an increased acid load that must be processed by the kidneys. In patients with compromised renal function, hyperchloremic metabolic acidosis can develop along with worsening dehydration, uremia, nausea, and bone loss. The exact level of acceptable renal function for consideration for continent diversion is somewhat controversial. In one study looking at short-term change in renal function in 168 patients (124 continent diversion vs. 44 ileal conduit), the mean decrease in estimated glomerular filtration rate (eGFR) from before to after surgery in the two groups was 4.1 mL/min and 10.3 mL/min, respectively, at a median follow-up of 18.7 months. There was no significant difference in this drop between those with eGFR of 60 mL/min or higher and those whose eGFR was between 40 and 59 (Winters et al, 2013). On the other hand, in a prospective study of 484 patients undergoing two types of neobladder procedures, preoperative lower eGFR was highly correlated with the risk of subsequent decline in eGFR of more than 10 mL/min by 3 years (Skinner et al, 2012). As a general rule, a serum creatinine level of less than 1.7 to 2.2 mg/

dL (150 to 200 $\mu\text{mol/L}$) or an estimated creatinine clearance (eGFR) of greater than 35 to 40 mL/min is recommended for patients considering continent diversion (Hautmann, 2003; Hautmann et al, 2013). However, decision making in individual patients can at times be less clear-cut. Acute upper tract obstruction caused by the tumor often results in a transient rise in creatinine, which would be expected to improve after cystectomy and should be taken into account when counseling patients. There is no evidence that orthotopic diversion leads to progressive renal dysfunction in patients with normal renal function before surgery.

Body Habitus

Obesity is not a contraindication for orthotopic diversion, although placing the urethral sutures and working with the thick bowel mesentery may be challenging. **In fact, an obese patient may be better served with orthotopic diversion because of the difficulty constructing a functional conduit stoma with a very thick abdominal wall.**

Manual Dexterity and Willingness to Do Self-Catheterization

The need to do occasional or routine self-catheterization is reported in 10% to 50% of men and in up to 30% to 60% of women (see later). In general, it is impossible to predict which patients will require catheterization to empty, and retention can occur many years after the initial surgery. **Thus all patients considered for continent diversion should be willing and able to do self-catheterization.** We try to have each patient meet with a nurse or enterostomal therapist before surgery to go over this technique. This is particularly important in women, in whom the potential need to do self-catheterization is higher and sometimes technically more difficult than in men. Although most patients are hesitant about this potential requirement, it is rare for a patient to decide against an orthotopic diversion because of this once he or she has been educated about it.

Urethral Stricture Disease or External Sphincter Damage

Severe urethral stricture disease in men and women is a **contraindication for orthotopic diversion.** Poor external sphincter function in a man who is highly motivated to undergo orthotopic diversion may be managed with a concomitant or delayed artificial urinary sphincter device (Simma-Chiang et al, 2012). Similarly, a woman with significant stress incontinence might undergo a concomitant Burch or pubourethral sling procedure, although she would most likely be dependent on intermittent catheterization to drain properly if that were done.

Prior Pelvic Radiation

It is not uncommon for patients to require surgical management of invasive bladder cancer after previous failed radiation therapy or after radiation treatment of a prior pelvic malignancy. In the series from University of Southern California, 8.5% of 1471 patients had some prior pelvic radiation. This exposure can significantly increase the difficulty of the surgery and can affect wound healing and postoperative complications. Many surgeons are hesitant to offer orthotopic diversion in this setting.

Patients with prior radiation are at increased risk of several complications, even with an ileal conduit diversion. Kim and Steinberg (2001) found an increased risk of surgical complications, especially those that required percutaneous or surgical intervention, in 23 patients undergoing cystectomy and conduit after radiation compared with 23 matched controls. Chang and colleagues (2004) evaluated outcomes of ileal conduits in 36 patients with prior radiation. They found that ureteroileal complications occurred in 9% of patients by 5 years and concluded that it was appropriate to use ileum for diversion rather than a colon conduit (Chang et al, 2004).

The complications and ultimate functional outcome of orthotopic neobladders in patients with prior pelvic radiation have been

evaluated by a number of authors. Bochner and colleagues described their early experience with salvage surgery and orthotopic bladder substitution after failed radical radiation therapy. A total of 18 patients who had prior radiation therapy (minimum dose, 60 Gy) for bladder or prostate cancer were evaluated. Operative characteristics, postoperative outcomes, and complications (related or unrelated to the urinary diversion) were found to be similar in irradiated and nonirradiated patients (Bochner et al, 1998). This series was recently updated by Eisenberg and colleagues with a total of 48 patients undergoing neobladder reconstruction (32.4% of all patients with the same level of irradiation who underwent salvage cystectomy). Age and higher American Society of Anesthesiologists (ASA) score were associated with more early complications, but not the type of urinary diversion. However, these were clearly a highly selected group of patients who had the least visible damage to the external sphincter and were thought likely to have a good outcome. In spite of this, urinary incontinence was more common than in the larger series of nonirradiated patients (Eisenberg et al, 2010).

Nieuwenhuijzen and colleagues reported on 27 patients who underwent salvage cystectomy, 9 of whom had an orthotopic diversion. Eight of them achieved complete daytime continence, similar to results expected in nonirradiated patients (Nieuwenhuijzen et al, 2004). Hautmann also reported on 25 patients (18 males and 7 females) who underwent neobladder construction after high-dose irradiation. This constituted 2.5% of the entire group of neobladder patients and a quarter of those who underwent salvage cystectomy at that institution. Early and late outcomes were similar to those in the larger group of nonirradiated patients. Hautmann concluded that indications to be considered for a neobladder in irradiated patients include absence of preoperative incontinence or stricture, no fistula formation, and no severe bowel radiation damage (Hautmann et al, 2009).

It is clear that in carefully selected patients, orthotopic lower urinary tract reconstruction can be performed after definitive, full-dose pelvic irradiation. Even selected women with a history of pelvic irradiation may be appropriate candidates for orthotopic reconstruction with good clinical outcomes (Stein et al, 2002; Lee et al, 2004). However, these are challenging procedures that clearly require technical expertise and keen intraoperative judgment. Previous high-dose prostate radiation (external beam or brachytherapy) or a vaginal implant for cervical cancer cause more scarring in the rhabdosphincter area than does external beam radiation for either bladder cancer or other malignancies. Interstitial seed implants for prostate cancer often end up in the levator muscles and urogenital diaphragm and may result in severe scarring around the area of the external sphincter.

Preoperative evaluation including cystoscopy is mandatory to evaluate the integrity of the mucosa around the area of the sphincter. However, it may not be possible to accurately predict the degree of radiation damage found at surgery, so **careful intraoperative tissue assessment and determination of the condition of the urethra, ureters, and bowel must be performed to make a final decision about the feasibility of orthotopic diversion** (Abbas et al, 2001). These patients should always be counseled preoperatively that the orthotopic diversion may not be possible.

Prior Prostate Surgery or Bowel Resection

Prior abdominal or pelvic surgery may also present challenges for the surgeon performing orthotopic diversion. **Patients who have had a prior radical prostatectomy may have a particularly difficult dissection around the proximal urethra at the prior vesicourethral anastomosis.** Nevertheless, this is often feasible with careful dissection. The location and health of the proximal urethra can be assessed endoscopically both preoperatively and at surgery, and acceptable continence can be obtained in selected patients assuming that they had good continence before cystectomy (Schuster et al, 2003; Huang et al, 2012). Huang and colleagues reported on 24 patients who underwent ileal neobladder construction after cystectomy following prior radical prostatectomy (20) or prostatectomy plus adjuvant radiation (4). Nine patients had fair

or poor continence before surgery, and 6 of those underwent artificial sphincter placement either at the time of cystectomy or after. However, 11 of the 13 men with good preoperative continence, including 1 who had prior radical prostatectomy and radiation, regained good continence (0 or 1 pad per day) after neobladder construction. There were no rectal injuries and no anastomotic strictures in this series (Huang et al, 2012).

One challenge in these surgeries is to identify the prior vesico-urethral anastomosis to ensure that the bladder is entirely resected. Flexible cystoscopy at the time of the apical dissection can assist in this regard. In conclusion, with careful dissection a patient who was continent after the initial radical prostatectomy surgery can be expected to have an acceptable result with a neobladder.

A patient with multiple prior bowel resections may be at risk of developing chronic diarrhea or even short bowel syndrome after an additional 45 to 60 cm of small bowel is resected. In these patients, alternatives to orthotopic diversion such as a sigmoid neobladder might be entertained. In general, prior bowel resections can be managed by carefully dissecting out all of the small bowel, taking down any adhesions before performing the diversion. **It is critical to identify the old bowel anastomosis and, whenever possible, take that down and use that site as one end of the continent reservoir.** This avoids potential devascularization of the bowel segment between the old and new bowel anastomoses.

KEY POINTS: PATIENT-RELATED FACTORS

- Adequate renal function (eGFR exceeding 35 or 40 mL/min) is recommended for patients considering continent diversion.
- Older age and obesity are not contraindications to orthotopic diversion.
- Orthotopic lower urinary tract reconstruction can be performed after definitive, full-dose pelvic irradiation and after prior radical prostatectomy in carefully selected male and female patients.
- In patients with prior bowel resection the prior anastomosis should be taken down and that segment used for the orthotopic diversion rather than choosing a new site, to avoid devascularization of the bowel.

CONTINENCE MECHANISM IN PATIENTS UNDERGOING ORTHOTOPIC DIVERSION

An understanding of the anatomy of the urethral continence mechanism in men and women is crucial to preserving this function at the time of radical cystectomy. The surgical dissection at the prostatic apex in men and bladder neck in women must be carefully and precisely performed to achieve optimum continence while taking care not to compromise the oncologic effectiveness of the surgery.

Much of what has been learned of the rhabdosphincter complex comes from elegant neuroanatomic studies of the female urethra. Colleselli and colleagues performed extensive microneuroanatomic dissections, histologic examination, and three-dimensional reconstructive imaging to better define the urethral sphincteric and rhabdosphincteric anatomy in women. The female urethral sphincter system consists of smooth muscle innervated by the autonomic nervous system and striated muscle supplied by somatic nerves. There is general agreement that the autonomic nerves that serve the smooth muscle sphincter originate in the pelvic plexus. These autonomic fibers emerge from the pelvic plexus and course along the lateral aspect of the rectum and vagina toward the bladder neck and very proximal urethra. Some of these fibers branch off from a thick fiber at the lower margin of the lateral vaginal wall and enter the bladder neck and cranial portion of the urethra from the dorsolateral aspect. These autonomic nerves do not appear to play a significant role in the innervation of the rhabdosphincter

or the continence mechanism and are essentially sacrificed during the exenterative portion of the operation without compromising continence (Colleselli et al, 1998).

Innervation of the voluntary urinary sphincter system, however, is a matter of some controversy. **Most investigators agree that the rhabdosphincter is supplied primarily by the branches of the pudendal nerve** (Borirakchanyavat et al, 1997; Stenzl et al, 1997; Colleselli et al, 1998). Although these dissections were performed on female cadavers, the observations and findings have been similarly described in men (Strasser and Bartsch, 2000). Collectively, these findings have allowed a more precise and anatomic approach to maintain the continence mechanism in all patients undergoing cystectomy and orthotopic substitution.

In the same study, Colleselli and colleagues found that the major portion of the striated muscle that corresponds to the striated rhabdosphincter is located on the ventral and lateral aspects (omega shaped) of the urethra. No clearly defined line could be identified between the transverse smooth muscle cranially and the striated muscle caudally. Rather, a gradual transition was noted in the middle third of the urethra, with intermingling fibers of both types of muscle (Colleselli et al, 1998). This area has been found to correspond to the area of continence region on fluorourodynamic studies performed on women who had undergone orthotopic reconstruction after cystectomy (Grossfeld et al, 1996). Branches off the pudendal nerve coursing beneath the levator muscle can be traced to the rhabdosphincter. Delicate fibers from the perineal portion of the pudendal nerve course underneath the urogenital diaphragm, entering the caudal portion of the urethra laterally (Colleselli et al, 1998; Hinata et al, 2012).

In a neuroanatomic study performed in male human cadaveric pelvis, similar anatomic findings and innervation were described. Strasser and Bartsch described the male rhabdosphincter as an independent muscle unit that is not in direct contact with the fibers of the levator ani muscle. These dissections demonstrated that the male sphincter does not form a horizontal muscular ring around the membranous urethra. Rather, the male rhabdosphincter is a muscular coat situated ventral and lateral to the membranous urethra and prostate, the core of which is an omega-shaped loop that surrounds the membranous urethra. The innervation of the male rhabdosphincter was also found to originate from fine branches that arise off the pudendal nerve. These authors suggested that injury to either the rhabdosphincter or the pudendal innervation may impair the sphincter mechanism in men (Strasser and Bartsch, 2000).

SURGICAL TECHNIQUES FOR CONTINENCE PRESERVATION DURING RADICAL CYSTECTOMY

Anterior Apical Dissection in the Male Patient

The technique of radical prostatectomy with an extended bilateral pelvic lymphadenectomy is well established (Stein and Skinner, 2004). Attention to anatomic and surgical detail is important to optimize functional and clinical outcomes in patients undergoing orthotopic diversion. Minimal manipulation of the muscle fibers of the rhabdosphincter, fascial attachments, and corresponding innervation is essential to providing optimal urinary continence (Colleselli et al, 1998; Stenzl et al, 1998; Strasser and Bartsch, 2000; Stein et al, 2001b). Several fundamental key surgical issues in the preparation of the urethra in patients undergoing orthotopic diversion deserve special mention.

In a standard cystectomy the bladder and prostate are completely freed off the rectum and mobilized posteriorly before the urethral dissection. Posterior dissection should not extend distal to the apex of the prostate. If a nerve-sparing approach is planned, the urethra may be divided after the lateral pedicles are taken down to the bladder (anterior branches of the internal iliac vessels) before the posterior dissection is performed. The prostate is then dissected in a retrograde fashion off the rectum and bilateral neurovascular bundles, and the posterior pedicles are divided last.

In either approach, all fibroareolar connections along the anterior bladder wall, prostate, and undersurface of the pubic symphysis are divided. The endopelvic fascia is incised adjacent to the prostate, and the levator muscles are gently swept off the lateral and apical portions of the prostate. The superficial branch of the deep dorsal vein is identified, ligated, and divided. With tension placed posteriorly on the prostate, the puboprostatic ligaments are identified and slightly divided just beneath the pubis and lateral to the deep dorsal venous complex (DVC), which courses between these ligaments. Care should be taken to avoid any extensive dissection in this region. The puboprostatic ligaments need to be incised only enough to allow proper apical dissection of the prostate.

Several methods can be performed to properly control the DVC as discussed in Chapters 114 and 115. We use absorbable suture to avoid the risk of erosion of suture, clips, or staples into the urethral anastomosis. Once the venous complex has been ligated, it may be divided close to the apex of the prostate. Any bleeding from the transected venous complex can be controlled with an absorbable suture. **Care should be taken to avoid deep suture bites into the complex or levator muscles, which could injure the continence mechanism.** The DVC suture can then be used to suspend the venous complex anteriorly to the periosteum of the symphysis pubis to re-establish anterior fixation of the DVC and puboprostatic ligaments, which may enhance continence recovery (Bauer et al, 2011).

The anterior urethra is then incised just beyond the apex of the prostate. Six 2-0 absorbable monofilament or woven polyglycolic acid sutures are placed in the urethra circumferentially under direct vision, carefully incorporating only the wall of the urethra without incorporating the levator muscles. Placing the urethral sutures at this time rather than after the bladder has been removed avoids the retraction of the urethra that makes subsequent accurate placement difficult. The urethral catheter is clamped and divided distally. Two additional sutures are then placed, incorporating the rectourethralis muscle posteriorly and the caudal extent of the Denonvilliers fascia. After this, the posterior urethra is divided and the specimen removed. The urethral sutures are tagged to identify their location and are placed under a towel until the urethroenteric anastomosis is performed.

Frozen-section analysis of the circumferential distal urethral mucosal margin (prostatic apex) on the cystectomy specimen is performed to exclude tumor involvement. If there is no evidence of tumor, orthotopic reconstruction may be performed. If there is tumor at the prostatic apex, the urethral stump can be excised or a total urethrectomy may be performed at this time to obtain a negative margin, and a cutaneous diversion constructed.

Preservation of the Urethra in the Female Patient

When orthotopic diversion is considered in female patients, several technical issues should be noted to optimize the continence mechanism (Stein et al, 2001b; Stein and Skinner, 2004). A standard female cystectomy includes removal of the uterus, cervix, and ovaries (anterior exenteration). However, in selected females with clinically lower-stage disease, a number of authors have advocated preservation of the uterus and ovaries (Chang et al, 2002; Zippe et al, 2005; Djaladat et al, 2012; Ali-El-Dein et al, 2013). It appears that preserving the uterus and its supportive ligaments eliminates the risk of vaginal fistula, improves sexual function, and may decrease urinary retention in women undergoing neobladder reconstruction (see later). Whether the uterus is removed or not, **when-ever possible the bladder is dissected completely off the anterior vaginal wall rather than excising it.** However, a deeply invasive tumor on the posterior bladder or trigone may necessitate excision of a portion of the anterior vaginal wall. This does increase the risk of subsequent pouch-vagina fistula but is not an absolute contraindication to orthotopic reconstruction. A patient with a significant tumor at the bladder neck or with palpable extension into the vaginal wall is a poor candidate for neobladder and should undergo en bloc urethrectomy and cutaneous diversion.

In developing the posterior pedicles, if a hysterectomy is planned the posterior vagina is incised at the fornix behind the cervix. If the

patient has undergone prior hysterectomy, a sponge stick in the vagina facilitates identification of the vaginal apex. In that case the vagina is usually not entered. Before dissecting off the bladder, the posterior vascular pedicles coursing around the vagina to the bladder are developed and divided. The vaginal apex may be grasped with a clamp to provide countertraction, and scissors are used to dissect right along the lateral vaginal wall. This develops the posterior pedicle coming around the rectum and vagina toward the bladder, which can be controlled with hemoclips, vascular staples, or a LigaSure (Covidien, Mansfield, MA) or similar device. Care is taken to dissect along the midlateral vaginal border, rather than dissecting back along the rectum or anterior into the bladder.

The issue of nerve-sparing cystectomy in women is controversial. Some authors have suggested that preservation of the sympathetic nerves coursing along the lateral vaginal wall may contribute to maintaining continence in women undergoing orthotopic diversion (Stenzl et al, 1995a; Hautmann, 1997; Turner et al, 1997; Stenzl et al, 1998; Bhatta et al, 2007). Others have not made any special effort to preserve the autonomic nerves and have successfully relied on the pudendal innervation of the rhabdosphincter complex for continence (Stein et al, 1997, 2004; Ali-El-Dein et al, 2002; Ali-El-Dein, 2009). Thus it appears that preservation of the perivaginal nerves may not be absolutely required to maintain continence in women.

Once the posterior pedicles have been divided, careful dissection of the bladder off of the anterior vaginal wall is performed sharply. Care must be taken to dissect in the proper plane to prevent entry into the posterior bladder and reduce the amount of bleeding in this vessel-rich area. **It is absolutely critical not to compromise the oncologic success of the surgery by inadvertent dissection into the bladder.** Dissection is carried caudally to the vesicourethral junction. Tugging on the Foley catheter balloon to position it at the bladder neck assists in identifying this junction.

Once the posterior dissection is completed, the fatty tissue overlying the anterior urethra is swept off the endopelvic fascia and the vesicourethral junction is carefully identified. Again, tugging on the Foley catheter allows the surgeon to visualize the junction between the urethra and bladder. **The endopelvic fascia and periurethral tissue anteriorly should not be disturbed in this process. The proximal urethra in the female extends well above the endopelvic fascia (Fig. 99-3).** Careful sharp dissection is used to free the bladder neck and an initial 0.5 cm of urethra off the vagina. At this point the specimen is attached only by the urethra itself.

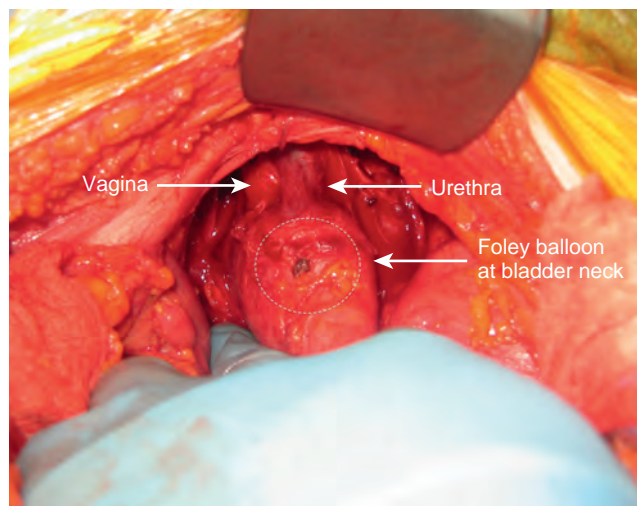


Figure 99-3. Preparation of the female urethra for an orthotopic neobladder. The fatty tissue overlying the anterior urethra is swept off the endopelvic fascia and the vesicourethral junction is carefully identified by positioning the Foley catheter at the bladder neck. Note that the endopelvic fascia and periurethral tissue anteriorly are not disturbed.

After the site for the incision is marked just distal to the vesicourethral junction, the Foley catheter can be removed and a pedicle clamp placed across the bladder neck, which prevents any tumor spill from the bladder when the urethra is transected. The proximal urethra is sharply divided just distal to the bladder neck. The female urethra does not retract away after division as it does in the male, so sutures can be placed after removal of the bladder. Frozen-section analysis is performed on the urethral margin of the cystectomy specimen to exclude any tumor. Once the decision is made to perform the orthotopic diversion, 8 to 10 individual 2-0 absorbable sutures are placed circumferentially through the urethra, tagged, and set aside.

In the case of a deeply invasive posterior bladder tumor, the anterior vaginal wall may be removed en bloc with the cystectomy specimen by incision along the long axis of the anterolateral vaginal wall. This leaves the anterior vaginal wall attached to the bladder specimen. Again, the Foley catheter balloon facilitates identification of the vesicourethral junction. A rim of anterior vaginal wall must be preserved proximal to the urethra to close the vagina so that the vaginal suture line is not directly abutting the vesicourethral suture line to decrease the risk of subsequent fistula. The vagina may be closed in a clamshell or horizontal manner. Other reconstructions to increase vaginal volume are feasible, but it may be difficult to perform a complex vaginal reconstruction (e.g., a rectus myocutaneous graft) along with a neobladder procedure simply because of a lack of adequate room in the pelvis.

The vagina is then closed at the apex with absorbable suture and then suspended. One may suspend the vagina to the Cooper ligament or to preserved cut ends of the round ligaments to prevent postoperative vaginal prolapse. However, we routinely perform a sacrocolpopexy incorporating a short strip of permanent mesh to fix the vagina to the sacral promontory at a more natural angle without any tension. This may be important to support the neobladder and avoid a possible cause of late voiding difficulty. Regardless of the form of vaginal reconstruction, a well-vascularized omental pedicle graft should be placed between the reconstructed vagina and the neobladder and secured to the endopelvic fascia at either side of the urethral stump to separate the suture lines and prevent fistula formation between the vaginal and urethral anastomosis, which may help support the pouch posteriorly.

KEY POINTS: CONTINENCE MECHANISM AND SURGICAL TECHNIQUES FOR CONTINENCE PRESERVATION

- The innervation of the striated urethral rhabdosphincter arises from the branches of the pudendal nerve and is most important to maintain continence in patients with an orthotopic neobladder.
- The striated rhabdosphincter muscle fibers are concentrated in the area anterior and lateral to the proximal urethra.
- In male patients, one should obtain careful control of the DVC and avoidance of deep suture bites into the pelvic floor muscles.
- In female patients, the endopelvic fascia and levator muscles should not be disturbed.

TECHNIQUES FOR ORTHOTOPIC BLADDER SUBSTITUTION

Choice of Bowel Segment

A number of different procedures for orthotopic reconstruction incorporating different segments of bowel have been described. There are clearly some physiologic indications to use various segments of intestine, but the surgeon's preference may be even more influential. It has been suggested that **excellent functional and clinical outcomes with voiding can be achieved regardless of the**

segment of bowel chosen as long as the principles of preservation of the rhabdosphincter as a continence mechanism and construction of an adequate capacity, low-pressure reservoir are maintained (Parekh et al, 2000b; Lee et al, 2003). Ideally, the surgeon performing orthotopic urinary diversion will be comfortable using a variety of the techniques described later so that he or she can adapt the technique to the needs of the individual patient.

Reservoirs made of detubularized ileum or ileum and colon together appear to have the greatest compliance and lowest likelihood of generating intermittent high-pressure contractions. Hohenfellner and colleagues elegantly evaluated the properties of gut smooth muscle layers (circular and longitudinal) of ileal and cecal segments in a canine model. The circular muscle layer of ileum was found to be most distensible, followed by the colonic circular and longitudinal ileal layers. The longitudinal layer of the colonic segment was relatively nondistensible (Hohenfellner et al, 1993). Studies in humans showed that the urodynamic characteristics of the ileum appear to be superior to those of the colon (Berghlund et al, 1987; Lytton and Green, 1989; Davidsson et al, 1992; Schrier et al, 2005; Chen et al, 2009). Stomach and sigmoid colon have been found to have particularly poor compliance and high pressures (Santucci et al, 1999). Schrier and colleagues found that neobladders made of ileum had larger capacity, lower filling pressures, lower maximum capacity pressures, and better compliance. The distal small bowel mesentery also tends to have the greatest mobility and generally reaches to the urethra without much difficulty. In patients with short ureteral length because of malignancy or other pathology of the ureters, an ileal pouch with a "tail" (such as the Studer) can be extended to reach all the way to the renal pelvis. A final advantage of ileum is the atrophy of the intestinal mucosa as it is exposed to urine over time. This results in decreased mucous production and decreased reabsorption of urinary electrolytes in the mature reservoir. Mucosal atrophy appears to be more reliable in small bowel than in large bowel reservoirs (Norlen and Trasti, 1978; Mills and Studer, 1999).

The primary disadvantage of using distal ileum lies in the potential loss of absorption of vitamin B₁₂. This segment may also have been unacceptably damaged by prior pelvic radiation or may be unavailable because of multiple prior bowel resections or inflammatory conditions such as Crohn disease. Whenever ileum is available, we preferentially use it for orthotopic diversion.

Bladder replacement using stomach has also been described, although it has not been a popular technique (Adams et al, 1988; Nguyen, 1991; Hauri, 1998; Lin et al, 2000). The primary advantage of gastric segments is that the gastric mucosa excretes chloride and hydrogen ions, effectively reversing the acidosis of renal insufficiency. The excreted acid from a stomach segment can also reduce the risk of bacterial colonization, and there is less mucous production. However, the disadvantage of using stomach is that compliance is worse than ileum and some patients will develop dysuria or hematuria from the excreted acid (Nguyen, 1991; Lin et al, 2000). Combining gastric and small or large intestinal segments can counteract some of these side effects and may be ideal from a purely metabolic standpoint (Lockhart et al, 1993). This construction can theoretically be performed in a patient with compromised renal function when continent diversion is contraindicated. It may also provide another option in a patient with prior high-dose pelvic radiation or multiple previous bowel resections. Few urologists have been trained in the surgical anatomy of the stomach, and most who perform a significant number of cystectomies currently rarely, if ever, use this type of diversion.

Isolation of the segment of bowel to be used for the diversion must be performed carefully to preserve blood supply to the pouch, as well as to the bowel anastomosis. If using ileum, one should avoid deep incision into the mesentery at the proximal bowel division to avoid compromising the blood supply to the reservoir. In addition, in patients who have had previous bowel resection it is important to take down the old anastomosis rather than choosing another site nearby because that could result in a poorly vascularized segment between the new and old bowel anastomoses.

Need to Prevent Reflux

The deleterious effect of vesicoureteral reflux in children is well accepted, especially in the face of infection. In the context of urinary diversion the importance of reflux was first identified in patients undergoing ureterosigmoidostomy (Clarke and Leadbetter, 1955; Wear and Barquin, 1973) and, subsequently, ileal conduit urinary diversion (Shapiro et al, 1975; Middleton and Hendren, 1976). It has been believed that the frequent long-term deterioration of renal function and upper tract changes seen in up to 50% of patients with ileal conduit urinary diversions by 15 years are the result of high-pressure reflux of infected urine (Clark et al, 1999; Madersbacher et al, 2003). Mean time to development of kidney problems in conduit patients is 5 years, and the incidence of such complications seems to increase steadily with time (Clark et al, 1999).

However, studies that have compared refluxing versus nonrefluxing urinary diversion have been limited, in general, by short follow-up, patient selection bias, retrospective design, or relatively small patient numbers. Richie and colleagues showed a protective effect of nonrefluxing anastomoses in a dog model (Richie et al, 1974). Kristjansson and colleagues found no difference in colon conduits with nonrefluxing anastomoses versus ileal conduits with refluxing anastomoses. However, continent diversions with antireflux techniques appeared to result in less upper tract scarring and bacteriuria (Kristjansson et al, 1995a, 1995b). Studies by both Elder and Hill showed that upper tract deterioration was common in both colonic and ileal conduits, although each had high rates of stomal stenosis and ureteroenteric stenosis (Elder et al, 1979; Hill and Ransley, 1983). Althausen showed better results using nonrefluxing colon conduits, but the follow-up in this study was only 3 years (Althausen et al, 1978). Song and Hautmann each found no differences in renal function or hydronephrosis in refluxing or nonrefluxing orthotopic neobladders in nonrandomized retrospective studies (Hautmann et al, 2006; Song et al, 2006). All of these studies were retrospective and nonrandomized and in general included relatively small numbers of patients.

With orthotopic diversion, most patients void by Valsalva maneuver with relaxation of the external sphincter. The resulting increase in pressure in the reservoir should be transmitted equally to the rest of the system, limiting any resulting back pressure even without an antireflux mechanism (Thoeny et al, 2002; Studer et al, 2006). However, free reflux into the upper tracts of the Studer pouch is often visible on cystogram with as little as 300 mL of filling, well within the typical voided volume of these patients. It is likely that there is some retrograde flow of urine in these patients at times. In patients who require intermittent catheterization to empty, such reflux could potentially occur at relatively high pressures when the reservoir is full. Finally, although symptomatic infections are uncommon (see later), it is not unusual for these patients to have asymptomatic bacteriuria, especially if they are doing self-catheterization. Steven and Poulsen reported 34% 3-year and 24% 5-year prevalence rates for bacteriuria in 166 men undergoing orthotopic reconstruction (Steven and Poulsen, 2000).

Medium- to long-term results with a refluxing type of reservoir such as the Studer pouch suggest that normal renal function and preserved upper tract anatomy are possible in the majority of patients (Thoeny et al, 2002; Perimenis et al, 2004; Minervini et al, 2005; Studer et al, 2006). Thoeny and colleagues examined long-term results in 76 patients with a Studer pouch with 5 or more years of follow-up and found preserved renal function and anatomy in 95% of the patients (Thoeny et al, 2002).

It is clear that any mechanism introduced to prevent reflux may also potentially cause upper tract obstruction. Initial experience with the intussuscepted Kock nipple valve showed that it provided reliable protection against reflux and seemed to have few drawbacks. However, as surviving patients were followed out to 10 years and beyond, it became clear that approximately 5% of patients experienced obstruction from stenosis of the afferent nipple valve, and an additional 5% developed stones on or extrusion of the afferent nipple valve (Stein et al, 1996). Afferent valve obstruction was often clinically silent. Patients who were not followed

carefully occasionally developed acute renal failure and bilateral hydronephrosis with significant renal damage, underscoring the need for careful lifetime follow-up in patients with urinary diversion. Similarly, ureteroileal obstruction with the antireflux Camey–Le Duc ureteral implantation technique has been reported to occur in 7% to 29%, compared with less than 3% for a direct ureteroileal anastomosis (Pitts and Muecke, 1979; Le Duc et al, 1987; Shaaban et al, 1992; Roth, 1997; Pantuck et al, 2000).

Abol-Enein and Ghoneim developed a serous-lined ureteral implantation technique with an ileal neobladder and reported their intermediate experience (mean follow-up of 38 months) in 450 patients. In this large series, 96% of upper tracts remained unchanged or improved; reflux was observed in only 3% of patients. Anastomotic ureteral stricture occurred in 3.8% of patients, an incidence similar to that of most refluxing ureteroileal anastomoses (Pantuck et al, 2000). The T pouch was designed building on this technique to provide protection from reflux while avoiding some of these complications of the Kock nipple valve. This is accomplished by preserving optimum blood supply to the tunneled ileal afferent limb segment while allowing the ureters to be directly implanted into the ileum, allowing for ureters that are dilated or must be divided high (Stein et al, 1998b; Stein and Skinner, 2006). With 33 months' median follow-up, renal function and anatomy were preserved in 90% of patients, with only 2% developing stenosis related to the afferent T limb during this time (Stein et al, 2004). In recent years the technique has been modified to avoid tapering the afferent limb in an attempt to further limit the development of late stenosis.

Shaaban and colleagues (2006) performed a small prospective randomized clinical trial evaluating whether prevention of reflux is beneficial. They studied 60 patients who all had normal renal function preoperatively and no hydronephrosis. In each patient one randomly chosen ureter was implanted in an antireflux manner (using an extraserosal tunnel), and the other was implanted directly into a small tubularized chimney on a standard W ileal neobladder. At 2 years' median follow-up, the researchers found more deterioration in the renal units drained with the antireflux technique, which resulted in five cases of documented obstruction, than in those with a direct refluxing anastomosis (Shaaban et al, 2006).

We recently completed a larger prospective randomized trial with 484 patients undergoing radical cystectomy randomized to receive either a Studer or T pouch urinary diversion. At 3 years there were no differences in renal function or urinary tract infections between the two groups. However, the patients with the T pouch were more likely to require diversion-related secondary procedures than those with the Studer construction (Skinner and Skinner, 2010; Skinner et al, 2012; Fahey et al, 2013).

As the overall medical and surgical therapy for bladder cancer improves and patients live longer after cystectomy and urinary diversion, placing them at further long-term risk for renal deterioration, reflux prevention may become a more important issue. The basic question remains whether any benefit in upper tract protection afforded by the antireflux technique outweighs the potential risk of upper tract obstruction from the antireflux technique itself in patients with bladder cancer. Further clarification of this question awaits the long-term results of these prospective randomized trials.

KEY POINTS: CHOICE OF BOWEL SEGMENT AND THE NEED TO PREVENT REFLUX

- Reservoirs made from ileum or combined ileum and colon appear to have the best physiologic properties for orthotopic diversion.
- Isolation of the segment of bowel to be used for the diversion must be performed carefully to preserve blood supply to the pouch and bowel anastomosis.
- The addition of an antireflux mechanism does not appear to be necessary for preservation of the upper tracts and prevention of infections, at least in the intermediate term.

General Perioperative Management

Perioperative management of patients undergoing cystectomy and orthotopic diversion is not significantly different than for patients undergoing other types of diversion. Preoperative history should focus on prior abdominal or pelvic surgery or radiation, current voiding patterns and continence, and general medical problems and social support, as well as patient priorities and preferences. If colon may be used for the diversion, a colonoscopy is recommended to rule out polyps or tumors.

There is no consensus on the ideal management of ureteral stents or catheters in patients undergoing orthotopic diversion. Most authors recommend the use of ureteral stents in the early postoperative period (Mattei et al, 2008). We use 8-Fr plastic pediatric feeding tubes or 7-Fr single-J urinary diversion stents and tie them to the urethral catheter so that they can be removed at the same time and the patient has fewer external bags to manage. They also use a 24-Fr stiff hematuria catheter, which facilitates routine irrigation of the pouch and is left in for approximately 3 weeks. The disadvantage of this system is the need to irrigate the catheter several times daily to ensure that the catheter does not plug up with mucus. Many surgeons alternatively use externalized ureteral stents brought through the skin and drained separately. The latter allow for less urine to pass through the pouch while it is healing and may decrease dependence on attentive nursing. A pelvic drain should be placed in every patient. In general, we leave the drain until the pouch has healed because of occasional late leakage if the catheter gets plugged at home.

Postoperative hospitalization in the past averaged approximately 8 to 10 days, primarily because of delayed feeding and postoperative ileus. We recently adopted an Early Recovery after Surgery (ERAS) protocol that has allowed routine discharge 3 to 5 days after surgery (Daneshmand et al, 2014). The protocol includes avoiding bowel preparation and nasogastric tubes, decreasing narcotic pain management (including epidural narcotics), instituting early feeding, and using a μ -opioid antagonist that blocks the effects of narcotics on the bowel. The μ -opioid antagonist alvimopan was recently demonstrated to reduce hospital stay in a double-blind, placebo-controlled randomized trial of 280 cystectomy patients (Lee et al, 2014). Other components vary among programs, and the individual contribution of each component to the overall pathway is less well studied (Karl et al, 2014).

When patients return at the 3-week postoperative mark, if there is minimal drainage from the drain (<100 mL during 24 hours), the catheter is removed, followed by the drain. Routine pouchograms or radiographic studies of the neobladder are not routinely performed unless a significant output from the drain is observed. Patients receive education throughout the perioperative period regarding catheter management, pelvic floor exercises, and proper voiding technique.

Surgical Techniques

A large number of modifications of the techniques presented next have been described in a small number of patients, and this is by no means an exhaustive list.

Ileal Reservoirs

Most ileal reservoirs use from 60 to 75 cm of terminal ileum, which is detubularized and folded in a variety of ways to attempt to create a spheric shape. Modifications primarily include variations in the exact folding technique and variations in management of the ureters, with or without an antireflux mechanism. In general, all reservoirs are closed with continuous absorbable suture. **The use of nonabsorbable suture and metal staples should be avoided because of the potential for stone formation (Stein et al, 1994b; Suriano et al, 2013).** Absorbable staples have been developed, and some authors have found them useful, although they tend to be somewhat bulky and awkward to use (Bonney and Robinson, 1990; Olsson et al, 1995; Montie et al, 1996).

The two most popular configurations around the world are the Hautmann W-neobladder (and its various modifications) and the Studer pouch neobladder. Both are relatively simple constructions and allow direct ureteroileal anastomosis, which has been shown to have the lowest risk of subsequent stricture. The T pouch and extraserosal tunnel techniques both provide an antireflux mechanism when that is felt to be advantageous.

Camey II

The Camey II orthotopic substitute (Camey, 1990) is a modification of the original Camey bladder substitute (Lilien and Camey, 1984), which was a simple segment of ileum anastomosed to the ureters and urethra. The modification includes detubularization and folding to eliminate peristaltic activity. A total of 65 cm of ileum is isolated, with an area of the ileum identified to reach to the region of the urethra in a tension-free manner. After the integrity of the bowel is restored, the mesenteric trap is closed and the isolated portion of ileum is opened along the antimesenteric border for the entire length, except the area previously identified for the urethral anastomosis. In this region, the ileal incision is directed toward the mesenteric border. The ileum is then placed in a transverse U orientation. The medial borders of the U are sutured together with a running absorbable suture. A fingertip opening is made in the pre-selected area for the ileourethral anastomosis, the entire ileal plate is brought down to the pelvis, and the urethral anastomosis is performed. The ureteroileal anastomosis is then performed via a Le Duc technique (Le Duc et al, 1987). The reservoir is completed by folding the ileal plate and suturing with a running absorbable suture. The ends of the U are anchored to the pelvic floor to reduce tension (Fig. 99-4). A modification of the Camey II has been described by Barre and colleagues (1996). This places the ileum in a Z configuration and reportedly has the advantages of shorter length requirements, improved reservoir capacity, and potentially improved functional (continence) results (Barre et al, 1996).

Orthotopic Kock Ileal Reservoir (Hemi-Kock)

The Kock ileal reservoir was first used as a continent cutaneous ileal reservoir incorporating intussuscepted nipple valves for both the afferent (antireflux) and efferent (continence) limbs (Kock et al, 1982; Skinner et al, 1984). This subsequently evolved into an orthotopic form of diversion in which the afferent intussuscepted limb was maintained to prevent urinary reflux (Fig. 99-5) (Ghoneim et al, 1987; Skinner et al, 1991). Skinner and colleagues performed more than 500 of these procedures from 1982 to 1995, with excellent continence and a low ureteroileal stricture rate of less than 3% (Skinner et al, 1988; Elmajian et al, 1996). Schreiter described an S-shaped modification of the orthotopic Kock ileal reservoir (Schreiter and Noll, 1989). With long-term follow-up, late complications associated with the afferent intussuscepted antireflux nipple developed in a small but significant number of patients (Stein et al, 1994a, 1996). These included stone formation on exposed staples (5%), stenosis of the afferent nipple ostium thought to be secondary to a compromised blood supply (4%), and extussusception or prolapse of the afferent limb (1%). These complications often occurred more than 10 years after construction of the reservoir and were clinically silent until the patient developed bilateral hydronephrosis or even renal failure (Stein et al, 1996). The technical difficulty of the intussuscepted nipple valve and the associated complications, along with the development of effective alternative techniques, has made this neobladder procedure primarily of historical interest.

Serosus-Lined Extramural Tunnel

Abol-Enein and Ghoneim demonstrated that an effective antireflux mechanism could be made by bringing the ureters into a reservoir through extramural serous-lined tunnels. These authors believed that the construction of an extramural serous-lined tunnel provides several advantages. Metallic staples or synthetic materials are not

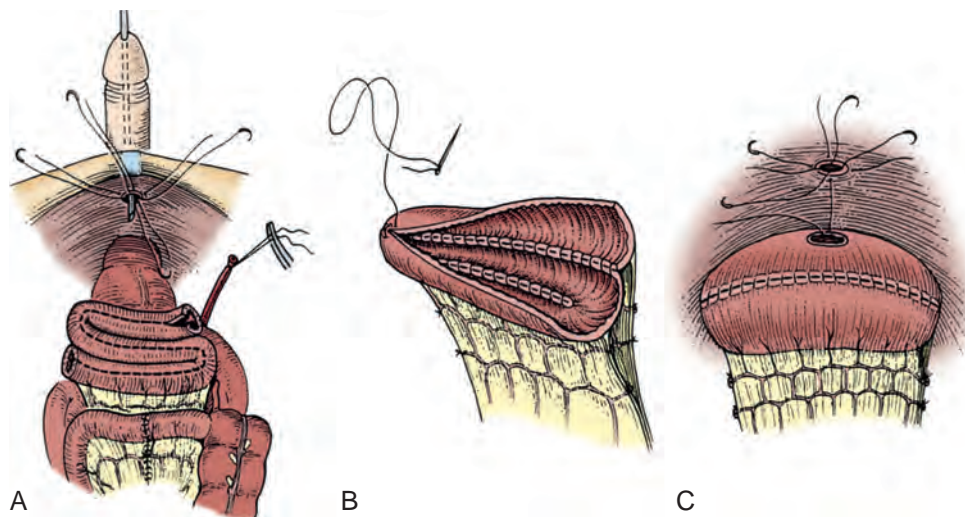


Figure 99-4. Construction of the modified Camey II. A, The ileal loop is folded three times (Z shaped) and incised on the antimesenteric border. B, The reservoir is closed with a running suture to approximate the incised ileum. C, The urethral anastomosis is performed, and the ureters are implanted using a Le Duc antireflux technique.

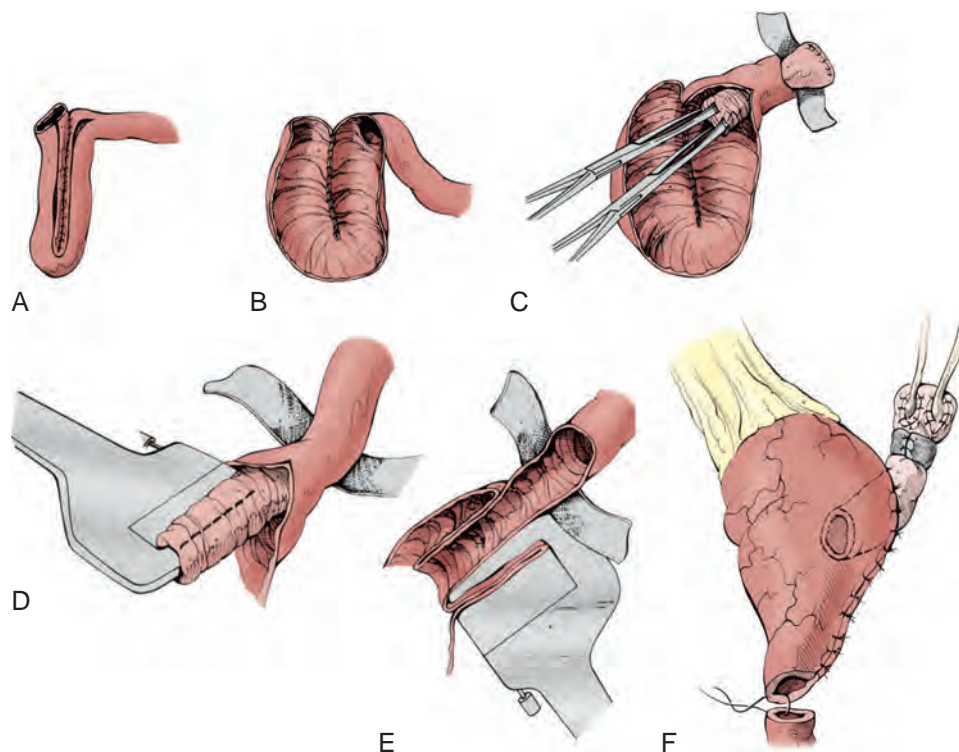


Figure 99-5. Construction of the Kock ileal reservoir. A, A total of 61 cm of terminal ileum is isolated. Two 22-cm segments are placed in a U configuration and opened adjacent to the mesentery. The more proximal 17-cm segment of ileum will be used to make the afferent intussuscepted nipple valve. B, The posterior wall of the reservoir is then formed by joining the medial portions of the U with a continuous running suture. C, A 5- to 7-cm antireflux valve is made by removing the mesentery under that segment and then intussuscepting the afferent limb with the use of Allis forceps clamps. D, The afferent limb is fixed with two rows of staples placed within the leaves of the valve. E, The valve is then fixed to the back wall from outside the reservoir with additional surgical staples. F, After completion of the nipple valve, the reservoir is completed by folding the ileum on itself and closing it, leaving the most dependent end of the suture line open for the urethral anastomosis.

required. The serous-lined tunnel protects the implanted portion of the ureter from exposure to urine so that sound healing without scarring is ensured. Moreover, a relatively short segment of bowel is used, and the procedure is versatile and not technically difficult (Abol-Enein and Ghoneim, 1993, 1994). The authors updated their excellent results in 450 patients with this technique and demonstrated that the serous-lined extramural tunnel is an effective and durable antireflux technique, with more than 93% of patients having unidirectional, unobstructed urinary flow (Abol-Enein and Ghoneim, 2001).

A 40-cm ileal segment is isolated from the distal ileum and arranged in a W configuration. The antimesenteric border of the isolated intestine is opened, and the edges of the medial flaps are joined with a running absorbable suture. On either side, the serosal surface of the two lateral flaps are joined by a seromuscular continuous suture of silk (3-0). This forms two serous-lined intestinal troughs. Each ureter is laid down in its corresponding trough. A mucosa-to-mucosa anastomosis is performed with the spatulated ureter and the intestinal mucosa at the distal end of the trough. The mucosal edges on each side are then approximated over the reimplanted ureter. The anterior wall of the pouch is then closed in a side-to-side fashion. The suture line of the most dependent portion of the pouch close to the urethral stump is reopened to make a hole that will be anastomosed to the urethra (Fig. 99-6).

Good results with this technique have been reported by others (Papadopoulos and Jacobsen, 2001). A modification of this orthotopic substitute with a serous-lined extramural ureteral reimplantation technique has also been reported by Kato and colleagues (2001) with similar results. The primary disadvantage of this technique is the requirement for long ureteral length, inability to accommodate dilated ureters, and a possibly increased risk of ureteral strictures (Kato et al, 2001).

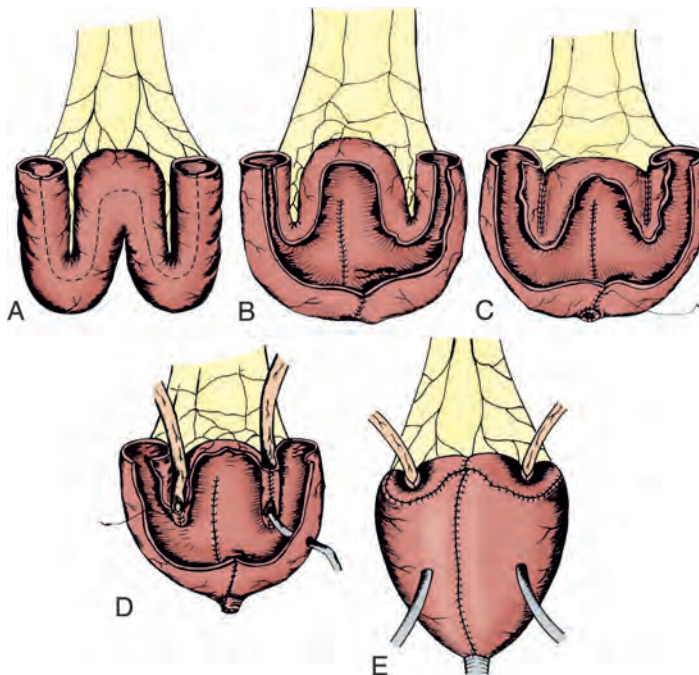


Figure 99-6. Construction of the serous-lined, extramural ileal neobladder (Ghoneim). A, A 40-cm segment of ileum is isolated and fashioned into a W configuration. B, The ileum is opened along the antimesenteric border for the entire length. C, The incised mucosa is joined in the middle with a running suture. The two lateral ileal flaps are joined by a seromuscular continuous suture to make the backing for the serous-lined ureteral tunnels. D, The spatulated ureters are laid into each trough, anastomosed to the intestinal mucosa, and stented. The tunnel is then closed over the implanted ureter. E, The anterior wall of the reservoir is formed by folding the ileum side to side. The reservoir is then anastomosed to the urethra.

Ileal Neobladder (Hautmann Pouch)

The Hautmann pouch ileal neobladder was developed by Hautmann and colleagues (Hautmann, 2010). This neobladder is an intentionally large-capacity, spheric (W configuration) ileal reservoir that is constructed in an attempt to optimize initial volume and potentially reduce nighttime incontinence. A segment of terminal ileum of approximately 70 cm is selected. The bowel is reconstituted, and the mesenteric trap is closed. The ileal section that reaches the urethra most easily is identified and marked with a traction suture along the antimesenteric border. The isolated bowel segment is then arranged in either an M or W shape and is opened along the antimesenteric border except for a 5-cm section along the traction suture where the incision is curved to make a U-shaped flap.

The four limbs of the M or W are then sutured to one another with a running absorbable suture. A small full-thickness segment of bowel is excised in the site for the urethral anastomosis, which is then performed with the sutures tied from inside the neobladder. Once the ileal neobladder is situated in the pelvis and the urethral sutures are tied, the ureters are implanted from inside the neobladder through a small incision in the ileum at a convenient site. The remaining portion of the anterior wall is then closed with a running absorbable suture (Fig. 99-7).

Initially Hautmann used an antireflux ureteral anastomosis as described by Le Duc and colleagues (Le Duc et al, 1987). However,

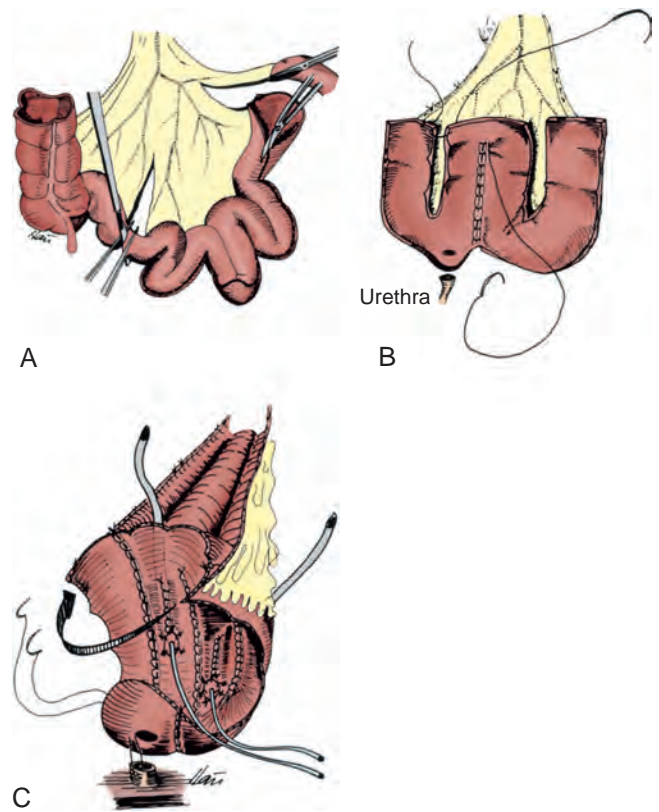


Figure 99-7. Construction of the Hautmann ileal neobladder. A, A 70-cm portion of terminal ileum is selected. The isolated segment of ileum is incised on the antimesenteric border. B, The ileum is arranged into an M or W configuration with the four limbs sutured to one another. C, After a buttonhole of ileum is removed on an antimesenteric portion of the ileum, the urethral anastomosis is performed. The ureteral anastomoses are performed using a Le Duc technique or direct implantation and are stented, and the reservoir is then closed in a side-to-side manner. As an alternative, the two ends of the W may be left slightly longer as a short chimney on either side for implantation of the ureters.

ureteroileal strictures were fairly common, and beginning in 1997 he modified this technique and now uses a freely refluxing, open end-to-side anastomosis implanted into short tubularized segments at each end of the W. This resulted in a decrease in the risk of ureteroileal stenosis from 9.5% to 1% (Hautmann, 2001; Hautmann et al, 2006).

This pouch has a larger initial capacity than the Studer pouch, which may assist in earlier continence. However, it may also result in an increased incidence of late urinary retention and increased electrolyte reabsorption from the pouch. Sevin has reported a modified Hautmann ileal neobladder in which only 40 cm of ileum is used to reduce these potential issues with acceptable clinical outcomes (Sevin et al, 2004). The classic configuration of the pouch also could not accommodate short ureters, but in the revised technique one or both ends of the W can be left long to anastomoses to one or both shortened ureters (Hollowell et al, 2000).

Studer Pouch

The ileal bladder substitute as initially described by Studer and colleagues used a long, afferent, isoperistaltic, tubular ileal segment. It is believed that the long segment functionally prevents vesicoureteral reflux when the patient voids by Valsalva maneuver (Studer et al, 1989, 1996). It is straightforward to construct and has become one of the most popular form of orthotopic diversion in the United States. The advantages of this bladder substitute include the simplicity of construction, the lack of a requirement for surgical staples, and the ability to accommodate short ureters. The reservoir portion uses the optimal double-folded U configuration as originally described by Kock (Kock et al, 1989). Studer's group reported on 480 of these procedures performed from 1985 through 2005 with excellent long-term results in terms of continence, preservation of renal function, and a ureteroileal stricture rate of less than 3% (Studer et al, 2006). The original description used a 20-cm afferent segment, with 40 cm used for the reservoir. In more recent years Studer has advocated using a somewhat shorter afferent ileal segment, with similar results (Studer et al, 2006).

The terminal portion of the ileum (54 to 56 cm long) is isolated approximately 15 to 20 cm proximal to the ileocecal valve. The distal mesenteric division is made along the avascular plane between the ileocolic artery and terminal branches of the superior mesenteric artery. The proximal mesenteric division, however, is short and provides a broad vascular blood supply to the reservoir. In addition, a small window of mesentery and 5 cm of small bowel proximal to the overall ileal segment are discarded, ensuring mobility to the pouch and small bowel anastomosis. Bowel anastomosis is performed using staplers.

The Studer pouch is created from 40 to 44 cm of distal ileum with each limb of the U measuring 20 to 22 cm and a proximal 15-cm segment of ileum used as the afferent limb. If ureteral length is short or compromised, a longer afferent ileal segment (proximal ileum) may be used. The proximal end of the isolated afferent ileal segment is closed with absorbable suture. The isolated ileal segment is opened about 2 cm away from the mesentery, and the incised ileal mucosa is then oversewn with two layers of a running 3-0 polyglycolic acid suture (Fig. 99-8).

T Pouch Modification

In an effort to preserve an antireflux mechanism but avoid the potential long-term complications seen with the Kock nipple valve, as well as to allow for more flexibility in managing the ureters, Stein and Skinner developed the T pouch as a modification of Ghoneim and Abol-Enein's serous-lined ureteral tunnel and updated their results with intermediate follow-up of 209 patients (Stein et al, 2004; Stein and Skinner, 2006). The technique is modified for construction of an antirefluxing afferent limb in the T pouch. The ileum is divided between the proximal afferent ileal segment and the 44-cm segment, and the antireflux mechanism is created by

anchoring the distal 3 to 4 cm of the 15-cm afferent ileal segment into the serosal-lined ileal trough formed by the base of the two adjacent 22-cm ileal segments. Mesenteric windows of Deaver are opened between the vascular arcades on the T limb. A series of 3-0 silk sutures is then used to approximate the serosa of the two adjacent 22-cm ileal segments at the base of the U, with the sutures being passed through the previously opened windows of Deaver to anchor the afferent limb (Fig. 99-8D, E1, and E2). Initial descriptions of the T pouch included tapering the distal portion of the afferent segment after it had been fixed into the tunnel to decrease its diameter and decrease the risk of reflux. However, these efforts appeared to be associated with occasional late stenosis of the end of the afferent valve. In 2004 the author (E.C.S.) stopped tapering the distal afferent limb with improved results.

When the incision in the U limb of reservoir reaches the level of the afferent ostium, it is extended directly lateral to the antimesenteric border of the ileum and carried upward (cephalad) to the base of the ileal segment. This incision provides wide flaps of ileum that are brought over the afferent ileal segment and sutured in two layers to create the antireflux mechanism in a flap-valve technique. An interrupted mucosa-to-mucosa anastomosis is then performed between the ostium of the afferent ileal limb and the incised intestinal ileal flaps with 3-0 polyglycolic acid sutures (see Fig. 99-8E2). The rest of the neobladder is constructed in the same fashion as the Studer pouch.

Colon and Ileocolic Pouches

Orthotopic neobladders constructed completely of colon are a good option for patients with multiple previous small bowel resections or who have diseased ileum. Colon segments are less distensible than ileal segments and may be more likely to produce higher-pressure waves causing incontinence (Khafagy et al, 2006). As a consequence, initial volume should be larger than for an ileal pouch. Combined colon and ileal segments can mitigate this problem.

Orthotopic Mainz Pouch (Mainz III)

The Mainz ("mixed augmented ileum and cecum") pouch was initially described as a continent catheterizable reservoir that was subsequently modified into an orthotopic neobladder (Thuroff et al, 1986; Eisenberger et al, 1999). A 10- to 15-cm segment of cecum, in continuity with a 20- to 30-cm segment of ileum, is isolated. An ascending ileocolostomy is performed. The entire segment of bowel is opened along the antimesenteric border, sacrificing the ileocecal valve. The bowel is placed in a W configuration, with the first limb of the W made from cecum and the other limbs made from the ileum. The adjacent three limbs are sutured together with an absorbable suture, forming the posterior plate of the reservoir.

At the cephalad portion of the cecum, tunneled ureterocolonic anastomosis is performed. A buttonhole incision is made in the cecum at the base of the reservoir, and a ureterocolonic anastomosis is performed. After this, the reservoir is closed side to side with absorbable suture (Fig. 99-9).

Le Bag Pouch

The Le Bag ileocolonic bladder substitute was initially described by Light and Engelmann. A 20-cm segment of ascending colon and a corresponding length of terminal ileum are isolated, and bowel continuity is restored. The antimesenteric border is incised for the entire length of the colon and ileum to make two flat sheets (one small and one large bowel). These sheets are then sewn to each other to form the posterior plate. Initially, in the early experience with this neobladder, the incision in the small bowel commenced 2 inches from the cut end so that this intact tube of ileum could be anastomosed end to end to the urethra. This technique was subsequently modified because the small intact ileal segment was thought to promote urinary incontinence because of peristalsis. After this, the entire length of small bowel was incised (Light and Engelmann,

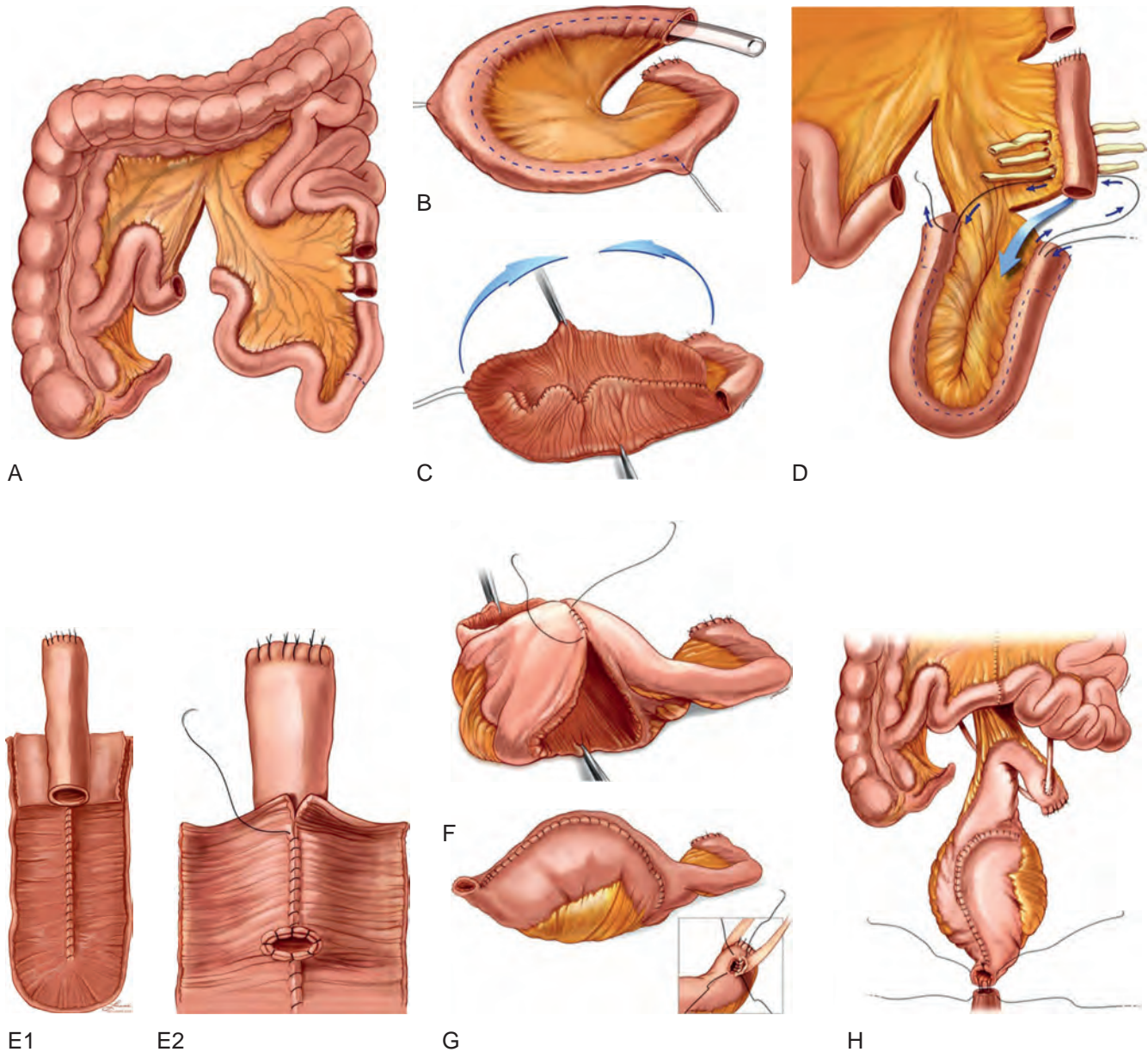


Figure 99-8. Construction of the Studer neobladder (modified). A, Designated segments of terminal ileum for construction of the orthotopic Studer pouch ileal neobladder. Note that the distal mesenteric division is made between the ileocolic and terminal branches of the superior mesenteric artery, which extends into the avascular plane of the mesentery. In addition, a small window of mesentery and a 5-cm segment of proximal small bowel are discarded to allow mobility to the pouch and small bowel anastomosis. B, The Studer pouch is constructed from an isolated 44-cm ileal segment (placed in an inverted U configuration), which forms the reservoir portion of the pouch, and a proximal 15-cm segment of ileum to form the afferent limb. The two 22-cm ileal segments are opened 2 cm adjacent to the mesentery beginning at the apex and carried upward to the ostium of the afferent segment. C, The previously incised ileal mucosa is then oversewn with two layers of a running 3-0 polyglycolic acid suture starting at the apex and running upward to the afferent limb. The reservoir is then closed by folding it in half in the opposite direction to which it was opened. D, Construction of the antireflux mechanism in the T pouch. The ileum is divided between the proximal afferent ileal segment and the 44-cm segment. The dotted line depicts the incision line on the U limbs. Mesenteric windows of Deaver are opened between the vascular arcades adjacent to the serosa. Placement of small Penrose drains through each mesenteric window helps facilitate passage of sutures. The distal 3 to 4 cm of the afferent ileal segment is anchored into a serosal-lined ileal trough formed by the base of the two adjacent 22-cm ileal segments, using 3-0 silk sutures. E1, The previously anchored distal 3- to 4-cm afferent ileal segment is tapered over a 30-Fr catheter on the antimesenteric border. The incision of the bowel provides wide flaps of ileum that covers the tapered distal afferent ileal segment to form the antireflux mechanism in a flap-valve technique. E2, A mucosa-to-mucosa anastomosis is performed between the ostium of the afferent segment and the edges of the ileal flaps using interrupted 3-0 polyglycolic acid suture. The mucosal edges of the ileal flaps are brought over the tapered distal portion of the afferent ileal segment and sewn using a continuous 3-0 polyglycolic acid suture. F, Once the reservoir is folded in half, the anterior wall is closed with a two-layer 3-0 polyglycolic acid suture that is watertight. Note that the anterior suture line is stopped just short of the (patient) right side to allow insertion of an index finger, which will become the neobladder neck. Conversely a new buttonhole can be created at the most dependent portion of the pouch. G, Each ureter is spatulated and a standard bilateral end-to-side ureteroileal anastomosis is performed using interrupted 4-0 polyglycolic acid suture. H, The reservoir is anastomosed to the urethra using the previously placed urethral sutures. (Copyright 2012 Laramie Studio. Used with permission.)

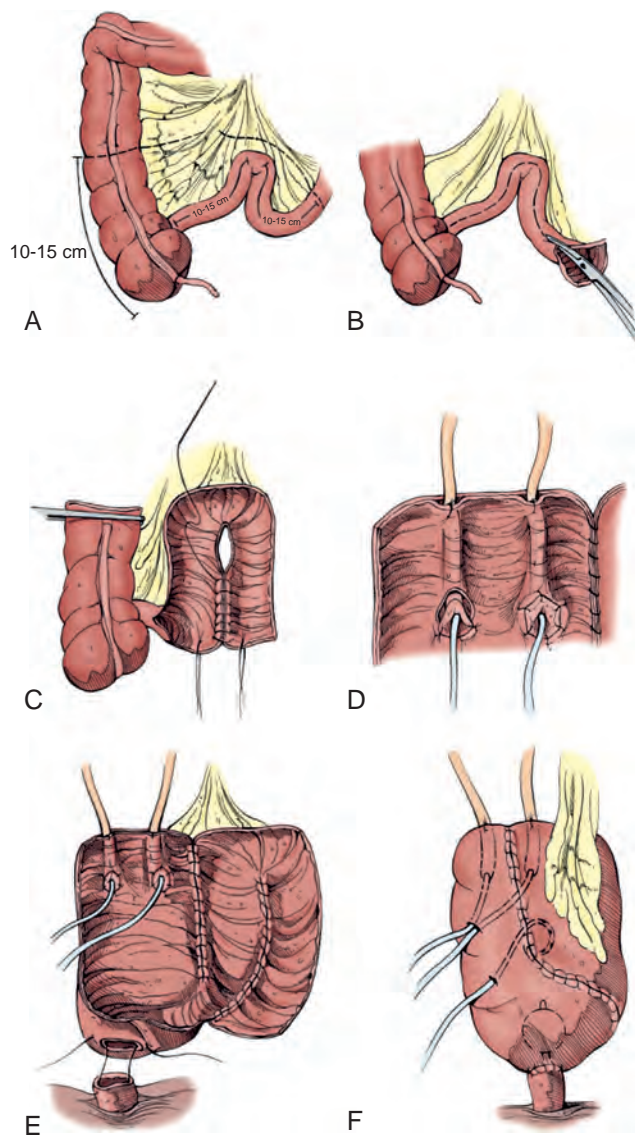


Figure 99-9. Construction of the Mainz ileocolonic orthotopic reservoir. A, An isolated 10 to 15 cm of cecum in continuity with 20 to 30 cm of ileum are isolated. B, The entire bowel segment is opened along the antimesenteric border. An appendectomy is performed. C, The posterior reservoir is closed by joining the opposing three limbs together with a continuous running suture. D, An antireflux implantation of the ureters through a submucosal tunnel is performed and stented. E, A buttonhole incision in the dependent portion of the cecum is made to provide for the urethral anastomosis. F, The reservoir is closed side to side with a cystostomy tube and the stents exiting.

1986; Light and Marks, 1990; Kolettis et al, 1996), and the urethra was anastomosed, end to side, to the cecum. The ureters are then brought into the colonic segment and implanted within the reservoir, and the neobladder is closed anteriorly (Fig. 99-10).

A modified version of the Le Bag ileocolonic neobladder has been reported by Baniel and Tal in which a Studer-like ileal chimney is incorporated as the afferent limb (Baniel and Tal, 2004).

Right Colon Pouch

An orthotopic substitute using the right colon without ileum has been reported (Goldwasser et al, 1986; Mansson and Colleen, 1990; Goldwasser, 1995; Mansson et al, 2003). The entire right colon and cecum are isolated, and a transverse ileocolonic

anastomosis is performed to provide bowel continuity. The ileal stump at the ileocecal valve is closed with a running absorbable suture. The colonic segment is then opened along the anterior taenia, leaving the proximal 2 to 3 inches of cecum intact. An appendectomy is performed, and the ureters are implanted in an antireflux fashion within the reservoir. The colon is then folded in a Heineke-Mikulicz manner and closed with a running absorbable suture. The ureterocolonic anastomosis is then performed.

Sigmoid Pouch

Patients who are candidates for radical cystectomy often have a redundant sigmoid colon, which is readily available for use. The only concern is the potential compromise of the vasculature of the distal colon segment because of interruption of branches of the internal iliac artery during the cystectomy. It is important, therefore, to maintain as much of the vascular supply to both ends of the bowel anastomosis as possible. Some patients will complain of frequent stools or rectal urgency for a period of time after sigmoid colectomy.

The use of the sigmoid in construction of an orthotopic substitute was initially described by Reddy and Lange (Fig. 99-11). A 35-cm portion of descending colon and sigmoid is isolated and arranged in a U configuration on the basis of the inferior mesenteric artery. The medial taenia of the U is incised down to an area just short of the urethral anastomosis. The incised medial limbs of the U are then brought together with an absorbable suture. Ureteral implantation is performed in a tunnel antireflux fashion. A small button of colon is removed from the most dependent portion of the reservoir, and the urethroenteric anastomosis is performed. The reservoir is then closed side to side (Reddy and Lange, 1987).

A modification of this technique was reported by DaPozzo and colleagues in which the entire bowel is detubularized and then folded in a Heineke-Mikulicz fashion to provide a more spheric reservoir (DaPozzo et al, 1994).

Use of Minimally Invasive Techniques for Orthotopic Diversion

Over the past 15 years a number of surgeons have performed cystectomy using laparoscopic or robotic-assisted techniques (Gill et al, 2002; Pruthi and Wallen, 2008; Stephenson and Gill, 2008; Wang et al, 2008; Yuh et al, 2008). Initial attempts to perform the diversion completely intracorporeally were fraught with difficulty, and the procedure was gradually replaced with extracorporeal construction after removal of the bladder through a small midline incision (Haber et al, 2008). This has allowed construction of continent diversions, both cutaneous and orthotopic. The Studer ileal neobladder has been the most popular because of ease of mobilization of the segment and simpler bowel anastomosis with a low abdominal incision. In the case of orthotopic neobladders, some authors then re-establish the pneumoperitoneum and use robotic assistance to complete the urethral anastomosis. Others perform the anastomosis in an open fashion (Pruthi and Wallen, 2008).

Postoperative recovery in most series has only been modestly improved compared with open series, with longer operative times but decreased blood loss. Some series have reported reduced ileus and shorter hospital stay (Haber et al, 2008; Huang et al, 2008; Wang et al, 2008; Ng et al, 2010; Nix et al, 2010), but these were generally selected patients. Other unselected large series have shown that postoperative complications were equivalent or even increased compared with open series (Yuh et al, 2012; Messer and Parekh, 2013; Raza et al, 2013). Recently the concept of constructing the neobladder intracorporeally has been revived in an attempt to improve recovery (Goh et al, 2012) but this is a technically difficult procedure even in the hands of surgeons with extensive robotic experience. Robotic cystectomy and urinary diversion are covered extensively in Chapters 96 and 100.

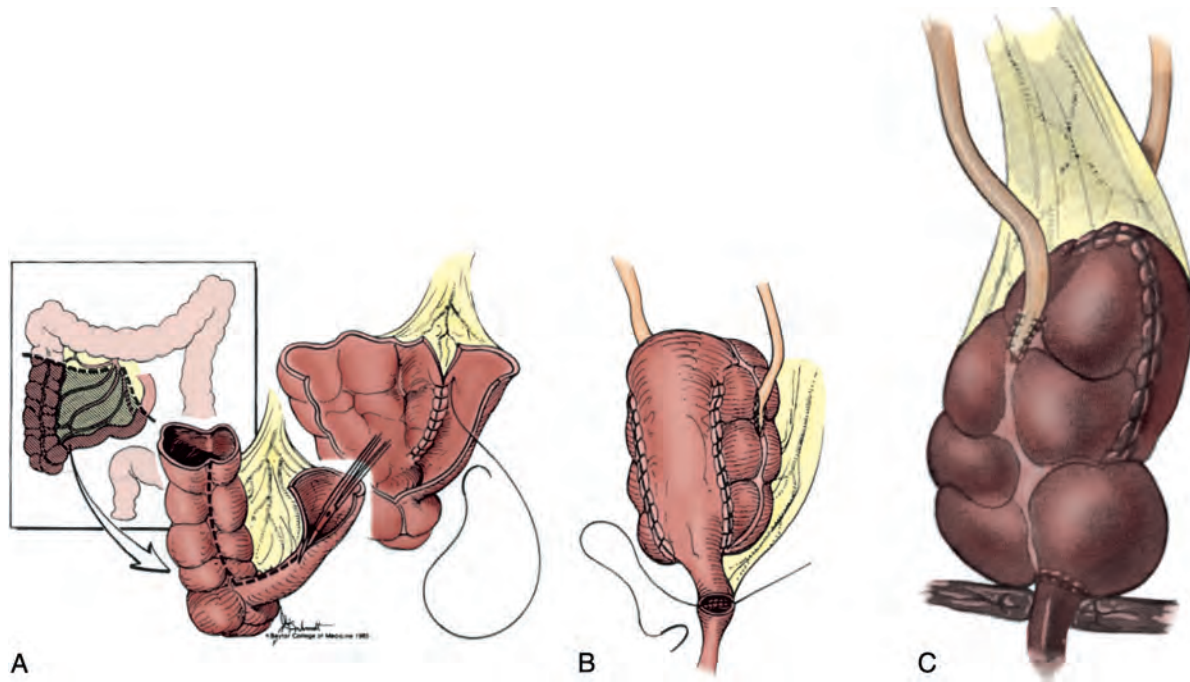


Figure 99-10. Construction of Le Bag (ileocolonic) orthotopic reservoir. **A**, A total of 20 cm of ascending cecum and colon, with a corresponding length of adjacent terminal ileum, is isolated. The bowel is opened along the entire antimesenteric border, and the two incised segments are then sewn to each other. This forms the posterior plate of the reservoir. **B**, This reservoir is folded and rotated 180 degrees into the pelvis with the most proximal portion of the ileum (2 cm nondetubularized) anastomosed to the urethra. **C**, Modification is performed with complete detubularization of the bowel segment, which is then anastomosed to the urethra. (Copyright Baylor College of Medicine.)

RESULTS AND COMPLICATIONS OF ORTHOTOPIC URINARY DIVERSION

Early and Late Complications

A complete discussion of the early complications of radical cystectomy and diversion is outside the scope of this chapter. Complications of radical cystectomy and diversion are common, and many are severe and potentially life-threatening (Konety et al, 2006; Quek et al, 2006; Ali-El-Dein et al, 2008; Shabsigh et al, 2009; Hautmann et al, 2010, 2011). Early complications including bleeding, thrombotic events, infection, and cardiovascular and pulmonary complications are not directly related to the urinary diversion and do not appear to be different in patients undergoing different types of diversion. Gastrointestinal complications are also common after cystectomy and are at least partially related to the need for a bowel anastomosis, which is common to all types of diversion. Similarly, urine leak and ureteral complications are possible with any type of diversion. A number of authors have shown that the overall rate of complications, hospital stay, and reoperation rates are not increased by use of continent diversion compared with ileal conduit diversion (Benson et al, 1992; Gburek et al, 1998; Parekh et al, 2000a).

Urine leaks may be more common in continent diversion than in conduits because of the long suture lines, but with good catheter drainage and properly managed stents and drains these usually resolve with observation alone as long as a urinoma does not form. If a patient has an undrained leak, an attempt at percutaneous drainage and/or bilateral nephrostomy tube placement is preferable to open surgical repair. The latter is extremely difficult during the first few weeks after the initial surgery and is likely to be complicated by enterotomies and a risk of fistula formation. In our

experience approximately 5% of patients require some sort of percutaneous drain or nephrostomy tube placement during the early postoperative period to manage these problems.

Both early and late complications may also be influenced by other factors such as prior radiation therapy, diabetes, and other comorbidities. Late complications are also influenced by tumor recurrence and the use of adjuvant or salvage systemic chemotherapy or radiation, and these causes may be difficult to separate out from causes related to the surgery. Late complications not directly related to the diversion include bowel obstruction, ventral hernia, thrombotic events, and cardiovascular problems common to patients in this age group. Hautmann has made the point that most late complications increase with time and are best described using Kaplan-Meier curves rather than as simple percentages (Hautmann et al, 2011). Ventral hernias are quite common and may be in part related to the need for increased abdominal pressure to empty the neobladder. The poor fascial strength associated with advanced age and smoking undoubtedly contributes to this risk as well.

The primary late complications of orthotopic diversion that are directly related to the diversion itself include incontinence, urinary tract infection, ureteroileal or afferent limb obstruction, urethral stricture, upper tract and pouch stones, vaginal fistula, and pouch rupture. Other than incontinence, these complications tend to be less common in orthotopic diversion than in continent cutaneous diversion, and many if not most can be managed by endoscopic procedures and rarely require open surgical revision (Rowland et al, 1995; Hautmann et al, 2011).

Although symptomatic urinary infections do occur, asymptomatic colonization of the neobladder with bacteria is also very common, although less common than in continent cutaneous diversion unless the patient is on intermittent self-catheterization

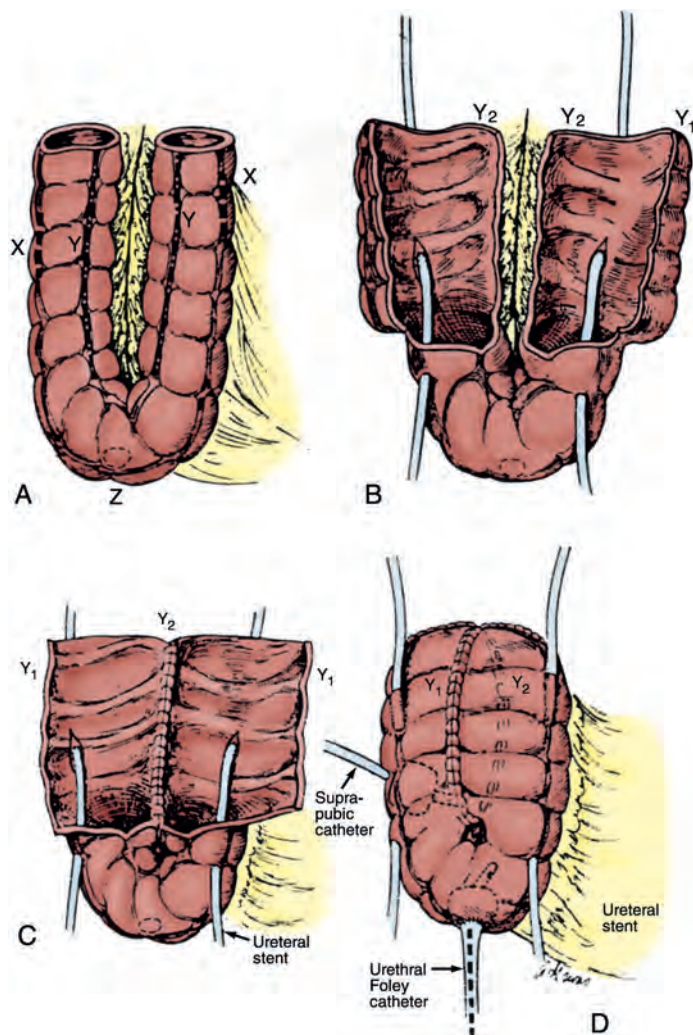


Figure 99-11. Construction of the sigmoid (Reddy) neobladder. **A**, A 35-cm segment of descending and sigmoid colon is isolated and folded into a U shape. **B**, The colon is incised along the medial taenia down to a point a few centimeters short of the entire colon. A buttonhole is made in the caudal portion of the colon that is later anastomosed to the urethra. **C**, The medial portions of the U are sewn together, and a tunneled ureterocolonic anastomosis is performed. **D**, The colonic pouch is closed by folding the reservoir side to side, and it is anastomosed to the urethra.

(Suriano et al, 2008). Wood and colleagues looked at 66 patients undergoing orthotopic refluxing ileal neobladder, 11 of whom (17%) were doing intermittent self-catheterization. Positive urine cultures were found in 39% (Wood et al, 2003). Symptomatic urinary tract infections are unusual after the initial 90-day postoperative period. Hautmann and colleagues found a cumulative risk of febrile infections of only 5.7% in 923 patients undergoing ileal neobladder with median follow-up of 72 months. Infections were most common in the first year and occurred in 13.6% of those with poor emptying compared with only 3.4% in those who emptied well (Steven and Poulsen, 2000; Hautmann et al, 2011). An effort to sterilize the urine with culture-specific antibiotics in the initial postoperative period after the catheter has been removed is often successful. However, after that initial attempt, treatment of asymptomatic bacteriuria is likely to simply encourage development of resistant organisms. If local symptoms suggest an infection, it should be confirmed whenever possible by a culture in this patient population. A patient who develops a febrile infection after the initial few months should be evaluated for possible upper tract obstruction and incomplete emptying.

Pouch perforation is rare in continent diversion in general, especially in orthotopic diversion because outlet resistance is usually low. The risk may be increased in patients who have had previous radiation therapy. It is a potentially life-threatening complication when it occurs. We have seen at least two deaths caused by pouch perforation of an orthotopic diversion that was unrecognized when the patients were admitted to an outside hospital. Patients with a perforation typically have acute abdominal pain and distention, often with signs of sepsis. CT cystogram is usually diagnostic. In general, these patients should be managed with exploration and repair, although conservative management with percutaneous drains has been described (Mansson et al, 1997; Singh and Choon, 2004; Hautmann et al, 2013).

The rate of ureteroileal stricture is identical to that in ileal conduit diversion, and is influenced by the type of anastomosis. The direct end-to-side Leadbetter or the combined Wallace anastomoses with interrupted fine absorbable sutures have been shown to have the lowest risk of stricture, approximately 3% to 6% (Pantuck et al, 2000; Hautmann et al, 2011). Obstruction from an antireflux valve has been seen in both hemi-Kock pouches and in the extraserosal tunneled afferent limb of the T pouch (Stein et al, 1996, 2004). These may be clinically silent until the patient develops bilateral hydronephrosis or even renal failure. Diagnosis may be suspected on CT or ultrasonography and can be confirmed on retrograde pyelography or antegrade nephrostogram. CT scans will often be misinterpreted by radiologists or urologists unfamiliar with the anatomy and/or the specific type of neobladder. The obstructing antireflux segment may be managed by endoscopic incision of the valve mechanism. It can be technically challenging to find the afferent limb in some cases, and special techniques may be necessary to catheterize and incise it (Dunn et al, 2007).

Pouch stones were very commonly seen in the Kock neobladder because of the use of surgical staples to maintain the intussuscepted nipple valve, with the incidence increasing steadily with time (Stein et al, 1996). Stones have been rare in the Studer and Hautmann neobladders, which are made entirely with absorbable suture (Studer et al, 2006; Hautmann et al, 2011). Recently several authors have advocated use of a metal GIA stapler to speed up the construction of an ileal neobladder. In one such series of 50 patients, stones were found in 6% of patients with only 20 months' median follow-up (Fontana et al, 2004; Barbalat et al, 2012). It is predictable that the incidence of such stones will increase with more follow-up, and although they can be managed endoscopically this carries significant cost in both money and inconvenience for the patients and may lead to further complications (Suriano et al, 2013).

Pouch-vaginal fistula is a unique complication of orthotopic neobladder in women that can be quite difficult to repair. The reported incidence in larger series is 5% to 10%, and the risk is increased if a portion of the anterior vaginal wall is excised along with the cystectomy specimen and in irradiated patients (Ali-El-Dein et al, 2008; Granberg et al, 2008). Prevention methods include leaving the vagina intact whenever it is safe from an oncologic standpoint, careful watertight closure of the vaginal cuff when it is opened, and placement of an omental flap between the vagina and neobladder, secured to the perivaginal tissue on either side of the urethral anastomosis (Stein and Skinner, 2006). In the early postoperative period any concern about vaginal urinary leakage should be evaluated with a lateral cystogram before removal of the catheter. Fistula should also be ruled out in any woman with persistent significant incontinence after the first few months of recovery. This is most easily done with a careful pelvic examination and with methylene blue instilled into the neobladder if necessary.

Beyond the initial few weeks a pouch-vaginal fistula is unlikely to heal spontaneously or with catheter drainage or percutaneous nephrostomy tubes alone. Repair may be attempted transvaginally, although reported success varies (Rapp et al, 2004; Smith, 2005; Ali-El-Dein et al, 2008; Ali-El-Dein and Ashmallah, 2013). Repair may ultimately require transabdominal exploration or even conversion to a cutaneous form of diversion.

Continence

In evaluating the continence results and clinical outcomes of various series of cystectomy and orthotopic neobladders, several considerations must be kept in mind. The prevalence and severity of urinary incontinence may be influenced by a number of variables including age and gender of the patients, prior treatments (such as radiation or prostate surgery), surgical techniques, and surgeon experience. In addition, the definitions of continence, the techniques used to collect the information (e.g., chart review, telephone interview, or anonymous validated questionnaire), and the length and diligence of follow-up have varied tremendously among different reports (Thuroff et al, 1996; Hautmann et al, 2013). Although there is general consensus that the ideal tool for studying functional outcomes is a validated patient-completed questionnaire, all the tools available today have significant drawbacks. The widely used Bladder Cancer Index (BCI) was developed to be applicable to all types of urinary diversion. It captures urinary leakage but not details such as the severity of incontinence or pad use (Gilbert et al, 2007). Only a few reports have used questionnaires such as these to evaluate neobladder patients (Stein et al, 2009; Jentzmik et al, 2012; Ahmadi et al, 2013). **In summary, one should use caution in attempting to compare continence results from different series of patients with orthotopic diversion.** We have summarized results from some of the largest series in Tables 99-1 and 99-2.

Common observations from series of patients undergoing orthotopic diversion include a gradual period of improvement in daytime continence over the first 6 to 12 months with a slower improvement in nighttime continence even into the second year. In general, patients with orthotopic neobladders can achieve very good daytime continence. In a pooled analysis of 2238 patients with various forms of orthotopic neobladder, daytime incontinence was reported in an average of only 13% of patients. Risk factors for daytime incontinence included advanced age of the patient (older than 65 years), use of colonic segments, and in some series lack of nerve-sparing techniques. Other series have identified hysterectomy in women and diabetes as a risk factor for worse continence results (Steers, 2000; Kessler et al, 2004; Anderson et al, 2012; Ahmadi et al, 2013).

Nighttime incontinence remains one of the most bothersome sequelae of neobladders, occurring in 7% to 70% of patients (Steers, 2000). Most series report that 50% to 75% of patients have good nighttime continence (see Tables 99-1 and 99-2). Nocturnal incontinence after orthotopic reconstruction results in part from the absence of neurologic feedback and sphincter detrusor reflex, as well as decreased sphincter tone at night. There is also initially an excess of urine production at night with an inability to concentrate the urine and a reversal of the normal antidiuretic effect of nighttime dehydration because of secretion of water by the bowel mucosa, which decreases with time (El Bahnasawy et al, 2000). In elderly patients there is also a physiologic nocturnal diuresis associated with increasing age. The frequency and amount of urinary leakage at night is also dependent on how often the patient wakes to urinate. Instructing the patient to completely empty immediately before bedtime and to awaken two or three times with the assistance of an alarm clock if necessary may significantly reduce nighttime incontinence. We and others have observed that nighttime incontinence may improve as late as 24 months after surgery, and it is not a cause of major disturbance in quality of life for most patients (Elmajian et al, 1996; Granberg et al, 2008).

Kessler and colleagues assessed various factors influencing urinary continence after radical cystectomy and ileal orthotopic bladder substitution in 331 male patients. In a multivariate analysis, the time to achieve daytime continence and the ultimate rate of success were significantly higher in patients younger than 65 and in those with attempted nerve-sparing techniques. Older men and those with diabetes gained continence more slowly (Kessler et al, 2004). There are currently no randomized trials evaluating the importance of nerve-sparing, and all retrospective studies suffer from significant selection bias.

In women, preservation of the uterus may significantly affect the functional results of neobladder construction. Anderson and colleagues retrospectively reviewed 49 women who underwent cystectomy and neobladder procedures. Of the women, 31% had had a prior hysterectomy, 29% underwent hysterectomy at the time of cystectomy, and 40% had the uterus preserved. Women with the uterus preserved had better daytime continence (Anderson et al, 2012). Ali-El-Dein also reported on a small group of women who underwent uterine-sparing cystectomy with excellent short-term results (Ali-El-Dein et al, 2013). There is also suggestion that sexual function may be better preserved with this approach (Zippe et al, 2005; Bhatt et al, 2006).

Decreased urethral sensitivity has been proposed as a potential factor contributing to urinary incontinence after radical cystectomy and orthotopic diversion. It has been suggested that conscious or unconscious sensation of urine leakage in the membranous urethra may normally produce either a reflex or voluntary contraction with increased tone of the external urethra (Kessler et al, 2007). This may be impaired in some patients with an orthotopic diversion. This reflex may also diminish with age and contribute to gradually decreasing continence in some individuals after orthotopic reconstruction (Hugonnet et al, 1999; Madersbacher et al, 2002). To some degree this worsening continence with age might be offset by the lack of problems related to prostatic enlargement, detrusor hypertrophy, and overactive bladder, all of which are common in elderly patients.

Ahmadi and colleagues recently reported on a group of 263 male patients without prior radiation who were at least 12 months out from a cystectomy and neobladder (Studer or T pouch). They were mailed the validated BCI with some additional questions designed to elucidate the types and degree of wetness of pads and the impact of mucous leak. Response rate was 68%, and 139 of 179 responders used pads at least sometime, half of whom used them both day and night. Forty-seven percent used pads in the day, with a third of those using a small pad or minipad, and almost half found that the pad was usually dry or only slightly wet. Nighttime use was 72%, with most using a medium or heavy pad. Older age and diabetes correlated with worse outcomes. The degree of incontinence and the urinary function scores on the BCI did not correlate well with the degree of bother from these symptoms, which was generally low (Ahmadi et al, 2013). Stein and colleagues previously reported results using the same questionnaire in 56 women. They found that 23% had frequent leakage or no control during the day and 34% during the night, with 61% requiring self-catheterization at least once daily. These results may more accurately reflect the true patient experience compared with reports from chart reviews.

The evaluation and management of urinary incontinence after orthotopic diversion should be delayed until the neobladder has had time to expand. This may take 6 months to a year after surgery (Grossfeld et al, 1996; Studer et al, 2006; Granberg et al, 2008). Physical therapy with biofeedback focused on the pelvic floor muscles may help some patients attain initial continence (Parekh et al, 2003). Urodynamic investigation may be indicated to ensure adequate capacity, without pressure waves, especially if colon is used for the neobladder. If reduction in maximal urethral closure or low Valsalva leak pressure is demonstrated, transurethral injection of bulking agents may be considered, but it has had only marginal results in our experience. Alternatively, in men an artificial urinary sphincter or urethral sling can be considered and may provide a more definitive treatment (Simma-Chiang et al, 2012). In women, although injection of urethral bulking agents provides a minimally invasive approach with some positive results (Tchetgen et al, 2000), it is best used for women with minimal symptoms of incontinence, with overall success rates below 50% and with less than optimally durable responses (Wilson et al, 2004). Newer agents that do not absorb over time may have improved results. Pubovaginal sling procedures for incontinence may be more effective than bulking agents in women with incontinence after orthotopic reconstruction; however, most of these patients will subsequently need to perform intermittent catheterization. It is important to note that one should avoid blind passage of needles or sling

TABLE 99-1 Results with Orthotopic Diversion in Series with Predominantly or Only Male Patients

AUTHOR	TYPE OF RESERVOIR	NO. OF PATIENTS	FOLLOW-UP (mo)	MEAN AGE (yr)	MORTALITY (%)	COMPLICATIONS*				IC (%)†	ANTIREFLUX MECHANISM
						EARLY (%)	LATE (%)	DAY (%)	NIGHT (%)		
Thuroff et al (1986)	Mainz, ileocecal	61	46	NA	NA	5	18	95	86	13	Submucosal tunnel
Mansson and Colleen (1990)	Right colon	67	70	61	3	4	29	NA	NA	37	Le Duc
Studer et al (1996)	Studer, ileum	200	30	64	2	NA	NA	90	80	0.5	Isoperistaltic limb
Cancrini et al (1996)	Studer, ileum	96	28	60	6	6	24	98	83	NA	Isoperistaltic limb
Barre et al (1996)	Camey II, ileum	110	32	62	1	NA	NA	93	74	1	Le Duc
Elmajani et al (1996)	Kock, ileum	295	42	66	1	7	12	87	86	8	Nipple valve
Kolettis et al (1996)	Ileocecal (Le Bag)	38	14	61	0	8	8	91	80	3	Le Duc and Bricker
Hautmann et al (1999)	W, ileum	363	57	63	3	15	23	96	95	6	Le Duc
Steven and Poulsen (2000)	Kock, ileum	166	32	62	0	12	23	98	80	32	Nipple valve
Hollowell et al (2000)	W, ileum	50	20	62	2	10	20	93	86	4	Isoperistaltic "chimney"
Abol-Enein and Ghoneim (2001)	Serous-lined extramural, ileum	450	38	47	0.8	9	8	93	80	2	Serous-lined extramural ureter
Constantinides et al (2001)	Ileal S pouch	52	30	63	3.8	10	18	95	88	3.8	None
Stein et al (2004)	T pouch, ileum	209	33	69	1.4	5	14	87	72	25	T limb mechanism
Laguna et al (2005)	Sigmoid	49	38	63	0	NA	5	89	10	0	Submucosal tunnel
Ahmadi et al (2013)	Ileum (Studer or T pouch)	179	54	70	NA	NA	NA	83†	47†	9.5†	T limb (54%)

*Complications reported related to urinary diversion; definitions vary by report.

†Continence results from validated patient-completed questionnaires.

IC, intermittent catheterization to empty neobladder; NA, not available from report.

TABLE 99-2 Results of Orthotopic Diversion in Series Limited to Female Patients

AUTHOR	TYPE OF RESERVOIR	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	MEAN AGE (yr)	MORTALITY (%)	COMPLICATIONS*			CONTINENCE		ANTIREFLUX MECHANISM
						EARLY (%)	LATE (%)	DAY (%)	NIGHT (%)	IC (%)	
Stenzl et al (2001)	Ileum	102	26	59	0	5	12	82	72	12	None
Granberg et al (2008)	Ileum (Studer)	59	29	62	0	22	5	90	57	35	None
Ali-Ei-Dein et al (2008)	Ileum, serous-lined extramural tunnel	192	51	54	2	16	35	92	72	16	Serosus-lined extramural ureter
Stein et al (2009)	Ileum (Studer or T pouch)	120 (n = 56 for continence results)	103	66	2.5	32	26	77†	66†	61† (39% dependent on IC to void)	T pouch 45%
Jentzmik et al (2012)	Ileum (Hautmann)	131	56	61	1.7	16	NA	82.4†	75.9†	58†	None
Anderson et al (2012)	NA	49	37	60	NA	NA	NA	57	45	31	NA

*Complications reported related to urinary diversion; definitions vary by report.

†Continence results from validated patient-completed questionnaires.

IC, intermittent catheterization to empty neobladder; NA, not available from report.

material into the pelvis in these patients because of a high risk of injury to the pouch or a loop of bowel stuck to the pubic symphysis. Use of infrapubic bone anchors or a prepubic approach may provide the safest surgical options (Quek et al, 2004).

Urinary Retention

Failure to empty or urinary retention (also often called *hypercontinence*) has been reported in 4% to 25% of patients undergoing orthotopic reconstruction and is much more common in women than in men (Steers, 2000; Nagele et al, 2006). Stein and colleagues, using chart review, reported that 25% of 209 patients with an orthotopic T pouch required at least occasional intermittent catheterization (20% of men and 43% of women) (Stein et al, 2004). Later, in one of the few studies using an anonymous patient questionnaire, 61% of 58 women required self-catheterization at least sometimes, and 39% required self-catheterization routinely to void (Stein et al, 2009). In the companion study of 179 male patients from the same institution, 9.5% used self-catheterization at least sometimes, but only 1 patient could not urinate at all without catheterization (Ahmadi et al, 2013). Although these types of studies are felt to more accurately reflect patient experience than chart review, they do suffer from the response bias inherent in mailed questionnaires.

Patients with incomplete emptying may have acute retention but more often have urinary infections or the new onset of overflow incontinence on presentation. They may also be discovered on routine follow-up with a palpable suprapubic mass, or distended reservoir or new-onset hydronephrosis on imaging. The development of retention may occur early but is often a late event, so the reported rates are heavily influenced by the length of follow-up of the series. Risk factors for urinary retention in patients with an orthotopic reservoir include the use of excessive intestinal length for the reservoir (>60 cm of ileum) and the use of prostate-sparing or nerve-sparing surgical procedures (Steers, 2000; Steven and Poulsen, 2000; Stein et al, 2004; Ji et al, 2010). Some authors have suggested that the location of the urethral anastomosis in the neobladder may contribute to retention in men because of folding of the neobladder (Thurairaja and Studer, 2008), but our experience using the end of the suture line for the urethral anastomosis in an ileal neobladder has resulted in a similarly low incidence of retention (Stein et al, 2004; Ahmadi et al, 2013). **Actual stricture of the neobladder-urethral anastomosis is rare.** In the series from Ulm with 923 patients and 72-month median follow-up, such strictures developed in only 11 patients (1.2%) in the absence of tumor recurrence. More distal urethral strictures developed in an additional 8 patients (Hautmann et al, 2011).

Rectal or vaginal examination and cystoscopy should be performed in patients who develop retention, to rule out a urethral anastomotic stricture or tumor recurrence. Urinary retention is best managed by intermittent self-catheterization (Steers, 2000). Pharmacologic intervention for patients with urinary retention does not appear to be an effective measure to improve this voiding dysfunction. Biofeedback training in pelvic floor relaxation may be helpful, and some authors have suggested that many of these patients have a flap of mucosa causing the obstruction that may be incised endoscopically with good effect (Thurairaja and Studer, 2008). Others have not found this to be a common cause of retention (Simon et al, 2006). Patients should be advised during the first few years of follow-up of the importance of adequate emptying and the need to consciously relax the external sphincter along with using Valsalva pressure during voiding.

A significant number of patients with orthotopic reservoirs will develop abdominal wall or incisional hernias postoperatively. In the series from Ulm the estimated risk by Kaplan-Meier analysis was 4% at 5 years and 6% by 10 years (Hautmann et al, 2011). In a prospectively followed patient population, it was as high as 13% at 3 years (Skinner, unpublished data). These fascial defects will reduce the efficiency in completely evacuating the neobladder by reducing the ability to effectively increase intra-abdominal pressure. These hernias should be identified and surgically repaired.

In women it appears that posterior prolapse of the pouch may contribute to late retention, and posterior support by means of omental flaps and sacrocolpopexy has been advocated (Ali-El-Dein et al, 2002; Stenzl and Höltl, 2003; Lee et al, 2004; Stein and Skinner, 2004). Ali-El-Dein and colleagues elegantly studied the possible causes of chronic retention after radical cystectomy and orthotopic bladder substitution in women. A total of 136 women underwent a standard radical cystectomy and orthotopic substitution, with 100 patients evaluable at a mean follow-up of 36 months. Overall, 95% of the women were continent during the day, 86% were continent at night, 2% were completely incontinent, and 16% were in chronic retention. Video-urodynamics showed that retention appeared to be mechanical in nature; the pouch has fallen back in the wide pelvic cavity, resulting in acute angulation of the posterior pouch-urethral junction. In addition, herniation of the pouch wall through the prolapsed vaginal stump was observed in most patients. Pelvic floor electromyography demonstrated complete pelvic floor silence during voiding, suggesting that urinary retention was not related to a neurogenic cause. The authors suggested that transposition of the omentum behind the reservoir, suturing of the peritoneum on the rectal wall to the vaginal stump, suspension of the vaginal stump by the preserved round ligaments, and suspension of the pouch near the dome to the back of the rectus muscle at cystectomy would help reduce the incidence of chronic retention (Ali-El-Dein et al, 2002). We have routinely performed a formal sacrocolpopexy suspension of the vaginal apex to the sacrum, but that alone has not eliminated retention. Preservation of the uterus and its ligament support structures may significantly reduce the risk of retention in women and should be considered when feasible (Anderson et al, 2012; Ali-El-Dein et al, 2013).

KEY POINTS: CONTINENCE AND URINARY RETENTION

- Daytime continence develops gradually over 3 to 6 months in most patients and is ultimately achieved in 80% to 90% of both male and female patients.
- Persistent nocturnal incontinence is common, observed in 20% to 50% of patients. Nocturnal continence may continue to improve beyond 12 months from surgery.
- Factors influencing continence rates include age, intestinal segment used, and possibly the application of a nerve-sparing technique.
- Failure to empty or urinary retention has been reported in 4% to 10% of men and 20% to 60% of women.

Follow-up for Patients with Orthotopic Diversion

There is no consensus on the ideal follow-up regimen for patients with orthotopic diversion. Imaging techniques include intravenous urography (rarely performed today), CT urography, magnetic resonance imaging, and ultrasonography. Physicians in the United States tend to depend more on radiographic imaging, whereas those in Europe often rely more on ultrasound evaluation. Regardless of the type of imaging, the follow-up regimen can be divided into three time segments:

- Early evaluation (first 4 months) to identify early ureteroileal anastomotic strictures caused by technical difficulties or poorly vascularized distal ureters.
- Middle period (4 months to 3 years) primarily focused on detecting cancer recurrence. This is best managed with CT or other cross-sectional imaging, which also allows evaluation of the upper tracts and reservoir for stones or obstruction. The frequency of the follow-up can be risk-adapted according to the pathologic findings at the time of cystectomy and the risk of subsequent recurrence.
- Long-term follow-up (beyond 3 years) to detect pouch stones, late upper tract obstruction, and urothelial carcinoma arising in the urethra or upper tracts.

BOX 99-1 Suggested Follow-up Protocol for Bladder Cancer Patients after Cystectomy and Orthotopic Diversion

EVERY 4 MONTHS FIRST YEAR, THEN EVERY 6 MONTHS TO 3 YEARS, THEN ANNUALLY

Physical examination including pelvic and rectal examination
Serum comprehensive metabolic panel, complete blood count

ANNUAL VISITS ONLY

Voided urine cytology
Urethral wash cytology (if carcinoma in situ on pathology)
Vitamin B₁₂ level
Prostate-specific antigen (if prostate cancer on pathology)

IMAGING DEPENDING ON CYSTECTOMY PATHOLOGY

Stage pT3 or N+ or higher: computed tomography (CT) of abdomen and pelvis with intravenous contrast, CT of chest or chest radiograph at each visit

Stage pT2 or lower: CT and chest radiograph at 4 and 12 months, then annually to 5 years, then every 2 years thereafter (may replace with ultrasonography after 3 years)

Our current follow-up scheme is shown in [Box 99-1](#), but others have been described ([Thurairaja and Studer, 2008](#); [Yafi et al, 2012](#)). We routinely perform digital rectal examination and cytology on both voided urine and in selected cases urethral wash in male patients, especially those with CIS in their primary pathology. It does require a cytologist with experience in looking at urine specimens from neobladder patients to be adept at evaluating them. Women should be evaluated with bimanual examination and voided cytology, because urethral recurrence will not be evident on CT scan. Cystoscopy should be performed in any patient who develops new-onset retention, a change in voiding pattern, or hematuria.

KEY POINTS: COMPLICATIONS FROM ORTHOTOPIC NEOBLADDERS AND RECOMMENDED FOLLOW-UP

- Early morbidity and mortality of cystectomy and orthotopic diversion are not increased compared with ileal conduit.
- Undrained urine leak is best managed using percutaneous drains and bilateral nephrostomy tubes when necessary. Early open surgical revision should be avoided.
- The majority of late urologic complications related to the neobladder can be managed using endoscopic techniques.
- Patients require regular follow-up imaging to identify upper tract obstruction and stones, which may be clinically silent.
- Follow-up should include rectal and pelvic examination and urethral cytology to identify urethral recurrence, which occurs in approximately 10% of males and rarely in females.

Quality of Life after Orthotopic Urinary Diversion

During the past two decades, there has been an increasing focus on quality-of-life issues and outcomes in various urologic diseases. This has been aided by the development of new, health-related quality-of-life instruments for use specifically in urology. Health-related quality of life can be defined as a patient's evaluation of the impact of a health condition and its treatment on relevant aspects of his or her life. Quality-of-life issues are becoming increasingly important in selection of the type of urinary diversion and are likely to play a larger role in future management of patients undergoing lower urinary tract reconstruction after cystectomy.

Initial studies in the 1980s pioneered comparative evaluation regarding quality-of-life issues in patients with different forms of urinary diversion after cystectomy. They demonstrated that, in general, patients were satisfied with their diversion and adapted reasonably well socially, physically, and psychologically. Boyd and colleagues studied patients with ileal conduit diversions compared with patients primarily with continent cutaneous diversion. Patients with an ileal conduit had the lowest expectations of that form of diversion but also had the poorest self-image, with a greater decrease in sexual desire and in all forms of physical contact (sexual and nonsexual) ([Boyd et al, 1987](#)). Mansson and colleagues demonstrated that urinary diversion affects most aspects of life in all patients. Although problems related to the diversion procedure tend to be fewer in patients with continent cutaneous reservoirs than in patients with ileal conduits, both forms of diversion could be associated with serious social, sexual, mental, and emotional problems ([Mansson et al, 1988](#)). This group also demonstrated the importance of how quality-of-life data are collected in terms of the results obtained ([Mansson et al, 2004](#)).

Hobisch and colleagues used both standardized and institutionally developed questionnaires to compare 69 patients with orthotopic diversion with 33 patients who underwent an ileal conduit. Patients with the continent diversion were more likely to recommend the procedure to friends, more likely to describe themselves as feeling "completely safe" with their diversion (74.6% vs. 33.3%), and more likely to feel "not handicapped at all" (92.8% vs. 66.7%). However, the ileal conduit patients were significantly older, more likely to be female and unmarried, and less likely to be working ([Hobisch et al, 2000](#)). All these factors can affect quality of life.

Bjerre and colleagues compared health-related quality of life in patients undergoing an orthotopic neobladder (38 patients) or an ileal conduit (29 patients) form of diversion. Despite higher daytime and nighttime urine leakage in the bladder substitute group, the urine leakage affected conduit patients more severely, and they scored higher on a leakage distress scale. The ileal conduit group was also found not to retain healthy body image as well as patients with a bladder substitute ([Bjerre et al, 1995](#)).

Hart and colleagues reported on a total of 221 patients (25 ileal conduit, 93 cutaneous Kock pouch, and 103 orthotopic neobladder) who completed four self-reported questionnaires including a profile of mood states and adapted versions of the sexual history form, body image dissatisfaction scale, and quality-of-life questionnaire. This study compared self-reports of emotional distress; global quality of life; sexuality; body image dissatisfaction; urinary diversion problems; and problems with social, physical, and functional activities. Regardless of the form of urinary diversion, the majority of patients reported good overall quality of life, little emotional distress, and few problems with social, physical, or functional activities. Problems with urinary diversion and sexual function were identified as most common. **After controlling for age, the researchers found no significant differences in any quality-of-life area among the urinary diversion subgroups** ([Hart et al, 1999](#)).

Weijerman and colleagues compared quality-of-life issues in patients undergoing either an orthotopic or a cutaneous continent urinary diversion. Quality-of-life assessment in this study revealed only a minor advantage for an orthotopic placement. It is important to note that quality-of-life assessment was found to be favorable for both types of urinary diversion ([Weijerman et al, 1998](#)). McGuire and colleagues used a well-validated survey to assess the impact of different forms of urinary diversion on overall quality of life in patients with locoregional bladder cancer after cystectomy. This study evaluated a total of 92 patients, including 38 with neobladder, 16 with Indiana pouch, and 38 with an ileal conduit. The mean physical scores were 48.4, 48.4, and 41.4 and mean mental scores were 51, 55.7, and 48.2 in the three groups, respectively. These results were not statistically different from one another or from published age-based and sex-based population norms, except for the mental score in the conduit group ([McGuire et al, 2000](#)). Autorino similarly used a validated tool for assessment of overall quality of life, the 36-Item Short Form Health Survey (SF-36), and found that the cystectomy patients scored worse than

the general Italian population in most domains but that there was no difference between the neobladder and conduit patients (Autorino et al, 2009).

There have been a number of efforts to develop a new tool that is more specific to patients with muscle-invasive bladder cancer. A few such validated questionnaires include the Functional Assessment of Cancer Therapy–Bladder (FACT-BL), the European Organisation for Research and Treatment of Cancer 30-item quality-of-life questionnaire for patients with muscle-invasive bladder cancer (EORTC QLQ-BLM30), the BCI, and the Vanderbilt Cystectomy Index (FACT-VCI) (Cookson et al, 2003; Gilbert et al, 2007). Each has its advantages and disadvantages, especially when applied to a specific group of patients. Large and colleagues used the FACT-VCI to compare 45 women who underwent an Indiana pouch procedure with 47 who underwent a neobladder construction and found no significant differences between the two groups on any of the quality-of-life domains (Large et al, 2010). Gilbert and colleagues validated and used the BCI and found that neobladder patients scored significantly worse on that index, influenced largely by a higher rate of urinary leakage and dribbling for the neobladder patients than for the conduit patients (on these measures the conduit patients scored better than untreated bladder cancer patients with their native bladder) (Gilbert et al, 2007).

Most of the studies that have evaluated and compared quality-of-life issues in patients undergoing various forms of urinary diversion have been criticized for methodologic problems that limit their conclusions (Gerharz et al, 2005; Porter et al, 2005; Gerharz, 2007). Critical analyses of the current quality-of-life literature suggest that there is not enough evidence to conclude that there is a clear quality-of-life advantage for patients undergoing continent diversion. Porter and Penson performed a systematic review to determine if any differences exist in health-related quality-of-life outcomes among different types of urinary diversion after radical cystectomy. Of 378 initial articles, only 15 studies met all their inclusion criteria. None of the studies were randomized trials, and only one was prospective. **Common limitations included unvalidated health-related quality-of-life outcome instruments, use of general health-related quality-of-life outcome instruments only, lack of baseline data, cross-sectional analysis, and retrospective study design.** The authors found that the current body of published literature is insufficient for it to be concluded that any form of urinary diversion is superior to another on the basis of health-related quality-of-life outcomes (Porter and Penson, 2005). Gerharz came to similar conclusions (Gerharz et al, 2005; Gerharz, 2007). Clearly, to better understand and evaluate these quality-of-life issues in patients undergoing various forms of urinary diversion, future studies in this area must incorporate prospective data collection, provide longer-term follow-up, and incorporate validated disease-specific health-related quality-of-life outcome instruments. With all instruments, the functional outcomes of different diversions and quality of life remain very difficult to assess, and it is extremely difficult to develop a single instrument that allows detailed comparison among different types of diversions.

In summary, there are not clear data showing an overall quality-of-life advantage for patients undergoing neobladder reconstruction, and most patients will clearly adapt to whatever specific challenges their urinary diversion presents to them. Nevertheless, when presented with the option, most patients will choose orthotopic diversion simply because it seems the most natural and avoids a permanent stoma, and having this option may encourage patients to more readily undergo definitive treatment of their bladder cancer. Patients must, however, have realistic expectations about the risk of incontinence and the possible need for self-catheterization.

KEY POINTS: QUALITY OF LIFE AFTER URINARY DIVERSION

- Most quality-of-life studies that have evaluated and compared patients undergoing various forms of urinary diversion have been criticized for methodologic problems that limit their conclusions.
- The current body of published literature is insufficient to conclude that any form of urinary diversion is superior to another on the basis of health-related quality of life outcomes.

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The complete reference list is available online at www.expertconsult.com.



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Patient Selection

Preoperative Care

Patient Position and Port Placement

Creation of Ileal Conduit

Creation of Modified Studer Neobladder

Postoperative Care

Outcomes

Operative Technique

Learning Curve

Hospital Stay

Complications

Functional Outcomes

Intracorporeal versus Extracorporeal Diversion

Future Direction

The conventional laparoscopic approach to intracorporeal urinary diversion has evolved since 1992 and its adaption was hindered by prolonged operative times, limitations of instrument maneuverability, and a steep learning curve (K.O., 1992; Sanchez de Badajoz et al, 1992; Potter et al, 2000). The compromise resulting from these difficulties led to hybrid procedures in which extirpation and lymph node dissection were performed by conventional laparoscopy and diversion was completed using a modified open approach (Haber et al, 2007).

The robot-assisted surgical approach for pelvic urologic oncology has existed since the mid-2000s (Menon et al, 2003; Guru et al, 2008), and the technique for robot-assisted radical cystectomy (RARC) with lymph node dissection has been established (Poch et al, 2013). Early oncologic outcomes after RARC and lymph node dissection are safe and efficacious (Hellenthal et al, 2010, 2011). Several perceived advantages of robot-assisted approaches for bladder cancer include less pain, minimal blood loss, and earlier return of bowel function, which ultimately help in a quicker return to previous quality of life (Challacombe et al, 2011). Despite smaller incisions and advances in extirpation, recovery has relied mainly on return of bowel function (Johar et al, 2013). More than 1700 cases of RARC have been registered in the International Robotic Cystectomy Consortium database (IRCC)—a quality assurance conglomerate of 58 surgeons at 33 institutions in 11 countries. Based on data published in 2013 from the IRCC, approximately 18% of procedures have been performed with the complete intracorporeal approach (Ahmed et al, 2014). Two commonly performed procedures with the complete intracorporeal approach include the ileal conduit and a modified Studer neobladder.

PATIENT SELECTION

One of the contraindications for the minimally invasive approach is decreased pulmonary compliance resulting from the inability to tolerate the steep Trendelenburg position, especially with prolonged operative duration during intracorporeal diversion. Use of ileum is contraindicated in patients with short bowel disease, severe inflammatory bowel disease, and changes related to extensive

KEY POINTS: INTRODUCTION

- A steep learning curve, prolonged operative times, and limitations of instrument maneuverability have hindered progress in minimally invasive urinary diversion with conventional laparoscopy.
- Advantages of robot-assisted approaches for bladder cancer possibly include less pain, minimal blood loss, and earlier return of bowel function.
- Approximately 18% of RARCs have been performed with the complete intracorporeal approach.

radiation. Absolute and relative contraindications for neobladder are similar to open surgery. The absolute contraindications include involvement of the urethra distal to the prostate, inadequate renal (serum creatinine >2 mg/dL), and poor hepatic function (Parekh and Donat, 2007).

PREOPERATIVE CARE

A clear-liquid diet 12 hours before surgery has become the standard; meanwhile, solid diet intake has been allowed up to 6 hours before surgery (Smith et al, 2011). Mechanical bowel preparation with oral antibiotics preoperatively is avoided. Bowel preparation can lead to electrolyte imbalance especially in elderly patients, and in some cases intracorporeal opening of bowel may lead to spillage of liquid content, which is annoying and can also become a source of infection. Several studies have shown no advantage to oral mechanical bowel preparation before surgery (Cerantola et al, 2013).

Intermittent pneumatic compression and leg stockings are recommended. To avoid significant cardiovascular complications (≤5%), anticoagulant treatment is recommended with low-molecular-weight heparin based on the body weight before and up to 4 weeks after surgery (Johar et al, 2013). Broad-spectrum intravenous antibiotics are preferably administered up to 1 hour before the start of the procedure.

KEY POINTS: PATIENT SELECTION AND PREOPERATIVE CARE

- Decreased pulmonary compliance is a **contraindication** for the minimally invasive approach.
- **Absolute contraindications** for the neobladder are same as for open surgery.
- Mechanical bowel preparation should be avoided.
- Anticoagulant treatment can help avoid significant cardiovascular complications ($\leq 5\%$).
- Preoperative broad-spectrum intravenous antibiotics are preferably given **up to 1 hour** before the start of the procedure.

PATIENT POSITION AND PORT PLACEMENT

After the induction of general endotracheal anesthesia, a nasogastric tube and a Foley urinary catheter are inserted. The patient is placed in lithotomy position with arms adducted and padded. The legs are also abducted and slightly lowered on spreader bars or stirrups. The patient is positioned in a steep Trendelenburg position and the abdomen is insufflated with a Veress needle or the Hasson technique. A **six-port transperitoneal approach** is used and all the ports after the camera port are placed under direct vision and more cephalad. This positioning of the ports helps in small-bowel maneuvering during urinary diversion and extended lymph node dissection along the aortic bifurcation. In the six-port configuration, the camera port is placed above the umbilicus (midline or on the left side). Two robotic ports are placed symmetrically at the level of or just below the umbilicus on the left and right sides, lateral to the rectus sheath. While performing the neobladder procedure, the third (right-assistant) and fourth (left-side) ports (12 to 15 mm) are placed just above and medial to the anterior superior iliac spines. The robotic arm could be used alternatively with an assistant instrument or by inserting an additional

robotic arm inside the 15-mm laparoscopic port for stapling during neobladder creation. A 5-mm (12-mm for neobladder) port is placed between the camera and the right robotic arm port. An extra short 12-mm port is inserted in the suprapubic area for bowel reanastomosis while performing the marionette ileal conduit. This port helps in aligning the bowel during reanastomosis and can be extended and converted to a Pfannenstiel incision for specimen removal in male patients.

A 0-degree lens is used during this procedure. Occasionally it is advantageous to use a 30-degree down lens for a deep female pelvis during extended lymph node and vascular pedicle dissection. The use of a “**technique of spaces**” is important in completing extirpation of the bladder and adjacent organs; the division of the procedure into well-defined steps facilitates teaching and keeps the procedure focused. The **four spaces** of dissection are **periureteral, lateral pelvic, anterior rectal, and retropubic space** (Poch et al, 2013). Extended lymph node dissection is performed up to the aortic bifurcation, which helps with the crossing of the left ureter to the right side for the urinary diversion. After the bladder with adjacent organs and the lymph nodes are placed in the specimen bags and transferred to the pelvis, attention is directed toward the intracorporeal ileal urinary diversion. **Before embarking on intracorporeal neobladder, the robotic arms are dedocked from the ports and the steep Trendelenburg position is reduced to 10 degrees to 15 degrees** for ease of urethra-neobladder anastomosis. Tables 100-1 and 100-2 summarize the steps and instruments used in the creation of robot-assisted intracorporeal ileal conduit and neobladder, respectively.

CREATION OF ILEAL CONDUIT

Transfer of Left Ureter and Selection of Bowel

The left ureter is crossed underneath the sigmoid colon and over the great vessels to the right side. It is important to identify patients with duplication of ureters, so that they can be implanted separately or together, depending on the caliber of the ureter. **If the length of the left ureter is short, the sigmoid is retracted with the fourth arm; occasionally a 30-degree down lens helps to identify and**

TABLE 100-1 Steps and Instruments Required for Intracorporeal Ileal Conduit

SURGICAL STEP	CAMERA	RIGHT ROBOTIC ARM	RIGHT BEDSIDE ASSISTANT	LEFT ROBOTIC ARM	FOURTH ROBOTIC ARM	SUTURE	COMMENTS
Selection of bowel segment and placement of marionette stitch	0° or 30°↓	Atraumatic Cadere forceps	Introduce Keith needle with marionette stitch	Atraumatic Cadere forceps	Cobra grasper	60-in 1-0 silk with Keith needle (SA7)	Outside clamp holding marionette stitch
Isolation of bowel and creation of conduit	0°	Atraumatic Cadere forceps	Laparoscopic stapler via right assistant port	Atraumatic Cadere forceps	Cobra grasper		60-mm Endo GIA stapler (purple)
Ureteroileal anastomosis	0°	Scissor, needle driver		Needle driver	Cobra grasper hook	5-in 4-0 Vicryl RB-1 (J304)	5-in 3-0 chromic for securing stent
Restoration of bowel	0° or 30°↓	Grasper, needle driver	Stapler via new suprapubic port (Xcel 12 mm; 75-mm long B12SRT) laparoscopic scissor	Cobra grasper	Cobra grasper	Silk suture (tension reduction)	Short suprapubic port for 60-mm Endo GIA stapler

TABLE 100-2 Steps and Instruments Required for Intracorporeal Neobladder

SURGICAL STEP	CAMERA	RIGHT ROBOTIC ARM	RIGHT BEDSIDE ASSISTANT	LEFT ROBOTIC ARM	FOURTH ROBOTIC ARM	SUTURE	COMMENTS
Neobladder-urethral anastomosis	0°	Scissor, needle driver	Manipulate Foley, ± perineal pressure	Needle driver	ProGrasp forceps	4-0 (Quill) 3-0 Monocryl RB1 (Ethicon)	2 Ligaloop strings, thin caliber Penrose drain
Isolation of bowel	0°	Atraumatic Cadieere forceps	Laparoscopic stapler	Atraumatic Cadieere forceps	ProGrasp forceps		60-mm laparoscopic stapler (Echelon); Endo GIA (Ethicon)
Detubularization of bowel Configuration of neobladder	0°	Scissor	Laparoscopic: scissor and needle driver	Atraumatic Cadieere forceps	ProGrasp forceps	2-0 V-Loc, 3-0 V-Loc (Covidien)	Chest tube (24 Fr) (helps expose antimesenteric border)
Uretero-neobladder anastomosis	0° or 30°↓	Scissor, needle driver	Laparoscopic: scissor and needle driver	Needle driver	ProGrasp forceps	4-0 Vicryl 4-0 V-Loc 4-0 Quill 3-0 Biosyn	2 single J 40-cm ureteral stent
Closure of neobladder	0°	Needle driver	Laparoscopic: scissor and needle driver	Needle driver		3-0 V-Loc	Foley catheter; Jackson-Pratt drain

KEY POINTS: PATIENT POSITION AND PORT PLACEMENT

- Intracorporeal diversion is performed with a six-port transperitoneal approach.
- All of the ports are placed more cephalad to help in the maneuvering of the bowel.
- For the neobladder, a 15-mm laparoscopic port can be used alternatively with an assistant instrument or by inserting an additional robotic arm.
- A 0-degree lens is used during intracorporeal urinary diversion.
- The “technique of spaces” is used for the extirpation of the bladder, which divides the entire procedure into well-defined steps to facilitate teaching and to keep the procedure focused.
- Before the intracorporeal neobladder creation, the robot should be undocked and the steep Trendelenburg position should be reduced to facilitate urethra-neobladder anastomosis.

free the proximal left ureter. A 12-cm long segment of ileum is identified (15 to 20 cm proximal to the ileocecal valve). Adequate bowel length on the ileocecal end of the bowel should be left in place to avoid kinking after the conduit is exteriorized and repositioned.

The Marionette Stitch

A 60-inch 1-0 silk suture using a Keith needle is introduced via the hypogastrium of the anterior abdominal wall and is passed through the distal end of the bowel segment (future stoma), then it is brought back through the same location on the anterior abdominal wall (Fig. 100-1). The marionette stitch is held together using a surgical instrument; not tying the marionette stitch allows free movement of the bowel segment during the creation of the conduit. The marionette stitch manipulates the bowel segment to

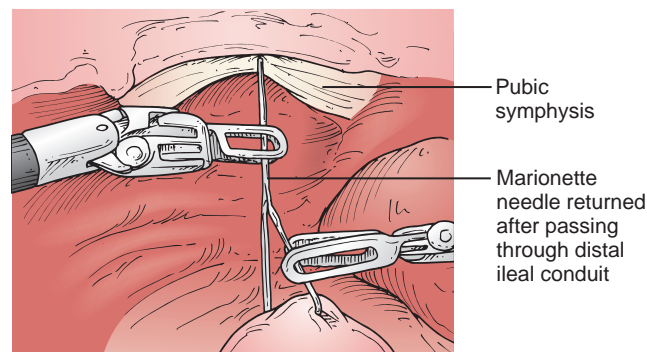


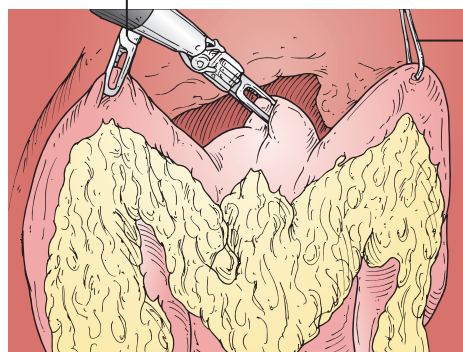
Figure 100-1. Keith needle used to transfer marionette stitch (placed into the stomal [distal] end of ileal conduit) out to the exterior for clamping.

adjust for the limitation of fixed ports and it enables mobilization of different areas of the conduit into the surgical field. The marionette stitch is especially helpful in patients with a limited distance between physical boundaries of the abdomen/pelvis and the true operative space. The marionette stitch can be placed further down in the pelvis to keep the operative field in range of optimal mechanical joint movements of the robotic instruments.

Isolation of the Bowel Segment and Creation of the Ileal Conduit

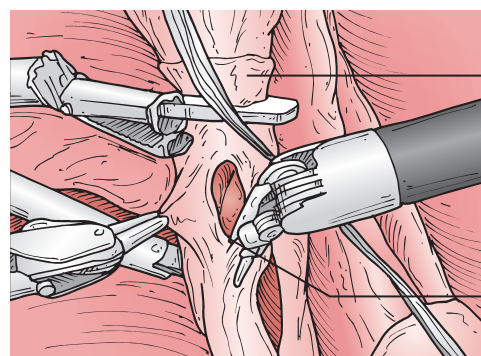
The fourth arm is used to hold the proximal segment of the bowel at stretch opposite to the stoma end (held by the marionette stitch); meanwhile the hook cautery is used to incise the peritoneum of the bowel mesentery. It is important to keep the appropriate orientation of the bowel and to avoid mesenteric narrowing of the base of the conduit (which limits mesenteric blood supply). Another alternative is to use a vascular stapler across the mesentery, which makes this process quicker. After the two mesenteric windows are created

Fourth arm holding and retracting bowel for vascular identification



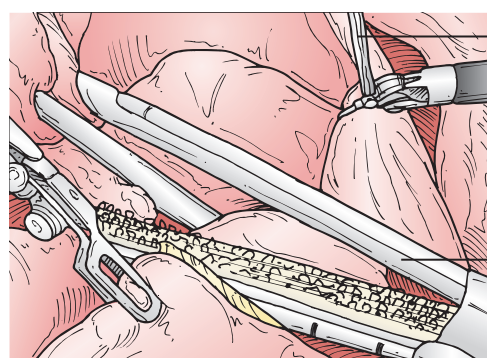
Distal (stomal) end with marionette suture

Figure 100-2. Bowel segment with mesenteric windows and the marionette stitch.



Distal end of ureter held by fourth arm
Logitudinal incision of ureter

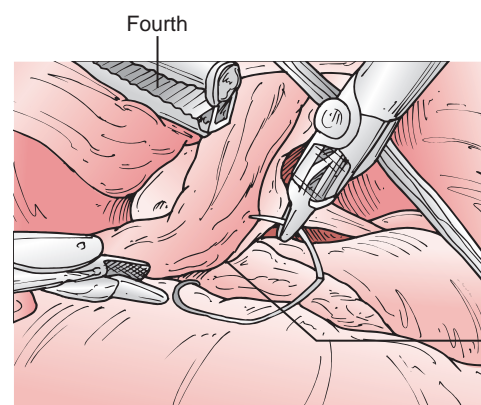
Figure 100-5. Left distal (cut end) of ureter held with fourth robotic arm and spatulation performed by right robotic scissor. (Note that lowering of the marionette stitch allows the conduit to remain away from the surgical field.)



Marionette suture separates distal

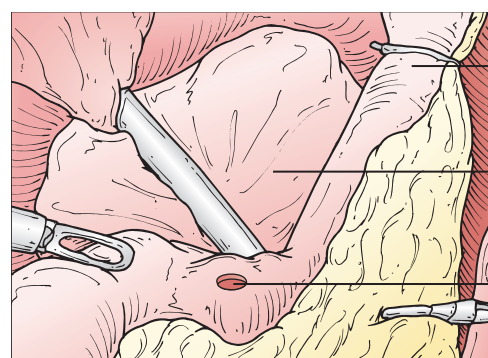
Stapler fixed length conduit for bowel isolation

Figure 100-3. Proximal end of ileal conduit isolated using a laparoscopic stapler (note the distal [stomal] end can be seen as controlled with the marionette stitch).



Interrupted ureteroileal anastomosis

Figure 100-6. Ureteroileal anastomosis performed with running sutures.



Distal end of conduit held by marionette stitch

Specimen bag in pelvis

Opening for ureteroileal anastomosis

Figure 100-4. Proximal opening for left ureteric anastomosis after isolation of the bowel segment for the ileal conduit.

(Fig. 100-2), a 45-mm Endo GIA stapler is used to divide the bowel proximally and distally (Fig. 100-3). The incised ends are held together using a 0-silk suture to avoid malrotation during anastomosis. The bowel reanastomosis is not established at this point. In our experience, ileal conduit segment washout has been abandoned, as it does not impact infection and avoids spillage during stent manipulation and ureteroileal anastomosis.

Ureteroileal Anastomosis

Two openings are created on either side of the proximal end of the conduit using either scissors or an electrocautery hook (Fig. 100-4).

After the marionette is lowered, the ureter is implanted with minimal traction and stretching of the proximal end of the ileal conduit. After the efflux of clear urine is seen, the spatulation is performed for wide anastomosis with ease. The fourth arm is used to retract the cut end of the distal ureter, and spatulation of the proximal ureter is performed (Fig. 100-5). We prefer to implant the left ureter first for ease of anastomosis.

The two commonly used techniques of anastomosis include Bricker and Wallace. A Bricker anastomosis is a refluxing end-to-side anastomosis and is easy to perform while keeping the two renal units separate. Meanwhile the Wallace technique joins the ends of the two ureters in a Y fashion, anastomosing a single limb to the proximal portion of the ileal conduit (Rehman et al, 2011).

A few key issues should be remembered while performing this anastomosis. The position in which the anastomosis is carried out is not the final position in which the proximal end of the conduit will lie. The trick is to place the initial suture in the conduit opening first (outside in) and then into the angle of the incision in the ureter (inside out). The suture on the conduit side should be perpendicular to the proximal staple line of the conduit. This helps to align the ureter and avoids back-walling of the ureter. This initial suture sets the stage for a proper alignment and placement of the subsequent sutures. Interrupted sutures can also be run along both sides halfway up to the middle of the anastomosis, after which the stent is placed. Van Velthoven-type, double-armed, 4-0 Vicryl sutures approximately 5-cm long can also be used to suture the angle of the spatulation and can continue along both sides (Fig. 100-6). After completion of anastomosis of the posterior wall, the ureteral stent is introduced. A metal laparoscopic suction tube is passed into the distal conduit through the 15-mm right

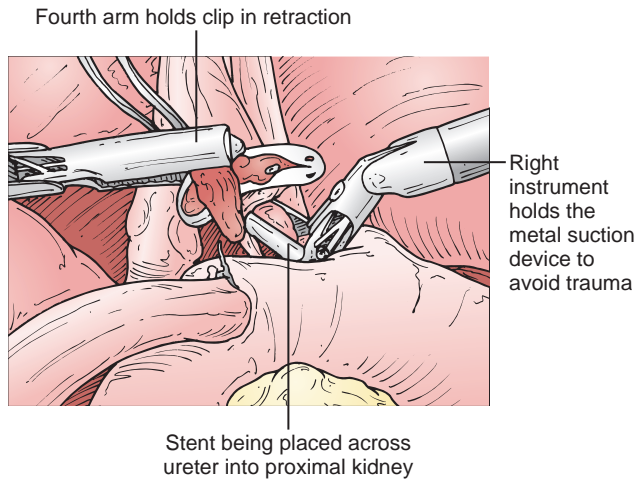


Figure 100-7. Metal suction tip held in place with robotic arm to insert single J stent across the anastomosis.

assistant port. The metal laparoscopic suction tube is pushed gently across the conduit and positioned at the junction of the conduit and the ureteric anastomosis. The metal suction tip is held in place by the robotic needle driver to allow passage of a stent through it without damaging the anastomosis (Fig. 100-7). This maneuver helps to facilitate threading of the 90-cm, 8.5-Fr, single-J ureteral stent with a guidewire into the renal pelvis. The guidewire is kept in the stent until it is secured to the conduit using 3-0 chromic stitches to prevent accidental dislodgment of the stent. The guidewire is removed only after the suture is placed, as it is difficult to identify the stent because of a lack of tactile feedback. The distal end of the ureter is excised completely and sent for final histopathology. The ureteroileal anastomosis is then completed. The distal ends (external portion) of both ureteric stents are left draining through the 15-mm side port. The exterior portions of the stents should not be clamped to the drape, which avoids accidental dislodgment during in vivo manipulation of the ileal conduit.

After the left side is anastomosed, the marionette is manipulated to turn the conduit on the other side and the right ureteric anastomosis is performed in a similar fashion.

Restoration of the Bowel

The two cut ends of small bowel are held in place by a stay silk suture. We prefer to reanastomose the bowel after the two ureters are anastomosed. This helps ease conduit manipulation and helps tailor the bowel reanastomosis to avoid kinking or tension. A new suprapubic port is inserted for ease of alignment of bowel reanastomosis. A 60-mm Endo GIA stapler is inserted through the short 12-mm suprapubic port. An end-to-end anastomosis is performed after both ends of the bowel are aligned along their antimesenteric borders (Fig. 100-8). The open ends of the two anastomosed intestinal segments are stapled by firing an Endo GIA stapler horizontally via the right assistant port (Fig. 100-9). A secure stay suture is placed to reduce tension and to support the edge of the antimesenteric border. The mesentery window is closed using a 3-0 silk suture.

Prestoma Preparation

The robot is left docked and the instruments are removed. The surgeons scrub to create the stoma opening by making a cruciate incision in the anterior fascia and inserting the four stay sutures to anchor the conduit after it is externalized. After completion of four fascial sutures, the robotic arms are reinserted. The pelvis is exam-

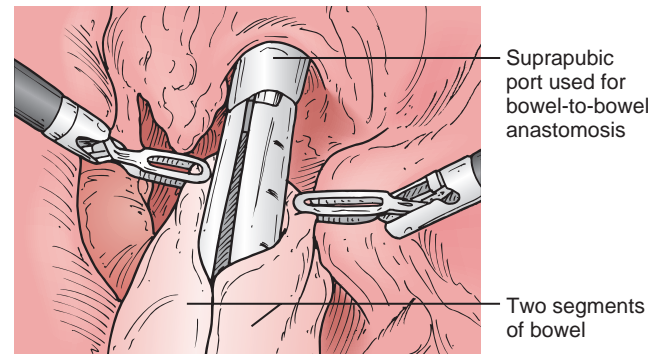


Figure 100-8. Extra short suprapubic (12 mm) port inserted for side-to-side bowel anastomosis held in place with graspers.

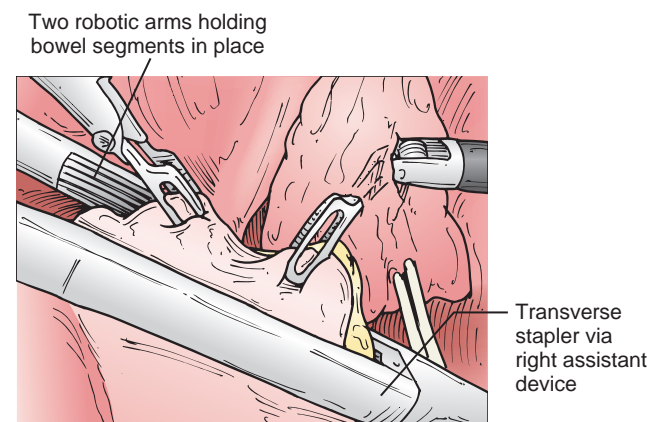


Figure 100-9. Alignment for transverse closure of bowel anastomosis performed via the right assistant port.

ined for any bleeding, and strings of all specimen bags are removed via the suprapubic port. A vascular clamp is introduced via the stoma opening under direct vision into the abdominal cavity to remove the marionette suture and the free ends of the ureteric stents. A Jackson-Pratt drain is introduced via the right assistant port and the robot is dedocked after the robotic instruments have been removed. Finally the distal end of the conduit is brought out gently through the stoma site, assuring proper orientation after the pneumoperitoneum is lowered.

KEY POINTS: CREATION OF ILEAL CONDUIT

- To avoid kinking of the conduit when it is exteriorized and repositioned, adequate length of the bowel at the ileocecal junction should be retained.
- The marionette stitch is not tied to allow free movement of the bowel segment during the creation of the conduit.
- As the ileal conduit segment washout does not impact infection and causes more spillage, it has been abandoned.
- The ureteral stent guidewire is removed only after the tagging suture is placed, as the lack of tactile feedback makes it difficult to identify the stent.
- The exterior portions of the ureteral stents should not be clamped so as to avoid accidental dislodgment.

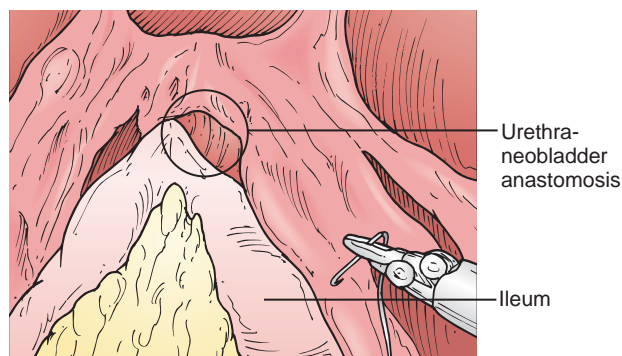


Figure 100-10. Tension-free ileum to urethra anastomosis is the first step of the intracorporeal neobladder creation. (Courtesy Professor Peter Wiklund, MD, PhD.)

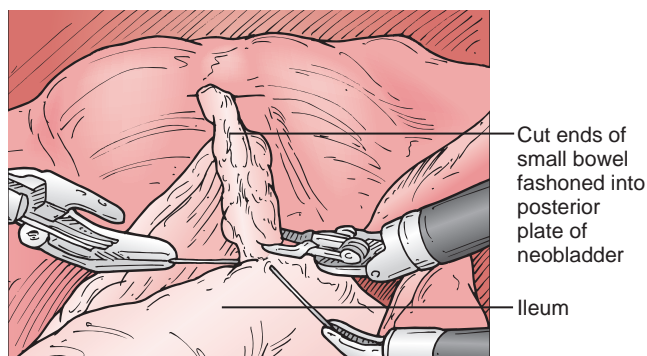


Figure 100-11. Reconfiguring and creation of posterior plate of neobladder. (Courtesy Professor Peter Wiklund, MD, PhD.)

CREATION OF MODIFIED STUDER NEOBLADDER

The small bowel is assessed for its tension-free ease of approximation to the urethral stump with minimal traction. The significant difference between various approaches is the performance of early enterourethral anastomosis advocated by the Karolinska group. The alternate approach uses the fourth arm to hold traction at the future urethral anastomosis site in the small bowel and to perform anastomosis after the posterior plate of the neobladder is constructed.

Neobladder-Urethral Anastomosis

The ileum is sufficiently mobilized to perform a tension-free neobladder-urethral anastomosis. Using robotic scissors, an opening is made at the most dependent, tension-free antimesenteric portion of the ileum. The anastomosis is performed by the Van Velthoven technique with a 4-0 Quill suture (Fig. 100-10). Some anecdotal experiences have suggested that the V-Loc suture (Covidien, Minneapolis, MN) should not be used because of the sharper and larger barbs that may traumatize the neobladder. In situations where it is difficult to approximate the bowel to the urethra easily, the neobladder is held in position between two customized Penrose drains rolled around the intestine (urethral end of the future neobladder). A silicone catheter is used to identify easily the urethral stump, similar to urethrovesical anastomosis during robot-assisted radical prostatectomy.

Various maneuvers are advocated if it is difficult for the ileum to reach the urethra: reducing Trendelenburg positioning, using the Penrose drain for gentle stretching and traction, releasing and incising the peritoneum over the mesentery, stapling the medial/proximal portion of the mesentery (care is needed to avoid risking ischemia to the isolated bowel segment), and, finally, dissecting the ileum around the ileocecal region.

Isolation of Bowel

The orthotopic neobladder is tailored based on the Studer principles using a 40-cm segment of terminal ileum for the body of the neobladder and approximately 10 to 15 cm for the afferent limb. The intestine is isolated using a laparoscopic 60-mm bowel stapler. The bedside assistant can use the hybrid 15-mm port to insert the stapler for ease of alignment with the bowel. The ileum is stapled 40 cm proximal to the ureteroileal anastomosis. Integrity of small bowel is usually restored using staplers; however hand-sewn anastomosis has also been reported as safe. The stapler-based reanastomosis is performed based on a side-to-side method.

Detubularization of Bowel

The distal 40 cm of the isolated ileal segment is detubularized along the antimesenteric border with cold scissors or by inserting

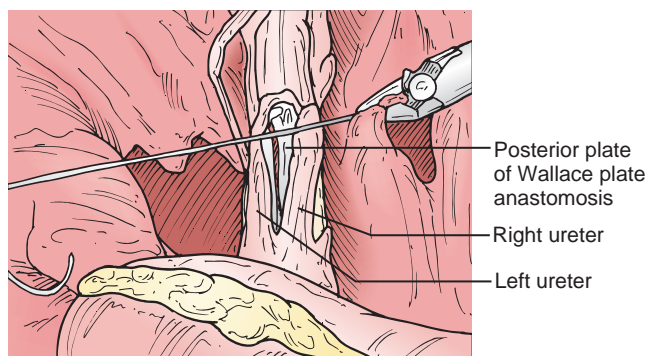


Figure 100-12. Two sides of ureters are configured using a running suture after the edges are aligned and held in place. (Courtesy Professor Peter Wiklund, MD, PhD.)

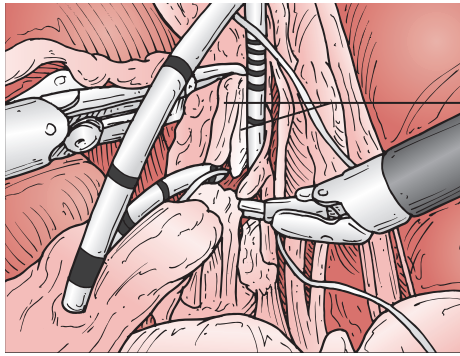
a 24-Fr chest tube for ease of identification of the most antimesenteric portion. A 10-cm proximal isoperistaltic afferent limb is left intact to anastomose the ureters.

Modified Studer Neobladder

The posterior part of the Studer neobladder is closed using absorbable running sutures (2-0 or 3-0 V-Loc). A 0-degree or 30-degree down lens can be used for this portion of the procedure (Fig. 100-11). After the posterior part is sutured, the distal half of the anterior part of the reservoir is also sutured in a similar fashion. The anterior part of the reservoir is not sutured completely and is closed toward the end of the procedure. The USC group advocates 90-degree counterclockwise rotation of the pouch at this stage.

Uretero-Neobladder Anastomosis

The Bricker anastomosis is performed between the ureters and the afferent limb. A 4-0 Vicryl or a 3-0 Biosyn suture is used for anastomosis. The left ureter is transposed to the right side by creating a tunnel under the sigmoid mesentery. During the Wallace anastomosis the ureters are spatulated and joined at the posterior walls of the ureters. The Wallace plate is sutured to the afferent limb of the Studer reservoir, using a 4-0 Vicryl or a Quill suture (Fig. 100-12). Two single-J 40-cm ureteric stents are introduced before closing the ureters (Fig. 100-13). The stents are passed through the afferent limb and mobilized up to the ureters. The stents can be brought out via the midline just above the pubic symphysis or internalized by using double J stents.



Two ureters are arranged in Wallace fashion to anastomose with proximal end of Studer neobladder

Figure 100-13. Anastomosis is performed and helps align right and left ureter to create Wallace plate. (Courtesy Professor Peter Wiklund, MD, PhD.)

Closure of the Neobladder

The remaining part of the reservoir is closed toward the completion of the neobladder. The balloon of the indwelling catheter is filled with 10 cc of water. The neobladder is checked for any anastomotic leakage. A Jackson-Pratt drain is placed in the pelvis away from the urethra-neobladder anastomosis.

KEY POINTS: CREATION OF MODIFIED STUDER NEOBLADDER

- The significant difference among various approaches at neobladder formation is in initially performing the enterourethral anastomosis.
- The bowel can be mobilized to the urethra by holding the neobladder in position between two customized Penrose drains rolled around the intestine.
- Maneuvers to help the ileum reach the urethra include:
 - reducing Trendelenburg position.
 - using the Penrose drain to hold the ileum.
 - incising and releasing the peritoneum over the mesentery.
 - stapling the medial/proximal portion of the mesentery.
 - dissecting the ileum around the ileocecal region.
- Use of the hybrid 15-mm port by the bedside assistant can help ease alignment of the stapler with the bowel.
- The anterior part of the reservoir is closed toward the end of the procedure.

POSTOPERATIVE CARE

Optimizing fluid balance and avoiding overhydration should help manage fluid shift in this patient population with advanced age. Cochrane meta-analysis showed no advantage to leaving the nasogastric tube after surgery (Nelson et al, 2007). Pelvic drainage is preferred; we use both a drain as well as the Foley via the urethra as a drain (removed postoperative day 1 in ileal conduits). Adequate pelvic drainage and stenting of ureters, especially at the anastomosis, have already proven helpful in healing and reduction of metabolic acidosis, possibly because of minimal reabsorption. Drains can usually be removed at discharge. The ureteral stents if exteriorized to skin are removed a week after surgery. If the stents are internalized, removal of the double J stents is recommended with cystoscopy when the neobladder has healed at 3 to 4 weeks. The urethral catheter can be removed approximately 3 to 4 weeks postoperatively after the absence of any leak is confirmed on pouchography. Irrigation of the neobladder is recommended every 8 hours to avoid mucus plugging and catheter blockage.

Enhanced Recovery after Surgery

Multimodal perioperative pathway, especially enhanced recovery after surgery (ERAS), has recently evolved with more than 20 key components and has been tailored by several cystectomy experts (Karl et al, 2014; Patel et al, 2014; Xu et al, 2015). Recent modifications include early use of alvimopan, intraoperative goal-oriented fluid optimization, immediate initiation of oral diet, and reduced narcotic use. Xu and colleagues (2015) compared traditional pathway to an enhanced recovery protocol and reported decreased opioid usage per day, incidence of ileus, and hospital stay; however, they reported more pain. Opioid use for breakthrough pain underwent a radical change from opioid PCA (patient-controlled analgesia) and epidurals to high-dose acetaminophen and/or ketorolac.

KEY POINTS: POSTOPERATIVE CARE

- In patients with advanced age, optimization of fluid balance and avoidance of overhydration helps to manage fluid shifts and to control complications.
- Pelvic drainage and stenting of ureters help in bowel recovery and reduce metabolic acidosis.
- The neobladder irrigation is recommended every 8 hours to avoid mucus plugging and catheter blockage.

OUTCOMES

Intracorporeal urinary diversion attempts to minimize bowel manipulation and to reduce postoperative pain with minimal wound retraction and smaller incisions. The first published report of robot-assisted intracorporeal neobladder appeared in 2003 (Beecken et al, 2003). Several factors have facilitated performance of the procedure with an intracorporeal technique. First, RARC and the extended pelvic lymph node dissection technique have been standardized with oncologic results equivalent to standard open techniques (Raza et al, 2015). Second, the understanding of the robot-assisted surgical platform along with improving console-based surgical skills have allowed the robotic surgeons to optimize the use of this technology. The advantage of the EndoWrist technology in robot-assisted surgery allows surgeons to use the mechanical wrist for suturing and reconstructive purposes with minimal effort in comparison to conventional laparoscopy. This section addresses various key factors that define the acceptance of intracorporeal urinary diversion based on operative technique, learning curve, hospital stay, complications, functional outcomes, and comparison between intra- and extracorporeal outcomes.

OPERATIVE TECHNIQUE

One of the major limitations of incorporating intracorporeal diversion has been prolonged operative time (Balaji et al, 2004; Hubert et al, 2006). Initial reports of operative times up to 450 minutes made this approach unacceptable, as the patient population is at risk because of age and comorbidity. More recent literature shows that overall operative times have been reduced (almost equivalent to the open approach), and the technique is standardized. Open conversion is rare, with only two technique-related reports (Table 100-3).

In one of the largest reported series of 100 consecutive robot-assisted intracorporeal ileal conduits, median overall operative time was 352 minutes with an estimated blood loss of 300 mL and no conversion (Azzouni et al, 2013). In a separate combined series of 36 intracorporeal neobladders and 9 ileal conduits, Jonsson and coworkers (2011) reported an acceptable median operative time (460 minutes for ileal conduits and 480 minutes for neobladders).

TABLE 100-3 Comparisons of Operative Parameters for Robot-Assisted Intracorporeal Urinary Diversion

SERIES (YEAR)	PATIENTS	DIVERSION	OVERALL OPERATIVE TIME (min)	DIVERSION TIME (min)	CONVERSION TO OPEN	INTRAOPERATIVE DIFFICULTY/ COMPLICATIONS
Goh et al (2012)	15	Ileal conduit 7 Neobladder 8	450	NR	0	0
Azzouni et al (2013)	100	Ileal conduit	352	123	0	0
Canda et al (2012)	25	Ileal conduit 2 Neobladder 23	624	NR	1	Inability to anastomose
Pruthi et al (2010)	12	Ileal conduit 9 Neobladder 3	318	180	0	0
Tyritzis et al (2013)	70	Neobladder	420	NR	4	2 Cardiopulmonary compromise 2 Technical difficulty: prolonged operative time, inability to anastomosis
Ahmed et al (2014)	167	Ileal conduit 106 Neobladder 61	414	NR	NR	NR

NR, not reported.

with no conversion. Pruthi and colleagues (2010) in their early series (3 neobladders and 9 ileal conduits) had an excellent mean operative time of 318 minutes. The quicker operative times reported by this group are possibly attributed to the U configuration and the use of absorbable staplers for configuring the neobladder. Rehman and coworkers (2011) in a series of 9 ileal conduits reported a mean operative time of 346 minutes and described one postoperative patient with iatrogenic necrosis of the ileal conduit, which was revised and was possibly related to an initial experience with the intracorporeal approach. The key issue during the early experience is maintaining orientation during and at the completion, as no opportunity exists to correct orientation after the ports are removed and the stoma is retrieved. Goh and colleagues (2012) in their initial experience of seven ileal conduits reported a median operative time of 450 minutes, which was consistent with the early adaption of the intracorporeal approach.

LEARNING CURVE

Collins and coworkers (2014) evaluated the learning curve of intracorporeal neobladders and found that overall operative times and the risk of conversion were reduced from 30% to 10% after only 10 consecutive procedures. A reduction in complications was observed in both early (70% to 30%) ($P < .05$) and late (50% to 0%) ($P = .011$) categories as the surgeons gained experience with intracorporeal neobladder. The mentoring effect was helpful in reducing overall operative time, and it helped avoid open conversion during early experiences. Conversion of intracorporeal neobladder to open was associated with an increase in overall length of stay.

HOSPITAL STAY

The literature does not show evidence of significant reduction in hospital stay except for the University of North Carolina series that showed a reduced average stay of 4.5 days (Pruthi et al, 2010). In the IRCC comparative study (Ahmed et al, 2014) median hospital stay was marginally longer with intracorporeal urinary diversion (9 days vs. 8 days, $P = .086$).

COMPLICATIONS

It is difficult to attribute all reported complications to urinary diversion, as the patients also underwent radical cystectomy and a lymph node dissection, which can be morbid and responsible for a portion of reported complications. The possible attributed advantages in terms of reduced bowel manipulation, decreased insensible losses, and minimal need for analgesia can possibly help reduce the significant morbidity of this procedure.

Based on literature (only describing case series >10) overall early (30-day) and late (90-day) complications were up to 73% and 81%, respectively (Table 100-4). High-grade complications were observed in up to 37%, and sepsis was the most common cause of these complications. The reoperation rate at 30 days was as high as 17%; meanwhile the readmission rate ranged between 22% and 60%.

FUNCTIONAL OUTCOMES

The most significant functional outcomes related to the neobladder are return of continence and sexual function. Canda and colleagues (2012) evaluated 23 patients who underwent intracorporeal Studer neobladder and found that 61% were fully continent and 22% experienced mild daytime incontinence. Erectile function was evaluated based on the International Index of Erectile Function scores with poor return of results attributed to limited follow-up and decreased libido. Goh and coworkers (2012) at 3-month follow-up had complete return of daytime continence in six patients and only one patient required conversion to a continent cutaneous pouch. Tyritzis and colleagues (2013) showed that 74% of men and 67% of women were continent (either no or one pad per day). A total of 81% of patients who underwent a nerve-sparing procedure were potent with or without oral medications at 12 months. A total of 67% of females also remained sexually active after surgery.

INTRACORPOREAL VERSUS EXTRACORPOREAL DIVERSION

The IRCC compared outcomes (935 patients) between intracorporeal (167 patients, including 106 ileal conduits and 61 neobladders)

TABLE 100-4 Comparisons of Clinical Outcomes following Robot-Assisted Intracorporeal Urinary Diversion

AUTHOR (YEAR)	TYPE/NUMBER	COMPLICATIONS (%) (30 DAYS, 90 DAYS)	MOST COMMON COMPLICATION	HIGH-GRADE COMPLICATION (%)	REOPERATION (%) (30 DAYS)	READMISSION (%) (90 DAYS)	MORTALITY (%) (90 DAYS)
Azzouni et al (2013)	Ileal conduit	100 NR, 81	Infection	19	0	16	1
Goh et al (2012)	Ileal conduit (7)/ Neobladder (8)	15 73, 13	Infection	13	0	60	0
Pruthi et al (2010)	Ileal conduit (9)/ Neobladder (3)	12 42, 17	—	8	17	17	0
Canda et al (2012)	Ileal conduit (2)/ Neobladder (25)	25 52, 28	Infection	28	0	24	8
Tyritzis et al (2013)	Neobladder	70 48, 51	Infection	37	4.5	NR	1.4
Ahmed et al (2014)	Ileal conduit (106)/ Neobladder (61)	167 35, 41	Infection	18	8	12	1.6

NR, not reported.

(18%) and extracorporeal urinary diversion (Ahmed et al, 2014). Only eight of 18 institutions had performed intracorporeal urinary diversion, and in 55% of these eight centers the intracorporeal approach was performed with a volume of less than 100 robot-assisted radical cystectomies per year. Operative times were comparable, suggesting experienced robotic surgeons were engaged in advanced reconstructive robot-assisted surgery. A total of 35% of intracorporeal and 43% of extracorporeal urinary diversions presented with a complication within 30 days of surgery. **Readmission rates at both 30-day (5% vs. 15%, $P \leq .0001$) and 90-day (12% vs. 19%, $P = .011$) were lower in the intracorporeal group. Blood transfusions were significantly lower in the intracorporeal group (7% vs. 16%, $P = .022$). Gastrointestinal-related complications were significantly lower in the intracorporeal group (10% vs. 23%, $P \leq .001$), supporting the notion that minimal bowel manipulation and open bowel exposure may help in lowering complications and might possibly help with early recovery. In the intracorporeal group, 90-day mortality was lower (1.6% vs. 4.9%, $P = .043$), which may be explained based on patient selection and experience of the robotic surgeon until randomized controlled studies clearly show a difference. The number of patients returning to the operating room was higher in the intracorporeal group (8% vs. 6%, $P = .421$).**

KEY POINTS: OUTCOMES

- Prolonged operative time has limited the incorporation of intracorporeal diversions.
- It is critical to maintain proper orientation of the bowel and the conduit during and at the completion of the procedure, as no opportunity exists to correct orientation after the ports are removed and the stoma is retrieved.
- Mentoring is helpful in reducing overall operative time and open conversions during early experience.
- Sepsis is the most common cause of complications following intracorporeal urinary diversion.
- Return of continence and return of sexual function remain the most significant functional outcomes related to the intracorporeal neobladder.
- Readmission rates, blood transfusions, and gastrointestinal-related complications are significantly lower in the intracorporeal group.
- Reoperation rates are noted to be higher in the intracorporeal group.

FUTURE DIRECTION

After the safe inclusion of RARC and lymph node dissection in our armamentarium, urinary diversion is now being performed worldwide. The biggest technical challenges of pelvic reconstruction with conventional laparoscopy have been suturing and the ability to maneuver in narrow spaces. The depth of image with three-dimensional magnification and the ability of the EndoWrist to assist with intracorporeal suturing using the surgical robot have made intracorporeal urinary diversion possible in a safe and time-sensitive fashion.

Randomized controlled trials are ideal for safety and functional outcomes; they are meanwhile supplemented, however, with standardized registry-based outcomes. A permanent place for intracorporeal urinary diversion in urologic surgery will depend not only on optimal operative times but also on a reduction in morbidity and a quicker return of quality of life. These parameters have to be properly measured and must demonstrate improvement in comparison to the standards set with open urinary diversion.

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Injuries of the External Genitalia

Bladder Injuries

Urethral Injuries

The lower urinary tract may sustain injury through a wide variety of mechanisms. Although rarely life-threatening, mismanagement of these injuries can lead to considerable long-term morbidity. Optimal outcomes can be achieved by employing appropriate imaging and identifying the best timing and approach for intervention.

In the acute setting, it is important to distinguish between scenarios when immediate reconstruction is appropriate, such as testicular rupture, and when reconstruction is best delayed, such as pelvic fracture urethral injury. Appropriate management at the time of injury also facilitates delayed reconstruction—placement of a large-bore suprapubic tube at the midline for urethral injury makes delayed posterior urethroplasty easier to perform.

Improved technology and wider availability have made imaging more useful in lower urinary tract trauma, allowing for prompt and accurate diagnosis of injury. Better localization of the site of injury also allows the surgeon to select more direct or minimally invasive approaches for repair. Ultrasonography is routinely performed for scrotal trauma and is being performed more widely for diagnosis of penile fracture. Penile fracture localized to the ventral surface of the corpora can be repaired via a penoscrotal incision with excellent exposure. High-resolution computed tomography (CT) cystography can pinpoint the site of bladder rupture, making laparoscopic repair an excellent option. Retrograde urethrography can diagnose pelvic fracture urethral injury and differentiate between injuries where primary realignment is feasible and where suprapubic tube placement is the better alternative.

INJURIES OF THE EXTERNAL GENITALIA

Penis

Traumatic injuries to the genitalia are uncommon, in part because of the mobility of the penis and scrotum. Blunt phallic traumatic injury is usually of concern only with an erect penis, when fracture of the tunica albuginea may result. In general, prompt surgical reconstruction of most penile injuries usually leads to adequate and acceptable cosmetic and functional results.

Fracture

Etiology. Penile fracture is the disruption of the tunica albuginea with rupture of the corpus cavernosum. Fracture typically occurs during vigorous sexual intercourse, when the rigid penis slips out of the vagina and strikes the perineum or pubic bone, producing a buckling injury.

The tunica albuginea is a bilaminar structure (inner circular, outer longitudinal) composed of collagen and elastin. The outer layer determines the strength and thickness of the tunica, which

varies in different locations along the shaft and is thinnest ventrolaterally (Hsu et al, 1994; Brock et al, 1997). The tensile strength of the tunica albuginea is remarkable, resisting rupture until intracavernous pressures increase to more than 1500 mm Hg (Bitsch et al, 1990). When the erect penis bends abnormally, the abrupt increase in intracavernosal pressure exceeds the tensile strength of the tunica albuginea, and a transverse laceration of the proximal shaft usually results.

Although penile fracture has been reported most commonly with sexual intercourse, it also has been described with masturbation, rolling over or falling onto the erect penis, and other scenarios (Al Ansari et al, 2013). Penile fracture may occur more frequently in “stressful situations” such as extramarital sex (Kramer, 2011). In the Middle East, self-inflicted fractures predominate owing to the practice of taqaandan, in which the erect penis is forcibly bent during masturbation or as a means to achieve rapid detumescence (Zargooshi, 2009).

Mydlo (2001) reported that 94% of fractures in Philadelphia, Pennsylvania, were a result of sexual intercourse; Zargooshi (2009) described 76% of fractures in Kermanshah, Iran, as being due to self-manipulation. The tunical tear is usually transverse and 1 to 2 cm in length (Asgari et al, 1996; Mydlo, 2001). The injury is usually unilateral, although tears in both corporeal bodies occur in 10% of injuries (Mydlo, 2001; El-Taheer et al, 2004). Bilateral corporeal injuries are more commonly associated with urethral injury (Koifman et al, 2010). Although the site of rupture can occur anywhere along the penile shaft, most fractures are distal to the suspensory ligament. Injuries associated with coitus are usually ventral or lateral (Mydlo, 2001; Lee et al, 2007), where the tunica albuginea is the thinnest (Hsu et al, 1994).

Diagnosis and Imaging. The diagnosis of penile fracture is often straightforward and can be made reliably by history and physical examination. Patients usually describe a cracking or popping sound as the tunica tears, followed by pain, rapid detumescence, and discoloration and swelling of the penile shaft. If Buck fascia remains intact, the penile hematoma remains contained between the skin and tunica, resulting in a typical “eggplant deformity.” If Buck fascia is disrupted, hematoma can extend to the scrotum, perineum, and suprapubic regions (Fig. 101-1 on the Expert Consult website). The swollen, ecchymotic phallus often deviates to the side opposite the tunical tear because of hematoma and mass effect. The fracture line in the tunica albuginea may be palpable. Because fear and embarrassment are common, the patient’s presentation to the emergency department or clinic is sometimes significantly delayed.

The incidence of urethral injury is significantly higher in the United States and Europe (20%) than in Asia, the Middle East, and the Mediterranean region (3%), probably owing to the different etiology—intercourse trauma versus self-inflicted injury (Eke, 2002;



Figure 101-1. Eggplant deformity—the classic appearance of a penile fracture sustained during intercourse, with hematoma of the penile shaft and ecchymosis extending into the scrotum.

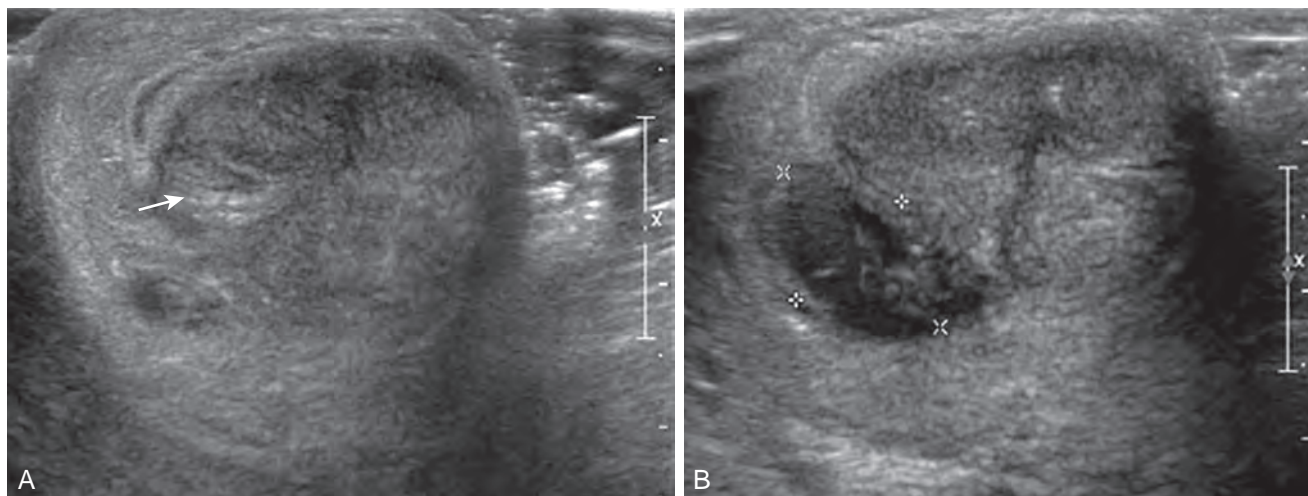


Figure 101-3. A, Ultrasound examination demonstrates ruptured tunica albuginea (arrow) in a patient with a suspected penile fracture. B, Hematoma adjacent to ruptured tunica.

Zargooshi, 2009; Jack et al, 2004; Derouiche et al, 2008). Most urethral injuries are associated with gross hematuria, blood at the meatus (Fig. 101-2 on the Expert Consult website), or inability to void, although the absence of these findings does not definitively rule out urethral injury (Tsang and Demby, 1992; Mydlo, 2001; Jack et al, 2004; Koifman et al, 2010). Given that urethral injury occurs frequently, preoperative urethrography should be considered when urethral injury is suspected. However, because urethrography can be time-consuming and inaccurate (Kamdar et al, 2008), intraoperative flexible cystoscopy is now often performed routinely just before catheter placement at the time of penile exploration when urethral injury is suspected.

The typical history and clinical presentation of penile fracture usually make adjunctive imaging studies unnecessary. However, when the history and physical examination are equivocal for penile fracture, ultrasonography can establish the diagnosis (Koifman et al, 2010). Ultrasonography (Fig. 101-3) has become the preferred imaging study to evaluate for penile fracture because it is rapid, readily available, noninvasive, inexpensive, and accurate. Penile ultrasound is most useful for ruling out fracture in patients with low clinical suspicion or to identify the location of the tear, potentially guiding the choice of incision (El-Assmy et al, 2011).

Magnetic resonance imaging (MRI) has been reported to be a noninvasive and accurate alternative means of demonstrating disruption of the tunica albuginea (Fedel et al, 1996; Uder et al, 2002). However, because of the expense, limited availability, and time requirements involved, MRI has not been employed widely for the evaluation of patients with symptoms and physical findings suggestive of penile fracture. Cavemosography is discouraged in the evaluation of a suspected penile fracture because it is time-consuming and unfamiliar to most urologists and radiologists (Beysel et al, 2002; Morey et al, 2004).

False fracture has been reported in patients who present with penile swelling and ecchymosis, and some even describe the classic "snap-pop" or rapid detumescence typically associated with fracture (Feki et al, 2007). Physical examination may be inadequate for definitive diagnosis of a corporeal tear in these circumstances (Shah et al, 2003). Surgical exploration (Fig. 101-4 on the Expert Consult website) or evaluation with MRI should be considered (El-Assmy et al, 2010). Another condition that may mimic penile fracture is rupture of the dorsal penile artery or vein during sexual intercourse (Armenakas et al, 2001; Bar-Yosef et al, 2007).

Management. Multiple contemporary publications recommend that suspected penile fractures be promptly explored and surgically repaired. Because most penile fractures occur ventrally or laterally, a ventral vertical penoscrotal incision is usually pre-



Figure 101-5. Surgical exploration through a ventral vertical incision showing excellent exposure of the site of the tunical tear and associated urethral injury.

ferred for direct exposure to the fracture (Fig. 101-5) (Mazaris et al, 2009). Alternatively, small lateral incisions may be used for localized hematomas or palpable tunical defects (El-Bahnasawy and Gomha, 2000; Nasser and Mostafa, 2008). The distal circumcising incision may be appropriate when the location of the fracture is uncertain because it provides exposure to all three penile compartments. Closure of the tunical defect with interrupted 2-0 or 3-0 absorbable sutures is recommended; deep corporeal vascular ligation and excessive debridement of the delicate underlying erectile tissue should be avoided.

Induction of an artificial erection with saline or colored dye may aid in locating the corporeal laceration (Shaer, 2006). Partial urethral injuries should be oversewn with fine absorbable suture over a urethral catheter. Complete urethral injuries should be debrided, mobilized, and repaired in a tension-free fashion over a catheter (Fig. 101-6). Therapy with broad-spectrum antibiotics and 1 month of sexual abstinence are recommended. In uncircumcised patients, the distal circumcising incision may place the distal prepuce at risk for ischemia. Although a ventral vertical incision is preferred, if a distal circumcising incision is required, performing limited circumcising at the conclusion of the repair should be strongly considered.

Outcome and Complications. Surgical reconstruction results in faster recovery, decreased morbidity, lower complication rates, and

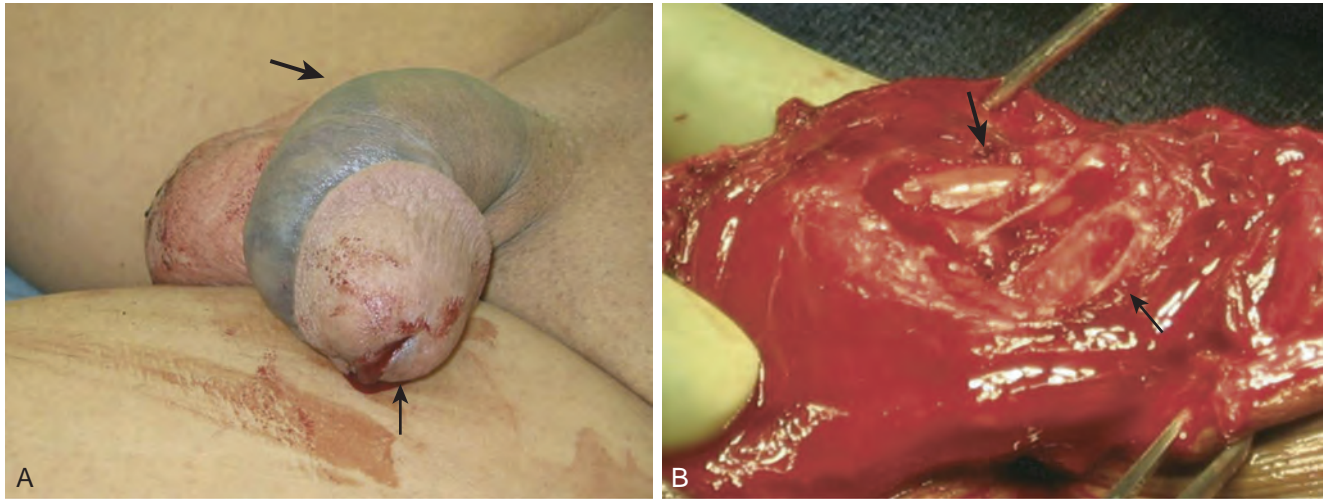


Figure 101-2. A, Large arrow indicates pronounced ecchymosis and swelling in this patient with a penile fracture sustained during intercourse. Small arrow indicates blood at the urethral meatus. B, During surgical exploration and repair, urethral laceration with an exposed Foley catheter is noted (large arrow). Small arrow indicates laceration of corpus cavernosum.



Figure 101-4. Transverse laceration of left corpus cavernosum (arrow) associated with penile fracture, successfully repaired through a circumcision incision.

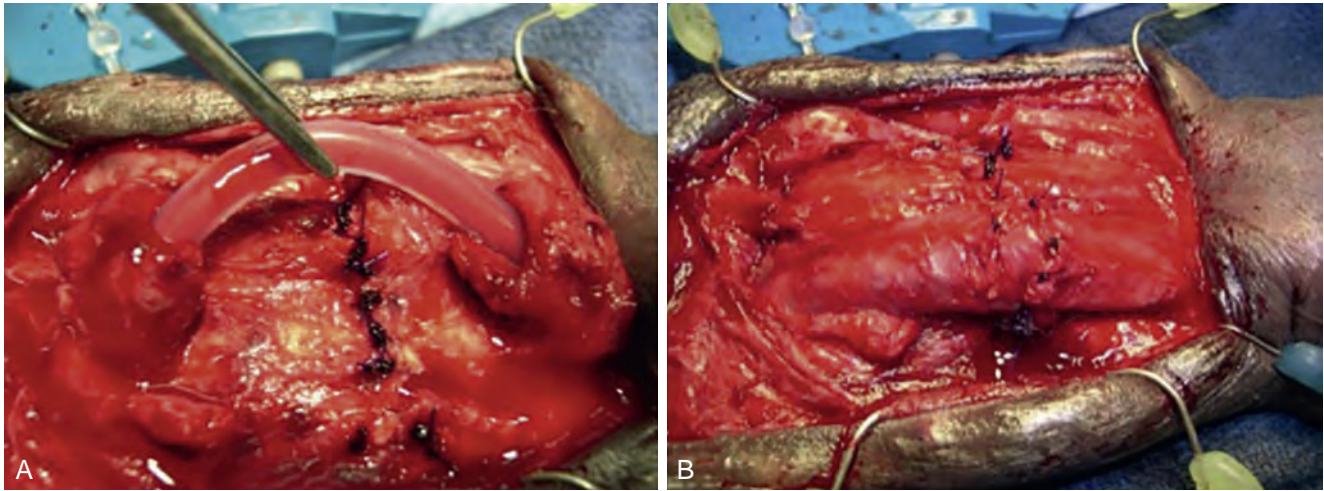


Figure 101-6. A, Completely transected urethra secondary to penile fracture. Repair of bilateral tunical rupture was performed previously. B, Anastomotic repair of the urethra.

lower incidence of long-term penile curvature (Nicolaisen et al, 1983; Orvis and McAninch, 1989; Hinev, 2002; El-Taher et al, 2004; Muentener et al, 2004). Although repair results in penile curvature in less than 5% of patients (El Atat et al, 2008), conservative management of penile fracture has been associated with penile curvature in more than 10% of patients, abscess or debilitating plaques in 25% to 30%, and significantly longer hospitalization times and recovery (Meares, 1971; Nicolaisen et al, 1983; Kalash and Young, 1984; Orvis and McAninch, 1989). Zargooshi (2009) reported in a surgical series of 352 patients that surgical management of penile fractures resulted in erectile function in nearly all patients. Although surgery is better than conservative management, surgical delay of up to 7 days after the time of injury does not adversely affect the results of repair (El-Assmy et al, 2011; Kozacioglu et al, 2011).

Gunshot and Penetrating Injuries

Gunshot Wounds. Most penetrating wounds to the genitalia are due to gunshots (Mohr et al, 2003; Phonsombat et al, 2008; Bjurlin et al, 2013), and most require surgical exploration. Treatment principles include immediate exploration, copious irrigation, excision of foreign matter, antibiotic prophylaxis, and surgical closure. Gunshot injuries to the phallus are rarely isolated wounds—nearly all victims have significant associated injuries, including abdominal, pelvic, lower extremity, vascular, or additional genitourinary injuries (Bandi and Santucci, 2004; Kunkle et al, 2008; Najibi et al, 2010). Excellent cosmetic and functional outcomes can be expected with immediate reconstruction (Gomez et al, 1993; Cavalcanti et al, 2006). An artificial erection may be induced to ensure penile straightness, and plication techniques may be used to correct any curvature resulting from closure of a large corporeal injury (Kunkle et al, 2008).

Urethral injuries have been reported in 15% to 50% of penile gunshot wounds (Miles et al, 1990; Goldman et al, 1996; Mohr et al, 2003; Cinman et al, 2013). Retrograde urethrography should be strongly considered in any patient with penetrating injury to the penis, especially with high-velocity missile injuries, blood at the meatus, or difficulty voiding and when the trajectory of the bullet was near the urethra (Goldman et al, 1996; Mohr et al, 2003; Bandi and Santucci, 2004; Phonsombat et al, 2008; Cerwinka and Block, 2009). Alternatively, intraoperative retrograde urethral injection of methylene blue or indigo carmine may identify the site of injury and the adequacy of closure. If a catheter has already been placed, pericatheter injection may help to ascertain urethral integrity.

Urethral injuries resulting from penetrating trauma should be closed primarily by use of standard urethroplasty principles

whenever possible—excellent results have been reported (Miles et al, 1990; Bandi and Santucci, 2004). Patients with urethral injury and extensive tissue damage from high-velocity weapons or close-range shotgun blasts may require staged repair and suprapubic urinary diversion (Bandi and Santucci, 2004), especially injuries located in the penile urethra (Cavalcanti et al, 2006).

Animal and Human Bites. The morbidity of animal bites is directly related to the severity of the initial wound. Most victims are boys, and dog bites are the most common injury (Gomes et al, 2001; Van der Horst et al, 2004). Infectious complications are unusual because treatment is sought early. Initial management of dog bites includes copious irrigation, debridement, and immediate primary closure along with prophylactic use of broad-spectrum antibiotic (Wolf et al, 1993; Cummings and Boullier, 2000; Bertozzi et al, 2009). Tetanus and rabies immunizations should be used as appropriate. Because of the risk of polymicrobial infection and the antimicrobial susceptibilities of typical organisms, recommended empirical antimicrobial therapy choices include a β -lactam antibiotic with a β -lactamase inhibitor (i.e., amoxicillin-clavulanic acid), a second-generation cephalosporin with anaerobic efficacy (i.e., cefoxitin, cefotetan), or clindamycin with a fluoroquinolone (Talan et al, 1999).

Human bites produce contaminated wounds that often should not be closed primarily. Most individuals with human bite injuries seek medical attention after a substantial delay and are more likely to present with gross infection. Empirical antibiotic administration is warranted with amoxicillin/clavulanic acid or moxifloxacin (Talan et al, 2003).

Amputation

Traumatic amputation of the penis, although rare, is usually the result of genital self-mutilation. Psychosis is present in 65% to 87% of patients performing genital self-mutilation (Greilshheimer and Groves, 1979; Aboseif et al, 1993; Romilly and Isaac, 1996). Psychiatric consultation should be sought in all such cases.

Reconstruction of the urethra and reanastomosis of the corporeal bodies with microsurgical repair of dorsal penile vessels and nerves achieves remarkably good results. Patients should be transferred to a facility with microsurgical capabilities; however, if such a facility is unavailable, macroscopic anastomosis of the urethra and corporeal bodies can be performed with good erectile results, albeit with potential compromise of sensation and skin loss (Bhanganada et al, 1983; Razzaghi et al, 2009). Every attempt should be made to locate, clean, and preserve the severed portion in a “double bag” technique. The distal penis should be rinsed in saline solution, wrapped in saline-soaked gauze, and sealed in a

sterile plastic bag, and the bag should be placed into an outer bag with ice or slush (Jeziar et al, 2001). Hypothermic injury to the amputated segment can occur if it is in direct contact with ice for a prolonged period. Successful reimplantation is possible after 16 hours of cold ischemia time or 6 hours of warm ischemia (Lowe et al, 1991). If the severed part is unavailable, the penile stump should be formalized by closing the corpora and spatulating the urethral neomeatus, similar to a partial penectomy procedure for malignant disease.

Microvascular reconstruction of the dorsal arteries, vein, and nerves is the preferred method of repair for an amputated penis. Adequate erectile function is possible with microvascular reanastomosis and macroscopic replantation, with more than 50% of men able to achieve erection with either technique (Bhanganada et al, 1983; Lowe et al, 1991; Aboseif et al, 1993). However, complications such as urethral strictures, skin loss, and sensory abnormalities all are less common with microvascular repair (Jeziar et al, 2001).

Normal penile sensation returns in 0% to 10% of patients after macroscopic replantation (Bhanganada et al, 1983; Lowe et al, 1991), whereas sensation is present in more than 80% of patients with microscopic replantations (Jordan and Gilbert, 1989; Lowe et al, 1991; Jeziar et al, 2001). Penile skin necrosis, sometimes complete, is often a troublesome problem, although it is less common with microsurgical repair. This is because the blood supply of the skin is independent of the corporeal bodies and because without repair of the superficial vascular structures, the penile skin is essentially a free graft (Jeziar et al, 2001). Split-thickness skin grafts are applied when the native skin becomes necrotic (Ozturk et al, 2009). An alternative strategy is to denude the phallus of all skin and bury it in the scrotum, leaving the glans exposed, followed by separation of the structures after 2 months (Bhanganada et al, 1983; Jordan and Gilbert, 1989). Adjuvant techniques after penile replantation include the use of hyperbaric oxygen to promote healing (Landström et al, 2004; Zhong et al, 2007) or medical leeches on the penis after macroreplantation to augment venous outflow and decrease edema (Mineo et al, 2004).

KEY POINTS: STEP-BY-STEP APPROACH TO PENILE REATTACHMENT

- Suprapubic cystostomy
- Closure of the tunica albuginea with 3-0 absorbable suture
- Two-layer urethral closure over a catheter with fine absorbable suture
- Minimal dissection along the neurovascular bundle to identify severed vessels and nerves
- Microscopic anastomosis of the dorsal artery with 11-0 nylon
- Microscopic dorsal vein repair with 9-0 nylon
- Microscopic epineural repair of dorsal nerve with 10-0 nylon
- Skin coverage

Zipper Injuries

Zipper injuries to the penis more often happen to impatient boys or intoxicated men. Multiple maneuvers are available to free the entrapped skin and to remove the mechanism. After a penile block, the zipper slider and adjacent skin can be lubricated with mineral oil, followed by a single attempt to unzip and untangle the skin (Kanegaye and Schonfeld, 1993; Mydlo, 2000). The cloth material connected to the zipper can be incised with perpendicular cuts in between each zipper tooth to release the lateral support of the zipper, allowing the device to fall apart and release the trapped skin (Oosterlinck, 1981). A bone cutter or similar tool can be used to cut the median bar (diamond-shaped connection) of the slider. This maneuver allows separation of the upper and lower shields of the slider, and the entire zipper falls apart (Flowerdew et al, 1977; Saraf

and Rabinowitz, 1982). Also, a screwdriver may be placed between the upper and lower shields of the slider, and a twisting action separates the two shields from the median bar and unravels the zipper (Raveenthiran, 2007). Another technique involves cutting the anterior shield with a wire cutter (Maurice and Cherullo, 2013). Some children may require more than local anesthesia or sedation; circumcision or an elliptical skin excision can be performed in the operating room under anesthesia (Yip et al, 1989; Mydlo, 2000).

Strangulation Injuries

Accidental injuries with thread, hair, or rubber bands occur in children, but child abuse must be considered in such cases. Any child with unexplained penile swelling, erythema, or difficulty voiding should be examined closely for a hidden strangulating hair or string. Adults may place objects around the shaft as a means of sexual pleasure or to prolong an erection. The constricting device can reduce blood flow, cause edema, and induce ischemia; gangrene and urethral injury may develop in delayed presentations. Emergent treatment requires decompression of the constricted penis to allow blood flow and micturition. Depending on the constricting device, significant resourcefulness may be required of the physician.

String, hair, and rubber bands can be incised. Initial attempts to remove a solid constricting device causing penile strangulation involve lubrication of the shaft and foreign body and attempted direct removal. Edema distal to the strangulation often makes removal difficult. A string or latex tourniquet can be wrapped around the distal shaft to decrease swelling and to improve the odds of removing the device with lubrication. If the constricting object cannot be severed or removed, a string technique should be considered (Browning and Reed, 1969; Vahasarja et al, 1993; Noh et al, 2004). A thick silk suture or umbilical tape is passed proximally under the strangulation object and wound tightly around the penis distally toward the glans. The tag of suture or tape proximal to the ring is grasped; unwinding from the proximal end pushes the object distally. Glanular puncture with a needle or blade allows escape of dark trapped blood and improves the odds of removing the object with the string method (Browning and Reed, 1969; Noh et al, 2004).

Plastic constricting devices can be incised with a scalpel or an oscillating cast saw (Pannek and Martin, 2003), but metal objects present a more difficult challenge. Readily available hospital equipment (ring cutters, bolt cutters, dental drills, commercially available rotary tools, orthopedic and neurosurgical operative drills) may be inadequate to cut through heavy iron or steel items. The use of industrial drills, steel saws, hacksaws, saber saws, and high-speed electric drills has been reported (Perabo et al, 2002; Santucci et al, 2004). Occasionally, fire department and emergency medical services equipment may be required to cut through iron and steel rings. The phallus should be protected from thermal injury, sparks, and the cutting blade by use of tongue depressors, sponges, or malleable retractors; continuous saline irrigation may be used for cooling. Such elaborate undertakings are best accomplished in the operating room under anesthesia. If decompression is delayed and the patient is distended and unable to void, a suprapubic bladder catheter should be placed. Outcomes are generally good with device removal alone, although the surgeon should be prepared to consider reconstructive techniques such as skin grafting if the strangulation injury causes skin necrosis (Ivanovski et al, 2007).

Testis

Etiology. Although the testis is relatively protected by the mobility of the scrotum, reflexive cremasteric muscle contraction, and the tough fibrous tunica albuginea, blunt injury (usually the result of assault, sports-related events, and motor vehicle accidents) can result in rupture of the tunica albuginea, contusion, hematoma, dislocation, or torsion of the testis. Testicular injury results from blunt trauma in about 75% of cases (McAninch et al, 1984; Cass and Luxenberg, 1991), whereas penetrating injuries secondary to firearms, explosions, or impalement account for the remaining cases.

Although only 1.5% of blunt testis injury involves both gonads, about 30% of penetrating scrotal trauma results in bilateral injury (Cass and Luxenberg, 1988, 1991). Similar to penetrating urethral injuries, penetrating scrotal trauma (roughly 80%) usually involves neighboring structures, including the thigh, penis, perineum, bladder, urethra, or femoral vessels (Gomez et al, 1993; Cline et al, 1998; Simhan et al, 2012). In contemporary military conflicts, genital wounds account for a larger percentage of urologic injuries because of the powerful explosive weapons involved and absence of protective body armor over the genitalia (Thompson et al, 1998; Waxman et al, 2009). Blast injuries are typically associated with extensive scrotal skin loss, multiple projectile injuries of both testes, and concomitant extensive destruction of the lower extremities and abdomen.

Diagnosis. Rupture of the testis must be considered in all cases of blunt scrotal trauma. Most patients complain of exquisite scrotal pain and nausea. Swelling and ecchymosis are variable, and the degree of hematoma may not correlate with the severity of testicular injury; absence does not entirely rule out testicular rupture, and contusion without fracture can manifest as significant bleeding. Scrotal hemorrhage and hematocele along with tenderness to palpation often limit a complete physical examination. Concomitant urethral injury should be suspected and evaluated when examination reveals blood at the meatus or if the mechanism of injury or hematuria suggests this possibility. Penetrating injuries mandate careful examination of surrounding structures, especially the femoral vessels.

Ultrasonography can be helpful to assess the integrity and vascularity of the testis in equivocal cases. Ultrasonography is rapid, readily available, and noninvasive. Because it may be operator dependent, false-positive and false-negative studies range from 56% to 94% (Fournier et al, 1989; Corrales et al, 1993; Herbener, 1996; Dreitlein et al, 2001). Ultrasound findings suggestive of testicular fracture include a heterogeneous echo pattern of the testicular parenchyma and disruption of the tunica albuginea (Fig. 101-7) (Micallef et al, 2001; Buckley and McAninch, 2006). Although ultrasonography may assist in detection of testicular fracture or hematoma (Guichard et al, 2008), a normal or equivocal ultrasound study should not delay surgical exploration when physical examination findings suggest testicular damage; definitive diagnosis is often made in the operating room. Although MRI may effectively demonstrate testicular integrity, its widespread use is not the norm because of expense, limited availability, and potential delay in definitive surgical care of the patient (Serra et al, 1998; Muglia et al, 2002; Kim et al, 2009).

Differential diagnosis of testicular fracture includes hematocele without rupture, torsion of the testis or an appendage, reactive

hydrocele, hematoma of the epididymis or spermatic cord, and intratesticular hematoma. A nonpalpable testis in a trauma patient should raise the possibility of dislocation outside the scrotum. This entity usually occurs after motorcycle crashes when extreme forces on the scrotum expel the testis into surrounding tissues such as the superficial inguinal pouch (50%) or to a pubic, penile, pelvic, abdominal, or perineal location (Schwartz and Faerber, 1994; Bromberg et al, 2003). Bilateral dislocation after trauma has been reported (Bromberg et al, 2003; O'Brien et al, 2004). Manual or surgical reduction of the displaced testis is indicated. Finally, approximately 5% of spermatic cord torsions are believed to be precipitated by trauma; torsion should be considered in all cases of significant scrotal pain without signs or symptoms of major scrotal trauma (Elsaharty et al, 1984; Manson, 1989; Lrhorfi et al, 2002).

Management. Early exploration and repair of testicular injury is associated with increased testicular salvage, reduced convalescence and disability, faster return to normal activities, and preservation of fertility and hormonal function (Kukadia et al, 1996). Minor scrotal injuries without testicular damage can be managed with ice, elevation, analgesics, and irrigation and closure in some circumstances.

The objectives of surgical exploration and repair are testicular salvage, prevention of infection, control of bleeding, and reduced convalescence. Transverse scrotal incision is preferable in most cases. The tunica albuginea should be closed with small absorbable sutures after removal of necrotic and extruded seminiferous tubules. Even small defects in the tunica albuginea should be closed because progressive swelling and intratesticular pressure can continue to extrude seminiferous tubules. Every attempt to salvage the testis should be performed; loss of capsule tissue may require removal of additional parenchyma to allow closure of the remaining tunica albuginea. A flap or graft of tunica vaginalis may be used to cover a large defect in the tunica albuginea in an otherwise salvageable testis (Fig. 101-8); synthetic grafts are not recommended for this purpose (Ferguson and Brandes, 2007). Significant intratesticular hematomas should be explored and drained even in the absence of testicular rupture to prevent progressive pressure necrosis and atrophy, delayed exploration (40%), and orchiectomy (15%) (Cass and Luxenberg, 1988). Significant hematoceles should also be explored, regardless of imaging studies, because up to 80% are caused by testicular rupture (Vaccaro et al, 1986; Buckley and McAninch, 2006).

Penetrating scrotal injuries should be surgically explored to inspect for vascular and vasal injury; the same principles of salvage, hemostasis, and reconstruction apply as in blunt trauma. The vas deferens is injured in 7% to 9% of scrotal gunshot wounds (Gomez et al, 1993; Brandes et al, 1995). The injured vas should be ligated with nonabsorbable suture, and delayed reconstruction should be performed if necessary. Approximately 30% of gunshot wounds injure both testes, and exploration of the contralateral testis should be considered, depending on the findings of physical examination and the path of the projectile.

Outcome and Complications. Nonoperative management of testicular rupture is frequently complicated by infection, atrophy, necrosis, chronic unrelenting pain, and delayed orchiectomy. Testicular salvage rates exceed 90% with exploration and repair within 3 days of injury (Del Villar et al, 1973; Schuster, 1982; Fournier et al, 1989; Cass and Luxenberg, 1991) versus orchiectomy rates threefold to eightfold higher with conservative management and delayed surgery (Cass and Luxenberg, 1991). Testicular salvage rates with conservative management are 33%, with delayed orchiectomy rates between 21% and 55% (Schuster, 1982; Cass and Luxenberg, 1991; McAleer and Kaplan, 1995). Approximately 45% of patients initially managed conservatively ultimately undergo surgical exploration for pain, infection, and persistent hematoma (Del Villar et al, 1973; Cass and Luxenberg, 1991). Convalescence and time of return to normal activities are significantly reduced after early surgical repair.

In contrast to blunt testis rupture, for which salvage rates are very high, penetrating testicular trauma has historically been associated with gonad salvage in only 32% to 65% of cases (Bickel et al, 1990;

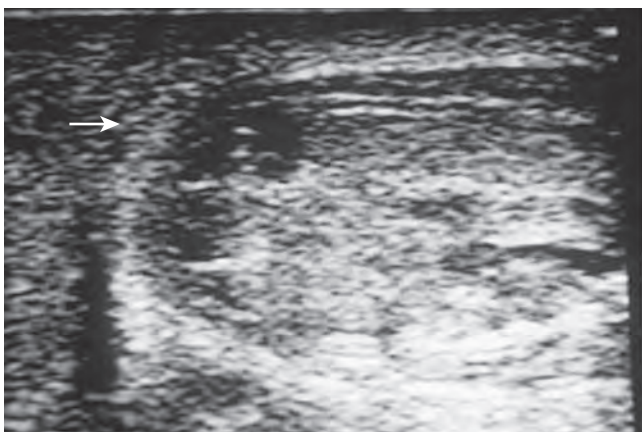


Figure 101-7. Ultrasound examination demonstrates hypoechoic intratesticular areas (arrow) consistent with testicular rupture sustained by blunt trauma. Scrotal exploration revealed large hematocele and exposed seminiferous tubules.

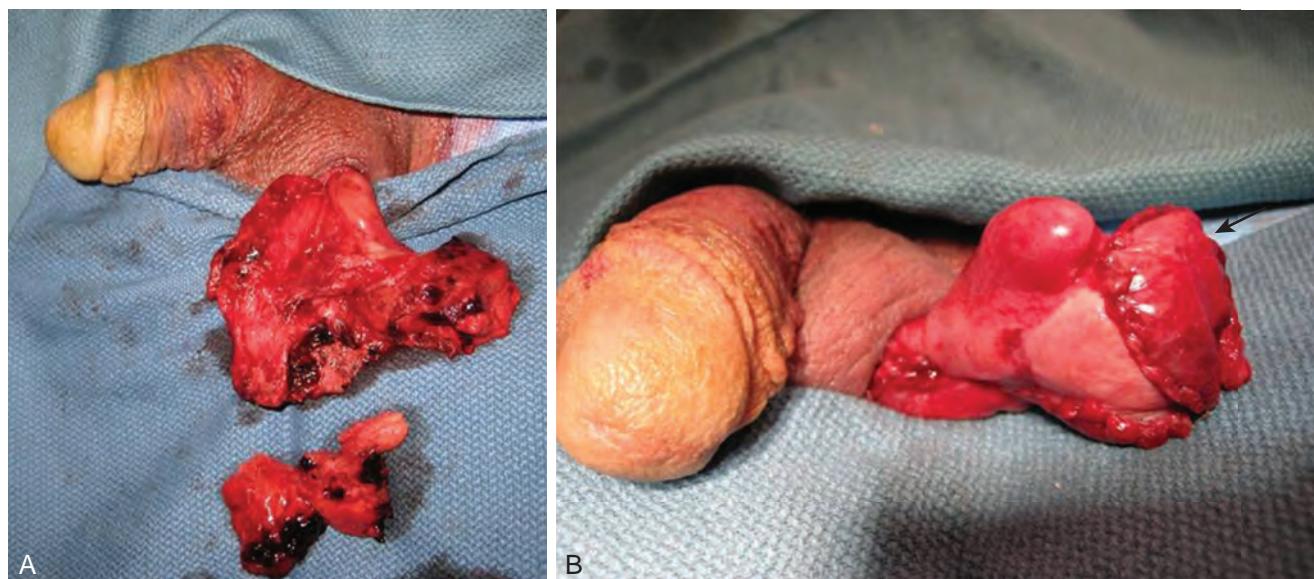


Figure 101-8. A, Testicular rupture after blunt trauma. B, Reconstructed testis after debridement and closure. Arrow indicates placement of a tunica vaginalis graft.

Gomez et al, 1993; Brandes et al, 1995; Cline et al, 1998). Improved salvage rates of 75% have been reported in more recent civilian (Phonsombat et al, 2008; Simhan et al, 2012; Bjurlin, 2013) and combat series (Waxman et al, 2009). Most surgical patients have adequate preservation of hormonal and fertility function (Kukadia et al, 1996). Sperm production has been documented in men with appropriately repaired bilateral testis rupture and bilateral penetrating injuries (Pohl et al, 1968; Brandes et al, 1995).

Urologists may be consulted for opinion and guidance with regard to boys with a solitary testis who play a contact sport. Testicular injuries are exceedingly rare in boys involved in individual or team contact sports and recreational activities (McAleer et al, 2002; Wan et al, 2003a, 2003b). Parents should be appropriately counseled, and a protective cup device should be recommended. The American Academy of Pediatrics Committee on Sports Medicine and Fitness recommended that many factors be considered regarding whether to allow a child with a solitary testis to play sports; their recommendation was an unqualified yes in this circumstance (Committee on Sports Medicine and Fitness, 2001).

Genital Skin Loss

Etiology. Necrotizing gangrene secondary to polymicrobial infection in the genital area, or Fournier gangrene, is the most common cause of extensive genital skin loss (McAninch et al, 1984). Skin loss is iatrogenic, caused by the necessity for acute debridement of necrotic genital skin when the patient is seen initially.

Penile skin loss can result from traction by mechanical devices, such as farm or industrial machinery, or by suction devices, such as vacuum cleaners. Because the superficial penile tissue is loose areolar tissue, it is often torn free without damage to the underlying structures. Significant scrotal skin loss resulting from penetrating trauma is uncommon, but it has been seen more recently in battlefield explosive injuries (Fig. 101-9).

Penile burns, although rare, are often full-thickness burns because the penile skin is so thin (Horton and Dean, 1990). Constricting bands placed on the penis can result in significant skin loss, although a more common injury involves direct pressure necrosis under the band, which usually heals well with device removal alone.

Diagnosis and Initial Management. Although both cellulitis and Fournier gangrene are commonly associated with significant genital edema and erythema, skin ischemia is the hallmark of Fournier gangrene. The finding of loss of scrotal rugae is highly



Figure 101-9. Extensive loss of scrotal skin from explosive blast injury. Note numerous concomitant shrapnel injuries to the thigh.

suggestive of tissue necrosis. Scrotal ultrasonography (Kane et al, 1996; Morrison et al, 2005) and CT may reveal subcutaneous air, a helpful indicator of necrotizing infection (Fig. 101-10).

In most cases of Fournier gangrene, multiple debridements of ischemic or frankly necrotic skin are required over a period of several days until active infection is controlled. Wounds are treated with frequent wet-to-dry dressing changes or with vacuum-assisted closure therapy (Czymek et al, 2009) until primary coverage is planned. Inspection at least daily by the surgical team is mandatory. Suprapubic urinary diversion should be strongly considered for extensive injuries to simplify wound care and to prevent urethral

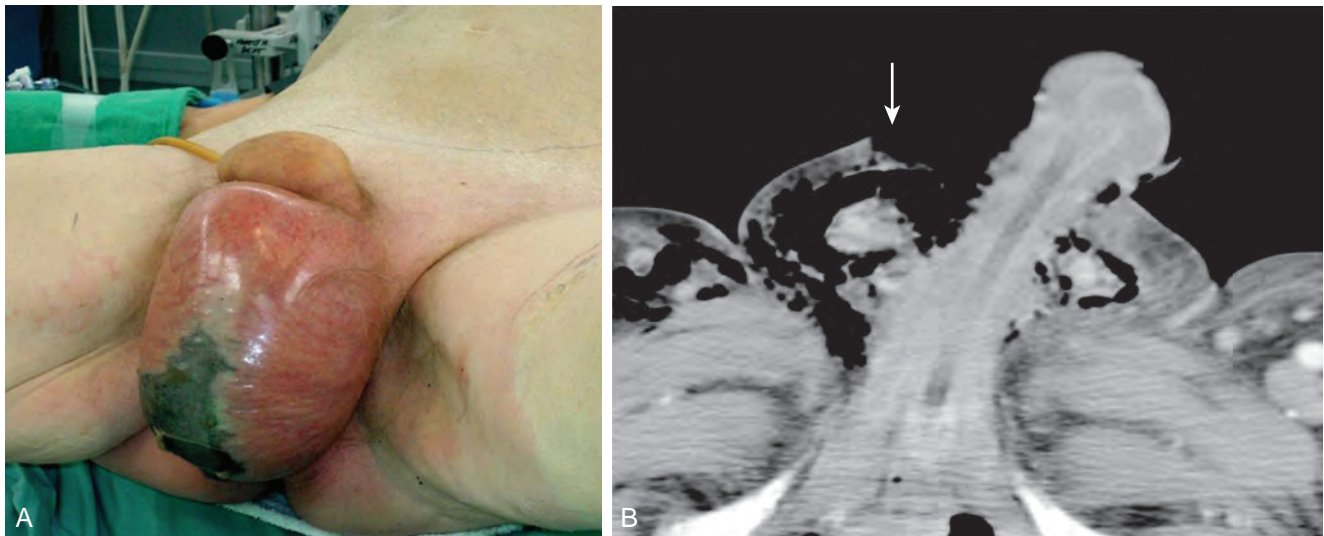


Figure 101-10. A, Large erythematous scrotum with central necrosis suggestive of necrotizing infection. B, Computed tomography scan reveals subcutaneous air in the scrotum (arrow) secondary to Fournier gangrene.

complications related to prolonged catheterization. Hyperbaric oxygen treatment has been advocated as an adjunctive measure to promote wound healing, although we do not recommend this owing to the considerable increased expense and logistical complexity in the absence of proven benefit (Mindrup et al, 2005).

Genital burns are largely treated similar to other burns, with early resection of burn eschar and coverage with split-thickness skin grafts when possible. Partial-thickness skin loss or genital burns may be treated with silver sulfadiazine cream. For deep penile electrical burns, a conservative approach is warranted because the ultimate outcome usually is autopenectomy and/or death as a result of extensive concurrent injuries (Medendorp et al, 2007).

Penile Reconstruction

In selected uncircumcised patients, mobilization of redundant foreskin may allow primary closure of middle to distal penile skin loss (Horton and Dean, 1990). Scrotal rotation flaps can be used for more proximal defects if skin loss is limited, but the hair-bearing nature of scrotal skin risks an unacceptable cosmetic result (Zhao et al, 2009). Local flaps, such as from the abdomen and thigh, also can be used but are cosmetically inferior to split-thickness skin grafts. Skin coverage with avulsed skin should be avoided because it often becomes necrotic.

Thick (0.012- to 0.015-inch), nonmeshed, split-thickness skin grafts (McAninch et al, 1984) are preferred for penile reconstruction. Meshed grafts can be used but have a tendency to contract and are cosmetically inferior to unmeshed grafts. Grafts are usually harvested from the anterior thigh with a pneumatic dermatome. If grafts are to be used, care must be taken to remove any subcoronal skin remaining after debridement. Lymphatic obstruction of this distal foreskin, if it is not excised, results in circumferential lymphedema (McDougal, 2003). Graft stabilization in the immediate postoperative period may be achieved with either a tie-over-bolster technique or with a circumferential vacuum dressing (Weinfeld et al, 2005; Senchenkov et al, 2006). Skin grafts placed on the penile shaft never regain normal sensation (Horton and Dean, 1990), although sexual function is often preserved because of intact sensation in the glans.

Scrotal Reconstruction

Scrotal skin loss defects of up to 50% can often be closed directly. For extensive injuries, the testes may be placed in thigh pouches,

treated with wet dressings, or placed under vacuum pressure dressings until reconstruction (Cummings and Boullier, 2000; Gomes et al, 2001; Cuccia et al, 2009). Thigh pouches are not recommended initially, until the infection is stabilized, because transmission of the infectious process into uninvolved tissues may occur. During scrotal reconstruction, local skin flaps should be mobilized initially to cover as much of the tissue defect as possible (Fig. 101-11 on the Expert Consult website). Meshed split-thickness skin grafts can be employed for remaining reconstruction. In addition to providing an excellent cosmetic result, meshing allows exudate to escape from the interstices, improving graft take. The spermatic cords and testes are sewn together in multiple areas before grafting to prevent a bifid neoscrotum (Tan et al, 2011). The neoscrotum may appear unnaturally tight initially, but after 6 to 12 months the testes eventually occupy a more natural dependent position. Thigh flaps can be used to reconstruct the scrotum when the testes have been buried in the thighs after traumatic or surgical scrotal removal (Morey and McAninch, 1999). Fibrin sealant has proved useful as a tissue glue to promote healing and to reduce drainage during complex genital reconstruction cases (Morris et al, 2006).

KEY POINTS: GENITAL TRAUMA

- Although penile fracture usually can be diagnosed based on history and physical examination, penile ultrasonography is a readily available, inexpensive, rapid, and accurate imaging modality that may be useful to guide clinical management.
- Gunshot wounds to the penis should be repaired primarily to prevent deformity and erectile dysfunction.
- Animal bites should be irrigated, debrided, and closed primarily, whereas most human bites should be left open.
- Blunt scrotal injury can be evaluated by ultrasonography for testicular rupture. Penetrating scrotal injuries should undergo surgical exploration to assess and repair deep tissues and remove contamination.

BLADDER INJURIES

Etiology. The urinary bladder is generally protected from external trauma because of its deep location in the bony pelvis. Most blunt

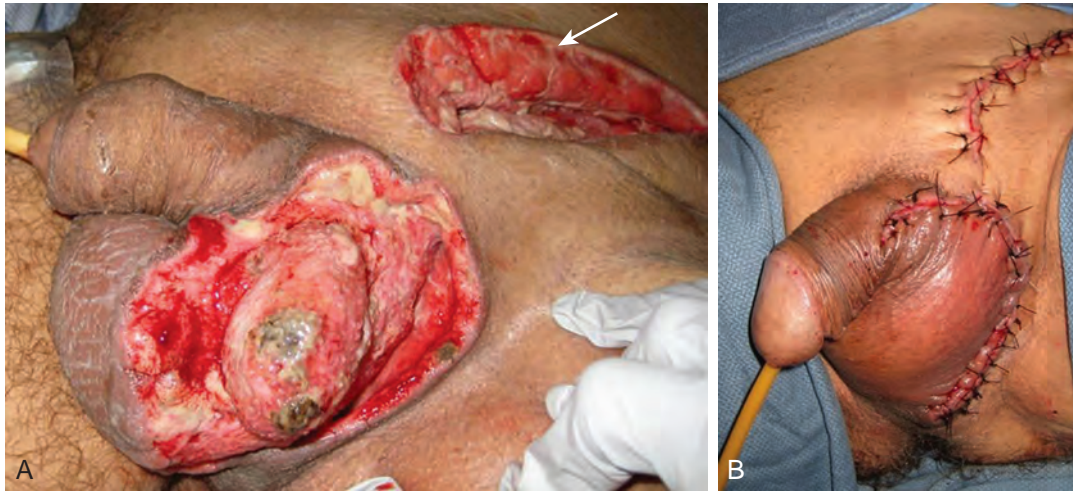


Figure 101-11. A, Scrotal defect before final debridement and closure of left hemiscrotum for Fournier gangrene. Arrow indicates an inguinal counterincision made owing to extension of infection to the inguinal canal. B, Delayed primary closure. The right testis and tunica vaginalis were mobilized off the overlying scrotal tissue, which was then used to close the scrotal defect.

bladder injuries are the result of rapid-deceleration motor vehicle collisions, but many also occur with falls, crush injuries, assault, and blows to the lower abdomen. Disruption of the bony pelvis tends to tear the bladder at its fascial attachments, but bone fragments also can directly lacerate the organ. Other important causes of bladder rupture include penetrating trauma, iatrogenic surgical complications, and spontaneous rupture in patients with a history of neuropathic disease, preexisting bladder disease, or prior urologic surgery.

Bladder injuries that occur with blunt external trauma are rarely isolated injuries—80% to 94% of patients have significant associated nonurologic injuries (Cass, 1984; Volpe et al, 1999; Hsieh et al, 2002; Parry et al, 2003; Bjurlin et al, 2009). Mortality in these patients with multiple injuries is usually related to nonurologic injuries and ranges from 8% to 44% (Carroll and McAninch, 1984; Cass and Luxenberg, 1987; Corriere and Sandler, 1989; Volpe et al, 1999; Alli et al, 2003; Parry et al, 2003). **The most common associated injury is pelvic fracture, which is associated with 83% to 95% of bladder injuries** (Cass, 1989; Corriere and Sandler, 1989; Morey et al, 2001; Parry et al, 2003). Conversely, bladder injury has been reported to occur in only 5% to 10% of pelvic fractures (Cass, 1989; Peters, 1989; Aihara et al, 2002). Sudden force applied to a full bladder may result in a rapid increase in intravesical pressures and lead to rupture without pelvic fracture.

Penetrating bladder trauma also is associated with significant nonurologic injuries and mortality rate. Nearly half of all bladder injuries are iatrogenic (Dobrowolski et al, 2002); **obstetric and gynecologic complications are the most common causes of bladder injuries during open surgery** (Dobrowolski et al, 2002; Gomez et al, 2004).

Diagnosis. Extraperitoneal bladder injury is usually associated with pelvic fracture. Intraperitoneal injuries can be associated with pelvic fracture but are more commonly due to penetrating injuries or burst injuries at the dome by direct blow to a full bladder. Appropriate diagnostic imaging is important because of the marked influence on management.

Clinical Signs and Symptoms. Bladder rupture does not occur as an isolated, asymptomatic event in normal individuals. Conscious patients present with pronounced nonspecific symptoms such as suprapubic pain combined with inability to void. Physical signs include suprapubic tenderness, lower abdominal bruising, muscle guarding and rigidity, and diminished bowel sounds. Associated abdominal and pelvic injuries may mask bladder symptoms. Higher suspicion for bladder injury is similarly warranted in patients who are unresponsive because of intoxication or altered sensorium.

Immediate catheterization should be performed when blunt bladder rupture is suspected because **the most reliable indicator is gross hematuria, which is present in nearly all cases** (Iverson and Morey, 2001; Hsieh et al, 2002; Parry et al, 2003; Gomez et al, 2004). If blood is noted at the meatus or the catheter does not pass easily, retrograde urethrography should be performed first because urethral injuries occur concomitantly in 10% to 29% of patients with bladder rupture (Cass, 1989; Dobrowolski et al, 2002).

Radiographic Imaging. Imaging of the bladder is performed on the basis of clinical suspicion. After blunt external trauma, the absolute indication for immediate cystography is gross hematuria associated with pelvic fracture—approximately 29% of patients presenting with this combination of findings have bladder rupture (Morey et al, 2001). Relative indications for cystography after blunt trauma include gross hematuria without pelvic fracture and microhematuria with pelvic fracture. **The diagnosis of bladder rupture is extremely low in these atypical groups (e.g., 0.6% in patients with pelvic fracture and microhematuria), but the index of suspicion should be raised by associated clinical indicators of bladder injury.** Conversely, penetrating injuries of the buttock, pelvis, or lower abdomen with any degree of hematuria warrant cystography.

Retrograde or stress cystography is nearly 100% accurate for bladder injury if performed appropriately. The bladder should be filled in cooperative and conscious patients to a sense of discomfort

KEY POINTS: CLINICAL INDICATORS OF BLADDER INJURY

- Suprapubic pain or tenderness
- Free intraperitoneal fluid on CT or ultrasound examination
- Inability to void or low urine output
- Clots in urine or clots noted in bladder on CT
- Enlarged scrotum with ecchymosis
- Abdominal distention or ileus

and otherwise to 350 mL. For a plain film technique, three images are obtained: one before administration of a contrast agent, one full-bladder anteroposterior film, and one drainage film. Posterior extravasation of the contrast medium can be missed without a drainage film. Significant bladder distention is required to visualize small tears. False-negative studies have been reported with retrograde instillation of only 250 mL (Peters, 1989; Morey and Carroll, 1997). Although hematuria and mechanism of injury mandate consideration of upper tract imaging studies, upper and lower urinary tract injuries are almost never coincident (0.4%) (Cass and Luxenberg, 1990).

A dense, flame-shaped collection of contrast material in the pelvis is characteristic of extraperitoneal extravasation (Fig. 101-12). Depending on fascial integrity, contrast material may extend beyond the confines of the pelvis and be visualized in the retroperitoneum, scrotum, phallus, thigh, or abdominal wall. The amount of extravasation is not always proportional to the extent of bladder injury. Intraperitoneal extravasation is identified when contrast material outlines loops of bowel and/or the lower lateral portion of the peritoneal cavity.

Because CT is now routinely used to assess trauma patients, concomitant CT cystography is frequently selected as a more efficient means to assess the bladder. CT cystography is as accurate and reliable as plain film cystography in evaluation of suspected bladder injury (Fig. 101-13), as long as the bladder is filled in retrograde fashion with contrast material diluted to 2% to 4% (6:1 with saline) to a volume of 350 mL (Peng et al, 1999; Hsieh et al, 2002). Drainage films are not required after CT cystography because the



Figure 101-12. Plain film cystogram reveals extraperitoneal bladder rupture with extravasation into the scrotum. Surgical exploration revealed anterior bladder neck and prostatic urethral laceration.

retrovesical space can be well visualized with axial images (Morey and Carroll, 1997). Dilution of the contrast material is mandatory because undiluted contrast material is so dense that the CT quality is compromised by scatter artifact. **Clamping the urethral catheter in an attempt to allow antegrade distention of the bladder by intravenous contrast medium is inadequate for diagnosis of bladder rupture—retrograde filling is required.** Conventional abdominal CT of a trauma patient may show findings suggestive of bladder injury, but it is not considered to be adequate for bladder evaluation without retrograde contrast distention (Mee et al, 1987; Udekwe et al, 1996; Hsieh et al, 2002).

Management. The usual treatment of uncomplicated extraperitoneal bladder ruptures, when conditions are ideal, is conservative management with urethral catheter drainage alone (Fig. 101-14). A large-bore (22-Fr) Foley catheter should be used to promote adequate drainage; if output is poor, fluoroscopic cystography should be considered to ensure proper catheter placement. Cystography is necessary to verify complete healing before catheter removal 14 days after injury; occasionally, extravasation may persist

for several additional weeks, but it resolves with continuation of urethral catheter drainage, after which radiographic confirmation of healing is essential. Bone spicules within the bladder wall (Fig. 101-15 on the Expert Consult website) may compromise healing. Antimicrobial agents are instituted on the day of injury and continued for at least 1 week to prevent infection of the pelvic hematoma.

Several authors (Cass, 1989; Kotkin and Koch, 1995) have reported fewer complications, such as fistula, failure to heal, clot retention, and sepsis, with open repair (5% overall) versus conservative management (12% overall). For this reason, blunt extraperitoneal injuries warrant immediate open repair to prevent complications such as fistula, abscess, and prolonged leak in the presence of any complicating features. If a patient whose condition is stable is undergoing exploratory laparotomy for other associated injuries or internal fixation of pelvic fracture, it is prudent to perform surgical repair of the extraperitoneal rupture at the same setting. The anterior bladder wall is entered, and the tear is closed intravesically with absorbable suture. The perivesical pelvic hematoma should not be disturbed. When internal fixation of pelvic fractures is performed, concomitant bladder repair is recommended because urine leakage from the injured bladder onto the orthopedic fixative hardware is prevented, reducing the risk of hardware infection. Drainage of the repaired bladder can be safely accomplished with a large-bore Foley catheter alone, and cystography performed 1 week after repair should verify bladder healing.



Figure 101-13. Computed tomography cystogram demonstrates contrast material surrounding loops of bowel consistent with intraperitoneal bladder rupture.

KEY POINTS: INDICATIONS FOR IMMEDIATE REPAIR OF BLADDER INJURY

- Intraperitoneal injury from external trauma
- Penetrating or iatrogenic nonurologic injury
- Inadequate bladder drainage or clots in urine
- Bladder neck injury
- Rectal or vaginal injury
- Open pelvic fracture
- Pelvic fracture requiring open reduction and internal fixation
- Selected stable patients undergoing laparotomy for other reasons
- Bone fragments projecting into bladder

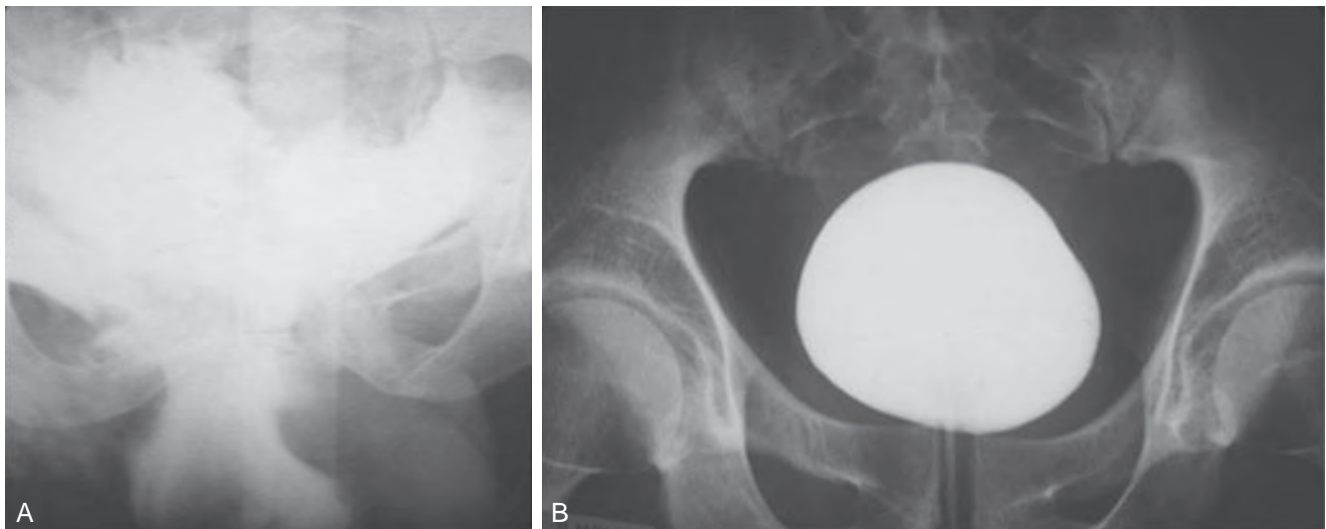


Figure 101-14. A, Dense flame-shaped pattern of contrast extravasation in the pelvis secondary to extraperitoneal bladder rupture. B, Repeat cystogram in the same patient after 2 weeks of catheter drainage shows a completely healed bladder.



Figure 101-15. Computed tomography cystogram of a patient with extraperitoneal bladder rupture after a motor vehicle/pedestrian collision and extensive pelvic fracture. *Arrow* indicates a fragment of bone in the bladder, removed at the time of laparotomy and repair of the bladder.

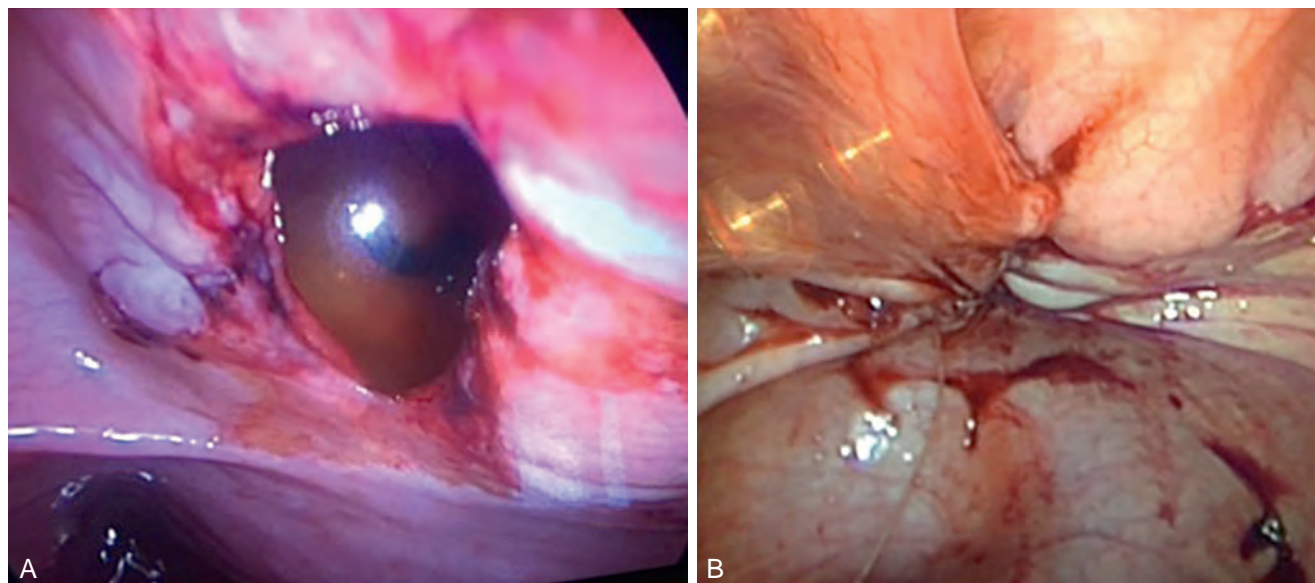


Figure 101-16. A, Intraoperative image of laparoscopic bladder repair, with a flexible cystoscope inside the bladder. B, Appearance of bladder after two-layer closure.

All penetrating or intraperitoneal injuries resulting from external trauma should be managed by immediate operative repair. In a national study of patients with bladder trauma, operative repair was associated with a 59% reduction in mortality (Deibert and Spencer, 2011). These injuries are often larger than suggested on cystography and are unlikely to heal spontaneously, and continued leak of urine causes a chemical peritonitis. Although most injuries are repaired with open surgery, select patients may undergo laparoscopic repair (Fig. 101-16) (Kim et al, 2008). When bladder injuries are explored after penetrating trauma without preliminary imaging, the ureteral orifices should be inspected for clear efflux; ureteral integrity also may be ensured by intravenous administration of indigo carmine or methylene blue or retrograde passage of a ureteral catheter. Any penetrating injury involving the ureteral orifice or intramural ureter warrants primary closure with stented reimplantation of the ureter. A perivesical drain should be employed. In patients with intraperitoneal rupture, antimicrobial agents are administered for 3 days in the perioperative period only. If the bladder has been repaired, a cystogram is obtained 7 to 10 days after surgery (Corriere and Sandler, 1989). Several more recent studies have shown that suprapubic tube drainage provides no benefit over urethral catheter drainage alone (Volpe et al, 1999; Alli et al, 2003; Parry et al, 2003), although maximal urinary drainage using both is recommended when complex injuries are encountered. When concurrent rectal or vaginal injuries exist, the organ walls should be separated, overlapping suture lines should be avoided, and every attempt should be made to interpose viable tissue in between the repaired structures. Fibrin sealant injected over the bladder wall closure may help reduce complications when intervening tissue is unavailable (Evans et al, 2003).

Outcomes and Complications. Prompt diagnosis and appropriate management of bladder injuries promote excellent results and minimal morbidity. Serious complications are usually associated with delayed diagnosis or treatment because of misdiagnosis, delayed presentation, or complex injuries resulting from devastating pelvic trauma. Unrecognized bladder injuries may manifest as acidosis, azotemia, fever and sepsis, low urine output, peritonitis, ileus, urinary ascites, or respiratory difficulties. Unrecognized bladder neck, vaginal, and rectal injury associated with the bladder rupture can result in incontinence, fistula, stricture, and difficult delayed major reconstruction. Severe pelvic fractures may cause a transient or permanent neurologic injury and result in voiding difficulties despite an adequate bladder repair.

URETHRAL INJURIES

Posterior Urethral Injuries

Etiology. Urethral disruption injuries typically occur in conjunction with multisystem trauma from vehicular accidents, falls, or industrial accidents. Fracture of the anterior pelvic ring or pubic diastasis are almost always present when urethral disruption is encountered, and a greater degree of displacement has been correlated to a higher risk of urethral injury (Basta et al, 2007). “Straddle fractures” (Fig. 101-17 on the Expert Consult website) involving all four pubic rami and fractures resulting in vertical and rotational pelvic instability are associated with the highest risk of urologic injury (Mundy, 1996; Koraitim, 1999; Brandes and Borelli, 2001). Urethral injury has been reported to occur in approximately 10% of male patients and up to 6% of female patients with pelvic fractures (Koraitim, 1999; Black et al, 2006). Girls younger than age 17 years have a higher risk of urethral injury compared with women, perhaps owing to greater compressibility of the pelvic bones (Hemal et al, 1999).

Because the posterior urethra is densely adherent to the pubis via the urogenital diaphragm and the puboprostatic ligaments, the bulbomembranous junction is more vulnerable to injury during pelvic fracture than the prostatomembranous junction (Colapinto and McCallum, 1977; Brandes and Borelli, 2001). Endoscopic and urodynamic evaluation has confirmed that the membranous urethral sphincter complex tends to remain functionally intact while being avulsed vertically, posteriorly, or laterally from the underlying bulb (Mundy, 1997; Andrich and Mundy, 2001). In children, injuries are less common (Tarman et al, 2002) but are more likely to extend proximally to the bladder neck because of the rudimentary nature of the prostate (Devine et al, 1989; Al-Rifaei et al, 1991; Boone et al, 1992).

Diagnosis

Examination. Urethral disruption is heralded by the triad of blood at the meatus, inability to urinate, and palpably full bladder. Because these and other classic findings, such as a “high-riding” prostate or a “butterfly” perineal hematoma, may frequently be absent (Sandler and Corriere, 1989; Esposito et al, 2005), urethral disruption is often first detected when a urethral catheter cannot be placed by the emergency department trauma team or when it is misplaced into a pelvic hematoma. Pelvic hematoma often obscures the prostatic contour, resulting in a misdiagnosis of

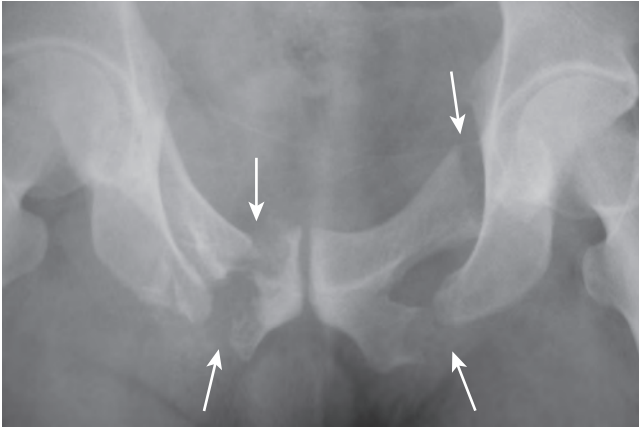


Figure 101-17. Anteroposterior film of the pubis shows a straddle fracture involving all four pubic rami (*arrows*) in a patient with a posterior urethral disruption in whom initial perineal posterior urethroplasty failed because of severe bone distortion. Reconstruction was successfully performed by an abdominoperineal technique.



Figure 101-18. Pelvic fracture urethral disruption injury and marked vulvar edema and ecchymosis in a female patient.

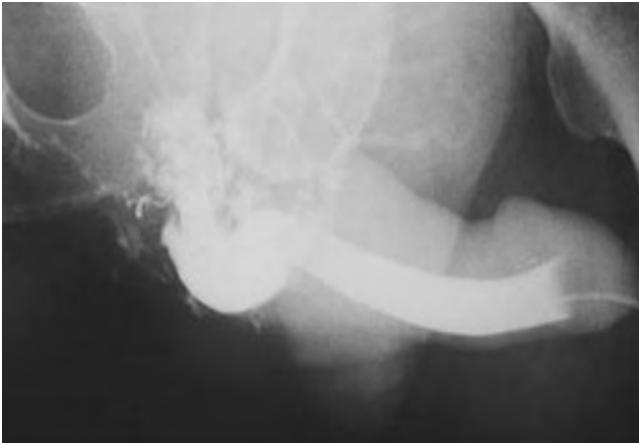


Figure 101-19. Retrograde urethrogram in a patient with a pelvic fracture shows complete disruption of the posterior urethra.

impalpable prostate (Koraitim et al, 1996). Although much more rarely than male patients, female patients also may develop proximal urethral avulsion injuries. They present with vulvar edema (Fig. 101-18) and blood at the vaginal introitus, indicating the need for careful vaginal examination in all female patients with pelvic fracture (Perry and Husmann, 1992).

Urethrography. When blood at the urethral meatus is discovered, an immediate retrograde urethrogram should be performed to rule out urethral injury (Fig. 101-19). A small-bore (16-Fr) urethral catheter is placed unlubricated 1 cm into the fossa navicularis, and the balloon is filled with 1 cm of water to achieve a snug fit (Sandler and Corriere, 1989). Alternatively, a Brodney clamp or rolled gauze bandage can be used to provide penile traction. Patients should be placed in an oblique or lateral decubitus position, and it is preferable to perform the study under fluorography when it is available; 25 mL of contrast medium is injected gently by a 60-mL catheter-tip syringe, and the film is taken during injection. Direct inspection by urethroscopy is suggested in lieu of urethrography in female patients with suspected urethral injury (Perry and Husmann, 1992; Koraitim, 1999).

Initial Management

Immediate Open Reconstruction. Immediate anastomotic reconstruction of posterior urethral disruption injuries in men has been



Figure 101-20. Initial management of urethral disruption injury in a female patient with suprapubic catheter drainage alone leads to complete urethral obliteration. This injury was successfully reconstructed via delayed retropubic approach.

abandoned because of its association with unsatisfactory outcomes, such as impotence and incontinence, stricture formation, and operative blood loss (Webster et al, 1983; Koraitim et al, 1996). In cases of female urethral disruption related to pelvic fracture, most authorities suggest immediate primary repair, or at least urethral realignment over a catheter, to avoid subsequent urethrovaginal fistulae or urethral obliteration (Fig. 101-20) (Koraitim et al, 1996; Dorairajan et al, 2004; Black et al, 2006). Concomitant vaginal lacerations also must be closed acutely to prevent vaginal stenosis. Delayed reconstruction is problematic because the female urethra is too short (about 4 cm) to be amenable for mobilization during an anastomotic repair when it becomes embedded in scar (Podesta and Jordan, 2001); however, we have found that a suprapubic approach with partial pubectomy provides excellent exposure enabling female bladder neck reconstruction.

Suprapubic Cystostomy. Immediate suprapubic tube placement remains the standard of care in men with posterior urethral injuries. Placement may be accomplished through a small infraumbilical incision, which allows inspection and repair of the bladder and proper placement of a large-bore catheter at the bladder dome. Trocar suprapubic tube placement is safe and expedient when the bladder is obviously distended and no other indications for surgery exist; however, over the long term, smaller “punch” suprapubic tubes are less robust, tending to fracture or become obstructed with debris and often requiring urgent replacement.

Increasingly, patients with pelvic ring fracture undergo early surgical fixation by orthopedists to decrease bleeding, improve healing, and speed ambulation (Connor et al, 2003). Although orthopedists frequently suggest that a suprapubic tube not be placed if anterior pubic hardware is used in pelvic fracture repair because of concern that the suprapubic tube will lead to hardware infection (Patterson, 1995), we and others (Borrelli and Brandes, 2004; Bepple et al, 2007) have repeatedly found that suprapubic cystostomy can be used safely without complications throughout the course of care (Fig. 101-21 on the Expert Consult website). We use a large-bore (24-Fr) Foley catheter placed high in the bladder and tunneled through the skin as high as possible on the lower abdominal midline to keep the tube away from the plated symphysis.

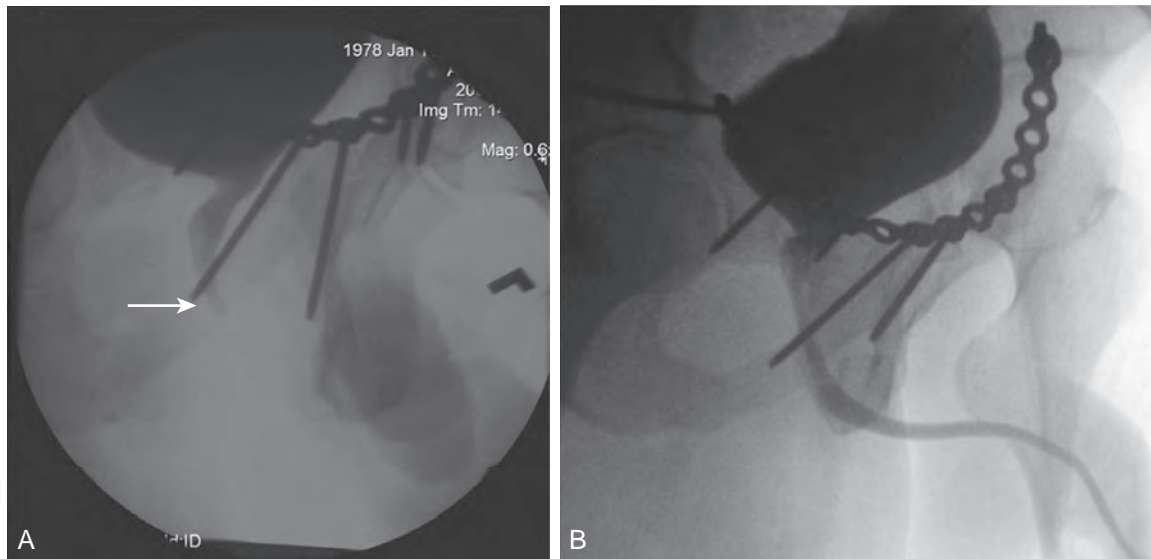


Figure 101-21. A, Defect in the urethra (*arrow*) seen on an antegrade urethrogram in a patient after pelvic fracture urethral disruption and internal fixation of anterior pelvic fracture. B, Postoperative voiding urethrogram demonstrates normal-caliber urethra after perineal urethroplasty.

Primary Realignment. An attempt at primary realignment of the distraction with a urethral catheter is reasonable in patients whose condition is stable (Elliott and Barrett, 1997) and can be done either acutely or within several days of injury. We prefer a simple technique consisting of passing a coude catheter antegrade from an anterior cystostomy to the urethral meatus, then tying it to another catheter that is drawn back into the bladder. Various more elaborate approaches have been described, frequently with retrograde and antegrade flexible cystoscopes (Follis et al, 1992; Routt et al, 1996; Elliott and Barrett, 1997; Porter et al, 1997; Asci et al, 1999; Mouraviev et al, 2005; Hadjizacharia et al, 2008), although we have observed that prolonged endoscopic realignment attempts risk infection of the pelvic hematoma (Morey et al, 1999) and cannot be recommended.

When the urethral catheter is removed after 4 to 6 weeks, it is imperative to retain a suprapubic catheter because many patients, despite realignment, will develop posterior urethral stenosis. If the patient voids satisfactorily through the urethra, the suprapubic catheter can be removed 7 to 14 days later. Primary realignment sometimes may allow healing without stricture (Elliott and Barrett, 1997; Leddy et al, 2012), but mild stenosis 1 to 2 cm in length develops in many patients (Kotkin and Koch, 1996; Routt et al, 1996; Asci et al, 1999). Patients managed with suprapubic tubes alone virtually always develop complete stenosis requiring posterior urethroplasty (Kotkin and Koch, 1996; Mouraviev et al, 2005). Although realignment may not always prevent symptomatic stenosis, it may allow resultant strictures to be managed endoscopically or ease the difficulty of open posterior urethroplasty by bringing the prostate and urethra into alignment and shortening the length of the stricture (Mouraviev et al, 2005; Hadjizacharia et al, 2008; Koraitim, 2012).

Incomplete urethral tears are best treated by stenting with a urethral catheter. We and others (Al-Ali and Husain, 1983; Mundy, 1991; Kotkin and Koch, 1996) have not seen any evidence that a gentle attempt to place a urethral catheter can convert an incomplete into a complete transection. Caution is warranted because misplacement outside the bladder is possible; radiographic confirmation of adequate positioning is imperative. In no case is traction used after urethral catheter placement; it is unnecessary and may cause incontinence (Asci et al, 1999).

Complex Injuries

Some authors advocate open exploration with realignment in cases of high-riding or "pie-in-the-sky" bladder or associated bladder neck tear in male patients (Webster et al, 1983). Associated rectal

injuries require open exploration, repair, irrigation, and placement of drains.

Delayed Reconstruction

In posterior urethral disruption, the rupture defect between the two severed ends fills with scar tissue, resulting in a complete lack of urethral continuity. This separation is not a stricture; it is a true urethral rupture defect filled with fibrosis. At 3 months, scar tissue at the urethral disruption site is stable enough to allow posterior urethroplasty to be undertaken safely, provided that associated injuries are stabilized and the patient is ambulatory. Suprapubic cystostomy drainage should be maintained until the associated injuries have healed and the patient can be appropriately positioned for the reconstructive procedure.

Preoperative Evaluation. Before the reconstructive procedure is planned, imaging studies are necessary to delineate the characteristics of the urethral rupture defect. A cystogram and retrograde urethrogram should be obtained simultaneously ("up-and-down-ogram," Fig. 101-22). The patient is asked to attempt to void with the bladder filled. Ideally, the prostatic urethra should be visualized as the bladder neck opens, enabling measurement of the distance between the severed urethral ends. If the bladder neck does not open, flexible endoscopy should be used to supplement radiographic imaging (Mundy, 1997). It is uncertain whether the appearance of the bladder neck on preoperative imaging correlates with bladder neck behavior postoperatively (Mundy, 1997; Koraitim, 2010), making it difficult to predict bladder neck incompetence or obstruction. MRI has been used successfully to define the length of the defect and to determine the extent and direction of urethral dislocation (Dixon et al, 1992) and the extent of prostatic displacement, and it may help in planning the surgical approach (Koraitim and Reda, 2007).

Endoscopic Treatments. Endoscopic treatments such as direct-vision internal urethrotomy are best reserved for selected short urethral stenoses, such as partial distraction injuries for which early catheterization achieved urethral continuity. In most cases, when preoperative evaluation indicates defects 1 cm or longer, endoscopic procedures such as cutting through the pelvic scar to provide a channel between the two ends of the avulsed urethra ("cut-to-the-light" procedure) are ineffective and have no advantage other than reduced operative time (Levine and Wessels, 2001); aggressive endoscopic treatments have been associated with complications such as coring of a false passage that inadvertently bypasses the bladder neck (Turner-Warwick, 1989). Cut-to-the-light or similar core-through procedures typically require multiple

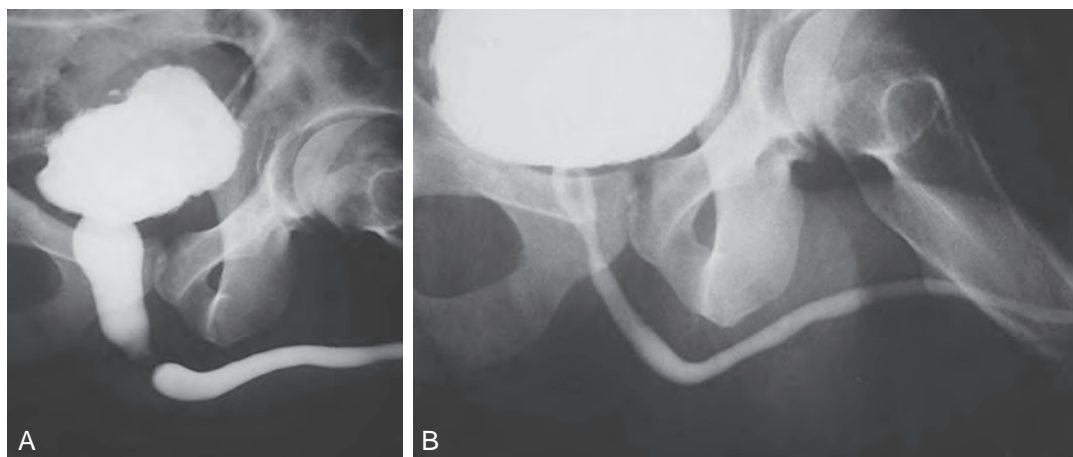


Figure 101-22. A, Combined cystogram and urethrogram 4 months after pelvic fracture shows complete posterior urethral disruption injury. B, Postoperative appearance reveals normal urethral caliber.

urethrotomies or long-term dilation by the patient or urologist to keep the channel open. Inevitably, the fibrosis contracts, leading to difficult self-catheterization, false passage, or acute urinary retention. In such cases, a 3-month period of “urethral rest” via suprapubic urinary diversion is advised before open reconstruction (Terlecki et al, 2011).

Surgical Reconstruction. Open posterior urethroplasty through a perineal anastomotic approach is the treatment of choice for most urethral distraction injuries because it definitively cures the patient without the need for multiple procedures. When preoperative studies have determined that the prostatic urethral apex can be reached by a perineal approach, the patient is placed in the high lithotomy position, and a midline or lambda-shaped incision is made. The bulbar urethra is freed and mobilized from the site of urethral rupture to the midsrotum. The scar tissue of the urethral rupture defect is excised, and the prostatic urethra is identified at the apex of the prostate. Care must be taken to excise carefully and meticulously all fibrotic tissue from the proximal urethral margin until at least a 28-Fr bougie passes without resistance (Fig. 101-23 on the Expert Consult website) (Turner-Warwick, 1989; Morey and McAninch, 1997). The bulbar urethra is then anastomosed in a tension-free manner to the prostatic urethra.

In 95% of patients, posterior urethral anastomosis is successfully achieved through a perineal approach alone (Carr and Webster, 1997). Adjunctive maneuvers such as corporeal separation, inferior pubectomy, and corporeal rerouting have been routinely implemented if direct anastomosis proves difficult (Mundy, 1997; Flynn et al, 2003). Others have found these maneuvers, especially suprapubic rerouting, to be unnecessary and/or unhelpful (Morey and McAninch, 1997; Rosenstein and Jordan, 2003; Cooperberg et al, 2007; Kizer et al, 2007).

Total removal of the symphysis pubis, first reported by Pierce in 1962 (Pierce, 1962), has been recommended when severe injuries result in complicating features such as fistula or marked displacement or retropubic fixation of the prostate (Netto, 1985; McAninch, 1989; Asci et al, 1999). Alternatively, a combined abdominoperineal approach (with or without partial pubectomy) has proved helpful in cases of severe fibrosis, fistula, previous failed anastomotic urethroplasty, and associated bladder neck injury and in pediatric cases (Waterhouse, 1976; Al-Rifaei et al, 1991; Koraitim, 2003, 2005; Pratap et al, 2006). It is important to limit the lithotomy time to 5 hours or less to prevent lower extremity complications (Anema et al, 2000) when any complex urethral reconstruction is undertaken.

Complications

Erectile Dysfunction. Some degree of impotence is noted in 82% of patients with pelvic fracture and urethral distraction injury (Flynn et al, 2003), although the average reported rate is approximately 50% (Corriere et al, 1994; Routt et al, 1996; Elliott and Barrett, 1997; Asci et al, 1999; Koraitim, 2005). The etiology is multifactorial and variably attributed to cavernous nerve injury, arterial insufficiency, venous leak, and direct corporeal injury (Narumi et al, 1993; Munarriz et al, 1995; Shenfeld et al, 2003). Factors that correspond to the severity of the injury, such as diastasis of the pubic symphysis, lateral displacement of the urethra, and long urethral gap, have been found to correlate with erectile dysfunction (Koraitim, 2013).

Some surgical series have shown a small number of patients with new-onset or worsened erectile dysfunction after reconstruction (Tunc et al, 2000); however, the complications of the original pelvic injury are difficult to differentiate from the complications of attempts to repair urethral and bladder injuries. Accounts of greater risk of erectile dysfunction and incontinence with primary realignment were published before the advent of flexible endoscopes (Koraitim et al, 1996). Several studies have shown that patients treated with modern techniques of primary endoscopic realignment have rates of impotence and incontinence similar to those of patients who have had either no treatment or delayed open reconstruction (Kotkin and Koch, 1996; Asci et al, 1999; Koraitim, 2005;

Mouraviev et al, 2005). These studies support the conclusion that these complications are usually the result of the injury itself and not of the treatment (Follis et al, 1992; Elliott and Barrett, 1997; Porter et al, 1997; Corriere, 2001). Some patients who become impotent after injury spontaneously recover erectile function 1 or 2 years later (Turner-Warwick, 1989; Morey and McAninch, 1997; Koraitim, 2005).

Many patients who become impotent as a result of pelvic fracture have some degree of arterial insufficiency (Armenakas et al, 1993; Matthews et al, 1995). Because patients with impotence may be more vulnerable to restenosis after posterior urethroplasty as a result of bulbar urethral ischemia, some experts have suggested that “at-risk” patients undergo preoperative penile arterial duplex Doppler studies to identify candidates suitable for initial penile revascularization (Matthews et al, 1995; Rosenstein and Jordan, 2003). However, indications for penile revascularization as a treatment for post-traumatic erectile dysfunction are extremely limited (Kawanishi et al, 2004). Overall rates of incontinence, anejaculation, and areflexic bladder are low (2% to 4%) (Corriere et al, 1994; Elliott and Barrett, 1997; Asci et al, 1999; Anger et al, 2008), and these conditions tend to be secondary to the original injury.

Recurrent Stenosis. After posterior urethroplasty, 5% to 15% of patients have recurrent stenosis at the anastomosis (Mundy, 1996; Flynn et al, 2003; Koraitim 2005; Cooperberg et al, 2007). Endoscopic treatment (e.g., with direct-vision internal urethrotomy) is often successful in this setting because most fibrotic tissue has been eliminated (Netto et al, 1989; Koraitim 2003).

Incontinence. Urinary continence after urethral distraction is the rule rather than the exception, despite destruction of the external sphincter from either the injury itself or the subsequent repair. Incontinence rates after reconstruction are low—less than 4% (Koraitim, 2005). The mechanism of continence is thought to be largely attributable to bladder neck function (Iselin and Webster, 1999). Urodynamic data show that a significant proportion of patients also have identifiable distal rhabdosphincteric function (Whitson et al, 2008).

Anterior Urethral Injuries

In contrast to posterior urethral distraction, anterior injuries are most often isolated (Kiracofe et al, 1975). Most occur after straddle injury and involve the bulbar urethra, which is susceptible to compressive injury because of its fixed location beneath the pubis. A smaller percentage of injuries to the anterior urethra are the result of direct penetrating injury to the penis.

As with posterior urethral injury, a high index of suspicion must be maintained in all patients with blunt or penetrating trauma in the urogenital region, and urethrography should be performed in any case of suspected urethral injury (Husmann et al, 1993). Clinical signs of anterior urethral injuries include blood at the meatus, perineal hematoma, gross hematuria, and urinary retention. In severe trauma, Buck fascia may be disrupted, resulting in blood and urinary extravasation into the scrotum (Fig. 101-24 on the Expert Consult website). The primary morbidity of straddle injury is urethral stricture, which may become symptomatic years later (Park and McAninch, 2004).

Initial Management

Armenakas and McAninch (1996) proposed a simple, practical classification scheme dividing anterior urethral injuries on the basis of radiographic findings into contusion, incomplete disruption, and complete disruption. Contusions and incomplete injuries can be treated with urethral catheter diversion alone. Initial suprapubic cystostomy is the standard of care for major straddle injuries involving the urethra (Park and McAninch, 2004); however, primary anterior urethral realignment has shown promising results with respect to stricture rate and erectile dysfunction in patients with straddle injuries of lesser magnitude (Ying-Hao et al, 2000; Yu et al, 2007).

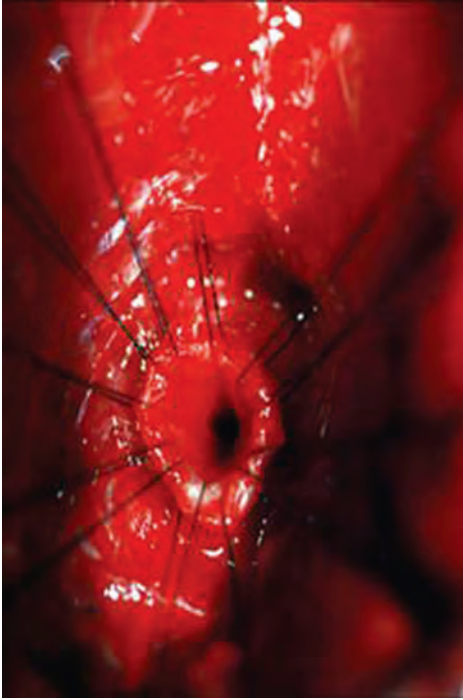


Figure 101-23. Intraoperative view of normal membranous urethra after fibrotic tissue was excised during perineal bulbomembranous urethroplasty.

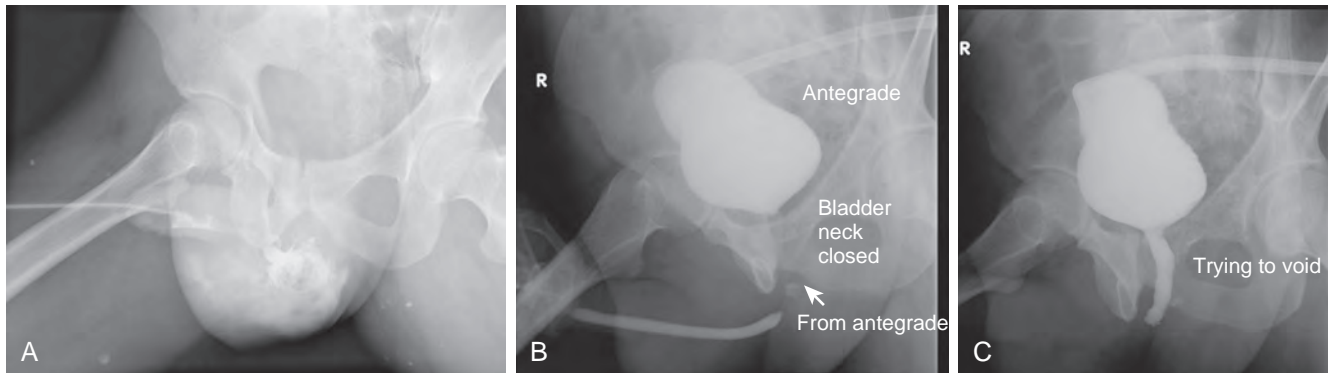


Figure 101-24. A, Extravasation of contrast medium seen in the scrotum on a retrograde urethrogram in a patient with a straddle injury. B, Retrograde and antegrade urethrograms show distal limit of urethral patency, but the bladder neck does not open. C, Repeat antegrade urogram study showing proximal limit of urethral patency.

Primary surgical repair is recommended for low-velocity urethral gunshot injuries (Kunkle et al, 2008); catheter alignment alone is associated with a far worse stricture rate (Husmann et al, 1993). Debridement of the corpus spongiosum after trauma should be limited because corporeal blood supply is usually robust, enabling spontaneous healing of most contused areas (Kiracofe et al, 1975; Husmann et al, 1993). Initial suprapubic urinary diversion is recommended after high-velocity gunshot wounds to the urethra, followed by delayed reconstruction.

Delayed Reconstruction


Before any planned procedure, a retrograde urethrogram and voiding cystourethrogram should be obtained to define the site and length of the obliterated urethra clearly. Urethral ultrasound examination may help delineate the length and severity of stricture. Retrograde injection of saline combined with antegrade bladder filling fills the urethra proximally and distally, and a 10-MHz sonogram clearly defines the nondistensible segment to be excised. Dense fibrous tissue from trauma often demonstrates a fixed, nondistensible appearance sonographically with significant shadowing (Morey and McAninch, 2000). Ultrasound imaging of urethral strictures may be more accurate than retrograde urethrography (Mitterberger et al, 2007), although it is highly operator dependent and not widely used at the present time.

Anastomotic urethroplasty is the procedure of choice in the totally obliterated bulbar urethra after a straddle injury. The typical scar is 1.5 to 2 cm long and can readily be completely excised. The proximal and distal urethra can be mobilized for a tension-free, end-to-end anastomosis. This is a highly successful procedure in more than 95% of cases (Santucci et al, 2002; Jordan et al, 2010).

Endoscopic incision through the scar tissue of an obliterated urethra is a hopeless procedure doomed to failure. Partial urethral narrowing can initially be treated by endoscopic incision or dilation with greater success. Repeated endoscopic manipulation is neither clinically effective nor cost-effective for the treatment of urethral strictures (Greenwell et al, 2004). Patients who undergo repeated endoscopic procedures are also more likely to require complex reconstructive procedures such as grafts (Park and McAninch, 2004; Hudak et al, 2012). Open repair should be delayed for several weeks after instrumentation to allow the urethra to stabilize, and a 2-month period of suprapubic urinary diversion may be prudent preoperatively to optimize conditions for repair of complex or recurrent strictures that have been catheter dependent (Terlecki et al, 2011). Finally, UroLume stents are contraindicated in the setting of traumatic urethral strictures (Wilson et al, 2002).

KEY POINTS: LOWER GENITOURINARY TRACT INJURIES

- Although most bladder injuries are associated with pelvic fractures, only 10% of patients with pelvic fracture have bladder injuries.
- Intraperitoneal bladder injury from external trauma requires urgent operative repair.
- Prompt suprapubic catheter drainage is recommended for initial management of pelvic fracture urethral disruption injury; although primary realignment may be performed in stable patients, close follow-up is essential because of the high rate of stricture formation.
- Posterior urethroplasty by excision and primary anastomosis is the treatment of choice for urethral distraction injuries, although a single attempt at endoscopic treatment may be reasonable for short stenoses.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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102

Development, Molecular Biology, and Physiology of the Prostate

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Developmental and Cell Biology

Endocrine Control of Prostate Growth

Regulation of Prostate Growth by Steroids and Protein Growth Factors

Regulation of Prostate Growth at the Molecular Level: Steroid Receptors

Prostatic Secretions and Proteins

Coagulation and Liquefaction of Semen

Prostate Secretions and Drug Transport

The focus of this chapter is on the development, anatomy, histology, and physiology of the prostate and seminal vesicles, the male sex accessory glands that contribute to seminal fluid. A general and molecular knowledge regarding the formation and physiologic function of the prostate is becoming increasingly important because reactivation or recapitulation of developmental processes appears to occur during pathologic processes such as benign prostatic hyperplasia (BPH) and the development of aggressive prostate cancer (Marker, 2008; Schaeffer et al, 2008; Pritchard et al, 2009). In addition, the physiologic processing of prostate-specific antigen (PSA) and other cellular constituents of the prostate has begun to play increasingly important roles in the development of clinical prostate biomarkers (Mikolajczyk et al, 2004; Vickers et al, 2011; Loeb and Catalona, 2014).

DEVELOPMENTAL AND CELL BIOLOGY

Prostate

Regional Differentiation of the Lower Urinary Tract

The prostate is a derivative of the primitive endoderm (gut tube). Regional differentiation of the primitive gut tube into foregut, midgut, and hindgut is followed by a swelling at the caudal end that creates the cloaca. The *cloaca*, a Latin term meaning “sewer,” receives output from both the urinary and intestinal tracts and represents the fully differentiated state in birds, reptiles, amphibians, marsupials, and monotremes. In placental mammals, however, the cloaca is divided by the urorectal septum during embryogenesis to create separate urinary and digestive outlets. The ventral urinary compartment is called the *primitive urogenital sinus*, which further segments into the urinary bladder at its cranial end and the urethra at its caudal terminus.

Prostate Budding

In males, the prostate develops just caudal to the bladder neck via the proliferation of epithelial buds extending out from the urogenital sinus epithelium. Prostate buds invade at stereotyped locations that pattern the future development of distinct prostate

lobes in the rodent and, potentially, zones in the human. These regions prepare for epithelial bud invasion by “mesenchymal condensation,” a process in which urogenital sinus mesenchymal cells (cells constituting loose connective tissue that will differentiate into stromal elements) become closely packed together (reviewed in Thomson, 2008). This condensation occurs in both males and females and is therefore androgen *independent*. In contrast, epithelial budding is strictly androgen *dependent* and represents the first events in prostate development that are identifiable at the light microscopic level. Prostate budding requires intricate epithelial-mesenchymal interactions (Fig. 102-1). In humans, prostate budding occurs during the 10th week of gestation. In mice, prostate budding occurs on the 17th day of gestation, 2 days before birth. It is important to note that androgen exposure is not only *necessary* but also *sufficient* to drive prostatic differentiation and growth in the embryo. This fact, along with the ability to easily manipulate androgen levels in experimental animals, makes the prostate a particularly appealing subject for the study of epithelial cell fate determination (Cunha et al, 1987; Schaeffer et al, 2008). Prostate buds initially grow as solid epithelial cords that subsequently (postnatal days 1 to 14 in mice) branch and canalize (Sugimura et al, 1986) as part of a sophisticated branching morphogenesis program.

Cytodifferentiation

In the mouse, the urogenital sinus epithelium begins as a homogeneous cell compartment that differentiates (after birth in mice) into distinct basal (adjacent to stroma) and luminal layers (Wang et al, 2001). Intervening epithelial cells, called *intermediate cells*, are present that have features of both basal and luminal cells. A fourth cell type, the neuroendocrine cell, is present in large numbers before prostate epithelial budding and decreases during embryonic development (Aumuller et al, 2001). The development of this cell type during mouse embryogenesis has not been well characterized, and the source of these cells has been variously proposed to be neural crest or urogenital sinus endoderm (Aumuller et al, 2001; Goldstein et al, 2008), illustrating the need to further delineate lineage commitment events in prostate epithelium.

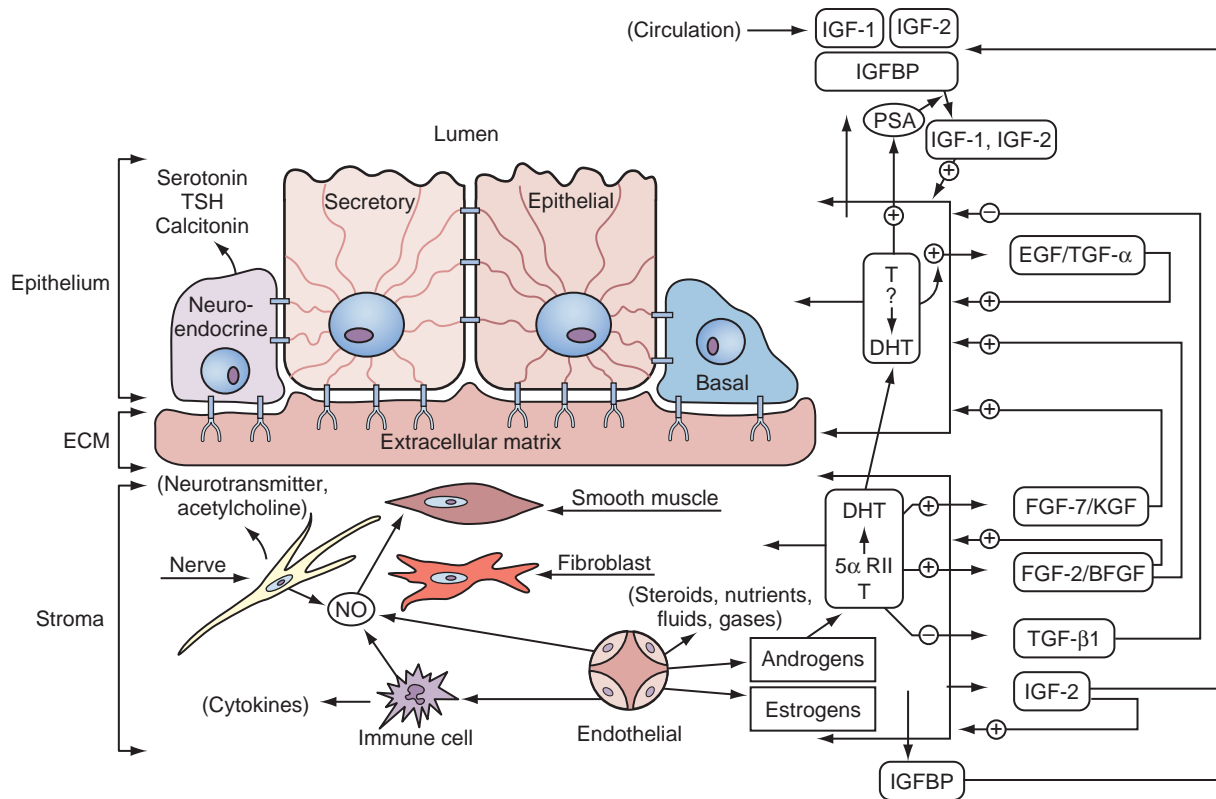


Figure 102-1. Stromal-epithelial interactions. Shown is a schematic of the types of stromal-epithelial interactions in information transfer and regulation within the prostate. Testosterone and growth factors interact on and between stromal and epithelial cells. The production of growth factors is either stimulated or inhibited by androgens. The growth factors can function on the same cell (autocrine) or on distant cells (paracrine). Nitric oxide (NO) is formed from nerve cells, endothelial cells, or macrophages and affects smooth muscle contraction (see text for details). Important features in this schematic are (1) three types of prostate epithelial cells—neuroendocrine, secretory, and basal; (2) five important prostatic stromal cells—smooth muscle, fibroblast, immune cells, endothelial cells, and nerve cells; (3) testosterone converted to dihydrotestosterone (DHT) by 5 α -reductase in the stromal compartment; (4) three sources of NO production in the prostate—nerve, immune cells (e.g., macrophages), and endothelial cells; and (5) stromal-epithelial interactions mediated through various growth factors (see text). BFGF, basic fibroblast growth factor; ECM, extracellular matrix; EGF, epidermal growth factor; FGF, fibroblast growth factor; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; KGF, keratinocyte growth factor; PSA, prostate-specific antigen; T, testosterone; TGF, transforming growth factor; TSH, thyroid-stimulating hormone.

Molecular Features of Prostate Development

Induction of Prostate Budding. Although androgen receptor (AR) signaling through dihydrotestosterone (DHT) is the primary motivating force behind prostate development, it specifies only the timing of events, not their location. The AR signaling machinery is present diffusely throughout the lower genitourinary tract (Takeda et al, 1985; Berman et al, 1995). Prostate epithelial buds form at precise locations through mechanisms that are not understood. This spatial control may involve paralogous homeobox (*Hox*) genes, which are transcriptional regulators that govern differential gene expression along the craniocaudal (head to tail) and proximodistal (e.g., shoulder to fingertip) axes in a variety of tissues, including the genitourinary tract (reviewed in Beck et al, 2000; Kmita and Duboule, 2003). In vertebrates, the paralogous *Hox* genes exist as four similar clusters (clusters A, B, C, and D), each of which resides on a separate chromosome and encodes genes whose chromosomal position from 3' to 5' mirrors their expression pattern in the embryo. The paralogous genes are distinct from other, more distantly related transcription factor families that also contain DNA-binding homeobox motifs, such as the NK family, whose members are expressed in a more discrete, organ-specific manner (e.g., see the discussion

of Nkx3.1, later). Paralogous *Hox* genes are sequentially numbered from 1 to 13, with the higher numbers in the 5' position showing the most distal or caudal expression patterns. Accordingly, *Hoxa13*, *Hoxb13*, and *Hoxd13* are *paralogs* on chromosomes 7, 17, and 2, respectively, and have overlapping expression patterns and functions in distal genitourinary tract development. *Hoxb13* regulatory elements have been characterized that restrict its function to the caudal end of the genitourinary and digestive tracts and can be used to engineer androgen-independent prostatic expression of genes of interest (McMullin et al, 2009). Homozygous mutations in individual *Hox* genes result in subtle changes in prostatic branching patterns (Podlasek et al, 1997) and/or defective epithelial maturation (Economides and Capecchi, 2003). Mutations involving more than one of these genes results in significantly more severe urogenital phenotypes, such as significant prostate hypoplasia in *Hoxd13/Hoxb13* compound mutant mice or failure of separate urinary and gastrointestinal tract outlets to form in *Hoxa13/Hoxd13* compound mutants (Kondo et al, 1997; Warot et al, 1997).

Mesenchymal condensation occurs in both males and females, so it is not sufficient to drive prostate development but may be necessary. Condensation of the ventral mesenchymal pad is defective in mice lacking the gene for Noggin (see the section on the

transforming growth factor- β [TGF- β] family, later, for further discussion of the roles of Noggin in prostate development), which antagonizes binding of bone morphogenetic protein (BMP) ligands to their receptors (Cook et al, 2007). This observation suggests that BMP signaling enhances mesenchymal condensation, either by direct action on mesenchyme or through regulation of epithelial-derived factors important in this process. Condensed mesenchyme is highly enriched for expression of fibroblast growth factors (FGFs) that are essential for epithelial bud outgrowth. For example, mice with engineered mutations of the mesenchyme-specific growth factor *Fgf10* gene generate small abortive epithelial buds and fail to grow prostates (Donjacour et al, 2003).

Epithelial Budding. The earliest event seen in the epithelium during prostate development appears to be the upregulation of sex-determining region Y-box 9 (*Sox9*), an androgen-dependent transcription factor, induced via mesenchymal-dependent FGF signaling (Huang et al, 2012). *Sox9* appears to be crucial for the initiation of prostate epithelial lineage. After this, there is increased epithelial expression of the NK homeobox transcription family member *Nkx3.1*. This transcription factor influences the degree of branching in the mature mouse prostate, where it can also act as a tumor suppressor (Bieberich et al, 1996; Bhatia-Gaur et al, 1999; Abate-Shen et al, 2008).

Mutations in the transcriptional regulator p63 (*TP63*) (Signoretto et al, 2000) or in the AR signaling axis (reviewed in Cunha et al, 1987) can also abolish prostate induction. Of note, a striking aspect of the induction of prostate epithelial budding is the finding by Cunha and Lung (1978) that AR signaling is required in the mesenchyme but dispensable in the epithelium. Thus the action of androgens appears to be indirect, leading to the hypothesis that mesenchymal cells secrete inductive factors in response to androgens called *andromedins* (Yan et al, 1992). *TP63* has transcriptional repressor and activator activities that balance differentiation and stem and progenitor cell functions in epithelia (McKeon, 2004). The transcriptional targets of *TP63* in prostate epithelial cells (PrECs) remain to be elucidated (Grisanzio and Signoretti, 2008).

Noggin mutations selectively impair budding of the ventral lobes of the prostate, leaving anterior and dorsolateral budding unimpaired (Cook et al, 2007). Overall, however, the process appears to be a very robust one, with evidence of prostate epithelial bud formation persisting in the presence of a variety of genetic mutations that affect future steps in prostate ductal morphogenesis, particularly branching morphogenesis.

Once set in motion, prostate growth and homeostasis continue to require androgens throughout life, and this requirement appears to continue to be indirect, through mesenchymal or stromal AR signaling. Epithelial branching morphogenesis occurs through signaling cascades that inhibit further outgrowth along the long axis of an extending epithelial bud while stimulating lateral growth at its tip (Hogan, 1999). Through engineered deletion of genes in transgenic mice, several individual genes and components of classic morphogenetic pathways have been shown to be required for branching morphogenesis. Indeed, morphologic aberrations seen on interruption of a cellular pathway may be the most sensitive measure of a role for that pathway in regulation of prostate growth. Accordingly, a wide variety of genes and pathways have been strongly implicated in prostate branching morphogenesis, only a few of which are covered here. For a more comprehensive perspective, including additional pathways such as those centered around Notch and Forkhead proteins, the reader is referred to recent reviews (Leong and Gao, 2008; Matusik et al, 2008).

Nkx3.1 and Sox9. *Nkx3.1* helps determine the branching pattern of the prostate, as demonstrated by the reduced numbers of duct tips seen in mice with engineered *Nkx3.1* deletion (Bhatia-Gaur et al, 1999). This relatively subtle phenotypic change may be important, however, as indicated by a dramatic decrease in the ability of *Nkx3.1*-mutant prostates to manufacture mature secretory proteins (Bhatia-Gaur et al, 1999). In addition to its role in the initiation of prostate development, *Sox9* appears required for bud growth and branching as well as ductal outgrowth (Thomsen et al, 2008).

Fibroblast Growth Factors. The FGF family of related secreted peptides promotes growth in recipient cells by binding to cell surface receptors and activating intracellular second-messenger cascades. Epithelial branching morphogenesis, be it in the lung, salivary gland, mammary gland, or prostate, requires such signals to proceed. Of the FGFs, *Fgf-7* (keratinocyte growth factor) and *Fgf-10* have been studied most extensively in prostate development. Both of these ligands preferentially bind to *Fgfr-2* over the three other family members (*Fgfr-1*, *Fgfr-3*, and *Fgfr-4*) (reviewed in Thomson, 2001, 2008). Ligand binding activates the intracellular microtubule-associated protein kinase (MAPK) pathway, leading to enhanced activity of growth-promoting transcription factors and increased proliferation.

Fgfr-2 is expressed on developing PrECs, where it can interact with its coreceptor *Frs-2 α* . *Fgf-7* and *Fgf-10*, in contrast, are secreted by prostate mesenchyme. This arrangement, along with androgen-independent growth of prostate organ cultures exposed to these ligands, has led to the proposal that they act as andromedins (Yan et al, 1992; Lu et al, 1999). Accordingly, *Fgf-10*-deficient mice have almost complete failure of prostate development, and mice lacking *Fgfr-2* or *Frs-2 α* demonstrate prostate hypoplasia and decreased epithelial branching (Donjacour et al, 2003).

Hedgehog Signaling Pathway. Across a variety of organs, elaboration of secreted hedgehog (Hh) ligands (Sonic hedgehog, Indian hedgehog, and Desert hedgehog) by epithelial cells and reception in adjacent mesenchyme coordinate the activities of the Gli family proteins in regulating hedgehog pathway target genes. In the mesenchyme of developing prostate, several Hh target genes have been identified (Yu et al, 2009), including the cytokine *Cxcl14*, the insulin-like growth factor-binding protein *Igfbp3*, and the delta/notch-like epidermal growth factor-related receptor *Dner*. The roles of these particular genes in prostate development have yet to be ascertained, but, as a whole, Hh pathway target genes have been implicated in placement of prostate epithelial buds and in subsequent ductal branching and outgrowth. In particular, buds form in the absence of the dominant Hh ligand in the prostate (Berman et al, 2004) but are mislocalized in prostates of mice bearing mutations of downstream effectors of the pathway, Gli proteins (Doles et al, 2006). Later in development, Hh ligands enhance epithelial outgrowth and branching (Freestone et al, 2003), which proceed abnormally in prostate organ cultures treated with Hh pathway antagonists (Lamm et al, 2002; Freestone et al, 2003; Berman et al, 2004). In adult animals the pathway may play a role in homeostasis, as indicated in a failure of prostates to regenerate after castration of animals treated with antibodies or small molecules that block Hh signaling (Berman et al, 2004). Taken together, these data indicate a growth-promoting role for the pathway in prostate epithelium, one that may have clinical relevance in pathologic prostate growth (reviewed in Shaw and Bushman, 2007).

Transforming Growth Factor- β Superfamily. TGF- β superfamily members include TGF- β itself, as well as growth and differentiation factors (GDFs) and BMPs. These factors act through transmembrane receptors and the SMAD family of intracellular signal transducing proteins (Schmierer and Hill, 2007). Little is known about GDFs in the prostate, but both TGFs and BMPs are likely to play important roles. In organogenesis this superfamily is best known as a mesenchymal mediator of epithelial growth suppression, but (less frequently) they can also stimulate growth and/or be produced by epithelial cells. TGF- β 1 inhibits net growth of the prostate but can stimulate growth in certain regions of the gland, particularly in the distal tips of the ventral prostate (Tomlinson et al, 2004a). Although the mechanism for growth promotion by TGF- β 1 is unclear, the growth suppressive effect could quite reasonably relate to its ability to suppress levels of another mesenchymal growth factor, FGF-10 (Tomlinson et al, 2004b) (see FGF section, earlier). A similar mechanism could remain in place in mature males, in whom TGF- β signaling in proximal ducts is believed to help to maintain prostate epithelial stem cells in a quiescent (growth-suppressed) state (Salm et al, 2005). BMP-4 and BMP-7 exert important and highly localized growth-suppressive activities in prostate development that help guide branching morphogenesis and prevent overproduction and

TABLE 102-1 Summary of the Anatomy and Cell Biology of the Prostate Gland

COMPONENTS	PROPERTIES
DEVELOPMENT	
Seminal vesicles	From wolffian ducts through testosterone stimulation
Prostate	From urogenital sinus through dihydrotestosterone stimulation
PROSTATE ZONES	
Anterior fibromuscular	30% of prostate mass, no glandular elements, smooth muscle
Peripheral	Largest zone, 75% of prostate glandular elements, site of carcinomas
Central	25% of prostate glandular elements; surrounds ejaculatory ducts
Transitional	Smallest zone, surrounds upper urethra complex, sphincter
	5% of prostate glandular elements, site of benign prostatic hyperplasia
	15%-30% of prostate volume
EPITHELIAL CELLS	
Basal	Small and flattened undifferentiated, nonsecretory cells with a low proliferative index (<1%) that express keratins 5, 14, and 18
Intermediate	Proliferating cell type that has characteristics intermediate between basal and secretory cells, including production of basal and secretory cell keratins
Columnar secretory	Terminally differentiated, nondividing, rich in acid phosphatase and prostate-specific antigen; 20 μ m tall, most abundant cell, keratins 5 and 18
Neuroendocrine	Terminally differentiated, nonproliferating cells that express serotonin, chromogranin-A, neuron-specific enolase, and synaptophysin proteins
STROMAL CELLS	
Smooth muscle	Rich in α -actin, myosin, and desmin
Fibroblast	Vimentin rich and associated with fibronectin
Endothelial	Associated with fibronectin; alkaline phosphatase positive
TISSUE MATRIX	
Extracellular matrix	
Basement membrane	Type IV and V collagen meshwork that is laminin rich and supports basal cells, stem cells, transit-amplifying cells, and secretory epithelium
Connective tissue	Type I and type III fibrillar collagen; elastin
Glycosaminoglycans	Sulfates of dermatan, chondroitin, and heparin; hyaluronic acid
Cytoplasmic	Tubulin, α -actin, and intermediate filaments of keratin
Nuclear matrix	Dynamic structure of the nucleus that directs the functional organization of DNA into loop domains; contains ribonuclear proteins

disorganized epithelial growth. Like TGF- β , BMPs are most active during epithelial budding and subsequent prostate branching (Lamm et al, 2001; Tomlinson et al, 2004a; Grishina et al, 2005) (embryonic day 17 through postnatal day 5 in the mouse). Activation of BMP signaling suppresses branching morphogenesis, as indicated by experimental addition of exogenous BMP-4 or BMP-7 protein to prostate organ cultures (Lamm et al, 2002; Grishina et al, 2005) or by genetic deletion of the BMP inhibitor Noggin (Cook et al, 2007). BMP inactivation can show the opposite effect, as epithelial overgrowth of prostates with genetic deletion of BMP-7 (Grishina et al, 2005).

Prostate Zonal and Lobar Anatomy. The rodent prostate is divided into paired anterior, dorsolateral, and ventral lobes. Each empties into the urethra separately at its proximal extreme, with the distal end floating freely in the pelvic cavity. In contrast, the human prostate, like that of most primates and canine species, grows as a single organ encircling the urethra. The individual prostate zones, however, have distinct architectural and molecular features and have a propensity to develop distinct pathologies (Table 102-1). For instance, the transitional zone surrounding the urethra has the propensity to undergo BPH, making males vulnerable to urinary obstruction, whereas the peripheral zone, which contains the majority of the glandular elements of the prostate, is the most

common site for prostate cancer. In rodents, the anterior, ventral, and dorsolateral lobes are named for the distinct locations of the urethra from which they originate. Each lobe also has a different branching pattern with a distinctive histologic appearance. These differences, reviewed by Timms (2008), have been likened to different zones of the human prostate histologically (Price, 1963), molecularly (Berquin et al, 2005; Thielen et al, 2007), and in terms of propensity to be affected by disease (the dorsolateral prostate, for instance, is most similar to the human peripheral zone). In mice, mRNA transcripts for spermine-binding protein, probasin, and renin-1 are specific for ventral, dorsolateral, and anterior lobes, respectively (Cook et al, 2007), whereas human zone-specific gene expression has not been as well characterized.

Although the gene expression patterns of individual human prostate zones have not been extensively studied, there have been efforts to characterize the zonal distribution of prostate-secreted proteins, in particular of PSA, at least in the adult prostate. For instance, Mikolajczyk and colleagues described BPSA (BPH-related PSA) as a form of unbound PSA that is increased in the transition zone of the prostate (Mikolajczyk et al, 2000a). In contrast, the proPSA zymogen (a precursor of PSA) has been found to be preferentially detected in the peripheral zone (Mikolajczyk et al, 2000b).

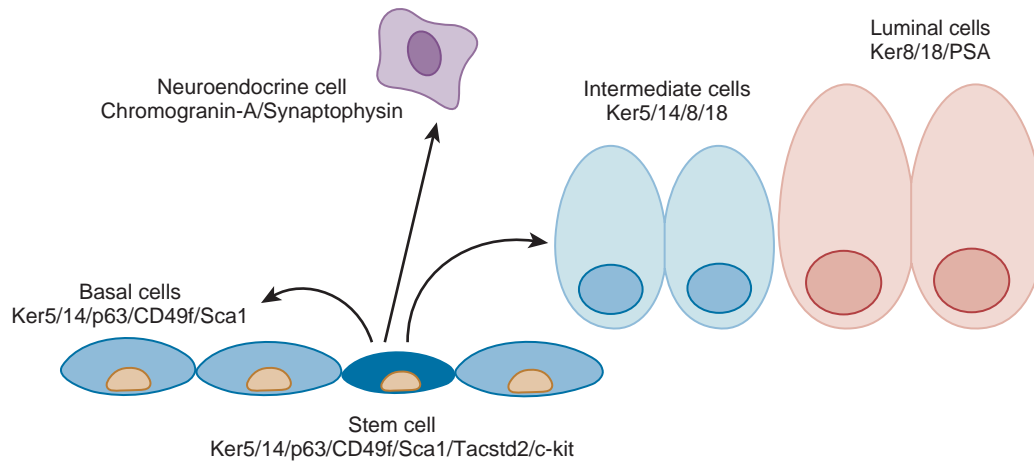


Figure 102-2. Hypothetical cell differentiation in adult prostate. Basal cells (*medium blue*) express basal cell proteins, including cytokeratin (CK) proteins 5 and 14, p63, CD49f, and Sca1. Stem cells within the basal cell compartment (*dark blue*) express basal cell proteins, as well as Tacstd2 and c-kit. Basal stem cells populate the basal cell compartment (*medium blue*) and eventually intermediate cells (*light blue*). Intermediate cells proliferate and differentiate into quiescent luminal cells (*orange*). Neuroendocrine cells (*purple*) are also believed to derive from epithelial stem cells. Formal lineage tracing has not been performed in all of these cell types; thus the true differentiation pathway remains to be determined. (Modified from Wang Y, Hayward S, Cao M, et al. Cell differentiation lineage in the prostate. *Differentiation* 2001; 68[4-5]:270–9.)

KEY POINTS: EMBRYONIC DEVELOPMENT

- The wolffian ducts develop into the seminal vesicles, epididymis, vas deferens, ampulla, and ejaculatory duct. The developmental growth of this group of glands is stimulated by fetal testosterone and not DHT.
- Through tissue recombination experiments in mice and rats, the developing urogenital sinus mesenchyme and epithelium have been shown to partner in prostate development. That is, the development, growth, and function of the male and female urogenital tract require stromal-epithelial interaction and action of steroid sex hormones. Androgen acts on the mesenchyme to indirectly induce prostate epithelial outgrowth during development and homeostasis in adulthood.

Prostate Cell Types

The prostatic epithelium in the human is composed of two major cellular compartments: epithelial cells and stromal cells (see Table 102-1). The prostate epithelial compartment consists of basal epithelial cells, intermediate cells, neuroendocrine cells, and luminal secretory epithelial cells (reviewed by De Marzo et al, 1998a). The stromal compartment architecturally serves as structural support and consists predominantly of connective tissue, smooth muscle cells, and fibroblasts. Most prostate cell types have been characterized *in vitro* (Peehl, 2005).

In most glands with renewing cell populations, there is a steady-state flow of cells from mostly quiescent stem cells to a more rapidly dividing pool of transient proliferating cells. This proliferating population finally reaches terminal differentiation, characterized by metabolically active secretory epithelium. In the prostate, cell lineage has not been rigorously determined but has been inferred from a variety of sources. A hypothetical differentiation scheme for prostate epithelium is presented in Figure 102-2. As in most multi-layered epithelia, stem cells reside in the basal compartment and appear to give rise to all of the other epithelial cell types, as well as neuroendocrine cells. These include fully differentiated secretory cells that line glandular lumens (luminal cells), neuroendocrine

cells that secrete bioactive peptides, and intermediate cells that show phenotypic features that are intermediate between basal cells and luminal cells.

Luminal Epithelial Cells

The luminal epithelial cell is the “workhorse” of the prostate gland, responsible for epithelial barrier integrity and production of prostatic secretion. Luminal cells constitute most of the prostate epithelium. These tall (10 to 20 μm) columnar secretory epithelial cells are terminally differentiated and have a low proliferative index (De Marzo et al, 1998a); they are easily distinguished by their morphologic features and abundant secretory granules and enzymes. Secretory cells produce a variety of proteins that characterize prostatic differentiation, including PSA, acid phosphatase, AR, leucine amino peptidase, and 15-lipoxygenase-2 (Shappell et al, 1999; Bhatia et al, 2003). They are also rich in keratin filaments (subtypes 8 and 18) (van Leenders and Schalken, 2003). Secretory cells appear in rows like a picket fence with each cell connected to the next by cell adhesion molecules (CAMs); the apical aspect of these cells projects into the lumen, with the base attached to a basement membrane through integrin receptors (Knox et al, 1994). The nucleus is at the base just below a clear zone (2 to 8 μm) of abundant Golgi apparatus, and the upper cellular periphery is rich in secretory granules and enzymes. The apical plasma membrane facing the lumen possesses microvilli, and secretions move into the open collecting spaces of the acinus. These epithelial cells ring the periphery of the acinus and produce secretions into the acini that drain into ducts connected to the urethra.

Basal Cells

Basal cells (reviewed by De Marzo et al, 1998a) are the smallest of epithelial cells. They have a low mitotic index and are a minor population, accounting for less than 10% of the total cell number. Basal cells express a distinct keratin subtype profile (subtypes 5 and 14) compared with the columnar epithelial cells (subtypes 8 and 18). These cells are typically pyramid shaped with relatively little cytoplasm and condensed chromatin. Basal cells rest on the basement membrane wedged between the bases of adjacent, tall, columnar epithelial cells. The basal cell compartment has long been

considered the likely source of the epithelial stem cells of the prostate because they are relatively undifferentiated with a low proliferative index (approximately 1%) and almost devoid of secretory products, such as PSA and prostatic acid phosphatase (PAP) (see Fig. 102-2). Indeed, when mice are castrated after implantation with human prostate primary xenografts and then restimulated with testosterone, the basal cell population is highly overrepresented, consistent with the concept that the human basal compartment also contains prostate epithelial stem cells (Huss et al, 2004).

Prostate Epithelial Stem Cells

Recent experimental work in the mouse has provided powerful functional evidence for stem cell populations in the prostate, localizing them to the basal compartment, particularly in the proximal portions of prostatic ducts. These experiments used *in vivo* grafting assays to demonstrate critical stem cell characteristics including the ability of long-lived cells to proliferate indefinitely and to give rise to more differentiated phenotypes. Tsujimura and colleagues demonstrated DNA label-retaining PRECs with long-term proliferative potential that were preferentially localized to the proximal segments of prostatic ducts of adult males (Tsujimura et al, 2002). Further studies have mapped the stem cell properties of proximal duct cells to those expressing the mouse stem cell antigen Sca1, the basal cell integrin α_6 (Itga6 or CD49f), the tumor-associated calcium signal transducer Tacstd2 (also known as *Trop2*), and the stem cell factor receptor c-kit (Burger et al, 2005; Xin et al, 2005; Lawson et al, 2007; Goldstein et al, 2008; Leong and Gao, 2008).

Intermediate Cells

Intermediate cells are so named because they possess phenotypic characteristics intermediate between basal and luminal cells. Similarities of these cells to prostate cancer cells have marked them as hypothetical substrates for neoplastic transformation (Verhagen et al, 1992; De Marzo et al, 1998b), although their susceptibility to carcinogenesis is unknown. These investigators proposed that intermediate cells fulfill a transient amplifying function, providing a short-term amplification function for the long-term proliferative capabilities of basal stem cells. Intermediate cells produce basal cell keratins (5 and 14) and the secretory cell keratins 8 and 18 (De Marzo et al, 1998b; Schalken and van Leenders, 2003). Uzgare and colleagues (2004) reported transient amplifying properties of human intermediate cells in culture: a high proliferative fraction with the ability to proliferate for a limited number of generations. Survival of terminally differentiated secretory luminal cells and proliferation of intermediate cells require androgens potentially acting indirectly through the secretion of androgen-regulated growth factors by the stromal compartment (androgens) (Uzgare et al, 2004).

Neuroendocrine Cells

Neuroendocrine cells are cells that release hormones in response to neural stimulation. In the prostate, neuroendocrine cells reside among the more abundant secretory epithelial cells in the normal prostate gland as well as in the urothelium of the prostatic urethra (Aumuller et al, 2001). There are two types of neuroendocrine cells: the first is open and possesses specialized microvilli that protrude into the lumen; the second is closed with long dendrite-like processes that extend to nearby epithelial cells and basal cells close to afferent and efferent nerves (diSant-Agnese and deMesy-Jensen, 1984; diSant-Agnese et al, 1985; Abrahamsson, 1999; Vashchenko and Abrahamsson, 2005).

Thinking on the origin of prostatic neuroendocrine cells has evolved. Aumuller and associates (2001) demonstrated that neuroendocrine cells are readily identified in male and female urogenital sinus epithelium before human prostate development, suggesting that these might represent a separate lineage that is independent of prostate epithelium. More recently, Goldstein and coworkers (2008) showed that neuroendocrine, basal, and secretory luminal cells can

all originate from a common pluripotent *Trop2*-expressing prostate epithelial stem cell precursor.

Current evidence suggests that neuroendocrine cells can influence growth, differentiation, and secretory activity of the prostate epithelium through paracrine and autocrine mechanisms (Abrahamsson, 1999; Vashchenko and Abrahamsson, 2005). Neuroendocrine cells bring about their regulatory activity by the secretion of hormonal polypeptides or biogenic amines such as serotonin. High-pressure liquid chromatography measurements have shown that normal human prostatic tissue contains approximately 1400 ng of serotonin per gram of tissue, and this would certainly emphasize the importance of these cells (Davis, 1987). Higgins and Gosling (1989) have studied the structure and intrinsic innervations of the normal human prostate and have observed acetylcholinesterase-containing nerves associated with smooth muscle in both the peripheral and the central parts of the prostate. In addition, they have shown that the majority of the acini in the peripheral and central regions possess a rich plexus of autonomic nerves and that vasoactive intestinal peptide-positive nerve fibers are found in relation to the epithelial lining acini in the central and peripheral regions of the gland. Lepor and Kuhar (1984) characterized and studied the location of the muscarinic cholinergic receptor in human prostatic tissue and localized it to the epithelial cells. This is consistent with the neuropharmacology of muscarinic cholinergic agonist, which has a marked effect on increasing prostatic secretion. However, the α_1 -adrenergic receptor has its effect in the human prostatic stromal compartment. This is of clinical importance because of the use of selective α_1 -adrenergic antagonists to alleviate bladder outlet obstruction secondary to BPH (Lepor, 1993). Recent work has demonstrated three subtypes of the α_1 -adrenergic receptor (α_{1A} , α_{1B} , and α_{1D}). Of these, the α_{1A} receptor appears to be linked to smooth muscle contraction of the prostate (Lepor et al, 1993).

Neuroendocrine cells are terminally differentiated (i.e., nonproliferating) and do not express detectable AR, PSA, or Bcl-2. These cells release peptide hormones or prohormones by fusion of intracellular granules with the cell membrane and exocytosis of their contents. In addition to serotonin, neuroendocrine cells produce numerous bioactive macromolecules (major examples include bombesin, neuron-specific enolase, calcitonin gene family members, thyroid-stimulating hormone-like peptide, somatostatin, synaptophysin, and parathyroid hormone-like peptide). Neuroendocrine factors appear likely to influence the growth, differentiation, and secretion of epithelium of the prostate in both normal and malignant conditions (Vashchenko and Abrahamsson, 2005).

KEY POINTS: PROSTATE EPITHELIAL CELL TYPES

- The prostatic epithelium in the human is composed of two major cell compartments: epithelial cells and stromal cells.
- The epithelial cell types include mature secretory and terminally differentiated cells, neuroendocrine cells, intermediate cells, and basal cells.
- Prostatic stem cells reside in the basal compartment and are enriched in the proximal portions of prostatic ducts.

Stroma and Tissue Matrix

The noncellular stroma and connective tissue of the prostate make up what is termed the *ground substance* and the *extracellular matrix* in what was first suggested by Arcadi (1954) to play an important role in prostate function and disease. The extracellular matrix has long been recognized as one of the important inductive components during normal development of many different types of cells (Cunha, 1976; Hay, 1981; Bissell et al, 1982; Getzenberg et al, 1990; Risbridger et al, 2005). Classic tissue recombination experiments by Cunha and colleagues (1987) have clearly shown the direct importance of the isolated embryonic mesenchyme to the induction of differentiation of normal prostatic epithelial cells (see earlier discussion).

The epithelial cells rest on the basement lamina or membrane, which is a complex structure containing, in part, collagen types IV and V, glycosaminoglycans, complex polysaccharides, and glycolipids. This layer forms an interface to the stromal compartment that provides structural support for the basal cells and their progeny. It consists of an extracellular matrix, ground substance, and a variety of stromal cells, including the fibroblasts, capillary and lymphatic endothelial cells, smooth muscle cells, neuroendocrine cells, and axons (reviewed in [Taylor and Risbridger, 2008](#)).

The **cytomatrix** (cytoplasmic skeleton) terminates in the center of the cell by direct attachment to the **nuclear matrix**. The prostatic epithelial cell therefore has direct structural linkage via the matrix system from the DNA to the plasma membrane. The cytomatrix then makes direct contact with the basement membrane, extracellular matrix, and ground substance of the stroma. This entire interlocking tissue scaffolding or superstructure is termed the **tissue matrix** and may have dynamic properties in ordering and controlling biologic processes as well as in the transport of secretions from the sex accessory tissues ([Getzenberg et al, 1990](#); [Konety and Getzenberg, 1999](#); [Etienne-Manneville, 2004](#); [Miner and Yurchenco, 2004](#); [Hallmann et al, 2005](#)).

Understanding the biologic components of the tissue matrix system within sex accessory tissues is of paramount importance to understanding its physiology. The laminin proteins are glycoproteins of the extracellular matrix that mediate attachment of cells to the type IV collagen of the basement membrane ([Miner and Yurchenco, 2004](#); [Yurchenco et al, 2004](#); [Hallmann et al, 2005](#)). Laminin is produced by epithelial cells but not by fibroblasts; it is a large molecule (approximately 800 kD) with molecular domains that interact with the type IV collagen of the basement membrane and with integrin-type receptors within the cell surface glycocalyx of the epithelial cell ([Aumailley et al, 2005](#)). Laminins are the major anchor filaments in the basement membranes of epithelial cells that stabilize attachment of hemidesmosomes via $\alpha_6\beta_4$ integrin ([Brar et al, 2003](#); [Miner and Yurchenco, 2004](#)). The key functional properties of the laminins are cell adhesion, proliferation, differentiation, growth, and migration. Laminin surrounds the basement membrane of prostate acinar epithelial cells, capillaries, smooth muscle, and nerve fibers but not lymphatics, lymphocytes, or fibroblasts; the laminin structure and its distribution are disrupted in BPH and higher-grade prostatic intraepithelial neoplasia and higher-grade prostate neoplasms ([Sinha et al, 1989](#); [Brar et al, 2003](#); [Miner and Yurchenco, 2004](#)).

In summary, the development and maintenance of the prostate occurs through androgen-dependent and highly regulated tissue morphogenesis in processes involving epithelial cell differentiation, proliferation, and apoptosis ([Cunha et al, 2004](#)). Communication through numerous extracellular interactions is directed to the intracellular cytoskeleton and then to the nuclear matrix, which ultimately regulates a variety of transcriptional cell functions that control such critical phenotypic qualities as cell size and shape, cell motility, epithelial cell turnover, proliferation, and differentiation ([Getzenberg et al, 1990](#); [Pienta et al, 1993](#); [Miner and Yurchenco, 2004](#)).

Seminal Vesicles and Their Development

The sex accessory tissues include the epididymis, ampullae, seminal vesicles, prostate, Cowper (bulbourethral) gland, and glands of Littre. All of these glands have reproductive roles, but the seminal vesicles work in tandem with the prostate and provide an important counterpoint to its biology and pathologic processes. The seminal vesicles are two saccular glands that pair with the vasa deferentia to form the ejaculatory ducts that empty into the craniodorsal aspects of the prostate. Together with the prostate, the seminal vesicles produce seminal fluid that nurtures, protects, and facilitates sperm transport for mammalian reproduction. The division of labor between the prostate and seminal vesicles is surprisingly variable among species. At one end of the spectrum is the dog, a species in which seminal vesicles are absent and the prostate must therefore carry out the functions that are divided between the two glands in

other species. Most mammals, including humans, rats, and mice, occupy the other end of the spectrum, in which the seminal vesicles produce most of the seminal fluid, with the prostate playing a minor role. In species with both glands, physiologic cooperation between the two glands is also appreciable at the molecular level. For example, the major secretory protein product of the seminal vesicles is semenogelin, a 52-kD protein that serves as a substrate for proteolytic enzymes produced by the prostate, including PSA. Proteolysis of semenogelin yields a variety of peptide byproducts that are believed to serve reproductive and antimicrobial functions in humans ([Curry and Atherton, 1990](#)). In mice and rats, seminal vesicle and prostate products cooperate to coagulate the ejaculate into a firm copulatory plug in the vagina during mating. The plug serves as a temporary barrier to further mating by the female, potentially blocking impregnation by competing males.

Seminal vesicles develop from the mesonephric (wolffian) ducts shortly before the onset of prostate development. Seminal vesicle development is strictly dependent on an intact AR signaling pathway, including the ligand testosterone (reviewed in [Wilson et al, 1981](#)). This requirement contrasts to development of the human prostate (see later), which, in addition to an intact AR pathway, requires conversion of testosterone into the more potent 5α -reduced androgen, DHT ([Andersson et al, 1991](#); [Mahendroo and Russell, 1999](#)).

Thick smooth muscle layers constitute the muscular stroma of the seminal vesicles, which surrounds a short columnar-to-cuboidal epithelium. The epithelium has distinct basal and luminal layers that are notable for unusually variable nuclear size and shape, a feature that is also found in prostate cancer ([Epstein and Netto, 2007](#)). Another notable feature of the epithelium of the seminal vesicles, the almost invariable appearance of gold-colored intracytoplasmic pigment, is usually absent in prostate cancer and helps to clarify any confusion between the two entities. Seminal vesicle pigment is thought to derive from cellular byproducts of nonviable sperm ingested by the seminal vesicle epithelium (spermatophagy).

The seminal vesicles are extremely resistant to disease. Given their proximity, shared functions, and similar endocrine requirements to the prostate, it is striking that diseases of the seminal vesicles in humans are vanishingly rare. In contrast, prostate disease, at least in Western cultures, is a nearly universal rite of passage into old age (see subsequent chapters on BPH and prostate cancer). Accordingly, contrasting gene expression between seminal vesicles and prostate has been used as a strategy to discover the molecular basis of prostate cancer risk ([Thompson et al, 2008](#)).

ENDOCRINE CONTROL OF PROSTATE GROWTH

The prostate, like other sex accessory tissues, is stimulated in its growth, maintenance, and secretory function by the continued presence of certain hormones and growth factors. Foremost among these is testosterone, which is converted within the prostate into the more active androgen DHT. Testosterone is synthesized in the Leydig cells of the testes from pregnenolone by a series of reversible reactions. However, once testosterone is converted by 5α -reductase into DHT or converted by aromatase into estrogens, the process is irreversible: **testosterone can be converted to DHT or estrogens, but estrogens and DHT cannot be converted to testosterone**. Androgens, estrogens, and adrenal steroids are believed to have strong effects on different cells and tissues in the body that can vary with development and age. These vary from embryonic development to puberty and on into adult maintenance and aging. Therefore, androgen ablation or androgen treatments have a wide variety of physiologic effects that merit consideration.

The generalized endocrine physiology of the prostate is depicted in [Figure 102-3](#). The hypothalamus releases a small 10-residue polypeptide (decapeptide) referred to as **luteinizing hormone-releasing hormone (LHRH)**, also called **gonadotropin-releasing hormone (GnRH)**. Under the stimulation of LHRH the pituitary releases luteinizing hormone (LH), which is transported to the testes and acts directly on the Leydig cells to stimulate de novo steroid synthesis and

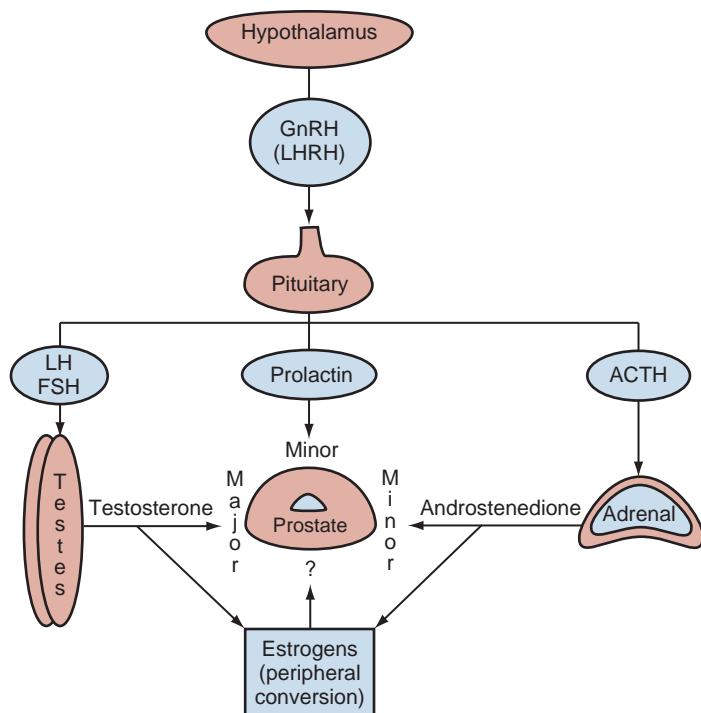


Figure 102-3. Simplified endocrinology of the prostate. Luteinizing hormone–releasing hormone (LHRH), also known as gonadotropin-releasing hormone (GnRH), stimulates the pituitary to release the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the Leydig cells of the testes to synthesize testosterone. Testosterone is the major serum androgen stimulating prostate growth. Peripheral conversion of testosterone by aromatization forms the estrogens in the male. The adrenal gland is under stimulation by adrenocorticotropic hormone (ACTH) and releases the minor androgens, such as androstenedione, which is also converted peripherally to estrogens. Prolactin has also been shown to have a minor effect in stimulating androgen-induced prostate growth. The prostate can produce its own growth factors (autocrine or paracrine) or respond to circulating growth factors.

release of testosterone, the major serum androgen of the body. Most of the estrogen in the male is derived from peripheral conversion of androgens to estrogens through aromatization. Exogenous estrogens, such as diethylstilbestrol, block androgen action not primarily by direct effects on the prostate but indirectly through blocking pituitary function. The estrogen causes a negative feedback on LH release that reduces the serum signal for testicular testosterone production; therefore, estrogen acts as an effective “chemical castration.”

Recent studies in prostate cancer biology have revealed that prostate cancer cells are capable of *de novo* androgen synthesis, leading to renewed interest in steroid 17 α -hydroxylase/17,20-lyase blockade (e.g., abiraterone), or direct AR antagonism (e.g., enzalutamide); however, it is doubtful that benign prostatic epithelial cells produce intracrine androgens in clinically significant amounts, because castration leads to nearly complete involution of the prostate. In addition, the adrenal secretes a weak androgen, androstenedione; however, this also is not a major influence on prostate physiology because castration leads to almost complete involution of the prostate, meaning that insufficient adrenal androgens are present to stimulate any meaningful growth of the normal prostate. Similar to serum testosterone, androstenedione can undergo aromatization to estrone. Overproduction of androstenedione, such as occurs in certain forms of congenital adrenal hyperplasia, may stimulate prostate growth; however, again, the role of normal circulating adrenal androgens in regulating prostate growth is minor. The presence of a nontesticular minor androgen source has led to

the concept of total androgen blockade for the treatment of advanced prostate cancer, whereby both an LHRH agonist and a nonsteroidal antiandrogen are combined to eliminate testosterone production and block any residual androgen stimulation of the prostate from the adrenal gland. With the realization that prostate cancer cells can produce intracrine androgens and various constitutively active AR splice isoforms, true androgen blockade will require further addition of drugs of the newer class such as abiraterone and enzalutamide.

Androgen Production by the Testes

Because the testes produce the major serum androgen supporting prostate and sex accessory tissue growth, it is important to briefly review this function. In the normal human male the major circulating serum androgen is testosterone, which is almost exclusively (approximately 95%) of testicular origin. **Under normal physiologic conditions the Leydig cells of the testis are the major source of the testicular androgens.** The Leydig cells are stimulated by the gonadotropins (primarily LH) to synthesize testosterone from acetate and cholesterol. The spermatic vein concentration of testosterone is 40 to 50 $\mu\text{g/dL}$, approximately 75 times more concentrated than the level detected in the peripheral venous serum (Hammond, 1978), which is approximately 600 ng/dL . Other androgens also leave the testes by the spermatic vein; these include androstenediol, androstenedione (3 $\mu\text{g/dL}$), dehydroepiandrosterone (DHEA) (7 $\mu\text{g/dL}$), and DHT (0.4 $\mu\text{g/dL}$). The concentrations of these androgens are much lower in the spermatic vein than the concentration of testosterone, with all being less than 15% of the concentration of testosterone.

The total testosterone that enters the plasma is referred to as the *testosterone blood production rate* and is 6 to 7 mg/day in the human. Although other steroids, such as androstenedione from the adrenals, can be converted by peripheral metabolism to testosterone, they account for less than 5% of the overall production of plasma testosterone. The plasma half-life of testosterone is only 10 to 20 minutes, which means that a man undergoing bilateral simple orchiectomy is functionally castrated within 1 to 2 hours of surgery. Hence, the most rapid method of androgen suppression for the purposes of immediate relief of spinal cord compression from prostate cancer metastasis is surgical castration.

The average testosterone concentration in the plasma of a man is approximately 611 $\text{ng/dL} \pm 186$, with a normal range of 300 to 1000, which is equal to 10.4 to 34.7 nmol/L in SI units (Table 102-2). Serum testosterone level is not remarkably related to age between 25 and 70 years, although it does decline gradually to approximately 500 ng/dL after 70 years of age. It is recognized that plasma concentrations of testosterone can vary widely in an individual on any one day and may reflect both episodic and diurnal variations in the production rate.

Metabolic androgens such as 17-ketosteroids are then secreted into the urine as water-soluble glucuronide or sulfate conjugates. The total 17-ketosteroid level in the urine in adult men is 4 to 25 mg/24 hr and is not an accurate index of testosterone production, because other steroids from the adrenals as well as nonandrogenic steroids can be metabolized to 17-ketosteroids. Only small amounts (25 to 160 $\mu\text{g/day}$) of testosterone enter the urine without metabolism, and this urinary testosterone represents less than 2% of the daily testosterone production.

Although testosterone is the primary plasma androgen inducing growth of the prostate gland and other sex accessory tissues, it appears to function as a prohormone in that the most active form of the androgen in the prostate is not testosterone but rather DHT (Farnsworth and Brown, 1963; Anderson and Liao, 1968; Bruchovsky and Wilson, 1968) (Fig. 102-4). The formation of DHT involves the reduction of the double bond in the A ring of testosterone through the enzymatic action of the enzyme 5 α -reductase (Fig. 102-5). There are at least two isoforms of this enzyme (type 1 and type 2). Type 2 5 α -reductase expression predominates in human accessory sex tissues and is localized to the fibromuscular stromal compartment (Silver et al, 1994). The type 1 isoform predominates

TABLE 102-2 Average Plasma Levels of Sex Steroids in Healthy Human Males

STERIOD (COMMON NAME)	PLASMA CONCENTRATION (ng/dL)	RELATIVE MOLARITY	DAILY BLOOD PRODUCTION RATE (mg/day)	RELATIVE ANDROGENICITY (RAT VP ASSAY)
Testosterone	611 ± 186	100	6.6 ± 0.5	100
Dihydrotestosterone	56 ± 20	9	0.3 ± 0.06	181
5 α -Androstane-3 α ,17 β -diol (3 β -androstenediol)	14 ± 4	2	0.2 ± 0.03	126
5 α -Androstane-3 β ,17 β -diol (3 β -androstenediol)		<2	<0.3	18
Androstenediol	161 ± 52	26	0.21	
Androsterone	54 ± 32	9	0.28	53
Androstenedione	150 ± 54	25	1.4	39
Dehydroepiandrosterone	501 ± 98	81	29	15
Dehydroepiandrosterone sulfate	135,925 ± 48,000	17,619		<1
Progesterone		30	4.5	
17 β -Estradiol	2.5 ± 0.08		0.4	0.75
Estrone		4.6	0.8	0.04

VP, ventral prostate.

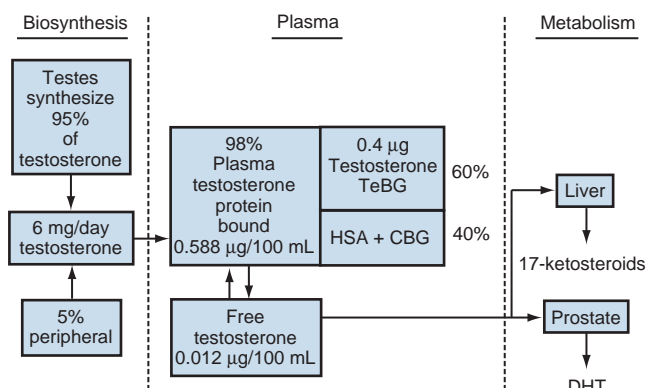


Figure 102-4. Quantitative assessment of the testicular biosynthesis, plasma transport, and metabolism of testosterone. Plasma testosterone is bound to sex steroid-binding globulin (SSBG), human serum albumin (HSA), and cortisol-binding globulin (CBG). All numbers are average values for the normal adult male. DHT, dihydrotestosterone; TeBG, testosterone-binding globulin.

in skin, in prostatic epithelia, and to a lesser extent in prostatic fibromuscular stroma. Inhibition of 5 α -reductase by finasteride appears to be largely selective for the type 2 isoform (Iehle et al, 1995; Habib et al, 1997); the newer agent dutasteride inhibits both type 1 and type 2 5 α -reductase. Both drugs appear to exert similar effects in terms of reduction in prostatic volume and serum PSA concentration, suggesting that the type 2 isoform is the only clinically significant isoform present in the prostate. DHT concentration in the plasma of normal men is low, 56 ± 20 ng/dL, in comparison to testosterone, with a concentration 11-fold higher at approximately 611 ng/dL (see Table 102-2). In summary, although DHT is a potent androgen (2 to 10 times as potent as testosterone in many bioassay systems), its low plasma concentration and tight binding to plasma proteins diminishes its direct importance as a circulating androgen affecting prostate and seminal vesicle growth. In contrast, DHT is of paramount importance within the prostate, where it is formed from testosterone. DHT is the major form of androgen found within the prostate gland (5 ng/g tissue wet weight) and is fivefold higher than testosterone. In the prostate, DHT binds to ARs and activates the receptors to regulate a variety of cellular processes. In summary, DHT becomes the major

androgen regulating the cellular events of growth, differentiation, and secondary functions in the prostate.

The normal adult male plasma levels of some important steroids are summarized in Table 102-2. These values are derived as averages from numerous studies. Individual values can fluctuate with age, time of day, medications, stress, hospitalization, and environmental changes. For this reason, serum measurements of testosterone should be done only in the morning (e.g., 8:00 AM), because late afternoon measurements can drop by as much as 25% by diurnal variation alone (Brambilla et al, 2009).

Adrenal Androgens

There is evidence that overproduction of adrenal steroids can stimulate growth of the prostate gland. For example, in humans, abnormal virilism has been observed in immature males with a hyperfunctioning adrenal cortex. In rodents, overstimulation of the adrenals can also induce limited prostate growth even in the absence of testicular androgens. For example, administration of exogenous adrenocorticotrophic hormone to castrated animals does significantly increase the growth of sex accessory glands (Tullner, 1963; Tisell, 1970; Walsh and Gittes, 1970). However, the effect of normal levels of adrenal androgens on the prostate in noncastrated humans and adult male rats does not appear to be significant because adrenalectomy has little effect on prostate size, DNA, or morphologic characteristics of the sex accessory tissue (Mobbs et al, 1973; Oesterling et al, 1986). Furthermore, after castration in animals, with the adrenals intact, the prostate will finally diminish to a very small size (90% reduction in total cell mass). Finally, the small involuted ventral prostate in the castrated rat cannot be significantly reduced further by additional adrenalectomy or hypophysectomy (Kyprianou and Isaacs, 1987). In castrated rats, the DHT level in the prostatic tissue is approximately 20% that in normal intact animals. Adrenalectomy lowers the DHT to undetectable levels without further diminution in prostate growth. This indicates that a threshold level of DHT is required in the prostate to stimulate growth and that the castrate level is below this threshold. It has also been concluded similarly that the human prostate does not restore itself after castration, indicating that adrenal androgens are insufficient to compensate for the loss of testicular function. Quantitative morphometry of the human prostate (Oesterling et al, 1986) also confirms that the adrenal gland has little effect on the epithelial cell size of the normal prostate.

The adrenal steroid DHEA and the conjugate dehydroepiandrosterone sulfate (DHEAS) as well as androstenedione are androgens

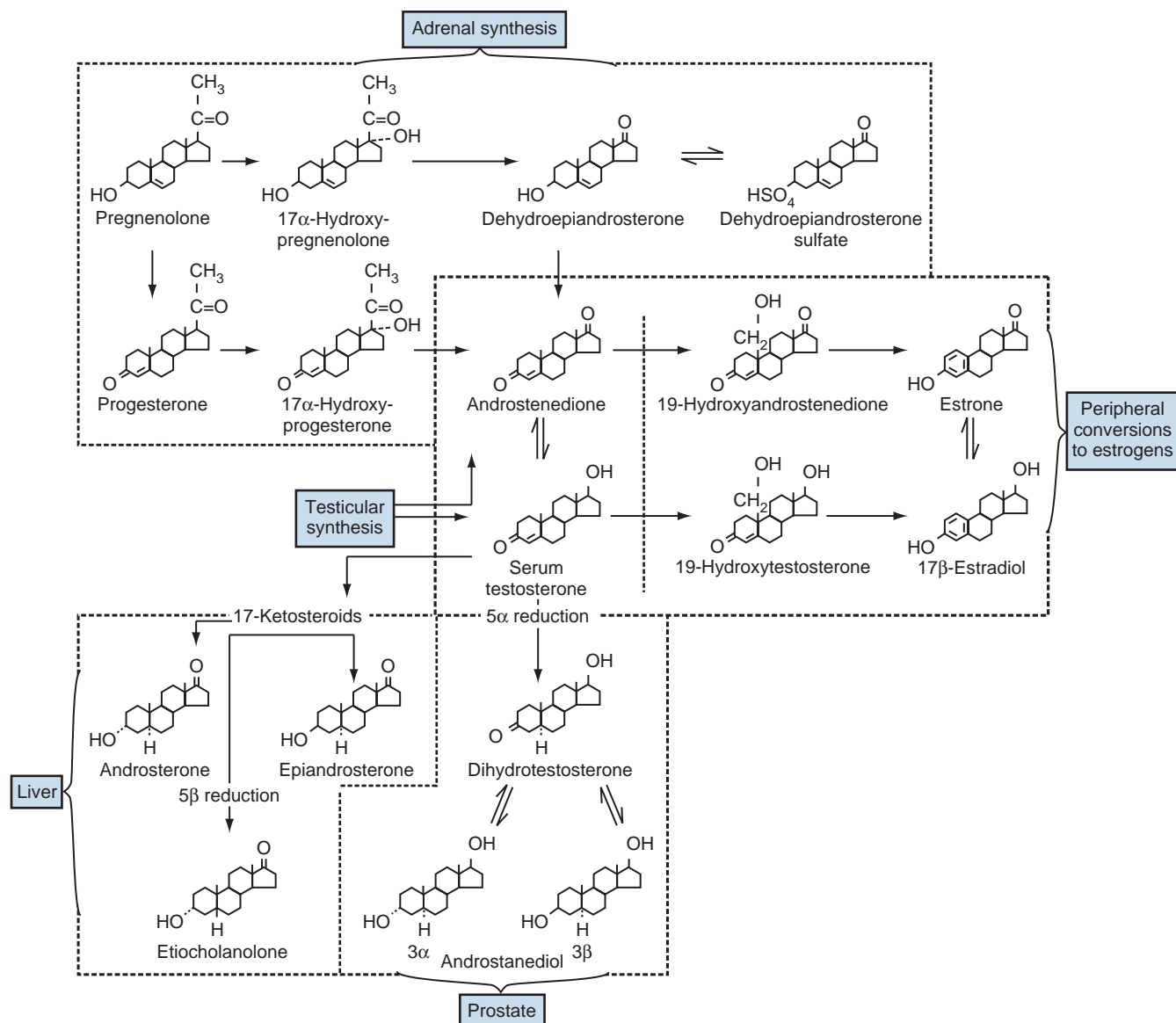


Figure 102-5. Overview of the synthesis and metabolism of testosterone in four main body compartments: adrenal synthesis of androstenedione; peripheral conversion of androgens (androstenedione and testosterone) to estrogens; formation of active androgen (DHT) within the prostate; and inactivation in the liver of testosterone to three types of 17-ketosteroids.

synthesized from acetate and cholesterol (see Fig. 102-5) that are secreted by the normal human adrenal glands. Essentially all of the DHEA in the male plasma is of adrenal cortex origin, and the production rate in males is 10 to 30 mg/day. **Less than 1% of the total testosterone in the plasma is derived from DHEA** (Horton, 1976; MacDonald, 1976). The prostate and seminal vesicles of the rat and the human prostate can slowly hydrolyze DHEAS to free steroids through prostatic sulfatase enzymatic activity, but the degree of conversion is low; hence, DHEAS is not a potent androgen.

A second adrenal androgen is androstenedione, and the plasma concentration in adult men is approximately 150 ± 54 ng/dL (see Table 102-2). The blood production rate of androstenedione in human males is 2 to 6 mg/day, with approximately 20% of the androstenedione being generated by peripheral metabolism of other steroids. **Androstenedione cannot be converted directly to DHT.** An important role for androstenedione in the male may be its peripheral conversion to estrogens through the aromatase reaction (see Fig. 102-5).

The adrenal gland also produces C21 steroids (e.g., progesterone). The plasma production rate at 0.75 mg/day is low, producing

a low plasma progesterone concentration of 30 ng/dL. Although progesterone is weakly androgenic, it does not exert a significant effect on the prostate at the low concentrations present in normal male plasma. **In summary, under normal conditions, the adrenals do not support significant growth of prostatic tissue.**

Estrogens in the Male

The estrogen receptors (ERs) are differentially expressed in the prostate. In the mouse, ER- α is expressed early (1 week) in the stroma of the ventral prostate but by 2 weeks is preferentially expressed in the epithelia, and ER- α is absent altogether in the ventral prostate by 4 weeks. In contrast, ER- β exists in the epithelial compartment as the dominant ER by the fourth week. It is interesting to note, however, that knockout mice for ER (both isoforms) are able to form grossly normal prostates, although fertility may be limited in the ER- α group (Couse et al, 2001). Only small amounts of estrogen are produced directly by the testes. In the plasma of young healthy human males, 75% to 90% of the estrogens are derived from the peripheral conversion of androstenedione and testosterone to

estrone and estradiol through the aromatase reaction (see Fig. 102-5) (Horton, 1976; MacDonald, 1976). The androgenic C19 steroids (testosterone and androstenedione) are converted to the estrogenic C18 steroids first by removal of the 19-methyl group and then by the formation of an aromatic or phenolic steroid A ring (aromatase reaction), present in both estradiol and estrone. Estradiol is formed from testosterone and estrone from androstenedione; these two estrogens are interconvertible. The daily production of estradiol in the human male is 40 to 50 μg , and only 5 to 10 μg (10% to 25%) can be accounted for by direct testicular secretion (see Table 102-2).

Androgen-Binding Proteins in the Plasma

Less than 2% of the total testosterone in human plasma is free or unbound; the remaining 98% is bound to several different types of plasma proteins (see Fig. 102-4). The plasma proteins that bind steroids include human serum albumin, sex hormone-binding globulin (denoted SHBG or SHBG), corticosteroid-binding globulin (also named *transcortin*), progesterone-binding globulin, and, to a lesser extent, α_1 -acid glycoprotein. Under normal conditions, the total amount of testosterone bound to progesterone-binding globulin and α_1 -acid glycoprotein is nominal and is usually ignored. SHBG levels are suppressed by circulating androgens as well as anabolic steroids and may be decreased by diabetes and obesity.

The regulation of the amount of androgen that is free is an important physiologic variable and varies in different species. The total amount of steroid bound depends on two factors: (1) the *affinity* of the steroid to bind to a specific protein and (2) the *capacity*, which is the maximal potential binding when all of a binding protein is saturated with bound steroid. The capacity is governed by the amount of binding protein in the plasma. Serum albumin has a relatively low affinity for testosterone, but, given its abundance, it has a high capacity. In contrast, SHBG has a high affinity for binding steroids, but the protein is present in relatively low concentrations; however, the plasma molarity of each binding protein exceeds the plasma molarity for total testosterone concentration. The majority of testosterone bound to plasma protein is associated with SHBG. For example, Vermeulen (1973) has calculated that in the normal human male, 57% of testosterone in the plasma is bound to SHBG and 40% is bound to human serum albumin. Less than 1% is bound to corticosteroid-binding globulin, and only 2% of the total testosterone is free (see Fig. 102-4). The normal plasma free testosterone level is therefore 12.1 ± 3.7 ng/dL or 0.42 nM; this non-protein-bound "free testosterone" is bioavailable to diffuse into the sex accessory tissue and into liver cells for metabolism. In addition, a large percentage of the SHBG is saturated, whereas only a small fraction of the total capacity of corticosteroid-binding globulin and albumin is used under normal conditions. As testosterone levels increase in the plasma, the order of increasing saturation of the plasma proteins proceeds from SHBG to corticosteroid-binding globulin to albumin. Therefore, the binding of androgen is a dynamic equilibrium between various serum proteins. Because less than 5% of total testosterone is present in the free form, separate measurement of bound and free testosterone is typically not recommended, and in general only total testosterone is measured.

The total plasma levels of SHBG can be altered by hormone therapy. Administration of testosterone decreases SHBG levels in the plasma, whereas estrogen therapy stimulates SHBG levels (Forest et al, 1968; Vermeulen et al, 1969; Burton and Westphal, 1972). Estrogen also competes with testosterone for binding to SHBG, but estrogen has only one third the binding affinity of testosterone. Therefore, administration of small amounts of estrogen increases the total concentration of SHBG, and this effectively increases the binding of testosterone and thus lowers the free testosterone plasma concentration.

Because only free testosterone is bioavailable, the binding of testosterone to plasma proteins inhibits net testosterone uptake into the prostate (Lasnitzki and Franklin, 1972). It is apparent that

androgenic activity is regulated in part by the extent of binding of an androgen to the steroid-binding proteins in the plasma.

KEY POINTS: ENDOCRINE CONTROL OF PROSTATE GROWTH

- Free testosterone in the plasma is converted in the prostate by 5 α -reductase type 2 into DHT, which is 2 to 10 times more active than testosterone.
- DHT, testosterone, and estrogens are responsible for multiple metabolic actions in the prostate (growth, differentiation, and biologic functions). Free testosterone can be converted to estrogens, but estrogens cannot be converted to testosterone.

REGULATION OF PROSTATE GROWTH BY STEROIDS AND PROTEIN GROWTH FACTORS

There are multiple levels of prostate growth regulation, which include steroid hormone action, growth factors, and direct cell-cell communication and interactions with the extracellular matrix. These interactive types of growth control are accomplished by several generalized systems, as depicted in the schematic in Figure 102-6. They include the following:

- *Endocrine factors* or long-range signals arriving at the prostate by serum transport of hormone originating from the secretions of distant organs; endocrine factors include serum steroid hormones such as testosterone and estrogens and serum peptide hormones such as prolactin and gonadotropins.

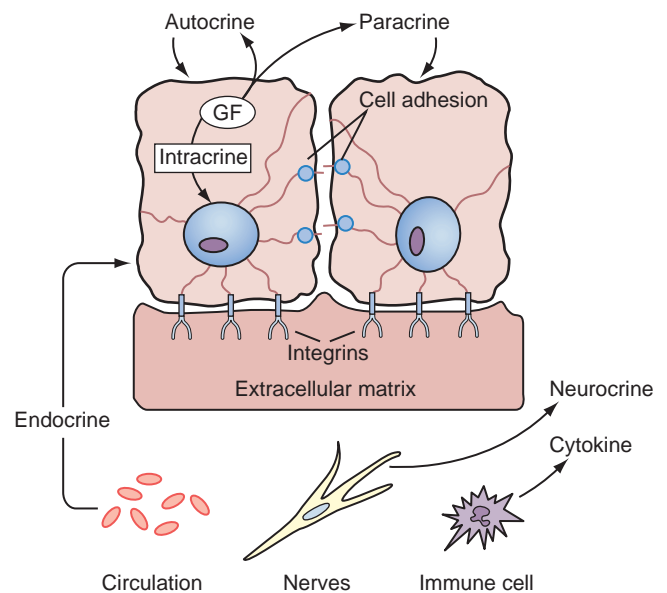


Figure 102-6. Types of growth control. Endocrine signals are carried through the circulation from distant organs. Paracrine signals are produced in proximity by neighboring cells. Autocrine signals feed back on the same cells from which they are produced. Intracrine signals are a special subset of autocrine signals that never leave the cell but rather act locally within that cell. Cytokines are paracrine-like factors (typically) that are made by immune cells. Neurocrine factors are released by nerves. Cell adhesion molecules directly link neighboring cells, often through association with cognate adhesion molecules. Cells are also bound to the extracellular matrix through interactions with other cell adhesion molecules (e.g., integrins). GF, growth factor.

- *Neuroendocrine signals* originating from neural stimulation, such as 5-hydroxytryptamine (serotonin), acetylcholine, and norepinephrine.
- *Paracrine factors* or soluble tissue growth factors that stimulate or inhibit growth, which are elaborated over short ranges between neighboring cells within the prostatic tissue compartment (FGFs, epidermal growth factor).
- *Autocrine factors* that are produced and released by a cell and then fed back on the same cell's external membrane receptors to regulate its own growth or function; for example, autocrine motility factor.
- *Intracrine factors*, which function like autocrine factors but work inside the cell.
- *Extracellular matrix factors*, which are insoluble tissue matrix systems and make direct and coupled contact by being attached through integrins and adhesion molecules of the basal membrane and couple cytoskeleton organization with the extracellular matrix components, which include the glycosaminoglycans, such as heparan sulfate (Getzenberg et al, 1990).
- *Cell-cell interactions* of the epithelial or stromal cells occurring through tight membrane junctions on intramembrane proteins such as the CAMs (e.g., E-cadherin) that couple neighboring cells.

Of these seven growth control systems, the first extensively studied on the prostate was the endocrine effect of androgenic steroids, such as testosterone, in the regulation of prostate growth through changes in serum testosterone levels and conversion to DHT. However, androgens alone are not sufficient for full prostate growth. In the past two decades, extensive progress has been made in the understanding of the other systems, particularly the interactive role of growth factors and their receptors. At present, the roles of these receptors in cell signaling to the nucleus and of the structural elements in cellular control involving the tissue matrix are being developed. These mechanisms are reviewed next, starting with androgen action at the cell level beginning with the arrival of testosterone in the serum.

Androgen Action at the Cellular Level

Testosterone in the serum arrives at the prostate bound to albumin and to the steroid-binding globulins. By diffusion, free testosterone enters the prostate cell, where it is then subjected to a variety of steroid metabolic steps that appear to regulate the activity of the steroid hormone and its downstream effectors. A simplified schematic of the temporal sequence of intracellular events is depicted in Figure 102-7 and includes the following:

- Cellular uptake of testosterone.
- Testosterone conversion to DHT by metabolism of 5 α -reductase.
- DHT or testosterone binding to specific ARs in the cytoplasm.
- Dimerization and activation of the steroid receptor by a variety of post-translational steps, including, for instance, phosphorylation.
- Active nuclear transportation of the activated AR in an adenosine triphosphate (ATP)-dependent fashion.
- Chromatin remodeling through interaction with coregulatory molecules.
- Transactivation or transrepression, through interactions with other coactivators or corepressors, in a histone acetyltransferase-dependent process.
- Binding of the activated receptor-coactivator complex to androgen response elements, which are short, specific sequences of DNA recognized specifically by AR dimers.
- Gene regulation. The receptor acts as a transcription factor, and when it is bound to the DNA and matrix in proximity to androgen target genes it increases the RNA polymerase II transcription of the DNA into mRNA. The transcribed message (mRNA) is large and contains introns, exons, and a poly-A tail. The intron portion is excised from the initial RNA species, so that only the exon portion is retained in the final message. The trimming and processing of the mRNA are accomplished on the nuclear matrix as it is transported through the nucleus and out through the nuclear pore complex. The stabilized mRNA is transported into the cytoplasmic compartment to be translated at the ribosome.

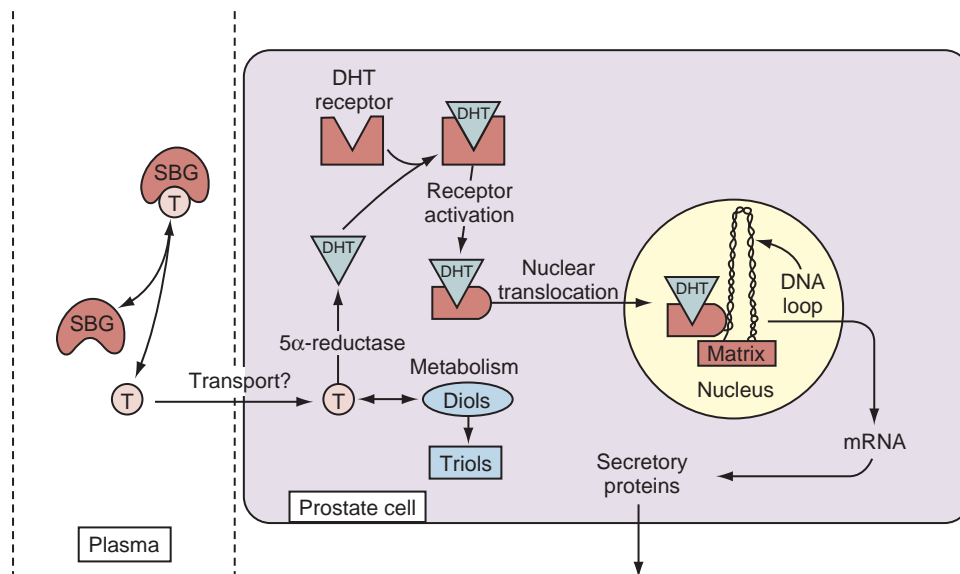


Figure 102-7. Simplified schematic of the effects of testosterone in activating transcriptional targets in an epithelial cell. In the plasma, testosterone (T) is bound to serum-binding globulins (SBG), such as testosterone-binding globulin and albumin. Unbound testosterone is transported by passive diffusion into the prostate, where it is enzymatically converted to dihydrotestosterone (DHT) by 5 α -reductase (type 2) and further metabolized to diols (3 α or 3 β) and irreversibly metabolized into the more water-soluble triols (6 α or 7 α). DHT binds to a cytoplasmic receptor (androgen receptor) that is activated and translocated to the nucleus. There the androgen receptor localizes in matrix acceptor sites and subsequently activates or represses certain target genes by regulating production of their mRNA. The RNA is then transported to the cytoplasm, where it is translated into a variety of proteins (e.g., secretory proteins such as prostate-specific antigen).

into protein, which is then transported to specific cellular sites. Depending on the target gene, some proteins will undergo storage in secretory granules poised for secretion into the lumen on command during the physiologic process of ejaculation.

The epithelial cell is the primary unit in secretion, but specific genes are also activated in the stromal cells, and these events are also regulated by testosterone, estrogens, and growth factors in a similar chain of events. However, not all cells respond in the same manner to androgens or estrogens. For simplicity, these steps are discussed in relation to the epithelial cells. Androgens and estrogens, both together and separately, can affect prostate cells through interaction with receptors, and it appears that estrogens might have their primary effect on the stromal cells.

5 α -Reductase and Androgen Metabolism within the Prostate

After the free testosterone in the plasma has entered the prostate cells through diffusion, it is rapidly metabolized to other steroids by a series of prostatic enzymes (Isaacs et al, 1981, 1983; Isaacs and Coffey, 1981; Bruchovsky and Dunstan-Adams, 1985). More than 90% of testosterone is *irreversibly* converted to the main prostatic androgen DHT (Fig. 102-8) through the action of the reduced form of nicotinamide-adenine dinucleotide phosphate (NADP) and the enzyme 5 α -reductase located on the endoplasmic reticulum and on the nuclear membrane. The enzyme 5 α -reductase reduces the

unsaturated bond in testosterone between the 4 and 5 positions to form the 5 α -reduced product DHT. The K_m for testosterone is 8.3 nM, and the serum level of testosterone is only in the range of 0.5 to 3.0 nM, indicating that the enzyme cannot be saturated because the testosterone substrate would be less than the K_m value. Bruchovsky and Dunstan-Adams (1985) reported a 10-fold increase in the maximal velocity in the stromal tissue compared with the epithelium. They observed 262 pmol of DHT formed in 30 minutes per milligram of protein from testosterone measured in the stroma and less than 10% of that amount with a maximal velocity of 19 for the epithelium. The stromal K_m was 76 nM and the epithelial K_m was 13 nM. These differences between stromal and epithelial kinetics were used to deduce the existence of two different isoenzymes of 5 α -reductase (Andersson et al, 1991).

In the human, rat, and monkey there are two isozymes of 5 α -reductase (Table 102-3). The human and rat 5 α -reductase isozymes are composed of 254 to 260 amino acids with a molecular weight of 28 to 29 kD. These enzymes are N- and O-glycosylated and have a high percentage of hydrophobic amino acids that are distributed throughout the enzyme. The chromosomal localization of the human 5 α -reductase isozyme genes has been reported; the type 1 enzyme is at the extreme tip of the short arm of chromosome 5, and the human type 2 gene is on the short arm of chromosome 2. There is a 49% homology between type 1 and 2 enzymes in the human. The properties of these enzymes have been reviewed in detail by Russell and Wilson (1994), and the effects on prostate growth by McConnell (1995). The effect of finasteride

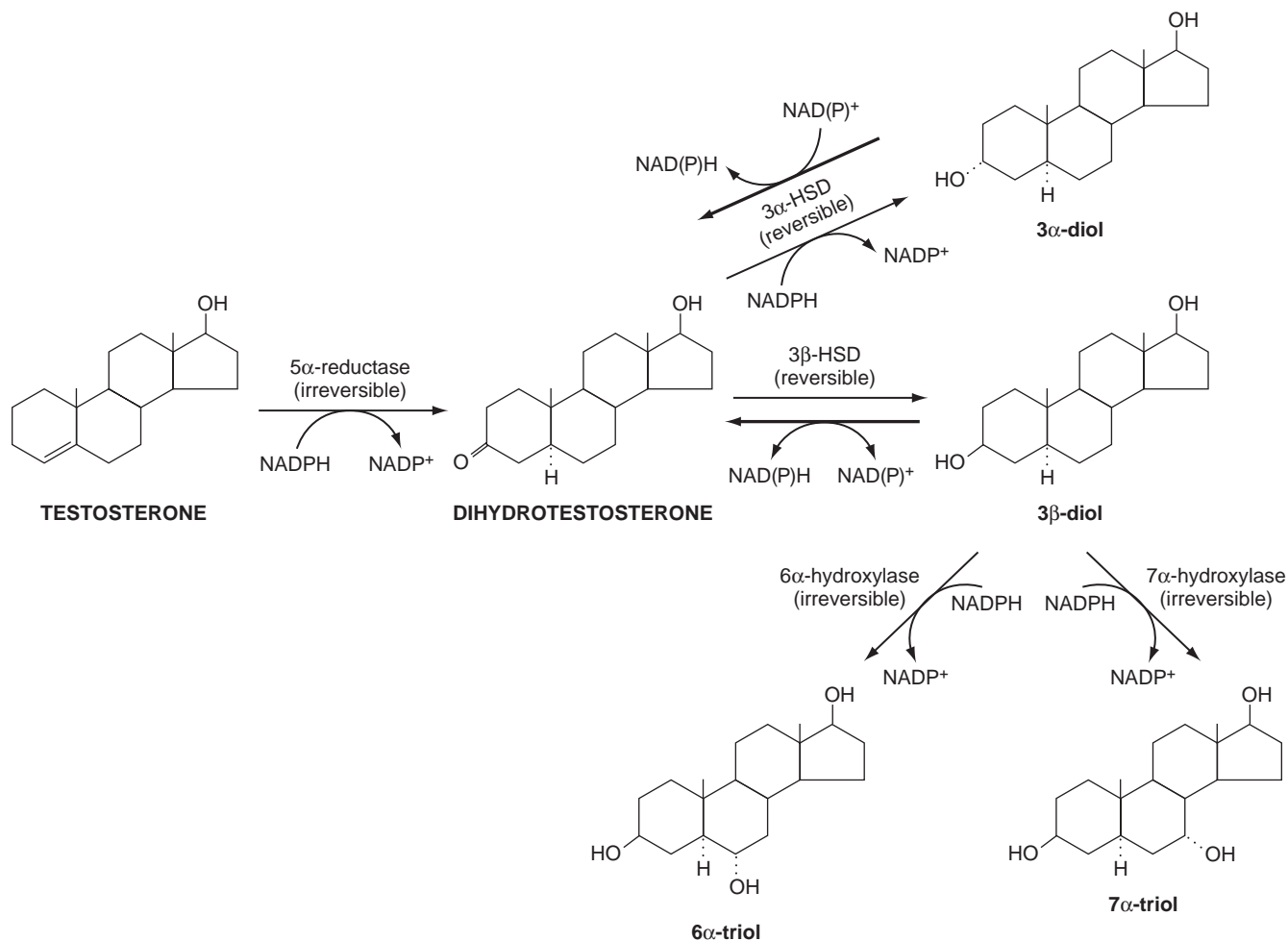


Figure 102-8. Metabolic pathways for testosterone within the prostate. Testosterone is irreversibly metabolized by 5 α -reductase to dihydrotestosterone (DHT), which is then reversibly converted into 3 α -diol and 3 β -diol. The 3 β -diol is irreversibly inactivated to the more soluble 6 α -triol and 7 α -triol. 3 α -HSD, 3 α -hydroxysteroid dehydrogenase.

TABLE 102-3 Properties and Distribution of 5 α -Reductase Types 1 and 2

	TYPE 1	TYPE 2
Chromosome	5p15	2p23
Molecular weight	29,000	28,000
Amino acids	259	254
Exons	4	4
Introns	5	5
Homology	49%	49%
pH optima	Alkaline (6-8.5)	Acidic (5.0)
K _m testosterone (μ M)	1.5	0.1-1.0
Ki finasteride (nM)	325	12
Half-life (hr)	20-30	20-30
5 α -Reductase deficiency	Normal	Mutated
PROSTATE CELLS		
Human		
Luminal epithelial	±	—
Basal epithelial	—	+
Stromal	±	+
Skin	+	—
Rat		
Prostate cells		
Luminal epithelial	—	—
Basal epithelial	+	—
Stromal	—	+

on 5 α -reductase activity has been reviewed by [Rittmaster \(1994\)](#). The type 1 enzyme is in the skin and in the adult scalp and is believed to be involved in hair formation. It is present to lesser degrees in the prostate epithelium and stroma. This isoform is found in normal levels in men with congenital 5 α -reductase deficiency. The type 2 enzyme is mutated in 5 α -reductase deficiency and is the dominant isoform present in the prostate gland. The type 2 enzyme appears in the basal cells of the epithelium and in the stromal cells but is absent in the secretory epithelial cells. This has raised the possibility that DHT stimulation of epithelial cells is derived from DHT converted within the stromal or basal cells. [Silver and coworkers \(1994\)](#) have studied the cell type-specific expression of these reductases, as well as their regulation. It appears that the 5 α -reductase type 2 in the prostate does not change dramatically in individuals undergoing short-term androgen ablation.

[Berman and associates \(1995\)](#) have studied the distribution of the two 5 α -reductase isozymes in the urogenital tract of the fetal rat. At 17 to 21 days of development the expression of type 1 gene predominated in the epithelial cells; the type 2 gene was limited to the mesenchymal cells. This is true in both the testosterone-dependent and DHT-dependent anlagen of the urogenital tract. These investigators observed that androgens could stimulate the expression of the type 2 gene in the urogenital tract but not of the type 1 gene. They suggested that the type 2 5 α -reductase gene exhibits positive feedback control in that the product of the enzyme, DHT, can stimulate expression of the gene; however, no evidence for such regulation of either 5 α -reductase gene was detected in the fetus.

In summary, 5 α -reductase is of great importance because the product DHT is important in the differentiation of the prostate during fetal development and because mutations in 5 α -reductase give rise to a rare form of pseudohermaphroditism. In prostate physiology, expression of the 5 α -reductase gene is regulated by androgens in both the prostate and liver. It is also believed that 5 α -reductase is involved in male pattern

baldness, acne, and hirsutism as well as in BPH. The 5 α -reductase inhibitors finasteride (type 2 inhibitor) and dutasteride (type 1 and 2 inhibitor) are clinically useful drugs in the treatment of BPH and male pattern baldness when they are given to appropriate patients.

After DHT is formed from testosterone in the prostate, it is then subjected to a series of reversible metabolic reactions to form 3 α -diol (5 α -androstane-3 α ,17 β -diol) and 3 β -diol (5 α -androstane-3 β ,17 β -diol) (see [Fig. 102-8](#)). The enzymes that perform this transformation of DHT are 3 α - or 3 β -hydroxysteroid oxidoreductases. These enzymes use NADP as a cofactor, but in contrast to 5 α -reductase they can also use nicotinamide-adenine dinucleotide (NAD). The equilibrium for the metabolism of DHT favors the formation of DHT, that is, the 3-hydroxy group of 3 α -diol and 3 β -diol is oxidized to the 3-ketone that is present in DHT. It is known that 3 α -diol administered to animals is a strong androgen through its rapid conversion to the effective DHT. On the other hand, 3 β -diol is not effective as an androgen because it is rapidly and irreversibly converted to the triol form by hydroxylation in the 6 α or 7 α position (see [Fig. 102-8](#)). The triols are dead-end products of testosterone metabolism but are water soluble and inactive as androgens because they cannot re-form DHT. Steroids also can form glucuronide or sulfate conjugates and be secreted in a more soluble form. In summary, testosterone is irreversibly metabolized to DHT that is in equilibrium with other reduced steroids primarily through oxidation and reduction at the 3 position. The steroids are inactivated by being irreversibly hydroxylated to the inactive triols.

Androgen Regulation of Stromal-Epithelial Interactions

It is now apparent that there is a dynamic and reciprocal interaction between the functions of epithelial cells and those of stromal cells ([Steiner, 1993](#); [Cunha, 1994](#); [Sikes et al, 1995](#); [Cunha et al, 2003, 2004](#)). These crosstalk interactions are mediated through the spatial organization of extracellular matrix elements that form the basement membrane linkage. This linkage presents, filters, and organizes the two-way paracrine signals and the flow of information between those two cellular compartments. For example, fluids, gases, nutrients, hormones, and many growth factors arriving in the prostate through the circulation must first pass through the stromal ground substance, the extracellular matrix, and the basement membrane before reaching the base of the secretory epithelial cells. Early in development, the functions of the epithelial and mesenchymal (stromal) elements vary as to their cell types, compositions, properties, and interactions. It is the integrated system biology of these two tissue elements as well as their dynamics during aging that play a vital role in the prostate's functions as a unit and gland. Indeed, it is the breakdown of these tissue interactions that is one of the hallmarks of the abnormal growth of the prostate that starts very early in life and is initiated at some time just after maximum virilization, at approximately 25 years of age. The prostate is extremely susceptible to permanent early alterations in form and structure as a consequence of genetic, environmental, dietary, or metabolic factors with aging ([Risbridger et al, 2005](#)). In fact, it is essential to establish the link between hormonal (androgens and estrogens) changes that occur during the fetal or neonatal period that imprint and hence may result in onset of late-life disease. With aging, during a period of 50 to 60 years, this organ slowly progresses through the transition from normal zonal histologic anatomy and function to the early signs of BPH, to prostatic inflammatory atrophy, to prostatic interepithelial neoplasia, and finally to various types of prostatic adenocarcinoma. This concept has been thoroughly documented in several rodent models ([Rajfer and Coffey, 1978, 1979](#); [Naslund and Coffey, 1986, 1987](#); [Prins and Birch, 1995](#); [Singh et al, 1999](#); [Prins et al, 2001](#); [Risbridger et al, 2005](#)).

Cell Adhesion Molecules

Cell-cell and extracellular matrix interactions are becoming major targets for understanding how the phenotype of a cell is regulated.

Transmembrane receptors on the cell surface extend out through the plasma membrane and form a bridge directly connecting the cytoskeleton with proteins and receptors located within the extracellular matrix or on neighboring cells. The CAMs are divided into four major types: (1) integrins, which link the cell to the basement membrane and extracellular matrix components through heterodimer interactions; (2) cadherins, which link the cell to neighboring cells through homotypic polymers; (3) selectins, which link the cell to carbohydrate moieties primarily on the vascular system; and (4) immunoglobulin (Ig) superfamily adhesion molecules. The most extensively studied of these CAMs in the prostate in order of interest have been E-cadherins, which bind PrECs to one another, and CD71, which binds to transferrin, as well as several of the integrin molecules. These bindings have been surveyed in prostate tumor cell lines in vitro (Rokhlin and Cohen, 1995), but more extensive work needs to be carried out in vivo in the normal developing prostate and in prostate cancer.

The integrins are made up of two covalently linked heterodimers termed α and β subunits. These integrins serve externally to contact the extracellular matrix receptors of fibronectin, fibrinogens, collagen, and laminin as well as glycosaminoglycans in the proteoglycans of the extracellular matrix. The integrin receptor domains inside the cell compartment serve as focal points for determining the structure and organization of the cytoskeleton. Approximately eight subunits of α and β can interact in different heterodimers that are tissue specific and can be of several types even on one cell. Different combinations may have varying degrees of binding activity for extracellular matrix components. For example, $\alpha_3\beta_1$ binds to laminin, collagen, and fibronectin and does so by recognizing a triplet of amino acids in those proteins made up of arginine, glycine, and aspartic acid (RGD).

Other types of transmembrane receptors also extend out of the cell to make direct cell-cell contact with the neighboring cell by recognizing similar receptors and forming homodimer bonds. Certain homophilic dimers that require calcium for interactions to form cell-cell bonds with neighboring cells are termed *cadherins*. Four of the cadherin types have been cloned. They contain 723 to 748 amino acids that are composed of a single peptide, an extracellular region with three repeated domains, a hydrophobic transmembrane region, and a long cytoplasmic tail. There is approximately 50% homology across species and between integrins. The cadherins are classified into three subtypes: E-cadherins, found in adult epithelial cells (also earlier termed *uvomorulin*, cell CAM 120/80, ARC-1, or L-CAM); N-cadherins, found in neural tissues of muscle (also termed A-CAM); and P-cadherins, found primarily in placenta and epithelium (Albelva, 1994). In the prostate cell, for example, E-cadherins extending out of the surface membrane make contact with the neighboring cell and form a homodimer, and the E-cadherin extending inside the cell by passing through the membrane would form as an organizing center that binds a complex of three cytoplasmic proteins termed *catenins* α , β , and γ . This complex is localized to the zonula adherens of the cell and participates in junction formation and stabilization of the cytoskeleton. These interlocking matrix systems interact to form a structural network extending externally from cell-cell contact and the extracellular matrix interactions and then internally to cytoskeleton organization and centrally, terminating by direct contact with the nuclear matrix that forms tissue-specific DNA organization.

The interactions of the nonhistone tissue matrix regulate many aspects of DNA functions involved in growth and differentiation (Getzenberg et al, 1990; Boccardo et al, 2003). The nonhistone proteins such as high-mobility group (HMG) proteins include HMGI/Y (HMGA) that participate in numerous cellular processes, such as regulation of inducible gene transcription, integration of retroviruses into chromosomes, and induction of malignant transformation (Reeves and Beckerbauer, 2003). Through protein-DNA and protein-protein interactions, the members of the HMGA family can influence growth, cell proliferation, differentiation, and cell death; they influence chromosome dynamics by acting as architectural transcription factors affecting several genes that have an impact on tissue structure and organization. This class of genes is often

upregulated in cancer (Reeves and Beckerbauer, 2003). These types of tissue matrix interactions are essential to the understanding of stromal-epithelial interactions because they form direct structural linkages and communications between the stroma and the epithelial nuclear DNA. In summary, under the influence of hormones (estrogens and androgens) and diet, it is the regulation of chromatin structure and organization through the histone and nonhistone pathways that replaces and maintains the tissue organization as well as interactions in health and disease.

The discussion, to this point, has concerned primarily insoluble elements in inducing stromal-epithelial interactions, but soluble hormones such as steroids, vitamins, and growth factors are also important (Sikes et al, 1995). The prostate stromal cells contain steroid receptors and respond to both androgens and estrogens (see earlier discussion). Androgens and estrogens can alter the formation of collagen (Coffey and Walsh, 1990) and other extracellular matrix components, such as glycosaminoglycans, in the prostate (DeKlerk et al, 1984; DeKlerk and Human, 1985; Kofoed et al, 1990; Horsfall et al, 1994).

In summary, different components of matrix interactions can have either an inhibitory role in negative regulation of normal prostate growth or a positive role in establishing tumor growth. There have been many hypotheses concerning the mechanism of these epithelial-stromal interactions, but they have yet to be fully resolved.

KEY POINTS: CELL ADHESION MOLECULES

- Transmembrane receptors on the cell surface extend out through the plasma membrane and form a bridge directly connecting the cytoskeleton with proteins and receptors located within the extracellular matrix or on neighboring cells.
- The CAMs are divided into four major types: *integrins*, which link the cell to the basement membrane and extracellular matrix components through heterodimer interactions; *cadherins*, which link the cell to neighboring cells through homotypic polymers; *selectins*, which link the cell to carbohydrate moieties primarily on the vascular system; and Ig superfamily adhesion molecules.

REGULATION OF PROSTATE GROWTH AT THE MOLECULAR LEVEL: STEROID RECEPTORS

In almost all cells in the body, steroids can enter the nucleus, but only a few cells can retain this steroid within the nucleus for any length of time. The cells that retain the steroid have receptors that are steroid specific, which can regulate specific steroid-sensitive genes within the nucleus to alter the expression of certain proteins. The AR's affinity for the nuclear acceptor site to which it binds in the nucleus is probably a compilation of binding to specific sequences on DNA (androgen response elements) as well as tissue-specific binding to coregulatory factors. The uptake and binding of the AR in the nucleus are regulated by the presence of the androgen ligand bound to the receptor, resulting in receptor activation. When androgens are not present, the receptor decreases its affinity for nuclear binding and can easily be removed; indeed, under castrate conditions, receptors may leak back out into the cytoplasm (Husmann et al, 1990). Immunohistochemical techniques indicate that in the presence of androgen the AR localizes primarily to the nucleus.

The prostate and seminal vesicles contain steroid-specific and high-affinity (10^{-9} to 10^{-10} M K_d) saturable (100 to 1000 fmol of receptor per milligram of DNA equivalents of tissue) ARs that were first described by Liao and Fang in 1969. There are 5000 to 20,000 molecules of these receptors per cell, far more than can bind to the androgen response element sites, which are probably fewer than 400. Classic AR function has been characterized as a genomic

process, wherein certain transgenes are regulated by the activated AR. More recently, however, attention has been focusing on the nongenomic mechanisms of androgen action (Benten et al, 1997; Jones et al, 2004). Nongenomic androgen action is characterized by extremely rapid changes in cellular physiology, typically measured in seconds or minutes, as opposed to the longer times required for target gene regulation to be translated into protein changes. Whether nongenomic androgen action occurs through the same ARs involved in genomic regulation still remains to be determined. The properties and hormonal regulation of ARs as well as their uses have been reviewed in detail (Germann, 2002; Black and Paschal, 2004; McEwan, 2004).

Androgen Receptor

The cloning of the human AR and its expression was a hallmark in the study of the mechanism of androgen action (Chang et al, 1988b; Lubahn et al, 1988). This led to the study of the sequence of the gene and its protein product—and how this is altered in inherited androgen insensitivity syndromes—as well as receptor function (Chang et al, 1995).

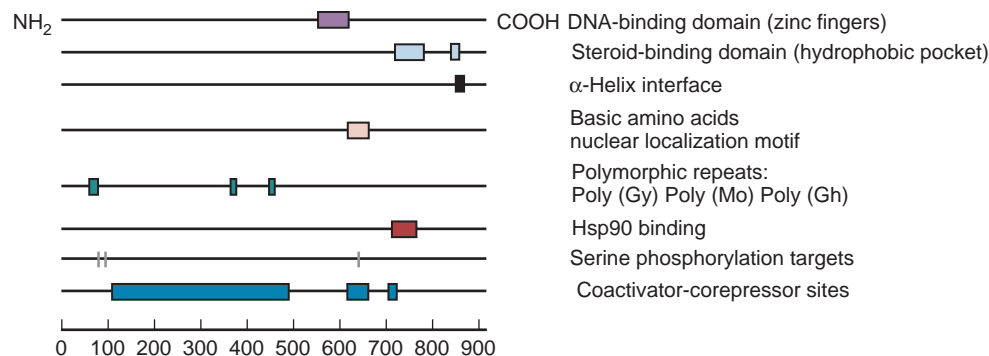
The AR gene is on the long arm of the X chromosome at position Xq11.2-q12. Because there is only one X chromosome in a male, it is a single-copy gene. The coding sequence on this gene is divided into eight exons that are transcribed and processed into mRNA and then subsequently translated into protein. The total genomic DNA spans a minimum of 80 kilobases (Marcelli et al, 1990) but forms a final message of only 10.6 kilobases, that is, only 17% of the total gene, with an open reading frame of 2757 base pairs. This is similar to the organization of many other steroid receptors that also contain information from eight exons, such as the progesterone and ERs. The AR is a member of the nuclear receptor superfamily, which is a group of ligand-inducible transcription factors. The nuclear receptor superfamily has more than 200 members at present (Escriva et al, 2004). All of these receptors share certain structural features that allow them to regulate gene expression, although the ligands for many of these receptors have yet to be identified (so-called orphan receptors). Such receptors include the glucocorticoid receptor, the retinoic acid receptors (RXR and RAR), the vitamin D receptor, the estrogen and progesterone receptors, the peroxisome proliferator-activated receptor (PPAR- γ), and many orphan receptors. Like other steroid receptors, the AR is divided into three distinct, modular domains: the amino-terminal domain, the DNA-binding domain, and the carboxyl-terminal ligand-binding domain. Despite the similarity in structural organization of all of the nuclear receptors, activation of different receptors results in markedly different cellular responses. Mutational analyses of the

human AR have allowed a detailed mapping of a variety of different functions, which are diagrammed schematically in Figure 102-9.

Upstream (5' direction) of the transcriptional initiation site is the regulatory element of the gene that controls its expression. It is unusual in that it contains the GC box rather than the classic TATA and CCAAT, which are commonly found in promoters of polymerase II-dependent genes. Closer to the initiation site located only 70 base pairs upstream is a 50-base pair purine-rich region that is a *cis*-acting element for AR transcription. There are other *cis*-acting elements, including an AP-1 (which is bound by a heterodimer of c-Fos and c-Jun) and a RARE (retinoic acid response element) as well as a cyclic adenosine monophosphate (cAMP) response element (AR/CRE1). This suggests that the regulation of expression of the AR gene may involve cAMP, activation of c-Fos/c-Jun, or retinoids (Kuiper et al, 1989; Faber et al, 1993; Mizokami et al, 1994; Young et al, 1994). Activation of the AR appears to be a function of multiple steps including initial complex formation with certain chaperonins, binding of ligand, post-translational modifications, dimerization, nuclear localization, and binding of the receptor to certain transcriptional coactivator complexes that remodel chromatin, target the initiation site, and stabilize the RNA polymerase II machinery for repeated rounds of transcription. Each of these features is discussed in the context of known structural features of the receptor as diagrammed in Figure 102-10.

Chaperonin Binding

Immediately after nascent production of the protein in the ribosome, the receptor forms complexes with several other proteins, referred to as *chaperonins*. These chaperonins form an aggregate complex, which is known as the 8S complex, in reference to the size of the complex on sucrose gradient sedimentation analysis. This chaperonin complex includes at least eight known components (Hsp90, Hsp70, Hip, p60, p23, FKBP51, FKBP52, and Cyp40), which serve to sequester the receptor into an inactive pool (see Fig. 102-10). By analogy to the progesterone receptor, which has had the most detailed scrutiny in regard to the molecular biology of the chaperonin complex (Nair et al, 1996; Pratt and Toft, 1997; Smith, 2000), the AR can dissociate into a monomeric form (4S on sucrose gradient centrifugation) that is in equilibrium with the 8S form, with the preponderant species existing in the chaperonin complex. This larger complex may be particularly favored by virtue of mass action alone, because the heat shock proteins tend to be among the most abundant proteins in the cell. Although the AR is uncomplexed, it is susceptible to various different post-translational processing steps, including phosphorylation or glycosylation. Such interactions may then inhibit reassociation with the chaperonins,



Shown are the coordinates of all known functional elements

Figure 102-9. Structure of the human androgen receptor protein. The androgen receptor is divided into several functional domains including the DNA-binding domain (consisting of two zinc fingers), a steroid-binding domain (consisting of a hydrophobic pocket), a nuclear localization motif, and several coactivator-corepressor binding sites. There are three polymorphic repeats of glycine, proline, and glutamine, with varying sizes among different populations. The relative positions of the functional elements are shown to scale.

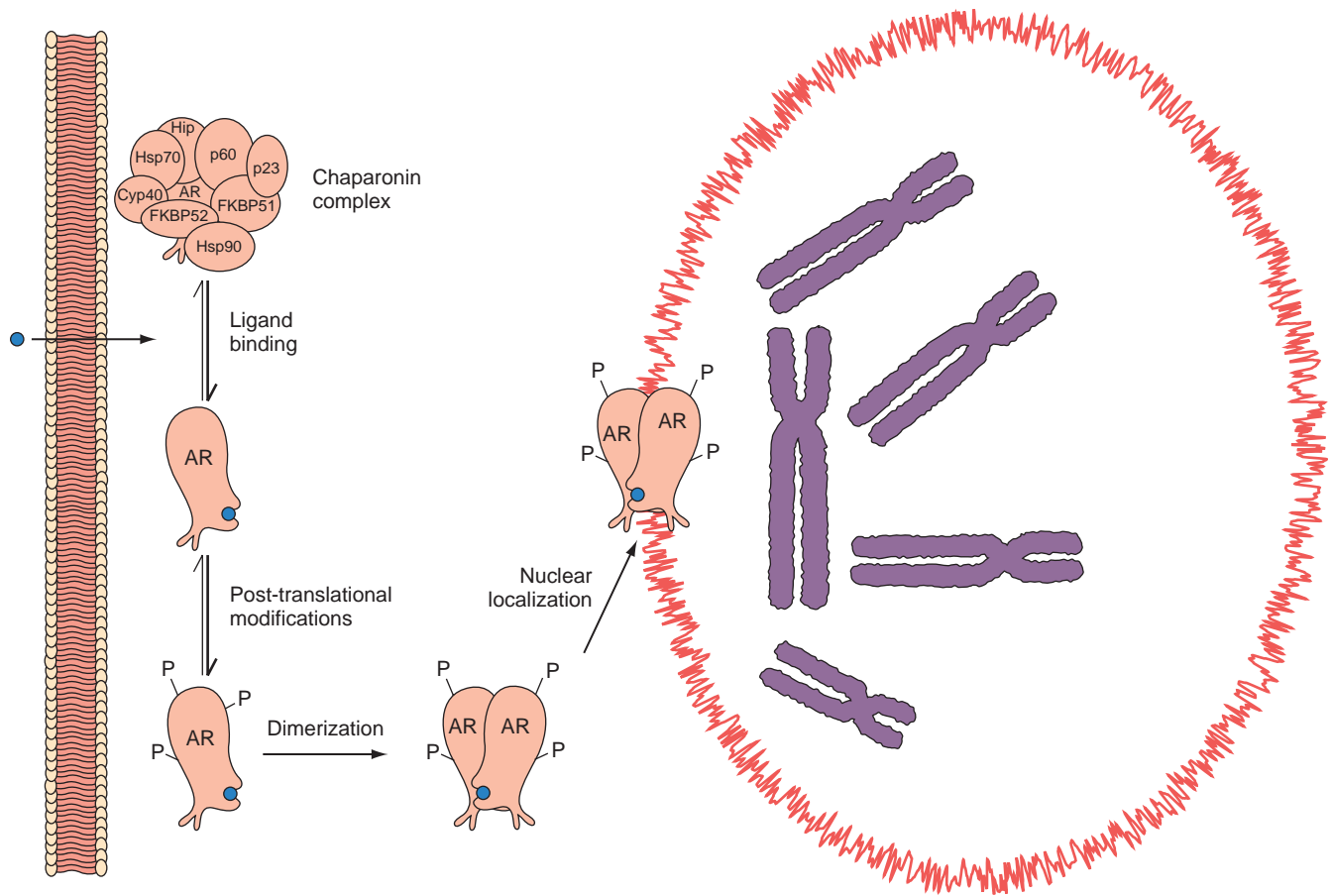


Figure 102-10. Mechanism of androgen receptor (AR) activation by ligand. Androgen enters the cell membrane by passive diffusion and binds the androgen receptor in the cytoplasm. The AR exists in equilibrium with the chaperonin complex, consisting of at least eight different components, including Hsp90, Hsp70, Hip, p60, p23, FKBP51, FKBP52, and Cyp40. Once activated by binding ligand, post-translational modifications occur, such as phosphorylation. Contemporaneously, dimerization occurs, and the activated modified androgen receptor is translocated to the nucleus by active transport.

leading to ligand-dependent activation, ligand-independent activation, or receptor inactivation with proteasome-mediated degradation. Evidence for such a mechanism includes a PEST sequence similar to one in the vitamin D receptor that is present in the hinge region of all known mammalian ARs, suggesting that it may function in proteasome-mediated AR turnover. Moreover, proteasome inhibition leads to a significant increase in AR isoforms (Sheflin et al, 2000).

DNA-Binding Domain

Near the end of exon 1 and extending into exon 3 is the coding sequence for the DNA-binding domain. The DNA-binding domain of the AR consists of 72 amino acids rich in cysteine and encoding two zinc finger motifs, which allows specific recognition of certain DNA sequences referred to as *androgen response elements*. Such elements typically consist of a palindromic repeat separated by a three-nucleotide spacer—for example, GG(A/T)ACAnnnTGTCT (Roche et al, 1992). X-ray crystallography of certain steroid receptors (glucocorticoid receptor and progesterone receptor) has shown that the first zinc finger directs sequence specificity of binding by directly contacting the DNA bases in the major groove; the second zinc finger functions to stabilize the protein-DNA complex by contacting the sugar-phosphate backbone. Although the protein-DNA interaction appears to be largely limited to the zinc finger motifs, sequences in the amino terminus appear to be important in stabilizing these structures because mutations in this region result in a mildly diminished DNA-binding affinity. This DNA-binding domain of the zinc

fingers in the steroid receptor molecule is highly conserved. In this region of exon 2 to 3, there is a 79% homology with the progesterone receptor, a 76% homology with the glucocorticoid receptor, and a 56% homology with the ER (Chang et al, 1988a, 1988b). The closest homology of the AR is with the progesterone receptor (Lubahn et al, 1988; Marcelli et al, 1990). Mutations of amino acids in this area of the AR can make the receptor unable to activate androgen-sensitive genes (Govindan, 1990), which is the basis of one of the inherited androgen-insensitivity syndromes—testicular feminization.

The DNA-binding domain binds to its cognate DNA-regulatory site, referred to as a *hormone response element*. Hormone response elements can be divided into different groups on the basis of common structural features for which whole groups of receptors are capable of binding. Class I hormone response elements include the glucocorticoid receptor, the progesterone receptor, and the mineralocorticoid receptor and are characterized by a half-site consensus sequence of TGTCT. Class II hormone response elements include the ER, whose prototype half-site sequence is TGACC. The hormone response elements to which ARs have been shown to bind belong to the class I subgroup (Tan et al, 1990). A consensus sequence for the androgen response element has been determined by an RNA-binding site selection assay with an AR fusion protein to be GG(A/T)ACAnnnTGTCT (Roche et al, 1992). Such binding sites are characterized by an inverted palindromic repeat with a dyad axis of symmetry, indicating that the receptors are binding in a head-to-head fashion. However, the androgen response element of the rat probasin promoter has been found to be a direct repeat

(Schoenmakers et al, 2000). Surprisingly, x-ray crystallography data reveal that AR dimers bind to direct repeat target sequences in a head-to-head fashion, maintaining the normal orientation of an inverted repeat target sequence (Shaffer et al, 2004). To date, only the AR has been found to bind to a direct repeat target sequence with an orientation normally expected for an inverted repeat. This difference may represent one way ARs maintain specificity of target gene regulation.

Ligand-Binding Domain

Ligand-dependent activation is characterized by ligand-receptor dimerization, post-translational modifications (e.g., phosphorylation), nuclear translocation, and subsequent target gene activation (or repression). It is believed that binding of either DHT or testosterone to the ligand-binding domain can facilitate these processes, although the binding affinity for DHT is significantly higher than for testosterone. Binding of the androgen to the carboxyl-terminal ligand-binding domain is required for activation; however, deletion of the ligand-binding domain can lead to a constitutively active AR. In prostate cancer, various splice isoforms have been identified that lead to constitutively active function (Hu et al, 2011). Thus, at least part of the interaction with the chaperonin complex involves the carboxyl portion of the receptor (Marcelli et al, 1990). However, small point mutations in the ligand-binding region can lead to significant changes in the characteristics of AR action. For instance, a single point mutation in the ligand-binding domain of the AR (codon 877, Thr→Ala) identified in the LNCaP cell line of prostate cancer renders it weakly inducible by inappropriate steroids such as progesterone while it retains the ability to be stimulated by androgens. Marcelli and coworkers (1990) reported that mutations in the AR at amino acid 587 or 794 are inactive in the assay for androgen binding and for transcriptional activation. However, the removal of amino acids from 708 to the carboxyl end at 917 (i.e., the entire ligand-binding domain) leads to the synthesis of a receptor protein that does not bind androgens but is still constitutively active in activating transgenes. As new drugs have become available for prostate cancer androgen axis suppression, resistance to these new agents (e.g., abiraterone and enzalutamide) may involve some of the AR splice isoforms, or potentially even upregulation of other steroid receptors (Sharifi, 2014).

Dimerization

The identification of the palindromic structure of certain hormone response elements for all steroid receptors led to the proposal that these transcription factors bind to the DNA as a dimer. Subsequent analysis of the receptor-DNA interactions has confirmed this hypothesis, and dimerization is now thought to represent an important step in the regulation of steroid receptor action. A hydrophobic heptad repeat within the ligand-binding domain at codons 859 to 880 is conserved among all steroid receptors and is thought to be necessary for high-affinity dimerization. Removal of these sequences leads to low-affinity dimerization, presumably through the action of the DNA-binding zinc fingers on the palindromic androgen response elements. Abolishment of the DNA-binding domain does not inhibit the strong affinity dimerization present in the ligand-binding domain. The strong dimerization signal appears to be related to a hydrophobic α -helix interface formed by the conserved heptad (Centenera et al, 2008).

Post-Translational Modifications

Once the AR has been bound to steroid ligand and dissociated from the chaperonin complex, it is susceptible to a variety of post-translational modifications, any one of which may significantly affect the function and turnover of the receptor. For instance, the AR can be acetylated (Fu et al, 2004) or phosphorylated (Goueli et al, 1984). In the rat ventral prostate it has been reported that this occurs through a nuclear cAMP-dependent protein kinase (Kempainen et al, 1992). Receptor phosphorylation may be an

important mechanism in the nuclear translocation of steroid receptors as well as in DNA binding and transcriptional regulation. The stimulation for phosphorylation appears to be optimal with the binding of an androgen agonist, because antagonists such as flutamide appear to favor the dephosphorylated state, suggesting that the phosphorylation status may be associated with the ultimate activity of the receptor (Wang et al, 1999). Both serine and tyrosine residues have been found to be phosphorylated in other steroid receptors (Landers and Spelsberg, 1992; Sadar et al, 1999). In addition to phosphorylation by protein kinase A, ARs also appear to stimulate mitogen-activated protein kinases, which may provide a different level of regulation of gene activity because such kinases often modulate other transcription factors, such as Elk-1 (Peterziel et al, 1999). The prostate is a rich source of acid phosphatases, and some have suggested that these enzymes may be active in regulating the phosphotyrosyl residues of the AR, thus playing a role in dephosphorylation and inactivation of ARs (Goldsteyn et al, 1989), although this relationship is certainly not causal.

Nuclear Localization

After activation by the binding of steroid ligand the AR is transported to the nucleus across the nuclear pore complex by a process involving at least two nuclear localization signals, one for import and one for nuclear export. Evidence for nuclear localization signal-dependent nuclear translocation is well established and can be found in a variety of nuclear proteins, including the SV40 large T antigen. In most cases it consists of a stretch of basic amino acids. The prototype nuclear localization signal from the SV40 large T antigen is PKKKRKV, although various other basic sequences have also been implicated in nuclear localization signaling. The nuclear localization of the AR appears to involve multiple steps, including the binding of the basic amino acid nuclear localization signal to importins α and β , docking of an importin-cargo complex to the nuclear pore, translocation to the nucleus, and Ran-GTP-mediated release of the cargo (Rao et al, 2002). Two regions of steroid receptors have gained most attention as regulators of receptor trafficking. The first region is the second DNA-binding zinc finger region, together with the flanking hinge region (NL1) consisting of a bipartite signal including flanking leucines and the core signal ⁶²⁸RKLLK-KLGN (Kempainen et al, 1992; Ylikomi et al, 1992; Poukka et al, 2000). However, this one putative nuclear signal peptide is not sufficient by itself for high-efficiency translocation; and by analogy to other steroid receptors, additional nuclear localization signals may exist in the steroid-binding domain (Kempainen et al, 1992). NL1 acts constitutively and participates in rapid nuclear import that is facilitated by importin- α binding (Savory et al, 1999). A number of coregulators of steroid receptor-mediated transactivation interact with regions that encompass NL1 (Jackson et al, 1997; Moilanen et al, 1998; Powers et al, 1998; McKenna et al, 1999). Some of these proteins, such as SNURF and Ubc9, lose their ability to interact with AR when the region overlapping with the bipartite NL1 is destroyed (Moilanen et al, 1998; Poukka et al, 2000). A second signal, NES^{AR}, is located in the ligand-binding domain (Saporita et al, 2003) and is a nuclear export signal that facilitates export of AR when it is not complexed to ligand. Between the NL1 and NES^{AR}, the AR is actively shuttled between the cytoplasm and nucleus, presumably to tightly regulate its intrinsic ability to activate or repress gene expression.

Transcriptional Activation Domains

Once the AR has achieved active localization into the nucleus it must find and bind to its target sequences in the genomic DNA. The precise mechanism by which receptor localization occurs to target genes is still unknown; however, there is emerging evidence indicating it is a highly orchestrated process (O'Malley, 2008). For instance, it is now known that so-called pioneer factors such as FOXA1 are targeted to specific chromosomal sites by epigenetic signaling, and then the ARs bind to these sites to subsequently regulate the target genes (Lupien et al, 2008). Once the AR has properly localized within the target chromatin sites, it must coordinate

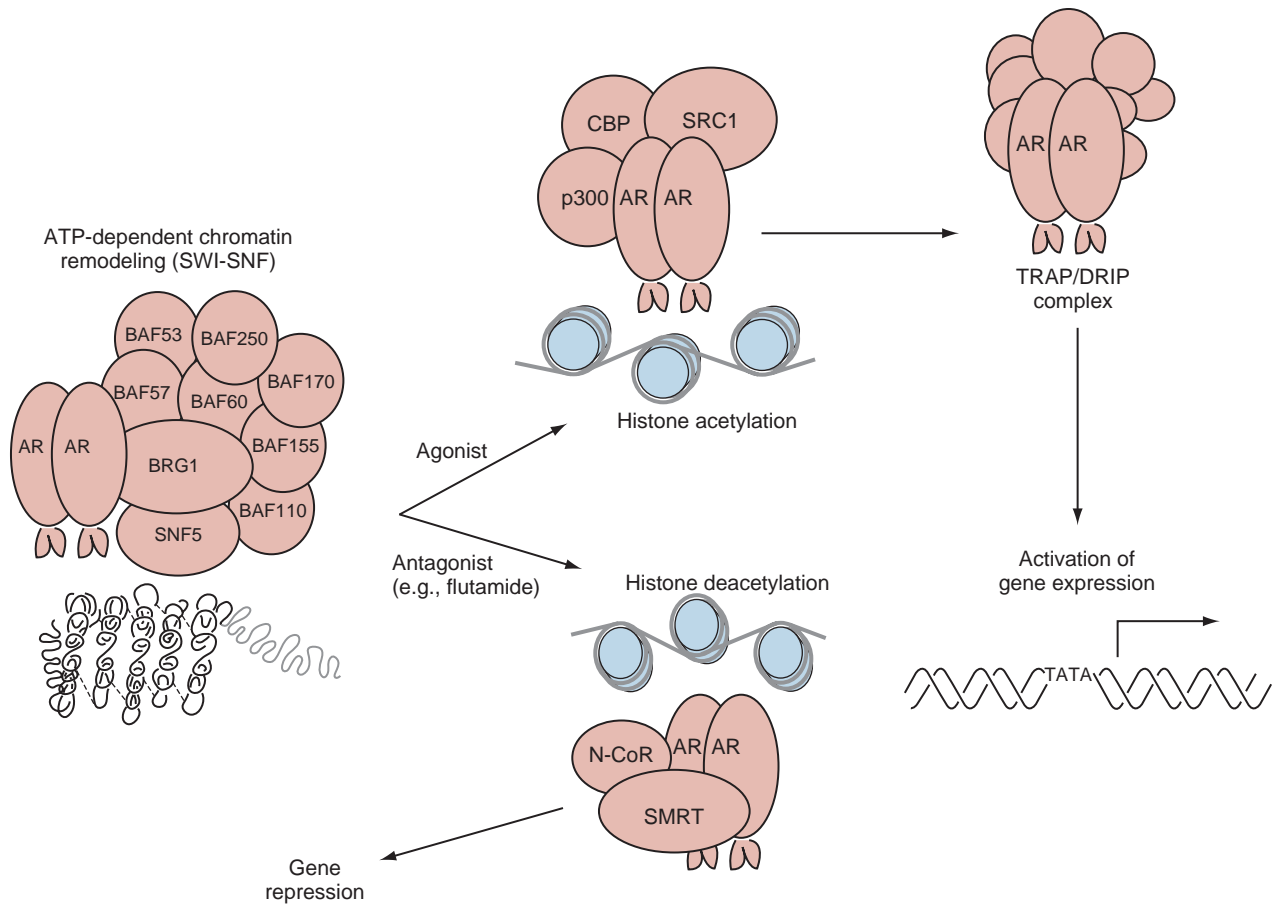


Figure 102-11. Mechanism of action of the nuclear-activated androgen receptor (AR). Once the androgen receptor has been translocated to the nucleus it undergoes several steps (many of which may occur contemporaneously): (1) chromatin remodeling in an adenosine triphosphate (ATP)-dependent fashion via the SWI-SNF complex; and (2) agonist (i.e., dihydrotestosterone [DHT])-mediated histone acetylation in a process involving multiple transmission factors including p300, CBP, and SRC1. In the case of a certain antagonist, histone deacetylation may be favored, and the activated nuclear receptors complex with repressors of gene expression such as N-CoR and SMRT. (3) The activated androgen receptor complexes then associate with other γ -trans-acting factors via the TRAP/DRIP (thyroid receptor-associated protein/D receptor-interacting protein) complex at sites typically upstream of the target gene known as *androgen response elements*. This complex then leads to androgen-regulated activation of gene expression.

binding to a number of associated factors referred to as *coactivators* and *corepressors* that subsequently regulate gene expression (Fig. 102-11). A list of recently identified coactivators is provided in Box 102-1. Most of these factors interact promiscuously with many steroid receptors, although more AR-specific factors are routinely being discovered. Because the number of potential coregulators clearly exceeds the capacity for direct interaction by a single receptor, the most likely mechanism is that transcriptional activation by AR involves multiple factors that act in both a sequential and a combinatorial manner to reorganize chromatin templates (Pollard and Peterson, 1998). The precise timing and sequence of binding of these factors remain to be elucidated; however, in general, one can break down the processes empirically into chromatin or nucleosomal remodeling (an energy-dependent process), histone acetyltransferase activity, and subsequent recruitment of TATA-binding protein (TBP)-associated factors, all of which promote an increased rate of gene transcription by RNA polymerase II. Under certain conditions, such as binding of an AR antagonist (e.g., flutamide), the histone acetyltransferase activity is actually inhibited and transrepression may occur. Such inhibition of gene expression appears to involve the nuclear corepressor proteins N-CoR and SMRT (Glass and Rosenfeld, 2000). Other proteins may play a similar role, such

as the *HBO1* gene (Sharma et al, 2000). Amino-terminal deletions in region 46-408 result in dominant negative suppression of hormone-inducible transgene activation, indicating that the coactivator functions require an interaction within that site and that in the absence of this region the receptor forms dysfunctional complexes in the chromatin (Palvimo et al, 1993).

The transcription domain of the AR is coded in exon 1, which is the largest of the exons, containing 1607 base pairs. Analysis of this region reveals three homopolymeric repeated regions, including a repeat of approximately 20 glutamines, followed by a space containing 8 repetitive prolines and 23 repetitive glycine units (see Fig. 102-11). The glutamine repeats form a β sheet that helps form a polar zipper, which favors certain protein-protein interactions. Fusion of this type of polymeric glutamine repeat with the DNA-binding domain of GAL4 in yeast results in a GAL4-directed increase in transcriptional activity, demonstrating the importance of this region in promoting transgene activation (Gerber et al, 1994).

Studies demonstrate that these polyglutamine repeats appear to interact directly with the carboxyl terminus of the transcription factor p160 (Irvine et al, 2000). In the normal population this repeat varies over a length of 11 to 31 residues, resulting in a true allelic polymorphism. This means that different people have alleles

BOX 102-1 Abbreviated List of Putative Androgen Receptor Coactivators

ARA24, ARA54, ARA55, ARA70, ARA160
 ART-27, ARIP3
 β -Catenin
 BRCA1, BRCA2
 CARM1, CBP, c-Jun, Cdc25B, cyclin E
 FHL2 (specific to androgen receptor)
 GT198
 HBO1
 Ku
 MAGE 11
 Oct-1
 p68 helicase, p160, pp32-Rb
 pCAF, p300, PGC-1, PNRC, p54nrb
 RAC3
 RNF-4
 SNURF
 SRC1, SRC1a, SRC3, SRCAP
 TIF2
 Tip60
 TRAM-1
 TRAP/DRIP/GRIP/NRIP
 Ubc9, UBCH7
 Zac1

of variant polyglutamine repeat units. This variation is racially defined, and it has been suggested that this may be related to the differences in the incidence rates of prostate cancer in different ethnic groups. The most common CAG repeat length in whites is a modal value of 21; in African-Americans, it is shorter at 18; and in Asians, it is longer at a mean of 23. The longer the glutamine repeats, the lower the activity of the AR in activating target genes. Patients with X-linked spinal and bulbar muscular atrophy, termed *Kennedy disease*, possess a larger glutamine repeat in the range of 40 to 60. The ARs in Kennedy disease exhibit markedly less transactivation activity (Laspada et al, 1991). Moreover, men with male factor infertility are found to have longer than average polymorphisms of the AR than normal controls (Tut et al, 1997). Genetic studies of inherited diseases of androgen insensitivity and overvirilization as well as changes in the AR mutation associated with prostate cancer and its biologic properties will be of great help in unraveling the role of the human AR in relation to its structure.

KEY POINTS: ANDROGEN RECEPTOR

- The AR, an intracellular steroid-binding protein, is activated by androgens, resulting in both genomic and nongenomic actions, which in turn regulate cellular action.
- This regulation is central to prostate development, growth, and homeostasis and occurs in both the stromal and epithelial compartments.

Androgen Receptor–Dependent Chromatin Remodeling

Part of the tissue and gene specificity in the recognition of receptors and DNA may depend on the organization of the DNA within the nucleus (Getzenberg et al, 1990). The steroid-receptor complex can interact only with genes that are in regions that are “open” or in the transcriptionally active form. Studies show that these open regions of chromatin (euchromatin) can extend up to 100,000 base

pairs in length, or more than 10-fold the size of a typical gene, which usually ranges from 1000 to 10,000 base pairs. It is unknown how such a large range of DNA is altered in conformation, but it may be through binding to structures like the nuclear matrix, which can order large loop domains in the region of 60,000 to 120,000 base pairs. Nuclear receptors are thought to interact with chromatin remodeling complexes in an ATP-dependent fashion, in a process directed in part by “pioneer factors” including FOXA1 (Lupien et al, 2008), and this may be among the earliest steps in the ultimate regulation of certain target genes (Glass and Rosenfeld, 2000).

During cell division, chromosomal organization is spatially regulated at each of the critical phases of mitosis (Williams and Fisher, 2003). Epigenetic regulation of chromosome structure and function is highly ordered during cell division, differentiation, and development (Lam et al, 2005; Margueron et al, 2005). In fact, chromosomal proteins are required to maintain such ordered structure for euchromatin, heterochromatin, and centromeric chromatin to sustain normal cell and tissue functions. To achieve such coordinate regulation, the protective packaging of DNA is engineered through an elegant system of tightly wound DNA around an eight-component histone core called a *nucleosome*. This core consists of dimers of H2A, H2B, H3, and H4, whose ability to compact DNA is directly regulated by post-translational modifications. The selective regulation of such post-translational histone modification constitutes a major regulatory mechanism for gene expression and is referred to as the *histone code* (see Fig. 102-11). Histone modifications include acetylation, phosphorylation, ubiquitinylation, and methylation (Downs and Jackson, 2003; He et al, 2003; Cosgrove et al, 2004; Cosgrove and Wolberger, 2005; Lam et al, 2005).

ARs are known to interact with structural components of the chromatin organizing complexes. Such complexes include the multisubunit human SWI-SNF complex, which has been shown to remodel mononucleosome and polynucleosome templates in an ATP-dependent manner (Peterson and Tamkun, 1995). The isolated hSWI-SNF ATPase subunits BRG1 and hBRM also have these activities (Phelan et al, 2000).

The transcriptional activation of nuclear receptors (neuroendocrine cells) requires multiple factors including SWI-SNF complex, CPB/p300, and steroid receptor coactivator (SRC) family members, which are large and contain numerous subunits, many of which make contact with a variety of nucleosome components and the nuclear matrix (Huang et al, 2003). Such components include BAF53a, BAF57, BAF60, BAF110, BAF155, BAF170, BAF250, BRG1, BRM, and SNF5. Because condensed chromatin renders genes inaccessible for transcription, the combination of a steroid receptor and SWI-SNF complex formation appears to be critical for appropriate nucleosomal remodeling to allow appropriate target genes to be accessible for gene regulation (Sudarsanam and Winston, 2000; Huang et al, 2003). Once the receptor SWI-SNF complex, CPB/p300, and other mediators have successfully “opened” the structure of the chromatin to allow transcriptional regulation, the AR must interact with a distinctly different set of cofactors. Post-translational histone modification clearly appears to be requisite for chromosome remodeling and optimal gene expression (Ewen, 2000; He et al, 2003). In most models tested the rates of gene transcription actually correlate with the degree of modification of histones through acetylation, phosphorylation, ubiquitinylation, and methylation. In other words, hyperacetylated histone regions correspond to the highest gene-transcriptional regions, whereas the hypoacetylated histone regions correspond to the lowest gene-transcriptional regions (Pazin and Kadonaga, 1997). A number of histone acetyltransferase complexes have been found to be associated with nuclear receptors, including the AR. These complexes include p/CAF, a homolog to the yeast GCN5, which participates in the yeast SAGA complex. This complex includes factors that possess activity but also TBP and a number of TBP-associated factors. The p/CAF protein has been found to be associated with the retinoic acid receptor and may be involved with multiple nuclear receptors. It is also known to bind to other histone acetyltransferase (HAT) proteins, including CBP/p300, which is known to acetylate not only histones but other transcription factors as well. The CBP/p300

complex is an essential coactivator for many genes and may actually serve as a molecular scaffold in stimulating gene transcription (McKenna et al, 1999; Huang et al, 2003; Marshall et al, 2003). Such complexes include the SRC1 coactivator, among others. More recently, the modifiers of the histone code have expanded considerably to include sophisticated enzyme-mediated alterations in the histones H2A, H2B, H3, and H4 by phosphorylation, ubiquitinylation, and methylation, which open the chromatin, allowing the recruitment of important transcription factors that allow normal cell functions (Lam et al, 2005; Margueron et al, 2005). The list of coactivators associated with nuclear receptors and the AR in particular is extensive and almost certainly incomplete. A short list of factors found to be associated with the receptor at this level of gene regulation is given in Box 102-1. Among the most important factors is SRC1, which has mild HAT activity and seems to be required for optimal stimulation of steroid-dependent transcription. Additional factors include steroid receptor RNA activator (SRA), a structural RNA necessary for the coactivator complex to function optimally (McKenna et al, 1999), and p160 coactivator, which appears to be required for hormone-dependent activation and to directly interact with the polyglutamine repeats found in the amino-terminal transactivation domain (Irvine et al, 2000).

Most genes have a regulatory region immediately upstream of the transcriptional start site. The regulatory region is divided into a core *promoter element* that is present in all genes as well as other upstream elements that serve to regulate the overall gene expression pattern. This promoter element specifies the site to which RNA polymerase II will attach to the DNA and will determine the actual point for the initiation of transcription. The RNA polymerase will copy or transcribe the DNA code into mRNA, a process termed *transcription*. This promoter area starts at -16 nucleotides to +32 upstream from the gene initiation site. This region of -32 to +16 was originally referred to as the *Goldberg-Hogness box* or *TATA box* and has a consensus sequence of TATAAAAG. The RNA polymerase II enzyme binds to this TATA box as one of the initial steps in transcription. Farther upstream from the TATA box is a second gene control element termed generically the *hormone response element*, which has been identified in many genes regulated by steroid hormones and is one of multiple sites where the receptor binds to the DNA. As stated earlier, in androgen-regulated genes, this area is termed the *androgen response element*; in estrogen, the *estrogen response element*; and in glucocorticoid, the *glucocorticoid response element*. This hormone response element area may contain several discrete sequences, but its overall role is to modulate the frequency of transcription initiation vis-à-vis interactions with transcriptional factors. In independent analysis, thyroid hormone receptors were found to be associated with affinity purified proteins, which were found to markedly enhance ligand-dependent cell-free transcription. This complex was referred to as *TRAP*, for thyroid receptor-associated proteins (Fondell et al, 1996). In a similar set of experiments, the same type of complex was isolated for the vitamin D receptor and was called *DRIP* for D receptor-interacting proteins (Rachez et al, 1998). Subsequent analysis revealed that they shared at least nine proteins, and this activator-recruited cofactor complex (TRAP/DRIP/ARC) is part of a large composite coactivator complex used by a variety of transcription factors for the regulation of certain target genes. Such transcription factors include sterol regulatory element-binding protein (SREBP), nuclear factor- κ B (NF- κ B), and VP16 (Sun et al, 1998; Gu et al, 1999; Ito et al, 1999; Naar et al, 1999; Ryu et al, 1999).

In summary, the TATA box tells where RNA polymerase binds and where the initiation of transcription is to start and the hormone response element regulates how frequently it is to be transcribed when it is bound to a hormone receptor. This is accomplished by the presence of certain cofactors in the TRAP/DRIP complex. Because the hormone response element of DNA sequence has been shown to be independent of its position or its orientation, it resembles what has been called the *transcription enhancer element* that has been found in many other types of genes. The hormone response element section can vary in its location upstream from the initiation of the gene from -20 to -6000 for various different types of

hormones. With the steroid hormones, it appears to reside about -140 nucleotides upstream from the initiation site. For example, in the glucocorticoid receptor recognition element, the site for glucocorticoid receptor recognition is approximately -140 and contains a sequence of nucleotides of AAAATGGAC. Deletion mapping experiments have indicated that the receptor-binding domain located in the hormone response element is indeed required for receptor binding and is necessary for steroid-mediated control of transcription.

Once the DNA is transcribed into mRNA, a series of adenine units are added to the end (called the *poly-A tail*) and then the mRNA is cut and spliced on small nuclear particles (called *spliceosomes*) located on the nuclear matrix, and this splicing removes the intron portion of the message. The final mRNA is shipped out of the nucleus, believed to occur on the structural components of the nuclear matrix, and passes through the pore complexes of the nucleus and out to the ribosomes where the mRNA is then translated into protein product, a step termed *translation*. The proteins have specific amino acid sequences that instruct the cell where to ship the protein in relation to secretory granules or to the membrane area. The protein can also be modified after translation by the subsequent addition of carbohydrates to become glycoproteins or to be phosphorylated by kinases. Under appropriate signals, such as neurologic control, secretory proteins can then be excreted into the lumen of the prostate. This is a process that occurs when secretory proteins of the prostate and seminal vesicles are formed into the ejaculate. A schematic example of this process is shown in Figure 102-7, and such a system would include PSA and acid phosphatase as well as many other protein products that are regulated in their synthesis by androgens through receptor interactions.

During embryonic development, the AR appears first in the mesenchyme of both the rat ventral prostate and seminal vesicles and a few days later in the epithelial cells, but it is unknown what regulates this timing. **In the development of the seminal vesicles and the wolffian duct, testosterone appears to be the primary androgen in glandular development, and in the ventral prostate that forms from the urogenital sinus the androgen is primarily DHT.** Both testosterone and DHT can bind to the AR; however, on a molar basis, DHT is 3 to 10 times more potent. This decrease in potency of testosterone is believed to be caused by the rapid off rates of the testosterone once it is bound so that equilibrium results in less receptor occupancy compared with DHT at similar tissue levels. A report indicates that in some cases, AR-mediated transcriptional regulation can occur even in the absence of direct interaction of the AR with the specific androgen response elements (Kallio et al, 1995). The report stated that the ARs are able to elicit both transrepression and transactivation without interacting directly with the specific DNA elements. This may indicate that the AR can bind to regulatory units within the transcription factors and thus alter their properties even in the absence of direct DNA binding to an androgen response element.

The next part of this discussion is focused on the structure of the nucleus, where the genetic information of the genes, the AR interactions, and the mRNA processing occur and are integrated. This is within a highly ordered structure of the nucleus that is determined by a residual scaffolding framework, called the *nuclear matrix*, which provides three-dimensional organization to both the nucleus and the DNA.

Role of the Nuclear Matrix in Androgen Action

The DNA may be identical in every cell of different tissues in the body, but it appears to be organized in a different three-dimensional array in different cell types. This spatial organization of DNA appears to be determined in part by nuclear architecture and structure dictated by the scaffolding element termed the *nuclear matrix*. Therefore, more may be required than just a steroid receptor and a DNA sequence with an androgen response element to determine the high tissue specificity of androgen hormone action. It may require regulation of DNA conformation and three-dimensional structure. There is strong evidence to support the belief that

structural components of the nucleus may organize the DNA into different topologic constraints that permit specific steroid receptor interactions themselves. It is also believed that these structural modifications of DNA topology may be an integral part of differentiation. The nuclear matrix has been proposed to be an important structural element in this type of DNA organization (Getzenberg et al, 1990; Boccardo et al, 2003). The matrix facilitates the location of target genes and their conformation and facilitates their cointeraction with steroid receptors. Barrack and Coffey first showed that the nuclear matrix is a major target for androgen and ER binding (Barrack and Coffey, 1980; Barrack, 1987). Because the matrix has been implicated in many important nuclear events, it would provide an ideal target for androgen action. The nuclear matrix has been defined as the dynamic structural subcomponent of the nucleus that directs the functional organization of DNA into loop domains and provides sites for the specific control of nucleic acids (Nelson et al, 1986; Getzenberg et al, 1990). Conceptually, it can be viewed as the nuclear equivalent to the cytomatrix or cytoskeleton. The nuclear matrix contains residual nuclear elements, including the pore complex lamina, the residual nucleolus, and an internal ribonucleoprotein particle network attached to a dynamic fibrous protein mesh (Berezney and Coffey, 1977). The nuclear matrix may be isolated by sequential extractions using nonionic detergent, brief digestion with DNase I, and a hypertonic salt buffer wash. The residual nuclear matrix structures represent only 15% or less of the original total nuclear mass. More than 98% of the DNA, 70% of the RNA, and 90% of the nuclear proteins have been extracted, and the remaining structure is essentially devoid of histones and lipids.

The nuclear matrix has been implicated as an important structural component in a wide variety of biologic functions. There are approximately 50,000 DNA loop domains in a nucleus, each containing about 60 kilobase pairs of DNA, and these loops are attached at their bases to the nuclear matrix (Pardoll et al, 1980; Vogelstein et al, 1980; Luke and Coffey, 1994). This loop organization is maintained during interphase and throughout metaphase (Nelson et al, 1986). Topoisomerase II, an enzyme that modulates DNA twisting and topology, is associated with the nuclear matrix and the mitotic chromosome scaffold. Many studies with a wide variety of systems have demonstrated that active genes are associated with the nuclear matrix, whereas transcriptionally inactive genes are not close to the matrix. This location of active genes on the matrix provides evidence that the matrix plays an important organizing role in differentiation, placing genes in different configuration.

Androgens can activate DNA synthesis and cell replication in target tissues. The nuclear matrix also serves an important role in DNA replication. The matrix contains fixed sites for DNA synthesis (Pardoll et al, 1980) located at the base of the DNA loop. During DNA synthesis the DNA loop domains are reeled down through the attached replicating complex that is fixed on the matrix. Therefore, the DNA replication fork, DNA polymerase, and newly replicated DNA have been shown to be associated with the nuclear matrix. It is easy to visualize how hormone action and alteration in the nuclear matrix structures could impinge on the androgen regulation of DNA synthesis and growth in a prostate cell.

The nuclear matrix is also associated with mRNA synthesis during transcription. Ciejek and colleagues (1982) observed that more than 95% of the unprocessed mRNA precursor for ovalbumin is associated with nuclear matrix of the chick oviduct. When the intron portions of the RNA were spliced out, the mature mRNA was released from the nuclear matrix. This led them to suggest that the nuclear matrix is involved in RNA processing. Marriman and van Venrooij (1985) reported that all RNA cleavage products and RNA processing intermediates are firmly bound to nuclear matrix. Once again, alterations in nuclear matrix structures with steroid receptor interactions could alter important steps in transcription and RNA processing. The nuclear matrix contains the attachment sites for the small nuclear ribonucleoprotein particles that are part of the nuclear spliceosome system central to the nuclear processing of RNA to the final mRNA, which is transported out to the cytoplasm to be translated.

Ahmed and colleagues have carried out an extensive series of studies of the phosphorylation of the nuclear matrix and related proteins in the ventral prostate of the rat after androgen stimulation and withdrawal (Ahmed and Goueli, 1987; Ahmed et al, 1993; Tawfic et al, 1993, 1994). They have shown that the nuclear matrix can be phosphorylated by casein kinase 2 (CK-2). One of the targets of this phosphorylation is nucleolin, which is an abundant nucleolar phosphoprotein involved in the synthesis of ribosomal DNA and exquisitely regulated by androgens (Tawfic et al, 1994). Another important protein in nucleolar function that is required for growth is B23, which is also regulated by CK-2 (Tawfic et al, 1993).

In summary, the nuclear matrix is an important structural modulator of nuclear regulation and is an ideal target for hormonal regulation. Indeed, the nuclear matrix is a major site of steroid hormone receptor binding (Barrack and Coffey, 1982; Donnelly et al, 1983; Wilson and Colvard, 1984; Alexander et al, 1987; Barrack, 1987; Metzger and Korach, 1990; Luke and Coffey, 1994). In the prostate, more than 60% of all nuclear ARs are associated with the nuclear matrix (Barrack and Coffey, 1982). The matrix is also a target for many other types of regulatory interactions, including the nuclear products of oncogenes and viral proteins that can also induce growth regulation similar to hormone-induced growth. For example, the nuclear matrix is reported to be a cellular target for the retrovirus Myc oncogene protein and the polyoma large T antigen. All of these transformation proteins that bind to the nucleus are believed to be early molecular events in carcinogenesis or transformation. Therefore, the observation that ARs interact with the matrix has precedence with the matrix as a common target in factors that regulate cell structure and function.

KEY POINTS: ANDROGEN RECEPTOR STRUCTURE AND FUNCTION

- The AR is a ligand-activated transcriptional regulator that on binding to androgen dissociates from chaperonins, is actively modified by a variety of methods to an active stage, is actively translocated to the nucleus, and associates first with pioneering factors that direct where in the chromatin the receptor will function and then associates with a large number of coactivators and repressors to regulate target gene expression.
- The transport of the AR is reciprocal, which is to say that it is both localized to the nucleus and actively transported out of the nucleus.
- The AR binds to DNA target sequences as a dimer, which can be direct or inverted repeats; however, the receptor always binds with the same orientation.
- The regulation of the AR appears to be one of the most important "gatekeepers" of prostate development and physiology.

PROSTATIC SECRETIONS AND PROTEINS

Prominent, Nonpeptide Components of Prostatic Secretions

The seminal plasma is formed primarily from the secretions of the sex accessory tissues, which provide a suitable environment for survival and function of spermatozoa. The sex accessory tissues include the epididymis, ampullae, seminal vesicles, prostate, Cowper (bulbourethral) gland, and glands of Littre. The average volume of the normal human ejaculate is approximately 3 mL, ranging from 2 to 6 mL, and it has two components: spermatozoa and seminal plasma. Spermatozoa, which represent less than 1% of the total ejaculate, are present in the range of 100 million/mL. The major contribution to the volume of seminal plasma (average 3 mL) comes from the seminal vesicles (1.5 to 2 mL), from the prostate (0.5 mL), and from the Cowper gland and glands of Littre (0.1 to 0.2 mL). During ejaculation the secretions of these glands are released in a sequential manner (Amelar, 1962;

Amelar and Hotchkiss, 1965; Tauber and Zaneveld, 1976; Zaneveld and Tauber, 1981). The first fraction of the human ejaculate is rich in sperm and prostatic secretions, such as citric acid. The level of fructose, which represents a major secretory product of the seminal vesicles, is elevated in the later fraction of ejaculate. More recently, seminal albumin was measured in seminal plasma and the authors demonstrated an association with sperm morphology but not several other semen parameters (Elzanaty et al, 2007). The overall chemical composition of normal human and rodent prostatic secretions and seminal plasma has been widely studied, and the results have been summarized in excellent reviews (Mann and Mann, 1981; Zaneveld and Tauber, 1981; Aumuller and Seitz, 1990; Daniels and Grayhack, 1990; Chow et al, 1993; Gonzalez et al, 1993; Elzanaty et al, 2007). An analysis of expressed prostatic secretions in a small cohort of men revealed that citrate, myo-inositol, and spermine metabolite measurements could potentially differentiate controls from men with prostate cancer (Serkova et al, 2008), with tissue analysis also suggesting that spermine and citrate can distinguish benign from cancerous prostate (Giskeødegård et al, 2013).

In relation to other body fluids the seminal plasma is unusual because of its high concentrations of potassium, zinc, citric acid, fructose, phosphorylcholine, spermine, free amino acids, prostaglandins, and enzymes (most notably acid phosphatase, diamine oxidase, β -glucuronidase, lactate dehydrogenase (LDH), α -amylase, PSA, and seminal proteinase).

Citric Acid

One of the major anions in human seminal plasma is citrate (mean, 376 mg/dL), which is present in the range of 20 mM or 60 mEq/L. This is compared with the chloride ion (155 mg/dL) at 40 mM. Citrate is a potent binder of metal ions, and the seminal plasma concentration of citrate, 20 mM, is comparable to that of the total divalent metals at 13.6 mM (calcium, 7 mM; magnesium, 4.5 mM; zinc, 2.1 mM). Prostatic citrate levels approximate 15.8 mg/mL (Zaneveld and Tauber, 1981), and the values for seminal vesicle citric acid secretions are almost 100-fold less, being only 0.2 mg/mL. Citric acid is formed in the prostate at 100 times higher concentration than is seen in other soft tissues (e.g., prostatic tissue, 30,000 nmol/g; other tissues, range of 150 to 450 nmol/g). The concentration of citrate in the ejaculate is 500 to 1000 times higher than that in the plasma. Prostatic secretory epithelial cells form citrate from aspartic acid and glucose. The high concentrations within the prostate result partly from the inability of the prostate cell mitochondria to oxidize citrate readily once it is formed; therefore, the rate of citrate synthesis far exceeds the rate of citrate oxidation (Costello and Franklin, 1989, 1994; Kavanagh, 1994).

Fructose

The source of fructose in human seminal plasma is the seminal vesicles (Mann and Mann, 1981). Patients with congenital absence of the seminal vesicles also have an associated absence of fructose in their ejaculates (Phadke et al, 1973). The seminal vesicle secretion contains smaller amounts of other free sugars such as glucose, sorbitol, ribose, and fructose, and these sugars usually amount to less than 10 mg/dL. In comparison, the concentration of the reducing sugar fructose is approximately 300 mg/dL in human seminal secretion, and it has a level of 200 mg/dL in seminal plasma. The fructose of the seminal plasma appears to provide an anaerobic and an aerobic source of energy for the spermatozoa (Mann and Mann, 1981) and has been indirectly linked to forward sperm motility and seminal viscosity (Gonzalez et al, 1993; Fabiani et al, 1995).

Fructose levels are under androgenic regulation, but many factors, such as storage, frequency of ejaculation, blood glucose levels, and nutritional status, can also affect seminal plasma concentration (Mann and Mann, 1981); these considerations may account for the wide variations encountered in different semen samples from the same patient. Furthermore, plasma levels of androgens do not always correlate with seminal plasma fructose

levels; therefore these levels are not a reliable index of the androgenic state of the subject. Seminal fructose levels have also been proposed to be under sympathetic control (Lamano-Carvalho et al, 1993; Kempinas et al, 1995).

Polyamines

Polyamines are the most basic (positively charged) small organic molecules in nature. They occur ubiquitously in tissues at high concentrations and are believed to be involved in diverse physiologic processes that share a relationship to cell proliferation and growth. Indeed, polyamines can serve as growth factors for cultured mammalian cells and bacteria and as inhibitors of enzymes, including protein kinases.

The exact role of polyamines at the molecular level still eludes science, but they represent important biologic compounds and are found at high levels in the ejaculate. Polyamines may affect the gating and transport of substances through membrane channels. From a clinical perspective, polyamines (spermidine and spermine) have been investigated as markers of androgen deprivation therapy among men with advanced-stage prostate cancer (Cipolla et al, 1994). Other researchers (Heston, 1991; Kadmon, 1992; Madhubala and Pegg, 1992; Love et al, 1993) have investigated the role of polyamines in the pathophysiology of prostate cancer. The first and rate-limiting step in polyamine synthesis within the prostate is controlled by the enzyme ornithine decarboxylase (ODC). ODC gene expression has been demonstrated to be increased in BPH tissue (Liu et al, 2002). ODC can be inhibited by difluoromethylornithine (DMFO), which in turn inhibits polyamine synthesis. DMFO has been proposed as an agent for chemoprevention of prostate cancer (Kadmon, 1992).

Spermine levels in normal human seminal plasma range from 50 to 350 mg/dL and originate primarily from the prostate gland, which is the richest source of spermine in the body. Spermine $[\text{NH}_2-(\text{CH}_2)_3-\text{NH}-(\text{CH}_2)_4-(\text{CH}_2)_4-\text{NH}-(\text{CH}_2)_3-\text{NH}_2]$ is a basic aliphatic polyamine and, because of its four positive charges, binds strongly to acidic or negatively charged molecules such as phosphate ions, nucleic acid, and phospholipids. When semen is allowed to stand at room temperature, acid phosphatase enzymatically hydrolyzes seminal phosphorylcholine to form free inorganic phosphate ions, which then interact with the positively charged spermine and precipitate as large, translucent salt crystals of spermine phosphate. Polyamines can also form amide bonds and make their covalent addition to protein carboxylic groups (Williams-Ashman et al, 1975), and this modification may be involved in regulatory function.

There has been much interest in spermine and other related polyamines, such as spermidine and putrescine, because of the rapid and dramatic changes in levels and ratios associated with many types of cells that have been induced into growth. Williams-Ashman and colleagues have investigated in detail the biosynthesis and regulation of polyamines in the male reproductive tract and have characterized the enzymatic reactions that progress from ornithine to putrescine to spermidine to spermine (Williams-Ashman et al, 1969, 1972, 1975). Polyamines are oxidized enzymatically by diamine oxidase (present in the seminal plasma) to form highly reactive aldehyde compounds that can be toxic to both sperm and bacteria (Le Calvé et al, 1995). The formation of these aldehyde products produces the characteristic odor of semen. It is also possible that these aldehydes or polyamines may, themselves, protect the genitourinary tract from infective agents. Relationships between spermine levels in seminal plasma and sperm count and motility have also been suggested (Stamey et al, 1968; Fair and Parrish, 1981; Fair et al, 1993; Le Calvé et al, 1995). Like citrate, spermine can also be quantified within prostatic tissue by magnetic resonance spectroscopy (van der Graaf et al, 2000).

Phosphorylcholine

Other positively charged amines are at high concentrations in the ejaculate, including choline and phosphorylcholine, which

are usually found as components of lipid or as lipotropic factors. The semen of mammals is rich in choline $[(CH_3)_3-N^+-(CH_2)_2-OH]$. In humans, phosphorylcholine predominates, whereas in most other species much higher levels of α -glycerylphosphorylcholine are present, often exceeding 1 g/dL of seminal plasma. Seligman and associates (1975) have demonstrated that phosphorylcholine is a highly specific substrate for PAP, which is also active in seminal plasma. The result of this enzymatic activity is the rapid formation of free choline in the first ejaculate. In contrast, α -glycerylphosphorylcholine is secreted primarily in the epididymis and is not readily hydrolyzed by acid phosphatase. For these reasons, Mann and Mann (1981) have suggested that the level of α -glycerylphosphorylcholine can be used as an index for assessing the contribution of the epididymal secretion to the ejaculate. The secretion from the epididymis is also under androgenic control. The function of these choline compounds is unknown; it appears that they are not metabolized by spermatozoa, nor do they affect the respiration of the sperm (Dawson et al, 1957).

Prostaglandins

The richest sources of prostaglandins in the human are the seminal vesicles (Pourian et al, 1995). Prostaglandins are present in seminal plasma at a total concentration of 100 to 300 μ g/mL. Von Euler (1934) proposed the name prostaglandins for the active components in seminal plasma in the belief that they originated from the prostate gland, but Eliasson (1959) established that the primary source of prostaglandin is the seminal vesicles, not the prostate; however, the original name has survived. Prostaglandins have a wide distribution in mammalian tissues but at much lower concentrations than in the seminal vesicles (Vane and Botting, 1995).

There are more than 90 different prostaglandins present in the human, with 15 prostaglandins present in human semen, and they are all 20-carbon hydroxy fatty acids with a cyclopentane ring having two side chains; as such, they are derivatives of prostanoic acid. The 15 types of prostaglandins within the prostate are divided into four major groups, designated A, B, E, and F according to the structure of the five-membered cyclopentane ring. Each of these groups is further subdivided according to the position and number of double bonds in the side chain (therefore, PGE₃ indicates prostaglandins of E type with three double bonds in the side chain). The E group of prostaglandins is the major component in the male reproductive tract, whereas the F group predominates in the female system. Fuchs and Chantharaski (1976) have summarized the reported levels of human seminal plasma prostaglandins and report the following mean values (μ g/mL): PGE₁, 20; PGE₂, 15; (PGE₁ + PGE₂) – 19-OH, 100; PGA₁ + PGA₂, 9; (PGA₁ + PGA₂) – 19-OH, 31; PGB₁ + PGB₂, 18; (PGB₁ + PGB₂) – 19-OH, 13; PGF_{1 α} , 3; and PGF_{2 α} , 4.

These compounds are potent pharmacologic agents that have been implicated in a wide variety of biologic events in the male, including erection, ejaculation, and sperm motility and transport, as well as in testicular and penile contractions. In addition, prostaglandins from seminal fluid deposited in the vagina have been reported to affect cervical mucus, vaginal secretion, and sperm transport in the female genital tract. Prostaglandin E has been related to the immunosuppressive effects of seminal plasma mediated through the extracellular organelles, or “prostatosomes” (Kelly et al, 1991).

Zinc

The high level of zinc in human seminal plasma (140 μ g/mL) appears to originate primarily from secretions of the prostate gland (488 ± 18 μ g/mL) (Bedwal and Bahuguna, 1994). The prostate has the highest concentration of zinc (50 mg/100 g dry weight) of any organ. Byar (1974) has reviewed many of the early experiments and concepts related to zinc in the reproductive tract. Zinc levels are elevated or stable in BPH, whereas there is a marked decrease in zinc content associated with prostatic adenocarcinoma.

The localization of zinc-65 in the human prostate by radioautography appears to be within the epithelial cells; however, in the lateral prostate of the rat, large quantities of zinc were also associated with the stroma and particularly with the basal membrane and the elastin protein component (Chandler et al, 1977). Oral intake of zinc does not alter zinc levels in prostatic fluid.

Many physiologic roles have been postulated for zinc since the classic studies of Gunn and associates (1956, 1965), who correlated endocrine effects on zinc uptake and concentration in the prostate of the rodent. There are many important zinc-containing metallo-enzymes, but the concentration of zinc in the prostate probably exceeds that present in zinc-associated enzymes. Zinc is known to bind many proteins (Sansone et al, 1991). Johnson and associates (1969) characterized zinc-binding proteins in the prostatic secretion of the dog, on hydrolysis, as containing only eight types of amino acids. Heathcote and Washington (1973) described a zinc-binding protein in human BPH that was rich in histidine and alanine. Jonsson and colleagues (2005) suggested that one possible role of zinc in semen may be to regulate the activity of PSA by binding to semenogelins I and II and fragments thereof. There have been other studies on zinc-binding proteins from the prostate (Reed and Stitch, 1973; Fair et al, 1976), and additional information on these interesting proteins is needed.

An important role for zinc in prostatic secretion has been postulated in the studies of Fair and associates (1976), which suggest the direct role of zinc as a prostatic antibacterial factor. In the study of 36 normal men free from bacterial prostatic infections, the mean value of zinc in the prostatic secretion was approximately 350 μ g/mL, with a wide range of 150 to 1000 μ g/mL. In comparison, the prostatic fluid obtained from 61 specimens collected from 15 patients with documented chronic bacterial prostatitis had a reduction of more than 80% and averaged only 50 μ g/mL, with a range of 0 to 139 μ g/mL. The authors proposed a lower limit of normal at 150 μ g/mL. In addition, in vitro studies of free zinc ions at concentrations normally found in prostatic fluid have confirmed the bactericidal activity of zinc against a variety of gram-positive and gram-negative bacteria. However, a considerable portion of the zinc in the prostate appears to be bound to unique proteins, such as metallothionein, and it is not certain how this might alter the biologic properties of zinc (Suzuki et al, 1994, 1995). Yan and colleagues (2008) reported that assessment of decreased zinc in a normal human PREC in vitro resulted in increased single-strand DNA breaks (Comet assay) and differential expression of several genes (Affymetrix HG-U133A gene chips) involved in cell cycle progression, apoptosis, transcription, and DNA damage response and repair. Hence, a zinc deficiency may compromise DNA integrity in the prostate. In prostate cancer the ability of prostate cells to accumulate zinc is lost during disease progression and may be in part caused by the genetic and epigenetic alterations produced by zinc depletion.

Prostatic Secretory Proteins

The predominant secretory proteins of the sex accessory tissues have been reviewed (Lilja and Abrahamsson, 1988; Aumuller and Seitz, 1990; Aumuller et al, 1990; Lilja, 1993a, 1993b; Rittenhouse et al, 1998; Saedi et al, 2001; Diamandis and Yousef, 2002; Yousef and Diamandis, 2002). High-resolution, two-dimensional electrophoresis profiles of the major secretory protein markers from human ejaculate, seminal plasma, and prostatic secretions have been reported (Edwards et al, 1981; Carter and Resnick, 1982; Rui et al, 1984; Tsai et al, 1984; Dube et al, 1987; Aumuller and Seitz, 1990).

With regard to the prostate, several secretory proteins are found in abundance and have clinical significance. These include primarily PSA (human kallikrein 3 [hK3, protein; or KLK3, gene]) and human kallikrein 2 (hK2 or KLK2), but also prostate/CLK-L1 (Yousef et al, 1999; Lwaleed et al, 2004; Clements, 2008), PAP, and prostate-specific protein (PSP-94), also called β -microseminoprotein (β -MSP). Table 102-4 lists some characteristics of the major secretory proteins in the sex accessory tissues.

TABLE 102-4 Major Proteins Secreted by the Sex Accessory Tissue

PROTEIN OR GENE IDENTIFICATION	MOLECULAR WEIGHT (kD)	SEMINAL PLASMA (mg/nL)	ACTIVITY
Prostate-specific antigen (PSA) (hK3 [protein] or <i>KLK3</i> [gene])	33-36	0.70	Serine protease; arginine esterase
Human kallikrein 2 (hK2 or <i>KLK2</i>)	28.4	0.012	In vivo activation of proPSA, arginine esterase
Human kallikrein L1 (<i>KLK-L1</i>)	Unknown	Unknown	Serine protease, also in testes, breast, adrenal, uterus, thyroid, and salivary glands
Human kallikrein 11	Approximately 40	0.002-0.037	Serine protease, also in breast, ovary, and prostate
Prostatic acid phosphatase (PAP)	102-106	0.3-1.0	Phosphotyrosyl protein phosphatase
Prostate-specific transglutaminase	17	Unknown	Involved in the formation of stable, functional peptide-bound glutamine and primary amine groups
Semenogelins I and II	50, 63	2 mM*	Have chymotrypsin-like activity; inhibit PSA activity in the semen
Prostate-specific membrane antigen (PMSA)	Approximately 120	Unknown	Has a structure identical to glutamate carboxypeptidase II and folate hydrolase I; found in kidney, testis, ovary, brain, salivary gland, small intestine, colon, liver, spleen, breast, and skeletal muscle
Prostate stem cell antigen (PSCA)	Approximately 24	Unknown	A prostate cancer-associated tumor antigen Northern blot and in situ data show that PSCA is predominantly prostate specific in normal tissues and is overexpressed in greater than 80% of prostate cancers
Prostate-specific protein (PSP-94), β -microseminoprotein (β -MSP)	10.7-16	0.6-0.9	Also found in epithelial cells of antrum of stomach
Immunoglobulins	160	0.007-0.022	Human IgG
C3 complement	Approximately 178	0.018	An integral part of the complement cascade (C3 activates alternate pathway)
Transferrin	77	0.18	A plasma protein that transports iron through the blood to the liver, spleen, and bone marrow

*Only given in mM concentrations.

Table 102-5 illustrates the number of sample, median, and ranges of components of prostatic secretions among normal male reproductive parameters.

Prostate-Specific Antigen

PSA is a secreted serine protease, first demonstrated in human prostatic tissue in 1970 (Ablin and Soanes, 1970), found in seminal plasma in 1971 (Hara et al, 1971), purified from prostatic tissue in 1979 (Wang et al, 1979), measured in the serum of men in 1980 (Kuriyama et al, 1980), cloned at the gene level in 1987 (Lundwall and Lilja 1987), and widely used as a clinical marker of prostate cancer by 1988 (Seamonds et al, 1986; Chan et al, 1987; Stamey et al, 1987; Oesterling et al, 1988).

The discovery of PSA resulted from a search of the ejaculate and prostatic fluid by immunoprecipitation to find specific proteins for forensic use. In 1971, Japanese workers isolated, from the seminal plasma, a protein that was proved to be antigenically specific for semen; they reported its chemical and physical characteristics and termed it γ -seminoprotein (Hara et al, 1971). Several years later, in an attempt to develop this protein further as a forensic

marker for semen identification, γ -seminoprotein was purified from human seminal plasma. These seminal proteins, initially called γ -seminoproteins, have now been shown by sequence to be the same as PSA.

PSA is a glycoprotein acting as a serine protease of molecular weight 33 kD that contains 7% carbohydrate (Watt et al, 1986) and is found almost exclusively in the epithelial cells of the prostate (Armbruster, 1993; Rittenhouse et al, 1998). It consists of a single polypeptide chain and contains 240 amino acids and an O-linked carbohydrate side chain attached to a serine residue (Watt et al, 1986). PSA acts physiologically like a serine protease and an arginine esterase with both chymotrypsin-like and trypsin-like activity. The sequence of the protein is similar to that of other kallikreins (Rittenhouse et al, 1998) involved in prostatic cell regulatory mechanisms. Lilja (1985) and Watt and coworkers (1986) reported that one of the structural proteins of the seminal fluid, semenogelin, causes the ejaculate to clot. Semenogelin is the predominant seminal vesicle-secreted protein and one of the physiologic substrates for PSA. One possible biologic role of PSA is to lyse the clot in the ejaculate, but it is at present unknown why this clotting and lysing mechanism is important to reproductive physiology.

TABLE 102-5 Components of Prostatic Secretions

VARIABLES	N	MEDIAN	RANGE
Age (yr)	916	34	20-64
Time of sexual abstinence (days)	916	4.0	1.0-60
Semen volume (mL)	916	4.0	1.0-15
Sperm concentration ($\times 10^6$ mL ⁻¹)	916	44	0.1-568
Total sperm count ($\times 10^6$ mL ⁻¹)	916	167	0.4-2400
a (%)	916	14	0-80
b (%)	916	28	0-80
a + b (%)	916	50	0-90
c (%)	916	16	0-50
d (%)	916	33	0-100
Total a + b ($\times 10^6$ per ejaculate)	916	83	0-1200
Normal forms (%)	916	5.0	0-20
Tail defects (%)	916	11	1.0-85
DFI (%)	267	15	3.0-90
HDS (%)	267	7.0	1.0-40
NAG (mU/mL ⁻¹)	506	6.0	1.0-15
PSA (mg/L ⁻¹)	900	890	66-3400 or higher
Zinc (mmol/L ⁻¹)	900	2.0	0-7.0
Fructose (mmol/L ⁻¹)	900	14	0-39
FSH (IU/L ⁻¹)	351	5.0	1.0-45
LH (IU/L ⁻¹)	351	3.0	1.0-13
Testosterone (nmol/L ⁻¹)	351	13	3.0-31
Inhibin B (ng/L ⁻¹)	351	150	14-450
SHBG (nmol/L ⁻¹)	351	26	2.0-88

DFI, DNA fragmentation index; FSH, follicle-stimulating hormone; HDS, high DNA stainability; LH, luteinizing hormone; NAG, *N*-acetylglucosamine; PSA, prostate-specific antigen; SHBG, sex hormone binding globulin. From Elzanaty S, Erenpreiss J, Becker C. Seminal plasma albumin: origin and relation to male reproductive parameters. *Andrologia* 2007;39:60-5.

The PSA gene (*hKLK3*) is a member of a human tissue kallikrein gene family that includes *hKLK1*, *hKLK2*, *hKLK3*, and *KLK-L1* (Lundwall, 1989; McMullen et al, 1991; Berg et al, 1992; Carbin et al, 1993; Clements, 1994; McCormack et al, 1995; Rittenhouse et al, 1998; Nelson et al, 1999; Yousef and Diamandis, 2003). To date there are more than 15 different human kallikreins, with expression noted in prostate, breast, ovarian, and testicular cancers (Obiezu and Diamandis, 2005). These genes are all located on chromosome 19 (Reigman et al, 1992; Yousef et al, 1999; Yousef and Diamandis, 2003). The ectopic expression of PSA has been reported in smaller concentrations in the tissue of malignant breast tumors (Yu et al, 1994a, 1994b, 1994c), normal breast tissue, breast milk, female serum, and adrenal and renal carcinomas; however, for practical and clinical purposes, PSA is an androgen-dependent and prostate organ-specific (but not a cancer-specific) marker. A limitation of PSA as a tumor marker is demonstrated in the substantial overlap in values between benign and malignant prostate disease (Oesterling et al, 1988; Partin et al, 1990).

Most work regarding the molecular biology and biochemistry of PSA is based on extensive study of purified protein from seminal fluid in which the concentration of PSA is nearly a million-fold higher than that found routinely in serum (McCormack et al, 1995). The concentrations found in seminal plasma range from 0.5 to 5.0 mg/mL, whereas normal serum concentrations in men aged 50 to 80 years without prostatic disease range from 1.0 to 4.0 ng/mL (Catalona et al, 1991).

Prostate-Specific Antigen Derivatives

PreproPSA (261 amino acids) is processed in the endoplasmic reticulum of prostatic epithelial cells, where a 17-peptide leader sequence is cleaved to form proPSA. Seven more peptides are then cleaved from the propeptide to form the active PSA peptide (Rittenhouse et al, 1998). The cleavage of the proPSA inactive (zymogen) precursor of PSA is performed primarily in vivo by hK2 (Lilja, 1985; Villoutreix et al, 1994; Rittenhouse et al, 1998). In addition to its cleavage at the -7 residue, proPSA can also be cleaved at the -2 or -5 residue to produce catalytically inactive PSAs termed [-2]proPSA and [-5]proPSA. Finally, additional forms of inactive PSA can be formed by internal cleavages at various regions within PSA (presumably occurring in the seminal fluid after PSA is secreted). These cleaved isoforms comprise BPSA.

A small proportion of active PSA diffuses into the circulation, where it is rapidly bound or complexed by covalent attachment to protease inhibitors (most commonly, α_1 -antichymotrypsin) (Lilja et al, 1991; Stenman et al, 1991; Christensson et al, 1993; Lilja, 1993a; McCormack et al, 1995; Partin and Carter, 1996; Polascik et al, 1999). Inactive PSA can also enter the bloodstream, where it circulates in an unbound state as free PSA (fPSA).

Depending on the monoclonal antibodies used to measure serum PSA, the amounts of free and complexed PSA, as well as proPSA isoforms, can be detected. This has high clinical usefulness because the various PSA derivatives have associations with benign and cancerous prostatic tissue. In prostate cancer, the loss of gland architecture and basal cells results in a decrease in the luminal processing of proPSA to active PSA (and thus an increase in proPSA) and in addition a decrease in the processing of active PSA to BPSA (thus decreasing the amount of fPSA). Thus, increased levels of BPSA in the serum are found in benign disease, whereas proPSA (and particularly [-2]proPSA) and bound PSA are associated with prostate cancer (reviewed in Balk et al, 2003 and Tosoian and Loeb, 2010).

Human Kallikrein 2

Human kallikrein 2 (hK2 [protein] or *KLK2* [gene]) is a prostate-specific serine protease closely related to PSA (Rittenhouse et al, 1998). hK2 was first demonstrated from a low-stringency hybridization screen of a human liver genomic library in 1992, and the amino acid sequence is predicted to have 80% homology with PSA (hK3, *KLK3*) (Young et al, 1992). The striking homology between these two "prostate-specific" proteins suggested a close physiologic relationship. More recently, recombinant hK2 has been expressed and purified (Kumar et al, 1996; Mikolajczyk et al, 1998). Unlike PSA, hK2 is shown to be trypsin-like with selective cleavage at arginine residues and has a more potent (20,000-fold greater than PSA) protease activity (Mikolajczyk et al, 1998). Monoclonal antibodies to hK2 have been developed and have a low incidence of cross-reacting with PSA (Finlay et al, 1998). As mentioned earlier, physiologically, hK2 cleaves proPSA to generate the enzymatically active form of PSA in the prostate (Kumar et al, 1996). Immunohistochemical studies have shown hK2 to be increased in expression from normal to metastatic, poorly differentiated prostatic epithelium (Darson et al, 1997), and studies of hK2 in the serum of men with prostate cancer have suggested clinical usefulness for early detection of prostate cancer (Partin et al, 1999; Vickers et al, 2010).

Human Kallikrein L1

Attempts to find other novel human kallikrein-like genes on chromosome 19 have identified yet another member of the human kallikrein gene family, *KLK-L1* (Nelson et al, 1999; Yousef et al, 1999). Nelson and associates (1999) constructed a cDNA library enriched through subtraction with the cDNAs from four other normal tissues to yield an expressed sequence tag identifying a gene that they have called *prostase*. The sequence of prostase exhibits features similar to the other members of the kallikrein family. Yousef and coworkers (1999) also found *KLK-L1* in breast tissue

and demonstrated that it is hormonally regulated. Although the clinical usefulness of the members of the kallikrein gene family has not yet been determined, it is under investigation.

Human Kallikrein 11

Human kallikrein 11 (hK11) is a serine protease that shares similarities to human kallikrein 3 (hK3) or PSA with significant homologies at the levels of nucleotide and protein structure (Diamandis and Yousef, 2002). Localization of hK11 in epithelial cells of various organs has been demonstrated immunohistochemically, and hK11 has been further detected in amniotic fluid, milk of lactating women, cerebrospinal fluid, follicular fluid, and breast cancer cytosols. The highest levels of hK11 were observed in prostatic tissue extracts and seminal plasma, in which it was present at 300-fold lower levels than PSA. Elevated serum levels of hK11 were found in 60% of men with prostate cancer; the ratio of hK11 to total PSA was able to reduce the number of biopsies required, and the data were similar to those gleaned from fPSA assays (Diamandis and Yousef, 2002; Nakamura et al, 2003).

Human Kallikrein 14

Human kallikrein 14, a trypsin-like human kallikrein-related peptidase (KLK), has been shown to exert a significant and dose-dependent effect on semen liquefaction (Emami and Diamandis, 2008; Emami et al, 2008). Liquefaction of human semen involves proteolytic degradation of the seminal coagulum and release of motile spermatozoa. Several members of human kallikrein-related peptidases are implicated in semen liquefaction, functioning through highly regulated proteolytic cascades. Among these, *KLK3* (also known as *prostate-specific antigen*) is the main enzyme responsible for processing of the primary components of semen coagulum. *KLK14* recently has been identified as a potential activator of *KLK3* and other KLKs (Emami et al, 2008; Emami and Diamandis, 2008). Borgono and associates (2003) measured seminal plasma levels of *KLK14* by an enzyme-linked immunosorbent immunoassay (ELISA) in 36 human semen samples and found *KLK14* to be 0.6 to 23.6 $\mu\text{g/L}$ (mean 10.8; median 10.7 $\mu\text{g/L}$). Semenogelin I and semenogelin II are degraded by PSA to form various biologically active peptides involved in semen liquefaction and release of motile spermatozoa. Semenogelins I and II, through chelation with the excess of free zinc, are also directly cleaved by *KLK14*, in the same manner as PSA. In addition, *KLK14* has also been demonstrated to be a potential biomarker for ovarian and breast cancer (Borgono et al, 2003).

KEY POINTS: SECRETORY PROTEINS—KALLIKREINS

- Secreted prostate proteases exert a significant and dose-dependent effect on semen liquefaction
- Among the most well-studied secreted prostate proteins are hKLK3 (PSA) and a homologous protease, hK2, which functions to cleave PSA.
- PSA and its processed derivative (i.e., BPSA, fPSA, [–2]pro-PSA), as well as hK2, have various associations with benign prostatic tissue and prostate cancer and are currently being used to aid in prostate cancer screening.

Prostate-Specific Transglutaminases

Human prostate-specific transglutaminase 4 belongs to a family of enzymes that irreversibly cross-link peptide-bound glutamine residues through reactions with either lysines or primary amines such as polyamines (Dubbink et al, 1998). Transglutaminases are located throughout the body, but they are highly tissue specific. Dubbink and coworkers (1998) described a new prostate-specific transglutaminase with 35-kilobase genomic DNA and consisting of 13 exons and 12 introns. The main transcription initiation site is located 52 base pairs upstream of the translational start code. At least one

splice variant has been described, and a transglutaminase 4 gene (*TGM4*) promoter was analyzed by sequencing and transfection experiments and found at –1276 to –563. Subsequently, an Sp1 binding site (promoter) required for basal activity of *TGM4* was identified (Dubbink et al, 1999). The *TGM4* promoter was characterized by deletion mapping and mutational analysis. These researchers determined that positions between –113 and –87 were essential for core activity of the promoter. The sequences identified are binding sites for the Sp1 and Sp3 transcription factors; however, their precise role in *TGM4* regulation was not deduced from experiments described (Dubbink et al, 1999). Of importance is the fact that the major gel-forming proteins in semen, semenogelins I and II, are substrates for transglutaminase 4 (Peter et al, 1998). Esposito and Caputo (2005) reviewed the range of substrates for transglutaminases in detail and characterized the molecular basis of transglutaminase-catalyzed reactions and also assessed possible physiologic function and pathophysiologic processes resulting from such interactions. The transglutaminase for the prostate is transglutaminase 4; it weighs 77 kD, is androgen regulated, and is found extracellularly. Transglutaminases catalyze the post-translational modification of proteins by formation of polymerized cross-linkages between the γ -carboxamide group of protein-bound glutamine residues and the ϵ -amino group of protein-bound lysine residues, which results in a stabilized molecular complex. There is evidence to suggest that the biochemical affinity of transglutaminase 4 for acyl-type substrates such as kinesin proteins in protein secretions of the semen may be important for correct extrusion of transglutaminase 4 from the coagulating gland (Esposito and Caputo, 2005).

An and coworkers (1999) also described cloning of *TGM4* (human prostate-specific transglutaminase) and its promoter in the elements of –1 to –500 and also at –520 to –1400. In addition, this group applied Northern blot hybridization and reverse transcription polymerase chain reaction (RT-PCR) analysis to confirm prostatic specificity and Gleason grade-specific expression by RT-PCR and noted significant downregulation in high Gleason grade as well as in metastatic tissue extracts. From a protein perspective, Birckbichler and colleagues (2000) revealed by quantitative immunofluorescence that prostate cancer was significantly decreased compared with normal prostate and prostatitis patients, but this is in contrast to what was observed with RT-PCR results (An et al, 1999), in which the higher Gleason grade tumors tended to be significantly decreased. This discrepancy of results needs to be rectified in larger experiments comparing RT-PCR with protein expression to determine whether this is a technical problem or rather one of translation of transglutaminase 4 mRNA versus protein in the malignant disease process.

Semenogelins I and II

Semenogelin I and semenogelin II are dominant proteins in human semen coagulum that are degraded by PSA to form various biologically active peptides, which in combination with fibronectin give rise to the gel-like coagulum of newly ejaculated semen (Lilja, 1985; Malm et al, 1996; de Lamirande et al, 1997). The genes encoding semenogelins I and II are located in separate regions 11.5 kilobase pairs apart on chromosome 20. The major biologic function of semenogelin involves **capacitation**, which is defined as a series of changes in cell membranes, enzyme activities, and ion fluxes that sperm undergo as they traverse the female urogenital tract to reach the zona pellucida and fertilize the egg (de Lamirande et al, 1997). It has been demonstrated that biologically active peptides from semenogelin I and semenogelin II proteolysis scavenge superoxide anion and may affect sperm oxidase to serve as natural regulators of sperm capacitation (de Lamirande et al, 2001; de Lamirande, 2007). Semenogelins from the seminal vesicles and zinc ions from the prostate play a significant role in semen aggregation at the time of sperm ejaculation and also in sperm motility by binding to the sperm and then interacting with zinc (de Lamirande, 2007; Yoshida et al, 2008). It is of physiologic and possibly pathophysiologic importance that these major gel-forming proteins in semen, semenogelins I and II, are substrates for transglutaminase 4 (Peter

et al, 1998). Both of these proteins originate from the glandular epithelium of the seminal vesicles and are produced in high concentrations; however, in the epididymis, only semenogelin I is expressed. There is evidence by immunohistochemistry that other cell types including the vas deferens, prostate, and trachea demonstrate strong signals for semenogelins I and II, and weaker but positive signals were seen in skeletal muscle cells and in the central nervous system (Lundwall et al, 2002).

Prostate-Specific Membrane Antigen

Reviews of the biochemistry and biology of the prostate-specific membrane antigen (PSMA) in human tissues and prostate cancer surveys describe the differential regulation of the molecule, its enzymatic functions, and its potential as a biomarker for in vivo imaging, targeted therapy, and immunotherapy (Elgamal et al, 2000; Ghosh and Heston, 2004).

The gene encoding PSMA is located on chromosome 11p11-12 and codes for a type II membrane glycoprotein (molecular weight approximately 100,000 Da) with intracellular (1 to 18 amino acids), transmembrane (19 to 43 amino acids), and large extracellular (44 to 750 amino acids) domains (Israeli et al, 1994; Ghosh and Heston, 2004; Davis et al, 2005). The cDNA (2.65 kb GenBank accession number M99487) encoding PSMA was first reported by Israeli and colleagues in 1993 and its deduced amino acid sequence determined (Israeli et al, 1994). It encodes a 750-amino acid protein with a predicted molecular mass of 84 kD (excluding carbohydrates). The hydrophobic amino acids found on amino acid residues 20 to 43 suggested that this protein is a type II integral membrane protein with a small intracellular domain and a large extracellular domain (Fair et al, 1997). The promoter for PSMA has been cloned (Good et al, 1999), and PSMA has been expressed and purified from a baculovirus expression system (Lodge et al, 1999). A portion of the transmembrane domain of this protein (amino acid residues 1250 to 1700) shares 57% homology with the human transferrin receptor mRNA (Mahadevan and Saldanha, 1999). Alternative splicing variants of PSMA (PSM'-PSA' extracellular domain protein) are under investigation to better understand the clinical significance of this important membrane protein found within the prostate (Liu et al, 1997; Grauer et al, 1998; Murphy et al, 1998; Ghosh and Heston, 2004; Rajasekaran et al, 2005). PSMA has been crystallized and its structure deduced at 3.5-Å resolution. These analyses reveal a homodimer with structural similarity to the transferrin receptor, a receptor for iron-loaded transferrin that lacks protease activity (Davis et al, 2005). However, unlike the transferrin receptor, the protease domain of PSMA (glutamate carboxypeptidase II) contains a binuclear zinc site, catalytic residues, and a proposed substrate-binding arginine patch.

PSMA is strongly expressed in the prostate and is upregulated in prostate cancer and in the neovasculature of other tumors (Silver et al, 1997; Chang et al, 1999b, 2001). In the prostate there are three alternatively spliced variants of PSMA. However, only one of these isoforms (PSM' located at the 5' end of PSMA cDNA) is known to be differentially expressed in normal tissue, BPH, and prostate cancer (Elgamal et al, 2000; Rajasekaran et al, 2005). PSMA mRNA expression within prostate cancers is also in the hormone-deprived state, contrary to PSA mRNA, which often demonstrates lower, even absent expression in the hormone-deprived state (Henttu et al, 1992; Israeli et al, 1994; Wright et al, 1995; Rajasekaran et al, 2005). The association of PSMA with prostate cancer makes it a favorable target for the development of imaging molecules and therapeutics (Lupold and Rodriguez, 2004; Davis et al, 2005; Chandran et al, 2008).

Despite its name, PSMA is also expressed in many nonprostatic tissues, including the kidney, small intestine, and nervous system. PSMA in the central nervous system metabolizes the brain neurotransmitter *N*-acetyl-aspartyl-glutamate or NAAG (named NAALADase). In the intestine, PSMA is found in the proximal small intestine, where it removes γ -linked glutamates from poly- γ -glutamated folate (folate hydrolase 1), or as a carboxypeptidase, glutamate carboxypeptidase II.

Prostate Stem Cell Antigen

Reiter and coworkers (1998) identified prostate stem cell antigen (PSCA), a cell surface antigen that is expressed in the prostate (among other tissues including bladder). The PSCA gene encodes a 123-amino acid glycoprotein, with 30% homology to stem cell antigen 2 (Sca-2). Like Sca-2, PSCA is a member of the Thy-1/Ly-6 family and is anchored by a glycosylphosphatidylinositol linkage. By use of mRNA in situ hybridization, PSCA expression was localized in normal prostate to the basal cell epithelium, the putative stem cell compartment of prostatic epithelium; hence, PSCA may be a marker of prostate stem or progenitor cells. Hara and associates (2002) performed an analysis of PSA, PSMA, and PSCA mRNA level on peripheral blood by RT-PCR in 58 patients with prostate cancer and 71 patients with nonmalignant disorders. The results were 7 of 58 (12.1%) for PSA, 12 of 58 (20.7%) for PSMA, and 8 of 58 (13.8%) for PSCA; zero samples were positive for nonmalignant diseases. A hierarchical summary of prognostic value for the three biomarkers was as follows: PSCA was higher than PSA, which was higher than PSMA for RT-PCR of the 58 patients with prostate cancer. Note that in this group of patients, when the RT-PCR result was positive for PSCA the patients had a lower disease progression-free survival than with the other two biomarkers. The PSCA expression increased with higher Gleason score and cancer stage as well as with progression to metastasis and may be a useful biomarker for staging of prostate cancer (Hara et al, 2002). Han and associates (2004) performed immunohistochemistry analysis of PSCA by a 246-patient tissue microarray; the results revealed that a PSCA staining intensity of 3.0 correlated with adverse prognostic features including Gleason score of 7.0 ($P = .001$), seminal vesicle invasion ($P = .005$), and capsular involvement ($P = .033$). However, after multivariate analysis, PSCA did not hold up as an independent predictor of PSA recurrence. Zhigang and Wenly (2004) studied BPH, low-grade prostatic interepithelial neoplasia (LGPIN), high-grade prostatic interepithelial neoplasia (HGPIN), and prostate cancer at the tissue level by immunohistochemistry and at the mRNA level by in situ hybridization. In BPH and LGPIN the staining of PSCA protein and mRNA was weak or negative and less intense and uniform than in HGPIN and prostate cancer. There was moderate to strong PSCA protein as well as mRNA expression in 8 of 11 (72.7%) HGPIN and in 40 of 48 (83.4%) prostate cancer specimens that were examined by immunohistochemistry and in situ hybridization analyses. When the prostate cancer specimens examined by immunohistochemistry and in situ hybridization analyses were compared with BPH (20%) and LGPIN (22.2%) samples, the results were statistically significant ($P < .05$, respectively). The expression level of PSCA increased with high Gleason grade, advanced stage, and progression to androgen independence ($P < .05$, respectively). In addition, in this study, protein immunostaining and in situ hybridization mRNA stain showed a high degree of correlation between PSCA protein and mRNA overexpression in prostate cancer, supporting the potential of PSCA as a prognostic biomarker. Clearly, the value of this protein to the biology of prostate epithelial tissue morphogenesis and also as a new biomarker for diagnosis and treatment of prostate cancer is yet to be realized.

The potential use of PSCA, a membrane surface antigen that is highly expressed in the prostate, as a novel prostate targeting medical device for diagnostics (blood immunoassays or medical imaging) and therapy (vaccines or immunotherapy) is currently being actively studied (Olafsen et al, 2007; Raff et al, 2009). Here is another unique opportunity to use prostate developmental knowledge as a possible tool to manage prostate cancer because of its amplification during carcinogenesis.

Prostatic Acid Phosphatase

Acid phosphatase activity is more than 200 times more abundant in prostatic tissue than in any other tissue and is the source of the high levels of acid phosphatase in ejaculate. Phosphatase enzymes hydrolyze many types of organic monophosphate esters to yield

inorganic phosphate and alcohol. Many phosphatase enzymes exhibit optimal activity *in vitro* in the acid (pH 4 to 6) or alkaline (pH 8 to 11) ranges and are thus classified broadly as either acid or alkaline phosphatase.

Acid phosphatase activity may be further defined by factors that inhibit its enzymatic activity. For example, erythrocyte acid phosphatase is particularly sensitive to inhibition by 0.5% formaldehyde or copper ions (0.2 mM), whereas PAP activity is far more sensitive to inhibition by fluoride ions (1 mM) or L-tartrate (1 mM).

Osteoclasts are also a rich source of tartrate-insensitive acid phosphatase. Minor elevations in serum acid phosphatase levels can accompany Paget disease, osteoporosis, nonprostatic bone metastasis, and other conditions of increased bone resorption as well as metastatic prostate cancer. All acid phosphatases hydrolyze a wide range of natural and synthetic phosphomonoesters, and this has provided a wide variety of assay systems and the expression of different units of activity, depending on the assay. These synthetic substrates include, in part, phenylphosphate (Gutman and Gutman, 1938); phenolphthalein phosphate; paranitrophenyl phosphate, also called *Sigma 104*; and thymolphthalein phosphate (Roy et al, 1971). The specificity of these substrates varies with the type and source of acid phosphatase; it appears that thymolphthalein phosphate may be the most specific substrate for assaying serum levels of prostate-specific acid phosphatase, but specific antibodies are now available for immunoassays. Interest in acid phosphatase assays in serum as a measure of prostate cancer metastasis before definitive therapy has decreased with the availability of the more sensitive and specific PSA assay (Burnett et al, 1962).

The natural substrate for PAP may be phosphorylcholine phosphate, which is rapidly hydrolyzed in the semen (Seligman et al, 1951). The biologic functions of this enzyme and its reactions are not known, but it is of interest that PAP can hydrolyze protein tyrosine phosphate esters, natural products of many oncogene protein tyrosine kinases (Li et al, 1984; Lin and Clinton, 1986). By magnetic resonance spectroscopic techniques, it has been shown that the ratio of intracellular choline to citrate levels within the prostate can help differentiate normal from cancerous prostatic tissue (Scheidler et al, 1999). Further clinical testing is required before this finding will influence clinical practice. It is unknown whether acid phosphatase is a regulatory factor in the tyrosyl protein kinase systems that are so essential as signaling mechanisms in growth factor function.

Human PAP is a glycoprotein dimer of molecular weight 102,000 and contains about 7% carbohydrate by weight, composed of 15 residues per mole of neutral sugars (fructose, galactose, and mannose), 6 residues per mole of sialic acid, and 13 residues of N-acetylglucosamine (Chu et al, 1977). The protein can be dissociated into two subunits of 50 kD. The activity of the purified human enzyme is 723 U/mg with α -naphthyl phosphate, and the seminal plasma contains 0.3 to 1 g/L or 177 to 760 U/mL. The high enzymatic activity of PAP is not characteristic of accessory tissues in many other species; the level is 1000 times higher per gram of tissue in the human prostate than in the rat prostate. The clinical aspects of PAP were reviewed by Romas and Kwan (Lowe and Trauzzi, 1993; Romas and Kwan, 1993).

Prostate-Specific Protein 94 (β -Microseminoprotein and β -Inhibin)

A major, cysteine-rich, nonglycosylated 16-kD protein that contains 94 amino acids has been found in prostatic secretions and named *prostate-specific protein 94* (PSP-94); it is one of the three predominant proteins secreted in the prostate glands and found in seminal fluids along with PSA and PAP. This protein had previously been designated β -inhibin and also β -MSP (Dube et al, 1987; Ulvsback et al, 1989). Transcripts of mRNA for this protein have also been identified in nongenital tissues (Ulvsback et al, 1989). The human gene for PSP-94 has been mapped to chromosome 10 (q11.2), and there are three glucocorticoid response elements and one estrogen response element in the promoter region of the first intron.

Based on these observations the gene is likely regulated by hormones in humans (Nolet et al, 1991; Ochiai et al, 1995) because this also was reported in studies of the rat lateral prostate (Kwong et al, 2000). Also, Valtonen-Andre and associates (2008) demonstrated that in young, healthy males the PSP-94 levels in the serum correlate well with those in the seminal plasma ($r = 0.50$, $P < .001$). An automated immunoassay was performed with an AutoDELFIA 1235 (Wallac) and produced median values of PSP-94 in 205 young men that were 12 mg/L (2.5th to 97.5th percentile, 4.9 to 26 mg/L) in serum and 0.53 g/L (2.5th to 97.5th percentile, 0.13 to 2.0 g/L) or 1.8 mg (2.5th to 97.5th percentile, 0.32 to 6.6 mg) in seminal plasma. These data provide a solid basis for evaluation of this biomarker both in healthy men and in those with prostate cancer.

One of the main biologic functions of PSP-94 is the inhibition of follicle-stimulating hormone (Garde et al, 1999). Whereas follicle-stimulating hormone is made by the pituitary gland, the prostate has been shown to be an extrapituitary source of follicle-stimulating hormone. There are follicle-stimulating hormone receptors in the prostate, and it appears that an autocrine or paracrine regulation of this hormone influences prostate epithelial proliferation (Ben-Josef et al, 1999; Porter et al, 2001). Also, Chan and colleagues (1999) used *in situ* hybridization to study expression of PSP-94 in human prostates. They found that fetal prostate at 6 to 7 months synthesizes PSA and PAP but not PSP-94, and this observation appears to relate to the development of the prostate gland. Zonal anatomic distribution of PSP-94 in the adult prostate demonstrated that the protein is expressed mostly in the acini of the peripheral zone rather than the central or transitional zones. Anahi Franchi and associates (2008) studied the PSP-94 and its potential interaction with human spermatozoa and its possible role in fertility. Using purified PSP-94, they demonstrated a specific interaction at the sperm surface. Also, using dual-antibody ELISA technology, the authors noted that of 62 patients being assessed for fertility, fertile men had a lower concentration of the protein than subfertile men and suggested that semen quality may be affected by the concentrations of PSP-94. **Another function of PSP-94 may be to interact directly with spermatozoa in a manner that can affect the quality of sperm structure and function.**

In the area of cancer, Chan and coworkers (1999) found that PSP-94 expression is markedly downregulated with increasing Gleason grade of prostate cancer. Furthermore, Shukeir and coworkers (2003) demonstrated a significant decrease in growth of the highly metastatic Dunning R3327 subline MatLyLu rat prostate model transfected with parathyroid hormone-related protein by treatment with varying doses of commercial PSP-94 purified from human seminal plasma (0, 0.1, 1.0, and 10 μ g/kg/day). Serum levels of parathyroid hormone-related protein and calcium were used to monitor the efficacy of treatment with PSP-94. **Hence, PSP-94 is an effective inhibitor of hormone-independent, late-stage prostate cancer metastasis in this Dunning MatLyLu animal model.** The PSP-94 molecule has not yet been crystallized; however, Joshi and Jyothi (2002), in a computer-simulated molecular model, have predicted its structure and calculated its binding activity and related biologic activity (follicle-stimulating hormone inhibition) and immunogenic properties. Using a three-dimensional structure constructed by nuclear magnetic resonance (NMR), Ghasriani and associates (2006, 2009) have shown the PSP-94 molecule to consist of two distinct domains that form a rather extended structure. The two domains are connected to each other by the peptide backbone, one disulfide bond, and interactions between the amino and carboxyl termini and are oriented to give the molecule a rather extended structure. In addition, Ghasriani and associates (2009) have demonstrated the specific molecular interactions of the PSP-94 with cysteine-rich secretory protein 3 (CRISP-3) by applying multidimensional NMR. The CRISP proteins are ubiquitous among organisms and snake venoms, and they are reported to be calcium ion channel blockers; however, the relevance of these observations of protein-protein interactions to seminal plasma is yet to be determined.

Protein C Inhibitor

Human semen contains several enzymes and inhibitors of the hemostatic coagulation system (Lwaleed et al, 2004; Fernandez and Heeb, 2007). In human semen, PSA exists as a molecular complex with protein C inhibitor (PCI), and the latter provides some inhibitory consequences for actions of PSA. The predominant structural proteins of coagulated semen are those proteins secreted by the seminal vesicle including semenogelins I and II and fibronectin, and these proteins remain stable in the seminal vesicle's secretions for up to 20 hours at 37°C but rapidly cleave into small peptides on mixing with the proteases (e.g., PAP, hKLK2 [PSA], hKLK3, hKLK14) of prostatic secretion (Lwaleed et al, 2004; Fernandez and Heeb, 2007). The human PCI gene is located in chromosome 14q32.1 and is a serine protease inhibitor that corresponds to a region containing the genes of related serpins (SERPINA5) (Suzuki et al, 1987; Fernandez and Heeb, 2007; Suzuki et al, 2007). PCI is a heparin-dependent inhibitor of activated protein C (APC) that is immunologically and functionally identical to a heparin-dependent urokinase inhibitor (plasminogen activator inhibitor type 3). PCI also inhibits several other blood coagulation and fibrinolytic factors (e.g., FXa, FXI, plasma kallikrein) (Lwaleed et al, 2004; Espana et al, 2007; Fernandez and Heeb, 2007; Suzuki et al, 2007). Suzuki and associates (2007) also demonstrated that digestion of human seminal coagula with PSA releases PCI and PSA-PCI complex from the coagula into the soluble phase, suggesting the presence of active PCI within the semen coagula. PCI then forms a "ternary protein complex" with PSA and semenogelin II in the seminal plasma. The binding of semenogelin II to PSA and PCI is influenced by the molecular microenvironment, including pH, ionic strength, heparin, negatively charged dextran sulfate, divalent cations, and particularly by zinc. These observations suggest that binding of PCI to semenogelins in seminal vesicles regulates the PSA-catalyzed degradation of semenogelins in seminal plasma; the complex formation among PCI, PSA, and semenogelins is modulated by several factors in seminal plasma. Espana and colleagues (2007) determined that PCI is secreted at very high levels in the seminal vesicles in an active form and also occurs in high concentrations in the seminal plasma. The concentration of PCI in 40 seminal plasma samples ranged from 2.2 to 3.7 mM (i.e., about 220 mg/L), and 45% of the seminal PCI was functionally active when assayed immediately after ejaculation. Notably, infertile men had significantly decreased seminal PCI levels (0.6 to 3.2 mM). However, the concentration of PSA in seminal plasma far exceeds the capacity of PCI to inhibit this molecule and hence the biologic role of PCI in seminal plasma. Espana and colleagues (2007) used purified PCI to assess several functional aspects of PCI, and evidence indicated that PCI is involved in human reproduction at several key steps, including fertilization. Hence, PCI is abundant in the seminal fluid and it plays a key role in the interaction among semenogelins, PSA, and likely other proteins in semen, resulting in protein-protein interactions critical to semen coagulation and liquefaction. A balance of seminal fluid coagulative proteins, active enzymes, and metabolites is required to effect sperm motility and successful fertilization (Lwaleed et al, 2004; Espana et al, 2007; Fernandez and Heeb, 2007; Suzuki et al, 2007).

Leucine Aminopeptidase

Aminopeptidases hydrolyze the amino-terminal amino acid from small polypeptides. Leucine aminopeptidases are particularly active against the substrate L-leucyl-glycine, and some of these enzymes are referred to as *arylamidases* because the optimal substrate is L-leucyl- β -naphthylamine. The human prostate is rich in the arylamidase type of leucine aminopeptidase, with a presence in prostatic fluid of 30,000 units/mL.

Leucine aminopeptidase is a product of the epithelial cells of the prostate (Niemi et al, 1963) and is secreted into the lumen of the acini (Kirchheim et al, 1964; Vafa et al, 1993). Rackley and associates (1991) demonstrated that extracts from prostatic carcinoma

contained less leucine aminopeptidase activity than did tissue obtained from BPH.

Lactate Dehydrogenase

The isoenzyme ratios of LDH in human semen may be altered in a patient with prostate cancer (Oliver et al, 1970; Grayhack et al, 1977). LDH (molecular weight 150 kD) is composed of four subunits (each of 35 kD) of only two different types of proteins, denoted M and H. The LDH of muscle has four M units, and that of heart has four H units. Five isoenzymes of LDH can be found in tissues with a four-subunit composition as follows: LDH I, MMMM; LDH II, MMMH; LDH III, MMHH; LDH IV, MHHH; and LDH V, HHHH. The M and H subunits appear to be the same in all tissues, but the amounts of LDH I to V can vary. Denis and Prout (1963) observed increased levels of LDH IV and V in prostate cancer tissue. Several investigators have observed elevated ratios of LDH V/LDH I in human prostate cancer (Elhilali, 1968; Oliver et al, 1970; Flocks and Schmidt, 1972).

Immunoglobulins, C3 Complement, and Transferrin

There are many reports establishing the presence of Igs in human seminal plasma (Liang et al, 1981; Gahankari and Golhar, 1993). It is possible to measure levels of IgG from 7 to 22 mg/dL and those of IgA from 0 to 6 mg/dL; however, IgM is at low, often undetectable levels (Friberg and Tilley-Friberg, 1976). The complete source of these antibodies is not known, although they are found in expressed prostatic fluid (Grayhack et al, 1979) and may be related to infections (Fowler et al, 1982). They are usually found at lower levels in seminal plasma than in blood, but the possibility of diffusion across the "blood-seminal plasma barrier" has not been eliminated (see discussion by Friberg and Tilley-Friberg, 1976).

Expressed prostatic fluid contains considerable amounts of the C3 component of complement, present at 1.82 mg/dL, and this increases nearly 10-fold in fluid collected from patients with prostatic adenocarcinoma to levels of 16.9 mg/dL (Grayhack and Lee, 1981). Prostatitis has also been shown to be related to C3 in men with chronic prostatitis (Blenk and Hofstetter, 1991). Prostatitis and BPH increase the level only approximately twofold. In the same manner, transferrin, an iron-carrying protein, is increased, going from levels of 5.3 mg/dL in normal prostatic fluid to 42.4 mg/dL in prostatic carcinoma (Grayhack and Lee, 1981).

John and colleagues (2003) conducted a prospective study of the ejaculate of 88 patients with chronic prostatitis by surveying IgG, IgA, and IgM and interleukin-1 α , soluble interleukin-2 receptor, and interleukin-6. The control group consisted of 96 normal ejaculates according to the World Health Organization criteria. Ejaculates of patients with chronic prostatitis increased during symptoms and subsided when clinical symptoms decreased. The authors observed that a combination of the humoral immune (IgA and interleukin-6) changes and T-cell-rich infiltrates is suggestive of an autoimmune component of the disease. Alexander and coworkers (2004) studied a group of patients with chronic granulomatous prostatitis consisting of histologically diffuse nonspecific inflammatory changes that include epithelioid histiocytes and occasional multinucleate giant cells admixed with lymphocytes and plasma cells. They have identified an association between the major histocompatibility locus antigen HLA-DRB2*1501 and granulomatous prostatitis and have suggested the possibility that it may be an autoimmune disease.

Zinc α_2 -Glycoprotein

In the seminal plasma, zinc α_2 -glycoprotein (ZAG) is synthesized by PreCs and secreted into seminal fluid (Ding et al, 2007), and it constitutes about 30% of the proteins present in the seminal fluid (Poortmans and Schmid, 1968). The ZAG glycoprotein is found in many body fluids with a molecular mass of 41 kD, and the crystal structure is quite similar to that of a class I major histocompatibility complex (Burgi and Schmid, 1961; Burgi et al, 1989; Sanchez et al,

1999; Delker et al, 2004; Hassan et al, 2008a, 2008b). In addition, ZAG is assigned to the chromosome 7q22.1 based on fluorescent hybridization karyotyping (Hassan et al, 2008a). The crystal structure of ZAG consists of a large groove analogous to class I major histocompatibility complex peptide-binding grooves, and the structure and environment of the groove reflect its role in immunoregulation and in lipid catabolism (Sanchez et al, 1999; Hassan et al, 2008b). ZAG appears naturally in blood, sweat, seminal fluid, breast cyst fluid, cerebrospinal fluid, and urine and is also found in secretory epithelial cells of the liver and the gastrointestinal tract (Tada et al, 1991; Hassan et al, 2008a, 2008b). Biochemically, ZAG stimulates lipid degeneration in adipocytes and appears to be involved in cachexia, a wasting syndrome that can affect people with cancer, acquired immunodeficiency syndrome, and other terminal illnesses (Hirai et al, 1998; Bing et al, 2004; Russell and Tisdale, 2005; Hassan et al, 2008b). The purification and characterization of ZAG from human seminal plasma revealed that it was bound to prolactin-inducible complex (PIP) (Hassan et al, 2008a). With the use of a ZAG tryptic peptide as a standard and a high-flow liquid chromatography–tandem mass spectrometry assay, serum levels in six healthy men were calculated as 3.65 (0.71) mg/L (Bondar et al, 2007). Furthermore, the concentration of ZAG and PIP has been reported to increase dramatically in carcinomas; therefore it has been considered as a good biomarker for prostate, breast, oral, and epidermal carcinomas (Hassan et al, 2008b). Thus ZAG is a protein regulated by glucocorticoids and has the ability to affect fertilization and lipid mobilization (adipokine).

Seminal Vesicle Secretory Proteins

Williams-Ashman (1983) presented a classic review on regulatory features of development and function of the seminal vesicles. The secretory proteins of the seminal vesicles are major proteins and enzymes involved in the rapid clotting of the ejaculate (Cunha et al, 1992). The major clotting protein has been termed *semenogelin* (Lilja and Abrahamsson, 1988). It has been shown to be the seminal vesicle-specific antigen. These clotted proteins from the seminal vesicles serve as substrates for PSA that enzymatically lyse the clot through their protease activity (Lilja, 1985; Aumuller and Seitz, 1990). Beyond the coagulation reaction it is not known what role these seminal vesicle proteins play, but their effects on fertility and uterine sperm motility have been studied in the mouse (Peitz and Olds-Clarke, 1986). Many of the proteins secreted by the seminal vesicles are under androgen regulation (Higgins and Hemingway, 1991; Hagstrom et al, 1992). More recent work (Harvey et al, 1995) has identified an androgen-regulated protease with elastase-like activity within seminal vesicle secretions. The semenogelins I and II are secreted in abundance by the seminal vesicles; and in addition to having coagulum-forming functions and being cleaved by kallikrein-like peptidases to generate biologically active products, the semenogelins are assumed to activate sperm hyaluronidase, affect sperm motility, possess antimicrobial activity, serve as substrates for transglutaminase, and have amyloid properties (Jonsson et al, 2006; de Lamirande, 2007; Hassan et al, 2008b).

In addition, cholesterol and sphingomyelin-rich small, lipid membrane-confined exosome-like vesicles (prostasomes) have been isolated from human semen, and these structures provide an additional source of several hundred proteins that are quite important to fully understanding the biology of reproduction as well as improving our knowledge of the semen coagulation and liquefaction system (Ronquist and Brody, 1985; Arienti et al, 1999; Poliakov et al, 2009). Prostatasomes contain numerous proteins that can affect fertility, promote sperm motility, and stabilize the acrosome reaction (Delves et al, 2007). Sucrose gradient purified prostasomes have been observed by electron microscopy, and their composition has been surveyed after trypsin digestion by liquid chromatography–mass spectrometry (Poliakov et al, 2009). A diversity of structural and functional proteins involved in fertilization, cell adhesion, apoptosis, immunity, metabolism, signal transduction, transport, angiogenesis, and so on have been identified in prostasomes and have opened a new source of urologic scientific investigation to

pursue new biomarkers of disease and elucidate mechanisms of fertility (Delves et al, 2007; Poliakov et al, 2009).

COAGULATION AND LIQUEFACTION OF SEMEN

Within 5 minutes after ejaculation, human semen coagulates into a semisolid gel. On further standing for a 5- to 20-minute period, the clot spontaneously liquefies to form a viscous liquid (Huggins and Neal, 1942; Tauber and Zaneveld, 1976; Mann and Mann, 1981). Calcium-binding substances, such as sodium citrate and heparin, do not inhibit the coagulation process, nor are prothrombin, fibrinogen, or factor XII required because they are absent in seminal plasma (Mann and Mann, 1981). The seminal clot is formed of fibers 0.15 to 10 nm in width, and its morphologic appearance differs from that of a blood fibrin clot (Huggins and Neal, 1942; Tauber and Zaneveld, 1976; Mann and Mann, 1981). Factors affecting blood coagulation do not regulate semen viscosity (Amelar, 1962). From these observations and others, it appears that the coagulation of human semen is different from that of blood.

Examination of split human ejaculates indicates that the first fraction, originating primarily from the Cowper gland and the prostate, contains the liquefaction factors. The final fraction of the ejaculate, enriched in seminal vesicle secretions, is responsible for the coagulation of the ejaculate (Lilja et al, 1987).

It has long been known that prostatic fluid has a dramatic, fibrinolytic-like activity and that 2 mL of this secretion can liquefy 100 mL of clotted blood in 18 hours at 37°C (Huggins and Neal, 1942; Mann and Mann, 1981). The factors involved in such proteolytic activity in semen have been resolved (Huggins and Neal, 1942; Syner et al, 1975; Tauber et al, 1975, 1976; Tauber and Zaneveld, 1976; Mann and Mann, 1981; Zaneveld and Chatterton, 1982; Lilja et al, 1987). Two types of seminal plasma proteolytic enzymes appear to be major factors in the liquefaction process: plasminogen activators and PSA. Two plasminogen activators have been isolated from seminal plasma; they have molecular weights of 70 and 74 kD and appear to be related to urokinase (Propping et al, 1974). It is believed that the plasminogen activators originate from the prostatic secretions.

The seminal plasma contains a variety of other proteolytic enzymes, including pepsinogen, lysozyme, α -amylase, and hyaluronidase. In addition, human semen inhibits the activity of the proteolytic enzyme trypsin, and this is the result of the presence in the seminal plasma of such proteinase inhibitors as α_1 -antitrypsin and α_1 -antichymotrypsin. Coagulation and liquefaction vary in different species. For example, the semen of the bull or dog does not coagulate, whereas rodents, such as the rat and guinea pig, ejaculate a firm pellet that does not appear to liquefy (Tauber et al, 1975, 1976; Tauber and Zaneveld, 1976). In rodents the plugs form through the action of an enzyme called *vesiculase*, which comes from the anterior lobe of the prostate and reacts with seminal vesicle secretions. Because of this action, the anterior lobe of the rodent prostate is also called the *coagulating gland*. Vesiculase is not identical to thrombin because it does not coagulate fibrinogen, nor does thrombin clot the secretions of the seminal vesicles. Williams-Ashman and associates (1977) have established that vesiculase has transamidase activity, catalyzing the formation of γ -glutamyl-lysine cross-links in a clottable protein derived from the seminal vesicles. This seminal vesicle protein, which serves as a substrate for vesiculase, is a basic substance with a molecular weight of 17.9 kD; it has been characterized as to its physical properties.

In summary, it appears that seminal plasma coagulation and liquefaction are under enzymatic control but the biologic purpose of this process has not been resolved. Several key enzymes (e.g., hKLK2 [PSA], hKLK3, hKLK14, PAP) and proteins (e.g., semenogelins, PSP-94, ZAG) of the seminal vesicles and prostate gland are involved in this coagulation and liquefaction system. There have been reports that some infertile men may have impairment of the liquefaction process (Bunge and Sherman, 1954; Bunge, 1970; Eliasson, 1973; Amelar et al, 1977; Jonsson et al, 2006; de Lamirande,

2007; Anahi Franchi et al, 2008; Hassan et al, 2008b; Poliakov et al, 2009).

KEY POINTS: COAGULATION AND LIQUEFACTION OF SEMEN

- PSA is one of several serine proteases secreted by the prostate in high concentrations into the ejaculate. Although its main function may relate to regulation of semen coagulation, it has proved to be a valuable marker of prostate disease states.
- PCI is abundant in the seminal fluid, and it plays a key role in the interaction among semenogelins, PSA, and likely other proteins in semen, resulting in protein-protein interactions critical to semen coagulation and liquefaction.

PROSTATIC SECRETIONS AND DRUG TRANSPORT

Aumuller and Seitz (1990) have reviewed the secretory mechanism for the sex accessory tissues. Isaacs (1983) also reviewed the concepts related to the fluid and drug transport properties of the prostate and seminal vesicles and has compared the composition and volume of prostatic secretion under basal stimulation and under neurologic stimulation during ejaculation or pilocarpine stimulation. Isaacs calculated that under neurologic stimulation there is a 205-fold increase in the total potassium, chloride, and sodium output over the basal secretory rate, and he has shown that the prostate is capable of secreting five times its total content of sodium and chloride during this active secretion. These findings show the tremendous transport powers of this system. Smith and Hagopian (1981) have studied the transepithelial voltage changes during prostatic secretion in the dog and have concluded that although sodium may move passively through the plasma in the prostatic fluid during ejaculation, the movements of potassium and chloride ions involve active transcellular transport. Isaacs and associates (1983) have shown that the androgen-induced secretions can be blocked in the presence of estrogen, although the growth properties and biologic properties of the androgen on the prostate are not markedly altered. This would suggest a direct effect of estrogen in blocking a major transport system in the prostate.

Only a few compounds, including ethanol, iodine, and a few antibiotics, are capable of entering the semen by simple diffusion (Reeves, 1982). Drugs entering prostatic secretions have been of interest because of the prevalence of prostatitis and the need for new modalities of chemotherapy. Earlier, Stamey and colleagues had made extensive studies of the ability of chemotherapeutic agents to concentrate in the prostatic fluid of humans and dogs (Hessl and Stamey, 1971; Stamey et al, 1973), and many other investigators have also contributed to this knowledge (Madsen et al, 1968, 1976, 1978; Fowler et al, 1982). Few drugs reach concentrations in the prostatic secretion that approach or surpass their concentrations in blood, but some exceptions are the basic macrolides erythromycin and oleandomycin, sulfonamides, chloramphenicol, tetracycline, clindamycin, trimethoprim, and fluoroquinolones (Reeves, 1982).

In general, these drugs are assumed to pass across the membrane by nonionic diffusion, possibly by lipid solubility, through the membrane; when they reach the more acidic prostatic fluid they are protonated and acquire a more positive charge. Thus the charged drugs become relatively trapped within the prostatic secretions. Several factors are critical, including the pKa of the drug and the pH of the prostatic secretions, as well as the drug binding to proteins in each compartment. Basic drugs would be more positively charged in acidic prostatic fluid than in blood. Slight changes in pH can have large effects on this nonionic diffusion. Samples of prostatic secretions from humans varied widely in pH from 6 to 8, with a mean value of 6.6; however, with prostatic inflammation the pH tended to be 7 or higher (White, 1975). Although prostatic

secretions are slightly acidic, the pH of freshly ejaculated human semen is slightly alkaline (pH 7.3 to 7.7); on standing, semen first becomes more alkaline with the loss of carbon dioxide and then later acidic owing to accumulation of lactic acid. Drugs may be developed in the future that are transported into the prostate as therapeutic agents, as chemoprotectors, or as a route to the semen to regulate fertility; however, more must be learned about the fundamental transport system in and out of the male reproductive tract before such an approach is feasible.

KEY POINTS: PROSTATIC SECRETIONS AND DRUG TRANSPORT

- Only a few compounds, including ethanol, iodine, and a few antibiotics, are capable of entering the semen by simple diffusion.
- A few exceptions for drugs are the basic macrolides erythromycin and oleandomycin, sulfonamides, chloramphenicol, tetracycline, clindamycin, trimethoprim, and fluoroquinolones. Perhaps these molecules, because of their lipid solubility, are transported by nonionic diffusion.

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The complete reference list is available online at www.expertconsult.com.



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Etiology

Pathophysiology

Epidemiology

Natural History of Untreated Benign Prostatic Hyperplasia

Surgery for Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a pathologic process that is one but certainly not the only cause of lower urinary tract symptoms (LUTS) in aging men, also described as “male LUTS.” Despite intense research efforts in the past five decades to elucidate the underlying etiology of prostatic growth in older men, cause-and-effect relationships have not been established. For example, androgens are a necessary but not the only causative aspect of BPH. Previously held notions that the clinical symptoms of male LUTS—in the past erroneously called “prostatism”—are simply due to a mass-related increase in urethral resistance are too simplistic. It is now clear that a significant portion of male LUTS is due to age-related detrusor dysfunction and other conditions such as polyuria, sleep disorders, and a variety of systemic medical conditions unrelated to the prostate-bladder unit.

Historically, voiding symptoms have been related to obstruction of the bladder outlet (Chapple et al, 2008). The traditional association in men is with the prostate, the so-called symptoms of “prostatism.” However, it is well recognized that voiding symptoms poorly correlate with underlying pathophysiology (de la Rosette et al, 1998). Similar symptoms can be produced by any other form of obstruction, such as a urethral stricture or, conversely, by poor function of the lower urinary tract in circumstances in which there is impaired detrusor contractility. This has led to the recognition that, although LUTS may commonly be related to bladder outlet obstruction (BOO) as a result of benign prostatic obstruction, which is often associated with benign prostatic enlargement resulting from the histologic condition of BPH, this is not invariably the case. For example, women also commonly present with voiding symptoms (Irwin et al, 2006). Lepor and Machi (1993) have shown that age-matched community-dwelling men and women have similar levels of symptom frequency and severity. Failure to empty can be related either to an outlet obstruction or to detrusor underactivity of the bladder, or to a combination of both. Postmicturition symptoms, such as postvoid dribbling, occur in both sexes, but most often in men, in whom these symptoms are highly common, are very troublesome, and cause significant interference with quality of life (Reynard et al, 1996). Storage symptoms are currently largely encompassed by the term *overactive bladder syndrome*, which is defined as urgency, frequency, nocturia, and urge incontinence, and which is believed to be correlated with an underlying detrusor overactivity (Abrams et al, 2003). These symptoms tend to be more bothersome than voiding symptoms, especially if they are associated with incontinence. Storage symptoms in both sexes are commonly associated with urinary infections or, more rarely, with other conditions such as bladder stones, carcinoma, or carcinoma in situ in the bladder.

This conception can be shown as partially overlapping populations (Fig. 103-1). While many men over the age of 40 will develop

histologic hyperplasia (i.e., BPH), not all will have bothersome LUTS. Of those who do, some will and others will not develop measurable enlargement of the prostate, which may be referred to as benign prostatic enlargement (BPE). It is common for men to have BPE without having LUTS and vice versa. BOO may also be present with or without LUTS and with or without BPE, and in some cases BOO (i.e., stricture, etc.) exists in men with BPH (Roehrborn, 2008).

Undoubtedly, the constellation of cellular pathologies that give rise to the symptoms of LUTS is far more complex than we currently realize. Only by unraveling these complexities, however, will we be able to design alternative strategies to treat successfully and possibly prevent the adverse impact of BPH on lower urinary tract function.

ETIOLOGY

Histopathologically, BPH is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate and thus correctly referred to as *hyperplasia* and not *hypertrophy*, as is often found in the older literature. The observation of new epithelial gland formation is normally seen only in fetal development and gives rise to the concept of embryonic reawakening of the stromal cell's inductive potential (Cunha et al, 1983; Isaacs, 2008). The precise molecular etiology of this hyperplastic process is uncertain. The observed increase in cell number may be due to epithelial and stromal proliferation or to impaired programmed cell death leading to cellular accumulation. Androgens, estrogens, stromal-epithelial interactions, growth factors, and neurotransmitters may play a role, either singly or in combination, in the etiology of the hyperplastic process.

Hyperplasia

In a given organ, the number of cells, and thus the volume of the organ, is dependent upon the equilibrium between cell proliferation and cell death (Isaacs and Coffey, 1989). An organ can enlarge not only by an increase in cell proliferation but also by a decrease in cell death. Although androgens and growth factors stimulate cell proliferation in experimental models, the relative role of cell proliferation in human BPH is questioned because there is no clear evidence of an active proliferative process. Although it is possible that the early phases of BPH are associated with a rapid proliferation of cells, the established disease appears to be maintained in the presence of an equal or reduced rate of cell replication. Increased expression of antiapoptotic pathway genes (e.g., *BCL2*) supports this hypothesis (Kyprianou et al, 1996; Colombel et al,

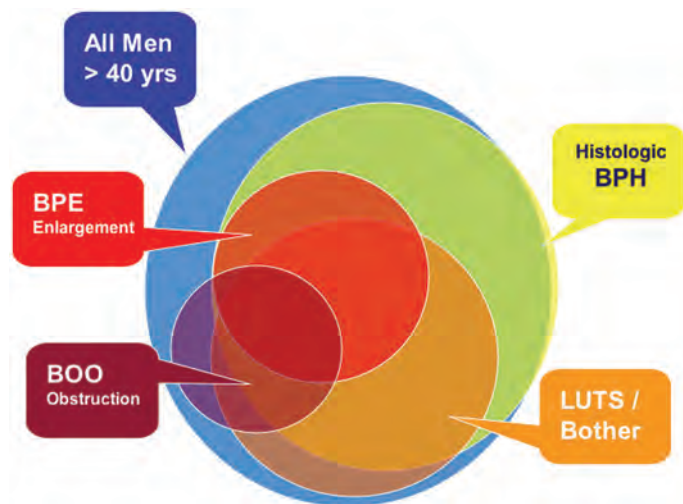


Figure 103-1. Diagram showing the relationship between histologic hyperplasia of the prostate (BPH), lower urinary tract symptoms (LUTS), benign prostate enlargement (BPE), and bladder outlet obstruction (BOO). The size of the circles does not represent actual proportions but rather illustrates the partial overlap between the different disease definitions. (From Roehrborn CG. Pathology of benign prostatic hyperplasia. *Int J Impot Res* 2008;20[Suppl. 3]:S11–8.)

1998). Androgens not only are required for normal cell proliferation and differentiation in the prostate but also actively inhibit cell death (Isaacs, 1984). In the dog, experimental BPH can be produced by androgens combined with estradiol (Walsh and Wilson, 1976; DeKlerk et al, 1979; Berry et al, 1986b; Juniewicz et al, 1994). Despite a significant increase in gland size, there is actually a reduction in the rate of DNA synthesis compared with untreated controls (Barrack and Berry, 1987), indicating that androgens and estrogens both inhibit the rate of cell death. Neural signaling pathways, especially α -adrenergic pathways, may also play a role in balancing cell death and cell proliferation (Anglin et al, 2002).

The hyperplasia results in a remodeling of the normal prostatic architecture (Untergasser et al, 2005). Epithelial budding from pre-existing ducts and the appearance of mesenchymal nodules characterize the early stages of the process, but the tissue phenotype of patients with established disease is highly variable.

BPH may be viewed as a stem cell disease (Barrack and Berry, 1987). Presumably, dormant stem cells in the normal prostate rarely divide, but when they do, they give rise to a second type of transiently proliferating cell capable of undergoing DNA synthesis and proliferation, thus maintaining the number of cells in the prostate. When the proliferating cells mature through a process of terminal differentiation, they have a finite life span before undergoing programmed cell death. In this paradigm, the aging process induces a block in this maturation process so that the progression to terminally differentiated cells is reduced, reducing the overall rate of cell death. Indirect evidence for this hypothesis comes from the observation that secretion, one parameter of epithelial cell differentiation, decreases with age, suggesting that the number of differentiated cells capable of secretory activity may be decreasing (Isaacs and Coffey, 1989). A survey of human BPH specimens for a marker of cellular senescence (senescence-associated β -galactosidase) demonstrated a higher portion of senescent epithelial cells in men with large prostates, suggesting that an accumulation of those cells may play a role in the development of prostate enlargement (Choi et al, 2000). More recent studies support the hypothesis that impaired cell senescence may play a significant role in the etiology of BPH (Castro et al, 2003).

Hormones may exert their influence over the stem cell population not only with advancing age but also during embryonic and neonatal development (Naslund and Coffey, 1986). The size of the

prostate may be defined by the absolute number of potential stem cells present in the gland, which in turn may be dictated at the time of embryonic development. Studies in animal models have suggested that early imprinting of prostatic tissue by postnatal androgen surges is critical to subsequent hormonally induced prostatic growth. As with the hormonal regulation of adult prostatic tissues, sex steroid hormones may exert their imprinting effect directly or indirectly through a complex series of signaling pathways (Lee and Peehl, 2004).

Role of Androgens

Although androgens do not cause BPH, the development of BPH requires the presence of testicular androgens during prostate development, puberty, and aging (McConnell, 1995; Marcelli and Cunningham, 1999). Patients castrated prior to puberty or who are affected by a variety of genetic diseases that impair androgen action or production do not develop BPH. It is also known that prostatic levels of dihydrotestosterone (DHT) as well as the androgen receptor (AR) remain high with aging despite the fact that peripheral levels of testosterone are decreasing. Moreover, androgen withdrawal leads to partial involution of established BPH (Peters and Walsh, 1987; Isaacs, 2008).

Assuming normal ranges, there is no clear relationship between the concentration of circulating androgens and prostate size in aging men. In the Olmsted County Study of Urinary Symptoms and Health Status among Men cohort (median age 60.9), serum bioavailable testosterone levels were found to decline with increasing age, while the estradiol/bioavailable testosterone ratio increased (Roberts et al, 2004). Bioavailable testosterone correlated negatively and estradiol/bioavailable testosterone ratio correlated positively with prostate volume, but this association was much less apparent after age adjustment. Baseline data from a large BPH medical therapy study confirmed the absence of a relationship between serum testosterone, serum prostate-specific antigen (PSA), and prostate volume (Marberger et al, 2006) (Table 103-1). Conversely, in a 20-year follow-up study, Parsons and colleagues (2010) showed that higher baseline serum DHT levels were associated with an increased risk of BPH. The odds ratios (ORs) for the second, third, and fourth quartiles of DHT were 1.83 (95% confidence interval [CI] 0.96 to 3.47), 1.50 (0.79 to 2.85), and 2.75 (1.46 to 5.19), respectively (P trend = .02). A higher testosterone-to-DHT ratio, however, was associated with a 42% decreased risk of BPH (Parsons et al, 2010; Trifiro et al, 2010).

In the brain, skeletal muscle, and seminiferous epithelium, testosterone directly stimulates androgen-dependent processes. In the prostate, however, the nuclear membrane-bound enzyme steroid 5α -reductase converts the hormone testosterone into DHT, the principal androgen in this tissue (see Fig. 103-1) (McConnell, 1995). Ninety percent of total prostatic androgen is in the form of DHT, principally derived from testicular androgens. Adrenal androgens may constitute 10% of total prostatic androgen, although the importance of this stored hormone source in the etiology of BPH is negligible. Inside the cell, both testosterone and DHT bind to the same high-affinity AR protein (Chatterjee, 2003). DHT is a more potent androgen than testosterone because of its higher affinity for the AR. Moreover, the DHT-receptor complex may be more stable than the testosterone-receptor complex. The hormone receptor then binds to specific DNA binding sites in the nucleus, which results in increased transcription of androgen-dependent genes and ultimately stimulation of protein synthesis (Andriole et al, 2004). Conversely, androgen withdrawal from androgen-sensitive tissue results in a decrease in protein synthesis and tissue involution. Besides inactivation of key androgen-dependent genes (e.g., PSA gene), androgen withdrawal leads to the activation of specific genes involved in programmed cell death (Kyprianou and Isaacs, 1989; Martikainen et al, 1990). Despite the importance of androgens in normal prostatic development and secretory physiology, there is no evidence that either testosterone or DHT serves as the direct mitogen for growth of the prostate in older men. Indeed, neither hormone is mitogenic to cultured prostatic epithelial cells (McKeehan et al,

TABLE 103-1 Absence of Significant Relationship between Serum Testosterone and Serum PSA and Prostate Volume

BASILINE TESTOSTERONE CATEGORY (ng/mL)*	NO. OF INDIVIDUALS (N = 4254)	AGE (yr)	PSA (ng/mL)	PROSTATE VOLUME (mL)	BMI (kg/m ²)	BASILINE SFI SCORE
≥300	3092	66.5	4.0	54	27.0	6.8
275-300	291	65.3	3.8	56	28.2	6.6
250-275	269	66.2	3.9	55	28.1	6.4
225-250	225	65.3	4.0	57	29.0	7.2
200-225	143	64.8	3.9	56	30.1	5.9
175-200	115	66.5	4.0	56	29.5	6.8
150-175	67	66.2	3.6	56	29.5	5.8
<150	52	68.7	4.0	61	31.0	5.6

BMI, body mass index; PSA, prostate-specific antigen; SFI, Sexual Function Inventory.

*For nanomoles per liter, divide by 28.8.

Modified from Marberger M, Roehrborn CG, Marks LS, et al. Relationship among serum testosterone, sexual function, and response to treatment in men receiving dutasteride for benign prostatic hyperplasia. *J Clin Endocrinol Metab* 2006;91:1323–8.

1984). In the rat ventral prostate, differential gene expression experiments failed to demonstrate direct activation of mitogenic pathways (Wang et al, 1997). However, many growth factors and their receptors are regulated by androgens (see later). Thus the action of testosterone and DHT in the prostate is mediated indirectly through autocrine and paracrine pathways.

Androgen Receptors

The prostate, unlike other androgen-dependent organs, maintains its ability to respond to androgens throughout life. In the penis, AR expression decreases to negligible rates at the completion of puberty (Roehrborn et al, 1987; Takane et al, 1991a, 1991b). Thus, despite high circulating levels of androgen, the adult penis loses its ability for androgen-dependent growth. If the penis maintained high levels of ARs throughout life, presumably the organ would grow until the time of death. In contrast, AR levels in the prostate remain high throughout aging (Barrack et al, 1983; Rennie et al, 1988). In fact, these data suggest that nuclear AR levels may be higher in hyperplastic tissue than in normal control tissues. Age-related increases in estrogen, as well as other factors, may increase AR expression in the aging prostate, leading to further growth (or to a decrease in cell death), despite decreasing levels of androgen in the peripheral circulation and “normal” levels of DHT in the prostate.

The potential role of AR mutations, polymorphisms, or other alterations in the pathogenesis of BPH is unclear (Chatterjee, 2003). A polymorphism in the number of CAG repeats (short versus control) in the AR gene has been associated with larger prostate size and an increased risk of surgery (Giovannucci et al, 1999a, 1999b). However, another study from the Netherlands showed no relationship between the number of CAG repeats and BPH (Bousema et al, 2000). A study of Finnish men found that short CAG repeats were significantly less common in men with BPH compared with control subjects (Mononen et al, 2002). Given the significant variation in reported findings, if short CAG repeats play a role in BPH pathogenesis, it is likely to be minor (Hoke and McWilliams, 2008).

Dihydrotestosterone and Steroid 5 α -Reductase

Intraprostatic DHT concentrations are maintained but not elevated in BPH. Initial studies of resected prostatic tissue suggested that prostatic DHT levels were higher in the hyperplastic gland than in normal control tissues. However, the controls used for these early studies were largely accident victims. Ongoing metabolism of DHT after death lowers the level of this androgen in cadaveric tissues. This was clearly shown in a study by Walsh and colleagues (1983) in which prostatic surgical specimens from men without BPH were used as the control. These investigators demonstrated that DHT

levels are the same in hyperplastic glands as in normal glands. However, the aging prostate maintains a high level of DHT as well as a high level of ARs; thus the mechanism for androgen-dependent cell growth is maintained. There is little question that androgens have at least a permissive role in the development of the disease process.

Two steroid 5 α -reductase enzymes have been discovered, each encoded by a separate gene (Russell and Wilson, 1994). Type 1 5 α -reductase, the predominant enzyme in extraprostatic tissues such as skin and liver, is normally expressed in the 5 α -reductase deficiency syndrome and is inhibited by dutasteride but not substantially by finasteride. Type 2 5 α -reductase is the predominant prostatic 5 α -reductase, although it is also expressed in extraprostatic tissues. Mutations in the type 2 enzyme are responsible for the clinical phenotype observed in the 5 α -reductase deficiency syndrome. It is exquisitely sensitive to inhibition by finasteride and dutasteride (Carson and Rittmaster, 2003). Clearly, the type 2 enzyme is critical to normal development of the prostate and hyperplastic growth later in life. The role of type 1 5 α -reductase in normal and abnormal prostate growth remains to be defined. There is growing evidence to suggest that the type 1 isoenzyme may play a more important role in prostate cancer compared to BPH, as increased levels of mRNA expression, protein, and functional enzymes have been demonstrated in prostate cancer (Thomas et al, 2008). Given that finasteride produces prostate size reduction identical to that with dual type 1/type 2 inhibitors and roughly equivalent to that with castration, it is unlikely that type 1–derived DHT is critical to hyperplastic growth.

Immunohistochemical studies with type 2 5 α -reductase-specific antibodies show primarily stromal cell localization of the enzyme (Thigpen et al, 1993; Silver et al, 1994). Epithelial cells uniformly lack type 2 protein, and some basal epithelial cells stain positively. Type 1 5 α -reductase protein could not be detected in BPH or prostate cancer using initially available antibodies, although trace levels of type 1 mRNA have been seen in normal prostates, BPH, and cancer (Shirakawa et al, 2004). A study with a selective type 1 antibody demonstrated positive staining in only 7% of BPH cases (Thomas et al, 2003). In the same study, type 1 enzymatic activity was found in only 2 of 29 BPH specimens.

These data demonstrate that the stromal cell plays a central role in androgen-dependent prostatic growth and that the type 2 5 α -reductase enzyme within the stromal cell is the key androgenic amplification step. Thus a paracrine model for androgen action in the gland (Fig. 103-2) is evident. In addition, it is possible that circulating DHT produced in the skin and liver may act on prostate epithelial cells in a true endocrine fashion (McConnell, 1995). If dual type 1/type 2 5 α -reductase inhibition has clinical utility over selective type 2 inhibitors, it is likely to be due to inhibition of peripherally produced DHT.

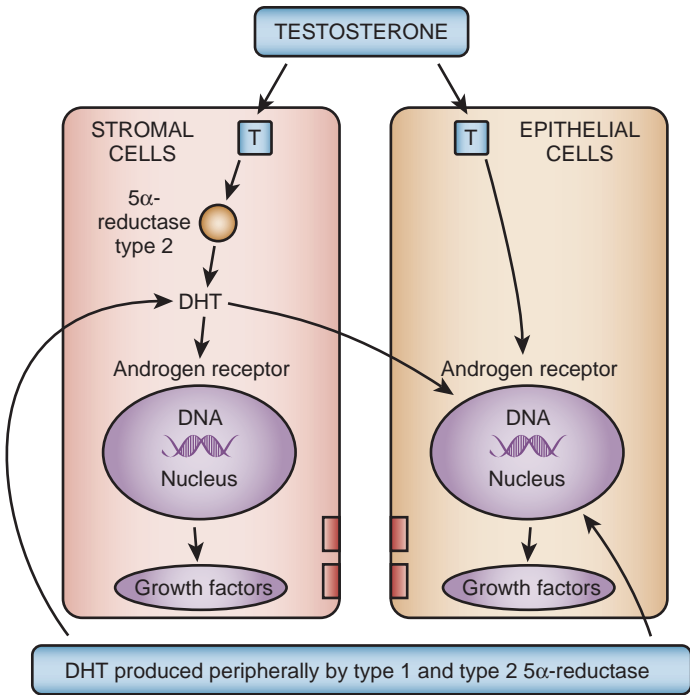


Figure 103-2. Testosterone (T) diffuses into the prostate epithelial and stromal cell. T can interact directly with the androgen (steroid) receptors bound to the promoter region of androgen-regulated genes. In the stromal cell, a majority of T is converted into dihydrotestosterone (DHT)—a much more potent androgen—which can act in an autocrine fashion in the stromal cell or in a paracrine fashion by diffusing into epithelial cells in close proximity. DHT produced peripherally, primarily in the skin and liver, can diffuse into the prostate from the circulation and act in a true endocrine fashion. In some cases the basal cell in the prostate may serve as a DHT production site, similar to the stromal cell. Autocrine and paracrine growth factors may also be involved in androgen-dependent processes within the prostate. (From Roehrborn CG. Pathology of benign prostatic hyperplasia. *Int J Impot Res* 2008;20[Suppl. 3]:S11–8.)

Immunohistochemical studies in open enucleated BPH specimens show considerable intra- and interprostatic 5 α -reductase, making studies of its distribution based on single or one-time biopsy material very difficult (Sherwood et al, 2003).

Polymorphisms in the type 2 steroid 5 α -reductase enzyme (SRD5A2) have been reported, but their linkage to BPH is uncertain. The SRD5A2 gene on chromosome 2p23 frequently encompasses A49T and V89L substitutions and a TA dinucleotide repeat polymorphism. The 89L allele has been associated with lower enzyme activity, whereas the 49T allele has been associated with higher activity. Longer TA repeats are associated with mRNA instability and thus decreased enzyme activity. The number of L alleles, but not testosterone alleles or TA repeats, in one study correlated significantly with the presence of BPH (Salam et al, 2005). In the Olmsted County Study population, consistent associations between SRD5A2 genotypes and BPH were not demonstrated, although there was a weak correlation between V89L polymorphisms and prostate volume (Roberts et al, 2005).

Androgen withdrawal may partially exert its effect on the prostate through vascular effects (Buttayan et al, 2000). Castration induces acute and drastic vasoconstriction of blood vessels in the rat prostate (Hayek et al, 1999). This effect does not appear to be mediated through vascular endothelial growth factor (VEGF) (Burchardt et al, 2000). There is indirect evidence to suggest that abnormalities in the prostatic vascular system produced by other disease states (e.g., diabetes) may be a risk factor for BPH (Parsons et al, 2006; Parsons, 2007).

TABLE 103-2 Comparison of ER- α and ER- β Expression and Activities in the Prostate Gland

	ER- α	ER- β
Localization	Stromal	Epithelial
Proliferation	Epithelial squamous metaplasia Stromal proliferation	Antiproliferative
Differentiation	Epithelial dysplasia	Prodifferentiation
Immune response		Anti-inflammatory Antioxidant
Expression	Dysregulated in prostate cancer Silenced in early cancers Re-emergence with progression	Dysregulated in prostate cancer ↓ Organ-confined disease ↑ In metastatic prostate cancer

ER, estrogen receptor.
From Prins GS, Korach KS. The role of estrogens and estrogen receptors in normal prostate growth and disease. *Steroids* 2008;73:233–44.

Role of Estrogens

There is animal model evidence to suggest that estrogens play a role in the pathogenesis of BPH; the role of estrogens in the development of human BPH, however, is less clear. In the dog, where estrogens act synergistically with androgens to produce experimental BPH, estrogen appears to be involved in induction of the AR (Moore et al, 1979). Estrogen may, in fact, “sensitize” the aging dog prostate to the effects of androgen (Barrack and Berry, 1987). The canine prostate contains an abundance of high-affinity estrogen receptors (ERs). In the dog, estrogen treatment stimulates the stroma, causing an increase in the total amount of collagen (Berry et al, 1986a, 1986b). There are at least two forms of the ER: Estrogen receptor α (ER- α) is expressed by prostate stromal cells, and estrogen receptor β (ER- β) is expressed by prostate epithelial cells (Prins et al, 1998). The estrogenic response of the prostate is determined by the type of ER present within the prostatic cells. Experiments in knockout mice suggest a “constraining influence” of estrogens on the prostate (Krege et al, 1998). In vitro studies suggest that upregulation of ER- α in cultured prostate stromal cells is also associated with upregulation of fibroblast growth factor (FGF)-2, FGF-7, and other growth factors; the addition of androgens down-regulated the ER and various stroma-derived growth factors (Smith et al, 2000, 2002).

Different actions may be mediated by the stromal ER- α and epithelial ER- β (Prins and Korach, 2008). Evidence also indicates that estrogen action mediated through the separate receptors may contribute to the etiology and progression of multiple prostate disease states (Table 103-2). These findings provide new avenues and alternative approaches for the treatment of prostate diseases, including prostate cancer, with novel therapies directed at ERs or estrogen metabolism. Since the two types of ER may play distinct and perhaps opposing roles in many diseases of the prostate, including cancer progression, it is possible that receptor-specific agonists and antagonists may prove beneficial in therapeutic strategies in future clinical trials. A recent randomized, placebo-controlled study using an ER- β agonist in men with male LUTS failed, however, to show any effect on symptoms, serum PSA, prostate size, and urodynamic parameters (manuscript submitted).

Serum estrogen levels increase in men with age, absolutely or relative to testosterone levels. There is also suggestive evidence that

intraprostatic levels of estrogen are increased in men with BPH. Patients with larger volumes of BPH tend to have higher levels of estradiol in the peripheral circulation (Partin et al, 1991). In the Olmsted County Study cohort, in men with above-median levels of bioavailable testosterone, the serum estradiol level correlated positively with prostate volume, even after adjusting for age (Roberts et al, 2004). Data on obesity, serum testosterone, estradiol, and prostate volume are conflicting (Zucchetto et al, 2005). Although there are relatively low concentrations of classic high-affinity ERs in human BPH (Farnsworth, 1996; Sciarra and Toscano, 2000), there may be a sufficient amount for biologic activity.

From experimental studies with aromatase inhibitors, it appears that decreases in intraprostatic estrogen in animal models may lead to reduction in drug-induced stromal hyperplasia (Farnsworth, 1996, 1999). At present, however, the role of estrogens in human BPH is not as firmly established as the role of androgens. Species variation and cause-and-effect relationships are problematic.

There are high levels of progesterone receptor in the normal and hyperplastic prostate. However, the role of the progesterone receptor in normal prostatic physiology as well as in BPH remains to be defined.

Regulation of Programmed Cell Death

Programmed cell death (apoptosis) is a physiologic mechanism crucial to the maintenance of normal glandular homeostasis (Kerr and Searle, 1973). Cellular condensation and fragmentation precede phagocytosis and degradation, during which the apoptotic cell is phagocytosed by neighboring cells and degraded by lysosomal enzymes. Apoptosis occurs without activation of the immune system but requires both RNA and protein synthesis (Lee, 1981). In the rat prostate, active cell death occurs naturally in the proximal segment of the prostatic ductal system in the presence of normal concentrations of plasma testosterone (Lee et al, 1990). Androgens (presumably testosterone and DHT) appear to suppress programmed cell death elsewhere in the gland. Following castration, active cell death is increased in the luminal epithelial population as well as in the distal region of each duct. Tenniswood (1986) suggested that there is regional control over androgen action and epithelial response, with androgens providing a modulating influence over the local production of growth regulatory factors that varies in different parts of the gland. Members of the transforming growth factor- β (TGF- β) family are likely candidates for this regulatory step (Martikainen et al, 1990).

In the rat prostate, at least 25 different genes are induced following castration (Montpetit et al, 1986). Normal glandular homeostasis requires a balance between growth inhibitors and mitogens, which respectively restrain or induce cell proliferation but also prevent or modulate cell death. Abnormal hyperplastic growth patterns, such as BPH, might be induced by local growth factor or growth factor receptor abnormalities, leading to increased proliferation or decreased levels of programmed cell death.

Stromal-Epithelial Interaction

There is abundant experimental evidence to demonstrate that prostatic stromal and epithelial cells maintain a sophisticated paracrine type of communication. The growth of canine prostate epithelium can be regulated by cellular interaction with the basement membrane and stromal cells. Isaacs and Coffey (1989), using a marker of canine prostatic epithelial cell function, demonstrated that epithelial cells grown on plastic quickly change their behavior. The cells begin to grow rapidly and change their cytoskeletal staining pattern. In contrast, if the cells are grown on prostatic collagen, they maintain their normal secretory capacity and cytoskeletal staining pattern and do not grow rapidly. This is strong evidence that one class of stromal cell excretory protein (i.e., extracellular matrix [ECM]) partially regulates epithelial cell differentiation. Thus BPH may be due to a defect in a stromal component that normally inhibits cell proliferation, resulting in loss of a normal "braking" mechanism for proliferation. This abnormality could

act in an autocrine fashion to lead to proliferation of stromal cells as well.

Further evidence of the importance of stromal-epithelial interactions in the prostate comes from the elegant developmental studies of Cunha and colleagues, which demonstrate the importance of embryonic prostatic mesenchyme in dictating differentiation of the urogenital sinus epithelium (Cunha et al, 1980, 1983, 2003; Cunha and Donjacour, 1987; Cunha, 1994, 1996). The process of new gland formation in the hyperplastic prostate suggests a "reawakening" of embryonic processes in which the underlying prostatic stroma induces epithelial cell development (McNeal, 1990). Many of the prostatic stromal-epithelial interactions observed during normal development and in BPH may be mediated by soluble growth factors or by the ECM, which itself has growth factor-like properties. This model is even more intriguing, given the cellular localization of 5 α -reductase (and thus DHT production) in the prostatic stromal cell (Silver et al, 1994).

The complexity of the stromal-ECM-epithelial relationship is revealed in studies of the ECM signaling protein CYR61. CYR61 is an ECM-associated protein that promotes adhesion, migration, and proliferation of epithelial and stromal cells. A variety of growth factors increase the expression of CYR61 (an early immediate response gene) in both cell types, and the suppression of CYR61 expression by an antisense oligonucleotide significantly affects normal cell morphology (Sakamoto et al, 2003, 2004a, 2004b). CYR61 expression is significantly increased in human BPH tissues and is induced by lysophosphatidic acid (an endogenous lipid growth factor).

As our understanding of stromal-epithelial cell relationships in the prostate increases, it is possible that therapies may be designed to induce regression of established BPH by modulating these autocrine/paracrine mechanisms.

Growth Factors

Growth factors are small peptide molecules that stimulate, or in some cases inhibit, cell division and differentiation processes (Steiner, 1995; Lee and Peehl, 2004). Cells that respond to growth factors have on their surface receptors specific for that growth factor that in turn are linked to a variety of transmembrane and intracellular signaling mechanisms. Interactions between growth factors and steroid hormones may alter the balance of cell proliferation versus cell death to produce BPH (Fig. 103-3). Lawson's group was the first to demonstrate that extracts of BPH stimulate cellular growth. This putative prostatic growth factor was subsequently found on sequence analysis to be basic fibroblastic growth factor (bFGF) (Story et al, 1989). Subsequently, a variety of growth factors

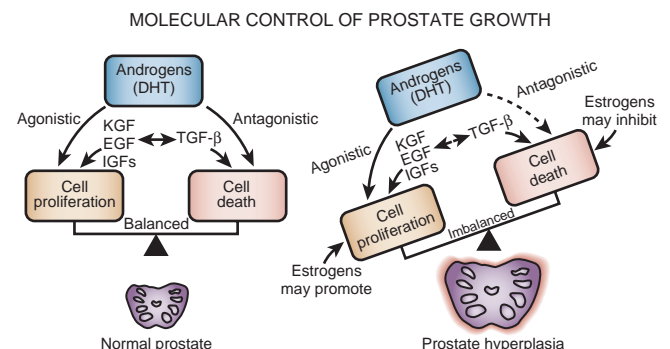


Figure 103-3. Prostate hyperplasia is probably due to an imbalance between cell proliferation and cell death. Androgens play a necessary but probably permissive role. Growth factors are more likely to be sites of primary defects. DHT, dihydrotestosterone; EGF, epidermal growth factor; IGFs, insulin-like growth factors; KGF, keratinocyte growth factor; TGF- β , transforming growth factor- β .

have been characterized in normal, hyperplastic, and neoplastic prostatic tissue. In addition to bFGF (FGF-2), acidic FGF (FGF-1), Int-2 (FGF-3), keratinocyte growth factor (KGF [FGF-7]), TGF- β , and epidermal growth factor (EGF) have been implicated in prostate growth. TGF- β is a potent inhibitor of proliferation in normal epithelial cells in a variety of tissues. In models of prostatic cancer, there is evidence that malignant cells have escaped the growth inhibitory effect of TGF- β (McKeehan and Adams, 1988). Similar mechanisms may be operational in BPH (Salm et al, 2000), leading to the accumulation of epithelial cells (Kundu et al, 2000). Growth factors may also be important in modulating the phenotype of the prostate smooth muscle cell (Peehl and Sellers, 1998).

There is mounting evidence of interdependence between growth factors, growth factor receptors, and the steroid hormone milieu of the prostate (Rennie et al, 1988; Lee and Peehl, 2004). Although data on the absolute level of growth factor and growth factor receptors in hyperplastic as opposed to normal tissue are conflicting, it is likely that growth factors play some role in the pathogenesis of BPH. However, further research is necessary to establish the role of growth factors in a disease process in which cellular proliferation is not obvious.

If cellular proliferation is a component of the BPH process, it appears that growth stimulatory factors such as the FGF-1, -2, -7, and -17 families, VEGF, and insulin-like growth factor (IGF) may play a role, with DHT augmenting or modulating the growth factor effects. In contrast, TGF- β , which is known to inhibit epithelial cell proliferation, may normally exert a restraining influence over epithelial proliferation that is lost or downregulated in BPH (Wilding et al, 1989; Sporn and Roberts, 1990, 1991; Peehl et al, 1995; Cohen et al, 2000; Lee and Peehl, 2004). TGF- β 1 is a potent mitogen for fibroblasts and other mesenchymal cells but is also an important inhibitor of epithelial cell proliferation (Roberts and Sporn, 1993). TGF- β 1 also regulates ECM synthesis and degradation and can induce cells to undergo apoptosis. In addition, TGF- β upregulates the production of bFGF, which is known to be an autocrine growth factor for prostate stromal cells (Story et al, 1993), and at least on one prostate smooth muscle cell line (PSMC1), TGF functions as an autocrine mitogen (Salm et al, 2000). Thus upregulation of TGF- β 1 (which is expressed in prostate stromal cells) during BPH would favor expansion of the stromal compartment.

Indirect evidence to support this view comes from studies of reconstituted mouse prostate (Yang et al, 1997). Interestingly, the observation that TGF- β 1 may regulate smooth muscle contractile protein expression suggests that TGF- β isoforms may be physiologic regulators of prostatic smooth muscle function (Orlandi et al, 1994). Cohen and colleagues (2000) found that stromal cells isolated from BPH specimens exhibited a blunted TGF- β growth inhibition relative to normal stromal cells and that the blunted response appeared to be due to a reduction in TGF-mediated increase in IGF binding protein 3 (IGFBP-3) expression. TGF- β may stimulate the overexpression of versican (chondroitin sulfate proteoglycan 2) in the ECM through inhibition of key metalloproteases (ADAMTS lineage) that normally degrade versican, leading to accumulation in the ECM (Cross et al, 2006). An increased risk for BPH was described in patients with a codon 10 polymorphism in TGF- β (Li et al, 2004).

The first evidence of increased FGF-2 levels in BPH came from the studies of Begun and coworkers (1995), who demonstrated a two- to threefold elevation of FGF-2 in BPH compared with histologically normal glands. Further studies have demonstrated that both FGF-2 and FGF-7 are overexpressed in BPH tissues (Ropiquet et al, 1999). The major target of FGF-2 is thought to be the stroma itself (autocrine), although transgenic mice overexpressing FGF-2 develop glandular epithelial hyperplasia (Konno-Takahashi et al, 2004). KGF, a member of the FGF family (FGF-7), is produced in prostatic stromal cells (Yan et al, 1992). However, cell surface receptors for stroma-derived KGF are expressed exclusively in epithelial cells. As a result, FGF-7 (or a homolog) is the leading candidate for the factor mediating the stromal cell-based hormonal regulation of the prostatic epithelium. There is direct evidence that

FGF-7 plays this role in the androgen-dependent mesenchymal-epithelial interactions involved in development of the seminal vesicle (Alarid et al, 1994). Abnormalities in stromal FGF-7 production or epithelial FGF-7 receptor could promote epithelial cell proliferation. Indirect evidence supporting this hypothesis comes from a study of transgenic mice overexpressing FGF-7 that develop atypical prostatic hyperplasia (Kitsberg and Leder, 1996). McKeehan's laboratory demonstrated that FGF-10, a homolog of FGF-7, is expressed at high levels in the rat prostate, specifically in stromal cells of smooth muscle origin (Lu et al, 1999; Nakano et al, 1999). FGF-10 expression is increased by androgens and may have a mitogenic effect on prostate epithelium. Other studies suggest that cells expressing FGF-7 are localized in the stroma immediately adjacent to the epithelium, suggesting that the epithelial cells may induce FGF-7 expression. The paracrine factor most likely responsible for this effect is the cytokine interleukin (IL)-1 α (Giri and Ittmann, 2000; Lee and Peehl, 2004).

Some investigators have speculated that local hypoxia in the prostate (perhaps from atherosclerosis or other vascular events) is the initial event that induces FGF production (Lee and Peehl, 2004). Further growth of BPH nodules could impede blood flow, leading to further hypoxia (Parsons and Kashefi, 2008; Parsons et al, 2008). Hypoxia leads to upregulation of hypoxia-inducible factor-1, which in turn increases the secretion of FGF-2 and FGF-7 from stromal cells.

Other growth factors implicated in BPH include FGF-17 (Polnaszek et al, 2004), FGF-10, and VEGF (Walsh et al, 2002). It remains difficult to ascertain which of the growth factors and growth factor receptors are key mediators of the BPH disease process and which are bystanders.

A unique animal model provides additional evidence that FGF-like factors may be involved in the etiology of BPH. A transgenic mouse line expressing the Int-2/FGF-3 growth factor demonstrated androgen-sensitive epithelial hyperplasia in the male mouse prostate that was histologically similar to human and canine BPH (Tutrone et al, 1993).

IGFs, binding proteins, and receptors also appear to be important modulators of prostatic growth, at least as it relates to cell growth in culture (Peehl et al, 1995; Lee and Peehl, 2004). A transgenic mouse model with overexpression of IGF-1 demonstrated prostate gland enlargement (Konno-Takahashi et al, 2003). Studies of BPH tissue demonstrate a higher concentration of IGF-2 in the periurethral area than in the peripheral zone (Monti et al, 2001). A study of Chinese men demonstrated a significant correlation between circulating IGF-1 and IGFBP-3 levels and BPH (Dahle et al, 2002), but a study of the Olmsted County Study cohort data failed to demonstrate any relationship between serum IGF-1 and prostate volume (Roberts et al, 2003).

Other Signaling Pathways

Sympathetic signaling pathways are important in the pathophysiology of LUTS, as is evident from the use of drugs interfering with the adrenergic nervous system, such as α -adrenergic receptor blockers, which are highly effective for the treatment of LUTS (American Urological Association Practice Guidelines Committee, 2003). In addition, there is increasing evidence that sympathetic pathways may be important in the pathogenesis of the hyperplastic growth process (McVary et al, 1994, 2005). α -Blockade, in some model systems, can induce apoptosis (Anglin et al, 2002). α -Adrenergic pathways can also modulate the smooth muscle cell phenotype in the prostate (Lin et al, 2000). All the components of the renin-angiotensin system (RAS) are present in prostatic tissue and may be activated in BPH (Dinh et al, 2001, 2002; Fabiani et al, 2001). Either with or without sympathetic modulation, local RAS pathways may contribute to cell proliferation and smooth muscle contraction.

The early growth response 1 gene (*EGR1*) transcription regulation pathway was found to be active in a BPH cell line (Mora et al, 2005). Also of interest is the finding that α_2 -macroglobulin, a large protein that binds PSA and many growth factors, is very highly

expressed in human prostate and is upregulated in BPH (Lin et al, 2005). Trapping and inactivation of inhibitory molecules could promote growth pathways.

Potential Role of Inflammatory Pathways and Cytokines in Benign Prostatic Hyperplasia

An additional source of growth factors in human BPH tissue may be the inflammatory cell infiltrates seen in many men with BPH. In the 1990s, descriptive studies suggested a link between inflammation and BPH-related growth. Theyer and associates (1992) reported extensive infiltration of human BPH tissues by activated T cells. Peripheral blood and tumor-infiltrating T cells are known to express VEGF, a potent epithelial mitogen (Blotnik et al, 1994; Freeman et al, 1995). T cells are known to produce and secrete a variety of other growth factors, including heparin-binding EGF-like growth factor and bFGF/FGF-2. Thus T cells present in the local prostate environment were thought to be capable of secreting potent epithelial and stromal mitogens that promote stromal and glandular hyperplasia.

In the last 5 years, specific inflammatory mediator pathways have been studied in detail to elucidate the potential role of these pathways in BPH pathogenesis (Fig. 103-4). A large number of cytokines

and their receptors are seen in BPH tissue (Konig et al, 2004). Specifically, significant levels of interleukins IL-2, IL-4, IL-7, and IL-17, interferon- γ (IFN- γ), and their relevant receptors are found in BPH tissue (Kramer et al, 2002; Steiner et al, 2003a, 2003b). IL-2, IL-7, and IFN- γ stimulate the proliferation of prostatic stromal cells in vitro. Prostatic epithelial cell senescence results in increased expression of IL-8, which can promote proliferation of nonsenescent epithelial and stromal cells (Castro et al, 2004). Macrophage inhibitory cytokine 1 is expressed in normal prostate tissue but significantly downregulated in BPH (Kakehi et al, 2004; Taoka et al, 2004). Chronic inflammation in BPH is also associated with focal upregulation of cyclooxygenase-2 in the glandular epithelium (Wang et al, 2004). To date, however, no firm cause-and-effect relationships have been established between prostatic inflammation and related cytokine pathways and stromal-epithelial hyperplasia.

Recent work from an Italian laboratory suggests that the metabolic syndrome may be a clinical determinant of a higher risk for prostatic inflammation and thus for male LUTS and BPH, and that AR activation by testosterone (in a rabbit model) and DHT may have a protective effect upon prostatic inflammation (Vignozzi et al, 2012a, 2012b; Gacci et al, 2013). This work, if confirmed, effectively establishes a link between the role of androgenic steroids and prostatic inflammation in the pathophysiology of male LUTS and BPH.

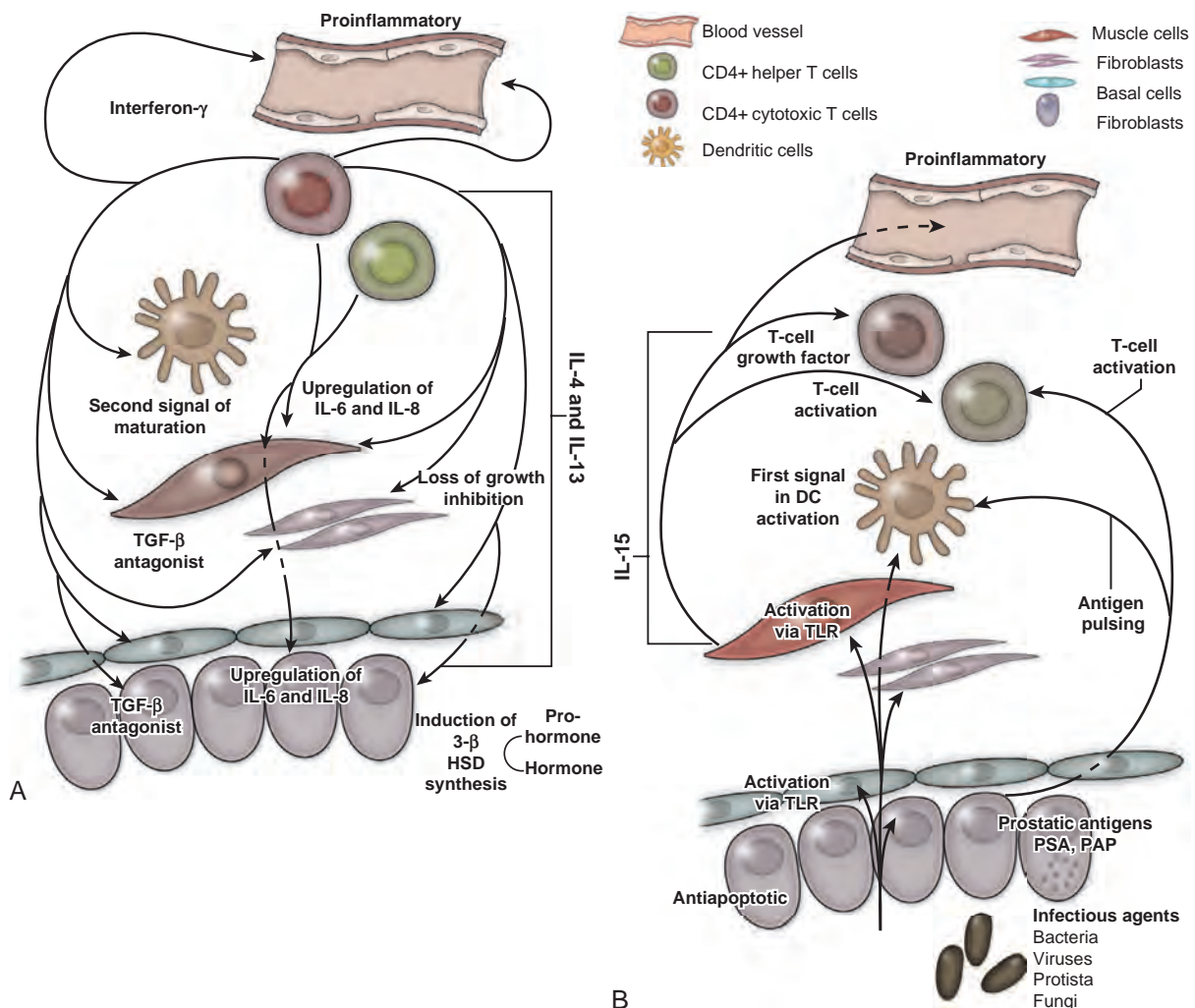


Figure 103-4. A, Tissue effect of T cell-derived proinflammatory cytokines on the pathogenesis and progression of immune inflammation and stromal growth in the aging prostate (T cells indicated in red). B, Role of smooth muscle cells (indicated in red) in maintenance and propagation of immune infiltration in the aging prostate. DC, dendritic cell; HSD, hydroxysteroid dehydrogenase; IL, interleukin; PSA, prostate-specific antigen; PAP, prostatic acid phosphatase; TGF- β , transforming growth factor- β ; TLR, toll-like receptor. (From Kramer G, Mitteregger D, Marberger M. Is benign prostatic hyperplasia [BPH] an immune inflammatory disease? *Eur Urol* 2007;51:1202–16.)

A review of BPH as a potentially autoimmune disease was published by [Kramer and coworkers \(2007\)](#). [Figure 103-4](#) illustrates the immunologic key features of chronic inflammation in BPH and the present interpretation of these changes in the development and progression of BPH. A summary of clinical observations regarding the role of inflammation in clinical BPH and suggesting it as a therapeutic target was published recently ([Gandaglia et al, 2013](#)).

Genetic and Familial Factors

There is substantial evidence that **BPH has an inheritable genetic component**. Sanda and colleagues conducted a retrospective case-control analysis of surgically treated BPH patients and control subjects at Johns Hopkins ([Partin et al, 1994](#); [Sanda et al, 1994](#)). The BPH patients were men whose resected prostate weights were in the highest quartile (>37 g) and whose age at prostatectomy was in the lowest quartile. The **hazard/function ratio for surgically treated BPH among first-degree male relatives of the BPH cases compared with the first-degree male relatives of the controls was 4.2 (95% CI, 1.7 to 10.2), demonstrating a very strong relationship (Table 103-3)**. The results did not appear to be due to differences in health-seeking behavior between the two groups. A segregation analysis showed that the results were most consistent with an **autosomal dominant inheritance pattern**. Utilizing this model, approximately 50% of cases of men undergoing prostatectomy for BPH at less than 60 years of age could be attributable to an inheritable form of the disease. In contrast, only about 9% of men undergoing prostatectomy for BPH at more than 60 years of age would be predicted to have a familial risk. In addition, monozygotic twins demonstrate a higher concordance rate of BPH than dizygotic twins ([Partin et al, 1994](#)).

In a community-based cohort study of more than 2000 men, Roberts and colleagues found an elevated risk of moderate to severe urologic symptoms in men with a family history of an enlarged prostate and a family history of BPH compared with those with no history ([Roberts et al, 1995](#)). Analysis of the subjects who participated in the U.S. finasteride clinical trial identified 69 men who had three or more family members with BPH, including the proband ([Sanda et al, 1997](#)). Regression analysis demonstrated that **familial BPH was characterized by large prostate size, with a mean prostate volume of 82.7 mL in men with hereditary BPH compared with 55.5 mL in men with sporadic BPH (Sanda et al, 1995)**. Serum androgen levels and the response to 5 α -reductase inhibition were similar in familial and sporadic BPH. A more recent familial aggregation study in the finasteride database confirmed that a strong family history of early onset and large prostate volume is more likely to be associated with inheritance of risk than symptom severity or other factors ([Pearson et al, 2003](#)).

These studies clearly demonstrate the presence of a familial form of BPH and suggest the presence of a gene contributing to

the pathogenesis of the disease. The studies of [Meikle and coworkers \(1997, 1999\)](#) also support a genetic basis for BPH. Preliminary studies demonstrate evidence of DNA mutations ([White et al, 1990](#)), DNA hypomethylation ([Bedford and van Helden, 1987](#)), abnormalities of nuclear matrix protein expression ([Partin et al, 1993](#)), miscellaneous genetic polymorphisms ([Werely et al, 1996](#); [Konishi et al, 1997](#); [Habuchi et al, 2000](#)), and abnormal expression of the Wilms tumor gene (*WT1*) ([Dong et al, 1997](#)) in human BPH. By analyzing 14 single nucleotide polymorphisms associated with prostate cancer, genetic variants in 2q31 and 5p15 were found to be associated with aggressive BPH in a Chinese population ([Qi et al, 2013](#)). However, the specific gene or genes involved in familial BPH or that contribute to the risk of significant prostatic enlargement in sporadic disease remain to be elucidated.

Other Etiologic Factors

Androgens and soluble growth factors are clearly not the only important factors for the development of BPH. All mammalian prostates studied have testosterone, DHT, and ARs as well as most of the known growth factor signaling pathways; however, only dog and man develop BPH. Interestingly, another glandular organ that remains androgen responsive throughout life, the seminal vesicle, does not develop hyperplasia. Obviously, other mechanisms or cofactors must be present in these two unique species making them susceptible to the disease. Nonandrogenic substances from the testis, perhaps transmitted through the vas deferens or deferential blood vessels, for example, may play some role ([Dalton et al, 1990](#)). Rats with intact testes treated with exogenous androgen demonstrate a greater degree of prostatic growth than castrated rats treated with androgen. [Sutkowski and coworkers \(1993\)](#) have demonstrated that human spermatocele fluid is mitogenic to both human prostatic epithelial and stromal cells in culture. Similar results have been seen in castrated versus testes-intact dogs treated with exogenous androgen and exogenous testosterone and estradiol combination ([Juniewicz et al, 1994](#)). In addition to increases in prostate weight, the incidence of histologic BPH was significantly higher in the dogs with intact testes. [Grayhack and colleagues \(1998\)](#) have identified a putative substance that may be a candidate for such a factor.

Prolactin has long been speculated to play a role in BPH because of the known effects of this hormone on prostate cells in vitro. Transgenic mice overexpressing the prolactin gene develop significant enlargement of the prostate ([Wennbo et al, 1997](#)). However, despite the documented presence of prolactin receptors in the human prostate and low circulating levels of the hormone, the role of prolactin in human prostate disease is unclear. In a mice knockout model, prolactin-mediated hyperplastic prostate growth involved epithelial-stromal interaction through epithelial prolactin/prolactin receptor signals. The stromal fibromuscular AR could

TABLE 103-3 Family History of Early-Onset BPH Increases Risk of Clinically Significant BPH

BPH (%)* RELATIVES	FREQUENCY OF CLINICAL BPH		AGE-ADJUSTED		SIGNIFICANCE‡	
	CASE RELATIVES	CONTROL RELATIVES	ODDS RATIO (UNADJUSTED)†	RELATIVE RISK OF CLINICAL BPH‡	CHI- SQUARE	P VALUE
All first-degree male relatives	28.3	8.6	4.2 (1.7-10.2)	4.4 (1.9-9.9)	13.36	.0003
Fathers of proband	33.3	13.2	3.3 (1.1-10.2)	3.5 (1.3-9.5)	5.94	.0148
Brothers of proband	24.2	3.9	8.0 (1.6-40.5)	6.1 (1.3-29.7)	6.85	.0089

*Percent of informative male relatives with history of prostatectomy (open or transurethral) for BPH (60 case relatives and 105 control relatives).
†Chi-square analysis of proportions; Taylor 95% confidence intervals in parentheses.
‡Cox proportional hazards survival model. Censored outcome—prostatectomy. Time variable—age at death or current age. Values in parentheses indicate 95% confidence intervals.
BPH, benign prostatic hyperplasia.
From Sanda MG, Beaty TH, Stutzman RE, et al. Genetic susceptibility of benign prostatic hyperplasia. J Urol 1994;152:115–9.

modulate such epithelial-stromal interacting signals, such that by targeting the stromal AR with a degradation enhancer, a reduction of prostate size was observed, an observation that might be used in future therapy (Lai et al, 2013).

Molecular profiling, fingerprinting, microarrays, and high-throughput screening tools have uncovered new genes, as well as known genes not previously associated with BPH. Preliminary findings from the Getzenberg laboratory (Prakash et al, 2002; Sakamoto et al, 2004b; Shah et al, 2004; Minnery and Getzenberg, 2005) and other groups (Fromont et al, 2004; Dhanasekaran et al, 2005) suggest that new markers for BPH and new therapeutic targets will be forthcoming in the next few years.

PATHOPHYSIOLOGY

The pathophysiology of BPH is complex (Fig. 103-5). Prostatic hyperplasia increases urethral resistance, resulting in compensatory changes in bladder function. However, the elevated detrusor pressure required to maintain urinary flow in the presence of increased outflow resistance occurs at the expense of normal bladder storage function. Obstruction-induced changes in detrusor function, compounded by age-related changes in both bladder and nervous system function, lead to urinary frequency, urgency, and nocturia, the most bothersome BPH-related complaints. Thus an understanding of BPH pathophysiology requires detailed insight into obstruction-induced bladder dysfunction.

Pathology

Anatomic Features

McNeal (1978) demonstrated that BPH first develops in the periurethral transition zone of the prostate (Fig. 103-6). The transition zone consists of two separate glands immediately external to the preprostatic sphincter. The main ducts of the transition zone arise on the lateral aspects of the urethral wall at the point of urethral angulation near the verumontanum. Proximal to the origin of the

transition zone ducts are the glands of the periurethral zone that are confined within the preprostatic sphincter and course parallel to the axis of the urethra. All BPH nodules develop either in the transition zone or in the periurethral region (McNeal, 1978, 1990). Although early transition zone nodules appear to occur either within or immediately adjacent to the preprostatic sphincter, as the disease progresses and the number of small nodules increases, they can be found in almost any portion of the transition or periurethral zone. However, the transition zone also enlarges with age, unrelated to the development of nodules.

One of the unique features of the human prostate is the presence of the prostatic capsule, which plays an important role in the development of LUTS (Caine and Schuger, 1987). In the dog, the only other species known to develop naturally occurring BPH, symptoms of BOO and urinary symptoms rarely develop because the canine prostate lacks a capsule. Presumably the capsule transmits the "pressure" of tissue expansion to the urethra and leads to an increase in urethral resistance. Thus the clinical symptoms of BPH in man may be due not only to age-related increases in prostatic size but also to the unique anatomic structure of the human gland. Clinical evidence of the importance of the capsule can be found in series that clearly document that incision of the prostatic capsule (transurethral incision of the prostate) results

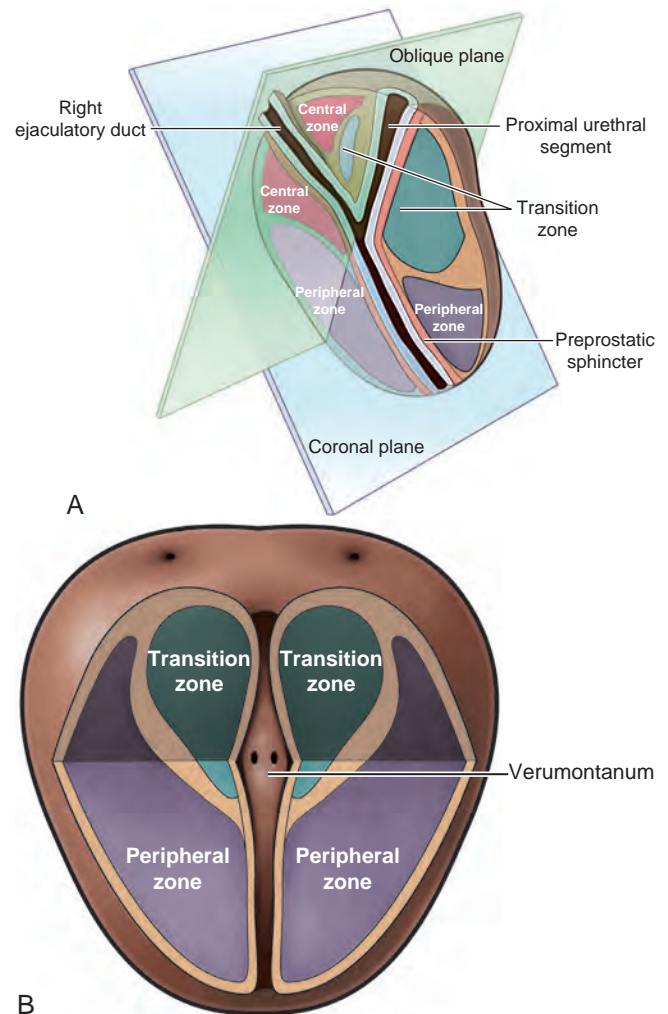


Figure 103-6. Zonal anatomy of the prostate as first described by McNeal (1978). Sagittal (A) and coronal (B) sections of the prostate showing the peripheral zone, transition zone, central zone, verumontanum, and proximal urethral segment, as well as the preprostatic sphincter and ejaculatory duct. (From Roehrborn CG. Pathology of benign prostatic hyperplasia. Int J Impot Res 2008;20[Suppl. 3]: S11-8.)

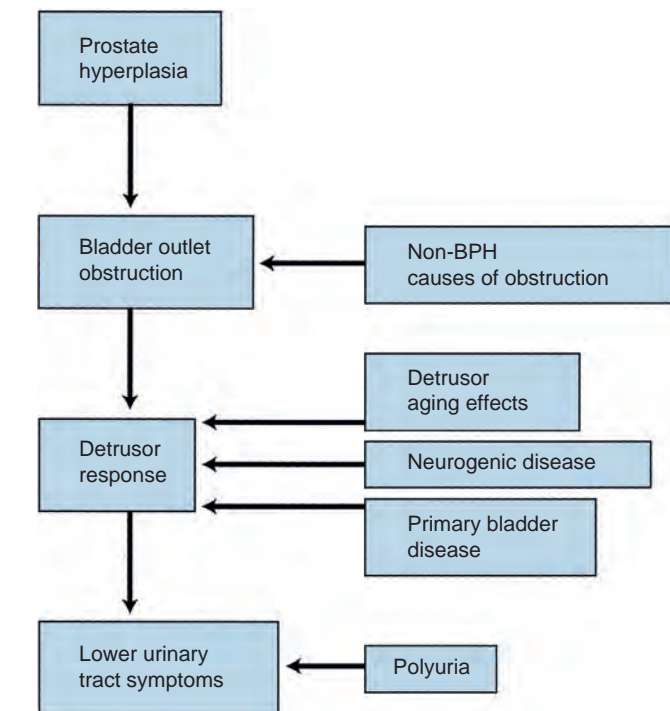


Figure 103-5. The pathophysiology of benign prostatic hyperplasia (BPH) involves complex interactions between urethral obstruction, detrusor function and dysfunction, and urine production.

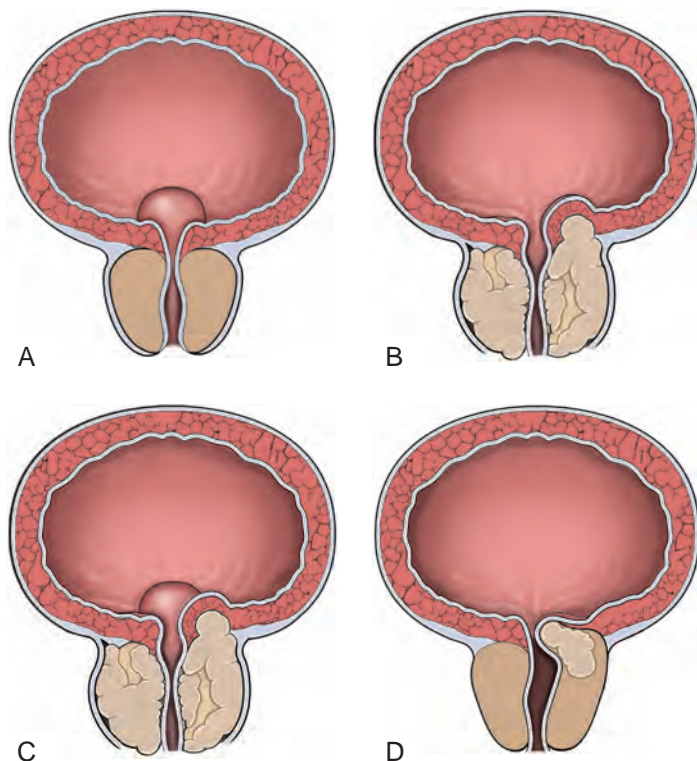


Figure 103-7. Diagrams of hyperplastic prostatic tissue obstructing the prostatic urethra, forming “lobes.” A, Isolated middle lobe enlargement. B, Isolated lateral lobe enlargement. C, Lateral and middle lobe enlargement. D, Posterior commissural hyperplasia (median bar). (After Randall [1931], from Roehrborn CG. Pathology of benign prostatic hyperplasia. *Int J Impot Res* 2008;20[Suppl. 3]:S11–8.)

in a significant improvement in outflow obstruction, despite the fact that the volume of the prostate remains the same.

The size of the prostate does not correlate with the degree of obstruction. Thus other factors such as dynamic urethral resistance, the prostatic capsule, and anatomic pleomorphism are more important in the production of clinical symptoms than the absolute size of the gland. In some cases, predominant growth of periurethral nodules at the bladder neck gives rise to the “middle lobe” (Fig. 103-7). The middle lobe must be of periurethral origin because there is no transition zone tissue in this area. It is not clear whether middle lobe growth occurs at random in men with BPH or whether there is an underlying genetic susceptibility to this pattern of enlargement.

Histologic Features

BPH is a hyperplastic and not a hypertrophic process; that is, there is a net increase in the number of cells and not in the size of the cells. Histologic studies document an increase in the cell number (McNeal, 1990). In addition, thymidine uptake studies in the dog clearly indicate an increase in DNA synthesis in experimentally induced BPH (Barrack and Berry, 1987). The term *benign prostatic hypertrophy* is pathologically incorrect.

McNeal’s studies demonstrate that the majority of **early periurethral nodules are purely stromal in character** (McNeal, 1990). These small stromal nodules resemble embryonic mesenchyme with an abundance of pale ground substance and minimal collagen. It is unclear whether these early stromal nodules contain mainly fibroblast-like cells or whether differentiation toward a smooth muscle cell type is occurring. In contrast, **the earliest transition zone nodules represent proliferation of glandular tissue** that may be associated with an actual reduction in the relative amount of

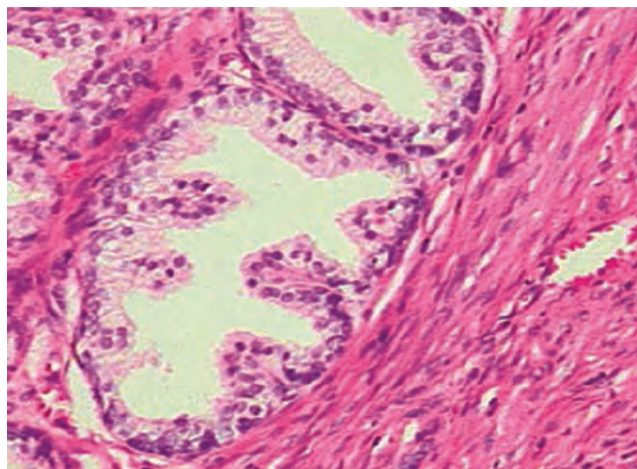


Figure 103-8. Stromoglandular hyperplasia of the prostate showing glandular (upper left) and stromal (lower right) tissue (hematoxylin and eosin stain). (From Roehrborn CG. Pathology of benign prostatic hyperplasia. *Int J Impot Res* 2008;20[Suppl. 3]:S11–8.)

stroma. The minimal stroma seen initially consists primarily of mature smooth muscle, not unlike that of the uninvolved transition zone tissue. These **glandular nodules are apparently derived from newly formed small duct branches** that bud off from existing ducts, leading to a totally new ductal system within the nodule. This type of **new gland formation is quite rare** outside embryonic development. This proliferative process leads to a tight packing of glands within a given area as well as an increase in the height of the lining epithelium. There appears to be hypertrophy of individual epithelial cells as well. Again, the observed increase in transition zone volume (TZV) with age appears to be related not only to an increased number of nodules but also to an increase in the overall size of the zone.

During the first 20 years of BPH development, the disease may be predominantly characterized by an increased number of nodules, and the subsequent growth of each new nodule is generally slow. Then a second phase of evolution occurs in which there is a significant increase in large nodules. In the first phase, the glandular nodules tend to be larger than the stromal nodules. In the second phase, when the size of individual nodules is increasing, the size of glandular nodules clearly predominates.

There is significant pleomorphism in stromal/epithelial ratios in resected tissue specimens. Studies from primarily **small resected glands demonstrate a predominance of fibromuscular stroma** (Shapiro et al, 1992). Larger glands, predominantly those removed by enucleation, demonstrate primarily epithelial nodules (Franks, 1976) (Fig. 103-8). However, an increase in stromal/epithelial ratios does not necessarily indicate that this is a “stromal disease”; stromal proliferation may well be due to “epithelial disease.”

Importance of Prostatic Smooth Muscle

Regardless of the exact proportion of epithelial to stromal cells in the hyperplastic prostate, there is no question that **prostatic smooth muscle represents a significant volume of the gland** (Shapiro et al, 1992) (Fig. 103-9). Although the smooth muscle cells in the prostate have not been extensively characterized, presumably their contractile properties are similar to those seen in other smooth muscle organs. The spatial arrangement of smooth muscle cells in the prostate is not optimal for force generation; however, there is no question that **both passive and active forces in prostatic tissue play a major role in the pathophysiology of BPH**. The factors that determine passive tone in the prostate remain to be elucidated. The series elastic elements in the stromal and epithelial cells and (most important) the ECM contribute to passive tissue force, independent of active smooth muscle contraction. However, **stimulation of the adrenergic nervous system clearly**

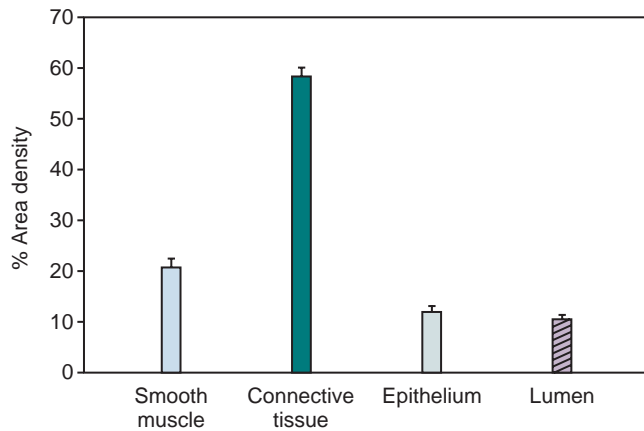


Figure 103-9. Prostate sections obtained from men with symptomatic benign prostatic hyperplasia were analyzed by double immunoenzymatic staining and quantitative image analysis. The percent area density of smooth muscle and connective tissue is significantly greater than glandular epithelium and glandular lumen area density (mean \pm SEM). (From Shapiro E, Becich MJ, Hartanto V, et al. The relative proportion of stromal and epithelial hyperplasia is related to the development of symptomatic benign prostate hyperplasia. *J Urol* 1992;147:1293–7.)

results in a dynamic increase in prostatic urethral resistance. Blockade of this stimulation by α -receptor blockers clearly diminishes this response. However, α -blockade does not decrease passive tension in the prostate, which may be an equal determinant of urethral resistance.

Several additional observations on the prostatic stromal/smooth muscle cell are important. It is generally assumed that the stromal cells are resistant to the effects of androgen withdrawal. In short-term studies, androgen ablation appears to affect primarily the epithelial cell population. In general, however, stromal cells have much slower turnover rates than epithelial cells. If the effect of androgen ablation is primarily to increase cell death rates, a decrease in stromal cell numbers may not be appreciated until a year or more of therapy. Thus further study is required to determine whether the stromal cell is really resistant to androgen withdrawal. Likewise, it cannot be assumed that hormonal therapy has no effect on the stroma even if stromal cell volumes are not decreased. In a variety of smooth muscle cell systems (e.g., vascular and myometrial), contractile proteins, neuroreceptors, and ECM proteins are regulated by a variety of hormones and growth factors. In vitro, androgens have been shown to modulate the effects of α agonists on prostate smooth muscle cells (Smith et al, 2000). Thus a given therapy may affect stromal cell function without decreasing the absolute number or volume of cells.

Studies of human tissue samples by Lin and colleagues (2000) have clearly shown that the smooth muscle cells from men with BPH have a significant downregulation of smooth muscle myosin heavy chain and a significant upregulation of nonmuscle myosin heavy chain. This myosin expression pattern is typical of de-differentiated smooth muscle and indicates either proliferation or loss of normal modulation pathways.

Active smooth muscle tone in the human prostate is regulated by the adrenergic nervous system (Roehrborn and Schwinn, 2004). The α_1 -adrenoreceptor nomenclature has been standardized (Hieble et al, 1995) to reconcile differences in nomenclature based on pharmacologic and molecular studies. Receptor binding studies clearly demonstrate that α_{1A} is the most abundant adrenoreceptor subtype present in the human prostate (Lepor et al, 1993a, 1993b; Price et al, 1993). Moreover, the α_{1A} receptor clearly mediates active tension in human prostatic smooth muscle. It is still unclear whether other factors may regulate smooth muscle contraction. Endothelin and endothelin receptors (Kobayashi et al, 1994a, 1994b; Imajo et al, 1997; Walden et al, 1998) have been reported

in human prostate. However, the physiologic role of this potent contractile agent in prostate smooth muscle function remains to be defined. Various components of the kallikrein-kinin system (e.g., bradykinin) may play a role in the regulation of both smooth muscle proliferation and contraction in the prostate (Walden et al, 1999; Srinivasan et al, 2004).

The presence of type 4 and type 5 phosphodiesterase isoenzymes in the prostate and the detrusor muscle of the bladder implies that phosphodiesterase inhibitors may be appropriate candidate therapies for BPH-related LUTS (Uckert et al, 2001, 2008, 2009). In fact, placebo-controlled trials have verified a beneficial effect of commercially available drugs for the treatment of erectile dysfunction (ED) in men with LUTS and BPH (McVary et al, 2007; Roehrborn et al, 2008; Stief et al, 2008).

The role of adrenergic stimulation in the prostate may exceed simple smooth muscle contraction. Adrenergic neurotransmitters are known to regulate expression of contractile protein genes in cardiac myocytes (Kariya et al, 1993) and to be involved in the development of cardiac hypertrophy (Matsui et al, 1994). Interestingly, evidence suggests that testosterone may regulate the expression of adrenergic receptors, at least in the kidney (Gong et al, 1995). It is possible that adrenergic neurotransmitters may play a role in prostatic smooth muscle cell regulation as well as contraction (Smith et al, 2000). α -Adrenergic blockade in patients with documented BPH leads to a significant downregulation of normal contractile protein gene expression, specifically smooth muscle myosin heavy chain.

Autonomic nervous system overactivity may contribute to LUTS in men with BPH. McVary and coworkers (2005) demonstrated that autonomic nervous system activity, as measured by a standard set of physiologic tests, plasma, and urinary catecholamines, correlates positively with symptom score and other BPH measures. Serum norepinephrine increase after tilt predicted prostate size (transition zone).

The Bladder's Response to Obstruction

Current evidence suggests that the bladder's response to obstruction is largely an adaptive one. However, it is also clear that many lower tract symptoms in men with BPH or prostate enlargement are related to obstruction-induced changes in bladder function rather than to outflow obstruction directly. Approximately one third of men continue to have significant voiding dysfunction and mostly storage symptoms after surgical relief of obstruction (Abrams et al, 1979). Obstruction-induced changes in the bladder are of two basic types. First, the changes that lead to *detrusor instability* or decreased compliance are clinically associated with symptoms of frequency and urgency. Second, the changes associated with decreased *detrusor contractility* are associated with further deterioration in the force of the urinary stream, hesitancy, intermittency, increased residual urine, and (in a minority of cases) detrusor failure. Acute urinary retention (AUR) should not be viewed as an inevitable result of this process. Many patients presenting with AUR have more than adequate detrusor function, with evidence of a precipitating event leading to the obstruction.

Much of our knowledge of the detrusor's response to obstruction is based on experimental animal studies. Limited information is available on the natural history of the human bladder's response to obstruction. Gosling and colleagues have demonstrated that the major endoscopic detrusor change, trabeculation, is due to an increase in detrusor collagen (Gosling and Dixon, 1980; Gosling et al, 1986). Severe trabeculation is associated with significant residual urine (Barry et al, 1993), suggesting that incomplete emptying may be due to increased collagen rather than impaired muscle function. Severe trabeculation, however, is seen in fairly advanced disease. In experimental animal models, the initial response of the detrusor to obstruction is the development of smooth muscle hypertrophy (Levin et al, 1995, 2000). It is likely that this increase in muscle mass, although an adaptive response to increased intravesical pressure and maintained flow, is associated with significant intra- and extracellular changes in the smooth muscle

cell that lead to detrusor instability and in some cases impaired contractility. Obstruction also induces changes in smooth muscle cell contractile protein expression, impaired energy production (mitochondrial dysfunction), calcium signaling abnormalities, and impaired cell-cell communication (Levin et al, 1995, 2000).

There is considerable evidence that the response of the detrusor smooth muscle cell to stress (increased load related to outlet obstruction) is not as adaptive as the response of skeletal muscle to stress. In the latter case, a relatively normal repertoire of contractile protein genes are upregulated and an increased number of normally organized contractile units assemble in the muscle cell. In the detrusor smooth muscle cell, load-induced hypertrophy leads to a change in myosin heavy chain isoform expression (Lin and McConnell, 1994; Cher et al, 1996) and to a significant alteration in the expression of a variety of thin filament-associated proteins (Mannikarottu et al, 2005a, 2005b, 2006). Taken together, these observations strongly suggest that smooth muscle cells revert to a secretory phenotype in response to obstruction-induced hypertrophy. One consequence of this phenotypic switch is increased ECM production. The detrusor smooth muscle cell is a key contributor to the complex of symptoms associated with prostatic obstruction. Additional research in this area is required (Christ and Liebert, 2005).

In experimental animal models, unrelieved obstruction is associated with the development of significant increases in detrusor ECM (collagen) (Levin et al, 1995, 2000). This also appears to be the case in the human, although cause-and-effect relationships have not been established (Gosling et al, 1986). In addition to obstruction-induced changes in the smooth muscle cells and ECM of the bladder, there is increasing evidence that obstruction may modulate neural-detrusor responses as well (Steers et al, 1990, 1999; Clemow et al, 1998, 2000). Altered neural control of micturition has been noted in aging rats, including reduced bladder contractility, impaired central processing, and altered sensation (Chai et al, 2000).

Independent of obstruction, aging produces some of the same changes in bladder function, histology, and cellular function (Nordling, 2002). There is suggestive evidence from animal models that atherosclerosis and the resultant chronic bladder ischemia or hypoxia induced by other mechanisms (e.g., increased bladder wall tension) may contribute to bladder pathology (Tarcan et al, 1998; Azadzi et al, 1999, 2003, 2008; Azadzi, 2003).

EPIDEMIOLOGY

Definitions

The study of epidemiology determines the distribution and determinants of diseases in humans. From this evolve the components of descriptive epidemiology, which is the description of disease incidence, mortality, and prevalence by person, place, and time, and analytical epidemiology, which is the search for determinants of disease risk that may serve to increase prospects for prevention (Oishi et al, 1998). Epidemiologists assess and compare rates of diseases within one population stratified by sex, age, and other demographic and socioeconomic parameters, and between populations of different culture, ethnicity, lifestyle, and diet.

The following definitions of rates are important to understand:

- **Incidence:** number of diseased people per 100,000 population per year
- **Prevalence:** number of existing cases per 100,000 population at a distinct target date
- **Mortality:** number of deaths per 100,000 population per year
- **Fatality:** number of deaths per number of diseased

Although for highly fatal conditions (i.e., those with a high fatality and mortality rate) the incidence rate (i.e., the rate of people developing the condition in a year) is of preeminent interest, for conditions such as BPH, which are rather benign in their course, the prevalence rate (i.e., the number of men having the condition at a given point in time) is of greater interest.

There is no globally accepted epidemiologic definition of BPH; thus prevalence and incidence rates must be viewed in the context

KEY POINTS: ETIOLOGY AND PATHOPHYSIOLOGY

- The development of BPH requires an intact androgen signaling pathway, but androgens do not cause the disease.
- In the absence of obvious cellular proliferation, the hyperplastic process must be due to an imbalance between cell death and cell proliferation, leading to cell accumulation in both the epithelial and stromal compartments.
- BPH is said to be a “stromal disease,” but it remains unclear whether the initiating events occur in the stromal compartment, the epithelial compartment, or both.
- BPH stroma is a complex mixture of smooth muscle cells and ECM. Much of a given patient’s urethral resistance is due to the passive elastic properties of the prostate tissue that cannot be “relaxed” with α -adrenergic blockade.
- Paracrine and autocrine growth factors seem to be the primary factors that stimulate or inhibit stromal and epithelial growth.
- Inflammation, common in BPH specimens, may play a role in the pathogenesis of the disease through cytokines that promote cell growth or lead to smooth muscle contraction.
- BPH can have a familial inheritance, especially if large prostate volumes and surgical intervention as a young age are seen in the pedigree.
- The bladder’s response to obstruction is only partially adaptive. Smooth muscle cells subjected to increased load undergo hypertrophy, but the phenotype of the cell changes, ECM production is increased, contractile protein expression is altered, and cell-to-cell signaling is impaired.
- Aging, perhaps through vascular mechanisms, leads to further alteration in bladder biology that in all likelihood amplifies the effects of obstruction. Prostate growth is only one component of LUTS in aging men. Physicians tend to overlook the significant contribution of aging, bladder dysfunction, nervous system changes, and systemic disease that in many cases has more impact on symptoms than the size of the prostate.

of the definitions chosen by the investigator reporting the data (Barry, 1990a, 1990b). The prevalence of BPH thus can be calculated based on histologic criteria (autopsy prevalence) or on clinical criteria (clinical prevalence). Since the clinical definitions vary widely, it is easier to compare the autopsy or histologic prevalence of BPH. Despite the low mortality and fatality rates for BPH in modern series, a review of these data is interesting and revealing from a historical point of view.

Lastly, descriptive epidemiologic studies can be divided into cross-sectional (a population stratified by baseline parameters is assessed one single time to determine if and how certain measures change depending on the parameter of interest) and longitudinal (a population is assessed at baseline and at regular intervals to study the changes in parameters of interest stratified by age or other demographic criteria). Considering the cost and logistical difficulties involved with longitudinal follow-up of a cohort over time, it is obviously easier to perform cross-sectional studies. The majority of studies addressing LUTS and clinical BPH are cross-sectional in nature and are discussed below. Furthermore, there are by definition no longitudinal autopsy studies of any condition, and histologically based longitudinal studies are exceedingly difficult to carry out because of the need for repetitive tissue procurement.

Descriptive Epidemiologic Studies

Histologic or Autopsy Prevalence

The definition of BPH is the presence of stromoglandular hyperplasia in a surgical specimen or, in the case of autopsy series, in whole

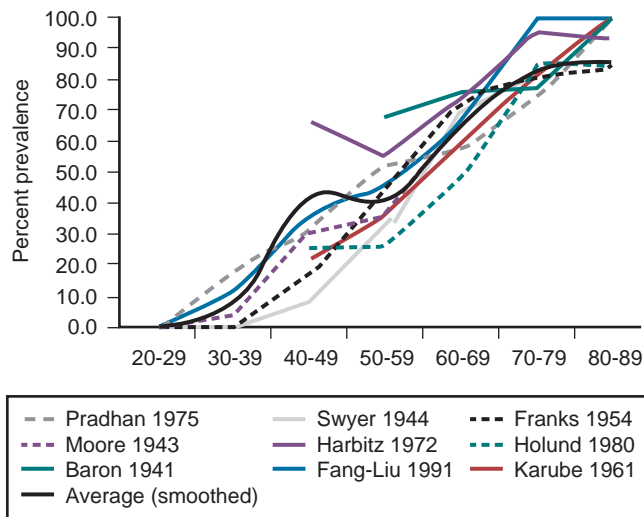


Figure 103-10. Age-stratified autopsy prevalence of histologic benign prostatic hyperplasia from different series and (smoothed) average. (From Berry SJ, Coffey DS, Walsh PC, et al. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;132:474-9.)

prostates removed after death from men not dying from prostate conditions. The 1984 landmark study by Berry and colleagues summarized the data from five studies demonstrating that no men under the age of 30 had evidence of BPH, and that the prevalence rose with each age group, peaking at 88% in men in their 80s. Figure 103-10 demonstrates the age-stratified prevalence based on several rigorously performed autopsy studies in the United States, England, Austria, Norway, Denmark, China, Japan, and India. The prevalence increases rapidly in the fourth decade of life, reaching nearly 100% in the ninth decade. It is striking that the age-specific autopsy prevalence is remarkably similar in all populations studied regardless of ethnic and geographic origin (Moore, 1943; Swyer, 1944; Franks, 1954; Karube, 1961; Harbitz and Haugen, 1972; Haugen and Harbitz, 1972; Pradhan and Chandra, 1975; Holund, 1980; Berry et al, 1984; Carter and Coffey, 1990).

Cross-sectional Studies of Clinical Prevalence

Descriptive epidemiology relies on the presence of a single universally accepted definition of *disease*. The definitions of BPH, however, have undergone several changes in the past decade, and at present no single criterion can be applied. In the past the term *prostatism* was used, incorrectly referring to the prostate as the sole source of the typical LUTS found in aging men. Tage Hald pointed out that there are at least three inter-related phenomena that can be assessed independently, namely the symptoms (formerly called “prostatism”), enlargement of the prostate gland, and presence of obstruction (Nielsen et al, 1994). In a given patient, all three, two of the three, or only one of the three entities might be present. Paul Abrams coined the term *lower urinary tract symptoms* to replace the old and inappropriate term *prostatism* (Chapple et al, 2008). When evaluating elderly men, one can therefore stratify them by the level of LUTS into mildly, moderately, and severely symptomatic according to a standardized symptom severity and frequency questionnaire (Barry et al, 1992a). The same patients then can be further classified based on the degree of prostatic enlargement as measured by digital rectal examination (DRE), transrectal ultrasonography (TRUS), or magnetic resonance imaging (MRI), and lastly by the presence and degree of BOO as measured by flow rate recordings or invasive pressure-flow studies. The diagram in Figure 103-1 attempts to illustrate the difficulties in using different disease definitions. Of all men over the age of 40, a certain proportion will develop histologic hyperplasia of the prostate (i.e., “BPH”). Of those, some but not all will develop LUTS, while others may have

LUTS as a result of reasons other than BPH (e.g., overactive bladder or other bladder- and detrusor-related conditions, urethral stricture, stones, inflammation). Prostate enlargement occurs in some but again not all men with histologic BPH and LUTS, and some men with enlarged glands may not have any symptoms at all. Lastly, urodynamically proven obstruction may be present in men who have either one, several, or all of histologic BPH, LUTS, and enlarged glands, whereas others may have obstruction without having any evidence of BPH (e.g., urethral stricture, prostate cancer, primary bladder neck sclerosis). In addition to the mere enumeration of symptoms by frequency of occurrence, the bother associated with the symptoms, interference with activities of daily living, and the impact the symptoms have on quality of life are important distinguishing characteristics.

Accordingly, when studying the prevalence of *clinical BPH*—admittedly an imprecise term for the above-described constellation of LUTS, bother, interference, and quality-of-life impact, with or without enlargement, obstruction, and so on—disease definitions may be applied that take either one or several of these items into consideration. For the subsequent discussion, it is important to recognize that very few if any clear cutoff points have been established that allow differentiation between whether a disease is absent or present (e.g., one might argue that a prostate volume over 30 mL constitutes “clinical BPH,” but others might argue for a higher or lower cutoff point; similar observations may be made for symptoms, degrees of obstruction, etc.). Thus rather than describing the true prevalence of a “disease” in populations, one can describe the distribution of certain attributes of that disease in different populations stratified by age. Figure 103-11 illustrates the different estimates of prevalence of “disease” when different definitions are applied, ranging from autopsy prevalence to a combination of clinical threshold parameters and insurance examination data (Berry et al, 1984; Garraway et al, 1991; Chute et al, 1993; Gu et al, 1994; Jolleys et al, 1994; Bosch et al, 1995a; Guess, 1995; Moon et al, 1995; Overland et al, 2001).

Symptom Severity and Frequency

From a pragmatic point of view, studies of symptom severity and frequency are of greatest importance in a disease that is rarely fatal and is characterized by its effect on the quality of life. The development, validation, and translation with cultural and linguistic validation of the standardized, self-administered seven-item American Urological Association Symptom Index (AUASI, also known as the International Prostate Symptom Score [IPSS]) has been a pivotal event in the clinical research on LUTS and BPH (Barry et al, 1992a, 1992b; O’Leary et al, 1992). With the total score running from 0 to 35 points, patients scoring 0 to 7 points are classified as mildly symptomatic, those scoring from 8 to 19 points as moderately symptomatic, and those scoring 20 to 35 points as severely symptomatic. The instrument is an integral part of virtually every epidemiologic study as well as treatment studies in the field, and the availability of validated translations in many common languages allows cross-cultural comparisons of unprecedented scope. Socioeconomic factors do not seem to influence responses to the questionnaire (Moon et al, 1994), and fundamentally similar responses are obtained when the questionnaire is self-administered, read to the patient, mailed in, or administered in some other way (Barry et al, 1995a), or readministered in a scrambled format (Barnboym et al, 1999). However, there is no question, that subtle differences in comprehension of the translated questionnaire, as well as different perception of the symptoms, willingness to admit to the symptoms, acceptance of symptoms as a natural sign of aging, and other factors are at least partially the cause of cross-cultural differences in symptom severity reported in the literature.

Figure 103-12 shows the prevalence of at least moderate to severe symptoms stratified by decade of life as reported in 11 cross-sectional population-based studies from around the world (Garraway et al, 1991; Chute et al, 1993; Hunter et al, 1994; Norman et al, 1994; Bosch et al, 1995a; Moon et al, 1995; Tsukamoto et al, 1995; Hunter et al, 1996; Sagnier et al, 1996; Homma et al, 1997;

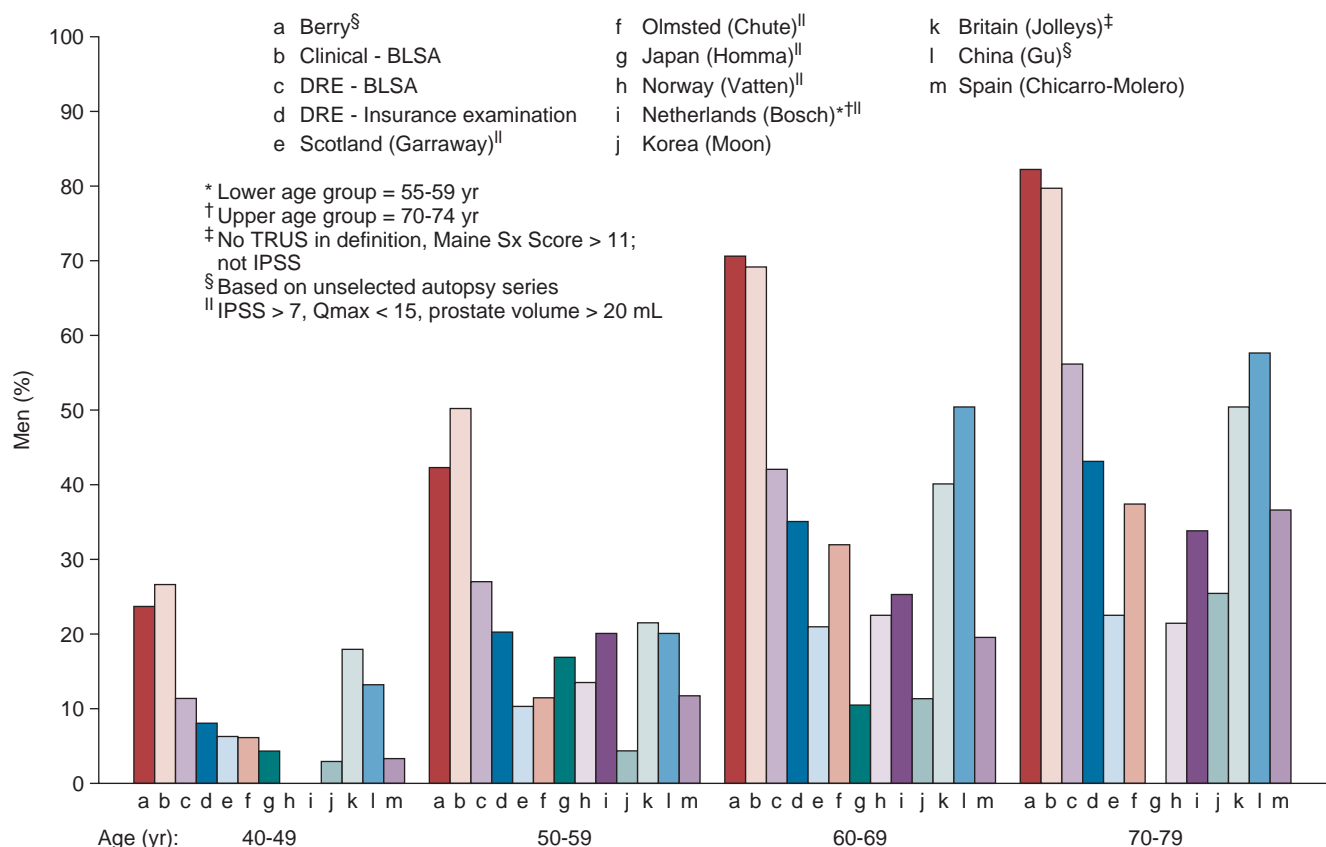


Figure 103-11. Prevalence of disease using autopsy series, clinical diagnosis, low maximum flow rate, palpable prostatic enlargement by digital rectal examination (DRE), and community-based studies. BLSA, Baltimore Longitudinal Study of Aging; IPSS, International Prostate Symptom Score; Qmax, peak flow rate; Sx, Symptom; TRUS, transrectal ultrasonography. (Data from Berry et al, 1984; Garraway et al, 1991; Chute et al, 1993; Gu et al, 1994; Jolleys et al, 1994; Bosch et al, 1995a; Moon et al, 1995; Homma et al, 1997; Chicarro-Molero et al, 1998; Overland et al, 2001.)

Overland et al, 2001). A very large international investigation of LUTS in Asian men was undertaken by Homma and colleagues (1997), in which 7588 men from Japan, China, Taiwan, Korea, the Philippines, Thailand, Singapore, Pakistan, India, and Australia were queried. The finding of 18%, 29%, 40%, and 56% of men in their 40s, 50s, 60s, and 70s, respectively, having moderate to severe symptoms is in line with the other studies reported both from Asia and from Europe and North America. In addition to the major community-based studies listed, other studies have been published with similar findings, but often done under less stringent conditions (Nacey et al, 1995; Tay et al, 1996). Despite the significantly different proportion of men admitting to moderate to severe symptoms, a clear trend toward an increase in symptom scores with advancing age is noticeable in all reported studies.

Bother, Interference, and Health-Related Quality of Life

Bother and interference with activities of daily living due to LUTS are equally if not more important than the enumeration of symptom frequency and severity alone (Garraway et al, 1993b; Roberts et al, 1994b). Embarrassment resulting from symptoms has been found to be an important determinant in seeking medical care (Roberts et al, 1994b). LUTS and clinical BPH only marginally affect overall quality of life as measured, for example, with the Medical Outcomes Study 36-item short form health survey (Hunter et al, 1995). Accordingly, several instruments were developed and validated to assess bother, interference, and the disease-specific quality of life and sexual function (Epstein et al, 1992; Barry et al, 1995b; Hansen et al, 1995; Lukacs et al, 1995; O'Leary et al, 1995; Donovan et al, 1996).

These instruments have not been as widely applied to cross-sectional descriptive epidemiologic studies as compared to the IPSS score. However, as observed for symptom severity and frequency, both bother and interference scores increase with advancing age, and disease-specific health-related quality of life (HRQOL) measures are significantly worse in men with higher symptom frequency and severity ratings in population-based studies done in Olmsted County in the United States, in Forth Valley in Scotland, in France, and in a small fishing village in Japan (Shimamaki-mura) (Girman et al, 1998).

Prostate Size

Prostate size can be estimated by DRE, although the reliability across observers is in general considered poor (Roehrborn et al, 1997). An analysis of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial verified the significant errors associated with the DRE-assessed prostate size (Pinsky et al, 2006). In addition, DRE tends to underestimate true prostate size as determined by TRUS or other imaging modalities. The magnitude of the underestimation increases with increasing prostate size from 25% up to 50% or more (Roehrborn et al, 1997). For the purpose of epidemiologic studies, TRUS and MRI measurements are preferred, although MRI measurements are somewhat expensive when attempting cross-sectional examinations of populations. TRUS volume measurements using the prolate ellipsoid volume formula are the most widely accepted measure of prostate volume, with reasonable statistical performance characteristics particularly when performed by a single or several well-trained examiners (Sech et al, 2001).

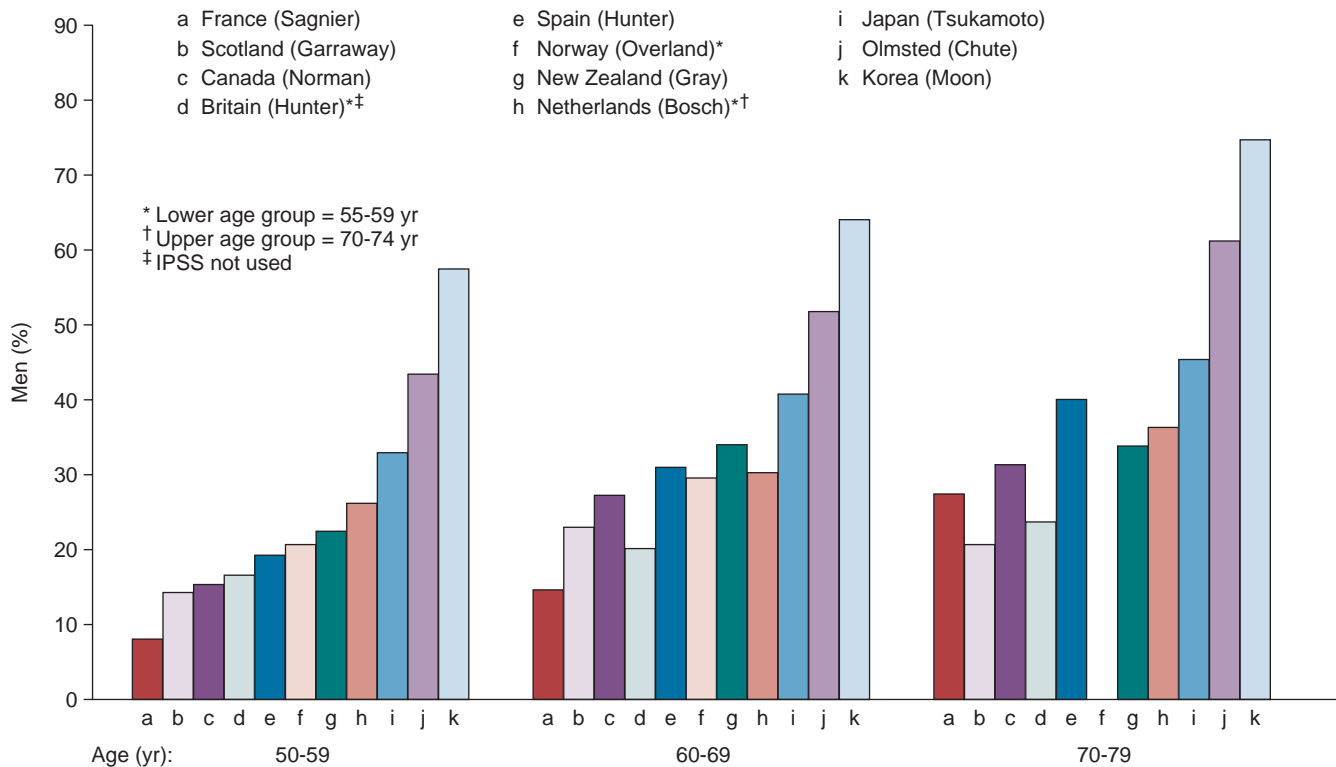


Figure 103-12. Prevalence of at least moderate to severe symptoms stratified by decade of life as reported in cross-sectional population-based studies from around the world. IPSS, International Prostate Symptom Score. (Data from Garraway et al, 1991; Chute et al, 1993; Hunter et al, 1994, 1996; Norman et al, 1994; Bosch et al, 1995a; Moon et al, 1995; Tsukamoto et al, 1995; Sagnier et al, 1996; Homma et al, 1997; Overland et al, 2001; Gray et al, 2004.)

Three-dimensional TRUS appears to provide even more accurate measurements, although such technology is not available in urologists' offices for the most part (Giubilei et al, 2005).

In general, in all cross-sectional studies prostate volume as assessed by TRUS has been found to increase slowly but steadily with advancing age. The slight differences in the absolute volume measures, and the different slopes of increase with advancing age, may be caused by differences in the population examined as follows (Fig. 103-13).

A cohort of 344 men between 40 and 60 years old with no evidence of BPH who were enrolled in an alopecia study had baseline endorectal coil MRI measurements done (Roehrborn et al, 2000a). Mean total prostate volume (TPV) increased from 31.3 to 33.7, 36.1, and 43.1 mL in increments of 5 years. MRI tends to yield prostate volume measurements approximately 10% larger compared to TRUS. A series of 100 men ages 40 to 80 years without BPH or LUTS underwent TRUS measurements of TPV and TZV. TPV increased from 22.1, 29.1, and 41.5 to 43.2 mL, and TZV from 7.2 to 9.9, 19.0, and 19.6 mL, by decade (Benaim et al, 1998). A cross-sectional study of 611 Norwegian men from 55 to 70 years of age exhibited increases in TPV from 26.5 to 31.0 to 32.0 mL in increments of 5 years (Overland et al, 2001), and Jakobsen examined patients between 30 and 50 years by TRUS, the mean TPV being 23.9 and 25.7 mL per decade of life (Jakobsen et al, 1988). TPV and TZV were assessed in 1104 men above the age of 40 years in a Spanish cross-sectional study, yielding increases from 23.4 to 41.9 mL for TPV and from 7.9 to 21.9 mL for TZV (Chicharro-Molero et al, 1998). Finally, the baseline data from the Olmsted County Study provided data on men from 40 to 79 years of age (Oesterling et al, 1993).

Overall, TPV increases in these cross-sectional studies from approximately 25 mL for men in their 30s to 35 to 45 mL for men in their 70s, while TZV increases from 15 to 25 mL for similarly aged men. The similarities between the TPV and TZV

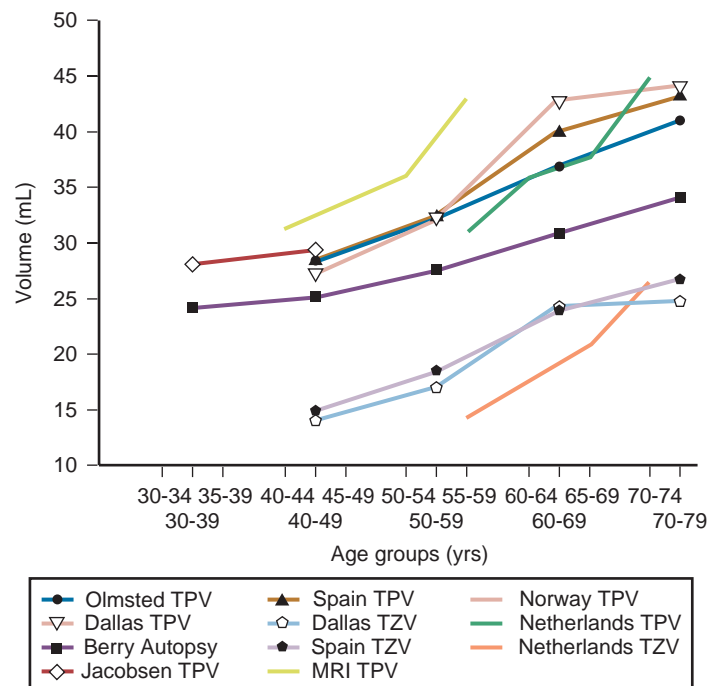


Figure 103-13. Mean estimates for total prostate volume (TPV) and transitional zone volume (TZV) based on one autopsy series (Berry et al, 1984), one series of baseline MRI measurements in men with alopecia (Roehrborn et al, 2000b), and cross-sectional population-based studies (Torp-Pedersen et al, 1988; Oesterling et al, 1993; Bosch et al, 1994; Benaim et al, 1998; Chicharro-Molero et al, 1998; Overland et al, 2001).

measurements done in the different studies are striking particularly when considering the different measurement methods used (see Fig. 103-13).

Measures of Obstruction

Subvesical obstruction can only be measured by invasive pressure-flow studies, while nonintubated free flow rates provide at best an indirect measure for the probability of obstruction being present (Abrams, 1995). Unfortunately, no large-scale cross-sectional studies have been done employing pressure-flow studies because of the invasive and costly nature of the test, and it is unlikely that significant data sets will ever become available.

It is commonly accepted that a maximum flow rate of less than 10 mL/sec indicates a high probability of obstruction, while a flow rate of greater than 15 mL/sec indicates a low probability, with the 10- to 15-mL/sec range presenting an intermediate range. The utility of this categorization is reduced by several observations. First, the maximum flow rate is somewhat dependent of the voided volume (Girman et al, 1993). This has prompted some to propose a nomogram to correct for this phenomenon; however, at present no single nomogram is accepted universally (von Garrelts, 1956, 1957, 1958; Scott and McIlhane, 1961; Beck and Gaudin, 1969; Susset et al, 1973; Siroky et al, 1979, 1980; Drach and Steinbronn, 1986; Haylen et al, 1989). A high degree of diurnal variability (Golomb et al, 1992) and within-subject day-to-day variability (Barry et al, 1995c) further reduces the utility of flow rate recording in defining disease.

Aging men and women experience a decrease in the maximum urinary flow rate that is nearly linear in nature. In the Olmsted County Study, the median flow rate decreased from 20.3 mL/sec for men 40 to 44 years old to 11.3 mL/sec for men 75 to 79 years old (Girman et al, 1993), and similar declines have been reported from other cross-sectional studies. When applying combined thresholds such as at least moderate symptoms (>7 points) on the IPSS score and a maximum flow rate of less than 15 mL/sec, in the Olmsted County Study 17% of men in their 50s, 27% of men in their 60s, and 35% of men in their 70s would fall into such a category (Jacobsen et al, 1995b), versus 14.4%, 28.6%, and 38.7% of men in the respective age groups in a Spanish population-based study (Chicharro-Molero et al, 1998).

Analytical Epidemiologic Studies

Analytical epidemiologic studies address the search for determinants of a disease. Inasmuch as a clear disease definition is lacking, such a search could attempt to find determinants for LUTS, prostate growth, and/or BOO, consistent with the previously outlined concepts. The presence of functioning testes at the time of puberty (hormonal factor) as a required permissive element has long been established and accepted (McConnell, 1991), and age has been shown to be the most critical determinant of all aspects of this complex entity. Numerous other demographic and environmental factors have been suggested as risk factors or contributors to the disease process. When evaluating the associations identified, one has to critically ask whether or not other factors could contribute to the association without there being a cause-and-effect relationship. For example, it seems intuitive that the husbands and family members of nurses are more likely to seek medical care and practice preventive medicine. Therefore the detection rates of prostate cancer in a cohort of nurses' husbands might be higher not due to a truly higher incidence rate of cancer, but due to an increased rate of seeking medical attention and an increase in the number of diagnosed cases of cancer. Such pitfalls are abundant in epidemiologic studies and have to be suspected and carefully ruled out.

Religion

The case-control study by Morrison (1978), the cohort study by Lytton and colleagues (1968), and the Normative Aging Study (Glynn et al, 1985) all revealed Jewish religion to be associated with

a higher prostatectomy rate (2.2- to 2.6-fold increase). However, the fact that Jewish religion is not associated with an increase in the diagnosis of BPH allows the speculation that Jewish patients are more likely to see a physician or to be offered surgical therapy.

Socioeconomic Factors

Araki and associates (1983) found higher rates of BPH in higher income groups, while in contrast Glynn and colleagues (1985) reported higher rates of surgery in lower income groups. One might argue that higher income groups might have better access to health care, while lower income groups might submit more readily to the suggestion of a surgical procedure. Education and socioeconomic status do not influence responses to the IPSS (Moon et al, 1994; Badia et al, 2001), but they do appear to influence both expectations from treatment for BPH and perception of improvement, with patients in higher income strata requiring a larger drop in symptom scores following treatment to perceive subjectively similar levels of improvement (Padley et al, 1997). This finding suggests at least some impact of socioeconomic factors not in the growth of the prostate or measures of obstruction, but rather in the perception of symptoms. Data from the Olmsted County Study suggest a relationship between care-seeking behavior and physician visit and retirement status. Bivariate analysis suggested significant associations between a propensity to seek care for physical reasons and retirement (OR 2.0, 95% CI 1.1 to 2.6), age of 65 years or more (OR 1.9, 95% CI 1.5 to 2.4), incomplete high school education (OR 1.6, 95% CI 1.1 to 2.2), and an annual income of less than \$25,000 (OR 1.4, 95% CI 1.1 to 1.9). Multivariable logistic regression analysis demonstrated that retired men were more likely to have a high propensity to seek care (OR 1.7, 95% CI 1.2 to 2.4), with the other variables no longer being significant (Roberts et al, 1997a).

Our understanding of the impact of some socioeconomic factors on LUTS and BPH has deepened with the help of two studies, the European Prospective Investigation into Cancer and Nutrition and the Epidemiology of LUTS (EpiLUTS) studies and the Boston Area Community Health (BACH) survey (Rosen et al, 2008; Kaplan et al, 2009) (Table 103-4). It is likely that the longitudinally designed BACH survey, with a balanced enrollment of men and women stratified by age and race/ethnicity, will in the future contribute significantly to our understanding of LUTS in both men and women. A symptom-based cluster analysis was performed in both cohorts and remarkably similar clusters of symptoms were identified, allowing for an in-depth analysis of their association with comorbidities and other factors (Rosen et al, 2008). In the BACH survey, decreasing household income and increasing difficulties in paying for health care were associated with increasingly more severe symptom clusters (Hall et al, 2009).

Sexual Activity and Vasectomy

Ekman (1989) suggested that the increase in the fibromuscular stroma is a result of sexual activity, and many authors since then have attempted to find relevant associations. Morrison (1992) reported a 49% reduction in risk for prostatectomy in widowed versus single men; a similar association could not be verified by other authors. Cross-sectional data from the Olmsted County Study suggest that the frequency of ejaculation has no effect on LUTS, peak urinary flow rates, or prostate volume; the apparent protective association appears to be an artifact caused by the confounding effects of age (Jacobsen et al, 2003). The decrease in sexual ability and frequency of sexual activity with advancing age, exactly when the prevalence of BPH increases, in fact might suggest a reverse relationship, namely a causative effect of BPH on sexual function (Altwein and Keuler, 1992).

Recent evidence suggests a strong correlation between the severity of LUTS and impairment of sexual function, that is, ED as well as ejaculatory disturbances (Boyle et al, 2003; Chung et al, 2003; Rosen et al, 2003). Cross-sectional questionnaire-based data from various countries suggest that ED and ejaculatory disturbances increase with advancing age but also within each decade of life

TABLE 103-4 Overview of the EpiLUTS Study and BACH Survey

EPI LUTS	BACH
DESCRIPTION Cross-sectional, population-representative, Internet-based survey conducted in the United States, the United Kingdom, and Sweden in 30,000 (U.S., 20,000; U.K., 7500; Sweden, 2500) men and women ages 40–99 years (mean age, 56.6 years)	Population-based epidemiologic survey among 5503 randomly selected adults residing in Boston, ages 30–79 years, in three race/ethnic groups (2301 men, 3202 women; 1767 black, 1877 Hispanic, 1859 white respondents)
LUTS PREVALENCE 1 LUTS at least sometimes: 72.3% (men), 76.3% (women) 1 LUTS at least often: 79.99% (men), 52.5% (women)	LUTS (AUASI \geq 8): 18.7% (men), 18.6% (women); increased with age (10.5% for 30–39 years to 25.5% for 70–79 years), no difference by race/ethnicity (16.2%–19.3%)
BOTHER Rates of bother were lower for LUTS classified as at least “sometimes” than those classified as at least “often”; however, leaking urine during sexual activity, which was reported infrequently, was highly bothersome (82.1% men; 87.2% women), whereas terminal dribble, which was reported frequently, was less bothersome (40.6% men; 40.2% women)	Mean bother scores were higher in those with LUTS (vs. no LUTS) and for women vs. men
TREATMENT SEEKING Treatment seeking was low but most common in those in the voiding + storage + postmicturition subgroup: 29.1% men, 27.5% women; prescription medication use was also highest in this subgroup (17.6% and 10.4%, respectively)	Prescription medication use for urinary symptoms was low even among those with AUASI \geq 8, at 9.8% (men) and 2.1% (women)
COMORBIDITIES Comorbid conditions were most common in the voiding + storage + postmicturition subgroup, with significant associations for LUTS with arthritis, asthma, chronic anxiety, depression, diabetes (men only), heart disease, irritable bowel syndrome, neurologic conditions, recurrent UTI, and sleep disorders; childhood nocturnal enuresis was significantly associated with most LUTS subgroups	LUTS (AUASI \geq 8) was associated with heart disease, diabetes (men only), and depression

AUASI, American Urological Association Symptom Index; LUTS, lower urinary tract symptoms; UTI, urinary tract infection.

From Kaplan SA, Roehrborn CG, Chapple CR, et al. Implications of recent epidemiology studies for the clinical management of lower urinary tract symptoms. *BJU Int* 2009;103(Suppl. 3):48–57.

with increasing LUTS symptom severity (Fig. 103-14). While these correlations do not necessarily imply a causative mechanism, it is possible that similar pathophysiologic events underlie the development of both problems in the aging male, the most obvious being ischemia in both the genital and lower urinary tract organs (McVary, 2005). A logistical regression analysis of the EpiLUTS data also documented a strong relationship between various domains of sexual and ejaculatory dysfunction and LUTS (Wein et al, 2009) (Table 103-5).

Sidney (1987) analyzed the Kaiser Permanente database and initially found a relative risk (RR) of 1.2 for the diagnosis of BPH among men who had a vasectomy. However, after 5 years of follow-up, the RR was 0.97 and not significant. There does not appear to be a relationship between vasectomy and BPH development or prostate size (Jakobsen et al, 1988), and in the Massachusetts Male Aging Study, Meigs and coworkers (2001) did not find that vasectomy increased the risk of being diagnosed with BPH.

Alcohol and Liver Cirrhosis

Alcohol may decrease testosterone production and plasma testosterone levels and increase clearance of testosterone (Chopra et al, 1973). Despite this hypothetical reason for a lower incidence of BPH in men who drink, inverse relationships have been described. Both Morrison (1992) and Sidney and colleagues (1991a) reported

by multivariate analysis an adjusted RR of 0.49 and age-adjusted RR of 0.75, respectively, for the risk of having surgery for BPH when taking in more than three glasses of alcohol per day. However, one might argue that the poorer health in heavy drinkers might bias physicians against surgery. Glynn and coworkers (1985) in fact found no increased risk for either the clinical diagnosis or surgical rates. A recent analysis of the Prostate Cancer Prevention Trial also showed an inverse relationship between a diagnosis of BPH and alcohol intake, that is, a somewhat protective effect (Kristal et al, 2008). A meta-analysis of alcohol intake, BPH, and LUTS demonstrated that consumption of alcohol decreases the likelihood of BPH, but not LUTS, in all six strata. Compared with no alcohol, an alcohol intake of 36 g/day or greater was associated with a 35% decreased likelihood of BPH (OR 0.65) (Rees, 2009).

Of five studies examining the relationship between liver cirrhosis and BPH based on autopsy material, four found a lower prevalence of BPH in men with cirrhosis (Bennett et al, 1950; Stumpf and Wilens, 1953; Robson, 1966; Frea et al, 1987), while one study—admittedly with some design flaws—found a higher prevalence (Wu, 1942). Since most cirrhosis cases are alcohol induced, the separation of the effects of alcohol versus cirrhosis is virtually impossible.

On the other hand, nonalcoholic fatty liver disease, which is part of the metabolic syndrome, is associated with BPH in men and with overactive bladder in women (Uzun et al, 2013).

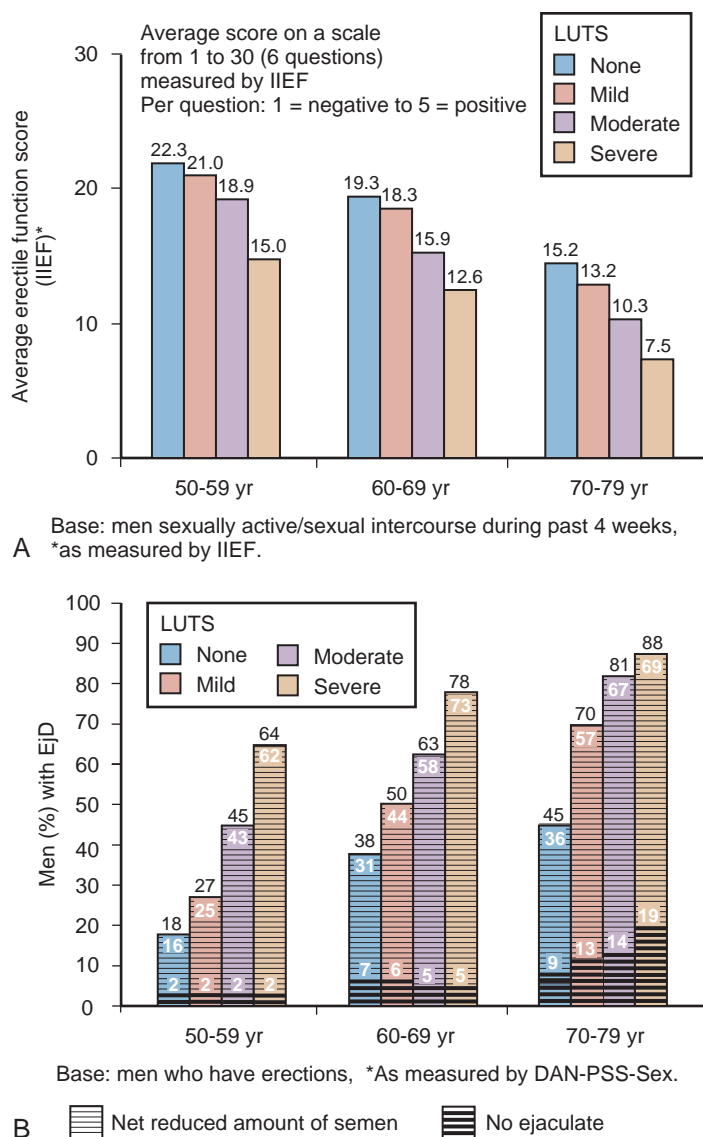


Figure 103-14. Erectile function (A) decreases and ejaculatory disturbances (EJ; B) increase with advancing age, but within each decade of life they also decrease and increase, respectively, with increasing severity in lower urinary tract symptoms (LUTS). DAN-PSS-Sex, Danish Prostatic Symptom Score; IIEF, International Index of Erectile Function. (From Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male [MSAM-7]. *Eur Urol* 2003;44:637-49.)

Hypertension

The sympathetic nervous system, via α -adrenergic fibers and receptors, plays an important role in both hypertension and the symptoms of BPH. However, since both hypertension and LUTS/BPH increase with advancing age, it is difficult to prove a causal relationship between these two conditions (Boyle and Napalkov, 1995). The previously cited studies by Glynn and Sidney and their colleagues (Glynn et al, 1985; Sidney et al, 1991a) did not find an association. In a small clinic cohort study with methodologic flaws, Pressler and associates (1997) reported an increase in the incidence of hypertension of 15%, 18%, and 31% for men with mild, moderate, and severe symptoms. Autonomic hyperactivity has been implicated in the development of both LUTS and ED in the aging male, but conclusive clinical data are lacking (McVary et al, 2005). In the EpiLUTS study, both heart disease and hypertension were associated with more severe LUTS symptom constellations (Coyne et al, 2009).

Further studies are needed to better understand the common underlying pathophysiologic mechanisms and a potential cause-and-effect relationship.

Smoking

Smoking cigarettes appears to increase both testosterone and estrogen levels because of the nicotine level, and thus should have a positive and inductive effect on the development of BPH. However, since severe smoking causes other health problems, surgery rates are probably a poor indicator for a possible correlation, since physicians are biased against surgery in heavy smokers. Seitter and Barrett-Connor (1992) indeed found no correlation between smoking and prostatectomy rates, and Glynn and associates (1985) failed to identify a correlation between smoking and the clinical diagnosis of BPH. Sidney and coworkers (1991a) followed 16,000 men over 15 years and found a negative correlation between being a smoker at baseline and subsequent risk of prostatectomy. Daniell (1993a) examined the records of 345 patients who underwent prostatectomy and found smaller gland volumes in smokers and a lower age-adjusted prevalence of ever-smokers compared to a control group. Roberts and colleagues examined this issue in the Olmsted County Study (Roberts et al, 1994a) and later in a Japanese population (Roberts et al, 1997b). In Olmsted County only 16% of the over 2000 men in the study were current smokers, which appears low but understandable considering the population mix in Rochester, Minnesota. A biphasic association was found, with light to moderate smokers being less likely to have moderate to severe LUTS, and heavy smokers having at least the same risk as never-smokers.

An update from the Olmsted County Study suggests that smoking is associated with decreased urinary flow rates and moderate to severe symptoms, but not with enlarged prostate volume or increasing serum PSA (Rule et al, 2005). This is in contrast to earlier studies suggesting a relationship between smoking and prostate size (Kupeli et al, 1997). In the EpiLUTS study, ex-smokers had an increased risk of having more severe symptom constellations and never-smokers had a decreased risk, while the risk for current smokers was not a factor (Coyne et al, 2009).

Recent evidence from the Olmsted County Study verified the absence of a meaningful clinical association between current smoking and urinary retention (Sarma et al, 2009), and in the BACH survey no correlation between smoking and LUTS was observed (Maserejian et al, 2012).

Any relationships between current or past smoking and LUTS/BPH are likely to be weak and of limited clinical significance.

Physical Activity, Diet, Obesity, Body Mass Index, and the Metabolic Syndrome

Chyou and coworkers (1993) examined 33 food items in relationship to prostatectomy rates, and found only beef intake to be significantly associated. Araki and colleagues (1983) reported increased clinical diagnosis of BPH in men with higher milk consumption and lower consumption of green and yellow vegetables. Overall, there is no convincing evidence for any individual diet factor to play a major role in the development of LUTS/BPH.

The relationships between LUTS/BPH and obesity, body mass index (BMI), and the metabolic syndrome have recently been of great interest (Hammarsten et al, 1998; Hammarsten and Hogstedt, 1999, 2001; Rohrmann et al, 2005; Gupta et al, 2006; Kasturi et al, 2006). Metabolic syndrome is a clinical constellation of metabolic abnormalities, including obesity, glucose intolerance, dyslipidemia, and hypertension, that increase the risk of cardiovascular disease and result primarily from modifiable risk factors, particularly physical inactivity and dietary practices endemic to Westernized societies (Haffner and Taegtmeier, 2003). There are plausible biologic considerations: adipose tissue is the main source of aromatization of testosterone to estrogen, and men with lower BMI have higher serum testosterone levels (Eldrup et al, 1987).

TABLE 103-5 Logistic Regression of Decreased Sexual Enjoyment and Activity as Well as Predictors of Erectile Dysfunction (ED), Ejaculatory Dysfunction (EJD), and Premature Ejaculation (PE)

COVARIATES	DECREASED SEXUAL ENJOYMENT	SEXUAL ACTIVITY	ED (IIEF: EF < 21)	EJD	PE
DEMOGRAPHIC			+†	+†	-†
Age					
BMI					
Hispanic vs. white					
Black vs. white					
Asian vs. white					
Other vs. white		+*			
Sweden vs. United States			-†		
United Kingdom vs. United States					
LUTS					
Weak stream	+†	+†	+†		
Split stream	+*		+†		
Intermittency					+*
Hesitancy					
Straining					
Terminal dribble					+*
Perceived frequency	+*	+*			
Nocturia					
Urgency					
Urgency with fear of leaking	+*		+*	+*	
Urgency incontinence					
SUI (laugh/cough)	-*				
SUI (physical activity)					
Leak for no reason		+*			
Other leaking					
Nocturnal enuresis					
Leak during sex	+†	+†	+*	+*	
Incomplete emptying	+†	+*			+*
Postmicturition incontinence					
Dysuria	+*	+†	+*		
Bladder area pain	+†				+*
Pain during sex	+†	+†			
COMORBID CONDITIONS					
Heart disease		+†			
Hypertension			+†		
Diabetes			+†		
Prostate cancer	+†	+†		+†	
Bladder cancer	+†	+†			
Prostatitis	+†	+*			-†‡
Depression			+†	+†	
Neurologic conditions					
CONCORDANCE INDEX	0.86	0.86	0.77	0.73	0.62

–, negative values for point estimates; +, positive values for point estimates. BMI, body mass index; IIEF-EF, International Index of Erectile Function; LUTS, lower urinary tract symptoms; SUI, stress urinary incontinence.

* $P < .01$

† $P < .001$.

‡Not having a history of prostatitis is associated with premature ejaculation.

From Wein AJ, Coyne KS, Tubaro A, et al. The impact of lower urinary tract symptoms on male sexual health: EpiLUTS. BJU Int 2009;103(Suppl. 3): 33–41.

BMI was negatively associated with surgically treated BPH in the Kaiser Permanente cohort study (Sidney et al, 1991a), and with a clinical diagnosis of BPH in the Normative Aging Study (Glynn et al, 1985). In contrast, in a study of 68 men by Soygur and coworkers (1996), the average prostate weight increased both with age and with increasing obesity together with an increase in serum estradiol levels. Daniell (1993b) also found larger adenomas in more obese men undergoing prostatectomy. Both of these studies report a positive correlation between obesity and prostate size, but neither between obesity and symptom severity. Several caveats must be mentioned: DRE is less likely to yield a diagnosis of BPH and prostate enlargement in very obese patients due to anatomic obstacles, and patients with high BMI may be biased against surgical interventions.

Men ages 40 to 75 years who were participants in the Health Professionals Followup Study and who were without prior diagnosis of cancer or prostatectomy provided data on weight, height, and waist and hip circumferences. After adjustment for age, smoking, and BMI, abdominal obesity was related to prostatectomy (OR 2.38) and to frequent urinary symptoms among those without prostatectomy (OR 2.00). BMI, hip circumference, and waist-to-hip ratio were not associated with BPH independently of waist circumference. **These results suggest that abdominal obesity in men may increase the frequency and severity of urinary obstructive symptoms and may increase the likelihood that such obese men will undergo a prostatectomy** (Giovannucci et al, 1994).

Hammarsten and Hogstedt (1999) examined 250 patients with LUTS and found non-insulin-dependent diabetes mellitus, hypertension, tallness, obesity, high insulin levels, and low levels of high-density lipoprotein cholesterol to be risk factors for the development of BPH. They suggested a causal relationship between high insulin levels and the development of BPH, and hypothesized increased sympathetic nerve activity in men with BPH. In a hospital-based case-control study, overweight was modestly inversely related to BPH. The hypothesis of reduced testosterone levels in obese individuals may explain the different BPH risk and the need to be tested (Zucchetto et al, 2005). Parsons (2007) performed a comprehensive literature review and found that factors that potentially increase the risk of BPH and LUTS include obesity and diabetes, while factors that potentially decrease the risk include increased physical activity and moderate alcohol consumption (Table 103-6). Parsons and Kashefi (2008) also performed a comprehensive literature review and found eight studies ($N = 35,675$) that were eligible for a pooled analysis of the effect of physical activity levels stratified into light, moderate, and vigorous categories, with a sedentary category for reference. Compared to the sedentary group, the pooled ORs for BPH or LUTS were 0.70, 0.74 and 0.74 for men engaging in light, moderate, and heavy physical activity, respectively. Physical activity thus appears to reduce the risks of BPH and LUTS. Similar findings of increased likelihood of LUTS with increasing BMI and decreasing likelihood with greater physical activity were also reported from the EpiLUTS study (Coyne et al, 2009).

The evidence at present suggests a positive relationship between lack of physical activity, obesity, BMI, and other measures of the metabolic syndrome and both LUTS and BPH (including prostate volume), while increased physical activity appears to have a protective effect.

Medications

Very limited information is available. Cold medications containing α -sympathomimetic drugs exacerbate LUTS by the expected effect on the smooth muscles of the bladder outlet. A careful analysis of the data from the Olmsted County Study demonstrated that daily use of antidepressants, antihistamines, or bronchodilators is associated with a 2- to 3-point increase in the IPSS compared to age-matched nonusers, and daily use of antidepressants is associated with a decrease in the age-adjusted flow rate (Su et al, 1996).

Correlations between Parameters

As noted, all relevant parameters such as symptom severity and frequency, bother, interference, disease-specific HRQOL, maximum flow rate, and prostate volume tend to worsen with advancing age. However, reported correlations between these parameters as well as urodynamic pressure-flow studies are in general weak with some exceptions. Strong correlations exist, as one might expect, between subjective measures such as symptom severity and frequency (IPSS score), bother, disease-specific HRQOL, and interference scores (Barry et al, 1995b; Girman et al, 1999) (Fig. 103-15).

Weak numerical correlations can arise artifactually, regardless of whether true physiologic relationships exist (Girman, 1998). Correlations are further affected by intraindividual variability of measured parameters, day-to-day variability, measurement errors associated with the technique or equipment, or the natural history of the condition itself (Bruskewitz et al, 1982; Diokno et al, 1992; Barry et al, 1995c; Sagnier et al, 1996).

It is furthermore crucial to consider the population utilized to evaluate correlations. A correlation is more easily identified if patients exhibiting the full spectrum of the parameters of interest are included. In most LUTS/BPH studies, however, patients are excluded based on thresholds imposed, making it more difficult for a significant correlation to emerge. There are many examples in clinical medicine in which weak numerical correlations exist but strong clinical relationships are well accepted (Wilson and Cleary, 1995).

The absence of meaningful baseline correlations for symptoms, flow rate, and prostate volume in a tightly controlled population of men with LUTS and BPH enrolled in a BPH treatment study is shown in Table 103-7.

An example of how restriction of the full range of parameters affects correlations is shown in Figure 103-16. Volunteers without known prostatic diseases were asked to fill in an AUASI score and perform a flow rate recording. When all data are considered, a clear relationship exists, with the maximum flow rate decreasing with increasing symptom severity ($r = 0.4$; $P < .05$). However, when considering only those patients typically seen in a BPH study, namely, those with a score above 10 points and a maximum flow rate between 5 and 15 mL/sec, the correlation within that cohort exhibiting a limited range of observation on both scales is very weak ($r = 0.08$; not significant) and the regression line becomes flat (see Fig. 103-16).

The correlations observed between symptoms, flow rate, and prostate volume in true community-based population studies without artificially imposed entry criteria are consequently somewhat higher than those seen in BPH clinic or trial populations. In the Olmsted County Study, after adjusting for age, the odds of moderate to severe symptoms were 3.5 times greater for men with prostatic enlargement (>50 mL) than for men with smaller prostates, while the odds were similarly increased (2.4-fold) for men not achieving a peak urinary flow rate of 10 mL/sec (Girman et al, 1995). Men with enlarged prostates were about twice as likely to have bother due to symptoms (OR 2.4) or activity interference (OR 1.8) relative to men with smaller prostates (Girman et al, 1999). In a similar study from the Netherlands, Bosch and coworkers (1995b) reported numerically weak but statistically significant correlations between the IPSS and TPV ($r = 0.19$, $P < .001$), peak flow rate ($r = -0.18$, $P < .001$), and postvoid residual urine volume ($r = 0.25$, $P < .001$).

While weak correlations between prostate volume and symptoms as well as flow rate have been accepted, attention has also focused on correlations between the transition zone of the prostate and physiologic measures. A stronger correlation between the transition zone and symptoms ($r = 0.48$, $P = .03$) and peak urine flow ($r = -0.34$, $P = .05$) was reported first by Kaplan and colleagues (1995), who also showed a significant correlation between transition zone index (TZV/TPV) and symptoms ($r = 0.75$), peak urine flow ($r = -0.71$), and—somewhat unexpectedly—detrusor pressure at peak urine flow ($r = 0.43$). These data were generated from a relatively small cohort of 61 men with BPH. Invasive pressure-flow

TABLE 103-6 Cohort Studies of Modifiable Risk Factors Associated with Decreased or Increased Risk of LUTS and/or BPH

STUDY	OUTCOME MEASURE (RISK FACTOR)	REFERENCE CATEGORY	OR (95% CI)
DECREASED RISK OF BPH AND LUTS			
Health Professionals Follow-up Study	Clinical BPH:		
	Alcohol intake 30.1-50 g/day	Alcohol intake 0 g/day	0.59 (0.51-0.70)
	Walking ≥ 2 hr/wk	Walking 0 hr/wk	0.73 (0.63-0.84)
Massachusetts Male Aging Study	Clinical BPH (physical activity 862 kcal/day or greater)	Physical activity ≤ 140 kcal/day	0.50 (0.3-0.9)
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	Clinical BPH (alcohol intake ≥ 60 g/day)	Alcohol intake < 5 g/day	0.60 (0.5-0.7)
	TURP likelihood (alcohol intake ≥ 60 g/day)	Alcohol intake < 5 g/day	0.40 (0.3-0.7)
	Nocturia (alcohol intake ≥ 60 g/day)	Alcohol intake < 5 g/day	0.80 (0.7-1.0)
Third National Health and Nutrition Examination Survey (NHANES III)	LUTS:		
	Alcohol intake ≥ 1 drink/day	Never	0.59 (0.36-0.97)
	Physical activity > 6 times/wk	Physical activity 0 times/wk	0.49 (0.29-0.84)
INCREASED RISK OF BPH AND LUTS			
Baltimore Longitudinal Study of Aging	LUTS:		
	Diabetes	No diabetes	2.80 (1.10-7.10)
	Fasting glucose > 110 ng/dL	Fasting glucose ≤ 110 ng/dL	2.60 (1.01-6.70)
	Prostate ≥ 40 mL:		
	BMI > 35 kg/m ²	BMI < 25 kg/m ²	3.52 (1.45-8.56)
	Diabetes	No diabetes	2.25 (1.25-4.11)
	Fasting glucose > 110 ng/dL	Fasting glucose ≤ 110 ng/dL	2.98 (1.70-5.23)
Flint Men's Health Study	LUTS:		
	Diabetes	No diabetes	1.95 (1.49-2.57)
	Hypertension	No hypertension	1.29 (1.04-1.61)
Health Professionals Follow-up Study	BPH surgery (waist circumference > 109 cm)	Waist circumference < 89 cm	2.38 (1.42-3.99)
	LUTS (waist circumference > 109 cm)	Waist circumference < 89 cm	2.00 (1.47-2.72)
Second Nord-Trøndelag Health Study (HUNT-2)	LUTS:		
	BMI ≤ 40 kg/m ²	BMI < 25 kg/m ²	1.79 (0.90-3.56)
	Diabetes	No diabetes	1.25 (1.04-1.49)
	Waist/hip ratio ≤ 0.94	Waist/hip ratio ≤ 0.85	1.32 (1.15-1.50)
NHANES III	LUTS:		
	Diabetes	No diabetes	1.67 (0.72-3.86)
	Hypertension	No hypertension	1.76 (1.20-2.59)
	Increase in BMI between age 25 yr + highest BMI ever	No increase	1.90 (0.89-4.05)
	Waist circumference > 102 cm	Waist circumference < 94 cm	1.48 (0.87-2.54)

BMI, body mass index; BPH, benign prostatic hyperplasia; CI, confidence interval; LUTS, lower urinary tract symptoms; OR, odds ratio; TURP, trans-urethral resection of the prostate.

From Parsons JK. Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. *J Urol* 2007;178:395-401.

studies are not performed in community-based studies, and thus comparative data from population-based studies cannot be reviewed. However, the finding of a relationship between measures of obstruction and prostate volume is rare, with most authors denying such a relationship in series of BPH clinic or trial patients (Bosch et al, 1995c; Yalla et al, 1995; Ezz el Din et al, 1996; Witjes et al, 1997; d'Ancona et al, 1998; Homma et al, 1998; Kuo, 1999; Steele et al, 2000). Data from the Olmsted County Study suggest no stronger correlation between symptoms and peak flow rates with TZV ($r = 0.17$, $P = .001$ and $r = -0.20$, $P < .001$, respectively) than with TPV ($r = 0.16$, $P < .001$ and $r = -0.16$, $P < .001$, respectively). The TZV/TPV weakly correlated with the AUASI ($r = 0.08$, $P = .103$) and peak urinary flow rate ($r = -0.08$, $P = .0823$) (Corica et al, 1999). In a large BPH treatment trial, the TZV also did not correlate more strongly with other measures compared to the TPV.

The correlation between serum PSA and prostate volume, both total and transition zone, has recently been described in greater

detail (Roehrborn et al, 1999b). Although the individual variability is significant, precluding an accurate prediction of prostate volume by serum PSA in individual patients, there is a strong log-linear relationship between these parameters that can be shown in both population-based and clinical studies (Hochberg et al, 2000; Morote et al, 2000; Hedelin et al, 2005). The relationship is further influenced by patients' age, with older patients having a greater increase in prostate volume per unit of serum PSA (Fig. 103-17). In Asian men similar relationships exist; however, in general both prostate volume and serum PSA tend to be smaller/lower (see Fig. 103-17B) (Gupta et al, 2005). Relationships between other PSA-derived parameters have recently been examined, and a certain subform of PSA (BPSA) has been shown to be more strongly related to BPH compared to total serum PSA (Canto et al, 2004).

With the exception of age, correlations between various measures of LUTS and BPH are modest in community-based population studies and weak in BPH clinic and trial populations. The

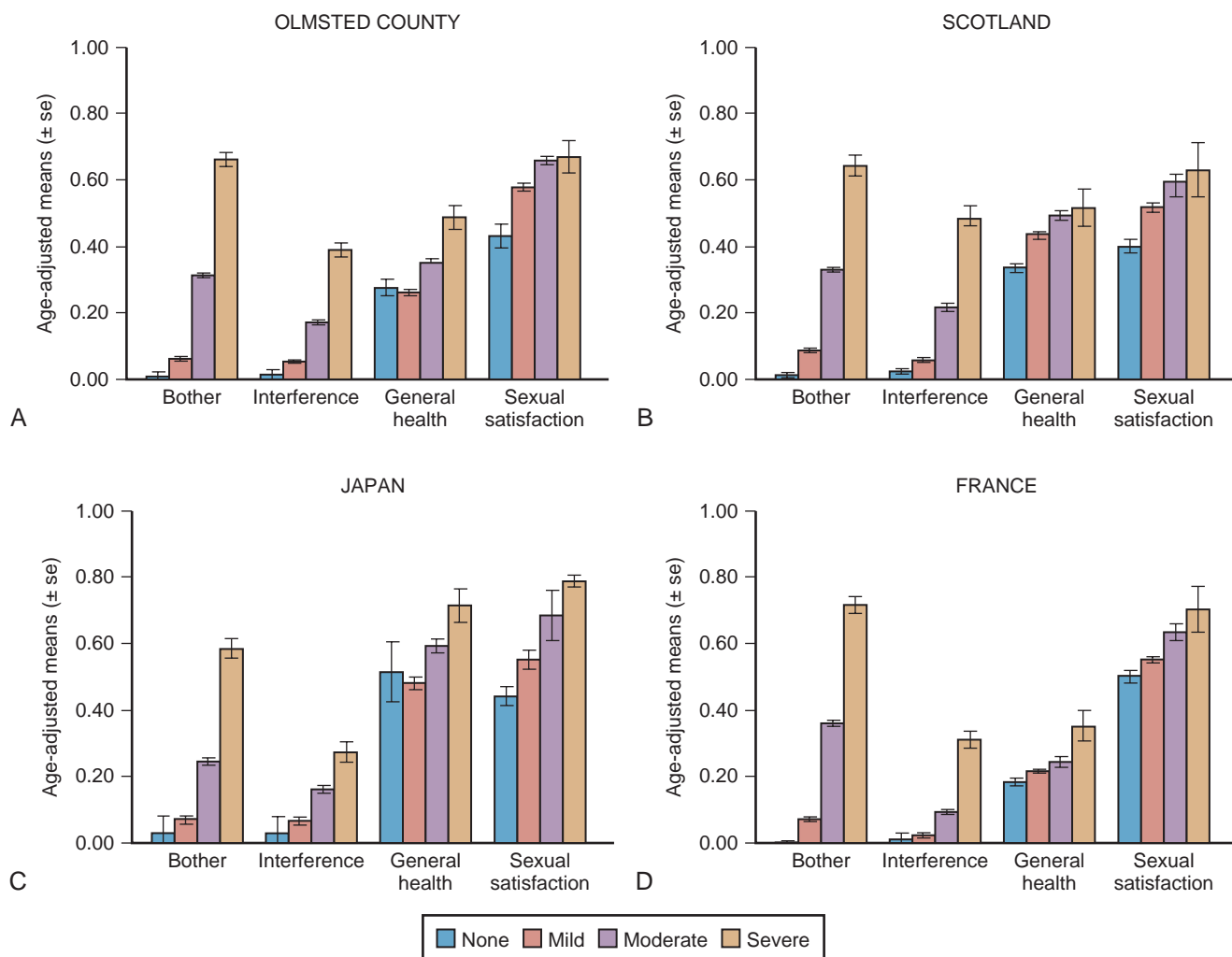


Figure 103-15. A-D, Age-adjusted means of disease-specific health-related quality of life measures after transformation to a 0-to-1 scale stratified by levels of symptom severity and frequency (International Prostate Symptom Score). (From Girman CJ, Jacobsen SJ, Tsukamoto T, et al. Health-related quality of life associated with lower urinary tract symptoms in four countries. *Urology* 1998;51:428–36.)

TABLE 103-7 Correlation Table between Baseline Parameters in a BPH Treatment Study*

	PSA	Q _{MAX}	IPSS	TPV	TZV
Age	0.092 <0.0001	-0.078 <0.0001	-0.069 <0.0001	0.152 <0.0001	0.154 <0.0001
PSA		-0.031 0.111	-0.016 0.423	0.384 <0.0001	0.352 <0.0001
Q _{max}			-0.117 <0.0001	-0.059 <0.001	-0.047 <0.05
IPSS				0.020 0.293	0.005 0.761
TPV					0.775 <0.0001

BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; Q_{max}, peak flow rate; TPV, total prostate volume; TZV, transition zone volume.

*This study included 2800 men older than age 50 years, an IPSS score >12, Q_{max} <15 mL/sec, serum PSA between 1.5 and 10 ng/mL, and TPV >30 mL (TZV not specified). Note the lack of strong correlations except for age and serum PSA versus volume between parameters.

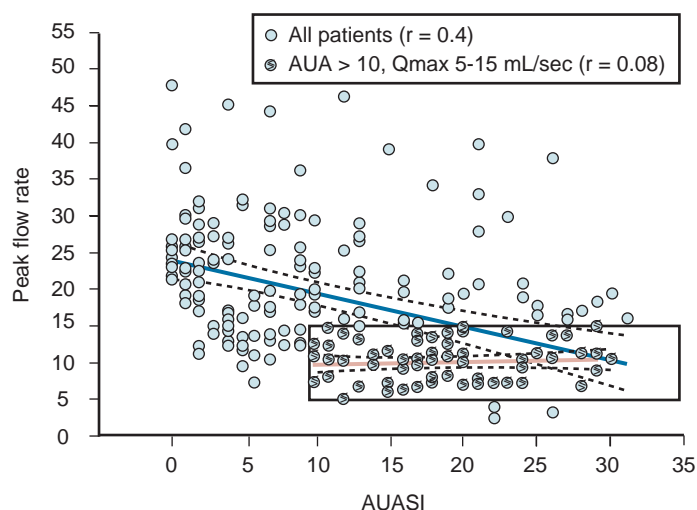


Figure 103-16. Correlation and regression (95% confidence interval) between symptom score and maximum flow rate (Q_{max}) in volunteers ($r = 0.4$; $P < .05$). When only those volunteers with a symptom score above 10 points and a flow rate between 5 and 15 mL/sec (●) are considered, the correlation is virtually absent ($r = 0.08$; not significant), as indicated by a flat regression line (black). AUASI, American Urological Association Symptom Index.

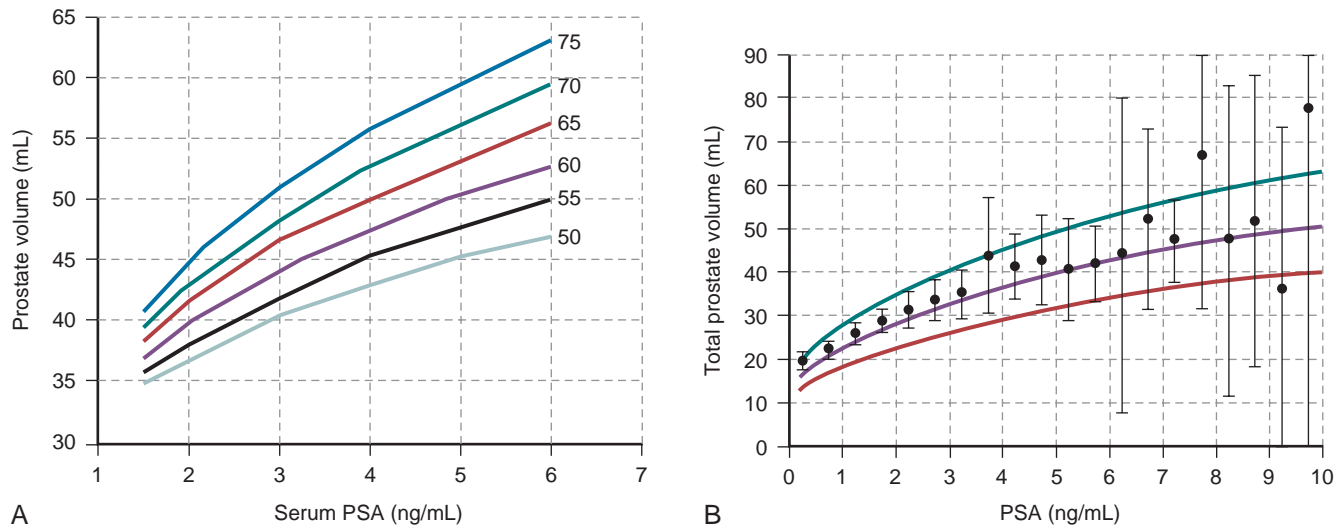


Figure 103-17. Prediction of prostate volume based on serum prostate-specific antigen (PSA) stratified by age in white men (A) and in Japanese men (B). (A, From Roehrborn CG, Boyle P, Gould AL, et al. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology* 1999;53:581–9; B, from Gupta A, Aragaki C, Gotoh M, et al. Relationship between prostate specific antigen and indexes of prostate volume in Japanese men. *J Urol* 2005;173:503–6.)

relationship between serum PSA and prostate volume is moderate, and influenced by age and race and ethnic origin. Neither symptoms nor flow rate nor prostate volume measures can predict presence and degree of obstruction reliably.

NATURAL HISTORY OF UNTREATED BENIGN PROSTATIC HYPERPLASIA

The natural history of a disease process refers to the prognosis of the disease over time. In other words, the measurement of changes in parameters of interest and the incidence rates of significant outcomes constitute what is commonly referred to as the natural history of a disease. It is important for clinicians to gain as good an understanding as possible of the natural history of any illness, since the benefits and risks of any therapeutic interventions should always be balanced with the risks involved in just watching the disease (i.e., the natural history). In fact, the degree to which natural history must be studied depends on the seriousness of the disease, as well as the risks involved with the therapeutic intervention. For example, it proves to be crucial to understand the natural history of abdominal aortic aneurysms and how their prognosis is determined by their size in order to adequately counsel patients regarding surgical interventions, which have considerable risks in themselves.

Clinical Parameters and Outcomes of Interest

Table 103-8 lists the beneficial and harmful changes in measurable parameters and outcomes, which are of interest in both the natural history and treatment of LUTS and BPH. They may be divided further into direct or biologic and indirect or proxy outcomes (Eddy, 1990, 1992). The biologic or direct outcomes are those that are immediately noticeable by the patients (e.g., symptom changes, infections, death), while the indirect or proxy outcomes are not directly noticeable but may predict future changes in direct outcomes (e.g., changes in pressure-flow parameters may predict episode of retention). The parameters and outcomes are dichotomous (yes or no, e.g., retention or no retention), categorical (grades of severity, e.g., grades of obstruction measured by pressure-flow studies), or continuous (scales of severity, e.g., symptom score, maximum flow rate). Accordingly, the most common ways to measure such outcomes are probabilities or rates of occurrences for

TABLE 103-8 Beneficial and Adverse Changes in Parameters and Outcomes

BENEFICIAL CHANGES		HARMFUL CHANGES	
Probability of symptom improvement	D D	Probability of symptom worsening	
Magnitude of symptom improvement	D Co	Magnitude of symptom worsening	
Magnitude of bother improvement	D Co	Magnitude of bother worsening	
Magnitude of quality-of-life improvement	D Co	Magnitude of quality-of-life worsening	
Flow rate improvement	I Co	Flow rate worsening	
Residual urine volume reduction	I Co	Residual urine volume increase	
Prostate size reduction	I Co	Prostate size increase	
Pressure-flow parameter improvement	I Co	Pressure-flow parameter worsening	
	D D or Ca	Urinary incontinence	
	D D or Ca	Erectile dysfunction	
	D D	Acute urinary retention	
	D D	Need for treatment/surgery	
	D D or Ca	Hematuria	
	D D	Urinary tract infection	
	D D	Bladder stones	
	D D	Bladder diverticula	
	D D or Ca	Detrusor failure	
	D D or Ca	Upper tract obstruction/deterioration	
	D Co	Azotemia/renal failure	
	D D	Death	

Left center column: D, Direct/biologic; I, Indirect/proxy outcome.
Right center column: D, Dichotomous; Ca, Categorical; Co, Continuous outcome.

dichotomous or categorical outcomes, and measures of central tendency (mean or median) and variability (standard deviation or standard error or CI) for outcomes measured by continuous scales.

Methods of Studying Natural History of Benign Prostatic Hyperplasia

The natural history of BPH can theoretically be evaluated by studies of a variety of designs:

- Longitudinal studies of untreated cohorts of men diagnosed with LUTS and clinical BPH by any definition (*watchful waiting cohorts*)
- Studies of the behavior of men diagnosed with LUTS and BPH and enrolled in controlled studies of LUTS and BPH (*control groups*) and receiving either
 - no treatment (compared to active intervention),
 - placebo treatment (compared to medical treatment), or
 - sham treatment (compared to device or surgical treatment)
- Longitudinal studies of unselected (i.e., undiagnosed) men living in the community who are less likely to progress and request or require therapy (*longitudinal population-based studies*)

There are problems associated with either of the approaches. Concerning the *watchful waiting cohorts*, the first question to be resolved is whether or not it is ethical (or feasible) to enroll symptomatic men in such a study even if the disease studied is not fatal. Second, the very fact that the patients had an initial and presumably subsequent contacts with health care providers in the course of the study will bias them, leading to changes in outcome parameters of interest presumably different from those observed in an age-matched cohort of men similar in all parameters at baseline, but who did not choose to participate (a cohort one might call, in analogy to genetic language, “wild-type”). Further, many diagnosed men will in the course of such natural history study become more and more symptomatic and therefore desire and receive treatment, making them ineligible to further participate in the study and thus reducing the number of men available for analyses. Lastly, a very important bias is introduced by the fact that patients in such cohorts are selected based on thresholds imposed by inclusion and exclusion criteria. In general, patients are selected to participate who are more symptomatic, that is, those with higher symptom scores and lower maximum flow rates. By the principle of trial conduct, patients then repeat the symptom and flow rate assessment during follow-up (or after treatment). However, the same inclusion/exclusion criteria are not applied to the follow-up measurements,

which leads to a unilateral regression to the mean, suggesting (falsely) an improvement in the parameter of interest.

To determine the effect that the stringency of pretrial screening has on the outcome of placebo treatment, a cohort of 145 volunteers were invited to fill in the IPSS score and perform a flow rate recording twice within a month without receiving any therapy or instructions whatsoever (Sech et al, 1998). Although many patients experienced either an increase or a decrease in both parameters, the mean values did not change significantly (IPSS 12.1 vs. 11.7 points, peak flow rate 17.7 vs. 17.4 mL/sec; not significant). However, when typical BPH trial conditions were applied and only those patients who had an IPSS score above (>7, >10, >15) and a flow rate below (<15, <12, <10 mL/sec) a certain threshold were considered for analyses, a unilateral regression to the mean took place by which the “more” symptomatic volunteers (i.e., patients) still experienced considerable natural variability on the occasion of the second assessment, but the net effect was toward “improvement,” that is, lower scores and higher flow rates. For example, when only considering patients with IPSS scores greater than 10 points, the mean difference between first and second assessment was between 19.9 versus 18.8 points or –1.1 (*P* < .05). Similarly, when only patients with a peak flow rate less than 12 mL/sec were considered, the mean difference between the first and second assessment was 9.3 versus 10.9 mL/sec or +1.6 mL/sec (*P* < .01) (Table 103-9).

This experiment clearly illustrates that a unilateral regression to the mean induced and controlled by the stringency of the inclusion criteria can result in a significant “improvement” in any parameter for which a threshold is set at the baseline screening. Such purely mathematical effect is likely at work in many if not all studies where the outcome parameters are measured using a numerical scale of some sort, and where baseline screening criteria are applied.

Control groups of men being randomized to receive either no treatment, placebo treatment, or sham treatment, while being compared to a matched group of men receiving active therapeutic interventions, also suffer from a variety of biases. As with the *watchful waiting cohorts*, they have initial and constant contact with health care providers and know from the design of the study that they are randomized to the perceived less effective or ineffective arm, and thus they may have a lower threshold than community-dwelling men to cross over to active therapy. On the other hand, owing to a sense of obligation, they may elect to be followed until the trial is over, and then choose an active treatment. They are also subject to the regression to the mean bias discussed before, since they were subjected to inclusion/exclusion criteria.

Longitudinal population-based studies, although difficult and expensive to conduct, are likely the best vehicle to understand

TABLE 103-9 Effect of Stringency of Pretrial Screening on Outcome of Placebo Treatment*

SELECTION		MEAN ± SD	RANGE	MEAN DIFFERENCE (95% CI)	T TEST	N
All subjects	No. 1	12.1 ± 8.8	0-32	–0.39	0.133	145
	No. 2	11.7 ± 9.0	0-32	–1.1 to 0.29		
>7 at No. 1	No. 1	17.8 ± 6.5	9-32	–0.97	0.035†*	88
	No. 2	16.8 ± 7.7	0-32	–2.0 to 0.08		
>10 at No. 1	No. 1	19.9 ± 5.6	11-32	–1.1	0.036†*	70
	No. 2	18.9 ± 6.9	0-32	–2.2 to 0.1		
>15 at No. 1	No. 1	22.0 ± 4.6	16-32	–1.4	0.026†*	54
	No. 2	20.6 ± 6.6	0-32	–2.8 to 0.01		

*Mean ± standard deviation (SD) and range for American Urological Association Symptom Index for test no. 1 and test no. 2, mean difference between the two tests, and the 95% confidence interval (CI) for the difference, for all subjects and for subjects censored based on test number 1 score greater than 7 points, greater than 10 points, and greater than 15 points. Note the reduction in the number of patients available for follow-up due to censoring, which affects the power of the statistical test.

†Statistical comparison between test no. 1 and test no. 2 by *t* test.

From Sech SM, Montoya JD, Bernier PA, et al. The so-called “placebo effect” in benign prostatic hyperplasia treatment trials represents partially a conditional regression to the mean induced by censoring. *Urology* 1998;51:242–50.

the natural history of the disease. The regression to the mean bias does not apply, as the participants are not selected based on inclusion and exclusion thresholds. Since no formal diagnosis is established, the natural history may take place unencumbered by preconceived notions about symptoms, end points of trials, and anything else leading to a bias in a watchful waiting cohort of diagnosed and thus labeled men or in a control group of diagnosed men. One must realize, however, that the very need to monitor the natural history—that is, the need to ask questions and perform tests and interventions—conflicts with the notion of the “natural history,” and thus some biases are likely to be unavoidable even in the most ideal setting.

Watchful Waiting Studies

Following cohorts of men diagnosed with LUTS and/or BPH conservatively (*watchful waiting cohorts*) was attempted by some investigators in the past, but the few published reports are of limited scientific rigor and informational value, and have significant shortcomings. Inclusion and exclusion criteria are poorly defined, follow-up and compliance are poor, assessment instruments are either not defined or insufficient, and patient accounting is incomplete. The studies do provide answers regarding the probability of symptom changes and the magnitude of flow rate changes.

Five such studies were reported between 1919 and 1988 with a total enrollment of 456 patients and a follow-up ranging from 3 to 6 years (Clarke, 1937; Craigen et al, 1969; Birkhoff et al, 1976; Ball et al, 1981; Kadow et al, 1988). A change in symptom status was reported for all 456 patients, while none of the studies utilized a quantitative symptom severity scale. Data on urinary flow rate and residual urine were available for 223 and 197 patients, respectively. The peak urinary flow rate deteriorated in 66% and improved in 20%. Residual urine increased (35%), decreased (37%), and remained unchanged (28%) in about the same number of all patients. The mean change in peak flow rate (in those patients for whom data are available) was +2.2 (from a mean of 9.0 to 11.2) mL/sec or 24%, while the mean change in residual urine was +37 (from a mean of 115 to 152) mL or 32%. Data on symptom improvement were reported as a dichotomous outcome (improved versus not improved). The mean probability for any improvement in symptom severity in these studies is 42.5% (90% CI 30.8 to 54.8) as calculated by meta-analytical methods (Eddy and Hasselblad, 1992).

A superior approach, namely to follow a *no-treatment control group* of men diagnosed with LUTS and BPH, was chosen by Wasson and coworkers (1995). A total of 556 men with moderate symptoms and a Madsen-Iversen symptom score between 10 and 20 points (0- to 27-point scale) were randomized to either undergo transurethral resection of the prostate (TURP) or be watched conservatively. There were 47 treatment failures (defined as death, recurrent infection, residual urine volume over 350 mL, development of bladder calculus, incontinence, a symptom score of 24 or higher, or a doubling of serum creatinine from baseline) in the watchful waiting arm ($N = 276$) versus 23 in the surgery arm ($N = 280$) over 3 years of follow-up (RR 0.48, 95% CI 0.3 to 0.77). Sixty-five (24%) of the men assigned to watchful waiting underwent surgery during follow-up, 20 of them for treatment failure. The majority of these men were classified as more bothered at baseline, and about 40% of patients in this category experienced an improvement in the degree of bother from urinary difficulties, a proportion strikingly similar to the overall estimate of 42.5% from the natural history studies. At 3 years of follow-up, the patients randomized to watchful waiting who did not fail or cross over to surgery had a small but noticeable improvement in nearly all outcomes measured, including a +0.4-mL/sec increase in the maximum flow rate.

More recently, a 60-month update was reported providing data on 966 patient-years of follow-up on the TURP patients and 990 patient-years on the watchful waiting patients (Flanigan et al, 1998). The treatment failure rate was 21% for the watchful waiting group and 10% for the TURP group, and all outcomes were better for the TURP-treated patients (Table 103-10). During follow-up, 76 (27%) of the watchful waiting patients crossed over to TURP; the 5-year Kaplan-Meier estimate of the crossover rate was 36%, and twice as many patients crossed over electively as compared to post-treatment failure protocol-dictated crossover. The most significant factor predicting elective crossover was high baseline bother due to urinary symptoms (Fig. 103-18). When separately analyzed, the patients crossing over from watchful waiting to TURP had fewer improvements in outcome parameters compared to those randomized to TURP initially (Table 103-11). In many instances the differences between the groups were statistically and clinically significant. A reduction in symptom score by –11 points (high baseline symptom group) and an improvement in maximum flow rate by 8.7 mL/sec (low baseline flow rate group) after TURP is expected; however, in those men undergoing TURP after an unsuccessful trial of watchful waiting, the improvements were only –8 points and +4.7 mL/sec. This allows the speculation that, during the period of watchful

TABLE 103-10 Extended Follow-up Treatment Outcomes by Intention to Treat in the Veterans Affairs Cooperative Study Comparing Watchful Waiting with TURP

OUTCOME	TURP (N = 280)	WATCHFUL WAITING (N = 276)	RELATIVE RISK‡	P VALUE
Treatment failure	28	58	0.476	.0004
Death	16	12	1.311	.562
Urinary retention	1	9	0.110	.011
High residual	5	19	0.259	.003
Azotemia*	3	2	1.479	1.000
Bladder stones	0	1		.496
Incontinence	4	8	0.493	.259
High symptom score†	1	13	0.076	.0008
Lost to follow-up	16	18	0.876	.726
Withdrawal of consent	57	36	1.561	.023
Prostate cancer	24	11	2.151	.035

TURP, transurethral resection of the prostate.

*Azotemia defined as doubling of baseline creatinine value or greater than 3.0 mg/dL.

†High symptom score defined as 21 or greater on two consecutive measurements or 24 or greater on one measurement.

‡Relative risk of TURP compared to watchful waiting.

From Flanigan RC, Reda DJ, Wasson JH, et al. 5-Year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. J Urol 1998;160:12–6; discussion 16–7.

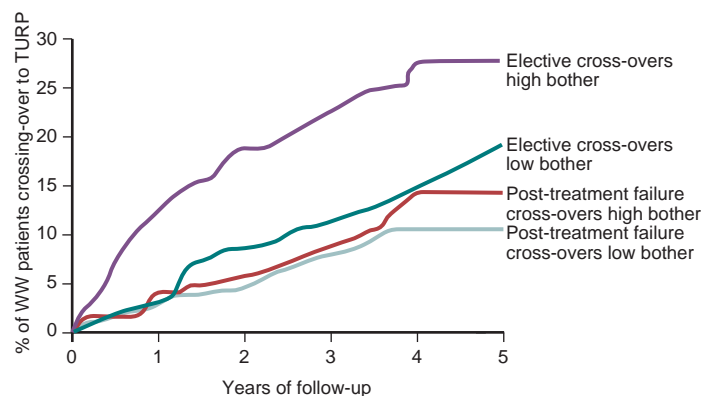


Figure 103-18. Percent of patients crossing over from watchful waiting (WW) to transurethral resection of the prostate (TURP) by baseline bother scores and elective versus post-treatment failure protocol dictated. (From Flanigan RC, Reda DJ, Wasson JH, et al. 5-Year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. *J Urol* 1998;160:12-6; discussion 16-7.)

TABLE 103-11 Changes from Baseline to 60 Months of Follow-up for Patients Initially Randomized to TURP (1), Randomized and Remaining on Watchful Waiting (2), and Those Randomized to Watchful Waiting but Crossing Over to TURP at Some Point during Their Follow-up (3)

	GROUP	HIGH BASELINE	LOW BASELINE
Symptom score	1	-11.0*†	-7.7*†
	3	-8.0‡	-6.2‡
	2	-5.8	-2.2
Maximum flow rate	1	4.6†	8.7*†
	3	2.9‡	4.7‡
	2	-2.2	2.2
Residual urine	1	-100*†	-19
	3	-81‡	-24
	2	-50	-7
Bother score	1	-34.9†	-14.7†
	3	-42.3‡	-7.2
	2	-10.7	1.6

*P value group 1 vs. group 3.

†P value group 1 vs. group 2.

‡P value group 3 vs. group 2.

From Flanigan RC, Reda DJ, Wasson JH, et al. 5-Year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. *J Urol* 1998;160:12-6; discussion 16-7.

waiting prior to crossover, some irreversible damage might have occurred preventing symptom and flow rate improvements to the same degree as observed in those men initially treated by TURP.

Djavan and colleagues (2004) followed a group of 397 men presenting to a urology clinic with mild LUTS, defined as scoring less than 8 points on the IPSS. These men were followed for 4 years beginning with a watchful waiting protocol and were re-evaluated every 3 months for 48 months' total time. The cumulative incidence of clinical progression, defined as worsening of the IPSS with migration from mild to moderate (IPSS 8 to 18 points) or severe (IPSS 19 to 35 points) symptoms, was assessed. The likelihood of migrating or transitioning from one health state to another was 6%, 13%,

15%, 24%, 28%, and 31% at 6, 12, 18, 24, 36, and 48 months, respectively.

Placebo and Sham Control Groups in Randomized Trials

Data from control groups treated with placebo or sham and compared to matched groups of patients treated with medications or devices are available to address many of the parameters and outcomes of interest.

Placebo Control Groups. For the Clinical Practice Guideline for the diagnosis and treatment of BPH published by the Agency for Health Care Policy and Research (AHCPR) in 1994, data on 1417 patients treated in 45 placebo arms of placebo-controlled trials were analyzed (McConnell et al, 1994). Table 103-12 allows a direct comparison between the watchful waiting studies discussed above and these placebo groups, both summarized by meta-analytical techniques. For none of the examined parameters can a significant difference between the two treatment modalities be identified. However, several points deserve discussion. As opposed to the longer-term follow-up in the watchful waiting studies, the placebo studies are part of short- to mid-term medical treatment trials ranging from 3 days to 52 weeks in duration (mean 13 weeks). In all these studies the patients are blinded as to the treatment arm, and thus have in most cases at least a 50:50 (or better in cases of 2:1 or 3:1 randomization) chance of receiving active drug. Dropping out of such studies because of failure does not have the same ramification as it does in watchful waiting studies, where the patients willingly assumed a conservative treatment approach knowing that it might fail (i.e., they might fail and go on to active treatments). In contrast, in some placebo-controlled studies a promise—either tacit or openly—is made stating that, following the conclusion of the trial, either the patient would be eligible for “free” active treatment or he would be “moved up” on the surgical waiting list (this phenomenon is unique to those studies conducted in the United Kingdom). The inactive preparation given should theoretically add to the placebo effect, and thus improve the outcome above those noted for watchful waiting studies. The probability for a patient to experience improvement, however, is estimated to be about 40% in the uncontrolled watchful waiting studies, the randomized watchful waiting versus TURP study, and the combined placebo arms. The changes in peak flow rate and residual urine are similar, and similarly small, for these three groups as well. It becomes evident that 40% of patients report some improvement, and the minimal fluctuations of peak flow rate and residual urine represent the “placebo effect” background against which the more substantial changes in these parameters achieved by active treatment modalities must be seen.

Sham Control Arms of Device Treatment Trials for Benign Prostatic Hyperplasia. In recent years a multitude of minimally invasive device treatments for BPH have been developed and tested in randomized, sham-controlled, open, single-blind, or even double-blind trials. While the majority of these trials compare various types of heat treatments (transrectal or transurethral hyperthermia or thermotherapy) with a sham treatment, one investigator compared balloon dilation with “sham” cystoscopy alone in a randomized, double-blind trial involving 33 men with BPH (Lepor et al, 1992b).

The outcomes of the balloon dilation versus cystoscopy trial, one multicenter trial using transrectal or transurethral hyperthermia in comparison with a sham control (Abbou et al, 1994), and five transurethral microwave thermotherapy trials and their respective sham control arms can be used for analyses (Blute et al, 1993; Ogden et al, 1993a, 1993b; Bdesha et al, 1994; de la Rosette et al, 1994). Although the mean pretreatment severity score differed from trial to trial, the mean improvements in symptom severity in the sham groups ranged from 5.2% to 15.6% (on a 100% scale), while the active thermotherapy-treated patients had improvements ranging from 27.0% to 37.8%, or in most cases twice the improvement as the sham control. The multicenter hyperthermia trial represents the exception, in that the actively treated cohort had an

TABLE 103-12 Comparison of Outcomes after Watchful Waiting and Placebo Treatment

OUTCOMES	WATCHFUL WAITING	PLACEBO
Total no. of patients	456	1417
FLOW RATE		
Probability for flow rate increase	19.7%	35.8%
Probability for no change in flow rate	14.2%	41.1%
Probability for flow rate decrease	66.1%	23.1%
Mean pre- and post-treatment flow rate (mL/sec)	9.0-11.2	9.1-9.7
Difference (mL/sec) and percent change	+2.2/+24.4%	+0.6/+6.6%
RESIDUAL URINE		
Probability for decrease in residual urine	35.0%	38.0%
Probability for residual urine to remain unchanged	28.0%	26.1%
Probability for increase in residual urine	37.0%	35.9%
Mean pre- and post-treatment residual urine (mL)	115-152	87-76
Difference (mL) and percent change	+37/+32.2%	-11/-12.6%
SYMPTOMS		
Probability for symptom improvement	41.7%	41.7%
Probability for symptoms to remain unchanged	25.8%	53.5%
Probability for symptom worsening	32.4%	4.7%
Mean probability for symptom improvement*	41.7%	41.7%
90% CI for symptoms improvement*	30.8-54.8	26.3-65.1

CI, confidence interval.

*Calculated by confidence profile method using hierarchical Bayes (Eddy and Hasselblad, 1992).

Modified from McConnell JD, Barry MJ, Bruskewitz RC, et al. Benign prostatic hyperplasia: diagnosis and treatment. Clinical Practice Guideline No. 8. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1994. p. 1-17.

improvement similar to the sham control group, which is well within the range of the other sham control trials. The changes in peak urinary flow rate followed a similar pattern. With few exceptions the changes in peak flow rate were either very modest improvements or deteriorations (0.5, 0.6, -0.2, and -1.0 mL/sec), while the active treatment arms reported substantial improvements with the exception of the hyperthermia trial.

Placebo/Sham Effect and Baseline Symptom Severity. An area of considerable interest is the question as to what degree the placebo/sham effect depends on the baseline status of the patients. This could pertain to baseline symptom severity, baseline bother, quality of life, baseline flow rate, and all other imaginable parameters. Although few investigators have thus far reported data stratified by baseline parameters, results from a multicenter, placebo-controlled, 12-month α -blocker trial (terazosin) can be analyzed (Roehrborn et al, 1996). While the active drug-treated cohort had almost twice the improvement within each stratum, the placebo-treated patients had improvements ranging from 1.4 points (4.6%) to 7.5 points (21.4%) in order of increasing baseline severity score. The improvement for the placebo cohort overall was 3.3 points (10.6%).

A similar increase in the placebo effect with increasing baseline symptom severity has been reported for patients treated with finasteride in Phase III trials (Gormley et al, 1992). It might be speculated that the baseline symptom severity may also affect the sham effect seen in device trials. This phenomenon might be due to increased expectations in patients with more severe baseline symptoms, or simply due to a regression to the mean.

Natural History and Disease Progression in Long-Term Placebo Arms. The distinction between changes in parameters and rates of outcomes observed in placebo and sham control groups versus the longitudinal population-based studies becomes blurred when the placebo control is carried out over a period of time long enough to allow natural history changes to take place and confound the situation.

The Proscar Long-Term Efficacy and Safety Study (PLESS) followed a cohort of over 3000 men with moderate symptoms and enlarged prostate glands randomized to treatment with finasteride 5 mg daily versus placebo over 4 years (McConnell et al, 1998). In most control arms, both placebo and sham, the combined placebo effect interfering with the natural history of the disease is maintained for the entire duration of the study. In this 4-year trial, however, both the mean symptom score and mean maximum flow rate slowly drifted back to baseline after a typical initial placebo response (McConnell et al, 1998). The changes occurring in measurable parameters after the initial placebo effect has taken place thus can be considered to represent the natural history of the disease. The rates of outcomes such as AUR or surgery, as well as changes in prostate volume, which are less or not at all susceptible to the placebo effect, are also valid measures of the natural history of the disease.

The almost 1500 men in the placebo arm of this trial allowed for a detailed analysis of the placebo response and the subsequent natural history stratified by baseline parameters. It had been shown that in men with BPH there is a relatively strong correlation between prostate volume and serum PSA. In PLESS, only 10% of patients underwent baseline and yearly volume measurements by endorectal coil MRI. Based on the assumption that serum PSA would be a good proxy parameter for prostate volume, the analysis was initially performed for serum PSA and based on all 1500 men treated with placebo.

When stratifying the population by serum PSA into tertiles or thirds of patients with PSA levels from 0 to 1.3, 1.4 to 3.2, and 3.3 to 10 ng/mL, three distinctly different patterns regarding symptom score and maximum flow rate changes emerge (Fig. 103-19) (Roehrborn et al, 1999a). While the initial placebo response in the lowest PSA tertile for both symptom score and flow rate was maintained over the entire 4 years of follow-up, the middle tertile experienced a slow deterioration of symptoms back to baseline and in essence the natural history and progression of disease negated any

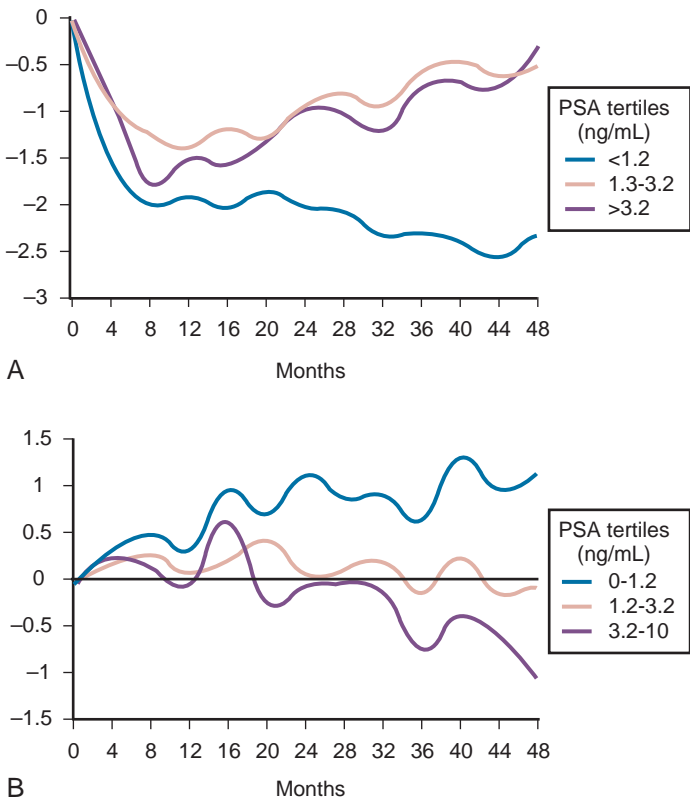


Figure 103-19. Mean changes for symptom score (A) and peak flow rate (B) in placebo-treated patients in Proscar Long-Term Efficacy and Safety Study stratified by baseline serum prostate-specific antigen (PSA) levels. (From Roehrborn CG, Boyle P, Gould AL, et al. Serum prostate-specific antigen [PSA] is a reliable surrogate for prostate volume. *Urology* 1999;53:581-9.)

flow rate gains. In the highest PSA tertile, the symptom score increased steadily over time following an initial placebo response of -1.5 points. Over the subsequent years, the score increased by 0.5 points/yr, bringing it at the end of the study back to the original baseline level. The initial response in terms of flow rate improvement was completely negated by the progression/natural history after 2 years, and at the end of the study, this group of patients registered a net worsening of the flow rate by a mean of -1.0 mL/sec (see Fig. 103-19B). Similar results regarding the changes in symptom and maximum flow rate over time were obtained when the 150 patients for whom prostate volume measurements were available were divided into tertiles (14 to 41 mL, 42 to 57 mL, 58 to 150 mL). PLESS also periodically assessed bother due to urinary symptoms, disease-specific quality of life, aspects of sexual function, and overall sense of well-being. Surprisingly, serum PSA at baseline also predicts, after an initial placebo response, the rate of deterioration of bother, quality of life, and certain aspects of sexual function (Bruskewitz et al, 1999) (Fig. 103-20).

The Medical Therapy of Prostatic Symptoms (MTOPS) study followed 3045 men treated with either placebo, doxazosin, finasteride, or combination doxazosin-finasteride therapy for 4 to 5 years and was designed as a progression study (Bautista et al, 2003; McConnell et al, 2003). The composite end point captured either a worsening of 4 points or more on the IPSS score verified twice within 4 weeks, AUR, socially unacceptable incontinence, recurrent urinary tract infection, or renal insufficiency due to BPH (Table 103-13). The worsening of 4 points or more was chosen to reflect a clinically meaningful worsening of LUTS symptomatology. Despite an overall numerical improvement in the IPSS by -4.9 points in the placebo group (intention-to-treat cohort), about 14% of placebo-treated patients experienced a verified worsening by 4

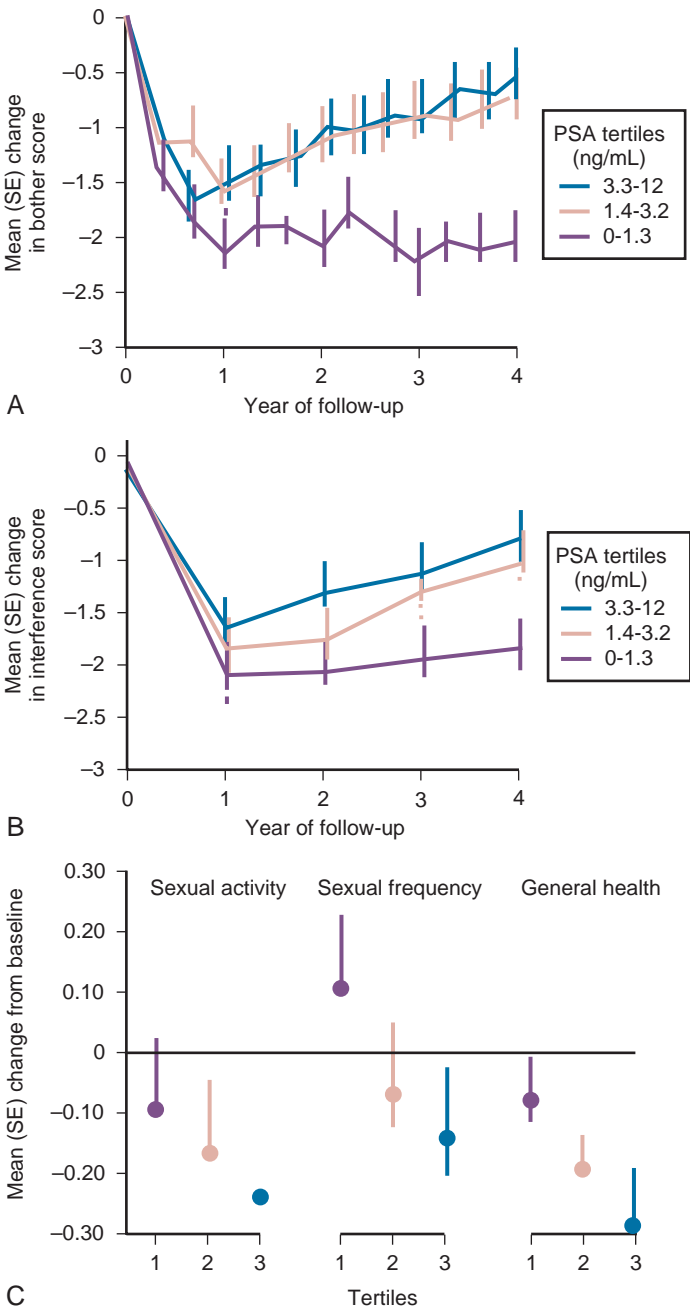


Figure 103-20. Mean changes for bother (A), for interference with activities of daily living (B), and for sexual activity, frequency, and perception of general health (C) in placebo-treated patients in Proscar Long-Term Efficacy and Safety Study stratified by baseline serum prostate-specific antigen (PSA). SE, standard error. (From Bruskewitz R, Girman CJ, Fowler J, et al. Effect of finasteride on bother and other health-related quality of life aspects associated with benign prostatic hyperplasia. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. *Urology* 1999;54:670-8.)

points or more over the course of the study for an incidence of 3.6 per 100 patient-years (see Table 103-13).

PLESS and its placebo control group allowed the study of natural history and disease progression in a cohort selected for moderate symptoms and other evidence of disease (in contrast to a population-based study) on the background of the initial combined placebo responses. In MTOPS, approximately 14% of placebo-treated patients experienced a 4-point or greater worsening in the IPSS over 4 years of follow-up.

TABLE 103-13 Clinical Progression of BPH in Placebo-Treated Patients in MTOPS

EVENT	RATE OVER DURATION OF STUDY	CUMULATIVE NUMBERS OF EVENTS AT 4 YEARS	CUMULATIVE INCIDENCE (95% CI) AT 4 YEARS
Clinical progression overall	4.5	122	17 (14-20)
≥4 points IPSS increase	3.6	97	14 (11-17)
Acute urinary retention	0.6	18	2 (1-4)
Socially unacceptable incontinence	0.3	6	<1 (0-1)
Urinary tract infections	0.1	1	<1 (0-1)
Renal insufficiency due to BPH	0.0	0	0
Invasive therapy due to BPH	1.3	37	5 (3-7)

BPH, benign prostatic hyperplasia; CI, confidence interval; IPSS, International Prostate Symptom Score; MTOPS, Medical Therapy of Prostatic Symptoms.

From McConnell J, Roehrborn CG, Bautista O, et al. The long-term effects of doxazosin, finasteride and the combination on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349:2385-96.

TABLE 103-14 Changes in Status of Symptom Severity from One Survey to the Next

SEVERITY	YEAR	NO. PATIENTS	SEVERITY IN FOLLOWING YEAR (%)			
			NONE	MILD	MODERATE	SEVERE
None	Baseline	293	83.6	12.3	2.7	1.4
	Year 1	223	83.9	9.0	2.2	4.9
Mild	Baseline	88	18.2	55.7	11.4	14.8
	Year 1	84	33.3	52.4	8.3	6.0
Moderate	Baseline	38	7.9	31.6	26.3	34.2
	Year 1	27	3.7	33.3	22.2	40.7
Severe	Baseline	35	22.9	17.1	11.4	48.6
	Year 1	31	9.7	22.6	12.9	54.8

Patients who underwent prostatectomy in preceding year were excluded from next survey.

Modified from Diokno AC, Brown MB, Goldstein N, et al. Epidemiology of bladder emptying symptoms in elderly men. *J Urol* 1992;148:1817-21.

Relationship between Placebo/Sham Effect and Perception of Improvement. Barry and associates (1995d) reported an important observation by assessing the relationship between changes in the AUASI and patients' global rating of improvement in over 1200 men treated in a medical treatment trial for BPH. They noted that a mean decrease in the AUASI of 3.1 points was associated with a slight improvement; however, this relationship was strictly dependent on the baseline AUASI. For patients to perceive a slight, moderate, or marked improvement, increasing drops in the AUASI were required with increasing baseline symptom severity. For patients starting with a lower versus higher baseline score, the drop had to be -7.4 versus -15.3 points, respectively, to perceive a marked improvement, -4.0 versus -8.7 for a moderate improvement, -1.9 versus -6.1 for a slight improvement, -0.2 versus -2.0 for no improvement, and +3.3 versus +1.2 for worsening to be perceived.

Longitudinal Population-Based Studies

Diokno and coworkers (1992) provided estimates of the prevalence, incidence, and remission of LUTS in 803 community-dwelling men age 60 years or older. The annual incidence of prostate surgery was 2.6% and 3.3% during years 1 and 2 of follow-up. The prevalence of at least one symptom was 35%, with annual incidence rates during years 1 and 2 of follow-up of 16.4% and 16.1%. Remission was also noted in that 22.9% of those having severe symptoms at baseline were asymptomatic at follow-up. Table 103-14 details the changes in symptom severity from one survey to the next. The tendency for fluctuation and spontaneous remission of symptoms as well as the

regression to the mean become evident from an analysis of these data.

Garraway and colleagues conducted a study of LUTS in four villages in the Forth Valley in Scotland in men 40 to 79 years old, defining BPH as a prostate volume of over 20 mL by TRUS and a maximum flow rate of less than 15 mL/sec, and applying a lower threshold to the symptom severity (Garraway et al, 1993a, 1993b; Guess et al, 1993; Tsang and Garraway, 1993). By this definition the prevalence of BPH increased at baseline from 14% in men in their 40s to 43% in men in their 60s, and about one-half of men reported interference with activities of daily living as a result of LUTS and BPH. One- and 3-year follow-up data have been reported (Lee et al, 1996). From baseline to 3 years the proportion of men with moderate symptoms increased from 34% to 45%, and significant increases in symptom level occurred for 8 of 12 symptoms queried as well as for the AUASI (increase from 6.37 to 7.88 from baseline to year 3, $P < .0001$) (Lee et al, 1996). Parallel to symptom frequency and severity, bothersomeness of symptoms increased over time (see Fig. 103-20), and the proportion of men reporting interference with two or more activities increased from 26% to 41%, with three or more activities from 18% to 27%, and with four or more activities from 15% to 18%. This study clearly demonstrated LUTS and BPH being a progressive disease, albeit with a very flat slope of progression (Fig. 103-21).

The most informative natural history study to date is the Olmsted County Study of Urinary Symptoms and Health Status among Men, which has given us much information about prevalence and severity of urinary symptoms, bother, worry and embarrassment, quality of life resulting from symptoms, and the

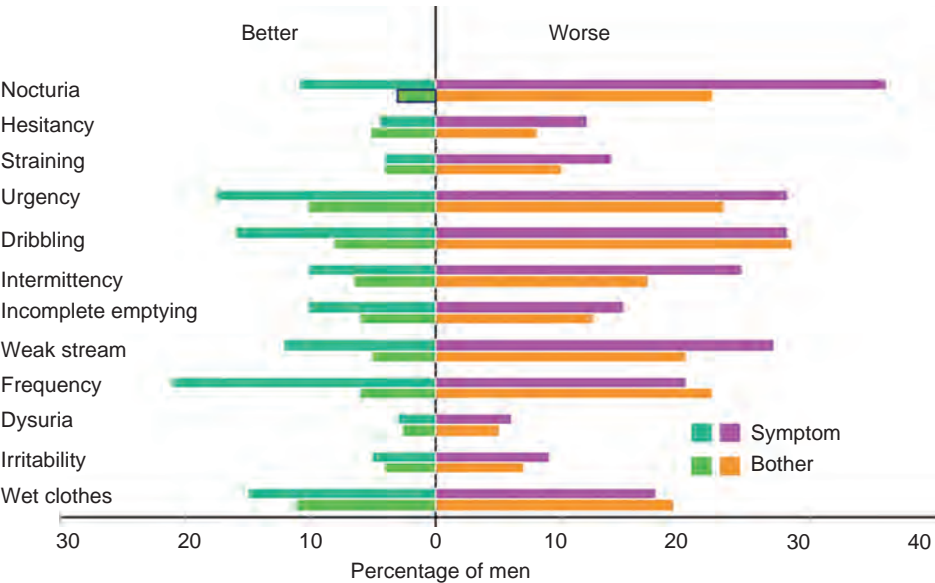


Figure 103-21. Changes in urinary symptoms and bothersomeness status between baseline and 3 years in a Scottish population-based study. (From Lee AJ, Russell EB, Garraway WM, et al. Three-year follow-up of a community-based cohort of men with untreated benign prostatic hyperplasia. *Eur Urol* 1996;30:11–7.)

TABLE 103-15 Change in LUTS Severity Classification: Age-Adjusted Percentage of Men and Women with LUTS Severity at Follow-up by LUTS Severity at Baseline

BASELINE (PREVALENCE)	FOLLOW-UP IN MEN				BASELINE (PREVALENCE)	FOLLOW-UP IN WOMEN			
	NONE	MILD	MODERATE	SEVERE		NONE	MILD	MODERATE	SEVERE
None (18.1)	26.8	69.9	2.8	0.5	None (13.7)	38.9	58.8	1.8	0.5
Mild (62.7)	12.2	77.0	10.3	0.5	Mild (67.4)	11.8	71.9	15.9	0.4
Moderate (18.4)	7.0	41.3	47.5	4.2	Moderate (17.0)	4.4	40.9	46.6	8.1
Severe (0.8)	0.8	1.0	36.7	61.5	Severe (1.9)	0	21.7	60.0	18.3

From Maserejian NN, Chen S, Chiu GR, et al. Treatment status and progression or regression of lower urinary tract symptoms in a general adult population sample. *J Urol* 2014;191:107–13.

relationship between symptoms and other parameters such as flow rates, prostate volume, and PSA (Oesterling et al, 1993; Girman et al, 1994, 1995; Guess et al, 1995; Jacobsen et al, 2003; Sarma et al, 2003; Rule et al, 2005).

With continued follow-up of this cohort, data have emerged regarding the longitudinal changes in symptoms and flow rate over time in this population-based study. Of 904 men reporting none to mild symptoms (AUASI 0 to 7 points) at baseline, 118 reported moderate to severe symptoms (AUASI >7 points) at 18 months, and 196 at 42 months' follow-up (Jacobsen et al, 1995b). However, 47 men who had developed moderate to severe symptoms at 18 months had no to mild symptoms at 42 months. At 42 months of follow-up, an average increase in the IPSS of 0.18 (95% CI 0.13 to 0.24) points per year of follow-up was recorded. The average annual symptom score slope and variability in slope increased with patient age at baseline from a mean of 0.05 ± 1.06 (standard deviation) per year among men in their forties to 0.44 ± 1.35 per year for men in their sixties, and decreased to 0.14 ± 1.42 per year for men in their seventies (Jacobsen et al, 1996). More recently, 92 months' data showed an annual change of 0.34 points/yr, with 31% of all men reporting at least a 3-point increase. The greatest annualized increase was observed in men in their sixties with 0.6 points/yr (Rhodes et al, 2000).

The BACH survey enrolled 5502 participants ages 30 to 79 years of black, Hispanic, or white race/ethnicity (Piccolo et al, 2014). In 5-year follow-up interviews with 4144 participants, symptom progression, defined as an increase in AUASI by greater than 3 points, was reported by 21% to 33% of participants, and regression

(decrease ≥ 3) by 30% to 44% of participants, most commonly women and Hispanics. Age and higher BMI were associated with progression (*P* < .01) but not regression (Maserejian et al, 2014) (Table 103-15).

Peak flow rate measurements in a subset of about 500 men from the Olmsted County Study showed a median peak urinary flow rate slope decrease of –2.1% per year (25th percentile –4.0, 75th percentile –0.6). Peak urinary flow rate declined more rapidly with decreasing baseline rate and increasing baseline age, prostate volume, and symptom severity (all *P* = .001). When the variables were simultaneously adjusted for each other, a rapid decline (negative slope 4.5% or greater per year) was more likely in men 70 years old or older and those with a flow rate less than 10 mL/sec at baseline compared to those 40 to 49 years old and those with a flow rate of 15 mL/sec or greater, respectively. Prostate volume and symptom severity were not statistically significant predictors of a rapid decline in peak urinary flow rate when variables were considered simultaneously (Roberts et al, 2000).

Based on TRUS, the growth of the prostate in these men 40 to 79 years old was estimated to be about 0.6 mL/yr or 6 mL per decade of life. However, prostate growth followed an exponential growth pattern, with a slope estimate of 0.4 mL/yr for men ages 40 to 59 years at baseline and of 1.2 mL/yr for those 60 to 79 years at baseline (Rhodes et al, 1995, 1999). An updated analysis revealed a median growth rate of about 1.9%/yr independent of age and symptoms. However, a higher baseline serum PSA and larger prostate volume predicted greater annualized volume increases.

Complications

Many of the complications of progressive BPH are rare, and much of the knowledge comes from studies of men presenting with such complications for treatment (i.e., cases) rather than observing cohorts of men for the development of complications.

Mortality

Between 1950 and 1954, 17 of 24 countries reported mortality rates of greater than 10 per 100,000, while between 1985 and 1989 data were available for 61 countries, with only one reporting a greater than 10 per 100,000 mortality rate (Boyle et al, 1996). If the mortality rates from 1950 were applied to 1990, 13,681 fewer deaths occurred in the United States alone than expected, a major but unheralded health care achievement.

Bladder Stones

In a large autopsy study the prevalence of bladder stones was eight times higher in men with a histologic diagnosis of BPH (3.4%) compared to controls (0.4%), but no increased incidence of ureteral or kidney stones was found (Grosse, 1990). In a study comparing watchful waiting and TURP in men with moderate symptoms, only 1 of 276 patients assigned to watchful waiting developed a bladder stone in 3 years of follow-up (Wasson et al, 1995). The self-reported rate of a bladder stone in a cross-sectional study in 2002 Spanish men was 0.7% (Hunter et al, 1996).

In clinical practice the risk of bladder stone development is small and screening is only indicated if clinical circumstances warrant it (e.g., hematuria, stuttering of urination).

Bladder Decomensation

Urologists search for a progression from a normal mucosa to advancing trabeculation and development of cellules and diverticula, with ultimate detrusor muscle failure in mind, when evaluating the bladder in men with BPH endoscopically. However, when the process starts, whether it really is related to BPH and obstruction, and when an intervention is necessary to prevent decomensation with resultant inability to void are unclear.

Biopsies from trabeculated, obstructed bladders show dense connective tissue deposition, a finding similar to that seen in animals experimentally obstructed (Gosling and Dixon, 1980; Levin et al, 1990, 2000; Chapple et al, 1991). However, bladder fibrosis is seen in both sexes with advancing age and may be a normal consequence of aging (Lepor et al, 1992a).

The critical question is whether or not delayed intervention might lead to progressive irreversible loss of bladder function and miss a window for cure. There is no direct evidence for this from longitudinal population or clinic patient studies. However, in a Department of Veterans Affairs (VA) cooperative study comparing watchful waiting with TURP, those patients who crossed over from the conservative arm to TURP later in the trial had not as significant an improvement in symptoms and flow rate compared to those who underwent TURP at the beginning after randomization (Flanigan et al, 1998).

Urinary Incontinence

Incontinence is one of the most feared complications from surgical intervention for BPH. While it may be the result of BPH secondary to overdistention of the bladder (overflow incontinence) or to detrusor instability estimated to affect up to one half or more of all obstructed patients (urge incontinence) (McConnell et al, 1994), it also is associated with aging, and in a community study an incidence of incontinence of 24% in men and 49% women over 50 years of age was reported (Roberts et al, 1998). In the VA cooperative study a 4% incidence of incontinence in both the surgical and conservative treatment arms was reported (Wasson et al, 1995). The self-reported rate of incontinence in a cross-sectional study in 2002

Spanish men was 6.1% (Hunter et al, 1996). In MTOPS the rate of socially unacceptable incontinence was 0.3 per 100 patient-years (McConnell et al, 2003).

Urinary Tract Infections

In older surgical series urinary tract infections (UTIs) constituted the main indication for surgical intervention in about 12% of patients (Holtgrewe et al, 1989; Mebust et al, 1989). Although one might intuitively assume that increased amounts of residual urine would predispose to the development of UTIs, clear evidence is lacking. Hunter and colleagues (1996) quoted a rate of 5.2% self-reported episodes of UTI in a cross-sectional survey of 2002 men in Madrid, Spain. The best data to date come from the MTOPS study, where the incidence of UTIs in the placebo-treated patients was only 0.1 per 100 patient-years (McConnell et al, 2003).

Upper Urinary Tract Deterioration and Azotemia

The AHCPR BPH guidelines reported a mean of 13.6% (range from 0.3% to 30%) of patients presenting for TURP with evidence of renal failure based on predominantly older studies (McConnell et al, 1994). Patients in renal failure have an increased risk for complications following TURP compared to patients with normal renal function (25% versus 17%) (Holtgrewe et al, 1989; Mebust et al, 1989), while the mortality increases up to sixfold (Holtgrewe and Valk, 1962; Melchior et al, 1974a, 1974b). In the large database of patients who had upper tract imaging prior to surgery, 7.6% of 6102 patients in 25 series had evidence of hydronephrosis, of whom one third had renal insufficiency (McConnell et al, 1994).

The term *silent obstruction* or *silent "prostatism"* has been used to describe the constellation of asymptomatic patients who eventually develop renal failure resulting from BOO, a situation both rare and important (Mukamel et al, 1979). In the VA cooperative study, only 3 of 280 surgically treated patients and 1 of 276 patients in the watchful waiting arm developed renal azotemia, defined as a doubling of serum creatinine from baseline (Wasson et al, 1995). In none of the cohort or population-based studies have cases of renal failure clearly attributable to BPH been reported. However, the self-reported rate of an episode of renal failure in a cross-sectional study in 2002 Spanish men was 2.4% (Hunter et al, 1996).

In MTOPS, there was not a single case of renal insufficiency resulting from BPH in over 3000 men followed for over 4 years (McConnell et al, 2003). However, one has to be careful not to overinterpret these findings. Participants in MTOPS were screened at baseline, and one might argue that some at higher risk for developing renal failure were excluded from participation.

Hematuria

It has always been recognized that patients with BPH might develop gross hematuria and form clots with no other cause being identifiable. Recent evidence suggests that, in those patients predisposed to hematuria, the microvessel density is higher compared to controls. Some renewed interest in the issue of BPH-related hematuria stems from the observation that finasteride appears to be a reasonable first-line therapy, apparently influencing the expression of VEGF (DiPaola et al, 2001). The self-reported rate of hematuria in a cross-sectional study in 2002 Spanish men was 2.5% (Hunter et al, 1996). Precise population estimates and incidence rates are not available, and the clinical management is dictated by the circumstances.

Acute Urinary Retention

Acute urinary retention (AUR) is for several reasons one of the most significant complications or long-term outcomes resulting from BPH. It has in the past represented an immediate indication for surgery. Between 25% and 30% of men who underwent TURP had AUR as their main indication in older series (Holtgrewe et al, 1989; Mebust et al, 1989), and today most patients failing to void

TABLE 103-16 Descriptive Studies on the Incidence of Acute Urinary Retention

AUTHOR/ YEAR	DESCRIPTION OF COHORT	CASES	COHORT	YEARS OF FOLLOW-UP	PERCENT OVERALL	PERCENT/ YEAR	IR/1000 PATIENT-YEARS	95% CI
Ball et al, 1981	Watchful waiting study	2	107	5	1.9	0.37	3.7	
Craigien et al, 1969	Watchful waiting study						15.0	
Birkhoff et al, 1976	Watchful waiting study	10	26	3	39	13	130	
Wasson et al, 1995	TURP vs. watchful waiting VA cooperative study	8	276	3	2.8	0.9	9.6	
Hunter et al, 1996	Self-reported prior events in Spanish men	102	2002	?	5.1		50.9	
Barry et al, 1997a	Prostatectomy candidates	40	500	4	8	2.5	25	
Meigs et al, 1999	Health Professionals Followup Study, self-reported	82	6100	3	1.3		4.5	3.1-6.2
Roberts et al, 1997a	Community cohort 40-49 years old	57	2115	4			6.8	5.2-8.9
McConnell et al, 1998	Placebo group of PLESS	99	1376	4	7.2	1.8	18	
Andersen et al, 1997	Placebo groups of 2-year BPH studies	57	2109	2	2.7	1.35	13.5	

BPH, benign prostatic hyperplasia; CI, confidence interval; IR, incidence rate; PLESS, Proscar Long-Term Efficacy and Safety Study; TURP, transurethral resection of the prostate; VA, Veterans Administration.

after an attempt at catheter removal still undergo surgery. For this reason alone, AUR is from an economical standpoint as well as from the viewpoint of the patient an important and feared event. For the patient it presents as the inability to urinate without increasing pain, eventually a visit to the emergency room, catheterization, follow-up visits to the physicians, an attempt at catheter removal, and either recovery of spontaneous voiding or surgery, both a painful and time-consuming process. In older literature the risk of recurrent AUR was cited as being 56% to 64% within 1 week of the first episode, and 76% to 83% in men with diagnosed BPH (Breum et al, 1982; Klarskov et al, 1987; Hastie et al, 1990).

The etiology of AUR is poorly understood, and obstructive, myogenic, and neurogenic causes all may play a role (Kaplan et al, 2008). Prostate infection, bladder overdistention (Powell et al, 1980), excessive fluid intake, alcohol consumption, sexual activity, debility, and bed rest have all been mentioned (Stimson and Fihn, 1990). Prostatic infarction has been suggested as being an underlying event causing AUR (Graversen et al, 1989). Spiro and colleagues (1974) found evidence for infarction in 85% of prostates removed for AUR versus 3% of prostates in men having surgery for symptoms only. In contrast, in a study by Jacobsen and coworkers (1997) there was no evidence of infarction in six prostatectomy specimens removed from men who had surgery for AUR. Anjum and associates (1998) found fundamentally similar rates of infarction in 35 men with AUR versus 35 men with no AUR (1.9% versus 3.0%).

From a clinical and prognostic point of view, spontaneous AUR should be separated from precipitated AUR, although this is by no means consistently done in the literature. Precipitated AUR refers to the inability to urinate following a triggering event such as non-prostate-related surgery, catheterization, anesthesia, ingestion of medications with sympathomimetic or anticholinergic effects or antihistamines, or other events. All other

AUR episodes are classified as spontaneous (Roehrborn et al, 2000a). The importance of differentiating the two types of AUR becomes clear when evaluating the ultimate outcomes of patients. Following spontaneous AUR, 15% of patients had another episode of spontaneous AUR and a total of 75% underwent surgery, whereas after precipitated AUR, only 9% had an episode of spontaneous AUR and 26% underwent surgery (Roehrborn et al, 2000a).

Descriptive Epidemiology (Table 103-16). Older estimates of occurrence of AUR range from 4 to 15 to as high as 130 per 1000 person-years, as calculated by Jacobsen and colleagues (1997) based on published studies (Craigien et al, 1969; Birkhoff et al, 1976; Ball et al, 1981). This leads to 10-year cumulative incidence rates ranging from 4% to 73%. The self-reported rate of AUR in a cross-sectional study in 2002 Spanish men was 5.1% (Hunter et al, 1996).

More recent data from carefully controlled studies in better defined populations shed additional light on the incidence rates in community-dwelling men and clinical BPH populations. AUR occurred in the VA cooperative study over 3 years in 1 man after TURP and in 8 of 276 men in the watchful waiting arm, for an incidence rate of 9.6 per 1000 person-years (Wasson et al, 1995). Barry and coworkers (1997a) reported outcomes of 500 men, diagnosed with BPH by urologists, who were candidates for prostatectomy by established criteria but elected to be followed conservatively. In 1574 person-years, 40 episodes of AUR occurred at a constant rate throughout the 4 years of follow-up for an incidence rate of 25 per 1000 person-years.

During 15,851 person-years of follow-up in the Health Professionals Followup Study, 82 men reported an episode of AUR for an incidence rate of 4.5 per 1000 person-years (95% CI 3.1 to 6.2) (Meigs et al, 1999). Of the 2115 men ages 40 to 79 years in the Olmsted County Study, 57 had a first episode of AUR during 8344 person-years of follow-up (incidence rate of 6.8 per 1000 person-years, 95% CI 5.2 to 8.9) (Jacobsen et al, 1997).

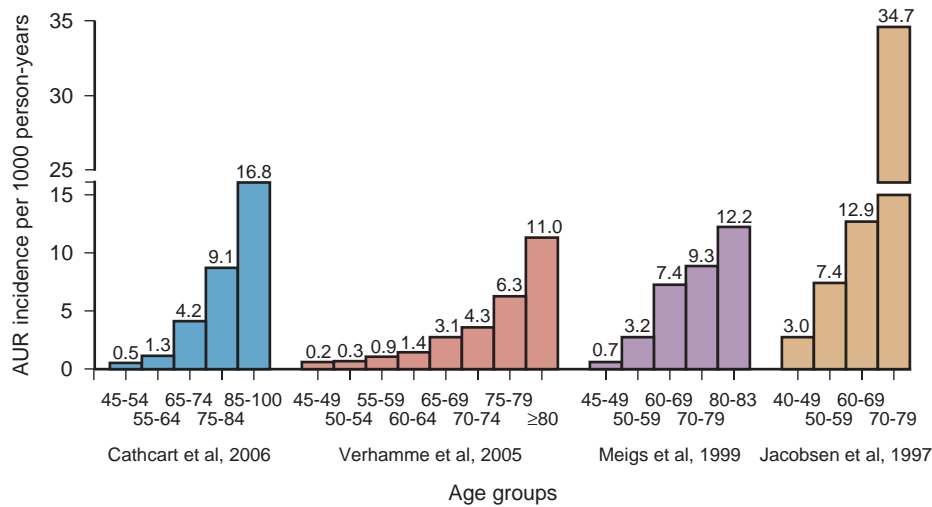


Figure 103-22. Increase in incidence of acute urinary retention (AUR) with age in four large studies. (From Kaplan SA, Wein AJ, Staskin DR, et al. Urinary retention and post-void residual urine in men: separating truth from tradition. *J Urol* 2008;180:47–54.)

The first excellent data from men diagnosed with BPH stem from PLESS (McConnell et al, 1998). In PLESS, 1376 placebo-treated men with enlarged prostates and moderate symptoms had complete follow-up over 4 years, of whom 99 experienced an episode of AUR for a calculated incidence rate of 1.8 per 100 person-years. The placebo treatment groups from three 2-year studies with a similar patient population were meta-analyzed by Boyle (1998). Of 2109 patients, 57 experienced AUR over the 2 years with a constant hazard for an incidence rate of 14 per 1000 person-years. In the MTOPS placebo group, the incidence rate was 0.6 per 100 patients-years for a cumulative incidence of 2%.

Analytical Epidemiology

Age. Several well-controlled studies provided considerable insights into the risk factors for AUR. Perhaps the most significant of these risk factors is age. Studies from European countries and the United States demonstrate a nearly linear increase in the age-specific incidence of AUR for men ranging in age from 40 to over 80 years (Jacobsen et al, 1997; Meigs et al, 1999; Verhamme et al, 2005; Cathcart et al, 2006) (Fig. 103-22).

Lower Urinary Tract Symptoms. Increased symptom severity is associated with increased risk of AUR in several large population-based or cohort studies (Table 103-17). In the Health Professionals Followup Study in men with mild symptoms, incidence of AUR increased from 0.4 per 1000 person-years for those 45 to 49 years old to 7.9 per 1000 person-years for those 70 to 83 years old. In men with symptom scores of 8 to 35, rates increased from 3.3 per 1000 person-years for those 45 to 49 years old to 11.3 per 1000 person-years for those 70 to 83 years old. Men with a clinical diagnosis of BPH and a symptom score of 8 or greater had the highest rates (age-adjusted incidence, 13.7 per 1000 person-years). All seven LUTS comprising the AUASI individually predicted AUR. The sensation of incomplete bladder emptying, having to void again after less than 2 hours, and a weak urinary stream were the best independent symptom predictors. Use of medications with adrenergic or anticholinergic side effects also predicted AUR (Meigs et al, 1999).

The Olmsted County Study analyses focused on age, symptom severity, maximum flow rate, and prostate volume (Jacobsen et al, 1997). Incidence rates per 1000 person-years for men in their 40s to their 70s increased from 2.6 to 9.3 if they had mild symptoms and from 3.0 to 34.7 if they had more than mild symptoms (see Table 103-17).

Urodynamic Parameters. The RR for AUR increased for older men, men with moderate to severe symptoms (3.2 times), those with a flow rate under 12 mL/sec (3.9 times), and those with a prostate volume greater than 30 mL by TRUS (3.0 times), all compared to a baseline risk of 1.0 for the corresponding groups

TABLE 103-17 Incidence of AUR by Patient Age and AUASI Score in Two Population-Based Studies

AGE GROUP	NO. AUR EVENTS/1000 MAN-YEARS (95% CI)	
	HEALTH PROFESSIONALS FOLLOWUP STUDY*	OLMSTED COUNTY STUDY OF URINARY SYMPTOMS AND HEALTH STATUS AMONG MEN†
AUASI ≤7		
40-49		2.6 (0.8-6.0)
45-49	0.4 (0.02-1.8)	
50-59	1.2 (0.4-2.6)	1.7 (0.3-4.8)
60-69	3.6 (1.9-6.1)	5.4 (2.0-11.6)
70-79		9.3 (3.4-20.3)
70-83	7.9 (4.1-13.5)	
AUASI >7		
40-49		3.0 (0.4-10.8)
45-49	3.3 (0.2-14.4)	
50-59	10.0 (5.4-16.8)	7.4 (2.7-16.1)
60-69	14.1 (9.4-20.2)	12.9 (6.2-23.8)
70-79		34.7 (20.2-55.5)
70-83	11.3 (6.4-18.3)	

AUASI, American Urological Association Symptom Index; AUR, acute urinary retention; CI, confidence interval.

*Total of 82 AUR episodes in 6100 men with a crude incidence of 5.2/1000 patient-years (95% CI 4.1 to 6.4) in 15,851 patient-years of follow-up.

†Total of 57 AUR episodes in 2115 men with an overall incidence of 6.8/1000 patient-years (95% CI 5.2 to 8.9) in 8344 patient-years of follow-up.

From Kaplan SA, Wein AJ, Staskin DR, et al. Urinary retention and post-void residual urine in men: separating truth from tradition. *J Urol* 2008; 180:47–54.

(Fig. 103-23). The highest RR by proportional hazard models exists for 60- to 69-year-old men with more than mild symptoms and a flow rate of less than 12 mL/sec (10.3 times), and for 70- to 79-year-old men except if they had mild symptoms and a flow rate over 12 mL/sec. All other stratifications of men over 70 years had RRs ranging from 12.9 to 14.8 times (all compared to men 40 to

49 year old with mild symptoms and a flow rate over 12 mL/sec, for which the baseline risk is 1.0).

Prostate Volume and Serum PSA. While age in community-dwelling men is an important risk factor, in BPH trial populations of men who already are diagnosed with BPH, other factors can be analyzed. In the placebo groups of three 2-year studies (Marberger et al, 2000) and a 4-year study (PLESS) (McConnell et al, 1998; Kaplan et al, 2000; Roehrborn et al, 2000a) prostate volume, serum PSA, and symptom severity all were predictors of AUR episodes.

Over 4 years in PLESS, the incidence increased from 5.6% to 7.7% in men with a serum PSA of under 1.4 ng/mL from mild to severe symptoms, and from 7.8% to 10.2% for those with a serum PSA of over 1.4 ng/mL (Kaplan et al, 2000). In the 2-year

studies the rate of AUR was eightfold higher in those with a serum PSA of over 1.4 ng/mL (0.4% versus 3.9%), and threefold higher if the prostate volume was over 40 mL (1.6% versus 4.2%) (Marberger et al, 2000; Roehrborn et al, 2001). A detailed analysis showed a near-linear increase in risk for AUR with increasing thresholds of serum PSA (Fig. 103-24) in PLESS, an observation that applies to both spontaneous and precipitated AUR (Roehrborn et al, 1999c). The risk for both types of AUR increases with increasing serum PSA as well as prostate volume stratified by tertiles (Fig. 103-25). Similar observations were made in MTOPS, where the risk for AUR increased with increasing prostate volume as well as increasing baseline serum PSA (Fig. 103-26), as well as in the 2-year Phase III studies comparing dutasteride with placebo (Roehrborn

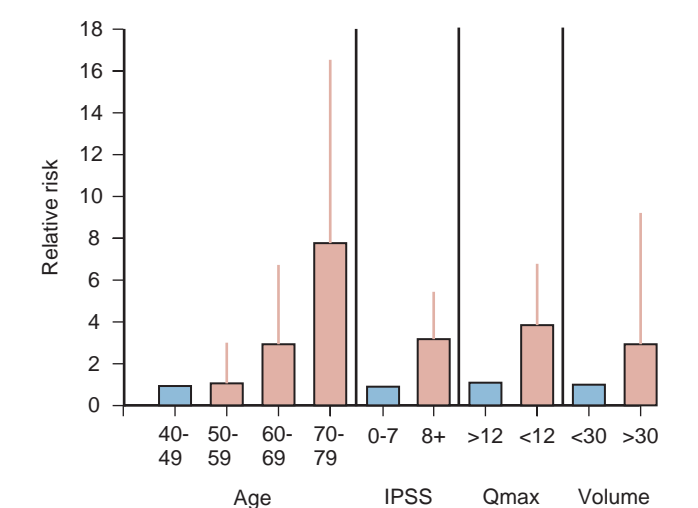


Figure 103-23. Relative risk of acute urinary retention in Olmsted County Study of Urinary Symptoms and Health Status among Men by age, symptom severity (IPSS), peak flow rate (Qmax), and prostate volume. The shaded column represents the baseline and a relative risk of 1.0; the vertical line represents the 95% confidence interval. IPSS, International Prostate Symptom Score. (Data from Jacobsen SJ, Jacobson DJ, Girman CJ, et al. Natural history of prostatism: risk factors for acute urinary retention. *J Urol* 1997;158:481–7.)

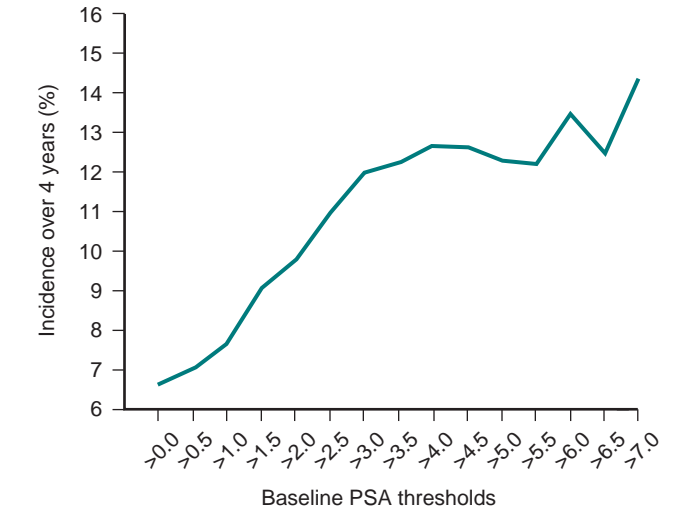


Figure 103-24. Incidence of spontaneous or precipitated acute urinary retention in the Proscar Long-Term Efficacy and Safety Study over 4 years stratified by increasing thresholds of serum prostate-specific antigen (PSA) at baseline. (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. *Urology* 1999;53:473–80.)

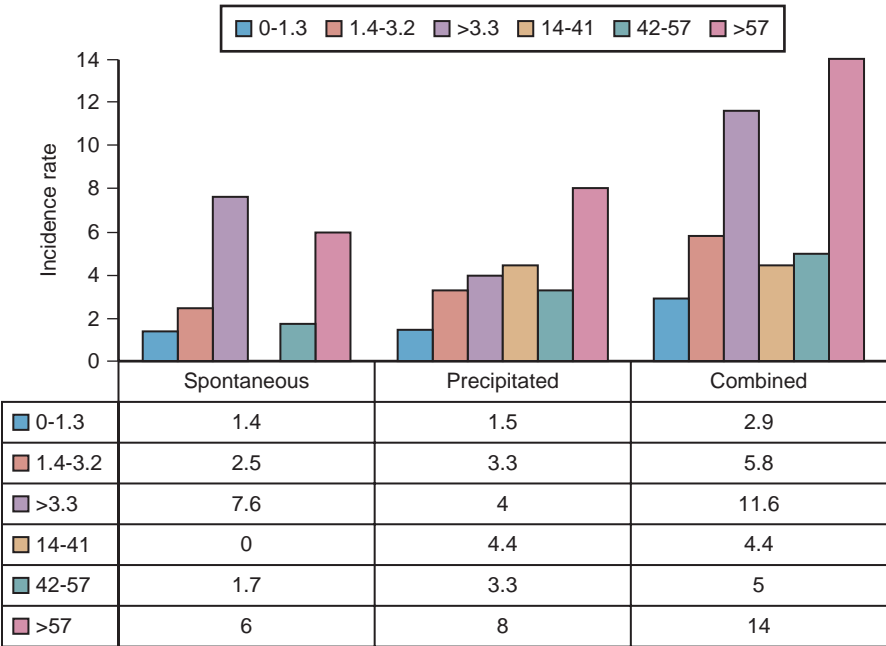


Figure 103-25. Spontaneous, precipitated, or combined acute urinary retention incidence over 4 years in the Proscar Long-Term Efficacy and Safety Study stratified by tertiles of serum prostate-specific antigen or prostate volume at baseline. (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. *Urology* 1999;53:473–80.)

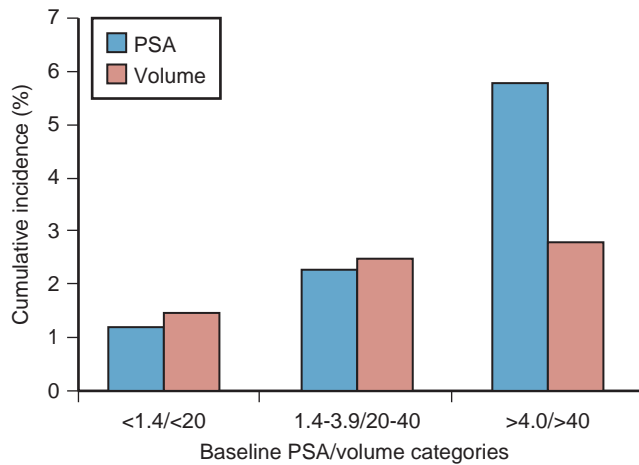


Figure 103-26. Cumulative incidence of acute urinary retention in placebo-treated patients in the Medical Therapy of Prostatic Symptoms study stratified by baseline prostate volume and baseline serum prostate-specific antigen (PSA). (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. *Urology* 1999;53:473–80.)

et al, 2002). An analysis of over 100 possible outcome predictors alone or in combination revealed a combination of serum PSA, urinating more than every 2 hours, symptom problem index, maximum urinary flow rate, and hesitancy as being only slightly superior to PSA alone in predicting AUR episodes (Roehrborn et al, 2001).

SURGERY FOR BENIGN PROSTATIC HYPERPLASIA

Both surgery and AUR represent distinct end points in the disease progression of BPH. There are, however, distinct differences. AUR is an outcome mandating management, and surgery is one of the commonly employed management styles. AUR is probably one of the clearer indications for surgery, leaving the treating physician little choice in a patient who failed a trial without catheter. However, most patients undergo surgery not for AUR but for symptoms (Holtgrewe et al, 1989). Depending on local practice pattern, AUR accounts for 5% to over 30% of the indications for surgery. AUR can be compared to a bone fracture. It is impossible for the physician in his or her interaction with the patient to increase or decrease the probability for that outcome to occur. Furthermore, once it has occurred, no interaction or consultation can undo it. In contrast, it is easy to see how patients can be influenced in their decision to undergo surgery by the consultation with the physician. The interaction style, the quoted probabilities of beneficial and harmful outcomes to occur, and many other factors cause considerable variability in the incidence rates of prostate-related surgery, an observation that caused the AHCPR to develop guidelines for the treatment of BPH (Wennberg et al, 1988). This situation is similar to that for myocardial infarction (MI) and coronary artery bypass graft (CABG). The analytical epidemiology of MIs is well understood, and risk factors are characterized. Not all MIs result in CABGs, and in fact CABGs are frequently performed for indications other than a recent MI. Consequently, there is abundant literature focusing on the geographic variation in the usage of CABG. From this brief discussion it becomes clear that surgery for BPH is a softer end point than AUR from an epidemiologic point of view, and data on rates of prostatectomy need to be interpreted in light of variation in its use, from provider to provider, region to region, health care plan to health care plan, and over time.

KEY POINTS: EPIDEMIOLOGY AND NATURAL HISTORY

- There is no globally accepted epidemiologic definition of BPH, and thus prevalence and incidence rates must be viewed in the context of the definitions chosen by the investigator reporting the data.
- Despite the significantly different proportion of men admitting to moderate to severe symptoms, a clear trend toward an increase in symptom scores with advancing age is noticeable in all reported studies.
- In general, in all cross-sectional studies prostate volume as assessed by TRUS has been found to increase slowly but steadily with advancing age.
- Analytical epidemiologic data suggest a limited role of classical determinants of the disease such as religion, socioeconomic factors, sexual activity, alcohol intake, hypertension, dietary factors, and others. There is conflicting evidence regarding smoking and some evidence suggesting dietary factors, obesity, and increased BMI as determinants of disease severity.
- All relevant parameters such as symptom severity and frequency, bother, interference, disease-specific HRQOL, maximum flow rate, and prostate volume tend to worsen with advancing age. However, reported correlations between these parameters as well as urodynamic pressure-flow studies are in general weak, with some exceptions. Strong correlations exist between measures of symptom severity and frequency (IPSS), bother, disease-specific HRQOL, and interference scores.
- The natural history of the disease has been studied in many longitudinal population-based studies as well as in placebo and sham control groups of treatment trials of men diagnosed with the condition. These studies suggest, in general, a worsening of LUTS and BPH with time. There are several key baseline parameters allowing a stratification of patients according to the risk of progression. Age, symptom severity, flow rate, prostate size, and serum PSA are useful predictors of the risk of progression.
- Complications of LUTS and BPH such as mortality, urinary tract infections, bladder decompensation, bladder stones, hematuria, urinary incontinence, upper urinary tract deterioration with renal insufficiency, and others are, in general, rare in properly supervised patients.
- The two most significant progression events are AUR and the need for BPH-related surgery. Although not exceedingly common, there is a significant baseline incidence rate and the risk is cumulative; that is, with increasing time of observation the incidence rate increases linearly.
- The risk of AUR and need for surgery is to some degree predictable from baseline parameters with advancing age, increased prostate size, and higher serum PSA levels representing the most significant risk factors.

Of all prostate surgeries, TURP and laser ablation of the prostate are still clearly the most common procedures and the best studied ones. Cross-sectional descriptive data on incidence rates are available from the Medicare database. While in 1962 TURP constituted over 50% of all major surgeries performed by American urologists, this number had dropped to 38% by 1986 (Holtgrewe et al, 1989; Mebust et al, 1989). Although the number of TURPs performed on Medicare patients declined from an all-time peak of 258,000 in 1987 to 168,000 in 1993—a reduction by 34%—it remains second only to cataract surgery on the list of Medicare's most costly surgical procedures. A 20% sample of Medicare beneficiaries was examined to further specify rates of TURP in the United States. In 1990, the rates of TURP (including all indications) were approximately 25, 19, and 13 per 1000 for men over the age of 75, 70 to 74, and 65 to 69, respectively. The 30-day mortality following TURP for the

treatment of BPH decreased from 1.20% in 1984 to 0.77% in 1990 (Lu-Yao et al, 1994). Compared to 1984 to 1990, age-adjusted rates of TURP for BPH during 1991 to 1997 declined further by approximately 50% for white (14.6 to 6.72 per 1000) and 40% for black (11.8 to 6.58 per 1000) men (Wasson et al, 2000). Medicare databases are only relevant to those men over 65 years enrolled in Medicare, and therefore are less interesting from a longitudinal epidemiologic point of view.

Older series of the natural history of BPH, such as the one reported by Craigen and colleagues (1969) projected somewhat unrealistic estimates of 35% incidence of prostatectomy at 1 year and 45% at 7 years. Diokno and coworkers (1992) reported an annual incidence rate of 2.6% and 3.3% for years 1 and 2 in his cohort of men followed longitudinally. Frequency, hesitancy, straining, and an interrupted stream were all associated with an increased risk.

The first study of substantial quality reporting on incidence rates and risk factors of prostate surgery was the Baltimore Longitudinal Study of Aging (Arrighi et al, 1990, 1991; Guess et al, 1990). Over 1000 men were followed for 30 years with yearly symptom assessments, questionnaires, and examinations. Age, incomplete emptying, and change in size and force of stream were all independently associated with the risk of prostate surgery, as was a reportedly enlarged prostate by DRE. Of 464 men without risk factors, only 3% required surgery during follow-up. For men with one risk factor the cumulative incidence was 9%, for those with two risk factors 16%, and for those with three risk factors 37%. In the VA Normative Aging Study, a similar study, nocturia and hesitancy emerged as independent predictors of surgery in 1868 men ages 49 to 68 followed for over 20 years (Epstein et al, 1991). Age and five LUTS (dysuria, incontinence, trouble initiating flow, nocturia, and slow stream) were associated with the risk of surgery in 16,219 men over 40 years enrolled in the Kaiser Permanente Health Plan in California, of whom 1027 men underwent prostatectomy over 12 years of follow-up (Sidney et al, 1991a, 1991b).

In the VA cooperative trial comparing surgery with watchful waiting, 65 of 276 (24%) patients assigned to watchful waiting crossed over to surgery within 3 years of follow-up, of whom 20 met predefined end points (azotemia, high residuals, incontinence, or high symptom scores). High baseline bother score was a strong predictor of requiring surgery (Wasson et al, 1995).

The probability of undergoing surgery over 4 years increased from 10% in those men diagnosed with BPH who had mild symptoms to 24% in those with moderate and 39% in those with severe symptoms at baseline, as reported in a natural history and observation study by Barry and coworkers (1997b).

The Olmsted County Study and the placebo-treated patients from the PLESS study provide additional insights into the risk factors for undergoing prostate surgery in either community-dwelling men or men enrolled in a BPH treatment trial.

In the Olmsted County Study, during more than 10,000 person-years of follow-up 167 men were treated, yielding an overall incidence of 16.0 per 1000 person-years. There was a strong age-related increase in risk of any treatment from 3.3 per 1000 person-years for men 40 to 49 years old to more than 30 per 1000 person-years for those 70 years old or older. Men with moderate to severe symptoms, depressed peak urinary flow rates (<12 mL/sec), enlarged prostate (>30 mL), or elevated serum PSA (≥ 1.4 ng/mL) had about four times the risk of BPH treatment as those who did not. After adjustment for all measures simultaneously, an enlarged prostate (hazard ratio 2.3, 95% CI 1.1 to 4.7), depressed peak flow rate (hazard ratio 2.7, 95% CI 1.4 to 5.3), and moderate to severe symptoms (hazard ratio 5.3, 95% CI 2.5 to 11.1) at baseline each independently predicted subsequent treatment. Overall nearly 1 in 4 men received treatment in the eighth decade of life. These data suggest that men with moderate to severe LUTS, impaired flow rates, or enlarged prostates are more likely to undergo treatment, with increases in risk of similar magnitude to those associated with adverse outcomes such as AUR (Jacobsen et al, 1999) (see Fig. 103-23).

Over 1500 patients with moderate LUTS and enlarged prostate glands were followed in the PLESS study on placebo for 4 years. Of these, 10% or 2.5% per year underwent surgery for BPH (McConnell et al, 1998). While the hazard of undergoing surgery was linear (i.e., it remained constant throughout the duration of the study), it was different when patients were stratified by either prostate volume or serum PSA in tertiles at the beginning of the study (Fig. 103-27). Similar to the incidence of AUR, the rates of surgery increased from 6.2% to 14.6% for patients in the lowest to the highest PSA tertile, and from 6.7% to 14.0% for patients in the lowest to the highest prostate volume tertile.

In MTOPS, the incidence of invasive therapy for BPH in the placebo group increased nearly linearly when stratifying by baseline serum PSA or prostate volume (Fig. 103-28) (McConnell et al, 2003).

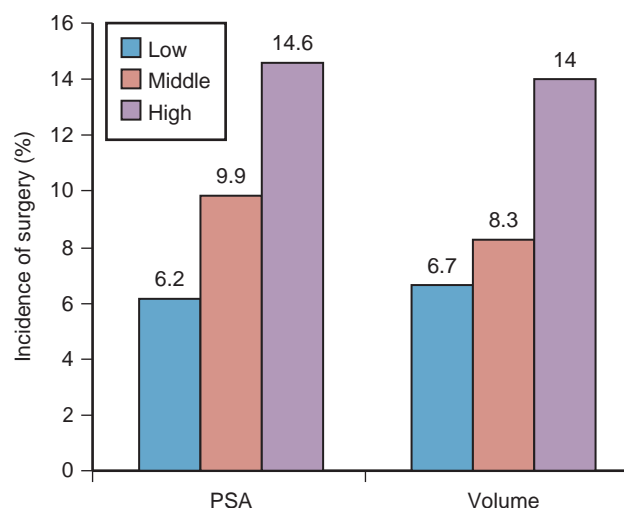


Figure 103-27. Incidence of surgery stratified by tertiles of serum prostate-specific antigen (PSA) and prostate volume in placebo-treated patients in the Proscar Long-Term Efficacy and Safety Study. (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. Urology 1999;53:473-80.)

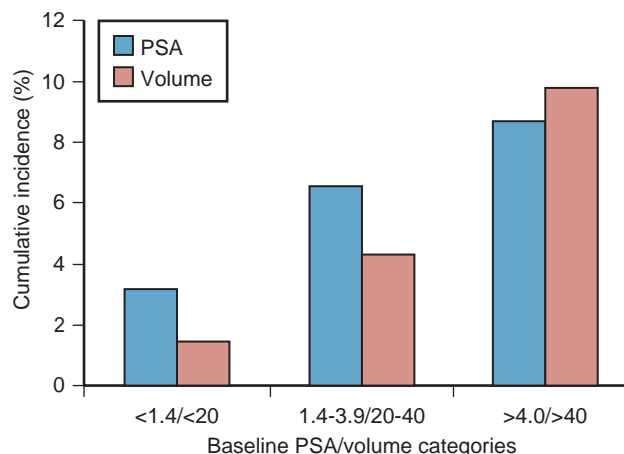


Figure 103-28. Cumulative incidence of invasive therapy (surgery) for benign prostatic hyperplasia in placebo-treated patients in the Medical Therapy of Prostatic Symptoms study stratified by baseline prostate volume and baseline serum prostate-specific antigen (PSA). (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. Urology 1999;53:473-80.)

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Diagnosis

Assessing the Effectiveness and Safety of Medical Therapy for Lower Urinary Tract Symptoms

Nonsurgical Therapy for Benign Prostatic Hyperplasia

Medical Therapy for Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia

Therapy with α -Adrenergic Blockers

Androgen Manipulation

Combination Therapy with α -Blocker and 5 α -Reductase Inhibitor

Anticholinergic (Antimuscarinic) Receptor Blockers

Phosphodiesterase Inhibitors

Phytotherapy

Acute Urinary Retention

Future Strategies for Nonsurgical Therapy for Male Lower Urinary Tract Symptoms

The term *benign prostatic hyperplasia* (BPH) has had very different connotations over the last 20 years. To the urologist, pathologist, radiologist, patient, and pharmaceutical companies it has had varying and often confusing meanings and definitions. It is important, however, that terminology be clear. Correctly speaking, BPH is a microscopic diagnosis characterized by cellular proliferation of the stromal and epithelial elements of the prostate, made by a pathologist. The radiologist or urologist may scan the prostate either with ultrasound or with three-dimensional imaging studies and confirm prostate enlargement, but this should be described as *benign prostatic enlargement* (BPE) (Haas and Resnick, 2000). To the urodynamicist, the hallmark of synchronous elevation of voiding pressure and a low urinary flow rate should be described as *bladder outlet obstruction* (BOO) (Nitti, 2000).

Most important, we need to move away from the practice of describing the constellation of lower urinary tract signs and symptoms that develop in the male population in association with aging and prostatic enlargement as BPH or clinical or symptomatic BPH and move toward the universal use of the term *lower urinary tract symptoms* (LUTS) to describe the clinical or symptomatic condition with which we are dealing (Abrams, 1994). The patient himself is typically concerned about the impact of his LUTS on quality of life rather than the presence of cellular proliferation, prostatic enlargement, or elevated voiding pressures. The transition from *clinical BPH* to *LUTS*, however, has been very variable over the last 20 years with regard to its adoption in different countries, with gradual acceptance by most national and international guidelines (Chapple and Abrams, 2013; Oelke et al, 2013). This transition has been delayed by the strong adoption by the pharmaceutical companies of BPH as a clinical syndrome and the acceptance by many of the regulatory authorities, such as the U.S. Food and Drug Administration (FDA), of the same terminology.

What we may have called *microscopic BPH* in the past is true histologic BPH; macroscopic BPH should be categorized as BPE, and clinical BPH as the complex of symptoms is more correctly called *LUTS*.

Histologic BPH describes a proliferative process of the stromal and epithelial elements of the prostate (Bartsch et al, 1979). The

proliferative process originates in the transition zone and the periurethral glands (McNeal, 1978; Shapiro 1990). It is rarely identified in males younger than 40 years (Berry et al, 1984). The autopsy incidence of BPH is age dependent, the proliferative process being present in approximately 70% and 90% of men in their seventh and ninth decades of life, respectively. The development of microscopic BPH requires aging and the testes as the source of androgens (Walsh, 1984). Androgens play a passive role in the proliferative process. The specific molecular events that initiate and promote histologic BPH have yet to be identified and characterized. Growth factors, such as epidermal growth factor (EGF), are involved through autocrine and paracrine stromal epithelial interactions (Steiner, 2000).

BPE can most easily be identified by digital rectal examination (DRE) and provides a relatively crude estimate of prostate size when compared with measurements obtained using transrectal ultrasonography (Bosch et al, 2005) or magnetic resonance imaging (MRI). Knowledge of prostate size may be clinically relevant in terms of selecting appropriate medical or surgical therapy. A strong correlation exists between serum prostate-specific antigen (PSA) levels and prostate volume (Roehrborn et al, 1999), and as a consequence, in the absence of adenocarcinoma, the PSA value may be used as a surrogate for prostate volume (Roehrborn et al, 2001). The transition zone (inner gland) accounts for the majority of BPH tissue. The transition zone volume can be quantified using transrectal ultrasonography (Lepor et al, 1994) or MRI (Tempany et al, 1993). There is no consensus regarding the extent of enlargement required to establish the diagnosis of BPE; however, prostate volume of approximately 20 mL may be regarded as normal (Garraway et al, 1991) before BPH develops, and volumes up to and greater than 100 mL are encountered clinically. Volumes greater than 30 to 40 mL appear to correlate with risk of LUTS and BPH progression (Jacobsen et al, 1997).

Patients may have LUTS, urinary retention, an overactive bladder (OAB), urinary tract infection (UTI), hematuria, or renal insufficiency (Jepsen and Bruskewitz, 2000). Historically, the pathophysiology of LUTS was often attributed to BOO secondary to BPE. This hypothesis was supported by epidemiologic data suggesting that the prevalences of BPH, BPE, and LUTS are age

dependent and therefore causally related (Isaacs and Coffey, 1989). This rather overly simplistic concept of the pathophysiology of LUTS has been challenged by more recent reports demonstrating only weak relationships among prostate size, severity of BOO, and severity of symptoms (Barry et al, 1993; Bosch et al, 1995; Girman et al, 1995; Yalla et al, 1995; Chapple and Abrams, 2013). However, there are numerous epidemiologic data to confirm that LUTS or histologic BPH is a slowly progressive condition and that men with a larger prostate (or higher PSA) are at significantly greater risk of LUTS progression, impaired quality of life, and complications such as acute urinary retention (AUR) (Roehrborn et al, 2001).

The International Consultation on Urological Diseases' (ICUD's) 6th International Consultation on New Developments in Prostatic Diseases and Prostate Diseases on male LUTS endorsed the appropriate use of the current terminology—namely, *lower urinary tract symptoms, benign prostatic hyperplasia, benign prostate enlargement, and benign prostatic obstruction*—and recommended that terms such as *clinical benign prostatic hyperplasia* or the *benign prostatic hyperplasia patient* be abandoned (Chapple and Abrams, 2013).

Adoption of this correct terminology is particularly important when treating the male patient with the OAB and especially patients with nocturia.

DIAGNOSIS

The complex of symptoms (LUTS) is not specific for BPH, BPE, or BOO. It is advantageous, however, that LUTS describes the symptoms without attributing a cause. LUTS is not sex, age, or disease specific (Abrams, 1994). The risk of using the term *clinical BPH* is that it gives a false diagnostic permission to treat the patient, which may be translated into treatment without a proper diagnosis (Chapple and Abrams, 2013).

The initial diagnostic challenge in these patients is to establish that the symptoms are, in fact, a result of benign prostate disease. This is the primary focus of initial evaluation and diagnostic testing. Fortunately, nonprostatic causes of symptoms can be excluded in a significant majority of patients on the basis of history, physical examination, and urinalysis. Additional diagnostic testing is necessary in patients in whom the diagnosis is still unclear after initial evaluation. These tests may also have a modest (but still unproven) value in predicting the response to treatment. The following recommendations concerning the initial evaluation of men with LUTS reflect the consensus opinion for several independent groups. The American Urological Association (AUA) BPH guidelines committee reported in 1994, 2003, 2006, and 2010 (McVary et al, 2011). The European Association of Urology (EAU) has also published guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction (Oelke et al, 2013). Algorithms for the management of LUTS and BPH are shown in Figures 104-1 to 104-3.

Initial Evaluation

Medical History

A detailed medical history should be taken to identify other causes of voiding and storage dysfunction or comorbidities that may complicate treatment. Specific additional areas to discuss when taking the history of a man with LUTS include a history of hematuria, UTI, diabetes, nervous system disease (e.g., Parkinson disease or stroke), urethral stricture disease, urinary retention, and aggravation of symptoms by cold or sinus medication. Current prescription and over-the-counter medications should be considered to determine whether the patient is taking drugs that impair bladder contractility (anticholinergics) or that increase outflow resistance (sympathomimetics). A history of prior lower urinary tract surgery raises the possibility of urethral or bladder neck stricture. Use of a bladder diary and frequency-volume chart (recording times and volume) will help identify patients with polyuria or other nonprostatic disorders.

Physical Examination

A DRE and a focused neurologic examination should usually be performed. In addition, examination of the external genitalia is indicated to exclude meatal stenosis or a palpable urethral mass, and an abdominal examination is necessary to exclude an overdistended, palpable or percussable bladder. The DRE and focused neurologic examination are performed to detect prostate or rectal malignancy, to evaluate anal sphincter tone, and to rule out any neurologic problems that may cause the presenting symptoms. The presence of induration is as important a finding as the presence of a nodule and should be correlated with a serum PSA value so that the need for prostatic biopsy can be assessed and acted on.

DRE establishes the approximate size of the prostate gland. Estimation of prostate size is important to guide the most appropriate pharmacologic or interventional approach. DRE provides a sufficiently accurate measurement in most patients. The size of the prostate is not critical in deciding whether active treatment is required. Prostate size does not correlate precisely with symptom severity, degree of urodynamic obstruction, or treatment outcomes (Roehrborn et al, 1986; Simonsen et al, 1987). If a more accurate measurement of prostate volume is needed to determine whether to perform open prostatectomy rather than transurethral resection of the prostate (TURP) or some other procedure such as laser vaporization or enucleation, ultrasound (transabdominal or transrectal) (Bosch et al, 2005) or MRI scanning is more accurate than cystourethroscopy. A larger gland, and consequently a higher PSA, is associated with a greater risk of BPH progression (Roehrborn et al, 2001).

Urinalysis

A urinalysis should be done by use of either a dipstick test or microscopic examination of the spun sediment to rule out UTI and hematuria, either of which strongly suggests a non-BPH pathologic process as a cause of symptoms. Because serious urinary tract disorders are relatively uncommon, the positive predictive value of screening for them is low, and the effectiveness of early detection and intervention is unproven. However, in older men with LUTS and a higher prevalence of these disorders, the benefits of an innocuous test such as urinalysis clearly outweigh the harms involved. The test permits the selective use of renal imaging and endoscopy for patients with the greatest chance of benefiting from them. More important, urinalysis assists in distinguishing UTIs and bladder cancer from benign prostate disease. These conditions may produce urinary tract symptoms (e.g., frequency and urgency) that mimic LUTS or BPH. If a dipstick approach is used, a test that includes leukocyte esterase and nitrite tests for the detection of pyuria and bacteriuria should be used.

The positive predictive value of urinalysis for cancer or other urologic diseases is around 4% to 26%, depending on the patients screened and the rigor of follow-up studies (Mohr et al, 1986; Messing et al, 1987; Mohr et al, 1987). Urine cytology should always be requested in men with severe storage symptoms and dysuria, especially if they have a smoking history. Carcinoma in situ of the bladder may have serious consequences if overlooked.

Serum Creatinine Measurement

Although the measurement of serum creatinine was recommended in the initial evaluation of all patients with LUTS to exclude renal insufficiency caused by the presence of obstructive uropathy (McConnell et al, 1994; Denis et al, 1998), at the Fifth International Consultation on BPH it was suggested that serum creatinine determination should be optional. The AUA guidelines on BPH no longer recommend routine creatinine measurement in the standard patient. However, it is well established that patients with renal insufficiency have increased risk for postoperative complications. The risk is 25% for patients with renal insufficiency, compared with 17% for patients without the condition (Mebust et al, 1989). Moreover, the mortality increases up to sixfold for patients

BASIC MANAGEMENT OF LUTS IN MEN

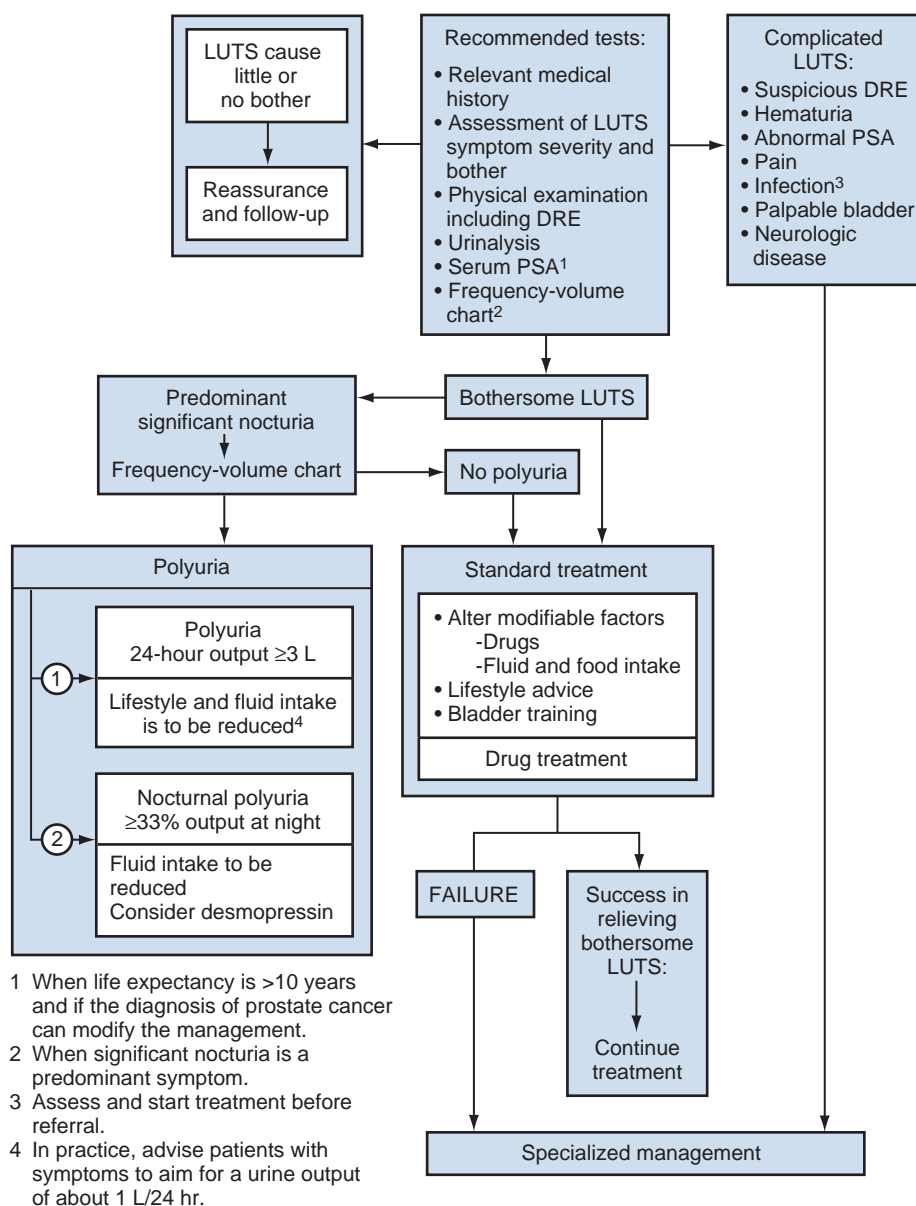


Figure 104-1. International consensus guideline (2009) algorithm for management of lower urinary tract symptoms (LUTS): basic management. DRE, digital rectal examination; PSA, prostate-specific antigen. (From Abrams P, Chapple C, Khoury S, et al. Evaluation and treatment of lower urinary tract symptoms in older men. *J Urol* 2009;181[4]:1779–87.)

treated surgically if they have renal insufficiency (Holtgrewe and Valk, 1962; Melchior et al, 1974). Of 6102 patients evaluated in 25 studies by intravenous urography (IVU) before prostate surgery, 7.6% had evidence of hydronephrosis (McConnell et al, 1994). Of these patients, 33.6% had associated renal insufficiency. Elevated serum creatinine in a patient with LUTS is an indication for imaging studies (usually ultrasound) to evaluate the upper urinary tract. In a retrospective analysis of 345 patients who had undergone prostatectomy, 1.7% ($n = 6$) had occult and progressive renal damage (Mukamel et al, 1979). These patients had minimal or no urinary symptoms. Measurement of serum creatinine is one modality to identify such at-risk patients. In a recent large-scale study of older Korean men ($N = 3713$), those with severe LUTS and prostate enlargement were at increased risk of deteriorating renal function irrespective of prostate volume (Kwon et al, 2012). Creatinine assessment was recommended in the 2013 ICUD guideline on male LUTS (Chapple and Abrams, 2013).

Serum Prostate-Specific Antigen

Prostate cancer can lead to LUTS by producing bladder outflow obstruction similar to BPH. Moreover, localized prostate cancer commonly coexists with BPH. In most men with a 10-year or greater life span, the knowledge of concomitant prostate cancer may well alter management of LUTS. The detection of a large nodular prostate cancer on DRE would no doubt alter therapy; however, the early detection of small-volume prostate cancer in an 80-year-old man is unlikely to increase life expectancy. A PSA test and DRE increase the detection rate of prostate cancer over DRE alone. **Therefore, measurement of the serum PSA value should be performed in patients in whom the identification of cancer would clearly alter LUTS management** (Abrams et al, 2009; McVary et al, 2011; Oelke et al, 2013). There is significant overlap between the serum PSA values of men with BPH and men with clinically localized prostate cancer. Twenty-eight percent of men with histologically proven BPH

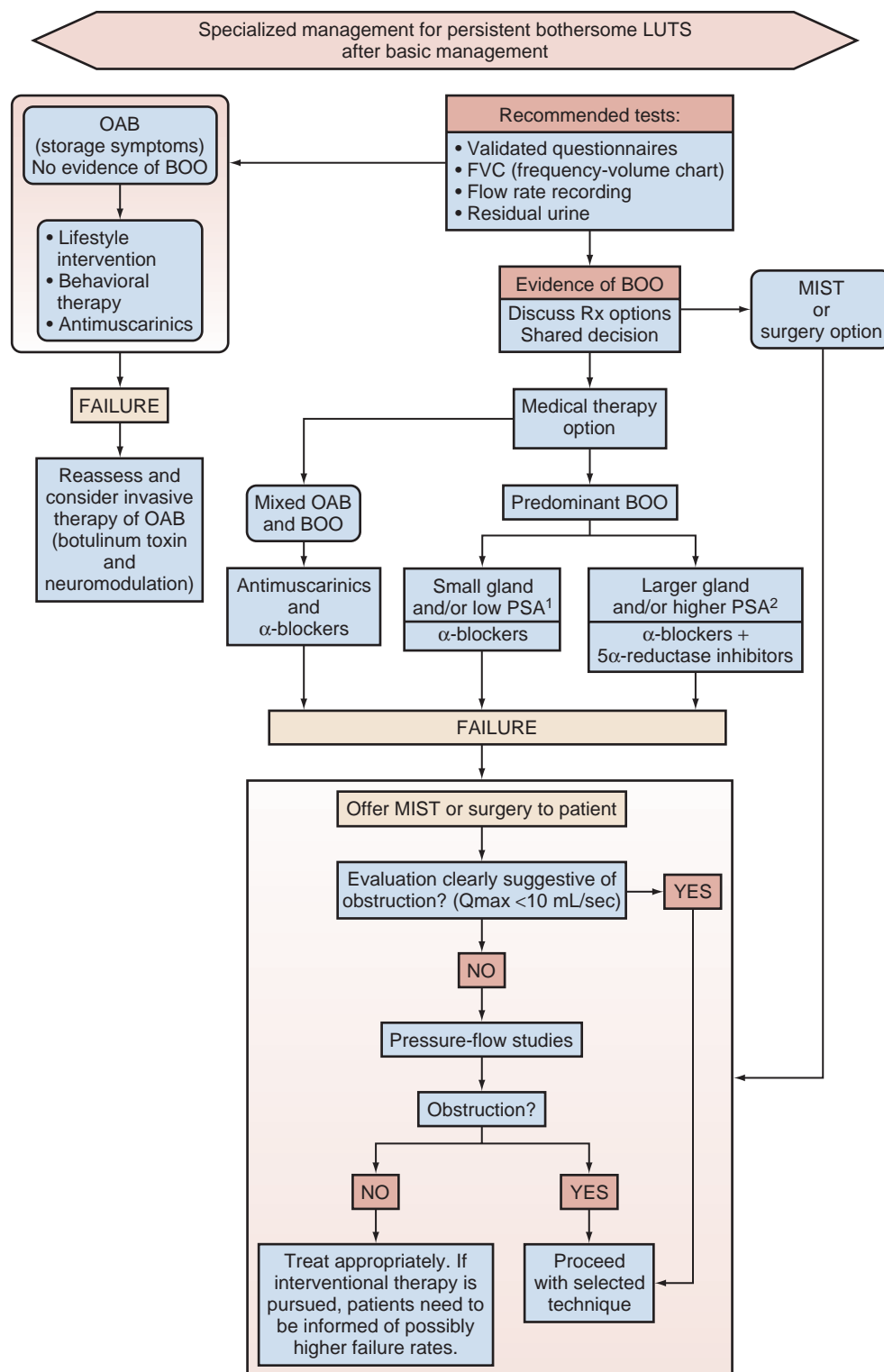


Figure 104-2. International consensus guideline (2009) algorithm for management of lower urinary tract symptoms (LUTS): specialized management. 1, PSA <1.5 ng; 2, PSA >1.5 ng; BOO, bladder outlet obstruction; MIST, minimally invasive surgical treatment; OAB, overactive bladder; PSA, prostate-specific antigen; Rx, treatment. (From Abrams P, Chapple C, Khoury S, et al. Evaluation and treatment of lower urinary tract symptoms in older men. *J Urol* 2009;181[4]:1779–87.)

have a serum PSA greater than 4.0 ng/mL (McConnell et al, 1994). Serum PSA trends over time (PSA velocity), measurement of free versus complexed PSA, and PSA density may help to improve the specificity of PSA in men with BPH. Newer markers such as the p2PSA and Prostate Health Index (PHI) score (Lazzeri et al, 2013)

or urinary PCA3 test result can also help to differentiate BPH from prostate cancer.

In the absence of prostate cancer, the PSA value provides a guide to prostate volume, an indication of the likelihood of response to therapy with 5α-reductase inhibitors, and an

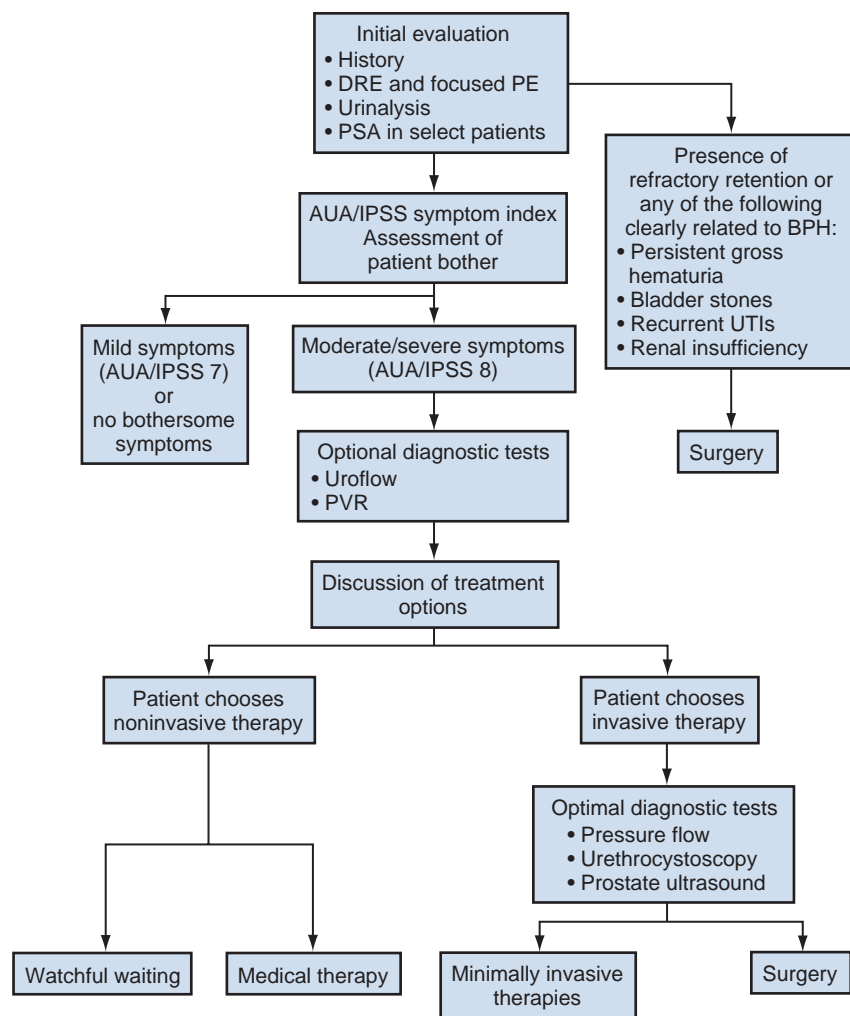


Figure 104-3. American Urological Association (AUA) guideline algorithm for management of benign prostatic hyperplasia (updated 2006). DRE, digital rectal examination; IPSS, International Prostate Symptom Score; PE, physical examination; PSA, prostate-specific antigen; PVR, post-void residual; UTI, urinary tract infection. (From Kaplan SA. Update on the American Urological Association guidelines for the treatment of benign prostatic hyperplasia. *Rev Urol* 2006;8[Suppl. 4]:S10–7.)

indication of the risk of LUTS or BPH progression. However, in men with LUTS already treated with a 5 α -reductase inhibitor (e.g., finasteride or dutasteride) serum PSA is reduced 40% to 50% after 12 months of treatment (Guess et al, 1993). Failure to establish a baseline (pretreatment) PSA level may therefore complicate interpretation of future PSA values. Men who are taking these agents should have their PSA value doubled to correctly assess their risk of harboring a prostatic adenocarcinoma and should be watched for any increase from nadir values. Provided that this is done, recent evidence suggests that 5 α -reductase therapy actually increases the sensitivity of PSA as a detector of cancer (Andriole et al, 2011).

Symptom Assessment

The AUA Symptom Index or the identical International Prostate Symptom Score (IPSS) is recommended as the symptom scoring instrument to be used for the baseline assessment of symptom severity in men with LUTS (Abrams et al, 2009, McVary et al, 2011). When this system is used, symptoms can be classified as mild (0 to 7), moderate (8 to 19), or severe (20 to 35) (Barry et al, 1992b). The symptom score should also be the primary determinant of treatment response or disease progression in the follow-up period. Although other symptom score questionnaires are used, the IPSS is now the U.S. and international standard.

However, the IPSS cannot be used to establish the diagnosis of LUTS or BPH. Men (and women) with a variety of lower urinary tract disorders (e.g., infection, tumor, neurogenic bladder disease) will have a high IPSS. Nonetheless, the IPSS is a good instrument to grade baseline symptom severity, assess the response to therapy, and detect symptom progression in men managed by watchful waiting. Optimal treatment decisions in individual patients will also need to take into account how a given level of symptoms affects each man's quality of life (degree of bothersomeness).

The IPSS was developed from the AUA score developed by the measurement committee of the AUA (Barry et al, 1992a, 1992b). Each question on the IPSS can yield 0 to 5 points, producing a total symptom score that can range from 0 to 35. This seven-question set is internally consistent (Cronbach alpha, 0.85) and reliable (test-retest correlation, 0.93). The index correlates strongly with patients' global ratings of their urinary difficulties ($r = 0.78$) and is sensitive to treatment response.

Johnson and colleagues (2009) showed that patients with a low education status are more likely to misunderstand the American Urological Association Symptom Score whether they are managed in a public hospital or a university practice. They tend to misrepresent their symptoms and therefore may receive inappropriate treatment. Eight percent of university hospital and almost 25% of public

hospital patients under-reported their moderate symptoms as mild, and 33% of university hospital and 16% of public hospital patients over-reported their mild symptoms as moderate. When the questionnaire is administered by a medical professional (even though the questionnaire is recommended to be “self-administered”), many of the inaccuracies disappear. The use of the additional bother score or quality-of-life scale may usefully guide appropriate treatment.

Although the IPSS correlates well with quality of life measures (Sagnier et al, 1995), there is still a need for sensitive LUTS- and BPH-specific quality-of-life instruments. Furthermore, because storage symptoms often predominate, there is a need for better methods of quantifying urgency and frequency and recording any incontinence. The standardization subcommittee of the International Continence Society has usefully categorized the range of likely symptoms into three groups: storage, voiding, and postmicturition (Abrams et al, 2003). Subdividing the IPSS into the four obstructive and three storage questions may also be useful. There is now level 1 evidence that recording an IPSS helps to identify patients with LUTS presumed to be secondary to benign prostatic obstruction and that it can be used to monitor change with treatment. A modified short form of the AUA Symptom Index known as the UWIN has also been validated (Barqawi et al, 2011). The AUA Symptom Index and the UWIN were correlated well in a study of 278 men (Crawford et al, 2011). A series of other systems (such as the King's Health Questionnaire, International Consultation on Incontinence Modular Questionnaire on male LUTS [ICIQ-MLUTS], Danish Prostatic Symptom Score [DAN-PSS], and Overactive Bladder Symptom Score [OABSS]) may be more sensitive to changes in storage symptoms or useful for research studies. **A voiding diary with frequency and volume recordings may also be helpful**, especially in the presence of significant nocturia (Weiss, 2006; Chapple and Abrams, 2013). These should be recorded for a minimum of 3 days and ideally for 7 days (Homma et al, 2002).

Clearly, symptom scores alone do not capture the complete picture of a prostate problem as perceived by the individual patient. Symptom impact on a patient's lifestyle must be considered as well. An intervention may make more sense for a moderately symptomatic patient who finds his symptoms very bothersome than for a severely symptomatic patient who finds his symptoms quite tolerable.

Additional Diagnostic Tests

Additional testing should be considered after the initial evaluation if there is a significant chance the patient's LUTS may not be the result of BPH or BOO. Patients with normal initial evaluation findings and only mild symptomatology on the IPSS (scores 0 to 7), or even those who have moderate symptoms but are minimally bothered, do not need additional diagnostic evaluation and can be considered for simple monitoring and observed (Kaplan, 2006). Men who have developed serious complications should be treated surgically in most cases. Urinary flow rate, postvoid residual (PVR) urine, and pressure-flow urodynamic studies are appropriate tests to consider in the evaluation of men with moderate to severe symptoms (IPSS 8 to 35). The value of pressure-flow studies is debatable, especially in men who elect watchful waiting or medical therapy as their management option. **Cystoscopy should not be done routinely** but is optional during later evaluation if invasive treatment is strongly considered. Urinary flow rate and PVR are generally recommended tests, and frequency-volume chart recordings are recommended by most (Abrams et al, 2009; Jones et al, 2010; McVary et al, 2011; Oelke et al, 2013).

It may be appropriate for the physician to offer treatment alternatives to the patient without performing any further diagnostic tests. Especially if the patient chooses watchful waiting or non-invasive therapy, invasive diagnostic tests may not be necessary. Conversely, if the patient elects an invasive treatment option, it may be appropriate for the physician to consider further evaluation.

Diagnostic Tests in Men Who Require Surgery for Lower Urinary Tract Symptoms or Benign Prostatic Hyperplasia

In general, surgery is recommended if the patient has refractory urinary retention (failing at least one attempt of catheter removal) or high-pressure chronic retention (HPCR) or any of the following conditions clearly secondary to BPE or BOO: recurrent UTI, recurrent gross hematuria (resistant to 5 α -reductase inhibitor therapy), bladder stones, renal insufficiency, or large bladder diverticula (Abrams et al, 2009; National Institute for Health and Care Excellence [NICE], 2010; McVary et al, 2011; Oelke et al, 2013). If there is reason to suspect that the patient's retention may be a result of detrusor hypocontractility, then urodynamic studies (e.g., filling cystometry) may be helpful. Pressure-flow urodynamic studies are not informative if the patient cannot urinate. Cystoscopy may be helpful to consider before the operative procedure to help plan the most prudent approach. The presence of infection and hematuria in patients should prompt appropriate evaluation and therapy for these conditions before treatment of LUTS.

Uroflowmetry

In general, uroflowmetry is recommended (by the AUA [McVary et al, 2011]) for specialist investigation (sixth International Consultation [Abrams et al, 2009]) or is required before invasive treatment (EAU [Oelke et al, 2013]). Uroflowmetry involves the electronic recording of the urinary flow rate throughout the course of micturition. It is a common, noninvasive urodynamic test used in the diagnostic evaluation of patients with symptoms of BOO. The results of uroflowmetry are nonspecific for causes of the symptoms. For example, an abnormally low flow rate may be caused by an obstruction (e.g., hyperplastic prostate, urethral stricture, meatal stenosis) or by detrusor hypocontractility. The Agency for Healthcare Research and Quality guideline panel reached the following conclusions regarding uroflowmetry (McConnell et al, 1994), which still apply:

- Flow rate measurements are inaccurate if the voided volume is less than 125 to 150 mL.
- Flow rate recording is the single best noninvasive urodynamic test to detect lower urinary tract obstruction. Current evidence, however, is insufficient to recommend a given cutoff value to document the appropriateness of therapy.
- The peak flow rate (PFR; Qmax) more specifically identifies patients with BOO than does the average flow rate (Qave).
- Although Qmax decreases with advancing age and decreasing voided volume, no age or volume correction is currently recommended for clinical practice.
- Although considerable uncertainty exists, patients with a Qmax greater than 15 mL/sec appear to have poorer treatment outcomes after prostatectomy than patients with a Qmax of less than 15 mL/sec.
- A Qmax of less than 15 mL/sec does not differentiate between obstruction and bladder decompensation (or detrusor underactivity, which is present in 9% to 48% of men undergoing urodynamic evaluation for non-neurogenic LUTS) (Osman et al, 2014).

Despite its limitations, flow rate recording has demonstrated some sensitivity in identifying BOO resulting from BPE. Scott and coworkers (1967) and Shoukry and associates (1975) found that Qmax correlated better than symptoms with the presence or absence of obstruction as determined by pressure-flow studies. Siroky and coworkers (1979) concluded that uroflowmetry was able to separate physiologically unobstructed and obstructed patients. Gleason and colleagues (1982) found that Qmax distinguished between normal men and patients with BPE, urethral stricture, or prostatitis. However, they also noted that a subgroup of patients with a decompensated detrusor muscle could not be separated from the obstructed men on the basis of Qmax alone.

Chancellor and colleagues (1991) found that flow rate recording cannot distinguish between BOO and impaired detrusor contractility as the cause for a low Qmax. None of eight measured,

noninvasive urodynamic parameters was significantly different for 31 patients with outlet obstruction than for 14 patients with impaired detrusor contractility. Abrams and associates studied the value of uroflowmetry before prostatectomy (Abrams, 1977; Abrams et al, 1979). Failure rates for surgery were found to decrease with the addition of flow rate measurement to symptom assessment in preoperative evaluation.

Qmax appears to predict surgical outcome in some studies. In one study reported by Jensen and coworkers (1984), 53 patients underwent prostatectomy based on clinical indication alone. All three groups according to level of Qmax experienced improvements in symptom score after surgery, but the group with a Qmax less than 10 mL/sec before treatment had a better overall subjective outcome as assessed by global subjective judgment.

In another study, which included men studied with flow rates before and 6 months after prostatectomy (Jensen et al, 1988a), subjective evaluation revealed an overall symptomatic improvement rate of 80% after surgery. The difference in success rates for men falling above or below the cutoff value of Qmax of 10 mL/sec was not significant ($P = .2$). When a Qmax cutoff of 15 mL/sec was used, success rates for men above or below the cutoff value differed significantly.

McLoughlin and coworkers (1990), using urodynamic testing and a cutoff value of 12 mL/sec, evaluated 108 men with clinical BPH before and 1 year after surgery and determined that with use of a Qmax cutoff of less than 12 mL/sec as an indicator for obstruction, only 3% of patients would have been subjected to an unnecessary TURP. These authors believed that routine pressure-flow studies or cystometrograms were not indicated, but that the screening of flow rates followed by further urodynamic testing in patients with a Qmax greater than 12 mL/sec should be considered. Very low rates do not appear to portend poor treatment outcome. In one study of 84 patients undergoing surgery for symptomatic BPH (Donkervoort et al, 1975), patients with a preoperative Qmax less than 7 mL/sec improved symptomatically as much as patients with a Qmax greater than 7 mL/sec.

Neither subjectively assessed symptoms nor quantified symptom-score analyses correlate strongly with uroflowmetry measurements; they are independent assessments. Patients with a PFR greater than 15 mL/sec may have somewhat poorer outcomes after surgery than those with a Qmax less than 15 mL/sec (although the majority of patients still improve). Other investigators report similar findings for different Qmax cutoff values (e.g., 12 mL/sec). Patients with very bothersome LUTS suggestive of BOO but having a Qmax greater than 15 mL/sec may benefit from further urodynamic testing (i.e., pressure-flow studies) to reduce the number of surgical treatment failures.

Postvoid Residual Urine

PVR urine is the volume of fluid remaining in the bladder immediately after the completion of micturition. Studies indicate that PVR urine normally ranges from 0.09 to 2.24 mL, with the mean being 0.53 mL (Hinman and Cox, 1967). Seventy-eight percent of normal men have PVR values of less than 5 mL, and 100% have volumes of less than 12 mL (Di Mare et al, 1963). The AHCPH BPH guideline panel reached the following conclusions regarding PVR (McConnell et al, 1994):

- Residual urine volume measurement has significant intraindividual variability that limits its clinical usefulness.
- Residual urine volume does not correlate well with other signs or symptoms of LUTS and BPH.
- Large residual urine volumes may predict a slightly higher failure rate with a strategy of watchful waiting. However, the threshold volume defining a poorer outcome is uncertain.
- It is uncertain whether residual urine volume predicts the outcome of surgical treatment.
- It is uncertain whether residual urine volume indicates impending bladder or renal damage.
- Residual urine volume can be measured with sufficient accuracy noninvasively by transabdominal ultrasonography.

The Fourth International Consultation initially recommended PVR determination in the initial assessment and during monitoring of patients under watchful waiting or other conservative treatment regimens (Denis et al, 1998). However, the latest male LUTS ICUD report (Chapple and Abrams, 2013) states that the level of evidence for PVR in the standard patient is weak and based mainly on expert opinion—that is, a level 5, grade D recommendation.

PVR measurement can be performed by noninvasive (ultrasound) and by invasive (catheterization) methods. Invasive techniques are accurate if performed correctly but carry a small but clinically significant risk of discomfort, urethral injury, UTI, and transient bacteremia. Small portable and less expensive devices can be used to measure PVR, with reported accuracy comparable to that with more expensive ultrasound units and catheterization. Birch and coworkers (1988) reported that of 30 men with BPH, 66% had wide variations in PVR when three measurements were done on the same day. In 34% of patients, there was no difference among the three measurements. In 58%, at least two volumes were significantly different. In 8% of patients, all three were different. In most patients, two measurements were statistically similar whereas the third one yielded quite different results. Bruskewitz and colleagues (1982) found similarly wide variations of the measured amount when they performed repetitive measurements of PVR (repeated two to five times) by in-and-out catheterization on 47 men before prostatectomy. They also found no correlation between the amount of residual urine and any cystoscopic or urodynamic findings, symptoms, or the presence or absence of a history of UTIs. Most clinical studies demonstrate minimal correlation between PVR and baseline measurements of symptoms, flow rate, or urodynamic measures of obstruction (Griffiths and Castro, 1970; Shoukry et al, 1975; Abrams and Griffiths, 1979). However, Neal and associates (1987) found a significant association in 253 men among PVR, age, “below-normal” Qmax, and high urethral resistance. Low voiding pressure, however, did not correlate well with PVR. The authors concluded that outflow obstruction is related to the development of increasing amounts of PVR urine. In the AUA outcome study, Barry and colleagues (1993) found a significant correlation between high PVR and low flow rates but no correlation with IPSS.

Traditionally, urologists have assumed that increasing amounts of PVR denote LUTS or BPH progression and are thus an indication for surgery. This concept underlies the common inclusion of PVR in each individual government’s appropriateness criteria. Unfortunately, data are lacking to support the predictive value of PVR. Andersen (1982) studied 104 men with BPH and reported two patterns of BPH progression. The slow course was characterized by the development of high levels of PVR that resulted in decompensation of the detrusor muscle and eventually led to urinary retention. The fast course was associated with uninhibited detrusor contractions (UDCs). The amount of PVR, the presence of UDCs, and symptoms correlated poorly in the study. Nevertheless, Andersen recommended PVR as a safety parameter when measured longitudinally throughout the clinical course of a patient with prostatism.

Data from the Veterans Affairs (VA) Cooperative Study Group randomized trial comparing TURP with watchful waiting demonstrated that PVR does not predict the outcome of surgery, and there was little evidence to support criteria that require a certain amount of PVR before surgery is justified (Wasson et al, 1995). In addition, high PVR did predict a slightly higher failure rate for watchful waiting. However, the majority of men with large residual urine volume did not require surgery during the 3-year duration of the trial. In summary, PVR is best viewed as a safety parameter. Men with significant PVR should certainly be monitored more closely if they elect nonsurgical therapy, particularly if antimuscarinic therapy is chosen.

Pressure-Flow Studies

If the initial evaluation, flow rate, and PVR are not sufficiently suggestive of BOO, further urodynamic assessment by pressure-flow studies should be considered, especially if an invasive treatment is

considered (i.e., surgery) or if surgical treatment has failed (McConnell et al, 1994; Denis et al, 1998; Abrams et al, 2009; McVary et al, 2011). Pressure-flow studies differentiate between patients with a low Qmax secondary to obstruction and those whose low Qmax is caused by impaired detrusor contractility. They should be performed when the distinction between the two will affect therapeutic decisions. Patients with a history of neurologic diseases known to affect bladder or sphincteric functions, as well as patients with normal flow rates (Qmax > 15 mL/sec) but bothersome symptoms, may also benefit from urodynamic evaluation, especially if surgical therapy is contemplated.

The value of pressure-flow measurement in predicting treatment outcome is uncertain. In a study by Abrams and colleagues (1979), the inclusion of pressure-flow data in the preoperative evaluation and indication for surgery reduced the subjective failure rate to 12%, down from 28% when patients were certified as candidates for surgery without the urodynamic data. However, a 28% failure rate is significantly higher than that reported in other TURP series (McConnell et al, 1994). Jensen and Andersen (1990) recommended invasive urodynamic testing for patients with a Qmax greater than 15 mL/sec. For the population in their study, this would have resulted in an additional 9% of patients being excluded from surgery and a decrease in failure rate to 8.3%. The support for this recommendation may be questioned, however, in light of earlier work by Jensen and coworkers (1988b, 1988c) that found most unsatisfied patients are incorrectly classified preoperatively even with urodynamic testing.

Pressure-flow studies do permit more accurate categorization of patients. Abrams and associates (1979) used pressure-flow plots in addition to flow rate measurement. The study found that in about half the cases the patients with LUTS could be correctly classified as obstructed or nonobstructed by Qmax alone, but that the addition of the detrusor pressure at Qmax allowed correct classification in two thirds of the group. The remaining one third of the patients were assessed by pressure-flow plot. In many of these patients, both pressure and Qmax were low, indicating a decompensating detrusor muscle as the source for the low Qmax.

Pressure-flow studies provide much more specific insight into detrusor function and the cause of voiding dysfunction than do flow rate measurements. However, a number of outcome-based investigations demonstrate a modest additional value of pressure-flow studies over symptom and flow rate evaluation. Discussion of treatment options and the nature of the investigation with the patient is recommended before pressure-flow testing is organized.

Filling Cystometry (Cystometrography)

Filling cystometry alone adds limited information to the evaluation of most men with LUTS and is not recommended in routine cases. The test may have value in the evaluation of patients with OAB or known or suspected neurologic lesions and LUTS, but pressure-flow studies provide more specific information.

Urethrocystoscopy

Urethrocystoscopy is not recommended to determine the need for treatment because the linkage between the endoscopic appearance of the lower urinary tract and the treatment outcome is poorly documented and available information suggests that the relationship is minimal (McConnell et al, 1994). The test is recommended for men with LUTS who have a history of microscopic or gross hematuria, urethral stricture disease (or risk factors such as history of urethritis or urethral injury), bladder cancer or suspicion of carcinoma in situ, or prior lower urinary tract surgery (especially prior TURP). Urethrocystoscopy may be considered in men with moderate to severe symptoms who have chosen (or require) surgical or other invasive therapy to help the surgeon determine the most appropriate technical approach.

For example, if urethrocystoscopy reveals a large middle lobe, transurethral incision of the prostate (TUIP) is unlikely to be successful. The decision to perform an open prostatectomy or laser

vaporization may be appropriately influenced by the shape of the gland, as well as its size. Urethrocystoscopy is therefore performed to select (or rule out) specific techniques, not to determine the need for treatment.

Imaging of the Upper Urinary Tract

Upper urinary tract imaging is not recommended in the routine evaluation of men with LUTS unless they also have one or more of the following: hematuria, UTI, renal insufficiency (ultrasound recommended), history of urolithiasis, or history of urinary tract surgery (McConnell et al, 1994; Denis et al, 1998; Kaplan et al, 2006; Abrams et al, 2009). IVU before LUTS or BPH treatment was performed by 73.4% of urologists in the United States in the late 1980s (Holtgrewe et al, 1989). IVU is associated with a 0.1% incidence of significant adverse events. Ultrasound imaging is now preferred but is unnecessary in the uncomplicated case.

The presence or history of hematuria, renal insufficiency, or UTI and/or a history of stones or prior urinary tract surgery increases the likelihood that imaging will demonstrate clinically significant findings (Juul et al, 1989; Andrews et al, 2002). Although there are no conclusive data on the combined incidence of the important clinical predictors just listed, approximately one third of all men with LUTS have one or another indication for urinary tract imaging.

ASSESSING THE EFFECTIVENESS AND SAFETY OF MEDICAL THERAPY FOR LOWER URINARY TRACT SYMPTOMS

The role of treatment for any disease process depends on the magnitude of the clinical effect and the incidence and severity of treatment-related morbidity. Assessing the effectiveness of medical therapies for LUTS requires defining clinically relevant end points, identifying quantitative and reliable clinical outcome measures, eliminating investigator and patient bias, accounting for the placebo response, and enrolling the proper number of patients so that only clinically significant changes are statistically significant. Assessing the safety of medical therapies requires a rigorous effort to identify all treatment-related clinical, biochemical, teratogenic, and mutagenic adverse effects associated with drug treatment.

Clinical End Points

The clinical consequences of BPE or BOO include LUTS and associated reduction of quality of life; detrusor dysfunction characterized by detrusor acontractility, detrusor overactivity, and detrusor fibrosis; incomplete bladder emptying; acute and chronic urinary retention; UTI; renal insufficiency; and hematuria (Shapiro and Lepor, 1995). The goals of treatment include relieving LUTS, decreasing BOO, improving bladder emptying, ameliorating detrusor overactivity, reversing renal insufficiency, and preventing disease progression, which may include a deterioration of symptoms, future episodes of gross hematuria, UTI, AUR, or the need for surgical intervention.

Quantitative Outcome Measures

Symptoms

The primary objective of the AUA Symptom Index or IPSS was to provide a universally accepted instrument to quantify the impact of therapeutic interventions on LUTS (Barry et al, 1992b). There is no standardized format for reporting changes in the AUA symptom score or other quantitative indices of symptom severity after treatment. Symptom response has been reported as a percentage of patients achieving a threshold response or as group mean changes in a symptom score. The literature typically reports the percentage of men achieving a 30% to 50% reduction in the symptom score. Expressing the symptom response as a single threshold response

does not discriminate the overall magnitude of the clinical effect. When the baseline symptom scores are mild to moderate, small and clinically insignificant changes correspond to large percentage changes. When baseline symptom scores are severe, relatively large absolute changes may not be clinically significant. Symptom outcome should be expressed both as a percentage of patients achieving a threshold reduction response and as group mean changes in the symptom score.

The clinical significance of changes in the AUA Symptom Index was reported by [Barry and colleagues \(1995\)](#). A total of 1165 patients participated in a randomized, double-blind, placebo-controlled study of medical therapy and completed the AUA Symptom Index at baseline and after 3 months of treatment. The absolute and percentage changes in AUA Symptom Index and BPH Impact Index were correlated with five global ratings of symptom improvement. The group mean changes in AUA Symptom Index for patients rating their improvement as markedly, moderately, or slightly improved, unchanged, or worse were -8.8 , -5.1 , -3.0 , -0.7 , and $+2.7$, respectively. The relationship between the patients' global ratings of improvement and the AUA Symptom Index and BPH Impact Index changes were dependent on the baseline AUA Symptom Index. This important study provides the data required to determine sample sizes and interpret the clinical significance of symptom improvement in BPH clinical trials. A 3-point change appears perceptible to symptomatic men.

Bladder Outlet Obstruction

Experimental animal models of BOO have demonstrated profound changes in bladder ultrastructure, cellular composition, metabolism, and function resulting from BOO ([Levin et al, 2000](#)). These experimental observations must be cautiously extrapolated to man, because the response to BOO depends on the species and the severity and duration of obstruction. Animal studies demonstrate that under experimental conditions, BOO causes alterations likely to adversely affect bladder function. The justification for measuring and treating BOO in males is to reverse or prevent these deleterious consequences of obstruction.

Because synchronous pressure-flow urodynamic measurements do not correlate with severity of bladder dysfunction, severity of symptoms, or response to therapy, it is difficult to require these studies when evaluating the effectiveness of medical therapy for LUTS. Long-term studies are needed to determine whether urodynamic measurements predict disease progression. At the present time, the primary use of urodynamic testing is to discriminate the differential diagnosis of males presenting with multiple potential causes for LUTS.

Uroflowmetry represents a noninvasive and inexpensive but indirect indicator of urinary performance as a measure of BOO ([Siroky, 1990](#)). The reporting of PFR has been standardized ([Abrams et al, 2003](#)). At the lower spectrum of PFR, a relatively small absolute change (i.e., 4 to 6 mL/sec) corresponds to a relatively high percentage change, whereas at the higher end of PFR, a relatively large absolute change (i.e., 12 to 17 mL/sec) corresponds to a relatively modest percent change. The clinical significance of the changes in PFR cannot be defined, owing to the lack of correlations with relevant clinical, physiologic, or biochemical outcomes.

Bladder Emptying

The clinical significance of a PVR is controversial. [Barry and colleagues \(1993\)](#) reported no correlation between AUA symptom score and PVR. It has been suggested that PVR may predispose to UTI and irreversible bladder dysfunction secondary to stasis and overdistention. **There are no data clearly documenting that the incidence of UTI is related to PVR.** Another limitation of PVR measurements is variability over short intervals of time ([Bruskewitz et al, 1982](#)). It is imperative to measure the PVR on several occasions if this parameter will influence treatment decisions.

There is no standardization for reporting changes in PVR. Typically, the data are presented as absolute group mean changes. The

majority of LUTS and BPH clinical trials exclude patients with high baseline PVR (>300 mL) because of the potential risks of randomization to a placebo or ineffective treatment group. **Therefore, the majority of patients enrolled in clinical trials have clinically insignificant baseline PVR, potentially undermining the relevance of most trials to "real-world" practice.**

Detrusor Overactivity

The definition of detrusor overactivity is the development of a detrusor contraction exceeding 15 cm H₂O at a bladder volume less than 300 mL ([Jepsen and Bruskewitz, 2000](#)). The clinical significance of OAB in men with LUTS or BPH is unresolved. There is no evidence that men with detrusor overactivity electing watchful waiting are predisposed to develop disease progression. The presence of OAB does not reliably predict response to medical or surgical treatment. **Therefore, improvement of OAB is not always a standard outcome measure in clinical trials.**

Urinary Tract Infection, Renal Insufficiency, and Hematuria

Unlike other manifestations of BOO, the diagnosis of UTI, renal insufficiency, and hematuria is not controversial and the requirements for measurement are noninvasive and inexpensive. Because these events are not disease or gender specific, one must be cautious in assuming a causal relationship. There is no convincing evidence that UTI in the aging male population is associated with either a PVR or BOO. It is reasonable to assume that renal insufficiency occurs secondary to urinary retention if renal failure is reversed after catheter drainage. Hematuria may be associated with prostatic vascularity and may sometimes respond to medical therapy with a 5 α -reductase inhibitor.

Because the incidences of UTI, renal insufficiency, and hematuria are relatively uncommon and non-disease-specific events in the aging male population ([McConnell et al, 2003](#)), it would be extremely difficult to design a prospective study to determine whether any LUTS treatment prevents these events in an unselected cohort of men.

Eliminating Bias

Bias may be defined as a systematic error or difference between the true value and that actually attained from all causes other than sampling ability. The only mechanism to ensure that the potential bias of the patient and the investigator does not influence the outcome is a randomized, placebo-controlled, double-blind design. Because patients are typically randomized to receive a drug or its matching placebo, any effect of the investigators' bias would occur equally in the intervention and control groups.

The importance of eliminating bias cannot be overemphasized in clinical trials. Some patients are very enthusiastic about receiving the "new" treatment. In the absence of a blinded randomization, these patients may be disproportionately directed into the active treatment groups. A patient receiving a known placebo would be reluctant to report any adverse events or clinical response. An investigator may be inclined to censor various outcomes if treatment group assignment is known. Although subjective outcome measures such as symptoms are more likely to be influenced by the placebo response, quantitative outcome measurements such as PVR and PFR are also subject to a placebo response, but not prostate volume.

The placebo effect can be substantial in trials of drug treatment of LUTS ([Nickel, 1998](#)). Roehrborn has elegantly written about this effect ([Roehrborn, 1996](#)). **Trials should therefore include a placebo run-in period before recording baseline values;** these baseline values have already incorporated the placebo effect before any comparison is made. Ideally, a 4-week placebo run-in period before initiation of treatment should be included in any trial design.

Similarly, the statistical concept of "regression toward mean" should also be taken into account in trial design. If measuring urinary symptom scores or flow rate measurements, for instance, then in any population there will be some individuals whose values

will be recorded at the extremes of the range for that population. These individuals, when followed up with sequential measurements of the same parameters, will tend to produce values that are less extreme and closer to the mean for the population being studied. Again, incorporating a placebo run-in period will allow this process to occur, at least to a degree, so that subsequent measurements from the baseline values determined after the placebo run-in period are more likely to be in response to a true treatment effect than to these two potentially confounding and misleading processes.

Sample Size

It is a general misconception that the validity of a clinical trial is directly proportional to the number of patients enrolled. One of the objectives of a clinical trial is to determine whether the difference observed between two different treatment groups is clinically relevant. If the sample size of the clinical trial is properly determined in the early planning phase, a statistically significant outcome represents a clinically significant outcome. Calculation of sample size with provisions for adequate levels of significance and power is an essential part of planning a trial. Enrolling an excessive number of patients may result in an overpowered study; that is, a small and clinically insignificant difference may be statistically significant. Conversely, enrolling insufficient numbers of patients may result in an underpowered study; that is, a large and clinically significant difference may not be statistically significant. The larger the number of patients enrolled in a study, the smaller is the change that is required to achieve statistical significance. Therefore, the reader must examine the magnitude of the between-group difference and make a judgment about clinical significance.

Adverse Events

For a drug to enter into clinical investigation in humans, it must be shown to elicit no significant chemical, behavioral, physiologic, teratogenic, mutagenic, or carcinogenic effects in at least two animal models. The typical untoward or adverse events captured in a clinical trial include physical findings, laboratory results, and complaints. A comprehensive physical examination and a battery of general laboratory tests are performed at baseline and at the completion of the trial to capture any untoward events. The patients' complaints are typically captured at each study visit. The adverse clinical effects may be expected or unexpected.

Complaints may be elicited by means of a checklist or by the patients' unsolicited recall of an event. Adverse clinical events are typically greater with a checklist. The assessment of adverse events should determine the frequency and severity of the events and whether an event was severe enough to terminate participation in the study. The majority of clinical trials are powered based on outcome measures and not adverse events. There is a tendency for studies to be underpowered to detect serious adverse events, which may therefore show up only later, in postmarketing surveillance studies.

NONSURGICAL THERAPY FOR BENIGN PROSTATIC HYPERPLASIA

Watchful Waiting or "Self-Help"

A significant proportion of men with LUTS will not choose medical or surgical intervention because the symptoms are not bothersome, the complications of treatment are perceived to be greater than the inconvenience of the symptoms, and there is a reluctance to take a daily pill owing to side effects and/or the cost of treatment. Reassured that the symptoms are not caused by cancer or other serious genitourinary pathology, or that the delay in treatment will not have irreversible consequences, watchful waiting is often the patient-driven treatment of choice in the absence of absolute indications for intervention. Of 670 consecutive men with LUTS or BPH referred to 39 urologists in the Netherlands, 41%

elected watchful waiting (Stoevelaar et al, 1999). It is unreasonable to discourage an informed patient with severe symptoms and no other consequences of LUTS or BPH from pursuing watchful waiting despite the safety and effectiveness of medical therapy. Watchful waiting does not imply the total absence of intervention. The severity and bothersomeness of symptoms may be improved by simple measures such as decreasing total fluid intake especially before bedtime, moderating the intake of alcohol- and caffeine-containing products, and maintaining time-voiding schedules.

The impact of watchful waiting was examined in a study of 556 patients with moderate symptoms of BPH randomized to TURP versus watchful waiting (Wasson et al, 1995). The changes in all outcome measures were significantly greater in the TURP group. A relevant outcome for patients selecting watchful waiting is disease progression. During 3 years of follow-up, treatment failure was observed in 23 (8.2%) and 47 (17%) patients randomized to TURP and watchful waiting, respectively. Treatment failure in the watchful waiting group was most often the result of increasing PVR or symptom score. Significant renal impairment was not seen.

Brown and colleagues (2007) evaluated the effectiveness of self-management as a first-line intervention for men with LUTS in a randomized controlled trial (RCT) set in a teaching hospital and a district general hospital in London. A total of 140 men were randomized between standard care and a self-management program devised from a consensus meeting (Brown et al, 2004) which consisted of three small group sessions of standardized urinary education and lifestyle advice. Self-management significantly reduced the frequency of treatment failure and reduced urinary symptoms. A multicenter RCT of self-management showed that a rigorously structured behavioral program could significantly reduce LUTS severity and decrease objective symptoms such as nocturia, urgency, and frequency compared with standard care alone (Yap and Emberton, 2010). A Chinese study has shown there is additional benefit for self-management advice in men already receiving α -blocker therapy (Chen et al, 2012). Self-management could be considered as first-line treatment for men with LUTS. The self-management program advice given is summarized here (Yap et al, 2009).

Main Components of Self-Management Program for Men with Uncomplicated Lower Urinary Tract Symptoms

Education and Reassurance

- Discuss the causes of LUTS, including normal prostate and bladder function.
- Discuss the natural history of BPH and LUTS, including the expected future symptoms.
- Reassure that no evidence of a detectable prostate cancer has been found.

Fluid Management

- Advise a daily fluid intake of 1500 to 2000 mL (minor adjustments made for climate and activity).
- Avoid inadequate or excessive intake on the basis of a frequency-volume chart.
- Advise fluid restriction when symptoms are most inconvenient (e.g., during long journeys or when out in public).
- Advise evening fluid restriction for nocturia (no fluid for 2 hours before retiring).

Caffeine and Alcohol

- Avoid caffeine by replacing with alternatives (e.g., decaffeinated or caffeine-free drinks).
- Avoid alcohol in the evening if nocturia is bothersome.
- Replace large-volume alcoholic drinks (e.g., pint of beer) with small-volume alcoholic drinks (e.g., wine or spirits).

Concurrent Medication

- Adjust the time when medication with an effect on the urinary system is taken, to improve LUTS at times of greatest inconvenience (e.g., during long journeys and when out in public).
- Replace antihypertensive diuretics with suitable alternatives with fewer urinary effects (via the patient's general practitioner).

Types of Toileting and Bladder Retraining

- Advise men to double-void.
- Advise urethral milking for men with postmicturition dribble.
- Advise bladder retraining. Using distraction techniques (pre-terminated mind exercise, perineal pressure or pelvic floor exercises), aim to increase the minimum time between voids to 3 hours (daytime) and/or the minimum voided volume to between 200 and 400 mL (daytime). The urge to void should be suppressed for 1 minute, then 5 minutes, then 10 minutes, and so on, increasing on a weekly basis. Use frequency-volume charts to monitor progress.

Miscellaneous

- Avoid constipation in men with LUTS.

Patients' and physicians' views on treatment may not always be in agreement. In particular, patients prefer therapies affecting long-term disease progression over those that provide short-term symptom improvement, which contrasts with the beliefs of their physicians. Improved physician-patient communication may help determine best treatment options and may result in better compliance and increased treatment success (Emberton, 2010). The Self-Assessment Goal Achievement (SAGA) questionnaire has been developed to identify treatment goals and assess goal achievement in patients with LUTS and may promote patient-physician interaction and help patients establish realistic treatment goals, which may in turn improve treatment adherence and outcomes (Brubaker et al, 2011).

MEDICAL THERAPY FOR LOWER URINARY TRACT SYMPTOMS AND BENIGN PROSTATIC HYPERPLASIA

Medical therapies extensively investigated for LUTS and BPH include α -adrenergic blockers, 5 α -reductase inhibitors, aromatase inhibitors, and numerous plant extracts. Newer therapies include antimuscarinic drugs, β_3 -agonists, phosphodiesterase inhibitors (PDEIs), and several combinations of these agents. α -Adrenergic blockers and 5 α -reductase inhibitors, and the combination of both of these, are emphasized in this chapter because the safety and efficacy of drugs in these classes have been critically examined, and these drugs are widely prescribed for the treatment of LUTS and BPH. Aromatase inhibitors are briefly reviewed for historical interest. Plant extracts are also reviewed, because these agents are widely used in some parts of the world, despite the lack of properly designed clinical trials. Because plant extracts are not classified as drugs, the marketing and claims are not critically scrutinized by regulatory agencies.

Impact of Medical Therapy

Before the 1980s, prostatectomy was the only widely accepted intervention for LUTS and BPH. The enthusiasm for medical therapy has been supported in part by the limitations of prostatectomy, which include the morbidity of the surgical procedure, failure to invariably achieve a successful outcome, and a small but significant re-treatment rate (Lepor, 1993). Although medical therapies do not achieve the same level of efficacy as prostatectomy, the attractive features of medical therapy relative to prostatectomy are that clinically significant outcomes are obtained with fewer, less serious, and reversible side effects. Because the indication for intervention in the overwhelming majority of patients with LUTS is to improve quality of life by relieving symptoms (Emberton et al, 2008), the lower morbidity of medical therapy is of paramount importance in patient-driven treatment decisions.

In 1990, TURP was second only to cataract surgery in terms of expenditures paid by the U.S. Medicare program. Medical therapy is currently considered the preferred treatment alternative for those individuals who lack absolute indications for surgery. Because the overwhelming majority of men undergoing TURP lack absolute indications for intervention (Mebust et al, 1989) and prefer nonsurgical options (Emberton et al, 2008), the number of prostatectomies performed throughout the world has decreased significantly.

A survey of the U.S. Medicare database also revealed that the absolute number of prostatectomies decreased from 250,000 in 1987 to 116,000 in 1996 to 88,000 in 2000 (Wasson et al, 2000) and has stabilized since then. This 55% reduction in TURP has occurred despite the progressively increasing number of men enrolled in the Medicare program and the overall increase in U.S. spending on BPH (Wei et al, 2005). Similar reductions in TURPs have been reported from France, Canada, Denmark, Germany, and the United Kingdom.

Approximately 30% of American men older than 50 years have moderate to severe symptoms (Chute et al, 1993; Lepor and Machi, 1993). Based on the demographics of the U.S. population, approximately 6.5 to 8.7 million men are eligible to discuss LUTS and BPH treatment options (Jacobsen et al, 1995; Wei et al, 2005). The overwhelming majority of these men would not elect prostatectomy owing to the risks associated with surgical intervention. These individuals are potential candidates for medical therapy.

Selecting Candidates for Medical Therapy

The ideal candidate for medical therapy should have symptoms that are bothersome and negatively affect quality of life so that the patient is willing to make a long-term commitment to medical therapy, providing the drug is effective and adverse experiences are minimal. There are currently no scientific data to support offering medical therapy to individuals with absolute indications for intervention. Individuals with recurrent urinary retention, recurrent UTIs, renal insufficiency, bladder calculi, and recurrent gross hematuria may develop life-threatening consequences from their BOO if it is not managed surgically. Until properly controlled clinical studies unequivocally demonstrate favorable outcomes, patients with absolute indications for intervention should be discouraged from selecting medical therapy. If informed patients are willing to accept potential risks, medical therapy may be offered with a proviso for careful follow-up and future prostatectomy if medical therapy proves ineffective.

Preventing Benign Prostatic Hyperplasia with Medical Therapy

A potential role of medical therapy is to prevent the development of LUTS or BPH or its progression. There are several factors limiting the enthusiasm for preventing the development of LUTS and BPH. The clinical manifestations of LUTS and BPH are rarely life-threatening. Preventative intervention would have to be initiated before the fifth decade of life, coinciding with the development of BPH (Partin, 2000). The long-term exposure to drug-induced adverse events and the prohibitive costs are the primary limitations of prevention therapy. In addition, effective medical and surgical therapy exists when LUTS or BPH ultimately does become clinically evident. Because there are no clinical, biochemical, or genetic predictors of BPH development or progression, every male is potentially at risk. The ability to identify those individuals who are predisposed to develop LUTS or BPH refractory to medical therapy would provide a more compelling rationale for prophylaxis. There is good evidence that men with very large prostates (and usually higher PSA values) are at greater risk for developing urinary retention (Jacobsen et al, 1997) and that medical therapy (finasteride or dutasteride) can significantly decrease this risk of developing urinary retention (McConnell et al, 1998; Roehrborn et al, 2004). The decision to offer preventative therapy for urinary retention depends on the risk of the events, cost associated with treatment, and patient preferences for intervention.

THERAPY WITH α -ADRENERGIC BLOCKERS

Rationale for α -Adrenergic Blockers

The rationale for α -adrenergic blockers in the treatment of LUTS is based on the hypothesis that the pathophysiology of LUTS is in part caused by BOO, which is mediated by α_1 adrenoceptors associated

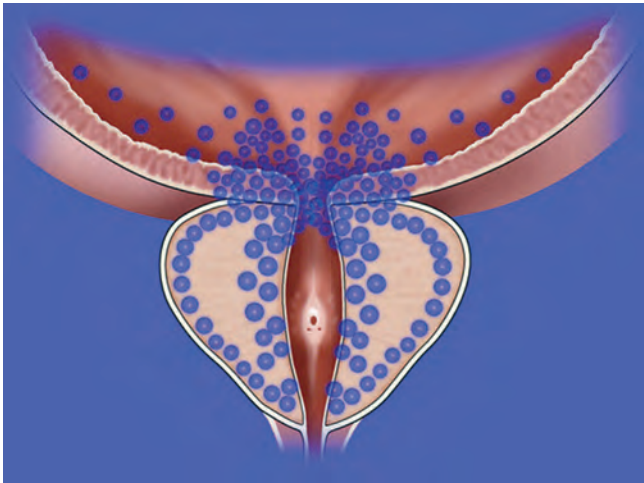


Figure 104-4. Distribution of α_1 -adrenergic receptors in the lower urinary tract.

with prostatic smooth muscle (Caine et al, 1976, 1978) (Fig. 104-4). The importance of this dynamic obstruction was supported by morphometric studies demonstrating that smooth muscle is one of the dominant cellular constituents of BPH, accounting for 40% of the area density of the hyperplastic prostate (Shapiro et al, 1992). Caine and coworkers reported that the human prostate contracts in the presence of the α -adrenergic agonist norepinephrine. Several investigators subsequently demonstrated that the tension of prostate smooth muscle is mediated by the α_1 adrenoceptor (Hieble et al, 1985; Lepor et al, 1988; Gup et al, 1989). Lepor and coworkers were the first investigators to characterize the α_1 adrenoceptors in the human prostate using radioligand binding studies. These investigators subsequently reported that 98% of the α_1 adrenoceptors are localized to the prostatic stroma (Kobayashi et al, 1994). The importance of the adrenergic innervation of the prostate was further supported by the observation of high levels of norepinephrine in the human prostate (Lepor, 1990). Although the finding of high levels of smooth muscle α_1 adrenoceptors and norepinephrine in the human prostate suggests an important role of the adrenergic innervation in prostatic function, it cannot be assumed that these factors are directly responsible for LUTS. Lepor (1990) reported no significant differences among norepinephrine levels, α_1 adrenoceptor density, and isometric contractile responses to phenylephrine (Gup et al, 1989) in BPH tissues obtained from men with symptomatic and asymptomatic BPH. Other investigators have shown α_1 adrenoceptor levels to be higher in prostatic adenoma relative to prostatic capsule (Yamada et al, 1987; Kawabe et al, 1990). These observations simply show regional differences of α_1 adrenoceptors in the prostate and do not prove that LUTS is caused by upregulation of the α_1 adrenoceptors.

The most definitive evidence that blockade of prostate α_1 adrenoceptors relieves BOO was the observed direct relationship between the area density of prostate smooth muscle and the change in the PFR in 26 patients undergoing prostatic biopsy before initiation of α -blocker therapy with terazosin (Shapiro et al, 1992). Although the prostates of the patients achieving symptom improvement had a significantly greater group mean area density of smooth muscle compared with those of nonresponders, a direct relationship between prostate smooth muscle area density and change in symptom scores was not observed. These observations suggest that nonprostate smooth muscle-mediated α_1 adrenoceptor events may also be responsible for the effectiveness of α blockade and that α_1 -mediated symptom improvement and decreases in BOO are mediated by different mechanisms.

Classification of α -Adrenergic Blockers

α -Adrenergic blockers may be classified according to α adrenoceptor selectivity and serum elimination half-life (Table 104-1).

TABLE 104-1 Classification of α -Adrenergic Blockers and Recommended Doses

CLASS OF α -BLOCKER	DOSE
NONSELECTIVE	
Phenoxybenzamine	10 mg bid
α_1	
Prazosin	2 mg bid
Alfuzosin IR	2.5 mg tid
Indoramin	20 mg bid
LONG-ACTING α_1	
Terazosin	5 or 10 mg qd
Doxazosin	4 or 8 mg qd
Alfuzosin SR	10 mg qd
SUBTYPE SELECTIVE	
Tamsulosin	0.4 mg qd
Silodosin	4-8 mg qd
Naftopidil	25-75 mg/day

bid, twice a day; IR, immediate release; qd, once a day; SR, sustained release; tid, three times a day.

Phenoxybenzamine, a nonselective α -blocker, was shown to be highly effective for LUTS and BPH (Caine et al, 1976, 1978). The limitation of phenoxybenzamine was the high incidence and severity of adverse clinical events. Berthelsen and Pettinger (1977) described two subtypes of the α adrenoceptors (α_1 and α_2). Prazosin was one of the first α_1 adrenoceptor antagonists to be investigated for the treatment of LUTS and BPH (Hedlund et al, 1983). The efficacy of phenoxybenzamine and prazosin is comparable; however, prazosin is better tolerated, implying that efficacy and toxicity are mediated primarily by the α_1 and α_2 adrenoceptors, respectively (Lepor, 1989). Prazosin and other α_1 antagonists, including alfuzosin (Jardin et al, 1991) and indoramin (Ramsay et al, 1985), require at least twice-daily administration owing to the relatively short serum elimination half-lives. The next advance in the development of α -blockers was the development of advanced drugs with serum elimination half-lives that allowed for once-a-day administration. Terazosin (Lepor et al, 1992) and doxazosin (Gillenwater et al, 1995), tamsulosin (Chapple et al, 1997; Narayan and Tewari, 1998; Wilt et al, 2002b), and extended-release (ER) alfuzosin (van Kerrebroeck et al, 2000; McNeill et al, 2005) are long-acting α -blockers that have been shown to be safe and effective for the treatment of LUTS and BPH.

Molecular cloning studies have identified three subtypes of the α_1 adrenoceptors (Andersson et al, 1997). Price and coworkers (1993) reported that the mRNA encoding the α_{1A} adrenoceptors is predominant in the human prostate. The fact that the α_{1A} mRNA is translated does not mean the encoded protein is translated. Lepor and associates reported that with use of autoradiographic (Kobayashi et al, 1994) and immunohistochemical (Walden et al, 1997) techniques, the α_{1A} adrenoceptors and α_{1B} adrenoceptors are predominant in the human stroma and epithelium, respectively. Prostate smooth muscle tension was shown to be mediated by the α_{1A} adrenoceptors (Forray et al, 1994).

Tamsulosin is a once-daily administered α_1 antagonist that exhibits some modest degree of selectivity for the α_{1A} versus the α_{1B} adrenoceptors and no selectivity for the α_{1A} versus the α_{1D} adrenoceptors (Foglar et al, 1995). The pharmaceutical industry has developed α_1 antagonists that are 1000-fold selective for the α_{1A}

adrenoceptors versus α_{1B}/α_{1D} (Forray et al, 1994). Recently silodosin has been introduced. This agent shows 162:1 selectivity for α_{1A} adrenoceptors versus α_{1B} adrenoceptors.

Interpreting the α -Adrenergic Blocker Literature

Meta-analyses derived from the α -blocker literature are often misleading because all of the data for a given drug are combined independent of dose and study design.

Study Designs

Four study designs have been used to investigate α -blockers for LUTS and BPH: titration to fixed dose, titration to response, titration to maximal dose, and randomized dose withdrawal.

Patients enrolled in **titration to fixed dose** studies receive one of several predetermined final doses independent of clinical response unless significant adverse effects are encountered. An advantage of this study design is that dose-dependent efficacy and safety of different doses are determined. A disadvantage is the requirement for a large sample size to identify statistically significant differences between placebo and all of the treatment groups.

Titration to response design allows the investigators to titrate the dose to a threshold response or maximal dose. An advantage of this design is a smaller sample size because all patients receiving active treatment are analyzed as a composite group independent of final dose. A disadvantage of this design is that the maximal therapeutic effect may be underestimated if the titration is not to maximal response. The data are also misleading if expressed in terms of group mean changes according to final dose because all nonresponders are titrated to the maximal dose in the absence of toxicity.

A **randomized dose withdrawal** design begins with an open-label dose titration. All responders are randomized to active drug or placebo. An advantage of this design is the enrichment of responders. A disadvantage is that the results are not generalizable to untreated patients.

A **titration to maximal dose** design, like titration to response, requires a relatively small sample size because there is only one active treatment group. This study design defines maximal clinical response achievable in practice, providing the maximal dose is also the most efficacious tolerable dose.

Dose Response

Multicenter, randomized, placebo-controlled studies have consistently shown that symptom and flow improvement is dependent on the dose of the α_1 -blockers. The differences between the effectiveness of different doses were often not statistically significant because these dose-ranging studies were not adequately powered to show significant differences between dose groups. MacDiarmid and coworkers (1999) have provided the most compelling evidence for a positive correlation relationship between dose and effectiveness of α_1 -blockers in the treatment of LUTS and BPH. Responders to 4 mg of doxazosin were randomized in a double-blind manner to receive 4 mg or 8 mg of doxazosin. The improvement observed in the 8-mg group was 3.7 symptom units greater than in the 4-mg group ($P = .03$). In phase 3 trials, the impact of dose observed in the responders is diluted by the lack of effect in the nonresponders. In clinical practice, nonresponders are withdrawn from treatment.

Review of the Literature

Several reviews have summarized the extensive clinical experiences with α -blockade in LUTS and BPH (Chapple, 1998; Djavan and Marberger, 1999; Lowe, 1999; Lepor et al, 2000; Kaplan, 2008). To date there have been at least 15 systematic reviews of α -blockers in the literature (Yuan et al, 2013), all showing them to be superior to placebo in symptom improvement.

Nonselective and short-acting α_1 antagonists are used less commonly in clinical practice owing to tolerance and the requirement for multiple daily doses. Randomized, double-blind,

placebo-controlled studies have reported the safety and efficacy of phenoxybenzamine (Caine et al, 1978; Abrams et al, 1982), prazosin (Hedlund et al, 1983; Kirby et al, 1987; Le Duc et al, 1990; Ruutu et al, 1991; Chapple et al, 1992), indoramin (Iacovou and Dunn, 1987; Chow et al, 1990; Stott and Abrams, 1991), and IR alfuzosin (Ramsay et al, 1985; Carbin et al, 1991; Jardin et al, 1991; Hansen et al, 1994). With the exception of alfuzosin, these studies typically enrolled relatively small numbers of patients into short-term single-dose studies without quantitative assessment of symptom improvement. Multicenter, randomized, double-blind, placebo-controlled studies have examined the safety and efficacy of the long-acting α -blockers terazosin, doxazosin, tamsulosin, and sustained-release (SR) alfuzosin. In general, patients enrolled in these studies had moderate to severe symptoms, PVR less than 300 mL, and no absolute indications for surgical intervention. Representative studies are reviewed to illustrate the safety, efficacy, and most effective use of α -blockers in LUTS and BPH. The reader is referred to the original articles for more comprehensive outcome assessments.

Terazosin

Randomized, double-blind, multicenter, placebo-controlled studies have consistently demonstrated the efficacy and safety of terazosin for LUTS and BPH (Di Silverio, 1992; Lepor et al, 1992; Lloyd et al, 1992; Brawer et al, 1993; Elhilali et al, 1996; Lepor et al, 1996; Roehrborn et al, 1996) (Table 104-2). The multicenter, double-blind, parallel-group, randomized, placebo-controlled study of once-a-day administration of terazosin to patients with symptomatic LUTS or BPH reported by Lepor and associates (1992) is representative of the expectations of terazosin therapy. Two hundred eighty-five patients entered the double-blind treatment receiving either placebo or 2, 5, or 10 mg of terazosin once daily. Statistically significant decreases from baseline obstructive, irritative, and total symptom scores were observed for all terazosin treatment groups. The levels of improvement in the symptom scores were dose dependent. The levels of improvement in the symptom scores were dose dependent. The 5- and 10-mg terazosin treatment groups exhibited a significantly greater mean decrease in obstructive scores relative to the placebo group (Fig. 104-5).

A statistically significant improvement from baseline was seen in the peak and mean urinary flow rates for all the treatment groups. The effect of terazosin on PFR was also dose dependent. The 10-mg treatment group exhibited a significantly greater increase from baseline in peak and mean urinary flow rates relative to the placebo group. A significantly greater proportion of patients in the 10-mg terazosin treatment group exhibited a greater than 30% improvement in PFR compared with the placebo group. Overall, the adverse events in the four treatment groups were minor and reversible. Although higher incidences of asthenia, flu syndrome, and dizziness were observed in the terazosin treatment groups, the differences from placebo were not statistically significant. There was a significantly greater incidence of postural hypotension in the 5-mg terazosin group than in the placebo group. The incidence of syncope for all terazosin-treated patients was less than 0.5%.

There is legitimate concern regarding whether the results of multicenter studies conducted primarily at tertiary medical centers are generalizable to community practice. Roehrborn and coworkers (1996) reported the results of the Hytrin Community Assessment Trial (HYCAT), which enrolled 2084 men into a 1-year randomized double-blind study comparing the safety and effectiveness of terazosin versus placebo. The overwhelming majority of the patients were enrolled by urologists in community practice, and the daily dose of terazosin was titrated up to 10 mg based on the discretion of the principal investigators. The treatment-related improvements (terazosin minus placebo) in the AUA Symptom Index score and urinary PFR were 1.4 mL/sec and 3.9 symptom units, respectively. The treatment-related incidences of dizziness, asthenia, and peripheral edema were 5.9%, 4.6%, and 3.1%, respectively.

TABLE 104-2 Efficacy of Terazosin in Benign Prostatic Hyperplasia

STUDY	ENROLLED (NO.)	RANDOMIZED TREATMENT (MONTHS)	DOSE (mg)	GROUP MEAN DIFFERENCE FROM PLACEBO	
				PFR (mL/sec)	SYMPTOM SCORE
Lepor et al, 1992	285	3	2	+1.1	−1.0
			5	+0.6	−1.3*
			10	+1.9†	−2.3‡
Brawer et al, 1993	160	6	Titration to response§	+1.4*	−3.5*
Roehrborn et al, 1996	2084	12	Titration to response§	+1.4*	−4.0‡
Elhilali et al, 1996	224	6	Titration to response§	+1.3	−1.8

**P* < .05.
†*P* < .01.
‡*P* < .001.
§Maximal dose 10 mg.
PFR, peak flow rate.

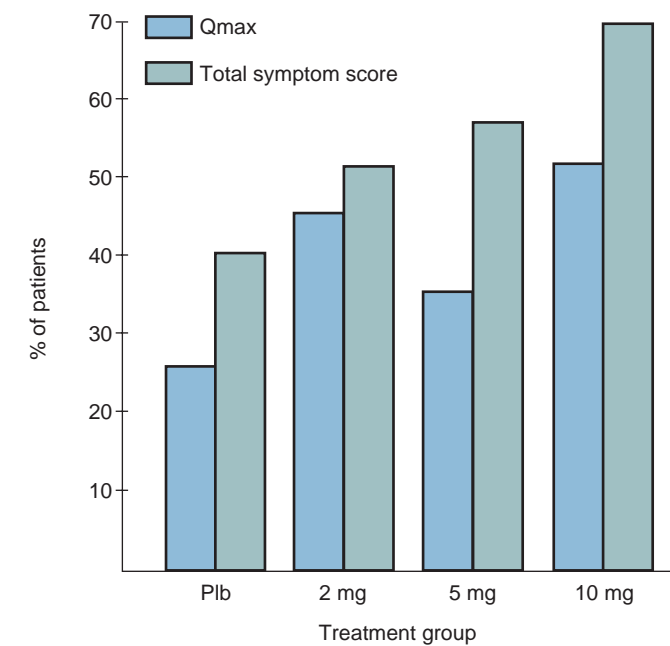


Figure 104-5. Two hundred eighty-five patients were enrolled in a randomized double-blind study comparing placebo (Plb) and 2-mg, 5-mg, and 10-mg terazosin administered once daily. Percentages of patients experiencing more than 30% improvement in total symptom scores and peak urinary flow rates are shown. (From Lepor H. Medical therapy for benign prostatic hyperplasia. *Urology* 1993;42:483–501.)

Kirby (1998) examined the mean changes in blood pressure according to whether patients were normotensive or hypertensive at baseline (Table 104-3). In general, in normotensive men, small, clinically insignificant decreases in blood pressure were noted. Untreated hypertensive men had larger and clinically significant decreases in blood pressure. In men with medically controlled hypertension, terazosin had no clinically significant effect on blood pressure, whereas in men with poorly controlled medically treated hypertension, terazosin significantly lowered blood pressure.

Doxazosin

The half-life of doxazosin is longer than that of terazosin (22 vs. 12 hours). The efficacy, safety, and durability of clinical response of doxazosin has been demonstrated in multicenter, randomized, double-blind, placebo-controlled studies (Chapple et al, 1994; Fawzy et al, 1995; Gillenwater et al, 1995) (Table 104-4) and a

TABLE 104-3 Effect of Terazosin on Blood Pressure in Normotensive and Hypertensive Men

	TREATMENT-RELATED CHANGES IN SYSTOLIC BLOOD PRESSURE/ DIASTOLIC BLOOD PRESSURE (mm Hg)	
	NORMOTENSIVE MEN	HYPERTENSIVE MEN
No antihypertensive treatment	−3.1/−1.7	−13.7/−10.7
Antihypertensive treatment	−2.8/−0.2	−12.6/−11.5

long-term open-label extension study. Fawzy and associates (1995) reported a 16-week multicenter, randomized, double-blind, placebo-controlled titration-to-response study in 100 normotensive patients with LUTS and BPH. Of the 41 evaluable patients receiving doxazosin, 88% underwent titration to the maximal dose (8 mg). The group mean changes in PFR and symptom score were significantly greater in the doxazosin group compared with the placebo group (see Table 104-4). The magnitudes of these treatment-related effects were similar to those of terazosin. The systolic blood pressure changes in normotensive patients were greater than those with terazosin. The treatment-related incidences of dizziness, fatigue, headache, somnolence, hypotension, and nausea were 20%, 8%, 8%, 6%, 8%, and 8%, respectively. The percentages of patients withdrawing because of an adverse event were 14% and 2.1% in the doxazosin and placebo groups, respectively. The treatment-related incidence of adverse clinical events in this doxazosin study appears slightly higher than that of terazosin and may be a result of its greater effect on blood pressure.

Gillenwater and coworkers (1995) reported a multicenter, randomized, double-blind, placebo-controlled titration-to-fixed dose study comparing placebo versus 2, 4, 8, and 12 mg of doxazosin in 248 men with mild-to-moderate essential hypertension. The group mean changes in PFR and Boyarsky symptom score are summarized in Table 104-4 according to treatment groups. Because relatively small numbers of patients were randomized into the individual treatment groups, the failure to demonstrate statistical significance between placebo and some of the active treatment groups reflects the small sample size. The group mean improvement in PFR was dose dependent and statistically significant relative to placebo for all active treatment groups. The mean improvements in symptom scores relative to placebo for the group were statistically significant for the 4- and 8-mg doxazosin groups. Statistically and clinically significant changes in systolic blood pressure were observed between

TABLE 104-4 Efficacy of Doxazosin in Benign Prostatic Hyperplasia

STUDY	ENROLLED (NO.)	RANDOMIZED TREATMENT (MONTHS)	DOSE (mg)	GROUP MEAN DIFFERENCE FROM PLACEBO	
				PFR (mL/sec)	SYMPTOM SCORE
Chapple et al, 1994	135	3	4	+1.5	NR
Fawzy et al, 1995	100	4	Titration 2-8 mg	+2.2*	-3.2†
Gillenwater et al, 1995	248	3.5	2	+1.4	-2.5
			4	+2.2‡	-4.7*
			8	+3.2*	-3.9†
			12	+3.5*	-2.1

* $P < .01$.† $P < .001$.‡ $P < .05$.

NR, not reported; PFR, peak flow rate.

the placebo and the 4-, 8-, and 12-mg doxazosin groups. Lowering of blood pressure was a desirable outcome in these hypertensive patients. The overall treatment-related incidences of dizziness and fatigue were 15% and 10%, respectively. The percentages of patients withdrawing because of an adverse event in the doxazosin versus placebo groups were 11.1% and 4.1%, respectively. **Statistically significant changes in symptom scores and PFR relative to baseline have been reported in a long-term open-label doxazosin extension study (Lepor, 1995).** The initial improvements in symptom scores and PFR in 450 patients were maintained for up to 42 months. Kirby (1995) summarized the effects of doxazosin on blood pressure in normotensive and hypertensive men enrolled into two double-blind, placebo-controlled trials (Fawzy et al, 1995; Gillenwater et al, 1995). The treatment-related group mean reductions in sitting systolic blood pressure in the normotensive and hypertensive patients were 3 and 17 mm Hg, respectively. The treatment-related group mean reductions in sitting diastolic blood pressure in the normotensive and hypertensive patients were 4 and 3 mm Hg, respectively.

The controlled-release gastrointestinal therapeutic system (GITS) formulation of doxazosin reduces the plasma peak-to-trough ratio to minimize the need for titration. To compare the two formulations in 795 men with LUTS or BPH, doxazosin standard was initiated at 1 mg/day, titrated to 2 mg/day after 1 week, to 4 mg/day at 3 weeks, and to 8 mg/day at 7 weeks if indicated. This regimen was compared with doxazosin GITS initiated at 4 mg once daily and titrated to 8 mg once daily after 7 weeks if indicated, and to a placebo group over 13 weeks. The symptoms of LUTS were measured with the IPSS, which has seven questions (covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency) scored 0 (absent) to 5 (severe). On the IPSS, there was an improvement of -8.4 and -8.0 with doxazosin standard and GITS, respectively, compared with -6.0 in the placebo group. Doxazosin standard and GITS produced clinically comparable increases in mean peak urinary flow rate, compared with placebo, with a greater improvement observed earlier after treatment with doxazosin GITS than with the doxazosin standard. A similar number of patients in both doxazosin groups were titrated to the maximum dose of 8 mg for both formulations. The incidence of adverse effects was slightly higher with doxazosin standard than doxazosin GITS and placebo, which caused a similar incidence.

The aforementioned study and another with 680 men were combined to further analyze the comparison between doxazosin standard and GITS (Kirby et al, 2003). In addition to confirmation of the results given earlier, a subgroup reporting sexual dysfunction at baseline had a modest clinical improvement in sexual function with both preparations of doxazosin. Treatment-related adverse events occurred in 16.1% of patients on doxazosin GITS, 25.3% of patients on doxazosin standard, and 7.7% of placebo patients. Headache

and dizziness occurred in 6.0% and 5.3% of doxazosin GITS patients compared with 5.1% and 9.1% of doxazosin standard patients, respectively (placebo, 4.5% and 1.9%, respectively). Fewer patients on doxazosin GITS (5.7%) or placebo (2.6%) discontinued treatment because of adverse events than on doxazosin standard (7.2%). The reduction in blood pressure was not clinically significant in the normotensive patients, but there were clinically significant reductions in blood pressure with both preparations of doxazosin. A comparison of the nonconcurrent multicenter, randomized, double-blind, placebo-controlled studies of terazosin (see Table 104-2) and doxazosin (see Table 104-4) shows similar efficacy. Studies of doxazosin versus tamsulosin (Kirby et al, 2003) and doxazosin versus alfuzosin (de Reijke et al, 2004) revealed only minor differences in safety and efficacy.

α -Blockers such as doxazosin may influence smooth muscle growth in the prostate. In BPH patients treated with α_1 -adrenoceptor antagonists, there is a decreased expression of myosin heavy chain mRNA, a functional marker for the smooth muscle phenotype (Lin et al, 2001).

Biopsy and prostatectomy specimens from untreated and doxazosin-treated BPH patients suggest that doxazosin may induce apoptosis in both the epithelial and stromal cells with little effect on cell proliferation. The apoptosis was associated with a decrease in α -smooth muscle actin expression and stromal regression. Another study showed that the mean pretreatment baseline apoptosis was 1.9% and 1.0% for the epithelial and stromal prostate components. The mean apoptotic indexes increased after 3 months of doxazosin treatment for BPH to 6% in the glandular epithelial and 12% in the smooth muscle cells. By 12 months after treatment, epithelial apoptosis had decreased to constitutive levels, whereas the apoptotic index of prostatic stromal cells remained high (Kyprianou et al, 1998).

In primary cultures of human prostate stroma cells, doxazosin increased apoptosis and decreased cell numbers. Transforming growth factor- β 1 (TGF- β 1) also decreased cell numbers, and because doxazosin increased the levels of TGF- β 1 in the cells, it was suggested that the effect of doxazosin may be mediated through TGF- β 1 (Ilio et al, 2001).

The ability of doxazosin to induce apoptosis may be shared with the other quinazoline-based α_1 -adrenoceptor antagonists terazosin and prazosin, although it seems unlikely that this effect is α_1 -adrenoceptor mediated (Gonzalez-Juanatey et al, 2003). The apoptotic effects of the quinazoline-based α_1 -adrenoceptor antagonists may be linked to their ability to inhibit hERG potassium channels, which has been demonstrated using cloned channels expressed in *Xenopus* oocytes (Thomas et al, 2004).

Recent data also suggest that doxazosin may have a mildly beneficial impact on sexual function in men with LUTS and BPH (Kirby et al, 2005). The mechanism for this effect is uncertain but may be the result of a vasodilatory action within the corpora cavernosa.

TABLE 104-5 Efficacy of Tamsulosin in Benign Prostatic Hyperplasia

STUDY	ENROLLED (NO.)	RANDOMIZED TREATMENT (MONTHS)	DOSE (mg)	GROUP MEAN DIFFERENCE FROM PLACEBO	
				PFR (mL/sec)	SYMPTOM SCORE
Kawabe et al, 1990	270	1	0.1	+0.3	NR
			0.2	+2.6	NR
			0.4	+2.1	NR
Abrams et al, 1995	313	2¼	0.4	+1.7*	-1.3†
Lepor, 1998	756	3	0.4	+1.3‡	-2.8‡
			0.8	+1.7‡	-3.2‡
Narayan et al, 1998	735	3	0.4	+0.6	-1.5†
			0.8	+0.9†	-2.2†

* $P < .05$.† $P < .01$.‡ $P < .001$.

NR, not reported; PFR, peak flow rate.

Tamsulosin

Tamsulosin is currently the most widely used α_1 antagonist investigated for LUTS and BPH (Foglar et al, 1995). One of the features of tamsulosin is that it exhibits some degree of specificity for the α_{1A} adrenoceptors (Foglar et al, 1995). The efficacy and safety of tamsulosin has been investigated in four multicenter, randomized, double-blind, placebo-controlled studies (Kawabe et al, 1990; Abrams et al, 1995; Lepor, 1998; Narayan et al, 1998) (Table 104-5).

Lepor (1998) and coworkers reported a multicenter, randomized, double-blind, placebo-controlled study of 756 American men with clinical LUTS and BPH randomized to receive placebo or 0.4 or 0.8 mg of tamsulosin for 13 weeks. The mean changes in AUA symptom score, PFR, and adverse events are summarized in Table 104-5. The symptom score improvements were significantly greater in the 0.8-mg tamsulosin group compared with the 0.4-mg group. The treatment-related incidences of dizziness, asthenia, rhinitis, and abnormal ejaculation in the 0.4-mg group were 5%, 3%, 3%, and 6%, respectively, and in the 0.8-mg group they were 6%, 3%, 9%, and 18%, respectively. The mean changes in systolic and diastolic blood pressure in the placebo and tamsulosin groups were not significantly different for both hypertensive and normotensive patients. In the patients who were hypertensive and uncontrolled, the systolic blood pressure changes in the placebo, 0.4-mg, and 0.8-mg groups were -8.4, -7.2, and -10.2 mm Hg, respectively.

Of the 618 patients who completed the 13-week randomized study reported by Lepor (1998) and coworkers, 418 (68%) continued into the 40-week extension study on the same double-blind medication and dose. The symptom and flow rate improvements observed at the end of the 13-week study were maintained throughout the 40-week extension study.

Narayan and associates (1998) reported the results of a randomized, double-blind, placebo-controlled trial comparing the safety and effectiveness of 0.4 and 0.8 mg of tamsulosin versus placebo. Seven hundred thirty-five men were randomized in the study. The active treatment was 13 weeks. The treatment-related improvements in the AUA symptom score and PFR were comparable with those reported by Lepor (1998) and coworkers. The differences between 0.4 mg and 0.8 mg were not statistically significant; however, the study lacked statistical power to show clinically significant differences between the active treatment groups. The treatment-related incidences of asthenia, dizziness, rhinitis, and abnormal ejaculation observed for the 0.4-mg tamsulosin group were 2%, 5%, 3%, and 11%, respectively. The incidences of retrograde ejaculation and rhinitis were significantly greater in the 0.8-mg group compared with the 0.4-mg group. No statistically or clinically significant differences were observed for systolic blood pressure between any of the treatment groups.

A systematic review of tamsulosin therapy for LUTS/BPH has been published (Wilt et al, 2002b). This included 14 studies with a total of 4122 patients. The mean change in symptom score was 12% for the 0.4-mg dose and 16% with the 0.8-mg dose. Improvements in flow rate were 1.1 mL/sec for both doses. In general, adverse events were mild and included dizziness, rhinitis, and abnormal ejaculation. These increased in a dose-dependent manner, with discontinuations resulting from such effects similar to placebo at 0.2 mg but increasing to 16% with the 0.8-mg/day dose.

Alfuzosin

Jardin and colleagues (1991) reported the first large-scale, multicenter, randomized, placebo-controlled trial demonstrating that alfuzosin was safe and effective for the treatment of LUTS and BPH (Table 104-6). A long-term open-label extension study showed that the effectiveness of alfuzosin was durable up to 30 months (Jardin et al, 1994). The primary limitation of alfuzosin was a requirement for multiple daily doses (2.5 mg three times a day or 5 mg twice a day). In the absence of any demonstrable advantage over the once-a-day drugs such as terazosin, doxazosin, and tamsulosin, there was no compelling reason to prescribe alfuzosin.

ER or SR alfuzosin is a new formulation that allows for a once-daily dosing regimen without dose titration. Buzelin and coworkers (1997a, 1997b) reported the first randomized, multicenter, placebo-controlled trial evaluating the safety and effectiveness of SR alfuzosin for the treatment of LUTS and BPH. Three hundred and ninety patients were randomized to once-daily 5 mg alfuzosin versus placebo for 12 weeks. The treatment-related improvements in the IPSS and PFR were -1.6 symptom units and 1.3 mL/sec, respectively. The incidences of dropouts because of adverse events were 4.6% and 7.1% in the SR alfuzosin and placebo groups, respectively. The 2-mm Hg change in systolic and diastolic blood pressure was not significantly different from that in the placebo group. The incidences of dizziness and asthenia were similar in the SR alfuzosin and placebo groups.

SR alfuzosin (10 mg once a day) has been compared with IR alfuzosin (2.5 mg three times daily) and placebo (van Kerrebroeck et al, 2000). After a 1-month placebo lead-in, 447 patients were randomly assigned in equal proportions to the three treatment groups for 3 months. The improvements in the IPSS were 6.9, 6.4, and 4.9 in the alfuzosin 10 mg/day, alfuzosin 2.5 mg three times a day, and placebo groups, respectively. The symptom improvement observed in both active treatment groups was significantly greater than that in the placebo group. The improvements in the filling and voiding subscores and quality-of-life index were also significantly greater in the active treatment group relative to the placebo group. The improvements in the PFR were 2.3 mL/sec, 3.2 mL/sec, and 1.4 mL/sec in the SR alfuzosin, IR alfuzosin, and placebo groups,

TABLE 104-6 Efficacy of Alfuzosin in Benign Prostatic Hyperplasia

STUDY	ENROLLED (NO.)	RANDOMIZED TREATMENT (MONTHS)	DOSE (mg)	GROUP MEAN DIFFERENCE FOR PLACEBO	
				PFR (mL/sec)	SYMPTOM SCORE
Jardin et al, 1994	518	6	7.5-10	1.5*	-1.0†
Buzelin et al, 1997b	390	3	5 bid	1.3†	-1.6‡
van Kerrebroeck et al, 2000	447	3	10 qd	0.9*	-2.0‡
			2.5 tid	1.8†	-1.5‡

* $P < .05$.† $P < .001$.‡ $P < .01$.

PFR, peak flow rate.

respectively. The modest improvements in the PFR were significantly greater in both active treatment groups compared with placebo. The incidences of dizziness were 2.1%, 4.7%, and 1.3% and of asthenia were 3.5%, 0.7%, and 2.6% in the SR alfuzosin, IR alfuzosin, and placebo groups, respectively. No sexual dysfunction was reported in the 10-mg/day alfuzosin group. There were no statistically or clinically significant treatment-related effects on blood pressure in normotensive or hypertensive patients. Of those men who were hypertensive at baseline, the mean reductions in the standing blood pressure were 8.1, 8.6, and 5.8 mm Hg, respectively, in the SR alfuzosin, IR alfuzosin, and placebo groups.

In an open extension of the ALFORTI trial there was a 35% improvement from baseline in quality of life (van Kerrebroeck et al, 2000). Some part of this effect may be the result of a mildly beneficial impact on sexual function (van Moorselaar et al, 2005).

Because of the lack of adverse effects and blood pressure changes, alfuzosin has been described as a uroselective drug (Kirby, 1998). SR alfuzosin exhibits no pharmacologic uroselectivity for any of the α_1 subtypes (Andersson et al, 1997). In vivo studies in the conscious rat have shown that alfuzosin reduces urethral pressure without significantly altering blood pressure (Martin et al, 1995). This experimental observation does not prove clinical uroselectivity because terazosin and doxazosin do not alter blood pressure in normotensive patients. Another explanation for the lack of adverse events has been the low penetration of alfuzosin into the brain (Rouquier et al, 1994).

The long-term effectiveness of IR alfuzosin 2.5 mg three times a day is supported by an open-label prospective 3-year trial involving 3228 men with LUTS or BPH (Lukacs et al, 2000). The improvements in symptom score in BPH-specific health-related quality-of-life index observed at the 3-month visit were maintained throughout the 36 months of follow-up. A total of 20.1% of the men withdrew from the study. Only 4.2% of the men discontinued therapy because of an adverse event. Only 0.3% of men experienced AUR.

Silodosin

In Japan, silodosin, a selective α_1 -adrenergic receptor antagonist, is the LUTS-BPH market leader and received FDA approval in October 2008 (Watson Pharmaceuticals, Parsippany, NJ). In two phase 3 studies, 8-mg once-daily silodosin taken for 12 weeks resulted in significant and rapid improvement of IPSS compared with placebo. Silodosin was shown to increase urine flow in 2 to 6 hours after the initial dose. Improvement of symptoms was realized in 3 to 4 days, with the majority of patients, including men on concomitant cardiovascular medications, achieving at least a three-point improvement in IPSS score, regardless of age or severity of symptoms. It was associated with a low incidence of orthostatic hypotension and syncope, fainting, and dizziness (Marks et al, 2009). As the newest agent available, silodosin has had to satisfy more rigorous cardiovascular requirements from the FDA than other, older agents. Silodosin demonstrated minimal effects on the cardiovascular system, without any meaningful prolongation of the QT interval. The most

common drug-related side effect was retrograde ejaculation (better described as anejaculation). Rates of discontinuation of therapy because of retrograde ejaculation were low. The second most commonly reported adverse event was dizziness, the rate of which was only slightly higher than in placebo-treated patients. There were no reported events of symptomatic orthostatic hypotension or dizziness when administered with a single dose of medication for erectile dysfunction (ED) in healthy men.

A randomized, double-blind, placebo-controlled study comparing silodosin with tamsulosin or placebo was conducted at 88 centers in Japan (Kawabe et al, 2006). Men aged 50 years or older with an IPSS of 8 or higher, a quality-of-life score of 3 or more, a PFR of less than 15 mL/sec, a prostate volume of 20 mL or more, and a PVR urine volume of less than 100 mL were eligible for enrollment. Patients were randomized to receive silodosin 4 mg twice daily, tamsulosin 0.2 mg once daily (i.e., a lower dose than used in the United States or Europe), or placebo, for 12 weeks; 457 men were randomized (silodosin, 176; tamsulosin, 192; and placebo, 89). Changes in the total IPSS from baseline in the silodosin, tamsulosin, and placebo groups were -8.3, -6.8, and -5.3, respectively. There was a significant decrease in the IPSS versus placebo in the silodosin group from 1 week. In the early-stage comparison, silodosin showed a significant decrease in IPSS versus tamsulosin at 2 weeks. Changes in quality of life from baseline were -1.7, -1.4, and -1.1 in the silodosin, tamsulosin, and placebo groups, respectively. Silodosin showed a significant improvement in quality-of-life score versus placebo. In the subgroup of patients with severe symptoms (IPSS ≥ 20), silodosin also gave a significantly better improvement than placebo (-12.4 vs. -8.7). The incidence rates of adverse events and drug-related adverse events were, respectively, 88.6%, 82.3%, and 71.6% and 69.7%, 47.4%, and 36.4%, respectively. The most common adverse event in the silodosin group was abnormal ejaculation, which occurred more often in the silodosin than in the tamsulosin group (22.3% vs. 1.6%). However, only five men (2.8%) discontinued treatment for abnormal ejaculation. It is unclear how men in other populations will respond to this effect. Measurement by Noguchi and colleagues (2008) of intraurethral pressure in the prostatic urethra and intraluminal pressure in the vas deferens in anesthetized male dogs given the α_1 -adrenoceptor agonist phenylephrine and then a series of α_1 -adrenoceptor antagonists showed that silodosin had the highest selectivity for the vas deferens (7.5-fold), followed by naftopidil (4.3-fold), alfuzosin (3.8-fold), tamsulosin (2.6-fold), and prazosin (2.5-fold). These results suggest that high tissue selectivity for the vas deferens over the urethra may contribute to the incidence of abnormal ejaculation.

A recent meta-analysis of silodosin included four RCTs with a total of 2504 patients and suggested that silodosin is an effective therapy for LUTS in men and is not inferior to 0.2-mg tamsulosin (Ding et al, 2013). In addition, a recent review suggests that silodosin is a rapidly efficacious and safe agent in the treatment of LUTS or BPH in men. A lack of clinically important cardiovascular side effects makes it of potential use in the elderly. The higher risk of ejaculatory dysfunction may make it unsuitable for younger men (Osman et al, 2012). In a urodynamic study of 57 patients,

the storage phase of the pressure flow study showed that the bladder capacity at first desire to void increased significantly, the number of patients with UDCs reduced, and mean detrusor pressure at maximum flow significantly decreased from 72.5 to 51.4 cm H₂O, after 4 weeks' treatment with 8 mg silodosin. The mean Bladder Outlet Obstruction Index score decreased significantly from 60.6 to 33.8 (Matsukawa et al, 2009).

Naftopidil

Naftopidil, a relative α_{1D} -adrenoceptor-selective antagonist, seems more effective for patients showing a dominant expression of the α_1 -adrenoceptor subtype. The α_1 -adrenoceptor antagonists tamsulosin hydrochloride and naftopidil were administered to 96 patients with LUTS or BPH for 8 weeks in a crossover study. With the administration of both drugs, the IPSS significantly decreased and the maximum urinary flow significantly increased. Whereas Naftopidil monotherapy decreased the IPSS for storage symptoms, tamsulosin monotherapy decreased the IPSS for voiding symptoms (Ikemoto et al, 2003). It has been suggested that its preference for the α_1 -adrenoceptor subtype may give naftopidil benefits for the storage symptom component of LUTS. A Cochrane systematic review found relatively few published data on naftopidil (Garimella et al, 2009), although a recent patient preference study showed no substantial differences between it and silodosin (Masuda et al, 2012).

Effects of α -Adrenergic Blockers on Bladder Outlet Obstruction

The primary objective of medical therapy is to improve urinary symptoms. The relevance of urodynamic studies for assessing the clinical use of medical therapy for LUTS is controversial. A drug that improves urodynamic parameters of BOO without relieving LUTS would be of limited clinical usefulness. Conversely, a drug that relieves LUTS without improving urodynamic parameters of BOO would still be of great clinical importance. There are relatively few randomized, placebo-controlled studies examining the effects of α -blockers on pressure-flow parameters. One of the limitations to designing these urodynamic studies is the definition of a clinically significant outcome.

Martorana and colleagues (1997) reported a randomized, double-blind, placebo-controlled study examining the effect of 1 month of alfuzosin, 2.5 mg three times a day, on pressure-flow urodynamic parameters. The changes in detrusor pressure at maximum flow, detrusor opening pressure, and maximum detrusor pressure were significantly greater in the alfuzosin treatment group compared with the placebo group. There were no significant differences between the effects of alfuzosin and those of placebo on PFR.

α -Blockers and Sexual Function and Sexual Side Effects

Sexual function is complex and includes multiple domains such as sexual desire (libido), erectile function, and ejaculatory function. Erectile and ejaculatory functions are frequently reduced in patients with LUTS and can affect their quality of life. Therefore the treatment of LUTS should aim to maintain or even restore sexual function. α_1 -Adrenoceptor antagonists lack major effects on sexual desire in placebo-controlled studies (van Dijk et al, 2006). Reports on erectile function are inconsistent, with both beneficial and adverse effects being reported, but ED can occur in some patients without clear differences among drugs. Ejaculatory dysfunction during treatment may represent (relative) anejaculation. It occurs more frequently with tamsulosin and even more so with silodosin (see earlier) than with other drugs of this class.

α -Adrenergic Blockers in the Elderly

The adverse events associated with terazosin and doxazosin that may be particularly problematic in the elderly are dizziness and orthostatic hypertension. Kaplan and colleagues (1997) reviewed a personal series of 36 men with LUTS or BPH older than 80 years

treated with terazosin or doxazosin. α -Adrenergic blockers were well tolerated, and no serious adverse events were observed. This experience was not of adequate size to address the incidence of falls. Pooled analysis of multicenter, randomized, placebo-controlled studies of terazosin (Zhang and Manski, 1998), doxazosin (Kaplan and D'Alisera, 1998), and tamsulosin (Chapple et al, 1997) has revealed that the incidences of adverse events are not age dependent. It is important to emphasize that men enrolled into these studies were highly selected and so the tolerability and safety findings are not generalizable to all elderly men.

Data from population studies such as the 5872-participant Osteoporotic Fractures in Men study and a population-based case-control study using data from a managed care organization in Southern California with more than 3 million members suggest that moderate and severe LUTS independently increase the 1-year risk of falls, particularly recurrent falls, in community-dwelling older men (Parsons et al, 2009) and that there is a modest increase in risk of hip fractures associated with exposure to α -blockers, which requires further investigation (Jacobsen et al, 2008).

Formal clinical trials of tamsulosin observed a 12% incidence of orthostatic hypotension in patients taking 0.4 mg tamsulosin, and a 6% incidence in patients taking placebo 4 to 8 hours after administration, but without urgent treatment being required (U.S. Food and Drug Administration, 1997).

Bird and associates (2013) looked at U.S. health care claims data for men aged 40 to 85 years who were first prescribed tamsulosin or a 5 α -reductase inhibitor between January 2001 and June 2011 and who developed hypotension requiring hospital admission. These researchers observed an increased rate ratio for severe hypotension with tamsulosin treatment (42.4 events per 10,000 person-years) versus 5 α -reductase inhibitor treatment (31.3 events per 10,000 person-years). The greatest increase in risk varied in magnitude from 151% to 256% and was observed during the first 8 weeks of new drug use and the first 8 weeks after restarting drug treatment, suggesting a first-dose phenomenon similar to that occurring with nonselective α antagonists. This suggests that physicians should warn patients regarding a first-dose phenomenon with tamsulosin. A smaller increase in risk for hypotension, varying from 19% to 36%, persisted during maintenance tamsulosin treatment. A recent Cochrane review also found higher rates of dizziness with larger tamsulosin doses (0.8 mg, 17% dizziness; 0.4 mg, 9%; 0.2 mg, 3%), suggesting a dose-dependent effect (Wilt et al, 2002b).

α -Adrenergic Blockers and the Treatment of Lower Urinary Tract Symptoms and Coexisting Hypertension

Approximately 30% of men treated for LUTS or BPH have coexisting hypertension (Boyle and Napalkov, 1995). The α -blockers terazosin and doxazosin are established agents for the treatment of hypertension. The overwhelming clinical evidence demonstrates that terazosin and doxazosin lower blood pressure primarily in hypertensive men and that the blood pressure lowering is clinically significant (Fawzy et al, 1995; Gillenwater et al, 1995; Kirby, 1995; Lepor et al, 1997; Kirby, 1998; Lowe et al, 1999).

An interim analysis of the Anti-Hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) undermined the use of doxazosin in men at risk for developing congestive heart failure (ALLHAT Collaborative Research Group, 2000). In this study of 24,335 patients with hypertension and at least one other coronary risk factor, men were randomized to chlorthalidone, doxazosin, amlodipine, or lisinopril. A significant increased risk of congestive heart failure in the doxazosin group relative to the chlorthalidone group was the basis for the decision to discontinue the doxazosin arm of the antihypertensive trial. There was no significant increase in congestive heart failure between doxazosin and the other antihypertensive agents. Comparable levels of blood pressure reduction were achieved by both drugs. The ALLHAT study questions the role of doxazosin as first-line therapy for the treatment of hypertension. The study does not assess the relative risks and benefits of doxazosin in men with BPH and hypertension, nor does it have any bearing on the use of doxazosin

in combination with other antihypertensive agents. Doxazosin remains an acceptable agent to treat LUTS that coexists with hypertension. It should be at the discretion of the physician managing the hypertension to add additional agents for treating the hypertension. It is interesting to note that a current first-choice antihypertensive agent, carvedilol, with both β -blocker and potent and selective α_1 -adrenoceptor blockade effects has recently been shown to have a positive benefit for men with hypertension and LUTS or BPH (Lewandowski et al, 2013).

Mechanism of Adverse Events Associated with α -Adrenergic Blockade

Dizziness and asthenia are the adverse events most commonly associated with α -blocker therapy. Elucidating the mechanism of action for these adverse events is essential for α_1 subtype drug development programs. It has been assumed that dizziness and possibly asthenia were caused by cardiovascular effects. Lepor and colleagues (2000) correlated the incidence of adverse events associated with terazosin relative to blood pressure changes. Men experiencing dizziness and asthenia did not exhibit greater changes in blood pressure while on terazosin therapy. Only postural hypotension was associated with greater changes in blood pressure. α_1 -Adrenergic-mediated dizziness and asthenia are likely the result of effects at the level of the central nervous system (CNS). Therefore, it cannot be assumed that developing an α -blocker that eliminates effects on blood pressure will significantly improve the tolerability of α -blockers.

α -Blockers and Intraoperative Floppy Iris Syndrome

Intraoperative floppy iris syndrome (IFIS) complicates approximately 2% of cataract surgery cases. The clinical manifestations of IFIS are poor preoperative pupil dilation, iris billowing and prolapse, and progressive intraoperative miosis. Surgical complications are increased when IFIS is not anticipated or recognized by the surgeon. Since IFIS was first described in 2005 (Chang et al, 2005), its association with the α_1 -adrenergic antagonist tamsulosin has become well established. It appears that α_{1A} is the predominant receptor subtype in the iris dilator muscle, as well. The persistence of IFIS long after the discontinuation of tamsulosin suggests a semi-permanent muscular atrophy and loss of tone. It is not clear how long one must take tamsulosin before experiencing these chronic muscular changes. Anecdotal reports suggest that IFIS does not occur until patients have been on tamsulosin therapy for approximately 4 to 6 months. IFIS can also occur up to several years after discontinuation of tamsulosin. IFIS has also been reported but less commonly with non-subtype-specific α_1 -adrenergic antagonists, such as terazosin, doxazosin, and alfuzosin. According to an online survey, 95% of members of the American Society of Cataract and Refractive Surgery believe that tamsulosin made cataract surgery more difficult, and 77% believed it increased the risks of surgery (Chang et al, 2008).

Being able to elicit a prior history of tamsulosin use now enables cataract surgeons to anticipate IFIS and to use alternative methods of managing the complication. Prevention of IFIS by withdrawing tamsulosin preoperatively has not shown consistent benefit. Therefore, in a patient with a known diagnosis of cataract, prescribing physicians may wish to consider involving the patient's cataract surgeon before initiating tamsulosin or α -blocker treatment. Patients should also be encouraged to report any prior or current history of α_1 -antagonist use to their ophthalmic surgeon before undergoing any eye surgery. Intraoperative sub-Tenon lidocaine reduces significantly the incidence of IFIS in patients taking oral α -adrenergic inhibitors (Klysiak and Korzycka, 2014).

Comparison of α -Adrenergic Blockers

Because the therapeutic effect and adverse events associated with α -blockers are both dose dependent, the effectiveness and tolerability of two different α -blockers can be determined only in a

randomized, double-blind, placebo-controlled trial. It is imperative that these studies be appropriately powered to show statistically significant effects for effectiveness and tolerability.

Buzelin and coworkers (1997a) reported a randomized, placebo-controlled study comparing α -blockers (IR alfuzosin, 2.5 mg three times a day, versus tamsulosin, 0.4 mg/day). The improvements in Boyarsky symptom score and PFR and the incidences of dizziness and asthenia were not significantly different between the two treatment groups. The effects of alfuzosin and tamsulosin on systolic and diastolic supine or standing blood pressures in the hypertensive patients were also not significantly different. This study suggests that IR alfuzosin and tamsulosin have equivalent effectiveness and tolerability. The obvious benefit of tamsulosin is that the dose does not have to be titrated.

The recommended daily doses of terazosin, doxazosin, tamsulosin, and SR alfuzosin are 10 mg, 8 mg, 0.4 mg, and 10 mg, respectively. The clinical data suggest that terazosin, 10 mg, and doxazosin, 8 mg, are more effective than tamsulosin, 0.4 mg, and alfuzosin, 10 mg (see Tables 104-2, 104-4, 104-5, and 104-6) but the incidences of asthenia and dizziness appear to be higher for terazosin and doxazosin. **The apparent better tolerability of tamsulosin and SR alfuzosin may simply be because of degree of α_1 -blockade, and not uroselectivity.** Assessing the relative efficacy and tolerability of daily terazosin, 10 mg, or doxazosin, 8 mg, versus tamsulosin, 0.4 mg, or SR alfuzosin, 10 mg, would address this issue. In the absence of these studies, nonconcurrent studies can be compared, recognizing the potential impact of differences in study design, patient selection, recording of adverse events, and administration.

Terazosin and doxazosin exhibit very similar pharmacologic and pharmacokinetic properties. It is therefore not surprising that the effectiveness and tolerability of these two agents are also comparable. The effectiveness of terazosin and doxazosin are both dose dependent, with the greatest recorded improvements in symptom scores observed at the 10-mg and 8-mg daily doses, respectively. These doses have both been shown to be significantly more effective than lower doses. Although the incidence of adverse events is dose dependent, the 10-mg and 8-mg doses of terazosin and doxazosin are, in general, well tolerated.

Terazosin is unit priced so that there is no financial disincentive to titrate up to the 10-mg dose. There is no significant cost advantage between 10 mg of terazosin and 8 mg of doxazosin. **Thus, until data from randomized, double-blind comparative trials demonstrate the contrary, 10 mg of terazosin and 8 mg of doxazosin should be considered equivalent.**

Tamsulosin and SR alfuzosin have been positioned as uroselective α_1 -blockers. Randomized studies have shown that 0.8 mg of tamsulosin is significantly more effective at relieving symptoms than the 0.4-mg dose (Lepor, 1998). No dose-ranging studies have been performed with SR alfuzosin. Unfortunately, an 0.8-mg tamsulosin dose has not been manufactured. Whereas the 0.8-mg tamsulosin dose appears to result in less asthenia than terazosin and doxazosin, the incidence of dizziness is comparable and the incidences of rhinitis and abnormal ejaculation are markedly greater. **Tamsulosin, 0.4 mg, is the most appropriate dose owing to the cost and adverse events associated with the 0.8-mg dose.** The advantage of 0.4 mg of tamsulosin is that this clinically effective dose can be administered without dose titration.

The major advantage of 0.4 mg of tamsulosin and SR alfuzosin is the lack of requirement for dose titration. For men with urinary retention, tamsulosin and SR alfuzosin will likely decrease the time to voiding trial because of the lack of titration to an effective dose. The data suggest that tamsulosin and SR alfuzosin exhibit less effect on blood pressure in hypertensive men compared with terazosin and doxazosin.

Summary

Multicenter, randomized, double-blind, placebo-controlled studies have unequivocally demonstrated the safety and efficacy of α -blockers for the treatment of LUTS. The clinical response is rapid and dose dependent. Long-term open-label studies have

demonstrated that the clinical response is durable. The long-acting α_1 -blockers are well tolerated. The α_1 -blockers are safe in the elderly (once first-dose effects are guarded against) and diminish LUTS. The effect on risk of falling and fractures needs further investigation. Terazosin and doxazosin significantly lower blood pressure only in hypertensive patients. Direct comparison studies of the α -blockers are sparse and involve small numbers of patients, and therefore any claims of superiority cannot be justified.

ANDROGEN MANIPULATION

Rationale for Androgen Manipulation

The rationale for androgen suppression is based on the observation that the embryonic development of the prostate is dependent on the androgen dihydrotestosterone (DHT) (Shapiro, 1990). Testosterone is converted to DHT by the enzyme 5 α -reductase. The genetic deficiency of 5 α -reductase in males results in a rudimentary prostate and in feminized external genitalia (Walsh et al, 1974). The development of BPH is also an androgen-dependent process (Coffey and Walsh, 1990). Castration and pharmacologic agents suppressing testosterone and DHT synthesis or action have been shown to reduce prostate volume in men with established LUTS or BPH (McConnell, 1990). Peters and Walsh (1987) demonstrated that androgen suppression causes regression primarily of the epithelial elements of the prostate. Reducing prostate volume is thought to decrease the static component of BOO resulting from

BPE. The primary limitation of the androgen suppression hypothesis is that the pathophysiology of LUTS is not sufficiently dependent on prostate size.

Classification of Pharmacologic Agents

Surgical castration was reported to be an effective treatment for enlarged prostates in the 1890s (White, 1895; Cabot, 1896). Scott and Wade (1969) reported the first study investigating androgen suppression (medical castration) for LUTS and BPH. Cyproterone acetate, an antiandrogen, was reported to decrease symptoms and increase PFR in the majority of treated patients. The pharmacologic strategies of androgen suppression that have been investigated for LUTS and BPH over the past three decades are summarized in Table 104-7.

Caveats Related to Interpreting Androgen Manipulation Studies

The efficacy of androgen suppression in LUTS and BPH is presumed to be mediated by reduction of prostate volume. Maximal reduction of prostate volume after initiation of androgen suppression is achieved within 6 months (Peters and Walsh, 1987; Gormley et al, 1992). Therefore, randomized treatment must last at least 6 months to capture maximal therapeutic effect. Because the mechanism of action is by means of reduction of prostate volume, it is reasonable to assume that men with larger prostates achieve the greatest therapeutic benefit. The majority

TABLE 104-7 Androgen Suppression: Classification of Pharmacologic Agents and Dosages

DRUGS	DOSAGE	REFERENCE
GONADOTROPIN-RELEASING HORMONE ANALOGUES		
Leuprolide	3.75 mg IM qd mo	Schroeder et al, 1986 Keane et al, 1988 Eri and Tveter, 1993b
Nafarelin acetate	400 mg SC qd	Peters and Walsh, 1987
Cetorelix	1 mg SC qd \pm loading dose Three dosage regimens	Lepor et al, 1997 Debruyne et al, 2008
PROGESTATIONAL AGENTS		
17 α -Hydroxycortisone	200 mg IM weekly	Meiraz et al, 1977
Megestrol	250 mg PO tid 40 mg PO tid	Donkervoort et al, 1975 Geller et al, 1979
ANTIANDROGENS		
Flutamide	100 mg tid 250 mg tid	Caine et al, 1975 Stone, 1989
Oxandrolone	200 mg IM weekly	Ostri et al, 1989
Bicalutamide	50 mg qd	Eri and Tveter, 1993a
Zanoterone	100-800 mg qd	Berger et al, 1995
5α-REDUCTASE INHIBITORS		
Finasteride	5 mg PO qd 5 mg PO qd 5 mg PO qd 5 mg PO qd 5 mg PO qd	Gormley et al, 1992 Finasteride Study Group, 1993 Andersen et al, 1995 Marberger et al, 1998 McConnell et al, 1998
Dutasteride	0.5 mg PO qd 0.5 mg PO qd 0.5 mg PO qd	Roehrborn et al, 2002 Debruyne et al, 2004 Roehrborn et al, 2004

IM, intramuscular; PO, by mouth; qd, once a day; SC, subcutaneous; tid, three times a day.

of randomized, double-blind, placebo-controlled clinical trials evaluating androgen suppression enrolled men with larger prostates (Gormley et al, 1992 [finasteride]; Eri and Tveter, 1993a [Casodex] and 1993b [leuprolide]; McConnell et al, 1998 [finasteride]; and Roehrborn and colleagues, 2008a, 2010 [dutasteride]). The results of studies enrolling a disproportionate number of men with large prostates may not be generalizable to the “typical” patient with LUTS or BPH.

Review of the Literature

The overwhelming majority of drug studies evaluating androgen suppression were not randomized, enrolled small numbers of patients, and used qualitative outcome measures. This section reviews only multicenter, randomized, double-blind, placebo-controlled trials. Finasteride, a type 2 5 α -reductase inhibitor, and dutasteride, a dual inhibitor of both type 1 and type 2 5 α -reductase, represent the paradigm for androgen suppression and are emphasized in this section.

Finasteride

Finasteride is a competitive inhibitor of the enzyme 5 α -reductase (Vermeulen et al, 1989). Finasteride lowers serum and intraprostatic DHT levels. At least two isozymes (types 1 and 2) of 5 α -reductase exist (Jenkins et al, 1992). Finasteride is a selective inhibitor of the type 2 isozyme. Finasteride does not reduce DHT levels to castrate levels because circulating testosterone is converted to DHT by type I isozymes that exist in skin and liver (Thigpen et al, 1993). Gormley and coworkers (1992) reported the first multicenter, randomized, double-blind, placebo-controlled trial (often referred to as the North American Finasteride Trial) investigating the safety and efficacy of finasteride in 895 men with LUTS and BPH. The patients were randomized to receive placebo or 1 or 5 mg of finasteride for 1 year. The mean baseline prostate volumes in the placebo and 1- and 5-mg finasteride groups were 61, 61, and 59 cm³, respectively. The primary outcome measures were group mean changes in a modified Boyarsky symptom score (maximum score, 36) and PFR (Figs. 104-6 and 104-7). The group mean changes in symptom score, PFR, and prostate volume are shown in Table 104-8. The group mean percentage changes in symptom score at 12 months in the placebo and 1- and 5-mg finasteride groups were -2%, 9%, and 21%, respectively. The mean percentage changes in PFR were 8%, 23%, and 22% in the placebo and 1- and 5-mg finasteride groups, respectively. The mean percentage changes in prostate volume were -3%, -18%, and -19% in the placebo and 1- and 5-mg finasteride groups, respectively. The difference between the mean changes in PFR and prostate volume was statistically significant for both the 1- and the 5-mg finasteride groups versus the placebo group. The difference between the mean changes in symptom scores was statistically significant only for placebo versus 5 mg of finasteride. The dose-dependent symptom response was not associated with a dose-dependent prostate volume or PFR response. The changes in prostate volume were not directly related to the magnitude of the clinical response to finasteride. These observations suggest that the efficacy of finasteride may not be mediated exclusively by reduction of prostate volume. The incidences of decreased libido, ejaculatory disorder, and impotence were significantly greater in the finasteride groups compared with the placebo group. The treatment-related incidences of decreased libido, ejaculatory disorder, and impotence in the 1- and 5-mg treatment groups were 4.7%, 2.7%, and 3.7%, respectively, and 3.4%, 2.7%, and 1.7%, respectively. The percentage of patients withdrawing because of an adverse clinical event was equivalent in the three treatment groups. Prostate volume regression was maximal at 6 months. The greatest change in symptom scores and PFR occurred within the first 2 months of initiation of active treatment.

Andersen and associates (1995) reported the results of a multicenter, randomized, double-blind, placebo-controlled study investigating the safety and efficiency of finasteride in 707 Scandinavian patients maintained on randomized treatment for 2 years. The

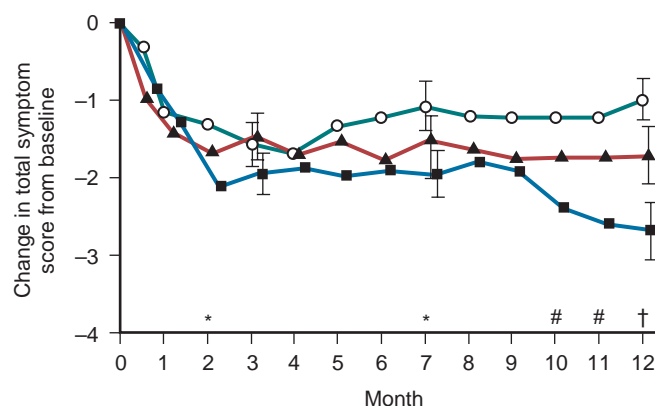


Figure 104-6. Mean (\pm standard error) change in the total symptom score in men with benign prostatic hyperplasia during treatment with placebo (circles), 1 mg of finasteride (triangles), or 5 mg of finasteride (squares). The asterisks ($P \leq .05$), the pound symbols ($P < .01$), and the dagger ($P < .001$) indicate significant differences between the finasteride-treated groups and the placebo group. Month 0 represents the baseline. (From Gormley GJ, Stoner E, Bruskewitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. *N Engl J Med* 1992;327:1185–91. Copyright © 1992 Massachusetts Medical Society.)

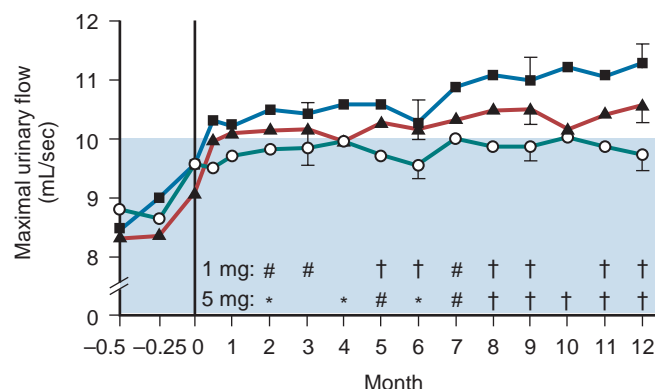


Figure 104-7. Mean (\pm standard error) maximal urinary flow rates in men with benign prostatic hyperplasia during treatment with placebo (circles), 1 mg of finasteride (triangles), or 5 mg of finasteride (squares). The blue area indicates the range in which urinary flow was considered to be obstructed. Month 0 represents the baseline. Values before month 0 were obtained during the 2-week placebo run-in period. The asterisks ($P < .05$), pound symbols ($P < .001$), and daggers ($P < .01$) indicate significant differences between the finasteride-treated groups and the placebo group. (From Gormley GJ, Stoner E, Bruskewitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. *N Engl J Med* 1992;327:1185–91. Copyright © 1992 Massachusetts Medical Society.)

mean baseline prostate volumes in the placebo and finasteride groups were 41.7 and 40.6 cm³, respectively. A modified Boyarsky symptom score was used to capture changes in symptom score. The differences in the group mean changes in the symptom score and PFR between finasteride and placebo after 12 and 24 months on active treatment are summarized in Table 104-8. The differences between the group mean changes in symptom scores and PFR after 1 year of randomized treatment are slightly less than in the North American Finasteride Study. This may be attributed to the smaller baseline prostate volumes.

Although the proportion of patients experiencing any adverse clinical event and the number of withdrawals caused by adverse clinical events were similar to those in the finasteride and placebo groups, there were more patients with sexual dysfunction in the finasteride versus placebo groups (19% vs. 10%). The placebo

TABLE 104-8 Efficacy of Finasteride for Benign Prostatic Hyperplasia

STUDY	ENROLLED (NO.)	RANDOMIZED TREATMENT (MONTHS)	DOSE (mg)	GROUP MEAN DIFFERENCE FROM PLACEBO		
				PFR (mL/sec)	SYMPTOM SCORE	PROSTATE VOLUME (cm ³)
Gormley et al, 1992	895	12	1	+1.6*	−0.8	−13.0*
			5	+1.8*	−1.7†	−12.3*
Finasteride Study Group, 1993	750	12	1		NR	NR
			5	+1.3†	−1.3‡	NR
Andersen et al, 1995	707	12	5	+1.4‡	−1.2†	NR
		24	5	+1.5‡	−2.2‡	NR
Marberger et al, 1998	3720	12	5	0.6‡	−1.0*	−7.6
		24	5	0.8‡	−1.7*	−9.6
McConnell et al, 1998	3040	48	5	1.7*	−1.6*	NR

* $P < .001$.† $P < .05$.‡ $P < .01$.

NR, not reported; PFR, peak flow rate.

response returns to baseline after 1 to 2 years, whereas the finasteride response remains stable. Andersen and colleagues (1995) interpret this to show that finasteride halts or alters the natural history of the disease.

Marberger and coworkers (1998) reported the results of a 2-year randomized, placebo-controlled trial of 3270 men receiving finasteride versus placebo that are comparable with those from the report of Andersen and associates (1995). The mean baseline prostate volumes in the placebo and finasteride groups were 39.2 and 38.7 cm³, respectively. The baseline prostate volume is the lowest of all the finasteride trials. The treatment-related improvements in the quasi-AUA symptom score at 1 and 2 years were 1.0 and 1.7 symptom units, respectively. The incidences of AUR were 1.0% and 2.5% in the finasteride and placebo groups, respectively.

Stoner (1994) and associates reported on the safety and efficacy of 3 years of therapy with finasteride. Patients participating in the North American and International Finasteride Studies were offered the opportunity to participate in an open-label extension study after completing 1 year of randomized therapy. The long-term (3-year) efficacy and safety analysis was limited to the 543 patients randomized to 5 mg. Of the 543 patients, 297 (55%) completed 3 years of treatment and were evaluable. Of the 246 unevaluable patients, 178 were dropouts and 68 were placed in a category indicating insufficient data. Inspection of the group mean changes in outcome measures reveals that the most precipitous changes in symptom scores, PFR, and prostate volume occurred between the 12- and the 18-month assessments, which coincides with transferring from blinded to unblinded treatment. After 18 months, the time-dependent changes were stable, suggesting durability of response. A subsequent report of the open-label extension study demonstrated the durability of finasteride effective up to 5 years (Hudson et al, 1999).

Boyle and coworkers (1996) reported a meta-analysis of six randomized, placebo-controlled clinical trials with finasteride. The mean group changes in symptom scores and PFR correlated with the mean baseline prostate volume. This observation accounts for the variability of treatment effect observed in the different studies.

The Proscar Long-Term Efficacy and Safety Study (PLESS) represented at the time the longest-duration multicenter, randomized, double-blind, placebo-controlled study reported in the medical therapy of BPH literature (McConnell et al, 1998). The 3040 men with moderate to severe urinary symptoms were randomized to receive daily finasteride, 5 mg, versus placebo for 4 years. A quasi-AUA symptom score was used. The baseline prostate volume in the study population was approximately 55 cm³, indicating a bias for enrolling men with markedly enlarged prostates. The mean

group changes in symptom score, PFR, and prostate volume throughout the study are shown for the finasteride and placebo in Figure 104-8. The treatment-related effects of finasteride on symptom score, PFR, and prostate volume were 2.0 symptom units, 1.7 mL/sec, and 32% size reduction for those patients on active treatment at the end of the study. The symptom and PFR improvement was modest and consistent with prior finasteride trials. PLESS demonstrated the durability of symptom and flow improvements with finasteride and very modest progression of these end points in the placebo group.

The unique findings of PLESS were related to incidences of both AUR and surgical intervention for LUTS and BPH (Fig. 104-9). The cumulative incidences of AUR at 4 years in the finasteride and placebo groups were 7% and 3%, respectively (57% risk reduction). The cumulative risk rates for undergoing BPH-related surgery were 10% and 5% in the placebo and finasteride groups, respectively (55% risk reduction). In men with prostate volumes greater than 55 cm³, the risk reduction of AUR and/or surgical intervention for finasteride was 70%. The risk reduction for AUR and BPH-related surgery was clinically relevant, especially in men with very large prostates. Men with significantly enlarged prostates and LUTS should therefore be advised of their significant risk of urinary retention and the beneficial effects of finasteride.

The PLESS study also provided insights into the impact of finasteride on the detection of prostate cancer. The decision to pursue the diagnosis of prostate cancer in the study was left at the discretion of the principal investigator and therefore represents standard practice. The detection of prostate cancer was not significantly different in the placebo and finasteride group, suggesting that finasteride does not mask the diagnosis of prostate cancer (Andriole et al, 1998).

Tammela and Kontturi (1993) reported a randomized, double-blind, placebo-controlled study examining the effects of finasteride on BOO in 36 men on a routine waiting list for prostatectomy. The mean prostate volumes in the finasteride and placebo study groups were 50 and 48 cm³, respectively. The mean baseline detrusor pressures at maximum flow in the placebo and finasteride groups were 115 and 126 cm H₂O, respectively, indicating that the patients were severely obstructed. The group mean changes in detrusor pressure at maximum flow were +3 and −39 cm H₂O in the placebo and finasteride groups, respectively. Although the difference between placebo and finasteride was highly statistically significant, the overwhelming majority of the finasteride-treated patients remained obstructed after treatment. The marked treatment-related changes in detrusor pressure were not associated with statistically significant changes in symptom scores. The authors did not comment on whether the changes in detrusor pressures correlated

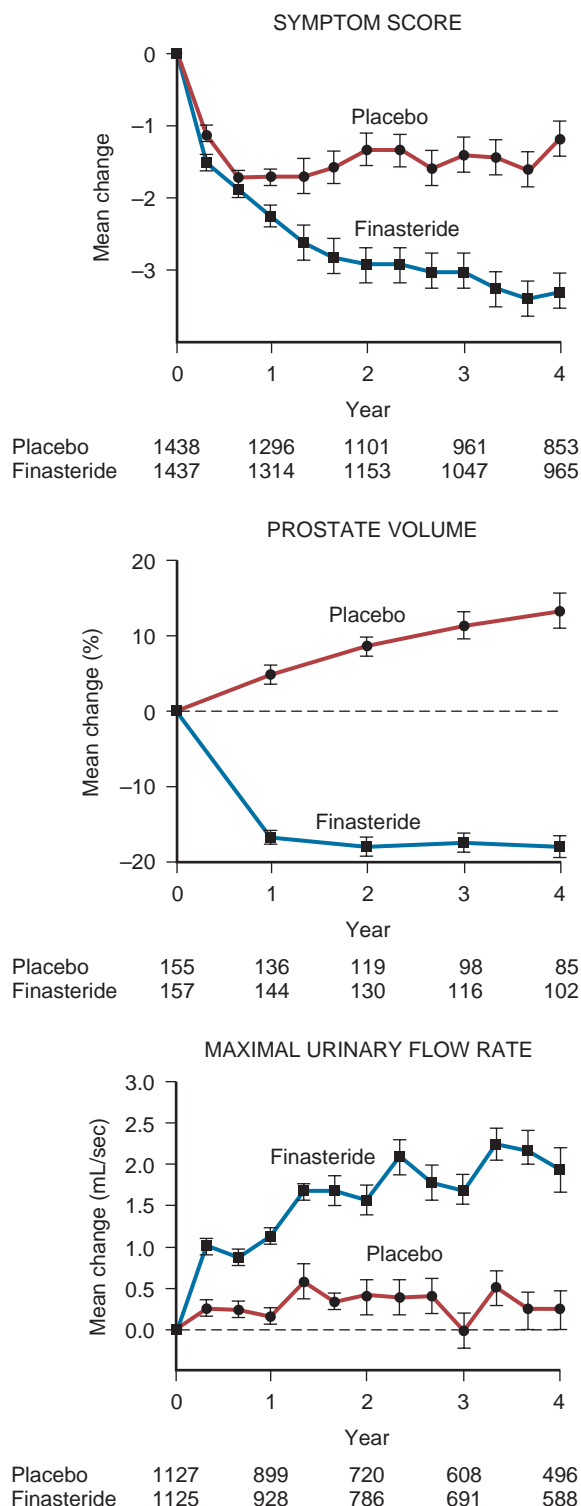


Figure 104-8. The effect of finasteride or placebo on symptom scores (on the quasi-American Urological Association Symptom Index), prostate volume, and maximal urinary flow rate over time. Values are mean (\pm standard error) changes from baseline. The numbers below the panels show the numbers of patients with valid data who remained in the study. (From McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *N Engl J Med* 1998;338:557-63.)

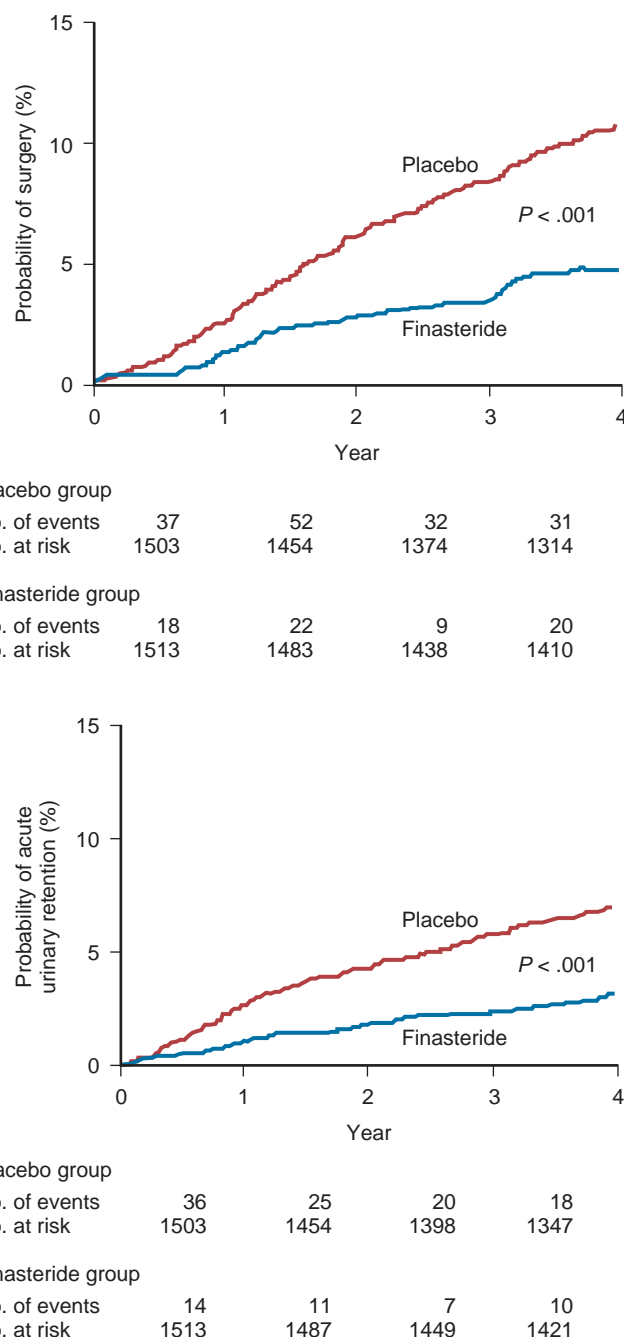


Figure 104-9. Probability of undergoing surgery for benign prostatic hyperplasia or the development of acute urinary retention during the 4-year study period in the placebo and finasteride groups. The figure shows life-table analyses of the proportion of men with each outcome. The numbers of events shown below the graphs are those that occurred during each 1-year interval. The numbers of men at risk are those at the beginning of the respective 1-year intervals. Data on men who died, were given a diagnosis of prostate cancer, or were lost to follow-up were censored at the time of death, diagnosis of prostate cancer, or discontinuation of therapy. (From McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *N Engl J Med* 1998;338:557-63. Copyright © 1998 Massachusetts Medical Society.)

with changes in prostate volume. Of the patients participating in the randomized, double-blind study, 27 completed a 4-year open-label extension study (Tammela and Kontturi, 1995). The detrusor pressure at maximum flow showed further improvements over time.

PSA has become widely accepted as a screening instrument for prostate cancer (Tchetgen and Oesterling, 1995). An elevated or significantly rising PSA value is often an indication for prostatic biopsy. Finasteride reduces group mean serum PSA levels approximately 50% (Guess et al, 1993). The effect of finasteride on individual serum PSA levels is highly variable. **Because of the variable effect on PSA, men who are candidates for early detection of prostate cancer should have their PSA level determined before beginning finasteride therapy.** A biopsy should be considered if the PSA level is elevated or for progressively rising PSA levels after initiation of therapy.

The Prostate Cancer Prevention Trial (PCPT) (Thompson et al, 2003) showed that finasteride reduced the incidence of diagnosed prostate cancer (vs. placebo). There was an increased incidence of high-grade disease, possibly because of the volume change effect, which was also seen with dutasteride in the later REDUCE trial (Andriole et al, 2011). See Chapter 107 for further details of PCPT and REDUCE.

Gross hematuria is a relatively rare, yet troublesome, manifestation of LUTS and BPH. Puchner and Miller (1995) reported an uncontrolled personal experience of 18 LUTS and BPH patients treated with finasteride for refractory gross hematuria secondary to BPH. Of the 18 reported cases, 12 patients had undergone a prior prostatectomy. Finasteride was very effective in relieving the postprostatectomy gross hematuria. Miller and Puchner (1998) reported a follow-up series that demonstrated the long-term effectiveness of finasteride for the treatment of hematuria from BPH. Carlin and coworkers (1997) reported resolution of gross hematuria in 12 of 12 men treated with finasteride. **These preliminary observations have been confirmed by a randomized, double-blind, placebo-controlled study by Foley and associates (2000) demonstrating that finasteride prevents recurrent gross hematuria secondary to BPH.** Gross refractory hematuria recurred within 1 year for 63% and 14% of men randomized to placebo and finasteride, respectively.

Dutasteride

Dutasteride is a dual inhibitor of 5 α -reductase 1 and 2 and therefore has a greater impact on suppressing serum DHT levels (Clark et al, 2004). In an RCT of 4325 men (2951 completed) Roehrborn and colleagues (2002) reported that serum DHT was reduced by 90.2%. The symptom score was improved by 4.5 points (21.4%) ($P < .001$), and the maximal flow rate improved significantly by 2.2 mL/sec ($P < .001$) at 24 months. The risk reduction for AUR was 57%, and the risk reduction for BPH-related surgery was 48% compared with placebo. Debruyne and colleagues (2004) reported the pooled results of a 2-year open-label extension study in which both dutasteride- and placebo-treated groups received dutasteride 0.5 mg/day. Significant improvements in symptom scores and maximal flow rates were observed in both study groups. It was concluded that long-term treatment with dutasteride results in continuing improvements in both symptoms and urinary flow and that the risk reduction for AUR and BPH-related surgery was durable over 4 years. **Similar to finasteride, the principal side effects were loss of libido and ED, but these were most frequently seen at the start of therapy and declined over time with treatment.** Roehrborn and coworkers (2004) reported similar results and confirmed 93% suppression of DHT at 4 years. The results of the REDUCE study of dutasteride versus placebo in terms of their ability to prevent prostate cancer have been reported by Andriole and colleagues (2009). **A 23% reduction in prostate cancer overall was seen in the dutasteride arm, but with a small increase in Gleason 8+ cancers in the treatment arm.** In December 2010 the FDA Oncologic Drugs Advisory Committee voted against use of dutasteride for reduction in the risk of prostate cancer, and the manufacturer has withdrawn this application. **Beneficial effects on symptoms, Qmax, and risk**

of progression were also seen in this group of men at high risk for LUTS and BPH progression as well as for a prostate cancer diagnosis. More recent publications have explored the relative benefits of tamsulosin and dutasteride in the 4-year Combination of Avodart and Tamsulosin (CombAT) study (Montorsi et al, 2011; Roehrborn et al, 2011, 2012) and show a benefit for combination therapy and correlation between patient satisfaction and the improvement in IPSS. The only genuine head-to-head comparison of finasteride and dutasteride, published by Nickel and colleagues in 2011, reported similar reductions in prostate volume and improvements in Qmax and LUTS and similar adverse events in 1600 men with enlarged prostates.

Zanoterone

Zanoterone is a steroidal competitive adrenoceptor antagonist (Juniewicz et al, 1993). Berger and coworkers (1995) reported a multicenter, randomized, double-blind, placebo-controlled study in 463 patients receiving placebo and 100, 200, 400, or 800 mg of zanoterone for 6 months. The group mean changes in AUA symptom score were not reported; however, the differences between placebo and all of the zanoterone groups were not statistically significant. It is interesting to note that the differences between the percent group mean changes in serum PSA in all of the active treatment groups were significantly greater than those in the placebo group, despite the lack of an apparent drug effect on prostate volume. Fifty-six percent and 22% of all zanoterone patients reported breast pain and gynecomastia, respectively. The incidence and severity of adverse clinical events and the equivocal efficacy precluded further development of this drug for LUTS and BPH.

Flutamide

Flutamide is an orally administered nonsteroidal antiandrogen that inhibits the binding of androgen to its receptor (Sufrin and Coffey, 1973). The first reported randomized, double-blind, placebo-controlled trial in LUTS and BPH examined the safety and efficacy of flutamide in 31 men with symptomatic BPH (Caine et al, 1975). Statistically significant differences were not observed between placebo and 300 mg of flutamide for symptoms, prostate size, PVR, and PFR. Stone (1989) reported a multicenter, randomized, double-blind study comparing flutamide and placebo in men with LUTS and BPH. Eighty-four patients were randomized to receive 24 weeks of either flutamide, 250 mg three times a day, or placebo. Of the 84 patients, 58 (69%) and 12 (14%) were evaluable at 12 and 24 weeks on double-blind treatment. The small sample size at 24 weeks precludes any meaningful conclusions. The between-group comparisons of group mean changes from baseline for placebo versus flutamide were not statistically significant at any time point. The incidences of breast tenderness and diarrhea in the flutamide group were 53% and 11%, respectively. Although the interim analysis was reported in 1989, a subsequent report of the multicenter study has not been published.

Cetorelix

Cetorelix is a gonadotropin-releasing hormone antagonist that has been investigated for LUTS and BPH. A potential advantage of a gonadotropin-releasing hormone antagonist over the luteinizing hormone-releasing hormone agonists in the treatment of LUTS/BPH is the ability to titrate the level of androgen suppression. This would be clinically relevant if different levels of androgen suppression mediate prostate size reduction and adverse events (hot flashes, decreased libido, ED). An open-label study of 11 men demonstrated that cetorelix reduced prostate volume and improved LUTS without significant adverse events. Lepor and coworkers (1997) reported a proof-of-concept randomized, double-blind, placebo-controlled study of cetorelix in men with LUTS or BPH. After an 8-day placebo lead-in, men received daily subcutaneous injections of placebo or 1 mg of cetorelix (group C₀₁) for 27 days. One group received loading doses of 10 mg of cetorelix on the first 4 days of active

treatment (C_{10}). Maximal lowering of testosterone was observed within 24 hours. The testosterone level was reduced to castrate levels in the C_{10} group and to intermediate testosterone suppression level in the non-loading-dose group (C_{01}) (approximately 0.20 ng/dL). Men exhibiting a clinical effect were followed for 1 year. In the C_{10} and C_{01} groups, treatment-related improvements in AUA symptom score were 3.0 and 2.0 symptom units, respectively. In both the C_{10} and the C_{01} groups, the treatment-related improvement in PFR was 2.0 mL/sec. The treatment-related reductions of prostate volume were 5.5 and 3.0 cm³, respectively. The treatment-related incidence of hot flushes and sexual dysfunction in the C_{01} group was negligible. During the open-label extension, prostate volume did not return to baseline, suggesting a prolonged effect on the disease. Because of problems with the drug formulation, phase 3 studies with cetrorelix were not pursued until recently (Debruyne et al, 2008).

In this dose-finding study, three dosing regimens were explored: one or two injections weekly for 4 weeks. In all groups a rapid improvement in mean IPSS was obtained, with a peak effect of −5.4 to −5.9 (placebo, −2.8). Changes from baseline and differences from placebo were statistically significant up to week 20. Placebo response was less sustained than usually seen with oral preparations. A subsequent study showed that intramuscular injections achieved rapid symptom and flow improvements that were maintained for 6 months (Debruyne et al, 2010).

The primary disadvantage of cetrorelix and other gonadotropin-releasing hormone antagonists will be the requirement for an injection and the cost. If single-injection therapy provides desirable clinical response (e.g., over 6 months) with minimal adverse events, there may exist a role for these antagonists in the treatment of LUTS and BPH.

Chlormadinone Acetate

Fujimoto and colleagues explored the use of a potent progesterone-derived antiandrogen, chlormadinone acetate (CMA), in 114 men in a multicenter, single-cohort prospective study. This agent is used clinically as a hormonal contraceptive. They found a decrease of 25% in prostate volume at week 16, with improvements in symptom scores and flow but deterioration in sexual function (Fujimoto et al, 2013), so it may have a role in sexually inactive older men.

Aromatase Inhibitors

The rationale for aromatase inhibition is that estrogens may be involved in the pathogenesis of BPH. The estrogenic effect most likely mediates stromal-epithelial interactions that regulate the proliferative activity of the prostate. Several observations support the role of stroma in the development of BPH and the influence of estrogens on prostatic stroma. The inductive potential of prostatic mesenchyme (stroma) is supported by the observation of Cunha and colleagues (1980) in a mouse embryonic animal model. Coffey and Walsh (1990) reported that estrogen treatment of castrated beagles produced a threefold to fourfold increase in the total amount of prostatic stroma. Estrogens also greatly enhanced the ability of androgens to induce BPH in a canine model (Walsh and Wilson, 1976; DeKlerk et al, 1979). This synergistic effect may be mediated by the ability of estrogens to upregulate prostatic adrenoceptor content. Stromal hyperplasia can be induced in the prostates of dogs and monkeys treated with aromatizable androgens and prevented by aromatase inhibitors such as atamestane (Habenicht et al, 1987; Habenicht and el Etreby, 1989).

Atamestane is a highly selective aromatase inhibitor that lowers both serum and intraprostatic levels of estradiol and estrone (el Etreby et al, 1991). Gingell and coworkers (1995) reported a multicenter, randomized, double-blind, placebo-controlled study comparing placebo and 400 mg of atamestane in 160 patients with LUTS and BPH. Atamestane resulted in a statistically significant decrease in serum estradiol and estrone levels and a statistically significant increase in serum testosterone. No statistically significant group mean differences were observed for changes in Boyarsky symptom score, PFR, or prostate volume between the

atamestane and the placebo groups. One of the explanations contributing to the failure of atamestane to achieve clinical efficacy was the increase in testosterone. The development of atamestane for LUTS and BPH was suspended because of these negative clinical findings. The failure to demonstrate that atamestane causes regression of established BPH or clinical improvement does not negate the influence of estrogens in the pathogenesis of BPH.

Finasteride and dutasteride are the only drugs available so far that achieve androgen suppression with acceptable tolerability. Both symptoms and flow rates are improved, especially in men with larger glands. Impotence and decreased ejaculatory volume are the primary treatment-related adverse experiences. The literature also suggests that finasteride and dutasteride may be offered to men with hematuria secondary to friable prostatic tissue and to men with LUTS and enlarged prostates who elect to reduce their risk of developing urinary retention.

Summary

Multicenter, randomized, double-blind, placebo-controlled studies of finasteride and dutasteride support their role in the treatment of LUTS and BPH. Finasteride reduces prostate volume approximately 20%. The overall treatment-related improvements in symptom score (approximately 1.0 symptom unit) and PFR (approximately 1.5 mL/sec) relative to placebo are modest. Long-term safety and durability of efficacy have been demonstrated for finasteride. The adverse clinical events associated with finasteride are minimal and are related primarily to sexual function. Finasteride is effective in the management of gross hematuria associated with BPH, especially in the presence of friable prostate tissue. Dutasteride is an inhibitor of both type 1 and type 2 5 α -reductase and has efficacy and side effects similar to those of finasteride. Finasteride and dutasteride alter the natural history of urinary retention in men with LUTS and enlarged prostates. In selected patients with larger prostates, over longer time periods, dutasteride appears to have symptomatic benefits greater than tamsulosin. In the REDUCE study, dutasteride reduced the incidence of prostate cancer by 23% with a small increase in high-grade tumor incidence, about which patients should be informed. Antiandrogens have also been investigated for LUTS and BPH. These studies failed to demonstrate statistically significant treatment-related efficacy. The equivocal efficacy and problematic toxicity of antiandrogens limited the enthusiasm for marketing these drugs for the treatment of LUTS and BPH. The role of gonadotropin-releasing hormone antagonists requires further study.

COMBINATION THERAPY WITH α -BLOCKER AND 5 α -REDUCTASE INHIBITOR

Lepor and coworkers (1996) reported the first multicenter, randomized, double-blind trial comparing placebo, finasteride, terazosin, and combination therapy (finasteride and terazosin) in 1229 U.S. veterans with clinical BPH. Of the 1229 patients randomized, 1007 (81.9%) completed the 1-year randomized treatment on assigned study medication.

The mean group differences between finasteride and placebo were not statistically significant for AUA Symptom Index, Symptom Problem Index, BPH Impact Index, and PFR. The mean group differences between terazosin versus placebo and terazosin versus finasteride for all of the outcome measures other than prostate volume were highly statistically significant. The group mean differences between combination therapy and terazosin for all of the outcome measures other than prostate volume were not statistically significant owing to the lack of treatment-related efficacy of finasteride over this period. The VA study demonstrated the superiority of α -adrenergic blockade over androgen suppression for the treatment of LUTS and BPH over a 1-year interval. Prostate volume decreased approximately 20% in the finasteride and combination groups. The numbers of patients withdrawing from the study

TABLE 104-9 Comparison of Placebo, Finasteride, Doxazosin, and Combination Therapy in the PREDICT Study

OUTCOME MEASURES	DIFFERENCES BETWEEN FINAL AND BASELINE STUDY VISITS			
	PLACEBO	FINASTERIDE	DOXAZOSIN	COMBINATION THERAPY
International Prostate Symptom Score	-5.7	-6.6	-8.3*	-8.5*
Peak flow rate (Qmax)	1.4	1.8	3.6*	3.8*
Acute urinary retention	1.5	1.1	0	0.0

* $P < .05$ relative to placebo.

PREDICT, Prospective European Doxazosin and Combination Therapy Trial.

because of adverse clinical events in the finasteride, terazosin, and combination groups were similar.

A multicenter, randomized, double-blind, placebo-controlled study comparing placebo, doxazosin, finasteride, and combination therapy confirmed the findings of the VA Cooperative Study (Kirby et al, 2003). In the Prospective European Doxazosin and Combination Therapy Trial (PREDICT), 1089 men were randomized in equal proportions to one of the just discussed four treatment groups for 1 year. The daily dose of doxazosin was titrated up to 8 mg. The baseline prostate volume was approximately 36 cm³. The group mean improvement of AUA symptom score and PFR and change in prostate volume between baseline and final study visit are shown in Table 104-9.

A multicenter, double-blind study compared SR alfuzosin (5 mg), finasteride (5 mg), and combination therapy in 1051 men receiving active treatment for 6 months (Debruyne et al, 1998). The improvement in IPSS was not significantly different in the alfuzosin versus combination groups. At 6 months, there were no significant differences between PFR among any of the treatment groups.

Medical Therapy of Prostatic Symptoms (MTOPS) Trial

The results of all three large-scale studies just described appear to suggest that the role of 5 α -reductase inhibitors as generalized monotherapy for LUTS may be somewhat limited, a finding at variance with some of the original studies on finasteride. An additional, longer-term trial, which had been progressing in parallel to these studies, generated important new information on both the clinical potential of 5 α -reductase inhibitors as monotherapy and the potential of drug combinations. The Medical Therapy of Prostatic Symptoms (MTOPS) trial, a prospective, randomized, double-blind, multicenter, placebo-controlled trial, was established to determine whether medical therapy can prevent or delay the progression of LUTS or BPH in the long term. Further elucidation of the natural history of BPH, determining baseline factors associated with more rapid disease progression, was a secondary aim of the study.

In 18 academic centers across the United States a total of 3047 patients were recruited and randomized to receive doxazosin, finasteride, a combination of both, or placebo. Mean age of participants was 62.6 years; most were white (82.6%), with 8.8% black and 7.2% Hispanic participants. The inclusion and exclusion criteria allowed men with all prostate sizes to be enrolled, as long as the serum PSA was less than 10 ng/mL. This resulted in a wide distribution of prostate sizes and serum PSA values, allowing for stratified analyses of subsets based on these criteria (McConnell et al, 2003).

Disease progression was defined as a worsening of LUTS according to the AUA symptom score (AUA symptom score is identical to IPSS scoring system). Progression was deemed to have occurred in the case of one of the following: a 4-point rise in AUA symptom score confirmed by a second visit within 4 weeks; a 50% increase in creatinine relative to baseline levels; AUR; two or more UTIs within 1 year or a single episode of urosepsis caused by BOO; and socially unacceptable incontinence. The first occurrence of any of these events indicated LUTS or BPH progression. Progression as an end point represented a novel concept at the time of the initiation of the MTOPS study, although PLESS as well as the dutasteride studies later used AUR and surgery as end points in the study design

(McConnell et al, 1998; Roehrborn et al, 2002). Entirely novel was the concept of using a threshold to define symptom progression. Based on data from the VA Cooperative Study, in which men perceived general improvement in their symptom status once the AUA symptom score improved by more than 3 points, a threshold of 4 points was chosen—to be confirmed within 4 weeks—to indicate global subjective worsening of symptom status.

To assess the natural history of LUTS and BPH, Qmax, prostate volume, sexual function, and quality of life were regularly recorded with respect to BPH symptoms. Transrectal ultrasound and DRE were used to evaluate prostate volume, the Sexual Function Inventory questionnaire evaluated sexuality, and the Short Form-36 Health Survey instrument recorded quality of life scores. Prostatic biopsies were obtained at baseline and at 5 years (or at primary end point) in 37% of study participants who volunteered to take part in a biopsy substudy. Patients were randomized to receive 5 mg finasteride and doxazosin placebo, 5 mg finasteride and doxazosin titrated up to 8 mg, titrated doxazosin and finasteride placebo, or two placebo drugs.

The results of the MTOPS trial suggest that the combination of doxazosin and finasteride exerts a clinically relevant, positive effect on rates of disease progression. Men who received combination therapy were significantly less likely to experience LUTS and BPH progression than those receiving either monotherapy or placebo, with risk reduction rates of 39% for doxazosin, 34% for finasteride, and 67% for combination therapy compared with placebo.

Invasive therapy and AUR risk were significantly reduced by finasteride and combination therapy (by 69% and 64% and by 79% and 67%, respectively), whereas all treatment regimens (placebo, doxazosin, finasteride, and combination) brought about a significant improvement in AUA symptom score (4.0, 6.0, 5.0, and 7.0, respectively) and Qmax (1.4, 2.5, 2.2, and 3.7 mL/sec, respectively) at 4 years (Figs. 104-10 and 104-11). AUA symptom score and Qmax improved significantly more in the combination therapy group compared with the monotherapy groups, whereas adverse events were similar to previously reported studies.

In addition to indicating the potential benefits of combination therapy, MTOPS provided important data regarding the natural history of untreated LUTS and the prediction of LUTS patients who will respond most effectively to medical treatment. Although the patients receiving finasteride alone or in combination experienced the expected decrease in prostate volume, patients on placebo or doxazosin alone experienced an increase in prostate volume from a baseline of 34.0 mL by 9.3 (30.3%) (placebo) and from 36.4 mL by 9.9 (31.4%) (doxazosin), respectively. Stratified by PSA quartiles, total prostate volume in both placebo and doxazosin-treated patients increased from 4.9 mL (24.9%) to 16.2 mL (34.5%) from the lowest to the highest quartile for an annualized growth of 1.1 to 3.6 mL/yr. These findings suggest that doxazosin, despite its apoptotic effect (Glassman et al, 2001), does not interfere with the natural growth tendency of the prostate gland and that baseline PSA is a useful predictor of future prostate growth in men with LUTS and BPH.

Examination of baseline measures and the disease outcomes of 737 patients treated with placebo revealed that PSA, Qmax, PVR, and prostate volume at baseline correlated with clinical progression of the disease and the need for BPH-related surgery ($P = .03$ to

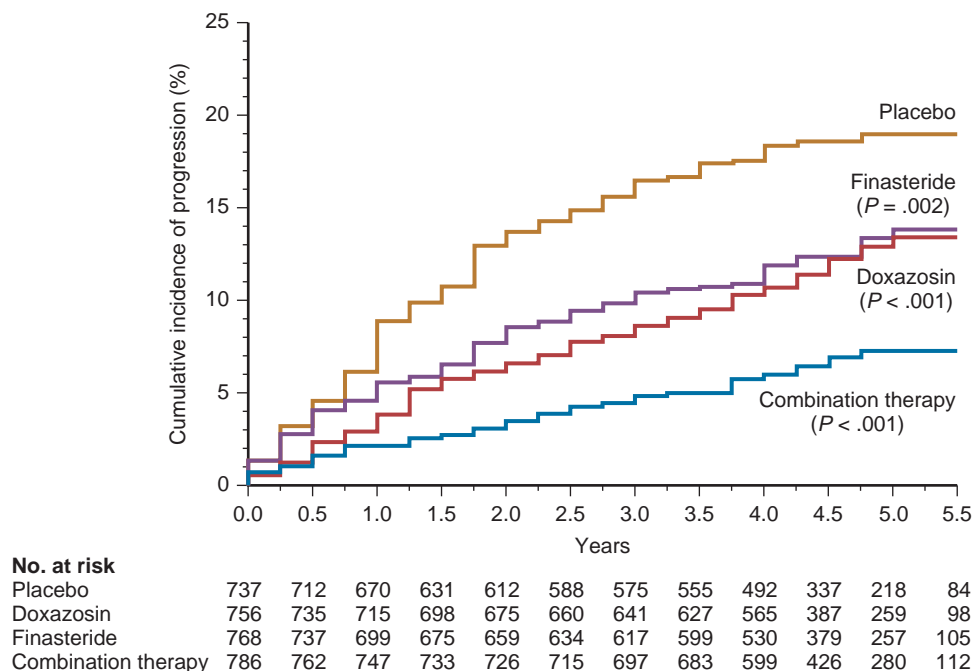


Figure 104-10. Cumulative incidence of progression in the Medical Therapy of Prostatic Symptoms (MTOPS) trial. (From McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349[25]:2387–98.)

< .001). Age was linked to clinical progression ($P < .001$), and AUA symptom score correlated with need for surgery ($P = .002$). Baseline PSA and prostate volume correlated with risk of AUR ($P = .03$ to $.003$). Risk of progression, BPH-related surgery, and AUR increased alongside levels of serum PSA. In medically treated patients, however, baseline values were variably predictive of LUTS or BPH outcome. In doxazosin-treated patients, for example, PSA, Qmax, and prostate volume were predictive of outcome; however, this was not true of patients treated with finasteride alone or combined therapy.

The number needed to treat (NNT) to prevent a case of LUTS or BPH progression as defined in MTOPS in the overall population was 8.4 for the combination therapy group and 13.7 and 15.0, respectively, for the doxazosin- and finasteride-treated patients. For those men treated with combination therapy who had a baseline PSA of more than 4.0 ng/mL, however, the NNT was 4.7, and for those with a prostate volume over 40 mL it was 4.9, suggesting that combination therapy becomes an economically stronger option in patients at higher risk for progression.

The link between sexual dysfunction and severity of LUTS was also confirmed by the MTOPS data. A correlation was observed between LUTS and five domains of sexual dysfunction (libido, sexual function, ejaculatory function, the patient's assessment of his sexual problems, and overall satisfaction). In addition, men with larger prostates were more likely to have low libido, low overall sexual functioning, reduced ejaculatory function, and greater sexual problems.

Another study of combination therapy in LUTS and BPH using dutasteride and tamsulosin has been reported by Barkin and colleagues (2003). Three hundred twenty-seven patients were treated with both drugs for 24 weeks, and then the α -adrenergic blocker was withdrawn for a further 12 weeks; of those patients with an IPSS less than 20, 84% continued without noticeable deterioration of their symptoms. In contrast, in the 27% of patients with more severe symptoms (IPSS higher than 20), 42.7% reported a worsening of their symptoms compared with 14% of those who remained on combination therapy. It was concluded that a 5 α -reductase inhibitor can be used in combination with an α -adrenergic blocker to achieve rapid onset of symptom relief in

patients at risk of underlying disease progression and the α -adrenergic blocker can then be discontinued. In patients with severe symptoms, combination therapy should be continued for a longer term.

Combination of Avodart and Tamsulosin (CombAT) Study

Roehrborn and colleagues (2008a, 2010) have reported the 2-year and 4-year results of the CombAT study. In men with a pretreatment PSA between 1.5 and 10 ng/mL, the combination of dutasteride and tamsulosin was more effective than either drug alone. It is interesting to note that in men with larger prostates, although the tamsulosin effect was rapid, over time dutasteride was the more effective agent. The 4-year data showed that combination therapy was significantly superior to tamsulosin monotherapy but not dutasteride monotherapy at reducing the relative risk of AUR or BPH-related surgery. Further analysis also showed that men with a prostate volume of 40 mL or more and baseline PSA levels of 1.5 ng/mL or higher had greater reductions in the risk ratio (RR) of AUR or BPH-related surgery and greater reductions in the RR of clinical progression and symptom deterioration on combined therapy or dutasteride monotherapy than on tamsulosin monotherapy (Roehrborn et al, 2011). In addition, combined therapy with dutasteride plus tamsulosin provided better long-term control (up to 4 years) of both storage and voiding LUTS compared with monotherapy for men with prostate volumes of 30 mL or greater (Montorsi et al, 2011; Roehrborn, 2012).

The inclusion criteria for the MTOPS and CombAT studies were different for prostate volume and PSA at entry. Whereas the baseline characteristics for age, total IPSS, Qmax, and PVR were remarkably similar (Table 104-10), the patient groups were significantly different with regard to mean prostate volume (36.3 mL vs. 55.0 mL) and mean PSA (2.4 ng/mL vs. 4.0 ng/mL) for MTOPS and CombAT, respectively. This resulted in significantly different outcomes and responses to medication. In the patients with larger prostates in the CombAT study, the 5 α -reductase inhibitor dutasteride achieved greater improvements (reductions in IPSS) compared with the α -blocker tamsulosin in both symptom score (-5.3 vs. -3.8) and flow rate ($+2.0$ mL/sec vs. $+0.7$ mL/sec), something not seen in

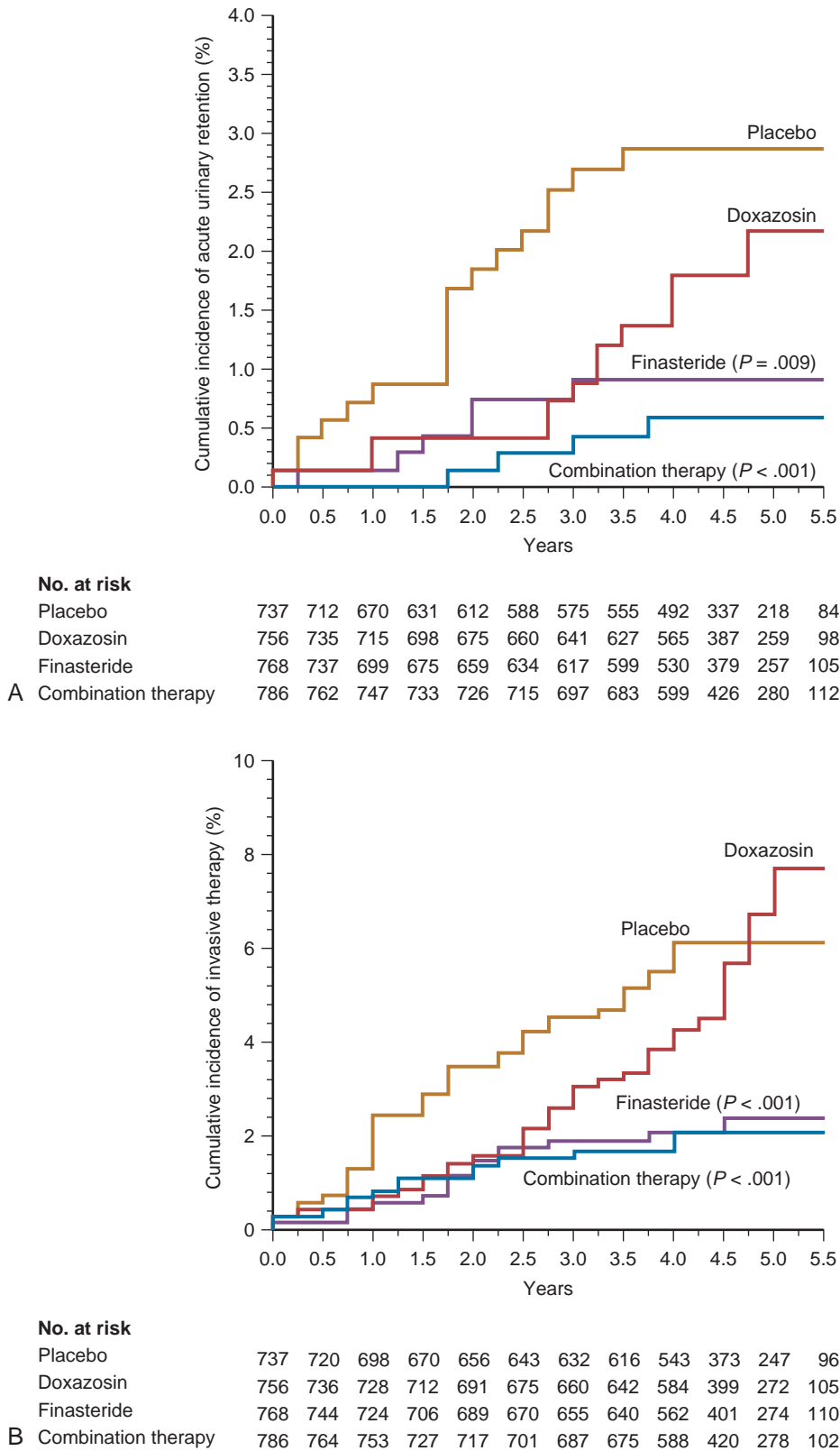


Figure 104-11. Cumulative incidence of acute urinary retention (A) and invasive therapy for benign prostatic hyperplasia (B) in the Medical Therapy of Prostatic Symptoms (MTOPS) trial. (From McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349[25]:2387-98.)

TABLE 104-10 Baseline Characteristics of CombAT Study Relative to MTOPS study

MEAN ± STANDARD DEVIATION	CombAT* (N = 4844)	MTOPS† (N = 3047)
Age (years)	66.1 ± 7.01	62.6 ± 7.3
Total IPSS	16.4 ± 6.16	16.9 ± 5.9
Total prostate volume (mL)	55.0 ± 23.58	36.3 ± 20.1
Serum PSA (ng/mL)	4.0 ± 2.08	2.4 ± 2.1
Qmax (mL/sec)	10.7 ± 3.62	10.5 ± 2.6
Postvoid residual volume (mL)	67.7 ± 64.87	68.1 ± 82.9

*Roehrborn et al, 2008a.

†McConnell et al, 2003.

CombAT, Combination of Avodart and Tamsulosin; IPSS, International Prostate Symptom Score; MTOPS, Medical Therapy of Prostatic Symptoms; PSA, prostate-specific antigen.

other comparative studies. The comparable improvements with combination therapy (dutasteride and tamsulosin) were −6.3 and +2.4 mL/sec.

ANTICHOLINERGIC (ANTIMUSCARINIC) RECEPTOR BLOCKERS

There is an overlap between symptoms traditionally regarded as being caused by LUTS and BPH and those ascribed to the syndrome of OAB. OAB symptoms may coexist with LUTS and BPH or BOO and may be either secondary to that obstruction or unrelated. Telephone surveys in the United States (Stewart et al, 2003) and in Europe (Milsom et al, 2001) show about 12% to 16% of the adult population admit to OAB symptoms. In Europe, 60% of those with symptoms had consulted a medical practitioner about the symptoms, and two thirds reported that they had an effect on daily living. Traditionally, in the treatment of OAB symptoms the use of antimuscarinic (commonly called *anticholinergic*) agents is often used in women. However, in men there was always anxiety that these antimuscarinic agents decrease detrusor contractility and could, in theory, increase the risk of urinary retention, particularly in a man with significant obstruction. If AUR did not result, then the risk of increasing PVR might lead to other complications such as infection.

There have been small studies and anecdotal evidence showing that antimuscarinic agents can be used judiciously with efficacy and with minimal side effects. More recently, newer antimuscarinic agents have been introduced. Tolterodine studies have shown symptomatic benefit without increased AUR in men with OAB with proven BOO (Abrams et al, 2006), suggesting that antimuscarinics can be safely administered in men with BOO. Abrams and colleagues (2006) investigated a total of 222 men older than 40 years with BOO and detrusor overactivity confirmed by pressure-flow studies who were enrolled and were randomized to tolterodine (2 mg twice daily in 149) or placebo (in 72) for 12 weeks; 87% completed the trial. Primary end points were Qmax and detrusor pressure at maximal flow rate (pdetQmax). Median treatment differences in Qmax (−0.7 mL/sec, 95% confidence interval [CI] −1.6 to 0.4) and pdetQmax (−7 cm H₂O, 95% CI −3 to 11) were comparable. Tolterodine significantly reduced the Bladder Outlet Obstruction Index score versus placebo (−9 vs. 0, $P < .02$), although the urodynamic significance of these changes has been questioned. There were significant treatment differences in volume to first detrusor contraction (+59 mL, 95% CI 19–100) and maximum cystometric capacity (+67 mL, 95% CI 35–103), favoring tolterodine over placebo ($P < .003$). Change in PVR was significantly greater among patients treated with tolterodine (+25 mL) than placebo (0 mL, $P < .004$), but there were no significant between-group differences in the incidence of adverse events. Urinary retention was reported by one patient treated with placebo. Tolterodine did not appear to

adversely affect urinary function in men with OAB and BOO. Urinary flow rate was unaltered, and there was no evidence of clinically meaningful changes in voiding pressure and PVR or urinary retention. Tolterodine was also well tolerated. These results suggest that antimuscarinics could be safely administered in men with BOO.

Martin-Merino and colleagues (2009) showed in a population-based, retrospective cohort study using a large primary care database of patients who received antimuscarinic agents for more reasons than just urologic symptoms that the overall incidence of AUR in the study cohort (1844) was 1.0 per 1000 person-years, with the incidence rate increasing with age. Roehrborn and coworkers concluded that men prescribed antimuscarinic agents, particularly for urogenital conditions, should be closely monitored during the first 30 days of treatment for signs or symptoms of urinary retention, when the risk was fourfold higher than later (Martin-Merino et al, 2009).

Blake-James and colleagues (2007) performed a systematic review of the available literature and, when there were sufficient data, performed a meta-analysis to assess the safety and efficacy of antimuscarinic therapy in men with LUTS or BPH. They analyzed five RCTs and 15 observational studies of good quality (Table 104-11). Minimal changes were reported in Qmax or IPSS overall, although storage symptoms scores did appear to improve in one RCT. PVR did increase, but minimally, and there was no convincing increase in AUR rates. The authors concluded that although the therapy was safe, more studies were required to define the efficacy of antimuscarinic therapy for men with LUTS or BPH.

Combination Therapy: α -Adrenergic Blockers and Anticholinergic (Antimuscarinic) Receptor Blockers

Response of the OAB symptoms seen in men with LUTS or BPH raises the possibility that a combination with α -blocker therapy could reduce the risk of retention or deteriorating bladder function, but also could add to the treatment of the remaining obstructive symptoms of LUTS or BPH (Athanasopoulos et al, 2003).

In a Korean randomized study (Lee et al, 2005), 211 men with OAB symptoms and urodynamically proven BOO were randomized (1:2) into two groups, one given doxazosin (4 mg once daily) only and the other given propiverine (20 mg once daily) plus doxazosin for an 8-week trial. Significant improvements were noted in each group after treatment in urinary frequency, maximum flow rate, average micturition volume, and IPSS. Improvement in urinary frequency (23.5% vs. 14.3%, $P = .004$), average micturition volume (32.3% vs. 19.2%, $P = .004$), and storage (41.3% vs. 32.6%, $P = .029$) and urgency ($P = .019$) symptoms were more significant in group 2, given propiverine plus doxazosin. PVR urine was found to be significantly increased only in group 2, but this was not accompanied by urinary retention. Patient satisfaction rates were found to be significantly higher in group 2 than in group 1 ($P = .002$). Overall adverse event rates were higher in group 2 ($P = .002$), although discontinuation rates and discontinuation rates resulting from adverse events were not different between the two groups, suggesting that combination therapy consisting of α_1 -adrenoceptor antagonists with antimuscarinics represents an effective and relatively safe treatment modality in select patients with OAB coexisting with benign prostatic obstruction.

Kaplan and coworkers (2006), in a double-blind placebo-controlled trial in 95 centers in the United States, enrolled 879 men with the usual LUTS and BPH parameters often found in trials, but who also had proven frequency (minimum eight times a day) and urgency (at least three episodes per 24 hours as recorded in voiding diaries) and randomized them among tolterodine 4 mg daily, tamsulosin 0.4 mg daily, a combination of tolterodine and tamsulosin, and placebo over a 12-week period. The combination group showed a significant benefit over placebo in response to a patient-reported single-item question determining the perception of benefit (80% vs. 62%). This was the primary end point. Data supplied suggest an NNT of 5, which is reasonable. It is interesting

TABLE 104-11 Summary of Outcomes of Randomized Controlled Trials of Antimuscarinic (Anticholinergic) Treatment

OUTCOME	ABRAMS ET AL, 2006	LEE ET AL, 2005	ATHANASOPOULOS ET AL, 2003	SAITOH ET AL, 1999	DAHME ET AL, 1995
Number of patients	221	228	50	134	70
Agent	Tolterodine	Propiverine + doxazosin	Tolterodine + tamsulosin	Propiverine + tamsulosin	Flavoxate
Qmax (mL/sec)	−0.3 vs. +0.5	+1 vs. 1.7	+1.32 vs. +1.16	+0.5 vs. +2.9	−0.1 vs. +0.1
P	NS	NS	NS	NS	NS
PVR, mL/sec	+25 vs. +0	+20.8 vs. −4.7	−4.2 vs. −8.2	+24 vs. −9.5	−2 vs. −6
Change, P	Up, 0.004	Up, 0.002	NS	NS	NS
VFC, mL	+59 vs. −31	—	+100.4 vs. +30.4	—	—
Change, P	Up, 0.003	—	Up, <0.001	—	—
MCC, mL	+67 vs. −8.0	—	+36.4 vs. +0.8	—	—
Change, P	Up, <0.001	—	Up, 0.002	—	—
Frequency episodes	—	−1.9 vs. −0.9	—	−1.74 vs. −1.87	—
Change, P	—	Down, 0.004	—	NS	—
Nocturia episodes	—	−0.7 vs. −0.6	—	−1.32 vs. −0.65	−0.6 vs. −0.8
Change, P	—	NS	—	Down, 0.004	NS
Urge, IPSS	—	−1.2 vs. −0.7	—	−0.62 vs. −0.55	—
Change, P	—	Down, 0.02	—	NS	—
IPSS total	—	−7.4 vs. −7.3	—	−5.01 vs. −5.51	—
P	—	NS	—	NS	—
IPSS storage	—	−3.8 vs. −2.9	—	−2.99 vs. −0.22	—
Change, P	—	Down, 0.03	—	—	—

Change is intervention arm versus change in control; statistical significance between groups $P < .05$.

IPSS, International Prostate Symptom Score; MCC, volume at bladder capacity; NS, not significant; PVR, postvoid residual; Qmax, maximum flow rate; VFC, volume at first contraction.

From: Blake-James BT, Rashidian A, Ikeda Y, et al. The role of anticholinergics in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis. *BJU Int* 2007;99:85–96.

to note that neither drug used alone was significantly better than placebo in terms of patient perception of benefit, although the tamsulosin arm showed IPSS improvement (Fig. 104-12). There were only minor adverse events, which were equally distributed in the groups.

The data suggest that in this population of men with LUTS but enriched by recruitment of men with OAB symptoms (24% reported episodes of incontinence at baseline, for instance), a treatment strategy targeting both the bladder and the prostate was needed for maximal benefit to be achieved. Kaplan and colleagues (2006) postulate that the best candidates for this form of combination therapy might be those men not immediately responding adequately to α -blocker therapy alone.

Once again, the added expenses of combination therapy need to be considered, although the NNT rate is encouraging. In a study using pooled data from two large, phase 3, double-blind RCTs in men with OAB, it was shown that trospium extended-release (XR) was safe and effective with significantly reduced frequency and urgency incontinence but was associated with two episodes of retention (2.1%), both in men older than 75 years (MacDiarmid et al, 2011).

The benefits of flexible-dose fesoterodine were tested in a study of 943 men with residual symptoms of OAB after treatment with an α -blocker for LUTS or BPH. Although many of the outcome parameters were no better for fesoterodine than for placebo, there were significant improvements in urinary frequency and symptom bothersomeness for the fesoterodine group (Kaplan et al, 2012). Finally, a recent study of solifenacin plus tamsulosin oral controlled absorption system (OCAS) did not find significant improvement in

IPSS in the total study population but did find significant efficacy with regard to urinary frequency and voided volume and quality-of-life benefits as measured by IPSS, quality-of-life score, and Patient Perception of Bladder Condition score over tamsulosin OCAS monotherapy in men with both voiding and storage symptoms of LUTS (Van Kerrebroeck et al, 2013). Current European guidelines suggest that antimuscarinics can be added to α -blockers to address storage symptoms when monotherapy with α -blockers is inadequate (Oelke et al, 2012).

The short-term data suggest that combination of antimuscarinic and α -blocker therapy is safe with minimal risk of retention or AUR in carefully selected men. It would seem advisable to avoid treating men with a substantial residual urine (200 mL or more in most studies), and men on treatment who report increased hesitancy or who show signs of increasing PVR or clinical evidence of retention should be warned to stop the antimuscarinic element of the combination therapy immediately. Men with significant obstruction and large, persistent residual urine volumes should be considered for surgical therapy rather than the addition of antimuscarinic agents.

β_3 Agonist (Mirabegron)

Mirabegron is the first of a new class of drugs. β_3 agonists enhance bladder relaxation during bladder filling by blocking the β_3 adrenoceptors in the detrusor muscle. Mirabegron can increase bladder capacity without blocking contractility. Herschorn and colleagues (2013) reported that 25- and 50-mg doses were well tolerated and associated with significant improvements in incontinence episodes

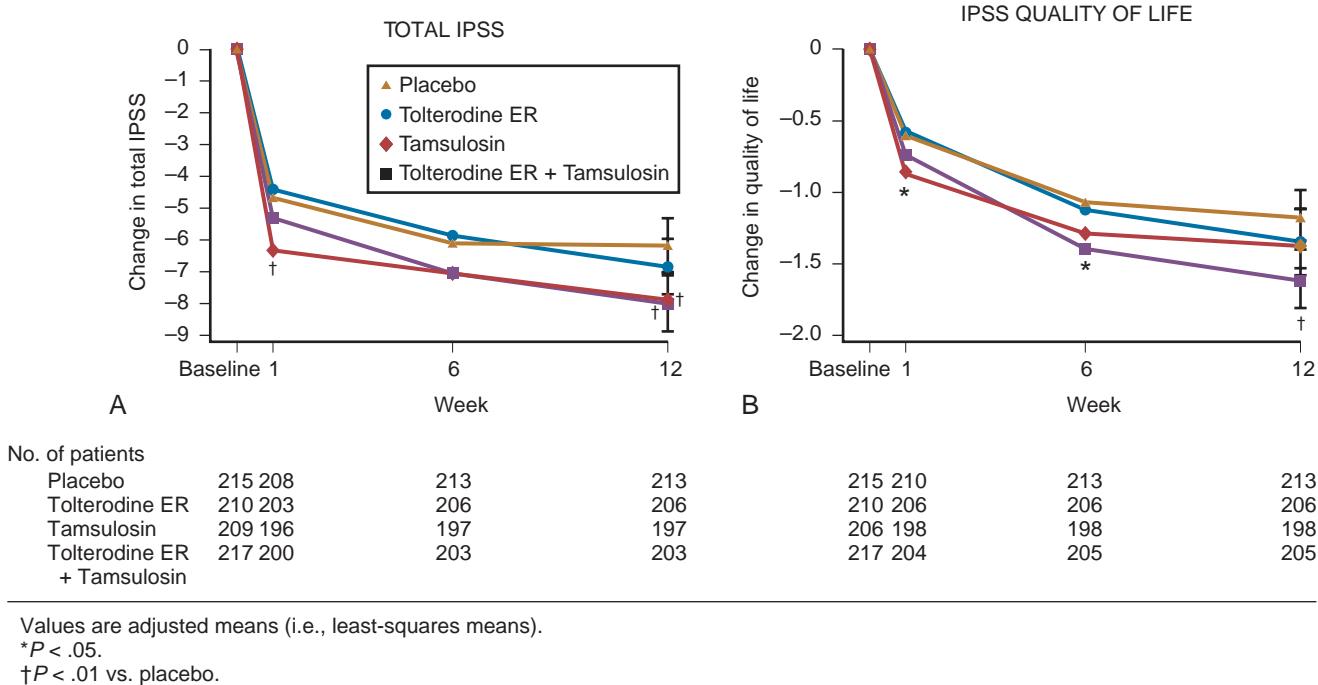


Figure 104-12. Response of lower urinary tract symptoms to tolterodine, tamsulosin, or combination versus placebo. ER, extended release; IPSS, International Prostate Symptom Score. (From Kaplan SA, Roehrborn CG, Rovner ES, et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 2006;296:2319–28.)

and micturition frequency. Mirabegron has now received regulatory approval in Japan, the United States, and much of Europe. See Chapter 77 for more detail.

PHOSPHODIESTERASE INHIBITORS

The rationale for the use of PDEIs in the treatment of LUTS and BPH was initially based on demographic data showing the frequent occurrence of both ED and LUTS in men as they age (Table 104-12). This raised the possibility of a common underlying mechanism at least contributing to both processes, which in turn raised the possibility of new treatment options that might affect both processes. After the first clinical report in 2002 of improvement in LUTS in men given sildenafil (Viagra) for their ED (Sairam et al, 2002), there has been growing interest in the role of PDEIs as treatments for LUTS and in particular for the management of the many men with both conditions, who are commonly found in our clinics. The scientific basis is rapidly becoming stronger, and there is now good level 1 evidence from multiple clinical trials clearly showing improvement of LUTS after treatment with a range of PDEIs versus placebo (McVary et al, 2007a, 2007b; Roehrborn et al, 2008b; Stief et al, 2008; Porst et al, 2011) (Table 104-13) or versus tamsulosin (Oelke et al, 2012). However, in the studies so far available, there have been no significant changes in Qma, suggesting that the effects of PDEIs alone may be either more focused on bladder muscle function than on prostatic tissue or that the effects are more profound on storage symptoms than on bladder outflow obstruction itself. The relationship between the management of LUTS and ED has been well reviewed (Kohler and McVary, 2009). ED is commonly found in men who are at risk for LUTS. This association is found throughout the western world as well as in Asian studies. The pathophysiologic link between these conditions is not yet clear, but several theories have been described with various levels of supporting data (Fig. 104-13). It is likely that there is an overlap between the roles of each of these candidate mechanisms, and an ultimate effect leading to smooth muscle relaxation in pros-

tatic, bladder neck, or erectile tissues appears to be crucial. Candidate mechanisms include the following:

1. *Pelvic atherosclerosis.* The pelvic atherosclerosis theory suggests that just as penile ischemia leads to smooth muscle loss in the penis, so smooth muscle damage in the bladder would decrease compliance and predispose to replacement of bladder smooth muscle with collagen and fibrosis. Reduced nitric oxide synthase (NOS) expression is seen with ischemia. Furthermore, conditions promoting pelvic atherosclerosis such as hypertension, smoking, hypocholesterolemia, and diabetes mellitus are implicated in both ED and LUTS.
2. *Autonomic hyperactivity.* Autonomic hyperactivity and particularly increased sympathetic tone is seen in various components of the metabolic syndrome and has been implicated in the development of LUTS (McVary, 2005).
3. *The calcium-independent Rho/Rho-kinase activation pathway.* Abnormal activation of the Rho/Rho-kinase pathway is involved in the pathogenesis of hypertension, vasospasm, and arteriosclerosis and is a potent target of new therapies for these diseases. RhoA/Rho-kinase may suppress endothelial nitric oxide synthase (eNOS). Rho-kinase appears to play a key role in the regulation of force and velocity of actomyosin cross-bridging in smooth muscle by inhibiting myosin phosphatase-mediated dephosphorylation of the regulatory chain of myosin II. This calcium-independent pathway leads to smooth muscle contraction, probably by creating mediators of α adrenergic (nor-epinephrine) and endothelin-1 (ET-1) promoted smooth muscle contraction. Abnormal Rho-kinase activation or upregulation contributes to a lack of smooth muscle relaxation in the urinary tract and thus to changes in bladder compliance and to LUTS.
4. *Reduced nitric oxide levels* (probably the best explored process so far). Nitric oxide is a nonadrenergic, noncholinergic (NANC) mediator of smooth muscle activity. Burnett and coworkers (1995) reported NOS activity in the prostate. Takeda and associates (1995) showed prostate smooth muscle tension is mediated by nitric oxide. NO activates soluble guanylate cyclase (sGC) of smooth muscle cells, which in turn increases cyclic guanosine monophosphate

TABLE 104-12 Summary of Epidemiologic Studies Associating Lower Urinary Tract Symptoms (LUTS) with Erectile Dysfunction (ED)

STUDY	STUDY DESIGN OR NAME	N	FINDINGS
Braun et al, 2000	Cologne Male Survey	4000	LUTS in 72.2% of patients with ED vs. 37.7% without ED; prevalence risk highly significant.
Blanker et al, 2001	Krimpen Community Cohort	3924	ED RR: 1.8-7.5 for increasing urinary complaints; risk of ED greater with LUTS than with smoking or cardiac symptoms.
Moreira et al, 2003	Brazilian Cohort Study	428	ED incidence RR: 3.67 if self-reported BPH—2-yr follow-up; addresses temporality of BPH → ED.
Boyle et al, 2003	UrEpik study	4800	IPSS >7 showed odds ratio of 1.39 of having ED in a weighted multiple regression model, including age; similar odds ratios: heart attack, hypertension, and smoking.
Vallancien et al, 2003	Cross-Sectional European Survey	1274	55% of patients with mild LUTS had ED vs. 70% with severe LUTS; significance maintained after multiple regression analyses.
Rosen et al, 2003	Multinational Survey of the Aging Male	12,815	RR 3.7-7.6; IPSS correlated with IIEF, sexual activity, and ejaculatory parameters; controlled for age and comorbidities; older men still sexually active.
Braun et al, 2003	Cologne Male Survey	4489	Prevalence of LUTS in men with ED was about 72.2% (n = 621) vs. 37.7% (n = 1367) in men with normal erections; the odds ratio was 2.11, even after controlling for age.
Chung et al, 2004	Cross-Sectional Community Survey	2115	LUTS correlated with ED; sexual satisfaction and libido inversely correlated with LUTS.
Ponholzer et al, 2004	Austrian study	2858	RR for ED in men with LUTS (IPSS >7) was 2.2; controlled for age, vascular risk factors, and predominance of obstructive or irritative symptoms.
Hansen, 2004	Danish study	3442	LUTS predicted ED after multiple regression; RR 2.3-3.4; overall LUTS prevalence 39% and ED prevalence 29%.
Elliott et al, 2004	U.S. Veterans Administration Survey	181	ED correlated with obstructive LUTS after controlling for age, depression, hypertension, and coronary artery disease on multivariate analysis.
Terai et al, 2004	Japanese Cross-Sectional Survey	2084	RR: 1.5; ED correlated with LUTS (IIEF vs. IPSS); correlation remained after controlling for age.
McVary et al, 2004	MTOPS Secondary Analysis	3000	AUASS correlated with ED and other domains; included correlation with maximum flow rate (multivariate analysis controlled for confounders).
Shiri et al, 2005	Finnish Cohort Study	1126	RR of ED incidence with DAN-PSS score 7-11 was 2.7, RR was 3.1 for DAN-PSS >12 over a 5-yr period; addresses temporality of BPH → ED.
Paick et al, 2005	PLESS study and Questionnaire	2981	2% increase in ED risk for unit increase in PLESS LUTS survey, significant after controlling for age.
Brookes et al, 2008	BACH Study Subset Analysis	2301	Multivariable regression model of ED found strong association of AUASS and ED independent of age; nocturia, incontinence, and prostatitis strongest factors; no differences found across race or ethnicity.

AUASS, American Urological Association symptom score; BACH, Boston Area Community Health; BPH, benign prostatic hyperplasia; DAN-PSS, Danish Prognostic Symptom Score; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; MTOPS, Medical Therapy of Prostatic Symptoms trial; PLESS, Proscar Long-Term Efficacy and Safety Study; RR, relative risk.

From Kohler T, McVary K. The relationship between erectile dysfunction and lower urinary tract symptoms and the role of phosphodiesterase type 5 inhibitors. *Eur Urol* 2009;55:38–48.

(cGMP) levels. This in turn is responsible for smooth muscle cell relaxation and penile erection, for instance. This process is most likely to involve activation of potassium channels by cGMP leading to hyperpolarization and closure of voltage-dependent calcium channels. Intracellular levels of calcium are reduced with an effect on myosin and its detachment from actin and muscle relaxation.

Clinical investigation really began in 2000 with a study of 112 men being studied for their response to sildenafil but whose urinary symptoms were also prospectively assessed by IPSS and measurement of Qmax over a 3-month period (Sairam et al, 2002). This open-label descriptive study was the first study to measure parameters of both ED and urinary symptoms and showed an

improvement in LUTS as well as ED in response to sildenafil. Similar smaller studies were followed by RCTs using sildenafil, tadalafil, and vardenafil (McVary et al, 2007a, 2007b; Roehrborn et al, 2008b; Stief et al, 2008). These initial trials are summarized in Table 104-13. Other PDEIs (udenafil, UK-369003 [Tamimi et al, 2010], mirodenafil) have also shown efficacy in trials.

The first RCT published that elucidated the impact of PDEIs on LUTS was by McVary and colleagues (2007a). This was the first proper randomized controlled study and was a 12-week double-blind placebo-controlled investigation performed in 41 centers in the United States between March 2004 and May 2005. Men with both ED (scoring lower than 25 on the International Index of Erectile Function [IIEF]) and LUTS (scoring higher than 12 on IPSS)

TABLE 104-13 Mean Changes from Baseline to End Point in Total International Prostate Symptom Score (IPSS), IPSS Subscores, and Maximum Flow Rate in Double-Blind, Randomized, Placebo-Controlled Clinical Studies of Phosphodiesterase Type 5 Inhibitors

STUDY	DURATION	TREATMENT	N	TOTAL IPSS*	IPSS STORAGE SUBSCORE*	IPSS VOIDING SUBSCORE*	Qmax (mL/sec)
TADALAFIL							
McVary et al, 2007b	12 wk	Placebo	143	−1.7	−1.0	−0.7	0.9*
		Tadalafil 5 mg/20 mg	138	−3.8†	−2.2†	−1.7†	0.5*
Roehrborn et al, 2008b	12 wk	Placebo	210	−2.3	−1.0	−1.3	1.2*
		Tadalafil 2.5 mg	208	−3.9†	−1.6	−2.2†	1.4*
		Tadalafil 5 mg	212	−4.9†	−1.9†	−2.9†	1.6*
		Tadalafil 10 mg	216	−5.2†	−2.0†	−3.1†	1.6*
		Tadalafil 20 mg	208	−5.2†	−2.1†	−2.3†	2.0*
Porst et al, 2011	12 wk	Placebo	164	−3.6	−1.3	−2.3	1.1*
		Tadalafil 5 mg	161	−5.6†	−2.3†	−3.3†	1.6*
Egerdie et al, 2012	12 wk	Placebo	200	−3.8	−1.6	−2.2	1.2*
		Tadalafil 2.5 mg	198	−4.6	−1.9	−2.7	1.7*†
		Tadalafil 5 mg	208	−6.1†	−2.5†	−3.6†	1.6*
Oelke et al, 2012	12 wk	Placebo	172	−4.2	−1.6	−2.6	1.2*
		Tadalafil 5 mg	171	−6.3†	−2.2	−4.1†	2.4*†
		Tamsulosin 0.4 mg	165	−5.7†	−2.2	−3.5†	2.2*†
SILDENAFIL							
McVary et al, 2007a	12 wk	Placebo	162	−1.9	VNR‡	VNR‡	0.2*
		Sildenafil 50 or 100 mg	179	−6.3†	VNR†‡	VNR†‡	0.3*
VARDENAFIL							
Stief et al, 2008	8 wk	Placebo	110	−3.6	−1.6	−1.9	1.0§
		Vardenafil 10 mg	104	−5.9†	−2.7†	−3.2	1.6§

*Mean change from baseline to end point.

† $P < .5$.

‡Subscores were reported graphically without actual values.

§Change calculated by subtracting results reported at 8 wk from baseline.

¶Twice daily.

Qmax, maximum flow rate; VNR, value not reported.

Modified from Giuliano F, Ückert S, Maggi M, et al. The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. *Eur Urol* 2013;63:506–16.

with no evidence of prostate cancer were enrolled; 369 men in total were randomized between sildenafil (189 men) and placebo (180 men). They were assessed according to a range of other parameters (e.g., BPH Impact Index, quality-of-life score, self esteem and relationship questionnaire) and, as expected, men's ED improved. However, their IPSS and other urinary symptom scores improved as well. IPSS improved by 6.32 points compared with 1.93 for placebo. BPH Impact Index score improved by 2 points compared with 0.9 for placebo, and the quality-of-life score improved by 0.97 compared with 0.29 for placebo. It is interesting to note that men with more severe LUTS improved more (by 8.6 compared with 2.4 in the less severely symptomatic men). **There was no significant difference in Qmax, which led the authors to suggest that possibly other mechanisms were involved than simply smooth muscle relaxation in the bladder and prostate.** They pointed out that other phosphodiesterases were present in the prostate, particularly types 4 and 11, and that these may have a part to play.

In answer to questions raised about this study, more information was subsequently provided regarding baseline IPSS scores. These data showed baseline IPSS scores of 20.76 (± 5.6) for those randomized to sildenafil and 20.55 (± 5.5) for those randomized to placebo. The sildenafil group improved by 6.32 points compared with 1.93 for the placebo arm. The subsequent data also indicated that the

improvement in IPSS score was greater in those men whose ED also responded—that is, an IPSS improvement of 7 versus 3.2 in those whose ED did not respond ($P < .0001$).

The second RCT (McVary et al, 2007b) investigated tadalafil. This study was designed to establish a proof of principle before larger and more definitive trials. It was a double-blind, placebo-controlled, randomized multicenter study in 21 centers in the United States. It included first a 4-week washout phase, but also a 4-week single-blind placebo run-in period before determination of baseline values and compliance, to reduce the placebo effect and the reversion to the mean phenomenon. Then followed the double-blind phase, randomizing men between tadalafil and placebo. Men in this study were chosen on the basis of their urinary symptoms (men over 45 with LUTS by IPSS of 13 or higher and a Qmax of 4 to 15 mL/sec, PSA level below 10, and PVR less than 200 mL). They were randomized to placebo or tadalafil at 5 mg for 6 weeks, after which the dose was escalated to 20 mg daily for a total of 12 weeks. The study ran between November 2004 and July 2005. As before, a range of parameters were measured. Of 281 men, 138 were randomized to tadalafil and 143 to placebo. There was a moderate response at 6 weeks, but a greater difference between the two arms by 12 weeks. Baseline IPSS scores in the tadalafil arm improved by 3.8 points, whereas the placebo arm baseline IPSS of 18.3 improved by 1.7

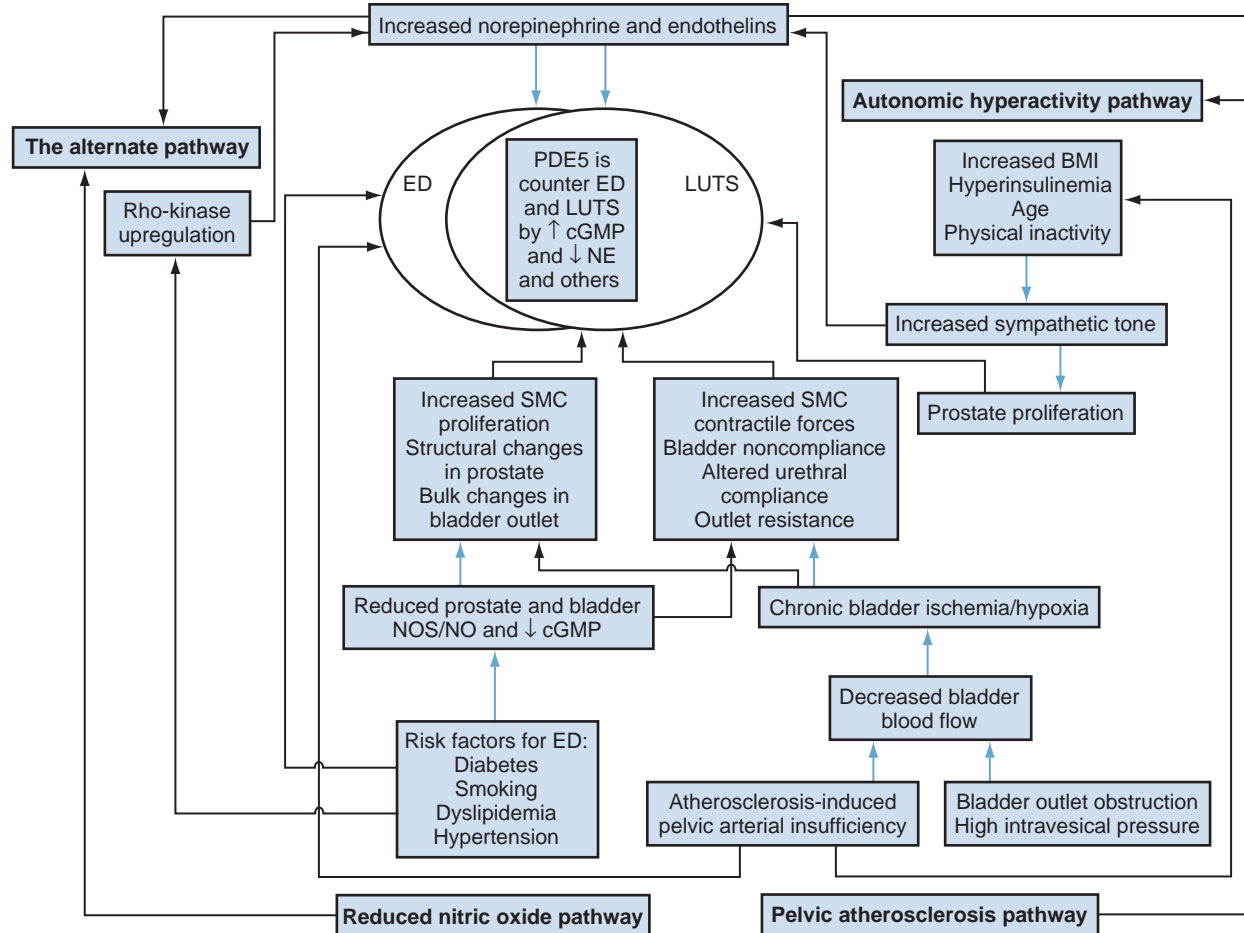


Figure 104-13. Theories linking pathophysiology of erectile dysfunction (ED) and lower urinary tract symptoms (LUTS). BMI, body mass index; cGMP, cyclic guanosine monophosphate; NE, norepinephrine; NO, nitric oxide; NOS, nitric oxide synthase; PDE5, phosphodiesterase type 5; SMC, smooth muscle cell. (From Kohler T, McVary K. The relationship between erectile dysfunction and lower urinary tract symptoms and the role of phosphodiesterase type 5 inhibitors. *Eur Urol* 2009;55:38–48.)

points; $P < .001$, thus indicating a net improvement of 2.1 points for the active arm. Whether a 2-point change is clinically significant or easily perceived by men is uncertain, but it is comparable to the response to α -blocker treatment in the meta-analysis performed by the AUA BPH guideline update panel (McVary et al, 2006, 2011). If the placebo run-in period is included, then the active-arm response of 7.1 points on IPSS (± 0.6) is similar to that in the sildenafil study (6.32 points). More convincingly, men in the tadalafil group were more likely to show a 3-point or greater improvement in IPSS by 12 weeks than men in the placebo group (60.9% vs. 42.7%), indicating an NNT of 5.5, which is seen as reasonable and representing effective therapy (Bandolier, 2003).

Roehrborn and coworkers (2008b) built on this proof of principle experience with a dose-finding study—a larger study of 1058 men performed in 92 centers in 10 countries. Men were randomized to placebo or 2.5, 5, 10, or 20 mg of tadalafil once daily. This randomized, double-blind, placebo-controlled 12-week study also included a 4-week single-blind placebo run-in period (during which the IPSS of 67 men improved from the “moderate/severe” range to the “mild” category) and generally similar inclusion criteria and outcome assessments, with the IPSS response to the 5-mg tadalafil regimen being the primary outcome.

Daily administration of 5 mg of tadalafil led to a statistically significant net improvement of 2.6 points in IPSS compared with placebo (4.87 vs. 2.27), again similar to α -blocker responses. Most of the response was seen by 8 weeks, and there was minimal further improvement at the higher doses (Fig. 104-14). There was no

significant change in Qmax at any dose, nor were there changes to PSA or PVR.

Stief and colleagues (2008) investigated vardenafil in a similar fashion in a randomized, double-blind, placebo-controlled phase 2b study undertaken in 16 centers in Germany between October 2005 and June 2006. Men were randomized to vardenafil 10 mg twice daily (109 men) and placebo (113 men) and assessed at 4 and 8 weeks. This was another proof-of-concept study and did not include a placebo run-in period. Eventually 105 men took vardenafil and 110 placebo. Vardenafil was associated with a significant improvement in IPSS versus placebo. IPSS score improved from 16.8 to 11 (or by approximately 5.9) with vardenafil compared with 16.8 to 13.2 (3.6) on placebo—that is, a mean difference of 2.3 points, again similar to an α -blocker response to alfuzosin or tamsulosin. There were small but not significant improvements in Qmax (15.9 to 17.5 mL/sec). This was a relatively young cohort and had reasonable Qmax values at baseline, so a study with older men and lower flow rates might more readily assess whether there is any effect of PDEIs on the flow aspects of BPH and LUTS.

Despite men reporting significant improvements in IPSS (mean difference between treatments 4.2, $P < .001$), detailed urodynamic studies (Dmochowski et al, 2010) comparing once-daily tadalafil 20 mg with placebo during a 12-week RCT showed that urodynamic measures remained largely unchanged during the study, with no statistically significant or clinically adverse difference between tadalafil and placebo in change in detrusor pressure at maximum urinary flow rate or any other urodynamic parameter assessed,

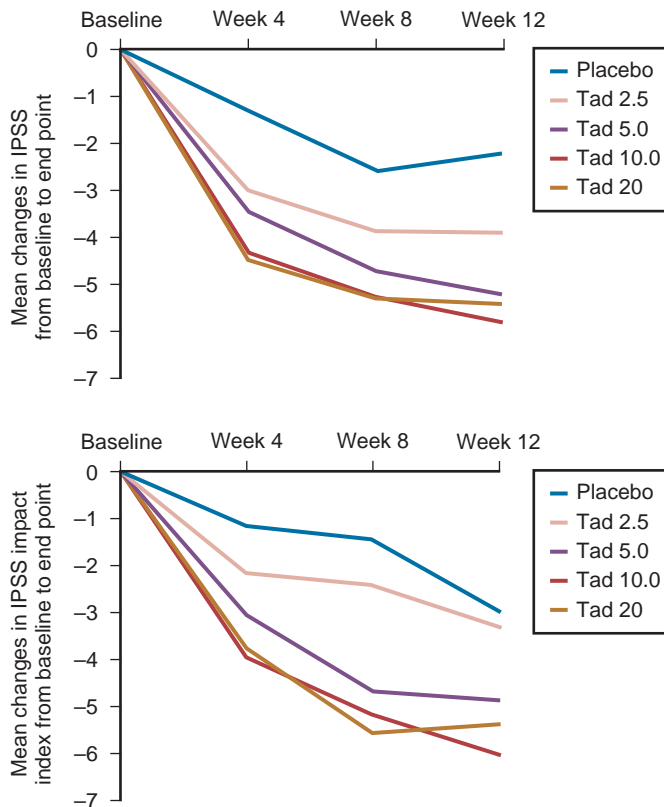


Figure 104-14. Response of lower urinary tract symptoms to tadalafil. Mean change in International Prostate Symptom Score (IPSS) and Benign Prostatic Hyperplasia Impact Index after treatment with placebo or tadalafil (Tad) at 5, 10, and 20 mg/day. (From Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. *J Urol* 2008;180:1228–34.)

including maximum urinary flow rate, maximum detrusor pressure, Bladder Outlet Obstruction Index score, or bladder capacity. A study of urodynamics in men before and after randomization to tamsulosin 0.4 mg and the now standard-dose tadalafil 5 mg (group 1; $n = 20$) or tamsulosin 0.4 mg and placebo (group 2; $n = 20$) once daily for 30 days pdetQmax showed a significant reduction in the tamsulosin-tadalafil group (13 ± 17.0) compared with the tamsulosin-placebo group (-1.2 ± 14.35) group ($P = .03$). Qmax increased in both groups: tamsulosin-tadalafil, 1.0 ± 2.4 , and tamsulosin-placebo, 1.4 ± 2.4 (Regadas et al, 2013).

Further good-quality studies have confirmed the benefits of PDEIs. Tadalafil has become the dominant agent because of its half-life and convenient 5-mg daily dose and has now been licensed widely for prescription for male LUTS. Analysis of the pooled data of 1500 men in the four international tadalafil RCTs suggested that tadalafil showed consistent efficacy compared with placebo across multiple subgroups—for example, age, prostate volume, previous therapy, symptom severity, and presence of hypogonadism (Porst et al, 2013). Similar responses were shown in men with or without ED (Broderick et al, 2010; Brock et al, 2013) (indicating that improvement is not just because of better sexual function) and in other racial groups such as Asian men (Yokoyama et al, 2013).

Combination Therapy: α -Adrenergic Blockers and Phosphodiesterase Inhibitors

PDEIs and α -blockers in combination reduce adrenergic tone in prostate, bladder neck, and cavernosal smooth muscle tissue in

organ bath studies (Oger et al, 2009; Angulo et al, 2012), leading researchers to consider combining PDEIs and α -adrenergic blocker medication in man. So far, evidence for combination therapy with α -adrenergic blockers and PDEIs is limited. Kaplan and colleagues (2007), in a 12-week open-label single-center pilot study, randomized 62 men among 25 mg of sildenafil (21 men), 10 mg of alfuzosin (20 men), and a combination of both agents (21 men). IPSS improved by 11.8% on sildenafil (i.e., decreased from 16.9 to 14.9), by 15.6% on alfuzosin, and by 24.1% on a combination of sildenafil and alfuzosin, suggesting that there may be a synergistic benefit from the use of both agents.

Improvement in Qmax was observed in all groups, but patients receiving combination therapy had greater improvement (29.6%) than patients receiving either only alfuzosin (21.7%) or only tadalafil (9.5%). IPSS was significantly improved in the alfuzosin group (27.2%) and was more marked in the combination therapy group (41.6%). There was a small nonsignificant increase in IPSS in the tadalafil only group (8.4%).

Liguori and colleagues (2009), in a randomized, open-label, three-arm study, gave 66 men with ED and LUTS tadalafil, alfuzosin, or tadalafil and alfuzosin and found that IIEF Erectile Function domain (IIEF-EF) sexual function scores did improve with alfuzosin alone (+15%). As expected, sexual function scores were more obviously improved with tadalafil alone (+36.3%), but the greatest improvement was experienced with combination therapy (+37.6%).

Improvement in Qmax was observed in all groups, but patients receiving combination therapy had greater improvement (29.6%) than patients receiving either only alfuzosin (21.7%) or only tadalafil (9.5%). IPSS was significantly improved in the alfuzosin group (27.2%) and was more marked with the combination therapy (41.6%); a small increase, although not statistically significant, was also observed with tadalafil (8.4%).

Udenafil has been administered to 120 men with LUTS-BPH and ED (Chung et al, 2009). Men on stable α -blocker therapy for their LUTS or BPH were given 100 mg of udenafil for 8 weeks. LUTS and ED improved significantly compared with baseline (IPSS improved from 14.3 to 11.5 and IIEF improved from 11.95 to 18.32). No significant changes in blood pressure or heart rate were reported in this study or in a similar study in which mirodenafil was added to α -blocker therapy (Bang et al, 2013). This is an important issue; the concomitant use of α -blockers and PDEIs may lead to symptomatic hypotension in some patients because both are vasodilators. Clearly urologists should proceed with caution, but Lee and coworkers suggest that the combination of a phosphodiesterase type 5 inhibitor (PDE5I) with losartan, nifedipine, amlodipine, doxazosin or tamsulosin could be a safe pharmacologic strategy for physicians simultaneously treating ED and its comorbidities and increasing response rates to PDE5Is (Lee et al, 2012).

Gacci and colleagues (2012) performed a meta-analysis of 12 published reports (7 on PDE5Is vs. placebo in 3214 men, and 5 on the combination of PDE5Is and α_1 -adrenergic blockers vs. α_1 -adrenergic blockers alone, in 216 men). They concluded that use of PDEIs alone led to a significant improvement in sexual function and IPSS compared with placebo and the combination of α_1 -adrenergic blockers and PDE5Is led to a significant improvement in sexual function, IPSS, and Qmax compared with α_1 -adrenergic blockers alone.

It seems reasonable to suggest that concomitant treatment with PDEIs should be initiated only once the patient has been stabilized on his α -blocker therapy. In those patients stable on α -blocker therapy, PDEIs should be initiated at the lowest recommended starting dose. In those men already taking an optimized dose of PDEIs, α -blocker therapy should be initiated at the lowest dose. Any stepwise increase in α -blocker dose may be associated with further lowering of blood pressure in patients taking PDEIs.

Studies so far suggest that vardenafil may be administered at any time with tamsulosin, whereas men given vardenafil and terazosin at the same time are more prone to hypotension. This effect was minimized by giving vardenafil and terazosin at doses separated by a time interval of 6 hours. The coadministration of doxazosin (4

and 8 mg daily) and tadalafil (5 mg daily or 20 mg as a single dose intermittently) leads to further blood pressure lowering, and this combination is not recommended.

Conclusions

PDEIs will have a role in LUTS and BPH. There is now good level 1 evidence of a beneficial effect of PDEIs on urinary symptoms. The mechanisms of effect are still unclear but the subject of extensive research because so many other body systems are also affected. It is likely that PDEI treatment will be valuable, especially for men with LUTS and significant ED. Recent U.S. data indicate that the proportion of men reporting moderate or severe LUTS ranges from 8% in those 30 to 39 years old to 26% in those 70 to 79 years old, and the prevalence of ED is also high and increases dramatically with age, with 10% of 30- to 39-year-old and 59% of 70- to 79-year-old men reporting mild-to-moderate or moderate-to-severe symptoms—clearly a substantial number of men who may request treatment (Brookes et al, 2008). It is now well recognized that patients with LUTS should be questioned about also having ED, and likewise patients with ED should be asked about concomitant LUTS (Kirby et al, 2013).

Further data on safety and cost-effectiveness, especially for combination therapy, are needed. Currently PDEIs are more expensive than α -blockers or 5 α -reductase inhibitors, which are now off patent protection in many countries and health care systems. Studies are needed to determine if costs may be reduced by using combination therapy initially followed by later withdrawal of the more expensive agent.

KEY POINTS: PHOSPHODIESTERASE INHIBITORS

- There is an as yet undetermined link between LUTS-BPH and ED.
- PDEIs improve urinary symptoms scores.
- PDEIs alone do not improve flow rates.
- The combination of α -adrenergic blockers and PDEIs may lead to a synergistic benefit, thereby improving LUTS and flow rates.
- The combination of α -adrenergic blockers and PDEIs may lead to symptomatic hypotension.
- PDEIs or a combination of α -adrenergic blockers and PDEIs may be of value in therapy for men with both ED and LUTS.

PHYTOTHERAPY

The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS and BPH is common. Phytotherapeutic agents for LUTS and BPH have gained widespread use since about 1990 (Lowe and Fagelman, 1999). These agents are popular in Europe, particularly in France, Austria, and Germany, where they are often prescribed and their costs reimbursed (Lowe et al, 1998). European data (Fourcade et al, 2008) show that although α -blocker monotherapy was the most frequently prescribed treatment (62.5% overall, 87.1% in Germany, 46.1% in France), phytotherapy was very popular (23.5%), followed by 5 α -reductase inhibitor monotherapy (3.75%). Combination therapy was rare. Treatment varied according to the severity of the symptoms ($P = .008$), with phytotherapy being given to patients with the lowest IPSS, and combination therapy to those with the highest IPSS. However, use in the United States has escalated. It has been estimated that over \$1 billion was spent per year in the United States alone for these products (Lowe and Fagelman, 1999). These agents have been marketed to “promote prostatic health,” and therefore it is not surprising that many men try them. Additional factors that contribute to their widespread use include being “natural” products (not “medications”), presumed safety, ease of accessibility (no prescription

TABLE 104-14 Origin of Plant Extracts

SPECIES	COMMON NAME
<i>Serenoa repens</i> , <i>Sabal serrulata</i>	Saw palmetto berry, American dwarf palm
<i>Hypoxis rooperi</i>	South African star grass
<i>Pygeum africanum</i>	African plum tree
<i>Urtica dioica</i>	Stinging nettle
<i>Secale cereale</i>	Rye pollen
<i>Cucurbita pepo</i>	Pumpkin seed
<i>Opuntia</i>	Cactus flower
<i>Pinus</i>	Pine flower
<i>Picea</i>	Spruce

BOX 104-1 Components of Plant Extracts

PHYTOSTEROLS

- β-Sitosterol
- Δ5-Sterol
- Δ7-Sterol
- Stigmasterol
- Campesterol

PHYTOESTROGENS

- Coumestrol
- Genistein (isoflavone)
- Flavonoids
- Fatty acids
 - Free
 - Esterified

TERPENOIDS

- Lectins
- Polysaccharides
- Aliphatic alcohols
- Plant oils

necessary), and their roles in avoidance of prostate surgery and prevention of prostate cancer (falsely assumed). The widespread availability of these products in health food stores, vitamin shops, traditional pharmacies, and supermarkets, as well as on numerous websites on the Internet, has contributed to their use and reflects the demand for these phytotherapeutic agents.

Origin of Phytotherapeutic Agents

Phytotherapeutic products are not the actual plant but are extracts derived from the roots, the seeds, the bark, or the fruits of the various plants used (Table 104-14). Although single plant preparations are available, many companies manufacture combination products (two or more plant extracts) in an attempt to provide “enhanced” efficacy (never proven), to improve marketability, and to provide a unique product that can be registered because there is no patent protection for these products. Only the monopreparations are evaluated and reviewed here.

Composition of the Phytotherapy Extracts

The composition of plant extracts is very complex. They contain a wide variety of chemical compounds, which include phytosterols, plant oils, fatty acids, and phytoestrogens (Box 104-1). Which of these is the active component is not clear. Both the free fatty acids and the sitosterols have been thought to be the active components.

BOX 104-2 Suggested Mechanisms of Action of Plant Extracts

Inhibition of 5 α -reductase
 Anti-inflammatory action
 Interference with growth factors
 Antiandrogenic effects
 Estrogenic effects
 Inhibition of aromatase
 Decrease of sex hormone-binding globulin
 Alteration of cholesterol metabolism
 Action on α -adrenergic receptors
 Free radical scavenging
 Alteration of lipid peroxidation
 Modulation of prolactin-induced prostatic growth
 Protection of bladder and detrusor function
 Placebo effect

Most of the plant extracts are unique. First, the plants are not identical, owing to natural variability. Second, the extraction processes used by the various manufacturers are frequently different and use various substrates for the process. Thus, even if the phytotherapeutic compounds produced by two different companies contain the same plant, the exact composition of the final products is probably different and the content of the “active” component in each preparation may also be different. For example, analysis by ConsumerLab of free fatty acid content in 27 different saw palmetto products showed variability from 0% to 95%, with only 17 containing more than the presumed standard amount of 85% (ConsumerLab, 2000). There is minimal adulteration of “BPH” herbal preparations with α -blockers or 5 α -reductase inhibitors (Elterman et al, 2010).

Mechanism of Action

In general, the mechanisms of action of the phytotherapeutic agents are unknown (Lowe et al, 1998). Many in vitro experimental studies have been undertaken to elucidate this; thus, there are numerous proposed mechanisms of action (Box 104-2). Almost all these studies use supraphysiologic doses that are many times higher than the standard doses used clinically. The biologic effects are typically examined in tissue culture, which might not be an accurate reflection of in vivo effects (Lowe and Ku, 1996). The three mechanisms of action that have received the greatest attention are anti-inflammatory effects, 5 α -reductase inhibition, and growth factor alteration.

The anti-inflammatory effects are modulated by effects on prostaglandin synthesis. Plant flavonoids are inhibitors of both cyclooxygenase and lipoxygenase enzymes (Bach and Walker, 1982; Buck, 1996). Flavone, a phytoestrogen commonly found in plants and herbs, has been shown to be a strong inhibitor of cyclooxygenase (Mower et al, 1984; Alcaraz and Ferrandiz, 1987). *Serenoa repens* (Permixon) has been shown to inhibit phospholipase A₂ activity, thereby decreasing arachidonic acid metabolites and prostaglandin E₂ synthesis (Plosker and Brogden, 1996). In addition, in two different studies, Paubert-Braquet and colleagues (1994, 1997) demonstrated inhibition of the production of lipoxygenase metabolites and leukotrienes by neutrophils by *S. repens* and *Pygeum africanum* (Tadenan).

The most widely suggested mechanism of action of *S. repens* is as a 5 α -reductase inhibitor (Plosker and Brogden, 1996), reducing the conversion of testosterone to DHT and potentially leading to reduction of prostate volume (Gormley et al, 1992). Although inhibition of 5 α -reductase activity by *S. repens* was found in some experimental models (Sultan et al, 1984), other in vitro and in vivo data have not confirmed this effect (Rhodes et al, 1993; Weisser et al, 1996).

Two ex vivo experiments have demonstrated conflicting results. Pretreatment with *S. repens* for 3 months before suprapubic prostatectomy demonstrated a decrease in prostatic DHT and an increase in prostatic testosterone concentrations compared with controls, which suggests inhibition of 5 α -reductase activity (Di Silverio et al, 1998). In a similar pretreatment study using *Sabal serrulata* (IDS-89) for 3 months, prostate tissue levels of 5 α -reductase, 3 α -hydroxysteroid, and 3 β -hydroxysteroid oxidoreductase were not different compared with placebo (Weisser et al, 1996). An in vivo experiment of healthy male volunteers demonstrated a reduction of serum DHT levels with finasteride but not with *S. repens* (Strauch et al, 1994). Clinically, in a large multicenter trial comparing *S. repens* with finasteride, no effect on PSA levels and only a 6% reduction in prostate volume were noted for *S. repens*-treated patients, whereas the finasteride-treated patients had reduction of PSA levels by 41% and prostate volume by 18% (Carraro et al, 1996).

S. repens causes disruption of nuclear membrane in cell culture but has no effect on the integrity of the cell membrane (Bayne et al, 1999); therefore, the intracellular theory has been promulgated. Whether this supraphysiologic cell culture experiment actually reflects what is happening in vivo is uncertain and unproved.

Plant extracts are also thought to act by altering growth factor-induced growth and proliferation. In vitro studies with *P. africanum* demonstrated an inhibitory effect on both basic fibroblastic growth factor (bFGF)- and EGF-induced human and rat prostate fibroblast proliferation (Paubert-Braquet et al, 1994; Yablonsky et al, 1997). Subsequent experiments with *S. repens* have also shown inhibition of bFGF- and EGF-induced proliferation of human BPH prostate cells from biopsy specimens (Paubert-Braquet et al, 1998). In addition, an ex vivo experiment in men treated with *S. repens* before prostatectomy demonstrated reduced levels of tissue EGF, particularly in periurethral tissue (Di Silverio et al, 1998).

Although experimental data have suggested numerous possible mechanisms of action for the phytotherapeutic agents, it is uncertain which, if any, of these proposed mechanisms is responsible for the clinical responses.

***Serenoa repens* (Saw Palmetto Berry)**

The extract of the berry of the American saw palmetto, or dwarf palm plant, *S. repens* (also known by its botanical name of *S. serrulata*), is the most popular phytotherapeutic agent consumed for LUTS and BPH. Although numerous clinical trials with saw palmetto berry extracts have been published, many were uncontrolled open-label studies, which provides little useful information in determining the efficacy of these phytotherapies. Even though placebo-controlled studies have been published, most of them are flawed and none of them would meet the generally accepted criteria developed by the International Consultation on BPH for assessing treatment results in men with LUTS (Denis et al, 1998). Previous studies were of limited value because of their small numbers of patients, short duration (only 1 to 3 months), and lack of use of standardized symptoms scores. For example, nocturia was the only symptom available for analysis in all the studies reviewed in two meta-analyses (Wilt et al, 1998; Boyle et al, 2000). In the meta-analysis by Wilt and colleagues (1998) of 18 trials involving 2939 patients using various *S. repens* monopreparations and combination products, the mean weighted difference for nocturia between patients and individuals taking a placebo was -0.76 times per evening (-1.22 to -0.32) for 10 trials. In the meta-analysis by Boyle and coworkers (2000) of 13 trials involving 2859 patients using only the Permixon brand of *S. repens*, the attributable reduction of nocturnal urinations was 0.50 (± 0.01) times per night. Wilt and coworkers conducted a systematic review, first published in 1998 and updated in 2002, 2009, and again in 2012 (MacDonald et al, 2012) to evaluate the efficacy and adverse events of *S. repens*. Initially their analysis was mildly supportive of the efficacy of *S. repens*. In the 2009 update, 9 new trials involving 2053 additional men (a 64.8% increase) were included. For the main comparison—*S. repens* versus placebo—3 trials were added with 419 patients and 3 end points (IPSS, peak urine flow, prostate size). Overall, 5222 patients

BOX 104-3 Inherent Weaknesses of Meta-Analyses

Pooled results incorporate biases of individual studies
 New sources of biases created
 Incomplete selection of studies
 Publication bias (only positive trials usually published)
 Language bias
 Heterogeneity of the studies
 Inclusion or exclusion criteria
 Poor study designs
 Poor assessments of efficacy
 Variable placebo response rates
 Short study durations

from 30 randomized trials lasting from 4 to 60 weeks were assessed. Twenty-six trials were double blinded, and treatment allocation concealment was adequate in 18 studies. With these extra data and especially the double-blind, placebo-controlled trial reported by Bent and coworkers (2006), Tacklind and colleagues (2009) concluded that *S. repens* was not superior to placebo in improving IPSS or Qmax or for reducing prostate size. For nocturia, *S. repens* was significantly better than placebo (weighted mean difference -0.78 nocturnal visits, 95% CI -1.34 to -0.22 , $P < .05$) in 9 short-term Permixon trials but not in a high-quality trial. *S. repens* was also not superior to finasteride or to tamsulosin. Overall, the latest analysis (MacDonald et al, 2012) concluded that *S. repens* therapy does not improve LUTS, Qmax, or nocturia compared with placebo in men with BPH, even at double and triple the usual dose.

Despite inherent weaknesses in meta-analyses (Box 104-3), these analyses attempt to maximize the information available from clinical trials using *S. repens* in the treatment of symptomatic BPH and LUTS and to provide the best information available until the appropriate placebo-controlled, randomized clinical studies are conducted. However, approximately 35% of the prior meta-analyses performed are not reproduced in subsequent RCTs (LeLorier et al, 1997). Current meta-analysis suggests that *S. repens* is not more effective than placebo for treatment of LUTS. The Complementary and Alternative Medicine for Urological Symptoms (CAMUS) study was set up to address these deficiencies and concluded that increasing doses of a saw palmetto fruit extract did not reduce LUTS more than placebo (Barry et al, 2011) and did not affect serum PSA more than placebo, even at relatively high doses (Andriole et al, 2013) but did appear safe (Avins et al, 2013).

Pygeum africanum (African Plum)

In addition to the proposed mechanisms of actions previously discussed, *P. africanum* has been postulated to have additional beneficial effects on LUTS by having a protective effect on the obstructed bladder. Using a rabbit model with partial BOO, Levin and associates (1996) demonstrated that changes in bladder mass, decrease in compliance, and alterations in contractile response to various forms of stimulation could be tempered by pretreatment with *P. africanum*.

A review of the published experience with *P. africanum* (Tadenan) identified 2262 patients treated with this extract: 1810 in open-label studies and 452 in comparative trials (Andro and Riffaud, 1995). Twelve double-blind, placebo-controlled studies were completed from 1972 to 1990. Only one study enrolled more than 100 patients, and none was longer than 12 weeks or used standardized symptom scores. A 2-month open-label study (Breza et al, 1998) and a 2-month comparison trial of 50 mg twice daily versus 100 mg daily (Chatelain et al, 1999) both demonstrated a reduction in IPSS score of approximately 40% (5.7 and 6.4 units) and an improvement in PFR of approximately 18% (2.1 and 1.7 mL/sec) over baseline. However, without a placebo arm, the actual magnitude of drug effect cannot be determined. Thus, without at least the data from the Tadenan-IPSS study, the efficacy of *P. africanum* cannot be determined. In addition, there are few other significant data

available with regard to any of the other *P. africanum* extracts. Thus, none of those trials meets the guidelines recommended by the International Consultation conferences on BPH. Another meta-analysis for the Cochrane collaboration (Wilt et al, 2002a) concluded that an effect was possible but not proven. Therefore the data concerning the efficacy of *P. africanum* are not conclusive.

Hypoxis rooperi (South African Star Grass)

Hypoxis rooperi (Harzol) has been studied in both a 6-month double-blind, placebo-controlled trial of 200 patients (Berges et al, 1995) and, subsequently, an open-label follow-up (Berges et al, 2000). In the initial study, statistically significant improvements were documented for symptom scores (IPSS), quality of life, PFRs, and PVRs (Berges et al, 1995). The placebo group showed appropriate mild improvement in these parameters. The IPSS improved by 7.4 units for β -sitosterol patients and 2.3 units for placebo. Similarly, peak urinary flow rates improved by 5.2 mL/sec for treated patients compared with 1.1 mL/sec for placebo. **This magnitude of improvement has not been observed with any other medical therapy previously evaluated for LUTS/BPH.**

During the follow-up study, patients were able to remain on or switch over to Harzol therapy. For those 38 patients who continued Harzol therapy, IPSS improvements were maintained. The 27 patients who received placebo initially and were then treated with Harzol demonstrated similar levels of improvement in IPSS scores and PFRs. Surprisingly, the 14 patients who stopped therapy still maintained similar levels of improvement over the next 12 months. This suggests that intermittent therapy could be an option.

Another product (Azuprostat) contains primarily β -sitosterols from *H. rooperi* as well as from *Pinus* (pine) and *Picea* (spruce). Although this is a combination preparation of extracts, its proposed active ingredient, β -sitosterol, is common to all three. This product (Azuprostat) was evaluated in a 6-month randomized, placebo-controlled trial with 177 patients (Klippel et al, 1997). Significant improvements in IPSS scores, PFRs, and PVRs were found. IPSS scores improved by 8.2 units for treated patients and 2.8 units for placebo. PFRs improved by 8.9 mL/sec for treated patients and 4.4 mL/sec for placebo. This magnitude of improvement has not been reported for any type of medical therapy for LUTS or BPH. It is hard to believe these results, in which the mean post-treatment PFRs are 19.4 mL/sec—a normal value for younger men and not for the typical age of men in the study. If these results are reproducible, they would rival the results of surgical intervention.

Wilt and associates (1999) also produced a meta-analysis for β -sitosterol products. It included four trials (two mentioned earlier and two earlier suboptimal ones) encompassing three different products: Harzol, Azuprostat, and WA184, all of which have different amounts of β -sitosterol. WA184 did not improve Qmax (Kadoff et al, 1986). Again, this meta-analysis is tempered by the same factors mentioned previously. The researchers' conclusion was that **β -sitosterol does improve urologic symptoms and urinary flow rates, but its long-term effectiveness, safety, and ability to prevent the complications of LUTS/BPH are unknown (Wilt et al, 1999).**

Lycopenes and Other Extracts

Ilic and Misso (2012) in a systematic review of the eight best lycopene studies felt that it was not possible to support or refute the use of lycopene for the prevention or treatment of BPH. Isoflavones (Soylife 40) were studied in 176 men with "only slight superiority" to placebo (Wong et al, 2012). The other extracts listed in Table 104-14 (*Urtica dioica*, *Cucurbita pepo*, *Secale cereale*, and *Opuntia*) have even fewer relevant clinical studies published. Of these extracts, *S. cereale* (Cernilton) had two placebo-controlled trials published more than two decades ago that did not have standardized scores, used different doses of the preparation, lasted 12 and 24 weeks, and enrolled only 103 and 60 patients (Buck et al, 1990). Wilt and associates (1999) in a systematic review and meta-analysis of Cernilton concluded that it modestly improves overall urologic symptoms including nocturia but that additional trials are needed

to evaluate clinical effectiveness (MacDonald et al, 1999). Zhang and colleagues (2008) have reported a randomized, double-blind, placebo-controlled clinical trial of a flaxseed lignan extract containing 33% secoisolariciresinol diglucoside (SDG). SDG was evaluated for its ability to alleviate LUTS in 87 patients with LUTS and BPH, with repeated measurements conducted over a 4-month period using treatment doses of 0 (placebo), 300, or 600 mg of SDG per day. After 4 months of treatment, 78 of the 87 patients completed the study. For the 0-, 300-, and 600-mg/day SDG groups, respectively, the IPSS decreased -3.67 ± 1.56 , -7.33 ± 1.18 , and -6.88 ± 1.43 (mean \pm standard error [SE], $P = .100$, $< .001$, and $< .001$ compared with baseline), the quality-of-life score improved by -0.71 ± 0.23 , -1.48 ± 0.24 , and -1.75 ± 0.25 (mean \pm SE, $P = .163$ and $.012$ compared with placebo and $P = .103$, $< .001$, and $< .001$ compared with baseline), and the number of patients whose LUTS grade changed from “moderate/severe” to “mild” increased by 3, 6, and 10 ($P = .188$, $.032$, and $.012$ compared with baseline). Qmax insignificantly increased by 0.43 ± 1.57 , 1.86 ± 1.08 , and 2.7 ± 1.93 mL/sec (mean \pm SE, no statistical significance reached), and postvoiding urine volume decreased insignificantly by -29.4 ± 20.46 , -19.2 ± 16.91 , and -55.62 ± 36.45 mL (mean \pm SE, no statistical significance reached). The observed decreases in IPSS and quality-of-life score were correlated with the concentrations of plasma total lignans. Zhang and coworkers (2008) concluded that dietary flaxseed lignan extract appreciably improved LUTS, and the therapeutic efficacy appeared comparable to that of α_{1A} -adrenoceptor blockers and 5 α -reductase inhibitors.

Summary

Most phytotherapeutic preparations are plant extracts with different components manufactured by different extraction procedures, which prevents comparison of the preparations. Although numerous in vitro experiments have been conducted to determine their possible mechanisms of pharmaceutical action, it is uncertain which of the actions demonstrated in vitro might be responsible for clinical responses in vivo. Appropriate randomized placebo-controlled clinical trials monitored by an outside agency are needed to ascertain and to confirm the efficacy of these products. Phytotherapies for LUTS and BPH should be scrutinized and subjected to trials just as are all regulated drugs.

ACUTE URINARY RETENTION

Management of Acute Urinary Retention

AUR is the commonest urologic emergency managed by most urologists worldwide. Furthermore, it will be encountered by most physicians whatever their specialty and is commonly witnessed on surgical and elderly care wards. AUR may be spontaneous, in which case it is usually associated with previous LUTS or BPH. Alternatively, it may be precipitated by some other factor such as the effects of various medications, particularly anticholinergic or sympathomimetic agents, commonly found in cough and cold remedies. Urinary infection, excessive fluid intake, and the consequences of surgery (postoperative pain or the effects of anesthesia or analgesia or loss of mobility) may precipitate AUR. Obviously there can be an overlap between these two rather artificial divisions, and AUR in a man with symptomatic or silently progressing BPE or BOO may well be precipitated by one of these other factors.

Population-based cohort studies from the United States (Jacobsen et al, 1997; Meigs et al, 1999), from Holland (Verhamme et al, 2005), and also from the United Kingdom (Cathcart et al, 2006) defined the incidence, although it varies among populations. Verhamme and colleagues, in a study based on Dutch general practitioner records covering essentially the whole male population of Holland, reported an incidence of 2.2 AUR events per 1000 man-years, of which 40% were precipitated (Fig. 104-15). AUR was the first symptom in 49% of men designated as suffering from LUTS or BPH, and in this group the risk of AUR was 11 times higher (18.3 per 1000 man-years). They concluded that AUR was of

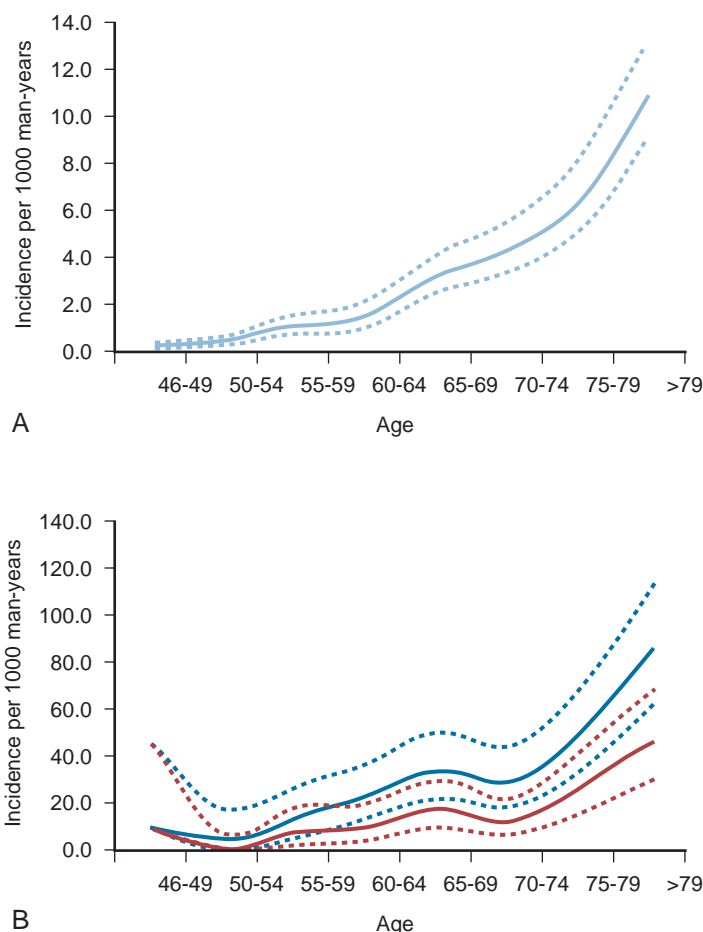


Figure 104-15. Incidence of acute urinary retention in the general population of Dutch men (A) and in the lower urinary tract symptoms and benign prostatic hyperplasia population (B). (From Verhamme KM, Dieleman JP, van Wijk MA, et al. Low incidence of acute urinary retention in the general male population: the triumph project. *Eur Urol* 2005;47:494–8.)

low incidence in the general population but substantial in the LUTS and BPH population. Cathcart and colleagues (2006), reviewing national U.K. figures, reported 3.1 AUR episodes per 1000 man-years.

These figures are lower than in the two U.S. cohort studies. Jacobsen and coworkers (1997) found an incidence of 6.8 events per 1000 man-years in the Olmsted County Study, and the Health Professionals Follow-up Study (Meigs et al, 1999) reported a rate of 4.5 per 1000 man-years. There may be selection bias here, as the prevalence of BPH and LUTS in these U.S. studies is much higher than in the European studies (33% of the Olmsted County men had an IPSS of greater than 8, and 30% of the men in the Health Professionals Study had a diagnosis of BPH or LUTS compared with just 8% in the Dutch men). Analysis of the placebo arms of a series of large studies such as the PLESS evaluation of finasteride, MTOPS, and the CombAT study indicate that increasing age, the presence of LUTS, a low Qmax, and prostatic enlargement and/or raised PSA increase the risk of AUR.

When AUR develops, most men are catheterized for a period or taught intermittent self-catheterization. At some variable point the catheter will usually be removed and a trial without catheter (TWOC) performed (Emberton and Fitzpatrick, 2008). It is reasonable to speculate that urinary retention is caused in part by dynamic as opposed to static outflow obstruction because a significant proportion of men void spontaneously after catheter removal (Taube and Gajraj, 1989). If urinary retention is caused by increased sympathetic activity at the level of the prostatic smooth

muscle, an α -blocker should increase the likelihood of spontaneous voiding after catheter removal.

The chance of successful voiding after a period of AUR was improved by the use of alfuzosin (McNeill et al, 2005) and tamsulosin (Lucas et al, 2005). In a multicenter study a total of 360 men with AUR underwent emergency catheterization and were blindly randomized to alfuzosin 10 mg once daily or placebo for 3 days (first phase). All patients with successful TWOC, regardless of treatment, were then again blindly randomized to alfuzosin 10 mg once daily or placebo for 6 months (second phase). Alfuzosin significantly increased the successful TWOC rate (146 of 236, 61.9%) compared with placebo (58 of 121, 47.9%; $P = .012$). In the second phase, 14 (17.1%) of the 82 alfuzosin-treated patients versus 20 (24.1%) of the 83 placebo-treated patients required prostate surgery, 5 (36%) of 14 versus 13 (65%) of 20 within 1 month, and 8 (57%) of 14 versus 17 (85%) of 20 within 3 months of treatment. Emergency surgery because of AUR relapse was the main cause of failure in both groups (11 [78.6%] of 14 in the alfuzosin group and 16 [80.0%] of 20 in the placebo group). Compared with placebo, alfuzosin improved the Kaplan-Meier survival rates by 9.6% ($P = .04$), 11.4% ($P = .04$), and 8.3% ($P = .20$), with surgical risk reductions of 61%, 52%, and 29% at 1, 3, and 6 months of treatment, respectively. High PSA values and the post-TWOC residual urine volume significantly increased the risk of AUR relapse and prostate surgery (McNeill et al, 2005).

An economic analysis (Annemans et al, 2005) suggests that treatment with alfuzosin before and after a successful TWOC reduces treatment costs in the first 6 months. Unfortunately, even those who succeed will have a high rate of subsequent failure to void and 80% of those who will fail do so within 6 months (Cathcart et al, 2006). At that point surgery and/or pressure-flow studies are indicated.

Medical Therapy in the Prevention of Acute Urinary Retention

Large-scale, randomized, double-blind, placebo-controlled trials of long-term duration are necessary to determine whether a medical therapy prevents a relatively uncommon event such as AUR. In the MTOPS trial, finasteride or combination therapy with finasteride and doxazosin, but not doxazosin alone, reduced the incidence of AUR (McConnell et al, 2003). Debruyne and colleagues (2004) reported data for dutasteride that suggested similar results. Because men with large prostates have on average a threefold greater chance of developing urinary retention (Jacobsen et al, 1997), enrolling men with large prostates would enhance the probability of observing an effect on AUR. The 3-year open-label prospective study of alfuzosin supported a 0.3% risk of retention (Lukacs et al, 2000). This is markedly lower than the predicted risk of developing urinary retention in an age-matched cohort of men (Jacobsen et al, 1997) but may be more a delay rather than prevention. The trial data suggest a role for 5 α -reductase inhibitor drugs in the prevention of AUR.

FUTURE STRATEGIES FOR NONSURGICAL THERAPY FOR MALE LOWER URINARY TRACT SYMPTOMS

The nonsurgical management of LUTS and BPH evolves slowly year after year with the occasional significant breakthrough. Medical therapies provide improvement over watchful waiting for most patients (Hutchison et al, 2007), but the therapeutic response to medical therapy remains less than that to prostatectomy. As Clifford and Farmer (2000) noted in a meta-analysis of α -blocker and finasteride studies, "neither finasteride nor α -blockers approach the efficacy of prostatic surgery in terms of improvement in either symptoms or flow rates"; therefore, scope exists to develop novel strategies that may be more effective than existing therapies. Since the last edition of this text, the biggest change in management has been the acceptance of the PDE5I pathway as important in LUTS management, and the use of PDE5Is alone or in combination with

α -adrenergic blockers has become an effective reality. Developing other classes of drugs to relax smooth muscle and further targeting nonprostatic factors are potential opportunities (Fig. 104-16).

Langenstroer and associates (1993) reported that human prostate contains endogenous endothelin and that endothelin elicits a very potent contraction in the human prostate. Kobayashi and colleagues (1994) have characterized the binding properties of endothelin receptor subtypes in the human prostate. The contractile response elicited by endothelin in the human prostate is not abolished by pretreatment with selective α_1 -blockers, which suggests that relaxation of prostatic smooth muscle in BPH may also be achieved by endothelin antagonists. The involvement of the inflammatory pathway in the pathogenesis of LUTS and BPH now appears fairly clear, but mechanisms to modify the inflammatory process are still in the developmental stages. Trials with agents such as cyclooxygenase-2 (COX-2) inhibitors have shown improvements in therapeutic effectiveness when combined with α -blockers (Jhang et al, 2013). Investigations of the links between metabolic syndrome, lipid metabolism, the sex-steroid environment, and the inflammatory pathways may also yield useful agents in the future. Other potentially modifying agents for LUTS include growth factors such as vitamin D₃ receptor analogues (e.g., elocalcitol), oxytocin antagonists, and modulators of the cannabinoid system (e.g., fatty acid amide hydrolase inhibitors), but these need further evaluation in clinical studies. Other compounds, such as transient receptor potential vanilloid antagonists, Rho-kinase inhibitors, purinergic receptor blockers, hexokinase inhibitors, and endothelin targeting drugs, are still at experimental stages (Füllhase et al, 2014). Over the next 5 years, LUTS and BPH treatment will become even more patient specific and is likely to become more gene based to take into account the genetic and hereditary variations in the disease, although at the moment it seems unlikely that any single gene polymorphisms will exhibit a strong enough correlation with LUTS or BPH parameters to be clinically useful in the short term (Berges et al, 2011).

Nonprostatic factors also contribute to LUTS and BPH. LUTS have a complex pathophysiology involving far more than just the prostate and the bladder, and manipulation of the other pathways that influence LUTS, such as the endocrine, renal, neurologic, and cardiovascular pathways, may yield the next significant improvement in male LUTS management. Our present understanding of the pathophysiology of LUTS and BPH is rudimentary. We must develop a greater understanding of the pathophysiology of symptoms. This knowledge will result in more effective use of existing therapies and will provide the rationale for the next generation of therapeutic modalities.

KEY POINTS: EVALUATION AND NONSURGICAL MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA

- BPH is the commonest cause of LUTS in men beyond middle age.
- Evaluation requires a history and symptom score (IPSS) and a careful physical examination including a DRE.
- Uroflowmetry and ultrasound estimation of PVR urine volume are often helpful; a PSA measurement is requested when a diagnosis of prostate cancer would alter the management of the individual patient.
- Medical therapy with either an α -blocker or (if the prostate is large) a 5 α -reductase inhibitor is now the usual first-line management of uncomplicated LUTS.
- Combination therapy with both an α -blocker and a 5 α -reductase inhibitor has been demonstrated to be the most effective means of preventing disease progression and seems likely to become the standard of care in appropriate cases.
- Antimuscarinic agents and PDEIs are useful adjuncts for men with storage symptoms or ED. The true importance of these agents will become clearer with time.

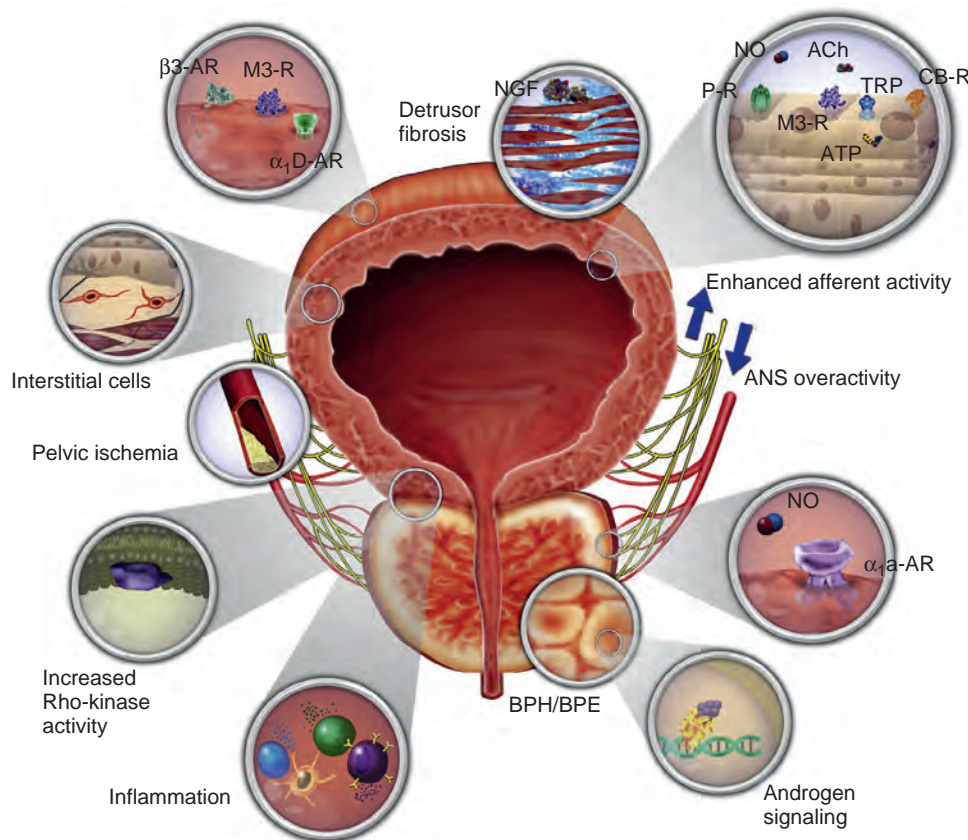


Figure 104-16. Pathophysiological mechanisms and targets for future nonsurgical therapy. (From Soler R, Andersson KE, Chancellor MB, et al. Future direction in pharmacotherapy for non-neurogenic male lower urinary tract symptoms. *Eur Urol* 2013;64:610–21.)

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The complete reference list is available online at www.expertconsult.com.

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Epidemiology and Marketshare

Workup

Defining Outcomes

Presurgical Factors

Specific Technologies

Conclusion

Urinary obstruction as a result of benign prostatic disease has probably been recognized to some degree since the earliest days of medicine. One of the earliest descriptions of benign prostatic hyperplasia (BPH) was offered by Morgagni in the eighteenth century (Morgagni, 1760). Early treatments for BPH centered on open procedures with both suprapubic and perineal approaches. These surgeries were often bloody and led to unacceptable mortality and morbidity. Transurethral resection of the prostate (TURP) offered another option between watchful waiting and open prostatectomy (OP), but with rudimentary equipment and an incomplete understanding of the postoperative physiology, this procedure continued to have an elevated morbidity and even mortality.

With the introduction of medical management in the 1990s, we began to see a decrease in the need for surgery to treat lower urinary tract symptoms (LUTS) related to BPH. Medical management provided a lower-risk treatment option for patients over the previously unchallenged surgical treatments, yet at a cost of lower benefit in urologic outcomes and the need for ongoing therapy. However, despite the strides made in optimal medical management, many patients still need or request additional surgical treatment.

The expanding endoscopic options including many minimally invasive surgical techniques (MISTs) allowed the practitioner to add many other treatments into the continuum between surgical approaches and medical management. Subsequently, the urologist witnessed an explosion in procedures available for the treatment of LUTS and BPH. These new technologies are often embraced with excitement; however, many do not live up to these initial expectations, which were often based on small series of patients followed for short duration.

As the pressure to accept a new technology grows with increasing marketplace competition, the urologist must be careful in embracing each new technology until the results have been thoroughly vetted. Often when new technologies or techniques are compared with the classic monopolar TURP (M-TURP), outdated data are quoted that do not reflect contemporary TURP results. In addition, there is a considerable placebo effect inherent to all LUTS-BPH treatments, and with nonrigorous study design, such as an uncontrolled single-series cohort, any inherent placebo or sham effect will be credited to the new technology.

In this chapter, we will discuss the many treatment options available to the patient and urologist for the treatment of LUTS and BPH. Special attention will be paid to advantages or disadvantages of different techniques and differences in patient outcomes. TURP held a unique position as the only endoscopic treatment for many decades, and the depth and variety of literature surrounding the procedure are impressive. This treatment is still clearly considered the gold standard, and almost any new technology inherently ends

up being compared with TURP in a randomized controlled trial (RCT) setting or by expert opinion.

EPIDEMIOLOGY AND MARKETSHARE

Marketshare

With the rise of α -blocker therapy for treatment of LUTS and BPH in the 1980s, there has been an ongoing decrease in the rates of surgical treatment for BPH. Analysis of Medicare databases at multiple points has shown this continual decrease (Lu-Yao et al, 1994; Wasson et al, 2000), with a 5% decrease per year seen between 1999 and 2005. However, in this study period between 1999 and 2005 there was a 44% overall increase in surgical treatment of BPH (all treatment options) mostly brought on by a 529% increase in thermotherapy or laser treatment (Yu et al, 2008).

The most recent installment of this series (Malaeb et al, 2012) showed an overall peak in surgical treatment for LUTS and BPH in 2005 with a subsequent 19.8% decrease until the end of the study in 2008. Throughout the entire study period, use of TURP continued to decrease, even with the introduction of the bipolar resection system. Thermotherapy and laser therapy also had an overall decrease between 2005 and 2008; the only treatment option with an increase after 2005 was laser vaporization.

Additional insight can be drawn by examining the case log of urologists undergoing certification or recertification. An examination of 3995 case logs showed that 59% of urologists performed solely TURP, with 8% performing exclusively laser procedures. The proportion of laser procedures increased from 11% of the total to 44% of the total between 2004 and 2010. While there was no difference in age between those performing exclusively TURP or any laser procedure, practitioners utilizing laser procedures were more likely to have larger case volumes. Interestingly, after 2008, the percentage differential was fairly stable between any laser procedure (44%) and standard TURP (56%), possibly indicating some saturation (Lowrance et al, 2013).

See the Expert Consult website for further details.



Epidemiology of Surgical Treatment for Benign Prostatic Hyperplasia

The prevalence of both LUTS attributed to BPH and histologic BPH increases with age. The Baltimore Longitudinal Study (Guess et al, 1990) examined 1057 men and found that "prostatism" or BPH voiding dysfunction increased progressively from 26% in the fifth decade of life to 79% in the eighth decade of life. Prevalence of symptoms related to an enlarged prostate increased from 26%

Socioeconomic factors affecting laser use and adoption were evident from analysis of payer data in Florida that examined both inpatient and ambulatory surgery discharges for laser prostatectomy or TURP. Socioeconomic areas were characterized by lowest, medium, and highest tertiles after being identified by ZIP code. A better socioeconomic environment correlated with offering laser prostatectomy and with a more rapid adoption of the technique (Schroek et al, 2013).

of men aged 40 to 49 to 46% of men older than 70 in the Olmsted County study (Chute et al, 1993).

The prevalence of the histologic evidence of BPH follows a similar correlation with age. Men in their eighth decade (82%) were more likely to have histologic evidence than men in their fourth (8%) decade in the study by Berry and colleagues (1984). The autopsy study from Robson (1964) found prevalences of histologically confirmed BPH in prostates with gross enlargement of 14%, 37% and 39%, respectively, in men 50 to 59, 60 to 69, and older than 70 years.

Increasing Age

The risk of surgery related to BPH was noted to be considerably greater for a man age 80 years than a man age 40 years in the Veterans Administration Normative Aging Study, which was carried out prospectively from 1961 to 1982 (Glynn et al, 1985). The retrospective New Haven hospital study (Lytton et al, 1968) also found an increasing incidence of surgery for BPH through the eighth decade.

Effects of Benign Prostatic Hyperplasia Medications

The successes of medical therapy for LUTS and BPH have led to the previously decreased rates of surgical management of BPH. Subsequently, patients are now older at the time of surgical intervention than they were in previous years (Vela-Navarrete et al, 2005) and frequently have an increase in medical comorbidities (Choi et al, 2012).

An interesting retrospective review of a single Canadian institution further highlighted changes in patients undergoing intervention for LUTS and BPH (Izard and Nickel, 2011). Patients who underwent TURP in the years 1988, 1998, and 2008 were compared with regard to preoperative use of BPH medications, indications for surgery, postoperative complications, and preoperative BPH-related events. Whereas TURP decreased by 60% between 1988 and 1998, an increase was noted in the percentage of total clinic patients undergoing TURP between 1998 and 2008. The indication for surgery of "failure of medical management" increased from essentially zero in 1988 to 36% in 1998 and to 87% in 2008. Troublingly, adverse preoperative BPH-related events such as acute urinary retention (AUR) and hydronephrosis were more common in 2008 than in 1988. In addition, postoperative complications and patients discharged with a catheter were more common in 2008 than 1988. This highlights the change in the type of patient who undergoes surgery and that medical therapy may be leading to a decompensated bladder and urinary tract. This is consistent with the findings of Flanigan and colleagues (1998), who found that patients who underwent immediate TURP had a more significant improvement in peak flow rates and symptom scores than men who underwent an extended period of watchful waiting. It appears that there is a consequence to the delay in effective treatment for many men. However, baseline characteristics of men who have significant deterioration in voiding without treatment have not been defined.

Prostate Size

Despite an overall lack of correlation between prostate size and bladder outlet obstruction (BOO), a correlation does seem to exist between prostate volume and the decision for surgical intervention. Although the data came from a period before medical treatment, Berry and coworkers (1984) did find a correlation between prostate size and the decision for surgical intervention. More contemporary data on the correlation between prostate size and need for surgery are sure to be skewed by multiple factors. The now common use of 5 α -reductase inhibitors (5ARIs) will decrease both prostate size and the risk for surgery (McConnell et al, 1998; Roehrborn et al, 2002), suggesting that smaller glands are less likely to need treatment.

However, any other large conclusion on an increased prostate size leading to surgery may have been contaminated by the use of the other class of BPH treatments. Although not altering prostate gland size, α -blockers allow for the relief of symptoms while

the overall prostate growth continues unchecked. In cases in which these medications later failed, the patients who proceeded to surgery then had larger glands. This fact contaminates the concept that larger glands would lead to more surgical intervention because the common use of these medications induces a selection bias.

KEY POINTS: EPIDEMIOLOGY AND MARKETSHARE

- The incorporation of medical management and new technologies has changed which treatment options are selected for the treatment of LUTS and BPH.
- Laser-based treatments are increasingly used, although multiple factors have affected acceptance.
- Multiple factors in the past decades have changed the type of patient who typically advances to surgical management of BPH. Increasingly these are more challenging clinical scenarios.

WORKUP

The evaluation of LUTS and BPH should always include a detailed medical history with attention paid to assessment of LUTS using a validated questionnaire. A focused physical examination should include a brief neurologic screen, abdominal examination, and genitourinary examination including digital rectal examination (DRE). Urinalysis is another recommended test, and men with a predominant symptom of nocturia should complete a frequency-volume chart (voiding diary). An algorithm for the basic and more detailed workup can be seen in Figures 105-1 and 105-2 (McVary et al, 2011). The specific goals for the patient should be clearly defined from the standpoints of both the patient and the treating physician.

Screening of men for prostate cancer has become a more controversial topic in recent years. The American Urological Association (AUA) BPH guidelines (McVary et al, 2011) recommend the consideration of screening appropriately aged men with LUTS who have a life expectancy of longer than 10 years. The recent guidelines for the detection of prostate cancer recognize that the greatest benefit for prostate-specific antigen (PSA) screening is for men 55 to 69 years of age (Carter et al, 2013). This screening should include DRE and serum PSA if the patient so elects after an informed discussion. Although serum PSA has chiefly been used as a screening tool for prostate cancer, it may also be used as a surrogate for prostate volume, which can be a critical factor in the choice of BPH therapy. For this reason itself, we endorse its use.

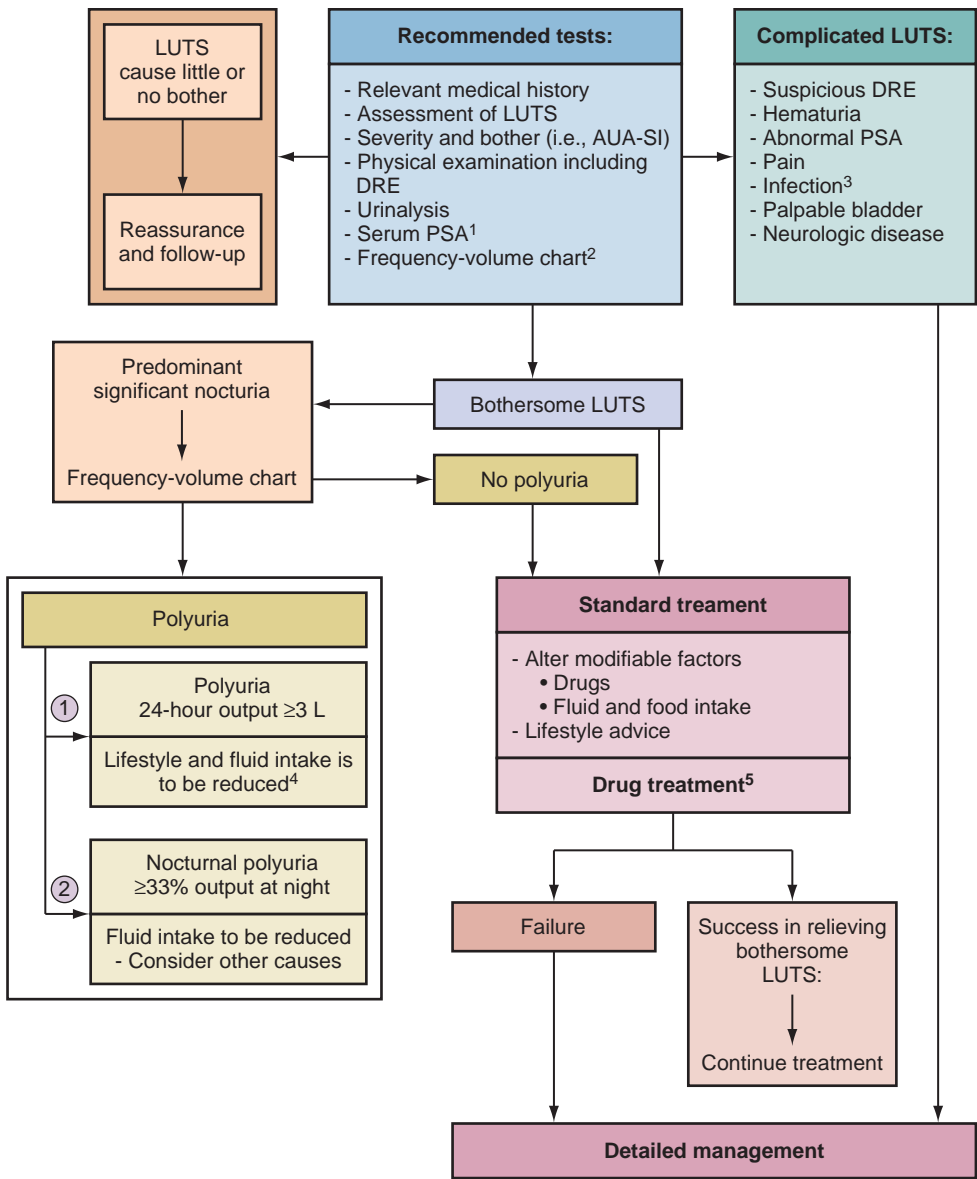
The goals for treatment should be used to guide the clinical evaluation. During the evaluation, the patient's voiding pattern should be assessed along with any general medical problems that may have an effect on the voiding pattern. The role of BPH in the overall voiding pattern should be assessed, particularly with respect to the possible benefits of any treatment. The necessity for treatment along with the probability of success of any treatment should be factored in and weighed against the risk of treatment. Finally, the physician's assessment along with the rationale should be explained to the patient using terms that the patient is able to understand.

DEFINING OUTCOMES

Response Rates

Subjective

Use of validated questionnaire data has become customary in the reporting of symptoms, but other data can be more open to interpretation. How severely a patient defines his dysuria or hematuria after a procedure can affect how they are included in what is often



¹ When life expectancy is >10 years and if the diagnosis of prostate cancer can modify the management. For the *AUA PSA best practice statement: 2009 update*, see: www.auanet.org.
² When significant nocturia is a predominant symptom.
³ Assess and start treatment before referral.
⁴ In practice, advise patients with symptoms to aim for a urine output of about 1 L/24 hr.
⁵ See Figure 105-2.

Figure 105-1. Basic management of lower urinary tract symptoms (LUTS) in men. AUA-SI, American Urological Association Symptom Index score; DRE, digital rectal examination; PSA, prostate-specific antigen. (Modified from McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011;185:1793–803.)

a binary scoring system defining the absolute presence or absence of a symptom.

Objective

Although the most reproducible of results across studies, objective data are also dependent on accurate reporting and thus can be affected by many confounding variables. The most frequent confounders noted are the reporting of changes in patients with long-term follow-up. These data are prone to contamination from multiple sources including patients lost to follow-up and patients who are nonresponders and received additional treatment. Rarely are intent-to-treat analyses reported in series, and in reality the end

points reported typically include those patients who are treatment responders who continued to return for future appointments.

Need for Secondary Procedures

The issues surrounding reporting of secondary procedures have been well delineated in previous versions of the BPH guidelines. In summary, the defined metrics for re-intervention are, in general, rendered by the treating physician. These are difficult to classify because treatment may be triggered by subjective complaints, objective findings, or a combination of the two. **These thresholds can vary by patient or treating physician, and both same-study and cross-study reproducibility and reliability are challenging.** In

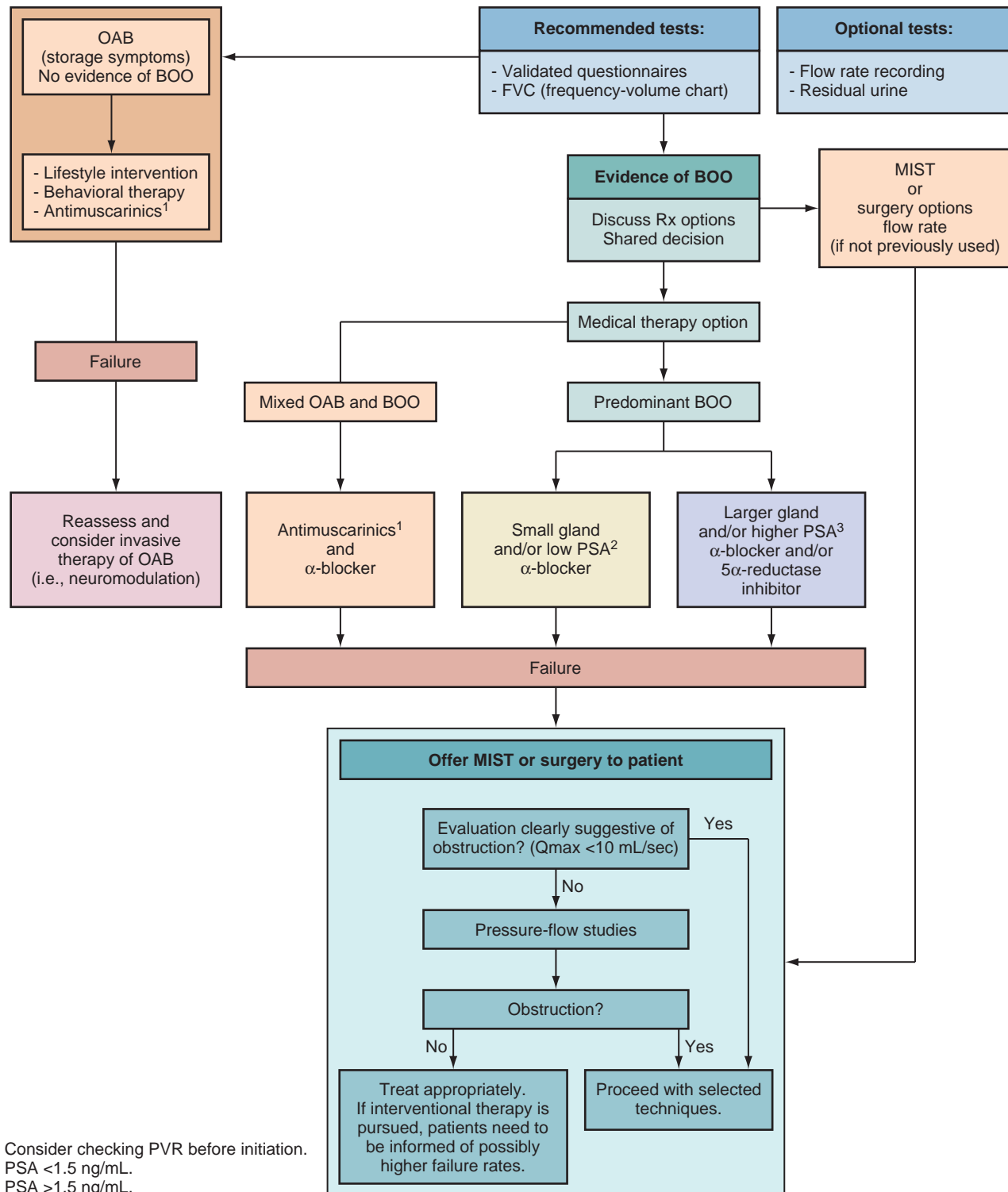


Figure 105-2. Detailed management for persistent, bothersome lower urinary tract symptoms (LUTS) after basic management. BOO, bladder outlet obstruction; MIST, minimally invasive surgical treatment; OAB, overactive bladder; PSA, prostate-specific antigen; PVR, postvoid residual; Rx, treatment. (Modified from McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011;185:1793–803.)

addition, patients involved in trials may be more closely followed and carefully scrutinized, causing both the patient and physician to change the threshold (in either direction) at which they may customarily initiate treatment. **Although treatment failures are clearly an important end point because they can lead to an increased overall cost of health care, the current literature can make these issues difficult to interpret clearly.**

Comparisons to Other Treatments

Comparing surgical procedures with one another and with medical management in an equitable way can be challenging. In particular, when comparing studies involving an intervention (which by the nature of the intervention usually does not include a placebo) with those that use a placebo lead-in (common in medication studies),

the former treatment will take full credit for the placebo effect and the true intervention effect, and the latter for only the true intervention effect. Although for the patient these outcomes may feel the same, the comparisons are inherently flawed.

In general, when any new procedure is being accepted into the armamentarium of the urologist, studies begin with a small number of patients from a narrowly defined cohort. If success is seen there, then larger cohorts with broader inclusion criteria follow. Frequently these findings are compared with historical improvements and morbidities seen in early TURP data. These comparisons are somewhat unfair because they compare a current technology with a historical, and often inferior, data set. Studies making broad conclusions based on comparisons with historical controls should be viewed with skepticism.

If a technology truly appears successful, it moves on to the eventual RCT comparing the new technology with another treatment approach. Although the comparative effectiveness trial is a high bar to pass, caution must still be taken when interpreting these results. For instance, the comparison to TURP assumes that the surgeons performing the comparative technique are sufficiently trained and can produce predictable results.

Table 105-1 outlines expected complication rates based on the differing technologies. **Table 105-2** outlines expected outcomes in voiding parameters and is drawn only from RCTs. In constructing tables comparing outcomes and complications, the inequalities of good data with high levels of evidence come to the forefront. Many technologies have meta-analyses of large RCT trials, whereas other included data were dependent on large case series.

TABLE 105-1 Expected Complication Rates after Endoscopic Benign Prostatic Hyperplasia Procedures

	M-TURP	B-TURP	TUNA	TUMT	HoLEP	PVP	TUVP	TUIP
Transient urinary retention	4.3-6.8 ^a	3.3-3.7 ^b	23 ^c	10-24 ^d	2.7-5.9 ^e	5.2-9.9 ^e	2-9.8 ^f	4.9-11.3 ^g
UTI	4.1-6.2 ^a	2.6-8.4 ^c	4 ^c	15-20 ^h	0.9-2.7 ^e	4.2-12 ^e	0 ^f	IE
Bladder neck contracture	2-3.2 ^a	0.5 ^b	IE	0 ^d	1.2-1.5 ^e	1.1-5 ^e	0.5-1 ^f	IE
Urethral stricture	3.4-4.1 ^a	0.5-4.7 ⁱ	0.5 ^c	0-2 ^h	1.9-4.4 ^e	1-6.3 ^e	1.9-3.3 ^f	2.9-8.8 ^g
Incontinence	0.6-1.5 ^a	0-1 ⁱ	IE	IE	0.9-1.1 ^e	0-0.4 ^e	0-2 ^f	0.3-1.8 ^g
Blood transfusion	2-4.4 ^a	1.5-2.3 ⁱ	Very rare	0 ^d	0-1 ^e	0 ^e	0-0.5 ^f	1.1 ^j
Clot retention	4.9-7.2 ^a	2.7-7.9 ⁱ	IE	1 ^d	0 ^k	0 ^k	0-0.5 ^f	IE
Postoperative hematuria	3.5-15.7 ^a	1 ^b	6-28 ^c	1-26 ^d	0 ^k	0.7 ^k	0 ^f	4.3 ^l
Dysuria	0.8 ^a	0 ^b	8-14 ^c	14 ^d	1.2 ^k	8.5-13.9 ^e	2.9 ^f	IE
Urgency	2.2 ^a	0.2 ^b	10 ^c	IE	5.6 ^k	0 ^k	0 ^f	IE
Storage symptoms	IE	IE	IE	18-31 ^d	IE	IE	21 ^f	IE
Reoperation for non-BPE cause	1.1 ^a	0.2 ^b	0 ^c	IE	1.9-2.8 ^e	IE	5.4 ^f	9.6-18.4 ^g
Reoperation for BPE	0.5 ^a	0.2 ^b	19 ^c	4 ^d	0 ^k	0.7-5.6 ^e	2.4 ^f	IE
Capsular perforation	0.1 ^a	0 ^b	IE	IE	0.2 ^k	0 ^k	0 ^f	IE
Conversion to TURP	n/a	0 ^b	n/a	n/a	0 ^k	3.5 ^k	0 ^f	IE
TUR syndrome	0.8-2.5 ^a	0 ^b	0 ^c	0 ^d	0 ^k	0 ^k	0 ^f	IE
Bladder mucosal injury	0 ^a	0 ^b	0 ^c	IE	3.3 ^k	0 ^k	0 ^f	IE

^aMeta-analysis of RCTs (Ahyai et al, 2010; Mayer et al, 2012; Omar et al, 2014).

^bMeta-analysis of RCTs (Ahyai et al, 2010; Omar et al, 2014).

^cMeta-analysis of systematic review (Bouza et al, 2006).

^dMeta-analysis of RCTs (Hoffman et al, 2012).

^eMeta-analysis of RCTs with data from systematic review (Ahyai et al, 2010; Kuntz, 2006).

^fMeta-analysis of RCTs (Hammadeh and Philp, 2003; Poulakis et al, 2004; Ahyai et al, 2010).

^gMeta-analysis of RCTs with some data supplemented by large case series (Lourenco et al, 2010; Orandi, 1985).

^hReview article (Floratos et al, 2001).

ⁱMeta-analysis of RCTs with some data from systematic review (Ahyai et al, 2010; Omar et al, 2014; Issa, 2008).

^jMeta-analysis of RCTs (Lourenco et al, 2010).

^kMeta-analysis of RCTs (Ahyai et al, 2010).

^lLarge case series (Orandi, 1985).

BPE, benign prostatic enlargement; B-TURP, bipolar transurethral resection of the prostate; HoLEP, holmium laser enucleation of the prostate; IE, insufficient evidence; M-TURP, monopolar transurethral resection of the prostate; n/a: not applicable; PVP, photoselective vaporization of the prostate; RCT, randomized controlled trial; TUIP, transurethral incision of the prostate; TUMT, transurethral microwave therapy; TUNA, transurethral needle ablation of the prostate; TUR, transurethral resection; TUVP, transurethral vaporization of the prostate; UTI, urinary tract infection.

Data courtesy Dr. Jean-Nicholas Cornu.

TABLE 105-2 Expected Change in Objective Measures at 12 Months (Mean Change \pm Standard Deviation)

	M-TURP	B-TURP	HoLEP	PVP (120 W)
Decrease in AUA symptom score	71% \pm 11	71% \pm 10	79% \pm 11	67% \pm 9
Decrease in prostate volume	46% \pm 19	46% \pm 5	59% \pm 14	44% \pm 12
Decrease in PVR	77% \pm 19	83% \pm 14	85% \pm 13	84% \pm 14
Increase in Qmax (mL/sec)	12.1 \pm 6	13.3 \pm 4	17.1 \pm 4	12.5 \pm 2

AUA, American Urological Association; B-TURP, bipolar transurethral resection of the prostate; HoLEP, holmium laser enucleation of the prostate; M-TURP, monopolar transurethral resection of the prostate; PVP, photoselective vaporization of the prostate; PVR, postvoid residual.

Data courtesy Dr. Jean-Nicholas Cornu.

This is merely a sign of the available studies conducted. Although any comparison across technologies and time periods may be considered unequal, we attempted to use data from meta-analyses and RCTs, filling in data from large series only when necessary.

PRESURGICAL FACTORS

Indications for Treatment

The most common indication for TURP has shifted considerably in the last few decades. **Although this previously was the presence of voiding symptoms without formal subjective or objective quantification, we now recognize that the indication is more likely to be moderate-to-severe voiding symptoms attributed to BPH that are refractory to medical therapy.** Almost always, both questionnaires and objective data (e.g., uroflow, urodynamics and pressure-flow studies) augment the history and physical examination findings before the decision for surgical management of this condition is made.

AUR can often be indicative of an end-stage bladder. Although the presence of painful urinary retention at a low volume (<500 mL) may be considered a potentially positive sign for a nonatonic bladder, definitive assessment of bladder function can be made definitively only by pressure-flow studies. In a report from [Taube and Gajraj \(1989\)](#), 15 of the 34 men with less than 900 mL drained when the catheter was placed were able to later void without surgical intervention. This was in contrast to only 2 of 29 men who were able to resume normal voiding when more than 900 mL of urine was drained. In a patient with AUR triggered by ingestion of medication such as α -agonists or anticholinergics, it is reasonable to initially place a catheter and allow for the medication to leave the system with subsequent supervised decatheterization. In patients with other situational incidents leading to AUR (postoperative or acute bacterial prostatitis), a similar plan can be used, allowing the exacerbating incident to be treated or allowed to run its course. In the community-based Olmsted County Study ([Jacobsen et al, 1997](#)), 57 of the 2115 men studied developed AUR. Half of these episodes of AUR were related to surgical procedures, and ultimately only 8 of these 57 patients required TURP within 6 months of the incident. The addition of an α -blocker during a spontaneous episode of AUR leading to catheterization is commonly used and has been shown to increase the percentage of patients subsequently passing a voiding trial from 47.9% to 61.9% ($P = .012$) when compared with placebo ([McNeill et al, 2005](#)).

Recurrent and robust gross hematuria is a legitimate indication for treatment of the prostate once other causes (e.g., infection, carcinoma, trauma) have been excluded. This may be done as either a scheduled procedure in the case of a recurrent condition or in the acute setting in a patient with clot retention or continued hemorrhage despite more conservative management options ([Borth and Nickel, 2006](#)). The use of 5 α -reductase inhibitors may also be of benefit in a patient with repeated episodes that are not serious enough to require surgical intervention ([Foley et al, 2000](#)).

The findings of **bladder calculi, bladder diverticula**, and other signs of end-stage bladder decompensation are additional possible indications for surgical intervention, provided medical management has been previously attempted. **Recurrent urinary tract infections** (UTIs) resulting from an elevated postvoid residual (PVR) urine level are also an indication for considering intervention; however, bacterial prostatitis (both acute and chronic) should be excluded as a possible source of these infections. A bladder diverticulum is not an absolute indication for surgery; however, if the diverticulum is associated with recurrent UTI or progressive bladder deterioration, surgical intervention may be warranted. Although bladder calculi are classically an indication for surgical treatment of BPH, the most recent AUA clinical guidelines state that bladder calculi themselves should be treated when diagnosed, and a trial with medical management may be considered once the calculi have been removed.

Bilateral hydronephrosis with renal functional impairment requires relief of the obstruction with the paramount goal of preserving the upper tracts and renal function. With catheterization and relief of obstruction, postoperative diuresis may ensue. If the level of obstruction is confirmed at the bladder outlet, the treating physician should proceed to definitive care only after the patient's general medical condition has been optimized and any sequelae of the obstruction (e.g., impaired renal function, edema) have been fully evaluated or have returned to a baseline status. In the case of bilateral hydronephrosis (or elevated serum creatinine) unrelieved by catheter placement, additional studies should be considered. In patients with long-standing BOO leading to a hypertonic and thickened bladder, the ureters could be obstructed at the level of the bladder and ureteral stenting may be required. Because routine screening for upper tract dilation is not currently recommended in patients with BPH, the urologist should continue to consider its presence in these settings. [Sarmina and Resnick \(1989\)](#) documented previously unrecognized renal failure in 3.7% of the 909 men treated for BPH between 1980 and 1986. They estimated that more than 5% of men with unrelieved BPH-related BOO would have chronic renal insufficiency and concluded that risk would be higher in those with a history of enuresis, UTI, urinary retention, and a history of symptoms for more than 1 year.

An elevated or increasing PVR has been postulated as a possible indication for surgical intervention. However, the urologist should remember that there can be significant variability in this value when assessed over time ([Bruskewitz et al, 1982](#)). The aforementioned "classic" indications for BPH treatment are still relevant, and under these circumstances it is reasonable to forego a trial of medical or conservative therapy and proceed directly to surgical intervention. However, in general, patients should undergo a trial of medical management before proceeding to surgical intervention. Once medical management has failed, patients should be considered for surgical therapy to relieve obstruction and improve LUTS and overall quality of life. Surgery is considered for patients with moderate-to-severe symptoms (AUA symptom score [AUASS] higher than 8) in whom appropriate medical management has failed ([McVary et al, 2011](#)).

Although the validated AUA symptom score is an important questionnaire for the urologist when evaluating a patient with LUTS, it does not completely replace a careful history because it is not diagnostic of LUTS and BPH. The symptom characteristics that the patient reports should carefully be defined through the use of both the AUASS and an interview, and surgery should be used carefully in patients with predominant storage symptoms unless these symptoms are thought to be a result of problems emptying the bladder.

OP was the mainstay of treatment for LUTS from BPH for decades and is still an excellent treatment option. Covered in detail elsewhere in this text, this treatment is useful in men with very large glands, which still may be a challenge for endoscopic treatment, and in men who need treatment for large or multiple concomitant bladder calculi or diverticuli.

Antibiotic Coverage

Antibiotic coverage for surgery should be carefully considered for each patient with reference to the AUA Best Practice statement ([Wolf et al, 2008](#)). The minimum coverage would include either the use of a fluoroquinolone or trimethoprim-sulfamethoxazole (TMP-SMX). However, if the patient has an indwelling catheter (urethral or suprapubic), then extended coverage should be considered.

Sepsis is still an occasional occurrence after TURP, and antibiotics should be carefully selected. A European series ([Vivien et al, 1998](#)) with 857 patients had a bacteremia or septic shock rate of 2.3%. Risk factors for bacteremia or sepsis included preoperative bacteriuria and surgery longer than 70 minutes. The center where the surgery was performed was noted to also be a risk factor, implying that surgeon factors such as antibiotic choice or technique may be a factor.

The practice of extended antimicrobials is supported by the frequency with which patients with indwelling catheters have a positive (and often polymicrobial) urine culture (Warren et al, 1982). The spectrum of these organisms is variable, with factors such as local patient population, facility specifics, and previous antimicrobial treatment all affecting the latent organisms. In addition, patients with long-term catheters are often exposed to antimicrobials, and they may have an increased risk of resistance (Bjork et al, 1984).

Histologic Specimen

In an era before PSA screening, prostate cancer was frequently diagnosed by the examination of the pathologic specimen obtained during TURP. With the increase in many treatment options that do not procure a specimen, there is some concern that we may be missing clinically significant cancers. The advent of common PSA screening was shown to decrease incidentally found cancer from 12.9% to 8.0% in one series (Mai et al, 2000). A series from Tombal and colleagues (1999) looking at a 13-year period around the time of the incorporation of PSA screening found a decrease in all T1 cancers from 23% to 7% of specimens from BPH treatments with a greater effect on T1b disease (decrease from 15% to 2%). Patients with incidentally found prostate cancer during TURP were more likely to have organ-confined disease and lower Gleason scores than men in whom cancer was detected by prostate biopsy (Helfand et al, 2009). The recently published study from Meeks and coworkers (2013) concluded that in men with a PSA under 4 ng/mL, the finding of a clinically significant cancer would occur in only 1 of 382 TURPs, making a total of 390 such cancers detected nationally in a 3-year period. In a pool of 60,000 laser vaporizations, 163 clinically significant cancers would be missed. Taken in concert, these studies indicate that in men who have undergone adequate PSA screening, relatively few clinically significant prostate cancers would be missed by use of a technology that does not obtain a pathologic specimen.

Matching Treatment with Patient

Multiple patient factors may lead the urologist to recommend a particular treatment option for a patient; each treatment has its own inherent risk, benefit, and safety profile. Some patient factors to consider are prostate size, previous surgical intervention, history of urinary retention, inability to stop ongoing anticoagulation, surgeon experience, and, of course, patient preference. Factors more specific to the surgeon would include surgeon experience with different treatments and their availability at that institution. Historically, the urologist used DRE or cystoscopy to estimate prostate size. DRE has been found to overestimate small glands and underestimate large ones, even when performed by an experienced endoscopic savant. During cystoscopy, each centimeter above the normal 2.5-cm prostate length would roughly equate with an additional 10 g of additional prostate weight. Although these may give the treating physician a general idea of prostate size, these types of assessments have been shown to be inaccurate. **If gland size may lead the urologist to choose between two different treatment techniques, the patient may be well served by undergoing office transrectal ultrasonography (TRUS) to precisely assess prostate size before deciding on the surgical intervention.** Most urologists have an algorithm wherein they use prostate volume to dictate their recommendation for surgical intervention, with a very large gland leading the urologist to bipolar transurethral resection of the prostate (B-TURP) or OP and a smaller gland leading toward laser or photoselective vaporization of the prostate (PVP). However, more and more data are being generated showing efficacy of laser methods in larger glands (discussed in the laser TURP section). We prefer the use of laser TURP for glands with a volume less than 100 mL, with B-TURP for glands 100 to 150 mL and OP for glands larger than 150 mL. Regardless of the specific cutoffs used for each technology, it is a wise urologist who adheres to the AUA guideline suggestion that the choice of approach should be based on the patient's individual

characteristics including anatomy, the surgeon's experience, and discussion of the potential benefit and risks of complications (McVary et al, 2011).

Additional factors that may also lead to the use of conventional loop resection over laser treatment include the presence of a median lobe or a ring of intravesical prostate. The use of a loop in this situation may be preferable because it allows a less than well-versed surgeon an option to reach out and "pull" the protruding prostate away from the bladder wall during resection. With increasing age and comorbidity, patients may now frequently be on anticoagulation when the urologist recommends surgical therapy. The inability of these patients to come off of their anticoagulation may lead the urologist to a difficult decision with regard to treatment options. Patients unable to cease anticoagulation for surgery may frequently be counseled that a treatment such as laser TURP may limit their surgical risk because this technique appears to have improvements over TURP in terms of bleeding risk.

KEY POINTS: PRESURGICAL FACTORS

- In general, patients should undergo a trial of medical management before proceeding to surgical intervention. Patients in whom medical management fails may be considered for surgical therapy.
- Perioperative antibiotic coverage should not be neglected because serious adverse outcomes still occur.
- Both patient and physician factors should be considered when selecting the appropriate surgical treatment for patients.

SPECIFIC TECHNOLOGIES

Nonlaser Options

Monopolar Transurethral Resection of the Prostate

TURP involves an endoscopic approach via the patient's urethra to surgically remove the inner portion (primarily the transition zone) of the prostate that encircles the urethra. An electrified wire loop is used to remove the portion of the prostate between the bladder neck and the verumontanum to a depth of the surgical capsule. The current is carried from the cutting loop through the tissue (and patient) to the return electrode in the grounding pad. Although the procedure is still considered the gold standard for BPH treatment, the morbidity associated with it has led to the development of many endoscopic alternatives to the classic M-TURP.

The original M-TURP requires the use of a nonionic irrigant (water, glycine, sorbitol) to allow electroresection of the prostate. The use of an ionic solution (i.e., normal saline) leads to dissipation of the cutting current and poor cutting efficacy. Troublingly, these nonionic solutions are hypo-osmolar and can be problematic when absorbed through open prostate sinuses into the systemic circulation. To combat this, many of the newer treatment options have adapted to accommodate the use of an iso-osmolar solution such as normal saline.

The first transurethral resection was developed in the United States during the early 20th century. The original optical system was a small series of lenses, which was updated to a solid glass rod lens system with fiberoptic lighting by Hopkins (1976). The addition of a video system that does not require the urologist to apply the eye to the lens is another significant adaptation that has improved both visualization and training.

Technique (from Preoperative Area to Recovery Room)

Preoperative. In general, TURP is performed using general or spinal anesthesia. Traditionally, TURP was accomplished with the patient under spinal anesthesia so the anesthesiologist could monitor for signs of transurethral resection (TUR) syndrome resulting from hyponatremia. However, this practice has become less commonplace for this indication, although the method remains useful.

Restall and Faust (1979) highlight many reasons that regional anesthesia is a desirable choice in patients undergoing transurethral prostatic surgery. Excellent skeletal and smooth-muscle relaxation allows easy filling of the bladder and reduces bladder spasms. However, neurologic deficits, potential bleeding tendencies, chronic low back pain, and osseous metastases are potential problems. In addition, the lack of patient acceptance may also limit the use of regional anesthesia (Brunner and Echenhoff, 1977).

Once adequate anesthesia has been initiated, the patient should be positioned and secured in the dorsal lithotomy position and padded appropriately to prevent positioning injury, with special attention paid to the patient's legs. **The patient's buttocks should be placed near the table edge so that the table does not impede the full course of the scope. If not positioned far enough down the table, the anterior portions of the prostate may be difficult to reach,** particularly in patients with fixed pelvic anatomy from previous pelvic injury, orthopedic history, radiation, or trauma. Adequate antibiotic coverage should be given as detailed previously. A quick abdominal examination will provide a baseline for any subsequent intraoperative examination should a perforation occur during the procedure and lead to prevesical irrigant accumulation. Shaving of the genitals and perineum is not required, and any variety of standard skin preparations may be used on the lower abdomen, genitalia, and perineum. If required, a grounding pad should be placed on the leg outside of the surgically prepared area with the grounding pad placed on the contralateral leg to any previous joint replacement surgeries. Use of the O'Connor type rectal shield provides ready, sterile access to the rectum in case the prostate needs to be lifted anteriorly for resection. Irrigating fluid should be maintained at body temperature and placed at the lowest height relative to the patient to provide adequate visualization. **Fluid level may be raised during the procedure if visualization becomes obscured because of bleeding.**

Intraoperative. Before the resectoscope is inserted, it should be assembled to make certain all elements are appropriately fitted and in working order. The use of a video camera mounted to the lens is largely standard at this point because few urologists prefer to place the eye directly to the lens. Some urologists prefer an instrument that permits a continuous flow of irrigating fluid. This can be accomplished either via a passive mechanism into the cystoscopic drape or with the aid of a machine that allows for an active removal of the fluid from the bladder.

The plan for resection can be varied by any number of patient factors, and in general the best approach is the one best practiced and understood by the urologist. Despite the multiplicity of approaches, some generalizations are proposed here with the consideration that the surgeon should always take an organized and systematic approach.

Before the resection is begun, the bladder should be inspected for any bladder pathology (e.g., tumor, diverticuli). The presence of an unsuspected bladder tumor may necessitate a change in plan, with resection of the bladder tumor performed immediately and TURP scheduled for the future after pathologic staging is complete. The bladder neck, trigone, and position of the ureteral orifices, verumontanum, and external sphincter should be noted, and their relationship to the prostatic adenoma confirmed. If the surgeon has difficulty identifying the ureteral orifices, indigo carmine may be given intravenously by the anesthesiologist, with the efflux seen coming from the orifices a few minutes later. The type of irrigant used is based on the type of resection planned, but in general normal saline is used for bipolar resection and glycine or water is used for monopolar resection. In situations in which the cutting element does not seem to be functioning, there is a general algorithm to check: The connection to the scope and generator should be checked, the irrigating fluid should be inspected to verify that it is commensurate with the generator technology being used, and, if a monopolar technology is being used, one should check that the patient is properly grounded. The opening of the procedure should start with resection of any impediment to movement of the irrigating fluid. The presence of a middle lobe should lead the surgeon to start the resection there. The numerical choice of current is also

dependent on the surgeon's preference, but mixed currents typically provide a great hemostasis with less cutting ability. Once a median lobe has been removed, the lateral lobes of the prostate may then be tackled by the resectionist.

When resecting the lateral lobes, some surgeons prefer to resect the floor of the prostatic urethra initially (between the 5 and 7 o'clock position), whereas others use a modification of the Nesbit (1943) "encirclement" approach (Fig. 105-3 on the Expert Consult website). In the Nesbit approach, resection is initiated at the 11 o'clock to 9 o'clock and the 1 o'clock to 3 o'clock positions. The resection exposes but does not resect the bladder neck fibers and carries the resection proximally to the base of the verumontanum, avoiding any injury to the external sphincter (Thompson, 1975; Greene, 1979).

Surgeons starting with the prostatic floor usually start by resecting a "channel" at either the 5 or 7 o'clock position and resecting down to the surgical capsule of the prostate (Fig. 105-4). By finding the surgical capsule early in the procedure, the depth of the resection is set. The channel is then widened (usually laterally) and then carried up the lateral walls toward the anterior aspect of the prostate, following the surgical capsule as the depth of resection. The resectionist may note that the lateral lobes will begin to "fall" into the fossa as they are resected, making subsequent resection easier. Ultimately, the area between the 5 and 7 o'clock positions is then resected at the final stages of the procedure to smooth out the prostatic floor and finish the procedure without undermining the bladder neck during multiple movement of the scope.

In either resection schema, the initial stages of the resection should involve long, smooth tissue cuts. The produced prostate chips should be long and canoe-like in appearance, with a length equivalent to the extended resection loop. A synchronized, rocking motion with the resectoscope allows the resectionist to follow the prostate shape and achieve the desired chip shape and resection. One should avoid cutting chips of insufficient length or thickness because this is inefficient and may lead to an irregular resection bed that hides bleeding areas. As the resection progresses, the surgeon may need more deliberate pressure on the resectoscope to reach more lateral and anterior aspects of the prostate. For surgeons using the O'Connor shield, digital elevation of the prostate may aid in resection. In general, aggressive resection of the anterior and apex of the prostate is postponed until the end of the procedure. The anterior aspect of the prostate fossa has the least depth of adenoma and is easily perforated. In addition, **the sphincter has a slight tilt, with the anterior portion of the sphincter being the most proximal in the urethra.** Although emptying the bladder may allow this anterior portion to become more visible to the surgeon and aid in resection, adequate fluid should be kept in the bladder to avoid inadvertent bladder perforation with the loop extended.

Over-resection (including capsular perforation) in any area before the major portion of the adenoma has been removed may expose large venous sinuses. Exposing these sinuses will predispose to bleeding and fluid extravasation and absorption and compromise the resection and patient outcome. **The prostate apex is best resected at the end of the procedure in a bloodless field where resection can be done precisely to avoid injury to the external sphincter.** A finger placed in the rectum via the O'Connor shield may also aid in the resection at the apex. A limited amount of residual tissue may be left near the verumontanum, because it is certainly preferable to repeat the procedure than to make the patient incontinent with an overzealous resection near the apex.

Hemostasis should be maintained throughout the procedure. Arterial bleeding is characterized by its bright red color and persistence even with irrigation running over the area of hemorrhage. In addition, this type of bleeding will persist during filling and drainage of the bladder. Arterial bleeding should always be controlled, and precise fulguration is paramount. If vision is obscured, the cutting loop may be advanced to place the loop on an area of bleeding, with the fulguration current then used to control the arterial end. "Ricochet" or "bounce" bleeding from the opposite wall or a cryptic bleeding site that requires further, deeper resection should also be kept in mind (Greene and Holcomb, 1979).

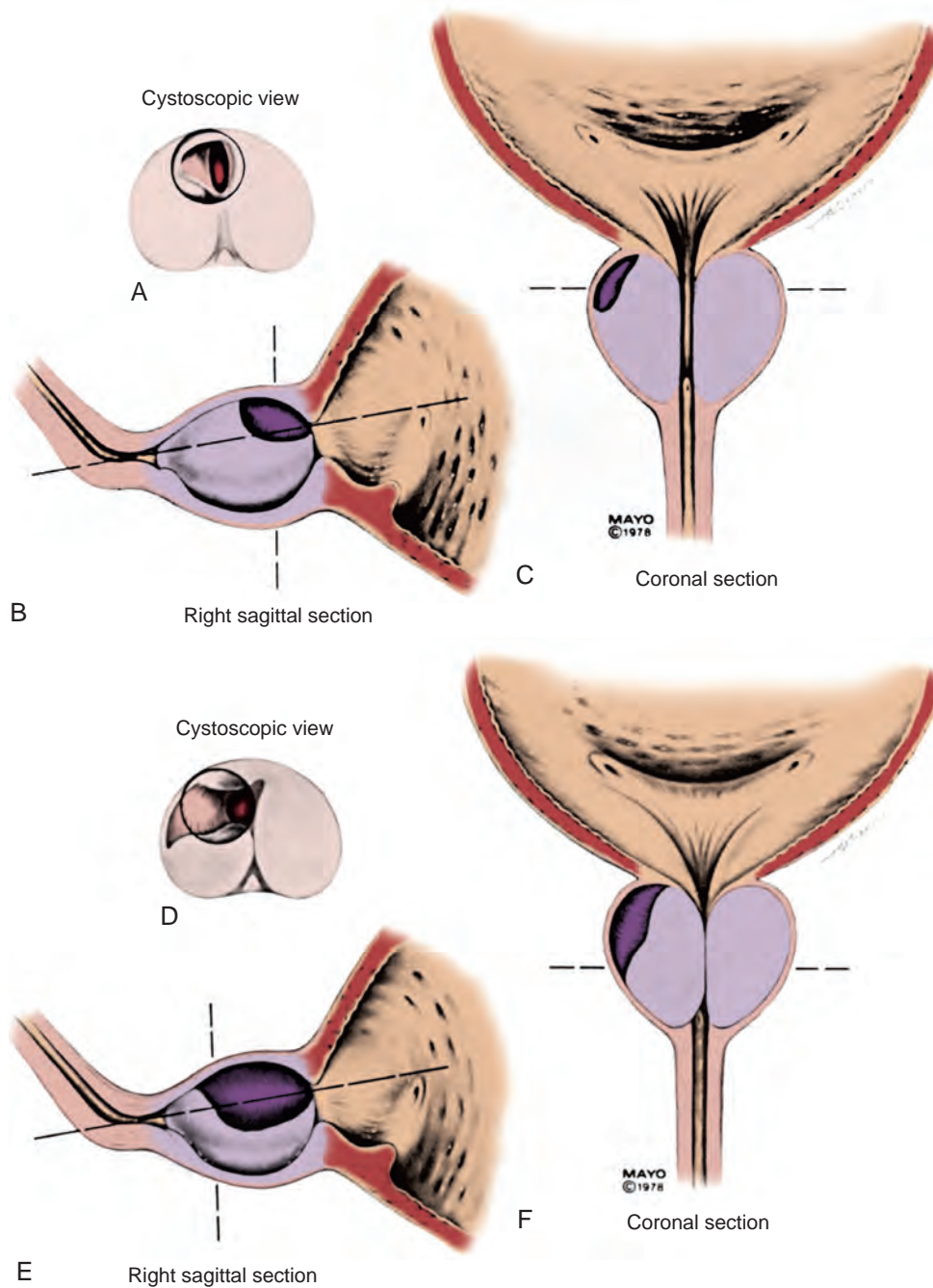


Figure 105-3. Approach to transurethral resection of the prostate by starting the resection anteriorly. A to C, First stage of resection of the prostate. The resection is begun at the 12 o'clock position, and the tissue at the bladder neck and the adjacent adenoma are resected in quadrants. D, The midportion of the gland is resected starting at the 12 o'clock position and carrying it down to the 9 o'clock position. E and F, The sagittal and coronal section views are shown.

Continued

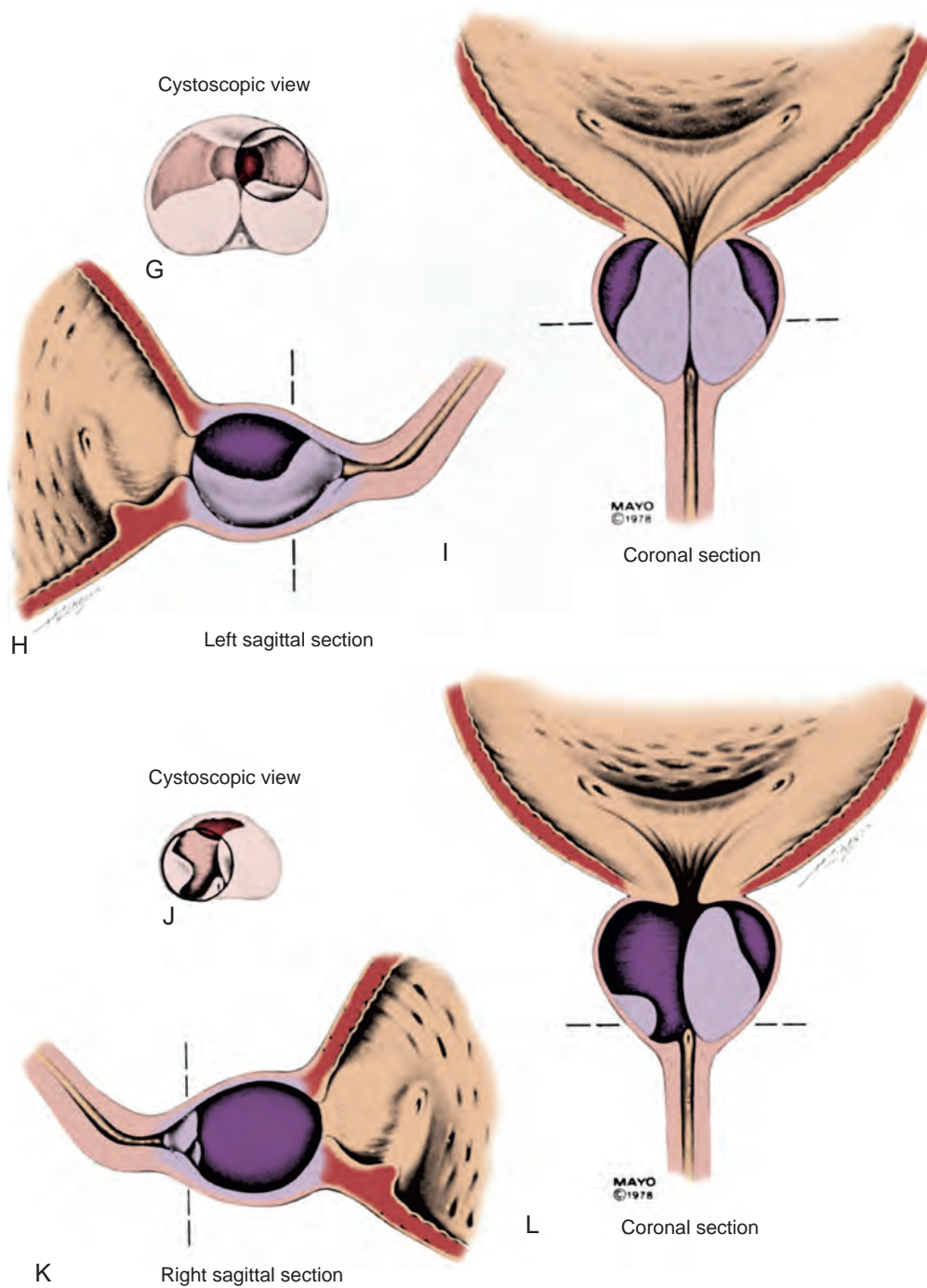


Figure 105-3, cont'd G, The resection is now begun at the 12 o'clock position, and the left side of the patient's gland in the midfossa is resected down to the 3 o'clock position. H and I, Sagittal and coronal sections are shown. J, The midportion of the gland is resected farther down from the 9 o'clock position to the 6 o'clock position. K and L, Sagittal views.

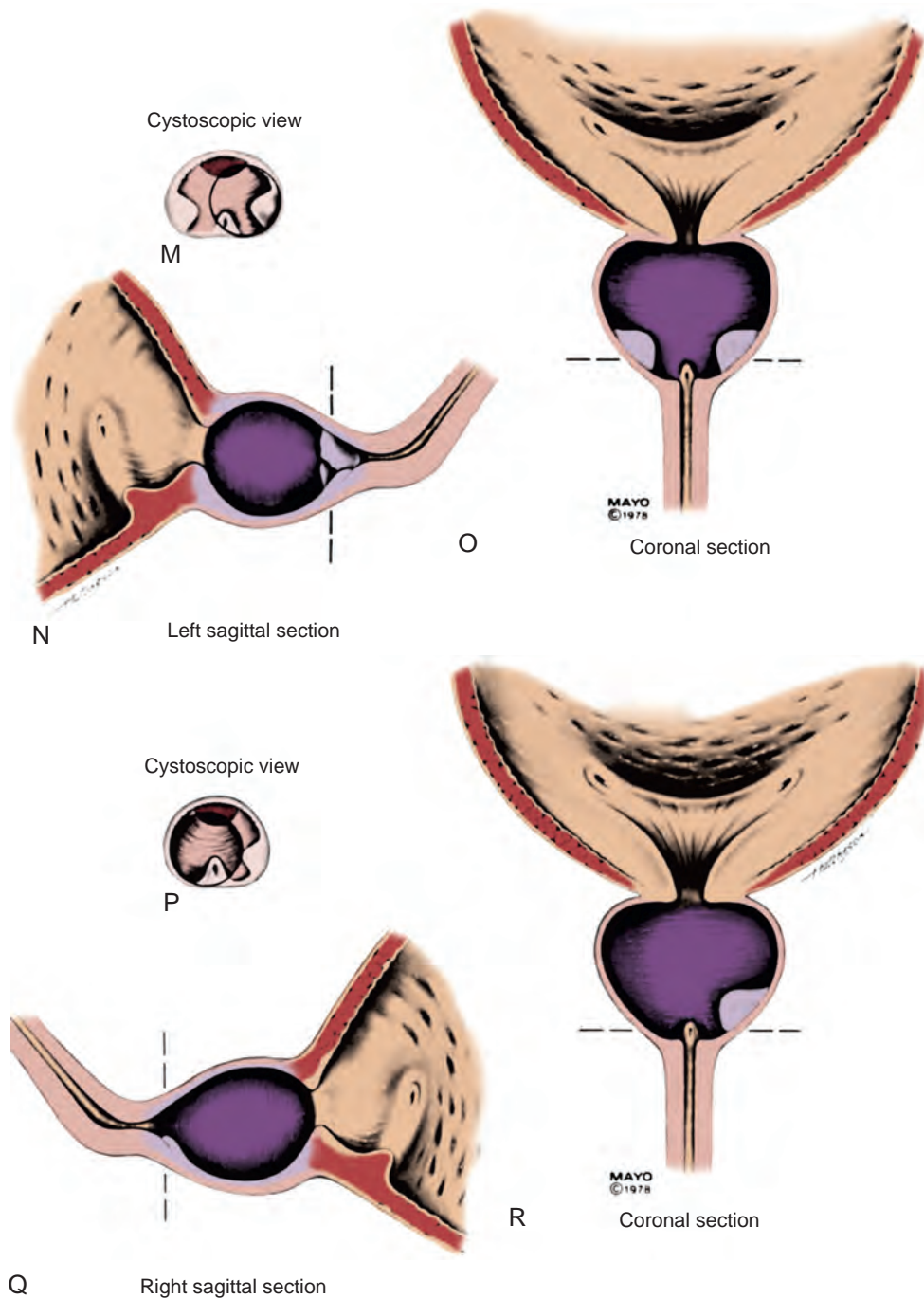


Figure 105-3, cont'd M to O, The tissue remaining at the apex is now resected. Resection is initiated next to the verumontanum and carried toward the 12 o'clock position. P to R, Residual tissue is carefully cleared on the patient's right side.

Continued

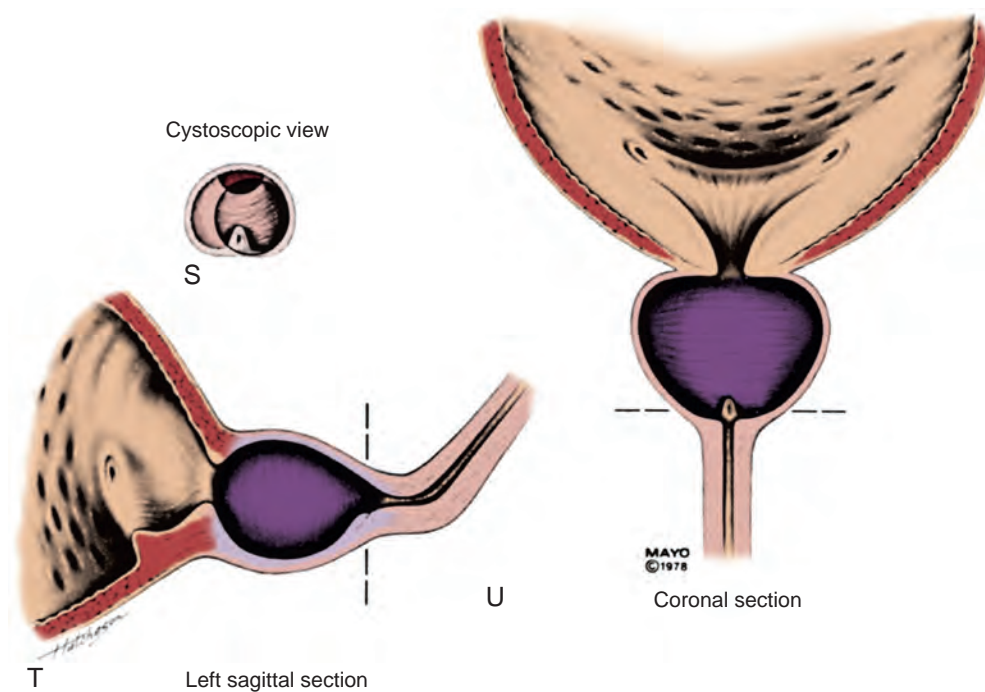


Figure 105-3, cont'd S to U, The remaining residual tissue is cleared from the patient's left side, leaving an unobstructed view from the verumontanum through the bladder neck into the bladder. (©1978, the Mayo Foundation.)

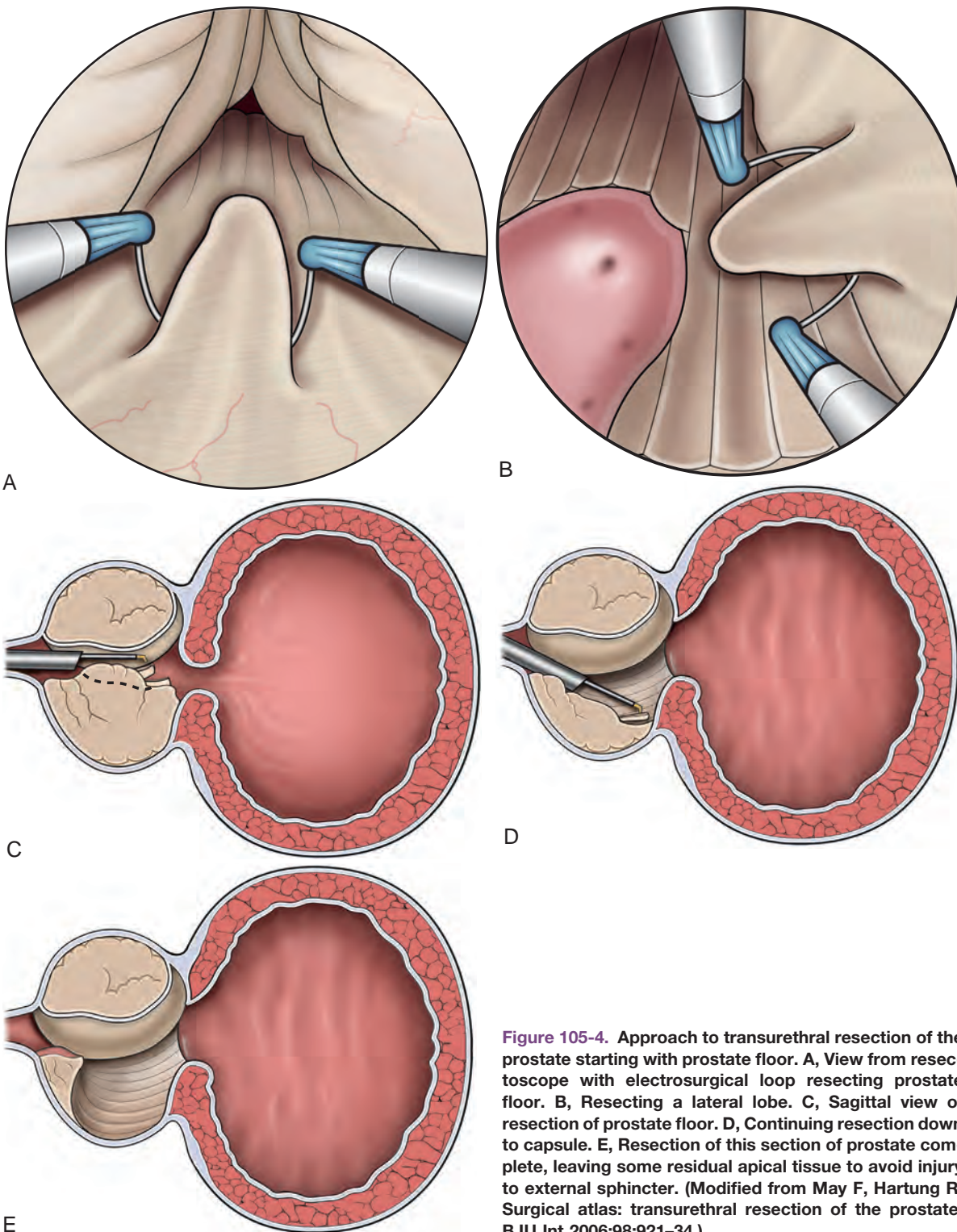


Figure 105-4. Approach to transurethral resection of the prostate starting with prostate floor. A, View from resectoscope with electrocautery loop resecting prostate floor. B, Resecting a lateral lobe. C, Sagittal view of resection of prostate floor. D, Continuing resection down to capsule. E, Resection of this section of prostate complete, leaving some residual apical tissue to avoid injury to external sphincter. (Modified from May F, Hartung R. *Surgical atlas: transurethral resection of the prostate*. BJU Int 2006;98:921–34.)

Identifying bleeding at the bladder neck (particularly anteriorly) can be facilitated by nearly emptying the bladder.

Venous bleeding can be more vexing and typically appears darker in color than arterial bleeding. Venous bleeding will often disappear with a full bladder because it applies pressure to the prostatic fossa. Identifying venous sinuses may be difficult owing to the lack of persistent bleeding with rapid irrigation influx, and controlling of the bleeding with fulguration may be even more challenging. Once again, the cutting loop may be used to temporarily tamponade any bleeding with precise fulguration. If the venous bleeding is unable to be completely controlled (as is frequently the

case), a catheter may be inserted and the balloon inflated and pulled to traction for tamponade of venous bleeding.

Before the operation is terminated, all tissue must be removed from the bladder, with careful attention paid to make sure prostatic chips have not fallen into any bladder diverticuli that may exist. An Ellik or Toomey syringe may help facilitate removal of any tissue. The prostatic fossa should be examined again as one of the final steps, with control of any arterial bleeding. A large-bore catheter should be carefully placed into the bladder with the use of a wire catheter guide if required. The amount of fluid placed in the balloon should be tailored to the volume of resected tissue to avoid the

catheter balloon falling into the excavated prostatic fossa. In our practice, the Foley catheter is usually placed to traction for a short time, with release of traction based on residual hematuria. The use of continuous bladder irrigation (CBI) is not compulsory but can be used if the irrigant is not clear at the end of the procedure.

Placement of a three-way catheter at the end of the procedure does not commit the patient to CBI, because the inflow port can always be obstructed with a catheter plug. If CBI is elected, skilled nursing is preferable; an unrecognized obstruction to the outflow tract can lead to bladder distention and a worsening of bleeding. Intermittent irrigation may also be used but requires extra attention to the inflow and outflow patterns.

Postoperative. Most patients undergoing TURP have an uneventful postoperative course (Mebust, 1993). The diet can quickly be advanced in the postoperative period, and the patient may ambulate on the day of surgery if there is a mild degree of hematuria. When ordering postoperative fluids, one should remember that even an uncomplicated resection involves fluid absorption of 800 to 1000 mL (Oester and Madsen, 1969). Patients with persistent complaints of bladder spasms or rectal discomfort should prompt the clinician to examine the catheter to make sure it is not obstructed.

In the absence of significant capsular perforation or persistent bleeding, the catheter can be removed in 24 to 48 hours. If minor bleeding persists beyond this timeframe, the patient may be discharged to home with the catheter in place with close outpatient follow-up. Whereas a wide variety of practice patterns exist, patients may be discharged to home with or without the catheter; we typically discharge patients on postoperative day 1. The use of narcotics for pain control is almost never necessary, and they should be avoided at discharge.

The use of stool softeners in the postoperative period (extending out a month from surgery) is likely beneficial because passage of hard, impacted stool may precipitate bleeding. Patients should avoid activities that place excessive or uneven pressure on the perineum (i.e., horseback riding, use of a riding lawn mower) for 4 to 6 weeks to not incite any postoperative bleeding while the freshly resected prosthetic bed re-epithelializes. Epithelialization of the prostate bed occurs by migration and proliferation of transitional cells for the resected margins. This usually requires a few weeks, and patients frequently report dysuria during this time. The long-term use of phenazopyridine is discouraged but may help patients overcome this dysuria in the immediate postoperative period. Patients should be warned that this medication may make bodily fluids appear red-orange in color and can stain contact lenses. Patients should be warned that they will frequently pass tissue or eschar with some minor delayed bleeding for 1 to 4 weeks from the time of the procedure, to alleviate any anxiety when this occurs. It is our practice to have the patient refrain from any sexual activity because of concern about precipitous bleeding, even though this is clearly a matter of expert opinion.

Patients with long-standing obstruction (particularly those with urgency and frequency preoperatively) will often experience a continuation or exacerbation of these symptoms in the postoperative period. If proper bladder emptying can be verified, an anticholinergic medication during this time may help the patient feel more comfortable. It is our practice to warn men with preoperatively documented detrusor overactivity that patience will be required in the months after surgery to see if this resolves. Such caution goes a long way in encouraging patients to adopt a strong coping mechanism rather than a polypharmacy approach.

Outcomes. Although morbidity data for men after TURP are commonly cited in a negative fashion, these data should not detract from the large number of men who benefit from the procedure. The number of patients who judge their voiding symptoms to be "better" or "much better" depends partly on the initial severity of symptoms and duration of follow-up but is, in general, above 75% and can be as high as 93% (Bruskewitz et al, 1986; Fowler et al, 1988; Lepor and Rigaudo, 1990). The review for the Agency for Health Care Policy and Research (McConnell et al, 1994) indicated an overall symptomatic improvement of 88% for TURP. This data review indicated that, in general, surgical

procedures (OP, TURP, transurethral incision of the prostate [TUIP]) produced about an 80% improvement in symptom scores compared with 30% to 40% for placebo and nonsurgical therapies. The large, multicenter Veterans Administration study was conducted before the common use of medical treatment for BPH and compared TURP and watchful waiting (Wasson et al, 1995). TURP was considerably more effective than watchful waiting in improving symptoms and avoiding treatment failure. More substantial benefit was noted in men with severe urinary symptoms; men who were substantially bothered had a 91% chance of improvement compared with 62% in those who were bothered less significantly.

Considerable and durable changes in AUASS, quality-of-life (QoL) score, maximum flow (Q_{max}), and many other voiding and lifestyle metrics have been observed with TURP. The procedure's symptomatic durability was recently shown by Masumori and colleagues (2010) in their analysis of patients available 12 years after TURP. Although patients started out with an overall fairly low AUASS (16.7), they improved by 75% at 3 months postprocedure. The difference was less pronounced (40% decrease compared with baseline) but still statistically significant at 12 years. QoL scores followed a similar pattern, with a 67% decrease at 3 months compared with baseline, a decrease that was still significant but less pronounced (52%) at 12 years. The patients with confirmed BOO by pressure-flow study performed better than those without this finding. Patients with urodynamic study (UDS) findings of detrusor overactivity or underactivity did not differentiate themselves with regard to change in AUASS compared with the rest of the cohort. In an analysis 7 years after M-TURP, Nielsen and colleagues (1989) found an improvement in maximum urine flow of 106% at 1 year with a 28% improvement at 7 years. Of the 44 patients still able to be evaluated at 7 years, 16% required repeat resection.

In general, recent data on M-TURP need to be drawn from the procedure as the control group in RCTs. Marked reductions in AUASS and QoL score are typically seen with significant improvements in Q_{max} and UDS parameters. An increase in Q_{max} from 125% to 175% and a reduction in AUASS of 75% are frequently seen. In addition, rarely does a competing technology have a lower risk of BPH-specific re-treatment.

In RCTs comparing TURP with other treatments for LUTS and BPH, TURP is usually at least equivalent if not superior in terms of outcomes focusing on improvements in voiding, with most other treatment options having better safety and adverse events profiles.

Transurethral Resection of the Prostate in the Anticoagulated Patient. A controlled study by Dotan and colleagues (2002) looked at patients undergoing bridging with low-molecular-weight heparin and early resumption of warfarin after stopping warfarin 5 days preoperatively. The average change in hemoglobin was not statistically different, and although the study group did more frequently require transfusion, this difference was also not significant (NS).

Chakravarti and coworkers (1998) used a different strategy; patients underwent only a 2-day cessation of warfarin before surgery, with intravenous heparin substitution during cessation. Only 11 patients were studied, and they had a modest decrease in hemoglobin (1.6 g/dL) with surgery. However, three patients were readmitted within 30 days for bleeding issues. In a multicenter study of 612 patients (Descasez et al, 2011), 33% were on blood thinners before surgery (55 on warfarin, 74 on clopidogrel, and 62 on aspirin). All patients discontinued warfarin and clopidogrel for surgery, with most patients being bridged until surgery with some form of heparin. Only 3 patients continued their aspirin through surgery, with the majority of those stopping aspirin also getting a heparin bridge. Follow-up was taken out to 3 months; patients undergoing any form of anticoagulation had higher rates of transfusion (1.9 vs. 1.0, $P = .026$), bladder clots (13 vs. 4.7, $P < .001$), and thromboembolic events (2.4 vs. 0.7, $P = .02$). Follow-up studies have found differing results (Raj et al, 2011; Taylor et al, 2011).

A dose-escalating, randomized, double-blind, placebo-controlled trial on a heparinoid medication showed a dose-dependent increase in blood loss when given during the time of TURP. Bleeding was so

significant at the highest dose that the study was stopped prematurely (ten Cate et al, 1987). Aspirin has also been studied in the perioperative period. A well-designed prospective, randomized, double-blind, placebo-controlled study looked at patients randomized to 150 mg of aspirin or placebo for 10 days before TURP. With no difference in intraoperative blood loss, the aspirin group had a significantly higher postoperative blood loss. There was no statistical difference in transfusion requirements, but more units of blood were used in the group on aspirin (Nielsen et al, 2000). Two older controlled studies concluded there was no difference in blood loss for patients continuing aspirin through surgery (Thurston and Briant, 1993; Ala-Opas and Gronlund, 1996).

In summary, TURP in the anticoagulated patient carries significant risk, and authors have postulated that laser options may be preferable in patients who are unable to come off of anticoagulation for surgery (Descaseaud et al, 2009).

Complications. Despite decades of use, M-TURP still has a considerable intraoperative complication rate. Although the overall complication rate has improved, there is still at least a 3% chance of intraoperative complications (Ahyai et al, 2010), primarily hemorrhage leading to transfusion. However, with other MISTs requiring more frequent reoperation, the perioperative and late complication rates of M-TURP continue to make it a viable option in the correctly chosen patient. The overall morbidity of TURP continues to approach 20% when studies include blood loss requiring transfusion, infections, strictures, sexual dysfunction, urinary incontinence, urinary retention, and the development of TUR syndrome (Mebust et al, 1989; Borboroglu et al, 1999).

Intraoperative and Perioperative. There is always the possibility of absorption of the irrigating fluid into the patient's systemic circulation during resection of prostatic tissue and TUR syndrome does still occur. Much of our current understanding of the cause of TUR syndrome starts with work from the 1950s (Hagstrom, 1955; Harrison et al, 1956). The prostatic venous system has a pressure of approximately 10 mm Hg, and fluid at a pressure exceeding this will lead to fluid absorption when these vessels are exposed during resection. The absorption of the hypo-osmolar irrigating fluid leads to an acute dilutional hyponatremia with resulting neurologic changes (confusion, nausea, vomiting, visual changes, hypertension, tachypnea, and bradycardia). Now with the use of isotonic, iso-osmolar irrigating solution and the bipolar electroresection system, this risk has theoretically been eliminated. TUR syndrome was seen in 2% of patients in the AUA cooperative study (Mebust et al, 1989). Larger glands (>45 g) and longer resections (>90 minutes) were risk factors. The recent meta-analysis of RCTs found a lower incidence, with only 0.8% of patients developing TUR syndrome (Ahyai et al, 2010). Most authors agree that TUR syndrome is caused by dilutional hyponatremia, but there have been alternate causes proposed. Hoekstra and colleagues (1983) and Ryder and colleagues (1984) noted elevated serum ammonia levels after glycine irrigant resections. Excessive glycine absorption led to liberation of ammonia from metabolic pathways, leading to immediate or delayed encephalopathic symptoms.

Several steps can be taken to prevent this complication. Use of a bipolar resection method should certainly be considered. The height of the irrigating fluid above the patient should be carefully chosen. Madsen and Naber (1973) demonstrated that the ideal height of the fluid was 60 cm above the patient. From their work, this appears to be the minimal height to maintain good vision but also not lead to excessive systemic fluid absorption. Increasing the height 10 cm above this leads to increased pressure in the prostatic fossa and a greater than twofold increase in systemic fluid absorption. Diagnosis of this condition is made by assessment of neurologic status and comparison with laboratory values. Serum sodium should be obtained in long, large resections postoperatively (or intraoperatively if concern exists). A serum sodium level of less than 120 mEq/L indicates a significant dilution and may lead to coma or seizures. Transient visual disturbances or blindness indicate central nervous system toxicity and are obviously very distressing to all the parties involved.

If profound central nervous symptoms are noted, judicious administration of hypertonic saline should be instituted. Formulas exist to help guide this resuscitation; overly rapid correction of hyponatremia may lead to a demyelinating lesion of the brain (central pontine myelinolysis).

In either resection approach, the scope may need to make multiple trips across the prostatovesical junction, leading to trigone undermining. If during initial resection the dorsal aspect of this junction becomes overly resected, these trips may become more challenging as the scope is forced to move "uphill" and increase the detachment of the trigone from the posterior prostate base.

Ureteral injury is an uncommon complication. Identification of the ureteral orifices should be attempted before resecting. The 70-degree lens and intravenous injection of an agent that colors the urine (methylene blue, indigo carmine) may be of aid to identifying the ureteral orifices. If the resectionist is still unable to identify them because of a high bladder neck or large median lobe, resection should begin in the midline, taking down the median lobe as described earlier. After this is accomplished, the ureteral orifices may become more apparent to the resectionist without the mass effect of the median lobe obscuring the view.

Hemorrhage in the resected area is a common complication both during and after TURP. Every effort should be made to achieve hemostasis during the operation to prevent the need for a return to the operating room. The risk of transfusion in patients undergoing TURP is low, but transfusion still occurs and patients should be counseled appropriately. Ideally, hemorrhaging areas are controlled as the procedure is ongoing. In general, arterial bleeding should be fulgurated during the procedure, although the resectionist may continue to resect arterial bleeding until the capsule is exposed and fulgurate a bleeding vessel at this level. This practice should be engaged in carefully, but is reasonable. Venous bleeding is classically more difficult to control. Fulguration of open venous sinuses should be attempted, but this may be ineffective even in the most trained hands. In these cases, balloon tamponade may be most effective. Once arterial bleeding has been controlled, a large balloon (30 mL) Foley may be placed with 50 to 60 mL of water in the balloon. The catheter may then be put to traction for a short time to see if this relieves bleeding. In certain cases, it may be prudent to continue traction overnight. The Veterans Administration cooperative study of 3885 patients found a transfusion rate of 2.5% (Mebust et al, 1989). Other early data reported high transfusion rates, with over 20% of patients receiving transfusion (Doll et al, 1992). More recent data from an analysis of RCTs found that 4.4% of patients would require transfusion (Mayer et al, 2012).

Perforation may occur at many places during the resection—the prostatovesical junction, the prostatic capsule, and the bladder itself are all possibilities. The electroresection itself or overdistention of a thinned area of the prostatic capsule may lead to frank perforation, with visual evidence often being subtle. The glistening fat of the periprostatic or perivesical spaces is usually a telltale sign of perforation. In unclear cases, cystography (with drainage films) may be used to assess the degree of perforation and the drainage pattern. **Extravasation related to prostatic resection is almost always extraperitoneal.** If bladder perforation occurs near the dome, then cystography should be considered to rule out an intraperitoneal rupture, which would require open closure. Extraperitoneal rupture caused by resection with limited extravasation can almost always be managed with extended catheter drainage and careful observation. In cases of extraperitoneal rupture occurring with extensive extravasation, percutaneous or open drainage may be required.

Persistent penile erection may develop at any point during the procedure and may drastically limit endoscopic movement. Detumescence may occur spontaneously without active management. When this does not occur, detumescence may be encouraged with pharmacologic agents such as phenylephrine (Lue et al, 1986). The anesthesiologist should be alerted to injection of this vasoactive substance because overly judicious use may lead to systemic cardiovascular changes. Considerable attempts should be made with

vasoactive substances, but if these all fail, perineal urethrostomy can be used to gain access in a dire situation.

Postoperative. Original estimates of the incidence of **bladder neck contracture** were 2% (Greene and Holcomb, 1979). Subsequent data have shown this to be a fairly consistent 2%, although a large range (2% to 21%) was found by Ahyai and colleagues (2010). This complication is thought to result from over-resection of the tissue at the bladder neck paired with injudicious fulguration of this area. Undermining of the trigone may create a flap that then heals as a membrane. Patients with this complication customarily report excellent flow rates in the immediate postoperative period, which slowly decrease in the coming weeks, months, or years. This course will be well exaggerated over the usual progression of BPH-type symptoms of a weakening stream. The average interval of development is approximately 6 months from the time of the surgery, but has ranged from 3 weeks to 10 years (Greene and Holcomb, 1979). If serial flow rates are available during this time, the results will predictably get worse as the contracture develops. **Prompt office cystoscopy should be performed to verify the diagnosis.** Gentle dilation in the office with sounds or a dilating balloon may be attempted. If dilation does not prevail, then evaluation in the operating room may be required with endoscopic incision. If the bladder opening appears completely obliterated, intravenous administration of methylene blue and use of suprapubic pressure may help to identify a jet of blue urine to lead the urologist toward the opening (usually located anteriorly). An open-ended ureteral catheter may be placed into the narrowed opening and guide incision of the constricted ring. Incision may be made with a Collins knife or optical urethrotome until the ring springs open. In general, incisions are made aggressively in the patient with a bladder neck contracture after TURP because the sphincter is still anatomically far away; this is in contrast to anastomotic contractures after radical prostatectomy, which sit very close to the sphincter. Once the band has been opened wide enough to accept the cystoscope, additional resection should be avoided because it may exacerbate the healing reaction and cause restenosis. Intractable bladder neck contractures may require an open VY-plasty to solve the problem.

The incidence of **urethral stricture** after TURP has a large variation in reported incidence. The weighted mean in Mayer and colleagues (2012) revealed that this occurs in 4.1% of cases in the 34 analyzed RCTs, although the severity and necessary treatments were not outlined. The cause of urethral stricture is thought to be resectoscope trauma, catheter use, or bacterial infection in the postoperative period. The surgeon should be careful to select an appropriately sized resectoscope sheath to prevent any unneeded trauma. Interesting data from Emmett and colleagues (1957) showed that only 62% of men who underwent urethral calibration had a urethral meatus and fossa navicularis of 28 Fr or greater. **Calibration and gentle dilation of the meatus along with careful visual inspection of the urethra on insertion of the cystoscope may help in preventing trauma that may lead to stricture.** The resectoscope should always be well lubricated. The role of a urethral catheter leading to stricture formation is supported by a comparison of patients with suprapubic versus urethral catheters, wherein the former had a lower incidence of stricture formation (Hammarsten and Lindqvist, 1992).

The internal sphincter predominates as a continence mechanism in men. During the course of a normal resection, this sphincteric mechanism is resected or rendered incompetent (Rolnick and Arnhem, 1949). Without exception, the surgeon must **preserve the external sphincter mechanism** or the patient will have total or stress urinary incontinence. This injury may be caused by errant resection or excessive fulguration around the striated muscle fibers. The verumontanum is an invaluable landmark and should be preserved not only as a landmark during the ongoing resection, but also for any future identification during cystourethroscopy. Resections that are terminated proximal or adjacent to the verumontanum are unlikely to result in significant injury to the external sphincter. However, the extent of the complex smooth and striated muscle fibers making up the external sphincter is not always clearly demarcated. The anterior portion of these muscular fibers is the least substantial, and the sphincter lies on a tilt with the dorsal

portion being the most proximal and therefore most likely to extend into the resection. The poor understanding of the complexities of the external sphincter is most evident when one considers the extent of incision during an external sphincterotomy. This purposeful act often requires considerable depth and length and highlights our poor understanding of post-TURP incontinence. Nonetheless, caution in over-resection of the distal portions of the prostate should be exercised. Even in contemporary studies this is a continued problem. The study by Ahyai and colleagues (2010) found a 0.6% incidence of stress urinary incontinence, and some studies have reported up to 5%. However, this is often a transient issue and rarely requires additional intervention.

Significant hemorrhage in the immediate postoperative period is most often the result of incompletely controlled hemostasis during surgery. Minor hemorrhage requiring minimal irrigation is fairly common, with a wide variability in occurrence among practitioners (Mayer et al, 2012). **Some delayed postoperative bleeding is frequently noted around 1 to 4 weeks postoperatively and is frequently accompanied by some sloughed tissue or eschar.** Outside of this period, the likelihood of bleeding decreases as the time after surgery lengthens. Limited bleeding may occur for many weeks after the initial resection, but it is usually limited and transient in nature. This customarily responds to curtailing physical activity and increasing fluid intake.

Postoperative urinary retention after any BOO procedure is a common finding. Variability is different based on surgical technique and procedure type. In general, prolonged catheterization is used due to persistent bleeding or surgeon preference. In major case series, the incidence ranges from 6.5% to 7.1% of cases and does not appear to have changed over time (Mayer et al, 2012).

The need for re-treatment may arise for many reasons. **Incomplete resection (likely at the apex or anteriorly), poor patient selection, diagnostic error, and intraoperative technical errors are all possible causes.** The need for re-treatment may be related to urethral stricture, bladder neck contracture, regrowth of BPH, or residual BPH left at the previous surgery. In the meta-analysis of RCTs, Ahyai and colleagues (2010) found a rate of 0.5% re-intervention for BPH-type symptoms, with another 0.1% requiring secondary treatment for other causes (e.g., bladder neck contracture, urethral stricture). The need for surgical revision does appear to increase with increasing gland size, with preoperative retention also being a risk factor (Reich et al, 2008).

Urinary storage symptoms are a common finding after any BOO procedure wherein the urethral epithelium is disrupted. The raw prostatic fossa takes time to re-epithelialize, and the patient will likely frequently experience symptoms of **urgency or dysuria** during this time. Although wide ranges have been reported for both urgency (0% to 38%) and dysuria (0% to 22%), the physician can expect an average of 2.2% and 0.8%, respectively (Ahyai et al, 2010).

Ejaculatory problems are a significant concern because the bladder neck is resected as part of the procedure. In the TURP arm of randomized series compared with holmium enucleation, the TURP groups had new incidences of retrograde ejaculation of 62% and 78% (Briganti et al, 2006; Wilson et al, 2006). Multiple large series have reported on the effects of TURP with regard to a **change in erection quality**. In a trial of 644 men, 30% noted an improvement in erections after procedure, whereas only 20% noted worsening function. The percentage of men engaging in sexual activity before and after surgery was essentially identical (Muntener et al, 2007). Another series showed that a capsular perforation during surgery had a relative risk (RR) of 1.12 in postoperative erectile dysfunction (ED) (Poulakis et al, 2006), whereas other studies have not found an increase in risk (Jaidane et al, 2010). **In a comparative study of patients undergoing either TURP or transurethral resection of bladder tumor (TURBT), the baseline voiding and erectile function in the TURBT group was statistically far superior.** However, after prostate resection, the TURP group displayed significant improvements in almost all International Index of Erectile Function (IIEF-15) subdomains, with an impressive improvement in erectile function (improving from 7.18 to 20.74).

After TURP, the groups were no longer statistically different with regard to voiding and sexual function (Jaidane et al, 2010).

Conclusion. Although most men improved in overall quality of life and the important symptom and urodynamic outcomes with M-TURP, the morbidity and adverse events are such that multiple different and, in general, less invasive treatment options have been developed. Many of these technologies do not achieve the same efficacy as TURP, but they are associated with less risk or fulfill a particular treatment niche.

Bipolar Transurethral Resection of the Prostate

Concept. Bipolar resection uses a specialized resecting loop that incorporates both the active and the return portions of the circuit on the same electrode. Consequently, the current does not need to run through the patient to a return electrode (in the form of a grounding pad), and current is kept at the site of the resection. This innovation in design has also allowed for the resection to take place in ionic irrigating solution and has eliminated most of the risk of TUR syndrome.

True bipolar systems meet the criteria set by the International Electrosurgical Commission, which requires both active and return poles to be attached in a single system. Frequently a dual loop design is used wherein both loops are in close proximity to each other at the end of the cutting electrode. In this design, the electrical energy is able to connect between the loops and supply the resecting energy there. Another form of bipolar technology is the Gyrus PlasmaKinetic (PK) Tissue Management System (Olympus Surgical Technologies America, Maple Grove, MN), wherein energy is initially transmitted from the loop into the surrounding saline. This is a commonly used B-TURP technology in the United States, and the mechanism is described in detail here. The saline is vaporized into gas around the loop, with additional energy from the loop then converting the gas to plasma. The excited sodium ions of the plasma give this technology the characteristic orange glow. Once created, the plasma molecules are able to be excited for use in resection. This seems like a dynamic and explosive process, but it actually allows tissue resection at lower temperatures with a lower voltage. In practice, this allows for a more simultaneous cutting of tissue with sealing of vessels, leading to the overall improved hemostasis recognized in studies.

Although the PK loop and scope look almost identical to the conventional monopolar systems, the loop is made of platinum-iridium instead of the standard tungsten. This specialized loop is able to withstand the electrical and thermal stresses that come with the plasma use (Issa, 2008). When the coagulation setting in this system is used, a different process takes place. Plasma is not created, and the input energy from the generator is used to increase the tissue temperature and seals the vessels in the prostate. The depth of energy transmission is not as important as previously seen with the monopolar system. In addition, the lower voltage and temperature used in a plasma system minimize tissue charring and may lead to a decrease in unnecessary tissue coagulation and a subsequent decrease in storage symptoms.

Technique. B-TURP and M-TURP have an almost identical technique with regard to approach to the resection. However, the resectionist may note that the bipolar technology allows for quicker resections; bleeding vessels are less likely to be encountered because the simultaneous cutting and sealing of vessels decrease time spent controlling hemorrhagic areas. The previous generator with the PK system would often have trouble overcoming the additional energy needed to ignite the plasma. The newer SuperPulse generator has increased capacity and has made this less of an issue. However, the resectionist may still note a drag on the loop as it first comes in contact with the tissue.

Outcomes

Single-Cohort Studies. With the B-TURP similarity to its monopolar predecessor, comparative trials quickly arose. Compared with other treatment systems, relatively few single-cohort studies of B-TURP are available in the literature. One of the large early studies reported excellent results with the PK system (Falsaperla et al,

2007). With a relatively short mean catheterization time of 1.3 days, the authors found a mean increase in Qmax of 190% at 12 months after the procedure. AUASS decreased by an average of 79%. Complications were relatively infrequent, with AUR, urethral strictures, bladder neck contracture, and urinary incontinence recorded in only 1.57%, 2.57%, 1.28%, and 0.77% of patients, respectively. A smaller study published around the same time had equally impressive results and included a high percentage (49%) of patients with urinary retention (Ho et al, 2006). Patients had improvements in mean Qmax (6.5 to 18.3 mL/sec) and AUASS (22.6 to 6.5) at 1 year. Plateaus in these improvements were noted at around 3 months.

Comparative Studies. In the excellent review of the bipolar technology by Issa (2008), a 10-year Medline review of outcomes of both M- and B-TURP was conducted for the years 1997 to 2007. He found a similar efficacy with regard to AUASS, QoL score, peak urinary flow rate, and residual urine. Multiple comparisons of the bipolar and monopolar technology have been published by a European consortium (Mamoulakis et al, 2012). Using the Autocon II 400 ESU system (Karl Storz, Tuttlingen, Germany) (Fig. 105-5 on the Expert Consult website), they were able to conduct an RCT comparing monopolar versus bipolar techniques. This generator has a touchscreen system that allows for selection of either a monopolar or bipolar current. Although the study states it is double-blind, the researchers reported that surgeons could not be blinded at procedure and only the assessors were blinded to treatment selected. In addition, resection technique, power settings, irrigant, and anesthesia type were not standardized across treatment centers. Improvements were pronounced in both groups with no difference in voiding outcomes at 6 weeks. The only significant difference over the short follow-up in this study was the decrease in serum sodium, although there was no statistical difference in occurrence of TUR syndrome, mostly because of the low incidence of the event overall. Widespread application of these findings may be difficult because this is a rarely used platform and this is the only RCT using this technology.

Regarding the more commonly studied PK technology, Patankar and colleagues (2006) reported on a 3-week follow-up. Robust changes in AUASS and Qmax were noted in both groups with no statistical difference. Differences in blood loss and time with catheter favored the bipolar group, with postoperative complications such as hematuria, clot retention, and blood transfusion appearing to be more common in M-TURP patients.

A meta-analysis of RCTs found similar results with no difference in AUASS, QoL score, Qmax, or change in PVR (Ahyai et al, 2010), whereas another meta-analysis of RCTs looking at flow rates at 12 months found a slight (0.72 mL/sec) weighted mean increase in the flow rates for B-TURP (Mamoulakis et al, 2009). This finding is not clinically significant and was mostly bolstered by the large difference in a highly weighted study.

A recent large meta-analysis and systematic review was published by Omar and colleagues (2014). They examined 949 abstracts and found 24 trials acceptable for inclusion in the review. No statistically significant differences were found in terms of AUASS or QoL score between groups. The analysis of Qmax revealed improvements that were more significant in the bipolar group at 3, 6, and 12 months but were once again skewed by a few largely weighted studies. The meta-analysis could not show homogeneity between studies and the result was not clinically significant. A second meta-analysis evaluating outcomes only at 12 months found that bipolar devices demonstrated no significant difference in AUASS or prostate volume reductions compared with M-TURP. However, B-TURP seemed associated with a better maximum flow and a lower PVR (Cornu et al, 2014).

Complications. Issa (2008) also reviewed complications from the years 1997 to 2007. The overall rate of adverse events was lower with B-TURP (15.5% vs. 28.6%, $P < .001$) compared with M-TURP. This was mostly fueled by lower rates of bleeding, transfusion, time with catheter, CBI need, hyponatremia, and TUR syndrome differences. Although the overall rate of complications was statistically significant, these individual subgroups consistently favored B-TURP, with only occasional statistical significance.



Figure 105-5. Bipolar loop. (© 2014 Courtesy Karl Storz Endoscopy-America.)

Intraoperative and Perioperative. Although the most exciting innovation with the bipolar technology is the **ability to perform the resection in an ionic iso-osmolar solution**, other possible improvements in outcomes may be related to this advancement in technology. A well-recognized complication of M-TURP is the bleeding risk, which may lead to repeat irrigations and prolonged catheterization. The energy profile of the bipolar system has a cut-and-seal effect on vessels that should improve hemostasis and lead to decreased bleeding complications and transfusion rates (Issa, 2008).

In the meta-analysis of patients undergoing B-TURP, no patient developed TUR syndrome. Mamoulakis and colleagues (2009) concluded that by treating 50 patients with B-TURP, one case of TUR syndrome could be prevented. The hemostasis achieved during bipolar resection has allowed for reductions in many bleeding measures. An RR of 0.53 for blood transfusion and 0.48 for clot retention were found with bipolar resection when compared to monopolar resection, with 2.3% and 2.7% of patients having these complications, respectively, in the bipolar group (Omar et al, 2014). The improved hemostasis and absent risk of TUR syndrome allows the urologist a longer resection time and the ability to treat larger glands. Improved visualization may also lead to a decrease in capsular perforations and operating time (Erturhan et al, 2007). A decrease in overall immediate reoperation rate (odds ratio [OR], 0.43) was also found in another meta-analysis. (Cornu et al, 2014).

Postoperative. There are many different types of bipolar systems, all using different mechanisms. The TURis systems (Olympus) were originally mistakenly labeled as bipolar systems (Issa, 2008). In reality, the return electrode in these systems was the outer resectoscope sheath. This could potentially expose the patient's entire urethra and penis to the return energy. Ho and colleagues (2006) reported a 6.3% **urethral stricture** rate during procedures in which the TURis system was used. The review of Issa (2008) found an overall risk of urethral stricture of 4.7%, which was higher than in the TURP group (2.7%, $P = \text{NS}$). However, other authors have not found this difference. (Michielsen and Coomans, 2010). The meta-analysis from Cornu and coworkers (2014) found that there was no difference between M-TURP and B-TURP for the incidence of urethral stricture or stress urinary incontinence.

Other late complications such as **bladder neck contracture** and need for **re-treatment of BPH** do not appear to be much different from those found with conventional M-TURP (Ahyai et al, 2010). Overall reoperation rates at 1 year were low in both M-TURP and B-TURP groups and were not statistically different (Cornu et al, 2014). Once again, the improved hemostatic properties of the bipolar technology were evident in the postoperative care; patients are more likely to have reduced **catheter and hospital times** (Singh et al, 2005; de Sio et al, 2006).

Conclusion. Results for the bipolar resection system are encouraging, and this technology will likely replace M-TURP as the gold standard for treatment of BPH in the coming years. Although clinical outcomes are roughly equivalent, the improved hemostasis of the procedure and use of isotonic irrigating solution allow for longer and safer resections. Different systems use different approaches to meet the bipolar standards, but finding differences among systems with regard to outcomes is challenging at this point.

Transurethral Vaporization of the Prostate



See the Expert Consult website for details.

Transurethral Microwave Therapy

Overview and Concept. The objective of transurethral microwave therapy (TUMT) is to locally thermoablate prostate tissue while maintaining normal temperatures in the surrounding nontargeted tissue. This concept uses a specialized urethral catheter with an antenna that generates radially emitted electromagnetic (EM) waves. These EM waves are in the frequency of 915 to 1296 MHz and penetrate tissue to induce changes that produce localized heat. Treatments that achieve temperatures below 44°C

are designated "hyperthermia," those achieving temperatures above 44.5°C as "thermotherapy," and those achieving temperatures above 65°C as "thermoablative" (Perlmutter et al, 1993).

Prostate parenchyma destruction occurs once a crucial **thermal dose** has been reached. This occurs as part of the multiplicative product of the temperature and exposure duration. Therefore, the critical values are the temperature achieved in the gland (not necessarily the same as the temperature generated by the machine) and the period over which that temperature is able to be maintained. **Optimally, the thermal dose should be confined to the prostate gland with minimal to no heating of the nontargeted surrounding tissues such as the external urethral sphincter, bladder neck, and rectum.** Collateral damage to these tissues will induce complications and may limit the treatment effect by inducing automatic shutdowns in the machine. In addition, this misplaced heat may cause significant patient discomfort and inability to tolerate the procedure in the office setting.

The potential advantages of the microwave technology include the convenience of an in-office procedure with rapid patient convalescence and minimal anesthesia requirements. It is the least operator dependent of the treatments for BPH and has an easy learning curve. Patient selection is crucial to achieving results; there are particular factors that need to be examined when considering TUMT. Patient factors such as prostate volume, gland configuration, and the patient's ability to undergo a transurethral treatment under local anesthesia must all be carefully considered. Prostates with marked middle lobe configurations may distort catheter positioning because the middle lobe will go largely untreated and project the microwave in unintended and unsafe locations. Prostate volumes at the extremes (<25 or >100 g) may impede uniform heating and lead to suboptimal results. Those smaller prostates may lead to unsafe heating of extraprostatic locations, inducing complications such as sphincter injury. It is important that patients with pacemakers, defibrillators, and pelvic or penile prosthesis be excluded from treatment because these devices may undergo significant electrical or mechanical damage from TUMT systems. Patients who have undergone previous invasive BPH treatments may have unexpected transmission of the microwaves with dire results.

Significant differences exist among microwave treatment system designs. These include differences affecting antenna design, the heating pattern generated, and the treatment protocol; such differences should be carefully considered when choosing microwave treatment for patients. The original design was considerably investigated but later advanced to a high energy (HE-TUMT) platform that inventors hoped would enhance treatment effect. It appears that the antenna design dictates the heating pattern more than the frequency of wave energy used (Bolmsjö et al, 1996). Currently, the primarily used systems available are the CoreTherm (ProstaLund, Lund, Sweden), Prolieve (Boston Scientific, Boston, MA), Prostatron (Urologix, Minneapolis, MN), TherMatrx (American Medical Systems, Minnetonka, MN), and Cooled ThermoTherapy (Urologix, Minneapolis, MN) (Fig. 105-10).

The various TUMT platforms generate intraprostatic temperatures of 45° to 70°C. The early systems supplied heat ranges from 42° to 44°C and had rather disappointing results. As devices became more advanced, the intraprostatic treatment temperatures increased. The HE-TUMT nomenclature is applied to the more advanced devices at the higher end of this thermal range. Much of the advancement to using higher temperatures was precipitated by the ability of catheter cooling to reduce urethral temperatures during use and reduce intraprocedural patient discomfort.

In these protocols, the energy was slowly increased to allow the patient to gradually adjust to the rising temperature. When heat is applied to the prostatic parenchyma, there is a natural response with vasodilation of local vessels to physiologically dissipate the heat. While making the procedure more tolerable, this slow increase of energy increased procedure times and decreased efficacy. Heat-shock or high-intensity TUMT has been used to decrease this compensatory vasodilation. In this variation, the heat is delivered quickly so that the prostate vessels undergo thrombosis, resulting in improved heat entrapment in the prostate and decreased

Overview and Concept. Prostate vaporization was first performed in 1995 (Kaplan and Te, 1995) and is contemporary with many of the other MISTs. However, this technique used the same set of equipment as TURP at that time with the exchange of the resecting loop for an element with a larger surface area. Strategically, these modifications allowed for a large surface area over which the current could be delivered to the tissue and did not involve tissue resection. These changes allowed for the use of a higher energy that led to controlled tissue vaporization with simultaneous underlying tissue coagulation. This provided the urologist with an improved visual field in which to work and did not require the capital involved with the purchase of new equipment seen with other TURP alternatives at this time.

The power distribution along the electrode provides the advantages of transurethral vaporization of the prostate (TUVP). As the leading edge of the electrode makes first contact with the virgin tissue (low electrical resistance), a high volume of energy is delivered and leads to tissue vaporization. The lagging edge of the electrode interacts with tissue that has already been desiccated to some degree and has a higher resistance. The interaction with the higher tissue resistance at lagging edge leads to additional tissue desiccation along with vessel coagulation. Overall, this leads to a combination of tissue vaporization at the leading edge, with the lagging portion of the electrode then providing almost instantaneous tissue coagulation. This was verified by a two-stage in vivo study with small numbers. Tissue was first treated with either cutting or coagulating current, with a specimen taken by TURP. Examination of the specimen verified that when the cutting current is used, tissue destruction occurs in the form of vaporization with minimal coagulative necrosis. The converse is also true: Coagulative necrosis predominates when coagulating current is used (Juma, 1996).

A variety of different electrodes were used initially, including the VaporTrod (Fig. 105-6; formerly ACMI, now produced by Olympus)—a grooved roller electrode, the most studied of the monopolar options. Additional options included fluted and spiked varieties (Figs. 105-7 and 105-8). Each of these options provided an irregular edge for tissue contact wherein electrical charge would accumulate (Narayan et al, 1996). Whereas all were conceptually slightly different, working elements were easily fitted to existing equipment with fairly similar results.

The technology was updated in the late 1990s, and procedures are now customarily done with bipolar current, allowing the use of iso-osmolar solution as irrigant. The use of bipolar current concentrated the current at the end of the instrument as described earlier in the B-TURP section. Initial bipolar vaporizations were done with the Gyrus (now part of Olympus) Axipolaire, which was a nonrotating element that was an 80:20 platinum-iridium alloy

that was separated from the stainless steel return electrode by a ceramic insulator. This operated by forming a vapor pocket at the tip of the device, which had a high temperature. When this pocket was brought into contact with the prostate tissue, vaporization would occur, but the electrical circuit would be completed with the low-impedance saline allowing the active electrode to arc to the return electrode. Current was not required to pass through the patient, and deeper tissue heating would not occur.

Currently, Olympus markets the updated variation of the bipolar technology that uses PK technology. The PlasmaButton electrode (Fig. 105-9) uses a half-spheric shape that provides a large surface area for current accumulation. Plasma is generated in a similar fashion to that described in the B-TURP section. However, because of the large surface area of the working element, tissue contact is almost always required to create the orange corona.

Unlike with other TURP alternatives, general or regional anesthesia is typically required. Because all tissue is vaporized, no pathologic specimen is available for examination.

Technique

Preoperative. In general, the procedure is done using general or regional anesthesia. Once this has been established, the patient should be carefully placed into the dorsal lithotomy position with



Figure 105-7. Fluted electrode. (Courtesy Olympus, Inc.)



Figure 105-6. Vaportrode electrode. (Courtesy Olympus, Inc.)



Figure 105-8. Spiked electrode. (Courtesy Olympus, Inc.)



Figure 105-9. PlasmaButton electrode. (Courtesy Olympus, Inc.)

all pressure points carefully padded. Adequate antibiotic coverage should be given and a standard skin preparation should be used. A grounding pad will be required for a monopolar approach but is unnecessary if a bipolar technology is used. Appropriate irrigating fluid should be maintained at body temperature and placed at a height that allows adequate visualization without compromising patient safety.

Intraoperative. As described by Kaplan and Te (1995), the operative technique is similar to standard TURP. Standard transurethral resection equipment is used. The major difference is the use of a specially designed electrode for vaporization, which replaces the standard loop TURP electrode. This technique was originally described with the VaporTrode and required a nonionic solution because it was a monopolar technology. The VaporTrode is a spheric electrode on a transverse-oriented axis that will roll as it is drawn along tissue. This allows continuous contact with tissue. The Olympus PlasmaButton electrode has replaced this in many urologists' armamentaria because this technology allows the procedure to be done with normal saline irrigation. The PlasmaButton electrode has a half-moon shape that provides a large surface area for contact with tissue but without the moving parts of the VaporTrode.

As always, the scope and moving pieces should be examined and checked before being placed into use. An obturator is usually used to place the resectoscope sheath. The bladder should once again be examined for any pathology before beginning; the location of the ureteral orifices and verumontanum should also be identified.

Although alternate strategies certainly exist, the initial technique is described here. **The cutting current is used for vaporization, and the fulguration current setting will lead to tissue coagulation.** Common monopolar power settings are 200 to 240 W for cutting current and 60 W for coagulation. The bipolar technology uses settings of 280 W and 140 W.

In this technique, the surgeon begins by vaporizing the middle lobe from the bladder neck to the verumontanum (between the 5 and 7 o'clock positions). This will open a large channel for fluid irrigation and continued visualization. The vaporization is accomplished with overlapping sweeps of the electrode that simultaneously deepen and widen the channel. The depth of the treatment remains the same; visualization of the white fibers of the surgical capsule marks the desired depth of vaporization.

Once a sufficient channel has been opened for irrigation flow, the lateral lobes are then vaporized starting at the 1 o'clock position to the 5 o'clock position and moving in a clockwise fashion. The urologist should encounter minimal bleeding with this technique, with any hemorrhagic area controlled at the time of identification. Use of the electrode to place pressure on the bleeding area with use of the coagulation setting is very effective. The coagulation setting uses a lower-energy setting and will coagulate tissue with minimal further vaporization.

After the left lobe has been completed, the right lobe may be vaporized starting at the 11 o'clock position and moving counterclockwise down to the 7 o'clock position. This will complete all but

the anterior area of the vaporization. The volume of irrigant in the bladder will often change the surgeon's perspective on the magnitude of the cavity in the prostatic fossa because a full bladder will naturally pull the prostatic fossa open. When vaporizing the anterior portions of the prostate, one may find that this is easier with a bladder at a lower overall volume.

Vaporization of tissue around the prostatic apex can be a problem during the procedure, with concerns of energy advancing beyond visualization and causing sphincteric injury. The risk of sphincteric injury must be balanced against the risk of symptom recurrence; avoidance of sphincteric injury is paramount. Owing to these difficulties and fear of unrecognized vaporization depth, one group described a hybrid technique of resection of apex tissue with fulguration of the resected bed afterward. Although economically less sound because of the use of two electrodes, this is a possible approach (Tefekli et al, 2005). Once hemostasis has been controlled, the scope can be removed and a Foley catheter is placed. The catheter should be irrigated and the return of clear to light pink irrigation fluid should be confirmed before terminating the procedure.

Postoperative. Patients can expect the catheter to be removed within the first 24 hours. We commonly remove this in the morning of the day after surgery as long as there is minimal bleeding and no unforeseen intraoperative complication occurred. Patients should be able to void shortly thereafter. Some authors have performed the procedure as a same-day discharge procedure because of the improved hemostasis (Eaton and Francis, 2002). Convalescence should be fairly rapid; however, trauma or pressure to the perineum should be avoided with similar instructions as those given to patients undergoing TURP. An eschar or other solid tissue mass may be passed around 7 to 14 days after the operation.

Outcomes. Outcomes for both the monopolar and bipolar studies are presented in the following paragraphs. **Overall, initial results of monopolar TUVF were similar to TURP, with a decrease in some adverse events. Long-term durability came into question, and enthusiasm for TUVF waned toward the late 1990s to early 2000s. The update to the bipolar technology renewed some interest in the technique, and although long-term durability is untested, it is a promising improvement.** However, in almost all studies, maximum prostate volume is limited to 70 to 80 g, making the applicability of the technology to large glands unknown.

Animal and in Vitro Studies. A canine model examining the grooved rolling cylinder (Richard Wolf Medical, Vernon Hills, IL) provided some basic understanding of coagulation depth and peripheral heating (Perlmutter et al, 1995). Perlmutter and colleagues found that multiple passes in the same area did increase the depth of coagulated zone (78% deeper than a single pass). Temperatures at the neurovascular bundle and rectal wall were unchanged by the procedure, and a 2°C rise was noted at a distance of 6 to 7 mm from the fossa cavity. The prostate capsule measurements were 5 mm from the edge of the vaporization margin, and a 4.3°C increase was noted there. Wattage was noted to increase both coagulation depth and width when applied to the canine liver during the same study. In general, coagulated tissue was not seen deeper than 2 to 3 mm from the prostatic fossa cavity. The largest change in temperature was noted in the irrigating fluid, which the researchers concluded acted as a heat sink during the procedure.

Chronic histopathologic changes in the prostate after vaporization were defined by Benjamin and colleagues (1997). Throughout the healing process, no extension of the initial 2-mm necrotic area occurred. Re-epithelialization of the fossa was ongoing by the third week after surgery, with epithelial stratification at 5 weeks.

Single-Cohort Studies. Kaplan and Te (1995) reported on their first 25 patients treated with VaporTrode. Initial results were encouraging, with significant changes in AUASS (17.8 to 4.2) and Qmax (7.4 to 17.3 mL/sec) at 3 months. Improvements in these values were seen at 1 week, and the catheter was removed at a mean of 14.6 hours from the end of surgery. All 14 patients who had erections preoperatively had retrograde ejaculation after the procedure, but the lower cost associated with a shortened hospital stay encouraged more study. Kaplan and Te reported on their first 114

patients in 1998 (Te and Kaplan, 1998) and had data out to 18 months in some patients. AUASS and Qmax changes were durable to at least 12 months. No patients required transfusion, and a mean hemoglobin decrease of 1.7 g/dL was reported. A high percentage of patients (89%) had their catheter removed within 24 hours, and although there was no increase in erectile dysfunction (ED) incidence, 84% of patients reported retrograde ejaculation. Other early adopters reported similar results (Narayan et al, 1996).

Studies naturally evolved into RCTs comparing TUVF with TURP until Botto and colleagues (2001) reported on the use of bipolar vaporization. A Gyrus system (now part of Olympus) was the first to use bipolar vaporization; the electrode had a riverboat-wheel type of configuration. At 3 months, 42 patients reported a decrease in mean AUASS from 19 to 9 and an increase in mean maximum flow from 7.9 to 19.7 mL/sec. Urethral stricture occurred in 2 patients, and 4 patients reported dysuria. Bladder irrigation was required in one patient for up to 3 days, but no transfusions and an overall low risk of bleeding were reported.

Dincel and colleagues (2004) reported on 20 patients who underwent vaporization using the PK Tissue Management System (Olympus) with an older electrode. Improvements in AUASS (72%), QoL score (61%), and Qmax (111%) were noted. Prostate volume and PSA both decreased by a little over 50%, confirming significant tissue removal with the procedure. By measuring size and operating room time, the researchers were able to calculate an average of 2.8 minutes for each gram of prostate vaporized.

The contemporary mushroom-shaped PlasmaButton electrode (Olympus) was reported on by Reich and colleagues (2010). No major intraoperative or postoperative complications were noted in this initial report. No clinical signs of fluid absorption were noted, and in the 12 patients for whom breath ethanol technique (Cumings et al, 1995) was used, no patient demonstrated an increase in ethanol concentration, implying minimal fluid absorption. Thirteen percent of patients continued platelet inhibitors throughout the procedure. Decrease in hemoglobin was minimal (1.1 g/dL). No transfusions were needed, although 53% of patients needed postoperative irrigation and 1 patient continued on the catheter for 8 days because of hemorrhage. Improvements in AUASS (61%), Qmax (174%), and PVR (77%) were all significant. One patient needed to be converted to TURP because of bleeding. This patient had a large gland (>100 g) and was among the first 5 patients treated in the study.

The single-center Zurich experience described the results of this technology in 83 consecutive patients (Kranzbuhler et al, 2013). Each patient had a preoperative mean Qmax of over 10 mL/sec, which is atypical for LUTS and BPH treatment studies. This increased nonsignificantly to 14 mL/sec directly after catheter removal. After 6 weeks, all functional outcomes (AUASS, QoL score, PVR) improved significantly when compared with baseline values, with further improvements in AUASS and QoL score at 6 months compared with the 6-week values. The PSA reduced by an average of 60% at 12 months. In one patient with a large prostate (110 mL), a conversion to B-TURP was necessary because of obscured visualization by bleeding. Many patients (31%) were on antiplatelet medications during the treatment.

Comparative Studies

Monopolar Studies. Six early RCTs of monopolar vaporization and resection with 1 year of follow-up were analyzed by Hammadeh and Philp (2003). They were able to analyze more than 200 patients in each group and found essentially identical changes in AUASS (–73% in both groups) and Qmax (216% with TUVF, 191% with TURP) between the different techniques. Complication profiles were fairly similar, although this was better studied by Poulakis and colleagues (2004). This study included patients anywhere within the first year of follow-up and compared occurrence of complication rates. The researchers found that TUVF had an improved profile compared with TURP with respect to operative duration, catheterization time, hospital stay, blood transfusion, and clot retention. Re-intervention for LUTS and BPH and postoperative urinary retention were less likely to occur in the TURP group.

Of these six early trials with 1-year follow-up, the study by Galucci and colleagues (1998) included only patients with obstruction on preoperative UDS. At 3 months post-procedure, 92.5% of the TURP group was unobstructed by UDS standards, with 88.6% of the TUVF group unobstructed. A small percentage of the TUVF group (1.4%) was still obstructed on UDS and underwent TURP; no patient in the TURP cohort was obstructed on follow-up UDS. Similar changes were noted in AUASS, Qmax, detrusor pressure at maximum flow rate (PdetQmax), and PVR between groups. However, a surprising 18.6% of the TUVF group had transient stress urinary incontinence, with 5.7% of the total cohort having true stress urinary incontinence at 12 months after surgery. This surprising presence of incontinence was attributed to a possible unseen depth of coagulation near the apex that was unanticipated by the surgeon.

While TUR syndrome was still a possibility because of the use of hypo-osmolar fluid, a study using ethanol-labeled glycine as the irrigant showed that vaporization led to less (672 mL) fluid absorption than resection (1347 mL, $P < .005$). This was thought to be a result of the sealing effect of vaporization techniques on the prostatic sinuses and vessels.

Another of these six early trials followed patients to a total of 5 years after randomization to M-TURP or TUVF (Hammadeh et al, 2003). A total of 53 of the original 104 patients were analyzed. Both groups had statistically improved AUASS, QoL score, PVR, and Qmax compared with their respective preoperative values. Although there was no statistical difference between groups at 5 years, trends toward an advantage with TUVF could be seen.

An RCT with 10-year results from patients undergoing TURP, contact laser prostatectomy, and electrovaporization was published in 2010 (Hoekstra et al, 2010). Whereas 91% of patients could be accounted for, only 44% of the original 150 patients were available for analysis. Only TURP still had a statistically significant improvement at 10 years with regard to maximum flow rate and PSA. The TURP and contact laser prostatectomy groups had prostate volumes roughly equal to the prostate volume at study start, but the vaporization group was noted to have an increase at the 10-year mark compared with the baseline value (43 g from 28 g, $P < .05$). Although failure rates were not statistically different, TURP had a failure rate roughly half that of vaporization and contact laser prostatectomy.

Bipolar Studies. Multiple studies compared the newly available bipolar vaporization technology to M-TURP in RCTs. Reports on PK technology at 12 months (Karaman et al, 2005) and then at 36 months (Kaya et al, 2007) found a decrease in operating room and catheterization time, and although no patients in the bipolar group required transfusion, two TURP patients did. AUASS improvement was statistically better in the vaporization group, although the TURP group had an uncharacteristically modest change in AUASS (only 45% reduction). The early results seemed to favor bipolar vaporization, but the 36-month results were less favorable. Although a bias related to follow-up could certainly be a factor in this change, with only 40.5% of TURP patients and 65.8% of TUVF patients analyzed, results were heavily in favor of TURP. At 3 years, TURP had improved AUASS (–74%) and Qmax (263%) compared with TUVF (–64% and 140%, respectively). Three patients in the vaporization group required re-treatment for BPH (one in the TURP group), and the patients in the vaporization group were overall less satisfied with treatment (48% vs. 60%, $P = \text{NS}$). Differences in ED and retrograde ejaculation rates were not significant.

The higher rate of complications with greater clinical efficacy was also noted by the higher recatheterization rate in the bipolar group (30% vs. 5%), with clot evacuation (19% vs. 0%) more often needed in the TURP group (Dunsmuir et al, 2003). Change in hematocrit was greater and more irrigation was required in the M-TURP group in the results of Hon and colleagues (2006). Although no difference in systemically absorbed fluid was noted, four M-TURP patients required transfusion compared with no vaporization patients ($P = .02$).

The use of the TURis vaporization seemed to further improve the results when compared with M-TURP. The single-center report from

Geavlete and colleagues (2010) found that the PlasmaButton system led to a better improvement in AUASS, QoL score, and Qmax with less significant hematuria, transfusion, and clot retention compared with M-TURP at 6 months. In their report at 18 months (**Geavlete et al, 2011**), they also included a B-TURP group. The bipolar vaporization group fared better than either TURP group with regard to capsular perforation, operating room time, and catheterization time. Outcomes such as postoperative AUASS, QoL score, and Qmax were equivalent among all groups at the 18-month point, with all groups improved compared with baseline.

Complications

Intraoperative and Perioperative. It appears that the simultaneous vaporizing and coagulating properties of the vaporization technology leads to an overall decreased risk of intraoperative bleeding risk. There is **less blood loss** (**Kupeli et al, 2001**), although the overall low risk of **transfusion** in most RCTs makes a statistical difference difficult to achieve; a range of 0% to 2% was seen in a systematic analysis of RCTs (**Ahyai et al, 2010**). Other intraoperative complications such as **capsular perforation** or **conversion to TURP** are also rare, with conversions to TURP for bleeding seeming to occur more frequently in larger glands (**Kranzbuhler et al, 2013**).

Postoperative. The largest postoperative risk associated with TUVF is the **need for re-treatment** for LUTS and risk of unplanned **postoperative recatheterization**. The meta-analysis by **Ahyai and colleagues (2010)** found that 8.2% of patients required recatheterization after TUVF, which was among the highest rates of the analyzed techniques. The increased hemostasis achieved intraoperatively appears to lead to a decreased postoperative risk of **clot retention** (**Geavlete et al, 2010**).

The inability to accurately judge the depth of energy dispersion led many early adopters to be concerned about inadvertent coagulation, particularly around the apex. Although not statistically significant, the slight increase in **incontinence** compared with TURP seen in the review by **Hammaddeh and Philp (2003)** may be a product of the energy dispersion. Although still not rigorously studied, the increased risk of new **ED** (12% vs. 5%) when compared with TURP also increased the concern of unwanted depth of coagulation. The risk of postoperative dysuria also appears to be more common in TUVF (**Ahyai et al, 2010**).

As described in the B-TURP section, the TURis or TUVis system uses the outer resectoscope sheath as the return electrode. In a study looking at the use of this system, a small series of calamitous complications was noted. In three consecutive patients, one patient had **bladder necrosis** leading to severe storage symptoms and two patients had complete **urethral necrosis** with resulting urethrocucutaneous fistula (**Robert et al, 2012**). Our preference is for use of the PK system as opposed to the TURis or TUVis system.

Conclusion. Prostate electrovaporization continues to be a viable option for treatment of LUTS caused by BPH. Results are comparable to TURP with regard to improvements in voiding symptoms. Although prostate electrovaporization initially was a very popular option for treatment of LUTS and BPH, widespread acceptance was likely tempered by questions about durability with a concern about dysuria and re-treatment rates. The excellent hemostasis of the procedure leads to excellent intraoperative visualization. While this was a significant innovation in its time, it appears that laser vaporization is likely to supplant it as the preferred form of prostate vaporization.



Figure 105-10. Cooled ThermoTherapy transurethral microwave therapy catheter. (Courtesy Urologix, Inc.)

procedure times. This process is supported by the fact that prostates with a more significant vessel density are less likely to respond well to treatment in general (d'Ancona et al, 1999a).

Mechanism of Action. The mechanism by which TUMT causes the reduction in LUTS caused by BPH is **not completely understood**. Multiple theories exist and are not mutually exclusive. These theories focus on altering prostate innervation or morphologic tissue changes in the prostate.

Nerve Degeneration and Sensory Changes. The first of these theories rests on the **dynamic concept of prostatic obstruction** wherein the tone of the smooth muscle of the prostate causes obstruction. This has been studied by investigators by examining tissue after TUMT wherein a biopsy was obtained. Ten patients underwent OP after TUMT; specimens were evaluated using histologic immunohistochemical stains. The urethra was well preserved; compared with controls, the specimens were found to have "disrupted" nerve fibers; with axons rarely being found. The authors suggested that thermal damage to the adrenergic fibers essentially induced a "long-term α -blockade" (Perachino et al, 1993). This theory has few adherents.

The denervation may also be specifically targeted to the smooth muscle fibers of the prostate. A carefully controlled study using a prostate chip taken at the beginning of the procedure was stained using a nonspecific neuromarker protein gene product in both a control group of 10 patients and in 10 patients who had undergone TUMT a week before. Stained fibers were seen in all layers of the control biopsy specimens. Almost all of the study group biopsy specimens had nerve fibers in the lamina propria and epithelial layer. However, all but one study group specimen showed an almost complete absence of nerve fibers in the smooth muscle layer. The TUMT-treated patient without the smooth muscle nerve fiber changes had a small prostate (20 g). The findings of a preferential smooth muscle destruction of muscle fibers were noted even without a large degree of necrosis in the specimen (Brehmer et al, 2000). Whereas the aforementioned study noted changes in only

some nerve fibers, there is still the possibility of a later-onset denervation of the other fiber groups. Animal studies looking at heat treatment of dog sciatic nerves found almost no histologic changes immediately after a heat treatment similar in duration and temperature of TUMT. However, segmental demyelination and axon loss were noted 3 weeks later, with changes persisting out to a year (Vujaskovic et al, 1994).

A more specific look at the subgroup of nerve fiber destruction in TUMT was completed by a group binding assay specific for the α_1 receptor. Twenty-five patients were included. Ten of these patients received TUMT before the cold-punch biopsy and then subsequent TURP. Five patients had TUMT then retropubic prostatectomy. The control group underwent TURP ($n = 10$). A **statistically significant difference in the mean α_1 -adrenergic receptor density was found between the control (96.4 fmol/mg) and the TUMT-treated group (71.3 fmol/mg)**. The receptors in all groups continued to have a similar dissociation constant (ability to bind their ligand) (Bdesha et al, 1996).

In an interesting study using electrical stimulation to examine the prostatic urethra in 13 patients before and after TUMT, the large majority of patients had improvements in symptoms, with the most favorable effect noted in storage symptoms (nocturia primarily). The decrease in urinary urge effectively was parallel to the increase in sensory threshold. The authors postulated that the decreasing prostatic urethral sensation may lead to decreased input in the urethra-detrusor excitatory reflexes with an overall improvement in perception of voiding symptoms (Brehmer and Nilsson, 2000).

Morphology Changes. When heat is applied to a specific portion of the prostate to a sufficient temperature and duration, an **area of necrosis is created**. This area of necrosis eventually contracts to form a scar and reduces overall prostate volume. In a study looking at heat gradients in the prostate and histologic effects, patients underwent TUMT, followed by surgical tissue retrieval at varying later times. During the microwave procedure, temperature mapping was performed at multiple prostatic sites using fiberoptic thermosensors. Microwave treatments resulted in peak prostate temperature of 80°C with penetration of heat deep into the prostate parenchyma. Histologic changes were related to temperatures in the prostate. Mean temperatures increased rapidly with radial distance from the urethra to a maximum of 54°C at a distance of 0.5 cm from the urethra. As temperature increased beyond this distance from the urethra, temperature decreased exponentially but remained above 45°C at a distance of 1.6 cm radially. Pathologic findings were similar in all specimens, with sharply circumscribed intraprostatic hemorrhagic necrosis at sites where 60 minutes of a minimum of 45°C was elicited by treatment. The borders of the areas of necrosis and the viable tissue were sharply demarcated. The mean range of this border was from 0.5 to 2.5 cm from the urethra with a mean distance of 1.6 cm. The researchers also did note, but poorly explained, an area of devitalized but noninflammatory tissue between the necrotic and normal areas (Larson et al, 1996).

A similar study explained this area between necrotic and normal tissue. Patients exposed to TUMT had an area of necrosis in a discrete area 20 to 25 mm from the urethra in the prostatic tissue. Within the area surrounding the necrosis, widespread apoptosis was noted (Brehmer, 1997). The root cause of the apoptosis could not be elicited in that study, but other work has shown that cell death results from apoptosis then necrosis based on an increasing heat load applied to the tissue (Harmon et al, 1990). Cultured prostatic stromal cells exposed to moderate hyperthermia of only 47°C for an hour confirmed the possibility of heat-induced apoptosis; 76% of cells were apoptotic. Cells also did undergo necrosis (14% of the sample), which further solidifies that there is a "thermal load" at which cells preferentially die of necrosis or apoptosis (Brehmer and Svensson, 2000). The **reduction in prostate volume appears to be related to the energy platform used; the low-energy protocol decreased size by only 14%, whereas higher-energy protocols decreased size by 25%** (Devonec et al, 1993).

Technique

Preoperative. The benefit of a MIST selection is the ability to perform the procedure in the office, typically using just local

anesthesia. As always, the patient's ability to tolerate the procedure should be considered. Overnight admission is not needed, and patients are usually sent home directly after recovering from the procedure. Cystoscopy is required before TUMT because the **presence of a median lobe is an exclusion criterion.** The median lobe would not be treated during the procedure, and its presence may also direct the catheter away from the midline, altering the treatment. The prostatic length must be measured during the cystoscopy. A prostatic length of less than 25 mm is not suggestive of an enlarged prostate and would make the procedure technically challenging and perhaps unsafe. Prostate size should be 30 to 100 g for TUMT.

Contraindications to the procedure include implanted pacemakers, defibrillators, inflatable penile prosthesis, artificial urinary sphincters, and metal implants in the pelvis such as a total hip replacement. Patients with urethral strictures should also be excluded from treatment because the catheter may be difficult to place and the correct position may be difficult to verify. Patients who have undergone previous invasive BPH treatment should also be excluded because this is an untested group and there may be unexpected projection of microwaves into aberrant locations. Comorbid conditions such as peripheral arterial disease with claudication, prostate cancer, bladder cancer, and underlying neurologic disorders should also lead the patient and surgeon to choose a different treatment method.

Intraoperative and Perioperative. The specialized catheter is inserted per urethra and advanced into position. The anterior wall of the rectum is monitored by the placed rectal thermometer probe. The preset program can then be started, with an automated program running for the duration of the procedure and monitoring urethral and rectal temperatures. The balloon of the catheter remains in the bladder, keeping the catheter in place while the EM waves are emitted into the transition zone of the prostate (Fig. 105-11). One role that the surgeon plays in this procedure is to provide occasional "vocal" anesthesia to the patient in the form of calming the patient and providing reassurance to an awake patient. Continuous monitoring of patient comfort is critical. Unexpected discomfort may imply misplacement of the catheter. Significant injuries have occurred when such advice is not heeded.

Postoperative. A benefit of TUMT is the benign postoperative course. Perioperative complications are unlikely and patients do

not require hospital admission. Patients may return home directly from the procedure, and convalescence is rapid. **Postoperative catheterization for a period of days is almost certain** with previous generations of TUMT but is becoming less common. Higher energy platforms have led to an overall lower rate of the standard transient postoperative urinary retention, but patients should be carefully counseled about this risk.

Outcomes. Thermotherapy or microwave therapy continues to be a treatment for BPH owing to the relative ease of use and ability to be done as an office-based procedure. Because of the many different technology platforms, trials are difficult to group into larger analyses. **In general, the studies available are very heterogeneous and are frequently single-cohort and noncomparative trials having short-term follow-up; they should be judged carefully and individually.** An obvious lesson learned from these trials is that the higher-power systems have superior results compared with their lower-power predecessors.

Predicting Outcomes. Initial work published on predicting outcomes of TUMT focused on the Prostatron 2.5 platform. This work defined early cutoff points to help guide the urologist in the care of patients after TUMT (d'Ancona et al, 1999a). **Outcomes were evaluated at 6 months, limiting the long-term scope of the study, but good response was independently predicted by preprocedural variables such as younger age at treatment, larger prostate volume, and higher grade of BOO.** The energy used on the prostate during the procedure was also predictive of response but has less usefulness because it is post priori. Because PSA is a surrogate for prostate volume, pretreatment PSA was also found to be helpful in predicting outcomes in some studies (Djavan et al, 2000) but not in others (Laguna et al, 2002).

Ability to predict outcomes based on initial AUASS has been more difficult. In one controlled study the proportion of patients achieving an AUASS of less than 9 (mild symptoms) was similar among patients in both the moderate and severe symptoms groups. Of the patients in the moderate symptoms group, 50% migrated to the mild group, many patients stayed in the moderate group (38%), and some worsened to the severe group (12%). Of those already in the severe group according to pretreatment AUASS, 14% continued to have severe symptoms while many patients improved to the moderate (36%) and mild groups (49%) (Larson et al, 1998). Because many urologists may prefer this treatment in patients at higher risk of surgery, the usefulness in higher-risk patients has also been studied. In a study of an HE-TUMT device, the treatment was equally efficacious in high (3 or 4) or low (1 or 2) American Society of Anesthesiologist (ASA) scores (d'Ancona et al, 1999b) with no differences in post-treatment catheterization or ability to tolerate the procedure.

Single-Cohort Studies. Despite the ease of use and relatively low complication rates, the major concerns with TUMT are the reduced overall LUTS improvement compared with other treatment options and the lack of durability. One vexing study using an older, low-energy transurethral microwave therapy (LE-TUMT) machine (Prostatron 2.0) demonstrated initial significant improvement in patient level of satisfaction with treatment (Hallin and Berlin, 1998). However, over the 4-year period there was a progressive, marked decrease in the number of satisfied patients from 62% at 1 year to only 23% at 4 years. The initial improvements in symptoms and increase in flow rates were followed by reversal of these findings at the 4-year follow-up. In addition, two thirds of the patients in the study received additional BPH treatment within the 4 years for which they were followed. These concerns were further justified when studies showed a cumulative risk of subsequent TURP re-treatment of 40.5% at 5 years of follow-up, and a percent cumulative risk of any re-treatment (including α -blockers) of 57% (Keijzers et al, 1998). Another LE-TUMT protocol confirmed the high re-treatment rates, with 35% of patients requiring additional treatment within 3 years (Daehlin and Frugard, 1999). Studies of early, low-energy systems looking at changes in both subjective and objective measures of improvement have found varying results. Almost all of the low-energy studies showed an improvement in subjective symptom scores, but often without

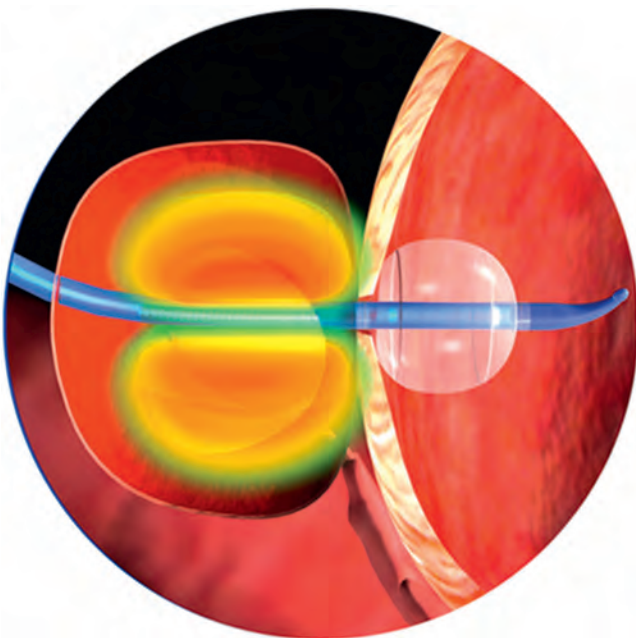


Figure 105-11. Transurethral microwave therapy catheter treating the transition zone of the prostate. (Courtesy Kevin T. McVary.)

changes in objective measurements such as maximum flow, residual urine, or UDS features such as peak detrusor pressures. With the upgrade to high-energy (HE) devices, changes in objective metrics became more common. Although more energy is used, the high-energy protocols are still well tolerated under local anesthesia (Eliasson and Wagrell, 2000). When heat-shock protocols are used, the shorter duration of treatment also leads to an increased initial pain score but a similar post-treatment pain score (Francisca et al, 2000).

Using an HE-TUMT device (Targis), a group of investigators demonstrated significant improvement in AUASS, QoL score, Qmax, and PVR that was durable at 24 months (Thalmann et al, 1999). UDS was routinely performed in patients, and improvements in mean detrusor opening pressure and detrusor pressure at maximum flow were also significantly improved 6 months after treatment. A cavity in the prostatic fossa (similar to those seen in patients after TURP) was noted in 77% of patients, and TRUS demonstrated a decrease in prostate volume from 57.6 to 42.4 mL. Despite these positive results, 13% of patients required re-treatment.

In a recent TUMT study, the findings of many previous studies were reiterated (Mynderse et al, 2011). The Cooled ThermoCath catheter with a Targis system was used under a 30-minute heat-shock protocol. The percentage of patients requiring any sort of postoperative catheterization (50%) was less than in previous TUMT studies, and only 3% of patients required catheterization for more than 7 days. At the final follow-up at 5 years post-treatment, a 43% improvement in AUASS and 39% increase in Qmax was noted. Unfortunately, 29% of patients required additional BPH-related treatment; 9% of the overall cohort required surgical treatment.

To summarize symptomatic improvement with HE-TUMT, patients will have a 60% reduction in symptom scores noted at 3 months of follow-up. This tends to become slightly better at the 6- and 12-month points. There is no significant difference among HE-TUMT devices in the reduction in symptoms. At 3 years, symptom improvements worsen to only 45% improvement, but re-treatment is seen in close to 20% of patients (Floratos et al, 2001). The aggregated changes in Qmax represent a 50% improvement seen at 3 months and stability at 12 months (Gravas et al, 2003), with studies rarely reporting a post-treatment Qmax greater than 15 cm/sec.

Patients with urinary retention represent a more challenging BPH group to treat. In one of the first HE-TUMT studies of men with AUR, 94% of men were able to spontaneously void at 4 weeks after treatment (Djavan et al, 1999c). Although no pressure-flow studies were obtained, this group likely represents a cohort with functional detrusor muscle. Contrary to this, in a study that included chronic urinary retention patients, the 1-year failure rate was 25% and the mean catheterization time was 38 days (Floratos et al, 2000). In a study of surgically high-risk patients with AUR, 87% were able to void spontaneously (3 months post-procedure), and 7.3% experienced repeat urinary retention within 2 years (Berger et al, 2003).

Comparative Studies

Transurethral Microwave Therapy versus Sham. Many sham-controlled studies involving TUMT have been performed. This is likely because of the low morbidity of producing a sham equivalent arm, as minimal anesthesia is required. These sham studies are interesting in that they highlight the placebo effect present in BPH treatment. The placebo effect of a sham study was most notably highlighted by Nawrocki and colleagues (1997). In this study, patients were randomized to one of three groups—TUMT, simulated TUMT, and observation—with 6-month follow-up. The simulated TUMT group underwent a process identical to TUMT except the generator ran a simulated program that included machine noise, screen readouts, and heat emission by a pad placed under a blanket. No statistical changes were noted in objective measures such as pressure-flow outcomes or urodynamic variables. Surprisingly, there was a statistically significant decrease in AUASS for both the TUMT (19 to 9.5) and simulated TUMT group (17.5 to 9.5). The untreated group did not note this change (AUASS changed

from 18 to 17). These results are interesting in that they highlight the perceived benefits of TUMT (in terms of reported AUASS changes seen in both the TUMT and simulated TUMT group) but showed no objective changes in any of the groups. Merely performing a sham treatment reduced AUASS in a significant fashion.

Other prospective sham studies (without untreated groups) did show improvements in peak flow to complement the decrease in AUASS. Studies of the Targis thermoablation system (Urologix) (Larson et al, 1998) and Dornier Urowave system (Dornier MedTech, Munich, Germany) (Roehrborn et al, 1998b) both exhibited this response with overall similar findings. The Dornier Urowave system provided decreases in the AUASS for both the treatment and sham groups. Treatment group AUASS decreased from 23.6 to 12.7 at 6 months, with a decrease of 23.8 to 18.0 in the sham group. Although both study groups had a significant decrease, the change in the treatment group was statistically superior. Peak flow rates were improved in the treated (7.7 to 10.7 mL/sec) and untreated groups (8.1 to 9.8 mL/sec), with improvement in the treated group being statistically superior.

The study of the Targis system had a similar pattern of findings. Both the treatment and sham groups had statistically significant improvements in AUASS—a mean decrease from 20.8 to 10.5 in the treatment group and a lesser, but still significant decrease in the sham group (21.3 to 14.3). Flow rates improved from 7.8 to 11.8 mL/sec in the treated group, with a less impressive increase occurring in the sham group (7.8 to 9.8 mL/sec) (Larson et al, 1998).

Transurethral Microwave Therapy versus α -Blocker. Some authors have stated that on the continuum of BPH treatment, TUMT should stand between medical management and more aggressive treatments such as TURP and OP (Djavan et al, 1998a). The underlying precept for this view is that the single, low-risk procedure could remove the hassle and cost of years of medical treatment. Although patients undergoing TUMT do have a frequent need for additional BPH re-treatment, the results are not far different from those in patients in whom medical management fails. In an investigation of re-treatment in patients using α -blockers, results were assessed at 3 years; failure rates of 27% (tamsulosin), 37% (alfuzosin), and 49% (terazosin) were noted (de la Rosette et al, 2002). One RCT compared TUMT with α -blocker therapy (terazosin). Mean AUASS and Qmax were improved for both groups; TUMT had a more pronounced effect at both 6 and 12 months. TUMT resulted in a 35% improvement in AUASS compared with α -blockers, and a 22% improvement in Qmax. The terazosin group had a sevenfold higher actuarial treatment failure rate (Djavan et al, 2001). However, the definition of failure was qualitatively different between groups, and the findings should be interpreted cautiously.

Transurethral Microwave Therapy versus Transurethral Resection of the Prostate. Concerns about the durability of TUMT are common despite the improvement seen in uncontrolled studies and sham comparisons; many studies had higher than acceptable re-treatment rates, with TUMT often failing only months after surgery. As always, comparison to the gold standard treatment is necessary before any treatment is considered a standard practice. Whereas changes in the energy delivered by the system improved many patient outcomes, comparison to TURP further highlighted the weaknesses of the TUMT intervention.

A randomized trial using the HE-TUMT Prostatron 2.5 system included 6 months of follow-up (Ahmed et al, 1997). The primary end points for the study included AUASS, maximum flow, residual urine, detrusor pressure at maximum flow, and prostate volume. All outcomes in the TURP group were improved. The TURP group had improvement in all outcomes, but in the TUMT cohort, only the AUASS was improved and multiple other factors worsened. In general, the incidence of adverse events was higher with TURP, but the TUMT group had prolonged postoperative retention.

Contemporary studies of the same machine had very different results. At 1 year of follow-up there was a decrease of 78% in the Madsen-Iversen symptom index in the TURP group; a decrease in the TUMT group was also noted (68%). Maximum flow rate

improved by 100% (TURP) and 69% (TUMT), and both groups had relief of bladder outlet symptoms by urodynamic parameters. Although the effects in the TURP group were pronounced in all accounts, they were not statistically different than the TUMT group. Groups were equivalent with regard to need for re-treatment, but the TURP group needed more frequent returns to the operating room for coagulation (three vs. zero patients). The TUMT group had a longer duration of catheterization, with one patient requiring 35 days. Correspondingly, the TUMT group had an increased risk of postoperative UTI, with one patient requiring readmission to the hospital for infection. In addition, postoperative irritative symptoms were more common in the TUMT group (29% vs. 14%) (d'Ancona et al, 1997).

A similar randomized study with longer follow-up (median 33 months) displayed improvements in the TUMT group with respect to urinary flow (improved 64%) and AUASS reduction (–60%), although these paled in comparison to those in the TURP group (+214% in Qmax and –85% in AUASS). With a longer follow-up the re-treatment rates in this study should be carefully examined. A re-treatment rate of 19.8% in the TUMT group and 12.9% in the TURP group were not statistically different ($P = .28$); however, the reasons for re-treatment appeared to have different causes. In the TUMT group, 10 of the 14 patients underwent additional BPH treatment (TURP, laser prostatectomy, transurethral needle ablation of the prostate [TUNA], α -blockers), whereas only 1 of the 8 patients in the TURP group required this type of re-treatment (α -blockers). Although there was no statistical difference in the number of patients undergoing re-treatment, it appeared that the TUMT group was more likely to need re-treatment for residual BPH (Floratos et al, 2001).

More recently a multicenter, randomized trial released 5-year follow-up results to complement the previously released results at 1 and 3 years. At the initial 12-month follow-up the researchers concluded that there was no statistical difference among treatments with regard to Qmax, detrusor pressure, and prostate volume; however, the change in each of these was more pronounced in TURP patients. A longer postprocedural catheter time (14 vs. 3 days) was seen in the TUMT group. Adverse events were graded according to severity, with the TUMT group undergoing more mild or moderate events (often characterized as “expected”) and the TURP group having more “serious” events (e.g., clot retention requiring readmission) (Wagrell et al, 2002). The 5-year data (66% of the original patients available) showed that 16% of the TUMT patients were considered to have experienced treatment failure, but only 6% of the TURP group (Mattiasson et al, 2007). In studies using UDS to classify the obstruction, TURP proved superior. A comparison at 30 months of HE-TUMT versus TURP found that one third of the TUMT patients remained “obstructed” on UDS, whereas only 14% of the TURP group maintained this UDS classification of “obstructed” (d'Ancona et al, 1998).

A recent Cochrane review of TUMT analyzed the six trials comparing TUMT and TURP. The pooled mean AUASS of TURP decreased by 77%; a 65% reduction was seen in TUMT. The pooled mean peak urinary flow increased by 119% with TURP and by 77% with TUMT, with a weighted mean difference favoring TURP by 5.08 mL/sec (Hoffman et al, 2012). In a study comparing quality-of-life outcomes between TURP and TUMT, a 41-question assessment was completed before and after surgery. Metrics of overall well-being, urinary symptoms, sexual function, daily activities, social activities, and psychological well-being were assessed. Both treatment modalities had a significantly positive effect on aspects of life, with perception of activities of daily living along with perception of urinary difficulties improving. Although both treatments were efficacious in improving quality measures, TURP did have a greater impact than TUMT in the 147 patients examined (Francisca et al, 2000).

Complications

Intraoperative and Perioperative. Much of the argument for the use of TUMT over TURP in the treatment of BPH is the decreased complication rate, particularly in the perioperative period. Higher rates of early re-treatment for procedural complications are seen for

TURP compared with TUMT. Unfortunately, most of the TUMT trials do not have a comprehensive review of adverse events. This leads to a potential bias because those reporting may have had lower than average complication rates. In almost all cases patients are able to tolerate the procedure in an office setting. Patient reports of a sensation of local, perineal warmth or an urge to urinate are common but do not limit the ability to complete treatment. Although some practitioners may advocate sedatives or analgesics for every patient, a randomized comparison proved that topical anesthesia alone was sufficient (Djavan et al, 1998b). With careful monitoring and correct placement of the catheter and rectal temperature probe, injury to surrounding structures should not occur. Errant reports of severe complications such as penile necrosis and urethral fistulae have been seen in the U.S. Food and Drug Administration (FDA) registry but are likely a result of improper catheter placement or poor monitoring of the patient during the procedure (Walmsley and Kaplan, 2004).

Postoperative. Contrary to the perioperative profile described previously, in general the long-term complication rates favor TURP. Re-treatment rates for BPH are significantly higher for TUMT than TURP. Re-treatment rates were discussed at length earlier and will not be further elaborated on here. Complications such as postprocedural hematuria leading to transfusion are rare after TUMT. Urethral stricture and bladder neck stenosis are occasional complications with a cumulative risk of about 2% (Floratos et al, 2001). Transient incontinence is seen in about 2% of patients, with permanent incontinence being extremely rare. Post-treatment convalescence is fairly rapid, with a mean recovery at home of 5 days and with 55% of patients spending less than 3 days at home (Ramsey et al, 1997). Prolonged catheterization times and AUR with the early generations of TUMT were the rule and not the exception. Almost all studies demonstrated an increased time with catheter compared with TURP, and catheterization durations of up to 2 weeks are not unusual (de la Rosette et al, 1997).

In an effort to reduce the catheterization times and postprocedural symptoms, attempts were made to use biodegradable urethral stents (Dahlstrand et al, 1997), temporary urethral stents (Djavan et al, 1999a), and periprocedural α -blockade (Djavan et al, 1999d). α -Blockade reduced postoperative retention from 12% in TUMT alone to 2% in TUMT with periprocedural α -blockade. In a prospective comparison of α -blockers and urethral stents, stents were more effective at 2 weeks, reducing symptom scores and improving flow rates. No patient with a urethral stent had retention 1 week after TUMT (compared with 11% of patients with TUMT alone), but 11% of patients with urethral stent needed early removal because of clot formation or stent migration (Djavan et al, 1999b).

Coinciding with prolonged catheterization, UTI in the post-TUMT patient is a common finding. Reports of incidence are sporadic, but numbers as high as 13.5% (Dahlstrand et al, 1995) have been published, with most large studies reporting an incidence in the low- to mid-single-digit percentages. With higher-energy protocols, the effects on sexual function have been more pronounced. Although sexual dysfunction has not been rigorously studied with validated questionnaire data from preprocedural and postprocedural periods, few reports have high rates of this finding. One report found only 5% of patients to have new ED (Kirby et al, 1993), and 55% of patients still graded sex as “very satisfying” (Francisca et al, 1999). In the TURP cohort of this comparative study, only 21% of the TURP group gave the answer “very satisfying.”

Reports of ejaculatory dysfunction after TUMT follow a similar pattern but have also not been rigorously studied. Most reports have reported low event numbers, with many reporting no change at all. A fairly high 44% incidence was reported in one study, which stands out against otherwise benign reports (de la Rosette et al, 1996). A study dedicated to sexual outcomes found that 74% of the patients had antegrade ejaculation after the procedure (Francisca et al, 1999). In the Cochrane review of TUMT versus TURP, TUMT was associated with a decreased risk of retrograde ejaculation, stricture treatment, hematuria, blood transfusion, and TUR syndrome. TUMT did have an increased risk for dysuria, urinary retention, and BPH symptom re-treatment. (Hoffman et al, 2012).

Conclusion. TUMT is a technology that is used to apply heat to the prostate; the mechanism of action is still in debate even 20 years after its introduction. Although a technically easier procedure than many of its counterparts, it carries a **potentially prohibitive need for re-treatment** because of persistent LUTS and BPH. It does have a favorable overall complication rate compared with TURP, but the risk of eventually requiring re-treatment needs to be weighed carefully when considering TUMT for a patient. One should note that any assessment of long-term durability and measure of voiding symptoms after TUMT will suffer from a selection bias, because it will include only patients who were responders and did not advance to other treatments. **Overall, the summation of the large volume of literature on TUMT further cements the place of TUMT in the continuum of treatment for BPH.** In general, the patient will experience an improvement in symptoms that is not as pronounced as with TURP, but TUMT has an overall more appealing safety profile and avoids the inherent risks of anesthesia. The use of this technology as a replacement for medical therapy is reasonable.

Transurethral Needle Ablation of the Prostate

Overview and Concept. The TUNA system is composed of a radio-frequency (RF) generator, a disposable urethral endoscopic catheter that attaches to a reusable catheter handle, and an optics system. The treatment concept and design was originally FDA approved in 1996 and was significantly updated in 2003. The procedure was first performed in 1993 (Schulman et al, 1993). The specialized urethral endoscopic catheter is used for this procedure and is attached to a reusable control handle. This rigid scope is placed into the urethra and advanced into the prostate under direct vision. The device uses an embedded lens that is at either 0 or 15 degrees based on the surgeon's preference. Once the device is in position, needles are deployed from the end of the catheter into the prostatic parenchyma. The needles deploy at an acute angle to each other and at a right angle to the longitudinal axis of the catheter. The needles have a variable length that can be adjusted to different prostate widths and sizes. The urethra is protected from heat energy by polytetrafluoroethylene (PTFE) and nylon sheaths that extend out to cover the proximal portions of the treatment needles. The urethra is untreated and not denuded, so the patient should theoretically have minimal local symptoms. The protective sheaths also have a thermocouple that monitors the temperature at the edge of the sheath. The needles and shield are adjusted by controls on the catheter handle (Figs. 105-12 and 105-13).

As with ultrasonography, the lower the frequency generated, the greater the depth of tissue penetration of the RF energy (or sound waves in the case of ultrasound). **Low-energy monopolar**

RF has excellent tissue penetration. The RF flows into the prostate parenchyma and interacts with the water molecules in the cells. This interaction creates localized heat around the needles. The heat energy has a fairly low dissipation into unwanted tissue because the temperature decreases as the distance from the needles increases (temperature decreases by a factor of $1/\text{radius}^4$). **When an adequate amount of heat has been applied to the tissue, a spheroid area of coagulative necrosis is created, which later undergoes cavitation.** This cavitation should lead to an overall size decrease in the prostate, although there is some thought that the treatment area actually later becomes scar tissue and does not lead to a significant decrease in prostate size. Retrograde ejaculation should be minimized because the bladder neck is unaffected.

The original systems were reactive to a change in tissue impedance. The platform redesign called the Precision Plus, now marketed by Urologix, in 2003 introduced a system that **measures both temperature and impedance**. In the older, entirely impedance-based system, the generator delivered energy while the impedance of the tissue between the needles was monitored as if part of a completed circuit. The impedance increased as the tissue between the needles desiccated and was destroyed. Once the impedance reached a certain level, the treatment in this area was complete; the tissue was desiccated and no longer able to conduct current. The level of output energy delivered was operator dependent, and the rate and amount of energy delivered was vital to creating a successful lesion. If too little energy was delivered, the lesion would be small and incomplete. If the energy was delivered too quickly, tissue would desiccate too rapidly, with an inadequate total thermal load (a product of delivered energy and time), and the treatment would be less effective. The size of the created lesions was proportional to the area of tissue in contact with the needle and the quantity of energy that was delivered. In a magnetic resonance imaging (MRI) study looking at changes in prostate volume, the mean area of necrosis was 7.56 mL (constituting 11.28% of total prostate volume) (Huidobro et al, 2009).

The modern system is more straightforward. In this system, the needles have thermocouple electrodes at the tips that are able to monitor the temperature of the target tissue, and the overall tissue impedance is also monitored. Currently the only device available in the United States is marketed by Urologix.



Figure 105-12. Transurethral needle ablation handpiece. (Courtesy Urologix, Inc.)

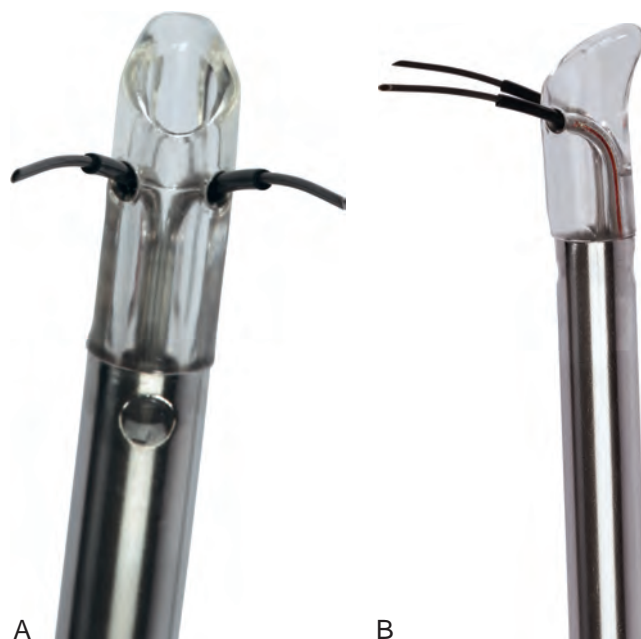


Figure 105-13. A and B, Deployed transurethral needle ablation needles. (Courtesy Urologix, Inc.)

Technique

Preoperative. TUNA is indicated in men with bothersome LUTS who are refractory to medications and have prostate sizes up to 80 g. Sterile urine should be verified before the procedure. TUNA is not recommended for patients with metallic pelvic prostheses. In addition, a defibrillator or a pacemaker may receive EM interference from the procedure, and these devices should be considered contraindications. A benefit of TUNA is that the procedure can be done with the patient under local anesthesia. TUNA can be performed safely in the office setting without postoperative admission, although a 23-hour admission is not uncommon after the procedure. The procedure should be done with a minimum of viscous urethral lidocaine, but oral or intravenous sedation (e.g., diazepam) may also be of benefit in the anxious patient. There is significant variation in the degree of anesthesia given by providers of this type of care (Bouza et al, 2006).

Preprocedural TRUS is performed to gauge the prostate size, anatomy, and prostate width. Cystoscopy is also performed routinely to rule out any bladder pathology and verify the distance from the bladder neck to verumontanum. The prostate length and width are of particular importance because the length will determine the number of levels at which needle deployment will be required. Prostate of 3 cm or less will be treated at two different zone levels. A length of 3 to 4 cm will require three levels of treatment. Prostates larger than 4 cm will require four zones of treatment. The length into the prostate to which the needles are deployed is based on the prostate width.

Intraoperative. The patient is positioned in the dorsal lithotomy position on a table. A grounding pad is applied to the patient's back in the lumbar area or over the sacrum. The anesthesia of choice is then given. The viscous lidocaine is given per meatus, with a penile clamp left in place to keep the lidocaine in the urethra for 10 minutes. If a periprostatic block is elected, then this is done similarly to the block for a prostate biopsy. The specialized cystoscope is placed per urethra under direct vision. The needles are deployed using controls at the catheter handle base and are able to be rotated 180 degrees to engage the prostate lobes based on these controls. The length of the Teflon shield on the needles should be adjusted so that the prostatic urothelium is spared from any treatment effects (usually 4 to 6 mm). The scope often needs to be pressed into the lobe for the needles to "grab" and keep the catheter from being pushed away from the lobe as the needles are advanced. Needles are deployed directly laterally into the lobes (at the 8 to 10 o'clock position and the 2 to 4 o'clock position).

Once deployed, the needles are placed through the urethral mucosa into the prostatic parenchyma. Once the ideal needle location has been verified and the Teflon sheaths have been advanced to protect the urothelium, the generator is activated. Thermocouples monitor the urethral and needle-tip temperature. The energy is slowly increased until the tissue temperature is reached. The needle tips are more than 6 mm from the prostatic capsule to ensure that no damage to structures outside the capsule occurs. The needle tips are then heated to at least 100°C. It takes only 20 to 30 seconds to reach the treatment temperature, and once it has been achieved the area is treated for 2 to 3 minutes. The delivered energy is adjusted by the software to maintain the temperature.

The needles treat a discrete area around and between the tips, creating an area of coagulative necrosis. For treatment of the entire gland, multiple planes in each gland must be treated. The number of zones and planes required for treatment is dependent on prostate size and shape (Fig. 105-14). In general, the needles are first deployed in a plane 1 cm below the bladder neck into the parenchyma, with subsequent placements at 1-cm intervals in the prostate and with the last placement 1 cm proximal to the verumontanum. The length to which the needle is deployed into the prostate parenchyma is calculated by the software based on the dimensions of the prostate including the width and other measurements from the preprocedural TRUS. During the treatment, temperatures near the needle tips will rise to 115°C within 20 seconds of generator activation. Temperatures are then maintained at that level for 2 to 3 minutes. This temperature and duration should

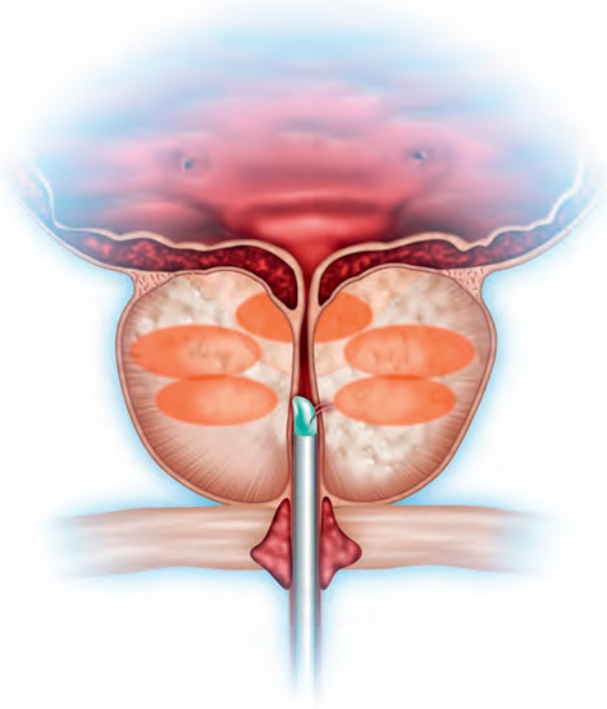


Figure 105-14. The treated prostate in transurethral needle ablation. (Courtesy Kevin T. McVary.)

cause the desired local tissue necrosis. The tissue temperature should be monitored throughout the procedure along with the urethral temperature. The machine is automatically equipped to shut down if the urethral temperature increases to a potentially harmful level. Treatment is complete once all of the predetermined areas of the prostate have been treated.

Postoperative. Patients are able to return home after the procedure, and convalescence is rapid. A few days of irritative symptoms are normal and likely minimized because of the minimal effacement of the urethral mucosa. If a urinary catheter is placed, it is maintained for 1 to 3 days based on surgeon preference. Antibiotics can be used for up to 2 weeks, and NSAIDs are continued for 10 days. The empirical antibiotic treatment is to avoid bacterial proliferation that forms an abscess in the cavitated necroses of the post-TUNA prostate (Barmoshe et al, 2006). Most patients are able to return to work in 2 to 3 days.

Outcomes. Whereas TUNA does show improvements in both subjective and objective measures of voiding, the results are less impressive than those found with TURP. Studies using UDS frequently show that patients do not migrate from an obstructed classification. A prohibitive need for re-treatment also attenuates enthusiasm. Comparisons to TURP are found in the literature, but no such comparisons of TUNA to medical treatment exist. Although it may have an overall lower rate of efficacy, the treatment is relatively safe, with few if any major adverse events.

Single-Cohort Studies. There is a consensus that TUNA treatment provides improvements in both subjective and objective measure of voiding, at least in short-term studies. However, there is a surprising lack of long-term data published, with only a handful of reports on patients further than 2 years from procedure. A comprehensive study primarily using an early generation of TUNA devices was completed by Rosario and colleagues in 1997 (Rosario et al, 1997). A total of 71 patients who were all found to have obstruction on pressure-flow studies were enrolled. Patients completed a 5-day voiding diary before the procedure and before each visit. Analysis completed at 12 months found a variety of positive results. Significant improvements were seen in multiple subjective outcome

measures, including AUASS (21.9 to 10.6), QoL score (4.8 to 2.2), number of daytime voids (8.7 to 5.6), and number of nighttime voids (2.7 to 1.7). At 1 year, 45 of the original 71 patients underwent repeat UDS. A statistical but clinically questionable decrease in PdetQmax was noted (97 to 82 cm H₂O). None of the patients were able to move into the “unobstructed” portion of the Abrams-Griffiths nomogram and 78% remained “obstructed.” No significant change in prostate volume or PSA was noted. Only 54% of patients were “completely satisfied” with the treatment. A total of 22 (30.1%) went on to additional treatment with TURP. The study by [Steele and Sleep \(1997\)](#) reported a more impressive decrease at 2 years in PdetQmax (92.4 to 58.9 cm H₂O). Maximum flow increased from 6.6 to 11.2 and AUASS decreased from 22.4 to 9.5. A total of 6 patients from the initial 47 patients required TURP during the study period. The researchers attempted to determine any preprocedural values that predicted failure but were unable to find any significant correlations.

In one of the larger noncomparative studies, [Roehrborn and colleagues \(1998a\)](#) studied 130 patients prospectively. Improvements were once again seen in AUASS (23.7 to 11.9) and Qmax (8.7 to 14.6 mL/sec). Surprisingly, 13.1% of patients reported an improvement in AUASS with either a decrease or no change in their peak urinary flow. Conversely, 4.8% of patients noted an increase in Qmax without an improvement in AUASS. Treatment duration was quick (mean 37.4 minutes). Although no patient required general anesthesia to complete the procedure, 22% reported some degree of pain. Most patients (59.2%) were able to void after the procedure. Of those who did require catheterization, the mean duration was 3.1 days, although 1 patient did require a catheter for 35 days.

In one of the few studies with data beyond 2 years, [Zlotta and colleagues \(2003\)](#) enrolled 188 patients into a multicenter study. At 5 years post-procedure, 121 patients were still available for analysis, with another 10 patients reaching 4 years. Significant improvements were seen in Qmax (40.7%), AUASS (−58.4%), QoL score (−55.1%), and PVR (−31.8%). Patients had a fairly large prostate at baseline—a mean size of 53.9 mL—and, once again, no appreciable change in volume was noted with the procedure. In addition, the PSA did not have any significant change with treatment. Of the 176 patients (2 deaths, 10 lost to follow-up) remaining at final analysis, 23.3% required some form of re-treatment. Of the total cohort, 6.4% received additional medical treatment, 3.7% underwent a second TUNA procedure, and 11.1% underwent unspecified surgery.

In one of the few studies examining TUNA in patients with AUR, 20 patients were included. Inclusion criteria included good detrusor function on UDS. In all patients, a trial of void after initial catheterization had also failed. Although all patients remained obstructed by Schafer coefficient after procedure, 17 of the 20 were able to spontaneously void. Five patients later progressed to receiving TURP for symptoms ([Millard et al, 1996](#)). In their review, [Bouza and colleagues \(2006\)](#) analyzed the available data and found that TUNA could reliably reduce symptom scores and QoL values by 50% to 60% compared with preprocedural values. They concluded this improvement was maintained over time, with a downward trend noted after 3 years. According to objective parameters, improvements were more modest but still statistically significant. A 30% to 35% improvement over baseline values was noted in objective measures such as Qmax, with even more poor outcomes on measures obtained from UDS. Of studies assessing patients with acute or chronic AUR, 70% of patients could spontaneously void within the first few weeks after the procedure.

Comparative Studies. Very few studies comparing TUNA with other treatments exist, and of these comparative studies a randomized design was used only in a minority. Although most studies report the standard subjective and objective measure of voiding, complications are irregularly reported. Follow-up beyond 3 years is rare in any type of study, and conclusions regarding long-term durability of this procedure should be made with caution.

Transurethral Needle Ablation versus Other Minimally Invasive Surgical Techniques. In a nonrandomized treatment protocol comparing patients selecting TUNA, TUMT, or high-intensity focused ultrasound (HIFU) for treatment of BPH, discouraging results were found with regard to MIST treatments ([Ohigashi et al, 2007](#)). Although statistical decreases were seen in all three MIST treatments with regard to AUASS at 6 months after treatment, with HIFU (52%) performing better than TUNA (45%) or TUMT (38%), all three treatments no longer had statistically significant improvements at 24 months. Although a large number of patients were lost to follow-up, re-treatment rates were surprisingly high, with 34% of TUMT, 36% of TUNA, and 58% of HIFU patients requiring re-treatment by 3 years. At 5 years, re-treatment rates ranged from 54% to 68% for the groups. In an interesting analysis, the researchers found that an initial Qmax of less than 10 mL/sec and an AUASS greater than 19 were risk factors for re-treatment. This is suggestive that patients with more severe metrics of BOO may be better suited to a different form of treatment. Although data were accumulated only for 3 months post-treatment in their non-randomized trial, [Arai and colleagues \(2000\)](#) found that patients who had undergone TUNA rated their satisfaction with the procedure more highly than those having undergone TUMT. A few studies have compared TUNA to TUVF ([Schatz et al, 1997, 2000; Minardi et al, 2004](#)). The analysis of these outcomes reports that TUVF has a higher risk of adverse events and more significant improvements in subjective and objective voiding outcomes ([Bouza et al, 2006](#)).

Transurethral Needle Ablation versus Transurethral Resection of the Prostate. TUNA was rigorously compared with TURP in an RCT that had data reported at multiple time points. The first installment occurred at 1 year post-randomization and showed that both procedures were efficacious but with superiority in the TURP cohort ([Bruskewitz et al, 1998](#)). A significant decrease was seen in AUASS in both arms at 1 year, with TURP (64% decrease) having a statistical advantage compared with TUNA (55% decrease). Measured prostate volume actually increased in the TUNA group (+2.4%), whereas the TURP group had a 17% reduction ($P = .014$). Peak urinary flow also underwent a more significant improvement in the TURP group (147.6%) compared with TUNA (72.4%), although both groups improved compared with their respective baselines. Longer hospital stay was noted in the TURP group because all patients in the TUNA group went home the day of the procedure. The second installment focused more primarily on UDS changes noted between the treatment arms ([Roehrborn et al, 1999](#)). Changes in the Abrahms-Griffith number and detrusor pressure at peak flow were superior in the TURP group. When comparing UDS changes with symptom improvements, the researchers were not able to predict which preprocedural UDS findings could predict postprocedural subjective success. The final publication from this series occurred after 5 years post-treatment ([Hill et al, 2004](#)). Cautious conclusions should be drawn from these results because at least half of the initial cohort did not provide data at the 5-year mark and in some categories only 20% of the initial cohort was analyzed. Both treatments were found to be effective for BPH, but TURP was superior in almost all metrics. AUASS improvements were more profound from years 1 to 4 for TURP. Peak flow was better at all analyzed time points in the TURP group compared with TUNA. TUNA did have a lower rate of adverse events but a higher need for re-treatment (13.8%) compared with 1.8% in TURP group. Another RCT by [Cimentepe and colleagues \(2003\)](#) had overall results that were more favorable for TUNA, but still not exceeding TURP. They reported no postoperative complications in the TUNA group other than a 7% risk of re-treatment over 18 months.

A meta-analysis of RCTs ([Bouza et al, 2006](#)) concluded that TUNA and TURP were fairly equivalent in results at 3 months, with TURP providing superior results after that point. Results for symptom score were improved by a factor of 1.3 at 1 year and 1.49 at 3 years. QoL score had less of a disparity, with a factor difference in results of 1.14 at 1 year and 1.34 at 3 years. Maximum flow of the TURP group was at least double the improvement seen in TUNA throughout the entire analysis.

Complications. The excellent systematic review and meta-analysis by Bouza and colleagues (2006) analyzed the total complication rates of both open and comparative trials. The researchers found that TUNA had a much higher rate of secondary procedures (OR 7.4) compared with TURP but was safer with a lower rate of complications (OR 0.14). They noted that differences were particularly notable in risk of sexual disorders and postoperative bleeding.

Intraoperative and Perioperative. In the study by Steele and Sleep (1997) a mild post-procedural hematuria was seen in all 47 patients. At 1 month postprocedure, 8% continued to have some degree of irritative voiding symptoms. Pain during the procedure is a fairly common finding, reported in 22% of patients in one series (Roehrborn et al, 1998a).

Postoperative. In the previously discussed comprehensive study by Rosario and colleagues (1997), patients were routinely sent home with catheters after initial problems with postprocedure retention. Likely as a result of this, they had a high rate of UTI (14%). Only 5.8% of patients reported any sexual dysfunction, although the rigor with which this was investigated in the individual trials is suspect. Dysuria was noted in 7% of patients in the review, whereas other studies have reported the incidence of this to be as high as 25% (Ramon et al, 1997). Perineal pain both during and after procedure is a common finding; 50% of patients in one study had pain lasting 1 to 2 weeks, and 23% used pain medication for control of this pain (Daehlin et al, 2002). From the comparative trials, Bruskewitz and colleagues (1998) noted a 12.7% incidence of ED in the TURP group. No TUNA patients reported ED. A decrease in ejaculation was noted in the TURP group 54% of the time, and only 13% of TUNA patients noted the same complaint. At final analysis of this cohort (Hill et al, 2004), 41% of the TURP group reported retrograde ejaculation but no TUNA patients reported this. Prolonged catheterization is unlikely because 90% to 95% of patients have been shown to be catheter free within 1 week of treatment (Chapple et al, 1999).

Conclusion. The role of TUNA in the continuum of BPH treatments is difficult to ascertain owing to the insufficient evidence and a lack of high-quality studies with significant long-term data. Although TUNA statistically improves symptoms, the results with regard to QoL score and urinary flow rates are not as impressive as with TURP. The reduction in prostate volume is negligible because the cavitated areas are putatively replaced with scar, leading to minimal significant change in overall prostate volume. A large initial volume of research was generated, but little has been published in the last few years. Likely this technology is headed toward a minimal role as more durable and impressive options continue to evolve. Although overall the procedure is very safe, it is a less attractive option than other MISTs.

Transurethral Incision of the Prostate

Overview and Concept. A dynamic role of peripheral condensation of the prostatic stroma acting as a capsule leading to BPH-associated LUTS has been proposed (Hutch and Rambo, 1970; Ohnishi, 1986). The alleviation of symptoms seen in patients with BPH treated with α -blockade also supports this capsular contraction or prostatic hypertonicity leading to symptoms. Clearly, capsular constriction could further exacerbate the symptoms derived from an already hyperplastic prostate. The practice of incising the prostate or bladder neck for reduction in voiding symptoms has been verified as early as reports dating back to the 1800s. In their review, Hedlund and Ek (1985) credit Guthrie in 1834 with the first disruption of the bladder neck as a treatment.

TUIP is an operative approach to disrupt the prostatic capsule to alleviate voiding symptoms. This procedure can be considered in many with small prostates (<30 g), although surgeons have tried this in larger glands. In general, a unilateral or bilateral incision is made through the bladder neck and can be extended all the way distally to the verumontanum. This incision is usually made posterolaterally (in the region of the 5 and 7 o'clock positions). The ideal patient for this procedure is a young man with a small

prostate who is concerned about either a loss of ejaculation or future fertility. This procedure has a lower risk of retrograde ejaculation (particularly if only done unilaterally) than other BPH treatment options. However, if retrograde ejaculation is truly being avoided, authors have avoided bladder neck and complete capsular incision (Orandi, 1987).

Technique. The most critical part of the preoperative care before TUIP is correct patient selection. Patients with large glands or significant symptoms are unlikely to achieve significant benefit and will require additional treatment. Many studies exclude patients with a median lobe from the procedure, and this should be considered as a potential contraindication. However, other authors have found that the presence of a median lobe is not a contraindication and opine that with incision of the prostate the median lobe will often become atrophic (Orandi, 1985).

The technique itself is fairly simple and technically straightforward. A cold knife, hot knife, resectoscope with a thin loop or even an end-firing holmium laser can be used to complete the procedure. The incision should be started distal to the ureteral orifice. The incision is carried through the bladder neck into the prostate, ending before the verumontanum. The depth of incision should visualize the surgical capsule at a minimum, although more aggressive surgeons may prefer to see periprostatic fat as they incise through the capsule. Hemostasis should be achieved, but significant bleeding should not be encountered (Fig. 105-15). The patient can have the catheter removed and can be discharged to home quickly after surgery (day of surgery or the next day). Convalescence should be rapid with few or no postoperative irritative symptoms.

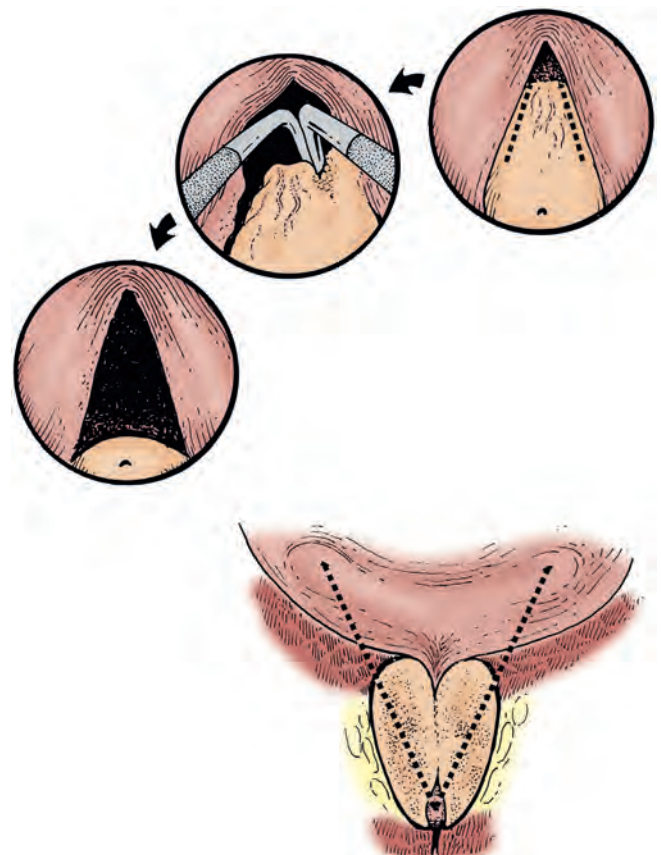


Figure 105-15. Transurethral incision of the prostate. The incision is started at the ureteral orifice and carried through the bladder neck up to the verumontanum. This procedure is done bilaterally. (From Mebust WK. A review of TURP complications and the National Cooperative Study, lesson 24, volume VIII. AUA Update Series 1989: 189–90.)

Outcomes

Single-Cohort Studies. Compared with other BPH treatments, TUIP has generated less significant and rigorous research. Only a few large series exist, and they are primarily focused on few authors. In a rigorous study by [Sirls and colleagues \(1993\)](#), a small group of patients were rigorously evaluated with both subjective and objective measures to evaluate the procedure. UDS was routinely performed along with interviews and questionnaires in 41 patients. Data were reported only if patients were followed for a minimum of 12 months. Significant changes were seen in mean peak urinary flow (increased from 10 to 15 mL/sec) and Madsen-Iversen symptom scores (decreased from 12.5 to 6.9). The mean detrusor pressure at maximum flow decreased from 85 to 44 cm H₂O, which was significant statistically but left many patients remaining in the obstructed (29%) or equivocal (43%) classification by the Abrams-Griffiths nomogram. Additional subjective information was obtained by interview. Although no objective questionnaire was used to evaluate sexual function, only 11% of patients reported new retrograde ejaculation. In addition, only 67% of patients reported being overall satisfied with the procedure. In the large series published by [Orandi \(1985\)](#), 646 patients over a 15-year period were assessed. Although not randomized, many patients during that time underwent TURP, and some matching of results was attempted.

Comparative Studies

Transurethral Incision of the Prostate versus Transurethral Resection of the Prostate. The trials comparing TUIP and TURP are of generally poor methodologic quality, with nonuniformity prohibiting any large meta-analysis. Specifics on randomization are most notably missing. In addition, these trials sample a fairly homogeneous group of patients with small prostates. In a randomized study, [Jahson and colleagues \(1998\)](#) evaluated patient prostate volume primarily with DRE (TRUS in some circumstances). In those evaluated by TRUS the average prostate volume was less than 27 g in both groups. The findings are notable in that TURP took longer than TUIP and had a larger estimated blood loss but did provide a larger improvement in postoperative Q_{max}. Ten patients in the TUIP group required reoperation compared with only 3 in the TURP group ($P = .039$).

Another randomized study by [Tkocz and Prajsner \(2002\)](#) included only patients with a prostate volume less than 30 g by TRUS. The age range of included patients was 51 to 78 and assessment was made at 24 months. Whereas both groups had statistical improvements in AUASS, PdetQ_{max}, and Q_{max}, there was no significant difference between groups in these metrics. Retrograde ejaculation was seen in only 12% of the TUIP group compared with 32% of the TURP group, although it was unclear if this was a statistically significant difference.

The largest randomized series was published by [Soonawalla and Pardanani \(1992\)](#). This series excluded patients with glands larger than 30 g. Patients were randomized to either TURP ($n = 110$) or TUIP ($n = 110$); the TUIP group did have a small volume of prostate resected for histopathologic examination. A surprising number of patients (38 of 110) undergoing TURP received a blood transfusion. Peak flow rates were increased in both the TURP (157%) and TUIP (145%) groups.

A fairly recent analysis of randomized trials involving TUIP was published by [Lourenco and colleagues \(2010\)](#). They concluded that the available randomized trials were of “poor to moderate quality” and that in many comparisons only a few trials could be included because some trials did not report methods or results comprehensively enough. TURP had a more significant improvement in flow rates, but conclusions on changes in symptom scores could not be drawn from the data.

Complications

Intraoperative and Perioperative. Hemorrhage should be controlled quickly, although significant bleeding and transfusion are rare. If capsular perforation occurs (either intentionally as part of the procedure or because of an overly zealous incision), in general it can be treated with prolonged postoperative catheterization. In the series by [Orandi \(1985\)](#), 11% of patients had temporary urinary retention after TUIP. Significant hemorrhage was rare, with only

0.9% of patients requiring transfusion. The previously discussed analysis of RCTs ([Lourenco et al, 2010](#)) more confidently reported morbidity data. A higher rate of blood transfusion was found in TURP but was fueled by two studies with abnormally high rates of 35% ([Soonawalla and Pardanani, 1992](#)) and 80% ([Nielsen, 1988](#)).

Postoperative. Retrograde ejaculation is less of a concern with TUIP than with other forms of BPH treatment. Reported rates of retrograde ejaculation range from 0% to 37% but are likely to be toward the lower end of this range. The incidence of this complication is less likely with one incision ([Turner-Warwick, 1979](#)) but other reports came to the conclusion that two incisions did not increase the risk ([Hedlund and Ek, 1985](#)). When compared with TURP, TUIP had a lower risk of retrograde ejaculation (RR 0.54, $P < .001$) but a higher risk of reoperation (RR 2.40, $P < .01$). The risk of ED with either treatment was not different. In addition, the researchers found no difference between treatments with respect to urinary retention, urinary infection, stricture, or incontinence ([Lourenco et al, 2010](#)). In the [Orandi \(1987\)](#) series, 2.9% of patients developed urethral stricture, and a total of 9.6% required repeat prostatic surgery. In less than 1% of patients were complications of incontinence or bladder neck contracture encountered.

Summary. TUIP offers reasonable results in correctly selected patients. It does appear to have a lower risk of retrograde ejaculation compared with other treatment options, particularly TURP. The operation is of short duration and a minimal hospital stay is required. This treatment should be discouraged in a patient with a larger prostate gland but may be of benefit in patients particularly concerned about retrograde ejaculation.

KEY POINTS: NONLASER OPTIONS

- M-TURP is still an important treatment for LUTS and BPH but will continue to progress to B-TURP owing to the multiple improvements in the safety profile.
- MIST treatments such as TUNA and TUMT have been plagued by a high need for re-treatment and likely fill a role between medical management and more invasive and effective treatments for LUTS and BPH.
- TUIP is a reasonable treatment option in the carefully selected patient.

Laser Treatments

Laser treatment of BPH has been an increasingly common choice for urologist and patients. Over the last decade, laser technology has become more refined, leading to improved treatments and outcomes. The term *laser* was derived from the acronym for “light amplification by stimulated emission of radiation.” **Laser prostate treatments rely on the prostate interacting with the light energy and converting it to local thermal energy.** The volume of tissue that is heated by the laser depends on multiple variables including light scatter, reflection, and, most important, absorption. Initial laser technologies relied on tissue coagulation and were eventually abandoned in favor of lasers with a preference for vaporization. **The temperature to which the tissue is heated determines whether the tissue is vaporized or coagulated.** Below the vaporization temperature, the tissue proteins are denatured, leading to coagulative necrosis with delayed tissue death and sloughing. Vaporization occurs when the tissue is heated above the vaporization (boiling) temperature, which leads to intracellular water vaporization and quick tissue destruction.

The amount of tissue that is heated beyond a target temperature during laser treatment of the prostate is based on characteristics of the laser and tissue. Laser characteristics include the irradiation time and power along with delivery characteristics such as power intensity, beam angle, and spread. Tissue variables such as carbonization and light scatter affect tissue heating also and response to the applied energy. An appeal of the laser technologies is the ability to

allow for ambulatory or outpatient surgery or to mimic a more invasive treatment option with a minimally invasive approach (e.g., holmium enucleation replacing OP).

Several characteristics of lasers are discussed briefly here. The wavelength of the laser is the distance between the sinusoidal waves of the laser energy and is measured in nanometers. Energy of a laser is measured in joules and is the amount of work or heat that the laser produces. The laser power is measured in watts and is the amount of energy that the laser produces in a certain amount of time.

Laser Safety

The incorporation of laser energy into the operating room has allowed for many new techniques for the treatment of BPH. The ability to destroy tissue is important for prostate treatment, but when used errantly can lead to unintended consequences such as injury of the patient or operating room personnel. In particular, the human eye is at the highest risk for accidental exposure owing to lack of a protective layer (like the epidermis for most of the body).

The portion of the eye that is injured depends on the wavelength used. For lasers with a larger wavelength such as holmium or thulium lasers, the cornea is at greatest risk. The potassium-titanyl-phosphate (KTP), lithium-triborate (LBO), and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers are particularly dangerous because this wavelength is focused on the retina. The lens of the eye focuses this energy on the retina, causing an increased intensity of up to a factor of 100,000 (Donnell, 2014).

The regulation of the operating environment is standardized by the Occupational Safety and Health Administration (OSHA). **Lasers are classified by their inherent wavelength, maximum output power, and risk of damaging the eye or skin.** All the lasers used by urologists are Class 4 lasers (the highest classification) and can cause permanent eye damage from a variety of exposures including indirect beam contact.

The safe use of lasers in surgery should be done as part of a **culture of safety**. Appropriate OSHA-approved signage should be displayed outside the room so that personnel entering the room are aware of the use of lasers. Appropriate laser-rated protective eyewear should be worn by all persons in the operating room (including the patient) and should be accessible to those entering the room. Any windows or other portals for laser light to leave the operating room should be appropriately blocked to prevent the escape of laser light.

The laser technician or surgeon should review the laser before each case to inspect for any visible signs of damage, and all laser operators should have received appropriate training. Your institution likely has a laser safety officer who can be consulted with any questions regarding laser use or safety.

Holmium and Prostate Enucleation

Overview and Concept. The holmium:yttrium-aluminum-garnet (Ho:YAG) laser emits light at 2140 nm but has a pulsed instead of continuous energy emission. This wavelength is strongly absorbed by water (and water-rich tissues) and has an absorption length of 0.4 mm with excellent hemostatic properties (Kuntz, 2006). The light is easily transmitted along flexible quartz fibers and creates a high-energy density that leads to vaporization with a superficial coagulation zone. The heat from the tissue-fiber interaction is dissipated over a short distance (2 to 3 mm) and causes coagulation of small to medium-sized vessels.

Although this laser has many uses in urology, in general it is now used to precisely incise tissue when used for BPH treatment. Historically, the holmium laser was used also for holmium laser ablation of the prostate (HoLAP), but its hemostatic properties were found wanting when compared with other contemporary laser technologies. **Primarily it is now used to enucleate the prostate in a procedure named holmium laser enucleation of the prostate (HoLEP).** This procedure allows the surgeon to follow anatomic planes to enucleate entire lobes of the prostate. In general, these lobes are then pushed into the prostate with subsequent morcellation.

Holmium laser resection of the prostate (HoLRP) was the precursor procedure to HoLEP. In HoLRP, large sections of the prostate were cut away and pushed into the bladder for later retrieval. **However, with the incorporation of morcellation, the pieces resected could be larger (now entire lobes), and HoLRP fell out of favor for the more efficient HoLEP.** Laser enucleation represents the endoscopic response to open simple prostatectomy and is the most technically advanced for laser prostate surgery. Many reviews and meta-analyses of HoLEP make this the most rigorously analyzed laser technique (Gravas et al, 2011).

Although it is a treatment with excellent results, a difficult and exaggerated learning curve has consistently been seen in adopters of this technique. The enucleation of lobes is not without possible complication, but the morcellator requirement can lead to significant injury to the urinary bladder with catastrophic complications (bladder fibrosis, cystectomy, and need for urinary diversion).

Technique

Preoperative. This technique is probably not necessary for small glands (with many alternatives available) and may be more suitable for patients with a larger gland who would previously have undergone OP. Crossmatching of blood may not be necessary as a routine precaution for this procedure, but the urologist may be well advised to consider a preoperative type and screen for blood products. Antibiotics should be administered as described earlier for TURP. In general, HoLEP is done in a hospital (or outpatient surgery center) using regional or general anesthesia. Patients should be counseled that an overnight stay is expected, with catheter removal the next day.

Intraoperative. Both HoLRP and current HoLEP technology use the Ho:YAG laser generator. An end-firing 550-micron fiber is delivered through a continuous-flow laser resectoscope (usually 26 Fr in size). The laser resectoscope has a modification in which the inner sheath contains a fiber guide to stabilize and prevent fiber movement while in use. A 6-Fr open-ended catheter may also be used as a fiber guide when placed through the sheath. An offset lens of 30 degrees is used along with normal saline irrigation.

The HoLEP technique was initially described by the group from New Zealand led by Gilling (Fraundorfer and Gilling, 1998). The use of the morcellator modified the technique from the HoLRP to the HoLEP. Initially, the size of the pieces that could be removed from the prostate was limited to a size that was small enough to be retrieved through the modified resectoscope. With the addition of morcellation, larger pieces were able to be fragmented and removed, making enucleation possible. These whole prostate lobes were moved into the bladder after enucleation, with morcellation then commencing after the entire enucleation was complete.

An 80- or 100-W generator is used. In general, the power settings are 2.0 J at 50 Hz, giving the surgeon a total of 100 W. **The procedure begins with a bladder neck incision at the 5 and 7 o'clock positions.** These incisions are carried down to the surgical capsule, which is identified by its reflective fibers running longitudinally. This is an important distinction because the landmark will mark the depth for the remainder of the procedure. **The incisions are lengthened distally to just proximal to the verumontanum.** Incisions are widened laterally by following the surgical capsule to undermine the lateral lobes. This allows for improved visualization with a larger channel of irrigation influx to the bladder and sets up later steps in the case.

A transversely oriented incision is made between the distal aspects of the previously extended bladder neck incisions. This begins the undermining of the median lobe in a retrograde fashion. **The surgical capsule is followed as the median lobe is lifted off the capsule.** The beak of the scope may be used to retract the median lobe to improve visualization. This step is complete once the median lobe has been enucleated and advanced into the bladder. Care should be taken to not undermine the bladder during the latter portion of this step. **The incisions made at the distal aspects of the lateral lobes are now developed to enucleate the lateral lobes.** These incisions are developed laterally up the walls, once again following the surgical capsule. Initially this is

done circumferentially at the apex of the prostate and then carried proximally toward the bladder neck, separating the adenoma from the capsule. An incision at the 12 o'clock position is then made down to the capsule. The surgical capsule is now followed from both the inferior and 12 o'clock position until the entire lobe is free and can be moved into the bladder. The procedure is repeated on the other side and hemostasis is achieved using a defocused laser beam to coagulate any bleeding.

Morcellation is then used to remove the large adenoma pieces from the bladder; the morcellator digests these large pieces down to more manageable strips of tissue. A dedicated scope or nephroscope with a 5-mm working channel is used. The morcellator itself has two blades within a long hollow inner lumen. The bladder is distended to keep the bladder wall away from the morcellator's moving pieces. A foot-operated variable suction is applied to the morcellator to draw the adenoma pieces toward the morcellator. Once the pieces are engaged, the morcellator's guillotine action slices off fragments of tissue. These smaller fragments are able to be suctioned through the lumen of the morcellator. A unique complication of the morcellator is bladder injury, and the operator should be careful to stop suctioning if the blade engages the bladder mucosa. Small, residual fragments may be removed with the flow of irrigation through a resectoscope sheath or with a large-bore syringe.

An alternate technique of lobe fragmentation or "mushroom" technique involves leaving the lobes attached at a stalk and then resecting the lobes down into pieces suitable to come through the resectoscope (Hochreiter et al, 2002). A urethral catheter is then carefully placed after all the fragments have been removed. Of course, this technique allows for preservation of the tissue for histologic examination, and the morcellated pieces should be sent to the pathologist for examination. Additional hybrid holmium resection and enucleation techniques have been described that improve the learning curve and have decreased complication rates compared with traditional HoLEP (Helfand et al, 2010).

Postoperative. A minimum of an overnight hospital stay is generally accepted, and patients can expect to be discharged on the first postoperative day. In the absence of a definitive capsular perforation, the catheter can be removed first thing in the morning. If a large perforation has occurred, the catheter should be left for a few days and then removed in the clinic without further repercussions. Whereas most bladder injuries during morcellation are superficial and require no additional treatment, large extraperitoneal or intraperitoneal bladder injuries may require exploration and closure. Unless there is a large degree of extravasation of irrigant from an extraperitoneal injury, these can usually be managed conservatively with extended catheterization.

Outcomes

Single-Cohort Series. Large series of patients appeared quickly. One of the early adopters reported on 552 patients retrospectively in 2005. Elzayat and colleagues (2005b) found a 200% increase in Qmax to complement a 75% improvement in AUASS at 1 year. A short mean catheterization (1.4 days) and hospital stay (1.5 days) were also observed. Authors quickly reported on successful treatment of large glands, customarily removing more than 100 g at surgery (Moody and Lingeman, 2001). The ability to handle such large glands quickly made this a unique endoscopic treatment because most other technologies did not include gland sizes larger than 70 or 80 mL in studies. Studies looking at patients with AUR displayed the effectiveness of the treatment. In a study of patients with a mean volume of 670 mL urine drained at initial catheter placement, only 1.75% of patients were unable to void after surgery (Elzayat et al, 2005a). In another study of patients with urinary retention, all patients were able to void after surgery (Peterson et al, 2005).

Longer-term data continued to be encouraging. In a review of 118 cases by Elzayat and Elhilali (2007), objective data were available on only 26 patients at 6 years, but mean flow increased from 6.3 to 16.2 mL/sec and mean AUASS decreased from 17.3 to 5.6 ($P < .0001$ for both). The researchers observed that 8% of their first 50 patients required re-treatment but only 1.5% of the later 68

patients required re-treatment, hinting that a significant learning curve may be expected. Enucleated tissue weight and total energy used were increased in the latter group, possibly explaining the lower re-treatment needs. Krambeck and colleagues (2010a) reported on their data from 1065 HoLEP patients. Although the researchers had a mean follow-up of less than a year at 287 days (range 6 to 3571 days), they observed an increasing maximum flow and a decreasing AUASS when stratifying patients by time from procedure. This further solidified the long-term efficacy of the procedure.

The popularity of HoLEP has been hampered by concerns about a steep learning curve. This was evident in the analysis of the first 125 patients undergoing the procedure performed by a self-taught surgeon (Placer et al, 2009). In skilled hands, HoLEP can treat glands over 175 g with a reported outcome equivalent to OP with a low morbidity (Krambeck et al, 2010b), but it has been estimated that a self-taught trainee must perform at least 20 procedures on moderate-sized glands before being able to reliably reproduce high-quality results (El-Hakim and Elhilali, 2002).

An advantage of the HoLEP technique is that it appears that prostate size does not influence efficacy in a surgeon with experience in this technique. When researchers broke down prostate size into three groups with increasing size, they found that whereas mean resected tissue weight increased among groups, the groups all had immediate and profound changes in AUASS, flow rates, and residual volume. Complication rates were roughly equivalent, with only a slight increase in bleeding noted with increasing prostate size (Kuntz et al, 2004b).

Comparative Series

Holmium Laser Enucleation of the Prostate versus Transurethral Resection of the Prostate. A large RCT looking at HoLEP vs. M-TURP was initially composed of 200 urodynamically obstructed patients who were randomized to HoLEP or M-TURP. Results were released in two reports. Prostate volumes were measured by TRUS and were approximately 50 g in both groups, and patients had high PVRs (>200 mL in both groups). Follow-up was available out to 36 months; operative and 12-month statistics were published in the initial report. The researchers reported a significant decrease in hemoglobin (1.3 vs. 1.8 g/dL), catheterization time (27.6 vs. 43.4 hours), and hospital stay (53.3 vs. 85.8 hours) in an initial report (Kuntz et al, 2004a). Operative time was longer in the HoLEP group (94.6 vs. 73.8 minutes). Peak flow rates improved from 4.9 to 23.1 in the HoLEP group, and in the TURP group improved from 5.9 to 25.5, at 12 months without differences seen between groups. Residual volume in the HoLEP group was superior compared with TURP (4.8 vs. 16.7 mL at 6 months and 5.3 vs. 26.6 mL at 12 months), although with such low volumes that this is likely not clinically significant. AUASSs were in the low 20s in both groups preoperatively and 4.3 (HoLEP) and 5.5 (TURP) at 1 month. At 36-month assessment, PVR continued to be significantly lower in the HoLEP group (202 mL vs. 8.4 mL). The statistical difference between AUASSs was no longer present, but both groups had a very low score (2.7 for HoLEP, 3.3 for TURP). Flow rates were not different between groups and were over 27 mL/sec in both groups (Ahyai et al, 2007). Other RCTs have verified the increased operative time and decreased catheterization and hospital time (Tan et al, 2003; Montorsi et al, 2004).

The 7-year follow-up of Gilling's data was recently published (Gilling et al, 2012). Thirty-one of the initial 61 patients were included. Data from the initial operation were reviewed and are in agreement with the increased operating room time and prostate tissue weight removal. Catheterization (17.7 vs. 44.9 hours) and hospital time (27.6 vs. 49.9 hours) were once again lower for HoLEP vs. TURP. The researchers concluded that HoLEP is at least equivalent to TURP with regard to durability. In their data, 3 of the TURP patients required additional intervention for BPH (compared with none in the HoLEP group).

Multiple meta-analyses have been performed looking at RCTs of HoLEP vs. TURP. Lourenco and colleagues (2008) found increased rates of Qmax for HoLEP compared with TURP (weighted mean difference of 1.48 mL/sec). Symptom scores trended toward an

advantage for HoLEP but did not quite meet statistical significance. Lourenco and colleagues and the researchers who performed another meta-analysis (Tan et al, 2007) found shorter catheter and hospital times. With different RCTs included, the analysis of flow rates did not meet statistical significance in the latter review.

The most convincing data for the usefulness of HoLEP was published in the meta-analysis of RCTs by Ahyai and colleagues (2010). They concluded that operating room time was indeed increased, but that owing to the large weight of adenoma removed in studies, HoLEP and TURP have similar time efficiency (weight of adenoma removed versus operating room time). Catheter time was also found to be shorter in the HoLEP group. It is most interesting to note that statistical superiority in support of HoLEP was seen with regard to change in AUASS and Qmax. The authors concluded that HoLEP was the only endoscopic procedure that has shown superiority to TURP. For longer-term data, Cornu and colleagues (2014) analyzed results after 3 to 8 years post-procedure. Although data could be reliably drawn from only the two studies in the analysis, results still appear to favor HoLEP.

Holmium Laser Enucleation of the Prostate versus Open Prostatectomy. HoLEP is so effective in treating BPH that it has even been compared favorably with OP. Two randomized trials looked at the use of HoLEP versus OP in large glands. A study wherein all glands were greater than 70 g (mean size of 113 g in the HoLEP and 124 g in the OP groups) had a standard randomization (Naspro et al, 2006). The authors found decreases in time to catheter removal (4.1 vs. 1.5 days), patient in-hospital time (5.4 vs. 2.7 days), and risk of transfusion of blood (seven vs. two patients) for HoLEP. Operative time was shorter in the OP group (72 vs. 58 minutes), and this group had a larger weight of adenoma removed (87.9 vs. 59.3 g). Patients underwent repeat urodynamic assessment at 12 months and had uroflow and AUASS available out to 24 months. Comparable urodynamic improvements were seen in both OP and HoLEP groups. Qmax improved from 7.8 mL/sec in the HoLEP group to 26.6 mL/sec initially and 19.2 mL/sec at 2 years. The OP group initially voided at 8.3 mL/sec, which improved to 24.3 mL/sec at 1 month and 20.1 mL/sec at 2 years. **Between groups, there was no statistical difference in voiding rates at any time.** AUASS was also assessed for patients in both groups. Initial scores were high in both groups (20.11 in HoLEP and 21.6 in OP group), decreased to 6.9 and 4.7 at 1 month, and were 7.9 and 8.1 at 2 years in the HoLEP and OP groups, respectively. **There was no statistical difference at any time point in the AUASS between groups.** Five-year follow-up was available in another study looking at patients all with glands over 100 g (Kuntz et al, 2008). Once again, large changes were seen in AUASS with treatment. The HoLEP group AUASS decreased from 22.1 preoperatively to 2.3 at 1 year, with the OP group having a drop from 21.0 to 2.3; difference between groups was not statistically significant. Operative time was longer, but no patients received transfusion in the HoLEP group (compared with 13% in the OP group) and HoLEP patients had shorter lengths of hospitalization and catheterization. At 5 years, AUASS was 3 in both groups, demonstrating excellent durability for both of these treatment options. PVR and Qmax were not different between treatment groups. Bladder neck contractures and urethral strictures were noted in both groups, but there was no statistical difference in likelihood of these delayed complications or difference in requirements for intervention for complications.

Holmium Laser Enucleation of the Prostate in the Anticoagulated Patient. Tyson and Lerner (2009) looked at 13 patients continuing warfarin and 25 patients continuing aspirin during HoLEP compared with 39 controls. Groups were equivalent; there were no statistically significant differences in outcomes between the groups, and no patient received transfusion in the study. However, the average INR was 1.5 in the group on warfarin, with only two patients having an international normalized ratio (INR) above 2 in the study. Another study (Hochreiter et al, 2002) looking only at patients on warfarin found an average INR in the therapeutic range at 2.7 (range 2.1 to 3.9). These researchers examined 19 patients and compared with 137 controls using their "mushroom technique." No patients required blood transfusion,

but 2 patients in the warfarin group had clot retention that was managed conservatively with irrigation. Of patients in the therapeutic range of warfarin, only 2 patients even had hematuria postoperatively.

Complications

Intraoperative and Perioperative. Although the use of the morcellator has led to decreased operative times compared with HoLRP (Gilling et al, 1998), it does enable a unique complication in that morcellator-mediated bladder injury can occur. These injuries are usually superficial, but deeper and more significant injury is certainly possible because the morcellator engages tissue indiscriminately. Keeping a reasonable volume of irrigant in the bladder and a bloodless field may help visualization and reduce this risk. Reported ranges of these injuries vary widely, with one study reporting an 18.2% occurrence (Montorsi et al, 2004).

Another unique complication is the possibility of incomplete evacuation of the adenoma leading to postponed morcellation. This is usually caused by a malfunction of the morcellating device or poor hemostasis leading to obscured vision. During either enucleation or morcellation there is the possibility of injury to the ureteral orifice. This outcome has been examined in only a few series. The report of Shah and colleagues (2007) found a 2.1% chance of occurrence, whereas another series (Kuntz et al, 2004b) found that of the four such injuries that occurred, three were in the group with the largest prostates (>80 g).

Capsular perforation typically occurs as the resection is carried along in the plane between the prostate adenoma and the surgical capsule. Although carrying into the adenoma in this area will cause bleeding, an error to the other side will lead to capsular perforation. Many authors classify these perforations into categories including "threatened," "covered," or "free" and use the degree of perforation to guide management. In general, authors have managed complete or "free" capsular perforation with prolonged catheterization (a few days), with no change in management for other types of perforation. The incidence of this complication has been reported to be as high as 9.6% (Shah et al, 2007); another large review placed the incidence lower, at 1.5% (Kuo et al, 2003).

The overall risk of hemorrhage during HoLEP is fairly minimal. A defocused holmium laser beam can be used to control most bleeding, and conversion to another form of transurethral intervention is a rare event. It does appear that the risk of bleeding increases with increasing gland size, although the correlation was fairly weak. (Kuntz et al, 2004b). Bleeding is also well controlled by the hemostatic properties of the holmium laser. Some series have reported a transfusion rate as high as 1.7% after HoLEP (Shah et al, 2007), but data incorporated into the meta-analysis of Lourenco and colleagues (2008) found that HoLEP had a decreased RR of transfusion compared with TURP (RR 0.27).

Postoperative. Urinary urgency and other storage symptoms are a common finding after HoLEP and thought to be caused by the high amount of laser energy applied to the capsule during enucleation (Shah et al, 2007). In attempts to grade the severity of these symptoms, Larner and colleagues (2003) found that most patients characterized the symptoms as mild (defined as causing minimal bother). **Transient urinary incontinence** occurs with some frequency but usually resolves with time. In the study by Shah and colleagues (2007), 10.7% of patients reported initial incontinence; only 0.7% of the cohort maintained this complaint permanently. A similar pattern was seen in another large study in which 4.2% initially reported stress-type incontinence but only 0.5% had this complaint at the last visit before publication (Elzayat et al, 2005b). This condition may be avoided by careful incision at the 12 o'clock position with care to not incise distal to the verumontanum. The depth and length of the required incision may be mistaken by a more novice surgeon (Shah et al, 2007).

The incidence of **bladder neck contracture** is 0% to 3.2% (Shah et al, 2007); it appears more likely to occur in smaller prostates (Kuo et al, 2003). The surgeon may consider a prophylactic bladder neck incision in patients they deem at higher risk for this complication. **Urethral stricture** is a common finding, with studies reporting an incidence as high as 7% (Seki et al, 2003) and a more

recent meta-analysis finding a rate of 4.4% (Ahyai et al, 2010). The large-diameter instruments used during the procedure may predispose to this occurrence. Although the location of the stricture was not frequently reported, one group found this to occur more frequently at the meatus (Seki et al, 2003).

Retrograde ejaculation is a common finding after HoLEP. Two randomized trials found incidence rates of 75% and 78% (Briganti et al, 2006; Wilson et al, 2006). However, one of these trials found that changes in IIEF domains were minimal (Briganti et al, 2006).

Conclusion. HoLEP is an interesting treatment option overall. Although there are concerns about an exaggerated learning curve, results are comparable if not superior to those of TURP. Patients have a significantly decreased catheterization and hospital times. Whereas the time in the operating room is increased compared with TURP, many studies show equivalent efficiencies in tissue removal, offsetting the increased surgical time. In addition, it appears that re-intervention rates for BPH may be lower. Complication profiles show HoLEP to have a lower rate of transfusion and similar rates of bladder neck contracture and urethral stricture compared with TURP.

Prostate Ablation and Vaporization

Overview and Concept. The KTP- and LBO-labeled lasers are a derivative of the Nd:YAG laser. The 1064-nm wavelength Nd:YAG laser beam is passed through a KTP or LBO crystal that doubles the frequency of the light and decreases the wavelength to the desired 532 nm. **This wavelength is selectively absorbed by hemoglobin, which acts as an intravascular target for the light energy.** The improved energy density compared with the Nd:YAG laser leads to preferential vaporization, with the hemoglobin absorption improving hemostasis because a thin (0.2 mm) layer of coagulation would be created outside the area of vaporization. The laser energy freely moves through irrigating fluid without a loss of power.

The original KTP laser (GreenLight PVP [American Medical Systems]) used a 532-nm wavelength and was available in 80- and 100-W settings. The LBO laser (GreenLight HPS and XPS [American Medical Systems]) also uses a 532-nm wavelength like the KTP. This laser offered higher-energy 120-W (HPS) and 180-W (XPS) settings. This 180-W setting allows for even more efficacy in vaporization and coagulation (Malek et al, 2011). The 180-W fiber (MoXy Fiber [American Medical Systems]) also has improvements including a built-in water cooling system with automatic safety system that protects the fiber from overheating.

Although the Nd:YAG was originally thought to be the ideal laser fiber for treatment of BPH (Anson et al, 1993), the large amount of prostate sloughing that occurred after visual laser ablation of the prostate (VLAP) because of the extreme depth of laser penetration was later found to be undesirable. The delayed bulk prostate sloughing would often lead patients to develop intermittent voiding and urinary retention postoperatively. The failure to sufficiently vaporize tissue was evident in an in vivo canine study (Kabalin et al, 1995).

In general, VLAP used a larger wavelength laser than the currently used KTP or LBO but the technique was similar to the current technique. As the power of the laser improved, the term *ablation* gradually migrated to *vaporization* because of the immediate removal of tissue visualized during surgery as opposed to the delayed sloughing of tissue seen with ablation. An early canine study comparing the Nd:YAG with the KTP laser displayed the advantages of a laser system that favored vaporization over ablation and coagulation. In this small study, **KTP resulted in significant increases in defect size in the prostates, leaving a thin but effective layer of coagulated tissue** (Kuntzman et al, 1996). Unsurprisingly, as the power of the laser has increased, there have been corresponding improvements in the tissue vaporization (Kang et al, 2008; Malek et al, 2011; Rieken et al, 2013).

The advantage of the PVP technology is the combined vaporization and coagulation. While tissue volume is decreased by the

vaporization, coagulation leads to almost instantaneous hemostasis with closure of venous sinuses, reducing absorption of irrigation fluid.

Technique

Preoperative. A standard preoperative workup should be completed for PVP. Routine cystoscopy is not necessary unless there is a particular concern. Concurrent infection should be ruled out and treated before the operation. Many physicians advocate the use of TRUS to determine prostate size because they have a maximum prostate volume at which they will choose another treatment option instead of PVP. The knowledge of gland size also allows the physician to know the rough estimate of operative time to allow appropriate operating room scheduling. **Patients taking anticoagulation can be managed in many different ways before this procedure.** It is our preference to allow patients who are already on antiplatelet medications to continue these throughout the operative period. However, we do prefer that patients requiring ongoing warfarin therapy be bridged to heparin, which is stopped for the procedure.

Intraoperative. The laser fiber is a 600-micron side-firing probe with the energy produced by the fiber at a 70-degree angle to the fiber longitudinal axis. **Vaporization occurs by sweeping the fiber along the prostate parenchyma, sequentially vaporizing layers of the prostate from the inside out.** Vaporization of the prostate is complete when the capsule fibers are visible. **The distance between the laser fiber and prostate tissue (working distance) is important for many reasons and is often difficult to control for the vaporization novice.** A distance too close will lead to possible "contact vaporization" and resulting damage to the laser fiber. A distance too far will lead to inefficient energy use with more tissue coagulation (and a subsequent increase in postoperative storage symptoms). If in tight quarters, such as at the beginning of the case when the lateral lobes may still be in contact, lower power should be used. Tissue buildup on the fiber should be avoided because this leads to fiber degradation and possibly to shortened fiber life and further inefficiencies.

Management of the bladder neck is an important part of the procedure and is usually the first step. In general, we prefer to use a lower power setting (80 W) in this area. **The ureteral orifices should clearly be identified before beginning treatment of the bladder neck.** A single midline incision of the prostate or two incisions at the 5 and 7 o'clock positions allow for the bladder neck to spring open and level the prostate fossa with the trigone of the bladder. After this is complete, the laser fiber should be pointed in a medial or lateral direction to allow for visualization of the vaporization, which is often lost with vaporization straight posteriorly. In addition, any potential injury to the ureteral orifices should be minimized by orienting the laser beam laterally. Aggressive coagulation at the bladder neck should be avoided. We customarily do not vaporize the anterior portion of the prostate in this area to leave a rim of intact urothelium to prevent circumferential vaporization and possible bladder neck contracture. In patients concerned about retrograde ejaculation, incision of the bladder neck fibers should be avoided.

Movement of the fiber into position for vaporization should be done preferentially with a minimization of cystoscopic motion. A continuous, even motion of the sweeping action of the fiber is vital to minimize large and irregular crater formation in the prostate. Bleeding in a recessed portion of the prostate has the potential to be a significant problem because the vessels are unable to be visualized. The angle and time of the laser fiber sweeps are important factors. If the angle is changed too rapidly, insufficient energy will be transferred, leading to poor vaporization. However, if the laser beam is left on tissue for too long a time (slow sweep), a crater will be formed as the energy accumulates in one area. The sweep angle at which the fiber is turned is also an important factor. It may help the novice to imagine that the laser energy is like hot water on snow. Research from an in vitro study found that the most efficient vaporization occurred when the angle was between 15 and 30 degrees. The depth of coagulation was minimized at 30 degrees of sweep (Ko et al, 2012).

Bleeding is more frequently seen at the prostate apex, median lobe, and bladder neck (particularly at the posterolateral aspects where the blood supply of the prostate enters). If bleeding is not severe, the laser may proceed with caution, focusing on the areas directly adjacent to the bleeding vessel because this may allow for hemostatic control of the feeding areas. If pulsatile, arterial bleeding is recognized, the coagulation mode on the laser may be used. This should once again be used on the area around the bleeding along with the bleeding area itself.

If bleeding is unable to be controlled, a Bugbee electrode may be placed through the working bridge. This allows for the placement of pressure on the vessel to stop continued bleeding (improving visualization) and then controlled coagulation. The surgeon should keep in mind that the irrigating fluid will likely have to be changed to something nonionic. If all else fails, a larger sheath and possibly the resecting loop should be inserted to help control bleeding. Such need is markedly infrequent in experienced hands. When vaporization is complete and hemostasis is verified, the bladder should be examined one more time to ensure there is no erroneous laser damage. A catheter should then be placed and irrigation of the bladder should verify clear irrigant.

Throughout the procedure, the surgeon should be aware of inefficient vaporization. Large bubbles should be visible coming from the tissue throughout vaporization as an indication of efficient energy use. When this is not seen, the laser energy is being used inefficiently and most likely is causing coagulative necrosis or charring of the tissue. When the tissue is charred, the subsequent vaporization will be more challenging, leading to excessive energy use. Unnecessary coagulative necrosis should be avoided because this would lead to more pronounced postoperative dysuria and possible passing of tissue per urethra.

Postoperative. In almost all cases the catheter can be removed the day of or the day after surgery. Bleeding should be minimal in the postoperative period, although patients will customarily pass some tissue with minimal bleeding 7 to 10 days from the surgery date. In cases of minor but continued bleeding, patients can be encouraged to increase fluid intake with careful outpatient follow-up. It is our custom to discharge patients home the day of surgery, with them removing the catheter the next day at home.

Dysuria in the postoperative period is caused by technical inefficiency during the procedure as tissue is being coagulated more than vaporized. The degree of dysuria is correlated with the volume of coagulated tissue (Choi et al, 2008). Patient characteristics that may lead to a risk of dysuria include a large median lobe, previous prostatitis, dense or fibrous prostate tissue, or previous treatments that change prostate tissue characteristics (TUNA, TUMT). In general, sterile pyuria should be noted and can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) if severe. Although dysuria can be a common finding in these patients, the physician should always consider re-evaluation for an unexpected complication such as a tissue flap or retained fiber fragment. Even in the best vaporizations, a layer of coagulated tissue will remain that could potentially lead to a subacute prostatitis and an increased risk of UTI. If a true infection is suspected because of either prolonged dysuria or a positive urinalysis or culture, culture-directed antibiotic therapy should be initiated and culture should be repeated after completed therapy.

Outcomes. The rapid acceptance provided a considerable number of early studies looking at the outcomes of the lower-energy laser fibers. Because the manufacturer continues to update the laser power over time, long-term results have become more difficult to incorporate into practice; frequently a new power level is available as the research from the previous generation is being released. Overall, the PVP technology has been viewed to have a forgiving learning curve with a favorable safety profile.

Single-Cohort Studies. The first pilot study looking at the use of the 80-W KTP laser was published by Hai and Malek (2003). Ten patients were treated and then followed for a year. Significant improvements in AUASS, QoL score, Qmax, and PVR were noted initially with durability to a year. This was quickly followed by a multicenter trial study of 145 patients (Te et al, 2004). Once again,

improvements 12 months after the procedure were noted in AUASS (−82%), QoL score (−77%), Qmax (190%), and PVR (−78%).

The change in urodynamic parameters even with the 80-W laser was encouraging. In urodynamically obstructed patients who underwent PVP, a decrease in Schafer obstruction grade from 3.6 to 1.1 was noted at 12 months ($P < .0001$) with a decrease in PdetQmax from 75.0 to 36.6 cm H₂O (Hamann et al, 2008). The authors also found that the mean number of nighttime (3.5 to 1.2) and daytime (7.2 to 5.7) voids decreased with treatment.

Data became available on the 500 patients treated with the 80-W fiber in 2008 (Ruszat et al, 2008). With a mean follow-up of 30.6 months, the results of patients with 3 years of follow-up showed a mean AUASS of 8.0, QoL score of 1.3, and Qmax of 18.4 mL/sec, proving treatment durability. In patients with 5 years of data (only 5.4% of the cohort), there was not an appreciable difference in these numbers compared with the data at 3 years. The re-treatment rate of the cohort was 6.8%, with a rate of urethral strictures of 3.6% and 4.4% for bladder neck contracture. Dysuria and bladder neck contractures were more common in smaller glands, but larger glands did not lead to a higher risk of re-treatment. In another study evaluating the use of the 80-W laser in large prostates, re-intervention because of residual adenoma was 23% in the larger-gland (>80 mL) group compared with only 10.4% ($P = .09$) in the group with glands smaller than 80 mL (Pfitzenmaier et al, 2008).

As the improved hemostatic qualities of the laser were recognized, challenging patient populations were tested. Patients requiring anticoagulation were able to be safely treated (Sandhu et al, 2005). Although many of the other endoscopic treatments were not rigorously tested on large glands, the improved visualization during vaporization allowed many early adopters to attempt treatment of large glands (>80 g). The International GreenLight Users (IGLU) Group compiled some of the early data on 120-W laser treatment of patients both with large glands and undergoing anticoagulation (Woo et al, 2008). For all the studied patients there were improvements in Qmax, PVR, AUASS, and prostate volume compared with baseline. The use of anticoagulants did not significantly increase complications. Large glands did not alter outcomes beyond the expected larger change in prostate volume. A reduction of 52.5% was seen in larger glands compared with 42.3% in glands smaller than 80 mL ($P < .001$).

Retrospectively reviewed 3-year results of the 120-W HPS reported durability and indicators of response (Cho et al, 2012). Preoperative AUASS was 21.7 and reached a nadir of 11.5 at 6 months but was not statistically higher at 3 years (13.4). Maximum flow followed a similar pattern, improving to 15.7 mL/sec from 8.7 mL/sec at 6 months with a value of 13.9 mL/sec at 3 years. Predictors of response were reported as AUASS greater than 19, with even higher scores being more likely to respond. All voiding diary parameters were predictors under univariate analysis, but only nocturia remained a significant predictor when multivariate analyses were performed. Patients customarily underwent UDS, and the BOO index (BOOI) and bladder contractility index were predictors of a good outcome. Operative time and energy used during the procedure were not predictive. Another case series on the 120-W HPS was published almost concurrently. The authors reported on 75 patients at 36 months and found improvements of 60.2% in AUASS, 80.9% in QoL, 138.7% in Qmax, and 82.6% in PVR compared with baseline. The median prostate volume was reduced by 50.4% (Zang et al, 2012).

In one of the few large studies examining the 180-W XPS, data were collected prospectively from seven European centers accumulating a total of 201 patients (Bachmann et al, 2012). Mean follow-up was 5.8 months. Improvements were seen in AUASS (19.6 to 9.4), QoL score (3.9 to 1.4), Qmax (8.4 to 21.0 mL/sec), and PSA (5.5 to 2.0 ng/dL) at 6 months. These findings were considered analogous with previously published 120-W data by the authors. Impaired visibility because of bleeding was not influenced by active anticoagulation, but capsular perforation, a smaller gland, and preoperative catheterization were risk factors.

Comparative Studies. In one of the first RCTs comparing 80-W PVP with TURP, Bouchier-Hayes and colleagues (2006) compared the results of trainees who had performed between 35 and 325 TURPs but had done at most 5 laser prostatectomies. They exhibited comparable improvements in Qmax (149% for TURP, 167% for PVP) and AUASS (roughly 50% decreases in both groups). This study exhibited the relative ease of performing the procedure and went on to conclude that PVP was 22% cheaper than TURP primarily because of the shorter hospital stay. Another RCT comparing the 80-W PVP and TURP focused on patients with glands larger than 70 g (Horasanli et al, 2008). Operating time favored TURP, whereas time in the hospital and time with catheter favored PVP. Differences in the final AUASS, Qmax, and PVR favored TURP within the follow-up period. Blood transfusion was more common in the TURP group, whereas the PVP group had an increased risk of postoperative retention and need for re-intervention (17.9% in the first year). The summary of these results shows the excellent safety profile but decreased efficacy of the lower-energy PVP (especially in larger glands).

In an RCT comparing the 120-W HPS to TURP, Al-Ansari and colleagues (2010) found dramatic improvements in Qmax, AUASS, and PVR in both groups out to 36 months. TURP did outperform in many metrics (Qmax, AUASS, PVR, mean PSA, mean prostate volume), although the differences were not statistically significant. Although intraoperative complications were significantly fewer in PVP, a strikingly high 93% of patients experienced dysuria or urge and 11% required re-treatment for residual adenoma (compared with only 1.8% of the TURP group, $P = .001$). Mean catheterization and mean hospital stay did favor PVP. Another RCT looking at the HPS versus TURP was completed the following year (Capitán et al, 2011). Once again, similar improvements were seen in Qmax, AUASS, and QoL; however, these improvements appeared to be more rapid in the PVP group. It is interesting to note that the researchers further stratified the AUASS questionnaire and did not find an increase in storage symptoms for the PVP group. Intraoperative, early, and late complications did not differ between groups.

In their review of both 80- and 120-W PVPs in RCTs, Thangasamy and colleagues (2012) consistently found that catheterization and hospital stays were shorter in patients undergoing PVP by 1.91 and 2.13 days, respectively. Operative times were shorter in the TURP cohort by almost 20 minutes, with PVP having a risk ratio of 0.16 for blood transfusion compared with TURP. Other complications were not statistically different. In this group of mixed laser powers, six of the nine studies found no differences in functional outcomes. The one study that favored PVP was an 80-W study that never appeared to reach final publication. The two studies favoring TURP both specifically looked at patients with large prostates (>70 g) and had a laser power of 80 W. In their analysis of 120-W PVP, Cornu and colleagues (2014) found a decrease in catheter time (mean 23 hours) and length of stay in hospital (mean 1.84 days).

Few studies have reliably compared the new XPS and previous HPS systems. In a nonrandomized series of consecutive patients, Ben-Zvi and colleagues (2013) found that mean operating time and mean lasing time were decreased in the XPS group with comparable energy delivery. The significantly different reductions in PSA (54% in HPS vs. 79% in XPS, $P < .01$) show that the XPS surely has a higher efficiency of tissue vaporization, although notable clinical parameters (AUASS, QoL, Qmax, PVR) were not different between groups. Postoperative retention was higher in the HPS group (16% vs. 6%).

Use of Photoselective Vaporization of the Prostate in Anti-Coagulated Patients. A total of 116 men were included (36 on warfarin, 9 on clopidogrel, and 71 on aspirin), and all continued on their medications through the perioperative period while undergoing 80-W PVP. (Ruszat et al, 2007). These groups were compared with 92 controls who were not on anticoagulants or antiplatelet medications. The control group was younger and had a lower ASA class. The average INR was 2.0 (range 1.3 to 2.9), with 14 of the 36 patients on warfarin having an INR of 2 or less. No patients required transfusion, but patients in the study group did have an increased hospital time (3.8 days vs. 2.8) and were more likely to have CBI

for 24 hours (17% vs. 5%). In particular, patients with an INR greater than 2 required CBI postoperatively. Other studies have shown the same risk of transfusion in a group of patients on mixed forms of anticoagulants or antiplatelet medications (Sandhu et al, 2005). An uncontrolled study reporting on 43 patients continuing warfarin during surgery showed no patient requiring transfusion. Two patients did require prolonged catheterization subsequent to bleeding, but 70% of patients were discharged home within 24 hours of surgery (Woo and Hossack, 2011). A Cochrane review that compared laser treatment methods with TURP found an overall reduced risk of transfusion with laser prostatectomy (Hoffman et al, 2004). Based on the aforementioned evidence and our own clinical experience, we routinely perform PVP on patients on antiplatelet medications but prefer men on warfarin to bridge to heparin, with no anticoagulation given around the time of the surgery.

Complications

Intraoperative and Perioperative. Overall, the safety profile of the PVP technology is excellent. TUR syndrome is not reported in any series because normal saline is used as irrigation. Blood transfusion is exceedingly rare, and patients on anticoagulation do not appear to be at a significantly increased risk. PVP had a lower risk (OR 0.10) for perioperative blood transfusion when compared with M-TURP (Cornu et al, 2014). Capsular perforation has been reported with PVP with ranges of 0.2% to 1% of cases (Rieken et al, 2010). Some surgeons may find the visualization of the capsule more difficult with the PVP, particularly early in the learning curve. Maintaining a proper sweeping motion and serially removing tissue in a circumferential fashion will avoid irregularities in vaporization depth and avoid perforation. If capsular perforation occurs, increased bleeding is usually noted and conversion to TURP is more common (Bachmann et al, 2012). Although rates are largely unreported, ureteral orifice injury can occur from errant laser energy. The ureteral orifices should be identified before beginning the vaporization; taking care to not extend the fiber into the bladder when vaporizing the bladder neck should minimize the possibility of this occurring.

Postoperative. Postoperative dysuria and storage symptoms are fairly common after PVP. In large series examining these outcomes, the adverse events were usually self-limiting, resolving either spontaneously within 3 months or with the help of anti-inflammatories or antibiotics. The reported incidence of these symptoms ranges from 0% to 25.7% and is, in general, higher than data reported from TURP studies (Naspro et al, 2009). As stated earlier the inefficient use of laser energy should be minimized in an effort to decrease this risk to patients. In a small series of patients, Matoka and Averch (2007) found that preoperative finasteride use and lower preoperative AUASS were predictors of postoperative irritative symptoms.

Infectious complications may be more common after PVP owing to the necrotic tissue that occurs with coagulation. Epididymitis has been reported in 5% to 7% of patients; UTI has been reported in 1% to 20% of patients (Chughtai and Te, 2011). Treatment of these conditions may be more challenging because of the presence of the necrotic tissue and its ability to harbor and feed bacteria. The treating physician should consider longer courses of antibiotics in these patients.

Because the sheath used for PVP is typically smaller than those customarily used for TURP, the risk of urethral stricture should be lower. The surgeon should minimize movements of the sheath, with a preference for laser fiber movement to further lower this risk. Only 2.8% of patients had urethral stricture, and an RR of 0.65 was calculated compared with TURP (Thangasamy et al, 2012). A more recent meta-analysis did not verify this finding; comparable rates of stricture (and bladder neck contracture) were found between 120-W PVP and M-TURP (Cornu et al, 2014).

Reoperation rates specifically for residual adenoma vary significantly based on study type and laser power. In their summary of PVP technology, Gravas and colleagues (2011) compared the reoperation rates of 80-W KTP with TURP at different time frames. After 6 months the rates were 18% versus 0%; 10% versus 3.4% after 12 months; and 6.7% versus 3.9% after 24 months for PVP and TURP,

respectively. Other authors have found rates of 7.7% (Hai, 2009) and 6.8% (Ruszat et al, 2008) at 5 years, although both studies had high attrition rates. In an analysis of only 120-W studies, a slight increase in need for reoperation for residual BPH was found, but the authors commented on an overall small sample size (Cornu et al, 2014).

In the large XPS series by Bachmann and colleagues (2012), 10% of patients developed dysuria despite high laser energies used. Although it was a short-term study, incidence of re-treatment for residual adenoma was only 0.5% and of postoperative retention was only 2.8%. Temporary incontinence was observed, but fairly rarely (5.8%). At least partial conversion to TURP was influenced by prostate size; 2%, 6.5%, and 16% of resections required this in prostate volumes of below 40 mL, 40 to 80 mL, and more than 80 mL, respectively.

Changes in erectile function in patients undergoing PVP are still being more clearly elucidated; however, early results are encouraging. In 105 men undergoing PVP who completed the Sexual Health Inventory for Men (SHIM) preoperatively and 12 months after surgery, there was clearly no worsening of erectile function. In those men who were catheter free before surgery, statistically insignificant improvements were seen in erectile function (Kavoussi and Hermans, 2008). Mild but statistically significant improvements were noted in all IIEF-15 subdomains in a similarly structured trial of 45 men (Paick et al, 2007).

Conclusion. The early laser techniques focused on coagulation. More contemporary techniques use laser power to vaporize large portions of the prostate in an essentially bloodless field. While coagulation is still part of the laser vernacular, a de-emphasis on broad coagulation has resulted in reduced postoperative irritative symptoms with a preference for laser technology that chiefly leads to prostate vaporization.

The early and lower-power PVP technology appears to have been less efficient against larger prostate glands, with long operative times and high re-treatment rates. However, the excellent hemostasis and vaporization of PVP have allowed for the treatment of many challenging patients, such as those on anticoagulation, that has not been attempted with many other endoscopic modalities for treatment of BPH.

Thulium

Overview and Concept. The thulium:yttrium-aluminum-garnet (Tm:YAG) laser is a continuous wave of 2013-nm energy and has recently been introduced for the treatment of BPH. With a similar wavelength to the holmium laser, this energy undergoes absorption in the irrigant but without the intermittent nature of holmium. The continuous energy emission has been suggested to lead to a cleaner incision, and with a slightly shorter wavelength than holmium, absorption by tissue is theoretically more pronounced and efficient (Chung and Te, 2009). However, such claims are putative until scientific proof is offered. As the emitted wavelength reaches closer to the ideal in soft tissue, theoretically there will be a decrease in scattered thermal damage (Schomacker et al, 1991), which may lead to decreased scarring and stricture formation. However, in an animal model there was a wider thermal damage zone than predicted, similar to that seen with holmium (Fried and Murray, 2005).

Technique. As with other laser technologies, thulium may be used to either vaporize or incise tissue, although the early clinical use has been to incise tissue to enucleate the transition zone of the prostate. This technology has introduced a new technique wherein the prostatic lobes are “peeled” like a tangerine off the prostatic capsule (Xia, 2009). The anatomy followed during prostate enucleation with thulium is similar to that followed during HoLEP. The procedure is essentially analogous to HoLEP, including morcellator use when the surgeon selects this option.

Some authors have used a resection-type technique wherein multiple incisions are made in the prostate parenchyma down to the capsule. Smaller sections of prostate are then liberated from the capsule, leading to small prostate chips that can be irrigated through the resectoscope sheath. This eliminates the need for using the often

troubling morcellator. Catheter drainage is maintained at least overnight and can customarily be removed once hematuria has resolved (usually 1 to 3 days postoperatively). Patients can usually be discharged home the same day as catheter removal.

Outcomes

Single-Cohort Series. In an early retrospective review of the technology, 56 patients were reviewed (Szlaue et al, 2009). Maximum flow at day of discharge was improved from 8.1 mL/sec to 19.3 mL/sec, with a decrease in average residual urine to 57 mL from 151 mL. At a median follow-up of 9 months, PSA was reduced by 56% and the AUASS decreased from 19.8 to 8.6. The authors pointed out a slightly lower acquisition cost for the thulium compared with holmium. They did estimate that 56% to 70% of the tissue was removed by their “vaporesection” approach compared with the 30% to 85% for HoLEP.

Bach and colleagues (2010) reviewed patients who underwent enucleation and morcellation (“vapoenucleation”) with at least 12 months of follow-up. At 12 months, maximum urinary flow rate improved from 3.5 to 23.3 mL/sec (range of 6.6 to 47.9 mL/sec). AUASS decreased from 18.4 to 6.8, and QoL score improved from 4.6 to 1.5. Patients who had preoperative TRUS volume greater than 60 mL were not more likely to have improvements in voiding parameters.

In a study looking exclusively at patients with prostate volumes greater than 75 mL, with 70% having a volume greater than 100 mL, the AUASS decreased from 21.1 to 3.9, with a 248% increase in maximum flow. Mean prostate volume assessed by TRUS decreased from 108 to 13.8 mL. PSA had a similarly large decrease from 9.53 to 0.93 ng/dL, and IIEF score improved by 1 point with treatment (Iacono et al, 2012). Taken as a whole, the improvements seen with these thulium-based removals of the transition zone are largely equivalent to those seen with HoLEP.

Comparative Series

Thulium Resection versus Transurethral Resection of the Prostate. In a trial comparing standard M-TURP with thulium resection, 100 patients were randomized (Xia et al, 2008). Thulium treatment was superior with regard to catheterization time, hospital stay, and hemoglobin change with surgery. Treatment times were similar. Changes in symptom scoring and urodynamic findings had comparable changes; rates of late complications were also similar. A total of 158 patients were evenly randomized to receive either B-TURP or thulium enucleation in the report published by Yang and colleagues (2013). Operative time was 18 minutes longer in the thulium group, but significant decreases were noted in catheterization and hospital days with thulium resection. AUASS, QoL score, Qmax, and PVR had similar outcomes between groups even out to 18 months.

Tang and colleagues (2014) performed a systematic literature review and meta-analysis of studies comparing TURP and thulium resection. Both randomized and nonrandomized trials were included, along with both M-TURP and B-TURP. These researchers found a statistically significant longer operative time in the thulium group, although the clinical significance of the 9-minute weighted mean difference is likely inconsequential. Neither technique displayed consistent superiority with regard to AUASS, QoL score, PVR, or Qmax. The authors were also able to analyze complication rates and found decreased odds of receiving transfusion with thulium resection (OR 0.28, $P = .04$). Complications they deemed as “local,” including need for recatheterization, incontinence (stress or urge), UTI, and retrograde ejaculation, did not have significant differences between treatment options. Thulium did seem to display lower odds of developing urethral stricture (OR 0.29, $P = .007$).

Thulium Enucleation versus Holmium Laser Enucleation of the Prostate. A randomized comparison of thulium and holmium enucleation was published by Zhang and colleagues (2012). A total of 133 consecutive patients were randomized to a similar enucleation technique with the different fibers at a single center. Thulium required a longer operation time by approximately 10 minutes and had similar outcomes with regard to postoperative AUASS, Qmax, and PVR. PSA reductions were more modest than in most other enucleation studies (30% in the HoLEP group and 43% in

the thulium group) but were not statistically different when compared. Complications were sparsely reported, but there was no appreciable difference in catheterization times.

Complications

Intraoperative and Perioperative. The learning curve associated with thulium resection of the prostate has not been adequately studied, but it is safe to assume that it will be similar to that of HoLEP. Most studies did not report or did not have any intraoperative complications. In a study using the morcellator for evacuation of prostate lobes after enucleation, no patients experienced incomplete morcellation or ureteric orifice injuries, but 1.3% had bladder wall injuries caused by the morcellator (Iacono et al, 2012).

Postoperative. Early complications were analyzed by Bach and colleagues (2010), who defined rates of symptomatic UTI (6.8%), bleeding (5.6%), and immediate re-treatment for residual BPH (2.2%). Blood transfusion was required in 2.2% of patients. Mild storage symptoms were observed frequently (27%), but most resolved within 1 month of surgery. They found that with a cutoff prostate size of 60 mL there was no difference in rates of complications based on prostate size.

In one of the first thulium enucleation studies published, a prohibitively high reoperation rate of 10.7% was seen in the relatively short follow-up period (Szlaue et al, 2009). The most common was need for reoperation for residual prostate hyperplasia and was attributed primarily to the learning curve associated with the procedure because all of these occurred within the first 20 cases. The authors used a technique wherein the prostate is resected off the capsule in small pieces (vaporesection, not true enucleation) and commented that they felt the learning curve for this technique would be shorter than that for HoLEP.

In their series of large prostates (all greater than 75 mL) undergoing thulium resection, 2.7% of patients required early recatheterization after surgery. Continued postoperative hematuria resulted in 2.7% of patients requiring blood transfusion. Transient urge incontinence was noted in 6.7% of patients, but it had resolved in all at 1 year of follow-up. UTI was reported in 12.8% (Iacono et al, 2012).

Conclusions. Initial results from this new laser technology are encouraging. It appears that there is potentially an improvement in tissue removal rate compared with other technologies owing to the combined vaporization and incision that occurs with this technology. Theoretically it may have advantages compared with holmium enucleation with regard to tissue interaction, but certainly more populated and longer studies are required to evaluate this newcomer.

KEY POINTS: LASER TREATMENTS

- Laser treatments are the fastest growing option in treatment of LUTS and BPH but should be used as part of a culture of safety in the operating room.
- HoLEP is a very effective treatment option with excellent results that are often comparable to those historically seen with OP. There is a significant learning curve associated with the procedure, and catastrophic complications (mostly caused by the morcellator) have been observed.
- PVP is a growing and very safe treatment option for BPH and LUTS. Results in patients on anticoagulation have been encouraging.
- Thulium is the newest addition to the laser family and has some theoretical advantages, although scientific data are lacking.

Failed, Failing, and Future Directions


See the Expert Consult website for details.



CONCLUSION

Although OP and M-TURP had high complication rates, they did provide excellent treatment for the age-old problem of LUTS and BPH. Many new suitors have been introduced to the market in an effort to achieve maximum results with a more acceptable safety profile, but each new technology has led to previously unconsidered complications and new paradigms to consider. The trainee and even veteran urologist should be conscientious to carefully examine the results of each new treatment because new studies too frequently attempt to mislead or overstate their results by not including a rigorous design or adequately controlling for a placebo effect.

In reality, the gold standard operation for any patient is the one that meets his needs and expectations while still being safe. This decision should include a careful consideration of the patient factors, but the surgeon's familiarity with and ability to safely perform the selected procedure should also be factors.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com.



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Prostate Stents

Concept. The concept of placing a stent into the prostate for relief of infravesical obstruction has a long track record. Stents can be classified into many categories including temporary or permanent, epithelializing, or nonepithelializing. In general, the temporary varieties are used to combat the edema that accompanies many of the minimally invasive treatment options and are removed when the edema has resolved. Although previously used in a wide variety of patients, permanent stents have largely been relegated to use in older men with medical comorbidities that severely restrict their treatment options because of the inability to tolerate any level of anesthesia.

The mechanism of action of these prostatic stents is straightforward: The stent provides a rigid framework that, once in place in the prostatic fossa, pushes outward to open the prostatic lumen. In the epithelializing version, the stent is incorporated into the urethra as the urothelium grows into the stent, which should prevent encrustation or migration. Stents have been commonly used for treatment of the enlarged prostate; other indications wherein stents have been used in the urethra include the treatment of detrusor-sphincter dyssynergia (Chancellor et al, 1999; Chartier-Kastler et al, 2000; Gajewski et al, 2000), postbrachytherapy obstruction (Konety et al, 2000), and complications of radical prostatectomy (Meulen et al, 1991).

The no longer produced UroLume (American Medical Systems) was an epithelializing permanent stent that was made of alloy wire in a woven shape that could expand to 42 Fr within the prostatic urethra. It came in varying lengths, with a stent as short as 1.5 cm. Because of some of the shortcomings with this stent (e.g., incomplete epithelialization leading to encrustation, stent migration), second-generation stents were developed including the Memokath (Engineers and Doctors A/S, Hornbaek, Denmark). These spiral stents would expand when flushed with hot water, with a portion of them being secured at the prostatic apex.

Data. Initial clinical trials in the United States and Europe demonstrated efficacy in treatment of LUTS caused by BPH. In a study headed by Oesterling and colleagues (1994), patients were grouped into those with urinary retention and those without retention. In the nonretention group, 80 of the 95 patients were able to be evaluated at 12 months, and 52 had data available at 24 months. The Madsen symptom score decreased from a modest 14 to 5.9 and 5.4 at 12 and 24 months. The maximum urinary flow increased from 9.1 to 13.0 and 13.1 mL/sec, respectively. In the retention group, a mean Madsen symptom score of 6.1 was noted at 12 months. This group had a Qmax of 11.7 mL/sec at 1 year post-treatment.

The European equivalent of this study examined 135 healthy men, of whom roughly a third had retention (Guazzoni et al, 1994). In the nonretention group, the Madsen score decreased from 14.1 to 6.4 at 12 months; Qmax increased from 9.3 to 15.7 mL/sec. In the retention group, the mean symptom score was 4.5 after stent placement and the Qmax was 13.1 mL/sec.

Masood and colleagues (2004) reported on 62 men with follow-up of 12 years. A total of 47% of the stents were removed for a variety of reasons including malpositioning, migration, and patient dissatisfaction. Most (62%) of these removals occurred within the first 2 years after stent placement. The authors cautioned the use of careful case selection and surgeon experience.

In a review of results (Armitage et al, 2007) with the UroLume, of 176 men who could be identified as depending on catheterization before stent placement, 84% were able to void spontaneously after stent placement.

Perry and colleagues (2002) reported on the use of a Memokath stent in 211 men who were unfit for surgery; a reduction in AUASS of 59.6% was present at 3 months, with almost no change in the next 7 years. It is interesting to note that these frail older men were more likely to die with their stent in situ (38%) than to require removal (23%).

Conclusion. Although originally a popular procedure for men unfit for surgery, the clinical application broadened, but eventually the procedure was abandoned except as a palliative treatment or in

patients who are unable to tolerate any other procedure owing to medical comorbidities. The high failure and removal rates, with an often difficult removal, were overall prohibitive, especially compared with many other suitable options.

Prostate Urethral Lift

Concept. The prostatic urethral lift (PUL) is marketed under the name UroLift (NeoTract, Pleasanton, CA) and is a new treatment option for BPH that works by altering prostatic anatomy without ablating tissue. These permanent transprostatic implants take the forms of sutures that are delivered by a handheld device through a cystoscope to mechanically open the prostatic urethra by compressing the prostate parenchyma (Fig. 105-16). The sutures have T-shaped bars on the ends of the suture and are spring loaded and placed so that the bars are set with one outside the prostate and the other within the prostatic urethra lumen. The suture is placed on tension and once activated pulls the lumen of the prostatic urethra toward the capsule, opening the prostatic urethral lumen. The bar within the urethra is quickly covered by a re-epithelialized urethra so that the device is not exposed to the urinary tract for an extended period. In harvested tissue after implantation the biologic response to the implant was benign (Woo et al, 2011).

The particular advantages of this technology include the low rates of local symptoms along with a minimization of any impact on sexual factors such as ED and ejaculatory problems. Because

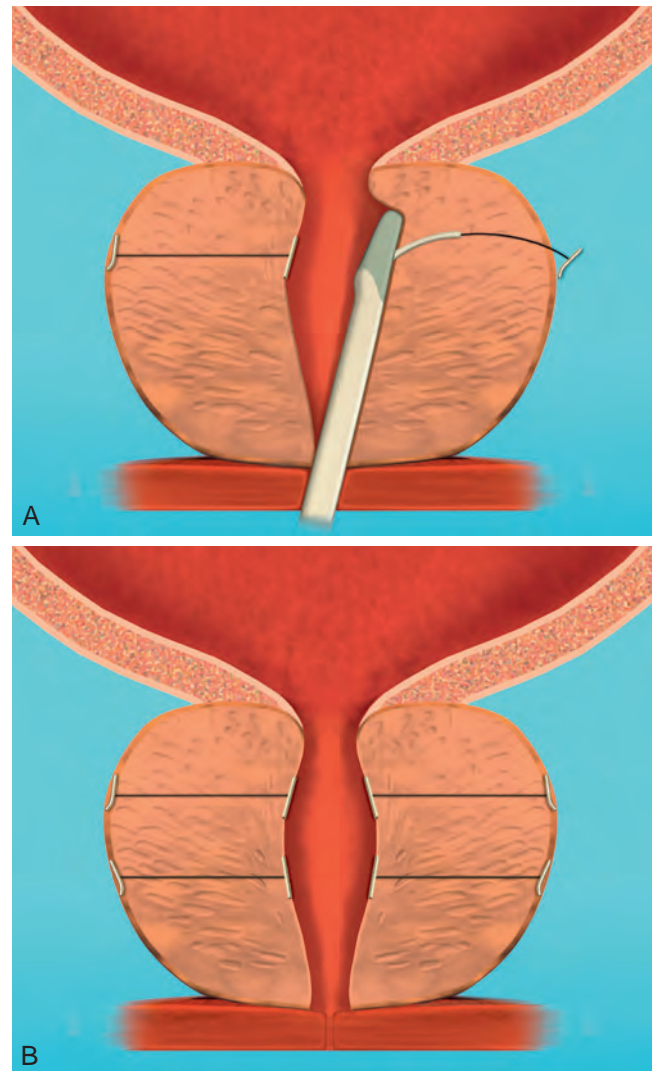


Figure 105-16. A and B, Placement of UroLift. (Courtesy NeoTract, Inc.)

the procedure is nonablative and the urethral mucosa largely stays intact, there should be a minimization of dysuria and other storage symptoms along with more severe complications such as bladder neck contracture and postoperative incontinence. The implants are placed anterolaterally in the prostate, so injury to the neurovascular bundles or dorsal venous complex should not occur (Fig. 105-17). The bladder neck is largely unaffected; therefore ejaculatory function should not be hindered.

The procedure is done through a rigid cystoscope sheath and can typically be done in the office setting with only local anesthesia. Overall, the procedure is well tolerated with minor and self-limited postoperative adverse events.

Data. A prospective, randomized trial evaluated a total of 206 men, with 140 undergoing PUL and 66 undergoing a sham procedure (Roehrborn et al, 2013). Unblinding occurred at 3 months after procedure; the study group was then followed to 1 year. The mean procedure time was 66 minutes. In the North American arm, 99% of the procedures were completed using local anesthesia. Patients in the PUL group experienced AUASS reduction from 22 at baseline to 18, 11, and 11 at 2 weeks, 3 months, and 12 months, respectively (all $P < .001$). Maximum flow rates in the PUL group were improved by 4.4 mL/sec at 3 months and 4.0 mL/sec at 1 year, which were both statistically significant compared with baseline.

In comparison of groups at 3 months, changes in AUASS in the treatment group were 88% greater than in the sham group ($P = .003$). Reductions were noted in both storage and voiding symptoms. No perioperative adverse events were recorded in either group, but procedure-related adverse events appeared to be more common in the PUL group, with the most common being dysuria (34%), hematuria (26%), and pelvic pain or discomfort (18%).

Further publication from this study group evaluated changes in sexual function (McVary et al, 2014a). There was no evidence of erectile or ejaculatory dysfunction after PUL, and questionnaire scores were modestly improved and statistically different from baseline at 1 year. Ejaculatory bother was most improved, with a 40% improvement seen compared with baseline. SHIM score was most improved in men with severe ED at baseline. This larger study verified the findings previously published in initial testing (Woo et al, 2012).

Durability at 2 years was demonstrated by Chin and colleagues (2012). They reported a 42% improvement in AUASS in patients evaluated at 2 years. Peak flow was improved at a minimum of 30% compared with baseline at all follow-up intervals.

Verdict. This is a promising new addition to the urologist's armamentarium. Theoretically it offers many advantages over many currently used BPH procedures. Despite ease and convenience, the

usefulness of the more minimally invasive options usually is limited by their long-term durability, with often unacceptable need for re-treatment. As long-term data become available from the initial trials, the urologic community will better understand the role of prostate urethral lift in the treatment of BPH.

Prostate Embolization

Concept. After the first reported case by DeMeritt and colleagues (2000), this procedure did not gain more widespread use until recently. In general, access is gained at one of the femoral arteries and pelvic angiography is performed to evaluate the iliac tree and prostatic arteries. Once the catheter has been advanced into the prostatic arteries, an embolizing agent (alcohol, microspheres) is then infused through the catheter until stasis is seen in the prostatic vessels. Although usually just one femoral access is gained, the procedure can be done on the prostatic vessels either unilaterally or bilaterally, although it appears the bilateral procedures incur better results (Bilhim et al, 2013).

As seen commonly with embolization of blood-rich organs (e.g., kidney), a postembolization syndrome of pain and fever is customary. As tissue is not directly removed or ablated, there should be minimal other local symptoms; however, gaining the access to the femoral vessels may lead to local problems at that area including pseudoaneurysm or bleeding (Stone and Campbell, 2012). In addition, intravascular contrast agents are used, making a contrast allergy a contraindication. The angiography needed during this procedure opens the patient up to a sometimes surprising radiation exposure.

Possible technical problems are the inability to access the prostatic arteries because of tortuosity, vessel atherosclerosis, or aberrant pelvic arterial anatomy. In the study by Bilhim and colleagues (2012), the prostatic artery was found to arise from five different arterial trunks, with the most common site being the internal pudendal artery (34%). In 43% of the patients, there were two prostatic arteries on one side. Anastomoses to adjacent arteries were commonly found.

Data. In one of the early, small published series, modest but statistically significant improvements in AUASS were seen (6.5 points, $P = .005$) at a mean follow-up of 7.9 months. Peak urinary flow increase was only 3.85 mL/sec ($P = .015$), with a reduction of 26% in PSA and 27% in prostate volume. The procedure was unable to be completed in 6.7% of patients, and 28.6% of patients met criteria for clinical failure. There was one major complication, which included an ischemic area of the bladder wall. Mean procedure time was 85 minutes (range 25 to 135), with patients undergoing a mean fluoroscopy exposure time of 35 minutes (range 15 to 45 minutes) (Pisco et al, 2011). After the learning curve has been overcome, one author estimated the procedure can routinely be done in 90 to 120 minutes (Carnevale and Antunes, 2013).

A total of 11 patients with urinary retention were studied by Antunes and colleagues (2013). Ten of the 11 patients were catheter free at a minimum follow-up of 1 year with a mean AUASS score at that time of 2.8 (range 1 to 7). UDS was performed before and after treatment. PdetQmax decreased from a mean of 85.7 to 51.5 cm H₂O. All patients had a BOOI of greater than 40 before treatment, with only 30% being clearly unobstructed (BOOI <20) and 40% characterized in the equivocal range (BOOI 20 to 40). Almost all patients reported mild, transitory pelvic pain; 3 patients had minor rectal bleeding.

In a trial done in the United States, 72 patients were screened and 20 met inclusion criteria. At 3 months post-procedure, a 49% reduction in AUASS was noted in the 13 patients supplying data. In patients with at least 6 months of follow-up ($n = 5$), prostate volume decreased by an average of 18%. The procedure lasted on average 72 minutes, with an average of 30 minutes of fluoroscopy time (Bagla et al, 2014). In another report, criteria for qualifying for the procedure allowed only approximately one third of patients seen in initial consultation to proceed (Pereira et al, 2012).

Later, larger series became available, although most data is concentrated from a small number of centers. A prospective study of

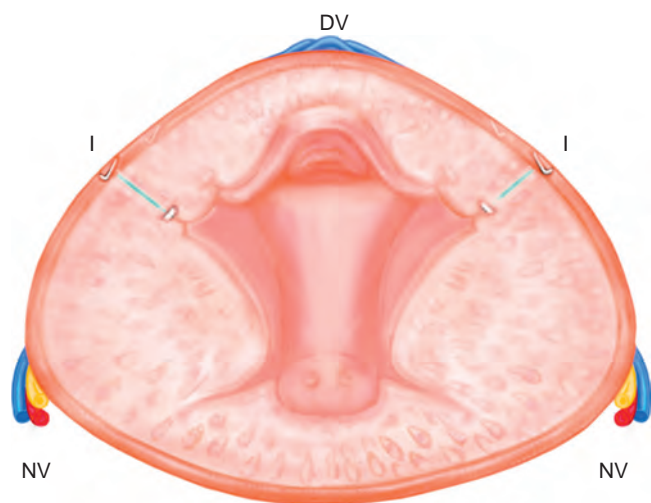


Figure 105-17. Placement of implants (I) in the anterolateral position in the prostate between the dorsal veins (DV) and neurovascular bundles (NV). (Courtesy NeoTract, Inc.)

255 patients was published by [Pisco and colleagues \(2013\)](#) recently. Technical success (defined as bilateral arterial occlusion) during the procedure occurred 97.9% of the time. The procedure itself was not painful in 76% of cases, with only one patient reporting severe pain during the procedure.

Clinical success was uniquely and capriciously defined as an improvement in AUASS of at least 25% of the initial score and a score lower than 18. Patients started with a large range of preprocedural AUASS scores (range 4 to 35) and had a mean prostate volume of 83.5 mL with a mean maximum flow of 9.2 mL/sec. Cumulative rates of clinical success were 82%, 81%, 78%, 75%, 72%, 72%, 72%, and 72% at 1, 3, 6, 12, 18, 24, 30, and 36 months, respectively. Clinical failure seen at 1 month had no direct correlation with the reduction in prostate volume; however, it appeared that failures were more common if only unilateral embolization occurred.

At 3 months, the mean AUASS was reduced by 54% and the QoL score by 49%. Over the same period, maximum flow improved by 35%, prostate volume shrunk by 18%, and IIEF score improved by 10.6%. In those patients with data at 1 year after the procedure, the absolute scores were not appreciably different than those at 3 months. Despite the fact that the urinary tract was not entered, 7.6% of patients received antibiotics for a UTI, although many of these patients were possibly infected at the time of the procedure. Other adverse events such as rectorrhagia (2.4%), AUR (2.4%), and hematospermia (0.4%) were transient in nature.

Verdict. A technically challenging and highly variable pelvic anatomy may limit the widespread acceptance of this technology, with only expert interventionists performing the procedure. Completed studies have largely been nonrigorously performed, and the application of the generated data makes it difficult to predict the role of prostate embolization in the treatment of LUTS and BPH. The many problems with these embolization reports include (1) a reliance on imaging-based reduction in prostate volume, (2) naive prostatic-centric concepts of BPH, (3) lack of control patients, (4) an unconventional definition of clinical improvement, (5) uniform failure to account for a placebo effect, thus leading one to assume that the improvement in LUTS or other outcomes were related to prostatic embolization (intervention effect remains unknown), and (6) ignoring LUTS as the motivating complaint and the ultimate arbitrator of success.

Prostatic Injections

Concept. References to intraprostatic injection for management of prostate disease date back more than 100 years ([Plante et al, 2004](#)). The ease of application and overall low start-up costs make this an attractive option. An injectable is commonly administered via a transperineal or transurethral approach into the prostatic parenchyma, with the injected substance theoretically causing localized changes to reduce prostate volume.

A wide variety of solutions have been tried in animal models. Agents reported to have been used in human studies include acid mixtures ([Talwar and Pande, 1966](#)), pepsin-iodine concoctions ([Payr, 1936](#)), ethanol, and now botulinum neurotoxin type A (BoNTA). Historically, anhydrous ethanol was the most widely studied injectable, but BoNTA has been more widely studied in the last few years.

Data

Anhydrous Ethanol. Anhydrous ethanol treatments of the prostate for LUTS and BPH have been primarily studied in non-U.S. markets. Investigative trials are underway in the United States to allow ethanol to formally gain FDA approval for the use in the prostate ([Plante et al, 2007](#)). Although the mechanism of action with human prostate cells is not entirely delineated, it is likely that there are proapoptotic mechanisms that are induced ([Plante et al, 2013](#)). Other possible mechanisms include hemorrhagic coagulation necrosis caused by vessel thrombosis and occlusion ([Goya et al, 1999](#)).

In a study of 35 patients with a mean follow-up of 50 months (range 47 to 56 months), initial significant changes were noted in

AUASS (−75%), Qmax (+247%), and prostate volume (−30%) at 3 months ([Sakr et al, 2009](#)). At 4-year follow-up, 25 of the initial 35 patients had data for reporting; improvements compared with pre-injection data were 55% in AUASS, 187% in Qmax, and 5.2% in prostate volume. Nine patients (26% of the initial cohort) required some form of re-treatment (TURP, reinjection, or medical therapy) during the study period. In a study with a long follow-up but a high attrition rate, 23% of patients required alternative treatment ([El-Husseiny et al, 2011](#)).

In 36 patients followed to 1 year after treatment, AUASS (46% reduction) and QoL scores (48% reduction) were significantly decreased at last visit. Maximum flow improved throughout the study period, with improvements significant at 3 months (78%), 6 months (137%), and 12 months (154%). Reports on potential nonresponders and patients needing re-treatment were not included, and it was unclear if these were consecutive patients ([Magno et al, 2008](#)).

In a phase I/II trial evaluating varying doses of ethanol injection, the most common reported adverse events were hematuria (42%), irritative voiding symptoms (39%), pain and discomfort (28%), and transient urinary retention (22%) when absolute reporting was used ([Plante et al, 2007](#)). However, when stratified to AUA guidelines, these percentages were 0%, 2.7%, 5.4%, and 16.2%, respectively. Patients were randomized to a low, medium, or high dose adjusted for prostate size and had a roughly 50% decrease in AUASS and QoL scores across doses. Injection was done transurethrally; the average procedure lasted 25 minutes. Moderate or severe pain during the procedure was reported by 6.7% and 12.2% of patients, respectively.

Botulinum Toxin. BoNTA is produced by *Clostridium botulinum* and has an already established use in urology for the care of patients with neurogenic voiding dysfunction. Although the exact mechanism to improve voiding when injected into the prostate is not completely understood, this exotoxin may have influence over both the static and dynamic components of BPH ([Chuang et al, 2006a](#)). In a placebo-controlled animal study, male rats 1 week after BoNTA injection were noted to have an increase in apoptotic cells with decreases in proliferative cells and the α_{1A} receptor. No significant change was noted in the presence of the androgen receptor. In rats killed 2 weeks after injection, these effects were less notable ([Chuang et al, 2006b](#)). This validated an earlier study wherein BoNTA injection led to a generalized apoptotic atrophy of the rat prostate thought to be caused by denervation ([Doggweiler et al, 1998](#)). In an interestingly designed study, [Silva and colleagues \(2009\)](#) concluded that BoNTA induced prostate atrophy in the rat that could have been the result of sympathetic nerve impairment, with the data indirectly suggesting that sympathetic neural drive played a role in prostate size regulation.

A dose response was established by [Lin and colleagues \(2007\)](#), who studied the effects of two doses of BoNTA (100 U and 200 U) on prostatic contractile function and structural changes. The higher dose produced a more pronounced atrophic change in the smooth muscles cells of the dog prostate. Under electrostimulation, prostate urethral pressure response was statistically lower in only the 200-U group.

A placebo-controlled trial in humans found a 65% reduction in AUASS at 2 months after injection. PSA was reduced by 51% and prostate volume was reduced by 68% compared with baseline, corroborating the findings of induced cell atrophy seen in animal studies ([Maria et al, 2003](#)). Of the 15 patients receiving BoNTA injection, 13 noted improvements in voiding. No patients in the placebo group experienced benefits from saline injection. Four control group patients later received BoNTA, with 17 patients having longer follow-up data. Reductions in AUASS, serum PSA, peak flow rate, and prostate volume appeared durable at 1 year.

In a cohort of 60 patients with a prostate volume of over 60 mL with an unsatisfactory response to combination medical therapy, 30 were randomized to BoNTA injection ([Kuo et al, 2009](#)). Although injection did reduce prostate volume and improve AUASS and QoL scores, the long-term therapeutic benefits were minimal compared with the control group. At 6 and 12 months after injection, only

the QoL score in the study group was statistically different than in the group continuing combination therapy. At the end of the study, 3 patients in the treatment group and 2 patients in the control group progressed to TURP for relief of LUTS. Surprisingly, despite not receiving any placebo drug or sham procedure, the control group had statistically significant improvements in AUASS, QoL scores, and prostate volume at 6 and 12 months.

A phase II dose-ranging placebo-controlled RCT was published in 2013 (Marberger et al, 2013). Significant improvements from baseline values were found in AUASS, maximum flow, and prostate volume at 12 weeks in all groups (including normal saline placebo). No significant differences were found between the doses of BoNTA and placebo. Adverse events were comparable across study groups.

A multicenter, double-blind, sham-controlled study verified these results and included 315 patients (McVary et al, 2014b). Whereas decreases in AUASS were seen in both the BoNTA (−6.3) and placebo (−5.6) groups, there was no difference between BoNTA and placebo. The authors concluded that although the treatments

were well tolerated, no increased efficacy was seen with BoNTA over saline injection.

Verdict. Anhydrous ethanol will still need to gain FDA drug approval in the United States before widespread acceptance. The low start-up cost and relative ease of delivery compared with other BPH treatment options will likely make this a very successful treatment option in developing nations and areas with otherwise sparse urologic care. Full acceptance in developing nations will likely depend on the comparative clinical efficacy. Re-treatment rates from preliminary reports appear to be prohibitively high for widespread acceptance in areas with a diversity of treatment options.

BoNTA is a new treatment option with an already established record for use in urology. Although the exact mechanism of action is still debatable, published results continue to help us further understand the importance of neural input to the prostate. Data from RCTs have provided unexceptional results with unexpectedly positive control group effects.

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Indications for Simple Prostatectomy

Preoperative Evaluation

Operating Day Preparation

Surgical Technique

Postoperative Management

Complications

Summary

The treatment options for bladder outlet obstruction resulting from benign prostatic hyperplasia have been expanded dramatically over the past 2 decades with the development of medical and minimally invasive therapies. The current medical therapies for lower urinary tract symptoms include selective long-acting α_1 -adrenergic antagonists, such as terazosin (Hytrin) (Lepor, 1995; Roehrborn et al, 1996), doxazosin (Cardura) (Gillenwater et al, 1995), tamsulosin (Flomax) (Abrams et al, 1995), and alfuzosin (Uroxatral) (Jardin et al, 1991; Buzelin et al, 1997), and the 5 α -reductase blockers, such as finasteride (Proscar) (Gormley et al, 1992; Andersen et al, 1995; Lepor et al, 1996), and dutasteride (Avodart) (Roehrborn et al, 2002, 2004). Minimally invasive procedures include visual laser ablation of the prostate (Cowles et al, 1995), transurethral electrovaporization of the prostate (Kaplan et al, 1996), transurethral needle ablation (Schulman et al, 1993; Campo et al, 1997), transurethral microwave thermotherapy (Ogden et al, 1993; Javle et al, 1996), interstitial laser coagulation (Muschter and Hofstetter, 1995), bipolar transurethral resection of the prostate (bipolar TURP) (Botto et al, 2001; Eaton and Francis, 2002), and transurethral incision of the prostate (Cornford et al, 1997). However, these approaches are usually reserved for men with moderate symptoms and a small- to medium-sized prostate gland (Reich et al, 2006). For larger prostate glands, open simple prostatectomy has been frequently performed. Lately, holmium laser enucleation of the prostate (HoLEP) with the holmium:yttrium-aluminum-garnet (Ho:YAG) laser has been performed as a minimally invasive alternative to open surgery (Gilling et al, 1998). However, the learning curve with HoLEP is considered steep (Razzak, 2013). Most recently, as urologists have gained experience in minimally invasive therapy, a simple prostatectomy has been performed more frequently using a laparoscopic or robotic approach (Sotelo et al, 2005, 2008). This chapter describes simple prostatectomy technique using an open and robot-assisted laparoscopic approach.

For patients with acute urinary retention, persistent or recurrent urinary tract infections (UTIs), severe hemorrhage from the prostate, bladder calculi, severe symptoms unresponsive to medical therapy, and/or renal insufficiency as a result of chronic bladder outlet obstruction, TURP or simple prostatectomy is indicated. When compared with TURP, simple prostatectomy offers the advantages of lower re-treatment rate and more complete removal of the prostatic adenoma under direct vision and avoids the risk for dilutional hyponatremia (the TUR syndrome) that occurs in approximately 2% of patients undergoing a traditional monopolar TURP (Mebust et al, 1989; Roos et al, 1989). Several contemporary series have demonstrated objective improvement in urinary

symptoms after simple prostatectomy (Tubaro et al, 2001; Gacci et al, 2003; Varkarakis et al, 2004). The disadvantages of open simple prostatectomy, compared with those of TURP, include the need for a lower midline incision and a resultant longer hospitalization and convalescence period. There also may be an increased potential for perioperative hemorrhage (Serretta et al, 2002). However, robot-assisted laparoscopic simple prostatectomy results in a significantly decreased risk for perioperative hemorrhage and transfusion (Clavijo et al, 2013).

Open simple prostatectomy can be performed by either the retropubic or the suprapubic approach. In retropubic prostatectomy the enucleation of the hyperplastic prostatic adenoma is achieved through a direct incision of the anterior prostatic pseudocapsule. This approach to open simple prostatectomy was popularized by Terrence Millin (1945), who reported the results of the procedure on 20 patients in *The Lancet* in 1945. The advantages of this procedure over the suprapubic approach are (1) excellent anatomic exposure of the prostate, (2) direct visualization of the prostatic adenoma during enucleation to ensure complete removal, (3) precise transection of the urethra distally to preserve urinary continence, (4) clear and immediate visualization of the prostatic fossa after enucleation to control bleeding, and (5) minimal to no surgical trauma to the urinary bladder. The disadvantage of the retropubic approach, as compared with the suprapubic prostatectomy, is that direct access to the bladder is not achieved. This may be important when one considers excising a concomitant bladder diverticulum or removing bladder calculi. The suprapubic approach also may be the preferred method when the obstructive prostatic enlargement includes a large intravesical median lobe.

Suprapubic prostatectomy, or transvesical prostatectomy, consists of the enucleation of the hyperplastic prostatic adenoma through an extraperitoneal incision of the lower anterior bladder wall. This approach to open prostatectomy was first performed by Eugene Fuller in New York in 1894; it was later popularized by Peter Freyer in London, England, who described the procedure in 1900 and later reported the results of his first 1000 patients in 1912 (Freyer, 1900, 1912). The major advantage of this suprapubic procedure over the retropubic approach is that it allows direct visualization of the bladder neck and bladder mucosa. As a result, this operation is ideally suited for patients with (1) a large median lobe protruding into the bladder, (2) a clinically significant bladder diverticulum, or (3) large bladder calculi. It also may be preferable for obese men, in whom it is difficult to gain direct access to the prostatic pseudocapsule and dorsal vein complex (Culp, 1975). The disadvantage, compared with the retropubic approach, is that direct visualization of the apical prostatic

adenoma is reduced. Furthermore, hemostasis may be more difficult because of inadequate visualization of the entire prostatic fossa after enucleation.

Since the performance of the initial laparoscopic radical prostatectomy in 1997 (Schuessler et al, 1997) and the introduction of the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) in 2000, the minimally invasive approach, especially the robotic approach, for radical prostatectomy has gained wide popularity. As urologic surgeons gain more experience with the robotic instruments, the robot-assisted laparoscopic simple prostatectomy has been gradually gaining acceptance (Sotelo et al, 2008; Yuh et al, 2008; John et al, 2009). The major advantages of the robot-assisted laparoscopic simple prostatectomy approach over the open approaches are excellent hemostasis, negligible need for transfusion, shorter hospital stay, and better visualization because of pneumoperitoneum and magnification (Matei et al, 2012). This approach also can manage a large median lobe, bladder diverticulum, or large bladder stones. The disadvantages of robot-assisted laparoscopic simple prostatectomy, compared with the open approaches, include the need for a general anesthesia, a steep learning curve, and a longer operative time, especially in the initial experience (Matei et al, 2012). Therefore the robotic simple prostatectomy approach should be considered by urologic surgeons who have extensive experience in robotic surgery, especially in robot-assisted laparoscopic radical prostatectomy.

INDICATIONS FOR SIMPLE PROSTATECTOMY

The indications for prostatectomy, by either open or laparoscopic approach or transurethral resection, include (1) acute urinary retention; (2) recurrent or persistent UTIs; (3) significant symptoms from bladder outlet obstruction not responsive to medical therapy; (4) recurrent gross hematuria of prostatic origin; (5) pathophysiologic changes of the kidneys, ureters, or bladder secondary to prostatic obstruction; and (6) bladder calculi secondary to obstruction.

Simple prostatectomy should be considered when the obstructive tissue is estimated to weigh more than 75 g. If sizable bladder diverticula justify removal, suprapubic or robotic prostatectomy and diverticulectomy should be performed concurrently. If the prostatectomy is performed without the diverticulectomy, incomplete emptying of the bladder diverticulum and subsequent, persistent infection may occur. Large bladder calculi that are not amenable to easy transurethral fragmentation also may be removed during the procedure. Simple prostatectomy should be considered when a patient presents with ankylosis of the hip or other orthopedic conditions that prevent proper positioning for TURP. Also, it may be wise to perform a simple prostatectomy in men with recurrent or complex urethral conditions, such as urethral stricture or previous hypospadias repair, to avoid the urethral trauma associated with TURP. Finally, the association of an inguinal hernia with an enlarged prostate suggests a simple procedure, because the hernia may be repaired by the same lower abdominal incision (Schlegel and Walsh, 1987; Brunocilla et al, 2005) or laparoscopically/robotically (Do et al, 2011; Nakamura et al, 2011).

Contraindications to simple prostatectomy include a small fibrous gland, the presence of significant prostate cancer, and previous prostatectomy or pelvic surgery that may obliterate access to the prostate gland.

PREOPERATIVE EVALUATION

In deciding whether to perform a simple prostatectomy for symptomatic obstruction resulting from benign prostatic hyperplasia, it may be necessary to consider the upper and lower urinary tracts. Usually the patient will have already completed the International Prostate Symptom Score (IPSS) questionnaire and had a peak urinary flow rate determination. The postvoid residual urine volume

also may have been verified with abdominal ultrasonography. A cystoscopic examination is not indicated in the routine evaluation of a patient with obstructive voiding symptoms (McConnell et al, 1994). However, cystoscopy should be performed in men with hematuria, suspected urethral stricture, and bladder calculus or diverticulum. It also can be helpful in confirming the presence of a large median lobe or in assessing the length of the prostatic urethra.

Before performing a simple prostatectomy the presence of significant prostate cancer should be determined. All men should undergo a digital rectal examination and have a serum prostate-specific antigen determination. If the digital rectal examination detects induration or nodularity, or the serum prostate-specific antigen level is elevated, a transrectal ultrasound-guided biopsy of the prostate gland should be performed. Men participating in an active surveillance program for a very low-risk prostate cancer may consider a simple prostatectomy for symptomatic obstruction if he clearly understands the potential risks and benefits of the surgery. Transrectal ultrasonography, by itself, is not indicated as a first-line diagnostic test for evaluating the prostate gland to detect early, curable prostate cancer. However, it can be useful in determining prostate size.

The upper urinary tracts should be evaluated preoperatively in men with known renal disease, abnormal renal function, recurrent UTI, or hematuria. This can be accomplished by computed tomography in patients with normal renal function or by renal ultrasonography in men with compromised renal function.

Before surgery the patient should undergo a complete medical evaluation consisting of a detailed history, thorough physical examination, and appropriate laboratory assessment. Most patients will be of an age with an increased risk for cardiovascular and pulmonary disease, hypertension, diabetes mellitus, and other medical conditions. All abnormalities uncovered in this evaluation should be addressed. The patient's medications should be reviewed, and attention should be given to the agents such as aspirin and nonsteroidal anti-inflammatory agents that can contribute to perioperative bleeding. **These medications should be discontinued and therapeutic anticoagulation reversed before surgery.** In addition, a chest radiograph, electrocardiogram, routine electrolyte studies, coagulation studies, and a complete blood cell count are usually required for these patients before surgery.

Men in urinary retention should have an evaluation of renal function. If the serum creatinine value is elevated, surgery should be delayed until this parameter stabilizes. Urinalysis is performed to rule out a UTI; and, if an infection is suspected, a urine specimen should be sent for culture and sensitivity. If an infection is present, appropriate antimicrobial therapy must be instituted before surgery to prevent urinary sepsis (Serretta et al, 2002).

Historically, 3% to 10% of men undergoing an open simple prostatectomy will require one or more units of blood in the perioperative period (Serretta et al, 2002; Varkarakis et al, 2004; Zaragooshi, 2007). Thus it may be prudent to have 1 or 2 units of blood available intraoperatively for an open approach. For a robot-assisted laparoscopic simple prostatectomy approach, type and screen is sufficient.

Finally, the patient must be informed of the benefits and risks associated with simple prostatectomy and written informed consent obtained. The benefit to be achieved is improved urination. Potential risks include urinary incontinence, erectile dysfunction, retrograde ejaculation, UTI, injury to adjacent structures, bladder neck contracture, urethral stricture, and the need for a blood transfusion. Other potential untoward effects include deep vein thrombosis and pulmonary embolus. For robotic or laparoscopic approach, open conversion also should be listed as a rare, yet potential, risk.

OPERATING DAY PREPARATION

The patient is placed on a clear liquid diet for a day before the procedure and self-administers an oral bowel preparation the day

before the surgery. He is kept without oral intake after midnight and self-administers a Fleet enema the morning of surgery. The type of the anesthesia to be used and the risks associated with it are discussed and finalized with the patient and his family in conjunction with the anesthesiologist. One dose of a second-generation cephalosporin is administered before making the incision. Compression stockings and sequential compression devices in the lower extremities are used to minimize the risk for deep vein thrombosis.

SURGICAL TECHNIQUE

Anesthesia

The preferred anesthesia is general endotracheal anesthesia. Spinal or epidural anesthesia may be used only in an open approach when there is a medical or anatomic contraindication to general anesthesia or when the patient simply prefers regional anesthesia.

Open Simple Prostatectomy (Retropubic and Suprapubic Approach)

Proper Positioning of the Patient

Once anesthesia has been induced the patient is positioned on the operating table in the supine position. If a cystoscopic examination is to be performed, the patient is prepared and draped in the usual manner for a transurethral diagnostic procedure. Flexible cystoscopy, in this situation, will obviate major repositioning of the patient. After the cystoscopy the table is placed in a mild Trendelenburg position without extension.

Incision and Development of the Space of Retzius

The suprapubic area is shaved, prepared, and draped in the usual sterile manner. A 22-Fr urethral catheter with a 30-mL balloon is passed into the bladder and connected to a sterile closed drainage system, and the balloon is inflated with 30 mL of saline. A lower midline incision from the umbilicus to the pubic symphysis is made. It is deepened through the subcutaneous tissue. The linea alba is incised, allowing the rectus abdominis muscles to be separated in the midline. The transversalis fascia is incised sharply to expose the space of Retzius. At the superior aspect of the wound the posterior rectus abdominis fascia is incised above the semicircular line to the level of the umbilicus, and the peritoneum is mobilized cephalad starting at the pubic symphysis and swept anterolaterally. The pelvis is inspected for any abnormalities, and the inguinal area is examined for hernias. If a hernia is identified, it can be repaired using the preperitoneal approach (Schlegel and Walsh, 1987). A self-retaining Balfour retractor is placed in the incision and widened.

Retropubic Simple Prostatectomy

Exposure of the Prostate

A well-padded, malleable blade is connected to the Balfour retractor and used to displace the bladder posteriorly and superiorly. The anterior surface of the bladder and prostate are exposed. With the use of DeBakey forceps and Metzenbaum scissors, the preprostatic adipose tissue is gently removed to expose the superficial branch of the dorsal vein complex and the puboprostatic ligaments (Fig. 106-1).

Hemostatic Maneuvers

Before proceeding with enucleation of the prostatic adenoma it is important to achieve complete control of the dorsal vein complex as well as the lateral pedicles at the bladder neck (the main arterial blood supply to the prostate gland) (Walsh and

Oesterling, 1990). To accomplish this task the endopelvic fascia is incised laterally and the puboprostatic ligaments are partially transected, similar to the maneuver in an anatomic radical retropubic prostatectomy (Reiner and Walsh, 1979). In patients with marked prostatic enlargement this maneuver can be easier because the enlarged prostate gland protrudes out from beneath the pubic symphysis. A 3-0 Monocryl suture on a $\frac{5}{8}$ -inch circle-tapered needle is passed in the avascular plane between the urethra and the dorsal vein complex at the apex of the prostate and tied (Fig. 106-2A).

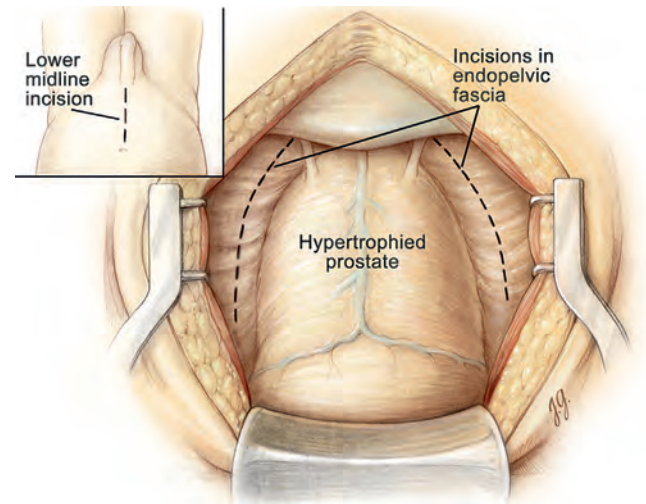


Figure 106-1. Retropubic simple prostatectomy. The space of Retzius has been opened, and the periprostatic adipose tissue has been dissected free from the superficial branch of the dorsal vein complex. The endopelvic fascia is incised bilaterally (dotted lines), and the puboprostatic ligaments are transected bilaterally. (© Brady Urological Institute.)

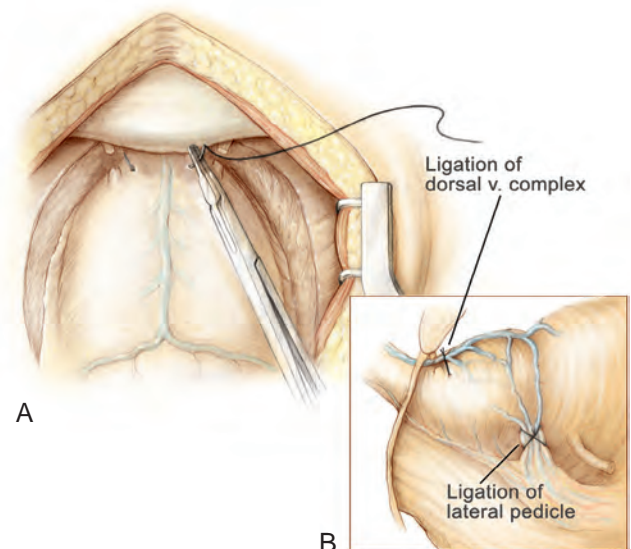


Figure 106-2. Retropubic simple prostatectomy. A, A 2-0 chromic suture on a $\frac{5}{8}$ -inch circle-tapered needle is passed in the avascular plane between the urethra and the dorsal vein complex at the apex of the prostate. A tie is grasped and tied around the dorsal vein complex. B, With 2-0 chromic suture material on a CTX needle, a figure-of-eight suture is placed through the prostatovesicular junction just above the level of the seminal vesicles to control the main arterial blood supply to the prostate gland. When placing this suture, care must be taken to avoid entrapment of the neurovascular bundles located posteriorly and slightly laterally. (© Brady Urological Institute.)

The superficial branch of the dorsal vein at the bladder should be coagulated or ligated.

At this point attention is focused on securing the lateral pedicles at the prostatovesical junction. The 30-mL balloon of the catheter is used to identify the junction between the bladder and the prostate. The balloon is then deflated, and 2-0 chromic suture material on a large CTX needle is used to place a figure-of-eight suture deep into the prostatovesical junction at the level where the seminal vesicles approach the prostate gland bilaterally (see Fig. 106-2B). With this maneuver, the main arterial blood supply to the prostate adenoma is controlled. Having secured the dorsal vein complex earlier, the major sources of hemorrhage for this operation have been eliminated.

Enucleation of the Adenoma

With a sponge stick on the bladder neck to depress the bladder posteriorly, a No. 15 blade on a long handle is used to make a transverse capsulotomy in the prostate 1.5 to 2.0 cm distal to the bladder neck (Fig. 106-3). The superficial branch of the dorsal vein complex is transected as the transverse capsulotomy is made. It does not bleed because hemostasis of the dorsal vein complex has previously been controlled both proximally and distally. The incision is deepened to the level of the adenoma and extended sufficiently lateral in each direction to permit complete enucleation. A pair of Metzenbaum scissors is used to dissect the overlying prostatic pseudocapsule from the underlying prostatic adenoma. Once a well-defined plane is sufficiently developed, the index finger can be inserted between the prostatic adenoma and the pseudocapsule to further develop the plane laterally and posteriorly (Fig. 106-4). A pair of Metzenbaum scissors is then used to incise the anterior commissure from the bladder neck to the apex, separating the lateral lobes of the prostate anteriorly. The posterior prostatic urethra is exposed, and the index finger is inserted down to the verumontanum. The mucosa of the urethra overlying the left lateral lobe is divided sharply at the level of the apex under direct vision without injury to the external urinary sphincter. With the aid of a Babcock clamp, the left lateral lobe is removed safely. This maneuver is then repeated for the right lateral lobe. If a median lobe is present, the overlying mucosa is incised at the level of the bladder neck and this lobe is removed (Fig. 106-5). In this manner the entire prostatic adenoma is removed with preservation of a strip of posterior

prostatic urethra. Because the capsulotomy was a transverse rather than longitudinal incision there is little risk that the incision will be inadvertently extended into the sphincteric mechanism during the enucleation process, which would compromise subsequent urinary continence.

The prostatic fossa is carefully inspected to ensure that all of the adenoma has been removed and that hemostasis is complete. If hemorrhage is persistent, 4-0 chromic suture material can be used to place a figure-of-eight suture in the bladder neck at the 5- and 7-o'clock positions, as in suprapubic prostatectomy (Fig. 106-6). When placing these sutures it is necessary to visualize the ureteric orifices so that they are not incorporated. Indigo carmine dye may be given intravenously to aid in the visualization of the ureteric orifices if necessary. If the bladder neck appears obstructive at the completion of the operation, it may be appropriate to perform

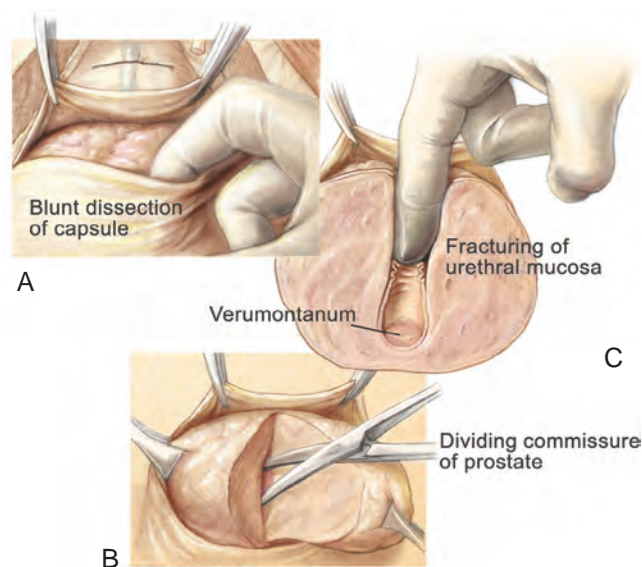


Figure 106-4. Retropubic simple prostatectomy. A, With blunt dissection with the index finger, the prostatic adenoma is dissected free laterally and posteriorly. B, Metzenbaum scissors are used to divide the anterior commissure to visualize the posterior urethra and verumontanum. C, The index finger is then used to fracture the urethral mucosa at the level of the verumontanum. With this last maneuver, extreme care is taken not to injure the external sphincteric mechanism. (© Brady Urological Institute.)

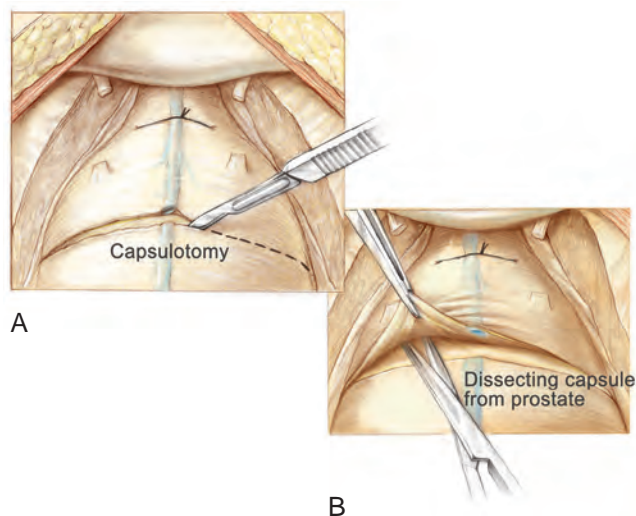


Figure 106-3. Retropubic simple prostatectomy. A, With the superficial branch of the dorsal vein complex secured proximally and distally, a No. 15 blade on a long handle is used to make the transverse capsulotomy. B, Metzenbaum scissors are used to develop the plane anteriorly between the prostatic adenoma and the prostatic pseudocapsule. (© Brady Urological Institute.)

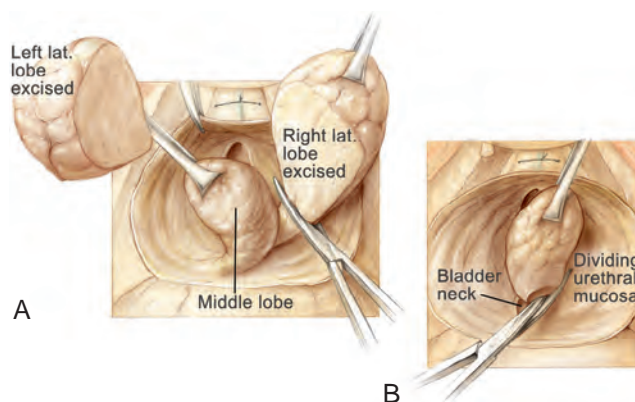


Figure 106-5. Retropubic simple prostatectomy. A, After removal of the left lateral lobe of the prostate, the right lateral lobe is excised with the aid of a tenaculum and Metzenbaum scissors. B, Finally, the median lobe is removed under direct vision. (© Brady Urological Institute.)

a wedge resection at the 6-o'clock position and advance the bladder mucosa into the prostatic fossa.

Suprapubic Simple Prostatectomy

Exposure of the Prostate

The anterior bladder wall is identified, and two 3-0 Vicryl stitches are placed on each side of the midline below the peritoneal reflection. A vertical cystotomy is made with an electrocautery. With the use of a pair of Metzenbaum scissors, a cystotomy is then extended cephalad and caudally to within 1 cm of the bladder neck. Several pairs of stay sutures are placed using 3-0 Vicryl on each side of the midline to facilitate exposure (Fig. 106-7). A figure-of-eight suture using 3-0 Vicryl is placed and tied at the most caudal position of the cystotomy to prevent further extension of the cystotomy incision during blunt finger dissection of the adenoma. Alternatively, a transverse bladder incision can be used. After inspecting the bladder, a well-padded, malleable blade is placed in the bladder, connected

to the Balfour retractor, and used to retract the bladder cephalad. The bladder neck and prostate gland now can be visualized. A narrow Deaver retractor can be placed over the bladder neck and used to further expose the trigone. Indigo carmine dye may be given intravenously to aid in the visualization of the ureteric orifices if necessary.

Enucleation of the Adenoma

An electrocautery is used to create a circular incision in the bladder mucosa distal to the trigone (Fig. 106-8). Care is taken not to injure the ureteric orifices. With the use of a pair of Metzenbaum scissors, the plane between the prostatic adenoma and prostatic pseudocapsule is developed at the 6-o'clock position (Fig. 106-9). Once a well-established plane is created posteriorly, the prostatic adenoma is dissected circumferentially and inferiorly toward the

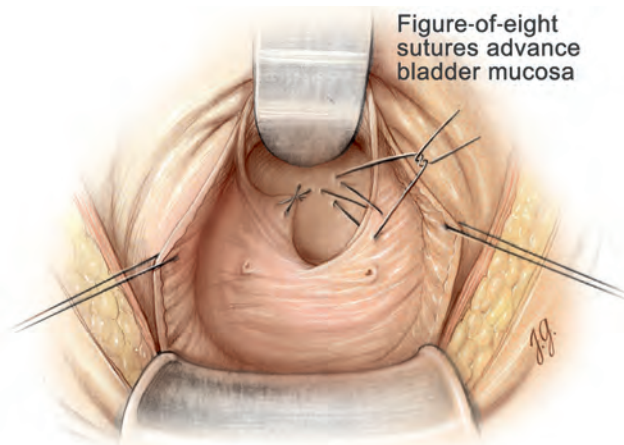


Figure 106-6. Hemostatic maneuver during open simple prostatectomy. After enucleation of the entire prostatic adenoma, a 0-chromic suture is used to place two figure-of-eight sutures to advance bladder mucosa into the prostatic fossa at the 5- and 7-o'clock positions at the prostatovesicular junction to ensure control of the main arterial blood supply to the prostate. (© Brady Urological Institute.)

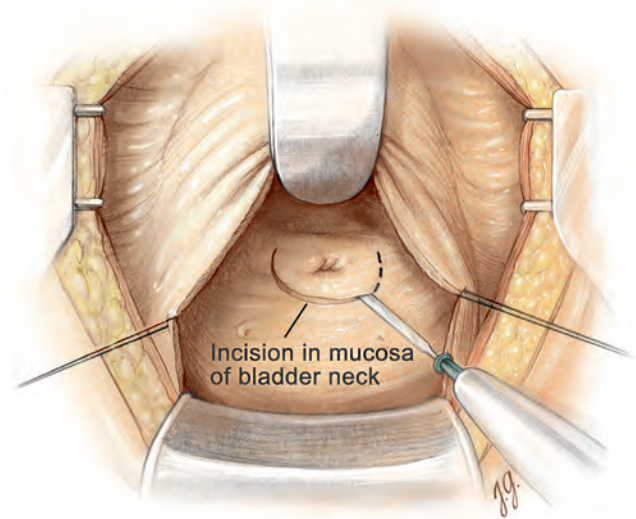


Figure 106-8. Suprapubic simple prostatectomy. With adequate exposure of the bladder neck, a circular incision in the bladder mucosa is made distal to the trigone, using an electrocautery. (© Brady Urological Institute.)

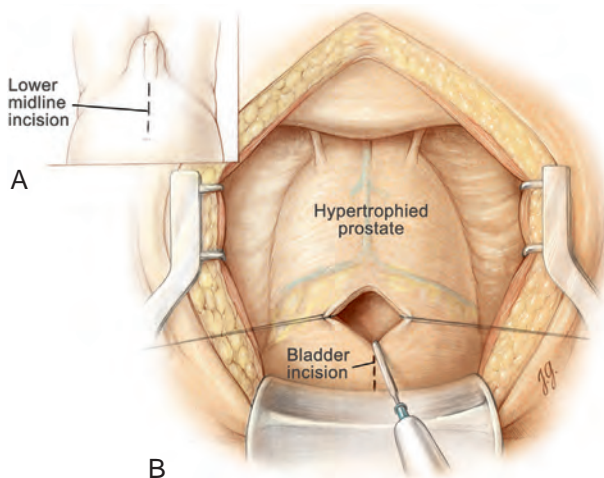


Figure 106-7. Suprapubic simple prostatectomy. A, A lower midline incision is made from the umbilicus to the pubic symphysis. B, After developing the prevesical space, a small, longitudinal cystotomy is made with an electrocautery. (© Brady Urological Institute.)

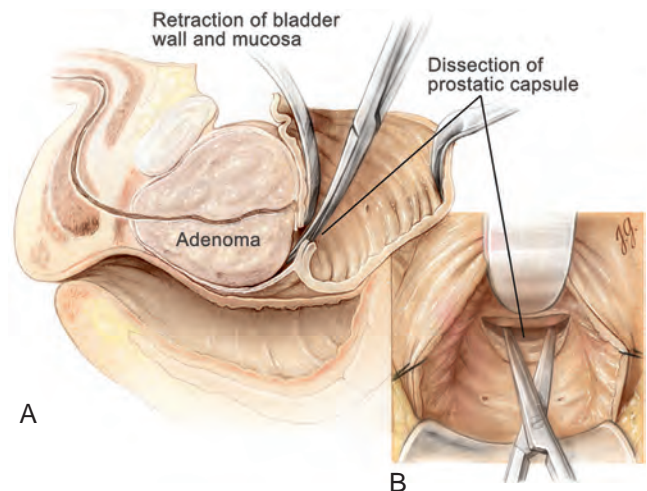


Figure 106-9. Suprapubic simple prostatectomy. A, Starting at the bladder neck posteriorly, Metzenbaum scissors are used to develop the plane between the prostatic adenoma and the prostatic pseudocapsule (lateral view). B, Anterior view of the same maneuver. (© Brady Urological Institute.)

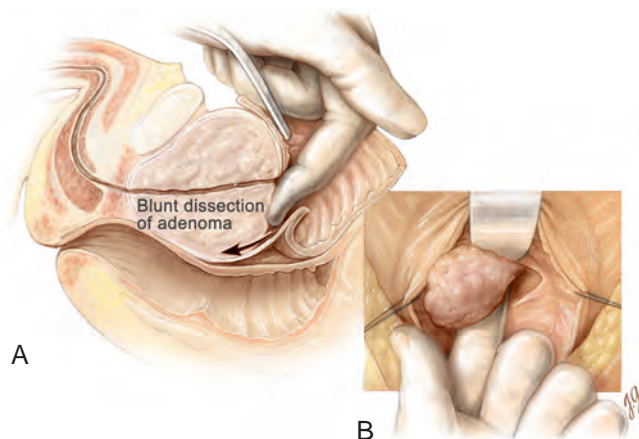


Figure 106-10. Suprapubic simple prostatectomy. A, Using the index finger, the prostatic adenoma is enucleated from the prostatic fossa (lateral view). B, Anterior view of the same maneuver. With extremely large prostate glands, the left, right, and median lobes should be removed separately. (© Brady Urological Institute.)

apex, using blunt dissection (Fig. 106-10). At the apex the prostatic urethra is transected using a pinch action of the two fingertips and avoiding excessive traction so as not to avulse the urethra and injure the sphincteric mechanism. At this point the prostatic adenoma, either as one unit or separate lobes, can be removed from the prostatic fossa.

Hemostatic Maneuvers

After enucleation of the adenoma the prostatic fossa is inspected for residual tissue. If found, these nodules are removed by sharp or blunt dissection. The prostatic fossa also must be examined for discrete bleeding sites that frequently can be controlled with an electrocautery or 4-0 chromic suture ligatures. In addition, a 0-chromic suture is used to place two figure-of-eight sutures to advance the bladder mucosa into the prostatic fossa at the 5-o'clock and 7-o'clock positions at the prostatovesical junction to ensure control of the main arterial blood supply to the prostate (see Fig. 106-6). With this maneuver, hemostasis is usually complete.

If hemorrhage remains pronounced despite the hemostatic sutures, a size 2 nylon purse-string suture can be placed around the vesical neck, brought out through the skin, and tied firmly, as described by Malament (1965). This maneuver closes the bladder neck and tamponades the prostatic fossa. The nylon suture is removed by cutting it at the skin and applying gentle traction on postoperative day 2 or 3. Plicating sutures can be placed transversely in the posterior prostatic pseudocapsule to prevent further bleeding, as described by O'Connor (1982).

Closure

After inspecting for complete adenoma removal and hemostasis, a 22-Fr, three-way Foley catheter with a 30-mL balloon is inserted through the anterior urethra and prostatic fossa into the bladder. Alternatively, a 22-Fr, two-way Foley catheter with a 30-mL balloon and a 20- to 24-Fr Malecot suprapubic tube are placed into the dome of the bladder. The suprapubic tube exits the bladder via a separate stab incision at the lateral aspect of the dome, avoiding the peritoneal cavity (Fig. 106-11). The suprapubic tube is secured with a 4-0 chromic purse-string suture.

In the suprapubic approach, with the urethral catheter in place, the prostatic pseudocapsule is closed (see Fig. 106-11) using 2-0 absorbable sutures. In the retropubic approach, the cystotomy incision is closed in two layers using 2-0 absorbable sutures (Fig. 106-12).

Fifty milliliters of water is then placed in the balloon to ensure the Foley catheter balloon remains in the bladder and does not

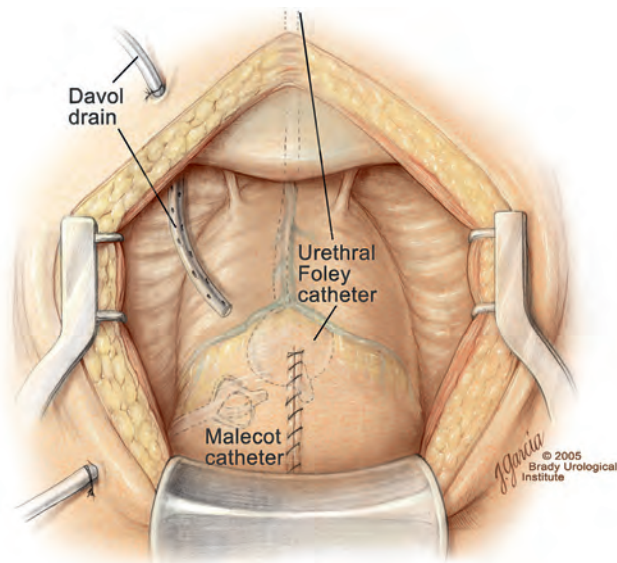


Figure 106-11. Closure during suprapubic simple prostatectomy. After placement of a urethral catheter and a Malecot suprapubic tube, the cystotomy is closed in two layers using a running 2-0 Vicryl suture, enforced by tying of multiple interrupted 3-0 Vicryl stay sutures. A closed Davol suction drain is placed on one side of the bladder and exits via a separate stab incision. (© Brady Urological Institute.)

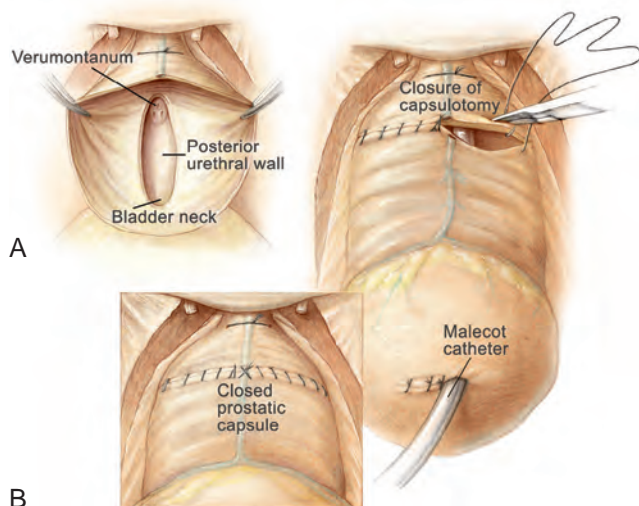


Figure 106-12. Closure during retropubic simple prostatectomy. A, View of the prostatic fossa and posterior urethra after enucleation of all the prostatic adenoma. Note that the verumontanum and a strip of posterior urethra remain intact. B, After placement of a urethral catheter and, if needed, a Malecot suprapubic tube, the transverse capsulotomy is closed with two running 2-0 chromic sutures. The two sutures are tied first to themselves and then to each other across the midline to create a watertight closure of the prostatic pseudocapsule. (© Brady Urological Institute.)

retract into the prostatic fossa. The bladder is then irrigated with saline to ensure continued hemostasis and test the closure for leakage. A small closed-suction drain is placed via a separate stab incision lateral to the prostate and bladder on one side to prevent hematoma and urinoma formation. The pelvis is irrigated with copious amounts of normal saline solution, and the rectus fascia is reapproximated with a size 1 polydioxanone (PDS) suture on a needle in a running fashion. The skin is closed with skin staples or

4-0 absorbable suture. The drain is secured to the abdominal wall, and the urethral catheter is secured to the lower extremity.

Robot-Assisted Laparoscopic Simple Prostatectomy

Proper Positioning of the Patient

The positioning of the patient for this procedure is same as that for robot-assisted laparoscopic radical prostatectomy. After general endotracheal anesthesia has been induced, the patient is positioned on the operating table in the supine position. Both arms are padded and tucked to the side. The legs are placed in the low lithotomy position in a spreader bar. The patient is secured to the operative table at the level of the shoulders with a heavy cloth tape. The lower abdomen is shaved, prepared, and draped in the usual sterile manner. A 16-Fr urethral catheter is passed into the bladder and connected to a sterile closed drainage system. The balloon is inflated with 10 mL of saline. The operative table is placed in the maximum Trendelenburg position.

Abdominal Access, Insufflation, and Trocar Placement

The transperitoneal approach is favored over the extraperitoneal approach because of the greater working space in the setting of a massively enlarged prostatic adenoma. Intraperitoneal access is obtained with a Veress needle through umbilical puncture site. After adequate insufflation at 15 mm Hg, the peritoneal cavity is entered through a vertical supraumbilical incision using 12-mm STEP trocar, followed by confirmation of the proper placement with a robotic camera. Alternatively, the initial entrance can be achieved using the Visiport device and 0-degree lens and camera. Adhesions are lysed laparoscopically, if present. One additional 12-mm STEP trocar is placed on the right side, then three 8-mm robotic trocars are placed bilaterally (two on the left, one on the right), and then one additional 5-mm trocar is placed on the right side, all under direct laparoscopic vision. The da Vinci Robotic System is then docked between the patient's legs. Typically, three robotic instruments are used (fenestrated bipolar forceps and ProGrasp forceps on the left side and monopolar scissors on the right side).

Development of the Space of Retzius

The anterior peritoneum is taken down lateral to the medial umbilical ligaments to displace the bladder posteriorly. Applying posterior and cephalad traction on the urachus, the space of Retzius is developed using both blunt and sharp dissection. Periprostatic adipose tissue is then removed. Endopelvic fascia is taken down carefully to expose the prostatic contour. Control of the deep dorsal vein complex or prostatic lateral pedicles is not necessary.

Bladder Neck Incision

The anterior bladder neck is divided transversely using monopolar scissors until the urinary catheter is visualized. After identifying the catheter, it is grasped by an assistant or the fourth robotic arm with ProGrasp forceps and pulled anteriorly before widening the bladder neck incision. **To better visualize the intravesical component of the prostate and the trigone, the bladder neck incision in this approach should be wider and more cephalad compared to the narrow incision at the vesicoprostatic junction in a typical robot-assisted laparoscopic radical prostatectomy.** When a large median lobe is encountered, it is lifted anteriorly by the assistant or the ProGrasp forceps. Bilateral ureteric orifices are identified to avoid inadvertent injury. Indigo carmine dye may be given intravenously to aid in the visualization of the ureteric orifices if necessary.

Enucleation of the Adenoma

An electrocautery of the robotic monopolar scissors is used to create a circular incision in the bladder mucosa distal to the trigone.

Care is taken not to injure the ureteric orifices. With the use of monopolar scissors, the subcapsular plane between the prostatic adenoma and prostatic pseudocapsule is developed initially at the 6-o'clock position. **While developing the plane between the prostatic adenoma and pseudocapsule, it is crucial to have an experienced assistant or the robotic fourth arm with forceps to optimize the visualization of the dissection plane and provide traction.** Alternatively, prostatic adenoma can be manipulated during dissection using stitches placed in the lateral lobes (Sotelo et al, 2008). **Compared to the open simple prostatectomy approach, the dissection plane should be better visualized at all times during this procedure.** Once a well-established plane is created posteriorly, the prostatic adenoma is dissected circumferentially and inferiorly toward the apex, using both blunt dissection and limited electrocautery. At the apex the prostatic urethra is transected while avoiding excessive traction. At this point the prostatic adenoma, either as one unit or separate lobes, can be removed from the prostatic fossa and set aside.

Hemostatic Maneuvers

Prostatic fossa is carefully inspected, and hemostasis is achieved by limited electrocautery or suture ligatures. Posterior bladder mucosa is advanced into the posterior prostatic pseudocapsule using 3-0 polysorb sutures between the 5- and 7-o'clock position. Then, cystotomy incision is closed in two layers in a running fashion with 2-0 absorbable sutures. A 22-Fr, three-way Foley catheter is inserted. A watertight closure is confirmed using normal saline irrigation by Foley catheter. A closed-suction pelvic drain is placed through the lateral 8-mm robotic trocar site and secured to the skin.

Adenoma Extraction and Closure

Hemostasis is reconfirmed with lower insufflation pressure (<10 mm Hg). The prostatic adenoma is placed inside of the entrapment bag and extracted through extension of the supraumbilical trocar site. The rectus abdominis fascial defect of the extraction incision is closed using No. 1 PDS suture in a figure-of-eight fashion. The skin edges are reapproximated using 4-0 Biosyn subcuticular suture.

POSTOPERATIVE MANAGEMENT

In the recovery area the outputs from the pelvic drain and urethral catheter (and suprapubic tube, if present) are monitored. In addition, it is routine to verify the hematocrit. If significant hemorrhage is noted, the urethral catheter may be placed on traction so that the balloon containing 50 mL of saline can compress the bladder neck and prostatic fossa. Constant and reliable traction can be maintained by securing the catheter to the abdomen. In addition, continuous bladder irrigation can be initiated to prevent clot formation. For most patients these measures are adequate and effective. However, if excessive bleeding persists after these measures, the urethral catheter can be removed in the operating suite and a cystoscopic inspection of the prostatic fossa and bladder neck can be performed to identify and fulgurate discrete bleeding sites. If marked hemorrhage should continue to persist, re-exploration should be strongly considered.

On the evening of the day of surgery the patient is asked to perform the dorsiflexion and plantarflexion exercises while awake and perform pulmonary exercises. Effective pain management consists of intravenous opioids by a patient-controlled analgesic pump.

On the first postoperative day the patient is started on a clear liquid diet and asked to ambulate four times per day. Pulmonary exercises are continued. If the hematuria is resolved, continuous bladder irrigation can be discontinued with a urethral catheter (and suprapubic tube, if present) placed for gravity drainage. Also, the balloon in the urethral catheter is partially deflated to 30 mL of saline and residual clots are removed by irrigation.

On the second postoperative day, if urine is clear and both suprapubic tube and urethral catheter were placed intraoperatively, the urethral catheter may be removed and the suprapubic tube is clamped to allow a voiding trial. The patient is encouraged to ambulate and continue pulmonary exercises. When the patient tolerates a regular diet, oral analgesics can be given and parenteral opioids discontinued. Appropriate discharge instructions are reviewed with the patient at this time in preparation for discharge on the second day after surgery. The pelvic drain is removed if the drainage is low. Pathologic examination of the enucleated prostatic adenoma should be performed.

On discharge from the hospital the patient is encouraged to gradually increase his activity. If the patient has a clamped suprapubic tube and voids well with a minimal postvoid residual urine volume, the suprapubic tube is then removed in the clinic a week after surgery. If only the urethral catheter was used without a suprapubic tube, it is removed in the clinic a week after surgery. The patient should be able to resume full activity 4 to 6 weeks postoperatively with outpatient visits at 6 weeks and 3 months.

COMPLICATIONS

The overall rate of morbidity and mortality associated with simple prostatectomy is extremely low. Historically, excessive hemorrhage had been a major concern. But with modern surgical techniques, blood loss is now minimal and the need for a blood transfusion is uncommon (Zargooshi, 2007). In retropubic simple prostatectomy, controlling the dorsal vein complex distal to the apex of the prostate and ligating the lateral pedicles to the prostate at the prostatovesical junction markedly reduces venous and arterial bleeding, respectively. Nevertheless, it may still be prudent to have 1 to 2 units of autologous blood available at the time of open simple prostatectomy. **In laparoscopic simple prostatectomy with or without robotic assistance, pneumoperitoneum significantly decreases the perioperative hemorrhage and almost eliminates the need for blood transfusion.**

Urinary extravasation can be of concern in the immediate postoperative period; this most likely results from an incomplete closure of the prostatic capsulotomy in retropubic simple prostatectomy or the cystotomy in suprapubic simple prostatectomy and robot-assisted laparoscopic simple prostatectomy. This will usually resolve spontaneously with continued catheter drainage. The drain should be left in place until urinary extravasation ceases.

After a simple prostatectomy, urgency and urgency incontinence may be present for several weeks to several months, depending on the preoperative bladder status. If the condition is severe, the patient may be given an anticholinergic agent such as oxybutynin (Ditropan). Stress incontinence and total incontinence are rare. With a precise enucleation of the prostatic adenoma, risk for injury to the external sphincter mechanism is minimal. If stress incontinence does result after the procedure, the patient may benefit from transurethral collagen injections for a mild condition or an artificial urinary external sphincter when the situation is more severe.

Late urologic complications are not common. Acute cystitis rarely occurs as long as the patient voids to completion. Acute epididymitis can occur occasionally if infected urine refluxes into the ejaculatory ducts.

Erectile dysfunction occurs in 3% to 5% of patients undergoing a simple prostatectomy; it is more common in older men than in younger men. Retrograde ejaculation occurs in 80% to 90% of patients after surgery. Also, 2% to 5% of patients will develop a bladder neck contracture 6 to 12 weeks after an open simple prostatectomy (Tubaro et al, 2001; Varkarakis et al, 2004). If a bladder neck contracture develops, the initial management should be dilatation with urethral sounds or a direct vision incision of the bladder neck using a Collings knife to create a 22-Fr opening.

The most common nonurologic adverse effects include deep vein thrombosis, pulmonary embolus, myocardial infarction, and a cerebrovascular event. The incidence of any one of these complications


is less than 1%, and the overall mortality rate resulting from this operation should approach zero (Varkarakis et al, 2004).

SUMMARY

Simple prostatectomy, whether performed by an open retropubic or suprapubic approach or a robot-assisted laparoscopic approach, is an excellent treatment option for (1) men with symptomatic bladder outlet obstruction as a result of benign prostatic hyperplasia causing a markedly enlarged prostate gland, (2) individuals with a concomitant bladder condition, such as a bladder diverticulum or large bladder calculi, and (3) patients who cannot be placed in the dorsal lithotomy position for TURP. With improved surgical technique these procedures can be routinely performed in a precise manner with minimal hemorrhage. Efficacy, in terms of durable improvement in symptom score and peak urinary flow rate, is superior to other treatment options available for the obstructing prostate gland, including TURP. Meanwhile, complications are minimal and the length of hospitalization has been markedly reduced. For most patients, the length of hospital stay is 2 days or less. Thus, for the properly selected individual, a simple prostatectomy is a highly effective and well-tolerated operation.

KEY POINTS

- Simple prostatectomy should be considered when the obstructive tissue is estimated to weigh more than 75 g or sizable bladder diverticuli or calculi exist.
- Before performing a simple prostatectomy, the presence of significant prostate cancer should be determined.
- Potential risks of simple prostatectomy include urinary incontinence, erectile dysfunction, retrograde ejaculation, UTI, bladder neck contracture, urethral stricture, deep vein thrombosis, pulmonary embolus, and the need for blood transfusion.
- Advantages of simple prostatectomy over TURP are a lower re-treatment rate, more complete removal of the prostatic adenoma under direct vision, and no risk for TUR syndrome.
- Disadvantages of open simple prostatectomy over TURP are a lower midline incision, longer hospitalization, and increased potential for perioperative hemorrhage.
- Compared to open simple prostatectomy, robot-assisted laparoscopic simple prostatectomy can be performed with smaller incisions with shorter hospital stay and decreased risk for perioperative hemorrhage and blood transfusion.
- Two approaches to open simple prostatectomy are retropubic and suprapubic.
- Compared to retropubic approach, suprapubic prostatectomy is ideal for men with a large median lobe, clinically significant bladder diverticulum, or large bladder calculi.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com.

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Epidemiology

Risk Factors

Etiology and Molecular Genetics

Chemoprevention

Conclusion

EPIDEMIOLOGY

Incidence and Mortality Trends

Incidence

Prostate cancer has been the most common noncutaneous malignancy in U.S. men since 1984, now accounting for 27% of all such cancers (Siegel et al, 2014) (Fig. 107-1). Among men alive today, it is estimated that 1 in 7 (15.3%) will be diagnosed with prostate cancer and 1 in 38 (2.6%) will die from this disease (Brawley et al, 2012a). Prostate cancer incidence varies by race/ethnicity, with African-Americans experiencing 59% higher incidence rates than whites (Table 107-1) (Siegel et al, 2014). The incidence rate rose by approximately 2% per year from 1975 to the late 1980s, related in part to the incidental detection of prostate cancer associated with the use of transurethral resection of the prostate for benign prostatic hyperplasia (Potosky et al, 1990). The incidence of prostate cancer rose dramatically from 1989 to 1992 after the introduction of a prostate-specific antigen (PSA) screening test (with U.S. Food and Drug Administration [FDA] approval for early diagnosis in 1992), fell precipitously until 1995, increased slowly until 2001, and has fluctuated year to year since (see Fig. 107-1), reflecting changes in screening practices (Siegel et al, 2014). The precipitous fall in incidence between 1992 and 1995 has been attributed to the “cull effect” of identifying previously unknown cancers in the population by the use of PSA screening, followed by a return to baseline incidence rates (Stephenson et al, 1996). For 2015, an estimated 220,800 new cases of prostate cancer will be diagnosed in the United States and the age-adjusted incidence rate is 152.0 per 100,000 men per year (Siegel et al, 2014).

Mortality

Prostate cancer mortality rates in the United States rose slowly between 1973 and 1990 (Fig. 107-2). This may have resulted from a gradual increase in the number of biologically lethal cancers or a decreasing use or effectiveness of therapy during this interval. In the early 1990s an abrupt rise in mortality was observed. This increase may have been caused by an increase in attribution bias occurring when the National Center for Health Statistics made a change from manual to automated methods for assignment of cause of death (Feuer et al, 1999). Subsequent to 1991, the peak mortality year, steady declines in prostate cancer mortality were reported in both Caucasians and African-Americans at an average rate of 4.1% per year. The magnitude of this decline is nearly 2.5 times larger than the increase in mortality seen as a result of attribution bias, so it seems likely that the observed declines since 1991 are real and clinically significant (Stephenson, 2005). Prostate cancer is the second leading cause of cancer death in the United States, accounting for 10% of all such events. In 2015, an estimated

27,540 men will die from prostate cancer in the United States, for an approximate annual rate of 23.0 per 100,000 population, representing a 45% decrease from the 1991 peak (Siegel et al, 2014). Furthermore, the mortality rate for prostate cancer in Caucasians in the United States has declined to a level lower than that observed prior to the introduction of PSA-based screening in 1987 (Tarone et al, 2000). Because the natural history of progressive prostate cancer is protracted relative to other common solid malignancies, it is associated with the fewest expected years of life lost, estimated at 5.9 and 1.8 years for clinically detected and screening-detected cancers, respectively (Friman et al, 1989; Liu et al, 2013). Prostate cancer was the leading single cause of death (35%) among those diagnosed with this disease between 1973 and 2008 in the U.S. Surveillance, Epidemiology, and End Results (SEER) program, but these men were still more likely to die from other causes (Epstein et al, 2012).

The observed decline in mortality since 1991 may be due to (1) early detection and stage migration from PSA screening, (2) increased utilization and effectiveness of curative treatments, (3) changes in the attribution of cause of death, (4) improvements in therapy for advanced disease, or (5) increased risk of death from secondary causes among men receiving prostate cancer therapy (Brawley et al, 2012b). The initial decline in mortality appears to have occurred too soon after the introduction of the PSA test to be attributable to screening (Etzioni et al, 1999). One hypothesis is that it is the result of the more aggressive treatment of prostate cancer that began in the 1980s (Walsh, 2000). Indeed, the vast majority of men diagnosed with prostate cancer since 1986 have received curative-intent therapy at a rate double that observed before 1986 (Etzioni et al, 2008; Welch and Albertsen, 2009). Modeling estimates based on data from various sources suggest that screening and treatment plausibly explain 45% to 70% and 22% to 33% of the decline in prostate cancer mortality since 1991, respectively (Etzioni et al, 2008, 2012, 2013).

Racial Differences

When interpreting reported racial differences in incidence and mortality, it should be emphasized that racial/ethnic categories are defined by the U.S. Office of Management and Budget not on the basis of biology but by a social/political/cultural basis. Observed disease-related differences between groups defined in this fashion may thus not reflect underlying differences in biology. Recognizing these caveats, it is noteworthy that African-Americans and Jamaicans of African descent have the highest incidence of prostate cancer in the world (Siegel et al, 2014). Although African-Americans have experienced a greater decline in mortality than Caucasians since the early 1990s, their death rates are still 2.4 times higher.

Differences in treatment patterns by race have consistently shown that African-Americans at every stage get less aggressive

therapy regardless of age, marital status, tumor risk, and comorbidities status compared to Caucasians, even within equal-access health care systems (Klabunde et al, 1998; Hoffman et al, 2003; Shavers et al, 2004; Gross et al, 2008; Nambudiri et al, 2012; Presley et al, 2013). Even among those treated with “watchful waiting,” African-Americans receive less intensive follow-up (Shavers et al, 2004). Among men ages 67 to 84 years in the SEER-Medicare data set, the racial disparity between African-Americans and Caucasians was highest (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.48 to 0.68) among those most likely to benefit (life expectancy

>10 years, Gleason score 7-10, or American Joint Committee on Cancer [AJCC] clinical stage T2b-T2c) (Presley et al, 2013). However, prostate cancer mortality among African-Americans and Caucasians is similar in equal-access health care systems (Graham-Steed et al, 2013). Many biologic, environmental, and social hypotheses have been advanced to explain these differences, including postulated differences in genetic predisposition; differences in mechanisms of tumor initiation, promotion, and/or progression; higher-fat diets, higher serum testosterone levels, or higher body mass index; structural, financial, educational, and cultural barriers to screening, early detection, and aggressive therapy; and physician bias. There are currently no data that clearly indicate if any of these hypotheses account for observed differences in incidence or mortality, and it seems likely that the source of the disparity is multifactorial.

The incidence of prostate cancer in other ethnic groups is lower than that of Caucasians and African-Americans (see Table 107-1). Interestingly, men of Asian descent living in the United States have a lower incidence compared to white Americans, but their risk is higher than that of men of similar backgrounds living in Asia (Haenszel and Kurihara, 1968; Yu et al, 1991). Likewise, Japanese immigrants have an incidence more comparable to men of similar ancestry born in the United States than to those living in Japan (Shimizu et al, 1991). These data implicate external factors (dietary, lifestyle, environmental) in the development of prostate cancer.

Global Incidence and Mortality

Prostate cancer is the second most common cancer and the sixth leading cause of cancer deaths worldwide, with an

TABLE 107-1 Prostate Cancer Incidence and Mortality by Race/Ethnicity, United States, 2006-2010

	INCIDENCE*	MORTALITY*
White	138.6	21.3
African-American	220	50.9
Hispanic/Latino	124.2	19.2
Asian-American and Pacific Islander	75	10.1
American Indian and Alaska Native	104.1	20.7

*Per 100,000, age adjusted to the 2000 U.S. standard population. Data from Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.

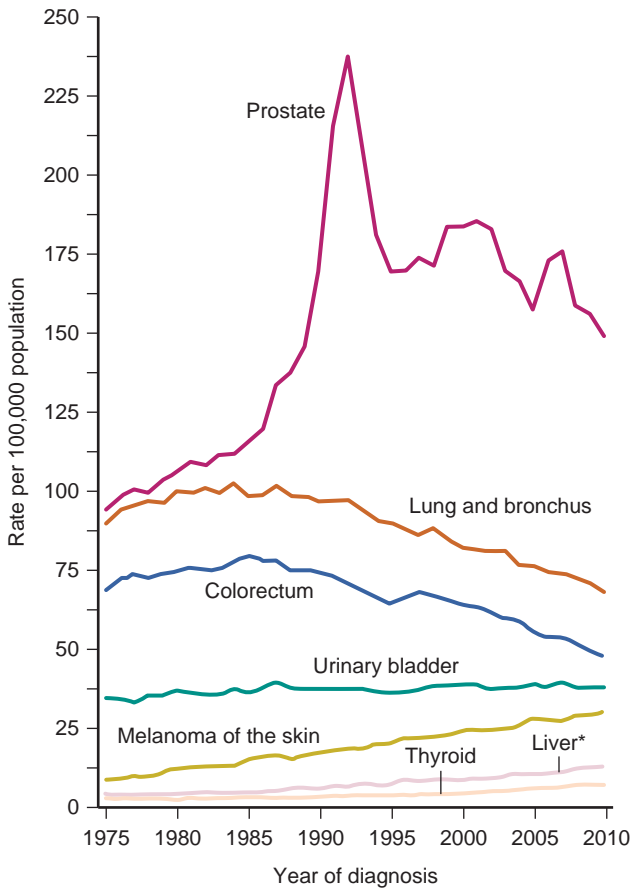


Figure 107-1. Age-adjusted cancer incidence rates for men, United States, 1975-2010. *Includes intrahepatic bile duct. (Modified from Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.)

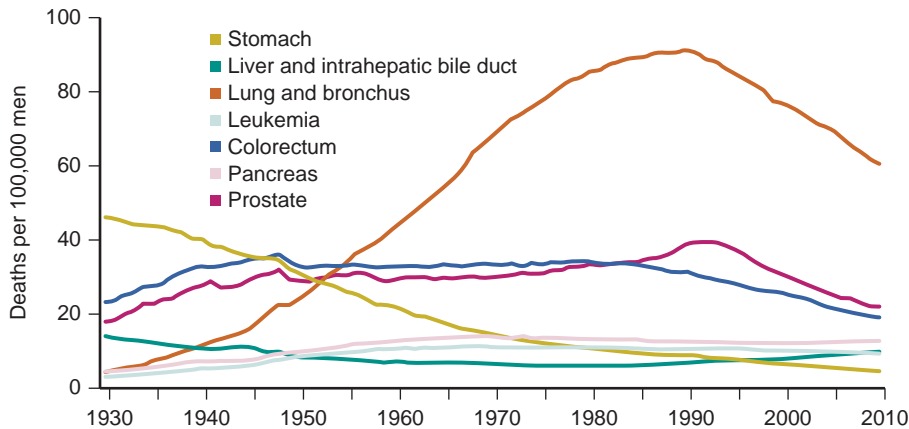


Figure 107-2. Age-adjusted cancer death rates for men, United States, 1975-2005. (Modified from Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.)

estimated 899,000 cases and 258,000 deaths annually (Center et al, 2012). By 2030, these rates are anticipated to increase to 1,700,000 and 499,000 as a result of global population growth and increased life expectancy. Prostate cancer incidence rates vary by 24-fold worldwide, primarily because of differences in screening practices, although the Westernization of lifestyle has also been suggested as a possible explanation (Hsing et al, 2000). Age-standardized incidence rates per 100,000 men are highest in the highest income regions of the world, including North America (85.6), the Caribbean (71.1), Australia and New Zealand (104.2), Western Europe (93.1), and Scandinavia (73.1), and lowest in Asia (7.2) and Northern Africa (8.1). In 32 of 40 countries analyzed, increasing incidence rates over the last one to two decades were observed, and they had stabilized in 8 countries, including the United States, Canada, and Australia, where there was early adoption of PSA screening.

Prostate cancer mortality rates varied 10-fold, with the highest age-adjusted rates per 100,000 men in the Caribbean (26.3), sub-Saharan Africa (18.3 to 19.3), and South America (16.2) and the lowest in Asia (3.1). Over the last two decades, mortality rates have declined in 27 of 53 countries analyzed and have increased in 10 countries. The decreasing trends in prostate cancer mortality were mainly observed in high-income countries where PSA screening has been adopted with variable penetrance (Collin et al, 2008), such as the United States (−4.3%), Canada (−3.1%), Western Europe (−2.3 to −4%), Australia (−2.3%), and New Zealand (−2.8%). Increasing prostate cancer mortality was seen among nations of central and eastern Europe, Asia, and Africa. Prostate cancer is the most common cancer among sub-Saharan Africans, with a mortality rate more than 5 times higher than African-Americans (Gronberg, 2003; Rebbeck et al, 2013). Interestingly, both incidence (~12%) and mortality rates (1.8% to 7.8%) have increased in China and South Korea over the same period (Sim and Cheng, 2005; Center et al, 2012). Using data from population-based cancer registries, the CONCORD study found that age-standardized 5-year survival rates vary greatly, ranging from 80% or higher in the United States, Australia, and Canada to less than 40% in Denmark, Poland, and Algeria, suggesting local influences on detection and therapy (Coleman et al, 2008).

Age at Diagnosis

Prostate cancer is rarely diagnosed in men less than 50 years of age, accounting for only 2% of all cases (Jani et al, 2008). Prior to the PSA era, median age at diagnosis was 70 years, falling to 67 years over the past decade, with 63% diagnosed after age 65 (Ries et al, 2008). The incidence rate in 2005 relative to 1986 (the year before PSA screening was commercially available) was 0.56 in men age 80 years or older, 1.09 in those 70 to 79 years, 1.91 in those 60 to 69 years, 3.64 in those 50 to 59 years, and 7.23 in men less than 50 years of age (Welch and Albertsen, 2009). This reflects a shift in diagnosis to an increasingly younger population after the introduction of PSA screening, with important implications for deciding on the need for and type of therapy. The proportions of men receiving curative-intent therapy have been relatively constant since 1985 at approximately 75% among men less than 70 years of age, 50% to 60% for men 70 to 79 years, and 20% for men 80 years or older (Welch and Albertsen, 2009). Currently, the proportion of men diagnosed with prostate cancer by age is 10.1%, 30.7%, 35.3%, 19.9%, and 4.4% for men less than 55 years, 55 to 64 years, 65 to 74 years, 75 to 84 years, and greater than 84 years, respectively (Brawley et al, 2012a). While age-specific incidence rates decline after age 70, the risk of prostate cancer death increases throughout life. The average age of death from prostate cancer is 77 years and has remained stable over the last three decades (Epstein et al, 2012).

Stage at Diagnosis

In addition to changes in incidence and mortality over the last several decades, there has been a substantial shift to a more

favorable stage at presentation of newly diagnosed disease. This clinical stage migration is largely if not exclusively accounted for by PSA screening (Catalona et al, 1993; Mettlin et al, 1993). Since the introduction of PSA testing, 81% of newly diagnosed men have localized disease, whereas the incidence of metastatic disease has decreased by 75% (Newcomer et al, 1997). Nonpalpable cancers (AJCC clinical stage T1c) now account for 60% to 75% of newly diagnosed disease (Gallina et al, 2008). Clinical stage migration has also been associated with improvements in 5-year disease-specific survival, which is 99.2% overall and 28% for men with advanced disease (Siegel et al, 2014).

The use of PSA screening has also resulted in a substantial downward pathologic stage migration as evidenced by an increase in the proportion of patients with organ-confined disease (Catalona et al, 1993; Jhaveri et al, 1999), and a decrease in the proportion with seminal vesicle involvement (Gallina et al, 2008). These observations have been consistent across the United States and Europe (Gallina et al, 2008). Since 1995, however, a slowing in this trend has been observed, suggesting a diminishing effect of PSA screening on pathologic stage migration (Dong et al, 2007). The improvement in pathologic stage has been seen for clinical stages T1 to T3 tumors and all tumor grades, and has resulted in improved cancer-specific survival after therapy for patients treated late in the PSA era (Jhaveri et al, 1999).

Effect of Screening on Incidence and Mortality

The use of PSA as a screening test has had the greatest impact on the incidence and potentially the mortality of prostate cancer worldwide. Since the introduction of PSA screening, lifetime risk of prostate cancer in the United States has doubled from 7.8% to 15.3% while the risk of dying from prostate cancer has decreased from 3% to 2.6% (Siegel et al, 2014). In the Prostate Cancer Prevention Trial (PCPT), 14% of men in the placebo arm were diagnosed by annual PSA screening within 7 years of enrollment (Thompson et al, 2003), suggesting that lifetime risk with regular screening may approach 20% (Boyle and Brawley, 2009).

Recently, the results of two large randomized trials assessing the effect of PSA screening on prostate cancer mortality were published. The U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial reported on 76,685 U.S. men ages 55 to 74 years randomized between annual screening and usual care (Andriole et al, 2012). Through 13 years of follow-up the incidence of prostate cancer in the screening group was 12% higher than in the control group (108 vs. 97 per 10,000 person-years, respectively). However, there was no difference in prostate cancer mortality between the groups (3.7 vs 3.4 deaths per 10,000 person-years in the screening and control groups, respectively; hazard ratio [HR] 1.09, 95% CI 1.87 to 1.4). The trial has been criticized for high rates of prescreening (44% reported undergoing PSA testing prior to enrollment), poor compliance with prostate biopsy, and 52% contamination by ad hoc screening in the control arm. There were also identical rates of noncompliance with PSA screening (15%) in the control and screening arms (Pinsky et al, 2010). Thus the trial does not fairly compare annual screening versus none and was likely underpowered to detect meaningful differences in prostate cancer mortality between the groups. The European Randomized Study of Screening for Prostate Cancer (ERSPC) included 162,243 men between the ages of 55 and 69 years randomized between PSA screening every 4 years or no screening (Schröder et al, 2012). After a median follow-up of 11 years, men in the screening arm had a 63% (95% CI 57% to 69%) increased incidence of prostate cancer compared to controls (97 vs. 56 cancers per 10,000 person-years) and a 21% (95% CI 9% to 32%) relative reduction in death from prostate cancer (3.9 vs. 5 cancer deaths per 10,000 person-years). Extrapolating the ERSPC results to the long-term U.S. setting suggests an absolute mortality reduction up to five times greater than that observed in the ESRPC (Gulati et al, 2011).

Soon after publication of results from the PLCO trial (Andriole et al, 2009) and the ERSPC (Schröder et al, 2009), the U.S.

Preventive Services Task Force (USPSTF) in 2012 recommended against routine PSA screening in healthy men regardless of age, race, or family history. It gave PSA screening a grade “D” recommendation, meaning that there was a moderate-to-high certainty that the service has no net benefit or that the harms outweigh the benefits (Moyer and U.S. Preventive Services Task Force, 2012). The future impact of these recommendations on PSA screening practices and national prostate cancer incidence rates is uncertain. Conflicting results of the impact of the publication of findings from the PLCO trial and the ERSPC in 2009 and the earlier recommendations by the USPSTF (2008) to discontinue screening among men 75 years of age or older have been reported (Moyer and U.S. Preventive Services Task Force, 2012). No differences in self-reported PSA testing were identified among men age 75 years or older in the National Health Interview Survey between 2005 and 2010 (Prasad et al, 2012), while in the SEER-Medicare population and the Veterans Health Administration (VHA) Pacific Northwest Network, a small but statistically significant reduction in PSA testing (29.4% vs. 27.8% and 25.4% vs. 24.3%, respectively) was observed in the periods before and after the 2008 USPSTF recommendations (Zeliadt et al, 2011; Ross et al, 2012). This may have explained part of the 25% reduction in prostate cancer incidence reported in the SEER registry among men 75 years of age or older between 2007 and 2009 (Howard, 2012). Among men less than 75 years of age, the PLCO trial and ERSPC results appeared to have had minimal impact on PSA testing rates among men in a commercial insurance database (−0.7% to −1.5% change after 2009) and in the VHA (−3% change after 2009) (Zeliadt et al, 2011; Goodwin et al, 2013). In a survey of primary care practitioners in university-affiliated practice after the 2012 USPSTF recommendations, approximately half agreed with the committee’s recommendations but more than 75% reported that they would be somewhat less likely to change their PSA screening practice or that it would not change at all (Pollack et al, 2012). Even among clinicians who agreed strongly with the recommendations, only 42% stated they would no longer order a PSA test or would be much less likely to do so.

KEY POINTS: EPIDEMIOLOGY

- In the United States, prostate cancer:
 - is the most common visceral malignancy in men.
 - is the second leading cause of cancer-related deaths.
 - incidence peaked in 1992 approximately 5 years after the introduction of a PSA screening test, declined until 1995, subsequently increased at a rate similar to that observed in the pre-PSA screening era, and has fluctuated year-to-year since 2001.
 - mortality has declined since 1991 and for Caucasians is now lower than before PSA screening was introduced.
- Worldwide, prostate cancer incidence and mortality rates:
 - vary significantly between countries and regions.
 - are highest in African-American and Jamaican men.
- PSA screening has induced a significant downward migration in age and stage (both clinical and pathologic) at diagnosis.
- PSA screening may have a beneficial effect on prostate cancer mortality; however, the absolute effect is small relative to the number needed to screen and treat to cure a single individual.

RISK FACTORS

Considerable evidence suggests that both genetics and environment play a role in the origin and evolution of prostate cancer. Traditional and molecular epidemiology and newer genome-based techniques have identified a number of potential risk factors associated with the development of prostate cancer.

Familial and Germline Genetic Influences

Epidemiologic and molecular evidence suggests that prostate cancer has a strong familial component as demonstrated by epidemiologic studies and germline genetic analysis. The first reports of familial clustering were published in the mid-20th century and suggested that the risk of developing prostate cancer was higher in those with an affected first-degree relative (Woolf, 1960). Subsequent case-control and cohort studies have confirmed this observation (Eeles et al, 1997), and twin studies demonstrate that the inherited component of prostate cancer risk is over 40%, substantially higher than for other common cancers (Lichtenstein et al, 2000). Relative risk (RR) increases according to the number of affected family members, their degree of relatedness, and the age at which they were affected (Table 107-2) (Zeegers et al, 2003). About 15% of all prostate cancer is estimated to be caused by germline factors (Carter et al, 1992).

Early linkage and segregation studies identified a number of candidate prostate cancer susceptibility genes (*HPC1/RNASEL*, *HPC2/ELAC*, and *MSR1*) and loci (*PCAP/1q42.2-q43*, *CAPB/1p36*, and *Xq27-q28*). Most subsequent studies have not replicated initial findings and the role of these genes/regions is not fully established (Eeles et al, 2014), although a recent population-based study identified variant *RNASEL* alleles as one of five predictive of prostate cancer-specific mortality (Lin et al, 2011). More recently, genome-wide association studies (GWAS) have emerged as a new approach to identify alleles associated with prostate cancer risk in an unbiased fashion (i.e., without prior knowledge of their position or function). Using this technique more than 70 prostate cancer susceptibility risk alleles, many confirmed in multiple studies, have been identified on chromosomes 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 17, 19, 22, and X (reviewed in Choudhury et al, 2012, and Eeles et al, 2014), which account for 25% to 30% of germline-determined risk. Studies in African-American and Japanese populations have identified additional risk alleles specific to these populations (Takata et al, 2010; Haiman et al, 2011). Reported GWAS for prostate cancer have generally included only common inherited variants (i.e., a minor allele frequency of ~5%) and in total have captured only a small fraction of the germline component of risk. As a consequence, the predictive value of most single alleles (rarely >1.5 times baseline risk) is too low to provide clinical utility as a way of identifying individual men at risk for developing prostate cancer. One approach to this challenge is to combine multiple risk alleles into a predictive model, because risk increases with the number of specific alleles carried. One such case-control study evaluated the ability of five loci (three on 8q24 and two on 17q) to predict the likelihood of prostate cancer in a population of 3161 men. The OR for prostate cancer in men who carried

TABLE 107-2 Family History and Risk of Prostate Cancer

FAMILY HISTORY	RELATIVE RISK	95% CONFIDENCE INTERVAL
None	1	
Father affected	2.17	1.90-2.49
Brother affected	3.37	2.97-3.83
First-degree family member affected, age <65 yr at diagnosis	3.34	2.64-4.23
>2 first-degree relatives affected	5.08	3.31-7.79
Second-degree relative affected	1.68	1.07-2.64

Data derived from meta-analysis assessing risk of prostate cancer for relatives of patients with prostate carcinoma (Zeegers et al, 2003).

four or five alleles was 4.47, and increased to 9.46 for those who carried all five alleles and had a positive family history (Zheng et al, 2008). While this study demonstrates the power of risk information contained within the germline, its clinical utility is limited by the fact that only a minority of the population (1.4%) carried all five risk alleles and that the model was unable to distinguish between the risk of low- versus high-grade disease. In a follow-up study, adding additional alleles only marginally improved the predictive value of the model (Sun et al, 2011).

The performance of predictive models based on germline alleles, and thus their clinical utility, may improve with the incorporation of rarer variants that confer higher risk. Several such variants with minor allele frequencies of approximately 1% have recently been described for prostate cancer. A recurrent mutation in the coding region of the *HOXB13* gene, which maps to an area of interest at 17q21-q22 identified by GWAS, was present in 1.4% of cases compared to only 0.1% of controls and was significantly more common in men with early-onset, familial prostate cancer (3.1%) than in those with late-onset, sporadic disease (0.6%) (Ewing et al, 2012). This mutation increases overall risk of disease almost five times, and more than eight times in men under age 55 years or with a family history (Witte et al, 2013). Several studies have suggested a familial coaggregation of prostate cancer with breast cancer (Thiessen, 1974; Tulinius et al, 1992; Goldgar et al, 1994), and there is clear evidence that both *BRCA1* and *BRCA2* carriers are at increased risk of prostate cancer, especially for early-onset disease. *BRCA1* has been estimated to increase risk by 1.8- to 3.5-fold and *BRCA2* from 4.6- to 8.6-fold in men under 65 (reviewed in Castro and Eeles, 2012). *BRCA*-associated cancers, especially *BRCA2*, are also more likely to present with higher grade, locally advanced, and metastatic disease and have worse cancer-specific and metastasis-free survival after prostatectomy (Castro et al, 2013).

The relative contribution of common and rare alleles to the overall germline risk of prostate cancer is illustrated in Figure 107-3. One interesting observation from GWAS is that most of the variant alleles that confer increased risk are found in noncoding regions of the genome (Choudhury et al, 2012; Eeles et al, 2014), such that

their underlying mechanism of action is not readily understood. Another common germline variation, copy number variants, has only recently begun to be studied in prostate cancer and their biologic and clinical relevance is as yet undetermined (reviewed in Barbieri et al, 2012).

Using germline information to predict the risk of developing prostate cancer for individuals or on a population basis has yet to be realized owing to the low penetrance of relevant alleles in the general population, cost, lack of ability of most alleles (alleles of *BRCA* being a notable exception) to predict for disease that is biologically significant, and lack of evidence that targeted prevention strategies or early intervention will have a meaningful impact on outcome. This body of knowledge, however, sets the stage for improved screening, prevention, and intervention strategies as the biologic function of each risk allele is understood.

KEY POINTS: FAMILIAL AND GERMLINE GENETIC INFLUENCES

- Both genetics and environment are important in the origin and evolution of prostate cancer.
- GWAS have identified multiple chromosomal loci and specific variant alleles in germline DNA that confer risk of getting prostate cancer.
- For commonly inherited variants, the predictive value is rarely more than 1.5 times baseline risk, which is too low to provide clinical utility as a way of identifying individual men at risk for developing prostate cancer. Models that include multiple risk loci or less common alleles that confer greater risk will be necessary to accomplish individual risk prediction.
- *HOXB13* and *BRCA* are two genes that substantially increase individual risk. *BRCA*-related tumors present with more aggressive clinical features.

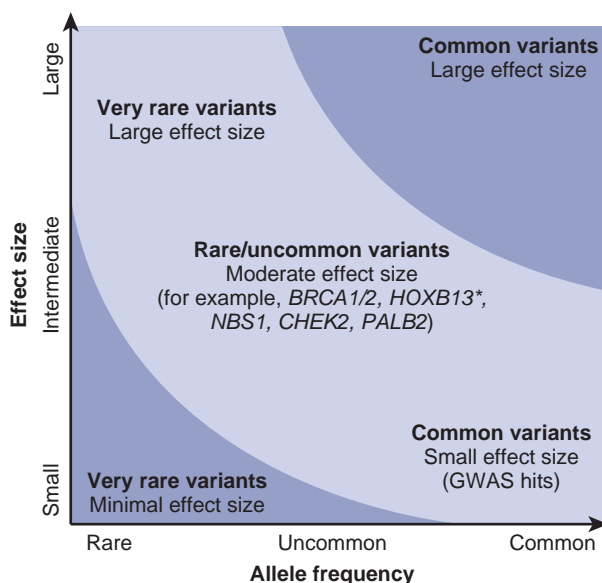


Figure 107-3. Germline influences on susceptibility to prostate cancer. The genetic architecture of prostate cancer illustrates that susceptibility is highly likely to be due to a mixed model of common and rare genetic variants. *More common in the Scandinavian population—carrier frequency between 3.5% and 4.6% (Laitinen et al, 2013; Karlsson et al, 2014). GWAS, genome-wide association study. (From Eeles R, Goh C, Castro E, et al. The genetic epidemiology of prostate cancer and its clinical implications. *Nat Rev Urol* 2014;11:18–31.)

Inflammation and Infection

Infections cause about 16% of all cancers worldwide (de Martel et al, 2012). Chronic inflammation leading to cellular hyperproliferation to replace damaged tissue contributes to the development of infection-associated cancers of the colon, esophagus, stomach, bladder, and liver (Coussens and Werb, 2002; De Marzo et al, 2007). Accumulating evidence suggests a similar process may underlie the development of prostate cancer, and although no specific infectious agent has been identified, inflammation caused by infection, dietary intake, or other causes likely contributes to development and progression of early-stage disease.

Inflammatory infiltrates and the histologic lesion called proliferative inflammatory atrophy (PIA) are frequent in clinical prostate specimens (De Marzo et al, 1999). PIA is a spectrum of lesions characterized by epithelial atrophy, low apoptotic index, and an increased proliferative index, usually associated with inflammatory infiltrates (Putzi and De Marzo, 2000). PIA appears to be a regenerative lesion developing as a consequence of infection or cell trauma resulting from oxidant damage, hypoxia, infection, or autoimmunity, and its hyperproliferative state may lead to cancer. PIA is often found adjacent to high-grade prostatic intraepithelial neoplasia (HGPIN) or early cancer (Putzi and De Marzo, 2000), and there is an identifiable genetic pathway between PIA, HGPIN, and cancer (Shah et al, 2001; Nakayama et al, 2003; Nelson et al, 2003).

Genetic alterations in genes that regulate the inflammatory response and mediate DNA repair, as well as histologic observations in prostate cancer, strongly suggest that compromised cellular defenses against inflammatory oxidants may initiate and/or perpetuate prostatic carcinogenesis (Klein and Silverman, 2008). Oxidative stress is mediated by reactive oxygen and nitrogen

species that bind DNA and cause mutations, and oxidant stresses from exogenous and endogenous sources are implicated in the accumulation of DNA damage that occurs with aging and subsequently leads to malignant change (Coussens and Werb, 2002).

Potential triggers for inflammation include dietary carcinogens (especially from cooked meats), estrogens, and infectious agents. Alone or together, these agents cause epithelial damage that results in an acute, chronic, and/or relapsing inflammatory response that results in epithelial cell hyperproliferation, DNA damage, accumulation of genetic defects, and ultimately precancerous lesions such as PIA and prostatic intraepithelial neoplasia (PIN) (Nelson et al, 2003) (Fig. 107-4).

There has been much interest and effort in trying to isolate and identify an infectious agent or agents that cause prostate cancer. Some, but not all, epidemiologic evidence suggests that prostate cancer may have an infectious etiology. For example, two meta-analyses examining 34 case-control studies reported statistically significant associations of prostate cancer with a history of sexually transmitted infection (STI) (RR 1.4) or prostatitis (OR 1.57) (Dennis and Dawson, 2002; Dennis et al, 2002). However, recent studies assessing the association between infection and prostate cancer have shown mixed results. In the Health Professionals Follow-up Study (Sutcliffe et al, 2006), a prospective study of 51,529 American male health professionals ages 40 to 75 years, no association was found between a self-reported history of gonorrhea or syphilis and prostate cancer, although the incidence of STI was very low in this

population. In addition, no overall correlation between prostate cancer and clinical prostatitis was found. Similarly in this cohort, no associations were observed between *Chlamydia trachomatis*, human papillomavirus (HPV)-16, HPV-18, and HPV-33 antibody seropositivity, and prostate cancer (Sutcliffe et al, 2007a). Conversely, in a small case-control study in African-American men (Sarma et al, 2006), a history of gonorrhea or prostatitis increased the odds of prostate cancer by 1.78-fold (95% CI 1.13 to 2.79) and 4.93-fold (95% CI 2.79 to 8.74), respectively, even after adjusting for potential confounders. Furthermore, men reporting 25 or more sexual partners had 2.80 times the odds of being diagnosed with cancer (95% CI 1.29 to 6.09) compared to men with 5 or fewer partners (additional data on this issue can be found in the section on Sexual Activity/Sexually Transmitted Infections).

Several studies have demonstrated evidence of viral pathogens in human prostate tissue, including HPV, human herpes simplex virus type 2, cytomegalovirus, human herpesvirus type 8, and BK virus (Strickler and Goedert, 2001; Zambrano et al, 2002; Samanta et al, 2003; Das et al, 2008). By and large these findings have not been confirmed, and a recent survey of The Cancer Genome Atlas using RNA-Seq found no evidence of DNA viral transcripts in prostate nor most other common tumors other than known virally associated cancers (Khoury et al, 2013). Initial reports of the association of the RNA virus xenotropic murine leukemia virus (MLV)-related virus (XMRV) with human prostate cancer proved unfounded (Lee et al, 2012).

In a study examining the bacterial flora of prostate cancer, Sfanos and Isaacs (2008) demonstrated the presence of 83 distinct microorganisms by sequencing bacterial 16S ribosomal DNA in core samples of 30 prostate cancers, most of which were not found by routine culture methods. The bacterium *Propionibacterium acnes* has been reported to be the predominant species in both benign and malignant prostate cancer and is associated with intraprostatic inflammation (Cohen et al, 2005; Alexeyev et al, 2006). This bacterium also induces an inflammatory response in prostate cell lines (Mak et al, 2012). Several animal models of bacterial-induced chronic prostatic inflammation induced by *P. acnes*, including a species isolated from a human prostatectomy specimen, have been established and should prove useful for testing the infection-inflammation-cancer hypothesis (Olsson et al, 2012; Shinohara et al, 2013). At present, no infectious agent has been proven to cause prostate cancer.

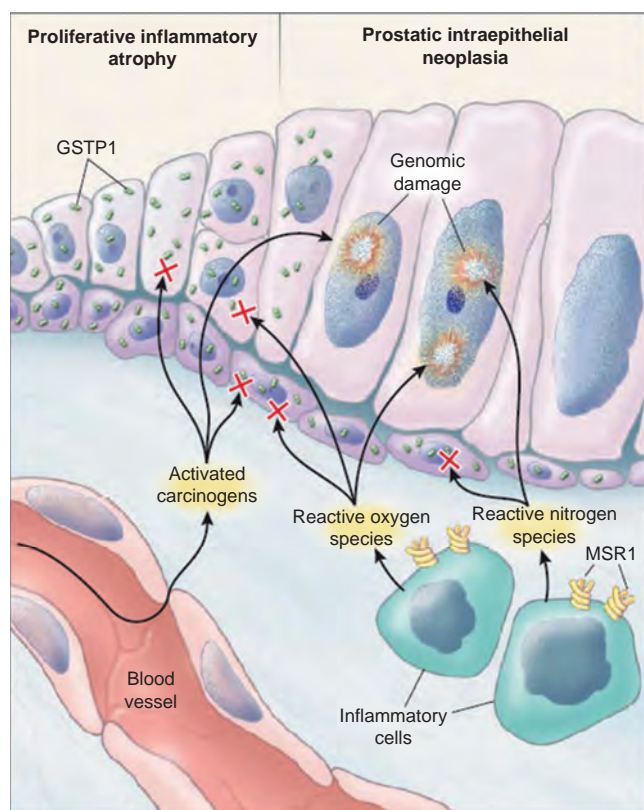


Figure 107-4. Effects of inflammation on early events in prostate cancer. Dietary carcinogens, activated by liver cytochrome P-450 enzymes, and oxidant carcinogens, elaborated by inflammatory cells (shown expressing the trimeric macrophage-scavenger receptor MSR1), can be detoxified in basal epithelial cells and in cells of proliferative inflammatory atrophy by the p-class glutathione S-transferase (GSTP1, shown as a dimer). Cells of prostatic intraepithelial neoplasia, devoid of GSTP1, undergo genomic damage mediated by such carcinogens. A red X indicates interception and detoxification of carcinogens. (From Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. *N Engl J Med* 2003;349:366–81.)

KEY POINTS: INFLAMMATION AND INFECTION

- Chronic inflammation leading to cellular hyperproliferation to replace damaged tissue contributes to the development of prostate cancer.
- Both genetic and histologic observations suggest that compromised cellular defenses against inflammatory oxidants are important in prostate cancer initiation and promotion.
- Inflammation may be triggered by diet, infection, estrogens, or other environmental agents.
- Some epidemiologic data suggests that a history of sexually transmitted infection or prostatitis is associated with a higher risk of prostate cancer. At present, no infectious agent has been proven to cause prostate cancer.
- Histologic evidence of inflammation, as manifested by proliferative inflammatory atrophy, is common in prostate cancer and may represent a key pathobiologic process in its development.

Molecular Epidemiology

Molecular epidemiologic approaches have identified many biomarkers of exposure measured in blood or tissue and evaluated them in relation to incidence or mortality. These biomarkers capture aspects of diet, environmental exposures, and hormonal

and other factors for which concentrations are partly genetically determined. A brief survey of major molecular epidemiologic studies relating to prostate cancer is presented.

Androgens

Androgens influence the development, maturation, and maintenance of the prostate, affecting both proliferation and differentiation of the luminal epithelium. Exposure of the prostate to androgens at key developmental times plays an important role in prostate carcinogenesis. Androgens are also important in the maintenance of established cancers, as supported by clinical experience where the majority of prostate cancers initially respond to androgen deprivation, by the central role of androgen receptor (AR) biology in castrate-resistant disease, and by results of the PCPT and Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trials, which demonstrated that inhibition of the conversion of testosterone (T) to the more potent dihydrotestosterone (DHT) by a 5 α -reductase inhibitor (5ARI) reduces the incidence of prostate cancer by 25% to 30% (Thompson et al, 2003, 2013; Andriole et al, 2010). Establishing the precise effect of androgens on risk is complicated by the complex biology of the androgen axis: (1) androgen levels are affected by both synthesis and metabolism, which are each controlled by multiple genes; (2) the biologic effects of an androgen are exerted at the cellular level by its interaction with the AR; and (3) intraprostatic and serum levels of specific androgens may differ. Polymorphisms in both synthetic and metabolic genes, including AR (Balic et al, 2002), the 5 α -reductase type 2 isoenzyme (Makridakis and Reichardt, 2004; Li et al, 2013), and genes involved in T biosynthesis (Chang et al, 2002), have been reported to affect risk. A meta-analysis of 47 published studies with 13,346 cases and 15,172 controls concluded that men with shorter CAG repeats in the AR were at higher risk for prostate cancer with an OR of 1.21 (95% CI 1.10 to 1.34), with the effect most evident in Caucasians and Asians (Sun and Lee, 2013). Polymorphisms in both the type 1 and type 2 5 α -reductase genes have been shown to affect both circulating and intraprostatic androgen levels (Lévesque et al, 2014).

High serum androgen levels have long been hypothesized to be a risk factor for prostate cancer. However, studies examining this association have been inconsistent, with only some studies finding an association between specific hormones and prostate cancer risk. A pooled analysis of 18 prospective studies assessing this association using data from 3886 men with prostate cancer and 6438 control subjects (Endogenous Hormones and Prostate Cancer Collaborative Group, 2008), failed to detect an association between the risk of prostate cancer and serum concentrations of T, calculated free T, DHT, dehydroepiandrosterone, androstenedione, androstanediol glucuronide, estradiol, or calculated free estradiol. The only positive finding was a modest inverse association between risk and serum concentration of sex hormone-binding globulin. The results suggest that one-time measurements of serum sex hormones in adulthood are not a good measure of prostate cancer risk. No studies have reported on intraprostatic androgen levels as a measure of risk in unaffected men.

Estrogens

Estrogens have both direct and indirect effects on prostatic growth and development and likely play a role in prostate cancer initiation and progression. Traditionally, estrogens have been considered protective against prostate cancer and have been used as a treatment for advanced disease. This treatment effect is primarily through a negative feedback on the hypothalamic-pituitary-gonadal axis, and also through a direct inhibitory effect of estrogens on prostate epithelial cell growth. However, there is increasing direct evidence that estrogens may act as procarcinogens in the prostate. In a novel study, isolated prostate progenitor cells from normal human prostate that were grown in three-dimensional culture to form prostatospheres expressed

estrogen receptor (ER)- α , ER- β , and estrogen-responsive G protein-coupled receptor 30 messenger RNA and protein, and grew in response to exogenous estradiol (Hu et al, 2011). When co-cultured with rat urogenital sinus mesenchyme and grown in a renal subcapsular model, subsequent exposure to T and estradiol resulted in the sequential induction of epithelial hyperplasia, PIN, and locally invasive prostate cancer in the human progenitor cells, providing direct evidence that these cells are estrogen sensitive and that estradiol is a carcinogen for human prostate epithelium. Proposed underlying mechanisms for this effect include epigenetic modifications (especially in utero), genotoxicity, induction of hyperprolactinemia, proinflammatory changes, and prostatic ER-mediated changes (reviewed in Nelles et al, 2011). The bulk of reported evidence relates to ER-mediated effects (Prins and Korach, 2008). ER- α expression, present in stromal and basal cells, is silenced in early prostate cancers and re-emerges with disease progression. Prostate epithelial ER- β may play an important role in cancer initiation, with loss of ER- β potentially contributing to disease progression in organ-confined disease (Prins and Korach, 2008). The re-emergence of ER- β expression in metastatic prostate cancer suggests a potential role in progression to castrate-resistant disease.

At a more macro level, age-related prostatic disease parallels increases in serum estrogens, and there is a low incidence of prostate cancer in cultures with diets rich in phytoestrogens (Denis et al, 1999). As for androgens, serum levels of estrogen do not correlate with prostate cancer risk (reviewed in Nelles et al, 2011), though it is clear that estradiol can be produced from T by intraprostatic aromatase (Ellem et al, 2004) and its potential biologic effects may not be evident from serum levels. Interestingly, an aromatase knockout mouse model demonstrated a lower risk of prostate cancer compared to wild-type mice after exposure to T and estrogen; the results suggest that intraprostatic estrogen production is important in prostate cancer development (Ricke et al, 2008). Similar to effects seen for androgen metabolism genes, polymorphisms in two estrogen metabolism genes, CYP1B1 and CYP19, have been observed to increase the risk of prostate cancer in a cohort of French men (Cussenot et al, 2007), and polymorphisms in CYP19A1 and UGT1A1 were associated with increased risk in the PCPT (Tang et al, 2011).

Insulin-like Growth Factor Axis

Insulin-like growth factors (IGFs) are peptide hormones that play an essential role in metabolism and body growth and exert influence on fundamental cellular processes, including proliferation, migration, and differentiation. The IGF axis consists of two ligands (IGF-I and IGF-II), two receptors (type I [IGF-IR] and type II/ mannose 6-phosphate receptor [IGF-IIR/M6P-R]), and six binding proteins (numbered IGFBP-1 to -6), the latter of which modulate IGF bioavailability (Biernacka et al, 2012). IGFs may also bind the insulin receptor, which shares many downstream targets with the IGF receptors, making the interaction of these molecules complex.

IGFs promote proliferation and inhibit apoptosis in normal prostate and tumor cells in vitro (Uzoh et al, 2011). The IGFbps can influence prostate growth independent of IGF. In particular, IGFBP-2 stimulates proliferation and IGFBP-3 promotes apoptosis and may mediate growth inhibition by 1,25-dihydroxyvitamin D (Chatterjee et al, 2004; Ingermann et al, 2010). IGFBP-3 can be cleaved by PSA, reducing its pro-apoptotic activity (Koistinen et al, 2002). In cell lines, IGF-1 can bind and activate the AR in the absence of androgen and promote androgen-independent growth (Krueckl et al, 2004).

Results of epidemiologic studies linking the IGF axis to risk have shown mostly null findings, though the data suggest a potential effect on cancer progression rather than initiation (reviewed in Uzoh et al, 2011). For example, in the PLCO trial there was no association of the IGF axis with risk of developing prostate cancer, but there was a suggestion that the ratio of IGF-1 to IGFBP-3 in obese men was predictive of disease aggressiveness (Weiss et al, 2007).

Leptin

Leptin, a peptide hormone produced by adipocytes, contributes to the control of body weight by appetite suppression and modulating energy utilization (Friedman, 2002). Obese men become leptin resistant and exhibit elevated plasma leptin (Chu et al, 2001). Epidemiologic studies assessing the association between circulating leptin concentrations and prostate cancer have yielded mixed results (Chung and Leibel, 2006). A meta-analysis concluded that a germline variant allele in the *LEP* gene is associated with a 1.2 to 1.3 times increased risk (He and Xu, 2013). There is evidence that leptin plays a role in the development of advanced disease (Ribeiro et al, 2006) by growth stimulation of the androgen-independent prostate cancer cell lines DU145 and PC-3 (Somasundar et al, 2004; Deo et al, 2008), inducing expression of vascular endothelial growth factor and basic fibroblast growth factor and stimulation of cell migration (Frankenberry et al, 2004). A variant allele in the gene for the leptin receptor, *LEPR*, was found to be the strongest predictor among five candidate genes for fatal prostate cancer in a Swedish population-based study (Lin et al, 2011).

Vitamin D, Vitamin D Receptor, and Calcium

Vitamin D (1,25-dihydroxyvitamin D₃) is an essential vitamin that is a part of the steroid hormone superfamily. Human sources include both dietary intake and sunlight exposure, which converts inactive to active vitamin D in the skin. Interest in vitamin D as a determinant of prostate cancer risk comes from epidemiologic observations (Schwartz, 2013):

1. Men living in northern latitudes with less sunlight-derived ultraviolet exposure have a higher mortality rate from prostate cancer.
2. Prostate cancer occurs more frequently in older men, in whom vitamin D deficiency is more common because of both less ultraviolet exposure and age-related declines in the hydroxylases responsible for synthesis of active vitamin D.
3. African-Americans, whose skin melanin blocks ultraviolet radiation and inhibits activation of vitamin D, have the highest worldwide incidence and mortality rates.
4. Dietary intake of dairy products rich in calcium, which depresses serum levels of vitamin D, is associated with a higher risk of prostate cancer.
5. Native Japanese, whose diet is rich in vitamin D derived from fish, have a low incidence of prostate cancer. In addition, prostate cancer cells express vitamin D receptor, and many studies have demonstrated significant biologic effects of vitamin D, including inducing cell cycle arrest and inhibiting invasion, cell migration, metastasis, and angiogenesis.

Like other steroidal regulators of prostate growth (i.e., androgens and estrogens), normal prostate epithelial cells can synthesize vitamin D, which in turn can inhibit their growth (Barreto et al, 2000). The enzyme that converts the prohormone 25-hydroxyvitamin D to the most active form of 1,25-dihydroxyvitamin D is diminished in prostate cancer, leading to a potential loss of autocrine-regulated growth inhibition (Whitlatch et al, 2002). Vitamin D receptor (VDR), which binds to 1,25-dihydroxyvitamin D from serum-derived (diet, sunlight, and paracrine sources) and autocrine sources, is also widely expressed by normal prostate epithelium (Krill et al, 2001). Polymorphisms resulting in a VDR with lower activity have been associated with increased risk for prostate cancer (John et al, 2005). Studies of plasma vitamin D levels and prostate cancer risk are mixed, with most showing no or a weak association (reviewed in Schwartz, 2013). However, there is a clear association of vitamin D levels and risk of lethal prostate cancer, as illustrated by findings in the Health Professionals Follow-up Study, where those with the highest baseline levels of plasma vitamin D had a substantially reduced risk of lethal prostate cancer, and some variant alleles in vitamin D metabolism genes and the VDR gene also modified risk (Shui et al, 2012).

A meta-analysis of 45 observational studies found null results for dairy, milk, calcium, or vitamin intake and risk of prostate

cancer (Huncharek et al, 2008). The Cancer Prevention Study II Nutrition Cohort, a prospective cohort of 65,321 men, demonstrated a modestly increased RR of 1.2 for total calcium intake (dietary and via supplements) and 1.6 for high dietary calcium intake alone (≥ 2000 vs. < 700 mg/day), but not for dairy intake (Rodriguez et al, 2003). The results suggest that very high calcium intake above daily recommendation may modestly increase risk, a finding mirrored by results of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) showing that high doses of vitamin E increase risk of diagnosis (see [Vitamins and Micronutrients](#)).

KEY POINTS: MOLECULAR EPIDEMIOLOGY

- Androgen exposure of the prostate plays an important but incompletely defined role in prostate carcinogenesis.
- Long-term absence of androgen exposure to the prostate appears to protect against the development of cancer, but a dose-response relationship between androgen levels and cancer risk has not been established.
- Polymorphisms in genes encoding for the androgen receptor and various enzymes related to androgen metabolism may be important determinants of prostate cancer risk.
- Estrogen is also important in prostate cancer development, and may have varying effects depending upon local tissue activity of ER- α and ER- β . Intraprostatic estrogen production may also be important in prostate cancer development.
- The IGF axis is important in prostate cancer risk and progression.
- Vitamin D and its interaction with its receptor modulate risk and disease aggressiveness.

Other Influences

Sexual Activity/Sexually Transmitted Infections

Sexual activity has been hypothesized to expose the prostate to infectious agents, which may increase the risk of cancer by direct infection with a carcinogenic organism (akin to HPV and cervical cancer) or by initiating an inflammatory response that has known downstream carcinogenic effects. A sexually transmitted etiology for prostate cancer was first proposed in the 1950s based on an observed increased prevalence in uncircumcised men (Ravich and Ravich, 1951). A groundbreaking meta-analysis by Dennis and Dawson (2002) suggested an elevated risk of prostate cancer among men with a history of STI (especially syphilis), increasing frequency of sexual activity, and a higher number of sexual partners; however, subsequent case-control and cohort studies have not always confirmed these observations (reviewed in Sutcliffe, 2010). Prospective studies that have included measurement of serologic markers of STI have generally reported null findings. For example, in the PLCO trial a borderline increased risk of prostate cancer for a history of any STI was observed, but null results were reported for serum levels of antibodies to *C. trachomatis*, HPV-16 and -18, human herpes simplex virus type 2, cytomegalovirus, and human herpesvirus type 8 (Huang et al, 2008). A prospective cohort study of more than 68,000 men in California reported that those with a history of prostatitis or longer duration of prostatitis symptoms had an increased risk of prostate cancer compared to men with no history (RR 1.30) or shorter duration of symptoms (Cheng et al, 2010). However, this risk disappeared in those screened for cancer, and a history of STIs was not associated with risk. More recent work has identified two nontraditional infectious agents, the protozoan *Trichomonas vaginalis* and the skin bacterium *P. acnes*, as potential causes of prostatic infection and inflammation that are associated with increased risk of prostate cancer (Sutcliffe, 2010; Shinohara et al, 2013).

Studies have also suggested a protective association between prostate cancer and frequency of ejaculation, with RR ranging from

0.66 to 0.89 (Giles et al, 2003; Leitzmann et al, 2004). In the Giles and colleagues (2003) study the protective effect was seen in men who reported more than five ejaculations per week in their 20s. The large prospective cohort study by Leitzmann and coworkers (2004) demonstrated a protective effect for men reporting 21 or more ejaculations per month in their 20s and 40s, in the previous year, and as a lifetime average. The biologic basis for this effect is not known.

Vasectomy

A relationship between vasectomy and prostate cancer risk was initially suggested in a case-control study by Honda and associates (1988) and seemingly confirmed a few years later with the report of an RR of 1.6 based on two large cohort studies (Giovannucci et al, 1993a, 1993b). Not all subsequent studies have been confirmatory (reviewed in Köhler et al, 2009) and the positive studies are limited by potential confounders, including differences in vasectomy rates between cases and controls and detection bias resulting from a higher likelihood that someone undergoing vasectomy will see a urologist for screening. Two more recent case-control studies, which are notable for their careful matching of rates of vasectomy and screening, showed no increased risk for prostate cancer after vasectomy when controlling for age at diagnosis, age at vasectomy, time since vasectomy, family history of prostate cancer, tumor stage, and race (Cox et al, 2002; Holt et al, 2008). At present, the weight of evidence does not support an increased risk of prostate cancer in men who have undergone vasectomy.

Smoking

Cigarette smoke may be a risk factor for prostate cancer because it is a source of cadmium exposure, it increases circulating androgen levels, and it causes significant cellular oxidative stress. Individual case-control and cohort studies have produced conflicting results on the association of smoking and risk, but a recent meta-analysis of 24 cohort studies that included more than 26,000 patients showed a 9% to 30% increase in both incident and fatal prostate cancer associated with smoking, which was attenuated in former compared with current smokers (Huncharek et al, 2010). Some studies have suggested an association with more advanced stage at diagnosis, perhaps related to less intensive screening (Byrne et al, 2010), and there is clear evidence that current smokers are at higher risk of biochemical recurrence, metastasis, and prostate cancer-specific mortality than nonsmokers across all treatment modalities even when intensity of screening is accounted for (Kenfield et al, 2011; Moreira et al, 2014).

Diet

Descriptive epidemiologic studies of migrants, geographic variations, and temporal studies suggest that dietary factors may contribute to prostate cancer development (Bostwick et al, 2004). The incidence of latent prostate cancers is similar around the world, but the incidence of clinically manifest cancers differs, with Asians having the lowest rates of clinical disease (Center et al, 2012). Thus the most convincing evidence for the role of diet and other environmental factors in modulating prostate cancer risk comes from migration studies showing an increased incidence of prostate cancer in first-generation immigrants to the United States from Japan and China (Muir et al, 1991; Shimizu et al, 1991). These observations suggest that diet may play a role in tumor progression, allowing latent cancers to become clinically evident. A strong positive correlation exists between prostate cancer incidence and the corresponding rates of several other diet-related cancers, including breast and colon (Bostwick et al, 2004). Nonetheless, several prospective studies have failed to show an association of self-reported dietary patterns or intervention with “healthy” foods and risk of prostate cancer. In the Health Professionals Follow-up Study, consumption of a diet rich in fruits, vegetables, whole grains, fish, and poultry had a risk of prostate

cancer similar to that of a more traditional diet of meat, fat, and processed grain (Wu et al, 2006). Similarly, in the European Investigation into Cancer and Nutrition cohort, total fruit and vegetable consumption was not correlated with overall prostate cancer risk, and in a randomized intervention trial of colon polyp prevention, consumption of a low-fat and high-fruit, -vegetable, and -fiber diet over 4 years had no effect on serum PSA (Shike et al, 2002; Key et al, 2004).

Epidemiologic studies have also suggested a moderate to strong association between total and specific fats and the risk of developing prostate cancer (Chan et al, 2005). However, results from large prospective studies showed no association between dietary fat intake and prostate cancer risk (Park et al, 2007; Wallstrom et al, 2007; Crowe et al, 2008). A meta-analysis of observational studies demonstrated only a weak association between higher intake of total fat and risk of prostate cancer (RR 1.2) (Dennis et al, 2004). Observations on the association of dietary fat and risk may have alternative explanations. Diets high in meat that are sources of fat are also usually low in vegetables, which contain nutrients that may protect against prostate cancer. Furthermore, meats and dairy products contain other constituents, such as zinc and calcium, that may affect prostate cancer risk.

The nutritional complexity of the typical Western diet, the association of healthier dietary habits with healthier lifestyle choices (physical activity and smoking avoidance), and the potential interaction of specific nutrients with genetic variability among individuals are significant limitations to understanding how diet influences risk. Masko and colleagues (2013) have summarized the state of preclinical and clinical evidence that specific dietary components may exert an influence on prostate cancer risk and progression. Recent revelations about the role of intratumoral androgen in driving castrate-resistant prostate cancer have increased focus on cholesterol as a risk factor (Sharifi, 2013). Intracellular cholesterol may be carcinogenic by being a proximate steroidal precursor to both T and DHT, as well as by enhancing Akt signaling (Lee et al, 2013). Recent molecular work has demonstrated that ABCA1 (ATP-binding cassette, subfamily A, member 1), the major cellular cholesterol efflux transporter, is preferentially downregulated by promoter hypermethylation in intermediate- to high-grade prostate cancers and that its expression levels are inversely correlated with Gleason grade (Lee et al, 2013). Coupled with epidemiologic evidence that lower levels of serum cholesterol and use of cholesterol-lowering agents (statins) reduce the risk of aggressive and advanced-stage disease, loss of cholesterol homeostasis may be a contributor to prostate cancer risk and progression (Platz et al, 2006, 2009).

Obesity

Obesity as measured by body mass index (BMI) has been suggested to be a risk factor for prostate cancer because of their common occurrence in middle-aged men and clear links to colon and breast cancer risk (Giovannucci, 1995; Madigan et al, 1998). White fat in mammals serves not only as an important energy reservoir, but also as an endocrine organ, with secretion of cytokines and agents with cytokine-like activity (tumor necrosis factor- α ; interleukin-1 β , -6, -8, and -10; and transforming growth factor- β) as well as their soluble receptors (Trayhurn and Wood, 2004). Treatment of obesity through reduction in fat intake and increased exercise has been shown to reduce oxidative stress, suggesting that lifestyle modification could be important in reducing the risk of prostate cancer (Roberts et al, 2002).

Three meta-analyses of observational studies have reported a modestly increased incidence of prostate cancer in obese men, with RR ranging from 1.01 per 1-kg/m² increase in BMI to 1.03 to 1.05 per 5-kg/m² increase (Bergstrom et al, 2001; MacInnis and English, 2006; Renehan et al, 2008). Three large prospective studies, examining the association between obesity and prostate cancer risk by stage and/or grade at diagnosis, suggested that obesity was associated with a lower risk of low-grade disease, but a greater risk of high-grade disease (Gong et al, 2006;

Rodriguez et al, 2007; Wright et al, 2007). Potential explanations for the latter observation include the association of obesity with higher serum estradiol, insulin, free IGF-1, and leptin levels, and lower free T and adiponectin levels, which have also been associated with more aggressive prostate cancer (Buschemeyer and Freedland, 2007). Another possible explanation is detection bias. Higher BMI has been shown to be associated with lower serum PSA (Baillargeon et al, 2005) and larger prostates (Freedland et al, 2006), which in obese men could lead to fewer prostate biopsies and more sampling error. However, given that the association between obesity and high-grade disease was also observed in the PCPT, a study in which all men underwent biopsy, it is unlikely that detection bias is solely responsible for this finding (Gong et al, 2006).

Obesity is associated with higher rates of biochemical failure after surgery or external beam radiotherapy and a 15% to 20% increase in prostate specific-cancer mortality per 5-kg/m² increase in BMI (Masko et al, 2013). These observations likely reflect higher grade and more locally advanced disease at presentation, technical challenges in surgery and radiotherapy in obese men, and more aggressive biology driven by adipocyte-derived biologic factors. This complex interplay and specific molecular mechanisms that may underlie the biologic effects of obesity are illustrated in Figure 107-5.

Alcohol Consumption

Alcohol consumption and risk of prostate cancer is of interest because of the association of alcohol with other cancers, its effect on estrogen and T, and the high content of polyphenolic compounds with antioxidant activity in red wine (Sutcliffe et al, 2007b). Epidemiologic studies, including both case-control and cohort designs, have reported mixed results, with some suggesting increased risk, some null, and some suggesting a protective effect of alcohol use (reviewed in McGregor et al, 2013). One contemporary case-control study found lower PSA levels and an increased risk of high-grade disease at detection in heavy drinkers (Zuccolo et al, 2013).

KEY POINTS: OTHER INFLUENCES

- Smoking increases the risk of disease recurrence and death resulting from prostate cancer.
- Diet likely affects the risk of getting prostate cancer and disease progression, but the nutritional complexity of the typical Western diet, the association of healthier dietary habits with healthier lifestyle choices, and the potential interaction of specific nutrients with genetic variability among individuals are significant limitations to understanding how.
- Obesity is associated with lower serum PSA, increases the risk of getting high-grade prostate cancer, and is associated with higher treatment failure rates and disease-specific mortality.

ETIOLOGY AND MOLECULAR GENETICS

Prostate cancer is unique among solid tumors in that it exists in two forms: a histologic or clinically occult form that can be identified in approximately 30% of men older than 50 years and 60% to 70% of men older than 80 years of age, and a clinically evident form that affects approximately 1 in 6 U.S. men. Latent prostate cancer is believed to have a similar prevalence worldwide and among all ethnicities, whereas the incidence of clinical prostate cancer varies dramatically between and within different countries. For this reason, an understanding of prostate cancer etiology must encompass the steps leading to both the *initiation* of histologic cancer and *progression* to clinically evident disease. The exact molecular relationship between latent and clinical cancers is not known, and it is likely that the progression from the former to the latter is a biologic continuum with overlap in the associated molecular events. Mutations, downregulation by promoter methylation and other mechanisms, and protein modification have all been implicated in progression of prostate cancer.

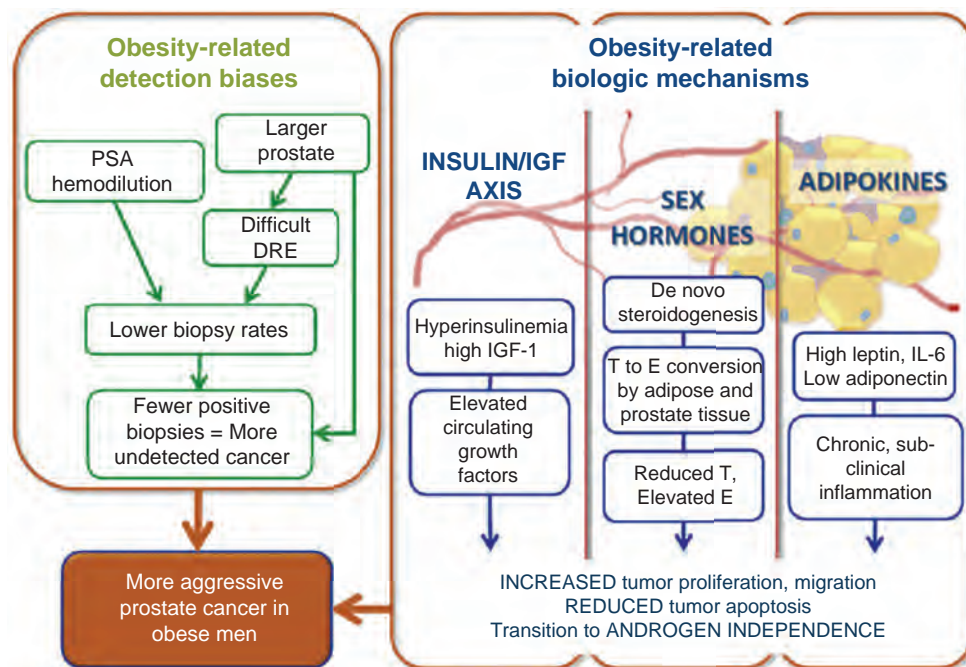


Figure 107-5. The complex interplay between detection bias and biology in obese men. DRE, digital rectal examination; E, estrogen; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; PSA, prostate-specific antigen; T, testosterone. (From Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. *Eur Urol* 2013;63:800–9.)

The Influence of Androgens

As previously discussed, androgens play an important role in prostate carcinogenesis. The primary androgen of the prostate is DHT, irreversibly catalyzed from T by 5 α -reductase. DHT binds to intracytoplasmic ARs with much greater affinity than T, and binding of DHT to the AR enhances translocation of the steroid-receptor complex into the nucleus and activation of androgen response elements (Steers, 2001). Type 1 5 α -reductase is expressed primarily in the skin and liver and to lesser extent in prostate, while the type 2 enzyme is expressed predominantly in prostate epithelium and other genital tissues (Andriole et al, 2004a, 2004b).

Functional type 2 5 α -reductase is a prerequisite for normal development of the prostate and external genitalia in males, and insufficient exposure of the prostate to DHT appears to protect against the development of prostate cancer. Males with inherited 5 α -reductase deficiency have minuscule prostatic tissue, and biopsies demonstrate stroma but no epithelium (Imperato-McGinley and Zhu, 2002). In addition to the lack of enzyme activity, a lack of T may also protect against the development of prostate cancer, as evidenced by the atrophic prostates seen in men after surgical castration (Wilson and Roehrborn, 1999). Nonetheless, there is evidence that even hypogonadal adults can develop prostate cancer (Morgentaler and Rhoden, 2006) and that their cancers may be driven by growth pathways that are independent of androgens (though they may still act through the AR, which is known to exhibit ligand promiscuity). For example, in the placebo arm of REDUCE, there was no association of serum T or DHT levels with risk of prostate cancer or with Gleason score (Muller et al, 2012). Locally weighted scatterplot smoothing analysis, a method that allows assessment of nonlinear associations, demonstrated that cancer detection was similar among men with low compared with normal baseline T levels and that higher T levels at baseline were associated with higher prostate cancer detection only if men had low baseline T (<10 nmol/L) (OR 1.23, 95% CI 1.06 to 1.43, $P = .006$). For men with normal baseline T (≥ 10 nmol/L), higher T levels at baseline were unrelated to prostate cancer risk (Fig. 107-6A). These results suggest a saturation point for T exposure as a risk factor for prostate cancer, and that further increases in T have no effect on risk, a hypothesis that is consistent with prior observations that serum androgen levels in adulthood do not predict risk of diagnosis. The saturation model hypothesis states that changes in serum T concentrations below the point of maximal androgen-AR binding will elicit substantial changes in prostate epithelial and cancer growth but that, once maximal binding is reached, the presence of additional androgen produces little further effect (Morgentaler and Traish, 2009) (Fig. 107-6B). This model is supported by animal studies showing that intraprostatic androgen levels and prostate mass in castrated rats are extremely sensitive to serum T around near-castrate levels, but plateau above this level (Wright et al, 1999) and similar findings in intact rats showing that normal prostate growth plateaus with increasing doses of exogenous T (Banerjee et al, 1994), as well as by numerous clinical observations in humans (reviewed by Morgentaler and Traish, 2009).

In summary, exposure of the prostate to androgens before or at puberty seems to be prerequisite for later development of prostate cancer, but beyond a certain level of exposure in adulthood the risk is not linear, at least as measured by serum androgen levels.

Stem Cells

Stem cells are required for the maintenance of high cell turnover tissues where cells continually need to be replaced, and like most epithelial organs, the prostate contains stem cells capable of multilineage differentiation. The existence of prostatic stem cells is suggested by studies demonstrating the ability of prostate epithelium to regress and regenerate with repeated cycles of castration and androgen replacement (Isaacs and Coffey, 1989; Bui and

Reiter, 1998; Tsujimura et al, 2002). Supportive evidence includes observations that (1) basal and luminal cells of prostate glands have distinct phenotypes, (2) cell culture experiments demonstrate that some prostate cancer cells are self-replicating while others are not, and (3) stem cell-enriched populations of cells can produce three-dimensional structures with basal cells and fully differentiated luminal cells in nude mice (Taylor and Risbridger, 2008). In theory, stem cells have the ability to self-renew and produce differentiated progeny that populate functional prostatic cells in both the stromal and epithelial compartments.

The epithelial cell layer of the prostate, from which cancers arise, contains four distinct cell types: basal, secretory luminal, neuroendocrine, and transit-amplifying cells that have distinct morphology and molecular phenotypes (Prajapati et al, 2013) (Fig. 107-7). Luminal cells, the predominant species, are nonproliferating, androgen dependent, and terminally differentiated; they secrete both PSA and acid phosphatase. Basal cells lack AR and are therefore androgen independent. Transit-amplifying cells express both basal and luminal cell markers, and likely represent an intermediate cell type between these two. Recent studies suggest that prostate stem cells comprise about 1% of the basal cell population, based on specific marker expression and growth characteristics (Collins et al, 2001). Various genetic events in these cells can result in tumor formation from any of these cell types (Maitland and Collins, 2008) (Fig. 107-8). The biologic processes that allow stem cells to become cancers may be different than for luminal cells: the former must remain in a protective niche that allows for generation of amplifying cells even without rapid cell growth; the latter may only require changes that lead to loss of growth control. Interestingly, there is evidence that stem cells contain *TMPRSS2:ERG* fusions that are thought to be one of the earliest events in prostate cancer initiation (Polson et al, 2013), and there is evidence in a mouse bacterial prostatitis model that infection-induced inflammation accelerates disease initiation by enhancement of basal-to-luminal cell differentiation and earlier appearance of PIN (Kwon et al, 2014). Stem cell biology makes them attractive targets for both prevention and therapy.

Somatic Genetic Changes Associated with Tumor Initiation and Progression

Substantial evidence exists that prostate cancer arises and progresses by core genetic alterations that activate oncogenes and inactivate tumor suppressors. These changes result most commonly from epigenetic and structural genomic changes, including amplification, deletion, somatic copy number aberrations, and chromosomal rearrangements that result in gene fusions with novel biologic properties. Unlike in many metabolic diseases, point and missense mutations resulting in altered proteins are rare in prostate cancer, estimated to occur in only about 1% of primary tumors (Taylor et al, 2010). As noted earlier, GWAS have shown that many germline mutations occur in non-coding regions of the genome, highlighting the potential role of regulatory molecules such as microRNA (miRNA) and long noncoding RNA (lncRNA) and suggesting an even deeper biologic complexity. A plethora of studies using next-generation sequencing, microarray data, and functional studies has led to an emerging comprehensive understanding of the temporal genomic events that occur in prostate cancer development and progression to the lethal phenotype of metastatic castrate-resistant disease, and an emerging molecular classification according to whether ETS family gene fusions are present or absent (Barbieri et al, 2012; Barbieri and Tomlins, 2014) (Fig. 107-9). This section highlights the most well-characterized genomic events in early-stage prostate cancer; for a comprehensive overview the reader is referred to a number of excellent primary sources (Taylor et al, 2010; Jerónimo et al, 2011; Prensner and Chinnaiyan, 2011; Frank and Miranti, 2013; Barbieri and Tomlins, 2014).

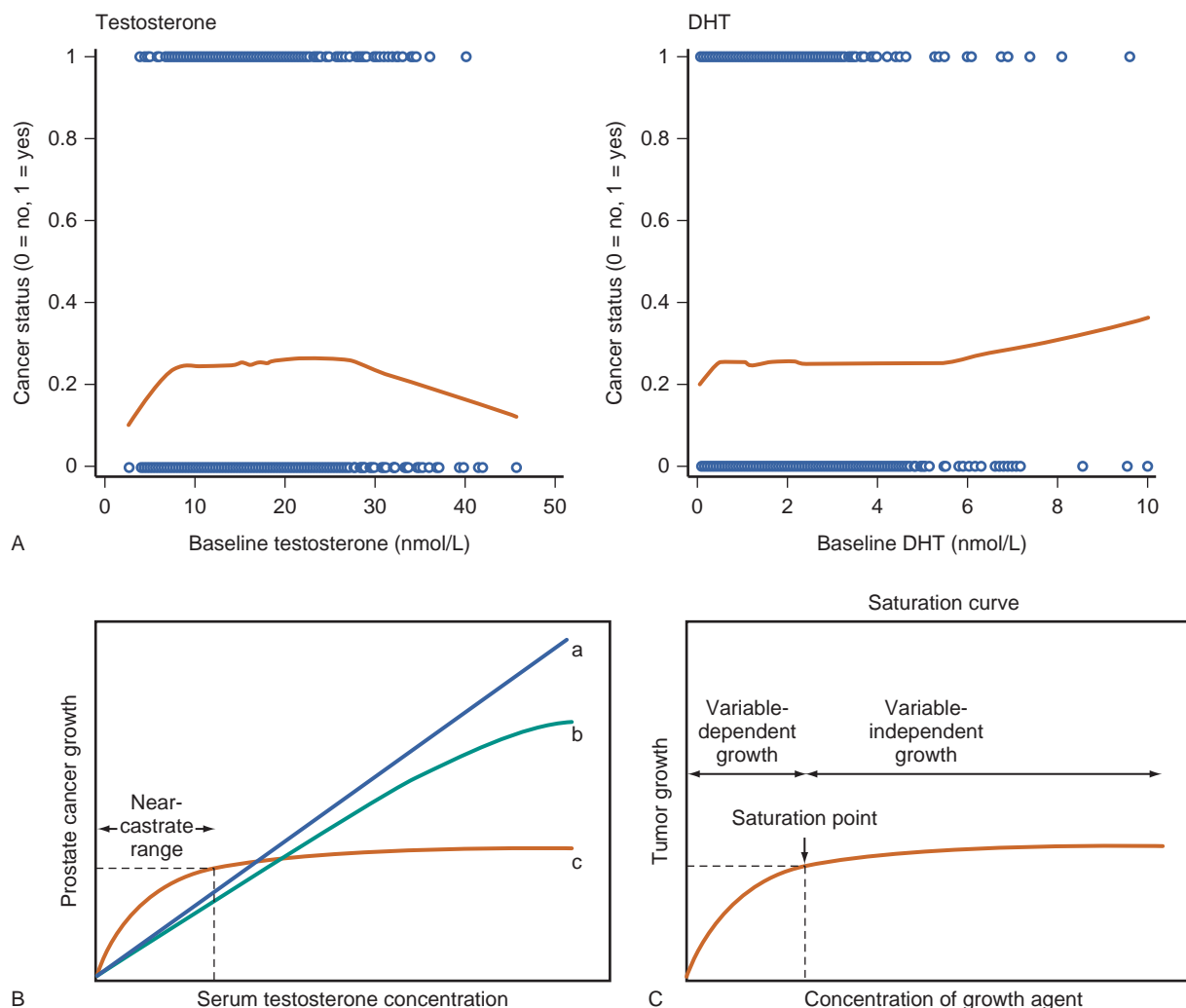


Figure 107-6. A, Locally weighted scatterplot smoothing of serum levels of testosterone and dihydrotestosterone (DHT) at baseline and final cancer status after considering all biopsies during 4 years of the REDUCE trial. The overlapping circles on the top and bottom of the chart represent each individual case. The left-hand portion of the curve for testosterone mimics that proposed in the saturation model for the effect of androgen on prostate cancer risk (see text). B, The traditional model of testosterone (T)-dependent prostate cancer growth suggested that greater serum T concentrations would lead to some degree of greater prostate cancer growth (curves a and b). The saturation model (curve c) describes a steep T-dependent curve at T concentrations at or below the near-castrate range, with a plateau representing little or no further growth above this concentration. C, The relationship between T and prostate cancer growth appears to follow a saturation curve, present in many biologic systems, in which growth corresponds with concentration of a key nutrient until a concentration is reached at which an excess of the nutrient is achieved. This type of curve is seen with hormones acting via binding to specific receptors, which have a finite number of binding sites. Once full binding is achieved (saturation), further increases in concentration of the hormone (or other nutrient) produce no further growth. (A, Modified from Muller RL, Gerber L, Moreira DM, et al. Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events trial. *Eur Urol* 2012;62:757–64; B and C, modified from Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. *Eur Urol* 2009;55:310–32.)

Epigenetic Changes

Epigenetic events affect gene expression without altering the actual sequence of DNA. Known mechanisms include DNA hyper- and hypomethylation, chromatin remodeling, and miRNA and lncRNA regulation.

DNA hypermethylation generally causes gene silencing and is the most well-characterized epigenetic alteration in prostate cancer, affecting more than 50 genes across a diverse number of

basic cellular processes, including hormone response (*ESR1*, *ESR2*, and *RARB*), signal transduction (*EDNRB* and *SFRP1*), cell cycle control (*CCND2* and *SFN*), DNA repair (*GSTP1*, *GPX3*, and *GSTM1*), inflammatory response genes (*PTGS2*), tumor suppressor genes (*APC*, *RASSF1A*, *DKK3*, *CDKN2A*, *CDH1*, and *CDKN1A*), tumor invasiveness (*CD44*), and apoptosis (Li et al, 2005; Jerónimo et al, 2011). DNA hypomethylation, which usually affects areas of the genome distinct from hypermethylated regions, causes activation of oncogenes and leads to genetic instability, and has been

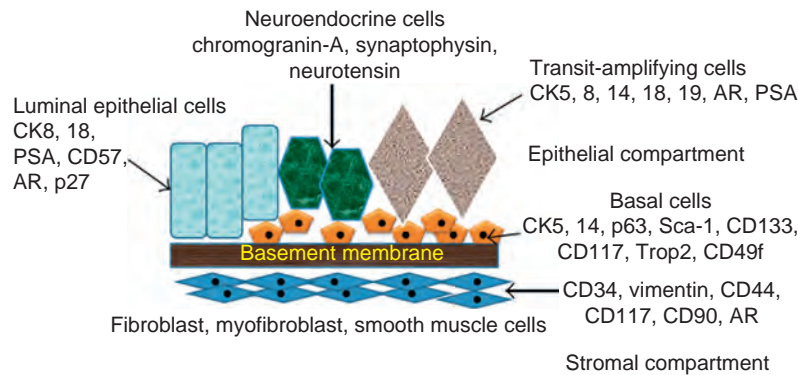


Figure 107-7. The epithelial and stromal cell compartments of a typical prostate gland. Each type of stromal and epithelial cell has a distinct location, morphology, and molecular phenotype. (From Prajapati A, Gupta S, Mistry B, et al. Prostate stem cells in the development of benign prostate hyperplasia and prostate cancer: emerging role and concepts. *Biomed Res Int* 2013;(2013):107954.)

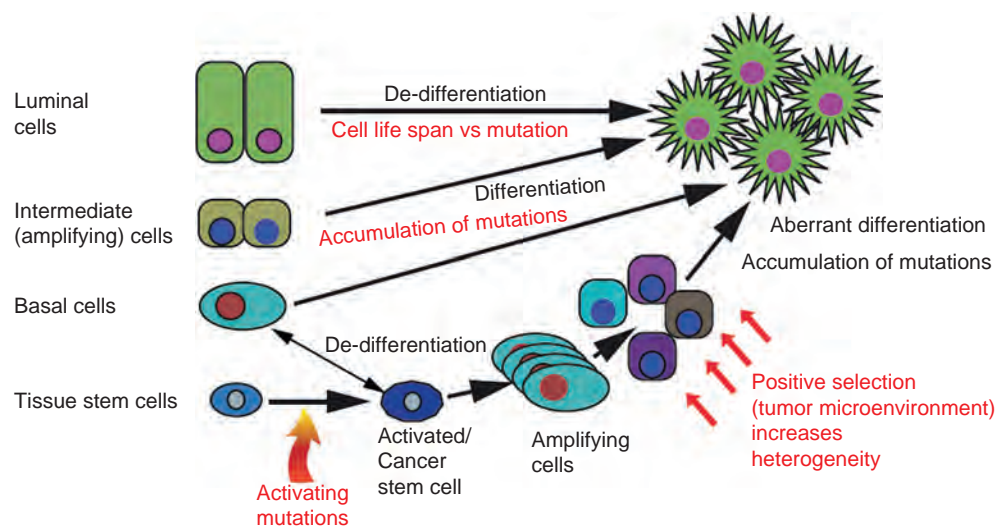


Figure 107-8. Prostate carcinogenesis and tissue stem cells. Luminal cell transformation to malignancy is shown in the green cells. This requires the induction of extended life span and some de-differentiation before acquisition of mutations, while retaining the androgen receptor (AR)-positive luminal phenotype. If the origin of the tumor cells is in the basal (blue) or transit-amplifying (tan) cells, then accumulation of mutations and differentiation is required to produce AR-positive tumor cells. A stem cell origin can occur either by direct activation of a tissue stem cell or by de-differentiation of a committed basal cell into an activated stem cell. The activated stem cell can then progress/differentiate toward the final AR-positive tumor in an aberrant recapitulation of normal prostate epithelium. To achieve this requires both multiple mutagenesis and a selective process for the fittest tumor cells, by interaction with the microenvironment, resulting in the generation of further heterogeneity. (From Maitland NJ, Collins AT. Prostate cancer stem cells: a new target for therapy. *J Clin Oncol* 2008;26:2862-70.)

reported for genes associated with tumor progression (*CAGE*, *HPSE*, and *PLAU*) (Li et al, 2005). Promoter methylation of some genes is influenced by diet and age, and is frequently seen in high-grade PIN and morphologically normal prostate tissue, suggesting that these events are drivers early in the development of prostate cancer (Henrique et al, 2006). Both hypo- and hypermethylation define a field cancerization effect in normal prostate tissue, as revealed by methylation microarray analysis of tumor-associated and non-tumor-associated normal prostatic tissue (Yang et al, 2013a). Clinical studies have shown that quantitative methylation analysis of the *GSTP1*, *APC*, *PTGS2*, *RASSF1A*, *MDR1*, *CDKN2A*, and *MGMT* genes can improve sensitivity and specificity for the diagnosis of cancer (Dobosy et al, 2007). These observations have clinical utility, as demonstrated by a study showing that the

methylation status of *GSTP1*, *APC*, and *RASSF1A* on prostate needle biopsy can be used to predict the likelihood of cancer on subsequent biopsy with a negative predictive value of 90% (Stewart et al, 2013).

Chromatin remodeling and histone post-translational modifications are also important epigenetic mechanisms of gene deregulation in prostate cancer. A number of histone-modifying enzymes have been reported to be altered, the best characterized of which is the histone methyltransferase polycomb protein EZH2. EZH2 overexpression is correlated with promoter hypermethylation leading to gene silencing and is associated with higher proliferation rates and disease recurrence (van Leenders et al, 2007). Other histone modifiers, including histone deacetylators, are upregulated in prostate cancer and are targets for both prevention and therapy

using agents that can inhibit or reverse their effects. Histone acetylation also appears important in regulating AR function (Jerónimo et al, 2011).

Newly discovered forms of noncoding RNA species, including miRNA and lncRNA, affect post-transcriptional gene expression. miRNAs are typically 18 to 25 nucleotides long and act by binding to and thereby silencing messenger RNAs that have complementary sequences (Garzon et al, 2009). lncRNAs are species of greater than 200 nucleotides that regulate gene expression by a variety of mechanisms. While numerous miRNAs have been demonstrated to affect the cell cycle, intracellular signaling, DNA repair, and adhesion/migration in prostate cancer, their main effects seem to be on suppression of apoptosis and AR regulation (Catto et al, 2011). lncRNAs are emerging as molecules with fundamental biologic and clinical importance in prostate cancer. Prostate cancer gene 3 (PCA3) is a lncRNA that can be detected in urine after a digital rectal examination (DRE) and has clinical utility both in cancer detection and in deciding on the need for subsequent biopsy after an initial negative biopsy (Marks et al, 2007). The expression levels of the lncRNA SCHLAP1 (second chromosome locus associated with prostate-1) have been shown to be associated with metastasis and prostate cancer-specific mortality after radical prostatectomy (Prensner et al, 2013). Finally, a previously unknown lncRNA called prostate cancer noncoding RNA 1 (PRNCR1) has been isolated from the “gene desert” region of 8q24, the germline susceptibility locus that is most repeatedly identified in GWAS, that is overexpressed in PIN and cancer, and that causes ligand-independent activation of the AR (Chung et al, 2011; Yang et al, 2013b).

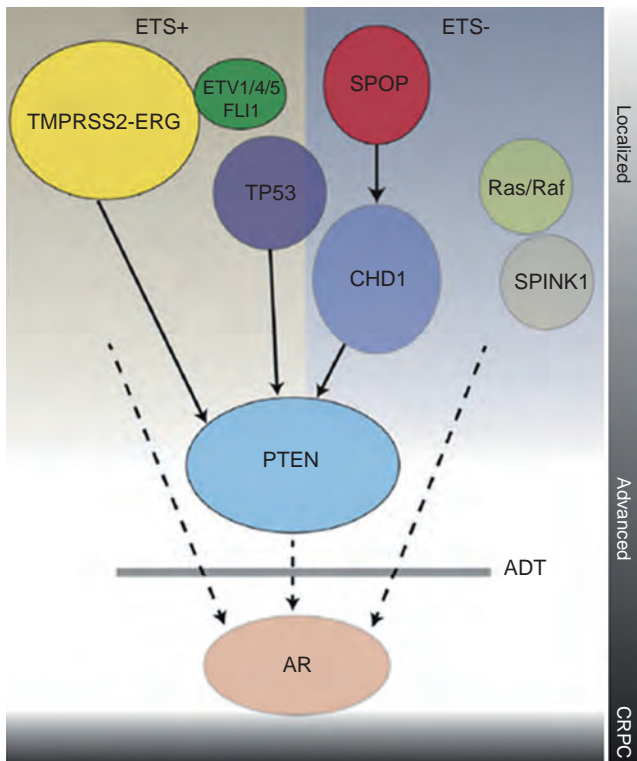


Figure 107-9. Molecular classification of prostate cancer. Genomic lesions in the time line of prostate cancer. Genes with common genomic lesions (including mutation, rearrangement, or copy number alteration) are shown. Solid arrows designate a temporal relationship between events; presumptive “early” lesions are at the top, with “later” lesions below. Tumors with ETS fusions (ETS+) are shown on the left; ETS– tumors are shown on the right. ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer. (From Barbieri CE, Tomlins SA. The prostate cancer genome: perspectives and potential. *Urol Oncol* 2014;32:53.)

There is a complex interplay between the described epigenetic mechanisms in prostate cancer. For example, several miRNAs are known to be regulated through promoter methylation or hypomethylating enzymes. At another level of complexity, both miRNAs and EZH2 independently interact with the ETS genes fusion axis (Jerónimo et al, 2011).

Androgen Receptor

As discussed earlier, germline polymorphisms of the AR gene are linked epidemiologically to prostate cancer risk. The role of the AR is well established in the progression of castrate-resistant prostate cancer, which is characterized by AR point mutations and amplification, alternative splice mechanisms, and ligand promiscuity, which make it exquisitely sensitive to low levels of intra-tumoral androgen and/or constitutively active (Scher and Sawyers, 2005). While these lesions are absent in early-stage disease, dysregulation of the AR signaling axis may occur earlier in disease progression, involving activating mutations in FOXA1 and amplification of NCOA2 that increase androgen-dependent proliferation (Barbieri and Tomlins, 2014). The PI3K/Akt pathway has reciprocal interactions with the AR, such that inhibition of one activates the other to maintain tumor viability and suggesting that blocking both pathways simultaneously may be needed for therapeutic efficacy (Carver et al, 2011). Finally, whole-genome analysis has demonstrated that rearrangement breakpoints are more common near AR binding sites, suggesting that AR-mediated transcription brings together distant genomic loci and predisposes to genomic rearrangements (Berger et al, 2011). For example, androgen signaling promotes corecruitment of AR and topoisomerase II beta (TOP2B) to sites of TMPRSS2:ERG genomic breakpoints, triggering DNA double-strand breaks and resulting in de novo production of TMPRSS2:ERG fusion transcripts (Haffner et al, 2010). These observations suggest that AR-mediated transcriptional activity acts as an early driver of genomic rearrangements in prostate cancer, and reinforces AR-mediated transcription as a critical signaling pathway in both primary and advanced disease (Barbieri and Tomlins, 2014).

Gene Fusions

Gene fusions resulting from chromosomal translocations are the most common genetic alteration in human cancers (Futreal et al, 2004). These were previously thought to be an oncogenic mechanism exclusively limited to hematologic malignancies and sarcomas, as exemplified by the BCR:ABL1 fusion protein in chronic myeloid leukemia. In 2005, Tomlins and colleagues identified recurrent genomic rearrangements in prostate cancer that resulted in the fusion of the 5' untranslated end of TMPRSS2 (an androgen-responsive, prostate-specific, transmembrane serine protease gene) to members of the ETS family of oncogenic transcription factors (Tomlins et al, 2005). Since then other important gene fusions involving the RAF kinase family and SPINK1 have been described, highlighting the fundamental importance of this genetic mechanism in the genesis of prostate cancers (Rubin et al, 2011) (Fig. 107-10A and B). These fusions, and other gross chromosomal rearrangements, occur by a process termed *chromoplexy*, wherein translocations and deletions arise in an interdependent manner and disrupt multiple cancer genes in a coordinated fashion (Baca et al, 2013).

ETS Family Gene Fusions. The most common fusion identified in localized prostate cancer involves TMPRSS2 or other promoters (SLC45A3, HERPUD1, or NDRG) fused to ERG (ETS-related gene) in 50% to 60% of patients (Kumar-Sinha et al, 2008; Rubin et al, 2011). Gene fusions involving other members of the ETS family, most commonly ETV1 (5% to 10%), ELK4 (5%), ETV4 (2%), and ETV5 (2%), also occur. Both TMPRSS2 and SLC45A3 are androgen responsive such that fusion of either of these genes to a growth-promoting gene of the normally androgen-indifferent ETS family brings a powerful signal for cellular growth under

androgen control. These fusions are not observed in benign prostate tissue or PIA, but are present in prostate stem cells, high-grade PIN, and early-stage, low-grade prostate cancer, suggesting that this is an early and seminal event in prostate tumorigenesis that may drive the transition from PIN to cancer (Rubin et al, 2011; Polson et al, 2013). Recent data from animal models suggest that defects in the PTEN/PI3K/Akt pathway in the presence of *TMPRSS2:ERG* fusions drive early tumor progression, the former stimulating proliferation and the latter cell migration that together may result in a more aggressive phenotype (Carver et al, 2009). However, there are mixed data on whether the presence of *TMPRSS2:ERG* fusions affect prognosis (reviewed in Rubin et al, 2011), such that tumor aggressiveness may not be determined by the fusion alone but by the presence of the fusion and which other specific genetic defects are present in an individual tumor.

The high specificity of the *TMPRSS2:ERG* fusion for cancer makes it an attractive target for clinical use. Fusion transcripts can be detected in the urine and clinical evidence suggests that, when combined with an assay for *PCA3*, its use can improve the detection of cancer in screened populations over PSA alone (Tomlins et al, 2011). Some data suggest that quantification of the *TMPRSS2:ERG* fusion in urine can predict both tumor volume and tumor aggressiveness, perhaps making it useful for selecting appropriate candidates for active surveillance (Lin et al, 2013). It has been observed that not all tumor foci within a prostate harbor ETS fusions, so that a positive urine test for *TMPRSS2:ERG* fusion in the face of a negative biopsy would suggest that cancer was missed as a result of sampling error, and that additional evaluation with magnetic resonance imaging or repeat biopsy is indicated. The presence of gene fusions that occur only in cancer also makes them targets for novel therapies (see Fig. 107-10A).

Other Gene Fusions. As noted, prostate cancers also are rarely observed to contain fusions involving *SPINK1* and *RAF* kinases. *SPINK1* fusions occur in about 10% to 15% of cancers, exclusively in ETS fusion-negative tumors, and in cell lines seem to drive tumor invasion (Tomlins et al, 2008). Fusions involving *RAF* kinases are even more rare and also define another ETS fusion-negative phenotype that is associated with aggressive cancers (Palanisamy et al, 2010). Both examples likely represent alternative growth pathways for ETS fusion-negative tumors and may represent distinct phenotypes (see Fig. 107-9).

NKX3-1

NKX3-1 is an androgen-regulated and prostate-specific gene belonging to the homeobox gene family that protects against DNA damage

and promotes DNA repair. Decreased expression of this gene by mutation, promoter methylation, or post-transcriptional events leads to epithelial DNA damage and increased rates of proliferation. Loss of *NKX3-1* function is seen in areas of bacterial-induced prostatitis in a mouse model (Khalili et al, 2010) and in human PIA, PIN, and most prostate cancers and is likely an early event in prostate tumorigenesis (Bethel et al, 2006; Bowen et al, 2013).

Phosphatidylinositol 3-Kinase (PI3K) Pathway

PI3K is one of the most frequently dysregulated signaling pathways in human cancer and plays an important role in both early- and late-stage prostate cancer, with alterations occurring in 25% to 70% of tumors (Barbieri et al, 2013). The pathway may be activated by several mechanisms and results in alterations in proliferation, cell survival, and invasion. Loss-of-function mutations in *PTEN* and *PHLPP1* and amplification and gain-of-function mutations in *PIK3CA* are the commonest mechanisms of PI3K activation in prostate cancer. *PTEN* deletions occur in about 40% of primary tumors, are a central mechanism of tumor progression, and are associated with the risk of advanced disease and poor prognosis (Frank et al, 2013).

SPOP Mutations

Mutations in *SPOP*, which encodes a subunit of a ubiquitin ligase, are the most common point mutations in primary prostate cancer, with a frequency of 6% to 15% (Barbieri and Tomlins, 2014). Tumors with *SPOP* mutations have several unique molecular characteristics. They do not occur in ETS fusion-positive tumors or in those with p53 abnormalities, usually lack defects in the PI3K pathway, and typically contain deletions in the *CHD1* gene and at 6q21. *CHD1* encodes a DNA helicase binding protein that regulates transcription epigenetically by chromatin remodeling, and *CHD1*-negative tumors have an increased frequency of chromosomal rearrangements. Like *RAF* kinase- and *SPINK1*-associated tumors, *SPOP* and *CHD1* mutations may define a distinct molecular subtype of prostate cancer (see Fig. 107-9).

TP53

The well-known tumor suppressor gene *TP53* activates the transcription of genes involved in cell cycle arrest, DNA repair, and apoptosis, and its dysregulation results in improved cell survival, genomic instability, and proliferation. About 25% to 30% of clinically localized cancers have lesions in this gene. Whole-genome analysis

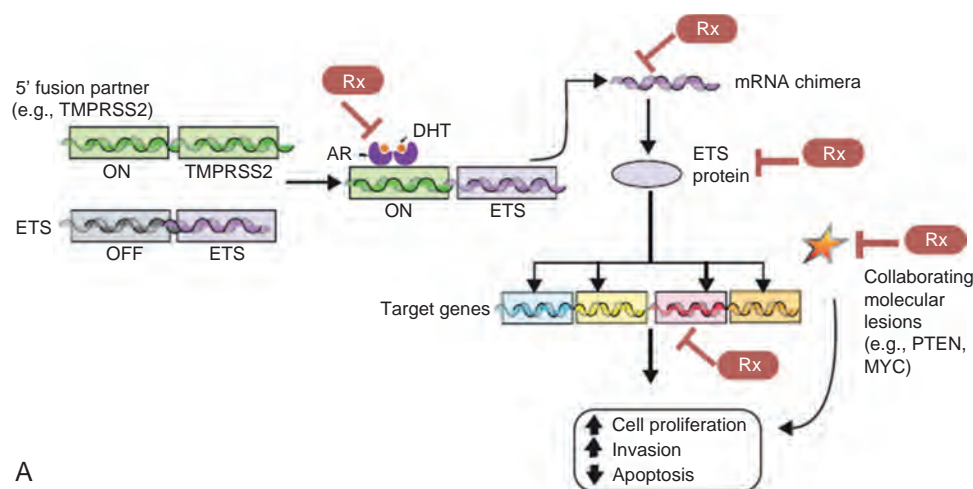
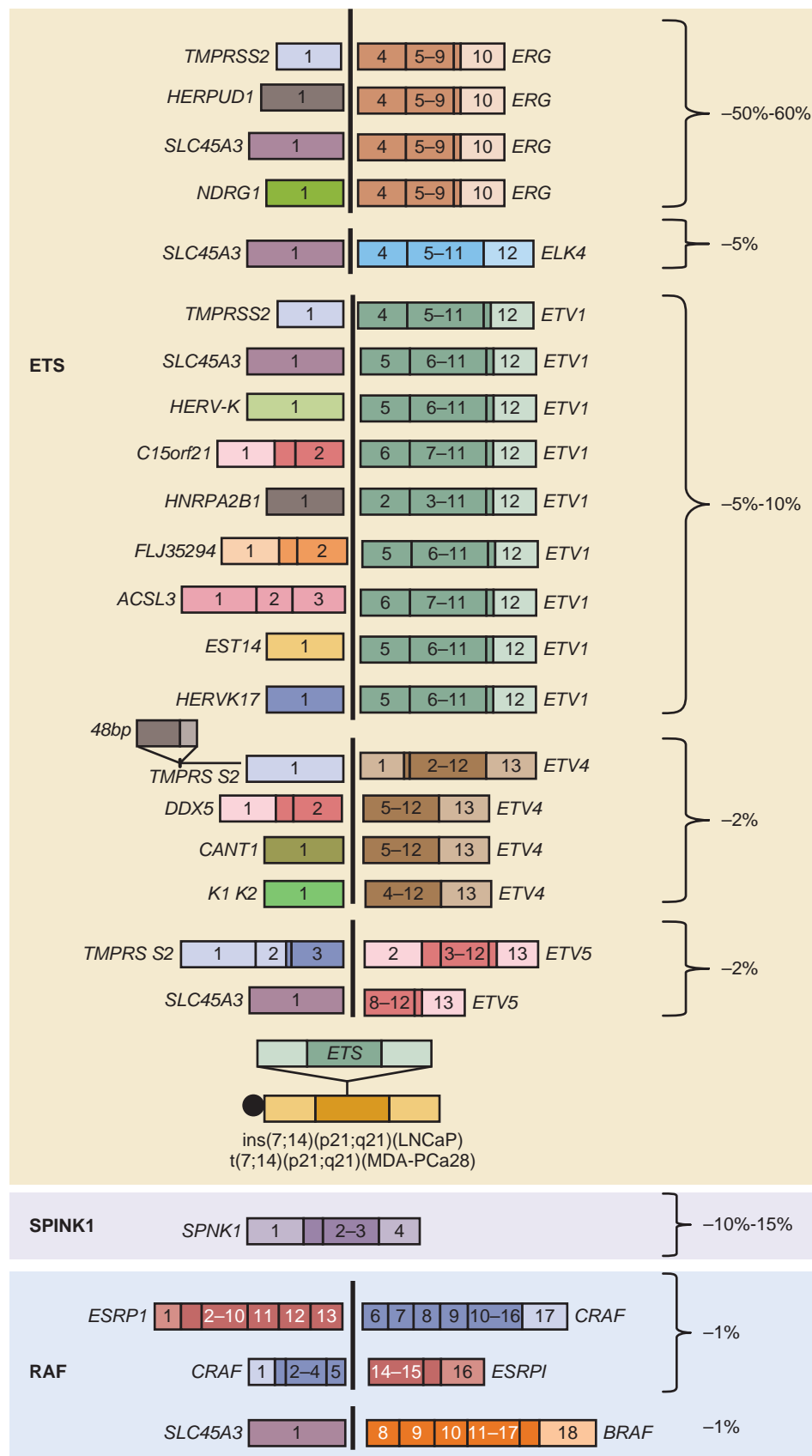


Figure 107-10. A, ETS gene fusions in prostate cancer. Potential therapeutic targets are high-lighted ("Rx").

Continued



B

Figure 107-10, cont'd B, Prostate cancer gene fusion classification. This schematic highlights gene fusions categorized into ETS rearrangements, RAF kinase gene fusions, and *SPINK1*-positive, ETS rearrangement-negative prostate cancers. The percentages highlight the estimated frequency of each gene fusion on the basis of published screens. (A, Modified from Muller RL, Gerber L, Moreira DM, et al. Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events trial. *Eur Urol* 2012;62:757-64; B, from Rubin MA, Maher CA, Chinnaiyan AM. Common gene rearrangements in prostate cancer. *J Clin Oncol* 2011;29:3659-68.)

suggests that in some cases disruption of *TP53* occurs early in tumorigenesis, following deletion of *NKX3-1* or *FOXP1* and fusion of *TPMRSS2* and *ERG* (Baca et al, 2013).

An Integrated Model of Prostate Cancer Tumorigenesis

A comprehensive, integrated model of the genetic and environmental events that underlie the genesis and progression of prostate cancer from germline susceptibility to castrate-resistant metastatic disease is now emerging (see Fig. 107-9). Early events in genetically susceptible men include environmental insults such as diet and infection that result in inflammatory insults to DNA integrity in prostate epithelium. Early genetic events that fuel the progression of precursor lesions to early cancers include *NKX3-1* deletion and ETS fusion or, alternatively, mutations in *SPOP* and *FOXA1* in ETS-negative tumors. Mutations in classic tumor suppressors such as *TP53* follow, leading to inactivation of the PI3K/PTEN/Akt pathway and disease progression, culminating in the multifaceted dysregulation of AR function and signaling that leads to lethal disease. While many gaps in understanding this process still exist, we are on the threshold of having a detailed molecular map with temporal sequencing that will allow advances in the most important clinical challenges facing the field: improved identification of those at risk of disease development who will be the best candidates for chemoprevention, improved identification of those with indolent tumors who can avoid or delay initial therapy, biologic measures of disease progression that identify those who need therapy, and targeted molecular therapy for those with progressive disease.

KEY POINTS: ETIOLOGY AND MOLECULAR GENETICS

- The primary androgen of the prostate is DHT, formed by the action of 5 α -reductase on testosterone. Functional type 2 5 α -reductase is a prerequisite for normal development of the prostate and external genitalia in males, and insufficient exposure of the prostate to DHT appears to protect against the development of prostate cancer.
- Prostatic stem cells are precursors with multilineage differentiation potential that give rise to all four cell types of prostatic epithelium. Stem cells can repopulate damaged or post-therapy depleted cancer epithelial cells and may give rise to prostate cancer directly.
- Prostate cancer arises and progresses by core genetic alterations that activate oncogenes and inactivate tumor suppressors. These changes result most commonly from epigenetic and structural genomic changes, including amplification, deletion, somatic copy number aberrations, and chromosomal rearrangements that result in gene fusions with novel biologic properties.
- Epigenetic regulation of gene expression by promoter methylation, hypomethylation, and chromatin remodeling is important in prostate cancer development and progression.
- miRNA and lncRNA are also important epigenetic mechanisms of modulating tumor growth and progression.
- The AR plays a central role in prostate cancer development and progression.
- Gene fusions, especially those involving androgen-sensitive promoters such as *TPMRSS2* and the ETS family of oncogenic transcription factors, are fundamental drivers of prostate cancer initiation and progression.
- Somatic mutations in a variety of genes with diverse biologic functions have been implicated in prostate cancer development and progression.
- Mutations, amplification, and ligand promiscuity of the AR are important determinants of progressive castrate-resistant prostate cancer.

CHEMOPREVENTION

Rationale

The ubiquity and mortality of prostate cancer make it an attractive target for chemoprevention, defined as the use of natural or synthetic agents that reverse, suppress, or prevent the carcinogenic process, thereby preventing the development of clinically evident cancer. The goal of chemoprevention is to decrease the incidence of a given cancer, simultaneously reducing both treatment-related side effects and mortality. Primary chemoprevention targets the general population of healthy individuals at risk to prevent the development of prostate cancer. Secondary prevention strategies target individuals with premalignant lesions (such as HGPIN) with the goal of preventing progression to frank cancer. Tertiary prevention aims to prevent the development of a second primary cancer in an affected individual. Numerous epidemiologic observations suggest associations between dietary and lifestyle factors and the risk for developing prostate cancer. The clinical rationale for chemoprevention is based on the fact that the risk factors for prostate cancer (age, ethnicity, and family history) are not modifiable (with the exception of PSA screening). The biologic rationale is that premalignant changes appear as long as 20 to 30 years before the appearance of cancer (Nelson et al, 2003; Umar et al, 2012), providing an opportunity to intervene before a malignancy is established by using lifestyle changes (dietary alterations, smoking cessation, exercise) or by chemoprevention. The challenge of chemoprevention is finding an effective intervention that has acceptable toxicity, as well as identifying a population of individuals at sufficiently increased risk for developing prostate cancer for whom chemoprevention is appropriate and cost-effective (Fig. 107-11).

One impetus for primary prevention is the limitations of screening that were highlighted by the PLCO trial and the ERSPC (discussed previously) that show no (PLCO) or modest (ERSPC) reductions in prostate cancer-related mortality but a substantial risk of overdiagnosis (defined as a cancer that would have remained undetected over a man's lifetime in the absence of screening). Although the safety and feasibility of expectant management have been well demonstrated, in the United States a diagnosis of prostate cancer in an individual generally leads to curative-intent therapy (Welch and Albertsen, 2009) since active surveillance has not been widely embraced because of concerns that clinical staging and grading will underestimate the threat posed by cancers (Carter et al, 2003; Harlan et al, 2003; Barocas et al, 2008). A recent population-based study showed that more than 70% of men ages

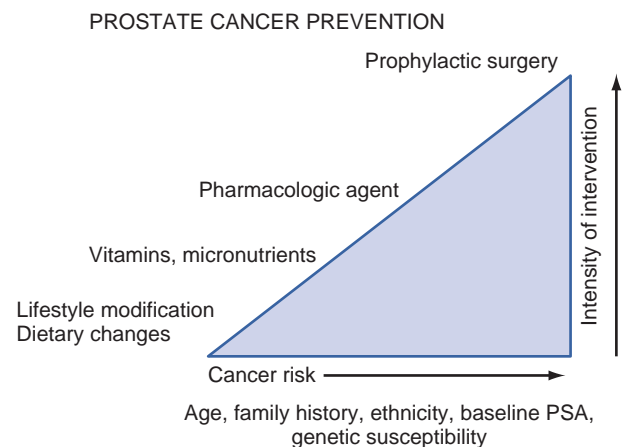


Figure 107-11. Framework for the prevention of prostate cancer based on a man's risk of developing the disease and the intensity of the preventive strategy. PSA, prostate-specific antigen. (Modified from Stephenson AJ, Abouassaly R, Klein EA. Chemoprevention of prostate cancer. *Urol Clin North Am* 2010;37:11–21.)

65 to 80 years with low- and intermediate-risk disease received some form of therapy after diagnosis (Wong et al, 2006). Given the protracted natural history of screening-detected cancers, it is unlikely that many of these men benefited from treatment in terms of preventing metastasis or death, though therapy is associated with significant impacts on quality of life and low but defined rates of treatment-related mortality. An effective primary prevention strategy would spare many men the burden of diagnosis and cure and reduce overdiagnosis associated with screening. When combined with aggressive early detection and treatment, chemoprevention also has the potential to reduce the mortality from prostate cancer, which remains the second leading cause of cancer deaths among men in the United States. A number of large, controlled, randomized trials that tested the ability of various agents to prevent prostate cancer have been reported in recent years and are reviewed here.

Pharmacologic Agents

5 α -Reductase Inhibitors

Prostate Cancer Prevention Trial. The PCPT was the first large-scale primary chemoprevention trial in men at risk for prostate cancer (Thompson et al, 2003). The study randomized 18,882 men age 55 years or older with a normal DRE and a PSA level of 3.0 ng/mL or less to finasteride 5 mg or placebo daily for 7 years. The rationale for finasteride (a selective type 2 5ARI) as a chemopreventive agent was based on the absence of prostate cancer in men with congenital deficiency of 5 α -reductase (the enzyme that converts T to DHT) and the critical role of androgens in the development of prostate cancer. Biopsy was recommended at the end of the study for all participants or “for cause” in men who had a PSA level of 4 ng/mL or greater (adjusted for the effect of finasteride) or an abnormal DRE. The primary end point was the prevalence of prostate cancer during the 7 years of the study. Ultimately, 9060 participants (48%) were evaluable for the primary end point.

The main finding of the PCPT was a 25% (95% CI 19% to 31%) reduction in the period prevalence of prostate cancer in men taking finasteride (18.4%) compared to placebo (24.4%). The relative benefit of finasteride versus placebo in reducing the risk of prostate cancer was apparent across all groups as defined by age, ethnicity, family history of prostate cancer, and PSA level at study entry, with HRs between 0.66 and 0.81. The risk reduction in the finasteride arm was seen in both clinically apparent tumors (those diagnosed “for cause” because of an elevated PSA or abnormal DRE) and end-of-study biopsies (men with PSA <4.0 ng/mL and normal DRE at study termination). Finasteride also reduced the risk of HGPIN (without associated prostate cancer) compared to placebo (HR 0.85, 95% CI 0.73 to 0.99, $P = .04$) (Thompson et al, 2007a). However, a significant increase in the prevalence of biopsy Gleason score 7-10 cancers was observed in men receiving finasteride (280 [37%]) compared to placebo (237 [22%]), particularly for biopsy Gleason score 8-10 cancers (90 [12%] in the finasteride arm vs. 53 [5%] in the placebo arm).

A number of relevant observations can be made about the results of the trial. Most surprising was the 24.4% prevalence of prostate cancer in the placebo arm, four times higher than the 6% assumed for the trial design. This discrepancy can be explained by the fact that the 6% assumption was based on SEER incidence estimates, which are derived from clinically evident cases, and not on the prevalence in men undergoing biopsy with PSA less than 4 ng/mL and normal DRE. The incidence of clinically evident cancers detected “for cause” by elevations in PSA or abnormal PSA was 7.2% at 7 years, similar to the cancer incidence in the screening arms of the ERSPC (8.2%) and the PLCO trial (7.4%) (Andriole et al, 2009; Schröder et al, 2009). Another observation was a marked effect of finasteride on the prevalence of biopsy Gleason score 2-6 tumors, no effect on the prevalence of biopsy Gleason score 7 tumors, and an increase in the prevalence of biopsy Gleason score 8-10 tumors. The higher incidence of biopsy Gleason score 8-10 tumors was restricted to those men undergoing “for-cause” biopsy, though this is partly explained by the low prevalence

of these high-grade cancers in men with PSA less than 4.0 ng/mL and normal DRE (20 of 3652 in the finasteride arm vs. 8 of 3820 in the placebo arm).

Secondary analyses of the PCPT have demonstrated an overall improved sensitivity of DRE as well as a higher accuracy of PSA for the diagnosis of prostate cancer in the finasteride arm (Thompson et al, 2006, 2007b). Finasteride-treated glands were also 28% smaller on average compared to those in the placebo arm, and data suggest that having a smaller prostate enhances the detection of cancer and proportionately more diagnosed cancers are high grade (Kulkarni et al, 2006). These effects of finasteride on the detection of prostate cancer should bias the PCPT in favor of the placebo arm and lead to a greater detection of all grades of prostate cancer with finasteride, further strengthening the results of the trial.

There are two areas of continued debate over the results of the PCPT. The first is that critics argue that finasteride prevents insignificant cancers and does little to prevent “potentially lethal” cancers. This criticism is based on the fact that the incidence of cancers in the control arm (24.4%) was significantly higher than a man's lifetime risk of developing prostate cancer (18%) and 4 times higher than the cancer incidence in screening trials over a similar time period. Finasteride also reduced the prevalence of low-grade cancers and did not appear to reduce the risk of high-grade cancers. However, in a secondary analysis of 93.4% of biopsy specimens that were subject to central pathology review, the rate of insignificant cancers as defined by the Epstein criteria (Epstein et al, 1994) among the biopsy Gleason 2-6 cancers detected in the finasteride (38%) and placebo (36%) arms was not significantly different (Lucia et al, 2008). Viewed in the context of “clinical relevance” as defined by current urologic practice, preventing biopsy Gleason 2-6 cancers by finasteride also prevents the anxiety, cost, and morbidity associated with their treatment. From a public health perspective, preventing the “burden of cure” in newly diagnosed patients should be added as a positive to the 25% reduction in risk of diagnosis and significant reduction in urinary symptoms associated with finasteride use.

The second question still under debate is whether finasteride induces the development of high-grade or aggressive cancers. Androgen deprivation therapy is known to change the appearance of prostatic epithelium in a way that could bias interpretation (Civantos et al, 1996). Thus the apparent increase in high-grade cancers in men treated with finasteride may be an artifact of these morphologic changes. However, when this was examined in the PCPT, there appeared to be no morphologic effect of finasteride on prostate cancer grading when specimens were reviewed by a panel of expert pathologists blinded to treatment arm (Lucia et al, 2008). Another potential explanation for the observed increase in high-grade tumors in the finasteride group is ascertainment bias. As stated above, finasteride has been shown to increase the sensitivity of PSA and DRE as well as decrease prostate volume by 28%, leading to a higher probability of finding the high-grade component of cancer (among men with Gleason 7-10 cancer) on biopsy. Indeed, the rate of upgrading from biopsy Gleason score 2-6 to pathologic Gleason score 7-10 among men treated by radical prostatectomy was higher in the placebo arm compared to the finasteride arm (Lucia et al, 2008).

If finasteride induces high-grade cancers, one would expect a higher proportion of cancers with adverse features by biopsy criteria or at radical prostatectomy in the finasteride arm. Among Gleason 7-10 cancers, use of finasteride was associated with more favorable features of tumor extent on biopsy specimens compared to placebo, including percent of positive cores (34% vs. 38%, $P = .016$), aggregate linear tumor length (7.6 vs. 9.2 mm, $P = .13$), bilaterality (23% vs. 31%, $P = .046$), and perineural invasion (14% vs. 20%, $P = .07$) (Lucia et al, 2007, 2008). Among the 528 men who were treated by radical prostatectomy, no significant difference in the rate of extraprostatic extension, seminal vesicle invasion, or lymph node metastasis was observed between the two arms and there were fewer pathologic Gleason 7-10 cancers among men treated with finasteride versus placebo (89 vs. 105).

In a secondary analysis of the PCPT that adjusted for the effects of finasteride on the detection of prostate cancer, the adjusted prostate cancer rates were estimated to be 21.1% for the placebo group and 14.7% in the finasteride group, a 30% risk reduction for all cancers (HR 0.70, 95% CI 0.64 to 0.76) and a non-statistically significant 14% increase in high-grade cancer (Redman et al, 2008). Accounting for the increased probability of upgrading to pathologic Gleason 7-10 cancer at radical prostatectomy among men with biopsy Gleason 2-6 cancers in the placebo arm, the investigators estimated the rate of true high-grade cancer to be 6% in the finasteride arm and 8.2% in the placebo arm, representing a 27% RR reduction in the rate of true high-grade cancers in men treated with finasteride (HR 0.73, 95% CI 0.56 to 0.96). Using different methodology in an independent analysis, Pinsky and colleagues (2008) concurred that the rate of true high-grade disease may have been lower in the finasteride group compared with the placebo group.

In a long-term follow-up study of all 18,880 men enrolled in the PCPT, some of whom had survival information out to 18 years, no significant differences between treatment groups were observed for overall survival at 15 years (78% vs. 78.2%; unadjusted HR 1.02, 95% CI 0.97 to 1.08, $P = .5$) or among 2401 men with prostate cancer at 10 years (79.3% vs. 79.5%; adjusted HR 1.01, 95% CI 0.85 to 1.2, $P = .9$) (Thompson et al, 2013) (Fig. 107-12). Considering all men enrolled in the PCPT and with additional follow-up, prostate cancer was detected in 989 of 9423 (10.5%) in the finasteride arm compared to 1412 of 9457 (14.9%) in the placebo arm, translating into a 30% reduction in the detection of prostate cancer (HR 0.7, 95% CI 0.65 to 0.76, $P < .001$)

with a nonsignificant increase in Gleason 7-10 cancers (HR 1.17, 95% CI 1.00 to 1.37, $P = .05$). Analysis of cancer-specific mortality was limited because of the small number of men in whom cause of death was ascertained. The absence of important survival differences between treatment arms (and among those with cancer) suggests that the apparent higher incidence of higher-grade cancers in men treated with finasteride does not translate to important survival differences at 15 years. While finasteride did not appear to reduce overall mortality, it was associated with a 43% reduction in the risk of low-grade cancers. Using survival data from the PLCO trial to project prostate cancer mortality from incidence patterns, Pinsky and colleagues (2013) estimated that use of 5ARIs had no impact on prostate cancer mortality based on the PCPT data using unadjusted (HR 1.02, 95% CI 0.9 to 1.2) and adjusted (HR 0.9, 95% CI 0.8 to 1.1) analyses for the effects of 5ARIs on cancer detection. Together, these studies suggest that the apparent increase in high-grade cancers with the use of 5ARIs does not translate into impacts on survival or mortality from prostate cancer.

In addition to the prevention of prostate cancer, 5ARIs have other benefits that need to be considered. As mentioned earlier, finasteride improves the sensitivity of PSA and DRE for prostate cancer detection (Thompson et al, 2006, 2007b). Furthermore, finasteride reduced the risk of prostatitis, acute urinary retention, and the need for surgical intervention. On the other hand, adverse effects more common with finasteride than placebo include impaired sexual or erectile function and endocrine effects. Pooled data from randomized trials indicate absolute differences of 2% (95% CI 1% to 2%) for gynecomastia, 3% (95% CI 1% to 6%) for

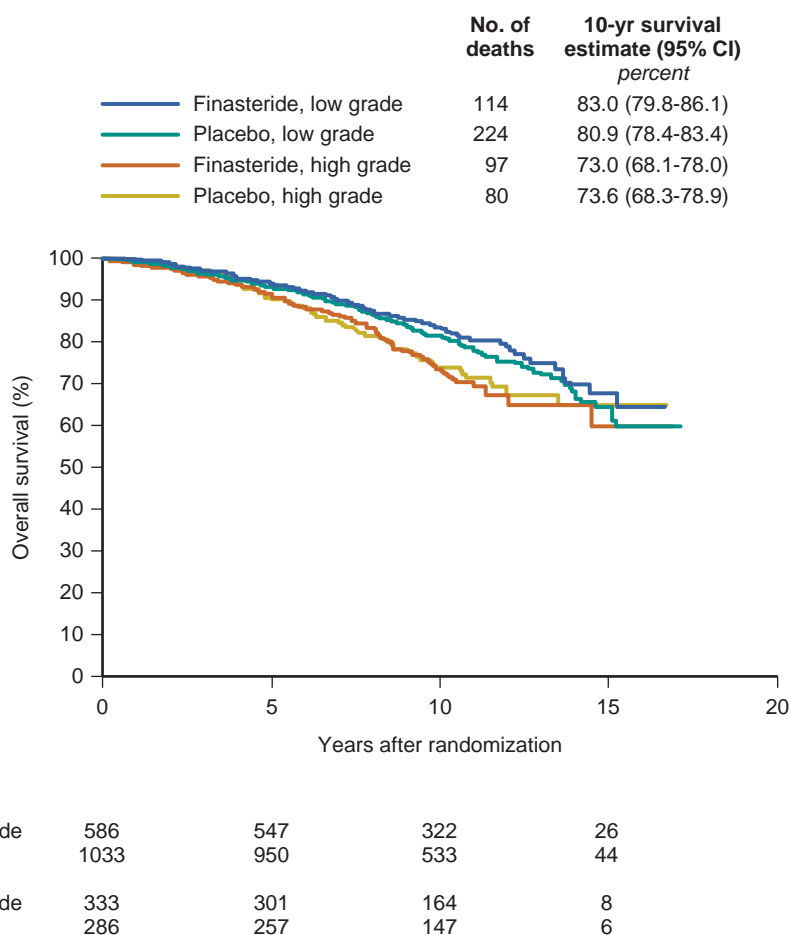


Figure 107-12. Overall survival of men with prostate cancer, according to cancer grade, in the Prostate Cancer Prevention Trial. (Modified from Thompson IM Jr, Goodman PJ, Tangen CM, et al. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med* 2013;369:603-10.)

decreased libido, 4% (95% CI 1% to 8%) for erectile dysfunction, and 4% (95% CI 8% to 17%) for reduced volume of ejaculate (Wilt et al, 2008). Sexual dysfunction was also assessed in the PCPT participants during the 7-year trial period using the Sexual Activity Scale. Compared to baseline scores, over the course of 7 years finasteride was associated with a slight increase in sexual dysfunction relative to placebo, equivalent to about half the effect of being 6.5 years older at randomization (Moinpour et al, 2007).

Reduction by Dutasteride of Prostate Cancer Events (REDUCE)

Trial. REDUCE is another large-scale, randomized, placebo-controlled primary chemoprevention trial using a different 5ARI called dutasteride, which is an inhibitor of both type 1 and type 2 isoforms of 5 α -reductase. Dutasteride has been shown to reduce the risk of prostate cancer in men treated for lower urinary tract symptoms related to benign prostatic hyperplasia (BPH) compared to placebo (Andriole et al, 2004b). Eligibility for REDUCE included men with a prior negative prostate biopsy (6 to 12 cores) within 6 months of enrollment who were 50 to 75 years of age and had baseline PSA of 2.5 to 10 ng/mL and prostate volume of 80 mL or less. The primary end point of REDUCE was the prevalence of cancer on study-mandated 10-core prostate biopsies performed at 2 and 4 years after randomization.

REDUCE accrued 8231 men, of whom 6726 (82.6%) underwent at least one biopsy and 1516 (22.5%) were diagnosed with prostate cancer. Dutasteride reduced the risk of prostate cancer over 4 years by 23% (858 in the placebo arm vs. 659 in the dutasteride arm, $P < .001$) and showed similar reductions in years 1 and 2 and years 3 and 4 (Andriole et al, 2010). There was no significant difference between groups in terms of cancer reduction on protocol-independent ("for-cause") biopsies (17% in both arms). As with finasteride in the PCPT, the benefit of dutasteride versus placebo in prostate cancer risk was apparent across all subgroups, including age, family history, and PSA level at study entry (RR reduction 22% to 32%). While there was no difference in the detection of Gleason 7-10 cancers throughout the study ($P = .8$), including Gleason 8-10 cancers (29 in the dutasteride arm vs. 19 in the placebo arm, $P = .15$), there was an increased risk of Gleason 8-10 cancers during years 3 and 4 of the study (1 in placebo vs. 12 in dutasteride, $P = .003$), although no additional Gleason 8-10 cancers were seen 2 years off-study among 2751 men assessed (Grubb et al, 2013). No deaths from prostate cancer were reported during the study, and there were no significant differences between treatment arms among detected cancers in terms of percentage or number of positive cores or tumor volume, even among Gleason 7-10 cancers. The rate of HGPIN was also significantly lower among men receiving dutasteride (3.8% vs. 4.9%, $P = .04$). Dutasteride also demonstrated beneficial effects on BPH outcomes (acute urinary retention and BPH-related surgery) and was generally well tolerated (15% drug-related adverse events in placebo arm vs. 22% in dutasteride arm). Dutasteride also appeared to have beneficial effects on PSA as a marker of prostate cancer (Marberger et al, 2012).

Summary. The PCPT and REDUCE confirm the consistency of effect of 5ARIs at reducing the risk of prostate cancer, with a similar magnitude of risk reduction across all subgroups. The fact that the results of REDUCE were congruent with those of the PCPT with respect to the magnitude of risk reduction, benefits on BPH end points, and minimal toxicity suggests that 5ARIs represent an effective primary prevention strategy. In 2010, the Oncology Drug Advisory Committee of the FDA convened to assess the evidence in support of 5ARIs as chemoprevention agents for prostate cancer. As part of its review, all biopsy specimens from the PCPT and REDUCE that showed prostate cancer were subject to central pathology review and regraded using the modified Gleason scale. The FDA reassessment showed a significant increase in Gleason 8-10 cancers across both trials (RR 1.7, 95% CI 1.2 to 2.3), suggesting that, for every 150 to 200 men treated with a 5ARI, one additional man would be diagnosed with high-grade prostate cancer to avert three to four low-grade cancers (Theoret et al, 2011). The committee believed that the post hoc exploratory analyses of PCPT and REDUCE did not provide convincing evidence that the increased incidence of high-grade cancer observed in both trials can be dismissed. The

FDA concluded that 5ARIs did not have a favorable risk-benefit profile for the chemoprevention of prostate cancer. Despite multiple analyses suggesting that detection bias accounted, at least in part, for the observed increase in the rate of high-grade tumors with 5ARIs, concern regarding this risk has all but eliminated the use of 5ARIs for prostate cancer prevention in common urologic practice. Several cost utility analyses have, however, suggested that chemoprevention with a 5ARI may be cost-effective in populations at high risk (Svatek, 2008; Kattan et al, 2011; Svatek and Lotan, 2011).

Toremifene Citrate

Toremifene citrate is a modulator of the ER and is FDA approved for the treatment of breast cancer. In vitro studies in prostate cancer have shown that low-dose toremifene selectively inhibits ER- α , which serves as a mediator of growth-stimulatory signal transduction and has direct antiproliferative effect through ER- β . A randomized trial in 1467 men with HGPIN failed to show a reduction in prostate cancer incidence at 3 years among those receiving toremifene citrate 20 mg daily versus placebo, even among select high-risk groups (Taneja et al, 2013).

Other Pharmacologic Agents

Interest in metformin as a chemopreventive agent is based on epidemiologic evidence showing a link between obesity, metabolic syndrome, and high circulating insulin levels and the development of various cancers. However, studies to date have failed to show a relationship between use of metformin and prostate cancer risk (Margel et al, 2013). Epidemiologic studies have shown an inverse relationship between nonsteroidal anti-inflammatory drug (NSAID) use and the risk of many cancers, including prostate cancer. However, a nested case-control study failed to show a dose-response or duration-response relationship between five different classes of NSAIDs (including aspirin) and the risk of prostate cancer (Mahmud et al, 2011).

Statins are widely used cholesterol-lowering drugs and are hypothesized to play a role in the prevention of cancer by inhibition of inflammation, angiogenesis, alteration of steroid-hormone biosynthesis or metabolism, cell cycle regulation, or promotion of apoptosis in tumor cells (Murtola et al, 2008). Several observational studies have shown an inverse association between statin use and risk of prostate cancer (including one that showed a reduction in mortality from prostate cancer) (Graaf et al, 2004; Shannon et al, 2005; Platz et al, 2006; Bansal et al, 2012; Marcella et al, 2012; Geybels et al, 2013), although others found no association (Flick et al, 2007; Agalliu et al, 2008) and two studies showed an increase in overall prostate cancer risk (Kaye and Jick, 2004; Murtola et al, 2007). Randomized trials of statin use to prevent cardiovascular disease reported no associations with prostate cancer incidence, though such trials were limited by short durations of statin use, brief follow-up periods, and relatively young participants who develop few cancers (Baigent et al, 2005; Dale et al, 2006; Browning and Martin, 2007). A meta-analysis of six randomized clinical trials, six cohort studies, and seven case-control studies found no association between statin use and overall prostate cancer incidence, but did find a protective association with advanced prostate cancer (HR 0.77, 95% CI 0.64 to 0.93) (Bonovas et al, 2008). This finding suggests an effect of statins at a late stage in carcinogenesis (e.g., tumor progression).

Vitamins and Micronutrients

Selenium and Vitamin E

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a randomized, placebo-controlled, population-based primary chemoprevention trial designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer (Lippman et al, 2005). The rationale for using selenium was based on a secondary analysis of the Nutritional

Prevention of Cancer Trial of oral selenized yeast for nonmelanoma skin cancer in which men randomized to selenium versus placebo had a 65% reduction in prostate cancer incidence over a mean follow-up of 4.5 years (Clark et al, 1996). The rationale for vitamin E was based on the Alpha-Tocopherol, Beta-Carotene (ATBC) Lung Cancer Prevention Study for lung cancer incidence and mortality in which male smokers were randomized to α -tocopherol (50 mg daily) and β -carotene (20 mg daily) alone or in combination versus placebo (The effect of vitamin E, 1994). On secondary analysis, the ATBC study found a statistically significant 32% reduction in prostate cancer incidence in those receiving α -tocopherol (Albanes et al, 1995).

SELECT randomized 35,533 men to four treatment arms (selenium + placebo, vitamin E + placebo, selenium + vitamin E, and placebo + placebo) (Lippman et al, 2009). Eligibility criteria included age 50 years or older for African-Americans, age 55 years or older for Caucasians, a DRE not suspicious for cancer, serum PSA 4 ng/mL or less, and normal blood pressure. The primary end point was biopsy-confirmed prostate cancer, though the indications for biopsy were not dictated by protocol. Although the study duration was planned for 12 years, the independent data and safety monitoring committee recommended discontinuation of the study after the second interim analysis at 7 years because the data convincingly demonstrated no effect on the risk of prostate cancer by either agent alone or in combination, and no chance of a beneficial effect of the hypothesized magnitude with continued supplementation (Lippman et al, 2009). HRs for prostate cancer were 1.13 (99% CI 0.95 to 1.13) for vitamin E, 1.04 (99% CI 0.87 to 1.24) for selenium, and 1.05 (99% CI 0.88 to 1.25) for selenium and vitamin E. A follow-up study that included an additional 54,464 person-years showed that dietary supplementation with vitamin E actually increased the risk of prostate cancer (HR 1.17, 95% CI 1.004 to 1.36, $P = .008$) (Klein et al, 2011) (Fig. 107-13). Secondary analyses also showed no effect on the risks of lung, colorectal, or overall cancer incidence, no effect on cardiovascular events, and no effect on overall survival.

The absence of a beneficial effect of these micronutrients on prostate cancer risk was also observed in other randomized trials (Gaziano et al, 2009; Algotar et al, 2013). Two randomized trials have evaluated the effect of selenium, vitamin E, and/or soy on the risk of prostate cancer among men with evidence of HGPIN on prior biopsy. Southwest Oncology Group trial 9917 randomized 423 men with HGPIN to selenium 200 μ g/day versus placebo and found no difference in the 3-year risk of prostate cancer (36% vs. 37%, $P = .7$), although men with lowest baseline plasma selenium levels experienced a non-statistically significant risk reduction (Marshall et al, 2011). A similar trial from the National Cancer Institute of Canada randomized 303 men with HGPIN to daily soy (40 g), vitamin E (800 units), and selenium (200 μ g) versus placebo and found no significant reduction in prostate cancer risk at 3 years (HR 1.03, 95% CI 0.7 to 1.6, $P = .9$) (Fleshner et al, 2011).

Together, these results suggest that neither selenium nor vitamin E should be used in the hope of preventing prostate or other cancers. The 17% increased prostate cancer risk associated with vitamin E in SELECT demonstrates the potential for seemingly innocuous yet biologically active substances to cause harm. The reasons why these trials failed to confirm the presumed cancer-preventive activity of micronutrients are uncertain. A possible explanation is that men in earlier trials were relatively deficient in these micronutrients compared to those enrolled in the more recent trials. Thus, micronutrients may have cancer-preventive activity in deficient individuals but have no benefit (and potentially harm) in those who are nutritionally replete.

Soy

Soy products are a concentrated source of isoflavones, including genistein, daidzein, and their metabolites, which inhibit benign and malignant prostatic epithelial cell growth, downregulate androgen-regulated genes, and reduce tumor growth in animal models. Migration studies and lower prostate cancer rates in Asian

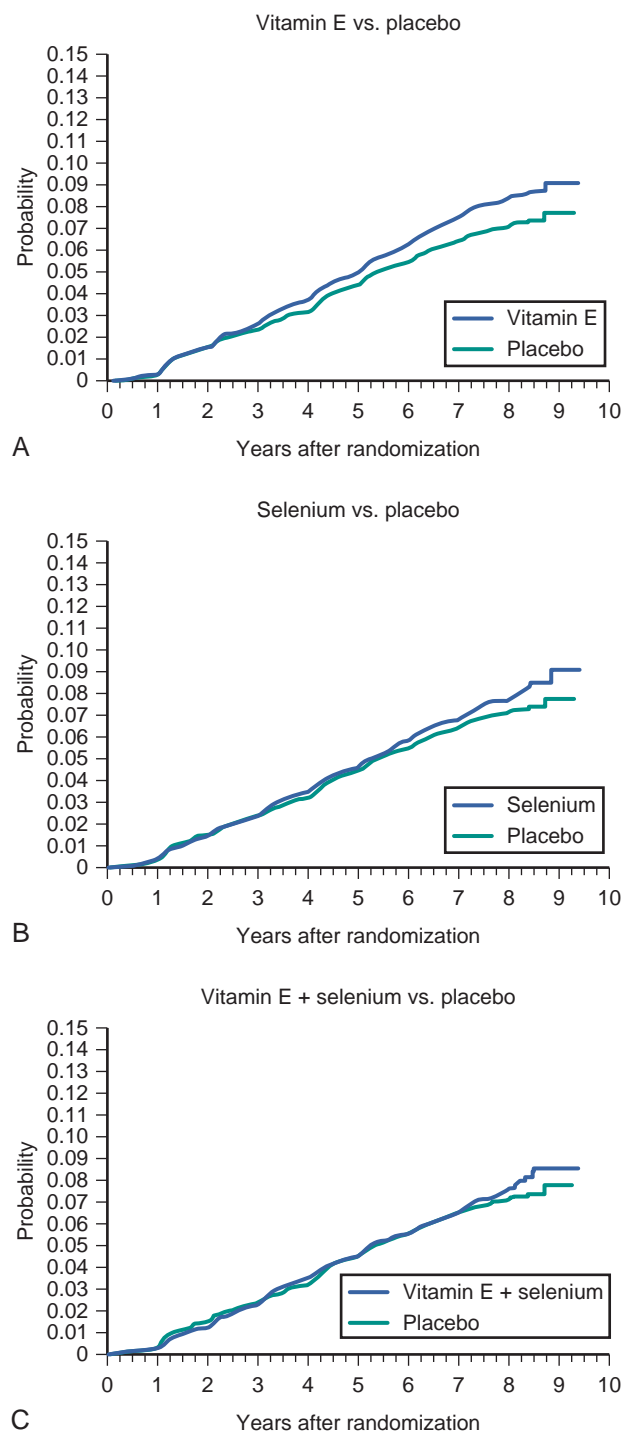


Figure 107-13. A-C, Cumulative incidence of prostate cancer detection over time by intervention group in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Those taking vitamin E alone (A) had a 17% increased risk of prostate cancer compared to placebo (HR 1.17, 99% CI 1.004 to 1.36, $P = .008$); rates of prostate cancer in the selenium alone arm (B) and the selenium plus vitamin E arm (C) were not different than placebo (HR 1.09, 99% CI 0.93 to 1.27, $P = .18$ and HR 1.05, 99% CI 0.89 to 1.22, $P = .46$, respectively). (Modified from Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011;306:1549–56.)

men, for whom soy is an important component of the diet, support its role as an anticancer agent. However, as mentioned, a randomized trial of daily selenium, vitamin E, and soy versus placebo failed to reduce the risk of prostate cancer in men with HGPIN (Fleshner et al, 2011).

Lycopene

Lycopene is a red-orange carotenoid found primarily in tomatoes and tomato-derived products and other red fruits and vegetables. Lycopene is a potent antioxidant and there is mixed epidemiologic evidence that lycopene consumption is associated with a lower risk of prostate cancer (Giovannucci, 1999). Two prospective nested case-control studies in PLCO trial and PCPT patients examined the association of lycopene (either by serum levels or reported intake of tomato-containing foods) and prostate cancer risk and found no protective effect (Peters et al, 2007; Kristal et al, 2011). A meta-analysis of three small randomized, placebo-controlled studies of 154 patients failed to show a protective effect of lycopene on prostate cancer risk (Ilic et al, 2011).

Green Tea Catechin

Interest in green tea as a chemopreventive agent is based on epidemiologic observations of a low incidence of prostate cancer among Asians with a high dietary intake. Green tea catechins (which account for 30% to 40% of extractable solids from dried green tea leaves) have been shown to induce apoptosis and inhibit prostate cancer cell growth in vitro. In a small randomized, placebo-controlled trial in 60 men with HGPIN, green tea catechin was associated with a lower risk of prostate cancer compared to placebo (1 vs. 9) (Brausi et al, 2008). Confirmatory trials are needed to better assess the role of green tea consumption in prostate cancer prevention.

KEY POINTS: CHEMOPREVENTION

- The goal of primary chemoprevention is to decrease the incidence of a given cancer, simultaneously reducing both treatment-related side effects and mortality.
- Effective chemoprevention requires the use of nontoxic agents that inhibit specific molecular steps in the carcinogenic pathway.
- Prostate cancer is an attractive and appropriate target for primary prevention because of its incidence, prevalence, treatment-related morbidity, and disease-related mortality.
- Target populations appropriate for primary prevention studies can be subdivided into those with low, intermediate, and high risk of developing prostate cancer. The molecular mechanisms that underlie disease progression are likely to be different for each target population, and the results from a particular trial may not be generalizable to other clinical scenarios.
- The PCPT demonstrated that finasteride reduces the period prevalence of prostate cancer by 25%. The apparent increase in high-grade disease in men taking finasteride may be due to true biologic effect or due to ascertainment bias induced by the effects of finasteride on PSA, DRE, and prostate volume. The use of finasteride as a chemopreventive agent does not affect long-term survival among those with and without prostate cancer.
- SELECT demonstrated that neither vitamin E nor selenium prevents prostate cancer, and that the use of vitamin E was associated with an increased risk of prostate cancer.

CONCLUSION

It is clear that the process of prostate carcinogenesis is complex. The interplay of constitutional, behavioral, and molecular and environmental factors, against the backdrop of various processes occurring during aging, interact to set into motion a series of events that ultimately are manifested through the diagnosis of prostate cancer. Complicating the understanding of this process are various confounds associated with the diagnosis of the disease in clinical trials, in the general population, and in epidemiologic studies. Additionally, the current inability to distinguish biologically significant from biologically insignificant disease complicates full understanding of the interaction of these factors.

Despite promising outcomes from clinical trials for chemoprevention of prostate cancer, the relatively low use of and lack of enthusiasm for 5ARIs by prostate cancer specialists and primary care practitioners despite endorsement by professional societies and the subsequent failure of these drugs to gain regulatory approval by government agencies highlight the challenges of developing new agents and approaches to chemoprevention. The FDA poses a substantial obstacle because of intense scrutiny over toxicity, as was seen with 5ARIs. As was seen with SELECT, the promise of micronutrients as chemopreventive agents has fallen well short of expectations, and they may potentially be harmful. Future directions will require genetic and molecular approaches for identifying at-risk patients and appropriate targets for chemoprevention.

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The complete reference list is available online at www.expertconsult.com.



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Biomarker Development

Blood-Based Biomarkers

Urine-Based Biomarkers

Tissue-Based Biomarkers

Summary

The field of prostate cancer biomarkers is currently in an era of rapid expansion. Over the past decade, appreciation of the heterogeneity of outcomes among men with clinically localized disease has matured. The clinical question has changed from one of diagnosis of prostate cancer to distinguishing aggressive from indolent disease. This fundamental adjustment in perspective has fueled avid research and development of novel biomarkers for prostate cancer.

Among urologic malignancies, prostate cancer has benefited greatly from the discovery and application of tumor markers. From its discovery in 1979 through clinical application in the late 1980s and 1990s, prostate-specific antigen (PSA) has evolved into an invaluable tool for detecting, staging, and monitoring prostate cancer in men. The widespread use of PSA screening has generated greater awareness about prostate cancer. During the PSA era, cancers identified when confined to the prostate have improved cure rates after either radical prostatectomy or radiation therapy. In the 1980s and early 1990s, most prostate cancers commonly arose through findings on an abnormal digital rectal examination (DRE) and/or elevated PSA, whereas today most prostate cancer arises as clinically nonpalpable (stage T1c) disease with PSA levels between 2.5 ng/mL and 10 ng/mL. Widespread application of PSA screening and the long natural history of prostate cancer have resulted in a stage migration to nonpalpable, clinically localized (stage T1c) disease and a parallel reduction in mortality (McCormack et al, 1995; Lilja, 1997; Pound et al, 1997; Stephenson and Stanford, 1997; Rittenhouse et al, 1998; Polascik et al, 1999; Pound et al, 1999; Diamandis et al, 2000). However, as mentioned, the clinical trajectory of these PSA-detected T1c cancers is far from homogeneous. Although PSA screening has improved survival, outcomes are not the same for all disease detected with PSA. Because many of these cancers may not pose a threat to survival (Diamandis et al, 2000; Yousef and Diamandis, 2001; Gretzer et al, 2002), the most common cause of mortality for *all* men with prostate cancer is heart disease. Our intention is not to downplay the influence of prostate cancer on the mortality of the approximately 30,000 men who die of prostate cancer annually in the United States, but rather to highlight the urgent need for reliable tools that allow the patient and physician alike to identify harmful cancers readily.

Although PSA is widely accepted as a prostate cancer tumor marker, it is organ specific and not cancer specific. Despite routine application of PSA assays, the limited specificity of this marker is highly controversial. There is significant overlap in serum PSA levels among men with cancer and men with benign disease. Elevated serum PSA levels may reflect alterations within the prostate secondary to tissue architectural changes such as cancer, inflammation, or benign prostatic hyperplasia (BPH). At the present time, serum PSA levels of 2.6 ng/mL are used as a threshold

to recommend prostate biopsy. With an extended pattern template biopsy approach, 40% of men presenting with an elevated PSA (serum PSA 4 to 10 ng/mL) may be diagnosed with cancer with a false-negative rate of 20%. In some instances, the biopsy needle may fail to sample representative areas (i.e., sample bias), failing to detect present cancer. To this end, application of PSA derivatives such as PSA density, PSA velocity, age-adjusted values, and, more recently, molecular derivatives have attempted to improve the performance of PSA.

There are four main domains in which clinically localized prostate cancer biomarkers are needed: (1) screening, (2) elevated PSA with prior negative biopsy, (3) pretreatment in men with a new diagnosis, and (4) postprostatectomy. By identifying men at greatest risk of harboring harmful disease, improved biomarkers used in screening could markedly reduce the number of men subjected to prostate biopsy. The cohort of men who have an elevated PSA, or for whom there is reasonable concern for cancer based on some other variable, after an initial negative biopsy represents a particularly vexing group. Although some biomarkers currently exist that address this situation, additional improvements in this regard would be helpful clinically. After a diagnosis of prostate cancer has been made, choosing a therapy can be challenging. Knowledge regarding biologic behavior could drastically improve the decision-making process for a patient contemplating therapy with curative intent (e.g., radical prostatectomy or radiation) versus active surveillance. Postprostatectomy biomarkers hold promise for improving the ability to identify candidates for adjuvant therapies.

New understanding of the molecular biology of carcinogenesis and prostate cancer is beginning to yield a new age in prostate cancer research. Advances in molecular oncology and breakthroughs in laboratory techniques have exponentially expanded the repertoire of innovative tools for discovery of novel ways of predicting the future. In this chapter, we discuss the process and phases of biomarker development, paying particular attention to scientific rationale and clinical application of blood-based, urine-based, and tissue-based biomarkers.

Several molecular approaches have been undertaken in pursuit of finding the optimal prostate cancer biomarker. An overview of basic cellular processes starts first with a DNA sequence (gene) that is transcribed to messenger RNA (transcript) and then translated to a protein that can carry out specific cellular functions (e.g., catalyze biochemical reactions leading to the formation of products such as metabolites). A guiding principle of prostate cancer biomarker development is that prostate cancer cells *a priori* are different in some molecular way compared with their benign counterparts. Another important observation is that aggressive prostate cancer cells are similarly different compared with their more indolent counterparts. The identification and quantification of these molecular

differences in tissues and bodily fluids form the basis of prostate cancer biomarker discovery.

BIOMARKER DEVELOPMENT

Although many groups are now developing methods for early detection of prostate cancer, the Early Detection Research Network (EDRN) has developed a particularly robust infrastructure for biomarker development. The EDRN is a program funded by the National Cancer Institute set forth with the objective to identify, develop, and validate promising biomarkers and technologies for early detection of cancer (Schedlich et al, 1987; Clements, 1989; Srivastava et al, 2001; Srivastava, 2014). The EDRN is part of the portfolio supported by the Division of Cancer Prevention. As suggested by its name, it is a network of academic centers working in collaboration with industry, public health groups, informatics centers, and patient advocates. The structure of the network consists of five scientific components, as follows.

The Biomarker Development Laboratories are responsible for discovery of novel biomarkers and technologies. They identify biomarkers and participate in the early phases of validation. The Biomarker Reference Laboratories facilitate the development and validation of assays that measure these new biomarkers. Without such efforts, results of assays may be difficult to reproduce when deployed at a different site. The Biomarker Reference Laboratories also assist in developing a more robust and efficient clinical assay. The Clinical Epidemiological Validation Centers are large clinical practices with infrastructure to procure ample clinical samples and to lead clinical trials. They are responsible for procuring samples for the Biomarker Development Laboratories. The Data Management and Coordinating Center is the spine of the network in the sense that it provides all the logistical and statistical support for all phases of development. This EDRN component is responsible for creating a reliable, secure, and practical means by which data may be collected for network studies. The fifth and final component is the Informatics Center, which is responsible for developing software for information management. As the EDRN experience grew, experts in oncology, clinical trials, biostatistics, and informatics came together and refined what is considered best practice for the development of new biomarkers (Young et al, 1995; Lilja, 1997; Rittenhouse et al, 1998; Pepe et al, 2001). Conceptually, progression of a biomarker through each of the five phases of development indicates increasing strength of evidence in favor of its clinical application.

Phase 1 consists of biomarker discovery. Although biomarker discovery may occur at any laboratory, the Biomarker Development Laboratories are intended to be factories of discovery along the lines of genomics, proteomics, glycomics, and metabolomics, in addition to traditional pathway science. The objective of this phase is to identify potential biomarkers and prioritize each for validation. The typical outcome of phase 1 development is a novel biomarker with some measure of test sensitivity and specificity in a subset of cancer and control subjects. In this way, a preclinical assay is moved forward into phase 2.

Phase 2 has the objective of measuring more reliably the sensitivity and specificity of the new biomarker in its ability to differentiate case status from control. The Biomarker Reference Laboratories often participate to optimize the clinical assay and assess the reproducibility of the assay in preparation for a clinical trial. It would not be unusual to see comparisons of biomarkers measured in tissue samples compared with levels from less invasive approaches such as voided urine or serum. If feasible, investigators may begin to study factors that affect expression of these biomarkers and the relationship of these biomarkers to cancer stage, grade, and prognosis. The clinical samples deployed at this stage tend to be more representative of the target population, and as a result, biomarkers may fail at this phase if they were initially developed on an overly selected set of tissues. The increasing inclination of many biomarker discovery programs is to employ more diverse cancer samples even during phases 1 and 2.

In phase 3, investigators examine the ability of new biomarkers to detect preclinical disease and evaluate how much lead time is provided by the biomarker relative to clinical presentation. The criteria necessary for a “positive test” are defined in this phase. Robust studies examining the impact of covariates on biomarker expression and measurement take place. Given the growing number of biomarkers, it would be common to see algorithms developed during this phase to support the use of panels of biomarkers as opposed to a single biomarker. The tissue repositories used for this phase are typically retrospective cohort studies in which clinical samples have been procured prospectively over time with careful annotation of clinical end points and risk factors. These subjects usually are identified before cancer is diagnosed, sometimes years before diagnosis. Although prospectively collected data are unnecessary in phase 3, the availability of such data provides for better statistical evaluations.

Having completed phase 3, a new biomarker would possess a validated clinical assay and strong evidence of ability to differentiate case from control according to its clinical indication conducted on a fairly robust sample of subjects. An understanding of factors that may affect measurement and expression of the biomarker is known, and plans are made for a prospective validation trial, which is phase 4.

In phase 4, indications for applying a new biomarker are clearly defined according to the labeling. Subjects are enrolled at the Clinical Epidemiological Validation Centers. Non-EDRN sites commonly are enlisted to satisfy the necessary power and recruitment timeframe. Potential subjects are identified for eligibility, given written consent, and are enrolled with careful annotation of all demographic, disease, risk factors, and cancer end points. The goal of phase 4 is to quantify the performance characteristics of a biomarker in the target population of interest. This quantification is typically done by examination of sensitivity, specificity, positive predictive value, and negative predictive value. Secondly, this phase also examines characteristics of cancers that are diagnosed using the biomarker, considers implementation feasibility and costs, and considers potential impact on overall mortality.

In contrast to drug studies, in which randomized clinical trials are conducted as validation of treatment effect, biomarkers are rarely tested with such trials given the large sample sizes, long durations, and prohibitive costs (Lundwall and Lilja, 1987; Andriole et al, 2009; Schröder et al, 2009). However, a robust clinical validation design specifically for biomarker discovery (Prospective Randomized Open, Blinded Endpoint [PROBE] study design) was proposed by Pepe and colleagues (2008) (Kumar et al, 1997; Lövgren et al, 1997; Takayama et al, 1997). Use of the PROBE design is intended to overcome spectrum bias, where there is differential selection of cases and controls. In addition, this approach overcomes ascertainment bias, defined as inclination for patients with different levels of the biomarker to undergo different diagnostic tests, because all subjects will receive the same testing. Within the EDRN, a common strategy has been to develop prospective registries to be used for validation studies by blinding samples, which are stored at the National Cancer Institute in Frederick, Maryland. In this way, validation studies can be performed using large cohorts for a series of biomarkers as long as sample size is sufficient.

Ultimately, it is desired that new biomarkers reduce the burden of cancer, and this takes place in phase 5—cancer control studies. With deployment over time, biomarkers are expected to identify cancers efficiently earlier in the disease course leading to greater construct validity. Achievement of a successful outcome in phase 5 requires reduction in cancer mortality that can be attributed to the biomarker use without prohibitive costs or overdiagnosis. This goal has been achieved by few biomarkers to date.

Inherently, the work necessary to take a biomarker from phase 1 through phase 5 often costs in excess of millions of dollars. A common strategy applied by the EDRN is to partner with multiple institutions and industry to fund work along different phases with a common goal of moving biomarkers into clinical practice that are likely to improve the health of a population. The approach of the

EDRN is not the only means by which biomarkers may be developed, but the outline developed by the EDRN scientists provides a rigorous framework for doing so.

Assessment of Biomarker Performance

In the previous section, we discussed study designs as applied by the EDRN in the development and validation of biomarkers. In this section, we briefly discuss common ways by which biomarker performance may be assessed. Typically, this assessment is conducted using the clinical grade assay in the intended population along the indicated clinical indications. Perhaps the most common means for assessing validity is calculation of sensitivity, specificity, and accuracy. Sensitivity is defined as the proportion of individuals with the disease who have a positive biomarker test, whereas specificity is defined as the proportion of individuals without the disease who have a negative test. Accuracy is the sum of true positives and true negatives divided by the total population. Sensitivity and specificity are graphically summarized using the receiver operating characteristic curve. This approach plots sensitivity on the vertical axis and $1 - \text{specificity}$ on the horizontal axis. In doing so, the area under the curve (AUC) is a measure of the accuracy of the test. An AUC of 1 signifies an ideal test, whereas an AUC of 0.5 indicates a poorly performing biomarker test.

Despite widespread use, sensitivity and specificity are not intuitive to interpret; positive and negative predictive values are often used instead. These values are calculated based on sensitivity and specificity and the prevalence of the disease. The definition of positive predictive value is the probability that a positive test indicates the presence of the disease state of interest. Similarly, negative predictive value is the probability that the patient does not have the disease state of interest when the biomarker test is negative. In many ways, these measures are more relevant to clinical practice, and there is an increasing tendency to use these as the end point for biomarker validation trials.

In prostate cancer early detection, it is useful to think in terms of pretest and post-test probability. When new biomarkers are introduced, the natural question becomes, "How much does this add to what we already know in terms of risk prediction?" The likelihood ratio (LR) is useful in this regard because the test indicates how much a new biomarker raises or lowers the probability of disease before biopsy. A positive LR is calculated as the probability of a positive test in patients with cancer divided by the probability of that test result in disease-free individuals. Similarly, a negative LR is calculated as the probability of a negative test result among healthy men divided by the probability of the same result among men with prostate cancer. An LR greater than 1 indicates that the test result increases the likelihood that a patient has cancer, whereas an LR less than 1 decreases the probability of the condition. In the literature, LRs greater than 5 or less than 0.2 are regarded as meaningful shifts in pretest probability.

At the present time, prostate biomarkers are proliferating at a greater rate thanks to the many innovations in high-throughput methods (Takayama et al, 2001; Prensner et al, 2012). Understanding the status of biomarkers with regard to U.S. Food and Drug Administration (FDA) approval and other approvals is helpful (Ablin et al, 1970; Sensabaugh, 1978; Kuriyama et al, 1980; Seamonds et al, 1986; Stamey et al, 1987; Oesterling et al, 1988; Füzéry et al, 2013). FDA approval is considered to be the final end point in the development process because it indicates governmental approval for a specific indication and provides for biomarker validity and safety. Such processes are not undertaken lightly and often cost millions of dollars. Currently FDA-approved biomarkers include PSA, free-to-total PSA ratio (%fPSA), Prostate Health Index (PHI), and PCA3. Another common term applied to new biomarkers is *CLIA-certified test*. The Clinical Laboratories Improvement Act (CLIA) laboratory standards established by the Centers for Medicare and Medicaid Services exist to ensure quality laboratory testing, but not necessarily biomarker validity or safety. The CLIA program examines performance characteristics of the tests with regard to laboratory precision, analytical sensitivity and specificity, reporting

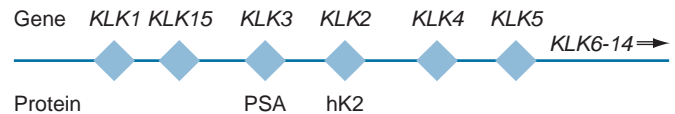


Figure 108-1. Human kallikrein gene map. Map of the human kallikrein locus and corresponding proteins as described by Yousef and Diamandis (2001).

ranges, reference ranges, and criteria for the test systems. In contrast to FDA approval, a CLIA-certified test allows businesses to offer the test for commercial use, but it does not guarantee a biomarker has undergone rigorous clinical validation.

BLOOD-BASED BIOMARKERS

Prostate-Specific Antigen

Initially developed as a biomarker for monitoring patients with prostate cancer after treatment, PSA has become a lightning rod for controversy in the setting of prostate cancer screening. Given its unique prominence, a clear understanding of PSA is needed to lay the foundation for other potential prostate cancer biomarkers. Also known as human kallikrein peptidase 3 (hK3), PSA is a member of the kallikrein gene family (Fig. 108-1). Originally, only three genes of this family of genes were identified: the pancreatic/renal kallikrein (*hKLK1*), human kallikrein 2 (*hKLK2*), and PSA (*hKLK3*) genes (Yu et al, 1994a, 1994b, 1994c; McCormack et al, 1995; Lilja, 1997; Rittenhouse et al, 1998; Diamandis et al, 2000). With the subsequent identification of 12 other kallikrein genes, this family of proteases now consists of 15 members and is described with a distinct nomenclature (Monne et al, 1994; Diamandis et al, 2000; Yousef and Diamandis, 2001). These proteins all are serine proteases and are located on the long arm of chromosome 19 within the region spanning q13.2-q13.4. These serine proteases have similar amino acid sequences, with human kallikrein peptidase 1 (hK1) expressing 60% and human kallikrein peptidase 2 (hK2) expressing 78% homology with PSA (Schedlich et al, 1987; Clements, 1989; Yu and Diamandis, 1995). Both hK2 and hK3 (PSA) are released in zymogen form from the prostatic epithelium and are found in seminal fluid and serum. Because they share structural homology, both can form complexes with endogenous protease inhibitors such as α_2 -macroglobulin (A2M) and α_1 -antichymotrypsin (ACT) (Levesque et al, 1995; Young et al, 1995; Lilja, 1997; Rittenhouse et al, 1998).

To understand PSA and its related derivative biomarkers, it is important to understand how PSA is processed. PSA begins as a zymogen, termed *preproPSA*, which contains a 17–amino acid leader sequence (Lundwall and Lilja, 1987; Oesterling et al, 1988; Partin et al, 1990). Cleavage of *preproPSA* results in an inactive 244–amino acid proenzyme termed *proPSA*. Finally, cleavage of a leader amino acid sequence of *proPSA* by hK2 produces the active form of PSA (Kumar et al, 1997; Lövgren et al, 1997; Takayama et al, 1997; Magklara et al, 2000; Meng et al, 2002). Other prostate kallikreins, such as hK4, also may have a role in cleavage of *proPSA* (Lilja and Weiber, 1984; Lilja, 1985; McGee and Herr, 1988; Takayama et al, 2001).

PSA was first identified and purified in the late 1970s, but widespread use in clinical urology did not occur for another decade (Ablin et al, 1970; Sensabaugh, 1978; Kuriyama et al, 1980; Seamonds et al, 1986; Stamey et al, 1987; Oesterling et al, 1988; Christensson et al, 1990; McCormack et al, 1995; Otto et al, 1998). Although ectopic expression of PSA has been reported in smaller concentrations in the tissue of malignant breast tumors (Yu et al, 1994a, 1994b, 1994c; Partin et al, 2003), normal breast tissue (Christensson et al, 1990; Monne et al, 1994; Zhang et al, 2000), breast milk (Lilja et al, 1991; Yu and Diamandis, 1995; Végvári et al, 2010), and adrenal and renal carcinomas (Sensabaugh, 1978; Levesque et al, 1995; McCormack et al, 1995), PSA is highly organ specific because it is primarily produced by prostatic luminal

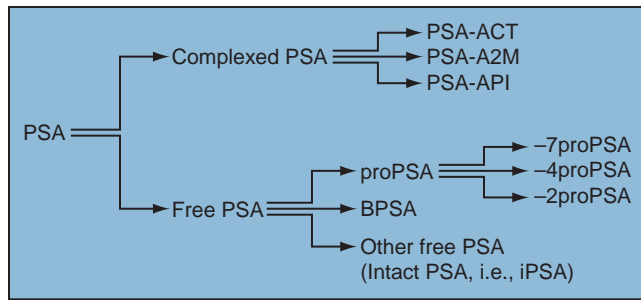


Figure 108-2. Molecular forms of prostate-specific antigen (PSA). Molecular derivatives of PSA include free PSA, such as proPSA (and the various clipped forms), benign prostatic hyperplasia-associated PSA (BPSA), and other free PSA forms such as intact, inactivated PSA. Complexed PSA includes free PSA that is bound to proteases such as α_1 -antichymotrypsin (ACT), α_1 -protease inhibitor (API), and α_2 -macroglobulin (A2M).

epithelial cells. As evidenced by its imperfect performance as a diagnostic biomarker, PSA is not cancer specific—there is substantial overlap in PSA values between men with benign versus malignant prostate disease (Oesterling et al, 1988; Partin et al, 1990; Catalona et al, 1991). On a per-gram basis, PSA is expressed to a greater degree in noncancerous relative to cancerous prostate tissue (Henttu et al, 1992; Magklara et al, 2000; Meng et al, 2002).

The function of this androgen-regulated protease is to liquefy semen through its action on the gel-forming proteins semenogelin and fibronectin within the semen after ejaculation (Lilja and Weiber, 1984; Lilja, 1985; Goldfarb et al, 1986; McGee and Herr, 1988). PSA is normally found in low concentration in serum (ng/mL). Within serum, PSA circulates in bound (complexed PSA) and unbound (free PSA [fPSA]) forms (Fig. 108-2). Three proteins that are known to bind to PSA in the blood are ACT, A2M, and α_1 -protease inhibitor (API) (Christensson et al, 1990; Vieira et al, 1994; McCormack et al, 1995; Otto et al, 1998). Binding of fPSA to ACT inactivates the protease, but the complex PSA-ACT remains immunodetectable (Meng et al, 2002; Partin et al, 2003).

Approximately 70% to 80% of PSA in serum is protein-bound, most to ACT in an irreversible fashion. Only 5% to 10% of PSA is bound to A2M, and 1% to 2% is bound to API. Binding of PSA to A2M still allows some proteolytic activity but renders the PSA-A2M complex undetectable by most current assays because all PSA epitope sites become masked (Fig. 108-3) (Christensson et al, 1990; Carter et al, 1992; Oesterling et al, 1993b; Zhang et al, 2000). PSA-ACT and PSA-API are detected by PSA assays, as is fPSA. fPSA without proteolytic activity is probably rendered inactive within the prostatic epithelial cell before release into the sera. This free inactive PSA does not form complexes with antiproteases, circulates unbound in sera, and is immunodetectable by current assays (Lilja et al, 1991; Oesterling et al, 1993a; Végvári et al, 2010). The primary release of PSA into the seminal fluid results in 10^6 -fold higher seminal concentrations than levels measured within serum (Sensabaugh, 1978; McCormack et al, 1995; Morgan et al, 1996; Fowler et al, 1999; Fowke et al, 2006). The concentrations found in seminal plasma range from 0.5 to 5.0 mg/mL, whereas the normal serum concentration in men 50 to 80 years old without prostate disease ranges between 1.0 and 4.0 ng/mL (Catalona et al, 1991; Fowke et al, 2006; Skolarus et al, 2007; Beebe-Dimmer et al, 2008).

PSA expression is strongly androgen dependent (Henttu et al, 1992; Ohwaki et al, 2010). Immunohistochemical detection of PSA within the prostate is characterized by bimodal peaks between 0 and 6 months of age and after 10 years of age, correlating directly with testosterone levels (Goldfarb et al, 1986; Stamey et al, 1987). Serum PSA becomes detectable at puberty with increases in luteinizing hormone and testosterone (Stamey et al, 1987; Vieira et al, 1994). In the absence of prostate cancer, serum PSA levels vary with age, race, and prostate volume. On a per-cell basis, PSA expression is similar between benign and malignant prostate

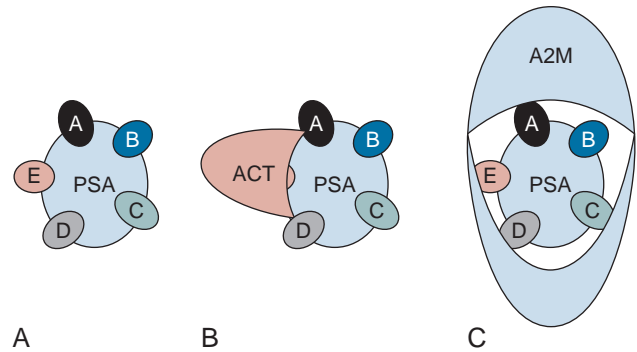


Figure 108-3. Prostate-specific antigen (PSA)-binding proteases. A, Free PSA with A to E representing immunoreactive epitopes of free PSA. B, α_1 -Antichymotrypsin (ACT) blocks the E epitope during binding. C, α_2 -Macroglobulin (A2M) blocks all immunoreactive sites on PSA, making this derivative difficult to measure in serum.

cells (Armitage et al, 1988; Dalton, 1989; Nadler et al, 1995; Meng et al, 2002).

In men without BPH, the rate of change in PSA is 0.04 ng/mL per year compared with 0.07 to 0.27 ng/mL per year in men with BPH who are 60 to 85 years old (Carter et al, 1992; Yuan et al, 1992; Oesterling et al, 1993b). Cross-sectional data suggest that PSA increases 4% per milliliter of prostate volume and that 30% and 5% of the variance in PSA can be accounted for by prostate volume and age, respectively (Oesterling et al, 1993a; Kirkali et al, 1995). Black men without prostate cancer have higher PSA values than white men (Simak et al, 1993; Morgan et al, 1996; Heidenreich et al, 1997; Fowler et al, 1999; Fowke et al, 2006). Fowler and colleagues (1999) demonstrated that, on a volume/volume basis, the benign prostatic tissue of black men contributes more PSA to serum than the benign prostatic tissue of white men, a difference that increases with age. Body mass index also appears to affect PSA levels: Increasing body mass index is independently associated with decreasing serum PSA (Tchetgen et al, 1996; Herschman et al, 1997; Fowke et al, 2006; Skolarus et al, 2007; Beebe-Dimmer et al, 2008). Data from Ohwaki and colleagues (2010) suggest that this association may be secondary to hemodilution, as indicated by a close correlation between changes in serial hematocrit and serial PSA levels (Rajaei et al, 2013).

Elevated serum PSA levels are probably a product of disruption of cellular architecture within the prostate gland (Stamey et al, 1987; Mejak et al, 2013). The loss of the barrier afforded by the basal layer and basement membranes within the normal gland is a likely site for the egress of PSA into the circulation. This barrier loss can occur in the setting of prostate disease (BPH, prostatitis, prostate cancer) and with prostate manipulation (prostate massage, prostate biopsy) (Wang et al, 1981; Ercole et al, 1987; Stamey et al, 1987; Morote Robles et al, 1988). Prostatic inflammation (acute and chronic) and urinary retention can cause PSA elevations to variable degrees (Armitage et al, 1988; Dalton, 1989; Nadler et al, 1995; Thompson et al, 2003; Etzioni et al, 2005; Marks et al, 2006). Prostatic trauma, such as occurs after prostate biopsy, can result in a temporary spike in serum PSA that persists for 4 or more weeks before returning to baseline values (Yuan et al, 1992; Thompson et al, 2006; Kaplan et al, 2012).

Studies of the effect of ejaculation on serum PSA have shown no significant change in PSA (Kirkali et al, 1995; McCormack et al, 1995; Woodrum et al, 1998) and a significant decrease in serum PSA (Christensson et al, 1993; Leinonen et al, 1993; Lilja, 1993; Simak et al, 1993; Stenman et al, 1994; Catalona et al, 1997a; Heidenreich et al, 1997) in men 30 to 40 years old or younger. In men 50 years old and older, ejaculation can lead to a transient increase in PSA that may rarely result in a false-positive elevation (Tchetgen et al, 1996; Herschman et al, 1997; Catalona et al, 1998; Partin et al, 1998). However, PSA appears to return to baseline within 24 hours (Rajaei et al, 2013). Men presenting with a new

PSA elevation should be asked whether they engaged in sexual activity within 24 hours of PSA testing, and if the answer is yes, they should be asked to abstain before a repeat blood draw. Long-distance cycling is another potential cause of false PSA elevation, with PSA levels increasing by approximately 10% after bicycle rides exceeding 55 km (Mejak et al, 2013).

Although the above-mentioned factors can cause small-scale changes in PSA levels, the presence of prostate disease (prostate cancer, BPH, and prostatitis) is the most important factor affecting serum PSA (Wang et al, 1981; Ercole et al, 1987; Morote Robles et al, 1988). It is primarily the impact of BPH and prostatitis on PSA levels that confounds the accuracy of PSA in the screening setting. Prostate-directed treatment (for BPH and prostate cancer) can reduce serum PSA by decreasing the volume of prostatic epithelium available for PSA production and by decreasing the amount of PSA produced per cell. The 5 α -reductase inhibitors (5ARI), such as finasteride and dutasteride, have been shown to lower PSA levels by roughly 50% after 12 months of treatment (Guess et al, 1993); this has resulted in the so-called doubling rule, whereby PSA levels are multiplied by a factor of 2 in men undergoing 5ARI therapy to guide decisions regarding prostate cancer risk. However, using a multiple of 2 may overestimate PSA values in the first 6 months of treatment and underestimate PSA levels after several years of treatment (Thompson et al, 2003; Etzioni et al, 2005; Marks et al, 2006). Additionally, compelling data from the Prostate Cancer Prevention Trial and other sources suggest that 5ARI therapy substantially improves the performance characteristics of PSA in the screening setting with an AUC of 0.76 (finasteride) versus 0.68 (placebo) (Thompson et al, 2006; Kaplan et al, 2012). Interpretation of PSA values always should take into account the presence of prostate disease, previous diagnostic procedures, and prostate-directed treatments.

Free Prostate-Specific Antigen

Although most serum PSA is found complexed to proteases (primarily ACT), 5% to 45% of PSA exists as enzymatically inactive fPSA (Table 108-1) (McCormack et al, 1995; Woodrum et al, 1998). PSA produced from malignant cells appears to escape proteolytic processing more frequently, resulting in a greater fraction of serum PSA complexed to ACT and a lower percentage of total PSA (tPSA) that is free compared with men without prostate cancer (Christensson et al, 1993; Leinonen et al, 1993; Lilja, 1993; Stenman et al, 1994; Catalona et al, 1997a). This principle led to the development of fPSA testing as a means to improve the accuracy of PSA as a prostate cancer screening biomarker, and the FDA has approved its use in men with a serum total PSA level of 4 to 10 ng/mL and a negative DRE (Catalona et al, 1998; Partin et al, 1998). The %fPSA is most useful in the setting of PSA levels less than 10 ng/mL because the positive predictive value of tPSA greater than 10 to 20 ng/mL has been shown to be approximately 80%.

Numerous studies evaluated %fPSA cut points to determine potential thresholds that optimize the performance of this tool. Christensson and coworkers (1993) measured fPSA and tPSA fractions in men with and without prostate cancer and found that a fPSA/tPSA cutoff of 0.18 (18% fPSA) significantly improved the

ability to distinguish between subjects with and without cancer compared with use of tPSA alone. When using %fPSA cutoff values ranging from 14% to 28%, 20% to 65% of unnecessary biopsies may be avoided, while maintaining sensitivity rates of 70% to 95% within the tPSA range of 4 to 10 ng/mL (Pound et al, 1997; Stephenson and Stanford, 1997; Catalona et al, 1998; Partin et al, 1998; Polascik et al, 1999; Pound et al, 1999; Veltri and Miller, 1999; Vessella et al, 2000). In a prospective, multi-institutional study of men 50 to 75 years old with PSA levels between 4 and 10 ng/mL and palpably benign prostate glands, a %fPSA cutoff of 25% detected 95% of cancers (sensitivity), while avoiding 20% of unnecessary biopsies (specificity) (Catalona et al, 1998; Gretzer et al, 2002). This resulted in an AUC for %fPSA that was significantly higher than that of tPSA (0.72 vs. 0.53). However, more recent data including men with 12-core prostate biopsy schemata showed a modest decrease in the AUC of %fPSA for cancer detection (Srivastava et al, 2001; Canto et al, 2004a; Srivastava, 2014). Although no single %fPSA threshold has been established, proposed cut points generally range from 15% to 25%. However, an important more recent development has been the increasing availability and usage of predictive tools that incorporate multiple clinical variables, such as tPSA, %fPSA, and DRE findings (Pepe et al, 2001; Hernandez et al, 2009; Zaytoun et al, 2011). In particular, the updated calculator based on results of the Prostate Cancer Prevention Trial (PCPT) provides a calibrated estimate of prostate cancer risk to facilitate shared clinical decision making (Fig. 108-4) (Andriole et al, 2009; Schröder et al, 2009; Ankerst et al, 2012).

Several studies have also evaluated the performance of %fPSA at tPSA levels less than 4.0 ng/mL because high-grade cancers do still occur at these low PSA levels (Thompson et al, 2004; Pepe et al, 2008). Catalona and colleagues (1997b) demonstrated that for men with PSA levels less than 4 ng/mL, a %fPSA cutoff value of 27% could detect 90% of cancers, while preventing 18% of unnecessary biopsies (Prensner et al, 2012). Comparison against PSA derivatives, such as prostate-specific antigen density, PSA velocity, and transition zone density, favored %fPSA in a similar cohort (Djavan et al, 1999; Füzyer et al, 2013). Haese and coworkers (1997) demonstrated that %fPSA in the tPSA range of 2 to 4.0 ng/mL does not substantially increase the number of biopsies needed to detect clinically significant prostate cancer compared with %fPSA in the 4 to 10 ng/mL range. In this study, a %fPSA cutoff value of 18% to 20% detected almost half of cancers and spared 73% of men from undergoing biopsy, with a biopsy-to-cancer ratio of 3:1 to 4:1.

In addition to contributing to detection, %fPSA may provide prognostic information. Serial measurement of %fPSA within archival serum demonstrated sustained differences between aggressive and nonaggressive prostate cancers (Carter et al, 1997). This study suggested that the longitudinal measurement of %fPSA changes not only may aid in detection but also may contribute information regarding disease behavior. Numerous studies reported on the correlation between %fPSA and pathologic outcomes, showing some correlation between low %fPSA and aggressive pathologic features (Morote et al, 2000; Aus et al, 2003; Shariat et al, 2006; Masieri et al, 2012). Additionally, Shariat and colleagues (2006) reported an independent association between lower %fPSA and biochemical recurrence in 402 men who underwent radical prostatectomy for clinically localized disease. These data stand in contrast to a study of 698 consecutive patients undergoing prostatectomy that found %fPSA did not independently predict aggressive pathologic features or biochemical recurrence (Graefen et al, 2002). Debate remains surrounding the utility of %fPSA as a prognostic biomarker.

There are some important caveats surrounding the interpretation of %fPSA in clinical practice for cancer detection. Factors such as prostatic manipulation, specimen handling, and assay variation have been shown to affect the interpretation of the ratio of fPSA to tPSA (Partin et al, 1996a, 1996b; Roth et al, 1998; Foj et al, 2014). Although there may be marginal changes in tPSA, fPSA levels may fluctuate, affecting the %fPSA calculation. Furthermore, because fPSA is cleared more rapidly from serum than complexed PSA

TABLE 108-1 Molecular Derivatives of Prostate-Specific Antigen

PSA TYPE	% IN SERUM
Complexed PSA	60-95
PSA-ACT	60-90
PSA-API	1-5
PSA-A2M	10-20
Free PSA	5-40

ACT, α_1 -antichymotrypsin; API, α_1 -protease inhibitor; A2M, α_2 -macroglobulin; PSA, prostate-specific antigen.

Enter Your Information

%freePSA %

Race

Age

PSA Level ng/ml

Family History of Prostate Cancer

Digital Rectal Examination

Prior Prostate Biopsy

Andersson DP, Hestler J, Book S, Goodman PJ, Vickers A, Hernandez J, Sokoll LJ, Sando MG, Wu JT, Leach RJ, Thompson IM. The Prostate Cancer Prevention Trial Risk Calculator 2.0 for the prediction of low versus high-grade prostate cancer. *Urology*, 2014, to appear.

PCPTRC 2.0 and Adjusted Risk Calculators

[PCPTRC 2.0](#)

[%freePSA](#)

[Download the R Code](#)

PCPTRC 1.0 and Adjusted Risk Calculators

[PCPTRC 1.0](#)

[BMI](#)

[PCA3](#)

[Finasteride](#)

[%freePSA](#)

[t-2proPSA](#)

[%freePSA and t-2proPSA](#)

[Prostate Volume and Number of Biopsy Cores](#)

[AUA Symptom Score](#)

[Finasteride with Volume](#)

[Finasteride with AUA Symptom Score](#)

[Download the R Code](#)

Results

Based on the provided risk factors a prostate biopsy performed would have a:

4% chance of high-grade prostate cancer,

10% chance of low-grade cancer,

86% chance that the biopsy is negative for cancer.

About 2 to 4% of men undergoing biopsy will have an infection that may require hospitalization.

Please consult your physician concerning these results.
[Click here](#) to watch a video overview of these results.

Figure 108-4. Web-based calculation of prostate cancer risk using the PCPT risk calculator operationalized by the University of Texas Health Science Center at San Antonio (<http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>). Distinct nomograms using different patient factors and biomarkers are available, and the output for the most commonly used nomograms gives the risk of high-risk cancer and any prostate cancer using a pictorial interface.

forms, the resulting calculated %fPSA is directly affected. It is recommended that PSA determinations be avoided for several weeks after prostatic manipulation (i.e., surgery, biopsy, cystoscopy) (Partin et al, 1996b; Lein et al, 1997; Björk et al, 1998). Lastly, fPSA decreases in a similar fashion as tPSA in the setting of 5ARI therapy, and the percentage of fPSA is not altered significantly by these medications (Keetch et al, 1997; Pannek et al, 1998).

The clinical setting in which %fPSA is most often used is in patients with an elevated PSA and a prior negative prostate biopsy result (Stephan et al, 1997; Hayek et al, 1999; Djavan et al, 2000). Stephan and colleagues (1997) reported a 5% cancer underdiagnosis rate when using a %fPSA value of 21% to trigger repeat biopsy, and Catalona and colleagues (1997a) reported that a threshold of 30% detected 95% of cancers and avoided 12% of repeat biopsies. More recent European data reported an AUC of 0.73 for %fPSA in a repeat biopsy population, exceeding that of PSA and PCA3 (Auprich et al, 2012). At a threshold of 18%, %fPSA demonstrated a sensitivity of 85% and specificity of 41%. However, the AUC for %fPSA was only 0.52 in another European repeat biopsy cohort, suggesting a need for other biomarkers in this setting (Scattoni et al, 2013).

Free Prostate-Specific Antigen Isoforms

Free PSA in serum comprises three isoforms: proPSA, BPH-associated PSA (BPSA), and intact fPSA (Mikolajczyk et al, 2002; Jansen et al, 2009). These three isoforms exist in approximately

equal concentrations in serum, and each has shown promise as a prostate cancer biomarker. As discussed earlier, PSA originates with a 17-amino acid chain that is cleaved to yield a precursor inactive form of PSA termed proPSA (Zhang et al, 1995; Kumar et al, 1997; Mikolajczyk et al, 1997, 2000, 2001; Peter et al, 2001). As depicted in Figure 108-5, the precursor form of PSA contains a 7-amino acid proleader peptide, in addition to the 237 constituent amino acids of mature PSA, and is termed proPSA or [-7]proPSA. This leader amino acid chain is cleaved by hK2, resulting in the active form of PSA. Incomplete removal of the 7-amino acid leader chain results in various other truncated or clipped forms of proPSA. These include proPSAs with 2, 4, and 5 leader amino acids ([-2]proPSA, [-4]proPSA, and [-5]proPSA), and all are primarily expressed in the peripheral zone of the prostate. With cellular disruption, these enzymatically inactive forms circulate as free PSA and may constitute most of the circulating fPSA in patients with prostate cancer (Fig. 108-6) (Mikolajczyk et al, 1997).

Reports by Mikolajczyk and colleagues (2000, 2001) revealed significantly elevated levels of these truncated forms of proPSA in prostate cancer tissue. In particular, the [-2]proPSA isoform, cleaved between leucine 5 and serine 6 of the propeptide, has shown increasing promise as a serum prostate cancer biomarker (Le et al, 2010; Lazzeri et al, 2012, 2013). Although the underlying biology behind the increased levels of [-2]proPSA in prostate cancer remains unclear, it may be that the decreased PSA processing in prostate cancer results in a relative increase in proPSA and its cleaved forms, in particular, [-2]proPSA. Additionally, Makarov and coworkers

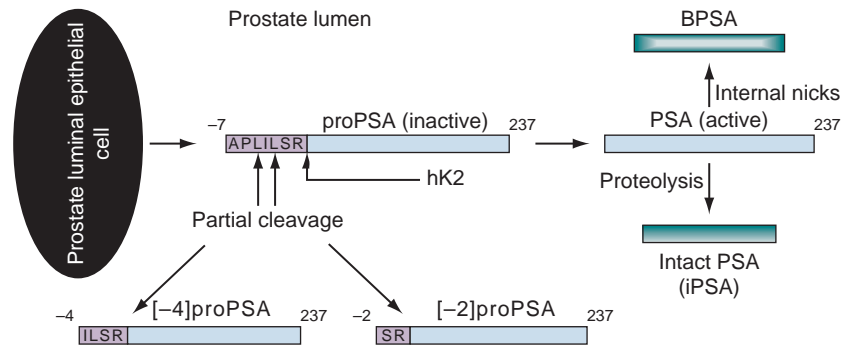


Figure 108-5. Differential cleavage and activation of pro-prostate-specific antigen (PSA). ProPSA is released from the prostate epithelial cell with a 7-amino acid leader sequence. hK2 cleaves the amino acid leader to activate PSA. Active PSA undergoes proteolysis to yield intact PSA (iPSA) and may undergo internal degradation to form benign PSA (BPSA). Partial cleavage of the 7-amino acid leader sequence yields inactive forms of proPSA (i.e., [-2]pPSA or [-4] pPSA).

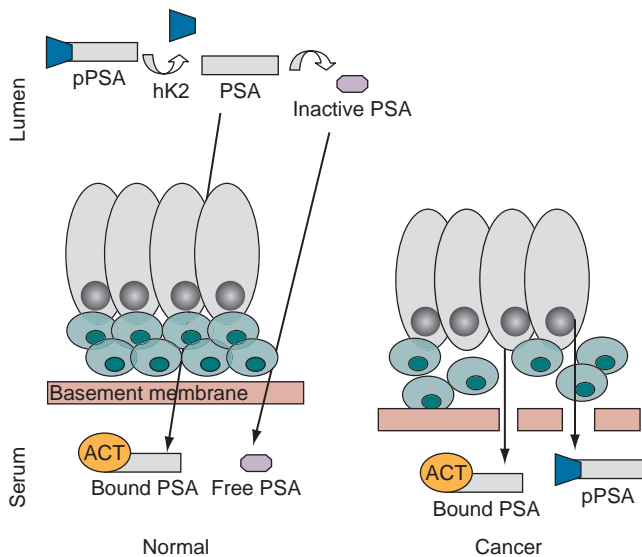


Figure 108-6. Prostate-specific antigen (PSA) synthesis in normal versus cancer tissue. ProPSA is secreted into the lumen, where the 7-amino acid leader sequence is cleaved by hK2 to yield active PSA. Some of the active PSA diffuses into the serum, where it is bound to proteases such as α_1 -antichymotrypsin (ACT). The luminal active PSA undergoes proteolysis, and the resulting inactive PSA also may enter the circulation to circulate in the unbound or free state. In prostate cancer, loss of the tissue architecture may permit a relative increase in bound PSA and proPSA in serum.

(2009) proposed that proPSA production may be driven by benign tissue adjacent to malignant prostatic epithelium.

From a clinical standpoint, there are numerous reports supporting the utility of [-2]proPSA in the screening setting, either before initial biopsy or before repeat biopsy (Le et al, 2010; Guazzoni et al, 2011; Lazzeri et al, 2012, 2013). Lazzeri and colleagues (2013) reported on a prospective European cohort of 646 patients with tPSA between 2 ng/mL and 10 ng/mL who were undergoing initial prostate biopsy. The %[-2]proPSA was a strong independent predictor of prostate cancer at biopsy in a model that included fPSA and tPSA, and the AUC for %[-2]proPSA was 0.67. The %[-2]proPSA was also a strong predictor of prostate cancer with Gleason score 7 or greater in this study. In the United States, a prospective National Cancer Institute EDNRN validation study demonstrated excellent performance characteristics for %[-2]proPSA (Sokoll et al, 2010). Including %[-2]proPSA in the base model consisting of fPSA and tPSA significantly improved the predictive accuracy, and %[-2]PSA

outperformed PSA and %fPSA in predicting the presence of prostate cancer at the time of biopsy in patients with a serum tPSA of 2 to 10 ng/mL. Additionally, %[-2]proPSA was closely correlated with increasing Gleason score. The levels of [-2]proPSA have been incorporated into a formula that also includes fPSA and tPSA and is termed the Prostate Health Index (PHI) (Lazzeri et al, 2013). The PHI is FDA approved for men 50 years old and older with tPSA 4 to 10 ng/mL and negative DRE. This test is discussed in more detail in Chapter 111.

Another isoform of fPSA, BPSA, is identical to mature PSA except for internal cleavages between Lys182 and Lys145 (Mikolajczyk et al, 2002). Its expression is generally limited to transition zone tissue, and it is highly expressed in the setting of BPH (Mikolajczyk et al, 2000; Wang et al, 2000; Canto et al, 2004b). BPSA is closely related to prostate volume and does not appear to have any prognostic capacity in terms of distinguishing potentially indolent from aggressive disease (Naya et al, 2004; de Vries et al, 2005). Although serum BPSA alone is unlikely to differentiate between hyperplasia and cancer, in combination with assays for [-2]proPSA, it may allow additional discrimination (Stephan et al, 2009; Rhodes et al, 2012).

So-called intact PSA comprises an additional fPSA subset that has been identified as a potential predictive serum biomarker (Nurmikko et al, 2000; Steuber et al, 2007a; Hori et al, 2013). Preliminary studies demonstrated that the ratio of intact PSA to fPSA may improve the accuracy of prostate cancer detection (Nurmikko et al, 2000, 2001; Steuber et al, 2002). However, some studies of intact PSA include proPSA in their intact PSA assay, making it difficult to determine the predictive value of intact PSA alone (Peltola et al, 2011). This parameter has been used primarily as part of a multikallikrein panel, which is discussed later on in this chapter (Vickers et al, 2008).

Prostate-Specific Membrane Antigen

The glycoprotein prostate-specific membrane antigen (PSMA) has been evaluated for many years as a potential serum, urine, or tissue biomarker of prostate cancer. A folate hydrolase, PSMA is found embedded within the cell membrane of all prostatic epithelial cells. It is a type II transmembrane protein with an extracellular C-terminus that exists as a dimer and binds glutamate and glutamate-like structures (Fair et al, 1997; Israeli et al, 1997). The gene for PSMA has been cloned, fully sequenced, and localized to the short arm of chromosome 11 (11p11-p12). Although PSMA is predominantly expressed in the secretory acinar epithelium of the prostate gland, it has been isolated in other tissues, including in the central nervous system (astrocytes and Schwann cells) and intestine (jejunal brush border). In the brain, PSMA functions to metabolize the neurotransmitter *N*-acetylaspartylglutamate. In the intestine, PSMA

works as a carboxypeptidase and is known as glutamate carboxypeptidase type II.

Of interest for diagnosis (Douglas et al, 1997), prognosis (Perner et al, 2007), and imaging (Ristau et al, 2014) is the discovery of elevated expression of this protein in tissue from prostate cancer compared with normal prostate tissue (Silver et al, 1997; Chang et al, 1999; Elgamal et al, 2000; Minner et al, 2011). Multiple monoclonal antibodies have been designed to identify the intracellular and the extracellular domains of the PSMA protein; however, few have shown “diagnostic promise” immunohistochemically or as serum and/or urine assays (Horoszewicz et al, 1987; Douglas et al, 1997). However, PSMA mRNA expression among prostate cancers is highest in the hormone-deprived state (Henttu et al, 1992; Israeli et al, 1994). During cancer progression, differentially expressed variants of PSMA have been identified. Of three alternatively spliced variants of PSMA, one, known as PSM', is differentially expressed in normal tissue, BPH, and prostate cancer. Su and colleagues (1995) demonstrated that the PSMA/PSM' ratio is upregulated threefold to sixfold in prostate cancer compared with BPH (0.76 to 1.6) and normal (0.075 to 0.45) tissue. Xiao and colleagues (2001) reported use of an immunoselective (surface-enhanced laser desorption ionization) assay for PSMA and were able to differentiate cases of prostate cancer from BPH. There is also evidence that increased tissue expression of PSMA may confer a worse prognosis in patients undergoing radical prostatectomy (Perner et al, 2007; Minner et al, 2011). The development of an accurate enzyme-linked immunosorbent assay for PSMA in serum has potential significance for diagnostic and prognostic evaluation for prostate cancer. However, at the present time, PSMA appears to have its greatest use in targeted imaging and therapeutics, and promising ongoing trials exist in both of these settings (Milowsky et al, 2007; Barrett et al, 2013; Tagawa et al, 2013; Osborne et al, 2014).

Human Kallikrein 2

hK2 shares many important properties with PSA and has demonstrated potential as another prostate cancer tumor marker (Young et al, 1992; Darson et al, 1997; Kumar et al, 1997; Rittenhouse et al, 1998; Lövgren et al, 1999; Becker et al, 2000a). Among many similarities, hK2 and PSA share 80% amino acid homology (see Fig. 108-1), exhibit similar specificity for prostate tissue, and are hormonally regulated by androgens. As discussed earlier, one of the key functions of hK2 is to activate the zymogen proPSA to the active PSA through cleavage of the amino acid presequence (see Fig. 108-6).

The concentration of hK2 in prostatic tissue, seminal fluid, and serum is less than 2% that of tPSA (Young et al, 1992; Darson et al, 1997; Lövgren et al, 1999). As with PSA, hK2 in serum may be either protein bound or free, with most existing in the free state. Critical to its utility as a biomarker, hK2 expression varies independent of PSA expression in tissue and serum (Tremblay et al, 1997). For example, in benign epithelium, PSA is intensely expressed compared with minimal immunoreactivity of hK2 (Tremblay et al, 1997; Darson et al, 1999). In contrast, in cancerous tissue hK2 is expressed more intensely. Tissue expression of hK2 appears to correlate with more aggressive pathologic features, including Gleason grade (Darson et al, 1997; Tremblay et al, 1997; Darson et al, 1999).

As a serum biomarker, hK2 has been studied extensively and continues to hold promise. Numerous studies have shown an association between serum hK2 levels and the presence of prostate cancer, suggesting that it may be used in conjunction with PSA to improve the selection of patients for prostate needle biopsy (Becker et al, 2000b; Nam et al, 2000; Vickers et al, 2007). Furthermore, men with low-grade disease have lower concentrations of serum hK2 than men with more aggressive cancer (Darson et al, 1999). To improve the performance of hK2 as a biomarker, studies evaluated the ratio of hK2 to fPSA and/or tPSA. For men with tPSA in the range of 4 to 10 ng/mL, hK2/fPSA significantly differentiated prostate cancer from BPH, whereas hK2/tPSA did not (Becker et al,

2000b). Data from a multicenter study demonstrated a statistically significant difference among men with biopsy results positive for cancer, looking at hK2 alone and in combination with fPSA/tPSA (Kwiatkowski et al, 1998). Combining %fPSA and hK2/fPSA, Partin and associates (1999) demonstrated an increased cancer detection rate within the tPSA range of 2 to 10 ng/mL. Serum hK2 also may offer prognostic information, with studies showing correlations with aggressive pathologic features and biochemical recurrence (Haese et al, 2001; Steuber et al, 2007b).

Perhaps the most promising use of hK2 as a prostate cancer biomarker is through the development of the 4Kscore, a multi-kallikrein panel reported by Vickers and coworkers (2008). These authors used a large cohort of men from the Göteborg arm of the European Randomized study of Screening for Prostate Cancer (ERSPC) to combine, within a statistical model, four kallikrein forms (tPSA, fPSA, intact PSA, and hK2) to predict accurately the presence of prostate cancer in men with a PSA 3.0 ng/mL or greater (AUC 0.84). These findings were validated in a separate ERSPC cohort (Rotterdam arm) in which it was suggested that use of the multi-kallikrein panel could avoid 513 of 1000 biopsies with only 54 of 177 missed low-grade cancers and 12 of 100 missed high-grade cancers (Vickers et al, 2010). Additionally, of 392 men in this arm who underwent radical prostatectomy during the period 1994 to 2004, the four kallikrein markers were independently associated with pathologically aggressive disease features and improved the accuracy of the base model (AUC 0.81 to 0.84) (Carlsson et al, 2013). A commercial assay based on this panel is now available (Parekh et al, 2014; Bryant et al, 2015).

Additional Kallikrein Tumor Markers

In addition to PSA (hK3) and hK2, 13 other kallikrein genes have been identified (Paliouras et al, 2007). All kallikreins are expressed in normal prostate tissue, and the expression products of these genes have demonstrated potential as prostate cancer tumor markers (Shaw and Diamandis, 2007). Many of these proteases have a highly conserved structural organization and have been shown to contribute to biologic events such as angiogenesis and growth factor release (Diamandis and Yousef, 2001). Study of these proteins suggests interaction among the kallikreins in pathways that affect normal physiologic and pathologic processes (Yousef and Diamandis, 2002). Among these genes, studies have evaluated *KLK4*, *KLK14*, and *KLK15* in particular as promising prostate cancer biomarkers, albeit primarily in tissue rather than serum (Schmitt et al, 2013). *KLK4* mRNA was found to be expressed at higher levels in most prostate cancer tissues compared with matched normal prostate tissues (Obiezu et al, 2002; Xi et al, 2004; Klok et al, 2007) and may represent a therapeutic target (Jin et al, 2013). *KLK14* and *KLK15* may be markers of poor prognosis (Stephan et al, 2003; Yousef et al, 2003; Rabien et al, 2008). Rabien and colleagues (2008) demonstrated the association of *KLK14* levels on immunohistochemical staining with biochemical progression after radical prostatectomy among men with prostate cancer. Similarly, Mavridis and colleagues (2013) showed an independent correlation between *KLK15* expression and biochemical recurrence in 150 patients who underwent radical prostatectomy for prostate cancer.

Endoglin

Endoglin is a transmembrane glycoprotein that is otherwise known as CD105 and serves as a cell surface coreceptor for transforming growth factor β 1 and β 3. It has a key role in angiogenesis and tends to be located and expressed in vascular endothelial cells. Although initial studies demonstrated increased endoglin expression in prostate cancer tissue (Wikström et al, 2002), investigators examined the possibilities for detecting endoglin in the plasma and in the urine of men with prostate cancer. Preoperative plasma endoglin is associated with node-positive disease in patients undergoing radical prostatectomy and independently predicts biochemical recurrence (Karam et al, 2008; Svatek et al, 2008). Similarly, when endoglin is used in combination with several other blood-based

biomarkers, further discrimination regarding the risk for biochemical recurrence is provided (Svatek et al, 2009). Endoglin also is expressed in the urine of men with prostate cancer compared with men with negative biopsy results after each group received a DRE. These urinary levels correlate with tumor volume and appear to be more accurate than PSA in the discrimination of biopsy outcome (Fujita et al, 2009). Although these initial studies have been intriguing, further validation in multi-institutional trials is required to understand better the clinical utility of endoglin as a prognostic biomarker.

Circulating Tumor Cells

Circulating tumor cells (CTCs) have long been touted as potential prognostic biomarkers and treatment response indicators. The excitement in this area of research goes back more than 20 years when investigators demonstrated the ability to detect PSA mRNA in the blood of men with advanced prostate cancer (Katz et al, 1994). Subsequent CTC research in prostate cancer has used a wide range of methods, capitalizing on features such as size, surface marker expression, and cellular plasticity that differentiate CTCs from circulating mononuclear cells in the blood (Pantel and Alix-Panabières, 2010; Danila et al, 2011b; Yu et al, 2011). Typically, CTCs are defined as being CD45 negative and positive for an epithelial marker such as epithelial cell adhesion molecule (EpCAM) and/or cytokeratin. Critically, there is no single gold standard definition or methodology for isolating CTCs. As a result, the development of CTCs as a prostate cancer biomarker has been relatively slow to evolve, and comparing data among studies continues to be challenging.

At the present time, there is only one FDA-approved methodology for identifying CTCs: CellSearch (Veridex, Warren, NJ). The CellSearch system uses antibodies against EpCAM for CTC capture and stains with antibodies against CD45 (negative) and cytokeratins 8, 18, and 19 (positive) to identify individual CTCs. With this system, a CTC count of 5 or more cells per 7.5 mL of blood at any time during the course of the disease has been associated with a poor prognosis in prostate, breast, and colorectal cancers (Cristofanilli et al, 2004; Shaffer et al, 2007; Cohen et al, 2008; de Bono et al, 2008). In a study of 422 patients with metastatic prostate cancer, using the Veridex platform, the investigators demonstrated that there was a difference between baseline numbers of cells and cells present 2 to 5 weeks after treatment (Fig. 108-7). For example, 57% of the patients had more than 5 cells per 7.5 mL of blood before treatment, and 39% had more than 5 cells per 7.5 mL after treatment (Shaffer et al, 2007). Similar studies lent further support to the potential use of CTCs as a response indicator, with conversion from unfavorable to favorable CTC counts (<5 CTCs) frequently occurring in men with advanced prostate cancer receiving hormonal agents or chemotherapy (de Bono et al, 2008; Danila et al, 2010; Reid et al, 2010). Further data demonstrating that CTC response

independently predicts survival in these settings are needed before CTCs can be used as an efficacy-response surrogate marker (Scher et al, 2009, 2013).

Many other platforms for CTC detection have been developed, and this continues to be an area of rapid growth in the biomarker space. Investigators at Harvard Medical School developed a microfluidic system known as the “CTC-Chip,” which has garnered a great deal of attention (Nagrath et al, 2007). This system has a high level of sensitivity, able to detect a single EpCAM-positive cell among 1 billion blood cells, and the capture efficiency has been improved further with an updated device (Nagrath et al, 2007; Stott et al, 2010a). Additionally, it provides the opportunity subsequently to isolate and characterize these CTCs further (Stott et al, 2010b). Going forward, the use of CTCs as a biomarker will likely revolve less around simple enumeration and more around the specific molecular alterations that can be identified—either within the cells or from cell-free nucleic acids—providing a real-time “liquid biopsy” in men with prostate cancer (Danila et al, 2011a; Dawson et al, 2013; Danila et al, 2014).

Autoimmune Responses

Although we classically think of biomarkers as substances that are abnormally expressed by the tumors, the response of the body itself to the presence of the cancer cell can be a target for biomarker development. Using a high-throughput approach, investigators at the University of Michigan were able to develop autoimmune profiles that could distinguish individuals with prostate cancer from individuals without the disease with a great degree of accuracy (Wang et al, 2005). Similar results were observed elsewhere, confirming the potential for autoimmune signatures as potential diagnostic biomarkers (Massoner et al, 2012). Other studies have identified changes in leukocyte surface marker expression that may correspond with changes in the tumor microenvironment and could correspond with tumor aggressiveness (Hao et al, 2012; Zhong et al, 2012). There is a possibility that immune system markers may serve to reflect not only the presence of disease but also metastatic potential.

URINE-BASED BIOMARKERS

Prostate Cancer Antigen 3

Given the ease of collecting urine specimens and the known shedding of prostate cells into the urine, this body fluid has long held promise as a potential biomarker source in prostate cancer (Truong et al, 2013). However, urinary biomarkers of prostate cancer came into clinical use only more recently. The first of these, PCA3, initially was described by Bussemakers and colleagues (1999), who used differential display and Northern blot analysis to compare normal and prostate cancer tissue. They were able to identify a prostate cancer-specific gene on chromosome 9q21-22 that, although it does not encode a protein, is one of the most sensitive and specific prostate cancer biomarkers. Although its function remains unknown, multiple studies have demonstrated that PCA3 is a long noncoding RNA that is not expressed outside of the prostate, and PCA3 levels in malignant tissue generally far exceed levels in benign tissue (de Kok et al, 2002; Popa et al, 2007). Early studies used reverse transcriptase polymerase chain reaction assays to detect PCA3 in urine and showed improved performance characteristics for PCA3 over PSA in diagnosing prostate cancer (Hessels et al, 2003; van Gils et al, 2007).

More recently, a transcription-mediated amplification assay was developed, offering improved sensitivity and quantitation relative to standard reverse transcriptase polymerase chain reaction (Groskopf et al, 2006). This commercial assay (Progenesa; Hologic) is both CE marked and FDA approved (2012) to assist with decisions in the setting of a prior negative prostate needle biopsy result. To enhance the sensitivity of PCA3 detection, urine samples are collected after an “attentive” DRE involving three firm strokes on each lobe of the prostate toward the median sulcus (Fig. 108-8).

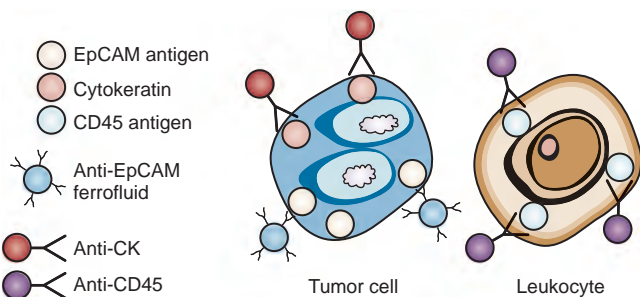


Figure 108-7. CellSearch Circulating Tumor Cell (CTC) cell enumeration system. The anti-EpCAM ferrofluid captures the cells, and they are validated with cytokeratin-positive and CD45-negative staining. EpCAM, epithelial cell adhesion molecule; CK, cytokeratin; CD45, CD stands for “cluster of differentiation,” which was originally known as leukocyte common antigen.

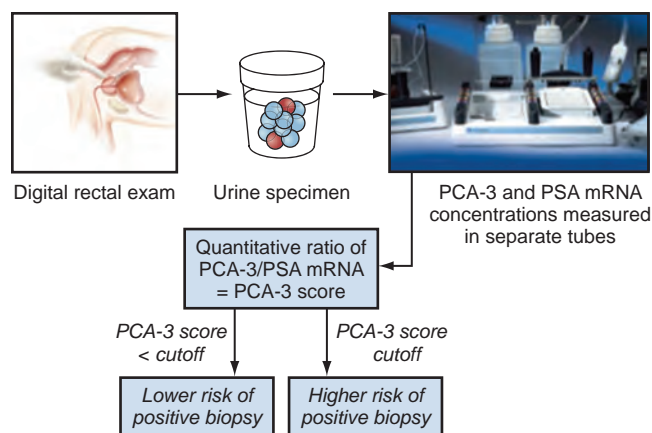


Figure 108-8. Prostate cancer antigen 3 (PCA3) assay protocol. Following an “attentive” digital rectal examination, urine is collected. Reverse transcriptase polymerase chain reaction determines the mRNA levels for PCA3 and prostate-specific antigen (PSA). The ratio of PCA3 to PSA determines the PCA3 score. The prostate cancer risk level suggests the need for biopsy. (From Groskopf J, Aubin SM, Deras IL, et al. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. *Clin Chem* 2006;52:1089–95.)

The first 20 to 30 mL of voided urine should be collected within 1 hour (Sokoll et al, 2008). The commercial PCA3 score is reported as the ratio of urine PCA3 mRNA to urine PSA mRNA \times 1000, normalizing PCA3 expression to PSA expression.

Numerous clinical studies have been performed to evaluate the utility of urine PCA3 to serve as a prostate cancer biomarker, and all have shown that PCA3 scores are closely correlated with the likelihood of a positive biopsy (Hessels et al, 2003; Deras et al, 2008; van Gils et al, 2008; Roobol et al, 2010b). Deras and colleagues (2008) reported that men with a PCA3 less than 5 had a 14% positive biopsy rate compared with a 70% positive biopsy rate in men with PCA3 greater than 100. However, in another study, patients with PCA3 greater than 100 had only a 52% positive biopsy rate (Roobol et al, 2010a). In contrast to PSA, PCA3 levels are independent of prostate size (Haese et al, 2008).

A critical challenge in using PCA3—or any biomarker reported as a continuous score rather than just “positive/negative”—is establishing appropriate cutoffs. Given that PCA3 scores represent a continuum of risk, different thresholds lead to differences in sensitivity and specificity of the assay. Multiple cutoffs have been proposed, most commonly 10, 25, and 35 (Haese et al, 2008; Crawford et al, 2012). Haese and colleagues (2008) reported on a cutoff of 35, with positive biopsy results in 39% of cases above the threshold versus 22% of cases below the threshold. In a comparative effectiveness review commissioned by the U.S. Agency for Healthcare Quality and Research, Bradley and colleagues (2013) showed that a threshold of 25 results in a sensitivity of 74% and specificity of 57% (false-positive rate of 43%). The lower threshold of 25 was used in the FDA approval studies.

There are increasing reports on the use of PCA3 in the initial screening setting of patients without a prior biopsy. Roobol and colleagues (2010b) reported on a cohort of 721 men, most of whom had not previously undergone a biopsy, and showed that PCA3 (AUC 0.64) outperformed PSA (AUC 0.58) in predicting cancer on subsequent biopsy. In a prospective, community-based evaluation of PCA3 in 1962 men before any prostate biopsy, prostate cancer was detected in 61% of men with a PCA3 35 or greater and 32% with a PCA3 less than 35 (Crawford et al, 2012). The AUC for PCA3 was 0.71 compared with an AUC of 0.57 for PSA. Another study of 3073 men undergoing initial biopsy demonstrated that PCA3 was an independent predictor of any prostate cancer and high-grade prostate cancer after controlling for additional clinical variables (Chevli et al, 2014). Although PCA3 performed better than PSA for

the detection of any cancer (AUC 0.70 vs. 0.60), they performed similarly for the detection of high-grade cancer (AUC 0.68 vs. 0.68).

To improve the predictive accuracy of PCA3, numerous nomograms have been developed that incorporate PCA3 along with other known clinical predictors to identify men most likely to have a positive prostate biopsy. For example, Chun and associates (2009) showed that PCA3 improves the accuracy of a base clinical model (AUC 0.73 vs. 0.68) and proposed a final model incorporating a PCA3 cutoff of 17. Similarly, Ankerst and colleagues (2008) reported on an updated version of the PCPT nomogram that includes PCA3 as a continuous variable. The final model outperformed the base PCPT model (0.70 vs. 0.65) and has been operationalized on the Web (as in Fig. 108-4). Given the available data to date, the comparative effectiveness review by Bradley and colleagues (2013) concluded that PCA3 appears to be superior to tPSA in diagnosing prostate cancer, but that further evidence is needed, and there is no evidence at this point that use of PCA3 leads to better health outcomes.

Gene Fusions

With the landmark discovery of the presence of gene fusions in prostate cancer by Tomlins and colleagues (2005), considerable work has been done to determine their potential utility as prostate cancer biomarkers. In particular, fusions of the 5' untranslated region of the androgen-regulated gene transmembrane protease, serine 2 (TMPRSS2) with v-ets erythroblastosis virus E26 oncogene homolog (ERG) or ets variant 1 (ETV1) were found to be nearly 100% specific for prostate cancer and present in at least 50% of PSA-screened prostate cancers. Both ERG and ETV1 are members of the erythroblastosis virus E26 transformation-specific (ETS) transcription factor family, and TMPRSS2:ERG fusions represent about 90% of all ETS gene fusions (Tomlins et al, 2009; Young et al, 2012).

Although tissue-based detection of the fusion using either chromosomal analysis (i.e., fluorescence in situ hybridization) or immunohistochemical staining for ERG has shown some utility, this biomarker appears to have its greatest potential as a urine-based assay (Laxman et al, 2006; Hessels et al, 2007; Laxman et al, 2008). A feasibility study that examined urine samples after DRE confirmed that the TMPRSS2:ERG fusion can be detected in the urine and may aid in the decision to proceed with a prostate biopsy (Laxman et al, 2008). Similar to PCA3, TMPRSS2:ERG levels are normalized to urine PSA mRNA expression. Tomlins and colleagues (2011) reported on the development and use of a clinical grade assay based on transcription-mediated amplification (similar to the PCA3 assay) in 1312 men before prostate biopsy. TMPRSS2:ERG outperformed serum PSA for predicting the presence of prostate cancer with an AUC of 0.65 to 0.71 versus 0.59 to 0.61. Additionally, in a subset of men who underwent prostatectomy, a higher urine TMPRSS2:ERG score was associated with increased tumor volume, higher grade disease, and non-organ-confined cancer.

Moving toward the concept that single biomarkers will probably not answer the important clinical questions in prostate cancer alone, many investigators have begun to multiplex markers, resulting in additive value. Specifically, given that TMPRSS2:ERG is found in only half of all prostate cancer foci (approximately 75% of men with cancer), its greatest utility would be in combination with other biomarkers. It has been evaluated closely in concert with PCA3, and the two biomarkers together appear to provide improved performance over either one alone (Hessels et al, 2007; Laxman et al, 2008; Salami et al, 2013). In the cohort of 1312 patients reported by Tomlins and colleagues (2011), combining TMPRSS2:ERG and PCA3 scores with the PCPT nomogram resulted in an AUC for predicting cancer of 0.75 to 0.79. TMPRSS2:ERG + PCA3 score groups also were shown to correlate with features of disease aggressiveness such as Gleason grade, although data in this area continue to be mixed (Gopalan et al, 2009; Leyten et al, 2014).

Two other large studies reported on the combination of TMPRSS2:ERG and PCA3 for predicting the presence of prostate cancer. Cornu and coworkers (2013) showed that PCA3 and

TMPRSS2:ERG were each independent predictors of prostate cancer in a multivariable model that also included other clinical parameters. More recently, [Leyten and colleagues \(2014\)](#) reported on the prospective use of the combined assay in 497 patients at six centers in Europe. The combination of PCA3 and *TMPRSS2:ERG* increased the performance of the ERSPC risk calculator from an AUC of 0.80 to 0.84. Additionally, the sensitivity of PCA3 increased from 68% to 76% when *TMPRSS2:ERG* was added. The combined test is commercially available as the Mi-Prostate Score (University of Michigan Health System), combining serum PSA, urine PCA3, and urine *TMPRSS2:ERG* to provide a quantitative risk estimate of the likelihood of detecting prostate cancer on prostate biopsy as well as the probability of detecting high-grade cancer. This test also may have a role in the management of patients on active surveillance for prostate cancer because it has been correlated with features of tumor aggressiveness in a prospective active surveillance cohort ([Lin et al, 2013](#)).

Other Urine Biomarkers

Metabolomics

Cancer cells have long been known to harbor substantial metabolic modifications. However, even with the explosion of molecular biology and the large amount of information that has been learned about cell cycle regulation, little attention has been directed to the differences that exist between the metabolic processes of the cancer cell versus normal cells. More recently, high-throughput proteomics and metabolomics platforms combining chromatography with mass spectroscopy have revealed many potentially important differences in metabolomics profiles between benign and malignant prostate tissues. As a result, large tissue-based metabolomics signatures have been identified that can accurately identify prostate cancer and may provide prognostic information ([Jung et al, 2013](#); [Kami et al, 2013](#); [McDunn et al, 2013](#)). Studies of patients who underwent radical prostatectomy have reported several different metabolites that may predict biochemical recurrence independent of standard clinicopathologic features ([Jung et al, 2013](#); [McDunn et al, 2013](#)).

Based on the initial tissue-based work, urinary metabolomics profiles of prostate cancer have been identified that appear to have potential clinical applicability. Among the molecules profiled, perhaps the most prominent metabolite is sarcosine, a metabolite of glycine that has been demonstrated in the urine of men with prostate cancer ([Sreekumar et al, 2009](#)). [Sreekumar and colleagues \(2009\)](#) reported that not only could urinary sarcosine help distinguish malignant from benign prostate tissue, but also that sarcosine was associated with progression to metastasis. The Prostarix assay (Metabolon) is a commercial metabolomics panel derived from this research that uses post-DRE urine. This laboratory-developed test, which does not have FDA approval at the present time, seeks to aid in decisions surrounding the need to perform a prostate needle biopsy.

Annexin A3

Another potential urine-based prostate cancer biomarker is annexin A3, which is inversely related to the presence of prostate cancer. This protein is part of a family of calcium and phospholipid binding proteins that have been shown to be altered in cancer ([Wozny et al, 2007](#); [Köllermaier et al, 2008](#)). Evaluating annexin A3 concentrations in urine obtained after DRE before prostate needle biopsy, [Schostak and colleagues \(2009\)](#) evaluated the potential clinical utility of urine-based annexin A3, either as a stand-alone biomarker or together with PSA. In a blinded study that consisted of training and evaluation sets of 243 and 264 men, respectively, these investigators showed that annexin A3 added to the ability of PSA to predict a positive needle biopsy with a combined AUC of 0.81. Using a multiplex approach, [Cao and colleagues \(2011\)](#) reported on the combination of urine annexin A3, PCA3, *TMPRSS2:ERG*, and sarcosine to help identify patients with prostate cancer. The

multimarker model demonstrated a high level of predictive accuracy with an AUC of 0.84 in patients with PSA 4 to 10 ng/mL and an AUC of 0.86 across all patients in their cohort.

MicroRNA

Based on the realization that most of the DNA in the genome does not encode protein sequences, the utility of these sequences in the regulation of gene expression has been under intense investigation. Among the most important components of this type of regulation are microRNAs (miRNAs). These are small (approximately 19 to 22 nucleotides), noncoding single-stranded RNAs involved in the regulation of mRNA. They have been detected in a wide range of biologic fluids and are being explored as potential biomarkers in a variety of malignancies. Given their potential mechanistic role, they may provide diagnostic and prognostic information. In prostate cancer, miR-141 has shown promise in numerous studies in terms of its association not only with prostate cancer but also potentially with disease aggressiveness ([Mitchell et al, 2008](#); [Bryant et al, 2012](#)). Additionally, [Casanova-Salas and colleagues \(2014\)](#) reported that urine miR-187 is an independent predictor of prostate cancer at needle biopsy. Although these findings need to be expanded to larger populations, this remains a promising family of potential markers.

TISSUE-BASED BIOMARKERS

α -Methylacyl Coenzyme A Racemase

α -Methylacyl coenzyme A racemase (*AMACR*) gene, located on chromosome 5, is upregulated in prostate cancer tissues ([Luo et al, 2002](#); [Rubin et al, 2002](#)). *AMACR* functions as an enzyme responsible for the β -oxidation of branched-chain fatty acids obtained in diets consisting of beef and dairy products. [Luo and colleagues \(2002\)](#) demonstrated that 88% of prostate cancer cases and untreated metastases and hormone-refractory prostate cancers were strongly positive for *AMACR*. Immunohistochemical studies by [Rubin and coworkers \(2002\)](#) showed that *AMACR* expression in biopsy tissue may provide 97% sensitivity and 100% specificity for prostate cancer detection. In combination with other markers, such as TP63, that aid in identifying basal cells absent in prostate cancer, measurement of *AMACR* has the potential for the development of molecular probes to aid in the detection of prostate cancer. As a result, *AMACR* immunostaining is commonly performed on prostate needle biopsy specimens to confirm the presence of cancer. *AMACR* also may have some prognostic utility because decreased staining levels are associated with an increased risk of disease progression ([Rubin et al, 2005](#)). Although other roles for *AMACR* as a biomarker have shown some promise—for example, as a urinary assay for prostate cancer detection—the performance of serum and urine tests has not been sufficient to warrant clinical use to date.

Epigenetic Modifications

Changes in gene expression may occur as a result of alterations in DNA, and epigenetic changes are changes not caused by alterations in DNA sequence. These epigenetic modifications include changes in DNA methylation and histone acetylation status. Segments within the gene promoter that are composed of GC-rich regions are termed *CpG islands*. Alterations in the methylation status of these regions may affect gene expression and have been shown to play a role in carcinogenesis ([Jones and Baylin, 2002](#)). Furthermore, cumulative effects of environmental exposures, such as diet and stress throughout life, may affect DNA methylation status and contribute to the risk of cancer development ([Li et al, 2004](#)). The products of numerous hypermethylated genes have been implicated in development of prostate cancer, including glutathione-S-transferase π (*GSTP1*), adenomatous polyposis coli (*APC*), retinoic acid receptors beta 2 (*RARB2*), and RAS association domain family protein isoform A (*RASSF1A*) ([Mahapatra et al, 2012](#)).

GSTP1 belongs to a family of detoxifying enzymes that are involved in metabolic reduction of electrophilic carcinogens and was the first tissue methylation biomarker to be discovered. [Li and coworkers \(2004\)](#) noted that the *GSTP1* gene was unmethylated in all normal human tissues and BPH but was hypermethylated in all 20 prostate cancer specimens analyzed. [Harden and coworkers \(2003a, 2003b\)](#) used polymerase chain reaction to detect hypermethylated *GSTP1* in prostate biopsy specimens, and *GSTP1* methylation was detected in 11 of 15 (73% sensitivity) prostate cancer cases and in none of 14 (100% specificity) benign control cases. Quantitation of *GSTP1* hypermethylation accurately detected CaP even in small, limited tissue samples. Elevated levels of *GSTP1* CpG hypermethylation have been detected in tissues from precancerous lesions (atypia and prostatic intraepithelial neoplasia) and within ejaculates, urine, and plasma from men with prostate cancer ([Nakayama et al, 2003](#); [Bastian et al, 2005](#)). [Cairns and coworkers \(2001\)](#) demonstrated the presence of elevated *GSTP1* hypermethylation in 79% of prostate cancer specimens. *GSTP1* methylation appears to occur early in prostate carcinogenesis, and methylation levels may correlate with features of tumor aggressiveness ([Jerónimo et al, 2001](#); [Zhou et al, 2004](#)). In a more recent meta-analysis, *GSTP1* promoter hypermethylation was shown to have a sensitivity of 82% and specificity of 95% for distinguishing malignant from normal prostate tissue ([Van Neste et al, 2012](#)).

In addition to *GSTP1*, hypermethylation of other genes has been noted to occur in almost 100% of prostate cancers ([Mahapatra et al, 2012](#)). *APC* is a tumor suppressor gene involved in apoptosis and cell migration, and mutation of *APC* is often an early event in colon carcinogenesis. In a retrospective analysis assessing patients with newly diagnosed prostate cancer, *APC* methylation was associated with an independent 50% increase in the likelihood of death from prostate cancer ([Richiardi et al, 2009](#)). *RASSF1*, a gene involved in cell cycle regulation, and *RARβ2*, a nuclear transcriptional regulator, are other key genes methylated in a large proportion of prostate cancers and shown to distinguish benign from malignant prostate in a number of studies ([Zon et al, 2009](#); [Van Neste et al, 2012](#)).

Perhaps the most clinically relevant aspect of these methylation changes is the discovery that they are frequently detectable in normal tissue adjacent to tumors, but not in normal tissue well away from the primary tumor ([Richiardi et al, 2013](#)). These changes may be useful indicators of the field effect that has long been known to exist—the presence of molecular changes in histologically normal tissue bordering a tumor. In patients with a prior negative biopsy, the identification of these molecular changes in the original biopsy tissue may suggest an increased likelihood of occult prostate cancer. [Trock and colleagues \(2012\)](#) showed that methylation of *APC* in histologically negative prostate biopsy specimens predicted the presence of prostate cancer in 86 men undergoing repeat biopsy, with a negative predictive value of 0.96 and sensitivity of 0.95. Using a quantitative commercial methylation assay (ConfirmMDx; MDxHealth) that assesses methylation of *GSTP1*, *APC*, and *RASSF1*, [Stewart and associates \(2013\)](#) showed a negative predictive value of 0.90 and sensitivity of 0.68 for the presence of cancer. In this retrospective study, methylation status was an independent predictor of the presence of prostate cancer on repeat biopsy, suggesting accurate identification of at-risk patients based on the “halo effect” of aberrant methylation.

Genomic Expression Profiles

For more than a decade, a great deal of attention has been devoted to discovering large sets of genes that, when evaluated together as a single biomarker assay, perform far better than any individual gene on its own. Advances in genomics have facilitated the evaluation of gene expression in formalin-fixed paraffin-embedded tissue, which means that archived prostate specimens can be interrogated for expression of gene profiles that are associated with aggressive disease features. Gene expression profiling has been explored in numerous settings, resulting in genomic classifiers for response to chemotherapy in breast and colorectal cancers ([Iwao-Koizumi et al, 2005](#); [Del Rio et al, 2007](#)).

Numerous laboratory-developed tests using genomic expression profiling for risk stratification in men with prostate cancer are being developed and commercialized, including Prolaris (Myriad Genetics), OncotypeDx (Genomic Health), and Decipher (GenomeDx Biosciences). The Prolaris test assesses 31 cell cycle progression genes, and many studies have demonstrated an association between this gene signature and the risk of progression and death from prostate cancer ([Cuzick et al, 2011, 2012](#)). [Bishoff and colleagues \(2014\)](#) retrospectively assessed the performance of this assay on prostate needle biopsy specimens from men who underwent subsequent prostatectomy, demonstrating an independent association between cell cycle progression score and biochemical recurrence. This assay and OncotypeDx are primarily intended to help with management decisions in patients with newly diagnosed prostate cancer. The OncotypeDx classifier uses gene sets in several biologic pathways and has been developed to predict the likelihood of aggressive pathologic features at the time of prostatectomy ([Knezevic et al, 2013](#); [Klein et al, 2014](#)). Finally, the Decipher assay is a 22-marker genomic classifier that has been evaluated using tissue from prostatectomy specimens. In men with high-risk disease and men with biochemical recurrence, the genomic classifier was independently associated with the development of metastatic disease ([Karnes et al, 2013](#); [Ross et al, 2014](#); [Den et al, 2015](#)).

Gene Susceptibility Loci

Although 40% of prostate cancer risk may be related to hereditary factors, relatively little is known about the specific germline mutations that may contribute to prostate cancer risk ([Lichtenstein et al, 2000](#)). Identification of these mutations causing increased prostate cancer risk could have important implications for screening and early detection of patients at high risk of developing prostate cancer. That said, if an individual is found to have a fivefold increase in his risk for prostate cancer, what should be done? Should the individual be screened more carefully or more frequently? Should he simply undergo a prostate biopsy or treatment? These big questions are being actively investigated as part of the prospective IMPACT study, investigating methods of targeted screening in men with a genetic predisposition to prostate cancer ([Bancroft et al, 2014](#)).

Targeted screening requires the ability to identify at-risk patients, and many susceptibility loci involved in the risk of development of cancer have been reported ([Monroe et al, 1995](#); [Lichtenstein et al, 2000](#); [Nam et al, 2003](#); [Simard et al, 2003](#)). Genome-wide association studies have become one of the most common means of identifying key germline alterations that may predispose to the development of prostate cancer. These are case-control studies looking at common genetic variants, most commonly single nucleotide polymorphisms (SNPs), to identify specific ones associated with the development of prostate cancer. Although identified SNPs are generally not thought to drive the increased risk of prostate cancer, they serve as a surrogate of other nearby alterations that may cause functional changes driving eventual carcinogenesis ([Goldstein, 2009](#)). Genome-wide association studies have identified numerous potential variant alleles that are associated with the development of prostate cancer, with the 8q24 region most frequently arising as an SNP hot spot ([Al Olama et al, 2009](#)). The increased risk of prostate cancer associated with any individual SNP is relatively low but collectively may account for 25% of heritable prostate cancer risk ([Kote-Jarai et al, 2011](#)).

Also, several specific genes have been identified as mutated in a disproportionate number of patients with prostate cancer and appear to be frequently responsible for cases of hereditary prostate cancer, in particular, *BRCA1*, *BRCA2*, *HOXB13*, and the mismatch repair genes associated with Lynch syndrome (e.g., *MSH2*) ([Ewing et al, 2012](#); [Raymond et al, 2013](#); [Bancroft et al, 2014](#)). Recurrent mutations in these genes have been discovered in numerous familial prostate cancer cohorts. For example, [Ewing and colleagues \(2012\)](#) showed that the recurrent *HOXB13* G84E mutation significantly increased prostate cancer risk (relative risk 20.1, 95% confidence interval 3.5 to 803) and was present in 3% of men with early-onset familial prostate cancer compared with only 0.6% of

men with late-onset nonfamilial cancer. This finding emphasizes one of the critical aspects of these genetics studies: Familial prostate cancer often manifests at an earlier age and may be more aggressive on average than nonhereditary prostate cancer (Gallagher et al, 2010; Lange et al, 2012).

SUMMARY

Early detection when cancer remains confined to the prostate not only improves cure rates but also decreases mortality from prostate cancer. Although the discovery and application of PSA have revolutionized current prostate cancer detection and management, stage migration and changes in the natural history of this cancer have outrun the currently maximized application of this tumor marker. Application of various PSA derivatives, although improving

sensitivity, risks impairing specificity. The discovery of molecular derivatives of PSA, PCA3, new kallikrein markers, and gene rearrangements is leading to significant improvements in the efficiency of prostate cancer detection.

Innovations and new understanding in the field of molecular oncology have provided a host of potential prostate cancer tumor markers. Because prostate cancer has been shown to be a heterogeneous disease, it is likely that application of a panel of markers will ultimately provide added sensitivity and specificity for detection of the disease. Identification of hypermethylated regions, such as for *GSTP1*, as well as tissue-based genomic classifiers may improve the diagnostic and prognostic potential of prostate needle biopsies substantially. Development of these markers from research into clinically applicable tools will require clear demonstration of clinical utility, showing that these new assays have a real impact in the clinical care of men with prostate cancer.

KEY POINTS

- Today, most prostate cancer arises as clinically nonpalpable (stage T1c) disease with PSA between 2.5 and 10 ng/mL. The evolving demographics and natural history of prostate cancer have resulted in stage migration to nonpalpable, clinically localized (stage T1c) disease and a parallel reduction in mortality.
- Although PSA is widely accepted as a prostate cancer tumor marker, it is organ specific and not disease specific.
- In serum, PSA circulates in both bound and unbound forms. Three proteins that are known to bind to PSA in blood are ACT, A2M, and API.
- Although prostate cancer cells do not produce more PSA than benign prostate epithelium, the PSA produced from malignant cells appears to escape proteolytic processing. Thus, men with prostate cancer have a greater fraction of serum PSA complexed to ACT and a lower percentage of total PSA that is free compared with men without prostate cancer.
- Finasteride (5 mg) and other 5 α -reductase inhibitors used for treatment of BPH have been shown to lower PSA levels by an average of 50%.
- The role for %fPSA is more applicable to PSA levels less than 10 ng/mL because the positive predictive rate of total PSA greater than 10 to 20 ng/mL has been demonstrated to be as high as 80%.
- The EDRN has established a five-phase model of biomarker development, paralleling the phases of clinical trials for therapeutic agents.
- Although FDA approval is often desired, it is not necessary for commercialization of new biomarkers provided the test is CLIA-certified and run in a CLIA laboratory.
- There are four main domains in which clinically localized prostate cancer biomarkers are needed: (1) screening, (2) elevated PSA with prior negative biopsy, (3) pretreatment in men with a new diagnosis, and (4) postprostatectomy.
- PSA originates as a 17-amino acid chain (preproPSA) that is cleaved to yield an inactive precursor form termed proPSA. Cleavage of a leader amino acid sequence of proPSA by hK2 produces the active form of PSA.
- PHI is a multiplex diagnostic serum assay testing [-2]proPSA along with free and total PSA. It has been FDA-approved for men 50 years and older with total PSA 4-10 ng/mL and negative DRE.
- Immunohistochemical studies reveal different tissue expression patterns for hK2 and PSA. In benign epithelium, PSA is intensely expressed compared with the minimal immunoreactivity of hK2. In contrast, in cancerous tissue hK2 is expressed more intensely.
- The 4Kscore is derived from a serum assay testing total PSA, free PSA, intact PSA, and hK2. It is a diagnostic test intended for use in men with an elevated PSA considering prostate biopsy.
- PCA3 is a long noncoding RNA that is detectable in the urine and serves as a diagnostic prostate cancer marker. The commercially available ProgenSA assay evaluates PCA3 in post-DRE urine and is FDA approved for use in patients with an elevated PSA and prior negative biopsy.
- The *TMPRSS2:ERG* gene fusion is present in at least 50% of PSA-screened prostate cancers. While also a tissue biomarker, its most promising application currently appears to be as a urine biomarker as part of a multiplex assay with PCA3.
- Segments within the gene promoter that are composed of GC-rich regions are termed CpG islands. Alterations in the methylation status of these regions may affect gene expression and have been shown to play a role in carcinogenesis.
- Key hypermethylated genes that may have a role in prostate cancer include *GSTP1*, *APC*, *RAR β 2*, and *RASSF1A*. Hypermethylation changes are frequently detectable in normal tissue adjacent to tumors.
- Circulating tumor cells are being used as novel tools to correlate with response to therapy, as well as provide valuable resources with which to study metastatic disease.

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The complete reference list is available online at www.expertconsult.com.

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Ultrasonographic Anatomy of the Prostate

Gray-Scale Transrectal Ultrasonography

Transrectal ultrasonography of the prostate (TRUS) has become a standard tool in the practice of urology. Many image-guided prostate cancer interventions, including initial prostate biopsy, follow-up biopsy for active surveillance, low- and high-dose brachytherapy, cryotherapy, and high-intensity focused ultrasound (US) rely on TRUS. Fiducial and radiofrequency markers are being placed under TRUS guidance for real-time tumor tracking of the prostate during radiation therapy (Linden et al, 2009; Das et al, 2014). Polyethylene glycol hydrogel injection into anterior perirectal fat to decrease rectal toxicity during prostate radiation therapy is another very new and evolving TRUS application (Strom et al, 2014). TRUS also has a role in benign conditions such as in the evaluation of treatment options for benign prostatic hyperplasia (BPH) and in some cases of male infertility. This chapter focuses primarily on the most common use of TRUS, namely prostate biopsy for the diagnosis of prostate cancer.

The detection and diagnosis of prostate cancer has benefited greatly from prostate-specific antigen (PSA) screening efforts along with the introduction and refinement of systematic TRUS-guided prostate biopsy techniques. However, these prostate cancer screening efforts are not without controversy (Gomella et al, 2011). When a decision is made to perform a diagnostic prostate biopsy, the 12-core TRUS prostate biopsy is considered the preferred and current standard of care technique (Bjurlin et al, 2013).

TRUS of the prostate was first described by Watanabe and colleagues (1968). The use of digitally directed prostate biopsy, common until the late 1980s, evolved into the expanded clinical use of TRUS-directed prostate biopsies. Improvements in US technology continued with the important introduction of the TRUS-guided systematic sextant (six core), biopsy protocol by Hodge and associates (1989). Concurrent with improved biopsy techniques including the increase in recommended biopsy cores to 12, the use of PSA screening increased the number of men undergoing early prostate cancer screening and prostate biopsy. Current estimates are that up to 1.3 million biopsies are performed annually in the United States alone (Aubry et al, 2013). Given the prevalence of clinically significant and insignificant prostate cancer and the frequency with which TRUS-guided prostate biopsies are performed, significant efforts have been focused on determining the appropriate indications for biopsy, the ideal technique by which to image and perform biopsy of the prostate, and how to best limit complications.

ULTRASONOGRAPHIC ANATOMY OF THE PROSTATE

The prostate lies between the bladder neck and the urogenital diaphragm, just anterior to the rectum, an ideal position to be imaged via TRUS. The prostate gland is traditionally described based on a pathologic zonal architecture. These divisions consist of the anterior fibromuscular stroma, which is devoid of glandular tissue; transition zone (TZ); central zone (CZ); periurethral zone; and peripheral

Prostate Biopsy: Techniques and Outcomes

Advanced and Investigational Techniques for Prostate Biopsy

zone (PZ). Unfortunately, these regions are not visible sonographically as distinct entities (Fig. 109-1).

However, the TZ often may be discernible from the PZ and CZ, particularly in glands with significant BPH. Located posteriorly, the normal CZ and PZ, from which a majority of adenocarcinomas arise, have a homogeneous echogenic appearance, whereas the anteriorly situated TZ is more heterogeneous. Frequently, calcifications along the surgical capsule known as the corpora amylacea highlight the plane between the PZ and TZ (multiple diffuse calcifications are a normal, often incidental ultrasonographic finding in the prostate and represent a result of age rather than a pathologic entity). Larger prostatic calculi associated with symptoms may be related to underlying infection or inflammation and require further evaluation (Geramoutsos et al, 2004).

The prostatic urethra traverses the length of the gland in the midline and thus must be imaged in the sagittal plane to be simultaneously viewed along the entirety of its course (Fig. 109-2A and B). The distended urethral lumen has a hypoechoic appearance, whereas periurethral calcifications may produce a thin echogenic outline. The smooth muscle of the internal sphincter extends from the bladder neck, encircling the urethra to the level of the verumontanum. These muscle fibers may be visualized sonographically as a hypoechoic ring around the upper prostatic urethra, giving it a funneled appearance proximally as it arises from the bladder neck. On reaching the verumontanum the urethra angles anteriorly and runs through the remainder of the gland to exit at the apex of the prostate. This angle gives the prostatic urethra an anteriorly concave appearance when viewed along its entire course in the sagittal plane.

The paired seminal vesicles (SVs) are positioned posteriorly at the base of the prostate (see Fig. 109-2C). They have a smooth, saccular appearance and should be symmetrical. The normal SV measures 4.5 to 5.5 cm in length and 2 cm in width. A cystic SV mass is presumptively benign, whereas a solid lesion has a very small probability of being malignant, especially if the patient has a primary neoplasm elsewhere. Schistosomiasis should be considered when making a differential diagnosis in patients who live in areas where infestation is endemic and have a solid SV mass (Al-Saeed et al, 2003). An absent SV is associated with a 79% ipsilateral renal agenesis. In the transverse plane, the vasa deferentia course just above their ipsilateral SV before diving caudally toward the prostate near the midline. Here they lie just medial to the tapering ipsilateral SV before the two structures fuse to form an ejaculatory duct. The ejaculatory ducts (occasionally seen as a hypoechoic structure) enter the gland posteriorly and empty into the urethra at the verumontanum (see Fig. 109-2C). Their course parallels that of the prostatic urethra distal to the verumontanum.

GRAY-SCALE TRANSRECTAL ULTRASONOGRAPHY

Gray-scale TRUS has become the most common imaging modality for the prostate. Most commonly used for prostate cancer

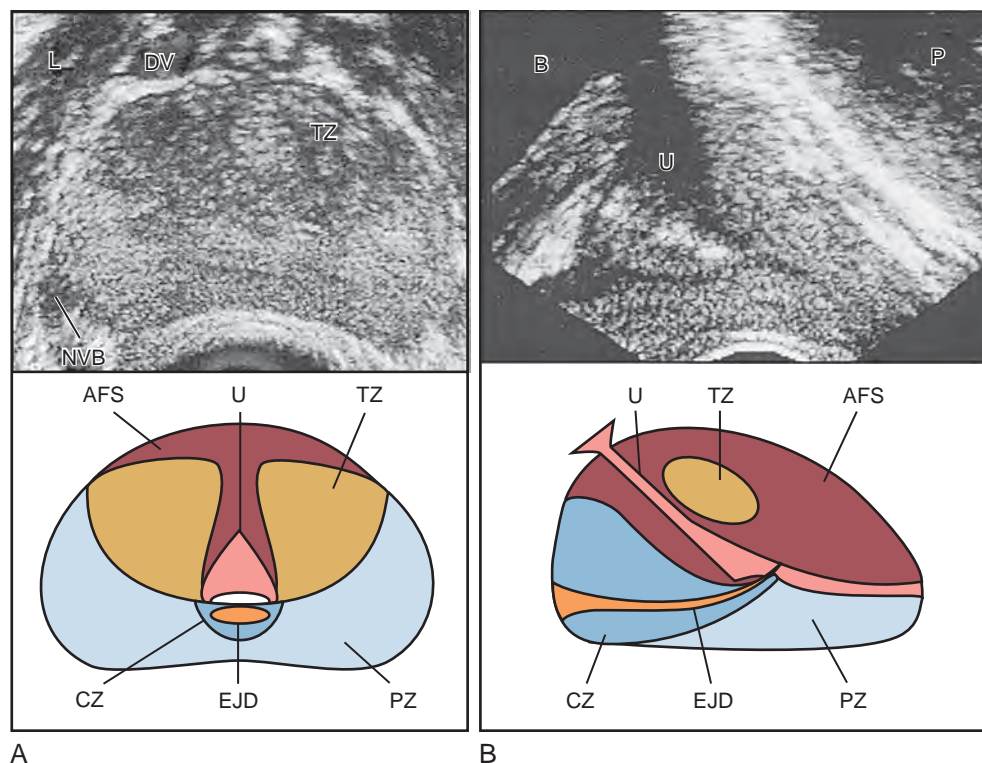


Figure 109-1. Normal prostate ultrasound images (*top*) with diagrams (*bottom*) at approximately the level of the verumontanum demonstrating zonal anatomy. **A**, Transverse view. **B**, Sagittal view. AFS, anterior fibromuscular stroma; B, bladder; CZ, central zone; DV, dorsal vein complex; EJD, ejaculatory ducts; L, levator muscles; NVB, neurovascular bundle; PZ, peripheral zone; TZ, transition zone; U, urethra.

detection, TRUS also may be used in the evaluation of other conditions, such as infertility (see Chapter 24), or basic prostate volume measurements for interventions such as brachytherapy or in the management of BPH.

Commercially available endorectal probes are available in both side- and end-fire models and transmit frequencies of 6 to 10 MHz. Most modern US machines have optimized self-programming for TRUS and biopsy. Some newer biplane probes provide simultaneous sagittal and transverse imaging modes. Probes provide a scanning angle approaching 180 degrees to allow simultaneous visualization of the entire gland in both the transverse and sagittal planes. Increasing frequency yields increased resolution. As the frequency of the probe is increased, the portion of the image that is in focus (focal range) is closer to the transducer (Kossoff, 2000). The commonly used 7-MHz transducer produces a high-resolution image with a focal range from 1 to 4 cm from the transducer (best for PZ where most cancers arise). Lower frequency transducers (e.g., older 4-MHz transducers) have a focal range from 2 to 8 cm but at lower resolution. Lower frequency transducers improve anterior delineation of large glands, increasing the accuracy of volume measurements, but provide poor internal architecture visualization. Acoustic properties of soft tissue are similar to those of water, but clinically useful US energy does not propagate through air. For this reason, a water-density substance, termed a *coupling medium*, is required. The coupling medium, usually sonographic jelly or lubricant, is placed between the probe and the rectal surface. If the probe is covered with a protective condom, the coupling medium is placed between the probe and the condom, as well as between the condom and the rectal surface.

Various studies have compared the TRUS prostate biopsy prostate cancer detection rates using the end-fire or side-fire probes. Prospective studies have confirmed that there is no significant

difference in positive biopsy rates in the initial or repeat biopsy setting (Raber et al, 2012). However, in this study the side fire transrectal probe is associated with a better patient tolerance.

Machine Settings

The image magnification is adjusted so that most of the prostate is visible without the image being too small to allow detection of abnormalities. In general, the magnification is low during prostate measurements so that the entire gland is seen. During biopsies, magnification is maximal for visualization of needle passage. The ultrasonographer can manually alter the brightness (or gain) slightly with each new patient and occasionally during imaging of different areas within the same prostate. The optimal brightness setting results in a medium-gray image of the normal PZ. This gray tone serves as the reference point for judging lesions as hypoechoic (darker than the normal PZ), isoechoic (similar to the normal PZ), hyperechoic (lighter than the normal PZ), or anechoic (completely black).

Techniques

The complete TRUS evaluation of the prostate includes scanning in both the sagittal and transverse planes to obtain a volume calculation. The CZ and PZ are inspected for hypoechoic lesions and contour abnormalities, and the SVs and vasa deferentia are fully visualized.

Probe Manipulation

Patients are usually scanned in the left lateral decubitus position (see Patient Positioning, later) to examine both the transverse and

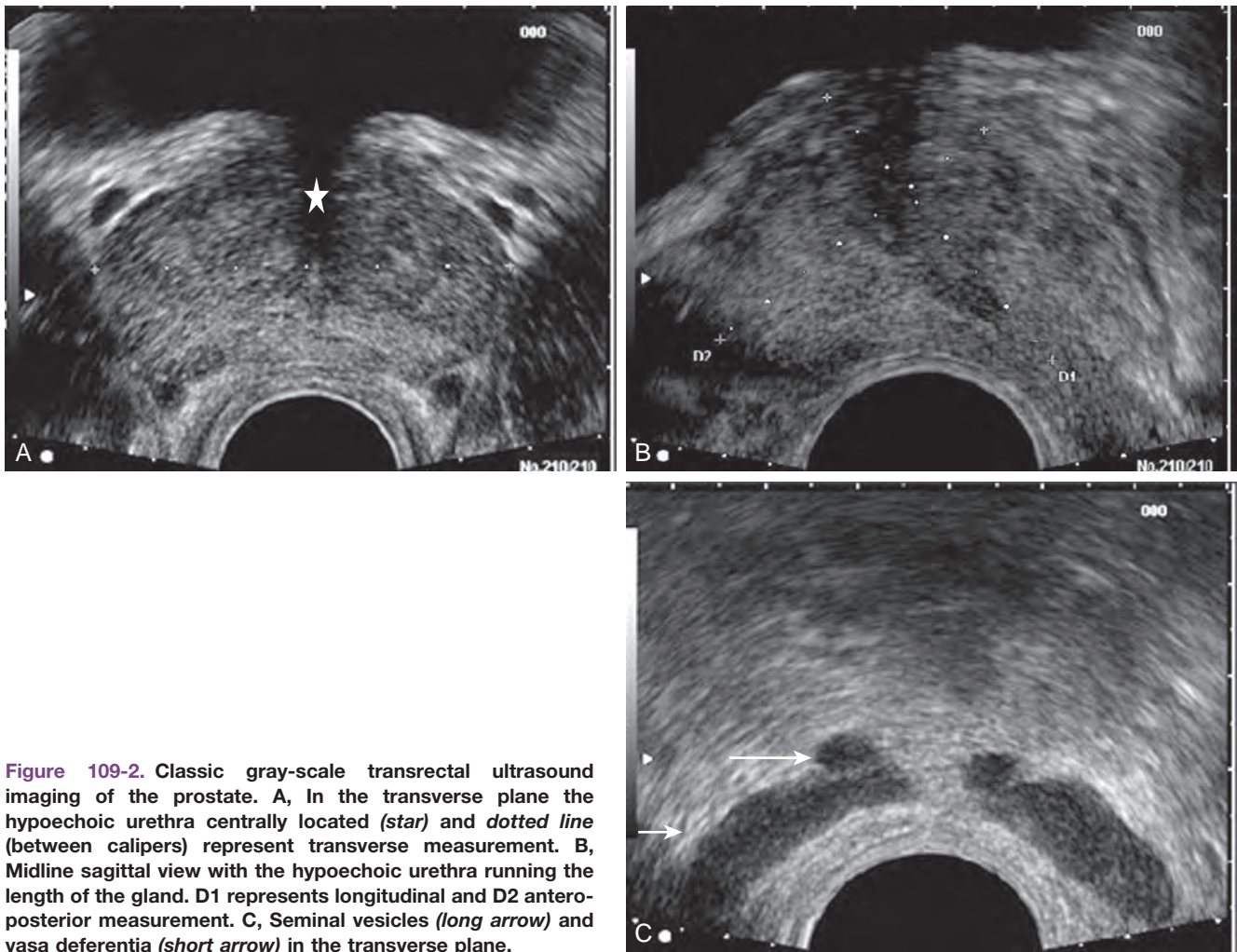


Figure 109-2. Classic gray-scale transrectal ultrasound imaging of the prostate. A, In the transverse plane the hypoechoic urethra centrally located (*star*) and dotted line (between calipers) represent transverse measurement. B, Midline sagittal view with the hypoechoic urethra running the length of the gland. D1 represents longitudinal and D2 anteroposterior measurement. C, Seminal vesicles (*long arrow*) and vasa deferentia (*short arrow*) in the transverse plane.

the sagittal planes. There are two approaches to probe manipulation for transverse imaging (see Fig. 109-2A). With radial and some biplane probes, advancing the probe cephalad into the rectum images the prostate base, the SVs, and the bladder neck. Pulling the probe caudally toward the anal sphincter images the prostatic apex and proximal urethra. Transverse imaging with end-fire, side-fire, and some biplane probes is accomplished by angling the handle of the probe right or left using the anal sphincter as a fulcrum (see Fig. 109-2B). Angling the probe toward the scrotum produces more cephalad images, and angling the probe toward the sacrum produces more caudal images.

There are also two approaches to probe manipulation for sagittal imaging. One method is rotation of the probe. Clockwise rotation yields images of the left side of the prostate, and counterclockwise rotation yields images of the right side. Alternatively, sagittal imaging can be accomplished by angling the probe up or down using the anal sphincter as a fulcrum. In the left lateral decubitus position, angling the handle of the probe down (toward the floor) images the right side of the prostate and angling the handle of the probe up (toward the ceiling) images the left side. Urologists often prefer angling the probe because this method is similar to manipulation of a cystoscope and is less uncomfortable for the patient.

Joint guidelines concerning the reprocessing of equipment used for TRUS biopsy have been published in a joint American Urological Association (AUA)/Society of Urological Nurses and Associates white paper (American Urological Association/Society for Urological Nurses and Associates, 2012).

Volume Calculations

A variety of formulas are used to calculate prostate volume and require measurement of up to three prostate dimensions. In the axial plane, the transverse and anteroposterior (AP) dimensions are measured at the point of widest transverse diameter (see Fig. 109-2A and B). The longitudinal dimension is measured in the sagittal plane just off the midline because the bladder neck may obscure the cephalad extent of the gland (see Fig. 109-2B). Most formulas assume that the gland conforms to an ideal geometric shape: either an **ellipse** ($\pi/6 \times \text{transverse diameter} \times \text{AP diameter} \times \text{longitudinal diameter}$), **sphere** ($\pi/6 \times \text{transverse diameter}^3$), or a **prolate (egg-shaped) spheroid** ($\pi/6 \times \text{transverse diameter}^2 \times \text{AP diameter}$). Despite the inherent inaccuracies that arise from these geometric assumptions, all formulas reliably estimate gland volume and weight, with correlation coefficients greater than 0.90 with radical prostatectomy specimen weights, because 1 cm³ equals approximately 1 g of prostate tissue (Terris and Stamey, 1991). The mature prostate is between 20 and 25 g and remains relatively constant until approximately age 50, when the gland enlarges in many men; the average prostate volume in a 60 to 70 year old is approximately 48 g (Griffiths, 1996).

Planimetry may be employed when a more precise determination of gland volume is required, such as for brachytherapy planning. With the patient in the lithotomy position, the probe is mounted to a stepping device and serial transverse images are obtained at set intervals (e.g., 3 to 5 mm) through the entire length

of the gland. The surface area of each serial image is determined, and the sum of these measurements is then multiplied by total gland length to yield the prostate volume.

Prostate gland volume can be used to calculate derivatives such as the PSA density (PSAD = serum PSA/gland volume). PSAD is a method to differentiate benign versus malignant disease with an elevated PSA and benign digital rectal examination. Higher PSA density values (>0.15 ng/mL/cc) are more suggestive of prostate cancer; lower values suggest BPH. An elevated PSAD has a sensitivity and specificity of 75% and 44%, respectively, for predicting cancer on repeat biopsy (Djavan et al, 2000). Unfortunately, there is high interoperator and intraoperator variability in PSAD determinations, and similar predictive information now can be obtained using serum free-to-total PSA ratio (Djavan et al, 2003).

Cystic Lesions of the Prostate

Cystic prostatic structures are common on TRUS. Simple cysts have the same sonographic appearance as in any other part of the body: they are thin walled, are anechoic, and show acoustic enhancement posterior to the cyst. Prostatic cysts may be congenital or acquired but are rarely clinically significant, regardless of cause.

Congenital prostatic cystic lesions may arise from either müllerian (müllerian duct cysts and prostatic utricles) or wolffian (ejaculatory duct and SV cysts) structures. An enlarged prostatic utricle is a diverticular projection from the posterior urethra at the level of the verumontanum (Cochlin, 2002) and appears as a midline anechoic structure. These are associated with genital anomalies, including hypospadias (most common), ambiguous genitalia, undescended testes, and congenital urethral polyps (Gregg and Sty, 1989). Müllerian duct cysts also appear as midline anechoic lesions that result from failure of the müllerian ducts to fuse with the urethra. They are generally ovoid to pear shaped, with the cyst neck oriented toward the verumontanum. When müllerian duct cysts are present, men should be evaluated for unilateral renal agenesis (McDermott et al, 1993).

Lateral paraprostatic cystic structures include SV and vas deferens cysts (wolffian in origin). Ejaculatory duct cysts are typically small, lie off of the midline, and may accompany ejaculatory duct obstruction/obliteration with azoospermia (Fig. 109-3). SV cysts can be caused by congenital or acquired obstruction of the ejaculatory duct and are associated with cystic renal disease; up to two thirds of men with SV cysts also may have renal agenesis (King et al, 1991). Acquired cysts of the TZ result from hemorrhagic degeneration of BPH nodules (Hamper et al, 1990), whereas those of the outer gland have no proven cause.

Prostate Cancer Imaging on Transrectal Ultrasonography

In early TRUS studies, hypoechoic lesions were considered pathognomonic for prostate cancer. All hypoechoic lesions within the PZ should be noted and included in the biopsy material (Fig. 109-4). The lack of a distinct hypoechoic focus does not preclude proceeding with biopsy, because 39% of all cancers are isoechoic and up to 1% of tumors may be hyperechoic on conventional gray-scale TRUS (Shinohara et al, 1989). A study of almost 4000 men revealed prostate cancer was detected in 25.5% with a hypoechoic lesion and in 25.4% without such a lesion with a per-core distinction of 9.3% for hypoechoic and 10.4% for isoechoic areas for cancer (Onur et al, 2004). Conversely, another study noted that biopsy samples taken when a prostate lesion is identified by TRUS are almost twice as likely to show cancer than when no lesion is visible (Toi et al, 2007). They concluded that the search for and targeting of hypoechoic lesions on TRUS remains important for prostate cancer diagnosis. Other disease processes such as granulomatous prostatitis (Terris et al, 1997), prostatic infarct (Purohit et al, 2003), and lymphoma (Varghese and Grossfeld, 2000) may produce hypoechoic lesions. There is a need to perform a biopsy on hypoechoic lesions, but these lesions are not pathognomonic for cancer as once thought.

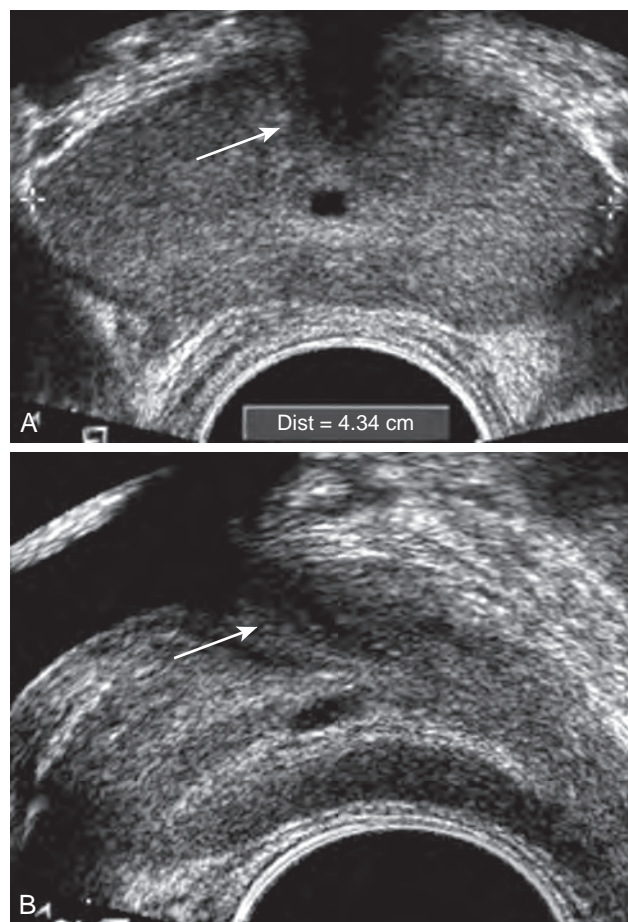


Figure 109-3. A hypoechoic midline cystic structure (arrow) arising from the ejaculatory duct is shown in the transverse (A) and sagittal (B) planes and demonstrates through-transmission classic for simple cysts.

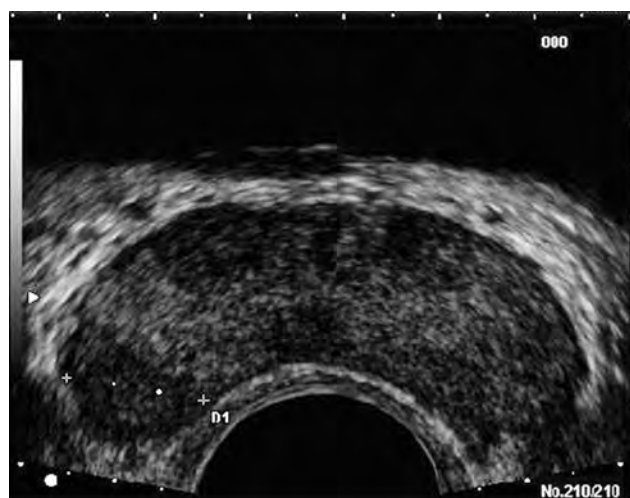


Figure 109-4. Classic hypoechoic peripheral zone lesion (dotted line between calipers) in the right mid-gland that transrectal ultrasound-guided biopsy proved to be a Gleason 3 + 3 = 6 adenocarcinoma.

Any focal contour abnormalities along the outer edge of the gland and any asymmetries in echotexture from the PZ of one lobe to that of the other are noted. Extracapsular extension of prostate cancer, although not well visualized if present as a microfocus, is suggested by a focal loss of the typically bright white periprostatic fat.

KEY POINTS: GRAY-SCALE TRANSRECTAL ULTRASONOGRAPHY

- TRUS technology has become a mainstay of many image-guided prostate interventions, including prostate biopsy, brachytherapy, cryotherapy, and high-intensity focused US.
- The classic zonal anatomy of the prostate is not evident on TRUS, but the PZ typically may be distinguished from the TZ, allowing biopsies to be reliably aimed toward the more commonly cancer-bearing PZ.
- Benign cystic lesions of the prostate typically demonstrate thin-walled architecture with sonographic through-transmission and may become symptomatic if infected.
- Several formulas exist for determining prostate volume on TRUS. For highly accurate volume determinations such as for brachytherapy, planimetry using a template is required.
- Hypoechoic foci seen on gray-scale TRUS should be considered suggestive of adenocarcinoma of the prostate and included in the biopsy specimen. However, up to 39% of cancers are not visible on routine gray-scale US imaging.

Transrectal Ultrasonography Appearance after Treatment

External-beam radiation monotherapy therapy usually results in decreased volume by 6 months after treatment. Irradiated prostates are diffusely hypoechoic, with poorly defined anatomy. Large hypoechoic tumors, particularly those not responding to therapy, show little change in echogenicity once irradiated, but smaller foci responding well to therapy tend to become isoechoic (Egawa et al, 1991). TRUS findings in general correlate poorly with pathologic findings and outcomes in irradiated prostates.

Initial postimplantation edema followed by long-term changes occurs with interstitial brachytherapy, as with external-beam radiation therapy (Whittington et al, 1999). With an ideal permanent implant, seeds should be distributed evenly throughout the gland, with periurethral sparing. These seeds are hyperechoic and demonstrate posterior shadowing. The prostate volume declines significantly after treatment, with a 37% size reduction at 1 year after treatment and over 50% reduction 8 years after implantation (Stone and Stock, 2007). This decline appears unaffected by the use of neoadjuvant hormonal therapy.

Androgen ablation with luteinizing hormone–releasing hormone analogues will cause an average 30% volume decrease with androgen deprivation in prostates with and without cancer (Whittington et al, 1999). The decrease ranges up to 60% in large glands and as little as 10% in small glands. Volume decreases by approximately 21% at 6 months using agents such as finasteride (Marks et al, 1997).

Post-radical prostatectomy TRUS is considered normal if there is smooth tapering of the bladder neck to the urethra (Kapoor et al, 1993). Many patients demonstrate a nodule of tissue anterior to the anastomosis, representing the ligated dorsal vein complex (Goldenberg et al, 1992). Any other hyperechoic or hypoechoic lesions or interruptions of the retroanastomotic fat plane are considered suspicious (Kapoor et al, 1993). Hypoechoic lesions have been reported in 75% to 95% of patients with locally recurrent cancer, and color Doppler has been used to improve cancer detection in the prostatic fossa (Tamsel et al, 2006). Patients with detectable PSA who are candidates for salvage radiation therapy were once considered for routine biopsy of the anastomotic area. Biopsy of the anastomotic region with PSA-indicated recurrence in the absence of a palpable nodule is not usually informative (Scattoni et al, 2004). However, biopsy of an abnormality seen on TRUS, even with a normal digital rectal examination, can be diagnostic of locally recurrent disease (Naya et al, 2005).

Transrectal Ultrasonography and Other Malignancies

Prostatic involvement with transitional cell carcinoma (TCC) from the bladder is generally not detectable by TRUS, but 71% of

prostatic stromal TCC lesions are hypoechoic. Prostatic TCC detected by TRUS must be confirmed by biopsy because granulomas resulting from instillation of bacillus Calmette-Guérin are common in patients with urothelial carcinoma and also are hypoechoic (Terris et al, 1997).

Extension to the prostate from the bladder, or urethral squamous cell carcinoma (SCC), is much more common than is primary prostatic SCC. Prostatic SCC appears as an irregular, anterior mass demonstrating relative hyperechogenicity (Terris, 1999).

Adenoid cystic/basal cell carcinoma of the prostate is rare but potentially fatal. Histologically, cribriform or adenoid cystic patterns predominate. Numerous cystic glands give this tumor an unusual appearance on TRUS, characterized by multiple, evenly distributed, small anechoic cysts (Iczkowski et al, 2003).

Prostatic sarcoma TRUS appearance is typified by an irregular, hypoechoic mass with an anechoic area consistent with necrosis (Terris, 1998). The echogenicity of rhabdomyosarcoma is similar to that of normal prostate tissue. Hematologic and lymphoid malignancies involving the prostate are generally not visualized with TRUS (Terris and Freiha, 1998). Biopsy specimens may demonstrate a lymphocytic infiltrate, but this is often attributed to chronic inflammation if no suspicion of nonprostate malignancy exists.

PROSTATE BIOPSY: TECHNIQUES AND OUTCOMES

Indications for Prostate Biopsy

A detailed discussion of the controversy concerning screening asymptomatic men for prostate cancer is discussed elsewhere (see Chapter 111). Before TRUS improvements and PSA testing became widespread, clinicians relied mainly on digital rectal examination to establish a suspicion of prostate cancer and performed digitally directed lesional biopsies. Today PSA-based screening of asymptomatic men has resulted in the adaptation of TRUS biopsy as the standard of care when prostate biopsy is used to identify prostate cancer (Bjurlin et al, 2013). In general the TRUS without a biopsy has little utility in the evaluation of a patient for prostate cancer. Overall it is estimated that an initial prostate biopsy carries a 30% rate of detecting prostate cancer. Fine-needle aspiration biopsy is no longer considered state-of-the-art in the diagnosis of prostate cancer (Heidenreich et al, 2014).

Early prostate cancer detection was markedly improved by PSA-based screening programs. These initiatives increased the rate of organ-confined and potentially curable disease (Catalona et al, 1993). The improvements led to the unintended consequence of the overdiagnosis and overtreatment of clinically insignificant cancers in many men. Historically, many clinicians would recommend prostate biopsy once a patient's serum PSA level rose above 4.0 ng/mL. Subsequent data from the Prostate Cancer Prevention Trial demonstrated that there is no safe PSA threshold that can rule out prostate cancer in any age range (Thompson et al, 2005). When examining men whose serum PSA level was 4.0 ng/mL or less, significant numbers were diagnosed with prostate cancer at all PSA levels, with an overall prostate cancer detection rate of 15% for all men with a PSA level less than 4.0 ng/mL and nearly 15% having a Gleason score of 7 or greater (Thompson et al, 2004).

Clinical trials that have attempted to provide an answer to the benefits of PSA screening have only added to the controversy (Gomella et al, 2011). Results from the European Randomized Screening for Prostate Cancer (ERSPC), demonstrated a net benefit, whereas the U.S.-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, showed no benefit on prostate cancer-specific survival (Hayes and Barry, 2014). Recommendations by organizations vary greatly on screening asymptomatic men for prostate cancer, with some supporting screening based on informed decision making and others rejecting the performance of PSA-based screening in an asymptomatic man (Gomella et al, 2011; Hayes and Barry, 2014). Considerations concerning overall health, age of the patient, family history, therapeutic options, wishes of the patient, and other risk factors all need to be considered in recommending prostate biopsy. In addition, concerns are growing over the potential

morbidity and mortality of prostate biopsy (Zlotta and Nam, 2012). A variety of online nomograms are available that may help with decision making (Nguyen and Kattan, 2013).

Organizations such as the AUA recommend shared decision making for men 55 to 69 years of age considering PSA-based screening, a target age group for whom benefits may outweigh harms (Carter et al, 2013). Outside this age range, the AUA recommends that PSA-based screening as a routine could not be recommended based on the available evidence. Most organizations have abandoned absolute PSA level cutoff values for prostate biopsy and are relying increasingly on risk stratification approaches and changes in PSA level over time. Men at elevated risk for having prostate cancer are those older than 50 years of age, or have a family history of prostate cancer and are older than 45 years, or African-Americans, or men with a PSA level greater than 1 ng/mL at 40 years and greater than 2 ng/mL at 60 years (Heidenreich et al, 2014).

Adjuncts to serum PSA testing have been advocated to improve the performance characteristics of PSA for prostate cancer detection, including free-to-total PSA ratio, PSA velocity, and PSAD, but are not uniformly reliable (Heidenreich et al, 2014). The National Comprehensive Cancer Network (NCCN) (2012) advocates the use of some of these PSA derivatives in the decision to perform TRUS biopsy. In the patient appropriate for prostate cancer screening they recommend TRUS prostate biopsy in the following situations: positive digital rectal examination regardless of PSA level; PSA 4 to 10 ng/mL based on patient risk benefit; PSA level 2.5 ng/mL or less and PSA velocity 0.35 ng/mL or greater per year; PSA level 2.6 to 4.0 ng/mL; PSA level 4.0 ng/mL or greater, especially if the free PSA level is 10% or less. As recommended by the NCCN, the presence of nodules on digital rectal examination usually should prompt TRUS biopsy regardless of PSA levels. In a recent study, 14% of cancers were diagnosed based on digital rectal examination alone (Okotie et al, 2007). However, the American Cancer Society guidelines now suggest that the prostate cancer screening can be performed with or without a rectal examination (Smith et al, 2014). In addition to an initial prostate biopsy, there are several indications for repeat prostate biopsy, as noted in Box 109-1.

The use of newer molecular techniques such as urinary determination of PCA3 to identify men at risk for a positive biopsy finding is evolving. Several studies have suggested that PCA3 provides supplemental information in determining the need for repeat prostate biopsy (Gittelman et al, 2013). In the largest study of this urinary marker to date, the mean PCA3 was 27.2 and 52.5 for patients without and with cancer, respectively, suggesting this is a useful tool in identifying patients at risk for prostate cancer before initial biopsy (Chevli et al, 2014).

Contraindications to Prostate Biopsy

Significant coagulopathy, severe immunosuppression, and acute prostatitis are all contraindications to prostate biopsy. With painful anorectal conditions or anal stenosis, prostate biopsy under general or regional anesthesia should be considered.

Preparing Patients for Biopsy

Patients should be informed of the risks and benefits of the procedure and informed consent obtained. Herbal supplements also should be discontinued because many contain undeclared agents. Low-dose aspirin does not need to be discontinued (Giannarini et al, 2007). Anticoagulant therapy (warfarin, clopidogrel, etc.) should be stopped 7 to 10 days before prostate biopsy. The novel oral anticoagulants apixaban, dabigatran, and rivaroxaban are stopped 2 to 5 days before (Culkin et al, 2014). Rivaroxaban may increase stroke risk if stopped; therefore bridging with some other anticoagulant such as heparin is recommended. For those patients with underlying coagulopathy or on warfarin, prostatic biopsy should not be performed until the international normalized ratio has been corrected below 1.5 if the patient has low risk for a thromboembolic event. Because of the higher risk for thromboembolic events (e.g., mechanical valves) on warfarin, bridging

BOX 109-1 Commonly Cited Indications for Transrectal Ultrasonography Alone and Transrectal Ultrasonography with Initial and Follow-up Prostate Biopsy

TRANSRECTAL ULTRASONOGRAPHY WITHOUT PROSTATE BIOPSY

- Treatment planning volume measurements: Brachytherapy, cryotherapy, benign prostatic hyperplasia therapy (e.g., transurethral microwave thermotherapy, radiofrequency ablation)
- Volume measurement during hormonal downsizing for external-beam radiation therapy or brachytherapy
- Placement of fiducial or radiofrequency markers for external-beam radiation therapy
- Evaluation of azoospermia: Ejaculatory duct cysts, seminal vesicle cysts, etc.
- Therapeutic aspiration or unroofing of prostatic cysts; drainage of prostatic abscess

INITIAL PROSTATE BIOPSY

- Initial diagnosis of prostate cancer based on informed decision making in an asymptomatic patient (based on PSA and patient-specific risk factors; see text)
- Suspicious digital rectal examination findings/prostate nodule (5%-30% cancer risk)
- To diagnose prostate cancer with symptoms suggestive of prostate cancer
- To diagnose prostate cancer with findings suggestive of metastatic disease (bone lesions and/or adenopathy)
- In the setting of prostate cancer detected on routine, transurethral resection of the prostate performed for presumed benign disease

REPEAT PROSTATE BIOPSY

- Rising and/or persistently elevated PSA
- Atypical small acinar proliferation (40% cancer risk)
- Extensive (multiple biopsy sites) with PIN (20%-30% cancer risk) (NOTE: isolated high-grade PIN is no longer considered an indication for repeat biopsy)
- Positive urinary PCA3 or other newer genomic tests such as Confirm MDx* methylation assay
- Suspicious lesion on prostate magnetic resonance imaging
- Differentiate local recurrence versus systemic disease with PSA recurrence after local ablative therapy

FOLLOW-UP PROSTATE BIOPSY

- Active surveillance follow-up protocol

PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen.

*Confirm MDx, MDxHealth, Irvine, CA.

Modified from Heidenreich et al, 2014; Thomsen et al, 2014; and Gomella and Amirian, 2015.

anticoagulation with unfractionated heparin or low-molecular-weight heparin is suggested.

A small amount of urine in the bladder is useful before the biopsy. This helps facilitate the examination by demonstrating the prostatic bladder junction.

Antibiotic Prophylaxis

An increasing frequency of complications has been recently noted with most postbiopsy hospitalizations resulting from infectious causes (Loeb et al, 2013). This has placed a renewed focus on antibiotic prophylaxis and other strategies to reduce postbiopsy

infectious complications. Unlike other lower urinary tract procedures, antimicrobial prophylaxis is recommended for all patients undergoing prostate biopsy, irrespective of risk factors. The 2014 updated latest AUA best practice policy recommended antibiotics for prostate biopsy include fluoroquinolones; first-, second-, and third-generation cephalosporins; and aminoglycoside (level of evidence, Ib) (American Urological Association, 2014). The 2014 update added oral trimethoprim-sulfamethoxazole as a prophylactic agent, and when using intramuscular or intravenous aminoglycoside or aztreonam as an alternative agent, metronidazole or clindamycin is no longer required. The intramuscular route is acceptable for all recommended agents, and the oral route is recommended only for quinolones (Table 109-1). For patients at risk for developing endocarditis or infection of prosthetic joints, pacemakers, and automated implanted cardiac defibrillators, prophylaxis should consist of intravenous ampicillin (vancomycin, if penicillin allergic) and gentamicin preoperatively, followed by 2 to 3 days of an oral fluoroquinolone. A 2011 Cochrane review on prophylaxis

for TRUS prostate biopsy demonstrated a reduction in bacteriuria, bacteremia, fever, urinary tract infection (UTI), and hospitalization with antibiotics compared to placebo or no treatment (Zani et al, 2011). There was no definitive evidence demonstrating superiority of longer course or multiple doses compared to a shorter course or single any-dose protocols.

As a result of the increasing resistance patterns to fluoroquinolones there has been recent interest in using individual culture data to guide antibiotic prophylaxis by using a rectal swab culture before biopsy (Taylor et al, 2012). The presence of fluoroquinolone-resistant organisms on a rectal swab culture has not always translated into clinical infection. In one multi-institutional study, rectal swab cultures immediately before biopsy in 136 men who received ciprofloxacin and gentamicin for prophylaxis had fluoroquinolone-resistant *Escherichia coli* in 22% of cultures (Liss et al, 2011). Only 5 (4%) patients had postbiopsy fever, and only 1 of them had a positive rectal screen for resistant *E. coli*. Although this result might have been prevented through targeted prophylaxis, the low overall complication rate raises questions about the cost-effectiveness of such a strategy. Additional studies are needed to define culture-directed therapy and compare its cost-effectiveness to empirical therapy based on local susceptibility patterns (Loeb, 2013).

TABLE 109-1 American Urological Association 2014 Best Practice Policy Recommended Antibiotics for Routine Prostate Biopsy*

DRUG	DOSAGE
FLUOROQUINOLONES†	
Levofloxacin	500 mg PO single dose
Ciprofloxacin	500 mg PO q12h
Ofloxacin	400 mg PO q12h
AMINOGLYCOSIDES‡	
Gentamicin	5 mg/kg IV single dose
Tobramycin	5 mg/kg IV single dose
Amikacin	15 mg/kg IV single dose
FIRST-GENERATION CEPHALOSPORINS	
Cephalexin	500 mg PO q6h
Cephadrine	500 mg PO q6h
Cefadroxil	500 mg PO q12h
Cefazolin	1 g IV q8h
Cefaclor	500 mg PO q8h
Cefprozil	500 mg PO q12h
Cefuroxime	500 mg PO q12h
Cefoxitin	1-2 g IV q6h
THIRD-GENERATION CEPHALOSPORINS	
Ceftizoxime	1 g IV q8h
Ceftazidime	1 g IV q12h
Ceftriaxone	1-2 g IV single dose
Cefotaxime	1 g IV q8h
ALTERNATIVE AGENTS	
Aztreonam	1-2 g IV q8h
Trimethoprim-sulfamethoxazole	1 double-strength tablet PO q12h

*The recommended duration of antimicrobial prophylaxis is 24 hours or less (level of evidence: Ib).

†Fluoroquinolones are associated with an increased risk for tendinitis and tendon rupture.

‡Aztreonam can be substituted for aminoglycosides in patients with renal insufficiency.

Modified from American Urological Association. Best practice policy statement on urologic surgery antimicrobial prophylaxis, <<http://www.auanet.org/content/media/antimicroprop08.pdf>>; 2008 (revised August 2011, updated January 1, 2014) [accessed 04.05.14].

Cleansing Enema

We routinely have patients self-administer a cleansing enema at home before biopsy. **This practice decreases the amount of feces in the rectum, thereby producing a superior acoustic window for prostate imaging.** The enema's effect on reducing infections is debatable. However, many clinicians may elect not to use an enema because this may allow more spontaneous performance of a prostate biopsy.

Analgesia

TRUS-guided infiltration anesthesia near the nerve bundles with local anesthetic can provide excellent pain control (Berger et al, 2003; Trucchi et al, 2005). A local prostatic block is achieved using 1% to 2% lidocaine, a long spinal needle (7-inch, 22-gauge), and TRUS guidance along the biopsy channel of the transducer. Multiple variations exist for the infiltration of local anesthetic for transrectal biopsy (Ismail and Gomella, 2013). We found that injecting 5 mL of lidocaine at the level of the SVs near the bladder base at the hyperechoic fat pad that demarcates the junction of the SVs and the prostate bilaterally produces an excellent block. Other approaches include infiltration of 10 mL starting at the junction of the SVs and infiltrating along the lateral aspect of the prostate from base to apex. **Direct infiltration into the prostate (intraprostatic injection) can augment the anesthetic benefit seen with periprostatic injection (Cam et al, 2008).** Saturation biopsy schemes may require up to 22 mL of 1% lidocaine. Caution is needed, however, to avoid direct intravascular injection because of the risk for systemic lidocaine absorption. Intrarectal (topical) instillation of a local anesthetic is inferior to periprostatic infiltration (Heidenreich et al, 2014). **Local anesthesia for transperineal biopsies also should include infiltration of the skin and subcutaneous tissues of the perineum initially.** US guidance then may be employed to aid infiltration of deeper tissues along the anticipated tracts of the biopsy needle.

Patient Positioning

Patients are usually placed in the left lateral decubitus position with knees and hips flexed 90 degrees. An armboard attached parallel to the table and a pillow between the knees helps maintain this position. The buttocks should be flush with the end of the table to allow manipulation of the probe and biopsy gun without obstruction. If necessary, the right lateral decubitus or lithotomy position can be used. **The lithotomy position is used by some clinicians and is preferred for transperineal biopsies, brachytherapy treatment planning, or placement of fiducial gold markers for external-beam therapy (Dehnad et al, 2003).**

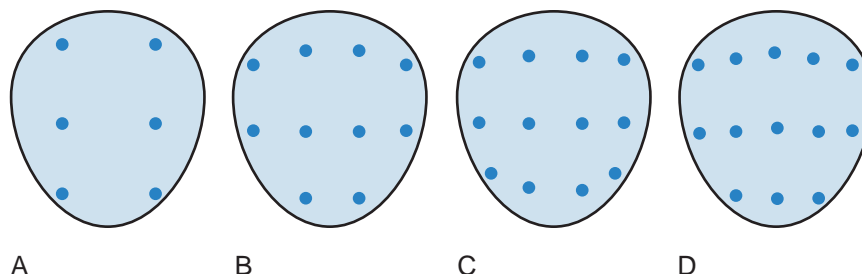


Figure 109-5. Various reported systematic biopsy schemes. Base is at the top of figure, apex is at bottom. A, Sextant biopsy scheme originally proposed by Hodge and associates (Hodge et al, 1989). B, The 10-core biopsy (Presti et al, 2000). C, The 12-core, or double-sextant, biopsy. This is the currently recommended sequence endorsed by the American Urological Association (Bjurlin et al, 2013). D, The 13-core, 5-region biopsy (Eskew et al, 1997).

Transrectal Prostate Biopsy Techniques

An initial digital rectal examination should be performed to evaluate for any prostate nodularity or anal pathologic processes. The prostate volume is determined, and imaging of the prostate in both the transverse and sagittal planes is begun. The examination usually starts at the base of the gland and extends to the apex. Most modern US units are automatically set for optimal prostate viewing, and the TRUS gray-scale examination of the prostate is conducted as previously described, noting the location and characteristics of any lesions (i.e., hypoechoic, hyperechoic, calcifications, contour abnormalities, cystic structures).

A spring-driven 18-gauge needle core biopsy device or biopsy gun that can be passed through the needle guide attached to the US probe is most often used. Most US units provide best visualization of the biopsy needle path in the sagittal plane. Images are typically superimposed with a ruled puncture path that corresponds to the needle guide of the TRUS unit. The biopsy gun advances the needle 0.5 cm and samples the subsequent 1.5 cm of tissue with the tip extending 0.5 cm beyond the area sampled (Kaye, 1989). Therefore, when sampling the PZ, the needle tip may be placed 0.5 cm posterior to the prostate capsule before firing; advancing the needle to or through the capsule can result in sampling of more anterior tissue, missing the most common location of cancers. Avoiding adjustment of the probe position while the biopsy needle is in contact with the rectal surface and applying pressure with the probe to compress the rectal mucosa before biopsy can minimize rectal bleeding. Pressing the probe against the rectum also minimizes the discomfort of the biopsy needle traversing the rectal mucosa, similar to pulling the skin tight to minimize the discomfort of phlebotomy.

The biopsy sample is typically placed in 10% formalin or per local protocol. An AUA white paper recently outlined the recommended processing of prostate biopsy samples, and the review did not provide compelling evidence that individual site-specific labeling of cores benefits clinical decision making regarding the management of prostate cancer (Bjurlin et al, 2013). The paper recommends packaging no more than two cores in each jar to avoid reduction of the cancer detection rate through inadequate tissue sampling.

Sextant Biopsy

The original sextant biopsy scheme (one core from the base, mid, and apex bilaterally) significantly improved cancer detection over digitally directed biopsy of palpable nodules and US-guided biopsy of specific hypoechoic lesions (Hodge et al, 1989). Taken in the parasagittal plane these cores sampled a portion of the PZ but also included a significant amount of tissue from the TZ. Subsequent studies of radical prostatectomy specimens demonstrated that the vast majority of adenocarcinomas arise in the posterolateral PZ (McNeal et al, 1988), thus explaining some of the false-negative results of standard sextant biopsy (Eskew et al, 1997).

Extended-Core Biopsy Techniques

Modifications to the standard sextant biopsy scheme initially focused on the importance of laterally directed cores (Terris et al, 1992). Numerous studies have shown improved cancer detection rates by incorporating additional laterally directed cores into the standard systematic sextant technique. At present, six cores are considered inadequate for routine prostate biopsy for cancer detection. Figure 109-5 depicts the originally proposed sextant technique and several common extended-core biopsy strategies.

Today the extended 12-core systematic biopsy that incorporates apical and far-lateral cores in the template distribution allows maximal cancer detection and avoidance of a repeat biopsy while minimizing the detection of insignificant prostate cancers. This approach has been endorsed in a recent AUA white paper (Bjurlin et al, 2013, 2014). Although increasing the cores from 6 to 12 results in a significant increase in cancer detection rate, increasing the number of cores to 18 or 21 (often termed *saturation biopsy*) as an initial biopsy strategy does not appear to result in a similar increase. However, a series of men from the Cleveland Clinic whose initial biopsy was by a transrectal saturation technique were less likely to have cancer identified during repeat biopsy. Further, if prostate cancer was diagnosed after negative initial saturation biopsy, it was much more likely to be clinically insignificant (Li et al, 2014). Their findings suggest saturation biopsy may be less likely to miss clinically significant cancer during initial prostate biopsy. At present, saturation biopsy is more likely to be considered in the setting of a prior negative biopsy (see later discussion).

TZ and SVs are not routinely sampled because these regions have been shown to have consistently low yields for cancer detection at initial biopsy (Epstein et al, 1997), but TZ and anteriorly directed biopsies may occasionally prove necessary to diagnose prostate cancer in those patients with persistently elevated PSA levels and prior negative biopsies (Mazal et al, 2001). However, there may be a limited role for TZ biopsies in men with gland size of more than 50 mL, with an additional yield of 15% cancer detection in these larger prostates (Chang et al, 1998). Today, magnetic resonance imaging (MRI) is often used to detect and guide biopsies of these anterior tumors that may escape standard TRUS prostate biopsy (Volkin et al, 2014). SV biopsy is not routinely performed unless there is a palpable abnormality, with some authors recommending SV biopsy when the PSA value is greater than 30 or if brachytherapy is being considered (Gohji et al, 1995).

Repeat and Saturation Prostate Biopsy

The dilemma of a patient who has had one or more negative prostate biopsies yet continues to have an elevated PSA value or abnormal digital rectal examination of concern for prostate cancer is a common clinical scenario. Often these patients have undergone multiple biopsies despite the well-documented decline in cancer detection with each successive biopsy (Djavan et al, 2003). Keetch

and coworkers (1994) reported an initial positive biopsy rate of 34% in 1136 men from their PSA-based prostate cancer screening program. Cancer detection rates then fell to 19%, 8%, and 7% on biopsy 2, 3, and 4, respectively. These findings were confirmed by results from an initial ERSPC series. In this cohort of 1051 men with PSA values between 4.0 and 10.0 ng/mL the initial cancer detection rate with sextant biopsy was 22%. Positive cores were then found in only 10%, 5%, and 4% of patients on subsequent biopsies 2, 3, and 4, respectively (Djavan et al, 2001a). In a contemporary follow-up from the same ERSPC study, positive predictive values (PPVs) for men without previous biopsy remained equal throughout the three subsequent screenings (25.5%, 22.3%, and 24.8%, respectively) (Bokhorst et al, 2012). Conversely, PPVs for men with a previous negative biopsy result dropped significantly (12.0% and 15.2% at the second and third screening, respectively). In men with and without previous biopsy, the percentage of aggressive prostate cancers (clinical stage >T2b, Gleason score ≥ 7) decreased after the first round of screening from 44.4% to 23.8% in the second round and 18.6% in the third. Repeat biopsies accounted for 24.6% of all biopsies, but yielded only 8.6% of all aggressive cancers.

The diminishing returns coupled with improved cancer detection rates on initial biopsy with extended-core protocols have led some researchers to examine saturation biopsy techniques (i.e., >12-core biopsy) in this difficult subset of patients with negative previous biopsy results. In a study of 57 men with an average of two prior negative sextant biopsies, a cancer detection rate of 30% was obtained, with an average of 22.5 cores per patient (Borboroglu et al, 2000). Similar protocols from the Mayo Clinic (Stewart et al, 2001) and Toronto (Fleshner and Klotz, 2002) demonstrated improved cancer detection rates. **A drawback to these techniques is that additional anesthetic requirements often require these saturation biopsies to be performed in a hospital setting.** More recent reports question the benefit of a follow-up saturation biopsy scheme, considering the attendant increased cost and potential morbidity. In a reassessment of their previous work on saturation biopsy, investigators at the Mayo Clinic performed a large prospective study of standard systematic and saturation biopsy techniques and did not find a significant increase in prostate cancer detection (Ashley et al, 2008).

The use of a second prostate biopsy in all cases of a negative finding on initial biopsy appears justified if there are concerns about undetected cancer. Third and fourth repeat biopsies, however, should be obtained only in selected patients with high suspicion for cancer and/or poor prognostic factors on the first or second biopsy (Djavan et al, 2005). **When performing repeat biopsy, attention should be placed on the apex, which may not be adequately sampled by the TRUS biopsy approach.**

The role of additional modalities continues to evolve in the setting of repeat biopsy. Techniques such as contrast-enhanced TRUS (CE-TRUS) and MRI targeted approaches discussed later in this chapter will have an impact on the approach to negative biopsy in the future (Halpern et al, 2005; Volkin et al, 2014). The use of newer molecular and genomic assays also will have an impact on the decision making in the future in the setting of a negative prostate biopsy (Gittelman et al, 2013; Partin et al, 2014; Gomella and Amirian, 2015).

Transperineal Prostate Biopsy

Transperineal biopsy offers an approach to the prostate in those patients lacking a rectum (e.g., surgical extirpation, congenital anomaly). The potential for reduced infectious and other complication rates and improved identification of apical tumors are now considered benefits to the transperineal biopsy technique (Chang et al, 2013). The main trade-off appears to be the need for more extensive anesthesia when using the perineum to approach the prostate.

The patient is positioned in dorsal lithotomy with the perineum shaved and prepped as for a sterile surgical procedure. An end-fire US transducer is used. Despite significant limitations in

visualization via this technique compared with TRUS, the prostate can and should be imaged in both the coronal and sagittal planes with calculation of the gland volume. Via the transperineal window, focal PZ hypoechoic lesions are difficult to visualize, as are the SVs. The urethra will appear as a hypoechoic midline structure and may be readily identified by following the corpus spongiosum proximally from the base of the penis. Once the boundaries of the gland have been clearly delineated in the coronal plane, a minimum of six cores should be taken, three from either side of midline.

The diagnostic yield of transperineal US-guided prostate biopsy was compared with that of TRUS-guided biopsies in a routine biopsy setting (Vis et al, 2000). By using radical prostatectomy specimens with TRUS biopsy-detected prostate cancer, simulated transperineal biopsies were performed and transrectal biopsies were repeated. Significantly, 82.5% of the known tumors were detected with the longitudinal transperineal approach versus 72.5% of cancer detection with repeat transrectal biopsy. The authors postulate that the longitudinal orientation of their cores allows more efficient sampling of the PZ, thereby improving cancer detection.

By using this approach in the repeat biopsy setting, Pinkstaff and associates (2005) obtained a mean of 21.2 cores (range, 12 to 41) in 210 men using a template perineal biopsy. The transperineal approach enhanced identification of TZ cancers not detected by previous transrectal prostate biopsy in high-risk patients. However, a Japanese randomized trial comparing transrectal and transperineal techniques for initial prostate biopsy, the cancer detection rate was similar for both, with higher complications noted in the transperineal approach (Hara et al, 2008). Therefore the authors concluded that transrectal prostate biopsy should be the preferred technique for initial prostate biopsy. An increased rate of urinary retention is noted for the transperineal approach, especially in the saturation biopsy setting (Moran et al, 2006). More recently, numerous benefits have been cited: possible improved cancer detection rates, improved anterior and apical sampling, reduced false-negative results, and reduced risk for underestimating disease volume and grade. **The increasing incidence of antimicrobial resistance and patients with diabetes mellitus who are at high risk for sepsis also favors transperineal biopsy as a sterile alternative to standard TRUS-guided biopsy (Chang et al, 2013).** The detection rate of anterior zone prostate cancer in patients undergoing initial and repeat transperineal prostate biopsy is increased by 10% in another series (Pepe et al, 2014).

The technique of three-dimensional (3D) transperineal mapping biopsy has been reported (Barqawi et al, 2011). This uses a transperineal brachytherapy template and can include over 50 mapping biopsy cores based on the size of the gland, far more than obtained with saturation biopsy. It may provide additional information and identify higher risk disease in men thought to have low-risk disease on standard 10- to 12-core TRUS biopsy. Further investigations are needed to establish the utility of this approach.

Transurethral Prostate Biopsy

Transurethral resection biopsy was once advocated for the diagnosis of TZ cancers or after negative TRUS sampling. In contemporary series, solitary TZ cancers, without concomitant PZ tumors, are estimated to occur in less than 5% of patients with prostate cancer (Pelzer et al, 2005). **With improved TRUS techniques including local anesthesia, the TZ can be adequately sampled, and the value of transurethral biopsy has been questioned for the vast majority of patients (Bratt, 2006).** In addition, MRI has shown utility in the identification of TZ and anterior prostate cancers and is particularly effective when used in a TRUS/MRI fusion biopsy system, further limiting the utility of the transurethral biopsy (Volkin et al, 2014).

Risks and Complications of Prostate Biopsy

Although generally considered a safe procedure, TRUS prostate biopsy can be associated with complications. The incidence of serious complications requiring hospitalization is relatively low (<1%). In a Canadian study of over 41,000 men with negative

biopsy results, the 30-day hospital admission rate after prostate biopsy increased from 1.0% in 1996 to 4.1% in 2010 (Nam et al, 2013). The majority of hospital admissions (72%) were related to bacterial infections. An overview of common complications include hematospermia, hematuria, rectal bleeding, prostatitis, fever greater than 101.3° F, epididymitis, urinary retention, and other complications requiring hospitalization (Heidenreich et al, 2014). Large screening series such as the PLCO and ERSPC show that prostate biopsy is not associated with excess mortality, and the overall rate of infectious complications is less than 1% (Pinsky et al, 2014). This low overall absolute risk for serious biopsy-related complications suggests that a fear of complications alone should not deter healthy men with a long life expectancy from pursuing early prostate cancer detection.

Postbiopsy Infections

Most infectious complications after TRUS biopsy are limited to symptomatic UTI and low-grade febrile illness, which can be readily treated with oral or intravenous antibiotics; however, increasing reports of hospitalizations and fatal sepsis after prostate biopsy are being reported (Wagenlehner et al, 2014). The contemporary risk for hospitalization for infectious complications ranges from 0.6% to 4.1%, with the reported incidence of UTI from 2% and 6% (Nam et al, 2013; Bjurlin et al, 2014). Although hospitalizations for sepsis are increasing after prostate biopsy, data suggest that the mortality in this group was not excessive when compared to that of other similar systemic infections (Loeb, 2013). Sepsis is the clinical syndrome characterized by a systemic inflammatory reaction to an infectious process; the symptoms are nonspecific and may include fever, hypothermia, tachypnea, tachycardia, altered mental status, and hypotension (American Urological Association/Society for Urological Nurses and Associates, 2012). Any patient who presents with a fever after a prostate biopsy should be assessed for the presence of sepsis. Septic shock refers to acute circulatory failure (hypotension) that persists despite adequate fluid resuscitation.

A main factor for severe infection seems to be the presence of fluoroquinolone-resistant fecal bacteria possibly due to use of these agents widely in health care settings, as well as other sources such as the food supply (Heuer et al, 2009). The use of targeted prophylaxis after rectal flora swabbing and culture has been shown to have some utility compared with empirical antibiotic prophylaxis in some series. Various bowel preparations are under investigation, but none have been shown to significantly reduce infection rates. As discussed previously, transperineal prostate biopsy is currently being evaluated to reduce infections, with limited data supporting this approach at present (Grummet et al, 2014).

Organisms reported to result in sepsis are predominantly *E. coli*, with high rates of resistance to fluoroquinolones, trimethoprim-sulfamethoxazole, and ampicillin. However, all isolates in this series were susceptible to second- and third-generation cephalosporins, amikacin, and carbapenems (e.g., imipenem, meropenem) (Loeb, 2013). Risk factors for prostate biopsy-related infection include: nonwhite race, increased number of comorbidities, diabetes mellitus, prostate enlargement, foreign travel, and recent antibiotic use. Another risk factor was the number of previous biopsies. The number of previous prostate biopsies significantly associated with an increased risk for infectious complications in men on an active surveillance protocol (Ehdaie et al, 2014). Familiarity with local antibiotic resistance patterns can aid in rapid treatment of symptomatic infection after prostate biopsy.

Bleeding

Even with normal coagulation parameters, bleeding is the most common complication seen after prostate biopsy. Prostate biopsy is considered to be intermediate risk for bleeding (Naspro et al, 2013). As noted, any potential medications that can alter coagulation parameters, including herbal remedies, should be held for 5 to 7 days before biopsy and those on warfarin managed as noted. Two

large European screening programs noted hematuria in 23% to 63% of men after sextant biopsy, with clot retention developing in 0.7% (Djavan et al, 2001b; Raaijmakers et al, 2002). Rectal bleeding is common and seen in 2.1% to 21.7% of patients (Enlund and Varenhorst, 1997; Djavan et al, 2001b). Rectal bleeding is typically minor and readily controlled with direct pressure by the US probe or digitally; persistent brisk blood loss per rectum may require more aggressive intervention for control. Additional measures include rectal tamponade with an inflated condom, anoscopy/colonoscopy with injection of epinephrine and polidocanol or use of sclerotherapeutic agents, angiography with embolization, transrectal exploration, and suturing (American Urological Association/Society for Urological Nurses and Associates, 2012).

Hematospermia, commonly seen after biopsy, is of minimal clinical importance but can cause significant anxiety if not discussed at the time of biopsy; 9.8% to 50.4% of men experience some blood in their ejaculate (Djavan et al, 2001b; Raaijmakers et al, 2002). In one study the mean duration of hemospermia was 4 (± 1.4) weeks, with the number of ejaculations before resolution at six (± 5.6). No factors predicted the duration of hemospermia (Abdelkhalek et al, 2013).

Other Complications

Excessive anxiety and discomfort from the endorectal probe may produce a moderate or severe vasovagal response in 1.4% to 5.3% of patients (Rodriguez and Terris, 1998; Djavan et al, 2001b) and may require termination of the procedure. Placing the patient in the Trendelenburg position and use of intravenous hydration usually resolve these symptoms, with further intervention as clinically indicated.

Acute urinary retention requiring temporary catheterization develops in 0.2% to 0.4% of patients after TRUS biopsy (Enlund and Varenhorst, 1997; Raaijmakers et al, 2002). Men with significantly enlarged glands and those with significant lower urinary tract symptoms, such as those with a high International Prostate Symptom Score (IPSS), are more prone to develop retention (Rodriguez and Terris, 1998; Raaijmakers et al, 2002). Any prostate biopsy may increase the IPSS, but this appears to be transient.

The effects of prostate biopsy on erectile dysfunction have been incompletely characterized. Very early studies suggested that erectile dysfunction after TRUS biopsy was due to damage to the neurovascular bundles (Zisman et al, 2001). Since that time the studies have been conflicting, with a more recent study suggesting erectile dysfunction is more pronounced in men who had a diagnosis of prostate cancer than in those who were cancer free (Helfand et al, 2013).

ADVANCED AND INVESTIGATIONAL TECHNIQUES FOR PROSTATE BIOPSY

Color and Power Doppler Transrectal Ultrasonography

Color Doppler imaging is based on the frequency shift in the reflected sound waves from the frequency of insonation and thus depicts the velocity of blood flow in a directionally dependent manner (Fig. 109-6A). Color assignment is based on the direction of blood flow related to the orientation of the transducer receiving the signal; flow toward the transducer is depicted in shades of red and flow away in shades of blue; the color is not specific for arterial or venous flow. Power Doppler imaging (also known as enhanced color Doppler, color amplitude imaging, or color angiography) uses amplitude shift to detect flow in a velocity and directionally independent manner (Bude and Rubin, 1996) (see Fig. 109-6B). The advantages of power Doppler imaging are its ability to detect slower flow and less reliance on the Doppler angle, making it more suitable for detection of prostate cancer neovascularity. Although power Doppler imaging offers improved sensitivity to small amounts of flow, neither modality has yet proved itself superior to the other for cancer detection.

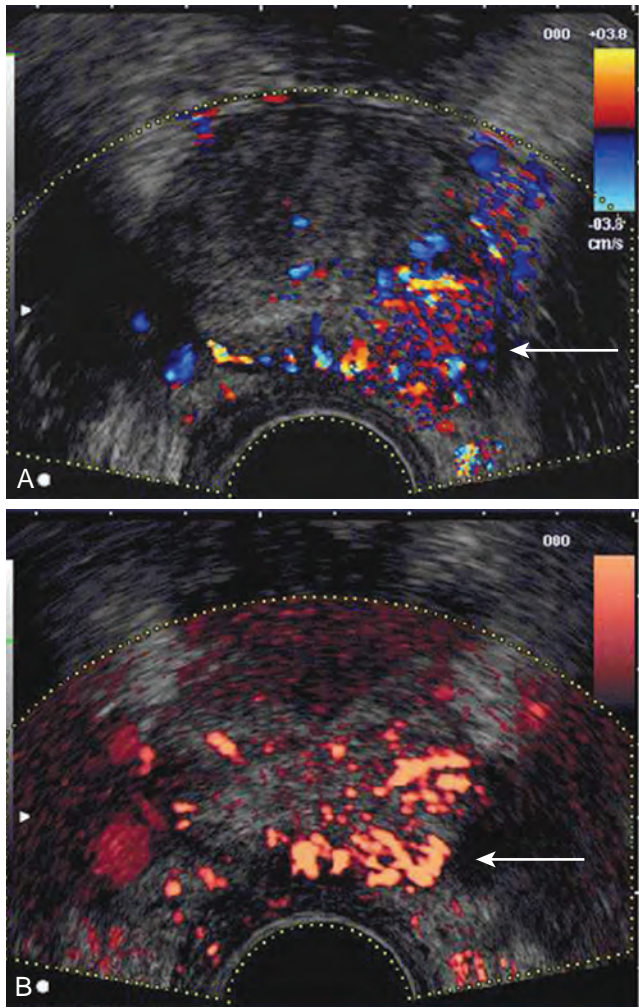


Figure 109-6. Color Doppler (A) transrectal ultrasonography (TRUS) and power Doppler (B) TRUS identify a Gleason 4 + 4 = 8 adenocarcinoma (arrows) in the left mid-gland.

One series found color Doppler sensitivity and specificity of 14.6% and 93.9%, respectively, to identify cancer (Halpern and Strup, 2000). Whereas Doppler modes showed an improved diagnosis versus gray-scale TRUS, 45% of cancers still went unidentified by any sonographic modality. Others have shown increased cancer detection rates using Doppler-targeted biopsy strategies, but none is sufficiently accurate to replace systematic biopsy (Halpern et al, 2002). Enhancements in the technical aspects of color Doppler TRUS, including the use of contrast agents (see later discussion), may provide the necessary improvements to specifically identify cancer sites in the future.

Multiple studies have shown that angiogenesis and the resultant increase in microvessel density that occurs within foci of prostatic adenocarcinoma correlates with the presence of metastases (Weidner et al, 1993), stage of disease (Bostwick et al, 1996), and disease-specific survival (Lissbrant et al, 1997; Borre et al, 1998). Interest in using color and power Doppler TRUS to aid in prostate cancer detection stems from studies of radical prostatectomy specimens demonstrating that foci of adenocarcinoma possess an increased density of microvessels compared with surrounding normal parenchyma (Bigler et al, 1993).

Patients with detectable color Doppler flow within their dominant tumor at the time of TRUS-guided biopsy are at a 10-fold increased risk for PSA recurrence after radical retropubic prostatectomy (Ismail et al, 1997). The presence of increased flow was also associated with higher Gleason grade, increased incidence of

SV invasion, and a lower biochemical disease-free (bNED) survival rate versus subjects without increased flow on preoperative TRUS (50% vs. 108% bNED at 31 months) (Ismail et al, 1997). Other investigators also have shown the association of power Doppler flow signals as an indicator of microvessel density with higher Gleason score and have suggested a correlation with outcome (Wilson et al, 2004).

Current unenhanced Doppler modalities are not able to identify the microvessels of prostate cancer, which are typically 10 to 15 microns in diameter. The flow signals associated with malignant foci detected by unenhanced color and power Doppler imaging are due to detection of larger feeding vessels (Ismail and Gomella, 2001). Intravenous microbubble US contrast agents, similar to those currently approved and used in echocardiography, have been infused systemically during gray-scale and TRUS Doppler imaging to amplify flow signals within the microvasculature of prostate tumors, allowing selective visualization of malignant foci in clinical trials (Halpern et al, 2000; Ismail and Gomella, 2001). These intravenous “bubble” contrast agents are constructed with air or higher-molecular-weight gas agents encapsulated (albumin or polymer hard shell, lipid or surfactant coated) for longevity and are generally 1 to 10 microns.

Using CE-TRUS for prospective prostate cancer detection, Halpern and associates (2001) demonstrated an increase in sensitivity from 38% to 65% versus baseline unenhanced imaging, without significantly altering specificity. Subsequent studies by our group and others have improved sonographic detection of malignant foci using CE-TRUS and targeted biopsy of enhancing lesions (Kundavaram et al, 2012). In a multi-institutional trial involving several European centers, CE-TRUS has been recommended for routine care in prostate biopsy (Wink et al, 2008). Imaging using microbubble contrast agents combined with 3D image reconstruction of enhanced power Doppler images also demonstrated increased diagnostic accuracy (Unal et al, 2000) (Fig. 109-7). Flash-replenishment imaging, a software modification, gives better visualization of small neovessels, down to the capillary level, for the detection of prostate cancer (Linden et al, 2007). Flash replenishment imaging uses a combination of high-power flash pulses to destroy contrast microbubbles, followed by low-power pulses to demonstrate contrast replenishment. A composite image is constructed depicting the vascular architecture through maximum intensity capture of temporal data in consecutive low-power images and can be used for real-time targeted transrectal biopsy of areas of increased or abnormal vascularity. Using this technique, we have demonstrated much finer vascular detail for targeting biopsy, and targeted biopsy cores were significantly more likely to be cancerous than random systematic biopsy cores (Linden et al, 2007). Future developments in these and other imaging modalities that can selectively visualize prostate cancers based on the presence of angiogenesis may ultimately allow more accurate localization of the sites of cancer.

The technique of elastography may prove superior to color Doppler imaging in identification of malignant areas in the prostate (Nelson et al, 2007; Sumura et al, 2007). It employs real-time sonographic imaging of the prostate at baseline, and under varying degrees of compression it adds information about stiffness of the prostate tissue (Fig. 109-8). Through computerized calculations, differences in displacement between ultrasonic images from baseline and during compression may be visualized and regions with decreased tissue elasticity (tissue stiffness) may be suggestive of malignancy. In a preliminary study of 404 cases with 151 cases positive for prostate cancer, the malignancy was found in 127 patients (84.1%) with real-time elastography directing the biopsy (Konig et al, 2005). Real-time elastography-targeted biopsy is an evolving method for increasing prostate cancer detection rates. Nevertheless, real-time elastography-targeted biopsies missed cancer in a high proportion of patients in one series of over 1000 men and therefore at present should be considered an additional technology to complement but not replace randomized biopsies (Salomon and Schiffmann, 2014; Salomon et al, 2014).

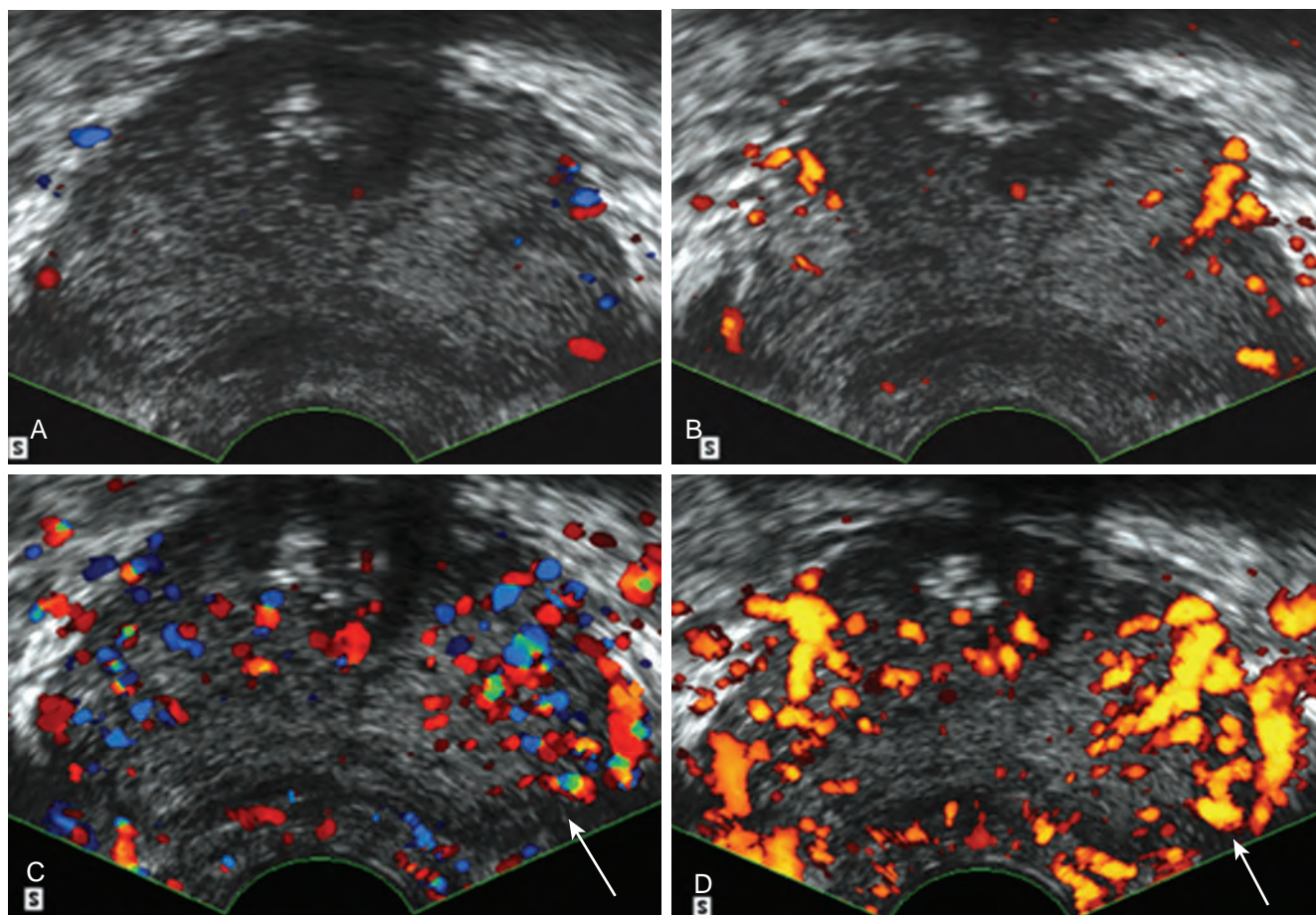


Figure 109-7. Unenhanced color (A) transrectal ultrasonography (TRUS) and power Doppler (B) TRUS fail to detect evidence of an underlying malignancy. After infusion of a microbubble contrast agent, color (C) TRUS and power Doppler (D) TRUS demonstrate an area of increased flow in the left mid-gland that proved to be a Gleason 3 + 4 = 7 adenocarcinoma on targeted biopsy (arrows).

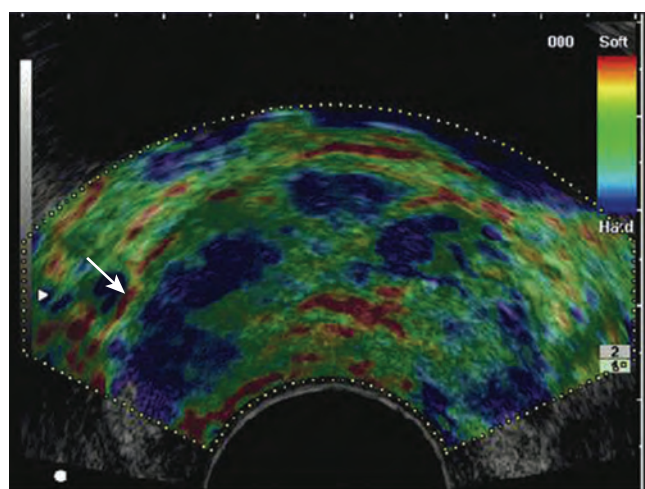


Figure 109-8. Elastography demonstrates an area of decreased compliance in the right base consistent with an underlying malignancy (blue near arrow). Note color scale in upper right corner indicating relative tissue “firmness.” Targeted biopsy of this region revealed a Gleason 4 + 4 = 8 adenocarcinoma.

Other Newer and Investigational Imaging and Biopsy Techniques

Prostate HistoScanning (Advanced Medical Diagnostics, Waterloo, Belgium) is a proprietary tissue characterization technology reported to differentiate, characterize, and visualize prostate tissue, based on the analysis of backscattered US. It is an evolving technology, and a recent study of 105 patients suggested that the system could not reliably identify and characterize prostate cancer in a routine clinical setting (Javed et al, 2014).

Computerized machine templates have been developed that convert two-dimensional US data into a 3D model and theoretically allow reproducible targeted spatial sampling (Bjurlin et al, 2014). Two systems are currently under study in the United States—the TargetScan (Best Nomos, Pittsburgh, PA) and Artemis (Eigen, Grass Valley, CA). Publications are limited at this time, but the ability of these systems to precisely perform biopsy in known areas of the prostate on a reproducible basis is appealing (Bjurlin et al, 2014).

Improvements in the design and application of multiparametric MRI have increased the ability to identify and localize prostate cancer. Functional MRI parameters such as dynamic contrast enhancement and diffusion-weighted imaging alone or in combination have improved prostate cancer detection (Turkbey and Choyke, 2012). However, the diagnosis and histopathologic grading of prostate cancer still requires tissue for diagnosis. Although theoretically appealing, significant technical difficulties exist in performing real-time MRI-directed prostate biopsies. At the present time,

there are three evolving techniques that combine MRI-guidance for targeted prostate biopsies, namely direct “in-bore” MRI, cognitive fusion, and MRI/US fusion via software-based image coregistration (Logan et al, 2014).

MRI, with or without endorectal coil, multiparametric MRI, and MR spectroscopy as combined modalities, might be able to guide and therefore limit the number of biopsies and cores for patients (Amsellem-Ouazana et al, 2005). The “in bore” MRI prostate biopsies are performed with the patient in the MRI unit. It requires highly specialized equipment and is limited by technical considerations such as limited space in the MRI, cost, and time considerations (Beyersdorff and Hamm, 2005). In one recent study of multiparametric MRI prostate biopsy in 223 men compared to TRUS biopsy, 142 (63.7%) had prostate cancer (Pokorny et al, 2014). TRUS prostate biopsy detected 126 cancers (56.5%), including 47 (37.3%) classed as low risk. MRI-directed biopsy detected 99 cases of cancer in 142 men (69.7%) with equivocal or suspicious MRI, of which 6 (6.1%) were low risk. The MRI pathway reduced the need for biopsy by 51%, decreased the diagnosis of low-risk prostate cancer by 89.4%, and increased the detection of intermediate-/high-risk prostate cancer by 17.7%. The estimated negative predictive values (NPVs) of TRUS biopsy and MRI biopsy for intermediate-/high-risk disease were 71.9% and 108.9%, respectively.

Cognitive fusion requires no additional equipment and relies on an experienced operator reviewing a suspicious lesion on MRI and then directing the biopsy needle in the direction of suspicious lesions during the standard TRUS biopsy procedure. A primary disadvantage of this technique is the inability to record and confirm biopsy needle placement as well as interuser variability (Logan et al, 2014).

One of the most promising biopsy techniques is TRUS/MRI fusion via a software platform. It combines the familiarity of real-time TRUS guidance with detailed information from a diagnostic multiparametric MRI and superimposes both images via software

image reconstruction. The reconstruction involves image registration or image matching. A prebiopsy MRI must identify target lesions suspicious for cancer based on imaging characteristics. Based on the particular software platform, these targets are delineated before or after MRI data have been loaded onto the software platform. TRUS of the prostate is performed and MRI and real-time TRUS images are superimposed, creating a 3D prostate reconstruction and allowing rapid identification of the MRI targets for biopsy in a few minutes. Two MRI/US fusion systems approved by the U.S. Food and Drug Administration are available in the United States: the UroNav platform (Phillips/Invivo, Gainesville, FL) and the Artemis platform with ProFUSE (Eigen). The UroNav system has been under study at the National Cancer Institute since 2004 and has the largest collection of published data to date. Several other manufacturers are developing systems both in the United States and abroad (Raskolnikov et al, 2014).

One significant difference between the UroNav and Artemis platforms is that the Artemis system employs a mechanical arm to direct the biopsy. The UroNav system employs a standard hand-held probe with localization and tracking data recorded by an external magnetic field generator integrated with existing freehand US technology.

When performing a TRUS/MRI fusion biopsy, system-specific MRI software is first used to identify lesions as low, moderate, or high risk for prostate cancer (Invivo) or on a 1 to 5 (normal to highly suspicious) scale (Eigen). The utility of the different scoring systems has yet to be investigated and fully defined in direct comparison with each other. Real-time image fusion allows the physician to direct the biopsy using standard TRUS spring-loaded needle biopsy technique (Fig. 109-9).

Preliminary results have been reported for these two U.S. TRUS/MRI fusion systems. A study at the University of California–Los Angeles involving 171 men demonstrated that 94% (16 of 17 patients) with a grade 5 (highly suspicious) MRI lesion had

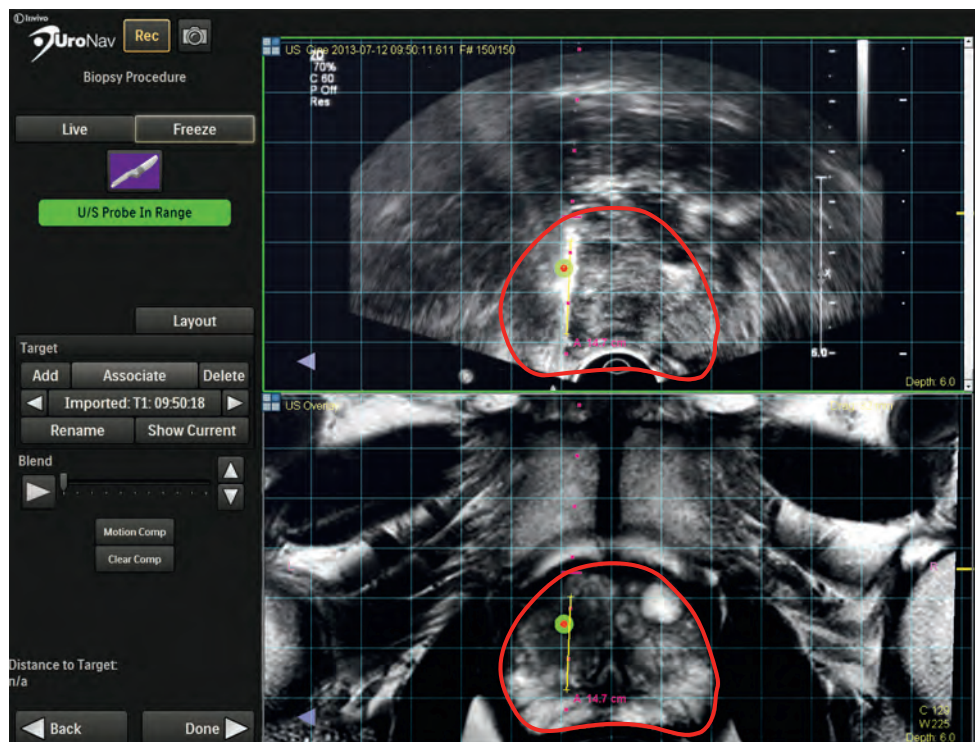


Figure 109-9. Example of a screen shot when performing transrectal ultrasonography (TRUS) using the UroNav (Invivo) TRUS–magnetic resonance imaging (MRI) fusion biopsy system. Upper panel is the real-time ultrasound; lower panel shows the MRI. The red line outlines the prostate and the green circle with the red dot represents the coregistered lesion of interest. The yellow line represents the needle tract. (Courtesy Dr. Peter Pinto, Urologic Oncology Branch, National Cancer Institute, Bethesda, MD.)


biopsy-positive prostate cancer. A 38% detection rate was found for intermediate- to high-risk prostate cancer identified only on targeted biopsy, with targeted cores three times more likely to detect intermediate- to high-risk disease versus systematic biopsy (Sonn et al, 2013).

An update series of 582 men studied on the UroNav system has demonstrated an increasing correlation between MRI suspicion and Gleason grade for prostate cancer with detection for Gleason 8 or greater prostate cancer showing a 98% sensitivity at the low-moderate cutoff and a 91% NPV at the moderate-high cutoff (Rais-Bahrami et al, 2013). Another TRUS/MRI fusion-guided biopsy study with the UroNav system demonstrated upgrading and detection of prostate cancer with higher Gleason score in 32% of patients compared with traditional 12-core biopsy alone (Siddiqui et al, 2013). Targeted biopsy with the TRUS/MRI fusion technique preferentially detected higher grade prostate cancer and missed lower grade tumors.


Technologies continue to evolve in improving the identification and diagnosis of prostate cancer. Beyond imaging technologies such as US and MRI, the use of genomic and other molecular markers will play an increasing role in determining the need for a biopsy and in identifying patients who are in need of a repeat biopsy (Partin et al, 2014). Color Doppler, US contrast agents, elastography, multiparametric MRI, and TRUS/MRI fusion are undergoing refinements as imaging methods to guide and enhance the accuracy of prostate biopsies (Hong et al, 2014). Until these techniques are proved superior in the localization and diagnosis of prostate cancer, systematic TRUS gray-scale 12-core needle biopsy will continue to be regarded as the gold standard for the diagnosis of prostate cancer.

KEY POINTS: PROSTATE BIOPSY

- TRUS and/or MRI alone cannot diagnose prostate cancer without a tissue biopsy.
- Local prostate anesthesia is commonplace and most useful when using extended-core biopsy schemes.
- Patients undergoing TRUS-guided prostate biopsy require oral antibiotic prophylaxis for up to 24 hours perioperatively.
- Sextant biopsy of the prostate for prostate cancer detection is inadequate, and systematic biopsy procedures should include a minimum 12 cores based on AUA recommendations.
- Advanced US techniques (color and power Doppler, elastography) can improve cancer detection but do not reliably identify all malignant foci and thus cannot obviate the need for systematic biopsy at the present time.
- TRUS/MRI fusion is a promising technique that takes advantage of the strengths of each modality when performing prostate biopsy

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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Prostatic Intraepithelial Neoplasia

Adenocarcinoma

This chapter covers the pathology of adenocarcinoma of the prostate from its precursor lesions to invasive carcinomas, from needle biopsies to radical prostatectomies. Other tumors involving the prostate are also discussed. In particular, practical points of pathology are emphasized, which are critical for urologists to know for the management of their patients.

PROSTATIC INTRAEPITHELIAL NEOPLASIA

Prostatic intraepithelial neoplasia (PIN) consists of architecturally benign prostatic acini or ducts lined by cytologically atypical cells, and PIN is subclassified into low-grade PIN (LGPIN) and high-grade PIN (HGPIN) (McNeal and Bostwick, 1986; McNeal, 1989) (Fig. 110-1). Diagnostic reports should not comment on LGPIN. First, pathologists cannot reproducibly distinguish between LGPIN and benign prostate tissue (Epstein et al, 1995). Second, when LGPIN is diagnosed on needle biopsy, these patients are at no greater risk of having carcinoma on repeated biopsy than are men with a benign biopsy finding (Epstein and Herawi, 2006). Evidence that HGPIN is a precursor to some prostate carcinomas includes the following: There is an increase in the size and number of HGPIN foci in prostates with cancer compared to prostates without carcinoma; with increasing amounts of HGPIN, there is a greater number of multifocal carcinomas; and biomarkers and molecular changes show similarity between HGPIN and carcinoma (Bostwick et al, 1996; Haggman et al, 1997). About 20% of HGPIN lesions harbor a *TMPRSS2:ERG* fusion gene, which is a common molecular abnormality detectable in about 50% of prostate cancers (Cerveira et al, 2006; Perner et al, 2007). The finding of zones of HGPIN from which there appears to be budding off glands of carcinoma is further histologic evidence that HGPIN is a precursor to some prostate carcinomas (McNeal et al, 1991).

The incidence of HGPIN on biopsy averages in the 4% to 5% range (Epstein and Herawi, 2006). There is a tremendous variation in the percentages reported, ranging from 0% to 25% (Epstein and Herawi, 2006). The most likely explanation accounting for this variation is interobserver threshold. The distinction between LGPIN and HGPIN is based on the prominence of the nucleoli. This is a subjective exercise, and those pathologists with a lower threshold regarding the definition of prominent nucleoli will have a higher incidence of HGPIN. The mean risk of cancer is 26.4% on subsequent biopsy within a year following the diagnosis of HGPIN, which is not significantly higher than the risk of carcinoma following a repeat biopsy after a benign diagnosis (Epstein and Herawi, 2006). In the majority of studies, serum prostate-specific antigen (PSA) levels, results of digital rectal examination, and transrectal ultrasonography findings do not enhance the prediction of who is more likely to exhibit carcinoma on repeat biopsy. PIN by itself does not give rise to elevated serum PSA values (Ronnett et al, 1993; Epstein and Herawi, 2006). For patients diagnosed with unifocal HGPIN on extended initial core sampling, a repeat

Subtypes of Prostate Adenocarcinoma

biopsy within the first year is unnecessary in the absence of other clinical indicators of cancer. Because of the lack of large studies on its long-term risk of cancer and the potential medicolegal consequences of not following up on an HGPIN diagnosis, a reasonable approach is to perform repeat biopsy 3 years following a diagnosis of HGPIN on a single core on needle biopsy (Godoy et al, 2011). HGPIN on greater than or equal to two cores is associated with a sufficiently high risk of subsequent cancer such that rebiopsy within a year of the initial PIN diagnosis is warranted (Abdel-Khalek et al, 2004; Merrimen et al, 2009, 2010). If a repeat prostate needle biopsy is performed, it should sample the entire prostate with relatively increased sampling of the initial sextant site where the HGPIN was found (Epstein and Herawi, 2006).

There are numerous benign and malignant mimickers of HGPIN. It may be difficult to distinguish between outpouchings or tangential sections of HGPIN with adjacent small atypical glands (PINATYP) as opposed to PIN with associated infiltrating carcinoma (Kronz et al, 2001). Most of these cases will require immunohistochemistry for basal cell markers, where cancer should be diagnosed only when there is a large cluster of entirely negative glands. The risk of carcinoma following a diagnosis of PINATYP is 40%, justifying a repeat biopsy within 6 months.

The significance of HGPIN on transurethral resection (TUR) is not clear, with conflicting data as to the risk for subsequent discovery of cancer (Gaudin et al, 1997; Pacelli and Bostwick, 1997). In an elderly patient with HGPIN on TUR, often no further workup is instituted. In a younger man, a more aggressive workup to rule out a clinically significant tumor may be warranted. HGPIN is a precursor lesion to many peripheral intermediate- to high-grade adenocarcinomas of the prostate. However, PIN need not be present for carcinoma to arise. Low-grade carcinomas, especially those present within the transition zone, are not closely related to HGPIN.

Intraductal carcinoma of the prostate (IDC-P) has either architectural or cytologic atypia that clearly exceeds that seen in HGPIN. IDC-P has, in several studies, been described in radical prostatectomy specimens (McNeal et al, 1986; McNeal and Yemoto, 1996b; Rubin et al, 1998; Wilcox et al, 1998; Cohen et al, 2007; Robinson et al, 2012). Rarely, IDC-P may be identified on biopsy material in the absence of infiltrating carcinoma (Guo and Epstein, 2006). IDC-P on prostate biopsies is frequently associated with high-grade cancer and poor prognostic parameters at radical prostatectomy (Guo and Epstein, 2006). These findings support the idea that in most cases IDC-P represents intraductal spread of carcinoma within preexisting ducts and acini and that IDC-P in the vast majority of cases should not be categorized as a preinvasive neoplastic condition. In the rare case in which IDC-P is treated by radical prostatectomy and no invasive cancer is found, the surgery is justified, as in these cases IDC-P is a high-grade preinvasive lesion that includes a high risk of developing invasive high-grade cancer. We recommend that patients with IDC-P only on biopsy be treated with definitive

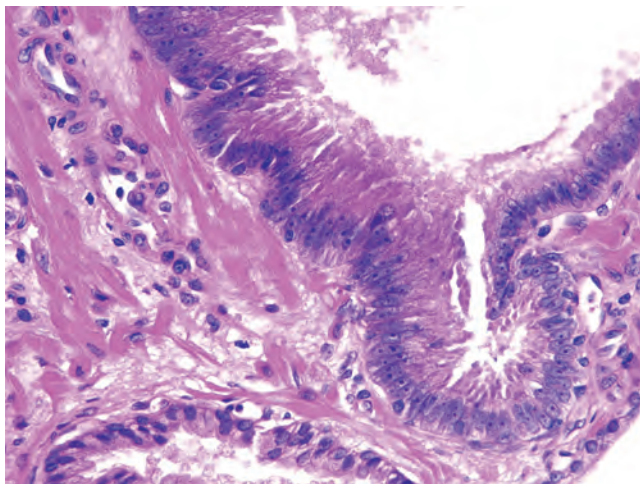


Figure 110-1. High-grade prostatic intraepithelial neoplasia. Note cytologically atypical cells with prominent nucleoli in an architecturally benign gland (top), contrasted to a benign gland (bottom).

therapy. In cases that are borderline between IDC-P and HGPIN, repeat biopsy is warranted.

ADENOCARCINOMA

Staging Classification

Stages T1a ($\leq 5\%$ cancer) and T1b ($>5\%$) adenocarcinomas of the prostate are clinically unsuspected tumors that are discovered in either TUR of the prostate (TURP) or enucleation specimens removed for benign prostatic hyperplasia (Epstein et al, 2007). Stage T1c disease refers to nonpalpable prostate cancer found on needle biopsy, usually performed for an abnormal serum PSA level. If a patient undergoes radical prostatectomy, stages T1a to T1c are converted to pT2 or pT3 if the tumor is organ confined or shows extraprostatic extension (EPE), respectively. Pathologic stage T2 is defined as tumor localized to the prostate, which is currently further subdivided into T2a to T2c depending on the extent of cancer. However, numerous studies have shown that subdividing pathologic stage T2 disease has no prognostic significance. The reason for this finding is that bilateral prostate cancer may represent (1) a dominant tumor nodule with contralateral small, low-grade, clinically insignificant tumor; (2) significant discrete right and left tumor nodules; or (3) a single, large, confluent tumor mass involving both sides. Consequently, the designation “pathologic stage T2c” (bilateral cancer) has no meaning, and it is expected that future TNM (tumor, node, metastases) classifications will be changed to reflect this finding. This author merely denotes “stage T2” without subclassification into “T2a” or “T2b” or “T2c” (Kheirandish and Chinegwundoh, 2011; van der Kwast et al, 2011). “Stage T2+” (stage T2x) refers to a tumor with no identifiable tumor in extraprostatic tissue but with a positive margin because of the surgeon’s cutting into the prostate (intraprostatic incision). Because the edge of the prostate has been left in the patient, the pathologic stage cannot be assessed in the area of the intraprostatic incision. Pathologic stage T3 represents a tumor that has extended out of the prostate gland, which is further subclassified into T3a and T3b, depending on whether the extraprostatic tumor is without or with seminal vesicle invasion, respectively. Microscopic bladder neck invasion is pT3a.

Location

In clinical stage T2 carcinomas and in 85% of nonpalpable tumors diagnosed on needle biopsy (stage T1c), the major tumor mass is located in the posterior portion of the prostate in the peripheral zone (McNeal, 1969; Byar and Mostofi, 1972; Epstein

et al, 1994b). Approximately 15% of radical prostatectomy specimens show predominantly anterior tumors, some in the transition zone and others in the anterior horn of the peripheral zone (Al-Ahmadie et al, 2008). Adenocarcinoma of the prostate is multifocal in more than 85% of cases (Byar and Mostofi, 1972). In many of these bilateral or multifocal tumor cases, the other tumors are small, low grade, and clinically insignificant. In cases with bilateral cancer at radical prostatectomy, the contralateral tumor to the positive biopsy side at radical prostatectomy is typically small. However, 20% have some contralateral adverse pathology in terms of size, EPE, grade, or margins (Yoon et al, 2008).

Spread of Tumor

Because the prostate lacks a discrete histologic capsule, *extraprostatic extension*, rather than *capsular penetration*, is the preferable term to describe a tumor that has extended out of the prostate into the periprostatic soft tissue (Ayala et al, 1989). Some authors use the term *capsular invasion* when they believe that the “capsule” is infiltrated by a tumor but the tumor does not extend out of the prostate. Because there is no such entity as the prostatic capsule, “capsular invasion” makes no sense. Peripherally located adenocarcinomas of the prostate tend to extend out of the prostate through perineural space invasion (Villers et al, 1989). EPE preferentially occurs posteriorly and posterolaterally, paralleling the location of most adenocarcinomas.

Further local spread of the tumor may lead to seminal vesicle invasion, which is diagnosed when a tumor extends into the muscle wall of the seminal vesicle. The most common route of seminal vesicle invasion is by tumor penetration out of the prostate at the base of the gland, with growth and extension into the periseminal vesicle soft tissue and eventually into the seminal vesicles. Less commonly, there may be direct extension through the ejaculatory ducts into the seminal vesicles or direct extension from the base of the prostate into the wall of the seminal vesicles. Almost never are there discontinuous metastases to the seminal vesicle (Ohori et al, 1993). Local spread of prostate cancer may also rarely involve the rectum, where it may be difficult to distinguish from a rectal primary tumor (Fry et al, 1979; Lane et al, 2008).

The most frequent sites of metastatic prostate carcinoma are lymph nodes and bones. Prostate cancer may present with metastases to the left supradiaphragmatic, typically the supraclavicular, lymph nodes (Cho and Epstein, 1987). Lung metastases from prostate carcinoma are extremely common at autopsy, and almost all cases involve bone as well (Varkarakis et al, 1974). Metastatic lesions usually take the form of multiple small nodules or diffuse lymphatic spread rather than large metastatic deposits. Clinically, prostate carcinoma metastatic to the lung is usually asymptomatic. In addition to lymph nodes, bones, and lung, the next most common regions for the spread of prostate cancer at autopsy are bladder, liver, and adrenal gland (Hess et al, 2006).

Tumor Volume

In general, the size of a prostate cancer correlates with its stage. EPE is uncommon in tumors less than 0.5 cm^3 , and tumors less than 4 cm^3 uncommonly show lymph node metastases or seminal vesicle invasion (McNeal et al, 1990). Tumor volume is also proportional to grade (see the following discussion). The location and grade of the tumor also modulate the effect of tumor volume (Christensen et al, 1990; McNeal et al, 1990; Greene et al, 1991). For example, transition zone tumors extend out of the prostate at larger volumes than do peripheral zone tumors because of their lower grade and greater distance from the edge of the gland. Reporting of tumor volume in various specimens is discussed later.

Grade

The Gleason system is based on the glandular pattern of the tumor as identified at relatively low magnification (Mellinger et al, 1967; Gleason and Mellinger, 1974) (Fig. 110-2). Cytologic features play

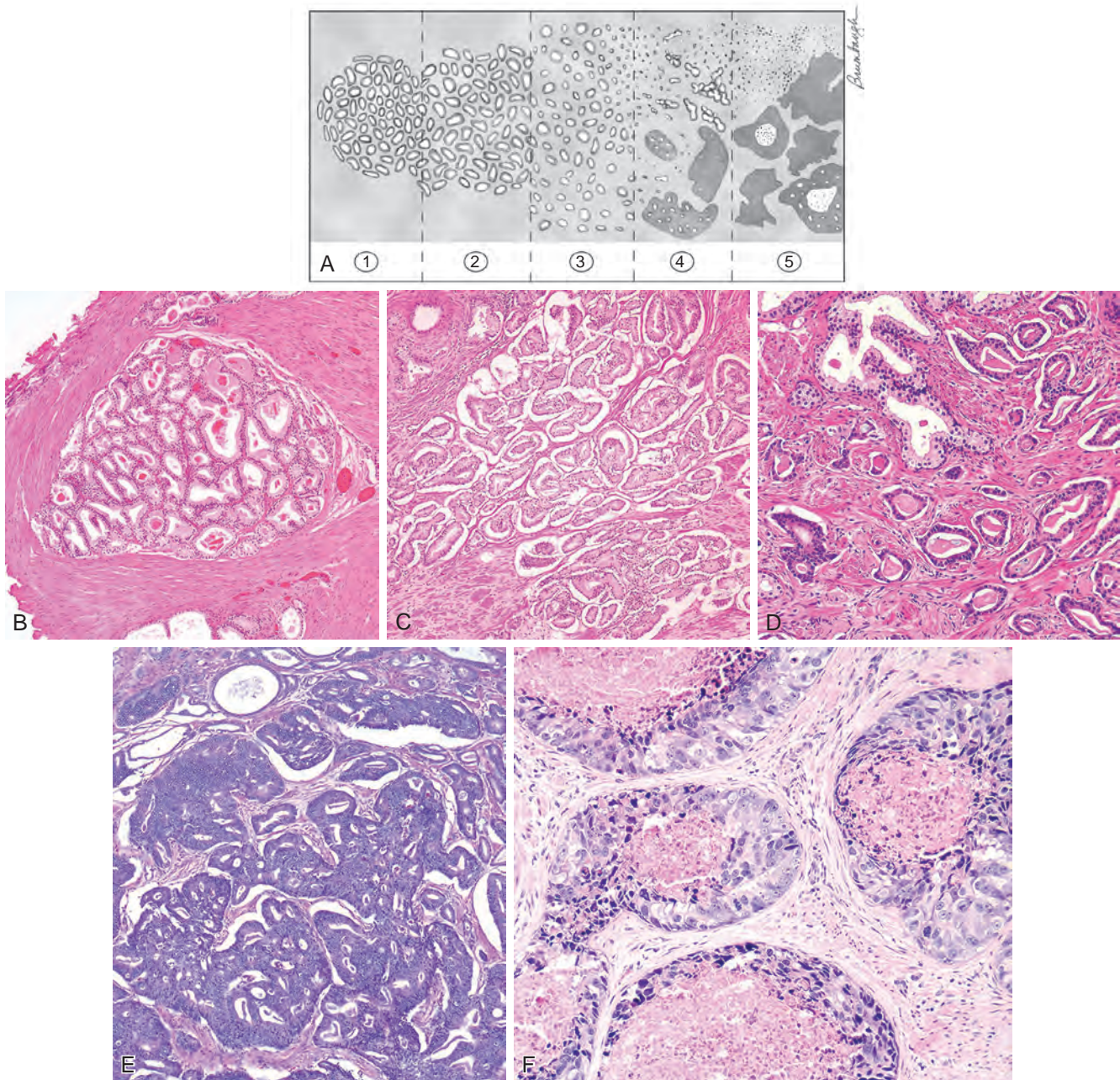


Figure 110-2. The Gleason grading system. **A**, Schematic diagram of the Gleason grading system. **B**, Gleason pattern 1: well-circumscribed nodule of closely packed glands. **C**, Gleason pattern 2: nodule with more loosely arranged glands. **D**, Gleason pattern 3: small glands with an infiltrative pattern between benign glands. **E**, Gleason pattern 4: large irregular cribriform glands. **F**, Gleason pattern 5: solid nests of tumor with central comedonecrosis.

no role in the grade of the tumor ([Box 110-1](#)). Architectural patterns are identified and assigned a grade from 1 to 5, with 1 being the most differentiated and 5 being undifferentiated (see [Box 110-1](#)). Although in the original Gleason system, the most common and second most common grades were combined, in 2005 the Gleason system was updated and modified with one change being that on biopsy the *most common* and *highest-grade* patterns on a given core were added to result in the Gleason score ([Epstein et al, 2005](#)). If a tumor has only one histologic pattern, then for uniformity, both patterns are assigned the same grade. In theory, however, the Gleason scores range from 2 ($1 + 1 = 2$), which represents tumors uniformly composed of Gleason pattern 1 tumor, to 10 ($5 + 5 = 10$), which represents totally undifferentiated tumors. Most cases with divergent patterns, especially on needle biopsy, do not differ by more than one pattern. It is reasonable to assign a full

Gleason score even to small foci of cancer on needle biopsy because it has been demonstrated that the grade assigned to these minimal cancers is just as accurate compared to cases with more extensive cancer on biopsy ([Steinberg et al, 1997](#)).

It is not recommended that Gleason score 2 to 4 be assigned for adenocarcinoma of the prostate on needle biopsy, because (1) most tumors graded as Gleason score 2 to 4 on needle biopsy are graded higher when reviewed by uropathology experts ([Steinberg et al, 1997](#)); (2) there is poor reproducibility in the diagnosis of Gleason score 2 to 4 on needle biopsy even among uropathology experts ([Allsbrook et al, 2001](#)); and (3) most important, assigning a Gleason score of 2 to 4 to an adenocarcinoma on needle biopsy is not necessarily associated with such favorable findings at radical prostatectomy ([Epstein, 2000](#)). Whereas 24% of pathologists rendered a diagnosis of Gleason score 2 to 4 on biopsy in 1991, this

BOX 110-1 2005 International Society of Urological Pathology Modified Gleason System**PATTERN 1**

Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3)

PATTERN 2

Like pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration
Glands are more loosely arranged and not quite as uniform as Gleason pattern 1

PATTERN 3

Discrete glandular units
Typically smaller glands than seen in Gleason pattern 1 or 2
Infiltrates in and among non-neoplastic prostate acini
Marked variation in size and shape

PATTERN 4

Fused microacinar glands
Ill-defined glands with poorly formed glandular lumens
Large cribriform glands
Cribriform glands
Hypernephromatoid

PATTERN 5

Essentially no glandular differentiation, composed of solid sheets, cords, or single cells
Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

decreased to 2.4% in 2001 and is even much less common in today's practice (Ghani et al, 2005). Consequently, a problem with the current system is that Gleason score 6 is typically the lowest grade assigned on biopsy material. However, the Gleason scale ranges from 2 to 10, so patients are consequently unduly concerned when told they have Gleason score 6 cancer on biopsy; they logically but incorrectly assume that their tumor is in the midrange of aggressiveness. Another consequence of the updated Gleason grading system is that there is an expanded definition of Gleason pattern 4 to include a broader range of histologic patterns and a greater proportion of cases. There are several prognostic consequences of the reclassification of many former Gleason score 6 tumors to Gleason score 7 in the modified system. Gleason score 6 tumors are currently more homogeneous and have a uniformly better prognosis. For example, virtually no organ-confined Gleason score 6 tumor is associated with progression after radical prostatectomy, whereas this occasionally occurred using the original Gleason system (Hernandez et al, 2008). In addition, Gleason score 6 carcinomas using the updated Gleason system do not have the ability to metastasize to lymph nodes (Ross et al, 2012). Multiple cores of Gleason score 6 still correlate with favorable findings at radical prostatectomy (Ellis et al, 2013). Using the modified Gleason system, in a study from Johns Hopkins of 6462 men, almost 95% and 97% of patients with Gleason score 6 cancer at biopsy and radical prostatectomy (no tertiary pattern 4 at radical prostatectomy), respectively, were predicted to be cured of disease at 5 years following radical prostatectomy (Pierorazio et al, 2013a). Using the modified Gleason system, this study showed that Gleason score 3 + 4 = 7 tumor has a very favorable prognosis with an estimated 5-year biochemical-free survival of 83% and 88% for biopsy and radical prostatectomy, respectively. Gleason scores 9 to 10 tumor had

almost twice the risk of progression compared to Gleason score 8. Oversimplification of the Gleason grade classification, such as combining Gleason scores 8 to 10 or classifying patients into low-, intermediate-, and high-risk categories based on Gleason scores less than 7, 7, and greater than 7, loses critical prognostic information. A more contemporary grouping of Gleason scores based on differing prognoses is as follows: Gleason scores ≤6; 3 + 4 = 7; 4 + 3 = 7; 8; 9 to 10, which reflect Grade Groups I to V (Pierorazio et al, 2013b). At the end of every biopsy report that shows carcinoma, we add the following:

The overall Gleason score for this case is based on the core with the highest Gleason score. Gleason scores can be grouped and range from Grade Group I (most favorable) to Grade Group V (least favorable).

Gleason score less than or equal to 6: Grade Group I

Gleason score 3 + 4 = 7: Grade Group II

Gleason score 4 + 3 = 7: Grade Group III

Gleason score 8: Grade Group IV

Gleason score 9 to 10: Grade Group V

The Gleason grade on biopsy material has also been shown to correlate fairly well with that of the subsequent prostatectomy specimen (Fine and Epstein, 2008). In general, a Gleason score less than or equal to 6 on biopsy corresponds to a Gleason score less than or equal to 6 in the radical prostatectomy in about 65% of cases. An unavoidable cause of discrepant grading between the biopsy and subsequent prostatectomy specimen is that caused by sampling error by the needle biopsy. The following factors are associated with upgrading from the needle biopsy to the radical prostatectomy: increased cancer extent on biopsy; increased serum PSA levels, smaller prostates; and fewer cores sampling the prostate (Epstein et al, 2012).

Some men with low-grade cancers develop high-grade tumors after several years. It is not clear whether the residual low-grade cancer progressed or whether there was a subsequent development of a multifocal, more aggressive tumor. Although, in general, larger tumors are high grade and small tumors are low grade, exceptions occur (Epstein et al, 1994a). There is a tendency to hypothesize that tumors begin as low-grade tumors and, on reaching a certain size, dedifferentiate into higher-grade lesions, accounting for the relationship between size and grade. Alternatively, high-grade tumors may be high grade at their inception but are detected at an advanced size because of their rapid growth. Similarly, low-grade tumors may evolve so slowly that they tend to be detected at lower volumes. From a practical standpoint, during a 2- to 3-year period after biopsy, more than 80% of men's prostate cancer grades remain stable (Sheridan et al, 2008).

Assessment of Needle Biopsy Specimens

Processing

When biopsy specimens are taken from different sextant areas of the prostate, they should be submitted to pathology in separate containers (Box 110-2). As long as cores are submitted in separate containers or the cores are in the same container yet specified by the urologist as to their location (i.e., by different colored inks), pathologists should assign individual Gleason scores to separate cores (Epstein et al, 2005). If cores are combined in a container without designation, some pathologists still attempt to assign separate scores for each core and others just provide an overall Gleason score as if all the cores were one long core.

Differential Diagnosis

The underdiagnosis of limited adenocarcinoma of the prostate on needle biopsy is one of the most frequent problems in prostate pathology (Epstein, 2004). There are also numerous benign mimickers of adenocarcinoma of the prostate (Srigley, 2004). In some of these cases, the use of antibodies to high-molecular-weight cytokeratin and p63 may resolve the diagnosis (Wojno and Epstein,

BOX 110-2 Reasons to Submit Needle Cores in Separate Jars for Each Sextant Site

- In “atypical” cases, the atypical site can be preferentially targeted on repeated biopsy, in addition to other sites.
- More specific location of cancer helps pathologists target additional tissue or block sampling in cases with no cancer on initial sampling of radical prostatectomy.
- Knowledge of sextant site helps pathologists to recognize certain diagnostic pitfalls (i.e., seminal vesicle tissue or central zone mimicking high-grade prostatic intraepithelial neoplasia at the base and Cowper gland mimicking cancer at the apex).
- With brachytherapy, this helps target areas where extra seeds can be distributed.
- Having a maximum of two cores per block or slide preparation with complete visualization of cores helps prevent missing small foci of cancer that could be “buried” in the paraffin block.
- Maximum of two cores per block or slide helps prevent core fragmentation where one cannot determine the number of involved cores, their percentage involvement, and the highest grade of cancer in the case.

1995). Benign glands contain basal cells and are labeled with these antibodies, whereas prostate cancer shows no staining. Immunohistochemistry with antibodies to α -methylacyl-CoA racemase, which preferentially labels prostatic carcinoma and HGPIN, can also be used as an adjunct in the diagnosis of limited cancer, yet pathologists must be careful because false-positive and false-negative staining with α -methylacyl-CoA racemase have been reported (Jiang et al, 2004, 2005). Nuclear immunoreactivity for ERG can be used as a surrogate for TMPRSS2:ERG gene fusion, a specific molecular event seen in approximately 50% of prostate carcinomas. The major limitation of this technique is that, on limited foci of carcinoma on needle biopsy, the sensitivity may be somewhat lower, to around 30% to 40%, and positivity does not exclude HGPIN (Tomlinson et al, 2012; Shah et al, 2013).

In certain cases, there are findings suggestive of, but not diagnostic of, carcinoma. The incidence of atypical needle biopsy specimens is about 5% (Epstein and Herawi, 2006). Pathologists should sign out atypical cases descriptively as “a focus of atypical glands” rather than using ambiguous terminology such as “atypical hyperplasia” or “atypical small acinar proliferation.” A comment should be added in the report describing why the focus is suggestive of cancer yet is not diagnostic, with a recommendation for repeat biopsy. In this way, there is no confusion in the urologist’s mind that the lesion is likely to be infiltrating cancer but that the pathologist is not comfortable in establishing the diagnosis. The likelihood of cancer after an atypical diagnosis is about 40% to 50% (Iczkowski et al, 1997; Chan and Epstein, 1999; Epstein and Herawi, 2006). Surprisingly, in men with a previous atypical biopsy result, the level of serum PSA elevation or the results of digital rectal examination do not correlate with the risk of a subsequent biopsy specimen showing carcinoma. Regardless of the serum PSA level, all patients with an initial atypical diagnosis on needle biopsy should undergo a repeat biopsy, typically within 6 months. Cases diagnosed as atypical have the highest likelihood of being changed on expert review, and urologists should consider sending such cases for consultation to attempt to resolve the diagnosis as either definitively benign or malignant before subjecting the patient to repeat biopsy (Chan and Epstein, 2005).

Prognosis

Adverse findings on needle biopsy, in terms of Gleason grade and tumor extent, generally predict adverse findings accurately in the

radical prostatectomy specimen. However, as a result of sampling error, favorable findings on needle biopsy do not necessarily predict favorable findings in the radical prostatectomy specimen. The ways in which cancer may be measured on needle biopsy include number of positive cores, total millimeters of cancer among all cores, percentage of cancer per core, and total percentage of cancer in the entire specimen. An equal number of studies claim superiority of one technique over the other, with no one technique adopted uniformly (Epstein, 2011). It is proposed that pathologists report the number of positive cores along with one other measurement of tumor extent. By combining needle biopsy grade with clinical stage and serum PSA values, the extent of cancer within the prostate can be more accurately predicted (Makarov et al, 2007).

Although there are some conflicting data, the cumulative analysis shows a higher incidence of EPE in men with perineural invasion on prostate needle biopsy (Cozzi et al, 2013). Perineural invasion on biopsy is prognostic in men undergoing external-beam radiotherapy, but is less so with brachytherapy (Harnden et al, 2007). Perineural invasion should be noted on the biopsy pathology report. There are data that atrophy and associated inflammation are linked with prostate carcinogenesis (DeMarzo et al, 2003). However, the hypothesis is that these factors are involved in the initiation of prostate cancer and are not proximately related to cancer by the time atrophy is identified on needle biopsy. Atrophy of all morphologic types is very common on needle biopsy and is not associated with an increased risk of cancer or PIN on subsequent biopsy (Postma et al, 2005).

Probably the most powerful predictor of prognosis on biopsy is the Gleason score, which can be used to predict multiple outcomes including (1) pathologic stage; (2) side-specific EPE; (3) EPE into the neurovascular bundle; (4) progression after radical prostatectomy; (5) candidates for brachytherapy; (6) prognosis after radiotherapy; (7) candidates for active surveillance; (8) intervention criteria following active surveillance; (9) prognosis following cryotherapy; (10) prognosis following high-intensity focused ultrasound (HIFU); and (11) candidates for focal therapy (Epstein, 2013).

Assessment of Transurethral Resection Specimens**Processing**

The recommended system is based on the percentage of the specimen involved by tumor, with 5% being the cutoff between stage T1a and T1b (Cantrell et al, 1981). All stage T1b tumors are detected by the processing of between 6 and 8 cassettes of a TUR specimen. By processing 8 to 10 cassettes, more than 90% of stage T1a lesions are identified (Newman et al, 1982; Murphy et al, 1986; Vollmer, 1986; Rohr, 1987). Depending on the institution, all TUR tissues may be examined in men younger than 65 years in whom aggressive therapy for stage T1a disease might be pursued.

Differential Diagnosis

One of the most common lesions to be confused with low-grade adenocarcinoma is adenosis (atypical adenomatous hyperplasia) (Gaudin and Epstein, 1994, 1995). Approximately 1.6% of benign TUR specimens and 0.8% of all needle biopsy specimens contain adenosis. It is characteristically found in the transition zone of the prostate, is frequently multifocal, and most often is an incidental finding in TURs performed for urinary obstruction. Although adenosis mimics carcinoma, there is no evidence suggesting that patients with adenosis have an increased risk of harboring or developing adenocarcinoma of the prostate.

Assessment of Radical Prostatectomy Specimens**Assessment**

Within institutions that do not totally embed radical prostatectomy specimens, there are sampling techniques that provide accurate

pathologic staging (Hall et al, 1992; Sehdev et al, 2001). Whole-mount sectioning of the prostate provides more aesthetically pleasing sections for teaching and publication, yet the information obtained by routine sections is identical.

Prognosis

Gleason Score. It is recommended that pathologists assign a separate grade to each dominant tumor nodule. Most often, the dominant nodule is the largest tumor, which is also the tumor associated with the highest stage and highest grade. In the unusual occurrence of a nondominant nodule (i.e., smaller nodule) that is of higher stage, one should also assign a grade to that nodule. If one of the smaller nodules is the highest-grade focus within the prostate, the grade of this smaller nodule should also be recorded. In general, this will be the exception; in most cases, separate grades will be assigned to only one or at most two dominant nodules. The Gleason score at radical prostatectomy correlates well with prognosis. The 5-year postoperative biochemical risk, free of disease, is 96.6%, 88.1%, 69.7%, 63.7%, and 34.5% for Gleason scores less than or equal to 6; 3 + 4 = 7; 4 + 3 = 7; 8; and 9 to 10, respectively (Pierorazio et al, 2013b). It is recommended that in radical prostatectomy specimens, the routine Gleason score, consisting of the most prevalent and the second most prevalent architectural patterns, be recorded along with a note stating that there is a tertiary high-grade pattern (Pan et al, 2000; Trock et al, 2009). The presence of a tertiary higher-grade component is associated with an increased risk of biochemical recurrence, typically raising the risk of recurrence to a level intermediate between those of cancers without a tertiary component in the same Gleason score category and cancers in the next higher Gleason score category.

Lymph Node Metastases. The incidence of lymph node metastases has declined markedly in recent years because earlier tumors are detected by screening techniques. The incidence of nodal metastases is related to the clinical stage, preoperative PSA level, and biopsy grade, with some surgeons not removing pelvic lymph nodes in men with a low risk of metastases. Because the presence of nodal metastases indicates a lack of curability, surgeons may perform staging pelvic lymphadenectomy with frozen sections. When microscopic metastases are identified at the time of frozen section, many urologists abort the radical prostatectomy because the procedure will not be curative. Other urologists perform radical prostatectomy in the face of microscopic metastases for local control if the patient has a relatively long life expectancy. Almost all patients with positive lymph nodes who undergo radical prostatectomy eventually show progression of their disease, indicative of distant occult metastases. The 15-year biochemical-recurrence-free, metastases-free, and cancer-specific survival for men undergoing radical prostatectomy with positive nodes is 7.1%, 41.5%, and 57.5%, respectively. Predictors of biochemical recurrence, metastases, and death from prostate cancer in multivariate analysis include prostatectomy Gleason score and the number and percent of positive lymph nodes, respectively (Pierorazio et al, 2013b). In cases in which the preoperative biopsy Gleason score is less than 8, the time to onset of distant metastases is sufficiently long that our surgeons proceed in these instances with radical prostatectomy even if the nodes are involved (Sgrignoli et al, 1994). Consequently we freeze pelvic nodes only when the biopsy score is 8 to 10. Another option is to freeze nodes only in cases in which the risk of metastases is sufficiently high, based on preoperative parameters.

Extraprostatic Extension and Seminal Vesicle Invasion. The prostatic capsule is not well defined histologically, especially at the apex, the base, and anteriorly (Ayala et al, 1989). Because the prostate lacks a discrete capsule, the term *extraprostatic extension*, rather than *capsular invasion* or *capsular penetration*, is recommended to denote non-organ-confined disease. It can be difficult to recognize EPE because the boundaries where the prostate ends can be vague and the tumor can also induce a dense desmoplastic response in the periprostatic adipose tissue (Epstein, 2001). The degree of EPE varies from only a few glands outside the prostate,

which we term *focal extraprostatic extension*, to cases with more extensive extraprostatic spread, which we designate *nonfocal extraprostatic extension*. The degree of EPE correlates with the risk of progression after radical prostatectomy (Epstein, 2001). Other more objective measurements of quantifying the extent of EPE have been proposed but they correlate well with the subjective “focal” versus “nonfocal” dichotomy, and none have proven sufficiently superior to recommend as the preferred method (Magi-Galluzzi et al, 2011; van Veggel et al, 2011). Seminal vesicle invasion is a much more dire prognostic finding, with a 65% 5-year progression rate after surgery (Epstein, 2001; Pierorazio et al, 2011).

Margins. Novara and Ficarra (2013) reported the mean rate of positive margins in the robotic-assisted radical prostatectomy series, published between 2008 and 2011 (each including >100 cases), to be 15%, which ranged from 6.5% to 32% (Novara and Ficarra, 2013). Only approximately 50% of men with positive margins progress after radical prostatectomy (Epstein et al, 1993). A major source of this discrepancy is that even in cases in which margins histologically appear to be positive, additional tissue removed from the site does not always show a tumor (Epstein, 1990). A few studies have documented the performance of frozen section along the length of the prostate in the region of the neurovascular bundle with a positive intraoperative margin resulting in resection of the ipsilateral neurovascular bundle (Schlomm et al, 2012; von Bodman et al, 2013). In one study, it was noted that it took 5 cryostats with 2 pathologists and 4 technicians to perform one case in about 35 minutes, which is not practical for most laboratories. The technique includes a low false-negative and false-positive rate compared to the permanent sections of the same slides. However, in two studies in which a frozen-section margin was positive in the region of the neurovascular bundle and the bundle was removed, only 23% to 25% of the bundles showed residual cancer. Arguments posited in support of this procedure are (1) without the frozen sections most of these patients would have had the bundles resected because of preoperative high-risk characteristics; and (2) the overall sum of saved neurovascular bundles was markedly higher than the unnecessary secondary wide excisions (Schlomm et al, 2012; von Bodman et al, 2013). The preponderance of studies shows that the distance from tumor to ink does not affect the risk of recurrence, although one conflicting study exists (Epstein, 1990; Epstein and Sauvageot, 1997; Emerson et al, 2005; Bong et al, 2009; Lu et al, 2012). Factors that can aid in the clinician's decision as to whether or not to administer adjuvant radiation therapy are the extent of positive margins and the grade of the tumor at the margins, and these factors have been shown to be prognostic (Chuang and Epstein, 2008; Shikanov et al, 2009; Brimo et al, 2010; Cao et al, 2010; van Oort et al, 2010; Huang et al, 2013).

Positive margins also may arise as a result of the surgical transection of intraprostatic tumor (intraprostatic incision); although also referred to as “capsular incision,” this term is not recommended, as there is no prostatic capsule. The reported incidence of intraprostatic incision ranges from 1.3% to as high as 71% (Epstein, 2001). In my opinion, much of this variation relates to the difficulties described in the preceding text in recognizing EPE. If an extraprostatic tumor associated with a desmoplastic stromal response at a margin is misdiagnosed as organ confined, it will be misclassified as a positive margin because of intraprostatic incision. The other relatively frequent site of intraprostatic incision is in the regions of the neurovascular bundles, where the urologist attempts to preserve the bundle for potency, yet cuts into the prostate. Only if both tumor and benign glands are transected in the same area and are present at the inked margin do I diagnose a positive margin as a result of intraprostatic incision. Intraprostatic incision is associated with an increased risk of postoperative progression equivalent to that associated with focal EPE and a positive margin (Chuang and Epstein, 2008).

In a multivariate analysis, Gleason grade, EPE, and margins of resection are strong independent predictors of biochemical progression.

Tumor Volume. There are conflicting studies regarding whether or not tumor volume independently predicts post-radical prostatectomy progression after grade and pathologic stage are

determined, with most of the larger series not showing prognostic significance (Epstein, 2001). Despite this fact, the International Society of Urological Pathology recommends that some objective measurement of tumor volume be reported in radical prostatectomy specimens (van der Kwast et al, 2011). The Society's rationale is that tumor volume is recorded for cancers in other organ systems. Because tumor volume is not an independent predictor and will in general not affect subsequent therapy, it is my recommendation that if one feels obliged to report a radical prostatectomy tumor, then the simplest and fastest method should be used, such as a rough estimate of the overall percentage of the prostate involved by the tumor.

Perineural and Vascular Invasion. The finding of perineural invasion in a radical prostatectomy specimen is very common, is not prognostic, and should not be included in the pathology report. Vascular invasion is uncommonly identified in radical prostatectomy specimens, seen in 7% of tumors smaller than 4 cc (most tumors seen today at radical prostatectomy are smaller than 2 cc) (McNeal and Yemoto, 1996a). Vascular invasion correlates with other adverse findings (i.e., EPE, grade, margins, tumor volume), yet still offers independent prognostic information beyond those of routinely noted findings (Epstein, 2001; Baydar et al, 2008).

Adenocarcinoma with Treatment Effect

One of the problems with evaluating carcinomas that have been treated with hormone therapy is that the grade often appears artifactually higher (Smith and Murphy, 1994). Pathologists should not assign a Gleason score to carcinomas with treatment effect. However, if other areas of the tumor do not show a pronounced hormone effect, these areas can be Gleason graded. It has been demonstrated that finasteride does not alter the histology of either benign or malignant tissue (Yang et al, 1999; Rubin et al, 2005).

Radiated adenocarcinoma of the prostate may either show no recognizable difference from nonradiated cancer or may show the effects of radiation damage. When signing out postradiotherapy biopsies, they should be diagnosed as either: (1) benign prostate tissue with radiation effect; (2) cancer without treatment effect (a Gleason grade is assigned); or (3) cancer showing treatment effect (no Gleason grade assigned). The latter diagnosis is associated with an equivalent prognosis to a noncancerous diagnosis (Crook et al, 2009). Radiation alters the histologic features of benign prostate tissue so that it may mimic prostate cancer (Bostwick et al, 1982). Radiation atypia in benign prostate glands may persist for a long time (up to 72 months) after the initial treatment, resulting in a significant pitfall in evaluating prostate biopsy specimens (Magi-Galluzzi et al, 2003). If clinicians are aware of such treatment, this information should be provided to the pathologist.

SUBTYPES OF PROSTATE ADENOCARCINOMA

Mucinous adenocarcinomas of the prostate gland behave like usual prostate carcinomas, including a propensity to develop bone metastases with advanced disease (Epstein and Lieberman, 1985; Ro et al, 1990). Mucinous adenocarcinoma of the prostate treated by radical prostatectomy is not more aggressive than nonmucinous prostate cancer (Osunkoya et al, 2008). Even in ordinary adenocarcinomas of the prostate without light microscopic evidence of neuroendocrine differentiation, almost half show neuroendocrine differentiation on evaluation with immunohistochemistry for multiple neuroendocrine markers (di Sant'Agnese, 1992). Most studies do not demonstrate a convincing relationship between the extent of neuroendocrine differentiation in ordinary prostate cancer and prognosis. Small cell carcinomas of the prostate are identical to small cell carcinomas of the lung (Tetu et al, 1989). In approximately 50% of the cases, the tumors are mixed small cell carcinoma and adenocarcinoma of the prostate. The average survival of patients with small cell carcinoma of the prostate is less than a year. There is no difference in prognosis between patients with pure

small cell carcinoma and those with mixed glandular and small cell carcinomas. Small cell carcinomas are not assigned a Gleason grade.

Between 0.4% and 0.8% of prostatic adenocarcinomas arise from prostatic ducts (Epstein and Woodruff, 1986; Christensen et al, 1991). In about 5% of prostatic carcinomas, tumors showing both ductal and acinar differentiation are found. When prostatic duct adenocarcinomas arise in the large primary periurethral prostatic ducts, they may grow as an exophytic lesion into the urethra, most commonly in and around the verumontanum, and this gives rise to either obstructive symptoms or hematuria. Tumors arising in the more peripheral prostatic ducts may present similar to ordinary (acinar) adenocarcinomas of the prostate and may be diagnosed on needle biopsy (Brinker et al, 1999). Tumors are often underestimated clinically because rectal examination findings and serum PSA levels may be normal. Most prostatic duct adenocarcinomas should be regarded as Gleason pattern 4 because of their shared cribriform morphologic features with acinar adenocarcinoma Gleason score 8 and a similar prognosis (Brinker et al, 1999). Exceptions are the PIN-like ductal adenocarcinoma, which is assigned Gleason pattern 3 (Tavora and Epstein, 2008) and the ductal adenocarcinoma with comedonecrosis, which is assigned a Gleason pattern 5. There are conflicting studies regarding whether or not a ductal adenocarcinoma component that is assigned a Gleason pattern 4 (or pattern 5 if accompanied by comedonecrosis) is associated with a worse prognosis than a comparably graded acinar carcinoma (Samaratunga et al, 2010; Seipel et al, 2013). Pure primary squamous carcinoma of the prostate is rare and is associated with poor survival (Parwani et al, 2004). These tumors develop osteolytic metastases and do not respond to hormonal therapy. More commonly, squamous differentiation occurs in the primary and metastatic deposits of adenocarcinomas that have been treated with estrogen therapy. Sarcomatoid carcinomas (carcinosarcomas) have also been reported within the prostate and have a dismal prognosis (Hansel and Epstein, 2006).

Mesenchymal Tumors

Sarcomas of the prostate account for 0.1% to 0.2% of all malignant prostatic tumors (Hansel et al, 2007). Rhabdomyosarcomas are the most frequent mesenchymal tumor within the prostate and are seen almost exclusively in childhood. Leiomyosarcomas are the most common sarcomas involving the prostate in adults (Cheville et al, 1995). A spindle cell lesion that can occur at any age and can closely simulate a leiomyosarcoma is an inflammatory myofibroblastic tumor, which may occur soon after TUR or without a history of TUR (Montgomery et al, 2006). There are also mesenchymal tumors of the prostate arising from the unique prostatic specialized stroma. These lesions range from prostatic stromal tumors of uncertain malignant potential (STUMP) to prostatic stromal sarcomas. On histologic examination, these lesions are variable; one subtype resembles a tumor seen in the breast and is termed *phyllodes tumor of the prostate* (Herawi and Epstein, 2006). Although most cases of prostatic STUMP do not behave in an aggressive fashion, occasional cases have been documented to recur rapidly after resection; cases with mixed STUMP and sarcomas exist, and a few STUMP have progressed to stromal sarcoma. Although many STUMP may behave in an indolent fashion, their unpredictability in a minority of cases and the lack of correlation between different histologic patterns of STUMP and sarcomatous dedifferentiation warrant close follow-up and consideration of definitive resection in younger individuals. Stromal sarcomas have the potential for metastatic behavior.

Urothelial Carcinoma

Primary urothelial carcinoma of the prostate without bladder involvement accounts for 1% to 4% of all prostate carcinomas (Sawczuk et al, 1985). Primary urothelial carcinomas of the prostate show a propensity to infiltrate the bladder neck and the surrounding soft tissue such that more than 50% of the patients present with stage T3 or T4 tumors (Greene et al, 1976). Twenty

percent of the patients present with distant metastases, with the bone (predominantly osteolytic), the lung, and the liver being the most common sites.

More commonly, urothelial carcinoma involves prostatic ducts and acini in patients with a history of carcinoma in situ (CIS) of the bladder who have been treated for a period of months to years with intravesical topical chemotherapy (Schellhammer et al, 1977; Mahadevia et al, 1986; Wood et al, 1989; Njinou Ngninkeu et al, 2003). Between 35% and 45% of cystoprostatectomies performed for urothelial carcinoma contain prostatic involvement. However, this number is dependent on the amount of histologic sampling of the prostate tissue and may be much higher in completely mapped specimens. If cystoprostatectomy is performed and only intraductal urothelial carcinoma is present, the prostatic involvement does not worsen the prognosis, which is determined by the stage of the bladder tumor (Esrig et al, 1996). Intraductal urothelial carcinoma of the prostate appears to involve the prostate by direct extension from the overlying urethra, which is usually involved by CIS. Intraductal and infiltrating urothelial carcinoma involving the prostate tends to be seen in higher-stage bladder tumors, in which the patients have a poor prognosis attributable to either advanced bladder or prostatic disease. A minority of these cases will have low-stage bladder tumor and a poorer prognosis, demonstrating the adverse effect of prostatic stromal infiltration (Esrig et al, 1996). **Urothelial carcinoma involving the prostate is substaged into pT1 when invasive carcinoma involves the suburethral tissue or pT2 when there is CIS involving prostatic acini with prostatic stromal invasion.** It is not clear how to report the staging of both the bladder urothelial carcinoma and prostatic involvement in cystoprostatectomy specimens. I report the findings in both the bladder and prostate, assigning separate stages for each organ. Alternatively, one can just report the bladder or prostatic stage, depending which is higher, and then describe the extent of disease in the other organ. **Extensive sampling of the periurethral area in cystoprostatectomy specimens performed for urothelial carcinoma is necessary to identify and to evaluate the prostate for urothelial carcinoma.**

Finally one may find direct invasion from bladder urothelial carcinoma into the stroma of the prostate. The distinction between poorly differentiated urothelial carcinoma and poorly differentiated adenocarcinoma of the prostate can be difficult. Approximately 95% of poorly differentiated prostatic adenocarcinomas show PSA staining, although it may be focal (Chuang et al, 2007). In some cases of poorly differentiated prostatic adenocarcinomas, there may be weak or negative PSA staining where the tumor reacts to a greater degree with newer prostate-specific markers, including p501S (prostein) and NKX 3.1 (Chuang et al, 2007). Although CK7 and CK20 are more frequently seen in urothelial carcinoma as compared to adenocarcinoma of the prostate, they may also be positive in adenocarcinoma of the prostate. The most sensitive and specific marker that labels urothelial carcinoma and not prostate carcinoma is GATA3 (80%) (Higgins et al, 2007; Chang et al, 2012). Less sensitive markers include uroplakin and thrombomodulin (49% to 69% sensitivity) and p63 and high-molecular-weight cytokeratin (60% to 70% sensitivity) (Chuang et al, 2007).

Miscellaneous Malignant Tumors

Primary prostatic lymphoma without lymph node involvement appears to be much less common than secondary infiltration of

the prostate (Bostwick and Mann, 1985). The most common form of leukemic involvement of the prostate is that of chronic lymphocytic leukemia, although monocytic, granulocytic, and lymphoblastic leukemias have also been found in the prostate (Dajani and Burke, 1976).

KEY POINTS

- LGPIN should not be commented on in diagnostic reports, because the diagnosis is not reproducible among pathologists and it lacks clinical significance.
- For patients diagnosed with HGPIN on 1 core of an extended initial core sampling, repeat biopsy within the first year is unnecessary in the absence of other clinical indicators of cancer. It may be reasonable to rebiopsy these men 3 years later because of the lack of substantial data on the long-term implications of focal HGPIN on biopsy. Repeat biopsy within a year is recommended following an initial biopsy showing that 2 or more cores are involved by HGPIN.
- Regardless of the serum PSA level, all patients with an initial atypical diagnosis on needle biopsy should undergo repeat biopsy; the risk of cancer is approximately 40%, and clinical findings are not helpful in predicting who is more likely to have cancer.
- Cases diagnosed as atypical have the highest likelihood of being changed on expert review. Urologists should consider sending such cases for consultation to attempt to resolve the diagnosis as either definitively benign or malignant before subjecting the patient to repeat biopsy.
- Tumor volume measured in the radical prostatectomy specimen does not independently predict postsurgical progression after the grade, the pathologic stage, and the margins are considered, and it should not be required for routine pathologic analysis.
- Gleason grade, whether it is assessed on needle biopsy, TUR, or radical prostatectomy specimens, remains one of the most influential prognostic factors.

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The complete reference list is available online at www.expertconsult.com.



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Diagnosis

Prostate cancer rarely causes symptoms at an early stage. The presence of symptoms suggests locally advanced or metastatic disease. Manifestations of locally advanced prostate cancer include obstructive urinary symptoms, ureteral obstruction causing renal failure, hematospermia or decreased ejaculate volume, and, rarely, impotence. Manifestations of metastatic disease include bone pain, pathologic fractures, anemia, and lower extremity edema; less common are malignant retroperitoneal fibrosis, paraneoplastic syndromes, disseminated intravascular coagulation (DIC), and paralysis. Locally advanced and metastatic disease are uncommon presentations because of widespread screening with prostate-specific antigen (PSA) testing and digital rectal examination (DRE). A histologic diagnosis of prostate cancer is typically made by prostate needle biopsy using transrectal ultrasound (TRUS) guidance before any symptoms develop.

After a diagnosis of prostate cancer, the goal of staging is the accurate determination of disease extent and risk for management decisions and prognostication. In addition to PSA level and DRE, the pathologic features on prostate biopsy (grade and volume of cancer) help inform management decisions. Imaging studies also may be used during the staging process to evaluate the locoregional extent of disease and/or to rule out metastases.

This chapter will review diagnostic and staging modalities for prostate cancer.

DIAGNOSIS

Screening

General Concepts of Screening

Screening refers to testing for disease in healthy, asymptomatic populations; whereas diagnosis is the identification of disease among individuals with signs or symptoms. The principal goal of screening is to improve overall health outcomes by identifying and treating disease at an earlier stage. Despite the common misperception that early diagnosis through screening is invariably beneficial, it also has the potential for harm (Welch, 2004). Strong evidence indicates that prostate cancer screening reduces the rates of advanced disease at the time of diagnosis (van der Cruijsen-Koeter et al, 2006; Aus et al, 2007) and more recent data shows that it also reduces prostate cancer mortality (Hugosson et al, 2010; Schröder et al, 2012), but controversy exists regarding the balance of benefit and harm (U.S. Preventive Services Task Force, 2008; Barry, 2009). The precise balance of benefits and harms is highly dependent on the patient's characteristics and preferences (Heijnsdijk et al, 2012).

During the PSA era, the mortality rate from prostate cancer has declined by more than 40% (Surveillance, Epidemiology, and End Results [SEER] Program), along with a 75% reduction in the proportion of advanced-stage disease at diagnosis. It was estimated by mathematical modeling that PSA screening could have accounted for 45% to 70% of this reduction in prostate cancer mortality in the

Staging

United States (Etzioni et al, 2008). However, randomized trials comparing the disease-specific outcomes of men who are screened and those who are not represent the highest level of evidence for screening.

Randomized Trials

The Prostate, Lung, Colon, and Ovary (PLCO) trial of the National Cancer Institute (NCI) and the European Randomized Trial of Prostate Cancer Screening (ERSPC) were initiated in 1993 to compare prostate cancer-specific mortality (primary end point) between screened and unscreened arms (Auvinen et al, 1996; de Koning et al, 2002; Schröder, 2003; Andriole et al, 2004). Reductions in high-grade cancer and locally advanced/metastatic disease with serial screening were reported in the ERSPC (van der Cruijsen-Koeter et al, 2006; Aus et al, 2007), as well as a 21% reduction in prostate cancer-specific mortality among those screened compared to controls at a median follow-up of 11 years (Schröder et al, 2014). However, in the ERSPC it was estimated that to prevent one prostate cancer death would require inviting for screening 781 men and diagnosing an additional 27 men at 13 years (Schröder et al, 2014). By comparison, there was no difference in prostate cancer mortality between the screened and control arms of the PLCO at a median follow-up of 13 years (Andriole et al, 2012). Further, the disparate findings between the studies may result from high rates of screening in the control arm of the PLCO before and during the trial (contamination) and lower power to detect a mortality difference given that the PLCO had approximately three-fold fewer events than the ERSPC (Barry, 2009).

These randomized trials emphasize the potential for overdiagnosis (detection of cancers that would have otherwise remained undetected) and overtreatment of prostate cancer with screening. Overtreatment is especially concerning among older men (older than 65 years), for whom treatment was associated with minimal benefit in a randomized trial of surgery versus watchful waiting (Bill-Axelson et al, 2011). Given that the average age at diagnosis today is approximately 66 years, the risk for overtreatment is high (National Cancer Institute, 2013).

Specialty Group Recommendations

Professional groups have published statements and guidelines on prostate cancer screening (Lim and Sherin, 2008; Lin et al, 2008; U.S. Preventive Services Task Force, 2008; National Comprehensive Cancer Network, 2014). In 2008 the U.S. Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to assess the balance of benefit and harm of screening among men 75 years of age or younger, whereas screening was not recommended for men 75 years or older. Subsequently, the USPSTF issued a grade D recommendation against prostate cancer screening. The American College of Preventive Medicine recommends against routine population screening with PSA and DRE (Lim and Sherin, 2008) and

suggests shared decision making for men 50 years of age or older with a life expectancy greater than 10 years. The American Cancer Society recommends that men with at least a 10-year life expectancy should have an opportunity to make an informed decision with their health care provider about prostate cancer screening beginning at age 50 for average-risk men and before age 50 for groups at higher risk (Wolf et al, 2010). Previously, the American Urological Association (AUA) recommended annual prostate cancer screening beginning at 50 years of age for average-risk men and earlier for men at higher risk (positive family history or black race). In 2013 the AUA issued updated guidelines that recommend shared decision making about screening for men 55 to 69 years of age (American Urological Association, 2013a). Based on the ERSPC, they suggest that a 2-year screening interval would preserve the benefits and reduce harms from screening. The National Comprehensive Cancer Network (2014) recommends offering baseline PSA screening at 40 years of age with the frequency of follow-up testing based on PSA test results. Similarly, the Memorial Sloan Kettering Cancer Center guidelines (2013) recommend performing a baseline PSA test between ages 45 and 49 and using PSA levels to guide screening intervals. More recently, the European Association of Urology adopted a risk-adapted approach using the baseline PSA level at 40 to 45 years of age to guide the subsequent screening interval (Heidenreich et al, 2013). For example, if the PSA level is greater than 1 ng/mL, screening should be done at 2- to 4-year intervals; whereas longer intervals up to 8 years can be used for men with a low baseline level. Overall, the appropriate age to start and discontinue screening (Ross et al, 2005; Catalona et al, 2006; Schaeffer et al, 2009) and the appropriate interval between screens will continue to be a matter of debate as additional randomized trials to address these questions are logistically unlikely (Carter et al, 1997a; Ross et al, 2000; Hugosson et al, 2003b).

Despite the controversy associated with prostate cancer screening and disparate recommendations from professional organizations, opportunistic prostate cancer screening is highly prevalent in the United States (Lu-Yao et al, 2003; Sirovich et al, 2003; Ross et al, 2004; Schwartz et al, 2004; Chan et al, 2006; Walter et al, 2006). Although prostate cancer screening remains controversial, men who present for periodic health examinations should be made aware of the availability of the PSA test so that they can make an informed decision whether to be screened.

Diagnostic Modalities

Digital Rectal Examination

Before the availability of PSA testing, physicians relied solely on DRE for early detection of prostate cancer (Cooner et al, 1990; Catalona et al, 1994b; Ellis et al, 1994; Schröder et al, 1998; Vis et al, 2001; Okotie et al, 2007). DRE has only fair reproducibility in the hands of experienced examiners (Smith and Catalona 1995) and misses a substantial proportion of early cancers (Cooner et al, 1990; Catalona et al, 1994b; Ellis et al, 1994). It has been suggested that the value of DRE for screening at PSA levels below 3.0 ng/mL is limited (Schröder et al, 1998; Vis et al, 2001). Because of the risk for prostate cancer among men with abnormalities on DRE and the simplicity of the examination, most urologists use PSA and DRE together for prostate cancer detection.

Further, PSA testing improves the positive predictive value (PPV) of DRE for cancer (Schröder et al, 1998). The PPV of DRE ranged from 4% to 11% in men with PSA levels of 0 to 2.9 ng/mL and from 33% to 83% in men with PSA levels of 3 to 9.9 ng/mL or greater (Schröder et al, 1998).

Overall, when DRE and PSA tests are used in prostate cancer screening, detection rates are higher with PSA testing than with DRE and highest with the tests together (Catalona et al, 1991). Because DRE and PSA tests do not always detect the same cancers (Okotie et al, 2007), the tests are complementary. In addition, many contemporary nomograms incorporate DRE findings to provide more personalized projections of prostate cancer risk (Thompson et al, 2006).

Prostate-Specific Antigen

PSA is a member of the human kallikrein gene family, is secreted in high concentrations (milligrams per milliliter) into seminal fluid, and circulates in bound (complexed) and unbound (free) forms that can be measured using assays approved by the U.S. Food and Drug Administration (FDA).

Factors Influencing Prostate-Specific Antigen. Serum PSA levels vary with age, race, and prostate volume. African-Americans without prostate cancer have higher PSA values than whites (Morgan et al, 1996; Fowler et al, 1999). PSA increases 4% per milliliter of prostate volume; and 30% and 5% of the variance in PSA levels can be accounted for by prostate volume and age, respectively (Oesterling et al, 1993).

PSA expression is strongly influenced by androgens (Young et al, 1991; Henttu et al, 1992). Serum PSA becomes detectable at puberty with increasing levels of luteinizing hormone and testosterone (Vieira et al, 1994). In hypogonadal men with low testosterone levels, serum PSA level may be low because of decreased expression and may not reflect the presence of prostate disease such as cancer (Morgentaler et al, 1996).

Metabolic factors can influence serum PSA levels. Obese men have slightly lower PSA levels than nonobese men (Baillargeon et al, 2005), possibly because of hemodilution (Bañez et al, 2007). Statin use may reduce PSA levels (Hamilton et al, 2008).

Another factor that can influence PSA levels includes the assay that is used in the measurement, potentially resulting in pseudo-acceleration or pseudo-deceleration if different assays are used for serial measurements (Loeb et al, 2008a). Recent studies have suggested that genetic factors may influence PSA levels and have raised the possibility of genetically adjusted PSA values in the future (Gudmundsson et al, 2010; Helfand et al, 2013).

Overall, the presence of prostate disease (prostate cancer, benign prostatic hyperplasia [BPH], and prostatitis) is the most important factor affecting serum PSA levels (Wang et al, 1981; Ercole et al, 1987; Dalton, 1989; Nadler et al, 1995). Although PSA elevations may indicate the presence of prostate disease, not all men with prostate disease have elevated PSA levels and PSA elevations are not specific for cancer.

It is postulated that serum PSA elevations occur from disruption of the normal prostatic architecture, allowing PSA to gain access to the circulation. This can occur in the setting of prostate disease (BPH, prostatitis, prostate cancer) and with prostate manipulation (e.g., prostate massage, prostate biopsy, transurethral resection) (Klein and Lowe, 1997). Although DRE can lead to slight increases in serum PSA level, the resultant change in PSA values falls within the error of the assay and rarely causes false-positive test results (Crawford et al, 1992).

Studies examining the effect of ejaculation on serum PSA have reported conflicting results (Simak et al, 1993; Kirkali et al, 1995; Tchetgen et al, 1996; Heidenreich et al, 1997; Herschman et al, 1997; Stenner et al, 1998; Yavasoglu et al, 1998). A repeat PSA test after 48 hours of sexual abstinence may be helpful for interpreting serum PSA levels that are minimally elevated.

Prostate-directed treatments (for BPH or prostate cancer) can lower serum PSA levels by decreasing the volume of prostatic epithelium available for PSA production and by decreasing the amount of PSA produced per cell (Shingleton et al, 2000).

5 α -Reductase inhibitors that are used for BPH treatment have been shown to lower PSA levels, including both type 2 isoenzyme inhibitors (finasteride) and dual type 1 and 2 isoenzyme inhibitors (dutasteride) (Guess et al, 1993; Roehrborn et al, 2002). Finasteride 1 mg (Propecia) used for male pattern hair loss (androgenic alopecia) results in the same decline in serum PSA levels as the 5-mg dosage used for the treatment of BPH (D'Amico and Roehrborn, 2007).

Men initiating treatment with 5 α -reductase inhibitors should first have a baseline PSA measurement and should be followed with serial measurements. Although the PSA level is often multiplied by 2 to estimate the "true" PSA level of a patient who has been taking a 5 α -reductase inhibitor for 12 months or more (Andriole et al,

1998), the PSA response to finasteride treatment can be highly variable (Marks et al, 2006). It has been suggested that the PSA should instead be multiplied by a factor of 2.3 after 2 years and 2.5 after 7 years of treatment (Etzioni et al, 2005; Thompson et al, 2007; Walsh, 2008). Because this “moving target” can complicate the use of PSA levels in daily clinical practice, some have recommended using the PSA nadir on finasteride as the new baseline and performing a biopsy for subsequent PSA increases (Morgentaler, 2007).

Surgical therapy for BPH can lead to reductions in the serum PSA level (Shingleton et al, 2000) and “reset” the PSA baseline to a variable extent by removing the main contributor to PSA production (transition zone).

Finally, prostate cancer treatments (medical or surgical) such as manipulation of the hormonal axis (e.g., luteinizing hormone-releasing hormone agonists, orchiectomy), radiation therapy, radical prostatectomy, and other ablative techniques (e.g., cryotherapy) lead to reductions in PSA levels.

The interpretation of PSA values should always take into account age, the presence of urinary tract infection or prostate disease, recent diagnostic procedures, and prostate-directed treatments.

Clinical Use for Diagnosis. The initial assays for PSA that were approved by the FDA in 1994 for early detection of prostate cancer detected both free PSA (fPSA) and PSA complexed (cPSA) to α 1-antichymotrypsin (ACT). Thus measurement of fPSA and cPSA by these assays is generally referred to as the serum PSA level (Smith et al, 1996). Specific assays that detect fPSA alone and PSA complexed to ACT alone have been evaluated and approved for prostate cancer detection (see later discussion).

It is now well established that the use of PSA values increases the detection of prostate cancers that are more likely to be organ-confined when compared to detection without PSA (Thompson et al, 1987; Mueller et al, 1988; Chodak et al, 1989; Rietbergen et al, 1999; Hoedemaeker, 2000). Observational studies and randomized trials have shown that both the future risk for prostate cancer and

the chance of finding cancer on a prostate biopsy increase incrementally with the serum PSA level (Catalona et al, 1991; Brawer et al, 1992; Labrie et al, 1992; Catalona et al, 1994a; Gann et al, 1995; Fang et al, 2001; Thompson et al, 2004; Andriole et al, 2005; Whittemore et al, 2005; Loeb et al, 2006; Lilja et al, 2007).

Gann and associates (1995) were the first to demonstrate the association between the baseline PSA level and subsequent prostate cancer detection, which has been verified by others (Fang et al, 2001; Antenor et al, 2004; Whittemore et al, 2005; Loeb et al, 2006). A recent study from the Malmo Preventive Project confirmed that baseline PSA measurements in the 40s predict the risk for prostate cancer metastasis and death more than 25 years later (Vickers et al, 2013).

In addition to predicting future risk, PSA is directly associated with the present risk for prostate cancer. The probability of detecting prostate cancer on biopsy increases directly with PSA across the full spectrum of PSA levels (Table 111-1) (Thompson et al, 2004).

In summary, both PSA and DRE are used to assess prostate cancer risk in conjunction with other clinical factors.

Triggers for Biopsy. The choice of a PSA threshold for recommending a prostate biopsy is controversial (Catalona et al, 1994a; Gann et al, 1995; Carter, 2004; Nadler et al, 2005; Thompson et al, 2005) and has previously been reviewed (Schröder et al, 2008). Gann and associates (1995) pointed out that “dichotomization of PSA results into normal and abnormal obscures important information contained in levels below the usual cutoff.” Data from the Prostate Cancer Prevention Trial clearly show that the risk for prostate cancer is continuous as PSA increases (Thompson et al, 2005). Some investigators have recommended against referring to PSA as “elevated” or “abnormal.”

The use of higher PSA thresholds risks missing important cancers during the window for cure, whereas the use of lower thresholds increases the proportion of unnecessary biopsies and overdiagnosis. Although PSA was initially approved using 4 ng/mL as the upper

TABLE 111-1 Prostate Cancer Detection as a Function of Serum Prostate-Specific Antigen Level and Digital Rectal Examination Findings in Contemporary Series

PSA LEVEL (ng/mL)	DRE FINDINGS*	CANCER DETECTION RATE (%)†	CANCER YIELD ON BIOPSY (%)‡	RATE OF HIGH-GRADE CANCER ON BIOPSY (%)§
0-1	–		8.8	0.9
1-2	–		17.0	2.0
0-2	–		12	1.4
		0.7	8	
2-4	–		15-25	5.2
		2	21	
4-10	+	11	17-32	4.1
		11-27	45-51	11.7
>10	–	41	43-65	19.4
	+	31-76	70-90	50.5
<4	–		15	2.3
	+	1-3	13-17	
>4	–	14	23-38	5.8
	+	14-38	55-63	20.6

*–, DRE nonsuspicious for cancer; +, DRE suspicious for cancer.

†Cancer detection rate is the number of cancers found in those screened (total number of detected cancers divided by the total number of men screened).

‡Cancer yield is the total number of cancers detected divided by the total number of men undergoing a biopsy. For digital rectal examination (DRE) (–) this indicates the positive predictive value of prostate-specific antigen (PSA) at a specified level when the DRE is not suspicious for cancer; for DRE (+) it is the positive predictive value of a suspicious DRE when the PSA is at a specified level.

§Gleason score of 7 or more.

Data in table extracted from the results of contemporary series (Crawford et al, 1996; Catalona et al, 1998; Schröder et al, 1998; Thompson et al, 2004; Andriole et al, 2005).

limit of normal, many clinicians subsequently adopted lower thresholds (2.5 to 3 ng/mL) to trigger a biopsy. In the ERSPC, most centers used a threshold of 3 ng/mL to trigger a prostate biopsy. However, a higher cutoff, such as 10 ng/mL, was recently suggested to reduce the potential harms for men older than 70 years of age (American Urological Association, 2013b).

A PSA level that is considered suspicious for prostate cancer should be remeasured before performing a prostate biopsy because of fluctuations in PSA levels that could create false-positive elevations (Eastham et al, 2003). However, according to the Choosing Wisely Campaign, empirical antibiotics should not be given to patients exclusively for an elevated PSA without any other urinary symptoms (American Urological Association, 2013b).

Numerous organizations now recommend using PSA together with other methods of risk assessment, such as family history, race, and DRE findings (Murphy et al, 2014).

Prostate-Specific Antigen Derivatives and Molecular Forms

Numerous variations on PSA-based screening have been proposed to improve test performance, including the adjustment of the PSA level for total prostate volume (PSA density [PSAD]) (Babaian et al, 1990; Veneziano et al, 1990; Littrup et al, 1991; Benson et al, 1992a, 1992b; Bazinet et al, 1994; Rommel et al, 1994; Catalona et al, 2000b; Djavan et al, 2002; Egawa et al, 2002; Naya et al, 2002; Gjengsto et al, 2005) or transition zone volume (Djavan et al, 1999; Taneja et al, 2001; Singh et al, 2004; Gjengsto et al, 2005) and the evaluation of rate of change in PSA (PSA velocity [PSAV]) (Carter et al, 1992b; Smith and Catalona 1994; Fowler et al, 2000; Fang et al, 2002; D'Amico et al, 2004, 2005; Roobol et al, 2004; Berger et al, 2005, 2007; Schröder et al, 2006; Loeb et al, 2007a, 2008b; Eggener et al, 2008). The discovery that PSA circulates in both bound (complexed) and unbound (free) forms and development of assays to measure these forms separately have resulted in the investigation of their use for prostate cancer detection (McCormack et al, 1995; Lilja, 1997, 2003; Polascik et al, 1999; Gretzer and Partin, 2003), and this topic has been reviewed previously (Jansen et al, 2009).

Volume-Based Prostate-Specific Antigen Parameters. Distinguishing between men with PSA elevations driven by BPH or cancer is difficult because PSA is not specific for cancer and the prevalence of BPH is high. Volume-based PSA parameters (with prostate volume typically determined by ultrasonography) have been evaluated to reduce confounding from BPH. These include PSA divided by prostate volume (PSAD), complexed PSAD (cPSA divided by prostate volume), and PSA transition zone density (PSA divided by transition zone volume) (Babaian et al, 1990; Veneziano et al, 1990; Littrup et al, 1991; Benson et al, 1992a, 1992b; Bazinet et al, 1994; Rommel et al, 1994; Djavan et al, 1999, 2002; Catalona et al, 2000b; Naya et al, 2002; Gjengsto et al, 2005).

Benson and colleagues (1992a, 1992b) suggested that adjusting PSA for prostate size—by dividing PSA by prostate volume (PSAD)—could help distinguish between PSA elevations caused by BPH and those caused by prostate cancer. A direct relationship between PSAD and the chance of cancer has been documented (Seaman et al, 1993; Bazinet et al, 1994; Rommel et al, 1994), and a PSAD of 0.15 or greater was proposed for recommending prostate biopsy in men with PSA levels between 4 and 10 ng/mL and normal DRE (Seaman et al, 1993; Bazinet et al, 1994). The usefulness of PSAD in prostate cancer detection has not been confirmed in all studies (Cooner, 1994; Taneja et al, 2001). An advantage of PSAD is that it has been directly associated with prostate cancer aggressiveness (Carter et al, 2002; Kundu et al, 2007) and therefore is currently used to help assess eligibility for active surveillance among men with prostate cancer (Tseng et al, 2010; Bul et al, 2013). PSA has been adjusted for the transition zone volume (Kalish et al, 1994), the prostatic region that is the major determinant of serum PSA in men without prostate cancer (Lepor et al, 1994).

In general, although PSAD and its associated measures are imperfect predictors of cancer, they represent an additional method of risk assessment with potential utility for counseling men with

intermediate PSA levels (4 to 10 ng/mL) regarding the need for prostate biopsy (Benson and Olsson, 1994) or repeat biopsy if PSA is persistently elevated (Keetch et al, 1996).

Prostate-Specific Antigen Velocity. Short-term fluctuations in PSA can occur between measurements in the presence or absence of prostate cancer, primarily as a result of physiologic variation (Carter et al, 1992a, 1995; Riehmman et al, 1993; Prestigiacomo and Stamey, 1996; Eastham et al, 2003). However, the rate of change in PSA (PSAV)—PSA corrected for the elapsed time between measurements (Carter et al, 1992b)—is associated with the risk for prostate cancer (Carter et al, 1992b; Smith and Catalona, 1994; D'Amico et al, 2004, 2005; Roobol et al, 2004; Berger et al, 2005, 2007; Sengupta et al, 2005; Schröder et al, 2006; Loeb et al, 2007a, 2007b, 2008b; Eggener et al, 2008; Vickers et al, 2009). Using frozen sera to measure PSA years before diagnosis, Carter and colleagues (1992b) showed that a PSAV greater than 0.75 ng/mL/yr was a specific marker for the presence of prostate cancer in men with PSA levels between 4 and 10 ng/mL. Other studies demonstrated that men with prostate cancer have more rapid rises in PSA levels than men without prostate cancer (Smith and Catalona, 1994; Carter et al, 1995; Raaijmakers et al, 2004b; Thompson et al, 2004; Loeb et al, 2008c). It was later shown that PSAV might be useful for prostate cancer detection among men with PSA levels below 4.0 ng/mL (Carter et al, 2006; Loeb et al, 2007b). Some investigators have suggested the use of lower PSAV thresholds of 0.4 ng/mL/yr for men with lower total PSA (tPSA) levels (Loeb et al, 2007b; Moul et al, 2007).

Some studies have failed to demonstrate the value of PSAV for prostate cancer prediction beyond that of a single PSA measurement (Roobol et al, 2004; Vickers et al, 2009). Differences among studies could be due to the method of calculating PSAV (Yu et al, 2006; Connolly et al, 2007) and the point in the PSA history at which PSAV is calculated (Carter et al, 1992b; D'Amico et al, 2004).

PSAV may play a role in the prediction of life-threatening prostate cancer (D'Amico et al, 2004, 2005; Carter et al, 2006). A PSAV value greater than 0.35 ng/mL/yr 10 to 15 years before diagnosis was associated with a fivefold increased risk for life-threatening prostate cancer more than a decade later (Carter et al, 2006); a PSAV value greater than 2 ng/mL/yr during the year before a prostate cancer diagnosis was associated with prostate cancer-specific mortality after radical prostatectomy or radiation therapy (D'Amico et al, 2004, 2005; Sengupta et al, 2005). A systematic review of studies up to 2007 suggested that PSAV before treatment provides no additional information regarding prostate cancer outcome when compared to PSA alone (Vickers et al, 2009). However, several large recent studies have shown that PSA kinetics enhance predictive value for overall and high-risk disease beyond tPSA level alone (Loeb et al, 2012; Wallner et al, 2013).

Free Prostate-Specific Antigen. Men with prostate cancer generally have a greater fraction of serum cPSA—and therefore a lower percentage of tPSA circulating in the free (unbound) form—than men without prostate cancer (Christensson et al, 1993; Leinonen et al, 1993; Lilja, 1993; Stenman et al, 1994; Catalona et al, 1995, 1998, 2000a; Keetch et al, 1997; Pannek et al, 1998; Woodrum et al, 1998; Gann et al, 2002; Roehl et al, 2002; Hugosson et al, 2003a; Raaijmakers et al, 2004a). This difference is thought to be due to differential expression of PSA isoforms by transition zone (zone of origin of BPH) tissue compared with peripheral zone tissue (where most prostate cancers arise) (Chen et al, 1997; Mikolajczyk et al, 1997, 2000a, 2000b).

fPSA levels vary directly by age and prostate volume and vary indirectly with the tPSA level (Woodrum et al, 1998). In addition, because assays differ in their ability to determine both fPSA and tPSA, results may differ depending on the assay or combination of assays used (Woodrum et al, 1998). The percentage of fPSA (%fPSA) does not appear to be significantly altered by race (Catalona et al, 2000a) or 5 α -reductase inhibitors (Keetch et al, 1997; Pannek et al, 1998).

%fPSA has been shown to significantly improve the ability to distinguish between individuals with and without prostate cancer, compared with tPSA alone (Christensson et al, 1993). The %fPSA

cutoff that optimizes sensitivity and specificity for cancer detection depends on prostate size, because overlap is greatest among men with enlarged prostates, with or without concomitant prostate cancer (Catalona et al, 1995).

%fPSA appears to be most useful in distinguishing between those with and without prostate cancer at intermediate tPSA levels. In men with PSA levels of 4 to 10 ng/mL and palpably benign prostate glands, a %fPSA cutoff of 25% detected 95% of cancers while avoiding 20% of unnecessary biopsies (Catalona et al, 1998). The value of %fPSA to predict prostate cancer at levels below 4.0 ng/mL is unclear (Gann et al, 2002; Roehl et al, 2002; Hugosson et al, 2003a; Raaijmakers et al, 2004a).

%fPSA (at a cutoff of 25%) and PSAD (using a threshold of 0.078) have been shown to have comparable specificity (at a sensitivity of 95%), whereas %fPSA does not require volume measurement (Catalona et al, 2000b). Thus %fPSA can be used to counsel men with PSA elevations in the range 4 to 10 ng/mL regarding their risk for cancer.

Complexed Prostate-Specific Antigen. Because men with prostate cancer have a greater fraction of tPSA that is complexed to proteins than men without prostate cancer, measurement of cPSA has been studied as a marker for detection (Brawer et al, 2000; Okegawa et al, 2000; Brawer, 2002; Parsons et al, 2004). When tPSA levels were between 4 and 10 ng/mL, cPSA provided improved specificity compared with tPSA and similar specificity compared with the percentage of fPSA at a sensitivity of 95% (Brawer et al, 2000), findings that were subsequently confirmed (Okegawa et al, 2000). Similar results were reported in the PSA range of 2.6 to 4.0 ng/mL (Parsons et al, 2004). Overall, at a high sensitivity, cPSA provides higher specificity than tPSA and comparable specificity to %fPSA in prostate cancer detection. A potential advantage of cPSA is the requirement for one assay.

Prostate-Specific Antigens Isoforms. PSA is secreted from the prostatic luminal epithelium in a precursor form (pPSA or proPSA) (see Chapter 108) (Mikolajczyk et al, 2001, 2004; Peter et al, 2001; Catalona et al, 2003, 2004; Gretzer and Partin, 2003; Khan et al, 2003; Lilja 2003; Canto et al, 2004; Lein et al, 2005; Makarov et al, 2008). Active fPSA can be further cleaved to benign PSA (bPSA) or intact PSA (iPSA) that is inactive and not complexed. Assays have been developed to measure these different isoforms.

The relative concentration of these isoforms differs in the presence of prostatic disease. bPSA is found preferentially in nodular BPH tissue from the transition zone and can be considered a marker for BPH (Mikolajczyk et al, 2000b; Canto et al, 2004), whereas a larger relative proportion of proPSA has been associated with prostate cancer (Mikolajczyk et al, 1997, 2000a, 2001; Peter et al, 2001). Large studies have suggested that proPSA may improve the identification of prostate cancer among men with PSA levels of 2 to 4 ng/mL (Catalona et al, 2003, 2004), 4 to 10 ng/mL (Khan et al, 2003; Mikolajczyk et al, 2004), and 2 to 10 ng/mL (Catalona et al, 2003), whereas other studies have not shown incremental predictive value of specific subtypes beyond %fPSA (Lein et al, 2005).

Human Kallikrein 2. Human kallikrein 2 (*hK2*) is a closely related serine protease in the PSA/kallikrein gene family that also has been evaluated for prostate cancer detection (Kwiatkowski et al, 1998; Partin et al, 1999; Becker et al, 2000, 2003; Haese et al, 2003; Bangma et al, 2004; Steuber et al, 2005; Vickers et al, 2008). Expression of *hK2* is higher in more poorly differentiated cancer tissues than in normal and benign tissues (Tremblay et al, 1997). Although some studies have suggested that the ratio of *hK2* and fPSA might improve the ability of PSA to identify men with prostate cancer (Kwiatkowski et al, 1998; Partin et al, 1999; Becker et al, 2000; Vickers et al, 2008), other analyses have not (Becker et al, 2003; Bangma et al, 2004). *hK2* does appear to correlate directly with grade and cancer volume and could be useful in patient assessment after diagnosis (Haese et al, 2003; Steuber et al, 2005).

Multiplex Tests. The discovery of these different PSA isoforms led to the development of combination tests. The Beckman Coulter Prostate Health Index (ϕ) is an FDA-approved test that combines tPSA, fPSA, and $[-2]$ proPSA using a mathematical formula. In prospective multicenter trials, the use of ϕ demonstrated improved

predictive accuracy for prostate cancer detection and high-grade disease compared to either tPSA or %fPSA (Catalona et al, 2011; Guazzoni et al, 2011). A similar test—the 4 kallikrein panel (4K)—also has been developed, combining tPSA, fPSA, iPSA, and *hK2* (Vickers et al, 2011). The 4K panel also has been shown to predict the likelihood of clinically significant prostate cancer (Carlsson et al, 2013; Parekh et al, 2014).

Other Markers

Prostate cancer gene 3 (*PCA3*) is a noncoding prostate-specific messenger RNA (mRNA) overexpressed in prostate cancer tissue compared to benign tissue (see Chapter 108) (Bussemakers et al, 1999; Marks et al, 2007; Deras et al, 2008; Haese et al, 2008; Nakanishi et al, 2008; Sokoll et al, 2008; van Gils et al, 2008; Whitman et al, 2008). Urine assays have been developed to measure *PCA3* mRNA (Sokoll et al, 2008), which is associated with the likelihood of a positive initial or repeat prostate biopsy (Marks et al, 2007; Deras et al, 2008; Haese et al, 2008). There are conflicting results on the association between *PCA3* and prostate cancer aggressiveness (Nakanishi et al, 2008; van Gils et al, 2008; Whitman et al, 2008).

Another urinary marker is the *TMPRSS2:ERG* gene fusion (Salagierski and Schalken, 2012). The concept of gene fusions has a long history in other forms of malignancy (e.g., *BCR-ABL* in leukemia), and previous studies suggested that *TMPRSS2:ERG* gene fusions had increased specificity for prostate cancer. As with *PCA3*, however, there is conflicting data on the association of *TMPRSS2:ERG* with prostate cancer aggressiveness. There also has been preliminary investigation into combining these and other investigational markers into multiplex urinary panels (Laxman et al, 2008).

Overall, in the future, it is likely that panels of serum and possibly urinary biomarkers will be used in combination with standard measures of risk (age, family history, race) to selectively identify men who should undergo further evaluation for the presence of prostate cancer (Etzioni et al, 2003).

STAGING

General Concepts of Staging

The clinical staging of prostate cancer uses pretreatment parameters to predict the extent of disease, both for assessment of prognosis and to inform decisions regarding appropriate treatment. Available pretreatment modalities used to predict disease extent in men with prostate cancer include DRE (clinical T stage), PSA and its derivatives, prostate cancer features on needle biopsy, and radiologic imaging. Pelvic lymph node biopsy is rarely performed before definitive therapy.

Clinical versus Pathologic Staging

Clinical staging is the assessment of disease extent using pretreatment parameters (DRE, PSA values, needle biopsy findings, and radiologic imaging), whereas pathologic stage is determined after prostate removal and involves histologic analysis of the prostate, seminal vesicles, and pelvic lymph nodes if lymphadenectomy is performed. Pathologic staging more accurately estimates disease burden and is more useful than clinical staging for outcome prediction (Pound et al, 1997). Biochemical recurrence-free survival and cancer-specific survival are both inversely related to the pathologic stage of disease (Roehl et al, 2004). The most important pathologic criteria that predict prognosis after radical prostatectomy are tumor grade, surgical margin status, extracapsular disease, seminal vesicle invasion, and pelvic lymph node involvement (Jewett, 1975; Walsh and Jewett, 1980; Epstein et al, 1990, 1993a, 1993b; Partin et al, 1993a; Pound et al, 1997).

Classifications

The Whitmore and Jewett staging system is now of historical interest (Jewett, 1956; Whitmore, 1956). Today, clinical staging is based

on the tumor, node, metastasis (TNM) classification system (Table 111-2). This system was first adopted in 1975 by the American Joint Committee on Cancer (AJCC) and since has undergone numerous modifications (Schröder et al, 1992; American Joint Committee on Cancer, 2010). In the most recent version, the TNM stage is combined with PSA level and Gleason score to classify newly diagnosed cases into prognostic groups. One potential problem is that a nonpalpable lesion identified by TRUS is considered T2 by the current TNM clinical staging system. However, TRUS findings do not predict tumor extent in PSA-detected nonpalpable lesions (Epstein et al, 1994; Ferguson et al, 1995), so many urologists classify men with nonpalpable disease as T1c regardless of TRUS findings.

TABLE 111-2 1997 and 1992 TNM Clinical Staging Systems for Prostate Cancer

1997	1992	DESCRIPTION
TX	TX	Primary tumor cannot be assessed
T0	T0	No evidence of primary tumor
T1	T1	Nonpalpable tumor—not evident by imaging
T1a	T1a	Tumor found in tissue removed at TUR; ≤5% is cancerous and histologic grade <7
T1b	T1b	Tumor found in tissue removed at TUR; >5% is cancerous or histologic grade >7
T1c	T1c	Tumor identified by prostate needle biopsy due to elevation in PSA
T2	T2	Palpable tumor confined to the prostate
T2a	T2a	Tumor involves one lobe or less
	T2a	Tumor involves less than half of one lobe by normal tissue on all sides
T2b		Tumor involves more than one lobe
	T2b	Tumor involves more than half of a lobe but not both lobes
None	T2c	Tumor involves more than one lobe
T3	T3	Palpable tumor beyond prostate
T3a	T3a	Unilateral extracapsular extension
T3b	T3b	Bilateral extracapsular extension
T3c	T3c	Tumor invades seminal vesicle(s)
T4	T4	Tumor is fixed or invades adjacent structures (not seminal vesicles)
T4a	T4a	Tumor invades bladder neck, external sphincter, and/or rectum
T4b	T4b	Tumor invades levator muscle and/or fixed to pelvic wall
N(+)	N(+)	Involvement of regional lymph nodes
NX	NX	Regional lymph nodes cannot be assessed
N0	N0	No lymph node metastases
N1	N1	Metastases in single regional lymph node, ≤2 cm in dimension
N2	N2	Metastases in single (>2 but ≤5 cm) or multiple with none >5 cm
N3	N3	Metastases in regional lymph node >5 cm in dimension
M(+)	M(+)	Distant metastatic spread
MX	MX	Distant metastases cannot be assessed
M0	M0	No evidence of distant metastases
M1	M1	Distant metastases
M1a	M1a	Involvement of nonregional lymph nodes
M1b	M1b	Involvement of bones
M1c	M1c	Involvement of other distant sites

TNM, tumor, node, metastasis; TUR, transurethral resection.

Prediction of Tumor Extent

Prostate-Specific Antigen

Despite controversy over its correlation with prostate cancer volume (Stamey et al, 2004), PSA level is associated directly with pathologic stage and tumor extent (Stamey et al, 1987, 1989). PSA value cannot be used alone to accurately predict disease extent for an individual patient because of significant overlap in PSA levels between stages, the variable contribution from BPH to PSA, and the fact that—on average—poorly differentiated tumors produce less PSA per gram of tumor (Partin et al, 1990). Despite these confounding factors, pathologically organ-confined disease is found in 80% of men with a PSA less than 4.0 ng/mL, 66% of those with PSA levels between 4.0 and 10.0 ng/mL, and fewer than 50% of men with PSA levels greater than 10.0 ng/mL (Catalona et al, 1997; Rietbergen et al, 1999). Also, 20% of men with PSA levels greater than 20 ng/mL and 75% of those with PSA levels greater than 50 ng/mL are found to have pelvic lymph node involvement.

In addition to the tPSA level, fPSA, hK2, proPSA, PSAD, and PSAV (see earlier discussion) have been evaluated as predictors of prostate cancer grade and extent (Carter et al, 1997b; Southwick et al, 1999; D'Amico et al, 2004, 2005; Carter et al, 2006, 2007; Kundu et al, 2007; Loeb et al, 2008d). Although prostatic acid phosphatase has been associated with pathologic stage and progression after radical prostatectomy (Moul et al, 1998; Han et al, 2001) the closer relationship between PSA level and disease extent has virtually eliminated the clinical use of this parameter (Heller, 1987).

Digital Rectal Examination

DRE is used to determine whether a lesion is palpable and is associated with local disease extent (clinical T stage). Also, an abnormal DRE was associated with an increased risk for detecting high-grade (Gleason 8 to 10) prostate cancer in a screened population (Gosselaar et al, 2008).

However, because of its poor sensitivity and lack of reproducibility, DRE can both overestimate and underestimate the extent of disease (Turner and Belt, 1957; Byar and Mostofi, 1972; Walsh and Jewett, 1980). In one series of 565 men with presumed organ-confined disease based on DRE, the sensitivity and specificity were 52% and 81%, respectively, for prediction of organ-confined disease (Partin et al, 1993b). Nevertheless, DRE can be used in combination with other parameters to help predict tumor extent.

Prostate Needle Biopsy

Histologic grade is the most important information obtained from prostate needle biopsy, and the Gleason grading system is the most commonly used (Gleason, 1966). At low-power magnification, the sum of a grade (1 to 5) assigned to the predominant pattern (occupying the largest area of the specimen) and the second most common pattern yield a score ranging from 2 to 10.

Contemporary studies have shown that tertiary Gleason patterns may affect prognosis (Patel et al, 2007), leading a 2005 consensus conference to recommend modification of the Gleason grading system (see Chapter 110). Accordingly, a biopsy Gleason score of 3 + 4 or 4 + 3 with a tertiary pattern 5 would be considered Gleason 3 + 5 or 4 + 5, respectively (Epstein et al, 2005). Recently, debate regarding the biologic potential of Gleason 6 tumors led to the suggestion of an alternative classification system, in which Gleason scores of 6 or less, 3 + 4 = 7, 4 + 3 = 7, 8, and 9 and 10 would be labeled as Gleason score prognostic grade groups 1 to 5 (Carter et al, 2012).

Although a higher Gleason grade is associated with worse prognosis, it is not used alone for risk prediction (Stein et al, 1991; Epstein et al, 1993a, 1993b; Partin et al, 1993a; Zincke et al, 1994). Other biopsy findings provide information regarding the extent of disease, including the number of positive cores, percentage of positive cores, and presence of perineural invasion. These features are associated with radical prostatectomy findings and have been used

to guide the selection of candidates for active surveillance programs (Egan and Bostwick, 1997; de la Taille et al, 1999a; Carter et al, 2002; O'Malley et al, 2002; Bismar et al, 2003).

Findings of seminal vesicle invasion or involvement of the periprostatic fat on prostate needle biopsy are associated with worse prognosis (Stone et al, 1998). Although some authors have recommended biopsy of the seminal vesicles and/or prostatic capsule to improve staging (Terris et al, 1993; Ravery et al, 1994; Vallancien et al, 1994; Stone et al, 1995, 1998), others suggest biopsy of these structures only when there is a large palpable tumor located at the base of the prostate (Guillemot et al, 1997; Terris et al, 1997).

Combined Use of Pretreatment Parameters

Nomograms and algorithms have been developed to integrate multiple clinical parameters for improved staging. Considering the primary T stage based on DRE findings, serum PSA level, and Gleason grade, these algorithms and nomograms have been shown to more accurately predict both cancer extent and long-term outcomes after treatment compared to any single parameter (Humphrey et al, 1991; Kleer and Oesterling, 1993; Kleer et al, 1993; Partin et al, 1993b, 1997, 2001; Kattan et al, 1998; Han et al, 2003; Stephenson et al, 2006; Makarov et al, 2007).

Several classification schemes have been proposed that correlate with clinical outcomes. D'Amico and associates (1998, 2001) demonstrated that stratification into low-risk (clinical stage T1 to 2a, PSA ≤ 10 ng/mL and Gleason score ≤ 6), intermediate-risk (stage T2b or PSA > 10 but < 20 ng/mL or Gleason score 7), and high-risk disease (stage T2c, or PSA > 20 ng/mL or Gleason score 8 to 10) was significantly associated with freedom from disease at 10 years after radical prostatectomy; 83% for low-risk, 46% for intermediate-risk, and 29% for high-risk disease. Other validated classification schemes have been developed since, including the Cancer of the Prostate Risk Assessment (CAPRA) score (Cooperberg et al, 2005, 2006; May et al, 2007). Pretreatment risk stratification using multiple parameters is useful for patient counseling.

Imaging

Numerous imaging modalities have been evaluated for staging prostate cancer. Radionuclide bone scan (bone scintigraphy) is the most commonly employed modality for the detection of skeletal metastases (Terris et al, 1991). Bone survey films (skeletal radiography) have lower sensitivity for the identification of distant spread and are typically used only to confirm a positive bone scan in men at low risk for bone metastases. Because bone metastases at diagnosis are rare in asymptomatic men in the PSA era, the routine use of bone scans in this population may lead to false-positive results, as well as unnecessary anxiety and cost (Chybowski et al, 1991). Accordingly, recent guidelines recommend the use of bone scans for patients with a PSA level greater than 20 ng/mL, Gleason score of 8 to 10, clinical stage T3 or T4, or clinical symptoms. By contrast, the Choosing Wisely Campaign recently has emphasized that routine bone scans are not necessary for men with low-risk prostate cancer (American Urological Association, 2013b).

Similarly, cross-sectional imaging to evaluate for lymphadenopathy is recommended for high-risk patients, such as those with clinical stage T3 or greater disease or greater than 20% nomogram probability of lymph node metastases. Given the rarity of lymph node involvement in contemporary screened populations, it appears that imaging is being overused (Kindrick et al, 1998; Cooperberg et al, 2002; Abraham et al, 2007).

Although magnetic resonance imaging (MRI) has been evaluated for staging prostate cancer for many years (Yu et al, 1999; Kurhanewicz et al, 2000) the technology has recently improved dramatically. In particular, the addition of functional sequences such as diffusion-weighted MRI and dynamic contrast-enhanced MRI in conjunction with the conventional T2-weighted MRI has improved the ability of MRI to characterize the locoregional extent of disease. It is currently used at some institutions for pretreatment planning before definitive local therapy or to assess candidacy for active

surveillance (Vargas et al, 2012; Somford et al, 2013). In addition, MRI images may be fused with TRUS to enable targeted prostate biopsy—for example, in patients with previous negative TRUS-guided biopsies (Sonn et al, 2014; Siddiqui et al, 2015).

Specialized techniques such as high-resolution MRI used in tandem with the intravenous administration of lymphotropic superparamagnetic nanoparticles may allow the detection of small and otherwise undetectable lymph node metastases in patients with prostate cancer (Harisinghani et al, 2003). These techniques, however, require further clinical evaluation before widespread use.

Advances in ultrasound imaging also are being studied for improving prostate cancer detection (Purohit et al, 2003). Color ultrasonography with power Doppler to evaluate the blood flow within prostate vessels and three-dimensional (3D) Doppler using contrast agents could improve the visualization of more subtle tissue alterations caused by cancer. Another new ultrasound-based technique is HistoScanning (BK Medical, Peabody, MA), a computer-aided process to help characterize potentially suspicious tissue (Simmons et al, 2012). Additional large-scale studies of these techniques are necessary before widespread use can be recommended.

Finally, monoclonal antibody radioimmunoscintigraphy (radio-labeled monoclonal antibody scan) has been used for identification of microscopic cancer deposits in regional and distant sites. The ProstaScint scan (Cytogen, Princeton, NJ) uses this technology but has had limited accuracy in the detection of lymph node metastases because the antibody targets an intracellular epitope that is exposed only in dying or dead cells (Troyer et al, 1997; Chang et al, 1999). Future generations of this technology circumventing this limitation are under development.

Molecular Staging

Molecular staging has focused on the detection of circulating prostate cancer cells either directly through centrifugation/immunostaining methods or indirectly by identifying the genetic material for prostate-specific biomarkers (e.g., PSA, prostate-specific membrane antigen) from circulating prostate cells (Moreno et al, 1992; Ts'o et al, 1997). Although these polymerase chain reaction (PCR)-based assays have been associated with pathologic stage, sensitivity for detecting circulating cancer cells is variable across studies (Cama et al, 1995; Israeli et al, 1995; de la Taille et al, 1999b). With the FDA approval of the semiautomated CellSearch system (Veridex, Janssen Diagnostics, Raritan, NJ) for monitoring metastatic breast and prostate cancer, considerable investigation is underway to determine whether circulating tumor cells have a role in the staging of early disease (Davis et al, 2008; Helo et al, 2009).

Several new tissue-based tests have been introduced that may improve prostate cancer risk stratification. The Prolaris test (Myriad Genetics, Salt Lake City, UT) measures a panel of cell cycle progression genes involved in the process of cancer proliferation (Cooperberg et al, 2013). The Oncotype DX Prostate Cancer Test (Genomic Health, Redwood City, CA) is a quantitative RT-PCR assay for 17 genes involved from five different pathways involved in prostate carcinogenesis (Knezevic et al, 2013). Preliminary studies of these tests suggest a potential ability to further refine classification schemes beyond the standard risk groups (Klein et al, 2014); however, further prospective validation studies are necessary to demonstrate whether these tests are cost effective.

Pelvic Lymphadenectomy

The presence of lymph node metastasis in men diagnosed with clinically localized prostate cancer portends a worse prognosis. Identification of patients harboring nodal metastases could have important implications for treatment selection. Although the prevalence of pelvic lymph node metastases correlates directly with T stage, serum PSA level, and biopsy grade, pelvic lymphadenectomy remains the most accurate way to detect occult nodal involvement (Parker et al, 1999).

PSA screening has resulted in a steady decline in the rates of metastases from 20% to 40% in the 1970s and 1980s to less than

4% today (Partin et al, 1997; Parker et al, 1999; National Cancer Institute, 2013). Currently, lymphadenectomy often is omitted before curative treatment (e.g., radical prostatectomy, radiation therapy) (Bishoff et al, 1995; Kawakami et al, 2006). Laparoscopic pelvic lymphadenectomy before treatment is typically reserved for patients with Gleason score greater than 8, extraprostatic extension on DRE, PSA value greater than 20 ng/mL, or suspicion of enlarged lymph nodes on radiologic evaluation and is rarely performed in the contemporary PSA era.

Given the individual variation in prostatic lymphatic drainage patterns (Mattei et al, 2008), some investigators favor an extended pelvic lymphadenectomy in lieu of a limited dissection (Bader et al, 2002; Burkhard et al, 2006). Considering the greater complication rates with a more extended pelvic lymph node dissection, risks may outweigh benefits for most men diagnosed with low-risk cancer today (Klein et al, 2008). Information regarding the therapeutic value of these strategies is confounded by stage migration and is difficult to evaluate without prospective trials.

KEY POINTS: DIAGNOSIS AND STAGING OF PROSTATE CANCER

- Although the value of PSA screening remains controversial, men who present for periodic health examinations should be made aware of the availability of the PSA test so they can make an informed decision about the need for routine screening.
- The combination PSA level, DRE, and other clinical factors (e.g., age, race, family history) can be used in combination to predict the risk that prostate cancer is present. The presence of prostate disease (prostate cancer, BPH, and prostatitis) is the most important factor affecting serum levels of PSA.
- PSA testing increases detection rates of prostate cancer and leads to the detection of prostate cancers that are more likely to be organ-confined when compared with detection without the use of PSA.
- The future risk for prostate cancer detection and the chance of finding cancer on a prostate biopsy increase incrementally with the serum PSA level.
- Biochemical recurrence-free survival and cancer-specific survival are both inversely related to the pathologic stage of disease.
- Pathologic criteria that predict prognosis after radical prostatectomy are tumor grade, surgical margin status, presence of extracapsular disease, seminal vesicle invasion, and pelvic lymph node involvement.
- The Gleason grading system is the most commonly used classification scheme for the histologic grading of prostate cancer.

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The complete reference list is available online at www.expertconsult.com.



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Background

Established Treatments

Other Treatments

Recommendations for Treatment by Patient Risk Group

The purpose of this chapter is to provide an overview of the management of clinically localized prostate cancer. In reporting differences in treatments, we have attempted to be objective but have included our editorial perspective. For balance, we have included in our suggested reading list several recent articles focusing on the relative advantages and disadvantages of the different management strategies, some expressing opinions contrary to ours. We have grouped treatments into *established treatments*, such as radical prostatectomy and radiotherapy, for which abundant published information is available, and *other treatments*, including active surveillance, primary hormone therapy, cryoablation, radiofrequency ablation, and high-intensity focused ultrasound (HIFU), for which data are more limited for localized disease.

BACKGROUND

Prostate cancer is the most common nonskin cancer and the second-leading cause of death from cancer in men in the United States. In 2014, it was estimated that 233,000 new cases would occur; it would be the cause of death for 29,480 men (Siegel et al, 2014). Because prostate cancer is prevalent in many countries and exhibits a wide spectrum of aggressiveness, different methods of treatment have been developed, and the preferred methods for detection and treatment are controversial. The prevalence of prostate cancer increases strikingly with age. Autopsy studies have documented microscopic foci of prostate cancer in about one fourth to one third of men in the fourth and fifth decades of life and in more than three fourths in the ninth decade (Sakr et al, 1993; Yin et al, 2008). Yet a disproportionately lower but still substantial number of men (about one in seven) are diagnosed with prostate cancer during their lifetime (Siegel et al, 2014). Because of effective treatment of some prostate cancers and the biologic indolence relative to life expectancy of others, only about 16% of men diagnosed with prostate cancer ultimately die of it. Prostate cancer is the cause of death in about 3% of the U.S. male population (Siegel et al, 2014). An additional unquantified proportion of men have prostate cancer-related morbidities but die of other causes.

The marked disparity between prevalence and incidence rates of prostate cancer on one hand and morbidity and mortality rates on the other has led some to conclude that many prostate cancers are harmless and perhaps would better be left undetected. Nevertheless, if the present trends of increasing life expectancy continue, given the current age-specific incidence, morbidity, and mortality rates of prostate cancer, this disease will become a far greater public health problem in the future (Li and Ekwueme, 2010). In the U.S. national Surveillance, Epidemiology, and End Results (SEER) Program database, the prostate cancer incidence was increased for

younger men whereas it was decreased in older men. Also, the incidence of poorly differentiated tumors increased whereas the incidence of well-differentiated tumors decreased significantly (Li and Ekwueme, 2010). Therefore, prostate cancer is being diagnosed in younger men, with more frequent diagnosis of those likely to benefit from treatment.

Since the 1980s, the methods of diagnosis of clinically localized prostate cancer have changed. Widespread screening with serum prostate-specific antigen (PSA) and digital rectal examination (DRE) has allowed earlier detection (Catalona et al, 1991; Catalona, 1993). Furthermore, with a remarkable stage migration, approximately 81% of cases are being detected at a clinically localized stage; metastases at the time of diagnosis are now rare in the United States (4%) as well as in Europe (Han et al, 2001a; Gallina et al, 2008; Siegel et al, 2014). The natural history of prostate cancer varies from indolent disease that might not cause symptoms during a patient's lifetime to highly aggressive cancer that metastasizes quickly and causes terrible suffering and untimely death. The challenge for the physician who manages patients with prostate cancer is to advise effective treatment in those for whom treatment is necessary. Selection of the appropriate treatment requires assessment of the tumor's potential aggressiveness and the general health, life expectancy, and quality-of-life preferences of the patient.

Patients whose tumor has a low malignant potential are predetermined to fare better with most treatments. Therefore, the treatment outcomes in any patient series may be influenced by the malignant potential of the tumors as well as by the treatment used. Accordingly, it is difficult to compare the results of different treatments because the populations of patients are usually heterogeneous and not strictly comparable. Furthermore, outcome measurements are not necessarily comparable among different forms of therapy (e.g., different definitions of biochemical progression for surgery and radiotherapy), confounding comparisons among them.

Prostate Cancer Screening

The conflicting results of two prospective, randomized trials of screening for prostate cancer from Europe and the United States have created controversy over the risks and benefits of early prostate cancer detection and definitive treatment (Andriole et al, 2009; Schroder et al, 2009). The European trial (European Randomized Study of Screening for Prostate Cancer [ERSPC]), which was twice as large and had less contamination with opportunistic screening of the control arm (PSA testing was not as widespread in Europe as in the United States at the time), used a screening interval of 4 years with a PSA cutoff of 3 ng/mL at most sites and

included a DRE during the first or second round of screening. The European trial showed that screening decreased the prostate cancer mortality rate by 20% (27% in men who were actually screened) (Schroder et al, 2009). The survival curves began to diverge at 6 to 7 years and continued to diverge at the time of the report. There was a 71% increase in the number of cancers detected in the screening arm and a 41% decrease in incurable disease at diagnosis. In this initial report, the authors estimated that 1400 men would have to be screened and 48 treated to save one life (Schroder et al, 2009; Gulati et al, 2011). In updated results at a median follow-up of 11 years, there was a 21% decrease in prostate cancer-specific mortality, and the same authors estimated that 1055 men would need to be screened and 37 cancers would need to be detected for prevention of one death from prostate cancer (Schroder et al, 2012b). Subsequently, based on the same ERSPC data, it was estimated that annual screening of men in the ERSPC aged 55 to 69 years would result in a 28% reduction in prostate cancer deaths (37% in those actually screened). The estimated number needed to screen to prevent one prostate cancer death was 98, and the number of cancers needed to be detected was five (Heijnsdijk et al, 2012). In a reanalysis of ERSPC data, Hanley pointed out that in estimating the reduction of overall average mortality, the ERSPC authors included the initial years of zero effect. This provides a diluted measure of the impact of screening. Assuming steady-state screening using the ERSPC protocol, Hanley estimated that there would be a 67% decrease in prostate cancer-specific mortality at 12 years of follow-up (Hanley, 2011).

The independent Göteborg population-based randomized screening trial screened younger men (aged 50 to 64), screened every 2 years, used lower PSA cutoffs of biopsy (3.4 ng/mL progressing to 2.5 ng/mL), and had only 3% screening of controls; 93% complied with a biopsy recommendation, and 77% had 14-year follow-up (Hugosson et al, 2010). In the screening arm there were 41% fewer advanced cases at diagnosis and a 44% lower prostate cancer-specific mortality rate that was significant across all age groups and was greatest in the youngest patients. In this trial, one third of patients were managed with active surveillance. In current empirical data from the Göteborg trial with 16 years of follow-up, the number needed to screen to avoid one prostate cancer death is 208 and the number needed to treat is 9 (Carlsson, personal communication, 2013).

The U.S. trial (Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer Screening Trial) of annual screening for 6 years with PSA and DRE showed no effect in the entire cohort at 7 years and no substantial increase in cases detected or decrease in incurable cases (Andriole et al, 2009). The results were released prematurely, just as the ERSPC trial was reporting that PSA screening saves lives, because of concerns by the PLCO study monitoring committee that screening showed no benefit, to offset the potential harms associated with treatment. A subsequent update of the PLCO trial continued to show no mortality difference in prostate cancer mortality in the entire cohort at 13 years (Andriole et al, 2012). However, the PLCO trial had severely limiting flaws:

1. Approximately 40% of the participants had been prescreened with PSA.
2. A higher PSA cutoff (4 ng/mL) was used.
3. In the control arm, 85% of the participants had had at least one PSA measurement, and in 96% of these, testing had taken place in the previous 2 to 3 years. In the screening arm of the PLCO trial, 85% of patients were tested during the study and as a group had more PSA tests (Pinsky et al, 2010).
4. In the screening arm, most patients with abnormal screening results did not undergo prompt biopsy.
5. The study was underpowered to demonstrate a mortality benefit of screening.

However, in a subset analysis of the PLCO trial (Crawford et al, 2011), a 44% decrease in the risk of prostate cancer-specific death was observed in the screening arm in men with no or minimal comorbidity, and the numbers needed to screen and treat to

prevent one death were 723 and 5, respectively. This benefit was not found among men with more significant comorbidities (Andriole et al, 2012).

Based on new evidence on the benefits and harms of PSA-based prostate cancer screening, the U.S. Preventive Services Task Force (USPSTF) in 2012 recommended against PSA-based screening in the general U.S. population, regardless of age or race (Moyer and USPSTF, 2012). However, USPSTF overestimated harms and underestimated benefits of PSA-based screening, with undue weight given to the PLCO trial and the Prostate Cancer Intervention versus Observation Trial (PIVOT). This recommendation also ignored the high-risk men with a family history of prostate cancer or those with African ancestry. In addition, reduction in metastatic disease as a result of PSA-based prostate cancer screening was not weighed against the side effects from treatment (Hartzband and Groopman, 2012; Scosyrev et al, 2012b). Screening dramatically reduced metastases at diagnosis in the ERSPC and Göteborg trials (Schroder et al, 2012a). The USPSTF recommendation has had a transformative effect because it changed the default option for prostate cancer screening. Research in cognitive science has shown that the default option transmits a powerful message to the public about how to weigh risk and benefit of screening (Hartzband and Groopman, 2012). Nevertheless, in spite of this USPSTF recommendation against screening, PSA-based screening continues to be recommended by physicians (Colbert and Adler, 2012). After reviewing the same evidence that the USPSTF reviewed, virtually all other professional organizations, including the American Cancer Society, American College of Physicians, American Society of Clinical Oncology, American Urological Association (AUA), European Association of Urology, and the 2013 Prostate Cancer World Congress recommend PSA testing for selected men with a shared decision making process (Basch et al, 2012; Carter et al, 2013; Heidenreich et al, 2013; Qaseem et al, 2013; Murphy et al, 2014; Smith et al, 2014). Moreover, the National Comprehensive Cancer Network (NCCN) provides guidelines for early prostate cancer detection in men who have elected to be screened (NCCN, 2014).

Pound and colleagues reported that the median time from PSA failure to the development of metastases after radical prostatectomy is 8 years and the median time from metastases to death is 5 years (Pound et al, 1999). Thus, the median time from diagnosis to death is more than 13 years. In the European trial there was no improvement in survival until after 7 years, confirming that a long observation period is necessary to assess the treatment outcomes in prostate cancer.

The United States trial has been portrayed as the underpinning for a proposed shift in the mindset of physicians and patients that screening for and treatment of prostate cancer do more harm than good. However, this trial was flawed at the beginning and will never be informative of the true impact of screening on prostate cancer death of healthy men managed with intelligent screening, prompt biopsy, and effective treatment.

There is other compelling evidence to suggest that early diagnosis through PSA testing and prompt, effective, and high-quality treatment save lives. This evidence comes largely from the cancer registries of the United States and World Health Organization databases. The percentage of men who have advanced prostate cancer at the time of diagnosis has decreased by 80% in the United States during the PSA era, and there has been a 45% decrease in the prostate cancer death rate during the PSA screening era (Boring et al, 1991; National Cancer Institute, 2014; Siegel et al, 2014). Using statistical modeling, Etzioni and colleagues (2008, 2012) estimated that the improvements in treatment explained 22% to 33% of the mortality decline, whereas the remainder of the decline probably was a result of other interventions, such as PSA-based prostate cancer screening.

Other studies have shown that in regions of the United States where more PSA testing is performed, there are lower rates of advanced prostate cancer and prostate cancer death (Colli and Amling, 2008). In a population-based study, PSA screening reduced the prostate cancer-specific mortality rate by 62% (Agalliu et al, 2007; Kvale et al, 2007). Globally, the death rate also has fallen

in countries where PSA testing is practiced, whereas it continues to rise in countries where it is not (Bouchardy et al, 2008).

The frequently cited decrease in prostate cancer mortality reported in the United Kingdom from 1992 to 2004 in the absence of widespread PSA screening is largely a result of the method of attributing the cause of death in the United Kingdom databases during that time. Before the PSA era, if a man with metastatic prostate cancer died of pneumonia, the cause of death was attributed to prostate cancer, but during the early years of the PSA era, the cause of death was attributed to pneumonia. Thus there was a spurious decrease in the prostate cancer mortality rate in the PSA era in the absence of widespread PSA screening (Hussain et al, 2008).

Characterization of the Primary Tumor

DRE and prostate ultrasound findings usually provide useful information about the extent of the primary tumor. The serum PSA data, including the total PSA level, the rate of change of PSA (PSA velocity and doubling time), the PSA density (serum PSA divided by prostate volume), the percentage of PSA in the free or complexed isoforms, and the Prostate Health Index are significantly associated with prostate cancer aggressiveness (Benson et al, 1992; Carter, 1997; Catalona et al, 1998; D'Amico et al, 2004; Thompson et al, 2004; Kundu et al, 2007; Catalona et al, 2011). The biopsy findings (Gleason score; the number of cores containing cancer; the distribution and volume of cancer in the biopsy cores; the presence of perineural space invasion, lymphovascular invasion, ductal, signet ring, or neuroendocrine differentiation) also correlate with cancer aggressiveness and the likelihood of the cancer's being organ confined (Loeb et al, 2010a). Prediction tables and algorithms have been developed to assist in this assessment (Partin et al, 1997, 2001; Makarov et al, 2007; Eifler et al, 2013). However, such statistical aids are more useful in groups of patients than in individual patients, and wide confidence intervals surrounding estimates of outcomes may limit the usefulness of risk assessment for an individual patient. Accordingly, it has been claimed that the simultaneous assessment of multiple variables in nomograms provides more accurate predictions than do tables for individual patients (Kattan, 2003).

Evaluation of the Patient

There is a general consensus about how extensive the initial staging workup should be. A radionuclide bone scan, abdominal-pelvic computed tomography (CT) scan, and magnetic resonance imaging (MRI) scan are not indicated if the tumor has a Gleason sum of less than 7 (or in some guidelines, 8) (NCCN, 2014), the serum PSA level is less than 10 ng/mL, and the biopsy findings do not reveal an extensive or highly aggressive cancer, because the likelihood of finding metastases is quite low. AUA and NCCN guidelines recommended avoiding a routine radionuclide bone scan in men with low-risk prostate cancer who have a PSA below 20 ng/mL and a Gleason score of 6 or less unless there is a suggestion of bony involvement.

In higher-risk patients contemplating surgical treatment, a more complete workup should be considered, including coagulation studies, if appropriate, a nuclear bone scan, and CT or MRI scan of the abdomen and pelvis to evaluate the primary tumor and regional lymph nodes and to rule out other possibly important conditions that might need to be addressed at the time of surgery. However, tumor-selective imaging tests such as monoclonal antibody scans, positron emission tomographic scans, magnetic resonance spectroscopy, and lymphotropic MRI are not widely used, although they might prove more useful in the future. Thus, with increasing availability of MRI technology with diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE) and the MRI-ultrasound fusion biopsy technique, there is increasing use of MRI to help improve accuracy of biopsy and to evaluate the local extent of the tumor (Hambrock et al, 2008; Liauw et al, 2013; Mullins et al, 2013; Siddiqui et al, 2013).

ESTABLISHED TREATMENTS

Conservative Management

Active Surveillance or Watchful Waiting

Active surveillance and *watchful waiting* are almost unique to prostate cancer. *Watchful waiting* refers to monitoring the patient until he develops metastases that require palliative treatment. *Active surveillance* or *expectant management* allows delayed primary treatment if there is biochemical or histologic evidence of cancer progression (Dall'Era et al, 2012). Active surveillance is a less established strategy in patients with a long life expectancy because criteria for selecting candidates and trigger points for instituting treatment have yet to be defined and validated. Currently, treatment is frequently initiated because of the patient's anxiety from living with untreated cancer combined with a rising PSA level or biopsy findings that suggest an increase in the volume or Gleason grade of the cancer.

Traditionally, deferred treatment has been reserved for men with a life expectancy of less than 10 years and a low-grade (Gleason score 2 to 6) prostate cancer. However, active surveillance is now being evaluated as a management strategy in younger patients with low-volume, low- or intermediate-grade (up to Gleason score $3 + 4 = 7$) tumors to avoid or to delay treatment that might not be immediately necessary. In one study, approximately 16% of patients with newly diagnosed prostate cancer would fulfill the criteria for active surveillance, about 10% chose surveillance, and an additional 4% who did not meet all criteria chose surveillance (Barocas et al, 2008). According to a more recent analysis, there has been a significant and steady rise in active surveillance since 2008; in 2011, 18.6% of patients with low-risk prostate cancer were receiving expectant management (Charnow, 2014).

In the very long-term follow-up (>30 years), there is a significant risk of cancer progression and prostate cancer-specific death in men with untreated localized prostate cancer (Popiolek et al, 2013). In this study, local progression (41%) and distant metastasis (18%) developed from localized prostate cancer.

Certain populations should be approached with an even greater level of caution when considering active surveillance. In African-American men, the progression risk was significantly increased in active surveillance (Iremashvili et al, 2013). In addition, African-American men who were candidates for active surveillance criteria had worse clinicopathologic features on final surgical pathology than Caucasian men (Abern et al, 2013; Ha et al, 2013; Iremashvili et al, 2013; Sundi et al, 2013). Also, patients with BRCA2 mutations have higher Gleason scores, more advanced tumor stage, and shorter median survival (Castro et al, 2013; Bancroft et al, 2014). Therefore they are not suitable candidates for active surveillance.

Statistical models have been generated in an attempt to predict which tumors can be observed without aggressive treatment. For example, Epstein and associates proposed a model involving preoperative clinical and pathologic features that would predict "insignificant tumors" (tumor volume less than 0.2 mL, Gleason score below 7, and organ-confined cancer) (Epstein et al, 1994, 1998). The preoperative features used in the model include no Gleason pattern 4 or 5 in the biopsy specimen, PSA density of 0.1 ng/mL/g or less, fewer than three biopsy cores involved (with a minimum of six total cores being obtained), no core with more than 50% involvement or PSA density of 0.1 to 0.15 ng/mL/g, and cancer smaller than 3 mm on only one prostate biopsy sample. Characteristically for statistical models, this model was reported to have a predictive value of 95% for identifying a "significant" cancer but a predictive value of only 66% for identifying an "insignificant" cancer (Epstein et al, 1994). Approximately 16% of the men in this series met criteria for an insignificant cancer (Epstein et al, 1994). Subsequently, Epstein and colleagues updated the model to include a free/total PSA ratio (0.15) and favorable needle biopsy findings (fewer than three cores involved, no core with more than 50% tumor, and Gleason score of 6 or lower) (Epstein et al, 1998).

Kattan and associates proposed another statistical model to predict small, moderately differentiated, organ-confined cancer on the basis of PSA, clinical stage, biopsy Gleason score, ultrasound-determined prostate volume, and variables derived from systematic biopsies (Kattan, 2003). They defined indolent cancer as being organ confined, less than 0.5 mL tumor volume, without poorly differentiated elements. Approximately 20% of their patients treated with radical prostatectomy met the criteria for indolent tumors according to their prediction model.

When the outcomes of men who underwent radical prostatectomy but would have otherwise been candidates for active surveillance were examined, 20% to 50% had Gleason score of 7 or above and/or extraprostatic disease, even with the most stringent criteria for selection (Suardi et al, 2008; Thaxton et al, 2010; Vellekoop et al, 2014). Some authors have claimed that even patients who do not fulfill such criteria may be legitimate candidates for active surveillance (Epstein et al, 1998; Reese et al, 2013). However, studies of active surveillance for men in different strata of low- and intermediate-risk prostate cancer suggest that there is proportionately more upgrading and upstaging in higher risk strata (Cooperberg et al, 2011). A potential untoward consequence of recommending active surveillance for all men who do not have obviously aggressive, clinically localized disease is that only men with clearly aggressive and often incurable disease would be treated immediately, whereas a substantial proportion of those with curable disease destined to progress would be managed with surveillance, often with multiple extended biopsy procedures that could contribute to infections, cause erectile dysfunction, complicate subsequent attempts at nerve-sparing surgery, and delay treatment until the window of opportunity for cure had closed (Fujita et al, 2009).

All prostate cancer patients are at risk for progression. In reports of active surveillance, patients are usually observed with semiannual PSA determinations and DRE and annual biopsies (Zietman et al, 2001; Choo et al, 2002; Klotz, 2003; el-Geneidy et al, 2004; Patel et al, 2004; Carter et al, 2007; Dall'Era et al, 2012). Intervention is recommended if Gleason pattern 4 or 5 is present, more than two biopsy cores are involved, or more than 50% of a biopsy core is involved. Progression is more likely in patients who have cancer present on every biopsy procedure. The absence of cancer on repeated biopsy significantly decreases the likelihood of progression (Carter et al, 2007). Accordingly, biopsy criteria have been reported to be more accurate than PSA criteria in predicting progression (Ross et al, 2010). Perineural invasion on biopsy during active surveillance is not associated with adverse pathologic outcomes (Al-Hussain et al, 2011). No study has found DRE or imaging studies to independently predict progression. Recent studies have suggested that the [−2] proPSA and PSA velocity risk count are associated with an increased risk of reclassification on active surveillance (Tosoian et al, 2012; Patel et al, 2014).

The percentage of patients with curable cancer at the time of progression has been reported to vary from 33% to 92%. In most studies of active surveillance, approximately 25% to 50% of patients, depending on their individual risk factors, develop objective evidence of tumor progression within 5 years (Neulander et al, 2000; Patel et al, 2004; Warlick et al, 2006; Duffield et al, 2009). Carter and colleagues reported that 59% remained on surveillance, 25% underwent curative treatment, and 16% withdrew, were lost to follow-up, or died of other causes (Carter et al, 2007). With a longer follow-up of the same cohort, Tosoian and associates reported that only 41% remained on active surveillance at 10 years. There were no prostate cancer deaths, although the follow-up was too short to assess mortality in this cohort with strict criteria for active surveillance (Tosoian et al, 2011). Although some studies suggest that most patients with Gleason score 6 or lower tumors do not suffer or die of prostate cancer with conservative management, those with higher Gleason score tumors have a substantial risk for morbidity and mortality (Albertsen et al, 1995; Johansson et al, 2004). Klotz and colleagues reported that of patients who underwent radical prostatectomy for evidence of

cancer progression during active surveillance, 58% had tumor extension beyond the prostate, and 8% had lymph node metastases (Klotz, 2006, 2009). In this series of men treated with surgery or radiotherapy for progression on active surveillance, the 5-year progression-free survival rate was only 47% (Klotz, 2009). Among the five early patients who died within 4 to 10 years of diagnosis, four had Gleason grade 6 disease at diagnosis and two met the Epstein criteria for “insignificant” cancer (Krakowsky et al, 2010).

A prospective, randomized clinical trial from Scandinavia reported that at 18 years of follow-up, rates of overall and prostate cancer-specific mortality as well as distant metastases and disease progression were significantly higher in patients managed with watchful waiting than in those treated immediately with radical prostatectomy (Bill-Axelsson et al, 2014). The number needed to treat to save one life was 8 overall and 4 in men younger than 65 years.

Early detection and treatment of organ-confined disease in younger men with longer follow-up are important factors in lowering the number needed to treat even further. Similarly, an observational study of Medicare patients treated with observation, radiation, or surgery showed a survival advantage for active treatment of men aged 65 to 80 years; however, the absolute difference in cancer-specific death at 12 years was small (Wong et al, 2006). Similarly, using the SEER Medicare-linked database, Abdollah and associates reported that radical prostatectomy decreases the risk of prostate cancer-specific mortality by half compared with observation in men older than 65 years (Abdollah et al, 2011).

In the recent Veterans Affairs Cooperative Studies Program PIVOT study, Wilt and colleagues reported that radical prostatectomy did not significantly reduce all-cause or prostate cancer-specific mortality, as compared with observation (Wilt et al, 2012). In men with prediagnosis serum PSA level higher than 10 ng/mL, there was an absolute risk reduction for prostate cancer-specific and all-cause mortality with treatment. In contrast, mortality was not significantly reduced in men with PSA lower than 10 ng/mL or in those with low-risk tumors. However, there was 60% decrease in metastasis rate and 37% decrease in prostate cancer-specific mortality rate in the radical prostatectomy arm. PIVOT was underpowered to detect a difference in survival and was conducted in Veterans Affairs hospitals where many men had relatively poor health. In addition, radical prostatectomies were performed with higher complication rates with worse cancer control outcomes compared with the series from the centers of excellence. In addition, a median follow-up of 10 years is insufficient to assess the mortality caused by prostate cancer. Therefore, using the PSA cutoff of 10 ng/mL for screening for prostate cancer as suggested by the PIVOT investigators would most likely result in more advanced prostate cancer at diagnosis and lead to a poorer prognosis. In contrast to the PIVOT study, in the Scandinavian Trial, intermediate-risk patients had the greatest benefit from radical prostatectomy and there was no benefit in high-risk patients (Bill-Axelsson et al, 2014).

One rationale for active surveillance is the belief that there is substantial overdiagnosis of prostate cancer as a result of widespread PSA screening coupled with aggressive biopsy regimens. *Overdiagnosis* often refers to a cancer detected by screening that would not be detected during the patient's lifetime without screening or would never cause disability or death (Loeb et al, 2014). It is axiomatic that any effort to detect cancer early will involve detection of some cancers that would not have been otherwise detected. Therefore, some overdiagnosis is necessary to reduce suffering and death from prostate cancer.

There are two methods of estimating the extent of overdiagnosis. The epidemiologic method applies only to populations, not to individuals. With this method, statisticians look at population trends in prostate cancer cases and use statistical models to estimate whether more cases are being diagnosed than should be, considering past incidence rates of prostate cancer and prostate cancer deaths. Statisticians estimate lead time in prostate cancer diagnosis with PSA screening (3 to 12 years) and use the lead time to estimate overdiagnosis; however, statistical models have not accurately

predicted the observed incidence of prostate cancer nor fully explained the observed decrease in advanced disease.

The second method of estimating overdiagnosis is for a pathologist to examine a surgically removed cancerous prostate gland and determine whether it contains only a tiny amount of cancer that has no high Gleason pattern glands and that is completely encapsulated within the prostate gland. If so, it is designated as an overdiagnosed cancer.

Some reports have estimated that 50% or more of prostate cancer cases are overdiagnosed (Etzioni et al, 2002; Draisma et al, 2003). However, recent studies suggest that epidemiologic estimates of overdiagnosis are exaggerated. Epidemiologic estimates based on statistical models from the United States and using data from the United States yield a 23% to 28% incidence of possible overdiagnosis (Draisma et al, 2009). Estimates in surgically treated patients based on clinicopathologic data range from 6% to 20% (Graif et al, 2007; Pelzer et al, 2007).

Estimates of overdiagnosis derived from older men should not be generalized to younger men. Prostate cancers diagnosed in younger men are more likely to cause harm in the long term, and it is uncertain whether all cases labeled as overdiagnosed are clinically insignificant. Contrary evidence suggests that screening with low PSA thresholds for biopsy in young patients detects tumors that fulfill the criteria for insignificant cancer in only 12% of patients (Krumholtz et al, 2002). Even among those that do, some tumors are multifocal or do not have a diploid complement of chromosomes. At present, no tumor marker or algorithm can identify indolent tumors with certainty.

Physicians discussing newly diagnosed prostate cancer with patients must decide on management based on the PSA level, the estimated tumor volume, and the Gleason score (up to one half of patients are upgraded on the basis of the radical prostatectomy specimen) (Pinthus et al, 2006; Suardi et al, 2008; Thaxton et al, 2010; Vellekoop et al, 2014) to select patients for immediate treatment or active surveillance. Repeated biopsies are always subject to sampling errors (Harnden et al, 2008) and may induce fibrosis in and around the prostate gland that could compromise subsequent nerve-sparing surgery, rendering it impossible to perform in more than half of patients (Barzell and Melamed, 2007), and may trigger inflammation leading to PSA fluctuations that are difficult to interpret.

Treatment is more likely to be successful if given earlier while the tumor is smaller and the prospects for potency-sparing surgery are greater. Deferred treatment is more appropriate for older patients with a limited life expectancy or comorbidities. Additional clinical and laboratory research are needed to define the parameters for safe use of active surveillance in younger men, including the appropriate selection criteria, follow-up procedures, and trigger points for intervention (Carter et al, 2003; Allaf and Carter, 2004; Wilt, 2008). It will also be necessary to determine the proportion of patients that would still have curable disease when they are treated at the time of objective disease progression. In many instances, active surveillance delays the treatment by only a few years; however, Freedland and colleagues reported that delays of more than 6 months conferred a 2.73-fold increased risk of progression in patients with low-risk prostate cancer (Freedland et al, 2006). Active surveillance frequently amounts to delayed treatment, and patients selected for active surveillance have cancers that are most curable with the fewest side effects. Some with curable disease would have surveillance until the opportunity for cure was lost, and it would be a mistake to treat patients only with incurable disease. For the present, patients who opt for active surveillance should be evaluated with DRE and PSA testing quarterly or semi-annually and should consider undergoing repeated prostate biopsy procedures yearly or biennially. In patients with a consistent PSA velocity exceeding 0.35 ng/mL/yr, there is a fivefold increased risk of prostate cancer death in the next two to three decades (Carter et al, 2006).

Although it is assumed that quality of life should be largely preserved with active surveillance, studies have demonstrated significant decrements in quality of life with time, including

waning erectile function, diminished urinary continence, and adverse psychological effects from living with untreated cancer (Hoffman et al, 2004). For example, in the Scandinavian study, men randomized to watchful waiting had a significantly worse quality of life than men randomized to radical prostatectomy (Johansson et al, 2009). This was especially true in men who received androgen deprivation therapy (ADT) (Johansson et al, 2009). A recent study reported that patients undergoing active surveillance and radical prostatectomy have a similar quality of life in most domains at 5 years of follow-up; however, at 6 to 8 years, active surveillance groups have more anxiety and depression (Bergman and Litwin, 2012).

If surveillance biopsy specimens show evidence of increased involvement by cancer, treatment should be instituted if the patient is otherwise healthy and has a 10-year or greater life expectancy. A rising PSA level alone is not an absolute indication for treatment in the active surveillance population; however, as stated earlier, PSA velocity risk count and [−2] proPSA are associated with risk for reclassification on active surveillance (Ross et al, 2010; Tosoian et al, 2012; Patel et al, 2014). Patients may change their mind about remaining on an active surveillance protocol; therefore the physician should review management options on follow-up visits.

In patients with a long life expectancy, there is a certain risk associated with active surveillance. Clearly, it can avoid or delay treatment for some patients, but there will inevitably be those who will miss their opportunity for cure and, tragically, ultimately progress to metastases and death from prostate cancer. Favorable outcomes have been reported in potential candidates for active surveillance treated with prompt nerve-sparing radical prostatectomy (Loeb et al, 2008).

The European prostate cancer screening trial has provided an unequivocally affirmative answer to half of the often-quoted aphorism of Willett Whitmore Jr. concerning prostate cancer, “Is cure possible when it is necessary?” The Scandinavian Prostate Cancer Study Group-4 trial of radical prostatectomy versus watchful waiting provides an affirmative answer to the second part, “Is cure necessary when it is possible?” The pendulum may swing too far toward active surveillance and then return more toward early active treatment.

KEY POINTS: CONSERVATIVE MANAGEMENT

- Prostate cancer treatment outcomes may be influenced by the malignant potential of the tumors as well as by the treatment used. Furthermore, outcome measurements are not necessarily comparable among different forms of therapy, confounding comparisons.
- Traditionally, deferred treatment has been reserved for men with a life expectancy of less than 10 years and a low-grade prostate cancer. Additional research is needed to define the parameters for safe use of active surveillance in younger men, including the appropriate selection criteria, follow-up procedures, and trigger points for intervention.
- A prospective, randomized clinical trial reported that patients with clinically localized prostate cancer managed with watchful waiting have significantly higher rates of local cancer progression, metastases, and death from prostate cancer than do those treated initially with radical prostatectomy. In addition, as discussed earlier, a prospective, randomized screening trial reported that prostate cancer screening with PSA and DRE reduces prostate cancer-specific mortality by 20% to 27% with early follow-up and up to 44% with longer follow-up. Because many of these patients were treated with radical prostatectomy, it may also be inferred to be evidence of the efficacy of radical prostatectomy for localized prostate cancer.

Radical Prostatectomy

Radical prostatectomy was the first treatment used for prostate cancer and has been performed for almost 150 years (Kuchler, 1866; Young, 1905). It is a technically formidable operation with considerable risks for side effects, and, as a result, simpler treatments have been sought for the treatment of early-stage disease. However, no treatment has supplanted radical prostatectomy, and it still remains the gold standard because of the realization that hormone therapy and chemotherapy are never curative, and not all cancer cells can be eradicated consistently by radiation or other physical forms of energy, even if the tumor is contained within the prostate capsule. Moreover, if the prostate gland remains in situ, it is possible for new prostate cancers to develop in the retained prostatic epithelium.

Innovations have led to the wider use of radical prostatectomy:

1. The development of the anatomic radical retropubic prostatectomy, which allows the dissection to be performed with good visualization and preservation of the cavernous nerves responsible for erectile function and preservation of the external sphincter muscle and yields urinary continence rates in excess of 90% (Walsh and Donker, 1982)
2. The development of extended ultrasound-guided biopsy regimens, performed with local anesthesia as office procedures (Arnold et al, 2001)
3. The widespread use of PSA testing, which has led to the majority of patients being diagnosed with clinically localized disease

In recent years, laparoscopic and robotic approaches have been developed for performing the operation.

The main advantage of radical prostatectomy is that it offers the possibility of cure with minimal collateral damage to surrounding tissues if it is skillfully performed (Han et al, 2001a; Hull et al, 2002). Furthermore, it provides more accurate tumor staging by pathologic examination of the surgical specimen. Also, treatment failure is more readily identified, potentially curative salvage radiotherapy can be undertaken, and the postoperative course is much smoother than in the past. Few patients require nonautologous blood transfusions. The hospital stay is usually 1 to 3 days, and operative mortality is rare in the modern era. Moreover, radical prostatectomy significantly reduces local tumor progression and distant metastases and improves cancer-specific and overall survival rates compared with watchful waiting (Bill-Axelson et al, 2008, 2014). Some patients with tumor recurrence after radical prostatectomy can be successfully treated with potentially curative postoperative radiotherapy (Stephenson et al, 2004b; Trock et al, 2008).

The potential disadvantages of radical prostatectomy are the necessary hospitalization and recovery period; a possibility of incomplete tumor resection, if the operation is not performed properly or if the tumor is not contained within the prostate gland; and a risk for erectile dysfunction and urinary incontinence. However, erectile dysfunction and rectal complications are less likely with nerve-sparing surgery than with radiotherapy, and good treatment options are available to treat both urinary incontinence and erectile dysfunction. Results reported from high-volume centers are more favorable than those from national surveys (Rabbani et al, 2000; Stanford et al, 2000; Kundu et al, 2004; Sanda et al, 2008; Pierorazio et al, 2013b).

In performing a radical prostatectomy, the surgeon must dissect in the proper tissue plane to remove the prostate from between the neurovascular bundles without permanently damaging the nerves or cutting into the prostate, or worse, leaving part of the prostate behind. Most prostate cancer patients have similar priorities. First they want to survive. Next, they want to remain continent. Third, they want to preserve their potency. These are their main priorities, but they want all three. This constellation of favorable outcomes is known as the "trifecta" (Eastham et al, 2008), and, understandably, patients want to achieve it as quickly and painlessly as possible. Often patients with newly diagnosed prostate cancer would like to avoid any treatment if possible or, after realizing that

treatment is necessary, seek the least burdensome option. This frequently leads to consideration of methods such as active surveillance, cryoablation, or high-frequency ultrasound ablation.

Surgical Approaches to Radical Prostatectomy

Perineal. Total perineal prostatectomy is an acceptable surgical treatment when performed by a surgeon familiar with this approach (Scolieri and Resnick, 2001). It is usually associated with less blood loss and a shorter operative time than the retropubic approach. The disadvantages are that it does not provide access for a pelvic lymph node dissection, there is a higher rate of rectal injury, and there is occasional postoperative fecal incontinence that does not occur commonly with other approaches (Bishoff et al, 1998). Also, it is more difficult to spare the cavernous nerves through the perineal approach.

Retropubic. The open retropubic approach was popularized because of surgeons' familiarity with the surgical anatomy; the lower risk for rectal injury and postoperative fecal incontinence; the wide exposure and ready access provided for pelvic lymphadenectomy; prostate excision with preservation of the neurovascular bundles; and the lower risk for cancer at the surgical margins.

Laparoscopic. The laparoscopic approach is the most daunting method of performing radical prostatectomy. It has been suggested that laparoscopic prostatectomy may be associated with less bleeding, better visualization, less postoperative pain, and shorter convalescence than the standard open approach. Laparoscopic prostatectomy can be performed through a transperitoneal or extraperitoneal approach, but the extraperitoneal approach poses logistical limitations, especially with the use of robotic assistance. The transperitoneal approach facilitates the lymphadenectomy but carries a higher risk of intestinal and vascular injury, urinary ascites, and postoperative ileus and intestinal obstruction.

Furthermore, laparoscopic prostatectomy is associated with a higher risk of severe complications. Hemostasis in the neurovascular bundles is difficult to achieve without applying thermal injury to the neurovascular bundles because of the relative difficulty in rapidly placing hemostatic sutures or applying hemostatic clips laparoscopically. Heat from a harmonic scalpel or electrocautery can irreversibly damage the cavernous nerves. Intraoperative blood loss is less with laparoscopic surgery. Rectal, ureteral, and vascular injuries and anastomotic leaks have also been more common with laparoscopic prostatectomy in some studies (Rassweiler et al, 2003).

A study comparing the results of laparoscopic and open radical prostatectomy revealed that although the laparoscopic approach was associated with less blood loss, of greater concern, it had higher rates of postoperative emergency room visits, readmissions to the hospital, and further surgery for complications (Touijer et al, 2008). Also, patients who underwent a laparoscopic radical prostatectomy were less likely to become continent than those treated with open prostatectomy.

When laparoscopic prostatectomy is performed by a skilled laparoscopic surgeon, reported continence and anastomotic stricture rates are comparable to those achieved with open surgery. It has been claimed that nerve sparing is equivalent or even better with laparoscopic surgery, but direct comparisons and validated results are lacking. The early reported rates of positive surgical margins have been higher with laparoscopic prostatectomy, and the adequacy of cancer control is as yet uncertain because of lack of long-term results (Touijer et al, 2009).

Robotic. Since the introduction of the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) in 2000, the majority of radical prostatectomies in the United States have been performed robotically. Robotic prostatectomy became popularized because of its greater technical ease for the surgeon, especially for tying sutures and performing the vesicourethral anastomosis, and lower blood loss, as in all laparoscopic approaches. It has been aggressively marketed as a less invasive, technologically more advanced method

of performing the operation with less pain and a quicker recovery. The availability of three-dimensional (3D) visualization and enhanced dexterity are its advantages over standard laparoscopic techniques. Robotic assistance has rendered minimally invasive radical prostatectomy technically feasible for many surgeons, whereas pure laparoscopic radical prostatectomy without robotic assistance is technically daunting and has a steep learning curve.

Earlier results were overall favorable (Smith, 2004; Webster et al, 2005; Menon et al, 2007, 2010). In more recent analyses of the impact of radical prostatectomy technique on surgical margin rates, cancer control, and outcomes, no superiority was seen between robotic and open radical prostatectomy for functional or oncologic outcomes (Pierorazio et al, 2013a; Silberstein et al, 2013). However, when a patient survey was used to assess functional outcomes in Medicare participants, robotic prostatectomy was associated with a trend toward more urinary incontinence and no difference in sexual function compared with open radical prostatectomy (Barry et al, 2012).

In terms of surgical incisions, usually six, albeit small, incisions are made in robotic surgery, and in most cases the procedure is performed transperitoneally; for open surgery, one incision 4 to 5 inches in length is made that does not enter into the peritoneal cavity. Comparative studies have shown that open prostatectomy has a similar recovery time and return to normal activity (Weizer et al, 2007; Wood et al, 2007). Meanwhile, robotic prostatectomy was associated with a significantly lower transfusion rate and shorter hospital stays compared with open radical prostatectomy (Tewari et al, 2012; Sammon et al, 2013) but a higher rate of incisional hernias (Carlsson et al, 2013).

Perhaps the most important consideration is that neither the laparoscopic nor the robotic approach has as long a track record of cancer control compared with the open approach (Touijer et al, 2009; Menon et al, 2010; Liss et al, 2012; Novara et al, 2012; Hruza et al, 2013). Even in an expert surgeon's hands, positive surgical margins were more frequent in robotic prostatectomy than open prostatectomy in the earlier studies (Williams et al, 2010; Novara et al, 2012). However, a recent meta-analysis reported lower positive surgical margin rates and complication rates in robotic prostatectomy compared with open radical retropubic prostatectomy and laparoscopic radical prostatectomy (Tewari et al, 2012), but these studies did not compare patients who were treated contemporaneously, and it is likely that patients treated with open prostatectomy had more advanced tumors.

A comparison of a sample of patients from the Medicare database who underwent minimally invasive or open prostatectomy in the earlier adoption period for robotic prostatectomy, from 2003 to 2005, revealed similar overall complication rates between minimally invasive and open prostatectomies; however, the men undergoing minimally invasive prostatectomy had more than a threefold higher rate of requiring salvage therapy for tumor recurrence within 6 months of surgery (Hu et al, 2008). In this study, the more experienced surgeons in minimally invasive radical prostatectomy had better results than less experienced surgeons; however, even the highest-volume minimally invasive surgeons had twice the rate of the patients requiring salvage treatment for cancer recurrence when compared with all surgeons performing open radical prostatectomy. Patients undergoing minimally invasive surgery also were 40% more likely to develop anastomotic strictures.

Schroek and colleagues compared patient satisfaction and regret after radical prostatectomy. Patients who underwent robotic prostatectomy were more than four times more likely to regret their decision (Schroek et al, 2008). The authors suggested that these patients were more likely to be regretful and dissatisfied because of the higher expectations for an "innovative" procedure. These results raise concerns that patients are being misled about the true risks and benefits of minimally invasive procedures to treat prostate cancer.

A population-based propensity-adjusted comparative assessment of robotic and open radical prostatectomy reported a lower rate for robotic prostatectomy in intermediate- and high-risk

patients and less use of additional cancer therapy within 6 months; however, patients undergoing open prostatectomy had less favorable tumor features (that might not be totally eliminated by propensity adjusting), and no data on the important end points of biochemical recurrence, metastases, and prostate cancer-specific mortality were reported (Hu et al, 2014).

Thus, the long-term outcome of cancer control is better documented for open prostatectomy. It is challenging to fairly compare functional outcomes among surgical techniques because of the inherent selection bias in these retrospective studies with different patient selection criteria and baseline comorbidities (Robertson et al, 2013; Yossepowitch et al, 2014). The recommendation for patients considering surgical treatment of their prostate cancer should be not to choose a technique but to choose an expert in a given technique. The importance of the surgeon's experience in reducing complications is well documented (Vickers et al, 2007, 2009; Klein et al, 2008; Abboudi et al, 2014; Thompson et al, 2014; Vickers, 2014).

Selection of Patients for Radical Prostatectomy

An ideal candidate for radical prostatectomy is healthy and free of comorbidities that might make the operation unacceptably risky. He should have a life expectancy of at least 10 years, and his tumor should be deemed to be biologically significant and completely resectable. The generally accepted upper age limit for radical prostatectomy is about 76 years. Older men are more likely to have metastases, and they have a greater risk for prostate cancer-specific death, despite higher death rates from competing causes (Scosyrev et al, 2012a).

Because imaging studies are not accurate for staging prostate cancer, preoperative clinical and pathologic parameters are often used to predict the pathologic stage and thus identify patients most likely to benefit from the operation (Partin et al, 1997, 2001; Makarov et al, 2007; Eifler et al, 2013). These parameters are frequently used in tables and nomograms designed to predict pathologic tumor stage or post-treatment recurrence-free survival probabilities (Kattan et al, 1998, 2000; Ross et al, 2001; Han et al, 2003). New methods of predicting the outcome after radical prostatectomy that incorporate cellular and biologic features to improve accuracy have been reported (Cooperberg et al, 2013; Karnes et al, 2013).

Patients with a low probability of resectable disease or a short life expectancy should not be advised to have surgery. Neoadjuvant hormone therapy does not enhance the resectability of prostate cancer and often increases the difficulty of performing nerve-sparing surgery (Soloway et al, 2002). Similarly, neoadjuvant chemotherapy rarely produces pathologic complete responses (Chi et al, 2008).

The surgeon should realistically counsel the patient on the nerve-sparing aspects of the operation. Nerve-sparing prostatectomy does not materially compromise cancer control in appropriately selected patients; however, it is inappropriate in men with advanced disease. The feasibility of performing nerve-sparing surgery is questionable when there is extensive cancer in the biopsy specimens, palpable extraprostatic tumor extension, serum PSA level above 10 ng/mL, biopsy Gleason score higher than 7, poor-quality erections preoperatively, current and future lack of a sexual relationship, or other medical conditions that may adversely affect erections (e.g., diabetes mellitus, hypertension, psychiatric diseases, neurologic diseases, or medications that produce erectile dysfunction).

Postoperative treatment of erectile dysfunction also should be discussed, including information on phosphodiesterase type 5 (PDE5) inhibitors, intraurethral and intracorporeal administration of vasodilators, vacuum erection devices, venous flow constrictors, and implantable penile prostheses. The discussion also should include the timing of the return of erections. The patient should be warned about the risk for development of Peyronie disease from injury to the penis during sexual activity without a rigid erection (Ciancio and Kim, 2000). He should also be informed

that early postoperative use of intracavernosal injection therapy with vasodilating drugs allows most patients to have normal erections (with arterial blood) shortly after the catheter is removed. This protects against the occurrence of atrophic changes in the penis and allows the resumption of sexual activity early in the postoperative period. If erectile function is a high priority for the patient, he should be reassured that erections almost always can be restored, regardless of whether nerve-sparing surgery could be performed.

The preoperative evaluation should consider the likelihood of success in achieving all goals of surgery and in determining whether the nerves can safely be spared. The surgeon should also discuss the possible need for and potential side effects of postoperative radiotherapy and/or hormone therapy if the final pathology specimen reveals adverse prognostic features or if the PSA does not reach undetectable levels.

Surgical Technique

Radical prostatectomy involves complete removal of the prostate gland and seminal vesicles and usually includes a modified pelvic lymph node dissection as well. The key steps in performing anastomotic nerve-sparing radical retropubic prostatectomy are as follows:

1. Pelvic lymphadenectomy
2. Opening of the endopelvic fascia and limited incision of the puboprostatic ligaments
3. Suture ligation and transection of Santorini dorsal venous complex
4. Dissection of the urethra at the apex of the prostate and transection of the urethra (sometimes the anastomotic sutures are placed at this point in the operation)
5. Dissection of the prostate from the neurovascular bundles
6. Securing and transection of the prostatic pedicles
7. Transection and reconstruction of the bladder neck
8. Dissection of the seminal vesicles and ampullary portions of the vasa deferentia
9. Performance of the vesicourethral anastomosis

The surgeon should strive for complete apposition of the bladder neck and the urethra, with a watertight, tension-free closure.

Pelvic lymphadenectomy is optional in patients at low risk for lymph node metastases. In fact, pelvic lymphadenectomy has been less frequently performed with robotic prostatectomy (Gandaglia et al, 2014). Patients who elect to undergo lymphadenectomy should decide in advance whether they wish to proceed with the prostatectomy if there are nodal metastases. If they do not wish to proceed, the excised lymph nodes are sent for frozen-section examination during the operation. Otherwise, intraoperative frozen-section analysis of pelvic lymph nodes is unnecessary. Some have argued that a more extensive pelvic lymphadenectomy yields better outcomes, but compelling evidence for this is lacking (Weight et al, 2008), and more extensive lymphadenectomy carries a greater risk for postoperative genital and lower extremity lymphedema and lymphocele (Bader et al, 2002; Allaf et al, 2004; Musch et al, 2008). Thromboembolic events and reinterventions are more common in patients with symptomatic lymphocele (Musch et al, 2008). It has been reported that pharmacologic venous thromboembolism prophylaxis reduces the risk of thromboemboli by 40%; however, prophylaxis is not used in many men who undergo radical prostatectomy (Weinberg et al, 2014).

The key to preserving urinary continence is to perform a meticulous dissection, avoiding injury to the external urinary sphincter. Preservation of the bladder neck is unnecessary to achieve good urinary continence. In patients with high-volume or high-grade tumors involving the base of the prostate, preservation of the bladder neck may risk positive surgical margins.

Meticulous dissection is also required to preserve the neurovascular bundles. In performing nerve-sparing surgery, the neurovascular bundles are identified at the apex of the prostate (the dissection can also be performed in an antegrade fashion beginning at the base), and the bundles are dissected free of the posterolateral surface of the prostate gland. Hemostatic sutures or clips may be used to control bleeding from the neurovascular

bundles. Use of electrocautery or a harmonic scalpel risks irreversible thermal injury to the neurovascular bundles.

The prostatic pedicles are suture ligated or hemoclipped and divided close to the gland, avoiding incision into the prostatic capsule. In performing the seminal vesicle dissection, care must be taken to avoid injury to the neurovascular bundles situated immediately lateral and posterior to them.

Postoperative Care

Patients should ambulate with assistance beginning on the afternoon or evening of surgery. The catheter may be removed 3 to 21 days after surgery, depending on the integrity and the amount of tension on the vesicourethral anastomosis. Removal of the catheter before 7 days is associated with a 15% to 20% risk of urinary retention.

After the catheter has been removed, Kegel exercises should be initiated. A protective pad is used until complete urinary control is achieved. The postoperative serum PSA level should be undetectable by 1 month after the operation, depending on the preoperative PSA level. Ultrasensitive PSA measurements frequently falsely classify patients as having tumor recurrence (Taylor et al, 2006).

Cancer Control

The principal objective of radical prostatectomy is to completely excise the cancer. Important cancer control end points are pathologically organ-confined disease with clear surgical margins, biochemical recurrence (detectable serum PSA), local progression, metastases, cancer-specific survival, and overall survival. As discussed earlier, depending on the Gleason score and the PSA doubling time, biochemical (PSA) evidence of recurrence usually precedes clinical metastases by a mean of about 8 years and cancer-specific mortality by about 13 years (Pound et al, 1999).

Nonprogression rates vary with clinical and pathologic risk factors. Independent clinical prognostic factors are tumor stage, Gleason score, preoperative PSA level, and treatment. Adverse prognostic features include non-organ-confined disease, lymphovascular space invasion, extracapsular tumor extension, positive surgical margins, seminal vesicle invasion, and lymph node metastases (Grossfeld et al, 2000; Shariat et al, 2004). In the PSA era, there has been a dramatic stage migration and improvement in prognostic features and treatment outcomes (Han et al, 2001b; Moul et al, 2002).

A rising serum PSA level is usually the earliest evidence of tumor recurrence after radical prostatectomy (Pound et al, 1999). Biochemical recurrence is frequently used as an intermediate end point for treatment outcomes; however, not all patients with biochemical recurrence ultimately develop metastases or die of prostate cancer. In rare instances with high-grade or neuroendocrine tumors that do not produce much PSA, there can be palpable evidence of recurrence despite an undetectable PSA level, indicating a role for DRE in monitoring of patients.

In hormone therapy-naïve men after radical prostatectomy, the median PSA at the time of a newly detected bone metastasis was 32 ng/mL, although a quarter of those metastases occurred at PSA levels of less than 10 ng/mL. Lower PSA at initial diagnosis of prostate cancer and higher Gleason score were correlated with metastasis development at lower PSA level (Loeb et al, 2010b).

The hazard of prostate cancer-specific recurrence continues to increase for at least 15 years after radical prostatectomy, and the risks for mortality may increase for 25 years or more (Shikanov and Eggener, 2011; Bill-Axelson et al, 2014). Therefore it is important to continue to monitor patients long after surgery (Popiolek et al, 2013).

Case selection and the duration and frequency of follow-up monitoring are also important determinants of postoperative outcomes. In Walsh's series of 4478 men who underwent anatomic radical retropubic prostatectomy from 1982 to 2011, without neoadjuvant or adjuvant therapy, during a median follow-up of 10 years

(range 1 to 29) the overall 25-year progression-free, metastasis-free, and cancer-specific survival rates were 68%, 84%, and 86%, respectively. There were significant differences in treatment outcomes between men treated in the pre-PSA and PSA eras. In each era, there were significant differences in progression-free, metastasis-free, and cancer-specific survival by risk groups (Mullins et al, 2012).

Radical prostatectomy also provides long-term cancer control in about half of highly selected men with high-risk or locally advanced disease (Freedland et al, 2007; Loeb et al, 2007; Ellis et al, 2013).

Urinary Continence

In general, urinary continence after radical retropubic prostatectomy is good and varies according to the experience and skill of the surgeon. For high-volume radical prostatectomy surgeons, more than 90% of men recover complete urinary continence. The return of urinary continence is associated with the patient's age: approximately 95% of men younger than 60 years can attain pad-free urinary continence after surgery; 85% of men older than 70 years regain continence. Relatively few require implantation of an artificial urinary sphincter or a sling procedure for stress urinary incontinence.

Erectile Function

Potency after radical prostatectomy is usually defined as the ability to maintain erections sufficiently rigid for penetration and sexual intercourse with or without the help of a PDE5 inhibitor. Most patients with intact libido and erections wish to maintain these functions. Others with poor-quality erections usually wish to have erections that at least offer some rigidity to provide sensory satisfaction for both sexual partners. The return of erectile function after radical prostatectomy correlates with the age of the patient, preoperative potency status, extent of nerve-sparing surgery, and era of surgery. In the most favorable candidates in whom preoperative potency is normal and bilateral nerve-sparing surgery can be performed, up to 95% in their 40s, 85% in their 50s, 75% in their 60s, and 50% in their 70s can attain recovery of erections sufficient for penetration and intercourse with or without the aid of a PDE5 inhibitor. However, in most instances, erections are not as good as they were preoperatively (Sivarajan et al, 2014).

Erections usually begin to return as partial erections 3 to 6 months after surgery and may continue to improve for up to 3 years or more (Burnett, 2005; Glickman et al, 2009). Patients should be encouraged to use erectile aids postoperatively, including PDE5 inhibitors, intraurethral suppositories, intracavernosal injections, or vacuum erection devices. Erection rehabilitation programs using intracavernosal injection therapy or PDE5 inhibitors might hasten the return of erections and increase the proportion of men who recover erections (Montorsi et al, 1997). However, it has been reported that "on-demand," rather than nightly, administration of PDE5 inhibitors was more efficacious in men with erectile dysfunction after bilateral nerve-sparing radical prostatectomy (Montorsi et al, 2008).

Complications

Anatomic nerve-sparing radical prostatectomy provides excellent cancer control with an acceptable complication rate in appropriately selected patients. The overall early complication rate after radical prostatectomy is less than 10% in experienced hands (Kundu et al, 2004). With a careful selection of patients and performance of necessary preoperative cardiovascular evaluation, perioperative mortality has been largely avoided (Mettlin et al, 1997; Kundu et al, 2004).

Early Complications. Early complications include hemorrhage; rectal, vascular, ureteral, and nerve injury; urinary leak or fistula; thromboembolic and cardiovascular events; urinary tract infection; lymphocele; and wound problems. It is advisable routinely to use support stockings and to ensure early ambulation. Prophylactic

anticoagulation and sequential compression devices are advisable in patients at high risk for thromboembolic complications. However, perioperative subcutaneous heparin injection may predispose to lymphoceles, and many surgeons reserve pharmacologic prophylaxis for high-risk patients (Orvieto et al, 2011).

Inadvertent injury to the obturator nerve can occur during the pelvic lymphadenectomy. When a tension-free primary nerve repair is not feasible, nerve grafting can be performed by a cutaneous or genitofemoral nerve graft. However, even without a nerve repair, conservative management with physical therapy can compensate for the deficit, and therefore many patients do not have a significant thigh adductor deficit after the injury (Kirdi et al, 2000).

Ureteral injury is a rare complication. A minor injury or ligation can be managed with removal of the ligature and ureteral stenting. Mobilization of the distal ureter and reimplantation should be performed for more severe injuries.

Although uncommon, a rectal injury can occur and be repaired primarily by a multiple-layer closure (Lepor et al, 2001; Roberts et al, 2010). However, a diverting colostomy should be considered in men with a large rectal defect, a history of pelvic radiotherapy, or long-term preoperative glucocorticoid therapy.

Late Complications. The most common late complications of radical prostatectomy are erectile dysfunction, urinary incontinence, inguinal hernia, incisional hernia with laparoscopic and robotic prostatectomy, and urethral stricture. Early rehabilitation measures, including Kegel exercises to increase the strength and the bulk of the external sphincter muscle and the use of a PDE5 inhibitor, vacuum erection device, and intraurethral or intracavernosal vasodilator, appear to be helpful in erectile function rehabilitation. Anastomotic or other urethral strictures should be managed initially with dilation, but internal incision and endoscopic injection of glucocorticoids may be required. For a long or persistent anastomotic stricture, a transurethral resection of the scar tissue cephalad to the external sphincter may be necessary. After the resection, an interval of catheter self-dilation of the anastomosis is usually required. Continued self-dilation or intermittent dilation by the urologist is required in difficult, persistent cases. Urethroplasty is rarely needed.

Management of Postoperative Biochemical Recurrence

Patients with detectable PSA (>0.1 ng/mL) after radical prostatectomy usually have persistent cancer, although some have only retained benign prostate tissue causing the PSA elevation. In the latter case, the serum PSA level increases slowly (Freedland et al, 2005). Of patients destined to have biochemical recurrence after radical prostatectomy, approximately 50% of recurrences appear within 3 years, 80% within 5 years, and 99% within 10 years. Rarely, recurrences appear more than 15 years after radical prostatectomy.

The PSA velocity or doubling time, the interval from surgery to biochemical recurrence, and the Gleason score usually reflect how rapidly the tumor is likely to progress (Freedland et al, 2005). In many patients, progression occurs relatively slowly, and only about one third actually develop metastases (Pound et al, 1999; Ward et al, 2004). Numerous studies have shown that patients with a rapidly rising PSA after biochemical recurrence have a high risk of progression to metastases and prostate cancer-specific mortality (Albertsen et al, 2004). In a study of men with a rising PSA after radical prostatectomy who did not receive immediate radiation therapy, the median time to metastases was 8 years after PSA elevation, but only 34% of men developed clinically apparent metastases (Pound et al, 1999).

If salvage radiotherapy is planned, it should be initiated before the PSA level rises much above 0.5 ng/mL (Cox et al, 1999). Patients most likely to have favorable responses to salvage radiotherapy are those with PSA recurrence long after surgery, a slowly rising PSA, low-grade tumor, and no seminal vesicle invasion or lymph node metastases. There is conflicting evidence concerning whether cancer at the surgical margins is a favorable or

unfavorable parameter for predicting response to postoperative radiation therapy, although reports suggest that patients with positive margins have a more favorable response rate. In one study, a multivariate analysis revealed that PSA doubling time, pathologic grade, and PSA at the time of salvage radiotherapy were independent predictors of clinical recurrence, whereas the interval from prostatectomy did not add independent predictive information (Ward et al, 2004).

With both adjuvant radiotherapy and salvage radiotherapy, the beneficial effects are controversial. Some patients fare well without it, whereas treatment in others who have distant metastases will fail despite the patient's having received it. Some patients with PSA recurrence are better managed with ADT than with salvage radiotherapy. Although many men with biochemical failure are treated with ADT, there are no data from prospective trials to address a possible progression-free or overall survival benefit. The most appropriate PSA level at which to institute hormone therapy is unknown. Because of the substantial side effects associated with long-term, continuous hormone therapy (decreased libido, impotence, hot flashes, osteopenia with increased fracture risk, metabolic alterations, and changes in mood), delayed or intermittent ADT is frequently used in patients who have biochemical recurrence, especially those with a slowly rising PSA level (Sharifi et al, 2005; Buchan and Goldenberg, 2010).

The Veterans Administration Cooperative Urological Research Group trials conducted in the 1960s did not show a survival benefit in patients with metastases treated with early ADT (Walsh et al, 2001). However, since then, other prospective, randomized clinical trials have suggested that early ADT is more effective than delayed ADT in patients with pelvic lymph node metastases (Messing et al, 1999) or those with locally advanced or asymptomatic metastatic disease (Immediate versus deferred treatment for advanced prostatic cancer, 1997). Nevertheless, it is uncertain whether these studies can be extrapolated to patients who have biochemical recurrence after primary treatment. A retrospective study reported no difference in early clinical outcome between early and delayed ADT in men with biochemical recurrence after radical prostatectomy (Moul et al, 2004). However, in high-risk patients, early ADT delayed the time to bone metastases.

High-dose bicalutamide administration has been reported to delay disease progression and yield overall survival results equivalent to those of treatment with orchiectomy among patients with PSA recurrence (Wirth et al, 2004). A possible advantage of this form of early hormone therapy is that it is associated with less risk for sexual dysfunction and osteoporosis than other forms of ADT. A disadvantage is a possible increased risk for cardiovascular complications and death associated with high-dose bicalutamide therapy.

Intermittent ADT is a reasonable alternative of providing early ADT while limiting the adverse side effects and expense of continuous ADT. There is accumulating evidence from prospective randomized trials that intermittent ADT is safe in patients without metastases and has survival outcomes comparable to those of continuous ADT (Carneiro and Da Silva, 1999; Lane et al, 2004; Calais da Silva et al, 2014; Buchan and Goldenberg, 2010; Crook et al, 2012; Sciarra et al, 2013).

Preoperative Androgen Deprivation Therapy. Preoperative ADT has been studied for tumor downstaging before radical prostatectomy in patients with locoregional prostate cancer. In general, the results have shown that although the rate of positive surgical margins is reduced, there is no benefit in terms of progression-free survival in the overall study population (Pal et al, 2014).

Although preoperative ADT might not uniformly be beneficial for localized disease, there might be a benefit in patients with high-risk disease. In a SWOG trial, patients with high-risk disease were randomized to receive either ADT alone or ADT with mitoxantrone. In patients receiving ADT alone in an *adjuvant* fashion in this study, biochemical recurrence-free survival was 92.5% at 5 years (Dorff et al, 2011). A Canadian Uro-Oncology Group trial also found improved biochemical progression-free survival with preoperative ADT in the highest-risk PSA group (PSA greater than 20 ng/mL) (Klotz et al, 2003). Similarly, in a retrospective institutional

study, among patients with high-risk disease, the time to biochemical recurrence was significantly longer in patients who had received preoperative ADT (Pal et al, 2014).

Several preoperative ADT trials have either been reported or are ongoing; these trials have assessed or are assessing the potential value of newly approved therapies for metastatic castration-resistant prostate cancer, such as abiraterone or enzalutamide, as preoperative ADT (Taplin et al, 2012).

Salvage Radical Prostatectomy

Radical prostatectomy can be performed in patients in whom other local treatments have failed (Pontes, 1994; Chen and Wood, 2003). However, the rate of complications is far higher, and the complications are more serious and difficult to manage (Stephenson et al, 2004a; Sanderson et al, 2006). Moreover, the prospects for long-term disease-free survival are more limited for salvage prostatectomy than for primary radical prostatectomy.

Most of the reported experience with salvage radical prostatectomy is from the pre-PSA era. Contemporary series of patients selected because of biochemical recurrence have lower morbidity and better cancer control rates (Stephenson et al, 2004a; Ward et al, 2005; Chade et al, 2011). Nevertheless, postoperative incontinence rates are as high as 44% and bladder neck contracture rates as high as 22% (Ward et al, 2005). The incontinence rate is even higher after brachytherapy, presumably because of the higher dose of radiation administered. Long-term progression-free survival rates after salvage prostatectomy in the absence of ADT have not been well documented.

KEY POINTS: RADICAL PROSTATECTOMY

- Radical prostatectomy was the first treatment used for prostate cancer, and it still remains the gold standard. An ideal candidate for radical prostatectomy is a healthy man with a life expectancy of at least 10 years. Preoperative clinical and pathologic parameters are often used to predict the pathologic stage and thus to identify patients most likely to benefit from the operation.
- A rising serum PSA level is usually the earliest evidence of tumor recurrence after radical prostatectomy and is frequently an intermediate end point for treatment outcomes. However, not all patients with biochemical recurrence ultimately develop metastases or die of prostate cancer.
- The most common late complications of radical prostatectomy are erectile dysfunction, urinary incontinence, hernia, and urethral stricture. The return of erectile function after surgery correlates with age of the patient, preoperative potency status, extent of nerve-sparing surgery, and era of surgery; the return of urinary continence is associated with the patient's age.
- The long-term outcome of cancer control is better documented for open prostatectomy.

Radiation Therapy

External beam radiotherapy most commonly involves the use of beams of gamma radiation, usually photons, directed at the prostate and surrounding tissues through multiple fields. To minimize radiation injury to the bladder and rectum, 3D conformal radiotherapy (3D-CRT), in which a computer alters the radiation beams to focus the radiation dose to the region of the prostate gland, was developed (Fraass et al, 1995). The most sophisticated form of 3D-CRT, intensity-modulated radiation therapy (IMRT), can provide localization of the radiation dose to geometrically complex fields (Zelevsky et al, 2006). Image-guided radiation therapy (IGRT) is a method in which imaging techniques are used to guide IMRT to the target area.

Heavy-particle therapy that uses beams of high-energy protons (Shipley et al, 1995; Rossi, 1999) or neutrons (Lawton et al, 1991; Russell et al, 1994) has also been used to treat patients with prostate cancer. Heavy-particle therapy is another form of 3D-CRT in which the radiation beam can be virtually stopped within the tissue, allowing high doses of radiation to be delivered to a localized region and smaller doses to surrounding normal tissues. However, proton beam therapy is extremely expensive, and limited long-term results have been reported (Shipley et al, 1995; Kagan and Schulz, 2010; Sheets et al, 2012; Gray and Efstathiou, 2013; Gray et al, 2013; Yu et al, 2013; Zietman, 2013; Hoppe et al, 2014; Yu et al, 2014). Although it has been reported that proton beam therapy has more gastrointestinal toxicity than IMRT (Sheets et al, 2012), a Medicare analysis of proton beam therapy versus IMRT reported no differences in genitourinary or gastrointestinal toxicity by 24 months after treatment (Yu et al, 2013, 2014).

A possible disadvantage of extreme conformal therapy with IMRT and heavy particles is that they can be too narrowly targeted, so that movement of the prostate caused by differences in rectal or bladder filling could result in geographic misses of the tumor, especially in the important posterior peripheral region of the prostate.

Radiation therapy has been extensively studied for localized prostate cancer. The outcomes of radiation therapy corrected for anatomic disease extent and other prognostic factors have been reported to be comparable to those of radical prostatectomy; however, this is misleading because the end points for determining treatment success or failure are different for radiotherapy and surgery (Gretzer et al, 2002).

Radiation Dose and Field of Treatment

There is evidence from prospective randomized trials that dose escalation and 3D definition improve results considerably (Pollack et al, 2002; Spratt et al, 2014). Currently, doses of 76 to 80 Gy or more have been shown to improve cancer control (Pollack et al, 2000; Dearnaley et al, 2007; Zelefsky et al, 2011). Low-risk patients are now frequently treated with 70 to 72 Gy, intermediate-risk patients with 75 to 76 Gy, and high-risk patients with 80 Gy or more. Doses above 75 Gy are now considered to be indicated; however, doses above 80 Gy have not been demonstrated to be beneficial.

Although the prostate itself can tolerate high doses of radiation, the rectal toxicity limits the dose that can be given in brachytherapy. Image guidance for better target definition is crucial for dose escalation, and high radiation doses require protection of normal tissues. IMRT produces steep dose gradients in which the gradient between 100% and 50% of dose can be as little as 1 to 1.5 cm. Radiation dose escalation requires precision in target definition and a high degree of accuracy in the daily placement of the radiation dose. IMRT offers a safer means of dose escalation (Michalski et al, 2013).

CT imaging is considered the standard imaging modality for 3D-CRT and 3D-IMRT, but CT is less precise than MRI. Therefore, larger margins are required to accurately ensure that the entire prostate gland receives the daily radiation dose. When CT imaging uses only the bone landmarks to localize the prostate gland, the daily radiation treatments might be directed inconsistently, and the rectum might receive increased doses of radiation (Karamanolis et al, 2009).

Radiation Side Effects

The main adverse side effects of radiation therapy are related to injury to the microvasculature of the bladder, rectum, striated sphincter muscle, and urethra. However, urinary incontinence or radiation-induced complications requiring surgical correction are uncommon. Approximately one third of patients experience acute symptoms of proctitis or cystitis during the course of radiotherapy, usually after the dose exceeds 50 Gy. In the great major-

ity, symptoms subside after the completion of therapy. About 5% to 10% have permanent symptoms, such as irritable bowel syndrome and intermittent rectal bleeding or bladder irritability and intermittent gross hematuria (Nam et al, 2014). In comparing morbidities after different radiation therapies, IMRT was associated with reduced gastrointestinal morbidity compared with 3D-CRT and proton therapy (Sheets et al, 2012). In some patients, chronic symptoms develop years after treatment. Some patients require laser cauterization or argon plasma coagulation of radiation-induced telangiectasia for bleeding from the bladder or the rectum (Artibani et al, 2007; Karamanolis et al, 2009). External beam radiotherapy causes more rectal toxicity and less urinary toxicity than brachytherapy (Ferrer et al, 2013).

A prior transurethral resection of the prostate is a relative contraindication to brachytherapy and external beam radiation therapy because the prostate does not hold the seeds well, and radiation after transurethral resection of the prostate is associated with an increased risk of urethral stricture (Devisetty et al, 2010). The presence of severe obstructive urinary symptoms is also a relative contraindication because of the risk of acute urinary retention, which is an even greater risk in patients treated with brachytherapy. Another relative contraindication is inflammatory bowel disease. On the other hand, radiotherapy can gradually relieve obstructive urinary symptoms in men with urinary outflow obstructive symptoms (Malik et al, 2011).

Approximately one half of patients develop erectile dysfunction after radiotherapy for prostate cancer. This is caused by injury to the vasculature of the cavernous nerves and to the corpora cavernosa of the penis, usually beginning about 1 year after the completion of treatment. Younger patients with good baseline erectile function are more likely to retain adequate erections. PDE5 inhibitors are useful in ameliorating the erectile dysfunction associated with radiotherapy (Merrick et al, 1999; Zelefsky et al, 2014). Lower doses of radiation to the penile bulb have been investigated as a means of minimizing radiation-induced erectile dysfunction (Roach et al, 2004). The use of adjuvant ADT also adversely affects erectile function. A study evaluating erectile function in men treated with radiotherapy reported that post-treatment erections were much worse if there was preexisting difficulty or if neoadjuvant ADT was used. However, in one study, a large percentage of patients treated with radiotherapy had never tried erectile dysfunction treatments (Alemozaffar et al, 2011).

Combined External Beam Radiation Therapy and Androgen Deprivation Therapy for Locally Advanced Prostate Cancer

Randomized clinical trials have demonstrated that patients with an intermediate- or high-risk tumor benefit from ADT in conjunction with radiotherapy, whereas those with lower-risk tumors do not. For example, Bolla and colleagues reported that a 3-year course of adjuvant hormone therapy started concurrently with external beam radiation improved local tumor control and survival in patients with locally advanced prostate cancer without significant differences in cardiovascular mortality (Bolla et al, 2002, 2010). Hanks and associates explored the optimal duration of ADT after radiation therapy (Hanks et al, 2003). They showed that 28 months of ADT before, during, and after radiation therapy compared with 4 months of ADT before and during radiation therapy provided significant improvement in all clinical end points except for overall survival (Hanks et al, 2003). However, an overall survival benefit of a longer course of hormone therapy was observed in patients with Gleason grade 8 to 10 disease.

In men with clinical stage T2b to 4N0 disease treated with radiation therapy, ADT of 3 or 6 months' duration improved external beam radiation therapy treatment outcomes (Denham et al, 2011). Concern has been expressed about the possible cardiovascular risks of ADT, particularly the risk of fatal myocardial infarction. Although some studies have reported an increased rate of cardiovascular deaths (D'Amico et al, 2007; Tsai et al, 2007), two prospective trials revealed that although ADT increased the risk of diabetes mellitus,

heart disease, and myocardial infarction, there was no detectable increase in the risk of cardiovascular mortality (Van der Kwast et al, 2007; Efsthathiou et al, 2008, 2009). In addition, a meta-analysis of randomized trials in men with unfavorable nonmetastatic prostate cancer showed that ADT did not increase the risk of cardiovascular death (Nguyen et al, 2011).

In a randomized trial, the combination of radiotherapy plus 6 months of ADT provided inferior survival compared with radiotherapy plus 3 years of ADT in the treatment of clinically localized prostate cancer (Bolla et al, 2009). In a post hoc analysis of three phase III studies of ADT therapy for intermediate-risk cancer treated with radiotherapy with a median follow-up of 10.9 years, 6 months of ADT improved prostate cancer–specific mortality compared with 3 to 4 months in patients with Gleason score 7 prostate cancer (D’Amico et al, 2011). Thus, longer courses of ADT are, in general, recommended for patients with higher-risk disease (Roach, 2014).

Radiation Therapy for Localized Prostate Cancer

No randomized trial has exclusively studied the additional benefit of ADT in the high-risk patients receiving radiotherapy for *localized* prostate cancer. However, on the basis of the randomized trials involving locally advanced disease, long-term concurrent ADT is recommended for unfavorable intermediate-risk, localized high-risk, and locally advanced prostate cancer (Roach, 2014).

In a retrospective cohort study, D’Amico and coworkers (2000) showed that 6 months of ADT (beginning 2 months before and continuing during and after radiation therapy) improved the PSA outcomes in intermediate- and high-risk patients but not in low-risk patients. In a subsequent randomized trial, D’Amico and colleagues (2008) confirmed that 6 months of ADT improved outcomes, mostly in the intermediate-risk patients; ADT was associated with an earlier onset of fatal myocardial infarcts in this study (D’Amico et al, 2007).

On the basis of these studies, **long-term ADT is usually recommended along with external beam radiotherapy in patients with locally advanced disease or localized high-risk disease. In patients with intermediate-risk, localized disease, short-term (6-month) ADT is usually recommended.**

End Points for Treatment Success or Failure

Evaluation of the outcomes of radiotherapy is complicated because cancer cells are not killed immediately after exposure to ionizing radiation. Rather, they sustain lethal DNA damage, but do not die until their next attempt to enter into cell division. Thus, the PSA level gradually decreases for up to 2 to 3 years after the completion of radiotherapy. Accordingly, the PSA level is usually monitored at 6-month intervals until it reaches a nadir. In patients treated with external beam radiotherapy, the prostate gland is not completely ablated and the remaining prostate epithelium continues to produce PSA. Also, inflammation in the prostate gland can produce transient PSA elevations, called a PSA “bounce” (Critz et al, 2003). PSA bounce occurs in about 20% of patients, usually during the first 2 years after treatment, and is more common with brachytherapy (Thompson et al, 2010). Patients with a PSA bounce are more likely to have biochemical failure, and a PSA bounce of greater than 1.4 ng/mL has been associated with biochemical failure, metastases, and prostate cancer death (Feigenberg et al, 2006). Adequate follow-up is necessary to discern whether a PSA increase indicates failure (Thompson et al, 2010).

The biochemical end point used to determine treatment success after external beam radiation therapy is controversial. Until recently, the most frequently used definition was the American Society for Therapeutic Radiology and Oncology (ASTRO) definition (Cox et al, 1999). It required three consecutive PSA increases measured 6 months apart and backdated the time of cancer progression to halfway between the PSA nadir and the first rising PSA level. Thus, it usually took years to determine whether tumor progression had occurred. Without long-term follow-up, the ASTRO definition yielded progression-free survival estimates that appeared 10% to

20% better than they actually were because it takes time for the PSA level to reach a nadir and even more time for three consecutive PSA increases to occur. Moreover, in clinical series there are always more patients with shorter follow-up than with longer follow-up. Thus, backdating of the time of the recurrence moves the time of the recurrence event to a point in the series where the denominator is larger, and therefore the impact of the recurrence on the survival curve is diminished.

The Phoenix definition has replaced the ASTRO definition (Roach et al, 2006). It eliminates backdating but requires the PSA level to rise by 2 ng/mL before treatment failure is declared. Thus the time to recurrence is further prolonged after the PSA level begins to rise, and often it takes a considerably longer time for the PSA level to increase by 2 ng/mL. In some patients, adjuvant ADT may be initiated before the PSA rises to 2 ng/mL. In practice, the Phoenix definition can yield results that are even more favorable than those obtained with the ASTRO definition. Accordingly, it is not possible to make fair comparisons between radical prostatectomy and radiotherapy by use of these outcome measurements (Hoffman et al, 2013).

Treatment Results of External Beam Radiotherapy

With conventional external beam radiotherapy, the 10-year cancer cure rates for patients with clinically localized prostate cancer were approximately 50% (Zietman et al, 2004). Better results have been achieved with 3D-CRT, IMRT, and dose escalation. However, with dose escalation, there is not only a higher chance for cure, but also a higher risk of rectal morbidity (Kuban et al, 2008). As discussed earlier, high-risk patients are frequently treated with 2 to 3 years of ADT after radiotherapy (Bolla et al, 1997; Pilepich et al, 1997). With this regimen, the 5-year progression-free probabilities have been reported to be 70% to 85% (Bolla et al, 1997; Kuban et al, 2008). There are limited data concerning the durable and favorable responses to radiation therapy, especially in young patients. A substantial proportion of patients who are unsuccessfully treated with radiotherapy have tumor recurrence within the radiation field, usually in the central part of the tumor. A decrease in the PSA to 0.5 ng/mL or less after radiotherapy (with or without ADT) is associated with improved prostate cancer–specific mortality rate (D’Amico et al, 2012).

Long-term outcomes support the use of dose-escalated radiotherapy to improve biochemical progression-free survival and distant metastasis rates. A retrospective study of patients with stage T1 to T3 disease treated with 3D-CRT or IMRT in doses of 64 to 86 Gy with or without ADT for a median of 6 months and a median follow-up of 8 years reported that the radiation dose and the use of ADT were both associated with a better biochemical-free survival rate and fewer metastases. However, there was a substantial decrease in PSA control between 5 and 10 or more years of follow-up (Zelevsky et al, 2011). Another long-term phase III study reported that combining ADT with radiotherapy improved the outcomes for intermediate- to high-risk prostate cancer and further supported a role for using higher radiation doses (Denham et al, 2011).

It has been questioned whether the benefits of radiation plus ADT are superior to ADT alone for locally advanced disease. A Scandinavian trial comparing ADT alone with ADT plus radiation in patients with locally advanced prostate cancer revealed that ADT plus radiotherapy halved the 10-year prostate cancer–specific mortality and substantially decreased overall mortality with fully acceptable risk of side effects compared with ADT alone (Widmark et al, 2009). This conclusion was further supported by a phase III study with a median follow-up of 6 years in which the addition of radiotherapy to ADT increased overall survival with little added morbidity. The authors concluded that **men with locally advanced, nonmetastatic disease should not receive ADT alone; rather, ADT combined with radiotherapy should be the new standard** (Warde et al, 2011).

In high-risk patients, external beam radiotherapy has also been combined with brachytherapy (Spratt et al, 2014). The

brachytherapy is usually given first, so that the external beam therapy can be discontinued if the patient begins to experience toxicity (Ragde et al, 1997; Critz et al, 1998; Ragde et al, 1998).

Stereotactic Body Radiation Therapy (CyberKnife)

Stereotactic body radiation therapy (SBRT) involves a linear accelerator mounted on a robotic arm, giving large doses of radiation in a small number of fractions (hypofractionation). Giving larger doses of daily radiotherapy may improve cure rates without increasing toxicity of treatment (Arcangeli et al, 2010).

Limited results have been published in a small number of patients with low-risk disease. These results provide some evidence of short- and intermediate-term safety and evidence of PSA decline, but evidence of long-term safety and efficacy is lacking (King et al, 2009, 2013).

Several phase I studies have reported that with early follow-up SBRT appears to be well tolerated. A phase I multi-institutional study of 5-fraction SBRT for low-risk prostate cancer, using IMRT to deliver 37 Gy/5 fractions with a median follow-up of 44 months, has shown acceptable toxicity rates so far, but further follow-up is needed. SBRT is less costly than standard IMRT (McBride et al, 2012). Another phase I study of men with stage T2b disease or lower, with treatments of 45, 47.5, and 50 Gy in 5 fractions and IGRT with an enema and a rectal balloon to minimize rectal motion, showed minimal toxicity with a median follow-up of 30 months (Boike et al, 2011).

Although initial reports indicated similar treatment efficacy, no long-term follow-up is available to draw conclusions about disease control or late toxicity (Buyyounouski et al, 2010; McBride et al, 2012). A recent report of quality of life after up to 5 years has somewhat allayed concerns over late toxicity (King et al, 2013). Therefore, more research is needed to put hypofractionated radiotherapy on a sound scientific basis (Kupelian et al, 2007; King et al, 2012).

Heavy-Particle Radiotherapy

High-dose proton or neutron beam therapy has been advocated as a more effective method of CRT, but there is no convincing evidence that treatment results are superior to those achieved with photons (Zietman et al, 2005; Martinez et al, 2011; Gray et al, 2013; Zietman, 2013; Hoppe et al, 2014). The gastrointestinal, genitourinary and sexual quality-of-life domains after proton beam therapy have been reported to be similar up to 2 years after therapy (Hoppe et al, 2014).

Brachytherapy

With brachytherapy, radioactive sources (seeds or needles) are implanted directly into the prostate gland, and sometimes into the surrounding tissues, to deliver a high dose of radiation to the tumor while sparing, to the extent possible, the bladder and the rectum. Modern brachytherapy for prostate cancer was originally unsuccessful because freehand implantation of the seeds provided a poor radiation dose distribution; however, newer external template-based techniques provide more uniform implantation patterns.

Brachytherapy has become popular for treatment of patients with clinically localized prostate cancer. It can be performed under general or regional anesthesia. The most commonly used permanent implants are iodine-125 (^{125}I), palladium-103 (^{103}Pd), or cesium-131 (^{131}Cs) seeds. Theoretically, palladium offers a higher radiation dose rate than would be expected to be advantageous for treatment of poorly differentiated tumors that have a shorter cell cycle. However, in practice, no significant advantage has been demonstrated for the use of palladium. Although high-dose rate (HDR) temporary implantation with iridium-192 wires has been used for more aggressive tumors, logistical considerations make it time-consuming, inconvenient, and less practical in many clinical settings.

Brachytherapy Radiation Dose and Fields

There is no preferred isotope (^{125}I , ^{103}Pd , or ^{131}Cs) for brachytherapy and no consensus on the use of supplemental external beam radiotherapy or ADT. Postimplant dosimetry is mandatory, including prescribed dose (D90 or V100 and the normal tissue dose). Brachytherapy is also operator dependent, and quality assurance is vital (Rosenthal et al, 2011).

After the implant has been completed, a post-treatment CT scan is routinely obtained to check the postimplant dosimetry. Dosimetry can be adversely affected by poor implantation or migration of the seeds after implantation. The radiation doses delivered to the prostate are approximately 145 Gy for iodine and 125 Gy for palladium, which are substantially higher than those for external beam radiotherapy. As with external beam radiotherapy, radiation dose is important with brachytherapy (Stone et al, 2007a; Kao et al, 2008). Biochemical recurrence is associated with dosimetry. HDR brachytherapy as a monotherapy has been reported to achieve results similar to external beam radiation in intermediate-risk prostate cancer (Rogers et al, 2012; Yamada et al, 2012).

Direct comparisons of radiation doses between external beam radiotherapy and brachytherapy are not valid; because of the much higher doses of radiation delivered, brachytherapy causes more ablation of the prostate gland. Thus in many patients treated with brachytherapy, post-treatment PSA levels decrease into the undetectable range. Despite this, brachytherapy is seldom used for the treatment of high-volume, high-risk prostate cancers, because IMRT is the preferred method for treatment of aggressive tumors (Spratt et al, 2014).

In patients who have an enlarged prostate gland, it can be technically challenging to implant the entire prostate volume, especially anteriorly. Accordingly, patients are often treated with ADT to shrink the prostate before brachytherapy is performed. Long-term ADT confounds assessment of the response to brachytherapy because it delays PSA rises that would signal tumor persistence or recurrence.

Transrectal ultrasound-guided brachytherapy is the standard approach. MRI is currently being investigated for use in preplanning and postplanning dosimetry with urethral sparing. MRI-CT fusion scans have also been used for this purpose (Bowes et al, 2013).

Results of Brachytherapy

Excellent short-term cancer control rates have been reported with brachytherapy. With the ASTRO failure criteria, 5- and 7-year progression-free survival estimates of 85% and 80%, respectively, have been reported for groups of largely low-risk patients (Ragde et al, 2001). Permanent brachytherapy alone also has been reported to be effective for intermediate-risk patients (Zelevsky et al, 2007). Low-dose rate brachytherapy as monotherapy for low- or intermediate-risk prostate cancer (most patients also receiving ADT) with a median dose of 151 Gy has been reported to yield excellent cancer control ($\leq 6\%$ risk of PSA recurrence at 10 years) (Morris et al, 2013).

External beam radiotherapy combined with permanent-source brachytherapy has been reported to have an efficacy similar to high-dose external beam radiotherapy alone, with possibly increased urinary toxicity (Lee et al, 2007). Dose escalation with brachytherapy boost has been reported to improve disease control and survival (Shilkrut et al, 2013).

A retrospective study reported that HDR monotherapy is safe and effective (median follow-up only 35 months) for intermediate-risk prostate cancer and may be superior to external beam radiotherapy with or without ADT (Rogers et al, 2012). This study adds to the existing literature in support of dose escalation (with HDR brachytherapy) (Martinez et al, 2011).

Side Effects of Brachytherapy

Urinary symptoms are more common after brachytherapy than after external beam radiotherapy, especially in patients with

prostatic hyperplasia. To avoid these problems, α -adrenergic blockers and ADT are usually administered before treatment. Urinary retention occurs in up to 22% of patients. Approximately 10% of patients require transurethral resection of the prostate after brachytherapy. If an aggressive transurethral resection of the prostate is performed, there is a high rate of incontinence, occurring in 20% to 40% of patients. However, a more conservative, "channel" transurethral resection or laser prostatectomy can usually restore voiding function while preserving continence. Preservation of erectile function has been reported in 62% to 86% of patients treated with brachytherapy alone. Impotence rates are higher when brachytherapy is combined with external beam radiotherapy. Furthermore, neoadjuvant ADT frequently used before brachytherapy adversely affects postoperative erectile function. PDE5 inhibitors may be helpful in restoring erections.

Proctitis and rectal injury are less common with brachytherapy than with external beam therapy, but erectile dysfunction occurs more commonly with brachytherapy than with external beam radiation. Other complications associated with brachytherapy include seed migration and rectourethral fistula (Theodorescu et al, 2000; Di Muzio et al, 2003).

Postoperative Radiotherapy as Treatment of Patients with Adverse Pathology

The management of patients with positive surgical margins after radical prostatectomy has recently been reviewed (Valicenti et al, 2013; Yossepowitch et al, 2014). Patients with extracapsular tumor extension, seminal vesicle invasion, or positive surgical margins might have retained cancer cells in the bed of the prostate, and postoperative radiotherapy may eradicate these cells. Radiotherapy administered proactively shortly after surgery (after urinary continence has been attained) in patients with undetectable PSA levels is called *adjuvant* radiotherapy. In contrast, radiotherapy given selectively to men with detectable postoperative PSA levels is called *salvage* radiotherapy. A theoretic advantage of adjuvant radiotherapy is that it is more likely to be successful when the tumor burden is the smallest; however, because PSA is a highly sensitive test, little is lost by delaying with careful monitoring, and most patients whose PSA will never rise will be able to avoid unnecessary postoperative radiotherapy. There is controversy about whether adjuvant or early salvage treatment is preferred as well as about the optimal radiation dose and additional use of ADT (Briganti et al, 2012).

Adjuvant Radiotherapy

There is no controversy regarding whether patients with adverse findings in the radical prostatectomy specimen benefit from adjuvant radiotherapy. However, because there is no convincing survival evidence, the role of adjuvant radiotherapy is debatable when compared with early salvage radiotherapy (Bolla et al, 2012). Adjuvant radiotherapy is usually administered to the bed of the prostate gland in doses in the range of 64 Gy to 72 Gy. It is advisable to wait at least 3 to 4 months after surgery to allow complete wound healing and return of urinary continence. Radiation to the whole pelvis is usually discouraged because of the higher risk for bowel complications (Joo et al, 2013). With adjuvant therapy, the radiation dose is less than for salvage radiotherapy, and there is less need for ADT.

Adjuvant radiotherapy is most likely to benefit patients with positive surgical margins or extracapsular tumor extension without seminal vesicle invasion or lymph node involvement. However, not all patients with extracapsular extension or positive margins have tumor recurrence without adjuvant radiotherapy, and many with highly adverse findings will have treatment failure with distant metastases despite adjuvant radiotherapy. Nevertheless, it is possible that some patients with seminal vesicle invasion or lymph node metastases might benefit from adjuvant radiotherapy with ADT (Cozzarini et al, 2004; Abdollah et al, 2014). There

is level 1 evidence demonstrating the benefits of adjuvant radiotherapy that makes a strong case for discussing it with all patients with adverse pathology findings on the radical prostatectomy specimen.

The SWOG 8794, European Organisation for Research and Treatment of Cancer (EORTC) 20911, and German Cancer Society (ARO 96-02) studies show that **adjuvant radiotherapy reduces the risk of biochemical recurrence by 50% to 60%**. An update of SWOG 8794 (but not EORTC 20911) showed that this benefit extended to a significantly lower risk of metastases and longer overall survival (Bolla et al, 2005; Thompson et al, 2009). The long-term update of EORTC 22911 for patients with pT3 disease or positive margins showed no benefit with regard to distant metastases or overall survival; however, there was a reduction of relapse (Bolla et al, 2012). These latter benefits have been questioned because the cause of death was not ascertained and the surveillance patients had twice as many highly aggressive cancers. Patients with positive margins, including those with high-grade cancers and seminal vesicle invasion, appeared to benefit the most (Van der Kwast et al, 2007).

The EORTC trial showed benefit not only in patients with positive surgical margins but also in those with extracapsular tumor extension and seminal vesicle invasion (Bolla et al, 2005). In the SWOG trial there was a lesser improvement but still a significant benefit for the subset with seminal vesicle involvement (Swanson et al, 2008).

Most patients with focally positive surgical margins, with or without extraprostatic tumor extension, are cured by radical prostatectomy (Eggerer et al, 2011; Spahn and Joniau, 2013). Because adjuvant radiotherapy can be associated with complications, if every patient with adverse pathology were treated, many would be exposed to these side effects unnecessarily. Also, not every patient whose disease progresses is destined to develop metastases and die of prostate cancer (Boorjian et al, 2010; Eggerer et al, 2011; Mauermann et al, 2013), as is reflected by the EORTC 22911 trials showing a progression benefit but not a survival benefit (Bolla et al, 2012). In addition, there is accumulating retrospective evidence that early salvage radiotherapy yields results that are comparable to adjuvant therapy while avoiding treatment in a substantial proportion of patients (Stephenson et al, 2007; Trock et al, 2008; Briganti et al, 2012). Thus the clinical trials of adjuvant radiotherapy have paved the way for early salvage radiotherapy.

Salvage Radiotherapy

Depending on the risk for tumor recurrence, some patients do not opt for adjuvant radiotherapy but rather choose to monitor their PSA levels and avoid further treatment unless there is convincing PSA evidence of tumor progression. Giving salvage radiotherapy early with a very low PSA could be an acceptable alternative to adjuvant radiotherapy (Briganti et al, 2012; King, 2012; Pfister et al, 2014). However, the results of a randomized trial that compared adjuvant radiotherapy with early salvage radiotherapy have not yet been reported.

A multi-institutional retrospective analysis reported that 50% of patients had disease progression at a median follow-up of 45 months after salvage radiotherapy, 10% developed metastases, and 4% died of prostate cancer. The actuarial 4-year progression-free probability was about 45%. In this series, predictors of progression were Gleason grade of 8 or higher, preradiation PSA level above 2 ng/mL, negative surgical margins, and PSA doubling time of 10 months or less (Stephenson et al, 2004b). However, in this series, salvage radiation was sometimes not instituted early in the course of tumor recurrence, as indicated by the relatively high PSA levels.

A retrospective study of men with PSA failure after radical prostatectomy that was unique in that patients received no treatment, salvage radiation therapy, or salvage radiation therapy with ADT reported that **salvage radiotherapy was associated with a threefold reduction in prostate cancer mortality**, and although the addition of ADT provided no additional decrease in the risk for mortality,

the patients who received ADT had higher-risk disease (Trock et al, 2008). Therefore, ADT probably provided additional benefit for these high-risk patients. The benefit was strongest in those with the shortest PSA doubling times, but it is possible that with longer follow-up, a significant benefit also might become apparent in patients with less aggressive tumors (Cotter et al, 2011). **This study has changed the previous dogma that patients with the most aggressive tumors (i.e., rapid PSA recurrence, seminal vesicle invasion, rapid PSA doubling time) do not benefit from salvage radiotherapy.**

A long-term randomized trial reported that whole pelvis radiotherapy improves progression-free survival in men with greater than a 15% risk of pelvic node involvement (Lawton et al, 2007). A matched-pair analysis of patients with lymph node metastases treated with ADT plus radiotherapy versus ADT alone with a median follow-up of 95 months revealed a better 10-year cancer-specific and overall survival with combined therapy. This compels consideration for the role for combined modality therapy in patients with lymph node metastases (Briganti et al, 2011; Kaidar-Person et al, 2013). However, the preponderance of evidence suggests that **pelvic radiotherapy increases toxicity but has no proven effect on survival** (Lawton et al, 2007; Pommier et al, 2007).

Approximately 50% of patients will have a durable response to salvage radiotherapy, but in the absence of clinical trial data, it is not possible to determine the extent to which it reduces clinical tumor recurrence, metastases, and prostate cancer-specific mortality. The location and number of positive margins may not be associated with the outcome after salvage radiotherapy. In general, Gleason grade 8 to 10 is associated with a poorer durable response rate (Bastide et al, 2010; Karlin et al, 2013).

The results of retrospective matched control analyses comparing adjuvant and salvage radiotherapy are conflicting. Several studies reported that adjuvant radiotherapy was superior because the biochemical progression rates were lower than after salvage therapy (Trabulsi et al, 2008; Budiharto et al, 2010; Ost et al, 2011). However, in these studies, a relatively high PSA cutoff triggered salvage therapy. In contrast, in a propensity-matched analysis of men with extraprostatic tumor extension with or without positive margins but with negative lymph nodes in which adjuvant therapy was given within 6 months after surgery and a PSA trigger of 0.5 ng/mL was used to trigger salvage therapy, no significant difference in biochemical recurrence-free rates was observed between adjuvant and salvage radiotherapy in patients with positive margins (Briganti et al, 2012).

Based on a literature review, improved 5-year biochemical progression-free survival rates were observed for patients who received early salvage radiotherapy (PSA ≤ 0.5 ng/mL) compared with patients treated with salvage radiotherapy with a preradiotherapy PSA value above 0.5 ng/mL. Whether the routine application of adjuvant radiotherapy in patients with initially undetectable PSA levels will be associated with demonstrable clinical benefit awaits the results of ongoing prospective trials.

Two prospective phase III randomized trials have been initiated to compare adjuvant versus early salvage therapy in high-risk patients (the Radiotherapy and Androgen Deprivation in Combination after Local Surgery [RADICALS] trial, conducted by the Medical Research Council, and the Radiotherapy—Adjuvant versus Early Salvage [RAVES] trial, conducted by the Trans Tasman Radiation Oncology Group). Pending the results of these trials, **adjuvant therapy should be strongly considered for patients with multiple or very high-risk tumor features—that is, extensive extracapsular tumor extension, multiple or broad-based positive surgical margins, seminal vesicle invasion, and lymph node metastases.** For patients with focally positive margins or minimal extracapsular tumor extension, monitoring PSA every 4 months with early salvage therapy being initiated when the PSA reaches 0.2 ng/mL and is verified to be rising may be more appropriate. In patients with a limited life expectancy, and especially those with Gleason grade 6 or 7 tumors, PSA levels may be monitored to measure the PSA velocity to help determine whether salvage radiotherapy is necessary (Cotter et al, 2011; Karlin et al, 2013).

Side Effects of Adjuvant Radiotherapy

Side effects of adjuvant radiotherapy include a 5% to 10% risk of radiation proctitis or cystitis and a 50% probability that **return of erectile function will be materially compromised.** Radiotherapy also can compromise borderline postoperative urinary continence, but radiotherapy-induced incontinence is relatively uncommon if therapy is delayed until normal urinary continence is well established (Van Cangh et al, 1998; Suardi et al, 2014). The dose of salvage radiotherapy that provides a balance between risks and benefits is not well defined. It has been suggested that, compared with a dose of 66 Gy, a dose of 70 Gy might be optimal in those without local recurrence. Higher doses may be needed in the presence of local recurrence (Shelan et al, 2013). Pending return of continence, ADT can be instituted to reduce the risk of tumor progression. Some patients with highly unfavorable prognostic features with distant metastases, in whom treatment is more likely to fail, probably derive significant benefit from postoperative ADT.

Combined Androgen Deprivation Therapy and Radiotherapy

In high-risk patients who opt for postoperative radiotherapy, **there is controversy about whether they also should receive ADT.** Clinical trials are underway to answer this question. The disadvantages of adding ADT in this setting are the expense and associated side effects. A prospective, randomized trial has demonstrated significantly improved survival in patients with lymph node metastases treated with early ADT (Messing et al, 1999). In a randomized trial of ADT plus radiotherapy versus radiotherapy alone, there was a survival advantage for patients receiving 6 months of ADT. However, all the benefit was observed in patients with no or minimal comorbidities. Men with comorbidities fared worse with ADT (D'Amico et al, 2008).

An increased risk of cardiovascular death has been reported to be associated with ADT (Tsai et al, 2007). In contrast, other studies have found no difference in fatal cardiac events with 4 months of ADT (Roach et al, 2008). A meta-analysis of eight randomized trials in men with unfavorable, nonmetastatic prostate cancer with a median follow-up of 7 to 13 years reported that the cardiovascular death rate was the same in those treated and those not treated with ADT. ADT was associated with lower prostate cancer-specific and all-cause mortality rates. Although randomized trials may not reflect comorbidity in the general population, these results allay some concern regarding the risks of giving ADT with radiotherapy (Nguyen et al, 2010, 2011).

Despite the conflicting results, patients should undergo cardiac risk evaluation before beginning ADT, particularly those with high-risk disease for whom 2 to 3 years of ADT is considered standard (Shelan et al, 2013). It is relevant that dose-escalated salvage radiotherapy (70 Gy) without ADT also has been reported to achieve good biochemical control (Shelan et al, 2013).

Preoperative Radiotherapy for High-Risk Prostate Cancer

Preoperative radiotherapy may have advantages over postoperative treatment. A phase I study for high-risk prostate cancer demonstrated no dose-limiting toxicity with 54 Gy given preoperatively (Koontz et al, 2013).

Comparison of Radiotherapy with Radical Prostatectomy

An important limitation of radiotherapy as a curative modality is tumor heterogeneity with respect to radiation sensitivity. Tumor persistence within the fields of radiation may occur in up to 40% of patients with clinically localized prostate cancer treated with radiation therapy (Stone et al, 2007b; Zelefsky et al, 2008; Crook et al, 2009). Thus in many patients there are some tumor cells that are not eradicated by therapeutic doses of radiation (Kaplan et al, 2008). Accordingly, even if the tumor is confined to the prostate, radiotherapy might not eradicate it. In one study, despite high-dose (>75 Gy) 3D-CRT, nearly half of patients had cancerous biopsy

findings more than 2.5 years after treatment (Zelevsky et al, 2011). In addition, cancerous biopsy findings after treatment are usually associated with a poor prognosis (Scardino and Wheeler, 1985; Stone et al, 2007b; Zelevsky et al, 2008). The patterns of failure after surgery are different from those after radiotherapy. No modality affords 100% local control. Surgery is more likely to fail at the margins, and radiotherapy is more likely to fail in the center of the tumor. The strategies of using ADT, dose escalation, and better dose placement are designed to improve the central local control.

A study of men treated with radiotherapy for stage T1 to T3 disease with a minimum follow-up of 23 years revealed that more than two thirds developed recurrence, and more than half died of prostate cancer. Half of the recurrences occurred after 10 years, and some recurrences developed after 20 years; however, late recurrences might represent a new primary tumor (Swanson et al, 2004).

A systematic overview of radiotherapy for prostate cancer involving more than 150,000 patients reported that there are no randomized studies to compare the outcomes of radiotherapy with radical prostatectomy for patients with low-risk disease. Risk-group comparisons of T stage, Gleason score, and PSA value have reported similar results between radiotherapy and surgery; however, different end points were used to define treatment failure (Nilsson et al, 2004). For instance, in applying the ASTRO criteria to patients treated with radical prostatectomy, the respective 5-, 10-, and 15-year progression-free rates improved from 85%, 77%, and 68% to 90%, 90%, and 90%, respectively (Gretzer et al, 2002). Similarly, in a study of conventional external beam radiotherapy in men with clinical stage T1 to T2 disease treated from 1991 to 1993, freedom from progression by use of the ASTRO criteria was 49% with backdating the time of recurrence and 42% without backdating (Zietman et al, 2004). A retrospective comparison of treatment success in low- and intermediate-risk disease of brachytherapy alone versus radical prostatectomy with or without postoperative radiotherapy reported similar prostate cancer-specific mortality (0.5%), but the median follow-up was only 2 years (Arvold et al, 2011).

The use of PSA nadir of 0.2 ng/mL for patients treated with combined external beam therapy and brachytherapy has been recommended. Failure to achieve this nadir by 60 months almost always is associated with persistent disease (Critz, 2002). However, because external beam radiotherapy is more organ sparing than brachytherapy, post-treatment PSA levels are usually higher in patients treated with external beam radiotherapy only, and thus these patients might not easily achieve a nadir of 0.2 ng/mL.

Valid comparisons of radical prostatectomy with radiotherapy using current treatment methods are lacking. However, the available evidence suggests that radical prostatectomy is more effective in achieving long-term progression-free survival in patients with clinically localized disease (Hoffman et al, 2013). In a population-based study of long-term survival in nearly 60,000 patients with clinically localized prostate cancer from the SEER cancer registry, radical prostatectomy yielded better results than radiotherapy (Lu-Yao and Yao, 1997). However, more favorable results from both treatments would be expected in the PSA era with recent technical advances in surgery and radiotherapy.

A comparison of health-related quality of life after primary treatment of localized prostate cancer in patients and spouses from multiple centers from 0 to 2 years after radical prostatectomy, brachytherapy, or external beam radiation therapy revealed that adjuvant ADT with radiotherapy was associated with worse quality-of-life outcomes. Patients receiving brachytherapy reported having more long-lasting urinary irritation, bowel and sexual symptoms, and transient problems with vitality or hormonal function. The adverse effects of prostatectomy on sexual function were mitigated by nerve-sparing procedures. After prostatectomy, urinary incontinence was observed in some patients, but urinary irritation and obstruction improved, particularly in patients with a large prostate gland. External beam radiotherapy was associated with less urinary irritation and more rectal side effects. Each treatment is associated with a distinct pattern of change in quality-of-life domains related to urinary, sexual, bowel, and hormonal function. These changes influenced satisfaction

with treatment outcomes among patients and their spouses or partners (Sanda et al, 2008). Evidence shows continued declines in functional outcomes over 15 years for both radical prostatectomy and radiotherapy (Resnick et al, 2013).

Secondary Radiation-Induced Malignancies

Concerns have been raised over the development of new primary prostate cancers and highly aggressive second malignancies after radiation therapy in about 1 of 70 patients living more than 10 years after treatment with radiotherapy for prostate cancer, especially radiation-induced cancers of the bladder and rectum; however, the true magnitude of risk is difficult to quantify (Herr and Carver, 2008; Oh and Sandler, 2008; Abdel-Wahab et al, 2009; Murray et al, 2013). A comparative study of second cancers after brachytherapy or radical prostatectomy compared with the general population with a median follow-up of 7.5 years revealed no increase in bladder cancer after brachytherapy, perhaps because of the limited follow-up or the fact that the radiation dose to surrounding tissues is less with brachytherapy (Hinnen et al, 2011).

KEY POINTS: RADIOTHERAPY

- External beam radiotherapy uses gamma radiation beams directed at the prostate and surrounding tissues through multiple fields. To minimize radiation injury to the bladder and the rectum, 3D-CRT, IMRT, image-guided radiotherapy, SBRT, and proton beam radiotherapy have been developed. Patients with a high PSA level, high Gleason score, or large-volume tumor benefit from ADT in conjunction with radiotherapy. Currently, the most frequently used definition to determine treatment success after radiation therapy is the Phoenix definition, which requires PSA increases of 2 ng/mL above the nadir PSA level.
- With brachytherapy, radioactive seeds or needles are implanted directly into the prostate gland to deliver a high dose of radiation to the tumor while attempting to spare the bladder and the rectum. Brachytherapy is used primarily for the treatment of patients with clinically localized prostate cancer, but it is seldom used for the treatment of high-volume, high-risk prostate cancers. Urinary symptoms are more common after brachytherapy than after external beam radiotherapy, especially in patients with prostatic hyperplasia.
- Adjuvant radiotherapy shortly after surgery is most likely to benefit patients with extensive positive surgical margins or extracapsular tumor extension without seminal vesicle invasion or lymph node involvement. Patients most likely to have favorable responses to salvage radiotherapy are those with PSA recurrence long after surgery, slowly rising PSA level, low-grade tumor, and no seminal vesicle invasion or lymph node metastases. However, mortality benefits have also been demonstrated in patients with rapid PSA doubling times and high-risk tumors. Adjuvant radiotherapy reduces relapse rates in patients with high-risk tumor features but does not increase overall survival. Early salvage radiotherapy produces durable responses in most patients with intermediate-risk tumor features. It is unknown whether early adjuvant radiation is better than delayed salvage therapy in patients with adverse pathology findings after radical prostatectomy.

OTHER TREATMENTS

Primary Hormone Therapy

Please see the Expert Consult website for details.



In the past, primary ADT had been used extensively in the treatment of men with localized prostate cancer, especially older men, those with significant medical comorbidities precluding the use of curative therapy, and those who did not wish to undergo curative therapy (Cooperberg et al, 2003; Shahinian et al, 2005). However, it is far less frequently used today because studies suggested increased risks of diabetes mellitus, cardiovascular disease, and osteopenia leading to fractures (Krupski et al, 2004; Saigal et al, 2007; Tsai et al, 2007; Keating et al, 2012). In addition, a recent study of more than 15,000 men with early-stage prostate cancer found that those who received primary ADT instead of surgery or radiotherapy did not live any longer than those who received no treatment (Potosky et al, 2014). Studies of patients matched on propensity to receive ADT did not find an increased risk for cardiovascular mortality with ADT, suggesting that unmeasured factors affecting treatment selection may confound the association (Alibhai et al, 2009; Efsthathiou et al, 2009; Kim and Freedland, 2010; Punnen et al, 2011). Nevertheless, because of these concerns, **primary ADT is not endorsed by the AUA Best Practice Guidelines or by the NCCN guidelines (Thompson et al, 2007; National Comprehensive Cancer Network, 2014).** Moreover, the American Society of Clinical Oncology practice guidelines did not make a strong recommendation for early ADT, even in patients with positive lymph nodes, because of the concern that any decrease in prostate cancer–specific mortality might be offset by an increased risk of nonprostate cancer mortality, with no overall survival benefit (Loblaw et al, 2007; Saigal et al, 2007).

ADT can be used for patients who need symptomatic palliation and who are unfit for curative therapy (Droz et al, 2010). There are limited published contemporary data of men treated with primary ADT for clinically localized prostate cancer. In a large population-based Medicare cohort study, primary ADT did not improve survival among the majority of elderly with localized prostate cancer compared with conservative management (Lu-Yao et al, 2008). However, it could not be ruled out that, in this study, men with higher-risk disease were more likely to have been treated with primary ADT; thus it is not possible to exclude a potential benefit of primary ADT.

A trial of antiandrogen monotherapy with high-dose bicalutamide in patients with localized or locally advanced prostate cancer found that survival was improved in patients treated with radiotherapy (presumably a synergistic effect); however, there was no benefit for patients treated with surgery, and antiandrogen monotherapy may be harmful in patients managed with surveillance, again suggesting that it may not be beneficial overall when used as the only treatment (Iversen et al, 2010).

KEY POINTS: PRIMARY HORMONE THERAPY

- Primary ADT is no longer regarded as appropriate definitive therapy for men with clinically localized prostate cancer, although it may be acceptable for select older men with evidence of progressive disease who have significant medical comorbidities that preclude the use of curative therapy, or those who do not wish to undergo curative therapy. Cardiovascular evaluation is prudent before treatment of men at risk for cardiovascular complications.
- Neoadjuvant preoperative ADT reduces the rate of positive surgical margins but does not significantly affect disease progression, except perhaps in selected patients with very high-risk disease.
- ADT therapy is never curative; nevertheless, many patients experience long-term remissions. Bilateral orchiectomy and estrogen administration have largely been replaced by luteinizing hormone–releasing hormone analogues. Antiandrogens produce less sexual dysfunction and osteoporosis but have a greater risk for adverse cardiovascular complications. Newer agents are currently being integrated into clinical practice.

Cryoablation

In 2008, an AUA Best Practice statement recognized cryoablation of the prostate as an established treatment option for men with newly diagnosed or radiorecurrent organ-confined prostate cancer. Cryoablation has been used as primary whole-gland therapy, as a salvage treatment option after radical prostatectomy or radiotherapy (Babaian et al, 2008), and as focal therapy for low-risk prostate cancer (see section on focal therapy). In general, patients with clinical stage T1c to T2 disease who have a life expectancy greater than 10 years, who have no evidence of metastatic disease, and who are not concerned with potency are considered candidates for whole-gland primary cryoablation. The role of cryoablation remains undetermined for patients with clinical stage T3 disease (Babaian et al, 2008).

Third-generation cryoablation is a procedure in which 12 cryoablation needles are stereotactically inserted through the perineum into the prostate with transrectal ultrasound guidance under general or spinal anesthesia. Argon gas is then used to cool the tissue to below -40°C . An ice ball forms in the tissue, and its expansion is monitored by transrectal ultrasonography. Simultaneously, a warming Foley catheter is inserted to protect the urethra and helium gas is used to warm and preserve the prostatic urethra. The rectum can be protected by injection of a saline solution in the space between the prostate and the rectum. A double freeze-thaw cycle results in more extensive tissue damage and cell death than a single cycle.

The proposed advantages of cryoablation are that it is minimally invasive, it does not involve radiation exposure or surgical risk, repeated treatments are possible, and preservation of potency is possible in some patients (Asterling and Greene, 2009).

Cryoablation can target the whole prostate gland or can be performed as a focal treatment, usually freezing half of the prostate (Finley et al, 2010). Many patients receive ADT before treatment. Some reports have claimed oncologic effectiveness equivalent to other conventional treatments for clinically localized prostate cancer (Bahn et al, 2002; Donnelly et al, 2002; Elkjaer and Borre, 2014); however, other studies have reported that the outcomes are not as good as with radiotherapy or surgery (Roach, 2010b).

Whole-Gland Primary Cryoablation

Cryoablation has been reported to be a safe, effective alternative as primary treatment for localized prostate cancer (Lian et al, 2011) and has been advocated in elderly men who may have underlying comorbidity that precludes radical prostatectomy (Loeb et al, 2007; Chin et al, 2012). Cryoablation is more suited for less bulky prostate cancer. Patients with gross extracapsular tumor extension or seminal vesicle invasion are usually treated with neoadjuvant hormone therapy to reduce the tumor volume and allow for easier inclusion within the ice ball; however, to date, there are no data to suggest that neoadjuvant or concurrent ADT improves postcryoablation outcomes.

There is no universally accepted definition for treatment failure after cryoablation, and in many studies the Phoenix or ASTRO definitions used with radiotherapy have been applied for this purpose. The Phoenix definition is claimed to be the best predictor of tumor recurrence (Pitman et al, 2012). The justification for using the Phoenix criteria is that prostate epithelial cells surrounding the urethra that are spared during cryoablation continue to produce PSA after treatment. Thus it might be argued that a small increase in PSA might not necessarily indicate tumor progression. In practice, an undetectable PSA level is seldom attained after cryoablation; hence, definitions of biochemical recurrence used for radiotherapy are not really appropriate for ablative treatments such as cryoablation. This is because a therapy that completely ablates tissue should result in lower post-treatment PSA level than radiotherapy that eradicates cancer cells but spares nonablated normal prostate tissue. Biochemical recurrence-free rates of 60% to 90% at 5 to 10 years of follow-up after cryoablation have been

reported (Long et al, 2001; Bahn et al, 2002; Donnelly et al, 2002; Prepelica et al, 2005; Cohen et al, 2008; Jones et al, 2008; Sverrisson et al, 2014). However, the use of the Phoenix definition could overestimate the effectiveness, as failure would not be declared by this definition until the PSA level rose by 2 ng/mL, and failure ultimately occurs in many patients who do not achieve a post-treatment PSA level of less than 0.6 ng/mL (Levy et al, 2009).

In many cryoablation programs, part of the follow-up protocol is biopsy at 3 to 6 months and again in 2 to 5 years after the treatment. Post-treatment positive biopsy rates of up to 47% have been reported (El Hayek et al, 2008; Donnelly et al, 2010; Ko et al, 2010; Lian et al, 2011; Chin et al, 2012), with most being in the range of 20% (Sverrisson et al, 2014). It is noteworthy that in some cases, positive biopsy rates have been calculated by dividing the number of positive biopsies by the number of patients in the entire treated cohort, including in the denominator those who did not undergo biopsy, thus diluting the positive biopsy rate. In some studies, only patients requiring subsequent intervention with radiotherapy or ADT were considered treatment failures, and patients who underwent repeat cryoablation for positive biopsy were not considered treatment failures unless they required other treatment modalities or failed by the ASTRO criteria.

Conflicting results have been reported on comparisons of cryoablation with other primary treatments for localized prostate cancer (Chin et al, 2008; Donnelly et al, 2010). Reports from the Cryo On-Line Database (COLD) Registry consisting of case report forms from selected patients who were treated with cryoablation have, in general, reported favorable treatment results with short-term follow-up. In contrast, a single-institution study comparing the outcomes from radical prostatectomy and cryoablation performed during the same period found that cryoablation had less favorable disease-free survival, regardless of the risk subgroup (Caso et al, 2012). A reason for the higher recurrence rate with cryoablation could be that in leaving the urethra in situ, some cancer cells may remain, and some benign periurethral prostatic epithelial cells might subsequently transform into cancer. The other more likely cause of the high recurrence rate is a high rate of insufficient treatment margins, especially peripheral margins.

Complications of cryotherapy have included urinary incontinence, urethral sloughing, osteitis pubis, transient penile paresthesia, perineal and rectal pain, rectal fistula, the need for a transurethral resection of the prostate for urinary obstruction, and erectile dysfunction (Pisters et al, 2008). Studies have reported conflicting evidence regarding comparisons of urinary and sexual bother with cryoablation compared with radical prostatectomy or radiotherapy (Donnelly et al, 2010; Malcolm et al, 2010; Caso et al, 2012); however, a preponderance of evidence indicates that cryoablation is associated with more erectile dysfunction (Asterling and Greene, 2009; Roach, 2010a). Approximately one third of previously potent men treated with whole-gland cryoablation might be expected to be potent after cryoablation. The morbidity profile is improved with current argon-based technology; however, a sudden death from argon gas emboli during prostate cryoablation has been reported (Sandomirsky et al, 2012). Complications associated with salvage cryoablation are more frequent than for primary treatment (Bales et al, 1995; Perrotte et al, 1999; Pisters et al, 1999). Adverse effects are less frequent than for HIFU treatment, but potency results are less favorable, being around 15% to 40% (Asterling and Greene, 2009).

Whole-Gland Salvage Cryoablation

Cryoablation has been used for salvage therapy in patients in whom radiotherapy, radical prostatectomy, or initial treatment with cryoablation has failed (Wenske et al, 2013) and who have a negative metastatic workup (Ismail et al, 2007; Pisters et al, 2009). However, because of the necessary preservation of a thin rim of periurethral tissue for whole-gland ablation or from a more substantial spared portion of the gland with subtotal treatment, the likelihood of cure is limited. The first post-treatment PSA is prognostic of treatment

failure; a PSA level of 0.5 ng/mL or lower correlates with a good outcome (Levy et al, 2009). Some studies have reported excellent survival outcomes and minimal associated morbidity. Others have reported that the main potential advantage of salvage cryoablation may be that it could delay the need for hormone therapy (Ng et al, 2007). Five-year biochemical recurrence-free survival rates after salvage radical prostatectomy have been reported to be more favorable than for salvage cryoablation or brachytherapy. As yet, there are no meaningful long-term outcome data for salvage cryoablation, such as prostate cancer-specific survival or overall survival (Spiess et al, 2013).

In summary, there is no substantial evidence to support cryoablation over the other therapeutic treatment options. Current cryoablation methods have a lower complication rate than earlier methods, but their effectiveness at achieving cancer control is not established. The reported results for salvage after radiotherapy are inferior to those reported for salvage radical prostatectomy. In many studies, the PSA results are confounded by concomitant hormone therapy. There remains concern about viable cancer cells near the warmed urethra, and, in general, the evidence for efficacy and safety in the literature is of limited quality.

High-Intensity Focused Ultrasound Ablation

Acoustic energy can be used with ultrasound focusing to generate heat within the prostate gland, thus ablating focal lesions or the entire gland. Transrectally applied HIFU can elevate the tissue temperature of the prostate up to 100°C (Madersbacher et al, 1995). Within several seconds, a lesion develops with a sharp and predictable volume, leaving the surrounding tissue intact. Mechanisms of action of HIFU involve mechanical interaction of ultrasound waves with tissue, producing coagulating heat, high pressure, cavitation bubbles, and chemically active free radicals that ultimately induce tissue destruction by coagulation necrosis (Chapelon et al, 1999). Days to months are required for necrosis and cavitation to occur. Because HIFU energy is nonionizing, treatment can be repeated.

Treatment is performed with use of general or spinal anesthesia and takes 1 to 4 hours, depending on the prostate volume, which should not exceed 40 mL. The rectal mucosa is cooled (Blana et al, 2004), and a limited transurethral resection of the prostate or a bladder neck incision is often performed at the beginning of the procedure to reduce the risk of postoperative urinary retention (Chaussy and Thuroff, 2003). Most patients require a urethral or suprapubic catheter for several days to weeks. Two commercially available devices for HIFU are most commonly used (Thuroff et al, 2003; Uchida, 2005; Uchida et al, 2005).

HIFU is usually well tolerated; the most common side effect is acute urinary retention, occurring in about 20% of patients. Other potential complications are urinary fistula (2%), incontinence (up to 10%), and erectile dysfunction (20% to 60%), in addition to dysuria, urethral stricture, and perineal pain (Blana et al, 2004; Pickles et al, 2005). One study reported a post-treatment potency rate of 25% (Ganzer et al, 2013). HIFU should be reserved for men with a life expectancy of less than 10 years and for whom sexual function is not an important issue (Marien et al, 2014). Re-treatment of patients is associated with an increase in urinary side effects, but sexual side effects are not significantly increased (Berge et al, 2014).

Clinical studies have reported mixed results regarding the efficacy and safety of HIFU therapy. An early multicenter HIFU study reported 83%, 72%, and 52% progression-free survival rates according to the Phoenix definition for progression in low-, intermediate-, and high-risk disease, suggesting equivalent results to external beam radiotherapy (Crouzet et al, 2010). The progression criteria used were any cancerous biopsy finding or a PSA rise of more than 0.4 ng/mL, but the durability of responses has not been documented (Blana et al, 2004).

HIFU has also been used to treat patients after radiotherapy failures, but limited results have been reported (Gelet et al, 2001).

Early outcomes reflect the risk characteristics of the tumors before radiotherapy. Adverse effects associated with salvage HIFU include rectourethral fistula, severe incontinence, and bladder neck contracture (Warmuth et al, 2010).

Negative biopsy rates have been reported in 64% to 93% of patients, PSA levels below 0.5 ng/mL in 55% to 84%, and 5-year progression-free survival in 60% to 70%. The most common complications were stress incontinence, infection, stricture, and erectile dysfunction (Rebillard et al, 2008). Current complication rates are lower than previously reported because of technical improvements and the frequent performance of transurethral resection of the prostate before HIFU (Rebillard et al, 2008).

Overall, there is insufficient information to recommend HIFU as a standard therapy for clinically localized prostate cancer. The preponderance of current evidence suggests that HIFU does not provide cancer control equivalent to surgery or radiotherapy. For instance, in a small series of patients treated with one commercially available device and no adjuvant hormone therapy (Koch et al, 2007), 10% of patients developed urinary retention after treatment, 20% were incontinent, and 5% had a rectal injury. Only 42% achieved PSA below 0.5 ng/mL and negative biopsy findings. On the other hand, HIFU has been extensively studied in Europe, where it is no longer considered experimental. The results with different machines may not be equivalent. The published reports from Europe are confounded by deficiencies in study design, inhomogeneous patient populations, undersampling of the prostate on biopsies, and frequent use of transurethral resection of the prostate and androgen ablation therapy. These limitations make it impossible to know the true safety or efficacy of HIFU (Koch et al, 2007).

More recently, a large multicenter French study with short follow-up and using the Phoenix definition for failure suggested that HIFU results were equivalent to those of external beam radiotherapy (Crouzet et al, 2010). Biopsy-proven recurrences occurred in 20% of patients with short-term follow-up. The long-term results of HIFU were recently reported in a retrospective review from one center (Ganzer et al, 2013). The actuarial biochemical disease-free survival results were favorable, and the PSA nadir after HIFU was predictive of biochemical failure.

In contrast, poor results with HIFU were shown in a British study of 42 patients with a 2-year follow-up (Challacombe et al, 2009). There was a 48% failure rate and one prostate cancer death; three severe strictures; two fistulae in salvage cases; and three cases that could not be performed because of rectal wall thickness. These investigators abandoned their HIFU program.

It is feasible to perform salvage radical prostatectomy after HIFU with acceptable tumor control, but the salvage complications are similar to those of salvage prostatectomy after radiotherapy (Lawrentschuk et al, 2011).

Focal Therapy for Prostate Cancer

Please see the Expert Consult website for details.



Focal Laser Ablation

Please see the Expert Consult website for details.



Photodynamic Therapy

Please see the Expert Consult website for details.



RECOMMENDATIONS FOR TREATMENT BY PATIENT RISK GROUP

The tumor is staged at the time of diagnosis, and the patient evaluated for comorbidities. The legitimate treatment options and their associated risks and potential benefits are discussed (Tables 112-1 and 112-2). Choice of therapy for an individual patient depends on the availability of high-quality delivery.

Focal therapy has been proposed as an alternative to active surveillance or radical treatment for localized prostate cancer (Marien et al, 2014; van den Bos et al, 2014). However, because prostate cancer is usually multifocal, the fundamental rationale of focal therapy is questionable. Some authors have reported that only the main “index” lesion is likely to progress. However, it has been argued that only 20% of prostate cancers are unilateral and unifocal; there is no reliable imaging modality to rule out aggressive disease; there is no proof that only the index lesion is the potentially lethal tumor; and 50% of prostatectomy specimens in patients with low-risk disease are found to have Gleason pattern 4 disease (Black, 2009).

Several different forms of thermal energy have been used for focal treatment of prostate cancer, including cryoablation, HIFU, laser ablation therapy, radiofrequency ablation, and photodynamic therapy (PDT). In implementing these different focal therapies, varying protocols for patient selection, follow-up, and outcomes have been used. This makes it challenging to make comparative assessments among treatments.

The results of a consensus project on focal therapy trial design in prostate cancer were recently reported (van den Bos et al, 2014). It was recommended that focal therapy should not be offered to patients with clinically insignificant disease who may not benefit from active treatment and in whom focal therapy could be considered overtreatment. Thus, patients with clinically localized Gleason score 3 + 4 disease are appropriate candidates for focal therapy. Nomograms and multiparametric MRI scans that may help identify regions of the prostate that do or do not need treatment may be used to help avoid including patients with lymph node metastases; however, patient age and the PSA density were not recommended as inclusion criteria. Furthermore, it was recommended that there be no limit to the size of the prostate treated, except in the case of HIFU, wherein treatment is not recommended for a prostate exceeding 40 mL. The primary end point of focal therapy should be focal ablation of clinically significant disease (defined as a dominant tumor >0.5 mL) with negative biopsy results at 12 months after treatment. A combination of biochemical, histologic, and imaging results can be used to evaluate tumor control achieved by focal treatment. Follow-up should include periodic PSA measurements and ultrasound-guided systematic whole-prostate biopsies and also targeted biopsies to be performed 6 to 12 months after treatment. Treatment failure is categorized as “in-field” or “out-of-field.” Low-grade, low-volume tumor foci (<3 mm, Gleason 3 + 3) found out of field are not designated as failures. In addition, complications of therapy and the patient’s functional status should be assessed. An accurate definition of biochemical failure cannot be made based on validated data at this time. Phase II and phase III trials of focal therapy are currently underway.

Focal Cryoablation

Focal targeted therapy has been proposed as a potential treatment for localized prostate cancer in an attempt to reduce morbidity, especially for patients who would otherwise be candidates for active surveillance (Ward and Jones, 2012; Durand et al, 2014). However, focal therapy relies on accurate tumor localization to achieve total tumor ablation. Extended pattern prostate biopsy

fails to provide reliable localization of tumors to specific regions of the prostate (Schulte et al, 2008). Therefore it is difficult to select which individual patients should be treated and where in the prostate to treat focally based on a prostate biopsy (Catto et al, 2011).

Favorable early results of focal cryoablation have been reported; however, results reported from the COLD Registry are confounded by selection bias. A matched-pair comparison of focal cryoablation and radical prostatectomy reported similar oncologic outcomes with short follow-up (Bahn et al, 2012); nevertheless, the drawbacks of this comparison were the definition of recurrence used and the short follow-up. Despite the promising data that continue to emerge for subtotal (including focal) cryoablation, **overall clinical experience is limited and long-term results are largely unavailable.** Focal salvage cryoablation is experimental.

Focal High-Intensity Focused Ultrasound Ablation

A pilot trial of focal HIFU was reported in which 60% or more of the prostate was ablated, treated locations were determined by MRI and template mapping biopsy, and the primary end point was only adverse events. Of the patients, 73% were hospitalized for less than 24 hours (Ahmed et al, 2012). The authors reported that 89% of patients had erections sufficient for penetration, 100% had continence at 12 months, and many had significantly decreased lower urinary tract symptoms. Positive biopsy results were present at 6 months in 23%. A commentary on this study pointed out that the study was small with short follow-up and no controls (Challacombe et al, 2012). The patients had very low-volume disease and might have fared equally well without side effects on active surveillance. The HIFU technique used requires a suprapubic catheter and carries a risk of urinary retention. Of the men treated, 17% had a urinary tract infection, 1 went into urinary retention, and 1 had a potentially devastating fistula; 39% had hematuria and 22% had dysuria. Moreover, only 30 of 39 men were free of cancer at 6 months, and 4 required re-treatment. **These results are substantially worse than those of radical prostatectomy or radiotherapy.**

Radiofrequency Interstitial Tumor Ablation

Radiofrequency interstitial tumor ablation (RITA) is a noninvasive technique for patients whose comorbidity precludes procedures that require general anesthesia or hospital admission. Heating prostate tissue to temperatures substantially above 38°C destroys it nonselectively, whereas some claim that *hyperthermia* at less elevated temperatures kills cancer cells selectively. **RITA-induced hyperthermia has been investigated as a treatment of the primary tumor, in combination with radiotherapy, and for salvage after radiotherapy failure** (Prionas et al, 1994; Zlotta et al, 1998; Shariat et al, 2005).

This office-based treatment can be repeated. Careful and constant monitoring is critical to limit the risk of damage to normal tissue (Shariat et al, 2005). Advantages claimed for hyperthermia are that it can be repeated and does not preclude the use of other therapies. However, **long-term data on complications and cancer control are not available** (Beerlage et al, 2000).

Laser-induced thermal therapy is a minimally invasive ablation technique that uses laser light to deposit high-energy photons locally in tissue, causing tissue destruction through rapid heating (McNichols et al, 2004). Energy is delivered to the prostate using laser fibers inserted transperineally through needles, most commonly under MRI guidance (Reynier et al, 2004). Focal laser ablation action is based on a photothermal effect. The technologically more advanced 980-nm diode lasers are increasingly used (Colin et al, 2012). Monitoring of the procedure can be achieved by using fluoroptic thermometry next to critical structures, such as the prostate apex or near the rectum, or by using magnetic resonance thermometry (Woodrum et al, 2010).

Focal laser ablation is a potential tool for focal therapy of low-risk prostate cancer. Precision, real-time monitoring, MRI compatibility, and low cost of an integrated system are the suggested advantages of this therapy. The feasibility and safety of this technique have been reported in phase I studies (Oto et al, 2013). In one study the procedure took 2.5 to 4 hours to complete. In this study, one third of the patients had a significant decrease in erectile function 6 months after treatment. Few data have been reported on other adverse effects and outcomes. Approximately 20% to 25% of patients had positive biopsy findings in the treated region of the prostate.

PDT is based on tumor cell destruction by light emitted from a laser fiber interacting with a photosensitizing drug delivered to the tumor tissue. The photosensitizing agent is administered intravenously and is activated by light from optical fibers inserted transperineally into the desired region of the prostate under transrectal ultrasonographic guidance (Kasivisvanathan et al, 2013). The absorption of a laser photon by the photosensitizing agent leads to a chain reaction that releases a singlet oxygen and antioxidant enzymes. Singlet oxygen kills tumor cells and destroys tumor vasculature. This results in an acute inflammatory response that attracts leukocytes. It has been reported that the photosensitizing agents accumulate preferentially in cancer cells (Zuluaga et al, 2013).

There are two types of photosensitizing agents. Tissue-activated photosensitizers require hours to days to achieve therapeutic concentrations within the tumor. These agents also accumulate the skin and eyes, and can be activated within those organs for some time after administration; therefore, protection of the skin and eyes against light is required. Vascular-activated photosensitizers have the advantage of having a short drug-light interval because they achieve peak concentrations in the vasculature within minutes. Because the clearance is also rapid, patients can be discharged on the day of treatment without light protection.

The laser fiber is inserted transperineally using a brachytherapy template under ultrasound guidance. After fiber placement, interstitial illumination must be conducted in a darkened room to prevent cutaneous photosensitization. Treatment of anteriorly situated lesions may be limited by pubic arch anatomy. Oncologic treatment outcomes and side effects have not been well documented because of the limited published studies.

TABLE 112-1 Definition of Risk Group

RISK GROUP	CLINICAL STAGE	PSA (ng/mL)	GLEASON SCORE	BIOPSY CRITERIA
Low	T1a or T1c	<10	2-6	Unilateral or <50% of core involved
Intermediate	T1b, T1c, or T2a	<10	3 + 4 = 7	Bilateral
High	T1b, T1c, T2b, or T3	10-20	4 + 3 = 7	>50% of core involved or perineural invasion or ductal differentiation
Very high	T4	>20	8-10	Lymphovascular invasion or neuroendocrine differentiation

TABLE 112-2 Recommended Treatment

RISK GROUP	LIFE EXPECTANCY (YEARS)	RECOMMENDED TREATMENT
Low	0-5	AS, HT
	5-10	AS, RT, HT, O
	>10	RP, RT, AS, O
Intermediate*	0-5	AS, HT, RT, O
	5-10	RT, HT, RP, O
	>10	RP, RT, O, HT
High*	0-5	AS, RT + HT, O
	5-10	RT + HT, HT, RP, O
	>10	RT + HT, RP + RT + HT, HT
Very high*	0-5	AS, RT + HT, O
	5-10	H, RT + HT, ST
	>10	RT + HT, RP + RT + HT, HT, ST, IT

*If there is more than a 20% probability of positive lymph nodes, AS, HT, ST + HT.

AS, active surveillance; HT, hormone therapy; IT, investigational multimodal therapy; O, others; RP, radical prostatectomy; RT, radiation therapy; ST, systemic therapy.

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The complete reference list is available online at www.expertconsult.com.

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113 Active Surveillance of Prostate Cancer

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Natural History of Prostate Cancer in the Prostate-Specific Antigen Era

Rationale for Noncurative Management of Prostate Cancer

Observational Strategies for Prostate Cancer: Watchful Waiting and Active Surveillance

Patient and Disease Factors Affecting the Choice of and Adherence to Active Surveillance

Comparative Outcomes of Treatment and Observational Strategies

Future Research Needs

Observational strategies for prostate cancer include watchful waiting and active surveillance (expectant management). Watchful waiting was a commonly utilized approach in the era prior to prostate-specific antigen (PSA)-based screening for prostate cancer, when most men were detected at an incurable stage and available treatments were associated with a high risk of morbidity. Thus physicians and patients were anxious to avoid treatment if at all possible, waiting until the disease progressed to intervene with a palliative approach. **In contrast, active surveillance has become a standard alternative to curative intervention for select patients diagnosed through PSA-based screening in whom it is judged that the natural history of the disease will be prolonged.** For these men, surveillance is thought to offer a more targeted approach to management, avoiding unnecessary treatment and its risk of associated side effects while allowing for curative intervention for those who experience disease progression on observation.

The interest in active surveillance as a method for reducing over-treatment of prostate cancer is evidenced by a National Institutes of Health (NIH) state-of-the-science conference on this topic ([Ganz et al, 2012](#)), a major focus of which was to outline the changes in the natural history of prostate cancer that occurred with PSA-based screening.

NATURAL HISTORY OF PROSTATE CANCER IN THE PROSTATE-SPECIFIC ANTIGEN ERA

PSA-based screening for prostate cancer led to earlier detection of prostate cancer (stage migration), and thus altered the course of the disease in the absence of treatment (natural history). The incidence and prevalence of prostate cancer increased with widespread PSA testing, as did the length of time that men live with their disease, as compared to the pre-PSA era. The stage migration that occurred, with application of curative intervention at an earlier stage, undoubtedly led to a reduction in prostate cancer mortality. However, the extent to which this reduction was due to PSA-based screening is debatable ([Etzioni et al, 2008a](#)). Further, because prostate cancer progresses slowly and is found most often in older men with competing risks of mortality, the extent to which these changes in the natural history have resulted in benefit and harm is also debatable ([Carter et al, 2013](#)).

Incidence and Prevalence

The widespread adoption of PSA-based prostate cancer screening in the late 1980s, combined with transrectal ultrasound-directed needle biopsy of the prostate, resulted in a dramatic increase in the incidence of prostate cancer that peaked in 1992-1993 ([Fig. 113-1](#)

and [Table 113-1](#)). The decline in incidence between 1992 and 1995 has been attributed to removal of prevalent cases from the population that would have been detected later. It is estimated that in the United States in 2010 there were 2,617,682 men living with a diagnosis of prostate cancer ([Howlader et al, 2013](#)). The lifetime risks of being diagnosed with or dying of prostate cancer (2008-2010) were 15.33% and 2.71%, respectively (all races). By comparison, for female breast cancer the lifetime risks of developing or dying of cancer were 12.29% and 2.74%, respectively, and for cancer of the colon/rectum (both sexes) the risks were 4.82% and 1.98%, respectively ([Howlader et al, 2013](#)). The discrepancy between the risks of diagnosis and of death for prostate cancer can be attributed to the ease of detection of cancer with a low biologic potential for harm ([Thompson et al, 2004](#); [Haas et al, 2007](#)), rather than the success of curative treatment of the lethal phenotype ([Schröder et al, 2012a](#)).

In addition to changes in the incidence and prevalence of prostate cancer, there have been changes in the pathologic interpretation of biopsies in the PSA era that have altered the natural history of the disease. For example, the Gleason grading system has evolved so that Gleason scores below 6 are not assigned on needle biopsies, and cancers previously graded as Gleason score 6 are now often graded as Gleason score 7 tumors ([Epstein et al, 2005](#)). This upgrading trend made it more likely that a patient previously assigned a Gleason score of low grade would be treated based on the assignment of a higher grade. It has been estimated that the upgrading trend improved the perceived cancer-specific survival by 26% ([Albertsen et al, 2005a](#)).

Natural History of Untreated Disease

The course of prostate cancer in the absence of treatment has been evaluated both in observational studies and in randomized trials. Estimates of cancer-specific mortality derived from pre-PSA-era studies would be higher when compared to estimates from PSA-era studies because of a lead time of 5 to 10 years with PSA-based screening and because of grade inflation (see earlier).

Observational Studies

The outcomes of men with moderately differentiated (Gleason score 5-7) and poorly differentiated (Gleason score 8-10) cancers managed without treatment in the PSA era (1992-2002) and the pre-PSA era (prior to 1992) were compared ([Lu-Yao et al, 2009](#)). Ten-year cancer-specific mortality without treatment for men ages 65 to 74 years with moderately differentiated cancers (Gleason score 5-7) diagnosed in the PSA and pre-PSA eras ranged from 2% to 6% and from 15% to 23%, respectively. For men with poorly

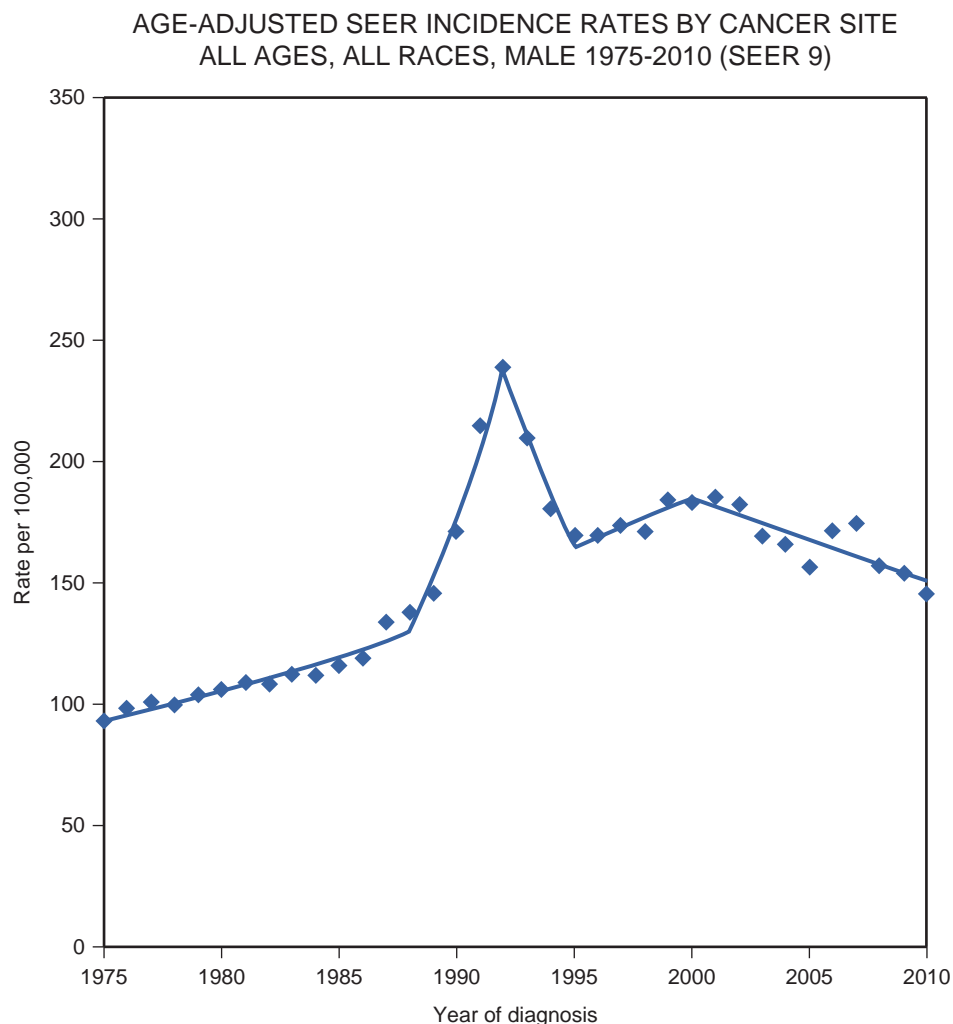


Figure 113-1. Surveillance, Epidemiology, and End Results (SEER) Program age-adjusted prostate cancer incidence. (Modified from Howlader N, Noone AM, Krapcho M, et al, editors. SEER cancer statistics review, 1975-2010. Bethesda (MD): National Cancer Institute, http://seer.cancer.gov/csr/1975_2010/; 2013. Based on November 2012 SEER data submission, posted to the SEER website, 2013.)

TABLE 113-1 The Joinpoint Trend in Surveillance, Epidemiology, and End Results (SEER) Program Cancer Incidence with Associated Annual Percent Change for Cancer of the Prostate between 1975 and 2010, All Races

TREND*	PERIOD
2.6	1975-1988
16.5	1988-1992
-11.6	1992-1995
2.4	1995-2000
-2.0	2000-2010

*Annual percent change (%).

Modified from Howlader N, Noone AM, Krapcho M, et al, editors. SEER cancer statistics review, 1975-2010. Bethesda (MD): National Cancer Institute, http://seer.cancer.gov/csr/1975_2010/; 2013. Based on November 2012 SEER data submission, posted to the SEER website, 2013.

differentiated cancers managed without treatment, 10-year cancer-specific mortality in the PSA and pre-PSA eras ranged from 25% to 38% and from 50% to 66%, respectively. In a competing risk model, the 15-year prostate cancer mortality in the PSA era was estimated to be 0% to 2% for men ages 55 to 74 years with Gleason score 6 or less managed conservatively (Parker et al, 2006). These low-grade prostate cancers make up two of three cancers found with initial PSA-based screening, and three of four or more with follow-up screening using 1- to 4-year screening intervals (Andriole et al, 2009; Schröder et al, 2009). Thus, the pool of disease carrying a low risk of cancer-related death without treatment over a 10- to 15-year period is large with PSA-based screening.

The final report of a follow-up over 32 years of 223 men with prostate cancer managed conservatively after a diagnosis in the pre-PSA era was recently published after all but 3 men had died (Popiolek et al, 2013). At diagnosis 56% of the men were age 70 years or above and intervention per protocol was androgen withdrawal for local or metastatic progression. The important findings from this study were that 64% of men remained untreated and none of these men developed metastatic progression or died of prostate cancer. Further, progression to distant metastasis or prostate cancer death was 13.9% and 12.3%, respectively, for Gleason score 6 or below but considerably higher at 18.2% and 22.7%, 30% and 20%, and 44.4% and 55.6% for Gleason score 3+4, 4+3, and 8-10, respectively. These data and those of Albertsen and colleagues (2005b)

suggest that prostate cancer progression and mortality increase slowly up to 15 years for men with low-grade disease, but do not rapidly increase beyond that time. The increase in mortality after 15 years among men with low-grade cancers in the study with the most complete follow-up (Popiolek et al, 2013) was considered an artifact resulting from small numbers of men surviving. What is unknown is whether or not death from prostate cancer among men with low-grade cancer occurs as a result of undiagnosed (missed) higher grades of cancer or of progression of low-grade to higher-grade cancer. Population data evaluating changes in stage and grade suggest that the former is more likely (Penney et al, 2013).

Randomized Studies

The control arms of randomized trials represent an opportunity for evaluating the natural history of prostate cancer. The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomized 695 men (mean age 65 years) to observation versus radical prostatectomy; 5% were diagnosed through PSA-based screening, 3 of 4 had palpable disease, and the mean PSA level was 13 ng/mL at diagnosis (Bill-Axelson et al, 2011). Recognizing that these men differ from those diagnosed today with PSA-based screening, the cumulative incidence of death from prostate cancer was 20.7% in the control group overall, and 11% for men with low-risk disease (PSA <10 ng/mL and Gleason score <7), similar to the cumulative incidence of death from prostate cancer of 12.3% at 30 years for men with Gleason score 6 cancers managed conservatively in the Swedish observational study (Popiolek et al, 2013). In the SPCG-4 study (Bill-Axelson et al, 2011), of seven men with low-risk disease who underwent surgery and died of prostate cancer, tumors in six patients were upgraded to Gleason score 7 or 8 at radical prostatectomy, further evidence that death from prostate cancer among men with low-risk disease occurs more likely from unrecognized high-grade disease rather than progression of low-grade to high-grade disease.

The Prostate Cancer Intervention versus Observation Trial (PIVOT) randomized 731 men diagnosed with localized prostate cancer to radical prostatectomy or observation (mean age 67 years; median PSA 7.8 ng/mL) (Wilt et al, 2012). In the observation group, bone metastases and prostate cancer death occurred in 10.6% and 8.4%, respectively, through 12 years. Death from prostate cancer occurred in 5.7% and 17.4% of men diagnosed with Gleason score below 7 and 7 and above, respectively, and in 6.2% and 12.8% of men with a PSA of 10 ng/mL or below and above 10 ng/mL, respectively. Stratified by D'Amico risk groups (D'Amico et al, 1998), death from prostate cancer occurred in 2.7%, 10.8%, and 17.5% of men with low-, intermediate-, and high-risk disease, respectively. Recognizing that men in the PIVOT study were more likely to have been diagnosed as a result of PSA-based testing as compared to men in the SPCG-4 study who were not, it is of interest that the cumulative incidence of death from prostate cancer in the SPCG-4 study among men with low-risk disease (11%) is comparable to that of men with intermediate-risk disease (10.8%) in PIVOT. These data could be interpreted as follows: outcomes for men with low-risk disease in the pre-PSA era are comparable with those of men diagnosed today with intermediate-risk disease, as a result of lead time with PSA-based screening and changes in the Gleason scoring system.

Stage Migration and Mortality Changes with Prostate-Specific Antigen–Based Screening

It has been well established that the addition of PSA testing to digital rectal examination results in the detection of prostate cancers that are more likely to be organ confined as compared to detection without PSA testing (Catalona et al, 1993). A trend of using lower PSA thresholds for recommending a prostate biopsy, the removal of more tissue at each prostate biopsy session, and the increasing use of multiple biopsy sessions after a negative prostate biopsy, all occurring during the PSA era, resulted in an

increase in nonpalpable, small-volume, low-grade cancers (Hilton et al, 2012). For example, Cooperberg and colleagues (2005), using data from a cancer registry, reported an increase from 30% to 47% in the proportion of men diagnosed with low-risk disease between the eras 1989-1992 and 1999-2002 while the proportion of men with high-risk disease during these same eras decreased from 37% to 16%. Coincident with the stage migration during the PSA era in the United States, there was a 75% reduction in the rate of advanced prostate cancer and a 40% reduction in the age-adjusted prostate cancer mortality (Howlader et al, 2013). However, it is difficult to know to what extent PSA-based screening or changes in treatment were responsible for the prostate cancer mortality decline. Indeed, ecologic studies have not consistently shown a relationship between PSA uptake and a decline in prostate cancer mortality (Lu-Yao et al, 2008).

Etzioni and associates (2008b) estimated that early detection as a result of screening accounted for 45% to 70% of the prostate mortality decline in the United States, and that changes in treatment explained 22% to 33% of the mortality decline (Etzioni et al, 2012). If half of the 40% mortality decline in the United States were due to PSA-based screening, the mortality reduction would approximate the relative mortality reduction of 20% that was observed in the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Schröder et al, 2012b).

KEY POINT: NATURAL HISTORY OF PROSTATE CANCER IN THE PSA ERA

- Lower PSA thresholds for recommending a prostate biopsy, the removal of more tissue at each prostate biopsy session, and the increasing use of multiple biopsy sessions after a negative prostate biopsy resulted in an increase in nonpalpable, small-volume, low-grade cancers.

RATIONALE FOR NONCURATIVE MANAGEMENT OF PROSTATE CANCER

PSA-based screening and treatment of prostate cancer at a localized stage can prevent prostate cancer death for some men (Schröder et al, 2012b; Wilt et al, 2012). However, the long natural history of most prostate cancers detected through screening and the associated competing mortality risks for many older men who are diagnosed through screening provide a large reservoir for overtreatment—especially if curative intervention is the downstream consequence of every screening-detected prostate cancer. Because curative intervention is associated with functional declines in quality of life, treatment that does not prevent disease progression and/or death from prostate cancer would risk treatment-associated harm without benefit.

Functional Outcomes and Quality of Life after Treatment for Localized Prostate Cancer

Few studies have evaluated the long-term functional outcomes after treatment for localized prostate cancer. In the Prostate Cancer Outcomes Study (Resnick et al, 2013b), investigators evaluated the outcomes of men undergoing radiotherapy and surgery for localized prostate cancer after a diagnosis in 1994-1995. At 15 years, declines in urinary, sexual, and bowel function were common, with domain-specific differences between radiation and surgery at 2 and 5 years following treatment. These quality-of-life declines in urinary, bowel, and sexual function occur to a significantly greater extent among those who undergo treatment for prostate cancer as compared to a normative aging population without a diagnosis of prostate cancer, and symptom distress is more common among men with prostate cancer who are treated compared to those not treated (Mols et al, 2009; Johansson et al, 2011). Sanda and colleagues (2008) prospectively evaluated health-related quality of

life after treatment (radiotherapy and surgery) for localized prostate cancer. They reported that a substantial proportion of men did not return to baseline function in the domains of bowel, sexual, and urinary function; that changes in quality-of-life domains were treatment specific; and that patient and partner outcome satisfaction were closely associated with changes in quality of life after treatment. Thus treatment for prostate cancer commonly results in quality-of-life changes that affect both the patient and his partner.

Risks of Overtreatment of Prostate Cancer

The risk of overtreatment of prostate cancer is high when prostate cancer is discovered on prostate biopsies triggered by PSA testing—the most common scenario. Findings from the Prostate Cancer Prevention Trial (PCPT) highlight the prevalence and ease of detection of low-grade prostate cancers (Thompson et al, 2004). Fifteen percent of men at a median age of 69 years with an average PSA of 1.5 ng/mL had prostate cancer found on a sextant biopsy; 85% of these were low grade. In the PSA range (2.1 to 4.0 ng/mL) at which many men today undergo a prostate biopsy, cancer was found in 25% on prostate biopsy and 80% of these were well differentiated. These data are consistent with an autopsy study in men without a prostate cancer diagnosis at an age and PSA similar to the PCPT (Haas et al, 2007). The authors found prostate cancer in 30% of men on careful step sectioning, and an ex vivo prostate biopsy using standard techniques would have detected half of these (15%), similar to the PCPT. The high prevalence of well-differentiated cancers on prostate biopsy has major implications because of the protracted natural history of these tumors even without treatment (see earlier). Since the average age at diagnosis of prostate cancer is 67 years, an age at which a substantial proportion of men have favorable-risk prostate cancers with a prolonged natural history, the opportunity for overdiagnosis and overtreatment is high if treatment follows diagnosis in most men.

Overdiagnosis is the detection of a cancer that would otherwise not have been diagnosed in the lifetime of the host. Treatment of men who would otherwise not have known about their cancer in the absence of PSA testing is *overtreatment*. Overtreatment exacts a cost to the health care system and potential harm to a patient, with no benefit. For a previously asymptomatic patient, the cost can be substantial in terms of quality of life, and thus the bar should be high for determining the need for curative intervention.

The rate of overtreatment in the United States is similar to the rate of overdiagnosis since the majority of men undergo curative intervention after receiving a prostate cancer diagnosis (Cooperberg et al, 2010a). However, overdiagnosis estimates vary as a result of differences in the metric used for quantification of overdiagnosis, modeling approaches used for estimation of overdiagnosis, and populations studied. Estimates of overdiagnosis ranging between 23% and 42% have been reported based on U.S. incidence (Heijnsdijk et al, 2009), and estimates as high as 66% have been reported from the Rotterdam section of the ESRPC (Draisma et al, 2009). Depending upon the age at diagnosis and the risk status (PSA and grade), the likelihood that a screening-detected cancer has been overdiagnosed can vary from below 5% to more than 75% (Gulati et al, 2011).

Miller and colleagues (2006) estimated the incidence of overtreatment among older men with lower-risk prostate cancer in the United States who were unlikely to benefit from treatment and reported overtreatment rates of 10% and 45% for surgery and radiation, respectively. Recently, it was found that the use of advanced treatment technologies has increased among men in the Medicare population least likely to benefit from treatment, despite increasing awareness of the extent of overtreatment for low-risk disease (Jacobs et al, 2013). Even among older adults, treatment rates for low-risk prostate cancer are high; 59%, 36.6%, and 15.8% of patients ages 75 to 79 years, 80 to 84 years, and 85 years or older were initially treated with radiation therapy in one study using Medicare data (Mishra et al, 2014). These data highlight an important disconnect between evidence and practice given the results from randomized trials comparing treatment to no treatment. Indeed, the

overdiagnosis and overtreatment of prostate cancer greatly contributed to the U.S. Preventative Services Task Force recommendation against generalized PSA screening in 2012.

Comparative Outcomes of Surgery and Observation for Prostate Cancer

The SPCG-4 study (Bill-Axelsson et al, 2011) randomly assigned 695 men (mean age 65 years) with localized prostate cancer to radical prostatectomy or watchful waiting. Unlike men diagnosed today with screening-detected prostate cancer, only 5% were screening detected, three of four had palpable cancers, approximately one in three had Gleason scores of 7 or more, and almost half of the men had PSA levels of 10 ng/mL or more. After 15 years of follow-up, men who underwent surgical treatment had significantly lower rates of distant metastatic disease and death from prostate cancer—an absolute between-group difference of 11.7% and 6.1%, respectively. Among men below age 65 years, there was a significant absolute between-group difference in rates of distant metastatic disease and prostate cancer death of 18.3% and 9.4%. However, for men age 65 years and above, surgery did not provide a benefit in terms of freedom from metastatic disease or prostate cancer death over 15 years of follow-up. These data highlight an important aspect of prostate cancer management: the unlikely probability that treatment will improve health outcomes for older men with favorable-risk disease.

The PSA-era PIVOT (Wilt et al, 2012) randomly assigned 731 men with localized prostate cancer and a mean age of 67 years to radical prostatectomy or observation. While follow-up through 12 years revealed no all-cause or cancer-specific mortality reduction with surgery, a subset analysis suggested an all-cause mortality reduction with surgery for men with a PSA above 10 ng/mL and those with intermediate- to high-risk disease. Other-cause mortality in this trial was higher than in other trials, suggesting that men enrolled had more comorbidities that could have influenced the results. This criticism of the trial ignores the fact that more than 30% of men with a life expectancy less than 5 years and 60% of those with a life expectancy of 5 to 10 years with a diagnosis of low-risk cancer undergo treatment for prostate cancer in the United States (Daskivich et al, 2011; Raldow et al, 2011).

The findings from the SPCG-4 study and PIVOT should inform practice for older men with low-risk disease, especially those with associated comorbidities unlikely to benefit from curative intervention. For these men, no treatment may be the most rational initial management considering that harm (quality-of-life decrement) is likely to outweigh any benefit (prostate cancer mortality reduction).

KEY POINTS: RATIONALE FOR NONCURATIVE MANAGEMENT OF PROSTATE CANCER

- The overdiagnosis and overtreatment of prostate cancer greatly contributed to the U.S. Preventative Services Task Force recommendation against generalized PSA screening in 2012.
- Curative intervention is associated with functional declines in quality of life; therefore treatment that does not prevent disease progression and/or death from prostate cancer results in overtreatment with no clear benefit.

OBSERVATIONAL STRATEGIES FOR PROSTATE CANCER: WATCHFUL WAITING AND ACTIVE SURVEILLANCE

Prostate cancer is in most cases a slowly progressive disease. However, early localized disease is curable, whereas metastatic disease is not. Thus a continued debate among clinicians is whether to treat early to prevent disseminated disease, or observe and delay

treatment until there is evidence of progression. The former risks harm from overtreatment of an indolent disease, whereas the latter risks missing an opportunity for cure among those destined to experience progression. An unmet need is to identify the relatively small proportion of men with localized disease and a lethal phenotype in whom death can be prevented by curative intervention, while avoiding treatment of the large pool of men with indolent disease that can be detected with screening.

It should be recognized that large-scale, long-term comparative studies of observation versus intervention among men with screening-detected prostate cancers do not exist. While PIVOT (Wilt et al, 2012) attempted to address the benefit (or lack thereof) of surgery versus observation for localized prostate cancer in the modern era, the study was underpowered because the enrollment goal could not be achieved (Thompson and Tangen, 2012). Therefore the evidence to support observational strategies for selected men with localized prostate cancer diagnosed in the modern era is based on the long natural history of favorable-risk disease (see earlier) and single-arm studies of men managed without treatment.

A distinction can be made between watchful waiting and active surveillance. As outlined by Parker (2004), these approaches differ in primary aim, patient and tumor characteristics, treatment timing, and treatment intent. The aim of watchful waiting historically was to avoid treatment altogether among men with a limited life expectancy and advanced disease detected in an era when screening was not routine. The rationale for this approach was that, for most, death from another cause was more likely than death from prostate cancer. For these men, treatment was delayed until evidence of disease progression (local or systemic) at which time palliative treatment was initiated, most often with castration. In contrast, active surveillance encompasses a more selective approach to identifying men with favorable-risk disease at low risk of harm without treatment, with the intent to intervene for cure in those who experience disease progression while avoiding treatment-associated harm for those who do not. The ideal candidate, the approach to monitoring, and the triggers that should prompt curative intervention among those being monitored were all identified by the NIH as priorities for future research in active surveillance (Ganz et al, 2012).

Identification of Candidates for Observation

Selection of patients for observation depends upon patient and tumor metrics, as well as a patient's personal preferences (Han et al, 2012). The age, comorbidities, and estimated life expectancy of the patient are important to consider given that prostate cancer can be a slowly progressive disease that may not have time to progress in those whose remaining years of life are limited. Tools for estimating life expectancy are available and their use is encouraged (Walz et al, 2007; Mohan et al, 2011; Cho et al, 2013; Cruz et al, 2013).

In terms of tumor metrics, natural history studies clearly demonstrate that the Gleason score is a powerful predictor of the risk of disease progression and dissemination; in addition, both stage and PSA level at diagnosis provide additional information regarding risk (Table 113-2). Finally, the preference of a patient for living with cancer or the side effects of treatment should be considered in decision making (Hayes et al, 2010; Liu et al, 2012). Patients with similar disease characteristics for whom both observation and curative intervention might be reasonable may have differing personal preferences. For some, willingness to accept a decline in quality of life to be rid of a cancer that has minimal chance of causing harm over a decade or more may seem reasonable, while others would rather live with a cancer and maintain their quality of life. An understanding of a patient's personal preferences should play a large part in shared decision making (Barry and Edgman-Levitan, 2012).

Watchful Waiting

Watchful waiting is a management option for localized disease in men who are not candidates for aggressive local therapy (radiation

TABLE 113-2 Prostate Cancer Risk Stratification*

RISK PROFILE	CRITERIA†	APPROXIMATE PROPORTION OF NEWLY DIAGNOSED CASES‡
Favorable		35%
Very low risk	<ul style="list-style-type: none"> • T1c • Gleason score ≤6 • PSA <10 ng/mL • Fewer than 3 biopsy cores positive, ≤50% cancer in any core • PSA density <0.15 ng/mL per gram 	
Low risk	<ul style="list-style-type: none"> • T1 or T2a • Gleason score 2-6 • PSA <10 ng/mL 	
Intermediate risk	<ul style="list-style-type: none"> • T2b-T2c or • Gleason score 7 or • PSA 10-20 ng/mL 	33%
High risk	<ul style="list-style-type: none"> • T3a or • Gleason score 8-10 or • PSA >20 ng/mL 	32%

*From D'Amico and colleagues (1998) and Epstein and coworkers (1994).

†Modified from National Comprehensive Cancer Network guidelines reported by Mohler and associates (2012) and based on T stage, Gleason score, PSA level, PSA density, and number and percentage of biopsy cores with cancer.

‡Proportions from Surveillance, Epidemiology, and End Results Program of the National Cancer Institute as reported by Shao and colleagues (2010).

PSA, prostate-specific antigen.

Modified from Carter HB. Management of low (favourable)-risk prostate cancer. *BJU Int* 2011;108:1684-95.

and surgery). Elderly men with a limited life expectancy and/or associated comorbidities could be considered ideal candidates for watchful waiting. Cancer-specific outcomes from the Swedish observation study (Popiolek et al, 2013) and those from the Connecticut Tumor Registry (Albertsen et al, 2005b) suggest that in the first 5 years of follow-up only men with the most aggressive disease (Gleason score 8-10) are at risk of prostate cancer death. Thus for men with a life expectancy below 5 years and asymptomatic localized disease, treatment should be withheld in the absence of the highest grades of cancer. Although men with Gleason scores below 8-10 could develop local symptoms, development of metastatic disease or death from prostate cancer is not likely in the absence of treatment within 5 years.

The likelihood of death from initially localized prostate cancer beyond 5 years in the absence of treatment is closely associated with patient age at diagnosis and Gleason score of the cancer (Albertsen et al, 2005b; Popiolek et al, 2013). Cancer-specific survival was more than 80% for men without poorly differentiated cancer at 10 years in the Swedish watchful waiting study, and was 65% and 28% at 15 years for those with Gleason score 7 and 8-10, respectively (Popiolek et al, 2013). Thus one could argue that, in the absence of poorly differentiated cancer, those men without a 10-year life expectancy should not be treated. The results from PIVOT comparing watchful waiting and prostatectomy generally support this conclusion (Wilt et al, 2012). However, as

compared to watchful waiting, prostatectomy resulted in absolute reductions of 9% to 11% in the rate of metastatic disease among men with PSA levels that were greater than 10 ng/mL or with intermediate- or high-risk disease at a median follow-up of 10 years (Wilt et al, 2012). One could draw several conclusions from these data. First, men with favorable-risk disease who have less than a 10-year life expectancy should not be treated for prostate cancer because harm will outweigh any benefit. Second, some men (but not most) with intermediate- and high-risk disease will benefit from curative intervention even when life expectancy is limited to 10 years or less, especially those with high-risk disease. Third, watchful waiting in men with intermediate- and high-risk disease who have more than a 10-year life expectancy may compromise the chance for cure in a substantial minority that will increase with time. Thus watchful waiting could be considered preferable for all men without high-risk disease who have less than a 5-year life expectancy, and an option for those without high-risk disease and a life expectancy below 10 years. Most urologists today would favor active surveillance (not watchful waiting) as an observational strategy for men without high-risk disease and a life expectancy of 5 to 10 years (Mohler et al, 2012).

Active Surveillance

Active surveillance as a management option for localized prostate cancer is offered to appropriate candidates who could also be offered aggressive local therapies (surgery and radiotherapy) with the intent to intervene if the disease progresses (Dall'Era et al, 2012; Bangma et al, 2013; Klotz, 2013). Active surveillance is not recommended for men with high-risk disease, or those with primary Gleason pattern 4 or 5, who have a substantial risk of harboring systemic disease at diagnosis (Eggerer et al, 2011) and of progression to metastatic disease in the absence of treatment (Wilt et al, 2012). However, active surveillance should be considered for those with very low-, low-, and intermediate-risk prostate cancer (see Table 113-2) depending on overall health state and life expectancy, as well as personal preferences. The National Comprehensive Cancer Network (NCCN) guidelines recommend active surveillance as the preferred management option for men with very low-risk disease and a life expectancy below 20 years and those with low-risk disease and a life expectancy below 10 years, and an option for those with low-risk disease and a life expectancy of 10 years or more or intermediate-risk disease and a life expectancy less than 10 years (Mohler et al, 2012).

The results of the PSA-era PIVOT that randomized men to watchful waiting versus prostatectomy suggest that men with intermediate- and high-risk disease can benefit from curative intervention within 10 years (Wilt et al, 2012). These data are consistent with the results of the SPCG-4 pre-PSA-era study that randomized men to watchful waiting versus prostatectomy and found that curative intervention significantly reduced rates of metastatic disease and prostate cancer death (Bill-Axelsson et al, 2011). The subset of men in PIVOT with intermediate- and high-risk disease are more like the men in the SPCG-4 study who were recruited in the pre-PSA era—a substantial proportion with palpable, high-grade disease and PSA levels above 10 ng/mL. Thus active surveillance among men with a life expectancy above 10 to 15 years would appear to be safest for those with very low- to low-risk disease.

The two major limitations in identifying the ideal candidate for active surveillance are (1) defining aggressive disease that will cause harm in the absence of treatment and (2) assessing disease within the prostate without removing the gland. Most agree that, without treatment, Gleason pattern 4/5 has the potential to progress beyond the prostate if given time (Albertsen et al, 2005b; Popiolek et al, 2013). However, pure Gleason pattern 3 would appear to be an indolent phenotype in most men, with limited chance of metastatic progression (Albertsen et al, 2005b; Popiolek et al, 2013). In more than 14,000 radical prostatectomies performed in men with Gleason pattern 3, no patient was found to have lymph node metastases (Ross et al, 2012). A cancer volume of less than 0.5 mL and pure Gleason pattern 3 confined to the

prostate has been considered a definition of indolent prostate cancer, and a number of schemes have been recommended for prediction of these tumors prior to treatment (Epstein et al, 1994; Steyerberg et al, 2007; Dong et al, 2008). However, there is growing recognition that this definition of indolence does not encompass a large proportion of men with more extensive low-grade disease for which treatment would be unnecessary. Thus, there is a greater focus on identifying those patients who have low-grade disease (no Gleason pattern 4/5) who can be safely monitored without immediate treatment.

Identification of patients with purely low-grade cancer is problematic at present because of disease misclassification. Currently used clinical criteria to select men for surveillance can underestimate disease grade and extent in a substantial minority of cases (Tosoian et al, 2013). Thus use of the term *progression* while on surveillance should be replaced with disease *reclassification*, since most patients meeting surveillance criteria who are found to have high-grade or more extensive disease on surveillance biopsies are thought to have been misclassified initially, rather than experiencing true disease progression (Inoue et al, 2014).

Epstein and colleagues (2012), in the largest study evaluating upgrading at radical prostatectomy in the modern era, found that 36% of men with Gleason score 5-6 on needle biopsy were found to have higher-grade disease at radical prostatectomy when tertiary grade was considered. The 10-year actuarial rate of upgrading on annual surveillance biopsies in a large active surveillance experience was approximately 30% (Tosoian et al, 2011). The similarity in the rate of upgrading at radical prostatectomy, and reclassification to high-grade disease on annual biopsies over a decade for men with low-grade cancer, strongly suggest that initial misclassification is the more common reason for reclassification on surveillance, and not “true” disease progression from low to high grade. For this reason, some have recommended “confirmatory” biopsies and/or extensive biopsy strategies with perineal brachytherapy templates to reduce the risk of biopsy misclassification prior to considering active surveillance (Barzell et al, 2012).

There is evidence that higher PSA and PSA density (volume-adjusted PSA), lower percentage of free PSA (fPSA) and higher proPSA, greater extent of low-grade cancer on biopsy (number of cores positive and percentage of positive cores), higher clinical stage, older age, black race, and suspicious findings on multiparametric magnetic resonance imaging (mMRI) are all associated with higher rates of misclassification on prostate biopsy (Tosoian et al, 2011, 2013; Carter, 2012; Stamatakis et al, 2013; Sundi et al, 2013; Cary et al, 2014). In practice, PSA, PSA density, cancer stage, and extent of low-grade cancer on prostate biopsy are most often used for selecting men for surveillance (see Table 113-2).

There is growing enthusiasm for the use of mMRI as a tool to help avoid misclassification of low-grade disease on prostate biopsy and to select men for active surveillance. The use of mMRI for biopsy targeting would appear to have higher sensitivity than transrectal ultrasound-guided systematic biopsies for cancers with Gleason scores above 6 (Turkbey et al, 2011; Hambrook et al, 2012; Siddiqui et al, 2013). Further, mMRI has been shown to have a high negative predictive value for the identification of men who will be reclassified under active surveillance (Fradet et al, 2010; Mullins et al, 2013; Hoeks et al, 2014). This technology, when used to direct prostate biopsies to suspicious areas, may be useful for excluding patients with high-grade disease from active surveillance (Sonn et al, 2014).

Definition of Progression and Triggers for Intervention on Observation

The definition of progression and triggers for intervention differ for active surveillance and watchful waiting since the goals are not the same—aggressive local therapy during a window of curability for active surveillance and palliative therapy in the face of progression for watchful waiting.

Watchful Waiting

Progression of disease among men on watchful waiting could occur as a result of local tumor growth and/or metastatic spread of disease to lymph nodes or bone. A clinician should be cognizant of the potential for local extension of disease resulting in lower urinary tract symptoms (irritative and obstructive) or upper tract obstruction from invasion into the trigone of the bladder, and for development of metastatic disease to lymph nodes or bone. Thus an evaluation that includes history and physical examination (including digital rectal examination of the prostate), PSA and creatinine measurement at 6-month intervals, and an annual bone scan would be a rational program of follow-up for these men. **While disease progression would most often be accompanied by increases in PSA, poorly differentiated cancers producing little PSA can progress without a rising PSA, especially with neuroendocrine differentiation. Thus follow-up should not rely on serial PSA measurements alone.** Symptomatic progression, evidence of upper urinary tract obstruction, or evidence of metastatic disease should trigger consideration of intervention with androgen deprivation therapy as palliative care before the development of irreversible renal or neurologic damage.

Active Surveillance

Most urologists would monitor a patient on surveillance with PSA measurement and digital rectal examination at least biannually, and perform surveillance prostate biopsies at 1- to 2-year intervals (Dall'Era et al, 2012). However, defining disease progression is problematic. Progression in active surveillance programs has been defined based on PSA kinetics or exceeding a given PSA threshold, increased extent of cancer or higher-grade disease on prostate biopsy, change in digital rectal examination, and proceeding to curative intervention. Yet PSA changes (Ross et al, 2010; Whitson et al, 2011) and exceeding a given threshold PSA value (Umbuhr et al, 2014) may not reflect progression of disease. A change in stage or digital rectal examination findings is unusual among patients with low-risk disease (Tosoian et al, 2011). Switching from surveillance to curative intervention may be triggered by a patient's personal preference or anxiety and not necessarily by a change in the cancer. Nevertheless, a younger age at entry into surveillance (Carter et al, 2003; el-Geneidy et al, 2004), higher baseline PSA (Patel et al, 2004; Eastham et al, 2008) and increasing PSA (Khatami et al, 2007), and higher clinical stage at baseline (Klotz, 2005), by baseline biopsy criteria (higher Gleason score and a higher percentage of positive cores) (Eastham et al, 2008), and on repeat biopsy results (Patel et al, 2004; Al Otaibi et al, 2008; Tseng et al, 2010) are associated with the risk of intervention in prostate cancer surveillance programs. Since cancer grade is the strongest feature associated with long-term freedom from disease in untreated men, there has been an effort to predict grade reclassification among men considered for surveillance or being monitored, through the use of prostate biopsy features, imaging, and biomarkers.

Repeat Prostate Biopsy. In a multi-institutional study that included over 23,000 men who underwent radical prostatectomy for treatment of prostate cancer, primary and secondary Gleason pattern 4-5 and seminal vesicle invasion were the strongest pathologic features predictive of prostate cancer-specific mortality (Eggener et al, 2011). **Thus the finding of high-grade disease (Gleason score 7 or higher) on surveillance biopsies has been considered a trigger for intervention in most active surveillance programs (Dall'Era et al, 2012).**

Defining progression on active surveillance based on a surveillance biopsy is difficult because of the rate of grade misclassification at diagnosis (Dall'Era et al, 2012). In a study evaluating men who underwent radical prostatectomy after a diagnosis of very low-risk disease from 2004 to 2012 (contemporary grading system), the upgrading rates to Gleason 3+4, 4+3, and 8-10 were 9%, 2.7%, and 0.9%, respectively, for Caucasians and two to three times higher for African-Americans (Sundi et al, 2013). **The risk of upgrading at radical prostatectomy is higher for men with low-risk versus**

those with very low-risk disease (Tosoian et al, 2013). For example, among men who underwent a radical prostatectomy after a diagnosis of low-risk or very low-risk disease (see Table 113-2), the rate of upgrading to Gleason score 7 or higher was 13% for very low-risk and 22% for low-risk disease, respectively (Tosoian et al, 2013). Thus the finding of high-grade disease on surveillance biopsies is more likely to represent disease misclassification at diagnosis rather than disease progression, and thus the term *reclassification* is recommended.

Biopsy reclassification on surveillance can be defined in terms of a greater extent of disease at biopsy and/or higher grade of disease at biopsy, both predictive of adverse features at radical prostatectomy (Dall'Era et al, 2012; Reese et al, 2013). The extent of cancer (number and percentage of cores with cancer and percentage of core involved with cancer) on prostate biopsy has been shown to correlate with both the extent and grade of cancer at radical prostatectomy (Epstein et al, 2012). Therefore these features are considered proxies for the presence of a higher-grade cancer for which treatment may be beneficial.

Extended Biopsy Schemes. To reduce the rate of biopsy misclassification prior to entry into active surveillance, some have recommended biopsies more extensive than a traditional 12-core sextant scheme that is generally recommended for assessment of an elevated PSA. Both transrectal saturation biopsies, sampling both transition and peripheral zones extensively, and transperineal template mapping biopsies have been evaluated.

Ploussard and colleagues (2014) compared a 21-core transrectal biopsy scheme to a 12-core transrectal approach for initial biopsies among men without a prostate cancer diagnosis and reported that detection of Gleason score cancer above 6 was no different between approaches. Linder and coworkers (2013) evaluated the ability of a 12-core transrectal biopsy and a transrectal saturation biopsy (median 27 cores) to accurately select candidates for active surveillance. In their study, which included radical prostatectomy findings to confirm biopsy results, there was no difference in the rate of upgrading between the two approaches.

Transperineal template mapping prostate biopsy has been shown to identify tumors (often anteriorly located) that are missed by transrectal biopsy sampling among men who might be considered suitable for active surveillance (Onik et al, 2009; Ayres et al, 2012; Barzell et al, 2012; Taira et al, 2013). The rate of upgrading on transperineal mapping biopsies is similar to the rate of upgrading in radical prostatectomy specimens in men considered appropriate for surveillance, suggesting that this approach may provide more accurate information for men who are willing to undergo a more invasive procedure. However, at present this approach would not be considered standard practice prior to embarking on surveillance. Some investigators believe that targeting lesions identifiable by mMRI may provide an alternative means of excluding the presence of high-grade cancer among men considering surveillance (Sonn et al, 2014).

Imaging. mMRI has been reported to have high sensitivity and specificity for high-grade prostate cancers and thus could be of value in reducing disease misclassification and selecting and monitoring individuals interested in active surveillance (Hoeks et al, 2014). Diffusion-weighted MRI, or the evaluation of the diffusion of water through tissues, has been shown to correlate indirectly with Gleason score (Vargas et al, 2011) and could provide an improvement in the ability to identify and target for biopsy the higher-grade cancers. Preliminary analyses of small cohorts of men suggest that, as compared to men without suspicious lesions on mMRI, those with suspicious lesions are at substantially greater risk of disease reclassification while on surveillance, including upgrading (Fradet et al, 2010; Margel et al, 2012; Mullins et al, 2013). Turkbey and associates (2013) evaluated men who underwent mMRI and subsequent radical prostatectomy and reported that mMRI had the lowest misclassification rate of prostate cancers that were more than 0.5 mL and/or Gleason pattern 4/5 as compared to other clinical criteria used to select men for active surveillance. In contrast, an evaluation of men who would be considered suitable for active surveillance—based on a 21-core transrectal biopsy, stage,

and PSA level—and who underwent MRI prior to radical prostatectomy demonstrated no benefit of MRI in predicting the presence of extraprostatic (pT3-4) disease or Gleason score 4+3 or higher (Ploussard et al, 2011). Variability in studies evaluating the use of mMRI in the active surveillance setting are likely due to differences in patient selection, mMRI protocols, and image interpretation. Thus the precise role of mMRI in active surveillance has yet to be clearly defined.

Biomarkers. Both serum and urinary biomarkers have been evaluated in active surveillance populations. **Volume-adjusted PSA (PSA density)** has been a consistent independent predictor of disease reclassification (both cancer volume on biopsy and grade) during surveillance (Tseng et al, 2010; Kotb et al, 2011; San Francisco et al, 2011; Cary et al, 2014), after adjusting for other predictors, including mMRI (Vourganti et al, 2012). As compared to surveillance programs that use PSA density as an enrollment criterion, those that do not do so report higher rates of grade reclassification on surveillance biopsies (Han et al, 2012). For example, the rate of grade reclassification was approximately 4% at each biopsy in a program using PSA density as an enrollment criterion (Tosoian et al, 2011) compared to 20% to 30% when PSA density was not used (Porten et al, 2011). Among men who meet strict criteria for surveillance, including a PSA density below 0.15 ng/mL per gram, there is a direct relationship between absolute PSA level and disease reclassification on surveillance (Umbehr et al, 2014). However, no PSA cut point had both high sensitivity and specificity for reclassification, including grade reclassification. In men who do not have Gleason pattern 4-5 at surveillance biopsy on active surveillance but who pass thresholds for volume reclassification (more than two cores positive and/or more than 50% involvement of any core with cancer), over 90% of those with a PSA level below 4 ng/mL have insignificant cancers that would not warrant curative intervention (Han et al, 2012). Thus continued monitoring may be safe for men with low-grade cancer who have absolute PSA levels below 4 ng/mL even when the extent of cancer on biopsy may disqualify them for surveillance using strict selection criteria.

PSA kinetics, specifically PSA doubling time, has been used in some surveillance programs as a trigger for intervention (Dall'Era et al, 2012). In the watchful waiting arm of the SPCG-4 study, both PSA at diagnosis and PSA velocity during the first 2 years of follow-up were associated with the development of lethal prostate cancer (Fall et al, 2007). However, regardless of the PSA velocity cut point, the ability to accurately classify men who did and did not die of prostate cancer was low. While PSA kinetics has been associated with adverse pathology in men on surveillance (Ng et al, 2009), PSA kinetics (velocity or doubling time) has not been consistently associated with disease reclassification (Ross et al, 2010; Whitson et al, 2011; Thomsen et al, 2014).

PSA isoforms (e.g., percentage of fPSA and proPSA) have been shown to be associated with the presence of more aggressive prostate cancer (Carter et al, 1997; Carter, 2012; Guazzoni et al, 2012). Thus it is not surprising that studies have shown a relationship between PSA isoforms and disease reclassification on surveillance. In conjunction with the percentage of cancer involvement in a biopsy tissue core, the percentage of fPSA was indirectly associated with biopsy reclassification in an active surveillance program (Tseng et al, 2010). The risk of biopsy reclassification (including volume and grade) among 321 men enrolled in active surveillance was 7.6% (95% confidence interval [CI] 4.5% to 11.8%) for men with a fPSA above 15% and a maximum percentage of core involvement with cancer less than 35%, compared to 29.2% (95% CI 20.3% to 39.3%) for those with a fPSA of 15% or below and a maximum percentage of core involvement with cancer of 35% or more. In addition, tissue and serum [−2]proPSA (p2PSA) levels were directly associated with the probability of biopsy reclassification and treatment while on surveillance (Makarov et al, 2009; Isharwal et al, 2011). Tosoian and colleagues (2012) evaluated baseline and longitudinal measures of total PSA, fPSA, p2PSA/fPSA, and the Prostate Health Index (PHI), which uses the formula $(p2PSA/fPSA) \times \%total\ PSA$ to evaluate three markers simultaneously. The authors reported that both baseline and longitudinal measures of all of the isoforms

were significantly associated with upgrading at biopsy, whereas total PSA was not. Longitudinal measures appeared to provide increased discrimination for grade reclassification as compared to baseline values. Like the PHI, which relies on the relationship between PSA, fPSA, and p2PSA, a panel of four kallikrein markers (total PSA, fPSA, intact PSA, and human glandular kallikrein or hK2) has been associated with “aggressive” prostate cancer among men with screening-detected cancers undergoing radical prostatectomy (Carlsson et al, 2013). The four-kallikrein panel has not been specifically evaluated in an active surveillance setting.

PCA3 (DD3), a noncoding messenger RNA that can be measured in urine, is overexpressed in prostate cancer (Bussemakers et al, 1999) and has been found to be associated with both the grade and volume of prostate cancer among men undergoing prostatectomy (van Poppel et al, 2012). A urinary assay measuring transcript levels of the fusion between the *TMPRSS2* gene and the *ERG* transcription factor (*TMPRSS2:ERG*) was reported to be directly associated with tumor size and Gleason score at prostatectomy, as well as upgrading of Gleason grade at prostatectomy (Tomlins et al, 2011). However, in an active surveillance population, the addition of the urinary markers PCA3 and *TMPRSS2:ERG* combined did not significantly improve the prediction of Gleason score above 6 as compared to PSA alone (Lin et al, 2013). Marker panels that combine serum and urinary assays may provide improved risk stratification for men considering surveillance but will need further evaluation before application to clinical practice.

KEY POINTS: OBSERVATIONAL STRATEGIES FOR PROSTATE CANCER: WATCHFUL WAITING AND ACTIVE SURVEILLANCE

- Active surveillance has become a standard alternative to curative intervention for select patients diagnosed through PSA-based screening in whom it is judged that the natural history of the disease will be prolonged.
- Most physicians typically monitor a patient on surveillance with PSA and digital rectal examination at least biannually, and perform surveillance prostate biopsies at 1- to 2-year intervals.
- The finding of high-grade disease (Gleason score 7 or higher) on surveillance biopsies has been considered a trigger for intervention in most active surveillance programs.

PATIENT AND DISEASE FACTORS AFFECTING THE CHOICE OF AND ADHERENCE TO ACTIVE SURVEILLANCE

Patient and Physician Perceptions

Treatment decision making for prostate cancer is complex for both patients and physicians, especially when facing multiple options without clear evidence for superiority of any single strategy. The concept of active surveillance for any malignancy poses particular challenges as a diagnosis of “cancer” often evokes many preconceived emotions. **The psychosocial burden of being diagnosed with prostate cancer makes selection of and adherence to active surveillance uniquely challenging.** Patients and partners may experience considerable anxiety, distress, and uncertainty when making prostate cancer treatment decisions, which must be addressed (Pickles et al, 2007).

Davison and Goldenberg (2011) surveyed men on active surveillance and determined that the physician's recommendation has one of the greatest impacts on treatment decision. **Physician attitudes are therefore critical to wider utilization of surveillance for low-risk tumors.** Particularly for younger men, surgery is most often chosen over active surveillance with physicians specifically recommending *against* active surveillance in the majority (75%) of patients (Sidana et al, 2012). Physician perceptions regarding active

surveillance may arise from a general lack of knowledge regarding this treatment approach, concern over how best to safely identify patients and implement active surveillance, and uncertainty over disease progression. As more long-term data regarding the efficacy of active surveillance become available, along with advances in imaging and molecular tumor analyses, many of these perceptions should change.

Studies report considerable variation in patient factors that drive treatment decision making for prostate cancer (Zeliadt et al, 2006). The desire for cancer eradication and preservation of quality of life, however, are predominant and common themes. This drive to completely rid oneself of cancer, however, particularly in younger patients, tends to lead toward aggressive treatment over active surveillance regardless of risk (Penson, 2012; Sidana et al, 2012). Upon specifically questioning men who select active surveillance compared with men selecting other treatments (radiation or surgery), men who choose surveillance cite a desire to avoid potential negative quality-of-life effects of therapy, particularly in regard to sexual functioning, as an important driver of their decision (Volk et al, 2014). Successful active surveillance is perceived by patients to be a well-organized treatment plan and part of an ongoing relationship with the health care provider and is not viewed as a final decision, but possibly the first of a sequence of treatment decisions (Volk et al, 2014). Patients should therefore understand that the goal of surveillance is to identify early signs of progression and that a certain number of men will be recommended for additional therapy over time. An analysis of 768 men with prostate cancer showed that men choosing active surveillance also commonly report a desire to avoid active or invasive treatment as a primary reason (Anandadas et al, 2011). To better understand important factors regarding the selection of surveillance, Goh and colleagues (2012) utilized a telephone-based survey to query men and showed that a better understanding of prostate cancer and less inconsistency in information received seemed to relate with reduced distress regarding patient decision making. A prostate cancer diagnosis carries a substantial psychological burden and it is important for patients to understand the natural history of their specific disease characteristics and the risk their particular cancer may pose before making treatment decisions. **With active surveillance, physicians must facilitate this understanding of the biology of prostate cancer and the likely indolent nature of their particular tumor** (Penson, 2012). Whereas a baseline fear of cancer recurrence is associated with poorer satisfaction with care after prostate cancer treatment, so too are declines in urinary, sexual, and bowel function (Resnick et al, 2013a). If the overriding fear of cancer can be adequately addressed, surveillance offers the ability to preserve function, leading to overall high satisfaction with care. Studies show that contemporary men who successfully adhere to active surveillance understand that their cancers are likely small and slow growing, making immediate treatment unnecessary (Volk et al, 2014). Davison and Goldenberg (2011) found that 55% of men reported low anxiety levels about the cancer progressing while on surveillance, which only comes from a clear understanding of the natural history of the disease.

Patient perceptions and understanding of active surveillance have improved over time (Mishra et al, 2013). This is primarily believed to be due to increased endorsement of active surveillance by national medical organizations along with increased emphasis on preserving quality of life. Analyzing anonymous Internet conversations, Mishra and associates (2013) reported that contemporary conversations emphasized concern over receiving unbiased recommendations from physicians regarding treatment options for prostate cancer. **These comments underscore the importance of a collaborative relationship between patient and physician when embarking on surveillance, which becomes critical for treatment selection and adherence.** Patient partners are often involved in treatment decision making for prostate cancer and therefore are important to be engaged in the physician-patient relationship (Zeliadt et al, 2011).

Future research should focus on developing concise recommendations for wider implementation of active surveillance with strong

consideration of patient and physician perceptions. Physicians must learn to integrate clinical, biologic, and likely image-based variables for careful risk assessment and how to adequately communicate these with patients. Research efforts will also need to focus on identifying interventions aimed at improving quality of life and treatment adherence while on surveillance, including coping mechanisms and spousal/partner support. The NIH consensus statement outlines more specific future research needs for prostate cancer survivorship particularly for men on active surveillance (Ganz et al, 2012).

Selection Criteria

The decision to manage prostate cancer with surveillance is based on both patient and disease factors. Diagnostic clinical characteristics are used to initially estimate disease risk and to determine which patients may be eligible for active surveillance. Certain tumor characteristics may pose different risks for different patients after consideration of age and performance status. While there are no level 1 data that determine the optimal selection criteria, it is generally accepted that men with low-risk, localized disease are the best candidates. Eligibility characteristics described from the experiences of several large published cohorts are presented in Table 113-3. Physicians and patients must decide which criteria are best for their particular practice patterns, and while different criteria may predict certain outcomes (i.e., pathologic, disease reclassification, treatment-free survival), none has been directly validated to predict disease-specific or overall survival. Once candidates are identified, the decision to proceed with active surveillance is based on careful discussion between physician and patient considering the patient's interest in and willingness to adhere to the recommended surveillance protocol.

The Epstein criteria were selected to identify potentially low-risk tumors and are among the most popular used for patient selection for active surveillance. By these criteria, "insignificant" tumors are predicted by clinical Gleason pattern 3 or less, clinical stage T1c and either (1) PSA density 0.1 ng/mL per gram or less, two or fewer positive biopsy cores, and no cores with greater than 50% involvement or (2) PSA density of 0.15 ng/mL per gram or less and cancer smaller than 3 mm on only one biopsy core. The NCCN now recommends active surveillance as primary treatment for men with "very" low-risk prostate cancer defined by PSA level 10 ng/mL or less, clinical stage T2a or less, Gleason grade 3+3 or less, PSA density 0.15 ng/mL per gram or less, two or fewer cores positive, and any single-core positivity 50% or less. The NCCN guidelines recommend offering the option of active surveillance for men presenting with low-risk disease defined as PSA level 10 ng/mL or less, clinical stage T2a or less, and Gleason grade 3+3 or less. The American and European Urologic Associations have similarly published guidelines for offering active surveillance for men with prostate cancer. Patient factors such as age, comorbid illness, and willingness to adhere to surveillance strategies must also be considered during patient selection.

More stringent criteria for offering active surveillance will reduce the number of candidates for this approach, and although some series describe results of surveying men with higher Gleason score tumors (3+4), these data must be interpreted cautiously (Ng et al, 2009; van den Bergh et al, 2009b; Klotz et al, 2010; Cooperberg et al, 2011). While more strict criteria may reduce the risks of disease misclassification, this further limits potential candidates. Because up to 33% of men with presumed low-risk disease may be incorrectly classified at diagnosis, a confirmatory prostate biopsy serves to reduce this risk (Iremashvili et al, 2012a).

Surveillance Strategies

As with selection criteria, there is no overall consensus on the optimal strategies for surveillance. Ongoing prospective studies integrating novel imaging and molecular analyses will allow for more personalized risk assessment and recommendations for surveillance. Currently, because tumor grade is the best predictor of

TABLE 113-3 Selection Criteria and Outcomes from Published Active Surveillance Series

	JOHNS HOPKINS (Tosoian et al, 2011)	UCSF (Porten et al, 2011)	PRIAS (Bul et al, 2013)	UNIVERSITY OF TORONTO (Klotz, 2012)	UNIVERSITY OF MIAMI (Eggerer et al, 2013)	ROYAL MARSDEN (Selvadurai et al, 2013)	MEMORIAL SLOAN KETTERING (Eggerer et al, 2013)
Entry criteria	PSA ≤10 ng/mL PSA density ≤0.15 ng/mL per gram Stage ≤T2a Grade ≤3+3 No. cores positive ≤2 Single-core positivity ≤50%	PSA ≤10 ng/mL Stage ≤T2a Grade ≤3+3* % Cores positive ≤1/3 Single-core positivity ≤50%	PSA ≤10 ng/mL PSA density ≤0.2 ng/mL per gram Stage ≤T2a Grade ≤3+3 No. cores positive ≤2	PSA ≤10 ng/mL Grade ≤3+3*	PSA ≤10 ng/mL Stage ≤T2a Grade ≤3+3 No. cores positive ≤2 Single-core positivity ≤20%	PSA ≤15 ng/mL Stage ≤T2a Grade ≤3+4 % Cores positive ≤50	PSA ≤10 ng/mL Stage ≤T2a Grade ≤3+3 No. cores positive ≤3 Single-core positivity ≤50%
Median follow-up	2.7 years	4.5 years	1.6 years	6.8 years	1.8 years	5.7 years	2.1 years
% free of treatment	54.4%	70%	75.6%	70%	95%	69%	80%
Disease- specific survival	100%	100%	100%	99%	100%	99%	Not recorded
Overall survival	98%	97%	99.3%	78.4%	98%	94%	Not recorded

*Denotes some intermediate-risk men are included.
PSA, prostate-specific antigen.

cancer biology, repeat prostate biopsies over time are the cornerstone of active surveillance. Early “confirmatory” biopsy serves to limit the risk of clinical undergrading resulting from sampling, estimated from surgical series to range from 20% to 30% on a typical 12-core transrectal biopsy (Conti et al, 2009; Smaldone et al, 2010; Suardi et al, 2010). Many clinicians therefore advocate for this repeat biopsy within 3 to 6 months of diagnosis. The pathologic outcomes after the first repeat biopsy are well described, with Gleason grade changes and thus risk reclassification occurring 2.5% to 28% of the time. These numbers are sensitive to selection criteria and biopsy technique. **The critical role of repeat prostate biopsy for successful identification of higher-risk disease during surveillance cannot be overemphasized.** When describing characteristics of two men presenting with low-risk features who subsequently died from prostate cancer after a period of surveillance within the Royal Marsden cohort, it was noted that both men were found to have higher-grade disease (Gleason 8 and 9) on first repeat biopsy 13 and 24 months after diagnosis, respectively (Selvadurai et al, 2013). Both patients were also found to have substantial tumor burdens on MRI.

Serial prostate biopsies are then variably performed from an annual basis to once every 3 to 4 years. Men within the Johns Hopkins cohort undergo yearly biopsies while the University of Toronto advocates for an initial confirmatory biopsy after 6 to 12 months and then every 3 to 4 years (Klotz, 2012). The risk of disease reclassification continues over time while on surveillance, likely a result of both undersampling and true histologic disease progression in either tumor grade or volume. Within the University of California, San Francisco (UCSF) cohort, the risk of grade progression to Gleason 3+4 or greater ranged from 22% to 30% with each surveillance biopsy (Cary et al, 2014). With a median follow-up of 5.7 years in the Royal Marsden series, the rates of adverse histology

(defined as ≥Gleason 4+4 or percent positive cores ≥50) at 2 and 5 years were 6% and 22%, respectively (Selvadurai et al, 2013).

Psychosocial Aspects

The common emotions of uncertainty and anxiety surrounding treatment decisions for prostate cancer also affect patient adherence to active surveillance protocols. Within a large cohort series of active surveillance, up to 13% of men ultimately received other treatments in the absence of clinical reclassification or progression, demonstrating how psychosocial factors may drive unwillingness to continue with surveillance (Dall’Era et al, 2008). Men on surveillance have unique and specific survivorship needs, which are important to address to maintain quality of life and avoid psychological distress over time. Identifying and describing these needs is important for implementing interventions aimed at improving adherence to active surveillance. Patient anxiety over time has been studied within the Prostate Cancer Research International: Active Surveillance (PRIAS) study (van den Bergh et al, 2010). Within this cohort, overall patient-reported anxiety and uncertainty regarding treatment decisions were generally lower than reported for other treatments for prostate cancer. Additionally, the authors noted that over time anxiety remained steady, suggesting that within an organized framework of careful monitoring patients fare well psychologically (van den Bergh et al, 2009a, 2010). The authors also identified that patients with a more neurotic personality tended to not tolerate surveillance as well as other patients. Better overall physical health, however, correlated with lower anxiety and distress (van den Bergh et al, 2010). **Because most men with prostate cancer will experience non-prostate-cancer-related mortality, this underscores the importance of implementing general physical and mental health improvement measures for men on surveillance.** The Prostate

Cancer Lifestyle Trial examined the role of lifestyle modifications and found that exercise and attention to stress management can improve treatment-free survival for men on surveillance (Frattaroli et al, 2008). Additional data from this trial suggest that comprehensive lifestyle changes can also affect prostate cancer gene expression and telomere length, therefore having positive impacts on both biologic and psychosocial factors (Ornish et al, 2008, 2013).

KEY POINTS: PATIENT AND DISEASE FACTORS AFFECTING THE CHOICE OF AND ADHERENCE TO ACTIVE SURVEILLANCE

- The psychosocial burden of being diagnosed with prostate cancer makes selection of and adherence to active surveillance uniquely challenging.
- Physician attitudes are critical to wider utilization of surveillance for low-risk tumors.
- Early “confirmatory” biopsy serves to limit the risk of clinical undergrading resulting from sampling, estimated from surgical series to range from 20% to 30% on a typical 12-core transrectal biopsy.

COMPARATIVE OUTCOMES OF TREATMENT AND OBSERVATIONAL STRATEGIES

Treatment-Free, Disease-Specific, and Overall Survival

Although studies have been completed directly comparing radical prostatectomy with watchful waiting, to date no prospective, randomized data exist comparing active surveillance with immediate treatment. Table 113-3 depicts the reported outcomes from contemporary active surveillance series, which can be used to counsel patients for this treatment approach. Disease-specific and all-cause

survival over the periods of study have been reportedly high and compare favorably with longer-term outcomes after prostatectomy or various forms of radiotherapy in similar-risk men (Cooperberg et al, 2010b; Eggener et al, 2011). In an effort to better estimate the excess risk of prostate cancer mortality with active surveillance versus immediate treatment, Xia and associates (2012) developed a simulation model for a hypothetical cohort of men ages 40 to 90 years with low-risk disease. With several assumptions inherent to modeling, the authors calculated an average increase in life expectancy of only 1.8 months with immediate treatment while men on surveillance remained free of treatment for an additional 6.4 years. Because measures of disease progression or reclassification are sensitive to entry criteria and variable definitions, treatment-free survival has emerged as another comparative relevant end point for surveillance and is depicted in Table 113-3 for selected studies. Figure 113-2 shows the estimated treatment-free survival and freedom from disease risk reclassification based on repeat biopsy characteristics from the Johns Hopkins cohort. When interpreting results from published series, careful consideration must be given to clinical characteristics at study entry, surveillance strategies, definitions of disease progression, and indications for secondary therapy.

Investigators from Johns Hopkins University have prospectively treated men with active surveillance for suspected low-risk prostate cancer, defined by Gleason score 6 or less, clinical stage T1c or less, PSA density 0.15 ng/mL per gram or less, two or fewer positive biopsy cores, and 50% or less single-core involvement (Tosoian et al, 2011). This study reported no deaths attributable to prostate cancer and no cases of metastatic disease after a median follow-up of 2.7 years (Tosoian et al, 2011). In this group, patients are surveyed with yearly prostate biopsy and, in over 600 men, 213 (33%) were risk reclassified based on histologic parameters (Gleason score or tumor volume) over time (Umbehr et al, 2014).

In a cohort of 450 low- and intermediate-risk men from Toronto, Canada with the longest median follow-up of 6.8 years, Klotz (2012) reported a 10-year overall survival of 68% with only 5 reported prostate cancer-specific deaths. A confirmatory biopsy was

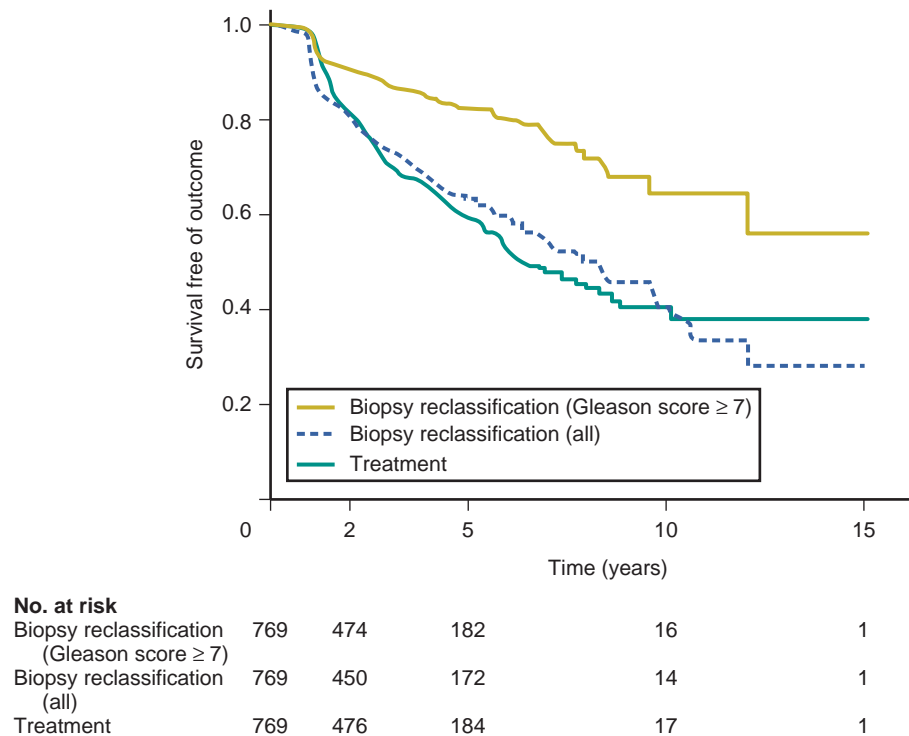


Figure 113-2. Estimated biopsy reclassification and treatment-free survival for men on active surveillance from the Johns Hopkins cohort. (Modified from Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 2011;29:2185–90.)

performed 6 to 12 months after the initial diagnosis and then every 3 to 4 years. Three of the five patients who died from prostate cancer underwent radical therapy and all five demonstrated a rapid PSA doubling time of less than 2 years.

The PRIAS study was initiated in 2006 and collects data on men treated with active surveillance in over 100 medical centers from 17 countries (Bul et al, 2013). With a median follow-up of 1.6 years and 2495 men, the study reported 75.6% treatment-free survival with no prostate cancer-specific deaths. Although still a very early series, this relatively large, multinational cohort is expected to contribute important data on this management strategy in the future.

Outcomes for African-American men on active surveillance have been reported and may differ from those for Caucasian men. The added risk of race to prostate cancer diagnosis and outcomes is well known and is important to consider when applying these data regarding active surveillance specifically to African-American men. **In a multivariate analysis of predictors for progression on repeat biopsy in an active surveillance cohort, African-American men were noted to have an independent increased risk for progression over their Caucasian counterparts (Iremashvili et al, 2012b).** In a separate cohort of men on active surveillance, African-American men were noted to have lower treatment-free survival (66%) than non-African-Americans (82%) after a median of 34 months (Odom et al, 2014). On multivariate analysis, African-American men were more likely to progress (odds ratio [OR] 4.46, 95% CI 1.52 to 13.10) and undergo treatment (OR 2.29, 95% CI 1.03 to 5.08).

Identifying other baseline predictors of risk reclassification and need for treatment may ultimately improve patient counseling and tailor surveillance strategies for men with prostate cancer. In a group of 465 men on surveillance at UCSE, negative confirmatory biopsy and lower PSA density were associated with lower rates of progression (Cary et al, 2014). **Analyzing the ability of selection criteria to predict pathology within a surgical cohort, Reese and colleagues (2013) demonstrated that PSA density greater than 0.15 ng/mL per gram and Gleason score of 3+4 were associated with adverse pathologic findings, suggesting that these factors may be more significant than biopsy positive core number or estimates of tumor percentage within each core.** The significant relationship between PSA density (≥ 0.15 ng/mL per gram) and adverse pathologic features at prostatectomy was also reported within the PRIAS group of men (Bul et al, 2013).

Outcomes after Secondary Treatment for Progression

While both watchful waiting and active surveillance offer treatment for progressive disease, the timing and approaches differ. Watchful waiting generally utilizes androgen deprivation therapy for symptomatic, metastatic progression while surveillance offers the opportunity to administer curative therapy for higher-risk, localized disease. A subset of patients also elect to undergo secondary treatment in the absence of clinical changes. Analyzing and understanding the outcomes of men who receive further treatment, particularly after a period of surveillance, is important for counseling men regarding the risks and expectations of this approach to managing prostate cancer.

In 192 men from the Johns Hopkins cohort who underwent delayed prostatectomy or radiotherapy, 9.4% experienced biochemical recurrence with a median follow-up of 2 years after delayed prostatectomy and 2.8 years after radiation (Tosoian et al, 2011). No men developed metastatic disease or died from prostate cancer. After radical prostatectomy, the majority of men (65%) had organ-confined disease and 27% of men had indolent disease (dominant nodule < 0.5 mL in size and no Gleason pattern 4 or 5). One patient had lymph node involvement at the time of surgery and one patient had seminal vesicle invasion (Duffield et al, 2009).

Investigators from the University of Toronto reported outcomes for 125 men treated with either prostatectomy (35 men) or radiotherapy (90 men) for curative intent after a period of surveillance (Klotz, 2012). Overall, higher rates of PSA failure (50.4%) after delayed treatment were reported for this series compared with others. Five-year biochemical recurrence-free survival after prosta-

tectomy was 62% versus 43% after radiotherapy. These figures must be interpreted with consideration of the higher disease risk of this cohort compared with that at Johns Hopkins. Of 36 treated men who presented with intermediate-risk disease, only one progressed to metastatic disease and death (Klotz, 2012).

Comparative pathologic outcomes for men undergoing immediate versus delayed prostatectomy after a period of surveillance can be studied, but must be interpreted cautiously. Compared with a group of similar-risk men undergoing immediate surgery, Dall'Era and associates (2011) reported no differences in rates of extraprostatic extension or positive margins for men undergoing surgery after a median of 18 months of surveillance. In a similar report from Johns Hopkins, rates of "noncurable" prostate cancer after delayed prostatectomy were low (23%) and did not differ from those of men undergoing immediate surgery (Warlick et al, 2006). Of 27 men from the PRIAS study undergoing radical prostatectomy after progression, 17% had evidence of pT3a disease on final pathology and 38% had positive surgical margins (Bul et al, 2013). Most men from these studies were treated with evidence of pathologic reclassification on surveillance needle biopsy and therefore must be compared to similar-risk men undergoing immediate surgery. **The majority of men classified as low risk at diagnosis remain untreated on surveillance.**

KEY POINTS: COMPARATIVE OUTCOMES OF TREATMENT AND OBSERVATIONAL STRATEGIES

- Disease-specific and all-cause survival from published active surveillance series have been high and compare favorably with longer-term outcomes after prostatectomy or various forms of radiotherapy in similar-risk men.
- The outcomes of men undergoing delayed radical prostatectomy or radiation therapy after a period of active surveillance appear similar to men treated immediately after diagnosis.

FUTURE RESEARCH NEEDS

Improvements in prostate imaging, biomarker discovery, and genetic profiling of prostate cancers will very likely change the approach to management of men diagnosed with localized prostate cancer. Currently, active surveillance is underutilized in part because of the dual concerns that a cancer has been misclassified on a prostate biopsy and the inability to define biologically which cancers have an aggressive phenotype. Thus there is both overtreatment of indolent disease and undertreatment of aggressive disease. mMRI, including diffusion-weighted imaging, magnetic resonance spectroscopy, and contrast-enhanced sequences, is being studied extensively for prostate cancer, and the role this plays in patient selection and surveillance strategies will soon be defined. Studies utilizing novel imaging modalities such as ^{18}F -sodium fluoride and ^{11}C -choline positron emission tomography are producing exciting data in prostate cancer and may one day play a role in surveillance of low-risk tumors (Scattoni et al, 2007; Jadvar et al, 2012).

Two gene expression assays are now commercially available for prostate cancer and are integrated with baseline clinical variables to provide more precise risk assessment for patients. The Oncotype DX® assay (Genomic Health, Inc., Redwood City, CA) measures expression levels of 17 specific genes within four molecular pathways and was designed to predict the risk of adverse pathology for men with NCCN very low-, low-, or intermediate-risk prostate cancer (Knezevic et al, 2013). The Prolaris® assay (Myriad Genetics, Inc., Salt Lake City, UT) measures 31 genes involved in cell cycle progression to predict disease progression and prostate cancer-specific mortality (Cuzick et al, 2011; Cooperberg et al, 2013). It is unclear how these gene expression assays will perform and, with reported ORs in the range of 1.5 to 3 for predicting low-risk disease, accurate classification may be poor (Pepe et al, 2004). Ongoing validation studies and head-to-head comparisons will better define

the role of these molecular tests in early-stage prostate cancer and how they will enhance treatment decision making.

In the future it is likely that men with newly diagnosed localized prostate cancer will have had an assessment of the prostate using mMRI, targeted biopsies of lesions considered suspicious, and gene expression signatures that focus on profiling the cancer based on molecular pathways associated with aggressiveness (Cooperberg et al, 2013; Donovan and Cordon-Cardo, 2013; Haffner et al, 2013; Liu et al, 2013). Together with serum and urine biomarkers, this new paradigm may enhance our current stratification systems that rely to a great extent on light microscopic grading. This multidimensional approach may improve the ability to select the most appropriate candidates for surveillance, as well as our ability to longitudinally monitor specific lesions within the prostate for evidence of disease progression.

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The complete reference list is available online at www.expertconsult.com.



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114 Open Radical Prostatectomy

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Radical Retropubic Prostatectomy: Surgical Anatomy

Surgical Technique

Postoperative Management

Complications

Surgical Modifications to Classic Anatomic Radical Prostatectomy

Salvage Radical Prostatectomy

Summary of Radical Retropubic Prostatectomy

Radical Perineal Prostatectomy

There is no better way to cure cancer that is confined to the prostate than total surgical removal. Radical prostatectomy is the only form of treatment for localized prostate cancer that has been shown in a randomized controlled trial to reduce progression to metastases and death from the disease (Holmberg et al, 2002; Bill-Axelson et al, 2008). Furthermore, on the basis of improved understanding of the periprostatic anatomy, today less bleeding and improved rates of postoperative continence and potency are seen (Walsh, 1998, 2000; Nielsen et al, 2008).

Technically, radical retropubic prostatectomy (RRP) is one of the most difficult operations in the field of urology. The three goals of surgery, in order of importance, are cancer control, preservation of urinary control, and preservation of sexual function. Great skill and experience in the selection of surgical candidates and operative technique are necessary to achieve all three. This chapter summarizes our experience, with the hope that it will shorten the reader's learning curve. A video demonstrating a detailed description of the surgical technique is also available (Walsh and Garcia, 2004).

RADICAL RETROPUBIC PROSTATECTOMY: SURGICAL ANATOMY

Venous and Arterial Anatomy

The veins of the prostate drain into the Santorini plexus. It is necessary to have a complete understanding of these veins to avoid excessive bleeding and to ensure a bloodless field in exposing the membranous urethra and the apex of the prostate. The deep dorsal vein leaves the penis under the Buck fascia between the corpora cavernosa and penetrates the urogenital diaphragm, dividing into three major branches: the superficial branch and the right and left lateral venous plexuses (Reiner and Walsh, 1979) (Fig. 114-1). The superficial branch, which travels between the puboprostatic ligaments, is the centrally located vein overlying the bladder neck and prostate. This vein is easily visualized early in retropubic operations and has communicating branches over the bladder itself and into the endopelvic fascia. The superficial branch lies outside the anterior prostatic fascia.

The common trunk and lateral venous plexuses are covered and concealed by the prostatic and endopelvic fascia. The lateral venous plexuses traverse posterolaterally and communicate freely with the pudendal, obturator, and vesical plexuses. Near the puboprostatic ligaments, small branches from the lateral plexus often penetrate the pelvic sidewall musculature and communicate with the internal pudendal vein. The lateral plexus interconnects with other venous systems to form the inferior vesical vein, which empties into the internal iliac vein. With the complex of veins and plexuses anasto-

mosing freely, any laceration of these friable structures can lead to considerable blood loss.

The prostate receives arterial blood supply from the inferior vesical artery. According to Flocks (1937), after the inferior vesical artery provides small branches to the seminal vesicle and the base of the bladder and prostate, the artery terminates in two large groups of prostatic vessels: the urethral and capsular groups (Fig. 114-2). The urethral vessels enter the prostate at the posterolateral vesicoprostatic junction and supply the vesical neck and periurethral portion of the gland. The capsular branches run along the pelvic sidewall in the lateral pelvic fascia posterolateral to the prostate, providing branches that course ventrally and dorsally to supply the outer portion of the prostate. The capsular vessels terminate as a small cluster of vessels that supply the pelvic floor. On histologic examination, the capsular arteries and veins are surrounded by an extensive network of nerves (Walsh and Donker, 1982; Walsh et al, 1983; Lue et al, 1984; Lepor et al, 1985). These capsular vessels provide the macroscopic landmark to aid in the identification of the microscopic branches of the pelvic plexus that innervate the corpora cavernosa.

The major arterial supply to the corpora cavernosa is derived from the internal pudendal artery. However, pudendal arteries can arise from the obturator, inferior vesical, and superior vesical arteries. Because these aberrant branches travel along the lower part of the bladder and anterolateral surface of the prostate, they are divided during radical prostatectomy. This may compromise arterial supply to the penis, especially in older patients with borderline penile blood flow (Breza et al, 1989; Polascik and Walsh, 1995; Rogers et al, 2004).

Pelvic Plexus

The autonomic innervation of the pelvic organs and external genitalia arises from the pelvic plexus, which is formed by parasympathetic, visceral, efferent, preganglionic fibers that arise from the sacral center (S2 to S4), and sympathetic fibers via the hypogastric nerve from the thoracolumbar center (Walsh and Donker, 1982; Lue et al, 1984; Lepor et al, 1985; Schlegel and Walsh, 1987; Walsh, 2007) (see Fig. 114-1). The pelvic plexus in men is located retroperitoneally beside the rectum 5 to 11 cm from the anal verge and forms a fenestrated rectangular plate that is in the sagittal plane with its midpoint at the level of the tip of the seminal vesicle.

The branches of the inferior vesical artery and vein that supply the bladder and prostate perforate the pelvic plexus. For this reason, ligation of the so-called lateral pedicle in its midportion not only interrupts the vessels but also transects the nerve supply to the

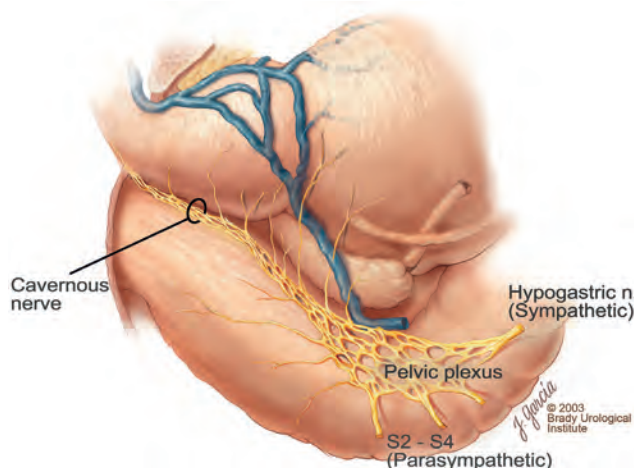


Figure 114-1. Location of the superficial and deep branches of the dorsal vein as they travel over the anterior and anterolateral surfaces of the prostate. Note the common trunk located immediately over the urethra. This is the site where the dorsal vein is transected. The pelvic plexus: The autonomic innervation of the pelvic organs arises from the pelvic plexus, which is formed by parasympathetic fibers that arise from the sacral center (S2 to S4) and sympathetic fibers via the hypogastric nerve from the thoracolumbar center. The pelvic plexus provides visceral branches that innervate the bladder, ureter, seminal vesicles, prostate, rectum, membranous urethra, and corpora cavernosa. The branches that innervate the corpora cavernosa enter in a spraylike distribution 20 to 30 mm distal to the junction of the prostate and bladder, where they continue distally posterolateral to the prostate. n., nerve. (© Brady Urological Institute.)

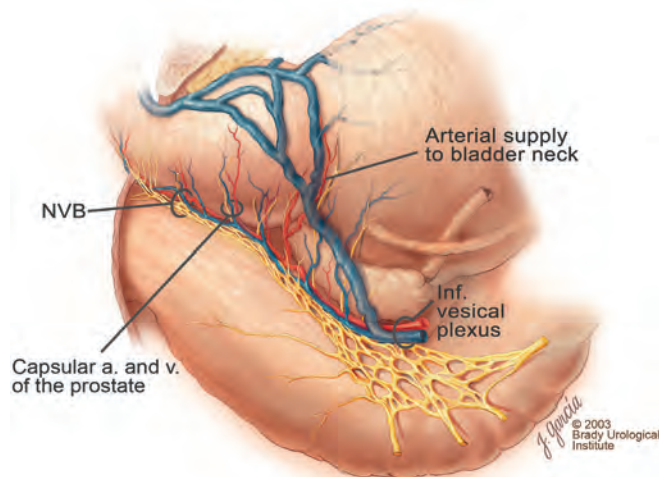


Figure 114-2. Arterial supply to the prostate. The inferior vesical artery terminates in two large groups of vessels. One group, the urethral vessels, enters the prostate at the posterolateral vesicoprostatic junction to supply the bladder neck and periurethral portions of the gland. The second group, the capsular branches, runs along the pelvic sidewall in the lateral pelvic fascia posterolateral to the prostate, providing branches that course ventrally and dorsally to supply the outer portion of the prostate. These capsular arteries and veins are intimately associated with the branches of the pelvic plexus forming the neurovascular bundle (NVB), which is used as the macroscopic landmark to aid in the identification of the microscopic branches of these nerves. Note at the apex that small branches of the nerves travel anteriorly away from the vessels. a., artery; inf., inferior; v., vein. (© Brady Urological Institute.)

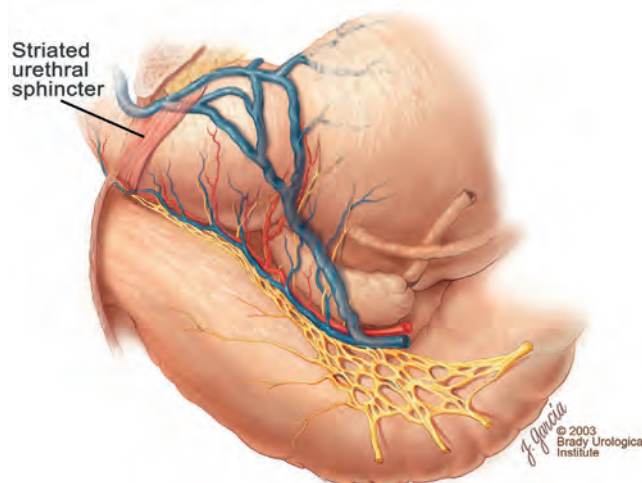


Figure 114-3. The striated urethral sphincter with its surrounding fascia is a vertically oriented tubular sheath that surrounds the membranous urethra. The dorsal vein complex travels through the sphincter complex. (© Brady Urological Institute.)

prostate, urethra, and corpora cavernosa. The pelvic plexus provides visceral branches that innervate the bladder, ureter, seminal vesicles, prostate, rectum, membranous urethra, and corpora cavernosa. In addition, branches that contain somatic motor axons travel through the pelvic plexus to supply the levator ani, coccygeus, and striated urethral musculature. The nerves innervating the prostate travel outside the capsule of the prostate and Denonvilliers fascia until they perforate the capsule where they enter the prostate.

The branches to the membranous urethra and corpora cavernosa also travel outside the prostatic capsule in the lateral pelvic fascia dorsolaterally between the prostate and rectum (see Fig. 114-1). Although these nerves are microscopic, their anatomic location can be estimated intraoperatively by use of the capsular vessels as a landmark. This structure, which is referred to here as the neurovascular bundle (NVB), has been termed the *NVB of Walsh* (Stedman's Medical Dictionary, 2000) (see Fig. 114-2). As emphasized by Takenaka and colleagues (2004) and Costello and colleagues (2004), the cavernous branches join the capsular arteries and veins in a spraylike distribution to form the NVB 20 to 30 mm distal to the junction of the bladder and prostate (see Fig. 114-2). The NVBs are located in the lateral pelvic fascia between the prostatic fascia and the levator fascia. At the apex of the prostate, the branches of the nerves to the cavernous bodies and striated sphincter also have a spraylike distribution both anteriorly and posteriorly with wide variation (Costello et al, 2004; Takenaka et al, 2005). After piercing the urogenital diaphragm, the nerve branches pass behind the dorsal penile artery and dorsal penile nerve before entering the corpora cavernosa (Walsh and Donker, 1982).

Striated Urethral Sphincter

The external sphincter, at the level of the membranous urethra, is often depicted as a "sandwich" of muscles in the horizontal plane. However, Oelrich (1980) demonstrated clearly that the striated urethral sphincter with its surrounding fascia is a vertically oriented tubular sheath that surrounds the membranous urethra. In utero, this sphincter extends without interruption from the bladder to the perineal membrane. As the prostate develops from the urethra, it invades and thins the sphincter muscle, causing a reduction or atrophy of some of the muscle (Fig. 114-3).

In the adult the fibers at the apex of the prostate are horseshoe shaped and form a tubular, striated sphincter surrounding the membranous urethra. Near the apex of the prostate, the edges fuse in the midline posteriorly (Fig. 114-4A). Thus, as Myers (1987) has shown, the prostate does not rest on a flat, transverse

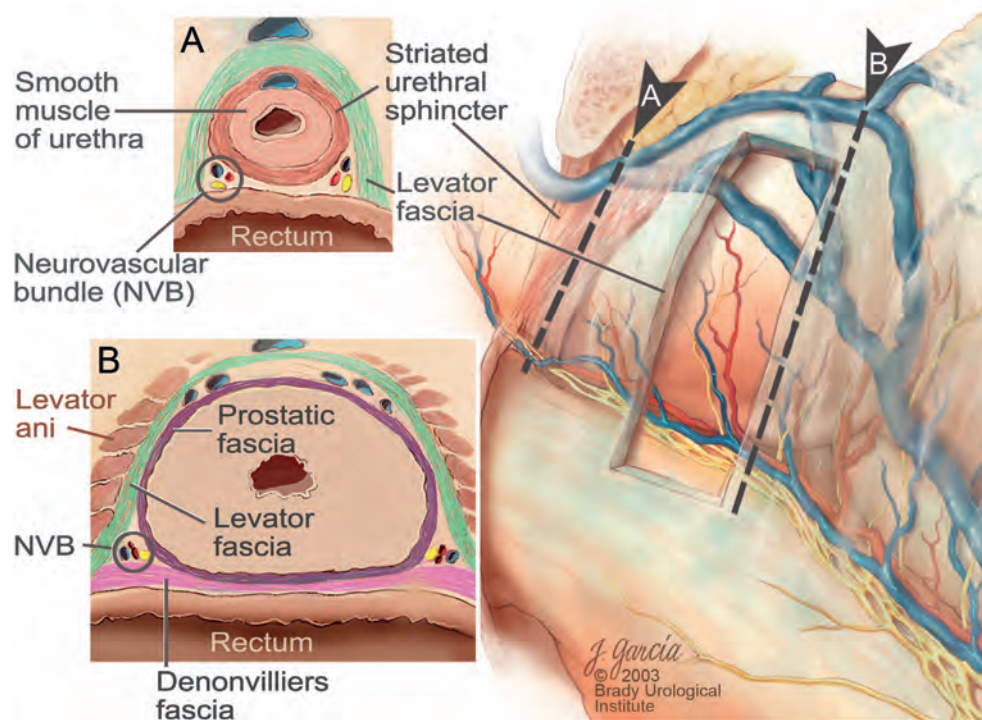


Figure 114-4. A, A cross section through the apex of the prostate demonstrating the relationship among the fascia surrounding the striated sphincter and smooth muscle of the urethra. Note that at this level, the striated sphincter circumferentially surrounds the urethra. Note that the neurovascular bundles (NVBs) are posterolateral to the circumferential striated sphincter. B, A cross section through the midportion of the prostate demonstrating the relationship between the levator fascia, Denonvilliers fascia, and prostatic fascia. Note that the NVBs are located between the layers of the levator fascia and prostatic fascia. In performing a proper nerve-sparing operation, the prostatic fascia must remain on the prostate. (© Brady Urological Institute.)

urogenital diaphragm like an apple on a shelf, with no striated muscle proximal to the apex. Rather, the external striated sphincter is more tubular and has broad attachments over the fascia of the prostate near the apex. This has important implications in the apical dissection and reconstruction of the urethra for preservation of urinary control postoperatively (Walsh et al, 1990).

The striated sphincter contains fatigue-resistant, slow-twitch fibers that are responsible for passive urinary control. Active continence is achieved by voluntary contraction of the levator ani musculature, which surrounds the apex of the prostate and membranous urethra. Some fibers of the levator ani (levator urethrae, pubourethralis) surround the proximal urethra and the apex of the prostate and insert into the perineal body in the midline posteriorly (Myers, 1991, 1994). The pudendal nerve provides the major nerve supply to the striated sphincter and levator ani. When patients are instructed to perform sphincter exercises postoperatively, they are actually contracting the levator ani musculature. However, because the striated urethral sphincter has similar innervation, patients are exercising this important muscle as well. Somatic motor nerves traveling through the pelvic plexus provide additional innervation to the pelvic floor musculature (Zvara et al, 1994; Costello et al, 2004; Takenaka et al, 2005).

Pelvic Fascia

The prostate is covered with three distinct and separate fascial layers: Denonvilliers fascia, the prostatic fascia (also called the *capsule of the prostate*), and the levator fascia. Denonvilliers fascia is a filmy, delicate layer of connective tissue located between the anterior walls of the rectum and prostate (see Fig. 114-4B). This

fascial layer extends cranially to cover the posterior surface of the seminal vesicles and lies snugly against the posterior prostatic capsule. This fascia is most prominent and dense near the base of the prostate and the seminal vesicles and thins dramatically as it extends caudally to its termination at the striated urethral sphincter. On microscopic examination, it is impossible to discern posterior and anterior layers of this fascia (Jewett et al, 1972). For this reason, one must excise this fascia completely to obtain an adequate surgical margin.

In addition to Denonvilliers fascia, the prostate is also invested with the prostatic fascia and levator fascia. Anteriorly and anterolaterally, the prostatic fascia is in direct continuity with the parenchyma of the prostate. The major tributaries of the dorsal vein of the penis and Santorini plexus travel within the anterior prostatic fascia. Laterally, the prostatic fascia fuses with the levator fascia, which covers the pelvic musculature, to form the lateral pelvic fascia (Fig. 114-5) (Myers, 1991, 1994). Posterolaterally, the levator fascia separates from the prostate to travel immediately adjacent to the pelvic musculature surrounding the rectum. The prostate receives its blood supply and autonomic innervation between the layers of the levator fascia and prostatic fascia (see Figs. 114-4B and 114-5).

In an effort to avoid injury to the dorsal vein of the penis and Santorini plexus during radical perineal prostatectomy, the lateral and anterior pelvic fasciae are reflected off the prostate. This accounts for the reduced blood loss associated with radical perineal prostatectomy. In performing RRP, the prostate is approached from outside these fascial investments. For this reason, the dorsal vein complex must be ligated and the lateral pelvic fascia must be divided (Walsh et al, 1983).

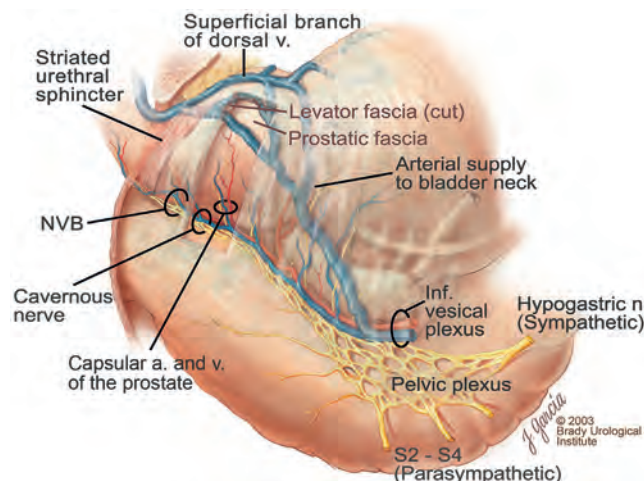


Figure 114-5. A lateral view illustrating that the prostate receives its blood supply and autonomic innervation between the layers of the levator fascia and prostatic fascia. a., artery; inf., inferior; NVB, neurovascular bundle; v., vein. (© Brady Urological Institute.)

SURGICAL TECHNIQUE

Preoperative Preparation

The preoperative assessment must include a focused review of systems; a complete medical, surgical, and anesthesia history; an inquiry of all prescription and nonprescription medications; a physical examination; and routine preoperative laboratory testing. Life-threatening complications associated with RRP are rare and include myocardial infarction, cerebrovascular accident (stroke), cardiac arrhythmias, pulmonary embolus, hemorrhage, and anesthesia reactions. The preoperative assessment must identify candidates who are at increased risk for these mortality events to intervene to attenuate these risks.

The preoperative assessment should identify factors that may add to the technical challenge of the surgical procedure, including prior abdominal or pelvic surgery and irradiation, prior transurethral surgery, extensive prostate biopsies, history of significant inflammatory bowel disease, prior use of mesh during inguinal or incisional hernia repairs, and the size of the prostate. Although none of these factors are contraindications for RRP, a greater level of skill and experience may be required to minimize complications.

The observation that up to 15% to 20% of men develop an inguinal hernia after RRP implied that this surgical procedure directly predisposes to the development of hernias (Regan, 1996; Lodding, 2001; Nielsen and Walsh, 2005). Approximately 15% of men undergoing radical prostatectomy will have a coexisting inguinal hernia detected if an appropriate inguinal examination is performed (Lepor and Robbins, 2007). In most of these cases, the inguinal hernias are asymptomatic. These observations suggest that an RRP may transform an asymptomatic inguinal hernia into a symptomatic hernia. Therefore examination of the inguinal canal with Valsalva should be performed, enabling properitoneal hernia repairs at the time of the radical prostatectomy.

Surgery is deferred for 6 to 8 weeks after needle biopsy of the prostate and 12 weeks after transurethral resection of the prostate. This delay enables inflammatory adhesions or hematomas to resolve so that the anatomic relationships between the prostate and the surrounding structures return to a nearly normal state before surgery. This is especially important if one hopes to preserve the NVBs intraoperatively and avoid rectal injury.

Donation of autologous blood is not performed at our institutions because transfusion rates are under 1%. Erythrocyte-stimulating proteins, which are not approved by the U.S. Food and Drug Administration, have been shown to raise the hematocrit on average percentage points, diminishing postprostatectomy anemia

(Rosenblum et al, 2000). The relatively higher discharge hematocrit attributable to the use of erythrocyte-stimulating proteins affects the pace of recovery because postoperative hematocrit has been shown to influence both time to work and return to activities (Sultan et al, 2006).

The American Urological Association recently published best practice guidelines for the use of prophylactic antibiotics for urologic surgical procedures (Wolf et al, 2008). The recommended prophylactic regimens for open or laparoscopic surgery involving entry into the urinary tract are a first- or second-generation cephalosporin or an aminoglycoside in combination with metronidazole or clindamycin. The duration of therapy should be no longer than 24 hours. We routinely use a first-generation cephalosporin alone and have an infection rate much less than 1%.

The preoperative management of anticoagulants and antiplatelet agents used for the treatment of specific medical conditions, such as prosthetic valves, atrial fibrillation, and coronary artery stent implants, should be performed in conjunction with the internist or cardiologist. With nearly 1 million coronary interventions occurring every year and the majority including an implant of a drug-eluting stent, managing prescribed antiplatelet therapy can create a dilemma balancing the risk for stent stenosis and perioperative bleeding. In the majority of cases, stent thrombosis is a catastrophic event resulting in life-threatening complications (Cutlip et al, 2001). A reasonable compromise for men with drug-eluting stents undergoing RRP is to preoperatively discontinue the thienopyridine while continuing aspirin therapy and restarting the thienopyridine as soon as clinically indicated (Grines et al, 2007).

Patients are prescribed a clear liquid diet on the day before surgery, are requested to drink half a bottle of magnesium citrate in the evening, and have an enema on the morning of surgery. They are admitted to the hospital on that day.

Special Instruments

RRP requires few special instruments. A fiberoptic headlight is essential because much of the procedure is performed beneath the pubis in an area where visualization can be difficult. A standard Balfour retractor with both narrow and wide malleable blades is useful during lymph node dissection and is necessary during radical prostatectomy to provide cranial and posterior retraction on the peritoneum and bladder. Coagulating forceps; small, fine, and regular right-angled clamps; Metzenbaum and Jamison scissors; and 2.5- to 4.5-power loupes are the only other specialized instruments that should be available.

Anesthesia, Incision, and Lymphadenectomy

General endotracheal anesthesia is the preferred anesthesia. The anesthesiologist is encouraged to maintain relative hypotension with systolic blood pressure of no more than 100 mm Hg and to limit the replacement of crystalloid to 1500 mL until the prostate is removed (Davies et al, 2004). The patient is placed in the supine position. The table can be flexed in obese men to increase the distance between the umbilicus and pubis.

The skin is prepared and draped in the usual way. A No. 16 Silastic Foley catheter is passed into the bladder, inflated with 20 mL of saline, and connected to sterile, closed, continuous drainage. The use of a 16-Fr catheter facilitates placement of sutures in the mucosa of the urethra. A right-handed surgeon always stands on the left side of the patient.

An extraperitoneal, lower abdominal incision is made extending from the pubis toward the umbilicus. The anterior fascia is incised down to the pubis, the rectus muscles are separated in the midline, and the transversalis fascia is opened sharply to expose the Retzius space. Laterally, the peritoneum is mobilized off the external iliac vessels to the bifurcation of the common iliac artery. Care is taken to preserve the soft tissue covering the external iliac artery that contains the lymphatics draining the lower extremity. Interruption of these lymphatics may lead to lower extremity edema and lymphocele formation. This maneuver is accomplished

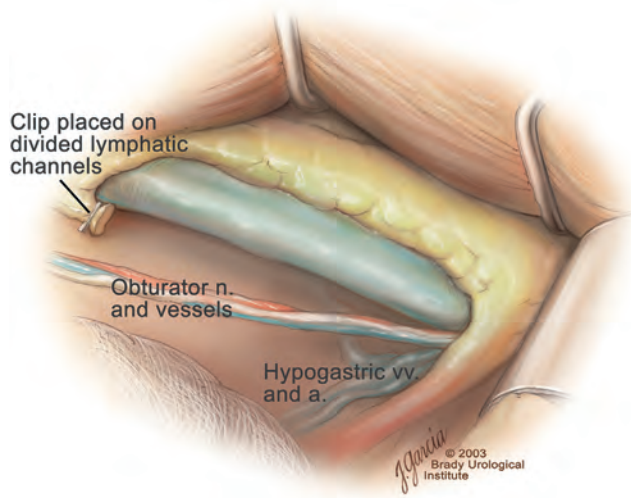


Figure 114-6. View of the right pelvis after completion of the staging pelvic lymph node dissection. Note that the fibroadipose tissue overlying the external iliac artery has not been disturbed and that the obturator nerve, obturator vessels, and hypogastric veins (vv.) over the pelvic floor have been skeletonized. a., artery; n., nerve. (© Brady Urological Institute.)

without dividing the vas deferens. Next, a self-retaining Balfour retractor is placed. Exposure for the lymph node dissection is facilitated by placement of a narrow, malleable blade attached to the Balfour retractor beneath the mobilized vas deferens to displace the peritoneum superiorly and a deep Deaver retractor to retract the bladder medially. Previously, when the vas deferens was routinely divided, some patients complained of persistent testicular pain that the authors attributed to excessive traction on the spermatic cord during this maneuver. However, if the vas deferens is not divided, the traction on the spermatic cord is absorbed by the vas deferens and persistent testalgia is rare.

Pelvic lymph node dissection is performed before the radical prostatectomy. The dissection is initiated on the ipsilateral side of the major tumor in the prostate by dividing the adventitia over the external iliac vein (Fig. 114-6). The lymphatics overlying the external iliac artery are preserved. The dissection proceeds beneath the external iliac vein out to the pelvic sidewall and then inferiorly to the femoral canal, where the lymphatic channels are ligated at a convenient point. There is no need to remove the Cloquet node. The dissection then proceeds cranially along the pelvic sidewall to the bifurcation of the common iliac artery, where the lymph nodes in the angle between the external iliac and hypogastric arteries are removed. Next, the obturator lymph nodes are removed with care to avoid injury to the obturator nerve. The obturator artery and vein are skeletonized but usually are left undisturbed and not ligated unless excessive bleeding occurs. The dissection then continues down to the pelvic floor, exposing the hypogastric veins. This extended dissection removes more lymph nodes than in a more limited dissection, improving staging and providing potential therapeutic benefit in some patients (Allaf et al, 2004; Palapattu et al, 2004). A similar procedure is performed on the opposite side. If the patient has a well-differentiated to moderately well-differentiated tumor (Gleason grade < 8) and the lymph nodes are normal to palpation, frozen-section analysis is not performed (Sgrignoli et al, 1994; Cadeddu et al, 1997).

Exposure

To expose the anterior surface of the prostate, it is necessary to displace the peritoneum superiorly. A malleable blade is used to retract the peritoneum superiorly and to gently displace the bladder posteriorly.

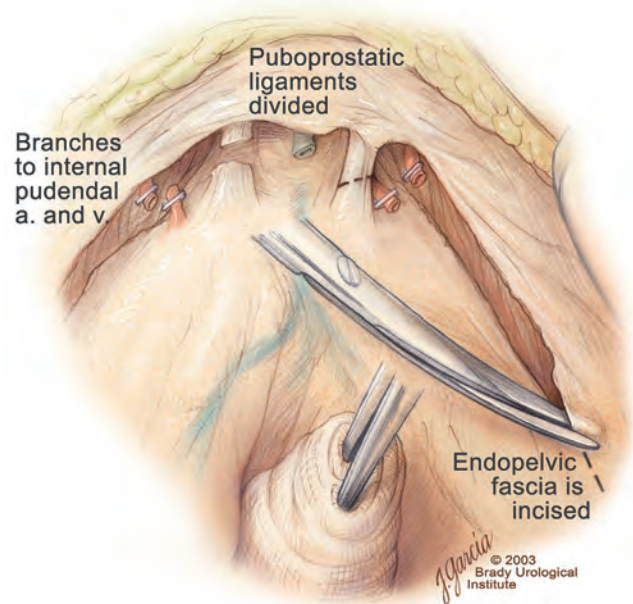


Figure 114-7. Incision in the endopelvic fascia and division of the puboprostatic ligaments. The incision in the endopelvic fascia is made at the juncture with the pelvic sidewall well away from the prostate and bladder. Anteriorly, near the puboprostatic ligaments, small arterial and venous branches from the internal pudendal vessels have been clipped and divided. The puboprostatic ligaments are divided superficially far enough down to expose the juncture between the apex of the prostate and the anterior surface of the dorsal vein complex. However, the pubourethral component of the complex is intact to preserve anterior fixation of the striated sphincter to the pubis. a., artery; v., vein. (© Brady Urological Institute.)

Incision in Endopelvic Fascia

The fibroadipose tissue covering the prostate is carefully dissected away to expose the pelvic fascia, puboprostatic ligaments, and superficial branch of the dorsal vein.

The endopelvic fascia is entered where it reflects over the pelvic sidewall, well away from its attachments to the bladder and prostate (Fig. 114-7). The point of incision is where the fascia is transparent, revealing the underlying levator ani musculature. Incision more medially can lead to entry into the lateral venous plexus of Santorini running alongside the prostate, resulting in persistent venous bleeding. Beneath this venous complex lie the prostatic arteries and the branches of the pelvic plexus that course toward the prostate, urethra, and corpora cavernosa.

The incision in the endopelvic fascia is then carefully extended in an anteromedial direction toward the puboprostatic ligaments. This allows the surgeon to palpate the lateral surface of the prostate. At this point, small arterial and venous branches from the pudendal vessels are encountered that perforate the pelvic musculature to supply the prostate. These vessels should be ligated with clips to avoid coagulation injury to the pudendal artery and nerve, which are located just deep to this muscle as they travel along the pubic ramus.

Division of the Puboprostatic Ligaments

The fibrofatty tissue covering the superficial branch of the dorsal vein and puboprostatic ligaments is gently teased away to prepare for division of the ligaments without injury to the superficial branch of the dorsal vein. After the superficial branch has been dissected away from the medial edge of the ligaments, it is coagulated and divided. After all fibrofatty tissue has been removed, a sponge stick is used to gently displace the prostate posteriorly and scissors are used to divide each ligament (see Fig. 114-7).

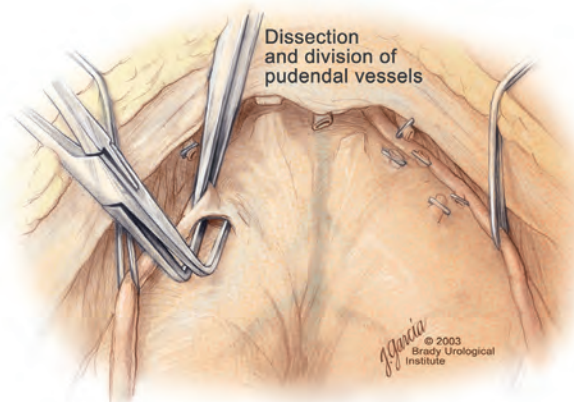


Figure 114-8. Preservation of bilateral large accessory pudendal arteries. The anterior prostatic fascia is elevated with a right-angled clamp to facilitate release of the accessory pudendal vessels. (© Brady Urological Institute.)

The dissection should continue down far enough to expose the juncture between the apex of the prostate and the anterior surface of the dorsal vein complex at the point where it will be divided. The pubourethral component of the complex should be spared to preserve the anterior fixation of the striated urethral sphincter to the pubis (Burnett and Mostwin, 1998).

Preservation of Accessory Pudendal Arteries

Arterial insufficiency is a factor contributing to erectile dysfunction in patients after nerve-sparing RRP. One source for this insufficiency may arise from accessory pudendal arteries that travel over the anterolateral surface of the prostate. These arteries have been found in 70% of cadaveric dissections and 7% of patients by selective internal pudendal angiography. Large visible accessory pudendal arteries are present in 4% of men (Rogers et al, 2004).

Because release of accessory arteries may be associated with significant blood loss necessitating prompt ligation and division of the dorsal vein complex, it is useful to have the contralateral dissection completed before accessory vessels are released. For this reason, when these vessels appear to be prominent and are present unilaterally, the endopelvic fascia and puboprostatic ligament on the contralateral side should be divided first. The surgical technique for preservation of the arteries begins with division of the endopelvic fascia lateral to the vessels and division of the puboprostatic ligament (the vessels are beneath the puboprostatic ligament) (Rogers et al, 2004). Next, a vessel loop is used to elevate the artery; then with sharp dissection and a right-angled clamp the accessory artery is released from its investing fascia (Fig. 114-8). As the dissection proceeds, venous tributaries are divided. At times, there may be substantial blood loss from the venous complex over the prostate; hemostasis, however, is usually easily obtained with a 4-0 running absorbable suture. The dissection must extend caudally beyond the site at which the dorsal vein complex will be divided.

Ligation of the Dorsal Vein Complex

The goal is to divide the complex with minimal blood loss while avoiding damage to the striated sphincter and inadvertent entry into the anterior apex of the prostate. With use of the sponge stick to push the prostate posteriorly, a 3-0 Monocryl suture is passed through the dorsal vein complex just distal to the apex of the prostate (Fig. 114-9). In placing this stitch, the surgeon should face the head of the table, holding the needle driver against the pubis perpendicular to the patient. Next, the needle is reversed in the needle holder and the same suture is placed through the perichondrium of the pubic symphysis (Fig. 114-10). Once this horizontal mattress

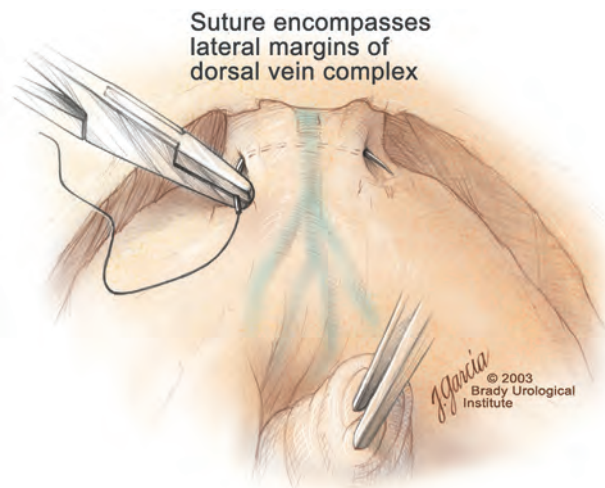


Figure 114-9. Steps in ligation and division of the dorsal vein complex. A 3-0 Monocryl suture is passed superficially through the dorsal vein complex just distal to the apex of the prostate. (© Brady Urological Institute.)

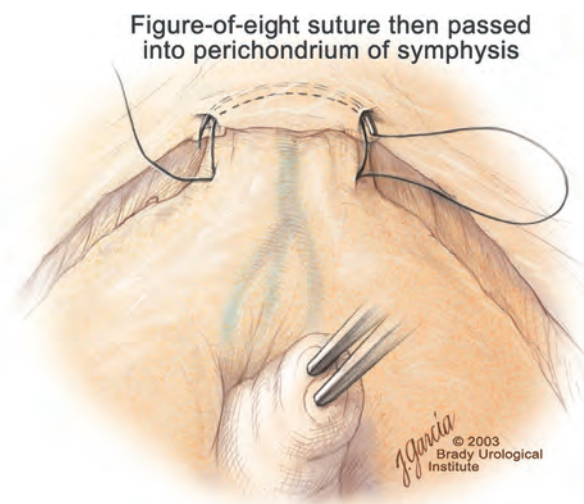


Figure 114-10. Next, the needle is reversed in the needle holder, and the same suture is passed through the perichondrium of the pubic symphysis. This maneuver is repeated to form a figure-of-eight horizontal mattress suture, which is then tied. (© Brady Urological Institute.)

suture is tied, three important goals are accomplished: (1) control of much of the venous bleeding without a “bunching” effect—this flat surface is much easier to divide; (2) recapitulation of the puboprostatic ligaments to provide additional anterior support of the striated sphincter; and (3) fixation of the dorsal vein complex anteriorly. This enables the surgeon to visualize the plane on the anterior apex of the prostate during division of the dorsal vein complex. The suture is not cut; it will be used once the dorsal vein is divided to oversee bleeders. Next a Babcock clamp is used to bunch the two edges of the endopelvic fascia. Then a figure-of-eight 2-0 Caprosyn suture is next placed through this bunched tissue on the anterior surface of the prostate near the bladder neck. This reduces bleeding from the proximal dorsal veins, which can be excessive in some patients who have incompetent venous valves (Fig. 114-11).

Apical Dissection

The apical dissection is the most complex and important step in the operation. The striated sphincter and the surrounding dorsal

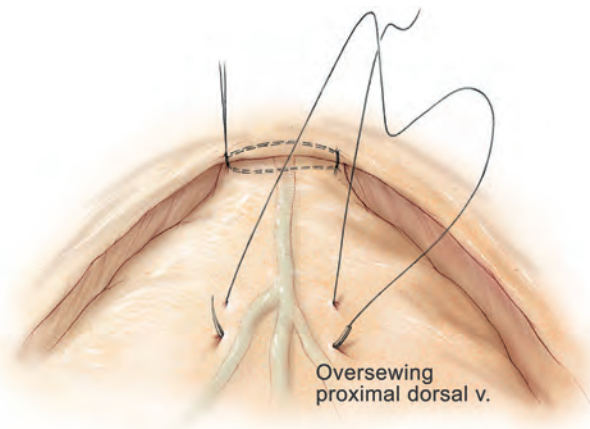


Figure 114-11. A figure-of-eight 2-0 absorbable suture is placed on the anterior surface of the prostate to reduce bleeding from the proximal dorsal venous complex. v., vein. (© Brady Urological Institute.)

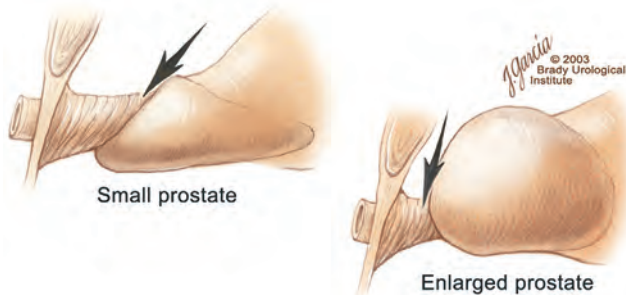


Figure 114-12. As Myers (1991) pointed out, there is marked variability in the shape of the apex of the prostate. In patients with a small prostate it can have a gentle slope, whereas in patients with an enlarged prostate, there can be an abrupt 90-degree angle. Knowledge of this variability is important to avoid excising excessive amounts of the striated sphincter. (© Brady Urological Institute.)

vein must be divided with care to avoid inadvertent incision into the apex of the prostate, the most common site for positive margins. Bleeding from the dorsal vein complex must be controlled without injury to the surrounding striated sphincter, the continence mechanism responsible for passive urinary control. During these maneuvers, the apical NVBs must not be injured by excessive traction, cautery, or inadvertent transection.

Division of the Dorsal Vein Complex. As Myers (1991) pointed out, there is marked variability in the shape of the apex of the prostate (Fig. 114-12). For this reason, we do not pass an instrument bluntly through the complex blindly. Rather, the dissection should be approached by direct division and visual assessment of the landmarks. With the application of gentle downward pressure on the anterior surface of the prostate with a sponge stick, Metzenbaum scissors or a No. 15 blade is used to divide the complex. This is usually started on the left edge of the complex where the junction with the apex of the prostate usually can be seen well (Fig. 114-13). Because the distal complex is fixed anteriorly, with downward pressure on the sponge stick, the exact plane between the juncture of the anterior surface of the prostate and the striated musculature can be visualized. Here loupes enable the surgeon to distinguish tissue textures and avoid positive margins. This is the most common site for positive surgical margins because it can be difficult to identify the anterior apical surface of the prostate. It also helps to rest the scissors on the anterior apex to find the correct plane.

There is one important caveat in performing this maneuver. As the dissection proceeds posteriorly, if the striated sphincter is

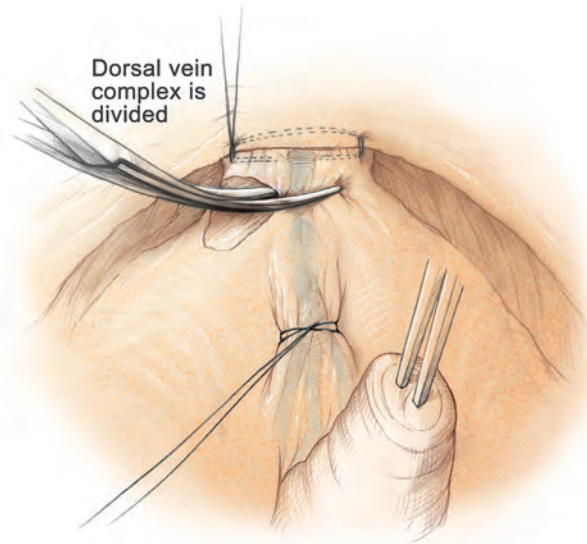


Figure 114-13. With a sponge stick depressing the prostate posteriorly, the dorsal vein complex is divided beginning at the left edge. (© Brady Urological Institute.)

Oversewing of striated urethral sphincter and dorsal vein

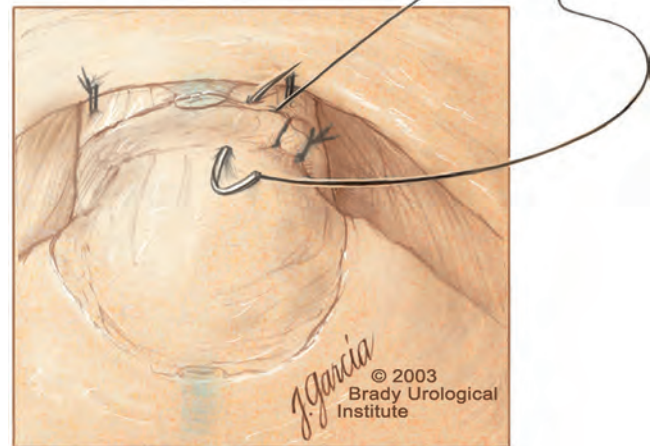


Figure 114-14. With the same 3-0 Monocryl suture that was used earlier to ligate the dorsal vein complex, the superficial edge of the distal striated urethral sphincter–dorsal vein complex is gently oversewn to perfect hemostasis. (© Brady Urological Institute.)

divided too close to the apex of the prostate, there is risk that the NVB may be damaged. As the NVB approaches the apex of the prostate, it is often fixed medially beneath the striated sphincter by an apical vessel (Walsh et al, 2000b). For this reason, the lateral edges of the sphincter along the urethra should be divided obliquely midway between the apex of the prostate and the pelvic floor. Absolute control of venous bleeding from the dorsal vein complex is mandatory so that the remainder of the procedure can be performed in a bloodless field. To achieve hemostasis, the 3-0 Monocryl suture on a $\frac{3}{8}$ -circle needle that was placed previously is used to oversee the superficial edges of the striated urethral sphincter–dorsal vein complex (Fig. 114-14). In placing this running suture, the surgeon should face the head of the table, holding the needle driver against the pubis perpendicular to the patient. If the needle driver is held loosely, the superficial edges of the complex can be easily approximated, forming a hood over the anterior urethra. Circumflex veins often are present at the posterior

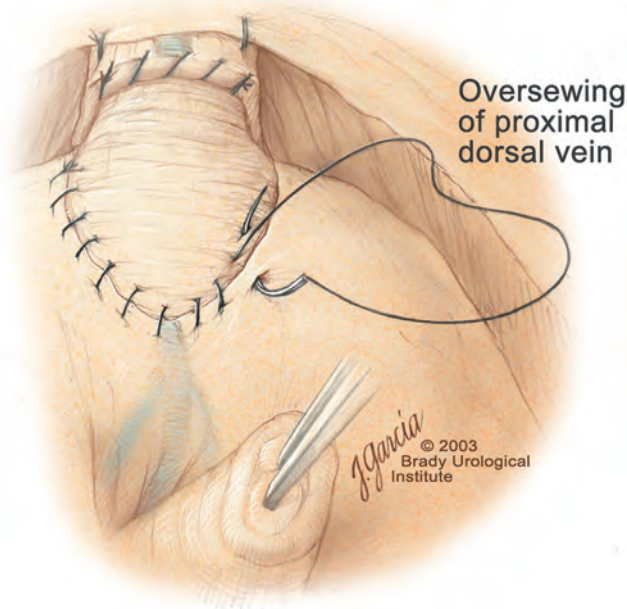


Figure 114-15. The dorsal vein complex over the anterior surface of the prostate is oversewn in the shape of a V with a running 2-0 absorbable suture. (© Brady Urological Institute.)

edge of the complex at the 5- and 7-o'clock positions; hemoclips often are used to control these bleeders. At the completion of this maneuver, hemostasis should be excellent.

Finally, to control back-bleeding from the anterior surface of the prostate, the edges of the proximal dorsal vein complex on the anterior surface of the prostate are sewn together with the preplaced 2-0 absorbable suture (Fig. 114-15). By pulling these edges together, tension on the prostatic fascia is evenly distributed, which can facilitate high release of the nerve bundles if the surgeon chooses to perform this maneuver (see detailed description later).

Division of the Urethra and Placement of Urethral Sutures. The urethra should be divided first in performing a standard nerve release. If more aggressive nerve preservation is performed, the urethral incision should occur after nerve release (see later). By gently displacing the prostate posteriorly with a sponge stick, the prostatic-urethral junction should be well visualized. The lateral bands of the striated musculature should be released as described earlier at their midpoint to free up as much of the urethra as possible. A right-angled clamp is then passed around the smooth musculature of the urethra near the apex of the prostate to ensure that the urethra is transected as close to the apex as possible (Fig. 114-16). This maneuver defines several key anatomic landmarks at the apex. First it defines the posterior urethra from the posterior component of the striated sphincter. Second, if excellent hemostasis has been obtained, the association between the posterior striated sphincter and the nerve bundle should be able to be appreciated. With scissors, the anterior two thirds of the urethra is divided with care to avoid damage to the Foley catheter. This provides excellent exposure for placement of six sutures in the distal urethral segment at the 1-, 3-, 5-, 7-, 9- and 11-o'clock positions. With 3-0 Monocryl on a $\frac{5}{8}$ circle tapered needle, the needle should incorporate just the urethral mucosa and submucosa but not the smooth muscle (Fig. 114-17). As stated previously, the surgeon should face the head of the table to place these sutures and should hold the needle driver against the pubis perpendicular to the patient. The first suture is placed in the mucosa and submucosa of the urethra at the 1- and 11-o'clock positions. By use of a 16-Fr catheter, the mucosa is easily identified. The smooth muscle should not be incorporated in this stitch because stitches in the smooth muscle delay the recovery of urinary control. If the urethral tissue appears flimsy, this suture should then be placed through the dorsal vein complex to improve tensile strength.

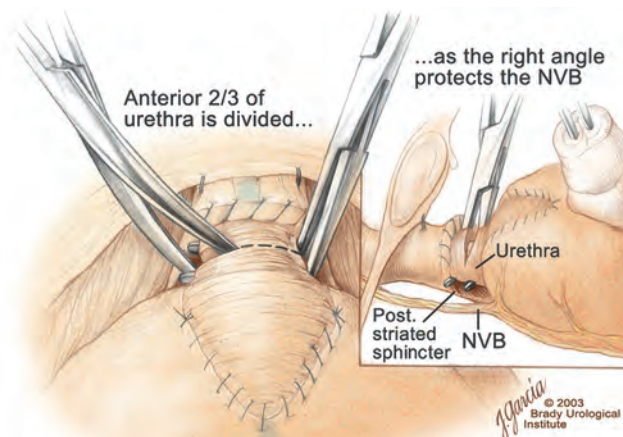


Figure 114-16. A right-angled clamp is placed around the smooth muscle of the urethra close to the apex of the prostate. Note in the inset that the neurovascular bundles (NVBs) are protected from injury by the posterior component of the striated sphincter, which is still intact. Also see Figure 114-5. Post., posterior. (© Brady Urological Institute.)

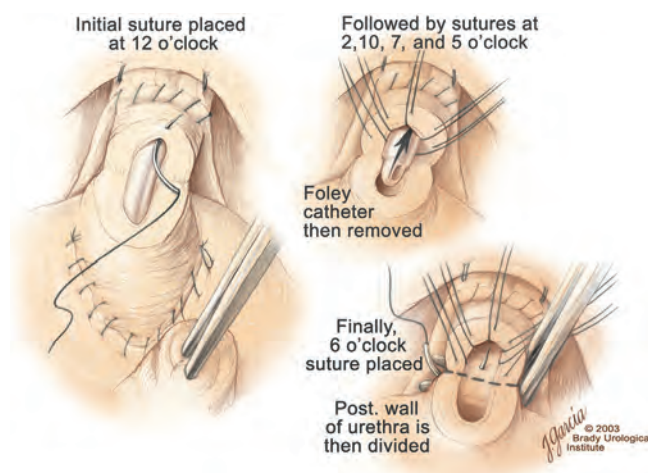


Figure 114-17. The 3-0 Monocryl sutures are placed in the distal urethral mucosa and submucosa at the 12-, 2-, 10-, 7-, and 5-o'clock positions. The Foley catheter is then removed, the 6-o'clock suture is placed, and the posterior wall of the urethra is divided. Post., posterior. (© Brady Urological Institute.)

Once the mucosa and submucosa have been elevated by these stitches, the remaining sutures are more easily placed. We place all sutures from outside of the lumen to the inside; however, if sutures are more easily placed beginning on the luminal surface and then proceeding outside, a French eye needle can be used to place these sutures through the lumen of the bladder at the end of the case. The sutures are covered with towels to avoid inadvertent traction or displacement.

The posterior band of the urethra is now divided to expose the posterior portion of the striated urethral sphincter complex (see Fig. 114-17). The posterior wall of the striated sphincter complex is composed of skeletal muscle and fibrous tissue. Identification and precise division of this complex are important in (1) obtaining adequate margins of resection for apical lesions, (2) identifying the correct plane on the anterior wall of the rectum to ensure that all layers of Denonvilliers fascia are excised, (3) avoiding blunt trauma to the NVBs that are located immediately posteriorly, and (4) preserving urinary continence.

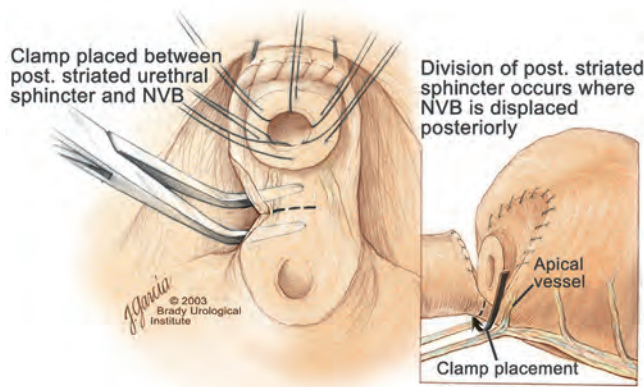


Figure 114-18. Division of the posterior component of the striated sphincter. A right-angled clamp is passed beneath the left edge of the striated sphincter midway between the apex of the prostate and urethra, at a site where the neurovascular bundles (NVBs) have fallen posteriorly. After the left edge of the complex is divided, a right-angled clamp is then passed along the right edge and the maneuver is repeated. post., posterior. (© Brady Urological Institute.)

To divide the posterior portion of the sphincter safely, a right-angled clamp is passed immediately beneath the left edge of this complex (Fig. 114-18). The clamp should pass midway between the apex of the prostate and the urethra. If it is passed too close to the apex of the prostate, it may damage the NVB. However, midway, the NVB is located more posteriorly and is beneath the right-angled clamp (Walsh et al, 2000b) (see Fig. 114-5).

The left border of the complex is then divided with scissors. Next, the right-angled clamp is placed beneath the right edge of the complex and the complex is divided. It is necessary to divide the complex from each side, because if division of the entire complex from one side is attempted, the contralateral NVB may be damaged. Finally, the central component of the complex is divided.

Identification and Preservation of the Nerve Bundle

Today, in most men who are candidates for surgery, it is safe to preserve both NVBs and rarely necessary to excise both of them (Walsh, 2001). With improved surgical techniques and the availability of phosphodiesterase type 5 inhibitors, most healthy potent men younger than 65 years should be potent after surgery. The neurovascular bundle is outside the prostate between layers of lateral pelvic fascia (the levator fascia and prostatic fascia). If nerve sparing is performed correctly, the prostatic fascia must remain on the prostate. This is called an *interfascial* dissection. Furthermore, when cancer extends through the capsule, it rarely penetrates more than 1 to 2 mm, and this much tissue is often present even when the neurovascular bundle is preserved (Hernandez et al, 2005). As Costello and colleagues (2004) have shown, the cavernous branches are positioned posterior to the capsular vessels and the nerves immediately adjacent to the prostatic capsule are nerves going into the prostate, not the cavernous nerves.

To avoid bleeding from the capsular arteries and veins, some surgeons dissect beneath the prostatic fascia. This is called an *intrafascial* dissection. Because this plane is directly on the prostatic parenchyma, the risk for positive surgical margins is high. For this reason, this approach should never be used. Many well-meaning surgeons believe that if they excise the NVB, they can avoid a positive surgical margin. Unfortunately, this is not the case because the NVB is not the most common site for positive margins. Rather, the most common site is the apex, followed by posterior and then posterolateral sites. In 22% the positive margins are multiple. In multiple studies, it has been demonstrated that the rate of positive margins in nerve-sparing and non-nerve-sparing procedures is the same (Ward et al, 2004). In Walsh's hands, the NVBs are preserved bilaterally in 87% of patients; one NVB is

excised in 13%. This has resulted in an overall rate of positive surgical margins of approximately 5% (Epstein, 2001). The NVBs are rarely if ever excised bilaterally. We have always thought that if there is capsular penetration bilaterally to the point at which it is necessary to excise both NVBs, the patient most likely has distant dissemination and is not curable. Between 1986 and 1999, only seven potent men had both NVBs excised. Four were not cured because they had positive lymph nodes, positive seminal vesicles, or positive surgical margins elsewhere. In the three other patients, it was not necessary to excise both NVBs because there was no capsular penetration on one side.

How is the decision made as to when and where to excise the NVB? Preoperatively, no definite decision is made. Consideration is given to the status of sexual function, but in impotent patients, we do not always excise the NVBs because there is evidence that the bundles provide both somatic and autonomic innervation to the continence mechanism and that patients who undergo excision of both NVBs have more incontinence than do patients in whom the NVBs are preserved (Nelson et al, 2003). Consideration is also given to other important factors such as the presence of a palpable apical lesion and a high probability of capsular penetration based on the Partin tables (Partin et al, 1997, 2001). However, no final decision is made until the time of surgery. When the endopelvic fascia is opened, if induration is palpable in the lateral pelvic fascia, the NVB on that side is widely excised. If there is no induration but the NVB appears to be fixed to the prostate at the time it is being released, it is also excised. However, the final decision about preservation or wide excision of the NVB does not need to be made until the prostate is removed. If there appears to be inadequate tissue over the posterolateral surface after the prostate has been removed, the NVB can then be widely excised.

Identification of the Neurovascular Bundle. This is where the tactile sensation provided by open surgery is so important. If induration is palpable in the lateral pelvic fascia, the bundle should be excised. Also, in gently releasing the bundle with a right-angled clamp, if the bundle is fixed to the prostate, it should not be preserved. When the NVB is released, there should be no upward traction on the prostate. Rather, the prostate should be rolled from side to side. Also with the catheter out, the prostate is softer and it appears easier to identify the correct plane for release of the NVB.

Standard Preservation of the Neurovascular Bundles. Standard nerve release begins after incision of the urethra, placement of urethra sutures, and release of the posterior striated sphincter. Recall that the lateral pelvic fascia is composed of two layers: the levator fascia and the prostatic fascia. The NVB travels between these two layers (see Figs. 114-4B and 114-5). With a right-angled clamp, the superficial layers of levator pelvic fascia are released. The use of loupes is helpful during this maneuver to ensure the prostatic fascia has not been violated. The magnification also facilitates a more gentle dissection with less traction on the NVB. A Babcock clamp or sponge stick is used during release of the NVB to manipulate the prostate. The clamp facilitates gentle elevation of the prostate during the release and can result in less traction on the NVB because the prostate is released from the bundle rather than the bundle being released from the prostate. This dissection should begin at the bladder neck, where this fascia forms a thick band (Fig. 114-19). When this band is divided, the prostate immediately becomes more mobile. The superficial fascia should be released from the bladder neck to the apex. This maneuver releases the bundle laterally, thus making it easier to perform the next step, in which the bundle is released posteriorly at the apex.

Once the superficial fascia has been released, the location of the NVB can be identified by the presence of a subtle "groove" on the posterolateral edge of the prostate (Fig. 114-20). By tracing this groove to the apex of the prostate, one can determine where the NVB begins to travel caudally and laterally away from the prostatic apex toward the urethra. Once the medial border of the NVB has been identified at the apex, the dissection in the midline can be safely carried posteriorly toward the rectum.

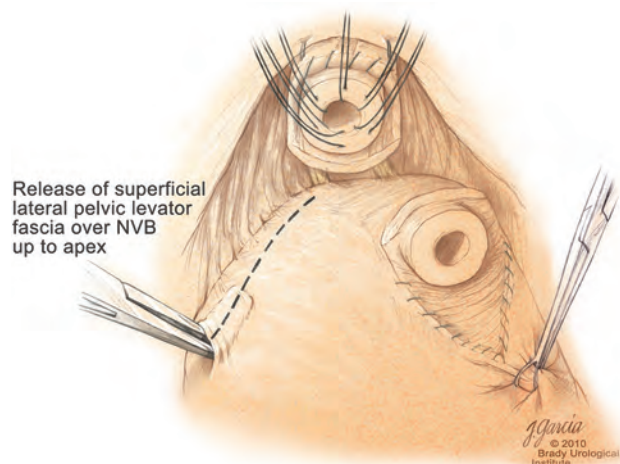


Figure 114-19. The lateral surface of the prostate is exposed by displacing the prostate on its side with use of a Babcock clamp. A right-angled clamp is then inserted under the superficial layer of the levator fascia, beginning at the bladder neck and continuing all the way out to the apex. NVB, neurovascular bundle. (© Brady Urological Institute.)

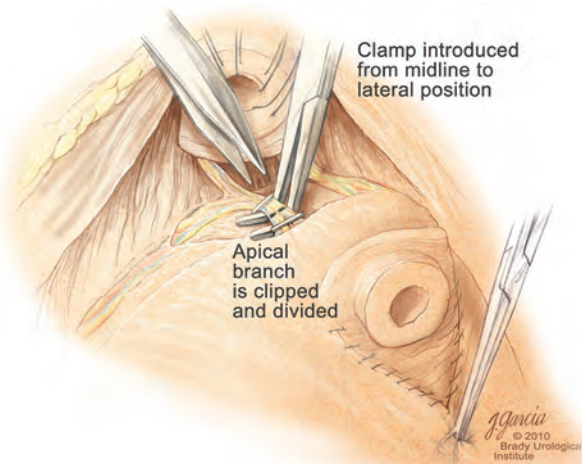


Figure 114-21. At the apex, there are often prominent apical vessels. Because the prostate has been elevated on its side across the midline, note that the neurovascular bundle (NVB) appears to be kinked. If this artifact is not recognized, the NVB can be inadvertently transected. Once these vessels are clipped and divided, the NVB returns to its natural straight course. (© Brady Urological Institute.)

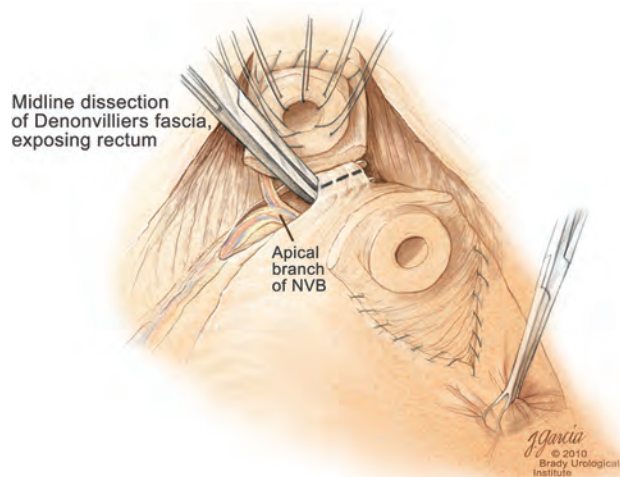


Figure 114-20. Once the levator fascia has been released, the neurovascular bundle (NVB) can be located by the presence of a subtle “groove” on the posterolateral edge of the prostate. This groove should be traced out to the apex of the prostate, and once the medial border has been identified, the dissection in the midline can be pursued, dividing residual layers of Denonvilliers fascia down to the rectum. (© Brady Urological Institute.)

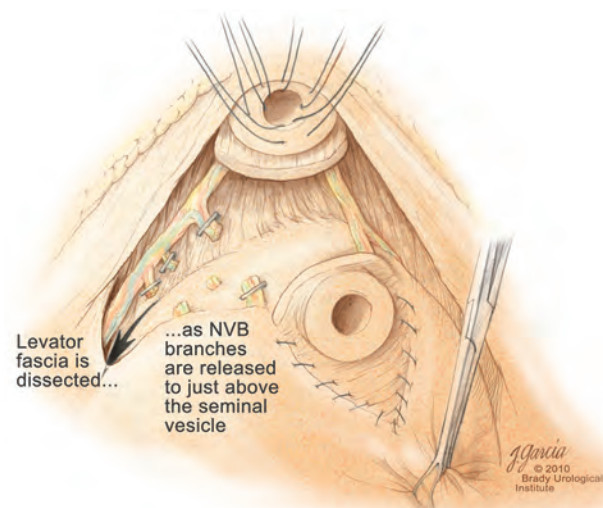


Figure 114-22. The neurovascular bundle (NVB) has been released to just above the seminal vesicle. (© Brady Urological Institute.)

The plane between the rectum and prostate having been developed in the midline, it is then possible to release the NVB from the prostate, beginning at the apex and moving toward the base, elevating and displacing the prostate over on its side. Beginning on the rectal surface, the bundle is released from the prostate by spreading a right-angled clamp gently. At the apex, there are often prominent apical vessels (Fig. 114-21). Because the prostate has been elevated on its side across the midline, this distorts the direction of the NVB by kinking it (see Fig. 114-21). If this artifact is not recognized, the NVB can be inadvertently transected. These vessels should be clipped and divided. Once the dissection has been initiated at the apex, it should proceed to the midpoint of the prostate. Because the superficial layers of the levator fascia have already been released, this dissection often proceeds easily. Furthermore, in using this plane, the Denonvilliers fascia and prostatic fascia remain on the

prostate; only the residual fragments of the levator fascia are released from the prostate laterally. At this point in the procedure, the bundle should be released to the seminal vesicle (Fig. 114-22).

The vascular branches to the NVBs are best controlled by small hemoclips placed parallel to the bundle. Thermal energy of any form (unipolar, bipolar, or harmonic scissors) should never be used on the NVB or its branches (Ong et al, 2004). Usually it is not necessary to clip the prostatic side of these tiny vessels; fine scissors should be used to divide them. The number of arterial and venous branches is extremely variable. By starting at the apex, however, one can easily identify them prospectively. If the fixation of the bundle to the prostate cannot be explained by vascular branches, the NVB should be excised. The surgeon should be aware that the bundle may travel more anteriorly in some patients. In these patients, one can confuse the groove with the potential

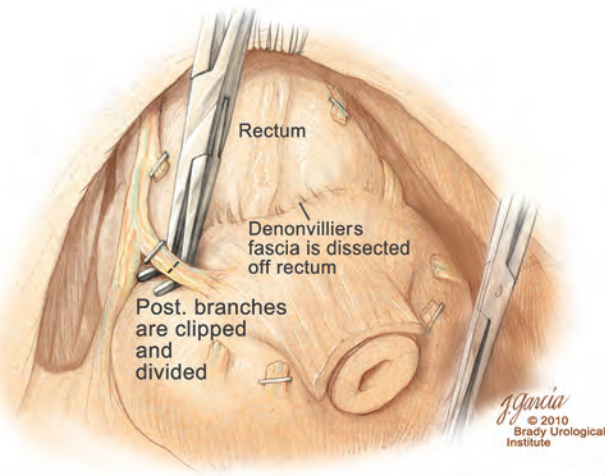


Figure 114-23. Posterior dissection. The attachment of Denonvilliers fascia to the rectum is released, maintaining all layers of Denonvilliers fascia over the posterior surface of the prostate and seminal vesicles. Prominent branches from the neurovascular bundle (NVB) to the posterior surface of the prostate are identified at the posterolateral angle of the rectum. By dividing these posterior branches, the NVB is free to fall away from the prostate posteriorly. Post., posterior. (© Brady Urological Institute.)

space between the prostate and rectum. This is another good reason to release the bundle at the apex first. In addition, some patients have many veins on the lateral surface of the prostate that anastomose between the Santorini plexus anteriorly and the NVB posteriorly. The apical approach to the bundle facilitates management of this condition as well.

Furthermore, to make certain the Denonvilliers fascia is maintained on the prostate, the NVBs should be released by dissecting from the rectal surface anteriorly. Using the principles described previously, positive surgical margins in patients with organ-confined disease that are caused by inadvertently cutting into the prostate are rare. Also, because the NVB is more mobile, it is easier to interrogate the surgical field with tactile sensation and magnification to find the correct plane. For this reason, even in patients with extraprostatic extension in the region of the NVB, it is possible to partially excise the bundle, preserve potency, and obtain negative margins of excision (Hernandez et al, 2005).

To avoid traction on the NVB, this dissection should continue cephalad to the level of the seminal vesicles (Masterson et al, 2008). At this point, the surgeon should look for a prominent arterial branch traveling from the NVB over the seminal vesicles to supply the base of the prostate (Fig. 114-23). This posterior vessel should be ligated on each side and divided. In doing so, the NVBs are no longer tethered to the prostate and fall posteriorly.

High Anterior Release of the Neurovascular Bundles at the Apex. The purpose of this approach is to speed up the recovery of sexual function and continence by reducing traction on the branches of the nerves to the cavernous bodies and striated sphincter or to avoid inadvertent transection of the small branches that travel anteriorly (Costello et al, 2004; Takenaka et al, 2004, 2005; Horninger et al, 2005; Menon et al, 2005; Montorsi et al, 2005). However, because there is less soft tissue at the apex, the risk for positive surgical margins could be increased by this approach. We select candidates for this approach using parameters that identify patients with a low risk for extraprostatic extension in the region of the NVB (Tsuzuki et al, 2005). Tsuzuki and colleagues (2005) have defined preoperative parameters to identify patients with a higher likelihood of extraprostatic extension in the region of the NVB. If patients have two or more of the following criteria, the risk for extraprostatic extension in the region of the NVB on that side is greater than 10%: prostate-specific antigen (PSA) level above 10 ng/mL, Gleason score higher than 6,

average percentage of biopsy core on the side involved greater than 20%, percentage of cores with tumor on that side greater than 33%, or an abnormal finding on digital rectal examination.

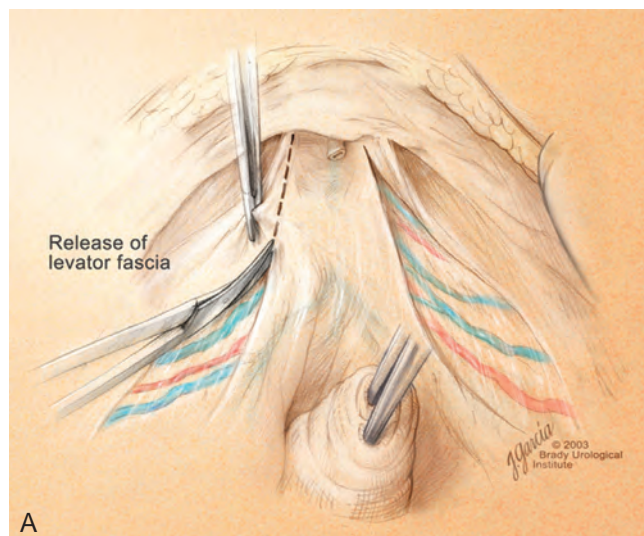
The procedure begins after ligation of the dorsal venous complex and before incision of the urethra. Once total hemostasis is obtained, the levator fascia over the anterior apex of the prostate is incised and the incision is extended distally along the lateral edge of the apex of the prostate, preserving the underlying prostatic fascia (Fig. 114-24). The prostatic fascia is the glistening white fascia immediately below the veins that travel along the lateral surface of the prostate. To identify the correct plane and avoid inadvertent incision into the prostate, it is essential to have excellent visualization and magnification. In many patients, these venous tributaries must be divided and controlled. Cautery should not be used. Instead, hemostasis should be achieved by use of small hemoclips. As the dissection proceeds distally, the levator fascia should be released from the lateral shoulders of the prostate, with care taken not to enter the underlying prostatic fascia. Because the recovery of sexual function at 12 months after unilateral high release was the same as with bilateral high release, we now routinely perform it on only one side, the side with the most favorable pathologic status. Once the dissection has extended distally beyond the apex of the prostate, the NVB is exposed and released. Because the levator fascia has previously been released, prominent NVB usually can be visualized lateral to the urethra. At this point, as described by Masterson and colleagues (2008), the NVB is released from the lateral surface of the prostate to just above the seminal vesicles (Fig. 114-25). This approach avoids traction on the NVBs and makes the subsequent steps in preservation of the NVBs much easier (Fig. 114-26).

Next, the urethra is transected and urethral sutures placed. The posterior component of the striated sphincter is transected. If high release of the levator fascia was performed only unilaterally, a right-angled clamp is inserted under the levator fascia at the apex on the side contralateral to the high release. This facilitates identification of the same dissection plane beneath the levator fascia as the contralateral side without the need for approaching the plane by first dividing the levator fascia from the outside (see Fig. 114-26).

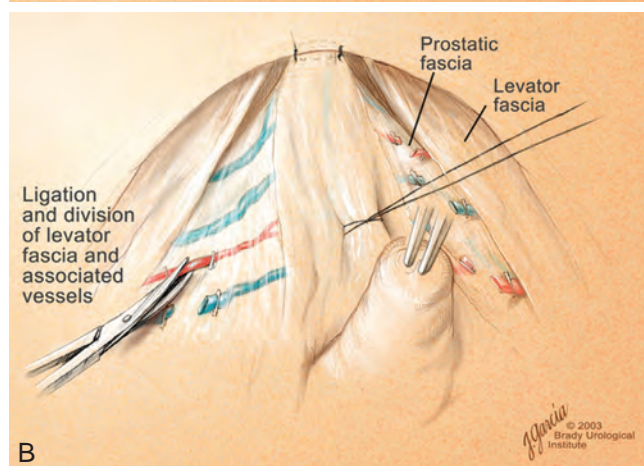
Wide Excision of the Neurovascular Bundles. Before excision of the NVB unilaterally, the contralateral NVB should be freed from the prostate, starting at the apex. This avoids traction injury, which can occur during wide excision of the contralateral bundle. The NVB to be excised is identified at the apex, and a right-angled clamp is passed from medial to lateral, immediately on the anterior surface of the rectum (Fig. 114-27). The bundle is divided without ligation in an effort to excise as much soft tissue as possible. Later, if bleeding is troublesome, the distal end can be clipped. The dissection is continued by dividing the fascia on the lateral surface of the rectum from the apex to the base so that the NVB and abundant fascial tissue are included in the specimen. This procedure is performed under direct vision, with the dissection terminating at the tip of the seminal vesicle, where the NVB is ligated and divided. In this way, the NVB and the lateral pelvic fascia are excised under direct vision in a more complete way than was previously possible (Fig. 114-28).

Posterior Dissection and Division of the Lateral Pedicles

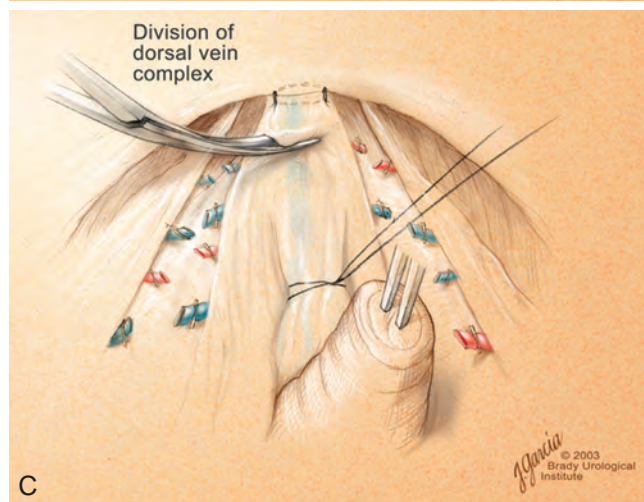
Once the NVBs have been either preserved at the apex or widely excised and the prostate has been mobilized to the level of the seminal vesicles, the catheter is replaced and, with light upward traction on the catheter, the attachment between the rectum and Denonvilliers fascia is divided in the midline posteriorly (Fig. 114-29). Because the NVBs have been freed up, traction can be applied to the catheter to gain exposure to the base of the prostate and seminal vesicles. However, to improve exposure, the sponge stick should never be placed on the prostate itself because it may displace tissue, producing a false-positive margin. Instead, the sponge stick should be placed on the catheter. In developing this plane, all layers of Denonvilliers fascia should be left covering the seminal vesicles.



A



B



C

Figure 114-24. High anterior release of the levator fascia. **A**, The levator fascia over the anterior apex of the prostate is incised along the lateral edge of the dorsal vein complex, preserving the underlying prostatic fascia. **B**, The dissection extends distally beyond where the dorsal vein was ligated. Venous tributaries are controlled with clips. **C**, The dorsal vein complex is divided to the urethra between the two preplaced dorsal vein sutures. (© Brady Urological Institute.)

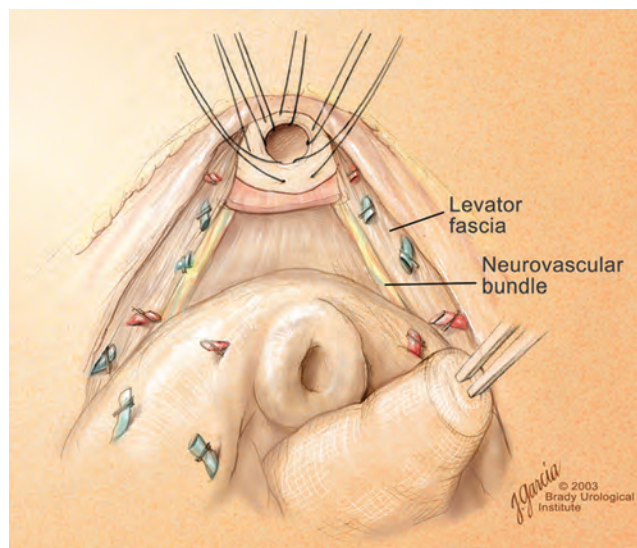


Figure 114-25. A view of the completed dissection. (© Brady Urological Institute.)

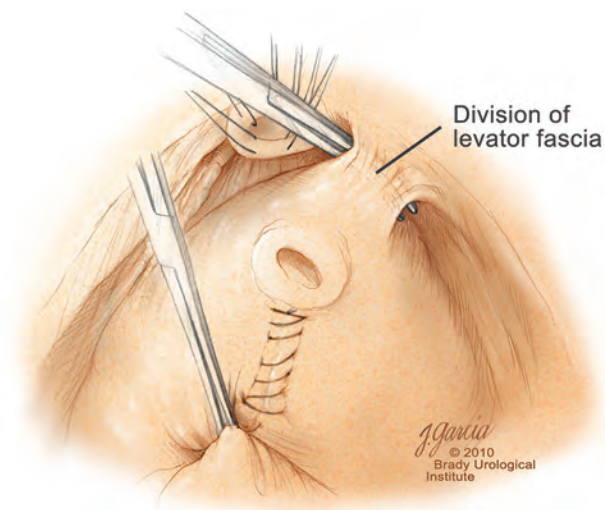


Figure 114-26. If high release of the levator fascia was performed only unilaterally, after the posterior component of the striated sphincter has been divided, a right-angled clamp is inserted under the levator fascia on the side contralateral to the high release at the apex. This facilitates identification of the same dissection plane beneath the levator fascia as the contralateral side without the need for approaching the plane by first dividing the levator fascia from the outside. (© Brady Urological Institute.)

At this point the lateral pedicle can be divided safely on the lateral surface of the seminal vesicles without injury to the NVB (see Fig. 114-29). The lateral pedicles are thick, and therefore they need to be divided in a sequential way: superficial, middle, deep (next to the seminal vesicles). If one tries to divide them all at once, this risks cutting into the overlying prostate.

Obvious arterial bleeders are simply controlled with hemoclips. With this approach, one can leave more soft tissue on the prostate and protect the NVBs from injury. The dissection proceeds superiorly onto the anterolateral surface of the junction between the bladder and the prostate. Finally, Denonvilliers fascia is divided over the tips of seminal vesicles to facilitate removal. At this point, many surgeons elect to divide the vasa deferentia and free up the seminal vesicles.

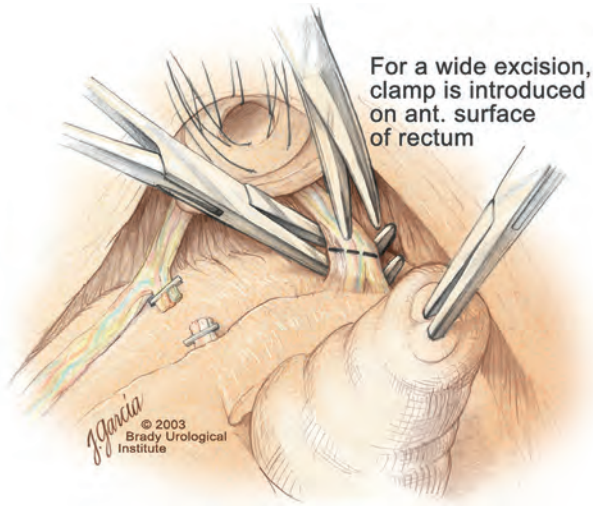


Figure 114-27. Wide excision of the neurovascular bundle (NVB). Once the contralateral NVB has been released and residual attachments of the rectum to the prostate at the apex are freed, a right-angled clamp is then passed directly on the anterior surface of the rectum from the midline laterally. If the right-angled clamp is passed lateral to medial, a rectal injury is more likely to occur. ant., anterior. (© Brady Urological Institute.)

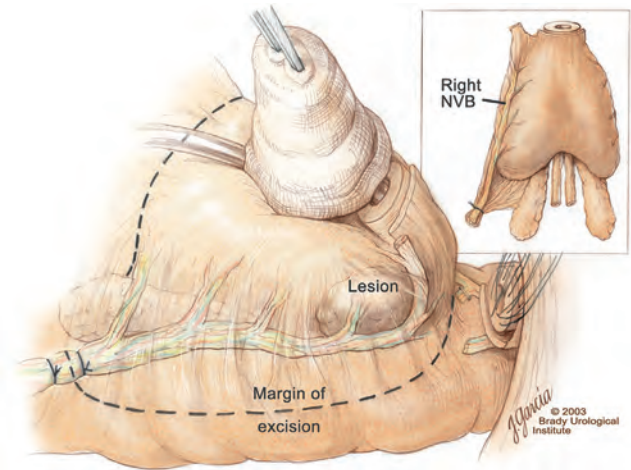


Figure 114-28. Extent of the division of the neurovascular bundle (NVB) from the apex laterally to the tip of the seminal vesicle, where the NVB is ligated. This provides excellent soft tissue covering the primary lesion. (© Brady Urological Institute.)

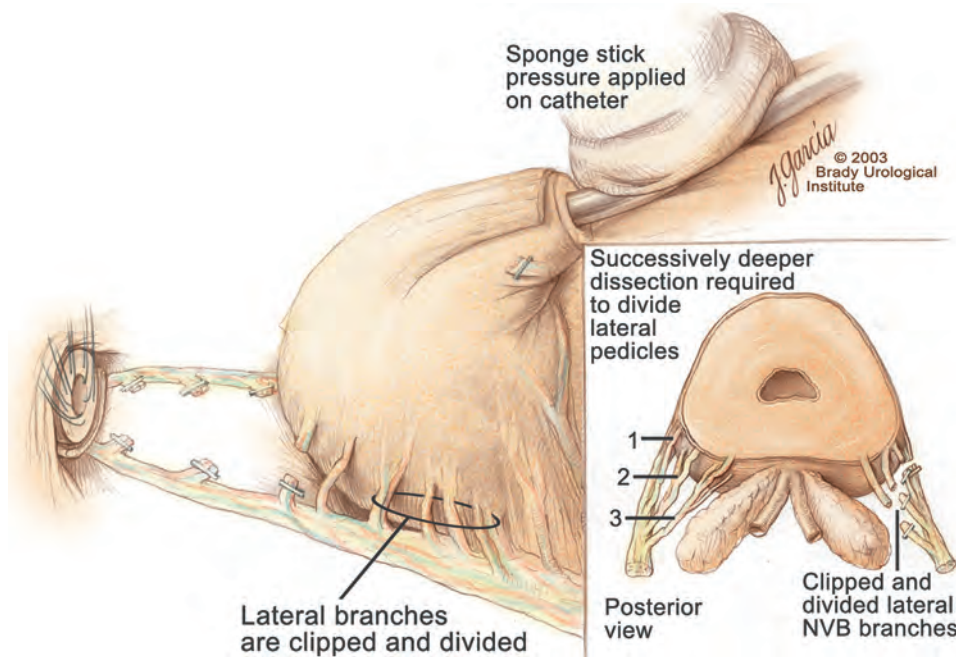


Figure 114-29. Lateral view demonstrating the location of the neurovascular bundle (NVB) after ligation of the posterior branch to the prostate. The site for division of the lateral pedicle is indicated. The lateral pedicle is thick and should be divided in layers: 1, superficially; 2, in the middle; and then (3) deep next to the seminal vesicle. Trying to divide this thick pedicle all at once risks cutting into the overlying prostate. (© Brady Urological Institute.)

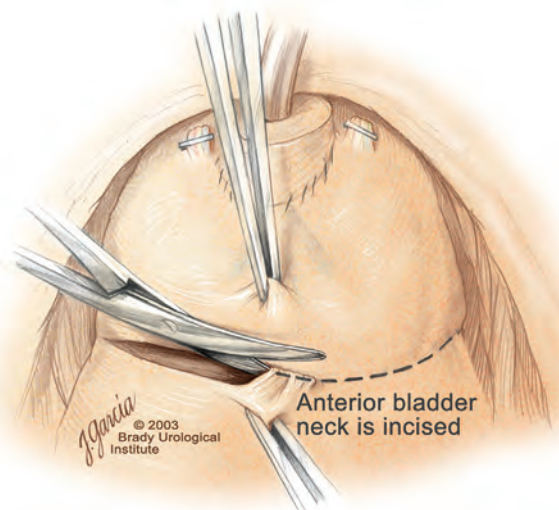


Figure 114-30. Division of the anterior bladder neck. (© Brady Urological Institute.)

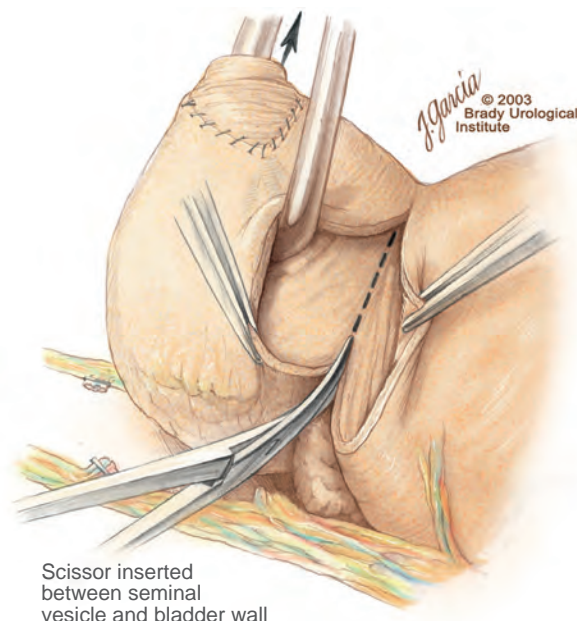


Figure 114-32. The plane between the anterior wall of the seminal vesicles and the posterior wall of the bladder neck for division of the posterior bladder wall. (© Brady Urological Institute.)

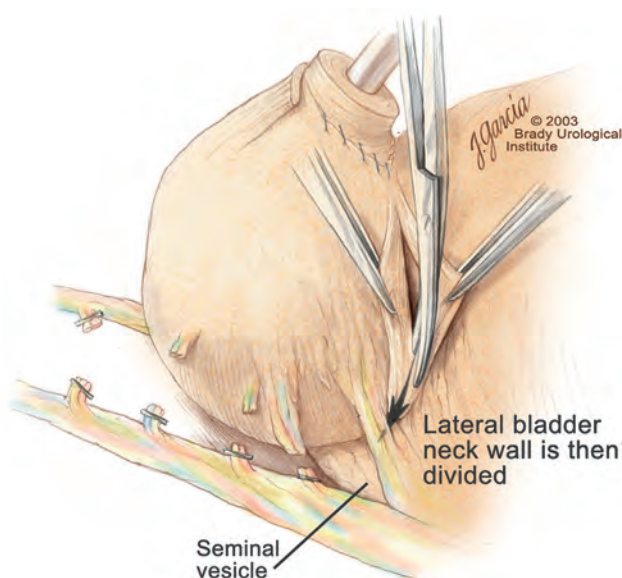


Figure 114-31. Ligation of the branches from the inferior vesical pedicle at 5- and 7-o'clock. This exposes the angle between the bladder and seminal vesicles. (© Brady Urological Institute.)

Division of the Bladder Neck and Excision of the Seminal Vesicles

The prostate has now been mobilized almost completely. The bladder neck is incised anteriorly at the prostatovesicular junction (Fig. 114-30). The incision is carried down to the mucosa, the mucosa is incised, the Foley balloon is deflated, and the two ends of the catheter are clamped together to provide traction. As the incision in the bladder neck is widened, branches running from the inferior vesical pedicle to the prostate are noted at 5- and 7-o'clock positions (Fig. 114-31). After these pedicles are divided, it should be possible to visualize the plane between the anterior surface of the seminal vesicles and the posterior wall of the bladder. By scissor dissection hugging the anterior surface of the seminal vesicles, the posterior bladder neck can be divided safely while observing the location of the ureteric orifices (Fig. 114-32).

After the posterior bladder wall is divided, the bladder neck is retracted with an Allis clamp, and the vasa deferentia are ligated with hemoclips and divided. The seminal vesicles are dissected free

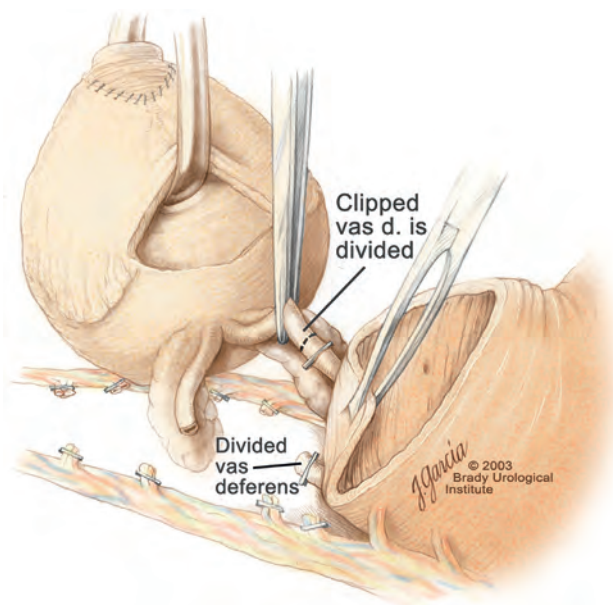


Figure 114-33. Dissection of the vas deferens and seminal vesicles. The left vas deferens has been divided and ligated. The seminal vesicles are carefully dissected free from the pelvic plexus with direct visualization and ligation of small arterial branches. d., deferens. (© Brady Urological Institute.)

from surrounding structures (Fig. 114-33). Recall that the pelvic plexus is located on the lateral surface of the seminal vesicles. To avoid injury to the pelvic plexus, the surgeon should perform this dissection with great care, especially laterally, and under direct vision should identify the small arterial branches that travel to the seminal vesicles and stay close to the seminal vesicles when these small vessels are ligated with small clips. As the tips of the seminal vesicles are freed, small arterial branches at the tip of each seminal vesicle should be identified, ligated, and divided. Any residual attachments of Denonvilliers fascia are then divided, and the specimen is removed. The specimen is inspected carefully

to identify any areas where the margin of resection is uncertain. If there is any concern about the margin on the posterolateral surface of the prostate, the NVB on that side should be excised.

The operative site is inspected carefully for bleeding. **Small bleeding vessels near the NVB should not be cauterized, to avoid injury to the fine nerve fibers.** Bleeding from these small vessels should be controlled with small hemoclips. If not, the patient may develop a hematoma between the rectum and bladder. Inflammation surrounding the NVBs secondary to this hematoma may delay the return of sexual function (Walsh et al, 2000b). To avoid this adverse event, a small opening can be made in the peritoneum in the rectovesical cul-de-sac to facilitate decompression of a hematoma if it develops.

Bladder Neck Reconstruction and Anastomosis

The bladder neck is reconstructed with a running suture or interrupted 2-0 absorbable sutures to approximate full-thickness muscularis and mucosa, forming a tennis racquet closure (Fig. 114-34). At this point, it is useful to have previously injected indigo carmine to facilitate visualization of the ureteric orifices; ureteral catheters are not usually necessary. **By incorporating the mucosa in the closure, troublesome hematuria can be avoided.** The closure is initiated in the midline posteriorly and proceeds anteriorly until the bladder neck is narrowed to approximate the diameter of the urethra. Interrupted or running 4-0 absorbable sutures are used to advance the mucosa over the raw musculature of the bladder neck. In this way, a rosette of mucosa covers the bladder neck, facilitating a mucosa-to-mucosa urethrovesical anastomosis. The suture at the 6-o'clock position is left long to facilitate placement of the urethral sutures for the final anastomosis (see later).

At this point, the bladder neck can be anastomosed to the urethra, or buttressing sutures can be used to intussuscept the bladder neck (Walsh and Marschke, 2002). These sutures prevent the bladder neck from pulling open as the bladder fills. The standard surgical technique described in this chapter emphasizes ample margins to ensure excellent cancer control, especially at the apex. Some surgeons preserve the puboprostatic ligaments and dissect beneath them closer to the apical prostate. Although this may preserve more of the striated sphincter, there is concern that it may lead to inadequate apical margins. The technique described herein may excise more striated musculature, and consequently it takes longer for some men to be pad free. Walsh and colleagues found that with intussusception of the bladder neck, 80% of men are pad free at 3 months and 98% at 1 year (Parsons et al, 2004).

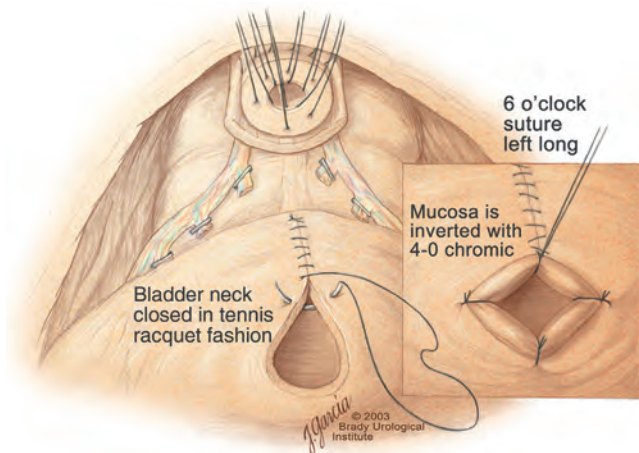


Figure 114-34. Tennis racquet closure of the bladder neck with a running 2-0 absorbable suture incorporating all layers of the bladder wall. The bladder mucosa is then advanced over the raw bladder edges with interrupted 4-0 absorbable suture material to ensure a mucosa-to-mucosa anastomosis. The posterior midline suture (at the 6-o'clock position) is left long. (© Brady Urological Institute.)

A 2-0 Maxon suture is placed into the edges of the posterior bladder wall, where the bladder was previously attached to the prostate, approximately 2 cm from the reconstructed bladder neck (Fig. 114-35). If any hemoclips are in this area, they should be removed because they may be folded into the bladder neck, causing a bladder neck contracture. The suture is tied in the midline. The next suture is placed more anteriorly. Before this suture is placed, it is wise to release tension on the anterior bladder wall by loosening the mal-leable blade. This will aid in identifying the loose perivesical tissue that should be incorporated into this stitch. A second figure-of-eight 2-0 Maxon suture is placed approximately 2 cm lateral to the bladder neck on each side (Fig. 114-36). At this point, the bladder neck should protrude beneath the anterior hood of tissue that was created by the anterior stitch, like a turtle that is poking its head outside its shell. When the bladder neck is filled with saline, it should be competent with little leakage. After this test is completed, the bladder should be emptied completely by placing a forceps through the bladder neck. The 6-o'clock suture should again be placed on traction to facilitate placement of the urethral sutures.

The operative site is inspected carefully for bleeding. A new silicone Foley catheter (16-Fr, 5-mL balloon) is placed through the urethra into the pelvis. The six 3-0 Monocryl sutures that were previously placed in the distal urethra are now placed through the

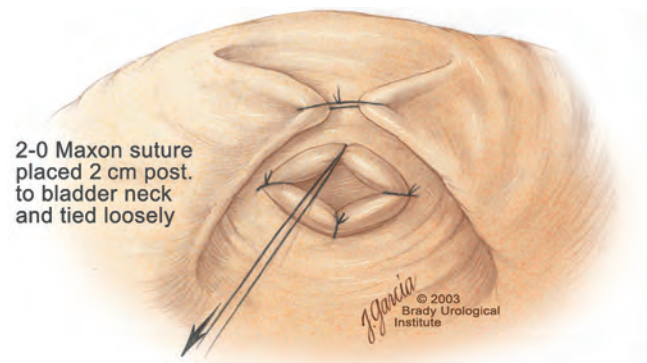


Figure 114-35. Intussusception of the bladder neck. A 2-0 Maxon suture is placed in the edges of the posterior bladder wall, where the bladder was previously attached to the prostate, approximately 2 cm from the reconstructed bladder neck and tied in the midline. post., posterior. (© Brady Urological Institute.)

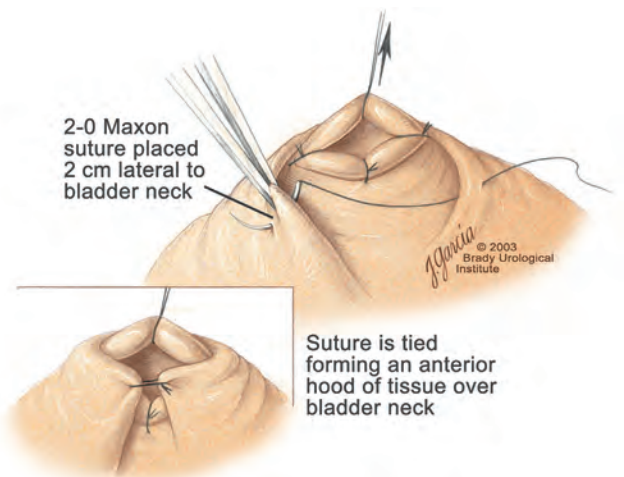


Figure 114-36. Intussusception of the bladder neck. A second figure-of-eight 2-0 Maxon suture is placed anteriorly about 2 cm lateral to the bladder neck on either side and tied. (© Brady Urological Institute.)

bladder neck in their corresponding positions from inside to outside (Fig. 114-37). Use of traction on the 4-0 suture that was placed at the 6-o'clock position to exteriorize the mucosa facilitates placement of the sutures. As mentioned previously, a French eye needle is used for placement of the 12-, 2-, and 5-o'clock sutures. The catheter is irrigated free of clots, the balloon is tested, and the catheter is placed through the bladder neck and inflated with 15 mL of saline. The catheter is no longer placed on traction while the sutures are tied. Instead, a Babcock clamp, which is placed on the anterior bladder wall close to the reconstructed bladder neck, is used to hold the bladder in place while the sutures are tied (Fig. 114-38). This ensures excellent coaptation of the mucosa to mucosa and has markedly reduced the probability of bladder neck contractures.

The anterior suture is tied initially. There should be no tension. If there is, the bladder should be released from the peritoneum. The 2-, 5-, 10-, 7-, and 6-o'clock sutures are tied sequentially. After all sutures are tied, the catheter is manipulated to make certain it is not caught in one of the sutures. The catheter is irrigated with saline to eliminate clots. After the operative site is irrigated vigorously with saline, a small suction drain is placed through the fascia (away from the midline) and directed into the

operative site in the midline, between (not through) the rectus muscles. The incision is closed with a running No. 2 nylon suture and skin clips. The catheter is carefully taped to the thigh.

POSTOPERATIVE MANAGEMENT

The postoperative recovery of men who undergo open RRP is often uneventful. The complication rates after open radical RRP have greatly improved over the past decade and were recently reviewed (Dasgupta and Kirby, 2009). Summary of the findings showed a marked decrease in length of stay (now averaging 1.7 days), lower urine leak rates (0.17%), lower need for transfusion (0.13%), lower postoperative ileus rate (0.6%), and a lower re-exploration rate for hemorrhage (0.08%).

Traditionally, men ambulate the evening of the procedure and are discharged on postoperative day 1 or 2. Pain control is achieved by intravenous patient-controlled analgesia with Dilaudid, fentanyl, or morphine on the night of surgery. In an effort to decrease the need for narcotics after surgery, men with normal renal function (preoperative creatinine < 1.2 mg/dL), no excess blood loss during the procedure (estimated blood loss < 1500 mL), and no history of uncontrolled diabetes or postoperative hematuria have received a dose of intravenous ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID) either before transfer to the recovery room or the morning after surgery. Recently, intravenous acetaminophen also has been administered to men for postoperative pain control with similar results but at present is quite costly. This combination of analgesic agents reduces postoperative ileus; however, when NSAIDs are used we have seen postoperative hematuria persist, often requiring repeated catheter irrigation. Patients are offered a clear liquid diet on the evening of surgery and a regular low-fat diet the next day. A single closed-suction drain is left in place until discharge or it produces less than 50 mL/day off of suction.

The urinary catheter is left in place for 7 to 10 days postoperatively, represents a source of significant bother (Lepor et al, 2001), and limits the return to activities and work (Sultan et al, 2006). Therefore the urinary catheter should be removed as soon as possible without compromising outcomes (e.g., urinary retention and bladder neck contracture). Most would agree that removing the urinary catheter in the presence of significant urine extravasation would be unwise. Although 80% of vesicourethral anastomoses exhibit no evidence of cystographic extravasation by the fourth postoperative day, removal of the urinary catheter at this time is not recommended because of the high rate of acute urinary retention (Patel and Lepor, 2003). Approximately 10% of men will exhibit moderate extravasation on postoperative cystograms performed 1 week after surgery. Routinely performing cystography at 1 week allows "early" removal of the urinary catheter while also identifying the small subset of men who might benefit from longer bladder drainage but requires patients to return to the hospital/clinic, exposes them to radiation, and incurs additional expense to the process. Alternatively, our experience has shown that the urinary catheter may be removed safely by the patients in their own home after 10 days. Bladder spasms will generally spontaneously subside, and reassurance is often sufficient. In cases of severe bladder spasms, an oral anticholinergic agent (oral oxybutynin [Ditropan] 5 mg) or diazepam (oral Valium, 5 to 10 mg) may be administered.

COMPLICATIONS

RRP is well tolerated, with minimal morbidity and low mortality (0.2%). Complications can be divided into those occurring intraoperatively and those occurring postoperatively.

Intraoperative Complications

The most common intraoperative problem is hemorrhage, usually arising from venous structures. Venous injury often can be

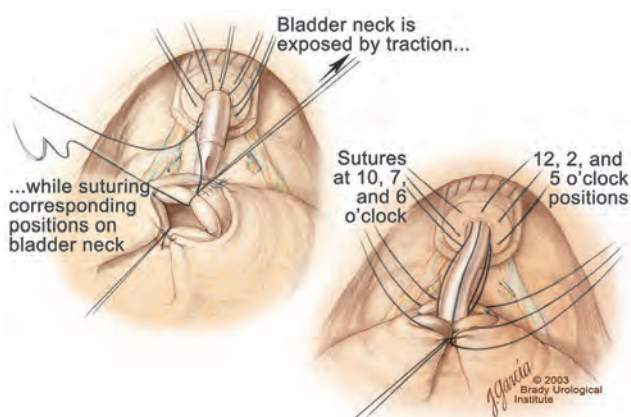


Figure 114-37. The bladder neck is exposed by placing traction on the 4-0 absorbable suture at the 6-o'clock position. The final anastomosis is performed by placing 3-0 Monocryl sutures at the 12-, 2-, 5-, 7-, and 10-o'clock positions. (© Brady Urological Institute.)

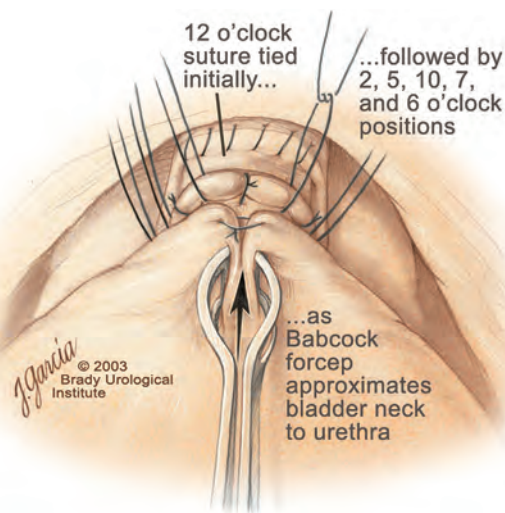


Figure 114-38. A Babcock clamp is used to displace the reconstructed bladder neck into the pelvis and is held in place until all sutures are tied. This maneuver ensures that there is excellent coaptation of the reconstructed bladder neck to the urethra while the sutures are being tied. (© Brady Urological Institute.)

controlled temporarily with packing, exposure, and suture or surgical clip ligation. If this is not successful, fine (No. 5-0) cardiovascular sutures may be required. Hemorrhage also can occur during incision in the endopelvic fascia, during division of the puboprostatic ligaments, or during exposure of the apex of the prostate with transection of the dorsal vein complex. If one understands fully the anatomy of the dorsal vein complex, this bleeding is usually satisfactorily controlled once the dorsal vein has been divided and carefully suture ligated. If there is troublesome bleeding from the dorsal vein complex at any point, the surgeon should completely divide the dorsal vein complex over the urethra and oversew the end. This is the single best means to control bleeding from the dorsal vein complex. While obtaining exposure for the prostatectomy, gentle traction must be put on the prostate. If the dorsal vein is not completely divided and ligated, this traction opens the partially transected veins and usually worsens the bleeding. With careful technique and a thorough knowledge of anatomy, the average blood loss during radical prostatectomy is 300 to 1000 mL routinely and rarely (<1%) requires intraoperative homologous blood transfusion. Because of these low transfusion rates, we no longer require the patients to donate/bank autologous blood before surgery. Every case does, however, get a type and screen sample obtained before initiation of surgery.

Less common intraoperative complications include obturator nerve injury during pelvic lymph node dissection, rectal injury, and ureteral injury. If the obturator nerve is inadvertently severed, an attempt should be made at reanastomosis with fine nonabsorbable sutures. Rectal injury is an infrequent (<0.3%) but serious complication. Rectal injury occurs during apical dissection in attempting to develop the plane between the rectum and Denonvilliers fascia. When a rectal injury occurs, the prostatectomy should be completed, the bladder neck should be reconstructed, and hemostasis should be excellent. It is critical to attempt to interpose omentum between the rectal closure and the vesicourethral anastomosis to reduce the possibility of a rectourethral fistula. This maneuver can be accomplished simply by making a small opening in the peritoneum; finding the omentum and fashioning a slender, well-vascularized pedicle that will be long enough to reach the pelvic floor; dividing the peritoneum in the rectovesical cul-de-sac; and feeding the end of an omental pedicle through this opening. The anal sphincter is digitally dilated widely by an assistant, and the rectal injury is clearly delineated. With excellent visualization, the edges of the rectal wound are freshened and closed in two layers. The omental pedicle is immobilized over the repair, with absorbable sutures, and the vesicourethral anastomosis is performed. The wound should be copiously irrigated with antibiotic solution, and the patient should be maintained for several days on broad-spectrum antibiotics for both aerobic and anaerobic bacteria. When this technique was used, all recovered without development of a wound infection, pelvic abscess, or rectourethral fistula (Borland and Walsh, 1992). However, if the patient has received prior radiotherapy (salvage prostatectomy), it is prudent to perform a diverting colostomy. Ureteral injury is also very rare and usually occurs secondary to inadvertent dissection within the layers of the trigone while attempting to identify the proper cleavage plane between the bladder and seminal vesicles. If this injury occurs, ureteral reimplantation should be undertaken.

Postoperative Complications

Life-threatening delayed hemorrhage is a rare complication of RRP. Significant bleeding after radical prostatectomy is defined as postoperative hemorrhage requiring the acute transfusion of blood to support blood pressure (Hedican and Walsh, 1994). Rarely a patient will require exploration for delayed bleeding, and most cases are managed expectantly. The mean blood product requirements for patients who were explored were comparable with those for patients managed conservatively, although total hospitalization was shorter in patients who underwent a secondary operation. In patients managed nonoperatively, the pelvic hematoma may drain through the urethrovesical anastomosis, resulting in symptomatic bladder

neck contractures and long-term problems with urinary control. In our experience (Hedican and Walsh, 1994) only 25% of men explored for delayed bleeding experienced prolonged mild incontinence. These results suggest that patients requiring acute transfusions for severe hypotension after radical prostatectomy should be explored early to evacuate the pelvic hematoma in an effort to decrease the likelihood of bladder neck contracture and incontinence.

Thromboembolic Events

Deep venous thrombosis (DVT) with pulmonary embolism is a major cause of mortality after radical prostatectomy. This recent review of over 45,000 surgical prostate procedures completed in Sweden demonstrated that the highest rates were seen when pelvic lymph node dissection was performed as part of the procedure and that the highest likelihood occurred between 14 and 28 days after the procedure, highlighting the need for continued attention to risk as long as 4 weeks after the procedure. Measures to prevent this complication include careful positioning on the operating room table to avoid compression of the veins in the lower extremity, use of intermittent compression devices, and early ambulation. With an 8-cm incision, Walsh did not have a thromboembolic event in over 700 cases, in contrast to a rate of 1.4% in his prior 700 cases (Walsh, personal communication). Although the mechanism behind this dramatic reduction is unknown, Walsh thinks that the shorter incision reduces exposure, dehydration, and traction on the external iliac veins during the procedure. Mini-dose heparin or low-dose, low-molecular-weight heparin is used at some centers (but not at ours).

Most importantly, all patients should be repeatedly informed of the signs and symptoms of DVT and pulmonary embolism before discharge and should be instructed verbally and in writing to call immediately if they have any of the following symptoms: swelling or pain in the leg, especially in the calf; sudden chest pain that is worse on taking a deep breath; hemoptysis; shortness of breath; or the sudden onset of weakness or fainting. We have found that the informed patient is the best way to reduce the morbidity and mortality from thromboembolic events. When patients develop DVT or pulmonary embolism events, twice-daily subcutaneous administration of low-molecular-weight heparin without monitoring of clotting factors appears to be at least as effective and safe as an adjusted-dose, intravenous administration of unfractionated heparin (Buller et al, 2003).

Bladder Neck Contracture

Bladder neck contractures historically occur in 0.5% to 10% of patients after radical prostatectomy, and the rate has diminished dramatically over the last decade. They arise from inadequate coaptation of the mucosal surfaces. This may be due to inadequate approximation at the time of surgery, urinary extravasation, or distraction of the bladder neck from a hematoma. The diagnosis should be considered in any patient who complains of a poor urinary stream or in patients who have prolonged unexplained incontinence. If treatment with simple cystoscopic dilation fails, direct cold-knife incision of the bladder neck at 3-, 6-, and 9-o'clock followed by intermittent self-catheterization for a limited time usually corrects the problem. In patients with recalcitrant bladder neck contractures, the injection of triamcinolone acetate (200 mg in 5 mL) at the bladder neck after cold-knife incision may be useful.

Urinary Incontinence

After radical prostatectomy, incontinence is usually secondary to intrinsic sphincter deficiency. Kim and associates (2013) demonstrated in a Surveillance, Epidemiology, and End Results (SEER) Program population that only 6% of over 16,000 men (over age 65) had undergone an "incontinence procedure" within the first 2 years after prostatectomy. In some men, the striated sphincter may


be poorly developed; in older men, it is thinner and contains more collagen (Burnett and Mostwin, 1998; Strasser et al, 1999). However, the predominant cause of this deficiency is injury during ligation and division of the dorsal vein complex. The smooth musculature of the urethra, which also contributes to continence, can be damaged by placement of large, deep sutures for the anastomosis or denervated by injury to the NVBs. Furthermore, the bladder neck must be supple, with a diameter that is not excessively large, because urinary continence can be hampered by the development of a bladder neck contracture or a wide bladder neck (Horie et al, 1999; Groutz et al, 2000). To avoid these complications, as outlined previously, it is important to preserve the striated sphincter during the apical dissection, to avoid tension on the final anastomosis, to reconstruct the bladder neck so that the opening is small and supple, and to accomplish a precise mucosa-to-mucosa anastomosis. Buttressing sutures to intussuscept the bladder neck to prevent it from pulling open as the bladder fills also have been reported (Walsh and Marschke, 2002). Finally, many men have detrusor hypertrophy and decreased bladder compliance from preexisting bladder outlet obstruction. It takes these patients longer to achieve full urinary control. For this reason, it is important to avoid excessive traction on the bladder intraoperatively, which may aggravate this condition.

It is beyond the scope of this chapter to review all of the literature on urinary incontinence. In a population-based longitudinal cohort follow-up study up to 24 months, Stanford and colleagues (2000) reported that after radical prostatectomy, 8.4% of men had either frequent urinary leakage or no control. In contrast, in the patient-reported outcome study by Walsh and associates (2000a) in which patients returned a validated questionnaire to an independent third party, 93% of the patients were wearing no pads at 1 year and 98% stated that they had no significant urinary problem. In a more recent study performed after introduction of the bladder neck intussusception, 98% of the patients were pad free at 1 year and no patient reported having a significant problem with urinary control (Parsons et al, 2004).

During their recovery, patients need constant encouragement and advice at regular intervals. The details of this program are reported elsewhere (Walsh and Worthington, 1995, 2001). Until urinary control has returned completely, patients are advised to reduce their fluid intake, avoid caffeinated beverages and alcohol, and stop α -adrenergic antagonists if they take them for the treatment of hypertension. Treatment with imipramine or α agonists in men who are not hypertensive can be helpful.

Erectile Dysfunction

Three factors are important in the recovery of erectile function after radical prostatectomy: age of the patient (younger than 65 years), status of potency preoperatively, and ability to intraoperatively preserve both NVBs. Walsh and colleagues (2000a) evaluated incontinence by a validated questionnaire sent to an independent third party for review. At 18 months, 86% of the patients were able to have unassisted intercourse with or without sildenafil citrate. Although a third of patients were taking sildenafil citrate, only 4% of men reported that they could not have intercourse without it. The recovery of sexual function occurred gradually: 38% were potent at 3 months, 54% at 6 months, 73% at 12 months, and 86% at 18 months. Recovery of sexual function also correlated with the age of the patient at the time of surgery: 100% in men 30 to 39 years, 88% in men 40 to 49 years, 90% of men 50 to 59 years, and 75% in men 60 to 67 years. These data were updated with a similar questionnaire (Parsons et al, 2004). At 3 months, 42% of the patients were potent; at 6 months, 49%; and at 1 year, 73%. In both series, most patients had both NVBs preserved. In patients in whom only one NVB is preserved, 65% of patients are potent. In patients with an accessory pudendal artery, preservation was associated with a twofold increase in the likelihood of recovery of erections (Rogers et al, 2004).

 High anterior release of the NVB as demonstrated in the video on the Expert Consult website is associated with significantly earlier recovery and return to baseline sexual function. In potent

men undergoing high anterior release, 93% were potent 12 months after surgery and 70% reported a return to their baseline erectile function. In men who preoperatively reported a frequency of intercourse more than once per week, 78% reported a return to their baseline sexual function at 12 months (Nielsen et al, 2008). Interestingly, this recovery and return to baseline function was noted in men who underwent either a unilateral or bilateral high release. This suggests that the improved sexual recovery associated with this technique is not likely due to preservation of anterior branches of the cavernous nerves but rather to improved accuracy in the preservation of the nerves with less traction. Other experienced surgeons also have noted improved recovery of sexual function using similar early nerve release techniques providing further merit to this technical modification (Masterson et al, 2008).

In patients who are medically cleared, phosphodiesterase type 5 (PDE5) inhibitors augment sexual recovery after radical prostatectomy. Until recently, however, the best dosing schedule (nightly or on demand) for these medications was unclear. In a small study, Padma-Nathan and associates (2008) reported improved recovery of sexual function in patients given nightly sildenafil versus patients given placebo. However, men in the placebo arm never received any therapy. In 2008, Montorsi and colleagues reported on a multi-institution randomized, double-blind study examining recovery of erectile function using either vardenafil "on demand," nightly, or placebo for 9 months. At the end of the blinded treatment period, vardenafil on demand was of greater benefit than nightly treatment. In a similarly devised trial, Pavlovich and colleagues (2009) noted no difference in recovery of sexual function in patients using either on-demand or nightly sildenafil, with a trend toward improved recovery in the on-demand arm. Thus on-demand dosing of PDE5 inhibitors appears to be the most effective method to aid in recovery of sexual function.

SURGICAL MODIFICATIONS TO CLASSIC ANATOMIC RADICAL PROSTATECTOMY

Since the initial report of the anatomic radical prostatectomy, refinements in the surgical technique have been made. Some modifications have minimized the short-term and long-term morbidity of the procedure or the oncologic outcome and have been incorporated into the classic operation (Walsh et al, 2000b; Walsh and Marschke, 2002; Rogers et al, 2004); others have demonstrated no or minimal measurable benefit or negative benefit and have been abandoned (Steiner et al, 1993; Parsons et al, 2004). Several modifications to the classic anatomic radical prostatectomy have been suggested to improve early return of urinary continence, erectile function, or both. These surgical modifications have focused on the function of the bladder neck in urinary control, dissection around the seminal vesicles, and placement of interposition nerve grafts when resection of the NVBs is required. Compelling anatomic and physiologic mechanisms have been proposed to explain how these modifications improve continence and potency. The evidence supporting these modifications is less compelling and often inconsistent. Retrospective studies comparing the impact of these technical modifications on quality-of-life outcomes fails to control for selection bias, varying methods for assessing outcomes, and varying skills of the surgeons performing the modified versus standard surgical techniques. These retrospective studies are appropriate for identifying a signal of clinical benefit. Ultimately, long-term randomized multicenter studies using validated quality-of-life questionnaires must be performed before these modifications become standard of practice, especially because these modifications have the potential to cause unexpected complications and may have a negative impact on oncologic control. One surgical modification that merits discussion for historical interest is the bladder tube to improve urinary continence outcomes. The initial reports suggested clinical benefit (Steiner et al, 1993; Seaman and Benson, 1996). Today, this surgical modification is no longer recommended, presumably because of high rates of anastomotic strictures, which most likely compromised urinary continence.

Bladder Neck (Sparing) Preservation

Investigators have proposed that preservation of as much of the bladder neck as possible at the time of removal of the prostate can hasten return of urinary control after RRP (Klein, 1992; Licht et al, 1994; Braslis et al, 1995; Lowe, 1996; Shelfo et al, 1998; Poon et al, 2000; Soloway and Neulander, 2000; Srougi et al, 2001; Deliveliotis et al, 2002). Klein (1992) was the first to suggest that modification of the bladder neck resection and reconstruction at the time of RRP might influence urinary control. The group at the University of Miami has reported on a large nonrandomized series of men who underwent RRP with bladder neck preservation (Braslis et al, 1995; Soloway and Neulander, 2000). In 2000 they reported only a 1% bladder neck contracture rate and 1% positive margins at the bladder neck site only and suggested that “extensive” resection at the bladder neck did not add to the curative nature of the procedure yet did not elaborate in detail on the return of urinary control.

In 1996, Lowe compared bladder neck preservation with bladder neck resection (classic method) in a nonrandomized group of nearly 200 men divided between bladder neck preservation and excision. No difference was seen in positive margins, and bladder neck preservation hastened the return of urinary control but did not improve overall continence in the long term (Lowe, 1996). Poon and colleagues (2000) and the group from Loma Linda also reported on a comparative study of 220 men divided into three groups: bladder neck preservation, classic tennis racquet closure, and anterior bladder tube reconstruction. Bladder neck contracture occurred in 10% overall and in 5%, 11%, and 18% by group, respectively. Urinary continence, ascertained by third-party telephone interview, demonstrated 12-month rates of 93%, 96%, and 97% by group, respectively (no difference). These authors concluded that there was no major difference between groups with respect to return of urinary control. Similarly, Deliveliotis and colleagues (2002) showed no difference in continence rates in the long term (1 year) but significant difference ($P < .05$) in the short term (3 to 6 months) when preservation of the bladder neck was exercised.

In several series, higher positive surgical margins were seen with bladder neck preservation. Srougi and colleagues (2001) from São Paulo, Brazil, reported on a planned enrollment of 120 men in a truly randomized trial between bladder neck preservation and classic reconstruction. Enrollment was stopped because the rate of positive surgical margins in the preservation arm was 10-fold higher (10% vs. 0%) compared with the classic reconstruction arm. Within the group of 70 who finished the trial, the authors measured continence rates and found no difference concluding that the external sphincter appears to play a more important role than the bladder neck in continence after radical prostatectomy. Marcovich and colleagues (2000) also demonstrated that bladder neck-sparing surgery resulted in significantly higher rates of positive surgical margins at the bladder neck compared with standard RRP (47% vs. 20%).

The feasibility of the Heidelberg technique for complete bladder neck preservation, which involves preservation of bladder neck circular fibers and urethra-urethral anastomosis, has been reported (Nyarangi-Dix et al, 2013). Nyarangi-Dix and coworkers (2013) randomized 208 candidates for open RRP or robotic-assisted laparoscopic radical prostatectomy to standard versus Heidelberg complete bladder neck preservation technique. Continence was assessed at 0, 3, 6, and 12 months by the 24-hour pad test, social continence by the number of pads per day, and quality-of-life outcomes by the validated Incontinence Quality of Life Questionnaire. Oncologic control was assessed by surgical margin status. At 0, 3, 6, and 12 months the mean loss of urine in the standard versus complete bladder neck preservation groups were 713 versus 237 g, 50 versus 16 g, 44 versus 6 g, and 25 versus 3 g, respectively. The percentage of men who were socially continent (use of none or one pad in 24 hours) at 3, 6, and 12 months in the standard versus complete bladder neck preservation groups were 55% versus 84%, 75% versus 90%, and 81% versus 90%, respectively. At all times, mean urine volume and percent of men socially continent was significantly greater in the complete bladder neck resection group. The positive

surgical margin rates between the standard (13%) versus complete bladder neck preservation (15%) groups were not significantly different, and the overall rate is similar to other contemporary series from high-volume centers (Razi et al, 2009). Although most positive surgical margins do not translate into disease recurrence, those occurring at the bladder neck are most worrisome (Razi et al, 2009). Only 2% of cases had positive surgical margins at the bladder neck. No mention was made if these bladder neck margins occurred in the standard or bladder neck preservation groups. It is unclear whether enrollment into the study was influenced by prostate cancer risk group. Overall, the 36% rate of pT3 disease is comparable to that in other series reported from high-volume centers (Poon et al, 2000). Nine percent of men randomized to complete bladder neck preservation were excluded from treatment analysis. The significant advantage of continence in the complete bladder neck preservation group was not observed at 12 months using an intent-to-treat analysis. The one potential complication of bladder neck preservation is bladder neck contracture. The authors make no mention of the rate of bladder neck contracture.

All would agree that the number one goal of anatomic radical prostatectomy is cancer control. These studies seem to agree that there is little difference in the positive margin rates (bladder neck only) with this modification. The randomized controlled trials suggest that there is a clinically significant difference in urinary continence up to 6 months that diminishes and is questionably clinically significant at 1 year. Finally, the high rate of bladder neck contracture and positive margins in some, but not all, studies makes this modification less than desirable. Long-term oncologic outcomes from the Heidelberg experience will provide the definitive evidence whether cancer control is compromised. Although the risks need to be weighed against the benefits, this modification warrants consideration. We do not perform bladder neck-sparing surgery.

Seminal Vesicle Sparing

The dramatic stage shift witnessed during the past two decades (Han et al, 2004) primarily brought about through early detection with PSA, has dramatically decreased the numbers of men presenting with regionally advanced disease (T3b) within the seminal vesicles (Poon et al, 2000; Han et al, 2001). Seminal vesicle involvement has been widely accepted as a poor prognostic feature; however, contemporary studies have demonstrated that few men (<5%) presenting with localized prostate cancer (near 0% in cT1c) have disease that has already spread to the seminal vesicle (Poon et al, 2000). Are we removing this tissue unnecessarily? Some investigators suggested that the close approximation of the seminal vesicles to the NVB, pelvic plexus, and bladder base and neck blood supply may allow the dissection in this area to play a major role in post-operative urinary and erectile function and have developed algorithms to predict seminal vesicle involvement before surgery (reviewed by Zlotta et al, 2004).

A modification to the classic anatomic radical prostatectomy has been proposed—seminal vesicle sparing. Korman and colleagues (1996) were the first to investigate the importance of complete resection of the seminal vesicle during RRP. They investigated the incidence of histologic evidence of cancer within the distal 1 cm of seminal vesicle tissue in 71 consecutive RRP specimens. Of 71 specimens, 12 had seminal vesicle invasion and 0 (0%) had disease in the distal 1 cm of the seminal vesicles bilaterally, which led the investigators (who advocated complete resection of the seminal vesicles at that time) to suggest that it is not necessary to remove the seminal vesicle in its entirety when the dissection is difficult. This might eliminate the potentially damaging dissection near other important anatomic structures.

In a follow-up study, Theodorescu and colleagues (1998) looked at the importance of complete seminal vesicle excision by comparing RRP with radical perineal prostatectomy (RPP). In two similar groups (stage, race, age, PSA level, and grade), 64% underwent RRP and 36% underwent RPP (seminal vesicles are not routinely removed). In the follow-up period, 45% of the men

in the perineal prostatectomy group demonstrated biochemical (PSA) elevation (>0.2 ng/mL) compared with only 18% in the retropubic prostatectomy group. When they broke down the perineal prostatectomy group on the basis of no seminal vesicle excision or seminal vesicle excision, the PSA recurrence rate was 69% versus 20%, respectively. The authors concluded that complete excision of the seminal vesicle during radical prostatectomy is essential for cancer control.

John and Hauri (2000) investigated the influence of seminal vesicle preservation during RRP on urinary continence. They observed 54 men, of whom 34 underwent RRP with seminal vesicle removal and 20 with seminal vesicle preservation. A modified pad test at 6 weeks and 6 months postoperatively demonstrated continence rates of 60% at 6 weeks and 95% at 6 months for the seminal vesicle preservation group compared with 18% at 6 weeks and 82% at 6 months for the seminal vesicle resected group. They concluded that seminal vesicle preservation may preclude damage to the pelvic nerves and maintain urinary continence during RRP.

Albers and associates (2007) reported the results of a trial of 317 men with PSA of 10 ng/mL or less, biopsy Gleason score 7 or less, and a total prostate volume of 50 mL or less randomized to standard RRP versus seminal vesicle-sparing RRP. Potency, lower urinary tract symptoms (LUTS), and continence were evaluated at baseline and multiple intervals postoperatively between 4 weeks and 1 year using the International Index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS), and assessment of pad usage, respectively. Continence was defined as 0 to 1 pads over a 24-hour interval and potency by an IIEF score greater than 15. The primary limitations of the study design were that outcome assessments were conducted by the urologist and the longest follow-up was only 1 year. The continence rates at 4 weeks (62% vs. 45%) and 12 months (96% vs. 86%) were significantly higher in the seminal vesicle-sparing group. Potency rates and the oncologic assessment were similar at 1 year. The small number of evaluable men at 1 year limits the reliability of these observations.

Mogorovich and associates (2013) examined the incidence of painful orgasm after radical prostatectomy. A questionnaire capturing several sexual function domains, including painful orgasm, was mailed to 1411 men who had undergone radical prostatectomy at a single institution between 2002 and 2006. Overall 11% of men completing the retrospective survey reported experiencing pain with orgasm and men undergoing bilateral seminal vesicle-sparing radical prostatectomy were 2.33 times more likely to have painful orgasms than men undergoing complete excision of the seminal vesicles. The incidence of painful orgasm for those men undergoing bilateral excision of the seminal vesicles was similar to that of age-matched men without prostate cancer. Therefore painful orgasm is likely a consequence of seminal vesicle preservation and should be considered in assessing the risk-benefit ratio of this procedure.

Zlotta and coworkers (2004) proposed performing excision of the seminal vesicles in men with PSA of 10 ng/mL or greater, biopsy Gleason score of 6 or greater, or more than 50% of biopsy cores positive for prostate cancer. Secin and associates (2009) conducted a decision analysis applying these criteria to 1406 men who underwent radical prostatectomy at their institution and, based on a calculated intermediate risk-benefit ratio of seminal vesicle excision, recommended rejection of the recommendations of Zlotta and coworkers.

The clinical evidence suggests that most men with low-risk disease can safely undergo seminal vesicle preservation. Because the nononcologic risks and benefits are uncertain, assuming any compromise of oncologic control remains a concern. Clearly, a double-blind (patient and third-party reviewer) randomized trial of this method must be performed to fully understand the conflicting results.

We do not perform seminal vesicle-sparing surgery. However, in low- and intermediate-risk disease cases in which the seminal vesicles are very large or encased in scar, we see little harm in not excising the distal-most aspect of the seminal vesicle.

Interposition Nerve Grafting

Although wide resection of both NVBs is rarely indicated when curative intent is the desired effect for anatomic radical prostatectomy (Walsh and Worthington, 2001), investigators have suggested interposition sural nerve grafts after unilateral and bilateral NVB resection during RRP (Kim et al, 1999, 2001a, 2001b, 2001c; Scardino and Kim, 2001; Walsh, 2001; Singh et al, 2004). Early studies in the rat provided experimental evidence documenting the beneficial effect of interposition nerve grafting after unilateral or bilateral cavernous nerve damage or resection (Burgers et al, 1991; Quinlan et al, 1991b; Ball et al, 1992a, 1992b). However, in humans, as opposed to the rat, the cavernous nerves are composed of many fibers that are separated by as much as 3 cm (Costello et al, 2004; Takenaka et al, 2004). This raises the legitimate question of whether it is possible to perform a classic end-to-end nerve graft. The precise pathophysiologic mechanism of cavernous nerve regeneration has yet to be fully understood; however, basic science studies and human clinical testing have suggested that return of parasympathetic function can be demonstrated after interposition grafting of the brachial plexus, facial nerves, and peripheral nerves.

It is universally accepted that preservation of erectile function after radical prostatectomy is quantitatively related to preservation of the autonomic innervation and that, with resection of both NVBs, recovery of erectile function satisfactory for spontaneous erection and intercourse is limited (Quinlan et al, 1991a). Kim and colleagues (1999) first suggested interposition sural nerve grafting at the time of anatomic radical prostatectomy to replace resected cavernous nerves. This group later reported on 28 men with bilateral non-nerve-sparing radical prostatectomy who underwent bilateral sural nerve grafts with 12-month follow-up that 26% had unassisted erections sufficient for intercourse, 26% had partial erections, and 43% had erections sufficient for intercourse with the aid of sildenafil citrate (Kim et al, 2001a). Sexual function returned 5 months after grafting at the earliest time. Another group (Singh et al, 2004) investigated the return of urinary control with respect to sural nerve grafting. They reported a series of 111 men with purposeful unilateral nerve excision, 53 of whom underwent unilateral sural nerve graft after the prostatectomy. At 12 months, 95% of the grafted group reported "complete" urinary control (leakage of only a few drops) compared with only 53% of the nongrafted group ($P < .012$). The authors suggested that the cavernous nerves may play a role in return of continence. These findings have yet to be validated and should be viewed cautiously until a randomized study can be conducted.

Most urologists performing RRP and NVB excision require the participation of a plastic surgeon to perform the harvest and implantation of the nerve graft material. Kim and Seo (2001) suggest that with experience, the urologic oncologist performing the RRP should feel comfortable with harvest of the nerve and placement of the graft with limited impact on surgical time and blood loss. Technically, the sural nerve (width of 1.5 to 3 mm, ovoid) graft is harvested with iris scissors through a 3-cm incision that is placed 1 cm inferior to the lateral malleolus. The saphenous vein will be encountered. Dissection should be carried out with loupe magnification. The nerve is divided at the distal end and the foot-side end fulgurated. A tendon stripper (6 mm in diameter) is used to strip the nerve proximally for approximately 20 cm toward the back of the calf, and a 1-cm incision is used to retrieve the proximal end. Fulguration of the proximal (leg) side of the nerve is also required. The graft is placed in cooled saline. The skin is closed, and compression stockings ensure decreased hematoma formation (Kim and Seo, 2001). The average length of nerve needed per side is 5 to 6.5 cm; however, 40-cm segments can be isolated for bilateral procedures with minimal sensory deficit (Kim and Seo, 2001). The nerve graft is reversed, and the distal nerve is attached to the proximal cavernous nerve endings under magnification; similarly, the proximal nerve end is attached to the distal cavernous nerve endings. The nerve endings can be identified at the time of resection and marked with a stitch through the use of the CaverMap nerve

stimulator (Canto et al, 2001). The nerves are attached to the nerve endings with 7-0 polypropylene sutures secured with microclips. After the procedure, suction drains are placed and directed away from the graft site.

Many questions remain with respect to the need for nerve grafting after wide excision of the NVB after RRP (Walsh, 2001). Davis and colleagues (2009) reported a large series of patients undergoing unilateral nerve-sparing procedures with randomization to sural nerve grafting or standard erectile dysfunction therapy. At 2 years, no difference in potency was noted in the two groups (71% in nerve graft group and 67% in the standard group). Bilateral nerve grafting has resulted in a 5-year cumulative recovery of erectile function permitting penetration of 34% and the rate of consistent penetration of 11% (Secin et al, 2007). The young age, excellent baseline erectile function, and motivation to preserve erectile function in the cohort may explain why erectile function was preserved in a very small subset of cases undergoing the bilateral nerve grafts. Thus, although the techniques of nerve grafting are safe and feasible, the overall benefits appear limited. We do not perform nerve-grafting surgery.

SALVAGE RADICAL PROSTATECTOMY

The goal of primary external-beam radiation therapy (intensity-modified or three-dimensional conformal) or primary brachytherapy in the treatment of clinically localized prostate cancer is to eradicate all of the tumor. Failure to achieve this goal leads to local progression, distant metastasis, and potentially death. The recognition of local recurrence after definitive radiation therapy is complex (American Society of Therapeutic Radiology and Oncology criteria, PSA nadir, PSA bump), yet all would agree that it portends a poor outcome with few options for salvage. This poor prognosis led to development of several options to salvage cure: cryosurgery (see Chapter 105), watchful waiting (see Chapter 108), androgen deprivation (see Chapter 109), and salvage prostatectomy. **Salvage radical prostatectomy has been used successfully to eradicate locally recurrent cancer after definitive radiotherapy, but complications are common and the effects on overall survival uncertain** (Rogers et al, 1995; Cheng et al, 1998; Garzotto and Wajzman, 1998; Gheiler et al, 1998; Tefilli et al, 1998a, 1998b; reviewed by Chen and Wood, 2003; Stephenson et al, 2004; Ward et al, 2005; Paparel et al, 2009). From the literature, the following generalizations can be made:

- The procedure (salvage prostatectomy) is reserved for patients with excellent health and with a life expectancy of more than 15 years.
- Patients must have no evidence of metastatic disease.
- Salvage surgery should be offered only to men who at initial presentation had unequivocally clinically localized prostate cancer.
- Prostate biopsy, histologic grade, clinical examination findings, and serum PSA levels must continue to suggest localized disease.

In summary, candidates for salvage surgery should be unrecognizable from the candidates we would choose for initial therapy with RRP and be highly motivated individuals who understand and accept the potentially higher morbidity associated with salvage surgery.

A single institution review of a salvage prostatectomy experience by Stephenson and colleagues (2004) recounted a series of nearly 100 men treated between 1984 and 2003 with either external-beam ($N = 58$) or interstitial ($N = 42$) radiotherapy. The authors saw a decrease in complication rates (overall from 33% to 13%, rectal injuries from 15% to 2%). They also reported urinary continence rates of 39% totally dry and 86% with one or fewer pad per day. Nearly 20% required an artificial sphincter. The 5-year actuarial recovery of potency rate for this group was 16% (Masterson et al, 2005). Another recent report recounted a 30-year experience with salvage retropubic prostatectomy and cystoprostatectomy for radioresistant adenocarcinoma of the prostate (Ward et al, 2005). From

1967 to 2003, they found sufficient data to comment on 199 men; 138 were treated with retropubic prostatectomy and 61 with cystoprostatectomy. Average follow-up was 7 years. Rectal injury occurred in 5% of radical retropubic prostatectomies and 10% of cystoprostatectomies. Incontinence was “zero pads” in 43% of the more contemporary cohort. Cancer-specific survival was 65% at 10 years.

Data on oncologic outcomes after salvage radical prostatectomy are limited. Eastham and colleagues report excellent local control and a 45% 5-year recurrence in patients with presurgical biopsies demonstrating a Gleason score of less than 8 (Paparel et al, 2009). However, the overall effect of salvage prostatectomy on prostate cancer-specific mortality remains unclear (Paparel et al, 2009).

Chade et al (2011) reported a systematic review based on 40 publications in the English literature between January 1980 and June 2011. Oncologic, complications and functional outcomes were compared using 1993 as a cut point to examine trends related to earlier versus later publications. The majority of cases were performed after 1993. Positive surgical margins in the earlier versus later publications ranged between 43% and 70% and 0 and 36%, respectively. Pathologic organ-confined disease in the earlier versus later publications ranged between 22% and 53% and 44% to 73%, respectively, suggesting that the decrease in positive margin rates is in part related to lower volume disease. The risk for rectal injury, anastomotic stricture, and Clavien 3 to 5 complications ranged between 0 and 19%, 0 and 41%, and 0 to 33%, respectively. Preservation of potency outcomes is limited to the later publications and ranged between 0 and 28%. Urinary continence rates in the earlier versus later publications ranged between 46 and 90%, and 0 and 83%, respectively. The 5- and 10-year biochemical free survival ranged between 47% and 82% and 28% and 53%, respectively. Complications and functional outcomes were better in the later series, suggesting that improved surgical technique may contribute to better oncologic outcomes. The tremendous range of outcomes and salvage radical prostatectomy is likely explained by selection bias, surgical experience, and methodology for assessing quality of the outcomes. Because of the extreme range of all reported outcomes, it is difficult to appropriately counsel potential candidates regarding risks and benefits. Because of the significant risks for complications even among highly experienced surgeons, candidates should be carefully selected for the procedure.

The surgical technique for salvage prostatectomy does not differ from that of classic radical prostatectomy. Radiation effects (vasculitis, ischemia, and fibrosis) can make the surgical dissection technically challenging (Chen and Wood, 2003). Special care should be taken in separating the apical region of the prostate, wide dissection of the NVBs, and dissection of Denonvilliers fascia near the base of the prostate because these regions represent the most common sites for rectal injury.

SUMMARY OF RADICAL RETROPUBIC PROSTATECTOMY

A number of advances have been made in the diagnosis and treatment of localized prostate cancer. Today, more men are diagnosed with curable disease at a younger age. Men are also living longer; a man 65 to 70 years old has a 50% chance of living for another 15 years. Open radical prostatectomy is an ideal form of treatment for patients who can be cured and who will live long enough to benefit from it. These are also the patients who will have the best quality of life postoperatively (Walsh, 2000).

Over the last decade there has been increasing adoption of robotic-assisted laparoscopic radical prostatectomy. Some experts claim that the open approach is of only historical interest because of superior outcomes after the robotic approach. Comparative effectiveness studies suggest that the robotic approach may compromise surgical margins (Williams et al, 2010), achieve inferior continence and equivalent potency (Barry et al, 2012), and yield higher dissatisfaction rates (Schroek et al, 2008) while greatly increasing cost

KEY POINTS: ANATOMIC RADICAL RETROPUBIC PROSTATECTOMY

- There is no better way to cure cancer that is confined to the prostate than total surgical removal.
- The three goals of the surgeon, in order of importance, are cancer control, preservation of urinary control, and preservation of sexual function.
- Surgery is deferred for 6 to 8 weeks after needle biopsy of the prostate and 12 weeks after transurethral resection of the prostate.
- A fiberoptic headlight and 2.5- to 4.5-power loupes are most useful because much of the procedure is performed beneath the pubis in an area where visualization can be difficult. Magnification can enable the surgeon to exert less traction on the NVBs and more easily identify the correct plane of dissection.
- Regional anesthesia is associated with less blood loss and a lower frequency of pulmonary emboli.
- If the patient has a well-differentiated to moderately well-differentiated tumor (Gleason grade < 8) and the lymph nodes are normal to palpation, frozen-section analysis is not performed.
- With the recent recognition that branches of the nerves innervating the striated sphincter and cavernous bodies may travel more anteriorly at the apex, an alternative technique involving high anterior release of the NVBs at the apex before division of the dorsal vein is described. This technique is associated with earlier recovery of sexual function.
- Today, in most men who are candidates for surgery, it is safe to preserve both NVBs and rarely necessary to excise both of them, thus making cavernous nerve replacement or transplantation unnecessary in most cases.
- The tactile sensation provided by open surgery is very important. If induration is palpable in the lateral pelvic fascia, the bundle should be excised. In gently releasing the bundle with a right-angled clamp, if the bundle is fixed to the prostate, it should not be preserved. With the laparoscopic technique, tactile sensation is muted; with the robotic-assisted technique, it is absent.
- Patients requiring acute transfusions for hypotension after radical prostatectomy should be explored to evacuate the pelvic hematoma in an effort to decrease the likelihood of bladder neck contracture and incontinence.
- Thrombophlebitis with pulmonary embolism is the major cause of mortality after radical prostatectomy. Measures to prevent this complication include careful positioning on the operating room table to avoid compression of the veins in the lower extremity, the use of intermittent compression devices, and early ambulation.
- We concluded that complete excision of the seminal vesicle during radical prostatectomy is essential for cancer control.
- Open radical prostatectomy is an ideal form of treatment for patients who can be cured and who will live long enough to benefit from it.

with comparable pain and length of hospital stay (Lepor, 2009). The primary advantage of the robotic approach is less blood loss. Even proponents of the robotic approach concede after 10 years there is no meaningful advantage of the robotic approach (Lavery et al, 2012). Despite public demand, the authors of this chapter continue to perform the open approach.

RADICAL PERINEAL PROSTATECTOMY

Please see the Expert Consult website for details.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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This section is included in honor and the memory of Marty Resnick, MD. This slightly modified version of his chapter in *Campbell-Walsh Urology*, 9th edition reflects his career efforts in the field of urology and his expertise in performance of the RPP.

Hugh Hampton Young described the first RPP for treatment of cancer in 1905. In 1939, Belt and colleagues modified the procedure, and until the description of the radical retropubic approach by Walsh, this approach represented the principal method for treatment of patients with localized prostate malignant disease. Furthermore, Walsh improved on the retropubic technique, demonstrating functional anatomic relationships that reduced intraoperative blood loss and improved outcomes of impotence and urinary continence (Reiner and Walsh, 1979; Walsh and Donker, 1982; Walsh et al, 1983).

Surgical and anatomic techniques of the retropubic prostatectomy were applied to the perineal approach, resulting in potency comparable with that of the early RRP results (Weiss et al, 1985; Weldon, 1988; Weldon and Tavel, 1988). In addition, the perineal approach offers visualization of the urethral dissection and anastomosis, resulting in excellent urinary continence similar to the results achieved through the laparoscopic approach. Finally, RPP demonstrates the proved long-term cancer control of RRP with low morbidity and rapid convalescence (Sullivan et al, 2000; Guillonnet al, 2002; Harris, 2003; Lotan et al, 2004; Silverstein et al, 2004).

Selection of Patients

Like the RRP, RPP is offered to patients with a life expectancy of more than 10 years who demonstrate a high likelihood of organ-confined disease. A nerve-sparing approach is accomplished for most of these patients, and the decision to excise a NVB is usually made intraoperatively on the basis of the adherence of the NVB to the prostate or preoperatively on the basis of the biopsy report or results of the digital rectal examination. A pre-RPP laparoscopic pelvic lymphadenectomy is deemed unnecessary if the biopsy Gleason score is below 7 and the serum PSA level is less than 10 ng/mL (low- to moderate-risk disease).

In patients with localized cancer, there are few contraindications to this procedure. Patients with severe ankylosis of the hips or spine and those with unstable artificial hip replacements may not tolerate the exaggerated lithotomy position. However, common degenerative disk disease is not a contraindication to positioning. Some patients, such as those having renal transplantation or those with severe inflammation secondary to placement of synthetic mesh for repair of a hernia or the morbidly obese, who may not be amenable to RRP, typically may undergo prostatectomy by the perineal approach (Yiou et al, 1999; Boczek and Melman, 2003). Additionally, a large (>100 g) prostate and a narrow pelvis can cause difficulties with this surgical approach.

Preoperative Care and Position

A full bowel preparation is administered on the day before surgery on the basis of surgeon preference; the patient is instructed to consume polyethylene glycol or administer a Fleet Phospho-Soda enema in the afternoon before surgery. Also, 1 g of neomycin is administered orally at 12:00, 2:00, 4:00, 6:00, 8:00, and 10:00 PM. This bowel preparation allows primary closure of any inadvertent rectal injury at the time of surgery without problem. A sample for blood type and antibody screen is obtained from all patients in the days or hours before surgery, but because blood loss is minimal and transfusion rarely required, a crossmatch is unnecessary; also, preoperative donation and storage of blood by the patient is not required.

In the preoperative holding area, antithromboembolic surgical stockings are positioned and the patient is administered a second-generation cephalosporin intravenously. Although perineal prostatectomy lends itself to regional anesthetics such as spinal or epidural anesthesia, most patients receive a general anesthetic. The only specialized instruments needed are curved and straight Lowsley



Figure 114-39. The modified exaggerated lithotomy position. The perineum is only slightly elevated and almost at a 90-degree angle with the floor. The legs are positioned at nearly a 75-degree angle with the floor.

tractors, a self-retaining retractor such as the mini-crescent or Thompson, and a headlight.

After induction of anesthesia, the patient is positioned supine so that when the leg portion of the operating table is lowered, the buttocks are extended beyond the table edge. Allen stirrups are stationed 2 inches cranially on the rail so there is ample room for the attachment of the self-retaining retractor. The patient is then placed in an exaggerated lithotomy position with the perineum almost parallel to the floor or in a modified exaggerated lithotomy position with the perineum only slightly elevated (Fig. 114-39). The perineum, anus, and scrotum are shaved, and the abdomen inferior to the umbilicus, penis, scrotum, perineum, anus, and both thighs are painted with povidone-iodine in the standard sterile fashion. After gowning, a sterile towel is sewn from the 9-o'clock to the 3-o'clock position around the anus at the mucocutaneous pigmentation line with silk suture, maintaining a sterile environment. Leg and perineal drapes are placed. The upright of the self-retaining retractor is secured to the table rail on the patient's left while the sterility of the upright is maintained.

Exposure of the Prostate

A curved Lowsley tractor is placed transurethral into the bladder and its wings opened. A curvilinear incision is made from a position just medial to the right ischial tuberosity to a position just medial to the left ischial tuberosity. The incision should not extend posteriorly beyond the 3- and 9-o'clock positions relative to the anus. Blunt dissection is employed to open and develop each ischiorectal fossa lateral to the central tendon, and the central tendon is then divided by electrocautery (Fig. 114-40). In the original description by Young (1905), the dissection is carried anteriorly along the external anal sphincter until arriving at the rectourethralis muscle (1905). However, with the Belt approach (Belt, 1939), which we prefer, the fibers of the external anal sphincter are dissected and retracted anteriorly with an appendiceal retractor; these fibers are not incised (1939). The longitudinal muscle fibers of the rectum are identified, and gentle traction is placed dorsally on the rectum by a dampened sponge. The plane is developed leading to the rectourethralis muscle, which is formed by fascicles of the rectal muscle, connecting the rectum to the perineal body. It appears as a strap of muscle tenting the rectum ventrally. Without any traction on the Lowsley tractor, the rectourethralis muscle is divided close to the apex of the prostate with vertically oriented scissors, allowing the rectum to fall dorsally; caution must be exercised to prevent rectal injury at this point of the procedure. Gentle pressure is then applied on the Lowsley tractor toward the anterior



Figure 114-40. Each ischiorectal fossa is dissected bilaterally, and the finger is bluntly brought beneath the central tendon. The central tendon will be divided with electrocautery as traction is maintained with the finger.

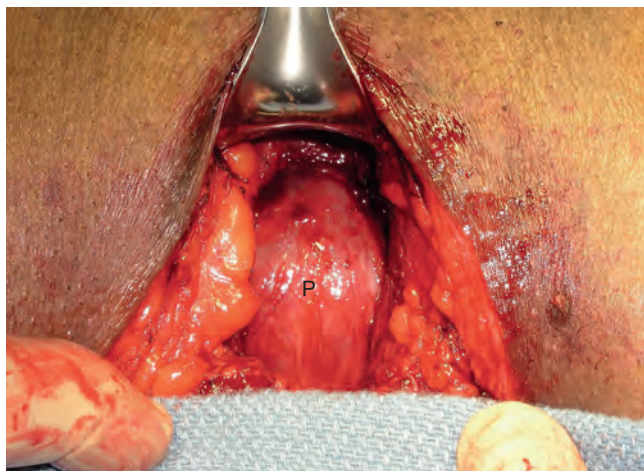


Figure 114-41. The external anal sphincter is retracted anteriorly, and the rectourethralis muscle is divided. The prostate (P) is delivered into the field of view.

abdominal wall. This maneuver delivers the prostate well into the field of view and allows the blunt, digital dissection of the prostate from the rectum in a cephalad direction until the base of the prostate is identified at the vesicoprostatic junction (Fig. 114-41). Classically, the proper plane is between the anterior and posterior leaves of Denonvilliers fascia.

Nerve-Sparing Dissection

Resumed traction on the Lowsley tractor toward the anterior abdominal wall again brings the prostate into the incision. If preservation of the NVBs is intended, the exposed anterior layer of Denonvilliers fascia is incised vertically in the midline from the vesicoprostatic junction to the apex of the prostate with a No. 15 blade scalpel. Avoiding use of electrocautery, careful lateral dissection with gentle lateral traction preserves the NVBs as they course between the layers of Denonvilliers fascia at the posterolateral edge of the prostate. The fascia and enclosed nerves must be sufficiently mobilized to allow eventual extraction of the prostate without stretching or damage of the bundles.

Attention is then directed toward the prostatic apex and urethra. The Lowsley tractor can be palpated within the urethra, and a right-angled clamp is placed with the open points facing cephalad on either side of the urethra to dissect the NVBs away from the urethra as they course distally. The No. 15 blade scalpel is again used to incise the posterior aspect of the urethra over the Lowsley tractor (Fig. 114-42). The curved Lowsley tractor is then replaced by a straight Lowsley, and the wings are opened in a vertical fashion.

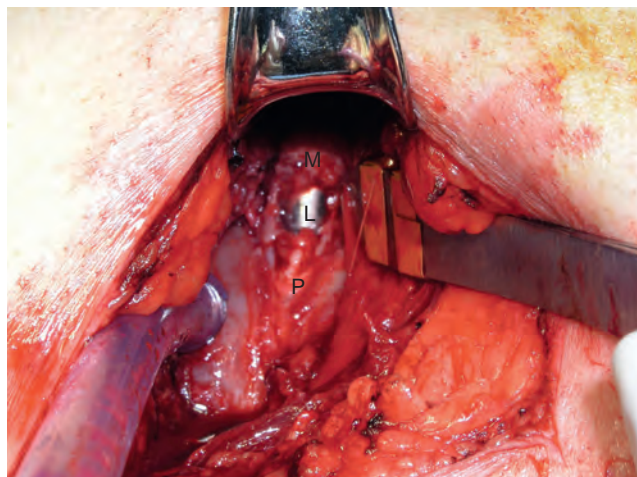


Figure 114-42. The anterior urethra is incised over the curved Lowsley tractor (L) between the membranous urethra (M) and prostate (P).

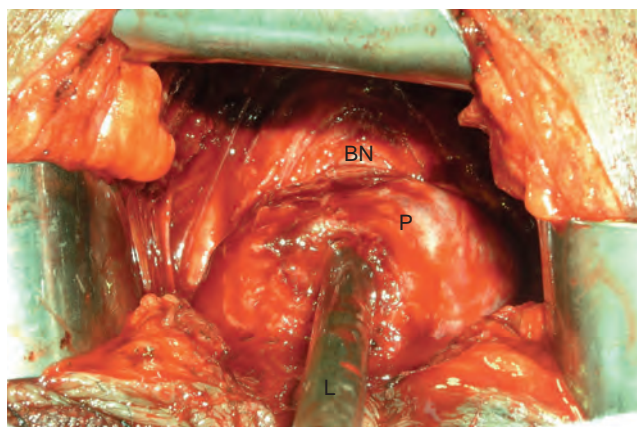


Figure 114-43. The urethra is divided, and the curved Lowsley has been replaced with a straight Lowsley tractor (L). The anterior prostate (P) has been dissected, and the puboprostatic ligaments are divided, exposing the bladder neck (BN).

With moderate traction on the Lowsley tractor, the remaining intact anterior aspect of the membranous urethra is sharply transected from the prostatic apex and the anterior prostate is freed to the bladder neck by sharp and blunt dissection.

The self-retaining retractor is attached to the previously placed upright, and blades are placed in the 3-, 9-, and 12-o'clock positions. Dissection is then directed over the anterior prostate from the apex toward the bladder neck. Traction on the Lowsley tractor aids in this portion by bringing the prostate into the incision. **The surgeon must be mindful not to dissect too far ventrally and to touch on the dorsal venous complex.** To sufficiently expose the anterior prostate, the puboprostatic ligaments are encountered and divided with scissors (Fig. 114-43).

The junction of the bladder neck and prostate base is then identified by palpating the wings of the Lowsley tractor. This junction is then further developed with blunt and sharp dissections, preserving the bladder neck. The bladder is entered anteriorly with a scalpel, the Lowsley tractor is removed from the urethra, and a long right-angled clamp is passed retrograde through the prostatic urethra and bladder neck. A 14-Fr red rubber catheter is then fed into the open right-angled clamp and pulled through the prostatic urethra; the ends are clamped together with a Kelly clamp, making a loop that may be used for manipulation of the specimen (Fig. 114-44). Traction on the catheter further delivers the prostate into the incision,

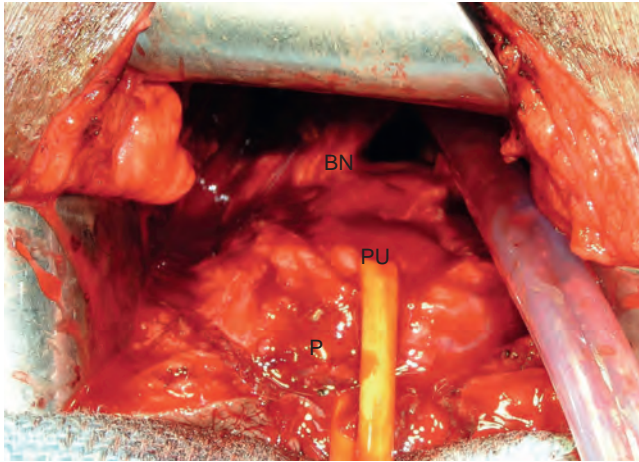


Figure 114-44. The bladder neck (BN) is incised, and a red rubber catheter is placed through the prostatic urethra (PU) and used to hold traction on the prostate (P).

and dissection of the anterior bladder neck is continued circumferentially around the prostate base. Identification of the ureteral orifices is generally unnecessary unless the dissection inadvertently involves the trigone. The lateral attachments and vascular pedicles are found coursing toward the base of the prostate and are dissected, sharply divided between right-angled clamps, and secured with 3-0 absorbable ties. To preserve the NVBs, the lateral pedicles should be divided close to the prostate, taking care not to compromise the surgical margin. Electrocautery is avoided during this phase.

The dissection is continued posteriorly at the bladder neck to separate it completely from the prostate. The red rubber catheter is then removed, and a right-angled clamp is passed along the midline posterior surface of the prostate with tips directed toward the base. The 14-Fr red rubber catheter is passed through the open tips of the right-angled clamp and pulled through, and the ends are secured together with a Kelly clamp, making a loop around the whole prostate. Traction then can be applied around the entirety of the prostate toward the incision, and an appendiceal retractor may be placed under the trigone, exposing the vasa deferentia and seminal vesicles (Fig. 114-45). Each vas deferens is grasped with a right-angled clamp, bluntly dissected, and divided with electrocautery. Each seminal vesicle is similarly grasped with a right-angled clamp, bluntly dissected, and divided, ligating the seminal vesicle artery with 3-0 absorbable ties. The complete surgical specimen is thus removed and passed off for pathologic examination.

Vesicourethral Anastomosis

On occasion, it may be necessary to reconstruct the posterior bladder neck with simple interrupted absorbable suture placed in a tennis racquet fashion. The ureteric orifices should be identified, and care should be taken to prevent damage to them.

The retractor placed at the 12-o'clock position is removed, and the red rubber catheter is placed retrograde through the penile urethra and clamped at the level of the glans so that traction can be applied to it while retaining it in the urethra. This catheter is used to identify and provide traction on the membranous urethra, enabling accurate anastomotic suture placement (Fig. 114-46). A 3-0 polyglycolic acid suture is placed from outside the anterior bladder neck at the 12-o'clock position and from inside to outside the membranous urethra at the same position and tied. While the assistant places traction on the red rubber catheter toward the contralateral side, the surgeon places sutures at the 2- and 10-o'clock positions. The red rubber catheter is removed, and a 22-Fr Silastic Foley catheter is carefully passed retrograde from the penile urethra and into the bladder. The 5-mL balloon is inflated with 15 mL of sterile water. Sutures are then placed at the 4-, 6-, and 8-o'clock positions and tied, completing the anastomosis.

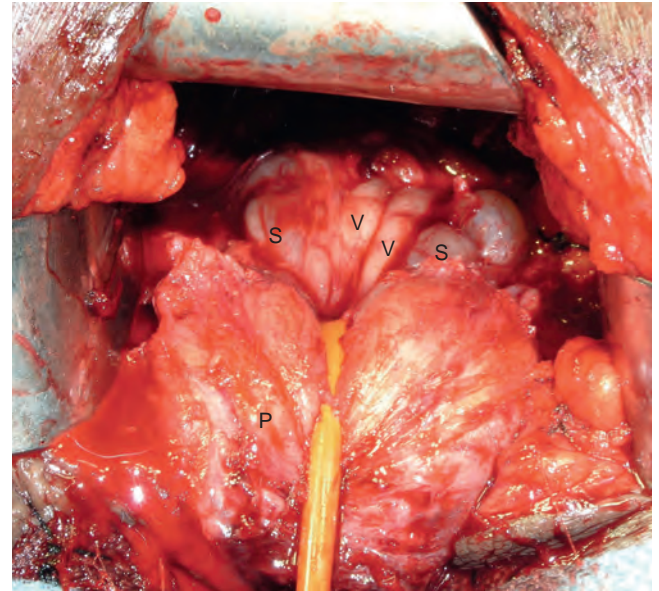


Figure 114-45. The bladder neck is freed from the prostate, and a red rubber catheter is clamped around the entirety of the prostate (P). Further dissection at the prostate base exposes the right and left vas deferens (V) and bilateral seminal vesicles (S).

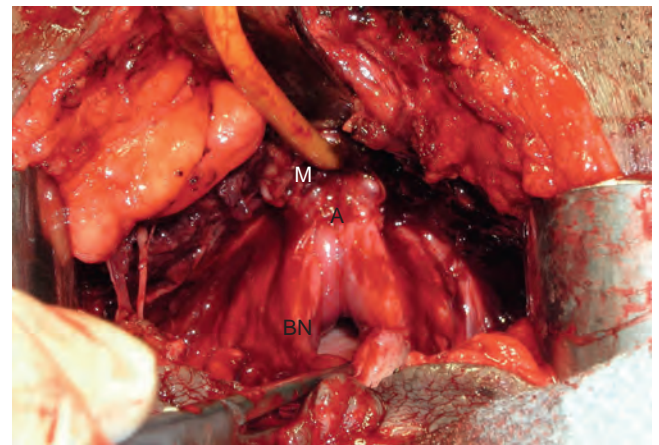


Figure 114-46. The specimen is removed from the field. A red rubber catheter emanates from the membranous urethra (M), and the bladder neck (BN) is open. The anterior aspect of the vesicourethral anastomosis (A) is complete. This exposure is unmatched with any other approach to radical prostatectomy.

Closure

The field is inspected for hemostasis and again for rectal injury. A Penrose drain is positioned near the vesicourethral anastomosis and brought through the incision. The levator ani is reapproximated with 2-0 absorbable sutures, avoiding damage to the NVBs and Penrose drain. The central tendon and Colles fascia are reapproximated, respectively, with 2-0 absorbable sutures; care must be exercised to use superficial "bites" posteriorly during this portion of the procedure because the anterior rectal wall is only a short distance away. The skin is closed with 4-0 absorbable suture interrupted in a vertical mattress fashion. The wound is dressed with a fluffed gauze dressing.

Postoperative Care

Patients are started on a clear liquid diet on the day of surgery and advanced to a regular diet as tolerated. Patients are encouraged to

ambulate routinely beginning the evening of surgery. Lower extremity sequential compression devices are used while the patient is in bed. **Rectal stimulation, instrumentation, and medication insertion are prohibited.** Furthermore, gentle irrigation of the catheter is performed only when absolutely necessary. The patient is provided oral analgesia and stool softeners. All patients are maintained on a prophylactic oral antibiotic until the catheter is removed. The Penrose drain is typically removed on postoperative day 1, and the urethral catheter is removed in the office 2 to 3 weeks after surgery, although it is recognized that earlier removal is feasible. **Patients are discharged on postoperative day 1 or 2** (Ruiz-Deya et al, 2001; Harris, 2003).

Pathologic Outcomes

RPP demonstrates excellent pathologic outcomes consistent with those of RRP. In a retrospective review, Korman and colleagues (2002) failed to demonstrate a significant difference in the incidence of positive margins between RPP specimens and those of RRP, 22% and 16%, respectively, and each had a 4% incidence of capsular incision. Furthermore, it has been shown that there is no significant difference in the time to PSA failure between patients who underwent RPP with complete excision of the seminal vesicles and those who underwent RRP (Theodorescu et al, 1998). A review of the literature demonstrates an incidence of positive margins of 15% to 44% of radical perineal specimens, with the prostate base being the most likely positive margin (Weldon et al, 1995; Iselin et al, 1999; Lance et al, 2001; Harris, 2003; Gillitzer et al, 2004). In the 20-year experience of Paulson, consisting of 1242 consecutive radical perineal prostatectomies for clinically organ-confined prostate cancer, 18% of patients with organ- or specimen-confined disease died either with or of prostate cancer. After 5 years, PSA failure (defined by PSA level > 0.5 ng/mL) occurred in 8%, 35%, and 65% of men with organ-confined, specimen-confined, and margin-positive disease, respectively. In patients with positive margins, the median time to PSA failure was 2.4 years; however, approximately 20% of patients with positive margins did not demonstrate biochemical failure. Cancer-associated death occurred approximately 10 years after the time of PSA failure (Iselin et al, 1999).

Morbidity

As a result of short operative times and relatively low blood loss, perioperative morbidity is low. Weldon and colleagues (1997) reported that 18% of their perineal prostatectomies experienced adverse events; however, most events were not serious, and no deaths were reported. Anastomotic strictures occur in 1% to 8% and usually within the first 4 months of surgery (Frazier et al, 1992; Levy and Resnick, 1994; Weldon et al, 1997; Gillitzer et al, 2004). Lower extremity neurapraxia, unique to the perineal approach, is often sensory and reported by Weizer and colleagues (2003) to occur in 25.5% of patients. **However, most series report an incidence of neurapraxia less than 2% and it is transient** (Weldon et al, 1997; Gillitzer et al, 2004). Keller (1999) reported a 0% incidence of neurapraxia in 284 prostatectomies and concluded that an operative time of less than 180 minutes is preventive. In experienced hands, **blood loss typically ranges from 200 to 800 mL and transfusions are necessary in approximately 5% of patients** (Weldon et al, 1997; Lance et al, 2001; Gillitzer et al, 2004). These rates of

transfusion are comparable with those of laparoscopic radical prostatectomy (Guillonnet et al, 2002; Rassweiler et al, 2003). Rectal injuries have been reported to occur during 1% to 11% of radical perineal prostatectomies (Parra et al, 1994, 1996; Levy and Resnick, 1994; Lassen and Kears, 1995; Weldon et al, 1997; Gillitzer et al, 2004). **When rectal injury is recognized at the time of surgery and repaired primarily with a two-layer closure, clinical sequelae are typically avoided.** If it is unrecognized or when it occurs in concert with postoperative urinary extravasation, a rectocutaneous or rectourethral fistula may develop. As with rectal injury, fecal incontinence occurs at a higher rate after RPP than after RRP. Bishoff and colleagues (1998) surveyed 227 patients 12 months after radical prostatectomy and reported that 18% of perineal patients had a new onset of fecal incontinence compared with only 5% in the retropubic group. In a prospective longitudinal assessment by Dahm and colleagues (2003), rectal urgency was the most common reported problem, and symptoms resolved over time; only 2.9% of patients reported involuntary stool leakage by 12 months after RPP. The exposure of the vesicourethral anastomosis generated with the perineal approach results in excellent continence outcomes. In a series of 220 cases, with incontinence defined as daily use of pads, Weldon and colleagues (1997) reported a 95% continence rate within 1 year, with younger age being a significant predictor of improved urinary continence. Yang and colleagues (2004) confirmed these results in a prospective study. **In studies comparing the outcomes of perineal prostatectomy and RRP, urinary continence was either improved by the perineal approach or not significantly different** (Parra et al, 1994; Bishoff et al, 1998; Gray et al, 1999; Sullivan et al, 2000; Lance et al, 2001). To date, studies comparing laparoscopic radical prostatectomy and perineal prostatectomy are not available. **A review of the literature demonstrates potency in 35% to 70% of patients after nerve-sparing RPP** (Lerner et al, 1994; Harris and Thompson, 1996; Weldon et al, 1997; Rabbani et al, 2000; Ruiz-Deya et al, 2001; Harris, 2003). At 24 months of follow-up, Weldon and colleagues (1997) reported 73% potency in 22 patients who had a bilateral nerve-sparing procedure and 63% potency in 28 patients who had a unilateral bundle preserved, although these results were not statistically different. Lerner and colleagues (1994) demonstrated unassisted potency in 22% of nerve-spared patients and an additional 30% who achieved vaginal penetration with pharmacotherapy.

Summary

The use of RPP for the treatment of localized prostate cancer has been facilitated by the emphasis on the identification of prostate cancer at earlier stages. This technique provides cancer control for localized prostate cancer similar to that with RRP.

KEY POINTS: RADICAL PERINEAL PROSTATECTOMY

- There are few contraindications to RPP.
- RPP demonstrates proved long-term cancer control.
- A nerve-sparing approach may be applied to RPP with excellent potency outcomes.
- RPP is renowned for rapid convalescence and overall low morbidity.

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Evolution of Minimally Invasive Laparoscopic Prostatectomy

Patient Selection

Instrumentation

Preoperative Preparation

Surgical Technique

Postoperative Management

Complications

Robotic Salvage Prostatectomy

Laparoscopic Pelvic Lymph Node Dissection

Summary

EVOLUTION OF MINIMALLY INVASIVE LAPAROSCOPIC PROSTATECTOMY

In the late 1970s and early 1980s several detailed anatomic studies performed in fetal and adult cadavers provided important insights into the periprostatic anatomy, especially that of the dorsal vein complex (DVC) (Reiner and Walsh, 1979), the neurovascular bundle (NVB) (Walsh and Donker, 1982), and the striated urethral sphincter (Oelrich, 1980). These observations provided a more anatomic approach to radical prostatectomy for prostate cancer, resulting in a significant reduction in operative morbidity. Subsequently, the anatomic, nerve-sparing open radical prostatectomy maintained a central role in the management of localized prostate cancer for more than two decades.

It was not until 1997 that an attempt at a less invasive approach to radical prostatectomy was explored. Schuessler and colleagues performed the first successful laparoscopic radical prostatectomy (LRP) in 1997. In their series of nine patients, operative duration was lengthy (8 to 11 hours) and the length of hospital stay was on average 7.3 days (Schuessler et al, 1997). Although the authors concluded that cure rates with LRP appeared comparable with those in open surgery, they could not define any significant advantages. As a result, LRP was not widely adopted in the field of urology.

Advances in task-specific surgical instrumentation, optics, digital video equipment, and computer and robotic technology opened a new frontier for minimally invasive laparoscopic prostatectomy. These advances led urologists to revisit LRP, spearheaded by two centers in France that reported on their techniques and early results (Abbou et al, 2000; Guillonnet and Vallancien, 2000). Their stepwise surgical approach to LRP proved to be both reproducible and teachable, although the learning curve remained challenging. Operative times were in a more acceptable 4- to 5-hour range with reported overall positive margin rates of 15% to 28%. This work rekindled worldwide interest in LRP, and in the ensuing years surgeons at a number of centers throughout the world acquired the skills and experience to perform this technique. However, advanced laparoscopic skills were necessary to perform a proficient LRP, especially for suturing of the vesicourethral anastomosis.

Computer-assisted surgical devices using mechanical robotic arms were adopted for use with radical prostatectomy in part due to their ability to aid the surgeon in performing the challenging task of laparoscopic suturing. One such device, the da Vinci Surgical

System (Intuitive Surgical, Sunnyvale, CA) quickly became the dominant robotic surgical device in the field of urology. By incorporating sophisticated wristed technology at the terminal ends of the robotic instruments, this robotic system offered surgeons the ability to operate, dissect, and suture with the facility of a human wrist. In addition, the 10× magnified, three-dimensional (3D) image provided by the specialized stereo-endoscope lens and camera offered an unprecedented view of the operative field and periprostatic anatomy, far superior to the 2D view of conventional laparoscopy. The first-generation robotic platform, originally launched in the United States in 2000, allowed for the surgeons to control three robotic arms simultaneously, two arms for robotic instrumentation and a third arm for control of the stereo-endoscope and camera. The second-generation da Vinci S system, made available in 2006, incorporated high-definition image capability with an additional fourth robotic arm for grasping and retraction. Finally the latest-generation robot, the da Vinci Si HD, which was launched in 2009, offered two separate surgeon consoles allowing two surgeons to operate simultaneously, providing an opportunity for improved operative efficiency and training.

Since its introduction into the United States in 2000, robotic-assisted laparoscopic prostatectomy (RALP) has rapidly grown in popularity with surgeons and patients alike. With rapid dissemination of this robotic platform into large tertiary referral centers and community hospitals throughout the country, RALP has become the dominant surgical approach for radical prostatectomy in the United States. There have been considerable and ongoing debates about the merits of RALP versus open surgery by either the retropubic or perineal route. Issues with equipment expense, the learning curve for the surgeon and surgical team, and patient-related outcomes remain. **Nonetheless, RALP has virtually replaced LRP in the United States, and the overwhelming majority of new surgeons have adopted RALP as their preferred surgical approach for prostate cancer.** Thus it seems virtually certain that the use of RALP will continue to proliferate.

This chapter highlights some of the surgical advances for both LRP and RALP. Further, technical details for the surgical dissection and currently available data on oncologic and functional outcomes are presented with reference to comparative effectiveness with radical retropubic prostatectomy (RRP). Finally, the authors review the role of robotic salvage prostatectomy, laparoscopic pelvic lymph node dissection (PLND), and complications of minimally invasive prostatectomy.

PATIENT SELECTION

Indications and Contraindications

The indications for LRP and RALP are identical to that for open surgery (i.e., patients whose cancer is suspected to be clinically localized). Patients should have a pathologically confirmed cancer clinically confined within the prostate (stage T1 or T2) or a cancer that extends beyond the margins of the prostate (T3) but still seems amenable to surgical extirpation with a wide resection. Based on the 2013 Revised Best Practice Statement by the American Urological Association (AUA), radiographic staging with CT and bone scan is recommended only for patients with suspected locally advanced disease, Gleason score of 8 or greater or prostate-specific antigen (PSA) level greater than 20 ng/mL. Absolute contraindications to minimally invasive laparoscopic prostatectomy include uncorrectable bleeding diatheses and the inability to undergo general anesthesia because of severe cardiopulmonary compromise. Patients who have received neoadjuvant hormonal therapy or who have a history of prior complex lower abdominal and pelvic surgery such as partial colectomy, inguinal mesh herniorrhaphy, or prior transurethral resection of the prostate (TURP) pose a greater technical challenge because of distortion of normal anatomic landmarks and adhesions but are not an absolute contraindication to LRP and RALP. In patients with a history of prior laparoscopic extraperitoneal mesh herniorrhaphy, a transperitoneal approach may be preferred over the extraperitoneal approach because dense adhesions in the retroperitoneal space often make attempts at initial access to the space of Retzius challenging.

Morbidly obese patients pose additional challenges due to the potential respiratory compromise encountered when placing these patients in a steep Trendelenburg position, as well as the relatively limited working space and limitations of trocar size and instrumentation length. Patients with large prostate volumes (e.g., >80 g) can have longer operative times, more blood loss, and longer hospital stay than those with smaller glands; however, long-term urinary outcomes appear comparable (Levinson et al, 2008, 2009; Link et al, 2008). Salvage surgery after failure of primary treatment (e.g., radiation, brachytherapy, cryotherapy, high-intensity focused ultrasound) has been successfully reported in properly selected patients but should be approached with caution because of the attendant risks and complications (Kaouk et al, 2008; Boris et al, 2009; Chauhan et al, 2011; Kaffenberger et al, 2013; Yuh et al, 2014). As a result of the effects of prior local radiotherapy or ablation, the tissue planes surrounding the prostate and especially between the posterior prostate and anterior rectum are often fibrotic and obliterated, increasing the risk for inadvertent entry into the rectum during salvage surgery. As a result, patients undergoing salvage prostatectomy need to be counseled on the potential risk for rectal injury and intestinal diversion in addition to the higher incidence of impotence and incontinence compared with surgery in the primary setting. Further discussion regarding the nuances of salvage robotic prostatectomy can be found in the Surgical Techniques section of this chapter. **It is strongly advised that these more complex patient scenarios be avoided in a surgeon's early experience with LRP and RALP; however, these patient features are not by themselves absolute contraindications for a minimally invasive approach to prostatectomy** (Brown et al, 2005a; Erdogru et al, 2005; Singh et al, 2005; Stolzenburg et al, 2005; Kaffenberger et al, 2013).

INSTRUMENTATION

Instrumentation required for LRP and RALP depends on the chosen approach and model of da Vinci system being used (i.e., three- vs. four-arm robot) in the case of RALP. **Box 115-1** lists suggested instrumentation for LRP and RALP. For LRP, the AESOP 3000 robotic arm (Intuitive Surgical) may be used to stabilize and control the laparoscopic lens and camera by handheld remote control, voice activation, or foot pedal control. Alternatively, a surgical assistant can be used for this purpose. During RALP, the use of the da

BOX 115-1 Suggested Instrumentation for Laparoscopic and Robotic-Assisted Laparoscopic Radical Prostatectomy

LAPAROSCOPIC RADICAL PROSTATECTOMY

- AESOP 3000 Robotic arm (Intuitive Surgical, Sunnyvale, CA) (optional)
- Monopolar electrocautery scissors
- Monopolar electrocautery hook device
- Bipolar forceps
- Ultrasonic shears
- Maryland dissector
- Laparoscopic needle drivers (two)
- Suction-irrigation device
- 10-mm, 0-degree and 30-degree laparoscope lens
- Veress needle
- 5-mm trocars (three)
- 12-mm trocars (two)
- 20-Fr van Buren urethral sound
- 18-Fr urethral catheter
- Small and medium-large Hem-o-lok clips (Teleflex Medical, Research Triangle Park, NC)
- 0 polyglactin suture (GS21) for dorsal venous complex
- 2-0 polydioxanone suture for posterior reconstruction
- 3-0 poliglecaprone (Monocryl) double-armed suture for anastomosis

ROBOTIC-ASSISTED LAPAROSCOPIC PROSTATECTOMY

- da Vinci S or Si HD Surgical System
- Endowrist Maryland bipolar forceps or PK dissector
- Endowrist curved monopolar scissors
- Endowrist ProGrasp forceps
- Endowrist large needle drivers (two)
- InSite Vision System with 0-degree and 30-degree lens
- 12-mm trocars (two)
- 8-mm metal robotic trocars (three if using a fourth robotic arm)
- 18-Fr urethral catheter
- Small and medium-large Hem-o-lok clips (Teleflex Medical)
- 0 polydioxanone suture for dorsal venous complex
- 2-0 polydioxanone suture for posterior reconstruction
- 3-0 Monocryl double-armed suture for anastomosis

Vinci S or Si HD system allows the surgeon to control a total of four robotic arms, with one being the stereo endoscope. The operation begins by using a 0-degree stereo endoscope and controlling a grasping forceps in the left robotic arm (such as the Maryland curved bipolar forceps or plasma kinetic dissector) and the curved monopolar scissors in the right robotic arm. The fourth robotic arm controls the ProGrasp forceps (Intuitive Surgical), a large atraumatic blunt grasper for retraction and exposure of tissues. The surgeon then toggles between control of any two of the three working robotic arms at any given time to allow for greater autonomy and to achieve optimal exposure and dissection.

PREOPERATIVE PREPARATION

Bowel Preparation

As with open surgery, a preoperative mechanical bowel preparation with magnesium citrate may be used. However, many surgeons have patients use a Fleet enema alone on the morning of surgery. A broad-spectrum antibiotic such as cefazolin is administered intravenously 30 minutes before skin incision.

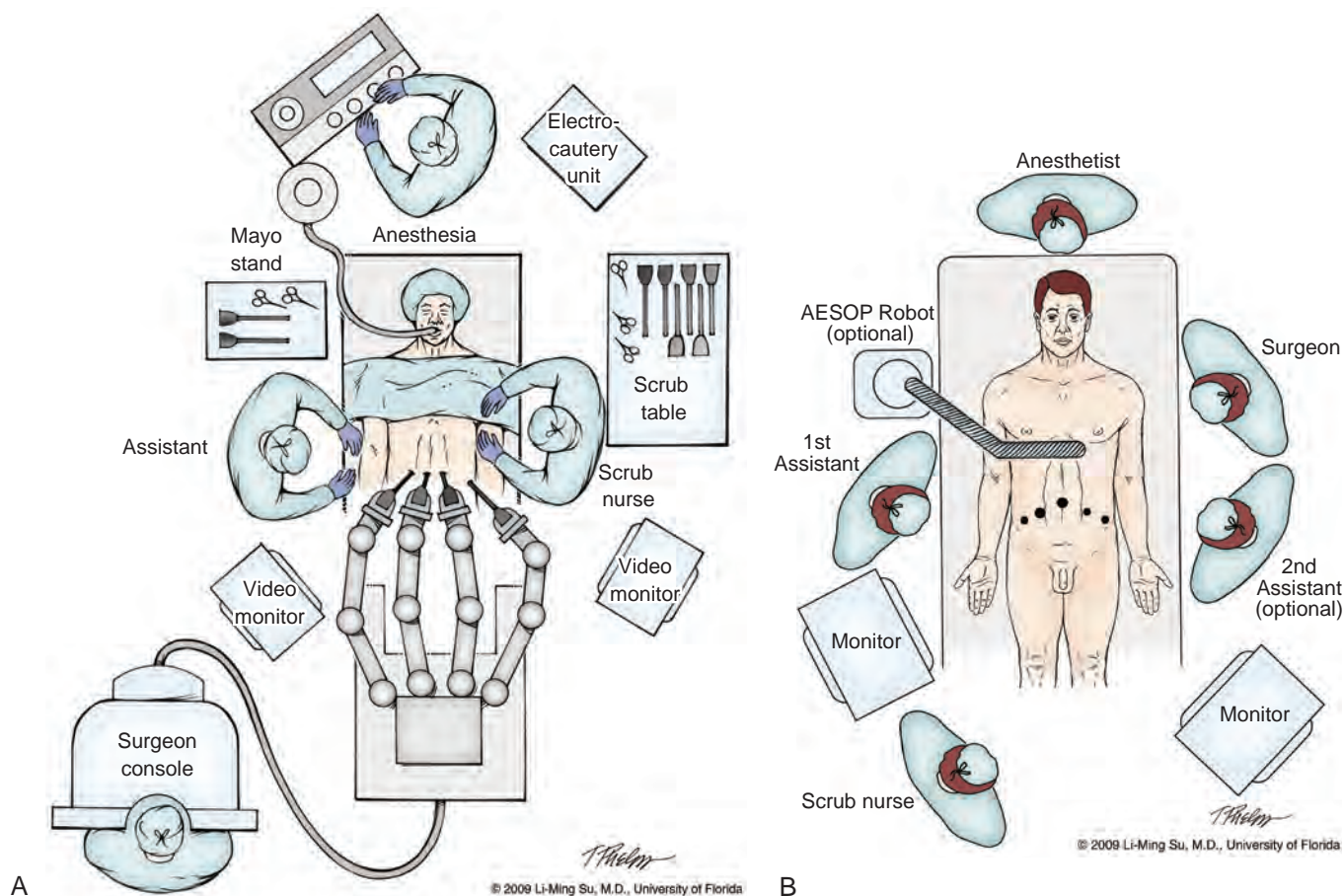


Figure 115-1. Operating room equipment and setup for robotic-assisted (A) and pure laparoscopic radical prostatectomy (B). (Copyright Li-Ming Su, MD, University of Florida, 2009.)

Informed Consent

In addition to bleeding, transfusion, and infection, patients undergoing LRP and RALP must be aware of the potential for conversion to open surgery. As with open surgery, patients must be counseled on the risk for impotence, incontinence, incisional hernia, and adjacent organ injury (e.g., ureter, rectum, bladder, small bowel). The risks with general anesthesia must be presented to the patient because LRP and RALP cannot be performed under regional anesthesia. In addition, it is appropriate for the surgeon to discuss his or her overall operative experience with radical prostatectomy, specifically in addition to the laparoscopic or robotic approach, and provide a realistic forecast of cancer control, as well as return to normal urinary and sexual function on the basis of each patient's unique characteristics.

Operating Room Personnel

LRP and RALP require that the surgical team, including the scrub technician, circulating nurse, and surgical assistant(s), be fully trained and skilled in the instrumentation, operative setup, and technical steps of these minimally invasive procedures. Only one skilled assistant is generally required for these procedures, but a second assistant may be used if available to provide retraction of tissues. For RALP, it is important for the tableside assistant to have adequate training in not only basic laparoscopy but also specifically the mechanics, setup, and troubleshooting of the robotic system. The scrub technician is also an integral part of the operative team and must be versed in the wide array of laparoscopic and robotic instruments that may be used to accomplish this procedure. Finally, using an anesthesiologist who is versed in the nuances and physiologic effects of prolonged pneumoperitoneum is vital in the

success of this operation. Typical operating room equipment and setup for RALP and LRP are shown in [Figure 115-1](#).

Patient Positioning

After induction of general endotracheal anesthesia, the patient is placed in a supine position in steep Trendelenburg with arms and hands carefully tucked and padded at the sides with egg-crate padding to avoid injury to the median and ulnar nerves ([Fig. 115-2A to C](#)). Sequential compression stocking devices are placed on both legs and activated. The patient's legs are spread apart and supported by spreader bars to allow for access to the rectum and perineum. Alternatively, the patient's legs may be placed in stirrups in the low lithotomy position. The patient is then secured firmly to the table using heavy cloth tape and egg-crate padding across the chest to help prevent the patient from sliding when in the steep Trendelenburg position (see [Fig. 115-2D](#)). Fixed shoulder rests should be avoided because this can result in compression injury to the shoulders and brachial plexus when in steep Trendelenburg. Slight flexion of the table at the level of the hips may be required to properly dock the robotic arms; however, exaggerated flexion should be avoided so as to minimize the risk for femoral neuropathia (see [Complications](#) section). An orogastric tube and urethral catheter are placed to decompress the stomach and bladder, respectively. Careful padding of vulnerable body parts such as the hips, shoulders, knees, and calves is important to prevent pressure injury and neuromuscular complications (see [Complications](#) section).

Anesthesia Considerations

Both LRP and RALP require general anesthesia. Because the patient's arms are tucked at the side and difficult to access, establishing

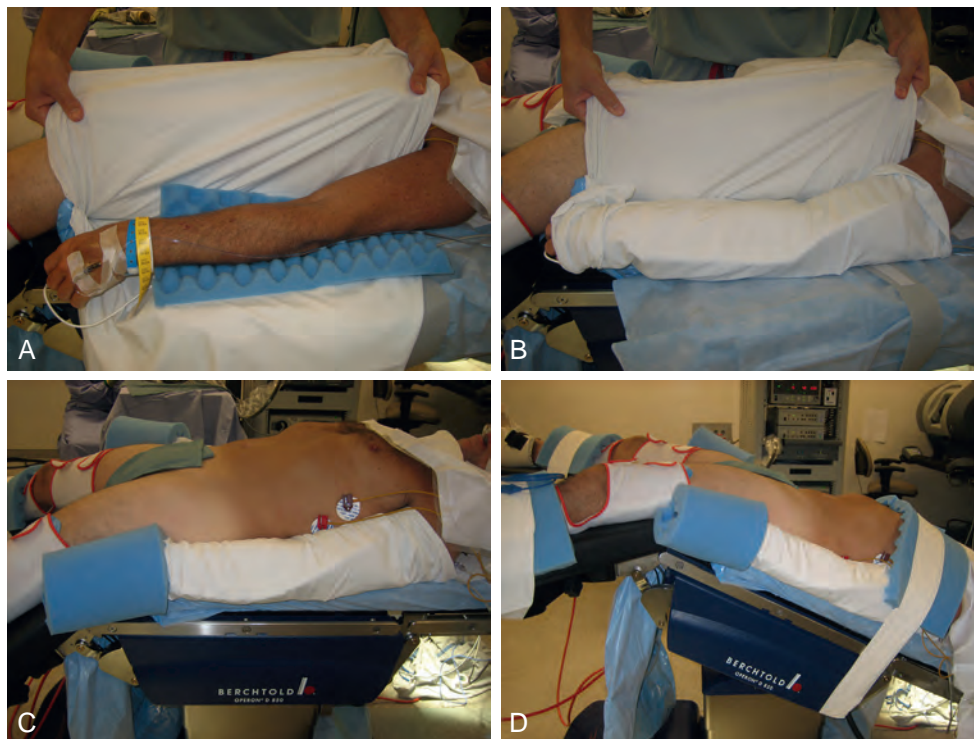


Figure 115-2. Patient positioning for robotic-assisted radical prostatectomy. During positioning on the operating room table, the draw sheet and egg-crate padding are used to help secure the patient's hands and arms to the side in the neutral position, taking great care to protect from injury to the median and ulnar nerves (A to C). To prevent the patient from sliding when in the steep Trendelenburg position, heavy cloth tape and egg-crate padding are placed across the patient's chest (D).

accurate pulse oximetry, blood pressure cuff placement, and intravenous access is critical before final patient positioning. The anesthesiologist must be aware of the potential consequences of carbon dioxide insufflation and pneumoperitoneum, including oliguria and hypercarbia. Prompt adjustments in minute and tidal volumes may be required by the anesthesiologist in the event of rising end-tidal CO₂ levels and hypercarbia, which may lead to systemic acidosis if left uncorrected (Meininger et al, 2004). This is especially true in the early experience of a robotic surgeon and his or her team because operative times generally can be long. Likewise, adjustments in CO₂ insufflation pressures may be required by the surgeon to reduce the risk for continued hypercarbia.

Increased intraocular pressure can occur in patients in an exaggerated Trendelenburg position, but in patients undergoing RALP this does not appear to have any apparent clinical long-term consequence, at least in healthy patients. However, there may be an increased risk for corneal edema and abrasion, making it even more important for the anesthesiologist to maintain good eye lubrication and protection. Taken together, given the potential for prolonged surgical times with a patient in the steep Trendelenburg position, especially in a surgeon's early experience, it is important to recognize these unique complications and maintain excellent communication between the surgeon and anesthesia team throughout the operation.

SURGICAL TECHNIQUE

Robotic-Assisted versus Pure Laparoscopic Approach

Most of the principles and considerations for the surgical dissection are similar regardless of whether a pure laparoscopic or robotic-assisted approach is used. For RALP, the da Vinci Surgical System is a master/slave system with three components: surgical robot (also called the patient side cart), surgeon console, and video

KEY POINTS: PATIENT SELECTION, INSTRUMENTATION, AND PREOPERATIVE PREPARATION FOR LAPAROSCOPIC AND ROBOTIC-ASSISTED LAPAROSCOPIC RADICAL PROSTATECTOMY

- Regarding patient selection, it is strongly advised that patients with more complex anatomic challenges (e.g., large prostate size, large median lobe, morbid obesity, prior pelvic surgery, after radiation, after TURP) be avoided in a surgeon's early experience with LRP and RALP; however, these patient features are not by themselves absolute contraindications for a minimally invasive approach to prostatectomy.
- Having a skilled bedside assistant who is well versed in basic laparoscopy, but also specifically in the mechanics, setup, and troubleshooting of the robotic system, can greatly facilitate RALP procedures.
- Both surgeon and anesthesiologist must be aware of the unique physiologic effects of prolonged pneumoperitoneum with patients in the steep Trendelenburg position, including hypercarbia and acidosis, corneal edema, increased intraocular pressure, and neurapraxia and take proper steps to prevent such complications.

cart. For the purpose of this chapter and for simplicity, the technique using the four-armed da Vinci Si HD system is described. The robot is docked at the foot of the operating table between the patient's legs. The tableside assistant is responsible for docking/undocking the robot, suction-irrigation, retraction of tissues, passing sutures into the operative field, and robotic instrument changes. The surgeon is seated at the surgeon console, which provides a 3D, 10× magnified, high-definition operative view and allows the

surgeon to have complete control of all camera movements and three additional robotic arms. The surgeon's thumb and index or third fingers are inserted into master controls that allow natural hand and wrist movements to be precisely replicated by wristed instruments at the terminal ends of the robotic arms in real time.

Surgeons highly skilled in laparoscopy may find the robotic technology unnecessary and discover that they are equally as facile with pure laparoscopic suturing and dissection as with the robot (Guillonnet, 2005). Most surgeons, however, think robotic technology significantly facilitates suturing of the vesicourethral anastomosis and aids in other aspects of the surgical dissection such as achieving the critical angles of dissection required to optimize cavernous nerve preservation.

Other than setup of the operating room and surgical fields, there is little difference in the surgical technique between LRP and RALP. In general, the following discussion of technique and the pros and cons of various maneuvers and approaches apply to either surgical approach.

Transperitoneal Approach

The most common approach to LRP and RALP is the transperitoneal anterior approach in which after transperitoneal access and insufflation, the space of Retzius is immediately entered and the prostate gland, seminal vesicle, and vasa are dissected from an anterior approach. This is in contrast to the transperitoneal retrovesical (or posterior) approach in which the seminal vesicles and vasa are initially approached and completely dissected behind the bladder near the cul-de-sac *before* the space of Retzius is entered. The transperitoneal access and approach is favored by most surgeons over the extraperitoneal approach because of the greater working space and familiar landmarks of the pelvis. For the purposes of this chapter, the transperitoneal anterior approach will be primarily described, with brief mention of the extraperitoneal approach.

Abdominal Access, Insufflation, and Trocar Placement

For a transperitoneal approach, pneumoperitoneum is established using either a Veress needle inserted at the base of the umbilicus or an open Hasson technique. After initial trocar placement, CO₂ insufflation pressure in general is maintained between 12 and 15 mm Hg. Secondary trocars are then placed under laparoscopic view. For RALP, an example of a trocar configuration is shown in Figure 115-3A. A 12-mm trocar is initially placed slightly inferior to or above the umbilicus for insertion of the stereo endoscope. In a morbidly obese or very tall patient, infraumbilical camera placement may be preferable to gain the proper visual angle to view the prostate gland. Three 8-mm metal robotic trocars are used by the working robotic arms of the surgeon while the assistant provides retraction, suction, and irrigation and passes clips and sutures via the 12- and 5-mm trocars placed along the patient's right side. The surgeon controls camera movement by depressing a foot pedal and using brief, simultaneous arm movements to control camera positioning and rotation. Endoscopes with either angled (30-degree) or straight-ahead (0-degree) viewing are available and interchangeable at various portions of the procedure. In general, most surgeons use the 0-degree endoscope lens throughout the operation; however, some surgeons prefer to switch to the 30-degree down lens when approaching the bladder neck, NVBs, and apical dissection. Figure 115-3B depicts the trocar configuration for LRP. The surgeon stands at the patient's left side and operates through the two pararectus trocars while one or two assistants use the lateral-most trocars. The endoscope is held and controlled by an automated endoscopic system for optimal positioning (AESOP) robotic arm or surgical assistant through the periumbilical trocar.

Extraperitoneal Approach

For an extraperitoneal approach, a 1.5-cm incision is made at the level just beneath the umbilicus and dissection is carried out down through the anterior rectus sheath. Using blunt finger dissection, a

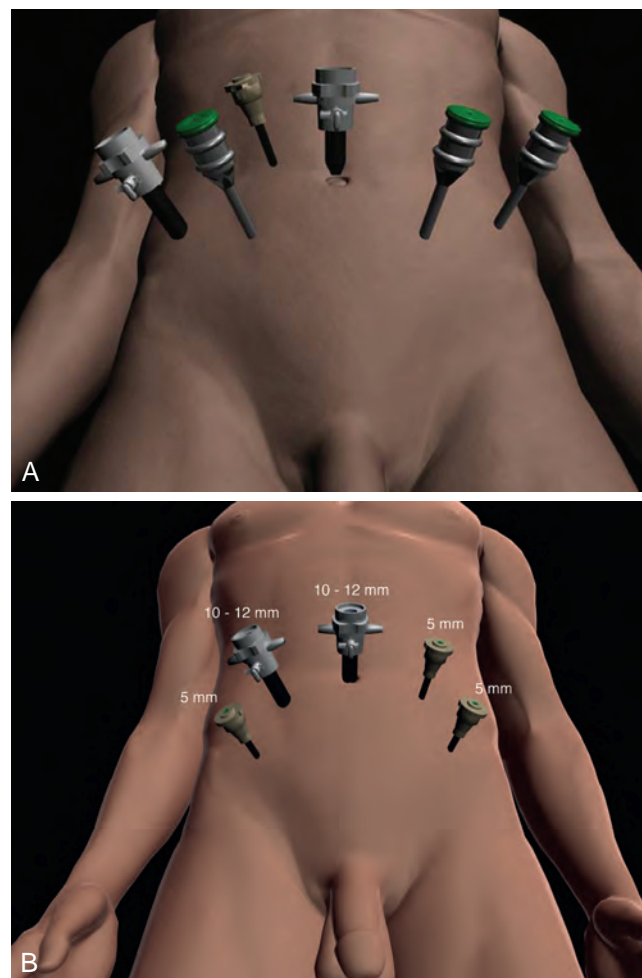


Figure 115-3. Trocar configuration for robotic-assisted laparoscopic prostatectomy (A) and laparoscopic radical prostatectomy (B).

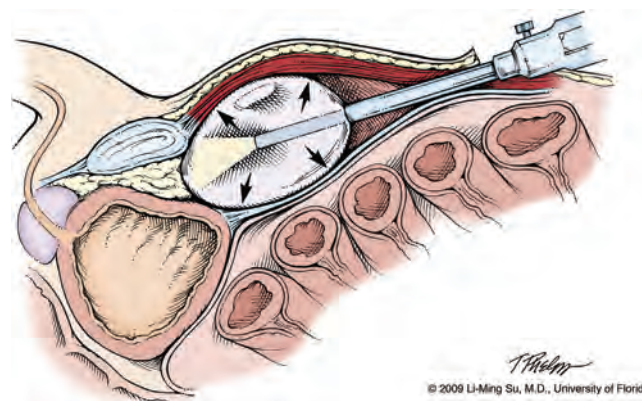


Figure 115-4. Creation of working space for extraperitoneal pure laparoscopic or robotic-assisted radical prostatectomy using a trocar-mounted balloon dilator device. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

space is created immediately anterior to the posterior rectus sheath and underlying peritoneum. A trocar-mounted balloon dilator device (PDB Balloon, Covidien Autosuture, Mansfield, MA) is inserted into the preperitoneal space anterior to the posterior rectus sheath and advanced down to the pubis along the midline. Using a 0-degree, 10-mm endoscope inserted through the balloon trocar, approximately 500 mL of air is inflated to develop the space of Retzius under direct laparoscopic view (Fig. 115-4). Secondary

trocars are then inserted as described previously in the discussion of the laparoscopic view. The operation then proceeds in the exact manner as in the transperitoneal anterior approach.

Pros and Cons of Extraperitoneal versus Transperitoneal Approach

In a retrospective comparison between extraperitoneal and transperitoneal LRP, [Hoznek and colleagues \(2003\)](#) found that the mean operative time was shorter with the extraperitoneal approach (169.6 vs. 224.2 minutes, $P < .001$), with the greatest time saved during access to the space of Retzius. They suggested that time to full diet was less with the extraperitoneal versus the transperitoneal LRP approach (1.6 vs. 2.6 days, $P = .002$) because the peritoneum had not been violated and postoperative ileus was minimized. [Eden and colleagues \(2004\)](#) found a statistically significant advantage in operative time, hospital stay, and return of early continence favoring patients undergoing extraperitoneal versus transperitoneal LRP, postulating that earlier return to urinary control may be secondary to less bladder dissection and, perhaps, less bladder dysfunction compared with transperitoneal LRP. Most studies, however, found little or no difference in operative time and perioperative outcomes between transperitoneal and extraperitoneal approaches ([Cathelineau et al, 2004](#); [Erdogru et al, 2004](#); [Brown et al, 2005b](#); [Atug et al, 2006](#)).

With an extraperitoneal approach, the simultaneous laparoscopic management of concurrent inguinal hernias using prosthetic mesh is feasible ([Stolzenburg et al, 2003](#)). Simultaneous inguinal herniorrhaphy has also been reported during transperitoneal LRP ([Allaf et al, 2003](#)); however, proper coverage of the mesh prosthesis is necessary using peritoneal flaps, omentum, or a second absorbable mesh to reduce the risk for direct contact between the mesh and bowel with subsequent fistula. The extraperitoneal technique may be preferable in patients with previous extensive abdominal surgery or morbid obesity. With the extraperitoneal approach, the peritoneum acts as a natural barrier, minimizing the potential for bowel injury and preventing the bowels from falling into the operative field and obscuring the surgeon's view. Furthermore, this approach helps confine any urine leak that may occur from the vesicourethral anastomosis within the extraperitoneal space. One limitation with the extraperitoneal approach is the reduced working space compared with the relatively larger working space of the peritoneal cavity gained with transperitoneal access. This is especially relevant when a well-meaning assistant attempts to clear the operative field of blood or smoke. Suctioning can evacuate CO₂ and rapidly collapse the already limited extraperitoneal working space, thus significantly compromising visualization. A second limitation to the extraperitoneal approach is in patients with a history of laparoscopic extraperitoneal mesh herniorrhaphy because the retropubic space is often obliterated, making attempts at extraperitoneal access challenging. Finally, higher CO₂ absorption has been reported with extraperitoneal versus transperitoneal insufflation, requiring a higher minute volume to compensate for hypercarbia and associated acidosis ([Meininger et al, 2004](#)). Overall, whether to use an extraperitoneal or transperitoneal approach for LRP or RALP is largely a matter of surgeon preference and experience and there is no consistently demonstrated advantage for either approach.

Developing the Space of Retzius

After abdominal access and trocar placement for the transperitoneal anterior approach, the pelvic contents are inspected ([Fig. 115-5](#)) and adhesions are lysed if present. The initial step is entry and development of the space of Retzius. The bladder is dissected from the anterior abdominal wall by dividing the urachus high above the bladder and incising the peritoneum bilaterally immediately lateral to the medial umbilical ligaments using monopolar scissors. The presence of prevesical fatty alveolar tissue confirms the proper plane of dissection within the space of Retzius. Applying posterior and

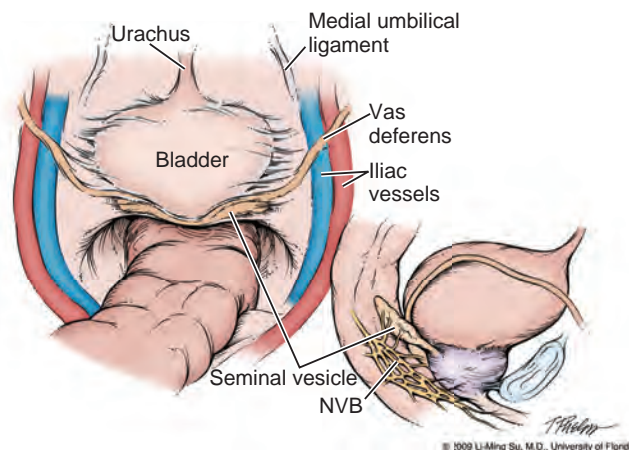


Figure 115-5. Initial transperitoneal view detailing the relevant landmarks within the male pelvis. NVB, neurovascular bundle. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

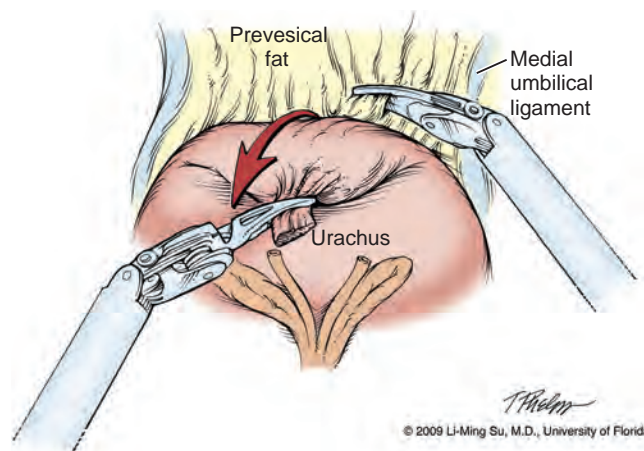


Figure 115-6. Division of urachus and entry into the space of Retzius. Cephalad traction on the urachus with the left hand helps identify the fatty alveolar tissue immediately anterior to the bladder, which marks the proper plane of dissection. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

cephalad traction on the urachus, the retropubic space is rapidly developed with a combination of blunt and sharp dissection along the relatively avascular plane ([Fig. 115-6](#)). Lateral dissection of the bladder is carried out down toward the crossing of the medial umbilical ligaments and vas deferens to ensure optimal mobility of the bladder, which minimizes tension when accomplishing the vesicourethral anastomosis. The fat overlying the prostate is removed using sharp dissection and electrocautery as needed, and the superficial branches of the DVC coagulated using bipolar electrocautery.

At this point, visible landmarks include the anterior aspect of the bladder and prostate, puboprostatic ligaments, endopelvic fascia, and pubis ([Fig. 115-7](#)). The endopelvic fascia and puboprostatic ligaments are sharply divided, exposing levator muscle fibers attached to the lateral and apical portions of the prostate. These fibers are meticulously preserved and bluntly dissected from the surface of the prostate exposing the deep DVC and urethra at their confluence with the apex of the prostate. Electrocautery is avoided if possible to minimize thermal damage to the external sphincter and nearby NVBs.

Accessory pudendal arteries traveling longitudinally along the anteromedial aspect of the prostate are easily recognized during LRP and RALP. Attempt at preservation of these arteries is important for erectile function because in some men these arteries may be the

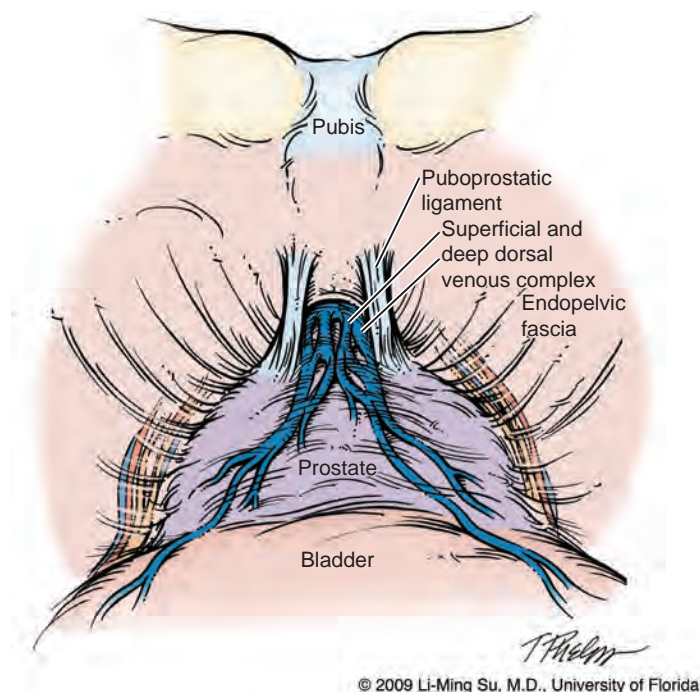


Figure 115-7. Retropubic view of the bladder and prostate after entry into the space of Retzius. The fatty tissue overlying the anterior aspect of the prostate has been removed, exposing the puboprostatic ligaments, superficial and deep dorsal venous complex, and endopelvic fascia. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

dominant source of arterial blood supply to the corpora cavernosa (Nehra et al, 2008). These accessory arteries can usually be preserved, although separation of the artery from the prostatic apex and deep DVC can be somewhat challenging.

Ligation of the Deep Dorsal Venous Complex

As with open surgery, different methods have been described for control of the deep DVC. A common observation, though, is that the profuse bleeding, which is sometimes encountered during open surgery, is less apparent because of the tamponade effect on venous bleeding offered by the pneumoperitoneum even when the DVC is inadvertently entered. During RALP, the ProGrasp forceps can be used for fixed cephalad retraction of the prostate and bladder to achieve optimal exposure of the DVC and prostatic apex before DVC ligation. Similar retraction can be applied by the surgical assistant during LRP. The deep DVC is suture ligated using a 0-polydioxanone suture or polyglactin suture as close to the pubis and as far from the prostatic apex as possible (Fig. 115-8). Securing the deep DVC as far distal from the prostatic apex as possible can help minimize iatrogenic entry into the prostatic apex during later division of the DVC. For this reason, it is our opinion that the puboprostatic ligaments should be completely divided before ligation of the DVC to allow for adequate exposure and access to the most distal portion of the DVC as it traverses beneath the pubic symphysis. The needle is passed beneath the DVC and anterior to the urethra.

An alternative method to DVC ligation is the use of a laparoscopic linear stapling device, which ligates and divides the DVC in one step (Ahlering et al, 2004b; Nguyen et al, 2008). With most techniques, the DVC is not divided until later in the operation and immediately before prostatic apical dissection and division of the urethra. A back-bleeding suture may be placed along the anterior base of the prostate to help identify the contour of the prostate and aid in subsequent bladder neck identification and transection.

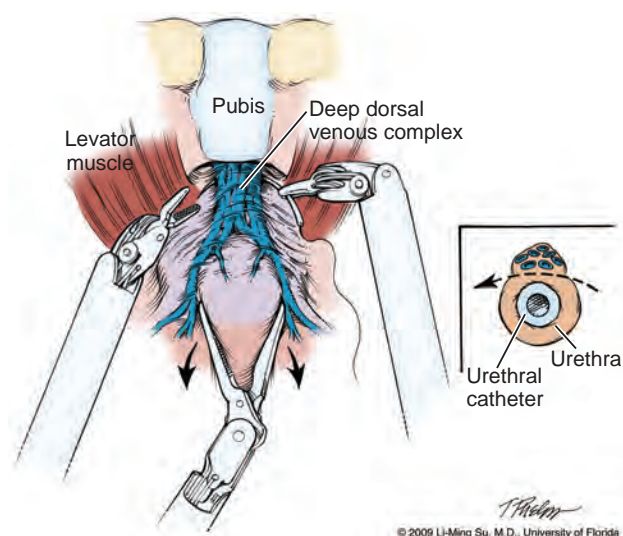


Figure 115-8. Ligation of the deep dorsal venous complex. A suture is passed from right to left, ligating the dorsal vein as distal as possible from the apex. Inset demonstrates the proper passage of the needle immediately anterior to the urethra. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

Bladder Neck Identification and Transection

Proper identification of the bladder neck during RALP and LRP can be initially challenging because of the lack of tactile feedback in delineating the precise margin between the prostate and bladder. Several maneuvers are helpful in identifying the proper plane of dissection and in minimizing inadvertent entry into the base of the prostate. First, visual identification of the point of transition of the prevesical fat to the anterior prostate can serve as a guide. Second, intermittent and repetitive caudal retraction of an inflated urethral catheter balloon can help identify and confirm the transition between bladder neck and prostate. Note that any deviation of the balloon away from the midline signifies the likely presence of a median lobe of the prostate. Third, using a forceps to grasp and retract the dome of the bladder in a cephalad direction results in tenting of the bladder neck at its attachment to the prostate. Finally, further confirmation of this margin between the bladder and prostate is made by a bimanual palpation or pinch of the bladder neck using the tips of two robotic or laparoscopic instruments.

The anterior bladder is divided horizontally using monopolar scissors along the midline until the urethral catheter is identified. The anterior bladder neck incision should not be carried too far laterally because branches of the bladder pedicle are often encountered, resulting in unwanted bleeding. The balloon is decompressed, and the tip of the urethral catheter is brought through the bladder neck opening and lifted anteriorly with the assistant applying countertraction externally at the penile meatus to “suspend” the prostate.

The posterior bladder neck is inspected for the presence of a median lobe and to locate the ureteric orifices. If a vertical drop-off of the posterior bladder neck mucosa is noted, this often suggests the absence of a median lobe. Alternatively, if a mass effect from a large median lobe is identified, it may be delivered out of the bladder by anterior retraction with a ProGrasp forceps. However, further exposure by a transverse or sagittal cystotomy may be required to visualize beneath the protruding median lobe and identify the posterior bladder neck. The posterior bladder neck is horizontally divided with monopolar scissors, staying again along the midline to avoid bleeding from the lateral pedicles (Fig. 115-9). Dissection is carried out in a 45-degree downward angle to avoid entry into the base of the prostate or creating a buttonhole in the posterior wall of the bladder. In case of a prior TURP, the bladder neck margin is

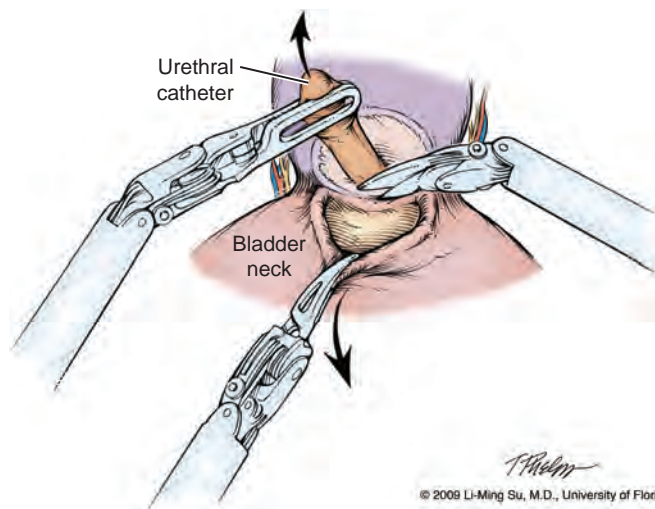


Figure 115-9. Division of the posterior bladder neck. An assistant or ProGrasp forceps is used to grasp and elevate the urethral catheter anteriorly, providing exposure to the posterior bladder neck. Dissection is carried out along the midline, avoiding bleeding from the lateral pedicles. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

less evident and often distorted as a result of prior resection and scarring. Careful inspection is made of the posterior bladder neck, paying specific attention to the location of the ureteric orifices because they are often found close to the posterior bladder neck margin. Attempt at bladder neck sparing should be avoided in post-TURP and median lobe cases. When in doubt, the posterior bladder neck should be divided slightly more proximally in these particular cases so as to avoid inadvertent entry into the prostate gland with a resultant positive bladder neck margin.

Dissection of the Seminal Vesicles and Vasa Deferentia

After bladder neck transection, the seminal vesicles and vasa deferentia are individually identified, dissected, and divided, minimizing electrocautery if possible to prevent damage to the nearby NVBs (Fig. 115-10). One unique distinction between the transperitoneal anterior and retrovesical approaches is in dissection of the seminal vesicles and vasa deferentia. During a transperitoneal retrovesical approach, the initial step of the operation is complete dissection of the vasa deferentia and seminal vesicles deep within the cul-de-sac. After abdominal access, the vasa are dissected from lateral to medial toward their confluence at the ejaculatory ducts. The seminal vesicles are found immediately lateral to the distal portion of the vasa and are dissected free from the nearby NVB using hemoclips while avoiding the use of thermal energy (Fig. 115-11). With the dissection of the seminal vesicles and vasa now completed under excellent vision, these structures are simply grasped and brought through the opening once the bladder neck is divided from the prostate base. This retrovesical approach to the seminal vesicles and vasa deferentia is particularly useful in cases of a median lobe in which identification and dissection of these structures by the anterior approach may be more challenging because of the physical presence of the protruding median lobe in addition to the presence of urine and blood in the operative field.

Development of the Plane between the Prostate and Rectum

Separation of the posterior prostate from the anterior rectal wall is a key surgical maneuver to avoid rectal injury but also permit adequate identification of the prostatic pedicles and establish the medial border of the NVBs. Development of this plane in an antegrade fashion is a maneuver often unfamiliar to surgeons experi-

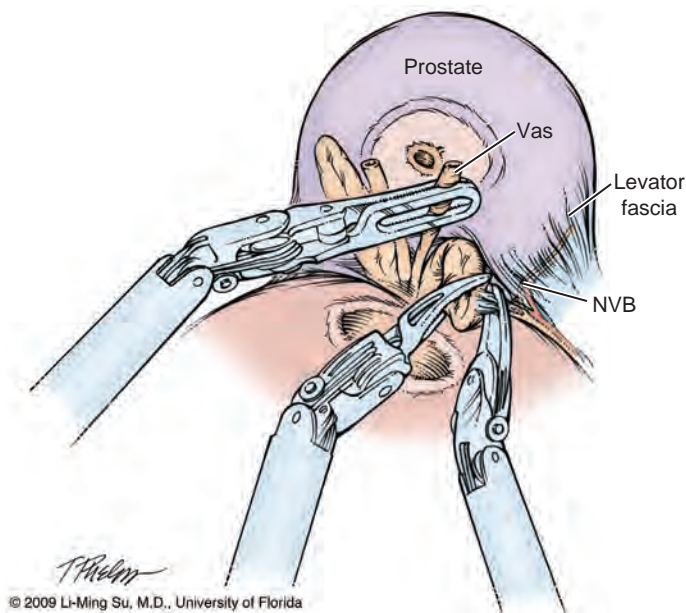


Figure 115-10. Dissection of seminal vesicles and vasa deferentia via the transperitoneal anterior approach. The seminal vesicles and vasa are identified and dissected within the opening created between the posterior bladder neck and prostate following division of the bladder neck. Hemoclips are used in lieu of electrocautery to avoid thermal injury to the nearby neurovascular bundles (NVBs). (Copyright Li-Ming Su, MD, University of Florida, 2009.)

enced with open surgery but one that is rapidly adaptable to laparoscopic and robotic approaches. Anterior retraction of the vasa deferentia and seminal vesicles by a surgical assistant or the robotic ProGrasp forceps helps with identification of the proper plane for the initial dissection (Fig. 115-12).

The Denonvilliers fascia is an inferior extension of the peritoneal cul-de-sac that lies between the prostate and rectum. With an intrafascial or interfascial dissection, Denonvilliers fascia can be separated from the posterior prostate by careful blunt and sharp dissection. The separation can be carried all the way to the prostatic apex and laterally to the medial aspect of the prostatic pedicle. The proper surgical plane is relatively avascular. When a wider margin of tissue is desired along the posterior aspect of the prostate, such as in cases of palpable disease, Denonvilliers fascia should be sharply incised just posterior to the junction of the seminal vesicle and prostate. This allows immediate entry into the anterior perirectal fat plane of dissection. Good visualization can be achieved as the dissection proceeds distally toward the apex staying between Denonvilliers fascia anteriorly and the anterior propria fascia of the rectum posteriorly.

Substantial bleeding typically suggests that the dissection may be too close to the prostate. If difficulty is encountered in establishing the proper plane of dissection, a new attempt can be directed to one side or the other of the initial entry point. Once the proper plane is entered, the dissection characteristically progresses rather smoothly by blunt dissection. The rectal wall should be mobilized far enough laterally and distally that there is sufficient separation for dissection of the NVB and prostatic apex.

Prostatic Pedicle Control

Various methods have been described for control of the prostatic pedicle. Some techniques use pure electrocautery, either monopolar or bipolar. Because of the propagation of thermal energy through tissue, which may result in damage to the nearby NVB, limitation of the use of electrocautery is advised and if possible avoided

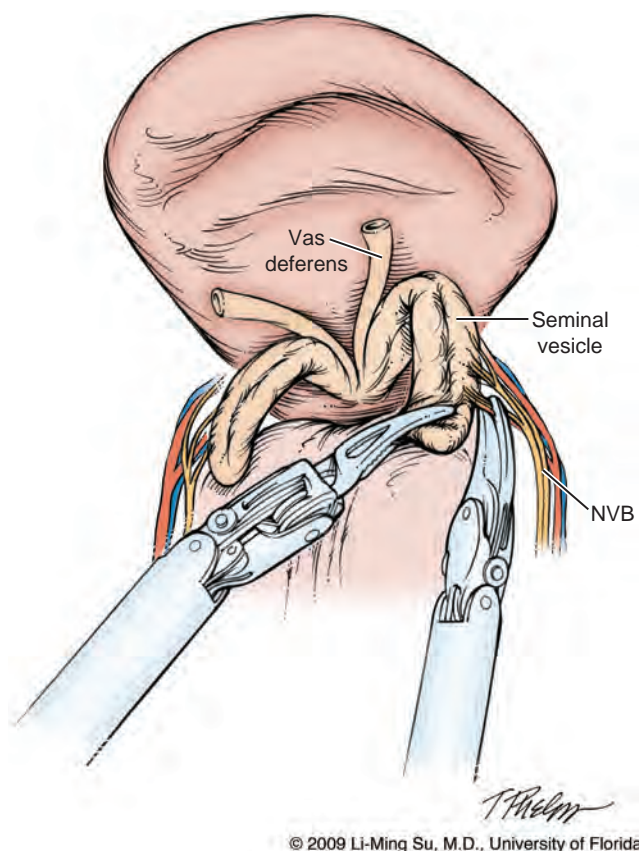


Figure 115-11. Dissection of the seminal vesicles and vasa deferentia via the transperitoneal retrovesical approach. The vasa and seminal vesicles are identified as the initial step in this approach deep within the retrovesical space. The neurovascular bundles (NVBs) are dissected off of the seminal vesicles in an antegrade direction from the tip toward the base using hemoclips. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

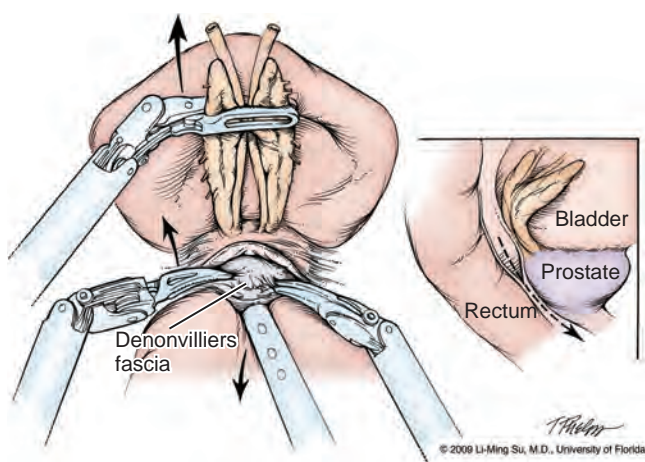


Figure 115-12. Development of the plane between the prostate and rectum. As the assistant or ProGrasp forceps is used to apply anterior traction on the seminal vesicles and vasa deferentia and downward traction on the rectum, a transverse incision is made in Denonvilliers fascia below the seminal vesicles, and blunt dissection is used to develop a plane between the posterior prostate and the rectum. *Inset* demonstrates the direction of dissection toward the prostatic apex without electrocautery. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

during division of the prostatic pedicle. Locking polymer Hem-o-lok clips (Teleflex Medical, Research Triangle Park, NC) are commonly employed, but engagement of the clipping mechanism does require good proximal and distal delineation and thinning of the pedicle tissue so that the clipping mechanism will engage. This is best facilitated by adequate mobilization of the rectum and lateral prostate for identification of the prostatic pedicle. Application of a temporary bulldog clamp to the pedicle with subsequent suturing of the pedicle after the prostate specimen has been removed also has been described (Ahlering et al, 2005; Gill et al, 2005). Regardless of the method used, though, successful division of the prostatic pedicle in the correct anatomic location is an important step in avoiding positive margins and damage to the nearby NVB.

Preservation of the Neurovascular Bundle

Preservation of the periprostatic parasympathetic nerve fibers important for erectile function is one of the key and most difficult maneuvers during radical prostatectomy, regardless of surgical approach. Increasingly, it is recognized that the periprostatic nerves of significance have a more diffuse and highly variable course than previously thought (Costello et al, 2004; Takenaka et al, 2004; Lunacek et al, 2005), but there is a confluence of nerves along the posterolateral aspect of the prostate commonly thought to be the predominant NVB. Nerve tissue extends posteriorly around the prostate, forming a virtual hammock of nerves. In addition, nerve fibers can be identified in the periprostatic tissue along the more anteromedial portion of the prostate gland, although there is still debate about their relative function and contribution to penile erections. A well-performed, nerve-sparing radical prostatectomy takes all of these considerations into account and preserves as much periprostatic nerve tissue as possible both from a qualitative and quantitative standpoint.

The superb visualization of the periprostatic tissues with laparoscopic surgery has led to a greater appreciation of the periprostatic fascial layers. Although there is some confusion in the literature regarding the terminology used for the various fascial layers, an *extrafascial* dissection typically implies dissection laterally between the lateral prostatic fascia and the levator fascia and posteriorly between Denonvilliers fascia and the anterior propria rectal fascia. An *interfascial* dissection is carried out laterally between the prostatic fascia and the levator fascia and posteriorly between Denonvilliers fascia and the posterior surface of the prostate (Fig. 115-13). This is the preferred approach in patients with presumed

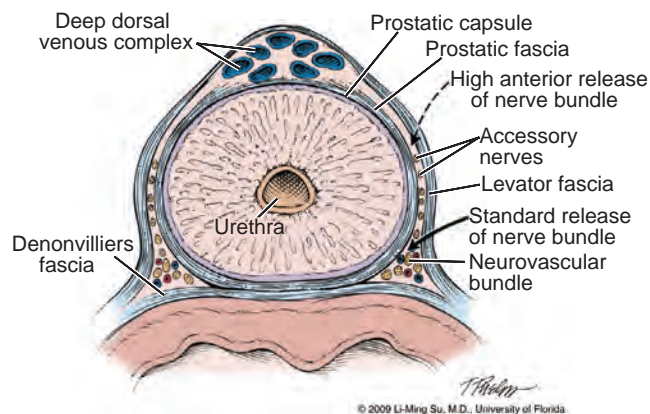


Figure 115-13. Cross section of the prostate demonstrating the periprostatic fascial planes with respect to the location of the neurovascular bundles (NVBs). The *dashed line* indicates the direction of interfascial dissection (i.e., between the levator and prostatic fascia) to accomplish a high anterior release of the NVB from the prostate and establish the lateral NVB groove. The *solid line* indicates the incision made for a standard release of the NVB. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

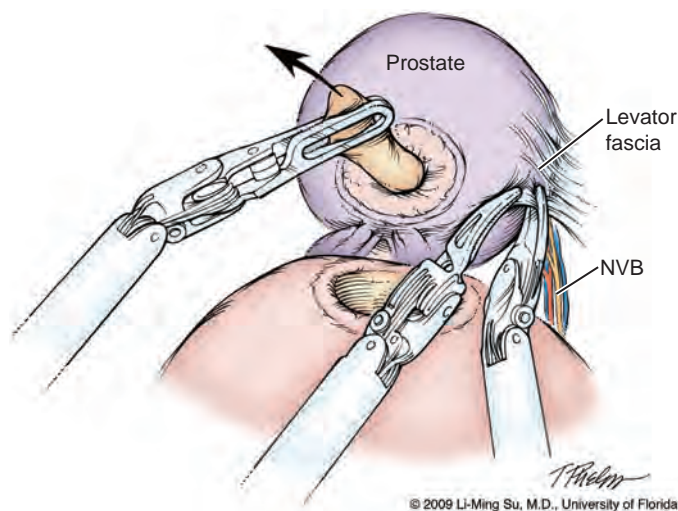


Figure 115-14. Entering into the interfascial plane of dissection for neurovascular bundle (NVB) preservation. The levator fascia is first incised along the anteromedial aspect of the midprostate, allowing entry into the interfascial plane of dissection. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

organ-confined disease because it permits safe preservation of the cavernous nerves without violating the anatomic limits of the prostate gland and capsule. Historically the periprostatic vasculature within the interfascial space has been used as a macroscopic landmark and visual surrogate for identifying and preserving the cavernous nerves. Patel and colleagues (2012) suggested that a dominant periprostatic artery specifically can be identified in 73% of cases during RALP and can serve as a consistent landmark for cavernous nerve preservation. Finally an *intrafascial* dissection is carried out between the prostatic capsule and the prostatic fascia and leaves virtually no periprostatic tissue overlying the prostate. Although technically feasible, this approach risks a higher incidence of positive margins because of the relatively closer dissection to the prostate gland. Even though these fascial layers as described do have some true integrity for intraoperative identification, it is also well recognized that they can be multilayered.

Damage to the NVB can occur because of direct incision, entrapment in a suture or clip, thermal injury, or traction. Some surgeons advocate release of the NVB from the prostate before mobilization of the specimen to help avoid traction injury. With the antegrade approach typically used for LRP and RALP, identification and at least partial release of the NVB along the lateral aspect of the prostate before controlling the prostatic pedicle can help drop the neurovascular tissue away from the gland and permit a more precise placement of hemoclips on the pedicle while preventing inadvertent entrapment of the nerve bundles. To accomplish this, the levator fascia is first incised sharply along the anteromedial aspect of the middle of the prostate entering into the interfascial plane of dissection (Fig. 115-14). Blunt dissection is carried out along the prostatic fascial plane gently dissecting the NVB off of the prostate in a posterolateral direction, thus partially releasing the NVB and developing a visible NVB groove. This groove serves as a visible landmark for precise hemoclip placement and division of the prostatic pedicle while avoiding entrapment of the NVB (Fig. 115-15). The ergonomics and scaled motion of the wristed robotic instruments are helpful in achieving this delicate dissection. During LRP, specially designed fine-tipped (0.8 mm) dissectors have been described to aid in NVB dissection and preservation (Su et al, 2004). Some discussion and debate has centered on how far anteriorly on the prostate the interfascial dissection of the nerve bundles should be performed. Whether high release (vs. standard release) of the NVBs preserves important nerves or simply allows for a physical handle to permit more precise, meticulous

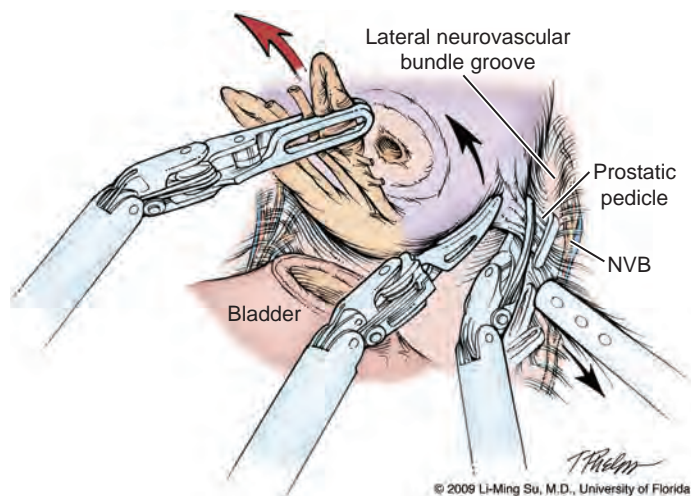


Figure 115-15. Developing the interfascial plane of dissection. Using blunt dissection, the nerve bundle is partially released from the prostate in a posterolateral direction, forming a visible lateral neurovascular bundle (NVB) groove. This step serves to delineate the prostatic pedicle and course of the nerve bundle and allow for precise placement of hemoclips, while avoiding nerve entrapment. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

dissection and preservation of the true cavernous nerves located at the 5- and 7-o'clock positions without direct manipulation of these main nerve fibers is uncertain (see Fig. 115-13). However, there is a general consensus that thermal energy should be minimized and, ideally, completely avoided during dissection of the NVB. These microscopic parasympathetic nerve fibers are highly susceptible to thermal injury, as shown in both animal and human studies (Ong et al, 2004; Ahlering et al, 2005). Bleeding along the NVB is relatively minimal and may require no specific hemostatic measures. There may be small arteries or larger veins that require suturing with small tissue bites to avoid entrapment of adjacent nerves.

Patients with extremely large prostate glands (especially those >100 g) offer a unique challenge during preservation of the NVB. Maneuvering a large prostate gland in the tight confines of the bony pelvis can be challenging, especially during exposure of the prostatic pedicles and NVB. Effective exposure of tissues by the surgical assistant, as well as the fourth robotic arm, is critical in such cases.

Apical Dissection

The prostatic apex is a common location for tumor involvement and the most common site of positive margins with radical prostatectomy. Further, the steps required for apical dissection are crucial to preservation of erectile function and avoidance of urinary incontinence. The visualization of the operative field and the ability to limit bleeding from the deep DVC facilitate apical prostatic dissection during LRP and RALP.

Up to this point in the operation, antegrade dissection has permitted complete mobilization of the lateral, base, and posterior prostate, leaving division of the deep DVC and urethra from the prostatic apex for last. It is critical to avoid entry into the anterior prostate during division of the deep DVC because this may result in an iatrogenic positive margin. Although the previously placed DVC stitch may become dislodged or divided during this step, further sutures to secure the deep DVC can be easily placed. Also, bleeding from the deep DVC during attempts at resuturing can be kept to a minimum by transiently increasing the CO₂ insufflation pressure to 20 mm Hg to improve the tamponade effect on venous bleeding. Once the DVC is divided, there should be good visualization of the prostatic apex and its junction with the urethra (Fig. 115-16). The anatomy of the prostatic apex is variable and should be carefully inspected before division of the urethra. As much

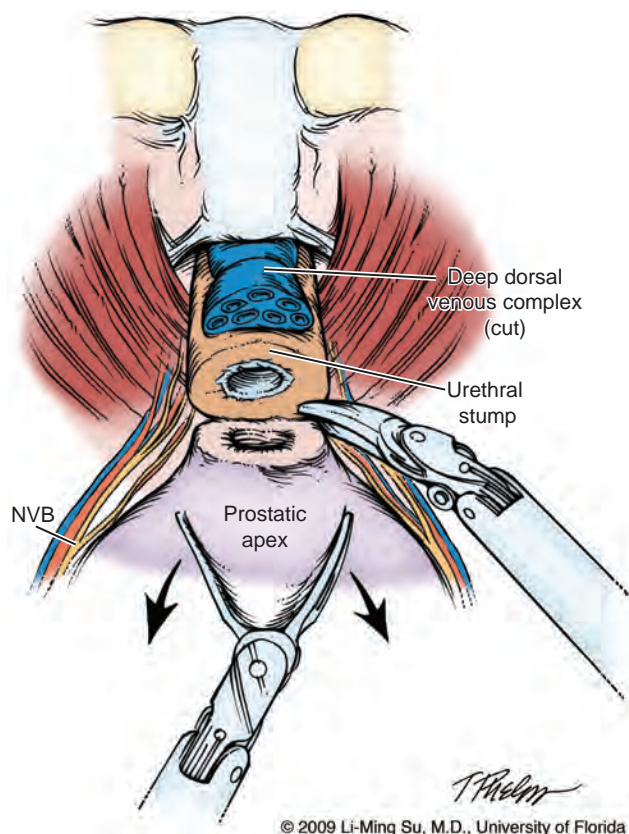


Figure 115-16. Division of urethra. After division of the deep dorsal venous complex, the anterior and posterior urethra is divided sharply without electrocautery. A small rim of urethra may be safely left on the prostate apex to avoid an iatrogenic positive apical margin. Great care must be taken to avoid damage to the nearby nerve bundles. NVB, neurovascular bundle. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

urethral length as possible should be maintained, but an overlying anterior lip of prostate must be recognized, as well as posterior extension of prostatic tissue beneath the urethra. Nevertheless, leaving a small rim of urethra along the prostatic apex may be advisable to reduce the incidence of apical positive margins because this does not appear to have an adverse effect on the return of urinary continence (Borin et al, 2007). Sharp dissection with limited use of electrocautery is preferred during the prostatic apical dissection and division of the urethra, to prevent thermal injury to the external striated sphincter and nearby NVBs.

Intraoperative Inspection of Prostate

On completely freeing the prostate gland and before entrapment of the specimen, the entire surface of the gland can be inspected laparoscopically to assess the adequacy of resection and integrity of the tissues covering the prostate specimen. If concern exists regarding a close surgical margin, additional tissue may be excised specific to the location of concern; however, with experience this should rarely be necessary.

Pelvic Lymphadenectomy

It is generally at this time that pelvic lymphadenectomy takes place, because prior mobilization of the bladder allows for excellent exposure of the obturator lymph node region and iliac vessels. The extent of pelvic lymphadenectomy remains controversial but can be tailored on the basis of patient-specific risk factors, including PSA, clinical stage, and Gleason score. Technical description of a standard

versus extended laparoscopic pelvic lymphadenectomy follows later in this chapter.

Entrapment of Specimens

The prostate and pelvic lymph nodes are entrapped within a 10-mm laparoscopic entrapment sack introduced into the abdomen by the surgical assistant through the 12-mm assistant trocar and stored in the abdomen until completion of the vesicourethral anastomosis.

Bladder Neck Reconstruction

The bladder opening is often slightly larger than the urethral lumen, but a parachuting effect can be achieved during the vesicourethral anastomosis that allows direct approximation of the bladder neck to the urethra. If the bladder neck opening is considerably larger than the urethra, a tennis racquet handle closure can be performed using absorbable suture either posteriorly or anteriorly to allow a better size match with the urethra. In the event of a large prostate gland, median lobe, or prior TURP, the bladder neck often may be disproportionately larger than the urethra and thus may require extensive reconstruction before performing the anastomosis. Often, in these circumstances, the ureteric orifices are located at or near the posterior margin of the bladder neck, where they are at risk for injury or obstruction during suturing of the anastomosis. In such cases the ureteric orifices can be imbricated by placing a few interrupted sutures at the 5- and 7-o'clock positions along the posterior bladder neck using 3-0 polyglactin or polydioxanone suture. This maneuver can help avoid inadvertent sutures passing through or near the ureteric orifices during the anastomosis while at the same time reduce the size of the bladder neck opening. Alternatively, ureteral stents may be placed to protect the integrity of the ureteric orifices during completion of the anastomosis and then removed immediately postoperatively or in a delayed fashion.

Posterior Support of the Vesicourethral Anastomosis

As a result of prostatectomy the posterior supportive layers of the bladder and prostate are divided, including Denonvilliers fascia and its confluence with the posterior rhabdosphincter. Reports of attempts at reconstruction of these posterior supportive structures have suggested improvement in earlier postoperative return of urinary control (Rocco et al, 2007), whereas others have found no significant benefit (Menon et al, 2008). Reconstituting the posterior support to the anastomosis is accomplished by reapproximating the remnant Denonvilliers fascia and posterior bladder neck to the posterior rhabdosphincter beneath the urethra using a running continuous 2-0 poliglecaprone (Monocryl) suture before completion of the vesicourethral anastomosis (Fig. 115-17). Although the exact mechanism remains unclear, suggested mechanisms include reestablishment of the posterior anatomic support to the bladder and urethra, improving urethral coaptation during voiding, reduced tension at the vesicourethral anastomosis, and increase in the functional length of the striated urethral sphincteric complex. Despite the ongoing debate on its effectiveness, many think this step at the very least reduces the distance between the bladder neck and urethra, thus facilitating completion of a tension-free vesicourethral anastomosis. Resuspension of the anastomosis and distal bladder neck to the arcus tendineus is used by some to restore anterior urethral support and preserve the vesicourethral angle (Tewari et al, 2007).

Vesicourethral Anastomosis

With LRP, the vesicourethral anastomosis is one of the most technically challenging aspects of the procedure because of the need for laparoscopic suturing. The da Vinci surgical robot greatly facilitates suturing of the anastomosis due to the ergonomics of the wristed robotic instrumentation. Although interrupted sutures may be used for the anastomosis, van Velthoven and colleagues (2003) described

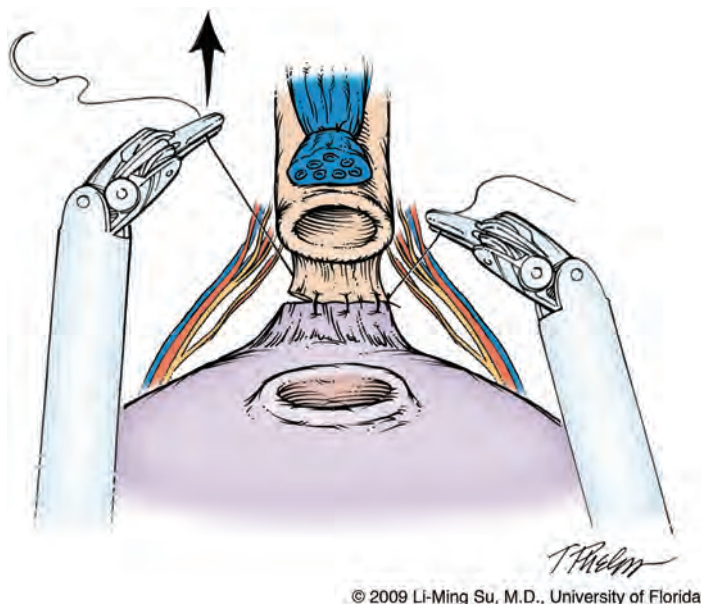


Figure 115-17. Modified Rocco stitch. Posterior support is provided to the vesicourethral anastomosis by reapproximating the remnant Denonvilliers fascia and posterior detrusor along the posterior bladder neck to the posterior rhabdosphincter using a running continuous 2-0 Monocryl suture. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

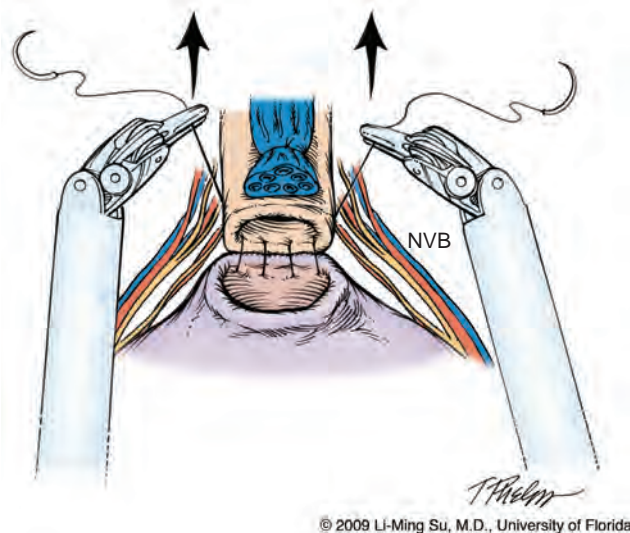


Figure 115-18. Running vesicourethral anastomosis. The posterior anastomosis is reapproximated after preplacing two or three suture throws on either side starting at the 6 o'clock position and cinching the sutures by lifting anteriorly. Great care must be taken to avoid incorporating the neurovascular bundles (NVBs) when placing sutures within the urethra. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

a running suture technique that distributes tension broadly across multiple points along the bladder neck and urethra. Typically, two separate sutures are tied together at their ends, each 6 to 8 inches in length. The anastomosis between the bladder and urethra begins posteriorly, leaving two needles to run progressively in an anterior direction on either side, finally ending at a single anterior tie. Dedicated mucosal eversion sutures at the bladder neck, commonly used during RRP, are unnecessary with the excellent running mucosa-to-mucosa anastomosis achieved with LRP and RALP. Multiple sutures are first placed through the urethra and bladder before progressive cinching of the anastomosis by lifting each arm of the suture in an anterior direction (Fig. 115-18). Either an assistant or the robotic ProGrasp forceps can be used to grasp one arm of the suture to maintain tension and approximation of the posterior anastomosis while the surgeon reapproximates the contralateral side of the anastomosis using the second suture. The final urethral catheter is passed under direct vision immediately before completion of the anastomosis, and the bladder is irrigated to make certain that there are no leaks. Further sutures may be required if a leak is identified.

Delivery of the Specimens and Exiting the Abdomen

Before undocking the robot and removal of the specimens, the pelvis and operative field should be carefully inspected for bleeding under low insufflation pressure (<10 mm Hg). The bowel should be examined closely to make certain there is no injury resulting from instrument exchanges. The string for the laparoscopic entrapment sack is transferred to the camera port site at the umbilicus and the abdomen is completely desufflated. The specimens within the entrapment sack are extracted intact through extension of the umbilical trocar site. The fascial defect is then closed by open suture placement, and the skin defects are closed with a subcuticular absorbable suture. Closure of the fascial defect for the 5-mm trocar sites is generally not necessary. Because of the potential risk for a trocar site hernia, it is advisable to close the 12-mm trocar sites with a Carter Thomason fascial closure device, especially if a bladed (vs. dilating) trocar is used.

POSTOPERATIVE MANAGEMENT

With the secure and watertight running anastomosis typically achieved, a pelvic drain may not be always necessary. However, a drain may be placed through one of the 8-mm robotic trocar sites and does not require a separate stab wound. The drain may evacuate an unanticipated urine leak or lymphatic fluid collection. Often, though, drainage is minimal and the drain typically can be removed on the first or second postoperative day. Parenteral narcotic medications may be required for the first 24 hours after surgery but should be used sparingly. Instead, ketorolac may be used in selected patients for postoperative pain control.

The duration of time required for the urethral catheter depends to a great extent on the preferred approach of the surgeon, as well as the extent of bladder neck reconstruction. The 2-week period commonly used with open surgery is in general unnecessary if a good running vesicourethral anastomosis is achieved. With 1 week or more of an indwelling urethral catheter, the vast majority of patients are able to void adequately with minimal risk for urinary retention and need for catheter replacement. Performing a cystogram before removal of the catheter is based on surgeon preference. If catheter removal before a week is planned, it may be advisable to obtain a cystogram to ensure there is no extravasation from the anastomotic site. In cases of extravasation, longer duration of the urethral catheter is required to allow for spontaneous healing. Although this may prolong the time to achieve complete urinary continence, long-term urinary outcomes do not appear to be affected (Patil et al, 2009). Some surgeons advocate suprapubic catheter drainage of the bladder with a specially designed anastomotic splint rather than a urethral catheter with good initial results (Tewari et al, 2008).

After LRP and RALP, some degree of postoperative ileus is not uncommon. Most patients can tolerate a regular diet within 24 hours of surgery, and hospitalization beyond the first postoperative day typically is not necessary. Patients can characteristically return to their preoperative activities shortly after catheter removal but must avoid strenuous activity up to 3 to 4 weeks after surgery.

KEY POINTS: TECHNIQUE OF LAPAROSCOPIC AND ROBOTIC-ASSISTED LAPAROSCOPIC RADICAL PROSTATECTOMY

- Use of a transperitoneal or extraperitoneal approach is based primarily on surgeon preference because there is no consistent advantage of one approach over the other.
- The robotic technology facilitates suturing and dissection for surgeons who may not have advanced laparoscopic skills.
- Identification of the precise margin between the bladder neck and prostate can be accomplished by using a set of physical maneuvers and visual cues.
- After division of the anterior bladder neck, the presence or absence of a median lobe should be defined before division of the posterior bladder neck.
- Complete mobilization of the plane between the posterior prostate and rectum is an important step in avoiding rectal injury and defining the medial aspect of the NVBs.
- Use of thermal energy should be minimized during control of the prostatic pedicles and dissection near the NVBs because thermal energy has been shown to be deleterious to cavernous nerve function in both animal and human studies.
- An interfascial dissection of the NVB is preferred in patients with presumed organ-confined cancer who desire NVB preservation for potency.
- An anterior or posterior protruding lip of prostate should be anticipated when dividing the prostatic apex from the urethra so as to avoid an iatrogenic positive apical margin.
- Bladder neck reconstruction may be required if there is a size discrepancy between the bladder neck and urethra, especially in patients with prior TURP, median lobe, or large prostate gland.
- The vesicourethral anastomosis is most efficiently accomplished with a running continuous suture.

Published results continue to emerge with regard to midterm outcomes of LRP and RALP both in the United States and abroad, suggesting comparable outcomes with RRP. Most of these reports, however, are case series. Few randomized trials have been conducted evaluating laparoscopic and robotic versus open techniques, and retrospective comparisons are limited by disparities in surgeon experience, the influence of patient selection, and nonstandardized methods of outcome assessment.

Perioperative Outcomes

Operative Time

The duration of surgery is typically longer with LRP or RALP compared with open surgery, especially early in a surgeon's experience. In fact, operating times are often used as a surrogate for assessing the "learning curve" with minimally invasive prostatectomy (Herrell and Smith, 2005). As both surgeon and operating team experience is gained, virtually all reported series have documented a substantial decrease in operative times that approach and in some series are less than those for open surgery. At experienced centers of excellence with LRP, operative times less than 3 to 4 hours are common (Turk et al, 2001; Salomon et al, 2004; Stolzenburg et al, 2008). Similar findings have been observed with RALP. Inexperience of both the console surgeon and the tableside operating team can lead to lengthy procedures initially. As a result, novice surgeons should pay particular attention to the unique complications that may occur as a result of prolonged pneumoperitoneum in the steep Trendelenburg position, including hypercarbia, acidosis, fluid overload, increased intraocular pressure, and neurapraxias, as discussed earlier in the Preoperative Preparation section of this chapter. Nevertheless once experience is gained, operative times of 3 hours and even less are routine (Smith, 2004; Badani et al, 2007; Patel et al, 2008).

Postoperative Pain

One of the distinct advantages of laparoscopy for many surgical procedures (e.g., laparoscopic nephrectomy) is its minimally invasive nature resulting in less postoperative pain than comparative open approaches. For radical prostatectomy, however, this advantage seems to be less dramatic because RRP is performed through an infraumbilical muscle-splitting incision. In addition, relatively little pain occurs after radical perineal prostatectomy. Some series have shown decreased pain in patients undergoing either LRP or RALP compared with RRP (Menon et al, 2002; Bhayani et al, 2003). Other reports have shown no substantial difference in postoperative narcotic use or patient-reported pain (Webster et al, 2005). **The lack of a significant advantage for laparoscopic prostatectomy from a postoperative pain perspective is attributable primarily to low pain scores even in the open surgical group.**

Intraoperative Blood Loss

Because most of the blood loss that occurs during radical prostatectomy is from venous sinuses, the tamponade effect from the pneumoperitoneum helps diminish ongoing blood loss during LRP and RALP. Further, the antegrade approach used during LRP and RALP allows earlier control of the prostatic pedicles and late division of the deep DVC compared with RRP, in which the DVC is divided early and the arterial supply to the prostate managed late in the operation. Thus the potential for ongoing bleeding is reduced during LRP and RALP as compared with open surgery. Both of these factors, as well as the excellent visualization with laparoscopy, account for the minimal blood loss reported in most laparoscopic and robotic series (Ficarra et al, 2009a).

Perhaps the most meaningful parameter clinically is the proportion of patients requiring transfusion of blood products. Most studies have shown a significant decrease in transfusion requirement for patients undergoing LRP or RALP compared with RRP (Tewari et al, 2003; Ahlering et al, 2004a). Others have shown no statistically significant difference if the transfusion requirement with RRP can be limited to only a few percent of patients (Farnham et al, 2006).

Hospital Stay

Over the past decade, hospital stay after radical prostatectomy has diminished remarkably regardless of the surgical approach. Some centers have reported a length of stay as short as 1 or 2 days after RRP (Holzbeierlein and Smith, 2000). With LRP and RALP, a hospital stay of only 1 day has become routine at many centers. Large population-based studies also have consistently demonstrated that RALP is associated with a shorter length of hospital stay and lower probability of prolong hospitalization (Trinh et al, 2012; Liu et al, 2013; Davis et al, 2014). Ileus and inability to tolerate a regular diet are the most common factors limiting early discharge. Pain control does not typically contribute to prolonged length of stay because long-term parenteral narcotics are rarely required. **With early discharge programs for radical perineal and RRP being commonly used at many centers within the United States, no distinct advantage exists with LRP or RALP, although discharge on the first postoperative day may be more easily accomplished routinely with the minimally invasive approaches.**

Functional Outcomes

The complications of radical prostatectomy with the greatest potential for an adverse effect on quality of life are urinary incontinence and erectile dysfunction. Greater surgical experience with radical prostatectomy and refinements in surgical technique have reduced the frequency with which these problems are observed in most radical prostatectomy series from centers of excellence. However, most large population-based studies show substantial rates of erectile dysfunction and incontinence after both RRP and radical perineal prostatectomy (Fowler et al, 1993). Whether laparoscopic or

robotic approaches offer improved functional outcomes is still a matter of debate, and comparison of published series is difficult because of differences in patient populations and methods of outcome assessment.

Urinary Incontinence. Urinary incontinence after radical prostatectomy is usually manifested as stress incontinence secondary to intrinsic sphincter deficiency. Although more than 90% of patients ultimately regain good urinary control and do not require pads for incontinence in reports from high-volume centers (Walsh, 1998; Catalona et al, 1999), other studies have shown that a substantial proportion of patients may be bothered by some degree of stress incontinence (Fowler et al, 1993). The exact physiologic mechanisms that contribute to urinary control after radical prostatectomy are not entirely understood and are likely multifactorial. However, surgical technique is undoubtedly a contributing factor (Smith, 2002).

With LRP and RALP, visualization of the prostatic apex is typically superb. The minimal bleeding and magnification of the operative field allow precise dissection of the prostatic apex with limited trauma to the periurethral striated sphincter and genitourinary diaphragm. As mentioned previously, the ability to more reliably accomplish a tension-free, watertight anastomosis under the superior and direct visualization offered by laparoscopic approaches in theory favors LRP and RALP over open surgery. A common observation after radical prostatectomy, regardless of surgical approach, is that urinary incontinence improves substantially within the first 3 to 6 months after surgery and to some extent for another year or more. Therefore the time points at which data on incontinence are collected are highly influential. Differences exist whether the information is gathered by questionnaire, the physician, or an independent third party. Further, even though validated instruments for assessment of incontinence exist, the manner and location in which the data are collected can affect results. Although the method used to evaluate continence in reported series varies, the recovery of urinary continence is in general excellent at 1 year after LRP and RALP with comparable and in some cases superior results compared to RRP in published comparative studies (Table 115-1). More recent reports of techniques that provide both posterior and anterior support to the vesicourethral anastomosis report even further improvements in urinary continence, especially at earlier time points (Tewari et al, 2007; Johnson et al, 2011).

Erectile Dysfunction. Preservation of erectile function after radical prostatectomy depends on precise and meticulous separation of the cavernous nerves within the NVB from the prostate gland (Walsh and Donker, 1982). The anatomic course of these nerves has been described but can be variable (Costello et al, 2004; Takenaka et al, 2004; Lunacek et al, 2005). Intraoperative localization using nerve stimulation has not been sufficiently accurate for clinical utility (Holzbeierlein et al, 2001). The principles and anatomic dissection for nerve preservation are the same regardless of surgical approach. It is still uncertain whether the magnified image of the operative field afforded by laparoscopy and the precision of the surgical instruments allow more anatomically accurate and less traumatic dissection of the NVBs, resulting in improved postoperative erectile function. As with incontinence, comparison of the published literature is difficult (Salomon et al, 2004). Differences in the method of assessment, definition of potency (e.g., spontaneous erections vs. intercourse), and patient selection complicate comparisons. In addition, the use of adjunctive therapies such as phosphodiesterase-5 inhibitors or vasoactive injections can substantially influence results. Also, in concordance with other nerve injuries, improvement in erectile function is a prolonged process that is ongoing for years after radical prostatectomy. **Results from published comparative series suggest that RALP may provide equivalent, or in some cases slightly better, erectile recovery compared to that with RRP when performed by experienced surgeons (see Table 115-1).** Furthermore, RALP potency outcomes appear superior to that of LRP at least in some single-surgeon observational series (Park et al, 2011; Willis et al, 2012). Thompson and colleagues (2014) reported higher sexual function scores after transition to RALP compared to RRP when performed by an experienced surgeon. Although this and

other published series report relative improvement in recovery of sexual function after RALP and LRP, patient-reported outcomes indicate that erectile dysfunction remains a major limitation even in modern surgical series. Sanda and colleagues (2008) demonstrated significant decline in patient-reported sexual scores and quality of life with infrequent complete recovery to baseline function even despite nerve-sparing surgery among men treated with both RALP and RRP. Nevertheless, most surgeons would agree that with regard to surgical technique, avoidance of traction, direct manipulation, hemostatic energy sources, and performance of a meticulous interfascial dissection during NVB preservation appear to be critical to optimizing postoperative recovery of potency.

Anatomic studies indicate that the cavernous nerves in the NVB course posterolateral to the prostate and urethra. A technique during RALP for preservation of more anteromedial periprostatic fascia in addition to the conventional NVB regions has been reported to significantly improve potency outcomes (Menon et al, 2005; Saveria et al, 2006). Although some neural tissue can be shown histologically to travel within the anterior and medial periprostatic fascia, the purpose and significance of these nerves and their relative contribution to erectile function remains uncertain. Nevertheless, the concept of optimizing both qualitative and quantitative preservation of nerve fibers traveling within the periprostatic fascial planes irrespective of whether they affect penile erections or urinary continence seems reasonable. In cases in which wider excision of the nerve bundles is required, incremental nerve preservation is often feasible without having to excise the entire NVB. Finally, cavernous nerve grafting and nerve advancement have been described; however, the true merits of these techniques remain unclear (Martinez-Salamanca et al, 2007; Zorn et al, 2008).

Oncologic Outcomes

Surgical margin status and biochemical recurrence have generally been used as surrogates for oncologic efficacy after radical prostatectomy.

Surgical Margins. The goal of radical prostatectomy is complete surgical removal of the entire prostate and its investing fascia, as well as the seminal vesicles. Because most adenocarcinomas of the prostate occur in the peripheral zone and approach the capsular margin, surgical technique can influence oncologic outcomes. Proper surgical dissection should allow negative margins with pathologic stage T2 tumors while also permitting complete excision and negative margins for some extracapsular lesions. Efforts to avoid urinary incontinence or erectile dysfunction by dissecting too closely to the prostatic apex or the posterolateral aspect of the prostate can compromise margins, regardless of the surgical approach. **Importantly, the method and detail of pathologic analysis of the surgical specimen can be highly influential in assessing surgical margin status.** Some reports have used only biopsies of remaining tissue after removal of the surgical specimen to assess margin status, whereas others rely on step-sectioned routine or whole-mount histology. According to the World Health Organization International Consultation Consensus Committee guidelines established for the pathologic analysis of prostatectomy specimens, whole-mount histologic sectioning may miss areas of extraprostatic extension in 7% to 15% of cases and positive margins in up to 12% compared with specimens analyzed by routine sectioning (World Health Organization International Consultation on Prediction of Patient Outcome in Prostate Cancer, 2004). This finding is thought to be due to the relatively thicker slices required during sectioning of the prostate for whole-mount technique compared with the serial 3- to 5-mm slices used during routine sectioning.

In most series of LRP and RALP, positive margin percentages decrease with experience (Ahlering et al, 2004b; Salomon et al, 2004; Rassweiler et al, 2005). This implies that inexperience with the surgery accounts for positive margins in some cases. Sometimes, this may be from difficulty in identifying the proper anatomic plane of dissection between the bladder neck and the base of the prostate. **The most common site of a positive margin, whether**

TABLE 115-1 Reported Comparative Functional Outcomes in Open, Robotic, and Laparoscopic Radical Prostatectomy

REFERENCE	TOTAL NO. PATIENTS	STUDY DESIGN	METHODS OF ASSESSMENT	DEFINITION	TIME OF ASSESSMENT	FUNCTIONAL OUTCOME RATE (%)
URINARY CONTINENCE						
Ficarra et al, 2009b	RRP, 105 RALP, 103	Prospective comparison	Validated questionnaire	0 pads	12 mo	RRP (88) RALP (97)
Di Pierro et al, 2011	RRP, 75 RALP, 75	Prospective comparison	Institutional questionnaire	0 pads	12 mo	RRP (80) RALP (89)
Krambeck et al, 2009	RRP, 564 RALP 286	Retrospective case series	Institutional questionnaire	0 pads	12 mo	RRP (93.7) RALP (91.8)
Rocco et al, 2009	RRP, 240 RALP, 120	Historical control	Interview	0-1 safety pad	12 mo	RRP (88) RALP (97)
Asimakopoulos et al, 2011	LRP, 64 RALP, 52	Randomized control trial	Interview	0 pads	12 mo	LRP (83) RALP (94)
Park et al, 2011	LRP, 62 RALP, 44	Retrospective case series	Interview	0-1 safety pads	12 mo	LRP (95) RALP (94)
Willis et al, 2012	LRP, 174 RALP, 175	Retrospective case series	Validated questionnaire	0-1 safety pads	12 mo	LRP (93) RALP (93)
POTENCY						
Ficarra et al, 2009b	RRP, 41 RALP, 64	Prospective comparison	Validated questionnaire	SHIM > 17	12 mo	RRP (49) RALP (81)
Di Pierro et al, 2011	RRP, 47 RALP, 22	Prospective comparison	Institutional questionnaire	Erections sufficient for intercourse	12 mo	RRP (26) RALP (55)
Krambeck et al, 2009	RRP, 417 RALP, 203	Retrospective case series	Institutional questionnaire	Erections sufficient for intercourse	12 mo	RRP (63) RALP (70)
Rocco et al, 2009	RRP, 214 RALP, 78	Retrospective case series	Interview	Erections sufficient for intercourse	12 mo	RRP (41) RALP (61)
Asimakopoulos et al, 2011	LRP, 64 RALP, 52	Randomized control trail	Validated questionnaire	Erections sufficient for intercourse	12 mo	LRP (32) RALP (77)
Park et al, 2011	LRP, 62 RALP, 44	Retrospective case series	Interview	Erections sufficient for intercourse	12 mo	LRP (48) RALP (55)
Willis et al, 2012	LRP, 174 RALP, 175	Retrospective case series	Validated questionnaire	Erections sufficient for intercourse	12 mo	LRP (67) RALP (88)

Modified from Ficarra et al, 2009a, 2009b.

LRP, laparoscopic radical prostatectomy; RALP, robotic-assisted laparoscopic radical prostatectomy; RRP, radical retropubic prostatectomy; SHIM, Sexual Health Inventory Score for Men.

the operation is performed via open or laparoscopic approaches, is the prostatic apex (Touijer et al, 2005). Insufficient removal of prostatic tissue at the apex in an effort to optimize urethral length and avoid incontinence can result in positive margins even with tumors that do not pathologically violate the capsule (i.e., stage pT2). As mentioned previously in the discussion of surgical techniques in this chapter, adhering to specific surgical principles can help reduce site-specific positive margins at the apex, bladder neck, and posterolateral regions of the prostate. Low positive margin rates have been reported by experienced centers with LRP and RALP reporting pT2-positive margins between 4% and 10% and pT3-positive margins between 21% and 35% (Guillonneau et al, 2003a; Lein et al, 2006; Badani et al, 2007; Smith et al, 2007; Patel et al, 2008; Stolzenburg et al, 2008). Results from published com-

parative studies of pathologic stage-specific positive margins among RRP, RALP, and LRP are shown in Table 115-2.

The primary factor that determines the positive margin rate in a given series is patient selection. As discussed earlier, the method and detail of pathologic analysis is also influential. Evaluating positive margin rates from one series to another, then, is not necessarily a comparison of surgical technique. A more accurate technical comparison is analysis of the pathologic results in stage T2 tumors in which a positive margin implies surgical violation of the prostatic capsule. Even in this circumstance, though, the methodology for pathologic sampling is important. Intrainstitutional comparisons from some studies have shown a reduced rate of positive margins with laparoscopic approaches compared with RRP. However, comparison of margin status between high-volume

TABLE 115-2 Reported Pathologic Surgical Margin and Biochemical Failure Rates in Open, Robotic, and Laparoscopic Radical Prostatectomy

REFERENCE	TOTAL NO. PATIENT	PATHOLOGIC STAGE	POSITIVE MARGIN RATE (%)	BIOCHEMICAL FAILURE RATE (%)	TIME INTERVAL FOR BFR
Park et al, 2014	RRP, 277 RALP, 730	T2	RRP (7.8) RALP (11.2)	RRP (7.9) RALP (3.2)	3 yr
		T3	RRP (36.5) RALP (44.7)	RRP (40) RALP (32.7)	
Vora et al, 2013	RRP, 95 RALP, 140	T3a-T4	RRP (51.4) RALP (47.1)	RRP (18.9) RALP (18.5)	3 yr
Robertson et al, 2013*	RRP, 7344 RALP, 6768 LRP, 4952	All stages	RRP (24) RALP (24) LRP (18)	RRP (N/A) RALP (8.7) LRP (8.7)	N/A
Punnen et al, 2013	RRP, 177 RALP, 233	T1-T3	RRP (23) RALP (29)	RRP (16) RALP (21)	2 yr
Silberstein et al, 2013	RRP, 961 RALP, 493	T2	RRP (8) RALP (10)	RRP (4.1) RALP (3.3)	2 yr
		T3a	RRP (23) RALP (21)		
		T3b	RRP (31) RALP (30)		
Tewari et al, 2012*	RRP, 167,184 RALP, 62,389 LRP, 57,303	T2	RRP (16.6) RALP (10.7) LRP (13.0)	N/A	N/A
		T3	RRP (42.6) RALP (37.2) LRP (39.7)		
Williams et al, 2010	RRP, 346 RALP, 604	All stages	RRP (7.6) RALP (13.5)	N/A	N/A
Smith et al, 2007	RRP, 509 RALP, 1238	T2	RRP (24.1) RALP (9.4)	N/A	N/A
		T3	RRP (60) RALP (50)		

*Systematic review and meta-analysis; reported rates are from pooled estimates from multiple studies.

BFR, biochemical failure rate; LRP, laparoscopic radical prostatectomy; RALP, robotic-assisted laparoscopic radical prostatectomy; RRP, radical retropubic prostatectomy.

centers with operations performed by experienced surgeons has shown no consistent advantage for one surgical approach over the other in achieving negative surgical margins (Brown et al, 2003; Khan et al, 2005).

Biochemical Recurrence. Biochemical recurrence after prostatectomy perhaps may provide a more accurate assessment of oncologic control than margin status. Guillonnet and colleagues (2003a) reported on their oncologic outcomes with 1000 consecutive LRPs performed over a 4-year period with a median follow-up period of 12 months. Their overall actuarial biochemical progression-free survival rate was 90.5% at 3 years. By pathologic stage, the rates were 92% for pT2a, 88% for pT2b, 77% for pT3a, and 44% for pT3b. Pavlovich and colleagues (2008) reported on 528 consecutive LRP patients with a mean follow-up of 13 months. The 3-year, actuarial, biochemical-free survival was 94.5% overall, 98.2% for pT2, and 78.7% for pT3 disease.

With regard to RALP, Badani and colleagues in 2007 reported on their large series of 2766 consecutive RALP patients with a mean follow-up period of 22 months. Their overall 5-year, actuarial, biochemical-free survival was 84% overall, 84% for pT2, and 66% for pT3 patients. It should be noted that their patient population included patients at higher risk than those in most reported series with a Gleason score of 7 or higher in 64% and a pathologic stage of pT3 or higher in 22% of their patients. A growing number of

studies have reported oncologic outcomes after RALP similar to those seen with open prostatectomy. In particular, stage- and risk-stratified positive surgical margin and biochemical-free recurrence rates appear to be comparable between RALP and RRP once the learning curve for robotic prostatectomy has been surpassed (see Table 115-2) (Schroek et al, 2008; Silberstein et al, 2013). In one large study comparing 277 RRP and 730 RALP cases, Park and associates (2014) reported no significant difference in T2-positive surgical margin rates between the two approaches, and similar 3-year biochemical-free recurrence survival for both T2 (92.1% vs. 96.8%, $P = .52$) and T3 cases (60.0% vs. 67.3%, $P = .27$). Other studies have reported similar results, even in high-risk disease (Masterson et al, 2013; Punnen et al, 2013; Vora et al, 2013). Taken together, the information available to date indicates that RALP and RRP offer similar disease control when performed by experienced surgeons, even in high-risk settings.

Randomized Comparisons of Open versus Minimally Invasive Prostatectomy

Although a number of studies have reported surgeon and institutional outcomes associated with robotic prostatectomy, direct comparisons of robotic prostatectomy to open radical prostatectomy

are remarkably scant. The vast majority of comparative evidence has been gained through observational studies and case series thus far, although efforts to better study robotic and open prostatectomy are currently underway through a randomized controlled trial (Gardiner et al, 2012). This trial will report oncologic efficacy through positive margin rates, biochemical failure rates, and subsequent salvage treatment-free rates, as well as other noncancer outcomes, such as complications and recovery of urinary and sexual function. Three trials comparing open prostatectomy to minimally invasive prostatectomy have been completed thus far. One study comparing laparoscopic prostatectomy to open prostatectomy confirmed that laparoscopic prostatectomy was associated with less blood loss and lower transfusion rates than open surgery (Guazzoni et al, 2005). Two other randomized controlled trials comparing laparoscopic prostatectomy to RALP did not demonstrate differences in perioperative outcomes, although RALP was associated with better postoperative erectile function and recovery of urinary continence than laparoscopic prostatectomy, perhaps reflecting the technical difficulty and steep learning curve associated with laparoscopic prostatectomy (Asimakopoulos et al, 2011; Porpiglia et al, 2013).

Economic Considerations

Both the duration of surgery and equipment expenses contribute to operating room costs for LRP and RALP, which typically are higher than those for open approaches (Link et al, 2004; Lotan et al, 2004; Scales et al, 2005). This is particularly true with robotic-assisted surgery. Current purchase cost of a da Vinci S system is approximately \$1.65 million, with an average cost of \$2400 for each multiple-use (10 lives) robotic instrument. For robotic instrumentation, this would translate to approximately \$1200 per case for the use of five separate robotic instruments with an additional \$325 per case for disposables (sterile robotic drapes and trocar seals).

In the study by Link and colleagues (2004), the factors that most influenced overall LRP cost in order of importance included operative time, length of hospital stay, and consumable items (e.g., disposable laparoscopic equipment and trocars). They found that the calculated cost equivalence between RRP and LRP could be met if disposable equipment was eliminated by using reusable items and operative times for LRP were reduced to 3.4 hours. Lotan and colleagues (2004) found that RALP costs were approximately \$1155 per case more than RRP if the initial purchase cost of the robot were excluded. A more recent systematic review reported that minimally invasive prostatectomy (RALP and LRP) was more costly than RRP in most studies reviewed, largely secondary to higher direct costs. For example, reported costs for minimally invasive radical prostatectomy ranged from \$5058 to \$11,806, compared to \$4075 to \$6296 for RRP (Bolenz et al, 2014). Another single-institutional study reported significantly higher operating room costs for RALP compared to RRP, and an average payment to cost differential of \$1325 for RRP and -\$4013 for RALP, indicating per case loss associated with minimally invasive prostatectomy (Tomaszewski et al, 2012). In a local cost analysis performed by Scales and colleagues (2005), they found that RALP would be less expensive than RRP in some practice settings in which RALP hospital stay was less than 1.5 days if case volumes increased to 14 cases per week. Others also have found this same inverse relationship of case volume to cost drawing from the United Kingdom National Health Service data (Close et al, 2013). These studies suggest that RALP may be more economically viable in high-volume centers.

These increased costs may be partially mitigated by shorter hospital stays compared with open surgery. The decrease in expense for hospital stay depends partly on the discharge day for the laparoscopic procedure but also the customary length of stay at a given hospital for open radical prostatectomy. Published reports detailing a length of stay of a week or more for RRP are not in concordance with other contemporary reports in which patients are discharged on the second or even first postoperative day after radical perineal or RRP (Holzbeierlein and Smith, 2000).

COMPLICATIONS

Complications Related to Patient Positioning

It is important to note that specific lower extremity neuropathies have been reported that are unique to this steep Trendelenburg positioning, especially after prolonged surgeries (Koc et al, 2012). The frequency of these lower extremity neuropathies appears to be low (1.3%) and transient. Of note, femoral nerve compromise has been described as a result of excessive hyperextension of the hip to allow for proper docking of the fourth robotic arm. This may result in compression of the femoral nerve as it courses beneath the inguinal ligament with resultant transient motor and sensory neuropathy. To minimize this complication, hyperextension at the hip should be minimized to only what is necessary for docking of the robotic arms and operative time should be kept to a minimum. Pneumoperitoneum in the steep Trendelenburg position also has been associated with a transient increase in intraocular pressure with decline to baseline pressures on returning the patient to the supine position (Awad et al, 2009). Among other potential causes, two operative variables appear to contribute significantly to this observation: including operative time (and hence higher central and orbital venous pressure) and end-tidal CO₂ level (with resultant increase in arterial CO₂ leading to choroidal vasodilation). Although the clinical effect of this transient phenomenon is unclear and generally unapparent in healthy individuals, it may pose particular concern in some elderly patients who have elevated intraocular pressures at baseline (e.g., glaucoma). It is unknown whether this effect is causally associated with the rare reports of acute visual loss after minimally invasive prostatectomy as a result of posterior ischemic optic neuropathy (Weber et al, 2007). Nevertheless, it is advisable that both surgeon and anesthesiologist inquire about preexisting ocular disease in the preoperative screening of patients who select to undergo minimally invasive prostatectomy.

Vascular and Bowel Injury

Vascular or bowel perforations are rare but can occur during placement of abdominal trocars. In addition, once safe trocar placement is established and the robot is docked, care must be taken to avoid injury along the path of the multiple instruments, which must be interchanged and directed toward the pelvis. The key to managing such major postoperative complications is prompt recognition and immediate repair of injury to bowel or blood vessels. Often, relatively minor injuries can be repaired laparoscopically, although there should be no hesitation to convert to an open approach in the face of a more complex injury.

Open Conversion

Open conversion is rare (<2%) and has been cited in the literature, usually during a surgeon's early experience with LRP or RALP, mainly as a result of failure to progress or uncertainty of dissection planes (Bhayani et al, 2004). With experience, the need for open conversion is rare; however, patients must be properly counseled on this possibility.

Rectal Injury

Rectal injuries, although uncommon during LRP and RALP (0.7% to 2.4%), have been reported and repaired successfully by laparoscopic means (Guillonneau et al, 2003b; Katz et al, 2003; Gonzalgo et al, 2005). Intraoperative recognition and repair of the injury is crucial. Multilayered primary closure with or without interposition of omentum between the rectum and anastomosis usually can avoid long-term problems, as well as the need for open conversion and intestinal diversion. Inadequate closure or lack of recognition can result in a rectourethral fistula. If a small rectal injury is suspected but not readily visible, insufflation of air into the rectum using a catheter inserted into the rectum with fluid within the pelvis

(i.e., air bubble test) often can demonstrate small bubbles at the site of the injury.

Thromboembolic Complications

The 2008 AUA Best Practices Statement recommends the routine use of intermittent pneumatic compression devices for laparoscopic and robotic urologic procedures. However, it does not recommend routine use of prophylactic anticoagulants for these procedures unless a patient has multiple known risk factors such as obesity, advanced age, malignancy, immobility, or a history of deep venous thrombosis (DVT). Nonetheless, because of the known venous stasis and hypercoagulable state that can occur during pelvic surgery in patients with known malignancy, these patients are still at risk (albeit low) for thromboembolic problems. The incidence of thromboembolic complications after LRP and RALP has been reported to be as low as 0.5%, in part as a result of faster postoperative patient mobilization and Trendelenburg positioning, which decrease venous stasis in the lower extremities compared to open surgery (Secin et al, 2008). The presentation of DVT in the lower extremities should prompt immediate anticoagulation and consideration for obtaining a pelvic computed tomography (CT) scan or ultrasonography to exclude a lymphocele, hematoma, or urinoma that could be compressing the external iliac vein, thus increasing the risk for a DVT.

Anastomotic Complications

Failure to achieve a watertight closure of the anastomosis can result in urinary extravasation and accumulation of urine even if a pelvic drain is placed. This is even more problematic with a transperitoneal approach because the entire abdominal cavity becomes accessible for urine egress. In such cases a cystogram should be performed to make certain there is some degree of integrity of the anastomosis. Fluid accumulation may require percutaneous drainage. Most small anastomotic leaks will resolve spontaneously with prolonged urethral catheter drainage. If complete disruption of the anastomosis has occurred, surgical revision—laparoscopic, robotic, or open—is indicated if the problem is recognized in the first few days after surgery.

Anastomotic stricture resulting in bladder neck contracture seemingly occurs at a lower rate after LRP and RALP compared with open surgical approaches, especially in the hands of experienced surgeons. Rates of less than 2% have been reported (Msezane et al, 2008; Webb et al, 2009). This implies that achievement of a watertight anastomosis with good mucosal approximation is the key measure in preventing postoperative bladder neck contracture.

Bleeding and Transfusion

Virtually all published reports have documented a distinct advantage for laparoscopic surgery in diminishing the amount of bleeding that occurs with radical prostatectomy. Transfusion requirements of 2% or less are commonly reported (Ficarra et al, 2009a). The tamponade effect of the pneumoperitoneum compresses venous bleeding, and the superb visualization allows prospective identification of bleeding vessels that require hemostasis. However, in addition to the risk for major vascular injury from the surgical dissection or trocar placement, there is the possibility of postoperative bleeding once the pneumoperitoneum is relieved. As mentioned previously, the pelvis and surgical field should be carefully inspected for the presence of bleeding at the end of the operation under low insufflation pressure. Because of the low incidence of postoperative bleeding, though, routine use of topical hemostatic agents along the prostate bed is not generally required.

Equipment Malfunction

The surgeon is highly dependent on sophisticated technology and equipment for performance of LRP and, in particular, RALP. Equipment malfunction, especially with RALP, can create problems that

make it difficult to progress with surgery and may result in case cancellation or conversion to pure laparoscopic or even open surgery. Zorn and colleagues (2007) identified recoverable errors in 0.4% of RALP cases performed at their institution. Lavery and colleagues (2008) found a 0.4% nonrecoverable malfunction rate in their multi-institutional study of high-volume RALP centers. Although the possibility of conversion to a pure laparoscopic or open surgical approach in the event of an unrecoverable equipment malfunction is extremely rare, patients need to be properly counseled in regard to this.

KEY POINTS: RESULTS AND COMPLICATIONS OF LAPAROSCOPIC AND ROBOTIC-ASSISTED LAPAROSCOPIC RADICAL PROSTATECTOMY

- Blood loss and transfusion rates are generally lower with LRP and RALP compared with open surgery and is in part attributed to improved visualization with anticipation of bleeding and the tamponade effect of pneumoperitoneum.
- Operative times are initially longer with minimally invasive approaches compared to open surgery but comparable once experience is gained.
- Excellent postoperative urinary continence is routinely achieved after LRP and RALP owing to the minimal bleeding and magnification of the operative field, allowing precise dissection of the prostatic apex with limited trauma to the periurethral striated sphincter in addition to the ability to reliably accomplish a tension-free, watertight anastomosis.
- Published comparative studies suggest comparable and in some cases superior potency outcomes with RALP compared to RRP in experienced hands.
- Stage- and risk-stratified positive surgical margin and early biochemical-free recurrence rates appear to be comparable among LRP, RALP, and RRP at experienced centers.
- Higher costs are still a concern, especially with the robotic-assisted approach, but may be partially offset but shorter hospital stays and higher case volumes.
- Increased intraocular pressure and rare cases of femoral neurapraxia have been reported, especially in prolonged cases with patients in the steep Trendelenburg position.
- Thromboembolic events, open conversion rectal injury, transfusion, and equipment malfunction are rare events with both LRP and RALP.

ROBOTIC SALVAGE PROSTATECTOMY

Biopsy-proved persistence or recurrence of cancer within the prostate after definitive nonsurgical treatments is a particularly challenging situation. Salvage surgery can be beneficial in selected patients but is associated with a significantly higher complication rate than with patients not previously treated. In particular, the incidence of urinary incontinence, erectile dysfunction, bladder neck contracture or anastomotic leak, and rectal injury is higher with salvage surgery. Nonetheless, surgical removal of the prostate offers a potentially curative option after failure of prior therapy and may have application in selected patients previously treated with radiation whether by external-beam, brachytherapy, or proton beam. In addition, patients treated with cryotherapy or high-intensity focused ultrasonography may be eligible for robotic salvage prostatectomy. Historically, salvage prostatectomy was performed relatively infrequently secondary to the technical challenges and the desmoplastic reaction caused by prior treatments. An additional concern was the relatively high reported rate of rectal injuries of more than 15% in some open salvage prostatectomy series (Chen and Wood, 2003). Despite this, in experienced hands robotic salvage prostatectomy has been shown to be feasible and safe in several reported series, with early outcomes comparable to those with open surgery (Kaouk et al, 2008; Boris et al, 2009; Chauhan et al, 2011; Kaffenberger et al, 2013; Yuh et al, 2014).

Patients most suitable for robotic salvage prostatectomy are those with biopsy-proved persistent cancer but with no evidence of disease outside the prostate. Considering the potential morbidity of the operation, proper selection of patients who may benefit from surgery is paramount. **Ideally, PSA should be less than 10 ng/mL because values above that level, especially in a previously treated patient, may indicate a high likelihood of extraprostatic disease.** A CT scan and bone scan should be obtained to assess for distant disease even in patients with relatively low PSA when considering salvage prostatectomy. In addition, patients should have a life expectancy of 10 years or more to derive benefit from surgery. Preoperative preparation is similar to that in patients undergoing standard RALP. Of note, a bowel preparation with magnesium citrate and Fleet enema the day before surgery is advisable given a potential higher risk for rectal injury.

Surgical Technique

Development of the extraperitoneal space along the pelvic sidewall, as well as the space of Retzius, can be more difficult in patients previously treated with external-beam irradiation. Caution must be used in dissecting the bladder from the iliac vessels because of the desmoplastic reaction that is often encountered. These tissue planes typically are preserved in patients who received brachytherapy, cryotherapy, or high-intensity focused ultrasonography.

Incision of the endopelvic fascia is performed to help identify the contour of the prostate. Suture control of the deep DVC may be best avoided as an initial step because clear identification of the prostatic apex can be difficult at this point and only minimal back-bleeding occurs. The bladder neck is identified primarily by exposing the lateral margins of the prostate and performing a pinch maneuver with the robotic instruments to demonstrate the prostate–bladder neck junction. The bladder neck may be pale and thickened. Administration of indigo carmine can help identify the ureteric orifices along the bladder trigone, which may be obscured by the fibrosis. Complete dissection of the seminal vesicles should be performed, because the incidence of invasion may be higher in patients with recurrent prostate cancer.

Even though typically there is fibrosis surrounding the entire prostate in a salvage setting, the posterior dissection can be the most difficult because of periprostatic inflammation and scarring as a result of prior treatment effect and the concern of rectal injury. The plane posterior to Denovilliers fascia, however, is typically well preserved, especially near the bladder neck. This facilitates dissection in the perirectal fat plane along the anterior rectal wall to minimize the risk for rectal injury but also to provide good mobilization of the posterior prostate and identification of the prostatic pedicle. A distinct advantage of a laparoscopic (vs. open) approach to salvage prostatectomy is the ability to perform antegrade release of the rectum from the posterior prostate under direct and magnified vision. Dissection in this plane should be performed using primarily sharp dissection with scissors. Blunt separation of tissues should use only minimal tension, and cautery is neither necessary nor advisable. Especially toward the prostatic apex, the dissection becomes even more crucial. This is the area of closest proximity between the rectal wall and the prostate and often the one with the most fibrosis. Despite this, using an antegrade approach, the tissues usually are well visualized so that the dissection can be performed sharply and safely. Often, the titanium capsules used with brachytherapy seeds are encountered during this portion of the dissection.

The deep DVC and the prostatic apex are better identified after the prostate has been mobilized. If the adhesions around the DVC are dense, it is preferable to simply incise the tissue sharply and place a hemostatic suture as required. The prostatourethral margin then should be readily identified and incised. Completion of the anastomosis is performed in the same manner as with a patient not previously treated, but the periurethral tissues may be quite pale and fibrotic. It becomes even more imperative to have a watertight mucosa-to-mucosa approximation.

Complications and Postoperative Care

The rectum should be carefully inspected after specimen removal. **An air bubble test can be performed to localize a small rectal injury that is suspected but is not visibly apparent.** A rectal injury can be repaired primarily, but it is essential that the repair be secure. Omentum may be mobilized to interpose between the bladder and rectum. If the quality of the repair is in doubt, a diverting colostomy should be performed.

The Foley catheter should be left indwelling for at least 2 weeks because of delayed healing with previously treated tissue. A cystogram may be useful to ensure complete anastomotic healing before catheter removal. Bladder neck contracture occurs less frequently than with open salvage prostatectomy but still may be observed and may manifest within a few weeks of catheter removal.

Incontinence occurs at a higher rate in the salvage setting even though most patients do regain complete or at least adequate urinary control. A nerve-sparing procedure to preserve erectile function, although feasible, is often technically difficult owing to the desmoplastic reaction along the periphery of the prostate. **Keeping in mind that the primary intent of salvage prostatectomy is curative, any attempt at preservation of the cavernous nerves should be approached with caution because of difficulty in assessing accurately the local tumor extent beyond the prostate.** Furthermore, the patients suitable for salvage prostatectomy are more likely to already have preexisting erectile dysfunction because of their prior treatment.

KEY POINTS: ROBOTIC SALVAGE PROSTATECTOMY TECHNIQUE AND COMPLICATIONS

- Robotic salvage prostatectomy is associated with a significantly higher complication rate than with patients not treated previously.
- Robotic salvage prostatectomy can be safely performed in selected patients who fail previous treatment, including prior external-beam radiotherapy, brachytherapy, cryotherapy, and high-intensity focused ultrasonography.
- Patients considering salvage prostatectomy ideally should have a PSA less than 10 ng/mL.
- A CT and bone scan should be obtained, and patients should have a life expectancy of 10 years or more, to derive benefit from salvage prostatectomy.
- A distinct advantage of a laparoscopic approach to salvage prostatectomy is the ability to perform antegrade release of the rectum from the posterior prostate under direct and magnified vision.
- Because of difficulty in accurately assessing the local tumor extent beyond the prostate, attempt at cavernous nerve preservation during robotic salvage prostatectomy should be approached with caution keeping in mind that the primary intent is cancer control.
- An air bubble test can be performed to localize a small rectal injury that is suspected but is not visibly apparent.

LAPAROSCOPIC PELVIC LYMPH NODE DISSECTION

Indications

Currently, PLND is rarely indicated as an independent staging procedure. In some patients with a significant risk for nodal metastasis, such as those with a high Gleason grade tumor, a large tumor volume, or a markedly elevated PSA level, PLND may be useful for staging and selection of therapy before external-beam irradiation. Also, staging PLND may have a role in some patients in whom radical perineal prostatectomy is planned. With RRP, LRP, or RALP, it is the usual practice that PLND be performed simultaneously with the radical prostatectomy.

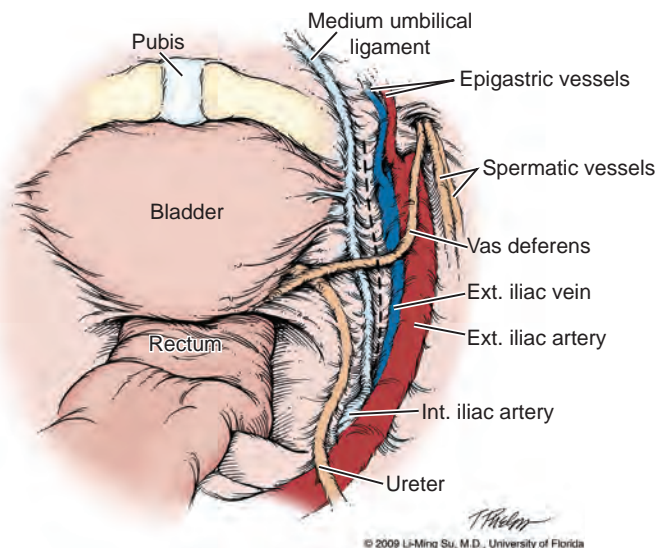


Figure 115-19. Laparoscopic pelvic lymph node dissection. Initial transperitoneal view of the obturator fossa and relevant anatomy. The dashed line indicates the longitudinal incision that is made in the peritoneum lateral and parallel to the median umbilical ligament back toward the bifurcation of the iliac vessels in efforts to provide exposure to the obturator fossa and lymph nodes. Ext., exterior; Int., interior. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

Expert opinion about the role of PLND in patients undergoing surgery for carcinoma of the prostate is evolving. Current debate centers around the anatomic boundaries for the procedure, the merits of an extended lymph node dissection, and whether there is any meaningful clinical (i.e., therapeutic) benefit to surgical removal of involved nodes. Most studies show histologic evidence of nodal metastasis in less than 5% of patients with low-risk features in the primary tumor. Consequently, PLND may not be required in patients with clinically localized prostate cancer with PSA less than 10 ng/mL and Gleason score of 6 or less based on the AUA 2013 Revised Best Practice Statement.

PLND is generally recommended in patients with intermediate- or high-risk parameters of the primary tumor, generally implying a PSA of greater than 10, a large palpable nodule, or a Gleason sum of 7 or greater. Historically, a limited or “standard” node dissection has been used by many surgeons. Most contemporary thought and evidence supports an extended node dissection in cases in which node dissection is indicated. The rationale for this approach is a significantly higher yield of nodal tissue and identification of nodal metastasis with extended versus a standard dissection.

Surgical Technique

In laparoscopic staging PLND, trocar configuration is similar to that for LRP and RALP but only one assistant trocar is generally necessary. Abdominal access is established, and an incision is made just lateral to the medial umbilical ligament back toward its confluence with the hypogastric artery and down to the pubis (Fig. 115-19). Great care must be taken to avoid injury to the nearby ureter. If PLND is performed during LRP or RALP, the dissection is simplified because previous mobilization of the bladder provides excellent exposure of the obturator space.

As with an open approach, a key initial step to standard laparoscopic PLND is separation of the nodal packet from the external iliac vein. The lymph node packet is grasped and retracted medially. A relatively avascular plane between the lymph node packet and lateral pelvic sidewall is identified and can be dissected bluntly. Dissection is carried out proximally to the iliac bifurcation and distally to the pubis, thus defining the lateral extent of the lymph

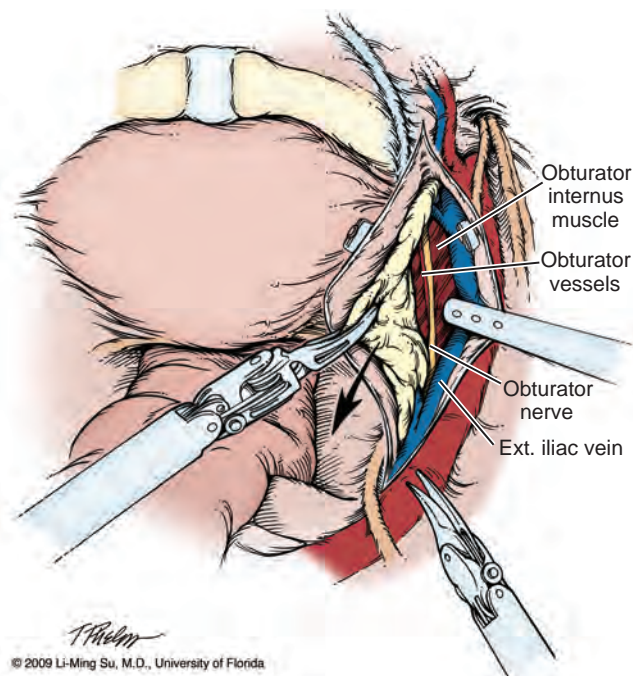


Figure 115-20. Initial dissection of a standard pelvic lymph node template. The vas deferens has been clipped and divided. With medial traction on the lymph node packet, the lateral extent of the dissection is defined using mainly blunt dissection. Ext., exterior. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

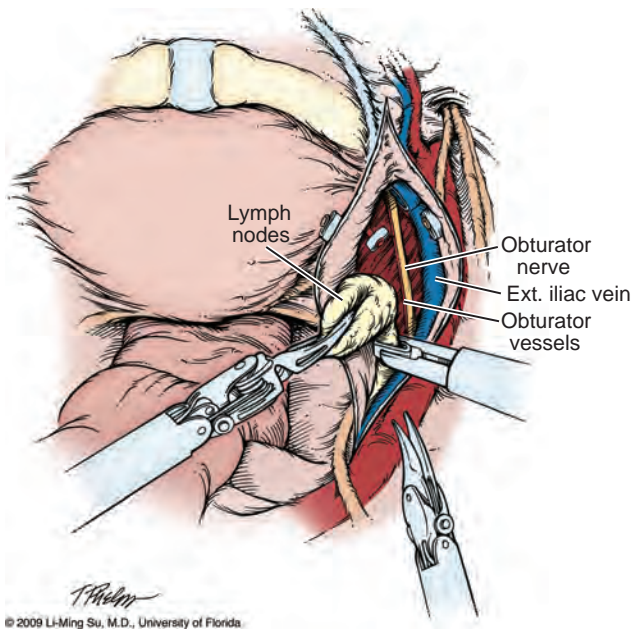


Figure 115-21. Final dissection of a standard pelvic lymph node template. The proximal and distal extent of the lymph node packet are clipped and divided, taking great care to avoid injury to the obturator nerve and vessels, as well as the accessory obturator vein. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

node packet. By retracting the lymph node packet medially, the precise course of the obturator nerve and vessels can be identified and protected (Fig. 115-20). After securing the distal extent of the lymph nodes with hemoclips, the packet is divided, retracted cranially, and bluntly separated from the obturator vessels and nerve by blunt dissection. Hemoclips are again placed on the proximal extent of the lymph node packet (Fig. 115-21). The lymph nodes

usually can be removed as a single packet and extracted either through the 12-mm trocar or by placing them in the entrapment sack along with the prostate specimen.

Some controversy remains about the precise anatomic boundaries of an extended node dissection for patients with prostate cancer. Commonly, though, the boundaries are 2 cm cephalad to the bifurcation of the common iliac artery at the point where the ureter crosses over the vessels and distally to the node of Cloquet. The lateral margin should be the genitofemoral nerve, and the medial border is the bladder wall. Complete removal of all nodal tissue surrounding the obturator nerve is essential, and the bladder pedicle should be skeletonized. Presacral nodes often are included with an extended dissection. Extended lymph node dissection can be performed laparoscopically and robotically. The da Vinci Si system allows more proximal angulation of the instruments, and this can significantly facilitate dissection around the bifurcation of the common iliac artery. A thorough dissection adds time to the surgical procedure, but this is true regardless of whether laparoscopic, robotic, or open surgery is performed.

No valid comparative studies exist to support the superiority of open versus laparoscopic PLND. Using lymph node count as a surrogate for adequacy of the dissection is problematic because the method and thoroughness of pathologic evaluation is perhaps even more influential than the anatomic extent of the surgical dissection. With careful attention to meticulous dissection, though, all of the fibrous, fatty, and lymphatic tissue within the commonly accepted anatomic boundaries for an extended lymph node dissection can be removed laparoscopically or robotically. Use of clips on identifiable lymphatic channels can minimize the occurrence of a postoperative lymphocele.

Complications

Because, by definition, PLND requires skeletonization of portions of the common iliac, external iliac, and hypogastric arteries and veins, the possibility of major vascular injury exists. A small venotomy or arteriotomy can be closed laparoscopically with a fine polypropylene (Prolene) suture. A major injury may require rapid conversion to an open approach. However, the incidence of major vascular injury resulting in enough bleeding to require transfusion is well under 1% with PLND.

Transection of the obturator nerve may occur. Direct repair with suturing of the ends of the obturator nerve can restore partial function. Ureteral injury is uncommon, but caution must be observed during the proximal portion of the dissection as the ureter crosses the anterior portion of the common iliac artery.

A transperitoneal approach is not protective against the formation of a lymphocele. Theoretically, the communication with the entire peritoneum would allow distribution and absorption of any lymphatic fluid throughout the peritoneal lining of the abdomen and decrease the risk for lymphocele. Despite this, however, a loculation of lymphatic fluid can occur. Asymptomatic lymphoceles do not necessarily require drainage or treatment. A larger collection can compress the bladder and cause new-onset or worsening irritative voiding symptoms. Compression of the external iliac vein can predispose a patient to DVT in the lower extremity. Secondary infection of lymphoceles also may occur. In the presence of symptoms or complications from a lymphocele, temporary placement of a percutaneous drain is typically successful. However, lymphatic fluid can reaccumulate, requiring repeat drainage with injection of a sclerosing agent or surgical opening of a window with marsupialization of the lymphocele wall by laparoscopic means.

SUMMARY

Over the past decade, LRP and RALP have become accepted surgical approaches for the management of patients with localized carcinoma of the prostate both in the United States and abroad. As expertise with these procedures is achieved, operative times

KEY POINTS: LAPAROSCOPIC PELVIC LYMPH NODE DISSECTION AND COMPLICATIONS

- PLND is generally recommended in patients with intermediate- or high-risk parameters of the primary tumor, generally implying a PSA of greater than 10, a large palpable nodule, or a Gleason sum 7 or higher.
- Although an extended PLND may yield a higher lymph node count, debate continues as to the extent of PLND and the clinical benefit of removing cancerous nodes.
- Use of clips on identifiable lymphatic channels can minimize the occurrence of postoperative lymphoceles.
- A transperitoneal approach is not protective against the formation of a lymphocele because loculation of lymphatic fluid can still occur within the peritoneal cavity.
- Symptomatic lymphoceles, which cause local problems such as venous or bladder compression, may require percutaneous or laparoscopic drainage.

diminish, with times similar to that for RRP. The robotic-assisted technique provides ergonomic advantages for the surgeon and facilitates suturing and other technical aspects of the operation for surgeons who do not have highly advanced laparoscopic skills.

Comparison of outcomes between reported series is imprecise because of differences in patient selection, methods of collecting and reporting data, and the technique of pathologic sectioning and analysis. However, intraoperative blood loss with LRP and RALP has been consistently reported as minimal and transfusion is required in only a small percentage of patients. Postoperative morbidity and return to activity are both improved compared with open surgery in most reports. Good results with postoperative urinary continence and erectile function are reported with mature LRP and RALP series and appear comparable and in some cases superior to RRP when performed by experienced surgeons. Pathologic tumor margin status and early biochemical recurrence rates seem to be comparable among laparoscopic, robotic, and open series overall (Parsons and Bennett, 2008; Ficarra et al, 2009a; Tewari et al, 2012; Silberstein et al, 2013).

Improvements in the available instruments are highly likely to advance even further the technologic capabilities of surgeons performing LRP and RALP. Equipment expense, especially with RALP, remains a significant issue for some hospitals, and not all may be able to offer this state-of-the-art technology. Nonetheless, there seems to be little doubt that minimally invasive approaches for radical prostatectomy, especially RALP, have become the dominant surgical treatment for localized prostate cancer in the United States and are having continued growth and acceptance worldwide.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Historical Perspective

HISTORICAL PERSPECTIVE

Two major advances in the radiotherapeutic management of adenocarcinoma of the prostate have occurred since the early 1980s. The first advance was the generation of linear accelerators and conformal techniques capable of delivering high doses of radiation deep within the pelvis while simultaneously respecting the normal tissue tolerance of the anterior rectal wall, prostatic urethra, femoral heads, and bladder neck. The second advance occurred when image-guided techniques were introduced for use during the insertion of radioactive sources directly into the prostate gland. Eliminating the former freehand technique has vastly improved the physician's ability to deliver high doses of radiation to the prostate gland while sparing interposed and juxtaposed normal structures. These two advances have increased the therapeutic ratio of radiation therapy (RT) in the management of prostate cancer. Specifically, decreased gastrointestinal (GI) toxicity has been documented (Deamaley et al, 1999) and improved cancer control has been suggested (Pollack et al, 1999).

The physical property that permits the photon radiation generated from a linear accelerator to penetrate deeply and spare normal tissue is the high energy of the beam. As the energy of the beam increases, the beam penetrates deeper before exerting its cytotoxic effect. Whereas orthovoltage and cobalt-60 units deposited their maximum dose within 1.25 cm below the skin surface, high-energy linear accelerators deliver the maximum dose of radiation at more than 15 cm below the skin surface. In addition, the use of multiple and conformal fields, as well as intensity-modulated and image-guided RT (Jani et al, 2003), has minimized the amount of rectum receiving the high-dose radiation volume, leading to lower rates of radiation-induced proctitis (Pollack et al, 1999).

With respect to image guidance and brachytherapy, transrectal ultrasonography (TRUS) has provided an improved monitoring system compared with freehand or fluoroscopically guided radioactive source deposition. Using this image guidance system, geometric feedback on source location within the prostate gland intraoperatively has provided the potential for delivering high doses of radiation within the prostate gland while limiting dose to the prostatic urethra and the anterior rectal wall. The theoretical advantage of brachytherapy is the physical property of rapid dose falloff (a few millimeters) because of the low energy of the radioactive sources used—only 21 and 28 keV for palladium-103 and iodine-125, respectively. This rapid falloff, however, also mandates millimeter precision in the placement of these sources to ensure that the tumor-bearing regions within the prostate gland are not underdosed. These issues are discussed in more detail in the brachytherapy sections.

In brief, the close of the 20th century saw the introduction of three-dimensional, conformal-based, image-guided RT using high-energy radiation beams and image guidance for the placement of permanent radioactive sources into the prostate gland. As discussed

Localized Disease

in this chapter, these advances in the radiotherapeutic management of adenocarcinoma of the prostate provided the basis for improvement in both quality of life and cancer control.

LOCALIZED DISEASE

Pretreatment Prognostic Factors

Recommendations for the treatment of clinically localized adenocarcinoma of the prostate should be made using the results of evidence-based medicine. Pretreatment prognostic factors have established roles in predicting outcome after external-beam RT (EBRT) (Pisansky et al, 1993; Zietman et al, 1994; Hanks et al, 1995; Lee et al, 1995; Zagars et al, 1995; Pisansky et al, 1997). These standard pretreatment factors include **prostate-specific antigen (PSA) level, biopsy Gleason grade, and American Joint Commission on Cancer Staging (AJCC) clinical stage**. Combining these three factors led to a definition of the three risk groups for patients managed with RT who have clinically localized disease. These three risk groups are as follows:

- **Low risk:** More than 85% 5-year PSA failure-free survival, AJCC clinical stage T1c-T2a and PSA level of 10 ng/mL or lower, and biopsy Gleason grade of 6 or lower.
- **Intermediate risk:** Approximately 50% 5-year PSA failure-free survival, AJCC clinical stage T2b or PSA higher than 10 ng/mL but no higher than 20 ng/mL, or biopsy Gleason grade of 7.
- **High risk:** Approximately 33% 5-year PSA failure-free survival, AJCC clinical stage T2c or PSA higher than 20 ng/mL, or biopsy Gleason grade of 8 or more; patients having at least clinical stage T3a disease are grouped with high-risk patients with localized disease.

Figure 116-1 shows 5-year actuarial data for 473 patients stratified using the clinical risk groups based on pretreatment PSA, biopsy Gleason grade, and AJCC clinical stage.

Pretreatment Risk Groups and Prostate Cancer-Specific Mortality

Data (D'Amico et al, 2003) now exist to support the significant association of the pretreatment risk groups and prostate cancer-specific mortality (PCSM) after EBRT, as shown in Figure 116-2. Specifically, in a multi-institutional study of 2370 radiation-managed patients, the relative risk of PCSM for patients with high-risk or intermediate-risk disease compared with low-risk disease was 14.3 (95% confidence interval [CI] 5.2 to 24.0, $p_{\text{Cox}} < .0001$) and 5.6 (95% CI 2.0 to 9.3, $p_{\text{Cox}} = .0012$), respectively. For illustration, Figure 116-3 contains the relative contribution of PCSM and non-PCSM after treatment to all-cause mortality stratified by the patients' age at the time of RT and the pretreatment risk group. These findings

have been validated by others at Johns Hopkins (Hernandez et al, 2007) and the Mayo Clinic (Boorjian et al, 2008).

Further Stratification of Intermediate Risk into Favorable and Unfavorable

The fraction of prostate biopsy samples found to contain prostate cancer is readily available information for all patients with PSA-

detected or clinically palpable prostate cancer. The fraction of positive biopsy results is obtained by dividing the number of positive cores by the number of cores sampled. Studies investigating the ability of the fraction of positive prostate biopsies $\times 100$ (percentage of positive biopsies) to predict pathologic end points after RT suggest a role for this clinical factor in predicting tumor volume (Terris et al, 1995), extracapsular extension (Badalament et al, 1996; Borirakchanyavat et al, 1997), seminal vesicle invasion (D’Amico et al, 1996), lymph node involvement (Conrad et al,

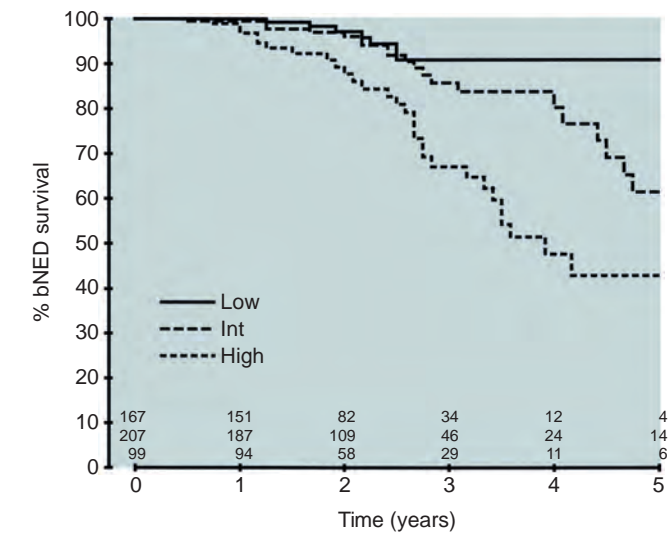


Figure 116-1. Prostate-specific antigen (PSA) failure-free survival stratified by risk group, defined using PSA value, biopsy Gleason grade, and 1992 American Joint Commission on Cancer Staging clinical T stage for 473 patients managed using external-beam radiation therapy. Pairwise, *P* values are as follows: low versus intermediate, *P* = .02; intermediate versus high, *P* = .0004; low versus high, *P* = .0001. bNED, biochemically no evidence of disease; Int, intermediate.

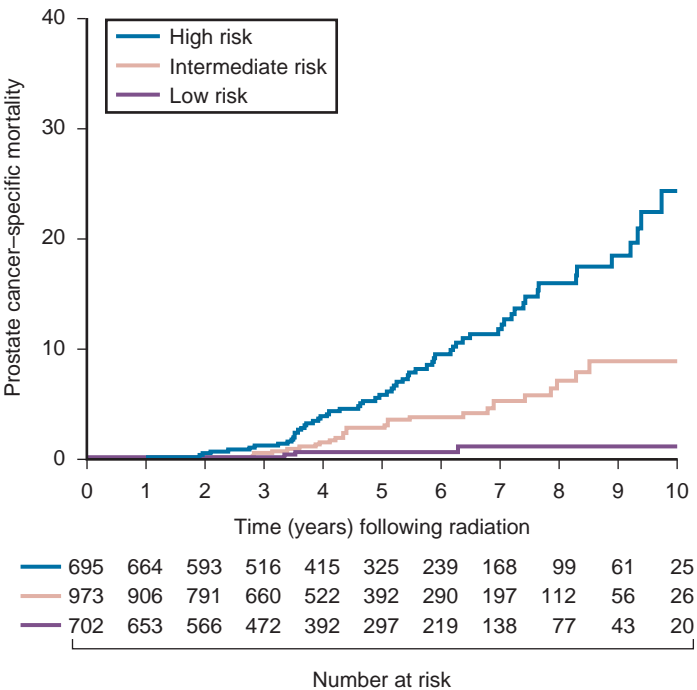


Figure 116-2. Pretreatment risk groups and prostate cancer-specific mortality after external-beam radiation.

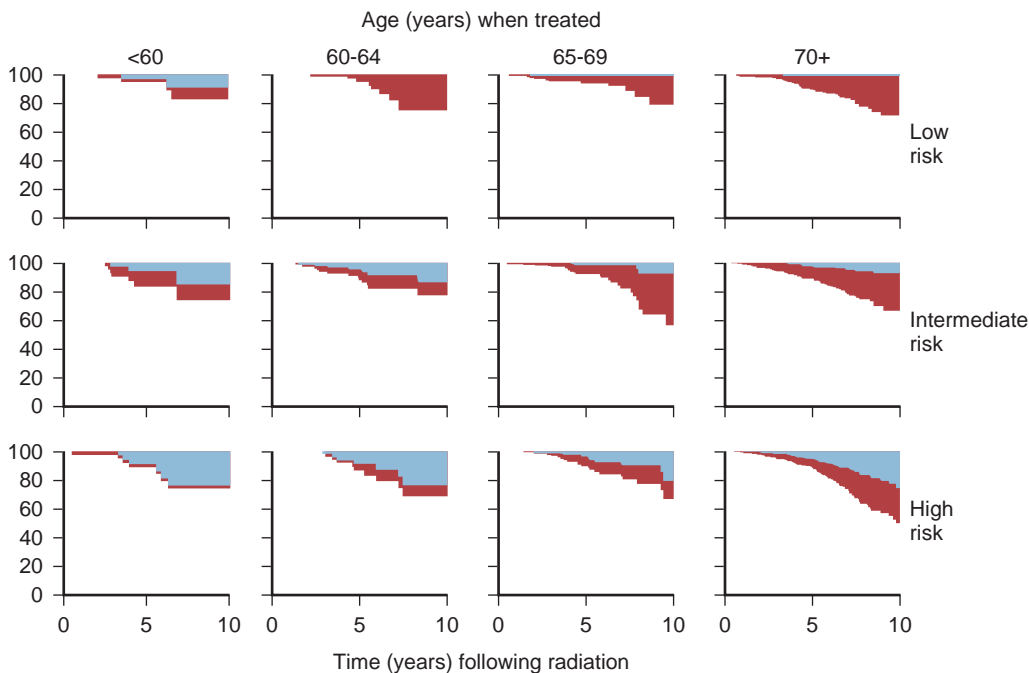


Figure 116-3. Relative contribution of prostate cancer-specific mortality (PCSM) and non-PCSM after treatment to all-cause mortality stratified by the patients' age at the time of radiation therapy and the pretreatment risk group.

1998), and percentage of Gleason grade 4 and 5 disease in the radical prostatectomy specimen (Epstein et al, 1994).

The percentage of positive prostate biopsy specimens has been shown to be an independent predictor of time to postoperative PSA failure after controlling for the established prognostic factors (D'Amico et al, 2000). The percentage of positive prostate biopsy specimens also has been shown to provide information in addition to the known prognostic factors for predicting PSA control after EBRT. Specifically, 473 men treated using three-dimensional (3D) conformal EBRT at the Joint Center for Radiation Therapy between 1989 and 1998 had detected PSA or clinically palpable prostate cancer. Figure 116-1 illustrates the ability of the previously described risk group system (D'Amico et al, 1998b) that was based on pretreatment PSA level, biopsy Gleason grade, and AJCC clinical stage to stratify patients according to PSA outcome. Specifically, 5 years after RT, 91%, 62%, and 43% of low-risk, intermediate-risk, and high-risk patients, respectively, had not experienced PSA failure as defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Panel (1997).

Figure 116-4 illustrates the clinically relevant stratification provided by the percentage of positive biopsy results in the previously defined intermediate-risk group on the basis of pretreatment PSA level, biopsy Gleason grade, and AJCC clinical stage. Specifically, patients in the intermediate-risk subgroups who also had less than 34% of the positive biopsy samples improved their risk stratification for PSA outcome by one category to low risk. Conversely, patients with more than 50% of positive biopsy samples performed less well than expected and were comparable with the high-risk patients.

Of particular importance, however, is that the majority of patients (158 of 207 [76%]) in the intermediate-risk group could be classified into either a 30% or an 85% 5-year PSA control high-risk or low-risk cohort, respectively, using the preoperative prostate biopsy data. Therefore, of the 473 study patients, all but 49 (10%) were classified into high-risk or low-risk groups regarding PSA outcome after RT, using the percentage of positive prostate biopsy results, PSA level, biopsy Gleason grade, and AJCC clinical stage.

Additional methods of stratifying intermediate risk into favorable and unfavorable have been proposed. Investigators from MD Anderson performed recursive partitioning analysis to divide radiation-managed intermediate-risk patients into subcategories and found those with Gleason 4+3 or clinical T2c were in an unfavorable group that had a 4.6 times higher risk for clinical or bio-

chemical failure than those with favorable intermediate risk (Gleason 6 and up to cT2b or Gleason 3+4 and cT1c) (Castle et al, 2013). A study from Memorial Sloan Kettering defined unfavorable intermediate risk as any patient having Gleason 4+3 or percentage of positive biopsy results of 50% or greater, or multiple intermediate risk factors (Gleason 7, PSA level of 10 to 20 ng/mL, cT2b/c) and noted a hazard ratio for prostate-cancer mortality of 7.39 ($P = .007$) compared with patients with favorable intermediate risk (Zumsteg et al, 2013).

Of note, a Harvard study also identified having two or more high-risk factors as a way of separating very high risk from standard high risk, with the former having a 4.8 times ($P < .001$) greater risk for prostate-cancer mortality than the latter (Wattson et al, 2012).

Percentage of Positive Prostate Biopsy Results and Prostate Cancer-Specific Mortality in Low-Risk and Favorable Intermediate-Risk Patients

With longer follow-up, the impact of the percentage of prostate positive biopsy findings on prostate cancer-specific mortality in low-risk and favorable intermediate-risk patients has become available (D'Amico et al, 2004). Specifically, from a series of 421 patients with low-risk (PSA ≤ 10 ng/mL and biopsy Gleason score ≤ 6) or favorable intermediate-risk (PSA > 10 to 15 ng/mL or biopsy Gleason score 7, but not both factors) disease who underwent 3D conformal radiation therapy (3DCRT) to a median dose of 70.4 Gy, a significant association between PCSM and the percentage of positive prostate biopsy samples at diagnosis was documented. In particular, the relative risk for PCSM after 3DCRT for patients with 50% or more compared with less than 50% prostate positive biopsy samples was 10.4 (95% CI 1.2 to 87, pCox = .03), 6.1 (95% CI 1.3 to 28.6, pCox = .02), and 12.5 (95% CI 1.5 to 107, pCox = .02) in men with a PSA of 10 ng/mL or less and Gleason score 6 or less, PSA of 10 ng/mL or less and Gleason score 7 or less, and PSA of 15 ng/mL or less and Gleason score 6 or less, respectively. By 5 years after 3DCRT, up to 10% as compared with 2% or less (log-rank $P \leq .01$) of these patients experienced PCSM if they had 50% or more compared with less than 50% prostate positive biopsy samples as shown in Figures 116-5, 116-6, and 116-7. For the purpose of illustration, Figure 116-8 contains the relative contributions of PCSM and non-PCSM after treatment to all-cause mortality stratified by the percent of positive prostate biopsy samples (<50% vs. $\geq 50\%$) and the PSA level and biopsy Gleason score at diagnosis.

Therefore the percentage of positive prostate biopsy results should be considered in conjunction with the PSA level, the biopsy Gleason grade, and AJCC clinical stage at diagnosis when counseling patients with newly diagnosed and clinically localized prostate cancer about both PSA outcome and, more important, the chance of avoiding PCSM after RT.

Pretreatment Prostate-Specific Antigen Velocity and the Risk for Prostate Cancer-Specific Mortality

Studies have documented that a pretreatment PSA velocity greater than 2 ng/mL/year is associated with an increased risk for biochemical recurrence, metastasis, and cancer-specific death after treatment with RT or RT and hormonal therapy (D'Amico et al, 2005; Palma et al, 2008). In particular, in men with otherwise low-risk disease undergoing EBRT, a pretreatment PSA velocity greater than 2 ng/mL/year increased the risk for death from prostate cancer x-fold, which translated into 19% (95% CI 2 to 39) compared with 0% of men dying of prostate cancer within 7 years after treatment with RT if the PSA velocity was more than as compared with 2 ng/mL/year or less, respectively. As a result, such men planning to undergo RT should be considered for RT and hormonal therapy because of the known survival benefit when adding hormonal therapy to RT in men with locally advanced (Pilepich et al, 1995, 1998, 2001; Bolla et al, 2002) or localized high-risk disease (D'Amico et al, 2008).

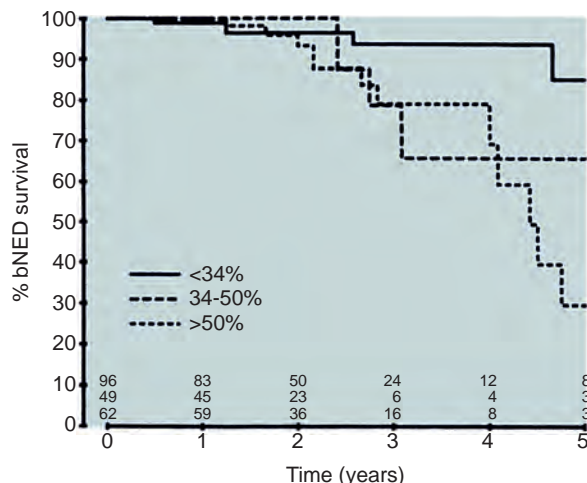


Figure 116-4. Prostate-specific antigen failure-free survival stratified by percentage of positive biopsies for 207 intermediate-risk patients managed using external-beam radiation therapy. Pairwise, P values are as follows: 34% versus greater than 34% to 50%, $P = .02$; greater than 34% to 50% versus greater than 50%, $P = .06$; 34% versus greater than 50%, $P = .002$. bNED, biochemically no evidence of disease.

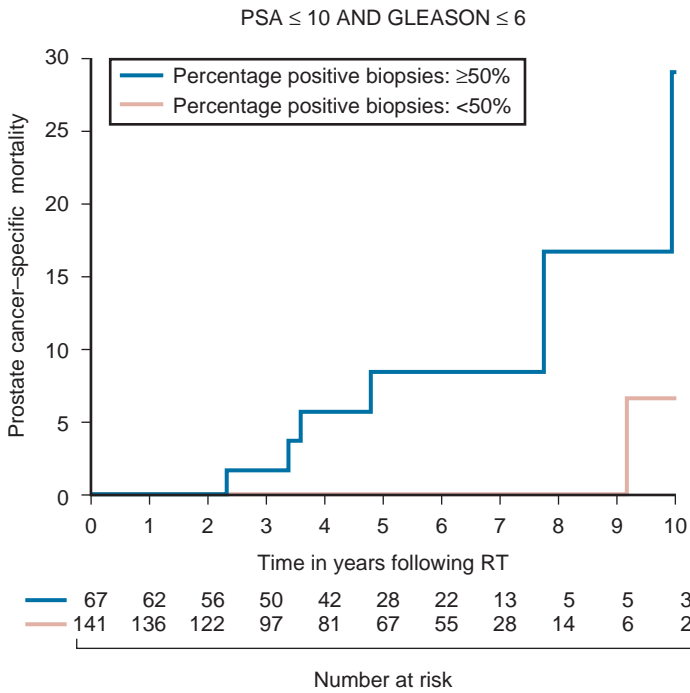


Figure 116-5. Prostate cancer-specific mortality following three-dimensional conformal radiation therapy for patients with 50% or more as compared with less than 50% prostate positive biopsy in men with a prostate-specific antigen (PSA) of 10 or less and Gleason score of 6 or less. RT, radiation therapy.

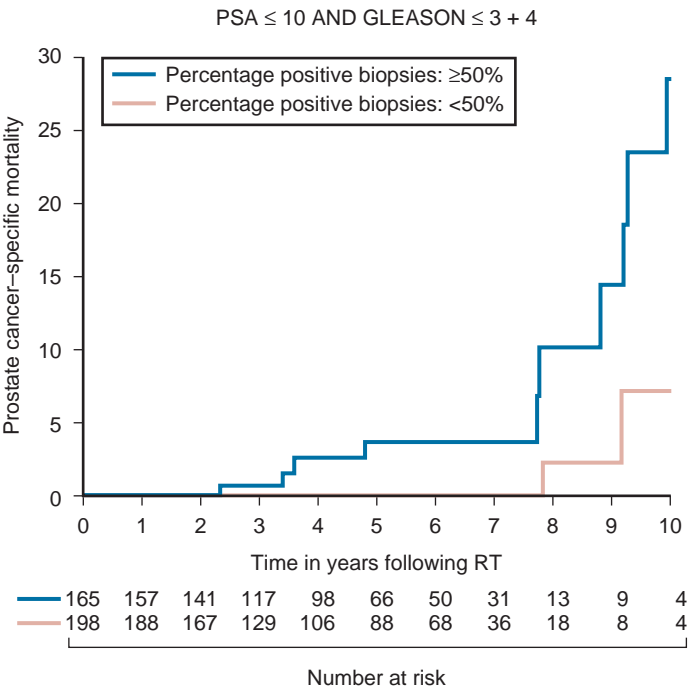


Figure 116-7. Prostate cancer-specific mortality following three-dimensional conformal radiation therapy for patients with 50% or more as compared with less than 50% prostate positive biopsy in men with a prostate-specific antigen (PSA) of 10 or less and Gleason score of 7 or less. RT, radiation therapy.

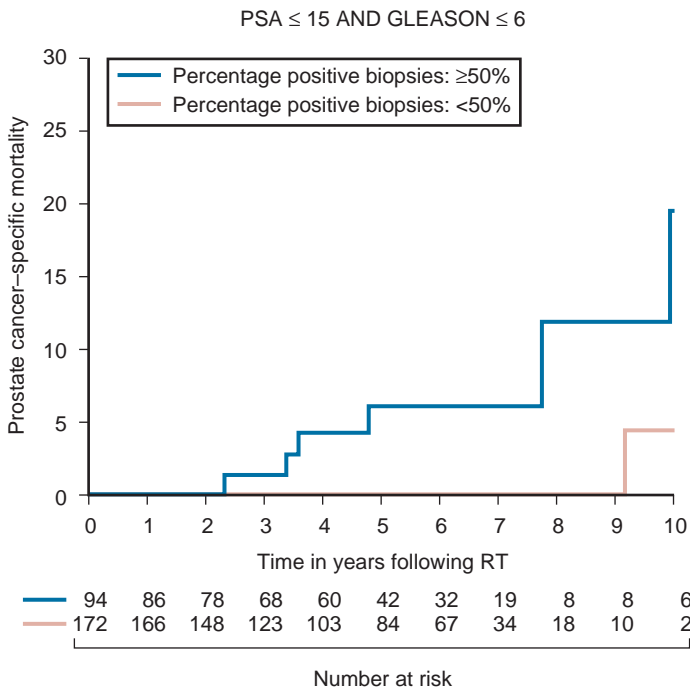


Figure 116-6. Prostate cancer-specific mortality after three-dimensional conformal radiation therapy for patients with 50% or more as compared with less than 50% prostate positive biopsy and a prostate-specific antigen (PSA) of 15 or less and Gleason score of 6 or less, respectively. RT, radiation therapy.

The Role of Multiparametric Magnetic Resonance Imaging

Multiparametric magnetic resonance imaging (MRI) combines morphologic and functional MRI sequences including T2-weighted, diffusion-weighted, dynamic contrast-enhanced (DCE) and magnetic resonance spectroscopic imaging, and its use in conjunction with an endorectal coil and a higher strength (3 tesla [T]) magnet may have significant prognostic utility. Researchers from the National Cancer Institute (NCI) found a strong correlation between **apparent diffusion coefficients (ADC)** derived from diffusion-weighted imaging and both Gleason score ($P = .003$) and clinical risk group ($P < .0001$) (Turkbey et al, 2011). In addition, in a study of 100 favorable-risk men who received radical prostatectomy, 3T multiparametric endorectal MRI was 75% and 95% accurate at predicting pathologic extracapsular extension and seminal vesicle invasion, respectively (Hegde et al, 2013). Therefore MRI may be a useful tool in further stratifying risk in patients who are borderline between two treatment options, such as intermediate-risk patients considering monotherapy with radiation alone versus combined modality therapy with radiation and short-course androgen deprivation therapy (ADT).

KEY POINTS: PRETREATMENT PROGNOSTIC FACTORS

- Prostate cancer-specific mortality can be estimated on the basis of the pretreatment PSA level, biopsy Gleason score, and clinical T category.
- The percentage of positive prostate biopsy samples, pretreatment PSA velocity, number of unfavorable factors, primary Gleason pattern, and multiparametric 3T endorectal MRI can add additional prognostic information for further stratification of risk, particularly in intermediate-risk disease that is heterogeneous.

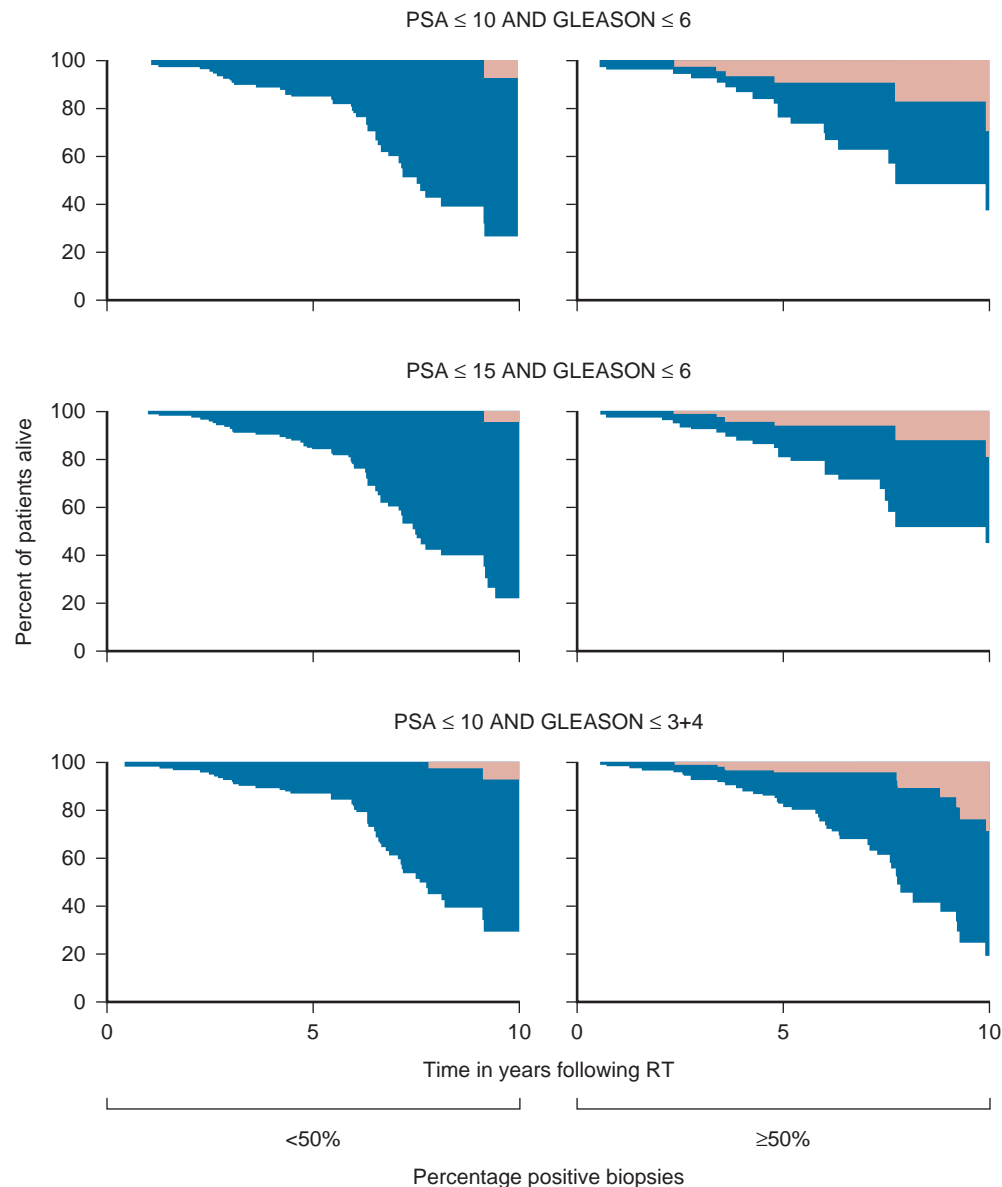


Figure 116-8. Relative contributions of prostate cancer–specific mortality (PCSM) and non-PCSM after treatment to all-cause mortality stratified by the percentage of prostate-positive biopsy (<50% vs. ≥50%) and the prostate-specific antigen (PSA) level and biopsy Gleason score at diagnosis. RT, radiation therapy.

Post-Treatment Prognostic Factors

Localized Disease: Evaluating the Response to Radiation

Prostate-Specific Antigen Follow-up: Definition of Failure.

Serum PSA is widely accepted as a surrogate end point for monitoring the success of definitive treatment for localized prostate cancer. The PSA-based definition of biochemical failure after radiotherapy has evolved over the past two decades. Unlike the situation after radical prostatectomy, residual benign glands may be responsible for a low level of PSA production but an “acceptable” PSA level after successful radiotherapy is markedly lower than the range of normal for an age-matched population because of marked atrophy of non-malignant acini (Grignon and Sakr, 1995).

Ablation of normal prostatic epithelium is dose dependent. Median PSA nadirs range from 0.6 ng/mL after 70 Gy, to 0.3 ng/mL for radiation doses of 79 Gy, to 0.1 ng/mL or less for those receiving EBRT and a brachytherapy boost (Roach et al, 2006). Nadir PSA value is a significant predictor of outcome, but no absolute nadir threshold can or should be used to define cure (DeWitt et al, 2003).

Although a standard definition of failure is essential for the purposes of clinical trials and reporting of data, it must be emphasized that establishing that a patient meets the criteria for biochemical failure is not justification for intervention.

The 1996 ASTRO Consensus Conference (1997) proposed a standardized definition of biochemical failure after radiotherapy. Recognizing that PSA stability after the nadir is important, three consecutive increases in PSA, with backdating of failure to midway between the nadir and the first increase, was proposed. Although the ASTRO definition provided uniformity in reporting of results, it became clear with additional data that it was not an ideal solution to the problem of defining biochemical failure after radiotherapy. Waiting for three rises delays the establishment of failure by 18 months or more (Cherullo et al, 2002), and backdating biases the Kaplan-Meier estimate, an effect that is worse with shorter follow-up (Roach et al, 2006). In addition, the original ASTRO consensus definition of biochemical failure was not predictive of clinical progression or survival and was not developed using data from patients treated with combined radiation and ADT or those treated with brachytherapy.

To address these issues, a second consensus conference was held in Phoenix, Arizona, in 2005, and recommended that the standard definition of **biochemical failure after radiotherapy**, with or without short-term androgen deprivation, be established as a rise of 2 ng/mL or more above the nadir (Roach et al, 2006). Failure is not backdated; if salvage treatment is instituted before meeting these PSA criteria, failure is considered to have occurred at the time of salvage. PSA rises that can be clearly attributed to other causes, such as laboratory error, prostatitis that responds to antibiotics, or a benign PSA bounce that resolves without any intervention in patients treated with brachytherapy, should not be declared as biochemical failures. This definition is known as the “Phoenix” or “nadir + 2” definition. If the original ASTRO consensus definition is used, results should be reported for a timeframe that is 2 years less than the median follow-up of the population. For example, biochemical control could be reported at 5 years for data with a median follow-up of 7 years to minimize the confounding effects of backdating.

Time to Nadir. Serum PSA declines slowly after completion of radiotherapy. Both the level and timing of the nadir have been correlated with distant metastases and cause-specific survival (CSS) (Hanlon et al, 2002; Pollack et al, 2002). Lee and colleagues (1996) reported that 75% of men whose PSA reached a nadir in less than 12 months had distant metastases by 5 years compared with 25% of those whose PSA took more than 12 months to reach a nadir ($P < .001$). Denham and associates (2008) analyzed the results of the Trans-Tasman Radiation Oncology Group (TROG) 9601 trial, which randomized 802 men with locally advanced prostate cancer to 66 Gy of EBRT with 0, 3, or 6 months of ADT. Biochemical failure before 24 months (cut point band < 1.5 years to < 2.5 years) was suggested as a surrogate for CSS. Buyyounouski and colleagues (2008) identified 18 months as the cut point for time to nadir that was optimal as a surrogate for CSS in a population of 211 failures amongst 1174 men treated with 3D conformal radiotherapy. The median dose of radiation was 72 Gy with a range of 67 to 82 Gy. An interval to biochemical failure less than 18 months was independently predictive of distant metastases ($P = .008$) and was the only predictor of prostate cancer-specific mortality ($P = .0003$). The actuarial 5-year distant metastatic rate for biochemical failures occurring before or after 18 months was 52% versus 20% ($P < .0001$), and the actuarial prostate cancer-specific mortality was 36% versus 6% ($P = .0001$).

The previous two reports were based either on “conventional” radiation doses (66 Gy) or a range of doses. Kapadia and associates (2012) studied the interval to biochemical failure for a population of 710 patients treated with dose-escalated radiotherapy in the range of 76 to 78 Gy, with or without ADT. Biochemical failures occurred in 21% and were measured from completion of radiotherapy and/or ADT. Biochemical failure before 18 months (short interval) predicted decreased CSS ($P < .0001$) and overall survival ($P < .0001$). Overall survival at 8 years was 78% for those without biochemical failure, 87% with a long interval to biochemical failure, and 38% with a short interval to biochemical failure ($P < .0001$, hazard ratio [HR] 3.7, CI 2.3 to 5.9). On multivariate analysis, biochemical failure before 18 months increased the risk for prostate cancer death ($P < .0001$) and all-cause mortality ($P = .003$), whereas biochemical failure after 18 months did not.

Significance of Nadir Value and Doubling Time. The level of PSA nadir achieved reflects the dose of radiation and the type of failure. With conventional dose radiotherapy, the median PSA nadir for patients with no evidence of disease (NED) in most series is 0.4 to 0.5 ng/mL (Zietman et al, 1996; Critz et al, 1999; Crook et al, 2000), whereas for those exhibiting local failure it is often greater than 1.0 ng/mL and for distant failure greater than 2 ng/mL. A study by Hanlon and colleagues (2004) ($n = 615$, follow-up median 64 months) reported that freedom from distant metastases was 96% for a nadir less than 1 ng/mL, 89% for nadirs 1.1 to 2 ng/mL, and 61% for nadirs greater than 2 ng/mL. Zelefsky and coworkers (2009) analyzed 844 patients treated with conformal radiotherapy to doses ranging from 64 to 81 Gy. A nadir less than 1.5 ng/mL at 2 years after treatment was predictive for long-term freedom

from distant metastases and prostate cancer mortality. The 10-year rates of distant metastases were 17.5% for men with nadirs greater than 1.5 ng/mL at 2 years compared to 7.9% for nadirs less than 1.5 ng/mL. In a stratified competing risks analysis, nadir PSA greater than 1.5 ng/mL at 2 years was an independent risk factor for distant metastases after adjusting for T stage, Gleason score, preradiotherapy PSA, and radiation dose ($P < .001$).

For patients treated with permanent seed brachytherapy Grimm and associates (2001) found that the lower the PSA nadir, the higher was the probability of success. A PSA nadir less than 0.5 ng/mL is associated with significantly better long-term freedom from biochemical failure (95.2% vs. 71.5%) (Ko et al, 2012). A PSA level at 5 years after brachytherapy is highly predictive of outcome, with 97.4% 10-year biochemical control in a cohort of 921 men with PSA less than 0.2 ng/mL at 5 years after brachytherapy (Ko et al, 2012). Hayden and coworkers (2010) found only one late biochemical relapse among 762 patients with a PSA less than 0.2 ng/mL at 48 to 60 months after implant. Crook and colleagues (2011) reported that with a mean dose to 90% of the prostate of 160 Gy, only 10% of patients at 5 years have a PSA level greater than 0.2 ng/mL, and two thirds of these patients are still showing a decreasing trend. These results are very similar to observations by Stock and associates (2009) in which only 10.9% of 742 patients had a PSA level greater than 0.2 ng/mL at 5 years. The 10-year freedom from biochemical failure was 98% for a 5-year PSA level less than 0.2 and 81% for a PSA level greater than 0.2 ng/mL. Grimm and associates (2001) reported that the proportion of patients with a PSA level less than 0.2 ng/mL continues to increase for up to 7 to 8 years.

The **postnadir doubling time** of the PSA level also correlates with the type of failure, with distant failures having shorter PSA doubling times of 3 to 6 months, whereas doubling times for those with local failures are a year or more. D’Amico and colleagues (2003) reported that a PSA doubling time of less than 3 months is associated with prostate cancer mortality. Doubling time, however, may not be an ideal surrogate end point. The calculation of doubling time depends on the number of values available, being more reliable with a wide range of values (Denham et al, 2008).

Valicenti and colleagues (2006) focused on PSA doubling time in an analysis of the Radiation Therapy Oncology Group (RTOG) trial 9202, which randomized 1514 men with T2c-4 prostate cancer to 65 to 70 Gy of EBRT and short-term neoadjuvant ADT plus or minus 24 months of adjuvant ADT. At 5 years, the actuarial CSS was 84.7% in the cohort of patients with a PSA doubling time less than 12 months compared to 94.3% for longer doubling times (HR 5.63, 95% CI 3.78 to 8.3). PSA doubling time was significantly associated with CSS.

Denham and associates (2008) in the analysis of the previously mentioned TROG 9601 trial used a cut point of PSA doubling time of less than 12 months. For these patients, the HR for prostate cancer death was 23.49 (CI 12.94 to 42.63, $P < .001$). If parameters such as interval to biochemical failure of less than 2 years and PSA doubling time of less than 12 months prove to be successful surrogates for prostate cancer-specific mortality, the required 7 to 8 years of follow-up in a clinical trial may be reduced to 2.5 to 3 years for accurate prediction of the superior treatment arm. Surrogates also may guide management of individual patients, suggesting earlier intervention in those with a PSA doubling time of less than 12 months while increasing the comfort level with continued observation in those with longer doubling times.

The manner in which PSA nadir and time to nadir reflect the type of failure requires explanation. Three sources of PSA potentially contribute to the nadir: residual benign prostatic epithelium, residual local prostate cancer cells, and subclinical disseminated micrometastases. The longer the time to nadir and the lower the absolute nadir, the more likely it is that only benign prostatic epithelium remains, hence the NED status. A higher radiation dose achieves a more complete ablation of normal epithelium and thus a lower nadir. For patients in whom radiotherapy fails to eradicate all the local tumor, the PSA declines progressively until the rate of growth of the surviving prostate cancer cells is greater than the death rate of those fatally damaged by the radiation, at which point the

PSA begins to rise, generally relatively slowly. In the third scenario, subclinical micrometastases continue to grow unchecked despite successful treatment of the primary tumor. This growth rate outstrips the rate of decline in the local tumor population relatively early after treatment, leading to a higher and earlier nadir and a more rapid doubling time.

Neoadjuvant Hormones and the Definition of Biochemical Failure. In the presence of residual benign epithelium or before the full effect of radiotherapy has been expressed, PSA may fluctuate or show several consecutive increases. When neoadjuvant androgen deprivation is used before radiotherapy, patients often start radiotherapy with an already undetectable PSA. If the PSA remains undetectable, it is impossible to determine a true nadir or time to nadir. A substantial proportion of patients treated with EBRT and ADT experience a PSA increase when the testosterone recovers. Zietman and colleagues (2005a) reported that the median time to PSA “bounce” (defined as an increase of 0.2 ng/mL) after EBRT (68.2 to 72 Gy) and ADT was 2.2 years. The median magnitude was 0.9 ng/mL, and 18.6% met the nadir + 2 definition of failure. Subsequently, as the effect of the radiotherapy is expressed, the PSA declines once again. Based on a data set of 1865 men treated with EBRT, Pickles (2006) and coworkers reported a bounce duration of 12.5 months and median height of 0.8 ng/mL, but only 2.1% met the nadir + 2 definition of failure. Interestingly, only 20% of bounces occurred during the testosterone recovery period, with the rest occurring once the testosterone had normalized. This may represent a delayed response to testosterone stimulation or may implicate other causes such as inflammation or instrumentation. Closer follow-up and more frequent PSA testing is more likely to detect PSA fluctuations or bounces. The Phoenix or nadir + 2 definition of failure is associated with fewer false calls of failure than the original ASTRO consensus definition of 3 rises after the nadir.

Brachytherapy and the Benign Bounce Phenomenon. Benign PSA bounces or spikes are a well-recognized phenomenon after prostate brachytherapy. A spike or bounce is most frequently defined as a rise greater than 0.2 ng/mL followed by a durable decline (Critz et al, 2000) and is seen after both low-dose-rate (LDR) and high-dose-rate (HDR) brachytherapy. Overall, approximately 35% of men will experience a PSA bounce of 0.2 ng/mL or greater after LDR brachytherapy (Critz et al, 2000; Merrick et al, 2002c; Ciezki et al, 2006; Toledano et al, 2006; Mitchell et al, 2008; Caloglu et al, 2011; Hinnen et al, 2012), but in younger men the frequency may reach 65% (Gomez-Iturriga et al, 2010). The mean increase is 1 ng/mL but can be up to 10 ng/mL, with 12% meeting the nadir + 2 definition of biochemical failure. Spikes may last as long as 12 to 18 months, and double peaks can be seen. Biopsies performed to investigate the rising PSA may show residual cancer with treatment effect (indeterminate) (Reed et al, 2003). Currently, there is no reliable way to discern whether a rising PSA in the first 3 years after brachytherapy represents treatment failure. Kirilova and associates (2011) investigated patients undergoing a PSA bounce with magnetic resonance spectroscopy and reported a diffuse increase in the ratio of choline to citrate across the gland, rather than a focal phenomenon that might be expected if the PSA increase were associated with tumor activity. It is recommended that a rising PSA within 30 months of brachytherapy be monitored. If the rise approaches 10 ng/mL, systemic staging is warranted, and, if the bounce persists beyond 30 months, a prostate biopsy is warranted. Only patience and careful follow-up demonstrate the subsequent spontaneous PSA decline to low levels.

Postradiation Therapy Biopsy

Although serum PSA nadir has been widely adopted as a surrogate end point to determine treatment efficacy, it cannot distinguish between local and systemic failure. Postradiotherapy prostate biopsies are a logical means of evaluating the local effect of radiotherapy. The major issues involve timing of the biopsies with respect to completion of radiotherapy, interpretation of indeterminate biopsies that show marked radiation effect, and the uncertainty imposed by sampling error.

Timing. In early reports, little was known about the rate of histologic clearance of irradiated tumor and failures were declared as early as 6 months after completion of radiotherapy (Scardino and Wheeler, 1985). It is now recognized that the time for histologic resolution of tumor parallels the time to serum PSA nadir and for the same reasons. Radiation causes postmitotic cell death, and fatally damaged cells may survive a limited number of cell divisions (Mostofi et al, 1992, 1993). Biopsies performed before histologic resolution is complete show a moderate-to-marked radiation effect (Crook et al, 1997a). The ultimate viability of these cells cannot be predicted. Crook and colleagues (Crook et al, 1995) determined that the optimal time to biopsy is 30 to 36 months after radiotherapy.

Interpretation. Gleason scoring of irradiated prostate cancer should be performed only if the histologic evidence of radiation effect is absent or minimal. Gleason’s original work was based on surgically obtained material that had not been exposed to prior radiotherapy or hormonal therapy. It is based on gland architecture, which is known to be markedly altered by radiotherapy. Inappropriate application of the Gleason scoring system to disintegrating malignant glands showing a marked RT effect (Siders and Lee, 1992; Grignon and Sakr, 1995) results in a false-positive biopsy often misinterpreted as high grade and may lead to unnecessary salvage therapy (Reed et al, 2003).

Radiation atypia in benign glands can be severe enough to mimic malignancy (Bostwick et al, 1982; Grignon and Sakr, 1995; Cheng et al, 1999). Anticytokeratin monoclonal antibody for high-molecular-weight keratin labels the basal cell layer of benign glands and therefore helps distinguish radiation atypia in benign glands from residual tumor where the basal cell layer would be absent (Brawer et al, 1989).

Scoring systems for the degree of radiation effect have been proposed (Dhom and Degro, 1982; Bocking et al, 1987) on the basis of cytoplasmic and nuclear changes (Box 116-1) and can be helpful in interpreting the biopsy (Crook et al, 1997b). Their importance is to emphasize the need to differentiate between biopsies showing no or minimal radiation effect and those showing marked treatment effect (Zelevsky et al, 2004). Failure to recognize these differences dilutes the prognostic significance of biopsy status and may lead to

BOX 116-1 Grading Scheme for Cytoplasmic and Nuclear Radiation Effect

The scores for cytoplasmic and nuclear changes are added together. A score of 5 to 6 represents marked treatment effect, 3 to 4 is moderate, and 0 to 2 is minimal.

CYTOPLASMIC CHANGES

- 0 No identifiable RT effect
- 1 Swelling and microvesicular change
- 2 Extensive vacuolation, macrovesicular change, and voluminous cytoplasm
- 3 Indistinct or ruptured cytoplasm or Lipofuscin pigment accumulation or Glands dilated or just single cells with no glandular formation or

NUCLEAR CHANGES

- 0 No identifiable RT effect
- Some swelling or smudging of nuclei but nucleoli still visible or
- Smudged and distorted chromatin or
- Nucleoli rare or absent or
- Large bizarre nuclei or
- Pyknotic small condensed nuclei

RT, radiation therapy.

inappropriate salvage therapy. Immunohistochemical stains for markers of cellular proliferation such as proliferative cell nuclear antigen (Crook et al, 1994; Ljung et al, 1996) and Ki-67 have been used in interpretation of the significance of residual tumor and are associated with subsequent failure (Crook et al, 2000).

Zelefsky and associates (2008b) studied 339 men treated with 3D conformal RT with a median follow-up of 10 years. The 2-year biopsy status was strongly predictive of 10-year biochemical NED rate, freedom from distant metastases ($P = .004$), and CSS ($P = .007$). Importantly, biopsies with marked treatment effect behaved as negative. This was confirmed by Crook and colleagues (2009) in a report on 361 men who participated in a randomized trial of 3 versus 8 months of ADT before conventional EBRT. Biopsies were performed between 24 and 30 months after completion of radiotherapy. In multivariate analysis biopsy status ($P < .0001$) and Gleason score ($P < .0001$) were the two strongest determinants of biochemical disease-free survival.

Imaging and Sampling Error. TRUS alone is of limited diagnostic use after radiotherapy because the increase in fibrosis alters the echogenic characteristics of the irradiated prostate (Crook et al, 1993; Svetec et al, 1998). MRI offers vastly improved soft tissue definition over either computed tomography (CT) or ultrasound. Multiparametric MRI has greater accuracy in the detection of recurrent prostate cancer after radiotherapy than T2-weighted imaging alone. Westphalen and colleagues (2010) reported that the addition of magnetic resonance spectroscopy to T2-weighted imaging in men with suspected recurrence after EBRT increased the area under the receiver operating curve (AUC) to 0.79 from 0.67, detecting recurrence in 37 of 64 men. Donati and associates (2013) compared T2-weighted imaging to T2 with the addition of diffusion weighting (DW) and DCE and found that T2 imaging with DW improved the AUC for two independent readers but that DCE offered no additional benefit in a study of 53 men with suspected recurrence. Arrayeh and associates (2012) reported that preradiotherapy and postradiotherapy endorectal 1.5 T MRI scans in 9 men with local recurrence were able to image the recurrence at the same site as the original dominant nodule, confirmed on whole-mount step-sectioned salvage prostatectomy.

Local therapy should be evaluated in terms of local tumor eradication. Local failures can be reduced by treatment refinements such as dose escalation and improvements in treatment planning and delivery. Systemic failures are a problem of selection of patients and a failure to recognize high-risk features that require a combined modality approach to address a potential systemic component. Postradiotherapy prostate biopsies are fraught with problems of timing, interpretation, and sampling error. Multiparametric MRI is a promising advance in the investigation of patients with suspected recurrence and can be used to guide confirmatory biopsies. Clearly viable residual tumor should be in evidence before considering radical local salvage for radiation failure.

KEY POINTS: POST-TREATMENT PROGNOSTIC FACTORS

- The level of PSA nadir achieved after RT reflects the pattern of failure. Specifically, a nadir greater than 2 ng/mL is associated with distant failure.
- The PSA doubling time after RT also predicts the pattern of failure. Specifically, a PSA doubling time of less than 3 months is almost always associated with distant failure.
- An interval to biochemical failure of less than 2 years and a PSA doubling time of less than 12 months may be surrogates for PCSM.

External-Beam Radiation Treatment

The question of whether the absence or presence of local control of a treated tumor is related to the subsequent development of metastatic disease was explored experimentally as far back as 1970. Mice

with sarcomas of the extremity developed fewer pulmonary metastases if their affected limbs were amputated early in the course of disease (Suit et al, 1970). Given that RT is a local treatment modality, one of the main goals of treatment is local control, with the expectation that only patients who achieved such control could be expected to be cured of their cancer. This principle was first examined in prostate cancer in the 1980s, when a relationship between treatment planning technique and cancer control was demonstrated in the Patterns of Care Studies (Leibel et al, 1984; Hanks et al, 1988). Patient treatment records were reviewed from 163 randomly selected radiation oncology departments located across the United States. Tumor control was better in patients who received higher doses of radiation to larger fields, at the expense of increased complications. These studies sparked an intense interest in and ongoing effort to improve outcomes in men with prostate cancer by providing the best treatment planning and delivery systems possible (Leibel et al, 1994).

Advances in Radiation Technology

Although EBRT has been used for decades to treat prostate cancer, it is still an evolving treatment. Until the 1970s, radiation oncologists had to treat cancers without precise knowledge of their location within the body. Knowledge of normal anatomy, routes of spread of a particular cancer, and limited information from diagnostic radiology were used for treatment planning (Asbell et al, 1980). Radiation oncologists became adept at designing radiation fields on the basis of skeletal anatomy. For the treatment of prostate cancer, the radiation portals were centered on the pubic symphysis and femoral heads. One group designed a rotating platform treatment; men with prostate cancer stood on a small mechanical platform that rotated 360 degrees while the radiation beam was aimed at the level of their pants pockets. This was considered advanced for its time. Later, radiation oncologists learned to use additional tools for treatment planning. The location of the prostate was inferred indirectly by introducing a contrast-filled Foley catheter and rectal tube into the patient. The prostate was assumed to be located in the space between these two organs, as shown in Figure 116-9. As recently as the mid-1980s, this technique was considered state of the art. In this era before CT, radiation treatment technique was sometimes referred to as **conventional radiation**.

The ability to visualize the prostate during radiation treatment planning arrived in the 1990s with the advent of CT scanners and use of CT scans for radiation planning. This was a dramatic breakthrough in radiation treatment for prostate cancer, because it allowed the ability to design radiation beams to directly target the prostate and for the first time accurately calculate doses received by nearby organs such as the rectum and bladder (Mohan et al, 1992; Niemierko et al, 1992). Clinicians knew as early as 1980 that they were making significant errors in field placement without CT data, but limitations in computer hardware and software allowed no solution to the problem (Rosenman et al, 1991; Fraass, 1993). They also knew that radiation doses received by surrounding organs caused morbidity, but had no way to calculate doses received by these organs without CT images for treatment planning. Fortunately, the significant and rapid improvement in computer availability, lowered costs, improved graphics, and rapid computational power has changed forever the field of radiation oncology. Men with prostate cancer are the direct beneficiaries of the new technologies, and prostate cancer is one disease for which the radiation treatment today bears little resemblance to that used as recently as the late 1980s (Fraass, 1995).

Therefore the 1990s began the era of 3D tumor visualization and treatment planning using CT scans. For the first time, the prostate and surrounding structures could be identified with increased precision, and the beam's eye view, a technique allowing visualization of the regional anatomy from the perspective of the beam apertures, enabled the design of plans that could more accurately treat the prostate target while minimizing dose to the surrounding normal tissues. The result is described as 3DCRT because the radiation beams conform to the shape of the treatment target (Fraass, 1995).

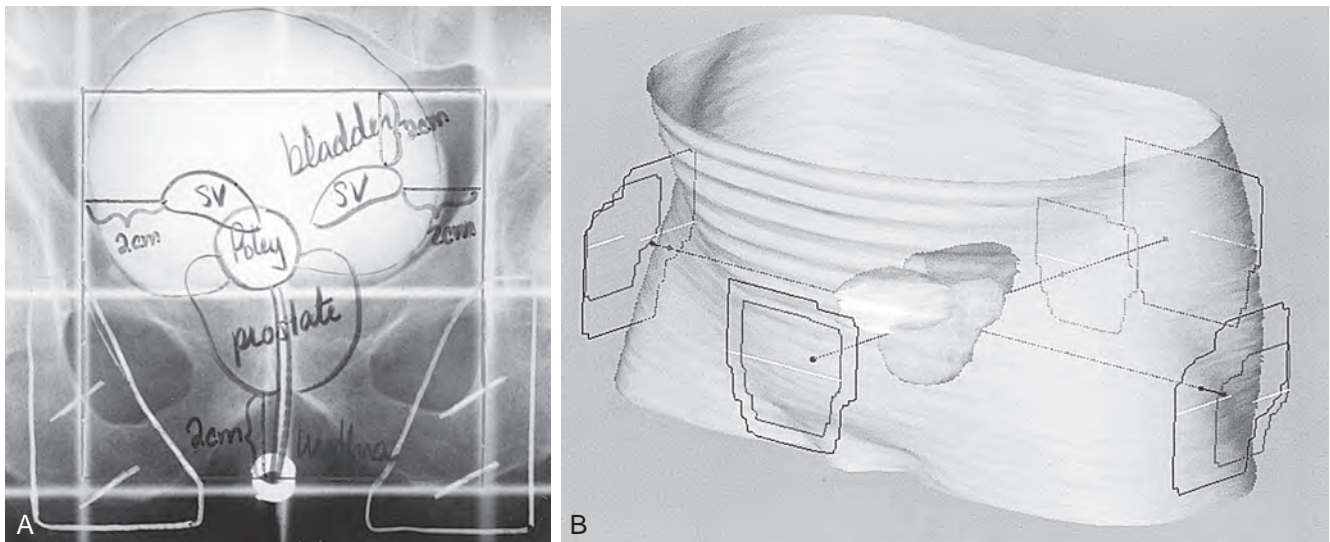


Figure 116-9. A, Conventional radiation therapy treatment portal, anterior view. The location of the prostate is inferred from the location of the Foley balloon and from contrast in the bladder, as well as from the location of the wire anal marker. B, Conformal radiation therapy portal, anterior view. The fully three-dimensional prostate volume is reconstructed from the planning computed tomography scan. SV, seminal vesicles.

One of the goals of conformal prostate radiation is to lower the dose to the surrounding normal tissues, such as the rectum and bladder, while simultaneously increasing the dose delivered to the prostate itself (Burman et al, 1991; Niemierko et al, 1992). All radiation oncologists agree that CT data allowed more accurate placement of the radiation fields. This was first demonstrated by Pilepich and colleagues (1982), who found a 53% error rate in field placement and portal size in patients simulated without CT data. In theory, better pretreatment visualization and localization of the prostate eliminate the need to enlarge the radiation portal to account for anatomic and geometric uncertainties. It follows that smaller radiation portals allow less irradiation of nontarget structures such as the bladder or rectum, thereby reducing treatment-related morbidity.

The ability to accurately calculate radiation doses to the prostate and surrounding organs facilitated further technologic developments that allowed delivery of higher radiation doses to the prostate in an attempt to increase local control and therefore cure rates while simultaneously lowering doses to surrounding organs in an attempt to decrease treatment-related morbidity. A major advance in the delivery of radiation came with the advent of **intensity-modulated radiation therapy (IMRT)**. IMRT is a sophisticated way of treatment delivery in which the intensity of radiation can be varied from each beam angle. IMRT requires the use of advanced software, specialized personnel, and hardware adaptations to linear accelerators (Burman et al, 1997). IMRT uses a new planning approach referred to as *inverse treatment planning*. This approach gives equal attention to the areas where radiation dose is to be minimized (i.e., organs) and the areas that are to receive high-dose treatment (i.e., prostate). With this technology, the prostate can receive a daily dose of 1.8 Gy while the majority of the adjacent bladder receives less than half of this dose. An example of an intensity-modulated beam is shown in Figure 116-10. The tight distribution of radiation around the prostate with avoidance of most of the rectum and bladder is seen on inspection of the figure.

In multiple treatment-planning studies, IMRT consistently demonstrated lowering of radiation doses to the rectum, bladder, femoral heads, and small bowel compared to 3DCRT (Table 116-1). These studies have changed the standard of care in prostate cancer radiation treatment. In 2000, almost every patient with prostate cancer in the United States treated with RT received conformal

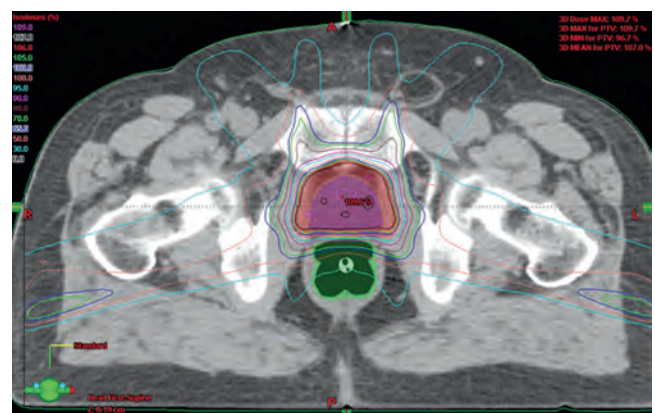


Figure 116-10. New intensity-modulated radiotherapy.

radiation; by 2009, almost 100% of prostate radiation was given using IMRT (Sheets et al, 2012).

A more recent and clinically important development was the addition of **image guidance** to prostate cancer RT. Image guidance was development based on a realization that (1) the daily location of the prostate within the pelvis throughout the course of RT is not identical (interfraction motion) (Ten Haken et al, 1991; Beard et al, 1996), and (2) the prostate is mobile even during a single session of RT (intrafraction motion) (Huang et al, 2002). Previously, radiation oncologists expanded the size of the radiation beam (i.e., radiated a larger area around the prostate) to accommodate prostate motion and accepted the risk for increased morbidity. With image guidance, this excessive expansion is no longer necessary because the location of the prostate can be verified daily before delivering radiation. This can be done with a daily ultrasound determination of the prostate location immediately before treatment while the patient is on the treatment table. Another option is to introduce radiopaque ("fiducial") markers into the prostate under ultrasound guidance and to use a commercially available software program to localize the prostate each day before treatment while the patient is on the treatment table. Neither approach, however, addresses the issue of intrafraction motion. One solution to the intrafraction

TABLE 116-1 Treatment Planning Studies Comparing Three-Dimensional Conformal Radiation Therapy versus Intensity-Modulated Radiation Therapy

REFERENCE	TREATMENT TARGET	DOSIMETRIC MEASURE	RECTUM IMRT/3DCRT	BLADDER IMRT/3DCRT	FEMORAL HEAD IMRT/3DCRT	SMALL BOWEL IMRT/3DCRT
Hardcastle et al, 2010	Prostate + SV	V25 (%) V50 (%) V75 (%)	68.5/89.1* 43.8/57.3* 9.9/23.2*			
Luxton et al, 2004	Prostate + SV (± LN)	Mean dose (– LN) (Gy) Mean dose (+ LN) (Gy)	36.8/38.5 45.5/54.1	33.3/35.7 46.2/57.3	12.4/28.2 14.9/31.2	25.9/36.3
Nutting et al, 2000	Prostate + SV + LN	Mean Dose (Gy) V20%-prescribed dose (%) V50%-prescribed dose (%) V80%-prescribed dose (%) V90%-prescribed dose (%)	34.9/38.5* 96.2/97.8 92.6/79.2* 27.1/65.0* 5.8/50.5*	35.3/41.6* 99.2/98.3 93.5/95.2 25.5/59.0* 7.0/52.2*		19.2/18.3 60.4/47.9* 37.0/37.3 11.8/19.5* 5.3/18.3*
Palma et al, 2008	Prostate	Mean EUD (Gy) V20 (%) V40 (%) V70 (%)	50.6/53.5* 34.3/75.2 17.1/66.8 4.1/7.1	32.4/43.2* 41.5/67.6 26.7/55.2	3.4/9.8	
De Meerleer et al, 2000	Prostate + SV	Max dose (Gy) V20 (%) V40 (%) V60 (%) V65 (%)	78.1/70.8 88.3/87.2 72.9/73.6 50.7/54.5 37.9/47.0	75.2/75.5 58.5/56.4 38.8/36.3	49.6/50.1 43.9/49.0 15.8/20.1	
Mock et al, 2005	Prostate + SV	Max dose (Gy) Mean dose (Gy)	48.9/53.9 41.7/45.7	35.1/42.9 18.9/21.5	29.1/36.3 20.9/28.9	
Kao et al, 2004	Prostate + SV	Max dose (Gy) Mean dose (Gy) V70 (%)	80.1/ 75.5* 39.1/ 49.2* 18.4/ 21.9*	79.6/ 76.1* 47.8/ 48.7 25.2/ 26.1		

*Statistically significant difference.

3DCRT, three-dimensional conformal radiation therapy; EUD, equivalent uniform dose; IMRT, intensity-modulated radiation therapy; LN, lymph nodes; SV, seminal vesicles.

Vx represents the percentage of an organ receiving X Gy of radiation dose.

motion problem is prostate immobilization, which can be achieved using an intrarectal balloon introduced into the rectum and inflated before daily RT. Inflation of the balloon pins the prostate against the pubic bone. Because the immobilized prostate does not move during treatment, small posterior margins can be used (Fig. 116-11), thus minimizing dose to the rectum (Sanghani et al, 2004). Another solution is to use technologies that allow real-time tracking of the prostate, which is possible with the Calypso System (Varian Medical Systems, Palo Alto, CA). The ability to account and correct for uncertainties in the location of the prostate on a daily basis allows for accurate delivery of radiation to the prostate while further lowering incidental doses received by surrounding organs. Therefore image guidance is now a recommended standard of care for prostate cancer RT (National Comprehensive Cancer Network [NCCN], 2012).

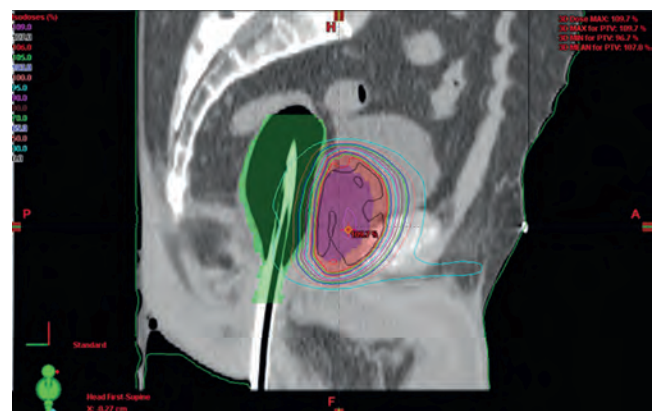


Figure 116-11. Balloon intensity-modulated radiotherapy. (Courtesy Fred Hacker, PhD, Department of Radiation Oncology, Brigham and Women's Hospital.)

KEY POINT: ADVANCES IN RADIATION TECHNOLOGY

- EBRT for prostate cancer has made several significant advances, including CT-based planning in the 1990s, IMRT in the early 2000s, and image guidance more recently.

Tumor Control after External-Beam Radiation Therapy

Because modern RT (IMRT with image guidance as the standard) for prostate cancer looks nothing like RT from the 1990s (pre-CT era) or even early 2000s (pre-IMRT), review of the literature on the efficacy of RT must take into consideration type of radiation used and dose delivered.

Two recently published trials compared RT to conservative management, demonstrating the ability of radiation treatment to improve survival in patients with prostate cancer. In both trials, patients were randomized to ADT with or without EBRT. In a multi-institutional trial sponsored by the National Cancer Institute of Canada (NCIC) and Medical Research Council UK (MRC) (NCIC CTG PR.3/MRC UK PR07), 1205 patients with high-risk or locally advanced prostate cancer were randomized from 1995 to 2005 to lifelong ADT (either bilateral orchiectomy or luteinizing hormone-releasing hormone [LHRH] agonist) with or without RT to 65 to 69 Gy (Warde et al, 2011). The addition of RT significantly improved overall survival: 7-year survival 66% for ADT versus 74% for ADT/RT ($P = .033$). In a Scandinavian trial (SPCG-7/SFUO-3), 875 patients with high-risk or locally advanced prostate cancer were randomized from 1996 to 2002 to lifelong ADT (3 months of combined androgen blockade followed by lifelong flutamide) with or without RT to a median of 70 Gy (Widmark et al, 2009). Again, RT decreased overall mortality: 10-year mortality was 39.4% for ADT versus 29.6% for ADT/RT ($P < .05$). These two trials show that RT improves overall survival in high-risk prostate cancer by an absolute magnitude of 8% (at 7 years) to 10% (at 10 years) compared to ADT alone. Of note, radiation doses used in the modern era for prostate cancer are much higher than those used in these trials and should be even more effective.

That higher dose radiation is more effective than lower dose radiation for prostate cancer was demonstrated by four randomized trials (Table 116-2). In an MD Anderson Cancer Center trial, patients with low-risk (20%), intermediate-risk (46%), and high-risk (34%) prostate cancers were randomized to receive 70 or 78 Gy without ADT (Kuban et al, 2008). Higher radiation dose improved 10-year freedom from failure rate from 50% (70 Gy) to 73% (78 Gy, $P = .004$) (Kuban et al, 2008). Further, this trial demonstrated that the reduction in biochemical failure may translate to a distant metastasis benefit ($P = .059$). The Proton Radiation Oncology Group (PROG) 95-09 trial randomized patients with low-risk and intermediate-risk prostate cancer to 70.2 or 79.2 Gy using a combi-

nation of conformal photon and proton radiation, without ADT (Zietman et al, 2005b, 2010). This trial also found a reduction in 10-year biochemical failure rates associated with higher radiation dose: 32.0% failure (low dose) versus 17.4% (high dose, $P < .001$) (Zietman et al, 2010). Subgroup analysis showed a benefit from higher dose applicable in both low-risk and intermediate-risk patients. A Dutch trial that randomized patients to 68 or 78 Gy included mostly high-risk prostate cancers (56%) (Peeters et al, 2006; Al-Mamgani et al, 2008). Approximately 21% to 22% of patients in each arm received 3 to 6 months of ADT per institutional practice. Higher dose radiation demonstrated improved disease control: 7-year freedom from failure rates were 45% for 68 Gy versus 56% for 78 Gy ($P = .03$) (Al-Mamgani et al, 2008). Subgroup analysis found a benefit from higher dose radiation for intermediate-risk and high-risk prostate cancers. A fourth trial by the MRC (RT01), which randomized patients to 64 or 74 Gy, differed from the others in that all patients received an LHRH agonist that started 3 to 6 months before and throughout RT (Deamaley et al, 2007). This study included a mixture of low-risk (24%), intermediate-risk (32%), and high-risk (43%) patients. Again, high-dose radiation improved biochemical progression-free survival (60% vs. 71% at 5 years, $P < .001$). In subgroup analysis, the benefit of dose escalation was seen in all prostate cancer risk groups.

Taken together, these trials consistently demonstrated improved cancer control outcomes from higher dose radiation which applied to prostate cancer patients in a variety of clinical settings including all risk groups and also with or without ADT. These trials provide level 1 evidence for the use of dose-escalated RT in prostate cancer, which is recommended as a standard of care by current guidelines (NCCN, 2012).

KEY POINTS: TUMOR CONTROL AFTER EXTERNAL-BEAM RADIATION THERAPY

- EBRT improves overall survival compared to conservative management with ADT alone.
- Four randomized trials that consistently showed that higher dose radiation improved disease control have led to the current standard of care, which is to use dose-escalated RT.

TABLE 116-2 Randomized Trials of Lower Dose versus Dose-Escalated Radiation Therapy for Prostate Cancer

STUDY	MEDIAN FU (yr)	PATIENT INCLUSION AND RISK, %	RADIATION TECHNIQUE	TREATMENT ARMS	CANCER CONTROL (%)
MD Anderson (Kuban et al, 2008) (N = 301)	8.7	Low: 20 Int: 46 High: 34	Conventional plus 3D conformal	70 Gy 78 Gy	10-yr freedom from failure 50 73 ($P = .004$)
PROG 95-09 (Zietman et al, 2010) (N = 391)	8.9	Low: 58 Int: 37 High: 4	3D conformal plus proton	70.2 Gy-equivalent 79.2 Gy-equivalent	10-yr biochemical failure 32.3 16.7 ($P = .0001$)
Dutch (Al-Mamgani et al, 2008) (N = 664)	5.8	Low: 18 Int: 27 High: 55	3D conformal	68 Gy 78 Gy*	7-yr freedom from failure 45 56 ($P = .03$)
MRC RT01 (Deamaley et al, 2007) (N = 843)	5.25	Low: 24 Int: 32 High: 44	Conformal	64 Gy 74 Gy†	5-yr biochemical progression-free survival 60 71 ($P = .0007$)

*21% to 22% of patients in each arm received androgen deprivation therapy, per institutional preference.

†All patients received androgen deprivation for 3 to 6 months before radiation and through radiation treatment.

3D, three-dimensional; FU, follow up; MRC, Medical Research Council; PROG, Proton Radiation Oncology Group.

Treatment Morbidity and Quality-of-Life Outcomes

These trials also clearly demonstrated the ability of improving radiation technology to lead to better cancer control. For many years, a radiation dose of 70 Gy was considered the maximum that could be safely delivered. With the advent of conformal RT, the ability to visualize and improve targeting of the prostate—and visualize and improve avoidance of surrounding organs—higher dose RT was made possible, with acceptable rates of treatment-related morbidity. However, further studies that demonstrated an association between radiation doses to organs and treatment-related morbidity presented opportunities for further improvement. For example, in the MD Anderson Cancer Center trial, the 5-year freedom from a complication above grade 2 was 26% in the 78-Gy arm and 12% for the 70-Gy arm, nicely demonstrating the relationship that can exist between dose and complications. When further analysis was

performed to identify factors other than total dose that might be used to predict for rectal toxicity, it was shown that the risk for complications increased from 25% to 46% when the rectal volume exposed to 70 Gy increased from less than 25% to greater than 25% (Pollack et al, 2002). Therefore newer technologies such as IMRT that can reduce radiation doses to these organs have the promise of reducing side effects associated with RT, which in general include **GI and genitourinary (GU) toxicity**.

Tables 116-3 and 116-4 summarize acute and late toxicity rates in published series comparing conformal radiation and IMRT for prostate cancer. Consistently in these series, IMRT was associated with lower rates of acute and late GI toxicity, but not GU toxicity, compared to 3DCRT, despite being used to give higher doses to the prostate. Therefore, paradoxically, advances in radiation technology have simultaneously allowed a higher radiation dose to be given while resulting in lower toxicity. The largest series of IMRT patients

TABLE 116-3 Acute Toxicity in Patients Treated with Three-Dimensional Conformal Radiation Therapy versus Intensity-Modulated Radiation Therapy

REFERENCE	N	RADIATION TECHNIQUE	RADIATION DOSE (Gy)	TOXICITY DEFINITION	GI TOXICITY (%)	P-VALUE	GU TOXICITY (%)	P-VALUE
Zelevsky et al, 2008a	1571	IMRT 3DCRT	81 66-81	CTCAE ≥ 2	3 1	0.04	37 22	0.001
Al-Mamgani et al, 2009	78	IMRT 3DCRT	78 78	RTOG ≥ 2	20 6	0.001	53 69	0.3
Sharma et al, 2011	293	IMRT 3DCRT	Median 76 Median 76	LENTTF ≥ 2	3DCRT higher (OR 4)	0.005		
Dolezel et al, 2010	232	IMRT 3DCRT	78 74	RTOG ≥ 2	16 35		33 27	
Alongi et al, 2009	172	IMRT 3DCRT	72-77.4 70.2-75.6	RTOG ≥ 2	6.6* 22.2*	0.004	6.6 12.3	0.19

*Rates of upper-GI toxicity.

3DCRT, 3D conformal radiation therapy; CTCAE, NCI Common Terminology Criteria for Adverse Events; GI, gastrointestinal; GU, genitourinary; IMRT, intensity-modulated radiation therapy; LENTTF, Fox Chase Modified Late Effects Normal Tissue Task Force radiation morbidity scale; RTOG, Radiation Therapy Oncology Group scoring system.

TABLE 116-4 Long-Term Toxicity in Patients Treated with Three-Dimensional Conformal Radiation Therapy versus Intensity-Modulated Radiation Therapy

REFERENCE	N	RADIATION TECHNIQUE	RADIATION DOSE (Gy)	FOLLOW-UP (yr)	TOXICITY DEFINITION	GI TOXICITY (%)	P-VALUE	GU TOXICITY (%)	P-VALUE
Zelevsky et al, 2008a	1571	IMRT 3DCRT	81 66-81	6.5 10	10-yr CTCAE ≥ 2	5 13	<.001	20 12	0.01
Al-Mamgani et al, 2009	78	IMRT 3DCRT	78 78	4.7 6.3	5-yr RTOG/EORTC ≥ 2	21 37	.16	43 45	1.0
Sharma et al, 2011	293	IMRT 3DCRT	Median 76 Median 76	3.3 7.2	5-yr LENTTF ≥ 2	8 20	.01		
Michalski et al, 2011	763	IMRT 3DCRT	79 79	3.5 4.6	RTOG/EORTC ≥ 2	IMRT < 3DCRT	.039		
Dolezel et al, 2010	232	IMRT 3DCRT	78 74	3.1 5.7	3-yr LENTTF ≥ 3	5 14	.03	7 9	0.18

3DCRT, 3D conformal radiation therapy; CTCAE, NCI Common Terminology Criteria for Adverse Events; GI, gastrointestinal; GU, genitourinary; IMRT, intensity-modulated radiation therapy; LENTTF, Fox Chase Modified Late Effects Normal Tissue Task Force radiation morbidity scale; RTOG/EORTC, Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer scoring system.

is from Memorial Sloan Kettering Cancer Center (Zelevsky et al, 2008c, 2012; Spratt et al, 2013). In this study, 10-year actuarial rates of grade 2 or greater GI toxicity with IMRT to 81 Gy was 5%, with less than 1% of patients developing grade 3 toxicity. In terms of urinary toxicity, 10-year rates of grade 2 or greater toxicity was 20% with IMRT; grade 3 GU toxicity was also rare. In a more recent update of this series, patient outcomes of those who received IMRT with image guidance (implanted fiducial markers) were compared to those who received IMRT without image guidance (Zelevsky et al, 2012). These patients were treated in recent years (2006 to 2009), because image guidance is a relatively new technology. Patients who received IMRT with image guidance had lower rates of late GU toxicity (3-year rates of grade ≥ 2 toxicity: 10.4% with image guidance vs. 20.0% without, $P = .02$), and rates of grade 2 or greater GI toxicity were low in both groups (1.0% vs. 1.6%, respectively; $P = .81$). These studies demonstrate that modern radiation treatment with IMRT and image guidance is safe, with modest rates of acute and long-term treatment-related GI and GU toxicity.

Patient-reported outcomes complement toxicity assessment by physicians to provide a fuller picture of a patient's experience after treatment. In one of the largest modern studies, 292 patients with a median age of 69 years who received either CRT or IMRT were followed prospectively using the validated instrument Expanded Prostate Cancer Index Composite (EPIC) (Sanda et al, 2008). Patients reported acute urinary and bowel symptoms that recovered over time. For example, at 2 months after RT, 12% of patients reported dysuria (compared to 1% at baseline), 23% weak stream (13% baseline), and 34% urinary frequency (16% baseline); symptoms improved by 6 months and were back to baseline levels by 12 months. Urinary incontinence was uncommon after RT. Acute bowel symptoms included urgency (18% at 2 months compared to 3% at baseline) and frequency (16% at 2 months compared to 2% at baseline), which partially recovered with longer time points of assessment. Patients also reported sexual dysfunction after RT in this older patient group. By 24 months after treatment, 60% of patients reported poor erections (compared to 37% at baseline); however, decline in sexual function was mostly from patients who received radiation in combination with ADT, whereas sexual function decline was more modest in patients who received RT alone. Patient-reported outcomes of modern IMRT with image guidance have not been well studied and should be better than these results and others in the literature of patients treated with conformal radiation or IMRT without image guidance.

With advancing radiation technology, which can reduce incidental radiation doses to the bladder and rectum, radiation-associated GU and GI toxicity and impact on patient-reported outcomes have declined over time. However, the anatomic structure causing radiation-associated erectile dysfunction is not known. Published reports suggest that erectile dysfunction after radiation is caused predominantly by vascular damage, and some data suggest that dose to the penile bulb may be correlated with erectile dysfunction (Roach et al, 2000; Fisch et al, 2001; Merrick et al, 2001). Further studies are needed; once an anatomic structure can be identified, radiation techniques can be used to minimize dose to this structure in an attempt to better preserve patient sexual function.

KEY POINT: TREATMENT MORBIDITY AND QUALITY-OF-LIFE OUTCOMES

- IMRT provides the ability to deliver higher doses of radiation with lower rates of GI toxicity.

Heavy Particle Beams

Since the 1950s, radiation oncologists have used particle beam therapy for their patients with cancer. The common application of

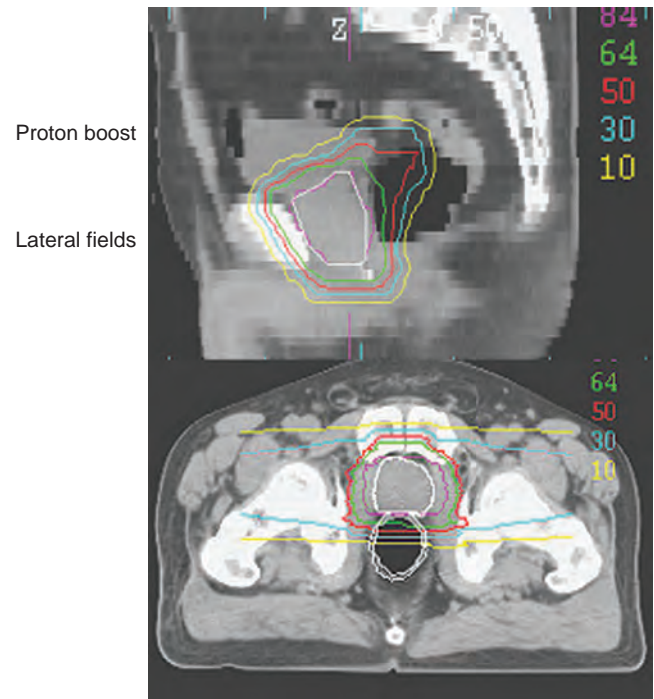


Figure 116-12. Proton beam therapy. (Courtesy Anthony Zietman, Massachusetts General Hospital.)

particle therapy is with the electron beam, which is created by all modern linear accelerators. Other particles such as protons, neutrons, helium ions, heavy ions (neon, argon, carbon), and negative ions are available as well. These **heavy particle beams** are difficult to produce and to control but have certain theoretic advantages over conventional x-ray and **electron beams**. They are more densely destructive in tissue, and the damage they create is less easily repaired by tumor cells. In addition, they travel differently in tissue and exhibit a **Bragg peak**, which refers to a sharp cutoff in dose at the end of the particle's range in tissue (Fig. 116-12). Beyond this depth, the tissue receives little or no radiation. Thus, with appropriate focus and application, it can be easier to spare the normal tissues surrounding the cancerous target.

The most commonly used particles are neutrons and protons. The RTOG sponsored a phase III trial in 1977 (Lawton et al, 1991) in which 91 patients with prostate cancer were randomly assigned to receive treatment with neutrons or conventional radiation (photons). At 10 years, survival was better in the neutron arm (46%) than in the photon arm (26%). However, patient characteristics were not equally balanced between the two arms. Poor prognosticators such as stage D1 disease were more common in the photon arm, and the observed survival difference between the two groups may have been due to this aspect more than to any therapeutic benefit of neutrons per se. However, the data were compelling enough to lead the NCI to fund the construction of several state-of-the-art neutron beam facilities. Again, trials were undertaken to study the efficacy and morbidity of neutron treatment. Because today's cyclotrons are large and extremely expensive, there are few national facilities using neutron beam treatment for cancer patients. In the mid-1980s, a second prospective randomized trial was undertaken by the RTOG. A group of 178 patients with prostate cancer were randomly assigned to receive either neutron beam or conventional photon treatment. The local control rate was higher for the patients who received neutron therapy than for those who received photons (89% vs. 68%), as was the 5-year rate of freedom from PSA failure (83% vs. 55%). However, survival rates were no different in the two arms. Morbidity was higher in patients who received neutron beam treatment and was described as severe in 11% compared with 3% for those who underwent photon irradiation.

In general, acceptance of neutron beam therapy by radiation oncologists has been limited because of the perception that complication rates are high without much gain in tumor control, as well as because of the limited availability and expense associated with neutron production. Over time, a form of conformal neutron beam therapy was developed and became possible in several centers (Forman et al, 1995). At Wayne State University, 300 patients were entered into a phase III trial and randomly assigned to conformal neutron therapy followed by standard CRT or CRT followed by a neutron therapy boost. A statistically significant difference in 5-year disease-free survival was seen for patients treated with neutrons first (93% compared with 73%, $P = .008$) (Forman et al, 2002). Treatment-related morbidity was the same for both groups in this study. A larger retrospective review from the same group of neutron therapy and photon CRT revealed a statistically significant improvement in 5-year relapse-free survival for the group that received neutrons as any component of their therapy. The effect was most pronounced for high-risk patients who had a 35% 5-year relapse-free survival rate versus 7% in the photon-only group ($P = .0004$). Although these data are provocative, one criticism is that the relapse-free survival in the photon-only group from Wayne State is much lower than that of other series reporting on the same population of patients.

Despite the data from Wayne State, most radiation oncologists believe that neutron beam therapy causes greater normal tissue damage than photon beam therapy. Investigators from the Catholic University of Louvain, Belgium, used a mailed questionnaire to assess quality-of-life changes in 262 patients who received mixed neutron-photon irradiation. Of the 230 patients who replied, 22% had four or more bowel movements per day. Retaining stool was a problem in 26% of the patients, and only 38% reported full bowel continence. The patients in this trial received neutron beam therapy using equipment that was not conformal. These data were sufficiently concerning to close their program and demonstrate the importance of up-to-date equipment and technology for the delivery of neutron beam therapy. Today, few patients with prostate cancer in the United States are treated with neutron RT.

Proton beams are also used to treat cancer. Although proton radiation is not a new treatment for prostate cancer, there has been significant recent interest in its use for prostate cancer (Zietman, 2007; MacReady, 2012). Protons are charged particles generated by

a linear accelerator, cyclotron, or synchrotron. Protons have the same theoretic advantage over photon as neutrons (i.e., they are more densely ionizing in tissue and have a sharp dose fall-off in tissue; see Fig. 116-11). In the 1980s, a prospective randomized trial was undertaken in men with locally advanced prostate cancer (Shipley et al, 1995). Patients treated with proton beams had a 95% incidence of clinical local control at 5 years, compared with a 64% incidence for those treated with photons. Although no grade 3 to 5 toxicities were reported in either arm of this trial, grade 1 and 2 rectal bleeding rates were higher in the proton group (32% vs. 12%, $P = .002$), as were urethral strictures (19% vs. 8%, $P = .07$). When the group with rectal bleeding was carefully analyzed, a relationship between the volume of rectum treated and the dose of protons given was established and guidelines were developed for future trials (Hartford et al, 1999).

Studies comparing proton therapy to modern IMRT for prostate cancer are mostly limited to treatment-planning studies, which have shown that proton radiation can reduce the volumes of nearby organs that receive low to medium—but not high—doses of radiation compared to IMRT (Table 116-5). For example, in a study by Trofimov and associates (2007), proton plans to 79.2 cobalt Gray-equivalent (CGE) were created for 10 patients using parallel opposed lateral fields, a commonly used technique for prostate cancer (Trofimov et al, 2007). They noted that proton therapy allowed a smaller proportion of the rectum to receive low doses of radiation (<30 CGE) compared to IMRT. However, proton plans did not reduce the volume of rectum receiving high doses of radiation. Another study by Vargas and colleagues (2008), using two proton beams but with angles optimized to minimize rectal and bladder dose, similarly demonstrated a reduction in rectal volume receiving low-to-moderate radiation doses, but minimal benefit in the volume of rectum receiving high-dose radiation (Vargas et al, 2008). Studies that found improvements in rectal sparing with proton therapy tended to find improvements in bladder sparing as well. Again, the most significant benefit was in reducing the volume of bladder receiving low-to-medium doses, but not high doses (Mock et al, 2005; Trofimov et al, 2007; Vargas et al, 2008; Chera et al, 2009). The study by Trofimov and associates (2007) reported better bladder sparing by proton therapy at doses lower than 30 CGE compared to IMRT, but protons actually resulted in a higher volume of the bladder receiving a high dose of 70 CGE (17% for proton vs. 11% for IMRT).

TABLE 116-5 Treatment Planning Studies Comparing Intensity-Modulated Radiation Therapy versus Conformal Proton Therapy

REFERENCE	TREATMENT TARGET	DOSIMETRIC MEASURE	RECTUM IMRT/PROTON	BLADDER IMRT/PROTON	FEMORAL HEAD IMRT/PROTON	SMALL BOWEL IMRT/PROTON
Chera et al, 2009	Prostate + SV + LN	Max dose (Gy)			32.7/37.6	48.1/51.0
		Mean dose (Gy)	40.9/16.6	42.1/21.2	22.1/30.6	27.3/10.4
		V10 (%)	92.7/35.1*	100/46.2*	V10: 98.0/93.5	V10 (cc): 242/86*
		V50 (%)	27.3/15.1	25.6/18.2	V30: 12.4/83.6*	V30 (cc): 123/43*
		V70 (%)	11.5/7.9	9.7/9.8	V45: 0/1	V45 (cc): 16/9
Vargas et al, 2008	Prostate ± SV	Mean dose (Gy)	34.8/14.2*	28.4/18.4*		
		V10 (%)	72.1/29.8*	60.0/36.4*		
		V30 (%)	55.4/20.7*	42.8/27.7*		
		V50 (%)	31.3/14.6*			
		V70 (%)	14.0/7.9*			
		V78 (%)	5.0/2.9*			
Trofimov et al, 2007	Prostate + SV	Mean dose (Gy)	39.4/29.2*	29.9/24.1*		
		V30 (%)	65.3/43.8*	44.5/32.8*		
		V50 (%)	34.4/28.2*	23.7/25.4		
		V70 (%)	14.5/14.0	11.4/17.3*		
		V75 (%)	9.7/10.3			

*Statistically significant difference.

IMRT, intensity-modulated radiation (photon) therapy; LN, lymph nodes; SV, seminal vesicles.

Similarly, [Vargas and colleagues \(2008\)](#) found bladder sparing at doses from 10 to 35 Gy, but not at doses above 60 Gy. The opposed lateral beam arrangement used in proton therapy raises concern over the dose received by femoral heads. Several studies identified similar or worse femoral head dose distributions using protons compared to IMRT, especially when pelvic nodes are included in the treatment target as reported by Chera and coworkers (mean femoral dose 31 CGE for proton vs. 22 Gy for IMRT) ([Mock et al, 2005](#); [Trofimov et al, 2007](#); [Chera et al, 2009](#)). However, the femoral doses delivered in these studies remained lower than the commonly accepted dose constraint of 45 Gy.

Whether the lowering of low-to-moderate doses of radiation to the rectum from proton therapy results in lower GI toxicity rates compared to IMRT is unknown; conversely, it is unknown if proton causes higher rates of GU toxicity or pelvic fracture rates as a result of somewhat higher doses to the bladder (at high dose regions) and femoral heads. To date, no clinical study has directly compared patient outcomes of proton therapy versus modern IMRT. Available studies include single-arm (proton therapy) series mostly from single institution or a few institutions ([Slater et al, 2004](#); [Coen et al, 2011](#); [Mendenhall et al, 2012](#)). These data suggest that proton therapy is safe and effective for prostate cancer treatment and likely results in cancer control and morbidity outcomes similar to that with IMRT. Because proton-beam treatment units are extremely expensive to construct and operate, proton therapy represents an expensive treatment option for prostate cancer that currently has not demonstrated a clinical benefit over standard IMRT.

KEY POINT: HEAVY PARTICLE BEAMS

- No clinical study has directly compared patient outcomes of proton therapy versus IMRT for prostate cancer.

Brachytherapy

Brachytherapy (“short” therapy) is the placement of radioactive sources into or near tumors for therapeutic purposes. The discovery of x-rays and the purification of radium in the early 20th century paved the way for the development of this form of therapy. Subsequent technical advances and refinements led to the increasingly accurate techniques currently in use, which are associated with greater efficacy and lower cost and morbidity rates. Since the early 1990s, the number of patients undergoing brachytherapy for early-stage prostate cancer has increased dramatically. The CaPSURE database reported an increase in the use of brachytherapy from 4% in 1990 to 15% by 2007 ([Cooperberg et al, 2010](#)).

Pasteau and Degrais described the temporary placement of radium-containing needles into the prostate through the urethra ([Pasteau, 1913](#)). During the 1920s, [Young \(1922\)](#) at Johns Hopkins performed prostate brachytherapy using intracavitary radium sources in the bladder, rectum, and urethra “cross-firing” into the prostate. This technique was refined at Memorial Hospital in New York by Benjamin Stockwell Barrington, who pioneered implanting needles containing radioactive radon gas into the prostate by a transperineal approach. During the 1970s, [Whitmore and colleagues \(1972\)](#) at Memorial Sloan Kettering in New York performed ^{125}I implantation in patients after they underwent lymph node dissection. The prostate was exposed by the retropubic approach for implantation. However, this “freehand” technique resulted in suboptimal distribution of seeds and poor dosimetry ([Zelefsky and Whitmore, 1977](#)).

[Holm and colleagues \(1983\)](#) described closed transperineal implantation with the aid of TRUS. With this approach, the needles used to insert the radioactive seeds could be visualized, with an improvement in the accuracy of seed placement compared with the retropubic approach. Surgical morbidity and cost were reduced. For this procedure, the patient is placed in the high lithotomy position

to maximize the transperineal exposure of the prostate. A transrectal ultrasound probe is then inserted and affixed to a mount or stabilizer through a stepping device. A template with a predrilled pattern of parallel holes is attached to the stepper. This permits accurate and reproducible imaging of the prostate throughout the procedure. The template pattern also can be superimposed over the ultrasound image by computer software in the ultrasound device. Needles of 17 or 18 gauge are inserted through the template into the prostate. The position of the needle tip can be confirmed by transverse or parasagittal imaging. Sealed metallic seeds containing the radioactive isotope are deployed as the needle is withdrawn ([Figs. 116-13 through 116-16](#)).

Computer programs using sophisticated algorithms to optimize dosimetric coverage of the entire prostate while minimizing dose to the intraprostatic urethra and rectum have been developed. [Stone and Stock \(1999\)](#) determined the number of seeds to be implanted on the basis of the size of the gland and the nomogram reported by [Anderson \(1976\)](#). The seeds are implanted using the empirical



Figure 116-13. Patient in the high lithotomy position with the transrectal ultrasound probe fixed to the stepper device. Needle containing radioactive seeds is implanted through the perineum using a grid system.

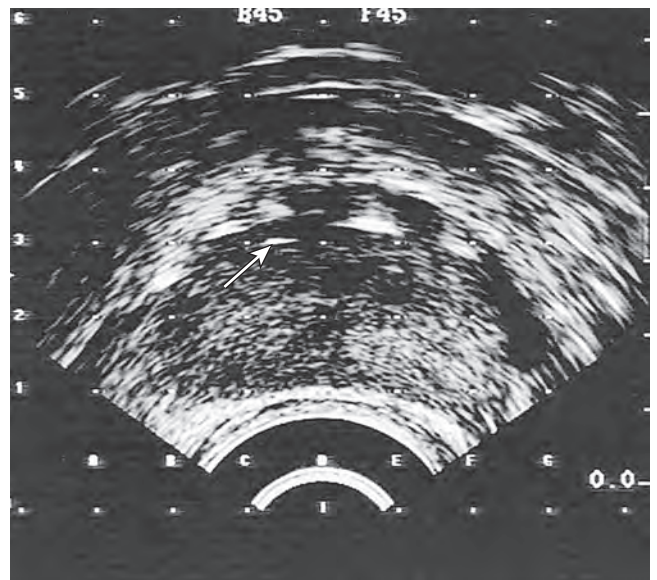


Figure 116-14. Transverse ultrasound image of the prostate. Several seeds are visible in the anterior gland. The arrow delineates the target location for the insertion of a needle.

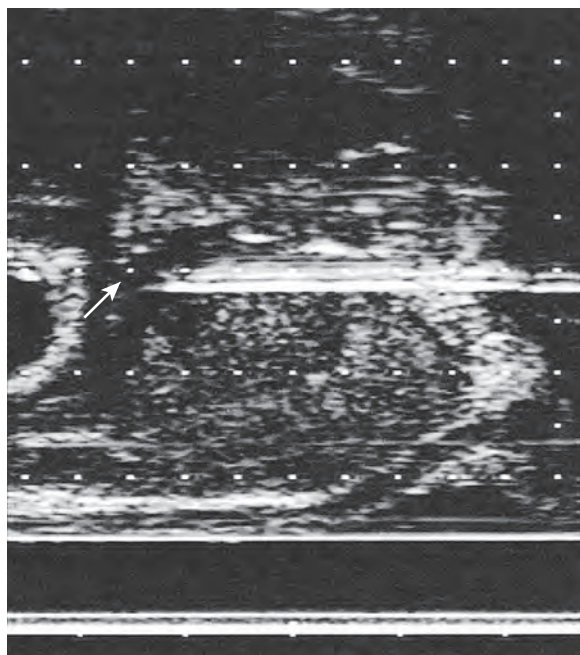


Figure 116-15. Parasagittal ultrasound image of the prostate. The arrow demonstrates that the needle depth goes to the prostatic capsule before deployment of the radioactive seeds.

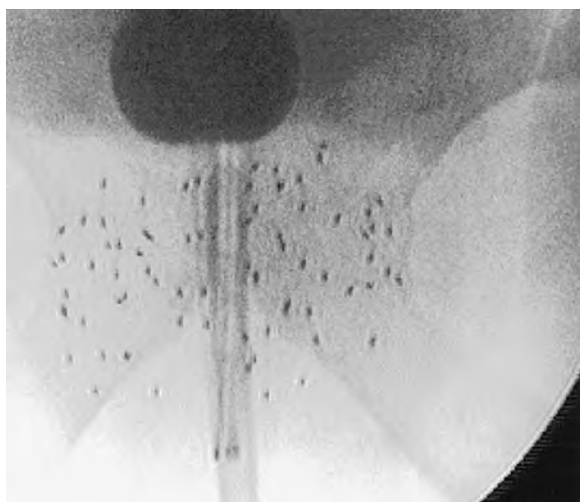


Figure 116-16. Intraoperative fluoroscopic image of the prostate demonstrating the placement of palladium-103 seeds.

rules defined by Patterson and Parker in the 1930s (Fletcher, 1980), preferentially sparing the urethra to reduce urinary morbidity (Wallner et al, 1995). Several methods for designing seed placement are currently in use for permanent radioactive seed implantation. The method popularized by Blasko and colleagues (1993) in Seattle uses preimplant transrectal ultrasound images obtained through a separate procedure with the patient in the same lithotomy position to calculate seed placement for an optimal dosimetric plan. Kaplan and coworkers (2000) described a method in which the dosimetric plan is calculated intraoperatively. Other methods for seed implantation using CT (Koutrouvelis, 1998) and an intraoperative MRI device (D'Amico et al, 1998a; Susil et al, 2004) also have been described. Cystoscopy is often but not always performed and can be useful to retrieve any loose seeds or blood clots from the bladder.

TABLE 116-6 Ideal Permanent Prostate Brachytherapy Postimplantation Guidelines

ORGAN	PARAMETER	CONSTRAINT
Prostate	Dose received by 90% of the prostate volume (D90)	>100% of prescription dose
	Volume of the prostate that received 100% of the prescription dose (V100)	>95% of the prostate
	Volume of the prostate that received 150% of the prescription dose (V150)	<50% of the prostate
Rectum	Volume of the rectum that received the prescription dose (R100)	<2 cm ³

Modified from Salembier C, Lavagnini P, Nickers P, et al; GEC ESTRO PROBATE Group. Tumour and target volumes in permanent prostate brachytherapy: a supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy. *Radiother Oncol* 2007;83:3–10.

Isotopes

There are several choices for isotopes for permanent seed implantation. ¹²⁵I emits low-energy x-rays at 27 keV, with a half-life of 59.6 days. The use of ¹⁰³Pd was introduced in 1986 because it has an energy spectrum similar to that of ¹²⁵I, with 21-keV x-rays, but with a significantly shorter half-life of 17 days. Higher activity seeds are required for ¹⁰³Pd versus ¹²⁵I to deliver a similar tumoricidal dose (i.e., 1.3 to 1.5 mCi per Pd seed vs. 0.4 to 0.5 mCi per I seed). The recommended monotherapy dose prescription for ¹²⁵I is 140 to 160 Gy and for ¹⁰³Pd is 110 to 125 Gy. When brachytherapy is combined with EBRT, brachytherapy doses ought to be lower (108 to 110 Gy for ¹²⁵I and 90 to 100 Gy for ¹⁰³Pd) (Davis et al, 2012).

Assessment of Permanent Implant Quality

The goal of prostate brachytherapy is to deliver a homogeneous dose to the prostate while minimizing dose to nearby sensitive normal structures such as the rectum and urethra. Postimplant dosimetry in these dose-limiting regions is important to assess implant quality. Postimplantation CT with or without MRI is performed to determine seed localization and reference the dose to the prostate and other structures of importance (Willins and Wallner, 1997; Mizowaki et al, 2002). A significant source of error in these calculations is prostatic edema, which is invariably observed after implantation (Prestidge, 1998; Waterman et al, 1998). Although clinical practice varies with postoperative imaging taking place between day 0 and day 60, early imaging/dosimetric calculation must consider the effect of postoperative edema. The American Brachytherapy Society (ABS) recommends using the D90 (the minimal dose covering 90% of the prostate volume) and the V100 and V150 (the percent volume of the prostate receiving 100% and 150% of the prescribed dose, respectively) as parameters to assess implant quality (Davis et al, 2012). Ideal implant parameters are shown in Table 116-6.

High-Dose-Rate Brachytherapy

Permanent seed implantation delivers a dose over a number of weeks to months depending on the isotope chosen, hence the term *low dose rate*. An alternative method of brachytherapy, which delivers short but high doses of radiation using temporary catheters, is **HDR brachytherapy**. For HDR brachytherapy, hollow catheters are placed through the perineum into the prostate and imaged using the same procedure as for LDR brachytherapy. A treatment plan is developed based on the use of a 1 to 10-curie iridium-192 source

that emits 400-keV gamma radiation and can be migrated along the length of each catheter at various positions for variable lengths of time on the order of seconds to minutes. The source is manipulated robotically to minimize radiation exposure to medical staff. The radiation dose is delivered in this way over several applications. No postimplantation dosimetry is required. HDR has been used primarily as a boost in combination with EBRT for patients with intermediate-risk or high-risk features, although it is becoming more common as monotherapy in patients with low-risk disease.

Outcome of Implants

Post-treatment biopsies can be used to assess the efficacy of local therapies to control cancer, but there are several limitations to using this technique in prostate cancer, which were discussed earlier within this chapter. Early studies of prostate brachytherapy included postimplantation biopsy; these studies showed a very low rate of 4% to 5% positive biopsy results 2 years after good dosimetry implants (Prestidge et al, 1997; Stone et al, 2004). More recently biochemical surrogates for cancer control have been used in addition to survival parameters.

Serum PSA is the most useful marker to assess relapse. A rising PSA level after irradiation predicts local or distant relapse, or both, often many years before clinical evidence of recurrence (Kaplan et al, 1993). However, the variability of PSA, especially at low levels, often makes interpretation problematic. In addition, the suppres-

sion of PSA with even short courses of antiandrogen therapy can complicate interpretation of results. A PSA bounce has been reported in approximately 30% of patients after brachytherapy (Critz et al, 2000; Hinnen et al, 2012). Some investigators have reported improved rates of cancer control in patients who experience a PSA bounce (Patel et al, 2004; Hinnen et al, 2012).

Table 116-7 summarizes the clinical outcomes of permanent implant monotherapy in several large series. Although these are retrospective single-institution studies (with the exception of RTOG 98-05), they represent results from a uniform population of patients. These results compare favorably with those of similarly selected patients treated with EBRT or radical prostatectomy (D'Amico et al, 1998b; Quaranta et al, 2004; Grimm et al, 2012). Early results with HDR used as monotherapy for patients with low-risk prostate cancer have demonstrated acceptable toxicity and early rates of biochemical freedom from relapse similar to those for permanent seed implants. Table 116-8 summarizes results of trials of HDR monotherapy.

Brachytherapy Combined with External Irradiation

Although outcomes in patients with low-risk prostate cancer using brachytherapy are excellent, biochemical control can be improved for intermediate-risk and the higher risk subset of intermediate-risk patients by combining brachytherapy with EBRT. EBRT is employed in these patients to treat the prostate and periprostatic tissues. This

TABLE 116-7 Actuarial Freedom from Biochemical Relapse: Implant Monotherapy and Combined Implant and External Beam

REFERENCE	NO. PATIENTS	MEDIAN FOLLOW-UP (mo)	BIOCHEMICAL DISEASE-FREE SURVIVAL BY RISK GROUP		
			LOW (%)	INTERMEDIATE (%)	HIGH (%)
Crook et al, 2011	776	54	95		
Henry et al, 2010	1005	59	72	74	58
Hinnen et al, 2010	601	69	88	61	30
Taira et al, 2010	463	74	97	96	
Prada et al, 2010	706	55	92	84	65
Morris et al, 2013	1005	90	94	94	
Sylvester et al, 2011	128	140	86	80	62
Lawton et al, 2011	101	97	92		
Zelevsky et al, 2012	877	49	98	94	

Modified from Morton GC, Hoskin PJ. Brachytherapy: current status and future strategies—can high dose rate replace low dose rate and external beam radiotherapy? Clin Oncol (R Coll Radiol) 2013;25:474–82.

TABLE 116-8 High Dose Rate Brachytherapy as Monotherapy for Low Risk Prostate Cancer

REFERENCE	NO. PATIENTS	MEDIAN FOLLOW-UP (mo)	BIOCHEMICAL DISEASE-FREE SURVIVAL (%)	HIGH DOSE RATE/ NO. FRACTIONS
Shah et al, 2012	252*	58	91	38 Gy/4
Prada et al, 2012	40*	19	100	19 Gy/1
Zamboglou et al, 2013	395	53	95	39 Gy/4–34.5 Gy/3
Barkati et al, 2012	79†	40	89	30 Gy, 31.5 Gy, 33 Gy, 34.5 Gy/3
Yoshioka et al, 2011	15	65	85	54 Gy/9
Demanis et al, 2011	298	62	97†	42 Gy/6 or 38 Gy/4

Modified from Morton GC, Hoskin PJ. Brachytherapy: current status and future strategies—can high dose rate replace low dose rate and external beam radiotherapy? Clin Oncol (R Coll Radiol) 2013;25:474–82.

*Includes higher risk.

†Includes some intermediate-risk patients.

strategy allows targeting of high-risk areas outside the prostatic capsule and increases the dose to the prostate itself. Typically, a dose of 4500 cGy of EBRT is delivered (compared with 7560 to 7920 cGy when EBRT is used alone). The dose of the implant boost in such combination therapy is generally 60% to 70% of the dose prescribed for patients treated with implant alone. Biochemical disease-free survival for high-risk men using this strategy can range from 80% to 90%, particularly when combined with androgen deprivation (Koontz et al, 2009; Taira et al, 2010; Merrick et al, 2011; Shilk-rut et al, 2013a, 2013b). HDR brachytherapy series with at least 5 years of follow-up also show very good biochemical control for both intermediate-risk (83% to 100%) and high-risk (74% to 91%) patients (Morton and Hoskin, 2013). The role of external beam with permanent seed brachytherapy versus brachytherapy alone for selected intermediate-risk men is being investigated in a randomized clinical trial by the RTOG (RTOG trial 0232).

Toxicity

Implant techniques and quality have a strong impact on the likelihood of radiation toxicity from prostate brachytherapy. Age, existing comorbid diseases such as peripheral vascular disease or diabetes mellitus, and tobacco use also may predispose to increased toxicity from treatment.

Determining incidence rates and severity of treatment-related morbidity also depends on the instrument used and how the information is gathered. The American Brachytherapy Society proposed as a minimal set of assessment criteria the International Prostate Symptom Score (IPSS) for assessing urinary function, the International Index of Erectile Function for erectile function, and RTOG toxicity grading criteria for rectal toxicity.

Urinary Toxicity

The IPSS tends to increase significantly immediately after implantation and then decrease, at a rate depending on the half-life of the isotope used (Sanda et al, 2008; Kollmeier et al, 2012). For HDR, brachytherapy appears to show a similar pattern with 15% to 18% showing grade 2 or greater acute urinary symptoms (Zamboglou et al, 2013). In recent series of permanent implants, the rate of chronic grade 2 or greater urinary toxicity is approximately 20% (Mohammed et al, 2012; Buckstein et al, 2013). The use of α -blockers before implantation may decrease the severity and duration of urinary symptoms (Merrick et al, 2002b). Wallner and colleagues (1995) reported the risk for urinary toxicity to be a function of the length of the urethra receiving a high dose. Grade 2 to 3 morbidity was observed when 20 mm + 11 mm of the urethra received more than 400 Gy with ^{125}I implants. Larger prostatic volumes—specifically, glands greater than 60.0 cm³—also were associated with higher rates of urinary toxicity. Terk and colleagues (1998) reported on 251 patients using the IPSS to assess urinary function before and after ^{125}I or ^{103}Pd implantation. Patients with a pretreatment IPSS above 20 demonstrated a 29% risk for developing urinary retention, and a pretreatment score less than 10 was associated with only a 2% risk. Although data are yet maturing, HDR brachytherapy appears to be very well tolerated, with low rates of chronic grade 3+ urinary morbidity (5% to 10%) (Barkati et al, 2012; Zamboglou et al, 2013).

Brachytherapy after TURP is associated with increased risk for urinary incontinence. Although this complication is quite uncommon in men without any preexisting urethral trauma (~3%), Mock and colleagues (2013) reported a 19% incidence in patients with one previous TURP and up to 53% in those with a history of multiple procedures (although numbers were small). Overall, significant postbrachytherapy obstructive symptoms refractory to medical management occur in approximately 2% to 3% of patients.

Rectal Toxicity

Acute minor rectal symptoms secondary to brachytherapy are usually self-limiting. Late rectal toxicity—specifically, rectal bleed-

ing secondary to radiation proctitis—can be a minor, self-limiting side effect of radiation or a major toxicity requiring surgical intervention such as argon plasma coagulation (Smith et al, 2001) or, in the worst cases, diverting colostomy. The rate of rectal bleeding after implant therapy has been reported to be approximately 1% (Zelevsky et al, 1999; Mohammed et al, 2012). The incidence of all significant rectal complications has been reported to be 1% to 2% (Barkati et al, 2012; Zamboglou et al, 2013). A postimplantation colostomy rate of 0.3% was observed in a study of Medicare claims (Benoit et al, 2000a, 2000b). The rate of rectal complications is correlated with the dose and the length of rectum receiving a high dose. For example, rectal complications have been observed more frequently when 17 mm² (± 5 mm) of the rectal wall received more than 100 Gy (Wallner et al, 1995). Wallner and colleagues (1995) accordingly recommended minimizing the amount of rectum receiving 100 Gy in ^{125}I implants. Merrick and colleagues (2003) reported that rectal complications were rarely observed when the rectal wall received 85% of the prescribed dose.

Potency

Impotence is defined by the National Institutes of Health (NIH) consensus on erectile dysfunction (ED) as the “inability to attain and maintain a penile erection sufficient to permit satisfactory sexual intercourse” (NIH Consensus Conference, 1993). The cause of implant-related ED is multifactorial. Factors such as underlying small vessel disease, cavernous nerve damage, and dose to the vascular tissues surrounding the penile bulb have been implicated in postimplantation ED (DiBiase et al, 2000; Merrick et al, 2001).

In any case, potency preservation rates for patients undergoing implantation are superior to those reported for patients receiving prostatectomy, EBRT, or neoadjuvant hormonal therapy/EBRT/brachytherapy boost (Sanda et al, 2008). Snyder and colleagues (2012) reported that 5 years after treatment potency was maintained in 76% of patients undergoing brachytherapy compared with 71% receiving EBRT plus brachytherapy, and 58% in those undergoing EBRT, brachytherapy, and androgen deprivation.

Potters and colleagues (2001) reported a 5-year potency maintenance rate of 76% with brachytherapy monotherapy and 56% with combined external beam and brachytherapy boost. The addition of hormones to external beam and brachytherapy boosted lower potency rates to 52%. Age was a significant prognostic factor in a univariate analysis (Merrick et al, 2002a), and the addition of external beam and a history of diabetes mellitus were significant factors in a multivariate analysis (Robinson et al, 2002). In a meta-analysis, the probability of maintaining potency at 1 year after treatment was 76% (69% to 82%) with brachytherapy monotherapy and 60% (48% to 73%) with external beam with brachytherapy boost (Robinson et al, 2002). When the probability of ED was adjusted for age, the difference between prostate brachytherapy and prostatectomy increased (Robinson et al, 2002).

Sildenafil citrate and other phosphodiesterase-5 inhibitors have been reported effective in 74% to 81% of patients who avail themselves of oral therapy for ED (Merrick et al, 2003; Raina et al, 2003).

KEY POINTS: BRACHYTHERAPY

- Prostate brachytherapy can be delivered as monotherapy for low-risk prostate cancer or in conjunction with EBRT (with or without ADT) for intermediate-risk and high-risk prostate cancer.
- Dose delivered to the rectum is directly related to the likelihood and degree of late morbidity from brachytherapy.

Hypofractionation and Stereotactic Body Radiotherapy

Fractionated radiotherapy has been used since the early days of radiation, when it was found that cure could be achieved with less

normal tissue injury when the radiation dose was split into many small fractions (Coutard, 1932). Standard fractionation for prostate cancer is 1.8 to 2 Gy per day. Moderate **hypofractionation** uses doses of 2.4 to 4 Gy per day, and extreme hypofractionation uses doses of 6 to 10 Gy per fraction (Cabrera and Lee, 2013). When doses in this range are given, treatment is often delivered less than 5 days per week to allow normal tissue recovery. An entire treatment course of extreme hypofractionation can be completed within 2 weeks.

Radiobiology of Hypofractionation

The rational basis for the use of hypofractionation for prostate cancer lies in the radiobiology and slowly proliferative nature of prostate cancer cells. Prostate cancer is believed to be acutely sensitive to the amount of radiation delivered at each treatment, such that providing a few treatments of high dose is more effective at producing cell kill than many fractions of 2 Gy. It is hypothesized that one could provide a lower total dose, thus lessening risk for normal organ injury, with similar prostate cancer control using higher than standard doses per fraction (Withers, 1985).

The support for this hypothesis is based on clinical studies in which the treatment dose was varied. The first report suggesting this relatively unique sensitivity to high dose per fraction was by Brenner and Hall (1999), who used the 3-year freedom from biochemical failure rates of 134 patients receiving permanent brachytherapy and 233 patients receiving EBRT to calculate an **alpha-to-beta ratio** of 1.5 Gy. This radiobiologic value is used to calculate the radiosensitivity of a tissue. For comparison, the alpha-to-beta ratio of head and neck cancers is thought to be between 13 and 16 Gy, whereas a late responding skin fibrosis has an alpha-to-beta ratio of 1.7 Gy (Zeman, 2009). Although intriguing, this study brought criticism for its use of several radiation modalities, which vary not only in dose per fraction but also in other radiobiologic qualities of the radiation delivered. However, more recent studies using large cohorts treated with EBRT only continue to support the premise of prostate cancer sensitivity to high dose per fraction. Dasu and Toma-Dasu (2012) evaluated the Phoenix-defined 5-year biochemical control from 11,330 patients treated with EBRT, accounting for overall treatment time, and found that, depending on risk category, the alpha-to-beta ratio varied from 1.0 to 1.7 Gy. A second study found an alpha-to-beta ratio of 1.4 Gy using 5969 patients receiving EBRT (Miralbell et al, 2012). Table 116-9 illustrates how hypofractionation may provide a greater effective dose to the prostate than to normal tissues.

Stereotactic Body Radiotherapy

Although prostate cancer's low alpha-to-beta ratio supports treatment with a few large fractions, care still must be taken to protect

the nearby bladder and rectum, which also are relatively sensitive to high dose per fraction. Thus the advent of extreme hypofractionation was concurrent with technology that provides high accuracy and conformality to the radiation dose cloud. **Stereotactic body radiotherapy (SBRT)** defines an external-beam RT that delivers a high dose each treatment using precisely targeted and highly conformal radiation. The total treatment length is between 1 and 5 fractions (Benedict et al, 2010). Recent linear accelerator technology making SBRT possible includes accurate 2D and 3D imaging of patients immediately before/after and even during treatment, improved dose calculation software, and intensity modulation. SBRT can be performed in a **traditional linear accelerator** or using a **CyberKnife system** (Accuray, Sunnyvale, CA), which is a megavoltage linear accelerator mounted on a robotic arm with six degrees of freedom in conjunction with intrafraction imaging capabilities to track target motion (Kilby et al, 2010).

Understanding of tumor and critical organ motion is essential to designing safe and effective SBRT plans. The prostate is a mobile structure within the pelvis, its position changing in relation to rectal and bladder filling (Schild et al, 1993; Adamson and Wu, 2009). For RT, two types of motion have been defined, interfraction motion, which encompasses changes in prostate position from one day to the next, and intrafraction motion, describing motion of the prostate during each treatment.

Patient positioning and treatment devices are helpful to minimize both types of motion. There appears to be no significance whether the patient is positioned supine or prone (Stroom et al, 1999; Wilder et al, 2010). However, use of an endorectal balloon can reduce prostate variability, particularly intrafraction motion (van Lin et al, 2005; Both et al, 2011). Other techniques that allow adjustment of the patient on the treatment equipment include implantation of permanent nonradioactive fiducial markers that are visible on kilovoltage imaging through the linear accelerator (Aubin et al, 2003; Middleton et al, 2011). This allows the treatment positioning to be corrected to the position of the prostate at that time (Fig. 116-17) (Schallenkamp et al, 2005). Further development of this concept has resulted in the use of implanted electromagnetic wireless transponders that work similar to fiducials but can provide intrafraction monitoring of prostate motion (Willoughby et al, 2006; Quigley et al, 2009). These transponders are larger than fiducial markers and typically require transperineal placement.

Finally, two imaging modalities have been used to document prostate location immediately before treatment delivery each day: **ultrasound** and **CT**. Transabdominal ultrasound imaging with a full bladder uses software to modify patient position on the linear accelerator to match the setup at time of planning (Trichter and Ennis, 2003). Use of this technology requires specialized training and can have significant interuser variability (Langen et al, 2003; Pinkawa et al, 2008). CT imaging uses a cone-beam technique allowing the kilovoltage extension of a modern linear accelerator to obtain a broad-beam CT image of a limited size (Barney et al, 2011). Again, software is used to adjust patient positioning to match the prostate position at planning. The disadvantage to the cone-beam CT technique is the additional dose received by the patient (van Zijteld et al, 2010).

Outcomes for External-Beam Hypofractionation

The evidence for prostate SBRT is still evolving. Five phase III trials of moderate hypofractionation (Table 116-10) have been published, and several more are pending.

A multi-institutional noninferiority trial from the NCIC randomized 936 predominantly low-risk men to 66 Gy in 2-Gy fractions over 6.5 weeks versus 52.5 Gy in 2.625 Gy over 4 weeks (Lukka et al, 2005). Median follow-up was 5.7 years. The 5-year risk for biochemical or clinical failure was 53% in the standard fractionation arm and 60% in the hypofractionated arm (difference -7%, 90% CI -12.6% to -1.4%). Although acute toxicity was slightly higher with hypofractionation (11.4% vs. 7%, difference -4.4%; 90% CI -8.1% to -0.6%), late toxicity was low for both arms (3.2%). The major weakness of this trial was the low dose used for

TABLE 116-9 Examples of Alpha-to Beta Principle for Prostate, Bladder, and Rectum

TISSUE OF INTEREST	ALPHA-TO-BETA RATIO (Gy)	EQUIVALENT DOSE IN 2-Gy FRACTIONS OF 37.5 Gy IN 5 FRACTIONS (Gy)
Prostate cancer	1.5	96
Rectum/bladder	3	79
Bladder	5	67

The biologically effective dose provided in 2-Gy fractions is shown calculated using the alpha-to-beta ratio. Although the rectum and bladder also can have temporary acute effects, only the alpha-to-beta ratio for the chronic late effects is provided. Time delay was not considered in equivalent dose calculation. Current standard dosing using intensity-modulated radiation therapy has shown acceptable safety profile up to 81 Gy in 2-Gy fractions (Van der Kogel, 2002; Alicikus et al, 2011).

TABLE 116-10 Randomized Trials of Moderate Hypofractionation

REFERENCE	N	MEDIAN FOLLOW-UP (yr)	DOSE TOTAL (Gy) (FRACTION [Gy])	OUTCOME STD VS. HYPOFX, %	LATE TOXICITY, %
Lukka et al, 2005	936	5.7	66 (2) 52.5 (2.625)	5-yr FFBF, * 53 vs. 60 (NS)	Gr3+ GI/GU, 1 vs. 2 (NS)
Yeoh et al, 2011	217	7.5	64 (2) 55 (2.75)	7.5-yr BRFS, 34 vs. 53 ($P < .05$)	NS
Arcangeli et al, 2011	168	5.8	80 (2) 62 (3.1)	5-yr FFBF, 79 vs. 85 ($P = .065$)	Gr2+ GU, 11 vs. 14 Gr2+ GI, 14 vs. 17 (NS)
Pollack et al, 2011	303	5.5	76 (2) 70.2 (2.7)	5-yr BF, 15 vs. 19 ($P = .34$)	Gr2+ GU, 8 vs. 18 ($P = .03$) Gr2+ GI, 4 vs. 6% (NS)
Kuban et al, 2010	204	4.7	75.6 (1.8) 72 (2.4)	5-yr FFBF, 94 vs. 97 (NS)	Gr2+ GU, 19 both Gr2 GI, 5 vs. 11 ($P = .06$ all grade GI)

Prostate-specific antigen failure defined using nadir + 2 ng/mL except where marked.

*Failure defined as three consecutive rises.

BF, biochemical failure; BRFS, biochemical relapse free survival; FFBF, free from biochemical failure; GI, gastrointestinal; GU, genitourinary; Hypofx, hypofractionation; Std, standard.

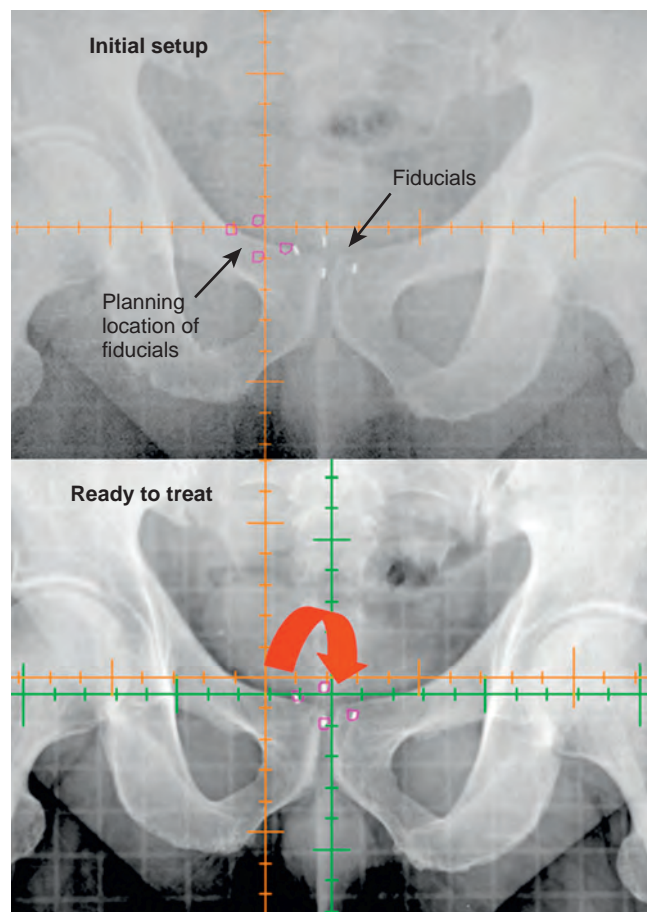


Figure 116-17. Kilovoltage imaging with fiducial markers for prostate localization and treatment positioning during radiotherapy treatment.

both arms that resulted in high failure rates. It was designed before development of the alpha-to-beta ratio hypothesis, and the hypofractionated dose was biologically less effective than the standard arm using an alpha-to-beta ratio of 1.5.

Yeoh and colleagues (2011) reported a randomized trial of 217 cT1-2 patients comparing 64 Gy in 2-Gy fractions over 6.5 weeks

to 55 Gy in 2.75-Gy fractions in 4 weeks. Median follow-up was 90 months and showed improved 7.5-year biochemical relapse-free survival in the hypofractionated arm (34% vs. 53%, comparatively, $P < .05$). Although this study offers support for the rationale of hypofractionation, the numbers are small and the total doses are again low.

A randomized controlled trial from Italy compared 85 men receiving 80 Gy in 40 2-Gy fractions over 8 weeks with 83 men receiving 62 Gy in 20 fractions of 3.1 Gy over 5 weeks (Arcangeli et al, 2012). All were high risk and received 9 months of ADT. With median follow-up of 70 months, 5-year freedom from biochemical failure was similar in both arms (79% vs. 85%, respectively, $P = .065$). Both arms were well tolerated, with GI/GU late toxicities occurring in 16% to 17% and 11% to 14%.

Pollack and colleagues (2011) reported the results of the Fox Chase randomized study of 303 men with intermediate-risk or high-risk cancer. Standard fractionation was 76 Gy in 2-Gy fractions versus 70.2 Gy in 2.7-Gy fractions. There were no significant differences in 5-year biochemical failure (15% vs. 19%, $P = .342$) and worse late grade 2+ GU toxicity in the hypofractionated arm (18% vs. 8%, $P = .028$).

The last published randomized trial of moderate hypofractionation comes from MD Anderson Cancer Center (Cabrera and Lee, 2013). This study randomized 204 predominantly low-risk and intermediate-risk men to 75.6 Gy in 1.8-Gy fractions or 72 Gy in 2.4-Gy fractions. With a median follow-up of 4.7 years, 5-year freedom from biochemical failure was not significantly different ($P = .23$) between standard fractionation (92%) and hypofractionation (92%). Toxicity was likewise similar, although there was a trend toward worse late GI toxicity with hypofractionation ($P = .058$).

Studies of extreme hypofractionation are as of yet early phase I/II studies. However, to date 10 different series of patients treated with 6.7 to 10 Gy per fraction have been published (Table 116-11). Although follow-up is generally short, biochemical outcomes for low-risk and intermediate-risk prostate cancer range between 90% and 100%. However, there is a marked increase in late morbidity compared to studies of moderate hypofractionation, with grade 2 urinary toxicity in some studies greater than 30%. Although it is a rare occurrence, one study did note a grade 4 rectal ulcer in a patient receiving 50 Gy in 5 fractions (Boike et al, 2011) and another reported a rectal fistula (Loblaw et al, 2013).

Ongoing studies will provide more information about the role and risk of hypofractionation. Three multi-institutional phase III noninferiority trials of moderate hypofractionation have recently completed or are actively enrolling. Dearnaley and colleagues

TABLE 116-11 Reported Series of Extreme Hypofractionation

REFERENCE	N	MEDIAN FOLLOW-UP (mo)	TOTAL DOSE/NO. FRACTIONS	OUTCOME, %	LATE TOXICITY, %
Madsen et al, 2007	Low: 40	41	33.5 Gy/5	4-yr FFBF, 90	Gr2+ GU, 20 Gr2+ GI, 8
Friedland et al, 2009	Low/int/high: 112 (21 received ADT)	24	35 Gy/5	Crude, 97	Crude Gr3 GI, 1
Boike et al, 2011	Low: 18 Int: 26	30	45 Gy/5 47.5 Gy/5 50 Gy/5	Crude, 100	Gr2+ GU, 31 Gr2+ GI, 18
King et al, 2012	Low: 67	32	36.25/5	4-yr BRFS, 94	Gr2+ GU, 7 Gr2+ GI, 2
McBride et al, 2012	Low: 45	44.5	36.25 Gy/5 37.5 Gy/5	3-yr BRFS, 98	Gr2+ GU, 19 Gr2+ GI, 12
Katz et al, 2013	Low: 211 Int: 81 High: 12 (57 received ADT)	60	35 Gy/5 36.25 Gy/5	5-yr BRFS Low: 97 Int: 91 High: 74	Gr2/3 GU, 11 Gr 2/3 GI, 5* ED, 25
Oliai et al, 2013	Low: 36 Int: 22 High: 12 (23 received ADT)	31	35 Gy/5 36.25 Gy/5 37.5 Gy/5	3-yr FFBF Low: 100 Int: 95 High: 77	Gr2/3 GU, 31 Gr2/3 GI, 9 ED, 19
Loblaw et al, 2013	Low: 84	55	35 Gy/5	5-yr BC, 98	Gr2+ GU, 8 Gr2+ GI, 5 ED, 43
Chen et al, 2013	Low: 37 Int: 55 High: 8 (11 received ADT)	28	35 Gy/5 36.25 Gy/5	2-yr BRFS, 99	Gr2+ GU, 21 Gr2+ GI, 1 ED, 21
Ju et al, 2013	Int: 41	21	35 Gy/5 36.25 Gy/5	2-yr BRFS 98	Gr2+ GU 44 Gr2+ GI 7

*Used rectal amifostine.

ADT, androgen deprivation therapy; BC, biochemical control; BRFS, biochemical relapse-free survival; ED, erectile dysfunction; FFBF, free from biochemical failure; GI, gastrointestinal; GU, genitourinary; Int, intermediate.

(2012) reported early toxicity data from the Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer study (CHHiP) study, showing late grade 2+ GI and GU toxicities for both conventional and hypofractionated IMRT. The RTOG completed enrollment of RTOG 0415, a noninferiority trial of low-risk men randomized to 73.8 Gy in 1.8-Gy fractions or 70 Gy in 2.5-Gy fractions. RTOG also has a randomized phase II trial comparing two hypofractionated regimens, 51.6 Gy in 12 fractions with 36.25 Gy in 5 fractions. The Prostate Fractionated Irradiation Trial (PROFIT) through the Ontario Clinical Oncology Group completed accrual of their noninferiority trial comparing 78 Gy in 2-Gy fractions with 60 Gy in 3-Gy fractions. Finally, there is one phase III trial of extreme hypofractionation, the Swedish ISRCTN 4590531, which randomizes intermediate-risk men to 78 Gy in 2-Gy fractions with 42.7 Gy in 6.1-Gy fractions.

The use of moderate hypofractionation for postoperative radiotherapy has been studied, which reduces the length of treatment without significantly increased morbidity. Kruser and colleagues (2011) treated 108 men with 65 Gy in 2.5-Gy fractions. Freedom from biochemical failure at 4 years was 67%. Late grade 2 GU and GI toxicity occurred in 15% and 4%, respectively, with no higher grade toxicities reported. Another study reported the outcomes of 61 men treated to 50 to 52.5 Gy in 20 fractions. Three-year disease-free survival was 74% with low toxicity profile (Lee et al, 2004). Further studies in this area are warranted.

KEY POINTS: HYPOFRACTIONATION AND STEREOTACTIC BODY RADIOTHERAPY

- Hypofractionation reduces the overall treatment course by delivering higher doses per fraction. Safe treatment delivery requires accurate patient setup and conformal treatment planning.
- Doses in the range of 2.6 to 3.1 Gy have been delivered in phase III trials with low morbidity. Patient risk selection and biologically effective doses have resulted in excellent biochemical control reported up to 5 years, but it is not clear if moderate hypofractionation is more efficacious.
- Early studies of extreme fractionation (6.7 to 10 Gy) show good biochemical control rates but the duration of follow-up is limited. Toxicity rates vary. Larger phase III trials are needed.

Radiation Therapy and Androgen Suppression Therapy

Androgen Suppression Therapy and Radiation

Among strategies to improve outcome for patients with intermediate-risk to higher risk prostate cancer, hormonal manipulation in combination with RT has demonstrated improvement in treatment

outcome compared with standard-dose radiation alone. As outlined in Table 116-12, trials have investigated radiation alone versus radiation in combination with androgen suppression as well as the duration of hormonal therapy with the radiation. A meta-analysis of prospective trials of androgen deprivation in nonmetastatic prostate cancer showed a 30% reduction in relative risk for prostate cancer-specific mortality and a 14% reduction in the relative risk for all-cause mortality with the use of ADT (Nguyen et al, 2011).

Androgen Suppression Therapy and Localized Disease

Several prospective randomized studies have investigated the role of androgen deprivation with radiation for men with intermediate to higher risk localized prostate cancer relative to radiation alone (D'Amico et al, 2008; Denham et al, 2011; Jones et al, 2011; Pisansky et al, 2013). Using between 3 and 8 months of androgen suppression, studies have typically shown an advantage to the addition of hormonal therapy in both overall and prostate cancer-specific survival.

The TROG performed a three-arm randomized trial comparing RT alone to RT plus 3 or 6 months of androgen suppression for 818 men with T2b to T4 disease (Denham et al, 2011). With 10.6 years of follow-up, the 6-month arm showed significant improvements in disease-free, metastasis-free, prostate cancer-specific, and overall survival relative to RT alone. D'Amico and colleagues (2008) studied 206 men, all with clinical T1/2 disease and followed for a median of 7.6 years. Their median PSA was 11 ng/mL, and 73% had a Gleason score of 7 or greater. Benefits in both overall and cancer-specific survival were noted. Of note, it appeared that the survival benefit may have been limited to only those men with no or minimal comorbid illness. RTOG 94-08 randomized 1979 men with T1b to T2b and PSA less than 20 ng/mL disease to RT alone versus RT with 4 months of combined androgen blockade (Jones et al, 2011). With a median follow-up of 9.1 years, the 10-year overall survival was 62% in the arm with androgen suppression compared to 57% in the RT alone arm. In unplanned subgroup analyses, it appeared that the 54% of men with intermediate-risk disease derived the greatest benefit with the low-risk group (35%) showing no significant benefit to hormonal therapy.

Androgen Suppression Therapy and Locally Advanced Disease

In RTOG 86-10, 456 patients with large (25 cm³), stage T2b to T4, Nx tumors randomly assigned to 4 months of total androgen suppression with RT given after the first 2 months had improved local control, disease-free survival, and freedom from metastases compared with patients receiving 65 to 70 Gy of RT alone (Roach et al, 2008). At a median follow-up of over 12 years, the 10-year overall survival rates were no different between the two arms but there was a significant improvement in disease-specific mortality of 36% versus 23% ($P = .01$).

In EORTC 22863, a phase III trial of androgen suppression, Bolla and colleagues (2010) reported an overall survival advantage for patients receiving 3 years of goserelin starting at the initiation of RT over RT to 70 Gy alone (Bolla et al, 2010). More than 90% of the 415 patients had either T3 or T4 disease, and the remaining were eligible owing to high-grade tumors. With 9.1 years of follow-up, there were significant improvements in both overall survival and CSS to the addition of androgen suppression.

Two multicenter randomized trials investigated the question of whether the addition of RT improved outcomes for men with locally advanced, localized disease receiving lifelong androgen suppression (Widmark et al, 2009; Warde et al, 2011). In the first, 875 men with a PSA of 70 ng/mL, N0, M0, and mostly T3 disease were randomized to 3 months of combined androgen blockade followed by lifelong flutamide with or without 70 Gy of RT. After a median of 7.6 years of follow-up, Widmark and colleagues (2009) reported a relative risk for cancer-specific death of 0.44 (95% CI 0.30 to 0.66, $P < .001$), favoring the addition of RT. In the second study, 1205 men with mostly T3 and T4 disease were randomized to lifelong

androgen suppression with or without 65 to 69 Gy of RT. With a median of 6 years of follow-up, Warde and colleagues (2011) reported a hazard ratio of 0.54 (95% CI 0.27 to 0.78) for CSS. The overall survival at 7 years was 74% (95% CI 90 to 78) for the combined arm versus 66% (95% CI 60 to 70) for the arm with androgen suppression alone.

Duration of Androgen Suppression

The optimal type, timing, and duration of androgen suppression in combination with RT remain to be defined. In RTOG 99-10, which randomized 1490 men, 84% of whom had intermediate-risk disease, to 4 versus 8 months of neoadjuvant and concurrent androgen suppression with radiation, no advantage was identified in biochemical control or overall survival to longer course treatment (Pisansky et al, 2013).

Several studies investigated duration of androgen suppression among men with higher risk disease. In RTOG 92-02, 1521 patients with stage T2c-T4, N0-1, M0 disease were randomly assigned to 4 months of total androgen suppression with radiation administered after 2 months or the same regimen followed by an additional 2 years of goserelin (Horwitz et al, 2008). A hypothesis-generating subgroup analysis revealed significant improvement in overall survival, 80% versus 69%, and disease-specific survival, 90% versus 78%, in patients with Gleason grade 8 to 10 tumors.

The EORTC randomized 970 men who had received 6 months of combined androgen blockade and RT to no further androgen suppression versus 30 months of an LHRH analogue (Bolla et al, 2009). Powered as a noninferiority study, at 6.4 years of follow-up, the 5-year cause-specific mortality was 4.7% (95% CI 2.7 to 6.7) versus 3.2% (95% CI 1.6 to 4.8), favoring long-term hormonal therapy.

In a study investigating RT with 18 months relative to RT with 36 months of goserelin for men with T3/T4, PSA greater than 20 ng/mL, or Gleason 8-10 disease, Nabid and colleagues (2013) reported that with 6.5 years of follow-up, the 5-year overall and CSS was not statistically different between the two arms. Additional follow-up will be needed to determine whether 18 months is noninferior to 36 months.

Should Pelvic Lymph Nodes Be Treated?

The question of timing of hormonal therapy and impact of radiation field size was addressed by RTOG 94-13, a four-arm study comparing whole-pelvis versus small-field radiation with 4 months of either neoadjuvant or adjuvant total androgen suppression. Eligible patients had adverse risk factors, with estimated risk for positive-node disease of more than 15%. A difference was initially seen in progression-free survival at 4 years, 54% versus 47% for the whole-pelvis versus prostate-only radiation, respectively ($P = .022$), but no difference was seen in overall survival (Roach et al, 2003). An update of this study showed a loss of this benefit in biochemical control, highlighting the need for additional studies investigating the inclusion of nodal volumes in men with a high risk for lymph node involvement (Lawton et al, 2007).

KEY POINTS: RADIATION THERAPY AND ANDROGEN SUPPRESSION THERAPY

- Randomized controlled trials have shown a survival benefit to the combination of radiation and hormonal therapy relative to either radiation or hormonal therapy alone for men with intermediate-risk to high-risk disease.
- For men with locally advanced, high-risk disease, 28 to 36 months of hormonal therapy appears superior to 4 to 6 months and the addition of radiation to lifelong hormonal therapy alone improves survival.
- For men with localized or locally advanced, intermediate-risk disease, 4 to 6 months of hormonal therapy improves survival relative to standard-dose radiation alone.

TABLE 116-12 Selected Randomized Controlled Trials Investigating the Use of Androgen Suppression Therapy with Radiation

STUDY	TNM STAGE (%)	GLEASON SCORE (%)	N	MEDIAN FOLLOW-UP (yr)	TREATMENT ARMS	OVERALL SURVIVAL: %	PROSTATE CANCER SPECIFIC MORTALITY: %	NOTES
LOCALIZED DISEASE								
TROG 96-01 (Denham et al, 2011)	T2b (26), T2c (34), T3,4 (40) N0M0	≤6 (44), 7 (38), ≥8 (17)	818	10.6	RT: 66 Gy RT + 3 mo AST RT + 6 mo AST	10 yr: 57.5 10 yr: 63.3* 10 yr: 70.8	10 yr: 22.0 10 yr: 18.9* 10 yr: 11.4	
DFCI 95-096 (D'Amico et al, 2008)	T1b (2), T1c (46), T2a (23%), T2b (30) N0M0	≤6 (28), 7 (58), ≥8 (15)	206	7.6	RT: 67 Gy RT + 6 mo AST	8 yr: 61 8 yr: 74	8 yr: 12 8 yr: 3	Benefit seen in the group without moderate-to-severe comorbidity
RTOG 94-08 (Jones et al, 2011)	T1 (49), T2 (51) N0M0	≤6 (62), 7 (28), ≥8 (9)	1979	9.1	RT: 66.6 Gy RT + 4 mo AST	10 yr: 57 10 yr: 62	10 yr: 8 10 yr: 4	
LOCALLY ADVANCED DISEASE: RT VERSUS RT + AST								
RTOG 86-10 (Roach et al, 2008)	T2 (30), T3,4 (70), N0 (92) N1 (8) M0	≤6 (30), ≥7 (70)	471	12.6	RT: 65-70 Gy RT + 4 mo	10 yr: 34 10 year: 43*	10 yr: 36 10 yr: 23	
EORTC 22863 (Bolla et al, 2010)	T1 (1), T2 (10), T3 (80), T4 (9) N0 (89), M0	≤6 (62), 7 (28), ≥8 (9)	415	9.1	RT: 70 Gy RT + 36 mo AST	10 yr: 39.8 10 yr: 58.1	10 yr: 30.4 10 yr: 10.3	
LOCALLY ADVANCED DISEASE: AST VERSUS AST + RT								
SPCG-7 (Widmark et al, 2009)	T1 (2), T2 (19), T3 (78), N0M0	NA	875	7.6	AST AST + RT: 70 Gy	10 yr: 61 10 yr: 70	10 yr: 24 10 yr: 12	
PR.3/PRO7 (Warde et al, 2011)	T2 (13), T3 (83), T4 (4), NXM0	≤7 (81), 8-10 (18)	1205	6	AST AST + RT: 65-69 Gy	7 yr: 66 7 yr: 74	7 yr: 19 7 yr: 9	
DURATION OF AST								
RTOG 92-02 (Horwitz et al, 2008)	T2 (45), T3 (51), T4 (4), N0 (97) M0	≤6 (38), 7 (31), ≥8 (24%)	1554	11.3	RT + 4 mo AST RT + 28 mo AST	10 yr: 51.6 10 yr: 53.9*	10 yr: 16.1 10 yr: 11.3	Overall survival advantage seen within the patients with Gleason 8-10
EORTC 22961 (Bolla et al, 2009)	T2c (19) T3 (73), T4 (4) N1 (3) M0	≤6 (47), 7 (30), ≥8 (18)	970	6.4	RT + 6 mo AST RT + 36 mo AST	5 yr: 81 5 yr: 85	5 yr: 4.7 5 yr: 3.2	
PCS IV (Nabid et al, 2013)	T1c (24), T2a (20), T2b (31%), T3 (24%)	NA	630	6.5	RT + 18 mo AST RT + 36 mo AST	5 yr: 86 5 yr: 91*	5 yr: 4.7 5 yr: 3.4*	
RTOG 99-10 (Pisansky et al, 2013)	T1b-T4, N0M0	≤7 (90)	1490	8.7	RT: 70.2 Gy + 4 mo AST RT + 8 mo AST	10 yr: 66 10 yr: 67*	10 yr: 5 10 yr: 4*	84% had intermediate-risk disease

*Not statistically significant.
AST: androgen suppression therapy; DFCI, Dana-Farber Cancer Institute; EORTC, European Organization for Research and Treatment of Cancer; NA: not available; PCS IV, Duration of Androgen Blockade Combined With Pelvic Irradiation in Prostate Cancers; RT, radiation therapy; RTOG, Radiation Therapy Oncology; SPCG, Scandinavian Prostate Cancer Group; TROG, Trans-Tasman Radiation Oncology Group.

TABLE 116-13 Physical Characteristics of Radionuclides Reviewed

RADIONUCLIDE	PHYSICAL HALF-LIFE	BETA ENERGY (MeV)	GAMMA ENERGY (keV)	CHELATE
Phosphorus-32	14.3 days	1.71	0	Orthophosphate
Strontium-89	50.6 days	1.46	0	Chloride
Rhenium-186	90.6 hr	1.07	137	HEDP
Samarium-153	46.3 hr	0.84	103	EDTMP

EDTMP, ethylenediamine tetramethylene phosphonate; HEDP, hydroxyethylidene diphosphonate.

Radiation Therapy for Palliation
Bone Metastases

In advanced prostate cancer, bone metastases are a common problem (Abrams et al, 1950; Gilbert and Dagan, 1976). Many therapies are available for the management of bone metastases, including surgery, medical management, and radiation. RT can treat most patients with highly effective symptom relief.

The hallmark of osseous metastases is localized pain, which is frequently continuous and unrelenting regardless of the site. The pain caused by bone metastases is not well understood but is likely a combination of direct action of tumor on bone, interactions of the tumor and its secreted factors with nerves in the periosteum, and action of inflammatory cells in the local bone metastasis environment (Peters et al, 2005; Joyce and Pollard, 2009; Jimenez-Andrade et al, 2010). The most serious complication of osseous metastases is spinal cord compression, which is discussed later.

Most bone metastases can be diagnosed by physical examination, plain radiographs, and bone scan. CT and MRI are sometimes required if there is suspicion of bone involvement, but x-ray and bone scans are negative if there is soft tissue involvement. A review of the currently available data on the use of externally applied radiation from prospective studies has shown overall response rates ranging from 85% to 100% using various treatment schedules (Madsen, 1983; Price et al, 1988; Cole, 1989). A single-fraction regimen (800 cGy × 1) appears to be as effective as other, more protracted regimens, is more cost-effective and less time-consuming for patients, and should be the preferred regimen for patients with uncomplicated nonspinal bone metastasis (Wu et al, 2003). A historically important and still frequently used regimen in the United States is 3000 cGy in 10 divided fractions, which provides adequate pain control for most osseous metastases but is not more effective than a single 800-cGy fraction.

Metastasis to a weight-bearing region raises many concerns. A pathologic fracture can be painful and disabling, both functionally and psychologically. Radiographic and clinical factors that warrant consideration of prophylactic surgical fixation include the following (Lane et al, 1980):

- An intramedullary lytic lesion 50% or greater of the cross-sectional diameter of the bone
- A lytic lesion involving a length of cortex equal to or greater than the cross-sectional diameter of the bone or greater than 2.5 cm in axial length

These patients should be evaluated by an orthopedic surgeon. If a pathologic fracture has occurred in a weight-bearing region, surgical fixation is required for pain control and to promote adequate healing. In all situations, postoperative radiation is required. Because prostate cancer produces primarily blastic metastases, pathologic fracture is correspondingly infrequent.

Spinal Cord Compression

Spinal cord compression is a medical emergency. Failure to diagnose and treat promptly can lead to significant morbidity, including paraplegia and autonomic dysfunction. The predominant symptom of cord compression is pain, which occurs in approximately 95% of patients (Gilbert et al, 1978). Pain usually precedes a diagnosis

TABLE 116-14 Clinical Efficacy and Toxicity of Radionuclides Reviewed

RADIONUCLIDE	RESPONSE RATE (%)	RESPONSE DURATION (mo)	TOXICITY
Phosphorus-32	60-80	≈5	++
Strontium-89	60-90	≈6	+
Rhenium-186	75-80	1-2	+
Samarium-153	75-90	2-3	+

of spinal cord compression by approximately 4 months. Symptoms, however, can progress rapidly to neurologic dysfunction in a matter of hours to days. When a patient has progressed to paraplegia, return of function is infrequent. Therefore early diagnosis and therapy are critical. The diagnostic tool of choice to evaluate spinal cord compression is MRI.

Once the diagnosis of spinal cord compression is made, the physician is left with the dilemma of how to treat. There are a few instances in which surgery should be considered as an option before radiation, including pathologic fracture with spinal instability or compression of the spinal cord by bone, unknown tissue diagnosis, or history of previous radiation to the same area.

When the diagnosis of cord compression is made or even suspected, all patients should receive corticosteroid therapy (e.g., dexamethasone). Steroids can decrease vasogenic edema and provide striking analgesic benefit. The loading dose of dexamethasone (Decadron) is 4 to 10 mg, followed by a maintenance dosage of 4 to 24 mg every 6 hours.

Systemic Radionuclide Therapy

The first report on the use of **systemic radionuclides** for the treatment of bone metastases was published by Pecher in 1942. Tables 116-13 and 116-14 provide a summary of the physical characteristics, and the clinical usefulness of the radionuclides are discussed. Historically, radioisotopes such as strontium-89 and samarium-153 have been the mainstay of systemic radionuclide therapy for men with castrate-resistant prostate cancer who have multiple, painful bone metastases. Although effective in providing substantial pain relief in a majority of patients, these agents also tend to suppress blood counts as a result of concomitant irradiation of bone marrow (Porter et al, 1993; Sartor et al, 2004).

A search for isotopes with similar palliative effects but fewer side effects ensued. The clinical development of radium-223 is a result of this search.

Clinical Experience with Radium-223

In 2013, the U.S. Food and Drug Administration approved ²²³Ra for use in men with castrate-resistant and painful bone metastasis who also have no soft tissue metastasis. This approval was based on a prospectively randomized study that found that six cycles of ²²³Ra

provided an increased time to first symptomatic skeletal event and, importantly, prolonged survival (from 11.3 to 14.9 months) compared to best standard of care (Parker et al, 2013).

By selective uptake in bone and the very short distance (<1 mm) over which the charged particle (i.e., alpha particle) acts, damage to surrounding hematopoietic tissues was minimal. In fact, there were no substantive differences in grade 3 or 4 adverse events between patients treated on the ^{223}Ra arm compared to those on the placebo arm. Taken together, these data support the incorporation of this agent as part of the management protocol for men with metastatic castrate-resistant prostate cancer, and, given the safety profile, Ra has the potential for use earlier in the natural history of metastatic prostate cancer.

KEY POINTS: RADIATION THERAPY FOR PALLIATION

- Spinal cord compression, bone metastasis, and pathologic fractures are conditions that require EBRT for palliation.
- Multiple, symptomatic bone metastasis can be treated with systemic radioisotopes.

Molecular Therapies and Radiation for Prostate Cancer

Given that nearly 50% of men with locally advanced prostate cancer will have a biochemical recurrence within 10 years of treatment (Bolla et al, 2002), new technologies that improve the therapeutic index of RT for local disease have the opportunity to significantly affect morbidity and mortality of prostate cancer. Ideally, these molecular-based therapies target vulnerable aspects of the cancer growth or the ability of the cancer to repair injury but do so in a targeted fashion so as to minimize effects on normal, noncancerous tissues.

Targeted RNA-Based Therapy

Ionizing radiation of mammalian cells causes multiple types of cellular injury, of which DNA double strand breaks are considered the most cytotoxic (Smith et al, 1999). Naturally occurring mutations in genes that sense or repair DNA damage are associated with increased sensitivity to irradiation (Helleday et al, 2007; Pollard and Gatti, 2009). Chemical or short-interfering RNA (siRNA) inhibition of DNA repair proteins, such as DNA-dependent protein kinase ATM, also results in cellular hypersensitivity to irradiation (Collis et al, 2003). Although these approaches have potential, they lack a means to selectively target cancer cells to avoid sensitization of surrounding noncancerous tissues.

RNA interference (RNAi) is a promising new therapeutic approach, but the challenge for translating RNAi therapy is delivery, particularly for specific cell types. One developing delivery approach is RNA aptamers, which are nuclease-stabilized targeting molecules capable of binding ligands in much the same way as antibodies (Dausse et al, 2009). Targeted RNA aptamers to the prostate-specific membrane antigen (PSMA) have been developed (Lupold et al, 2002), which are capable of targeting drugs, nanoparticles, and toxins to PSMA expressing prostate cancer cells and tumors (Farokhzad et al, 2004; Cheng et al, 2007). When conjugated to siRNAs and short-hairpin RNAs (shRNAs), these PSMA aptamers are also capable of delivering cell-selective gene knock-down (McNamara et al, 2006; Dassie et al, 2009). Because PSMA is highly expressed in nearly all localized prostate tumors (Sweat et al, 1998; Perner et al, 2007), it is likely that PSMA-targeted aptamer-shRNA chimeras could be employed to inhibit DNA-repair pathways in prostatic cells to enhance radiation-induced cell death in locally advanced prostate cancer. Experiments in animal models have revealed that PSMA-targeted aptamer-siRNA chimeras can target human prostate cancer cells, resulting in knock-down of target mRNA, and target protein, all culminating in more than a threefold increase in tumor growth delay after a single 6-Gy fraction of

radiation. Importantly, there was no evidence of off-target effects or nonprostate cancer radiosensitization (Ni et al, 2011). These data are provocative and support planned clinical translation.

Immunotherapy

Defects in major histocompatibility complex class I expression have been noted in 85% of primary prostate cancers and essentially all metastatic tumors (Blades et al, 1995). As with other tumors, these data suggest that evasion of host immunity may be a critical factor in prostate cancer development. Strategies designed to improve tumor antigen presentation to the host immune system are termed *cancer vaccines* and frequently employ targeted expression of cytokines in tumor cells. This approach results in improved cancer cell vaccine antigen presentation and activation of antigen-presenting cells, both of which are necessary to effect a cellular immune response. A number of cytokines have been tested for their efficacy in inducing an antitumor immune response (Dranoff et al, 1993). Granulocyte-macrophage colony stimulating factor (GM-CSF) has emerged as the most potent cytokine for activation of antigen processing and presentation by dendritic cells (Cella et al, 1997). When tumor antigens are presented in the context of high-level cytokine expression, cytotoxic T lymphocyte-based antitumor immune responses can be enhanced.

It has been suggested that therapies such as radiation can result in the presentation of tumor-associated antigens, which subsequently enhance vaccine-based immunotherapies. One such study using an autochthonous murine model of prostate cancer tested whether radiation in combination with a GM-CSF-based vaccine could augment the CD4 T-cell response (Harris et al, 2008; Wada et al, 2013). Although vaccine alone or radiation alone was not capable of priming an antitumor T-cell activation, the combination of radiation with vaccine substantively enhanced antitumor T-cell activation. This effect was dependent on the relative timing of radiation and vaccination. An interesting clinical trial that tested this general concept also has been completed (Gulley et al, 2005). In this phase I study, a PSA-targeted vaccine and radiation were used to treat men with localized prostate cancer. The combination resulted in significant T-cell responses in the majority of treated patients. These studies and others offer the promise of combination therapies that have both local and systemic anticancer potential.

The monoclonal antibody, ipilimumab, was found to target and block an immunologic checkpoint on T cells called cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (reviewed in Pardoll, 2012). It is known that CTLA-4 blockade can result in tumor regression and increased survival in patients with advanced melanoma (Hodi et al, 2010). Very interestingly, it was recently reported that a patient with advanced, metastatic melanoma who was receiving treatment with ipilimumab who also received palliative radiation to a single metastatic lesion exhibited rapid and substantial decrement in the size of multiple unirradiated metastatic lesions throughout her body. It is known that radiation can increase antigen presentation by certain myeloid cells (Zhang et al, 2007), suggesting that the systemic response seen in this patient resulted from an interaction of radiation and immune blockade that needs further examination. Negative regulation of T-cell activation by ipilimumab also has been tested in combination with radiation in the treatment of men with metastatic prostate cancer and appears to be safe and has evidence of enhanced efficacy (Slovin et al, 2013). Taken together, these data support an extrapolation of such concepts to the treatment of men with high-risk, nonmetastatic disease and provide a promise for enhanced local as well as distant micrometastatic disease immune surveillance.

Radio-Gene Therapy

Cytoreductive approaches to gene therapy that result in cytolytic or apoptotic cell death are generally grouped into three categories: (1) enzyme/prodrugs ("suicide gene" therapy), (2) oncolytics, and (3) cytotoxins. A rational combination of these approaches with a

more standard cytotoxic therapy such as RT may provide superior cell killing as a result of nonoverlapping modes of cell death.

Enzyme/Prodrug Gene Therapy

This method of gene therapy relies on the conversion of an inactive prodrug into a toxic drug using an enzyme vectored only to target tumor cells. In this way, active drug is limited to the transduced cells and adjacent surrounding cells. In this therapy, it is critical that the vector have high tumor cell specificity to minimize normal tissue toxicity. Prodrug-activating enzymes employed include those not normally found in humans such as cytosine deaminase, which catalyzes the conversion of nontoxic 5-fluorocytosine to cytotoxic 5-fluorouracil, and herpes simplex virus (HSV)–thymidine kinase, which assists in the conversion of ganciclovir to toxic ganciclovir triphosphate. Even when only a small percentage of cells contain the enzyme, substantial tumor reductions have been noted, given the significant cell death attributed to the bystander effect (Kim et al, 1998). A recently reported study of HSV–thymidine kinase and ganciclovir suicide gene therapy in combination with replication-competent adenovirus and radiation revealed this approach to be safe and associated with frequent negative post-treatment biopsies of the prostate (Freytag et al, 2007). To fully test this gene therapy approach, there is an ongoing multicenter randomized, double-blind control trial of an adenoviral vector that expresses the HSV–thymidine kinase gene that is delivered intraprostatically, followed by delivery of the oral antiherpetic drug valacyclovir and definitive radiation to the prostate versus placebo and definitive radiation to the prostate for men with newly diagnosed intermediate-risk prostate cancer (ClinicalTrials.gov identifier: NCT01436968). The primary end point of the trial is improvement in disease-free survival. The study will also evaluate CSS and prostate biopsy positivity 24 months after treatment. This is an exciting, contemporary investigation of this novel approach and will provide more definitive data as to the clinically relevant benefits of combined radiotherapy and gene therapeutics.

Oncolytics

Viruses alone can infect and kill tumor cells without insertion of a transgene. Certain viruses have, as part of their normal life cycle, a lytic phase that is lethal to the host cell. In the 1950s, the potential therapeutic activity of this lytic life cycle was documented when cervical cancer was treated with intratumoral injections of wild-type adenovirus with subsequent tumor responses (Smith et al, 1956). Examples of oncolytic viruses that could be used for therapy include adenovirus, vaccinia, Newcastle disease virus, HSV, influenza virus, and mumps virus. Adenoviruses are attractive vectors for gene transfer and therapy for several reasons. They have low pathogenicity for normal tissue, are not tumorigenic, and, when present, result in only mild-to-moderate clinical symptoms (Anderson, 1998). They also can effect relatively high gene transfer.

The adenovirus exerts its control over host cell growth regulation by a complex set of proteins that facilitate viral replication. Prostate-specific conditionally replicating adenoviruses can be designed by placing the genes regulating viral replication (including the early adenoviral genes, E1A) under the control of a prostate-specific promoter, resulting in a selectively replication-competent adenovirus. One potential limitation of such an approach is that E1A is known to interact with the androgen receptor in prostate cancer cells, thereby reducing the activity of both E1A and the androgen receptor and culminating in decreased viral replication and potency. Given that many patients treated with radiation are also treated with androgen-suppressive drugs, Johnson and colleagues (2013) modified the androgen receptor ligand-binding domain of the E1A–androgen receptor fusion, resulting in a virus that is activated for replication by both androgens and nonsteroidal antiandrogens. This novel virus is an ideal construct to be tested along with androgen suppression and radiation for those patients at high risk for recurrence.

The concept of combined-modality therapy, which has shown success in other tumor sites, will become more standard in prostate cancer management. The combination of gene therapy with conventional therapies such as RT and surgery provides new hope for uniform cure of patients with prostate cancer.

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The complete reference list is available online at www.expertconsult.com.



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117 Focal Therapy for Prostate Cancer

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Overview

Prostate Cancer Biology: Multifocality and the Index Lesion

Identifying the Patient Population for Focal Therapy

Ablative Technology

Overall Data

Follow-up after Focal Therapy

Salvage Therapy after Radiorecurrence

Conclusion

The prostate cancer pathway from screening and diagnosis through to treatment has recently been critically questioned in light of level 1 evidence pointing toward pathway-related harms that may outweigh the benefits in many men. As a consequence, guidelines on screening in prostate cancer have recommended limiting the systematic use of screening based on prostate-specific antigen (PSA) testing to avoid overdiagnosis and overtreatment. There is a clear requirement to improve the current therapeutic ratio with novel interventions. Recent interest has focused on applying magnetic resonance imaging (MRI) in men at risk, before biopsy, targeted biopsy based on MRI-derived suspicious lesions, active surveillance of low-risk disease, and tissue-preserving focal therapy in those who require treatment and have suitable disease.

Minimally invasive focal therapies in localized prostate cancer offer the potential to reduce side effects and the health care burden and costs associated with radical modalities such as surgery or radiotherapy. This chapter reviews the role of these approaches and the therapeutic dilemma that men with localized low-volume prostate cancer currently face, in the context of novel therapies that aim to find a middle ground—tissue-preserving focal therapy—that follows the paradigm of almost all other solid-organ cancers.

OVERVIEW

For most men with localized prostate cancer, there exists a challenging decision-making process. **Currently, the options often straddle two ends of a spectrum with active surveillance at one end and radical therapy, such as prostatectomy or radiotherapy, at the other.** For those men with high-risk disease, there is an absolute risk reduction in disease-specific death—of approximately 5% over 10 to 15 years—between watchful waiting (a lesser form of active surveillance that is palliative in its intention) and radical surgery, as demonstrated in the Scandinavian Prostate Cancer Group's SPCG-4 randomized controlled trial (RCT) (Bill-Axelsson et al, 2005, 2008). The more recent Prostate Cancer Intervention versus Observation Trial (PIVOT), which randomized men diagnosed in the early PSA screening era between watchful waiting and radical prostatectomy, showed no overall survival or prostate cancer-specific survival advantage over an 11-year period (Wilt et al, 2012). PIVOT did show a survival benefit for men with intermediate- and high-risk disease, and although these were subgroup analyses, they confirm the findings of SPCG-4 that treatment should be directed toward those men with clinically significant disease. However, although there is a small survival advantage for these men, it could be argued that the

morbidity from treatment (urinary incontinence, sexual dysfunction, rectal problems) questions the wholesale application of radical therapy to all men with intermediate- and high-risk disease.

The overtreatment of low-risk prostate cancer and limited effect on disease-specific mortality were further brought into context by two recent RCTs assessing the efficacy of population PSA screening. The North American Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial showed no difference in prostate cancer-specific mortality between the screened and unscreened arms with a mean follow-up of 7 years. This trial was significantly flawed because there was considerable contamination (informal PSA testing) in the control arm, potentially diluting any survival advantage of PSA screening. The fourth interim analysis from the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that 781 men would need to be screened and 27 men diagnosed (and often treated) to save 1 life within a 13-year period (Schröder et al, 2014). The effect was predominantly nested in a minority of countries, suggesting heterogeneity of study conduct, delivery, health care systems, and possibly disease types based on ethnic grounds. Although arguments rage about the strengths and weaknesses of each study, what is very clear is that any advantage from screening and treatment is likely to be small if all cancers are treated uniformly. We are therefore left with a stark choice: either to abandon the screening and diagnosis of prostate cancer as recommended by many high-level health care bodies that provide guidance to governmental institutions, or to find ways to identify men who are likely to benefit from treatment, and to these men offer therapies that reduce the impact on genitourinary and rectal function if they are suitable. **Tissue-preserving strategies aim to target the cancer and not the whole organ when it is morphometrically possible to do so and thus reduce damage to collateral tissues.**

Errors in the Current Diagnostic Pathway

Men at risk of prostate cancer are those with an elevated PSA level, abnormal digital rectal examination findings, a positive family history of prostate cancer, or a specific ethnic profile. Once a risk factor has been identified, patients are advised to undergo a transrectal ultrasound (TRUS)-guided biopsy. Annually, about one million men in Europe and one million in the United States undergo a TRUS biopsy. The problem with TRUS-guided biopsy is that the operator is unable to accurately determine the location of any significant cancer. The ultrasound examination is used to identify the prostate itself and not the suspicious lesion; this results in 10 to 12 biopsy specimens being taken blindly throughout the prostate. **This is in contrast to the approach taken in most other**

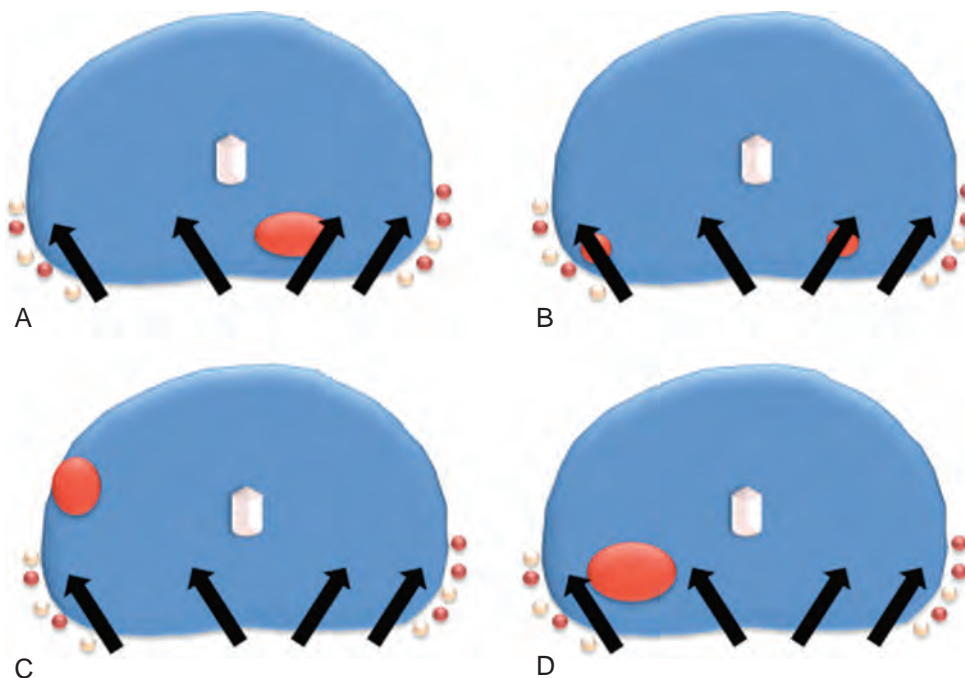


Figure 117-1. The errors of transrectal biopsy. A, Misclassification of significant disease. B, Overdetection of insignificant prostate cancer. C and D, Underdetection of clinically significant prostate cancer.

solid-organ cancers, wherein the lesion is identified, usually on imaging, to direct biopsies to the area of suspicion. The random and systematic errors in diagnosis, which are inherent in TRUS-guided biopsies of the prostate, lead to a number of problems.

TRUS biopsies overdiagnose clinically insignificant prostate cancer. A man who undergoes TRUS biopsy has a 1 in 4 chance of being diagnosed with prostate cancer (Thompson et al, 2003; Bangma et al, 2007). This compares with a 6% to 8% lifetime risk of having prostate cancer that will affect a man's life. These small low-grade lesions are detected by random chance (Djavan et al, 2001) (Fig. 117-1).

TRUS-guided biopsies miss clinically significant cancers. They have an estimated false-negative rate of 30% to 45% (Djavan et al, 2001; Scattoni et al, 2007). The clinician takes 10 to 12 biopsy specimens in a manner that attempts to obtain representative tissue from the peripheral zone (see Fig. 117-1). However, this systematic error leads to several parts of the prostate not being well sampled. First, the anterior part of the gland is missed as a result of its greater distance from the rectum. Second, areas in the midline are under-sampled owing to efforts to avoid the urethra. Third, the prostate apex is often inaccessible by the transrectal route (Crawford et al, 2005; Onik et al, 2009; Barzell et al, 2012; Lecomte et al, 2012).

TRUS-guided biopsies can be unrepresentative of the true burden of cancer. The random sampling error (see Fig. 117-1) can mean that a biopsy does not hit the cancer lesion through its greatest diameter, leading to either the size or the grade of cancer or both being underestimated (Kulkarni et al, 2006). Up to half of men deemed low risk on TRUS-guided biopsies can have a higher burden or grade or both when a more accurate biopsy test is applied (Barzell and Melamed, 2007; Onik and Barzell, 2008; Taira et al, 2010). As a result of the poor risk attribution, many men and their physicians choose radical therapies from which they derive little to no survival benefit.

TRUS-guided biopsy is unstable when repeated. The pathologic status derived from TRUS-guided biopsies can be unreliable if the test is reapplied, not only at discriminating clinically significant cancer from clinically insignificant prostate cancer, but also at attributing a noncancer status versus a cancer status in about a quarter of men subjected to serial testing (Roehl et al, 2002; Porten et al, 2011; Washington et al, 2012).

TRUS-guided biopsy can cause harm. It is associated with a number of complications, the most important being urinary tract infection (1% to 8%) that can result in life-threatening sepsis (1% to 4%). Hematuria (50%), hematospermia (30%), pain or discomfort (most), dysuria (most), and urinary retention (1%) can also be expected (Abdelkhalek et al, 2012; Batura and Gopal Rao, 2013; Loeb et al, 2013b; Pepe and Aragona, 2013).

Conceptual Basis for Focal Therapy

Overtreatment becomes less of a problem if the treatment is inexpensive and is associated with low rates of toxicity. Most current treatments do not share these attributes. At present, men can expect the following rates of toxicity from radical therapies on average: 30% to 90%, erectile dysfunction; 5% to 20%, incontinence; and 5% to 20%, rectal toxicity. Indeed, men may be willing to accept higher rates of genitourinary functional preservation with lower rates of survival. This is reinforced by data from a recent discrete choice experiment showing that men are willing to consider tradeoffs between survival and side effects; for instance, on average men would wish to see 25.7 additional months of survival conferred by treatment if that treatment leads to severe urinary incontinence (King et al, 2012).

Two strategies can be used to reduce this treatment burden. First, molecular characterization and imaging modalities may be used to identify men who have high-risk cancer that requires treatment. This has yet to prove fruitful, although imaging is showing some early promise (Kurhanewicz et al, 2008; Macura, 2008; Ahmed et al, 2009a; Turkbey et al, 2009). Second, minimally invasive therapies may be used in an attempt to reduce the side effects of treatment. Although this trend has resulted in intensity-modulated radiotherapy being promoted as the preferred method of care from the radiotherapeutic perspective, on the one hand, and robotic surgery on the other, these treatments are associated with high capital and considerable recurrent costs. For instance, a recent analysis has demonstrated that there were no statistically significant differences in quality-adjusted life-years (QALYs) among the various surgical methods; surgical methods tended to be more effective than radiation, although combined external beam and brachytherapy radiation treatment for high-risk disease was the exception.

Radiotherapy techniques were consistently more expensive than surgery, although both were expensive, with costs ranging from \$19,901 (robotic-assisted prostatectomy for low-risk disease) to \$50,276 (combined radiotherapy for high-risk disease) (Cooperberg et al, 2013). Others have shown that cost savings are not realized, at least in the first year and in the United States, between open and minimally invasive surgery (Lowrance et al, 2012). Others have shown that proton beam therapy is significantly more expensive, even if it theoretically improves cancer outcomes, compared with photon beam standard radiotherapy (Konski et al, 2007). In addition, there is little robust evidence that the toxicity profile has changed (Sanghani and Mignano, 2006; Berryhill et al, 2008). One way of reducing the side effects of radical therapy may be to direct treatment to only areas of cancer, to preserve tissue and avoid damage to key structures such as neurovascular bundles, external sphincter, bladder neck, and rectum (Ahmed et al, 2007; de la Rosette et al, 2010; Eggener et al, 2010; Lindner et al, 2010b; Karavitis et al, 2011a) (Fig. 117-2).

When compared with other solid-organ malignancies, prostate cancer is an outlier. Breast, renal, thyroid, liver, and pancreatic cancers all involve tissue-preserving therapies, if appropriate, which are dependent on location and burden of cancer. It is clear that these areas of oncologic surgery developed tissue preservation, as opposed to Halsted principles for wider surgical margins, as a result of upstream diagnostic tools that are reliant on finding measurable—by palpation or imaging—disease that would undergo targeted sampling followed by targeted treatment. The transrectal biopsy has facilitated the reverse for the prostate. Random blind sampling has forced our hands as clinicians so that we have to apply radical whole-gland principles. So, if multifocality is overlooked in other organs by targeting just the measurable index lesion—the lesion that is largest and has elements of the highest grade—it is a reasonable hypothesis that targeting these lesions in prostate cancer will be sufficient in leading to acceptable cancer control rates, possibly equivalent to whole-gland therapy. In prostate cancer, a safe strategy may be to target those lesions that meet widely acceptable thresholds for clinically significant cancer. Focal therapy certainly leads to fewer genitourinary and rectal side effects, if the results of early prospective studies are found to be reproducible across populations, centers, and surgeons (Ahmed et al, 2011a, 2012d; Bahn et al, 2012).

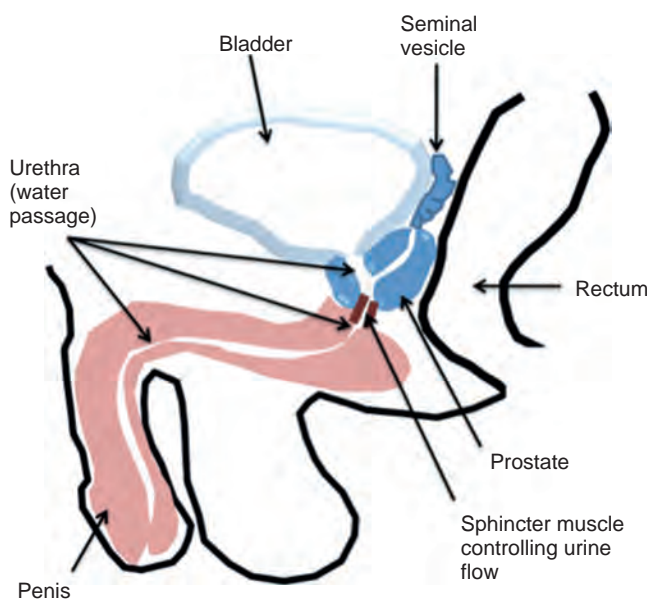


Figure 117-2. Depiction of why whole-gland radical therapies can cause genitourinary and rectal toxicities as a result of the proximity of sensitive structures that can undergo collateral damage from surgery or radiotherapy.

To balance the unfavorable risk-benefit ratio of current standard treatments, new approaches and novel technologies are being explored. Hitherto, prostate cancer therapy has been traditionally directed toward the whole gland rather than to the area of the gland harboring cancer. It is one of the outliers in terms of cancer therapy, with most other solid-organ cancers having therapy directed toward the tumor and not primarily toward the whole organ in the majority of cases. For the prostate, a consequence of whole-gland treatment is that surrounding structures are usually damaged, with related urinary, erectile, and bowel side effects. However, new evidence has highlighted that only the index lesion—largest by volume and/or grade—drives the natural history of the disease, although prostate cancer is multifocal in most men (Ahmed, 2009). Thus a new approach delivering treatment only to the area of the gland affected by significant disease might be a reasonable approach and the best way to preserve function while retaining the benefits of cancer control. This approach has been called *focal therapy* (Ahmed et al, 2007; Eggener et al, 2010).

It follows that treatment could be patient specific. It is straightforward to envisage hemiablation of unilateral prostate cancer in which the entire lobe that is affected, regardless of volume or position of cancer, is ablated. Indeed, this is the treatment that retrospective case series of cryotherapy have delivered (see later). True focal ablation in which the tumor alone is ablated with a margin of normal tissue is also probably without contention, with the main difficulty arising from the greater precision in localization and targeting leading to potentially greater residual cancer or undertreatment rates. However, unifocal ablation is possible in only 10% to 20% of men, whereas hemiablation of unilateral disease may be possible in 30% to 40% of localized prostate cancer. Because most men have two or three lesions per prostate, a hemiablation or unifocal ablative approach would limit the patient population that could potentially benefit from focal therapy.

If tissue preservation criteria cannot be met owing to the disposition of secondary small tumors near the neurovascular bundles or sphincter muscles, it could be argued that index lesion ablation in which the largest and highest-grade tumor is ablated is warranted (Figs. 117-3 and 117-4). This could be justified to derive the benefits of lower toxicity, provided cancer control is not compromised by not treating all secondary cancer foci (Scardino, 2009). What is the justification for the inclusion of index lesion ablation? First, there is evidence that the volume of a tumor determines disease progression and that this volume equates to about 0.5 mL (Stamey et al, 1993; Epstein et al, 1994). Second, within multifocal disease is the inclusion of a large proportion of small tumors that probably

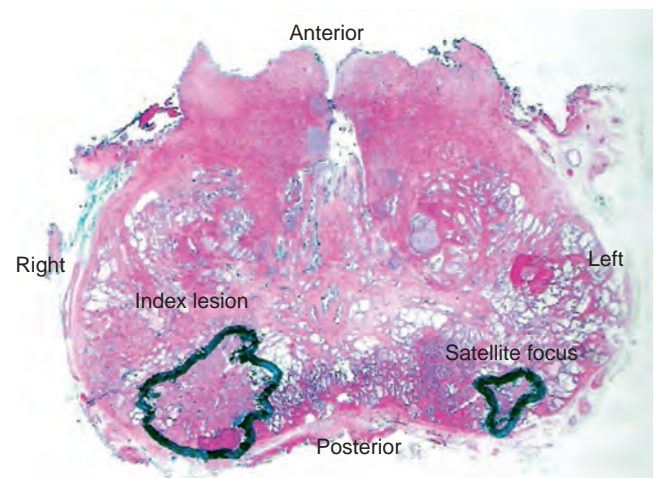


Figure 117-3. Whole-mount prostatectomy section demonstrating two lesions. On the right is the large index lesion and on the left the secondary or satellite lesion that many argue is usually clinically insignificant and does not drive the progression of the disease.

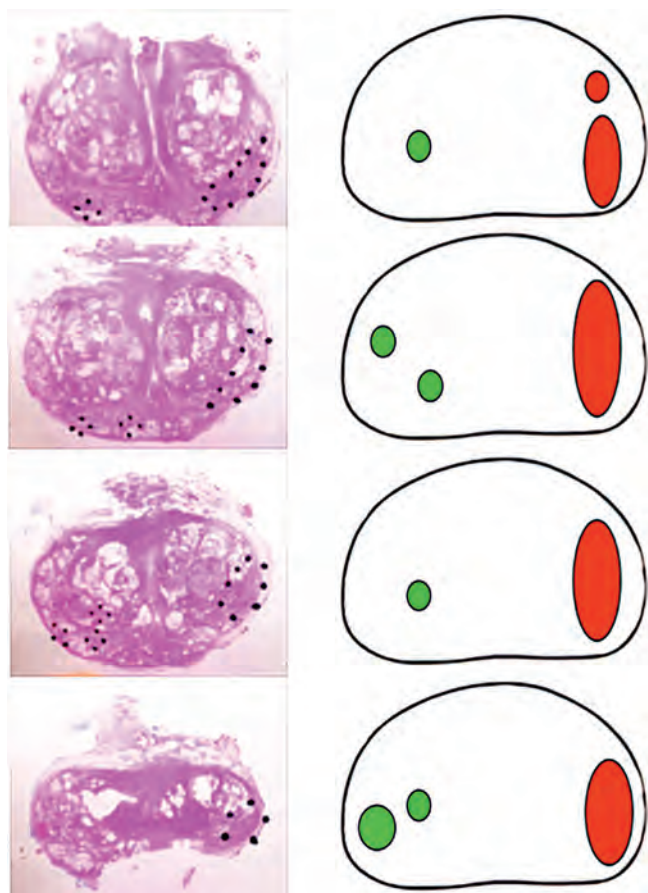


Figure 117-4. Sections taken from radical prostatectomy specimens and pathology diagram showing dominant Gleason pattern 4+3 lesion with secondary satellite Gleason pattern 3+3 prostate cancer.

represent clinically insignificant disease. Third, 80% of patients seem to have a dominant lesion, with the remaining lesions being of low grade (Gleason score 6 or lower) and a total volume of secondary lesions below 0.5 mL. Fourth, about 80% of men have a dominant tumor such as this, which also gives rise to most of the extracapsular extension (ECE). Lesions above 0.5 mL tend to yield Gleason scores of 7 or greater and are responsible for ECE if present. Foci of Gleason score less than 7 with volumes less than 0.5 mL may not contribute to disease progression over a 10- to 15-year period and therefore may not warrant treatment. Further corroborating evidence comes from elegant molecular genetic studies that point to a single lesion driving metastases and disease progression (Liu et al, 2009). It therefore seems reasonable to propose that ablation of the dominant lesion will give rise to disease control, provided the remaining lesions can be well characterized in the pretreatment evaluation. The argument has actually been taken further. There is growing traction that small, low-grade, and therefore clinically insignificant disease might be reclassified as a benign entity. Such a move, if carried out, would negate the concerns about multifocality in the vast majority of men newly diagnosed with localized prostate cancer.

PROSTATE CANCER BIOLOGY: MULTIFOCALITY AND THE INDEX LESION

If not all prostate cancer lesions are clinically significant, one might contemplate a shift from treatment directed toward the whole gland. Treatment could be directed only to cancer lesions that would cause a reduction in either quality or length of life. This represents a radical shift in how we treat the disease, but it

certainly is in tune with the paradigm shifts we have witnessed in breast, thyroid, kidney, and liver cancers, to name just a few. The concept of the index lesion therefore runs to the very core of attempts to reduce the harms of screening for and treatment of prostate cancer, because systematic biopsies that inadvertently detect indolent disease will need to be replaced by targeted precision biopsies directed at a lesion of concern.

Clinically Significant Disease and Tumor Multifocality

Tumor multifocality in solid organs is not a novel phenomenon. It is not only found in prostate cancer, but it is also well recognized at various rates of incidence in breast, thyroid, lung, and even renal cancers. In these cancers physicians have taken an approach to treat only the cancer that will cause harm, leaving small indolent tumors (often unknown of) and preserving healthy tissue. In breast cancer, lumpectomy and localized radiotherapy might now be favored over whole-breast adjuvant radiotherapy because recurrences predominantly occur in the area of surgical resection after lumpectomy (Vaidya et al, 2014). The importance of preservation of healthy thyroid tissue is well recognized by colleagues in head and neck oncology and has led to the renaming of clinically insignificant disease as *papillary microcarcinoma* (Piersanti et al, 2003). The small lung tumors found at high rates at autopsy that would have caused more harm by investigation and treatment are commonly called *pseudodisease* in recognition of their nonmalignant behavior. Such a concept is made easier because the diagnostic pathway in those malignancies involves detection of the clinical phenotype visually, with palpation, or by imaging. In other words, diagnosis and treatment are directed at measurable disease.

In stark contrast to this, prostate cancer is typically detected by a somewhat random deployment of 10 to 12 transrectal needles, and the disease is confirmed histologically via these microscopic samples. This technique was deemed adequate because the presence of disease in the prostate was all that was required to inform treatment directed at a whole-gland level. By virtue of finding many lesions through this biopsy strategy, the multifocality of the disease has been used as a rationale to treat the entire prostate. However, informed treatment decisions based on biochemical and pathologic parameters cannot be made when systematic errors in sampling of the prostate can lead to overlooking of clinically significant disease (disease that will lead to a reduction in quality or quantity of life) or undersampling, or when, conversely, clinically insignificant disease (disease that will never cause harm) is oversampled by clustering of the biopsy sites. In addition, even when disease in the prostate has been well characterized, it is sometimes difficult to predict the biologic behavior of individual cancers.

Along with multifocality, the idea that within the prostate separate cancers are behaving differently has long been recognized. In 1963 Halpert and colleagues surveyed 5000 autopsies following death from all causes (Halpert et al, 1963). In their survey they identified the presence of focal and diffuse tumors within the prostate gland. In younger men, focal tumors outnumbered diffuse tumors, but the researchers were not able to determine whether the focal tumors were precursors of diffuse tumors or if, indeed, the two types of tumors represented two forms of cancer with different biologic behavior. Thirty years after this publication, Villers and colleagues from Stanford University published their 3-mm step section analysis of 234 consecutive prostatectomies performed because of clinically detected prostate cancer from 1983 to 1989 (Villers et al, 1992). In this series a total of 500 adenocarcinomas were identified. A single cancer was found in 117 of the prostates analyzed. The remaining 117 specimens contained the clinically detectable lesion plus an additional 266 incidental tumors. Here, despite earlier studies describing diffuse tumors, the authors observed the distribution of normal tissue indicating expansion of the tumor from a single region of the gland.

Examining the Gleason grade of the dominant and secondary lesions in 100 consecutive radical prostatectomies, Karavitakis and colleagues (2011b) identified a total of 270 lesions. In the 170 satellite, secondary lesions identified, 87% were less than 0.5 mL and

99.4% had a Gleason score of 6 or less. In the 25 specimens in which two or more foci of cancer were identified, none contained the higher-grade, more aggressive disease in the secondary lesion.

Considering how size and growth of the index lesion affect outcomes in prostate cancer, Karavitis and colleagues (2012) examined the extent of positive surgical margins involving the index lesion and secondary lesions. Ninety-five consecutive whole-mount specimens from laparoscopic radical prostatectomy were examined. A total of 269 tumor foci were identified. Two of 160 (1.3%) lesions of volume less than 0.5 mL were involved in the positive surgical margin, whereas 0 of 132 lesions of volume less than 0.2 mL were involved. In the 19 cases in which multifocal cancer displayed a positive surgical margin, the index lesion was the cause in 13 cases and the index lesion plus a satellite lesion in the remaining 6 cases. In the other cases, the satellite lesion had a volume greater than 0.2 mL.

Tumor size was also found to be an important factor in PSA failure in a study by Nelson and colleagues, who analyzed 431 consecutive patients undergoing radical prostatectomy for localized prostate cancer (Nelson et al, 2006). In a multivariate analysis, tumor volume was found to be an independent predictor of PSA recurrence. The mean tumor volume for PSA recurrence was 6.8 mL.

When Wise and colleagues compared the impact of small independent cancers and the index lesion on PSA failure in 486 men treated with radical prostatectomy, they found that 83% of men had multifocal cancer within the prostate (Wise et al, 2002). Fifty-eight percent of these smaller secondary cancers were less than 0.5 mL in volume. Factors that independently predicted PSA failures were the presence of any Gleason grade 4 or 5 and the volume of the index lesion. Multiple small cancers appeared to reduce the risk of PSA failure by 14% for each additional cancer. An explanation for this is that as the index lesion increases in volume, smaller, indolent cancers are assimilated into it. There might also be a paracrine growth inhibition effect between the largest index and smaller secondary lesions, although both of these theories remain to be investigated. From these studies it starts to become clear that despite being multifocal, individual cancers within the prostate appear to express different behavior and that perhaps the most aggressive cancer is originating from a single site.

Index Lesion

There are two theories that explain multifocality of prostate cancer. One is of monoclonal expansion whereby tumors arise from the same original cell clone and multifocality is the result of intraprostatic metastasis. The other is of multiclonal expansion whereby each tumor is a separate independent lesion, genetically distinct, arising in a prostate that is predisposed to cancer through a field effect.

Specifically addressing this question, Cheng and colleagues examined the pattern of allelic loss for a tumor suppressor gene on chromosome 8p and the *BRCA1* gene on chromosome 17q in 19 patients with two or more distinct prostate tumors (Cheng et al, 1998). The pattern of allelic loss was compatible with independent tumor origin in 15 of 18 informative cases. The remaining 3 were inconclusive and could have occurred as a result of independent origin or monoclonal origin.

This raises the question: If multifocal tumors in the prostate do arise independently, do they exhibit differential behavior, and does the index lesion behave differently than the smaller secondary lesions? When one evaluates the evidence with respect to the hallmarks of malignancy, there is striking evidence demonstrating that small low-grade lesions (usually secondary) exhibit few of the traits that would qualify their status as cancer.

Reclassification of Low-Grade Low-Volume Prostate Lesions

The errors in the current pathway have been well described—namely, overdiagnosis, underdiagnosis, misclassification of risk,

and overtreatment. These errors could be overcome by a recalibration of what is classified as malignant. A recent National Institutes of Health–National Cancer Institute expert group meeting on active surveillance stated that “because of the very favorable prognosis of low-risk prostate cancer, strong consideration should be given to removing the anxiety-provoking term ‘cancer’ for this condition” (Ganz et al, 2012). Esserman and colleagues (2009) stated that “minimal risk lesions should not be called cancer,” with perhaps these lesions being called “indolent lesions of epithelial origin (IDLE).” Similar sentiments have been proclaimed elsewhere (Klotz, 2012b; Nickel and Speakman, 2012). As yet, there has been a lack of a systematic evidential approach to support such a contentious standpoint based on the current level of evidence.

The prostate is far from being an outlier. In lung cancer, there is a 1 in 6 incidence of what look to be malignant lesions histologically when autopsies are conducted. These lesions are now coined *pseudodisease* in recognition of their nonmalignant behavior (Black, 2000; MacMahon et al, 2005). In the thyroid, the autopsy incidence of indolent lesions is 1 in 2, leading to a different label of *papillary microcarcinoma* (Piersanti et al, 2003); and in the bladder, low-grade transition cell lesions have effectively been reassigned as nonmalignant by the term *papillary urothelial neoplasia of low malignant potential* (PUNLMP) (Jones and Cheng, 2006). Furthermore, another NIH consensus statement suggested that ductal carcinoma *in situ* should drop the term *carcinoma* from its terminology for the same reason (Allegra et al, 2010).

Prostate cancer is, in general, multifocal and consists of a dominant (as measured by tumor volume) focus—deemed the index lesion—and one or more separate, secondary tumor foci of smaller volume (see Figs. 117-3 and 117-4). Much bench-side and clinical evidence demonstrates that we need to rethink how we regard low-grade and low-volume lesions (Karavitis et al, 2011a). In this section, we discuss why low-Gleason pattern lesions with low volume—which in the current era are being designated as *prostate cancer*—could be regarded as nonmalignant, and perhaps called *IDLE lesions*. These lesions either have been shown to not meet the hallmarks of cancer or lack robust evidence to that effect, as opposed to the index lesion—the largest lesion with the highest grade—which seems to be primarily responsible for metastatic disease (Fig. 117-5).

The redesignation of low-volume Gleason 3+3 disease as a benign entity may represent another incremental step in the way the grading system has evolved over the years. Gleason patterns 1 and 2 are rarely assigned to prostate cancer in the current era (Egevad et al, 2012). For instance, there has been an accepted grading shift upward—the so-called Will Rogers phenomenon (Albertsen et al, 2005)—in other words, the changing definition of Gleason pattern 4 has led to the regrouping of cases previously considered Gleason 6 into the Gleason 7 category. In many cases of cancer patterns previously assigned to the lowest Gleason grade 1, recent advances in immunohistochemistry have demonstrated the presence of basal cells, identifying the cases as atypical adenomatous hyperplasia, a benign mimic of cancer (Epstein, 2000). Moreover, lesions with grades 1 and 2 have been recognized as biologically similar to grade 3, further discouraging the use of these grades. Here we discuss key evidence structured within the framework of the original six “hallmarks of cancer” famously elucidated by Hanahan and Weinberg (2000, 2011) (Fig. 117-6).

Tumor cells can generate their own growth signals and reduce their dependence on stimulation from the surrounding normal tissue microenvironment. Ross and colleagues (2011), using laser-capture microdissection, extracted neoplastic cells from radical prostatectomy specimens of 23 men with either Gleason grade 3+3=6 or 4+4=8 index lesions. mRNA expression of 18,344 unique genes was then elucidated in these extracted cells; 670 genes were discovered to be differentially expressed between Gleason sum 6 (3+3) and 8 (4+4) index lesions. The profile of upregulated genes in high-grade lesions resembled the pattern observed in embryonic, neuronal, and hematopoietic stem cells. It is important to note that endothelial growth factor (EGF) and endothelial growth factor receptor (EGFR) overexpression stimulates independent cell

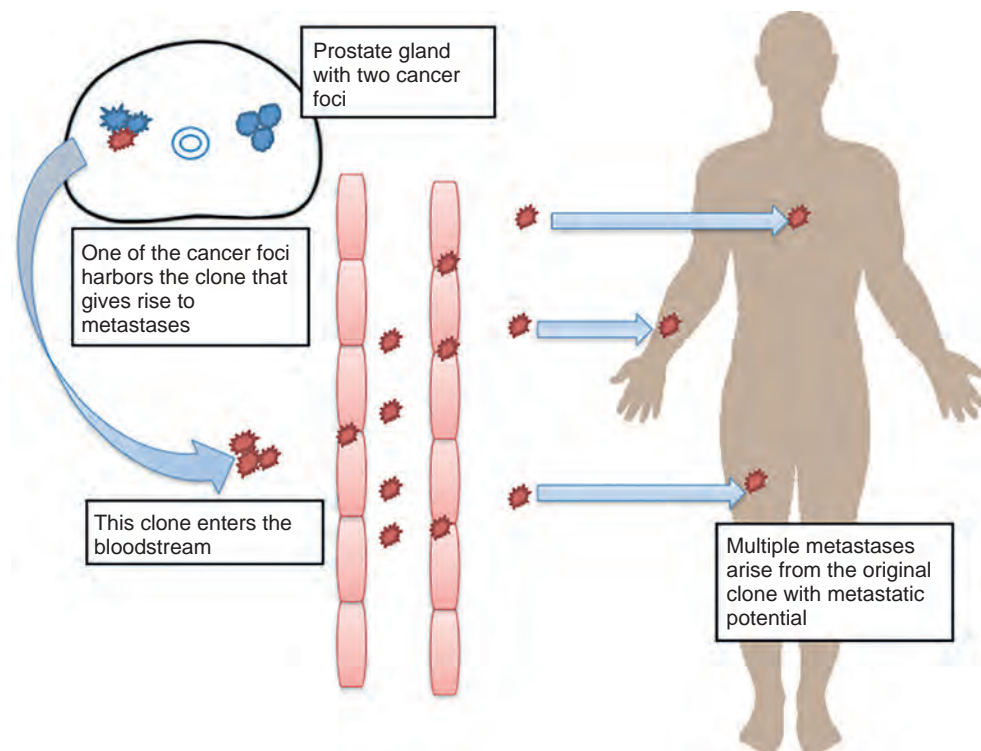


Figure 117-5. The index lesion hypothesis states that one cancer cell clone leads to metastases.

Insensitivity to growth inhibitory signals

Decreased expression p27^{kip1}
Increased methylation cyclin D2

Resisting cell death

Overexpression of Bcl-2
Overexpression of DAD1

Unlimited replicative potential

Decreased androgen signaling
Overexpression of ERG

Angiogenesis

Higher MVD
Increased expression of angiogenesis factors

Local tissue invasion and Metastasis

Overexpression of CXCR4
Monoclonal nature of invasion and metastases of lesions

Mortality rates in men with only low-risk lesions

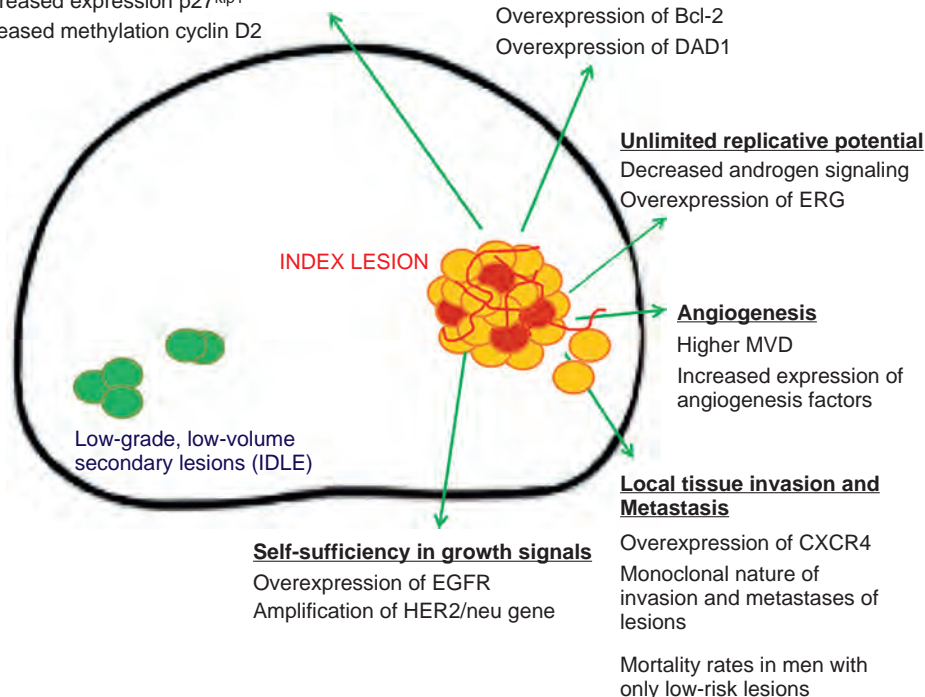


Figure 117-6. Numerous papers have demonstrated that low-volume, low-grade lesions do not demonstrate the hallmarks of malignancy as exemplified by Hanahan and Weinberg. EGFR, epidermal growth factor receptor; ERG, ETS (erythroblast transformation-specific)-related gene; MVD, microvessel density.

proliferation and cell motility through several signal transduction mechanisms including the MAPK, AKT, and RAS pathways. In addition to the upregulation of the EGFR itself in Gleason 4+4 index lesions, the group also demonstrated overexpression of *MAP2K4* and *RALA20*, the latter of which is a migration-promoting gene activated by EGF. Also, the downregulation of *RESP2* (which inhibits EGFR actions by resulting in the endocytosis of the receptor) was established. The investigators also noted that two genes that inactivate phosphor-AKT—*PHLPP* and *PML*—were downregulated in Gleason 4+4 cancer.

Cancer cells must be able to resist the normal antigrowth signals that push them into a quiescent phase of the cell cycle or enter into postmitotic phases that ensure specific cell differentiation. The D-type cyclins are involved in the regulation of transition from G₁ to S phases during the cell cycle. It has been reported that cyclin D2 is a direct target of Myc and that accumulation of cyclin D2 promotes the sequestration of p27, which is a cell cycle inhibitor, and this subsequently results in entry to the cell cycle. Inactivation of cyclin D2 may be a result of aberrant promoter hypermethylation. Using 101 radical prostatectomy specimens, [Padar and colleagues \(2003\)](#) reported that maximum Gleason pattern 3 tumors had significantly greater methylation frequency of cyclin D2 in comparison with those containing Gleason patterns 4 or 5. Transforming growth factor- β (TGF- β) can impede growth by the induction of inhibitors of cyclin-CDK complexes including p27^{kip1}. Using radical prostatectomy specimens, [Guo and colleagues \(1997\)](#) showed that there was progressively diminished p27^{kip1} immunostaining with increasing Gleason score in prostate neoplasms. All Gleason pattern 5 foci were totally negative for p27^{kip1} staining, suggesting that these cells are unresponsive to the growth-inhibitory effect of TGF- β . This loss of p27^{kip1} was associated with an increase in the proliferative index of the higher-grade prostate cancers.

The ability of cancer cells to resist programmed cell death (apoptosis) is key to ensuring continued growth and proliferation. [True and colleagues \(2006\)](#) used laser capture microdissection to acquire specific subpopulations of prostate cancer cells consistent with lesions containing Gleason patterns 3, 4, and 5 from 29 radical prostatectomy specimens. The group profiled transcript abundance levels using cDNA microarray analysis and developed an 86-gene model capable of differentiating between lesions containing Gleason pattern 3 from higher-grade patterns 4 and 5. This model was observed to be 76% accurate in characterizing an independent set of 30 primary prostate tumors. One specific discriminatory gene identified was *DAD1*, a gene encoding defender against death, which is a downstream target of the nuclear factor- κ B (NF- κ B) survival pathway and displays an antiapoptotic function. *DAD1* protein expression was subsequently elucidated by immunohistochemistry in tissue microarrays comprising formalin-fixed radical prostatectomy cores that, together, contained 131 benign and 306 cancerous samples. *DAD1* protein levels demonstrated a strong correlation with Gleason grade, with tumors of patterns 4 and 5 more likely to stain intensely compared with Gleason pattern 3. Another more familiar antiapoptotic gene is *BCL2*. Its role in carcinogenesis and development of castrate resistance in prostate cancer has been well established. Recently, [Fleischmann and colleagues \(2012\)](#) performed immunohistochemical analysis on a tissue microarray of 3261 radical prostatectomy specimens. *BCL2* expression was significantly upregulated in those lesions with a high Gleason score—that is, those lesions that included Gleason patterns 4 and 5 in contrast to those that were only pattern 3.

Mammalian cells appear to have an inherent autonomous function, independent of cell-to-cell signaling, which limits their replicative ability. Cancers disrupt this intrinsic pathway. [Tomlins and colleagues \(2007\)](#) used laser-capture microdissection to obtain 101 specific cell populations from 44 men and then separated the samples into two groups: low-grade, only Gleason pattern 3, and high-grade samples with Gleason pattern 4 or higher. The investigators identified significantly decreased androgen signaling in high-Gleason grade lesions, similar to metastatic prostate cancer, which may reflect dedifferentiation and explain the clinical association of

grade of the index lesion with prognosis. [Hendriksen and colleagues \(2006\)](#) also reported lower androgen signaling in high-Gleason pattern prostate cancer compared with low-Gleason pattern lesions. They suggested that localized prostate cancer cells become more aggressive by selectively downregulating androgen-responsive genes, resulting in increased tumor cell replication and proliferation, dedifferentiation, or reduced apoptosis. *TMPRSS2-ERG* translocations are the most prevalent genetic alterations in prostate cancer. This gene fusion results in overexpression of the ERG transcription factor. Although the association between ERG gene rearrangements and aggressive prostate cancer is controversial, it is becoming apparent that it plays a significant role in disease progression. Because *TMPRSS2-ERG* fusions lead to frequent alterations (460%) of the ERG proto-oncogene in early-stage prostate cancer, their evaluation in preneoplastic cells as well as multifocal lesions from the same patient has potential to define its role in prostate cancer onset, progression, and heterogeneity. In fact, evidence suggests that ERG protein expression can be used as a surrogate marker for ERG genomic rearrangements. One group established that ERG protein expression was statistically significantly higher in tumors with larger volumes and higher Gleason grade from radical prostatectomy specimens, presumably as a result of this transcription factor promoting tumor growth and proliferation ([Bismar et al, 2012](#)). Another group showed that *TMPRSS2-ERG* gene fusions predominantly resided in the index lesion but were also present in some secondary lesions as well as some histologically benign areas of prostate ([Furusato et al, 2008](#)). Other scientists have shown a strong relationship of expression of *TMPRSS2-ERG* fusion mRNA isoforms with pathologic measures of clinical outcome (seminal vesicle invasion, ECE) in lesions from radical prostatectomy specimens ([Wang et al, 2006](#)). They found expression of the fusion in benign glands of the prostate. This underlies the uncertainty of this particular gene fusion's role in prostate cancer development and progression.

Neovascularization is a normal physiologic process that takes place during embryonic development and wound healing. The process is also required for solid tumors to grow beyond 1 mm in diameter and for their subsequent rapid growth ([Folkman, 1995](#)). Malignant prostate cells secrete angiogenic molecules such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2, TGF- β , and cyclooxygenase-2. Raised levels of VEGF and increased microvessel density (MVD) are related to a poorer prognosis in prostate cancer ([West et al, 2001](#); [van Moorselaar et al, 2002](#)). Several observations suggest that higher-grade and larger-volume lesions are associated with increased angiogenesis. For example, there is a strong correlation between elevated MVD and higher Gleason score ([Brawer et al, 1994](#); [Erbersdobler et al, 2010](#)). In addition, [Mucci and colleagues \(2009\)](#) established that poorly differentiated tumors demonstrated greater MVD and irregularity of the blood vessel lumen with smaller vessels. In this study, during a 20-year follow-up period, bone metastases or cancer-related death occurred in 44 of 572 men. Lethal prostate cancer was 6 times more likely to occur in neoplasms exhibiting the smallest vessel diameter (based on quartiles). Also, cancers with the most irregularly shaped vessels were 17 times more likely to result in mortality. MVD was not linked to cancer-specific mortality after adjusting for clinical factors.

Cancers must exhibit the ability to invade local tissues and spread beyond the tissue and organ of origin. Evidence exists pointing to the lack of invasive and metastatic behavior of most prostate cancer lesions. For instance, when individual prostate cancer lesions, derived from one patient's primary prostate cancer specimen, were implanted into a murine model, only one lesion showed characteristics of local invasion and eventually formed metastases ([Lin et al, 2010](#)). CXCR4, a chemokine receptor, has been found to be upregulated in localized high-grade Gleason 4+4 index lesions in comparison with Gleason 3+3 index lesions. This G protein-coupled transmembrane receptor plays a key role in the directional migration of cancer cells to specific metastatic sites in response to its ligand CXCL12. The CXCR4 receptor has been associated with the establishment of lymph node and bone metastasis in

prostate cancer, possibly through activation of the RAS oncogene family member *RAP1A*, which has also been found to be upregulated in Gleason pattern 4 index tumor lesions relative to those containing solely a Gleason pattern 3. In addition, studies have suggested that hypoxia induces CXCR4 expression in tumor cells via hypoxia-inducible factor-1 α (HIF-1 α) (Schioppa et al, 2003; Staller et al, 2003). Larger-volume tumors, specifically the index lesion in prostate cancer, are significantly more likely to have central hypoxic areas. This results in the expression of the CXCR4 receptor on the tumor cell membrane, allowing the cancer cells to migrate or metastasize away from the area of low oxygen tension, down a CXCL12 concentration gradient, to areas of high oxygen concentration. The ligand CXCL12 is secreted at particularly high levels by lymph node and bone marrow stromal cells.

Investigators from Stanford (Stamey et al, 1999; Wise et al, 2002) have reported that percentage of Gleason pattern 4 and 5, cancer volume of the largest tumor, positive lymph node findings, and intraprostatic vascular invasion were independently associated with prostate cancer progression. Another group observed that 80% of secondary foci are less than 0.5 mL and have the same volume distribution as tumors found incidentally in patients who undergo cystoprostatectomy for bladder cancer (Nevoux et al, 2012). It has been proposed that tumor volume is associated with PSA recurrence (Nelson et al, 2006) and that prostate lesions smaller than 0.5 mL are clinically insignificant owing to the long doubling time of this cancer to result in metastases (Stamey et al, 1993). Schmid and colleagues observed that 79% of men with previously untreated prostate cancer of all clinical stages who underwent serial PSA measurements during a period of at least 12 months had a tumor-doubling time greater than 24 months (Schmid et al, 1993). Primary tumor volumes that theoretically lead to distant metastases tend to be at least 4 mL (McNeal et al, 1990). In that case, with an estimated tumor volume doubling time of 2 years, it would take about 12 years for a 0.5-mL lesion reach a volume of 4 mL. There also seems to be a strong correlation between pathologic and staging parameters of poor prognosis (extracapsular invasion, seminal vesicle invasion, metastases) with individual cancer lesion volume. Lesions measuring 0.5 mL had a 10% incidence of capsular invasion, whereas lesions measuring 4.0 mL had a 10% probability of seminal vesicle invasion. Lesions measuring 5.0 mL had a 10% incidence of metastases (Bostwick et al, 1993). There is a low incidence of Gleason pattern 4 or greater in secondary nonindex lesions, and very rarely are pathologic features such as seminal vesicle invasion or ECE found in secondary lesions (Bott et al, 2010; Karavitis et al, 2011b). Furthermore, there seems to be a correlation between index lesion volume and biochemical progression-free survival (Rashid et al, 1999; Fuchsjäger et al, 2010). Therefore the evidence certainly points to the index tumor as the one with malignant potential, rather than all lesions (Haggman et al, 1997).

A word of caution is, however, necessary. One group observed that one in four lesions that invaded the capsule were not the index lesion (Ruijter et al, 1996), and other scientists showed that tumors that locally invade are not necessarily large (Miller and Cygan 1994). In fact, circulating tumor cells and occasionally lymph node metastases have been found in men who have small lesions (0.2 mL) (Gburek et al, 1997; Schmidt et al, 2006). In a series of 239 patients with tumor volume less than 0.5 mL, investigators (Kikuchi et al, 2004) demonstrated that 43 cases were poorly differentiated, 11 had ECE, 6 had positive surgical margins, and 2 had positive lymph nodes, and 7 patients experienced progression within 5 years. Greene and colleagues (1994) assessed DNA ploidy status, which is an independent prognostic factor for localized prostate cancer. Of 141 separate cancers in 68 patients, the group discerned that 15% of those 0.01 to 0.1 mL and 31% of those 0.11 to 1.0 mL in volume were nondiploid. Thus, tumor volume in itself did not adequately describe the biologic potential of prostate cancer on its own and should be combined with other factors, predominantly Gleason grade (Andreoiu et al, 2010).

One paper that does counter this argument is from Haffner and colleagues (2013). In this study, whole genome sequencing was used to characterize the lethal cell clone in a single patient who

died of metastatic prostate cancer. It is interesting to note that the analysis revealed that the lethal clone arose from a small, low-grade cancer focus in the primary tumor. However, this study has a number of problems. First, the patient was treated with multiple therapies that might have altered the metastases that eventually were sequenced. Second, the Gleason 6 area supposedly causing metastases was within a larger tumor that covered almost the entire prostate. This Gleason 6 area would in no way be equivalent to a solitary 0.1-mL or 0.2-mL Gleason 6 lesion. Barbieri and colleagues (2014) have argued that the lethal subclone is unlikely to have originated as a small, low-grade lesion because several areas within the prostate showed the same types of mutation, making these very likely to be the same tumor. They state that the lethal area likely began as a relatively large, *SPOP*-mutant tumor displaying significant amounts of Gleason pattern 4 with a small area acquiring mutations in tumor suppressors *TP53* and *PTEN*, driving the metastatic phenotype. Lastly, even if it is true that this area caused a metastasis, it is likely a rare occurrence because otherwise the one third of the male population with small cancer lesions in the prostate would need to undergo radical therapies.

Although many have focused on this one case report, a number of other studies have demonstrated that metastases occur almost always from the index lesion. Further, Ross and colleagues (2012) have shown that pure Gleason 6 disease almost never metastasizes. This study evaluated radical prostatectomy databases at four academic centers for cases of Gleason score of 6 or lower with only those prostatectomies submitted and embedded in their entirety with pelvic lymph node dissections. Of 14,123 cases, 22 had positive nodes, although histopathologic review of 19 cases (3 cases were unavailable) showed higher grade than originally reported. In other words, no case of pure Gleason 6 on prostatectomy specimens demonstrated metastases to lymph nodes.

The molecular correlation of individual lesions with lymph node metastases has added further strength to the argument that, despite multifocality, prostate cancer disease progression is likely to be related to lesions that meet certain minimal grade and volume thresholds. *TMPRSS-ERG* gene fusions observed in lymph node metastases are shared with the index lesion and not small satellite low-grade lesions (Guo et al, 2012) or secondary high-grade and high-volume lesions (Perner et al, 2010). It is important to note that researchers have elucidated that metastatic deposits share one common cell of origin (Ahmed, 2009; Liu et al, 2009), although the question of whether the metastatic clone originated from the index lesion is something that was impossible to address in this case series owing to the nature of men from whom the tissue samples were taken.

Postmortem studies have confirmed a one in three incidence of so-called prostate cancer in men who died of other causes. Similar rates are seen on assessing the prostates taken from cystoprostatectomy specimens when men underwent surgery for high-risk or invasive bladder cancer (Nevoux et al, 2012). Therefore, because one third of men have prostate cancer that will not affect them within their lifetime, it is not surprising that small low-grade lesions have low (possibly absent) malignant potential (Sakr et al, 1996). In addition, such epidemiologic facts support the assertion that most prostatic lesions, especially those of low volume and low Gleason grade, currently called cancer do not demonstrate tissue invasion and eventual metastases.

Two groups have underlined the low malignant potential of Gleason grade 6 disease. Eggener and colleagues (2011) demonstrated that of 9775 men who had only Gleason 6 low-risk disease in radical whole-mount prostatectomy specimens, only 3 died of prostate cancer in a 15-year period. In fact, on review, 1 of these cases had a small amount of Gleason pattern 4 within it; the other 2 were not available for review. This finding cannot simply be accounted for by the success of surgery itself. Other groups have shown similar findings with biochemical recurrence (a surrogate outcome) in smaller cohorts of men (Miyamoto et al, 2009; Lee et al, 2011).

Clinical experience with active surveillance now suggests there is an estimated risk of metastasis of less than 1% at 2 to 8 years

(Dahabreh et al, 2012) and disease-specific mortality of 1% at 8 years while on surveillance (Klotz, 2012a) for men with low-risk disease as classified by a diagnostic TRUS-guided biopsy. The Toronto active surveillance series showed that all prostate cancer-related mortality occurred in men who had been reclassified as higher risk and who were offered radical treatment (Klotz et al, 2010). However, only one patient in this series who was treated after a relatively prolonged period of observation subsequently experienced progression to metastatic disease and death. Therefore, it is likely that reclassification of disease risk and subsequent radical treatment reflect undersampling of the prostate rather than true progression. Two recent reports from active surveillance cohorts from three regions that participated in the ERSPC study add a further shade of uncertainty for intermediate-risk disease. The first from Rotterdam and Helsinki looked at 509 men; 381 were low risk and 128 intermediate risk (Bul et al, 2012). During a median 7.4 years of follow-up, 221 men (43.4%) switched to deferred treatment, with 152 (39.9%) in the low-risk group undergoing treatment and 69 (53.9%) of the intermediate-risk group. Distant metastases were found in 1 low-risk and 3 intermediate-risk men. The Göteborg arm looked at 439 (45.4%) men managed with surveillance from a total of 968 in the screening group (Godtman et al, 2013); 224 (51.0%) were very low risk, 117 (26.7%) low risk, 92 (21.0%) intermediate risk, and 6 (1.4%) high risk. Two hundred and seventy-seven men continued on surveillance, of whom 133 (59%), 58 (50%), 46 (50%), and 3 (50%) were still on surveillance at study end in each group, respectively. Sixty men died during follow-up; only 1 man (intermediate risk) died from prostate cancer 12.7 years after diagnosis after having developed distant metastases at 8.6 years. However, despite a significant body of evidence demonstrating that this is a safe approach (Dahabreh et al, 2012), active surveillance seems to be infrequently offered to or chosen by men, with only 1 in 10 in the United States and 4 in 10 in the United Kingdom with low-risk disease undergoing active surveillance (Cooperberg et al, 2004; McVey et al, 2010). This may be physician or patient related but likely is a combination of both. With the uncertainty around longer follow-up, especially in the intermediate-risk group, this is hardly surprising, but it does point to the need for improved therapeutic interventions that can minimize the harms of treatment if that is what men and their physicians choose.

IDENTIFYING THE PATIENT POPULATION FOR FOCAL THERAPY

Any man with localized prostate cancer suitable for curative therapy should be regarded as suitable for some form of focal therapeutic intervention. Such a pragmatic approach would not limit the age to a lower or an upper boundary. However, focal therapy has been seen by many, predominantly in the United States, as an alternative to active surveillance, whereas others, predominantly in Europe, have argued that focal therapy should also be regarded as an alternative to radical therapies (Ahmed and Emberton, 2008).

The arguments for focal therapy to be carried out only in men suitable for active surveillance are (1) reduction of the potential psychological morbidity associated with men not having treatment for a cancer—that is, for patients, “some form of treatment is better than none,” and (2) reduction of the surveillance of cancer progression rate (about one third require delayed intervention within 5 years). Although up to 10% of men on active surveillance choose to have intervention within 5 years despite the absence of biochemical or histologic progression, questionnaire surveys have shown conflicting findings about the level of anxiety present in such cohorts. Furthermore, despite the progression rate, the mortality rate has been negligible, so it can be argued that most men can avoid treatment and those who have delayed intervention have a period of time free of treatment-related side effects. However, the period of low side effects could be extended if focal therapy were to be carried out at diagnosis or, indeed, at the time of disease progression after a period of surveillance. The argument against

men who are suitable for active surveillance undergoing focal therapy is that any treatment within this group is liable to be over-treatment. Any treatment, regardless of the encouraging functional outcomes that it may demonstrate, will carry greater morbidity than a management strategy in which two thirds of men with low-risk disease can avoid side effects of treatment and the others can delay such morbidity. Nonetheless, active surveillance is not without harm and burden, with surveillance blood tests and biopsies performed every 1 to 2 years (with their concomitant risk of complications), although the specific evidence with regard to repeat biopsy in active surveillance is conflicting (Fujita et al, 2009; Bergman et al, 2012; Hilton et al, 2012; Loeb et al, 2013a).

It can be argued that the emergence of focal therapy as a strategy to reduce the side effects of conventional whole-gland therapies requires us to evaluate its potential within men who, as a result of harboring intermediate- to high-risk localized disease, would undergo radical therapies (Figs. 117-7 to 117-10). Despite the higher-risk disease status, evidence suggests that the oncologic benefits of radical therapies would be seen only after 10 years. A strategy that treats the cancer and carefully monitors untreated tissue for de novo cancer may obviate the need for any further radical therapies in the future or delay it for a number of years, during which the man is free of treatment-related side effects. The problem with such a proposal is the risk of progression to metastases in intermediate- to high-risk disease. Any undertreatment of cancer foci resulting from poor localization of the tumor may allow a window of opportunity in which local curative treatment may not be successful. The prolonged natural history of prostate cancer, even in these groups, precludes such an argument.

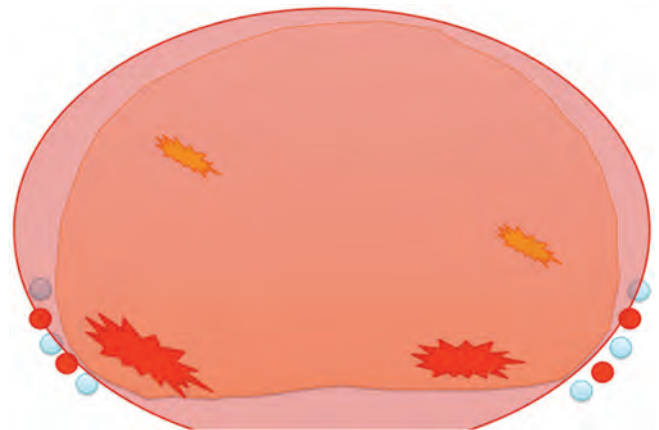


Figure 117-7. Schematic of a gland that would not be suitable for focal therapy owing to multifocal clinically significant prostate cancer lesions.

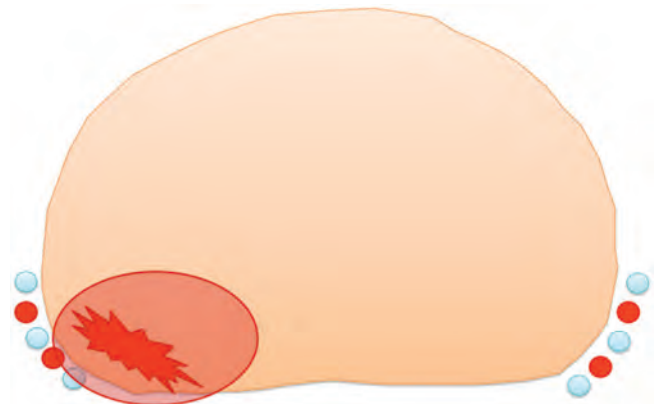


Figure 117-8. Unifocal lesion suitable for focal ablation.

TABLE 117-1 Definitions Commonly Used to Define Clinically Significant Prostate Cancer

DEFINITION	GLEASON GRADE	MAXIMUM CANCER CORE LENGTH	TEST IN WHICH TO USE
Epstein et al, 1994	≥3+4	≥3 mm	TRUS biopsy
Stamey et al, 1993	≥3+3	≥3 mm	TRUS biopsy
Harnden et al, 2008	≥3+4	≥3 mm	TRUS biopsy
Goto et al, 1996	≥3+4	≥2 mm	TRUS biopsy
Ahmed et al, 2011b (UCL Definition 2)	≥3+4	≥4 mm	Transperineal template or image-targeted biopsy
Ahmed et al, 2011b (UCL Definition 1)	≥4+3	≥6 mm	Transperineal template or image-targeted biopsy

TRUS, transrectal ultrasound; UCL, University College London.

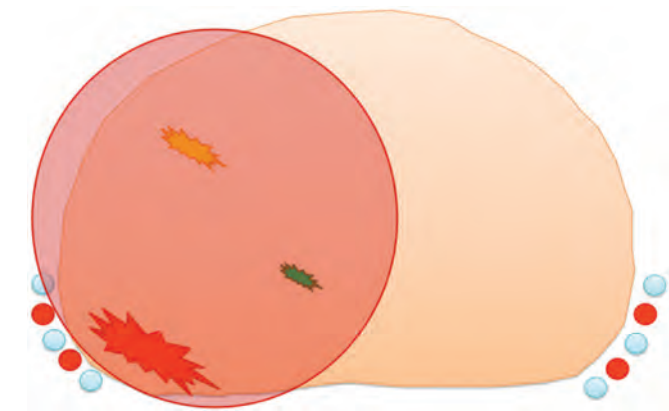


Figure 117-9. Unilateral cancer with multifocality suitable for hemiablation.

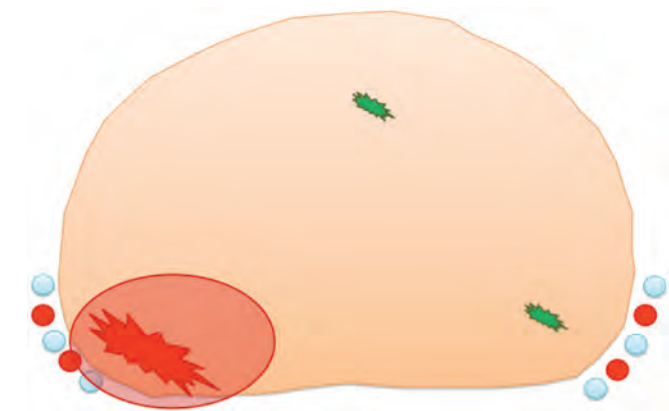


Figure 117-10. Multifocal prostate cancer but biologically unifocal—potentially suitable for index lesion ablation.

Localization of Disease

Focal therapy requires accurate localization of disease to drive precision ablation. Localization of disease requires histology and imaging, either alone or in combination, and therefore represents an additional health care burden that forms part of focal therapy intervention. An accurate localization strategy will more clearly define the patient population in terms of stage, grade, and disease burden.

Before discussing the performance characteristics of different biopsy strategies, it is important to define what level or threshold of disease we are expecting biopsy strategies to find. A number of definitions of significant disease have been published (Table 117-1). The Epstein, Stamey, Harnden, Goto, and Ahmed/University College

London (UCL) definitions all vary and have been validated using different reference standards—that is, TRUS, radical prostatectomy, or transperineal prostate mapping (TPM) (Stamey et al, 1993; Epstein et al, 1994; Goto et al, 1996; Harnden et al, 2008; Ahmed et al, 2011b). Overall, however, it seems that most studies have a widely used definition of clinically significant prostate cancer of 0.5 mL or greater in volume and/or Gleason grade 3+4 or higher. Several studies report on the detection rates of any cancer between biopsy strategies as opposed to the detection rate of clinically significant and clinically insignificant cancer.

A definition for clinically significant disease that has been validated using an accurate sampling strategy (either TPM or radical prostatectomy) must be agreed on. Biopsy strategies can then be compared using this definition to determine the most accurate method able to guide focal targeted therapy. It is likely that definitions will vary according to the patient’s baseline characteristics and other risk factors.

Biopsy

When considering focal therapy, the role of prostate biopsy is not only in cancer diagnosis but also in characterization and localization of individual lesions (Ho et al, 2011). Biopsy strategies have evolved considerably to accurately identify, characterize, and localize lesions while trying to minimize risks to patients and reduce overall costs. Some of these strategies include taking biopsies via different anatomic approaches (transrectal, transperineal), as well as increasing the number of cores taken (saturation, mapping) and decreasing the number of cores but improving their deployment into the gland (targeted).

Systematic Transrectal Ultrasound–Guided Biopsy

Currently, systematic TRUS-guided biopsy is still the standard of care (Heidenreich et al, 2014a). However, several studies have reported on the limitations of TRUS biopsy that hinder its ability to guide focal therapy. First, TRUS biopsy may miss up to 30% of clinically significant prostate cancer. Anterior regions of the prostate are frequently overlooked by TRUS biopsy, and it has been estimated that this is where approximately 30% of cancers reside (Bouye et al, 2009). Repeated TRUS biopsies do not seem to improve cancer detection rates. Studies have shown that detection rates on first, second, third, and fourth biopsies have been reported to be 14% to 22%, 10% to 15%, 5% to 10%, and 4%, respectively (Lujan et al, 2004; Djavan et al, 2005; Anastasiadis et al, 2006). Repeating TRUS biopsies because of negative results and a rising PSA level places men at increased risk of sepsis as well as causing anxiety from the uncertainty and delayed diagnosis. Second, TRUS biopsies are taken in a random manner and therefore cannot accurately localize individual areas of disease. Mayes and colleagues found that sextant TRUS biopsy has a low positive predictive value of 28%, with a high false-positive rate of 72% for detecting unilateral disease (Mayes et al, 2011). Washington and colleagues (2012) showed that although TRUS biopsy could identify lesions on the same lobe as the dominant lesion 81% of the time (95% confidence

interval [CI] 0.7 to 0.9), in only 22% was the correct location identified. The median number of cores per biopsy increased with successive biopsies: 14 cores for the first biopsy, 16 for the second round, and 17 for the third round. Because the patient is often in the left lateral position for TRUS biopsy, subsequent targeted treatment is somewhat difficult because there are no proper landmarks to clearly identify specific locations. Third, it is difficult to interpret whether the tumor is of small volume (and potentially insignificant on histology) or of large volume or high Gleason score (and potentially pathologically advanced) (Andriole et al, 2007). Indeed, when compared with the gold standard prostatectomy specimens, TRUS biopsy has been shown to understage or undergrade disease in up to 30% of cases (Epstein et al, 2005; Chun et al, 2010). Last, some of the additional harms of TRUS biopsy include rectal bleeding and potentially life-threatening postbiopsy sepsis.

Saturation Biopsy

Prostate saturation biopsy was initially introduced by Borboroglu and colleagues (2000) and consisted of taking at least 20 biopsy cores. Studies conflict in showing whether saturation biopsies provide more accurate disease diagnosis.

Transrectal Saturation Biopsy

De la Taille et al (2003) compared the cancer detection rates of taking 6, 12, 18, and 21 systematic TRUS biopsy samples. Overall, cancer detection rates for these groups were 22.7%, 28.3%, 30.7%, and 31.3% respectively. The 21-sample procedure statistically improved the cancer detection rate by 37.9% relative to the 6-sample procedure. There was no comment on the detection rate of clinically significant cancer detection rates in this study.

Epstein and coworkers (2005) performed saturation biopsy on consecutive radical prostatectomy samples. Using Epstein's criteria of insignificant tumor less than 0.5 mL, organ confined, seminal vesicles and lymph nodes negative for tumor, and no Gleason pattern 4 or 5, 71% of the cancers at radical prostatectomy were classified as insignificant, and 29% had been misclassified using standard biopsy schemes. The false-negative rate of saturation biopsy for clinically significant cancer was also reported as 11.5% with sensitivity and specificity of 71.9% and 95.8%, respectively.

Li and colleagues (2014) retrospectively compared 3338 men with a 12- to 14-core biopsy scheme (extended biopsy) with 438 men with a 20-core biopsy scheme (saturation biopsy). A higher rate of low-grade prostate cancer as defined by Gleason score below 6 was detected in the saturation biopsy group compared with the extended biopsy group (50.0% vs. 41.4%; $P = .015$). However, using Epstein's criteria for clinically insignificant disease, the saturation biopsy group did not detect a higher rate of clinically insignificant prostate cancer compared with the extended biopsy group (21.2% vs. 17.9%; $P = .223$).

Irani and colleagues (2013) performed an RCT comparing 12- versus 20-core TRUS biopsy. Patients were biopsy naive and had PSA levels less than 20 ng/mL and no nodule on digital rectal examination. No significant difference was found between the groups for cancer detection rate or for Gleason score, tumor length, and proportion of cancer affecting both lobes. Using D'Amico criteria for low-risk cancer (Gleason 6 and PSA level less than 10 ng/mL and T1c or T2a clinical stage), there was no significant increase in low-risk cancers detected in the 20-core biopsy group compared with the 12-core biopsy group (47% vs. 39%; $P = .32$).

Transperineal Saturation Biopsy

Novara et al (2010) examined 143 men with previous negative TRUS biopsy who underwent a 24-core freehand transperineal saturation biopsy; 26% of patients were found to have cancer. The majority of these (65%) had Gleason grade 6 disease, and only 1 patient had Gleason grade 8 disease. Twenty-one of 37 patients with cancer had radical prostatectomy; 8 of these were found to have pathologically locally advanced disease (pT3ab N0 cancers) and 4

to have ECE. It was not made clear whether this correlated with biopsy outcome. Eight of the 17 patients with a Gleason grade 6 on biopsy were found to have Gleason grade 7 on radical prostatectomy review.

Transperineal Saturation versus Transrectal Ultrasound Saturation Biopsy

Abdollah and colleagues (2011) matched 280 patients who underwent either TRUS or transperineal saturation biopsy taking 24 cores. Overall, the prostate cancer detection rate was 28.6%. There was no statistically significant difference in prostate cancer detection rate between the two approaches (31.4% TRUS vs. 25.7% transperineal). Complications of saturation biopsy are similar to those of TRUS and include hematuria, hemospermia, perineal hematoma, urinary tract infections (UTIs), acute urinary retention, and prostatitis.

Transperineal Template Prostate Mapping Biopsy

For transperineal template prostate mapping biopsy, the patient is placed in the lithotomy position with a brachytherapy grid against the perineum to guide the procedure. This has several advantages over the problems associated with TRUS biopsy (Fig. 117-11).

Firstly, the brachytherapy grid has 5-mm holes, allowing for systematic sampling of the entire prostate. This can ensure comprehensive coverage of the prostate and can sample areas commonly missed by TRUS biopsy (apex, anterior horn of peripheral zone, transition zone). Crawford and colleagues (2013) performed a computer-simulated study on 40 autopsy prostate specimens. The simulation used TPM with either 5-mm or 10-mm sampling. Overall, 5-mm sampling identified more cancers than 10-mm sampling (76% vs. 45%, respectively) and also detected tumors with a higher Gleason grade 4/5 (77% vs. 40%).

Systematic sampling provides a more precise, three-dimensional (3D) representation of location, volume, and extent of the disease (Barzell and Melamed, 2007; Onik et al, 2009). Studies have also reported the upstaging and upgrading of disease on TPM after previous TRUS biopsy. One study has shown that TPM upstaged in almost half (45.6%) of cases, and one third to one half (27.2% to 46%) of cases were upgraded (Barqawi et al, 2011) (Fig. 117-12).

Because the TPM biopsy is performed with the patient in the lithotomy position, this will often be the same position used for subsequent focal therapy. This aids subsequent treatment planning, as a fixed set of reproducible coordinates can allow targeted treatment.

Transperineal Prostate Mapping Biopsy versus Transrectal Ultrasound Biopsy

Lecornet and colleagues (2012) also performed computer simulation studies comparing standard TRUS biopsy, optimized TRUS biopsy, and TPM in the detection of clinically significant cancer using two definitions: (1) Gleason score of 7 or higher and/or lesion volume of 0.5 mL or more, and (2) Gleason score of 7 or higher and/or lesion volume of 0.2 mL or more (Ahmed et al, 2011b). Random localization error (RLE) to simulate errors introduced by imperfect needle placement, for example because of human error and needle deflection, was also incorporated into the analysis. The area under the curve (AUC) to detect and rule out definition 1 cancer was 0.69, 0.75, 0.82, and 0.91 for standard TRUS with RLE 15 mm, standard TRUS with RLE 10 mm, optimized TRUS, and TPM, respectively. For definition 2 cancer, the AUC was 0.67, 0.74, 0.81, and 0.91, respectively (see Figs. 117-4 and 117-5). The difference in AUC between the different biopsy strategies was greater for anterior lesions. Standard TRUS missed 47% of lesions 0.5 mL or greater and 79% of those 0.2 mL to 0.5 mL. Another similar simulation study performed by the same group showed that the accuracy

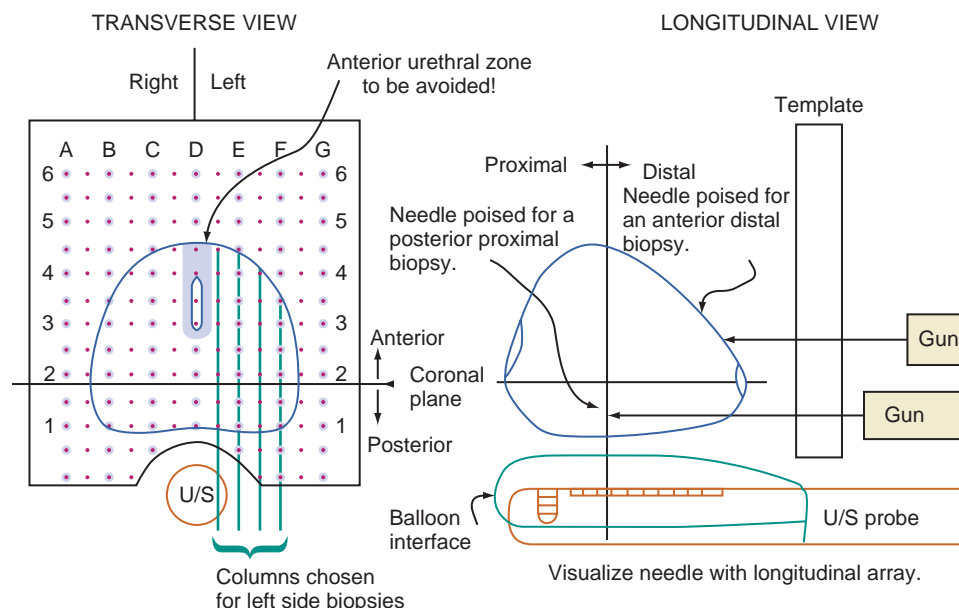


Figure 117-11. Diagram demonstrating how transperineal template-guided biopsies are carried out. If the sagittal length of the prostate is longer than the throw of the biopsy needle, then two biopsy specimens are taken from the same coordinate. U/S, ultrasound.

of TPM vs. standard TRUS (RLE 15 mm) was 0.91 versus 0.70, respectively, for lesions 0.2 mL or larger and 0.5 mL or larger (Hu et al, 2012).

Barzell and Melamed (2007) reported on 80 patients previously diagnosed with prostate cancer on TRUS biopsy who were considering focal cryotherapy and who were rebiopsied with TPM biopsy and repeat TRUS biopsy. Patients were deemed suitable for focal cryoablation if only unilateral cancer was found after repeat TRUS and TPM. TPM biopsies detected 36 of 36 (100%) unsuitable candidates; repeat TRUS biopsies picked up only 5 of 36 (14%). Sixty-one of 66 (92%) were considered suitable for focal cryoablation by repeat TRUS findings; however, only 30 of 66 (45%) were deemed suitable by TPM findings. Thus, repeat TRUS-guided biopsies had a false-negative rate of 47% (31 of 66) in excluding patients from focal cryoablation. The template map was reported as crucial in providing cryotherapy treatment to eligible men. It permitted selective targeted ablation of the areas of cancer while sparing uninvolved parts of the prostate. Recently, our own group has shown that in 291 men who underwent TPM biopsies and had previously undergone TRUS biopsy, about 90% were suitable for focal therapy if this included index lesion ablation (Singh et al, 2014).

Reported drawbacks of TPM, however, include the laborious process in terms of setup, anesthesia requirement, and greater histopathology processing time as a result of the increased number of samples, with the consequent costs. Complications of TPM include urine retention (5% to 10%), hematuria (2%), and temporary erectile dysfunction, although rates of sepsis are very low (<0.5%) (Hara et al, 2008; Merrick et al, 2008).

Imaging: Advances in Ultrasound

Increased vascularity or changes in blood flow are an important feature of prostate cancer and have been associated with higher Gleason grades (Wilson et al, 2004; Heijmink et al, 2006). These features have driven improvements in diagnostic imaging. In terms of TRUS, color Doppler imaging measures blood flow velocity and direction. Contrast-enhanced transrectal ultrasonography (CE-TRUS) involves detecting the difference in acoustic impedance between the contrast agent and adjacent tissue (Jakobsen et al, 2001). Elastography demonstrates the higher cell and vessel density in prostate cancer based on increased stiffness in comparison to the surrounding normal tissue (Aigner et al, 2012). Prostate HistoScan-

ning (PHS) works by extracting and quantifying statistical features from back-scattered ultrasound data to detect specific changes in tissue morphology and therefore distinguish between benign and cancerous tissue (De Coninck et al, 2013).

It was previously thought that hypoechoic nodules on ultrasound were caused by increased MVD. However, up to 30% of all prostate cancers are isoechoic, and it is estimated that a hypoechoic nodule has a 17% to 57% chance of being identified as prostate cancer (Frauscher et al, 2003). Artifacts can be caused by visceral motion or patient or probe movement that interrupts stable blood flow. There have been various studies comparing the aforementioned ultrasound techniques and their accuracy in diagnosing prostate cancer.

Zhao and colleagues (2013) compared TRUS with CE-TRUS in 65 patients. Targeted biopsy to abnormal CE-TRUS (CE-TRUS TB) areas were compared with systematic 12-core biopsy. The cancer detection rate of CE-TRUS targeted biopsies was significantly higher than systematic biopsies (75% vs. 48.2%, respectively). The sensitivity, specificity, and accuracy of CE-TRUS were also higher than those of TRUS (79.3%, 86.1%, and 83.1% vs. 65.5%, 69.4%, and 67.7%). Benign prostatic hyperplasia and acute and chronic prostatitis were reported to be important causes of false-positive results.

Brock and colleagues (2012) compared gray-scale ultrasound (GSU) and real-time elastography (RTE) in 353 patients. Overall, cancer was detected in 45.3% of patients. Detection rates for RTE and GSU were 51.1% and 39.4%, respectively. RTE had better sensitivity than GSU (60.8% vs. 15%); however, GSU had better specificity (68.4% vs. 92.3%). The negative predictive values of RTE and GSU were similar (87.8% vs. 83.1%). RTE was better at detecting Gleason grade above 7 than GSU (70.8% vs. 47.4%).

A further study by Brock and colleagues (2013) analyzed a combined approach of RTE and contrast-enhanced ultrasound (CEUS)-multiparametric ultrasound. Eighty-six patients with biopsy-proven prostate cancer were included. Imaging results were correlated with final pathologic evaluation on whole-mount slides after radical prostatectomy. RTE had a sensitivity and specificity of detecting prostate cancer of 49% and 73.6%, respectively. Of 86 target lesions identified by RTE, 58 (67.4%) showed a suspicious perfusion pattern on CEUS, 31 (36%) showed hypoperfusion, and 27 (31.4%) showed hyperperfused tissue. Normoperfusion was found in 28 identified target lesions (32.6%). Prostate cancer was found in 65.1% (56 of 86) of these lesions. CEUS revealed suspicious perfusion patterns in

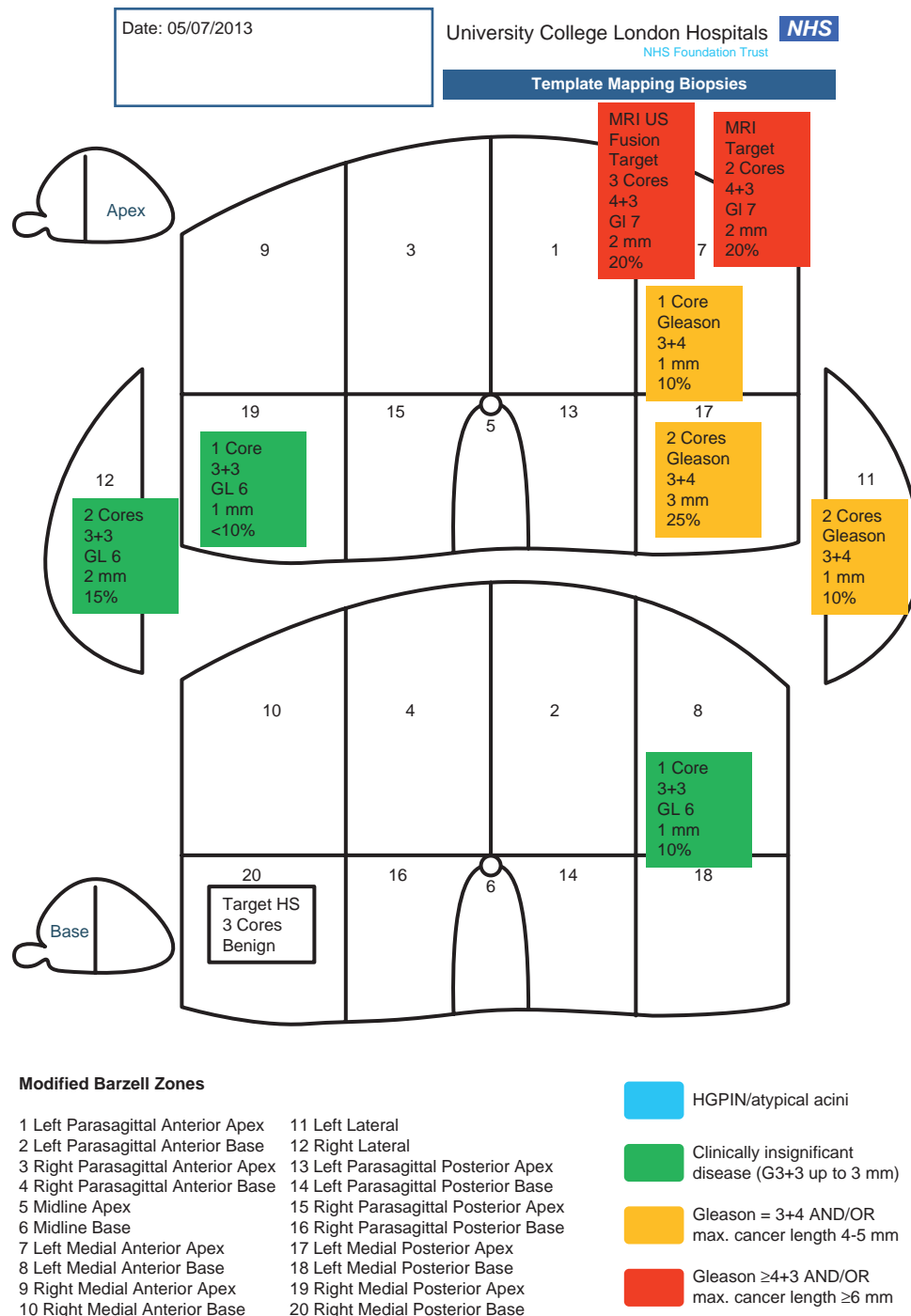


Figure 117-12. A zonal map depicting the results from a modified Barzell zone transperineal template prostate mapping case. The index lesion is on the left with UCL/Ahmed definition clinically significant cancer 1 and 2 on the left and clinically insignificant cancer on the right in two zones. The two high-risk areas (red) on the left were obtained through targeted biopsies based on the information provided by multiparametric magnetic resonance imaging.

92.9% of these lesions—either hypoperfusion (48.2%) or hyperperfusion (44.6%). Overall, if an RTE-positive target lesion showed a suspicious perfusion pattern, the likelihood of detecting cancer was 89.7%. A combination of RTE followed by CEUS reduced the false-positive detection rate from 34.9% to 10.3%.

Walz et al (2011) specifically evaluated the accuracy of RTE in identifying the index lesion for focal therapy in 32 patients. Criteria for the index lesion defined by this study were as follows: the largest suspicious lesion on RTE; on biopsy data, the lesion present in the lobe with positive cores (if the contralateral lobe had no positive

cores); the lobe with the higher percentage of positive cores or the higher percentage of cancer on core length (if positive cores were present in both lobes); and/or the lobe with the higher Gleason score. Of all patients, 87.5% had clinically significant prostate cancer defined as Gleason pattern 4 or 5 and/or cancer volume exceeding 0.5 mL and/or extraprostatic extension. The sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of RTE alone were 58.8%, 43.3%, 54.1%, 48.1%, and 51.6%, respectively. TRUS biopsies alone achieved 67.8%, 48.4%, 56.8%, 60.0%, and 58.1%, respectively. The combination of RTE

and biopsy data increased these values to 84.9%, 48.4%, 61.9%, 75.0%, and 66.1%. Overall, however, RTE alone would miss 40% of index lesions. This study did not perform target biopsies of the suspicious lesions observed on RTE, making it difficult to predict whether a combination of RTE-targeted biopsies with systematic biopsies may have increased accuracy to detect the index lesion.

There have been a few studies reporting on PHS. [Hamann and colleagues \(2013\)](#) looked at 80 men who consecutively underwent a systematic 14-core prostate biopsy supplemented by three PHS-targeted TRUS and transperineal biopsies. Twenty-eight men (35%) were found to have cancer. Targeted transperineal biopsy detected more lesions than targeted TRUS (82.1% vs. 53.6%). However, systematic TRUS and targeted transperineal biopsies performed almost equally in the detection of cancer (22 vs. 23; $P > .99$). The study was unable to report on the accuracy of PHS. [De Coninck and colleagues \(2013\)](#) compared random systematic biopsies with targeted PHS lesions; 58% of lesions suspicious on PHS were positive for cancer. However, the TRUS biopsy detected only 13% of cancers, much lower than standard TRUS detection rates of 45% to 50%, which calls into question the biopsy technique used.

[Javed and colleagues \(2014\)](#) reported on the ability of PHS to detect and localize prostate cancer compared with TRUS biopsy and transperineal biopsy. Tumor volumes of PHS-predicted lesions were also analyzed on radical prostatectomy histopathologic analysis. PHS had a sensitivity and specificity of 100% and 5.9%, respectively, when compared with TRUS biopsy. Compared with transperineal biopsy, PHS had a sensitivity and specificity for cancer detection in the posterior gland of 100% and 13%, respectively, and for the anterior gland, 6% and 82%, respectively. There was no correlation between total tumor volume estimates from PHS and radical prostatectomy specimens. Sensitivity and specificity of PHS for detecting tumor foci 0.2 mL or greater in volume were 63% and 53%, respectively. The estimated sensitivity for PHS to detect tumor greater than 0.5 mL was 37%. Index lesions were also biopsied, although no definition was given for the features of the index lesion—that is, cancer core length or Gleason grade. There was no correlation between measured tumor volume of suspected index lesions detected by PHS and radical prostatectomy histopathologic examination. These findings suggest that PHS is poor at localizing prostate cancer, assessing tumor burden, and detecting small foci of disease.

Multiparametric Magnetic Resonance Imaging

Recent innovations in MRI are also a further attempt to accurately localize prostate cancer extent without the need for invasive procedures and associated morbidity.

Multiparametric magnetic resonance imaging (mpMRI) involves different imaging parameters including T2-weighted imaging (T2W), dynamic contrast-enhanced (DCE) imaging, diffusion-weighted imaging (DWI), and magnetic resonance spectroscopy (MRS). On T2W, water appears bright, fat appears dark, and prostate cancer appears as areas of low signal. DCE images are rapidly acquired after administration of intravenous contrast. Uptake and release of contrast is more rapid in prostate cancer owing to the increased vasculature compared with surrounding tissues. DWI reflects the differential movement of water within tissues, according to their tissue architecture, cell density, cell membrane integrity, and presence of necrosis. Prostate cancer has restricted diffusion, appearing bright on longer b-value sequences and dark on an apparent diffusion coefficient map. MRS portrays the concentration of choline, citrate, and creatinine. The ratio of choline and creatinine to citrate is increased in prostate cancer ([Kurth et al, 2011](#)). The sensitivity and specificity of mpMRI have been reported to be 93% and 98%, respectively, in detecting and excluding high-grade cancers greater than 0.5 mL in volume ([Ukimura et al, 2013](#)). There are several ways to target based on the outputs of mpMRI—namely, in-bore MRI-guided biopsy, cognitive targeted biopsies, and magnetic resonance imaging-ultrasound (MRI-US) fusion-guided biopsy.

Magnetic Resonance Imaging-Guided Biopsy. A few studies have reported on real-time MRI guidance of needle biopsy. [Durmuş](#)

[and colleagues \(2013\)](#) performed MRI-guided biopsy on 87 patients. The needle guide was directed at the suspicious lesions on prebiopsy MRI, and then sagittal and oblique T2-weighted rapid acquisition was performed. Prostate cancer was diagnosed in 36 (41%) patients; 47% of these had a Gleason grade 7 or higher detected by MRI-guided biopsy. The whole gland was not sampled, so the true sensitivity and specificity of MRI-guided biopsy was not calculated. Another study found that in 15 of 27 (55.6%) patients, prostate cancer was detected by MRI-guided prostate biopsy. However no further characteristics were given regarding Gleason grade ([Anastasiadis et al, 2006](#)). A further study on 68 patients found a cancer detection rate of 59% ([Hambrock et al, 2010](#)). Radical prostatectomy was carried out in 20 of the 40 patients with tumor. Gleason grade 7 or higher was found in 50% of patients; 50% had tumor volume greater than 0.5 mL with Gleason grade 6. Limitations of MRI-guided biopsy include a lengthy process, because prebiopsy, real-time, and postbiopsy imaging have to be performed. There are also only a few centers equipped to perform this type of biopsy.

Cognitive Targeted Biopsies. Several studies have reported on use of mpMRI to target biopsies (MRI-TB). Cognitive targeted biopsies involve the physician reviewing magnetic resonance images to target suspicious lesions on MRI using ultrasound guidance. A recent systematic review comparing MRI-targeted biopsy versus systematic TRUS published by [Moore and colleagues \(2013\)](#) found a similar detection rate between these techniques. MRI-targeted cores had an overall cancer detection rate of 30% versus 7% of systematic cores (368 of 5441). MRI was not suspicious in 38% of men (225 of 599); 23% of these had cancer on a standard biopsy. However, crucially, only 2.3% of these had clinically significant cancer (broadly defined as greater than 5-mm cancer core length and/or any Gleason pattern greater than 3), which would have been missed by an approach targeting MRI lesions alone.

[Kasivisvanathan and colleagues \(2013\)](#) compared the accuracy of MRI-TB versus whole-gland systematic TPM biopsy using different definitions of clinically significant cancer. Using UCL definition 2 (maximum cancer core length 4 mm or more and/or Gleason grade 3+4 or greater), MRI-TB identified clinically significant cancer in 57% of men (103 of 182) compared with 62% (113 of 182) by TPM. TPM had a lower rate of misclassification of clinically insignificant or no cancer compared with MRI-TB (7% vs. 16%). Using the Goto definition, MRI-TB identified a greater amount of clinically significant cancer compared with TPM (difference 8% [95% CI 0.6 to 14.8], $P = .033$). When using the Harnden and Goto definitions for clinically insignificant cancer, MRI-TB performed better compared with TPM, which was statistically significant.

Magnetic Resonance Imaging-Ultrasound Fusion. Several studies have reported on MRI-US fusion, which involves combining a prebiopsy magnetic resonance image with a live ultrasound image at time of biopsy to guide more accurate biopsies. [Puech and colleagues \(2013\)](#) compared several biopsy strategies to see which was accurate in detecting clinically significant prostate cancer, defined as maximum cancer core length of 3 mm or greater or Gleason grade of 3 or higher. Ninety-five patients with suspicious lesions on MRI underwent 12-core systematic biopsy and 4-core target biopsy (TB) with TRUS guidance, with two cognitive target cores aimed visually (TB-COG) and two target cores using MRI-TRUS fusion software (TB-FUS). Clinically significant prostate cancer was detected by systematic TRUS in 52% ($n = 49$) and by TB in 67% ($n = 64$). In 12 of 51 (24%) MRI targets with positive systematic TRUS and TB results, TB led to Gleason score upgrading. In 79 MRI targets, 47% ($n = 37$) were positive with TB-COG and 53% ($n = 42$) with TB-FUS ($P = .16$). Neither technique was superior for Gleason score assessment. [Delongchamps and colleagues \(2013\)](#) compared the accuracy of visual TBs and computerized rigid and elastic MRI-TRUS fusion system with 10- to 12-core systematic biopsy in 391 patients. Overall, the rigid and elastic system TB performed significantly better than random biopsy ($P = .0065$ and $.0016$, respectively) in detecting overall and higher Gleason score cancer. In this study a TB-only strategy would have avoided unnecessary biopsy in 45% while limiting the number of cores in the other 55%. Another

study also showed that MRI-US fusion–targeted biopsies resulted in 22% additional cases of Gleason 3+4 or higher prostate cancer and 67% additional cases of clinically significant prostate cancer (Gleason $\geq 4+3$) compared with 12-core systematic biopsy (Siddiqui et al, 2013).

Pinto and colleagues (2011) compared MRI-US fusion–targeted biopsy under electromagnetic tracking with standard 12-core TRUS biopsy in 101 men; 54.4% of men had prostate cancer. Cancer was detected in 27.9%, 66.7%, and 89.5%, respectively, of patients with low, moderate, and high suspicion on MRI of having cancer. MRI-US fusion–guided biopsy performed better in the detection of cancer in MRIs with a low, moderate, and high suspicion of cancer compared with standard 12-core TRUS biopsy (4.8% vs. 3.8%, 20.7% vs. 12.3%, and 53.8% vs. 29.9%, respectively). Overall, MRI-US fusion–guided biopsy detected more cancer per core than standard 12-core TRUS biopsy alone for all levels of suspicion combined (20.6% vs. 11.7%, respectively). Electromagnetic tracking can also aid focal therapy because therapeutic instruments used in cryotherapy, high-intensity focused ultrasound (HIFU) ablation, or brachytherapy can be guided in real time.

The current drawbacks of MRI are its inability to differentiate between prostate cancer and prostatitis, inflammation, or prostatic intraepithelial neoplasia (PIN). MRI-guided biopsy is time-consuming, because patients have to have an initial MRI, which is then repeated at time of biopsy. MRI-US fusion also has some limitations. It relies on accurate prostate segmentation; the prostate needs to be outlined—manually or semiautomatically—on both MRI and ultrasound images (van de Ven and Barentsz, 2013). This segmentation is also a time-consuming task and is operator dependent. The fusion itself, however, is a relatively quick process, taking under 90 seconds in one study (Bubley et al, 2013), with error rates varying from 2.5 mm to 5 mm depending on whether nonrigid or rigid fusion is used.

We recently conducted a systematic review of the literature reporting on image-fusion devices used to guide and target biopsies in the detection of prostate cancer (Valerio et al, 2015) (Figs. 117-13

and 117-14). Fourteen studies used a paired cohort design. A total of 2293 men were included, with a sample size ranging from 13 to 582. Three studies were conducted in biopsy-naïve men, three were conducted in men with a previous negative TRUS biopsy, eight studies reported on a mixed cohort of men who were either biopsy naïve or had undergone a previous prostate biopsy, and one also included men with radiorecurrent disease.

Our systematic review showed that MRI-TRUS image fusion–targeted biopsies detect more clinically significant cancers using fewer cores compared with standard biopsy techniques. Most studies also showed a higher detection of clinically insignificant cancer, although four studies demonstrated a lower detection rate of clinically insignificant cancer by MRI-TRUS image fusion biopsies. The detection of clinically significant disease was 4.8% to 52% for standard biopsy and 13.2% to 50% for MRI-TRUS image fusion–targeted biopsy. Across all studies in which both rates were reported, the use of MRI-TRUS fusion allowed the detection of greater numbers of clinically significant cancers compared with standard biopsy. The absolute difference in detection rate between the two approaches was a median of 6.8% (range +0.9 to +41.4%) and always in favor of the MI-TRUS software-based approach.

There was substantial discrepancy in the definition of clinically significant disease. Only one study did not report the criteria for defining this outcome. In all the remaining studies, the presence of Gleason pattern 4 was considered clinically significant disease. In eight studies, maximum cancer core length was also considered, although the threshold above which clinically significant disease was defined ranged from 3 mm to 10 mm.

The detection rate of any cancer was 14.3% to 59% and 23.7% to 82.1% in the standard biopsy strategy versus MRI-TRUS image fusion biopsy. The absolute difference in overall detection of prostate cancer between the two approaches was median +6.9% in favor of the MRI-TRUS image fusion–targeted biopsy approach (range –8.8% to +53.2%). In four studies, standard biopsies detected more clinically insignificant disease than the software-based approach. MRI-TRUS image fusion biopsies detected 5% to 16.2% additional

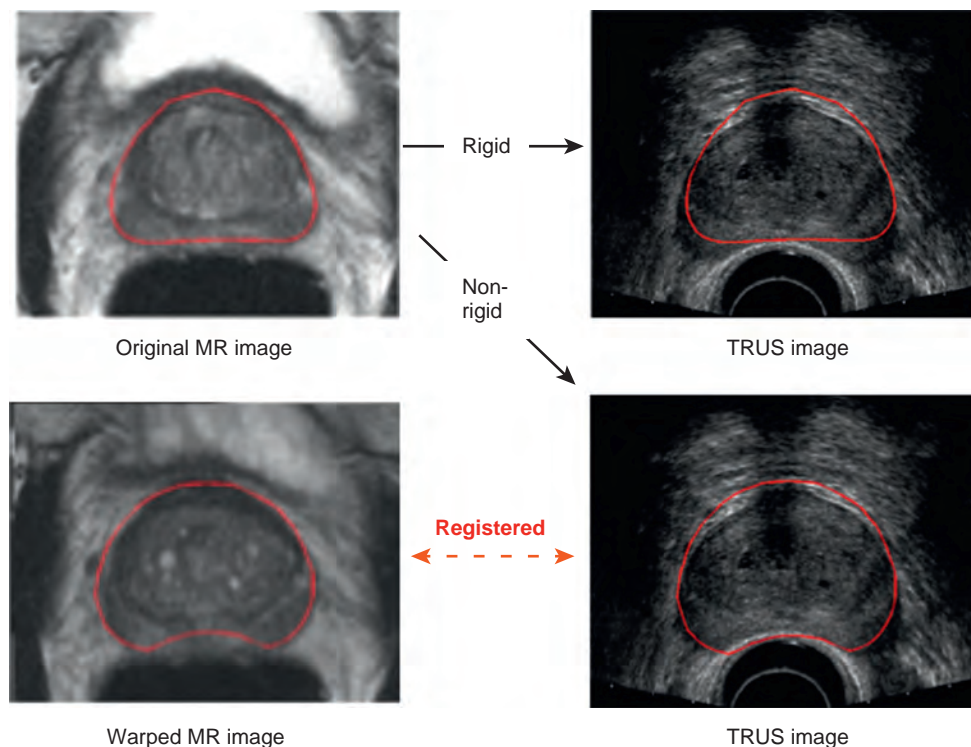


Figure 117-13. Targeted biopsies using fusion software can be carried out using either rigid or nonrigid fusion. The error for the rigid fusion is approximately 5 mm and for the nonrigid fusion approximately 2.5 mm. MR, magnetic resonance; TRUS, transrectal ultrasonography. (Courtesy Yipeng Hu and Dean Barratt, UCL SmartTarget.)



Figure 117-14. A nonrigid software fusion system developed for targeted transperineal interventions. The colored lesion is seen in the left anterior and has been precontoured on the area alongside the prostate capsule contour. (Courtesy Yipeng Hu and Dean Barratt, UCL SmartTarget.)

clinically significant cancers that were missed by standard biopsy alone. On the other hand, standard biopsies detected 0% to 12.4% additional clinically significant cancers that were missed by MRI-TRUS fusion biopsies. However, if the study using transperineal mapping biopsies is removed so that the standard biopsy is only a TRUS biopsy approach, this figure stood at 0% to 7%.

In all series, an image fusion approach was more efficient in detecting clinically significant disease. The median number of cores needed to detect one man with clinically significant cancer was 37.1 (interquartile range [IQR], 32.6 to 82.8; range 23.2 to 252) and 9.2 (IQR 4.6 to 24.8; range 4 to 37.7) for standard and MRI-TRUS image fusion–targeted biopsy, respectively. The median difference in number of cores required across the series was 32.1 cores (IQR +28.3 to +57; range +21.4 to +84.8) in favor of the targeted approach. In other words, to detect the same number of clinically significant cancers with standard biopsy, one would need to use approximately four times the number of cores as compared with an image fusion–targeted approach.

Two studies evaluated the outcomes of MRI-TRUS image fusion biopsies versus visual registration–targeted biopsy. One study did not report sufficient information by which to determine the primary outcome measure and a number of the secondary outcome measures. In the only outcome reported—namely, detection of any cancer—MRI-TRUS image fusion biopsies had a higher rate (53% vs. 47%; no *P* value given). The other study evaluated the two targeting approaches in 125 men with 172 targets in total. In a per-target analysis, MRI-TRUS image software biopsies detected more clinically significant cancers (20.3% vs. 15.1%; *P* = .05) and more cancer overall (32% vs. 26.7%; *P* = .14). It also had better efficiency compared with visual registration, requiring 9.8 rather than 13.2 cores to detect 1 man with clinically significant cancer (Wysock et al, 2014). Furthermore, there was no additional usefulness in visual registration targeting, whereas the image fusion approach detected 7.6% additional clinically significant cancers that would have been missed by the visual registration approach. However, the study was underpowered to show the demonstrated absolute difference in detection rate of approximately 5%, as it was powered a priori to demonstrate a 15% difference in detection rate.

For delivery of tissue-preserving focal therapy, accurate localization and characterization of clinically significant prostate cancer must occur. TRUS biopsy is unable to provide such information accurately. Saturation biopsies seem to add only a small additional benefit unless carried out with a template transperineal mapping technique. A transperineal route has several advantages in that it allows systematic coverage of the gland, which provides accurate localization that can be reproduced when providing focal therapy. There have been imaging developments to help improve guidance of biopsies to allow for more accurate sampling. Studies have shown that MRI has a higher sensitivity and specificity compared with TRUS in detecting clinically significant cancer. Targeted biopsies have been shown to detect more clinically significant lesions than random TRUS biopsy with fewer cores taken, with reduced costs from shorter biopsy times and histopathology processing times.

At the heart of the arguments for and against each modality of localization is the need for precision in excluding disease from untreated areas. Greater accuracy up front will logically translate into lower recurrence or de novo disease rates in untreated areas in the long term. Some clinicians and patients may accept the inaccuracy and uncertainty of tools for determining unilaterality—for example, use of TRUS biopsy—to avoid further (expensive and/or morbid) interventions, with the understanding that a higher recurrent or residual cancer rate is found in the untreated side. Provided that the interval between treatment and detection of cancer in the contralateral side is not sufficient for disease progression, patients could then have that side treated.

Biopsy data are commonly used to determine cancer risk. A targeted approach to lesions found on imaging may have an impact on the risk that a particular man is assigned. Features widely used to indicate high risk include Gleason score of 7 or higher, as well as parameters to indicate the amount of cancer, such as maximum cancer core length, maximum percentage cancer, and the number of positive biopsy specimens (Epstein, 2011). However, if a tumor is exposed to a greater sampling density than the rest of the prostate, it is likely that the proportion of cores that are positive, and the maximum cancer core length, will be greater compared with a TRUS

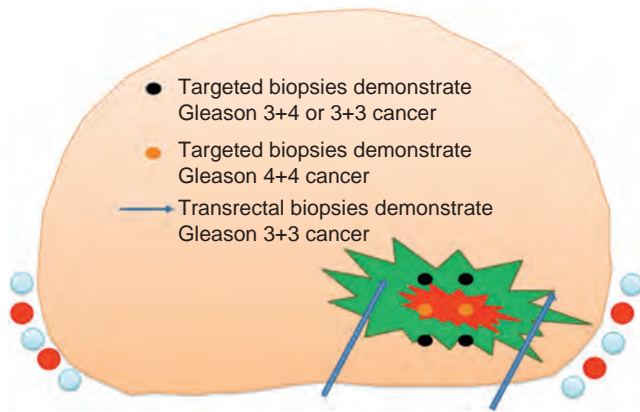


Figure 117-15. A Gleason 3+4 lesion in the left peripheral zone that through transrectal biopsies may be misclassified as very low risk and very high risk 4+4 through a true hit into the central pattern 4 using current risk stratification systems. In reality, the lesion is intermediate risk.

biopsy. In addition, higher Gleason patterns, if truly present, are more likely to be sampled (Fig. 117-15).

If the trend toward image-guided biopsy continues unchecked, it is likely that we will witness a systematic increase in risk attribution in the men subjected to biopsy if the standard criteria for attributing risk are applied (see Fig. 117-15). It is therefore likely that new risk prediction models based on targeted biopsies will be required. As a start to correct what could be regarded as an artificial increase in cancer risk derived from targeted biopsy, a risk stratification system that is independent of the number of positive cores could be considered.

ABLATIVE TECHNOLOGY

There are a number of ablative technologies that could potentially deliver focal therapy (Ahmed et al, 2009b). HIFU and cryosurgery conform closely to the desired attributes and at present are the only two modalities that have retrospective and prospective data demonstrating feasibility of focal ablation, low side effect rates, very good genitourinary preservation rates, and good early cancer control. Photodynamic and interstitial photothermal therapies have both shown promise in single-center studies and are at present undergoing multicenter evaluation (Lindner et al, 2009; Moore et al, 2009). Brachytherapy, stereotactic radiotherapy, irreversible electroporation, radiofrequency ablation (RFA), and toxin injections into the prostate have not been evaluated in a focal therapy protocol but could be delivered in a focal manner, as could magnetic resonance hyperthermia using magnetic nanoparticles (Rubinsky et al, 2008; Salvador-Morales et al, 2009).

Cryotherapy

Cryotherapy is the ablation of tissue by extremely cold temperatures. The first written report of its use was in 19th-century London, where Arnott applied ice-salt mixtures to breast and cervical cancers (Arnott, 1851). Cryotherapy exerts its effects via a number of pathways, namely:

1. Direct cytolysis through extracellular and intracellular ice crystal formation
2. Intracellular dehydration and pH changes
3. Ischemic necrosis via vascular injury
4. Cryoactivation of antitumor immune responses
5. Induction of apoptosis
6. Endothelial damage, which leads to platelet aggregation and microthrombosis

7. Injury that occurs during warming as a result of osmotic cellular swelling and vascular hyperpermeability

A number of factors affect the efficiency of tissue destruction, namely:

1. Velocity of cooling
2. Nadir temperature
3. Freezing duration
4. Velocity of thawing
5. Number of freeze-thaw cycles
6. Presence or absence of large blood vessels, which can act as heat sinks

Overall, a minimum freezing temperature of -40°C for a duration of 3 minutes is sufficient for tumor eradication (Hoffmann and Bischof, 2002). It has also been demonstrated that complete cell death is unlikely at temperatures greater than -20°C , although cells not destroyed by initial freezing to -20°C were destroyed with a second freeze cycle (Tatsutani et al, 1996). Histopathologic changes after cryotherapy in the prostate are divided into an early degenerative phase caused by coagulative necrosis and a later phase of repair—fibrosis, calcification, and hyalinization (Grampsas et al, 1995; Borkowski et al, 1996).

Although this source of energy is known to be very effective against prostate cancer, it was not before significant technologic developments were made that this source of energy became very attractive in prostate cancer. Mainly, third-generation cryotherapy devices are able to use gas-based systems to provide rapid freeze and thaw cycles (Fig. 117-16). Also, manufacturers have been able to develop multiprobe systems while decreasing the size of each cryoprobe, so the precision of ablation could be enhanced (Fig. 117-17). Finally, the toxicity has significantly decreased because of the use of safety measures, such as a continuous urethral warmer during the treatment, and the systematic use of thermocouples for verifying the temperature both in critical surrounding structures and in the treatment area.

Focal cryotherapy to an area of the prostate is delivered under transrectal ultrasound guidance using cryoneedles inserted via the perineum using a brachytherapy grid or in a freehand fashion. In addition, thermocouples are positioned in the same way, normally in the treatment area, in the Denonvilliers fascia, and in other key areas such as the rhabdosphincter and the neurovascular bundles at the discretion of the surgeon. A urethral cystoscopy is warranted before beginning the treatment, to verify the position of the needles; finally, a continuous urethral warmer to protect the urethra is inserted and maintained during the whole procedure (Figs. 117-18 to 117-25). In addition to the standardized technique, in 2008 the American Urological Association released a Best Practice statement to underline the optimal procedural requirements to deliver effective cryotherapy. The panel recommended a double freeze-thaw cycle and the use of rapid freezing up to -40°C with a slow, almost passive, thaw.

High-Intensity Focused Ultrasound

Ultrasound refers to mechanical vibrations above the threshold of human hearing (16 kHz) and has the ability to interact with tissue to produce biologic changes. Applying an alternating voltage across a piezoelectric material such as lead zirconate titanate generates ultrasound (Figs. 117-26 and 117-27). These materials oscillate at the same frequency as the alternating current, causing ultrasound waves that can propagate through tissues. This in turn causes alternating cycles of increased and reduced pressure (compression and rarefaction, respectively). Diagnostic ultrasound usually uses frequencies in the range of 1 to 20 MHz, but therapeutic HIFU uses frequencies of 0.8 to 3.5 MHz with delivery of energy levels within the ultrasound beams that are several times greater than the energy levels within diagnostic ultrasound. Therapeutic ultrasound can be conveniently divided into two broad categories: low intensity (0.125 to 3 W/cm^2) and high intensity ($>5\text{ W/cm}^2$). The former can stimulate normal physiologic responses to injury and accelerate other processes such as the transport of drugs across the skin. High-intensity ultrasound can selectively destroy tissue

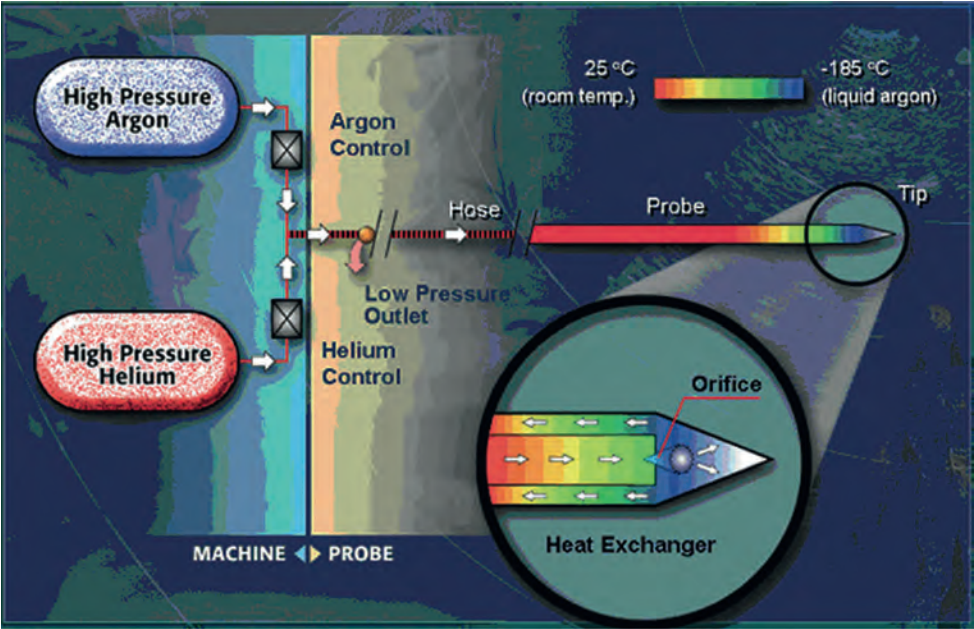


Figure 117-16. Diagram depicting the Joule-Thomson effect of cryotherapy.

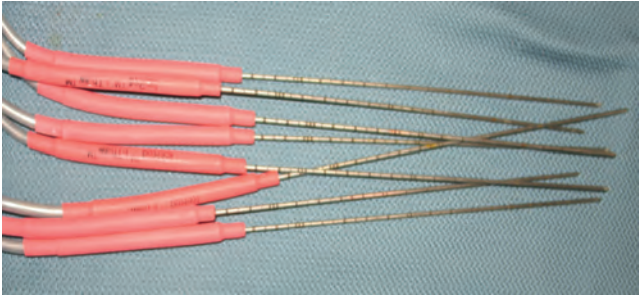


Figure 117-17. Cryotherapy probes (17 G in size)—IceRod cryotherapy needles (Galil Medical, Arden Hills, MN).



Figure 117-18. Available cryoablation systems for operative planning and real-time monitoring of freezing process. A, Presice Cryoablation System (Galil Medical, Arden Hill, MN). B, Cryocare CS (Endocare/HealthTronics, Austin, TX). (B, Used with permission of Endocare, Inc., a wholly-owned subsidiary of HealthTronics, Inc. © 2015 HealthTronics, Inc. All rights reserved.)

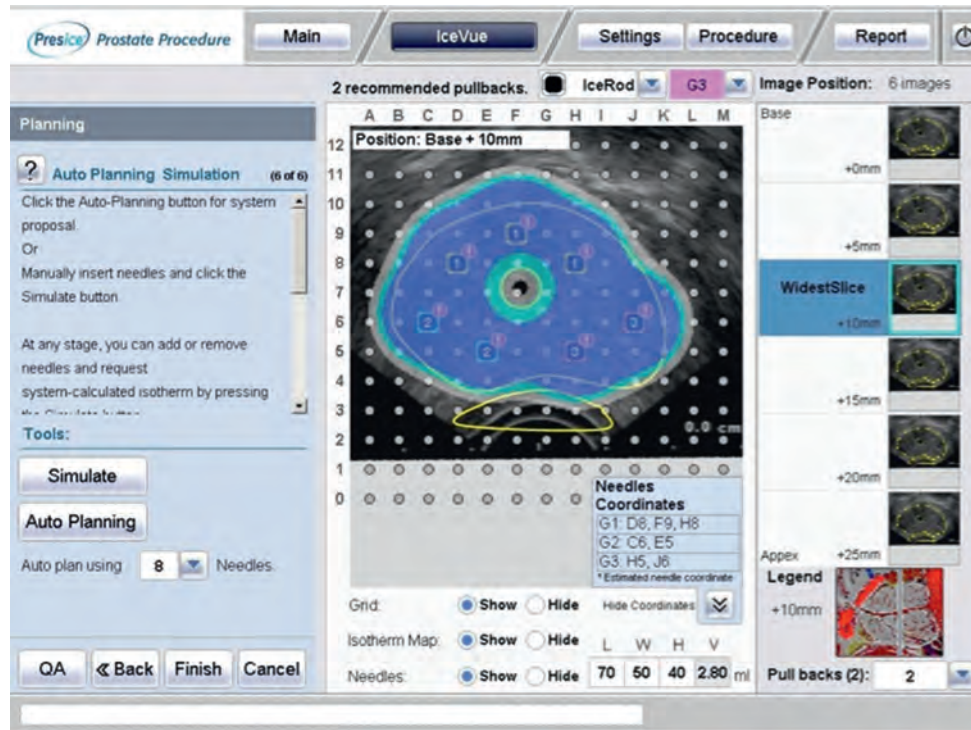


Figure 117-19. Screenshot of the Presice Cryoablation System (Galil Medical, Arden Hill, MN) user interface for preoperative simulation and isothermal mapping.

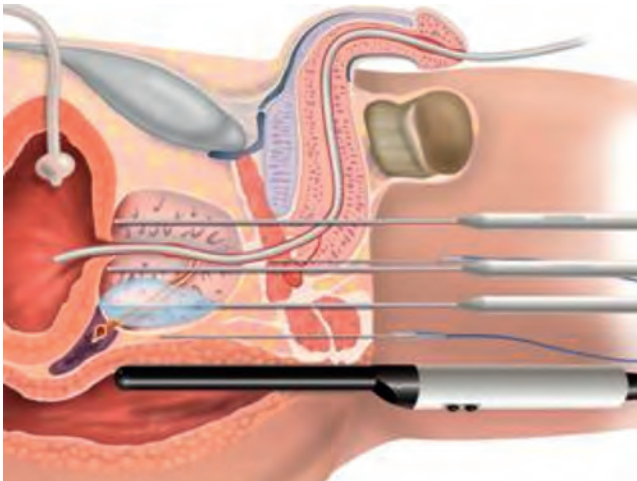


Figure 117-20. Cryotherapy is delivered using transperineal needles into the prostate under ultrasound guidance. (Courtesy Galil Medical.)

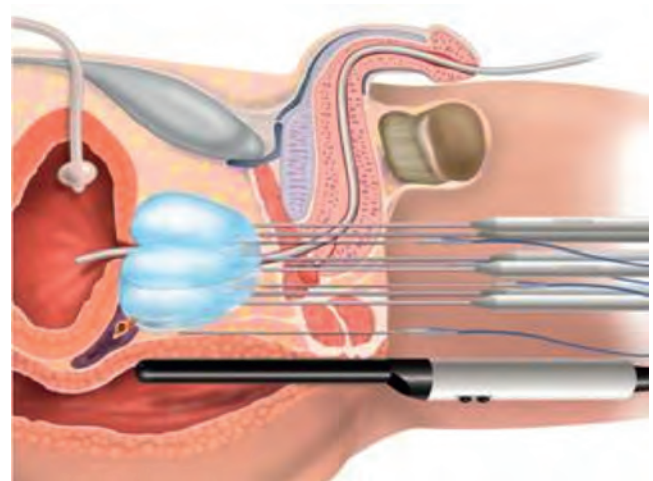
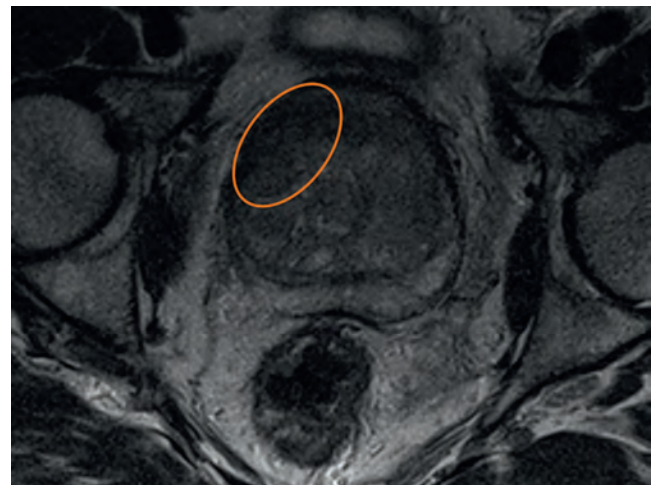


Figure 117-21. The ice ball that forms can take temperatures down to -40° to -60° C for cell kill. Two freeze-thaw cycles are delivered.

Figure 117-22. T2-weighted magnetic resonance imaging (MRI) scan of a 56-year-old man who had a prostate-specific antigen (PSA) level of 8.9 and a negative transrectal ultrasound (TRUS)-guided biopsy in 2008. Subsequently the PSA rose to 16 in 2009 and he underwent another TRUS biopsy, which showed Gleason 3+3 1-mm prostate cancer, so he underwent active surveillance. The PSA again rose to 18 in 2013, and another biopsy showed focal high-grade prostatic intraepithelial neoplasia. Finally, the PSA was 25 in 2014 and the MRI scan shown here was obtained, showing a right anterior lesion.



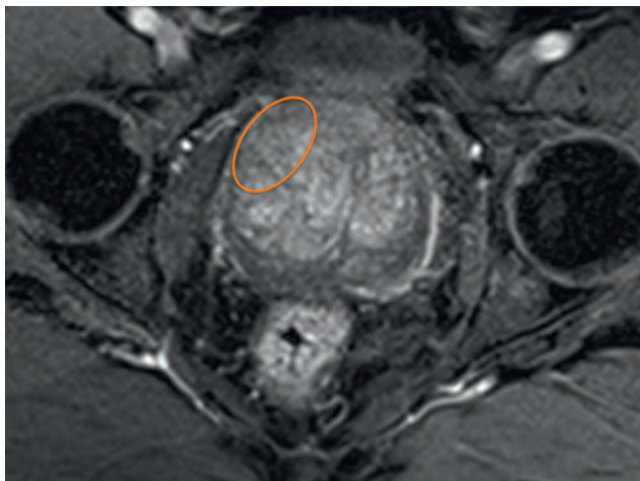


Figure 117-23. The lesion from the same patient as in [Figure 117-22](#) was confirmed on the other sequences (diffusion-weighted and dynamic contrast). Here, the dynamic contrast-enhanced scan using gadolinium contrast is shown. Targeted transperineal biopsies of this lesion showed four of four cores positive, with Gleason 3+4 and maximum cancer length involvement of 9 mm.

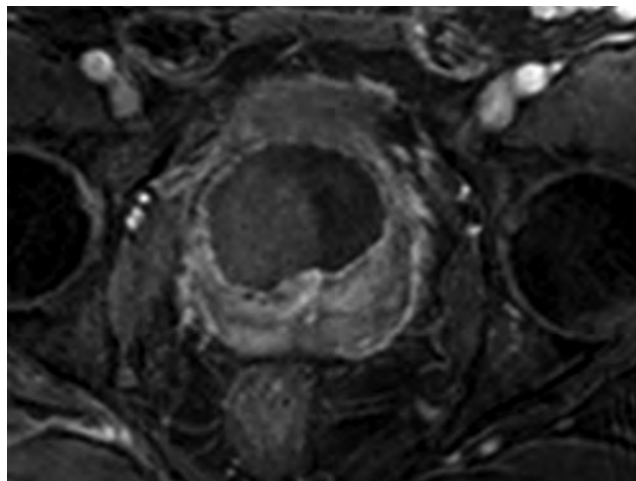


Figure 117-25. Early 2-week contrast-enhanced magnetic resonance imaging after focal cryotherapy in the man from [Figure 117-24](#) showed confluent lack of perfusion in the area of ablation. He had no urinary leakage, and erections were sufficient for penetrative sexual intercourse.

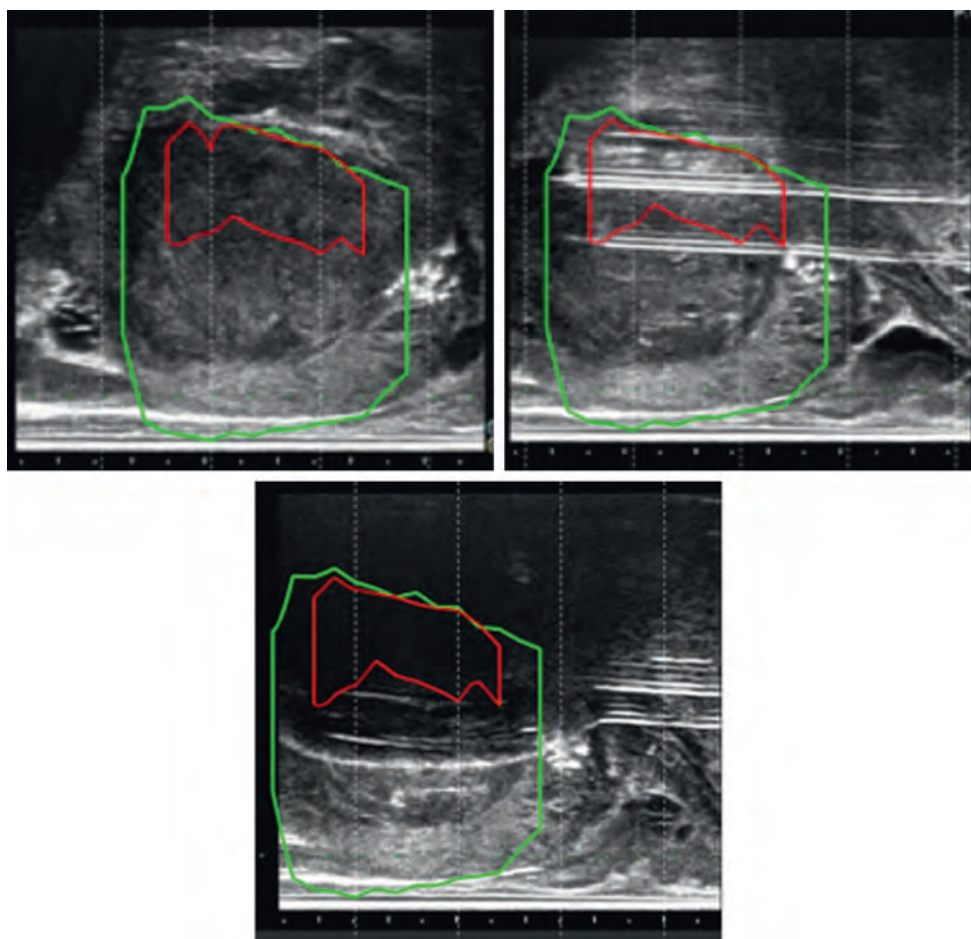


Figure 117-24. The man from [Figures 117-22](#) and [117-23](#) opted for focal cryotherapy after appropriate counseling. This was guided by image fusion so the needles could be placed accurately into lesion and ensure a margin was incorporated into the treatment. *Red* represents lesion contour from magnetic resonance imaging (MRI); *green* represents prostate contour from MRI.



Figure 117-26. One of the transrectal high-intensity focused ultrasound devices. This is the Sonablate 3G system (SonaCare Medical, Indianapolis, IN).



Figure 117-27. The Sonablate high-intensity focused ultrasound transrectal probe has two focal lengths: 3 cm and 4 cm.

if delivered in a focused manner (Hill and ter Haar, 1995) (Figs. 117-28 and 117-29).

HIFU relies on the physical properties of ultrasound, which allow it to be brought into a tight focus with an acoustic lens, a bowl-shaped transducer, or an electronic phased array. As ultrasound propagates through a tissue, zones of high and low pressure are created. When the energy density at the focus is sufficiently high (during the high-pressure phase), tissue damage occurs. The volume

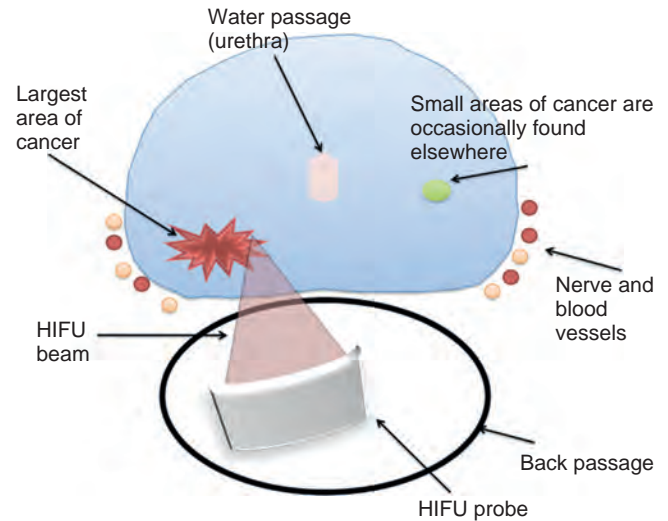


Figure 117-28. Diagram showing how a beam of high-intensity focused ultrasound causes cell destruction at the focal point but not in the near-field tissue owing to lower energy density.

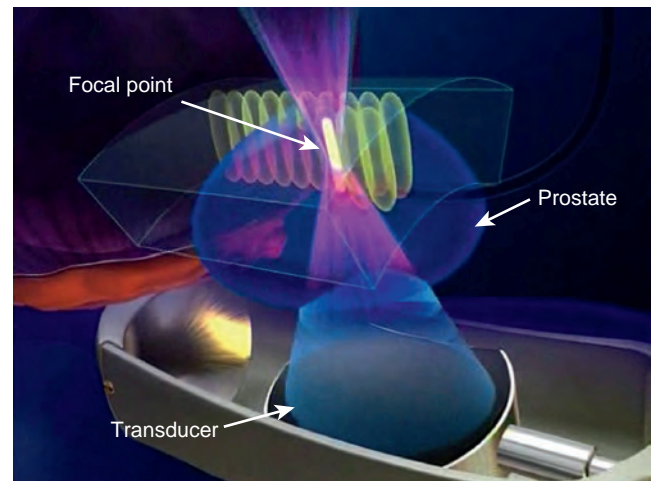


Figure 117-29. Diagram showing how the high-intensity focused ultrasound pulses are about the shape of cigars or grains of rice; these are placed next to one another with overlap to ensure coverage of targeted tissue.

of ablation (or lesion) after a single HIFU pulse or exposure is small and varies according to transducer characteristics. It is typically shaped like a grain of rice or cigar with dimensions on the order of 1 to 3 mm (transverse) \times 8 to 15 mm (along beam axis). To ablate larger volumes of tissue for the treatment of solid cancers, these lesions are placed adjacent to one another. The two predominant mechanisms of tissue damage are the conversion of mechanical energy into heat, and inertial cavitation. If tissue temperatures are raised above 56° C, then immediate thermal toxicity can occur, provided the temperature is maintained for at least 1 second. This will lead to irreversible cell death from coagulative necrosis. In fact, during HIFU the temperatures achieved are much greater than this, typically above 80° C, so even short exposures can lead to effective cell death. Inertial cavitation occurs at the same time but is neither as controllable nor predictable. It occurs as a result of the alternating cycles of compression and rarefaction. At the time of rarefaction, gas can be drawn out of solution to form bubbles, which then collapse rapidly. The mechanical stress and a degree of thermal injury induce cell necrosis (Kennedy, 2005). Histologically, the tissue changes that occur are homogeneous coagulative necrosis, with an

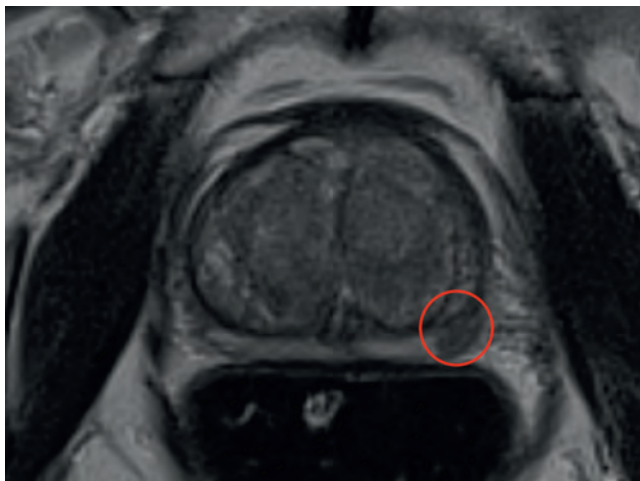


Figure 117-30. A 65-year-old man with prostate-specific antigen level of 6.5 who was found to have a lesion in the left peripheral zone on prebiopsy magnetic resonance imaging (MRI). This shows the T2-weighted MRI scan.

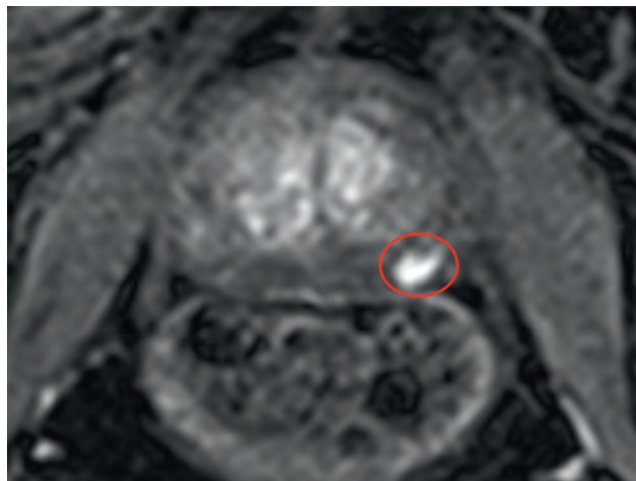


Figure 117-31. The same man from Figure 117-30 had this lesion confirmed on diffusion and dynamic-contrast magnetic resonance imaging. Here the early-phase contrast image is shown. This area underwent targeted template transperineal biopsies, and one biopsy showed Gleason 3+4 4 mm.

inflammatory response that follows leading to formation of granulation tissue—indicated by the presence of immature fibroblasts and new capillary formation—at the periphery of the necrotic area about a week after treatment. Polymorphonuclear leukocytes migrate deep into the treated tissue, and then at 2 weeks the boundary of the treated region is replaced by proliferative repair tissue. The repair process has not been investigated in detail at the cellular level beyond this time, but imaging techniques using CEUS or MRI show an eventual shrinkage of treated volumes, indicating that the necrotic area has been replaced by fibrous scar tissue.

The placement of the small HIFU lesions requires precise planning for an entire tumor to be ablated reliably. Furthermore, patient movement can lead to areas of viable malignant tissue remaining after treatment, and even in ideal situations other factors can prevent a successful treatment. The most important of these include the heat sink effect and calcification. The heat sink effect relates to one area that overheats in the HIFU pulses' pathway and thus prevents adequate ultrasound propagation to the targeted area; such a phenomenon occurs if the time between HIFU pulses is inadequate for tissue cooling or if an area is high in water content, such as a cyst. In addition, highly vascularized tissues might be more resistant to thermal ablation owing to the heat sink effect of their blood supply. Calcification simply leads to reverberation and shielding of the targeted area from parts of the HIFU pulse, leading to inadequate heating of the tissue. Technical improvements in this field are continuous, and at the time of writing this review, some companies have developed magnetic resonance–TRUS fusion systems for treatment planning purpose and real-time magnetic resonance monitoring during treatment, which are now being validated (Dickinson et al, 2013) (Figs. 117-30 to 117-40).

Regardless the approach and the device used, the technology is the same, and the procedure very similar. In all cases, the patient is under general or spinal anesthesia, a suprapubic or urethral catheter is positioned, and the treatment area is targeted using the available technology (TRUS, MR-TRUS fusion, or in-gantry MRI). In the past, some groups systematically performed transurethral resection of the prostate (TURP), considering the risk of urinary retention to be high; but when HIFU is delivered in a focal manner, this risk is low and TURP should not be part of the standard procedure anymore.

Photodynamic Therapy

Photodynamic therapy (PDT) uses a photosensitizing drug that is activated, after a given drug-light interval, by light of a specific wavelength. It requires tissue oxygen for the treatment effect,

with the activated drug forming reactive oxygen species, which are directly responsible for damage to the treated volume. The photosensitizing drugs are activated either while in the tissue or in the vasculature. Tissue-activated drugs have long drug-light intervals (typically hours to days), which means that the drug and light are given in separate treatment sessions. These drugs usually take a long time to be cleared from the body and can accumulate in the skin, requiring patients to be covered from sunlight (which could activate the drug and cause a sunburn-like reaction) for a few weeks. Some of the tissue-activated photosensitizers accumulate preferentially in tumor tissue. These include aminolevulinic acid (ALA), which is used in the diagnosis of bladder tumors and has also been assessed for use in the treatment of prostate cancer. Vascular-activated drugs have the advantage of a short drug-light interval (i.e., minutes), which allows the whole treatment to be done in a single session. They are usually cleared rapidly from the circulation, without accumulation in the skin, such that light restrictions are not necessary after a few hours.

Light delivery for prostate cancer, along with other interstitial tumors, uses low-power laser light directed to the treatment site by optical fibers. These fibers can deliver light only at the end of the fiber (like a torch) or along a cylindric diffuser (like a strip light). For prostate cancer, a transperineal approach is currently used, with hollow plastic needles placed in the prostate with use of transrectal ultrasound imaging. Cylindric diffusers of the desired length are then placed within the hollow plastic needles, and low-power laser energy, at a wavelength determined by the individual photosensitizer, is delivered to the prostate. Other approaches that have been used are transurethral light delivery and open insertion of fibers at laparotomy.

Focal Photothermal Therapy

Photothermal therapy uses laser fibers with the objective to raise the temperature directly in the treatment area. No photosensitizing agent nor oxygen tissue supply are needed. The ablation effect is claimed to be predictable, accurate, and restricted within the target area. In photothermal therapy, the patient is under general anesthesia or sedated with a urethral catheter placed but removed after the procedure. With a transperineal approach, an open-ended catheter is introduced into the target lesion, and after the correct placement has been verified, an optical laser fiber is inserted to deliver the treatment. Early in the clinical experience, MRI was used for treatment planning, and the placement of the fibers and the treatments were carried out under TRUS guidance. Lately, the use of

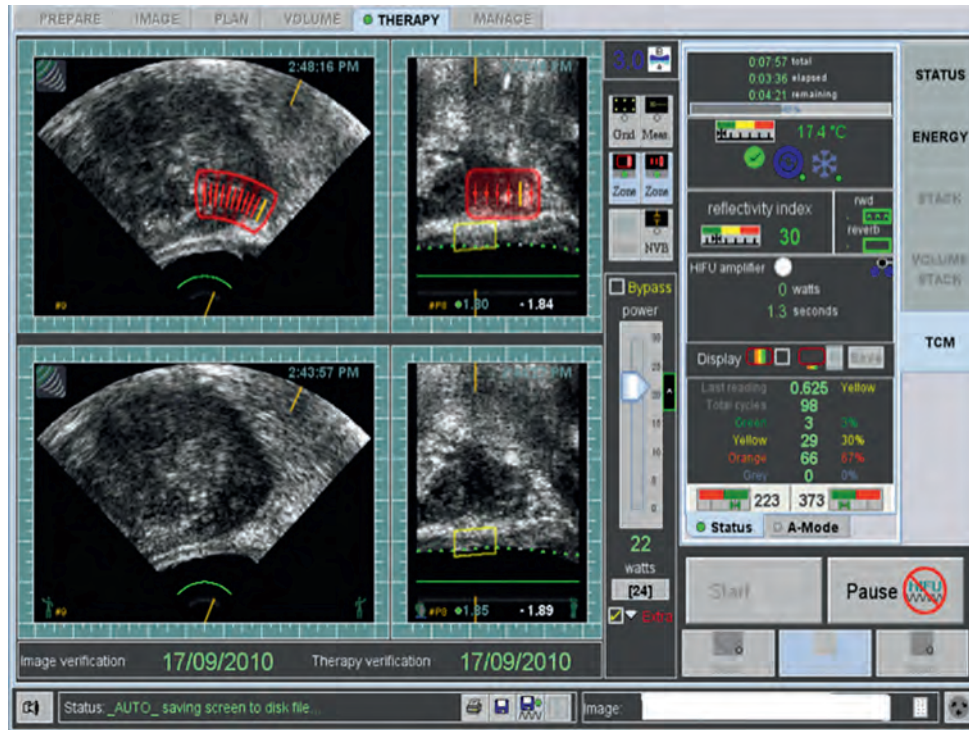


Figure 117-32. Screenshot of the Sonablate high-intensity focused ultrasound (HIFU) device. Treatment is delivered in blocks (red area). The lower two ultrasound images are pre-HIFU baseline images and allow a direct comparison. There are other safety features built into the device to prevent collateral damage. The power of each pulse can be controlled, giving fine control of the energy delivery into the prostate.

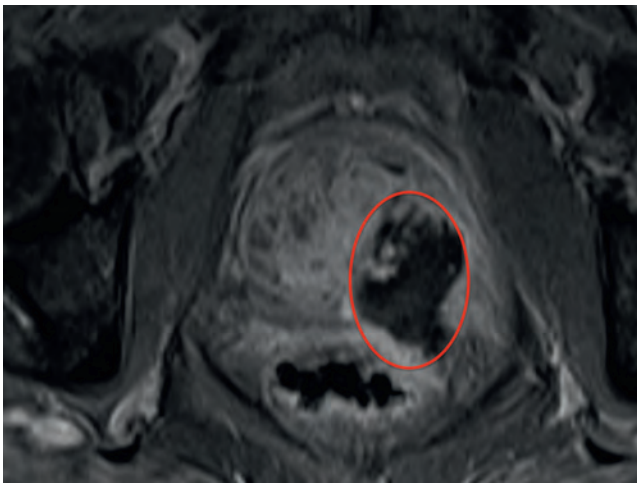


Figure 117-33. Post-treatment contrast magnetic resonance imaging in the man from Figures 117-30 to 117-32 shows confluent ablation and some extraprostatic damage, which are quite typical for high-intensity focused ultrasound and point to effect in microscopic extracapsular disease.

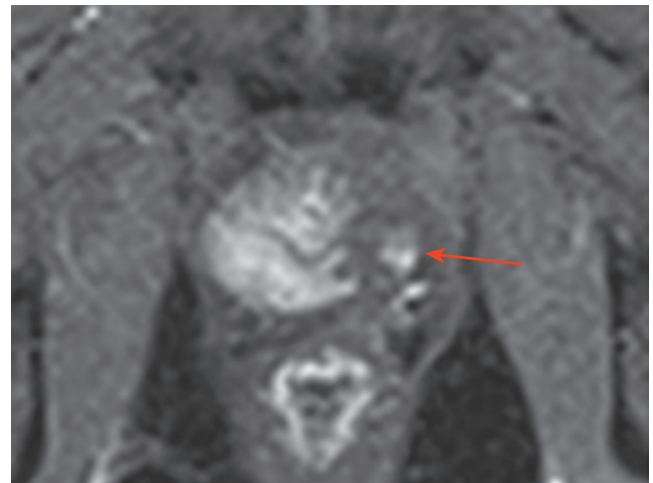


Figure 117-34. A 12-month scan from another man who underwent focal high-intensity focused ultrasound (HIFU) and was found to have a suspicious area of recurrence (arrow). This was confirmed on targeted biopsies as Gleason 3+4 2 mm. He chose re-treatment with HIFU in a focal manner.

magnetic resonance-compatible material has allowed in-gantry ablation under real-time MRI monitoring.

Focal Irreversible Electroporation

Irreversible electroporation causes tissue damage by permanently altering the cell homeostasis using low-energy direct current.

Indeed, the use of low voltage avoids local thermal effects and instead forms nanopores in the cellular membrane, which lead to cell death. The energy is delivered to the tissue from the generator to electrode needles inserted around the tumor. Irreversible electroporation has some key features that make it potentially very attractive. First, once the needles have been positioned, the treatment is very quick, usually less than 5 minutes. Second, it seems to

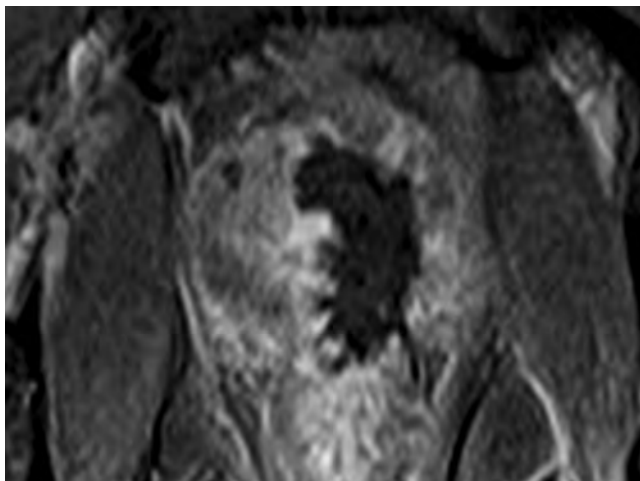


Figure 117-35. Early contrast magnetic resonance imaging after repeated focal high-intensity focused ultrasound shows excellent treatment effect. The patient was found to be cancer free on mapping template biopsies 2 years later.



Figure 117-37. A high b-value ($b = 1500$) axial scan has poor spatial resolution, but when areas have high signal, this indicates clinically significant cancer.

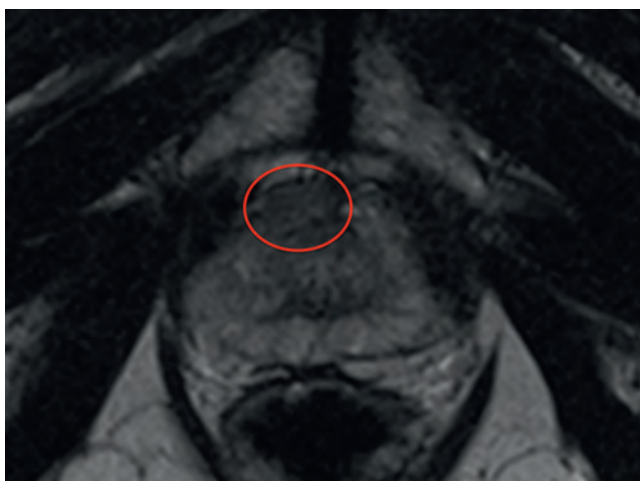


Figure 117-36. A 66-year-old man with a prostate-specific antigen level of 7.5 and normal rectal examination findings underwent prebiopsy magnetic resonance imaging (MRI) as part of a validating cohort trial called the Prostate MRI Imaging Study (PROMIS). This involves prebiopsy MRI that remains blind to the physician and the patient. The patient then undergoes a transrectal biopsy and a template mapping transperineal biopsy at a sampling frame of 5 mm. This image shows a discrete lesion anteriorly on T2-weighted MRI.

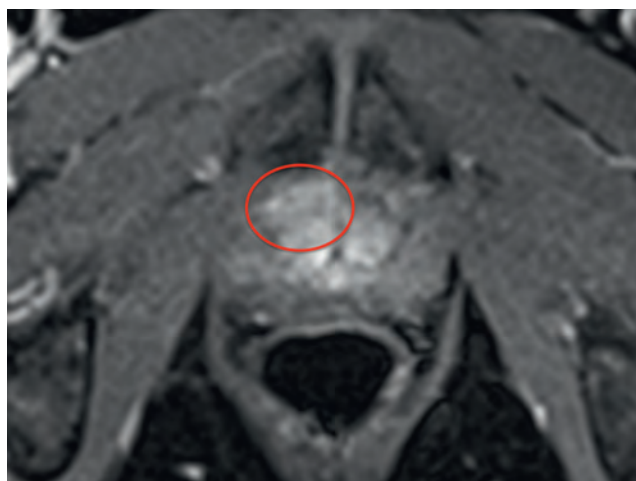


Figure 117-38. Contrast-enhanced scans were less helpful on their own, but a ground-glass enhancement was nonetheless concordant with the other sequences.

have tissue selectivity, so because of the different inner structure, nerves are possibly preserved, which is very important in the prostatic tissue given the presence of the neurovascular bundles.

The procedure is similar to the other needle-based sources of energy with the requirement for general anesthesia, a suprapubic or urethral catheter, and the electrode needles placed transperineally under TRUS control using a brachytherapy grid. However, whereas in cryotherapy, PDT, and photothermal therapy the needles are positioned in the treatments area or close to it, in irreversible electroporation the electrode needles are placed at the boundaries of the lesion to preserve the surrounding structures, which are then not in the electrical field (Li et al, 2011). Men are also fully paralyzed to avoid electrical stimulation (Figs. 117-41 to 117-43; also see Figs. 117-36 to 117-39).

Radiofrequency Ablation

RFA acts by converting radiofrequency waves to heat, resulting in thermal damage. High-frequency current flows from the needle electrode to target tissue with resultant ionic agitation and heat-producing molecular friction, denaturation of proteins, and cell membrane disintegration. The cellular and tissue effects of RFA vary with the duration of ablation and the local temperature achieved. This temperature-time dependence was demonstrated by in vitro studies in which irreversible cell injury of benign and malignant human cell lines were heated to 45° C for 60 minutes, 55° C for 5 minutes, and 70° C for 1 minute. These changes take 4 to 6 minutes at temperatures exceeding 50° C and occur almost immediately above 60° C. Temperatures greater than 105° C cause vaporization of tissue, resulting in gas formation and inefficient creation of radiofrequency lesions. The goal of RFA is to induce temperatures of 50° to 100° C throughout the tumor. Histologic analysis after RFA demonstrates typical coagulative necrosis characterized by cell membrane disruption, protein denaturation, and vascular thrombosis. Exophytic tumors that are surrounded by perirenal fat are

1. SIZE OF PROSTATE

Transverse: 5.0 cm Anterior-Posterior: 3.0 cm Cranio-Caudal: 4.2 cm Volume: 33 cm³

2. SECTOR (for UCL Definition Two disease) (Report strictly in order, and put a value 1-5* in each ROI). P = Posterior <1.7cm (measured from posterior capsule)

3. INDIVIDUAL LESIONS (Please draw and number measurable lesions on diagram below)

Base
Mid
Apex

Right Left

Risk category	Disease Threshold	MRI Score* (1-5)		
		R	L	Overall
Any cancer	Any Disease	5	3	5
Definition Two (Primary outcome)	≥ 0.2cc and/or ≥ 3+4	5	2	5
Definition One	≥ 0.5cc and/or ≥ 4+3	4	2	4
Dominant Gleason 4	≥ 4+3	3	2	3

Figure 117-39. This demonstrates the scoring proforma used by the radiologist in the trial.

TPM Zones	A/a/B	b/C	c	D	d	E/e	F/f/G
Apex		12	9	3		15	1
			19	15	5	13	17
		12	14	14	14	10	
Lateral	16	12					11
Base		10	4		2	8	
		15	14		9	12	
			20	16	6	14	18
		14	15	15	12	12	

No sample
No pathology to report
HGPIN / atypical acini
Clinically insignificant disease (G3+3 up to 3 mm)
Gleason = 3+4 AND/OR max. cancer length 4-5 mm
Gleason ≥4+3 AND/OR max. cancer length ≥6 mm

Note: The numbers in the grid are maximum cancer core lengths (mm).

Summary cancer							
Cancer core length		Overall Gleason		Maximal Gleason		Invasion	
UK	ISUP	Primary	Secondary	Primary	Secondary	Perineural	Lymphovas.
3	3	3	4	3	4	No	No

Figure 117-40. The template transperineal map confirms the index lesion is this right anterior tumor with Gleason 3+4=7 3 mm. There are low-volume Gleason 3+3=6 areas in the rest of the prostate that magnetic resonance imaging (MRI) could not detect, arguably a good trait for MRI to have.

better treated than central tumors in which vascular structures can act as a heat sink.

In practice, a grounding pad is placed on the patient, and the radiofrequency probe is inserted in the ablation zone. A computer-controlled generator provides an alternating current in the radio wave frequency of the electromagnetic spectrum. Bipolar RFA decreases the risk of accidental burns associated with monopolar RFA. The impedance of the tissue to this monopolar current leads

to local tissue hyperthermia, which is the basis for the cell kill effect. The temperatures reached during RFA depend on the generator's power, tissue impedance, heat conductivity, and heat dissipation via the local circulation. Commercially available RFA units are classified into temperature-based or impedance-based systems. This means that the computer-controlled generator provides energy to the probe based on either the average temperature achieved or the measured impedance of the tissue monitored during ablation.

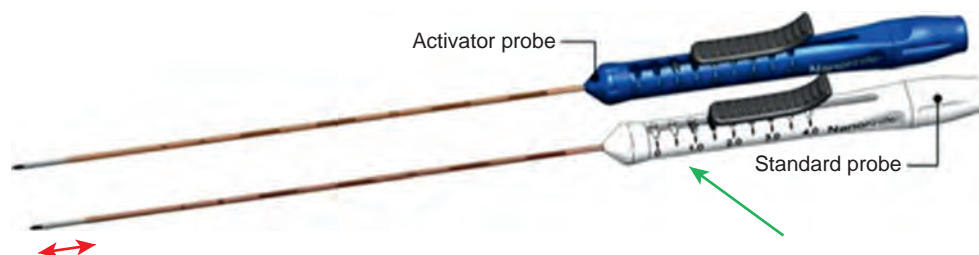


Figure 117-41. Probes used for irreversible electroporation. (Courtesy Angiodynamics.)

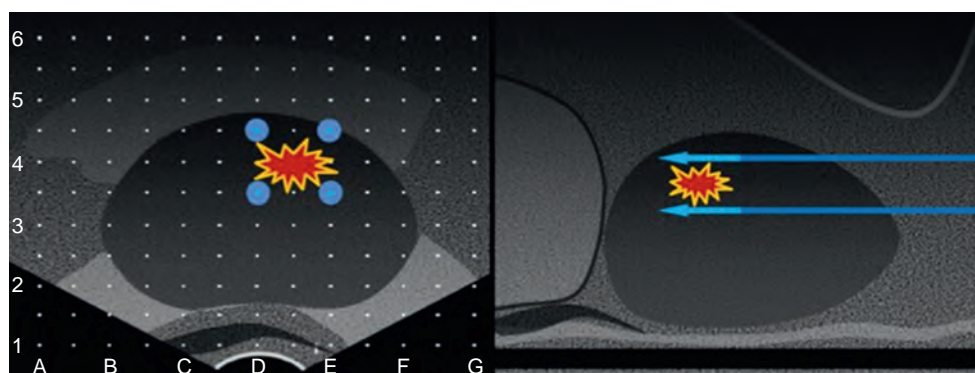


Figure 117-42. The probes are aligned around the edge of the lesion during irreversible electroporation treatment using the NanoKnife device.

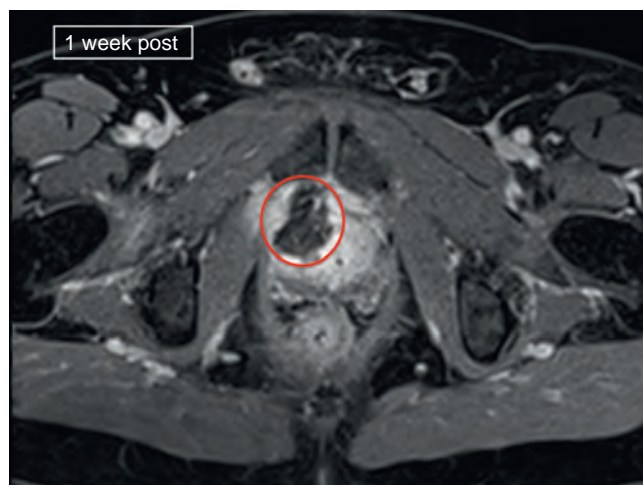


Figure 117-43. The man from Figures 117-36 to 117-40 underwent focal irreversible electroporation, and this shows that the ablative effect covers where the prostate cancer lesion was previously present.



Figure 117-44. Bipolar radiofrequency ablation can be carried out by the Encage device. (Courtesy Trod Medical).

Impedance rises toward infinity when tissues are desiccated during ablation or when there is charring. RFA technology can also be classified by dry and wet RFA. The latter allows constant infusion of saline during ablation to reduce the degree of charring and thus a premature rise in impedance. Currently, there is one device under evaluation in the prostate space (Figs. 117-44 and 117-45).

Outcomes

Focal Cryotherapy

Most of the actual knowledge regarding the outcomes of focal cryotherapy as first-line treatment comes from the COLD (Cryo On-Line

Database) Registry, an online database supported by a private manufacturer and independently managed by a research company (Watermark, Indianapolis, IN) and a medical advisory board. The registry has no restricted eligibility for patients, who are selected by their surgeon following local guidelines with the approval of the Institutional Review Board.

In a recent report from the COLD Registry, 1160 men were treated with focal cryoablation (Ward and Jones, 2012). In terms of cancer control, the 3-year biochemical disease-free survival (BDFS) was at 75.7%; the positive biopsy rate was 26.3% when considering only the patients who underwent biopsy because of biochemical failure, or 3.7% if the whole cohort of patients is considered the denominator. In terms of functional outcomes, urinary



Figure 117-45. This is a piece of beef “treated” with the Encage device and showing denaturation. Trials are ongoing for use of this device in humans.

incontinence was found in 1.6% of men, whereas 41.9% of men had new erectile dysfunction, and rectourethral fistula occurred in only 0.1% of the patients.

Despite the efforts of the researchers and the large sample size, the COLD Registry has some significant flaws, such as the absence of entry criteria, on-site quality control, and traceability of data as well as lack of patient-reported outcome measures (PROMs). Other small series have reported on outcomes after focal cryotherapy, but no series so far has had a comparative group, and none has had strict design in terms of outcome measures (Onik et al, 2008; Truesdale et al, 2010; Bahn et al, 2012).

Focal High-Intensity Focused Ultrasound

Some prospective development studies have rigorously and systematically evaluated the functional and oncologic outcomes using reliable and objective outcome measures and PROMs (Ahmed et al, 2011a, 2012d). In these trials, the rate of positive biopsies after focal HIFU ranged from 11% to 23%, whereas significant residual disease was found in 0% to 8% of men. Also, potency and continence were preserved in 86% to 95% and 95% to 100% of patients, respectively.

Other studies investigating focal HIFU have reported some interesting findings. In one case series including 12 patients with low-to-intermediate unilateral prostate cancer, with a follow-up of at least 7.5 years, the 5-year BDFS was 90%, and the 10-year BDFS 38%; cancer-specific survival (CSS) was 100% (El Fegoun et al, 2011). Another retrospective study compared the outcomes of focal HIFU with those of whole-gland HIFU in a similar group of patients differing only in tumor laterality (unilateral vs. bilateral) (Muto et al, 2008). No significant difference was seen in positive biopsy rate in the two groups (10.8% vs. 12.7%; $P = .85$).

Focal Photodynamic Therapy

Apart from one stage I study with no intention to completely ablate the tumor, only one stage IIa-b trial evaluating focal PDT using the agent WST-11 has been published so far (Moore et al, 2006; Azzouzi et al, 2013). In this study, optimal parameters for delivering PDT were evaluated along with toxicity in 85 patients having low- to intermediate-risk prostate cancer. Of these men, 68 (80%) had unilateral disease and were then treated by hemiablation according to the protocol standard operating procedure. At 6 months, and considering only the men having hemiablation, negative biopsy results were found in 17.4% to 38.1% of patients, according to the drug dose and the energy light. Based on validated PROMs, 9 patients reported new erectile dysfunction, and urinary symptoms slightly improved after treatment. However, it should be noted that

the functional outcomes refer to the whole study population, including patients having whole-gland treatment; also, no PROM specific for evaluating continence was used.

In summary, focal PDT has been assessed only in a stage IIa-b study with promising results in terms of toxicity and variable results in terms of efficacy. At the time of writing, a stage III (RCT) study comparing the oncologic outcome and the safety profile of PDT against active surveillance in men with very low-risk disease has achieved the recruitment target of 400 patients, with a randomization allocation of 1 : 1. Although many argue that these men do not represent the ideal population for an active treatment because active surveillance is a safe option for them, it needs to be acknowledged that this is the first stage III trial comparing focal therapy with a standard option.

Focal Photothermal Therapy

Photothermal therapy is a strict focal-based modality in which only small areas of cancer are treated. So far, two stage I and one stage IIa trials have been completed using focal photothermal therapy (Lindner et al, 2009, 2013; Oto et al, 2013). Overall, residual disease in the treated area was found in 22% to 33% of men who had a systematic biopsy after treatment. When reported, potency and full continence were preserved in 96% to 100% and 100% of men, respectively, although no specific PROM for continence assessment was used.

Although photothermal therapy is a promising new energy source with excellent genitourinary outcomes, the oncologic results are limited because only small areas of cancer have so far been targeted. Also, despite the small volume ablated, the operative time at the moment is still significant (around 2.5 to 4 hours). The technique would probably benefit from a larger multicenter stage IIb trial to explore the optimal parameters for successfully delivering energy and to explore reproducibility.

Focal Irreversible Electroporation

Only two case series including patients treated by focal irreversible electroporation have been reported (Brausi et al, 2011; Valerio et al, 2014). In the only study with protocol biopsy, residual disease was found in 27% of patients. Erectile function was preserved in 89% to 100%, whereas continence was maintained in 100%. This technology is very promising but is still in the early stage of assessment. A prospective development trial stage IIa using PROMs and targeted biopsy of the treated area will better clarify the short-term outcomes of this technology. We recently systematically reviewed these data.

OVERALL DATA

A number of series were identified evaluating focal therapy in the primary setting (Table 117-2) (Madersbacher et al, 1995; Zlotta et al, 1998; Beerlage et al, 1999; Souchon et al, 2003; Bahn et al, 2006; Moore et al, 2006; Ellis et al, 2007; Onik et al, 2007; Muto et al, 2008; Murat et al, 2009a; Lindner et al, 2010a; Raz et al, 2010; Truesdale et al, 2010; Ahmed et al, 2011a; El Fegoun et al, 2011; Tay et al, 2011; Ahmed et al, 2012d; Bahn et al, 2012; Chopra et al, 2012; Dickinson et al, 2012; Nguyen et al, 2012; Ward and Jones, 2012; Barret et al, 2013; Napoli et al, 2013).

This equates to 2232 men treated with focal therapy and reported in the literature. Six series used cryosurgery, 12 HIFU, 1 PDT, 3 photothermal therapy, 1 radiofrequency interstitial tumor ablation (RITA), and 1 MRI-guided brachytherapy, and 1 incorporated various ablation techniques. Median follow-up periods for the reported focal therapy series are 0 to 10.6 years (overall range 0 to 11.1).

In our systematic review, most of the studies used some form of preoperative MRI in combination with biopsy parameters as criteria to select patients for inclusion; some recent series use this modality for treatment planning (Table 117-3). The latest prospective trials combine mpMRI with template prostate mapping biopsy

Text continued on p. 2742

TABLE 117-2 Case Series of Focal Therapy Showing Disease Control Outcomes

SERIES	ABLATION TYPE	PSA (ng/mL)	GLEASON SCORE AT PREOPERATIVE BIOPSY	RISK CLASSIFICATION	FOLLOW-UP	PRESENCE OF ANY CANCER	PRESENCE OF CLINICALLY SIGNIFICANT CANCER	BDFS	PSA KINETICS (AT LAST FOLLOW-UP UNLESS OTHERWISE STATED)
Madersbacher et al, 1995	HIFU	24 mean (range 2-82.8)	NR	NR	Few hours (mean/median NR)	29/29 (100%)	NR	NR	NR
Zlotta et al, 1998.	RITA	NR	NR	NR	Mean/median NR (range 0 days-3 mo)	14/14 (100%)	NR	NR	NR
Beerlage et al, 1999	HIFU	10.8 mean (range 3.5-20)	NR	NR	8.5 days median (range 7-12)	13/14 (93%) 4/14 (29%) had residual tumor in the treated area	NR	NR	NR
Souchon et al, 2003	HIFU	NR	NR	NR	NR	NR	NR	NR	NR
Moore et al, 2006	PDT	6.95 median (range 1.9-15)	3+3: 6 (100%)	NR	NR	6/6 (100%)	NR	NR	NR
Bahn et al, 2006	Cryoablation	4.95 mean (range or SD NR)	≤6: 23 (74%) 7: 8 (26%)	NR	70 mo mean (range 2-107)	1/25 (4%)	NR	92.9%	NR
Onik et al, 2007	Cryoablation	8.3 mean (range or SD NR)	NR	Low: 26 (48%) Intermediate: 20 (36%) High: 9 (16%)	3.6 yr mean (range 1-10)	Only patients having biopsy: 4/30 (13%) All patients: 4/55 (7%)	NR	3-yr: 95%	Mean 2.4 (SD NR)
Ellis et al, 2007	Cryoablation	7.2 mean (SD 4.7)	≤6: NR (78.3%) 7: NR (20%) ≥8: NR (1.7%)	Low: 40 (66.7%) Intermediate: 14 (23.3%) High: 6 (10%)	12 mo median (range 3-36)	Only patients having biopsy: 14/35 (40%); 1/35 (3%) in the treated side All patients: 14/60 (23%); 1/60 (1.7%) in the treated side	NR	80.4%	Median 1.7 (IQR NR)
Muto et al, 2008	HIFU	5.4 median (range 0.2-25.1)	Unknown: 2 (6.9%) ≤6: 16 (55.2%) 7: 6 (20.7%) ≥8: 5 (17.2%)	NR	34 mo median (range 8-45)	At 6 mo: 3/28 (10.7%) At 12 mo: 4/17 (23.5%)	NR	2-yr Low risk: 83.3% Intermediate risk: 53.6%	At 36 mo: mean 1.89 (SD 1.51)

Murat et al, 2009a	HIFU	NR	NR	Low: 33 (59%) Intermediate: 23 (41%)	42 mo median (NR)	NR	NR	3-yr: 76% 5-yr: 60%	Nadir after first HIFU: 0.5 mean (NR) Nadir after secondary redo HIFU: 0.47 mean (SD NR)
Lindner et al, 2009	Photothermal laser	5.7 mean (SD 1.1)	3+3: 12 (100%)	Low risk: 12 (100%)	6 mo	6/12 (50%) 4/12 (33%) in the treated area	2/12 (17%)	NR	NR
Lindner et al, 2010a	Photothermal laser	4.2 median (range 2.9-14.8)	3+3: 2 (50%) 4+3: 2 (50%)	NR	1 wk	4/4 (100%) with no residual tumor in the treated area	NR	NR	NR
Raz et al, 2010	Photothermal laser	3.76 median (range 2.74-4.79)	3+3: 2 (100%)	Low: 2 (100%)	≤1 mo	NR	NR	NR	NR
Truesdale et al, 2010	Cryoablation	6.54 mean (SD 4.87)	≤6: 50 (65%) 7: 25 (32%) 8: 2 (3%)	Low: 44 (57%) Intermediate: 31 (40%) High: 2 (3%)	24 mo median (0-87)	Only patients having biopsy: 10/22 (45.5%); 3/22 (14%) in the treated area All patients: 10/77 (13%); 3/77 (3.9%) in the treated area	NR	72.7%	Mean 1.23 (SD 1.38)
El Fegoun et al, 2011	HIFU	7.3 mean (range 2.6-10)	≤3+3: 10 (83%) 3+4: 2 (17%)	NR	10.6 yr median (range 7.5-11.1)	1/12 (8%)	0/12	5-yr: 90% 10-yr: 38%	Median 1.5 (range 0.1-6.8)
Ahmed et al, 2011a	HIFU	7.3 median (range 3.4-11.8)	NR	Low: 5 (25%) Intermediate: 15 (75%)	12 mo	2/19 (11%)	0/19	NR	At 12 mo: mean 1.5 (SD 1.3)
Ward and Jones, 2012	Cryoablation	1149 (99%) available <4: 211 (18%) 4 to <10: 782 (68%) 10 to <20: 126 (11%) >20: 30 (3%)	1148 (99%) available ≤6: 844 (74%) 7: 240 (21%) ≥8: 64 (5%)	1157 (99%) available Low: 541 (47%) Intermediate: 473 (41%) High: 143 (12%)	21.1 mo median (SD 19.7)	Only patients having biopsy: 43/163 (26.4%) All patients: 43/1160 (3.7%)	NR	3-yr: 75.7%	NR
Tay et al, 2011	MRI-guided HIFU	NR	NR	NR	NR	0/1	NR	NR	NR
Chopra et al, 2012	MRI-guided HIFU	6.2 mean (range 2.7-13.1)	3+3: 2 (25%) 3+4: 4 (50%) 4+3: 2 (25%)	NR	<2 hr	8/8 (100%)	6/8 (75%)	NR	NR

Continued

TABLE 117-2 Case Series of Focal Therapy Showing Disease Control Outcomes—cont'd

SERIES	ABLATION TYPE	PSA (ng/mL)	GLEASON SCORE AT PREOPERATIVE BIOPSY	RISK CLASSIFICATION	FOLLOW-UP	PRESENCE OF ANY CANCER	PRESENCE OF CLINICALLY SIGNIFICANT CANCER	BDFS	PSA KINETICS (AT LAST FOLLOW-UP UNLESS OTHERWISE STATED)
Bahn et al, 2012*	Cryoablation	5.4 median (range 0.01-20)	3+3: 30 (41%) 3+4: 25 (34%) 4+3: 18 (25%)	Low: 24 (33%) Intermediate: 49 (67%)	3.7 yr median (range 1-8.5)	12/48 (25%) 11 had positive biopsy of the untreated side; 1 of the treated side	5/48 (10%) including the patient having positive biopsy in the treated side	NR	At 36 mo: mean 2.1 (SD 3.8)
Ahmed et al, 2012d	HIFU	6.6 median (range 5.4-7.7)	3+3: 13 (32%) 3+4: 24 (59%) 4+3: 4 (10%)	Low: 11 (27%) Intermediate: 26 (63%) High: 4 (10%)	12 mo	9/39 (23%)	3/39 (8%)	NR	Median 1.9 (IQR 0.8-3.3)
Dickinson et al, 2012*	HIFU	NR	3+3: 31 (35%) 3+4: 50 (57%) 4+3: 7 (8%)	NR	32 mo median (range 24-69)	20/72 (28%)	10/2 (14%)	Phoenix 71/87 (82%) Stuttgart 57/87 (66%)	NR
Nguyen et al, 2012	MRI-guided brachytherapy	5.0 median (IQR 3.8-6.9)	3+3: 280 (88%) 3+4: 38 (12%)	Low: 265 (83%) Intermediate: 53 (17%)	5.1 yr (IQR 2.8-7.3)	Only patients having biopsy: 17/24 (71%) All patients: 17/318 (5.3%)	NR	Phoenix: 5-yr: 91.5% 8-yr: 78.1% Phoenix and PSAV >0.75/yr 5-yr: 91.9% 8-yr: 86.2%	NR
Napoli et al, 2013	MRI-guided HIFU	8.8 median	3+3: 3 (60%) 3+4: 2 (40%)	NR	9 mo mean (range 7-14)	5/5 (100%)	NR	NR	NR
Barret et al, 2013	HIFU 21 (20%) Brachytherapy 12 (11%) Cryoablation 50 (47%) PDT 23 (22%)	6.1 mean (IQR 5-8.1)	3+3: 106 (100%)	Low: 106 (100%)	9 mo median (range 6-15)	NR	NR	NR	12-mo: median 2.7 (IQR 1-4.4)

*This series partially overlaps with one previously reported.
BDFS, biochemical disease-free survival; HIFU, high-intensity focused ultrasound; IQR, interquartile range; MRI, magnetic resonance imaging; NR, not reported; PSA, prostate-specific antigen; PSAV, PSA velocity; PDT, photodynamic therapy; RITA, radiofrequency interstitial tumor ablation; SD, standard deviation.

TABLE 117-3 Case Series of Focal Therapy Showing Toxicity and Functional Outcomes

SERIES	COMPLICATIONS	URINARY CONTINENCE	ERECTILE FUNCTION (ABILITY TO HAVE PENETRATIVE INTERCOURSE)	RECTAL TOXICITY
Madersbacher et al, 1995	NR	NR	NR	NR
Zlotta et al, 1998	NR	NR	NR	NR
Beerlage et al, 1999	NR	NR	NR	Rectourethral fistula: 0/14 (0%) Perineal pain: 14/14 (100%) Rectal bleeding: NR Diarrhea: NR PROM: NR
Souchon et al, 2003	NR	NR	NR	NR
Moore et al, 2006	Urinary retention: 1/6 (17%) Urethral stricture: NR UTI: 1/6 (17%) Outcome measure: NR	Pad-free: NR Leak-free: 5/6 (83%) PROM: AUA-7	1/3 (33%) PROM: Brief Sexual Function Inventory	Rectourethral fistula: 0/3 (0%) Perineal pain: NR Rectal bleeding: 2/6 (33%) Diarrhea: 2/6 (33%) PROM: NR
Bahn et al, 2006	NR	Pad-free: 28/28 (100%) Leak-free: NR PROM: NR	24/27 (88.8%) PROM: Brief Male Sexual Function Index	NR
Onik et al, 2007	NR	Pad-free: 24/25 (96%) Leak-free: NR PROM: NR	44/51 (86%) PROM: NR	NR
Ellis et al, 2007	NR	Pad-free: 55/55 (100%) Leak-free: 53/55 (96.4%) PROM: NR	24/34 (70.6%) PROM: NR (vacuum therapy and oral therapy for erectile dysfunction offered preoperatively)	Rectourethral fistula: 0/34 (0%) Perineal pain: NR Rectal bleeding: NR Diarrhea: NR PROM: NR
Muto et al, 2008	Urinary retention: NR Urethral stricture 1/25 (4%) UTI 1/25 (4%) Outcome measure: NR	Pad-free: NR Leak-free: NR PROM: UCLA-EPIC, IPSS	NR	NR
Murat et al, 2009a	NR	NR	28/52 (54%) PROM: IIEF-5	NR
Lindner et al, 2009	Urinary retention: No Urethral stricture: No UTI: No Outcome measure: NR	Pad-free: 12/12 (100%) Leak-free: 12/12 (100%) PROM: IPSS	NR (100%) PROM: IIEF-5	Rectourethral fistula: 0/12 (0%) Perineal pain: 3/12 (25%) Rectal bleeding: No Diarrhea: No PROM: NR
Lindner et al, 2010a	NR	NR	NR	NR
Raz et al, 2010	NR	NR	NR	NR
Truesdale et al, 2013	NR	Pad-free: 77/77 (100%) Leak-free: NR PROM: IPSS	NR PROM: IIEF	NR
El Fegoun et al, 2011	Urinary retention: 1/12 (8%) Urinary stricture: No UTI: 2/12 (16%) Outcome measure: NR	Pad-free: 12/12 (100%) Leak-free: NR PROM: IPSS	NR	NR

Continued

TABLE 117-3 Case Series of Focal Therapy Showing Toxicity and Functional Outcomes—cont'd

SERIES	COMPLICATIONS	URINARY CONTINENCE	ERECTILE FUNCTION (ABILITY TO HAVE PENETRATIVE INTERCOURSE)	RECTAL TOXICITY
Ahmed et al, 2011a	Urinary retention: No Urinary stricture: 1/20 (5%) UTI: No Outcome measure: NR	Pad-free: 19/20 (95%) Leak-free: 18/20 (90%) PROM: UCLA-EPIC, IPSS	19/20 (95%) PROM: IIEF-15	Rectourethral fistula: 0/20 (0%) Perineal pain: NR Rectal bleeding: NR Diarrhea: NR PROM: FACT-P
Ward and Jones, 2012	Urinary retention: 6/518 (1.1%) Urinary stricture: NR UTI: NR Outcome measure: NR	Pad-free: 499/507 (98.4%) Leak-free: NR PROM: NR	169/291 (58.1%) PROM: NR	Rectourethral fistula: 1/507 (0.2%) Perineal pain: NR Rectal bleeding: NR Diarrhea: NR PROM: NR
Tay et al, 2011	NR	NR	NR	NR
Chopra et al, 2012	NR	NR	NR	NR
Bahn et al, 2012*	NR	Pad-free: 73/73 (100%) Leak-free: NR PROM: NR	36/42 (86%) PROM: IIEF-5	Rectourethral fistula: No Perineal pain: NR Rectal bleeding: NR Diarrhea: NR PROM: NR
Ahmed et al, 2012d	Urinary retention: 1/41 (2.4%) Urethral stricture: No UTI: No Outcome measure: NR	Pad-free: 40/40 (100%) Leak-free: 39/39 (100%) PROM: UCLA-EPIC, IPSS	31/35 (89%) PROM: IIEF-15	Rectourethral fistula: suspicion in 1/41 (2.4%) Perineal pain: NR Rectal bleeding: NR Diarrhea: NR PROM: NR
Dickinson et al, 2012*	NR	Pad-free: 86/87 (99%) Leak-free: 56/66 (85%) PROM: IPSS, UCLA-EPIC	76/85 (89%) PROM: IIEF-15	Rectourethral fistula: 1/88 (1%) Perineal pain: NR Rectal bleeding: NR Diarrhea: NR PROM: NR
Nguyen et al, 2012	NR	NR	NR	NR
Napoli et al, 2013	NR	NR	NR	NR
Barret et al, 2013	Urinary retention: 9/106 (8%) Urethral stricture: 1/106 (1%) UTI: No Outcome measure: Clavien-Dindo classification (13% complication rate, 2% major)	Pad-free: 106/106 (100%) Leak-free: NR PROM: IPSS	NR PROM: IIEF-5	Rectourethral fistula: 1/106 (1%) Perineal pain: 1/106 (1%) Rectal bleeding: 0 Diarrhea: NR PROM: NR

*This series partially overlaps with one previously reported.

AUA, American Urological Association; FACT-P, Functional Assessment of Cancer Therapy-Prostate; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; NR, not reported; PROM, patient-reported outcome measure; UCLA-EPIC, University of California, Los Angeles Expanded Prostate Index Composite; UTI, urinary tract infection.

to minimize the possibility of leaving significant areas of cancer untreated. Other tools of preoperative assessment that have been used include transrectal Doppler ultrasound. In summary, among the primary selected studies, 2 series used only TRUS biopsy, 2 used TRUS biopsy and Doppler ultrasound, 6 used TRUS biopsy and MRI, and 4 used template prostate mapping and mpMRI. The preoperative assessment was not reported in 11 studies.

Furthermore, all reported series have treated all known areas of cancer, but no reported series have explicitly stated that therapy was

aimed at the index lesion and deliberately left low-volume, low-grade lesions untreated. Of ongoing trials, most are aiming to treat all known areas of cancer, and 3 trials explicitly aim treatment at the index or clinically significant lesions with surveillance of untreated low-volume, low-grade lesions.

In the largest series of 1160 men using cryoablation, and in another series using HIFU with multiple strategies (n = 88), it was not possible to determine the extent of tissue ablation per patient. Either hemiablation or focal ablation was used in the remaining

studies, with 12 using a hemiablation or extended “dog-leg” or “hockey-stick” approach (number of patients, 537; relative percentage of data available, 49%); 16 used focal or zonal ablation (562, 51%), and 3 used bilateral focal ablation when multifocal disease was present (65, 6%). Our systematic review of focal therapy series demonstrated the summary outcomes shown in [Table 117-3](#).

Side Effects, Complications, and Quality of Life

Fourteen series reported hospital stay, with median length of hospital stay of 1 day. Other perioperative outcomes are poorly reported, with only one study using a standardized classification of these outcomes (Dindo-Clavien classification). The most frequent complications, namely urinary retention, urinary stricture, and urinary tract infection, occurred in 0% to 17%, 0% to 5%, and 0% to 17%, respectively. Only five studies actually reported all of these. Urinary functional outcomes were reported using validated questionnaires in nine studies; physician reported rates were used in five studies. **Using validated questionnaires, the pad-free continence rate varies between 95% and 100%, and leak-free rates are reported at 83% to 100% (see [Table 117-3](#)).**

Erectile function is reported using validated questionnaires in 10 and physician reported rates in 3 studies. Considering only trials evaluating focal therapy with “intention to treat,” when validated questionnaires were used, erectile function sufficient for penetration was reported in 54% to 100% of patients (with or without phosphodiesterase type 5 inhibitor [PDE5I] medication). Physician-reported rates were 58.1% to 85%. One study evaluated the systematic use of a vacuum device and oral therapy (penile rehabilitation) after focal cryoablation. The results, based on nonvalidated outcome measures, found an ability to have penetrative sex in 70.6% (24 of 34) potent men. Historical rates of potency preservation after whole-gland cryotherapy have been 10% to 25%.

Rectal toxicity was often poorly reported. Presence or absence of rectourethral fistula, for instance, was explicitly reported in only 10 series. When reported, **rates of fistula were 0% to 1%**; 1 series reported that 1 of 41 men had grade 3 rectal toxicity conservatively managed as a possible rectourethral fistula. Finally, PROMs evaluating overall quality of life are uncommonly used in these studies, with only 3 publications reporting them; in 1 study using hemiablation HIFU, the patients reported stable quality-of-life scores measured using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) instrument, whereas another demonstrated a slight deterioration after focal HIFU using the same instrument.

Cancer Control

Apart from six early feasibility trials that verified the effect of tissue ablation by analysis of radical whole-mount prostatectomy specimens, nine series incorporated routine mandatory post-focal therapy biopsies in their protocol. In the early six series, the ablative technique was delivered to test the safety and pilot the efficacy of the treatment without the specific aim to completely ablate the whole tumor present. In all, 74 men had radical prostatectomy, and residual disease was found in 73 of them.

Of the remaining nine series, in three series only the treated side underwent biopsy, whereas in six series the contralateral side underwent biopsy, too. **When post-therapy biopsies were routinely offered, clinically significant cancer was present in 0% to 17% (total number of men, 202).** When also clinically insignificant cancer was taken into account, and excluding one feasibility trial aiming to evaluate safety rather than ablation, 4% to 50% of men had positive biopsies after treatment (total number of men, 255). When biopsies were offered only “for cause,” overall positive biopsy rates of 13% to 71% were demonstrated for all types of cancer; when considering all patients enrolled in these series, this percentage was 3.7% to 23%. None of these series reported the percentage of significant cancer among patients having biopsy. Two series evaluated the presence of residual tumor in the treated area; this amounted to 3% to 14% when considering only patients having biopsy and 1.7% to 3.9% when the denominator was all treated patients.

Biochemical control using Phoenix criteria was reported in 5 series. Other definitions used were American Society for Therapeutic Radiology and Oncology (ASTRO) (5 series), Stuttgart (1 series), and Phoenix plus PSA velocity over 0.75 ng/mL/yr (1 series). The results ranged from 86.2% at 8 years’ follow-up (318 men) to 60% at 5 years (56 men). PSA tended to decrease by 66% to 80% from baseline to 12 months. With respect to the need for secondary focal treatments, only 12 series reported this at 0% to 34%. Salvage local treatments—in which a different modality was used or if whole-gland therapy was eventually delivered—was reported in 14 series with rates of 0% to 33%. One feasibility trial had higher secondary focal (67%) and salvage treatment (83%); these upper percentages were not considered in the overall range because the intent to treat was not to destroy all tumor. The progression to metastatic disease was not reported in most of the studies, because the follow-up is too short to have a significant percentage of patients developing metastasis. Nevertheless, when it is indicated, it is extremely low (0% to 0.3%). When considering CSS, it is extremely high, as expected with the small numbers and short follow-up inherent in almost all reported series. No man died of prostate cancer after focal therapy in the defined follow-up period. Four men died of other causes in the follow-up period. **Trifecta outcome was reported in 3 studies, and ranged from 50% to 89% (no incontinence of urine; erections sufficient for penetrative sexual intercourse; cancer control at 12 months or more).**

FOLLOW-UP AFTER FOCAL THERAPY

Early feasibility studies demonstrated an absence of rectal toxicity and preservation of genitourinary function in up to 90% to 95% of men ([Ahmed et al, 2011a, 2011d](#)). They demonstrated impotence rates of approximately 15% with little to no incontinence. The studies used a variety of methods to identify unilateral disease including Doppler TRUS biopsies, TRUS alone, and template biopsies and in general showed poor reporting standards owing to their retrospective nature with short follow-up and typically small numbers of patients.

A strategy to evaluate focal therapy should be embedded in trials that ascertain the key medium-term outcome measures that will determine the success or otherwise of this proposed alternative to the standard of care. This is far from easy. The ideal outcomes—metastases and death—require trials of at least 10 years in duration owing to the long lead time bias inherent in the screen-detected population of prostate cancer, so surrogate markers of failure have been proposed within the standards of care. Radical surgery uses a PSA threshold of less than 0.2 ng/mL, and radiotherapy uses the ASTRO Phoenix consensus criteria of two consecutive rises above PSA nadir ([Roach et al, 2006](#)). On the other hand, active surveillance uses clinical, histologic, and biochemical measures of progression, with the last far from being validated ([van As and Parker, 2007](#)).

If focal therapy is to be proposed as a challenge to these existing strategies, it is likely that many of these measures may not be suitable. Although treating the cancer foci, it does so by leaving substantial amounts of prostate tissue untreated ([Figs. 117-46 to 117-48](#)). It cannot achieve unrecordable PSA levels, nor is it easy in such a setting to apply the ASTRO Phoenix criteria. Equally, progression as defined by active surveillance regimens may not readily translate to a man who has had all clinically significant cancer treated using hemiablation but still has 50% of the prostate still present, for instance. In addition, the optimal ablative modality to deliver focal therapy is far from clear, with cryosurgery, HIFU, PDT, photothermal therapy, and brachytherapy all emerging as likely candidates ([Ahmed et al, 2009b](#)). Whether there will be ablative-specific tissue responses that require adjustments in outcome measures is unclear, but will need to be investigated.

Biochemical Outcomes

Conventional therapies have used surrogate end points, primarily biochemical (PSA) outcomes, to determine the success or otherwise

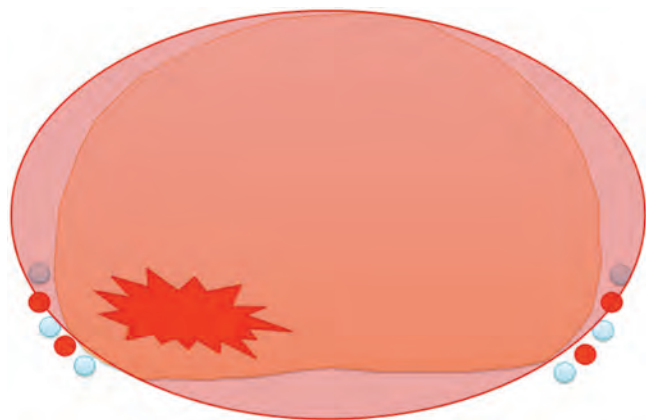


Figure 117-46. Failure or success of local therapies in prostate cancer depends on the margins of treatment, as with all other cancer surgery. Here, the whole prostate is removed and, apart from positive margins that might occur, the tumor is usually cleared along with the whole of the prostate. This can carry risks.

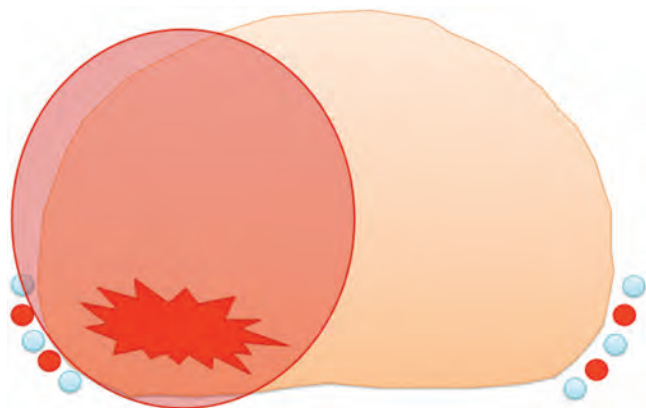


Figure 117-47. A hemiablation conducts a regional ablative template (the entire right side of the prostate) regardless of location, volume, or grade of the tumor. Here the large right peripheral zone lesion is treated with a wide margin but confined to lobe. There is a higher likelihood of complete ablation with less genitourinary toxicity compared with whole-gland treatment.

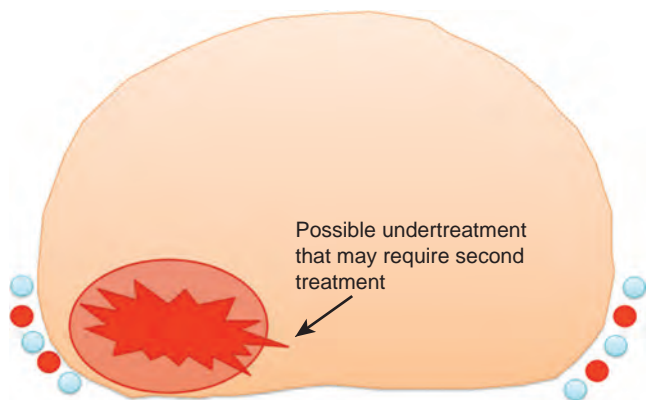


Figure 117-48. The large right peripheral zone lesion can also be treated a smaller margin in a zonal or focal ablation. There is a lower likelihood of complete ablation that must be balanced with less genitourinary toxicity and the ability to re-treat in a focal manner.

of radical surgery or radiotherapy (ASTRO Consensus Panel, 1997; D'Amico et al, 1998). Radiotherapy definitions tend to overestimate biochemical disease-free survival, in general with a 5-year lag in deeming a treatment failed compared with surgery. Even within these long-established therapies there can be wide variation in definitions used for failure, with over 166 definitions reported in the literature (Cookson et al, 2007). The definition of success for ablative technologies delivered in a whole-gland manner has not reached consensus (Aus, 2006; Ahmed et al, 2009a). Some have adopted ASTRO criteria or modified the acceptable increase above nadir to 1.2 ng/mL (deemed the Stuttgart definition) (Blana et al, 2009). Others, on the other hand, have determined that a PSA nadir upper threshold should be used, although there is no agreement on whether this should be 0.2, 0.4, or 0.5 ng/mL.

With untreated tissue remaining after focal therapy, it would seem unwise to use absolute biochemical parameters or even PSA kinetics alone without a form of standardization against a particular patient's volume of untreated tissue and volume of cancer ablated. PSA will vary according to the ablative technology, whether a particular device was used, the amount of tissue ablated, and any residual tissue that remains. With the last, the untreated tissue may be benign in its entirety or have clinically insignificant areas of low-volume, low-grade cancer that have been deliberately untreated to deliver tissue preservation. The parameters that may prove to be of greater use are discussed in the following sections.

Prostate-Specific Antigen Density

Stamey and colleagues (1987) were the first to correlate PSA serum values and volume of prostatic tissue, showing that the contribution from benign prostatic hyperplastic tissue was 0.30 ng/mL per gram of tissue and 3.5 ng/mL per cm³ of cancer tissue. PSA density may therefore be a good measure because it will allow for adjustment for residual tissue volume after focal therapy.

Nadir Prostate-Specific Antigen

Setting the PSA decrease relative to the percent of tissue ablated may be more pragmatic. The nadir could be defined by the amount of ablated tissue, with $x\%$ ablation leading to $x\%$ or greater decrease in PSA. Any increase from the nadir would need to be defined within the context of phase II 3- to 5-year trials that take into account the natural tendency for benign prostatic tissue growth and therefore PSA to increase with age (Vesely et al, 2003). The nadir could also be defined in a more intuitive manner by taking into account the proportion of pretreatment PSA that was likely to be attributed to the ablated tumor and the proportion secreted by ablated normal tissue. An accurate determination of cancer volume on MRI or ultrasound can aid in this calculation, whereas derived cancer volumes can be obtained from template TPM biopsies. This is likely to lead to a more robust PSA nadir so that 50% total tissue ablation is likely to lead to a PSA nadir less than 50% of pretreatment PSA, as the contribution to the total PSA is disproportionately higher from cancer tissue. This is borne out by early data from hemiablation strategies, which show a mean decrease of 80% in PSA occurring.

Prostate-Specific Antigen Kinetics

PSA kinetics (velocity [e.g., 1 ng/mL/yr] and doubling time [e.g., ≤ 2 to 3 years]) has been shown to be of some value in determining failure in evaluating progression in active surveillance (Dall'Era et al, 2008). Future trials will need to evaluate the PSA velocity and PSA doubling times that are predictive of failure, as well as velocity and doubling time adjusted for degree of prostate tissue remaining (PSA density kinetics).

Histologic Outcomes

Biopsies should be used to determine absence of disease within treated areas to verify short-term focal ablative success as well

as untreated areas to detect recurrent and de novo disease, respectively, in the medium to long term. However, TRUS-guided biopsies, if used for the latter objective, will be subject to the same systematic and random errors inherent in this test when applied in diagnosis of prostate cancer. So, a degree of targeting using noninvasive imaging to identify clinically significant lesions may be necessary. TRUS-guided biopsies used in this setting are also prone to detect clinically insignificant cancers (low volume, low grade), which are unlikely to influence disease progression; such foci may indeed have been missed on initial localization strategies (Ahmed, 2009). Therefore, their subsequent detection many years after focal therapy need not necessarily equate to the verdict of progressive, recurrent, or de novo cancer. Definitions related to clinical significance would need to take account of grade and cancer core length involvement as in diagnostic strategies—2 to 3 mm of cancer in any one core with absence of Gleason pattern 4 may be a starting point (O'Donnell and Parker, 2008), but such criteria will need careful validation. In addition, more accurate volume assessments of cancer foci, if present on surveillance imaging, will be needed. If they are not visualized on surveillance imaging, a post-treatment template transperineal mapping biopsy may be required to determine the disease burden of any cancer found on surveillance biopsies (Onik et al, 2009).

Biopsies will need to also take into account the therapeutic strategy used at baseline. Was the strategy one of ablating all measurable disease with absence of any cancer in untreated areas, or was some element of cancer accepted in untreated areas, for example, absence of any clinically significant areas (up to 3-mm low-volume, low-grade foci accepted)? In addition, were template mapping biopsies or TRUS-guided biopsies used to localize disease? If the latter, then disease found on surveillance biopsies may simply represent the sampling error of the initial localization tool used.

In summary, biopsies of the prostate for surveillance after focal therapy must be used in a more refined and accurate manner, taking into account the localization and therapeutic strategy used. Image-based targeting and, where necessary, template or saturation biopsies should be used in a similar manner to that before focal therapy. The key determination will be whether recurrence or de novo cancer found on surveillance after focal therapy is clinically significant or insignificant, with the latter triggering continued surveillance and the former warranting further treatment. Indeed, the need and chronology of further treatment may be an ideal parameter against which to assess focal therapy if the comparator arm is active surveillance, although such a determinant of failure is less obvious when radical therapies are considered. An outcome that may have application across all therapies and active surveillance is time to hormonal therapy, and this may serve as an important outcome in comparative trials in future.

Imaging Outcomes

Imaging may have a role in the pretreatment selection of focal therapy candidates (Turkbey et al, 2009). Early gadolinium contrast-enhanced MRI, within 1 to 2 weeks of treatment, has been shown to accurately predict areas of necrosis after whole-gland and focal HIFU as well as other modalities such as PDT, thus having a role in early verification of treatment effect (Kirkham et al, 2008). In addition, a number of authors have stated that multifunctional MRI (T2-weighted, dynamic contrast enhancement, diffusion, spectroscopy) seems to meet the ideal attributes for detection of clinically significant cancer, thus potentially being used to drive the delivery of focal therapy. A number of groups have demonstrated accuracy of over 85% to 90% for lesions that measure 0.2 mL or 0.5 mL in volume. The exclusion of significant lesions may be more important in focal therapy, and hence the negative predictive value; negative predictive values for 0.5-mL lesions have been demonstrated to be as high as 95% if multifunctional MRI is used before TRUS-guided biopsy (Villers et al, 2006; Puech et al, 2009). Because 0.5 mL is commonly used as the threshold at which prostate cancer lesions become clinically significant, the inherent ability of multifunctional MRI to be able

to detect large lesions and not detect small lesions may be its greatest attribute and may serve to justify its use not only in disease localization for focal therapy but also as a triage test before TRUS-guided biopsy (Ahmed et al, 2009a). These results, which used radical prostatectomy reference standard validation, need verification in other centers as part of multicenter trials. In addition, it would be key to also use validation against template mapping biopsies, a reference standard that would have less inherent selection bias owing to its applicability to all men.

It therefore seems logical that, in the medium to long term, surveillance of untreated areas of the prostate could be undertaken by mpMRI to detect recurrence of clinically significant cancer. A negative MRI would imply absence of clinically significant disease that requires no treatment. This would avoid any potential overtreatment after focal therapy. Other ultrasound imaging modalities (elastography, ultrasound tissue characterization [e.g., PHS], CEUS) that are starting to demonstrate promise in the detection of prostate cancer before treatment could also be applied after focal therapy (Hoyt et al, 2008; Atri et al, 2009; Gravas et al, 2009).

SALVAGE THERAPY AFTER RADIORECURRENCE

Over 400,000 men are diagnosed with prostate cancer every year in Europe (Ferlay et al, 2013). Many—estimated at 90,000—undergo primary radiotherapy (Cross and McPhail, 2008). Radiotherapy is an effective treatment in the majority of patients, but approximately 1 in 4 will experience biochemical failure indicated by a rising serum PSA level. Of those men with biochemical failure, half to three quarters have localized recurrence (an estimated 10,000 to 15,000) (Lee et al, 1997; Shipley et al, 1999; Kuban et al, 2003; Bannuru et al, 2011). These men might be suitable for further local treatment (Cross and McPhail, 2008). Men with recurrent prostate cancer usually have failure after the age of 65 years and thus have additional comorbidities and problems that have led to a number of quite varied treatment options being available, ranging from watchful waiting with delayed systemic androgen deprivation therapy (ADT) to local salvage therapies such as surgery or ablative therapy. In over 90% of men with recurrent prostate cancer, the strategy used is watchful waiting with delayed systemic ADT (Grossfeld et al, 2002; Agarwal et al, 2008; Boukaram et al, 2010) when indicated. Estimates for eventual ADT use within 5 years vary (50% to 90%) (Lukka et al, 2005; Kuban et al, 2008; Bolla et al, 2009; Kuban et al, 2011; Warde et al, 2011; Arcangeli et al, 2012).

Determination of Failure Using Prostate-Specific Antigen Criteria and Imaging

Serum PSA criteria for failure have a sensitivity and specificity of 60% to 70% (Roach et al, 2006). We and others have shown that mpMRI has high sensitivity (70% to 90%) for the presence of clinically significant disease at the time of biochemical PSA relapse, but the role of mpMRI as a surveillance tool alongside PSA testing is not yet known. Imaging is used to monitor treatments in many other solid-organ cancers, but the paradigm has not yet been accepted in management of prostate cancer until now. Kara and colleagues (2011) compared the role of DCE MRI (1.5T MRI) with TRUS in the follow-up (18 months from radiotherapy) of 172 patients who were treated with external beam radiotherapy (EBRT). The sensitivity and specificity of TRUS and T2-weighted MRI differed significantly—53.3% and 60% versus 86% and 100%—although the sensitivity of DCE MRI was greatest at 93% with a specificity of 100%. Haider and colleagues (2008) evaluated the role of mpMRI versus sextant biopsy in 33 men. On a sextant basis, DCE MRI had significantly better sensitivity (72% vs. 38%), positive predictive value (46% vs. 24%), and negative predictive value (95% vs. 88%) than T2-weighted MRI. Specificities were high for both DCE MRI and T2-weighted MRI (85% vs. 80%). TRUS biopsy, however, was the reference standard in these studies. MRI-targeted biopsies as well as whole-gland TPM biopsy studies from the UCL

group have shown promising accuracy rates in identifying radiorecurrent disease (Arumainayagam et al, 2010). One study looking at 26 men with biochemical failure after radiotherapy found that there was a similar rate of detection between MRI-targeted biopsies and TPM for clinically significant cancer: 85% (22 of 26 patients) compared with 92% (24 of 26 patients), respectively (unpublished data). These data indicate that a comparative effectiveness study is necessary.

Watchful Waiting with Androgen Deprivation Therapy

Watchful waiting with ADT is quite common (Berge et al, 2007). ADT provides symptomatic control but has limitations. First, it is palliative in intent (Pagliarulo et al, 2012; Payne et al, 2013; Heidenreich et al, 2014b). Second, there are common side effects. These include hot flushes (50% to 80%); breast tenderness or enlargement (up to 60%); lethargy (most); erectile dysfunction or decreased libido (10% to 17%) (Potosky et al, 2001); osteopenia or osteoporosis with consequent fracture (19%) (Shahinian et al, 2005); variable cognitive impairment (Jamadar et al, 2012); symptomatic anemia (13%) (Strum et al, 1997); metabolic syndrome (>50%) (Braga-Basaria et al, 2006); obesity, hyperglycemia, or diabetes (11%) (Derweesh et al, 2007); and cardiovascular disease (5%) (Saigal et al, 2007; Thomas and Neal, 2013).

Third, ADT is expensive, costing thousands per patient over his lifetime. In fact, because ADT does not cure the cancer, after an average of 2 years the cancer cells change and become resistant to ADT (so-called castration resistance). When this happens, new drugs are prescribed that can improve survival by a few months. However, these drugs carry a risk of more side effects and are very costly (tens of thousands of dollars every year). For instance, an incremental cost-effectiveness ratio (ICER) of many thousands of dollars per QALY is required compared with nonhormonal palliation (Bayoumi et al, 2000; National Institute for Health and Care Excellence [NICE], 2008; Lu et al, 2012) (approximately €8000 to €30,000 per year).

Detecting Distant Disease

Bone Scan

After primary treatment of prostate cancer, bone is the first site of relapse in more than 80% of patients. Plain film and bone scans form the mainstay of detection. Bone scans are able to detect metastases up to 18 months before plain film. There needs to be only a 10% change in bone mineral turnover to be detected by bone scans, whereas the bone must demineralize by 50% before a lesion is detected by plain film (Taoka et al, 2001). Bone scans and plain film have been shown to underestimate the true incidence of metastatic disease. Bubendorf and colleagues (2000) performed autopsies on 1589 men with prostate cancer (47% were unsuspected), and the incidence of metastatic bone disease was 90%. Bone scans are also well known for their high rate of false positives resulting from degenerative changes, inflammation, Paget disease, and trauma.

Choline Positron Emission Tomography/Computed Tomography Scan

A significant development in positron emission tomography (PET) radiopharmaceuticals has occurred. Several radiotracers able to visualize different tumor metabolisms are currently available, including fluorine-18 (^{18}F) fluorodeoxyglucose (FDG) for glucose metabolism; carbon 11 (^{11}C)/ ^{18}F -labeled choline and ^{11}C -acetate for lipid metabolism; ^{11}C -methionine for amino acid metabolism; and deoxy- ^{18}F -fluorothymidine for imaging cell proliferation (Picchio et al, 2011).

Among the different PET tracers evaluated for prostate cancer imaging, $^{11}\text{C}/^{18}\text{F}$ choline has been particularly investigated. Choline is an essential component of phospholipids of the cell membrane.

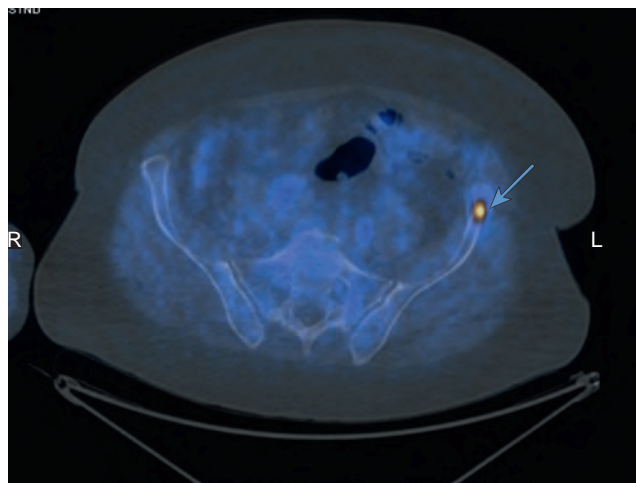


Figure 117-49. A choline positron emission tomography/computed tomography scan showing bony pelvic metastasis in a man with radiorecurrent prostate cancer.

Cell proliferation and upregulation of choline kinase are two mechanisms suggested for the increased uptake of this tracer in prostate cancer (Richter et al, 2010). The presence of choline transporters also seems to be involved in the process of its uptake in cancer cells (Müller et al, 2009). ^{18}F -choline has been shown to have a greater sensitivity and accuracy than ^{18}F -FDG PET/CT to detect prostate malignancy: sensitivity 73% versus 31% and accuracy 67% versus 53%, respectively (Hodolic et al, 2013). A high Gleason score and rising PSA level have been shown to increase rates of detection of ^{18}F -fluoromethylcholine (^{18}F -FCH) PET/CT. One study found that ^{18}F -FCH PET/CT detected prostate cancer recurrence in 97% of patients with Gleason score above 7, 82% of patients with Gleason score of 7, and 63% of patients with Gleason score below 7. Forty-three percent of patients in this study had recurrence in the prostatic bed, and 57% of patients had local metastasis. Currently, it is not recommended to perform choline/PET in patients with a PSA value below 1 ng/mL. Also, choline PET/CT has a low spatial resolution and is limited in the identification of small lymph node deposits (Fig. 117-49).

Whole-Body Magnetic Resonance Imaging

Recent advances in MRI have made it possible to image the whole body (WB-MRI) within a reasonable time of 50 to 60 minutes. DCE MRI and DWI complement conventional anatomic MRI techniques and provide a combined approach for assessing cancer anatomy, microstructure, and function. This enables the study of extraskelatal involvement, including lymph nodes and other soft-tissue metastases (Koh et al, 2007; Komori et al, 2007). Also WB-MRI is conducted without irradiation; therefore patients are not exposed to the cumulative radiation exposure of bone scans, plain films, and CT, which is more than several years of natural background radiation (Heliou et al, 2012; Lecouvet et al, 2012).

A few studies have reported good sensitivity and specificity of WB-MRI compared with current imaging tools. Lecouvet and colleagues (2012) compared DWI-WB-MRI with bone scanning, plain films, and CT in 100 patients; 68 were felt to have metastases. The sensitivities of bone scanning with plain films and WB-MRI for detecting bone metastases were 86% and 98% to 100%, respectively ($P < .04$), and specificities were 98% and 98% to 100%, respectively. The sensitivities of CT and WB-MRI for detecting enlarged lymph nodes were similar, at 77% to 82% for both; specificities were 95% to 96% and 96% to 98%, respectively. Sensitivities of the combination of bone scan and plain films plus CT versus WB-MRI for detecting bone metastases and/or enlarged lymph nodes were 84% and 91% to 94%, respectively ($P = .03$ to $.10$); specificities were 94% to 97% and 91% to 96%, respectively.

Another study compared the detection rate of metastatic disease by WB-MRI with bone scan in 39 patients diagnosed with local prostate cancer. It is interesting to note that the sensitivity for detection of skeletal metastases for both bone scan and WB-MRI was 70% (95% CI 0.42 to 0.98); the specificity was 100%, and the positive predictive value was 100%. WB-MRI and bone scan differed in the areas of detection. For instance, 7 patients had bone metastases on bone scan and 7 had skeletal metastases by WB-MRI, with concordant findings in only 4. Bone scan detected more rib metastases, whereas MRI identified more metastatic lesions in the spine (Venkitaraman et al, 2009). This study showed that WB-MRI and bone scan have similar specificity and sensitivity but may have to be used as complementary investigations to detect skeletal metastases from prostate cancer, rather than as alternatives.

The recognized limitations of these studies is that histology confirmation was not the reference standard because bone biopsies are not common practice and lymph node dissection is recommended only in patients who are suitable for further salvage therapy.

Biopsy of Radiorecurrent Cancer

Positive biopsies are currently the only way to confirm local relapse. However, it is well known that false-positive results can be observed owing to difficulties in distinguishing radiation-induced atypia of benign glands from malignancy (Bostwick et al, 1982; Miller et al, 1993; Crook et al, 2000). Tumor resolution after radiotherapy has no identifiable glandular morphology, and these remnants can be given a high Gleason score. Postradiotherapy prostate biopsies should be evaluated by a pathologist who is familiar with these findings (Boukaram et al, 2010; Kimura et al, 2010).

The time after radiotherapy at which to perform prostate biopsy was discussed previously. Crook and colleagues (2000) showed that 34% of positive biopsies that are obtained 12 months after radiotherapy convert to negative status by 24 to 30 months, whereas about 20% of the patients who have a negative post-treatment biopsy will later experience positive rebiopsy. Scardino (1983) also demonstrated a similar rate of 32% of men with a positive 12-month biopsy result transitioning to negative by 24 months. False negatives have been ascribed to sampling error, whereas false positives and indeterminate biopsies also frequently occur as a result of delayed tumor regression. These “false-positive” biopsies might be one of the reasons for possibly overdiagnosing radiorecurrent prostate cancer. Overall, these studies indicate that biopsies should take place at least 24 to 36 months after radiotherapy.

Transrectal Ultrasound-Guided Biopsy

Although TRUS systematic 10- to 12-core biopsies are standard care, they have inherent inaccuracies as a diagnostic strategy. In the setting of radiorecurrent disease, these errors can equally lead to inappropriate therapeutic decisions. First, TRUS biopsies miss clinically significant disease that is present. Second, they misclassify significant disease as insignificant. These two errors may lead to a man being recommended to effectively undergo palliative care with expectant management and hormones rather than potentially curative local therapy. Third, TRUS biopsies detect small-volume clinically insignificant disease that may inappropriately be attributed as the cause of biochemical failure when, in fact, micrometastases are present. This could lead to unnecessary local salvage therapy that carries variable rates of complications and side effects.

Transperineal Biopsies

Transperineal template prostate mapping biopsies have been shown to be more accurate in detecting both primary and radiorecurrent disease. TPM biopsies involve use of a 5-mm brachytherapy grid applied to the perineum and a TRUS probe to visualize the prostate. Biopsy cores are taken every 5 to 10 mm, with two biopsy cores taken in the same grid coordinate to cover mid-gland to base if the full length of the gland is not covered by one biopsy core. In a treatment-naïve prostate gland, 5-mm TPM has been shown to be

a more accurate diagnostic method when compared with current standard TRUS biopsy.

Magnetic Resonance Imaging for Diagnosing Local Recurrence

Kara and colleagues (2011) compared the role of DCE MRI (1.5T MRI) with TRUS in the follow-up (18 months from radiotherapy) of 172 patients who were treated with EBRT. The sensitivity and specificity of TRUS and T2-weighted MRI differed significantly—53.3% and 60% versus 86% and 100%—although the sensitivity of DCE MRI was greatest at 93% with a specificity of 100%. Haider and coworkers (2008) evaluated the role of mpMRI against sextant biopsy in 33 men. On a sextant basis, DCE MRI had significantly better sensitivity (72% vs. 38%), positive predictive value (46% vs. 24%), and negative predictive value (95% vs. 88%) than T2-weighted MRI. Specificities were high for both DCE MRI and T2-weighted MRI: 85% versus 80%. TRUS biopsy, however, was the reference standard in these studies. This is a poor reference standard compared with whole-mount histology and whole-gland transperineal template prostate mapping biopsies, so these results must be interpreted with some caution.

MRI-targeted biopsies as well as whole-gland TPM biopsies have shown promising accuracy rates in identifying radiorecurrent disease (Arumainayagam et al, 2010). One study looking at 26 men with biochemical failure after EBRT found that there was a similar rate of detection between MRI-targeted biopsies and TPM for clinically significant cancer detection: 85% (22 of 26 patients) compared with 92% (24 of 26 patients), respectively (Kanthabalan et al, 2013).

Whole-Gland Salvage Therapy

An alternative approach is further local treatment, so-called salvage therapy (Dudderidge et al, 2007). Whole-gland salvage surgery (radical prostatectomy or cystoprostatectomy) may be potentially curative but carries a high risk of side effects. These are rectal injury (5% to 10%) (requiring further major open reconstructive surgery) and incontinence necessitating use of pads (>50%), as well as poor quality of life (Bianco et al, 2005; Touma et al, 2005; Sanderson et al, 2006; Boukaram et al, 2010; Kimura et al, 2010; Chade et al, 2012; Yuh et al, 2014; Zugor et al, 2014). These occur because of the close proximity of nerves, muscle, and other organs, which inevitably have collateral damage because even keyhole surgery is not precise enough to overcome the fibrosis and scarring that result from the previous radiation. As a result, there is very poor uptake of this technique even if minimally invasive therapies such as cryotherapy are used (Table 117-4) (Ahmed et al, 2005; Galosi et al, 2007; Ismail et al, 2007; Ng et al, 2007; Pisters et al, 2008; Mouraviev et al, 2012; Spiess et al, 2013) and HIFU (Gelet et al, 2004; Rebillard et al, 2008; Zacharakis et al, 2008; Chalasani et al, 2009; Murat et al, 2009b; Berge et al, 2010; Ahmed et al, 2012b).

Salvage Radical Prostatectomy

Salvage radical prostatectomy offers satisfactory oncologic control with BDFS of 31% to 69% at 5 years and at 30% to 43% at 10 years (Bianco et al, 2005; Touma et al, 2005). However, this salvage method is not often performed owing to the high risks of morbidity. Complications such as incontinence (10% to 80%), anastomotic stricture (17% to 32%), and rectal injuries (3.3% to 50%) stem from fibrosis, merging of tissue planes used for dissection, and poor wound healing caused by radiotherapy. Studies reporting these outcomes have all emphasized the importance of an experienced surgeon because of the high technical demand.

Whole-Gland Salvage Brachytherapy

A number of studies have shown good CSS with salvage brachytherapy for radiorecurrent disease. Grado and colleagues (1999)

TABLE 117-4 Whole-Gland Salvage Outcome Summary

WHOLE-GLAND MODALITY	BIOCHEMICAL DISEASE-FREE SURVIVAL RATES	INCONTINENCE	RECTOURETHRAL FISTULA	FURTHER ENDOSCOPIC INTERVENTION
Radical prostatectomy	28%-87%	68%	0%-15%	10.9%-23.9%
High-intensity focused ultrasound (HIFU)	25%-62%	38%-50%	2%-4%	1.3%-36%
Cryotherapy	11%-86%	4.4%-13%	1%-4%	Not available

showed actuarial BDFS at 3 and 5 years for 49 patients to be 48% (95% CI 32% to 63%) and 34% (95% CI 17% to 51%), respectively. Aaronson and colleagues showed rates of 89.5% BDFS over 3 years in a small group of only 24 after exclusion of 14 (Aaronson et al, 2009). Brachytherapy appears to be a potentially useful salvage therapy that needs further evaluation. Common complications include lower urinary tract symptoms, hesitancy, nocturia, rectal bleeding, and frequent bowel movements. A serious complication is a prostatic-rectal fistula, which in one study occurred in 12% of patients. These complications were found to be higher than those of salvage cryotherapy (Ismail et al, 2007; Pisters et al, 2008).

Whole-Gland Salvage Cryotherapy

Salvage cryotherapy has shown good 5-year BDFS (40% to 58%), which can be up to 73% in patients who had low-risk disease before radiotherapy. It must be noted that these studies vary in their definition of biochemical failure (PSA >0.5 ng/mL vs. ASTRO vs. Phoenix definition) (Ahmed et al, 2005; Galosi et al, 2007). With improvements in technique and development of cryotechnology such as thermocouples that monitor the temperature at important sites within the prostate, and a urethral warming device used to prevent tissue sloughing, complication rates have improved, although they can still be high: incontinence 4% to 73%, rectourethral fistula 0% to 3.4%, perineal pain 5.6% to 39.5%, and urinary retention 0% to 67% (Ng et al, 2007; Nguyen et al, 2007). Sloughing and urethral stricture rates have been reduced from 10% to 15% to as low as zero. Erectile dysfunction has not improved (72% to 86%).

Whole-Gland Salvage High-Intensity Focused Ultrasound

A number of studies have looked at HIFU as a potential salvage therapy for radiotherapy failure cases. Murat and colleagues (2009b) treated 167 patients who had radiorecurrent disease with salvage HIFU. Patients were separated into low-, intermediate- and high-risk groups based on preradiotherapy disease risk; progression-free survival rates at 3 years were reported as 53%, 42%, and 25%, respectively. Ahmed and colleagues had 1- and 2-year progression-free survival rates of 62% and 48%, respectively, in patients who achieved a PSA nadir below 0.5 ng/mL (Ahmed et al, 2012b), in men in whom very few selection criteria were applied. Overall, common complications include incontinence (10% to 50%), bladder neck stenosis (17%), retention from urethral stricture (17%), erectile dysfunction (66.2% to 100%), and rectourethral fistula (3% to 16%) (Gelet et al, 2004; Rebillard et al, 2008; Chalasani et al, 2009).

Focal Salvage Therapy

Prior radiotherapy results in decreased vascularity and poor wound healing in tissues surrounding the prostate, so the relative inability of ablative therapies to sharply predict and demarcate boundaries of treatment results in a significantly greater risk of complications than with their primary counterparts. For instance, the treatment of apical lesions that are in close proximity to the urethra could lead to significant urethral and external sphincter damage. Despite good oncologic control, salvage radical prostatectomy is not widely performed owing to high morbidity. Brachytherapy, cryotherapy, and HIFU are also used as salvage

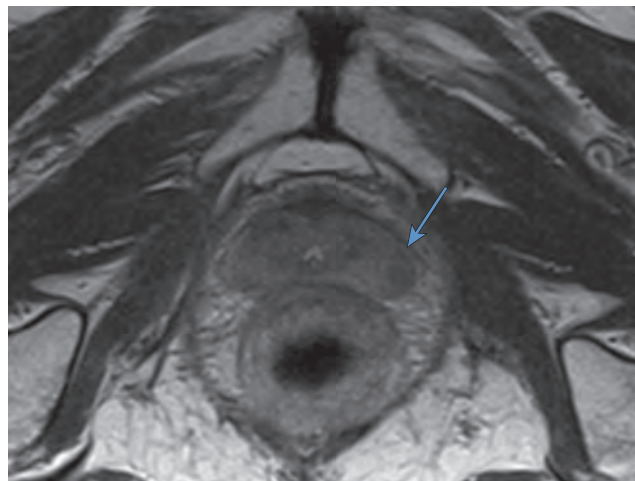


Figure 117-50. A 72-year-old man who had radiotherapy 6 years before presentation. His original disease was low risk. Biochemical failure occurred with a PSA of 3 ng/mL and rising. Multiparametric magnetic resonance imaging (mpMRI) (T2-weighted, diffusion-weighted, dynamic contrast-enhanced) showed left localized unilateral disease confirmed on template prostate mapping biopsy as unilateral Gleason 3+4 with some radiation effect. Bone scan and positron emission tomography/computed tomography were clear for metastases. Here the T2-weighted scan is shown.

therapies, but their long-term oncologic outcome is still unknown and the morbidity is still high. In primary therapy, these latter treatments are currently undergoing evaluation as part of tissue-preserving focal therapy strategies in which they target cancerous lesions in the prostate. Some early data suggest that a similar strategy could be adopted for radiorecurrent disease.

The goal of these ablative therapies is the same: maximum destruction of cancerous tissue with minimal damage to critical surrounding structures such as the urethra, the urinary sphincter, bladder neck, and rectum (Huang et al, 2007). However, potential problems of focal therapy in radiorecurrent disease include accurately localizing recurrent disease within the prostate, the margins of safe treatment that preserve oncologic efficacy while minimizing harm, and strategies of follow-up. These problems are common to the focal therapy story in treatment-naïve disease (Ahmed et al, 2012a) (Figs. 117-50 to 117-54).

Location of Recurrent Disease

There has been some debate regarding the multifocality and location of radiorecurrent disease. Two studies, conducted by Leibovici and colleagues (2012) and Huang and colleagues (2007), examined radical prostatectomy specimens in radiorecurrent disease. They showed that radiorecurrent disease is often bulky, high volume, bilateral (74%), and close to (67% to 74%) or involving the urethra (7%). They concluded that because biopsies were not able to accurately detect radiorecurrent disease, focal therapies might miss important areas of cancers that could lead to progression and metastatic spread.

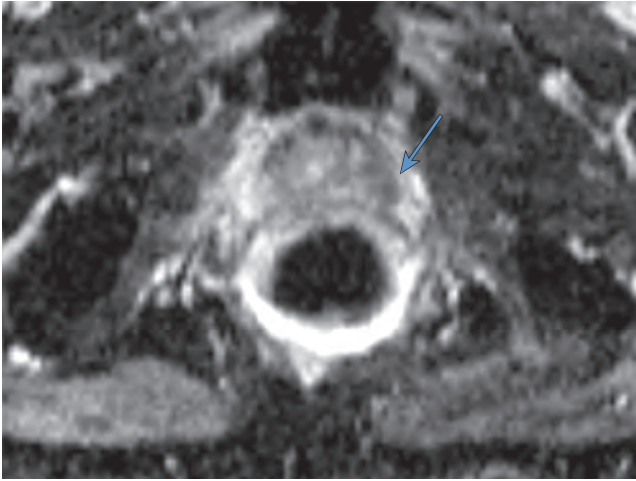


Figure 117-51. Diffusion-weighted apparent diffusion coefficient scan of same patient as in Figure 117-50.

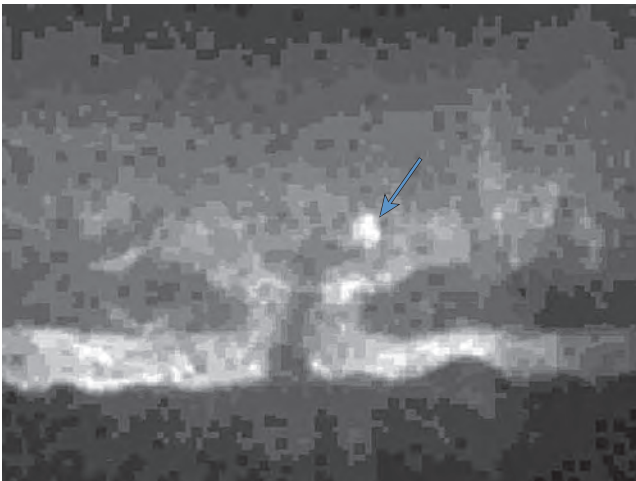


Figure 117-52. High b-value (1500) diffusion scan of same patient as in Figures 117-50 and 117-51.

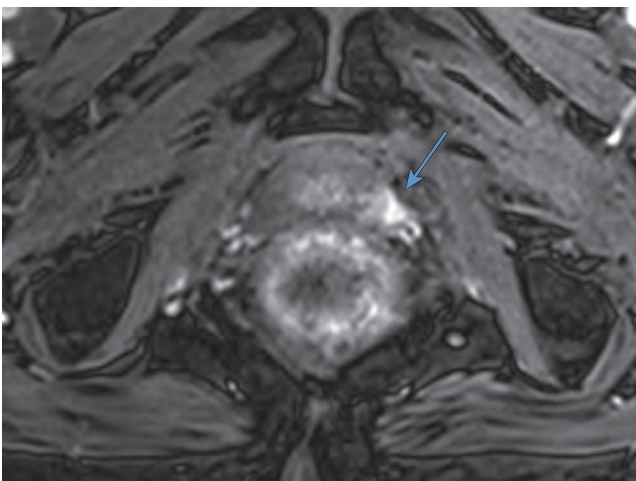


Figure 117-53. The same man as Figures 117-50 to 117-52 with significant enhancement in the lesion on dynamic enhancement.

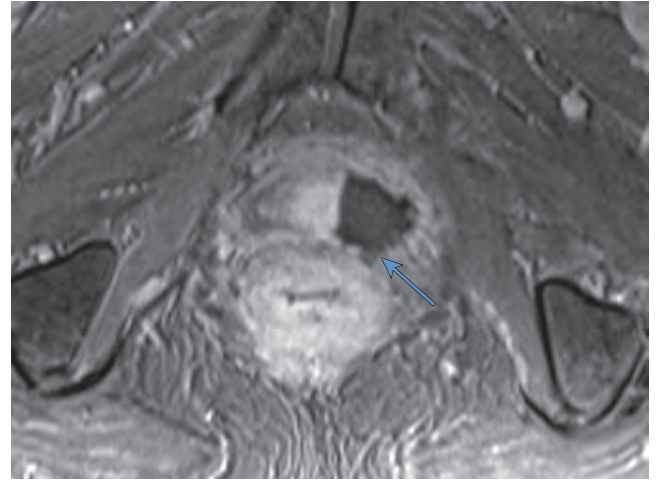


Figure 117-54. The man with radiorecurrent disease in Figures 117-50 to 117-53 underwent focal high-intensity focused ultrasound (HIFU) ablation using a hemiablation strategy. He was impotent before the HIFU treatment, but he remained pad free and leak free following treatment. The dynamic contrast-enhanced magnetic resonance image shows good ablative effect with absence of blood supply in the treated side. Post-treatment PSA values decreased to 0.2 ng/mL, 0.9 ng/mL, 0.5 ng/mL, and 0.03 ng/mL, measured trimonthly.

Huang and coworkers (2007) found that of 46 radical prostatectomy specimens, 90% had cancer foci at the apex. Furthermore, 28% of specimens in this study also had multifocal disease. However, other studies have shown that recurrence occurs at the initial cancer index lesion site (Cellini et al, 2002; Pucar et al, 2007). Cellini and colleagues (2002) found that in 118 patients, areas not initially affected by tumor had no evidence of disease recurrence at a median of 45 months of follow-up. There is a possibility that if only one focus is treated and multifocal disease is present, these areas can develop and metastasize; however, it may be more probable that the index lesion hypothesis may also be relevant in this setting.

We previously discussed the role of TPM biopsies and mpMRI in detection of localized recurrence. These modalities would in theory have the ability to provide 3D data to drive the focal delivery of ablative modalities for focal salvage.

Focal Salvage Brachytherapy

Kaplan and colleagues (2013) looked at the role of MRI fusion imaging to guide focal salvage brachytherapy. Twelve patients with pathologically confirmed recurrence of prostate cancer had MRI-US fusion image-guided intraoperative dosimetry. A median of 42 (range, 30 to 71) seeds containing iodine-125 (^{125}I) or palladium-103 (^{103}Pd) were placed, and isodose distributions were concentrated on the biopsy-proven abnormalities on MRI only. Total prescribed dose was 8000 cGy. Biochemical failure was defined using the previous ASTRO consensus definition. Toxicity was graded according to the Radiation Therapy Oncology Group (RTOG) and Late Effects Normal Tissue (LENT) criteria. Median follow-up after salvage brachytherapy was 48 months (range, 19 to 111). Three of 12 patients had biochemical failure; 4 of 12 patients had grade 2 or 3 RTOG toxicities including subacute grade 3 urinary retention and had grade 3 urinary incontinence after TURP was performed 5 years after salvage brachytherapy. This is a small study that used TRUS biopsy to confirm recurrence as well as the old ASTRO definition to determine biochemical failure. Another study by van Vulpen and colleagues (2012) delivered focal salvage ^{125}I brachytherapy to 16 patients with DCE MRI and biopsy-proven recurrence. Prescription dose to the recurrence was 144 Gy. After 6 months only 1 patient was found to have grade 3 toxicity according to the National Cancer Institute Common Toxicity Criteria.

Focal Salvage Cryotherapy

Eisenberg and colleagues (2008) performed a retrospective study on 19 patients. These patients were selected on the basis that they fulfilled Phoenix definition for biochemical failure, they had TRUS biopsy-confirmed recurrence, the recurrence was unilateral, and their glands were only partially treated with cryotherapy. Fifteen men had longer than 6 months' follow-up, which included trimonthly PSA and TRUS biopsy. The complication rates in this study were low; 1 patient developed mild stress urinary incontinence, 1 developed a urethral stricture that required dilation, and 1 developed a prostatic urethral ulcer managed with suprapubic catheter drainage with resolution after 6 months. Whether this represented a fistula was difficult to determine from the study report. Only 5 patients had available potency data, with 2 men maintaining potency and 3 impotent after treatment. According to the Phoenix definition of failure, 89%, 79%, and 79% of men were free of biochemical recurrence at 1, 2, and 3 years, respectively. Although 19 men were included, only 10 men were rebiopsied, with 90% (9 of 10) having no recurrence at 1-year biopsy. Overall, this was a small study with limited and poor follow-up. Although BDFS rates appeared to be good, not all patients were followed, and only half of these men had a biopsy after salvage treatment.

Focal Salvage High-Intensity Focused Ultrasound

Ahmed and colleagues (2012c) performed focal salvage HIFU in 39 patients. Disease recurrence was confirmed by mpMRI and either TPM (20 men) or TRUS biopsies targeted to the area of recurrence (19 men). Focal HIFU was either hemiablation (ablation of the lobe up to urethra) or quadrant ablation (ablation of one half of the lobe anterior or posterior). Patients with recurrence confirmed by TRUS biopsies underwent hemiablation. If there was multifocal cancer, then the patient underwent index lesion ablation if the untreated areas had 1 core or less with 3 mm or less of maximum 3+3 disease (on TPM) and/or no lesion on mpMRI.

Median follow-up was 17 months. Trimonthly PSA levels were measured, and validated questionnaires including the International Prostate Symptom Score (IPSS), the Expanded Prostate Cancer Index Composite urinary domain, and the International Index of Erectile Function 5-point scale (IIEF-5) were administered. Pad-free, leak-free continence status after treatment was 64%, and the pad-free rate was 87% as measured at last follow-up. Erectile function worsened, with IIEF-5 scores decreasing from a median of 18 to 13 at 6 months.

Twenty-three percent of patients developed Clavien 3b complications, although this was not fully discussed. One patient developed a rectourethral fistula, and this resolved spontaneously after 6 months of suprapubic catheter drainage and colostomy, as confirmed on repeat serial MRI studies and urethrograms, and with clinical symptoms. Forty-four percent achieved a PSA nadir below 0.5 ng/mL and the 1-year, 2-year, and 3-year BDFS rates were 86%, 75%, and 63%, respectively, using Phoenix criteria. However, when biopsy postsalvage was positive and requirement for ADT was included in the definition of failure, these rates decreased to 79%, 67%, and 45%, respectively. For men who did not achieve PSA nadir less than 0.5 ng/mL (56%), the 1-year, 2-year, and 3-year BDFS rates were much lower at 55%, 24%, and 0%, respectively.

Another recent study has shown that 48 patients were prospectively enrolled in two European centers wherein inclusion criteria were biochemical recurrence after primary radiotherapy, positive MRI, and one or more positive biopsies in only one lobe (Baco et al, 2014). Biochemical failure was defined using Phoenix criteria. Patients with obstructive voiding symptoms at the time of treatment underwent an endoscopic bladder neck resection or incision during the same anesthesia to prevent the risk of postoperative obstruction. After hemisalvage HIFU, the mean (standard deviation [SD]) PSA nadir was 0.69 (0.83) ng/mL at a median (interquartile range) follow-up of 16.3 (10.5 to 24.5) months. Disease progression occurred in 16 of 48 (33%). Of these, 4 had local recurrence in the untreated lobe and 4 bilaterally, 6 developed metastases, and 2 had

rising PSA levels without local recurrence or radiologically confirmed metastasis. Progression-free survival rates at 12, 18, and 24 months were 83%, 64%, and 52%, respectively. Severe incontinence occurred in 4 of the 48 patients (8%), 8 (17%) required one pad a day, and 36 of 48 (75%) were pad free. The International Continence Society questionnaire showed a mean (SD) deterioration from 0.7 (2.0) to 2.3 (4.5) for scores A and 0.6 (1.4) to 1.6 (3.0) for B. The mean (SD) IPSS and erectile function (IIEF-5) scores decreased from a mean (SD) of 7.01 (5.6) to 8.6 (5.1) and from 11.2 (8.6) to 7.0 (5.8), respectively. The mean (SD) European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLC-30) scores before and after hemisalvage HIFU were 35.7 (8.6) versus 36.8 (8.6). These data seem to again indicate feasibility and early encouraging and acceptable outcomes from a focal salvage strategy (Baco et al, 2014).

With up to one third of men who undergo curative radiation therapy for localized prostate cancer demonstrating biochemical failure within 5 to 8 years, there is a clinical need to find local curative salvage therapies. The irradiated pelvis, resulting in increased treatment toxicity, compromises salvage treatment. Although radical prostatectomy has a good oncologic outcome, it is not often performed owing to the high technical skill required to avoid significant complications, which often occur regardless of surgical skill. Whole-gland salvage ablative therapies have improved, resulting in decreased complication rates; however, their long-term oncologic outcome is still not available, and substantial side effects can still occur.

Through improved methods of detection, including frequent PSA measurements, mpMRI, and targeted image-guided prostate biopsy, as well as novel imaging that may improve the detection of micrometastatic cancer, those with radiorecurrent disease could be better identified. With improvements in localization of disease and the need for decreased toxicity and the avoidance of hormones, focal salvage ablative treatments may have a role. **Focal salvage treatment may provide a potential cure if patients are referred at an early stage when recurrence is suspected.**

At present there are few studies (and those lack robust data), although early signs are that toxicity may be significantly lower than with whole-gland salvage approaches. There is an urgent need for further large, prospective studies involving targeted focal ablative treatments to robustly evaluate harms and benefits of whole-gland and focal salvage therapy with medium- and long-term outcomes.

CONCLUSION

The therapeutic dilemma for men faced with a diagnosis of localized prostate cancer is a difficult one. It is not helped by the inherent inaccuracies of our current diagnostic pathway in which transrectal biopsies are used as the verification test. Tissue-preserving therapy relies on the accurate diagnosis, characterization, and localization of disease within the prostate so that therapy can be targeted to the cancer—something we do all the time with other tumors. Early series have shown that toxicity is very much lower. However, there is still much to determine. Reproducibility and longevity of cancer control are important for both physician and patient confidence. Indeed, with very little in the way of survival advantage for radical therapies versus surveillance in the long term, reproducibility across centers with acceptable disease control rates in the medium term may well be the level of evidence required to change practice.

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The complete reference list is available online at www.expertconsult.com.

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118 Treatment of Locally Advanced Prostate Cancer

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Definition

Trends in Incidence and Treatment

Natural History

Radical Prostatectomy

Radiation Therapy

Focal Ablative Therapy

Androgen Deprivation and Its Timing

Management of Delayed Sequelae

Clinical Trials

The widespread application of prostate cancer early-detection efforts in the United States has resulted in both an increased number of prostate cancers diagnosed and the earlier identification of these tumors. Despite the stage migration associated with prostate-specific antigen (PSA) testing and the growing number of low-stage and organ-confined tumors, at least 10% of men with newly diagnosed prostate cancer have locally advanced disease (T3NX/+M0). Although this proportion has declined somewhat, it remains significant and has been relatively constant during the past decade. Those men with locally advanced or metastatic prostate cancer at the time of presentation contribute disproportionately to prostate cancer mortality, and improved treatments for such men could have a significant positive impact on overall morbidity and mortality caused by this disease.

Currently, no consensus exists regarding the optimal management of locally advanced prostate cancer. Unlike with clinically localized and low-grade prostate cancer, for which comparable and excellent outcomes may be achieved with a variety of interventions, treatment of disease with local or regional spread by any single modality is associated with significant risk of recurrent disease. Ongoing interest in and the development and evaluation of combination therapy, as well as improvements in risk assessment, should improve cancer outcomes while minimizing treatment-related morbidity and adverse impact on quality of life in these patients. Two analyses suggest that men with higher-risk disease characteristics may have reductions in cancer-specific mortality and metastatic progression after radical prostatectomy compared with other treatment modalities (Cooperberg et al, 2010; Zelefsky et al, 2010).

DEFINITION

Traditionally, the identification of patients with locally advanced disease was based on clinical examination (e.g., digital rectal examination) and clear evidence of spread outside of the prostate capsule (clinical stage T3a), involvement of the seminal vesicles (cT3b), or involvement of adjacent organs (cT4) (Greene et al, 2002). However, the contemporary use of PSA testing has led to the majority of men diagnosed with prostate cancer initially having nonpalpable cancers (cT1c). **Features other than clinical T stage most often contribute to the identification of men with advanced disease and a concomitant increased risk of failure after primary therapy.** Thus improved methods of risk assessment have facilitated categorization

of men as “high risk” and involve consideration of variables such as serum PSA level and Gleason score in addition to clinical stage. The subsequent discussion focuses on this broader definition of locally advanced disease, with inclusion of those patients with regional or lymph node involvement without distant metastasis (T3-4N±M0).

Contemporary Risk Assessment

Multiple methods are currently available to accurately risk stratify men with prostate cancer (Partin et al, 1997; D’Amico et al, 1999; Tewari et al, 2001; Shariat et al, 2008). The Partin tables were initially constructed in the 1990s and updated in 2001 and 2013, assisting in the preoperative prediction of final pathologic stage in men with clinically localized prostate cancer undergoing radical prostatectomy (Partin et al, 2001; Eifler et al, 2013). Although clinical stage, serum PSA level, and Gleason score individually predict pathologic stage and prognosis, the combination of these three variables increases the accuracy of this assessment. These data continue to illustrate that a significant number of men thought to harbor organ-confined tumors have more advanced disease. The ability to assess pathologic stage permits better pretreatment counseling of patients and more appropriate selection of therapy and consideration of those with more advanced disease for novel clinical trials. **The most important pathologic criteria predicting prognosis after radical prostatectomy are Gleason score, surgical margin status, and presence of non-organ-confined disease (e.g., extracapsular extension, seminal vesicle invasion, lymph node involvement).**

In addition, to help predict pathologic stage, biopsy information has been incorporated into models estimating cancer outcomes, primarily PSA- or biochemical-free survival, after treatment. Whereas biochemical-free survival is a frequent end point of current prostate cancer studies, it merely represents an intermediate surrogate outcome variable; further trials and studies are necessary to confirm the utility of biochemical recurrence as a marker for reduced prostate cancer-specific survival after treatment. The most widely used tools to predict disease recurrence after local therapy are the nomograms developed by Kattan and colleagues (1998, 2000). In all pretreatment nomograms, clinical stage, biopsy Gleason grade, and pretreatment serum PSA level are incorporated to predict the continuous risk of disease progression after definitive local therapy; models for radiation therapy (RT) also include data on use of androgen deprivation (AD), total radiation dose, and combination

treatment (i.e., external beam and permanent brachytherapy). The radical prostatectomy nomogram was based on nearly 1000 patients with clinically localized disease (T1c-T3aNXM0); thus this model is not applicable for those men with evidence of seminal vesicle involvement or regional spread.

KEY POINTS: RISK ASSESSMENT

- Risk assessment is best performed by a combination of serum PSA level, T stage, cancer grade, and extent of cancer on biopsy.
- Imaging plays a limited role in identifying most patients with high-risk features for whom local therapy may fail.

To simplify risk stratification, men with prostate cancer can be grouped into fewer categories but with maintenance of ability to predict disease behavior and response to intervention. D'Amico and colleagues (1998) defined patients at low, intermediate, and high risk for biochemical failure, still based on pretreatment disease characteristics (clinical stage, PSA value, Gleason score). Recurrence after treatment may be due to unrecognized micrometastatic disease or persistence of locoregional disease. Other variations of simplified risk stratification have been developed and validated, with inclusion of features such as ethnicity and pathologic findings (Moul et al, 2001; Cooperberg et al, 2005). The Cancer of the Prostate Risk Assessment score, ranging from 0 to 10, provides another method to assess risk, with each 2-point increase in score doubling the risk of recurrence after prostatectomy. Although men with "low-risk" disease generally do well and are unlikely to have biochemical recurrence, men in the intermediate- and high-risk groups may have widely discrepant outcomes. Therefore men in these groups benefit from more modern and accurate risk prediction models and nomograms (Mitchell et al, 2005).

Imaging Modalities

Although observations on traditional gray-scale ultrasonography can identify extraprostatic disease, the general ability to improve cancer staging is limited (Figs. 118-1 and 118-2). Directed biopsy of the seminal vesicles or prostate capsule can be obtained to confirm cT3 disease. Smith and colleagues (1997) found that transrectal ultrasonography did not improve the ability to stage prostate cancer; the area under the curve was .69 and .74 for transrectal ultrasonography in predicting extracapsular extension and seminal vesicle invasion, respectively, compared with .72 and .69 for digital rectal examination, respectively. Salo and colleagues (1987) reported high sensitivity (86%), specificity (94%), positive predictive value (92%), and negative predictive value (89%) of ultrasonography in predicting extracapsular extension in patients undergoing radical prostatectomy. However, more contemporary studies suggest otherwise, with lower sensitivities (23% to 66%), specificities (46% to 86%), positive predictive values (50% to 62%), and negative predictive values (49% to 69%). The inaccuracy of ultrasound staging for prostate cancer is likely to be the result of significant interobserver variability, often subtle signs of extraprostatic spread, and lower-volume tumors currently diagnosed. In general, transrectal ultrasonography understages rather than over-stages prostate cancer. Newer ultrasound techniques such as color and power Doppler studies are under investigation to determine if observations of abnormal blood flow can increase the ability to detect and stage prostate tumors.

Endorectal magnetic resonance imaging (MRI) uses a magnetic coil placed in the rectum to achieve better visualization of the zonal anatomy of the prostate and may delineate subtle distinctions between T2a/b disease and T3 disease (Fig. 118-3). However, use of MRI alone or in combination with magnetic resonance spectroscopy for tumor staging remains controversial. Variable sensitivities (13% to 91%) and specificities (49% to 97%) have been reported

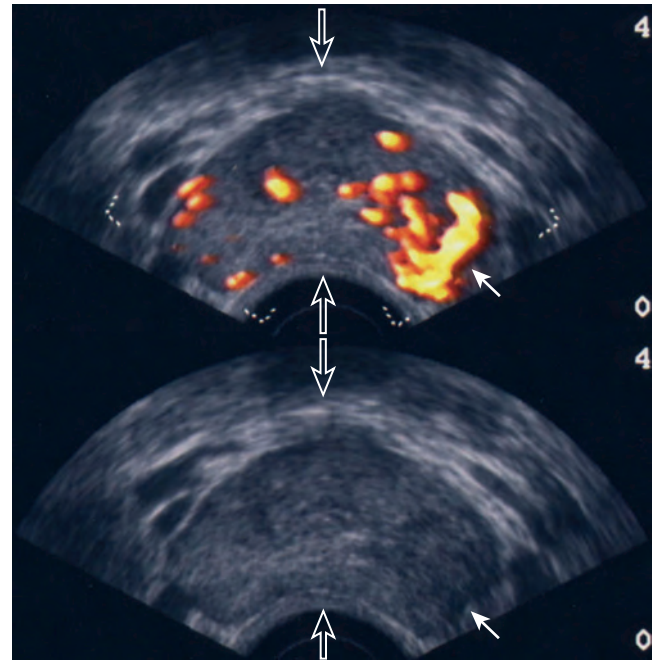


Figure 118-1. Transrectal ultrasound examination demonstrates increased flow on color Doppler study at the left posterior (*upper panel, arrow*) with corresponding hypoechoic area on gray-scale images (*lower panel, arrow*). Note the left lateral distortion and squaring of the capsule, suggesting extracapsular extension. (Courtesy Dr. Katsuto Shinohara.)

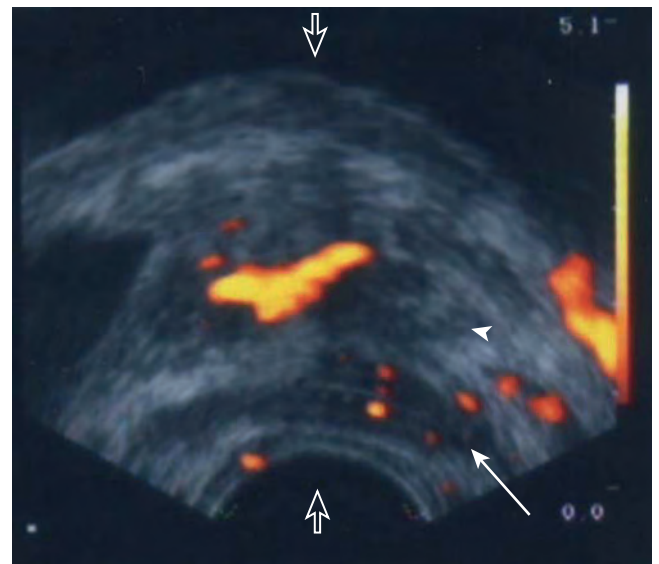


Figure 118-2. Transrectal ultrasound examination demonstrates hypoechoic tumor in the left base (*arrowhead*) with likely extension into the ipsilateral seminal vesicle (*arrow*). (Courtesy Dr. Katsuto Shinohara.)

for predicting extracapsular extension, in part attributed to variability in interpreting MRI and lack of uniform diagnostic criteria. In a cohort of 336 men with more than three cores involved with cancer, abnormal findings on digital rectal examination, and PSA level higher than 10 ng/mL undergoing radical prostatectomy, the specificity of MRI in predicting pT3 disease was 95% (Cornud et al, 2002). Thus the use of MRI may be best limited to those patients with higher-risk features.

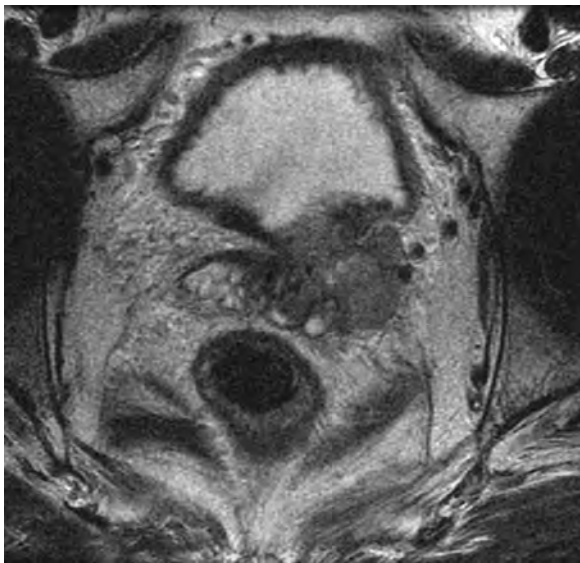


Figure 118-3. Axial T2-weighted magnetic resonance image shows tumor involving the seminal vesicle and bladder base and extending into the adjacent fat.

TABLE 118-1 Chromosome Abnormalities Associated with Pathologic Stage

CHROMOSOME ABERRATION (INDEPENDENT OR IN COMBINATION)	P VALUE
–8p	.001
–8p/–10q23 → qter	.002
–10q25 → qter	.029
–6p21	.031
–6q24 → qter	.031
–18cen-q12	.035
–5q31/–10q24 → qter	.04
–5q31 → qter/–8p	.04
–6p21/–10q24 → qter	.04
–6p12 → pter/–6q24 → qter	.04
–6q25 → qter/–11q23 → qter	.04
+7p11/–10q24 → qter	.04
–8p/–15q22	.04
–8p/–11q24 → qter	.42

Novel Markers

It is clear that traditional clinical and pathologic parameters are limited in their ability to accurately predict local extent of tumor before treatment. Given the importance of assessing true pathologic stage, novel markers of advanced disease are necessary. [Chu and colleagues \(2003\)](#) used comparative genomic hybridization in primary prostate specimens and identified chromosomal regions potentially useful in discriminating between organ-confined and locally advanced tumors ([Table 118-1](#)). Prediction of stage by a model incorporating six aberrations in a stepwise fashion was accurate in 91.1% of cases. Further metabolic, genetic, and proteomic signatures will likely better define and discriminate between organ-confined and non-organ-confined prostate cancer ([Ashida et al, 2004](#); [Paris et al, 2004](#); [Mehra et al, 2007](#); [Sreekumar et al, 2009](#)). Chromosomal rearrangements involving the androgen-regulated gene *TMPRSS2* and the ETS family genes are associated with higher pathologic stage, whereas the glycine metabolite sarcosine was more often elevated in metabolomic profiles of men with metastatic prostate cancer.

TRENDS IN INCIDENCE AND TREATMENT

Within the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE), [Cooperberg and colleagues \(2003\)](#) observed a significant decrease in the fraction of men presenting with high-risk disease characteristics, as defined by D’Amico criteria, from 40.9% in 1989-1990 to 14.8% in 2001-2002. However, alterations in cancer screening and use of PSA screening are likely to account for this reduction, with significantly fewer men presenting with elevations in PSA level higher than 20 ng/mL (32.8% to 7.2%); indeed, currently, higher Gleason grade defines a larger number of high-risk patients (61.5%). Overall, the presence of clinically advanced disease (i.e., T3-4) decreased from 11.8% to 3.5%, with a decline from 32.3% to 21.9% in the high risk group during the observation period. Similar findings were reported from Johns Hopkins, with 69% of men classified as high risk solely by Gleason score in the contemporary cohort (2001-2010) compared with 29% in the earlier cohort (1992-2000) ([Pierorazio et al, 2012](#)). Outcomes over time, however, were comparable with respect to PSA outcomes as well as metastasis-free and cancer-specific survival.

In men undergoing radical prostatectomy, the number with clinical evidence of locally advanced disease as defined by clinical stage (T3) has declined from 25.3% in 1987 to 2.8% in 2001 ([Ward and Zincke, 2003](#)). Although the use of PSA screening can account for part of this change, the more selective application of surgery and improved techniques of RT may also explain the decline in patients with cT3 disease undergoing prostatectomy. Within reports of men undergoing radical prostatectomy, the fraction of men with pT3 disease has decreased; these are highly selected patients with largely clinically localized disease at the time of treatment ([Table 118-2](#)). [Roehl and colleagues \(2004\)](#) reported that pathologically advanced disease decreased from 39% (1983-1991) to 31% (1992-2003). In men undergoing radical prostatectomy alone at the Cleveland Clinic, the overall rate of extracapsular extension declined from 65.8% (1987-1989) to 25.2% (2000-2001), and this trend was true for all clinical stages of tumor (T1c-T2b/c) as well as for pretreatment variables (PSA value, Gleason score).

KEY POINTS: TRENDS IN INCIDENCE AND TREATMENT

- Fewer men are presenting with locally advanced prostate cancer.
- There has been an increase in organ-confined cancers identified after radical prostatectomy.
- There is an increasing use of treatment modalities other than surgery for high-risk prostate cancers.

The [National Comprehensive Cancer Network \(2013, 2014\)](#) provided updated decision trees for men with prostate cancer to aid in treatment selection. High risk of recurrence includes men with clinically advanced disease, both cT3a and cT3b-T4. Bone scans are indicated in these men, as well as in those with PSA level greater than 20 ng/mL or Gleason score 8 or higher; pelvic computed tomography or MRI is also indicated for cT3-T4 disease or if the calculated probability of lymph node involvement is greater than 10%. In general, radical prostatectomy with extended pelvic lymphadenectomy is reserved for those high-risk men with low-volume tumors that can be completely excised. The alternative treatment strategy for these men with locally advanced disease and higher risk of biochemical failure is AD therapy combined with RT. The shift in treatment is also reflected within the CaPSURE database ([Meng et al, 2005](#)). A total of 6074 men with prostate cancer (clinical stage lower than T3aN0M0) were stratified according to risk group, of whom 26% were high risk. Fewer men in this group underwent radical prostatectomy compared with the low-risk cohort, with older age, advanced disease, and increased number of comorbidities significant predictors of treatment (external beam radiation or

TABLE 118-2 Pathologic Findings in Men Undergoing Radical Prostatectomy

AUTHOR (yr)	NO. PATIENTS	ERA	ECE	SEMINAL VESICLE/LYMPH NODE
Stamey et al (1998)	896	1988 1996	60% 25%	18%/NR 5%/NR
Quinn et al (2001)	732	1986-1999	42.8%	13.1%/2.3%
Hull et al (2002)	1000	1993-1998	25%	8.1%/6.9%
Han et al (2003)	2091	1982-1999	41%	4%/5%
Derweesh et al (2004)	1505	1987-1998 2000-2001	66% 25%	NR NR
Roehl et al (2004)	3478	1983-1991 1992-2003	25% 27%	14% (combined) 4% (combined)
Bott et al (2005)	1001	1988-2001	47%	10%/2%
Badani et al (2007)	2766	2000-2006	16.9%	5.1%/9%
Patel et al (2008)	1500	NR	13.8%	5.7%/NR
UCSF	2349	1986-2009	16%	11%/3%

ECE, extracapsular extension; NR, not reported; UCSF, University of California, San Francisco.

AD therapy) in multivariate modeling. In addition, more than half of high-risk men receiving radiation therapy also received AD, significantly more than in the low- and intermediate-risk groups ($P < .0001$). Data from the Surveillance, Epidemiology, and End Results cancer registry between 1998 and 2005 show that nearly half of men with cT3-4M0 prostate cancer receive a combination of AD and RT, while the rate of prostatectomy increased but was only 10% in 2005 (Lowrance et al, 2012).

NATURAL HISTORY

Active surveillance, with deferred treatment when necessary, is becoming a viable treatment alternative in men with prostate cancer. Multiple studies have suggested that cancer-specific mortality is low and primarily associated with higher-grade and higher-stage disease. Even in those low-risk cancers, however, an increased and unexpected progression of disease and associated prostate cancer mortality may be seen during an extended period (Johansson et al, 2004). In men with higher-risk disease characteristics, it has been recognized that disease progression occurs more rapidly and that some form of intervention is typically warranted in healthy patients. Nevertheless, the indications for active surveillance are expanding and appropriate selection may be facilitated by novel genomic tests (Cooperberg et al, 2011; Cary and Cooperberg, 2013).

Few reports address the specific question of outcome in men with locally advanced cancers merely observed for a prolonged period. Older studies such as that from Nesbit and Plumb (1946) have little relevance to current disease management. Other studies have included only a small number of patients with higher clinical stage. A range of clinical progression (22% to 75%), local progression (22% to 84%), and development of distant metastases (27% to 56%) has been reported during 5 and 10 years of follow-up. Overall survival ranging from 10% to 92% at 5 years and from 14% to 78% at 10 years is reported for patients who harbor cancers of high grade or stage. The Veterans Administration Cooperative Urological Research Group (VACURG) study reported a 58% overall 5-year survival in 248 men with clinical stage III disease treated with placebo (Byar, 1973). Comparable survival outcomes were reported within the Medical Research Council (MRC) study (Adib et al, 1997) randomizing previously untreated patients with locally advanced, nonmetastatic disease ($n = 501$) to early or delayed AD therapy (castration or luteinizing hormone-releasing hormone [LHRH] agonist). The median time to clinical progression and

death from prostate cancer in the 244 patients receiving delayed treatment was 10 months and 48 months, respectively.

In the analysis from Chodak and colleagues (1994), grade 3 tumors were significantly associated with disease-specific mortality (risk ratio 10.04) in men treated conservatively, compared with low-grade (grade 1) cancers. The 10-year disease-specific survival was 87% in men with grade 1 or grade 2 tumor and 34% with grade 3 tumor, with metastasis-free survival of 81% for grade 1, 58% for grade 2, and 25% for grade 3 diseases. Johansson and colleagues (1997) prospectively observed 642 men with prostate cancer diagnosed between 1977 and 1984 with any stage of disease. Of those men with clinically localized disease, 11% died of prostate cancer, with corrected 15-year survival comparable for those who received initial and deferred treatment. Conversely, the corrected 15-year survival was 57% in patients with locally advanced cancer. Approximately half of men had well-differentiated tumors, and only 6% of these men died of prostate cancer. Death from prostate cancer increased with moderately differentiated (17%) and poorly differentiated (56%) disease. These data are summarized in Table 118-3.

Albertsen and colleagues (1998) reported the long-term outcomes of watchful waiting in 767 men identified from the Connecticut Tumor Registry with clinically localized prostate cancer (1971-1984). The 15-year cancer-specific mortality in men with Gleason sum 6 was 18% to 30%, compared with the 25% to 59% risk of death from other causes. The chances of death from prostate cancer increased with Gleason score 7 (42% to 70%) and 8-10 (60% to 87%). It is likely that a significant proportion of this cohort had non-organ-confined disease because none of the men underwent PSA testing and therefore they probably had more advanced stages of disease compared with contemporary cohorts. In contrast to the report from Johansson and colleagues (2004), the annual mortality rate from low-grade prostate cancer appears to remain stable beyond 15 years after diagnosis (Albertsen et al, 2005) (Fig. 118-4). Men with high-risk prostate cancer, including those with locally advanced disease, are at significant risk of disease progression and cancer-specific death if left untreated.

RADICAL PROSTATECTOMY

The use of radical prostatectomy for management of locally advanced prostate cancer has decreased. In part, the shift in paradigm is due to the recognition that prostatectomy alone is often

TABLE 118-3 Conservative Management of Patients with Prostate Cancer

CLINICAL STAGE	NO. PATIENTS	PROGRESSION-FREE SURVIVAL		DISEASE-SPECIFIC SURVIVAL	
		%	95% CI (%)	%	95% CI (%)
T1-T2	300	48	37-59	81	74-88
T3-T4	183	47	33-61	57	45-68
M+	159	6	0.8-11	6	-0.1-12

CI, confidence interval.
From Johansson JE, Holmberg L, Johansson S, et al. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. JAMA 1997;277:467-71.

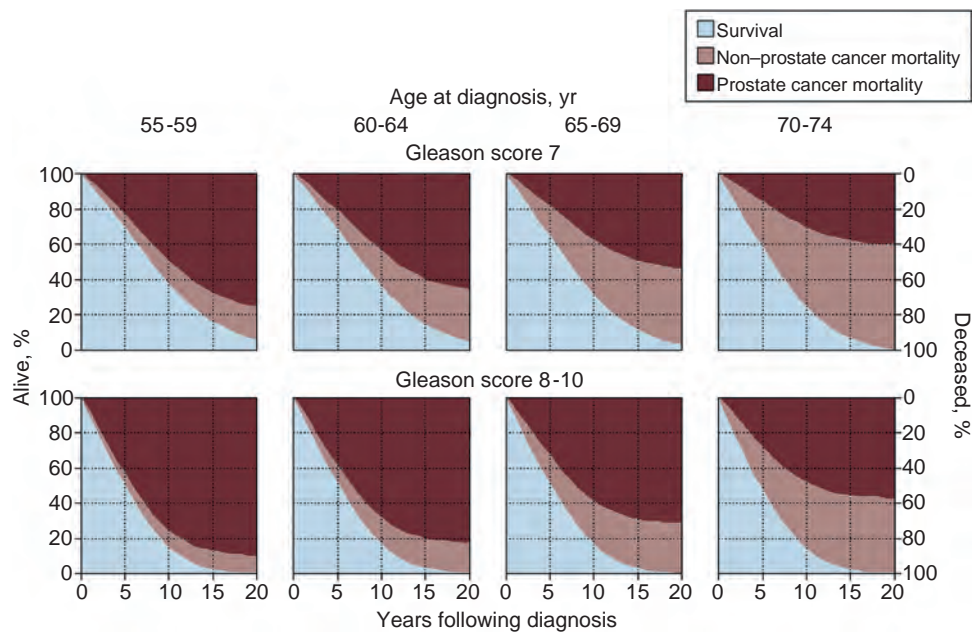


Figure 118-4. Prostate cancer mortality as a factor of Gleason grade and age at diagnosis in men managed conservatively. Brown-shaded areas represent proportion of patients dying of prostate cancer. Light brown-shaded areas represent death from competing causes. Light-blue areas represent proportion of patients alive. (Modified from Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095-101.)

insufficient. In addition, improved risk assessment has permitted better identification of these patients before treatment. Advances in delivery of RT and recognition that combined modality treatment (e.g., RT and AD) improved outcomes compared with monotherapy have further contributed to the migration away from surgery for high-risk and locally advanced tumors. Nevertheless, radical prostatectomy can cure some men with high-risk disease features, and the addition of adjuvant and combined therapy may further improve outcomes of surgery alone.

Surgery for Clinical Stage T3 Prostate Cancer

Several series report outcomes of radical prostatectomy for clinical stage T3 tumors (Table 118-4). In examining all reports, overall survival ranges from 64% to 96% at 5 years, 12.5% to 72% at 10 years, and 20% to 51% at 15 years after treatment. Earlier data reflected less accurate risk assessment and a potentially greater number of patients with unsuspected lymph node metastases and associated earlier progression and death. Less variability exists in more contemporary cohorts, in which the cancer-specific survival rates are 85% to 92% and 79% to 82% at 5 and 10 years, respectively, regardless of adjuvant therapy.

Pound and colleagues (1999) found that a reasonable outcome was possible after prostatectomy for clinical stage T3a disease, with a 52% 8-year recurrence-free survival. Similarly, Ward and Zincke (2003) reported 5- and 10-year cancer-free survival of 60% and 44%, respectively, without application of adjuvant AD. Freedom from local or systemic disease at 5 and 15 years after surgery was 73% and 67%, respectively (Ward et al, 2005). In the 812 patients from the series of Lerner and colleagues (1995), 10-year cancer-specific survival was 80%, with only 31% of men with clinical stage T3 disease dying of prostate cancer 15 years after radical prostatectomy. It is unclear, however, whether surgical intervention improves survival compared with alternative treatment strategies. Another interesting observation from the Mayo Clinic was that clinical over-staging was identified in 27% of patients, consistent with other reported rates of 7% to 26%, suggesting that uniformly excluding patients from prostatectomy on the basis of clinical staging may not be appropriate (Ward et al, 2005). The long-term update from this series demonstrated local recurrence-free, systemic progression-free, and cancer-specific survival of 76%, 72%, and 81%, respectively, at 20 years (Mitchell et al, 2012). Gerber and colleagues (1997) reviewed results in 298 men with clinical stage T3 disease undergoing radical prostatectomy and pelvic lymphadenectomy. Although

TABLE 118-4 Radical Prostatectomy for Higher Clinical Stage in Contemporary Series

AUTHOR (yr)	NO. PATIENTS	ADJUVANT TREATMENT	OVERALL SURVIVAL		CANCER-SPECIFIC SURVIVAL	
			5 Yr	10 Yr (15 Yr)	5 Yr	10 Yr (15 Yr)
Morgan et al (1991)	232	54%	85%	72%	89%	82%
van den Ouden et al (1994)	59	—	83%	—	90%	—
Lerner et al (1995)	812	60%	86%	70%	90%	80%
Gerber et al (1997)	242	NR	—	—	88%	70%
van den Ouden et al (1998)	83	0%	75%	60%	85%	72%
Pound et al (1999)*	55	0%	—	—	60%†	49%†
Ward et al (2005)	842	62%	90%	76% (53%)	95%	90% (79%)
Carver et al (2006)	176	36%‡	88%	75% (69%)	94%	85% (76%)
Loeb et al (2007)	288	15%	91%§	74%	92%§	88%
Freedland et al (2007)	56	0%	—	—	98%	91% (84%)
Xylinas et al (2009)	100	25%	85%	—	90%	—

*Updated data from Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am* 2001;28:555–65.

†Biochemical-free survival (PSA <0.2 ng/mL); 15-year actuarial metastasis-free survival of 82% in entire cohort.

‡Neoadjuvant therapy.

§Seven-year figures.

the overall 10-year cancer-specific survival was 57%, an apparent benefit of radical prostatectomy in some men with locally advanced disease was suggested by the increased survival (70%) in those who actually underwent prostatectomy and lymph node dissection. In a high-risk cohort undergoing surgery between 1987 and 2009, 37% had specimen-confined disease (pT2–pT3a) and a nomogram was developed incorporating PSA level, age, clinical stage, and biopsy Gleason sum to predict this with 72% accuracy (Briganti et al, 2012). Many men with clinical stage T3 disease have regional spread and may not benefit from prostatectomy; however, select patients (e.g., lower-volume disease) may benefit because local control may be achieved in most, and complete cancer excision is possible in some men.

Biochemical progression after radical prostatectomy is difficult to assess, given the frequent use of adjuvant therapy (e.g., RT or AD). Without the use of secondary treatment, 5-year biochemical relapse is higher than 60% (van den Ouden et al, 1998). In other series with variable use of adjuvant therapy, 5- and 10-year biochemical progression was observed in 42% to 49% and 59% to 62%, respectively. The impact of adjuvant therapy may be minimal with respect to clinical progression (i.e., biopsy-proven local recurrence or objective distant metastasis) after radical prostatectomy. Rates of clinical progression at 5, 10, and 15 years are 12% to 45%, 39% to 49%, and 50% to 71%, respectively.

Outcomes of Prostatectomy for Pathologically Advanced Disease

A significant minority of patients undergoing radical prostatectomy for clinically organ-confined disease will ultimately be found to have *pathologic* evidence of spread outside the prostate. Although these patients may be expected to have progression and survival rates comparable with those of patients with clinically advanced disease, as defined by grade and serum PSA level, those men who present with clinical stage T3 disease are likely to have greater tumor volume, higher grade, and increased likelihood of regional spread. Currently, the majority of men undergoing prostatectomy for pathologically advanced disease are categorized as high risk on the basis of serum PSA value or biopsy Gleason score. Nevertheless, there is overlap in the groups of men undergoing radical prostatectomy for *clinical* stage T3 and *pathologic* stage T3.

As discussed, pathologic stage after radical prostatectomy provides important prognostic information and is a powerful predictor

of outcome, considering all clinical and pathologic factors (Fig. 118-5). The presence of focal and established extracapsular extension increases the rate of clinical progression from 7% for organ-confined disease to 18% and 35%, respectively, at 5 years. Patients with evidence of seminal vesicle invasion or lymph node metastasis are highly likely to develop clinical progression (86% and 95%, respectively) after radical prostatectomy. In men undergoing radical prostatectomy for clinically organ-confined disease, Hull and colleagues (2002) reported 5-year PSA-free survival of 95%, 76%, 37%, and 18% for men with pathologic organ-confined disease, extracapsular extension, seminal vesicle invasion, and positive lymph nodes, respectively. In multivariate analysis, pathologic parameters increasing the relative risk (RR) for progression included extracapsular extension (RR 2.17 to 2.72), seminal vesicle involvement (RR 2.61), and lymph node involvement (RR 3.31). The presence of a positive surgical margin was associated with the greatest RR (4.37, range 2.90 to 6.58). This reinforces the concept that complete surgical removal of all prostatic tissue, regardless of clinical or pathologic stage, should be accomplished when prostatectomy is undertaken. Even with seminal vesicle invasion, however, men without concomitant lymph node involvement can achieve 15-year cancer-specific survival and biochemical relapse-free rates of 81% and 32%, respectively (Secin et al, 2006).

Biochemical progression after prostatectomy for pathologically advanced tumors depends on the definition applied. Five-year rates of biochemical recurrence have been as high as 65% to 72% when a PSA threshold of 0.2 ng/mL is used; less stringent thresholds such as 0.4 ng/mL may yield recurrence rates of 26% at 5 years and at least 50% at 10 years. In a cohort of 747 men with pT3bN0 tumors identified after prostatectomy, the 10-year biochemical recurrence-free, metastasis-free, and cancer-specific survival rates were approximately 25%, 70%, and 80%, respectively (Pierorazio et al, 2011). Seminal vesicle involvement not only increases the risk of biochemical recurrence but also significantly increases the risk of local recurrence after radical prostatectomy. With prolonged follow-up, Hawkins and colleagues (1995) reported local recurrence in nearly half of patients. This risk appears to be lower in contemporary series of patients because of improved selection of patients for surgery, improved surgical technique, and earlier use of secondary treatment either as adjuvant therapy or at the time of biochemical relapse. The minimally invasive approach has been increasingly applied in higher risk cases, and overall the outcomes appear reasonable and comparable to the open approach. Both oncologic and functional outcomes have not been reported to be significantly different,

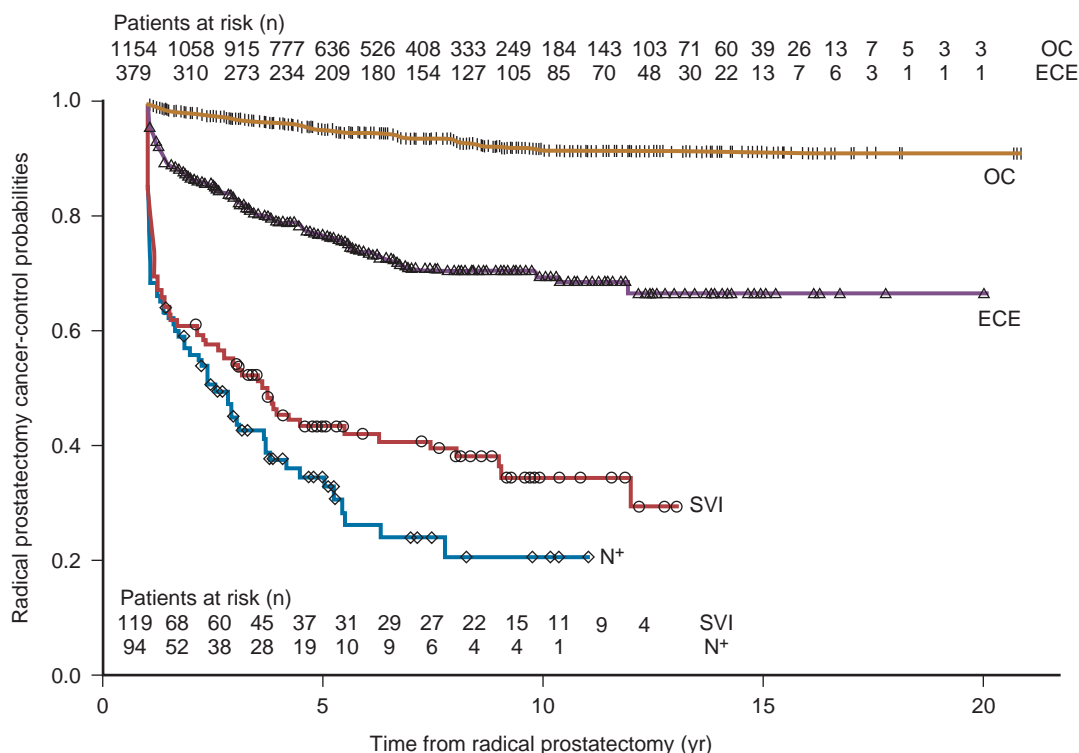


Figure 118-5. Probabilities of cancer control after radical prostatectomy based on pathologic stage. ECE, extracapsular extension; N⁺, node positive; OC, organ confined; SVI, seminal vesicle invasion. (Modified from Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ["trifecta"]. *Urology* 2005;66:83–94.)

although variability in performing and the extent of pelvic lymphadenectomy require further study (Pierorazio et al, 2013; Punnen et al, 2013).

Predictive models have permitted preoperative estimation of PSA-free survival after prostatectomy. Patients with higher biopsy Gleason score and more elevated serum PSA level are at increased risk of failure after surgery. **Overall, the actuarial PSA-free survival after surgery in high-risk men is approximately 50% at 5 to 7 years.** The validity of the Kattan preoperative nomogram was examined in a community-based cohort of patients undergoing radical prostatectomy (Greene et al, 2004). Interestingly, although the overall concordance index (.68) supported the applicability of the tool to a broad spectrum of patients, the nomogram underestimated recurrence in lower-risk men and overestimated recurrence in men at higher calculated risk. Indeed, up to half of men with Gleason sum 8-10 or higher PSA level (>20 ng/mL) may achieve prolonged disease-free survival with prostatectomy alone. Further refinements of risk assessment and novel markers will help determine which high-risk men and locally advanced tumors truly benefit from aggressive surgical intervention, either alone or in combination with other therapy.

Neoadjuvant Androgen Deprivation

To improve outcomes of radical prostatectomy in men with locally advanced or high-risk tumors, several investigators have assessed the use of neoadjuvant AD (NAD) before radical prostatectomy. In 1944 Vallet reported performing radical perineal prostatectomy after orchiectomy in a 59-year-old man with prostate cancer. Others reported the use and efficacy of diethylstilbestrol (DES) before surgery. In 1964 Scott evaluated the results of NAD in 31 men who were observed for 10 years. The majority of patients (52%) were alive and free of clinical recurrence. The prospective randomized trials of NAD in patients with stage cT1-T3 prostate cancer before radical prostatectomy are summarized in Table 118-5.

KEY POINTS: RADICAL PROSTATECTOMY

- Radical prostatectomy alone can result in cancer-free survival in at least half of men at 8 to 10 years despite clinically advanced disease.
- The risk of cancer recurrence after surgery can be quantitated on the basis of pathologic stage, cancer grade, and surgical margin status.
- Neoadjuvant androgen deprivation therapy before radical prostatectomy does not appear to improve cancer-specific or overall survival.

Various measures of outcome have been evaluated in these studies, including changes in digital rectal examination (clinical stage), appearance of tumor on imaging, detection of micrometastatic or circulating cancer cells, and pathologic features such as T stage, surgical margin and lymph node status, and histopathologic changes. Ultimately, the utility of NAD must be assessed by its impact on disease-specific survival or its current surrogate, biochemical-free survival. It is clear that NAD affects tumor behavior and biology, evaluable by changes in metabolic patterns of atrophy on magnetic resonance spectroscopy, lowering of serum PSA level, and histologic atrophy (fibrosis, vacuolization, glandular collapse). Studies have demonstrated that significant reductions in prostate volume (30% to 50%), tumor volume, and PSA level (90%) are consistently noted, with maximal effects occurring during the first 2 months of treatment. However, conflicting results have been reported with respect to pathologic downstaging after NAD in patients with clinical stage T3 cancer. **Overall, only 20% of such patients have organ-confined disease at the time of radical prostatectomy despite clinical downstaging in 32% to 90%.** Schulman and colleagues (2000) described 402 patients with cT2-T3N0M0 tumors randomized to either radical prostatectomy alone or 3

TABLE 118-5 Prospective Randomized Trials of Neoadjuvant Androgen Deprivation in Patients with Prostate Cancer (Stage cT1-T3) before Radical Prostatectomy

AUTHOR (yr)	LHRH AGONIST	ANTIANDROGEN	DURATION (mo)
Labrie et al (1997)	Leuprolide	Flutamide	3
Witjes et al (1997)*	Goserelin	Flutamide	3
Soloway et al (1995)†	Leuprolide	Flutamide	3
Hugosson et al (1996)‡	Triptorelin	Cyproterone	3
Dalkin et al (1996)	Goserelin		3
Goldenberg et al (1996)§		Cyproterone	3
Van Poppel et al (1995)		Estramustine	1.5

*Follow-up report: Schulman et al (2000).

†Follow-up report: Soloway et al (2002).

‡Follow-up report: Aus et al (1998).

§Follow-up report: Klotz et al (1999).

||Antimicrotubule agent derived from estradiol that also lowers serum testosterone levels.

LHRH, luteinizing hormone–releasing hormone.

TABLE 118-6 Pathologic Findings from Studies of Neoadjuvant Androgen Deprivation (NAD) in Patients with cT1-T3 Prostate Cancer before Radical Prostatectomy

AUTHOR (yr)	NO. PATIENTS	SEMINAL VESICLE		LYMPH NODE	
		CONTROL	NAD	CONTROL	NAD
Vailancourt et al (1996)	96	6%	0%	NR	NR
Soloway et al (1995)	282	22%	15%	5.8%	6.3%
Dalkin et al (1996)	56	14%	18%	NR	NR
Aus et al (1998)	122	14.5%	21.8%	16%	5.5%
Meyer et al (1999)	680	16%	17%	16%	14%
Klotz et al (1999)	213	14%	28%*	6.9%	3.3%
Schulman et al (2000)	402	23%	20%	23%	15%

* $P = .035$.

NR, not reported.

months of total androgen blockade followed by surgery. Pathologic downstaging was seen more frequently in the neoadjuvant group (15%) than in the prostatectomy-alone group (7%; $P < .01$); however, in men with cT3 disease, there was no difference in pathologic downstaging ($P = .18$) and the incidence of lymph node metastases ($P = .36$) in the neoadjuvant and surgery-alone cohorts. Thus whereas clinical downstaging may occur frequently, **pathologic downstaging is significantly less common after NAD, ranging between 8% and 31%.** Most studies do not show decreased seminal vesicle invasion (Table 118-6). Similarly, rates of lymph node metastases are not altered, with the incidence varying between 3.3% and 16% in both the prostatectomy-alone and NAD groups.

Klotz and colleagues (2003) provided long-term follow-up (median, 6 years) of a prospective randomized trial comparing 3 months of NAD before prostatectomy and surgery alone. There was no overall benefit of NAD as measured by biochemical recurrence (34% to 38%), although in the subgroup of men with PSA level above 20 ng/mL, those receiving NAD had greater PSA-free survival (53%) compared with those undergoing prostatectomy alone (35%, $P = .015$). Southwest Oncology Group (SWOG) 9109 was a phase II feasibility study of 16 weeks of goserelin and flutamide before radical prostatectomy in men with T3-T4N0M0 prostate cancer (Powell et al, 2002). Of the 55 patients who underwent prostatectomy, 31% had seminal vesicle invasion and 19% had lymph node metastasis. Organ-confined disease was identified in 67% of cases. At median follow-up of 6.1 years, 5-year progression-free and overall survival estimates were 70% and 90%, respectively. The study demonstrated the feasibility of 4 months of AD before surgery, with acceptable morbidity and outcomes comparable with RT for this population of patients. Extended follow-up at a median of 10.6

years revealed that only 55% had disease progression, with progression-free survival of 40% and overall survival of 68% (Berghlund et al, 2012).

Studies have also examined the incidence of positive surgical margins in those with cT3 disease. Witjes and colleagues (1997) reported similar rates of positive margins in men receiving NAD and those undergoing radical prostatectomy alone (43% and 59%, respectively; $P = .14$). Van Poppel and colleagues (1995) did not find a statistically significant difference between these groups with respect to positive margins—41.3% in the neoadjuvant cohort and 44% in the surgery-alone group. SWOG 9109 reported positive surgical margins in 30% of patients. In contrast, the randomized and nonrandomized studies of NAD in men with lower clinical stage (cT1-T2) clearly demonstrate a reduction in the rate of positive surgical margins. This advantage has not translated into improved long-term PSA-free survival. **For locally advanced tumors (specifically cT3), current data, both retrospective and prospective, do not support a significant benefit of NAD before surgery (Table 118-7).**

The apparent lack of benefit of NAD before radical prostatectomy in men with both lower-stage and locally advanced prostate cancer may be due to a number of factors. It has been suggested that 3 months of AD may be insufficient to cause an improvement in disease-free survival compared with prostatectomy alone. Meyer and colleagues (1999) followed 680 men treated with radical prostatectomy, of whom 292 received NAD. Although there was no difference in risk of biochemical recurrence between the two groups, patients receiving both an LHRH agonist and antiandrogen for more than 3 months had a significantly lower risk of PSA failure than did those treated with surgery alone (hazard ratio [HR] 0.52,

TABLE 118-7 Neoadjuvant Androgen Deprivation (NAD) Therapy for 3 Months before Radical Prostatectomy in Patients with Localized Prostate Cancer: Impact on PSA Recurrence after Surgery

AUTHOR (yr)	NO. OF PATIENTS	CONTROL	NAD	FOLLOW-UP (mo)
Fair et al (1997)	194	16%	11%	29
Aus et al (1998)	122	41%	35%	38
Meyer et al (1999)	680	30%	35%	38
Klotz et al (1999)	213	30%	40%	36
Schulman et al (2000)	398	32.5%	26.4%	48
Soloway et al (2002)	255	32%	35%	60

PSA, prostate-specific antigen.

TABLE 118-8 Trials of Chemotherapy, Hormonal Therapy, and Combined Chemotherapy–Hormonal Therapy before Radical Prostatectomy

	PETTAWAY ET AL (2000)	CLARK ET AL (2001)	KONETY ET AL (2004)	MAGI-GALLUZZI ET AL (2007)	CHI ET AL (2008)	NAD*
Number of patients	33	16	36	28	64	—
Clinical stage T3	55%	13%	75%	18%	39%	100%
Regimen	KAVE	E/VP-16	TEC	D	D	—
Androgen deprivation	3 mo	—	4–6 mo	—	6 mo	—
Organ confined	33%	31%	36%	18%	53%	21%
Positive margins	17%	44%	22%	25%	27%	37%
Positive lymph nodes	37%	13%	5.50%	14%	6%	21%
Seminal vesicle invasion	85%	—†	56%	39%	22%	39%
Undetectable preoperative PSA	50%	50%	45%	—	—‡	—
pT0	0%	0%	0%	0%	3%	0–4%

*Combined results of 23 trials of neoadjuvant hormonal therapy in cT3 disease.

†Grouped together with positive lymph nodes.

‡Median PSA 0.15 ng/mL (range 0.02 to 3.8).

D, docetaxel; E/VP-16, estramustine + etoposide; KAVE, ketoconazole + doxorubicin/vinblastine + estramustine; NAD, neoadjuvant androgen deprivation; PSA, prostate-specific antigen; TEC, paclitaxel + estramustine + carboplatin.

95% confidence interval [CI] 0.29 to 0.93). Subsequently, the Canadian Urologic Oncology Group (Gleave et al, 2001) randomized patients with clinically localized disease to either 3 or 8 months of NAD before radical prostatectomy. In the 500 patients with pathologic staging, positive surgical margins were identified in 23% of the 3-month group and 12% of the 8-month group ($P = .011$); organ-confined disease was found in 68% and 80% of the 3- and 8-month groups, respectively ($P = .0019$). In addition, the rate of non-specimen-confined disease or lymph node extension was greater in the 3-month group (25.6%) compared with the 8-month group (12.6%). However, despite evidence of continued biochemical and pathologic regression of the tumor between 3 and 8 months, no significant difference in PSA recurrence rates was observed at 4 years. Ongoing studies are evaluating the potential utility of other AD agents prior to surgery, including degarelix, abiraterone, and enzalutamide.

Neoadjuvant Chemotherapy and Chemotherapy–Hormonal Therapy

The role of chemotherapy in the treatment of prostate cancer has primarily been limited to men with the most advanced disease. Taxanes, alone or in combination with other agents, have proved effective in those with hormone-refractory prostate cancer, with significant PSA declines (>50%) in more than half of patients and measurable disease response in 28% to 75% (Oh, 2004). Mitoxantrone plus low-dose steroids has shown benefit in pain relief com-

pared with steroids alone and is approved for use in hormone-refractory disease (Tannock et al, 1996; Kantoff et al, 1999). On the basis of these observations, interest has increased in earlier use of chemotherapy in high-risk patients or those with locally advanced disease. These studies are summarized in Table 118-8.

Pettaway and colleagues (2000) treated 33 higher-risk patients with a 3-month combination regimen consisting of two 6-week cycles of ketoconazole and doxorubicin alternating with vinblastine and estramustine. In addition, concurrent AD was accomplished with an LHRH agonist and antiandrogen. Lower pathologic stage was found in 18% of patients with cT3 disease, and the overall positive surgical margin rate of only 17% suggests that the regimen may have improved the ability to resect the cancer above that achieved with NAD alone. A second report of chemotherapy and hormone therapy before surgery combined 4 to 6 months of NAD with paclitaxel, estramustine, and carboplatin in patients with androgen-dependent, high-risk prostate cancer (Konety et al, 2004). No patients were downstaged to pT0 after neoadjuvant therapy, and organ-confined disease was reported in 36%, with a 22% positive surgical margin rate. Overall, 45% remained without biochemical relapse, defined as PSA level above 0.05 ng/mL on three occasions, at median follow-up of 29 months, and no patient has had documented local recurrence. At 43 months of follow-up, Chi and colleagues (2008) reported a 3% complete pathologic response rate and distant relapse rate of 30% in patients treated with NAD and docetaxel.

Other centers have used chemotherapy without concurrent NAD. At the Cleveland Clinic, 16 patients with locally advanced

TABLE 118-9 Early Adjuvant Radiation Therapy for Locally Advanced Prostate Cancer (pT3N0M0)

AUTHOR (yr)	NO. OF PATIENTS	RADIATION DOSE (Gy)	PROGRESSION-FREE SURVIVAL	P VALUE	FOLLOW-UP (mo)
Morgan et al (1991)	33	—	64%	.02	11
	17	60-66	94%		
Stein et al (1992)	91	—	43%	.04	48
	24	55-60	75%		
Anscher et al (1995)	113	—	37%	.16	120
	46	55-65	55%		
Schild (1998)	228	—	40%	.0003	32
	60	57-68	90%		
Valicenti et al (1998a)	20	—	48%	.01	36
	15	64.8	85%		
Valicenti et al (1999)	36	—	55%	—	41
	36	59-70	88%		
Petrovich et al (1999)	40	—	69%	NS	60
	201	48	68%		
Eggerer et al (2005)	144	—	53%/37%*	.4/.9*	48
	58	NR	62%/38%*		
Thompson et al (2009)	211	—	61%†	.016	151
	214	60-64	71%†		

*Negative surgical margin/positive surgical margin.

†Metastasis-free survival at 10 years.

disease (clinical M0) underwent three cycles of oral estramustine and etoposide and subsequent surgery (Clark et al, 2001). Although grade 3 or grade 4 toxicity was seen in 34% of patients, surgery was not delayed in any individual and surgical outcomes were comparable with those in series of prostatectomy without neoadjuvant therapy. With a median follow-up of 14 months, 88% were free of disease and the early PSA failures occurred in the two patients with lymph node metastases.

Single-agent docetaxel is well tolerated before radical prostatectomy, with minimal toxicity (Oh et al, 2001; Dreicer et al, 2004). No cases of complete pathologic response were observed, but no lymph node metastases were identified in one series, whereas the other reported 11% with organ-confined disease. Two thirds and 24% of patients, respectively, experienced a more than 50% reduction in PSA level in response to docetaxel alone. Similar observations have been made using a novel nanoparticle-based formulation of paclitaxel, with no complete pathologic responses (Shepard et al, 2009). Combination therapy with mitoxantrone or estramustine has been reported in small numbers. Garzotto and colleagues (2010) treated 57 men with docetaxel and dose-escalated mitoxantrone during the 16 weeks prior to surgery. Half of patients were free of relapse at 5 years and the rate of positive surgical margins was 33%. Agents described in recent reports include granulocyte-macrophage colony-stimulating factor and thalidomide (Garcia et al, 2008), as well as the epidermal growth factor receptor inhibitor gefitinib (Vuky et al, 2009). It remains to be determined whether new, targeted agents (e.g., custirsen) and immunotherapy (e.g., sipuleucel-T, ipilimumab) will play a role in the neoadjuvant setting.

Adjuvant Radiation Therapy

Withholding regional or systemic therapy until after the prostate has been removed may (1) prevent delay in time to surgery, (2) reduce operative morbidity, and most importantly (3) identify those men with adverse pathologic features or evidence of residual disease who truly need additional therapy, thereby avoiding over-treatment in those found to have more favorable disease. The

selection of appropriate adjuvant therapy remains difficult because knowledge of the ultimate site of failure (discriminating local-regional from distant recurrence) determines the actual type, timing, and efficacy of such intervention.

Until recently, adjuvant RT was not clearly demonstrated to be beneficial after radical prostatectomy; older studies demonstrated no impact on development of distant metastasis or cancer-specific survival, and more recent data show improved biochemical control. Table 118-9 summarizes selected comparative series of adjuvant RT for pathologically advanced disease. In the matched pair analysis of Valicenti and colleagues (1999), early adjuvant RT was administered within 3 to 6 months of surgery with undetectable PSA; control subjects were observed until PSA recurrence. The reduction in risk of PSA relapse was 88% after adjuvant RT with 5-year PSA-free survival of 89%. Anscher and colleagues (1995) provided long-term follow-up (median, 10 years) in 46 patients receiving adjuvant RT after radical prostatectomy for pT3-T4 tumors. At 10 and 15 years, overall survival and disease-free survival in the RT group were 62% and 62% and 55% and 48%, respectively; these were not statistically different from the rates in the group not receiving adjuvant RT. In addition, development of distant metastases was comparable in the two cohorts. Nevertheless, local control was better after adjuvant RT (82% at 15 years) compared with surgery alone (53%).

The use of adjuvant RT is associated with a range of biochemical-free survival, from 50% to 88% at 5 years. This appears to be an improvement (30% to 50%) compared with the results of surgery alone in high-risk patients. Nevertheless, the benefit of adjuvant RT needed to be proven in appropriately designed clinical trials, of which the European Organisation for Research and Treatment of Cancer (EORTC) 22911 (Bolla et al, 2005) and SWOG 8794 (Thompson et al, 2006) have been reported. Both studies randomized patients with pathologically advanced disease, defined as extraprostatic extension (pT3) and/or positive surgical margins without lymph node metastasis, to either immediate RT or observation after surgery. In EORTC 22911, immediate RT was associated with improved biochemical relapse-free survival (74% vs. 53% without RT, $P < .001$) at 5 years. Similarly, SWOG 8794, with median 10.6 years of follow-up, supported immediate

RT with a nearly 50% reduction in biochemical recurrence (35% vs. 64% without RT; $P < .001$) in those with PSA less than 0.4 ng/mL after prostatectomy. In addition, adjuvant RT significantly reduced the risk of clinical local recurrence in both trials. SWOG 8794 demonstrated a surprisingly low risk of metastatic disease (16%) in patients with adverse pathologic features that was further reduced with adjuvant RT (7%) (Swanson et al, 2007), as well as improved freedom from subsequent AD. Moreover, both metastasis-free and overall survival were improved with adjuvant RT (HR 0.71 and 0.72, respectively) (Thompson et al, 2009). A third randomized, controlled trial studying adjuvant RT for pT3N0 tumors after prostatectomy achieving an undetectable PSA confirmed the benefit with respect to biochemical progression-free survival (HR 0.53) (Wiegel et al, 2009).

The decision to administer adjuvant RT is often based on various adverse pathologic features, not all of which carry the same prognosis; indeed, SWOG 8794 combined extracapsular extension, seminal vesicle invasion, and positive surgical margin within a single classification. Thus it is difficult to assess the outcomes of adjuvant RT when the populations are composed, variably, of those with positive surgical margins, extracapsular extension, seminal vesicle invasion, or a combination of these features. Those men with positive surgical margins are at an increased risk of biochemical recurrence. A decision analytical model examining this question demonstrated that the benefit may be limited to those with high likelihood of recurrent local, rather than distant, disease; thus initial RT was recommended for patients with low- to intermediate-grade disease without evidence of seminal vesicle invasion (Grossfeld et al, 2000). This report suggested that adjuvant RT should be considered in those patients with extensive or multiple positive surgical margins. Secondary analyses of EORTC 22911 also support the role of immediate RT in the specific subset with positive surgical margin (Van der Kwast et al, 2007). The treatment benefit of adjuvant RT was primarily seen in patients with positive surgical margins (HR 0.38, $P < .0001$), whereas no benefit was observed in those with negative margins independent of other risk factors. However, the report from Stephenson and colleagues (2004) suggests that the application of adjuvant RT in a broader group of men may be beneficial; 501 men received salvage RT for biochemical recurrence after radical prostatectomy, and 50% experienced disease progression after treatment at a median follow-up of 45 months. Although higher Gleason score and seminal vesicle invasion were poor prognostic variables in predicting response to salvage RT, selected patients with high-grade disease or other adverse features (e.g., rapid PSA doubling time) could still achieve a durable response. Indeed, more than half of patients with Gleason sum 8-10 and positive surgical margins had a PSA nadir of 0.1 ng/mL or less without subsequent rise above this level. **Thus early use of secondary therapy, be it RT or AD, may be beneficial in locally advanced tumors, as well as at the time of biochemical recurrence in select patients.** However, the optimal timing and how these interventions may differentially affect local control, development of distant disease, and survival remain to be determined. Trock and colleagues (2008) reported an improvement in overall survival in patients with pT3 disease receiving salvage RT, with 5-year overall survival of 98%.

In general, men with seminal vesicle invasion are at significant risk for distant metastasis and may not benefit from local or regional RT; nevertheless, some men with pT3b disease may have local recurrence alone. Valicenti and colleagues (1998b) identified a group of 53 men with pT3bN0 disease undergoing radical prostatectomy, with 35 achieving undetectable PSA after surgery. The biochemical-free survival (3 years) in the 15 patients receiving adjuvant RT was 86% compared with 48% in the 20 men who were observed ($P = .01$). In EORTC 22911, there was no statistically significant predictive impact of seminal vesicle invasion on the benefit from RT as measured by biochemical progression-free survival, regardless of whether PSA was less than or greater than 0.2 ng/mL after surgery (Van der Kwast et al, 2007). However, even with pT3b disease, there was a benefit of adjuvant RT in patients with positive surgical margins. Men in SWOG 8794 with seminal vesicle invasion

receiving RT had improved 10-year biochemical failure-free survival (36% vs. 12% for observation) but no significant improvement in metastasis-free and overall survival. Conversely, subgroup analysis of the ARO trial suggested that extracapsular extension without infiltration of the seminal vesicles was a predictor of better outcome with RT (Wiegel et al, 2014). **On the basis of limited data, it appears that men with seminal vesicle invasion who achieve a low PSA level (<0.3 ng/mL) after prostatectomy or have positive surgical margins may be a more favorable group in whom adjuvant RT may be considered.** Conversely, those men with more advanced disease never reaching an undetectable PSA level generally constitute a poor prognostic group likely harboring unrecognized lymph node or distant disease.

Traditionally, adjuvant RT has been delivered in lower doses compared with the dose for salvage therapy, with the range from 45 Gy to more than 60 Gy. Most contemporary series of adjuvant RT report doses greater than 60 Gy. Valicenti and colleagues (1998a) evaluated the dose response in a small number of patients ($n = 52$) receiving adjuvant RT for pT3N0 disease. The difference in 3-year biochemical-free survival between those treated with less than 61.2 Gy (64%) and more than 61.2 Gy (90%) was statistically significant ($P = .015$), suggesting that higher doses may be necessary. In 27 men with detectable PSA 6 months after prostatectomy, Schild and colleagues (1994) noted that RT doses of 64 Gy or more had improved 30-month freedom from failure (62%) compared with lower RT doses (17%; $P = .03$), supporting the hypothesis of a postoperative RT dose response similar to what has been observed for primary RT in prostate cancer.

KEY POINTS: ADJUVANT RADIATION THERAPY

- Adjuvant radiation therapy improves local control and reduces biochemical relapse in selected patients after radical prostatectomy and likely improves metastasis-free and overall survival.
- The benefit of adjuvant radiation therapy may be greatest in cases of positive surgical margins.
- Improved outcomes of adjuvant radiation therapy are associated with dose escalation (64 Gy).

Adjuvant Androgen Deprivation

Indirect evidence from the MRC and VACURG trials suggesting a benefit of early AD compared with delayed AD in men with various stages of prostate cancer served as the impetus for studying adjuvant AD after radical prostatectomy. In addition, evidence of a benefit of continued AD after therapeutic RT supports a potential role for combined systemic treatment after local therapy in the form of prostatectomy. However, limited clinical data are currently published on this issue in men with locally advanced tumors.

Beyer and colleagues (1993) retrospectively reviewed the outcomes of 86 patients undergoing radical prostatectomy and any form of adjuvant therapy (89% endocrine treatment). In the subset of patients with stage pT3N0 tumors, adjuvant treatment did not demonstrate an advantage with respect to time to progression or survival. Cheng and colleagues (1993) reviewed the Mayo Clinic experience with 1035 patients undergoing radical prostatectomy for pathologic stage C prostate cancer; a significant number ($n = 103$) received adjuvant AD with orchiectomy. Adjuvant therapy of any type (AD or RT) decreased the rate of progression but did not improve cancer-specific or overall survival, with no difference between the two modalities. Prayer-Galetti and colleagues (2000) presented data on 201 men with pT3 disease receiving adjuvant goserelin, demonstrating a 25.4% improvement in disease-free survival at median follow-up of 5 years ($P < .05$).

Recent publications provide some evidence supporting a benefit of early AD after radical prostatectomy in high-risk men with

locoregional disease spread. Zincke and colleagues (2001) retrospectively reviewed data on men with stage pT3b cancer and found that early, adjuvant AD positively affected time to progression and cancer-specific survival. These findings were true not only with seminal vesicle invasion but also with limited lymph node disease, with a 10-year cause-specific survival of 94% after prostatectomy and adjuvant AD with a single positive lymph node. Similar findings arose from the Eastern Cooperative Oncology Group study 7887 randomizing men with nodal metastases after radical prostatectomy (cT1-T2 disease) to immediate (adjuvant) or delayed AD (Messing et al, 1999). At a median follow-up of 11.9 years, men receiving adjuvant AD had improved overall (HR 1.84), cancer-specific (HR 4.09), and progression-free (HR 3.42) survival. A matched pair analysis of men with pT2-4N1 disease treated with prostatectomy suggested that adjuvant AD plus RT yielded significantly higher cancer-specific and overall survival rates at 10 years (86% and 74%, respectively) compared with adjuvant AD alone (70% and 55%, respectively) (Briganti et al, 2011).

RADIATION THERAPY

The contemporary trend is to treat high-risk or locally advanced prostate tumors with methods other than surgery. Although a plethora of studies describe the results of RT for clinical stage C and T3 disease, many were performed before the widespread use of serum PSA determinations for early detection and modern radiation techniques for treatment, such as three-dimensional conformal RT, intensity-modulated RT, and irradiation of the whole pelvis in addition to the prostate (Kupelian et al, 2003). In addition, contemporary data suggest that the optimal radiation dose is higher than that used in previous reports. In higher-risk patients, improved biochemical control has been observed with 81 Gy or more for external beam RT (Zelevsky et al, 2011). An earlier dose escalation trial demonstrated improved outcomes with 78 Gy compared with 70 Gy, with the greatest benefits in the high-risk group with PSA greater than 10 ng/mL (Kuban et al, 2008). In the treatment of men with locally advanced or high-risk prostate tumors, monotherapy with RT or permanent interstitial brachytherapy is likely to be inadequate. Yet it must be emphasized that the outcome measures with demonstrated benefit of AD plus RT compared with RT alone often do not include overall survival. The focus has shifted to improving outcomes by combining RT with AD, often in conjunction with whole-pelvis irradiation (Table 118-10).

Overall survival after RT alone for stage C cancer is approximately 60% to 70% at 5 years and below 50% at 10 years. In high-risk patients, defined by individual parameters alone or in combination, the 5-year progression-free survival rates after RT are typically less than 50%.

Neoadjuvant Androgen Deprivation and Radiation Therapy

The theoretical benefits of AD before RT in men with locally advanced cancers are the ability to reduce target volume and the potential cytotoxic synergy of radiation and hormone manipulation. Several Radiation Therapy Oncology Group (RTOG) trials (75-06, 83-07, 85-19) examined the combination of AD and RT in locally advanced disease, suggesting that the regimen was tolerable and improved local tumor control. On the basis of this information, RTOG 86-10 was designed to compare short-term AD combined with RT with RT alone (Pilepich et al, 2001; Roach et al, 2008). The phase III trial randomized 471 men with cT2-T4 tumors (surface area >25 cm² on rectal examination) to either goserelin plus flutamide for 2 months before and during external beam RT or RT alone. The 4 months of AD were associated with reduction in distant metastases and improvements in local control, disease-free survival, and cancer-specific mortality. At 10 years, the disease-free survival in the AD plus RT and RT-alone groups was 11% and 3%, respectively ($P < .0001$), whereas cancer-specific mortality was 23% and 36%, respectively ($P = .01$). No difference in overall survival between the two groups (43% AD plus RT vs. 34% RT) was found, although

men with lower Gleason sum (2-6) appeared to have a survival benefit from combined AD and RT. In men with Gleason sum 7-10, no significant improvement was observed from AD with respect to locoregional control or survival. Subsequent analysis of RTOG 86-10 (Chakravarti et al, 2003) revealed that loss of p16 expression on immunohistochemistry was associated with reduced overall survival ($P = .039$), disease-specific survival ($P = .006$), and higher risk of local progression ($P = .0007$) and distant metastasis ($P = .026$); overall survival was not significantly associated ($P = .07$) in multivariate analysis. Other correlative studies of tissue from RTOG 86-10 found that the proliferative marker Ki-67 was significantly associated with distant metastasis and cancer-specific survival but not with overall survival (Li et al, 2004).

Similar observations were made by Laverdière and colleagues (1997) in a prospective randomized study of 120 men with cT2b-T4 disease. Treatments included (1) external beam RT alone, (2) 3 months of NAD before RT, and (3) 3 months of NAD before RT and 6 months of adjuvant AD. Evidence of residual cancer on prostate biopsy was present in 62%, 30%, and 4% of the treatment arms, respectively, at 12 months and 65%, 28%, and 5% at 24 months. Biochemical-free survival at 12 and 24 months paralleled the biopsy data, with the difference between the neoadjuvant and adjuvant AD groups disappearing at 24 months. These observations not only supported neoadjuvant and concurrent AD with RT but also suggest a benefit of prolonged AD. In a group of men randomized to either 3 or 8 months of NAD before RT, of whom 31% were categorized as high risk, longer NAD did not improve freedom from or pattern of failure; the only benefit of 8 months of NAD was improved 5-year disease-free survival (71% vs. 42%) (Crook et al, 2009). Long-term outcomes (median 10.6 years) from the Trans-Tasman Radiation Oncology Group (TROG) 96.01 trial demonstrated that 6 months of neoadjuvant AD before RT at 66 Gy was associated with reduced PSA and local progression as well as event-free survival (HR 0.51) in men with cT2b-4N0M0 prostate cancer (Denham et al, 2011). While 3 months of neoadjuvant AD had no effect on distant progression or cancer-specific and all-cause mortality, 6 months of treatment decreased rates of all three compared with RT alone (HR 0.49, 0.49, and 0.63, respectively).

KEY POINTS: NEOADJUVANT ANDROGEN DEPRIVATION AND RADIATION THERAPY

- Neoadjuvant and concurrent androgen deprivation appears to be appropriate in high-risk patients undergoing radiation therapy.
- Adjuvant androgen deprivation after radiation therapy may benefit those with very high-risk disease.

Adjuvant Androgen Deprivation and Radiation Therapy

Several prospective studies have assessed the role of adjuvant AD after RT, as well as the appropriate duration of such therapy. RTOG 85-31 (Pilepich et al, 1997; Lawton et al, 2001) randomized 977 patients with T3NXM0 or T1-T2N+M0 prostate cancer to RT and either goserelin started during the last week of RT and continued indefinitely, or goserelin at the time of relapse (i.e., early or late AD). The groups were matched with respect to disease risk characteristics and fewer than 30% had lymph node involvement. Improved local control and biochemical disease-free and metastasis-free survival were noted in the adjuvant AD group at 8 years of follow-up, and this advantage was most prominent with Gleason sum 8-10. Overall survival was not statistically different at 5 years (75% vs. 72%) and 8 years (49% vs. 42%). In those patients with high-grade tumors, adjuvant AD improved cancer-specific (90% vs. 78%) and overall (80% vs. 69%) survival at 5 years.

In the EORTC 22863 study (Bolla et al, 1997), men undergoing external beam RT for clinically localized disease (cT1-T2 and grade

TABLE 118-10 Trials of Androgen Deprivation with External Beam Radiation Therapy

STUDY (AUTHOR, YEAR)	NO. PATIENTS	ELIGIBILITY	RT DOSE (Gy)	STUDY ARM	DISEASE-FREE SURVIVAL	OVERALL SURVIVAL	MEDIAN FOLLOW-UP
NEOADJUVANT							
RTOG 86-10 (Pilepich et al, 2001)*	471	cT2-4, ≥ 25 cm ²	44-46 WP 65-70 p	RT RT + nAD + cAD	3%† 11%†	34%‡ 43%‡	12.5 yr
Canadian trial (Laverdière et al, 1997)	120	cT2b-4	64 p	RT RT + nAD RT + n/c/aAD (6 mo)	22% 72% 90%	NR NR NR	24 mo
Canadian trial (Crook et al, 2009)	378		66-67 p	RT + nAD (3 mo) RT + nAD (8 mo)	58% 65%	81% 79%	6.6 yr
ADJUVANT							
RTOG 85-31 (Pilepich et al, 2003)	977	cT3, pT3 or N1	44-46 WP 65-70 p	RT RT + aAD (∞)	8% 32%	38% 53%	7.3 yr
EORTC 22863 (Bolla et al, 2002)	412	T1-2 + grade 3, T3-4	50 WP 70 p	RT RT + aAD (3 yr)	40% 74%	62%§ 78%§	66 mo
Swedish trial (Granfors et al, 1998)	91	T1-4, pN0-3, M0	50 WP 65 p	RT RT + orchiectomy	39% 69%	38%† 61%†	9.3 yr
RTOG 92-02 (Hanks et al, 2003)	1514	T2c-4 + PSA <150 ng/mL	44-50 WP 65-70 p	RT + n/cAD RT + n/c/aAD (2 yr)	28% 46%	79% 80%	5.8 yr
RTOG 94-13 (Roach et al, 2003)	1292	PSA <100 ng/mL + >15% risk of nodes	50.4 WP 70.2 p	n/cAD + WP n/cAD + pRT WP + aAD (4 mo) pRT + aAD (4 mo)	38% 34% 31% 38%	67% 69% 59% 68%	84 mo

*Updated data from Roach et al (2008).

† $P = .02$.‡ $P = .12$, different only for Gleason 2-6.§ $P = .0002$.||Updated data from Lawton et al (2007); lower survival with WP + aAD ($P = .027$).

aAD, adjuvant androgen deprivation; cAD, concurrent androgen deprivation; nAD, neoadjuvant androgen deprivation; p, prostate; PSA, prostate-specific antigen; RT, radiation therapy; WP, whole pelvis.

3, cT3-T4 and any grade) were randomized to RT alone or the addition of goserelin starting at the beginning of treatment and continuing for 3 years. This is the only study to demonstrate an overall survival benefit, with 5-year survival of 79% in the adjuvant AD group and 62% in the RT-alone group ($P = .001$). Disease-free survival was 85% and 48%, respectively, and local control was also improved with AD (97% vs. 79%). Of note, the cohort presented with very high-risk disease, with a median PSA level of 30 ng/mL, and this may account for the relatively low overall survival in the RT-alone cohort.

It does not appear that the method of AD affects the outcome of combined treatment with RT. Granfors and colleagues (1998) randomized men with cT1-T4pN0-3M0 cancer to either external beam RT alone or combined orchiectomy and RT; men treated with RT alone received AD at clinical disease progression. At median follow-up of 9.3 years, clinical progression in the RT-alone and RT-plus-AD patients was 61% and 31%, respectively ($P = .005$). Cancer-specific mortality was not different; overall mortality was

61% and 38%, respectively ($P = .02$). However, in men with negative lymph nodes, there was no significant difference in survival rates, and the poor survival was primarily due to metastatic disease at the time of initial treatment.

A meta-analysis of 2742 men treated for clinically localized prostate cancer within RTOG trials from 1975 to 1992 supports use of adjuvant AD in subsets of patients (Roach et al, 2000). Patients were stratified into four prognostic risk groups, and those in risk group 2 (cT3NX, Gleason 2-6; or cT1-T2NX, Gleason 7; or N+, Gleason 2-6) appeared to have improved disease-specific survival with addition of short-term (4 months) AD. In further refining the population of patients, limiting the analysis to men with bulky or cT3 disease alone demonstrated a significant survival advantage.

If adjuvant AD is of benefit, the duration of such therapy remains uncertain. RTOG 92-02 supports the use of long-term AD after initial AD with external beam RT (Hanks et al, 2003). Men with locally advanced tumors (cT2c-T4N0-1M0) received either 4 months of AD (2 months neoadjuvant and 2 months concurrent) with RT

or that and 24 additional months of AD. Long-term AD was beneficial in all end points evaluated *except* overall survival, with 5-year rates of both approximately 80%. Subset analysis of men with Gleason sum 8-10 noted improved overall survival with 24 months of AD (81%) compared with short-term AD (71%; $P = .044$), as well as improved disease-specific survival; these findings were confirmed during 10-year follow-up (Horwitz et al, 2008). D'Amico and colleagues (2004) described 206 men with clinically localized but higher-risk (PSA ≥ 10 ng/mL, Gleason sum ≥ 7 , cT3) prostate cancer randomized to RT alone (70 Gy) or RT with 6 months of AD. Overall and cancer-specific survival rates were improved with AD compared with RT alone. Actuarial 5-year survival and freedom from salvage AD were 88% and 82%, respectively, after early AD and 78% and 57% with RT alone. **Thus a limited period of AD (2 to 4 months) appears to be appropriate for those men with intermediate-risk cancers; more prolonged AD may be beneficial for those with high-risk disease characteristics, including high-stage cancers, or men with high pretreatment serum PSA values.**

Other aspects of RT for men with more advanced tumors require clarification, including the dose and extent (i.e., prostate only vs. prostate and pelvis) applied. RTOG 94-13 randomized men with an estimated risk of lymph node metastasis of 15% into one of four arms: (1) whole-pelvis RT plus neoadjuvant and concurrent AD, (2) prostate-only RT plus neoadjuvant and concurrent AD, (3) whole-pelvis RT plus adjuvant AD, and (4) prostate-only RT plus adjuvant AD (Roach et al, 2003; Lawton et al, 2007). Initial analysis suggested improved progression-free survival for whole-pelvis compared with prostate-only RT and no difference for the two types of AD. In comparing the four groups after longer follow-up, however, progression-free survival rates were similar, with significant difference only in overall survival among the groups ($P = .027$). Surprisingly, overall survival was worse in patients receiving whole-pelvis RT plus adjuvant AD compared with all other cohorts.

The differences in RT dose among the various prior and contemporary studies make comparisons of efficacy difficult because emerging data support doses greater than 72 Gy as being more effective (Cheung et al, 2005; Jacob et al, 2005). In addition, the role of combined external beam RT and brachytherapy (both permanent and high-dose rate) needs to be better elucidated. Brachytherapy has generally been used to treat patients with lower-risk features. Its use in those with high-risk disease characteristics, often in combination with AD and external beam RT, has been less well studied. Potters and colleagues (2005) noted a 63% biochemical-free survival in those treated with permanent prostate brachytherapy. A similar outcome has been noted with the use of high-dose-rate intensity-modulated brachytherapy with external beam RT (Demanis et al, 2005). Sylvester and colleagues (2003) treated men with interstitial permanent brachytherapy combined with moderate-dose (45 Gy) neoadjuvant external beam RT. In those with high-risk disease (by D'Amico criteria), the 10-year biochemical relapse-free survival was 48%; of note, AD was not used. Stock and colleagues (2004) evaluated a multimodal protocol using neoadjuvant and concomitant AD (9 months total), brachytherapy, and three-dimensional conformal RT in a high-risk cohort. The 5-year biochemical-free survival was 86%, with Gleason sum the only variable associated with PSA failure. Excellent local control was also demonstrated, with no patient harboring cancer on the last post-treatment biopsy.

Radiation Therapy and Chemotherapy

The role of chemotherapy in conjunction with RT is less well studied than that for surgery and chemotherapy. Khil and colleagues (1997) administered estramustine and vinblastine concurrently with RT (total, 65 to 70 Gy) in men with locally advanced disease. Although clinical control was reasonable at 5 years at 81%, only 48% of patients had a PSA level below 4 ng/mL at this time. Zelefsky and colleagues (2000) enrolled 27 patients with high-risk disease (Gleason sum ≥ 8 and PSA > 10 ng/mL; Gleason sum 7 and PSA > 20 ng/mL; cT3N0M0 and PSA > 20 ng/mL; cT4N0M0; cTXN1M0) in a phase II clinical trial of the same agents, with RT at 75.6 Gy.

Only modest increase in grade 2 toxicity was noted, and no late grade 3 or grade 4 toxicities were observed. The 2-year biochemical-free survival was 60%. An update reported median time to PSA relapse of 12 months, with 48% of patients receiving no additional therapy, and median time to metastasis had not been reached (Ryan et al, 2004).

An estramustine-based regimen has also been examined with etoposide before and during definitive RT (Ben-Josef et al, 2001). Actuarial disease-free survival and overall survival were 73% and 88%, respectively, at 3 years. Local control as determined by biopsy was 71% at 18 months. A phase I study examined concurrent docetaxel and RT (70.2 Gy) in 22 men (Kumar et al, 2004). The maximal tolerated dose was determined to be 20 mg/m², with diarrhea and dysuria the primary toxic effects. All patients were alive at last follow-up, and 77% had continued biochemical response. These promising results support further study of the combined use of RT and chemotherapeutic agents.

FOCAL ABLATIVE THERAPY

Advances in technology have provided methods to ablate prostate tissue while being minimally invasive. There is renewed interest in primary cryoablation, particularly as focal treatment for localized disease as well as salvage therapy, and high-intensity focused ultrasound (HIFU) appears promising. The ability to treat local disease within the prostate by these modalities may play a role even in men with locally advanced disease, most likely in combination with AD or other systemic therapy.

Cryoablation

Several series have been reported regarding primary cryoablation of the prostate and include many men with high-risk disease (Ahmed et al, 2009). Among 975 men undergoing cryoablation, 41% were high risk and 24% were stage cT3 in the report from Long and colleagues (2001). At a median follow-up of 24 months, the 5-year actuarial biochemical-free survival, defined as PSA less than 1 ng/mL, was 41%. A similar PSA outcome (35%) using the same definition was observed in another group of men with PSA 10 ng/mL or greater and/or Gleason sum 8 or higher undergoing primary cryoablation (Prepelica et al, 2005). However, use of more stringent PSA cutoff values may result in significantly worse outcomes, with 2-year rates of biochemical failure higher than 80% if thresholds of 0.5 or 0.2 ng/mL are applied (El Hayek et al, 2008). Chin and colleagues (2008) randomized men with clinical stage T2c-T3 disease to 6 months of AD and either cryoablation or RT at 66 Gy. At a mean follow-up of 37 months, there were no differences in disease-specific (95% to 97%) and overall (87%) survival, but cryoablation was associated with shorter PSA-free survival (28 months vs. 41 months) and higher biochemical failure (87% vs. 53%).

High-Intensity Focused Ultrasound

The role of HIFU continues to be elucidated, particularly in men with locally advanced prostate cancer. The limited existing data are confounded by frequent omission of risk stratification and common use of AD to reduce prostate size. At 1-year follow-up, 30 men with locally advanced or high-risk disease receiving AD plus HIFU had reasonable local control, with PSA less than 0.3 ng/mL and negative sextant biopsies in 90%; no patient had clinical disease progression (Ficarra et al, 2006). A larger series from Sumitomo and colleagues (2008) compared men receiving HIFU with and without NAD and without subsequent adjuvant therapy. In the 29% with high-risk cancers by D'Amico criteria, NAD reduced both positive biopsy rate and biochemical failure. Three-year disease-free survival was independently affected by stage cT2c or higher (HR 2.34) and lack of NAD (HR 2.19) in multivariable analysis. Parallel to studies of RT, outcomes of local treatment using HIFU may be improved when combined with NAD, primarily in men with intermediate- and high-risk disease characteristics.

ANDROGEN DEPRIVATION AND ITS TIMING

The VACURG and MRC trials suggest a benefit to early application of AD in men with locally advanced prostate cancer. The first VACURG study randomized 1050 patients with stage III disease and 853 patients with stage IV disease to placebo, 5 mg of DES, orchiectomy plus placebo, or orchiectomy plus 5 mg of DES. All three AD arms had significantly less progression than the placebo group had, but this did not translate into an overall survival benefit. The inability to demonstrate a survival benefit cannot be completely attributed to the increased cardiovascular deaths within the DES groups because survival in the orchiectomy plus placebo group was not significantly different from that in the placebo-alone group. The second VACURG study randomized 1506 men with stage III and stage IV disease to placebo or one of three doses of DES (0.2 mg, 1 mg, 5 mg). DES at 1 mg and 5 mg delayed progression of stage III disease, and patients receiving 1 mg had improved overall survival. However, the 5-mg dose of DES again resulted in increased cardiovascular death. Subsequent analysis suggested that immediate estrogen therapy was most beneficial in patients younger than 75 years with high-grade tumors (Gleason sum 7-10). The third VACURG study supported that only a subset of men with prostate cancer benefit from early AD. In men with stage II disease, 5-year survival was 48% with placebo and 75% with 1 mg of DES. Taken together, the VACURG data provide evidence of benefit for early AD with respect to disease progression and potential survival only in subsets of men with more aggressive disease (Byar, 1973; Byar and Corle, 1988). The studies also clearly show that alternatives to estrogen should be used, given the cardiovascular toxicity associated with higher doses of DES. The current ability to better monitor disease progression, with use of PSA kinetics and imaging modalities, may improve the outcomes of delayed AD by better determining when institution of AD is necessary.

The MRC also evaluated the issue of early versus delayed AD (orchiectomy or LHRH agonist) in 938 patients with prostate cancer, of whom 501 had locally advanced disease. The majority of deaths (67%) were attributed to prostate cancer. Cancer-specific mortality was 55% in the early AD group and 43% in the deferred group ($P = .001$). Overall survival was also improved in the immediate AD arm ($P = .02$). The reduction in prostate cancer death was primarily due to patients with M0 disease. This study also provides important data for comparison to other forms of treatment. Median time to death from prostate cancer (cT3M0) was 90 months, comparing favorably to EORTC 22863, in which median time was not reached after 65.7 months. Similarly, median overall survival in the MRC study was 64 months but not reached in EORTC 22864 (56.7 months of follow-up). Thus the apparent beneficial effects of combined AD and RT may be due in part to AD alone with uncertain incremental advantage of RT. The results from the Scandinavian Prostate Cancer Group Study 7/Swedish Association for Urological Oncology 3 (SPCG-7/SFUO-3) trial suggest an important role of RT, in addition to AD, in men with locally advanced disease (78% cT3) (Widmark et al, 2009). Men were randomized to either total AD followed by continuous flutamide or endocrine therapy combined with RT. At median follow-up of 7.6 years, both prostate cancer-specific and overall mortality were decreased in the group receiving AD plus RT (RR 0.44 and 0.68, respectively), and PSA recurrence was higher in men receiving AD alone (75%) compared with the RT group (26%). Despite limitations including the unconventional endocrine regimen and open study design, use of RT and potentially other local treatment modalities appears warranted in men with locally advanced prostate cancer. The MRC UK PR07 trial similarly compared AD only with AD and RT; in this study, patients had more advanced disease, AD was accomplished by either continuous LHRH agonist or orchiectomy, and pelvic nodes were treated with RT. The addition of RT to AD improved disease-specific (HR 0.54) and overall (HR 0.77) survival at 7 years (Warde et al, 2011).

Studer and colleagues (2004) evaluated the timing of AD in a study randomizing 197 asymptomatic men with prostate cancer to either immediate or deferred subcapsular orchiectomy; of note, patients were either unsuitable for or unwilling to undergo surgery

or RT. A significant fraction of the cohort had higher-risk features, with clinical stage T3 or higher in 67% and median serum PSA level above 46 ng/mL. Of the 92 men in the deferred treatment arm, 42% never required AD; the majority died of causes unrelated to prostate cancer. The median time to deferred AD was 3.2 years, the most common indication being skeletal metastases (45%) and ureteral obstruction (25%). Although overall survival was not different between the immediate and deferred groups ($P = .96$), a trend toward improved cancer-specific survival was noted in those men receiving immediate AD, with an HR for death from prostate cancer of 0.63 ($P = .09$).

To minimize adverse impact on quality of life, antiandrogen therapy alone has been proposed as an alternative to orchiectomy or LHRH agonists. Iversen and colleagues (2004) reported on the effects of 150 mg of bicalutamide in men with localized or locally advanced prostate cancer, the majority of whom were untreated initially (81%). At median 5.3 years of follow-up, survival in those with locally advanced disease was improved with bicalutamide compared with placebo (HR 0.68). Overall, risk of disease progression was reduced by 43%, with the greatest benefit in locally advanced tumors (HR 0.4). The combined analysis of the three Early Prostate Cancer bicalutamide trials ($n = 8113$) confirmed improved progression-free survival in the bicalutamide group (Wirth et al, 2004a). Overall survival was not different between the treatment and placebo arms in each trial, but men with locally advanced disease receiving bicalutamide alone (i.e., no surgery or RT) appeared to have improved survival. Although apparently promising in men with high-risk tumors, bicalutamide at 150 mg must be approached cautiously, both in men deferring local therapy and after definitive treatment. In analysis of the Early Prostate Cancer data (median follow-up of 5.4 years), men with localized prostate cancer receiving bicalutamide as primary therapy had an increased risk of death (HR 1.23, 95% CI 1.00 to 1.50) compared with surveillance alone. Immediate high-dose bicalutamide is not currently appropriate in men with low risk of disease progression, and potentially adverse effects should be sought in higher-risk patients with extended follow-up.

Wirth and colleagues (2004b) tested adjuvant flutamide (750 mg) after radical prostatectomy in men with pT3-T4N0 disease. Recurrence-free survival, defined as a single PSA value above 5 ng/mL or two PSA values above 2 ng/mL, was improved with flutamide (HR 0.51) at median follow-up of 6.1 years; however, overall survival was comparable (HR 1.04). Significant toxicity was associated with flutamide and accounted for nearly half of withdrawals from the treatment arm.

KEY POINTS: ANDROGEN DEPRIVATION

- Early androgen deprivation may improve survival.
- Alternative methods of androgen manipulation (antiandrogen, intermittent) remain investigational.

Intermittent Androgen Deprivation

Another approach to minimizing AD-related morbidity is the intermittent application of androgen suppression. Forty-nine patients (28 with cT3-T4N0M0 disease) were treated with total AD until the PSA level was less than 4.0 ng/mL between 24 and 32 weeks, after which treatment was withheld after 36 weeks (Sato et al, 2004). PSA level was then monitored and treatment was recommended when the PSA level reached either pretreatment level (when it was <15 ng/mL) or 15 ng/mL (when the initial PSA level was higher than that). During median follow-up of 126.1 weeks, mean time off treatment during cycles 1, 2, and 3 was 46.1, 36.9, and 23.3 weeks, respectively. No symptomatic or clinical disease was reported in the non-metastatic subgroup, and PSA failure was observed in 3 (11%) of these patients, with all patients alive at last evaluation. The optimal timing of intermittent AD for reduction of patient morbidity and

disease-specific end points remains to be determined, particularly in light of data from the trial of intermittent versus continuous AD in men with metastatic, hormone-sensitive prostate cancer (Hussain et al, 2013).

Quality of Life

The early institution of AD in men with prostate cancer, whether the cancer is localized or locally advanced, must be balanced against the known side effects and long-term morbidity. Only recently has the impact of AD on bone events, cognitive function, and quality of life been appreciated and reported. In comparing bicalutamide (150 mg) and castration with locally advanced but nonmetastatic disease, both sexual interest and physical capacity were better with bicalutamide monotherapy (Iversen et al, 2000). Although hot flashes were more common with castration, a trend toward reduced quality of life was associated with bicalutamide, including higher incidence of gynecomastia, breast pain, and asthenia. In the study of intermittent AD from Sato and colleagues (2004), many quality-of-life domains were improved during off-treatment cycles, including potency and social and family well-being.

The multimodal approach with AD and RT may increase the relative toxicity compared with each intervention alone. Schultheiss and colleagues (1997) reported that NAD was correlated with later gastrointestinal and genitourinary (grade 2 or higher) morbidity. Another study found that adjuvant AD after RT predicted for late grade 2 to grade 4 rectal toxicity (Sanguineti et al, 2002). Within RTOG 86-10, potency after RT with or without AD was similar at 81% and 74%, respectively. Chen and colleagues (2001) also found that the addition of AD did not further contribute to decline in sexual function after RT. Zelefsky and colleagues (1999) evaluated predictors of late toxicity in men treated with three-dimensional conformal radiotherapy. Although the 5-year actuarial likelihood of gastrointestinal and urinary toxicities was low (<10% overall), use of NAD was an independent predictor ($P = .01$) of post-treatment erectile dysfunction. The incidence of rectal morbidity and sexual dysfunction may be related to duration of AD longer than 6 or 9 months.

The benefits of adjuvant AD plus RT for locally advanced prostate cancer, both short and long term, appeared to outweigh the associated side effects in a number-needed-to-treat analysis (Jani et al, 2003). A model that compared treatment options while incorporating benefit and complications was constructed, and data from randomized trials of RT with or without AD for cT2c-T4N0-1 disease were input into the calculation. Even considering the increased incidence of side effects of long-term AD, this approach appeared to be better than short-term AD for virtually all end points evaluated.

Given concerns regarding AD and impact on body mass index, lipid profile, diabetes, and cardiovascular disease, Efstathiou and colleagues (2009) assessed the relationship between AD and cardiovascular events within RTOG 85-31. Adjuvant AD (median duration 4.2 years) was not associated with increased cardiovascular mortality. Additional evidence from RTOG 86-10 suggests that short-term NAD also does not increase the risk of fatal cardiac events.

MANAGEMENT OF DELAYED SEQUELAE

The direct comparison of prostatectomy and RT in the treatment of locally advanced prostate cancer is challenging and primarily based on historical studies. Even with the addition of neoadjuvant and adjuvant systemic therapy, leaving the prostate gland in situ poses potential problems. First, effective local control of some high-risk cancers may influence survival. Second, local recurrence may lead to the need for additional treatment of the prostate. At 10 years, local recurrence rates after RT for cT3 or stage C disease range from 24% to 74%. Holzman and colleagues (1991) reported that 36% of patients required transurethral resection of the prostate because of urinary obstruction after RT alone, without AD. Other morbidity included hydronephrosis (20%) and incontinence (13%). An older

report (Tomlinson et al, 1977) also demonstrated significant local complications of stage C prostate cancer with nonextirpative interventions—infection (80%), bladder outlet obstruction (75%), gross hematuria (45%), and ureteral obstruction (40%). Systemic therapy in the form of AD may not prevent local progression or reduce the need for palliative intervention. Despite orchiectomy for bladder outlet obstruction, 31% of men with locally advanced disease required transurethral prostate resection because of persistent voiding dysfunction after 60 days. Similarly, in 277 patients with cT2-T4 disease randomized to orchiectomy, RT, or both, rates of local disease control were comparable (Fellows et al, 1992). Studer and colleagues (2004) demonstrated that AD alone, whether it is instituted early or late, does not prevent local morbidity. More than half of the men in their study required transurethral resection of the prostate. In addition, delayed institution of AD was necessary because of ureteral obstruction (25%), anticipation of local complications (10%), and rectal infiltration (4%).

Quality of life is an increasingly important end point for prostate cancer. However, the impact of untreated local tumor progression or the various treatment modalities for locally advanced disease on quality-of-life outcomes is poorly characterized. Rosenfeld and colleagues (2004) examined the relationship between cancer stage and quality of life in 341 ambulatory men with prostate cancer. Instruments used included the Functional Assessment of Cancer Therapy (FACT), the urinary function subscale of the UCLA Prostate Cancer Index, and the Hospital Anxiety and Depression Scale (HADS). The stage of prostate cancer was significantly associated with most FACT subscales—increasing stage was negatively correlated with nearly every FACT subscale score; the observation persisted in multivariate models, accounting for covariables such as comorbidity and time since diagnosis. Interestingly, stage was more strongly associated with physical domains of health-related quality of life and there was no association with psychological symptoms as measured by HADS.

Berg and colleagues (2007) treated high-risk patients with RT monotherapy and characterized quality of life using validated instruments. Although mean scores for bowel function were similar to those for a normative control population, bowel bother and diarrhea were greater after RT. Patients who had clinical progression or required AD reported worse sexual, urinary, and social function and more sleeping problems and exhibited great declines in all domains over time. Data from CaPSURE (Wu et al, 2008) also suggest that men with high-risk cancer are likely to suffer negative effects beyond cancer outcomes. Use of AD with both surgery and RT was associated with a loss of sexual function that improved within 9 months, whereas the combination of external beam RT and brachytherapy resulted in continuous worsening of urinary function and bother.

Additional evidence from SWOG 8794 supports an adverse impact of multimodal therapy on quality of life (Moinpour et al, 2008). Men receiving adjuvant RT reported worse bowel and urinary function, but not erectile function, compared with surgery alone. Although symptom distress was significantly worse for the adjuvant RT group, likely correlating with bowel and urinary problems, there were no differences in other general measures of health-related quality of life, whereas global health-related quality of life was initially worse but continuously improved over time after adjuvant RT.

CLINICAL TRIALS

Given that outcomes of therapy are not optimal for those men with high-risk disease features, patients who present with such cancers should be considered for enrollment in novel clinical trials (<http://clinicaltrials.gov/>). Table 118-11 summarizes phase III clinical trials for high-risk or locally advanced prostate cancer; some of these have completed accrual and others are ongoing. The resulting data should answer some of the current questions regarding the optimal type and timing of traditional combination treatment, as well as the role of chemotherapy, in men with locally advanced and high-risk prostate cancer.

TABLE 118-11 Current and Pending Phase III Clinical Trials in Locally Advanced/High-Risk Prostate Cancer

STUDY	ELIGIBILITY CRITERIA	TREATMENTS
RADICAL PROSTATECTOMY		
Neoadjuvant		
CALGB 90203	Clinically localized, ≤60% 5-yr disease free, Gleason 8-10	Surgery alone vs. estramustine/docetaxel
Adjuvant		
SWOG 9921	Gleason 8-10, pT3b-4, PSA >20 ng/mL, N1, Gleason 7 and + margin	AD (2 yr) vs. AD + mitoxantrone/prednisone
VA Study 553	pT3b-4, pT3a and Gleason ≥7, pT2 and Gleason 8-10 and + margin, PSA >20 ng/mL	Surveillance vs. docetaxel/prednisone
SPCG 12	pT3a and Gleason ≥4+3, pT2 and + margin and Gleason ≥4+3, pT3b and Gleason ≥7	Surveillance vs. docetaxel
NCT 00667069	>pT2 or R1 N0/x and PSA ≤0.1 ng/mL	Immediate vs. delayed RT + triptorelin
MRC PR 10	After radical prostatectomy with PSA ≤0.2 ng/mL: pT3-4, Gleason 7-10, preoperative PSA ≥10 ng/mL, + margin	Immediate vs. delayed RT RT vs. RT + 6 mo AD vs. RT + 24 mo AD
EXTERNAL BEAM RADIATION THERAPY		
RTOG 0924	Gleason 7-10 and cT1c-2b and PSA <50 ng/mL, Gleason 6 and cT2c-4 or >50% biopsies and PSA <50 ng/mL, Gleason 6 and cT1c-2b and PSA >20 ng/mL	NAD + prostate/seminal vesicle RT + RT boost vs. NAD + whole-pelvic RT + RT boost
Neoadjuvant		
RTOG 9910	Gleason 2-6 and PSA 10-100 ng/mL, Gleason 7 and PSA <20 ng/mL, cT1 and Gleason 8-10 and PSA <20 ng/mL	8 wk NAD vs. 28 wk NAD
CAN-NCIC-PR12	≥T3a, Gleason ≥8, PSA >20 ng/mL	NAD + docetaxel vs. NAD
Adjuvant		
RTOG 9902	Gleason ≥7 and PSA 20-100 ng/mL, ≥cT2 and Gleason ≥8 and PSA <100 ng/mL	AD vs. AD + estramustine/etoposide/paclitaxel
NCT 116142	cT1-T2a and PSA <10 ng/mL or Gleason ≥4+3 or PSA velocity >2 ng/mL/yr, cT2c-4 and tertiary Gleason 5 or T3b or Gleason ≥3+4 with ≥50% cores positive	AD vs. AD + docetaxel
RTOG 0521	Gleason ≥9 and PSA ≤150 ng/mL, Gleason 8 and PSA <20 ng/mL and ≥cT2, Gleason 7 or 8 and PSA 20-150 ng/mL	AD vs. AD + docetaxel/prednisone
RTOG 1115	Gleason ≥9 and PSA ≤150 ng/mL and any T stage, Gleason 8 and PSA <20 ng/mL and ≥T2, Gleason 8 and PSA 20-150 ng/mL and any T stage, Gleason 7 and PSA 20-150 ng/mL and any T stage	AD (24 mo) + dose-escalated RT vs. AD (24 mo) + TAK-700 + dose-escalated RT
SPCG 13	cT2 and Gleason 4+3 and PSA 10-70 ng/mL, cT2 and Gleason 8-10 and PSA <70 ng/mL, cT3	AD vs. AD + docetaxel
ANDROGEN DEPRIVATION		
CAN-NCIC-PR3	cT3-4N0/M0, cT2 and PSA >40 ng/mL, cT2 and PSA >20 ng/mL and Gleason ≥ 8	AD alone vs. additional pelvic RT
NCT 00055731	Gleason >7, cT3-4, N1, PSA >20 ng/mL	AD vs. AD + docetaxel/estramustine

AD, androgen deprivation; NAD, neoadjuvant androgen deprivation; PSA, prostate-specific antigen; RT, radiation therapy.

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The complete reference list is available online at www.expertconsult.com.

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Radical Prostatectomy

Radiation Therapy

Cryotherapy

High-Intensity Focused Ultrasound

Summary

RADICAL PROSTATECTOMY**Definition of Biochemical Recurrence after Radical Prostatectomy**

Radical prostatectomy is one of the most common treatment modalities for localized prostate cancer, and despite refinements in surgical technique and improved patient selection, approximately 25% to 41% of men will develop prostate-specific antigen (PSA) recurrence 10 years after surgery (Amling et al, 2000; Hull et al, 2002; Roehl et al, 2004). It is clear that not all men with a detectable PSA level after surgery are destined to clinical progression, defined as development of metastatic disease, need for second-line treatment, or death from prostate cancer. A significant portion of men will have a detectable PSA level that plateaus and does not progressively rise. Several hypotheses exist as to why this phenomenon occurs. First, residual benign disease is left in the prostatic bed (often used as the rationale for a detectable PSA level after radiation therapy). Second, PSA is produced at very low levels by cells of nonprostatic origin (Diamandis and Yu, 1995). Third, PSA elevation is a result of residual low-grade prostate cancer destined to follow an indolent course (Amling et al, 2001).

In the prostate cancer literature, specifically after radical prostatectomy, there are more than 50 separate definitions of biochemical recurrence (Zincke et al, 1994; Moul et al, 1996; Cookson et al, 2007). A standard definition of PSA recurrence is needed that accurately predicts for progression to clinically relevant end points such as metastatic disease, need for secondary treatments such as radiation therapy and androgen deprivation therapy (ADT), and death from prostate cancer. This must be tempered by the need for this same definition to identify patients at sufficiently low PSA levels (disease burden) to intervene with second-line therapies at a point in the disease course that will be meaningful. Several groups have examined various definitions of PSA recurrence that make sense for clinical practice and for standardization of therapy both for patient care and research purposes.

Stephenson and colleagues (2006a) reviewed the Memorial Sloan Kettering experience of 3125 patients who underwent radical prostatectomy. They found that after a median follow-up of 49 months, 75 men developed distant metastatic disease. Using a goodness-of-fit (R^2) statistic, they examined 10 candidate definitions of PSA failure for their predictability of metastatic progression. They determined that a PSA value of at least 0.4 ng/mL followed by another increase was the best fit for metastatic progression, as well as high predictability for secondary therapy, continued PSA progression, and rapid doubling time. Furthermore, Amling and colleagues

(2001) determined significance in using a definition of PSA level of 0.4 ng/mL or greater. At a value of 0.2 ng/mL, only 49% of men subsequently developed a further rise in PSA level compared to 72% of patients with a PSA value of 0.4 ng/mL or greater. Lost in a "standard" definition of PSA recurrence is clinical progression risk and how it relates to different definitions of failure. For example, a PSA value of 0.1 ng/mL may mean a different clinical outcome in a patient who had a radical prostatectomy 8 years earlier with pathologic Gleason 6 disease versus a patient who had surgery 6 months earlier for high-volume Gleason 9 prostate cancer. Mir and colleagues (2014) addressed this issue by examining 14 definitions of biochemical recurrence and how they relate to the probability of subsequent rise in PSA level, use of secondary treatment, or clinical progression. In the entire cohort, a single detectable PSA level, even at low levels (≤ 0.1 ng/mL), was associated with a subsequent rise in 30% to 55% of patients. In patients with high-risk features, a detectable PSA level was associated with a PSA progression probability of 73% to 88% compared to only 18% to 25% in patients with low-risk features. The optimal definition for patients with a 5-year progression-free probability of less than 50% (high-risk patients) was a single PSA value of 0.05 ng/mL or greater, and the ideal cut point in those with a progression-free probability greater than 90% (low-risk patients) was a PSA value 0.4 ng/mL or greater.

Because of the wide variation in definition of biochemical recurrence, the American Urological Association Prostate Guidelines Panel for Localized Prostate Cancer released their recommendations for reporting PSA recurrence in 2007. Their goals in a unifying definition were to determine an early marker of treatment failure in advance of clinical progression, use a low enough value to allow for patients to be candidates for early salvage therapy, and for a standard definition to be used as comparison among different patient series. The American Urological Association (AUA) guidelines panel ultimately defined PSA recurrence as a value of 0.2 ng/mL or greater with a second confirmatory laboratory value (Cookson et al, 2007). This also has been adopted by the European Guidelines on Prostate Cancer (Heidenreich et al, 2008).

Natural History of Biochemical Recurrence after Prostatectomy

Recurrence of PSA normally precedes clinically meaningful events in an extremely protracted and variable manner. In the seminal article describing the natural history of biochemical recurrence after radical prostatectomy, Pound and associates (1999) determined that the median actuarial time from biochemical recurrence to

metastasis was 8 years. Furthermore, the median actuarial time to death was 5 years, although this depended on the time from biochemical recurrence to metastasis, because patients who developed metastatic disease early had decreased median survival (Pound et al, 1999). In their initial analysis they determined that the risk for metastasis depended on time to biochemical recurrence, Gleason score, and PSA doubling time. In a recent update, metastasis-free survival was 10 years, potentially reflecting improvements in patient selection and management. Established factors that predicted for metastasis-free survival included Gleason score and PSA doubling time, but time to biochemical recurrence was not found to be significant in this cohort (Antonarakis et al, 2012). Using cut points of Gleason score (≤ 6 vs. 7 vs. 8 to 10) and PSA doubling time (< 3 vs. 3 to 8.9 vs. 9 to 14.9 vs. ≥ 15 months) was valuable to stratify patients into distinct risk groups.

Predictive models of prostate cancer–specific mortality after biochemical recurrence have been established. In a large cohort of 379 men who experienced biochemical failure, median survival after 16 years still had not been reached, demonstrating the potential for prolonged survival (Freedland et al, 2005). However, risk for metastasis and eventual death is extremely variable and risk factors need to be identified to predict those needing early aggressive therapy and enrollment into clinical trials. Data demonstrate that PSA doubling time, pathologic Gleason score, and time from surgery to biochemical recurrence are predictive of prostate cancer–specific mortality (Freedland et al, 2005, 2006). Using a cut point of 3 years, the actuarial 15-year survival differed from 41% for those with recurrence at less than 3 years after surgery versus 87% for those who had biochemical recurrence later than 3 years after radical prostatectomy (Freedland et al, 2006). In fact, for every year in delay from prostatectomy to biochemical recurrence, the prostate cancer–specific mortality risk decreases by 24% (Freedland et al, 2006). Conversely, in a series of men with biochemical recurrence not receiving either neoadjuvant or adjuvant therapy, Boorjian and colleagues (2011) found that time from prostatectomy to biochemical recurrence was not significantly associated with systemic progression (demonstrable metastases on radionuclide bone scan or on biopsies outside of the prostatic bed) or prostate cancer–specific mortality. They determined that age, Gleason score, advanced tumor stage, and rapid PSA doubling time were predictive of clinical progression.

The majority of men who experience biochemical recurrence after radical prostatectomy will not succumb to disease. However, risk factors for aggressive progression to clinically relevant disease and death are extremely important for patient counseling, clinical trials, and early implementation of salvage therapies. Using an established nomogram for prostate cancer recurrence (Kattan et al, 1998), Stephenson and colleagues (2009) demonstrated that 15-year prostate cancer–specific mortality was 5% in the most favorable quartile of PSA recurrence whereas patients in the least favorable 5-year PSA progression-free probability had a 15-year prostate cancer–specific mortality of 38%. Further, it is important to note that evaluation of PSA after prostatectomy should occur indefinitely because up to 27% of men will experience recurrence after 5 years and these patients are still at risk for clinical progression (Ward et al, 2003).

Prediction of Biochemical Recurrence after Prostatectomy

Regardless of the definition chosen for biochemical recurrence, it is clear that almost all clinical recurrences are preceded by a detectable and rising PSA level. Predicting patients who will have biochemical recurrence is important in terms of counseling, identifying those likely to need secondary therapy, and potentially treating with neoadjuvant treatments on clinical trials. Several groups have evaluated clinical and pathologic factors that may contribute to risk for biochemical recurrence. Using data from large operative series in men with prostate cancer, it has become clear that clinical factors can be used to predict for biochemical failure. Roehl and associates (2004) evaluated their series of 3478 men and determined after multivariable analysis that the most important factors for predicting for

biochemical recurrence were pretreatment PSA level, clinical stage, Gleason sum, pathologic stage, and era in which the radical prostatectomy was performed. Other groups have confirmed the importance of biopsy Gleason score; clinical tumor, node, metastasis (TNM) stage; and PSA level before therapy and Gleason score and tumor stage postoperatively as the largest covariates for biochemical recurrence prediction (Han et al, 2003).

A good surgical outcome after radical prostatectomy always has been the eradication of disease while maintaining continence and potency. To achieve the goal of cancer control, it always has been important to achieve negative surgical margins, because this is a predictor of biochemical failure (Stephenson et al, 2005). It has become clear that this is especially true when considering pathologic stage. Compared to a negative margin, men with positive margins in pT2 prostate cancer had a 12% increased risk for biochemical recurrence, whereas in pT3a and pT3b, the increased risk was 12% and 18%, respectively (Budaus et al, 2010). In fact, in this cohort of patients, those with pT3a and negative margins had a decreased risk for biochemical recurrence over that of those with pT2 cancer with positive margins. The length of positive margin also has been predictive of biochemical recurrence, because those with margins greater than 1 mm have a statistically significant increased risk for biochemical failure (Shikanov et al, 2009). Others have found that multiple positive margins as well as location of margin may be prognostically significant (Sofer et al, 2002; Stephenson et al, 2005). These data emphasize the importance of meticulous surgical dissection and appropriate surgical planning in patients who are likely to have advanced pathologic stage because positive surgical margins substantially worsen prognosis. Similarly, it has been shown that surgeon experience is predictive of outcomes. Surgeons who have performed more than 250 cases have a recurrence probability of 8.1% compared to 26.8% in those who have performed only 10 cases (Klein et al, 2008). Differences in experience may be partially explained by a difference in rate of positive margins between the more and less experienced surgeons.

In the age of evidence-based medicine and data-driven decisions, it is important to use objective data rather than “gestalt” when treating patients with prostate cancer. One of the most important predictive tools was created by Stephenson and colleagues (2006b) and published in 2006. Using the parameters of clinical stage, serum PSA value, Gleason score, and systematic biopsy results, this group created a prognostic tool for presurgery that has a concordance index of 0.76 to 0.79 for predicting for disease progression defined as serum PSA value of 0.4 ng/mL or greater and confirmed with a higher value, secondary therapy, clinical recurrence, or positive lymph nodes on frozen section during radical prostatectomy. Postoperatively, a similar tool using PSA, Gleason score, presence of extracapsular extension, seminal vesicle invasion, lymph node involvement, margin status, and adjuvant radiation can predict 10-year biochemical recurrence survival and has a concordance index of 0.79 to 0.81 (Stephenson et al, 2005). One important improvement/modification of this tool is that it calculates the 10-year progression-free probability based on the current disease-free interval already achieved. Nomograms have become popularized, are easily accessible, and are frequently used in patient counseling. The most commonly used nomograms accessible online are presented in Table 119-1.

Ultrasensitive Prostate-Specific Antigen

Traditionally, the lower limits of PSA detection have been in the range of less than 0.1 and 0.2 ng/mL. In the early 1990s, ultrasensitive PSA (uPSA) testing was introduced and has brought about increased sensitivity but also controversy. It is thought that early second-line treatment in patients destined for clinical failure portends improved survival. However, this is tempered by the risk of overtreating those patients who may never experience clinical failure despite continuous detectable values of extremely low PSA. Hong and associates (2010) demonstrated the utility of the uPSA in predicting biochemical recurrence defined as two consecutive rises in PSA level of 0.2 ng/mL or greater. On multivariate analysis, they

TABLE 119-1 Online Risk Stratification Nomograms for Prostate Cancer

CLINICAL STATE	TITLE	WEBSITE	VARIABLES
Risk for prostate cancer	Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator	http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp	Race, age, PSA level, family history, digital rectal examination, prior prostate biopsy
Pretreatment	Memorial Sloan Kettering Pretreatment Nomogram	http://nomograms.mskcc.org/Prostate/PreTreatment.aspx	Pretreatment PSA level, age, biopsy Gleason score, clinical stage, number of positive biopsies
	Partin tables	http://urology.jhu.edu/prostate/partintables.php	PSA level, biopsy Gleason score, clinical stage
	UCSF CAPRA Score	http://urology.ucsf.edu/research/cancer/prostate-cancer-risk-assessment-and-the-ucsf-capra-score	Age, PSA level, biopsy Gleason score, clinical stage, percent of biopsy core positive
Post-treatment	Memorial Sloan Kettering Post-treatment Nomogram	http://nomograms.mskcc.org/Prostate/PostRadicalProstatectomy.aspx	Pretreatment PSA level, age, pathologic Gleason score, era of prostatectomy, months free of cancer, margin status, extracapsular extension, seminal vesicle involvement, lymph node involvement, hormone therapy, prior radiation therapy

PSA, prostate-specific antigen (test); UCSF CAPRA, University of California, San Francisco Cancer of the Prostate Risk Assessment.

found that an undetectable uPSA along with preoperative PSA level, pathologic stage, and pathologic Gleason score were all significant predictors of biochemical failure. Patients with a nadir PSA level of less than 0.001 had a 3-year biochemical recurrence-free survival of 95.5% compared to 41.5% for those with a nadir PSA level of 0.05 or greater (Hong et al, 2010). These findings were confirmed by Shen and coworkers (2005), who determined PSA relapse (two consecutive PSA levels of ≥ 0.1 ng/mL or greater) in those with PSA nadir of less than 0.01 was 4% compared to 89% for those with nadir of 0.04 or greater.

Ultrasensitive PSA has demonstrated clinical utility in several scenarios. For instance, patients with undetectable uPSA at 2 years have been found to be unlikely to develop PSA doubling time less than 9 months (defined as a high-risk recurrence) after biochemical failure (Chang et al, 2010). In fact, for every month without a detectable uPSA, the odds for high-risk recurrence were decreased by 4%. Furthermore, the uPSA value at 3 years after radical prostatectomy is also predictive of eventual biochemical failure, because patients with a PSA level between 0.04 and 0.1 have a 10.8 times greater likelihood of developing eventual biochemical recurrence compared to those with PSA level of 0.04 or less (Malik et al, 2011). This is clinically relevant because patients who are free of disease at the 3-year mark can be counseled about their low probability of ever developing clinically relevant recurrence, which may ease some anxiety. Even after controlling for risk factors, uPSA nadir seems to be effective in predicting biochemical recurrence. Patients with pathologic T3 prostate cancer with undetectable uPSA have a 5-year biochemical recurrence-free survival of 78% compared to 40% for those who have a detectable uPSA level (Eisenberg et al, 2010). Interestingly, in patients with low-risk disease, the difference between patients with undetectable versus detectable uPSA was only 91% versus 89%, respectively, arguing that perhaps the significance of testing may lie in patients with intermediate- and high-risk cancer.

The enthusiasm for uPSA has been lessened by questions of clinical utility. Clearly, not all patients who develop detectable uPSA are destined for “traditional” biochemical recurrence. In fact, using a cutoff of 0.05 ng/mL, Eisenberg and colleagues (2010) found that approximately two thirds of their study cohort who attained this level did not progress to biochemical failure at 5 years. Others have pointed out the significant variability of the “background noise” at

values of PSA in the ultrasensitive range and further questioned its clinical utility (Taylor et al, 2006). PSA doubling time is established as an important prognostic indicator of clinical failure after radical prostatectomy. What has not been established is whether the calculated PSA doubling time using uPSA is relevant to this end. Reese and associates (2011) from the University of California–San Francisco determined that uPSA calculated doubling times have poor agreement with standard PSA doubling time using traditional values and that typically the value with uPSA was artificially shorter. Therefore the usefulness of uPSA in deciding on secondary therapy is limited.

Imaging in Patients with Biochemical Recurrence after Radical Prostatectomy

Patients who experience biochemical recurrence after definitive radical prostatectomy are at risk for both local recurrence and distant failure. Identifying patients with local failure only is critical to initiate salvage therapies while sparing those with distant metastatic disease the burden of local salvage therapy. Traditionally, imaging techniques have been limited in the diagnosis of recurrence when PSA levels have been low. For instance, the routine use of bone scans in patients with PSA levels less than 10 ng/mL is of limited value because only 4% will demonstrate a positive scan (Dotan et al, 2005). Similarly, traditional computed tomography (CT) is unlikely to be positive in patients with PSA levels less than 10 ng/mL (Okotie et al, 2004). Conversely, transrectal ultrasound (TRUS) has demonstrated reasonable sensitivity at low PSA levels, especially with masses at the vesicourethral anastomosis. Scattoni and colleagues (2003) demonstrate that TRUS followed by biopsy was positive in 45% of patients with a PSA level of 0.5 ng/mL or less and had 100% sensitivity in patients with a PSA level of 2.0 ng/mL or greater.

Indium-111 capromab pentetide scanning (ProstaScint; Cytogen, Princeton, NJ) incorporates an immunoglobulin G monoclonal antibody that binds to prostate-specific membrane antigen (PSMA). Its use in patients with biochemical recurrence has been limited because sensitivities and specificities are approximately 60% to 70% (Apolo et al, 2008). Further limiting the clinical adoption of ProstaScint is that the monoclonal antibody has been found to bind to

intracellular domains exposed only at apoptosis or necrosis (Troyer et al, 1997). Newer generation antibodies such as J591, which are more specific to the external components of PSMA, are promising for both prostate cancer detection and potential therapy (Smith-Jones et al, 2003).

Positron emission tomography (PET)/CT scan has gained popularity in the recurrent prostate cancer population. Although the use of ^{18}F -fluoro-2-deoxy-D-glucose (FDG) has been limited by low sensitivity secondary to modest glucose consumption in prostate cancer cells, similar uptake in benign tissue or postoperative scar, and high urinary excretion limiting anatomic delineation, radiotracers such as acetate, choline, and fluorocholine have demonstrated promise (Martino et al, 2011). In fact, the U.S. Food and Drug Administration approved choline PET for the detection of prostate cancer recurrence, which has demonstrated improvement over FDG/PET scans (Picchio et al, 2003). Two radiotracers for choline have been studied with similar results; however, ^{11}C -choline has the advantage of low urinary excretion and quality pelvic imaging. Conversely, ^{18}F -choline demonstrates higher urinary excretion but has a longer half-life and makes it suitable for centers without a cyclotron (Picchio et al, 2011). The validity of choline PET has been seen at PSA levels below 2.5 ng/mL, because up to 90% of patients will demonstrate positive scans with a specificity of 50% (Rinnab et al, 2007). Similarly, approximately 50% of patients with PSA levels less than 5.0 ng/mL were found to have a positive focus using ^{18}F -fluorocholine PET/CT. Unfortunately, PET scan with choline may be limited in patients with very low levels of PSA recurrence, because only half will be positive in patients with PSA levels less than 1.0 ng/mL (Vees et al, 2007). Another study demonstrated positive scans in only 5% of patients with PSA levels less than 1.0 ng/mL and 15% in patients with PSA levels of 1.0 to 2.0 ng/mL (Giovacchini et al, 2010).

C^{11} -acetate PET scans are another modality gaining favor in the evaluation of recurrent PSA after radical prostatectomy, with sensitivity as high as 75% in 20 men with a median PSA level of 2.0 ng/mL (Sandblom et al, 2006). Almeida and colleagues (2012) found an overall detection rate of recurrent or metastatic disease using C^{11} -acetate PET/CT of 85%. Patients with PSA values of 0.4 to 1.0 ng/mL had a detection rate of 73%, and patients with PSA levels greater than 2.0 ng/mL had a detection rate of 93% (Fig. 119-1).

PET/CT has demonstrated promise in the detection of prostate cancer recurrence; however, its clinical utility is still questionable because salvage therapies are most effective at lower levels of PSA and awaiting the conversion of PET scans to positive may delay potential curative therapy.

Magnetic resonance imaging (MRI) can be used in the detection of local recurrence after biochemical failure. Sella and colleagues (2004) analyzed endorectal MRI in 48 patients with biochemical failure after radical prostatectomy and found sensitivity and specificity of 95% and 100%, respectively. Lesions were isointense to muscle on T1-weighted images and slightly hyperintense to muscle on T2-weighted images. The mean PSA value before imaging was 2.18 ng/mL but included 25 (64%) patients with PSA levels below 1.5 ng/mL. The addition of dynamic contrast enhancement (DCE) has demonstrated an increase in accuracy over standard MRI with sensitivity of 88%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 88%. This was despite lower PSA values (mean 1.9 ng/mL) (Casciani et al, 2008). Furthermore, the combination of DCE and magnetic resonance spectroscopic imaging has demonstrated sensitivities as high as 86% in patients with PSA levels in the range of 0.4 to 1.4 ng/mL range (Sciarra et al, 2008). Compared to PET/CT, multiparametric MRI performs better in identification of local recurrence, especially at low levels of biochemical failure (Panebianco et al, 2012).

Salvage Radiation Therapy

The state of a persistent or rising PSA level after radical prostatectomy is challenging for patients and clinicians alike. Despite surgical management in patients with clinically localized prostate cancer, up to 40% of men will continue to harbor or develop a detectable PSA level (Amling et al, 2000; Han et al, 2001; Hull et al, 2002; Roehl et al, 2004; Ward and Moul, 2005). Current limitations in imaging modalities to identify local versus metastatic disease, especially at low PSA levels, create a treatment dilemma for clinicians. Despite ADT being a noncurative treatment for a rising PSA value after radical prostatectomy, approximately 60% of patients will undergo ADT as second-line treatment (Agarwal et al, 2008). Salvage radiation therapy remains the clearest choice and best chance for long-term freedom from progression.

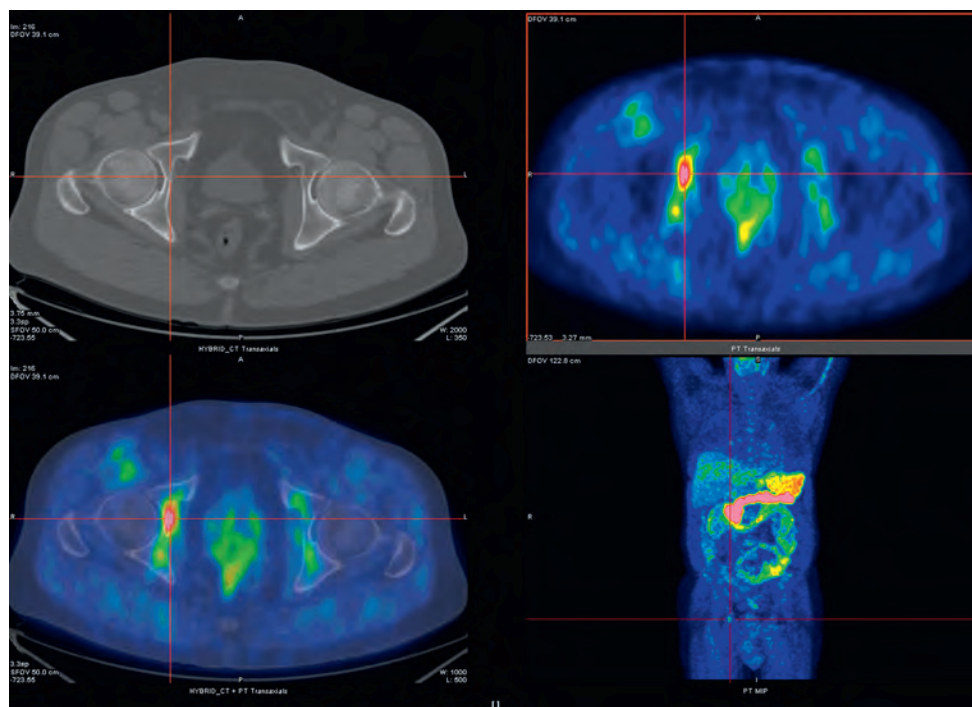


Figure 119-1. C^{11} -Acetate positron emission tomography scan in biochemical recurrence.

In 2004 a large multi-institutional group published the results of salvage radiation therapy in 501 patients who had a detectable or rising PSA level after radical prostatectomy (Stephenson et al, 2004b). Four-year freedom from progression was 45% despite including a significant portion of patients with high-risk features thought to predict for metastatic disease (high-grade disease and rapid PSA doubling time) (Stephenson et al, 2004b). On multivariable analysis, Gleason grade, pretreatment PSA level, PSA doubling time, surgical margins, use of ADT, and lymph node metastasis were significant for predicting probability of disease progression (Stephenson et al, 2007). Other groups have demonstrated similar 5-year biochemical recurrence-free survival in 35% to 46% of patients treated with salvage radiation (Buskirk et al, 2006; Bastide et al, 2010; Geinitz et al, 2012). Boorjian and associates (2009) demonstrated in their series of 856 men who received salvage radiation therapy that 534 (63.6%) achieved an undetectable PSA after therapy. On multivariable analysis, patients who received salvage radiation were at a 90% decreased risk for local recurrence, 20% decreased risk for late administration of ADT, and a 75% decreased risk for systemic progression.

Although several groups have demonstrated the value of salvage radiation therapy in improving biochemical end points, Trock and colleagues (2008) reported that salvage radiotherapy, compared to observation, also improved prostate cancer-specific survival. They found a threefold increase in prostate cancer-specific survival with salvage radiation compared to observation. This was identified in patients who received therapy within 2 years of biochemical recurrence and with a PSA doubling time of less than 6 months (Trock et al, 2008). Furthermore, salvage radiation has been demonstrated to improve all-cause mortality (Cotter et al, 2011).

Failure after salvage radiation therapy can be due to persistent local disease, recurrence of local disease, persistence of metastasis, or development of metastatic disease. It is important to identify factors that may predict for failure after salvage therapy for patient counseling and surveillance. Several groups have performed analyses on their patient cohorts undergoing salvage radiation and have identified risk factors for predicting success or failure. Buskirk and associates (2006) identified on multivariable analysis that pathologic stage T3a or less versus T3b, pathologic Gleason score, and presalvage radiation PSA levels were all predictive of biochemical relapse. Further, using these factors, a scoring system was created so that patients with no or one adverse feature had a 5-year freedom from biochemical failure rate of 69% compared to 6% in those with four or five adverse features (Buskirk et al, 2006). In addition, patients with a PSA nadir greater than 0.05 ng/mL after salvage radiation therapy have an increased risk for distant metastatic disease and worsened prostate cancer-specific survival (Geinitz et al, 2012). Using a large multi-institutional cohort of 1540 men, Stephenson and colleagues (2007) created a nomogram that predicts outcomes after salvage radiation therapy. PSA level before salvage radiation, pathologic Gleason score, PSA doubling time, margin status, lymph node status, and ADT were included for the nomogram and had a concordance index of 0.69. Although the overall progression-free survival was only 32% in the entire cohort, those with PSA levels before therapy of 0.5 ng/mL or lower had a progression-free survival of 48% (Stephenson et al, 2007). Interestingly, patients with high-risk features such as PSA doubling time less than 10 months or Gleason score of 8 to 10 had reasonable 6-year progression-free survival of 41% (Stephenson et al, 2007). Furthermore, time to biochemical failure has been found to predict for development of distant metastatic disease, prostate cancer-specific mortality, and overall mortality (Johnson et al, 2013).

Dose Response with Salvage Radiation Therapy

The primary treatment of prostate cancer with radiation therapy has taught us that higher dosages of treatment led to improved prostate cancer outcomes with limited side effects (Zietman et al, 2005). Using the same logic, many groups have developed protocols of salvage therapy, enhancing both the dosages administered and the planned targeting using intensity-modulated radiotherapy (IMRT)

versus conformal therapy, which was administered in older cohorts (Buskirk et al, 2006; Geinitz et al, 2012). In 1999 the American Society for Therapeutic Radiology and Oncology Consensus Panel released recommendations on salvage radiation stating that dosages of at least 64 Gy should be administered to the prostatic bed (Cox et al, 1999). The dosage recommendations have been reaffirmed in the recent AUA guidelines for adjuvant and salvage radiation therapy (Thompson et al, 2013). However, emerging evidence now demonstrates improvement with higher dosages.

De Meerleer and coworkers (2008) published their results with a planned target volume of 75 Gy in 37 fractions and demonstrated a biochemical freedom from disease of 67% at 5 years. There were no acute grade 3 gastrointestinal (GI) toxicities and only 3% genitourinary (GU) toxicities. Accordingly, there were minimal late GI or GU toxicities on further follow-up. Gleason score at radical prostatectomy, perineural invasion, and capsular perforation of disease were all significant predictors of biochemical recurrence. When stratifying patients into groups based on dosages of radiation of low (<64.8 Gy), moderate (64.8 to 66.6 Gy), and high (>66.6 Gy), the estimated cumulative rate of biochemical failure at 5 years was 57%, 46%, and 39%, respectively (Bernard et al, 2010). Most recently, Ost and others (2011b) demonstrated that using a median dosage of 76 Gy, they achieved 5-year biochemical recurrence-free survival of 56% and clinical recurrence-free survival of 86%. This was achieved while keeping toxicity rates low, with total GU grade 2 and 3 toxicities of 22% and GI grade 2 and 3 toxicities of 8%. Modern series of radiation therapy along with recent meta-analyses suggest improved cancer control with higher dosages of treatment (King, 2012; Ohri et al, 2012). Despite these findings, clinicians must temper some of the enthusiasm based on the potential for increased treatment-related morbidity. Results of the SAKK 09/10 trial examining 64 versus 70 Gy in salvage radiotherapy will eventually shed light on dose escalation in this particular treatment setting (<http://ClinicalTrials.gov>, 2015).

Concurrent Androgen Deprivation Therapy with Salvage Radiation

Theoretically, the use of systemic therapy with androgen deprivation may sterilize micrometastatic disease, shrink tumor burden making it more amenable to local salvage therapy, and potentially work in synergy with radiation therapy to treat remaining cancer cells. However, the concurrent administration of ADT with salvage radical prostatectomy is controversial, with mixed results in multiple series. In a cohort of 635 men with biochemical and/or local recurrence, the addition of hormonal therapy in addition to radiation therapy did not result in improved prostate cancer-specific survival (Trock et al, 2008). Prostate cancer-specific survival of 5 and 10 years was 0.96 and 0.86 for radiation alone and 0.96 and 0.82 for radiation in addition to hormonal therapy (Trock et al, 2008). This was further confirmed in a study of high-dose radiation therapy in which concurrent androgen deprivation did not improve biochemical recurrence. Patients were given 6 to 9 months of ADT in those with perineural invasion, seminal vesical involvement, and Gleason score of 8 to 10, which may have introduced a selection bias (De Meerleer et al, 2008). Conversely, Stephenson and associates (2007) determined that ADT with a mean duration of 4.1 months before or during radiation therapy led to improvement in progression-free probability. However, the administration of ADT was not standardized and some patients received as little as 1 month versus 24 months (Stephenson et al, 2007). In a modern series of high-dose salvage IMRT, the addition of ADT for 6 months improved biochemical recurrence-free survival with a hazard ratio of 0.33 (Ost et al, 2011b). Perhaps not all patients with biochemical relapse after radical prostatectomy may benefit from concurrent ADT. Soto and coworkers (2012) from the University of Michigan examined their results with salvage therapy and concurrent androgen deprivation after risk stratification. In the entire cohort, multivariable analysis demonstrated that concurrent ADT, Gleason score, and pre-radiation therapy PSA level were all predictors of progression-free

survival. On risk stratification, they determined that only the patients in the high-risk group (pT3 or greater, Gleason score of 8 or greater, or PSA level of 20 ng/mL or greater) benefited from the addition of androgen deprivation (Soto et al, 2012).

To date, the only randomized controlled trial examining this clinical question is the Radiation Therapy Oncology Group (RTOG) 96-01. This is a trial comparing salvage radiation therapy with and without 2 years of bicalutamide therapy for patients with pT3N0M0 and pT2 with positive margins. Although the primary end point is overall survival, an interim analysis has been presented in abstract form representing 771 patients with a median follow-up of 7.1 years. Patients who underwent bicalutamide in addition to salvage radiation had a freedom from biochemical progression of 57% compared to 40% in patients who underwent radiation therapy alone. Furthermore, patients who had the combination therapy had a rate of distant metastasis of 7.4% compared to 12.6% in the radiation alone arm (Shipley et al, 2011). Although we must wait until the final analysis with overall survival, these results are encouraging. The Radiotherapy and Androgen Deprivation in Combination after Local Surgery (RADICALS) trial is a randomized phase III controlled trial that evaluated the timing of radiotherapy (adjuvant vs. early salvage) and the duration of concurrent ADT. Patients will receive none, 6 months, or 2 years of androgen deprivation with a gonadotropin-releasing hormone analogue or bicalutamide. The outcomes evaluated are cause-specific and overall survival (Parker et al, 2007). Final results of these trials will determine the necessity and optimal duration of ADT.

Whole-Pelvis versus Prostatic Bed Radiation Therapy

Very few series evaluate the role of whole-pelvis versus prostatic bed-only salvage radiation therapy after biochemical recurrence. Just like radiation dosage and concomitant ADT, there are no mature randomized controlled trials that clearly demonstrate the added benefit of whole-pelvis radiation. Spiotto and colleagues (2007) evaluated their experience in 160 men who underwent both adjuvant and salvage radiation therapy, of which 114 were considered high-risk for lymph node involvement (Gleason score ≥ 8 , preoperative PSA > 20 ng/mL, seminal vesicle involvement, capsular extension, and lymph node positivity). Seventy-two patients received whole-pelvis radiation versus 42 who underwent radiation of only the prostatic bed. The benefit of whole-pelvis radiation was limited to those with high-risk features with 5-year biochemical

recurrence-free survival of 47% versus 21% for prostatic bed alone (Spiotto et al, 2007). On multivariable analysis, whole-pelvis radiation and preoperative PSA level of less than 1 ng/mL were predictors of biochemical recurrence-free survival (Spiotto et al, 2007). Furthermore, in patients with high-risk features, concurrent androgen deprivation with whole-pelvis radiation conferred improved recurrence-free survival (Spiotto et al, 2007).

In 2013, Moghanaki and colleagues published their series of 247 patients undergoing salvage radiation therapy. This study compared two separate institutions with differing approaches to salvage radiation, with one group performing prostatic bed radiation (135 patients) and the other group performing pelvic nodal radiation in addition to prostatic bed (112 patients). Pretreatment PSA values and pathologic Gleason score were independent predictors of biochemical recurrence, but whole-pelvis radiation was not an independent predictor associated with PSA recurrence-free survival. Even after separating patients by low-risk and high-risk features, there was no benefit to whole-pelvis irradiation. However, when examining a subset of patients with preradiation PSA levels of 0.4 ng/mL or greater, there was a 53% risk reduction in biochemical progression with whole-pelvis radiation (Moghanaki et al, 2013).

RTOG 0534 is a randomized controlled trial currently accruing patients with high-risk prostate cancer features on radical prostatectomy and with postsurgery PSA levels of 0.1 ng/mL or greater to less than 2.0 ng/mL. Patients will be stratified by seminal vesicle involvement, Gleason score, pretreatment PSA level, and stage. Patients will be randomized to prostatic bed radiation alone, prostatic bed radiation plus 6 months of androgen deprivation, and prostatic bed radiation therapy plus pelvic lymph node radiation therapy along with 6 months of ADT. Patients will undergo either three-dimensional conformal radiotherapy (3D-CRT) or IMRT at 64.8 to 70.2 Gy for the prostatic bed and 45 Gy to the pelvic lymph nodes. The primary objective is to evaluate freedom from biochemical progression, clinical failure, and overall survival. The results of this trial will help clarify this treatment dilemma (Figs. 119-2 and 119-3).

Adjuvant Radiation Therapy

The National Cancer Institute defines adjuvant therapy as additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy,

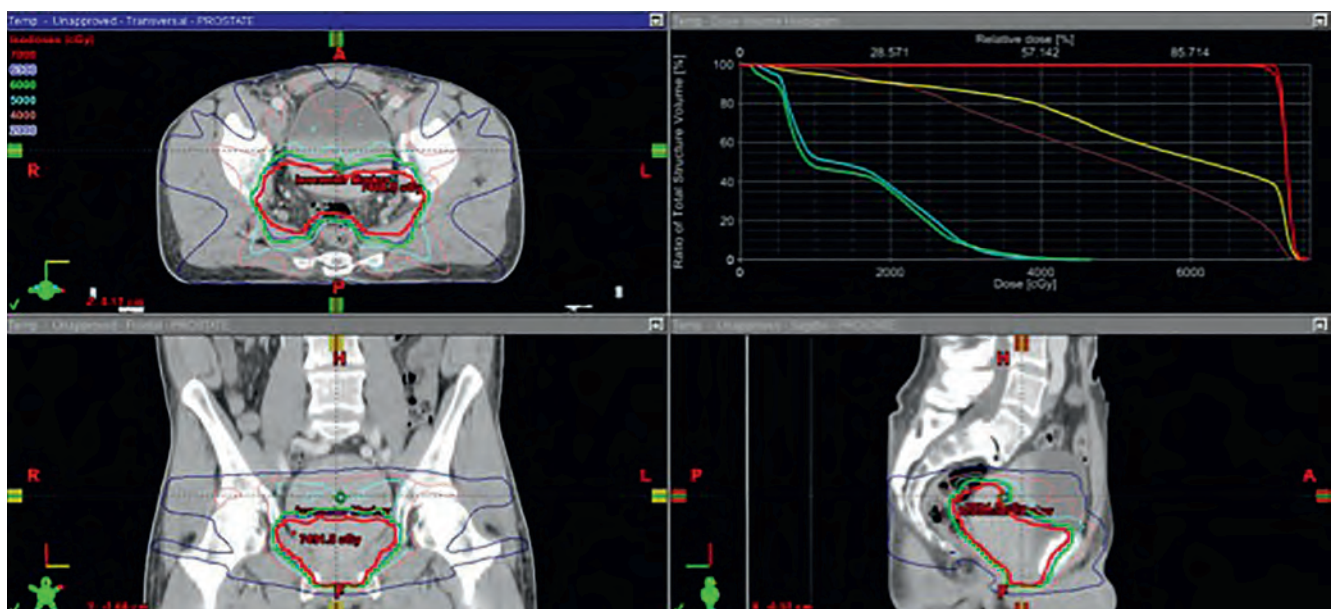


Figure 119-2. Prostate bed-only salvage radiotherapy after radical prostatectomy.

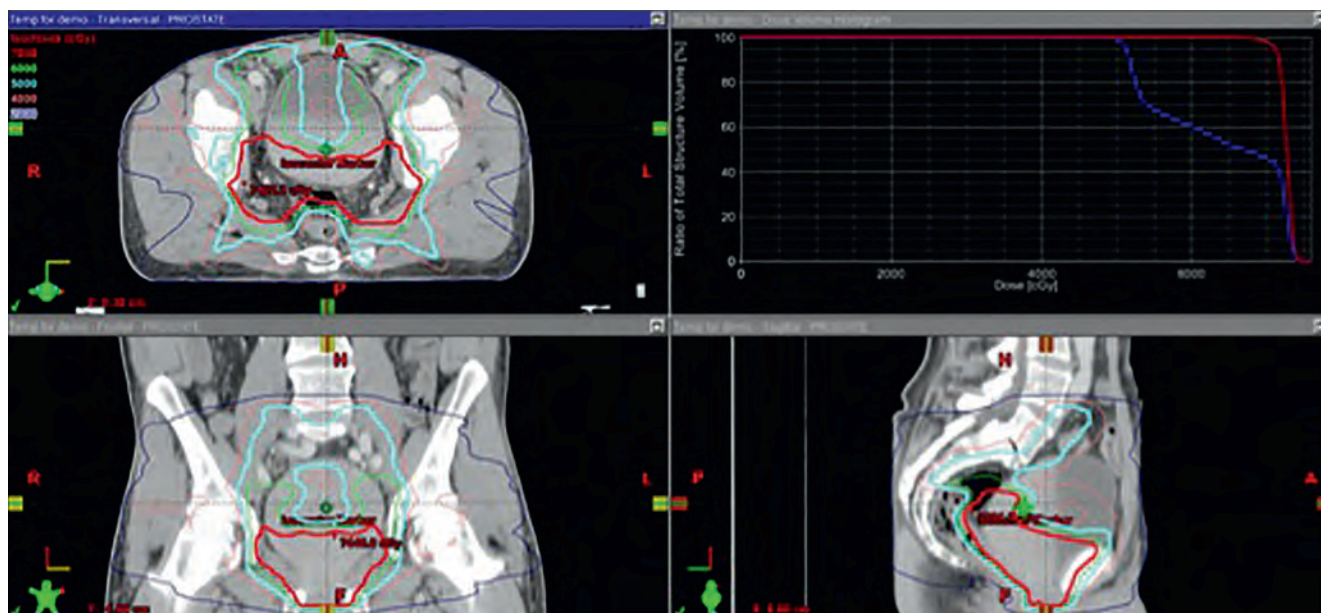


Figure 119-3. Whole-pelvis radiotherapy after radical prostatectomy.

targeted therapy, or biologic therapy (National Cancer Institute, 2015). After radical prostatectomy, patients at high risk for local recurrence are offered radiation therapy to prolong the disease-free interval. Typically, this is administered 4 to 6 months after radical prostatectomy when the PSA is still undetectable and when patients have regained urinary continence. Several well-performed, randomized clinical trials have demonstrated improved biochemical recurrence-free and cancer-specific survival with the implementation of adjuvant radiation therapy (Bolla et al, 2005; Thompson et al, 2006; Wiegel et al, 2009). In fact, the most recent AUA guidelines read, "Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy including seminal vesicle invasion, positive surgical margins, or extraprostatic extension because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression" (Thompson et al, 2013).

Southwest Oncology Group (SWOG) 8794 was initiated in 1987 and included 431 men with pT3 prostate cancer and/or positive surgical margins (Thompson et al, 2006). Patients were randomized into observation versus adjuvant radiation with 60 to 64 Gy in 30 to 32 fractions. Approximately two thirds of all participants had undetectable PSA at randomization (Thompson et al, 2006). At a median follow-up of approximately 12.5 months, the median metastasis-free survival in the adjuvant radiation therapy arm was 14.7 years compared to 12.9 years in the control group, which reached statistical significance (Thompson et al, 2009). Furthermore, the median overall survival was 15.2 years for the adjuvant therapy group compared to 13.3 years in the wait and see arm, again reaching statistical significance. The number of men with pathologic T3 disease who must be treated with adjuvant radiotherapy to prevent 1 death at a median follow-up of 12.6 years was 9.1 patients (Thompson et al, 2009). Therefore the authors conclude that adjuvant radiotherapy within 18 weeks after radical prostatectomy in a man with T3N0M0 prostate cancer significantly reduces the risk for PSA recurrence, metastasis, and need for hormonal therapy and increases overall survival (Thompson et al, 2009).

The European Organization for Research and Treatment of Cancer (EORTC) 22911 trial was initiated in 1992 and evaluated the role of postoperative radiotherapy after radical prostatectomy to a wait and see approach (Bolla et al, 2005). A total of 1005 patients were eventually randomized to either a wait and see approach or adjuvant radiation with 60 Gy. The primary end points included biochemical progression-free survival, clinical progression-free

survival, and local recurrence; however, during the trial, biochemical progression-free survival replaced local control as the primary end point. Kaplan-Meier estimated 5-year biochemical progression-free survival rate was 52.6% in the wait and see arm compared to 74% in the adjuvant radiation arm. Clinical progression-free survival, defined as no evidence of clinical, sonographic, radiographic, or scintigraphic recurrence, was also improved in the radiation group compared to the control group, as was locoregional failure at 5 years, which was significantly lower in the postirradiation group and 5.4% versus 15.4% in the wait and see group. There was no difference in overall survival (Bolla et al, 2005).

Finally, ARO 96-02, a German study, was published in 2009. Similarly to the other two phase III randomized controlled clinical trials, this was a comparison between adjuvant radiotherapy after radical prostatectomy and radical prostatectomy alone. A major difference in this trial from the other two is that patients had an undetectable PSA level after radical prostatectomy before randomization. A group of 388 patients with pT3 or pT4 but without nodal metastatic disease were randomly assigned after prostatectomy. Patients were included with and without positive margins. After exclusion of men for various reasons, 154 in the wait and see group and 114 in the adjuvant radiation group remained for final analysis. Radiation was delivered 6 to 12 weeks postoperatively when no voiding problems were present. Dose given was 60 Gy over 30 fractions from the seminal vesicle region to the apex, with some added security margin. Patients in the wait and see group underwent salvage therapy with radiation and/or hormone therapy on recurrence. The 5-year biochemical-free survival in the radiotherapy group was 72% versus 54% in the wait and see group (Wiegel et al, 2009).

Despite the well-performed phase III randomized controlled trials and the recent AUA guidelines, there exists some skepticism in regard to the optimal timing and necessity of adjuvant radiation. Opponents of pure adjuvant therapy argue that there is a risk for overtreating patients who are never destined to fail local treatment. In fact, a significant proportion of men with extracapsular extension, positive surgical margins, and/or seminal vesicle invasion at radical prostatectomy will not experience biochemical relapse (Eggerer et al, 2005; Swindle et al, 2005; Vis et al, 2006). Furthermore, there are significant local toxicities inherent to radiation therapy and patients should be counseled that treatment is not without consequence. In the SWOG study, there was a 3.2% rate of proctitis and bleeding, 6.5% rate of urethral stricture, and 17% rate

of total urinary incontinence, and there was a 4.2% rate of grade 3 or worse toxicities in the adjuvant radiation arm of the EORTC trial (Bolla et al, 2005; Thompson et al, 2006, 2009). Clearly, clinicians watching patients as they regain continence are hesitant to administer radiation doses that may at best halt urinary recovery and perhaps even worsen symptoms. However, with modern radiation targeting, accurate delivery of dosages may improve side effects. Further, increased doses of up to 70 Gy may improve long-term cancer outcomes and offset the deficits in quality-of-life outcomes associated with radiation therapy.

Subgroup analyses may indicate there are patient groups that may or may not benefit the most from adjuvant radiation. Van der Kwast and colleagues (2007) evaluated the results of a centralized review of the patients from the EORTC trial. Of the 1005 prostates, 552 were reviewed again, and only patients with a positive margin were found to have benefited from adjuvant radiation (Van der Kwast et al, 2007). The authors of ARO 96-02 also performed subgroup analysis and demonstrated that adjuvant radiation is favored in patients with positive surgical margins, PSA greater than 10 ng/mL, pT3a/b, and both Gleason stratifications (Wiegel et al, 2009). Finally, in the SWOG trial with the longest follow-up with the most clinically relevant end points of metastasis-free and overall survival, there was not a defined subgroup that did not benefit from adjuvant radiation (Thompson et al, 2009). Therefore, in adherence to the AUA guidelines, all men who are anticipated to have high-risk outcomes after radical prostatectomy should be counseled on the potential need for secondary treatment. After radical prostatectomy, all men with extracapsular extension, involved seminal vesicles, and/or positive margins should be counseled about the potential benefits of adjuvant radiation therapy.

Salvage versus Adjuvant Radiation Therapy for Prostate Cancer

Mature randomized controlled trials are lacking to evaluate salvage versus adjuvant radiation therapy. Several studies have compared the two, but there are inherent biases because patient cohorts who undergo salvage therapy already have demonstrated failure after radical prostatectomy whereas the adjuvant cohorts include up to 50% of patients who will not experience clinical progression. In a cohort of 192 men matched 1:1 by preoperative PSA levels, Gleason score, seminal vesicle invasion, and surgical margin, 5-year freedom from biochemical failure was 75% for adjuvant radiation versus 66% for salvage therapy. When examined from the end of radiation therapy, this was more significant, with 73% for adjuvant radiation versus 50% for salvage therapy (Trabulsi et al, 2008). This was despite a reasonable median presalvage radiation PSA level of 0.7. These findings were confirmed in a study of 219 patients subdivided into homogeneous subgroups based on lymphatic invasion and surgical margins in which they determined that adjuvant radiation in patients with high-risk features was associated with improved disease-free survival compared to salvage therapy (Budiharto et al, 2010). Furthermore, despite high-dose IMRT (74 to 76 Gy), adjuvant radiation therapy improved 3-year biochemical recurrence-free survival 90% versus 65% in salvage therapy (Ost et al, 2011a). Adjuvant therapy also demonstrated improvement in clinical progression-free survival. However, in subgroup analysis, early salvage therapy defined as delivery of radiation at a PSA level of 0.5 ng/mL or less demonstrated a 3-year biochemical recurrence-free survival of 86% compared to 46% for late treatment. The early group was comparable to 92% demonstrated by the adjuvant group ($P = .67$), demonstrating the potential role of early salvage radiation, which may spare the morbidity of radiation therapy to those patients who do not demonstrate a propensity to recurrence while treating early enough in the disease process to be meaningful (Ost et al, 2011a). Furthermore, in a propensity-matched analysis of adjuvant radiation therapy versus early salvage radiation (radiation delivered at a postoperative PSA ≤ 0.5 ng/mL) at least 6 months after radical prostatectomy, 2-year and 5-year biochemical free-survival were 91.4% and 78.4% for adjuvant therapy compared to

92.8% and 81.8% for early salvage radiation therapy, respectively (Briganti et al, 2012).

Clearly, randomized phase III clinical trials are desperately needed to determine the role of adjuvant radiation versus early salvage radiation therapy. As mentioned previously, the RADICALS trial is a multi-institutional phase III clinical trial examining adjuvant radiation within 22 weeks of surgery versus early salvage therapy at PSA relapse which is defined as either two consecutive rises in PSA level and a PSA value greater than 0.1 ng/mL or three consecutive rises in PSA (Parker et al, 2007). If biochemical recurrence is detected, patients will undergo either 66 Gy in 33 daily fractions over 6.5 weeks or 52.5 Gy on a 4-week treatment schedule. The Radiotherapy-Adjuvant Versus Early Salvage (RAVES) trial is a phase III trial randomizing patients with pathologic T3 disease and/or positive margins. Primary end point is biochemical cancer control with secondary outcomes including quality of life, toxicity, anxiety/depression, biochemical failure-free survival, overall survival, disease-specific survival, time to distant failure, time to local failure, time to initiation of androgen ablation, quality adjusted life years, and cost-utility. Finally, the French Groupe d'Étude des Tumeurs Uro-Génitales (GETUG-17) trial will evaluate a similar patient population but will randomize patients to immediate adjuvant radiation therapy versus observation patients and treating with salvage radiation when PSA levels reach a level of 0.2 ng/mL. Both groups will undergo a short course of ADT. As these trials complete accrual and mature, we will gain a better understanding about the timing of radiation therapy along with the utility of concomitant ADT.

Androgen Deprivation Therapy for Biochemical Failure after Radical Prostatectomy

ADT in the postprostatectomy setting has been underevaluated, and the scope of its utility is lacking. Unfortunately, randomized controlled trials are limited and the exact role in the comprehensive care of aggressive prostate cancer is not completely understood. Large retrospective series have demonstrated mixed results. Early ADT in men who have experienced biochemical recurrence has been found to decrease the rates of clinical metastasis in patients with high-risk features defined as Gleason sum greater than 7 or PSA doubling time less than 12 months (Moul et al, 2004). Delineation between early and late administration of androgen deprivation was significant at PSA cut points of 5 and 10 ng/mL (Moul et al, 2004). Similarly, the adjuvant ADT before signs of biochemical progression in select patients demonstrates improved 10-year progression-free and cancer-specific survival (Siddiqui et al, 2008). This was true even compared to a cohort of patients who received systemic therapy at PSA values of 0.4 ng/mL and above. Regardless of improvements in biochemical and cancer-specific outcomes, there is no evidence of improved overall survival (Siddiqui et al, 2008). Furthermore, the benefits in administration of ADT must be tempered by the potential for increased risk for cardiac disease and diabetes (Keating et al, 2006).

Not all patients who experience biochemical recurrence require ADT, and the identification of subgroups at highest risk for systemic failure will optimize selection and prevent morbidity. Patients with pathologic T3b tumors benefit from the adjuvant administration of ADT and experience improved 10-year biochemical progression-free survival of 60% versus 16% (Siddiqui et al, 2011). These patients also demonstrated improved local recurrence-free, systemic progression-free, and CSS. But again, there was no statistically significant improvement in overall survival (Siddiqui et al, 2011). Patients with high-risk features such as Gleason score of 8 or higher; PSA level 15 ng/mL or higher; pathologic stage T3b, T4, or N1; or Gleason score 7 with concomitant PSA value greater than 10 ng/mL or a positive margin, were found to have a biochemical failure-free survival of 92.5% at 5 years, with an overall survival of 95.9% in patients treated with adjuvant ADT as part of a randomized clinical trial (Dorff et al, 2011). Patients who have positive lymph nodes at radical prostatectomy are at highest risk for micrometastatic disease

and eventual systemic failure. In a randomized clinical trial of immediate versus deferred ADT, patients who received immediate therapy demonstrated improved overall survival, cancer-specific survival and progression-free survival at a follow-up of 11.9 years (Messing et al, 2006). Clearly, patients at the highest risk for local and systemic recurrence are those who likely benefit the most from adjuvant hormone therapy.

RADIATION THERAPY

Prostate-Specific Antigen Recurrence after Definitive Radiotherapy

Similar to PSA recurrence after radical prostatectomy, biochemical recurrence after definitive radiotherapy precedes clinical failure. This gives ample warning of potential disease progression to initiate secondary/salvage therapies. However, the definition of biochemical failure and threshold values has been controversial. In 1996, a multidisciplinary panel of experts met in San Antonio, Texas, to impart a definition of biochemical failure using the PSA. Their stated goals included creating a definition to be used in clinical practice as well as clinical trials. Furthermore, the definition should be valid for studies of dose intensity, brachytherapy, adjunctive hormones, and other systemic agents (American Society for Therapeutic Radiology and Oncology [ASTRO] Consensus Panel, 1997). The standard definition of PSA failure was determined as three consecutive rises in PSA level after a nadir PSA, with the date of failure as the midpoint between the nadir PSA and first failure. However, the panel made it a point to state that PSA failure is not equivalent to clinical failure and should not be used as a justification for additional treatment. Furthermore, PSA determinations should be obtained at 3- to 4-month intervals for at least 2 years and a minimum follow-up of 24 months completed before publication of any series (ASTRO Consensus Panel, 1997).

Although the ASTRO definition of biochemical failure with three consecutive rises above a nadir PSA created consensus among different series of definitive radiation, there were significant issues with the definition. Clearly, backdating biochemical failure biased event-free survival outcomes and was dependent on length of follow-up (Vicini et al, 1999; Thames et al, 2003). Furthermore, this definition was not linked to any clinically significant outcomes such as clinical failure or cancer-specific or overall survival. It also became evident that publications failed to incorporate patients with adequate follow-up (24 months), used the definition for alternative radiation methods, and included patients treated with ADT. In 2005, another multidisciplinary panel of experts met in Phoenix, Arizona, to discuss a new definition of biochemical failure after definitive radiation therapy for prostate cancer (Roach et al, 2006). This group defined PSA recurrence as a rise of 2 ng/mL or more above the nadir PSA and the date of failure was at call. Importantly, the stated biochemical outcomes should be 2 years short of the median follow-up for the group to avoid any overestimations of biochemical-free survival. Furthermore, the definition was created for use in patients who also received concurrent ADT (Roach et al, 2006).

It is now clear that the Phoenix definition of biochemical recurrence is more robust in predicting clinical outcomes. In a contemporary series of definitive radiotherapy for prostate cancer, 1831 men with clinical stage T1 to T4 prostate cancer without nodal or metastatic disease was compared using the ASTRO and Phoenix definitions of biochemical recurrence to predict for metastatic disease and cancer-specific and overall mortality (Abramowitz et al, 2008). Accounting for covariates such as T stage, initial hormonal treatment, Gleason score, radiation dosage, PSA level, and age, the Phoenix definition was found to be a significant predictor of metastatic disease, cancer-specific mortality, and overall mortality on univariate and multivariable analysis. The ASTRO definition was significant for metastatic disease and cancer-specific mortality to a lesser degree and not significant at all for overall survival (Abramowitz et al, 2008). In fact, on multivariable analysis,

PSA nadir + 2 ng/mL was the most significant predictor of all three outcomes compared to all other covariates confirming the validity of this definition of PSA recurrence (Abramowitz et al, 2008).

Postradiation Prostate-Specific Antigen Bounce

Postradiation PSA "bounce" is a varied definition of an elevated PSA of 0.1 to 0.5 ng/mL over the prebounce PSA level, with a subsequent decrease in PSA level (Cavanagh et al, 2000; Critz et al, 2000; Hanlon et al, 2001; Rosser et al, 2002). It is thought that this phenomenon occurs secondary to post-treatment prostatitis (Critz et al, 2000) or even from the delivery of a sublethal dosage of radiation with associated delayed cellular death. Rosser and colleagues (2002) defined PSA bounce among their cohort as a rise of PSA level of at least 0.5 ng/mL followed by a decrease to baseline value and found in their group of men that the bounce occurred at a mean time of 9 months from therapy and was associated with an improvement in biochemical recurrence-free survival compared to those who did not have a bounce. Conversely, Hanlon and colleagues (2001) defined PSA bounce as a rise in PSA level of at least 0.4 ng/mL over a 6-month period followed by a decrease in PSA level by any value. One third of their study cohort experienced a PSA bounce at a median time to bounce of 35 months (Hanlon et al, 2001). Although patients with a PSA bounce had 5-year biochemical rates of no evidence of disease (NED) of 52% versus 69% for those who did not bounce, the authors emphasize that clinicians should not use the existence of a PSA bounce as an indication of relapse. Series of brachytherapy in addition to external-beam radiation demonstrate similar rates of PSA bounce of approximately 35% (Cavanagh et al, 2000; Critz et al, 2000). It is quite clear that patients who undergo a transient rise in their PSA should be closely monitored, because not all men are destined for biochemical failure, let alone clinical failure.

Natural History of Prostate-Specific Antigen Recurrence after Definitive Radiation

PSA-only recurrence after definitive radiation therapy for prostate cancer leads to clinically relevant outcomes such as local and distant failure along with cancer-specific death. Lee and colleagues (1997) demonstrated in their cohort of 151 men that men with higher pretreatment PSA levels, higher Gleason scores, and higher stage were more likely to develop an increasing PSA profile (PSA \geq 1.5 ng/mL on two occasions). Furthermore, 5 years after PSA elevation, the estimated rate of local recurrence was 26% and distant metastasis was 47%. Overall survival and cause-specific survival (CSS) at 5 years were 65% and 76%, respectively. Although rapid PSA doubling time and short interval from treatment to PSA elevation were predictors of subsequent metastatic disease, Gleason grade was the only predictor for overall survival and CSS (Lee et al, 1997). Men with PSA elevation after definitive radiotherapy are candidates for salvage therapy. Defining those at greatest risk for local versus distant failure is key to deciding on second-line therapy. Further, patient comorbidity and age must be considered before the initiation of treatment.

Biopsy after Radiotherapy

The goals of biopsy after definitive radiation are to identify the presence or absence of locally residual or recurrent disease and to identify the grade of remaining disease. Crook and colleagues (2000) recommended biopsies to be performed at least 2 to 3 years after the completion of radiation therapy to decrease the rates of false-positive and false-negative biopsies. Biopsy based on ultrasound or magnetic resonance (MR) guidance should target abnormal lesions, the seminal vesicles, and a systematic sampling of the entire prostate gland. The information from prostate biopsy will guide further treatment strategies and should be reserved for patients in whom salvage local therapy is considered. One should keep in mind that tumor architecture is altered after radiation therapy

and may represent dedifferentiation of cancer cells. Further, Gleason grading after radiation therapy may or may not be accurate and its utility is controversial (Cheng et al, 1998, 1999; Letran and Brawer, 1998).

Imaging after Biochemical Recurrence Following Radiotherapy

Imaging of the prostate after definitive radiotherapy remains challenging with traditional modalities because of fibrosis and shrinkage of the prostate (Martino et al, 2011). TRUS has limited ability to identify suspicious lesions of the prostate and has a sensitivity and specificity profile no better than that of rectal examination (Crook et al, 1993). Furthermore, although CT is useful in patients with significantly elevated PSA levels (>20 ng/mL) for the detection of bone and lymph node metastasis, the ability to identify recurrent cancer after radiotherapy is limited. Recently, MRI has emerged as the most promising technique for identifying recurrent tumors of the prostate in biochemical recurrence.

T2-weighted MRI of the prostate is capable of excellent soft tissue differentiation; however, its use in postirradiated tissue is limited by diffusely decreased signal intensity in the prostate (Coakley et al, 2001). Sensitivity of T2-weighted MRI is as low as 27%, with limited positive predictive value of 32% (Kim et al, 2010). Therefore dynamic imaging studies have been pursued to better identify potential recurrent lesions amenable for salvage therapy. DCE gives the ability to identify vascularization of the prostate and tumor along with angiogenesis and capillary permeability characteristics (Franiel et al, 2011). When comparing DCE-MRI with T2-weighted MRI, DCE-MRI had better sensitivity (72% vs. 38%), positive predictive value (46% vs. 24%), and negative predictive value (95% vs. 88%). Specificity was similarly high for both groups (Haider et al, 2008). Yakar and colleagues (2010) determined that the combination of DCE imaging along with MR-guided biopsy of suspicious lesions led to a positive predictive value of 75% and 68% per patient and per tumor suspicious region, respectively.

MR spectroscopy distinguishes residual prostate cancer by identifying a relative increase of choline plus creatine-to-citrate ratio or by identifying an increase in the choline peak with no citrate identified. Using these criteria, MR spectroscopy has demonstrated sensitivity of 77% compared to sextant biopsy and rectal examination, which revealed sensitivities of 48% and 16%, respectively, in the same patient cohort (Pucar et al, 2005). However, it is important to note that benign glands can exhibit high choline levels after radiation and may cause false positive findings (Pucar et al, 2005). Furthermore, the addition of MR spectroscopy to T2-weighted imaging significantly improved the detection of locally recurrent prostate cancer after radiation therapy (Westphalen et al, 2010).

Diffusion-weighted imaging MRI (DWI-MRI) also has demonstrated feasibility in the clinical setting. Kim and colleagues found the utility alone and in combination with DCE imaging revealing an accuracy of biopsy as high as 83% (Kim et al, 2010). This was in comparison to T2-weighted MR, which demonstrated an accuracy rate of 67%. Further illustrating the benefit of DWI-MRI, Hara and colleagues (2012) found a sensitivity and specificity of 100% and 100%, respectively, on a per-patient basis when comparing MRI findings to a 22-core 3D prostate-mapping biopsy as the standard reference. On a region-by-region basis, the sensitivity and specificity were 69% and 91%, respectively. These data demonstrate the utility of MRI in patients with biochemical recurrence after radiation therapy. The optimal timing of MRI and level of PSA at imaging are yet to be determined and will need further investigation.

Salvage Radical Prostatectomy

Salvage radical prostatectomy is considered the most definitive way to eradicate localized radiorecurrent prostate cancer. Despite the infrequent use of salvage surgery in the setting of radiorecurrence, multiple studies have demonstrated the 10-year cancer-specific survival to be as high as 70% to 83% (Lerner et al, 1995; Bianco et al,

2005; Ward et al, 2005; Chade et al, 2011). However, survival outcomes directly correlate with pathologic stage whereby organ-confined disease and isolated extracapsular extension confer a 5-year progression-free probability of 77% and 71%, respectively. Conversely, those with seminal vesicle invasion and lymph node involvement have poorer 5-year outcomes of 28% and 22%, respectively (Bianco et al, 2005; Stephenson and Eastham, 2005). Given the high propensity for prostate cancer to recur despite radiation therapy, it is of utmost importance to treat with definitive salvage therapy before local invasion and metastasis. Preoperative PSA functions as a predictor of disease, because approximately two thirds of patients with a PSA lower than 10 ng/mL will have organ-confined disease. Furthermore, these patients have a 5-year progression-free probability of approximately 70% (Stephenson and Eastham, 2005). In a modern series of salvage prostatectomy after contemporary radiation, Heidenreich and associates (2010) found that 73% of patients had organ-confined disease, of which PSA doubling time of greater than 12 months, previous brachytherapy, and less than 50% of the biopsy core positivity were predictors of organ confinement, margin negativity, and lymph node negativity.

Despite successful cancer outcomes in traditional and contemporary series of salvage radical prostatectomy, the hesitance to perform such operations is due to the inherent risks for significant morbidity. Historically, up to 50% of patients who undergo salvage surgery will experience a major complication (Moul and Paulson, 1991). As a result of significant fibrosis from radiation, rectal injury rates of 6% to 15% and bladder neck contracture rates of 20% to 28% have been reported. Further, rates of urinary incontinence ranged from 40% to 60% (Lerner et al, 1995; Rogers et al, 1995). It is worth mentioning that in these surgical series, some patients had received preradiation pelvic lymph node dissection, retropubic brachytherapy, and nonconformal radiation delivery, which added to the morbidity. Because of the high complication rates, clinicians have been hesitant to perform salvage radical prostatectomy. This is reflected in the Cancer of the Prostate Strategic Urology Research Endeavor (CaPSURE) database, demonstrating that only 2% of patients underwent surgery as secondary treatment after radiation failure whereas 92% underwent noncurative ADT (Grossfeld et al, 2002).

With improved surgical techniques and patient selection, the morbidity in modern series of salvage radical prostatectomy has improved dramatically. In fact, major complication rates were reduced from 33% to 13% in one series, with rectal injury rates of 2% to 4% (Stephenson et al, 2004a; Heidenreich et al, 2010). Clearly, better surgical planning, meticulous attention to anatomy, and improved radiation delivery have played a major role in improved morbidity. Continence rates are now seen in the 70% to 80% range, and modern series even demonstrate that 16% to 18% of men can achieve erections sufficient for intercourse with or without the aid of PDE5 inhibitors (Stephenson et al, 2004a; Heidenreich et al, 2010). Given the improvement in morbidity outcomes and the knowledge that long-term cancer-specific outcomes can be achieved with radical surgery, patients who are at risk for radiation failure should be identified early and encouraged to undergo definitive therapy. However, because of the risk for devastating complications such as fistula, patient selection is of the utmost importance. **Patients selected for salvage radical prostatectomy should have biopsy-proved radiorecurrent prostate cancer, at least 10 years of life expectancy, lack of identifiable metastasis on imaging, and a PSA level of less than 10 ng/mL (Table 119-2).**

Within the last 10 years, there has been a preponderance of robotic-assisted laparoscopic prostatectomy procedures and, naturally, this approach has begun to gain favor among urologists willing to tackle salvage prostatectomy. Perceived advantages to the robotic approach include decreased blood loss, better visualization, and shorter hospitalization. There have been several smaller series of patients reporting both oncologic and morbidity outcomes in patients undergoing robotic salvage prostatectomy. In the two largest series, the biochemical failure rates were reported to be 18% and 33%. However, median follow-up in these series was limited

TABLE 119-2 Outcomes of Salvage Radical Prostatectomy for Radiorecurrent Prostate Cancer

STUDY	N	YEARS	MEDIAN FOLLOW-UP (yr)	% DISEASE-FREE INTERVAL (yr)	% CANCER-SPECIFIC SURVIVAL (yr)
Chade et al, 2011	404	1985-2009	4.4	37.5 (10)	83 (10)
Paparel et al, 2009	146	1984-2006	3.8	54 (5)	—
Ward et al, 2005	138	1967-2000	6.4	—	90 and 77 (5, 10)
Bianco et al, 2005	100	1984-2003	5	55 and 30 (5, 10)	73 and 60 (10, 15)

at 16 and 18 months, respectively (Eandi et al, 2010; Kaffenberger et al, 2013). Long-term studies are necessary to demonstrate oncologic efficacy. One area in which robotic surgery has shown equivalence if not improvement is in morbidity. In the three largest series of robotic salvage prostatectomy, only 1 of 63 patients has been reported to have suffered a rectal injury, six patients had bladder neck contractures, and 12 patients had anastomotic leakage. Urinary continence rates have been reported to range from 33% to 80%, depending on definition and follow-up (Boris et al, 2009; Eandi et al, 2010; Kaffenberger et al, 2013). Because both data and surgeon experience mature, both oncologic and morbidity outcomes will likely demonstrate improvement. Similar to open surgery, patient selection and close adherence to surgical principles are of utmost importance.

Salvage Cryotherapy

In the United States, approximately one third of men newly diagnosed with prostate cancer are treated with external-beam radiation and/or brachytherapy as the primary modality of therapy (Mettlin et al, 1998, 1999). Depending on the series and definition, approximately 30% to 40% of patients treated with primary radiation will have failure (Shipley et al, 1999; Crook et al, 2000; Touma et al, 2005; D'Amico et al, 2008). In the carefully selected patient, cryotherapy may be an effective and safe option for treatment of radio-recurrent disease.

Patients best suited for cryotherapy are those with localized treatment failure after radiation therapy with biopsy-proved disease, because approximately one third of patients with biochemical failure will have a positive biopsy result (Crook et al, 1995). Regardless of definition, biochemical failure determination and histologic failure are ideally identified at least 2 years after primary treatment to account for PSA bounce and ongoing histologic changes after radiation (Crook et al, 2000; Chin et al, 2007). In addition to standard multicore prostate biopsy, it may be prudent to include the seminal vesicles, because up to 29% may have involvement and predict for poor outcomes (Gheiler et al, 1998). Candidates for salvage cryotherapy should have a reasonable life expectancy and must undergo a full metastatic workup with cross-sectional imaging (CT abdomen/pelvis or MRI), along with a radionuclide bone scan (Babaian et al, 2008). Pelvic lymph node biopsy also may be considered in high-risk patients (Babaian et al, 2008). A presalvage PSA level of less than 10 ng/mL (ideally < 4 ng/mL) (Ng et al, 2007) and a PSA doubling time of 16 months or longer have been shown to be predictive for successful treatment (Spiess et al, 2006).

To date, there is no universal definition of success using salvage cryotherapy. Using a definition of 2 ng/mL above the postcryotherapy nadir, Pisters and colleagues demonstrated a 74% 2-year disease-free survival for patients with postradiation PSA less than 10 ng/mL and 58% for patients with preradiation Gleason score of 8 or less (Pisters et al, 1999). In a contemporary analysis of the COLD (cryo online data) Registry including 156 patients, 3-year biochemical disease-free survival using the Phoenix definition of nadir + 2 ng/mL was determined to be 66.7% (Spiess et al, 2013). Williams and associates (2011) report their outcomes in 176 patients with a mean follow-up of 7.46 years. Primary outcome of overall survival was 95%, 91%, and 87% at 5, 8, and 10 years,

respectively. Biochemical disease-free survival using the Phoenix definition was determined to be 47%, 39%, and 39%, respectively. Patients with a postcryotherapy nadir of greater than 1 ng/dL had a 6.6 times higher risk for recurrence, and 5-year disease-free survival was only 3%, highlighting this as an important prognostic factor.

Clearly, the success of any salvage therapy is tempered by the significant risks for side effects. Third-generation cryotherapy involves the adoption of a liquid argon gas system, smaller diameter probes, pinpoint thermocoupler, and continued use of TRUS guidance and urethral warmers. Historically, salvage cryotherapy was wrought with a high complication rate. In terms of urinary morbidity, one of the largest quality-of-life series of 112 men demonstrated 72% of men had urinary incontinence, with 66% of men describing their symptoms as moderate to severe. Only 33% felt satisfied by the therapy they had received (Perrotte et al, 1999). However, more recent data demonstrate improved urinary incontinence rates from 4.3% to 6.5% (Bahn et al, 2003; Donnelly et al, 2005; Pisters et al, 2008). This drastic improvement in results is likely due to the universal use of urethral warming, which helps protect the urinary sphincter mechanism. Erectile dysfunction has been difficult to gauge in salvage cryotherapy series secondary to inconsistent reporting and lack of validation. In the series from Perrotte and colleagues (1999), 15% of patients who were potent before treatment maintained erectile function sufficient for sexual intercourse. Ismail and coworkers (2007) report a rate of erectile dysfunction of 86%. Clearly, erectile dysfunction is a significant risk from the primary treatment and further cryotherapy is likely to worsen symptoms. Current exploration into nerve sparing and subtotal cryotherapy is underway. The most dreaded complication risk for salvage cryotherapy is urethrorectal fistula, which has decreased significantly in recent series. Current reports demonstrate more acceptable rates of 1% to 3.4% (Bahn et al, 2003; Ismail et al, 2007; Ng et al, 2007; Pisters et al, 2008). Other reported complications include urinary obstruction, urethral sloughing, urethral stricture, rectal pain, scrotal edema, and hematuria (Chin et al, 2007; Finley and Beldegrun, 2011). It is clear that in the carefully selected patient, salvage cryotherapy is a reasonable approach with adequate cancer-specific outcomes and limited morbidity (Table 119-3).

Salvage Brachytherapy

The evidence for salvage brachytherapy after radiation failure is lacking compared to salvage prostatectomy and salvage cryotherapy. However, several groups have published contemporary series, including modern techniques that not only demonstrate improved cancer control outcomes but also have comparable morbidity outcomes to those with cryotherapy and surgery. Randomized controlled trials of salvage therapies are desperately needed.

Burri and colleagues published their series of salvage brachytherapy after local failure with long-term follow-up (median 86 months). Before therapy, patients underwent a thorough evaluation with history and physical examination, routine laboratory studies, pelvic CT, bone scan, and PSA level. Furthermore, all patients had biopsy-proved local failure, including 30 men who underwent six-core seminal vesicle biopsy. At 10 years, patients had a 54% freedom from biochemical failure, 96% cancer-specific survival, and 74% overall survival (Burri et al, 2010). Interestingly, 11 patients

TABLE 119-3 Outcomes of Salvage Cryotherapy for Prostate Cancer

STUDY	N	TECHNIQUE	PSA CUTOFF (ng/mL)	RECURRENCE-FREE RATE (%)	MEAN/MEDIAN FOLLOW-UP (mo)	FISTULA	INCONTINENCE	RETENTION/LUTS	IMPOTENCE
Donnelly et al, 2005	46	Argon	0.3	51	20	2.2	6.5	4.3	46
Ng et al, 2007	187	Argon	Phoenix	56	39	2	40	21/10	—
Ismail et al, 2007	100	Argon	ASTRO	59	34	1	13	18	86
Pisters et al, 2008	279	Argon/nitrogen	ASTRO	59	22	1	5	—	69

ASTRO, American Society for Therapeutic Radiology and Oncology; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen (test).

underwent prostate needle biopsy at a median of 38 months; 6 of these had planned biopsy without signs of biochemical or local failure. Of these 6 patients, 4 had evidence of local failure. Toxicity was comparable to that of other salvage modalities, with 13 patients having grade 2 toxicity (obstructive urinary symptoms, urge incontinence, diarrhea), 3 patients with grade 3 toxicity (obstructive uropathy requiring TURP, fulguration for gross hematuria), and 1 patient with a grade 4 toxicity (urinary diversion for a prostatic fistula) (Burri et al, 2010). Furthermore, 25% of men who had pretreatment erectile function had at least sufficient erectile function for intercourse. A similar series of salvage brachytherapy demonstrates a cancer-free survival of 96% and biochemical relapse-free survival of 88% at a median follow-up of 30 months (Aaronson et al, 2009). This group also reports 1 patient with grade 2 urethral stricture, 5 patients with grade 2 gross hematuria, and 1 patient with grade 3 rectal hemorrhage. No patients had evidence of fistula (Aaronson et al, 2009). The evidence for salvage brachytherapy demonstrates a potential role after radiation failure. As with other treatment modalities, there is significant risk for morbidity. Therefore a thorough risk assessment of patients' other comorbidities must be evaluated, because some patients will succumb to other comorbidities. In fact, in 10 men who died during follow-up after salvage brachytherapy, only one was attributable to prostate cancer (Burri et al, 2010).

High-dose rate brachytherapy (HDRB) has gained attention because it has the ability to implant the seminal vesicles and treat extracapsular extension while limiting the dosage to surrounding organs through a conformal delivery (Syed et al, 2001; Hsu et al, 2005; Chen et al, 2013). In the largest series of HDRB, 52 patients underwent therapy with a median follow-up of 59.6 months. All patients had biopsy-confirmed recurrent disease, negative workup for systemic disease, and no previous prostatectomy. Patients received 36 Gy in six fractions in two separate implants a week apart (Chen et al, 2013). Five-year overall survival was 92% and biochemical recurrence-free survival was 51%. As expected, patients with lower post-therapy nadir were more likely to have biochemical-free survival (Chen et al, 2013). Only one patient had distant failure, with a nadir PSA of 7.2 ng/mL. Toxicity profile was excellent in this cohort, with only 1 patient having a grade 3 acute and late GU toxicity and no patients having any grade 3 or 4 acute or late GI toxicity (Chen et al, 2013). Whereas no factors were statistically significant as predictors for biochemical outcome, the factors that were borderline in significance were disease-free interval after initial definitive radiation, percent of positive cores at diagnosis, time from recurrence to salvage HDRB, and presalvage therapy PSA (Chen et al, 2013). Salvage HDRB is a promising modality for patients with radiorecurrent prostate cancer. As with low-dose rate brachytherapy, patients likely to be most suitable are those with prolonged disease-free interval from primary treatment to recurrence, longer PSA doubling times, Gleason score 6 or less, PSA level less than 10 ng/mL, and no evidence of extracapsular extension or seminal vesicle invasion (Beyer, 2003).

Salvage High-Intensity Focused Ultrasound

Salvage high-intensity focused ultrasound (HIFU) has been evaluated in the treatment of radiorecurrent prostate cancer with acceptable cancer control outcomes. In a large series of 167 men treated with HIFU for recurrent prostate cancer, local cancer control as defined by a negative prostate biopsy result was achieved in 122 (73%) of patients (Murat et al, 2009). Three-year progression-free survival was 53%, 42%, and 25% for the low-, intermediate-, and high-risk groups, respectively. Treatment with HIFU was associated with urinary morbidity, including urinary retention, urinary tract infection, urinary incontinence, and bladder outlet obstruction. Five patients developed a urethrorectal fistula. Similarly, in 46 patients undergoing salvage HIFU, 18 patients (39%) were deemed failures after a median follow-up of 9 months. One patient had a urethrorectal fistula, and two patients experienced urethrocuteaneous fistula (Berge et al, 2010). Although short- to intermediate-term follow-up has been demonstrated with HIFU, further studies are

necessary to establish its place as a viable alternative in the radio-recurrent setting.

Androgen Deprivation Therapy after Biochemical Recurrence Following Radiation Therapy to the Prostate

PSA elevation after definitive radiotherapy may be due to local versus distant metastatic disease. Patients with biopsy-proved local disease, no evidence of distant metastatic disease, and substantial life expectancy should be counseled about salvage local therapy such as prostatectomy, radiation approaches, and cryotherapy. Some patients may refuse local therapy, may have too many comorbidities to undergo potentially morbid procedures, or have decreased life expectancy. Even in younger patients who are candidates for local therapy, survey results demonstrate that up to 54% of clinicians would recommend observation or ADT. This is more pronounced in a scenario of older men, 78% of whom would be recommended for observation or ADT (Sylvester et al, 2001). The reality is that 93.5% of men undergo ADT as second-line therapy after radiation failure, and therefore this approach should be clearly defined (Agarwal et al, 2008).

Not all patients with biochemical recurrence after radiation approaches are destined for clinical failure. Defining the patient population who are at highest risk is important to treat the patients with early ADT who are likely to benefit while sparing the significant side effects to those who are at low risk to fail. PSA doubling time has consistently demonstrated the ability to predict for patients who are at highest risk for failure after radiotherapy and has been linked to freedom from biochemical recurrence, local relapse, distant metastasis, and overall survival (Pollack et al, 1994; Hanks et al, 1996; Lee et al, 2005; Zelefsky et al, 2005). Although multiple cut points under 12 months have been described to be significant for increased risk for clinical failure, it is likely that this end point is linear (D'Amico and Hanks, 1993); thus clinical judgment must be used, taking into consideration the patient's comorbidities and likelihood of prostate cancer-related death for the initiation of ADT. Furthermore, side effects of ADT therapy, including sexual side effects, hot flashes, decreased bone mineral density, decreased muscle mass, cognitive dysfunction, metabolic syndrome, potential cardiovascular morbidity, fatigue, anemia, and depression, must be taken into consideration (Green et al, 2002; Cherrier et al, 2003; Higano et al, 2004; Harle et al, 2006; Keating et al, 2006; D'Amico et al, 2007; Spry et al, 2009).

Considering the potential morbidity of ADT and the substantial cost, it is reasonable to start treatment in those patients at highest risk for distant failure. This is confirmed as patients with PSA doubling times less than 12 months have been demonstrated to benefit from ADT, with freedom from distant metastatic disease of 57% versus 78%. Further, patients who received ADT had median time from distant failure of 6 months compared to 25 months (Pinover et al, 2003). This benefit of therapy with ADT was not seen in the patient cohort with PSA doubling time greater than 12 months, confirming the notion that patients at decreased risk for systemic disease are unlikely to benefit from the early initiation of systemic therapy. Faria and colleagues (2006) reviewed their series of 113 men with long PSA doubling time of 26.4 months who experienced biochemical failure but did not undergo ADT. At a median follow-up of 43 months, no patients had died of prostate cancer but 12 patients had died from other causes (Faria et al, 2006). These data illustrate the importance of risk stratification in patients after biochemical recurrence following radiation therapy. The exact timing of ADT after failure is unknown, and results of clinical trials such as NCT00110162 examining the role of immediate versus delayed ADT in PSA-only recurrence are desperately needed (<http://ClinicalTrials.gov>, 2009). Finally, the ideal management of PSA recurrence in patients at high risk for failure may be the initiation of intermittent ADT. In a recent clinical trial, intermittent ADT was found to be noninferior compared to continuous therapy in patients with PSA levels greater than 3 ng/mL without evidence of metastatic disease. This came with the benefit of potential improvement in

physical function, fatigue, urinary problems, hot flashes, libido, and erectile function (Crook et al, 2012). Further studies are necessary to identify the ideal timing of ADT initiation, the benefits of intermittent ADT, and the ideal patient group who will benefit the most from therapy.

CRYOTHERAPY

Management of Biochemical Recurrence after Definitive Cryotherapy in Prostate Cancer

The determination of biochemical failure after definitive cryotherapy of the prostate for cancer is extremely varied in the literature. In fact, neither the AUA Best Practice Statements for PSA testing nor those for cryotherapy define what is considered a biochemical recurrence after whole-gland cryotherapy of the prostate (Babaian et al, 2008; Carroll et al, 2012). Biochemical recurrence after cryotherapy has been defined as PSA levels greater than 0.5 ng/mL, greater than 1.0 ng/mL, the ASTRO definition (three consecutive rises in PSA), and the Phoenix definition of nadir + 2 ng/mL (Shinohara et al, 1997; Koppie et al, 1999; Long et al, 2001; Bahn et al, 2002; Babaian et al, 2008; Cohen et al, 2008). A unifying definition that consistently predicts for clinical failure (local failure, metastatic disease, cancer-specific and overall survival) is needed. Further investigation is warranted to determine these values and definitions.

Depending on the definition used for biochemical recurrence, success rates of cryotherapy are extremely varied. Long and colleagues (2001) examined a group of 975 men who underwent cryotherapy as primary therapy for prostate cancer. Overall 5-year biochemical recurrence-free survival was 52% using a cutoff of 0.5 ng/mL and 63% using a cutoff of 1.0 ng/mL. Another group using a definition of biochemical failure as PSA nadir 0.5 ng/mL or greater or subsequent biochemical failure defined as PSA level increase of 0.2 ng/mL or greater for their cohort of 134 men (Shinohara et al, 1997). They determined that PSA nadir is an important factor in determining the risk for subsequent biochemical recurrence such that patients who achieved a nadir less than 0.1 ng/mL had a 21% risk for failure compared to 46% in patients who had a nadir above 0.5 ng/mL. Furthermore, patients with a nadir below 0.1 ng/mL had a biopsy failure rate of 7% compared to 60% in those who had nadir values of 0.5 ng/mL or greater. Further, in a large cohort of 590 patients with 5.4 years of follow-up, a PSA-based definition of biochemical failure of 0.5 ng/mL was compared to a definition of 1.0 ng/mL and to the ASTRO definition of three successive increases in PSA level. In patients with low-, medium-, and high-risk prostate cancer before therapy, the 7-year actuarial freedom from biochemical failure was 61%, 68%, and 61% for a cutoff of 0.5 ng/mL; 87%, 79%, and 71% for a cutoff of 1.0 ng/mL; and 92%, 89%, and 89% when using the ASTRO definition (Bahn et al, 2002). In a series with robust follow-up, Cohen and colleagues (2008) demonstrated 10-year biochemical disease-free survival of 80.1%, 74.2%, and 45.6% for low-, moderate-, and high-risk groups, respectively, using the Phoenix definition of biochemical failure. These data illustrate the importance of a unifying definition for PSA failure. Local failure tended to occur at the apex and seminal vesicles in this cohort. These data clearly indicate the vigilance necessary in patients after treatment with cryotherapy. Patients who have higher PSA nadir and post-treatment positive biopsies should be counseled about secondary treatment strategies to decrease risk for potential subsequent disseminated disease. Management strategies for cryotherapy failure are lacking, and the literature is incomplete for treatment options.

The case for repeated cryotherapy administration is based on small patient numbers. Koppie and colleagues (1999) reported their results with cryotherapy and found that in patients who underwent repeated cryotherapy for initial failure, only 8 of 24 patients achieved biochemical freedom from recurrence, defined as a PSA nadir of less than 0.5 ng/mL and without an increase of PSA level by more than 0.2 ng/mL on two consecutive occasions. Conversely, Bahn and others (Bahn et al, 2002) demonstrated a relatively favorable outcome in 31 patients undergoing repeated treatment with

5-year freedom from biochemical failure of 68%, 72%, and 91% based on definitions of 0.5 ng/mL, 1.0 ng/mL, and the ASTRO criteria (Bahn et al, 2002). The relative success rates of repeat treatments must be somewhat tempered by the risk for significant morbidity, especially in light of previous therapy (Cox and Crawford, 1995).

Salvage radiation therapy after failure of cryotherapy has been described in multiple series. Patients who have failed cryotherapy as defined by PSA recurrence and/or positive biopsy should undergo a directed history, physical examination, and evaluation to rule out locally advanced or distant metastatic disease. Choi and colleagues (2013) describe their results in nine patients with recurrent prostate cancer after cryotherapy using IMRT. They describe dosages of 72 to 81 Gy with minimal side effects and no patients experiencing grade 3 or higher toxicities. With a mean pretreatment PSA of 4.3 ng/mL, biochemical control using the ASTRO definition of three subsequent rises of PSA level, was achieved in seven patients at a median follow-up of 20.5 months (Choi et al, 2013). Other series of patients undergoing salvage radiation therapy after failed cryotherapy demonstrate biochemical control rates of 61% to 75% at median follow-up of 32 to 34 months (Burton et al, 2000; McDonough et al, 2001; Hepel et al, 2008). These success rates are high despite the inclusion of patients with intermediate- and high-risk disease, making salvage radiation therapy a feasible choice after cryotherapy failure.

Evidence for salvage radical prostatectomy after cryotherapy failure is lacking. In an early series, Grampas and colleagues describe their method using radical perineal prostatectomy in six patients with biopsy-confirmed, stage T3 prostate cancer. Although the authors described increased fibrosis, excessive bleeding, and distorted anatomy, there were no intraoperative or postoperative complications and the time of operation and hospital stay were no different from those with the standard primary perineal prostatectomy (Grampas et al, 1995). Furthermore, five of six patients achieved PSA levels less than 0.2 ng/mL and morbidity outcomes revealed only temporary incontinence and impotence (Grampas et al, 1995). More recently, a case of cryotherapy failure treated with salvage robotic prostatectomy has been described in a man with pathologic T3b, Gleason 5+3 recurrent prostate cancer. With the addition of complete ADT, his follow-up PSA level at 10 months was undetectable (Rodriguez et al, 2007). Total operative time reported was 210 minutes, blood loss was 50 mL, and hospital stay was 24 hours. There is a deficit in the literature describing salvage prostatectomy after cryotherapy for prostate cancer. However, similar to salvage prostatectomy after radiation therapy, acceptable results are likely in the hands of surgeons with high operative volume. The best candidates for salvage surgery are those with adequate life expectancy (longer than 10 years) and absence of metastatic disease.

HIGH-INTENSITY FOCUSED ULTRASOUND

Management of Biochemical Recurrence after Definitive High-Intensity Focused Ultrasound in Prostate Cancer

HIFU is considered by most as a minimally invasive modality for the treatment of localized low to intermediate grade prostate cancer. Despite the increasing popularity and use of this treatment modality, HIFU is classified as experimental according to the European Association of Urology Guidelines and remains unregistered in the United States (Heidenreich et al, 2012). Historically, the lack of long-term data on clinical efficacy and morbidity has limited the wide-spread use of HIFU. Furthermore, a lack of definitive definition on treatment-related success or failure has limited the ability to compare this modality to other definitive treatment options for localized prostate cancer. Although most groups agree that a positive biopsy result after HIFU is a treatment failure, there are myriad definitions for biochemical failure, including three consecutive rises of PSA level and the Phoenix definition of biochemical failure (Gelet et al, 2001; Uchida et al, 2009). After a careful review of multiple definitions for biochemical failure, Blana and colleagues

(2009) determined that PSA nadir + 1.2 ng/mL, the Stuttgart definition, was the most effective at predicting for clinical failure and has been proposed as the definition for biochemical failure after HIFU for prostate cancer.

In general, success rates after primary HIFU for localized prostate cancer are comparable to those with other treatment modalities. In a study of 227 patients with clinical T1 to T2, PSA level of 15 ng/mL or less, Gleason score of 7 or less, and prostate volume 40 mL or lower, the actuarial 5-year disease-free survival rate combining pathologic and biochemical outcomes was 66% (Poissonnier et al, 2007). Biochemical recurrence was defined in this cohort as a PSA greater than 1 ng/mL with three consecutive rises over the nadir PSA. Significant success rates were seen stratified by pretreatment PSA with 90% in those with PSA level of 4 ng/mL or less, 57% for those with a PSA level of 4.1 to 10 ng/mL, and 61% for patients with PSA level of 10.1 to 15 ng/mL. In a similar series of 140 men, the Phoenix definition of biochemical failure was applied with an actuarial biochemical failure-free survival rate at 5 and 7 years of 77% and 69%, respectively (Blana et al, 2008). Prostate volume before therapy and PSA nadir (PSA 0.5 ng/mL) were statistically significant independent predictors of biochemical failure. Therefore, it is safe to assume that ideal candidates for HIFU are those with clinically localized prostate cancers (T1 to T2), low PSA (<15 ng/mL), and low prostate volumes. Furthermore, patients who exhibit earlier detection of biochemical recurrence (regardless of the definition) and higher nadir PSA values are at high risk for failure and should be evaluated for potential salvage strategies.

One such strategy in localized failure of HIFU is salvage radiotherapy. Although the literature is lacking on such approaches, Riviere and colleagues (2010) published their large series on conformal radiation to a median dose of 72 Gy after local recurrence after HIFU. One hundred patients with approximately 3 years of follow-up were included in this evaluation. For patients with radiation only (83 patients), the 5-year progression-free survival was 72%. Stratified by risk groups, the 5-year rates were 93%, 67%, and 55% for the low-, intermediate-, and high-risk groups, respectively. On multivariable analysis, the PSA nadir using a threshold of 0.2 ng/mL was predictive of eventual failure. Although GI toxicity was low in this cohort of men, there were four grade 3 (4.7%), one grade 4 (1.2%), and one grade 5 (1.2%) urinary toxicity. The single death was after a cystectomy for hemorrhage. Obviously, larger series with more robust patient numbers will be required to establish radiation approaches after HIFU as standard of care.

Another approach to the patient with localized failure after HIFU is salvage radical prostatectomy. Again, treatment numbers are lacking and small series of men provide us with the most information to date. To that effect, the largest series of patients undergoing surgery after HIFU includes 15 men. Presalvage radical prostatectomy Gleason scores were 6 (3), 7 (9), 8/9 (3), with a median core biopsy involved of 42% (Lawrentschuk et al, 2011). Furthermore, the pretreatment median PSA was 3.8 ng/mL. Pathology after salvage prostatectomy demonstrated a high rate of increased stage with 9 of 14 men having pT3 prostate cancer. Of 15 men, 4 had a positive apical margin. Most interestingly, all patients on evaluation had residual, viable prostate cancer in the HIFU-treated zones of the prostate (Lawrentschuk et al, 2011). Despite the unfavorable pathologic findings on salvage prostatectomy, 13 of 15 men were found to have unrecordable PSA (<0.05 ng/mL) postoperatively. Surgical management revealed significant extensive periprostatic fibrosis, but despite these findings, continence rates in those with 12 months of follow-up (10 patients) were reasonably good, with 6 (60%) requiring no pads, 3 (30%) patients using 1 safety pad, and only 1 patient remaining incontinent at 18 months of follow-up. As expected, erectile function in this cohort was universally poor. It is obvious that surgical management after local therapy with HIFU is a more difficult operation with higher risk for post-therapy morbidity. It is also clear that despite localized therapy and low levels of PSA even at recurrence (median PSA 3.8 ng/mL), patients uniformly had higher stage and all patients had viable prostate cancer in the treatment zones. Therefore patients who demonstrate any rise in PSA after HIFU should be watched vigilantly; after distant

metastatic disease workup, patients with significant life expectancy should be offered salvage local therapy earlier rather than later. Furthermore, patients interested in local HIFU therapy should be counseled before therapy about the risk for residual disease and the potential need for secondary therapy if failure occurs.

SUMMARY

Patients who experience biochemical recurrence after primary therapy of prostate cancer are at higher risk for clinical progression as well as anxiety from disease progression. However, not all men with PSA progression will experience clinically significant outcomes such as metastasis, need for secondary treatment, and death from prostate cancer. Therefore risk stratification is of the utmost importance. Furthermore, advances in diagnostic imaging and therapeutics will improve the identification of those with local recurrence and enhance cancer eradication with limited morbidity.

KEY POINTS

- The AUA guidelines panel defined PSA recurrence as a value of 0.2 ng/mL or greater with a second confirmatory laboratory value. However, the risk for clinical failure (metastatic disease, need for second-line treatment, and death from prostate cancer) depends on multiple variables.
- Prognostic models (nomograms) for PSA recurrence both before and after definitive therapy of the prostate should be incorporated into clinical practice for patient counseling.
- Traditional imaging modalities (bone scan and CT scan) are of limited value in early PSA recurrence; newer imaging techniques such as multiparametric MRI and PET scanning may demonstrate more utility at lower PSA values.
- Patients at high risk for clinical failure after radical prostatectomy (extracapsular extension, seminal vesicle invasion, and positive margins) should be offered adjuvant radiotherapy based on randomized controlled trials.
- Early salvage radiation may offer the benefit of treatment at low disease burden while sparing therapy for those never destined for local failure. Randomized controlled trials are underway to answer this treatment dilemma.
- Candidates of local therapy after radiation failure must have biopsy-proved local recurrence, adequate life expectancy (at least 10 years), absence of metastatic disease, and a PSA less than 10 ng/mL.
- Patients considered for second-line definitive therapy after radiation, HIFU, and cryotherapy should be counseled extensively on the risk for subsequent treatment-related morbidity.

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The complete reference list is available online at www.expertconsult.com.



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[Historical Overview](#)[Molecular Biology of Androgen Axis](#)[Sources of Androgen](#)[Mechanisms of Androgen Axis Blockade](#)[Response to Androgen Blockade](#)[General Complications of Androgen Ablation](#)[Combination Therapy](#)[Timing of Therapy](#)[Economic Considerations](#)

HISTORICAL OVERVIEW

The response of prostate cancer to androgen ablation is among the most reproducible, durable, and profound of any systemic therapy for a solid tumor. The early and frequent descriptions of immediate relief of bone pain from metastatic prostate cancer following castration do not diminish the marvel of observing this phenomenon first hand. As is the case with many paradigm-shifting observations, endocrine therapy was based on a simple hypothesis. Described as a “biological syllogism,” [Huggins \(1947\)](#) noted a major premise, “In many instances a malignant prostatic tumor is an overgrowth of adult epithelial cells”; a minor premise, “All known types of adult prostatic epithelium undergo atrophy when androgen hormones are greatly reduced in amount”; and a conclusion, “Therefore, significant improvements should occur in the clinical condition of patients with far advanced prostate cancer subjected to castration.”

It had been known for at least a century that prostatic epithelium undergoes atrophy after castration ([Hunter, 1840](#)). The breakthrough in Huggins’s hypothesis was the recognition that benign prostatic epithelium and prostate carcinoma were biochemically analogous and they would respond in a similar fashion to androgen ablation. Emphasizing the importance of basic observations (“The evidence for the facts which represent the premises was obtained entirely in the laboratory” [[Huggins, 1944](#)]), studies on acid phosphatase provided the crucial link between benign and malignant prostate cells. Large amounts of acid phosphatase were found in the prostate glands of men and monkeys ([Kutscher and Wohlbergs, 1935](#)) as well as in primary and metastatic prostate cancer ([Gutman et al, 1936](#)), and the levels increased with androgen administration ([Gutman and Gutman, 1939](#)). Serum levels of acid phosphatase were increased in men with disseminated prostate cancer ([Barringer and Woodard, 1938](#); [Gutman and Gutman, 1938](#)). With localization of the enzyme to prostatic epithelial cells and primary and metastatic prostatic cancer cells ([Gomori, 1939](#)), the stage was set for Charles Huggins, R. E. Stevens, and Clarence V. Hodges to test the hypothesis in men with prostate cancer.

Despite negative results of castration in two men with prostate cancer reported by [Young \(1936\)](#), a series of 21 consecutive patients with locally advanced or metastatic prostate cancer underwent surgical castration at the University of Chicago. “A noticeable improvement occurred in the clinical status of all but three patients” with weight gain, resolution of anemia, and improvement in pain ([Huggins et al, 1941](#)). Other reported consequences of castration—a large appetite for food, loss of sexual desire and penile erections,

and hot flashes—remain the common side effect profile of androgen ablation therapy today. **Although this report was first to describe the benefits of androgen ablation in the treatment of prostate cancer, it also created a new disease state, castration-resistant prostate cancer.**

In considering these “failure cases” ([Huggins, 1942](#)), it was found that those men with small testes at time of castration had a poor prognosis, the first description of a more ominous prostate cancer arising in the hypogonadal man. Following castration, increases in the levels of urinary 17-ketosteroids, major metabolites of the adrenal gland, led to the hypothesis that adrenal androgens contributed to subsequent disease progression. The first reports of bilateral adrenalectomies for the treatment of castration-resistant disease ([Huggins and Scott, 1945](#)) are described later in a somewhat defensive manner ([Scott, 1954](#)), perhaps because of the lack of response and high perioperative mortality. Hypophysectomy and pituitary irradiation ([Murphy and Schwiippert, 1951](#)) were also investigated. Unfortunately, the benefits of surgical castration were soon equaled by the tenacity and inevitable progression of castration resistance, a state still synonymous with the lethal form of the disease. Even in accepting the 1966 Nobel Prize for this work, Charles Huggins admitted “Despite regressions of great magnitude, it is obvious that there are many failures of endocrine therapy to control the disease” ([Huggins, 1972](#)).

Direct ablation of the source of androgen, like surgical castration, is only one of the perturbations of the hypothalamic-pituitary-gonadal axis developed to treat prostate cancer. **The first central inhibition of the axis exploited the potent negative feedback of estrogen on luteinizing hormone (LH) secretion: estradiol is a thousandfold more potent at suppressing LH and follicle-stimulating hormone (FSH) secretion by the pituitary compared with testosterone (Swerdlloff and Walsh, 1973).** The effects of estrogen on the male phenotype, namely regression of androgen-sensitive tissues, have been exploited historically to produce the effects of castration without surgical removal of the testes. For example, capons (neutered roosters) were produced by placing estrogen pellets in the necks of the birds rather than by castration ([Scott, 1954](#)). Among the various estrogenic compounds, diethylstilbestrol (DES) has been most widely studied and used. Early studies indicating improved survival in men treated with both surgical castration and continuous DES ([Nesbit and Baum, 1951](#)) have not held up under further scrutiny, but the equivalence of DES compared to castration has. Indeed, given the effectiveness of the considerably less expensive estrogenic compounds, it is unfortunate that the associated cardiovascular toxicity has limited their widespread use.

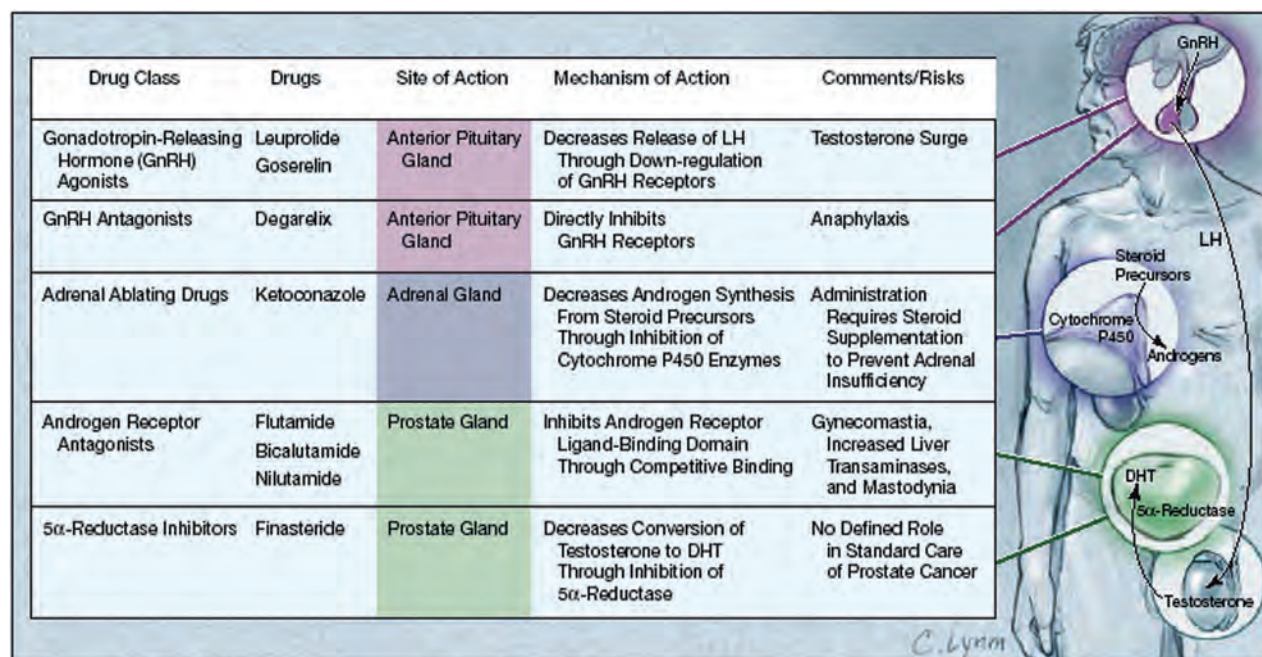


Figure 120-1. Hormonal interventions and endocrine axis in prostate cancer. DHT, dihydrotestosterone; LH, luteinizing hormone. (From Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. *JAMA* 2005;294:238–44.)

The first isolation of luteinizing hormone-releasing hormone (LHRH) by Andrew Schally and colleagues required the hypothalami of 165,000 pigs to obtain 800 μ g of the 10–amino acid peptide (Schally et al, 1971; Schally, 1992). This 1977 Nobel prize–winning work led to the development of synthetic LHRH analogues, peptides generated by substituting D-amino acid residues at certain locations in the natural compound, creating both LHRH agonists and LHRH antagonists. After an initial surge in LH release (and testosterone levels) in response to LHRH agonists, the loss of phasic pituitary stimulation results in plummeting LH levels. In the absence of LH, Leydig cell production of testosterone drops to castrate levels. Initially, the clinical utility of these agents was hampered by their short half-life, requiring daily injections to maintain suppression of the hypothalamic-pituitary axis. The generation of long-acting depot preparations, lasting several months, has established LHRH agonists as the dominant treatment in hormone therapy for prostate cancer. Recently, direct LHRH antagonists have been developed for clinical use. Lacking agonist action, these agents do not produce the surge in LH and testosterone. It is interesting that both classes of compounds were developed within a few years of the discovery of LHRH and yet it took decades to develop clinically useful agents.

Moving beyond strategies targeting the hypothalamic-pituitary axis, interruption of ligand-receptor interaction with antiandrogenic compounds is another way to reduce androgen action in prostate cancer. All antiandrogens inhibit androgen action by binding to the androgen receptor (AR) in a competitive fashion, and are classified as either steroidal or nonsteroidal. The steroidal antiandrogen cyproterone acetate is a derivative of 17-hydroxyprogesterone and suppresses LH release (and testosterone production) through its central progestational inhibitory effects. Therefore steroidal antiandrogens block androgen action at the cellular level and also reduce circulating testosterone levels, leading to the classic side effects of the hypogonadal state such as loss of libido and erectile dysfunction. On the other hand, the nonsteroidal antiandrogens have no antigonadotropic effects and simply block ARs, including those in the hypothalamic-pituitary axis. By blocking the normal inhibiting feedback of testosterone, the antiandrogens produce a paradoxical increase in LH and testosterone. Although this maintenance of testosterone

can preserve potency in some men, the peripheral conversion of this excessive testosterone to estrogen can lead to painful gynecomastia.

MOLECULAR BIOLOGY OF ANDROGEN AXIS

The AR is a member of the nuclear receptor superfamily, which includes receptors for the sex steroids (androgen, estrogen, progesterone), adrenal steroids (mineralocorticoids, glucocorticoids), thyroid hormones, vitamin D, and retinoids. These receptors act as ligand-inducible transcription factors—meaning they cause transcription of target genes within specific cells after ligands (e.g., testosterone) bind to them. All current forms of androgen deprivation therapy (ADT) function by reducing the ability of androgen to activate ARs, whether through lowering levels of androgen or by blocking androgen-AR binding (Fig. 120-1). Therefore ARs are not directly affected by ADT, leading many to hypothesize that castration-resistant prostate cancer is a result of reactivation of AR-mediated pathways.

A variety of molecular mechanisms are implicated in this process of castration resistance (Fig. 120-2). First, the AR pathway can become hypersensitive through a variety of molecular alterations and be activated by even lower levels of androgen (Linja and Visakorpi, 2004). In castration-resistant tumors, approximately one third of patients will show evidence of AR gene amplification—meaning many more copies of the AR gene are present (Koivisto et al, 1997; Linja et al, 2001). Second, the promiscuity of the AR for ligands other than androgen has been widely recognized. Mutations of the AR gene can also increase receptor activity (Tilley et al, 1996; Gottlieb et al, 1998; Taplin et al, 1999; Marcelli et al, 2000; Balk, 2002). Third, in an outlaw AR model, growth factor peptides such as epidermal growth factor and insulin-like growth factor-1 increase AR transcriptional activity in the absence of androgen (Culig et al, 1994). The cytokine interleukin-6 can activate ARs, as can protein kinases A and C (Nazareth and Weigel, 1996; Lin et al, 2001). If these ligands can reactivate AR signaling in the absence of androgen, then prostate cancer can still progress in the castrate state. Increased expression of AR coregulators, proteins involved in the complex that binds to DNA, has been found in hormone-refractory

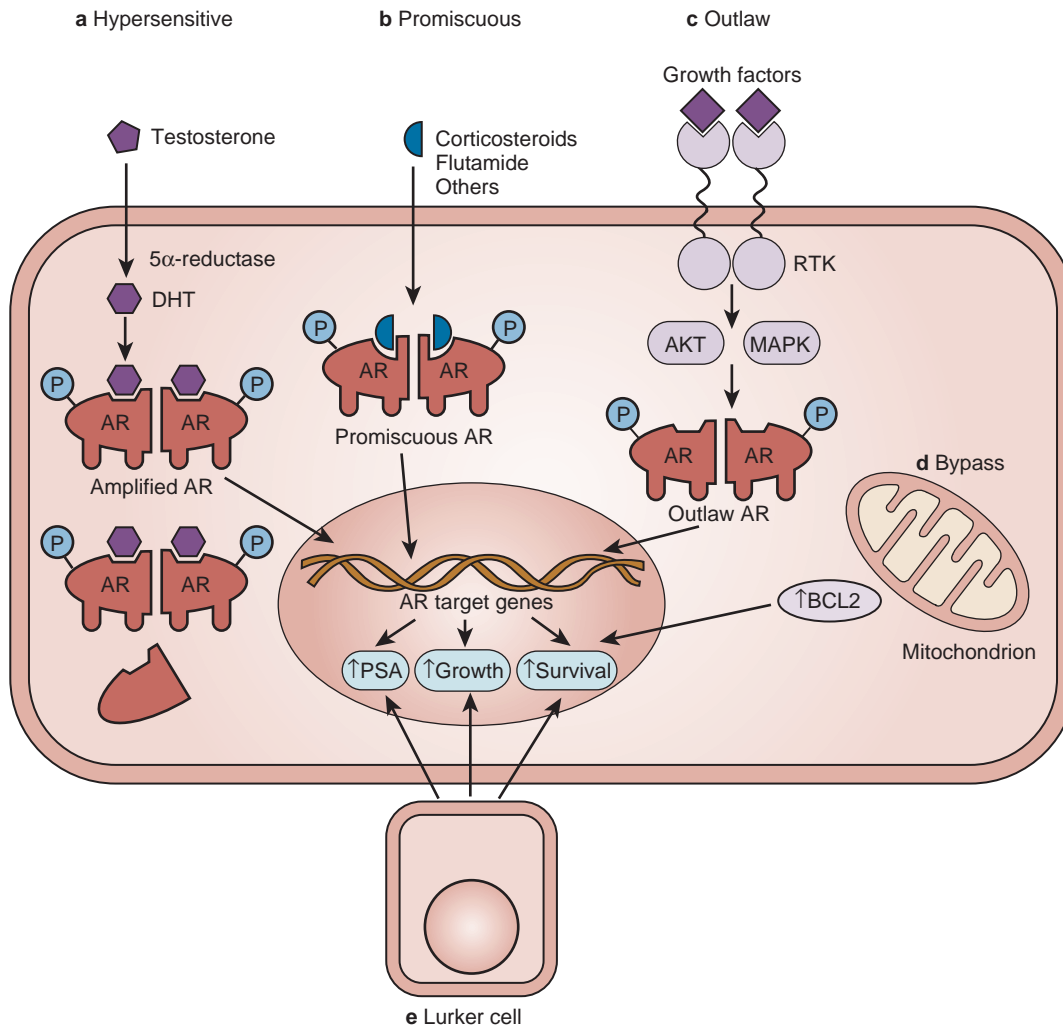


Figure 120-2. Five possible pathways (a to e) to castration resistance. AR, androgen receptor; DHT, dihydrotestosterone; MAPK, mitogen-activated protein kinase; P, phosphorylated; PSA, prostate-specific antigen; RTK, receptor tyrosine kinase. (From Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. *Nat Rev Cancer* 2001;1:34–45.)

prostate cancer, suggesting autonomous activation of the pathway (Yeh et al, 1999; Fujimoto et al, 2001; Gregory et al, 2001). Fourth, in a bypass AR model, activation of parallel or alternative survival pathways allows otherwise androgen-dependent prostate cancer cells to survive in the absence of androgen (Feldman and Feldman, 2001). Finally, in a lurker cell model, a small population of possible epithelial stem cells is preexistent in the prostate and androgen deprivation selects for the outgrowth of these castration-resistant cells. Rather than an acquired alteration, this model suggests an inherent quality of the prostate gland.

Even when prostate cancer progresses despite castrate levels of androgen, it is rarely resistant to androgen action. In 87% of patients with castration-resistant prostate cancer, the administration of exogenous androgen results in symptomatic tumor flare (Fowler and Whitmore, 1982). Therefore the term *androgen independent* is not completely precise: such a cancer is no longer dependent on androgen (and thus may be considered independent), but since it remains responsive to androgen it is not wholly independent of the influence of androgen. The term *androgen refractory* indicates a disease state wherein the cancer is able to progress in the absence of androgen, but is definition-neutral about a responsiveness to androgen. Likewise, the word “hormone” is quite broad and includes the host factors defining the field of endocrinology. Therefore the term *hormone independent* is vague: as evident from the

therapeutic response to secondary hormonal manipulation (estrogens and glucocorticoids), androgen-refractory prostate cancer is not actually independent of hormone action. The terms *hormone independent* and *hormone refractory* should be reserved for the rare cancers that are completely nonresponsive to any hormonal agent (Chang et al, 2005). Although the term *hormone-refractory prostate cancer* has been widely used to describe a state of progressive disease despite ADT, the term *castration-resistant prostate cancer* is more clinically precise and relevant (Scher et al, 2004, 2008b).

SOURCES OF ANDROGEN

Testosterone is the major circulating androgen, with 90% produced by the testes. Over half of testosterone is bound to sex hormone-binding globulin and 40% is bound to albumin. Only 3% of testosterone remains unbound and this is the functionally active form of the hormone. Following passive diffusion through the cell membrane into the cytoplasm, testosterone undergoes conversion to dihydrotestosterone (DHT) through the action of the enzyme 5α-reductase. Although the relative potency of testosterone and DHT are similar (as defined by the ability to cause half-maximal response in a prostate regrowth model), if the conversion of testosterone to DHT is blocked by the 5α-reductase inhibitor finasteride,

TABLE 120-1 Major Circulating Androgens

SOURCE	ANDROGEN	AMOUNT PRODUCED/DAY (mg)	RELATIVE POTENCY	RELATIVE POTENCY/AMOUNT PRODUCED
Testes	Testosterone	6.6	100	15.2
Testes and peripheral tissues	Dihydrotestosterone	0.3	160-190	533-633
Adrenal glands	Androstenedione	1.4	39	27.9
Adrenal glands	Dehydroepiandrosterone	29	15	0.5

13-fold more testosterone is required for the same effect (Wright et al, 1999). Both testosterone and DHT exert their biologic effects by binding to the AR in the cytoplasm, promoting the association of AR coregulators. The complex then translocates to the nucleus and binds to androgen response elements in the promoter regions of target genes (Heinlein and Chang, 2004).

Androgens produced by the adrenal gland—androstenedione and dehydroepiandrosterone—are stimulated by adrenocorticotrophic hormone (ACTH) released by the pituitary gland in response to corticotropin-releasing factor. Adrenal androgens negatively feed back on ACTH secretion: cortisol acts as the feedback signal. **Adrenal androgens are relatively weak compared to testosterone and DHT and are almost entirely bound to albumin (Table 120-1).** Adrenal androgens remain normal in men who have undergone orchiectomy (Walsh and Siiteri, 1975) and are insufficient to maintain prostatic epithelium in such men.

MECHANISMS OF ANDROGEN AXIS BLOCKADE

Four therapeutic approaches for androgen axis blockade are in current clinical use: (1) ablation of androgen sources, (2) antiandrogens, (3) inhibition of LHRH and/or LH release, and (4) inhibition of androgen synthesis (Box 120-1).

Ablation of Androgen Sources

Bilateral orchiectomy quickly reduces circulating testosterone levels to less than 50 ng/dL, which is considered the castrate range. Within 24 hours of surgical castration, testosterone levels are reduced by greater than 90% (Maatman et al, 1985). The Veterans Administration Cooperative Urological Research Group (VACURG) conducted a series of larger clinical trials demonstrating the clinical effectiveness of surgical castration in reducing pain and improving performance status in men with advanced disease (VACURG, 1967a, 1967b; Byar, 1973; Byar and Corle, 1988). Subcapsular orchiectomy has been advocated as a technique of ADT that avoids the psychological consequences of an empty scrotum (Desmond et al, 1988). Because this approach relies on the complete removal of all intratesticular tissue and Leydig cells, it is more dependent on technique than a simple orchiectomy to achieve ADT. In a properly performed operation, however, the hormonal and cancer responses are indistinguishable from a simple, complete orchiectomy (Zhang et al, 1996).

Antiandrogens

Cyproterone Acetate

The classic steroidal antiandrogen with direct AR blocking effects, cyproterone acetate also rapidly lowers testosterone levels to 70% to 80% through its progestational central inhibition (Jacobi et al, 1980; Goldenberg and Bruchovsky, 1991; Barradell and Faulds, 1994). An oral agent, the recommended dose is 100 mg two to three times per day. Side effects are consistent with the hypogonadal state and include loss of libido, erectile dysfunction, and lassitude. Severe cardiovascular complications can occur in up to

BOX 120-1 Therapeutic Approaches to Androgen Deprivation Therapy*

ABLATION OF ANDROGEN SOURCES

Orchiectomy

ANTIANDROGENS

Cyproterone acetate
Flutamide
Bicalutamide
Nilutamide
Enzalutamide

INHIBITION OF LHRH OR LH

Diethylstilbestrol
Leuprolide
Goserelin
Triptorelin
Histrelin
Cetorelix
Abarelix
Degarelix

INHIBITION OF ANDROGEN SYNTHESIS

Aminoglutethimide
Ketoconazole
Abiraterone

*Several agents have multiple sites of action.

10% of patients, limiting the use of cyproterone acetate (de Voogt et al, 1986). Gynecomastia occurs in less than 20% of men. Rare cases of fulminant hepatotoxicity have been reported (Parys et al, 1991). It has been used at doses of 50 to 100 mg/day for the treatment of hot flashes (Goldenberg and Bruchovsky, 1991).

Nonsteroidal Antiandrogens

By blocking the testosterone feedback centrally, the nonsteroidal antiandrogens cause LH and testosterone levels to increase. Testosterone levels reach about 1.5 times the normal levels of hormonally intact men (Neri, 1977). This allows antiandrogen activity without inducing hypogonadism: potency therefore can be preserved (Brufsky et al, 1997). However, in clinical trials specifically examining erectile functioning and sexual activity in men on flutamide monotherapy, long-term preservation of those domains was only 20%, not much different than men undergoing surgical castration (Schröder et al, 2000). The peripheral aromatization of increased testosterone to estradiol has been demonstrated after antiandrogen administration (Knuth et al, 1984), leading to the widely recognized gynecomastia and mastodynia associated with these

agents. Gastrointestinal toxicity, and most notably diarrhea, is more common with flutamide than the other nonsteroidal antiandrogens (Han and Nelson, 2000). Liver toxicity, ranging from reversible hepatitis to fulminant hepatic failure, is associated with all nonsteroidal antiandrogens and requires periodic monitoring of liver function tests (Lund and Rasmussen, 1988; Wysowski et al, 1993; Dawson et al, 1997; Thole et al, 2004).

Flutamide. A nonsteroidal antiandrogen, flutamide was the first “pure” antiandrogen (Neri et al, 1967). Because of the short half-life (6 hours) of the active metabolite, 2-hydroxyflutamide, this oral agent must be given three times a day at 250 mg per dose. Elimination of hydroxyflutamide is via renal excretion. Unlike the steroidal antiandrogens, there are no associated side effects of fluid retention or thromboembolism (Delaere and Van Thillo, 1991). In a randomized, double-blind study comparing flutamide to DES (3 mg/day) in metastatic prostate cancer, overall survival was significantly shorter with flutamide (28.5 months) compared to DES (43.2 months) (Chang et al, 1996).

Bicalutamide. A nonsteroidal antiandrogen with a long serum half-life (6 days), bicalutamide has a once-per-day dosing schedule and therefore likely better compliance. It is the most potent of the “first-generation” nonsteroidal antiandrogens (Kolvenbag and Nash, 1999) and the best tolerated (Kolvenbag and Blackledge, 1996; Fradet, 2004; Schellhammer and Davis, 2004). The pharmacokinetics of bicalutamide are not affected by age, renal insufficiency, or moderate hepatic impairment (Mahler et al, 1998). The R-isomer of bicalutamide has about a 30-fold higher binding affinity for the AR compared to the S-isomer and functionally processes the antiandrogen activity (Mukherjee et al, 1996). As with the other antiandrogens, bicalutamide is associated with maintenance of serum testosterone levels: in the majority of patients, these remain within the normal range (Denis and Mahler, 1996; Tay et al, 2004).

Bicalutamide as monotherapy has been most extensively studied and, as with flutamide monotherapy's inferiority to DES, bicalutamide monotherapy at a 50-mg/day dose was inferior to castration in survival of men with metastatic disease (Kaisary et al, 1995; Bales and Chodak, 1996; Kolvenbag and Nash, 1999). At a higher dose of 150 mg/day, however, bicalutamide monotherapy appears to have equivalent efficacy to medical or surgical castration (Tyrrell et al, 1998; Iversen et al, 2000; Anderson, 2003; Iversen, 2004; Iversen et al, 2004; Wirth et al, 2004, 2005; McLeod et al, 2006) in men with metastatic or locally advanced disease. In these large phase III studies, bicalutamide monotherapy (150 mg/day) had significantly better quality of life in the domains of sexual interest and physical capacity (Iversen, 2003). There was, however, a high rate of gynecomastia (66.2%) and breast pain (72.8%) (Iversen, 2003). More concerning, in men with low-risk, localized prostate cancer, bicalutamide was associated with significantly worse overall survival compared to watchful waiting (see later).

Nilutamide. The plasma half-life of nilutamide is 56 hours, and elimination is via hepatic clearance employing the cytochrome P450 system. Because steady-state plasma levels are achieved in 14 days on once-per-day dosing (Creaven et al, 1991), dosing recommendations are a single 300-mg daily dose for the first month of treatment followed by a single 150-mg daily dose (Mahler et al, 1998). About one quarter of men on nilutamide therapy will note a delayed adaptation to darkness after exposure to bright illumination (Creaven et al, 1991). Nilutamide is also associated with interstitial pneumonitis in approximately 1% of patients that can progress to pulmonary fibrosis (Pfizenmeyer et al, 1992). The early effects are usually reversible with cessation of nilutamide. In a small study, there was a suggestion of a role for nilutamide as an effective secondary hormonal agent (Desai et al, 2001).

Enzalutamide. This small molecule is an AR antagonist, but unlike bicalutamide, enzalutamide inhibits AR function by blocking nuclear translocation and DNA binding and has no agonist activity when AR is overexpressed (Tran et al, 2009). Early clinical trials with enzalutamide demonstrated prostate-specific antigen (PSA) declines in the majority of patients with castration-resistant prostate cancer (Scher et al, 2008a). A phase III clinical trial of enzalutamide in men with metastatic, castration-resistant prostate cancer who had

Overall survival

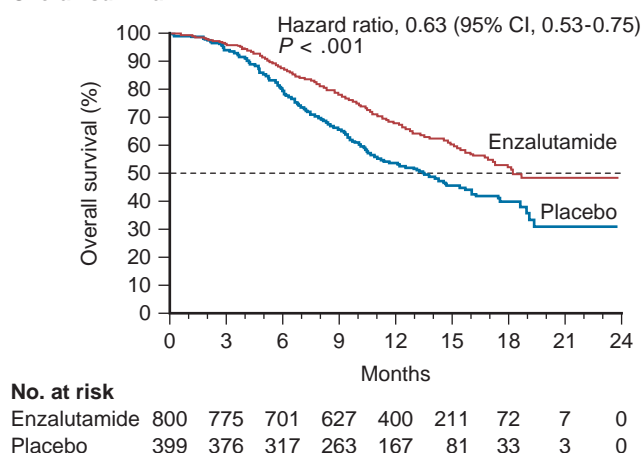


Figure 120-3. Overall survival among patients with metastatic, castration-resistant prostate cancer after receiving enzalutamide compared to patients receiving placebo after previous treatment with chemotherapy. CI, confidence interval. (From Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; 367: 1187-97.)

failed docetaxel chemotherapy showed significant improvements in overall survival and radiographic progression-free survival (Scher et al, 2012) (Fig. 120-3). Likewise, another phase III clinical trial of enzalutamide in men with metastatic castration-resistant prostate cancer who had not received chemotherapy also showed significant improvements in overall survival and radiographic progression-free survival (Beer et al, 2014). The most common side effects of enzalutamide are fatigue, diarrhea, and hot flashes. Seizures occurred in clinical trials of this agent, but in less than 1% of patients.

Antiandrogen Withdrawal Phenomenon

Patients treated with a combination of an antiandrogen and an LHRH agonist can experience a decline in PSA and even in objective responses with the withdrawal of the antiandrogen from the combination. Based on this response, it appears that the antiandrogen is actually exerting agonistic activity on prostate cancer cells. This phenomenon, first described with flutamide (Kelly and Scher, 1993), has now been demonstrated with all antiandrogens, including cyproterone acetate, as well as with DES and progestational agents (Kelly et al, 1997). Declines in PSA are seen within 4 weeks with flutamide withdrawal and within 6 weeks with bicalutamide and nilutamide withdrawal (Nieh, 1995). Between 15% and 30% of patients may have PSA declines of greater than 50% after antiandrogen withdrawal, and the declines have a median duration of 3.5 to 5 months (Scher and Kelly, 1993; Small and Srinivas, 1995). Objective, measurable tumor responses are observed less commonly. Overall survival has not been shown to be increased in those patients demonstrating the antiandrogen withdrawal phenomenon compared to those who have not (Small and Srinivas, 1995). Clinical trial designs of novel agents must take this phenomenon into consideration, given the possible confounding effects (Scher and Kelly, 1993). Prospective criteria to predict who will demonstrate this response have not been established, but it has been recognized that those with rapid PSA responses following androgen ablation have higher rates of antiandrogen withdrawal phenomenon.

It has been postulated that mutations in the AR gene may underlie this phenomenon, allowing the antiandrogen to behave as an activator of the AR (Taplin et al, 1995). The widely used prostate cancer cell line LNCaP expresses an AR with a specific point mutation that causes cell proliferation in the presence of

hydroxyflutamide; the identical mutation was found in human tumor samples from patients who had remarkable PSA declines after antiandrogen withdrawal (Suzuki et al, 1996). Similar point mutations in the AR have been described for bicalutamide to act as an agonist (Hara et al, 2003), with the structural basis of this mutation resolved by x-ray crystallography demonstrating the ability of bicalutamide to bind to the mutant AR in a fashion similar to DHT binding to the wild-type AR (Bohl et al, 2005).

Inhibition of Luteinizing Hormone–Releasing Hormone

Luteinizing Hormone–Releasing Hormone Agonists

The LHRH agonists exploit the desensitization of LHRH receptors in the anterior pituitary following chronic exposure to LHRH, thereby shutting down the production of LH and, ultimately, testosterone. The clinical utility of the current LHRH agonists is based on the creation of LHRH analogues by amino acid substitutions, particularly position 6 in the peptide, increasing their potency and half-lives. Pharmacologic depot preparations and osmotic pump devices allow dosing to extend from 28 days to 1 year, respectively (Ahmann et al, 1987). In a review of 24 trials involving more than 6600 patients, survival after therapy with an LHRH agonist was equivalent to that after orchiectomy (Seidenfeld et al, 2000).

The initial exposure to more potent agonists of LHRH results in a flare of LH and testosterone levels (Waxman et al, 1985). This phenomenon is seen with all available LHRH preparations and can result in a severe, life-threatening exacerbation of symptoms. The flare, associated with up to a 10-fold increase in LH, may last for 10 to 20 days (Weckermann and Harzmann, 2004). Fortunately, the coadministration of an antiandrogen functionally blocks the increased levels of testosterone (Labrie et al, 1987; Kuhn et al, 1989; Schulze and Senge, 1990). Although it had been argued that the administration of the antiandrogen should precede the administration of the LHRH agonist by a week, others have found no differences in PSA levels with the simultaneous administration of both agents (Tsushima et al, 2001). Given the predictable length of the flare phenomenon, antiandrogen coadministration is required for only 21 to 28 days.

Luteinizing Hormone–Releasing Hormone Antagonists

The LHRH antagonists bind immediately and competitively to the LHRH receptors in the pituitary, reducing LH concentrations by 84% within 24 hours of administration (Weckermann and Harzmann, 2004). The direct antagonistic activity eliminates the LH and testosterone flare, which is the major therapeutic advantage of these agents: there is no need for antiandrogen coadministration. Hormonally naive patients with impending spinal cord compression or severe bone pain for whom surgical castration is not appropriate may uniquely benefit from this class of agents: clinical response has been observed with the LHRH antagonist cetrorelix (Gonzalez-Barcena et al, 1995).

In clinical trials of the LHRH antagonist abarelix, testosterone levels dropped very quickly, with 34.5%, 60.5%, and 98.1% of men chemically castrate at 2, 4, and 28 days, respectively (Tomera et al, 2001). Compared to an LHRH agonist and an antiandrogen, abarelix monotherapy was equally effective in achieving castrate levels of testosterone (Trachtenberg et al, 2002). Ninety-percent of men with symptomatic prostate cancer treated in an open-label fashion had improvements in pain and/or disease-related problems (Koch et al, 2003).

Many of the first- and second-generation antagonists induced significant histamine-mediated side effects, complications not as often observed in third- and fourth-generation agents (Weckermann and Harzmann, 2004). Nevertheless, severe allergic reactions can occur with abarelix, even after previously uneventful treatment (Koch et al, 2003). Abarelix is approved in the United States for the treatment of advanced prostate cancer in patients who cannot take other hormonal therapies and have refused surgical castration.

Given the rare but serious allergic reactions, patients must be monitored for at least 30 minutes after administration.

FSH levels are only partially suppressed by LHRH agonists and are significantly elevated after surgical castration given the loss of inhibitory feedback. LHRH antagonists reduce both LH and FSH levels. In an androgen-insensitive prostate cancer xenograft model, cetrorelix significantly reduced tumor growth (Lamharzi et al, 1998), suggesting other factors stimulate tumor growth. In men with disease progression following surgical castration, treatment with abarelix reduced FSH levels by nearly 90% but did not meet criteria for PSA response (Beer et al, 2004a).

Unlike abarelix, the LHRH antagonist degarelix has no systemic allergic reactions, (Gittelman et al, 2008; Klotz et al, 2008). In a phase III study, degarelix was compared to leuprolide: at 1 year of treatment degarelix was not inferior to leuprolide, and based on this result it has been approved for use in the United States.

Inhibition of Androgen Synthesis

Aminoglutethimide

Aminoglutethimide inhibits the conversion of cholesterol to pregnenolone, an early step in steroidogenesis (Cash et al, 1967; Blankenstein and Bakker, 1985). Given its inhibition of a very proximal step in adrenal function, aminoglutethimide blocks production of aldosterone and cortisol. As the medical version of a total adrenalectomy, the use of this agent requires replacement of cortisone and fludrocortisone. Side effects include anorexia, nausea, skin rash, lethargy, vertigo, hypothyroidism, and nystagmus. Clinical responses have been observed in a subset of patients with androgen-refractory prostate cancer treated with aminoglutethimide plus cortisone (Sanford et al, 1976; Ponder et al, 1984). In the PSA era, treatment with aminoglutethimide (1000 mg/day) and hydrocortisone acetate (40 mg/day) resulted in a greater than 50% decline in PSA in 37% of patients, with median response times lasting 9 months (Kruit et al, 2004).

Ketoconazole

An orally active, broad-spectrum azole antifungal agent, ketoconazole interferes with two cytochrome P450–dependent pathways: by inhibiting 14-methylation it blocks the conversion of lanosterol to cholesterol, and it also blocks 17,20-desmolase, impacting on the conversion of C₂₁ to C₁₉ steroids. Based on the observation that some patients taking the drug developed gynecomastia, investigations of its effects on steroid synthesis demonstrated loss of adrenal steroid synthesis (Pont et al, 1982b) and testosterone synthesis by Leydig cells (Pont et al, 1982a). The effects were rapid, with testosterone levels dropping to the castrate level with 4 hours of administration in some cases (Trachtenberg et al, 1983). The effects were also immediately reversible, indicating dosing must be continuous (400 mg every 8 hours) to maintain low testosterone levels.

Early experience with ketoconazole in the treatment of prostate cancer showed this agent to be tolerable, durable, and effective (Trachtenberg and Pont, 1984) and it was palliative for those who had failed first-line androgen ablation therapy (Pont, 1987). Although ketoconazole is effective in rapidly bringing testosterone levels into the castrate range, with continuous treatment in the otherwise hormonally intact individual (no other surgical or chemical ADT), testosterone levels begin to rise and can reach low-normal ranges within 5 months of therapy (Vanuytsel et al, 1987). Therefore currently ketoconazole is used for men with castration-resistant prostate cancer, often as the first or second agent in so-called secondary hormonal manipulation (Small et al, 2004). In addition to gynecomastia (caused by alterations in testosterone/estradiol ratios [Pont et al, 1985]), ketoconazole is associated with lethargy, weakness, hepatic dysfunction, visual disturbance, and nausea (Wilkinson and Chodak, 2004; Scholz et al, 2005). Because of the adrenal suppression, ketoconazole is usually given with hydrocortisone (20 mg twice per day). Patients with higher levels of the adrenal androgen androstenedione had an improved survival

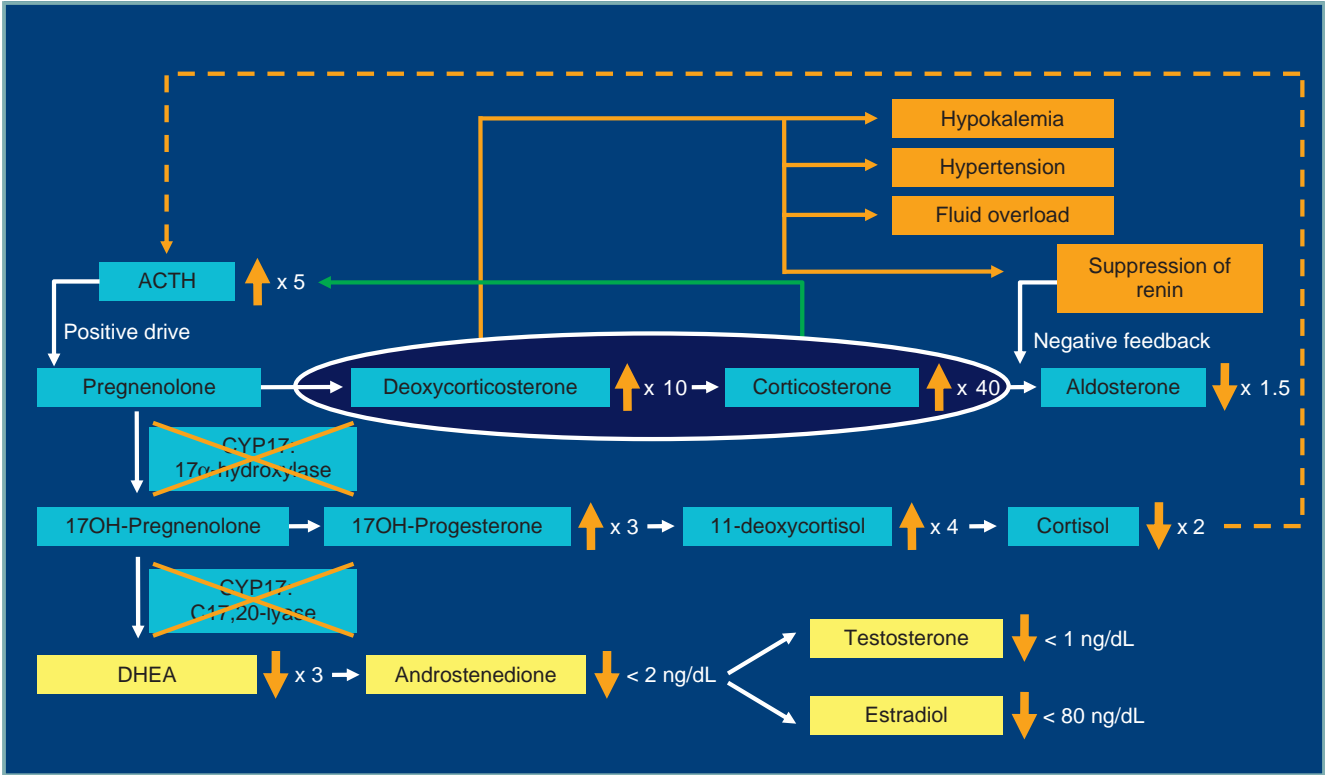


Figure 120-4. Mechanism of action of abiraterone, and potential side effects. ACTH, adrenocorticotropic hormone. (Modified from Attard G, Reid AH, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol* 2008;26:4563–71.)

in response to ketoconazole compared to those with lower levels, suggesting that ketoconazole is less effective in patients with low levels of androgen at baseline (Ryan et al, 2007).

Abiraterone

Unlike the less potent ketoconazole, which inhibits several cytochrome P pathways, abiraterone is a potent, selective, and irreversible inhibitor of cytochrome P17, a key enzyme in androgen synthesis (Chan et al, 1996). Specifically, abiraterone inhibits 17α-hydroxylase, resulting in excess synthesis of aldosterone and its precursors and causing a suppression of cortisol with a compensatory rise in ACTH. Abiraterone also inhibits C_{17,20}-lyase, resulting in suppression of testosterone to levels of less than 1 ng/mL (significantly lower than castrate levels of 50 ng/mL) (O'Donnell et al, 2004; Attard et al, 2005). Abiraterone was developed based on the hypothesis that castration-resistant prostate cancer remains driven by low levels of androgens. Although abiraterone is generally well tolerated, toxicities stem from the effects of blocking the conversion of pregnenolone to 17-hydroxypregnenolone, resulting in an increase in the mineralocorticoids deoxycorticosterone and corticosterone (Fig. 120-4). Untreated, this can result in hypokalemia, hypertension, and fluid overload (Attard et al, 2008). Coadministration of prednisone suppresses the increases in ACTH resulting from decreases in cortisol and mineralocorticoid excess. In men with metastatic castration-resistant prostate cancer after treatment with docetaxel, abiraterone plus prednisone significantly improved overall survival and progression-free survival compared to placebo plus prednisone (Fig. 120-5). Declines in PSA and radiographic responses occurred in 29% and 14% of men on abiraterone, respectively (de Bono et al, 2011). Similarly, in men with metastatic castration-resistant prostate cancer prior to chemotherapy, abiraterone plus prednisone significantly improved progression-free

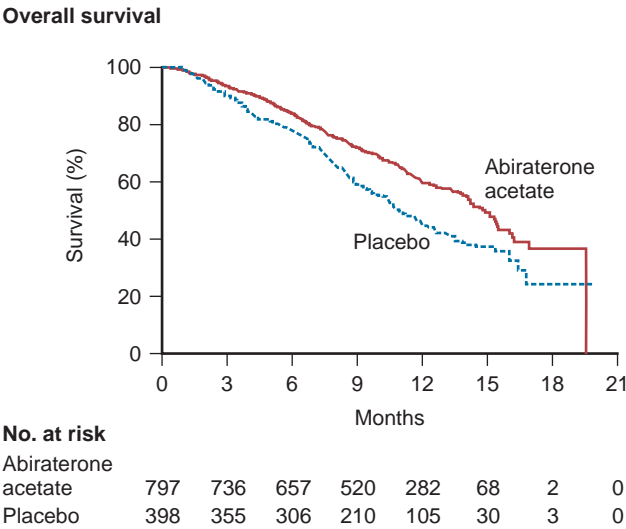


Figure 120-5. Overall survival among patients with metastatic, castration-resistant prostate cancer after receiving abiraterone plus prednisone compared to patients receiving placebo plus prednisone after previous treatment with chemotherapy. (From de Bono JS, Logothetis CJ, Molina A, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.)

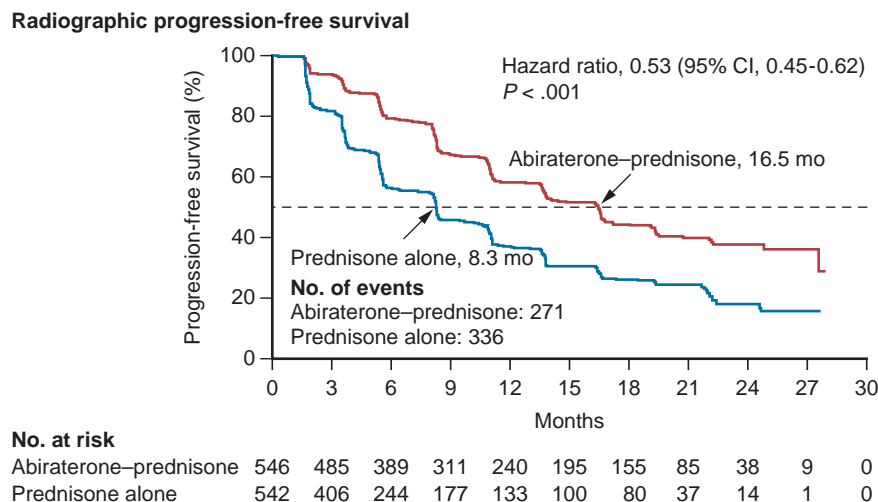


Figure 120-6. Radiographic progression-free survival in patients with metastatic, castration-resistant prostate cancer after receiving abiraterone plus prednisone compared to patients receiving placebo plus prednisone without previous treatment with chemotherapy. CI, confidence interval. (From Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013;368:138–48.)

survival and overall survival compared to placebo plus prednisone (Fig. 120-6) (Ryan et al, 2013).

RESPONSE TO ANDROGEN BLOCKADE

Following the initiation of ADT, the vast majority of prostate cancer patients will show some evidence of clinical response: the magnitude and rapidity of that response remain the best predictors of its durability. Assuming ADT effectively targets the androgen-sensitive population of prostate cancer cells, an incomplete or sluggish response is evidence of a significant androgen-refractory cell population. Early in the clinical use of PSA as a biomarker of prostate cancer, it was recognized that declines in PSA could predict response (Hudson et al, 1989; Aria et al, 1990; Cooper et al, 1990). For example, patients who had more than an 80% drop in PSA within 1 month of initiating ADT survived significantly longer free of disease progression (Aria et al, 1990). Likewise, the nadir PSA predicted the progression-free interval (Matzkin et al, 1992; Benaim et al, 2002a), as did pretreatment testosterone levels (Imamoto et al, 2001). A rise in PSA, evidence of the emergence of castration-resistant disease, preceded bone metastatic progression by several months, with a mean lead time of 7.3 months (Cooper et al, 1990; Miller et al, 1992).

More recent studies of PSA response to ADT have confirmed and amplified those observations. The odds ratio for progressing to castration-resistant disease within 24 months of starting ADT was almost 15 times higher for patients who did not achieve an undetectable PSA (Benaim et al, 2002a). For each unit increase in Gleason score, the cumulative hazard of castration-resistant progression was nearly 70% (Benaim et al, 2002b). In one cohort of Asian men, nadir PSA was the most accurate predictor of disease progression and was independently prognostic of survival; achieving a PSA level of 1.1 ng/mL or less at 6 months after initiating ADT was the most sensitive and specific predictor of progression at 2 years (Kwak et al, 2002). In men with newly diagnosed metastatic prostate cancer (stage D2) started on ADT, the absolute PSA level after 7 months of ADT was a strong, independent predictor of survival (Hussain et al, 2006). Median survival of men achieving a PSA of 0.2 ng/mL or less was 75 months, compared to 13 months for men whose nadir was greater than 4 ng/mL. The kinetics of PSA rise prior to ADT compared to the rate of PSA decline after ADT also

predicted outcome, specifically prostate cancer-specific mortality (D'Amico et al, 2005). If the pre-ADT PSA rise was rapid and the decline after ADT was slow, the cancer-specific mortality was significantly worse compared to that in patients with slow rises of PSA pre-ADT and rapid declines after ADT (D'Amico et al, 2004b).

Almost without exception, those men no longer responding to ADT (androgen-refractory) remain on ADT. Therefore factors influencing survival in that disease state should be considered in this discussion. In most cases available data are based on pre- or post-treatment responses to other systemic treatments (Galsky and Kelly, 2003). Consistently predictive variables (by both univariate and multivariate analysis) of survival in this state include performance status, serum lactate dehydrogenase, serum alkaline phosphatase, hemoglobin, and PSA response to secondary therapy (Smaletz et al, 2002). The survival of men treated on seven sequential chemotherapy protocols at one institution provided an early experience in developing predictive measures (Kelly et al, 1993). A 50% decline in PSA in response to chemotherapy was one of the most significant variables predicting survival. A nomogram based on a larger group of patients found that the presence of visceral disease, Gleason score, performance status, and baseline PSA, lactate dehydrogenase, alkaline phosphatase, and hemoglobin were useful in modeling prognosis (Smaletz et al, 2002; Halabi et al, 2003).

GENERAL COMPLICATIONS OF ANDROGEN ABLATION

Osteoporosis

The increased number of men being placed on androgen ablation therapy much earlier in the course of their disease allows the chronic manifestations of the hypogonadal state to emerge. Widespread androgen ablation therapy applied to an increasing aging population, already predisposed to loss of bone mineral density (BMD), has created an epidemic of osteopenia and osteoporosis. Fragile bones increase the risk of skeletal fracture. More than half of men meet the BMD criteria for osteopenia or osteoporosis—defined as more than 2.5 standard deviations below an age-specific reference mean—prior to the initiation of ADT (Wei et al, 1999; Conde et al, 2004). The longer a man remains on ADT, the greater the risk of fracture (Daniell et al, 2000; Krupski et al, 2004). After 5 years on ADT, 19.4% of men experienced fractures compared to 12.6% of controls (Shahinian et al, 2005); over 15 years the

cumulative incidence of fractures was 40% compared to 19% in noncastrate controls (Melton et al, 2003). It has been estimated that 4 years of ADT will place the average man in the osteopenia range (Wei et al, 1999). Prostate cancer was associated with an increased odds ratio for hip fractures of 3.7 (95% confidence interval [CI] 3.1 to 4.4) in a large Danish population-based study (Abrahamsen et al, 2007). Rarely discussed even 10 years ago, skeletal health is now becoming a major concern of patients and their physicians (Chen et al, 2002).

Treatment of osteoporosis begins with recognition. BMD of the hip as measured by dual-energy x-ray absorptiometry should be considered for all men who are anticipated to be on long-term ADT (Bae and Stein, 2004; Diamond et al, 2004). Smoking cessation, weight-bearing exercise, and vitamin D and calcium supplementation can help improve BMD. **Daily supplementation of calcium and vitamin D is recommended by the National Institutes of Health at doses of 1200 to 1500 mg/day and 400 IU/day, respectively** (Michaelson et al, 2008). Supplementation decreases the incidence of nonvertebral fractures in men and women over 65 years of age (Dawson-Hughes et al, 1997). Prevention of osteoporosis in men receiving ADT has been demonstrated in controlled studies using the bisphosphonate pamidronate (Smith et al, 2001). **In a randomized prospective study, once-weekly oral alendronate reversed bone loss associated with ADT and improved bone density; this benefit continued with ongoing treatment, suggesting chronic treatment is beneficial** (Greenspan et al, 2007, 2008). BMD also increased in men on ADT using the considerably more potent bisphosphonate zoledronic acid (Smith et al, 2003a). Bisphosphonate therapy should be considered in any man with evidence of osteopenia or osteoporosis (Bae and Stein, 2004). Transdermal estradiol also increases BMD in men with prostate cancer (Ockrim et al, 2004). Not surprisingly, serum testosterone and estradiol levels were much lower in men receiving LHRH agonists compared to those on a nonsteroidal antiandrogen; interestingly, markers of bone turnover were significantly higher in men on LHRH agonists compared to those on a nonsteroidal antiandrogen, suggesting the nonsteroidal antiandrogens may help maintain BMD (Smith et al, 2003b).

Hot Flashes

For over 100 years, hot flashes (also called hot flushes or vasomotor symptoms) have been recognized as a side effect of androgen ablation: in 1896, Cabot mentioned “uncomfortable flushes of heat, similar to those experienced by women at the time of menopause” in men undergoing castration for prostatic enlargement (Cabot, 1896; Stearns, 2004). Described as a subjective feeling of warmth in the upper torso and head followed by objective perspiration, hot flashes are not life-threatening but are among the most common side effects of androgen ablation, affecting between half and 80% of patients (Moyad, 2002; Spetz et al, 2003; Nishiyama et al, 2004). Occurring both spontaneously and precipitated by changes in body position, ingestion of hot liquids, or changes in environmental temperature, the exact etiology of hot flashes remains undefined. The proposed mechanisms include increases in hypothalamic adrenergic concentrations and alterations in β -endorphins and calcitonin gene-related peptides acting on the thermoregulatory center in the hypothalamus (Yuzurihara et al, 2003). Hot flashes generally decrease in both frequency and intensity over time but often persist in some men (Holzbeierlein et al, 2004).

Treatment of hot flashes should be reserved for those men who find them bothersome. Just as hot flashes are a consequence of alterations in the hormonal milieu, the mainstay of treatment has been based on efforts to influence that milieu (Kouriefs et al, 2002). In a double-blind, placebo-controlled crossover study, the progestational agent megestrol acetate (20 mg twice per day) significantly reduced the frequency of hot flashes (Loprinzi et al, 1994b). The dose can be reduced to 5 mg twice daily, which may help reduce the appetite-stimulating effect of this agent. The efficacy of cyproterone acetate is based on its progestational effects (Cervenak et al, 2000). Dosing should start at 50 mg/day and be

titrated to 300 mg/day. Estrogenic compounds such as low-dose DES and transdermal estradiol appear to be the most effective treatment, with up to 90% partial or complete resolution of symptoms (Miller and Ahmann, 1992; Smith, 1994; Gerber et al, 2000). With estrogen compounds, however, the cure may be worse than the disease; painful gynecomastia and thromboembolic effects have limited the utility of this approach. Clonidine, a centrally acting α agonist that decreases vascular reactivity, has been used with mixed results: in a placebo-controlled study, transdermal clonidine did not significantly decrease hot flashes (Loprinzi et al, 1994a). Antidepressant agents, particularly the selective serotonin reuptake inhibitor venlafaxine (12.5 mg twice daily), have reduced hot flashes in more than 50% of men (Quella et al, 1999; Loprinzi et al, 2004). In a phase III randomized, double-blind, placebo-controlled trial, the antiseizure agent gabapentin decreased hot flashes to a moderate degree (Loprinzi et al, 2009).

Sexual Dysfunction (Erectile Dysfunction and Loss of Libido)

The effects of ADT on sexual function are profound, as first described by Huggins and colleagues in 1941: “Sexual desire and penile erections were absent in all cases following castration.” **Loss of sexual functioning is not inevitable, however, with up to 20% of men on ADT able to maintain some sexual activity** (Rousseau et al, 1988; Clark et al, 2001). Specifically, between 10% and 17% of men undergoing ADT can maintain an erection adequate for intercourse (Tomić, 1983; Potosky et al, 2001). **Libido is more severely compromised, with approximately 5% of men maintaining a high level of sexual interest with ADT** (Potosky et al, 2001). Sexual desire is inversely related to the duration of androgen deprivation (Basaria et al, 2002). Loss of penile volume and penile length, loss of nocturnal penile tumescence, and, for those undergoing medical ADT, loss of testicular volume are common (Marumo et al, 1999; Higano, 2003).

Treatment for loss of libido is extremely difficult—if not impossible—for those on ADT. Likewise, medical treatments such as oral phosphodiesterase-5 inhibitors or local treatments such as intracavernosal injections of alprostadil can still be effective in selected patients but may not be used over the long term. If there is any fairness in the negative effects of ADT on sexual function, it is the decline in both libido and erectile functioning: despite no erections or desire, the majority of patient have little to no problem with their (lack) of sexual functioning (Potosky et al, 2001).

Cognitive Function

There is a strong suggestion that ADT is linked to subtle but significant cognitive declines in men with prostate cancer (Nelson et al, 2008). In both men and women, the hypogonadal state is associated with declines in cognitive functioning (Gouchie and Kimura, 1991; Sherwin and Tulandi, 1996). Testosterone supplementation improves verbal fluency (Alexander et al, 1998), but other controlled studies have found no effect of such supplementation on memory (Sih et al, 1997). In a small study, men with prostate cancer randomized to ADT performed worse in cognitive studies compared to men with prostate cancer under surveillance (Green et al, 2002); the declines were associated with tasks requiring complex information processing (Green et al, 2004). Compared to tests for other cognitive domains, tests for spatial ability uniquely declined in men on intermittent hormone therapy (Cherrier et al, 2003). In men on neoadjuvant ADT prior to radiotherapy, cognitive functioning declined (Jenkins et al, 2005). Unfortunately, the studies examining the effects of ADT on cognitive functioning have been small and underpowered. Not surprisingly given the many side effects of ADT, quality of life worsens specifically in the domain of emotional functioning in men receiving flutamide in addition to castration compared to placebo (Moynour et al, 1998). A short course of ADT (36 weeks) increased depression and anxiety scores on formal neuropsychological evaluations (Almeida et al, 2004);

major depressive disorder was prevalent in 12.8% of men on ADT, eight times greater than the national rate and 32 times the rate of men over 65 years of age (Pirl et al, 2002). Finally, psychological distress accounted for approximately one third of declines in a fatigue severity scale in men undergoing ADT (Stone et al, 2000).

Changes in Body Habitus

A loss of muscle mass and increase in percent fat body mass are common in men undergoing ADT, and these changes are most pronounced with the initiation of ADT (van Londen et al, 2008). After 1 year of ADT, the mean overall weight increases by 1.8% to 3.8%, which translates into about 5 pounds for a 200-lb man (Berruti et al, 2002; Smith et al, 2002; Smith, 2004). One study found that weight increased a median of 6 kg (13.2 lbs), with a range of 3 to 15 kg (6.6 to 33 lbs) (Higano et al, 1996). Since lean body mass usually decreases by the same magnitude, the weight gain is largely due to an increase in fat mass (Levy et al, 2008). The average increase in fat mass ranges from 9.4% to 23.8% (Berruti et al, 2002; Smith et al, 2002; Smith, 2004). As noted by Huggins and colleagues (1941), ADT is associated with an increase in appetite, and low testosterone is associated with increased insulin levels and abdominal girth (Seidell et al, 1990).

The Cancer Prevention Studies I and II (1959-1972 and 1982-1996, respectively) were large population-based studies of obesity and the risk of cancer mortality. The risk of death from prostate cancer in obese men was 34% (Study I) and 36% (Study II) when compared to men of normal weight (Rodriguez et al, 2001; Calle et al, 2003). Furthermore, men over the age of 65 who engaged in vigorous exercise more than 3 hours per week had a 70% reduction in prostate cancer-specific death (Giovannucci et al, 2005). The body composition changes associated with ADT may portend a worse prognosis for men with prostate cancer. Regular vigorous exercise may help patients limit the accumulation of fat and even prevent prostate cancer progression.

Diabetes and Metabolic Syndrome

Given the changes in body habitus, it is not surprising that metabolic syndrome, a clustering of specific cardiovascular disease risk factors related to insulin resistance, is present in more than 50% of men undergoing long-term ADT (Braga-Basaria et al, 2006). Unlike classic metabolic syndrome characterized by visceral fat accumulation, however, ADT preferentially increased subcutaneous fat: furthermore, high-density lipoprotein (HDL) cholesterol concentrations were increased (Smith et al, 2008a). Short-term ADT affected serum lipid and hemoglobin A_{1c} independent of statin therapy (Yannucci et al, 2006). In a small, but carefully controlled prospective study, ADT significantly decreased insulin sensitivity in men with prostate cancer (Smith et al, 2006). These findings were supported by a larger observational study (73,196 men with prostate cancer) in which there was a significant risk of developing diabetes with ADT (Keating et al, 2006). In a subset analysis of a phase III trial of the selective estrogen receptor modulator toremifene for the prevention of osteoporosis in men undergoing ADT, placebo-treated patients had increases in low-density lipoprotein (LDL) cholesterol and triglycerides, which were significantly decreased with toremifene (Smith et al, 2008b).

Cardiovascular Morbidity and Mortality

Given the generally adverse effects of ADT on body habitus, glucose metabolism, and lipid profiles, it is not surprising that studies have found ADT is associated with increased cardiovascular morbidity and mortality. The effects appear to be most pronounced in men with lower-risk prostate cancer treated with ADT. In a large (22,816 subjects) population-based registry, newly diagnosed prostate cancer patients who received ADT for at least 1 year had a 20% higher risk of cardiovascular morbidity compared to similar men who did not receive ADT (Saigal et al, 2007). In men over the age of 65 undergoing radical prostatectomy who also received ADT, the

cumulative incidence of cardiovascular death was 5.5% over 5 years compared to 2.0% in those not receiving ADT (Tsai et al, 2007). On the other hand, in men with locally advanced prostate cancer treated with radiation therapy and ADT, there was not an increase in cardiovascular mortality compared to men receiving radiation therapy alone (Efsthathiou et al, 2008).

Gynecomastia

Depending on the agents used in ADT, alterations in breast tissue are common. Gynecomastia (an increase in breast tissue) and mastodynia (breast tenderness) may occur together or independently. Estrogenic compounds such as DES induce gynecomastia in 40% of patients (Smith, 1996). Likewise, the peripheral conversion of testosterone to estradiol associated with the antiandrogens induces gynecomastia at high rates: 66.3% of men taking 150 mg of bicalutamide developed gynecomastia and 72.7% developed mastodynia.

Prophylactic radiation therapy (10 Gy) has been used to prevent or reduce painful gynecomastia (Payne et al, 2002) as a result of DES or antiandrogen therapy. Radiation has no benefit once gynecomastia has begun. Liposuction and subcutaneous mastectomy have been used to treat established gynecomastia (Higano, 2003). The selective estrogen receptor modulator tamoxifen has been used to treat mastodynia (Serels and Melman, 1998).

Anemia

The anemia associated with ADT is normochromic, normocytic and is very common: 90% of men receiving combined androgen blockade experienced declines in hemoglobin concentration of at least 10% (Strum et al, 1997). Although anemia can be further complicated by tumor growth in the marrow space, compromising hematopoiesis, even men with nonmetastatic prostate cancer experience anemia with ADT (Choo et al, 2005). Unfortunately, anemia (defined as hemoglobin <12 g/dL) is associated with a shorter survival in those patients who were anemic prior to initiation of ADT (Beer et al, 2004b). Declines in hemoglobin begin within 1 month of ADT initiation (Strum et al, 1997) and continue for 24 months (Choo et al, 2005). Compensatory mechanisms limit the symptomatic effects of anemia to a small subset (13%) of men (Strum et al, 1997).

The anemia with ADT is thought to be secondary to lack of testosterone stimulation of erythroid precursors and a decrease in erythropoietin production. In an animal model, however, erythropoietin levels increased after ADT (Voegeli et al, 2005). Whatever the etiology, clinically, patients respond to recombinant human erythropoietin. The anemia is reversible after stopping ADT, but this may take up to a year (Strum et al, 1997).

COMBINATION THERAPY

The advent of nonsurgical, reversible hormone therapy coupled with its profound effects on prostate cancer have led to broad investigations of the combination of ADT with nearly every other treatment applied to prostate cancer. In some cases, most notably external beam radiotherapy, the combination clearly improves the outcomes; in others, most notably radical prostatectomy, there is no obvious benefit.

With Radical Prostatectomy

In nonrandomized clinical trials of ADT prior to radical prostatectomy, the effects on the final surgical specimen were dramatic. Positive surgical margin rates fell from nearly 50% in hormonal intact patients to 15% in ADT patients (Lee et al, 1997). Glands with no evidence of malignancy (P0) were not uncommon. There was a nonsignificant trend toward improved biochemical outcome with neoadjuvant ADT. Based on these findings and a perception that neoadjuvant ADT reduced blood loss and rendered the

TABLE 120-2 Randomized Prospective Studies of Neoadjuvant ADT before RRP: No Significant Difference in Biochemical (PSA) Progression

STUDY	DESIGN	NO. PATIENTS	FOLLOW-UP	BIOCHEMICAL FAILURE RATE
Schulman et al (2000)	3 mo ADT* + RRP	192	4 yr	26.4%
	RRP alone	210		32.5%
Soloway et al (2002)	3 mo ADT† + RRP	138	5 yr	35.2%
	RRP alone	144		32.4%
Aus et al (2002)	3 mo ADT‡ + RRP	63	7 yr	50.2%
	RRP alone	63		48.5%
Klotz et al (2003)	3 mo ADT§ + RRP	112	6 yr	37.5%
	RRP alone	101		33.6%

*Goserelin and flutamide.
†Leuprolide and flutamide.
‡Triptorelin.
§Cypoterone acetate.
ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RRP, radical retropubic prostatectomy.

procedure easier to perform, three randomized prospective studies compared 3 months of ADT followed by radical retropubic prostatectomy (RRP) to RRP alone (Witjes et al, 1997; Soloway et al, 2002; Klotz et al, 2003) (Table 120-2). In both short (mean 15 months) and longer (4 to 7 years) follow-up, there was no significant difference in PSA progression between the groups. The lack of improved biochemical recurrence in these three randomized prospective trials using 3 months of neoadjuvant ADT before RRP argues strongly that this combination is not indicated in the treatment of prostate cancer.

With Radiation Therapy

Unlike the lack of long-term improved cancer-specific progression with the combination of ADT and radical prostatectomy, several phase III clinical trials have shown a benefit with the combination of ADT and external beam radiation in overall survival, cancer-specific survival, or freedom from disease progression. It should be noted that the benefit appears to be in men with locally advanced disease and/or those with high-grade, high-risk disease.

A phase III study comparing radiation alone to the combination of radiation and orchiectomy in men undergoing pelvic lymph node dissection was closed because of a high frequency of progression in the radiation-only arm (Granfors et al, 1998). A report based on this study at a median 9.3 years of follow-up demonstrated a significant difference in clinical progression (61% vs. 31%), overall mortality (61% vs. 38%), and prostate cancer-specific mortality (44% vs. 27%) in 91 men randomized to radiation alone versus radiation and orchiectomy, respectively (Granfors et al, 1998). These observations were supported by another study randomizing men with locally advanced prostate cancer to radiation alone versus radiation combined with goserelin for 3 years (Bolla et al, 1997). The significant disease-free and overall survival advantage of the combination was confirmed at a long-term analysis of the trial (Fig. 120-7) (Bolla et al, 2002). Clearly, in locally advanced, high-risk disease, the combination of radiation therapy with ADT is certainly better than radiation alone. A number of trials have been designed to address the timing of ADT (length, neoadjuvant, adjuvant) (Crook et al, 2004); some of the results are summarized in Table 120-3 and in several review articles (D’Amico, 2002; Lawton, 2003). Changes in the dose and field of the external beam radiation therapy make direct study-to-study comparisons difficult: unlike the uniformity of radical prostatectomy (complete ablation of the prostate), the optimum radiation technique remains undefined.

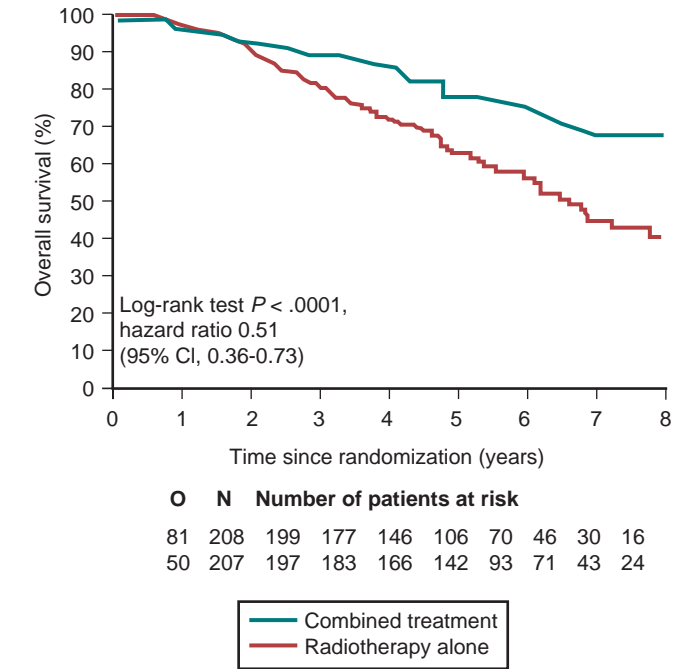


Figure 120-7. Kaplan-Meier estimates of overall survival by treatment group: 3 years of goserelin combined with external beam radiation versus external beam radiotherapy alone for locally advanced prostate cancer. CI, confidence interval. (From Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002;360:103–8.)

Combined Androgen Blockade

Among all the efforts to improve the efficacy of ADT, none has been as widely studied as combinations of the various forms of hormone therapy, particularly if mechanistically nonredundant. For example, ablation of the source of androgen (castration) coupled with inhibition of LHRH with DES was one of the first combinations studied clinically to suggest improved survival (Nesbit and Baum, 1951); upon closer scrutiny in the first VACURG study, the survival advantage of this combination was lost (Blackard et al, 1973). Likewise, an early experience with an LHRH analogue and

TABLE 120-3 Phase III Randomized Prospective Trials Comparing Primary RT Alone to a Combination with ADT, or 3 versus 8 Months of ADT with RT

TRIAL	TREATMENT ARMS	NO. PATIENTS	5-YEAR OVERALL SURVIVAL	5-YEAR CANCER-SPECIFIC SURVIVAL	5-YEAR PSA PROGRESSION
EORTC 22863 (Bolla et al, 1997, 2002)	Goserelin 3 yr vs. none	208 vs. 207	78% vs. 62%	94% vs. 79%	76% vs. 45%
RTOG 85-31 (Pilepich et al, 1997, 2005; Lawton et al, 2001)	Goserelin Lifetime adjuvant vs. none until relapse	477 vs. 468	75% vs. 71%*	91% vs. 87%*	54% vs. 21%
RTOG 86-10 (Pilepich et al, 2001; Shipley et al, 2002)	Goserelin + flutamide 4 mo (2 mo neoadjuvant, 2 mo concurrent) vs. none	226 vs. 230	72% vs. 68%†	85% vs. 80%	28% vs. 10%
RTOG 92-02 (Hanks et al, 2003)	Goserelin 2 yr adjuvant vs. none	761 vs. 753	80% vs. 78.5%‡	91.2% vs. 94.6%	28% vs. 55.5%
DFCI 95096 (D'Amico et al, 2004a)	Goserelin or leuprolide + flutamide 6 mo vs. none	102 vs. 104	88% vs. 78%		
Granfors et al (2006)§	Orchiectomy vs. none	45 vs. 46			
Canadian Multicenter (Crook et al, 2009)	Goserelin + flutamide 3 mo vs. 8 mo, neoadjuvant	184 vs. 194	81% vs. 79%¶	94% vs. 93%¶	58% vs. 65%¶

*The 5-year overall survival and cancer-specific survival differences between the two study arms were not significant. At 10 years of follow-up, however, the combination of adjuvant goserelin and RT compared to RT alone was significantly different: for overall survival, 49% versus 39%, respectively; for cancer-specific survival, 84% versus 78%, respectively.

†Difference not significant.

‡Difference not significant.

§During 14 to 19 years of follow-up, 87% of RT-only arm and 76% of the RT + orchiectomy arm died (log rank $p = .03$); prostate cancer mortality was 57% and 35%, respectively (log rank $p = .02$).

¶Difference not significant.

ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RT, radiation therapy.

an antiandrogen in 30 patients suggested improved outcomes compared to standard treatment (Labrie et al, 1983); upon extensive scrutiny in a meta-analysis of 27 prospective, randomized, international clinical trials of the combination of an antiandrogen with either castration or an LHRH agonist, the collective result was clinically insignificant (Prostate Cancer Trialists' Collaborative Group, 2000).

The concept of adding an antiandrogen to surgical castration or an LHRH agonist is based on the idea that, after the elimination of testicular androgens through surgical or medical castration, adrenal androgens still contribute to prostate cancer progression (Labrie et al, 1988; Miyamoto et al, 1998; Miyamoto and Chang, 2000). The fact that serum testosterone does not drop to zero following surgical or medical castration is clear evidence for additional sources of androgen (Geller, 1985; Sandow et al, 1988). The idea of trying to eliminate all sources of endogenous androgen in treating prostate cancer is not new: bilateral surgical adrenalectomy was performed with failure far outweighing success (Huggins and Scott, 1945). Eliminating all sources of endogenous androgen is also referred to, somewhat presumptuously, as "total androgen blockade" or "maximum androgen blockade"—as if such a state is actually achieved; the term *combined androgen blockade* (CAB) is more appropriate. The antiandrogens are nonspecific in blocking the binding of androgens to the AR: both testicular and adrenal androgens are affected. In concept, the approach is sensible and some clinical trials showed prolonged survival in patients with advanced prostate cancer treated with CAB compared to standard ADT (Crawford et al, 1989; Dijkman et al, 1997; Denis et al, 1998).

One study showing a survival advantage to CAB compared the antiandrogen flutamide (250 mg three times per day) in combina-

tion with *daily* leuprolide—a formulation not currently used—to placebo plus daily leuprolide in men with metastatic prostate cancer (Crawford et al, 1989). The combination therapy resulted in a significantly longer progression-free survival and longer overall median survival (35.6 vs. 28.3 months) when compared to the placebo-treated controls. In a hypothesis-generating subset analysis, the authors found that those patients with minimal metastatic disease (defined as the absence of metastases in the skull, ribs, long bones, and non-nodal soft tissue) enjoyed the largest survival benefit compared to similarly defined men receiving placebo. Another positive study compared orchiectomy plus the antiandrogen nilutamide to orchiectomy plus placebo (Dijkman et al, 1997): at 8.5 years of follow-up, the CAB group had significantly longer median time to progression (21.2 vs. 14.7 months) and higher overall survival (37 vs. 29.8 months). Finally, a study in which depot goserelin combined with flutamide was compared to orchiectomy showed increased survival in the CAB group (Denis et al, 1998).

Against the backdrop of these positive studies are a host of randomized trials showing no significant survival advantage for CAB. A landmark randomized clinical trial comparing surgical castration alone to surgical castration combined with flutamide in men with metastatic prostate cancer showed no significant survival advantage for those undergoing CAB (Eisenberger et al, 1998). Unlike the previous study suggesting an advantage of CAB in men with minimal metastatic disease (Crawford et al, 1989), stratifying outcome by disease burden—defined prospectively—was not significant.

In a clinical trial, when the variability in a possible outcome is large and the effect being studied may be small, confidence in the

interpretation of the result is dependent on the size of the study. When several studies testing the same idea in presumably the same patient population demonstrate both positive and negative results, concerns about the existence of a real treatment effect increase. Such is the case with many of the studies of CAB: because they consist of only a few hundred men or are based on subset analysis of a larger study, there is a risk that chance and not an antiandrogen drives the survival outcomes. Those favoring a role of CAB in prostate cancer management point to the selected studies supporting their point of view, only to be met by those against CAB who trot out the negative studies that support their point of view.

Fortunately, the idea of CAB has been very extensively studied: since the early 1980s, 27 randomized studies including 8275 men have been conducted, providing the basis for a meta-analysis comparing CAB to standard ADT (Prostate Cancer Trialists' Collaborative Group, 2000). In these 27 studies, 88% of patients had metastatic disease; the remainder had locally advanced disease. Interestingly, in studies recording specific cause of death, 20% died from causes other than prostate cancer: not everyone with metastatic prostate cancer dies from the disease. In the meta-analysis, the 5-year survival with CAB was 25.4% compared to 23.6% with standard ADT, a nonsignificant gain in favor of CAB of 1.8% (Fig. 120-8). Studies including the steroidal antiandrogen cyproterone acetate had a slightly worse outcome on the CAB arms (5-year survival 15.4% vs. 18.1% for ADT alone), suggesting increased non-prostate cancer deaths in those receiving cyproterone acetate. When studies examining the outcomes of the non-steroidal antiandrogens flutamide or nilutamide were considered independent of those with cyproterone acetate, the 5-year survival improved from 24.7% (standard ADT) to 27.6% for CAB. This 2.9% improvement was significant, but the meta-analysis had a 0% to 5% range of uncertainty about the true size of the benefit.

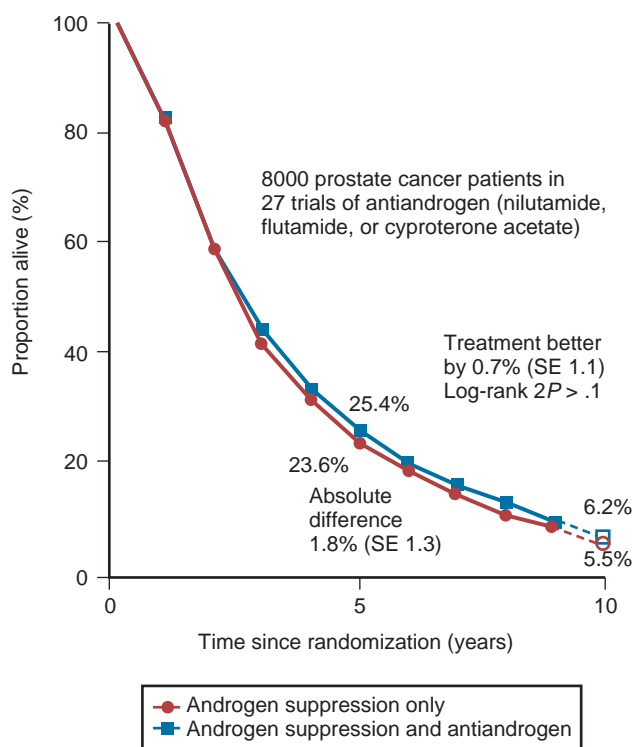


Figure 120-8. Meta-analysis of maximal androgen blockade versus testicular androgen suppression alone in 27 randomized trials and 8275 patients, with an average follow-up of about 5 years. Overall survival curves are for all men irrespective of the antiandrogen used. (From Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of randomised trials. *Lancet* 2000;355:1491-8.)

TIMING OF THERAPY

The timing of the initiation of ADT, although not as extensively studied as CAB, remains one of the most contested areas of prostate cancer management. The spectrum of opinions ranges from primary ADT at time of diagnosis to the initiation of ADT at the first sign of primary prostate cancer failure (early) to initiation of ADT only with objective evidence of distant metastatic disease (late) (Reese, 2000; Walsh et al, 2001; Loblaw et al, 2004; Miyamoto et al, 2004; Sharifi et al, 2005). Unfortunately, the clinical data to support the various perspectives are limited and it is not uncommon for proponents of a particular opinion to extrapolate data from one clinical state to another for which data do not exist. **There is no question that early ADT delays biochemical and clinical disease progression, but the effects of early ADT on survival remain unclear (Ryan and Small, 2005).** Likewise, there is no question that ADT is indicated in symptomatic, metastatic disease. For the sake of this discussion, ADT will be considered continuous, from initiation until death; intermittent ADT is discussed in a subsequent section. Likewise, this discussion focuses on overall and prostate cancer-specific survival resulting from ADT.

Continuous Androgen Deprivation Therapy: Immediate versus Delayed

It is useful to consider some facts about ADT and prostate cancer progression. First, the natural history of prostate cancer progression, even in the hormonally intact individual, is protracted. In a cohort of 304 men with a biochemical recurrence after radical prostatectomy, the median time from recurrence to metastasis was 8 years and from metastasis to death was 5 years (Pound et al, 1999). In updates of this study, the median time to prostate cancer-specific mortality had, initially, not been reached after 16 years of follow-up but was subsequently found to be 168 months (14 years) (Freedland et al, 2005; Makarov et al, 2008). Therefore, even in the absence of ADT, men with progressive prostate cancer live for a long time. Second, despite dramatic clinical responses, men undergoing ADT either will die of a non-prostate cancer cause (estimated at 20% based on the CAB meta-analysis) or will eventually demonstrate evidence of castration-resistant disease and die of prostate cancer. In a randomized prospective study of orchiectomy with or without the antiandrogen flutamide, only 7% of men were still alive at 10 years after the initiation of ADT (Tangen et al, 2003). In a study using a 5% national random sample of Medicare beneficiaries undergoing ADT for prostate cancer, the median overall survival after the initiation of ADT was 4.4 years, and after 8 years only 4.5% of the population was still alive (Krupski et al, 2004). Third, ADT is not an innocuous therapy: beyond the quality-of-life side effects discussed earlier, in a global sense men on ADT age more rapidly; the natural extension of more rapid aging is earlier death. Therefore the long natural history of prostate cancer progression coupled with the inevitability of its progression after ADT initiation in a population with a growing risk of death from all causes should temper enthusiasm to indiscriminately apply this therapy to all men with progressive prostate cancer.

The questions about the timing of ADT are not new. In 1973, the results of a large (more than 1900 men) study performed in the Veterans Administration of early versus late hormonal therapy were reported (Byar, 1973). In men with metastatic disease, death from prostate cancer occurred in 48% of those treated early versus 47% of those treated late. In men with locally advanced disease, death from prostate cancer occurred in 14% of those treated early versus 17% of those treated late. The lack of a survival benefit in men treated early coupled with the known side effects of therapy support the recommendation that hormonal therapy should be instituted in men with symptomatic disease. Since that time, several randomized studies have applied ADT at different times in the natural history of prostate cancer; the results of those studies must be considered within the context of when ADT is used and the circumstances of the study.

Results in Clinically Localized Disease

In the bicalutamide Early Prostate Cancer program, men were randomized to bicalutamide 150 mg or placebo in addition to standard care (See et al, 2003). End points of these trials included overall survival, progression-free survival, and tolerability. In the subset of men with clinically localized disease, the overall survival was significantly worse in those undergoing ADT with bicalutamide 150 mg compared to placebo (Iversen, 2004; Iversen et al, 2004). No specific cause for this decline in overall survival with ADT was identified, but it appeared to be the result of increased deaths from non-prostate cancer causes for those on bicalutamide.

In a community-based cohort study (Prostate Cancer Outcomes Study), men with localized prostate cancer treated with primary ADT within 1 year of diagnosis had a 91% cancer-specific survival but only a 66% overall survival at 5 years (Graff et al, 2007). A larger study of 19,271 men 66 years or older with localized prostate cancer who did not receive definitive local therapy found that primary ADT was associated with lower 10-year prostate cancer-specific survival compared to those on conservative management (Lu-Yao et al, 2008). Although this finding could be the result of more aggressive prostate cancers requiring immediate primary ADT, there was no increase in 10-year overall survival with primary ADT. The authors concluded that “primary ADT is not associated with improved survival in the majority of elderly men with localized prostate cancer when compared with conservative management” (Lu-Yao et al, 2008). Finally, in a retrospective, matched cohort study of patients who received adjuvant ADT (within 90 days of node-negative, radical prostatectomy) compared to those who did not, there was a 3% improved prostate cancer-specific survival (98% vs. 95%, respectively, $P = 0.009$) but no improvement in overall survival (83% in both groups) (Siddiqui et al, 2008).

Primary ADT—defined as the administration of ADT to men without metastases as sole therapy at the time of diagnosis—has been widespread particularly in men over 65 years old: in one study, up to 40% of these men received primary ADT (Shahinian et al, 2006). A retrospective cohort study from three integrated health care plans found that primary ADT was associated with neither a risk of all-cause mortality nor a risk of prostate cancer-specific mortality (Potosky et al, 2014). Primary ADT was associated with decreased risk of all-cause mortality only in men with high risk of prostate cancer progression. It therefore appears that primary ADT does not provide a survival benefit for most men with clinically localized prostate cancer.

These observations are important for several reasons. First, they resoundingly answer the claim that “ADT can’t hurt, so why not use it early?” In the Early Prostate Cancer study, men without ADT had significantly better survival. Second, when ADT is applied in situations in which the risk of death from prostate cancer is already low, demonstration of a prostate cancer-specific survival benefit from that therapy will be very difficult. If ADT itself increases overall mortality compared to no ADT, then demonstration of a prostate cancer-specific benefit will be nearly impossible. Third, men with localized, low-risk prostate cancer should not be treated with ADT without first being informed of these findings. Avoidance of prostate cancer progression and death may come at the expense of unnecessary side effects or a higher overall death rate. These data support the hypothesis that the more rapid aging associated with ADT will bring men with low-risk prostate cancer more quickly to their deaths.

Results in Lymph Node Metastatic Prostate Cancer

A randomized prospective study of immediate ADT compared to delayed ADT was performed by the Eastern Cooperative Oncology Group (ECOG) in men with histologic evidence of metastatic prostate cancer in regional lymph nodes after radical prostatectomy. At the time of the initial report, at 7.1 years of median follow-up, overall survival significantly ($P < .02$) favored the immediate ADT group compared to the delayed ADT group: in the immediate ADT group, only 3 of the 7 deaths were due to prostate cancer

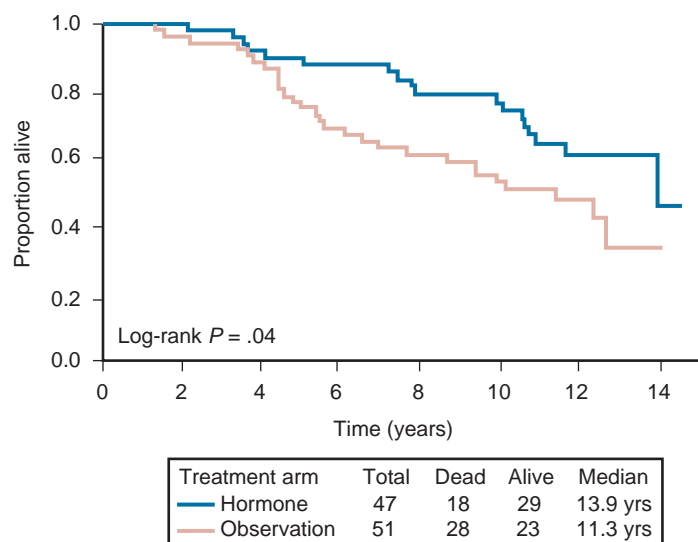


Figure 120-9. Long-term overall survival of men randomized to immediate hormone therapy compared to observation after radical prostatectomy with pelvic lymphadenectomy in men with node-positive prostate cancer. At median 11.9-year follow-up, overall survival in the immediate hormone therapy group was 64% (30/47) compared to 45% (23/51) in the observation group ($P = .04$, log rank). (From Messing EM, Manola J, Yao J, et al; Eastern Cooperative Oncology Group study EST 3886. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7:472-9.)

compared to 16 of the 18 cancer-specific deaths in the delayed ADT group (Messing et al, 1999). In an updated report, median overall survival was significantly longer in the immediate ADT compared to the delayed ADT group: 13.9 versus 11.3 years, respectively (Fig. 120-9) (Messing et al, 2003, 2004). Eight of 18 men in the immediate ADT group died of prostate cancer compared to 25 of 28 men in the delayed ADT group. Given the previous discussion of the increased non-prostate cancer death rate with bicalutamide 150 mg, it is interesting that there have been proportionally more non-prostate cancer deaths in the immediate ADT group (55%) compared to the delayed group (11%). Nevertheless, based on this randomized, prospective trial, there appears to be a benefit to immediately ADT in those men with histologic evidence of lymph node metastases at the time of radical prostatectomy.

There have been several criticisms of this study (Eisenberger and Walsh, 1999). First, the study was designed to enroll 240 patients, yet only enrolled 100. When a large difference in outcome is found in a small study, there is a risk of a type I error (assuming a treatment has an effect when in reality it does not). There was no evidence for an imbalanced randomization, but unrecognized prognostic factors can influence outcomes in smaller studies. Second, Gleason grading was not centralized and the absence of a correlation between histologic grade and survival suggests an imbalance may exist. This concern was partially addressed by a central pathologic review in a blinded fashion of a subset (51%) of the initial specimens. Based on this reanalysis, there was no significant difference in outcomes by treatment arm. Third, those on delayed ADT experienced disease progression and death from prostate cancer that was much more rapid than would have been expected from contemporary series of node-positive patients (deKernion et al, 1990; Zincke et al, 1992; Cadeddu et al, 1997). In contrast to the ECOG study, an observational study of 731 men with node-positive prostate cancer after radical prostatectomy between 1991 and 1999 found no significant difference in overall survival in those who received adjuvant ADT (within 120 days of surgery, $n = 209$) compared to those who did not (Wong et al, 2008).

The magnitude of the difference observed in the ECOG study has not been seen in larger similar—but not identical—patient populations. In a European Organisation for the Research and Treatment of Cancer trial of immediate versus delayed ADT in pN1-3M0 patients without local treatment of the primary tumor, 302 men were randomized to delayed ADT (n = 115) or immediate ADT (n = 119) (Schröder et al, 2004). At a median follow-up of 13 years, the median overall survival in the immediate ADT group was 7.6 years (95% CI 6.3 to 8.3 years) versus 6.1 years (95% CI 5.7 to 7.3 years) in the delayed ADT group. The 10-year cumulative incidence of death from prostate cancer was 55.6% in the delayed ADT group versus 52.1% in the immediate ADT group (Schröder et al, 2009) (Fig. 120-10). Based on these data, 20.8 patients would need to be treated with immediate ADT to spare one life at 5 years and 28.6 to spare one life at 10 years.

Results in Locally Advanced, Asymptomatic Metastatic Disease or Disease Not Suitable to Local Treatment

A trial of immediate versus delayed ADT in men with locally advanced or asymptomatic prostate cancer was conducted by the Medical Research Council (MRC) Prostate Cancer Working Party Investigators Group (1997). A total of 934 men were included (500 M0, 261 M1, and 173 Mx), with 469 randomized to immediate ADT and 465 randomized to delayed ADT. As originally reported, there was a significant survival advantage in the M0 group; on longer follow-up the overall survival advantage is not significant (Kirk, 2004). Overall, men in the delayed ADT arm died significantly more often from prostate cancer and had significantly more symptoms related to disease progression. Based on these data, the benefits of immediate ADT would seem to support its use.

There have been many criticisms of the MRC trial. First, 6% (29/465) of men in the delayed ADT arm “died from prostate cancer before treatment could be started,” meaning they died without ever

receiving ADT. Delayed ADT is not the same as no ADT. Second, 173 of the subjects included in the study were not staged (Mx). When nearly 1 in 5 men could have been incorrectly randomized, the impact on the study’s outcome could be significant. Third, almost 10% of men in the delayed group were treated only when they had developed spinal cord compression or pathologic fractures. The emergency implementation of hormonal therapy is a rare event in patients followed closely; it certainly should not occur in 10% of patients. Finally, the lack of a standardized follow-up protocol—follow-up and management were otherwise according to the participating clinician’s normal practice—may provide meaningful “real-world” results but likely introduces major deviations from rigorous clinical trial design.

Since the majority of men in the MRC study have died (92.5% in the immediate ADT group, 93.6% in the delayed ADT group), the data are now mature and unlikely to change significantly in the future (Kirk, 2004). Time to death from prostate cancer remains significantly in favor of the immediate ADT group ($P = .019$), whereas time to death from any cause is not significantly different between the groups ($P = .0914$). The total difference in prostate cancer-specific deaths was 46 men: 241 died from prostate cancer in the immediate ADT arm, 287 in the delayed ADT arm (Kirk, 2004); the impact of the 29 men in the delayed ADT who never received ADT on this result is unknown, but could reasonably be considered significant. Unlike the increased overall mortality for immediate ADT found in the Early Prostate Cancer bicalutamide 150 mg study for localized, low-risk disease, no similar increase was observed in immediate ADT in the MRC study of a higher-risk cohort.

Immediate versus delayed ADT was studied in another group (n = 985) of men not suitable for local treatment (refused local treatment; had decreased life expectancy, advanced local tumor stage, and/or severe comorbidities) (Studer et al, 2006, 2014). Unlike the MRC study, immediate ADT resulted in a significant, albeit small, improvement in overall survival but no difference in

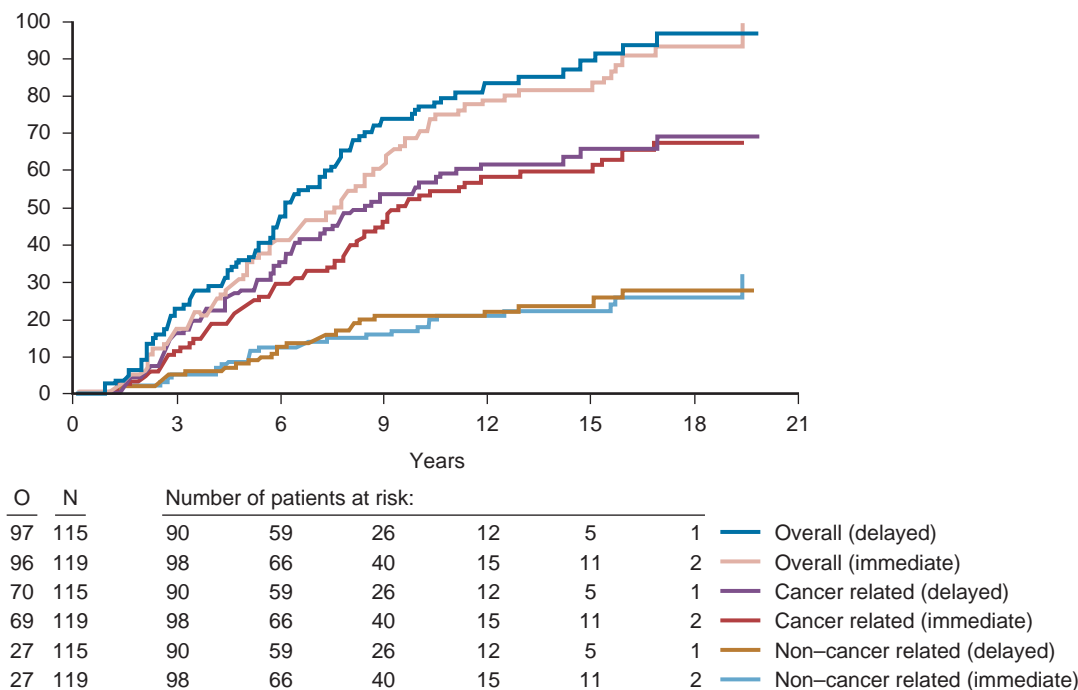


Figure 120-10. Overall mortality, cancer-related mortality, and non-cancer-related mortality with early versus delayed androgen deprivation therapy in men with T2-T3pN1-3M0 prostate cancer without local treatment of the primary tumor. (From Schröder FH, Kurth KH, Fossa SD, et al. Early versus delayed endocrine treatment of T2-T3 pN1-3 M0 prostate cancer without local treatment of the primary tumour: final results of European Organisation for the Research and Treatment of Cancer protocol 30846 after 13 years of follow-up [a randomised controlled trial]. Eur Urol 2009;55:14-22.)

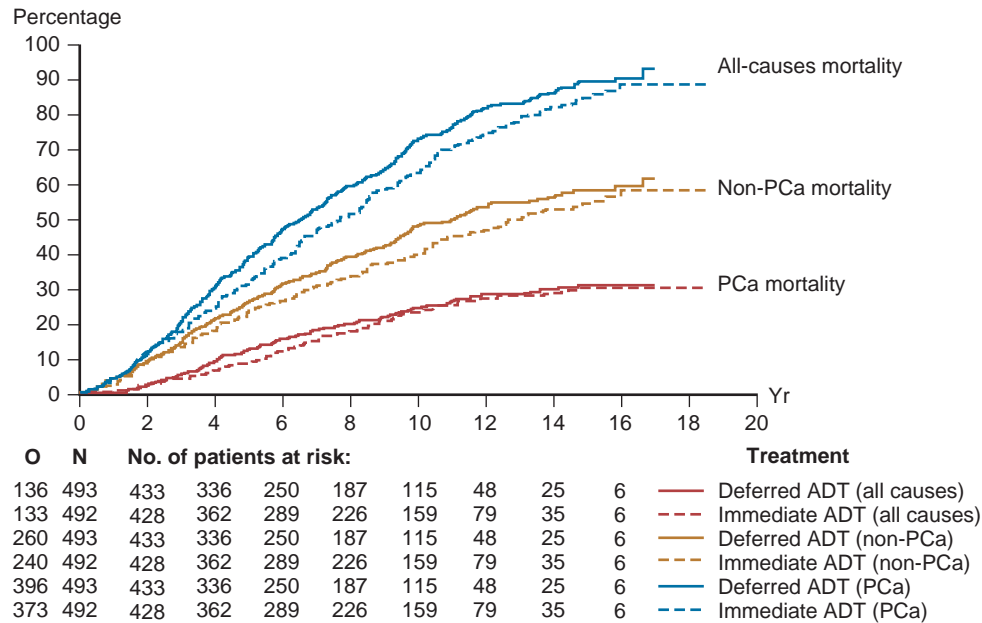


Figure 120-11. Prostate cancer (PCa), non-PCa, and overall mortality with deferred androgen deprivation therapy (ADT) versus continuous ADT. (From Studer UE, Whelan P, Wimpissinger F, et al; EORTC Genitourinary Cancer Group. Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: final results of EORTC randomized trial 30891 with 12 years of follow-up. *Eur Urol* 2014;66:829–38.)

prostate cancer–specific mortality or overall symptom-free survival (Fig. 120-11). Interestingly, in the delayed ADT arm, 30.8% died without ever needing treatment.

Immediate versus Delayed Androgen Deprivation Therapy: Integrating the Data

With the emerging data from ongoing clinical trials and the recently published results of new studies, it is possible to consider the timing of ADT from the perspective of the natural history of the disease.

1. There is no survival benefit to immediate ADT in low-risk, localized prostate cancer. In fact, from the perspective of overall survival, men treated in this fashion do significantly worse than those spared ADT in this setting.
2. In locally advanced, asymptomatic metastatic and clinically present but undefined prostate cancer treated in a community setting with limited disease monitoring, immediate ADT results in significantly better prostate cancer–specific survival but not better overall survival. On the other hand, in men deemed not suitable for local treatment, immediate ADT improved overall survival but not prostate cancer–specific survival.
3. In node-positive disease without primary treatment, there is no significant advantage to immediate ADT, although on balance there is a 1.5-year median survival advantage. In node-positive disease with radical prostatectomy, there is a significant survival advantage favoring immediate ADT, with a 2.6-year difference in median overall survival.

Intermittent versus Continuous Androgen Deprivation Therapy

The use of intermittent ADT has been studied in at least seven large randomized phase III clinical trials (Boccon-Gibod et al, 2007). The rationale for intermittent ADT is based on two complementary ideas. First, in preclinical animal models (Shionogi breast cancer

tumor, LNCaP prostate cancer tumor) exposure to androgen deprivation on an intermittent—rather than continuous—basis lengthened the time to the emergence of androgen-refractory cancer growth (Akakura et al, 1993; Sato et al, 1996). Since castration-resistant prostate cancer is synonymous with lethal prostate cancer, any manipulation of the hormonal milieu that can delay progression into this state would be welcomed. Second, many patients (and their physicians) have increasingly questioned the real benefit of continuous ADT, given the profound and often debilitating side effects associated with its use. With readily reversible ADT, recovery of normal testosterone levels should occur when androgen ablation is stopped. In theory, the quality-of-life side effects of ADT on intermittent treatment should be some fraction of those side effects when ADT is used continuously.

Intermittent ADT was studied in a group of men with a rising PSA after primary or salvage radiotherapy (Crook et al, 2012). Specifically, men were randomized to receive intermittent or continuous androgen deprivation with a primary end point of overall survival. Intermittent treatment was provided in 8-month cycles, with nontreatment periods based on PSA levels. At a median follow-up of 6.9 years, there were 268 deaths in the intermittent therapy group and 256 deaths in the continuous therapy group: median overall survival was 8.8 years in the intermittent group versus 9.1 years in the continuous group (Fig. 120-12). Based on a noninferiority trial design, intermittent therapy was not inferior to continuous therapy for overall survival. Disease-specific death (prostate cancer and related treatments) was more common in the intermittent therapy arm compared to the continuous therapy arm (120 versus 94, respectively). Conversely, deaths unrelated to prostate cancer were more common in the continuous therapy arm compared to the intermittent therapy arm (162 versus 148, respectively).

Attrition from intermittent androgen deprivation progressively increased over time as patients either developed castration-resistant prostate cancer or died of another cause. Attrition only occurred in 5% of men in the first interval, whereas 68% had stopped intermittent therapy by the third interval. On the other hand, duration of intermittent ADT progressively shortened over

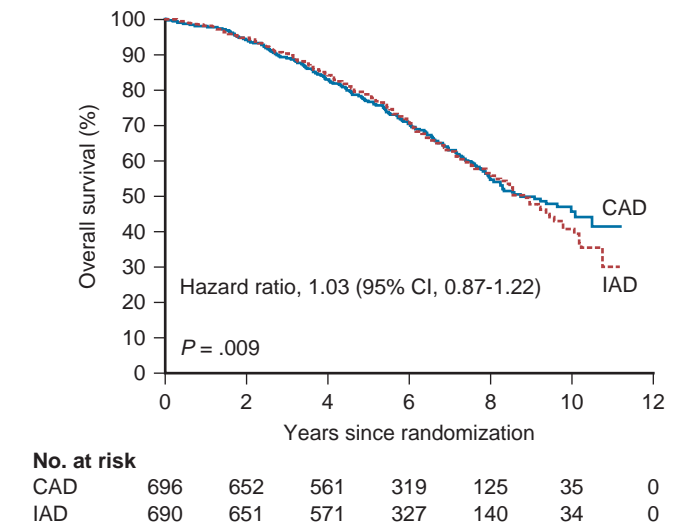


Figure 120-12. Overall survival in patients undergoing intermittent androgen deprivation therapy (IAD) compared to those undergoing continuous androgen deprivation therapy (CAD) in a cohort of men previously treated with primary or salvage radiation therapy. (From Crook JM, O’Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012;367:895–903.)

time: the median nontreatment interval between cycles was 20.1 months for the first treatment cycle, 13.2 months for the second cycle, 9.1 months for the third, and 4 to 5 months thereafter. A secondary end point, improved quality of life in the intermittent therapy arm, was associated with significantly better scores for hot flashes, desire for sexual activity, and urinary symptoms. For the functional domains of physical, role, and global health the intermittent therapy arm was slightly better, but the differences were not significant. Overall, concerning quality of life the authors concluded that “the difference is not as profound as one might expect” (Crook et al, 2012).

Noninferiority trials require fewer subjects than for an equivalence trial, making them easier to accrue and complete. It is important to recognize that noninferiority is not the same as equivalence; trial design is based on a definition of noninferiority if a prespecified upper margin of a hazard ratio is not exceeded. In this trial, the upper limit was 1.25, meaning up to 25% more men on the intermittent arm could die of any cause and intermittent treatment would still be considered noninferior. In this trial, the upper limit of the 95% CI was 1.22, which is below 1.25 and therefore met the prespecified definition.

Intermittent ADT was studied in a group of men with newly diagnosed metastatic prostate cancer (Hussain et al, 2013). After a 7-month induction of ADT in all patients, men whose PSA level had declined to 4 ng/mL or lower (indicating androgen sensitivity) were randomized to receive intermittent or continuous androgen deprivation with coprimary end points of overall survival and quality of life at 3 months after randomization. At a median follow-up of 9.8 years, median overall survival was 5.8 years in the continuous arm and 5.1 years in the intermittent arm (hazard ratio for death with intermittent therapy, 1.10; 90% CI 0.99 to 1.23) (Fig. 120-13). Unfortunately, these findings are statistically inconclusive: the CI for survival exceeded the upper boundary for noninferiority (1.20), meaning one cannot conclude that intermittent therapy was noninferior to continuous therapy. Furthermore, because the lower limit of the CI (0.99) did not exclude 1.00, one cannot conclude that intermittent therapy was significantly inferior to continuous therapy. A reasonable clinical interpretation of this statistically inconclusive study is that intermittent therapy is not superior to continuous therapy in men presenting with metastatic prostate cancer, and may be worse. In the words of the authors “given that nearly the entire confidence interval tends to

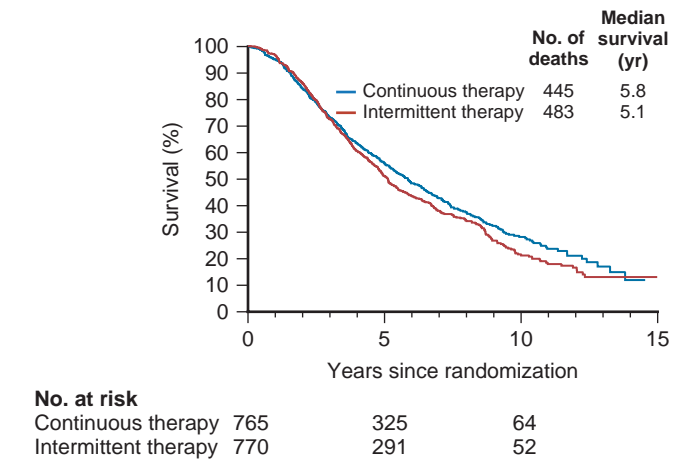


Figure 120-13. Overall survival in patients undergoing intermittent androgen deprivation therapy compared to those undergoing continuous androgen deprivation therapy in a cohort of men with newly diagnosed metastatic, hormone-sensitive prostate cancer. (From Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med* 2013;368:1314–25.)

favor continuous therapy, the results suggest that intermittent therapy may compromise survival” (Hussain et al, 2013). Quality-of-life scores were significantly better in the intermittent arm (less likely to report impotence, better mental health) at 3 months. At 9 and 15 months, the quality-of-life scores favored intermittent therapy but the differences were not significant.

The treatment schedules for intermittent androgen deprivation vary slightly between the rising PSA after radiation therapy trial (Crook et al, 2012) and the metastatic disease trial (Hussain et al, 2013): both used an induction period of ADT (8 months and 7 months, respectively). If the PSA was less than 4 ng/mL, both trials stopped ADT. Androgen deprivation was restarted if the PSA reached 10 or 20 ng/mL, respectively, or for clinical symptoms. In the metastatic disease trial, ADT could also be restarted when the PSA reached baseline. The development of castration-resistant prostate cancer required that the patient be on ADT and demonstrate clinical progression or PSA increases monthly for 3 months. In both trials castration-resistant prostate cancer was managed with continuous ADT. The treatment schedules provide some guidance in managing patients on intermittent ADT, but there is no consensus on the ideal schedule.

ECONOMIC CONSIDERATIONS

In the United States, the cost of drug therapy for ADT (LHRH agonists) in the Medicare program was \$761,000,000 in 1997 and rose to \$1.2 billion in 2003 (Holtgrewe et al, 2000; Shahinian et al, 2006). Indeed, in 2003, LHRH agonists were the second highest Medicare Part B expenditure. This expense is not unique to the United States: in 1997, the annual cost of these agents in Sweden was \$17,000,000 and in Germany the annual cost was \$142,000,000. In a study of 96 men undergoing ADT for prostate cancer over a 10-year period, the cost of LHRH agonists ranged from greater than 10.7 to 13.5 times the cost of bilateral orchiectomy and the cost of CAB was 17.3 to 20.9 times greater (Mariani et al, 2001). Clearly, the cost of ADT, as currently being delivered, is extraordinary.

Although DES is associated with increased cardiovascular toxicity, from a strictly cost point of view, it is the cheapest form of ADT, particularly at the 1-mg/day dose, with no prophylactic breast irradiation (Mariani et al, 2001). There is no significant survival advantage of LHRH agonists over orchiectomy so, from an economic perspective, LHRH agonists would only be more cost effective than orchiectomy if a patient only lived for a few months

KEY POINTS

- Androgen deprivation is one of the most effective therapies against any solid tumor; unfortunately, with time almost all prostate cancers will become androgen refractory.
- All current forms of androgen deprivation therapy (ADT) function by either lowering levels of circulating androgens or blocking the binding of androgen to the androgen receptor.
- Almost all castration-resistant prostate cancer remains sensitive to androgen; therefore ADT should continue in castration-resistant disease.
- Relative to testosterone and dihydrotestosterone, the adrenal androgens are weak.
- There are four general forms of ADT: (1) ablation of androgen sources, (2) antiandrogens, (3) inhibition of LHRH and/or LH, and (4) inhibition of androgen synthesis.
- Bilateral orchiectomy reduces testosterone by 90% within 24 hours of surgery.
- Nonsteroidal antiandrogens cause LH and testosterone levels to increase.
- Serious liver toxicity is a possible side effect of all antiandrogens.
- Antiandrogens can act as agonists on some tumors; antiandrogen withdrawal results in PSA declines in 15% to 30% of patients.
- Bicalutamide 150 mg monotherapy appears to have equivalent efficacy to medical or surgical castration for locally advanced or metastatic prostate cancer.
- Enzalutamide improves overall survival in metastatic, castration-resistant prostate cancer after treatment with chemotherapy.
- Abiraterone improves overall survival in metastatic, castration-resistant prostate cancer both before and after treatment with chemotherapy.
- All LHRH agonists induce a testosterone increase upon initial exposure. Coadministration of an antiandrogen functionally blocks the effects of testosterone.
- The magnitude and rapidity of the initial response to ADT are strong predictors of the durability of that response.
- The side effects of ADT include osteoporosis, hot flashes, sexual dysfunction, cognitive function alterations, changes in body habitus, gynecomastia, and anemia. These side effects can be progressive but are responsive to other treatments.
- There is no evidence that 3 months of neoadjuvant ADT prior to radical prostatectomy improves biochemical outcomes.
- There is considerable evidence that ADT combined with external beam radiation therapy improves overall survival, cancer-specific survival, and freedom from disease progression. The optimal timing and duration of ADT in this combination remains undefined.
- Based on a large meta-analysis of many clinical trials, combined androgen blockade with nonsteroidal antiandrogens provides about a 3% survival benefit at 5 years compared to standard ADT.
- The natural history of prostate cancer progression is protracted. Many men with evidence of disease will never require ADT.
- The use of ADT in low-risk, localized prostate cancer increases overall (non-prostate cancer) mortality.
- In lymph node metastatic prostate cancer, ADT improves overall survival if the primary tumor is removed but has no significant effect if the primary tumor is not removed.

after initiation of ADT. The 3-month formulations of leuprolide acetate and goserelin become more expensive than orchiectomy upon the administration of a second 3-month depot; specifically, the break-even point for leuprolide acetate is 4.2 months and goserelin is 5.3 months compared to orchiectomy (Mariani et al, 2001).

CAB is the most expensive form of ADT. Although there is no significant benefit of CAB over orchiectomy alone (Eisenberger et al, 1998), some patients may experience a large benefit. Assuming a cost-effectiveness threshold of \$100,000—meaning the expense of CAB minus the expense of orchiectomy—for each quality-adjusted life year, CAB would need to decrease the risk of disease progression by 20% compared to orchiectomy to be considered cost effective (Aronson et al, 1999). The earlier medical ADT is initiated, the more expensive it becomes: in models examining the cost effectiveness, ADT was most cost effective if initiated after patients became symptomatic from prostate cancer metastases (Bayoumi et al, 2000). In this model, LHRH agonists, nonsteroidal antiandrogens, and CAB had higher costs and lower quality-adjusted survival than orchiectomy.

If orchiectomy is just as effective and so much cheaper, why isn't it more widely used? In two studies that offered orchiectomy versus medical therapy for ADT, 70% of patients chose medical therapy (Iversen et al, 1998). Clearly, patients (and physicians) choose medical ADT for reasons other than efficacy or expense. Indeed, the use of ADT in all stages of prostate cancer has increased significantly between 1989 and 2001: for example, primary ADT rose from 32.8% to 48.2% in men with high-risk disease (Cooperberg et al, 2003). Avoiding the largely psychological quality-of-life issues unique to orchiectomy (disfigurement, permanence), ADT comes at an expense that would seem disproportionate to the risk, and yet society has chosen to accept the expense.

Perhaps most sobering about the costs of ADT is the significant variability with which ADT is used by urologists. In a study of 61,717 American men with incident prostate cancer from 1992 until

1999, the total variance in the use of ADT attributable to the urologist was approximately 21%, which was significantly more than that attributable to tumor characteristics (approximately 9%) or patient characteristics (approximately 4%). In other words, "the urologist who sees a patient may be a more important determinant of whether that patient will receive androgen deprivation therapy than the characteristics of the tumor (e.g., stage or grade) or the patient (e.g., age and comorbidity)" (Shahinian et al, 2006). The challenge for urologists is to offer this expensive form of treatment to those patients who need it and to avoid ADT in those who do not (Schellhammer, 2006).

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The complete reference list is available online at www.expertconsult.com.



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Clinical Considerations

Cytotoxic Chemotherapy

Novel Androgen Receptor–Directed Approaches

Immunotherapy

Targeted Treatments

Palliative Management

The Neuroendocrine/Anaplastic Phenotype

Conclusions

During the past several decades, endocrine manipulations that were developed to inhibit hormone-sensitive prostate cancer growth and differentiation have constituted the basic strategy for the systemic control of prostate cancer. Suppression of gonadal testosterone is the central principle of androgen deprivation therapy (ADT), and this represents one of the most effective systemic treatments known for solid tumors. Although the therapy is extremely effective initially, virtually all patients eventually develop biochemical and clinical evidence of treatment resistance. The outcomes with conventional endocrine therapy have changed significantly but only modestly during the past few decades. Progression-free and overall survival figures of patients with metastatic disease with various methods of ADT have ranged from 12 to 20 months and 24 to 36 months, respectively (Leuprolide Study Group, 1984; Crawford et al, 1989; Denis et al, 1993; Eisenberger et al, 1998). Whereas somewhat longer survival times are reported in the more recent studies, this is most likely because of a “lead time” effect observed in contemporary populations of patients. The development of ADT resistance (i.e., cancer progression despite castrate levels of serum testosterone) is a virtually universal state that affects all patients treated with ADT. Undoubtedly, further improvement in the outcome of patients with metastatic castration-resistant prostate cancer (mCRPC) rests on the use of nonhormonal approaches that can effectively control the growth of the disease. However, recent understandings of the biology of castration-resistant prostate cancer (CRPC) have also led to the development of next-generation androgen receptor (AR)–targeting therapies, and some of these have also led to substantial clinical benefits.

During recent years, clinical investigations testing nonhormonal approaches have shown that systemic chemotherapy improves survival and quality of life in patients with castration-resistant disease. Advances in the understanding of the biology of prostate cancer and the characterization of key molecular pathways have added an important new dimension for treatment and the opportunity to design disease-specific targeted treatment approaches. Evolving data suggest that targeted approaches may play an important role in the treatment of prostate cancer that may improve the outcome in patients.

Progress in cell and molecular biology during the past decade has also enhanced our understanding of the mechanisms involved in the progression of prostate cancer, and this may provide the opportunity for rational planning of the appropriate timing of systemic therapeutic intervention with the objective of preventing or delaying progression of disease to lethal proportions. Cancer cells demonstrating the castration-resistant phenotype can be identified during the early stages of development of prostate cancer. Somatic

alterations of the AR are frequently observed in patients with evidence of disease progression after androgen deprivation. It has also been demonstrated that during cancer progression, in the absence of androgens, a molecularly altered AR can still undergo ligand-dependent activation by other hormones such as estrogens and progestational agents, as well as non-ligand-dependent activation by growth factors and cytokines (Feldman and Feldman, 2001; Gelmann, 2002; Nelson et al, 2003). The observation that the AR can still be activated even after long-term gonadal ablation suggests that it continues to play an important role in prostate cancer growth and might indeed be a reasonable target for treatment in patients with castration-resistant disease, as exemplified by the success with abiraterone and enzalutamide.

In the presence of androgens, prostatic cancer growth is based on a cell proliferation rate that exceeds that of cell death (Isaacs et al, 1992). Androgen ablation primarily affects the cell death rate by inducing a swift apoptotic cascade. As the tumor progresses, the threshold of apoptosis progressively rises to a point at which cell proliferation exceeds cell death (Berges et al, 1995). This results in the accumulation of endocrine-independent cells that eventually dominate the biologic behavior of prostate cancer in late stages.

Preclinical data suggest that the relatively low growth fraction expressed by prostate cancer cells (compared with other common adenocarcinomas) may be a determining factor to explain the relative insensitivity to conventional cytotoxic chemotherapy. The proliferation rate of prostate cancer cells, which is directly proportional to the growth fraction, appears to increase with tumor progression especially after androgen ablation. Cell proliferation antigens, such as Ki-67 expressed by cycling cells, may have important prognostic and therapeutic implications, because most of the conventional cytotoxic chemotherapeutic agents available are usually more effective in tumors with high proliferative rates such as lymphomas, small cell lung carcinomas, and germ cell tumors.

Changes in differentiation pathways in prostate cancer have been increasingly emphasized, particularly in the form of neuroendocrine/anaplastic cells (diSant’Agnese, 1995). Evolving experience suggests that this aggressive clinical entity may be responsive to treatment regimens frequently used for comparable tumors at other sites with similar phenotypic characteristics, such as small cell carcinoma of the lung. There is strong evidence to support the relationship between prostate cancer growth and various peptide growth factors (Djakiew et al, 1991; Steiner, 1993; Hofer et al, 1995; Kaplan et al, 1999; Nelson et al, 2003). Peptide growth factors may also exert their effects through the activation of the AR. Androgens are capable of inducing stromal production of various growth factors that could replace the androgen requirements for cell growth and

differentiation (Lee, 1996). In addition, cytokines released primarily by stromal cells, such as interleukin-6, may also be important in the pathogenesis of prostate cancer. Indeed, small molecule inhibitors and other modalities of treatment (e.g., monoclonal antibodies) are being actively designed to target intracellular pathways associated with the expression of various growth factors and their receptors. Such strategies have involved inhibition of receptor tyrosine kinase activity and other intracellular molecular pathways of signal transduction as well as other critical pathways of cell growth and survival.

CLINICAL CONSIDERATIONS

Disease Assessment and Prognostic Considerations

Conventional staging criteria, such as the tumor, node, metastases (TNM) staging system, do not describe the extent of disease beyond a simple anatomic classification, and they are not very helpful in the management of patients with recurrent or advanced prostate cancer. Treatment practices have resulted in the creation of different disease states as described by Scher and colleagues (2008). This system of “clinical states” allows classification of patients into a more relevant fashion and is increasingly being used throughout the literature. Figure 121-1 illustrates the natural history of prostate cancer relative to treatment practices and identifies the various clinical states according to the response status to different therapies. Throughout this chapter, prognostic and therapeutic considerations are largely based on the concepts proposed by this classification model.

A complete disease evaluation is required to estimate the prognosis and to make therapeutic decisions. Critical baseline components should also be considered, including extent of disease, mode and site of progression (rising prostate-specific antigen [PSA] level alone, new bone metastasis, visceral and nodal metastasis), presence or absence of symptoms including bone pain, and response to previous endocrine treatment. Regular monitoring with serial bone scintigraphs and CT scans together with serum PSA levels provides important information in patients demonstrating evidence of disease progression while they are receiving hormone therapy. Usually the first manifestation of disease progression after hormone therapy is a rising serum PSA level. In patients with metastatic disease, a rise in serum PSA level precedes evidence of advancing disease on the bone scan, and during this time patients may remain relatively asymptomatic (Eisenberger et al, 1995). Routine evaluation of serum testosterone levels may provide important information for the choice of subsequent treatment. This is especially

important when there might be reasons to suspect treatment non-compliance or if the choice of previous treatment involved regimens known not to result in a sustained suppression of serum testosterone to castrate levels (e.g., monotherapy with nonsteroidal antiandrogens, low-dose estrogens, or 5 α -reductase inhibitors).

For several years, it was postulated that discontinuation of androgen suppression in patients who have not undergone orchiectomy may adversely influence the outcome of their disease in terms of progression and survival (Taylor et al, 1993). Similarly it has been shown that administration of exogenous testosterone and its derivatives may indeed produce a significant clinical flare resulting in severe pain and neurologic, urologic, and coagulation complications in a small proportion of patients (Fowler and Whitmore, 1981; Manni et al, 1988). In a retrospective analysis of 205 patients with castration-resistant disease treated with chemotherapy, Hussain and associates (1994) evaluated various prognostic variables including orchiectomy. A multivariate analysis failed to indicate a significant correlation between previous orchiectomy and improved progression-free and overall survival. In these patients, all medical forms of androgen deprivation were discontinued at least 4 weeks before initiation of chemotherapy and, contrary to that suggested by Taylor and colleagues (1993), this did not significantly affect outcomes. Until this issue is resolved, the general consensus is to maintain all patients on luteinizing hormone-releasing hormone (LHRH) agonists or antagonists indefinitely, even during the course of subsequent therapies including chemotherapy. Indeed virtually all clinical trials that test novel therapies for men with CRPC mandate the continued suppression of serum testosterone levels, either with chronic ADT or with surgical castration.

Another important management aspect relates to antiandrogen withdrawal effects (Scher and Kelly, 1993; Small et al, 2004). Discontinuation of antiandrogens (both steroidal and nonsteroidal) can result in short-term clinical responses expressed by decreases in PSA levels, symptomatic benefits, and (less frequently) objective improvements in soft-tissue and bone metastasis in a small proportion of patients. Because of this phenomenon, it has been recommended that in patients who appear to be progressing while on antiandrogens in combination with other forms of androgen deprivation (e.g., LHRH agonists), the first step should involve the carefully observed discontinuation of the antiandrogen including serial monitoring of PSA levels for a period of 4 to 8 weeks before embarking on the next therapeutic maneuver.

The subsequent step is to determine which modality of treatment should be used next, either administration of second-line hormonal manipulation (including novel AR-directed therapies) or cytotoxic chemotherapy. There is an increasing body of data on

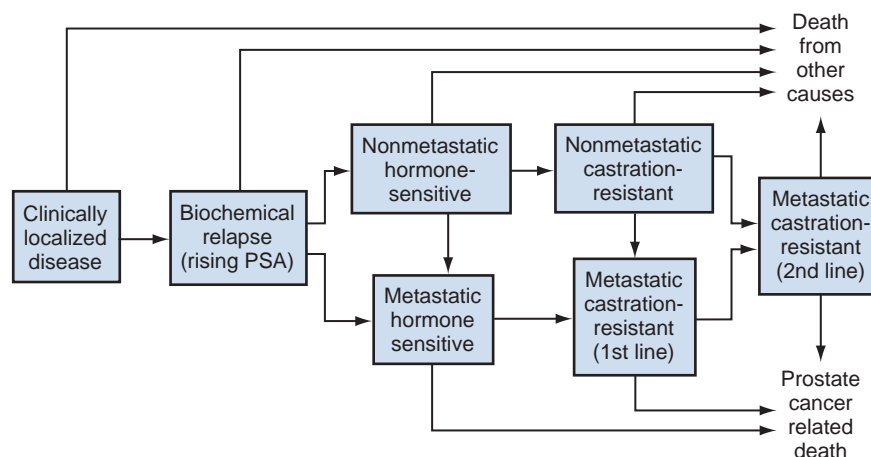


Figure 121-1. Prostate cancer clinical states. PSA, prostate-specific antigen. (Modified from Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008;26:1148–59.)

second-line endocrine therapies suggesting that there may be a role for this approach before institution of chemotherapy (Small et al, 2004; Ryan, 2006; Ang et al, 2009). Although initial response rates to the second-generation hormonal manipulations range between 20% and 60%, the median duration of such responses is short, ranging between 2 and 4 months. Agents that have been reported to produce some benefit in this setting include diethylstilbestrol (Smith et al, 1986), aminoglutethimide (Sartor and Myers, 1995), ketoconazole (Small et al, 2004), as well as corticosteroids (Storlie et al, 1995). Since around 2012, additional next-generation AR-targeting therapies have become available (e.g., abiraterone and enzalutamide) and have largely replaced the second-generation endocrine agents listed earlier. In view of the potential higher toxicity profile associated with cytotoxic chemotherapy, a sequential hormonal approach may be a reasonable alternative for those patients with relatively limited metastatic disease who remain asymptomatic at the time of disease progression (e.g., rising serum PSA value without other clinical manifestations or pain).

Another important consideration is the initial clinical assessment of the potential biologic behavior of these tumors when they become castration resistant. Evolving data evaluating the role of PSA dynamics suggest that the PSA doubling time (PSADT) predicts the rapidity of bone scan progression and survival (D'Amico et al, 2005; Armstrong et al, 2007; Robinson et al, 2008). Patients with PSADT shorter than 3 months have a particularly rapid clinical course and should possibly be considered for more aggressive management approaches. Similarly, patients with symptomatic bone pain or visceral-predominant disease might be better served with cytotoxic chemotherapy upfront. In addition, poorly differentiated and neuroendocrine tumors usually have a low likelihood of significant and durable responses to further AR-directed therapies. The anaplastic/neuroendocrine phenotype is rare and requires special therapeutic considerations (see later). It has been suggested that systematic biopsies of disease sites in patients with clinically aggressive disease and relatively low serum PSA levels may demonstrate evidence of a neuroendocrine phenotype by immunostaining, which may be of prognostic and therapeutic significance. The usefulness of systematic biopsies in all patients with extensive metastasis and relatively low PSA levels, however, needs to be better defined before routine clinical application.

Nonmetastatic Castration-Resistant Prostate Cancer

The extraordinary stage migration that has affected all stages of prostate cancer has profoundly modified the spectrum of the clinical presentation of patients with castration-resistant disease. An increasing number of patients now begin androgen-deprivation therapy (ADT) at very early stages of their disease course, often at the first sign of a rising PSA following local therapy, before clinical and radiologic evidence of metastasis is present. This group of patients, termed the M0 (nonmetastatic) castrate-resistant subset, is now seen in increasing proportions in the clinic. Given the changes in treatment practices with early initiation of androgen deprivation, it is conceivable that these numbers will continue to increase. At this time data on the natural history of these patients are evolving, but the strongest predictor of metastatic progression appears to be the PSA kinetics (PSA velocity, PSADT).

A number of clinical trials using second-line hormonal manipulations and noncytotoxic interventions (bone-targeted treatments) focusing on time to development of bone metastasis have provided some useful information. A report of 201 patients from a prospective clinical trial comparing the effects of the bisphosphonate zoledronate versus placebo in men with M0 castrate-resistant disease suggested that the time to radiographic metastasis may be very long. At 2 years, only 33% of these patients exhibited evidence of bone metastasis, with a median time to bone metastasis in this group of 30 months. The baseline PSA level (>10 ng/mL) and the PSA velocity independently predicted time to bone metastasis and survival (Smith et al, 2005). In a retrospective review of a similar group of patients who were prescribed ADT before the development of metastatic disease, the median time to clinical metastasis was 9 months.

The pretreatment PSA level and the PSA nadir on ADT predicted metastasis-free survival (Dotan et al, 2005). The wide difference observed with these two reports (30 months vs. 9 months for time to bone scan metastasis) underscores the heterogeneity of this group of patients and the need for careful prospective evaluation. Their outcome is dependent on various factors, among which are pre-ADT characteristics (pretreatment PSA level, PSADT, initial stage, Gleason score), as well as differential response to hormonal treatment. However, it is probable that the risk of metastatic progression might be best estimated by PSA kinetics constructs such as PSADT and PSA velocity.

At present there is no consensus regarding the most appropriate management for patients with nonmetastatic CRPC, although the sequential endocrine approach (using second-generation agents, e.g., ketoconazole) is the most commonly used therapeutic modality. It must be highlighted that there are currently no U.S. Food and Drug Administration (FDA)-approved drugs specifically indicated to treat men with M0 CRPC disease. This, in turn, creates a unique opportunity for drug development in this setting. To this end, a number of placebo-controlled phase III trials are currently underway to test novel AR-directed therapies in men with nonmetastatic CRPC who are at a high risk for developing radiographic metastases. In summary, more data are needed to characterize the natural history and to define the best treatment approach for the M0 CRPC subset, which represents an important evolving new paradigm.

Metastatic Castration-Resistant Prostate Cancer

Patients with mCRPC represent a heterogeneous population with respect to their clinical and disease characteristics at the time of disease progression on ADT. Metastatic prostate adenocarcinoma has an overwhelming predilection to involve the bone. Although the explanation for this unique metastatic pattern has not been completely elucidated, it may reflect the combination of various biologic factors (tumor-specific and host-specific) present at the time of metastatic spread. Circulating prostatic adenocarcinoma cells are arrested in the cortical and medullary bone spaces, where they subsequently adhere to bone surfaces through specific receptors for moieties such as integrins, collagens, laminin, and other bone-derived proteins. Cell growth is subsequently promoted by a number of factors such as hormones, growth factors, and stromal-epithelial interactions, most of which operate in the bone marrow. Expansion of tumor cells in the bone may cause pain, compression of spinal nerves or the spinal cord, or pathologic fractures. In addition, extensive bone marrow replacement may cause impairment in hematologic function (most often manifested as myelophthytic anemia and thrombocytopenia).

Clinical involvement of visceral sites (excluding lymph nodes) is less common, even in patients with widespread castration-resistant disease. Even more rare is the occurrence of visceral disease in the absence of any bone involvement. Data from prospective clinical trials involving men with mCRPC suggest that radiographic evidence of visceral metastasis is observed in fewer than 20% of patients, whereas about 30% to 40% have demonstrable soft-tissue nodal disease. Because the majority of tumor burden in metastatic prostate cancer is found in bone, responses to treatment (e.g., tumor shrinkage) in soft-tissue sites alone (e.g., nodal or visceral sites) might not reflect a major treatment benefit because it represents only a small proportion of the overall disease burden. For this reason, the evaluation of "response rate" as the primary end point in clinical trials of mCRPC is discouraged, and "progression-free survival" (PFS) (that takes into account radiographic progression of bone and/or soft-tissue disease) is a much more acceptable trial end point (Scher et al, 2008).

Patients with mCRPC may present with a range of hematologic deficiencies caused primarily by the disease or by its treatment. Anemia is the most common hematologic abnormality, which can be explained by a variety of factors, such as anemia of chronic disease, bone marrow invasion, blood loss, and, rarely, secondary to a microangiopathic hemolytic anemia usually associated with a consumption coagulopathy (disseminated intravascular

coagulation). A decrease in the red blood cell count of patients with advanced CRPC commonly results from a combination of factors, such as previous treatment with local irradiation of bone marrow (especially pelvic bones), systemic use of chemotherapy and radiopharmaceuticals, long-term androgen deprivation, as well as from extensive bone marrow invasion by a tumor resulting in substantial decrease in bone marrow reserves. The use of erythropoietin has been popular in the past. However, use of erythropoietin-stimulating agents has fallen out of favor and should be used with caution, because evidence is now mounting that these agents may increase mortality in cancer patients (Bennett et al, 2008). Thrombocytopenia (and, more rarely, leukopenia) is usually a complication of extensive radiation therapy or systemic chemotherapy. As an end-stage process, rapidly growing tumors with bone marrow involvement might result in pancytopenia. Thrombocytosis is also a nonspecific manifestation associated with many neoplastic conditions, including prostate cancer. However, clotting complications associated with thrombocytosis are rarely seen in men with prostate cancer, and treatment is not usually necessary.

Among the most important urologic sequelae of advanced prostate cancer is the development of obstructive uropathy. This complication, usually related to the primary disease or to pelvic/retroperitoneal adenopathy, can be devastating in terms of quality of life, and it may even present major therapeutic implications. In addition to an increased incidence of infection and pain, obstructed kidneys might critically impair renal function to a point where some chemotherapeutic agents (which depend largely on renal mechanisms for their clearance) cannot be safely used. In general, patients who are otherwise considered candidates for treatment with cytotoxic drugs are best managed by first relieving the obstruction either with placement of internal ureteral stents or by percutaneous nephrostomy tubes.

Finally, one of the greatest emergencies in oncology is the development of spinal cord compression (Sorensen et al, 1990). Because of the frequent involvement of vertebral bodies by metastatic prostate cancer, the incidence of cord compression is of particular concern (see later).

KEY POINTS: CLINICAL CONSIDERATIONS

- Evaluate the extent and aggressiveness of the disease before contemplating therapy.
- Realize that the critical determinants are presence or absence of radiographic metastases, biochemical versus clinical progression, and presence or absence of symptoms (e.g., pain).
- Understand that the presentation of mCRPC is heterogeneous, both in terms of distribution of metastatic sites and in terms of PSA kinetics (e.g., PSADT).
- Consider secondary hormonal manipulations before initiation of cytotoxic chemotherapy, especially in men with non-metastatic CRPC or in those who are asymptomatic.

CYTOTOXIC CHEMOTHERAPY

Evaluation of Treatment Efficacy

Measurement of therapeutic efficacy in the clinical trial setting for patients with advanced prostate cancer might be confounded by significant methodologic challenges. The most common metastatic site in these patients is bone, manifested by diffuse osteoblastic lesions that cannot be measured reliably by current methods (termed “nonmeasurable” disease). Soft-tissue or visceral metastatic sites that allow serial measurements (“measurable” disease) are uncommon and represent only a small fraction of the total metastatic burden of the disease. Selection of bidimensionally measurable disease sites to assess therapeutic efficacy with serial tumor measurements has been the subject of significant criticism, because

many patients may only harbor metastases in osseous sites. Furthermore, patients with soft-tissue metastasis (especially visceral metastases) are often considered a subgroup with biologic and clinical features distinct from those with bone-only metastases. As a result of these potential caveats, the evaluation of “response rate” as the primary end point in clinical trials of mCRPC has been discouraged, and the use of PFS (taking into account radiographic progression of bone and/or soft-tissue disease) has become a much more acceptable trial end point in instances where overall survival is not a feasible end point (Scher et al, 2008).

A number of prognostic models evaluating baseline and post-treatment characteristics have been developed to help dissect the heterogeneity of CRPC in the context of various cytotoxic and non-cytotoxic therapies (Smaletz et al, 2002; Halabi et al, 2003; Armstrong et al, 2007; Halabi et al, 2013b). Among numerous clinical and laboratory parameters with consistent prognostic significance across a range of therapeutic settings are the patient's functional status (performance status), presence of pain, baseline hemoglobin level, baseline PSA level, baseline alkaline phosphatase, baseline LDH level, extent of bone involvement (number of lesions or pattern/distribution of bone lesions), and presence of visceral disease. Quantitative methods to evaluate circulating tumor cell (CTC) numbers and various PSA constructs (e.g., >30% PSA reduction) are among the post-treatment parameters with the strongest prognostic significance (Scher et al, 2004; Armstrong et al, 2007; de Bono et al, 2008; Halabi et al, 2013a).

Preclinical observations have suggested that some drugs might reduce PSA secretion without affecting tumor growth, whereas other drugs may affect tumor growth without necessarily reducing PSA levels (Larocca et al, 1991; Eisenberger and Nelson, 1996; Seckin et al, 1996). Although these laboratory observations are likely to be clinically relevant, assays used to evaluate a separate drug effect on PSA secretion still require careful validation. A PSA consensus meeting developed by several leading investigators in the field generated initial guidelines with regard to the use of the PSA test for clinical trials in patients with CRPC (Bubley et al, 1999). These guidelines were updated and now also provide a consensus on the use of radiologic end points as well as clinical end points (e.g., pain) for the evaluation of men with advanced CRPC (Scher et al, 2008). Undoubtedly, new biomarkers are needed to enhance our ability to identify rapidly the active treatments for CRPC, and one such marker may be the enumeration of CTCs (both at baseline and after a period of treatment) (de Bono et al, 2008). Furthermore, evolving noncytotoxic and targeted therapies might require a new set of end points and identification of drug-specific intermediate biomarkers that reflect mechanism-specific biologic activity.

Clinical Trials of Cytotoxic Agents

Most of the chemotherapeutic agents available in oncologic practice have been used in patients with CRPC, either as single agents or in various combinations. Historical examples have included cyclophosphamide, 5-fluorouracil, estramustine, vinorelbine, etoposide, cisplatin, carboplatin, doxorubicin, mitoxantrone, paclitaxel, and docetaxel (Eisenberger, 1988). With the exception of docetaxel (and the related agent, cabazitaxel) and perhaps mitoxantrone, most other cytotoxic agents are no longer being used with frequency because they have not been associated with either symptomatic improvements or extension of survival. Evolving data with selected chemotherapy agents during the new millennium suggest that the survival of patients with advanced CRPC receiving first-line chemotherapy is now somewhere between 16 and 20 months (Petrylak et al, 2004; Tannock et al, 2004) as opposed to 6 to 12 months as previously described with historical agents (Eisenberger, 1988).

Mitoxantrone

A first step forward in the chemotherapeutic management of CRPC came with mitoxantrone. This agent, a semisynthetic anthracycline, had previously shown modest symptomatic benefits but with minimal evidence of objective antitumor activity (Osborne et al,

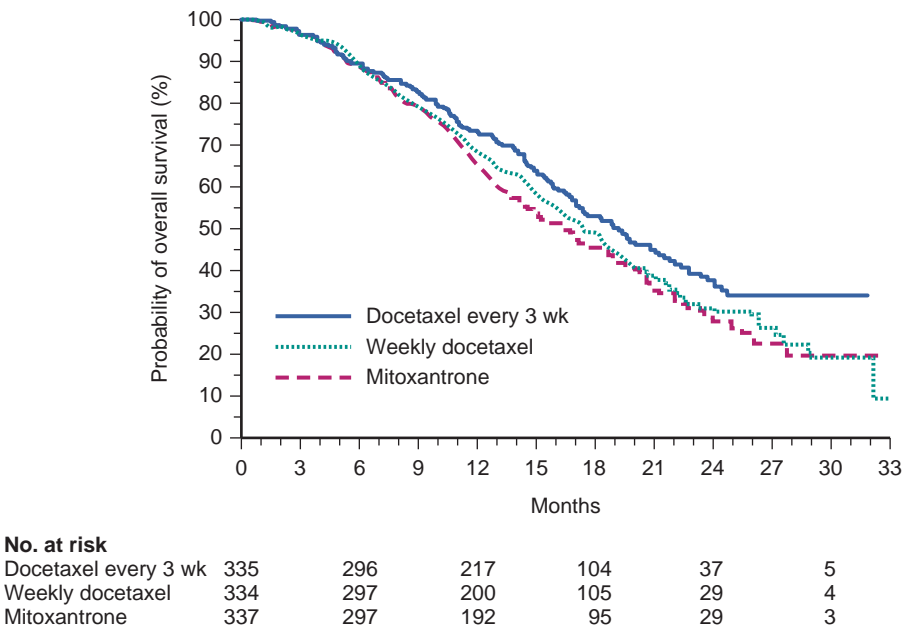


Figure 121-2. Overall survival in the TAX 327 study. (From Tannock I, DeWit R, Berry W, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502–12.)

1983; Rearden et al, 1995). In addition, mitoxantrone appeared to have its maximal palliative effect in combination with low-dose corticosteroids (Moore et al, 1994). In two seminal prospective randomized trials of mitoxantrone plus prednisone versus prednisone alone (Tannock et al, 1996) or mitoxantrone plus hydrocortisone versus hydrocortisone alone (Kantoff et al, 1999), the combination resulted in significant improvements of various quality-of-life parameters, including pain, but survival was not significantly improved in either trial. These studies provided the justification for the U.S. FDA to approve mitoxantrone with prednisone in 1997 for patients with *symptomatic* CRPC. Even though the use of first-line mitoxantrone has significantly diminished with the advent of more effective chemotherapy agents (docetaxel and cabazitaxel; see below), mitoxantrone is still useful for patients with docetaxel- and cabazitaxel-refractory disease, or in those with a marginal performance status in which the more toxic taxane agents may not be well tolerated.

Docetaxel

The next significant advance in the use of chemotherapy for CRPC came with docetaxel, a member of the taxane family. This agent acts by inducing apoptosis in cancer cells through TP53-independent mechanisms that are thought to be a result of the inhibition of microtubule depolymerization and the blockade of antiapoptotic signaling. The induction of microtubule stabilization intracellularly through β -tubulin interactions causes guanosine triphosphate-independent polymerization and cell cycle arrest at the G₂M phase. In addition, docetaxel has been found to induce BCL2 phosphorylation in vitro, a process that has been correlated with caspase-3 activation and loss of its normal antiapoptotic activity. Unable to inhibit the proapoptotic molecule BAX, phosphorylated BCL2 may also induce apoptosis through this alternate pathway. However, additional mechanisms might also be important, such as CDKN1B (p27) induction and repression of BCL-XL. Finally, it has emerged that docetaxel may exert part of its therapeutic effect by impairing association of the cytosolic AR to microtubules, thereby disrupting the transport of the ligand-bound AR from the cytoplasm into the nucleus on board the microtubules (Zhu et al, 2010; Darshan et al, 2011).

Early data with docetaxel monotherapy initially suggested that this compound might have significant activity in prostate cancer even as a single agent (Friedland et al, 1999; Picus and Schultz, 1999; Beer, 2004). In 2004, docetaxel became the chemotherapy drug of choice for the treatment of mCRPC based on a large phase III randomized trial, termed TAX 327 (Fig. 121-2), which demonstrated superiority beyond the previous standard: mitoxantrone plus prednisone (Tannock et al, 2004). The TAX 327 study enrolled 1006 patients with no previous chemotherapy treatment and with stable pain scores into one of three study arms (all with concomitant prednisone 5 mg twice daily): mitoxantrone 12 mg/m² intravenously every 21 days; docetaxel 75 mg/m² intravenously every 21 days; or docetaxel 30 mg/m² intravenously every 7 days. Patients remained on androgen suppression (e.g., LHRH agonists or orchiectomy), but all other second-line hormonal agents were discontinued. The anticipated treatment duration was 30 weeks (i.e., 10 cycles of therapy) in all study arms, although more patients completed treatment in the every-3-week docetaxel group than in the mitoxantrone group because of differences in disease progression rates (46% vs. 25%). After a median follow-up of 20.7 months, overall survival in the every-3-week docetaxel group was 18.9 months (with a pain response rate of 35% and a PSA response of 45%), compared to weekly docetaxel at 17.3 months (and 31% and 48%), respectively. This translated into a 24% relative reduction in the risk of death (95% confidence interval [CI] 6% to 48%, *P* = .0005) using 3-weekly docetaxel (see Fig. 121-2). Meanwhile, patients on the mitoxantrone arm experienced a median survival of 16.4 months, a pain response of 22%, and a PSA response of 32%. The conclusion of the TAX 327 trial was that every-3-week docetaxel was superior to both weekly docetaxel and every-3-week mitoxantrone. This was a landmark study, because it showed for the first time that chemotherapy could improve survival in mCRPC patients.

Toxicity in the 3-weekly versus weekly docetaxel groups was notable because of an increase in hematologic events in the every-3-week group (3% neutropenic fever vs. 0%; 32% grade 3/4 neutropenia vs. 1.5%), but slightly lower rates of nausea and vomiting, fatigue, nail changes, hyperlacrimation, and diarrhea. Neuropathy was slightly more common in the every-3-week group (grade 3/4 neuropathy in 1.8% vs. 0.9% in the weekly group). Quality-of-life responses as measured by the FACT-P instrument did not differ

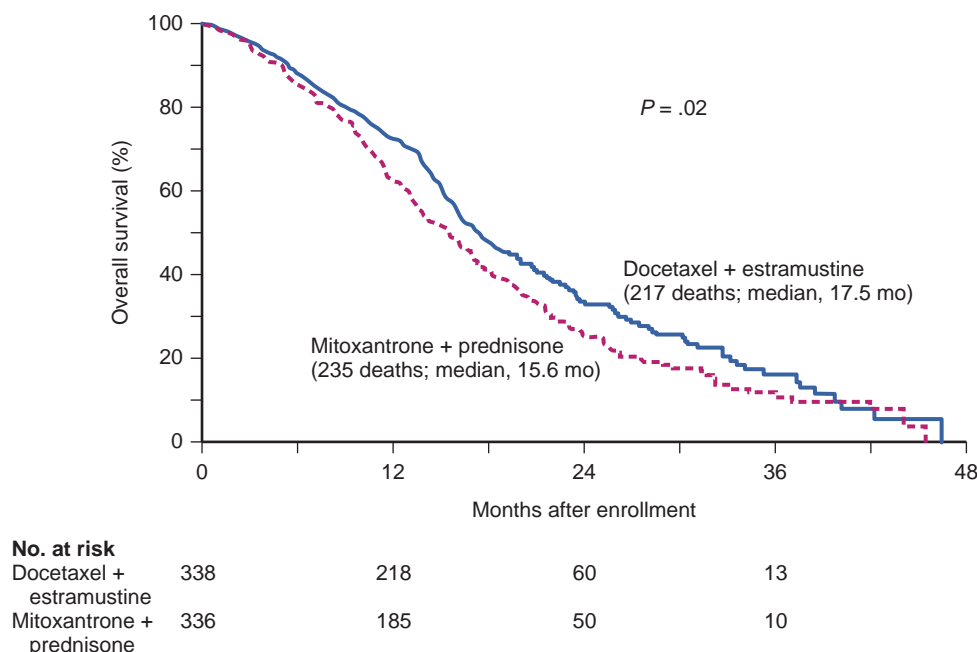


Figure 121-3. Overall survival in the Southwest Oncology Group 9916 study. (From Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513–20.)

significantly between the two docetaxel schedules but were more favorable than in the mitoxantrone group.

The Southwest Oncology Group (SWOG) 9916 study was the second large phase III trial (Fig. 121-3) to evaluate docetaxel (Petrylak et al, 2004). In this study, 770 patients with progressive CRPC were randomly assigned to oral estramustine (280 mg three times daily) plus docetaxel (60 mg/m² IV every 21 days) versus mitoxantrone (12 mg/m² IV every 21 days) plus prednisone. Median overall survival in the SWOG 9916 study was longer in the docetaxel-estramustine group than in the mitoxantrone-prednisone group (17.5 vs. 15.6 months, $P = .02$), with a corresponding hazard ratio (HR) for death of 0.80 (95% CI 0.67 to 0.97) (see Fig. 121-3). Because of the high rate of thromboembolic events with estramustine, prophylactic low-dose warfarin and aspirin were added to that study arm. Similarly, 20% and 15%, respectively, of patients in the docetaxel-estramustine arm had grade 3/4 gastrointestinal and cardiovascular toxicities. Although comparisons between the docetaxel arms across these two seminal trials may not be appropriate because of differences in schedule, patient populations, and docetaxel dosing (60 mg/m² in SWOG 9916 and 75 mg/m² in TAX 327), it was concluded that estramustine is unlikely to add significantly to the activity of single-agent docetaxel. For this reason, and because of its thromboembolic toxicities, estramustine is currently only a historic remnant and is no longer generally used in the United States.

A number of experimental agents have been investigated in combination with docetaxel in an attempt to improve on the efficacy of single-agent docetaxel. However, the results of most phase III trials of docetaxel-based combination therapy have been disappointing. Although serum vascular endothelial growth factor (VEGF) levels correlate inversely with survival, antiangiogenic agents (bevacizumab, aflibercept, and lenalidomide) combined with docetaxel have not improved overall survival. Combinations of bone-targeted agents such as atrasentan, zibotentan, and dasatinib with docetaxel have also produced disappointing results. Finally, high-dose vitamin D (calcitriol) combined with weekly docetaxel also demonstrated no survival advantage beyond docetaxel alone. Potential reasons for the failure of docetaxel-based combination therapies include marginal activity of the agents that were combined with docetaxel, lack

of well-conducted randomized phase II trials before initiating phase III studies, as well as dose reductions of docetaxel that were often required as a result of overlapping drug toxicities (Antonarakis and Eisenberger, 2013).

Cabazitaxel

Until recently, effective life-prolonging therapies for men with docetaxel-refractory prostate cancer were lacking. This changed in 2010, when the FDA approved yet another chemotherapy agent, cabazitaxel, for the treatment of mCRPC based on the results of a pivotal randomized phase III (TROPIC) trial (Fig. 121-4). Cabazitaxel is a novel tubulin-binding taxane that differs from docetaxel and paclitaxel because of its poor affinity for P-glycoprotein, the adenosine triphosphate-dependent drug efflux pump (Paller and Antonarakis, 2011). In preclinical studies using cancer cell lines and mouse xenograft models, cabazitaxel was shown to be active in both docetaxel-sensitive tumors as well as in those with primary or acquired docetaxel resistance (Attard et al, 2006). The first hint of cabazitaxel's safety and efficacy in men with prostate cancer came during phase I testing, where cabazitaxel was administered by intravenous infusion every 3 weeks at escalating doses of 10 to 25 mg/m² (Mita et al, 2009). In that study, the principal dose-limiting toxicity (DLT) was neutropenia. Given the lack of cross-resistance between this agent and docetaxel, and based on early reports of favorable responses in men with CRPC from this phase I trial, a phase III trial was launched to evaluate its activity.

The safety and efficacy of cabazitaxel in patients with advanced prostate cancer were definitively evaluated in the TROPIC trial conducted in 146 institutions across 26 countries, which recruited 755 men with mCRPC who had progressed after docetaxel-based chemotherapy (de Bono et al, 2010). Of these, 377 patients were randomized to receive mitoxantrone 12 mg/m² intravenously every 3 weeks (with oral prednisone 10 mg daily), and 378 patients were assigned to receive cabazitaxel 25 mg/m² intravenously every 3 weeks (plus prednisone). After a median follow-up of 12.8 months, overall survival in men receiving cabazitaxel was 15.1 months compared to 12.7 months in men receiving mitoxantrone (HR 0.70, $P < .0001$) (see Fig. 121-4) (de Bono et al, 2010). Compared to

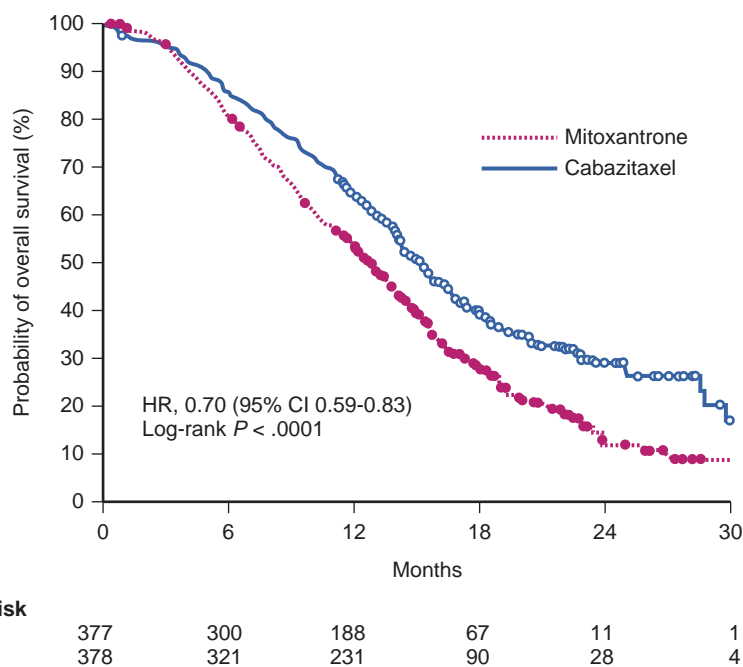


Figure 121-4. Overall survival in the TROPIC study. CI, confidence interval; HR, hazard ratio. (From de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376:1147–54.)

mitoxantrone, cabazitaxel also significantly lengthened PFS (2.8 months vs. 1.4 months, $P < .0001$), extended time to PSA progression (6.4 months vs. 3.1 months, $P = .001$), increased radiographic tumor response rates (14.4% vs. 4.4%, $P = .0005$), and increased PSA response rates (39.2% vs. 17.8%, $P = .0002$). There were no differences between the two treatment arms with respect to pain responses or time to pain progression. The results of this study formed the basis for the FDA's approval of cabazitaxel plus prednisone in June 2010 for the second-line treatment of docetaxel-refractory mCRPC.

In subset analyses, the survival advantage of cabazitaxel persisted regardless of whether patients experienced measurable disease or pain, or whether progression had occurred while receiving docetaxel or following a treatment holiday. In addition, cabazitaxel's survival benefit was most pronounced for men with Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (vs. 2), and for patients with disease progression within <3 months of docetaxel initiation (vs. ≥ 3 months of docetaxel initiation) (de Bono et al, 2010). The last observation implies that cabazitaxel may be effective even in men with truly docetaxel-refractory disease, providing clinical evidence that there may not be significant cross-resistance between docetaxel and cabazitaxel.

The most common serious adverse events related to cabazitaxel were hematologic, including greater than or equal to grade 3 neutropenia in 82% of patients (febrile neutropenia in 8%). Patients older than 65 years experienced a 6.6% higher rate of grade 3 neutropenia than younger patients. This degree of myelosuppression begs the question of whether a lower dose of cabazitaxel (e.g., 20 mg/m²) may have been more appropriate; a randomized phase III trial (PROSELICA) comparing the safety and efficacy of these two doses (25 mg/m² vs. 20 mg/m² every 3 weeks) is now being conducted. To this end, use of growth factor support should be strongly considered when administering cabazitaxel, especially in men more than 65 years of age or in those with poorer performance status, as reflected in several national guidelines (Mohler et al, 2010). Other nonhematologic toxicities included greater than or equal to grade 3 diarrhea (6%) and greater than or equal to grade 3 fatigue (5%). Diarrhea was more common in patients older than 65 as well as in

those with a history of previous radiation therapy. Encouragingly, although peripheral neuropathy (all grades) was observed in 14% of patients receiving cabazitaxel, only 1% of men developed grade 3 neuropathy (de Bono et al, 2010).

Given the activity of cabazitaxel in docetaxel-pretreated patients, it would be logical to evaluate cabazitaxel as first-line chemotherapy in men with CRPC. To this end, an international randomized phase III trial (FIRSTANA) of docetaxel versus cabazitaxel (20 mg or 25 mg/m²) in chemotherapy-untreated patients has completed accrual, and results are awaited. A separate phase II study (TAXYN-ERGY) is randomizing patients to first-line docetaxel versus first-line cabazitaxel, and this is allowing patients to switch to the alternative taxane agent if they do not achieve more than a 30% PSA decline within the first 4 cycles of chemotherapy. That trial is also collecting CTCs to examine the association between the AR and microtubules, in an effort to uncover mechanisms of response and resistance to taxane drugs.

KEY POINTS: CYTOTOXIC CHEMOTHERAPY

- Docetaxel is the standard first-line chemotherapy for mCRPC. It prolongs progression-free and overall survival, ameliorates pain, and improves quality of life.
- Toxicity of docetaxel includes myelosuppression, fatigue, peripheral edema, neurotoxicity, hyperlacrimation, and nail dystrophy.
- Cabazitaxel has emerged as a second-line chemotherapy option for patients with mCRPC who have had progressive disease during or after docetaxel treatment.
- Toxicity of cabazitaxel includes neutropenia (including febrile neutropenia) and diarrhea.
- Although it does not prolong survival, mitoxantrone has been approved to palliate symptoms associated with metastatic disease, and it is often used in patients who have previously received docetaxel and/or cabazitaxel, or in those who would not tolerate these agents.

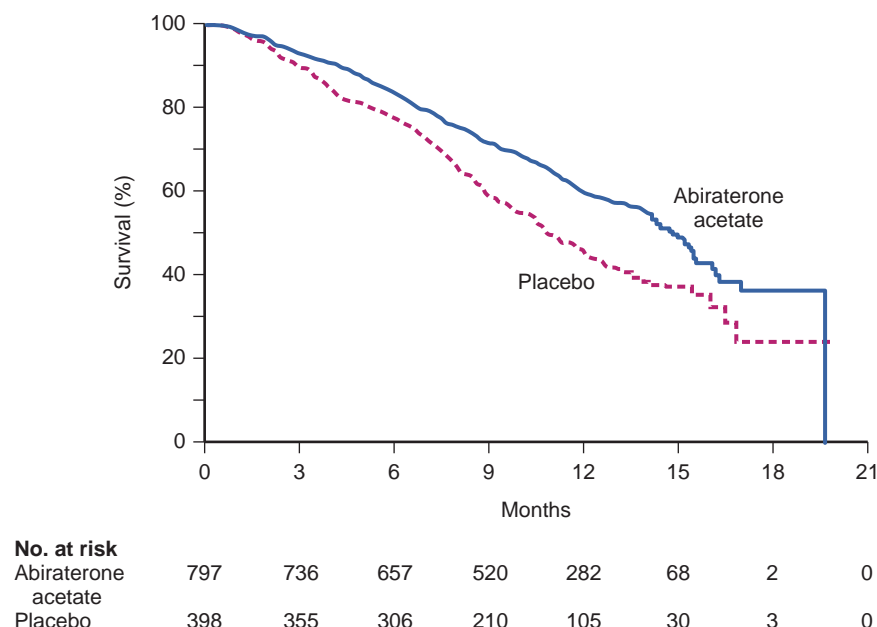


Figure 121-5. Overall survival in the COU-AA-301 study. (From de Bono JS, Logothetis CJ, Molina A, et al. Improved survival from metastatic prostate cancer with abiraterone acetate. *N Engl J Med* 2011;364:1995–2005.)

NOVEL ANDROGEN RECEPTOR-DIRECTED APPROACHES

CYP17 Inhibition: Abiraterone and Other Agents

It has been recognized that the AR and ligand-dependent AR signaling commonly remain active and upregulated in men with castrate levels of testosterone (i.e., <50 ng/dL) (Debes and Tindall, 2004). Standard hormonal therapies such as LHRH agonists/antagonists inhibit gonadal androgenesis but do not affect androgen synthesis from adrenal or other extragonadal sources that may account for up to 10% of total androgen production. It has also been suggested that CRPC itself may produce intratumoral androgens autonomously (Mostaghel et al, 2007). In addition, overexpression of CYP17 has been demonstrated in tumors of men with CRPC (Stigliano et al, 2007). All of this laboratory evidence suggests that CRPC is not androgen-independent and often remains hormone driven, implying that further suppression of nongonadal androgen sources might yield therapeutic gains.

The novel agent abiraterone acetate is an oral selective inhibitor of cytochrome P450 isoform 17 (CYP17), an enzyme that has both 17,20-lyase and 17 α -hydroxylase activity, and is a key regulator of extragonadal androgen synthesis. Phase I/II studies using abiraterone in men with CRPC (both before and after docetaxel) showed a substantial number of PSA responses (PSA declines $\geq 50\%$) and also some partial radiologic responses in men with bony and soft-tissue metastases (Attard et al, 2008; Danila et al, 2010). Furthermore, abiraterone retains its activity even in patients with previous ketoconazole treatment (a weak CYP17 inhibitor) (Ryan et al, 2010). Common side effects of abiraterone include hypokalemia, hypertension, and pedal edema. These effects are explained by a syndrome of secondary mineralocorticoid excess, which improves with use of the mineralocorticoid receptor antagonist eplerenone or with the addition of prednisone, which blunts the ACTH drive. Importantly, patients receiving abiraterone must also continue treatment with an LHRH agonist/antagonist, whereas the clinical activity of single-agent abiraterone is largely unknown.

To evaluate conclusively the efficacy and safety of abiraterone in men with CRPC, a pivotal multicenter placebo-controlled blinded randomized phase III trial (COU-AA-301) was conducted in men with docetaxel-pretreated ketoconazole-naïve mCRPC (de Bono

et al, 2011). This trial randomized men (2:1) to receive either abiraterone 1000 mg daily plus prednisone 10 mg daily ($n = 797$) or placebo plus prednisone ($n = 398$). The trial met its primary end point, demonstrating a median overall survival of 14.8 months in the abiraterone arm and 10.9 months in the placebo arm (HR 0.65, $P < .0001$) (Fig. 121-5). In addition, when compared to placebo, abiraterone prolonged radiographic PFS (5.6 vs. 3.6 months, $P < .0001$), improved time to PSA progression (10.2 vs. 6.6 months, $P < .0001$), and produced more PSA responses (38% vs. 10%, $P < .0001$). Further analysis showed that abiraterone had significant benefits compared with placebo in terms of pain relief, patient-reported fatigue, delaying pain progression, and prevention of skeletal-related events (Fizazi et al, 2012; Logothetis et al, 2012). Based on the results of the COU-AA-301 study, the FDA has approved abiraterone plus prednisone in April 2010 for the treatment of patients with mCRPC who have received previous docetaxel chemotherapy. The recommended dose of abiraterone is 1000 mg daily by mouth.

Because of the success of abiraterone in the postdocetaxel setting, a second randomized phase III trial (COU-AA-302) targeting men with docetaxel- and ketoconazole-naïve CRPC was undertaken. This double-blind placebo-controlled study recruited asymptomatic or mildly symptomatic chemotherapy-naïve patients with mCRPC and randomized them (1:1) to receive abiraterone (1000 mg) and prednisone (10 mg daily) or placebo and prednisone. The coprimary end points of this trial were radiographic PFS and overall survival. The study demonstrated a statistically significant difference in PFS in favor of the abiraterone arm (HR 0.43, 95% CI 0.35 to 0.52, $P < .0001$), representing a 57% reduction in the risk of radiographic progression with abiraterone (Ryan et al, 2013). The study also showed a strong trend toward improved overall survival, and significantly delayed initiation of cytotoxic chemotherapy (26.5 months vs. 16.8 months). In the final analysis, overall survival strongly favored the abiraterone arm (HR 0.79, 95% CI 0.66 to 0.95, $P = .015$), reflecting a 21% reduction in the risk of death, but not meeting the prespecified significance level set by the O'Brien-Fleming rule (that required a P value of $< .0035$). Once again, abiraterone produced additional benefits in the predocetaxel setting, including improved patient-reported quality-of-life outcomes (Basch et al, 2013). Based on the results of the COU-AA-302 trial, the FDA expanded the label for abiraterone to encompass all

patients with mCRPC (i.e., including those who have not received docetaxel chemotherapy). Of note, abiraterone is not currently approved for patients with nonmetastatic CRPC, a setting in which ketoconazole is still often used.

Other agents that target the androgen signaling pathway through CYP17 inhibition are also in clinical development. Orteronel (TAK-700) has a similar mechanism of action to abiraterone; it is a nonsteroidal CYP17 inhibitor with potentially greater 17,20 lyase selectivity (i.e., impairing androgen synthesis preferentially over corticosteroid synthesis). Orteronel has been evaluated in two large placebo-controlled phase III trials (with prednisone in both arms) in men with mCRPC who were either chemotherapy-naïve or docetaxel-pretreated. In the international ELM-PC5 (postdocetaxel) trial, although orteronel produced a significant improvement in PFS (HR 0.76, 95% CI 0.65 to 0.89, $P = .0004$), the study did not meet its primary survival end point (HR for survival: 0.89, 95% CI 0.74 to 1.06, $P = .19$) (Dreicer et al, 2014) and orteronel did not gain FDA approval. Interestingly, in countries where abiraterone was not available postprogression, survival was significantly improved with orteronel; whereas in countries where abiraterone was already approved; survival was not impacted probably because of subsequent treatment with abiraterone after patients came off the study. The phase III prechemotherapy (ELM-PC4) study has fully enrolled, and was a randomized trial of orteronel/prednisone versus placebo/prednisone. In this trial, PFS and overall survival are the coprimary end points, and the final results are awaited.

Androgen Receptor Modulation: Enzalutamide and Other Agents

A slightly different AR-directed approach has focused on the development of next-generation antiandrogens that include advantages beyond the established agents in this class (bicalutamide, nilutamide, flutamide). One such drug is enzalutamide, a potent oral nonsteroidal AR antagonist (Chen et al, 2009). Importantly, enzalutamide remains a strong antagonist of the AR in the castration-resistant state, even in the setting of overexpressed or constitutively activated AR (Watson et al, 2010). Unlike other antiandrogens that may also function as partial AR agonists, enzalutamide does not

exhibit any measurable agonistic activity. In addition to acting as an AR blocker, enzalutamide also disrupts the translocation of the AR from the cytoplasm (where it is inert) into the nucleus (where it acts as a transcription factor), while also impairing binding of the AR to the transcriptional complex at the androgen-response elements of DNA (Tran et al, 2009).

A phase II study of enzalutamide (160 mg orally daily) in men with chemotherapy-naïve ($n = 65$) or taxane-pretreated ($n = 75$) mCRPC showed preliminary evidence of potent activity (Scher et al, 2010). In that trial, greater than or equal to 50% of PSA declines were seen in 62% and 51% of chemotherapy-naïve and taxane-pretreated patients, respectively; objective tumor responses were observed in 36% and 12% of men with measurable disease, respectively. Radiographic PFS was 6.7 months in the docetaxel-pretreated patients and greater than 17 months in chemotherapy-naïve patients. In addition, 49% of patients had a decrease in their CTC counts, from unfavorable (≥ 5 CTC/7.5 mL blood) to favorable (< 5 CTC/7.5 mL blood) counts. Side effects of enzalutamide were generally mild and included fatigue (27%) and nausea (9%). Rare seizures (3/140 patients) were also reported, probably mediated by a direct effect of antagonism of central nervous system γ -aminobutyric acid receptors. One potential advantage of enzalutamide rather than abiraterone is the lack of a requirement for concurrent corticosteroid administration. In fact, data suggest that enzalutamide might potentially be less active if administered together with prednisone, perhaps because of promiscuous activation of AR by prednisone or by direct agonism of the glucocorticoid receptor (Scher et al, 2013).

A pivotal placebo-controlled double-blind phase III study (AFFIRM), randomizing 1199 patients with docetaxel-pretreated ketoconazole-naïve CRPC to enzalutamide ($n = 780$) or placebo ($n = 390$), was conducted to examine the effect of enzalutamide on overall survival. Patients receiving up to 2 previous lines of chemotherapy (one of which must have contained docetaxel) were the target population. The trial showed a 4.8-month improvement in median survival with enzalutamide compared to placebo (18.4 months vs. 13.6 months, HR 0.63, $P < .0001$) (Fig. 121-6) (Scher et al, 2012). A survival benefit was observed in all prespecified subgroups, although less benefit was seen in those with ECOG performance status of 2, similar to what was observed in the abiraterone

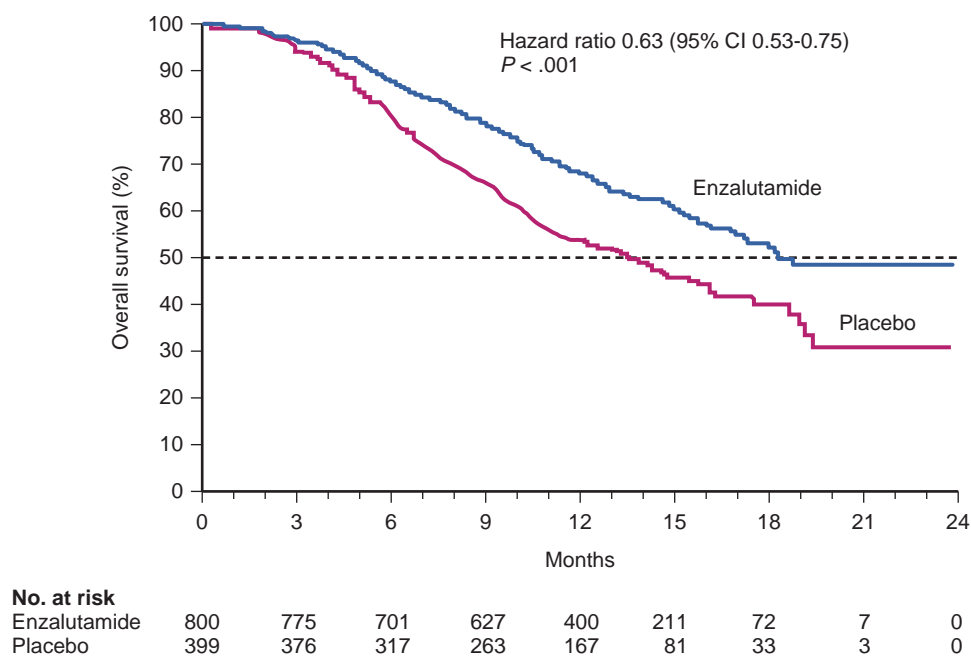


Figure 121-6. Overall survival in the AFFIRM study. (From Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187–97.)

trials. Confirmed PSA declines of more than 50% were seen in 54.0% compared to 1.5% ($P < .0001$) of patients receiving enzalutamide and placebo, respectively. Median time to progression was 8.3 compared to 3.0 months in the two arms (HR 0.25, $P < .0001$). Side effects were minimal and included fatigue, diarrhea, and hot flashes. Seizures were observed in about 1% of enzalutamide-treated patients. Based on the results of the AFFIRM trial, the FDA approved enzalutamide in August 2012 for the treatment of mCRPC in patients who have previously received docetaxel-containing chemotherapy.

To evaluate the efficacy of enzalutamide in the prechemotherapy setting, the PREVAIL study was designed. This was a phase III double-blind placebo-controlled trial in 1717 chemotherapy-naïve patients with asymptomatic or minimally symptomatic mCRPC who were randomized (1:1) to oral enzalutamide or placebo. At the time of an interim analysis, the study met its coprimary end points of radiographic PFS and overall survival. Compared to placebo, treatment with enzalutamide in the prechemotherapy setting resulted in a 29% reduction in the risk of death (HR 0.71, 95% CI 0.60 to 0.84, $P < .0001$) and an 81% reduction in the risk of radiographic progression (HR 0.19, 95% CI 0.15 to 0.23, $P < .0001$) (Beer et al, 2014). Based on the results on the PREVAIL trial, there is now strong evidence to suggest that enzalutamide can be used in all patients with mCRPC, regardless of whether or not they have received docetaxel chemotherapy.

Another next-generation AR signaling inhibitor is ARN-509. This is a novel antiandrogen (similar to enzalutamide) that also functions as a pure antagonist of the AR, while also inhibiting AR nuclear translocation and DNA binding (Clegg et al, 2012). ARN-509 might include potential advantages over enzalutamide in that it does not cross the blood-brain barrier and it has not been associated with seizures. Early evidence of clinical activity was obtained from a phase I study in 30 patients with progressive CRPC who received continuous daily oral ARN-509 at doses between 30 and 480 mg; a maximum efficacious dose of 240 mg daily was selected for phase II testing (Rathkopf et al, 2013). Adverse events with ARN-509 included fatigue (47%), diarrhea (30%), headache (20%), and hot flashes (13%). A phase II study of ARN-509 was then conducted, which enrolled three separate patient cohorts: men with nonmetastatic CRPC, men with mCRPC, and men with abiraterone-pretreated mCRPC (Rathkopf et al, 2012). In all three cohorts, a significant proportion of PSA responses gave evidence to clinical activity (although these responses were less frequent in each successive cohort owing to more advanced disease). This agent is now being studied in the SPARTAN trial, which is a multicenter blinded randomized phase III study for patients with nonmetastatic CRPC, in which metastases-free survival has been selected as the primary end point. In this study, patients are being randomized (2:1) to either ARN-509 or to placebo. Notably, ARN-509 is the first agent in prostate cancer that seeks regulatory approval in the nonmetastatic (M0) CRPC setting.

KEY POINTS: NOVEL ANDROGEN RECEPTOR-DIRECTED APPROACHES

- There is mounting evidence that CRPC is not androgen-independent and continues to rely on androgen/AR signaling.
- Abiraterone is a CYP17 inhibitor that depletes adrenal and intratumoral androgens. It is approved for the treatment of mCRPC, both before and after chemotherapy.
- Enzalutamide is a novel AR signaling inhibitor that blocks the AR and prevents nuclear translocation and DNA binding. It was shown to improve survival in men with mCRPC both in the prechemotherapy and postchemotherapy settings.
- Additional CYP17-targeting agents (e.g., orteronel) and AR-targeting agents (e.g., ARN-509) are in clinical development.

IMMUNOTHERAPY

An alternative or complementary strategy for the treatment of prostate cancer involves the use of immune-active agents. Cancer immunotherapy refers generally to approaches that attempt to treat cancer by activating immune responses against malignant cells while overcoming tumor-induced tolerance (Drake, 2010). Although not traditionally considered a disease amenable to immune-directed therapies, prostate cancer might in fact be an ideal target for immunologic attack because it is a slow-growing disease (allowing a stimulated immune system the time to generate an antitumor response), and it produces several tissue-specific proteins that may serve as tumor antigens: these include PSA, prostatic acid phosphatase (PAP), and others.

Entraining the immune system to overcome tumor-induced tolerance is the goal of nearly every cancer vaccine program, and active immunotherapy with vaccination against tumor-specific antigens has been pursued in many different cancer models including prostate cancer. A variety of approaches have been used, including dendritic cell-based therapies, adjuvants such as granulocyte-macrophage colony-stimulating factor (GM-CSF), viral carriers, single-antigen or whole-cell vaccines, genetically modified tumor cell vaccines, and DNA plasmid vaccines. More recently, strategies incorporating costimulatory molecules, cytotoxic T-lymphocyte antigen-4 (CTLA-4) blockade, PD-1 blockade, and intracellular viral or bacterial mediators have also been developed (Blattman et al, 2002; Mapara and Sykes, 2004; Webster et al, 2005; Harzstark and Small, 2009; Drake, 2010).

In prostate cancer, several of these immunologic approaches have been under clinical investigation, the most important of which is sipuleucel-T (an autologous PAP-loaded dendritic cell vaccine), which has gained FDA approval for patients with asymptomatic or minimally symptomatic mCRPC. Other immunotherapies that have entered late-phase clinical development include the GVAX allogeneic recombinant whole-cell vaccine (which failed to meet its primary end point in phase III trials), the ProstVac-VF recombinant poxviral PSA vaccine (currently in phase III testing), and CTLA-4 inhibitory approaches including ipilimumab (also in phase III testing).

Sipuleucel-T

Sipuleucel-T (Provenge) is a personalized vaccine that is derived from autologous CD54+ dendritic cells, the major class of antigen-presenting cells, which are apheresed from individuals and processed with a recombinant fusion protein composed of PAP and GM-CSF. PAP was chosen based on its prostate cell membrane localization and the success of preclinical models using it to generate prostate-specific immune responses and autoimmune prostatitis. Mixed activity was initially reported in early-phase trials using sipuleucel-T in patients with CRPC. In a randomized phase II/III trial comparing sipuleucel-T against placebo in 127 asymptomatic men with mCRPC, there was no significant difference in time to disease and pain progression ($P = .052$), which was the primary study end point (Small et al, 2006). However, patients randomized to placebo could cross over to receive the active vaccine at the time of progression, whereas those initially randomized to receive the active vaccine were treated at their physician's discretion at the time of progression. A 3-year update of this trial suggested a statistically significant improvement in overall survival for those patients assigned to receive sipuleucel-T initially ($P = .01$). Post hoc analyses also suggested that the benefits of sipuleucel-T might be limited to the subgroup of men with tumor Gleason sums of 7 or lower. Although preparation and production of large-scale quantities of individually tailored vaccine can be challenging, this vaccine was well tolerated, with minimal infusion-related fevers and rigors being the predominant adverse events (Small et al, 2006).

A second phase II/III trial that randomized 98 men with asymptomatic CRPC to either sipuleucel-T or placebo also failed to show a statistically significant improvement in time to progression (the primary end point of this study). However, post hoc pooled

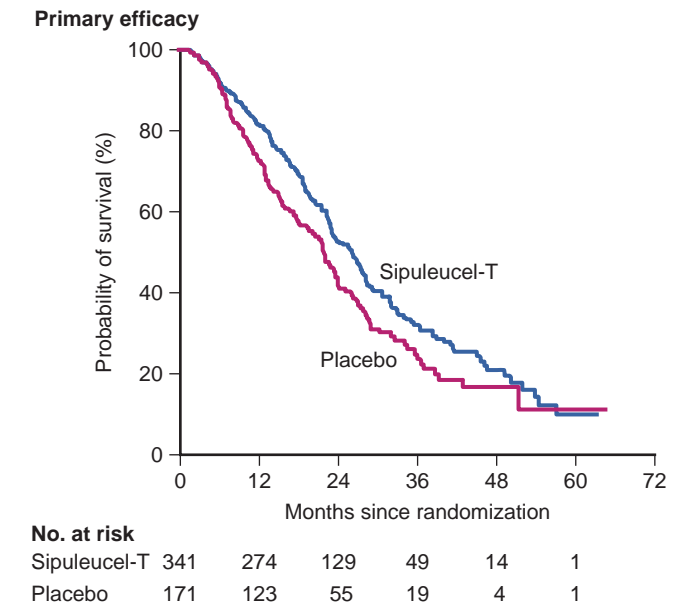


Figure 121-7. Overall survival in the IMPACT study. (From Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411-22.)

analyses of these two trials ($n = 225$) did show an overall survival advantage, with median survival being 18.9 months in the placebo group and 23.2 months in the sipuleucel-T group (HR 0.67, 95% CI 0.49 to 0.91, $P = .01$) (Higano et al, 2009). However, because overall survival was not the primary end point in either of these two trials, the FDA (justifiably) did not grant approval of this treatment at that time.

To evaluate definitively the clinical usefulness of sipuleucel-T in a larger patient population, a pivotal multicenter double-blind placebo-controlled randomized phase III trial (IMPACT) was conducted in men with asymptomatic or minimally symptomatic mCRPC (Kantoff et al, 2010a), finally leading to the FDA approval of this agent in April 2010. In this trial, 512 patients were randomized (2:1) to sipuleucel-T or to placebo, and the study was powered to detect an overall survival advantage. Notably, this study did not enroll men with visceral metastases or those taking narcotics for cancer pain, and most patients (85%) were chemotherapy naive. Impressively, median overall survival was 25.8 months in the sipuleucel-T group versus 21.7 months in the placebo group (HR 0.78, $P = .03$) (Fig. 121-7), despite 64% of patients on placebo crossing over to receive salvage sipuleucel-T at the time of disease progression. In the subset of patients with previous chemotherapy exposure, overall survival trended in favor of sipuleucel-T, but this effect was not statistically significant. Therefore, although this immunotherapy is approved for all patients with asymptomatic or minimally symptomatic CRPC, it will likely provide its largest impact in the prechemotherapy setting. In addition, it should not be used in patients with visceral disease, or in those requiring narcotic analgesics for cancer-related pain.

Similar to previous studies with sipuleucel-T, the IMPACT study detected no difference in PFS or PSA/radiographic response rates between the two treatment arms. Some investigators attribute the discord between progression-free and overall survival to a possible class effect of immunotherapy agents relating to their mechanism of action, which is distinct from cytotoxic therapies. Problematic end points such as PFS in CRPC (which may be confounded by bone scan flare or delayed-onset effects) might perhaps be better addressed by revised guidelines using outcomes that are tailored to immunologic agents (Hoos et al, 2010). These new immune-related response criteria may help in the future development of

additional immunotherapy agents for prostate cancer and other malignancies.

Because of the notion that immunotherapies are likely to have their biggest impact in the early-disease setting, sipuleucel-T has also been tested in combination with ADT in men with nonmetastatic biochemically-recurrent prostate cancer (Antonarakis and Kibel, 2013). Although the immunologic data from this trial appear encouraging, the mature clinical results are still awaited. In addition, other trials are currently testing the combination of sipuleucel-T with other AR-directed therapies. For example, one trial is examining the combination and sequencing of sipuleucel-T with abiraterone in men with mCRPC. Another trial is evaluating the optimal combination and sequencing of sipuleucel-T with enzalutamide. Both of these studies have not yet produced mature results. However, it is likely that immunotherapies will routinely be combined with other standard prostate cancer therapies moving forward so as to maximize clinical outcomes, especially if these agents do not have overlapping toxicities.

ProstVac-VF

ProstVac-VF is a PSA-targeted poxviral-based vaccine approach that has been developed through a series of iterative preclinical and clinical studies. The final version uses a heterologous prime-boost strategy (vaccinia prime, fowlpox boost), and incorporates a DNA plasmid containing the PSA gene plus three costimulatory molecules serving to increase PSA-specific immune responses (Madan et al, 2009). This particular vaccine is not a personalized product, is relatively inexpensive to synthesize, and is administered by repeated subcutaneous injections throughout several months. Similar to the clinical experience with sipuleucel-T, a randomized phase II study using this immunotherapy product demonstrated improved overall survival (a secondary end point) among men with mCRPC who received ProstVac-VF compared to those receiving an empty-vector placebo (25.1 vs. 16.6 months, HR 0.56, $P = .006$), whereas there was no impact on the primary end point of PFS (Kantoff et al, 2010b). Following from these encouraging results, and recognizing that this class of agents might produce a survival benefit without altering radiographic progression, a multinational randomized phase III trial has been launched in which 1200 men with chemotherapy-naïve asymptomatic or minimally symptomatic mCRPC are allocated (1:1:1) to one of three treatment arms: ProstVac-VF administered alone, ProstVac-VF plus subcutaneous GM-CSF, or placebo. The primary end point of this pivotal trial is overall survival, and final results are awaited.

In addition, there has been considerable interest in combining ProstVac-VF with other standard prostate cancer therapies in earlier disease settings. In a completed phase II study involving 42 men with nonmetastatic CRPC, patients were randomized to ProstVac-VF, followed by nilutamide versus nilutamide, followed by ProstVac-VF (Madan et al, 2008). This study suggested an improvement in overall survival in men receiving ProstVac-VF before nilutamide rather than the opposite sequence (6.2 vs. 3.7 years, $P = .04$). Another randomized phase II trial currently compares the combination of ProstVac-VF plus enzalutamide versus enzalutamide alone in men with nonmetastatic biochemically recurrent prostate cancer. Finally a separate randomized phase II study compares ProstVac-VF plus enzalutamide versus enzalutamide alone in men with mCRPC. These studies help to elucidate the role of combination immunohormonal therapy in various prostate cancer clinical states.

Immune Checkpoint Blockade

Because of ongoing host immunologic pressures on evolving tumors, cancers have developed mechanisms to escape immune surveillance, effectively inducing a state of immune tolerance (Drake et al, 2006). One way to inhibit immunologic evasion by tumor cells is through the blockade of the immune checkpoint molecule CTLA-4 (cytotoxic T lymphocyte-associated antigen-4), thus preventing the normal attenuation of antitumor T-cell responses (Hodi, 2007). In murine prostate cancer models, CTLA-4 inhibition has

been shown to potentiate T-cell effects and to induce tumor rejection including at metastatic sites (Kwon et al, 1999).

Several clinical trials using the monoclonal anti-CTLA-4 antibody, ipilimumab, have been conducted in men with mCRPC. These include phase I and II studies of ipilimumab monotherapy, or therapy in combination with radiation (Small et al, 2007), as well as a phase I study combining ipilimumab with GM-CSF (Fong et al, 2009). Encouragingly, across a broad range of phase I and II studies, greater than or equal to 50% of PSA reductions have been observed in about 10% to 20% of prostate cancer patients, and radiologic tumor responses were seen in about 5% of men (Slovin et al, 2013), which is particularly noteworthy given that PSA and tumor responses were rarely reported in the immunotherapy trials with sipuleucel-T or other therapeutic vaccines. Common side effects of ipilimumab include fatigue (42%), nausea (35%), pruritus (24%), constipation (21%), and rash (19%). In addition, because CTLA-4 normally serves to attenuate autoimmunity, immunologic toxicities resulting from an unchecked immune response might occur. Such immune-related adverse events include colitis (15% to 20%), hepatitis (5%), adrenal insufficiency and other endocrinopathies (2%), dermatitis/vitiligo (2%), and even hypophysitis (1%) (Dillard et al, 2010; Drake et al, 2014).

Based on these encouraging phase II data, ipilimumab entered phase III testing in the pre- and postchemotherapy settings. The first trial to be completed was a placebo-controlled phase III study in 799 men with mCRPC who had previously received docetaxel-based chemotherapy: all patients received a low dose of immunostimulatory radiotherapy to a bone metastasis (8 Gy) followed by treatment allocation to either ipilimumab (administered intravenously every 3 weeks for 12 weeks, and then every 12 weeks thereafter) or matching placebo. In this trial, although treatment with ipilimumab was associated with superior PSA response rates (13.1% vs. 5.3%, $P = .001$) and improved PFS (HR 0.70, 95% CI 0.61 to 0.82, $P < .0001$), there was no statistically significant improvement in overall survival although there was a strong trend favoring the ipilimumab arm (HR 0.85, 95% CI 0.72 to 1.00, $P = .053$) (Drake et al, 2014). Patients without visceral disease experienced the greatest benefit from ipilimumab, as well as those patients with normal hemoglobin and alkaline phosphatase levels. A second predocetaxel placebo-controlled phase III study is currently underway and has completed enrollment of 600 patients. In this trial, men with asymptomatic or minimally symptomatic CRPC have been randomized to ipilimumab or placebo; overall survival is the primary end point of this study and the results are awaited.

KEY POINTS: IMMUNOTHERAPY

- Sipuleucel-T is the first therapeutic vaccine to be approved by the FDA for the treatment of any cancer, and it is indicated for men with asymptomatic or minimally symptomatic mCRPC without visceral metastases or cancer-related pain requiring narcotics.
- ProstVac-VF is a poxviral-based PSA-directed prostate cancer vaccine that is administered by subcutaneous injection. It is currently in phase III testing for men with asymptomatic or minimally symptomatic mCRPC.
- Ipilimumab shows promising clinical activity in men with mCRPC, although a large trial in docetaxel-pretreated patients narrowly missed its primary survival end point. Although ipilimumab is not currently FDA-approved for prostate cancer, an ongoing trial is evaluating ipilimumab in men with mCRPC who have not yet received chemotherapy.
- The future of prostate cancer immunotherapies is likely to involve their use in the early-disease setting, or in combination with other standard prostate cancer therapeutics (hormone therapy and radiotherapy).

TARGETED TREATMENTS

Rational Target Overview

An understanding of the basic biology involved in the pathogenesis and progression of prostate cancer provides the opportunity to identify potential therapeutic targets for this disease. In general terms, the first therapeutic opportunity is the demonstration of a mutation or functional dysregulation of a target. Simply targeting overexpressed proteins has been less effective than the specific targeting of mutations that drive the bulk of the tumor growth. However, with the exception of the AR, this scenario is rare in prostate cancer. The second goal is identifying target causality, indicating the importance of the target alone or in combination with other aberrations in reproducing the phenotypic findings of prostate cancer. Finally there should be evidence from preclinical models that inhibition of the target leads to tumor regression or quiescence, not just growth restriction.

In prostate cancer, the AR is one potential therapeutic target, although there are many others. Given the molecular complexity of the prostate cancer cell and the relatively poor understanding of the role of non-AR pathways in prostate cancer progression and metastasis, the simultaneous inhibition of multiple pathways remains a common strategy to induce sustained and clinically meaningful patient responses. In addition, although a prostate cancer stem cell has yet to be conclusively demonstrated, prostate cancer clearly progresses from an androgen-dependent tumor (with features similar to the luminal differentiated glands of the prostate) to an AR-independent tumor (that has features of adult stem cells, including antiapoptotic mechanisms, chemotherapy resistance, and reliance on non-AR-related pathways).

To this end, candidate pathways currently under evaluation as targets for prostate cancer treatment include phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling, epidermal growth factor receptor (EGFR) signaling, mitogen-activated protein kinase (MAPK) signaling, angiogenesis signaling, apoptosis signaling, hedgehog signaling, insulin-like growth factor receptor (IGF-1R) signaling, Src kinase signaling, endothelin signaling, and several others (Wozney and Antonarakis, 2014). However, therapeutic approaches targeting these pathways have been largely unsuccessful, with few exceptions. Here we will outline some of the most promising efforts relating to therapies targeting the Akt/mTOR pathway, angiogenesis, and MET signaling, as well as apoptotic pathways. This section provides an overview of these select pathways as they pertain to prostate cancer rational targets and the approaches that are currently being developed for therapeutic purposes.

Phosphatidylinositol 3-Kinase/Akt/Mammalian Target of Rapamycin Pathway

The PI3K/Akt/mTOR pathway is an important signaling cascade present in many different types of human cancer. This pathway has been linked to cell survival, differentiation, proliferation, growth, metabolism, migration, and angiogenesis. Normally, signaling via this pathway begins with the binding of a growth factor to a receptor tyrosine kinase resulting in downstream activation of PI3K. Alternatively, PI3K activation can occur via Ras through G-protein-coupled receptors. PI3K phosphorylates its substrate, phosphatidylinositol 4,5-bisphosphate (PIP2) to produce phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 can proceed to bind to various signaling proteins and can initiate downstream signaling via Akt. This pathway is negatively regulated by the protein tyrosine phosphatase (PTEN) (often deleted in prostate cancer), which dephosphorylates PIP3 to PIP2 thereby terminating further signaling (Engelman, 2009; Courtney et al, 2010). The PI3K/Akt signaling cascade promotes cell survival and resistance to apoptosis through several different mechanisms, including interactions with the Bcl-2 family members BAD and BAX, nuclear factor- κ B (NF- κ B), and Mdm2. Also downstream of this pathway is the mTOR protein.

Activation of mTOR leads to increased protein synthesis through phosphorylation of ribosomal proteins and translation elongation factors. In this fundamental way, mTOR is an important modulator of cell growth. Multiple feedback loops and regulators control mTOR signaling, and the pathway integrates inputs from various metabolic, growth factor, and survival pathways (Dancey, 2010).

Laboratory data have provided compelling foundations for studying the role of inhibitors of PI3K and its downstream targets in prostate cancer. Taylor and colleagues (2010) performed genomic profiling of 218 primary or metastatic prostate cancers, integrating information about DNA copy number, mRNA expression profiles, and exon sequencing. A core pathway analysis showed that altered signaling in the PI3K pathway was present in nearly half of all primary prostate tumors and in virtually all metastatic tumors tested. About 40% of all cases demonstrated loss-of-function of PTEN through deletion, silencing mutation, or reduced expression. In contrast to many other cancers, activating mutations in the *PIK3CA* gene were rare. However, loss-of-function mutations in the regulatory subunits PIK3R1 and PIK3R3 were prevalent, suggesting another mechanism for constitutive activation of PI3K in prostate cancer (Taylor et al, 2010).

Despite these telling observations, attempts to target segments of the PI3K/Akt/mTOR pathway in prostate cancer patients have been modest. Studies of the mTOR inhibitors rapamycin, everolimus, and temsirolimus as single agents and in combination with the AR antagonist bicalutamide failed to demonstrate significant clinical activity in mCRPC (Amato et al, 2008; Nakabayashi et al, 2012; Armstrong et al, 2013). Nevertheless, based on preclinical data showing that mTOR inhibition can reverse chemotherapy resistance in PTEN-deficient prostate cancer cell lines, ongoing trials are examining the efficacy of combined treatment with mTOR inhibitors and docetaxel (Grunwald et al, 2002; Duran et al, 2012). Other novel mTOR inhibitors and combination therapies are also under investigation.

One possible explanation for the failure of single-agent mTOR inhibitors to show efficacy in prostate cancer is the hypothesis that mTOR blockade leads to feedback-driven upregulation of signaling molecules upstream in the PI3K pathway. Studies by Carver et al (2011) have demonstrated the existence of bidirectional crosstalk between PI3K signaling and AR signaling. For example, in a preclinical model, inhibition of the PI3K pathway resulted in activation of AR signaling in PTEN-deficient prostate cancer cells. Similarly, the AR antagonist enzalutamide appeared to upregulate Akt signaling by reducing levels of the regulatory phosphatase PHLPP (PH domain leucine-rich repeat protein phosphatase). Combined blockade with the dual PI3K/mTOR inhibitor, BEZ235, and enzalutamide led to reductions in tumor size in human prostate cancer xenograft models (Carver et al, 2011). This work provides a sound rationale for simultaneous targeting of both pathways.

Under this premise, BEZ235 is currently being studied in combination with abiraterone in men with advanced CRPC. A first-in-human phase I study (that enrolled patients with various solid tumors) showed that BEZ235 was tolerable, as no DLTs were observed at the doses tested. Frequently reported side effects were fatigue and gastrointestinal symptoms. A few tumor responses were seen; patients whose tumors demonstrated activated PI3K pathway signaling were the most likely to respond to treatment with BEZ235. Because of pharmacokinetic variability, the drug was reformulated to improve bioavailability, which initially delayed clinical development of this agent (Maira et al, 2008; Burris et al, 2010).

Efforts to develop the potent and specific Akt inhibitor, MK2206, are also seeking to capitalize on the preclinical observations that simultaneous AR blockade and PI3K pathway inhibition may be synergistic. Previous phase II studies of another putative inhibitor of Akt, perifosine, had been disappointing. However, correlative pharmacodynamic studies were not performed in perifosine-treated patients, and therefore it is unclear whether target inhibition was actually achieved in these studies (Posadas et al, 2005; Chee et al, 2007). Conversely, pharmacodynamic correlates to the phase I study that established the safety profile and maximum tolerated dose of MK2206 have confirmed its ability to target and inhibit Akt

in humans. The most frequent side effects of MK2206 are hyperglycemia, nausea, diarrhea, skin rash, and stomatitis (Yap et al, 2011). MK2206 is currently being investigated in conjunction with bicalutamide in a cooperative group trial enrolling men with PSA-recurrent prostate cancer after failed local therapy.

The pan-PI3K inhibitors BKM120 and PX-866 are also being tested in phase II trials of mCRPC. Both of these drugs potently inhibit wild-type and mutant class-I PI3K isoforms. Phase I studies have included very few patients with prostate cancer, although one man with mCRPC who received PX-866 experienced prolonged stable disease. Interestingly, although the two drugs are purported to have the same mechanism of action, their side effect profiles are distinct. DLTs on the PX-866 phase I study were primarily gastrointestinal symptoms, including diarrhea and transaminitis. During the phase I study of BKM120, similar gastrointestinal symptoms were seen, but the drug included additional toxicities such as rash, hyperglycemia, and neuropsychiatric effects (mood alterations, depression) (Bendell et al, 2012; Hong et al, 2012). As phase II trials move forward, attention to the correlative pharmacodynamic studies for these drugs is imperative. One such intriguing study combines BKM120 with enzalutamide.

Angiogenesis

Therapeutic strategies aimed at preventing the growth of tumor vasculature have yielded clinical benefits for patients with several types of cancers, most notably renal cell carcinoma. There is a strong preclinical basis for studying inhibitors of angiogenesis in prostate cancer, as this process appears to play an important role in prostate carcinogenesis and maintenance. One of the key factors in angiogenesis is hypoxia-induced factor-1 α (HIF-1 α), a transcription factor whose expression is regulated by oxygen levels and growth factor signaling. HIF-1 α controls expression of various genes including many that are involved in angiogenesis, such as VEGF. VEGF acts directly on endothelial cells to stimulate proliferation and to increase vascular permeability, forming the matrix on which neovascularization can occur. In this manner, both hypoxia-dependent and hypoxia-independent mechanisms can induce angiogenesis (Semenza, 2003). In prostate cancer, neovascularization is not only triggered by the hypoxic tumor microenvironment, but also by aberrant growth factor signaling. For example, prostate cancer cells may aberrantly express both the VEGF receptor and ligand. This suggests a dual role for this pathway involving both paracrine signaling that promotes angiogenesis as well as autocrine signaling that stimulates cell growth and proliferation (Ferrer et al, 1997, 1999).

Many drugs that inhibit VEGF signaling have been tested in prostate cancer, including several that have been FDA-approved for treatment of other solid tumors. The best known is bevacizumab, a humanized monoclonal antibody to VEGF. Bevacizumab was evaluated in a phase III cooperative group trial in patients with mCRPC. Participants were treated with docetaxel and either bevacizumab (15 mg/kg IV every 21 days) or placebo. More than 1050 patients were enrolled in the study. PFS improved in the bevacizumab arm (9.9 vs. 7.5 months, $P < .001$), but overall survival did not differ significantly between arms (22.6 vs. 21.5 months, $P = .18$) (Kelly et al, 2012). Grade-3 or higher toxicities were more common in the bevacizumab arm, as was treatment-related mortality. Serious adverse events attributed to bevacizumab included hypertension, gastrointestinal perforation/hemorrhage, mucositis, and pneumonitis. Based on the "negative" results of this study, the FDA has not approved bevacizumab for use in patients with advanced prostate cancer. Ongoing studies are evaluating its role in conjunction with a short course of ADT in the PSA-recurrent/nonmetastatic setting. It is also being studied in mCRPC patients in combination with the mTOR inhibitors everolimus and temsirolimus.

An alternative antiangiogenic strategy involves the use of the VEGF-trap molecule aflibercept. Aflibercept is a decoy receptor that binds circulating VEGF ligand, thereby preventing its association with cellular VEGF receptors. The drug was studied in a multinational phase III trial in symptomatic mCRPC patients. More than

1200 patients were randomized to receive docetaxel plus either aflibercept or placebo. In this trial, there were no significant differences in progression-free or overall survival, and toxicities were higher in the aflibercept arm (Tannock et al, 2013). The increase in toxicities in the interventional arm mimicked the higher rate of adverse events with the docetaxel-bevacizumab combination. Because of these negative findings, no further studies of aflibercept are planned in patients with prostate cancer.

Attempts to target VEGF signaling with small molecule inhibitors in men with prostate cancer have shown some promise in phase II studies, but only one of these agents (sunitinib) has entered phase III testing. Sunitinib is a promiscuous tyrosine kinase inhibitor that blocks VEGFR2 and platelet-derived growth factor- β . A phase III study was conducted in patients with mCRPC who progressed after docetaxel chemotherapy. In this trial, more than 870 men were randomized to single-agent sunitinib or placebo. Although PFS was superior for sunitinib (5.6 vs. 4.1 months, $P < .001$), there was no significant difference in overall survival compared to placebo (13.1 vs. 11.8 months, $P = .17$) (Michaelson et al, 2014). The results of this study also raise the question of whether an overall survival benefit may have been observed if sunitinib had been continued beyond radiographic progression in patients who were tolerating the drug well. This agent is not FDA approved for prostate cancer.

Despite the disappointing results from the aforementioned phase III trials, several drugs targeting angiogenesis in novel ways remain in clinical development. Perhaps the most promising of these is tasquinimod, a second-generation quinolone-3-carboxamide analogue. Tasquinimod inhibits angiogenesis by preventing the upregulation of HIF-1 α and the resultant aberrant VEGF expression. It also appears to induce expression of an endogenous anti-angiogenesis factor, thrombospondin-1. Through an alternative or complementary mechanism of action, the drug also inhibits S100A9, a protein involved in differentiation and cell cycle progression. Inhibition of S100A9 also prevents recruitment of myeloid derived suppressor cells (MDSCs), which are important players in the tumor microenvironment. MDSCs may participate in immune escape and other mechanisms by which tumors evade immunologic attack (Isaacs, 2010). A phase II study of tasquinimod was conducted in men with mCRPC who had not received chemotherapy. The primary end point was radiographic PFS at 6 months. More than 200 men were randomized (2:1) to receive tasquinimod or placebo. Median PFS was 7.6 months with tasquinimod versus 3.3 months with placebo ($P = .004$). The drug had minimal effects on PSA kinetics, and few men achieved a significant reduction in PSA. Common side effects of tasquinimod were fatigue, nausea, constipation, and anorexia. Grade-3 and higher toxicities included asymptomatic elevations in the lipase and amylase levels, anemia, and venous thrombosis (Pili et al, 2011). Based on these results, tasquinimod has advanced to a placebo-controlled randomized phase III trial for patients with similar characteristics to those in the phase II study. This trial will use overall survival and PFS as coprimary end points, and it has already completed the accrual of 1200 men with chemotherapy-naïve CRPC.

MET Signaling

The c-Met receptor tyrosine kinase has received considerable attention as a potential therapeutic target for many solid tumors, including prostate cancer. c-Met is the cell surface receptor for the hepatocyte growth factor (HGF). In normal tissues, stromal cells produce HGF, and signaling through c-Met occurs largely via paracrine mechanisms. HGF/c-Met signaling is thought to be important for many physiologic processes including embryogenesis, organogenesis, angiogenesis, wound healing, and repair of organ damage (Trusolino et al, 2010; Scagliotti et al, 2013). Activation of c-Met can lead to signaling via multiple signal transduction pathways, including Src kinase and the PI3K/Akt/mTOR and MAPK cascades. These pathways activate many cellular processes relevant to cancer, including proliferation, survival, and resistance to apoptosis. HGF/c-Met signaling also promotes invasiveness, motility, and metastasis

through changes in the structure of the cytoskeleton and altered integrin expression (Peters and Adjei, 2012).

Abnormal c-Met expression has been observed in a variety of human malignancies, including prostate cancer. Mechanisms responsible for aberrant c-Met signaling include gene amplification and chromosomal rearrangement. Activating mutations and alternative splice variants can also lead to overactive c-Met signaling (Jeffers et al, 1997; Peters and Adjei, 2012; Scagliotti et al, 2013). In prostate cancer, paracrine mechanisms are believed to be predominantly responsible for increased c-Met signaling (Knudsen and Edlund, 2004). High c-Met expression exists in approximately 50% of primary prostate tumors at diagnosis and has been universally observed in bone metastases (Knudsen et al, 2002). In vitro, many CRPC cell lines also express high levels of c-Met mRNA and protein, and they are responsive to HGF in a concentration-dependent manner (Knudsen and Edlund, 2004). Therefore, the relationship between AR signaling and c-Met expression has been investigated. To this end, the AR appears to regulate negatively c-Met expression by interfering with Sp1, a transcription factor that binds to the promoter region of the *c-MET* gene. In support of this hypothesis, high c-Met expression has been observed in castration-resistant xenograft models. These findings have led to the conclusion that expression of c-Met and signaling via the HGF/Met axis may be important for the progression of prostate cancer to the castration-resistant state (Verras et al, 2007).

In addition, the presumed importance of c-Met signaling in prostate cancer and its widespread expression in osseous metastases has led investigators to study inhibitors of this signaling pathway in patients with advanced prostate cancer. Although several Met-targeting strategies have been used, cabozantinib (XL184) is the most promising c-Met inhibitor in clinical development for the treatment of prostate cancer. It is an oral tyrosine kinase inhibitor that potently inhibits c-Met and VEGFR2 (as well as RET). In phase I testing, side effects with cabozantinib were manageable and included diarrhea, fatigue, decreased appetite, and rash. The main DLTs of this agent were hand-foot syndrome, mucositis, and elevations of liver enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) as well as lipase elevations. Clinical benefit was seen in a broad range of tumor types (Kurczok et al, 2011).

Based on the responses seen in this phase I study, an international phase II randomized-discontinuation trial was conducted in nine tumor types simultaneously, including a cohort of men with mCRPC. The dose selected for this phase II study was 100 mg daily. All patients received open-label treatment with cabozantinib during a 12-week lead-in stage, and the trial then randomized patients with stable disease at 12 weeks to cabozantinib or placebo. The study oversight committee suspended randomization after the lead-in stage after the accrual of 122 patients, because unprecedented improvements were seen on bone scans across multiple tumor types (including prostate cancer). At that point, median PFS in CRPC patients with cabozantinib was 23.9 weeks compared to 5.9 weeks with placebo (Smith et al, 2013). Ultimately, the study enrolled a total of 171 patients with mCRPC, almost half of whom had previously received chemotherapy. Although the partial radiographic response rate was only 5%, an additional 75% of patients had stable disease. As before, cabozantinib appeared particularly active in treating bone metastases, with 12% of patients showing complete resolution of disease on technetium-99 bone scan. Reductions in pain scores and narcotic use were also observed in a significant proportion of patients. Importantly, PSA changes did not correlate with the favorable results seen on imaging studies or other signs of clinical benefit; some patients exhibited rising PSA levels despite reductions in the size of soft-tissue lesions or bone metastases. The toxicity profile of cabozantinib in this study was similar to that reported in the phase I trial, although higher rates of grade-3 hypertension were seen (Smith et al, 2013).

Cabozantinib was studied in two phase III trials in men with mCRPC with progressive disease following treatment with docetaxel and a novel AR-directed agent (abiraterone or enzalutamide). The first study (COMET-1) evaluated the efficacy of single-agent

cabozantinib versus placebo, with a primary end point of overall survival. The second study (COMET-2) investigated the effect of cabozantinib versus mitoxantrone on quality-of-life measures and pain control; the primary end point of that study was the frequency of durable pain responses lasting at least 12 weeks (whereas overall survival was a secondary end point). These trials were considered the registrational studies for cabozantinib in advanced CRPC. Both studies failed to meet their primary end points.

Apoptosis Pathway

Another rational therapeutic approach for multiple cancer types including prostate cancer is the induction of tumor cell apoptosis. To this end, clusterin is a stress-induced antiapoptotic chaperone protein expressed in various cancers including prostate cancer (Zoubeidi et al, 2010), and it has received renewed attention because of the development of an antisense inhibitor to this protein. Importantly, expression of clusterin in prostate tumors increases after treatment with androgen ablation or chemotherapy (Miyake et al, 2000; July et al, 2002), conferring a more resistant phenotype. Custirsen is a novel intravenously administered antisense oligonucleotide moiety that inhibits clusterin at the mRNA level, increasing sensitivity to androgen deprivation as well as chemotherapy in prostate cancer cell lines and in xenograft models (Gleave and Miyake, 2005; Sowery et al, 2008).

In a randomized phase II trial of docetaxel administered with or without custirsen in 82 patients with mCRPC, PSA responses (58% vs. 54%) as well as PFS (7.3 vs. 6.1 months) were essentially similar in both arms. However, there was a trend in overall survival favoring the combination arm (23.8 vs. 16.9 months, $P = .06$), although survival was not the primary end point of this study, and confidence intervals around these estimates were wide and potentially confounded by subsequent therapies (Chi et al, 2010). Adverse events associated with custirsen in that trial included fatigue (48%), fever (30% to 50%), rigors (40% to 60%), diarrhea (40% to 60%) and rash (20% to 40%). Another phase II study of second-line chemotherapy plus custirsen in patients with docetaxel-pretreated CRPC has completed accrual, and outcomes are awaited.

Finally, two registrational placebo-controlled phase III trials of custirsen are underway. The first study (SYNERGY) randomized 1022 patients with chemotherapy-naïve mCRPC to receive standard docetaxel versus the combination of docetaxel plus open-label custirsen; overall survival was chosen as the primary end point in this trial. This study failed to meet its primary end point. The second study (AFFINITY) is currently randomizing 630 patients with docetaxel-pretreated CRPC to either cabazitaxel alone or cabazitaxel plus custirsen; the primary end point of this study is also overall survival. The overarching aim of these studies is to test definitively the hypothesis that clusterin inhibition may reverse chemotherapy resistance in CRPC.

KEY POINTS: NOVEL TARGETED TREATMENTS

- Despite negative studies with bevacizumab and aflibercept, angiogenesis remains a valid therapeutic target in prostate cancer, as exemplified by the novel agent tasquinimod.
- Because of the reciprocal interactions between the PI3K/Akt/mTOR pathway and the AR signaling pathway, dual inhibition of both pathways concurrently will likely represent the most fruitful therapeutic strategy.
- Cabozantinib is a novel small molecule inhibitor of c-Met and VEGFR2, with profound activity on CRPC bone metastases.
- Custirsen is an antisense oligonucleotide against clusterin mRNA, which may play a role in reversing resistance to taxane chemotherapies.

PALLIATIVE MANAGEMENT

Pain and Epidural Cord Compression

As in other disseminated malignancies, palliation of symptoms and maintenance of adequate quality of life represent the most important objectives in the management of advanced prostate cancer. Cancer-related pain is undoubtedly the most debilitating symptom associated with advanced-stage metastatic prostatic carcinoma. Prompt recognition of the various pain syndromes associated with this disease is critical to accomplish effective control of this devastating symptom. The most common pain syndromes and their respective therapeutic considerations are summarized in Table 121-1. Focal bone pain in patients with CRPC can be well controlled using external-beam localized radiation therapy. In general, it is also recommended that painful areas that are shown to be abnormal on bone scintigraphy should be evaluated with plain radiographs or CT imaging to exclude the presence of osteolytic lesions or pathologic fractures. Such considerations become even more important when the painful areas affect extremities and weight-bearing sites.

Epidural metastasis is fairly common and is a potentially devastating complication of systemic cancer. In view of the propensity for prostate cancer to metastasize to the vertebrae and paravertebral regions, the incidence of epidural cord compression is particularly high in this disease. Early diagnosis and treatment of epidural metastasis is critical in preserving ambulation and bowel and bladder function and aids in the management of back pain (Grossman and Lissignol, 1990; Gabriel and Schiff, 2004). Epidural cord compressions arising from vertebral bodies account for the majority of spinal cord compressions; less frequently they are associated with soft-tissue masses involving the paravertebral region. Most of these patients have abnormalities on bone scintigraphs and/or abnormal findings on radiography at the time of diagnosis. However, a deficit on neurologic examination may be the only finding in patients who exhibit soft-tissue epidural metastasis in the paravertebral region.

Spinal magnetic resonance imaging (MRI) is routinely used to exclude the possibility of significant epidural disease, and it has almost entirely replaced other methods such as CT myelography and conventional myelography. The first therapeutic intervention in patients with suspected or documented cord compression should include the administration of high doses of intravenous glucocorticoids. Dexamethasone at doses ranging from 16 to 100 mg daily is most commonly used. Patients are often administered an intravenous "loading dose" of 10 mg of dexamethasone followed by 4 to 10 mg every 6 hours; the optimal steroid dose remains relatively undefined. On improvement of symptoms, which can be accomplished promptly with glucocorticoids, the steroid dose may be tapered down throughout a 2-week to 3-week period.

Radiation therapy is often the mainstay of definitive treatment. However, reports suggest that decompressive surgery followed by radiation therapy may be superior to radiation therapy alone (Patchell et al, 2005). To this end, surgery should be considered in patients who present with evidence of progressive signs and symptoms during radiation therapy, develop or present with unstable pathologic fractures that require stabilization, or experience recurrence after radiotherapy. In addition, the overall prognosis of the underlying disease should be considered during the treatment selection. Chemotherapy is rarely used to treat epidural cord compression during the acute management of this complication.

Bone-Targeted Approaches

The pathogenesis of bone metastases in prostate cancer remains a subject of major study. Alterations in the normal process of bone absorption and formation, which usually follow an orderly and sequential path, appear to be a key determining factor in the development of bone metastasis associated with most malignant neoplasms (Roodman, 2004). Under normal physiologic conditions the process of bone remodeling is initiated by an increase in osteoclastic activity followed by an increase in osteoblastic differentiation and maturation, which results in the formation of new bone and

TABLE 121-1 Common Pain Syndromes in Metastatic Castration-Resistant Prostate Cancer

PAIN SYNDROME	INITIAL MANAGEMENT	OTHER THERAPEUTIC ALTERNATIVES
Localized bone pain	Pharmacologic pain management Localized radiotherapy (special attention to weight-bearing areas, lytic metastasis, and extremities)	Surgical stabilization of pathologic fractures or extensive bone erosions Epidural metastasis and cord compression should be evaluated in all patients with focal back pain Radiopharmaceuticals should be considered if local radiation therapy fails
Diffuse bone pain	Pharmacologic pain management “Multisite” or wide-field radiotherapy Radiopharmaceuticals	Corticosteroids Bisphosphonates or RANK ligand inhibitors Calcitonin Chemotherapy
Epidural metastasis and cord compression	High-dose corticosteroids Radiation therapy Surgical decompression and stabilization is indicated in high-grade epidural compressions, extensive bone involvement, or recurrence after irradiation.	Pharmacologic pain management Physical therapy for recovery of neurologic function
Nerve plexopathies caused by direct tumor extension or previous therapy (rare)	Pharmacologic pain management Radiation therapy (if not previously used) Neurolytic procedures (nerve blocks)	Tricyclic antidepressants (amitriptyline) Anticonvulsants (gabapentin, pregabalin)
Miscellaneous neurogenic causes: postherpetic neuralgia, peripheral neuropathies	Complete neurologic evaluation Pharmacologic pain management Discontinuation of neurotoxic drugs: docetaxel, platinum compounds	Tricyclic antidepressants (amitriptyline) Anticonvulsants (gabapentin, pregabalin)
Other uncommon pain syndromes: extensive skull metastasis with cranial nerve/skull base involvement, extensive painful liver metastasis, or pelvic masses	Radiation therapy Pharmacologic pain management Corticosteroids (cranial nerve involvement)	Chemotherapy Intrathecal chemotherapy may ameliorate symptoms of meningeal involvement

RANK, receptor activator of nuclear factor- κ B.

the repair of the initial absorption caused by osteoblasts. Bone loss associated with prostate cancer can result from an enhanced osteoclastic activity associated with long-term androgen suppression, which in turn can cause excessive resorption of bone mineral and organic matrix. Tumor cells may also cause mineral release and matrix resorption in the areas involved by metastatic disease (Galasko, 1986). In addition, various cytokines, growth factors, tumor necrosis factors, and bone morphogenic proteins have been shown in preclinical studies to play a major role in the induction of both osteoclastic and osteoblastic activity (Reddi and Cunningham, 1990). In prostate cancer, bone metastases are predominantly blastic, which reflects a predominance of osteoblastic activity in the process of bone remodeling (Roodman, 2004). This phenomenon may be a result of specific growth factor secretion that is responsible for the induction of osteoblasts. Unlike other bone-tropic malignancies, hypercalcemia is rare in metastatic prostate cancer. In fact, a significantly elevated serum calcium concentration is most frequently a result of the neuroendocrine prostate cancer phenotype (see later) and is mediated through parathyroid hormone-related protein (PTHrP) (diSant’Agnese, 1995; Nelson et al, 2007).

Bisphosphonates

Bisphosphonates have become an integral part of the management of metastatic prostate cancer involving the bones (Van den Wyngaert et al, 2009). These compounds reduce bone resorption by inhibiting osteoclastic activity and proliferation. Zoledronate is a

potent intravenous bisphosphonate first approved for the treatment of hypercalcemia and decreased bone mineral density in postmenopausal women (Green and Rogers, 2002). In patients with progressive CRPC and bone metastases, zoledronate was shown to reduce the incidence of skeletal-related events (e.g., pain, fractures) compared with placebo in a prospective randomized trial of 422 patients (Saad et al, 2004). In addition, zoledronate and pamidronate have also been shown to increase bone mineral density in patients with nonmetastatic prostate cancer receiving long-term androgen deprivation (Smith et al, 2001, 2003).

At present, zoledronate is indicated for the treatment of patients with progressive CRPC with evidence of bone metastasis, and it is administered at a dose of 4 mg intravenously repeated at intervals of 4 weeks for several months. Side effects of this agent include fatigue, myalgias, fever, anemia, and mild elevation of serum creatinine. Hypocalcemia has been described with the use of zoledronate, and concomitant administration of oral calcium supplements (1000 mg/day) and vitamin D (800 units/day) is often recommended. An unusual complication of zoledronate is the development of severe jaw pain associated with osteonecrosis of the mandibular bone (called osteonecrosis of the jaw [ONJ]). The etiology of this phenomenon is not well understood. However, it is most frequently seen in patients undergoing dental work or those with a history of poor dentition and chronic dental disease. Zoledronate should not be administered to patients with these problems. Other bisphosphonates have also been evaluated in prostate cancer, including alendronate, etidronate, ibandronate, and clodronate;

however, their benefit has not been conclusively established in prospective randomized clinical trials (Berry et al, 2006; Van den Wyngaert et al, 2009).

Receptor Activator of Nuclear Factor- κ B Ligand Inhibitors

Interactions between tumor cells and the bone marrow microenvironment have been postulated as an additional important mechanism in the pathogenesis of bone metastasis. Tumor-associated cytokines have been shown to induce the expression of the receptor activator of nuclear factor- κ B ligand (RANKL) that binds and activates RANK, which is found in osteoclasts (Brown et al, 2001). Inhibition of the RANKL system has been the focus of much research and represents an evolving bone-targeted strategy. Among the approaches used are monoclonal antibodies to RANKL and the use of recombinant osteoprotegerin (the natural decoy receptor of RANKL), both of which significantly inhibit osteoclastic function in vitro and in vivo (Schwarz and Ritchlin, 2007). Denosumab, a fully human monoclonal antibody against RANKL, was the first agent to enter clinical trials in patients with prostate cancer as well as breast cancer. In a phase II randomized study evaluating 50 patients with metastatic prostate cancer, denosumab (administered subcutaneously every 4 weeks) produced a reduction in bone resorption beyond that of zoledronate, as indicated by a lowering of urinary *N*-telopeptide levels, and it also resulted in fewer skeletal-related events (Fizazi et al, 2009).

Following from these encouraging results, a pivotal multicenter phase III double-blind randomized study was conducted comparing denosumab against zoledronate for the prevention of skeletal-related events in patients with bisphosphonate-naïve mCRPC. In that trial of 1904 patients, compared to men receiving zoledronate ($n = 951$), men receiving denosumab ($n = 950$) showed an improved time-to-first skeletal-related event (20.7 vs. 17.1 months, $P = .008$) and a longer time to first-and-subsequent skeletal-related events (HR 0.82, $P = .004$) (Fizazi et al, 2011). Notably, there was no difference in overall survival or PFS between study arms. Based partially on the results of this study (and partially on two other large randomized studies in metastatic breast cancer and other solid metastatic tumors), the FDA approved denosumab in November 2010 for the prevention of skeletal-related events in patients with bone metastases from solid tumors. Common toxicities of denosumab include fatigue, nausea, hypophosphatemia, and hypocalcemia (grade ≥ 3 in 5% of patients). ONJ also occurs in about 2% to 4% of patients, and prophylactic use of calcium and vitamin D supplementation is strongly encouraged. Therefore, denosumab is a reasonable alternative to zoledronate for the prevention of skeletal-related events in patients with mCRPC, and it also includes an advantage in that it does not require dose adjustment or monitoring for renal impairment. The recommended dose of denosumab is 120 mg administered by subcutaneous injection every 4 weeks.

Radiopharmaceuticals

The introduction of “bone-seeking” radiopharmaceuticals has provided a useful resource for the management of diffuse bone pain from widespread prostate cancer metastases (Pandit-Taskar et al, 2004) and it might even improve survival (Parker et al, 2013a). Historically the most commonly used compounds were the beta emitters strontium-89 (^{89}Sr) (Porter et al, 1993) and samarium-153 (^{153}Sm) (Sartor et al, 2004), although these agents will largely be replaced by the alpha emitter radium-223 (^{223}Ra). Initial studies with ^{89}Sr showed palliation of bone pain in 25% to 65% of patients with CRPC and diffuse bone pain (Jager et al, 2000). The pharmacokinetics of ^{89}Sr vary considerably according to the extent of bone involvement, but the half-life is generally 4 to 5 days. The retention of this isotope is significantly longer in patients with diffuse osteoblastic metastases compared to those with relatively limited bone involvement. It is important to recognize this factor because it affects the degree and duration of myelotoxicity associated with this radioactive compound (its most significant toxicity). The clinical experience with ^{153}Sm suggests that this isotope is associated with

a lower incidence of myelotoxicity, probably because of its shorter half-life of 2 days. Encouraging results were reported by Sartor and colleagues (2004) in a phase III trial comparing radioactive ^{153}Sm and nonradioactive ^{152}Sm , indicating that a dose of ^{153}Sm of 1 mCi/kg is both safe and effective palliation for patients with CRPC and severe bone pain. However, although ^{89}Sr and ^{153}Sm are both FDA approved for the palliative management of castration-resistant bone metastases, neither compound was demonstrated to provide a survival advantage. To this end, the novel alpha-emitting agent radium-223 will probably replace these beta emitters because of its capacity not only to palliate bone pain but also to improve overall survival in this setting.

Radium-223 is a novel alpha-emitting radiopharmaceutical that has received significant attention. Alpha particles are approximately 7000 times heavier than beta particles, and as few as one or two hits can be sufficient to cause cell death, in comparison with hundreds or thousands of hits required from beta particles. In addition, alpha particles have a very short path length ($<100\ \mu\text{m}$), which may spare surrounding healthy bone marrow, thereby limiting hematologic toxicities (Henriksen et al, 2003). A series of phase I and II trials demonstrated the safety of radium-223, together with evidence of biologic activity in terms of serum markers of bone turnover and PSA changes, and also raised the possibility that treatment with radium-223 might improve overall survival (Nilsson et al, 2005, 2007, 2012; Parker et al, 2013b).

These promising early-phase data led to the design of the phase III ALSYMPCA trial (Parker et al, 2013a), as a result of which radium-223 gained FDA approval for use in mCRPC patients with symptomatic bone metastases. This was an international, randomized, double-blind, placebo-controlled phase III study comparing best standard care plus radium-223 versus best standard care plus placebo in men with mCRPC who were chemotherapy-refractory or chemotherapy-ineligible. Enrollment was restricted to men with symptomatic bone metastases in the absence of known visceral disease or bulky lymph-node metastases. Radium-223 was administered at a dose of 50 kBq/kg (intravenously) every 4 weeks for a total of 6 doses. The primary end point of this trial was overall survival, which was improved by radium-223 compared to placebo (HR 0.70, 95% CI 0.58 to 0.83, $P < .001$); this translated into a median survival benefit of 3.6 months beyond placebo (Fig. 121-8) (Parker et al, 2013a). In addition, all of the secondary efficacy end points were also met, with a 6-month delay in median time-to-first symptomatic-skeletal event (HR 0.66, 95% CI 0.52 to 0.83, $P < .001$), and a significant improvement in quality of life measured using the FACT-P scale. Remarkably, the incidence of adverse events and serious adverse events was lower in the radium-223 group than in the placebo group. Diarrhea was the most common side effect in ^{223}Ra -treated patients. Hematologic toxicity was rare (e.g., grade 3/4 thrombocytopenia was seen in 6% of men receiving radium-223 vs. 2% for placebo). Based on the results of the ALSYMPCA trial, radium-223 would be a reasonable treatment choice for any patient with symptomatic bone-mCRPC without visceral or bulky nodal metastases. This agent may be used both in docetaxel-refractory patients and in those who are ineligible or uninterested in receiving chemotherapy.

THE NEUROENDOCRINE/ANAPLASTIC PHENOTYPE

Laboratory and clinical evidence indicates that alterations in the differentiation pathway of prostate cancer can be seen in a small proportion of patients with advanced-stage disease, giving rise to a neuroendocrine/anaplastic transformation (diSant'Agnese, 1995; Nelson et al, 2007). The therapeutic implications of this finding are of significance because tumors demonstrating this phenotype usually represent an inherently endocrine-resistant subtype and, in view of their different clinical and biologic properties compared with the usual adenocarcinoma of the prostate, these tumors also require different treatment strategies.

Such tumors possess a number of biologic characteristics unique to neuroendocrine tumors that can also arise from other organs,

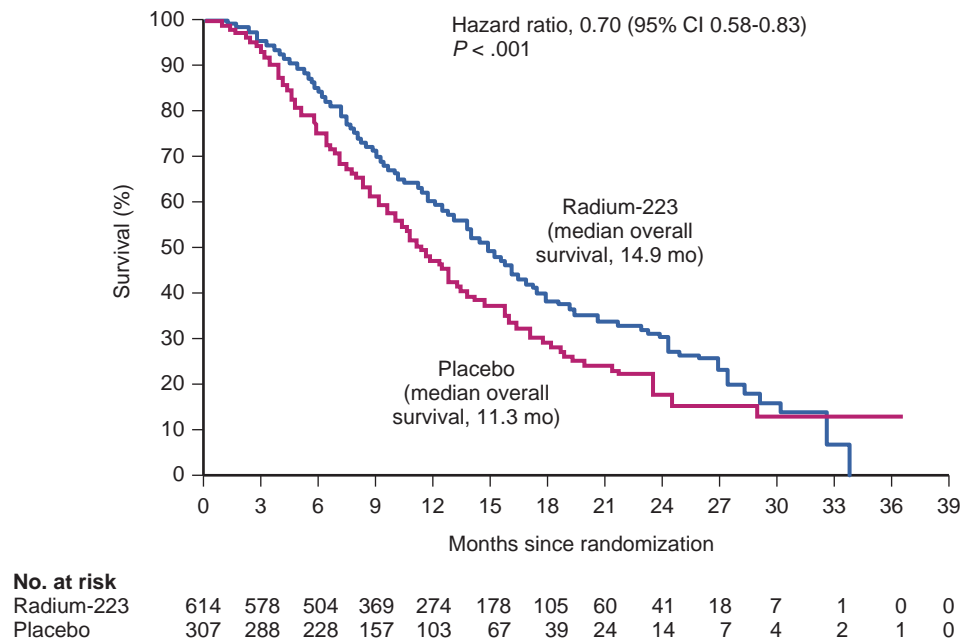


Figure 121-8. Overall survival in the ALSYMPCA study. (From Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213–23.)

KEY POINTS: PALLIATIVE MANAGEMENT

- Patients with back pain and a history of bone metastases should be evaluated for epidural cord compression. The clinical syndrome often includes at least one of the following signs and symptoms: back pain, focal neurologic deficit (leg weakness, sensory levels), or changes in bladder or bowel control.
- Initial management of suspected cord compression includes immediate MRI of the spine and initiation of high-dose intravenous corticosteroid therapy. Definitive treatment should include radiation therapy, surgical decompression, or both.
- Zoledronic acid and denosumab are both reasonable treatment options for the prevention of skeletal-related events in patients with castration-resistant bone metastases. Denosumab may include the advantage of not requiring renal dosing. Both agents can (rarely) cause ONJ.
- Radium-223 is a novel alpha-emitting radiopharmaceutical that the FDA has approved for the treatment of symptomatic bone metastases in CRPC patients without visceral metastases or bulky lymph node disease. The recommended dose is 50 kBq/kg intravenously every 4 weeks for a total of 6 cycles.

most commonly the lung. Among these are the expression of receptors to various neuroendocrine peptide growth factors, such as somatostatin, chromogranin A, and serotonin, as well as PTHrP and TP53 mutations. These tumors have an uncharacteristic clinical behavior (compared to the usual metastatic prostate cancer), reflected by frequent visceral involvement and rapidly growing soft-tissue metastases. Patients frequently present with subacute and often dramatic changes in their disease pattern characterized primarily by a rapidly growing soft-tissue mass (frequently involving the primary site but also with retroperitoneal masses), rapid development of visceral (especially liver) infiltration, osteolytic (as opposed to osteoblastic) bone metastasis, and a high incidence of parenchymal brain involvement (Fig. 121-9). Histologic evaluation is strongly encouraged. This frequently culminates with the demonstration of a small cell variant or a poorly differentiated neoplasm

on pathology with the presence of neuroendocrine markers on immunostaining (diSant'Agnese, 1995; Nelson et al, 2007). Interestingly, patients with this tumor phenotype either stop expressing PSA in the presence of major tumor progression or even have undetectable PSA levels at the time of this transformation.

Treatment of the neuroendocrine/anaplastic phenotype is often similar to that of patients with other neuroendocrine tumors (e.g., small cell carcinoma of the lung) and usually includes combinations of cisplatin and etoposide (Frank et al, 1995), or the combination of docetaxel plus carboplatin (Aparicio et al, 2013). One group has also reported doxorubicin-containing combinations as modestly efficacious (Papandreou et al, 2002). Radiation therapy is effective and should be considered in cases with bulky disease, with brain metastasis, or when local disease control in critical areas may have a positive impact on quality of life (pain, potential pathologic fractures, and bladder outlet obstruction). A combined chemotherapy and radiation therapy approach is frequently necessary to accomplish maximal disease control. Despite high initial response rates with chemotherapy and radiation treatment, the prognosis of these patients remains poor and is dependent on various factors, including extent and location of metastases. In general, survival is less than 12 months.

KEY POINTS: THE NEUROENDOCRINE/ANAPLASTIC PHENOTYPE

- Rapidly growing disease with the following clinical characteristics should prompt evaluation for the neuroendocrine/anaplastic phenotype: pelvic masses, visceral involvement, osteolytic metastasis with hypercalcemia (associated with high serum PTHrP), and brain metastasis.
- PSA is most commonly undetectable (or levels are low/declining) despite evidence of rapid disease progression. Serum chromogranin A and urine serotonin metabolites might be detected.
- These tumors are invariably unresponsive to hormonal manipulations but are transiently sensitive to radiation therapy and chemotherapy including platinum-etoposide combinations (or platinum-docetaxel combinations).

Clinical Characteristics :

- Rapidly growing soft tissue metastasis (visceral and pelvic masses)
- Relatively low or undetectable serum PSA
- Lytic bone metastasis
- Frequent brain metastasis
- Elevated plasma chromogranin levels
- Hypercalcemia

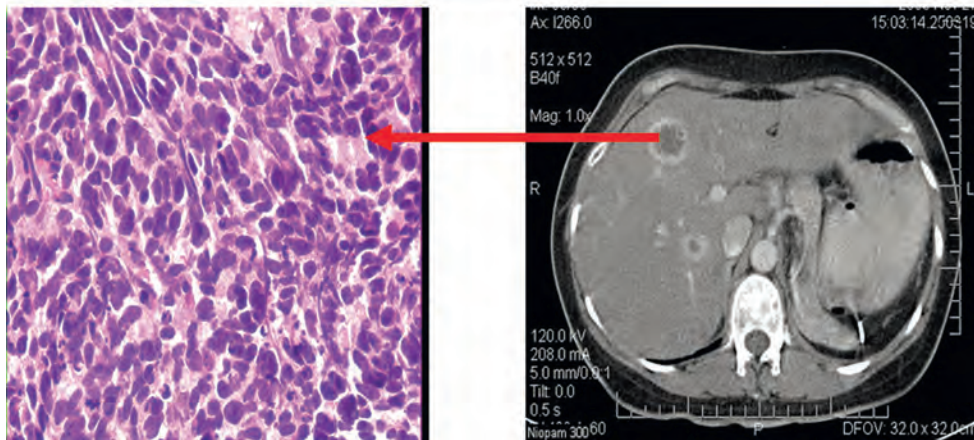


Figure 121-9. Neuroendocrine/anaplastic carcinoma of the prostate: clinical and pathologic features. PSA, prostate-specific antigen.

CONCLUSIONS

With more drugs at our fingertips for the treatment of CRPC than ever before, and an increasing number of novel therapeutic targets being discovered every day, we are still left with several challenges and unanswered questions. First we must determine how these approved and experimental therapies should ideally be sequenced in individual patients with CRPC to maximize the therapeutic benefit. Second, we need to develop strategies to combine these drugs optimally in a rational manner, taking advantage of our understanding of negative feedback loops and alternative pathway activation to overcome resistance to monotherapies. Only prospective trials incorporating biomarker-driven hypotheses will ultimately be able to address these key clinical questions. Thus the collection of tumor biopsy specimens or correlative samples may be essential in identifying novel targets or developing enrichment strategies moving forward. Third, we must design smarter trials with the goal of quickly yet reliably identifying agents that do not hold promise, while enabling those that do to move swiftly to registration studies. Finally we must select our patients more carefully based on clinical or molecular characteristics so as to identify the subset most likely to benefit from a particular therapy. Meanwhile several active agents are currently in phase III development, and some of these therapies are also likely to further expand our therapeutic arsenal in the near future for men with mCRPC.

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The complete reference list is available online at www.expertconsult.com.

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SECTION A Development and Prenatal Urology

122 Embryology of the Genitourinary Tract

John M. Park, MD

Kidney Development

Bladder and Ureter Development

Genital and Reproductive Tract Development

The study of embryology provides a useful foundation for the understanding of definitive human anatomy and various congenital disease processes. During the past few decades, a torrent of molecular information and novel experimental techniques has revolutionized the field of embryology, and the knowledge base continues to expand at an exponential rate. Elucidation of molecular mechanisms of genital development has stemmed from gene analysis, evaluation of disruptions of normal endocrine pathways, congenital abnormalities, and animal models. From the urologic surgeon's perspective, however, the classic, descriptive aspects of anatomic embryology continue to serve as an important reference point from which various congenital problems are solved clinically. The aim of this chapter is to provide a concise presentation of the essential facts of normal genitourinary system development, clarifying the important anatomic features and supplementing them with updated molecular information. Deliberate efforts have been made to separate the ever-expanding molecular information from that of the descriptive, anatomic embryology to keep the main "story" of genitourinary system development clear and understandable from a surgical point of view (Fig. 122-1). To help with visualization of the key events, various schematic drawings are provided. The goal of this chapter is not to provide potential explanations for every congenital defect that might occur in the genitourinary system but to select pertinent examples highlighting the fundamental concepts and principles.

KIDNEY DEVELOPMENT

Early Events

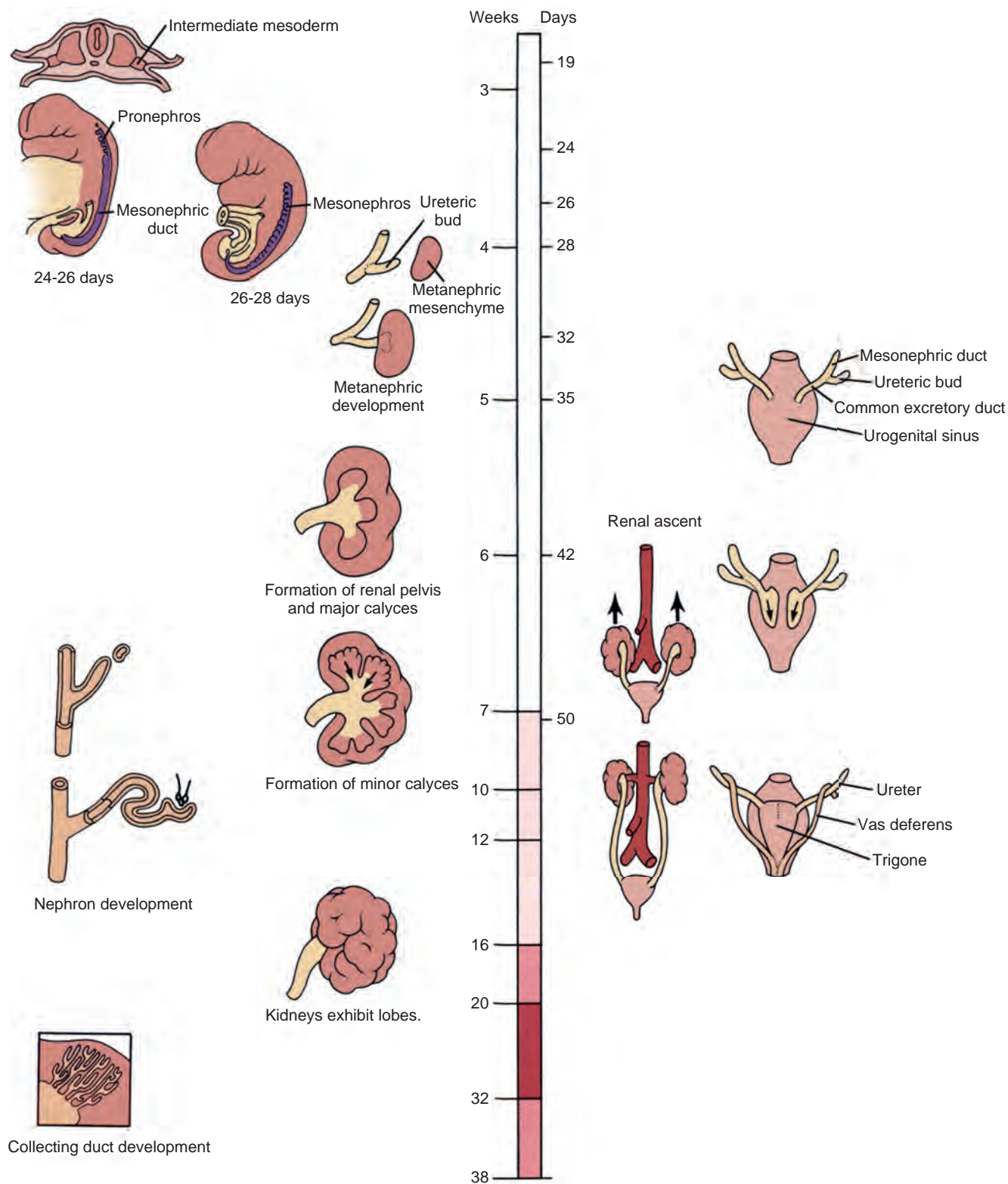
Mammals develop three kidneys in the course of intrauterine life. The embryonic kidneys are, in order of their appearance, the *pronephros*, the *mesonephros*, and the *metanephros*. The first two kidneys regress in utero, and the third becomes the permanent kidney. **Embryologically, all three kidneys develop from the intermediate mesoderm.** As the notochord and neural tube develop, the mesoderm located on either side of the midline differentiates into three subdivisions: *paraxial (somite)*, *intermediate*, and *lateral mesoderm* (Fig. 122-2). As the embryo undergoes transverse folding, the intermediate mesoderm separates away from the paraxial mesoderm and migrates toward the intraembryonic coelom (the future peritoneum). At this time there is a progressive craniocaudal development of the bilateral longitudinal mesodermal masses, called *nephrogenic cords*. Each cord is seen bulging from the posterior wall of the coelomic cavity, producing the *urogenital ridge*.

Pronephros and Mesonephros

The mammalian *pronephros* is a transitory, nonfunctional kidney, analogous to that of primitive fish. In humans, the first evidence of the pronephros is seen late in the third week, and it completely degenerates by the start of the fifth week. The pronephros develops as five to seven paired segments in the region of the future neck and thorax (Fig. 122-3A). Development of the pronephric tubules starts at the cranial end of the nephrogenic cord and progresses caudally. As each tubule matures it immediately begins to degenerate along with the segment of the nephric duct to which the tubules are attached.

The second kidney, the *mesonephros*, is also transient, but in mammals it serves as an excretory organ for the embryo while the definitive kidney, the *metanephros*, begins its development (Fig. 122-3B and C). There is a gradual transition from the pronephros to the mesonephros at about the 9th and 10th somite levels. Development of the *nephric ducts* (also called the *wolffian ducts*) precedes the development of the mesonephric tubules. The nephric ducts can be seen as a pair of solid longitudinal tissue condensations at about the 24th day, developing parallel to the nephrogenic cords in the dorsolateral aspect of the embryo. Its blind distal ends grow toward the primitive cloaca and soon fuse with it at about the 28th day. As the ducts fuse with the cloaca they begin to form a lumen at the caudal end. This process of canalization then progresses cranially in a reverse direction, transforming the solid tissue condensations into the definitive nephric ducts with excretory capability. Soon after the appearance of the nephric ducts during the 4th week, mesonephric vesicles begin to form. Initially, several spheric masses of cells are found along the medial side of the nephrogenic cords at the cranial end. This differentiation progresses caudally and results in the formation of 40 to 42 pairs of mesonephric tubules, but only about 30 pairs are seen at any one time because the cranially located tubules start to degenerate starting at about the 5th week. By the 4th month, the human mesonephros has almost completely disappeared, except for a few elements that persist into maturity as part of the reproductive tract. **In males, some of the cranially located mesonephric tubules become the efferent ductules of the testes. The epididymis and vas deferens are also formed from the nephric (wolffian) ducts. In females, remnants of cranial and caudal mesonephric tubules form small, nonfunctional mesosalpingeal structures termed the *epoöphoron* and *paroöphoron*.**

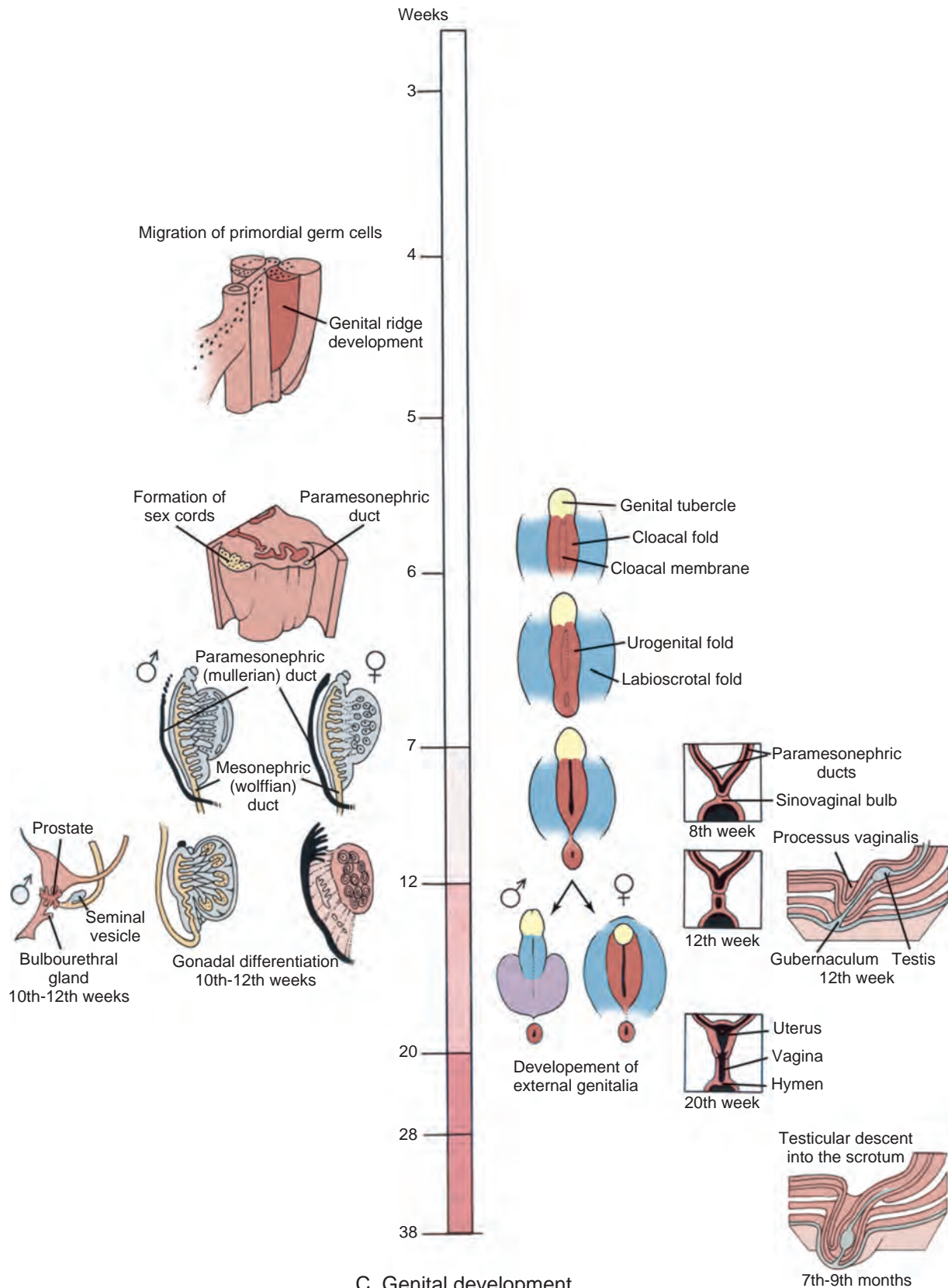
The mesonephric tubules differentiate into excretory units that resemble an abbreviated version of an adult nephron. Shortly after the cell clusters are formed they develop lumens and take the shape



A. Kidney development

B. Ureter and bladder development

Figure 122-1. A to C, Timeline and overview of genitourinary system development. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)



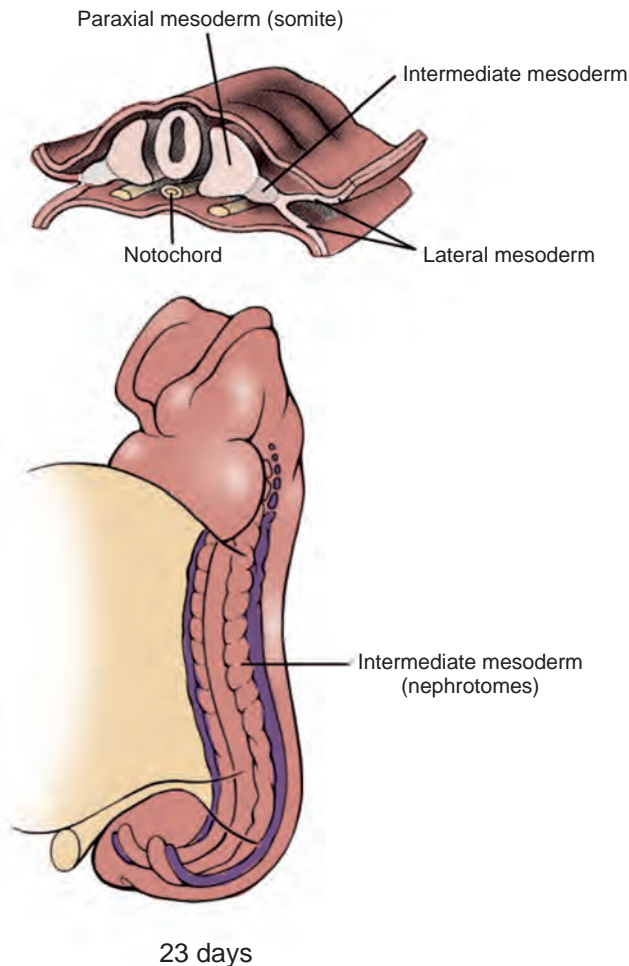


Figure 122-2. The intermediate mesoderm gives rise to paired, segmentally organized nephrotomes from cervical to sacral region. Cervical nephrotomes are formed early during the fourth week and are collectively referred to as the *pronephros*. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

of vesicles. As the vesicle elongates, each end curves in an opposite direction to form an S-shaped tubule. The lateral end forms a bud that connects with the nephric duct. The medial end lengthens and enlarges to form a cup-shaped sac, which eventually wraps around a knot of glomerular capillaries to form a renal corpuscle. The tuft of glomerular capillaries originating from a branch of the dorsal aorta invades the developing glomerulus; an efferent arteriole empties into a subcardinal sinus.

Metanephros

The definitive kidney, or the *metanephros*, forms in the sacral region as a pair of new structures, called the *ureteric buds*, sprout from the distal portion of the nephric duct and come in contact with the condensing blastema of *metanephric mesenchyme* at about the 28th day (Fig. 122-4). The ureteric bud penetrates the metanephric mesenchyme and begins to divide dichotomously. The tip of the dividing ureteric bud, called the *ampulla*, interacts with the metanephric mesenchyme to induce formation of future nephrons via mesenchymal-epithelial interaction. As the ureteric bud divides and branches, each new ampulla acquires a caplike condensation of metanephric mesenchyme, thereby giving the metanephros a lobulated appearance (Fig. 122-5).

The ureteric bud and metanephric mesenchyme exert reciprocal inductive effects toward each other, and the proper differentiation of these primordial structures depends on these inductive signals

(see the discussion of [molecular mechanisms of kidney development](#), later). The metanephric mesenchyme induces the ureteric bud to branch and divide, and in turn the ureteric bud induces the metanephric mesenchyme to condense and undergo mesenchymal-epithelial conversion. The **nephron**, which consists of the glomerulus, proximal tubule, loop of Henle, and distal tubule, is thought to derive from the metanephric mesenchyme, while the collecting system, consisting of collecting ducts, calyces, pelvis, and ureter, is formed from the ureteric bud (Fig. 122-6).

In principle, all nephrons are formed in the same way and can be classified into fairly well-defined developmental stages (Larsson et al, 1983) (Fig. 122-7). The metanephric mesenchyme first condenses to form a four- to five-cell layer condensate around the ampulla of the advancing ureteric bud. Near the interface of the ampulla and its adjacent ureteric branch, a cluster of cells separates from the condensate and forms an oval mass, called a *pretubular aggregate*. An internal cavity forms within the pretubular aggregate, at which point the structure is called a *renal vesicle* (stage I). Cells of the stage I renal vesicle are tall and columnar and are stabilized by their attachments to the newly formed basement membrane. It has not yet established a contact with the ampulla of the ureteric bud, but it subsequently forms a luminal connection. Multipotential precursors residing in renal vesicles ultimately give rise to all the epithelial cell types of the nephron (Herzlinger et al, 1992). Nephron segmentation into glomerular and tubular domains is initiated by the sequential formation of two clefts in the renal vesicle (stage II). Creation of a lower cleft, termed the *vascular cleft*, precedes formation of a comma-shaped body. Generation of an upper cleft in the comma-shaped body precedes formation of an S-shaped body. At this stage, the cup-shaped glomerular capsule is recognized in the lowest limb of the S-shaped tubule. Epithelial cells lining the inner wall of this cup will comprise the visceral glomerular epithelium, or podocyte layer. Cells lining the outer wall of the cup will form parietal glomerular epithelium, which lines the Bowman capsule. The glomerular capillary tuft is formed via recruitment and proliferation of endothelial and mesangial cell precursors. The rest of the S-shaped tubule develops into the proximal tubule, the loop of Henle, and the distal tubule. When the cup-shaped glomerular capsule matures into an oval structure, the nephron has now passed into stage III of development. Now the nephron can be divided into identifiable proximal and distal tubules. The stage IV nephron is characterized by a round glomerulus that closely resembles the mature renal corpuscle. The morphology of the proximal tubule resembles that of a mature nephron, whereas the distal segments are still primitive. In some species, such as rodents, all stages of nephron development are present at birth, whereas in others, such as humans, all nephrons at birth are in varying steps of stage IV. Mesenchymal cells that do not become tubular epithelium give rise to interstitial stromal cells, which differentiate into a diverse population including fibroblasts, lymphocyte-like cells, and pericytes. Overall, these events are reiterated throughout the growing kidney so that older, more differentiated nephrons are located in the inner part of the kidney near the juxtamedullary region and newer, less differentiated nephrons are found at the periphery (Fig. 122-8). In humans, although renal maturation continues to take place postnatally, nephrogenesis is completed before birth at around 32 to 34 weeks of gestation.

Collecting System

The dichotomous branching of the ureteric bud determines the eventual pelvicalyceal patterns and their corresponding renal lobules (Cebrian et al, 2004) (Fig. 122-9). In humans, the first nine branch generations are formed by approximately 15 weeks' gestation. By 20 to 22 weeks, ureteric bud branching is completed. Thereafter, collecting duct development occurs by extension of peripheral branch segments. Between 22 and 24 weeks of human fetal gestation the peripheral (cortical) and central (medullary) domains of the developing kidney are established. The renal cortex, which represents 70% of total kidney volume at birth, becomes

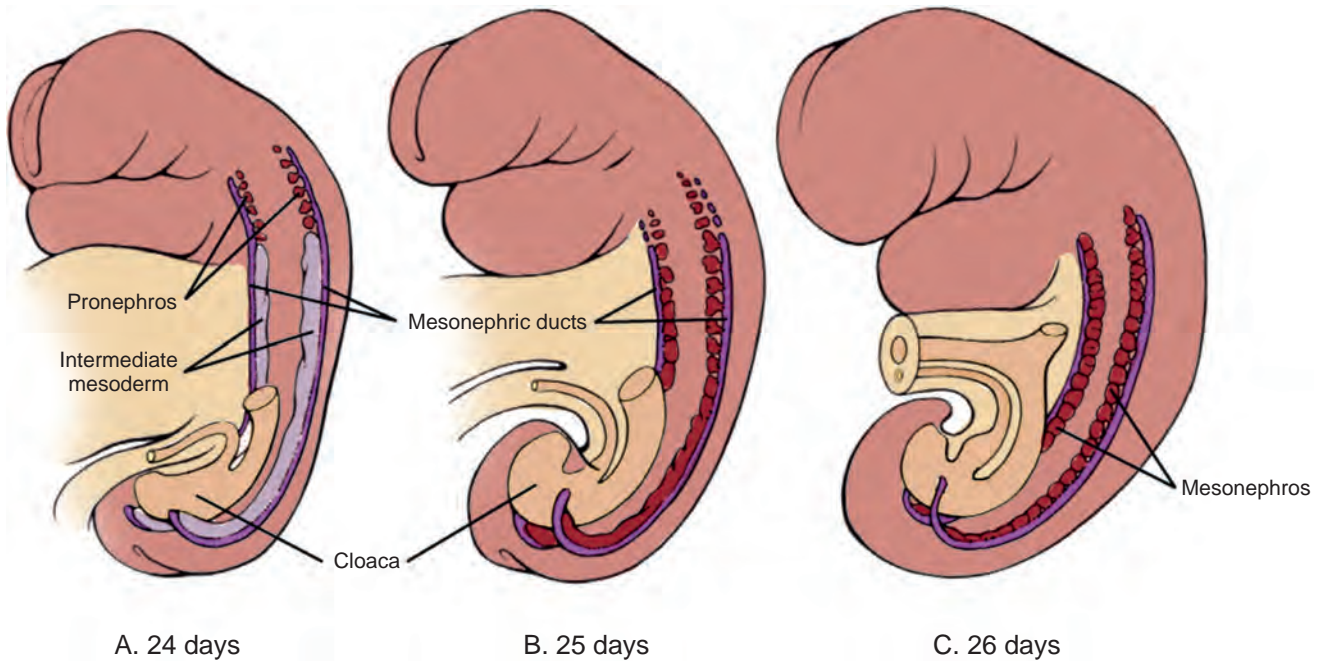


Figure 122-3. Development of pronephros and mesonephros. A, Pronephros develops in each of five to seven cervical segments, but this primitive renal structure degenerates quickly during the fourth week. The (meso)nephric ducts first appear on day 24. B and C, Mesonephric vesicles and tubules form in a craniocaudal direction throughout the thoracic and lumbar regions. The cranial pairs degenerate as caudal pairs develop, and the definitive mesonephros contains about 20 pairs confined to the first three lumbar segments. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

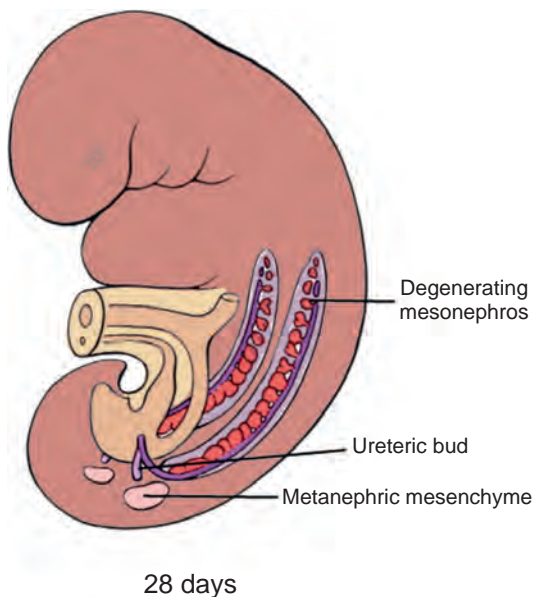


Figure 122-4. Metanephric mesenchyme condenses from the intermediate mesoderm during the early part of the fifth week and comes into contact with the ureteric bud, an outgrowth of the nephric duct, while the cranial mesonephros continues to degenerate. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

organized as a relatively compact, circumferential rim of tissue surrounding the periphery of the kidney. The renal medulla, which represents 30% of total kidney volume at birth, has a modified cone shape with a broad base contiguous with cortical tissue. The apex of the cone is formed by convergence of collecting ducts in the inner

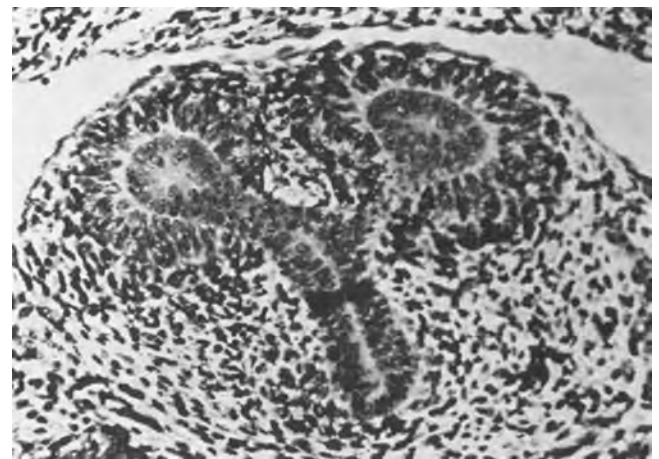


Figure 122-5. The ureteric bud divides to form enlarged tips, called ampullae, around which the metanephric mesenchyme condenses and begins nephron differentiation. The remaining mesenchymal cells remain stromal and continue to interact with tubular mesenchymal cells and dividing ureteric bud epithelial cells. (From Potter EL. Normal and abnormal development of the kidney. Chicago: Year Book Medical Publishers; 1972.)

medulla and is termed the *papilla*. Distinct morphologic differences emerge between collecting ducts located in the medulla compared with those located in the renal cortex. Medullary collecting ducts are organized into elongated linear arrays that converge centrally in a region devoid of glomeruli. In contrast, collecting ducts located in the renal cortex continue to induce metanephric mesenchyme. The most central segments of the collecting system, formed from the first five generations of ureteric bud branching, undergo

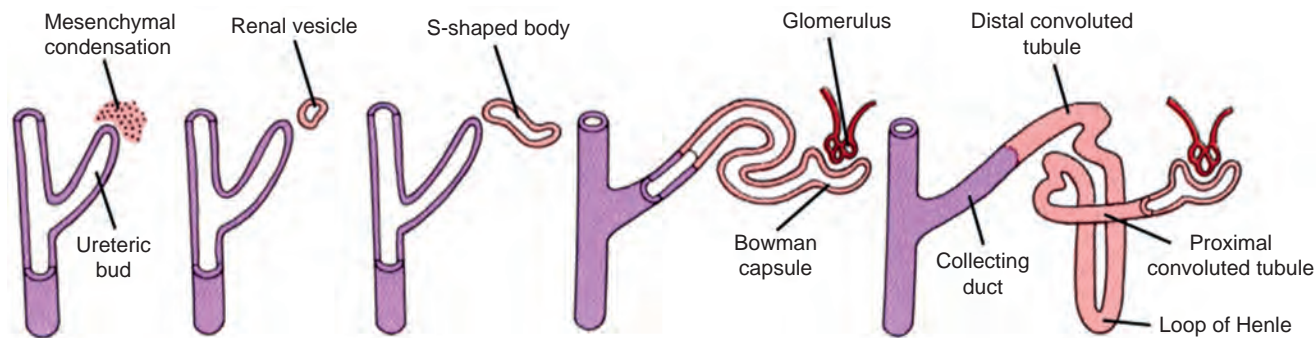


Figure 122-6. Development of the renal collecting ducts and nephrons. The tip of the dividing ureteric bud induces the metanephric mesenchyme (*in pink*) to condense, which then differentiates into a renal vesicle. This vesicle coils into an S-shaped tubule and ultimately forms a Bowman capsule as well as the proximal convoluted tubules, distal convoluted tubules, and loops of Henle. The ureteric bud (*in purple*) contributes to the formation of collecting ducts. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

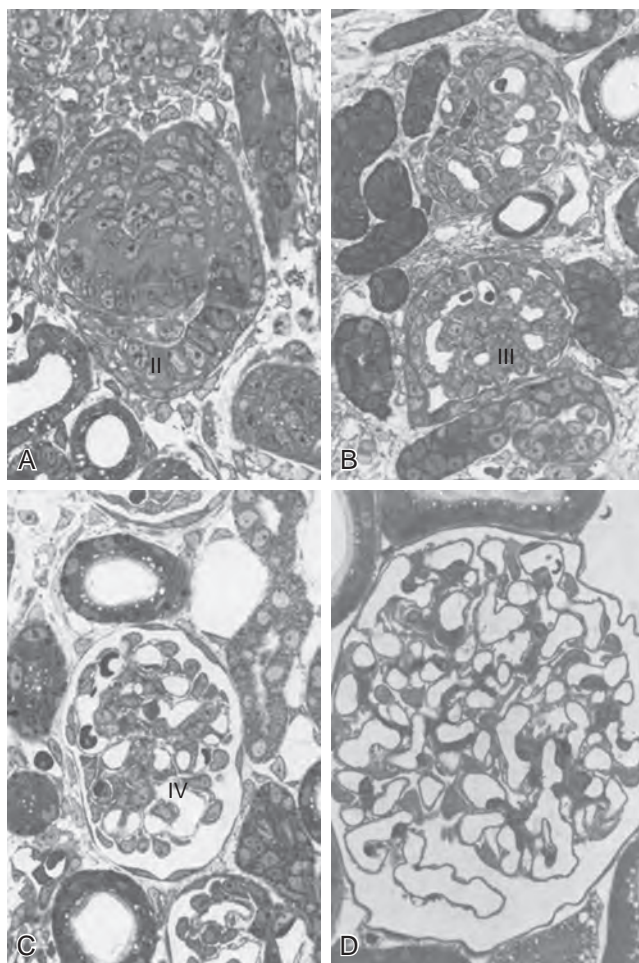


Figure 122-7. Nephron development as seen from a renal cortex of a 3-day-old rat. A, A developing nephron with S-shaped body (II). B, Oval glomeruli (III). C, Nephron now resembles that of mature tubules and glomeruli (IV). D, Mature superficial glomerulus from adult rat kidney. (From Larsson L, Maunsbach AB. The ultrastructural development of the glomerular filtration barrier in the rat kidney: a morphometric analysis. *J Ultrastruct Res* 1980;72:392.)

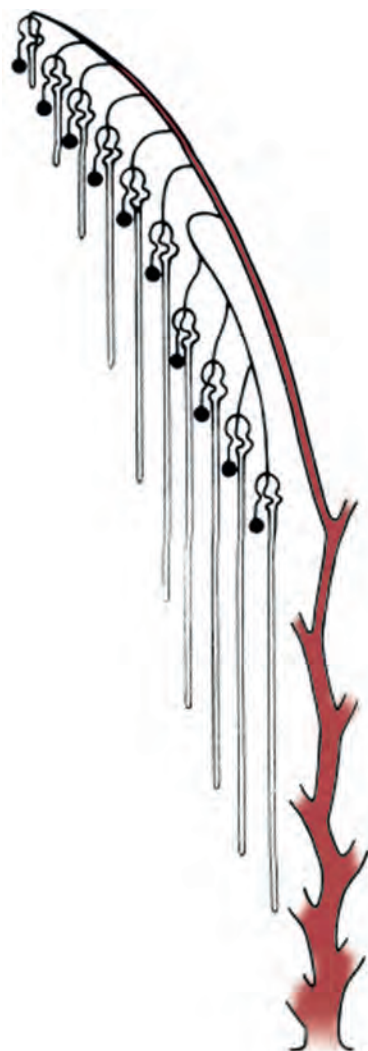


Figure 122-8. Schematic representation of progressive nephron differentiation. Older, more differentiated nephrons are located in the inner part of the kidney near the juxtamedullary region; newer, less differentiated nephrons are found at the periphery. (From Potter EL. Normal and abnormal development of the kidney. Chicago: Year Book Medical Publishers; 1972.)

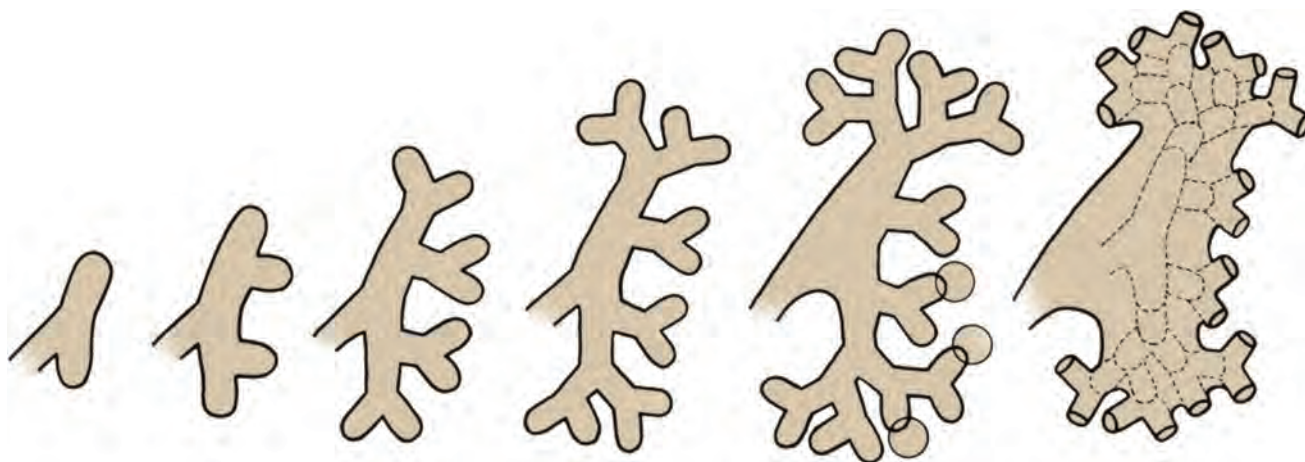


Figure 122-9. Dichotomous branching of the ureteric bud and subsequent fusion of the ampullae to form the renal pelvis and calyces. Circles indicate possible sites of infundibular development among the third, fourth, or fifth generations of branches and their subsequent expansions to give rise to the calyces. (From Potter EL. Normal and abnormal development of the kidney. Chicago: Year Book Medical Publishers; 1972.)

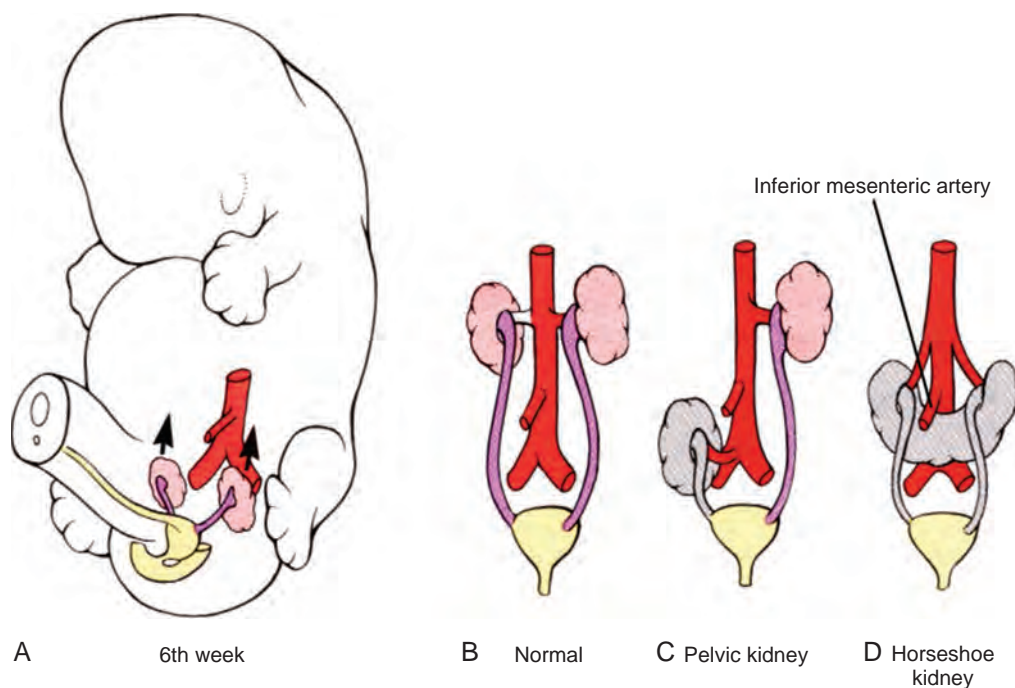


Figure 122-10. Normal and abnormal ascent of the kidneys. A and B, The metanephros normally ascends from the sacral region to its definitive lumbar location between the sixth and ninth weeks. C, Rarely, a kidney may fail to ascend, resulting in a pelvic kidney. D, If the inferior poles of the kidneys fuse before ascent, the resulting horseshoe kidney does not ascend to a normal position owing to entrapment by the inferior mesenteric artery. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

remodeling by increased growth and dilatation of these tubules to form the pelvis and calyces.

Renal Ascent

Between the sixth and ninth weeks the kidneys ascend to a lumbar site just below the adrenal glands (Fig. 122-10). The precise mechanism responsible for renal ascent is not known, but it is speculated that the differential growth of the lumbar and sacral regions of the embryo plays a major role. As the kidneys migrate they are

vascularized by a succession of transient aortic sprouts that arise at progressively higher levels. These arteries do not elongate to follow the ascending kidneys but instead degenerate and are replaced by successive new arteries. The final pair of arteries forms in the upper lumbar region and becomes the definitive renal arteries. Occasionally, a more inferior pair of arteries persists as accessory lower pole arteries. When the kidney fails to ascend properly, its location becomes ectopic. If its ascent fails completely, it remains as a pelvic kidney. The inferior poles of the kidneys may also fuse, forming a horseshoe kidney that crosses over the ventral side of the aorta.

During ascent the fused lower pole becomes trapped under the inferior mesenteric artery and thus does not reach its normal site. Rarely, the kidney fuses to the contralateral one and ascends to the opposite side, resulting in a cross-fused ectopy.

Molecular Mechanism of Kidney Development

The details of inductive interactions among metanephric mesenchyme, ureteric bud epithelia, and more recently the stroma are becoming clearer and provide insights into the complex regulatory mechanisms underlying renal development. **Formation of renal tubules and the collecting system occurs sequentially and requires dynamic interactions among epithelial, mesenchymal, and stromal cells.** Many of the early events in embryonic kidney development were first elucidated by manipulating lower vertebrate embryos and by using a mammalian in vitro organ culture system. Grobstein's pioneering work in the 1950s led to an organ culture technique (Grobstein, 1956) whereby the metanephric mesenchyme is separated from the ureteric bud during the early part of kidney development and grown in vitro on a filter. An inducer tissue, such as ureter or spinal cord, cultured on the opposite side of the filter then provides the inductive signal (Fig. 122-11). This ingenious experimental approach has established the kidney as a model system for studying the role of epithelial-mesenchymal interaction in organ development. The development of many other organs, including lung, salivary glands, gonads, prostate, and bladder, also require epithelial-mesenchymal

interaction for the controlled differentiation and proliferation of tissues.

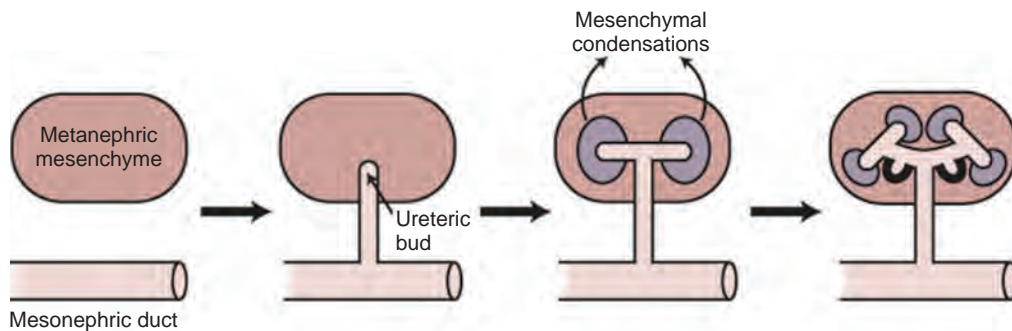
Formation of Nephric Ducts

The first recognizable event in renal development may be the formation of nephric ducts within the region of the intermediate mesoderm. The molecular signals responsible for this early event, in which seemingly unorganized mesenchymal cells aggregate to become an epithelial duct, remain essentially unknown, but details are beginning to emerge. The early intermediate mesoderm destined to become nephric ducts is distinguished by expression of the transcription factors LIM1, PAX2, and SIM1, but only LIM1 appears to be absolutely essential for nephric duct formation (Shawlot and Behringer, 1995). PAX2 may be important for maintaining other marker gene expression in the nephric ducts (Torres et al, 1995). Available data suggest a model in which few opposing secreted factors from the surrounding tissues cumulatively restrict LIM1 expression to the intermediate mesoderm. LIM1 then activates PAX2 expression to further orchestrate the formation of nephric ducts.

Ureteric Bud Outgrowth toward Metanephric Mesenchyme

The outgrowth of the ureteric bud from the nephric duct and its invasion into the condensing blastema of metanephric mesenchyme is a crucial initiating event in the development of the adult

A In Vivo Development



B In Vitro Transfilter Assay

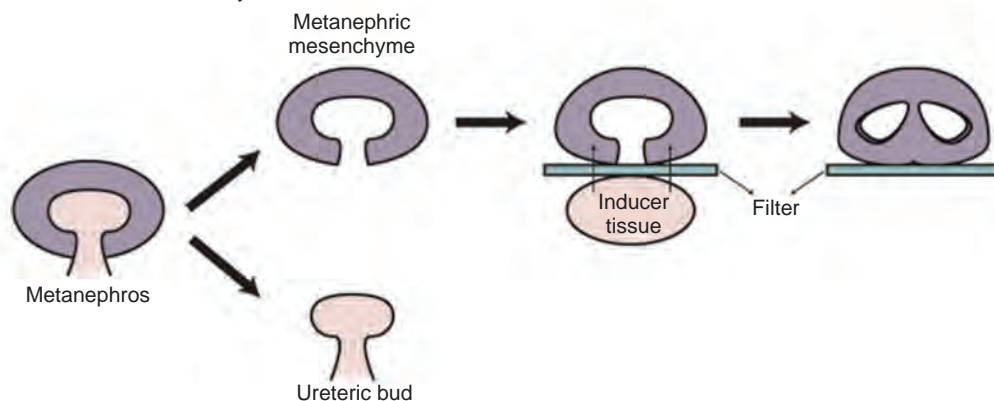


Figure 122-11. Schematic representation of in vivo kidney development (A) and an in vitro transfilter organ culture system of Grobstein (B). At an early stage of renal development, the metanephric mesenchyme is separated from the ureteric bud and cultured on a filter. If there is an inducer tissue grown on the opposite side of the filter, such as ureter and spinal cord, the metanephric mesenchyme will continue to differentiate into nephron structures. In the absence of inducer tissue, the metanephric mesenchyme will degenerate via apoptosis. (Modified from Vainio S, Muller U. Inductive tissue interactions, cell signaling, and the control of kidney organogenesis. *Cell* 1997;90:975.)

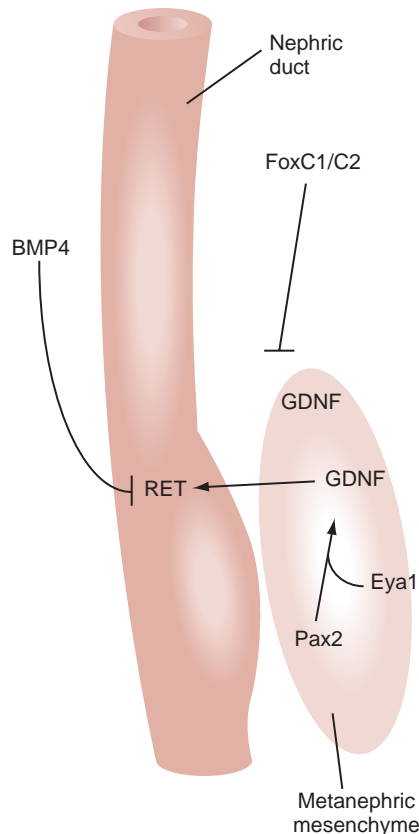


Figure 122-12. Inductive interactions during early kidney development. Glial cell line-derived neurotrophic factor (GDNF) is secreted from the metanephric mesenchyme and activates the RET receptor tyrosine kinase in the ureteric bud epithelium. The expression and localization of GDNF are positively regulated by *Eya1* and *Pax2* and negatively by *FoxC* transcription factors. The inducibility of nephric ducts to GDNF signaling is restricted by the action of bone morphogenetic protein-4 (BMP4). (Modified from Dressler GR. Tubulogenesis in the developing mammalian kidney. *Trends Cell Biol* 2002;12:390–5.)

kidney (*metanephros*). Many candidate genes have been identified to play a critical role in this process (see <http://golgi.ana.ed.ac.uk/kidhome.html>). In particular, several lines of experimental evidence have revealed a crucial role of the RET-GDNF-GFR α 1 pathway in the ureteric bud outgrowth (Fig. 122-12). Glial cell line-derived neurotrophic factor (GDNF) is a secreted peptide expressed in the metanephric mesenchyme that activates the RET receptor, which is expressed along the nephric duct. GDNF activation of RET requires the glycosylphosphatidylinositol (GPI)-linked protein GFR α 1, which is expressed in both metanephric mesenchyme and nephric duct. Gene knockout mutations in *Ret*, *GDNF* (Moore et al, 1996; Pichel et al, 1996; Sánchez et al, 1996), and *GFR α 1* (Cacalano et al, 1998) inhibit ureteric bud outgrowth. In organ culture systems, recombinant GDNF is sufficient to induce ectopic ureteric bud outgrowth (Sainio et al, 1997) (Fig. 122-13). However, the competence of the nephric duct to respond to GDNF is restricted along the anteroposterior axis. This anteroposterior restriction might be mediated by suppressors of RET signaling within the surrounding tissue, such as bone morphogenetic protein-4 (BMP4). Mice that are deficient for BMP4 show more broadened ureteric buds and/or secondary anterior buds, suggesting that full BMP4 activity is required to limit RET signaling to the caudal aspect adjacent to the developing metanephric mesenchyme (Miyazaki et al, 2000). Similarly, in organ culture, BMP4 can suppress the activity of GDNF to induce ectopic ureteric bud formation

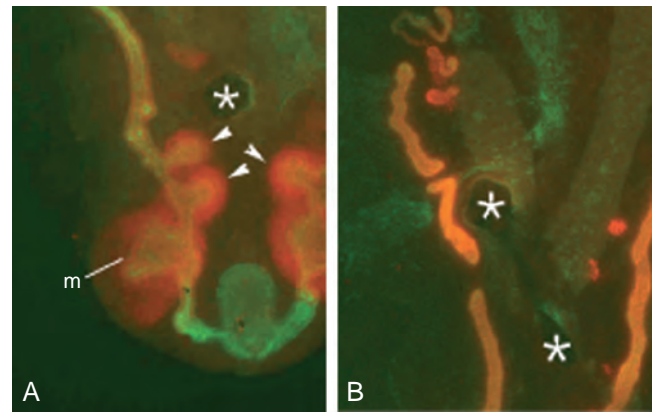


Figure 122-13. A, Stimulation of ectopic ureteric buds by glial cell line-derived neurotrophic factor (GDNF). To determine whether GDNF is sufficient to promote outgrowth of nephric duct epithelial cells, heparin acrylamide beads preadsorbed with recombinant GDNF (asterisk) were placed between two nephric duct organ cultures. The native metanephros (m) is seen anteriorly. GDNF alone induces multiple ectopic ureteric buds in the posterior nephric ducts (arrowheads). B, However, the effect of GDNF is suppressed when BMP4 is also added to the beads (asterisks). Cultures were stained with anti-cytokeratin (green) and anti-Pax2 (red) antibodies. (From Dressler GR. Tubulogenesis in the developing mammalian kidney. *Trends Cell Biol* 2002;12:390–5.)

(Brophy et al, 2001). Proper positioning of the ureteric bud is also controlled by the localized expression of GDNF within the metanephric mesenchyme. Both positive and negative regulators have been described for GDNF localization. Homozygous mutation of a transcription factor *Eya1* causes failure of ureteric bud outgrowth, and its metanephric mesenchyme lacks GDNF expression, suggesting that *Eya1* regulates GDNF expression (Xu et al, 1999). In humans, haploinsufficiency of *Eya1* results in a dominantly inherited disorder called *branchio-oto-renal syndrome*, which involves kidney and urinary tract anomalies (Abdelhak et al, 1997). Expression of PAX2 in the metanephric mesenchyme is also required for GDNF activation (Brophy et al, 2001). GDNF expression is also suppressed at the anterior boundary of the metanephric mesenchyme through the concerted action of the *FoxC1* and *FoxC2* transcription factors (Kume et al, 2000). Mutations in either *Fox* gene result in an expansion of GDNF expression and the formation of ectopic ureteric buds. Most *FoxC1* homozygous mutants have duplex kidneys, in which the upper ureter is dilated and connects aberrantly to ectopic nephric duct derivatives in males such as seminal vesicles and vas deferens. In the developing kidneys, *Slit2* is primarily expressed in the nephric duct, whereas *Robo2* is expressed in the metanephric mesenchyme (Piper et al, 2000). Mice deficient in *Slit2* or *Robo2* exhibit ectopic ureteric bud formation, multiple ureters and hydroureter, and anterior expansion of GDNF expression (Grieshammer et al, 2004). *SPRY1* negatively regulates GDNF-RET signaling. Loss of *Spry1* function in mice results in renal malformations, including multiple ureters, duplex kidneys and hydroureter, and increased expression of GDNF in the metanephric mesenchyme (Basson et al, 2006). The data therefore suggest that multiple factors regulate, both positively and negatively, the precise timing and localization of GDNF, which then functions as a guidance cue to activate RET.

Ureteric Bud Branching

Once the ureteric bud has contacted the condensing metanephric mesenchyme it undergoes a dichotomous branching morphogenesis (Cebrian et al, 2004). Many of the same factors that regulate the initial outgrowth of the ureteric bud also appear to be essential for the subsequent branching of the ureteric bud.

Ureteric bud branching is positively regulated by genetic and nutritional factors. PAX2, a paired-box type transcription factor that is mutated in humans with renal coloboma syndrome, is a positive regulator of ureteric bud branching. During renal development, *Pax2* is expressed in the nephric duct, ureteric bud, and metanephric blastema induced by ureteric bud branch tips. Mice with *Pax2* mutation exhibit decreased ureteric bud branching and renal hypoplasia (Porteous et al, 2000). Ureteric branching is also positively regulated by vitamin A and its retinoic acid receptor signaling, which promote Ret expression. *Rar α* and *Rar β 2* are expressed in stromal cells surrounding Ret-expressing ureteric bud branch tips. Mice deficient in these receptors exhibit a decreased number of ureteric bud branches and diminished expression of Ret (Batourina et al, 2001). Certain markers such as Wnt11 might already be compartmentalized to opposing poles of the dilated bud tips, even before a morphologic branch point is evident (Pepicelli et al, 1997). In mice deficient for the homeobox gene *Emx2* (Miyamoto et al, 1997), ureteric bud outgrowth into the metanephric mesenchyme appears normal but the leading edge never dilates and branching is suppressed. Thus ureteric development is arrested before the first branching event, and the resulting metanephric mesenchyme does not express any markers for induction. Similarly, mice with mutation of *Sall1* exhibit developmental arrest just after ureteric bud outgrowth and before dilation of the leading edge (Nishinakamura et al, 2001). In normal murine embryos, *Sall1* is expressed in the metanephric mesenchyme. Thus *Sall1* might control mesenchyme-derived signals that are necessary for ureteric bud dilation and the early branch point determination. Clearly, the pattern of ureteric bud branching and the expression of ureteric bud-specific genes are influenced by the metanephric mesenchyme. Indeed, the heterologous mesenchyme derived from lung primordia can not only change the pattern of ureteric bud branching to that of lung epithelia but also induce the ureteric bud tissues to express lung-specific genes (Lin et al, 2001). Studies have demonstrated that BMP/activin-like kinase-3 (ALK3) signaling negatively regulates early ureteric bud branching in vivo (Hartwig et al, 2008). The cell surface receptor ALK3 binds BMP2 and BMP4 with high affinity and is expressed in the nephric duct. Inactivation of ALK3 changes the pattern of primary ureteric bud branching from bifid to trifid and increases the number of first- and second-generation branches. These defects are associated with decreased formation of subsequent branch generations, resulting in a decreased complement of collecting ducts. These observations suggest that the pattern of early ureteric bud branching is a critical determinant of subsequent branching morphogenesis. Thus ureteric bud epithelial branching morphogenesis is controlled by both intrinsic and extrinsic factors working in concert to generate a kidney-specific branching pattern.

Tubulogenesis

Classic tissue recombination experiments focused almost exclusively on the relationship between metanephric mesenchymal cells and ureteric bud epithelial cells. It is now clear that at least three cell types are involved in the control of renal development: the ureteric bud tip cells, the condensed mesenchymal cells, and the stromal or interstitial mesenchymal cells (Fig. 122-14). It is not known whether the mesenchyme is a homogeneous cell population before its interaction with the ureteric bud. It is clear, however, that once induced by the ureteric bud the metanephric mesenchyme patterns itself into at least two different cell populations, a tubular one and a stromal one. The tubular cell population is thought to derive from mesenchymal cells in direct contact with the ureteric bud ampulla (Vainio et al, 1989; Stark et al, 1994; Torres et al, 1995), whereas the stromal cell population surrounds the tubular cells (Hatini et al, 1996). Once the mesenchyme has been patterned, the cells in the tubular zone undergo morphogenesis to become renal tubular epithelial cells. There is evidence that this process is dependent not only on signals from the ureteric bud but also on signals from the mesenchyme itself. One of these autocrine signals may be Wnt4, whose expression is induced in cells of the

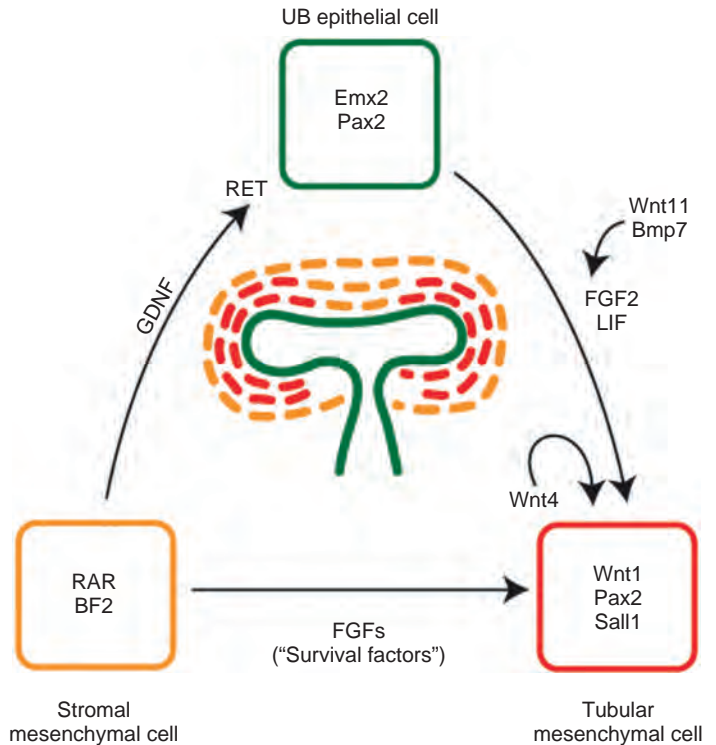


Figure 122-14. Cell-cell interactions promote nephrogenesis. Three major cell types—ureteric bud (UB) epithelial cells, condensing tubular mesenchymal cells, and stromal mesenchymal cells—are thought to play a critical role. At the UB tips, cells express unique markers such as *Emx2* and *Pax2*. The stromal cell lineage is marked by expression of retinoic acid receptors (RAR) and BF2. Presence of *Pax2*, *Wnt1*, and *Sall1* appears to be important for continued branching morphogenesis of the UB. *Wnt4* is activated in the tubular mesenchymal cells by the invading UB epithelial cells and stimulates the development of polarized epithelium in an autocrine fashion. Finally, fibroblast growth factors (FGFs), such as FGF2, along with leukocyte-inhibitory factor (LIF), may be critical as survival factors for the developing renal tubular epithelial cells. (Modified from Dressler GR. Tubulogenesis in the developing mammalian kidney. *Trends Cell Biol* 2002;12:390–5.)

tubular zone on interaction with the ureteric bud. In *Wnt4* gene knockout mice the ureteric bud forms and invades the metanephric mesenchyme, but subsequent development of epithelial tubules is abolished (Stark et al, 1994). This suggests that two signals are essential for renal tubule formation—initial ureteric bud-derived signals activating *Wnt4* expression in the metanephric mesenchyme and *Wnt4* itself as a mesenchymal autocrine signal. Signals from the stromal cell population also contribute to tubule formation, because tubulogenesis is perturbed in *Bf2* gene knockout mice (Hatini et al, 1996). The discovery that *Wnt4* acts as a downstream signal during the induction cascade leading to renal tubulogenesis leads to the question regarding the nature of the initial ureteric bud-derived signals. In vitro data suggest a role for fibroblast growth factor-2 (FGF2) and other uncharacterized factors secreted by the ureteric bud (Karavanova et al, 1996). Candidate molecules that may cooperate with FGF2 are *Wnt11* and *BMP7* (Kispert et al, 1996; Vukicevic et al, 1996). Localization of RET protein to the ureteric bud tips is reinforced by both GDNF (Pepicelli et al, 1997) and signals emanating from surrounding stromal cells. For example, retinoic acid receptors are expressed in the stromal cells and are required for stromal cell-mediated signaling to maintain high levels of RET expression in the bud tips (Mendelsohn et al, 1999; Batourina et al, 2001). Consistent with the role of retinoic acid receptors in maintaining RET expression in the dividing ureteric

bud, rats with vitamin A deficiency have smaller kidneys and fewer nephrons (Lelièvre-Pégurier et al, 1999). The cellular crosstalk among stromal, mesenchymal, and ureteric bud cells is further highlighted by gain- and loss-of-function experiments involving FGFs and BMPs. *Fgf7* null mutant mice have fewer branch points and correspondingly fewer nephrons, whereas ectopic FGF7 in organ culture can stimulate branching (Qiao et al, 1999). FGF1 and FGF10 affect elongation of the ureteric bud stalk before the branch-point decision is made (Qiao et al, 2001). Null mutations in *Bmp7* are associated with even more severe phenotypic anomalies, exhibiting limited branching morphogenesis and complete renal developmental arrest. Yet it is difficult to assess how FGFs and BMPs exert their collective effects on branching given the interplay among all the cell types present in the early kidney (Dudley et al, 1999). In addition to the proteins just mentioned, a growing list of growth factors, secreted peptides, and their receptors have been implicated in the control of branching morphogenesis, most by using a variety of in vitro model systems (Pohl et al, 2000; Davies, 2001). For many of these factors, however, genetic studies have not proved conclusive in assigning specific functional roles during ureteric bud branching in vivo, either because of potential redundancies or embryonic lethalties before the onset of kidney development. Nevertheless, the role of these factors in the renal development must be considered.

Mesenchymal-Epithelial Conversion

The inductive signals emanating from the ureteric bud promote condensation of the metanephric mesenchymal cells around the ureteric bud tips and subsequent tubulogenesis. Mice with null mutations of *Pax2* or *Wt1* fail to exhibit ureteric bud outgrowth, and in both cases the metanephric mesenchyme does not respond to induction even when recombined with strong inducers in vitro (Kreidberg et al, 1993; Brophy et al, 2001). The establishment of glomerular versus tubular cell fates is dependent on negative feedback between *Wt1* and *Pax2* (Ryan et al, 1995). During early kidney development, the expression domain of *Pax2* is complementary to that of *Wt1* in S-shaped bodies. *Wt1* expression is restricted to glomerular epithelial precursors (Pelletier et al, 1991), whereas *Pax2* expression is restricted to the portion that gives rise to tubular epithelial precursors of the proximal and distal nephron segments and later repressed in differentiated tubular epithelium (Dressler and Douglass, 1992). Evidence in support of Wnt proteins as mesenchyme inducers has been gained from in vitro induction assays using Wnt-expressing cell lines (Herzlinger et al, 1994; Kispert et al, 1998). Of the *Wnt* mutants examined to date, only *Wnt4*, which is expressed in the mesenchyme and not the ureteric bud, is crucial for propagation of the inductive signals. Although *Wnt4* mutant mesenchyme is able to aggregate in response to ureteric bud contact, these mutant aggregates do not form polarized epithelia. Rat ureteric bud cells secrete tubulogenic factors, such as leukocyte-inhibitory factor (LIF), which, together with FGF2, appears to stimulate growth and tubulogenesis in vitro (Plisov et al, 2001). Once induced to form aggregates, metanephric mesenchyme becomes polarized into an early renal vesicle. This vesicle is closely associated with the branching ureteric bud and will eventually connect to the ureteric bud epithelium to form a continuous tubule. Profound changes take place in the expression of cell adhesion molecules such as cadherins. Shortly after induction, metanephric mesenchyme expresses R-cadherin, cadherin-6, and E-cadherin, along with suppression of the mesenchyme-specific cadherin-11. Both R-cadherin and cadherin-6 mutants show defects in the rate of mesenchymal condensation and polarization (Mah et al, 2000; Dahl et al, 2002). Some renal vesicles in cadherin-6 mutants also fail to fuse to the ureteric bud epithelia, resulting in “dead end” tubules and a subsequent loss of nephrons.

Renal Vascular Development

The origin of intrarenal vasculature is not completely understood. Until recently it was thought that renal vasculature derived exclu-

sively from branches off the aorta and other preexisting extrarenal vessels (“angiogenic” hypothesis). There is evidence, however, that the renal vessels may originate in situ, within the embryonic kidney from vascular progenitor cells (“vasculogenic” hypothesis) (Loughna et al, 1996; Tufo et al, 1999). Using antibodies to Flk-1, a vascular endothelial growth factor (VEGF) receptor present in angioblasts and mature endothelial cells, it was demonstrated that endothelial cell precursors were already present in the prevascular rodent kidneys before any vessels were discernible from a morphologic standpoint. When embryonic kidneys are cultured at the usual atmospheric oxygen concentration, vessels do not develop. However, if the explants are cultured in a hypoxic atmosphere containing 5% oxygen, capillary sprouts develop within and outside the glomeruli, an effect that is inhibited by anti-VEGF antibodies (Tufo-McReddie et al, 1997). Depending on the developmental potential of the cells involved, both angiogenesis and vasculogenesis may play a role in the development of renal vasculature (Abrahamson et al, 1998).

BLADDER AND URETER DEVELOPMENT

Formation of Urogenital Sinus

At the third week of gestation the cloacal membrane remains a bilaminar structure composed of endoderm and ectoderm. During the fourth week the neural tube and the tail of the embryo grow dorsally and caudally, projecting over the cloacal membrane, and this differential growth of the body results in embryo folding. The cloacal membrane is now turned to the ventral aspect of the embryo, and the terminal portion of the endoderm-lined yolk sac dilates and becomes the *cloaca* (Fig. 122-15). According to the theories of Rathke and Tournoux regarding embryonic development, the partition of the cloaca into an anterior urogenital sinus and a posterior anorectal canal occurs by the midline fusion of two lateral ridges of the cloacal wall and by a descending urorectal septum. This process is thought to occur during the fifth and sixth weeks, and it culminates with the fusion of this urorectal septum with the cloacal membrane. However, some investigators have challenged this classic view with evidence that there is neither a descending septum nor fusing lateral ridges of the cloacal wall (van der Putte, 1986; Kluth et al, 1995). There is further evidence that the urorectal septum never fuses with the cloacal membrane (Nievelstein et al, 1998). According to these observations the congenital cloacal and anorectal malformations, which were previously thought to occur because of a failure of septum formation and its fusion with the cloacal membrane, may in fact occur from an abnormal development of the cloacal membrane itself (Nievelstein et al, 1998) (Fig. 122-16).

The nephric (wolffian) duct fuses with the cloaca by the 24th day and remains with the urogenital sinus during the cloacal separation. The entrance of the nephric duct into the primitive urogenital sinus serves as a landmark distinguishing the cephalad vesicourethral canal from the caudal urogenital sinus. The vesicourethral canal gives rise to the bladder and pelvic urethra, whereas the caudal urogenital sinus forms the phallic urethra for males and distal vaginal vestibule for females.

Formation of Trigone

By day 33 of gestation, the *common excretory ducts* (the portion of nephric ducts distal to the origin of ureteric buds) dilate and connect to the urogenital sinus. The formation of these final connections involves apoptosis, which enables the ureters to disconnect from the nephric ducts, and fusion, in which the ureteral orifice inserts into the urogenital sinus epithelium at the level of the trigone (Batourina et al, 2005). According to the classic view (Weiss, 1988), the right and left common excretory ducts fuse in the midline as a triangular area, forming the primitive trigone, structurally different from bladder and urethra. The ureteral orifice extrophies and evaginates into the bladder by day 37 and begins to migrate in a cranial and lateral direction within the floor of the bladder. During this process the nephric duct orifice diverges

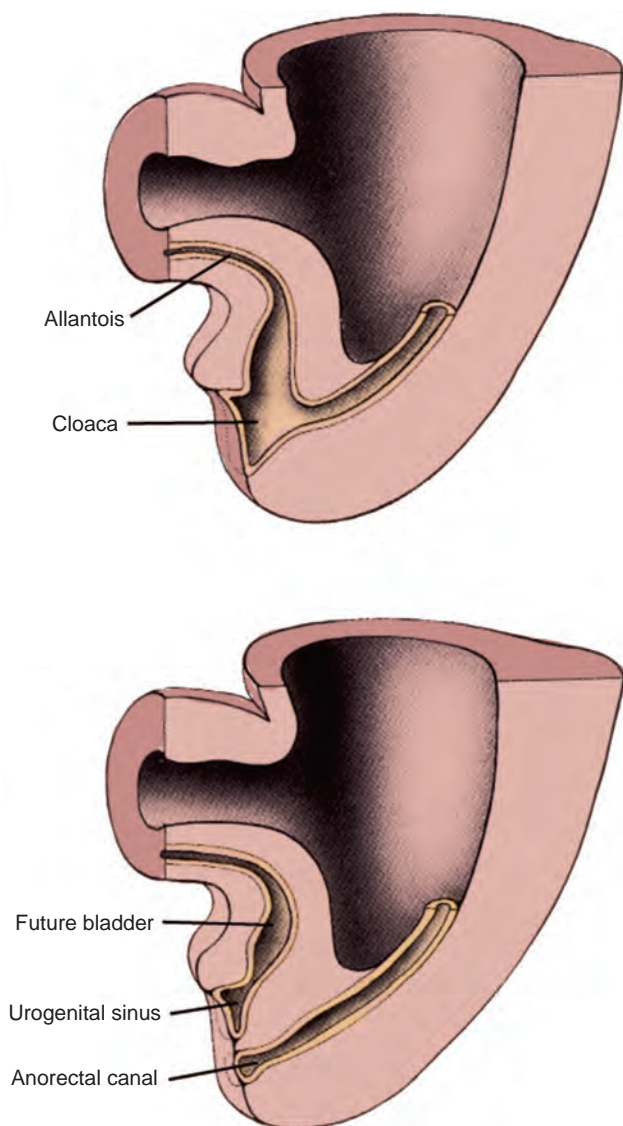


Figure 122-15. Development of the urogenital sinus. Between the fourth and sixth weeks the cloaca is divided into an anterior urogenital sinus and a posterior anorectal canal. The superior part of the urogenital sinus, continuous with the allantois, forms the bladder. The constricted narrowing at the base of the urogenital sinus forms the pelvic urethra. The distal expansion of the urogenital sinus forms the vestibule of the vagina in females and the penile urethra in males. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

away from the ureteral orifice and migrates caudally, flanking the paramesonephric (müllerian) duct at the level of the urogenital sinus. This is the site of the future verumontanum in males and vaginal canal in females. Studies, however, have challenged this classic mechanism of trigone development. With use of the cell lineage studies in mice, the trigone was found to form mostly from bladder smooth muscle cells with only a minor contribution from the ureters (Viana et al, 2007).

The embryonic pattern of ureteral orifice incorporation into the developing bladder is inferred primarily from clinical observations of duplex kidneys. The upper pole ureteral orifice rotates posteriorly relative to the lower pole orifice and assumes a more caudal and medial position. Weigert and Meyer recognized the regularity of this relationship between upper and lower pole ureteral orifices, which has come to be known as the *Weigert-Meyer rule*. According to this

concept, an abnormally lateral lower pole ureteral orifice may result from a ureteric bud arising too low on the nephric duct, therefore resulting in premature incorporation and migration within the developing bladder. In such a ureteral orifice, vesico-ureteral reflux is more likely to occur because of an inadequate intramural tunnel. In contrast, an abnormally caudal upper pole ureteral orifice may result from a ureteric bud arising too high on the nephric duct. It may drain at the bladder neck and verumontanum or remain connected to the nephric (wolffian) duct derivatives such as the vas deferens in males (Mackie and Stephens, 1977; Schwarz and Stephens, 1978). In females, the ectopic upper pole ureter may insert into the remnants of the nephric ducts (e.g., Gartner duct cyst) or vaginal vestibule (Fig. 122-17).

Anomalous development of the common excretory duct may lead to an ectopic vas deferens. In certain clinical situations the vas deferens is connected to the ureter rather than the verumontanum, so that both the ureter and vas drain into a common duct. This situation may occur when the ureteric bud arises too high on the nephric duct and the subsequent common excretory duct becomes too long, resulting in incomplete absorption into the developing bladder. This anomaly, although rare, should be kept in mind when evaluating males with recurrent epididymitis and ipsilateral hydronephrosis.

Development of the Ureter

In contrast to the previous discussion regarding the molecular aspects of renal development, little is understood at the molecular level concerning the events of ureteral development. Only a small amount of descriptive information and a few speculative theories are available regarding the molecular mechanism of smooth muscle cell and urothelial differentiation. Morphologically, the ureter begins as a simple cuboidal epithelial tube surrounded by loose mesenchymal cells that acquires a complete lumen at 28 days of gestation in humans. It was suggested that the developing ureter undergoes a transient luminal obstruction between 37 and 40 days' gestation and subsequently recanalizes (Alcaraz et al, 1991). It appears that this recanalization process begins in the mid-ureter and extends in a bidirectional manner both cranially and caudally. In addition, another source of physiologic ureteral obstruction may exist as the Chwalla membrane, a two-cell-thick layer over the ureteral orifice that is seen between 37 and 39 days' gestation. In humans, urine production is followed by proliferative changes in the ureteral epithelium (bilaminar by 10 weeks of gestation). The epithelium attains a transitional configuration by 14 weeks. The first signs of ureteral muscularization and development of elastic fibers are seen at 12 weeks of gestation. In both rats and humans the ureteral smooth muscle phenotype appears later than that of the bladder. Smooth muscle differentiation is first detected in the subserosal region of the bladder dome and extends toward the bladder base and urethra, whereas smooth muscle differentiation of the ureter occurs later within the subepithelial region in the ureterovesical junction, ascending toward the intrarenal collecting system (Baker and Gomez, 1998). In the embryonic ureter and bladder it is likely that epithelial-mesenchymal interactions are important in the development of urothelium, lamina propria, and muscular compartments, but the exact nature of this induction process is unknown. Before 10 weeks of gestation elastic fibers are few in number, poorly developed, and randomly arranged. After 12 weeks these fibers become more numerous throughout the ureter and are seen with specific orientation (Escala et al, 1989).

Although more than 30 genes have been found to be involved in the development of mammalian kidneys, only a few genes have been thus far demonstrated to concurrently cause both kidney and ureteral anomalies—*Agtr2*, *Bmp4*, *FoxC1*, *Pax2*, and *Eya1* (see the discussion of molecular mechanism of kidney development, earlier). A mutation of the *PAX2* gene has been identified in a human family carrying renal coloboma syndrome, a rare autosomal dominant syndrome characterized by optic nerve coloboma, renal anomalies, and vesicoureteral reflux (Sanyanusin et al, 1996). *EYA1* is mutated in patients with dominantly inherited disorder,

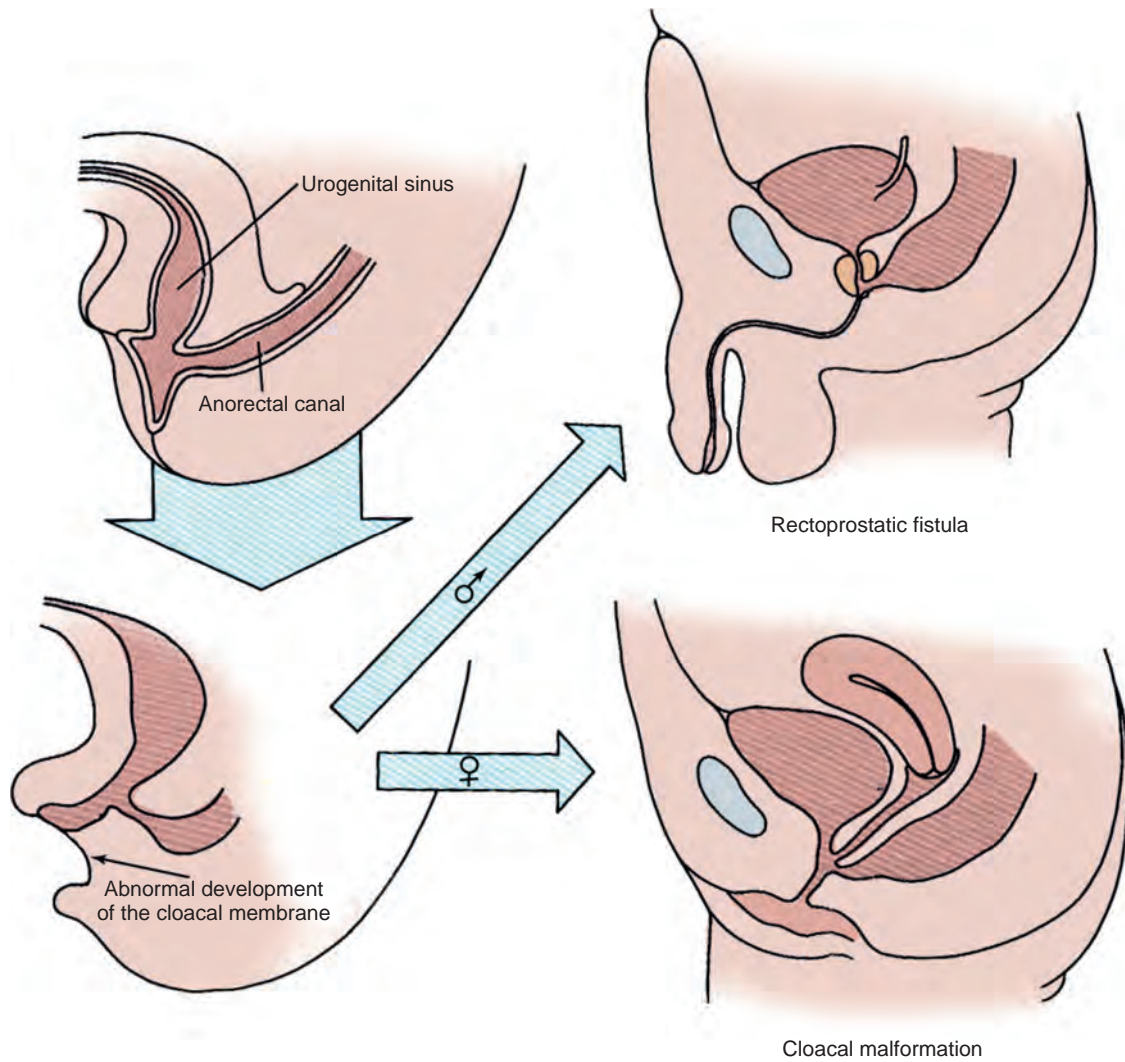


Figure 122-16. Abnormal development of cloacal membrane results in characteristic anomalies of the urogenital and lower gastrointestinal tract. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

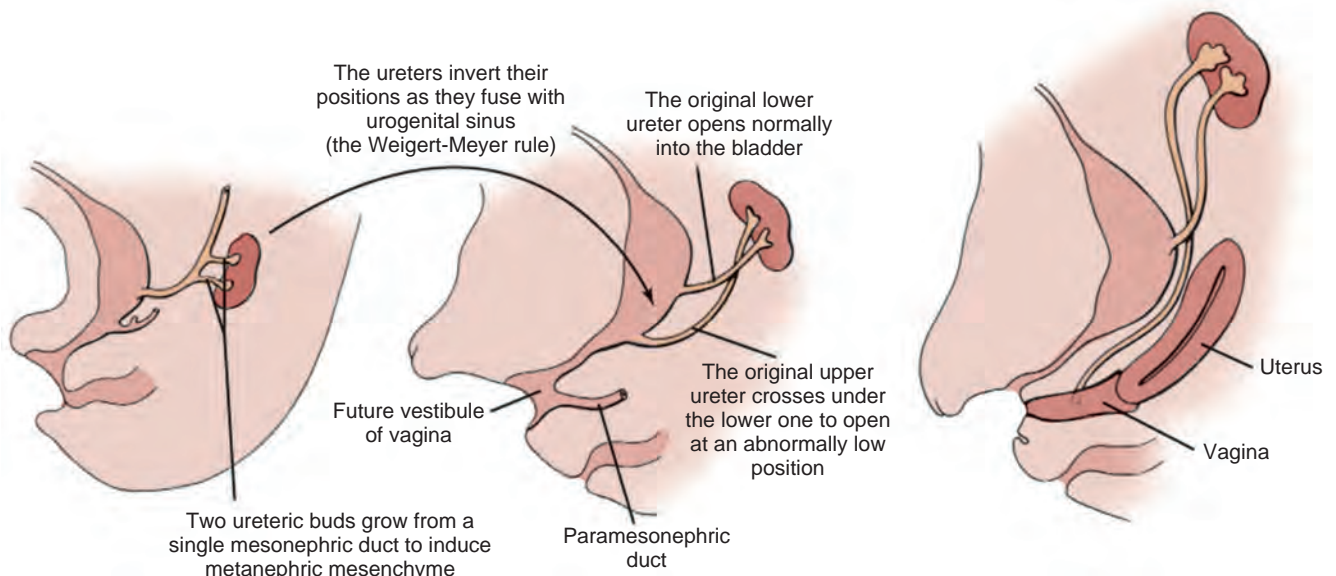


Figure 122-17. Development of an ectopic upper pole ureter draining into the vagina. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

branchio-oto-renal syndrome, which includes a duplex collecting system, renal hypoplasia and dysplasia, and renal agenesis (Abdelhak et al, 1997). *Pax2* is required for the growth and elongation of nephric ducts before ureteric bud formation, whereas *Eya1* appears to regulate the GDNF expression, which is a prerequisite for ureteric bud outgrowth. *Bmp4* and *FoxC1* appear to play a suppressive role in the ureteric bud outgrowth.

The renin-angiotensin system is present and active during fetal life. It is generally thought that the major role of this system in the fetus is to maintain fetal glomerular filtration and to ensure adequate urine production (Lumbers, 1995). There is growing evidence, however, that the renin-angiotensin system is also important for normal growth and development of the kidney and ureter. The kidney is able to produce all components of this system, and thus the local (intrarenal) production of angiotensin II may play a critical role in this regard. Renin messenger (m)RNA is detectable in the human mesonephros at about 30 days of gestation and in the metanephros at about 56 days of gestation (Schütz et al, 1996). A similar profile of expression is seen for angiotensinogen and angiotensin-converting enzyme (ACE). Mutant mice lacking ACE are found to have abnormal renal vasculature and tubules as well as increased renin synthesis in interstitial and perivascular cells (Hilgers et al, 1997). Pharmacologic inhibition of ACE in the neonatal rat produces irreversible abnormalities in renal function and morphology (Guron et al, 1997), supporting that an intact renin-angiotensin system is crucial for normal kidney development and maturation. In addition to the high rate of fetal loss, infants born to human mothers treated with ACE inhibitors during pregnancy have increased rates of oligohydramnios, hypotension, and anuria (Shotan et al, 1994; Sedman et al, 1995).

Both subtypes of angiotensin II receptors, AT1 and AT2, are expressed in the developing mesonephros and metanephros. AT2 expression predominates in the undifferentiated mesenchymal cells that surround the nephric duct at the time of ureteric bud outgrowth and declines with maturation, and this pattern of expression suggests AT2's role in embryonic renal development. AT1 is expressed in more differentiated structures and may be involved in modulating later stages of renal vascular development and acquisition of classic angiotensin II-mediated effects of vasoconstriction and sodium reabsorption. The function of the AT2 receptor is not defined completely, but when its gene, *Agtr2*, was inactivated genetically in mice these mutants demonstrated a significant incidence of anomalies in the kidney and urinary tract. Abnormal phenotype in these mice mimicked all the key features of human congenital anomalies of the kidney and urinary tract, such as ureteropelvic junction obstruction, hypoplastic kidney, vesicoureteral reflux, megaureter, and duplicated collecting system (Nishimura et al, 1999).

Because of its embryonic expression pattern, it was initially speculated that AT2 might play a role in regulating the initial outgrowth of the ureteric bud. Analysis of whole tissue sections showed that ectopic ureteric budding occurred in *Agtr2*-deficient mutant mice (Oshima et al, 2001). It was thus postulated that similar to *Bmp4*, AT2 might have a role in directing the site of ureteric bud outgrowth through its inhibitory effect. In other words, a defect in this process may lead to an abnormal timing and location of the ureteric bud outgrowth, resulting in congenital ureteral anomalies.

Recent evidence suggests that BMPs control formation of smooth muscle in the proximal ureter and pelvis. *BMP4*, expressed in the caudal mesenchyme cells, induces ureteral morphogenesis including smooth muscle differentiation and urothelial development (Brenner-Anantharam et al, 2007). Consistent with such a role, *Bmp4*- and *Bmp5*-mutant mice display hydronephrosis and hydro-ureter (Miyazaki et al, 2003).

Development of the Bladder and Continence Mechanism

By the 10th week of gestation the bladder is a cylindric tube lined by a single layer of cuboidal cells surrounded by loose connective tissue. The apex tapers as the urachus, which is contiguous with the

allantois. By the 12th week the urachus involutes to become a fibrous cord, which becomes the *median umbilical ligament*. The bladder epithelium consists of bilayered cuboidal cells between the 7th and 12th weeks, and it begins to acquire mature urothelial characteristics between the 13th and 17th weeks. By the 21st week it becomes four to five cell layers thick and demonstrates ultrastructural features similar to the fully differentiated urothelium. Between the 7th and 12th weeks the surrounding connective tissues condense and smooth muscle fibers begin to appear, first at the region of the bladder dome and later proceeding toward the bladder base. Collagen fibers first appear in the lamina propria and then later extend into the deeper wall between the muscle fibers (Newman and Antonakopoulos, 1989).

Bladder compliance is thought to change during development. When studied in whole organ preparation using fetal sheep bladders, bladder compliance is very low during early gestation and increases gradually thereafter (Coplen et al, 1994). The mechanism of these changes in bladder compliance is not known but may involve alterations in both smooth muscle tone and connective tissue composition. This phenomenon is also observed in developing human bladders (Kim et al, 1991). During gestation the bladder wall muscle thickness increases and the relative collagen content decreases. The ratio of thick-to-thin collagen fibers also decreases, whereas the amount of elastic fibers increases. These changes in compliance seem to coincide with the time of fetal urine production, suggesting a possible role for mechanical distention (Baskin et al, 1994). With fetal mouse bladders used as organ culture explants, bladder distention promoted a more orderly development of collagen fiber bundles within the lamina propria in comparison with decompressed bladder explants, suggesting that mechanical factors from accumulating urine may play a role during bladder development (Beauboeuf et al, 1998).

Similar to other organ development, the epithelial-mesenchymal inductive interactions appear to be necessary for orderly differentiation and proper development of the bladder. A modified Grobstein technique was applied to study the mechanism of bladder smooth muscle cell differentiation (Baskin et al, 1996). Undifferentiated rat bladder epithelial and mesenchymal rudiments were separated before bladder smooth muscle cell differentiation and then recombined to grow within the immunologically compromised host (athymic nude mouse). In the presence of epithelial cells, the mesenchymal cells differentiated into smooth muscle cells with sequential expression of appropriate smooth muscle markers, whereas in the absence of epithelial cells they involuted with evidence of apoptosis.

No functional study has been done to assess fetal continence mechanisms. Only a handful of ontogenic descriptions are available using human fetal specimens, providing a basis for speculative theories. A mesenchymal condensation forms around the caudal end of the urogenital sinus after the division of the cloaca and the rupture of the cloacal membrane. Striated muscle fibers can be seen clearly by the 15th week. At this time the smooth muscle layer becomes thicker at the level of bladder neck and forms the inner part of the urethral musculature. The urethral sphincter, composed of central smooth muscle fibers and peripheral striated muscle fibers, develops in the anterior wall of the urethra (Bourdelat et al, 1992). Beyond this point, sexual dimorphism develops in conjunction with the formation of the prostate in males and the vagina in females (Tichy, 1989). The urethral sphincter muscle fibers extend to the posterior wall of the urethra. In males these fibers project to the lateral wall of the prostate, whereas in females the muscle fibers attach to the lateral wall of the vagina.

GENITAL AND REPRODUCTIVE TRACT DEVELOPMENT

Formation of Genital Ridges and Paramesonephric Ducts

During the fifth week, primordial germ cells migrate from the yolk sac along the dorsal mesentery to populate the mesenchyme of the posterior body wall near the 10th thoracic level (Fig. 122-18). In

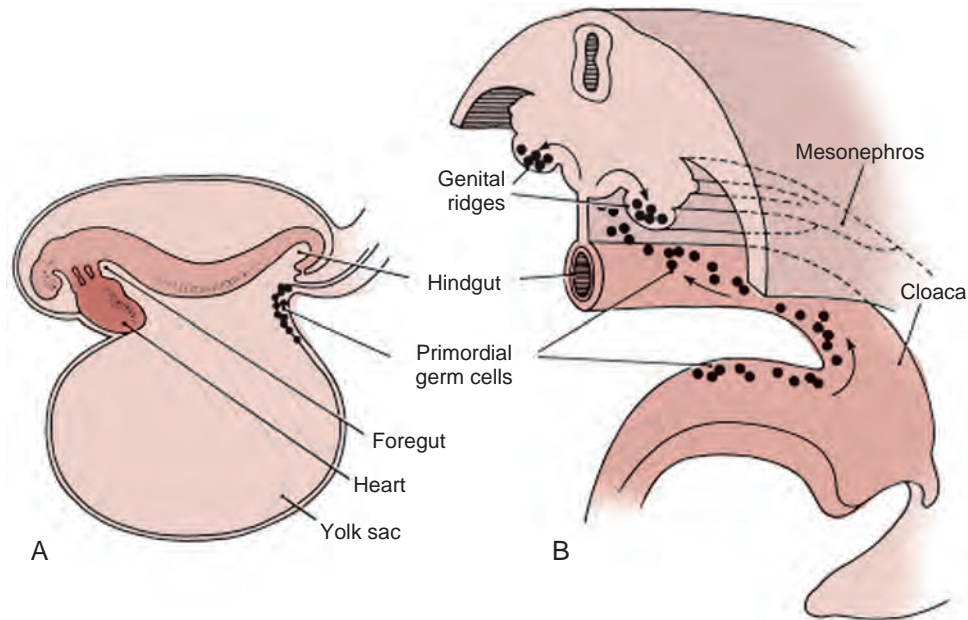


Figure 122-18. A, Site of the primordial germ cell origin in the wall of the yolk sac in a 3-week-old embryo. B, Migratory path of the primordial germ cells along the wall of the yolk sac and dorsal mesentery into the developing genital ridges. (Modified from Sadler TW. *Langman's medical embryology*. Baltimore: Williams & Wilkins; 1985.)

both sexes the arrival of primordial germ cells in the area of future gonads serves as the signal for the existing cells of the mesonephros and the adjacent coelomic epithelium to proliferate and form a pair of *genital ridges* just medial to the developing mesonephros (Fig. 122-19). During the sixth week the cells of the genital ridge invade the mesenchyme in the region of future gonads to form aggregates of supporting cells called the *primitive sex cords*. The primitive sex cords will subsequently invest the germ cells and support their development. The genital ridge mesenchyme containing the primitive sex cords is divided into the cortical and medullary regions. Both regions develop in all embryos, but after the sixth week they pursue different fates in the male and female.

During this time a new pair of ducts, called the *paramesonephric (müllerian) ducts*, begins to form just lateral to the nephric ducts in both male and female embryos (Fig. 122-20). These ducts arise by the craniocaudal invagination of thickened coelomic epithelium, extending all the way from the third thoracic segment to the posterior wall of the developing urogenital sinus. The caudal tips of the paramesonephric ducts adhere to each other as they connect with the urogenital sinus between the openings of the right and left nephric ducts. The cranial ends of the paramesonephric ducts form funnel-shaped openings into the coelomic cavity, which is the future peritoneum.

Development of Male Genital Structures

Under the influence of *SRY* (the sex-determining region of the Y chromosome), cells in the medullary region of the *primitive sex cords* begin to differentiate into *Sertoli cells* while the cells of the cortical sex cords degenerate. Sex cord cells differentiate into Sertoli cells only if they contain the *SRY* protein; otherwise the sex cords differentiate into ovarian follicles. During the seventh week, the differentiating Sertoli cells organize to form the *testis cords*. At puberty these testis cords associated with germ cells undergo canalization and differentiate into seminiferous tubules. Direct cell-to-cell contact between developing Sertoli cells and primordial germ cells is thought to play a key role in the proper development of male

gametes. This interaction occurs shortly after the arrival of the primordial germ cells in the presumptive genital ridge. The testis cords distal to the presumptive seminiferous tubules also develop lumen and differentiate into a set of thin-walled ducts called the *rete testis*. Just medial to the developing gonad the tubules of rete testis connect with 5 to 12 residual tubules of nephric ducts, called *efferent ductules*. The vas deferens also develops from the nephric duct. At this time the testis begins to become round, reducing its area of contact with the surrounding mesonephros. As the testis continues to develop, the degenerating cortical sex cords become separated from the coelomic (peritoneal) epithelium by an intervening layer of connective tissue called the *tunica albuginea* (see Fig. 122-20).

As the developing Sertoli cells begin their differentiation in response to the *SRY* protein, they also begin to secrete a glycoprotein hormone called *müllerian-inhibiting substance* (MIS). MIS causes the paramesonephric (müllerian) ducts to regress rapidly between the 8th and 10th weeks. **Small müllerian duct remnants can be detected in the developed male as a small tissue protrusion at the superior pole of the testis, called the *appendix testis*, and as a posterior expansion of the prostatic urethra, called the *prostatic utricle*.** In female embryos, MIS is absent; therefore the müllerian ducts do not regress. On occasion, genetic males have persistent müllerian duct structures (uterus and fallopian tubes), a condition known as *hernia uteri inguinale*. In these individuals either MIS production by Sertoli cells is deficient or the müllerian ducts do not respond to normal MIS levels.

During the 9th and 10th weeks, Leydig cells differentiate from mesenchymal cells of the genital ridge in response to the *SRY* protein. These endocrine cells produce testosterone. At an early stage of development testosterone secretion is regulated by placental chorionic gonadotropin, but eventually the pituitary gonadotropins assume control of androgen production. Between the 8th and 12th weeks, testosterone secretion by Leydig cells stimulates the nephric (wolffian) ducts to transform into the vas deferens. The cranial portions of the nephric ducts degenerate, leaving a small remnant of tissue protrusion called the *appendix epididymis*, and the region of nephric ducts adjacent to the presumptive testis differentiate into

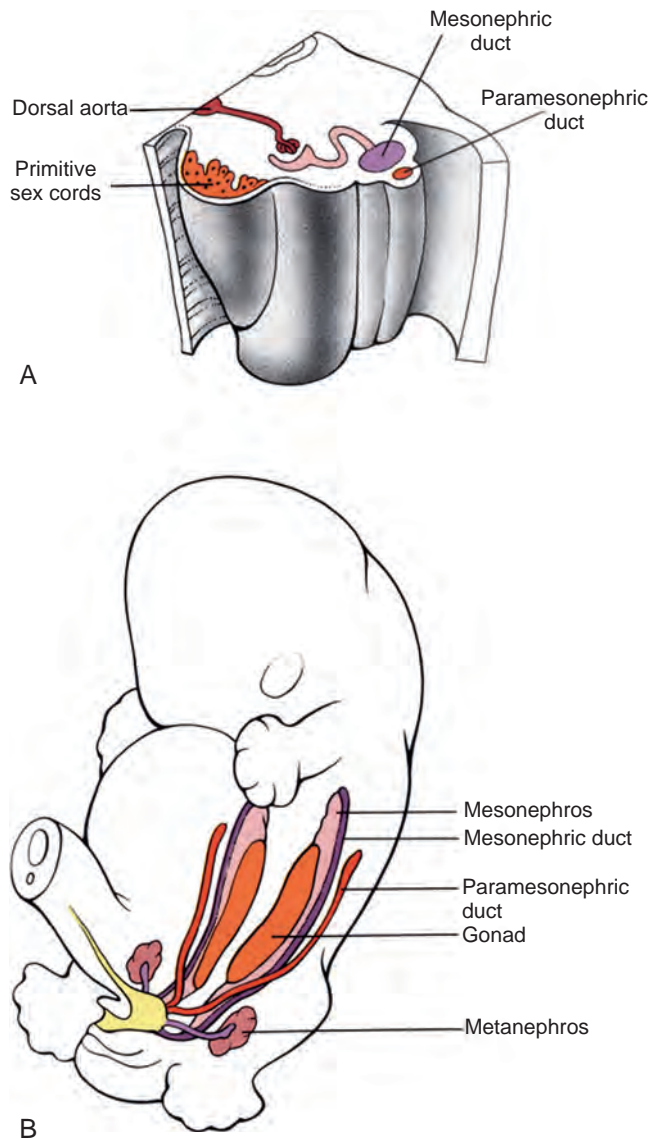


Figure 122-19. Formation of genital ridges and paramesonephric ducts. **A**, During the fifth and sixth weeks the genital ridges form in the posterior abdominal wall just medial to the developing mesonephros. The primordial germ cells induce the coelomic epithelial cells lining the peritoneal cavity and the cells of the mesonephros to proliferate and form the primitive sex cords. **B**, During the sixth week, the paramesonephric ducts develop lateral to the mesonephros. The caudal tips of the paramesonephric ducts fuse with each other as they connect with the urogenital sinus. (Modified from Larsen WJ. *Human embryology*. New York: Churchill Livingstone; 1997.)

the epididymis. During the 9th week, 5 to 12 nephric ducts in the region of the epididymis make contact with the sex cords of the future rete testis. It is not until the third month, however, that these tubules actually establish communication with the rete testis as the efferent ductules. Meanwhile, the nephric duct–derived tubules near the inferior pole of the developing testis degenerate, sometimes leaving a remnant of tissue protrusion called the *paradidymis*.

Prostate and Seminal Vesicle Development

The seminal vesicles sprout from the distal nephric ducts, whereas the prostate and bulbourethral glands develop from the urogenital sinus (Fig. 122-21). They therefore have different

embryologic origins. The initial event in prostatic development is an outgrowth of solid epithelial cords from the urogenital sinus epithelium into the surrounding mesenchyme during weeks 10 to 12 of gestation. This prostatic bud growth and subsequent branching morphogenesis occur in a specific spatial pattern that eventually establishes the lobar subdivisions of the mature prostate gland (Sugimura et al, 1986; Timms et al, 1994). The solid prostatic ducts are subsequently canalized from their urethral connections, proceeding distally toward the ductal tips. As the solid epithelial cords canalize, the epithelium organizes itself into two distinct cell types—luminal and basal cells (Hayward et al, 1996). At this time the prostatic mesenchyme differentiates into a layer of smooth muscle cells that surround the prostatic ducts (Hayward et al, 1996). At puberty, corresponding to a rise in circulating testosterone, the prostate size increases rapidly, along with functional cytodifferentiation of luminal cells, as evidenced by the expression of prostate-specific secretory proteins (Hayward et al, 1996).

Circulating androgens produced by fetal testes play a critical role in the development of the prostate. Cellular responses to circulating androgens are mediated by nuclear androgen receptors that are activated by either testosterone or dihydrotestosterone (DHT). The evidence for the requirement of androgens in establishing the prostate specificity of the urogenital sinus comes primarily from the absence of prostate development in mice and humans who lack functional androgen receptors (Lubahn et al, 1989; He et al, 1991), as well as from the development of the prostate in the female urogenital sinus exposed to androgens (Takeda et al, 1986). In the urogenital sinus, testosterone could activate androgen receptors by directly binding to the receptor and also through a local conversion of circulating testosterone into the more potent DHT by the enzyme 5 α -reductase (Russell and Wilson, 1994). DHT has a 10-fold greater affinity for the androgen receptor than testosterone (Deslypere et al, 1992). When 5 α -reductase is deficient, the urogenital sinus is specified to become the prostate but the overall prostatic growth and development are severely compromised (Andersson et al, 1991). Tissue recombination and grafting experiments using testicular feminization mice that lack functional androgen receptor have shown that the presence of androgen receptors in the urogenital sinus mesenchyme is required for prostate specification and differentiation (Cunha and Lung, 1978). The fact that mesenchymal but not epithelial androgen receptors are required for prostate-specific ductal growth and branching suggests that paracrine signals from the urogenital sinus mesenchyme mediate the action of androgens on the epithelium. Prostate development appears to be affected by the levels of estrogenic compounds as well (vom Saal et al, 1997; Timms et al, 1999), but their specific role has not been fully elucidated.

Prostate development requires inductive and reciprocal interactions between the urogenital sinus epithelium and mesenchyme. In addition to mediating the effect of androgens to the developing prostatic epithelium, paracrine signals from the urogenital sinus mesenchyme also appear to direct lobe-specific patterning of juxtaposed epithelium (Timms et al, 1995). The urogenital sinus mesenchyme, when combined with either embryonic or adult bladder epithelium (also a derivative of endodermal cloaca), will stimulate formation of prostatic ducts. In contrast, the urogenital sinus mesenchyme combined with epithelia of other anatomic origins, such as seminal vesicle (a mesodermal derivative), salivary gland, or esophagus, forms tissues with epithelial characteristics that resemble the anatomic origin of the partnering epithelium (Cunha et al, 1987). These observations suggest that prostate development is spatially restricted by prostate-inducing paracrine signals from the urogenital sinus mesenchyme and that epithelial potential to respond to signals from the urogenital sinus mesenchyme is restricted to the endodermal epithelia of similar embryonic origin as the prostate. The interactions between epithelium and mesenchyme are reciprocal. The presence of prostate epithelium plays a critical role in the differentiation of mesenchymal cells into the periductal smooth muscle cells (Hayward et al, 1998).

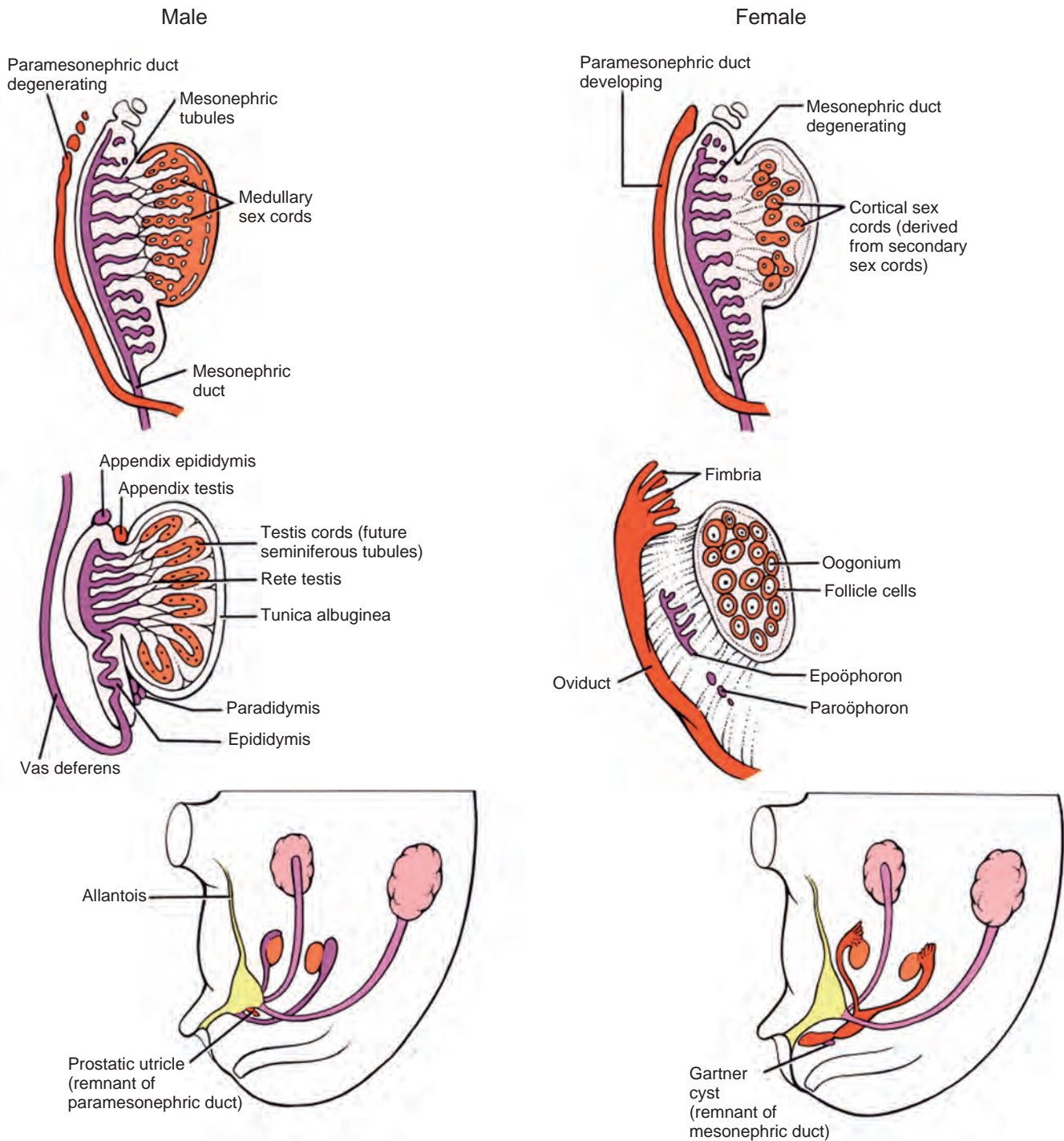


Figure 122-20. Male and female gonad and genital development. The male and female genital structures are virtually identical through the seventh week. In males, SRY protein produced by the Sertoli cells causes the medullary sex cords to become presumptive seminiferous tubules and causes the cortical sex cords to regress. Müllerian-inhibiting substance (MIS), a glycoprotein hormone produced by the Sertoli cells, then causes the paramesonephric ducts to regress, leaving behind appendix testis and prostatic utricle as remnants. Appendix epididymis and paradidymis arise from the mesonephric ducts. In females, cortical sex cords invest the primordial germ cells and become the ovarian follicles. In the absence of MIS, the mesonephric ducts degenerate and the paramesonephric ducts give rise to the fallopian tubes, uterus, and upper vagina. The remnants of the mesonephric ducts are found in the ovarian mesentery as the epoöphoron and paroöphoron, and in the anterolateral vaginal wall as the Gartner duct cysts. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

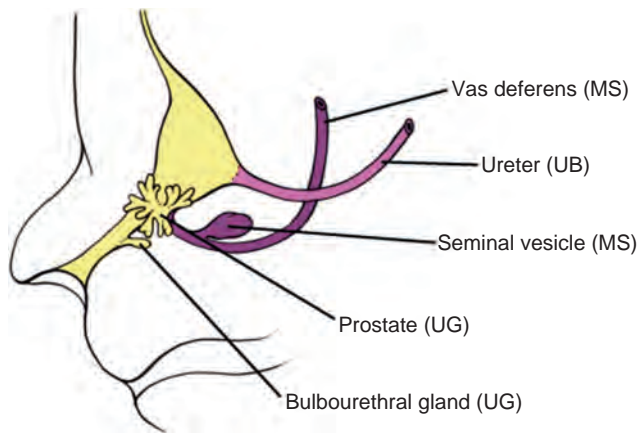


Figure 122-21. Development of male accessory sex glands. During the 10th week, the seminal vesicles sprout from the distal mesonephric ducts in response to testosterone whereas the prostate and bulbourethral glands develop from the urethra in response to dihydrotestosterone. Thus the vas deferens and seminal vesicle derive from the mesonephric ducts (MS), and the prostate and bulbourethral glands develop from the urogenital sinus (UG). UB, ureteric bud. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

Several candidate genes have been implicated in prostate development, but the nature of paracrine mesenchymal factors that drive urogenital sinus epithelial transformation into prostatic ducts remains unknown. Furthermore, the precise relationship and the embryologic sequence of these candidate molecules have not been clearly defined. The *Hox* family of homeobox genes may be involved in the proper differentiation of male accessory sex glands, including the prostate (Podlasek et al, 1997, 1999b). In particular, *Hoxa-13* and *Hoxd-13* transcription factors are expressed in both urogenital sinus and nephric ducts, and the loss-of-function mutation of these genes in mice results in agenesis of bulbourethral glands and defective morphogenesis of the prostate and seminal vesicles. Two members of the FGF family of secreted proteins, FGF7 and FGF10, are expressed in the urogenital sinus mesenchyme. In vitro organ culture experiments have shown that exogenous FGF7 and FGF10 can stimulate proliferation and branching of developing prostate tissue, but these factors do not appear to be androgen responsive (Thomson and Cunha, 1999). There is also evidence that secreted factor activin-A and its antagonistic binding protein follistatin may be important in the regulation of prostate epithelial development (Cancilla et al, 2001). Activin-A is expressed in both urogenital sinus epithelium and mesenchyme, whereas its receptors are found in the epithelium. Follistatin, an activin-A antagonist, is expressed in the urogenital sinus epithelium. Prostatic ductal growth and branching might therefore be a result of balanced interplay between activin-A and follistatin. Other implicated molecules in prostate development include Bmp4 (Lamm et al, 2001), growth hormone receptor (Ruan et al, 1999), insulin-like growth factor-1 (Ruan et al, 1999), Nkx3.1 (Bhatia-Gaur et al, 1999), sonic hedgehog (Podlasek et al, 1999a), p63 (Signoretti et al, 2000), prolactin (Steger et al, 1998), hyaluronan (Gakunga et al, 1997), fucosyltransferase-1 (Marker et al, 2001), and urokinase plasminogen activator (Elfman et al, 2001).

Development of Female Genital Structures

In female embryos the primitive sex cords do not contain the Y chromosome, do not elaborate SRY protein, and therefore do not differentiate into Sertoli cells. In the absence of Sertoli cells and SRY protein, therefore, MIS synthesis, Leydig cell differentiation,

and androgen production do not occur. Consequently, male development of the genital ducts and accessory glands is not stimulated and female development ensues. In females the primitive sex cords degenerate and the mesothelium of the genital ridge forms the secondary cortical sex cords. These secondary sex cords invest the primordial germ cells to form the ovarian follicles. The germ cells differentiate into oogonia and enter the first meiotic division as primary oocytes. The follicle cells then arrest further germ cell development until puberty, at which point individual oocytes resume gametogenesis in response to a monthly surge of gonadotropins.

In the absence of MIS and androgens, the nephric (wolffian) ducts degenerate, and the paramesonephric (müllerian) ducts give rise to the fallopian tubes, uterus, and upper two thirds of the vagina. The remnants of nephric ducts are found in the mesentery of the ovary as the *epoöphoron* and *paroöphoron* and near the vaginal introitus and anterolateral vaginal wall as *Gartner duct cysts*. The distal tips of the paramesonephric ducts adhere to each other just before they contact the posterior wall of the urogenital sinus. The wall of the urogenital sinus at this point forms a small thickening called the *sinusal tubercle*. As soon as the fused tips of the paramesonephric ducts connect with the sinusal tubercle, the paramesonephric ducts begin to fuse in a caudal to cranial direction, forming a tube with a single lumen. This tube, called the *uterovaginal canal*, becomes the superior portion of the vagina and the uterus. The unfused, superior portions of the paramesonephric ducts become the fallopian tubes (oviducts), and the funnel-shaped superior openings of the paramesonephric ducts become the infundibula.

While the uterovaginal canal is forming during the third month, the endodermal tissue of the sinusal tubercle in the posterior urogenital sinus continues to thicken, forming a pair of swellings called the *sinovaginal bulbs*. These structures give rise to the lower third of the vagina. The most inferior portion of the uterovaginal canal becomes occluded transiently by a block of tissue called the *vaginal plate*. The origin of the vaginal plate is not clear; it may arise from the sinovaginal bulbs, from the walls of the paramesonephric ducts, from the nearby mesonephric ducts, or from a combination of these tissues. The vaginal plate elongates between the third to fifth month and subsequently becomes canalized to form the inferior vaginal lumen (Fig. 122-22).

As the vaginal plate forms, the lower end of the vagina lengthens, and its junction with the urogenital sinus migrates caudally until it comes to rest on the posterior wall of definitive urogenital sinus (future vestibule of the vagina) during the fourth month. An endodermal membrane temporarily separates the vaginal lumen from the cavity of the definitive urogenital sinus. This barrier degenerates partially after the fifth month, but its remnant persists as the vaginal hymen. The mucous membrane that lines the vagina and cervix may also derive from the endodermal epithelium of the definitive urogenital sinus.

Development of External Genitalia

Unlike the rest of the developing embryo, the cloacal membrane, along with the oropharyngeal membrane (future oral cavity), is a bilayered structure in which the outer ectoderm remains in close contact with the underlying endoderm without the intervening mesoderm. Initially the cloacal membrane represents an elongated midline structure that extends from the root of the umbilical cord to the future site of the perineum distally. During the subsequent development this bilayered cloacal membrane "retracts" into the perineum as a result of cranial and medial migration of mesodermal cells into the anterior body wall between the ectoderm and the endoderm layers of the cloacal membrane. This mesenchymal migration brings about the closure of the inferior part of the anterior abdominal wall and causes the caudal portion of the cloacal membrane to position itself in the perineal region. These migrating mesodermal cells give rise to the musculature of the medial portion of the anterior abdominal wall, the mesenchymal portion of the anterior bladder wall, the pubic symphysis, and the

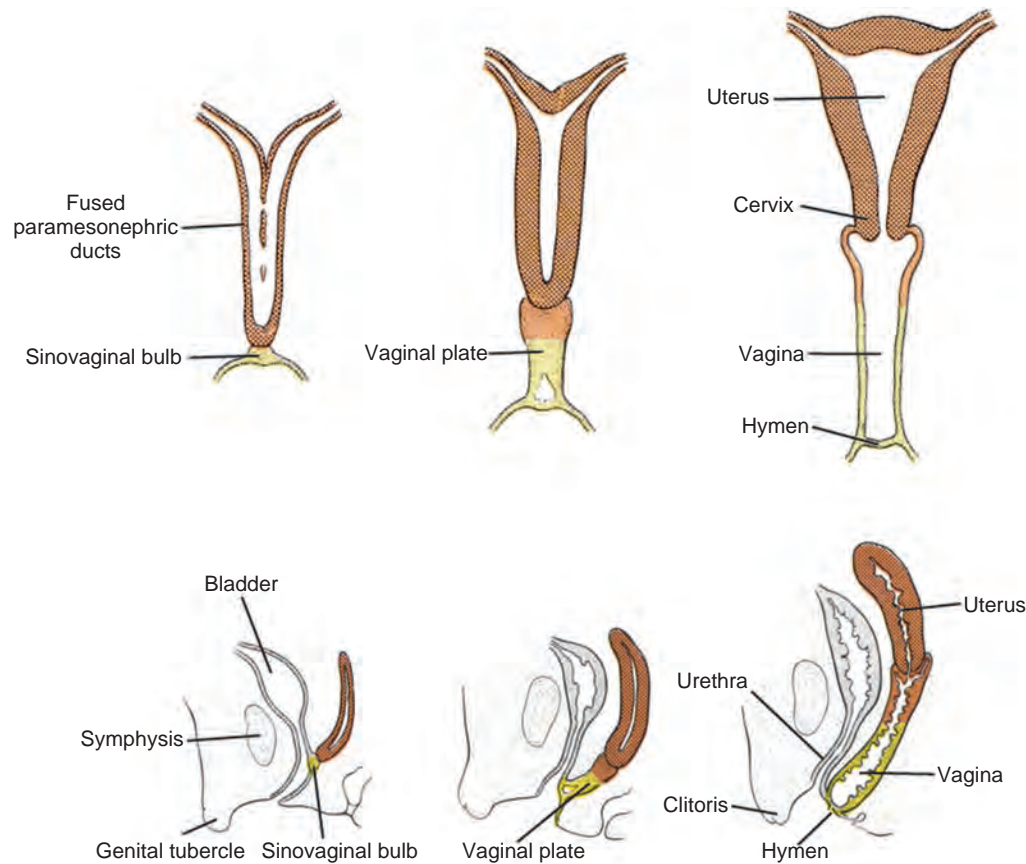


Figure 122-22. Development of uterus and vagina. During the 10th week the paramesonephric ducts fuse at their caudal ends to establish a common channel and come into contact with a thickened portion of the posterior urogenital sinus called the sinovaginal bulb. This is followed by development of the vaginal plate, which elongates during the third to fifth months and becomes canalized to form the inferior vaginal lumen. (Modified from Sadler TW. Langman's medical embryology. Baltimore: Williams & Wilkins, 1985.)

rudiments of the external genitalia (Vermeij-Keers et al, 1996). Failure of migration of these mesodermal cells into the midline results in bladder exstrophy and other associated genital defects (Langer, 1993; Vermeij-Keers et al, 1996).

The early development of the external genitalia is similar in both sexes. Migrating mesenchymal cells spread themselves around the cloacal membrane and pile up to form swellings. Early in the fifth week, a pair of swellings called *cloacal folds* develops on either side of the cloacal membrane. These folds meet just anterior to the cloacal membrane to form a midline swelling called the *genital tubercle* (Fig. 122-23). During the cloacal division into the anterior urogenital sinus and the posterior anorectal canal, the portion of the cloacal folds flanking the opening of the urogenital sinus becomes the *urogenital folds* and the portion flanking the opening of the anorectal canal becomes the *anal folds*. A new pair of swellings, called the *labioscrotal folds*, appears on either side of the urogenital folds.

The most popular hypothesis of external genital and urethral development is based on work performed in the early part of the 20th century. Most embryology texts today quote the mechanism of urethral development proposed by Glenister (1954). As the genital tubercle elongates in males, a groove appears on its ventral aspect (called the *urethral groove*) during the sixth week. In both sexes an ectodermal *epithelial tag* is present at the tip of the genital tubercle. The urethral groove is defined laterally by urethral folds, which are continuations of the previous urogenital folds surrounding the urogenital membrane. Initially, the urethral groove extends

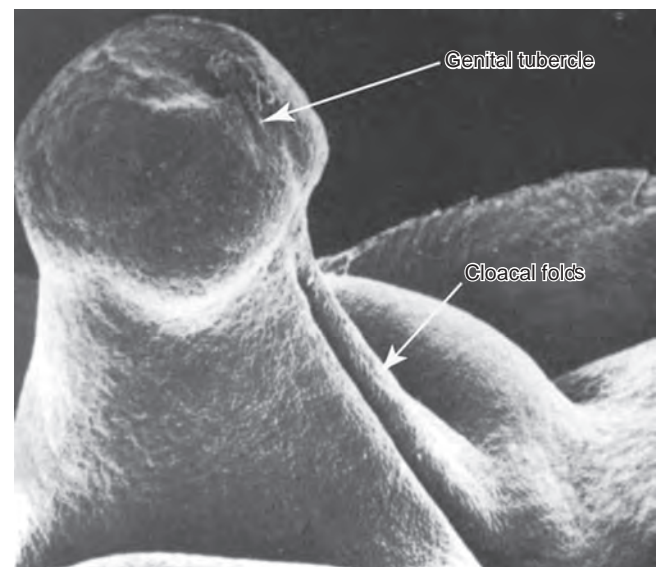


Figure 122-23. Early stages of cloacal fold development. (From Hamilton WJ, Mossman HW. Human embryology: prenatal development of form and function. New York: Macmillan; 1976; and Waterman RE. Human embryo and fetus. In: Hafez ESE, Kenemans P, editors. Atlas of human reproduction. Hingham [MA]: Kluwer Boston; 1982.)

only part of the way distally along the shaft of the elongating genital tubercle. The distal portion of the urethral groove terminates in a solid epithelial plate called the *urethral plate* that extends into the glans penis. The solid urethral plate canalizes and thus extends the urethral groove distally toward the glans. The urethral groove is thought to be lined by endoderm. Likewise, the solid urethral plate, the distal precursor of the urethral groove, is also believed to derive from the endodermal source. Clearly, fusion of the urethral folds

is the key step in the formation of penile urethra. A prerequisite of urethral fold fusion is the canalization of solid urethral plate and formation of the urethral groove bounded on each side by the urethral folds. If the urethral groove and urethral fold formations are abnormal, then the urethral fold fusion is likely to be impaired as well (Figs. 122-24 and 122-25).

The formation of the distal glanular urethra may occur by a combination of two separate processes—the fusion of urethral

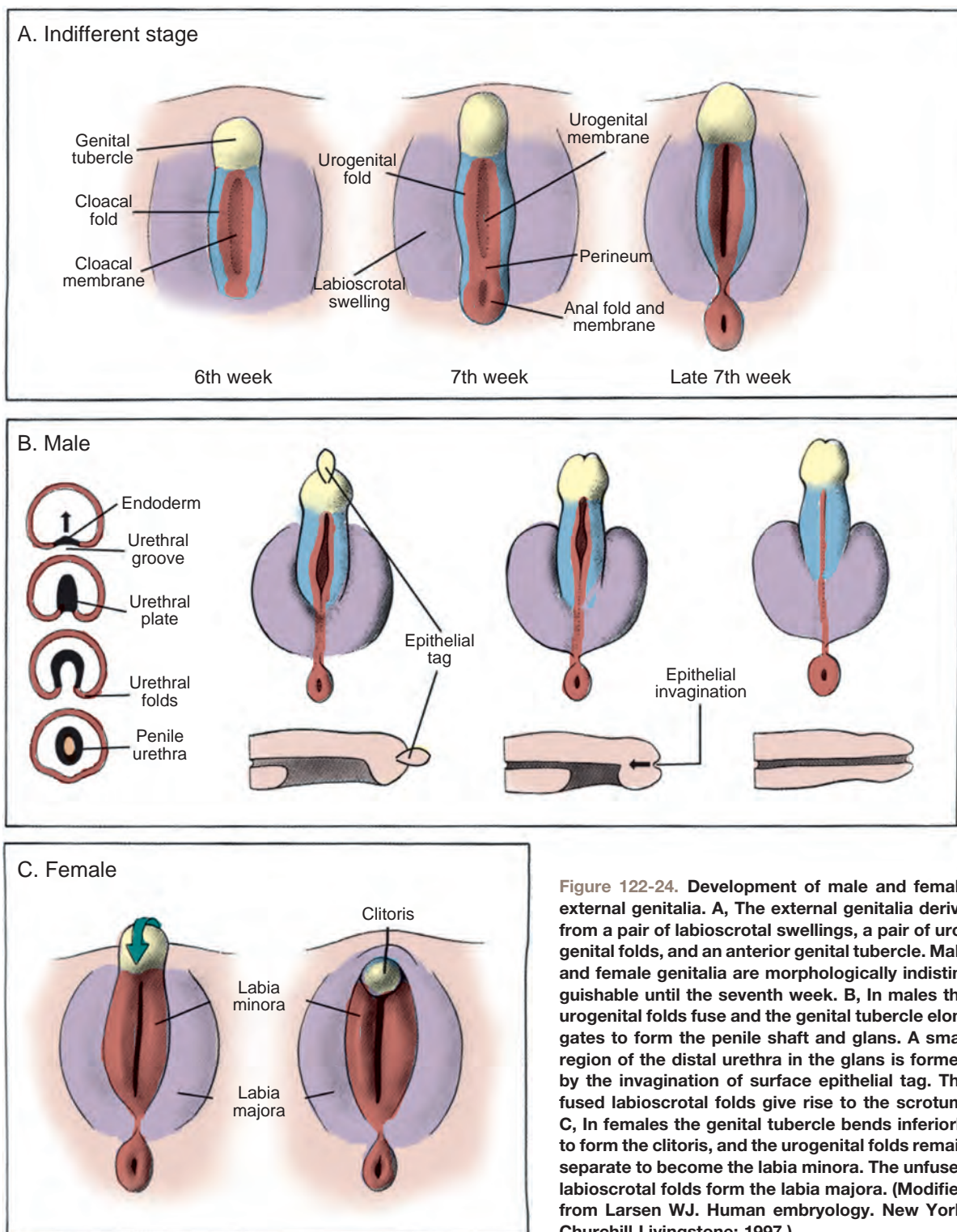


Figure 122-24. Development of male and female external genitalia. A, The external genitalia derive from a pair of labioscrotal swellings, a pair of urogenital folds, and an anterior genital tubercle. Male and female genitalia are morphologically indistinguishable until the seventh week. B, In males the urogenital folds fuse and the genital tubercle elongates to form the penile shaft and glans. A small region of the distal urethra in the glans is formed by the invagination of surface epithelial tag. The fused labioscrotal folds give rise to the scrotum. C, In females the genital tubercle bends inferiorly to form the clitoris, and the urogenital folds remain separate to become the labia minora. The unfused labioscrotal folds form the labia majora. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

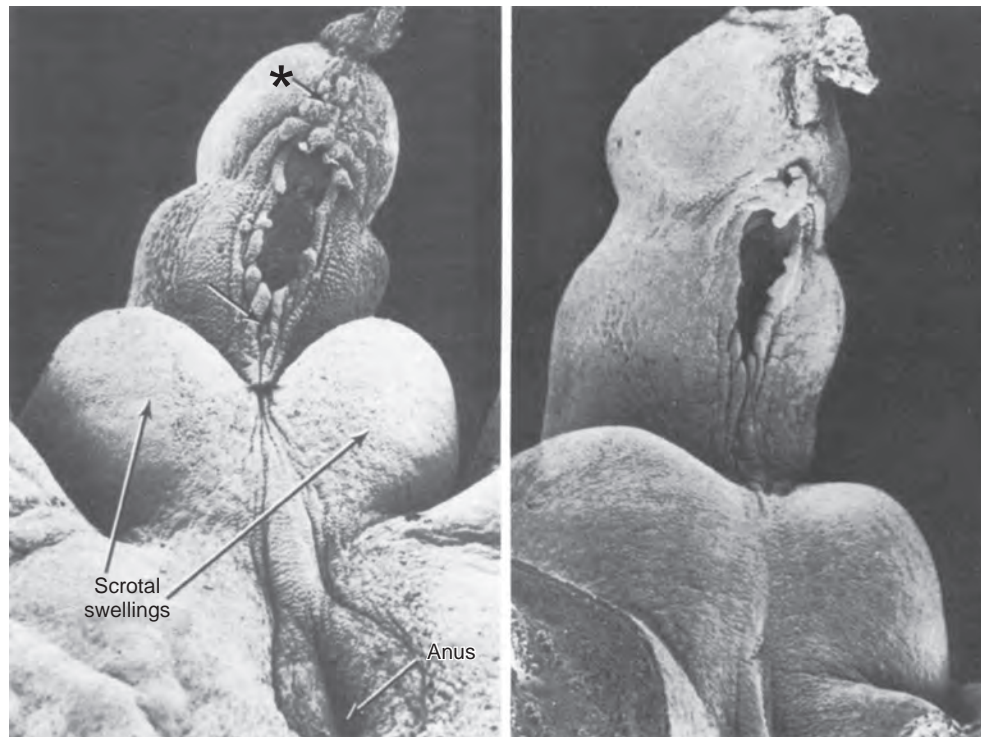


Figure 122-25. The epithelial tag (asterisk) and fusing urethral folds (arrows) in the developing male external genitalia. (From Waterman RE. Human embryo and fetus. In: Hafez ESE, Kenemans P, editors. Atlas of human reproduction. Hingham [MA]: Kluwer Boston; 1982.)

folds proximally and the ingrowth of ectodermal cells distally. It is generally thought that the stratified squamous epithelium of the fossa navicularis results from an ingrowth of surface ectoderm as far proximally as the valve of Guérin. The lacuna magna (also known as the sinus of Guérin), which can give symptoms of hematuria and dysuria in some boys, may form as a result of dorsal extension of this ectodermal ingrowth. It was suggested recently that the entire penile urethra might differentiate from the fusion of the endodermal urethral groove via the mechanism of epithelial-mesenchymal interactions (Kurzrock et al, 1999).

Development of external genitalia occurs via three main pathways: (1) androgen independent, (2) androgen dependent, and (3) endocrine and environmental influence. A complex interaction among these three pathways exists, and external genitalia development should be evaluated in the context of all three. Endocrine and environmental influences affect both androgen-independent and androgen-dependent pathways on a genetic and epigenetic basis.

The molecular basis of the sexual dimorphism in genital development is based on the presence or absence of the signaling via the androgen receptor. During embryonic weeks 9 and 10 SRY (sex-determining region of Y chromosome) causes differentiation of Leydig cells, which produce testosterone. In the presence of fetal testicular androgens the wolffian ducts persist and develop into the epididymis, vas deferens, and seminal vesicles. Testosterone is also a substrate for the enzyme, 5α -reductase, which converts testosterone to DHT. This even more potent androgen drives growth of the external genitalia and prostate. The effects of both testosterone and DHT are elicited following interaction of these hormones with the androgen receptor, a nuclear transcription factor. In the absence of functional androgen receptors, the wolffian ducts degenerate, the prostate does not develop from the urogenital sinus, and the external genitalia develop according to the female pattern.

The key role of androgen in sexually dimorphic development of the external genitalia has been corroborated through many experimental studies. In utero exposure of rodents to antiandrogenic compounds reduces the size of the genital tubercle and prevents the development of the scrotum. Likewise, in utero exposure of rats to 5α -reductase inhibitors leads to the development of hypospadias. Mice and humans with functional loss of androgen receptors via mutations demonstrate a complete feminization of the external genitalia.

The elongating phallus is covered externally by ectoderm that gives rise to the penile skin, whereas most of the substance of the penis is derived from mesodermal cells forming the corporeal bodies, connective tissue, and dermis. Corporeal tissue is first recognized as distinct dense mesenchymal condensations within the shaft of the developing penis. Little is known regarding the molecular regulatory mechanisms of the differentiation of penile mesenchyme into its various derivatives, but it is likely that this process is dependent on epithelial-mesenchymal interactions.

In the female, because of the absence of androgen receptor signaling via DHT, the primitive perineum does not lengthen and the labioscrotal and urethral folds do not fuse across the midline. The phallus bends inferiorly, becoming the clitoris, and the ostium of the urogenital membrane becomes the vestibule of the vagina. The urethral folds become the labia minora, and the labioscrotal folds become the labia majora. The external genitalia develop in a similar manner in genetic males who are deficient in 5α -reductase and therefore lack DHT.

Sonic hedgehog (Shh) is a gene that regulates development of two major body appendages, limbs, and the genital tubercle. *Shh* is expressed within the genital tubercle in urethral plate epithelium in mice and has been demonstrated to be involved in formation of the sexually undifferentiated stage and subsequent initiation of sex differentiation of the penis (Miyagawa et al, 2011). *Wnt5a*, β -catenin, and *Fgf8* act downstream of *Shh*, and β -catenin gain-of-function

mutations or exogenous upregulation of β -catenin can rescue genital tubercle development in *Shh*-null mice and recover *Fgf8* expression (Miyagawa et al, 2009a). The *Wnt*/ β -catenin pathway has been demonstrated to be essential in androgen-regulated pathways of genital tubercle development in embryonic mice, and overexpression of β -catenin resulted in masculinization of female mice characterized by prepuce hypertrophy and enlargement of the external genitalia (Miyagawa et al, 2009b). In human embryos, *SHH* is expressed in human fetal penises during development, with the greatest expression demonstrated with immunohistochemistry during urethral tubularization at 14 weeks of gestation (Shehata et al, 2011).

Molecular mechanisms of external genitalia development have been elucidated from understanding the genes involved in congenital syndromes affecting external genitalia. Autosomal dominant mutations in the chromodomain-helicase-DNA-binding protein 7 (*CHD7*) gene result in the CHARGE syndrome (coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies), and a variety of mutations in *CHD7* are found in over 75% of CHARGE syndrome patients (Blake and Prasad, 2006). Genital hypoplasia is more evident in males with CHARGE syndrome and may result in cryptorchidism, micropenis, and/or hypogonadotrophic hypogonadism. The syndrome of Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation (WAGR), which results from chromosomal deletion at 11p13 and affects the *WT1* gene, may result in hypospadias, cryptorchidism, or ambiguous genitalia. Denys-Drash syndrome and Frasier syndrome are both associated with defects in *WT1* and a spectrum of external genitalia abnormalities including ambiguous genitalia, hypospadias, and cryptorchidism (Le Caignec et al, 2007). Defective androgen receptors result in androgen insensitivity syndrome, which has a spectrum of phenotypes depending on the degree of defectiveness of the androgen receptor. A fully nonfunctional androgen receptor will result in an XY individual with phenotypically female external genitalia (Galani et al, 2008). Mutations in the androgen receptor gene are associated with defects in masculinization of the external genitalia and hypospadias, a triad of abnormal urethral, penile, and foreskin development (Wang et al, 2004). Defects in the aromatase gene, which converts testosterone to estrogen, result in elevated testosterone, which causes ambiguous genitalia in 46,XX individuals with virilization of the clitoris to a phallus-like structure (Lin et al, 2007).

Gonadal Descent

Morphologically, the human urogenital ridge is identical in both sexes at 7 to 8 weeks of gestation. Before gonadal differentiation, the testis lies near the developing kidney, loosely held in place by two ligamentous structures. The dorsal ligament is referred to as the *cranial suspensory ligament* (CSL), whereas the ventral ligament later develops into the *gubernaculum* (Fig. 122-26). Between 10 and 15 weeks, the testis remains close to the future inguinal region during the enlargement of the abdominal cavity while the ovary moves more cranially. The testis is anchored near the inguinal region by enlargement of the gubernaculum and regression of the CSL. As early as the 1700s, enlargement of the gubernaculum in males was observed to tether the testis near the groin while the kidney migrated cranially (Wyndham, 1943; van der Schoot, 1993). In females, the CSL continues to develop, keeping the ovary close to the kidney while the gubernaculum involutes. In males, androgen induces resorption of the CSL while the gubernaculum enlarges to become a plump ligamentous body, "holding" the testis close to the inguinal region. Starting in the seventh month, the gubernaculum begins to bulge beyond the external inguinal ring and descends to the scrotal location, while simultaneously it is hollowed out by the evaginating peritoneal diverticulum called the *processus vaginalis* (Heyns, 1987). The processus vaginalis allows the intra-abdominal testis to exit the abdominal cavity. The bulky distal end of the gubernaculum (known as the *bulb*) is resorbed in humans after completion of inguinoscrotal migration.

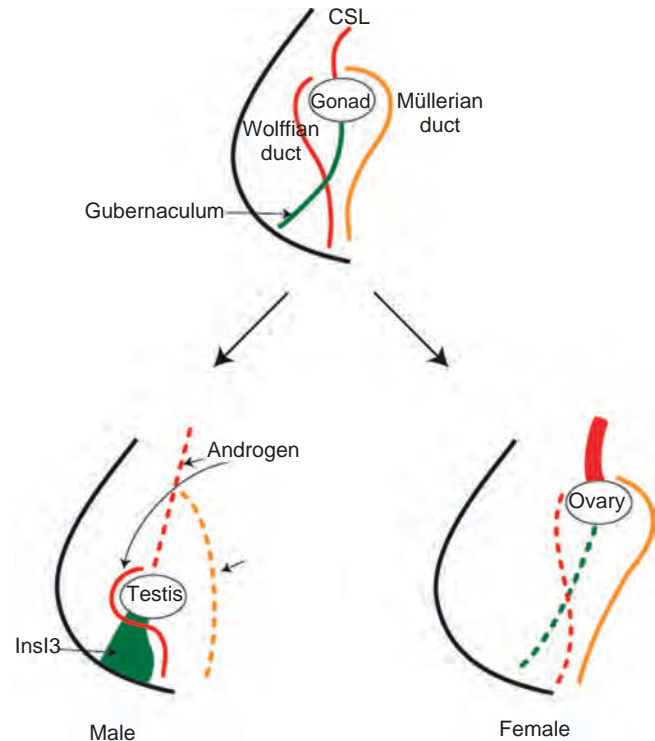


Figure 122-26. Mechanism of gonadal descent. The undifferentiated gonad is initially located high in the abdomen, anchored by the cranial suspensory ligament (CSL). In males, *InsI3* will cause the swelling and enlargement of the gubernaculum to pull the developing testis toward the inguinal region, whereas androgens will cause an involution of CSL. Owing to the action of müllerian-inhibiting substance, müllerian ducts will regress while androgens continue to stimulate the development of wolffian ducts into male genital ductal structures. In females, CSL persists because of the absence of androgens, and the gubernaculum remains thin as a result of the absence of *InsI3* activity, thereby keeping the ovary well within the pelvis.

Caudal enlargement of the gubernaculum during the early relative transabdominal movement of the testis is known as the "swelling reaction" or "gubernacular outgrowth." The proximal gubernacular cord appears to shorten during this process, as it becomes incorporated into the enlarging bulb (Wensing, 1986). Shortening of the cord may be an important mechanism to position the testis over the inguinal ring to permit abdominal pressure to push the testis out of the abdomen (Quinlan et al, 1988; Attah and Hutson, 1993; Husmann and Levy, 1995). Transection of the gubernacular cord can lead to either accidental testicular descent into the contralateral inguinal canal or aberrant intra-abdominal location (Frey and Rajfer, 1984; Beasley and Hutson, 1988; Attah and Hutson, 1993).

Although intra-abdominal pressure may not be a factor during the initial transabdominal descent, it is thought to be important during transit through the inguinal canal and the subsequent scrotal migration. Inguinoscrotal descent requires migration of the gubernaculum over a considerable distance, along with an increase in the length of the processus vaginalis. The force for movement may come from the intra-abdominal pressure, transmitted directly and indirectly to the testis via the lumen of the processus vaginalis and the gubernacular cord, respectively.

Although patients with defective androgen production or metabolism show varied manifestations of cryptorchidism, the exact role of androgen in testicular descent still remains unclear. During

intra-abdominal testicular descent, androgen appears to play a role in the regression of the CSL (van der Schoot, 1992). Gubernacular enlargement, in contrast, seems to occur independent of androgen activity, because it occurs in androgen-resistant mice and humans normally, being able to keep the testis close to the inguinal region (Hutson, 1985). The second migratory step—the inguinoscrotal phase—is thought to be more androgen dependent. Migration of the gubernaculum beyond the inguinal region is absent in gonadotropin-deficient mice (Grocock et al, 1988) and those with complete androgen resistance (Hutson, 1986). Regression of the gubernacular bulb after the completion of scrotal descent also appears to be androgen dependent because in humans with androgen resistance the gubernaculum remains enlarged (Hutson, 1986).

MIS is a glycoprotein produced and secreted by Sertoli cells and is responsible for regression of the müllerian ducts (Josso et al, 1993; Lee and Donahoe, 1993). Evidence for the role of MIS in testicular descent is conflicting. Some clinical observations support the role of MIS, including patients with persistent müllerian duct syndrome caused by genetic defects of MIS or its receptor gene (Josso et al, 1983). In this clinical scenario the testes are undescended and the gubernaculum is thin and elongated. Transgenic mice with MIS deficiency show a variable testicular position depending on their androgenic status: those with normal androgen receptors have normally descended testes, whereas those with androgen resistance have completely undescended testes (Behringer et al, 1994). A recent study on MIS-receptor knockout mice, however, failed to show any defect in gubernacular development and testicular positions (Bartlett et al, 2002).

INSL3 was identified as a novel gene product of the Leydig cells in 1993 (Adham et al, 1993). INSL3 is similar in structure to the peptide hormones relaxin or insulin and is expressed in both fetal and adult Leydig cells in a differentiation-dependent manner (Balvers et al, 1998). Mice lacking a functional *Insl3* gene demonstrate intra-abdominal cryptorchidism but otherwise no obvious defects in other male reproductive organs. Of more importance, early surgical correction of the cryptorchidism in these mice can restore normal fertility potential (Nef and Parada, 1999; Zimmermann et al, 1999). These are important findings because they reflect the phenotype most commonly observed in classic cryptorchidism in humans. Recently, a G protein–coupled receptor—LGR8—has been cloned with binding and functional response to INSL3 in transfected cells (Hsu et al, 2002; Kumagai et al, 2002). Moreover, mutations in this receptor in mice can lead to the development of cryptorchidism and have been linked to cryptorchidism in humans (Overbeek et al, 2001; Gorlov et al, 2002). Treatment of rat gubernacular explant with exogenous INSL3 leads to a rapid growth of the ligament, an effect that synergizes with androgen treatment (Kubota et al, 2002). It was also demonstrated that LGR8 was expressed in the rat gubernaculum (Kubota et al, 2002). Although INSL3 appears to be a good candidate for a responsible gene for cryptorchidism, to date no causative mutations have been identified in the human *INSL3* gene. Furthermore, because INSL3 is expressed in a differentiated testis, any factor that influences Leydig cell differentiation may also affect INSL3 expression and thereby cause cryptorchidism.

Treatment of pregnant mothers with diethylstilbestrol as a hormonal support during pregnancy was abandoned owing to a high rate of cryptorchidism and other genital defects (Stillman, 1982). The effect of environmental xenoestrogenic compounds has also been linked to the recent rise in cryptorchidism in humans (Toppari and Skakkebaek, 1998). In one study, mice were treated with diethylstilbestrol to induce cryptorchidism in male neonates (Emmen et al, 2000; Nef et al, 2000). It is interesting to note that the treated animals demonstrated a complete suppression of testicular *Insl3* expression on embryonic days 16 and 18.

The male knockout mice for the transcription factor *Hoxa-10* gene are viable but infertile. While they are normally virilized, they are bilaterally cryptorchid with a severely underdeveloped gubernaculum. Fetal localization studies have shown that *Hoxa-10* is expressed in the gubernaculum, as well as in the kidneys, but not in other reproductive tissues. Although its function and role are not

yet established, it appears to be another candidate regulatory gene for gubernacular development and testicular descent.

The spinal nucleus of the genitofemoral nerve (GFN) is located at L1-2 in the spinal cord and is sexually dimorphic (Goh et al, 1994). Transection of the GFN produced cryptorchidism (Lewis, 1948), and the initial thought—now proven faulty—was that the cremasteric muscle paralysis caused by denervation led to an abnormal traction of the testis through the inguinal canal. When this observation was revisited many years later, it was speculated that androgens may act via the GFN (Beasley and Hutson, 1987). The GFN innervates the gubernaculum from its posterior and caudal surface, so that distal transection would cause denervation of the gubernaculum (Tayakkanonta, 1963). Additional supporting evidence for the role of the GFN comes from the analysis of patients with spina bifida and animals with spinal cord transection (Hutson et al, 1988). In more than 300 boys with spina bifida, 23% had cryptorchidism, with a higher incidence found in those whose defect was higher than L4. In rats with neonatal spinal cord transection, approximately 40% had cryptorchidism when the lesions were midlumbar. Anatomic studies of the GFN identified calcitonin gene–related peptide (CGRP) as the primary neurotransmitter (Goh et al, 1994). The effect of CGRP on the rodent gubernaculum has been studied extensively. In male neonatal rats under anesthesia, the gubernaculum, which has not yet reached the scrotum, contracts rhythmically; this is enhanced by increased intra-abdominal pressure and direct application of exogenous CGRP (Park and Hutson, 1991). In organ culture, neonatal rat gubernaculum responds to CGRP in a dose-dependent manner but not to other neuropeptides (Park and Hutson, 1991). Although these findings are raising a strong speculation for the role of CGRP, its significance in human testicular descent remains uncertain.

The ovaries also descend and become suspended within the broad ligaments of the uterus. As in males, the female embryos develop a gubernaculum-like structure extending initially from the inferior pole of the gonad to the subcutaneous fascia of the presumptive labioscrotal folds. This “female gubernaculum” later penetrates the abdominal wall as part of a fully formed inguinal canal and becomes the *round ligament*. In females, although the gubernaculum does not shorten like that in males, it still causes the ovaries to descend during the third gestational month (by anchoring the ovaries in the pelvis) and places them into a peritoneal fold (the *broad ligament* of the uterus). This translocation of ovaries appears to occur during the seventh week when the gubernaculum becomes attached to the developing paramesonephric (müllerian) ducts. As the paramesonephric ducts fuse together in their caudal ends they sweep out the broad ligaments and simultaneously pull the ovaries into these peritoneal folds. In the absence of androgens, the female gubernaculum remains intact and grows in step with the rest of the body. The inferior gubernaculum becomes the round ligament of the uterus and attaches the fascia of the labia majora to the uterus, while the superior gubernaculum becomes the ligament of the ovary, connecting the uterus to the ovary. As in males, the processus vaginalis of the inguinal canal is normally obliterated, but occasionally it remains patent to become an indirect inguinal hernia.

Molecular Mechanism of Sex Development

At the beginning of gestation (first and second week in humans), embryos of the two sexes differ only by their sex chromosomes. The first visible sign of sexual dimorphism in mammalian embryos is when the bipotential gonad starts to develop into either a testis or an ovary in XY and XX individuals, respectively. This occurs at around 6 weeks of development in humans. Differentiation of the gonads leads to testicular and ovarian hormone production and subsequent induction of anatomic and physiologic differences.

Mammalian sex development involves a complex interplay of multiple cell types that occurs in a narrow window of time. Thus it is important to understand the temporal and spatial patterns of gene expression as well as the anatomic sequence of tissue movement and differentiation.

Both testis and ovarian development involve sex-specific pathways that appear to act antagonistically to one another. The normal role of *SRY* in XY gonads is to tip the balance in favor of the testis-specific pathway. *SRY* expression initiates an upregulation of *SOX9* expression. In mice, *Sox9* has been shown to stimulate *Fgf9* expression and subsequently, both FGF9 and SOX9 act together in a positive feedback loop and are thought to suppresses *Wnt4* (by unknown mechanisms), leading to the establishment of the testis-specific pathway. In the absence of *SRY* in XX individuals, *RSPO1* and *WNT4* are expressed at high levels and stabilize cytoplasmic β -catenin, which is then translocated into the nucleus, where it binds to the TCF/LEF (transcription factor/lymphoid enhancer-binding factor) and activates the transcription of target genes. Both *WNT4* and β -catenin suppress (by unknown mechanisms) the *SOX9*/FGF9 positive feedback loop, allowing the ovarian-specific pathway to progress.

In both sexes, before the expression of the male-determining gene *SRY*, a number of factors appear to play a role in urogenital ridge specification (Fig. 122-27). Because the urogenital ridge is the

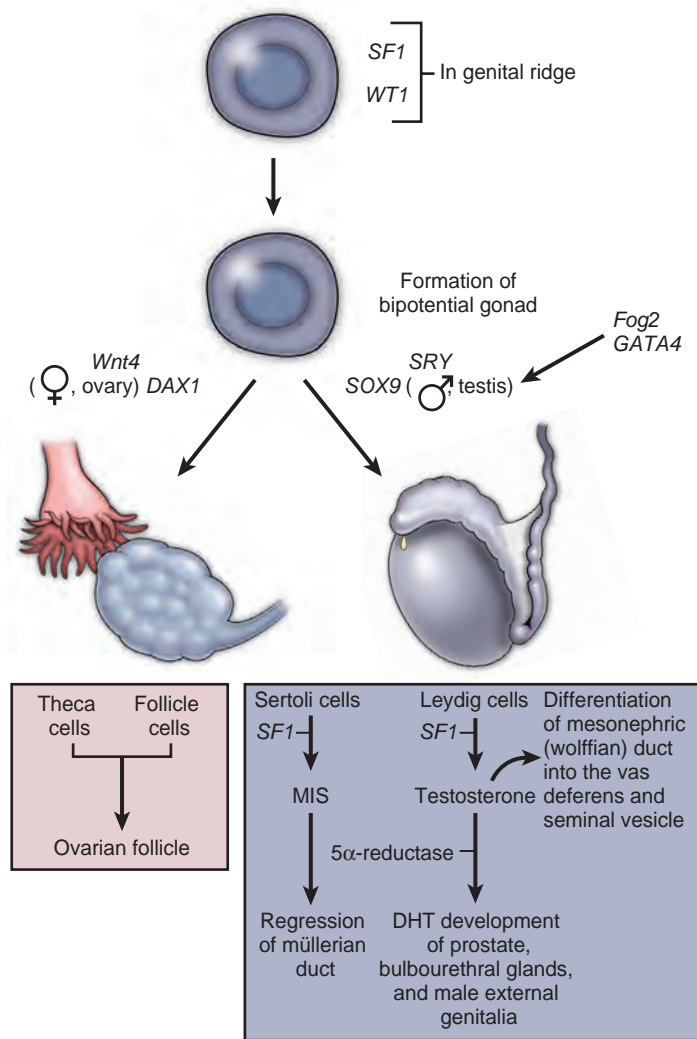


Figure 122-27. Molecular mechanism of male and female genital development. *SF1* and *WT1* expression is critical for genital ridge specification. *SRY* and *SOX9*, influenced by *GATA4* and *Fog2*, are important factors for specifying the differentiation of Sertoli cells. *SF1* is also critical in the regulation of müllerian-inhibiting substance (MIS) and other genes involved in androgen synthesis. No specific female factors have been identified, but *Wnt4* and *DAX1* are expressed with unique female patterns. DHT, dihydrotestosterone.

primordium for the gonad, kidney, and reproductive tract, multiple organs are affected by mutations of these genes. In the mouse gonad, *Wt1* is expressed early, suggesting a role in specifying coelomic epithelial cells in the development of urogenital ridge. The *Wt1* homozygous knockout mice do not form kidney, adrenal, or gonad cells (Kreidberg et al, 1993). Humans heterozygous for mutations in *WT1* exhibit abnormalities of the genital system in addition to abnormalities in renal development, including WAGR syndrome, Denys-Drasch syndrome, and Frasier syndrome. *WT1* appears to function upstream of *SF1* (steroidogenic factor 1) and *DAX1* (dosage-sensitive sex reversal, adrenal hypoplasia congenita, X chromosome) (Wilhelm and Englert, 2002). *Wt1* and *Sf1* enhance transcription of mouse *MIS* gene, whereas *Dax1* appears to suppress this interaction (Nachtigal et al, 1998). *SF1* also regulates the expression of other genes involved in male differentiation, steroidogenesis, and reproduction (Achermann et al, 2001). Although *SF1* stimulates *DAX1* transcription (Ikeda et al, 1996), *DAX1* in turn acts as a transcriptional repressor of *SF1*-regulated genes (Ito et al, 1997). In *Sf1* knockout mice, neither XX nor XY animals form gonads, and cells in gonadal remnant undergo apoptosis, suggesting that *SF1* is a necessary survival factor for early progenitors of a developing gonad (Luo et al, 1994). Data suggest that *SF1* and *DAX1* are both independently important for normal male gonadal differentiation. Other candidate genes have also emerged based on mouse gene deletion models and embryonic expression studies, although their functional significance in gonadal development is not fully elucidated yet; they include *Emx2*, *M33*, *Lhx9*, *Pod1*, *Dmrt1*, *Mro*, *Pn1*, and *Vn1* (Park and Jameson, 2005).

Mammalian embryos remain sexually undifferentiated until the time of sex determination. When the Y-linked master regulatory gene, called *SRY* (the sex-determining region of the Y chromosome), is expressed in the male, the epithelial cells of the primitive sex cords differentiate into Sertoli cells, and this critical morphogenetic event triggers subsequent testicular development. Once the testes are established, they produce androgens to give rise to the male phenotype. In the female gonads no morphologic change is observable at the time of *SRY* expression. It follows from this general picture that in mammals, sex determination is synonymous with testicular development, with the differentiation of Sertoli cells being the key event (McLaren, 1991). After three decades of search for the elusive mammalian testis-determining gene, the *SRY* gene was discovered in 1990 by Sinclair and colleagues (Sinclair et al, 1990). Since then, research has focused on identifying the putative regulatory mechanism operating downstream of *SRY* and the genetic control of *SRY* expression.

Although it has been known since 1921 that human males have an X and Y chromosome, the role of these "sex" chromosomes in human sex development was not elucidated until 1959. This question was answered by the examination of two individuals with unique chromosome abnormalities: one female with Turner syndrome (45,XO karyotype) and one male with Klinefelter syndrome (47,XXY karyotype). By 1966, analysis of many structurally aberrant Y chromosomes in humans led to the conclusion that the information necessary to initiate the male phenotypic development was present on the short arm of the Y chromosome. The identity of the protein encoded by the testis-determining region of the Y chromosome proved elusive. In the mid 1980s the DNA of sex-reversed males with 46,XX karyotype was examined. The genome in these individuals was found to contain small amounts of Y chromosome that had been translocated onto the X chromosome. Analysis of this DNA narrowed the location of the *SRY* to a relatively small region within the short arm of the chromosome. The role of *SRY* in human sex development has been further supported by studies using mice (Greenfield and Koopman, 1996). The comparable genetic locus in mice (*Sry*) is activated and expressed in the genital ridge 11.5 days after coitus, just before the initiation of testicular development. Moreover, when the DNA of female XY mouse chromosomes was analyzed with specific DNA probes for *Sry*, this locus was absent. Of greatest importance, it has been demonstrated that insertion of *Sry* into one of the X chromosomes of genetically female mouse

embryos converted these mice to phenotypic males (Koopman et al, 1991). These transgenic “female” mice exhibited testes, vas deferens, and an absence of the female reproductive tract. It was thought that identification of the SRY protein would rapidly lead to the identity of downstream elements regulating male sexual development. However, the binding of SRY protein to other genes or factors has not been demonstrated, and the molecular mechanism by which genes interact to determine sex remains speculative. Deletions of the SRY gene in humans cause XY male-to-female sex reversal, whereas SRY translocations to the X chromosome lead to XX female-to-male sex reversal (Harley et al, 2003). In the mouse, *Sry* expression occurs in a narrow temporal window in the developing Sertoli cells. The central region of the gonad demonstrates *Sry* expression first, followed by cephalad to caudal progression along the entire length of the gonad (Bullejos and Koopman, 2001). A closely related gene, *SOX9*, is the other definitive male-determining gene identified thus far. *SRY* and *SOX9* expression overlaps in cells of the Sertoli lineage. As the *SRY* expression diminishes, *SOX9* expression increases in the male. *SOX9*, which is weakly expressed in the undifferentiated gonad, is downregulated in the female (Sekido et al, 2004). Transgenic expression of *Sox9* in XX mice is sufficient to induce female-to-male sex reversal and male differentiation (Vidal et al, 2001). Heterozygous human *SOX9* mutation leads to campomelic dysplasia, a severe skeletal disorder with defective cartilage development; many of these patients have dysgenetic gonads (Foster et al, 1994). These individuals possess a normal *SRY* but may exhibit completely feminized genital structures. *Sox9* knockout mouse embryos have elevated levels of *Sry* expression, suggesting a possible negative feedback regulatory loop that downregulates *Sry* (Chaboissier et al, 2004). *GATA4* and *Fog2* are important in cardiac development but also appear to affect gonadal development as well. *GATA4* mutation eliminates expression of male differentiation markers *Sox9* and *MIS*. *Fog2* knockout mice have decreased expression of *Sry* and loss of *Sox9*, *MIS*, and *desert hedgehog*, but persistence of female gonad marker *Wnt4* (Tevosian et al, 2002). Similarly, triple mutants for insulin receptor, insulin-related receptor, and *Igf-1* receptor have low *Sry* and *Sox9* expression and exhibit male-to-female sex reversal, implicating a role for an insulin signaling pathway (Nef et al, 2003).

Proliferation of Sertoli progenitor cells is an important event in male gonad development, a process driven by *SRY* expression (Schmahl et al, 2000). One paracrine factor linked to this proliferation is FGF9. *Fgf9* knockout mice demonstrate varying degrees of male-to-female sex reversal (Colvin et al, 2001). In addition, FGF9 is a candidate male gonad-specific chemoattractant paracrine signal that induces migration of cells from the mesonephros (endothelial and peritubular myoid cells) into the gonad (Martineau et al, 1997). Migration of these cells is critical for the development of testis cord formation (Buehr et al, 1993) as well as *SOX9* expression (Tilman and Capel, 1999). Such migration is absent in females, presumably owing to absence of chemoattractants.

Once sex determination has occurred, the subsequent phenotypic differentiation depends mostly on the production of androgens. As bipotential gonad differentiates into testis, *Sf1* expression becomes restricted to Leydig cells and mediates expression of several gene-encoding enzymes that are required for testosterone biosynthesis, including *StAR*, *Cyp11a1*, *Cyp17*, and *3βHSD*. Factors for Leydig cell determination are not known, and, moreover, Leydig cell origin, whether from immigrant mesonephric cells or progenitors within the gonad, remains speculative. There is evidence that Leydig cell fate is dependent on paracrine signals (Yao et al, 2002; Brennan et al, 2003).

Relatively few genes have been shown to exhibit a female-specific pattern of gene expression early in gonadal development. Thus far, no female-determining gene has been identified. The *DAX1* gene was initially suggested as a pro-ovarian (or anti-testis) candidate gene because its duplication on an XY background was associated with impaired testicular development (Bardoni et al, 1994; Swain et al, 1998). However, loss of *DAX1* in XX background does not prevent ovary development (Yu et al, 1998). The list of

genes that demonstrate ovary-specific expression patterns is growing; these include *Fst* and *Stra8* (Park and Jameson, 2005). It has been postulated that there is a “Z-factor” that suppresses proteostic events in both XX and XY backgrounds (McElreavey et al, 1993). According to this hypothesis, the Z-factor, which normally suppresses testicular determination, is repressed by *SRY* in males, and in females, owing to absence of *SRY*, it will inhibit testicular development. Loss of the Z-factor in the XX background will result in female-to-male sex reversal, but gain-of-function in XY background may or may not result in male-to-female sex reversal, depending on whether the Z-factor can override the suppression effect of *SRY*-driven signaling. One candidate for such a Z-factor is *Wnt4*. XX mice deficient for *Wnt4* develop testis-like differentiation and nephric (wolffian) duct derivative (Vainio et al, 1999). It is curious to note that their external genitalia remain female. Furthermore, *Wnt4* is downregulated in males, whereas its expression remains strong in females (Yao et al, 2004). R-spondin 1 (*RSPO1*) encodes a secreted factor that can stabilize β-catenin as part of the canonical Wnt-signaling pathway and is expressed at high levels in mouse as well as human gonads around the critical time of gonad development. Its role in ovarian development was first implicated when a homozygous single nucleotide insertion within the *RSPO1* coding sequence was identified in four 46,XX testicular disorders of sex development (DSD) patients from a consanguineous family. In addition, a homozygous exonic deletion was identified in an unrelated sporadic case of 46,XX testicular DSD. In 46,XX female individuals, both *WNT4* and *RSPO1* are known to promote ovarian development and repress testis development (Parma et al, 2006).

KEY POINTS

- The genitourinary system develops from three embryonic sources: intermediate mesoderm, mesothelium of coelomic (future peritoneum) cavity, and endoderm of the urogenital sinus.
- The urinary system begins its development before the genital system development becomes evident. With the formation of nephric ducts, embryonic kidneys develop sequentially in the order of pronephros, mesonephros, and metanephros.
- The permanent kidney, the metanephros, develops as a result of inductive interactions involving the ureteric bud (an outgrowth of nephric duct), condensing blastema of metanephric mesenchyme, and stromal cells. The renal tubulogenesis occurs via mesenchymal-epithelial conversion, whereas dichotomous branching of the ureteric bud leads to the formation of the collecting system.
- The bladder and urethra develop from the endodermal urogenital sinus, which is an anterior portion of the cloaca after it becomes separated from the posterior anorectal canal.
- Morphologically, the genital development takes place about 3 weeks after the start of the urinary system development. Sexual dimorphism begins to take shape at about the seventh gestational week. Primordial germ cells migrate from the wall of the yolk sac to invade the posterior mesenchyme to establish the gonadal ridge.
- In males, driven by the *SRY* gene of the Y chromosome, mesenchymal cells of the developing testis differentiate to become the Sertoli cells. Sertoli cells produce *MIS* to cause degeneration of female müllerian ductal structures while stimulating the development of testosterone-producing Leydig cells. Under the influence of testosterone, male external genitalia develop, as well as prostate and other male accessory sex glands.
- Both gonads descend to pelvic location by the third month, but the testis descends into the scrotum with the aid of the gubernaculum at about the seventh month.

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Development of Renal Function and the Transition to Neonatal Life

Renal Homeostasis, Fluids, and Electrolytes

Clinical Presentation of Renal Dysfunction

Renal Replacement Therapy

Summary

While pediatric urologists and pediatric nephrologists train through very different pathways and are often thought by many in medicine to practice their crafts in relative separation, in fact the two specialties are tightly linked through the anatomic and functional effects of urinary tract malformations and acquired diseases. This chapter is designed to highlight areas of clinical practice wherein the collaborative expertise of nephrologists and urologists can best benefit acute and chronic patient care.

DEVELOPMENT OF RENAL FUNCTION AND THE TRANSITION TO NEONATAL LIFE

Nephrogenesis and Anatomic Development

The development of the human kidneys and urinary tract begins extraordinarily early in human development with the metanephric kidney appearing during the fifth to sixth week of gestation as the ureteric bud epithelium branches from the wolffian duct. **Nephrogenesis completes in utero at 36 weeks of gestation with approximately two thirds of nephrons developing in the third trimester.** Concomitant lower urinary tract development occurs from 8 to 10 weeks of gestation; urine production begins around 10 weeks of gestation. The process of centrifugal maturation of the kidneys results in deeper, juxtamedullary nephrons that are larger, more mature, and more completely functional than “younger” developing outer glomeruli at the time of birth (Fig. 123-1). The complex genetic, epigenetic, and biochemical pathways of induction, differentiation, and functional development are areas of significant research progress but remain unclear, and the vast majority of kidney and urinary tract malformations and “acquired” diseases remain with poorly understood etiologies and pathologic mechanisms and minimal therapeutic options. The majority of congenital renal and urinary tract disorders have anatomic and functional abnormalities of both the kidneys and the urinary tract, many with “mixed” anomalies including dysplasia, cystic malformations, varying degrees of obstruction or vesicoureteral reflux, and voiding dysfunction. The inter-relationships between the individual anomalies and the resultant final patient phenotype with progressive chronic renal disease remain unclear but are areas where collaborating pediatric nephrologists and urologists are likely to provide enhanced patient care through appreciation of the complexity of the overall picture and understanding of how expectant or therapeutic management can be expected to affect the final physiologic phenotype.

Hemodynamics, Glomerular Filtration Rate, and Tubular Function

As fetal life progresses, renal blood flow, glomerular filtration rate (GFR), tubular function, and urine flow all increase in magnitude and regulatory sophistication, although blood flow remains highest in the medulla and minimal in the developing cortical regions. It should be noted that renal blood flow and GFR are only 10% of those of an adult at the time of term delivery and are even lower in premature infants. **However, perinatal redistribution of renal blood flow leads to increases in cortical blood flow that, along with increased arterial pressure, glomerular permeability, and filtration surface area, result in a doubling of GFR in healthy infants by around 2 weeks of postnatal life.** For the first day or so after birth, creatinine values in infants reflect maternal renal function alone, but creatinine should never rise in a term newborn. Healthy term neonates will have a serum creatinine below 1.0 mg/dL by 1 week of age and will continue to decrease to around 0.3 mg/dL by 1 to 3 months after birth. Preterm infants, with “unfinished” nephron development, can be expected to have higher creatinine values (inversely proportional to gestational age) and slower decreases to 0.4 to 0.8 mg/dL by 6 months (Alinei and Guignard, 1987; Finney et al, 2000). It is now believed that many extremely premature infants may not normally complete nephrogenesis because of the multitude of perinatal and postnatal events and exposures following a preterm delivery, and these apparently small increases in creatinine may actually represent chronic kidney disease (CKD) caused by nephron deficits (Carmody and Charlton, 2013).

Fetal urine output increases exponentially during the second half of gestation to around 1.0 mL/min at birth but then rapidly declines to around 0.1 mL/min after delivery, reflecting the need to conserve water. However, neonatal urinary concentrating capacity is still quite limited by a short loop of Henle, low NaCl transport in the ascending limbs, low urea generation, and decreased response to arginine vasopressin (Ames, 1953). All of these functional activities of the nephron increase progressively through the first year or two of life to reach adult levels, but the overall immaturity of these operations places the infant at high risk for loss of fluid and electrolyte homeostasis if challenged by illness, overload, or depletion.

Neonatal sodium balance is also characterized by a progressive increase in reabsorptive capacity, a relatively slow excretory response to a sodium load, and very importantly, overall positive sodium

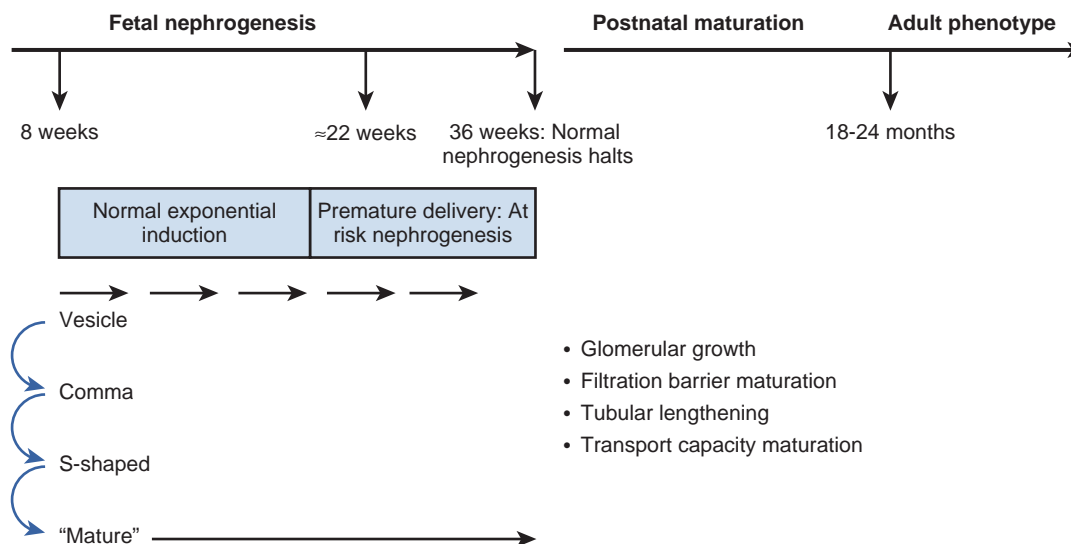


Figure 123-1. Time frame of nephrogenesis and renal maturation noting the extensive expected morphogenetic interval at risk in the event of preterm delivery.

balance needed for normal growth. However, premature infants, with even more immature mechanisms to control these factors, have higher obligatory sodium losses (as high as 5% or more in those infants <30 weeks of gestation) owing to relatively poor proximal and distal tubule transport functions and responses to aldosterone that eventually improve (Feld and Corey, 2004). In the meantime, many premature infants will require sodium supplementation to support normal growth.

Other tubular functions such as control of potassium, phosphate, calcium, and acid-base homeostasis are also less efficient in newborn infants than in adults, with preterm infants even more challenged by these tasks. Urinary phosphate excretion is low as a result of poor tubular responsiveness to parathyroid hormone, and calcium excretion is high, most likely linked to relatively poor sodium reabsorption (Webster and Haramati, 1985). Potassium excretion is limited by a number of factors, including unfavorable electrochemical gradient in the principal cells, low membrane permeability to K^+ , low tubular flow rates, and low sensitivity to mineralocorticoids (Benchimol and Satlin, 2004). Acid-base balance is also different in the newborn than the older child and adult, and infants have lower blood pH and bicarbonate levels because of a reduced threshold of HCO_3^- in the proximal tubule. Similarly, infants are unable to maximally acidify the urine by generation of ammonium, leading to additional low-level acidosis (Quigley and Baum, 2004).

Clinical Correlates

Effects of Obstruction/Maldevelopment on Transition

It should be noted that kidneys are not required for fetal survival as all solute and electrolyte control can be managed by exchange across the placenta. However, fetal urine output is mandatory for in utero airway branching and alveolar development such that low urine output states, whether from renal developmental catastrophes or obstructive lesions, result in pulmonary hypoplasia that may not be sufficient to sustain postnatal life or may not allow for life without pulmonary support systems. Unfortunately, the quantitation of amniotic fluid volumes and the assessment of fetal pulmonary development remain challenging and relatively inaccurate, making prognostic determinations extremely difficult unless multiple serial assessments are feasible.

Given the relative immaturity of the majority of all glomerular and tubular functions in the full-term newborn and even greater immaturity in the preterm infant, any additional processes that

compromise function can have significant impacts on the overall well-being of the neonate. Hypoxia, hypovolemia, hypoperfusion, nephrotoxic drugs, and fluid/electrolyte deficits or overloads all lead to more dramatic alterations in renal function and fluid and electrolyte balance during early infancy, and acute kidney injury (AKI) may have deleterious long-term effects that are not as apparent in the mature kidney exposed to the same challenges. The effects of kidney injury suffered in the neonatal period have been minimally studied in human adults, and since many of those injuries were not isolated to the kidneys, it is very challenging to determine causality; however, as we become more and more adept at saving the lives of the most extremely premature infants, we must be attentive to saving the long-term function of all organ systems.

Effects of Nephron Endowment

While in vivo determination of nephron number remains elusive, it is apparent that genetic endowment of nephron number is quite variable. Because functional nephron number declines consistently beginning in early adulthood (Winearls and Glasscock, 2011), it is logical that higher initial nephron counts may result in better long-term preservation of renal function in adulthood and through modern society's consistently lengthening life span. In a similar fashion, starting with lower nephron numbers may lead to the development of clinically significant renal insufficiency over time, a process that would clearly be exacerbated by the addition of acquired disease or other life events that cause renal damage, even if quantitatively small at the time. Since well over half of the genetically determined nephrons are formed after 30 weeks of gestation (Hinchliffe et al, 1991), pediatric practitioners should be additionally attuned to the continually increasing deleterious effects of premature delivery added to anatomic urinary tract defects plus recurrent illness, medication use, and other physiologic stressors. These synergistic effects are often subtle and masked by hyperfiltration of remaining nephrons, with clinically observable functional compromise occurring sometimes severely and rapidly when compensatory mechanisms are finally unable to maintain homeostasis. The long-term functional effects of decreased nephron number, whether determined by development or altered by disease or illness later in life, should be a point at which pediatric nephrologists and urologists should consistently focus together; preservation of remaining nephrons is important for everyone. Procedures that remove remaining nephrons should be very carefully considered and acute events that risk remaining nephrons should be aggressively managed.

RENAL HOMEOSTASIS, FLUIDS, AND ELECTROLYTES

Glomerular Filtration Rate, Tubular Function, and Hemodynamics

As described earlier, the transition from fetal to postnatal life is a period of rapid change in renal hemodynamics, filtration capabilities, and tubular function, with the majority of capabilities near adult levels by 6 to 12 months. Only fine-tuning of these processes occurs over the second 12 months of life. However, maturation of these functions is slowed by prematurity, anatomic abnormalities of the urinary tract, and other systemic illness such that the infants seen by pediatric urologists will very often have notable “developmental delays” in expected renal functional capacity. Recognition that apparently small changes in laboratory values may indicate significant underlying dysfunction can encourage special attention to drug choice, dosing, and monitoring; close observation of responses to fluid prescriptions; and rapid appropriate adjustments to the original plan. Indeed, many patients seen by the pediatric specialist will have subtle functional abnormalities that may be evident only when the stress of an acute event meets “normal” management practices. Since renal functional capacity never increases after the early events of the first 2 years after birth, the astute clinician is permanently wary of the child who exhibits any signs of functional insufficiency.

The measurement of GFR in infants remains difficult. Standard measurements of GFR by creatinine clearance or iothalamate/iohexol/inulin clearance are difficult because of the need for timed urine collections and timed blood draws and poor availability of laboratory assays. Nuclear imaging options also require accurate intravenous injections, timing, and data collection and results are not tightly reproducible in young children. Measurement of serum creatinine (also challenged by the multiple options of chemical assessment) remains the most common clinical approach to estimation of GFR using the Schwartz equation to correct for body mass (Schwartz et al, 2009). The use of serum cystatin C for measurement of GFR is gaining popularity as it is not excreted by the renal tubule and therefore is more accurate in settings of renal dysfunction, but it is not yet routinely available with rapid turnaround (Filler et al, 2002). In the meantime, clinicians should recognize that (1) creatinine change is a slow and relatively inaccurate marker of changes in GFR, especially when steady state is not achieved; (2) other indicators of renal function (fluid balance, electrolyte changes) may also indicate significant functional impairment; and (3) careful and accurate measurement of GFR may not be necessary in usual clinical practice but should be mandatory in research situations where functional outcomes are of primary interest.

Manifestations of Renal Immaturity

The reduced functional capacity of immature kidneys complicates the physiologic responses to external stress. The inability to maximally concentrate the urine contributes to the development of dehydration in the presence of illness or volume restriction, while the inability to maximally dilute the urine results in a slowed response to large fluid infusions and subsequent hyponatremia and volume overload. The hallmark of developmental proximal tubular “dysfunction” is acidosis resulting from suboptimal reabsorption of filtered bicarbonate, while distal tubular dysfunction is marked by relatively poor potassium secretion and resultant hyperkalemia. Metabolism and clearance of medications is often slowed in early childhood, and many drugs have unfortunately never been adequately studied for use in the young child. All of these developmentally normal concerns are exacerbated in the presence of renal anomalies.

The aberrantly formed tubules of dysplastic kidneys are unable to maximally reabsorb sodium or concentrate the urine, and obstructive nephropathies are commonly marked by aldosterone resistance of the distal tubule and subsequent hyperkalemia and acidosis. Therefore relatively mild childhood illnesses commonly result in dehydration with significant electrolyte disarrays in infants and children with underlying renal disease.

Fluid Prescriptions

Fluid and electrolyte prescriptions for hospitalized children unable to take enteral fluids are a mainstay of clinical care. In general, these prescriptions are a combination of “maintenance,” “replacement,” and “anticipated losses.” By definition, “maintenance” fluid needs are based on weight or body surface area and preserve homeostasis by correcting the obligatory daily losses of water and solute that occur at basal state. “Replacement” fluids and electrolytes are those needed to correct for losses occurring from acute illness, including vomiting, suctioning, diarrhea, third spacing, fever, excessive sweating, burns, and bleeding. Practitioners planning ahead also include “ongoing anticipated losses” and utilize additional fluids and electrolytes to proactively prevent dehydration or electrolyte disarray from expected outputs such as third-space drainage, ostomy losses, nasogastric suctioning, and continued vomiting.

In healthy young children, maintenance needs are based on normal energy expenditure and logically reflect the water and electrolyte content of human and cow’s milk as converted to hypotonic saline solution (0.2% [or ¼ normal] saline in 5% dextrose in water with 10 to 20 mEq/L of potassium chloride) (Holliday and Segar, 1957). However, the use of these fluids has recently become controversial because of the recognition of complications of hyponatremia in hospitalized patients (Holliday et al, 2003; Beck, 2007; Moritz and Ayus, 2007). The argument is centered on the classic “maintenance requirements,” which were derived for *healthy* children, while the usual hospitalized child, especially in today’s tertiary care centers, is often far from “healthy.” The frequency of nonosmotic stimuli of antidiuretic hormone (ADH) secretion (syndrome of inappropriate ADH secretion) is likely under-recognized; inappropriate ADH secretion occurs with malignancies, meningitis and other central nervous system disorders, pneumonia and other causes of respiratory distress, pain, postoperative situations, and a number of medications. It remains to be determined whether the development of hyponatremia in these circumstances is the result of the use of hypotonic fluid per se or of an overload of free water from inaccurate estimation of needs and/or inappropriate ADH secretion. However, many now advocate the use of isotonic saline as maintenance fluid in hospitalized children (Wang et al, 2014). **The astute pediatric urologist should not accept these recommendations without recognizing that none of the few studies comparing hypotonic versus isotonic fluids for maintenance use was performed in children with renal disease.** Given the challenges of the damaged kidney in managing salt and water overload and the high incidence of hypertension in this population, fluid

KEY POINTS: KIDNEY DEVELOPMENT

- Kidney and urinary tract development occur simultaneously and normal functional development is likely to be integrated across the system.
- Insufficient amniotic fluid adversely affects fetal lung development, resulting in a newborn with more than just kidney disease. The presence of adequate pulmonary function is usually associated with reasonably adequate renal function (for the short term).
- Renal and urinary tract maldevelopment can be expected to slow the normal postnatal changes in GFR and blood flow—patience is warranted.
- Nephron number itself may be critical for maintenance of long-term renal capacity. Developmental events that decrease nephron endowment or postnatal illnesses or procedures that reduce nephron number are likely to result in increased long-term risk for CKD.

and electrolyte prescriptions should be carefully tailored to individual patient needs and risks and constantly monitored.

KEY POINTS: MANIFESTATIONS OF RENAL IMMATURITY

- Control of fluid and electrolyte homeostasis evolves across the developmental spectrum of the newborn, infant, and young child, leaving the youngest and most immature children at highest risk for metabolic disarray.
- The presence of urinary tract anomalies and chronic renal dysfunction often prevents or delays the normal developmental improvements in glomerular and tubular function, often in complex ways.
- The management of fluids and electrolytes in children with urinary tract anomalies and chronic renal dysfunction should *not* be approached purely with algorithmic approaches that were designed for treatment of acutely ill children without renal disease. Individualized consideration of water and solute balance is needed for best practice.

CLINICAL PRESENTATION OF RENAL DYSFUNCTION

Hematuria

Hematuria is one of the most common reasons for referral to pediatric nephrologists and pediatric urologists. It is a fairly common finding, and the large differential diagnosis list is rather intimidating and time-consuming for many primary care physicians. Multiple studies have shown that the incidence of detecting blood in the urine ranges from 0.5% to 3% of evaluated children (Hogg, 2009), with results influenced by the definition of significant hematuria and the local practices for screening urinalyses. Only approximately 1 in 4 of these children will be found to have persistent hematuria on repeated testing (Vehaskari et al, 1979). Of children evaluated and followed with *persistent* hematuria lasting more than 6 months, two thirds had isolated hematuria only and 70% of those experienced eventual resolution. Of this cohort, 20% were diagnosed with hypercalciuria and/or stone disease, and only 10% were eventually diagnosed with chronic glomerulonephritis by biopsy after the additional development of proteinuria (Türi et al, 1989). This evidence provides **strong support for the concept that isolated microscopic hematuria is usually a benign condition that can be confidently diagnosed once relatively simple histories and assessments have been accomplished.**

While the vast majority of cases of hematuria are microscopic in nature, the development of asymptomatic gross hematuria is more likely to result in urgent referral and more aggressive evaluation. Studies suggest that two thirds of these evaluations will result in identification of an etiology for the hematuria, but one third of cases will remain enigmatic (Youn et al, 2006; Greenfield et al, 2007). While the frequency of individual diagnoses will vary between those patients seen by urologists and nephrologists, with more patients seen by urologists diagnosed with trauma and urinary tract infection and those seen by nephrologists more commonly diagnosed with glomerulonephritis, the differential diagnosis lists for macro- and microhematuria are essentially identical (Box 123-1).

Evaluation

Gross hematuria warrants acute evaluation while the detection of microhematuria warrants watchful waiting for several months in the absence of concerning history, physical examination findings, and proteinuria. Many patients, but not all, will come to specialty care with parts of the basic evaluations completed (Fig. 123-2).

Important elements of the history include timing of onset of the hematuria; persistence or intermittent nature; correlation with illness, exercise, or trauma; and the presence or absence of other symptoms, including abdominal/flank pain, dysuria/urgency, rash,

BOX 123-1 Causes of Hematuria in Children

MACROSCOPIC

Transient
Hypercalciuria/nephrolithiasis
Glomerulonephritis (all types)
Cystitis
Exercise
Congenital anomaly of urinary tract
Benign urethrorrhagia
Wilms tumor or bladder tumor
Bleeding dyscrasia
Renal vein thrombosis
Papillary necrosis
Nutcracker syndrome

MICROSCOPIC

Transient
Hypercalciuria/nephrolithiasis
Glomerulonephritis (all types)
Cystitis/pyelonephritis
Exercise
Congenital anomaly of urinary tract
Thin basement membrane disease
Drugs
Interstitial nephritis
Sickle cell disease/trait

swelling, joint symptoms, and headaches/vision changes (which may be associated with hypertension). Is the bleeding evident throughout voiding (as would be expected for glomerular or bladder bleeding) or is it at the end of voiding, indicating urethrorrhagia? The family history should be explored for evidence of hematuria, stone disease, CKD of any form, deafness, bleeding abnormalities, or sickle cell disease. The physical examination should be broad but with special attention to blood pressure, generalized rash, edema, perineal trauma, or abdominal, flank, or suprapubic tenderness.

The most critical diagnostic test is a fresh urinalysis—red blood cells and crystals degrade in stale urine. The urine should also be evaluated for protein, leukocytes, or nitrates. Microscopic evaluation should confirm more than 5 red blood cells per high-power field and should also note the presence or absence of crystals. Children without confirmed microhematuria on secondary evaluation should be considered to have transient hematuria and do not require ongoing evaluation. Glomerular causes of hematuria will be associated usually with brownish or greenish coloration of the urine, and red blood cell casts and dysmorphic red blood cells will be seen. Nonglomerular bleeding is more commonly reddish in color, there are no red cell casts present, and the red cells are uniform in size and shape, although crenation in concentrated urine may cause symmetrical shrinkage. Patients with suggestive symptoms or urinalysis findings consistent with infection should have a urine culture performed. Since hypercalciuria is one of the more commonly diagnosed causes of microhematuria, random urine samples sent for calcium and creatinine are warranted, with hypercalciuria diagnosed at ratios greater than 0.2 for children more than 5 years of age and greater than 0.4 for children ages 2 to 5 years (Sargent et al, 1993). Renal and bladder ultrasound examinations are used to screen for renal parenchymal or bladder causes for hematuria, although the yield in patients with long-standing asymptomatic hematuria is quite low. However, given the benign nature of ultrasonography, it is often used to provide reassurance to physicians and families that no anatomic problem or stone is underlying the hematuria.

Patients with proteinuria, hypertension, or symptoms of systemic disease are likely to have some form of glomerulonephritis

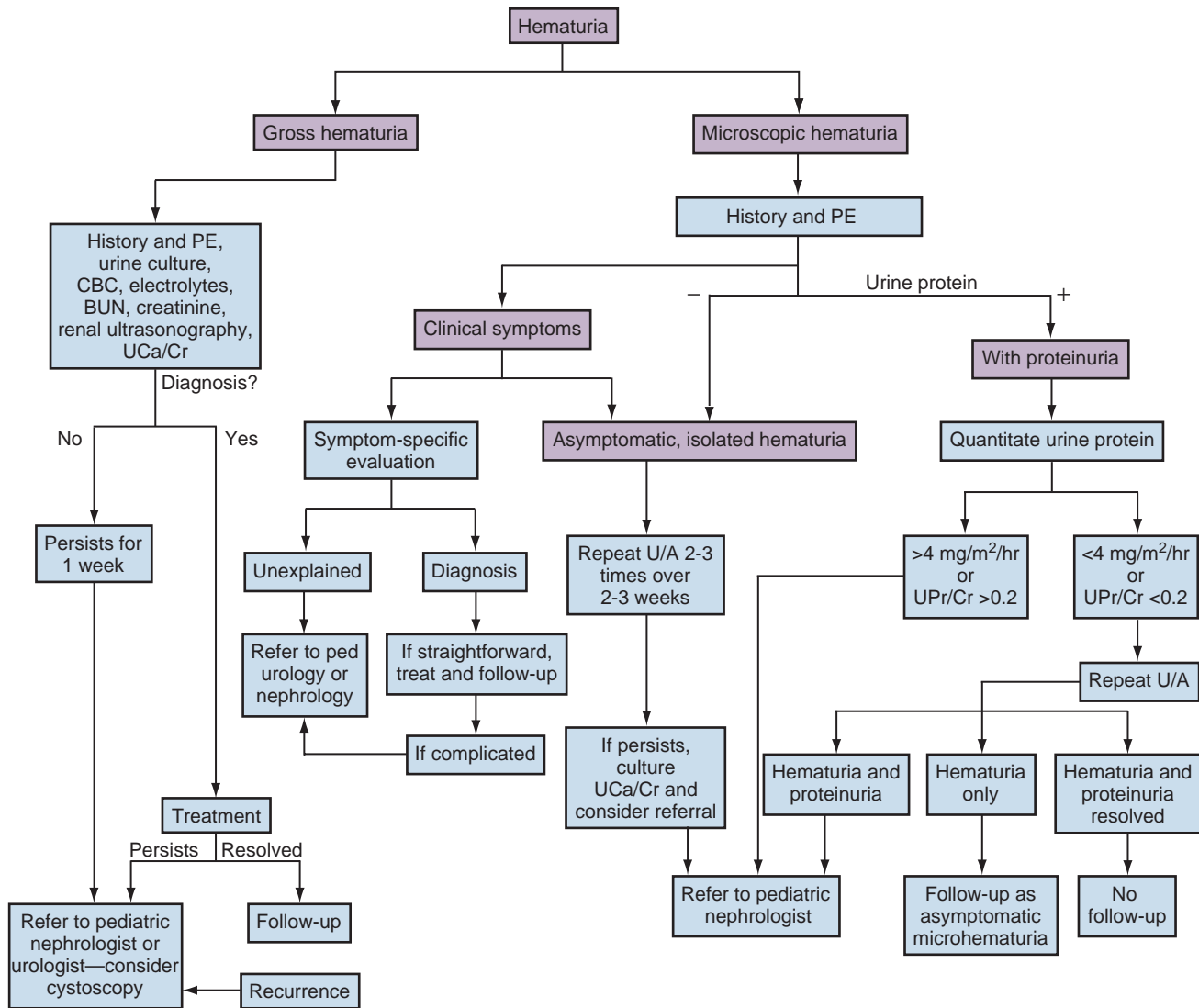


Figure 123-2. Algorithm for the treatment of hematuria. BUN, blood urea nitrogen; CBC, complete blood cell count; PE, physical examination; U/A, urinalysis; UCa/Cr, urinary calcium/creatinine ratio; UPr/Cr, urinary protein/creatinine ratio.

and will most commonly be further evaluated and managed by a pediatric nephrologist, with the initial evaluations including quantitation of urine protein, serum chemistries, blood counts, complement components C3 and C4, and antistreptolysin O. Depending on age (preteen and up) and symptomatology, systemic lupus erythematosus (SLE) serologies may be sent as well. It is important to note that large numbers of red blood cells in the urine may yield low-level positive readings on the urine dipstick for protein. Therefore all patients with gross hematuria should also have quantitative urine protein studies done (random protein/creatinine ratio should be <0.2) as part of their initial evaluations. In the rare instance in which renal ultrasonography indicates the presence of a mass or other anatomic abnormality, further evaluation with computed tomography, magnetic resonance imaging, nuclear imaging, voiding cystourethrography, or cystoscopy may be warranted as indicated by the suspected abnormality. It is important to note that cystoscopy and urethral dilation are *not* warranted for microscopic hematuria (Feld et al, 1998) if the sonogram is normal. Cystoscopy is occasionally beneficial for evaluation of recurrent gross hematuria if it can be performed during an episode of bleeding. Visualization of bleeding from both ureteric orifices indicates a glomerular source while unilateral bleeding suggests an upper urinary tract or vascular anomaly—although many remain resistant to exact diagnosis.

Hypercalciuria is a commonly identified etiology of both micro- and macrohematuria and may be asymptomatic or may be associated with dysuria. Hypercalciuria should be considered in any patient with hematuria, dysuria, and a negative urine culture. In children less than 4 to 5 years old a calcium/creatinine ratio of greater than 0.2 is diagnostic (as is a 24-hour urine calcium excretion of >4 mg/kg), while younger children normally have slightly higher values (up to around 0.5 in normal infants). Hypercalciuria can result from high dietary intake of calcium or sodium but is most commonly idiopathic in nature. It is important to note that calcium excretion can vary with dietary intake of calcium and sodium such that elevated ratios should be confirmed and better quantitated with 24-hour urine collections. Secondary causes should be considered in the appropriate clinical circumstances and include immobilization resulting from trauma (especially in adolescent males), loop diuretic use, renal tubular acidosis (RTA), hyperparathyroidism, malignancies, and sarcoidosis. While the incidence of eventual nephrolithiasis development in patients with hypercalciuria is variable, urine calcium excretion is the factor most associated with eventual stone formation (Bergsland et al, 2012), making preventive strategies of increased fluid intake, sodium restriction, mild protein restriction, and diuretic use worthy of consideration.

Management

The management of asymptomatic hematuria is routinely expectant as the majority of cases will resolve over time. It is important that families be aware that low-level persistent hematuria is not, in and of itself, harmful to renal function or blood counts and is *not* predictive of progressive renal disease (however, associated *proteinuria* is concerning). Patients diagnosed with significant abnormalities of the urinary tract or glomerulonephritis will be managed as appropriate for the specific disorder. A diagnosis of hypercalciuria should result in recommendations for high fluid intake and modest sodium restriction for all patients; thiazide diuretics are usually reserved for patients with dysuria who do not respond to conservative approaches or those with documented nephrolithiasis.

KEY POINTS: HEMATURIA

- Isolated asymptomatic microhematuria (defined as >5 red blood cells per high-power field) in children is most commonly a benign, transient, and self-limited condition.
- Family history of nephrolithiasis or renal disease can help guide the evaluation of hematuria in children.
- Recurrent or persistent microhematuria or gross hematuria requires further evaluation, although concerning abnormalities are uncommon in the asymptomatic patient.
- Cystoscopic examination is rarely indicated for children with hematuria and normal urinary tract imaging.
- Hypercalciuria (calcium/creatinine ratio >0.2 in children >4 years old) is a common cause of microscopic and gross hematuria and should be considered in all cases.
- The presence of significant proteinuria accompanying hematuria is indicative of glomerular disease and requires more aggressive evaluation.

Proteinuria

While the American Academy of Pediatrics discontinued recommendations for routine screening urinalysis for children and it may not be cost-effective (Sekhar et al, 2010), many practitioners maintain the practice and it remains a routine part of most pre-participation physical examinations for athletics (Sox and Christakis, 2005). In the pediatric population, proteinuria may be detected during routine screening, serendipitously as a part of an evaluation for another disorder for which urine studies were sent, or during the investigation of suspected renal or urinary tract disease. The circumstances of diagnosis along with the severity of proteinuria should be the primary guide for further evaluation. **In otherwise healthy patients, low-level positive dipstick evaluations discovered at screening will most likely prove to be transient or false positive on repeat studies.** Patients with medical illness and moderate- to high-level proteinuria should be thoroughly evaluated because they are most likely to have clinically important renal disease.

“Normal” Urinary Protein Excretion

The nephron filters, reabsorbs, secretes, and catabolizes proteins and provides an effective barrier against loss of plasma protein. Permeability of proteins across the glomerulus is dependent on molecular weight (MW) and electrical charge. The majority of small plasma proteins and peptides are freely filtered and then reabsorbed and catabolized quickly in the proximal tubule, whereas proteins of high MW and electronegativity such as albumin or immunoglobulin G (IgG) are poorly filtered but recaptured through the endocytotic receptor megalin (Dickson et al, 2014).

Final total daily urinary protein quantity varies with body mass and renal maturity and is influenced by both glomerular filtration characteristics and proximal tubular function. Normal corrected urinary protein excretion ranges from a protein/creatinine ratio of 0.7 in the immature newborn down to 0.2 or less in the mature individual (Table 123-1). When expressed quantitatively by timed

TABLE 123-1 Normal Urinary Protein Excretion

AGE	PROTEIN EXCRETION (mg/m ² /day): MEAN (RANGE)*	PROTEIN/ CREATININE RATIO (mg/mg)†
Premature infant (<30 days)	182 (8-377)	0.7
Term infant (<30 days)	145 (68-309)	0.7
2 mo-4 yr	100 (37-244)	0.55-0.7 (up to 1 yr) 0.4 (1-2 yr) 0.3 (2-3 yr)
5-10 yr	85 (21-234)	0.2
>10 yr	63 (22-181)	0.15-0.2

*Data from Miltenyi M. Urinary protein excretion in healthy children. Clin Nephrol 1979;12:216-21.
†Modified from Guignard J-P, Santos F. Laboratory investigations. In: Avner ED, Harmon WE, Niaudet P, editors. Pediatric nephrology. 5th ed. Philadelphia: Lippincott, Williams & Wilkins; 2004.

urine collections, normal urinary protein excretion is less than 4 mg/m²/hr (100 mg/m²/day) (see Table 123-1).

Etiology

Three sources account for clinically important urinary protein excretion: a breakdown in the glomerular barrier, tubular dysfunction, or excessive plasma protein concentrations that overwhelm the normal reabsorptive process. The most common clinical scenario involves a loss of glomerular integrity and excretion of high-MW proteins, including albumin. Whether caused by congenital or acquired podocyte disorders such as minimal change disease, post-streptococcal glomerulonephritis (PSGN), renal scarring, or long-standing diabetes, the structure and function of the glomerulus is altered such that the filtration barrier is disrupted, resulting in leakage of high-MW plasma proteins. These are the disorders that result in the highest urine protein levels and the features of the nephrotic syndrome, often with progressive loss of renal function.

Tubular proteinuria is characterized by abnormal excretion of the low-MW proteins normally reabsorbed by the proximal tubule. Tubular proteinuria is most commonly seen with AKI, as a side effect of chemotherapy or aminoglycoside use, or with the inherited tubulopathies such as Fanconi syndrome or Dent disease. In the pediatric population, disorders of excessive plasma protein concentrations resulting in overflow proteinuria are rare. However, hemoglobinuria from hemolytic crises, myoglobinuria from rhabdomyolysis, and hypergammaglobulinemic states may all be associated with elevated urine protein.

Measurement

Screening urine studies are routinely performed using semiquantitative dipstick assays. Because the strips change color upon binding of high-MW proteins, false-negative results can occur in very dilute urine samples and in cases of low-MW proteinuria. False-positives can occur in very alkaline urines, concentrated samples, or those contaminated with chlorhexidine or radiocontrast agents. False results can also be obtained with reagent strips that have been inappropriately stored or if appropriate timing between exposure and reading is not maintained. Positive results using dipstick techniques should be followed up with quantitative studies.

Quantitative urine protein determinations are performed using timed urine collections, typically for 24 hours. Such collections must be standardized to urine creatinine content and a sample containing greater or less than 15 to 25 mg creatinine/kg/24 hr

should be considered of suspect quality. Patients with unusually high or low muscle mass or obesity may be difficult to assess, but progress over time can usually be followed using the patient as his or her own control. More recently the use of a protein/creatinine ratio in spot urine samples has gained acceptance, and the availability of age-dependent normative values (see Table 123-1) has made this technique quite popular in spite of approximately 20% error rates (Shaw et al, 1983). Finally, while the test for “microalbumin” is able to detect very low levels of urine albumin, its use should be limited to the assessment of the early phases of diabetic nephropathy because of high cost.

Causes

Proteinuria may best be categorized as transient, orthostatic, or fixed (Box 123-2). Transient proteinuria is defined by the disappearance of urinary protein following one or more positive tests. Transient proteinuria accounts for the vast majority of “cases” of isolated proteinuria and results from heavy exercise, fever, and significant heat or cold stress. The degree of proteinuria is mild to moderate (<1 g/24 hr, protein/creatinine ratio <1.0), and repeated assessments should be made in the absence of the probable stressor prior to more involved evaluation.

Orthostatic proteinuria is the next most frequently diagnosed form of isolated proteinuria and is most commonly seen in otherwise healthy adolescents. By definition, orthostatic proteinuria is that which is present only in the upright position and is not associated with abnormal renal function or hypertension. Its cause is unknown, and it may eventually resolve or may be permanent (Springberg et al, 1982). Recumbent collections or samples will be negative by dipstick with protein levels less than 100 mg/8 to 12 hr (or protein/creatinine ratio <0.2), while the upright collections will be positive by dipstick with protein levels 300 to 900 mg/12 to 16 hr. Orthostatic proteinuria becomes less likely if the total daily

urinary protein content exceeds 1 g/day or if there is any degree of associated hematuria.

Persistent nonorthostatic proteinuria of any degree is indicative of some form of underlying renal disease (see Box 123-2) and should be more thoroughly evaluated. Nephrotic-range proteinuria, defined as greater than 40 mg/m²/hr or 3 g/24 hr, may be due to minimal change disease or any other form of potentially aggressive glomerulonephritis but is uncommon with congenital dysplasia, reflux nephropathy, obstructive uropathy, or tubular disorders. In these processes, the proteinuria is usually mild to moderate (500 to 1000 mg/day). These patients will most commonly be referred to a pediatric nephrologist for continued evaluation.

Evaluation

The evaluation of proteinuria is outlined in Figure 123-3. Otherwise healthy patients with isolated proteinuria found by routine screening should have repeated assessments performed after abstaining from potential causes of transient proteinuria. More accurate assessments with spot protein/creatinine ratios will also clarify false-positive dipstick results in patients with highly concentrated urine samples. Should these values be normal, no further evaluation is necessary. While hematuria occasionally occurs in association with the identical stressors known to cause transient proteinuria, the finding of proteinuria and hematuria should lead to consideration of more significant renal disease unless all issues resolve completely.

In healthy normotensive patients whose isolated proteinuria is confirmed on repeated sampling, evaluation for orthostatic proteinuria should be undertaken. The gold standard for confirmation of orthostatic proteinuria is the “split” 24-hour urine collection. Patients should be instructed to provide two consecutive timed collections, one consisting of daytime/active urine during waking hours and one consisting of nighttime/recumbent urine. Both samples should be submitted for protein and creatinine determinations. **A normal nighttime excretion associated with an abnormal daytime excretion (with the total protein excretion <1 g/day) is diagnostic of orthostatic proteinuria.** Alternatively, first-morning spot samples and midday samples can be assessed using protein/creatinine ratios. While existing data suggest that orthostatic proteinuria is indeed benign even if persistent, many specialists still suggest follow-up testing at least 1 year after the diagnosis in order to confirm the lack of any progression.

Proteinuria is occasionally found during an intercurrent illness or during screening for an invasive procedure, and it is usually transient, the result of the stress of the underlying problem that brought the child to attention. Should high-level proteinuria be detected on screening, accurate quantitation should be performed along with evaluation of serum creatinine and referral to nephrology. In other circumstances, the development of clinical concerns drives the evaluation. Signs and symptoms such as edema, hematuria, hypertension, failure to thrive, growth delay, vasculitic rash, urinary tract infection, recurrent abdominal pain, and a history of past renal disease are all indications for the evaluation for possible proteinuria (Hogg et al, 2000). In these circumstances it is prudent to thoroughly review the history and physical examination with an eye toward possible renal disease. Low to moderate levels of proteinuria, normal blood pressure, and the absence of hematuria, edema, or vasculitis are all reassuring. Values near normal on evaluation of serum creatinine may be reassuring but do not guarantee the absence of future worsening. In settings in which renal disease is suspected from history and examination, the suspected diagnosis should lead the evaluation process. The presence of associated edema, hypertension, and/or hematuria makes glomerular disease the most likely cause of proteinuria. Accurate quantitation of urinary protein and serum creatinine and electrolytes (including calcium and phosphorus), total protein and albumin, complement component C3, and streptococcal titers is needed. Quality renal ultrasonography will assess anatomy, size, and echogenicity. Nephrology evaluation may include additional serologic studies for rare diseases as indicated by the severity and form of illness.

BOX 123-2 Causes of Proteinuria

- Transient
 - Exercise
 - Fever
 - Stress/illness
- Orthostatic
- Drugs
 - Chemotherapy
 - Aminoglycosides
 - Heavy metal intoxication
- Tubular disease
 - Acute tubular necrosis
 - Interstitial nephritis
 - Cystic kidney diseases
 - Fanconi syndrome
 - Graft-versus-host disease
- Reflux nephropathy
- Glomerulonephritis: acute and chronic, all forms, including minimal change nephrotic syndrome
- Other chronic renal disease
 - Obstructive uropathy
 - Congenital renal dysplasia
 - Permanent residual dysfunction from acute disease (i.e., cortical necrosis, hemolytic uremic syndrome, glomerulonephritis)
- Diabetes mellitus
- Protein overload syndromes
 - Hemolysis
 - Rhabdomyolysis
 - Hypergammaglobulinemia

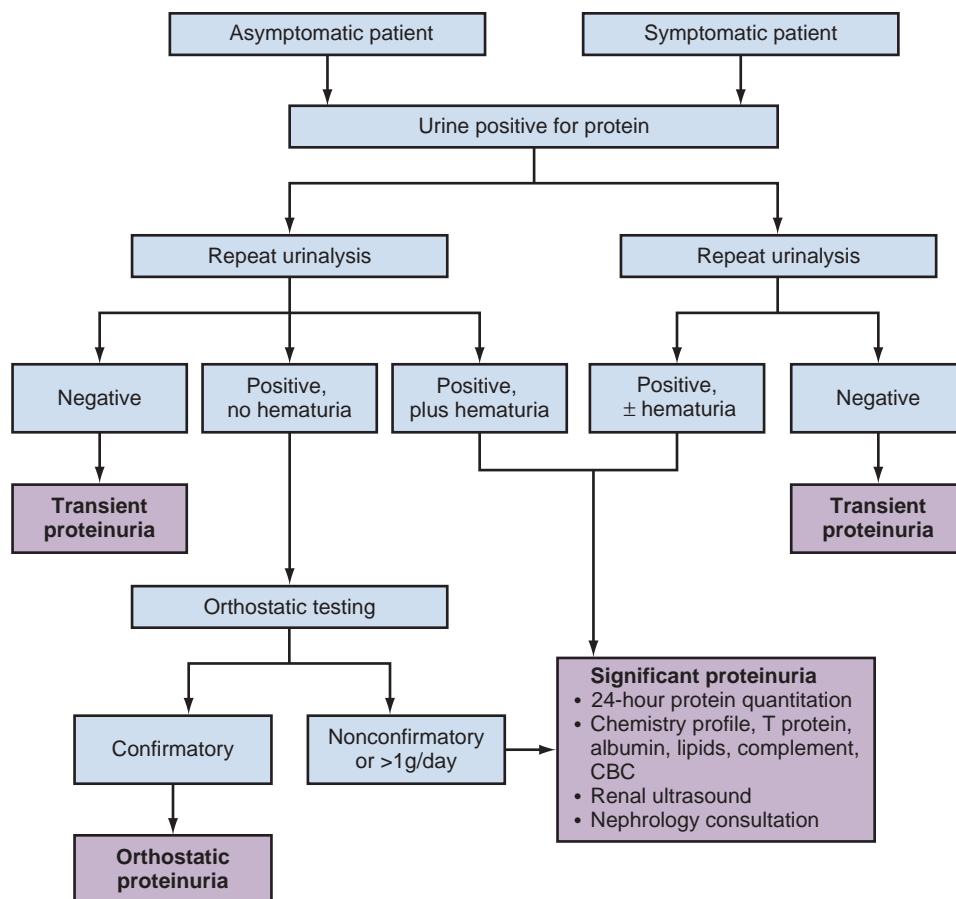


Figure 123-3. Evaluation of children with proteinuria. CBC, complete blood cell count.

Special mention should be made regarding the presentation and evaluation of proteinuria from reflux nephropathy. Reflux nephropathy may go undiagnosed for years and may present as asymptomatic proteinuria (commonly <1 g/day) with or without hypertension in the older child or adolescent. A careful history inquiring about past urinary tract infections or recurrent antibiotic use for fevers during early childhood may point to this diagnosis. Renal ultrasonography may be suggestive if renal asymmetry or parenchymal defects are seen but is insensitive in situations in which the scarred areas are small. Magnetic resonance imaging and nuclear imaging with a cortical agent such as dimercaptosuccinic acid (DMSA) are the most sensitive for diagnosis but more technically challenging in small children (McMahon et al, 2007). Voiding cystourethrography will be negative in a child whose reflux has resolved spontaneously and can be reserved for those in whom cortical imaging has confirmed scarring.

The time to refer a patient with proteinuria to a pediatric nephrologist depends upon the perceived severity of the underlying process, the comfort level of the treating physician, and the practical availability of nephrology services. The additional evaluations provided by a nephrologist will be dependent upon the suspected underlying process but may be expected to include more extensive biochemical testing such as complement assays and serologic studies for immune-mediated diseases, repeat quantitative urine studies for confirmation and trending, and specialized radiologic imaging. Percutaneous renal biopsy is usually needed for specific diagnosis and/or prognosis in cases of progressive or persistent glomerulonephritis.

Treatment

Transient proteinuria and orthostatic proteinuria are benign and do not require therapy. In acute or self-limited processes such as

AKI, postinfectious glomerulonephritis, or mild hemolytic uremic syndrome (HUS), proteinuria may persist for months following resolution of the primary disorder. Protein quantitation is usually of low degree (<1 g/24 hr or protein/creatinine ratio <1.0), should decline further with time, and does not require specific therapy. Worsening proteinuria is an indication for more detailed investigation.

In most circumstances of clinically important proteinuria, the treatment is directed toward cure or management of the primary disease, and changes in urinary protein excretion are often used as a marker of the success of treatment. Most acquired glomerular diseases are treated with immunomodulatory therapies such as corticosteroids, calcineurin inhibitors, cytotoxic drugs, or antibody therapies with varying degrees of success. Because many of these disorders are incurable or are only brought under control after permanent glomerular damage has occurred, the treatment of persistent proteinuria has become an additional option. Led by discoveries that showed benefits in renal life span in patients with nephropathy from type 1 diabetes mellitus (Cook et al, 1990), it is now routine practice to use angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) to decrease urinary protein excretion in patients with persistent high-grade glomerular proteinuria (>1 g/24 hr) (Webb et al, 2012). While not specifically proven effective in improving long-term renal outcomes in all forms of glomerular disease, especially in children, these agents clearly decrease urinary protein excretion by their hemodynamic effect of decreasing glomerular filtration pressure. Whether the long-term benefits are directly due to decreasing tubular protein or are secondary to reduction in the effects of hypertension so commonly associated with these disorders remains an area of debate. Likewise, the need for and efficacy of these agents in chronic low-grade proteinuria or purely tubular proteinuria remain unclear.

KEY POINTS: PROTEINURIA

- Asymptomatic, isolated proteinuria is a common finding on screening examinations and is usually transient.
- Persistent daily protein excretion greater than 150 mg/24 hr or a first-morning spot urine protein/creatinine ratio greater than 0.2 indicates the possibility of renal disease.
- The presence of hematuria, hypertension, edema, or systemic illness suggests glomerular disease and more urgent evaluation.
- Judicious treatment of chronic proteinuria with ACEIs can lower proteinuria and may lengthen renal life span.

Glomerular Disease

Whereas larger anatomic complications of the urinary tract are the most common issues managed by pediatric urologists, the pediatric nephrologist spends a significant portion of his or her practice addressing glomerular disease. While the pediatric urologist will not be expected to maintain expertise in the details of these disorders, it is quite appropriate to have a basic working understanding of their presentations, evaluations, and short-term prognoses since many children with any abnormalities in urinalysis will be first referred to a urologist.

The glomerular disorders may be transient or progressively damaging and the frequency of occurrence varies across the developmental spectrum of childhood and adolescence. Some progress very rapidly and others have more indolent courses and may present with incidental findings of hematuria and/or proteinuria in an otherwise healthy patient. While many disorders may be presumptively treated based on clinical features, renal biopsy remains the gold standard for diagnosis.

Over the years, much has been made of the differences and similarities of the numerous forms of “nephrotic syndrome” and “glomerulonephritis” with significant attempts to separate the two, but it is critical to understand that there are significant overlaps among the clinical presentations and outcomes of all of these disorders. The wise clinician utilizes clinical data, biopsy results, response to therapy, and clinical course to chart the expected course for any individual patient. **Classically, nephrotic syndrome is a clinical constellation including heavy proteinuria (for children defined as >40 mg/m²/hr), hypoalbuminemia (defined as albumin <2.5 g/dL), and edema, with or without hyperlipidemia.** Nephrotic syndrome may be genetically inherited, secondary to other illnesses, or a primary idiopathic process. These disorders appear to be due to acquired or congenital defects in the integrity of podocyte cytoskeletal structure and cell-cell interaction and are areas of intense research activity ([Grahammer et al, 2013](#)). Nephrotic syndrome may be isolated without evidence of “nephritis” or may be a significant component of any form of glomerulonephritis. **Glomerulonephritis is diagnosed in clinical scenarios in which there is evidence of glomerular inflammation as evidenced by the presence of hematuria, proteinuria, decreased GFR, and/or hypertension.** Glomerulonephritis may also be genetically inherited, secondary to other illnesses, or a primary idiopathic process. Given the breadth of the differential diagnoses possible, there is reason to narrow the field by making a few early investigations and then continuing the evaluation with a more narrowed focus.

Evaluation

Several simple assessments and questions can help narrow the differential diagnosis and assist in decision making regarding urgency of further evaluation:

1. *How old is the patient?* If less than 1 year of age, the ultimate process is most likely an inherited disorder. A number of glomerular diseases are more common in younger children while others cluster more commonly in adolescents ([Box 123-3](#)).

BOX 123-3 Common Age Ranges for Presentation of Glomerular Diseases**<1 YEAR**

Congenital infections

Diffuse mesangial sclerosis

Genetic diseases:

Congenital and infantile nephrotic syndromes

Denys-Drash and Frasier syndromes

1-10 YEARS

Postinfectious glomerulonephritis (GN)

Minimal change disease

Idiopathic focal segmental glomerulosclerosis (FSGS)

Henoch-Schönlein purpura

Hemolytic uremic syndrome

≥7 YEARS

Systemic lupus erythematosus

Systemic vasculitis

Idiopathic crescentic GN

Membranoproliferative GNs

Immunoglobulin A nephropathy

Idiopathic and secondary FSGS

Membranous nephropathy

Alport syndrome

Nail-patella syndrome

Pulmonary-renal syndromes

2. *Is this an acute issue or is there evidence of long-standing disease?* Many of these disorders have indolent presentations and may have been present silently for quite some time prior to diagnosis (Alport syndrome, secondary focal segmental glomerulosclerosis [FSGS]). Others are directly the result of an acute event (PSGN and HUS). Basic investigations such as hemoglobin, renal ultrasonography (are the kidneys large, indicating an acute process, or small, indicating a chronic progressive process?), and parathyroid hormone (PTH) (assessing for evidence of renal osteodystrophy) can be very helpful. It is important to note that **hypertension, hematuria, and edema can occur in any of these disorders and are not indicative of a specific diagnosis.**
3. *Has the patient had recurrent asymptomatic gross hematuria?* If so, immunoglobulin A (IgA) nephropathy, Alport syndrome, or thin basement membrane disease are most likely.
4. *Is there any evidence of extrarenal involvement?* While not always easily visible, evidence of skin disease, vasculitis, sinopulmonary disease, or other organ system involvement usually portends a systemic disorder of some type and often a more aggressive clinical course.
5. *Is significant hypertension or renal insufficiency present?* If yes, then advanced or aggressive disease is likely and emergent evaluation by the nephrology service is warranted.

Diagnosis and Management

The use of the above questions can help narrow the differential diagnosis significantly. Patients with significant edema and heavy proteinuria without evidence of multisystem involvement are most likely to have one of the disorders causing nephrotic syndrome. Patients with hypertension and milder edema are more likely to have a form of glomerulonephritis. Patients with rash or other organ system involvement are likely to have a systemic vasculitis or other systemic illness. Renal biopsy is often a critical component of diagnosis in all of these disorders, and with the advancement of genetic diagnoses, evaluations of uncommon presentations often include mutation analyses.

Nephrotic Syndrome in Infants. The distinction between “congenital” and “infantile” forms of nephrotic syndromes is somewhat vague because all of the disorders can be present at birth or may present later in infancy. Infants with congenital nephrotic syndrome of the Finnish type (CNF) are often edematous at birth or very shortly after, and may be diagnosed prenatally owing to very high elevations in maternal α -fetoprotein levels indicative of fetal proteinuria. These infants are commonly born prematurely and the placenta is usually significantly larger than normal. CNF is due to a homozygous mutation in the *NPISH1* gene (encoding nephrin) and affected infants classically have severe nephrotic syndrome with high risks of infection and thrombosis because of extreme protein loss (Jalanko, 2009). Congenital forms of FSGS usually present during the first year of life, with the most common being due to homozygous mutations of the *NPISH2* gene (encoding podocin) (Jalanko, 2009). Other genetic mutations known to result in lesions of focal sclerosis include disruptions in α -actinin 4 and CD2-associated protein (Jalanko, 2009). Mutations in the Wilms tumor suppressor gene *WT1* are associated with infantile nephrotic syndrome in Denys-Drash and Frasier syndromes, with the glomerular pathology showing diffuse mesangial sclerosis (Jalanko, 2009). While nephrotic syndrome in infancy is currently commonly found to be genetic in origin, it is important to remember that congenital infections and inflammations can also result in nephrotic syndrome. Cytomegalovirus, syphilis, rubella, hepatitis B, congenital SLE, toxoplasmosis, human immunodeficiency virus (HIV), and malaria are all known to cause nephrotic syndrome and should be considered in all early presentations of the disorder (Jalanko, 2009).

Nephrotic Syndrome in Older Children

Minimal Change Nephrotic Syndrome. The vast majority of children and adolescents with nephrotic syndrome have minimal change nephrotic syndrome (MCNS) (85% to 90% of preschoolers and 50% of adolescents), although the definitive diagnosis is often unknown because patients who respond to corticosteroids rarely undergo biopsy. The presentation is usually with the acute onset of dependent edema, often including ascites, in an otherwise well child, although an antecedent illness is also common. Most children are normotensive and have normal serum creatinine, although mild elevations may be seen with severe hypoalbuminemia resulting in intravascular volume depletion. Hyperlipidemia is common. Microscopic hematuria may be present but is minimal in quantity, and polarized examination of the urine will note oval fat bodies. The course of MCNS is one of remission with corticosteroids followed in two thirds of patients by intermittent relapses that may be occasional or frequent. Cytotoxic drugs (cyclophosphamide or chlorambucil) or calcineurin inhibitors (cyclosporine or tacrolimus) are used in patients with frequent relapses and steroid toxicities. The vast majority of patients with MCNS will “outgrow” the disorder by adolescence, and progression to renal insufficiency or end-stage renal disease (ESRD) is extremely uncommon, so much so as to question the diagnosis of minimal change disease. Patients with relapsed nephrotic syndrome are at risk for infection with encapsulated organisms and thrombosis owing to the loss of IgG and antithrombotic proteins. In addition, side effects of the treatment medications and the unpredictable nature of relapses add to the frustration experienced by caregivers despite the “minimal” risk of long-term sequelae of the disease. While patients with classic presentations and response to steroids will rarely undergo biopsy, the light microscopy findings are of normal kidney tissue (or at most mild focal increase in mesangial matrix or cellularity), negative immunofluorescence, and diffuse podocyte foot process effacement.

Focal Segmental Glomerulosclerosis. FSGS is the second most frequent cause of nephrotic syndrome in the pediatric age group, accounting for 10% to 20% of cases and increasing in frequency with age. FSGS has recently been subdivided into a number of pathologically distinct forms with variable prognostic outcomes (Schell and Huber, 2012). Its presentation is variable, with some patients presenting with classic nephrotic syndrome and others with heavy asymptomatic proteinuria with or without hypertension

and renal insufficiency. It is more common in African-Americans, is usually not completely or consistently responsive to steroids, and may be associated with evidence of tubular dysfunction, most commonly glycosuria and concentrating defects. Microhematuria is common. Renal biopsy findings classically note segmental glomerular sclerosis or capillary loop collapse in focal areas of the cortex, more prevalent in juxtamedullary nephrons. Evidence of tubulointerstitial damage is frequent. Immunofluorescence may detect immunoglobulin M (IgM) or C3 but not in large quantities, and electron microscopy confirms the sclerotic/atrophic lesions along with podocyte effacement. Patients with FSGS suffer complications of infection and thrombosis similar to those seen in MCNS, and these are ongoing risks given the long-term persistence of heavy proteinuria. Progression to CKD and ESRD is very common in patients who do not respond to steroids and may be rather rapid (within 5 to 7 years). The disease recurs in approximately 30% of renal transplant recipients and may lead to loss of the graft. High-dose corticosteroids, calcineurin inhibitors, cytotoxic agents, mycophenolate mofetil, and plasmapheresis have all been used as single agents or in combination with variable success. ACEIs and/or ARBs along with lipid-lowering agents are commonly used as adjunctive therapies to decrease the severity of proteinuria and long-term complications of hyperlipidemia. Growing understanding of podocyte molecular pathophysiology, biomarker signatures of disease, and phenotype-genotype correlations will hopefully continue to improve our ability to understand and manage the progressive nature of this challenging disorder.

Other Etiologies of Nephrotic Syndrome. Membranous nephropathy is rare in childhood, increasing to 10% to 20% of nephrotic syndrome diagnoses in adolescents. Membranous nephropathy may be idiopathic or may be secondary to SLE, hepatitis B, nephrotoxins, or malignancy. It cannot be clinically differentiated from other forms of nephrotic syndrome and requires renal biopsy for diagnosis. Spontaneous remission occurs in approximately one third of patients, with others developing slowly progressive CKD. The pathophysiology of the majority of cases of idiopathic membranous nephropathy has recently been determined to be attachment of circulating IgG₄ autoantibodies to the M-type phospholipase A₂ receptor 1 on podocytes (Beck and Salant, 2014). These antigen-antibody complexes bind complement within the glomerular basement membrane (GBM) and subsequently result in disruption of the slit diaphragm structures, causing proteinuria. The classic silver stain and electron microscopic biopsy findings of immune deposits surrounded by varying degrees of new extracellular matrix and GBM are a response to injury. Secondary forms of membranous nephropathy are caused by preformed circulating antigen-antibody complexes resulting in a similar injury pattern. The prognosis of membranous nephropathy is variable, with spontaneous resolution in about one third of patients and slow progression to ESRD in the remainder.

Membranoproliferative glomerulonephritis (MPGN) is also uncommon in childhood and is another disorder that has recently undergone serious reconsideration of nomenclature and classification because of growing understanding of the pathophysiology of the subtypes of the disorder (Bomback and Appel, 2012). Now known collectively as C3 glomerulopathies, these disorders are due to aberrant activation of the complement system. These disorders may present with classic nephrotic syndrome, features of progressive nephritis, or mixtures. Heavy proteinuria is common, significant micro- or macrohematuria is usual, and the majority of cases have low levels of complement component C3. Biopsy findings reveal mesangial hypercellularity, capillary proliferation, and mesangial cell interposition and duplication of GBM as a result of deposits of complement components and immunoglobulin. Subendothelial and mesangial deposits predominate in type I MPGN (in the old system) and the deposits typically contain immunoglobulin and complement. Type II MPGN (also referred to as dense deposit disease) is typified by intense GBM and mesangial electron-dense deposits that contain C3 alone. Mixed variants still defy definitive classification. The usual course of these diseases is

progression to ESRD despite therapies that typically include steroids and other immunomodulators. Recently, the use of eculizumab, a humanized antibody that prevents activation of the membrane attack complex, has brought promise as a potential targeted agent to halt the damage from chronic complement activation ([Bombback and Appel, 2012](#)).

Glomerulonephritis. There are several forms of glomerular disease in which the finding of “nephritis” usually predominates and the findings of nephrotic syndrome are less common. However, these disorders are quite heterogeneous in their presentations, and the astute clinician remains open to the complete spectrum of diagnoses until hard evidence is obtained.

Infection-Related Glomerulonephritis. The epidemiology of kidney inflammation associated with infection is undergoing significant change and the major types now may be referred to as “postinfectious glomerulonephritis” and “glomerulonephritis associated with active infection” ([Nadasdy and Hebert, 2011](#)). The incidence of PSGN is declining in developed countries because of changes in immunization practice and more effective antibiotic treatment of streptococcal disease, but the disease remains common in the developing world ([Eison et al, 2011](#)). Concomitantly, glomerulonephritis related to acute and chronic infections with *Staphylococcus aureus*, HIV, and hepatitis B/C is becoming more common.

PSGN classically develops 7 to 10 days following pharyngitis or cellulitis/impetigo caused by specific strains of group A *Streptococcus* and is characterized by gross hematuria (often described as “cola-colored” urine), subnephrotic-range proteinuria, hypertension with volume overload, low complement component C3, and positive antistreptolysin O and antideoxyribonuclease-B antibodies. Varying degrees of AKI are seen, including oligoanuria and the need for temporary dialysis. Historically 90% of patients recover “completely,” although with increasing understanding of the long-term risks of AKI from any cause, this estimate may be overly optimistic. Given the usual history and clinical diagnostic criteria for PSGN, few patients are currently biopsied but findings are expected to show marked glomerular cellular proliferation with infiltrating polymorphonuclear leukocytes, immunofluorescence positivity for C3 and IgG, and subepithelial electron-dense deposits in “humps.” The most acute phase of the disease lasts around 10 to 14 days but proteinuria and hematuria may linger for 6 months or so.

The glomerulonephritis of active infection differs from postinfectious disease in that it requires persistent infection and is most commonly seen in untreated or poorly treated deep or occult infections such as osteomyelitis, endocarditis, vascular shunts, or deep abscesses ([Nadasdy and Hebert, 2011](#)). This form of nephritis is also typified by chronic infection with HIV and hepatitis B/C, although biopsy findings differ. *Staphylococcus aureus*-associated glomerulonephritis is most commonly seen with methicillin-resistant strains and may be associated with evidence of vasculitis and purpura. It also mimics IgA nephropathy on biopsy, showing heavy IgA deposition but with the features of subepithelial and subendothelial immune complex deposition that are not seen in classic IgA disease. C3 is not usually low and, if abnormal, is usually minimally so. Given the frequency of purpura, this disorder should be considered at any time that a diagnosis of Henoch-Schönlein purpura (HSP) is considered. Given the risks of worsening underlying infection, steroids or other immunosuppressants are inappropriate treatment for *Staphylococcus aureus*-associated glomerulonephritis ([Nadasdy and Hebert, 2011](#)).

Immunoglobulin A Nephropathy. IgA nephropathy is the most common form of biopsy-proven glomerulonephritis in most of the world and affects both children and adults. The pathogenesis is linked to abnormalities in galactosylation of IgA₁ and may have both genetic and environmental components ([Hogg, 2010](#)). The course of the disease may be very mild, with diagnosis made only because of urinary screening findings of hematuria, or destructive disease resulting in glomerulosclerosis and ESRD. Presentations vary also from asymptomatic hematuria with or without proteinuria, to intermittent gross hematuria with intercurrent illnesses, to

more aggressive forms with gross hematuria, nephrotic syndrome, hypertension, and renal insufficiency. Biopsy findings include varying degrees of mesangial hypercellularity with increased mesangial matrix with or without glomerulosclerosis. Immunofluorescence findings of IgA deposition are required and may be associated with C3, IgG, and IgM staining as well. Electron-dense deposits are found in the mesangium. Most cases eventually resolve (although episodes of hematuria with illness may recur for years), but 20% of children will progress to renal failure, usually over a period of years. Clinical features of poor prognosis include severe proteinuria, renal insufficiency, and hypertension at the time of diagnosis and the finding of fibrosis or crescent formation of glomeruli on biopsy. Specific treatment is not available, and it is important to avoid potentially toxic therapies for patients unlikely to develop severe disease. Patients with mild disease may be treated with vitamin E and/or ACEIs. Those deemed high risk for progression commonly are treated with high-dose corticosteroids with or without additional immunosuppressant drugs such as azathioprine, cyclophosphamide, or mycophenolate mofetil, although none of the few small randomized controlled trials is sufficient to advocate for any specific regimen ([Hogg, 2010](#)).

Henoch-Schönlein Purpura. In contrast to IgA nephropathy, with which it shares renal biopsy similarities, HSP is a systemic leukocytoclastic vasculitis involving capillaries of the gastrointestinal tract, kidneys, skin, and/or joints resulting in a clinical syndrome of abdominal pain, nephritis, nonthrombocytopenic purpura (classically on the posterior legs and buttocks), and arthritis. Approximately 50% of children with HSP will develop evidence of nephritis within the first 4 to 6 weeks of diagnosis but most will have mild, self-limited disease. The symptoms may flare intermittently over months or even years, generally with consistently less severe manifestations. However, up to 15% of children with HSP nephritis will develop a progressive course resulting in ESRD ([Kawasaki, 2011](#)). These children most commonly have heavy proteinuria and evidence of renal insufficiency and hypertension early in the course of the disease. The renal biopsy findings of HSP are indistinguishable from those of IgA nephropathy and the pathogenesis is also linked to immune complexes containing galactose-deficient IgA₁ ([Kawasaki, 2011](#)). Corticosteroids are beneficial for treatment of arthritis, skin lesions, and abdominal pain but have not been proven to be beneficial for mild renal disease. Aggressive disease is commonly treated with high-dose corticosteroids with or without additional immunosuppressant agents and even plasmapheresis, but randomized controlled trials of sufficient power have not been done to prove efficacy.

Alport Syndrome (Hereditary Nephritis). Hereditary nephritis mimics IgA nephropathy in its presentation with intermittent gross hematuria with intercurrent illness. Persistent microscopic hematuria may precede the onset of proteinuria for some time, and progressive renal dysfunction develops over years. **The hereditary nephritides are a spectrum of disorders all of which are due to mutations in the type IV collagen genes that make up the GBM.** Alport syndrome is the most severe variant and is due to mutations in the α_5 subunit of type IV collagen on the X chromosome, thereby accounting for the X-linked inheritance pattern seen in 85% of cases. The remaining cases are due to mutations in α_3 and α_4 subunits of collagen IV and are inherited in autosomal recessive or autosomal dominant patterns ([Noone and Licht, 2013](#)). Classic Alport syndrome is associated with sensorineural hearing loss, anterior lenticonus, and leiomyomatosis, although the timing of extra-renal manifestations varies widely. With growing understanding of the mechanisms of podocyte and GBM interactions, genotype-phenotype correlations are beginning to explain the wide clinical spectrum seen in this disorder ([Noone and Licht, 2013](#)). Renal biopsy is diagnostic (although it may be challenging if done early in the course) and shows thinning and thickening of the GBM with splitting and lamellation of the lamina densa. Treatment of Alport syndrome is currently supportive, but blockade of the renin-angiotensin-aldosterone system has been shown to decrease proteinuria and delay renal failure ([Kashtan et al, 2013](#)).

Lupus Nephritis and Antineutrophil Cytoplasmic Antibody–Mediated Diseases

Lupus Nephritis. Although SLE is relatively uncommon in childhood, it is important to recognize that nephritis is more common and severe in childhood-onset SLE (Vachvanichsanong and McNeil, 2013). Most commonly, renal involvement with SLE is diagnosed during the evaluation for the nonrenal manifestations of the disease (including constitutional symptoms, rash, hematologic abnormalities, and arthritis), and significant hematuria, heavy proteinuria, abnormal creatinine, and hypertension are common. Around 80% of children diagnosed with SLE will have some form of renal involvement during the course of their disease. Renal biopsy should be considered for all children with SLE because the histopathology, together with clinical manifestations, dictates the most effective treatment approaches (Vachvanichsanong and McNeil, 2013).

The most recent classification system of lupus nephritis (Weening et al, 2004) can be simplified into six categories: Class I—minimal mesangial (normal glomeruli), Class II—mesangial proliferative, Class III—focal endocapillary proliferative, Class IV—diffuse endocapillary proliferative, Class V—membranous, and Class VI—advanced sclerosing. Class IV nephritis is typically the most severe with the highest likelihood of progression to ESRD, but repeat biopsies are often indicated if the clinical course does not match the pathology of an earlier biopsy. Treatment of lupus nephritis is based on biopsy classification and disease severity but usually includes induction with high-dose corticosteroids and cytotoxic agents (usually cyclophosphamide), although mycophenolate is now used as induction therapy in many cases. Maintenance therapy with other immunosuppressive drugs such as calcineurin inhibitors and rituximab is also used. Long-term patient and renal survival now approximates 90% in Caucasian adults (Moroni et al, 2013), although the success rates in children seem to be a bit lower.

Antineutrophil Cytoplasmic Antibody (ANCA)–Associated and ANCA-like Vasculitis. Systemic vasculitis caused by antineutrophil cytoplasmic antibodies (ANCAs) is fortunately very rare in childhood. Granulomatosis with polyangiitis (formerly known as Wegener disease), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome) make up this group of disorders that are characterized by inflammation of small and medium-sized arteries in multiple organs, most commonly in the upper and lower respiratory tract and kidneys (Twilt and Benseler, 2014). Granulomatosis with polyangiitis is associated with cANCA—antibodies against proteinase 3 found in the cytoplasm of neutrophils. Microscopic polyangiitis is associated with pANCA—antibodies against myeloperoxidase. Eosinophilic granulomatosis with polyangiitis is not routinely associated with ANCAs but instead with significant eosinophilia. However, its clinical course and treatments are similar to ANCA-associated diseases. These disorders commonly present with a history of upper and lower respiratory tract complaints and diffuse constitutional symptoms such as fatigue, weight loss, and malaise, and the renal disease may be diagnosed incidentally at the time of a “sick visit.” Kidney involvement is seen in approximately 80% to 90% of children affected. Hematuria and proteinuria are the hallmarks, with rapidly progressive glomerulonephritis and hypertension common pictures. Renal biopsy shows necrotizing crescentic pauci-immune nephritis, usually severe. Final diagnosis is usually determined on the basis of ANCA results. Treatment usually consists of a high-dose corticosteroid and cyclophosphamide. The adjunctive use of rituximab and plasmapheresis has become more common, especially in cases with dialysis dependence and/or pulmonary hemorrhage, but few long-term data exist on which to base therapeutic decisions, especially in children, so most approaches mimic current treatments for adults.

Thrombotic Microangiopathies. Thrombotic microangiopathy (TMA) (Trachtman, 2013) is characterized by the clinical findings of microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury manifesting as varying degrees of hematuria, proteinuria, and decreased GFR. “Typical” HUS caused by infections with Shiga toxin–producing *Escherichia coli* (STEC-HUS) is a common cause of AKI in previously healthy children, and accounts for

approximately 90% of all TMA in childhood. “Atypical” forms of HUS may be acquired from infection (most commonly *Streptococcus pneumoniae*) or medication or may be familial (caused by functional abnormalities of the complement cascade). Pneumococcal HUS is usually quite severe and occurs concomitantly with invasive pneumococcal disease such as meningitis, sepsis, or pneumonia, and is more common in very young children. Thrombotic thrombocytopenic purpura (TTP) occurs as a result of defective processing of endothelial von Willebrand factor multimers from ADAMTS13 dysfunction, and is also quite rare.

Patients with STEC-HUS typically present with varying degrees of diffuse endothelial injury, including evidence of renal dysfunction, pancreatitis, respiratory distress syndrome, central nervous system dysfunction (including seizures, mental status changes, hemorrhage, and hemiparesis), liver failure, cardiac dysfunction, and/or intestinal ischemia. Symptoms develop days following an episode of hemorrhagic colitis. Laboratory findings show hemolytic anemia, thrombocytopenia, and evidence of renal dysfunction (hematuria, proteinuria, and decreased GFR) as well as other organ system biomarkers. The pathogenesis of STEC-HUS is due to gastrointestinal absorption of the Shiga toxin, binding of the toxin to endothelial cells, and subsequent inhibition of protein synthesis and cell damage. The damage to the endothelial cells activates the coagulation cascade, and activation of platelets results in microthrombi. Additional inflammation and complement activation likely add to the damage. Treatment of STEC-HUS is supportive with careful management of fluid and electrolyte balance, anemia, renal failure, and other organ system dysfunction as needed. Forty percent to 50% of patients will require dialysis.

Recent advances in the understanding of complement regulatory proteins have led to the discovery of multiple mutations and complexes of mutations that result in the rare familial forms of atypical HUS (Noris et al, 2012). It is likely that functional variations in complement control also impact the phenotype of TMAs induced by other mechanisms. Abnormalities in factor H, factor I, factor B, membrane cofactor protein, and C3 have been the most commonly detected, with most patients having only one mutation. The pattern of familial HUS is one of repeated episodes, commonly occurring after relatively mild upper respiratory infections and fairly rapid progression to ESRD. Interestingly, the process may not present until adulthood, highlighting the likelihood of environmental triggers superimposing onto a genetic susceptibility to cause disease. Treatment of previously undiagnosed atypical HUS usually includes plasma infusion with or without plasmapheresis. Eculizumab, a monoclonal antibody against complement component C5, acts by preventing the formation of the membrane attack complex as the final step in cell destruction. This drug is now considered standard of care when the diagnosis is confirmed, although the frequency of use remains controversial (Trachtman, 2013). Historically, prognosis for these disorders is quite poor, with most patients succumbing to CKD or other complications, including frequent recurrence following transplantation. It is hoped that eculizumab will improve the course for these patients.

Patients who develop atypical HUS but do not have familial forms present a quandary for nephrologists. Some have been found to have transient antibodies to complement proteins, some are taking medications that may be inciting (by unclear mechanisms), and others appear to be truly sporadic. The outcomes for these patients are not as severe as those who have familial disorders, and treatment remains controversial.

TTP is quite uncommon in childhood and, when seen, is most likely to be associated with SLE, although it can be spontaneous or associated with medications. The final common TMA pathway for this disorder is initiated by abnormalities in function of ADAMTS13. This protein should degrade ultralarge multimers of von Willebrand factor in order to halt platelet activation and the development of thrombi. ADAMTS13 activity can be suppressed as a result of genetic mutation or by autoimmune processes. Clinically, TTP mimics atypical HUS with the exception that diffuse neurologic abnormalities are frequent. TTP is effectively treated with plasmapheresis in most cases (Trachtman, 2013).

KEY POINTS: GLOMERULAR DISEASE

- Glomerular disorders are manifested by evidence of proteinuria with or without hematuria and with or without evidence of inflammation (decreased GFR, hypertension).
- Nephrotic syndrome is defined as edema, heavy proteinuria ($>40 \text{ mg/m}^2/\text{hr}$), hypoalbuminemia ($<2.5 \text{ g/dL}$), and hyperlipidemia. It may be present as an isolated disorder or as a part of any renal inflammatory disease.
- Minimal change disease and its associated nephrotic syndrome is the most common glomerular disorder in childhood and is a presumptive diagnosis in the absence of evidence of inflammatory disease. Its response to steroids and relapsing course assist in diagnosis.
- FSGS is poorly responsive to steroids and is likely to progress to ESRD over time.
- Acute PSGN presents with gross hematuria (classically described as “cola-colored”) following infection. Hypertension and mild decreases in GFR are common, but most patients recover without detectable sequelae.
- IgA nephropathy is also common and often presents as intermittent gross hematuria with or without proteinuria following intercurrent illness. Nephrotic-range proteinuria or abnormal GFR is indicative of poor long-term outcome.
- Renal biopsy is often needed for definitive diagnosis of glomerular disorders and determination of prognosis and appropriate treatment.
- Molecular genetics is dramatically changing our understanding of the pathogenesis of many glomerular diseases and may direct future treatment strategies to more effective targets.

Tubular Disorders

The role of the renal tubule is to refine the glomerular filtrate by reabsorption or secretion of solutes and ultimately create the urinary contents appropriate for physiologic homeostasis. The efficacy of the tubule as a reabsorptive organ can be best appreciated by recalling that normal GFR ($100 \text{ mL/min/1.73 m}^2$) results in an astounding 144 liters of filtrate entering the proximal tubule daily while only approximately 1% of that exits as urine. **The proximal tubule is responsible for the bulk of reabsorption, hence its high energy requirements and susceptibility to ischemia.** Sodium, chloride, glucose, phosphorus, low-MW proteins, bicarbonate, organic acids, and water are all transported across the proximal tubule while the loop of Henle transports sodium, potassium, chloride, and calcium. More distal parts of the nephron fine-tune sodium, chloride, calcium, magnesium, potassium, proton, and water content. The majority of these processes are driven in some way by active transport, usually by ATP-dependent activity of the basolateral Na^+/K^+ -ATPase. The sophistication of the tubular architecture and cellular arrangement is immense, and all parts of the nephron are able, under normal circumstances, to compensate for transient derangements in function in another area. However, chronic dysfunction of any transport system is not usually completely correctable by other mechanisms. Disorders of the tubule may be inherited or acquired (most commonly as a result of damage from ischemia or medication), may be transient or permanent, and may be specific for one molecule or more generalized. Clinical presentations commonly include failure to thrive, polyuria, and polydipsia.

Proximal Tubule Disorders

Fanconi Syndrome. Fanconi syndrome is the result of generalized proximal tubule dysfunction and is defined by tubular wasting of bicarbonate, phosphorus, amino acids, and glucose. It occurs as a result of inherited genetic defects, from heavy metal toxicity, and from a number of chemotherapeutic agents, most commonly ifosfamide and platinum derivatives. The diagnosis is made using

serum and urine electrolyte results that confirm wasting of the compounds mentioned earlier. Once the diagnosis of Fanconi syndrome is made, the search for the cause of the tubular disorder must begin.

The most common inherited disorder that results in Fanconi syndrome is *nephropathic cystinosis*, a disorder that was in fact first described by Fanconi himself (Nesterova and Gahl, 2013). Other causes of Fanconi syndrome include galactosemia, glycogen storage diseases, tyrosinemia, and other rare disorders. Cystinosis is a rare autosomal recessive disorder characterized by aberrant accumulation of cystine within lysosomes as a result of mutations in the *CTNS* (cystinosis) gene. While cystine crystal deposition occurs in most tissues, the proximal tubule is exquisitely sensitive, although it remains controversial as to whether the mechanism is through direct toxicity, aberrant energy production, or apoptosis. The severe form of the disease presents early in childhood with growth failure and electrolyte abnormalities that direct the evaluation toward Fanconi syndrome. Nephrocalcinosis and hypothyroidism are not uncommon, and corneal crystals are usually present on slit-lamp examination before 2 years of age. Carnitine malabsorption is also problematic. Definitive diagnosis is the finding of elevated white cell cystine levels with confirmation of specific molecular mutations by genetic testing. Renal function is normal early in the course but if untreated will decline, and progression to ESRD continues to occur even after effective treatment with cystine-depleting medications. Treatment of cystinosis includes management of the renal wasting of electrolytes as well as specific cystine-depleting therapy. Treatment of the Fanconi syndrome includes bicarbonate or citrate therapy (often at high doses because of wasting), as well as potassium, phosphorus, vitamin D, and thyroxine supplementation as needed. Close attention to nutrition is required, and many children will require a gastrostomy tube in order to provide adequate fluid, calories, and medications. Cystine-depleting therapy with cysteamine is of proven benefit in suppressing damage caused by cystine accumulation (Gahl et al, 2007). The drug acts by entering the lysosome and reacting with cystine to form a disulfide that can be transported from the lysosome. Early, adherent, and long-term treatment is necessary to maintain efficacy.

Proximal Renal Tubular Acidosis. Under normal circumstances the proximal tubule reabsorbs essentially all filtered bicarbonate. However, dysfunction in carbonic anhydrase or other transport proteins related to bicarbonate reabsorption will result in bicarbonate loss into the urine until a new steady state is reached at a lower serum bicarbonate concentration. When the level of filtered bicarbonate drops to the level of reabsorptive capacity, urinary bicarbonate loss ceases and urine pH remains low because of distal secretion of metabolic protons. Proximal RTA is a common feature of Fanconi syndrome but may also be isolated. It is quite common in premature infants and may persist for some months in older infants. Resolution in these cases is thought to be due to delayed maturation of bicarbonate transport mechanisms. Children with proximal RTA usually have growth failure, polyuria, and hypokalemia from acidosis-driven K^+ secretion. Treatment requires frequent high doses of citrate or bicarbonate along with potassium supplementation.

Dent Disease. Dent disease is another tubulopathy for which recent research has provided significant understanding (Chadha and Alon, 2009). Now recognized as clinically and genetically heterogeneous, Dent disease classically presents as an X-linked recessive disorder resulting in low-MW proteinuria, hypercalciuria, nephrocalcinosis and/or nephrolithiasis, and progressive renal failure. Patients may have additional tubular wasting of other electrolytes and meet full criteria for Fanconi syndrome. The disorder is due to inactivating mutations of the *CLCN5* gene that encodes the ClC-5 voltage-gated chloride channel. The exact mechanisms by which abnormalities in this channel result in the varied electrolyte disarrays seen in Dent disease remain unclear. Recently mutations in the *OCRL1* gene (responsible for Lowe syndrome, another cause of Fanconi syndrome) have been found in patients with Dent disease. Because this gene encodes a protein that controls cell membrane transport via lipid modification, the complexity of this spectrum of disorders can be expected to keep investigators busy for

some time. There is no specific treatment for Dent disease, and therapy centers on the management of stones and the complications of progressive CKD.

Hypophosphatemic Rickets. Hypophosphatemic rickets may occur as a result of a number of inherited or acquired abnormalities in the proximal tubular handling of phosphorus (Penido and Alon, 2014). Because the end result of these abnormalities is abnormal bone mineralization, the clinical picture of rickets includes widening of metaphyses of long bones, prominence of the costochondral junction, and genu valgum/varus after weight bearing begins. X-linked hypophosphatemia is the most common inherited form of rickets. It usually manifests clinical symptoms within the first 2 years of life, with males being more severely affected while the disease varies from asymptomatic hyperphosphaturia to severe disease in females. The *PHEX* gene that encodes a cell surface membrane-bound endopeptidase is mutated in many kindreds with this disorder. *PHEX* mutations are associated with high circulating levels of fibroblast growth factor-23 (FGF-23), a hormone that inhibits renal phosphate reabsorption and vitamin D production, but the exact mechanisms linking the mutated enzyme to FGF-23 and the final phenotypic changes remain unclear. Evaluation of suspected hypophosphatemic rickets should include radiologic bone studies, serum and urine calcium and phosphorus determinations (including calculation of the tubular reabsorption of phosphate; normal is >85%), and serum PTH, FGF-23, and vitamin D levels. Given the growing number of identifiable forms of hypophosphatemic rickets, it is appropriate to consult with a nephrologist and/or endocrinologist for current genetic testing options and to appropriately focus therapy. At this point, the mainstay of therapy for X-linked hypophosphatemia is supplementation with calcitriol and phosphorus, although the development of nephrocalcinosis and CKD may occur. Treatments focused on FGF-23 are currently in development.

Primary Renal Glucosuria. Primary renal glucosuria is a benign condition but one that frequently results in specialty referrals because of fears of diabetes mellitus. This "disorder" is most commonly found on routine urinalysis and is *not* associated with polyuria, polydipsia, hyperglycemia, or any other tubular dysfunction. The glucose leak is caused by a mutation in the proximal tubular Na⁺-glucose transporter gene *SGLT2*, and is inherited in an autosomal recessive fashion. The abnormality does not predispose to any disease state and does not require therapy.

Distal Tubule and Collecting Duct Disorders

Bartter Syndrome. Recent research efforts have elucidated a number of mechanisms responsible for Bartter syndrome (Chadha and Alon, 2009). Appearing as one would expect to see with chronic loop diuretic use, this autosomal recessive disorder is characterized by hypokalemic alkalosis, renal salt wasting, hypercalciuria, and hyperreninemic hyperaldosteronism with normal blood pressure. A number of phenotypes linked with a variety of mutations have now been described. The severe antenatal form is associated with polyhydramnios, preterm delivery, severe neonatal fluid and electrolyte disarray, and early-onset nephrocalcinosis while the classic variant is milder and often presents with growth delay, motor weakness, and milder metabolic disturbances. All forms are the result of aberrant epithelial transport of Na⁺ and Cl⁻ across the thick ascending limb of the loop of Henle. The antenatal form of the disease is caused by mutations in the gene for the furosemide-sensitive Na⁺,K⁺,2Cl⁻ cotransporter (NKCC2) responsible for high-quantity sodium, potassium, and chloride reabsorption. A milder form of the disease is caused by a mutation in the renal outer medullary potassium channel responsible for maintaining luminal K⁺ concentrations adequate for NKCC2 activity. Several additional phenotypes have been recently described, all with mutations in a variety of proteins and transporters ultimately responsible for chloride transport. Diagnosis of these disorders is based on clinical suspicion and supportive metabolic studies, and finally genetic sequencing. Treatment remains supportive, primarily with potassium chloride supplementation, often in combination with potassium-sparing

diuretics and drugs that slightly decrease GFR (ACEIs and nonsteroidal anti-inflammatory drugs [NSAIDs]) in order to decrease the filtered load of chloride. Long-term consequences of nephrocalcinosis and hypokalemia may result in progressive CKD.

Distal Renal Tubular Acidosis. Distal renal tubular acidosis (also known as type 1 RTA) results from abnormal H⁺ ion secretion in the distal nephron. As with proximal RTA, distal RTA is characterized by a normal anion gap hyperchloremic metabolic acidosis and is commonly detected either because of family history or during an evaluation for failure to thrive. These patients may be differentiated from those with proximal RTA by the presence of hypercalciuria and a persistently elevated urine pH. Over time these patients often develop stubborn stone disease. Treatment is by provision of base equivalent to normal distal proton secretion (usually no greater than 3 mEq/kg/day) along with potassium supplementation. While clearly a heritable disorder in many cases and given a number of likely target transporters and enzymes, genetic diagnosis of distal RTA remains elusive.

Type 4 RTA is distal RTA with hyperkalemia and is most commonly seen associated with obstructive uropathy, interstitial disease, or multicystic dysplasia. In these cases the pathophysiology results from impaired response to mineralocorticoid caused by damage to the cortical collecting duct. In rarer circumstances, true mineralocorticoid deficiency may be present or chronic medications may be causative. Hyperkalemia is usually out of proportion to the degree of renal insufficiency. Treatment is by replacement of needed base, but as a sodium salt alone given the hyperkalemia. Appropriate management of obstructive uropathy is warranted, but the persistence of chronic developmental damage makes significant improvement in the resistance to mineralocorticoid unlikely.

Gitelman Syndrome. Gitelman syndrome is an autosomal recessive disorder that on the surface looks much like Bartter syndrome, with hypokalemic alkalosis and renal salt wasting. However, the phenotype is much milder and most children present later in childhood without significant failure to thrive. Laboratory evaluation for Gitelman syndrome differs from that for Bartter syndrome by very low urinary calcium excretion and the presence of hypermagnesuria with hypomagnesemia, which may lead to tetany or weakness. The molecular defect in Gitelman syndrome is most commonly a mutation in the thiazide-sensitive electroneutral Na⁺,Cl⁻ cotransporter gene (*NCCT*). The hypocalciuria and hypermagnesuria are secondary effects of volume contraction and downregulation of the apical magnesium channel (Chadha and Alon, 2009). Treatment is with potassium and magnesium supplementation; amiloride is a common adjunctive therapy acting to spare both potassium and magnesium wasting.

Nephrogenic Diabetes Insipidus. Nephrogenic diabetes insipidus (NDI) is defined as collecting duct insensitivity to arginine vasopressin and may occur as a result of medications (most commonly lithium) or structural renal disease. In these cases the severity of water loss is relatively mild. However, inherited forms of NDI may be clinically dramatic, presenting with recurrent severe hypernatremic dehydration in the neonatal period, often with seizures. Developmental delays may occur owing to repeated episodes of hypernatremia, and failure to thrive is common because of the greater desire to ingest water rather than nutrients. Over time, the extremely high volume of urine output may result in hydronephrosis. Definitive diagnosis of NDI (and differentiation from central diabetes insipidus) is made using a water deprivation test. Baseline weight and urine and plasma osmolalities should be obtained, followed by withholding of fluids. Urine volume should be quantitated and weight checked every 1 to 2 hours. Urine osmolality should be checked hourly. At any point that weight loss is 3% or greater, a serum osmolality test should be done and an intravenous dose of vasopressin administered. Urine output should be observed and urine and serum osmolalities checked 60 minutes after the vasopressin dose, and access to fluids should be returned at that point. Patients with central diabetes insipidus will respond to vasopressin by decreasing their urine output, increasing urine osmolality, and decreasing serum osmolality. Patients with NDI will have no response. Infants should have this testing performed under

direct medical observation in order to avoid the risk of rapid and severe dehydration that can occur if weight loss is not accurately monitored or fluids are not reintroduced quickly when warranted.

The most common molecular defect causing NDI is a mutation in the arginine vasopressin receptor-2 gene (*AVPR2*) located on the basolateral side of collecting duct principal cells. In the absence of normal vasopressin signaling, aquaporin-2 (*AQP2*) trafficking is impaired, resulting in lack of appropriate *AQP2* activity to maintain normal water reabsorption (Wesche et al, 2012). This form of NDI is therefore inherited in an X-linked fashion. More uncommonly seen (around 10% of patients with NDI) are autosomal dominant or recessive mutations in the *AQP2* gene that also result in *AQP2* trafficking abnormalities as opposed to structural abnormalities in the water channel itself. Treatment of NDI centers on provision of adequate free water and calories with attempts to decrease the renal solute load by limiting protein and sodium. Adjunctive therapies with NSAIDs (to decrease GFR) or thiazide diuretics (to cause gentle sodium loss resulting in enhanced proximal salt and water reabsorption) may be needed in extremely polyuric infants. As infants mature and are able to clearly express thirst and then obtain fluids independently, the episodes of dehydration become less severe.

Pseudohypoaldosteronism Type I and Liddle Syndrome. These two very rare abnormalities are worthy of mention as examples of cortical collecting duct abnormalities. They also have a “yin-yang” relationship, with pseudohypoaldosteronism type I (PHA-I) being a phenotype of aldosterone resistance and Liddle syndrome a phenotype of apparent aldosterone excess. Two separate gene defects may be seen with mutations in the apical epithelial sodium channel (*ENaC*) subunits or in the mineralocorticoid receptor. PHA-I results from loss-of-function mutations in either gene while Liddle syndrome results from gain-of-function mutations in either gene (Chadha and Alon, 2009).

PHA-I presents in infancy, often very early and very dramatically, with polyuria, dehydration and profound hyponatremia, hyperkalemia, and acidosis that are commonly life threatening. The differential diagnosis includes salt-wasting adrenal insufficiencies (which are more common) with the differentiating fact that corticosteroids and mineralocorticoid therapies do *not* correct the electrolyte disarray. Treatment is with sodium chloride supplementation (often as saline to provide additional volume support) and potassium restriction or exchange resins. Sodium bicarbonate may also be needed to help with acidosis and management of hyponatremia and hyperkalemia. With time and the ability for the child to access salt and fluid independently, the risk of life-threatening electrolyte disarray decreases. Liddle syndrome is characterized by hypokalemic alkalosis and severe hypertension resulting from uncontrolled sodium reabsorption in the collecting duct. The hypokalemia and alkalosis are due to the requisite secretion of potassium and protons that occurs as a part of sodium exchange. Patients with Liddle syndrome are treated with amiloride or triamterene, which are direct *ENaC* inhibitors.

KEY POINTS: TUBULAR DISORDERS

- Polydipsia, polyuria, and poor growth are common features of renal tubular disorders.
- Type 4 RTA resulting from obstructive uropathy is the most common “tubulopathy” in pediatric patients.
- Evaluation of the tubular disorders should include evaluation of urinary sodium, potassium, calcium, magnesium, glucose, amino acids, uric acid, and phosphorus along with complementary serum studies as indicated by the suspected diagnosis.
- With the exception of patients with known obstructive uropathy, the finding of hydronephrosis in tubular disorders is most commonly due to long-standing polyuria.
- Determination of acid-base status may be a clue to diagnosis as a number of tubular disorders result in systemic acidosis or systemic alkalosis.

Nephrolithiasis

Epidemiology

Urinary tract stones in children have been recognized for centuries, yet we remain limited in our knowledge of modern trends of incidence, recurrence risk, and optimal management. The incidence is clearly increasing in the United States and has been estimated to be above 50 per 100,000 adolescents (Tasian and Copelovitch, 2014), up from 18 per 100,000 in 1989 (Stapleton, 1989). The causes of this increase remain undefined, although changing diets and lifestyle as well as obesity have been implicated (Jackson, 2014). The types of stones in some areas are changing as well, with a globalization of stone type distribution (Dator, 2010). This is manifest in the reduced frequency of uric acid and ammonium acid urate stones in developing countries, being replaced by a more Western distribution of predominantly calcium stones. The incidence of struvite stones in children has decreased significantly and presently represents about 10% to 20% of stones, in contrast to a reported 60% in pediatric studies from 1958 to 1985 (Diamond, 1991).

While many stones can be attributed to specific medical conditions, some with significant systemic medical implications, the majority must be considered idiopathic. Metabolic factors such as hypercalciuria or hypocitraturia can be associated with the occurrence of stones in children, but their relevance to the risk of recurrence and to defining the value of specific therapy remains tenuous.

Clinical Presentation

The clinical presentation of pediatric nephrolithiasis is distinct from that in adults, with fewer children having classic renal colic but instead often presenting in more subtle ways or being diagnosed by incidental detection. Approximately 60% of children will present with pain, including both abdominal and flank, 30% with hematuria, and 15% with dysuria. Asymptomatic presentation accounts for approximately 15% (Valentini and Lakshmanan, 2011). It should be kept in mind that stones in children may be associated with infection and fever as well as failure to thrive, and have been misinterpreted as appendicitis (Polito et al, 2009). In cases of recurrent abdominal pain, imaging will usually be undertaken and will usually, but not always, reveal the cause as a calculus.

The pattern of clinical presentation will define the urgency and modality of therapy, particularly when fever is present. The obstructing stone in the setting of possible urinary infection is an emergency.

Etiology

Stone formation in children is similar to that in adults, and the detailed description of stone formation in Chapter 52 is relevant to children as well. Particular types of stone formation, however, are seen specifically in children, and the potential for associated metabolic conditions that have systemic implications must be considered in any child with nephrolithiasis. Some of these conditions, such as primary hyperoxaluria, are more effectively treated with earlier diagnosis. Determining the underlying cause and initiating appropriate therapy permits reduced morbidity from recurrence as well as potential extraurinary manifestations.

The clinical context can aid in defining etiology. Overt structural defects of the urinary tract (e.g., obstruction with hydronephrosis), neuropathic bladder dysfunction, or recurrent urinary tract infections can suggest likely causes. Non-urinary tract disease (e.g., inflammatory bowel disease), prematurity (furosemide-induced nephrocalcinosis), steroid usage, known genetic abnormalities, and malignancy can also suggest a likely cause.

In the presentation of a first-time, isolated stone, the most readily available information will be whether the stone is radiopaque or radiolucent. In some cases the density can be estimated by Hounsfield units when computed tomography has been performed. Metabolic evaluation, which also provides the stone composition, is

usually deferred until after stone removal. In the event of smaller stones for which intervention is not immediately needed, basic evaluation can be undertaken.

Hypercalciuria is the most common metabolic cause of renal stones in children and, while most often idiopathic, can be associated with specific renal and systemic abnormalities. Systemic conditions include hypercalcemia resulting from hyperparathyroidism, which in turn may be due to several clinical syndromes. These include primary hyperparathyroidism as well as hyperparathyroidism in association with multiple endocrine neoplasia type 1 (MEN-1); a high index of suspicion for MEN-1 should be entertained in a child with hyperparathyroidism and stones (Romero Arenas et al, 2014). Recurrent stones, especially if associated with bone disease, should trigger an evaluation for hyperparathyroidism (Bhadada et al, 2008). Hypercalciuria with normal serum calcium levels is due to either excessive absorption of calcium from the gut (absorptive hypercalciuria) or renal leak in which urinary calcium is poorly reabsorbed in the tubules, leading to urinary supersaturation. Abnormal phosphate reabsorption can also be the basis for stone formation, although rarely.

RTA, most commonly type 1 (distal), is an important cause of nephrolithiasis in children. Approximately 70% of affected patients with type 1 RTA will have stones and about half are diagnosed through the initial presentation with stone. RTA is an inability to excrete hydrogen ions, leading to alkaline urine (and systemic acidosis). In children this can lead to failure to thrive, vomiting, or diarrhea. Calcium phosphate stones are most common. These patients have hypercalciuria, hypocitraturia, and alkaline urine pH; the hypercalciuria is further aggravated by acidosis-induced bone demineralization causing secondary hyperparathyroidism.

Hypocitraturia can be a significant contributing factor in stone formation. Citrate acts to reduce calcium crystallization through several mechanisms. The calcium/citrate ratio is considered a more useful indicator of stone risk than simply the concentration of citrate (Penido et al, 2013). The clinical importance of hypocitraturia lies in its being readily corrected with oral administration of citrate-containing drinks.

Children with severe seizure disorders are often treated with ketogenic diets, producing systemic acidosis leading to hypercalciuria and hypocitraturia (Sampath et al, 2007). Several anticonvulsants contribute to metabolic predisposition to stone formation, including topiramate and zonisamide.

Gastrointestinal diseases can be associated with nephrolithiasis, often as a result of chelating of intestinal calcium, which frees oxalate to be absorbed and subsequently excreted in the urine. The chelation of calcium is associated with steatorrhea, as in cystic fibrosis and inflammatory bowel disease.

Primary hyperoxaluria usually presents before the age of 6, often with multiple stones, and is associated with progressive renal failure and frequently recurring calcium oxalate stones. Primary hyperoxaluria type 1 (PH1) is due to deficiency in alanine:glyoxalate aminotransferase and can only be cured with liver transplantation, often combined with renal transplantation because of the chronic renal damage occurring from calcium oxalate deposition. Primary hyperoxaluria type 2 (PH2) is due to deficiency in glyoxylate reductase/D-glycerate dehydrogenase, which produces high levels of excretion of L-glyceric acid and oxalate.

Cystinuria is an X-linked inherited renal tubular defect of the reabsorption of four amino acids: cystine, ornithine, lysine, and arginine (COLA) (Claes and Jackson, 2012). Only cystine is insoluble as a dimer of two cysteine molecules joined by sulfide bonds. The cysteine molecules are much more soluble than cystine, an important factor in therapy using sulfide bond dissociation. These stones are usually radiopaque and are very hard, making lithotripsy difficult.

Dent disease produces nephrocalcinosis, proteinuria, renal dysfunction, and rickets as well as nephrolithiasis.

Another X-linked disorder associated with nephrolithiasis is Lesch-Nyhan syndrome, a defect in purine metabolism that produces uric acid stones. The clinical context is notable with mental retardation, self-mutilation, hyperuricemia, and premature gout.

Management consists of vigorous hydration, reduced purine intake, allopurinol, and urinary alkalinization.

Evaluation

An initial stone presenting in a child should prompt a formal metabolic evaluation. While this is not standard practice for all adults, the purpose in the child is to identify the few yet significant potential underlying systemic illnesses that can present with stone disease, as well as to identify those children at presumably higher risk of recurrence.

Initial evaluation is largely through imaging and seeks to define the stone location and burden, presence of any associated anatomic abnormalities or urinary obstruction, and possibly stone type based on radiolucency. Basic metabolic parameters should be obtained initially, including serum electrolytes, serum calcium and phosphate, and urinalysis with microscopic examination. Urinalysis should include the specific gravity, as an indication of hydration, and pH. Urinalysis should focus on the presence of pyuria and crystalluria. The appearance of crystals can be diagnostic for specific types of stone disease, including uric acid, cystine, and struvite stones. A spot urinary calcium/creatinine ratio can be useful as a baseline to identify very abnormal levels of urinary calcium.

Following stone removal, a formal metabolic evaluation can be undertaken to more precisely define the likely etiology and recurrence risk (Pietrow et al, 2002). Repeat serum studies should be performed, particularly if initial studies were borderline abnormal. A formal 24-hour urine collection should be attempted but may be very difficult in younger children. In those cases, a timed collection may be the best option, or the clinician may elect to use spot collections for calcium, oxalate, and citrate, indexed to creatinine level and calcium/citrate ratio. There are several commercial services that will perform stone risk profiles, yet the normal parameters for children are not well established and not specifically tied to recurrence risk. The impact of age on normal levels, particularly of calcium excretion, must be considered. Calcium excretion in the urine is very high in the newborn and gradually decreases through childhood. Urinary calcium/creatinine ratios in the newborn are as high as 0.50 but are less than 0.20 by early childhood.

Recurrence risk is of course a key clinical factor and is difficult to define. A rate of about 16% was noted in earlier studies (Diamond, 1991), and a rate of about 19% more recently (Pietrow et al, 2002). These authors demonstrated a higher recurrence rate in children with identified metabolic abnormalities. When variable follow-up was factored, a rate of 0.32 per patient-year was reported (Tekin et al, 2002). This study also demonstrated a reduction in recurrence risk with oral citrate therapy.

Medical Management

Immediate management of any child presenting with a possible stone consists in relieving obstruction when this may be associated with infection. Obstruction otherwise is usually partial and management is directed toward pain control and facilitation of stone passage. If high-grade obstruction is suggested, early decompression is indicated. Typically, the degree of hydronephrosis will be a rough indicator of the severity and acuity of obstruction, but this is not always so. In very acute stone-induced obstruction, the degree of dilation may be mild. In such cases functional imaging will reveal a delayed nephrogram pattern either on computed tomography, diuretic renography, or intravenous pyelography. Acute surgical management is discussed in Chapter 135 but will usually include percutaneous antegrade diversion or retrograde ureteral stenting.

Further facilitation of stone passage is based on vigorous hydration and medical management. Medical management can be as simple as NSAIDs to control pain and relax the ureteral smooth muscle, but may require drainage or definitive stone removal.

α -Blockade is used to more aggressively reduce ureteral smooth muscle tone to permit more rapid stone passage. While the results of various series are diverse, a formal literature review does suggest some value in these agents. Children showed a 55% passage rate of

ureteral stones in contrast to 44% in untreated children (Tasian et al, 2014). Although some series have suggested that stones pass more slowly in children, it has been our experience that proportionally larger stones will pass more readily in children than in adults. For this reason a period of watchful waiting in a minimally symptomatic child is a logical approach.

Once the stone has passed, the focus of therapy is prevention of further episodes and inhibition of any new stone growth. For all stone types the foundation of prevention is to reduce the concentration of lithogenic salts and create as nonlithogenic a urinary environment as possible. The first goal includes reducing the urinary excretion of lithogenic salts, particularly calcium and oxalate, as well as increasing urinary volume, which has the same effect. The second goal includes adjusting the urinary pH to limit crystal precipitation and to increase the concentration of inhibitors of crystallization, such as citrate. Reducing the lithogenic concentration is both direct by reducing the dietary content of calcium and oxalate, and indirect by reducing calcium secretion by the kidneys. Most importantly, this includes reducing dietary sodium intake (Escrignano et al, 2014). This reduces urinary calcium excretion because sodium and calcium are secreted through similar cellular ion channels. Indeed, it has been shown that reducing sodium intake is preferable to and more effective than reducing calcium intake in the prevention of nephrolithiasis. In more refractory cases, direct potassium citrate therapy may be of value. In children this is always difficult to define because there is no clear end point to therapy. Oral treatment with potassium citrate is effective in increasing urinary citrate levels and reducing calcium excretion and crystallization (Tasian and Copelovitch, 2014).

The use of medication to reduce stone formation in children is a challenging area in which to define best practices. In the recurrent stone former, the use of thiazide diuretics has the effect of limiting recurrent calcium nephrolithiasis, yet poses the question of the appropriate duration of therapy and what indicators can be used to define when reduction or discontinuation may be attempted. In our practice the use of thiazides is limited to those children with recurrent stone formation or growth as well as demonstrable hypercalciuria refractory to hydration and dietary interventions. Standard doses for diuresis are started but then may be reduced to a point that maintains a normal urine calcium level. Long-term compliance can be an issue, and the effects of long-term therapy are not well defined. Concerns for potassium wasting and hypocalciuria must be considered in use of thiazides.

In special situations, such as cystinuria, medical therapy is much more clearly defined. The principle of treatment in cystinuria is to reduce the concentration of urinary cystine to less than 300 mg/L (Pak, 1983) by creation of alkaline urine and the use of a cystine-binding agent to create a mixed cystine-drug disulfide bond to increase solubility. This can be accomplished by several agents, including D-penicillamine, α -mercaptopyrionylglycine (tiopronin [Thiola]), and captopril (Claes and Jackson, 2012). The first of these agents is associated with significant side effects, limiting its utility considerably. Medical management of cystinuria remains a major challenge, even with available medical agents, and the need for surgical intervention remains high.

PH1 is also amenable to specific medical management, although this is at best a temporizing solution (Cochar and Rumsby, 2013). Ultimately kidney and liver transplantation appears to be the definitive therapy. To limit stone recurrence and the impact of some forms of systemic oxalosis, pyridoxine is used starting at 5 mg/kg/day and titrated to a maximum of 20 mg/kg/day using urinary oxalate excretion as the end point (Hoyer-Kuhn et al, 2014). The target is a decrease of 30% or more. Potassium citrate at 0.10 to 0.15 mg/kg/day is also used to limit the risk of nephrolithiasis by alkalinizing the urine to a pH of 6.2 to 6.8. Vigorous hydration is, as with all other types of nephrolithiasis, an essential foundation for medical therapy.

Hypertension

For children and adolescents, hypertension is defined as blood pressure consistently greater than the 95th percentile for age, sex,

KEY POINTS: NEPHROLITHIASIS

- Approximately 60% of children will present with pain, including both abdominal and flank, 30% with hematuria, and 15% with dysuria.
- The incidence of struvite stones in children has decreased significantly, and presently represents about 10% to 20% of stones, in contrast to a reported 60% in studies of children from 1958 to 1985.
- Stone etiology may be suggested by the presence of non-urinary tract disease, such as inflammatory bowel disease, prematurity (furosemide-induced nephrocalcinosis), steroid usage, known genetic abnormalities, and malignancy.
- Initial evaluation is largely through imaging and seeks to define the stone location and burden, presence of any associated anatomic abnormalities, urinary obstruction, and possibly stone type based on radiolucency.
- Metabolic evaluation is recommended in all children presenting with stone but is usually deferred until after stone removal, which also provides the stone composition. In the event of smaller stones for which intervention is not immediately needed, basic evaluation can be undertaken.
- Hypercalciuria is the most common metabolic cause of renal stones in children and, while most often idiopathic, can be associated with specific renal and systemic abnormalities.
- RTA is an important cause of nephrolithiasis in children, most commonly type 1 (distal) RTA. Approximately 70% of affected patients with type 1 RTA will have stones and about half are diagnosed through the initial presentation with stone. RTA is an inability to excrete hydrogen ions, leading to alkaline urine (and systemic acidosis).
- Primary hyperoxaluria usually presents before the age of 6, often with multiple stones, and is associated with progressive renal failure and frequently recurring calcium oxalate stones.
- Cystinuria is an X-linked inherited renal tubular defect of the reabsorption of the four amino acids cystine, ornithine, lysine, and arginine (COLA).
- Recurrence risk is a key clinical factor but is difficult to define. In earlier studies, a rate of about 16% was noted in contrast to about 19% more recently.
- Immediate management of any child presenting with a possible stone consists in relieving obstruction when this may be associated with infection. Obstruction otherwise is usually partial and management is directed toward pain control and facilitation of stone passage.

and height with normal blood pressure continuously increasing from birth to adulthood (Table 123-2). Depending on the setting, the prevalence of hypertension in children is estimated at 1% to 4.5% and is clearly increasing, most predominantly as a result of the obesity epidemic affecting the young (Lande and Kupferman, 2014). In the past, the pediatric nephrologist was the “hypertension specialist” for children because the most common causes of hypertension were renal in origin. While the etiologies have shifted to metabolic syndrome in most age groups, the nephrologist continues to play a major role in the evaluation and management of childhood hypertension, especially the complex and severe hypertension often seen in children with kidney disease. Given the prevalence of childhood obesity (with approximately 25% to 35% of U.S. children classified as overweight or obese) it is critical that all physicians treating children encourage healthy nutrition and exercise regimens. Extensive searches for other etiologies of hypertension are not always warranted, but the astute physician will recognize that children with secondary causes of hypertension may also be overweight, and carefully consider an individualized approach to evaluation to maximize the likelihood that the cause of high blood pressure is appropriately attributed and managed.

TABLE 123-2 Pediatric Definitions of Hypertension

Normal	SBP or DBP <90th percentile for age and gender
Prehypertensive	SBP or DBP from 90th to <95th percentile or BP >120/80 mm Hg even if <90th percentile up to 95th percentile
Stage 1 hypertension	SBP or DBP 95th to 99th percentile + 5 mm Hg
Stage 2 hypertension	SBP or DBP >99th percentile + 5 mm Hg

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

In cooperative older children, blood pressure should be measured in a calm environment with the child in a sitting position with the arm resting comfortably at heart level. Blood pressure assessments in infants are usually obtained in the arm with the child supine and commonly require multiple measurements until consistent values are obtained. The appropriate-sized cuff is one that covers at least two thirds of the distance between the olecranon and the acromion, and the bladder should encircle the arm.

Unfortunately, there have been no further updates on the definitions of hypertension in children since the fourth report of the [National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents \(2004\)](#), and currently there are no plans to update that report. The tables in that report, stratified by age, sex, and height, therefore remain the standard for defining hypertension and its differing stages. These normative data are derived from auscultatory measurements, while recommendations suggest that 24-hour blood pressure monitoring with oscillometric measurements are most appropriate for diagnosis of hypertension, even though the two methods give different readings. From a practical clinical perspective in a pediatric urology practice, many children will have clear hypertension that will require ongoing medication management that is most commonly handled by the nephrology service. Patients with borderline readings in the urology settings may comfortably be referred to nephrology for the evaluations noted later and further decision making. Of most importance is that consistent, careful, and technically appropriate blood pressure measurements be made on essentially all children in the pediatric urology clinic so that suitable referrals may be made as needed.

While primary hypertension is now quite prevalent in the pediatric age group, renal parenchymal and renovascular disorders remain the most common causes of secondary hypertension, accounting for more than 75% of cases ([Brady and Feld, 2009](#)). The most common causes to be encountered in a pediatric urology practice will be obstructive uropathies (most frequently ureteropelvic junction and posterior urethral valve obstructions), reflux nephropathy, and chronic parenchymal disease of almost any form, including cystic diseases. In these instances, hypertension may be severe, even in the youngest of neonates ([Flynn, 2012](#)). On occasion, patients with acute glomerulonephritis or HUS will be referred to a urologist because of gross hematuria, and hypertension may be noted as a significant clinical finding. **It should be remembered that immobilization (commonly following severe trauma) and skeletal traction can result in hypertension, especially in teen males.** Given its increasing frequency, primary hypertension will be seen in the pediatric urology clinic, is found in all ethnic groups, and is usually asymptomatic. These patients will most commonly be overweight, have a positive family history of hypertension, and have hypertensive responses to stressful events. Inactivity and sleep apnea are also commonly associated. Even the child with apparent straightforward enuresis could have upper tract disease,

thereby serving as a reminder that essentially *all* children in a urology practice should have their blood pressures measured.

In the absence of identified urinary tract abnormalities, evaluation for an etiology for childhood hypertension is most logically carried out in the pediatric nephrology or cardiology environment. After confirmation of abnormal blood pressure, recommended workup includes a minimum of urinalysis, complete serum biochemical profile, renal ultrasonography, and echocardiogram. As mentioned earlier, 24-hour ambulatory blood pressure monitoring is becoming more frequently utilized and is especially helpful when masked hypertension or white-coat hypertension is a possible diagnosis ([Flynn and Urbina, 2012](#)). Additional studies as indicated by history and clinical picture may include plasma renin and aldosterone, thyroid studies, plasma cortisol, urinary catecholamines, and renal arteriography (reserved for severe hypertension with suspicion of renovascular disease). Genetic testing for the rare single-gene defects causing hypertension (Liddle syndrome, apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism) is now available but, given costs, should be reserved for cases in which there is evidence for one of these disorders (early severe hypertension, hypokalemic alkalosis, and/or suppressed plasma renin) ([Brady and Feld, 2009](#)).

Severe acute hypertension, while uncommon, requires emergent treatment, often with parenteral therapy (nicardipine being currently in favor). While avoided in adult practice, oral nifedipine is still used in severe pediatric hypertension without significant concern for cardiac ischemia, most commonly as an initial therapy while awaiting intravenous access and drug delivery. The goal of emergent therapy is to lower the mean blood pressure by 20% to 30% to avoid end-organ damage from hypertension without compromising blood flow.

The treatment of chronic pediatric hypertension is most commonly focused on the etiology of the elevated blood pressure. Primary, or essential, hypertension may be addressed with lifestyle modification, including exercise, weight loss, sodium restriction, and smoking cessation, as long as there is no evidence of end-organ involvement (most commonly left ventricular hypertrophy). If lifestyle modifications have not resulted in change in 3 to 6 months, pharmacologic therapy is warranted. For those patients in whom lifestyle modifications are not welcomed, pharmacologic therapy may best be started earlier. Patients with renal/urinary tract etiologies of their hypertension are most commonly treated with ACEIs or ARBs. While very effective in controlling blood pressure from angiotensin-mediated causes, there is risk of AKI from loss of renal autoregulation in states of dehydration, and patients must be counseled to contact their physicians or hold medications when dehydration is suspected or likely. The other risk of ACEI/ARB therapy is the teratogenic effects of these medications when taken during pregnancy. It is critical that prescribing physicians carefully instruct patients and families about these potential serious side effects when choosing therapy. Calcium channel blockers (most commonly amlodipine) are also commonly used, especially if abnormal renal function limits ACEI/ARB use. β -Adrenergic blockers (atenolol, metoprolol) and mixed α - and β -blockers (labetalol) may be used as well. Clonidine is also quite effective, especially in circumstances in which central nervous system involvement in the hypertension is suspected. Essentially all classes of antihypertensives used in adults are used and are effective in children, and progress has been made by regulatory incentives for randomized, controlled studies of new agents in children. It is unlikely that many older agents will ever be appropriately studied in children, but many have long clinical practice track records that provide guidance to the careful practitioner ([Blowey, 2012](#)). Goals of chronic therapy are blood pressures less than the 90th percentile for age, sex, and height, and many advocate for lower levels for children with chronic heart and/or kidney disease.

Acute Kidney Injury

AKI is defined as an abrupt loss of homeostatic capability that includes but is not limited to acute renal "failure." Over the last

KEY POINTS: HYPERTENSION

- Hypertension is defined as blood pressure greater than the 95th percentile for age, sex, and height.
- Proper technique, equipment, and patient cooperation are vital in measuring accurate blood pressure in children.
- Primary hypertension is now the most common cause of hypertension in childhood and is strongly linked to obesity, inactivity, and poor nutrition.
- Evaluation for hypertension should include consideration of renal causes as well as family history and lifestyle issues.
- Echocardiography is an important component of evaluation because left ventricular hypertrophy is common in pediatric hypertension (approximately 40%).
- With careful attention to dosing and strategic approaches designed to address the likely cause of hypertension, many drug regimens will be effective in controlling blood pressure in children of all ages.

TABLE 123-3 KDIGO Criteria for Acute Kidney Injury

STAGE	SERUM CREATININE (SCr) CHANGES	URINE OUTPUT CHANGES
I	SCr increase ≥ 0.3 mg/dL in 48 hr or 1.5-1.9 times baseline	< 0.5 mL/kg/hr for 6-12 hr
II	SCr increase 2.0-2.9 times baseline	< 0.5 mL/kg/hr for 12 hr
III	SCr ≥ 3.0 increase or SCr > 4.0 mg/dL or If < 18 yr of age, estimated creatinine clearance < 35 mL/min/1.73 m ²	< 0.5 mL/kg/hr for 24 hr or < 0.3 mL/kg/hr for 12 hr

Modified from Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Pt. 1). *Crit Care* 2013;17:204.

decade, the recognition of renal compromise as an epidemiologic risk factor for patient morbidity and mortality has helped lead a change in terminology that allows for categorical definitions of acute renal dysfunction instead of the past binary definitions that were never standardized. In 2005 the Acute Dialysis Quality Initiative developed a multidimensional stratification system for AKI called RIFLE (for risk, injury, failure, loss, and ESRD) using graded criteria for changes in GFR and changes in urine output in order to define AKI. This approach recognized the often-independent changes in serum creatinine levels and urine volume in the various settings and etiologies leading to functional insufficiency. This initial stratification strategy has since been utilized by several different groups to define a lower threshold, remove the end-stage outcomes (in order to focus on areas that might be treatable), provide modifications that are useful in pediatrics (Fortenberry et al, 2013), and harmonize the various approaches. While a number of these strategies are still in use in research, the most recent consensus criteria are those from the *Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012)* (Table 123-3).

Etiology and Evaluation

The etiologies of AKI also have been changing in the last decades in the developed world. The most common causes (Box 123-4) have shifted from primary renal diseases such as acute glomerulonephritis and HUS to secondary effects of systemic illness or its treatment (sepsis, ischemia, complications of complex surgi-

BOX 123-4 Causes of Acute Kidney Injury

Decreased true intravascular volume

- Third-space losses: sepsis, trauma, burns, nephrotic syndrome
- Gastrointestinal losses
- Salt wasting: renal or adrenal
- Diabetes insipidus: central or renal

Decreased apparent intravascular volume: congestive heart failure

Acute tubular necrosis/cortical necrosis

- Hypoxic-ischemic insults
- Medications: aminoglycosides, intravenous contrast agents, nonsteroidal anti-inflammatory drugs, chemotherapeutics
- Exogenous toxins: ethylene glycol, methanol
- Endogenous toxins: hemoglobin, myoglobin

Tumor lysis syndrome and uric acid nephropathy

Interstitial nephritis

- Medication induced: anticonvulsants, antibiotics
- Idiopathic

Glomerulonephritis: all causes

Vascular disorders

- Hemolytic uremic syndrome
- Renal artery or vein thrombosis

Infection

- Pyelonephritis
- Sepsis

Obstructive lesions

- Obstructed single kidney
- Bilateral ureteral obstruction
- Urethral obstruction

cal procedures such as congenital heart disease repair). However, the pediatric urologist may become involved with patients with any of these disorders and should be prepared to aid the team in investigating possible causes for acute declines in kidney function. It is also important to note that, while necessary to thinking and planning for therapy, the past concepts of “prerenal” versus “intrinsic” versus “postrenal” classifications are less critical. For example, the differentiation between oliguria and increased creatinine caused by decreased perfusion pressure compared to that caused by intrinsic tubular necrosis is difficult, especially in the complex intensive care unit environment. It is also apparent that not all regions of the kidney are evenly involved in the progression of AKI. Therefore it is best to make a diagnosis of AKI and recognize the risks and approaches to that determination than be mired in borderline laboratory results complicated by time and medications. Likewise, in most critically ill children the causes of AKI are likely to be multiple, and the astute clinician will consider all of them as potential targets for improvement. Obstructive lesions (congenital or acquired) may often present a picture of “acute-on-chronic” dysfunction with worsening of function owing to infection, edema, or postoperative surgical problems. This being said, assessment of renal function beyond change in creatinine and recent urine output may be reasonable, especially when considering effective renal perfusion. As shown in Table 123-4, decreased perfusion in the absence of tubular damage may be differentiated from established necrotic injury using a combination of urinary concentrating ability, urine solute characteristics, and urinalysis. Fractional excretion of urea (and with less sensitivity and specificity, fractional excretion of uric acid) is most useful in the setting of active diuretic use, which obviously alters the ability of sodium excretion to mark the presence of impaired tubular function (Diskin et al, 2010).

The advances in pediatric critical care practice have created an environment for enhanced understanding of the pathophysiology

TABLE 123-4 Urine Studies and Results for Differentiation of Renal Damage from Underperfusion

TEST	RENAL HYPOPERFUSION	ESTABLISHED DAMAGE
BUN/creatinine ratio	>20	<20
Urine specific gravity	>1.020	≈1.010
Urine osmolality	>350	≈300
Urine sodium	<20 mEq/L	>30 mEq/L
Fractional excretion of sodium	<1%	>2%
Fractional excretion of urea	<35%	>50%
Fractional excretion of uric acid	<12%	>20%
Urine microscopy	Normal ± hyaline casts	Proteinuria, cellular casts (type depending on primary etiology), eosinophils (interstitial nephritis)

BUN, blood urea nitrogen.

and treatment options for children with AKI. With improved diagnostic criteria, it is estimated that between 12% and 70% of high-risk neonates develop AKI (Carmody and Charlton, 2013) and that around 10% of all children admitted to a pediatric intensive care unit develop AKI, with that number rising to around 80% in the most seriously ill (Devarajan, 2011). It is now recognized that AKI is an independent risk factor for mortality in children (Fortenberry et al, 2013) and that fluid overload is an additional independent risk for mortality (Foland et al, 2004).

It is important to recognize that AKI is an evolving process with damage occurring at different rates and with varying severity over time, in different parts of the kidney, and in response to new noxious events. Changes do not occur in stepwise fashion: serum creatinine increases continuously, urine sediment increases over time, ultrasonography may reveal normal kidneys (but usually with no baseline for renal volume or echogenicity), renal blood flow is rarely examined directly, and biopsies are very rarely performed for AKI in children. For all these reasons, the severity of damage is often unclear and management defaults to preserving remaining function, avoidance of additional insults, supportive care, and watchful waiting. The outcomes of AKI are not as benign as previously believed. Of pediatric survivors of AKI in a large tertiary referral center (where the most common causes of AKI were complications of congenital heart surgery, neonatal care, and marrow and solid organ transplantation), 10% developed ESRD in the 3 to 5 years after discharge and 60% had evidence of renal damage (microalbuminuria, hyperfiltration, decreased GFR, or hypertension) over the same timeframe (Askenazi et al, 2006). These results indicate a need for ongoing follow-up of children with AKI and better strategies for maintenance of renal health for this at-risk population.

Management of AKI remains problematic and largely supportive, although recent research discoveries of new biomarkers of early AKI may help identify new therapeutic targets and allow earlier detection and protective strategies. Furosemide and “renal dose” dopamine have been shown *not* to be effective in improving outcomes, although urine output may increase and maintenance of effective perfusion pressure is essential. Likewise, *N*-acetylcysteine, fluids, sodium bicarbonate, statins, fenoldopam, and theophylline have all failed to show consistent benefits as treatment options. Hopefully, improved diagnosis, including the use of early and more specific biomarkers, and better understanding of the bimodal effects of some treatments (e.g., too little fluid resuscitation is clearly harmful, excessive fluid is also deleterious) may allow highly focused therapies that may improve outcomes.

Management

Current treatment strategies should include restoration of adequate renal blood flow and avoidance of nephrotoxic drugs. Fluids should be given to restore intravascular volume with the reminder that aggressive fluid administration without careful attention to cardiovascular responses risks the morbidity and mortality induced by fluid overload—risks that appear with as little as 10% excess fluid (Foland et al, 2004). Hypertension may occur in a number of cases

of AKI and is likely to be the result of fluid overload as well as intrinsic renal responses. Care to determine fluid balance is needed to appropriately direct therapy, and ACEIs, while effective in lowering blood pressure, may actually worsen renal compromise by further decreasing effective GFR. Hyponatremia is common with AKI, most usually from iatrogenic fluid overload with hypotonic fluid. Hyperkalemia develops from decreased filtration, acidosis, tissue damage, and catabolism. Acidosis develops from impaired secretion of normal acid production, increased acid production resulting from ischemia and catabolism, and compromise of respiratory compensation in the critically ill. Hypocalcemia and hyperphosphatemia are also common and require attention to nutritional support.

In extremely critically ill children, continuous renal replacement therapy (CRRT) most commonly by continuous venovenous hemofiltration has become increasingly utilized, although peritoneal dialysis (PD) and intermittent hemodialysis (HD) are still used. Modality choice is most often based on center experience and preference (Sutherland et al, 2014).

KEY POINTS: ACUTE KIDNEY INJURY

- AKI is defined as the inability of the kidneys to acutely regulate fluids and electrolytes because of a sudden drop in GFR.
- AKI is common in critically ill children and results in increased acute morbidity and mortality as well as long-term risks for CKD.
- Creatinine and blood urea nitrogen are insensitive markers of AKI. New and better options for diagnosis of early AKI are in development.
- Changes in serum creatinine and severity of oliguria are the center of new staging criteria for AKI.
- Treatment of AKI remains largely supportive, but dialysis therapies for even the smallest children are increasingly used with growing technical success.

Chronic Kidney Disease

CKD is a state of irreversible kidney damage that remains stable or progresses to ESRD over time. After years of increase from 1990 to 2003, the incidence of children initiating renal replacement therapy in the United States has decreased slightly with 1161 children beginning ESRD treatment in 2012, representing around 15 new ESRD patients per 1 million children. This contrasts with approximately 115,000 new ESRD patients in the adult population (350 per 1 million population). Approximately 7500 children were receiving dialysis or had functioning renal transplants in 2012 (United States Renal Data System, 2014c). The incidence and prevalence of pediatric CKD less severe than ESRD are not known. Given the shortened life span of children on dialysis and the growing shortage of organs available for transplantation, early detection and improved management of CKD are crucial in order to prevent or improve grave outcomes.

TABLE 123-5 Classification of Chronic Kidney Disease for Children Older than Age 2 Years

STAGE	DEFINITION	GFR (mL/min/1.73 m ²)
1	Normal or ↓ GFR (with kidney damage)	≥90
2	Mild ↓ GFR (with kidney damage)	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 or dialysis

GFR, glomerular filtration rate.

Etiology

The causes of CKD and ESRD in children are quite different than those in adults, with approximately 36% of cases resulting from cystic/hereditary/congenital disorders and 22% from glomerular disease (contrasted with nearly half resulting from diabetes and another third from hypertension in adults) (United States Renal Data System, 2014a). In 2002 the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) outlined a classification system for CKD that has since become widely accepted (Table 123-5). It is important to note that this classification does not officially apply to children less than 2 years of age who have not yet reached normal renal functional maturity, and the system applies to patients with kidney disease for greater than 3 months. Stages 1 and 2 require evidence of kidney damage, defined as structural (on biopsy) or functional (proteinuria, hypertension, or abnormal imaging). Higher stages are classified by GFR measurements alone. Recent work from the CKiD (CKD in Children) Study has modified the previously used Schwartz equation to better estimate GFR in children using both creatinine and cystatin C (Schwartz et al, 2009), although the standard Schwartz equation— $\text{GFR (mL/min/1.73 m}^2\text{)} = 0.413 \times \text{height (cm)}/\text{serum creatinine (mg/dL)}$ —remains in use in common clinical practice.

CKD in children is associated with proteinuria of varying degrees, hypertension, acidosis, electrolyte disorders, renal osteodystrophy, dyslipidemia, anemia, growth failure, uremia, neurocognitive delays, and decreased quality of life, with each of these unfortunate effects adding needs for pharmacologic support, nutritional supplementation, and strategies to maximize normal development. The psychosocial impacts of CKD on the family are significant. In the case of congenital anatomic disorders, intervention should be considered to ensure regular voiding, maintain adequate drainage of the urinary tract, and prevent infection. Medical management can delay the development and effects of metabolic disarray but is rarely effective in halting the process completely (Wong et al, 2012; Mas-sengill and Ferris, 2014).

Medical Complications of Chronic Kidney Disease

The proteinuria of CKD may be low grade or nephrotic range, with severity directly correlated in most diseases with speed of decline in GFR. The use of ACEIs/ARBs is common to decrease hyperfiltration of remaining nephrons, suppress renal fibrosis, and slow progressive decline in GFR. The effectiveness of this approach appears to vary with the etiology of the disease process, but most clinicians attempt use of renin-angiotensin blockade to blunt the inexorable declines expected with CKD.

Children with cystic dysplasia, obstructive uropathies, and tubulopathies exhibit disrupted renal concentrating capacity and may require sodium and water supplementation and special attention during times of acute illness that risk dehydration. In contrast, children with chronic glomerulonephritis may need salt and water restriction to prevent edema and hypertension.

Hypokalemia occurs in children with tubulopathies and requires potassium supplementation, while children with obstructive uropa-

thies and advanced CKD usually require potassium restriction and/or removal.

Progressive acidosis is common in children with CKD, with the development of an anion gap acidosis owing to reduced excretion of the organic and inorganic acids produced as a result of normal metabolism. If uncorrected, chronic acidosis results in retardation of linear growth as well as decreased bone mineralization. Oral alkali therapy (with bicarbonate, acetate, or citrate) corrects the abnormalities.

Renal osteodystrophy results from abnormalities of calcium, phosphorus, and vitamin D that occur in CKD and result in rickets, osteopenia, secondary hyperparathyroidism, and growth failure along with other bone disturbances. Treatment requires suppression of PTH by supplementation with vitamin D analogues, calcium supplementation and phosphorus restriction, and/or the use of oral phosphate binders. Aluminum salts are no longer used because of complications of neurotoxicity with long-term use.

Anemia is nearly universal as CKD progresses and is commonly due to reduced renal production of erythropoietin, iron deficiency, or both. However, chronic inflammation (most commonly associated with diseases such as SLE or other immune-mediated glomerulonephritides) and hyperparathyroidism also contribute. Treatment requires restoration of normal iron stores and parenteral (commonly subcutaneous) erythropoiesis-stimulating agents. Both short-acting recombinant erythropoietin and longer-acting glycosylated forms are in current use.

Poor appetite, limited food options, and oromotor dysfunction all contribute to impaired nutrition and poor linear growth. Infants with advanced CKD commonly require enteral tube feedings in order to achieve the necessary caloric intake for growth and often develop oral aversions that may require significant therapy to improve. However, growth delay is closely associated with neurocognitive delays in development, and aggressive maintenance of necessary nutrition is imperative for long-term outcomes. Enteral feeding may be used at night in order to maintain normal social eating behavior patterns while supplementing needed calories for growth. Protein restriction is *not* recommended. Short stature results from poor nutrition, renal osteodystrophy, electrolyte imbalance, and derangements in the growth hormone–insulin-like growth factor-1 axis. Once adequate caloric intake is established, treatment with recombinant human growth hormone is indicated if the height standard deviation score is less than –2. Unfortunately, a number of barriers continue to disincentivize growth hormone use, including daily subcutaneous injections, high cost, and cultural factors.

Uncontrolled hypertension is an independent predictor for progression of CKD. Therefore hypertension should be treated with goals at or below the 90th percentile for age, sex, and height.

Uremic complications, including platelet dysfunction, bleeding, pericarditis, and encephalopathy, occur late in CKD if at all and are most commonly seen in patients with ESRD who are undialyzed or insufficiently dialyzed. Management of these complications is by aggressive dialysis. A few patients will develop nausea, fatigue, and subtle encephalopathy (usually noted as poor school performance) at lower levels of blood urea nitrogen than usually seen at ESRD. These patients may benefit from earlier institution of renal replacement therapy.

KEY POINTS: CHRONIC KIDNEY DISEASE

- The KDOQI classification system of levels of CKD is now in wide use for children, although it technically does not apply to those less than 2 years of age.
- Management of CKD includes treatment of electrolyte and acid-base imbalances, calcium and phosphorus disorders, anemia, hypertension, and growth and nutritional deficiencies.
- The multifactorial nature of CKD demands the efforts of a skilled team to manage the medical, educational, and psychosocial needs of a child and family in order to maximize the health, developmental, and social outcomes for all.

RENAL REPLACEMENT THERAPY

When renal insufficiency is so severe, either acutely or chronically, that accumulating electrolytes, waste products, or fluid are life threatening, renal replacement therapy is indicated. The incidence of ESRD in children has decreased slightly since 2008, with 1161 children beginning care for ESRD in 2012, and the prevalence has plateaued at approximately 7500 ([United States Renal Data System, 2014c](#)). The same treatment options available for adults are available for all but the smallest of premature infants, and include HD, PD, CRRT, and renal transplantation. This section reviews the indications, limitations, and necessary processes for each modality.

Dialysis

HD, PD, and CRRT are all potential therapies for severe AKI. Indications for initiation of any dialysis therapy include failure of medical management of fluid overload (including hypertension and pulmonary edema), uremia, hyperkalemia, acidosis, or other electrolyte disarray. Softer indications include the need for fluid/electrolyte removal to allow for improved nutrition or a clinical course trajectory that anticipates failure of medical management. The ideal timing of initiation of dialysis remains an area of controversy because data do not support improved renal outcomes with earlier initiation of dialysis. However, delayed initiation clearly complicates the processes for access placement and results in a more critically ill patient.

Continuous Renal Replacement Therapy

In many institutions, CRRT has become the preferred modality for the child with severe AKI, especially in the setting of fluid overload and poor cardiovascular status ([Sutherland and Alexander, 2012](#)). Advances in CRRT technology now allow for tightly controlled, gradual, constant removal of fluid and electrolytes and easy titration of extracellular fluid components even in the setting of hemodynamic instability. This may be accomplished in small children, although the smallest infants remain technically challenging patients. The advantages of CRRT include gradual yet continuous fluid and solute exchange with minimal cardiovascular instability compared to standard HD, in which the rapid high-volume extracorporeal blood flow, rapid fluid removal, and rapid electrolyte shifting are often not tolerated in an unstable patient. While PD also provides gradual removal of fluid and electrolytes, there is limited ability to control ultrafiltration and the repeated changes in intra-abdominal pressure often cause cardiorespiratory complications. Also, in acute settings wherein body wall edema is common and newly placed abdominal catheters are prone to leak, the ability to maximize dialysis and fluid removal is limited. These problems are obviated when using CRRT.

The most common CRRT method used today is continuous venovenous hemofiltration using a large-bore double-lumen venous dialysis catheter. Dialysis is accomplished using filtration alone across a semipermeable membrane, by high-clearance filtration using in-line high-volume replacement fluids, or with counter-current dialysis. Efficiency is limited by the size of the patient, size of the access, and blood flow rates tolerated by the patient. Anticoagulation is usually required and is most commonly citrate-based regional anticoagulation in which citrate is infused into the system at the exit point from the catheter, calcium is chelated, and the coagulation cascade is suppressed. Calcium is then reinfused at the entry point to the patient to maintain normal patient coagulation and calcium levels. The primary limitation of CRRT use is system clotting that occurs even with adequate anticoagulation. Smaller catheters, lower blood flow rates, and cardiac instability all increase the likelihood of circuit failure. Circuit failure usually results in significant blood loss and time off dialysis, and commonly requires access replacement (because catheter thrombosis is also frequent). Given the frequency of AKI in patients requiring extracorporeal membrane oxygenation (ECMO), the combined use of ECMO and

CRRT is also becoming more frequent. CRRT may be connected directly into ECMO circuits, and the usual heparin anticoagulation is more than sufficient to provide coverage for the additional tubing and membranes. Outcomes for pediatric patients requiring CRRT are dependent on multiple variables, including underlying disease and its severity, comorbid conditions, and degree of fluid overload. Patients with pulmonary, cardiac, or liver disease or with solid-organ/stem cell transplants have poorer outcomes (mortality rates of 49% to 69%), whereas those with renal disease, inborn errors of metabolism, and tumor lysis fare better (mortality rates of 16% to 27%) ([Sutherland et al, 2014](#)).

Peritoneal Dialysis

Acute PD may be successfully performed in any child with an intact peritoneal cavity. Given its relatively gentle nature and the lack of need of large-bore vascular catheters, PD has long been the mainstay of acute dialysis in pediatrics, especially for smaller patients. PD works by utilizing the semipermeable nature of the peritoneal membrane to accomplish exchange of water and solute. Intracapillary perfusion pressure within the membrane is quite low, but in the absence of abdominal compartment syndrome it will be higher than intra-abdominal pressure, and exchange occurs freely. However, there is no ability to titrate ultrafiltration volume and solute exchange as can be done with pumps in HD and CRRT. PD depends on osmotic pressure (using varying degrees of dextrose) to control ultrafiltration. Chronic treatments are usually nightly for 8 to 12 hours. Standard dialysate solutions are designed to remove sodium, potassium, urea, and phosphorus and deliver calcium and base equivalents (acetate or lactate) that are subsequently converted to bicarbonate. Custom-made dialysate solutions may be designed and made by hospital pharmacies for short-term use in unusual situations.

The only absolute contraindication to PD is an inadequate peritoneal cavity that may be compromised by congenital anomaly (uncorrected gastroschisis, omphalocele, or diaphragmatic hernia) or chronic sclerosis and loss of surface area from repeated surgery or infection. Acute infection and recent abdominal surgeries are relative contraindications given the unlikely nature of resolving infection with an indwelling catheter and the potential for leakage through recent incisions. However, in situations in which CRRT is likely to be ineffective or harmful (e.g., tiny infants), PD may still provide a short-term bridge even with significant risks and complications. In a recent study from Canada ([Bosch et al, 2014](#)), of 90 children receiving renal replacement therapy in a quaternary care pediatric intensive care unit, 46% received PD and 54% received CRRT, with younger and smaller children more frequently being placed on PD and larger children prescribed CRRT. The outcomes of the two groups in terms of length of stay, complications, and survival to discharge were not different. The most effective peritoneal catheter placement is surgical, with generation of a subcutaneous tunnel that decreases the risk of infection, dislodgement, and leak. Short-term use of an "acute" catheter placed with local anesthesia and the Seldinger technique is now rare because effective bedside anesthesia is now routine in the units that would offer these technologies.

For chronic dialysis, the most important decision point is actually the choice of modality ([Schaefer and Warady, 2011](#); [Warady et al, 2014](#)). The choice of HD versus PD is a complex one and includes many social factors as well as technical/medical issues. The advantage of PD is that it is designed to be provided at home. Nightly PD allows for more normal work and school schedules, and activities of daily living unencumbered by dialysis procedures. However, this requires very significant family support and investments in personal responsibility, time, energy, space, and determination, factors not always available in families with the stress of chronic illness. The complication rates of PD in families that are not able to manage these expectations are high, and ultimately increase the medical and psychosocial burden on the family. The pediatric nephrology team should assess these issues early in the evaluation of a child with advancing CKD. Advanced education

levels are not needed in the family in order to successfully manage PD, and in fact many older children and adolescents participate actively in much of their care, but the willingness to learn and dedication to standards of care are absolute requirements. The medical advantages of PD include daily dialysis that can be tailored more exactly to patient metabolic needs, less need for fluid and nutritional restrictions, preservation of vasculature, lack of blood loss, preservation of residual renal function, and improved growth compared to HD. From the perspective of a pediatric urologist, it is important to recognize that PD can be successfully accomplished in children with vesicostomies, ureterostomies, or other gastrointestinal and/or genitourinary diversions or accesses. Given the limitations in abdominal wall surface area in small children, and the need for dry, infection-free PD catheter exit sites, careful collaborative planning for surgical complications, repairs, revisions, and takedown is imperative.

While improvements continue with changes in technique and equipment, infection remains the most common complication of PD and occurs more commonly in younger children (0.85 infections per year in ages birth to 2 years) compared to older children (0.6 infections per year) (Zaritsky and Warady, 2011). Infection can affect the exit site, the catheter tunnel, and/or the peritoneal cavity. Peritonitis manifests most commonly with abdominal pain and cloudy dialysate fluid, with a diagnosis made by documenting more than 100 white blood cells/mL of fluid and greater than 50% neutrophils. The majority of peritonitis in PD is bacterial, with fungal infections accounting for less than 5% (Bosch et al, 2014). In the United States, bacterial infections are equally split between gram-positive and gram-negative organisms, although this distribution is not seen worldwide. Peritonitis is best treated with intraperitoneal antibiotics and may be successfully managed at home. The choice of antibiotics must be made with culture and sensitivity results, and intraperitoneal heparin is often used to decrease the likelihood of inflammation-induced fibrin clots and catheter dysfunction. The cure rates of infections depend on the infectious agent, with *Staphylococcus* and some gram-negative bacteria and fungi having high failure rates requiring catheter replacement. The long-term importance of PD-associated peritonitis is the association with peritoneal scarring and membrane failure leading to the loss of dialytic capacity. Membrane failure eventually occurs even in the absence of infection, so movement toward transplantation should be considered for all.

Hemodialysis

HD uses extracorporeal perfusion to accomplish clearance of water and solutes across an artificial semipermeable membrane and therefore requires large-bore vascular access. HD may be used for management of acute or chronic renal failure, and is especially effective for rapid dilute and fluid removal during shorter treatment times. HD remains a common chronic dialysis modality and is used in a bit more than half of all new ESRD starts in patients less than 19 years of age (United States Renal Data System, 2014b). However, it is much more frequently utilized in older adolescents (in whom vascular access is less problematic) and in urban areas where patients have easy access to pediatric dialysis centers. It is important to note that many states prohibit community-based dialysis units from providing treatments to patients less than age 16, which may make HD practically impossible for patients without nearby children's facilities; in those environments, PD is obviously encouraged. Advantages of HD usually focus on the minimal technical assistance required of the patient and family and the decreased treatment time. Home/nocturnal HD programs for children exist in only a few centers and are very time and labor intensive for all parties involved. Vascular access is encouraged to be via arteriovenous fistula (most commonly by an arterial-venous anastomosis in the wrist or antecubital fossa) or implantation of an artificial arteriovenous graft in the same location. However, in children less than 20 kg (and in some larger ones) these fistulae are technically difficult to create and maintain, and many children continue HD through double-lumen central catheters despite their clotting and

infection risks and known long-term damage to central vascular integrity. Complications of HD accesses include infection, catheter kinking, stenosis of fistulae inflow/outflow with potential aneurysm and thrombosis, and development of unsightly or painful venous collaterals. Thrombosis and stenosis are especially problematic in the smaller patients in whom catheter/vessel ratios are higher and blood flows are lower. Other challenges with HD include cramping, nausea, hypotension during treatments resulting from the need to remove 2 to 3 days of accumulated fluid and solutes over 3 to 4 hours, higher requirements for erythropoiesis-stimulating agents because of chronic blood loss in the circuit, and higher rates of metabolic bone disease. These problems aside, HD is especially efficient in older children with AKI in the absence of cardiovascular instability, and line placement does not require the surgical expertise needed for peritoneal catheter placement. In acute settings, HD treatments may be performed daily (or more often), and HD remains the mainstay of management of intoxications.

Renal Transplantation

The desired "end point" of all ESRD care for children is renal transplantation. Recent statistics note a significant survival benefit to transplantation over dialysis in all young age groups (United States Renal Data System, 2014c), and quality of life with a functioning graft is undoubtedly greater compared to life with dialysis. Preemptive transplantation prior to the initiation of dialysis is a goal for all patients with well-managed CKD, inactive primary diseases, and families with histories of excellent compliance. These "early" procedures occur with around 25% of pediatric transplants, the vast majority from living donors (Collins et al, 2013). Given similar graft survival rates, there is increasing use of unrelated living donors. Deceased donor graft availability remains challenging, although current regulations award elements of priority to those patients less than 18 years old and prioritize younger and healthier donors to pediatric recipients (United States Renal Data System, 2014b). These changes, as well as ongoing improvement in surgical and long-term immunosuppressive therapy management, enable recent (2003-2010) pediatric 1-year and 5-year living donor graft survival rates of 96.5% and 84.3% and deceased donor graft survival rates of 95.1% and 78.0%, respectively. Five-year graft survival for patients with congenital/structural lesions (comprising higher numbers of younger patients) is now 85% for living donor grafts and 70% for deceased donor grafts (North American Pediatric Renal Trials and Collaborative Studies [NAPRTCS] Data Coordinating Center, 2010). Contraindications to renal transplantation are few and include active malignancy, multisystem organ failure, and concerns of severe nonadherence. Previous barriers such as HIV infection, ABO blood group incompatibility, and T-cell crossmatch positivity are no longer absolute contraindications but do require special preparative and postoperative management procedures that are not routinely available in all centers. Similarly, transplantation in the presence of diseases with high rates of recurrence post-transplant (FSGS, inherited forms of HUS, or primary oxalosis) should occur within programs that are capable of accomplishing the unique strategies most likely to result in long-term graft success. Renal transplantation in the infant remains rare because of higher technical failure rates. The vast majority of programs aspire to aggressive nutrition and growth in babies with the goal of transplantation at around 10 kg.

Postsurgical immunosuppression now most commonly includes antibody induction with either anti-T cell preparations or interleukin-2 receptor blockade followed by tacrolimus, mycophenolate mofetil, and prednisone (NAPRTCS Data Coordinating Center, 2010). Steroid-sparing and steroid-free protocols are now more common and have not significantly changed the acute rejection rates. The success of these immunosuppression regimens can be noted in the now 10% rate of rejection within the first year for all donor types, having been approximately 50% in 1997 (United States Renal Data System, 2014b). The expected side effects of increased infection and malignancy rates are noted, with approximately 10% of all deaths after pediatric transplantation attributable

to malignancy (Mynarek et al, 2014), as are consistent increases in Epstein-Barr virus and BK virus complications.

Involvement of pediatric urologists in the planning, evaluation, and management of renal transplantation is key, but the extent of involvement in each area varies significantly based on center design and individual patient needs. Patients with congenital urinary tract anomalies are usually well known to their pediatric urologists, who will seamlessly transition into the planning and management needed to ensure adequate lower urinary tract function after transplantation. Other patients (primarily those with cystic or acquired disorders) may never have had urologic complaints and come to urology for the first time during evaluation for transplantation. Therefore, transplantation evaluation and management may include a wide range of potential studies from basic determinations of urinary tract health and urodynamics all the way to complex surgical correction of preexisting abnormalities and creation of urinary reservoirs or drainage systems. The role of the pediatric urologist in the transplant event itself is most commonly determined by patient needs and program tradition, but it is also important for the pediatric urologist to remain available and involved even long after the transplant procedure in order to maintain careful and expert observation and management of the urinary tract as the patient continues to grow and mature. Urinary tract infections post-transplant are also often recalcitrant to treatment, especially in patients with complex anatomy, and urologic expertise to maximize drainage is imperative to save functional renal tissue and prevent systemic spread of infection.

KEY POINTS: DIALYSIS AND RENAL TRANSPLANTATION

- CRRT by continuous venovenous hemofiltration is increasingly used as the primary dialysis therapy for children with severe AKI in the setting of multisystem organ failure.
- PD is the most common renal replacement therapy used for small infants, and remains a common choice throughout the pediatric age range for its opportunities to maintain school attendance and home management.
- PD can be successfully maintained in small infants with urinary diversions but requires careful collaboration between the urology and nephrology teams.
- HD is rapid and highly efficient, but is more technically feasible in larger children.
- Choice of chronic dialysis modality is best made with careful consideration of patient/family psychosocial factors, anticipated nutritional needs, expected time to consideration for transplantation, and near-term surgical needs.
- Renal transplantation offers the best long-term outcomes for children with renal disease and should be aggressively considered.
- Children with complex anatomy, rare diseases, or disorders likely to recur post-transplantation, or those with other complicating factors, should have transplantation planning and management organized in experienced centers.

SUMMARY

Effective collaboration between pediatric nephrologists and pediatric urologists is of utmost value to children with renal disease. Many areas of practice overlap, and while there may be differences in opinion regarding best approaches, there is rich advancement in careful appreciation of the expertise of both specialties. Both specialties have increasingly expert teams of health care providers who add support and guidance to families managing these complex issues. Our success in caring for these disorders has clearly improved and, working together, we have even more to offer future generations of children with kidney and urinary tract disease.

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124 Perinatal Urology

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Fetal Imaging

Fetal Diagnosis

Specific Diagnoses

Antenatal Management of Fetal Uropathies

Postnatal Management of Antenatally Detected Urologic Renal Abnormalities

Neonatal Urologic Emergencies

Summary

FETAL IMAGING

The increased use of maternal-fetal ultrasound has led to the development of the field of perinatal urology. **Antenatal hydronephrosis (ANH)** is identified in 1% to 3% of all pregnancies and is one of the most common birth defects detected (Livera et al, 1989; Blyth et al, 1993; Gunn et al, 1995; Sairam et al, 2001; Shamshirsaz et al, 2012). In addition to hydronephrosis, renal cystic disease, renal agenesis, stones, and tumors have also been diagnosed prenatally. For the urologist, these prenatal findings have created numerous challenging clinical and scientific dilemmas.

Ultrasonography continues to be the mainstay of fetal imaging. With experience, this modality provides intricate detail and diagnostic capability that is similar to that of ultrasonography in the neonate. Ultrasound evaluation facilitates screening of large numbers of fetuses with no radiation exposure and is nearly universally available. The potential advantages of three-dimensional (3D) ultrasonography in imaging of urologic diagnoses are unclear.

Fetal magnetic resonance imaging (MRI) is a valuable adjunct when further delineation of anatomic detail is believed to be necessary to optimize diagnosis and/or management strategy (Estroff, 2009; Storm et al, 2011; Chauvin et al, 2012). As with ultrasonography, there is no radiation exposure. Use of complementary computed tomography is controversial because the additive information may not outweigh the added risk of fetal and maternal radiation exposure.

The discussion here centers on the diagnosis of prenatal urologic abnormalities and the postnatal implications, the rationale behind prenatal intervention, and clinical experience in managing children with prenatal and neonatal urologic abnormalities. Further detailed discussion regarding evaluation and management of many of these entities when they occur beyond the perinatal period is presented in other chapters in this textbook.

FETAL DIAGNOSIS

A large prospective study of 11,986 Swedish women conducted between 1978 and 1983 identified renal anomalies in 0.28% of fetuses; over two thirds of the anomalies were hydronephrosis (0.18%) (Helin and Persson, 1986). Similarly, a British prospective screening study of 6292 pregnant women at 28 weeks' gestation demonstrated hydronephrosis in 1.40% of patients, with postnatal confirmation in 0.65% (Livera et al, 1989). These authors defined ANH as an **anteroposterior diameter (APD)** of the renal pelvis greater than 5 mm but noted the lack of consensus on the definition of ANH (Scott and Renwick, 1993; Scott et al, 1995; Scott and Renwick, 1999). With the rapid improvement of ultrasound technology, the incidence of detection of renal anomalies may be

changing. In a more recent prospective cohort study (1999 to 2003), a 0.76% incidence of urinary tract abnormalities was detected that was increased as compared with an earlier cohort from the same institution (0.3%, 1989 to 1993) (Mallik and Watson, 2008). However, many variations in the definition and management of ANH exist in the literature and clinical practice, including method and frequency of in utero testing, radiographic documentation, classification, and postnatal management (Benacerraf et al, 1990; Corteville et al, 1992; Fernbach et al, 1993; Adra et al, 1995; Thompson and Thilaganathan, 1998; Chudleigh et al, 2001; Lee et al, 2006). This variability may significantly alter the incidence reported within the literature.

Regardless, when an abnormality of the urinary tract is determined by antenatal ultrasonography, several questions should be raised by the ultrasonographer and consulting urologist. Combinations of specific findings direct the differential diagnosis and permit a more accurate prognosis and tailoring of postnatal evaluation. The principal findings and their implications are listed in Table 124-1.

Diagnostic Findings

Kidney

There are critical elements to an antenatal ultrasound examination that may help identify urologic pathology. A constellation of aberrations may indicate pathology, particularly when placed in context with other clinical findings. Specific details of the examination need to be reported to assist antenatal counseling. **The ultrasound evaluation of the kidney should comment on number, location, size, duplication, renal parenchyma (echogenicity), pelvic dilation, calyceal dilation, urothelial thickening, and cystic disease.**

Kidneys should be the appropriate size for gestational age and relatively symmetrical (Chitty and Altman, 2003). Large differences in size may indicate contralateral compensatory growth. Absence of the kidney in the normal location may represent ectopia or agenesis or dysplasia. **The normal kidney should be elliptical and have distinctive internal echolucency, representative of normal medullary pyramids (Fig. 124-1).** The appearance of the medullary pyramids should not be confused with renal calyceal dilation. The echogenicity of the kidney should be slightly less than that of the corresponding spleen or liver. Abnormalities of echogenicity with or without hydronephrosis may indicate renal disease. Isolated increased echogenicity has been associated with renal parenchymal disorders, but it has also been shown to be of no clinical significance (Estroff et al, 1991; Carr et al, 1995; Mashiach et al, 2005). When occurring with hydronephrosis it may indicate renal dysplasia, particularly if there is accompanying decreased amniotic fluid (Kaefer et al, 1997b).

TABLE 124-1 Elements of Prenatal Urologic Ultrasonographic Diagnosis

PARAMETER	COMMENT	POSSIBLE CAUSES
Hydronephrosis	Variable severity; may include pelviectasis and/or caliectasis	Obstruction, reflux
Caliectasis	Intrarenal dilation; more indicative of significant pathologic process	Obstruction, reflux
Pelvic anteroposterior diameter	Measured in the coronal plane, variable; in extremes may predict clinical outcome; caution should be exercised in overreliance on these measurements	Increased in obstruction, reflux
Renal parenchyma	Echogenicity should be less than that of liver or spleen; lucent medullary pyramids should be seen	Increased echogenicity in dysplasia, obstruction, ARPKD
Urothelial thickening	Increased thickness of pelvic lining	Variable dilation as with reflux or occasionally obstruction
Duplication	Separation of renal pelvic sinus echoes when no hydronephrosis seen	Possible associated reflux or obstruction; look for dilated ureter and ureterocele
Cystic structures, renal	Simple cysts rare	MCDK, ADPKD
Cystic structures, intravesical	May be very large and fill bladder; thin walled	Ureterocele
Urinoma	Fluid collection around kidney; perinephric or subcapsular	Obstruction
Bladder filling	Fill and void cycles may be demonstrated over time	Urine production
Bladder wall thickness	Must be interpreted in context of bladder filling	Obstruction, neurogenic dysfunction
Keyhole sign	Dilated posterior urethral; difficult to image	Posterior urethral valves
Oligohydramnios	Markedly reduced amniotic fluid; usually considered as no pocket of fluid >2 cm	Poor urine output because of obstruction and/or renal failure

ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; MCDK, multicystic dysplastic kidney.



Figure 124-1. Ultrasound appearance of normal fetal kidney with echolucent medullary pyramids distinguishable from the more echogenic cortical parenchyma. The cortical parenchyma should be of lower echogenicity than adjacent liver or spleen.

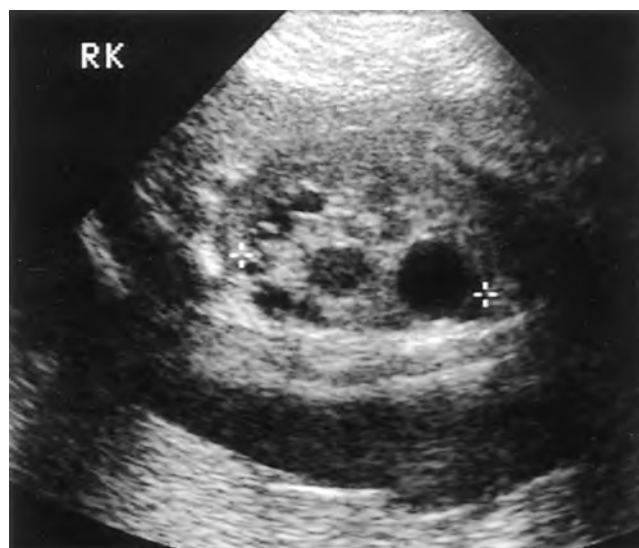


Figure 124-2. Multicystic dysplastic kidney with large, multiple, variable-sized cysts without a central large cystic area. As here, most cases show virtually no parenchyma.

Renal cystic disease can be seen in utero. Autosomal recessive polycystic kidney disease (ARPKD) may manifest with large, bright or echogenic kidneys because the numerous small renal cysts cannot be resolved by ultrasonography. In contrast, a multicystic dysplastic kidney (MCDK) typically manifests as a large noncommunicating macrocyst (Fig. 124-2). A single cyst may represent a dilated renal calyx or diverticulum, an atypical MCDK, severe hydronephrosis, or a nontribal structure.

Ureter, Bladder, and Urinoma

In addition to kidney-specific findings, ureteral dilation, bladder filling and emptying, bladder wall thickness, intravesical cystic structures, dilation of the posterior urethra (keyhole sign), urinoma, amount of amniotic fluid, intra-abdominal or pelvic mass, and external genitalia should be noted. **Hydroureter is best seen in cross section of a full bladder but is often difficult to detect**

(Fig. 124-3). Duplication and ureteral ectopia may also make this a difficult diagnosis.

Although the bladder is sometimes difficult to image well, visualization of the bladder can be very informative because a full bladder implies renal function. Inability to identify the bladder on repeat studies should raise the question of bladder exstrophy. Increased bladder wall thickness may indicate outlet obstruction, and dilation of the posterior urethra (keyhole sign) is strongly suggestive of posterior urethral valves (Fig. 124-4). In duplex



Figure 124-3. Fetal ultrasonography showing a dilated, tortuous ureter (arrow). These may be associated with reflux, valves, ectopic ureters, ureterocele, and ureterovesical junction obstruction. In this case the ureter is associated with a dilated upper pole indicating an ectopic ureter or ureterocele.



Figure 124-4. Fetal ultrasonography at 22 weeks' gestation of a male with posterior urethral valves. The bladder is thick walled and has a dilated posterior urethra (keyhole sign). There was also bilateral hydronephrosis, echogenic renal parenchyma, and a perinephric urinoma.

systems, ureterocele may manifest as an intravesical cystic structure and a dilated upper pole.

Perineal urinoma may indicate an obstructive condition (Yerkes et al, 2001) (Fig. 124-5). Typically it will have the appearance of an anechoic structure around the kidney or be in a subcapsular location. When identified, a urinoma or urinary ascites is often associated with severe bladder obstruction or posterior urethral valves, in which the urinoma may indicate a pop-off mechanism. A urinoma also may be associated with a unilateral hydronephrotic or obstructed kidney (Mandell et al, 1994). The pop-off mechanism may be renal protective, particularly in cases of lower urinary tract obstruction (Adzick et al, 1985; Adorisio et al, 2011).

Amniotic Fluid

Critical to the evaluation of the urinary tract is the assessment of the amniotic fluid level and changes during pregnancy. After 16 weeks, amniotic fluid production shifts from placental transudate to fetal urine; and by 20 to 22 weeks the vast majority of amniotic fluid is fetal urine (Takeuchi et al, 1994). Consequently, reduced amniotic fluid or oligohydramnios identified after 18 to 20 weeks' gestation may be a result of urinary tract obstruction or poor renal development (Stiller et al, 1988).

External Genitalia

Proper identification of the external genitalia also can be very valuable in cases of gender-specific diagnoses, such as posterior urethral valves. In cases of virilization (e.g., congenital adrenal hyperplasia [CAH]), a clitoris may appear as a small phallus; therefore the presence of scrotal testes is critical for male gender assignment (Benacerraf et al, 1989; Bromley et al, 1994; Mandell et al, 1995). Megalourethra, or a dilated, elongated penile urethra, may be an isolated anomaly or associated with prune-belly syndrome (Dillon et al, 1994) (Fig. 124-6). Bilateral renal obstruction and bladder outlet obstruction in a female fetus would suggest a cloacal anomaly (Cilento et al, 1994; Ohno et al, 2000; Taipale et al, 2004) (Fig. 124-7).

Hydronephrosis

Hydronephrosis, or dilation of the renal pelvis, is the most common urologic abnormality found on ultrasound evaluation.



Figure 124-5. Appearance of a fetal perinephric urinoma associated with posterior urethral valves.



Figure 124-6. Fetal ultrasound appearance of a male with a dilated and patulous urethra typical of a megalourethra. This may be seen in prune-belly syndrome as well as in isolation. This child also had marked vesicoureteral reflux.

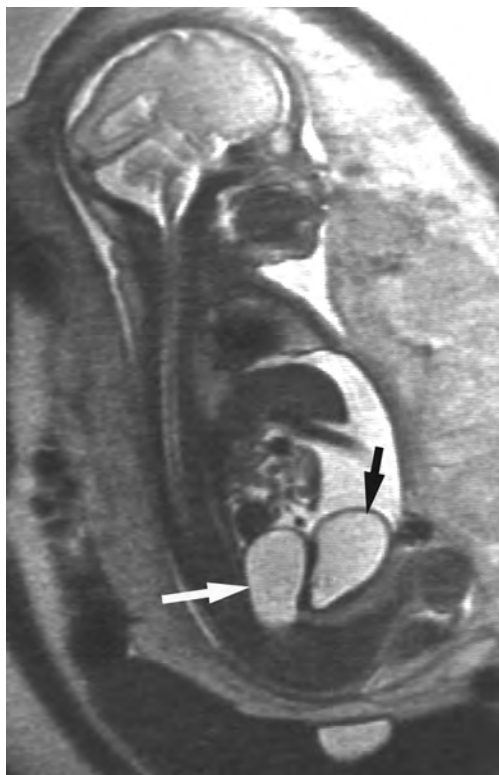


Figure 124-7. Fetal magnetic resonance image illustrating severe bladder dilation (*black arrow*) and a separate dilated pelvic structure behind the bladder (*white arrow*) in a female fetus at 22 weeks' gestation. The kidneys were bilaterally and symmetrically dilated with ureteral distention. This pattern can be seen with oligohydramnios and represents a urogenital sinus malformation with bladder outlet obstruction caused by vaginal distention from urine flowing into the urogenital sinus.



Figure 124-8. Severe fetal hydronephrosis with diffuse calyceal dilation arrayed around the markedly dilated renal pelvis. The renal parenchyma is stretched over the dilated collecting system, but this does not mean loss of functional potential. Corticomedullary differentiation is difficult to see in this configuration.

Numerous grading systems have been developed; however, there is no consensus on the best and most consistent method of reporting ANH (Fig. 124-8) (Fernbach et al, 1993). Measurement of the APD has been used widely, but there have been no formal studies to determine the interobserver and intraobserver reproducibility of ANH measurement. One of the disadvantages of use of the APD can be the failure to describe pelvic configuration, calyceal dilation, and the laterality of findings, which should be included. The APD can be affected by gestational age, hydration status of the mother, bladder hypertonicity, and degree of bladder distention. Because the dimensions of the renal pelvis may normally increase with gestational age, most investigators have adjusted threshold APD values for early and later gestational age. Unfortunately, a simple threshold APD value that separates normal from abnormal does not exist, because even severe cases of ANH have the potential to resolve without incident, whereas mild degrees of ANH have the potential to progress (Pates and Dashe, 2006).

Varying the minimal APD threshold can significantly alter the specificity and sensitivity of APD as a measure of ANH and postnatal pathology. To date there is no consensus on the optimal APD threshold for determining the need for postnatal follow-up. An APD cutoff of 15 mm for determining obstruction yielded a postnatal sensitivity of 73% and specificity of 82% (Coplen et al, 2006). A late gestational age APD cutoff of 10 mm would detect approximately 23% of abnormal kidneys, whereas a cutoff of 7 mm detected 68% (Ismaili et al, 2003). One large systematic review estimated that only 11.9% of total pathology included late gestational age APD of less than 9 mm, whereas 39% of total pathology was noted at APD levels below 15 mm (Lee et al, 2006). Nearly identical results have been demonstrated by other investigators (Wollenberg et al, 2005). What appears certain is that lower cutoffs will be more sensitive in detecting postnatal pathology but will incur a higher false-positive rate.

Categorizing Antenatal Hydronephrosis by Anteroposterior Diameter. There is near-total agreement that APD greater than 15 mm represents severe or significant hydronephrosis, and some would also agree that a lower threshold of 4 to 5 mm is an appropriate value for considering APD to be abnormal (Feldman et al, 2001; Ahmad and Green, 2005; Wollenberg et al, 2005; Lee et al, 2006; Coelho et al, 2007, 2008). Taking these limitations into consideration, we define ANH in the second and third trimesters using APD thresholds for which the best available evidence provides

prognostic information; along with these definitions the estimated distribution of the ANH based on the previously defined definition of APD is outlined in Table 124-2.

Alternative Measurements. The use of alternative grading systems, 3D volume measurements of the renal pelvis, or a hydronephrosis index to correct for bladder distention may provide a more precise evaluation of ANH (Duin et al, 2008; Nam et al, 2012). Some investigators have considered use of the Society for Fetal Urology (SFU) ultrasound grading system to classify ANH (Kim et al, 2013). MRI may also prove useful in prenatal evaluation with the advantages of high anatomic detail without ionizing radiation exposure. However, high cost and limited data currently confound the optimal use of this modality in the context of ANH (Savelli et al, 2007).

Diagnostic Accuracy

As both ultrasound and MRI technology improve, more accurate radiographic information is obtainable (Laifer-Narin et al, 2007). However, determining accurate postnatal diagnosis and prognosis remains challenging. Regardless of the diagnosis, early intervention is uncommon except in the potential case of severe obstruction or posterior urethral valves. In the vast majority of other cases, early

detection of ANH may be an impetus for future postnatal evaluation.

The ability to determine definitive postnatal pathology based on antenatal findings is difficult. As an example, in a systematic review of the ANH literature, Lee and colleagues attempted to determine the risk of a pathologic diagnosis for patients with varying severity of ANH (Lee et al, 2006). The review included 1308 patients who were identified with ANH and sufficient postnatal radiographic follow-up. The degree of ANH was defined by APD identified in a particular trimester. Approximately 36% of the patients had a postnatal pathologic diagnosis, and the overall risk for any pathologic process increased with increasing degree of ANH (Table 124-3). However, the risk of vesicoureteral reflux (VUR) remained consistent regardless of the degree of ANH, thereby implying that ANH is not an appropriate indicator for VUR.

Although earlier literature suggests that obstruction location can be determined prenatally in 88% of cases, many other researchers have reported a high false-positive rate (9% to 22%) (Hobbins et al, 1984; Scott and Renwick, 1993). The majority of false-positive findings in these studies involved nonobstructive causes of hydronephrosis, such as high-grade reflux, large nonobstructed extrarenal pelves, or transient hydronephrosis.

Early and accurate diagnosis of posterior urethral valves is critical; however, it can be difficult. The hallmark signs of an in utero diagnosis of posterior urethral valves have been described (e.g., oligohydramnios, dilated posterior urethra, thickened bladder, and hydroureteronephrosis). Other findings such as increased renal echogenicity and decreased amniotic fluid have also been suggested to be indicative of obstructive conditions (Kaefer et al, 1997b). Regardless, there are very few studies that have prospectively examined the clinical urologic implications of these findings alone or in combination (Lee et al, 2006). In one series of 22 fetuses, the false-positive rate was as high as 58% (Abbott et al, 1998), and in a population-based series the sensitivity in detecting valves was as low as 23% (Scott and Renwick, 1993).

Regardless of the degree or severity of the finding, after any antenatal detection of a urinary tract anomaly a thorough fetal survey must be conducted. Amniocentesis and karyotype should be considered if intervention or a major anomaly is

TABLE 124-2 Definition of Antenatal Hydronephrosis by Anterior Posterior Diameter and Estimated Severity Percentage Range

DEGREE	ANTEROPOSTERIOR DIAMETER		SEVERITY
	SECOND TRIMESTER	THIRD TRIMESTER	
Mild	4 to <7 mm	4 to <9 mm	56.7%-88.0%
Moderate	7 to ≤10 mm	9 to ≤15 mm	10.2%-29.8%
Severe	>10 mm	>15 mm	1.5%-13.4%

Data from Feldman et al, 2001; Ahmad and Green, 2005; Wollenberg et al, 2005; Lee et al, 2006; and Coelho et al, 2007, 2008.

TABLE 124-3 Risk of Pathology by Degree of Antenatal Hydronephrosis

POSTNATAL PATHOLOGY	DEGREE OF ANTENATAL HYDRONEPHROSIS (% [95% CI]*)					TREND P VALUE†
	MILD (N = 587)	MILD-MODERATE (N = 213)	MODERATE (N = 235)	MODERATE-SEVERE (N = 179)	SEVERE (N = 94)	
Any pathology	11.9 (4.5, 28.0)	39.0 (32.6, 45.7)	45.1 (25.3, 66.6)	72.1 (47.6, 88.0)	88.3 (53.7, 98.0)	<.001
Ureteropelvic junction obstruction	4.9 (2.0, 11.9)	13.6 (9.6, 18.9)	17.0 (7.6, 33.9)	36.9 (17.9, 61.0)	54.3 (21.7, 83.6)	<.001
Vesicourethral reflux	4.4 (1.5, 12.1)	10.8 (7.3, 15.7)	14.0 (7.1, 25.9)	12.3 (8.4, 17.7)	8.5 (4.7, 15.0)	.10
Posterior urethral valves	0.2 (0.0, 1.4)	0.9 (0.2, 3.7)	0.9 (0.2, 2.9)	6.7 (2.5, 16.6)	5.3 (1.2, 21.0)	<.001
Ureteral obstruction	1.2 (0.2, 8.0)	11.7 (8.1, 16.8)	9.8 (6.3, 14.9)	10.6 (7.4, 15.0)	5.3 (1.4, 18.2)	.025
Other‡	1.2 (0.3, 4.0)	1.9 (0.7, 4.9)	3.4 (0.5, 19.4)	5.6 (3.0, 10.2)	14.9 (3.6, 44.9)	.002

*Pointwise 95% confidence intervals were estimated by logistic regression with robust standard errors based on generalized estimating equations with a working independence correlation structure to adjust for clustering by study for all degrees of antenatal hydronephrosis except mild-moderate. Because only one study had subjects with mild-moderate antenatal hydronephrosis, the pointwise 95% CIs had to be estimated using logistic regression with unadjusted standard errors.

†Testing for trend in risks with increasing degree of antenatal hydronephrosis using logistic regression with robust standard errors based on generalized estimating equations with a working independence correlation structure.

‡Includes prune-belly syndrome, VATER (vertebral, anal, tracheo-esophageal and renal anomalies) syndrome, solitary kidney, renal mass, and unclassified causes.

CI, confidence interval.

Modified from Lee RS, Cendron M, Kinnamon DD, et al. Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. *Pediatrics* 2006;118:590.

suspected, because the incidence of concurrent chromosomal anomalies is relatively high in fetuses with concomitant urologic anomalies (Callan et al, 1990; Nicolaides et al, 1992; Snijders et al, 1995).

KEY POINTS: PRENATAL DIAGNOSTIC FINDINGS

- Ultrasonography is the mainstay of prenatal imaging. Selective use of fetal MRI may further delineate anatomic details and help with diagnosis and management.
- The normal kidney should be elliptical and have distinctive internal echolucency, representative of normal medullary pyramids.
- The appearance of the medullary pyramids should not be confused with renal calyceal dilation.
- Inability to identify the bladder on repeat studies should raise the question of bladder exstrophy.
- Dilation of the posterior urethra (keyhole sign) is strongly suggestive of posterior urethral valves.
- Reduced amniotic fluid or oligohydramnios identified after 18 to 20 weeks' gestation may be a result of urinary tract obstruction or poor renal development.
- Hydronephrosis, or dilation of the renal pelvis, is the most common urologic abnormality found on ultrasonography and is typically measured by the APD of the renal pelvis.
- The APD fails to describe pelvic configuration, calyceal dilation, and the laterality of findings.
- A threshold APD value that separates normal from abnormal does not exist.
- The risk of VUR per degree of ANH is similar, implying that ANH is not an appropriate indicator of VUR.
- Antenatal detection of any urinary tract anomaly should prompt a thorough fetal survey.

SPECIFIC DIAGNOSES

Ureteropelvic Junction Obstruction

The basic features of ureteropelvic junction (UPJ) obstruction in the fetus include dilation of the renal pelvis and collecting system with no evidence of ureteral dilation. Lee and associates (2006) demonstrated that increasing severity of ANH increased the likelihood of identifying postnatal UPJ obstruction. However, the threshold for recommending postnatal follow-up is largely arbitrary, and currently there are no long-term prospective studies to determine the degree of postnatal evaluation, particularly for mild and moderate cases of ANH. Nevertheless, in the case of significant unilateral hydronephrosis there is little rationale for in utero intervention or early delivery. In a few cases with massive dilation, therapeutic aspiration has been recommended for prevention of dystocia. In the case of bilateral UPJ obstruction the efficacy of in utero intervention is difficult to assess. Severe forms of UPJ obstruction may be associated with urinary ascites or perinephric urinomas, which may be a predictor of nonfunction of the kidney (Mandell et al, 1994; Adorisio et al, 2011).

Ureterovesical Junction Obstruction

Less common than UPJ obstruction, ureterovesical junction (UVJ) obstruction is characterized by ureteral dilation along with varying degrees of renal pelvic and calyceal dilation. The best way to detect ureteral dilation is at the level of the bladder, preferably in the transverse view. It is not uncommon for the distal ureter to be more dilated as compared proximally. The causes of this appearance may be primary obstruction of the UVJ, ectopic ureter inserting into the bladder neck, or high-grade VUR. Typically, the differentiation is made postnatally.

Cystic Kidneys

The distinction between severe unilateral hydronephrosis and MCDK occasionally may be unclear. The findings of multiple noncommunicating cysts, minimal or absent renal parenchyma, and the absence of a central large cyst are diagnostic of MCDK (Bearman et al, 1976; Sanders and Hartman, 1984). The appearance of noncommunicating cysts is essential to the diagnosis and should be distinguished from severe hydronephrosis (see Fig. 124-2). Real-time examination of the kidneys to help determine the communication of the calyces is essential. Doppler ultrasonography of the renal vasculature pulse pattern has also been reported to help make the distinction (Kaminopetros et al, 1991).

MCDK may be present in any ectopic location but typically is in the normal position. In addition, MCDK can be present in a duplex kidney, typically the upper pole. If detected early in the pregnancy, the MCDK will often involute over a period of time either prenatally or postnatally (Mandell et al, 1994).

Bilaterally enlarged echogenic kidneys without renal cystic disease, particularly if associated with hepatobiliary dilatation or oligohydramnios, suggest ARPKD (Smedley and Bailey, 1987; Townsend et al, 1988) (Fig. 124-9). Typically this is identified before 20 weeks' gestation, but later development has been reported (Mandell et al, 1991; Zerres et al, 2004). Genetic testing is possible in some cases, thereby allowing for early diagnosis and the option for early termination because postnatal mortality and morbidity are high (Wilson, 2004; Zerres et al, 2004).

The more challenging findings are normal-sized, diffusely echogenic kidneys that are not associated with other urologic lesions (Tsatsaris et al, 2002; Mashiach et al, 2005). A series of 19 cases (14 bilateral) included 10 patients with normal function who survived and 4 with ARPKD who died (Carr et al, 1995). In a separate multicenter retrospective study of 93 fetuses with hyperechogenic kidneys and a later diagnosis of nephropathy of varying cause, only one third of the fetuses had renal cysts irrespective of their diagnosis; 28 had ARPKD (only 3 with cysts) and 31 had autosomal dominant polycystic kidney disease (ADPKD) (9 with cysts). Typically, those with ADPKD appeared to have moderately enlarged hyperechogenic kidneys with increased corticomedullary differentiation. In addition, as opposed to renal cyst characteristics, associated malformations were the most helpful clue to identify a diagnosis (Chaumoitre et al, 2006).



Figure 124-9. Bilaterally enlarged, echogenic kidneys without grossly apparent cysts are typical of autosomal recessive polycystic kidneys. This appearance usually, but not always, becomes apparent by 22 weeks of gestation. In early-onset cases, oligohydramnios is seen.

Macrocystic disorders include the rare congenital multilocular cystic nephroma, which is characterized by segmental involvement of the kidney with variable macrocysts (Eble and Bonsib, 1998); cystic Wilms tumor, which typically has larger amounts of functioning parenchyma; and ADPKD, which may include heterogeneous cysts in size, location, and number (Reeders et al, 1986; McHugo et al, 1988; Ceccherini et al, 1989; Novelli et al, 1989).

Nonrenal cystic diseases can be confused with MCDK; however, these cystic anomalies are typically not in the renal fossa, and the conditions are unlikely to be confused in the presence of two normal kidneys. These cystic conditions include mesenteric duplication cysts, neurenteric cysts, bronchogenic cysts, extrathoracic pulmonary sequestration, and cystic neuroblastoma (Barr et al, 1990; Bagolan et al, 2000; Carpentieri et al, 2000; Granata et al, 2000; Uludag et al, 2001).

Duplication Anomalies and Ureterocele

Duplication anomalies are often recognized on the basis of upper pole hydroureteronephrosis, associated with either an obstructing ureterocele within the bladder or an ectopic ureter inserting outside the bladder (Vergani et al, 1999). Ureteroceles are identified as an intravesical, thin-walled cystic structure near the base of the bladder (Fig. 124-10). In cases of a very large ureterocele, the ureterocele may be mistaken for the bladder. Alternatively, in the setting of a ureterocele the upper pole may not always show hydronephrosis. The upper pole may appear as a cystic dysplastic unit without hydronephrosis and a concomitant ureterocele. This is often termed *ureterocele disproportion* (Share and Lebowitz, 1989). In addition, single-system ureteroceles are more likely to occur in boys and have variable degrees of hydronephrosis of the entire kidney.

Lower pole hydronephrosis may be present as a result of VUR (Fig. 124-11) or more rarely a lower pole UPJ obstruction. Occasionally, lower pole dilation is caused by obstruction of both the upper and lower pole ureter by a large ureterocele. Similarly, bilateral hydronephrosis may be secondary to an element of bladder outlet obstruction from prolapse of the ureterocele into the bladder neck (Sozubir et al, 2003).

In the absence of a ureterocele, upper pole hydroureteronephrosis suggests an obstructed ectopic ureter (Abuhamad et al, 1996). The dilated ectopic ureter can be mistaken for a ureterocele because of the impression that it creates on the back wall of the bladder. However, typically the ectopic ureter is much thicker than a ureterocele. Bilateral single-system ectopic ureters are uncommon but typically manifest with echogenic renal parenchyma, cystic disease, minimal bladder volume, and low amniotic fluid levels.

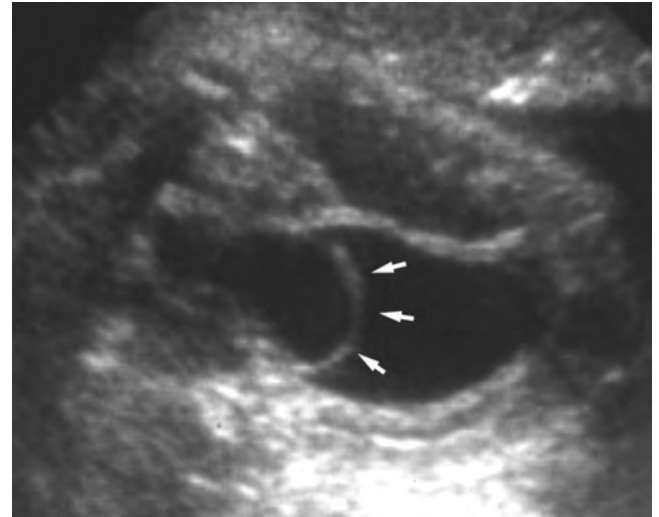


Figure 124-10. Fetal ultrasonography showing an intravesical ureterocele. The ureterocele is indicated by the arrows and partially fills the bladder. With this finding the ultrasonographer should examine the upper tracts to determine whether there is hydronephrosis in the entire affected kidney or only the upper pole, as shown in Figure 124-3.

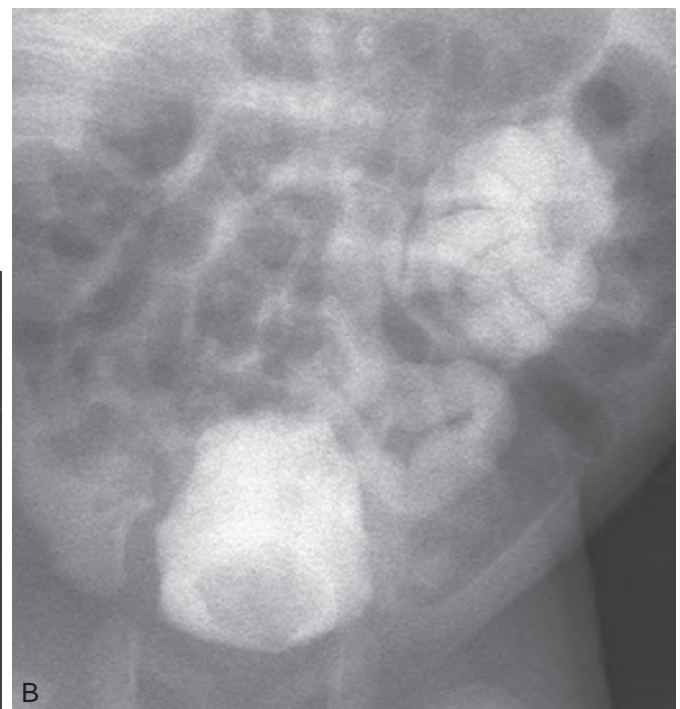


Figure 124-11. A, Image of a fetus at 28 weeks' gestational age with left lower pole hydronephrosis, hydroureter, and a ureterocele. B, Postnatal voiding cystourethrogram demonstrating lower pole vesicourethral reflux and the ureterocele.

Vesicoureteral Reflux

VUR cannot be definitively diagnosed on prenatal ultrasonography, although intermittent or varying degrees of hydronephrosis or hydroureter are suggestive of the diagnosis. Several studies have demonstrated that a high incidence of VUR is associated with prenatally detected hydronephrosis; however, the true incidence of VUR in children with a history of ANH is difficult to determine based on the variability of postnatal diagnostic management in the literature (Lee et al, 2006). In two systemic reviews of the ANH literature a 10% to 15% incidence of VUR was identified regardless of the degree of ANH (Lee et al, 2006; van Eerde et al, 2007), indicating that the severity of ANH is not indicative of VUR and may not be the appropriate trigger for postnatal evaluation. In a neonate with prenatally detected hydronephrosis, the importance of diagnosing VUR remains controversial, because VUR diagnosed on postnatal evaluation for ANH is associated with earlier resolution of VUR (Estrada et al, 2009; Skoog et al, 2010).

Posterior Urethral Valves

Perhaps the most important diagnosis to be made prenatally is that of posterior urethral valves in the male fetus. At the very least the finding of posterior urethral valves mandates prompt postnatal intervention, and in some cases prenatal intervention may be warranted. Fetal ultrasound findings include bilateral hydronephrosis, a thick-walled bladder with dilated posterior urethra, and, in more severe cases, dysplastic renal parenchymal changes with perinephric urinomas and urinary ascites (see Fig. 124-5) (Bellinger et al, 1983; Reuter and Lebowitz, 1985; Barakat et al, 1991; Dinneen et al, 1993; Hutton et al, 1994; Gunn et al, 1995; Kaefer et al, 1997a; Abbott et al, 1998). Massive bladder dilation can be seen to occupy a good proportion of the abdomen (Fig. 124-12). With progression of the pregnancy, the bladder may become more thick walled with increasing posterior urethral dilation (see Fig. 124-4). When characteristic ultrasound findings are present, the differential diagnosis includes prune-belly syndrome (with or without urethral atresia), massive VUR, and certain



Figure 124-12. Fetal magnetic resonance image showing massive bladder distention from posterior urethral valves. The dilated posterior urethra is seen below the bladder and indicated by the arrow.

cloacal anomalies (in genetic females) (Kaefer et al, 1997a; Oliveira et al, 2000; Osborne et al, 2011).

Bladder Exstrophy

Bladder exstrophy is a congenital abnormality affecting development of the lower abdominal wall, lower urinary and reproductive tracts, and musculoskeletal system. Prenatal diagnosis can be made with reasonable certainty using ultrasonography. Common observations in the fetus with bladder exstrophy include nonvisualization of the fetal bladder, a lower abdominal wall mass immediately inferior to a low-lying umbilicus, and diminutive genitalia (Gearhart et al, 1995). Patience and expertise in the ultrasonographer are important for recognition of the consistent negative finding on fetal imaging—absence of bladder filling—that is critical in making the diagnosis of bladder exstrophy. Other findings that may be evident to the experienced observer include normal kidneys in orthotopic position, normal vertebrae and spinal cord, abnormal symphyseal diastasis, and anteriorly displaced anus (Fig. 124-13). Additional prenatal MRI may be beneficial in excluding other cloacal anomalies and confirming the diagnosis of bladder exstrophy (Goldman et al, 2013).

Prenatal diagnosis of bladder exstrophy provides an opportunity for discussion of bladder exstrophy, complex reconstruction in neonates, follow-up care and outcomes, other organ system normality, and options of termination versus continuation of the pregnancy (Cacciari et al, 1999; Bischoff et al, 2012). The increasing ability to accurately diagnosis this and other complex diagnoses may have led to an increase in termination (Cromie et al, 2001).

Increasingly, the initial management of the newborn with bladder exstrophy is, perhaps, believed not to present an emergency state, and prenatal diagnosis may be helpful for several reasons. For example, at a center of excellence, expectant parent(s) who are interested may be offered advanced obstetric care, interaction with the pediatric urologic team, introduction to the pediatric hospital's support services, familiarity with the pediatric hospital itself, and interaction with parents of a child with bladder exstrophy.

Cloacal Exstrophy

Cloacal exstrophy (omphalocele, exstrophy, imperforate anus, spinal abnormality [OEIS]) is the most severe manifestation of the exstrophy-epispadias complex spectrum, carrying all of the findings associated with bladder exstrophy and renal, spinal, and bowel involvement in the form of a lateral enterovesical fistula. Cloacal exstrophy describes a rare grouping of component malformations. The cause is unknown but likely heterogeneous. Although postnatal identification of its associated gastrointestinal, spinal, and genitourinary systems delineates the extent and natural history of OEIS complex, prenatal findings may provide additional information regarding early detection, possible causative factors, and outcome. The association of twinning and OEIS complex suggests that abnormal developmental step(s) may occur as early as blastogenesis (Keppler-Noreuil, 2001; Keppler-Noreuil et al, 2007). Based on fetal ultrasound findings, Casale and colleagues (2004) raised a possible role of blighted conjoined twinning as a cause of cloacal exstrophy variants.

The prenatal diagnosis of cloacal exstrophy should be suspected with findings of nonvisualization of the bladder in association with a low-lying umbilicus, lower abdominal wall mass—typically omphalocele—and kidney (number, location, and/or appearance) and lumbosacral spine abnormalities (Fig. 124-14). Austin and colleagues (1998) reviewed 22 patients with prenatal ultrasound studies and cloacal exstrophy; they identified relatively common “major” criteria for prenatal diagnosis of cloacal exstrophy of nonvisualization of the bladder, a large midline infra-umbilical anterior wall defect, omphalocele, and lumbosacral anomalies and less frequently observed “minor” criteria including lower extremity defects, renal anomalies, ascites, widened pubic arches, hydrocephalus, and one umbilical artery. Additional ultrasound findings suggestive of cloacal exstrophy in the fetus include

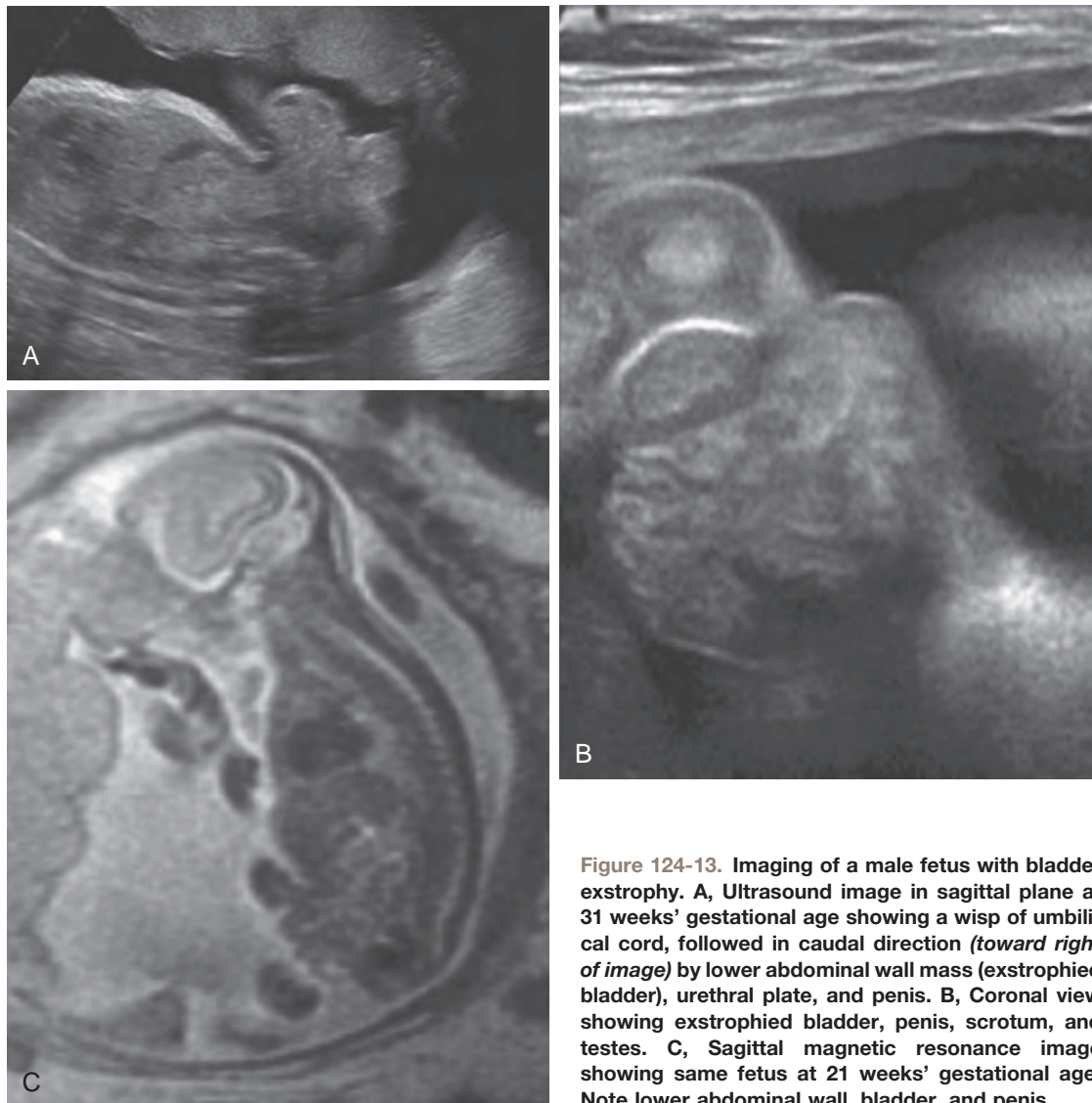


Figure 124-13. Imaging of a male fetus with bladder exstrophy. **A**, Ultrasound image in sagittal plane at 31 weeks' gestational age showing a wisp of umbilical cord, followed in caudal direction (*toward right of image*) by lower abdominal wall mass (exstrophied bladder), urethral plate, and penis. **B**, Coronal view showing exstrophied bladder, penis, scrotum, and testes. **C**, Sagittal magnetic resonance image showing same fetus at 21 weeks' gestational age. Note lower abdominal wall, bladder, and penis.

an elephant trunk–like image of the protruding bowel and/or hemi-vertebrae (Hamada et al, 1999; Wax et al, 2008). Prenatal MRI can be used to help confirm the prenatal diagnosis of OEIS (Calvo-Garcia et al, 2013).

The differential diagnosis in the setting of a fetus with an abdominal wall mass includes omphalocele, gastroschisis, bladder exstrophy, and cloacal exstrophy. The last two diagnoses would be entertained when nonvisualization of the urinary bladder is also noted. A study of 41 cases involving fetal abdominal wall mass from the database of the Centre of Fetal Care at Queen Charlotte's and Chelsea Hospital in London from 2000 to 2005 revealed that 25 cases were omphalocele (61%), 9 were gastroschisis (22%), 6 were body stalk anomaly (15%), and 1 case was cloacal exstrophy (2%). Seventeen cases (41%) were associated with other major malformations (Arnaoutoglou et al, 2008).

Cloacal Malformation

Abnormal early development in the fetus may result in lack of separation of the urinary, reproductive, and intestinal tracts, causing persistent cloaca (also known as *cloaca* or *cloacal malformation*) in the female. Direct communication of these three tracts deep to the skin surface results in single perineal opening. Persistent cloaca should be considered in any female fetus with hydronephrosis and a large cystic mass arising from the

pelvis as assessed by ultrasonography and/or MRI (Cilento et al, 1994; Suzumori et al, 2009). Chaubal and colleagues (2003) found calcified meconium to be an important sign in the prenatal sonographic diagnosis of cloacal malformation. Other authors have found that the prenatal ultrasound and MRI findings of fetal ascites, multicystic pelvic mass, bilateral hydronephrosis, and oligohydramnios are highly suggestive of the cloacal malformations associated with meconium peritonitis (Shono et al, 2007; Winkler et al, 2012).

Similar to the fetus shown in Figure 124-15, Liu and colleagues reported MRI findings of hydrocolpos with septate vagina and massive urinary ascites caused by cloacal malformation (Liu and Chen, 2009), and prenatal diagnosis of cloaca associated with esophageal atresia and tracheoesophageal fistula has also been reported (Mori et al, 2007). When present in the fetus with cloaca, urinary ascites develops from retrograde flow of urine from bladder into vagina(s), passing through cervix, uterus, and finally fallopian tube(s). The clinician should be suspicious of associated esophageal atresia and tracheoesophageal fistula with the finding of polyhydramnios in the fetus with suspected cloaca.

As with fetal diagnosis of other complex malformations, prenatal diagnosis of cloaca allows for parental counseling and planning of the delivery at a tertiary center that is well equipped with a neonatal intensive care unit and pediatric surgical and urologic expertise (Warne et al, 2002; Suzumori et al, 2009).

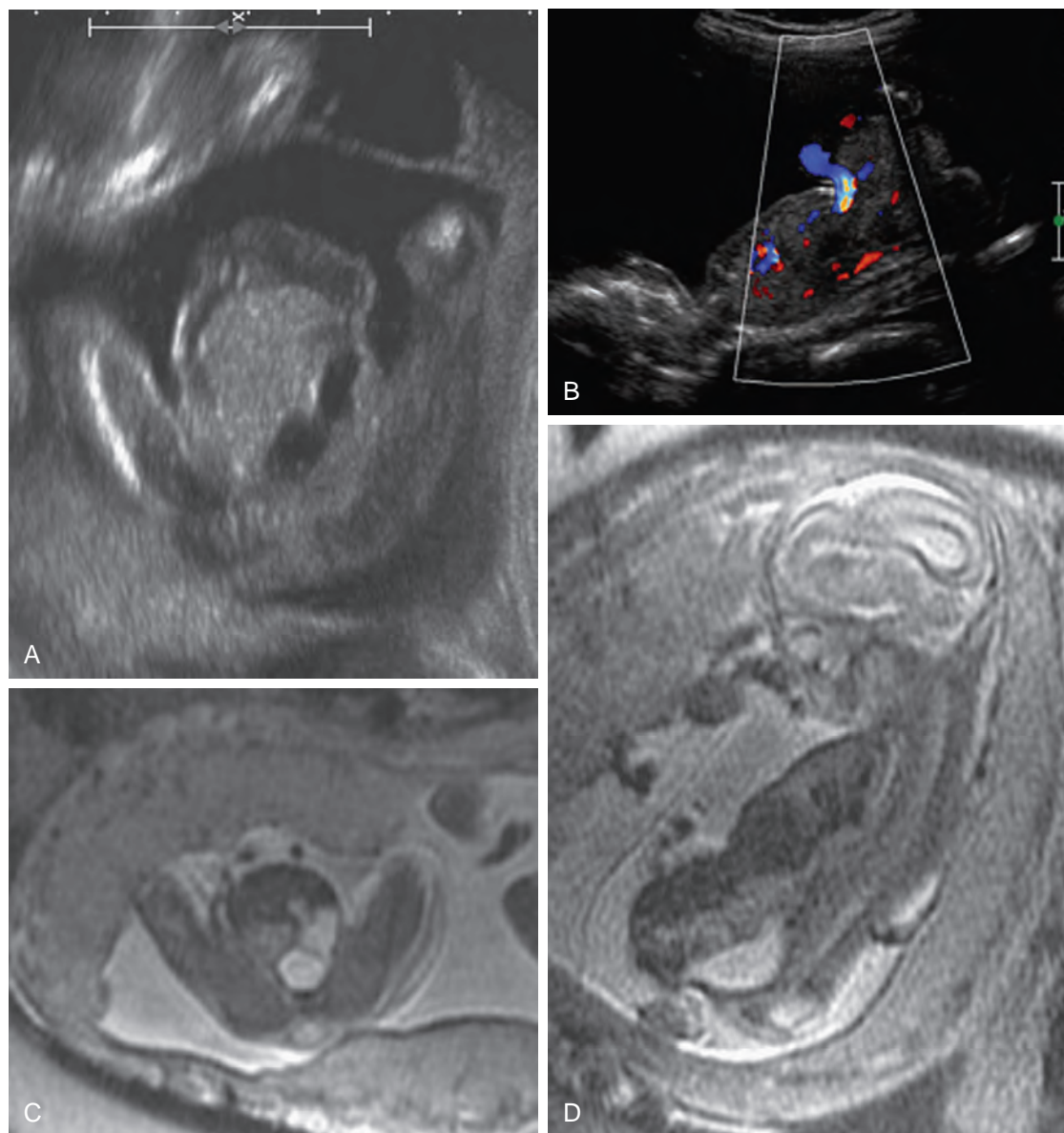


Figure 124-14. Appearance of cloacal exstrophy on imaging of a 19-week gestational age male fetus. **A**, Transverse ultrasound image through lower abdomen showing abdominal wall mass and consistent nonvisualization of the urinary bladder. **B**, Sagittal ultrasound view showing umbilical blood flow and lower abdominal wall mass immediately caudal to the umbilicus. **C**, Transverse magnetic resonance image showing omphalocele with liver and dilated distal left ureter. **D**, Sagittal magnetic resonance image with omphalocele, ureter, and terminal myelocystocele evident.

Congenital Adrenal Hyperplasia

CAH caused by deficiency of 21-hydroxylase is a disorder of the adrenal cortex characterized by cortisol deficiency, with or without aldosterone deficiency, and androgen excess. The severe classic form occurs in 1 in 15,000 births worldwide, and the mild nonclassic form is a common cause of hyperandrogenism. Neonatal screening for CAH and gene-specific prenatal diagnosis are now possible (Merke and Bornstein, 2005).

Reisch and colleagues recently reported the prenatal diagnosis of CAH caused by P450 oxidoreductase deficiency (autosomal recessive inheritance of CAH) as early as gestational week 12 by profiling maternal urine for steroid metabolite excretion. They identified significantly elevated levels of steroids of fetal origin (pregnenolone metabolite epiallopregnanediol and the androgen

metabolite androsterone) with concurrent lower values of estriol in maternal urine. Of the 20 patients, only 5 had evidence of prenatal morphologic features of CAH on ultrasonography (Reisch et al, 2013). Although the accuracy and usefulness of cell-free fetal DNA used prenatally to identify CAH remain unclear, further advances in these technologies may provide newer methods for noninvasive and highly accurate prenatal diagnosis of CAH (Colmant et al, 2013).

Clinical management of patients with CAH involves treating hormonal deficiencies, addressing issues related to genital ambiguity, avoiding morbidities, and communicating with the family about the risk of CAH in other members. Screening for CAH can reduce adrenal crises, avoid incorrect sex assignments, lower mortality (especially in males), and avoid inappropriate somatic growth and precocious puberty (Speiser, 2007).

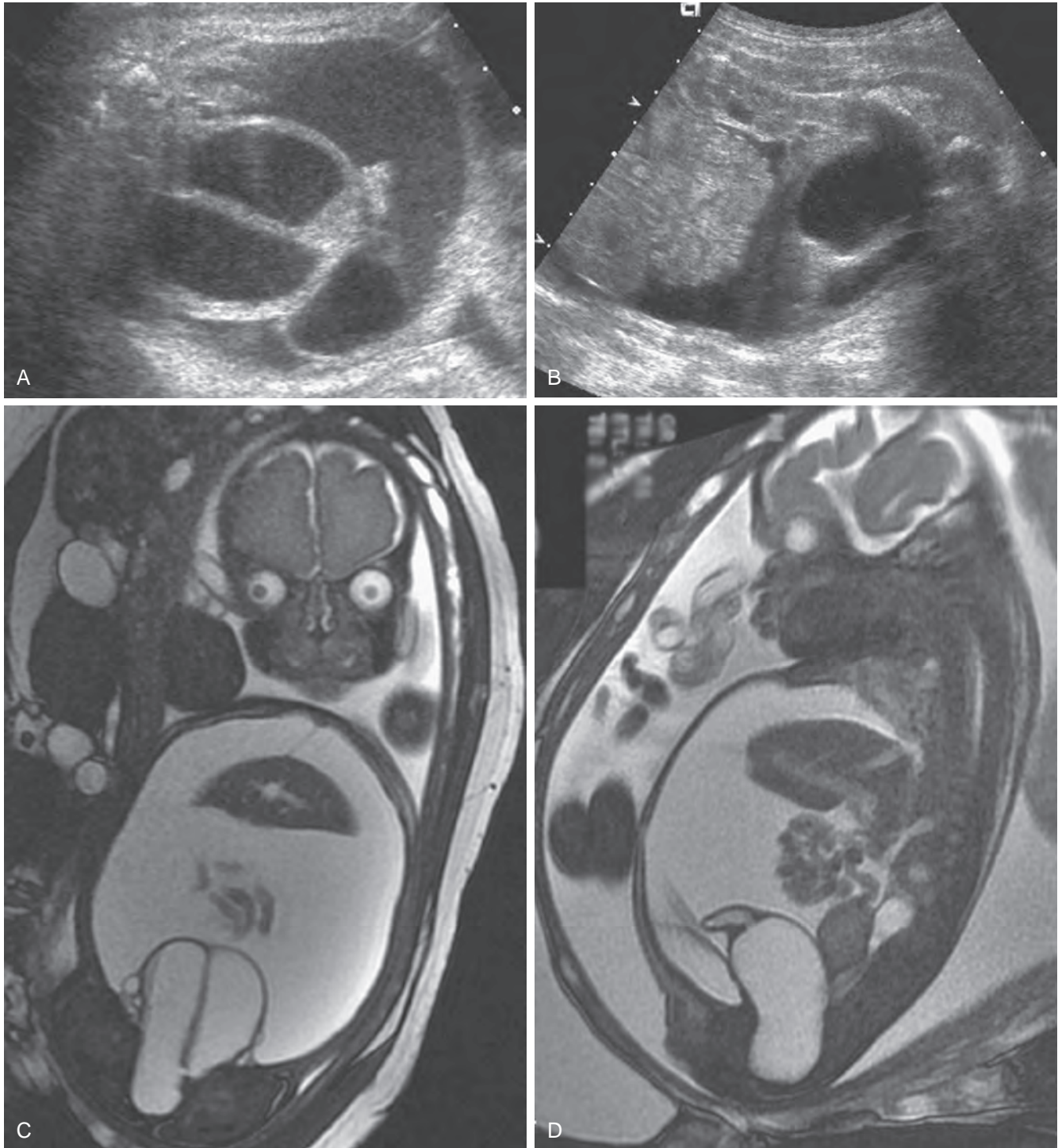


Figure 124-15. Imaging of a female fetus at 30 weeks' gestational age with cloaca. **A**, Transverse ultrasound view of abdomen showing dilated duplicate vagina, urinary bladder, and urinary ascites consistent with cloaca. **B**, Sagittal ultrasound image showing bladder, markedly distended vagina, kidney with mild hydronephrosis, and urinary ascites outlining bowel and liver. **C**, Coronal magnetic resonance image showing duplicate vagina and urinary ascites. **D**, Sagittal magnetic resonance image of bladder, distended vagina, cervix, uterus, and intra-abdominal organs outlined by urinary ascites.

The most common form of CAH is 21-hydroxylase deficiency (21-OHD). In its severe form, 21-OHD causes prenatal virilization of external female genitalia. Through molecular genetic analysis of fetal DNA, defects in 21-OH synthesis can be diagnosed in utero. Genital ambiguity in females can be reduced or eliminated with prenatal dexamethasone treatment, which successfully

suppresses fetal androgen production. Current data from large human studies show that prenatal diagnosis and treatment are safe in the short term for both the fetus and the mother. Preliminary data from long-term studies support these results (Nimkarn and New, 2009). Nimkarn and New (2009) also reported safety over the long term, but recommend that all subjects exposed to

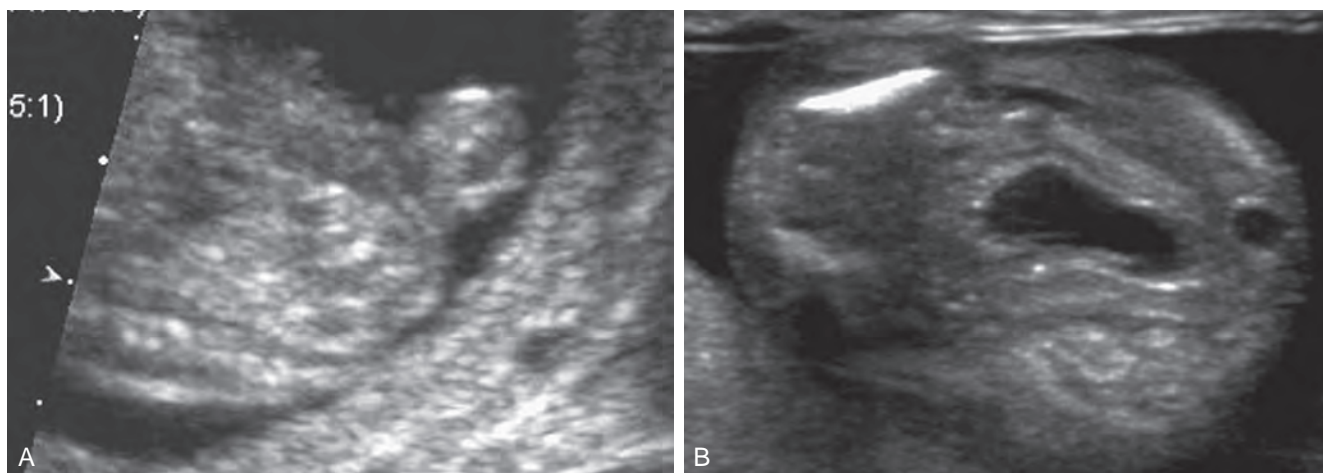


Figure 124-16. Ultrasound image of megalourethra in a male fetus at 15 weeks' gestational age. **A**, Sagittal view of dilated penile urethra. **B**, Transverse view showing thick-walled bladder and dilated posterior urethra in perineum.

dexamethasone treatment during fetal life have all aspects of their development followed closely. In a recent report of standardized cognitive function testing, CAH-affected girls treated with dexamethasone prenatally appeared to have better cognitive function than untreated CAH-affected girls. However, CAH-unaffected girls treated prenatally with dexamethasone had worse performance in cognitive testing. Cessation of prenatal treatment should stop as soon as possible once the diagnosis has been excluded (Maryniak et al, 2014).

Megalourethra and Prune-Belly Syndrome Association

Congenital megalourethra is a rare genital anomaly characterized by dilatation of the penile urethra with or without evidence of proximal or distal urethral obstruction (Fig. 124-16). Reports of the prenatal diagnosis of this condition in the literature are limited, but most note an overall poor perinatal outcome secondary to pulmonary hypoplasia and poor renal function (Sepulveda et al, 2005). In a recent report of 10 cases identified in a retrospective review, 4 of 10 either were terminated or died in the newborn period (Amsalem et al, 2011). Only 3 of the 10 had normal renal function beyond the newborn period. It is interesting to note that 2 of the 10 had concomitant anal atresia. There have been reports of spontaneous resolution (Nijagal et al, 2004). Some authors have reported cases with prune-belly-like features (Fisk et al, 1990; Wu et al, 1995). The clinician must also consider posterior urethral valves in the differential diagnosis when a dilated urethra is identified in a male fetus.

Myelomeningocele

Prenatal screening with α -fetoprotein (AFP) and ultrasonography has allowed the prenatal diagnosis of neural tube defects (NTDs) in current obstetric care, and the finding of open NTDs in a fetus has been considered an indication for potential in utero surgical treatment. D'Addario and colleagues (2008) evaluated the diagnostic accuracy of ultrasonographic signs that may be looked for in fetuses with NTDs. They confirmed the usefulness of evaluation of the posterior fossa in the diagnosis of NTDs, particularly in cases of small spinal defects that may be missed at ultrasound evaluation, noting that in 49 fetuses reviewed a small cerebellum was found in 96%, an effaced cisterna magna in 93%, and a small posterior fossa in 96%. Ventriculomegaly was present in 40 of 49 (82%) cases. With the finding of these associated features the NTD was identified in all but one fetus. Miller and colleagues (2006) studied the impact of prenatal MRI on diagnosis and neurosurgical treatment. Between 1999 and 2003 they reviewed 320 fetal MRI

studies that were performed at a single institution. Twenty-four fetuses were found to have central nervous system abnormalities. The diagnoses included spinal anomalies (e.g., scoliosis, myelomeningocele, and closed spinal dysraphism) and brain anomalies (e.g., ventriculomegaly with or without hemorrhage, intracranial cyst, craniosynostosis, and encephalocele). Fourteen of the 24 fetuses underwent surgery based on findings of prenatal MRI, and in 7 cases the pregnancy was terminated.

It is interesting to note that quantification of amniotic fluid glial fibrillary acidic protein (AF-GFAP) was recently reported as a potential biomarker of NTDs (Lopez et al, 2013). Enzyme-linked immunosorbent assay (ELISA) of AF-GFAP was conducted in 138 cases of NTDs, 70 healthy controls, and 27 AFP false-positive samples, and AF-GFAP levels were found to be elevated in 99.1% of open NTDs. AF-GFAP was negative in all cases of closed NTDs. Although highly preliminary, these data are very intriguing with regard to a potential additional biomarker for NTDs. Further studies multiplexing this marker and others (AFP, ultrasound findings) will be necessary to determine the most clinically effective biomarker panel.

Currently there is evidence that prenatal repair of myelomeningocele improves neurologic function. Myelomeningocele is the first nonlethal disease under consideration for fetal surgery (Adzick et al, 2011). However, as with any fetal intervention, the potential improvements in outcome must be balanced with maternal safety and well-being, in addition to the safety and well-being of the fetus (Hirose and Farmer, 2009). The randomized Management of Myelomeningocele Study (MOMS) clinical trial examined the efficacy of open fetal myelomeningocele repair as compared with postnatal repair (Adzick et al, 2011). In this study and others, there appeared to be an improvement in the need for neonatal shunting and motor outcomes at 30 months, but not without maternal and fetal risk (Danzer et al, 2009). Specifically, in the 183 randomized patients, significant differences were noted in shunt rates (40% fetal vs. 82% postnatal), motor function and anatomic level (32% of fetuses vs. 12% of postnatal children with two or more spinal levels better), rates of independent ambulation without orthotics (42% fetal vs. 21% postnatal), and Bailey Psychomotor Development Index scores (64.0 vs. 58.3) (Adzick et al, 2011). Further long-term comparative evaluation is necessary to determine the overall benefits of the fetal intervention.

As for postnatal bladder function after in utero repair, a study of 11 patients who underwent open in utero repair and 22 who underwent postnatal repair did not demonstrate any difference in the need for clean intermittent catheterization, incontinence between catheterizations, or anticholinergic or antibiotic use (Lee et al, 2012). In addition, urodynamic parameters including bladder capacity, detrusor pressure at capacity, detrusor overactivity, and the

presence of detrusor sphincter dyssynergia were not significantly different between the groups.

Renal Mass

Although congenital mesoblastic nephroma (CMN) is a rare benign congenital renal tumor, it is the most common solid renal tumor in the newborn period. Typically the prenatal diagnosis of CMN has been made on the basis of the findings of sonography in the third trimester. CMN is typically described as a hypoechoic homogeneous or heterogeneous solid renal mass with an echogenic rim that is not often well defined (Geller et al, 1997; Chen et al, 2003). A vascular ring sign—an anechoic ring surrounding the tumor—has been described for CMN (Kelner et al, 2003). Sonographic findings of CMN and Wilms tumor are similar, and absolute distinction often can be made only pathologically. Recently there have been a few reported cases of CMN identified by MRI (Chen et al, 2003; Linam et al, 2010; Ko et al, 2013). MRI may help delineate CMN from other masses and provide additional information with respect to adjacent structures.

Rhabdoid tumor of the kidney is relatively rare but a highly lethal malignancy of infancy. Prenatal detection of a renal rhabdoid tumor with mesoblastic components has been achieved in a 27-week fetus (Fuchs et al, 2004). The tumor appeared as a large mass in the left renal area with concomitant massive polyhydramnios. Ultrasound features alone did not distinguish the tumor from a benign lesion, but aggressive growth of the tumor indicated malignancy. Amniotic fluid cytology was performed but failed to confirm the diagnosis.

Leclair and colleagues (2005) reviewed outcome in 28 patients with prenatally diagnosed renal tumors from 20 institutions. The diagnosis was CMN in 26 patients and Wilms tumor in 2 patients. One or more complications were identified in 20 of the 28 patients (71%) during the perinatal period. Polyhydramnios was observed in 11 fetuses (39%), 2 had hydrops fetalis, and 7 developed acute fetal distress necessitating emergency cesarean section, of which 1 died in utero before delivery. Median gestational age of the 27 neonates born alive was 35 weeks (range 29 to 39), including 13 of the 28 patients reviewed (46%) who were born before term. Complications at birth included hemodynamic instability in 3 neonates, respiratory distress syndrome in 8 (30%), and hypertension in 6 (22%). Surgical complications occurred in 7 patients (26%), including tumor rupture in 1 and intraoperative bleeding with postoperative death in 1. At median follow-up of 42 months, 26 of the 27 children were in complete remission. Leclair and colleagues concluded that prenatally diagnosed renal tumors have an excellent oncologic outcome but a high risk of perinatal complications. Prenatal diagnosis should allow planning the delivery at a pediatric tertiary care center to avoid a potentially life-threatening condition in early neonatal life.

Although Beckwith-Wiedemann syndrome (BWS) and other overgrowth syndromes are difficult to diagnose prenatally, the presence of renal enlargement and other findings suggestive of overgrowth should raise the suspicion of these potential diagnoses. A prenatal diagnosis can be suggested by ultrasound; particularly with BWS, sonographic and MRI findings including macrosomia, polyhydramnios, omphalocele, macroglossia, hepatomegaly, and renal enlargement are helpful in distinguishing the condition (Vora and Bianchi, 2009; Storm et al, 2011). If an overgrowth syndrome is suspected, further genetic analysis can be offered (Vora and Bianchi, 2009). Other overgrowth syndromes to consider include Pallister-Killian, Sotos, Perlman, and Simpson-Golabi-Beckel syndromes, but these typically involve other systems not involved in BWS (Vora and Bianchi, 2009).

Renal Vein Thrombosis

Renal vein thrombosis (RVT) is a rare event. The incidence varies from 0.5 per 1000 admissions in neonatal intensive care units to 0.5% in autopsy findings. Antenatal ultrasound findings include an enlarged kidney, loss of corticomedullary differentiation, and

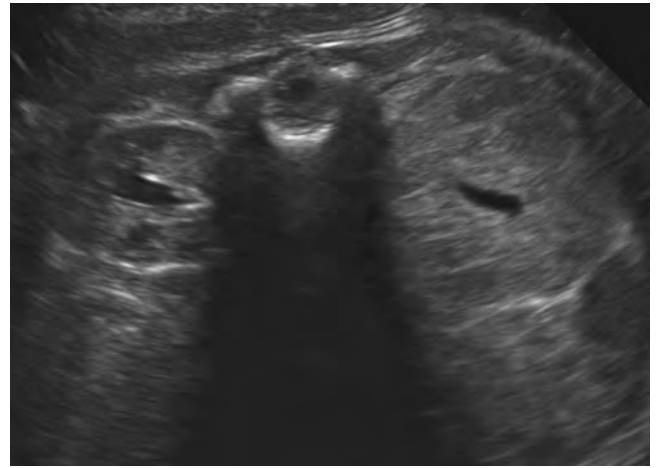


Figure 124-17. Antenatal ultrasound image at 38 weeks' gestation demonstrates an enlarged left hyperechoic kidney with loss of corticomedullary differentiation.



Figure 124-18. Antenatal ultrasound image at 36 weeks' gestation shows a left renal vein thrombosis extending into the inferior vena cava. Note the mural calcification of the inferior vena cava.

branching hyperechoic vessels (Fig. 124-17). Often, an inferior vena cava thrombus can be seen with decreased or no flow in the affected renal vein (Fig. 124-18). Diallo and colleagues (1998) reported a case of RVT that was diagnosed at 34 weeks' gestation by ultrasonography in a fetus showing signs of fetal distress. The typical pattern of renal enlargement, loss of corticomedullary differentiation, echogenic streaks, lack of definition of renal sinus echoes, and loss of venous flow in the affected kidney by Doppler imaging was observed. After cesarean section, full recovery at 1 week and a normal evolution at 1 month of life were reported.

Adrenal Mass

The differential diagnosis of prenatally diagnosed adrenal masses includes neuroblastoma, adrenal hemorrhage, adrenal and cortical renal cysts, adrenal adenoma and carcinoma, subdiaphragmatic pulmonary sequestration, BWS, duplication of the renal system, Wilms tumors, CMN, and mesenteric and enteric duplication cysts. According to Sherer and colleagues, the worldwide annual incidence of childhood adrenal cortical neoplasms ranges from 0.30 to 0.38 per 1 million children younger than 15 years. These neoplasms are even more unusual among infants, suggesting spontaneous resolution in some lesions, with only 23 cases reported in the literature (Sherer et al, 2008).

Curtis and colleagues (Sherer et al, 2008) developed an algorithm that facilitates the correct diagnosis of the suprarenal masses, subdiaphragmatic extralobar pulmonary sequestration, and neuroblastoma, allowing the correct diagnosis to be made prenatally in 95% of patients. Based on a literature review, the authors identified distinguishing features of the two lesions and created an algorithm on the basis of these distinctions. Typical findings on prenatal ultrasonography for subdiaphragmatic extralobar pulmonary sequestration include an echogenic mass that is left sided and can often be identified during the second trimester. Neuroblastoma is most often cystic, right sided, and identified in the third trimester.

Fang and colleagues (1999) reported adrenal hemorrhage confirmed in a neonate after first detection by ultrasonography at 21 weeks' gestational age. The echogenic right suprarenal mass became larger and hypoechoic on follow-up postnatal ultrasonography. With difficulty differentiating the lesion from cystic neuroblastoma, the authors performed a surgical exploration when the patient was 2 months old, and adrenal hemorrhage was confirmed, thus suggesting that adrenal hemorrhage can occur as early as the second trimester. Characteristic imaging features on ultrasonography, color Doppler imaging, and MRI help differentiate adrenal hemorrhage from neuroblastoma (Gocmen et al, 2005).

KEY POINTS: SPECIFIC DIAGNOSES

- Antenatal ultrasound findings suggestive of UPJ obstruction include dilation of the renal pelvis and collecting system with no evidence of ureteral dilation.
- The findings of MCDK include multiple noncommunicating cysts, minimal or absent renal parenchyma, and the absence of a central large cyst.
- Antenatal detection of ARPKD often is based on bilaterally enlarged echogenic kidneys without obvious renal cystic disease. Concomitant hepatobiliary dilatation or oligohydramnios further suggests the disease.
- Duplication anomalies are often recognized on the basis of upper pole hydroureteronephrosis in association with either an obstructing ureterocele or an ectopic ureter.
- Very large ureteroceles can be mistaken for the bladder.
- VUR cannot be definitively diagnosed on antenatal ultrasonography, although intermittent or varying degrees of hydronephrosis or a hydroureter is suggestive of the diagnosis.
- Antenatal findings of posterior urethral valves include bilateral hydroureteronephrosis, a thick-walled bladder with dilated posterior urethra, renal dysplasia, and/or perinephric urinomas and urinary ascites.
- Fetal characteristics of bladder exstrophy include nonvisualization of the fetal bladder, lower abdominal wall mass immediately inferior to a low-lying umbilicus, and diminutive genitalia.
- Antenatal findings of exstrophy in combination with omphalocele and with kidney and lumbosacral spine abnormalities suggest cloacal exstrophy.
- Hydronephrosis and a large cystic mass arising from the pelvis in a female fetus suggest a persistent cloaca.

ANTENATAL MANAGEMENT OF FETAL UROPATHIES

Up to 3% of all pregnancies involve fetal urinary tract anomalies. The vast majority of anomalies are associated with hydronephrosis. Severe obstruction that might warrant antenatal intervention comprises less than 5% of all detected anomalies.

The primary role for the perinatal urologist is to provide education and counseling for prospective parents in an objective manner. Often the patient is referred to the urologist after much information has been provided to the family. The counseling urol-

ogist should (1) provide reassurance and dispel misconceptions, (2) provide a reasonable differential diagnosis, (3) supply information regarding the natural history of the disease, (4) give antenatal recommendations, and (5) provide a postnatal management plan, which will be discussed further. The need for continued antenatal evaluation is debatable and unclear, particularly with mid- and late-trimester mild and moderate hydronephrosis. In the setting of severe unilateral or bilateral hydronephrosis, more regular follow-up is reasonable. If there is a suspicion of bladder outlet obstruction, regular follow-up is needed. In addition to normal fetal growth parameters, amniotic fluid volume, renal appearance (echogenicity, degree of hydronephrosis, cystic changes), and extrarenal fluid collections should be monitored closely.

Rationale and Indications for Fetal Intervention

Overall, the need to consider in utero intervention for obstruction is uncommon. However, in the specific cases in which it should be considered, the rationale for antenatal treatment of hydronephrosis is to maximize development of pulmonary and renal function. These two aspects of fetal development are closely linked because urine comprises more than 90% of amniotic fluid volume by the 16th week of gestation and because oligohydramnios during the second trimester is often associated with a lethal postnatal outcome secondary to pulmonary hypoplasia.

Before prenatal surgical intervention for obstructive uropathy, it is critical to assess the risk-benefit ratio. The time of onset of oligohydramnios has been shown to be an important determinant of outcome (Mahony et al, 1985; Mandell et al, 1992b). In fetuses in which adequate amniotic fluid was documented at up to 30 weeks' gestation in association with a urologic abnormality, pulmonary outcomes were satisfactory and postnatal clinical problems were related to renal disease. Therefore, in the setting of late-onset oligohydramnios there appears to be limited usefulness of urinary tract decompression or early delivery for pulmonary reasons. It is also unclear whether early delivery to permit earlier postnatal urinary decompression is beneficial. If early delivery is considered, maternal corticosteroid administration for pulmonary development should be considered. Neonatology colleagues should also be involved in any early delivery decision process.

The most widely accepted indicator of salvageable renal function is analysis of fetal urine. When the urinary sodium value is less than 100 mg/dL, urine chloride value is less than 110 mmol/L, and urine osmolality is less than 200 mOsm/dL, renal function appears to be salvageable with in utero intervention (Table 124-4).

TABLE 124-4 Indications and Conditions for in Utero Urinary Decompression

INDICES	COMMENT
Evidence of bladder outlet obstruction	Dilated bladder, hydroureteronephrosis
Normal karyotype	By amniocentesis
No systemic anomalies	For example, central nervous system, cardiovascular
Male fetus	—
Singleton	—
Oligohydramnios	Early onset: <25 wk
Noncystic kidneys	Degree of echogenicity is subjective; cysts are poor prognostic sign
Favorable urinary indices	Na <100 mg/dL, Cl <110 mg/dL, osmolality <210 mOsm/dL; or serial samplings trending toward normal; β_2 microglobulin <10-20 mg/L
Informed consent	Risks of partial treatment must be included

(Glick et al, 1985). The accuracy of these predictors has been challenged (Wilkins et al, 1987; Elder et al, 1990) and, more recently, serial aspirations of fetal urine have been reported to yield more valuable results (Johnson et al, 1995). Guez and coworkers (1996) published a report regarding 10 fetuses who underwent multiple urine samplings and in whom severe obstruction reduced sodium and calcium reabsorption. The researchers concluded that fetal urinary chemistries were reasonably predictive of severe but not moderate postnatal renal impairment.

Other investigators have suggested the use of fetal urinary β_2 microglobulin as an indicator of tubular damage. In normal postnatal kidneys, more than 99.9% of β_2 microglobulin is reabsorbed and metabolized in the proximal tubules; in postnatal renal disease with damage to this area, β_2 microglobulin is excreted in the urine. If urinary β_2 microglobulin is reflective of prenatal renal damage, including this parameter, poor renal outcome has been predicted with a specificity of 83% and sensitivity of 80% (Tassis et al, 1996). However, a 2007 systematic review of fetal urine as a predictor of postnatal renal outcome demonstrated that there was insufficient evidence to support β_2 microglobulin as a predictor of renal function (Morris et al, 2007). From 23 studies the researchers identified 572 women; the two most accurate fetal urine tests were urinary calcium and sodium. In this analysis, β_2 microglobulin was found to be less accurate (Morris et al, 2007).

Findings on antenatal ultrasound have also been examined with regard to prediction of long-term postnatal renal function. In a systematic review of 13 articles encompassing 251 women, oligohydramnios and the appearance of the renal cortex (increased echogenicity or cystic changes) at the diagnosis of lower urinary tract obstruction were the best factors to predict poor renal function (defined as creatinine >1.2 mg/dL) (Morris et al, 2009). In this particular study, gestational age at diagnosis (<24 weeks) was not predictive of renal function, which may reflect the inherent variability of the available literature.

Clinical Experience

The ability to diagnose severe prenatal hydronephrosis and advances in fetal intervention have helped develop prenatal surgery for obstructive uropathy. Harrison and colleagues (1982) described the initial report of fetal surgery in a 21-week-old fetus with bilateral hydronephrosis secondary to posterior urethral valves. After the 1986 report of the International Fetal Surgery Registry in which outcomes did not seem to justify risk, a de facto moratorium on in utero urinary tract shunting evolved (Manning et al, 1986).

More recently, with improved technology and renewed interest in fetal shunting, most cases have been reported by a small number of highly specialized centers actively engaged in prenatal surgery. The initial method of decompression with open surgery has largely been replaced by in utero shunt placement. The technique of shunt placement emerged from the University of California, San Francisco group (Harrison et al, 1982). The shunt is placed under ultrasound guidance using a Seldinger technique through a trocar (Fig. 124-19). Current practice uses the Rodeck shunt, which lies flat against the abdomen to minimize shunt dislodgment. Complications include shunt dislodgment and bowel herniation (Robitiaux et al, 1991). Amnioinfusion may be needed to improve visualization for shunt placement; however, this may lead to excessive fetal movement. Occasionally the fetus needs to be paralyzed for accurate placement. Very large bladders may cause the shunt to be placed too high in the abdomen, resulting in dislodgment from the bladder after it decompresses.

Fetoscopic methods for direct intervention to provide prolonged bladder drainage have also been explored (Quintero et al, 2000; Clifton et al, 2008; Sago et al, 2008; Ruano et al, 2010, 2014). The proposed advantage of fetoscopic intervention over vesicoamniotic shunting is to improve drainage and to restore normal cycling of the bladder. There are no studies to determine if this method of decompression is adequate in the face of significant prenatal bladder dysfunction. Furthermore, fetoscopic intervention also introduces the additional potential for iatrogenic injury to the urethra, bladder

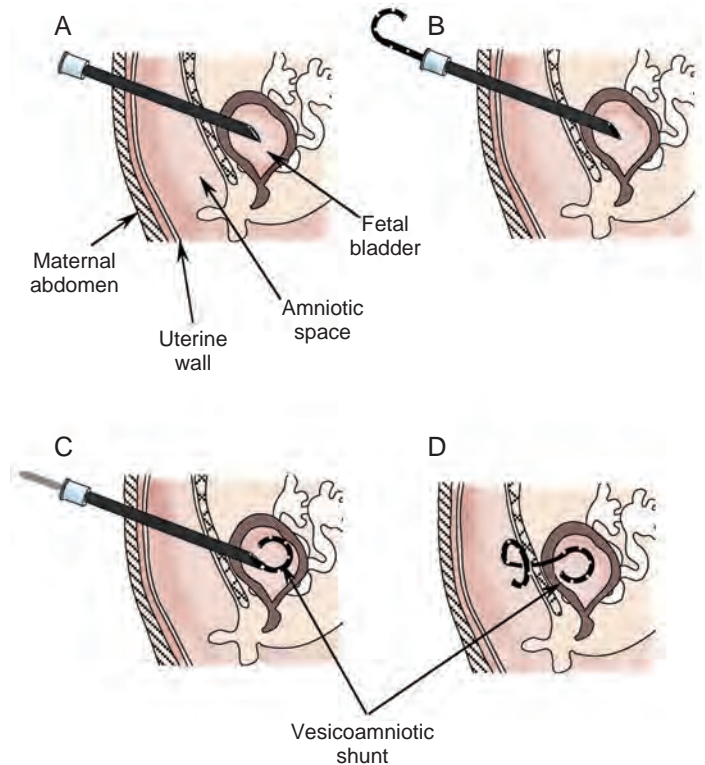


Figure 124-19. Diagram showing technique of fetal vesicoamniotic shunt placement. The fetal bladder is initially reached with needle, and a large-bore introducing sheath is passed into the bladder (A). Within this sheath, the shunt is passed (B and C). It is a double-pigtail shunt with holes at each end allowing free drainage between the bladder and amniotic space (D). (From Peters CA. Surgical management of fetal uropathies. In: Marshall FF, editor. Textbook of operative urology. Philadelphia: Saunders; 1996. p. 1063.)

neck, or external urethral sphincter. In a systematic review of the literature, 4 papers totaling 63 patients identified that fetal cystoscopy as compared with vesicoamniotic shunts had no significant improvement in perinatal survival (Morris et al, 2011). Overall, experience with fetoscopic or endoscopic valve ablation is currently at the case report and experimental levels, and long-term outcome data are unknown.

The indications and contraindications for intervention in prenatal obstructive uropathy are outlined in Table 124-4. Currently, serial bladder sampling over 3 days has been used to help determine if the fetus is a viable candidate. The serial nature of the procedure allows one to see the subsequent trend of urine osmolality and electrolyte composition as a reflection of fetal kidney response (Johnson et al, 1995). The principal reason for considering vesicoamniotic shunting is to prevent early neonatal pulmonary insufficiency and death. The risks that one accepts with intervention include induction of premature labor, perforation of fetal bowel and bladder, fetal loss, and fetal and/or maternal hemorrhage and infection.

More recently, the ability to influence renal outcome in male patients with posterior urethral valves but without oligohydramnios has been suggested as a possible indication for in utero intervention. In this setting the principal goal of intervention is not to prevent pulmonary hypoplasia and deaths but to prevent or delay end-stage renal failure. Although some reports have shown promise in the ability to distinguish those fetuses with likely early renal failure from those with later-onset failure, the specificity and accuracy of methods using a combination of ultrasound and urinary chemistries (sodium, β_2 microglobulin, and calcium) has not been well defined (Muller et al, 1993; Clautice-Engle et al, 1995; Domergues et al, 2000). In summary, precise identification of those

situations in which intervention may benefit the fetus with obstructive uropathy remains unclear.

Clinical Outcomes

To date, the reported long-term outcomes of antenatal intervention for severe obstructive uropathy (e.g., posterior urethral valves, prune-belly syndrome, urethral atresia) are mixed (Crombleholme et al, 1990; Johnson et al, 1994; Coplen et al, 1996; Freedman et al, 1999; Holmes et al, 2001; McLorie et al, 2001; Clark et al, 2003; Biard et al, 2005; Salam, 2006; Ethun et al, 2013; Tonni et al, 2013). Significant variability in patient selection and assessment of outcome within these studies has limited the ability to determine if prenatal intervention has altered the postnatal course. A large systematic review of the prenatal intervention for obstructive uropathy showed a statistically significant perinatal survival advantage with shunting (Clark et al, 2003); however, lack of randomization of patient selection in the trials reviewed may have biased the results. Of the studies that have reported long-term outcomes of in utero vesicoamniotic shunting, many of the children have renal insufficiency (57%) and growth impairment (86%) (Freedman et al, 1999; Holmes et al, 2001; Biard et al, 2005). Biard and associates (2005) reported on long-term follow-up (5.8 years) of patients who survived in utero shunting. These researchers noted acceptable renal function in 44%, mild impairment in 22%, and renal failure in 33%. Patients with prune-belly syndrome had the best renal outcome (57%), followed by those with posterior urethral valves (43%), and then urethral atresia (25%).

The European-based multicenter randomized clinical trial PLUTO (Percutaneous Shunting for Lower Urinary Tract Obstruction) was recently completed (Morris et al, 2013). The initial goal was to enroll 150 singleton pregnancies with ultrasound evidence of lower urinary tract obstruction to evaluate the safety and effectiveness of vesicoamniotic shunting as compared with conservative management. The study was stopped early because of poor enrollment; only 31 patients were enrolled and randomized (16 vesicoamniotic shunt patients and 15 controls). In the vesicoamniotic shunt group, there were 12 live births and 4 postnatal deaths at 28 days; and in the control group there were 12 live births and 8 postnatal deaths. All postnatal deaths were from pulmonary hypoplasia. Although underpowered, the study demonstrated a nonsignificant increase in survival in the vesicoamniotic shunt group. Consistent with the results of the systematic review of existing prenatal intervention data, there was minimal likelihood of surviving with long-term normal renal function.

Overall, it appears that select in utero intervention for the appropriate patient may reduce the risk of neonatal mortality. Improvement in renal function does not appear to be likely. Without doubt, more sensitive and specific markers to better identify which fetus will benefit from in utero shunting need to be defined.

KEY POINTS: ANTENATAL MANAGEMENT OF FETAL UROPATHIES

- Up to 3% of all pregnancies involve a urinary tract anomaly.
- The primary role for the perinatal urologist is to provide education and counseling for prospective parents in an objective manner.
- The need to consider in utero intervention for obstruction is uncommon.

POSTNATAL MANAGEMENT OF ANTENATALLY DETECTED UROLOGIC RENAL ABNORMALITIES

A child with a prenatal diagnosis of a urologic renal abnormality such as ANH should be carefully evaluated and followed by a pedi-

atric urologist from birth. The vast majority of these children appear entirely healthy and in the absence of prenatal ultrasound findings would not have any indications for regular urologic follow-up. Parental anxiety is common and should be addressed directly with prenatal counseling and education.

Unilateral Hydronephrosis

The presence of prenatally detected unilateral dilation of the kidney warrants postnatal ultrasound evaluation in a timely but nonurgent fashion (3 to 8 weeks of life) (Claudice-Engle et al, 1995). The most common diagnoses associated with this finding are UPJ obstruction, VUR, and UVJ obstruction and megaureter. Early ultrasound evaluation is unlikely to miss a significant abnormality. Normal postnatal ultrasound examination findings indicate that obstructive uropathy is not present; however, normal findings do not indicate whether the child has VUR (Tibballs and De Bruyn, 1996). It is important to keep in mind that a postnatal ultrasound evaluation performed within the first 48 hours of life may not yet demonstrate hydronephrosis or may underestimate the degree of hydronephrosis secondary to physiologic oliguria in the newborn.

The decision to obtain a voiding cystourethrogram (VCUG) or initiate prophylactic antibiotics in the newborn period is unclear. Although some groups advocate postnatal VCUG in any child with a history of ANH, others have questioned the value of this approach (Yerkes et al, 1999). Various guidelines and recommendations have been proposed with regard to VCUG usage, but no definitive studies have rigorously studied the likelihood of VUR based on consistent ultrasound findings or other clinical characteristics. The current trend in management of ANH minimizes postnatal prophylactic antibiotics and testing for VUR in cases of resolved ANH or in mild to moderate cases of persistent postnatal ANH owing to a lack of evidence for a benefit to screening (Nguyen et al, 2010).

In general, infants with severe ANH should be placed on a prophylactic antibiotic (amoxicillin, 10 to 25 mg/kg/day) and undergo VCUG. Severe ANH may be associated with an increased risk of febrile urinary tract infection and possibly may indicate a higher grade of VUR (Song et al, 2007; Grazioli et al, 2010). As for mild ANH, a prospective study of 192 infants with ANH noted that the majority of patients with mild ANH had no significant events during infancy (Coelho et al, 2007). In another study, female infants with a history of ANH and postnatal uropathy had a higher risk of febrile urinary tract infection (Coelho et al, 2008). Regardless, no appropriate prospective studies with coordinated and comprehensive postnatal follow-up have examined this question in a rigorous fashion to provide consensus guidelines (Lee et al, 2006; van Eerde et al, 2007; Skoog et al, 2010).

At our institution, children with moderate or severe ANH are placed on a prophylactic antibiotic at birth. These children undergo renal bladder ultrasonography and VCUG postnatally. Diuretic renography is reserved for those with persistent moderate or severe postnatal hydronephrosis not related to VUR. Infants with persistent mild hydronephrosis (unilateral or bilateral) on serial ultrasound evaluation or no postnatal hydronephrosis are observed and followed clinically. Infants with a significant degree of antenatal or postnatal ureteral dilation undergo ultrasonography, VCUG, and possibly diuretic renography (with technetium-99m mercaptoacetylglutrylglycine) if clinically indicated.

Perhaps the most challenging aspect of managing ANH is determining if and when postnatal surgical correction for obstruction is appropriate (Ransley et al, 1990). Some have suggested that regardless of the degree of ANH, moderate or severe postnatal hydronephrosis with evidence of decreased renal function should be an indication for surgical intervention (Chertin et al, 2006). Despite the improved anatomic detail afforded by real-time ultrasonography and the increasing experience with functional nuclear medicine studies, no radiographic or clinical gold standard for physiologically significant obstruction exists. Over time, hydronephrosis has been seen to improve whereas other kidneys appear to lose function. The natural history of ANH is not clearly defined.

The debate over the appropriate management of infants with unilateral ANH continues and may ultimately be determined by a combination of epidemiologic, radiographic, and new innovative biomarker discoveries. More accurate and reproducible prenatal and postnatal radiographic documentation of the degree of hydronephrosis and function combined with appropriate natural history data are needed to better categorize these infants. Finally, new serum or urine biomarkers indicative of ongoing renal damage will be critical in helping to further define which infants are truly at risk.

Bilateral Hydronephrosis

Infants with bilateral hydronephrosis may have posterior urethral valves, bilateral VUR, bilateral UPJ or UVJ obstruction, or a combination of these findings. **For the child with bilateral hydronephrosis suggestive of bladder outlet obstruction, an ultrasound evaluation and VCUG should be performed promptly.** In boys, the presence of posterior urethral valves is the most important diagnosis to be ruled out. In girls, an obstructing ectopic ureterocele would be the most likely cause of bladder outlet obstruction. In the event that an obstructive lesion is discovered, it should be corrected promptly. For children with suspected lower urinary tract obstruction (e.g., posterior urethral valves), prompt bladder decompression and antibiotic prophylaxis (amoxicillin 10 to 25 mg/kg/day) should be initiated before radiographic intervention.

Renal Agenesis, Renal Ectopia, and Unilateral Multicystic Dysplastic Kidney

Infants born with solitary kidneys (renal agenesis), renal ectopia, or unilateral multicystic dysplasia should be evaluated postnatally by ultrasonography. The need for a postnatal VCUG is controversial. Functional studies such as with dimercaptosuccinic acid (DMSA) are occasionally needed to confirm the diagnosis but may not be needed in all children. The need for further screening with VCUG is controversial. It has been reported that of infants with a solitary kidney, 30% have VUR, 11% UPJ obstruction, and 7% UVJ obstruction (Atiyeh et al, 1993; Cascio et al, 1999). Similarly, those with renal ectopia (simple or crossed fused ectopia) may also be at risk for VUR in the ectopic or contralateral kidney (30%) (Gleason et al, 1994; Guarino et al, 2004; Arena et al, 2007). However, other researchers report a very low incidence of associated urologic anomalies and do not recommend screening (Calisti et al, 2008).

An MCDK is primarily unilateral, isolated, and associated with a good prognosis. If at birth the ultrasound findings are not absolutely diagnostic of a classic MCDK, a DMSA study can be used to confirm the diagnosis with the absence of uptake. Patients with MCDK are often thought to be similar to those born with a solitary kidney. In addition, patients with MCDK have a reported increased frequency of VUR and UPJ obstruction in the contralateral normal kidney (Kaneko et al, 1995; Miller et al, 2004) but use of routine screening by VCUG remains controversial (Ismaili et al, 2005).

KEY POINTS: POSTNATAL MANAGEMENT OF ANTENATALLY DETECTED UROLOGIC RENAL ABNORMALITIES

- Infants with antenatal unilateral hydronephrosis should undergo an ultrasound evaluation 3 to 8 weeks after birth.
- Postnatal ultrasonography performed within 48 hours of birth may underestimate the degree of hydronephrosis.
- An infant with bilateral hydronephrosis consistent with bladder outlet obstruction should undergo ultrasound evaluation and VCUG promptly.

TABLE 124-5 Presenting Signs of Neonatal Urologic Emergencies

SIGN	ETIOLOGY	EVALUATION
Sepsis	Bladder outlet obstruction	Urine and blood cultures
	Vesicoureteral reflux	Ultrasound
	Megaureter	VCUG
	Ectopic ureter	
	Ureterocele	
	Ureteropelvic junction obstruction	
	Fungal infection with secondary obstruction	
Hematuria	Urinary infection	Urine Culture
	Renal vein thrombosis	VCUG
Hypertension	Renal vein thrombosis	Ultrasound
	Renal artery thrombosis	DMSA studies
Renal mass	Hydronephrosis	Ultrasound
	ARPKD	Computed
	Multicystic dysplastic kidney	tomography,
	Congenital mesoblastic nephroma	DMSA studies,
	Neuroblastoma	magnetic
	Wilms tumor	resonance imaging
Renal failure	Urinary obstruction	Urine culture
	Sepsis	Urine electrolytes
	Renal cortical necrosis	Ultrasound
	Renal dysplasia or agenesis	DMSA, MAG3 scan
Urinary ascites	Urinary obstruction	Ultrasound
		VCUG
Scrotal mass	Neonatal torsion	Examination
	Hydrocele	Ultrasound
	Tumor	

ARPKD, autosomal recessive polycystic kidney disease; DMSA, dimercaptosuccinic acid; MAG3, technetium-99m mercaptoacetyltriglycine; VCUG, voiding cystourethrogram.

NEONATAL UROLOGIC EMERGENCIES

During the neonatal period, various neonatal urologic emergencies can cause diverse signs and symptoms (Table 124-5). A thorough history and examination may identify other associated conditions. Even though many of the conditions may involve an isolated aspect of the urogenital system, the evaluation of the entire genitourinary system is warranted in the context of the overall health and care of the child.

Perineal Mass in a Female

The presence of a protuberant mass in the perineum of a newborn girl should suggest four principal diagnoses. The appearance usually indicates the most likely diagnosis. The most common entity producing this general finding in a newborn is a periurethral cyst. These are whitish in appearance and covered by a delicate but normal epithelium. The urethral meatus is adjacent but uninvolved. Incision and drainage are usually curative. Imperforate hymen with resulting hydrocolpos may arise with a

midline bulging of whitish tissue symmetrically between the labia and behind the urethra. A palpable abdominal mass may be present because of uterine distention, and occasionally hydronephrosis is found on ultrasonography. A separate fluid-filled cavity in the pelvis should be distinguishable and not confused with the bladder. Management of an imperforate hymen is incision and drainage, which is also appropriate for the less common vaginal stenosis. The substance drained is often milky white and may be of surprising volume. Subsequent intervention is seldom needed. **Prolapse of an ectopic ureterocele may have a similar appearance, distinguished by its often edematous, congested, or frankly necrotic appearance. On close examination, it may be seen emerging from the urethra in an eccentric fashion, usually posteriorly. A distended bladder may be palpable. Ultrasonography combined with early filling images on a voiding cystography should provide the diagnosis. Management of the ureterocele is discussed in Chapter 134. Urethral prolapse is uncommon in newborns but may be seen as a circumferential collar of edematous and ecchymotic tissue at the urethral meatus (Lowe et al, 1986). Topical measures such as skin moisturizers, hot compresses, and relief of aggravating factors (urethral catheter, prolonged coughing, or straining) may relieve the prolapse. If tissue necrosis is evident, surgical resection could be considered. Although uncommon in the neonatal period, botryoid sarcomata of the vagina may arise as a protuberant vaginal mass, usually with a distinctive, multilobulated appearance, and a solid pelvic mass may be seen on ultrasonography (Chapter 156).**

Abdominal Mass

The diagnosis of an abdominal mass in a neonate has become greatly simplified with the availability of ultrasound imaging. In many cases the identity of the mass will have been suggested prenatally. **The principal entities to be considered include hydronephrosis, cystic renal disease, adrenal hemorrhage, a dilated bladder, gastrointestinal duplications, and tumor (Hartman and Shochat, 1989; Schwartz and Shaul, 1989; McVicar et al, 1991; Chandler and Gauderer, 2004).** The likelihood of any abdominal mass being of urinary tract origin is high, with more than 60% being hydronephrosis or MCDK (Schwartz and Shaul, 1989). Physical examination should determine the location, size, texture, and mobility of the mass, as well as other abnormalities on examination, including limb, cardiac, and central nervous system findings. Ultrasonography is usually able to identify the organ of origin, the cystic or solid nature of the mass, and the condition of the uninvolved elements of the genitourinary tract and permit a more focused and detailed subsequent evaluation. It cannot be overemphasized that care must be taken to examine the entire abdomen.

Imperforate Anus

Up to 75% of all cases of imperforate anus have associated malformations, with genitourinary and spinal cord anomalies being the most common (Nah et al, 2012). **Prenatally, the presence of imperforate anus may be suggested by punctate calcifications in the intestinal lumen related to formation of meconium calcifications from exposure to urine (Mandell et al, 1992a).** An ultrasound examination and VCUG should be performed at the initial presentation to assess the urinary tract, and to assess the level of the rectourethral or vesical fistula in boys. Ultrasound examination of the spinal cord to assess for spinal cord tethering should be performed in the newborn period before complete ossification of the vertebral column. Initial management is usually a diverting colostomy, which should be constructed using the transverse colon and with separation of the proximal and distal limbs to limit the risk of fecal contamination in boys with a rectourethral fistula. Complications related to the confluence of the gastrointestinal and urinary tracts may occur, including infection and metabolic derangements.

Oligohydramnios, Potter Syndrome, Renal Agenesis

The anatomic features of Potter syndrome include oligohydramnios, limb contractures (particularly clubfeet), and compressed facies with low-set ears. If this syndrome is suspected, immediate ultrasonography permits confirmation of the diagnosis as evidenced by absent or bilaterally dysplastic or cystic kidneys. These children may die from respiratory failure in the first hours of life, although survival for several days has been reported. The role of the urologist is largely one of confirming the diagnosis and providing counseling to parents and staff in these tragic cases. Little specific therapy is available to the urologist.

Single Umbilical Artery

The presence of a single umbilical artery, occurring in about 0.3% to 0.55% of live births, has been associated with an increased incidence of genitourinary anomalies in the past (Vlietinck et al, 1972). Many of these early studies included stillborn fetuses in which the incidence of renal anomalies was about 60% (Thummala et al, 1998). More recent examination of the incidence has suggested that the degree of increase is relatively minimal—about 7.1% for all renal anomalies, including reflux with an incidence of 4.5% (Bourke et al, 1993). These authors recommended routine screening for a single umbilical artery, although the clinical significance of the anomalies identified is unclear. **A meta-analysis of 37 studies of single umbilical arteries indicated that it would require screening of 14 children with a single umbilical artery to identify 1 child with a renal anomaly, and the renal anomalies are typically of minimal significance (Thummala et al, 1998; Deshpande et al, 2009).** The authors did not recommend routine screening. If there is suspicion, a renal ultrasound examination is an adequate screening tool.

Sepsis

In infants with sepsis, a catheterized or suprapubically aspirated urine specimen for culture must be obtained before antibiotic therapy. If pyuria is present, urosepsis should be strongly considered. A screening ultrasound to assess the urinary tract is critical, as many cases of urosepsis include a sonographic abnormality. The most common causes include obstructive uropathy or high grade VUR. A normal ultrasound study does not rule out reflux, and in the presence of urosepsis, VCUG is essential when the patient's condition is stable. This should probably be obtained during the acute hospital admission. Further workup should be tailored to the findings of the initial examinations.

Infant boys with intact foreskins have a higher risk of urosepsis and may not have specific anatomic findings (Wiswell and Hachey, 1993; Schoen et al, 2000). These boys should undergo the usual evaluation with an ultrasound examination and VCUG to rule out obstruction and reflux.

Absence of Voiding

The normal time for the first postnatal void extends to 24 hours, and some healthy children wait even longer (Vuohelainen et al, 2008). The most useful physical finding to determine is whether the bladder is distended. Physical examination may precipitate voiding. Ultrasound examination may be obtained when there has been no void after 24 hours, the bladder is distended, or parental concern is high. Specific findings dictate management. The time to void after circumcision is predictable and depends in part on feeding times. Within 8 hours of circumcision, 75% of breastfed and 100% of formula-fed infants had voided (Narchi and Kulayat, 1998). A common cause of concern is the pinpoint meatus often seen with hypospadias in conjunction with delayed first void. The pinpoint meatus is virtually never obstructed. Passing a feeding tube is typically unnecessary, as the child will eventually void given enough time.

Hematuria

Hematuria in the newborn often does not represent a significant process. One possible explanation is maternal hormonal withdrawal producing urethral bleeding through an as yet unspecified mechanism. Urine cultures, examination, and ultrasound evaluation are recommended. The appearance of hematuria may occasionally be noted in the diaper, produced by urate crystals that have a characteristic rusty red color. Other causes include RVT, which is identified on ultrasound examination.

Hypertension

Neonatal hypertension is rare and should prompt a careful evaluation of the infant's urinary tract by ultrasound with Doppler to identify the uncommon renal artery thrombosis. Iatrogenic renal injury from umbilical artery lines has been described to produce hypertension. Radioisotope renal scanning may be confirmatory by demonstrating focal or diffuse renal nonperfusion.

Urinary Ascites

The differential diagnosis of neonatal ascites includes urinary obstruction, which should be specifically sought, most efficiently with an ultrasound examination and a VCUG (Checkley et al, 2003). Posterior urethral valves are probably the most common underlying cause. Unusually, other obstructive processes may cause urinary ascites (Chun and Ferguson, 1997; Adams et al, 1998; Cimator et al, 2003; Beetz et al, 2004). Electrolyte analysis of the ascitic fluid may reveal high creatinine levels indicative of urine, but creatinine levels may also have equilibrated with the serum across the peritoneum.

Specific Diagnoses

Renal Vein Thrombosis

RVT in neonates is a rare condition of low mortality but high morbidity (Brandao et al, 2011). In the neonate, RVT is suggested by enlarged kidneys, hematuria, anemia, and thrombocytopenia, often with a history of a prolonged delivery and prematurity. Approximately 20% of infants with gross hematuria are found to have RVT, and about 20% of neonates with RVT have bilateral involvement. The presumed cause is impaired renal blood flow in the setting of a neonate with normally low blood pressure, polycythemia, and dehydration, including adrenal hyperplasia and salt wasting (Brandao et al, 2011). Conditions that may exacerbate those factors may predispose to RVT. Up to 50% of neonates with RVT are found to have prothrombotic abnormalities and should be screened (Kuhle et al, 2004; Marks et al, 2005). Thrombosis is peripheral and does not usually propagate centrally.

The diagnosis of RVT is best made using ultrasonography, in which an enlarged kidney is evident and the thrombus may be visualized directly (Brandao et al, 2011). Management of RVT is directed initially at reversing any predisposing factors such as dehydration and secondary electrolyte imbalances. Specific treatment remains controversial but may include anticoagulation with heparin or fibrinolytic therapy with streptokinase. Each of these modalities can be associated with significant complications (Nuss et al, 1994; Bokenkamp et al, 2000). When treated with heparin, fewer patients are left with renal functional abnormalities (Zigman et al, 2000). Bilateral RVT requires more aggressive therapy to prevent end-stage renal failure (Marks et al, 2005).

Adrenal Hemorrhage

Adrenal hemorrhage is a relatively common condition, estimated to occur in about 1% to 2% of healthy infants. More small adrenal hemorrhages are being detected with routine perinatal ultrasonography. Predisposing factors include prolonged labor, birth

trauma, and large birth weight. RVT may be associated (Suga et al, 2000). An association with BWS has been reported in several cases (Anoop and Anjay, 2004; Merrot et al, 2004; Gocmen et al, 2005). Clinically, the neonate with adrenal hemorrhage may have anemia, shock, and an abdominal mass. Gross hematuria is unusual. Ultrasonography is the most efficient diagnostic measure and usually reveals an echogenic suprarenal mass (Schwarzler et al, 1999; Velaphi and Perlman, 2001). This may appear similar to a neuroblastoma, and further evaluation, particularly with MRI, may be necessary. Scrotal hemorrhage may also be a presenting sign of adrenal hemorrhage (Avolio et al, 2002; Duman et al, 2004). The imaging characteristics of an adrenal hemorrhage evolve with time, often providing a definitive diagnosis as the mass is seen to involute. Calcifications may later develop. **The late appearance of an adrenal hemorrhage is that of peripheral eggshell calcifications in contrast to stippled calcifications of neuroblastoma.** Management is almost always supportive and expectant, with rare need for intervention.

Renal Artery Thrombosis

Hypertension and hematuria in a neonate should suggest the possibility of renal artery thrombosis (Roth et al, 2003). The clinical setting is usually suggestive in that umbilical artery catheterization is the most common cause of this condition. Renal insufficiency may be a clinical feature of this condition, as well as proteinuria and congestive heart failure (Andreoli, 2004; Cachat et al, 2004). Thrombotic involvement of the aorta may be present as well. Ultrasound examination usually reveals the diagnosis and the extent of the thrombus. Management is dependent on the clinical setting, and unilateral involvement is best managed expectantly, although thrombolytic therapy may be appropriate (Ellis et al, 1997; Kavalier and Hensle, 1997; Gunnarsson et al, 2000). Control of hypertension is the most important aspect of management and occasionally requires removal of a nonfunctional kidney.

SUMMARY

With the increased use of maternal-fetal ultrasound, more genitourinary abnormalities are being detected prenatally. Although advances in imaging have increased the detection and characterization of these abnormalities, further work is needed to identify which abnormalities are clinically significant. Research directives should focus on identifying which infants require postnatal diagnostic imaging and intervention. Developments in the fields of imaging, proteomics, and genomics may provide the necessary information to not only detect the abnormality but also prognosticate which abnormalities require further testing and medical intervention.

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The complete reference list is available online at www.expertconsult.com.

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SECTION B Basic Principles

125 Urologic Evaluation of the Child

Thomas F. Kolon, MD, MS, and Douglas A. Canning, MD

Chief Complaint and History of Present Illness

Past Medical and Surgical History

Medications and Allergies in Pediatric Patients

Pediatric Urologic Examination

Pediatric Laboratory Evaluation

Pediatric Radiographic Evaluation

Pediatric Urodynamic Evaluation and Biofeedback Training

Office Surgical Procedures

Summary

Pediatric urology encompasses a spectrum of disorders ranging from complex congenital anomalies such as bladder or cloacal exstrophy to more routine but nevertheless important problems such as daytime wetting in a school-aged child. Thanks in part to the pioneers of past generations of pediatric urologists, most of these problems are easily diagnosed and treated. Despite the dramatic progress made over the past 50 years, new discoveries continue to contribute to improved care. These advances underscore the importance of continued investigation into the diagnosis and treatment of children with congenital or acquired pediatric urologic problems. This chapter focuses on the history and physical examination of the pediatric patient with a urologic problem. Particular emphasis is on clinical entities, examination techniques, and adjunct investigations that are unique to pediatric patients. The evaluation and treatment of a pediatric patient with a urologic problem are often complex. The reader may find further details about specific conditions in other chapters. This chapter presents an introduction to the nuances of the pediatric urologic evaluation.

CHIEF COMPLAINT AND HISTORY OF PRESENT ILLNESS

In most cases, the initial contact with the child and family is through a referring phone call from the parent, primary care physician, or, if prenatal evaluation is desired, the obstetrician. In many acute cases, the child's family is calling from a distance, and the urologist must decide with the referring clinician whether the child is healthy enough to be transferred or must first have his or her condition stabilized. Usually, even in remote areas, skilled general pediatric support is available. With coaching from the accepting team, most clinicians are able to manage complex problems in the stabilization phase of the triage process. A thorough understanding of the chief complaint, history of the present illness, and past medical history is essential to appropriate management of all pediatric patients with urologic problems.

"What can we do for your child?" usually begins the history in the pediatric patient with a urologic problem. In some cases, especially voiding dysfunction, the child can begin to answer

these questions, and it is worthwhile early in the interview to ask the child a few questions directly. This shows respect for the child, who may be an excellent historian despite young age. As soon as the child realizes that the interview is directed to him or her, rather than just to the parent, he or she will concentrate on the examination. If future therapy requires behavioral training that involves cooperation from the child, he or she may be more receptive. Additionally, it is often helpful to interview adolescents separately from their parents when asking sensitive questions, such as about sexual activity.

Abdominal Complaints

Children with acute abdominal pain should be seen immediately by a primary care physician or nonphysician provider and referred to urology if appropriate. An accurate history of the character of the pain may be the best indicator of the source of the pain. Details about the character of the pain, timing, acuity of onset, radiation, and migration are important and should be elicited directly from the child when possible. Associated loss of appetite, nausea, vomiting, or a change in bowel pattern may help to distinguish gastrointestinal from genitourinary sources. A thorough abdominal examination helps to rule out surgical abdominal disease. Causes of abdominal pain in children vary widely and are often unique to pediatric patients. Urologists usually suspect pyelonephritis, cystitis, or renal colic, but the differential diagnosis includes many nonurologic etiologies. Causes of intra-abdominal pain may include pyloric stenosis, midgut volvulus, appendicitis, intussusception, and constipation. Nonabdominal sources, such as sickle cell crisis or pneumonia, should also be considered. Occasionally, some children with spermatic cord torsion complain of abdominal pain and have few complaints referring to the scrotum. Usually an acute abdominal series is ordered, which shows considerable amounts of stool throughout the colon if constipation is the problem. Displacement of bowel away from an area of the abdomen is usually a harbinger for an abdominal mass. Most abdominal masses originate in genitourinary organs and should be evaluated immediately (Chandler and Gauderer, 2004) (Table 125-1). The most common malignant abdominal tumor in infants is

TABLE 125-1 Distribution of Abdominal Masses of 280 Patients in the Neonatal Period*

TYPE	NO.
KIDNEY (65%)	
Hydronephrosis (e.g., UPJ obstruction, UVJ obstruction, ureterocele)	80 (28%)
Multicystic kidney	63 (22%)
Polycystic kidney disease	18
Renal vein thrombosis	5
Solid tumor	13
Ectopy	4
TOTAL	183
RETROPERITONEUM (9%)	
Neuroblastoma	17
Teratoma	3
Hemangioma	1
Abscess	4
TOTAL	25
BLADDER (1%)	
Posterior urethral valves	2
FEMALE GENITAL SYSTEM (10%)	
Hydrocolpos	16
Ovarian cyst	13
TOTAL	29
GASTROINTESTINAL (12%)	
Duplication	17
Giant cystic meconium ileus	4
Mesenteric cyst	3
Ileal atresia	2
Volvulus (ileum)	2
Teratoma (stomach)	1
Leiomyosarcoma (colon)	1
Meconium peritonitis with ascites	1
Ascites	1
TOTAL	32
HEPATIC OR BILIARY (3%)	
Hemangioma (liver)	3
Solitary cyst (liver)	2
Hepatoma	1
Distended gallbladder	1
Choledochal cyst	1
Adenomatoid malformation of the lung	1
TOTAL	9

*Distended bladder, hepatomegaly, and splenomegaly were excluded in most series.

UPJ, ureteropelvic junction; UVJ, ureterovesical junction.

Data from [Griscom, 1965](#); [Emanuel and White, 1968](#); [Raffensperger and Abousleiman, 1968](#); [Wedge et al, 1971](#); and [Wilson, 1982](#).

neuroblastoma, followed by Wilms tumor ([Golden and Feusner, 2002](#)). Children with neuroblastoma typically relate a history of more constitutional symptoms than children with Wilms tumor. In newborns, the most common cause of an abdominal mass is hydronephrosis. If an abdominal mass is suspected, an abdominal ultrasound evaluation should be ordered. If the mass is solid, computed tomography (CT) or magnetic resonance imaging (MRI) is almost always required.

Scrotal Symptoms

A boy with acute scrotal pain must be presumed to have spermatic cord torsion regardless of age until proved otherwise. However, in some cases, an accurate history may save the boy an unnecessary surgical exploration. It is particularly important to interview the child as well as the parent. The differential diagnosis of acute scrotal pain includes testicular torsion, torsion of the appendix testis or appendix epididymis, epididymitis/orchitis, hernia/hydrocele, trauma, sexual abuse, tumor, idiopathic scrotal edema, dermatitis, cellulitis, and vasculitis such as Henoch-Schönlein purpura ([Gatti and Murphy, 2007](#)). Gradual onset of scrotal pain is more consistent with epididymitis, whereas abrupt pain suggests torsion of the spermatic cord or one of the appendices. Associated scrotal wall swelling, erythema, and superior displacement of the testis with an absent cremasteric reflex are very suggestive of spermatic cord torsion. However, the absence of edema or erythema or the presence of a cremasteric reflex does not rule out the possibility of acute testicular torsion, especially if the onset of pain was recent. The classic presentation of testicular torsion is the sudden onset of severe, unilateral pain that is often associated with nausea and emesis. A history of similar intermittent episodes may suggest intermittent testicular torsion. Traditionally, significant ischemic damage is believed to occur after 4 to 8 hours. **Testicular torsion represents a true surgical emergency**, and institutional transfers should be kept to a minimum, pending surgery and anesthesia availability. Patients presenting after 8 hours should still undergo surgical exploration because the viability of the testis is difficult to predict ([Beard et al, 1977](#); [Bartsch et al, 1980](#)).

Infants and children with an inguinal hernia or a hydrocele that changes in volume should be seen soon after diagnosis and more urgently if there is a history of inguinal or scrotal pain. Not all of these children need emergency surgery, but a few require surgical intervention within a short period. If there is a history of scrotal or inguinal pain, the child's parents should be taught to recognize the signs of an incarcerated inguinal hernia and instructed to go to the emergency department if symptoms occur before the planned surgical correction. **Infants with asymptomatic hydrocele rarely require surgery initially.** In most cases, the hydrocele resolves in the first year of life. We make an exception if the hydrocele is particularly large or palpable in the inguinal region. A large hydrocele with a palpable inguinal component or one that is enlarging may indicate the presence of an abdominoscrotal hydrocele. This type of hydrocele does not resolve spontaneously and usually enlarges tremendously. This hydrocele should be corrected usually at 6 to 12 months of age; an initial scrotal incision that decompresses the hydrocele makes the repair easier ([Luks et al, 1993](#); [Belman, 2001](#)).

Boys with undescended testes are among the most common referrals to the pediatric urologist. Undescended testes are present in 30% of preterm neonates and are present in 3% of full-term male infants at birth ([Ghirri et al, 2002](#); [Boisen et al, 2004](#)). Few undescended testes descend after 6 months of age. Although undescended testes do not represent a surgical emergency, **exploration for an undescended or absent testis should occur between 6 and 18 months of age** ([Berkowitz et al, 1993](#)). The only true emergency in cryptorchidism is a newborn phenotypic boy with bilateral nonpalpable testes because this patient may be a very masculinized girl with congenital adrenal hyperplasia (CAH). In prepubertal boys, concern for an undescended testis often reflects a retractile testis that results from a brisk cremasteric reflex and does not require surgical intervention. A retractile testis must be differentiated from an ascending testis, which may require an orchidopexy.

Varicocele is uncommon in a prepubertal boy but increases in incidence to around 15% by 15 years of age ([Schiff et al, 2005](#)). Varicoceles are primarily left-sided (90%) ([MacLellan and Diamond, 2006](#)). A right-sided varicocele in the absence of a left-sided varicocele should prompt an evaluation for a retroperitoneal process causing pressure on the right testicular vein. The initial gauge of testicular health is growth of the testes through puberty as measured by testis volume (via orchidometer or ultrasonography) ([Diamond et al, 2000](#)). Total testicular volume appears to correlate

more with future semen analysis than differential testicular volume; however, neither total nor differential testicular volume is a very good predictor of semen parameters (Christman et al, 2014). After puberty, semen analysis and hormonal levels should guide further treatment.

Prepubertal testicular and paratesticular tumors should be considered in the differential diagnosis of a scrotal mass. Although much less common than epididymal cysts or spermatoceles, a complaint of a painless testicular or paratesticular mass should be addressed immediately. A physical examination and scrotal ultrasonography should determine if the mass is concerning for neoplasia. In a contemporary series from a tertiary center, the most common prepubertal testis tumor was a teratoma followed by rhabdomyosarcoma, epidermoid cyst, yolk sac tumor, and germ cell tumor (Metcalf et al, 2003). This histologic distribution was corroborated by a multicenter review including four tertiary pediatric hospitals that demonstrated that 74% of prepubertal testicular tumors were benign, the most common being teratoma (48%). Yolk sac tumor accounted for only 15% of the tumors (Pohl et al, 2004). Although testicular tumors may arise in neonates as well as adolescents, the peak incidence of tumors in young children and infants occurs at age 2. In this specific population, yolk sac tumors are most common, and approximately 75% of tumors are malignant (Levy et al, 1994; Ciftci et al, 2001). Tumors of nontesticular origin such as leukemia and lymphoma must also be considered in pediatric patients.

Male Penile or Urethral Symptoms

Boys with painful priapism must be evaluated immediately. Pain may suggest ischemia of the corpus cavernosa, which can progress to corporeal fibrosis if untreated. Children with sickle cell anemia are especially at risk for priapism, with 75% of patients experiencing their first episode by age 20 years (Mantadakis et al, 1999; Adeyoyu et al, 2002). Outpatient treatment of this condition with penile corporeal aspiration and intracavernous injection of sympathomimetic drugs has been successful. Oral agents such as terbutaline or pseudoephedrine are not recommended in the management of acute ischemic priapism (>4 hours) (Montague et al, 2003).

Paraphimosis also requires immediate attention and manual reduction. In children, this procedure often requires a lidocaine penile block and some level of sedation. Conversely, phimosis is physiologic in young infants, and attempts to retract the foreskin manually in boys younger than 2 to 3 years old should be avoided. Phimosis in older children (potty trained) is typically treated with one or two courses of low-dose steroid cream and circumcision if medical treatment is unsuccessful (Ashfield et al, 2003).

Boys with hypospadias are seen routinely. Normally, we initiate the evaluation in the newborn period because most parents of a child with a congenital anomaly, even a relatively minor one such as hypospadias, desire an early opportunity to speak with a surgical specialist.

We evaluate children who have developed a complication after circumcision at the convenience of the family as long as there is no active bleeding, the child is voiding normally, and there is no injury to the penile shaft or shaft skin. Narrowing of the preputial ring after circumcision (cicatrix) may result in a trapped penis (Casale et al, 1999; Gillett et al, 2005). These infants usually can be managed with application of petroleum jelly to the penis for 4 to 6 weeks as healing continues. Alternatively, one or two courses of low-dose steroid cream as used for phimosis may also soften up the cicatrix enough to retract the ring and make the glans visible. As long as voiding remains normal during this period, the revision of the circumcision may be postponed until age 4 to 6 months when an outpatient surgical procedure can be performed. A more common complication, urethral meatal stenosis, may manifest at 6 months of age in circumcised infants (Upadhyay et al, 1998; Ahmed et al, 1999). This problem is also easily corrected in the office with a meatotomy under local anesthesia (Smith and Smith, 2000).

Female Genital Symptoms

Infant girls with introital masses commonly present to the pediatric urologist's outpatient office (Fig. 125-1). Vaginal masses may be palpable or may protrude from the introitus. The differential diagnosis of interlabial masses includes benign paraurethral cysts, hymen skin tags, urethral prolapse, imperforate hymen, prolapsed ureterocele, or, rarely, malignancies such as a vaginal rhabdomyosarcoma. Bladder outlet obstruction may result from a prolapsed ureterocele. Most of these lesions are differentiated by physical examination, but historical information such as pain, bleeding, or voiding difficulties helps solidify the diagnosis.

Urethral prolapse is relatively common, particularly in young African-American girls. Figure 125-1C shows urethral prolapse in a young girl. A urethral catheter demonstrates the circumferential prolapsed urethral tissue. The prolapse is through the meatus, forming a hemorrhagic, sensitive doughnut-shaped mass that bleeds with palpation or when in contact with the undergarments. Girls may have difficulty with urination depending on the size of the prolapse and whether it compromises the urethral meatus. Urethral prolapse often responds to topical application of estrogen and may be managed expectantly as long as voiding is normal (Redman, 1982). Rarely surgical excision is required.

Benign and malignant tumors of the vagina should be considered when vaginal bleeding occurs in young girls. A broad spectrum of entities including capillary hemangioma, rhabdomyosarcoma, and carcinoma may be associated with vaginal bleeding. Labial masses may be associated with hernia or hydrocele of the Nuck canal (Kizer et al, 1995). Labial adhesions (labia minora) are common and usually asymptomatic. Occasionally, a girl with labial adhesions complains of vaginal irritation from pooled urine. In this case, if the labial adhesions are not separated, the irritation may progress to irregular voiding that may exacerbate the problem of frequency and urgency. In some girls, a short course of estrogen cream applied to the labia may be effective; however, in many cases, separation of the adhesions, performed in the office after application of a local anesthetic cream, is required. Dense labial fusion may be associated with CAH, gonadal dysgenesis, or cloaca (Powell et al, 1995). A genitosinogram may be indicated in cases in which the urethra cannot be distinguished from the vaginal orifice and a urogenital sinus is suspected. Endoscopy of the common channel, urethra, and vagina and, in some cases, MRI have become more useful for surgical planning.

An adolescent girl who has not menstruated and in whom there is concern about a uterine or vaginal anomaly should be evaluated promptly. Many of these girls have an imperforate hymen or uterine anomaly that results in poor uterine drainage that may be uncomfortable. If such conditions are left untreated, retrograde drainage of the uterus may place the patients at risk of endometriosis and infertility (Rock et al, 1982). Patients with complete androgen insensitivity can also present with primary amenorrhea. Pelvic ultrasonography or MRI can delineate the anatomy further and guide intervention if necessary.

Sexual Abuse

Although genital injuries may be accidental, the possibility of physical or sexual abuse must be considered in all cases of genital trauma in girls or boys. Sexual abuse is common and includes any activity with a child before the age of legal consent that is for sexual gratification of an adult or a significantly older child. Sexual intercourse includes vaginal, oral, or rectal penetration, defined as entry into an orifice with or without tissue damage. Sex acts perpetrated by young children are learned behaviors and are usually associated with experiencing sexual abuse or exposure to adult sex or pornography. In 2011 in the United States, there were more than 850,000 reported cases of child maltreatment, including 61,472 cases of sexual abuse. More than half of these children were prepubertal at the time of the abuse. The perpetrator of the sexual abuse was most commonly a friend or neighbor, followed by a relative or day care worker (U.S. Department of Health and Human Services, 2012).

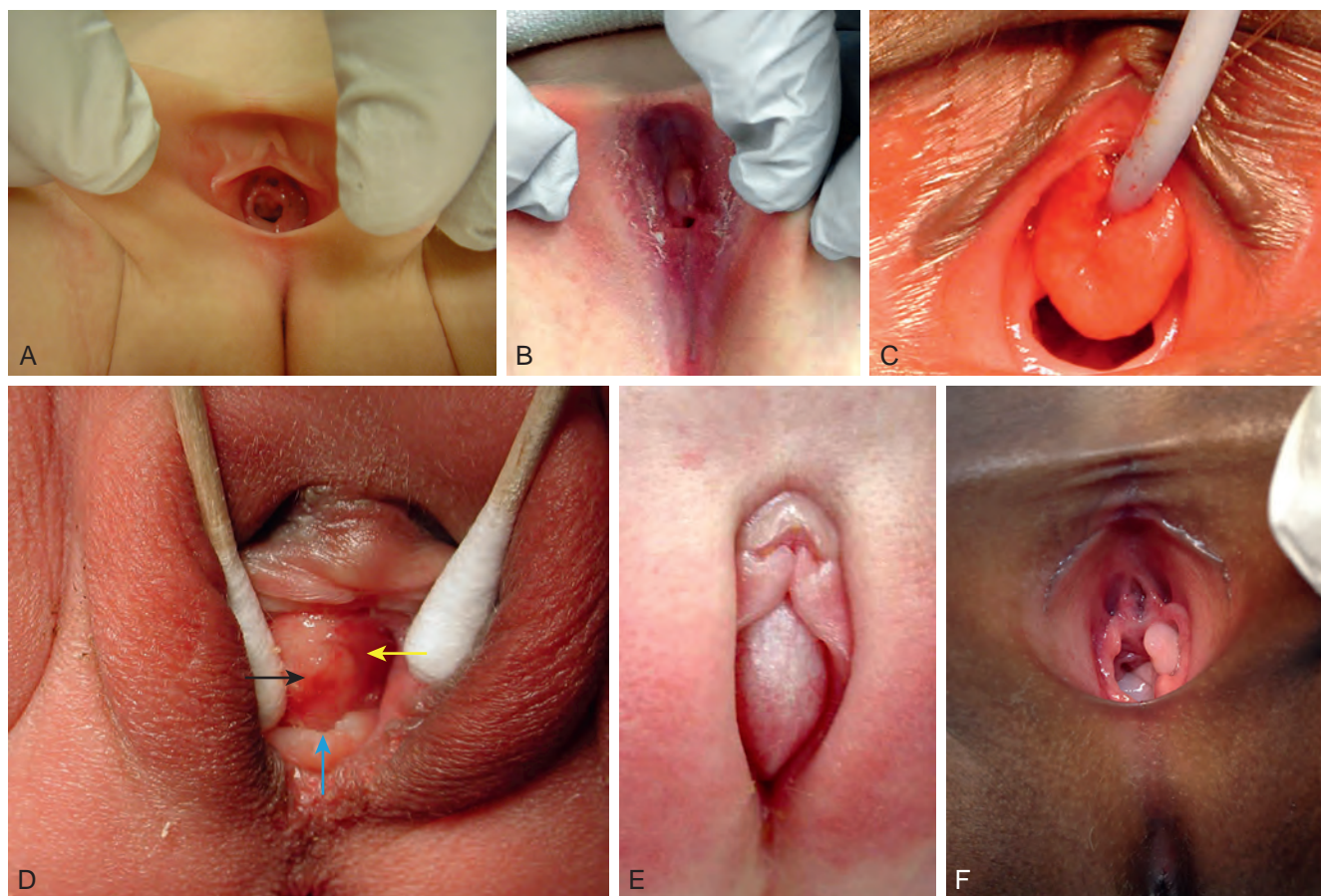


Figure 125-1. Female perineum examination. A, Normal. B, Labial adhesions. C, Urethral prolapse. D, Skene gland cyst (black arrow) with distorted urethral meatus (yellow arrow) and hymen (blue arrow). E, Imperforate hymen. F, Vaginal rhabdomyosarcoma.

The peak incidence of sexually transmitted infection is seen in the 10- to 14-year age group (Pandhi et al, 2003). In a study of women presenting to an urban sexual assault clinic, 43% were adolescents (Jones et al, 2003). Pelvic inflammatory disease rates are highest in females age 15 to 25 with 33% of infections in girls younger 19 years (Jenkins, 2000). Any pediatric patient with a sexually transmitted infection should be evaluated for sexual abuse. Although mode of transmission of human papillomavirus and herpes simplex virus is often unclear, *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infections in a prepubertal child should be reported to Child Protective Services (Bechtel, 2010).

The possibility of sexual abuse should be considered with associated physical symptoms, including vaginal, penile, or rectal pain, discharge, or bleeding or, less commonly, chronic dysuria, enuresis, constipation, or encopresis. In one study, 74% of pediatric patients with documented sexually transmitted infections had histories or signs of abuse (Pandhi et al, 2003). Sexual abuse should be considered when the vaginal mucosa is bruised or injected, the vaginal opening is dilated, or the hymen is damaged, showing a V-shaped notch or cleft (Walker, 1998). Despite these guidelines, the diagnosis of sexual abuse is often made by the history and not by the physical examination. In a review of 506 girls with a history of penetrative abuse referred to a sexual abuse clinic, only 11% had examination findings suggestive of sexual abuse (Anderst et al, 2009). Investigating the possibility of sexual abuse requires supportive, sensitive, and detailed history taking. Many hospitals have a sexual abuse team that can be consulted if sexual abuse is suspected. The key is to be aware of the possibilities when they might exist and to invite the team in early. A pediatric urologist is likely to be asked to evaluate the abdomen and perineum (Johnson, 2000). If abuse is suspected, it must be reported to the police. If the

perpetrator is a caregiver of the child or a parent, the state child welfare team must be contacted.

Voiding Symptoms

Voiding complaints and incontinence account for a large portion of any pediatric urology practice. Incontinence is classified as diurnal (daytime), nocturnal (nighttime), or both. If a child has never been dry, the incontinence is primary. If the child is wet after a dry interval greater than 6 months, the incontinence is secondary. **The ability to place children in categories based on the voiding history helps to focus the rest of the evaluation and guide further therapy.** The time and duration of the voiding disorder must be identified early in the interview. A thorough history obtained from the parents and the child is important to determine the actual pattern of voiding, which may differ from perceptions reported by the parent. Did symptoms begin before or after potty training? Is wetting associated with pain, urgency, or frequency? What is the character of the voiding? Is the urinary stream steady from beginning to end, or is it a stop-and-start (staccato) pattern suggestive of dysfunctional voiding? Are the symptoms worse at a particular time of the day? Does the child void frequently during the day but sleep through the night without wetting? Is wetting confined to the night, suggestive of primary nocturnal enuresis? Additionally, behavioral signs can be used to understand the etiology of functional incontinence further. Episodes of urgency in children are often suggested by holding maneuvers such as squatting, crossing legs (Vincent's curtsy), and sitting on the heel (Ellsworth and Caldamone, 2008). Poor potty habits may result in incomplete voiding or vaginal voiding. Giggle incontinence is encountered in young girls and refers to large volume incontinence that occurs only with laughter.

In this situation, the incontinence is associated with a complete emptying of the bladder and should be distinguished from stress urinary incontinence in adults because the treatment differs significantly (Berry et al, 2009).

The voiding history is incomplete without a record of the child's eating and drinking pattern. Does the child sip small amounts of water throughout the day rather than bolus drinking? Does the child drink large amounts of alternative liquids such as soft drinks, juices, or sports/energy drinks, which tend to be laden with salt and sugar and low in free water? What is the stooling pattern? Are bowel movements daily and soft, or are they firm, chunky, or pebblelike? Very few children are continent of urine and not stool. Conversely, children who retain stool nearly always retain urine. All of these are indicators of a dysfunctional emptying pattern, which may lead to urinary tract infection (UTI). Referencing a standardized stool chart, such as the Bristol stool form scale (Lewis and Heaton, 1997), may be helpful to clarify the stooling pattern further (Koh et al, 2010).

Children with daytime or nighttime wetting are evaluated routinely in the absence of other complicating problems. The care of children with nocturnal enuresis is individualized. Consideration of treatment should be reserved until after age 5. If the child does not perceive nighttime wetting as a problem, there is usually little advantage to treatment with medications or alarms. In our experience, only a few children younger than age 6 or 7 are bothered emotionally by nocturnal enuresis. Wetting during the day causes more concern and may indicate incomplete or infrequent voiding. Incomplete or infrequent voiding may lead to UTI, which may exacerbate wetting.

Although most voiding symptoms are secondary to voiding habits, more serious pathophysiology may manifest with similar complaints. After obtaining a careful history, any concerns regarding a structural etiology for voiding dysfunction should be investigated. Continuous leakage in between normal voiding patterns in a girl should raise concerns of an ectopic ureter. Symptoms suggestive of detrusor sphincter dyssynergia (e.g., difficulty emptying the bladder, urinary hesitancy, slow or weak urine stream, urinary urgency and/or frequency, dribbling urine after urination is complete) may represent occult spinal dysraphism. Urinary retention and stranguria may be caused by posterior urethral valves (PUV) or stricture in a boy or a bladder mass such as rhabdomyosarcoma in either a boy or a girl. Stranguria and retention should be red flags for the physician to delve deeper into the etiology of the symptoms. After a focused examination for epispadias, spinal dysraphism, or lower extremity weakness, a uroflow, postvoid residual, and ultrasound scan are usually appropriate first steps in the evaluation of voiding dysfunction and investigation of potential structural anomalies. Additional testing may include a voiding cystourethrogram (VCUG), retrograde urethrogram, spinal MRI or ultrasonography, and urodynamic evaluation.

Urinary Tract Infection

Febrile UTIs in newborns are treated emergently because newborns are particularly susceptible to significant renal damage if the infection is not treated promptly. These infants require intravenous antibiotics as early as possible after a urine culture has been obtained because they have a high prevalence of concomitant bacteremia (10% to 22%) (Pitetti and Choi, 2002). Appropriate antibiotic therapy administered without delay has been shown to reduce the incidence of scarring (Ransley and Risdon, 1981; Hiraoka et al, 2003). Some authors suggest this decreased incidence of scarring reflects a decreased likelihood of renal involvement rather than a true prevention of scar formation (Doganis et al, 2007).

Febrile UTIs in children older than newborns should also be treated promptly. Children of all ages with a severe UTI may be subject to renal scarring (Ransley and Risdon, 1981; van der Voort et al, 1997) and should be seen within 24 hours or sooner. **Children older than newborns with afebrile UTI should be seen semiurgently.** In practice, many of these patients are seen by their pediatrician and are seen in follow-up by a pediatric

urologist. Nearly all children with culture-proven UTI should be evaluated initially with ultrasonography, whereas the role of further evaluation with VCUG or renal nuclear scans continues to be investigated.

The evaluation for UTI is completed at the parent's convenience after the initial infection has been treated. In most cases, radiologic studies after a UTI in a child include a renal and bladder ultrasound scan looking for hydronephrosis or bladder changes that may be associated with obstruction and a VCUG to detect vesicoureteral reflux (VUR). However, a substantial number of cortical defects on technetium-99m (^{99m}Tc) dimercaptosuccinic acid (DMSA) scan occur in the absence of identifiable reflux (62% to 82%) (Majd and Rushton, 1992; Benador et al, 1997; Ditchfield and Nadel, 1998; Biggi et al, 2001; Ditchfield et al, 2002). This finding led to a re-evaluation of the role of VCUG as the initial investigation in a child with a UTI. **Infants younger than 6 months old and uncircumcised male infants are at increased risk for recurrent UTI** (Shim et al, 2009).

At the present time, the appropriate workup for a febrile UTI is in a state of flux. The American Academy of Pediatrics clinical practice guideline aims to enhance the clinical diagnosis of UTI in children 2 months to 2 years old (American Academy of Pediatrics, 2011). It attempts to rationalize the use of antibiotics for pediatric UTI and does not recommend a VCUG for a first-time febrile UTI with a normal ultrasound scan. However, the guideline based conclusions on limited and flawed data that have a very narrow scope of applicability. Very close follow-up of patients treated based on the American Academy of Pediatrics clinical practice guideline protocol is required to assess patient and physician adherence to the guideline and assess further the clinical impact in terms of population incidence of acute pyelonephritis and renal damage.

Hematuria

A practical approach to the evaluation of hematuria in children is presented in Chapter 123. Isolated microhematuria is very common and usually self-limited without a sign of an underlying disease (Vehaskari et al, 1979; Hogg, 2009). Most children with microscopic hematuria are evaluated and the source of the hematuria is never identified (Diven and Travis, 2000). The most commonly identified etiology of asymptomatic microhematuria and gross hematuria in children is hypercalciuria (Bergstein et al, 2005; Parekh et al, 2002). Microscopic hematuria in the absence of other symptoms is not an emergency in children.

Gross hematuria in children is less common than microscopic hematuria, with an estimated prevalence of 1.3 per 1000 (Ingelfinger et al, 1977). The most common diagnoses are UTI (26%), perineal irritation (11%), trauma (7%), meatal stenosis with ulceration (7%), coagulation abnormalities (3%), and urinary tract stones (2%). The most common glomerular causes of gross hematuria in children are poststreptococcal glomerulonephritis and IgA nephropathy. An antecedent sore throat, pyoderma, edema, or red blood cell casts suggest glomerulonephritis. IgA nephropathy can cause recurrent gross hematuria with flank or abdominal pain and may be preceded by an upper respiratory tract infection (Meyers, 2004). Adenovirus infection, hypercalciuria, and hyperuricosuria are other sources to consider. A renal and bladder ultrasound scan is usually performed for gross hematuria, although the yield is low (Fernbach, 1992). In contrast to adult patients, cystoscopic examination in children rarely reveals a cause for hematuria, but it should be performed when bladder pathology is a consideration.

Gross hematuria in a newborn is an emergency because it may indicate renal vein thrombosis or renal artery thrombosis. Both conditions may be life-threatening. Renal vein thrombosis has an incidence of 2 to 5 per 100,000 births, affects boys twice as often as girls, and has a left-sided predominance. The historical clinical triad includes hematuria (50%), abdominal mass (41%), and thrombocytopenia (29%) with 13% of patients presenting with all three findings. Preexisting clinical conditions associated with renal vein thrombosis include dehydration, sepsis, birth

asphyxia, congenital vein defects, polycythemia, maternal diabetes, traumatic delivery, indwelling umbilical venous catheter, and prematurity. Affected infants require resuscitation with intravenous fluids and, occasionally, anticoagulant or antithrombotic therapy (Kuhle et al, 2004; Chang et al, 2007). Renal artery thrombosis occurs primarily after umbilical artery or femoral artery catheterization; in infants of diabetic mothers; and in some cases of severe dehydration, hemoconcentration, coagulopathy, or vasculitis. The initial treatment involves withdrawal of the catheter and hydration. Both entities can be diagnosed with renal Doppler ultrasonography (Martin et al, 1988). **Gross hematuria after the newborn period, although not life-threatening, should be evaluated without delay.** Many children have an easy-to-recognize source such as UTI, urethral prolapse, trauma, and meatal stenosis with ulceration, coagulation abnormalities, or urinary tract stones. Less obvious sources include acute nephritis, ureteropelvic junction (UPJ) obstruction, cystitis cystica, epididymitis, or tumor (Diven and Travis, 2000; Meyers, 2004). Similar to adult patients, a thorough history including a specific description of the color of the urine, the presence of clots, and timing of hematuria such as terminal hematuria or hematuria on initiation of voiding should facilitate the diagnostic process. A directed history should include medications, exercise habits, propensity for bleeding diathesis, and a travel history to rule out exposure to infectious diseases such as schistosomiasis or tuberculosis.

Renal Trauma

A pediatric patient with trauma usually presents to the emergency department and is evaluated by the emergency medicine and trauma teams often with the assistance of the urology service. Blunt force trauma is the primary mechanism for major renal trauma (Mohamed et al, 2010). The kidney in children is particularly susceptible to trauma because of the limited visceral adipose tissue, limited chest wall protection, relatively increased renal size, and increased mobility of the kidney (Brown et al, 1998). A thorough history including mechanism of injury should be obtained from the patient or observers. **Epidemiologic data demonstrate that most renal injuries result from motor vehicle accidents; falls; or high-velocity activities such as sledding, skiing, all-terrain vehicle accidents, and skateboarding** (Margenthaler et al, 2002; Rogers et al, 2004). Injuries resulting from these types of accidents should alert the clinician to potential renal damage. The history should include any congenital renal anomalies, such as a UPJ obstruction, a solitary kidney, or renal ectopia. Finally, associated injuries must be evaluated. Any case of an abdominal injury in a toddler or young child without an antecedent history of blunt force trauma should be evaluated for physical abuse (Barnes et al, 2005).

Blunt force renal trauma represents a urologic emergency that requires immediate attention but does not usually require operative intervention. Conservative treatment of high-grade blunt renal injuries has been successfully described in children. Blunt trauma accounts for 89% of pediatric renal trauma with a renal exploration rate of less than 2%. Of grade IV renal injuries, 41% were successfully managed nonoperatively based on CT scan staging in hemodynamically stable children with an overall renal salvage rate greater than 99% (Buckley and McAninch, 2004). A consecutive series of 101 patients with blunt renal injury from The Children's Hospital of Philadelphia demonstrated that a nonoperative management strategy was advantageous and successful in 95% of pediatric blunt renal injuries (Nance et al, 2004). Penetrating trauma represents the remaining 11% of renal injuries with a renal exploration rate of 76%.

Children with high-grade injuries such as major vascular avulsion or extensive urinary extravasation, especially in the setting of UPJ disruptions, are at risk for failure of conservative management (Henderson et al, 2007). These patients warrant close urologic observation and repeated examinations. We recommend conservative management, recognizing that a complete evaluation is necessary to determine accurately which patients require further intervention.

Ambiguous Genitalia

Infants with ambiguous genitalia require immediate evaluation. Many infants require direct transfer from a referring hospital. **Because CAH may result in salt wasting, which may be life-threatening, infants with ambiguous genitalia must be evaluated quickly and stabilized (Forest, 2004).** If CAH is suspected, the infant should not be discharged home from the nursery before appropriate testing is complete. In some cases, a genotypic female neonate with CAH may be incorrectly identified as a male neonate. The correct diagnosis should be made as quickly as possible to establish the appropriate sex of rearing. Infants with ambiguous genitalia may also have other syndromes and may require further evaluation (Tables 125-2 and 125-3 on the Expert Consult website). A history of a discordant karyotype from an amniocentesis and infant phenotype should prompt an evaluation. The parents should be asked about a family history of infertility, amenorrhea, and infant mortality. Complete evaluation of infants with ambiguous genitalia should include evaluations from urology, endocrinology, genetics, and psychology. For differential diagnosis and treatment purposes, the most important physical finding is the presence of one or two gonads. If no gonads are palpable, all disorder of sex development (DSD) categories are possible. Of these, 46,XX DSD is most commonly seen followed by 45,X/46,XY. A palpable gonad is highly suggestive of a testis or, rarely, an ovotestis because ovaries and streak gonads do not descend. If one gonad is palpable, 46,XX DSD is less likely, whereas 45,X/46,XY, ovotesticular DSD, and 46,XY remain possibilities. If two gonads are palpable, 46,XY and rarely ovotesticular DSD are the most likely diagnoses.

In the immediate newborn period, all patients require a karyotype and laboratory evaluation by serum electrolytes, 17-hydroxycorticosteroid (17-OH) progesterone, testosterone, luteinizing hormone, follicle-stimulating hormone, and urinalysis. Chromosomal studies from an amniocentesis do not negate the need for a postnatal karyotype. When the karyotype is determined, serum analysis assists in narrowing the differential diagnosis. If the 17-OH progesterone level is elevated, a diagnosis of CAH can be made. Determining 11-deoxycortisol and deoxycorticosterone levels can help differentiate between 21-hydroxylase and 11 β -hydroxylase deficiencies. If the levels are elevated, a diagnosis of 11 β -hydroxylase deficiency can be made, whereas low levels confirm 21-hydroxylase deficiency. If the 17-OH progesterone level is normal, a testosterone/dehydrotestosterone ratio along with androgen precursors before and after human chorionic gonadotropin (hCG) stimulation helps elucidate the 46,XY DSD etiology. A testosterone/dehydrotestosterone ratio of greater than 20 is suggestive of 5 α -reductase deficiency. Serum levels of antimüllerian hormone (or müllerian-inhibiting substance) and inhibin B can also be measured in the immediate postnatal period to document the existence of normal testicular tissue. An immeasurable antimüllerian hormone level or a failure to respond to hCG in combination with elevated luteinizing hormone and follicle-stimulating hormone levels is consistent with anorchia. For the first 60 to 90 days of life, a normal gonadotropic surge occurs with a resultant increase in the testosterone level and its precursors. During this specific time period, hCG stimulation for androgen evaluation can be postponed. Examination of the internal genitalia can be achieved using many modalities, including abdominal and pelvic ultrasonography, MRI, fluoroscopy, endoscopy, and laparoscopy. An ultrasound scan should be the first radiologic examination performed because it is noninvasive, quick, and inexpensive.

Antenatal Hydronephrosis

In neonates with antenatally detected hydronephrosis and a normal bladder, the postnatal evaluation of the hydronephrosis begins within the first few days of life. Families are usually concerned about the diagnosis and anxious to establish a management plan. The postnatal evaluation can be scheduled at the family's convenience for most infants. This classification includes infants with a history of prenatal hydronephrosis who are not suspected to have bladder

TABLE 125-2 Syndromes Associated with Multisystemic Disease

SYNDROME	INHERITANCE	RENAL ANOMALIES	GENITAL ANOMALIES	ANOMALIES IN OTHER SYSTEMS
Aarskog-Scott			Shawl scrotum, cryptorchidism	Broad facies, short stature
Beckwith-Wiedemann		Wilms tumor		Macroglossia, gigantism, hepatoblastoma
Carpenter	AR		Small genitalia	Acrocephaly, polydactyly
Caudal regression		Hydronephrosis, renal agenesis	Vaginal and uterine agenesis	Imperforate anus, LS spine abnormality
Cerebro-oculofacial	AR	Renal agenesis	Cryptorchidism	Arthrogryposis, microcephaly, cataracts
CHARGE			Small genitalia	Coloboma, heart defects, ear anomalies
Cornelia de Lange			Small genitalia, cryptorchidism	Micromelia, bushy eyebrows
Curran		Renal agenesis		Acral anomalies
Donohue			Enlarged penis or clitoris	Hirsutism, elfin face, thick lips, low-set ears
Drash		Wilms tumor, glomerulonephritis	Mixed gonadal dysgenesis	
Dubowitz	AR		Hypospadias, cryptorchidism	Eczema, small stature, peculiar facies
Ehlers-Danlos	AR	Hydroureter		Skin hyperextensibility, poor wound healing
Fraser			Hypospadias, cryptorchidism	Cryptophthalmos
G			Hypospadias	Esophageal defect, low-set ears, abnormal facies
Holt-Oram		Renal anomalies		Defects of upper limb
Laurence-Moon-Biedl			Small genitalia	Obesity, retinal pigmentation, polydactyly
Marfan	AD	Renal duplication, hydroureter	Cryptorchidism	Aortic aneurysm, arachnodactyly
Mayer-Rokitansky		Renal agenesis	Duplex uterus, vaginal atresia	
Meckel-Gruber	AR	Renal cysts	Ambiguous genitalia, cryptorchidism	Microcephaly, polydactyly
Menkes		Hydronephrosis, reflux	Cryptorchidism	Kinky hair, CNS abnormality
Ochoa		Neurogenic bladder, hydronephrosis	Cryptorchidism	Aortic aneurysm, arachnodactyly
Opitz	AR		Hypospadias, cryptorchidism	Hypertelorism, mental retardation
Prader-Willi			Cryptorchidism	Hypotonia, obesity, mental retardation
Prune-belly		Hydronephrosis	Cryptorchidism	Hypoplastic abdominal muscle
Robert	AR	Hydroureter	Hypospadias, large penis, cryptorchidism	Hypomelia, growth retardation
Robinow	AD		Small genitalia, cryptorchidism	Flat face, short forearms
Rubinstein-Taybi	AR		Chordee	Hypoplastic maxilla, broad thumbs and toes
Rudiger	AR	Hydroureter	Small penis	Bicornuate uterus, coarse facies, stub nose
Russell-Silver	AR	Nonspecific renal anomalies	Small penis, hypospadias, cryptorchidism	Short stature, café au lait spots, skeletal asymmetry
Seckel	AR		Small genitalia, cryptorchidism	Small head, beak nose

Continued

TABLE 125-2 Syndromes Associated with Multisystemic Disease—cont'd

SYNDROME	INHERITANCE	RENAL ANOMALIES	GENITAL ANOMALIES	ANOMALIES IN OTHER SYSTEMS
Smith-Lemli-Opitz	AR		Hypospadias, cryptorchidism	Pernicious anemia, mental retardation, syndactyly, microcephaly
VATER		Hydronephrosis, renal dysplasia	Hypospadias	Vertebral anomalies, anal atresia, VSD, TE fistula, radial dysplasia
von Hippel-Lindau		Renal cyst, renal tumor		Pancreatic cyst, cerebral tumor, ichthyosis
Wolfram	AR	Hydroureter		Optic atrophy, deafness, diabetes
Zellweger	AR	Hydroureter	Hypospadias, cryptorchidism	Hypotonia, hepatomegaly

AD, autosomal dominant; AR, autosomal recessive; CHARGE, coloboma, heart anomaly, choanal atresia, retardation, and genetic and ear anomalies; CNS, central nervous system; LS, lumbosacral; TE, tracheoesophageal; VATER, vertebral, anal atresia, tracheoesophageal, renal; VSD, ventricular septal defect.

Data from Barakat AY, Seikaly MG, Perkaloustian VM. Urogenital abnormalities in genetic disease. J Urol 1987;136:778–85; Walker RD. Familial and genetic urologic disorders in childhood. AUA Update Series 1987;6:1–6; and Mininberg D. The genetic basis of urologic disease. AUA Update Series 1992;9:218–23.

TABLE 125-3 Chromosomal Syndromes Associated with Genitourinary Anomalies

CHROMOSOME NUMBER	CLINICAL FEATURES	RENAL ANOMALIES	GENITAL ANOMALIES
4 autosome	Microcephaly	Hydronephrosis	Hypospadias
Wolf-Hirschhorn syndrome	Hemangiomas		Undescended testis
4p trisomy	Hypertelorism		
4q	Cleft lip/palate Low-set ears		
8 autosome	Large, square head	Hydronephrosis	Hypospadias
Trisomy 8	Prominent forehead Widely spaced eyes Slender body and limbs	Horseshoe kidney Reflux	Undescended testis
9 autosome	Small cranium	Renal hypoplasia	Hypospadias
9p trisomy, 9p tetrasomy	Strabismus	Pancake kidney	Undescended testis
9p monosomy	Large nose Webbed neck		Infantile male genitalia
10 autosome	Microcephaly	Cystic kidney	Undescended testis
10q syndrome	Oval, flat face	Hydronephrosis	Small penis
10p syndrome	Microphthalmia Short neck		
11 autosome		High forehead Micropenis	
11q syndrome	Flat nose Wide glabella Cleft lip/palate		
13 autosome	Microcephaly	Horseshoe kidney	Undescended testis
Patau syndrome	Hypertelorism	Hydronephrosis	
Trisomy 13	Polydactyly Congenital heart disease	Cystic kidney	
15 autosome	Obesity		Hypogonadism
Monosomy 15q	Hypotonia		Cryptorchidism
Prader-Willi syndrome	Retardation		
18 autosome	Micrognathia	Horseshoe kidney	Undescended testis
Trisomy 18	Hypertonia	Hydronephrosis	Small penis
Edwards syndrome	Congenital heart disease		

TABLE 125-3 Chromosomal Syndromes Associated with Genitourinary Anomalies—cont'd

CHROMOSOME NUMBER	CLINICAL FEATURES	RENAL ANOMALIES	GENITAL ANOMALIES
20 autosome	Round face	Hydronephrosis	Hypospadias
20p syndrome	Short nose Dental abnormalities Vertebral abnormalities	Polycystic kidney	
21 autosome	Brachycephalic skull		Undescended testis
Trisomy 21	Congenital heart disease		Small penis
Down syndrome	Nasal hypoplasia Broad, short hands		
22 autosome	Microcephaly		Undescended testis
Trisomy 22	Preauricular skin tags Low-set ears Beaked nose Cleft palate		Small penis
Cat-eye syndrome	Coloboma	Renal agenesis	
Possibly from both 13 and 22 autosomes	Anal atresia Low-set ears Hemivertebrae Congenital heart disease	Horseshoe kidney Reflux	
Sex chromosome Y	Elongated legs		Small penis
Klinefelter syndrome	Gynecomastia		Small testes
XXY,XXXY	Eunuchoid body build		
XXXXY	Sparse body hair		
Sex chromosome	Short stature	Horseshoe kidney	Infantile genitalia
X Turner syndrome	Primary amenorrhea		
XO	Webbed neck Broad chest Coarctation of aorta		

Data from Barakat AY, Seikaly MG, Derkaloustian VM. Urogenital anomalies in genetic diseases. J Urol 1986;136:778–85; Walker RD. Familial and genetic urologic disorders in childhood. AUA Update Series 1987;6:1–6; and Mininberg D. The genetic basis of urologic disease. AUA Update Series 1992;9:218–23.

outlet obstruction based on the postnatal ultrasound scan. Additionally, the ultrasound scan must not demonstrate bilateral severe hydronephrosis, a solitary kidney, or a thickened bladder wall, and the infant should be thriving.

The postnatal history should also include the sex of the infant, laterality of the hydronephrosis, the level of obstruction (i.e., UPJ, ureterovesical junction, urethra), gestational age of onset, history of oligohydramnios, and any other associated anomalies. Access to prenatal records and fetal ultrasound scans is extremely useful. Additional tests to be scheduled include a repeat ultrasound scan and possibly a VCUG (for VUR or PUV) or a ^{99m}Tc mercaptoacetyltriglycine (MAG3) diuretic renal scan (for renal function and drainage). Most neonates are maintained on amoxicillin prophylaxis until this postnatal evaluation is completed. The differential diagnosis for antenatal hydronephrosis most commonly includes UPJ obstruction, VUR, ectopic ureter, ureterocele, megaureter (ureterovesical junction obstruction), multicystic dysplastic kidney, PUV, prune-belly syndrome (PBS), and megacystis-microcolon syndrome.

Certain conditions require more immediate intervention, especially when bladder outlet obstruction is present. If PUV are considered, the bladder should be drained with a feeding tube, and a VCUG should be performed at an appropriate interval. Conversely, if PBS is considered, urethral catheterization should be avoided if possible to minimize the risk of UTI. Additionally, a ureterocele may obstruct the bladder outlet and result in bilateral upper tract dilation. This situation can be ameliorated by placement of a urinary catheter.

An increasing number of pregnant women carrying a fetus with hydronephrosis seek prenatal evaluation with the urologist. These visits are scheduled within a week from the time of referral unless the following conditions exist: (1) There is bilateral hydronephrosis or hydronephrosis in a single system kidney, (2) there is oligohydramnios, and (3) there is evidence of significant cystic renal disease in a fetus less than 22 weeks' gestational age. In these cases, a more rapid consultation is preferred. After discussion with an obstetrician specializing in high-risk pregnancy, fetal intervention may be indicated in some cases of oligohydramnios, bladder outlet obstruction, and retained adequate renal function.

Congenital Anomalies in Neonates

Patients with major abdominal defects such as classic bladder or cloacal exstrophy require direct admission to the neonatal intensive care unit for stabilization and surgical planning. In many cases, a team is assembled and provides orthopedic, general surgical, and urologic care during the surgery (Jeffs, 1978; Lattimer et al, 1979; Gearhart, 1999). Patients with imperforate anus and variants such as a cloacal anomaly require initial decompression of the intestinal tract, usually within the first 24 to 48 hours (Chen, 1999). At the time of the colostomy, the urologist may evaluate the perineum and perform endoscopy to assess the urinary anomalies further. Procedures to correct these major defects must be planned by surgeons who are familiar with the potential risks and complications associated with the reconstruction of the urethra, vagina, and colon. The anesthesia team and neonatologists must be skilled in the management of the complex metabolic changes that may occur in infants who are under anesthesia for long periods and have critical postoperative care.

Spina bifida is the most common birth defect of the central nervous system, affecting about 1500 infants born each year in the United States. For many newborns with spinal dysraphisms, the diagnosis is made in utero, and fetal repair may be offered (Adzick et al, 2011). Evaluation and follow-up of newborns with a fetal repair are similar to the evaluation and follow-up of neonates who did not undergo fetal repair. Most of these infants do not experience urinary retention initially, but many develop spinal shock after neurosurgery in the newborn period and have a transient period of overflow urinary drainage. As soon as possible after closure of the spinal defect, a baseline renal and bladder

ultrasound scan is performed to evaluate for evidence of bladder or upper tract abnormalities. An initial urodynamic investigation is performed after resolution of the spinal shock to ensure that bladder storage pressures are not excessive (Bauer, 1998; Adzick et al, 2011). High-risk infants (infants with a detrusor leak point pressure >40 cm H₂O or detrusor-sphincter dyssynergia) are started on anticholinergic therapy and intermittent catheterization (Snodgrass and Adams, 2004). Infants with normal urodynamic findings require close follow-up because of the risk for subsequent neurologic deterioration secondary to spinal cord tethering (Tarcen et al, 2001).

KEY POINTS: CHIEF COMPLAINT AND HISTORY OF PRESENT ILLNESS

- Pediatric diagnoses should be triaged into the following categories: emergent, urgent, semiurgent, and routine.
- Acute scrotal pain must be evaluated emergently because of the risk of spermatic cord torsion, regardless of age.
- Neonates with bilateral hydronephroses or hydronephrosis in a solitary kidney should be evaluated immediately after birth in the newborn nursery.
- If CAH is suspected, the evaluation should be completed before hospital discharge.
- If sexual abuse is suspected, the sexual abuse team should be immediately consulted, and appropriate interventions should be initiated.

PAST MEDICAL AND SURGICAL HISTORY

A past medical and surgical history is always germane to the patient's current history and often provides insight into the current condition. Many pediatric congenital syndromes include urologic anomalies (see Tables 125-2 and 125-3 on the Expert Consult website), and the pediatric urologist should be aware of these associations. Additionally, an assessment of the child's developmental progress may be relevant to their urologic development, especially in the context of potty training and enuresis. A summary of developmental milestones is provided in Table 125-4.

Other pediatric conditions affect the timing of surgical intervention and affect the level of risk from anesthesia. In healthy children, a recent history of a respiratory illness or reactive airways disease increases the risk of general anesthesia (Schreiner et al, 1996; Parnis et al, 2001). Preterm infants are also at increased risk of anesthetic complications and postoperative apnea. As a result, many of these infants require postoperative cardiopulmonary monitoring. Neonates with a history of apnea are at highest risk (Murphy et al, 2008). Other infants have severe cardiac anomalies and may benefit from a pediatric anesthesiologist with cardiac experience. Although the pediatric anesthesiology team assesses the child for anesthetic risk, the pediatric urologist should be aware of these conditions as well. Finally, all bleeding dyscrasias, such as von Willebrand disease, should be evaluated by a pediatric hematologist before surgery.

MEDICATIONS AND ALLERGIES IN PEDIATRIC PATIENTS

Medications are typically dosed based on weight (e.g., milligrams per kilogram). An accurate weight must be obtained in pediatric patients before prescribing most medications. Additionally, many adult medications are contraindicated in children, and pediatric guidelines should be consulted. For example, aspirin has been associated with Reye syndrome in children and adolescents and is not recommended for the treatment of fever in children. Acetaminophen (10 to 15 mg/kg every 4 hours) or ibuprofen (5 to 10 mg/kg every 6 hours) is not associated with significant

TABLE 125-4 Developmental Milestones

AGE (mo)	GROSS MOTOR	FINE MOTOR	SOCIAL SKILLS	LANGUAGE
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with one hand held	Releases an object on command	Comes when called	1-2 meaningful words
18	Walks upstairs with assistance	Feeds from a spoon	Mimics actions of others	At least 6 words
24	Runs	Builds a tower of 6 blocks	Plays with others	2- to 3-word sentences

From Haslam RHA. Neurological examination. In: Behrman R, Kliegman R, Jenson H, editors. Nelson textbook of pediatrics. 16th ed. Philadelphia: Saunders; 2000.

adverse effects. However, overdoses of acetaminophen can lead to hepatic failure. Trimethoprim-sulfamethoxazole is contraindicated in preterm infants and full-term infants younger than 2 to 3 months old because of the risk of kernicterus. Sulfonamide medications can be initiated after 2 to 3 months of age (Fefer and Ellsworth, 2006).

Allergies should be recorded for all patients and be clearly documented. Among pediatric patients with urologic problems, children with myelomeningocele and children with an increased number of operations and/or surgery in the neonatal period are at increased risk for latex allergies, and latex precautions should be instituted in these patients (Pires et al, 2002).

KEY POINTS: PAST MEDICAL AND SURGICAL HISTORY AND MEDICATIONS AND ALLERGIES IN PEDIATRIC PATIENTS

- Congenital urologic anomalies are often associated with known syndromes, and the pediatric urologist should be aware of concurrent conditions.
- Pediatric pulmonary conditions have a direct impact on the anesthesia risk and should be evaluated before surgical intervention.
- Aspirin is associated with Reye syndrome and should be avoided in children.
- Patients with myelomeningoceles are at greater risk for latex sensitivity, and latex precautions should be used.

PEDIATRIC UROLOGIC EXAMINATION

General Examination

In most cases, the primary care physician has identified a problem that requires review by a pediatric urologist. However, because other processes may coexist, the urologist must be alert for evidence of disease in other organ systems. Although few children are severely ill when evaluated in the urologist's office, it is important to develop the skills to recognize an infant or child who requires hospitalization. The ability to determine when an infant requires an inpatient admission is particularly important because the metabolic reserve is less abundant in a newborn (Park, 2000). When attempting to determine the severity of illness, particularly in an infant or small child, observation of the child and a careful history from the parent may be more important than the vital signs or the physical examination. The child's color (pale or cyanotic), level of alertness, response to the parent's comforting, and quality of interaction with the examiner and the quantity of tearing while crying may provide considerable information about mental status and level of hydration. If the child's response in any of these areas suggests severe illness, the child should be transferred to the

emergency department, where appropriate resuscitation can be delivered while the diagnostic evaluation continues. In the acute emergency department setting, a full general and urologic examination must be performed by the evaluating medical team. Patients with hemodynamic instability must be emergently addressed.

In the office, vital signs should be recorded for every new patient, and for children with a history of renal anomalies or VUR, vital signs should be recorded on all subsequent visits. Because **blood pressure and heart rate change as a function of age**, reference ranges for blood pressure and pulse rates for boys and girls should be posted in the clinic near where the vital signs are taken (Bernstein, 2000). Assistants taking the blood pressure should be aware of the variation with age and should notify the team of blood pressure readings greater than the 90th percentile. On entering the room, a clinician can address both the child and the parent to encourage the child to participate in the examination process. Physical examination in young children can be challenging, and the clinician must attempt to create a favorable environment. Examining a child on his or her mother's lap can be useful in comforting a frightened child. Additionally, sitting or kneeling near a young child facilitates interaction at the child's level.

Abdominal and Flank Examination

When examining the abdomen, the examiner's other hand should be placed behind the flank to help palpate the kidney on either side. If the abdomen is supple, the approximate size and location of each kidney may be determined with deep palpation. An attempt should be made to feel the liver edge, spleen, and colon, particularly the descending colon. In the newborn, the liver may be palpable, sometimes 2 cm below the ribs on the left. When examining the left lower quadrant, an estimate should be made of the volume of stool in the descending colon. In infants, a large amount of gas may be present within the gastrointestinal tract. The abdominal wall is normally weak, especially in premature infants. An abdominal examination can be performed on a crying infant during inspiration when the anterior abdominal muscles are relaxed. Separation of the rectus muscles and umbilical hernias are common in newborns. The abdominal wall is lax and protuberant in boys with PBS. Occasionally, children with other types of bladder outlet obstruction or profound antenatal hydronephrosis also have considerable laxity of the abdominal muscles. The abdomen should be inspected for other abnormalities, such as ventral hernia, flaring of the rib cage, umbilical leakage, mass, or hernia. Unusual masses should be investigated immediately with ultrasonography.

Renal pathology is the cause of two thirds of neonatal abdominal masses (Pinto and Guignard, 1995). Cystic abdominal masses include hydronephrosis; multicystic dysplastic kidney; adrenal hemorrhage; hydrometrocolpos; intestinal duplication; and choledochal, ovarian, omental, or pancreatic cysts. Solid masses include neuroblastoma, congenital mesoblastic nephroma, hepatoblastoma, and teratoma. A solid flank mass may be due to renal venous thrombosis, which becomes apparent with signs of hematuria, hypertension, and thrombocytopenia. In neonates,

transillumination of the abdomen may assist in distinguishing between solid and cystic lesions.

Abdominal distention at birth or shortly afterward suggests either obstruction or perforation of the gastrointestinal tract often secondary to meconium ileus. Later distention suggests bowel obstruction, sepsis, or peritonitis. Abdominal wall defects may be present through the umbilicus (omphalocele) or lateral wall (gastroschisis). Omphaloceles are associated with other anomalies and syndromes, such as Beckwith-Wiedemann syndrome, conjoined twins, trisomy 18, meningomyelocele, and imperforate anus (Hassink et al, 1996; Chen et al, 1997; Kallen et al, 2000). In bladder exstrophy, the posterior bladder wall is visible through a midline defect in the abdominal wall, and a pubic diastasis is appreciated. In addition, a bifid clitoris or epispadias is present. In cloacal exstrophy, an omphalocele is superior to the cecal plate and lateral bladder halves with prolapsed ileum typically in the midline. A bifid clitoris or penis, imperforate anus, and spinal abnormalities also are present.

Many patients presenting with blunt force renal trauma have associated extrarenal injuries such as other solid organ injuries, a pneumothorax, pelvic fractures, and bladder or urethral injuries, and a complete physical examination is essential (Margenthaler et al, 2002; Mohamed et al, 2010). During an examination for renal trauma, the urine should be assessed for gross hematuria. Insertion of a urethral catheter should be postponed in the setting of gross hematuria until the lower urinary tract is assessed by the urology team.

Genital Examination

Scrotal Examination

The patient should be examined in a warm room supine in the frog-leg position with both legs free. To begin the scrotal examination, the inguinal canal should be inspected on each side for signs of asymmetry or mass. The examiner's nondominant hand closes the internal inguinal ring (Fig. 125-2). This maneuver prevents an intracanalicular testis from migrating into the abdomen. The inguinal canal is palpated to identify a fullness or mass suggestive of a hernia or hydrocele of the spermatic cord. The examiner may feel a "silk glove" sign (sensation of rubbing two pieces of silk together when gently palpating the cord at the pubic tubercle with a single finger) suggestive of a thickened patent processus vaginalis that may be present if a hernia is intermittent. The examiner's dominant hand is brought down to the scrotal area, and the testis is palpated. It is important to determine size, location, and texture of both gonads, with consideration of the anatomy of the testis, the epididymis, and the vas deferens, if palpable. The undescended testis

may be found in the inguinal canal; in the superficial inguinal pouch; at the upper scrotum; or, rarely, in the femoral, perineal, or contralateral scrotal regions. In an infant with a possible DSD, a symmetrical gonadal examination (gonads palpable on each side or impalpable on both sides) suggests a global disorder such as CAH or androgen insensitivity. Asymmetry in the gonadal examination suggests a localized problem, such as mixed gonadal dysgenesis or ovotesticular DSD.

The examiner should note the development and pigmentation of the labioscrotal folds along with any other congenital anomalies of other body systems. Abnormal phallic size, the position of the urethral meatus, and the amount of penile curvature should be described, and the number of perineal orifices should be noted. Another critical finding on physical examination is the presence of a uterus that can be palpated by digital rectal examination as an anterior midline cordlike structure. A thorough general physical examination must be performed as well. Blood pressure should be measured to rule out hypertension. The presence of hyperpigmentation should also be documented. Dysmorphic features indicating syndromic manifestations (e.g., short broad neck, widely spaced nipples, or aniridia) should be noted.

The acutely painful scrotum should be examined carefully to determine the true etiology. Testicular torsion may manifest with varied clinical findings, but the involved testis often demonstrates signs such as higher riding in the hemiscrotum, a transverse orientation, an anterior epididymis, absent cremasteric reflex, and tenderness of the testis and epididymis. In contrast, torsion of the appendix testis or appendix epididymis often results in localized tenderness at the superior pole of the testis or caput epididymis and is often associated with a reactive hydrocele. Additionally, in boys with thin scrotal skin, the "blue dot" sign can be seen reflective of a necrotic appendix. Epididymitis classically has a gradual onset and is not associated with nausea or emesis (Gatti and Murphy, 2007).

The normal newborn scrotum is relatively large. Its size may be increased with the trauma of breech delivery or by a newborn hydrocele, which can be distinguished from hernia by palpation and transillumination as well as by the absence of a mass in the inguinal canal. In the absence of volume changes within the hydrocele, the processus vaginalis is usually not patent, and the newborn hydrocele resolves by 1 year of age without surgery. Persistence of a hydrocele beyond 12 to 18 months even in the absence of volume changes usually indicates a patent processus vaginalis and is an indication for surgical ligation of the processus vaginalis and incision of the scrotal component of the hydrocele. Neonatal extravaginal testicular torsion can also occur prenatally resulting in a firm, enlarged, nontender mass in the hemiscrotum that is usually associated with dark discoloration of the overlying skin. A normal scrotal examination at birth and subsequent development of erythematous, tender, edematous hemiscrotum suggests postnatal extravaginal testicular torsion and should be addressed immediately with surgical intervention if the neonate is clinically stable.

Retractile testes in some cases may be difficult to distinguish from a low undescended testicle. Placing the child in a squatting (catcher's position) or legs-crossed position sometimes relaxes the reflex and facilitates palpation of the testis. A testis is descended if it can be manipulated to the base of the scrotum and remains there after release without tension. Testes that feel tethered during manipulation and cannot be manipulated to the base of the scrotum are at risk for becoming ascending testes. If doubt exists, a second examination 6 to 18 months later may be helpful to distinguish a retractile testis from a tethered testis. As the child ages, an ascending or tethered testis (both cryptorchid testes) becomes more and more difficult to manipulate into the bottom of the scrotum (Eardley et al, 1994; Clarnette and Hutson, 1997; Davey, 1997).

Scrotal masses can be transilluminated to determine if the component is primarily fluid, such as a tense hydrocele, or solid, such as a testicular tumor. If a firm intratesticular mass is palpated, a thorough examination of the lymph nodes should be performed to evaluate for lymphoma, leukemia, or metastatic disease. Patients with a nontender testicular mass and signs of precocious puberty should be evaluated for a Leydig cell tumor or less commonly a



Figure 125-2. Clinical examination of the male groin.

Sertoli cell tumor (Agarwal and Palmer, 2006). Epididymal cysts and spermatoceles can manifest as nontender extratesticular masses but are characteristically smooth and round and located within the epididymis. A scrotal ultrasound scan can differentiate these physical examination findings further.

Varicoceles (varicosities of the internal spermatic vein) almost always occur in the left scrotum and are bilateral in about 10%. Varicoceles should always be palpated with the boy standing and shown to drain when the child is supine. Grading is as follows: grade 1, palpated with Valsalva; grade 2, palpated without Valsalva; grade 3, visible through the skin without Valsalva. If the right side only is involved or if the varicocele does not decompress when the boy is supine, a possibility exists that a retroperitoneal tumor is present and compressing the vein.

Penile Examination

In a newborn, the foreskin is adherent to the glans. These glanular adhesions should not be separated, and the glans need not be inspected if the parents do not desire a circumcision. Glanular preputial adhesions usually separate before age 4 but may persist in some boys for longer periods. **In the absence of balanitis or UTI, the prepuce should not be retracted but allowed to separate naturally (Imamura, 1997).** If symptoms do develop, topical corticosteroids have been used successfully as an alternative to circumcision in some boys with adherent foreskin (Chu et al, 1999; Monsour et al, 1999; Orsola et al, 2000; Elmore et al, 2002).

The position of the urethral meatus is almost never abnormal in the uncircumcised penis with a circumferential foreskin. If the ventral foreskin is short or absent, or if there is a ventral or dorsal curvature, the boy should not be circumcised in the nursery by the obstetrician or the pediatrician and should be re-examined as soon as possible by the urologist to determine whether hypospadias or epispadias correction may be needed. The presence of a midline dimple on the ventral penile shaft should lead one to suspect a diagnosis of hypospadias, despite a normal-appearing foreskin. The severity of hypospadias is based on the position of the urethral meatus, the presence or absence of penile curvature, and the degree of ventral penile shaft skin coverage. Occasionally, when the foreskin is pulled back before a circumcision, the distal urethra and urethral meatus are enlarged (hypospadias variant—megameatus intact prepuce). If a megameatus is identified before circumcision in a newborn, the circumcision should be cancelled. The foreskin may be removed at the time of the urethral repair. However, because normal spongiosum is present on the ventral surface of the penis, repair of the urethra is not usually difficult even after a circumcision has been performed (Duckett and Keating, 1989).

Stretched penile length and girth should be measured. If the penis in a full-term infant is less than 2.0 cm, micropenis should be suspected; a karyotype should be performed, and the hypothalamic-pituitary-testicular axis should be assayed. **The penis should be examined in relation to the scrotum for evidence of penile concealment, buried penis, or webbed penis.** In these conditions, the penis is of normal size but buried or concealed beneath a prominent pubic fat pad; trapped by a narrowed, more proximal preputial ring; or tethered to the scrotum. If the penile shaft skin is shortened, correction may require a rotational flap of inner preputial skin to provide additional coverage for the ventrum of the penis after release of the narrowed preputial ring. If a newborn clamp circumcision is performed, more penile shaft skin than indicated is often removed, resulting in a scar and sometimes a secondary trapped penis. If there is encroachment of the scrotum onto the penile shaft, circumcision should be deferred until it can be done freehand in the main operating room under a general anesthetic, usually at 4 to 6 months of age (Casale et al, 1999; Williams et al, 2000).

Female Perineal Examination

Examination of the perineum in female infants and young girls should include examination of the urethral meatus, vaginal

introitus, and anus. An easy way to examine the perineum is to grasp the labia majora gently and pull outward and slightly lateral (see Fig. 125-1). This maneuver tends to define the various perineal folds better and provide for a consistent examination in nearly all cases (Redman, 1982). The clitoris is examined for evidence of hypertrophy that may be suggestive of DSD. Additionally, an introital mass should be examined for site of origin, laterality, symmetry, and signs of infection or irritation. Placing a small feeding tube into the urethral meatus can help distinguish between an asymmetrical prolapsed ureterocele or the circular edema and congestion associated with urethral prolapse. Skene duct cysts are paraurethral in location with a bulging whitish mass superior to the vagina and may manifest with signs of maternal estrogen effects, such as breast enlargement and edema of the vaginal introitus (Soyer et al, 2007). An imperforate hymen in infancy generally appears as a midline bulging, pearly white membrane.

In an adolescent girl, the examination may be performed with the mother present if the adolescent is in agreement. In general, bimanual examination in an adolescent girl is best performed in the operating room in the dorsolithotomy position. In the office, the girl can be examined in a frog-leg position. Gently spreading the labia majora in an inferior direction allows for inspection of the clitoral area and usually of the introitus. The vestibule is assessed for any evidence of discharge. The hymen should be inspected as well as the introitus. **An imperforate hymen may result in hydrometrocolpos and a lower abdominal mass.** In older girls, a small speculum may be used to evaluate the cervix and vaginal canal. Palpation of the vaginal walls and cervix and bimanual examination of the uterus completes the examination. A Valsalva maneuver may allow adequate assessment of the introital vaginal area. Vaginal discharge can be associated with vaginal voiding and is particularly common in children who hold the urine and subsequently dribble urine into the vagina. Treatment of dysfunctional voiding results in reduced vaginal drainage. Vaginal bleeding in a preadolescent girl may result from foreign bodies such as wadded toilet paper trapped in the vagina. Occasionally, other foreign bodies inserted intentionally or accidentally may be found.

Extended Physical Examination

In addition to the abdominal and perineal examination, an examination of the back should always be performed. The lower back should be examined for any evidence of presacral dimpling or other cutaneous markers of occult spinal dysraphisms. **An “atypical” presacral dimple may indicate spina bifida or cord tethering if the dimple is off center, more than 2.5 cm from the anal verge at birth or deeper than 0.5 cm (Soonawala et al, 1999).** In a series of 207 neonates with sacral and presacral cutaneous stigmata, 40% of patients with atypical dimples were found to have occult spinal dysraphism (Kriss and Desai, 1998). Other skin markers that suggest occult spinal abnormalities include subcutaneous lipoma, dermal sinus, tail, or a localized hair tuft (hypertrichosis) (Fig. 125-3). A combination of two or more of these congenital midline skin lesions is the strongest marker of occult spinal dysraphism (Gugisberg et al, 2004). We recommend an ultrasound scan of the lumbosacral spine in a newborn if any of these conditions exists (Unsin et al, 2000; Hughes et al, 2003). In the case of equivocal ultrasound studies and in children older than 6 months, we order MRI for a complete evaluation. A brief evaluation of the upper and lower extremities and of the back is performed for any evidence of asymmetry, length discrepancy, or misalignment of the spine.

If a neurologic examination is indicated, the examination should begin with observation of the child at the outset of the visit. Delays in development (see Table 125-4) often are identified by simple observation. A note is made of the level of alertness of the pediatric patient. Factors affecting the alertness of a newborn include the time of the last feeding, room temperature, and gestational age. One should suspect an underlying metabolic or infectious cause in cases of decreased alertness. Identification of a sensory level in association with a spinal cord lesion can be very difficult in an infant.



Figure 125-3. Clinical aspects of congenital median lumbosacral cutaneous lesions. **A**, Ulcerated hemangioma centered on a dermal sinus and deviation of the gluteal furrow. **B**, Isolated port-wine stain. **C**, Human tail. **D**, Faun tail. (From Guggisberg D, Hadj-Rabia S, Viney C, et al. Skin markers in occult spinal dysraphism: a review of 54 cases. *Arch Dermatol* 2004;140:1109–15.)

Differences in color or temperature can sometimes be observed, with the skin drier and cooler below the level of the cord lesion. Children older than 4 to 5 years are often capable of detailed sensory testing; however, success depends on the ingenuity and patience of the examiner. A child with a low spinal cord lesion may have a patulous anus and absence of contraction of the anal sphincter when stimulated in the anal region by a sharp object (anal wink). Changes in bladder function, such as new-onset urinary incontinence, may indicate a spinal cord lesion.

Often, the urologist may encounter signs of nonurologic or systemic illnesses during the physical examination. In an infant, generalized edema may occur with prematurity or hypoproteinemia. Localized edema suggests a congenital malformation of the lymphatic system. When confined to one or more extremities, edema may be a presenting sign of coarctation of the aorta in association with Turner syndrome. Vasomotor instability and decreased peripheral circulation are revealed by a red or purple color in a crying infant. Scattered petechiae in the infant may be present in the scalp and face after a difficult delivery. Café au lait spots are uniformly hyperpigmented, sharply demarcated macular lesions, the hues of which vary within the normal degree of pigmentation of the individual. These may be dark brown in African-American children. They may vary in size and may be large, covering a significant proportion of the trunk or limb. One to three lesions are common in normal children. Approximately 10% of normal children have café au lait macules. They may be present at birth or develop during childhood. If there are five or more spots each more than 5 mm in diameter in prepubertal patients or six or more spots more than 15 mm in postpubertal children, neurofibromatosis 1 (von Recklinghausen disease) should be suspected.

An exceptionally large head can be familial but may also suggest hydrocephaly, a storage disease, achondroplasia, cerebral gigantism,

neurocutaneous syndrome, or an inborn error of metabolism. Dysmorphic features such as broadened epicanthal folds, widely spaced eyes, micrognathia, and low-set ears are often associated with congenital syndromes that may suggest a genitourinary problem. Preauricular sinuses and pits may be the result of imperfect fusion of the tubercles of the first and second branchial arches. These anomalies may be unilateral or bilateral, may be familial, are more common in females and blacks, and sometimes are associated with other anomalies of the ears and face. Preauricular pits are present in bronchio-otorenal dysplasia, an autosomal dominant disorder that consists of external ear malformation, bronchial fistula, hearing loss, and renal anomalies. Macroglossia can be associated with Beckwith-Wiedemann syndrome, which also includes hepatosplenomegaly, nephromegaly, and hypoglycemia secondary to pancreatic beta cell hyperplasia in a large for gestational age infant. These infants are predisposed to a specific subset of childhood neoplasms, including Wilms tumor and adrenocortical carcinoma. Webbing of the neck in a female infant suggests intrauterine lymphedema in Turner syndrome, as do widely spaced nipples with a shield-shaped chest (Stoll and Kliegman, 2000).

The skin, hair, and nails should be evaluated with special focus on congenital or metabolic problems that may be associated with brittle or abnormal hair and nails or abnormal skin dryness (see Tables 125-2 and 125-3 on the Expert Consult website). Supernumerary nipples may occur in a unilateral or bilateral distribution along a line from the anterior axillary fold to the inguinal area. They are more common in African-American infants (3.5%) compared with white infants (0.6%). Accessory nipples may not have an associated areola and may be mistaken for congenital nevi. The association of supernumerary nipples with renal or urinary tract anomalies is controversial, with differing opinions concerning the

need for evaluation of the urinary system (Grotto et al, 2001; Ferrara et al, 2009). At the present time, there is not a consensus guideline that a renal bladder ultrasound scan is or is not recommended in these cases.

KEY POINTS: PEDIATRIC UROLOGIC EXAMINATION

- Renal pathology is the cause of two thirds of neonatal abdominal masses.
- Performing a scrotal examination in the legs-crossed position facilitates palpation of the testes.
- The inner preputial skin is adherent to the glans in infants and should not be forcibly retracted in the absence of balanitis or UTI.
- The lower back should be examined for evidence of cutaneous markers suggestive of occult spinal dysraphisms.

PEDIATRIC LABORATORY EVALUATION

Urine specimens may be obtained in many different ways. In the child who is not potty trained, a bagged specimen, although the most susceptible to contamination, is the easiest and least invasive to obtain. To minimize contamination with fecal or skin flora, a hole is cut in the diaper, and the perineal bag is brought through the hole in the diaper. A parent is instructed to watch the bag, and as soon as urine is noted (which can be easily seen because the bag is visible coming through a hole in the diaper), the bag should be removed. If the specimen is collected in the office, the bag is immediately drained and the urine plated and sent to the laboratory for culture. Using this method, skin contamination of the urine specimen is minimized, and the trauma of catheterization is avoided (Falcao et al, 1999). However, positive cultures must still be confirmed with catheterized specimens to be reliable. In most cases, we encourage catheterized specimens for the diagnostic reliability they provide.

Older children generally can provide a clean midstream urine specimen. Most studies have failed to show any benefit to formal cleansing of the introitus before obtaining the specimen. After a midstream urine specimen is collected, it is sent to the laboratory for urinalysis and culture. **Pyuria is defined as more than 5 white blood cells per high-power field (HPF) for girls and more than 3 white blood cells per HPF for boys.** Infection can occur without pyuria, and, conversely, pyuria may be present without UTI. Consequently, pyuria as an isolated finding is more confirmatory than diagnostic for UTI. Nitrate and leukocyte esterase assays are usually positive in infected urine. However, if the urine has not remained in the bladder for more than 1 hour, the conversion of nitrates to nitrites may not be complete, and the chemical strip may read negative despite the presence of nitrogen-splitting bacteria in the bladder.

If the culture grows more than 100,000 colonies of a single pathogen or if there are 10,000 to 50,000 colonies and the child is symptomatic, a UTI is likely to be present. Infection is possible with lower counts when urine is obtained via catheter or suprapubic aspirate (Ma and Shortliffe, 2004). **White blood cell casts and urinary sediment suggest renal involvement,** but these are rarely identified. If the child is not symptomatic and the urinalysis is normal, it is unlikely that the urine is infected. Microscopic hematuria is common in acute bacterial and viral cystitis. Gross hematuria may be present in viral cystitis but is less common in acute bacterial cystitis. If the child is symptomatic, the urinalysis is suggestive of UTI, and the culture grows more than one organism or less than 100,000 colonies, the clinician may start treatment with an antibiotic that is effective based on the sensitivities after repeating the culture. If a second catheterized culture is negative, the antibiotics are discontinued, and close follow-up is provided. This approach is particularly important in infants who may not demonstrate the usual signs and symptoms of infection that would be present in an older child.

Microscopic hematuria is common in children. Routine office screening with urinalysis for urinary abnormalities is no longer recommended. The actual time of onset for microscopic hematuria is often unknown. Normally, the first indicator is a positive urine strip test for blood. Most strips can detect concentrations of 5 to 10 intact red blood cells per milliliter. This concentration corresponds to 2 to 5 red blood cells per HPF. Improper interpretation of the dipstick, such as delayed reading or cross-contamination of urine from other chemically impregnated pads, may result in false-positive results. The urine should be dipped, the excess urine should be tapped off, and the strip should be read immediately at the recommended time. **Confirmation of microscopic hematuria after a positive dipstick examination requires a microscopic examination of the urine for the presence of red blood cells.** Microscopic hematuria may be defined as more than 5 red blood cells per HPF in at least two of three urinalyses over 2 to 3 weeks. An absence of red blood cells in the urine with a positive dipstick result suggests hemoglobinuria or myoglobinuria. A positive dipstick on a single specimen with microscopic confirmation should be viewed as an indication for further urine testing rather than as diagnostic until persistence is confirmed on subsequent studies.

PEDIATRIC RADIOGRAPHIC EVALUATION

Ultrasonography

Ultrasonography of the kidneys, ureters, and bladder is an extension of the physical examination. Ultrasonography provides a noninvasive evaluation that does not require sedation, ionizing radiation, or contrast agent injection and can be performed at the bedside in critically ill children. Additionally, the body habitus of young children allows for accurate imaging. Older children or children with significant skeletal abnormalities such as severe scoliosis or kyphosis often require other imaging modalities to assess the kidneys and collecting system accurately. A palpable mass within the abdomen can be localized and diagnosed with the aid of ultrasonography performed by a urologist with an interest in pediatrics. The examination should evaluate not only the genitourinary system but also adjacent organs such as the adrenal glands, liver, and spleen. The echogenicity of the parenchyma of the liver and spleen should be used as a comparison to assess the parenchyma of the right and left kidney, respectively. The density of the kidney and of the renal medullary pyramids; the wall thickness and configuration of the collecting system; and the presence or absence of caliectasis, pelvictasis, or ureterectasis all are important indicators of renal and ureteral pathophysiology (Hulbert et al, 1992). The luminal diameter of the ureters, thickness of the bladder wall, and volume of the bladder before and after voiding should be recorded (Palmer, 2006). If hydronephrosis or ureterectasis is present before voiding, the kidneys and ureters should be rescanned after voiding. A skillful ultrasonographer can provide anatomic detail about the insertion of the ureters and the degree of dilation of the ureter and can identify the jet of urine as it enters the bladder (Cvitkovic et al, 2001). Ultrasonography may also be used to measure postvoid residual urine accurately (Coombes and Millard, 1994). Increased thickness of the bladder wall may be suggestive of bladder outlet obstruction from PUV or urethral atresia. Trabeculation within the bladder, bladder diverticulum, and ureteral duplication or ureterocele all are easily identified with ultrasound. Children presenting with a febrile UTI are evaluated with ultrasonography to determine if a structural anomaly is present (Giorgi et al, 2005). **Ultrasonography in the absence of comparison studies or appropriate history cannot by itself distinguish obstructive from nonobstructive hydronephrosis.** A functional study such as a diuretic renal scan or magnetic resonance urography (MRU) is usually required for diagnosis. Ultrasonography is also sensitive in detecting solid renal masses, particularly masses that measure at least 1.5 cm in largest dimension. For smaller renal masses, the ultrasound findings should be considered preliminary and should be confirmed with CT or MRI (Jamis-Dow et al, 1996).

Ultrasonography is also frequently used to examine the scrotum (Diamond et al, 2000). It may also be used to assess blood flow if spermatic cord torsion is suspected and to distinguish between epididymitis and torsion of the appendix testis in cases in which tenderness is localized to the upper pole of the testis. In the setting of acute scrotal pain, Doppler ultrasonography has been reported to have a sensitivity of 78.6% and specificity of 96.9% in diagnosing surgical and nonsurgical scrotal conditions and has replaced testicular nuclear scan to rule out torsion (Blask et al, 2002). However, false-negative ultrasonography can occur and must be confirmed by a careful physical examination. Scrotal masses are evaluated by ultrasonography. Additionally, ultrasonography may be useful in distinguishing hernia from hydrocele or identifying abdominoperineal hydroceles (Finkelstein et al, 1986). However, one should not routinely perform ultrasonography or other imaging modalities in the evaluation of boys with cryptorchidism because these studies rarely assist in decision making. Ultrasonography is inadequate for routine use, with sensitivity and specificity to localize nonpalpable testis of 45% and 78%, respectively (Tasian and Copp, 2011).

When ultrasonography is used as a first-line test in suspected occult spinal dysraphism, optimal timing of the spinal ultrasound scan is before 6 months of age. Ossification of the posterior elements after 6 months of age prevents an adequate acoustic window. Agreement between ultrasonography and MRI is good, particularly for the detection of the low-lying spinal cord (90%) (Hughes et al, 2003).

Ultrasonography is also performed during routine prenatal care. The kidneys and bladder can be visualized at 15 weeks of gestation. Further details including the renal pelvis and corticomedullary differentiation are detectable after 20 weeks of gestation (Sty and Pan, 2006). Hydronephrosis remains one of the most common abnormalities detected by prenatal sonography (Fig. 125-4). After delivery, a repeat renal and bladder ultrasound scan is performed to assess the collecting system further and determine the appropriate evaluation and treatment if necessary.

Voiding Cystourethrography

VCUG is used to identify VUR, to evaluate the anatomy of the bladder outlet (bladder neck and posterior urethra) during bladder filling and voiding, and to assess the presence of residual

urine after micturition. Additional information regarding trabeculation of the bladder, bladder diverticula, and presence or absence of urachal abnormalities may be identified with a fluoroscopic VCUG (Fernbach, 2000; Goldman et al, 2000; McDonald et al, 2000). The VCUG begins with a plain film, followed by placement of a feeding tube rather than a Foley catheter. The balloon on a Foley catheter may obscure the anatomy of the bladder neck and trigone, particularly at the beginning of the study. The percentage of bladder filling when the reflux is first identified may also be an indicator of potential resolution of VUR. On subsequent examinations, improvement in VUR may be assumed if a smaller percentage of total bladder volume is refluxing into the ureter or if the reflux occurs at a greater percentage of total bladder filling (Mozley et al, 1994). On the plain film, abnormalities of the spine (e.g., sacral agenesis or spina bifida occulta), ribs, and pelvis and the presence or absence of stones within the kidney, ureter, or bladder should be noted. The gas pattern and volume of stool is particularly important in infants and in children with dysfunctional voiding in whom constipation may be an important part of the clinical pattern. Gas should normally be present in the rectum on a plain film by 24 hours of age. The bladder should be drained, and contrast medium should be gently infused. In children in whom a ureterocele is suspected, the first few images during filling of the bladder best demonstrate the ureterocele as a filling defect in the bladder. The bladder is filled slowly, and the child voids. Later filling images may involute a ureterocele, and it may appear as a bladder diverticulum.

Voiding views must be obtained in all cases, but particularly if bladder outlet obstruction such as PUV is suspected. In children in whom VUR is suspected or in patients with an ectopic ureter, cyclic VCUG must be performed in which at least two voiding cycles are completed. In some cases, the ectopic ureter that is draining to the bladder neck must empty for additional contrast material to reflux. If a second voiding cycle is not performed, one might miss reflux into the ectopic system (Hellstrom and Jacobsson, 1999; Polito et al, 2000). It is important to image the bladder neck during voiding in girls as well as boys. The presence of a "spinning top urethra" in a school-aged girl may be an important indicator of dysfunctional voiding (Saxton et al, 1988; Soygur et al, 2004). Vaginal voiding and subsequent emptying (or failure to empty) of the vagina should also be noted, which may be seen on the postvoid views.

In patients with a urogenital sinus, contrast VCUG may be modified to image the urethra and vagina simultaneously (Fig. 125-5). In this study, the urogenital sinus is intubated with

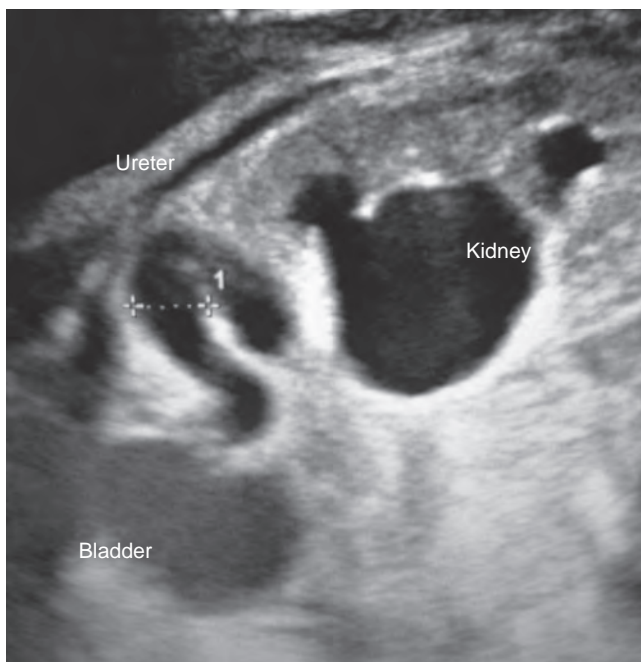


Figure 125-4. Prenatal ultrasound image showing hydronephrosis.

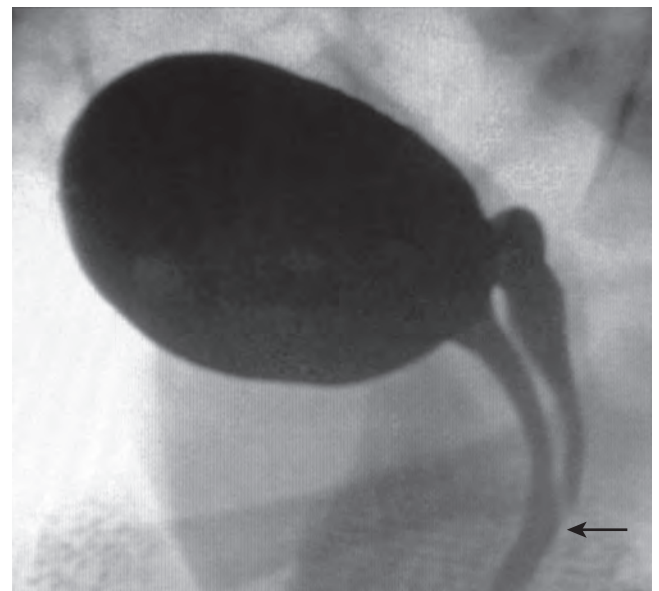


Figure 125-5. Genitogram of urogenital sinus showing confluence of the urethra and vagina (arrow).

a blunt-tipped catheter (which can be made by trimming the cone-shaped end of a feeding tube) and placed against the perineal opening. Contrast medium is injected retrograde to identify the point where the vaginal introitus meets the urethra to form the urogenital sinus. The study also aids in differentiating a cervical dimple from a prostatic utricle. If a cloaca is present, the sinogram provides detail about the position of the rectum, vagina, and urethra and about the point of confluence and the distance to the perineum (Shaul and Harrison, 1997; De Filippo et al, 1999). The distances of these structures help determine the approach required during surgery (Pena et al, 2004).

Renal Scintigraphy

A radionuclide renal scan is measured in two phases: cortical imaging and tubular imaging phase. Most radionuclide agents demonstrate renal tubular and renal cortical binding. Radionuclide studies are best suited to demonstrate changes in tubular or cortical transit that result from abnormalities of renal perfusion, secretion, and filtration. In most cases, the radionuclide study is inferior to CT, MRI, or ultrasonography for demonstration of anatomic alterations. ^{99m}Tc MAG3 is secreted in part by renal tubular function and may be used to approximate relative renal plasma flow. The MAG3 renal scan assists in differentiating obstructive versus nonobstructive dilation of the urinary tract. Proper interpretation of the information obtained from this study requires detailed knowledge of the factors affecting drainage of the upper urinary tract (Shulkin et al, 2008). If detailed imaging of the renal cortex is required to identify renal scarring, ^{99m}Tc DMSA should be used because it is more cortical-retentive, and the kidneys are imaged 3 to 4 hours after the injection (Majd and Rushton, 1992; Piepsz et al, 1999).

Renal scintigraphy scans using gallium-67-labeled or indium-111-labeled leukocytes may be helpful to diagnose and localize the site of pyelonephritis (Yen et al, 1999; Velasco et al, 2004). These techniques may be used to identify and guide therapy for children with focal segmental bacterial pyelonephritis in whom the duration of therapy is uncertain. In a prospective study by Yen and associates (1999), gallium-67 renal scan was more sensitive than DMSA scan in the diagnosis of acute pyelonephritis, especially in differentiating new lesions from old ones. These scans are particularly useful in patients with abnormal renal anatomy or in patients with diminished renal function in whom the DMSA scan may be less specific.

Computed Tomography

CT is used judiciously in specific pediatric clinical settings owing to the ionizing radiation required. CT is rarely used in neonates or infants with the exception of evaluation of a retroperitoneal or pelvic mass. Conversely, CT with intravenous contrast enhancement is the current imaging modality of choice for evaluation of pediatric abdominal trauma. Additionally, spiral CT in most cases has replaced the intravenous pyelogram (IVP) as the first-line study in children in whom stone disease is suspected; however, the relative value of CT compared with ultrasonography must be considered based on the clinical scenario because of the radiation burden of CT. In addition, CT with or without contrast medium enhancement is particularly important as an adjunct in children with suspected focal segmental bacterial pyelonephritis. CT is also particularly important in the diagnosis and staging of solid tumors of the chest and abdomen. Contrast medium-enhanced CT is particularly useful in cases of nephroblastomatosis, in which ultrasound shows little displacement of the renal capsule. It must be kept in mind that radiation doses from CT are cumulative over the life of an individual (Frush et al, 2003). With sufficient clinical information, the radiologist may be able to recommend other imaging modalities (e.g., ultrasonography, MRI) that do not use ionizing radiation.

Magnetic Resonance Urography

Although still expensive as an individual radiologic study, MRU may provide the best information about the anatomy and function of the genitourinary tract from a single study. Advantages of MRU include the avoidance of ionizing radiation, use in patients with impaired renal function, and higher quality contrast and spatial resolution in any plane relative to other imaging modalities (Wille et al, 2003; Grattan-Smith, 2008) (Fig. 125-6). If obstruction of the urinary tract is suspected, gadolinium followed by furosemide can be administered to assess renal drainage better. MRI with gadolinium should not be performed in a full-term infant before 2 months of age. Antenatal MRI is used to diagnose UPJ obstructions, ectopic ureters, abnormal ureteral buds associated with renal agenesis, and cloacal exstrophy in the fetus (Maas et al, 1997; Matsuki et al, 1998; Wille et al, 2003). When antenatal ultrasonography is equivocal, antenatal MRU provides additional anatomic detail especially in the diagnosis of ureteral pathology (Kajbafzadeh et al, 2008). Limitations of MRU at the present time include high costs and the requirement for sedation or anesthesia in most young patients. MRI has also been used in the evaluation and identification of an impalpable testis (Yeung et al, 1999; Lam et al, 2001). MRI with or without angiography has been more widely used with greater sensitivity and specificity, but its use is deterred by cost, low availability, and need for anesthesia (Kanemoto et al, 2005; Kantarci et al, 2010). At the present time, there is no radiologic test that can conclude with 100% accuracy that a testis is absent. In the workup of suspected renovascular hypertension, gadolinium-enhanced magnetic resonance angiography is a noninvasive modality with comparable accuracy to digital subtraction angiography (Hacklander et al, 2004).

Intravenous Pyelography

Because newer imaging techniques are now available, the IVP is included here for historical completeness. The plain film of the

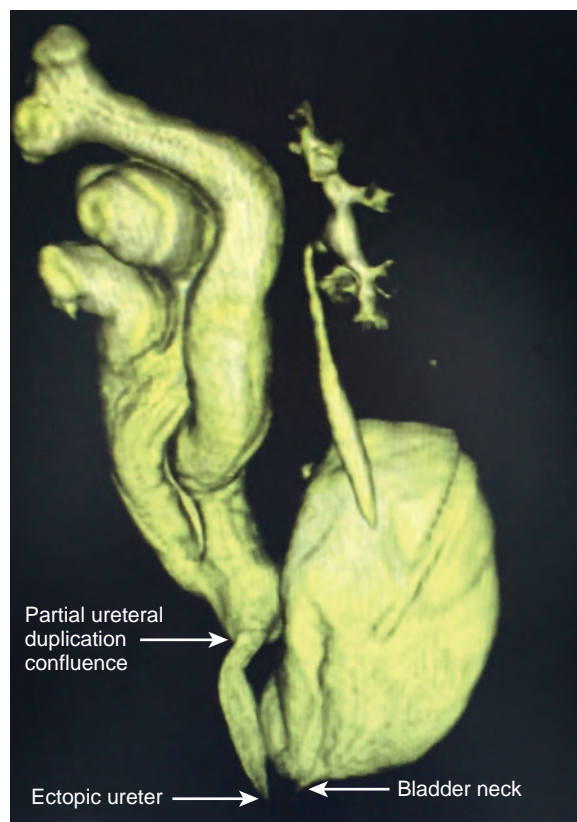


Figure 125-6. Magnetic resonance urogram showing partial ureteral duplication with an ectopic ureter past the bladder neck (found to enter the vagina).

abdomen should be inspected for calculi, spinal abnormalities, and an abnormal intestinal gas pattern. The nephrogram phase of the IVP identifies mass effects within the kidney and the presence or absence of scarring after pyelonephritis. Subsequent views can assess sequentially the anatomy of the renal cortex, calyces, fornices, renal pelvis, ureters, bladder, and urethra (Smellie, 1995). Subtle anatomic variations in normal anatomy of the renal calyces or of the UPJ that may be confusing on ultrasonography were previously clarified with the IVP. Today, the full anatomy may be elicited with CT urography or MRU.

KEY POINTS: PEDIATRIC LABORATORY EVALUATION AND RADIOGRAPHIC EVALUATION

- Microscopic hematuria diagnosed on dipstick evaluation should be confirmed with microscopic examination of the urine.
- Ultrasonography cannot definitively distinguish obstructive from nonobstructive upper tract urinary dilation.
- A VCUG should include multiple voiding cycles with images of voiding views.
- Nuclear medicine evaluation is increasingly used in the evaluation of patients with VUR.
- CT should be used judiciously in children because of the risks of ionized radiation.
- MRU provides functional and anatomic information about the entire urinary tract.

PEDIATRIC URODYNAMIC EVALUATION AND BIOFEEDBACK TRAINING

A well-equipped urology office has a urodynamic suite as part of the overall complex. Modern urodynamic systems allow accurate measurements of the intravesical pressures before, during, and after bladder contraction. From these measurements, estimates of bladder compliance and bladder outlet resistance may be made. With this information, the pediatric urologist may assess whether the bladder stores at pressures low enough to prevent renal damage and empties well enough to prevent UTI. The addition of fluoroscopic monitoring of the bladder and upper tracts during urodynamics greatly adds to the information garnered from the urodynamic study. However, the video-urodynamic suite needs to be located within a lead-lined room, which may preclude placement in every office.

Biofeedback training designed to help a child to improve bladder emptying may also be performed in the office. Biofeedback sessions should be done in a room that is separate

from the urodynamic suite because in most cases a different population of patients requires biofeedback training than would undergo urodynamic study (Yamanishi et al, 2000; Schulman, 2004). Biofeedback, if done properly, is time-consuming. The child must be relaxed and motivated for the session to be effective. Awareness of the pelvic floor muscle and urinary sphincter is a key factor to achieve successful biofeedback treatment. Biofeedback incorporating interactive computer games is available, with success rates approaching 90% after a mean of 4.9 sessions (Herndon et al, 2001).

OFFICE SURGICAL PROCEDURES

Successful outpatient surgery with local anesthetic depends on cooperation from the parent as well as the child. The balance is understanding the convenience of having the procedure in the office versus the advantage or risk of a general anesthetic in the main operating room. We believe many infants weighing less than 10 pounds may easily undergo an office circumcision with an anesthetic cream sometimes combined with injected local anesthetic (Hoebeker et al, 1997). In a meta-analysis by Brady-Fryer and colleagues (2004), dorsal penile nerve block was most effective at reducing circumcision pain compared with EMLA (eutectic mixture of local anesthetics) cream or placebo. We rarely perform office circumcision in older children. Infants older than 3 months are too big to be easily restrained, and the risk of bleeding postoperatively and skin separation is considerable if the skin edges are not sutured.

Numerous techniques may be used in the clinic for circumcision, including a Plastibell, Mogen clamp, and Gomco clamp. We use the Gomco clamp (Fig. 125-7A), which is a three-component device that includes a bell that fits over the glans of the penis and separates the glans from the inner preputial skin (Guazzo, 1999; Amir et al, 2000; Wan 2002). The clamp is applied, and the foreskin is trimmed away from the clamp. If the clamp is left in place for a considerable amount of time (usually about 5 to 10 minutes), there is very little separation of the skin postoperatively. If desired, a small nonstick bandage is placed beneath a transparent adhesive dressing. The bandage is removed the next day. The boy's parents are instructed to apply petroleum jelly to the incision during the healing period.

Complications after neonatal circumcision include bleeding, wound infection, meatal stenosis, and secondary phimosis (cicatrix) resulting from removal of insufficient foreskin or removal of insufficient inner preputial skin (Fig. 125-7B). Potentially serious complications are rare but include death, sepsis, amputation of distal part of the glans, removal of excessive foreskin, and urethrocutaneous fistula (Baskin et al, 1997; Hutcheson, 2004; Krill et al, 2011). After a circumcision, the cut edge of the preputial surface may occasionally graft to the inflamed glans tissue forming

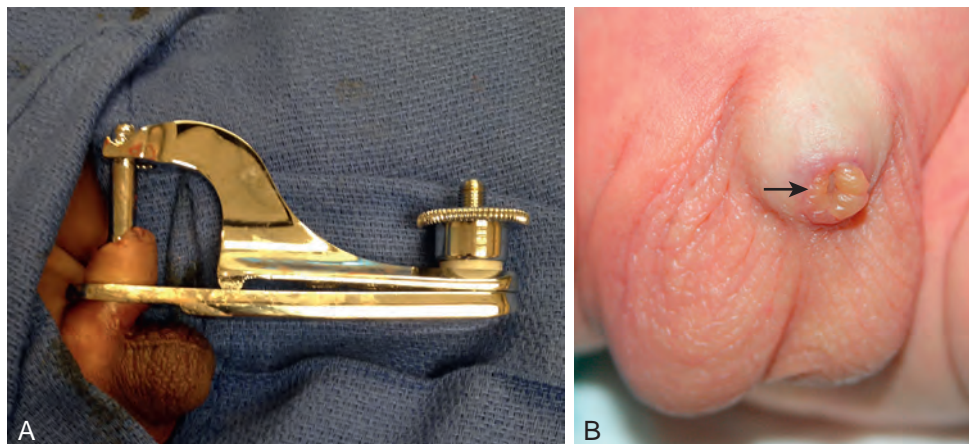


Figure 125-7. A, Gomco circumcision. B, Postcircumcision cicatrix (arrow).

a preputial-glanular bridge that may be incised in the office after application of local anesthetic cream and/or injection of local anesthetic. After administration of local anesthesia, the skin bridge is crushed with a hemostat clamp, and the skin bridge is sharply incised. No suturing is required in most cases. This procedure is easy and virtually painless. After the procedure, the parents apply petroleum jelly to the incised edges to prevent readherence.

Meatal stenosis is common after circumcision. It may result from contraction of the meatus after healing of the inflamed, denuded glans tissue that occurs after retraction of the foreskin or from damage to the frenular artery at the time of circumcision (Persad et al, 1995; Upadhyay et al, 1998). If the narrowing is pronounced enough to cause deflection of the urinary stream or dysuria, a meatotomy is indicated.

To perform a meatotomy in the office, an anesthetic cream is applied for 60 minutes and, if desired, additional lidocaine with 1% epinephrine may be injected with a 26-gauge needle to provide a small wheal at the ventrum of the urethral meatus. The ventral edge of the urethral meatus is clamped, and a small wedge of the scarred tissue is crushed with a straight hemostat and sharply excised. After the procedure, the parents are advised to apply a thin petrolatum ointment into the meatus to lubricate the cut edges and dilate the meatus twice daily for 2 weeks and as needed thereafter. Postoperatively, infants may be seen 2 to 3 months later to assess the result.


If a VCUG is required or if dysuria associated with vaginal pooling of urine contributes to a dysfunctional voiding pattern, we have occasionally separated labial adhesions in the office. These membranous adhesions are easy to separate on the midline with petroleum jelly on the physician's gloved fingertip, a probe, or the tip of a curved hemostat. A local anesthetic cream is applied to the labia before the procedure in hopes of easing the discomfort, which is minimal. After lysis of the adhesions, the child's parent must separate the labia and apply lubricating ointment such as petroleum jelly at least twice a day for 2 to 6 weeks while the labial tissue matures. With diligent postoperative care, recurrence is rare.

KEY POINTS: PEDIATRIC URODYNAMIC EVALUATION AND BIOFEEDBACK TRAINING AND OFFICE SURGICAL PROCEDURES

- A well-equipped urology office has a urodynamic suite and biofeedback training suite.
- Most infants weighing less than 10 pounds may easily undergo an office circumcision with an anesthetic cream combined with injected local anesthesia.
- Petroleum jelly is applied after circumcision, urethral meatotomy, or lysis of labial adhesions to prevent complications.

SUMMARY

The final goal of the surgical care of children is to ensure as normal an adult life as possible. For boys with PBS or PUV and for children of either sex born with bladder or cloacal exstrophy, the pediatric urologist should continue to act as consultant even after the child enters adulthood. **As children grow into adults, the pediatric team must develop a liaison with a skilled, interested adult urologic team. Using this method, a lifetime plan of care may be designed and carried out to ensure well-coordinated urologic therapy that addresses the complicated problems unique to this group of boys and girls.**

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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Safety

Nonionizing Modalities

Imaging has long been a critical component in urologic investigation and diagnosis for adults and children. However, with advances in imaging modalities and the unique urologic and psychosocial concerns of children, imaging in the pediatric setting must be viewed in the proper light. For instance, studies that are routine and tolerable in adults may require anesthesia or specially trained technicians in children. Doses may need to be adjusted and equipment may need to be available that is suitable for a child's smaller body. Urologists treating children need to be aware of these age-specific differences for the purposes of ordering, reading, and interpreting these tests. We describe the assets and liabilities of these tests with regard to common pediatric urogenital inquiries. A more in-depth look at the physical and technical details of each modality can be found in Chapters 2 and 3; only aspects unique to children are reiterated here.

SAFETY

Having decided on the necessity of imaging to evaluate the urinary tract, it is important in imaging of children to consider the doses of radiation given per study, the predictable need for future studies of similar radiation dose, the need for contrast agents, and the need for anesthesia or sedation to obtain adequate images. Although quantifying the radiation risk accurately for the individual patient is challenging, there is consensus that one should practice under the ALARA principle—as low as reasonably achievable (Don et al, 2013; ICRP et al, 2013). Because it is not possible at the present time to predict an individual's susceptibility to radiation effects, all patients should be treated as radiation sensitive (Kleinerman, 2009). We address the risks of radiation in this chapter only briefly because this topic is discussed in more depth in Chapter 2.

Although nonionizing radiation is considered a safer alternative, it is not without risk. When substituting computed tomography (CT) with magnetic resonance imaging (MRI), many children require anesthesia or sedation because of the longer acquisition times (Arthurs et al, 2012). This risk of sedation or anesthesia is typically higher than the risk of nephrogenic systemic fibrosis secondary to the use of gadolinium in a child with poor renal function or in the setting of immature renal function in a neonate (Thomsen et al, 2007; Karcaaltincaba et al, 2009). However, the small risk of contrast-induced nephropathy in children with poor renal function similarly exists with CT (Thomsen, 2007). Both contrast materials pose a higher, although still quite small, risk of allergic reaction (Arthurs and Bjørkum, 2013). The radiofrequency pulses creating the electromagnetic field can cause patient heating that must be monitored to prevent hyperthermia, which has been reported, although rarely (Kussman et al, 2004; Wang et al, 2007). The long-term safety of MRI exposure has been questioned based on revealed changes in gene expression related to magnetic field exposure (Bonassi et al, 2007; Kimura et al, 2008; Simi et al, 2008). Although no human data have been produced,

Ionizing Modalities

it is recommended to avoid fetal MRI in the first trimester. Ultrasonography has not been shown to cause gene expression changes and is regarded as safe at all ages.

Ionizing radiation is considered more harmful in children than in adults because of the greater radiosensitivity of developing tissues and potential for higher cumulative doses over the child's lifetime (Arthurs and Bjørkum, 2013). In children, the stochastic effects of repeated exposure (i.e., internal cell injury) can result in radiation-induced malignancies after a prolonged latent period. When evaluating the literature on ionizing radiation risk, care must be taken to determine if the risk reported is estimated, modeled, or measured from clinical practice. Variations in technique and patient age and size and varied intervening studies during the required long study intervals can make measured studies difficult to interpret. Acknowledging these significant limitations in determining ionizing radiation risks in children, there appears to be reasonable evidence to suggest a dose-related risk in children and in utero (Arthurs and Bjørkum, 2013). However, quantifying this risk is extremely difficult with the currently available data. Considerable work is being done to reduce radiation doses of individual tests, while still maintaining the necessary diagnostic accuracy to provide good care. Likewise, better medical decision making and offering nonionizing alternatives have gained momentum.

NONIONIZING MODALITIES

Ultrasonography

Prenatal Imaging

Various urologic conditions can be diagnosed prenatally with near certainty using sonography to investigate the presence and quality of the renal cortex, laterality of the abnormality, position of the abnormality within the abdomen and its association with other organs, and the presence of a normal amount of amniotic fluid (Dias et al, 2014). The features of a normal urinary tract include renal cortex that is isoechoic or slightly hypoechoic to the liver; the presence of discrete interfaces between the cortex and the medulla; the absence of cortical cysts; and the absence of masses or dilation of the collecting system, ureters, or bladder. Additionally, bladder cycling might be observed if patience is exercised, and attention should be placed on the placement of the umbilical cord and completeness of the anterior abdominal wall. The following survey of the types of abnormalities encountered is organized by salient features seen on prenatal ultrasound scans.

Hydronephrosis, Obstructive Uropathies, and Cystic Renal Lesions. Dilation of the renal collecting system and parenchymal cysts are the most common findings on prenatal sonography (Blyth et al, 1993). A differential diagnosis list that considers most possibilities includes hydronephrosis (obstructive and nonobstructive), multicystic dysplastic kidney, polycystic kidney disease (autosomal recessive and autosomal dominant), and cystic nephroma.

Although it has been debated that all cases of hydronephrosis represent obstruction in some form or another, most hydronephrosis follows a benign natural history, such that improvement or resolution is seen. More profound developmental abnormalities manifest as moderate to severe hydronephrosis because of high-grade obstruction, and the transition between dilated and nondilated urinary tract localizes the site of obstruction to the ureteropelvic junction, ureterovesical junction, or urethra. For example, a thickened bladder and dilated posterior urethra known as the “keyhole” sign is highly suggestive of a posterior urethral valve (Fig. 126-1). Cystic disease can mimic hydronephrosis on initial inspection but can be discriminated from it ultimately because cysts do not communicate with one another, but dilated calyces and pelvis do. In the case of multicystic dysplastic kidney (MCDK), the cysts are of varying sizes and randomly distributed throughout the renal parenchyma in addition to not communicating with one another and are unilateral (Fig. 126-2A). By contrast, bilateral cystic lesions should raise concern for polycystic kidney disease, of which there are two types: autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD). ARPKD is characterized by enlarged and homogeneously hyperechoic parenchyma that results from dilation of the collecting tubules (Fig. 126-2B). ADPKD is identified by the presence of enlarged

kidneys in which the parenchyma is almost replaced by cysts. A multilocular cystic nephroma is a benign cystic renal tumor that shares features with MCDK and cystic Wilms tumor. It also manifests as noncommunicating cysts of varying sizes but generally has more parenchymal tissue than MCDK. Multilocular cystic nephroma is a tumor of infancy, whereas (cystic) Wilms tumor occurs in children around 2 to 4 years old.

Midline Pelvic Cysts. A differential diagnosis list includes hydrometrocolpos (urogenital sinus anomalies), ovarian cyst, distended bladder, and urinary ascites. Hydrometrocolpos is distention of the uterus and vagina with mucus or blood and results from vaginal obstruction secondary to imperforate hymen, vaginal atresia, transverse vaginal septum, or retrograde flow of urine in urogenital sinus and cloacal malformations (Hill and Hirsch, 1985; Banerjee et al, 1992) (Fig. 126-3).

Renal and Abdominal Solid Masses. A differential diagnosis list includes neuroblastoma, congenital mesoblastic nephroma, Wilms tumor, renal vein thrombosis, renal artery thrombosis, adrenal hemorrhage, and rare renal solid tumors (rhabdoid, clear cell, angiomyolipoma) (Fig. 126-4).

Abdominal Wall Defects. Although generally quite rare, bladder exstrophy and prune-belly syndrome represent defects in formation of the abdominal wall with associated urogenital abnormalities.

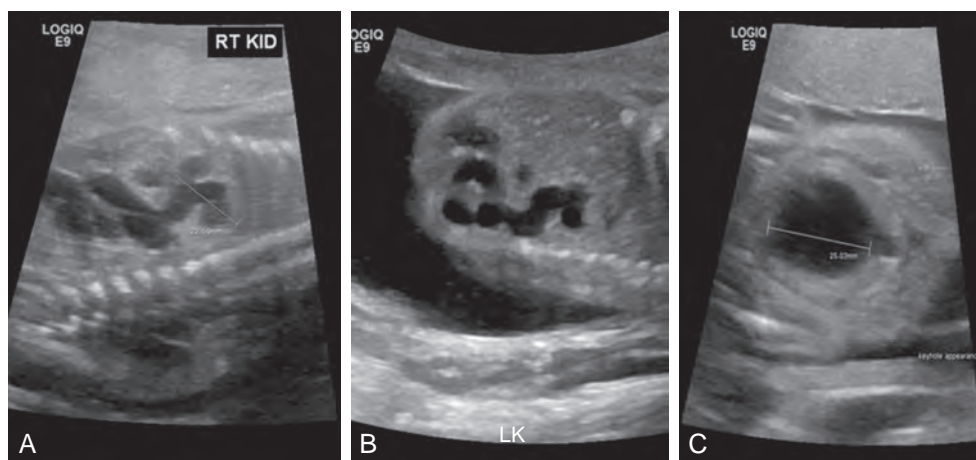


Figure 126-1. Prenatal sonogram demonstrating bilateral (A and B) hydronephrosis and hydro-ureter and the thickened bladder and “keyhole” sign (C) typically associated with bladder outlet obstruction, in this case of posterior urethral valve.

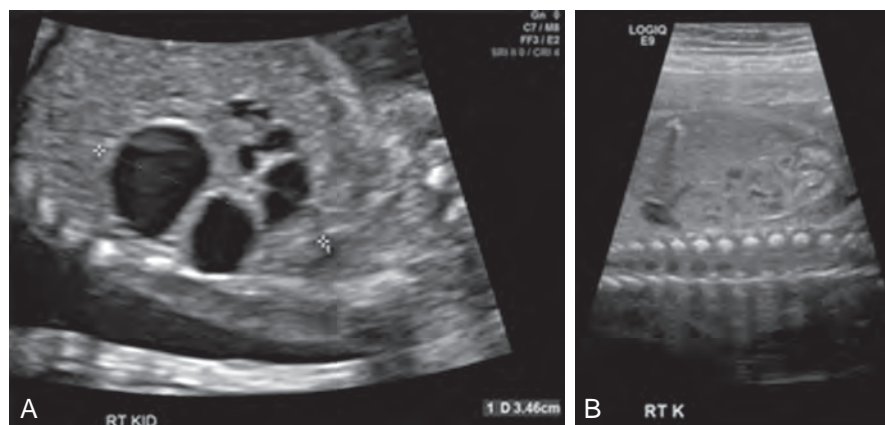


Figure 126-2. A, Prenatal sonogram demonstrating randomly distributed cortical cysts typically seen in multicystic dysplastic kidneys. B, Prenatal sonogram demonstrating homogeneously hyperechoic renal parenchyma of autosomal recessive kidney disease.

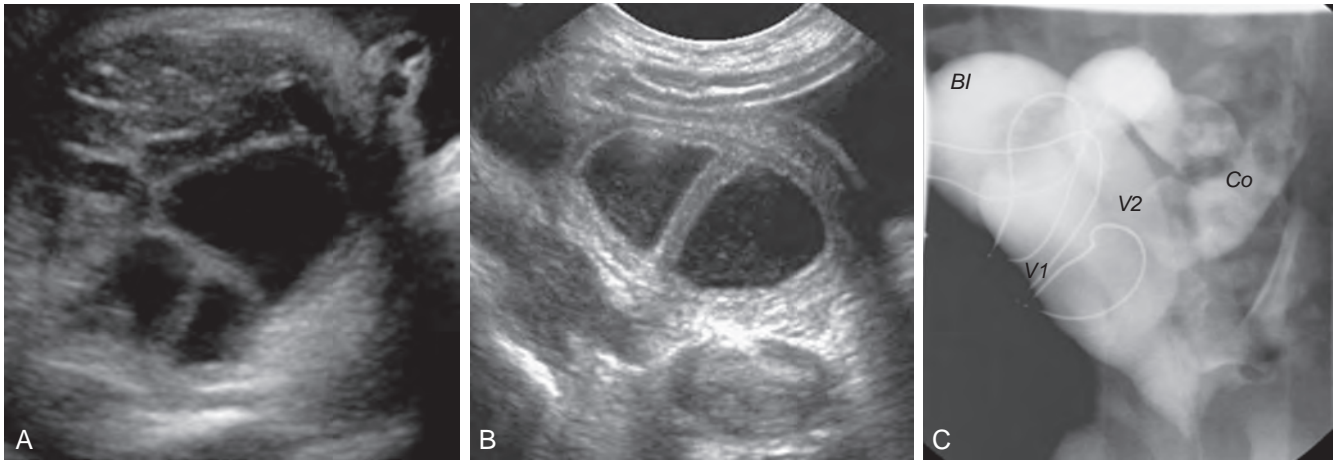


Figure 126-3. A, Prenatal sonogram performed for oligohydramnios in a 34-week female fetus demonstrating dual pelvic cystic structures below a dilated bladder. B, Postnatal sonography confirms the pelvic structures to be hemivaginas. C, Cystogram confirms the diagnosis of cloacal anomaly because the hemivaginas, dilated bladder, and distal colon are opacified with contrast medium injected into a single perineal opening. Bl, bladder; Co, colon; V1, hemivagina; V2, hemivagina.

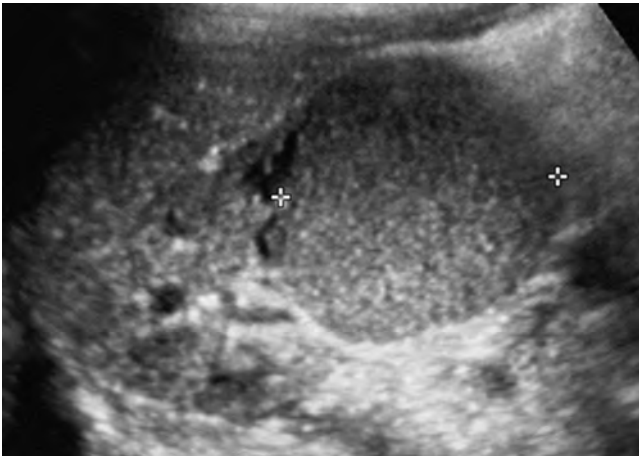


Figure 126-4. Nephroblastoma (Wilms tumor) detected by sonography.

Classic bladder exstrophy can be identified when the bladder is not visualized and instead possibly observing an irregular lower abdominal wall and inferiorly placed umbilicus. Prune-belly syndrome is suggested by observing hydronephrosis and hydroureter, a distended bladder, and the absence of testes in the scrotum in a male fetus (Fig. 126-5).

Upper Tract

It is important to recognize the subtle differences in the sonographic appearance of the kidney in a newborn compared with older children and adults. The distinct corticomedullary differentiation combined with a slightly hyperechoic renal parenchyma in infants compared with a mature kidney can be mistaken for hydronephrosis in a newborn by an inexperienced clinician (Fig. 126-6). Also, the degree of hydronephrosis can be underestimated in an early postnatal sonogram (i.e., up to 2 days after birth) and/or in the setting of dehydration.

Sonography is the ideal initial modality for identifying pediatric hydronephrosis and hydroureter. Many parameters have been proposed for standardization of hydronephrosis reporting, but variation among specialties persists (Zanetta et al, 2012). The Society

for Fetal Urology classification system is the most widely used by pediatric urologists and is based on the extent of calyceal dilation, involvement of minor calyces, and parenchymal thinning (Nguyen et al, 2010) (Fig. 126-7). Other pediatric urologists use a measure of renal pelvic anteroposterior diameter or a combination of classification systems to aid in decision making and risk stratification (Timberlake and Herndon, 2013). These inconsistencies in hydronephrosis reporting make it paramount that the clinician reviews the actual images when making clinical decisions.

Sonography in the setting of urinary tract infection (UTI) is typically used as an initial screening test to rule out obvious anatomic abnormalities that may warrant further investigation. It has been found to be very sensitive for the detection of significant renal abnormalities except for uncomplicated duplication anomalies and focal renal scarring (Horgan et al, 1984; Jequier et al, 1985; Kangarloo et al, 1985; Leonidas et al, 1985). It is often used to complement voiding cystourethrography (VCUG). Because clinical signs and symptoms suggest whether treatment should be intravenous or oral as well as its duration, imaging is generally performed in an acutely ill child only when the patient fails to improve or worsens despite appropriate antibiotic treatment. Most imaging algorithms are applied after treatment and in the interest of identifying risk factors for recurrent UTIs and anatomic abnormalities that increase the risk of complicated UTIs and associated renal injury. For patients requiring hospitalization, it is often advocated that screening sonography be performed before discharge to exclude obstruction. Otherwise, imaging is delayed until after discharge. In the absence of vesicoureteral reflux (VUR), hydronephrosis revealed by sonography can be evaluated further by diuretic renography, which in combination reliably localizes the site of obstruction in all cases (Shalaby-Rana et al, 1997; O'Hara, 2002). Despite its many advantages, standard gray-scale sonography is inferior in the detection of acute pyelonephritis or renal scarring compared with dimercaptosuccinic acid (DMSA). A normal sonogram is insufficient to risk stratify a child with acute pyelonephritis and is not a good predictor of VUR (Nelson et al, 2014). Advances to improve sonographic accuracy in detection of acute pyelonephritis are promising (McArthur and Baxter, 2012).

Contrast-enhanced and noncontrast voiding sonography is proving its accuracy for detection of VUR, but the technique is still in its infancy and not yet widely performed (Papadopoulou et al, 2009; Darge, 2010; Fallah et al, 2012). It uses the detection of echogenic microbubbles tracked in real time during voiding and bladder cycling. A five-point grading system has been developed similar to that used for VCUG (Darge and Troeger, 2002). Voiding

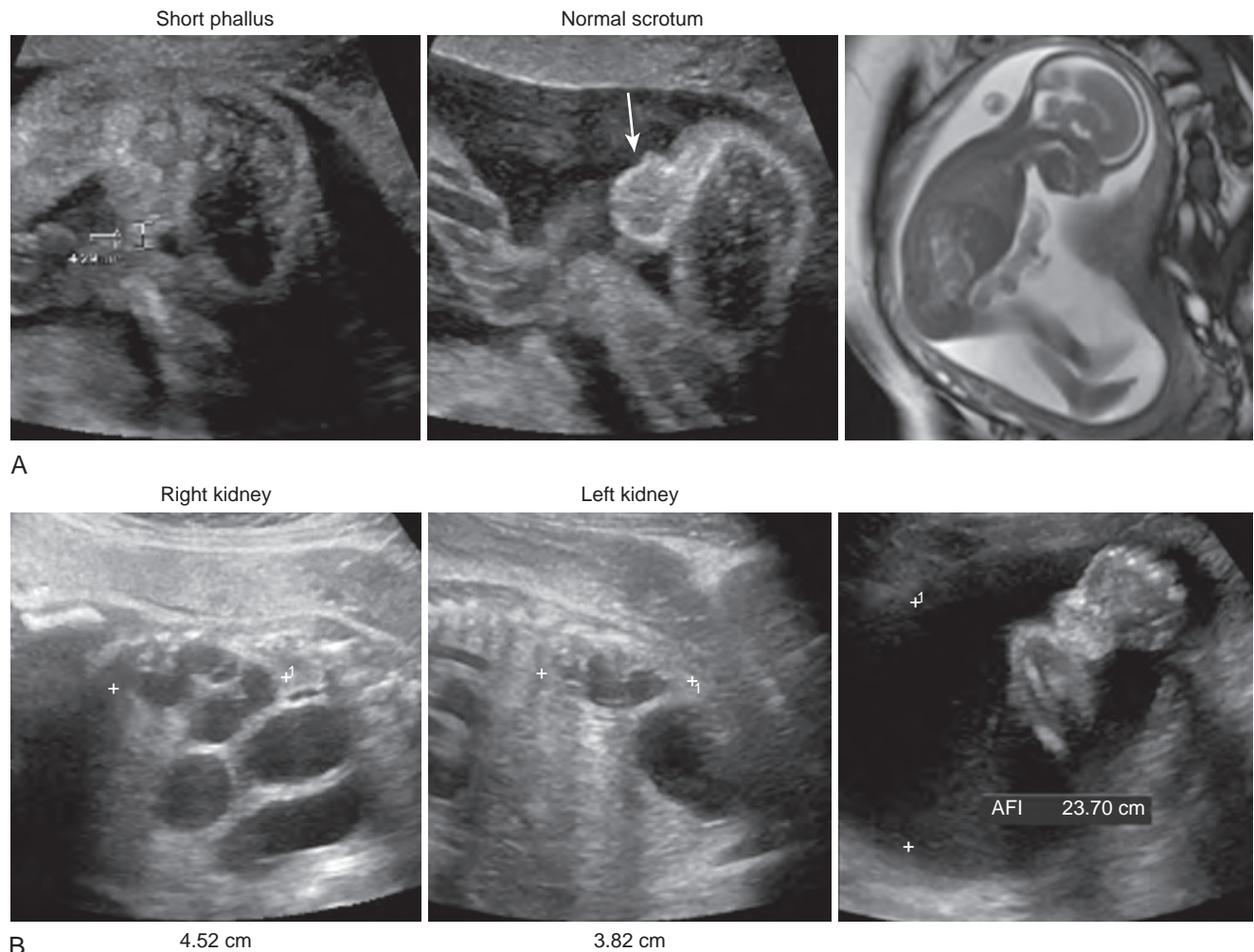


Figure 126-5. A, Prenatal sonography and magnetic resonance image of male fetus with classic bladder exstrophy. The kidneys were normal, and no hydroureter was seen, but the cord inserted low into the abdomen, the bladder was not visualized in pelvic views, and the phallus was short. B, Prenatal sonogram of male fetus with prune-belly syndrome demonstrating the presence of a high amniotic fluid index (AFI). Although prune-belly syndrome and posterior urethral valve share sonographic features, such as hydronephrosis and hydroureter, this case did not demonstrate a thickened bladder wall and distinct “keyhole” sign, which are typical of posterior urethral valve. Also, the testes were not seen in the scrotum, which is another prenatal clue that the diagnosis was prune-belly syndrome.

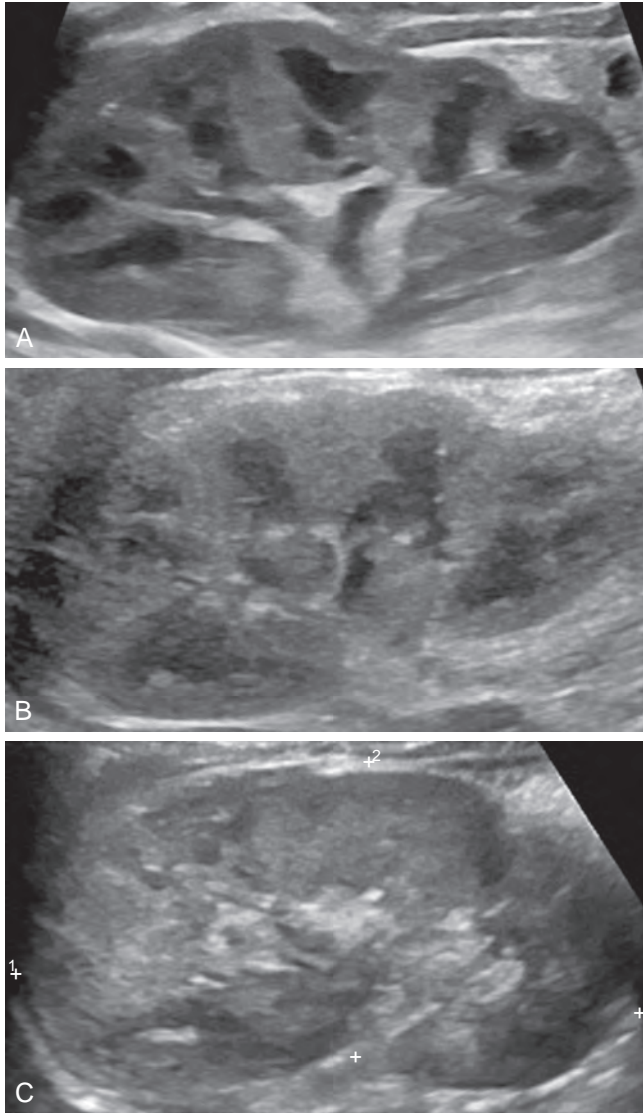


Figure 126-6. A and B, Postnatal sonograms demonstrating the high-contrast corticomedullary differentiation typical of the newborn kidney, which might be mistaken for dilated calyces. C, Renal sonogram in an older child for comparison.

sonography is associated with a higher cost because it is time-consuming, but it is promising as a nonionizing option for detection and monitoring of VUR (Piscitelli et al, 2008).

Children with stone disease will likely have a lifetime of screening and point-of-care imaging so an intentional effort to minimize the amount of radiation is needed. The parent and older child should be well informed of these intentions and play an active role in this plan especially if visiting an unfamiliar emergency facility or physician. Ultrasonography might be sufficient as an initial screening test or follow-up imaging in most children with acute renal colic from stones, as opposed to obtaining a CT scan or kidney-ureter-bladder film reflexively. Sonography is ideal for detecting hydronephrosis and hydroureter, which can direct further imaging if the calculi cannot be definitively identified. It can also reliably detect intraparenchymal calculi and nephrocalcinosis (Fig. 126-8A). On sonography, calculi appear echogenic with shadowing, not to be confused with peripelvic fat, which is echogenic without shadowing. A “twinkling” artifact can also be seen when using color Doppler to distinguish calculi from other hyperechoic signals (Lee et al, 2001; Lu et al, 2013) (Fig. 126-8B).

Although standard renal ultrasonography is an anatomic study, inference of function has been proposed using various techniques

and measurements (Grenier et al, 2013; Inchingolo et al, 2013; Peters et al, 2013). The main clinical question in the setting of hydronephrosis is whether it is caused by obstruction, is caused by VUR, or is a normal variant. Hydronephrosis secondary to obstruction can be evaluated using functional studies only. Hydronephrosis secondary to VUR is discussed later in this chapter. In the setting of bilateral hydroureteronephrosis, a thickened bladder, and poor emptying, VCUG should be performed to rule out a posterior urethral valve (Fig. 126-9). Otherwise, diuretic renography is the gold standard. There are promising advancements using computer-aided shape analysis and ultrasound elastography to measure the dilated collecting system and renal parenchymal or pelvic tension as an indirect measure of obstruction (Grenier et al, 2013; Kang et al, 2013; Peters et al, 2013). If these sonographic techniques prove accurate in assessing function, other ionizing techniques can be avoided or reduced dramatically.

Lower Tract

Bladder. Bladder sonography can be performed to assess anatomy and basic function. From an anatomic standpoint, sonography can be used to detect ureteroceles, large diverticula, bladder calculi, bladder debris, or suspicious bladder masses (Fig. 126-10). Bladder wall thickness is a more difficult proposition because this changes significantly with bladder volume and age. Many authors have tried to standardize measurements of the bladder wall and index this to volume to predict pathology or define normality, but this has not gained widespread use because of its complexity and variability (Kaefer et al, 1997; Yeung et al, 2004; Bright et al, 2010). Regardless, a grossly thickened bladder on sonography should be viewed with suspicion if the clinical picture is consistent with voiding dysfunction (Yeung et al, 2007). Simple functional assessment of bladder emptying can be quantified by measuring volumes before and after voiding.

Genitalia. Genital imaging is limited to essentially four basic conditions: acutely painful or enlarged scrotum, testicular and paratesticular masses, cryptorchidism, and ambiguous genitalia. Ultrasonography is always the initial and usually the only imaging modality needed. Overuse of ultrasonography for scrotal conditions is widespread because most scrotal conditions can be diagnosed on the basis of history and physical examination rather than imaging. Likewise, overzealous interpretation of scrotal imaging, especially when in contradiction to the clinician’s physical examination, should be avoided.

In the case of an acutely painful scrotum, color Doppler sonography can be useful in the differential diagnosis of a child with an equivocal clinical examination for torsion (Baker et al, 2000; Dajusta et al, 2013). Surgical exploration should not be delayed if torsion is suspected and waiting to perform imaging would compromise salvageability. Because of reported false-negative and false-positive results using color Doppler sonography, especially in infants, investigators have used high-resolution ultrasonography to image torsion of the spermatic cord itself, known as the “whirlpool” sign (Vijayaraghavan, 2006) (Fig. 126-11). High-resolution ultrasonography was shown to increase sensitivity to 96% (from 76% using color Doppler sonography) and to have 99% specificity (Kalfa et al, 2007). Salvageability of the testicle based on sonographic appearance is difficult to predict except in the setting of no arterial flow and parenchymal heterogeneity, in which case 100% were nonviable at exploration (Kaye et al, 2008).

Other nontorsion scrotal conditions can be seen with color Doppler sonography. Epididymo-orchitis can be visualized as hyperemia of the epididymis and/or testicle (Fig. 126-12). However, this finding on sonography must be correlated with the clinical presentation because it can also be seen in the setting of recent spontaneous detorsion. Torsion of a testicular or epididymal appendage can also be captured by a skilled technician as an upper pole or epididymal hypoechoic and avascular nodule with surrounding hyperemia. Acute idiopathic scrotal edema can be identified by the “fountain” sign or hyperemia of a thickened scrotal wall in the absence of any of the aforementioned diagnoses (Geiger et al, 2010).

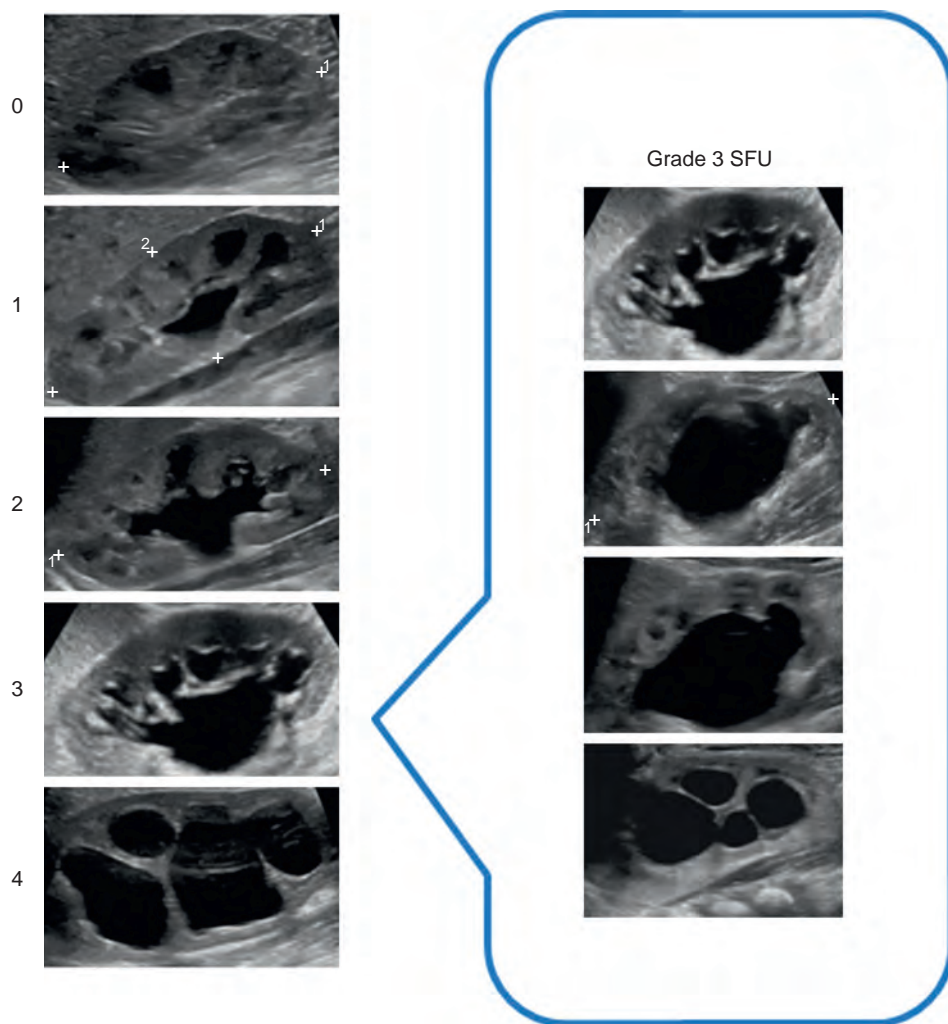


Figure 126-7. Society for Fetal Urology (SFU) criteria as demonstrated in postnatal sonograms. Grade 0 shows no central renal dilation; grade 1, renal pelvis only is visible; grade 2, major calyces can be identified; grade 3, major and minor calyces can be identified; and grade 4, features of grade 3 are present but with parenchymal thinning as well. Within grade 3, there are many different degrees of collecting system dilation that conform to the criteria.

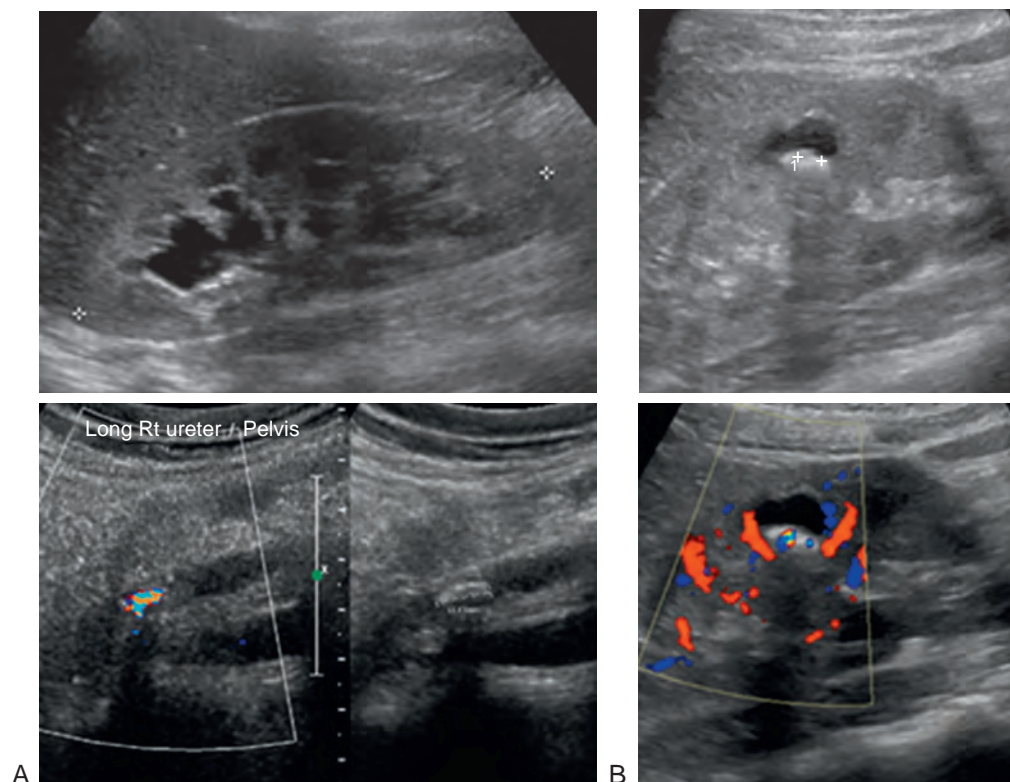


Figure 126-8. A, Renal sonogram demonstrating hydronephrosis and hydroureter associated with a mid-ureteral calculus. B, “Twinkling” artifact seen by color Doppler application to a renal calculus.

Pediatric testicular and paratesticular masses must be viewed in conjunction with the patient’s age and complete clinical picture but are generally well characterized by ultrasonography (Delaney and Karmazyn, 2013). The most common prepubertal primary testicular tumor is benign teratoma characterized by a heterogeneous mass with areas of solid, cystic, and calcified components (Pohl et al, 2004). Yolk sac tumor is a homogeneous well-vascularized mass (Fig. 126-13). An epidermoid cyst has the unique appearance of hyperechoic and hypoechoic rings or “onion rings” with no internal blood flow (Delaney and Karmazyn, 2013) (Fig. 126-14). In the setting of congenital adrenal hyperplasia, bilateral hypoechoic, hyperemic, heterogeneous adrenal rests can be seen in children who have inappropriate steroid replacement or poor compliance. Scrotal masses and their appearance are discussed in detail in Chapter 156.

Ultrasonography in the evaluation of routine cryptorchidism should not be pursued (American Urological Association, 2013). Multiple studies have confirmed its poor sensitivity in detecting and localizing the undescended testicle, and ultrasonographic findings do not alter the necessary treatment plan (Tasian and Copp, 2011). A reasonable exception would be cryptorchidism in an obese child who is difficult to examine, where the presence of an inguinal testis on sonography would simplify the surgical approach. Ultrasonography is the primary imaging modality in the setting of ambiguous genitalia or severe hypospadias with nonpalpable gonads for detection of müllerian structures, which can guide subsequent workup (Chavhan et al, 2008).

Magnetic Resonance Imaging

Upper Tract

MRI is generally used to characterize complex congenital anomalies when sonography cannot provide sufficient detail. It is not as helpful in the setting of infection, stones, or trauma. Precontrast MRI series may be sufficient to diagnose or confirm other congenital

anomalies with great detail such as ectopic ureters, renal duplication anomalies, renal cysts, and calyceal diverticula. Cost, accessibility, and need for sedation in young children limit its overall use.

In the evaluation of hydronephrosis, magnetic resonance urography is a plausible alternative to diuretic renography with far superior anatomic resolution and no radiation exposure. The detailed imaging can provide pinpoint localization of anatomic abnormalities, differential function, and assessment of drainage that can assist in surgical planning. Protocols and formulas have been developed to determine renal function and assess drainage (Jones et al, 2004). Many different protocols have been developed but are similar to those used in mercaptoacetyltriglycine (MAG3) diuretic renography. The contrast medium used is gadolinium-based. The child should be well hydrated, and furosemide (1 mg/kg; maximum 40 mg) is given. Timing of the furosemide administration, bladder catheterization, and patient positioning vary by protocol (Vivier et al, 2010a; Darge et al, 2013). Precontrast T2 sequences are obtained first followed by three-dimensional T2 sequences with fat saturation and 1-mm slice thickness. The contrast medium is slowly injected, and a T1 fat-saturated dynamic scan is continued until contrast medium has filled the ureters (Darge et al, 2013). Widespread adoption of this method has been limited because it requires complex post-processing by a clinician specialized in these techniques. It is possible to use free programs such as CHOP-fMRU (www.chop-fmru.com) or Image J (National Institutes of Health) to assist in generation of the functional analysis (Khrichenko and Darge, 2010; Vivier et al, 2010b). Its application in children is promising, but studies to confirm its equivalence to diuretic renography and widespread education on interpretation are still needed (Perez-Brayfield et al, 2003; Grattan-Smith and Jones, 2006).

Lower Tract and Genitalia

MRI can be used to evaluate the lower urinary tract but rarely with better sensitivity than a well-performed sonogram. The bladder can be seen quite well and usually is included in the series described

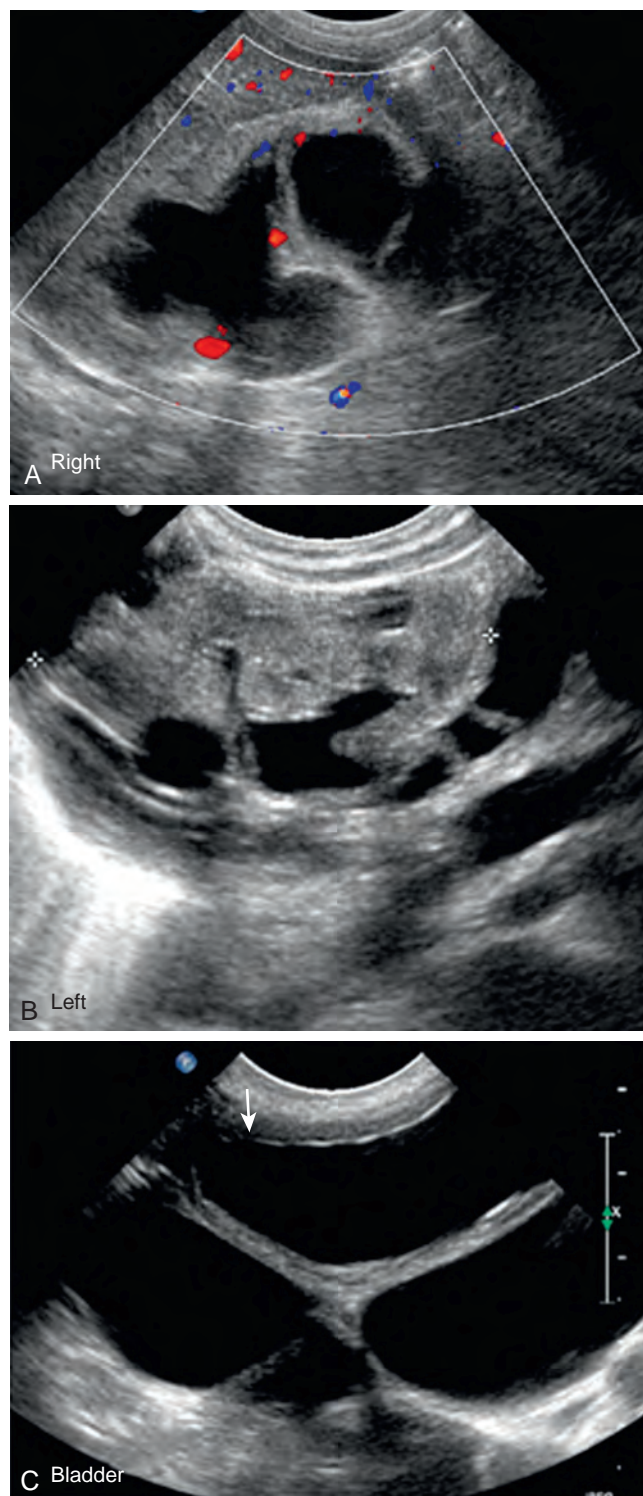


Figure 126-9. Sonographic example of an infant found to have posterior urethral valve. A and B, Images of the kidneys demonstrate echogenic renal parenchyma, moderate to severe hydronephrosis, and renal cortical cyst (upper pole left kidney). C, Image of the bladder demonstrates significant distal hydroureter bilaterally.

earlier for the upper tract. In the setting of disorders of sexual differentiation, sonography and urogenitography are typically the only studies needed for diagnosis and surgical planning. Sensitivity and specificity of MRI compared with sonography for identification of internal structures including gonadal detection are marginally

better at best (Gambino et al, 1992; Biswas et al, 2004; Mansour et al, 2012).

IONIZING MODALITIES

Conventional Radiography and Fluoroscopy

Upper and Lower Tract

Intravenous pyelography has fallen out of favor with the advent of the other modalities offering high-resolution anatomic studies and predictably reproducible functional studies. Intravenous pyelography consists of multiple sequential radiographs throughout the excretion and drainage of contrast material and in different focal planes to obtain anatomic and functional information. On a well-performed study, accurate localization of obstructive lesions and radiopaque stones can be seen. Drainage time can also be assessed, although not as precisely as in diuretic renography.

Retrograde pyelography involves injection of contrast medium into the ureteral orifice; this procedure requires anesthesia in a child. Retrograde pyelography is best used for intraoperative localization of an obstructive lesion identified preoperatively using other studies. However, free retrograde flow cannot be assumed to equate to free, unobstructed antegrade flow and vice versa, especially after a prior surgical repair. For example, small postsurgical tissue flaps can cause obstructed antegrade flow but give an unobstructed appearance on retrograde pyelography.

Plain abdominal radiography or a kidney-ureter-bladder film is used not only for detection of radiopaque stones but also for evaluation of constipation in children with voiding dysfunction. Few data support the accuracy of plain films in detecting or evaluating treatment for constipation (Reuchlin-Vroklage et al, 2005; Berger et al, 2012). However, radiography provides impressive visual evidence for parents who are dubious of the diagnosis of constipation despite the child's clinical signs and symptoms, which leads them to support treatment.

Fluoroscopic VCUG, also referred to as a micturating cystourethrogram, provides information on the lower urinary tract and, in the setting of VUR, valuable upper tract information as well. VCUG is an excellent high-resolution anatomic study of the bladder and urethra but can also provide valuable functional data with regard to bladder emptying. VCUG can be used to detect abnormalities of the bladder wall (e.g., trabeculation, ureterocele, diverticulum, bladder neck hypertrophy, tumors), urethra (e.g., posterior urethral valve, urethral stricture, diverticulum), bladder stones, bladder rupture, and foreign bodies (Figs. 126-15 and 126-16). The initial scout film can also identify many spinal abnormalities.

Cystourethrography has been delayed between 4 and 6 weeks after UTI, when it is indicated, on the premise that early VCUG might demonstrate mild transient VUR created by inflammatory changes at the trigone. However, because it is rare for clinically significant VUR present during infection to disappear after treatment and because the identification of even transient VUR during UTI might be clinically meaningful, a prolonged waiting period is unnecessary (Gross and Lebowitz, 1981; Craig et al, 1997). If VUR is detected on VCUG performed early in the course of febrile UTI, it should be considered that ureteral dilation caused by endotoxin overestimates the degree of VUR (Roberts, 1975; Hellström et al, 1987). Positional instillation of contrast cystography is used sparingly with good effect for diagnosis of occult VUR in selected children with negative VCUG but persistent febrile UTIs despite treatment of all other potential etiologies (Rubenstein et al, 2003; Hagerty et al, 2008b). The reliability of positional instillation of contrast cystography to unmask only clinically significant occult VUR is debatable. To avoid overtreatment, it should be used only as a last resort in patients with complicated febrile UTI. However, it is important to perform the test properly with passive instillation of contrast medium at a height of 1 meter above the bladder as

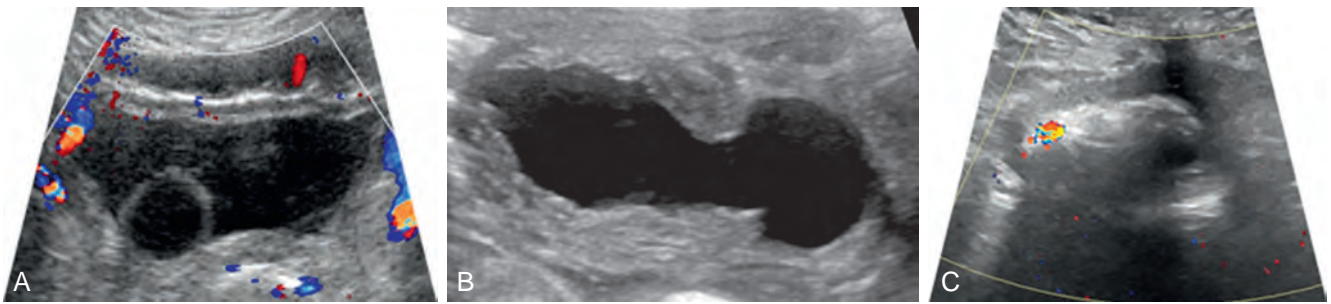


Figure 126-10. Sonographic images of the bladder reveal ureterocele (A), diverticulum (B), and large calculi with “twinkling” artifact (C).

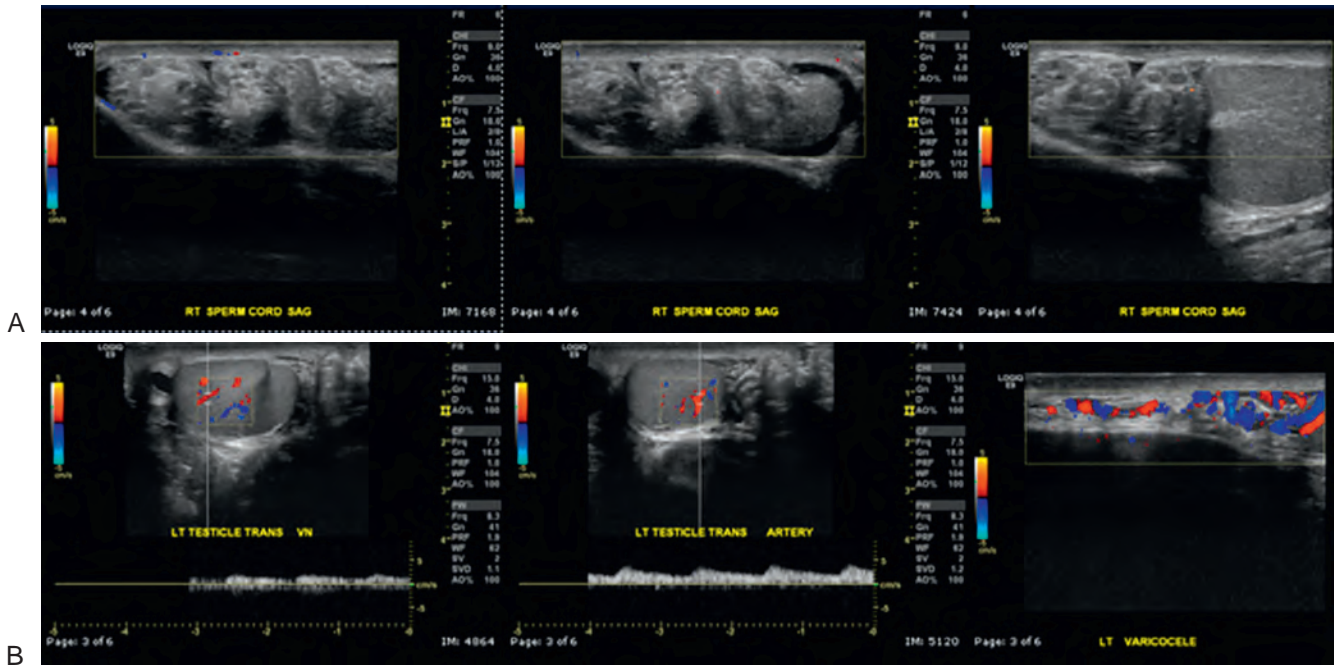


Figure 126-11. Scrotal sonogram in a 19-year-old man with acute onset of right testis pain. Doppler sonography (A) shows the “whirlpool” sign, which has been associated with torsion of the spermatic cord. Doppler sonography did not identify flow, as compared with the left testis (B), which demonstrated ample flow in the nontorsed cord and testis. An incidental left varicocele was noted as well.

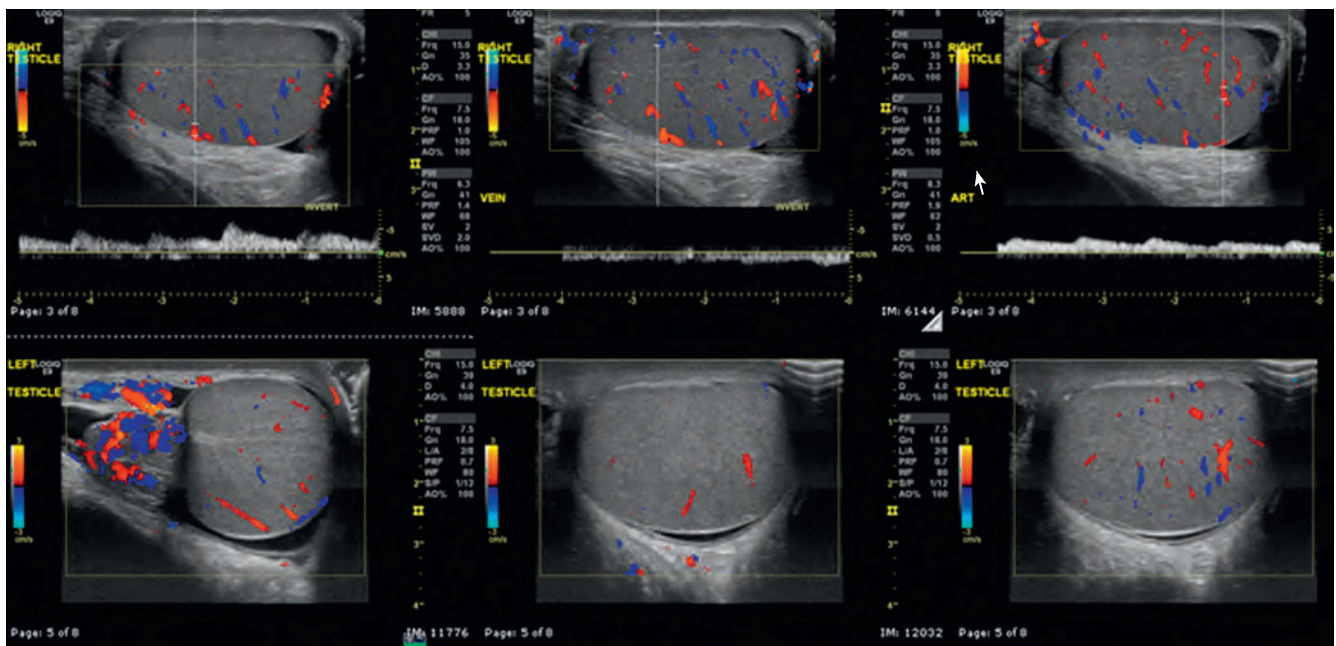


Figure 126-12. Scrotal sonogram in a 13-year-old boy with acute onset of left scrotal swelling showing hyperemia of the left epididymis consistent with epididymo-orchitis.

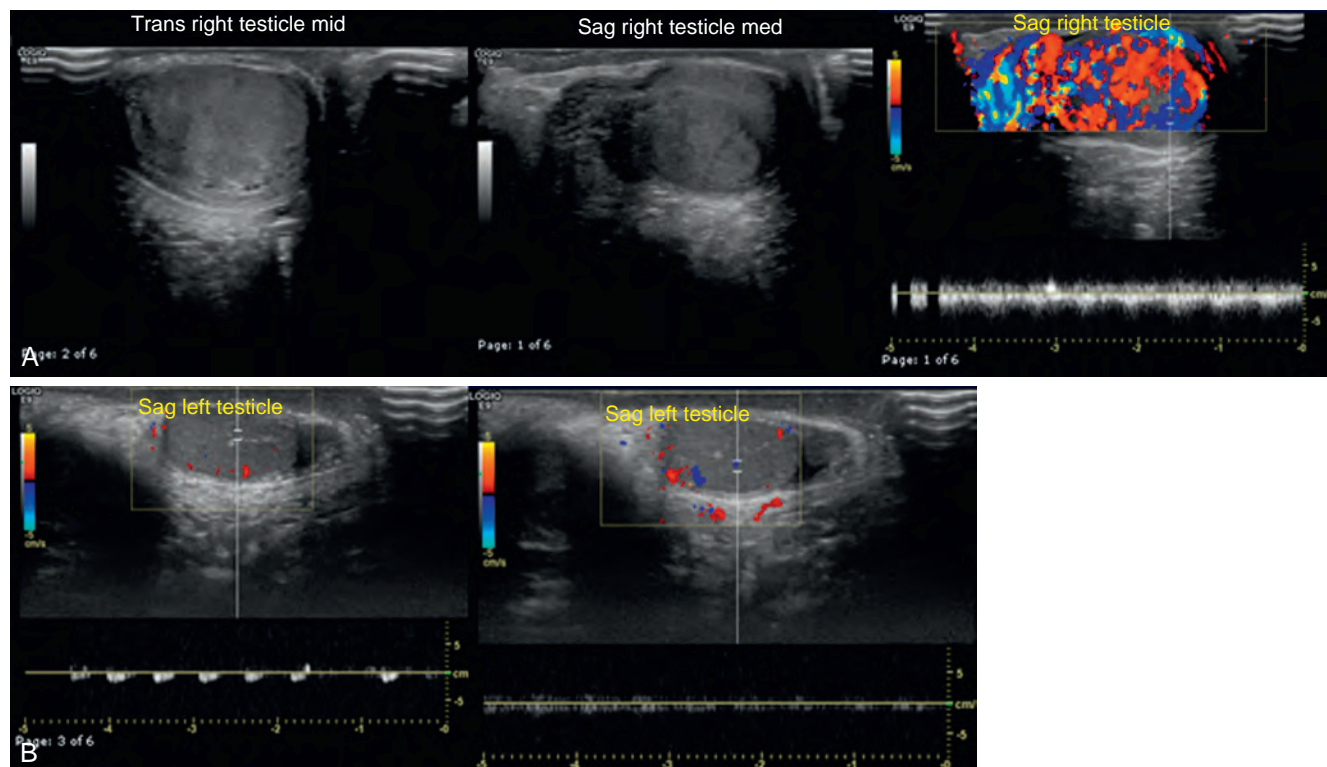


Figure 126-13. Scrotal sonogram in a 2-year-old boy for an enlarged right testis (A), ultimately found to be a yolk sac tumor. For comparison, the normal left testis (B) is shown.

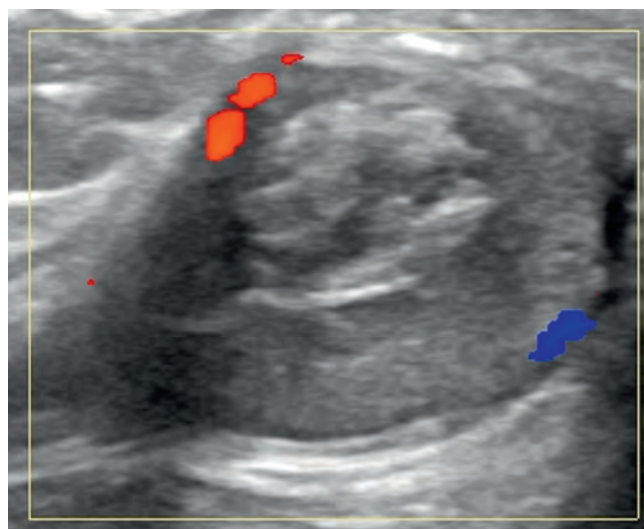


Figure 126-14. Testicular lesion with no internal blood flow and hyperechoic features found to be an epidermoid cyst.

originally described to avoid creation of purely iatrogenic VUR (Hagerty et al, 2008a).

Genitalia

Urogenitography can provide essential information for surgical planning and classification of patients with disorders of sexual differentiation. Typically, a catheter is placed within the single perineal opening, and contrast medium is injected under fluoroscopy to identify the confluence of urethral and vaginal structures as well as their orientation. Alternatively, a Foley catheter can be used with the balloon inflated and pressed up to the perineum with the tip in the perineal opening for retrograde filling (Chavhan et al, 2008).

The findings of urogenitography can be classified based on Shopfner's classification scheme (Shopfner, 1964) (Fig. 126-17).

Computed Tomography

Upper Tract

The role of CT in children is based less on its diagnostic capabilities than on its availability and quick acquisition time. This advantage is best realized in cases of blunt abdominal trauma and polytrauma. However, with advances in sonography and MRI, the need for CT in pediatric patients at the cost of potentially harmful radiation exposure is dwindling. CT has little role in the evaluation of pediatric hydronephrosis because it offers little advantage over ultrasonography with unwanted ionizing radiation. Similar to ultrasonography, it is a detailed anatomic study but with the ability to imply function in noncalcareous hydronephrosis with the addition of intravenous contrast medium and delayed images. Although a delayed nephrogram and ureteral drainage compared with the contralateral side signals obstruction, this is difficult to quantitate. CT can give detailed anatomic information in the setting of renal and ureteral anomalies in more complex patients (e.g., ectopic kidney, ectopic ureter, megaureter, duplication anomalies, renovascular anomalies), which may be helpful in surgical planning when sonography or MRI is inconclusive or unavailable. Likewise, CT has a limited role in the setting of childhood UTI and is best reserved for situations in which nonionizing modalities are inconclusive. MRI and CT can be helpful in assessing infections related to renal abscess, extraurinary fistulization, postoperative complications, or urinary obstruction (Fig. 126-18). The most obvious advantage of CT is in the detection of urolithiasis. CT is better than sonography at detecting and quantifying stone burden; however, it has been shown that this increased accuracy seldom has a clinical impact (Passerotti et al, 2009). Care should be taken to follow the ALARA principle when choosing to use CT in all patients, but especially in children with stone disease, who will likely have a lifetime of frequent imaging episodes.

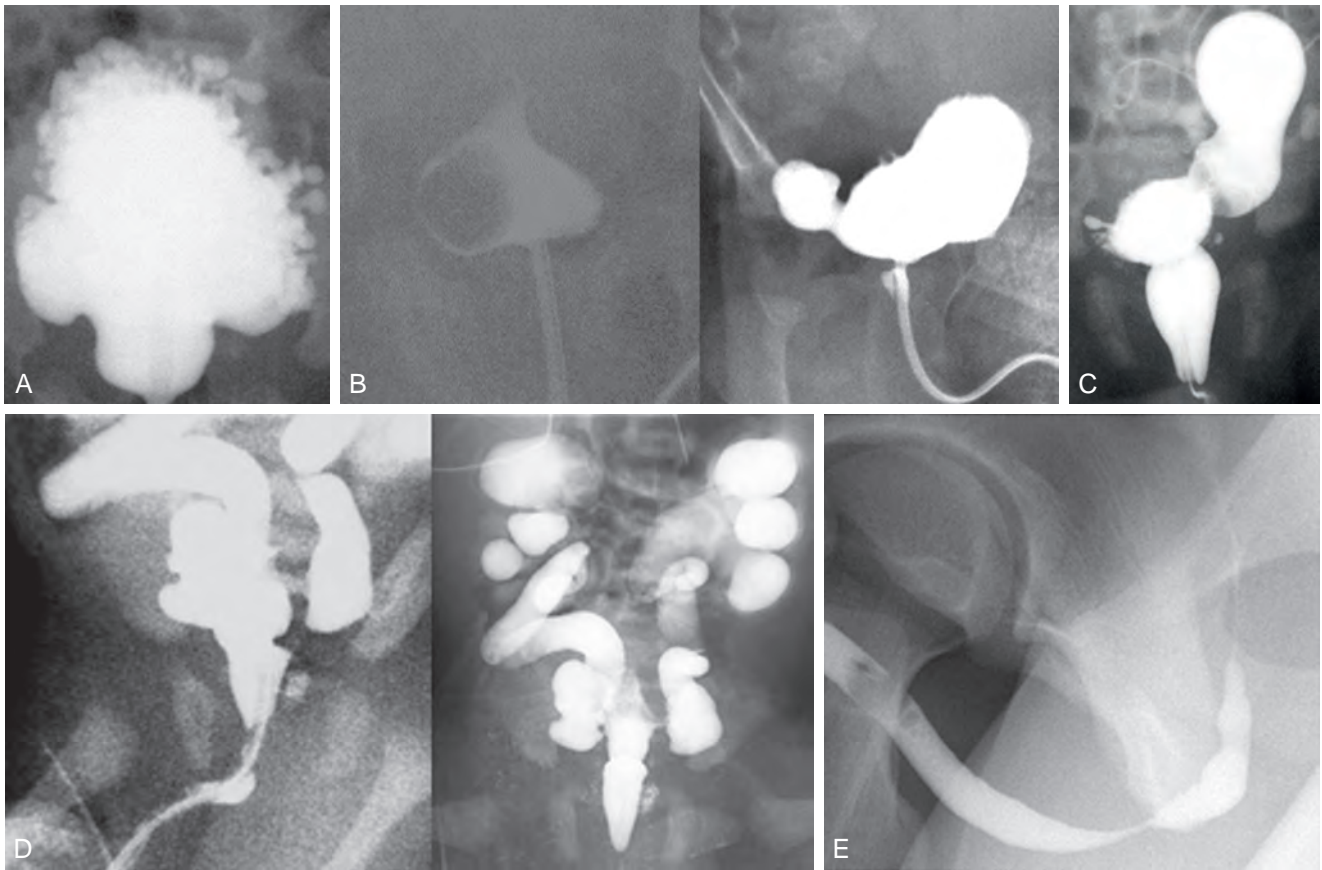


Figure 126-15. Various findings on voiding cystourethrography. A, Highly trabeculated bladder. B, Ureterocele within bladder (*left*) and everting (*right*). C, Large bladder diverticulum and elongated posterior urethra in child with posterior urethral valve. D, Elongated posterior urethra secondary to posterior urethral valve and bilateral grade 5 vesicoureteral reflux. E, Short distal bulbar urethral stricture.

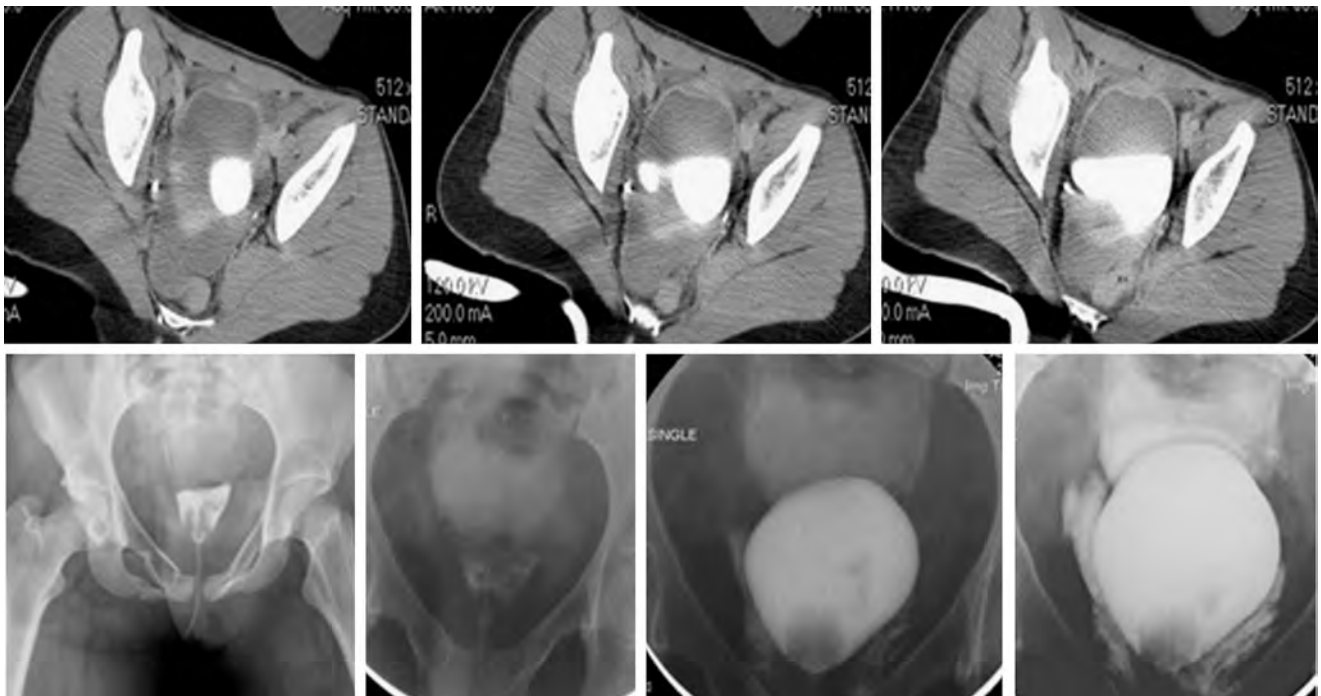


Figure 126-16. A 15-year-old girl with a pelvic fracture underwent a screening computed tomography scan that suggested a bladder injury, which was confirmed by contrast cystography. Note the extreme elevation of the bladder neck ("pie-in-the-sky") on the cystogram and clear demonstration of contrast medium collecting in the retroperitoneal space.

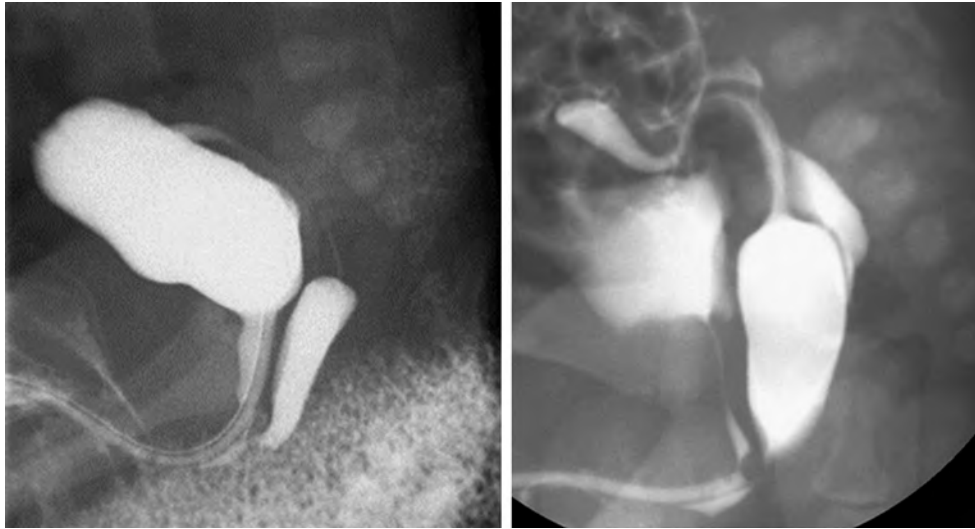


Figure 126-17. Genitogram of an infant girl with 46,XX ovotesticular disorder of sex development showing a low confluence of the urethra and vagina and reflux into the right fallopian tube. This is consistent with a Shopfner type III classification.

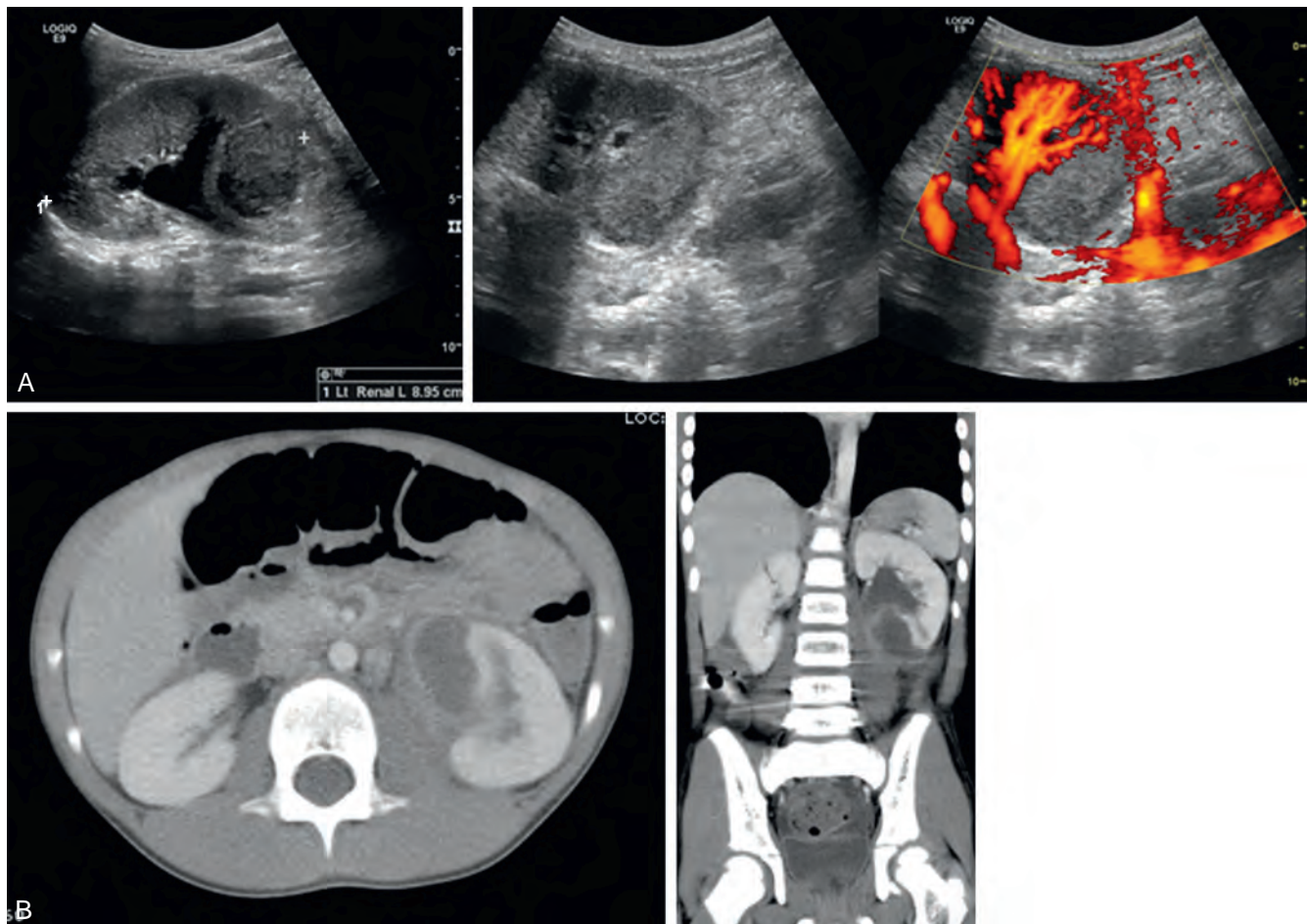


Figure 126-18. A 6-year-old boy presented with abdominal pain, elevated erythrocyte sedimentation rate and C-reactive protein, and inability to stand erect. **A,** Sonogram of the kidneys with Doppler views demonstrates a heterogeneous collection in the lower pole of the left kidney. **B,** On computed tomography scan, this region is confirmed as a renal abscess.

Lower Tract and Genitalia

CT of the lower tract and genitalia is typically reserved for detection of bladder or pelvic trauma. CT cystography can be performed either by antegrade/delayed filling or retrograde filling with a catheter to detect bladder or bladder augment rupture. Complete filling of the bladder with contrast medium is necessary to avoid missing small leaks secondary to insufficient intraluminal pressure or gravitational settling of contrast medium on the opposite side of the perforation. Although filling of the bladder with contrast medium could be performed with a conventional cystogram, CT can provide better anatomic resolution and immediate classification of such rupture as intraperitoneal or extraperitoneal, which would affect management options.

Nuclear Medicine

Renal Cortical Scintigraphy

Renal cortical scintigraphy using technetium-99m (^{99m}Tc)-DMSA relies on uptake by proximal tubular cells, a process that is dependent on renal blood flow (Majd and Rushton, 1992). Focal renal blood flow is decreased in sites of acute pyelonephritis, which corresponds to areas of relative photon deficiency seen on DMSA scans (Rushton and Majd, 1992). Although acute pyelonephritic lesions appear as areas of decreased peripheral uptake with preservation of the reniform contour, renal scars can be differentiated based on observation of volume loss, which interrupts the normal reniform outline, resulting in a concavity. These lesions can be focal, multifocal, or diffuse. Although it is possible for an experienced observer to distinguish between acute and chronic lesions, differentiation is frequently difficult in kidneys with acute pyelonephritis superimposed on preexisting renal scars. Using histopathologic criteria in a piglet autopsy study of induced acute pyelonephritis, sensitivity of DMSA for acute pyelonephritis was 87%, and specificity was 100% (Rushton et al, 1988). A similar experiment demonstrated slightly higher sensitivity with lower specificity but equivalent diagnostic accuracy when using single photon emission computed tomography detection compared to planar (pinhole) detection (Majd et al, 1996).

The timing of DMSA scintigraphy is determined by whether one is seeking to document the acute inflammatory changes of pyelonephritis or irreversible renal cortical scarring. Because inflammation is a transient process, acute changes are reliably seen when the DMSA scan is obtained within days of the acute episode and gradually resolve over the next 5 months such that by 6 months any lesion demonstrated on scintigraphy is likely a fixed scar (Stokland et al, 1996a, 1996b; Ghasemi et al, 2013). Acute DMSA scan lesions persist in 36% to 52% of kidneys (Rushton and Majd, 1992) (Fig. 126-19).

Diuretic Scintigraphy

The gold standard for differentiation of obstructive and nonobstructive hydronephrosis and hydroureter is diuretic renography. This imaging is accomplished with either ^{99m}Tc -diethylenetriamine-pentaacetic acid (DTPA) or, more commonly, ^{99m}Tc -MAG3. A strict protocol should be followed to ensure accurate and reproducible results (Majd, 1989; Conway and Maizels, 1992; Shulkin et al, 2008). The clinician should review the actual drainage images, regions of interest used, and curves because any variation in technique can lead to misleading results.

There are three key elements to successful diuretic renography: hydration, bladder drainage, and timing of diuretic administration. Ideally, an intravenous line is placed for hydration before the study in addition to encouragement of oral hydration before arrival for the study. Poor hydration or poor renal function can lead to false-positive results owing to a slow uptake curve and poor diuretic response. For this reason, it is best to wait until the child is at least 1 month old. A catheter is helpful in eliminating any concerns of bladder filling affecting upper tract drainage; difficult interpretation secondary to VUR, hydroureter, or voiding dysfunction; and increased gonadal radiation exposure secondary to radioactive urine (Mandell et al, 1997).

Intravenous furosemide (1 mg/kg) is ideally given when the dilated collecting system is determined to be maximally filled; however, timing of diuretic administration is largely institution specific. Other common protocols give the diuretic 20 minutes after injection of the tracer (F+20), right after the tracer (F+0), or 15 minutes before the tracer (F-15). Although we prefer the "Well

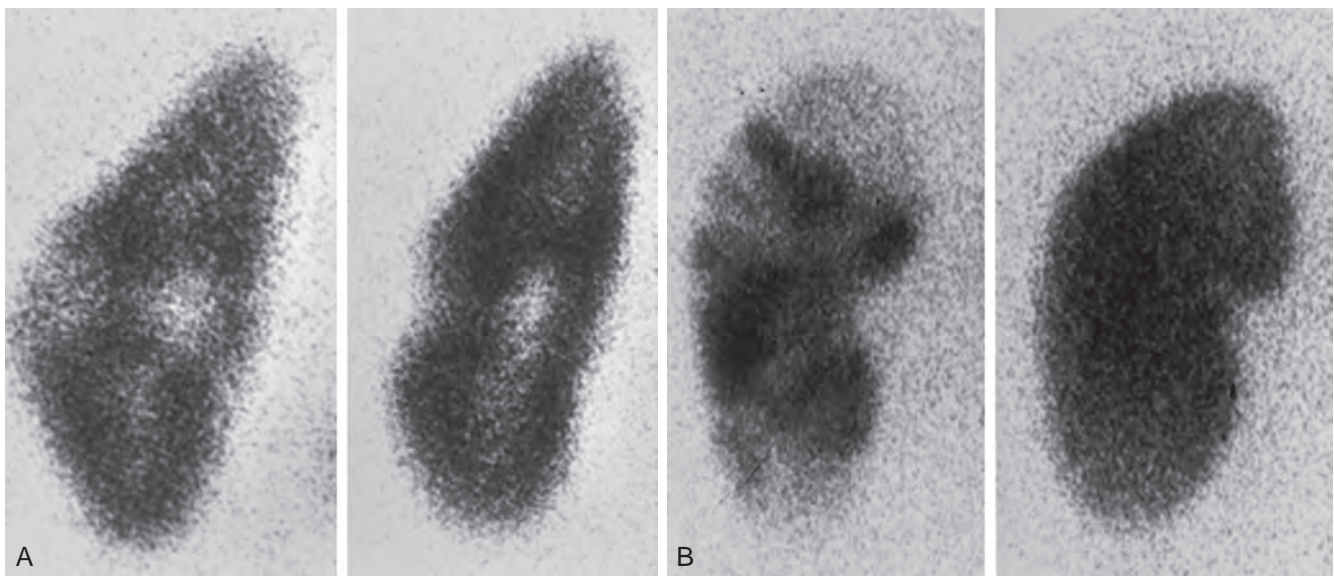


Figure 126-19. A and B, Dimercaptosuccinic acid renal scans in two different patients demonstrating areas of photopenia with preservation of the renal contour consistent with acute pyelonephritis. A, Formation of a renal scar is demonstrated, which can be differentiated from the acute lesion because of loss of the renal contour. B, Complete resolution of all areas of acute pyelonephritis is demonstrated after 6 months.

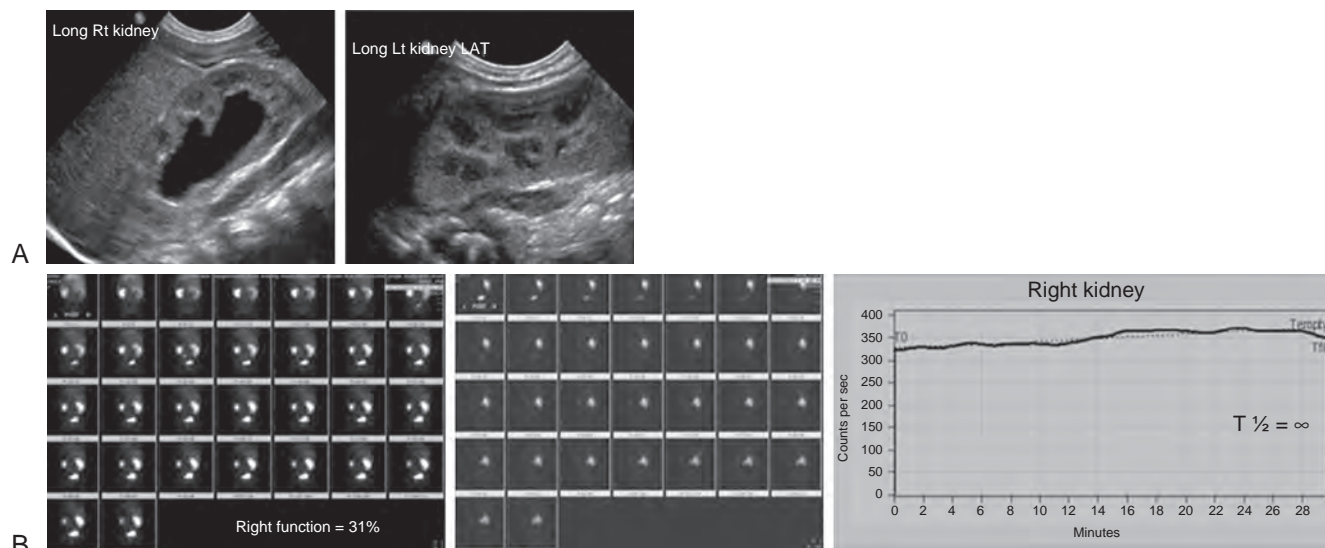


Figure 126-20. A, Renal sonogram demonstrating grade 3 hydronephrosis (mostly intrarenal dilation) without hydroureter. The left kidney is normal. B, ^{99m}Tc -Mercaptoacetyltryglycine furosemide renal scan showing high-grade ureteropelvic junction obstruction with reduced renal function from the right kidney (31%). The diuresis curve demonstrates no drainage and instead reflects continuous accumulation of tracer in the right collecting system.

Tempered" approach, it requires active participation of an experienced technician or radiologist (Conway and Maizels, 1992). The F+0 approach has shown reliable results in children with less experience needed, but it may be more difficult to interpret in slow-filling, capacious collecting systems (Wong et al, 1999). It is important to know which protocol is being used to interpret the test accurately and/or compare with previous studies. During the diuretic phase, the region of interest should be drawn around the collecting system, including the ureter only in cases of hydroureter. After completion of the diuretic phase recording, the child should be held upright for 5 minutes and allowed to void if no catheter was used. A repeat image is captured to assess residual activity after gravity-assisted drainage. Differential renal function, washout curves, and washout half-times can be computer-generated for proper interpretation of the test (Shalaby-Rana et al, 1997).

Management decisions are based on renal function, radiotracer washout half-time, shape of the washout curve, and gravity-assisted drainage. In contrast to adults, in children there are no established washout half-times that define an obstructed or unobstructed state. The washout curve is typically more revealing than the absolute half-time values, especially in young children or children after pyeloplasty in whom a dilated system may be slow to drain but not obstructed. A curve that initially slopes downward but then levels off or starts to rise (Homsy sign) is a sign of intermittent hydronephrosis secondary to the diuretic response but not indicative of obstruction (O'Reilly et al, 1996). These biphasic curves warrant further observation. In cases of equivocal washout curves, gravity-assisted drainage of less than 50% residual activity can be used to confirm obstruction (Wong et al, 2000). All the information acquired from the scan must be used to determine the proper management instead of one parameter in isolation (Figs. 126-20 to 126-24).

Radionuclide Cystography

Direct radionuclide cystography can be accurately used for detection of VUR with greater sensitivity and lower radiation

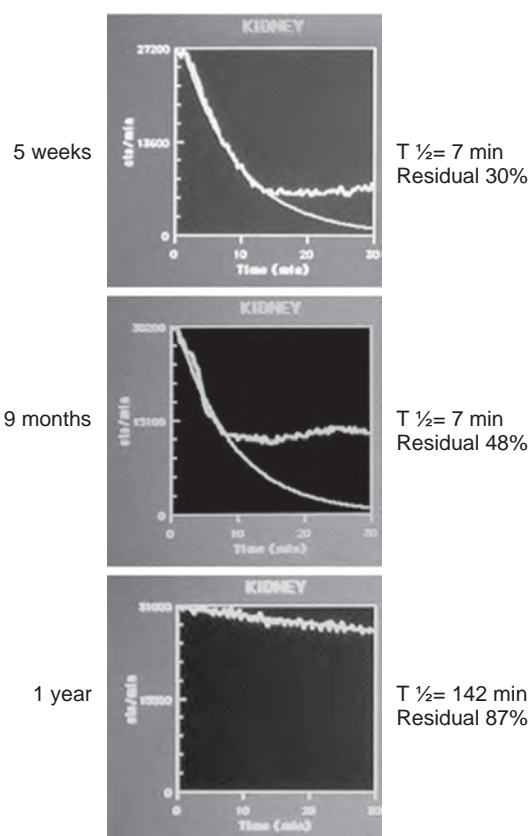


Figure 126-21. A single diuresis renogram may not be sufficient to exclude obstruction. In this example, three consecutive ^{99m}Tc -mercaptoacetyltryglycine diuresis renograms on the same patient demonstrate progressively poor drainage (prolongation of the half-time [$T_{1/2}$] and retention of tracer).

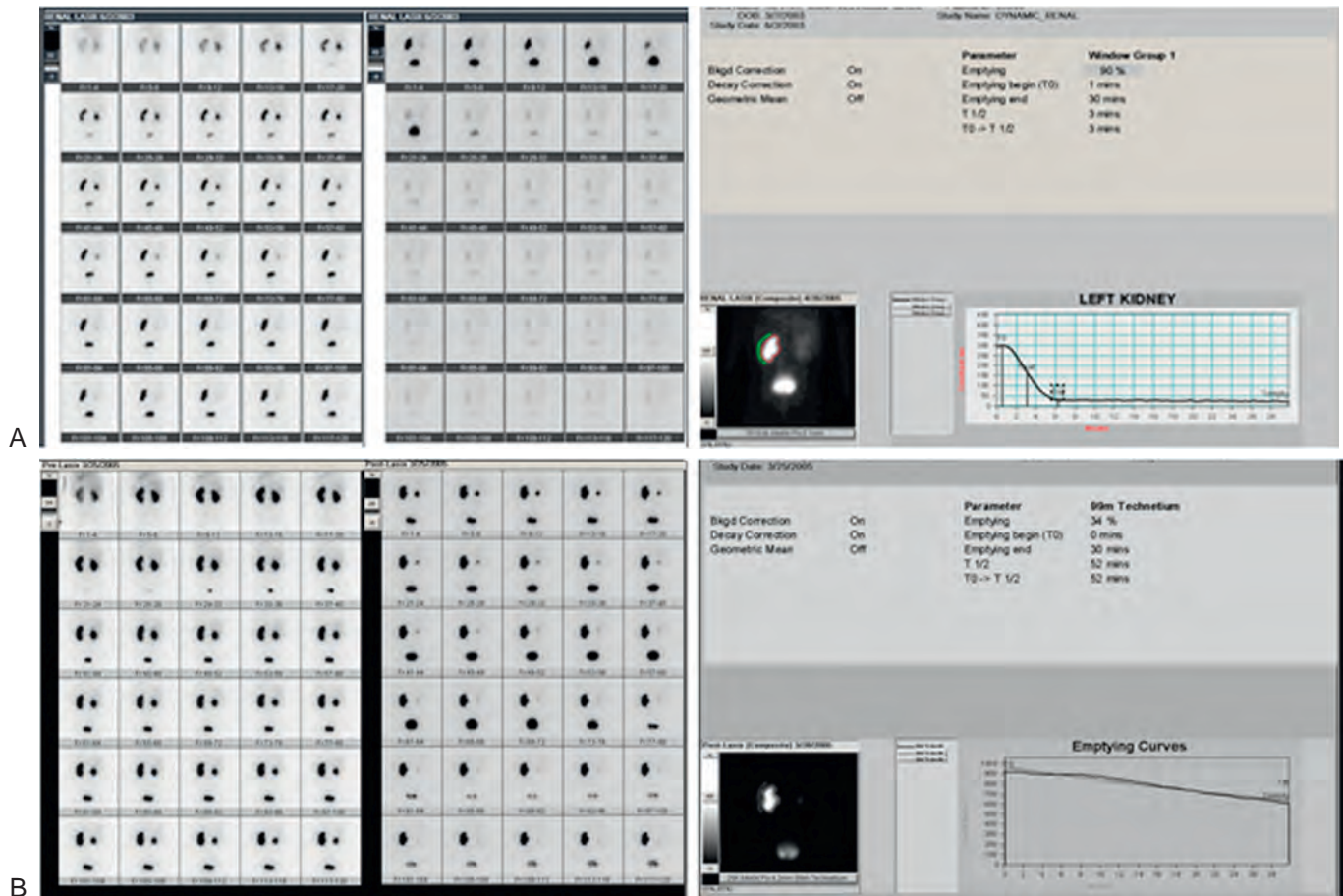


Figure 126-22. A and B, ^{99m}Tc -Mercaptoacetyltryglycine diuresis renograms performed on a 3-month-old infant with prenatally detected hydronephrosis. The dilated right collecting system appears to drain well initially (A), but on repeat renography at 2 years of age (B) demonstrates a prolonged half-time. Based on these findings, this child was managed with a pyeloplasty.

exposure than standard VCUG (Brown et al, 2000; Sukan et al, 2003; Unver et al, 2006). However, it lacks the anatomic resolution of the collecting system and urethra, still requires urethral catheterization, and is still a nonphysiologic measurement. Exact grading comparisons with VCUG can be difficult but are possible (Fretzayas et al, 1984; Zhang et al, 1987; Polito et al, 2000; Unver et al, 2006). Indirect radionuclide cystography can be performed without catheterization after radionuclide renography and provides a non-invasive, physiologic test, but it is not as sensitive as direct methods and so it is not routinely used to detect VUR (Bower et al, 1985) (Fig. 126-25).

Radionuclide Testicular Scanning

Testicular scintigraphy has been around since the 1970s and is typically promoted to distinguish between testicular torsion and inflammatory conditions of the testicle (e.g., epididymitis, orchitis, testicular appendage torsion) (Holder et al, 1981). The test is performed by intravenous injection of ^{99m}Tc pertechnetate followed by dynamic and static gamma images of the pelvis. Similar to renal scintigraphy, photon-deficient areas represent poor blood flow as in torsion, and photon-hyperdense areas can represent inflammation as in epididymitis. In

KEY POINTS

- The ALARA principle should be followed when considering imaging in children.
- A normal infant renal sonogram can be confused with mature hydronephrosis because of hypoechoic renal pyramids with a distinct corticomedullary junction.
- A normal sonogram is insufficient to risk stratify a child with acute pyelonephritis and is not a good predictor of VUR.
- Ultrasonography should not be performed for routine evaluation of cryptorchidism.
- CT and MRI may require sedation in a young child, and less intensive modalities should be used if possible.
- Diagnosis of obstruction in children with diuretic renography requires review of all parameters of the test because variations in technique can skew results considerably.

experienced centers, this technique can be very sensitive and specific (up to 100%) and potentially perform better than sonography in the setting of an acutely painful scrotum (Mendel et al, 1985; Flores et al, 1996; Wu et al, 2002). However, its lack of availability, invasiveness, and radiation

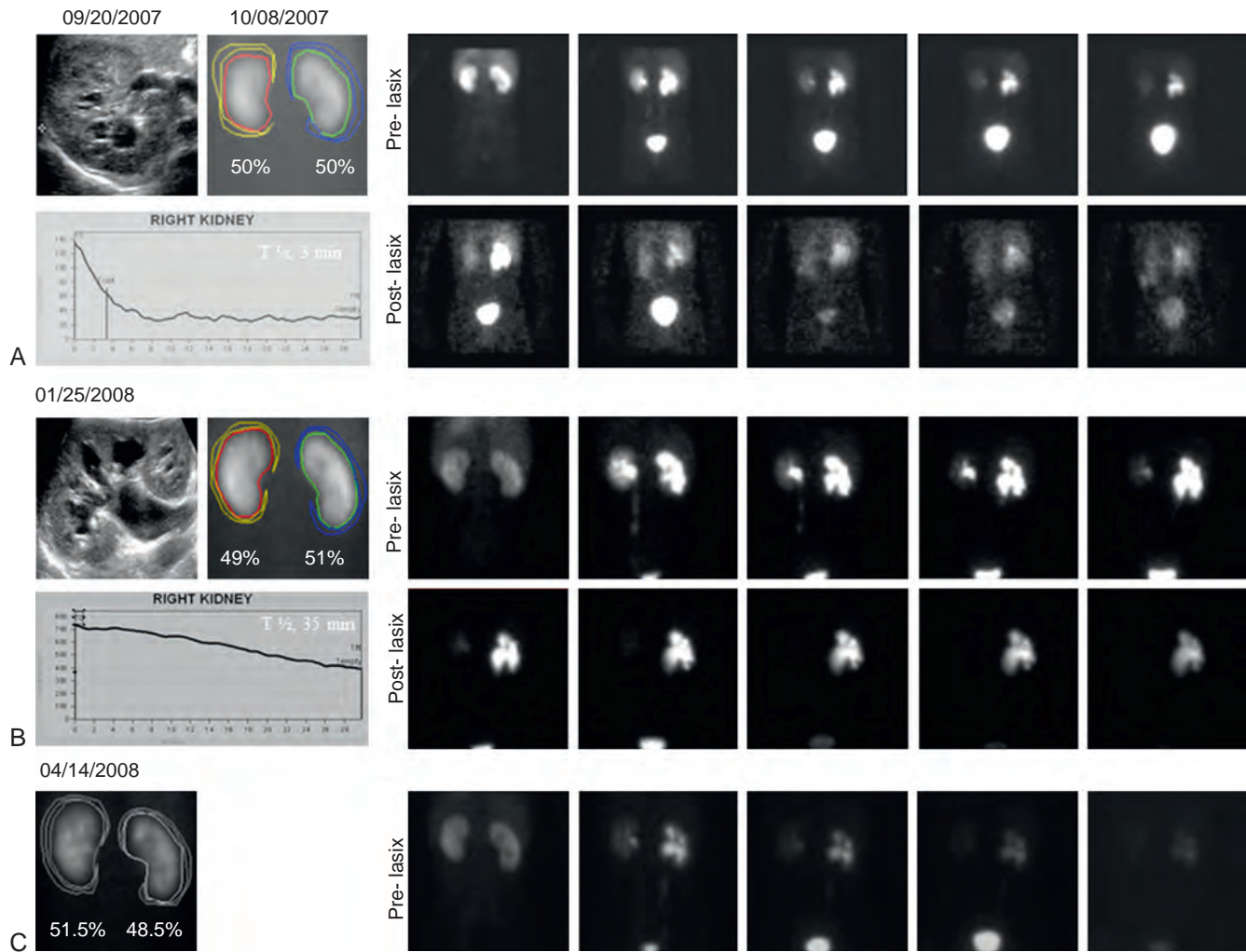


Figure 126-23. Ultrasound scan shows mild right hydronephrosis in a 7-year-old boy with right upper quadrant pain. A, Diuresis renogram shows nonobstructive drainage. The patient presented a second time with pain. This time, the sonogram showed increased dilation of the right collecting system. B, Diuresis renogram demonstrates worse drainage, and the patient reported pain after furosemide (Lasix) administration. C, After pyeloplasty, renography shows prompt spontaneous drainage; furosemide was not administered. T $\frac{1}{2}$, half-time.

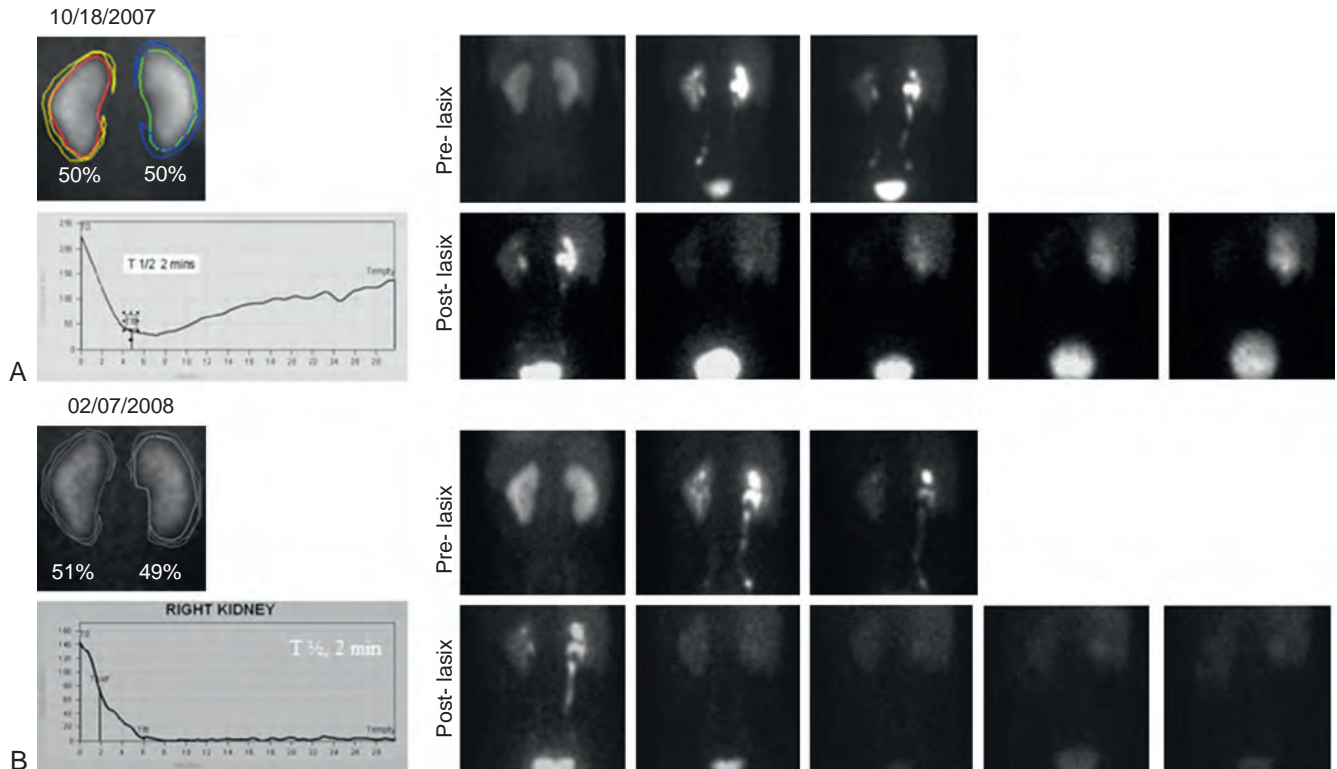


Figure 126-24. A, Initial diuresis renogram shows mild right hydronephrosis. After administration of furosemide (Lasix), there was rapid clearance of the tracer from the pelvicalyceal system with the washout half-time ($T_{1/2}$) of 2 minutes. A few minutes later, the patient developed right flank pain, and there was gradual accumulation of the tracer in the right kidney (rising second part of the curve) (A). B, Postoperative differential renal function remained stable, and drainage improved significantly.



Figure 126-25 Radionuclide cystography examples of mild (A), moderate (B), and severe (C) vesicoureteral reflux.

exposure limit its widespread adoption over ultrasonography. Perhaps the most appropriate use of testicular scintigraphy is in cases that are equivocal by examination and sonogram, but only if potentially testicle-saving surgery is not unreasonably delayed (Kodali et al, 2013).

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127 Infection and Inflammation of the Pediatric Genitourinary Tract

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Evaluation and Management of a Child with a Fever

Classification of Pediatric Urinary Tract Infections

Diagnosis of Pediatric Urinary Tract Infection

Management of Pediatric Urinary Tract Infection

Management of Post-Urinary Tract Infection

Sequelae of Pediatric Urinary Tract Infections

Uncommon Pediatric Urinary Tract Infections

Data from the Urologic Disease in America Project demonstrate just how significant a burden pediatric urinary tract infections (UTIs) are to the American public. This study indicates that 2.4% to 2.8% of all American children are affected annually by a UTI and these infections account for 1.1 million medical visits per year (Freedman, 2005). In addition, inpatient hospital costs alone for treatment of children admitted with pyelonephritis total more than \$180 million per year in the United States (Freedman, 2005).

UTIs are epidemic in children, but not all UTIs are the same. Some children have a single, sentinel UTI, whereas others suffer recurrent infections in infancy and into childhood and beyond. Some UTIs are associated with fever, and others only cause lower urinary tract symptoms or malodorous urine. Some UTIs lead to renal scarring, hypertension, and/or end-stage renal disease whereas others present no long-term sequelae. Unfortunately, at this time, there is no definitive way to predict whether a child will ever develop a UTI, to determine if they will develop further UTIs, or to determine if they will suffer long-term medical issues related to their infections. This chapter describes the pathogenesis, evaluation, and management of pediatric UTIs to facilitate the care provider's individualized management decisions for each child.

EVALUATION AND MANAGEMENT OF A CHILD WITH A FEVER

Infants and young children will frequently present to health care providers with the history of fever of undetermined etiology. Although an extensive discussion of the workup and management of febrile infants is beyond the scope of this chapter, it is important for all pediatric care providers to have a basic knowledge of the care of these patients. For children, a clinically significant fever is generally defined as a rectal temperature of 100.4° F (38° C) or higher (Sur and Bukont, 2007). In a previously healthy child 3 to 36 months of age, a temperature of 39° C or higher warrants further evaluation (Baraff et al, 1993; Baraff, 2000; American College of Emergency Physicians Clinical Policies Committee, 2003). In the vast majority of these children, the source of their fever will be a viral illness; however, 7% to 13% of these children, with no clear fever source, present with occult bacteremia and serious bacterial infections (Dagan et al, 1988; Baraff, 2000; Kadish et al, 2000). Serious bacterial infections in these patients include bacteremia, bacterial gastroenteritis, cellulitis, meningitis, osteomyelitis, pneumonia, septic arthritis, and UTIs. These infections are more common in children younger than 90 days and especially in children younger than 29 days. In children younger than 90 days, 7.2% experience a

serious bacterial infection, whereas 8.7% to 13% of children younger than 29 days will have such a serious infection (Baraff et al, 1993; Baker and Bell, 1999).

The goal of evaluating the febrile child is to ensure that serious infections are not missed and that proper treatment is initiated quickly. A summary of the evaluation and treatment of a child with a rectal temperature higher than 38° C is provided in Figure 127-1. In such an evaluation, the ability to detect a child appearing “toxic” is important, as these patients show a higher rate of serious infections. Signs and symptoms of toxicity include cyanosis, decreased activity, hyper- and hypoventilation, inability to interact with parents, irritability, lethargy, poor tone, poor perfusion, tachycardia, and poor eye contact (Sur and Bukont, 2007). It is important to keep in mind that although toxic appearance, age younger than 30 days, and rectal temperature of 39.4° C or greater are highly predictive of bacteremia, not one of these features guarantees the identification of a child with a serious bacterial infection, and absence of these features also does not rule out a serious infection (Pantell et al, 2004).

As will be discussed in more detail later in this chapter, the diagnosis of a UTI in children can be difficult because the symptoms can be nonspecific. In children aged 0 to 24 months, the presence of a fever higher than 40° C, history of a previous UTI, suprapubic tenderness, and uncircumcised penis are the most useful signs and symptoms in predicting a UTI in a febrile child (Shaikh et al, 2007). Other factors such as vomiting, diarrhea, poor feeding, and irritability are not sensitive or specific in screening for the presence of a UTI (Shaikh et al, 2007). In children older than 24 months, who are more verbal, the more classic symptoms of abdominal pain, back pain, dysuria, urinary frequency, and new-onset urinary incontinence are all predictive of UTI (Shaikh et al, 2007). One must have a high degree of suspicion and have an understanding of the possible causes of fever, especially in very young children, to diagnose the cause of the infection. UTIs are common, accounting for 7% of febrile infections in infants and 7.8% of febrile infections in children older than 24 months (Shaikh et al, 2008).

KEY POINTS: DIAGNOSIS OF URINARY TRACT INFECTION IN A CHILD

- Signs and symptoms of a UTI in young children may be nonspecific.
- UTIs are common in febrile infants.
- Children who appear toxic on evaluation require special attention.

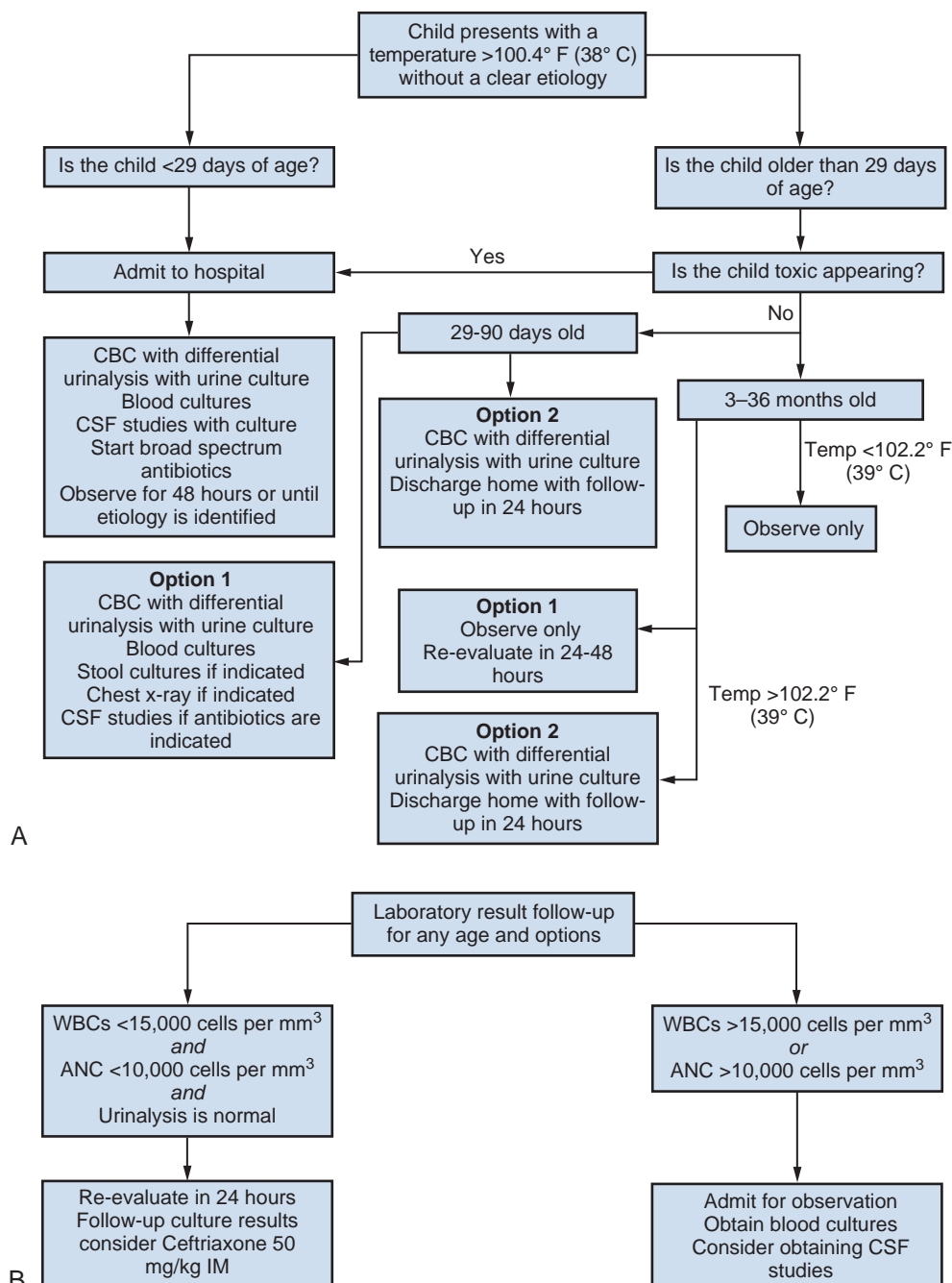


Figure 127-1. A, Algorithm for the treatment of a child aged 0 to 36 months with a fever higher than 100.4° F (38° C) with no etiology for the fever. B, Continued considerations for the treatment of a child aged 0 to 36 months with a fever higher than 100.4° F (38° C) with no etiology for the fever. ANC, absolute neutrophil count; CBC, complete blood count; CSF, cerebrospinal fluid; IM, intramuscular; WBCs, white blood cells.

Definition of a Urinary Tract Infection

What constitutes a “significant” clinical UTI in a child is somewhat controversial. Urine is normally sterile, so the presence of bacteria in a urine specimen begins to define whether a UTI is present. As will be discussed in more detail later in this chapter, the number of colony-forming units (CFU) per mL of urine used to define a UTI varies according to different criteria as well as by the method of collection. If a suprapubic aspiration was performed, then by some criteria recovery of any organisms defines a UTI. For catheterized specimens, recovery of at least 50,000 CFU/mL is required to define a UTI and 100,000 CFU/mL are required if the specimen was collected via a clean-catch method (Hoberman et al, 1994). These

different values in conjunction with the patient’s symptoms help define the likelihood of a true UTI.

Pathogenesis of Urinary Tract Infection Development in Children

The factors that contribute to UTI development in children are not yet completely understood. Host features, bacterial characteristics, and immune status all contribute to the development of pediatric UTIs. The role that factors from each of these areas play in pediatric UTI development is difficult to pinpoint, as these influences are in a constant state of flux, particularly in children. For instance,

immunity and gastrointestinal bacterial colonization are completely different in a newborn as compared to a 6-month-old child. In addition, host features such as circumcision status and toilet training may influence and change a child's risk of UTI development. In this section, we describe the current understanding about how factors from these different areas contribute to UTI development in children.

Bacterial Factors Leading to Pediatric Urinary Tract Infections

Bacteria may be divided into commensal and virulent bacteria. The term *virulence* comes from the Latin word for poisonous, *veneficus*, and is defined as the ability of an organism to cause disease in a host. Virulent bacteria that cause UTIs are otherwise known as uropathogenic bacteria. Virulent bacteria possess different adaptations and fitness factors that allow them to subvert or hijack host defenses and reside in an environment where they would not normally reside (Johnson, 1991; Stapleton, 2014). These virulence mechanisms allow the bacteria to attach initially to urogenital mucosal surfaces and then to interact with these tissues by setting off cascades of signaling and other immunologic response events and subsequently invade the bladder (Stapleton, 2014). Commensal bacteria may also cause UTIs, but commensals are defined by lacking the virulent traits that would allow bacteria to subvert a host's immune defenses.

Escherichia coli is the most commonly studied UTI-causing organism, as it is by far the most common bacterial UTI pathogen. Of the UTIs caused by *E. coli*, 80% are triggered by uropathogenic (virulent) *E. coli* (UPEC), whereas 20% of the *E. coli* causing UTIs are classified as commensal organisms (Krieger, 2002; Bien et al, 2012). This reflects the importance of virulence factors in UTI development. Virulence factors include properties that improve bacterial adherence to uroepithelial cells, properties that allow bacterial nourishment in otherwise adverse environments, properties that protect bacteria from the host's immune response, and toxins that allow bacteria to invade host cells (Fig. 127-2).

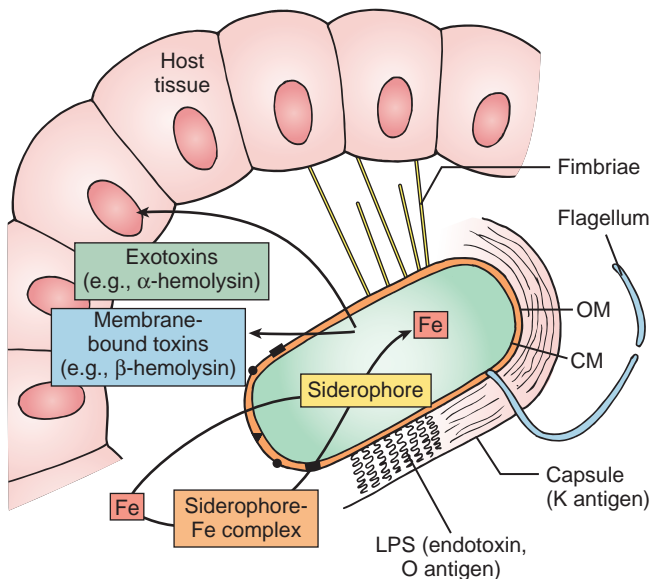


Figure 127-2. Schematic representation of an *E. coli* cell interacting with host tissue, highlighting features relevant to bacterial pathogenicity. Solid black circles, triangles, and rectangles indicate membrane proteins involved in transport, serum resistance, and so forth. CM, cystoplasmic membrane; LPS, lipopolysaccharide; OM, outer membrane. (Modified from Johnson JR. Virulence factors in *Escherichia coli* urinary tract infection. Clin Microbiol Rev 1991;4(1):80–128. Copyright 1991, American Society for Microbiology.)

Bacterial Fimbriae

Bacterial adherence is perhaps the best understood and is one of the most studied virulence traits. Adherence is considered the first step in UTI pathogenesis with special bacterial structures called *adhesins* mediating this process (Johnson and Stell, 2000; Guyer et al, 2001; Johnson et al, 2001; Schilling et al, 2001; Wullt et al, 2001). These adhesins are also known as pili or F antigens, and they are filamentous appendages that project from the bacterial cells. Fimbrial adhesins can be classified into mannose sensitive, which is more common, or mannose resistant (Krieger, 2002).

The most common mannose-sensitive adhesin is the type 1 fimbriae. Adherence of this fimbriae is blocked by solutions of D-mannose and by concanavalin A (Johnson, 1991). Receptors for type 1 fimbriae are found in the muscular layers but not the epithelium of the human bladder, ureteral epithelium, and kidney cell lines (Korhonen et al, 1981; Virkola et al, 1988; Fujita et al, 1989). Strains of *E. coli*, expressing mannose-sensitive adhesins alone, with no mannose-resistant adhesins, are more commonly associated with patients presenting with clinical symptoms of cystitis and/or asymptomatic bacteria rather than pyelonephritis, suggesting that type 1 fimbriae play a more important role in the colonization and/or infection of the bladder versus contributing to clinical symptoms of pyelonephritis (Brooks et al, 1981; Latham and Stamm, 1984; Gander et al, 1985).

One of the most studied mannose-resistant adhesins is the P fimbriae. These fimbriae were discovered to bind to and agglutinate erythrocytes of the P blood group (Kallén et al, 1980a, 1980b). The binding site for this adhesin appears to be α -galactose-(1-4), a digalactoside in neutral glycosphingolipids found on epithelial cells and red blood cells. The different P blood group antigens and phenotypes that would bind these fimbriae are found in up to 75% of the population (Johnson, 1991). Binding sites have been identified in the human kidney and bladder and isolates expressing P fimbriae have been identified in up to 70% of strains causing clinical symptoms of pyelonephritis (Johnson, 1991).

Other important adhesins that have been identified include S fimbriae, type 1C fimbriae, and O75X adhesions. Each of these has been studied and found to play a role in bacterial adherence, and the different receptors have been found in variable amounts throughout the human genitourinary tract (Table 127-1).

Following bacterial adherence, a signal transduction cascade results in the uptake of bacteria by the bladder's superficial umbrella cells (Fig. 127-3) (Martinez, 2000; Kau et al, 2005). These bacteria enter the bladder's epithelial cells, resulting in the formation of intracellular bacterial communities (IBCs) (Anderson, 2003). During the formation of these IBCs, these normally fast-growing bacteria become much slower and eventually multiply to fill most of the umbrella cell's cytoplasm (Kau et al, 2005). Eventually the bacteria within the IBCs flux out of the host cell, which may allow bacteria to spread within the urinary tract. The bacteria may then re-enter the bladder epithelial cell and form a quiescent reservoir within the cell, which may continue to go unrecognized by the host's immune response, allowing these bacteria to reside within the host and possibly result in recurrent infections (Justice et al, 2004).

Aerobactin

All living cells, including bacteria, need iron. *E. coli* uses iron for oxygen storage and transport, DNA synthesis, electron transport, and metabolism of peroxides (Bagg and Neilands, 1987). As part of the host's response to infection, the amount of available iron is reduced to the invading pathogen by decreasing intestinal absorption, synthesizing additional iron-binding proteins, and shifting iron from the plasma pool into intracellular storage (Johnson, 1991). Therefore, *E. coli* face a considerable challenge in acquiring and meeting their iron needs during an infection. The siderophore aerobactin extracts iron from host iron-binding proteins and then delivers the iron directly to bacterial iron centers (Carbonetti et al, 1986; de Lorenzo and Neilands, 1986; Williams

TABLE 127-1 Binding of *Escherichia coli* Adhesins to Human Kidney and Bladder Sections

TISSUE SITE	ADHESIN BINDING				
	S FIMBRIAE	P FIMBRIAE	TYPE 1 FIMBRIAE	TYPE 1C FIMBRIAE	O75X ADHESIN
KIDNEY					
Bowman capsule	+++	+++	—	—	+++*
Glomerulus	+++	+++	—	—	—
Proximal tubulus	++	++	+++	—	+++*
Distal tubulus	++	++	(+)	++	+++*
Collecting duct	++	+	(+)	++	+++*
Vessel walls	+++†	+++†	+++	+++†	—
BLADDER					
Epithelium	++	+	—	—	+
Vessel walls	+++†	+++†	++	+++†	—
Muscular layer	+	+	+++	+	+
Connective tissue	++	—	—	—	+++

*To basement membranes.

†Mainly to endothelial cells.

—, undetectable binding; +, weak binding; ++, moderate binding; +++, intense binding.

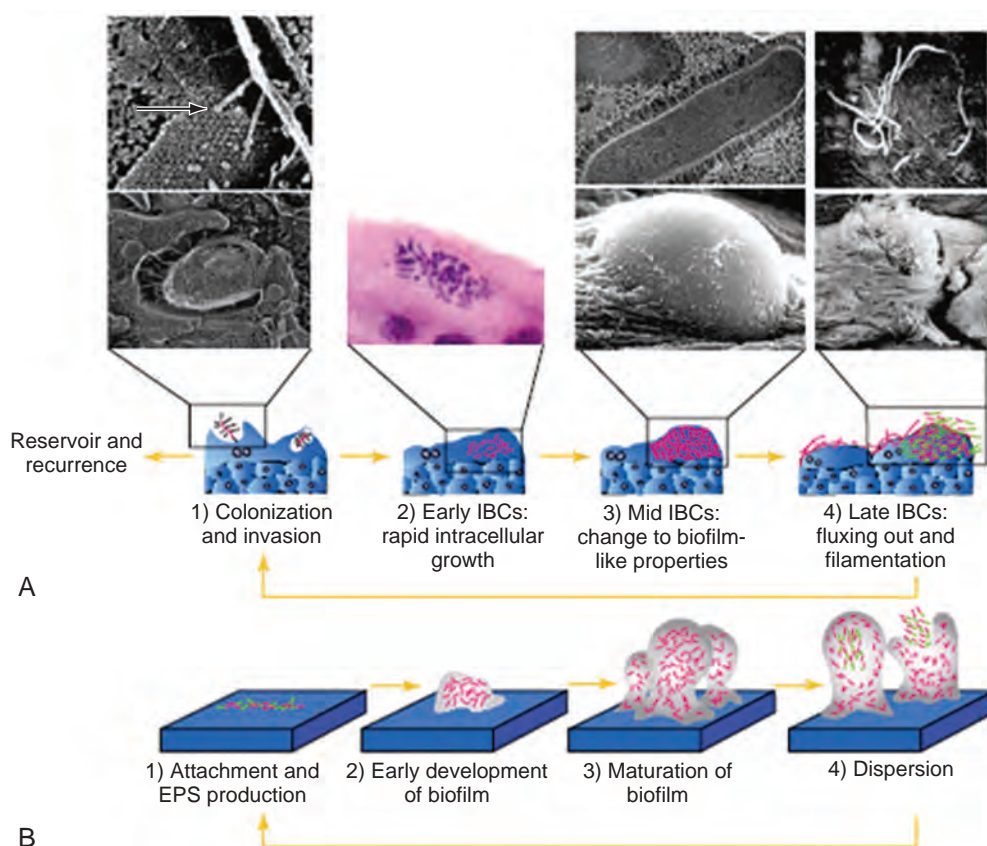
Modified from Johnson JR. Virulence factors in *Escherichia coli* urinary tract infection. Clin Microbiol Rev 1991;4(1):80-128.

Figure 127-3. **A**, Stages of bacterial invasion of uropathogenic *Escherichia coli* attaching to uroepithelial cell and subsequent formation of pod and dispersion. **B**, The similar stages compared with previously known biofilm formation on inert surfaces such as urethral catheters. EPS, extracellular polymeric substances; IBCs, intracellular bacterial communities. (From Kau A, Hunstad D, Hultgren SJ. Interaction of uropathogenic *Escherichia coli* with host uroepithelium. Curr Opin Microbiol 2005;8:54.)

and Carbonetti, 1986). Bacterial strains with the aerobactin system have a growth advantage in low iron conditions, including the serum and dilute urine.

Hemolysin

The cytolytic protein secreted by most hemolytic *E. coli* is known as alpha hemolysin (Cavaliere et al, 1984). Alpha hemolysin lyses erythrocytes of all mammals and is also toxic to a wide range of host cells contributing to inflammation, tissue injury, and impaired host defenses (Johnson, 1991). In human UTIs, hemolysin production is most common in bacterial strains from patients suffering pyelonephritis as compared to patients with cystitis symptoms.

Capsular Polysaccharide

Capsular polysaccharides, of which *E. coli* has more than 80 types, are linear polymers that coat the bacterial cell, interfering with antigen detection and protecting the cell from host defense detection (Jorgensen et al, 1976). The capsules of most uropathic *E. coli* are composed of group II polysaccharides and are otherwise known as K antigens. Encapsulated K bacterial strains are less well phagocytosed and also have anticomplementary activities, as compared to nonencapsulated strains, which leads to impaired bacterial clearance and complement activation (Howard and Glynn, 1971; Harber et al, 1986). The degree of host defense impairment tends to be proportional to the amount of polysaccharide (Howard and Glynn, 1971). Studies have shown that capsular polysaccharides are poor immunogens in animals and humans, with the K1 polysaccharide yielding a measurable antibody response in only one third of animals immunized with killed K1 bacteria in one study, and another study showing that only 12% of humans suffering pyelonephritis demonstrated an antibody response when the infecting organism was a K1 strain (Kaijser, 1981; Salit et al, 1988). These encapsulated strains have been found to be commonly associated with pyelonephritic UTIs rather than cystitis (Johnson, 1991).

KEY POINTS: BACTERIAL FACTORS

- UTI-causing bacteria may be subdivided into commensal and virulent types; although both cause UTI, virulent organisms cause the majority of UTIs.
- Virulent bacteria possess different adaptations and fitness factors that allow them to subvert or hijack host defenses and reside in an environment where they would not normally reside.
- There are a multitude of bacterial virulence factors that bacteria have, including properties that improve bacterial adherence to uroepithelial cells, properties that allow bacterial nourishment in otherwise adverse environments, properties that protect bacteria from the host's immune response, and toxins that allow bacteria to invade host cells.

Host Risk Factors Leading to Pediatric Urinary Tract Infections

Host factors that seem to affect the incidence of UTI development in children are associated with age, genetics, gender, race, anatomic, functional, and behavioral features.

Gender and Age

The only time that UTIs are more prevalent in boys than in girls is at an age younger than 1 year. At all other ages, even among the elderly, UTIs are far more prevalent in females than in males (Shortliffe and McCue, 2002). About 2.7% of boys, compared to 0.7% of girls, experience a UTI during the first year of life (Winberg et al, 1975). After 1 year of life, the incidence of UTI development drops to 0.03% to 0.2% in males and increases to 1% to 3% in

females (Foxman, 2002). It has been estimated that 7% of girls and 2% of boys suffer a UTI by the age of 6 years (Marild, 1998).

UTIs are common in febrile children, with an incidence of 3% to 5%; however, the risk is greater in girls than in boys after 2 months of age. Females aged 2 months to 2 years with a fever have a relative risk of UTI of 2.27 compared to males (American Academy of Pediatrics, 1999). In older children, especially in sexually active teenagers, there is also a female predominance of UTIs (Ma and Shortliffe, 2004).

Race

UTIs occur in all races, but they appear more commonly in Caucasian girls compared to girls of other races (Keeton and Hillis, 1975; Shaw et al, 1998; Shaw and Gorelick, 1999). In one study evaluating children less than 2 years of age, the authors found that UTIs were the most prevalent in Caucasian children, followed by Hispanic, and then African-American girls, whereas in boys UTIs were more common in Hispanics, followed by Caucasians, and they were least common in African-American boys (Bachur and Harper, 2001). Certainly circumcision status confounds this data, but several studies have shown that African-Americans have fewer UTIs, have lower rates of vesicoureteral reflux (VUR), and may be less likely to develop reflux nephropathy as compared to Caucasians and Hispanics (Kunin, 1968; Lohr et al, 1994; Hoberman and Wald, 1997; Pinto, 2004).

Genetics

Although certain individuals appear to be more prone to developing UTIs, no specific genes have been identified that are linked to developing these infections. Some observations on the occurrence of UTIs, however, lend evidence that there may be a genetic component to UTI development. Children with a history of VUR are still commonly susceptible to UTI development after their reflux resolves (Mansfield et al, 1995; Beetz et al, 2002). In addition, sisters of patients with recurrent UTIs have higher rates of significant bacteriuria compared to the general public (Stauffer et al, 2004). Moreover the two greatest risk factors for women aged 18 to 30 years to develop recurrent UTIs include age at first infection and a mother with a history of UTIs (Scholes et al, 2000).

As previously discussed, P fimbriae are a common virulence factor identified on UPEC. At the time of this adhesin's discovery, glycolipids characterizing the P blood group antigens were found on host uroepithelial cells, acting as bacterial receptors. As it was suspected that individuals with this P blood group phenotype would be more susceptible to UTI development, children with recurrent UTIs were tested for this phenotype. A study by Lomberg and coworkers (1983) identified that 97% of girls with recurrent pyelonephritis expressed the P1 blood group phenotype, in comparison to 75% of controls without UTI.

Other blood group antigens expressed on the urothelial surface also appear to influence UTI susceptibility. These include the ABO, Lewis, and secretor phenotypes. Adult women with Le (a-b-) and Le (a+b+) blood phenotypes are three times as likely to have recurrent UTIs compared to women with the Le (a-b+) phenotype (Sheinfeld et al, 1989). In addition, Jantusch and coworkers (1994) identified that in children with a history of UTIs, the frequency of Le (a-b-) is also increased. In addition, the nonsecretor phenotype of ABH blood group antigens (ABH Ag) has been identified as associated with renal scars seen on ^{99m}Tc-dimercaptosuccinic acid (DMSA) scans in children with VUR and UTIs (Kanematsu et al, 2005).

Circumcision

Multiple studies demonstrate that circumcision reduces the rate of UTI development in the first 6 months of life by almost tenfold (Roberts, 1986; Wiswell et al, 1987; Schoen et al, 2000). This risk appears to correlate with a period during the first 6 months of life when there is an increased amount of

uropathogenic bacteria colonizing the prepuce. This colonization appears to decrease and resolve by 5 years of age (Glennon et al, 1988; Wiswell et al, 1988). In a retrospective review, Wiswell and Roscelli (1986) examined the incidence of UTIs diagnosed by catheterization or suprapubic aspirate (SPA) in more than 200,000 males born in U.S. Army hospitals between 1974 and 1983. They found the UTI incidence in circumcised males was 0.11%, whereas the incidence of infection in uncircumcised males was 1.12%. This compared to an incidence of 0.57% in female children during this study period.

These findings have led to controversy regarding the advantages and disadvantages of routine circumcision in boys. The American Academy of Pediatrics (AAP) Task Force on Circumcision (2012), while weighing the risks and benefits of circumcision in boys (including the prevention of UTIs in neonates), stated that the health benefits of newborn male circumcision outweigh the risks. Although they could not justify routine circumcision in all males, they concluded that the benefits of circumcision are great enough to justify access to this procedure to families choosing it and to warrant third-party payment for the procedure. **However, the question of whether circumcision actually prevents infections later in life continues to be debated in the literature.** Using case-control methods, Singh-Grewal and coworkers (2005) identified that circumcision continues to decrease the rate of UTI development before and after 1 year of age. The degree of risk reduction, however, is dependent on the patient. In a meta-analysis, Singh-Grewal and coworkers (2005) identified that normal, healthy boys have a 0.5% to 1% risk of developing a UTI, and they calculated that approximately 111 healthy boys would need to be circumcised to prevent one UTI. Boys who have a history of recurrent UTIs and those who have high-grade VUR have a 10% and 30% risk of UTI recurrence, respectively (Singh-Grewal et al, 2005). These authors further identified that the number of boys who would need to undergo circumcision in these high-risk groups to prevent a UTI is 11 boys with a history of recurrent UTIs and 4 boys with a history of high-grade VUR.

When evaluating cost data, circumcision also appears to decrease the cost of UTI treatment in boys who develop a UTI who are less than 1 year of age. Schoen and coworkers (2000) identified that not only were uncircumcised males more likely to experience UTIs, but the cost of treating infections in uncircumcised boys was 10 times higher as compared to circumcised patients. This increased cost was accounted for by uncircumcised males developing UTIs at a younger age, and by a greater number of these patients requiring hospital admission to treat their infection. They concluded that newborn circumcision is a valuable preventive health measure and is also a long-term cost-saving measure.

Fecal and Perineal Bacterial Colonization

The vast majority of bacteria causing UTIs enter the bladder via the fecal-perineal-urethral route, whereby bacteria that colonize the gut, perineum, and periurethral area ascend via a retrograde fashion into the lower urinary tract (Stamey and Sexton, 1975; Pfau and Sacks, 1981; Yamamoto et al, 1997). As the saying goes, “you are what you eat,” and we are only beginning to understand the role that the fecal microbiota plays in human disease. **In women who suffer recurrent UTIs, studies demonstrate that the majority of these reinfections are caused by the same strain of UPEC that persists in the fecal microbiota for 12 or more months and circulates through the fecal and vaginal reservoirs to cause recurrent infections** (Russo et al, 1995; Hooton, 2001; Czaja et al, 2009). It is unclear whether the same is true in children suffering from recurrent UTIs, but this certainly could be one mechanism contributing to these pediatric infections.

Studies also demonstrate that women who suffer recurrent UTIs have increased vaginal and periurethral colonization with enteric organisms with concomitant loss of normally predominant and protective vaginal lactobacilli (Hooton et al, 1994; Gupta et al, 1998). **Clinical studies show that women lacking vaginal lactobacilli are at increased risk for vaginal colonization**

with *E. coli*. Exposure to antibiotics, especially trimethoprim-sulfamethoxazole (TMP-SMX), may eradicate these presumably protective lactobacilli (Stapleton, 2014). Whether a similar mechanism predisposes to UTI in children remains to be demonstrated; however, Hansson and coworkers (1989) did show that treatment of schoolgirls for nonurologic infections, usually otitis media, resulted in colonization and bacteriuria with organisms likely to cause a symptomatic infection.

Anatomic Abnormalities

Clearly, anatomic abnormalities of a child's genitourinary system may lead to UTI development. Infections associated with urinary tract malformation will usually appear before 5 years of age (Chang and Shortliffe, 2006). It is important to detect these abnormalities, as many may be surgically correctable, and persistence of these abnormalities may lead to renal damage and/or recurrent infections. Possible anatomic abnormalities include:

- Hydronephrosis
- Ureteropelvic or ureterovesical junction obstruction
- VUR
- Infection stones
- Infected nonfunctional renal segments
- Vesicointestinal or urethrorectal fistulae
- Vesicovaginal fistulae
- Infected necrotic papillae

Given the role that anatomic abnormalities play in pediatric UTI development, the AAP continues to recommend that a renal and bladder ultrasound (RBUS) be performed on all children aged 2 to 24 months after they have experienced their first febrile UTI (Subcommittee on Urinary Tract Infection et al, 2011).

Vesicoureteral Reflux

The role that VUR plays in UTI development and the controversies surrounding it will be discussed in greater detail later in this chapter and in Chapter 137. VUR has been identified in 1% to 2% of all newborns, but it is found in 25% to 40% of children after their first episode of UTI (Hellerstein, 1995; Greenfield and Wan, 1996). **Although VUR may be present in a child who has suffered a pyelonephritic infection, it is important to remember that the majority of children who have suffered from pyelonephritis do not have VUR.** Rushton and Majd found that in children suffering DMSA-proven pyelonephritis, only 37% were shown to have VUR (Rushton et al, 1992). Kidneys associated with higher-grade VUR (grades III-IV), however, were twice as likely to exhibit pyelonephritic changes on DMSA scan (Rushton et al, 1992). The role that VUR plays in UTI development is complex and not completely understood. Variables such as reflux grade, patient age, gender of the child, and presence of bowel and bladder dysfunction most likely contribute to UTI development in the presence of VUR.

Sexual Activity

Previous studies have shown that sexual activity increases the risk of UTI development. Kunin (1968) demonstrated that sexually active females suffer more UTIs than sexually inactive females. This finding has prompted some to suggest that UTI may be used as a marker of teenage sexual activity (Nguyen and Weir, 2002). However, this relationship remains unclear.

Bladder and Bowel Dysfunction

Bladder and bowel dysfunction, also known as dysfunctional elimination syndrome, is known to contribute to pediatric UTI and VUR. Koff and coworkers (1998) originally coined the term *dysfunctional elimination syndrome*, which defined children who were without any neurologic disorder but who suffered from infrequent voiding, constipation, and/or bladder overactivity. Generally, in addressing children with bladder dysfunction, there are two different entities: (1) overactive bladder and (2) dysfunctional voiding.

Dysfunctional voiding terminology is used to describe children with no neurologic issues who exhibit increased activity of their pelvic floor during voiding (Sillen, 2008). Overactive bladder is defined as urinary urgency with or without urge incontinence, usually with frequency and nocturia (Wein and Rovner, 2002). Children suffering from dysfunctional elimination will commonly present for evaluation of such symptoms as recurrent UTIs (with or without fever), daytime or nighttime urinary incontinence, urinary urgency, urinary frequency, constipation, and/or encopresis.

Children suffering bladder dysfunction are relatively common. In a study of more than 3500 school-age children, Hellström and coworkers (1990) found that 6% of girls and 3.7% of boys had daytime urinary incontinence and more than 8% of the girls showed a history of UTI. Another population-based study examined 1127 children aged 6 to 9 years and found that 29% reported at least one symptom suggestive of bladder dysfunction. Of these children, 9.4% of the girls and 2.8% of the boys had a reported history of a previous UTI (Hansen et al, 1997).

There also seems to be a significant association between bladder and bowel dysfunction and VUR. Bladder overactivity alone has been identified in 8% to 75% of children who also were found to have VUR (Taylor et al, 1982; Koff and Murtagh, 1983; Griffiths and Scholtmeijer, 1987; van Gool et al, 1992; Scholtmeijer and Nijman, 1994; Koff et al, 1998; Yeung et al, 2006). When examining children with VUR, the prevalence of all bladder dysfunction is reported to be between 18% and 50% (Snodgrass, 1991, 1998; van Gool et al, 1992; Scholtmeijer and Nijman, 1994; Koff et al, 1998; Homayoon et al, 2005; Yeung et al, 2006). When Koff and coworkers introduced the concept of dysfunctional elimination syndrome in 1998 they reported it to be present in 46% of their cohort suffering from VUR.

Treatment of a child's bladder and bowel issues reduces recurrent UTIs and improves VUR resolution. Treating children suffering from bladder overactivity with anticholinergics alone resulted in VUR resolution or improvement in 44% to 79% of children (Koff and Murtagh, 1983; Homayoon et al, 1995; Scholtmeijer and Nijman, 1994). Treatment of children suffering from dysfunctional voiding with biofeedback resulted in VUR resolution in 55% to 63% of cases and improvement in VUR grade after 1 year of therapy (Palmer et al, 2002; Kibar et al, 2007). Treating bladder dysfunction improves a child's incontinence and reduces the risk of UTI development. Schulman and coworkers (1999) treated 366 patients referred for voiding dysfunction with various treatments including antibiotic prophylaxis, biofeedback, anticholinergics, and psychological counseling. After a mean of 22 months, treatment resulted in the resolution of daytime wetting in 45% of patients, improvement in daytime incontinence in 37% of patients, and improvement or cure of nighttime wetting in 69% of patients. Sixty-four percent of the children never developed another UTI, and VUR resolved in 53% of patients. Treatment of constipation improves daytime and nighttime urinary incontinence and helps reduce the incidence of recurrent UTIs. In a study by Loening-Baucke (1997), 234 patients were treated for constipation. At baseline, 46% of these patients suffered from either daytime and/or nighttime urinary incontinence, whereas 11% had suffered at least one UTI. The UTIs were more common in constipated girls compared to constipated boys. Follow-up at least 12 months after starting constipation therapies showed that constipation was successfully relieved in 52% of the children. Relief of constipation resulted in the disappearance of daytime urinary incontinence in 89% and enuresis in 63%, and disappearance of all UTIs in all patients who were without any genitourinary tract anatomic abnormalities.

Neurogenic Bladder

Children with neurogenic bladders and elevated bladder storage pressures risk hydronephrosis and renal damage from these increased pressures. In addition to this increased pressure, the physiologic effects of UTI have also been demonstrated to increase intrarenal pelvic pressures and to contribute to an even greater likelihood of renal damage in these individuals (Hansen et al, 2003). When

left untreated, children with neurogenic bladders that fill or empty at abnormally high pressures appear to be at higher risk of developing UTIs and renal damage, possibly because of their inability to clear the bacteria spontaneously. Clean intermittent catheterizations facilitate the emptying of the bladders of patients with neurogenic bladder and lower chronic bladder distention and bladder pressure. Multiple studies demonstrate that 40% to 80% of individuals who intermittently catheterize develop chronic bacteriuria and/or pyuria and most are asymptomatic. Importantly, this catheter-associated asymptomatic bacteriuria (ASB) appears to lack morbidity most of the time (Geraniotis et al, 1988; de la Hunt et al, 1989; Joseph et al, 1989; Gribble and Puterman, 1993; Johnson et al, 1994; Schlager et al, 1995). Ottolini and coworkers (1995) concluded that in the absence of VUR, ASB in patients managed with clean intermittent catheterization is not a significant risk factor for renal damage and does not require antibiotic therapy. In addition, despite the fact that most of these children have urine colonized with bacteria, most can undergo urodynamic studies without the need for prophylactic antibiotics (Shekarritz et al, 1999).

Some clinicians prescribe daily prophylactic antibiotics for children who perform chronic clean intermittent catheterization. This practice may delay or decrease bacteriuria in the short-term, but in the long term these prophylactic antibiotics have not been shown to be beneficial and instead may lead to the development of bacterial resistance (Johnson et al, 1994; Clarke et al, 2005). Studies have also been performed evaluating the use of different catheters and their effect on UTI development. The use of sterile versus nonsterile, single versus multiuse, and lubricated versus nonlubricated catheters have shown no benefit in reducing the risk of UTI development (Schlager et al, 1995; Moore et al, 2007). Bakke and Vollset (1993) identified that risk factors for UTI development in men and women treated with intermittent catheterization included high mean catheterization volume in women and low frequency of catheterization in men. In addition, they found that patients managed with prophylactic antibiotics were less prone to developing bacteriuria, but were more prone to developing clinical UTIs. These findings point toward the role that timely, scheduled catheterizations play in preventing UTIs in those patients managed with clean intermittent catheterization.

Iatrogenic Factors

Catheter-associated UTI is the most common nosocomial infection, accounting for more than one million cases each year in U.S. hospitals and nursing homes (Tambyah and Maki, 2000). The risk of UTI increases with the duration that the catheter is in place, and the overall incidence of bacteriuria is 8% and ranges from 3% to 10% per day (Sedor and Mulholland, 1999). In children, nosocomial UTIs account for 6% to 18% of nosocomial infections on pediatric hospital services (Ford-Jones et al, 1989; Lohr et al, 1989). Nosocomial UTIs typically necessitate one extra hospital day per patient or nearly one million extra hospital days annually in the United States (Foxman, 2002). A 2000 report estimated that each episode of nosocomial UTI added \$676 to each hospital bill, and the annual cost of nosocomial UTI in the United States that year was between \$424 and \$451 million (Saint, 2000). The best way to avoid this morbidity and its related cost is the judicious use of urinary catheters and the removal of urethral catheters in hospitalized patients as soon as they are no longer medically necessary.

Immune Status

Generally, UTIs in young, healthy women are benign conditions with no long-term effects. In contrast, UTIs in young children and geriatric adults seem to be more complicated, with increased morbidity and long-term consequences (Shortliffe and McCue, 2002). Although this contrasting paradigm is incompletely understood, we know that the immune system is diminished at either end of the age spectrum, which may make younger and older individuals more

susceptible to urinary infections. Clearly, the first few months of life appear to be the time of greatest risk for the development of UTI (Chang and Shortliffe, 2006). This increased susceptibility may in part be a result of an immature immune system. Serum IgG is lowest from age 1 to 3 months, and serum IgA is also found in lower concentrations during the first several months of life and is known to be absent or almost absent along the urothelium during this time (Svanborg Eden et al, 1985; Flidner et al, 1986; Yoder and Polin, 1986). Urinary secretory IgA and total IgA increase during the first year of life and are higher in children who are breastfed (James-Ellison et al, 1997). Currently, the exact benefits of breastfeeding in UTI prevention remain unclear, but some case-control studies do confer a protective effect in breastfed children (Hanson, 1998). Pisacane and coworkers (1992) showed that full or partial breastfeeding may provide a protective effect against UTIs in the first 6 months of life.

The incidence of UTI among both women and men who are seropositive for HIV is also greater compared to the general population (Evans et al, 1995; Schonwald et al, 1999). This same trend holds true for children infected with the HIV virus, with 20% suffering bacterial UTIs with both common and opportunistic infections (Grattan-Smith et al, 1992). However, children with primary immunodeficiency diseases do not generally appear to be more prone to developing UTIs (Montini et al, 2011). Children with primary antibody-deficiency states as well as those with severe combined immunodeficiency syndromes affecting both T-cell and B-cell function, who are known to be prone to multiple bacterial infections, actually suffer very few UTIs (Sideras, 1995). When UTIs do develop in these children, associated abnormalities of their genitourinary anatomy commonly play a role (Forbes et al, 1976; International Nijmegen Breakage Syndrome Study Group, 2000). **Therefore, children with these immunologic disorders should be evaluated in a similar fashion to nonimmunocompromised children.**

When discussing the role that defects in one's immune system may play in UTI development, one should also consider the role that a strengthened immune system can play in UTI prevention. Based on these thoughts, there have been attempts to develop UTI vaccines. Since the mid-1990s, several vaccine approaches have been explored, including the use of heat-killed whole bacteria, bacterial cell extracts, and purified UPEC-associated virulence factors as antigens (Barber et al, 2013). A vaccination using a vaginal suppository containing 10 heat-killed strains of uropathogenic bacteria, known as Solco-Urovac, was studied in women (Uehling et al, 2003; Hopkins et al, 2007). In phase 2 clinical trials it was shown to reduce the risk of *E. coli*-associated UTI development in sexually active women between the ages of 20 and 50 years with a history of recurrent UTI. Unfortunately, no phase 3 trial was ever initiated, namely because there were no statistically significant levels in anti-*E. coli* antibody levels between vaccinated and placebo-control groups.

Other bacterial factors have been targeted as possible vaccine candidates, including the type 1 pilus-associated adhesin FimH and UPEC-associated iron acquisition systems. Vaccination with a purified FimH coupled with its periplasmic chaperone FimC has offered protection against UPEC in both murine and primate cystitis models (Langermann et al, 1997, 2000; Thankavel et al, 1997). Pathogenic UTI-causing bacteria rely on iron chelating molecules and receptors that allow them to scavenge essential iron from the host (Wiles et al, 2008). The use of purified bacterial iron receptor proteins for vaccination has shown mixed results. Two iron receptors tested as vaccines in mice, IreA and LutA, provided protection against cystitis, whereas vaccination with another iron receptor, Hma, has demonstrated protection against pyelonephritis, but not cystitis (Alteri et al, 2009).

These preliminary studies highlight how the focus on different virulence factors may serve as valuable vaccination candidates to prevent UTI from developing. However, similar to our current experience with anticancer chemotherapeutics, we must remember that the use of such factors in vaccine target development may result in inadvertent effects on members of the endogenous microfloras that

naturally colonize our bodies (Barber et al, 2013). Certain delivery methods and other adjuvants may be used in the future to prevent such side effects, and certainly such therapeutics may be useful for individuals susceptible to UTI development, whereas in others the costs and risks may not warrant vaccination.

KEY POINTS: HOST RISK FACTORS

- There is a multitude of host factors that may make a child more susceptible to UTI development.
- The only time when UTIs are more prevalent in boys than in girls is at less than 1 year of age.
- Circumcision reduces the rate of UTI development in the first 6 months of life by almost tenfold.
- Dysfunctional elimination syndrome is an important factor contributing to pediatric UTI development, and treatment of a child's bladder and bowel issues reduces recurrent UTIs and improves VUR resolution.
- In the absence of VUR, ASB in patients managed with clean intermittent catheterization is not a significant risk factor for renal damage and does not require antibiotic therapy.
- Catheter-associated UTI is the most common nosocomial infection and the majority of these infections may be prevented with the judicious use of indwelling catheters.

CLASSIFICATION OF PEDIATRIC URINARY TRACT INFECTIONS

There are several ways to classify UTIs: as complicated versus uncomplicated, as upper (pyelonephritis) versus lower (cystitis), and as first infection versus recurrent infections. A complicated UTI describes infections in individuals who have anatomic or functional abnormalities or the presence of foreign bodies such as ureteral stents or indwelling urethral catheters. This classification, however, may not be best applied to children, as infections in neonates or infants are presumed to be complicated because of the common occurrence of urinary tract anatomic abnormalities and the high risk of morbidity in these young patients (Benador et al, 1997; Smellie et al, 1998).

UTIs are usually classified as involving the upper urinary tracts, based on the patient's clinical symptoms. Children are generally assumed to have pyelonephritis when they present with a UTI associated with high fevers, nausea, vomiting, flank pain, or lethargy. On the other hand, cystitis is suspected when the child is afebrile and has only lower urinary tract symptoms including urinary urgency, frequency or dysuria, malodorous urine, and/or suprapubic tenderness. However using a child's presenting clinical symptoms to classify UTIs into lower and upper urinary tract involvement is not 100% accurate. DMSA scans are considered the gold standard for diagnosing a pyelonephritic infection (Fig. 127-4). Studies using DMSA scans have shown that although the majority of patients with fever and systemic clinical findings consistent with acute pyelonephritis (APN) have positive renal scans, there is still a high false-positive rate when relying on symptoms alone to distinguish pyelonephritis from cystitis. Rushton and Majd (1992) and Tappin and coworkers (1989) demonstrated that in patients presenting with fever and systemic symptoms, only 50% to 66% demonstrated acute inflammatory changes on DMSA scans. In addition, a small subset of patients who present with afebrile, seemingly lower UTIs may have a positive DMSA scan consistent with APN (Verboven et al, 1990). Differentiation of cystitis and pyelonephritis can also be difficult in children based on the nonspecific symptoms that children may present with at the time of their infection. This is especially true in infants younger than 90 days who commonly present with symptoms that are difficult to interpret, such as failure to thrive, diarrhea, irritability, lethargy, malodorous urine, asymptomatic jaundice, oliguria, or polyuria (Garcia and Nager, 2002; Chang and Shortliffe, 2006).

Recurrent UTIs can be further subdivided into unresolved bacteriuria, bacterial persistence, and reinfection. Unresolved



Figure 127-4. Representative DMSA scan showing right medial upper pole cortical defect consistent with scarring as indicated by arrow.

bacteriuria is most commonly caused by inadequate bacterial therapy, which could be secondary to noncompliance, antibiotic malabsorption, suboptimal drug metabolism, and resistant uropathogens that were unresponsive to the attempted therapy (Pewitt and Schaffer, 1997). In these instances, repeated directed treatment based on bacterial sensitivities determined by proper urine culture will typically result in resolution of the infection.

Bacterial persistence and reinfection occur after sterile urine has been documented following previous UTI therapy. In cases of bacterial persistence, typically the nidus causing the infection has not been eradicated. Usually the same pathogen is documented on urine cultures during subsequent UTI episodes, despite negative cultures after previous antibiotic treatment. The uropathogen typically resides in a location that is shielded from antimicrobial therapy. Protected sites include anatomic abnormalities, urinary calculi, necrotic papillae, or foreign objects (i.e., urinary catheters, ureteral stents) (Conrad et al, 1991; Richter et al, 2000; Schlager et al, 2001; Abrahams and Stoller, 2003; Kehinde et al, 2004). Identification of the nidus is important, as typically the infection will persist until the source is removed.

Biofilms and Intracellular Bacterial Colonies

Biofilms appear to play a role in bacterial persistence. Biofilms are structured communities of microorganisms encapsulated with a self-developed polymeric matrix and adherent to a living or inert surface (Tenke et al, 2012). Antibiotics that are usually adept at microbial eradication often are unable to eradicate bacteria within a biofilm. The failure of antimicrobial agents to treat biofilms has been associated with the following factors: (1) agents often fail to penetrate the full depth of a biofilm, (2) organisms within a biofilm often grow slowly and are resistant to the antibiotics that usually require active growth, (3) antimicrobial-binding proteins are poorly expressed in these biofilm bacteria, (4) bacteria within a biofilm activate many genes that alter the cell envelope, the molecular targets, and the susceptibility to antimicrobial agents, and (5) bacteria in a biofilm can survive in the presence of antimicrobial agents at a concentration 1000 to 1500 times higher than the concentration normally necessary to kill nonbiofilm-associated bacteria in the same species (Tenke et al, 2006).

Forms of biofilms may allow bacteria to exist both at a bladder and at a kidney level. Within the bladder, bacteria have been seen to invade bladder epithelial cells and to form biofilm-like clusters (IBCs) (Mysorekar and Hultgren, 2006). These will be discussed in greater detail later. In addition, after bacteria reach the kidney, they have been shown to adhere to the urothelium and papillae. In animal models these bacteria can adhere in thin biofilms to the urothelium before invading the renal tissue (Nickel

et al, 1987). It has been further shown that antibacterial agents are less effective against bacteria within these renal biofilms (Nickel et al, 1994).

In addition, biofilms have been shown to form in foreign bodies within the genitourinary tract. These foreign bodies include urinary catheters, ureteral stents, and urinary calculi. Organisms have been shown to ascend through urethral catheters via extraluminal and intraluminal routes. Organisms colonizing the external surfaces of catheters seem to originate from either the gastrointestinal tract or the perineum, whereas intraluminal bacteria appear to come from exogenous sources (Tenke et al, 2012). In fact, it has been shown that 68% to 90% of ureteral stents become colonized with bacteria whereas the rate of bacteriuria in the same patients is only 27% to 30% (Reid et al, 1992; Farsi et al, 1995).

Justice and coworkers (2004) offered possible explanations regarding how the same bacteria may cause recurrent infections without the presence of a nidus or foreign body within the urinary tract. In their work, they showed that after adherence (Fig. 127-5) the bacteria invade the superficial umbrella cells on the luminal surface of the bladder. This occurred within 1 to 3 hours of infection. After invasion, bacterial replication resulted in the loose collection of bacteria within the superficial umbrella cell cytoplasm, forming an early IBC. These bacteria within these IBCs continued to mature, forming an organized community with biofilm-like traits. As early as 12 hours after infection, some bacteria within the IBCs were seen to transform into rod-shaped, motile bacteria that then exited the bladder epithelial cells, presumably resulting in bacteriuria, but they were also found to facilitate the spread and colonization among other bladder cells. Late forms of these IBC bacteria differentiated into filamentous bacteria, which are elongated bacteria, and have the ability to release rod-shaped bacterial daughters that serve as a fresh population of uropathogens that can further invade superficial umbrella cells or disseminate into the genitourinary system. This life cycle, in and of itself, results in the self-perpetuation of bacteria within the bladder.

One host response to infection is that the bladder epithelium undergoes exfoliation in an attempt to rid itself of the bacteria (Mulvey et al, 1998, 2001). However, by developing the ability to invade and divide within the superficial umbrella cells, followed by release from these cells and reinvasion, these bacteria are able to evade this host response and remain within the bladder despite the elimination of these previously infected cells. In addition, Justice and coworkers (2004) further observed that the IBCs themselves can resist the host's immune response. Polymorphonuclear mononucleocytes (PMNs) are known to be rapidly recruited to the bladder and play a major role in clearing extracellular bacteria (Haraoka et al, 1999). It was observed that these PMNs were able to recognize infected versus uninfected superficial umbrella cells. However, the early and middle IBCs provided a safe haven for intracellular bacteria to continue to multiply by delaying the PMN's ability to access and engulf the intracellular bacteria. In addition, after the PMN gained access within the infected umbrella cell, they were unable to clear all of the bacteria. Therefore, a large number of bacteria were able to escape PMN activity. All of this taken together demonstrates how bacteria may establish and develop quiescent reservoirs within the bladder epithelium, and that, despite host immune responses, they might be allowed to persist and potentially result in recurrent infections from the same bacteria. It is important to keep in mind, however, that this work was performed using a murine model. Schlager and colleagues (2009) attempted to identify bacterial reservoirs in patients with neurogenic bladders. They obtained random bladder mucosal samples from 9 patients with neurogenic bladders while undergoing bladder augmentation, urinary diversion, or diagnostic cystoscopy, and they found no evidence of bacterial reservoirs in any of the samples. Clearly this is a small sample size and random bladder biopsies may not have the same yield in finding these reservoirs as compared to bivalving an entire mouse bladder and then examining it, but perhaps IBCs may not have a role in recurrent human UTIs. However, further analysis did show a significant B cell infiltration in the submucosa of patients with neurogenic bladder or VUR (Schlager et al,

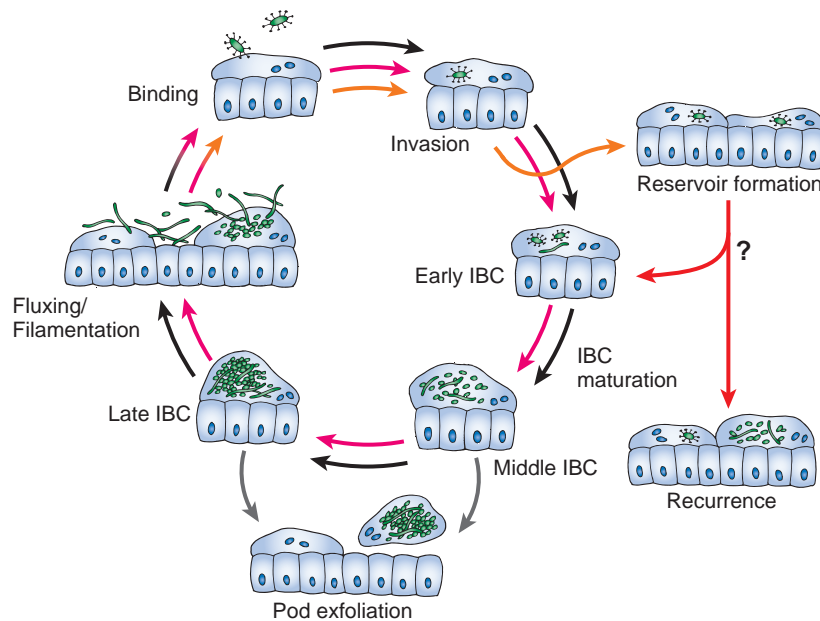


Figure 127-5. Urinary tract infection (UTI) pathogenic cascade model. This model depicts the sequence of events during the progression of establishment of a UTI based on the data presented in this report in conjunction with previous studies. The first round of the developmental process (black arrows) directly leads to the second round (magenta arrows) that completes at the time of massive exfoliation of the superficial umbrella cells. At this time, the reservoir is established (orange arrows). Exfoliation of epithelial cells occurs as a mechanism of the innate immune system (gray arrows). Events that lead to recurrence and the mechanism of bacterial growth during recurrence are unclear (red arrows and question mark); these events may include re-entry into the characterized cycle at the point of early intracellular bacterial community (IBC) formation. Bacteria (green) bind to and invade into superficial umbrella cells via type 1 pili (blue). Detachment from IBCs and fluxing out of infected cells likely involve flagella expression. (Modified from Justice SS, Hung C, Theriot JA, et al. Differentiation and developmental pathways of uropathogenic *Escherichia coli* in urinary tract pathogenesis. *Proc Natl Acad Sci U S A*. 2004;101(5):1333–8.)

2011). It was believed that these inflammatory changes might have been secondary to repeated bladder infection.

Bacterial reinfection occurs when a patient suffers a new recurrent UTI caused by a different uropathogen that is based on the documentation of proper urine cultures with each new infection. Often, bacterial persistence may be suspected (rather than reinfection), based on repeated urine cultures demonstrating the same bacterial species, most commonly *E. coli*. These recurrent infections, however, may actually be cases of reinfection rather than persistent occurrences. *E. coli* occurs in multiple serotypes, and careful serotyping of the infecting organisms may actually identify that these are different entities within the same bacterial family, resulting in these recurrent infections (Schlager et al, 2002).

Asymptomatic Bacteriuria

Asymptomatic bacteriuria (ASB) is defined as the presence of two consecutive urine specimens yielding positive cultures ($>10^5$ CFU/mL) of the same uropathogen in a patient who is free of any infectious symptoms (Kass, 1956). It remains unclear why certain individuals with ASB do not develop symptoms, especially because the organisms recovered from their urine are commonly the same as those seen in patients suffering symptomatic UTIs. In fact, the most common organism obtained from these ASB individuals is *E. coli* (Raz, 2003). One possible mechanism is that the organisms infecting these asymptomatic individuals may be less virulent, resulting in colonization rather than infection.

Some have suggested that the term *asymptomatic bacteriuria* is misleading, as some studies have shown that ASB is not always asymptomatic. Gaymans and coworkers (1976) noted that 30% of women in their study who were initially diagnosed with ASB later became symptomatic and required antibiotic therapy. Fur-

thermore, Savage (1975) found that whereas 1.6% of schoolgirls studied suffered from ASB, 60% to 70% of these children actually suffered from lower urinary tract symptoms, as well as daytime and nighttime incontinence that they admitted after careful questioning. Therefore these children with ASB may have actually been symptomatic.

ASB occurs in fewer than 1% of full-term infants and in 3% of premature infants (Edelmann et al, 1973). The identification of bacteriuria in these otherwise asymptomatic children is important as these young children may have few signs and symptoms in the face of an infection, and ASB may actually be a marker of underlying genitourinary disease. Given these issues, these infants should be treated with antimicrobial therapy and also should be imaged to evaluate for any congenital issues that could be leading to bacterial colonization (Whitworth, 1981). ASB occurs in 0.8% of preschool girls and even fewer preschool boys (Siegel et al, 1980). Children in this age group who are without VUR and/or other genitourinary abnormalities do not require antibiotics to clear their bacteria, as they do not appear to be at any risk for recurrent symptomatic infections, renal damage, or impaired renal growth (Sidor and Resnick, 1983).

The annual incidence of ASB in school-age girls ranges from 1% to 2%, although about 5% of all school-age girls are estimated to have ASB by the age of 15 years (Kunin et al, 1964; Meadow et al, 1969; Savage et al, 1969). In these school-age girls, spontaneous resolution occurred in 50% in one study, although the 50% who cleared their infection were found to harbor asymptomatic bacteria 1 year later (Raz, 2003). If these patients were treated with antibiotics at the time of identifying the ASB, 20% had persistent cure, whereas 80% had recurrence and some of these recurrent infections were symptomatic. Girls at this age who are found to have ASB are at very low risk for developing a decline in their renal function or

for developing hypertension (Lindberg et al, 1978; Kunin, 1985). As antimicrobial therapy in these individuals is unlikely to prevent later asymptomatic or symptomatic bacteriuria, and untreated individuals appear to be at low risk of developing long-term sequelae related to the bacteriuria, routine antimicrobial therapy is not recommended. Also, routine prophylactic antibiotics could certainly lead to increased antibiotic resistance in these individuals.

Screening children for ASB is not cost-effective. Kemper and Avner (1992) showed that given the sensitivity and specificity of our screening methods and the prevalence of bacteriuria in asymptomatic children, routine screening would result in 20% false-positives. In addition, they calculated that routine screening would cost \$2.9 million annually. As there is no evidence that detection and treatment of children with ASB prevents long-term consequences, they surmised that routine screening is not cost-effective or warranted.

Bacterial Nephritis

Acute bacterial nephritis occurs as the inflammation from bacterial infection within the kidney begins to spread throughout the kidney in an increasingly suppurative process with heavier leukocytic infiltrate and focal areas of tissue necrosis (Davidson and Talner, 1973). The advanced generalized form of acute nephritis has been termed *acute bacterial nephritis*, whereas the localized form has been called *acute focal bacterial nephritis* or *lobar nephronia* (Lee et al, 1980). In these individuals, clinical signs and symptoms of septicemia are often present (Thornbury, 1991). Computed tomography (CT) findings include global renal enlargement, inflammatory changes in the perirenal fat, and thickening of Gerota fascia (Soulen et al, 1989). On contrast images there may be ill-defined, nonhomogeneous-decreased parenchymal enhancement that typically is wedge shaped (Fig. 127-6).

Pyonephritis

If purulent exudate from APN accumulates in a dilated renal collecting system, pyonephrosis may occur (Thornbury, 1991). This condition commonly occurs in a hydronephrotic kidney secondary to an obstructed urinary outflow. CT findings typically include an enlarged kidney with a grossly dilated collecting system containing higher than usual fluid attenuation.

Acute Renal Abscess

Individuals presenting with a renal abscess often have symptoms similar to patients with pyelonephritis; however in up to 20% of renal abscess cases, the urine culture may be negative (Thornbury, 1991). This diagnosis is usually based on radiographic findings.

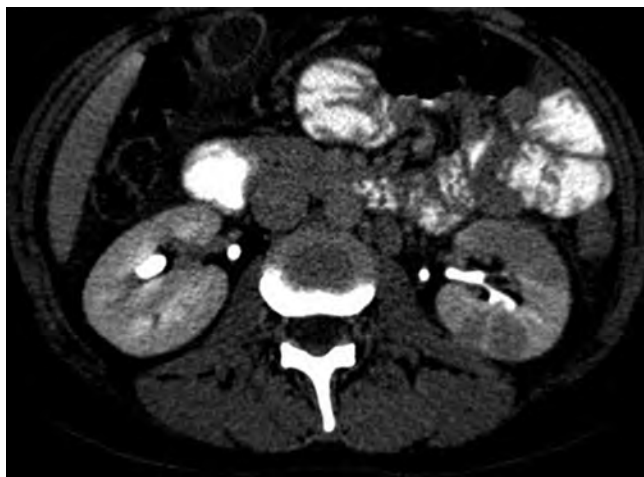


Figure 127-6. Computed tomography scan demonstrating lobar nephronia.

Ultrasound can detect an abscess as small as 1 cm in size and usually appears as a sonolucent area containing low-amplitude echoes (Soulen et al, 1989). CT appears to be the most sensitive and specific imaging modality to use in making the diagnosis of a renal abscess. Associated early CT findings include: (1) a well-defined area of low attenuation or decreased enhancement or (2) a striated, wedge-shaped zone of increased or decreased enhancement. In later phases, these areas may coalesce to form a well-defined mass with homogeneous internal attenuation features indicating purulent fluid.

KEY POINTS: CLASSIFICATION

- UTIs may be classified in a variety of ways.
- A UTI is commonly classified as pyelonephritis based on the patient's presenting symptoms, which commonly include fever, flank pain, nausea, and vomiting; however, based on DMSA studies only 50% to 66% of patients with these symptoms demonstrate acute inflammatory changes on their DMSA scan.
- ASB occurs in 0.8% of preschool girls and even fewer preschool boys. Children in this age group who are without VUR and/or other genitourinary abnormalities do not require antibiotics to clear their bacteria, as they do not appear to be at any risk for recurrent symptomatic infections, renal damage, or impaired renal growth.

DIAGNOSIS OF PEDIATRIC URINARY TRACT INFECTION

Defining what constitutes a UTI is surprisingly difficult. Although multiple international guidelines delineate the diagnosis, evaluation, and management of pediatric UTIs, they differ significantly and a consensus is lacking (Mori et al, 2007; Subcommittee on Urinary Tract Infection et al, 2011; Ammenti et al, 2012; Royal Children's Hospital Melbourne, 2011). At the most basic level, a UTI consists of the invasion of the urinary tract by organisms that result in pathologic changes. These pathologic changes may be caused directly by the infecting organism or by the host response to the infectious agent. In most cases, the individual also suffers symptoms from a UTI. To prove that a patient is experiencing a UTI requires a demonstration of the presence of the infecting organism in the urine and a confirmation that this organism is pathogenic. The presence of the infecting organism is routinely proven by urine culture. The presence of pathology within the urinary tract is frequently inferred by symptoms or by evidence of an immune response identified by urine or blood tests. As discussed in the following sections, controversy exists regarding the best method to obtain urine for analysis and culture as well as regarding the results that can be considered indicative of a true UTI.

Symptoms

The classic symptoms in an adult with a UTI, such as dysuria, frequency, urgency, or suprapubic or flank pain, become progressively more difficult to identify with decreasing age in the pediatric population. Symptoms in infants and young pediatric patients are typically nonspecific and include fever, irritability, poor feeding, jaundice, failure to thrive, vomiting, diarrhea, abdominal distention, or foul-smelling urine (Rudinsky et al, 2009; Craig et al, 2010; White, 2011).

Early after the neonatal period, fever is usually the primary symptom that leads to the diagnosis of a pediatric UTI. The overall prevalence of a UTI in febrile infants with no other identified source of fever is about 5% (Hoberman et al, 1993; Haddon et al, 1999). Fever lasting more than 2 days that is greater than or equal to 38°C without an identified source has been shown to have a positive likelihood ratio of 3.6 (confidence interval [CI] 1.4 to 8.8) of being an occult UTI (Shaikh et al, 2007). This likelihood increases with the duration and height of the fever. Although children with pyelonephritis tend to present with fever, as noted previously this is a

nonspecific sign and children with acute cystitis may also present with fever. Older children may complain of more classic symptoms such as dysuria, incontinence, changes in voiding habits, enuresis, or flank or abdominal pain (Shaikh et al, 2007). However, even when these symptoms are present they are nonspecific and, in one series of children aged 2 to 19 years with such symptoms, the prevalence of a UTI was only 7.8% (Shaikh et al, 2008). Other causes of lower urinary tract symptoms are frequently seen in patients with bladder and bowel dysfunction or vulvovaginitis. The lack of specific symptoms produced by a UTI frequently contributes to a lack of prompt diagnosis and treatment; however, the high prevalence of pediatric UTI dictates that it must remain a diagnostic consideration by clinicians caring for children.

Because the specificity of UTI symptoms is lowest in neonates and young children, as is the difficulty in obtaining urine for analysis and culture in this age group, the AAP 2011 guidelines contained an action statement to assist physicians in determining which febrile children between 2 and 24 months of age should be tested for a UTI (Subcommittee on Urinary Tract Infection et al, 2011). This statement recommends that if the clinician believes a febrile infant with no apparent source of fever is not so ill as to require immediate antimicrobial therapy, then the likelihood of UTI should be assessed. If the likelihood of a UTI is low (<1%), then the infant could be followed without urine testing. If the likelihood is higher, urinary evaluation should be considered. The probability of a UTI in girls has been shown to be greater than or equal to 1%, and the probability is 2% if they had two or more, or three or more, of the following risk factors, respectively: white race, age less than 12 months, temperature greater than or equal to 39° C, fever lasting 2 days or more, or absence of another source of infection (Gorelick and Shaw, 2000). The probability of a UTI in an uncircumcised febrile boy between 2 and 24 months exceeds 1% without any other risk factors. In a circumcised febrile boy, the probability of a UTI has been found to be greater than or equal to 1%, and the probability is 2% if they had three or more, or four or more, of the following risk factors, respectively: nonblack race, temperature greater than or equal to 39° C, fever lasting 2 days or more, or absence of another source of infection (Table 127-2) (Shaikh et al, 2007).

In addition to the symptoms previously noted, risk factors for UTI should be elicited, such as a history of a previous UTI. Children younger than 6 years of age with a documented UTI have been noted to have a 12% risk of recurrence per year in a community-based study (Conway et al, 2007). Other risk factors that should be evaluated include the presence of genitourinary anomaly, history of abnormal prenatal or postnatal ultrasounds, family history, and previous genitourinary or gastrointestinal surgery. Such risk factors will increase the probability of a UTI and the need for evaluation of a UTI in an unwell child. They may also point to predisposing conditions that require evaluation and treatment. The possibility of sexually transmitted diseases in older children and adolescents with symptoms of urethritis must be considered. Urethritis can be caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Ureaplasma urealyticum* as well as routine uropathogens.

At present, a multicenter diagnostic and prospective observational study (diagnosis of UTIs in young children [DUTY]) is underway and is recruiting 7000 children less than 5 years of age in the United Kingdom to help identify clinical predictors including signs, symptoms, and urine dipstick results that are most strongly associated with a UTI (Downing et al, 2012).

Physical Examination

Specific findings on physical examination in young children are rare and may consist of fever or lethargy. Even if another source of fever and infection such as otitis, upper respiratory infection, or gastroenteritis has been identified, the clinician must keep in mind that a concurrent UTI has not been excluded. It is not unusual for the pediatric urologist to see a child with a history of recurrent episodes of otitis following their first diagnosed UTI with DMSA scan, suggesting that the child had multiple previous episodes of pyelonephritis. The reduction in risk of a UTI when another infec-

TABLE 127-2 Diagnostic Accuracy of Symptoms and Signs of Urinary Tract Infection in Childhood

SYMPTOMS AND SIGNS	POSITIVE LIKELIHOOD RATIO (>1) (95% CI)	NEGATIVE LIKELIHOOD RATIO (<1) (95% CI)
CHILDREN 0 TO 2 YEARS		
Capillary refill >3 sec	4.8 (2.2-10.6)	0.99 (0.98-1.00)
Suprapubic tenderness	4.4 (1.8-12.4)	0.96 (0.90-1.01)
Refusal of fluid intake	4.4 (1.7-11.2)	0.99 (0.98-1.00)
Age <3 mo	3.9 (3.2-4.8)	0.87 (0.83-0.90)
Temperature >40° C	3.3 (1.3-8.3)	0.66 (0.35-1.25)
History of previous UTI	2.9 (1.2-7.1)	0.95 (0.89-1.02)
Uncircumcised males	2.8 (1.9-4.3)	0.33 (0.18-0.63)
Prolonged fever >24 hr	2.0 (1.4-2.9)	0.78 (0.65-0.81)
COMBINATION OF SYMPTOMS/SIGNS		
Temperature >39° C, >48 hr, no source of fever	4.0 (1.2-13.0)	
Temperature <39° C with a potential source of fever		0.37 (0.16-0.85)
CHILDREN OLDER THAN 2 YEARS		
Abdominal pain	6.3 (2.5-16.0)	0.8 (0.65-0.99)
New-onset urinary incontinence	4.6 (2.8-7.6)	0.79 (0.69-0.90)
Back pain	3.6 (2.1-6.1)	0.84 (0.85-0.95)
Frequency	2.8 (2.0-4.0)	0.72 (0.60-0.86)
Dysuria	2.4 (1.8-3.1)	0.65 (0.51-0.81)

CI, confidence interval; UTI, urinary tract infection.

From Bitsori M, Galanakis E. Pediatric urinary tract infections: diagnosis and treatment. Expert Rev Anti Infect Ther 2012;10(10):1153-64.

tious source has been identified may be smaller than anticipated, with several studies demonstrating a risk reduction of only about 50% (Bhat et al, 2011). In a study of 2411 febrile 1-year-old children, the prevalence of a UTI without an identified fever source was 5.9%, compared to 2.7% in those with a potential source (Shaw et al, 1998). In this study, the examining clinician incorrectly thought 64% of children with UTI had another source of fever. This highlights the need to consider the possibility of a UTI in any febrile infant, even if another source has been identified.

Both boys and girls should have an abdominal examination to assess for palpable abdominal mass that may indicate bladder distention or a flank mass consistent with hydronephrosis. Older children may experience suprapubic, abdominal, or flank tenderness. Costovertebral angle tenderness is suggestive of pyelonephritis. A careful examination of the external genitalia should be performed to rule out trauma, local irritation, urethral meatal stenosis or discharge, phimosis, foreign body, and anatomic abnormalities. Boys should be examined for testicular tenderness, which may be a sign of epididymo-orchitis. The introitus should be inspected in girls for discharge and signs of local irritation, ectopic ureter, or protruding urethral mass such as a prolapsing ureterocele. Examination of the back for signs of spina bifida occulta such as a prominent fat pad or asymmetric gluteal cleft or sacral dimple, along with a neurologic examination, may point to underlying neurologic causes of abnormal bladder function predisposing to UTIs.

Laboratories

Urine Collection Methods

Because of the nonspecific symptoms and signs, the diagnosis of a UTI requires the demonstration of an infectious agent or agents in

the urine. In addition, the AAP guidelines also require evidence of pyuria for the diagnosis of a UTI to help distinguish a true infection from ASB or contamination. **Unfortunately, the chance of collecting a contaminated urine specimen increases with the decreasing degree of invasive collecting methods.** Different guidelines suggest different methods of collecting urine specimens. The least invasive method of obtaining a urine specimen consists of affixing a collection bag to the perineum. This method has the highest chance of contamination by perineal and rectal flora as well as by white blood cells (WBCs) from outside the urinary tract, producing false-positive results. The urine from a collection bag only provides reliable information when the specimen is normal. A clean-catch midstream urine sample is also noninvasive but carries a higher chance of contamination from periurethral tissues than urine collected via more invasive methods including catheterization or SPA. The clean-catch urine is more reliable in an older girl or a circumcised boy or in an uncircumcised boy who will retract his foreskin compared to a younger girl or an uncircumcised boy who cannot retract the foreskin.

For young, non-toilet trained children less than 2 years of age, the AAP guidelines recommend either SPA or catheterization. The disadvantages of these methods include their invasiveness and the potential for trauma or infection and the fact that they may not be feasible as a routine procedure in primary care. The National Institute for Health and Care Excellence (NICE), Italian Society of Pediatric Nephrology (ISPN), and Royal Children's Hospital (RCH) Melbourne guidelines all recommend a clean-catch urine specimen when possible. Compared to SPA, the clean-catch urine for culture has a sensitivity of 75% to 100% and a specificity of 57% to 100% (Whiting et al, 2006; Bitsori and Galanakis, 2012). Compared to SPA, the catheterized urine has a sensitivity of 95% and a specificity of 99% (Roberts, 2012).

Catheter insertion should be performed in a sterile fashion. The use of intraurethral and/or topical lidocaine has been shown to be effective in reducing discomfort with bladder catheterization (Gerard et al, 2003; Vaughan et al, 2005; Mularoni et al, 2009). Successful catheterization in girls often requires a two-person technique. The labia majora should each be placed on gentle traction outward from the body and slightly lateral to help expose both the vaginal and urethral opening to facilitate the correct location for catheter insertion. This method, as opposed to one using a single hand and fingers spreading the labia laterally, more routinely exposes the normally recessed urethral opening and the surrounding anatomic landmarks. The exposure with this two-hand technique reduces the temptation to pull the labia too far laterally, which may occur with a single hand. Pulling the labia too far laterally can cause pain, making subsequent catheterization far more difficult and traumatic. After catheter insertion, the first several drops of urine obtained from a catheter should not be collected because they may contain urethral bacterial contamination.

The method of suprapubic aspiration involves prepping the skin and inserting a 22-gauge needle 1 to 2 cm above the pubic bone into the bladder and aspirating the urine into a sterile syringe. The reported success rates of obtaining urine by SPA are variable and although not routinely required, ultrasound confirmation of urine in the bladder, as well as guidance during the procedure, have demonstrated improved success rates (Gochman et al, 1991; Buys et al, 1994). Topical or local anesthetic may also be used but data confirming a significant reduction in discomfort with their use are lacking.

Urinalysis

Urinalysis routinely consists of urinary dipstick testing and microscopic examination. A urinalysis specimen should be performed on urine less than 1 hour after voiding if the specimen has been maintained at room temperature or less than 4 hours if refrigerated. Although a urine culture is the gold standard for diagnosis of a UTI, a culture requires at least 18 hours to demonstrate growth and 2 to 3 days to determine the final result and antibiotic susceptibilities. The urinalysis provides rapid information that may be used

to determine the likelihood of a UTI and the appropriateness of beginning antibiotic treatment for a presumed UTI.

Urine Dipstick Tests

The most frequently used dipstick tests for evaluation of UTI include leukocyte esterase and nitrite. Leukocyte esterase is released from white cells that are broken down in the urine and serves as a marker for pyuria. The sensitivity of leukocyte esterase for detecting UTI ranges from 47% to 95% in various studies with a summary estimate of 79% (95% CI 73% to 84%) (Hoberman et al, 1994; Williams et al, 2010). The specificity ranges from 64% to 92%, with false-positives resulting from other causes of inflammation or white cells in the urine (Subcommittee on Urinary Tract Infection et al, 2011). The summary estimate of leukocyte esterase specificity was 87% (95% CI 79% to 91%) in a large meta-analysis by Williams and colleagues (2010). Although it has been estimated by some that the leukocyte esterase test will miss more than 20% of children with a UTI, the AAP guidelines suggest the absence of leukocyte esterase in the urine helps distinguish individuals with ASB from those with a true UTI, as the absence of pyuria in children with a true UTI is rare (Bhat et al, 2011; Subcommittee on Urinary Tract Infection et al, 2011).

Urinary nitrite is reduced from dietary nitrates in the urine by gram-negative enteric bacteria. This conversion requires several hours to occur; thus a first-morning urine has the best sensitivity with this test. Frequent urination, as is often the case in infants and small children, may not permit enough time for the urine in the bladder to undergo significant conversion of nitrates to nitrites and therefore might result in a false-negative nitrite test more frequently than in older children (Mori et al, 2010). A dilute urine may also generate a false-negative test. Other reasons for false-negative tests include infection with gram-positive organisms that do not reduce nitrates. Because of false-negatives, the sensitivity of the nitrite test is about 50%, with a reported range from 8% to 95%. The specificity, however, is very high, at 98%, with a range from 90% to 100%, meaning a positive nitrite test is very likely to reflect a true UTI. In the large meta-analysis by Williams and coworkers (2010) the sensitivity and specificity for nitrites were 49% (95% CI 41% to 57%) and 98% (95% CI 96% to 99%), respectively.

If either leukocyte esterase or nitrite is positive, the sensitivity and specificity for UTI has been reported to be 88% (95% CI 82% to 91%) and 79% (95% CI 69% to 87%), respectively. (Williams et al, 2010). If either of these tests is positive, or the microscopic urine analysis is positive (see later) the sensitivity increases to 99.8% with a specificity of 70% (Subcommittee on Urinary Tract Infection et al, 2011). If both tests are negative, the presence of a UTI is much less likely, with a negative likelihood ratio of 0.22; however, based on the severity of the clinical picture, including a consideration of the patient's age, in many cases the safest course of action might be to continue antibiotics until culture results are available (Perkins et al, 2012). Although not widely used, some have suggested that the addition of the dipstick results for blood and protein to leukocyte esterase and nitrite results improves sensitivity and specificity. Ramlakhan and colleagues (2011) demonstrated that if a sample was negative for all four of these parameters, the sensitivity for ruling out a UTI was 97.4% (95% CI 91% to 99%) and a negative likelihood ratio of 0.10 (95% CI 0.02% to 0.39%). They noted the best test for confirming a UTI was a combination of leukocyte esterase and nitrite and blood, with a specificity of 97.1% (95% CI 94% to 99%) and positive likelihood ratio of 15.13 (6.99 to 32.76).

Urine Microscopic Examination

The traditional method of assessing pyuria by microscopy is on a centrifuged urine specimen with a threshold of 5 WBCs per high-power field (HPF); however, a threshold of 10 WBCs/HPF has been considered more reliable to predict UTI in children less than 2 years old by NICE, ISPN, and RCH Melbourne guidelines (Bitsori and Galanakis, 2012). Williams and coworkers (2010) reported the

sensitivity and specificity of 5 microscopic WBCs/HPF for determining UTI as 74% (95% CI 67% to 80%) and 86% (95% CI 82% to 90%), respectively. The true positive rate for 5 WBCs/HPF and for 10 WBCs/HPF has been reported as 67% (range 55% to 88%) and 77% (range 57% to 92%), respectively. False-positive rates for 5 and 10 WBCs/HPF have been reported as 21% and 11%, respectively (Gorelick and Shaw, 1999). Given the sensitivity and specificity of microscopic pyuria, there does not appear to be an advantage of microscopy for WBCs alone over leukocyte esterase for the determination of UTI, and the additive value of microscopy to dipstick results remains to be definitively demonstrated.

The most reliable rapid test for diagnosing a UTI consists of the microscopic identification of bacteria on both unstained and Gram-stained uncentrifuged fresh urine specimens (Gorelick and Shaw, 1999; Williams et al, 2010). Both the sensitivity and specificity for microscopic bacteria are improved by Gram stain (Subcommittee on Urinary Tract Infection et al, 2011). The sensitivity of microscopic bacteria on Gram-stained samples to determine a UTI is 91% (95% CI 80% to 96%) and on unstained samples it is 88% (95% CI 75% to 94%). The specificity on stained and unstained samples is excellent at 96% and 92%, respectively (Williams et al, 2010). Enhanced urinalysis uses a WBC counting chamber on uncentrifuged urine and uses the microscopy of a Gram-stained urine smear for detection of bacteria, and this improves predictive results but requires the availability of specialized equipment and personnel that are not routinely available in many clinical settings.

Urine Culture

A positive urine culture is essential for the diagnosis of a UTI. The definition of what constitutes a true positive urine culture based on the number of CFU per mL of urine is debated. As with most tests, the lower the threshold is set, the higher the likelihood of obtaining false-positive results and overtreating patients who do not have infection. Conversely, setting a higher threshold increases the chance of undertreating patients. Historically, the threshold used to diagnose a positive urine culture was greater than or equal to 10^5 CFU/mL of a uropathogen. However, this value was initially based on morning-voided urine samples in adult women and this cutoff may not be as applicable in children (Kass, 1962).

Factors that may reduce the concentration of bacteria in the urine of a child with UTI include frequency of urination as well as urine output. At present, there is a lack of uniform agreement on what colony count should be used as the threshold values for the diagnosis of a pediatric UTI. The 2011 AAP guidelines suggest that a reduction from greater than or equal to 10^5 CFU/mL be used in children aged 2 to 24 months. These new guidelines recommend that 50,000 CFU/mL, now including the requirement of a positive urinalysis for pyuria from a urine sample obtained by catheterization or SPA, be used for the diagnosis of UTI. Alternatively, the European Association of Urology suggests that 10^4 CFU/mL is indicative of UTI with a midstream specimen if associated with symptoms, but 10^5 should be used if there are no symptoms (Downing et al, 2012).

Other guidelines have taken into consideration the risk of contamination by various methods of urine collection and their threshold values have been adjusted accordingly. The RCH Melbourne Guidelines suggest that any gram-negative bacteria by SPA and greater than 10^5 CFU/mL by catheterization is consistent with UTI. The ISPN guidelines use greater than 10^4 CFU/mL by catheterization for a catheterized specimen and more than 10^5 CFU/mL for a midstream/clean-catch specimen (Bitsori and Galanakis, 2012).

Contamination is more likely in cases with low colony counts. It is also more likely in cultures with heavy, mixed growth of bacteria. In such cultures, however, one must consider the possibility of the existence of a true UTI along with a contaminated specimen when making treatment decisions. Contamination is also more likely in cultures growing nonpathogenic organisms. Such organisms include *Lactobacillus*, coagulase-negative staphylococci, *Corynebacterium*, alpha-hemolytic streptococci, and *Candida* (Bhat et al, 2011).

Serum Tests

A variety of different serum and urine tests have been evaluated for their ability to differentiate kidney infection in a child with UTI. When bacteria invade the kidney, Toll-like receptor signaling initiates an immune response involving the production of cytokines and chemokines, and urinary levels of interleukin-6 and interleukin-8 may be elevated (Montini et al, 2011). This local response may also be accompanied by a systemic response involving fever, elevated WBC, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin. Fever, ESR, and peripheral WBC count have not been shown to differentiate reliably the upper from the lower UTI (Garin et al, 2007). CRP has reasonable sensitivity but low specificity for diagnosing kidney involvement, limiting its use (Garin et al, 2007; Bhat et al, 2011). Procalcitonin rises in response to bacterial endotoxins, although its exact role in the inflammatory response is unknown. In a recent meta-analysis, procalcitonin was shown to be a more robust predictor compared with CRP or WBC for selectively identifying children who had APN during the early stages of UTI as well as those with late scarring as identified by DMSA scanning (Leroy et al, 2013). The sensitivity and specificity of a procalcitonin level greater than or equal to 0.5 ng/mL for detection of APN were 71% and 72%, respectively, and 70% sensitivity and 50% specificity for late renal scarring. Although the sensitivity and specificity for procalcitonin appear limited, it is possible that combining this information with other clinical and laboratory data will improve identification of individuals with kidney infection and guide subsequent clinical management including radiographic imaging (i.e., DMSA or voiding cystourethrogram [VCUG]).

KEY POINTS: SYMPTOMS AND LABORATORY ANALYSIS

- Symptoms of UTI in infants and young pediatric patients are typically nonspecific.
- Even if another source of fever and infection, such as otitis, or upper respiratory infection, or gastroenteritis has been identified, the clinician must keep in mind that a concurrent UTI has not been excluded.
- Urine from a collection bag only provides reliable information when the specimen is normal because of the high incidence of contamination.
- Guidelines vary in their diagnostic criteria for a UTI.
- Leukocyte esterase has a high sensitivity but a lower specificity. Urinary nitrite has a high specificity but lower sensitivity.

Radiographic Imaging

Controversies with Imaging Strategies

As with many of the other aspects related to pediatric UTI, there is a lack of consensus regarding imaging following a first febrile UTI in children. Part of this controversy relates to a lack of evidence supporting the use of routine imaging in decreasing long-term sequelae of kidney infections, including renal scarring, hypertension, and renal insufficiency or failure (Wennerstrom et al, 2000; Moorthy et al, 2005; Wan et al, 2012). Previously the standard evaluation consisted of an ultrasound and a VCUG. However, despite prevalence rates of VUR of more than 30% in many series of children with a febrile UTI, a lack of proven effectiveness of prophylactic antibiotics in preventing recurrent UTIs or renal scars in children with lower grades of VUR have led many to question the use of obtaining a VCUG in all children after their first UTI. Recommendations vary significantly between guideline committees and various advocates (Table 127-3). The NICE guidelines recommend routinely obtaining an ultrasound in children less than 6 months old, but these guidelines limit it in those more than 6 months to children with either a recurrent UTI or an atypical UTI

TABLE 127-3 Summary of the Five Imaging Recommendations

GUIDELINES	ULTRASOUND	VOIDING CYSTOURETHROGRAM	LATE DMSA SCAN
RCH	Yes	If boys <6 mo and/or positive ultrasonography	No
NICE			
<6 mo	Yes	If positive ultrasonography and/or atypical UTI*	
≥6 mo	If atypical UTI	If children with risk factors†	If atypical UTI* If atypical UTI*
TDA	No	If positive acute DMSA	If positive acute DMSA
AAP	Yes	If positive ultrasonography	No
ISPN	Yes	If positive ultrasonography and/or children with risk factors‡	If positive ultrasonography and/or VUR

*Seriously ill, poor urine flow, abdominal or bladder mass, raised creatinine, septicemia, failure to respond to correct antibiotic treatment within 48 hr, or infection with non-*Escherichia coli* organisms.

†Dilation on ultrasonography, poor urine flow, non-*E. coli* infection, or family history of VUR.

‡Abnormal prenatal ultrasonography of the urinary tract, family history of VUR, septicemia, renal failure, age <6 mo in a male infant, likely noncompliance of the family, abnormal bladder emptying, no clinical response to correct antibiotic treatment within 72 hr, or non-*E. coli* infection.

AAP, Academy of Pediatrics; DMSA, ^{99m}Tc-dimercaptosuccinic acid; ISPN, Italian Society of Pediatric Nephrology; NICE, National Institute for Health and Care Excellence; RCH, Royal Children's Hospital (Melbourne); TDA, top-down approach; UTI, urinary tract infection; VUR, vesicoureteral reflux. From La Scola C, De Mutis C, Hewitt IK, et al. Different guidelines for imaging after first UTI in febrile infants: yield, cost, and radiation. *Pediatrics* 2013;131:e665–71.

as defined by being seriously ill, by poor urine flow, by abdominal or bladder mass, by raised creatinine, septicemia, by failure to respond to treatment within 48 hours, or by infection with a non-*E. coli* organism (NICE, 2013). Conversely, the revised AAP guidelines recommended obtaining a renal ultrasound in all children less than 2 years of age with a febrile UTI, but these guidelines no longer recommend routinely performing a VCUG in these children if the ultrasound is normal (Subcommittee on Urinary Tract Infection et al, 2011). In a rebuttal to the AAP guidelines, the Section of Urology of the AAP noted that the revised guideline was based on conclusions that were premature and represented a misinterpretation of data and did not agree that a VCUG should not be routinely performed (Wan et al, 2012). Rather, they recommended that a VCUG remain as an accepted option at this time. They noted that some children with VUR, most frequently those with higher-grade VUR, do benefit from early detection and treatment that prevents subsequent kidney infection, damage, and loss of function.

Multiple studies now exist evaluating the potential sensitivity and specificity of various imaging guidelines after a first febrile UTI with respect to the identification of children with VUR, APN, or renal scars. One review demonstrated that the NICE and AAP protocols would miss 50% and 61% of children with grades III to V VUR and 62% and 100% of renal scars, respectively (La Scola et al, 2013). Another study demonstrated that the NICE protocol did not work as well in boys compared to girls with respect to negative predictive values (Wong et al, 2010). On the other hand, proponents of the NICE or AAP approaches note that significant numbers of children without high-grade VUR were spared the trauma, radiation exposure, and added expense by not undergoing a VCUG or a DMSA scan. In addition, proponents would note that those children possibly benefiting from the diagnosis of higher grades of VUR would be identified following a recurrent UTI and that prompt diagnosis and treatment of that recurrent UTI further minimizes the relatively low chance of renal damage and sequel in these children.

An alternative approach to imaging the child with a febrile UTI has been termed the *top-down approach* (TDA). Those advocating for a TDA recommend obtaining a DMSA scan in children after their first febrile UTI. By subsequently obtaining a VCUG in only those children with an abnormal DMSA scan, this approach may only miss 15% to 30% of children with dilating VUR; however, it does have a lower specificity than some of the other imaging guidelines (Hansson et al, 2004; Preda et al, 2007; Tseng et al, 2007; La Scola et al, 2013). The NICE guidelines recommend DMSA 4 to 6 months after acute infection for children younger than 3 years with atypical

or recurrent UTI and for children older than 3 years with recurrent UTI. The AAP guidelines do not recommend routine DMSA.

At present, it is fair to suppose that all imaging strategies fall short of the ultimate goal of being able to identify and test only those children that will benefit from the results of these tests. In addition, as with all testing, the clinician must ask if the results will alter the management of the child, and if the answer is *no*, then the test should not be ordered.

Ultrasound

Although the usefulness of obtaining an RBUS in all children with a UTI is questioned, the fact that it is noninvasive, is free from radiation exposure, and is widely available makes its routine use widely accepted for children with a history of UTI. The RBUS is frequently the initial imaging study and it demonstrates abnormalities in about 15% of infants and young children after their first febrile UTI (Subcommittee on Urinary Tract Infection et al, 2011). It is estimated that 1% to 2% of these children will exhibit an abnormality that requires additional evaluation or treatment (Alon and Ganapathy, 1999; Hoberman et al, 2003; Montini et al, 2008). Some suggest that an infant with a febrile UTI and normal prenatal third-trimester ultrasound may forego repeating another renal-bladder ultrasound; however, others report that more than 1/3 of children with a normal prenatal ultrasound will have an abnormality detected on ultrasound following their first UTI (Miron et al, 2007; Juliano et al, 2013). Unless the quality of the third-trimester prenatal ultrasound is known to be excellent, it seems prudent to obtain another ultrasound in infants and young children with a febrile UTI. In children older than several years, relative indications for obtaining RBUS include recurrent febrile UTIs, failure to respond as expected to antibiotic therapy, hypertension, and a family history of renal or urologic disease.

In addition to demonstrating the size, shape, and presence of both kidneys, ultrasound helps screen for previously undiagnosed congenital abnormalities, urinary tract obstruction, hydronephrosis, stones, pyonephrosis, and fluid collections such as renal or perirenal abscesses. If a child is unusually ill or not responding to treatment as expected, the clinician may want to obtain an ultrasound as soon as possible to rule out these conditions, because these conditions would warrant additional urgent interventions. A limitation of obtaining an ultrasound during the acute phase of pyelonephritis is the potential for inflammatory changes and edema to cause false-positive results. The inflammatory changes during the acute phase may cause an overestimation of renal size that may not be reflective of the true baseline size of the kidney. If

the infection and changes are localized, as in a case with an acute focal pyelonephritis (lobar nephronia), they might create the appearance of a mass or tumor. In addition, *E. coli* endotoxin may result in renal pelvis dilation that could be confused for hydronephrosis and lead to unnecessary testing (Subcommittee on Urinary Tract Infection et al, 2011).

Children with VUR and an abnormal renal ultrasound, as defined by the presence of hydronephrosis or a size discrepancy of greater than 1 cm, have been shown to be associated with significantly lower spontaneous VUR resolution rates than those with a normal renal ultrasound (Nepple et al, 2011). As one might expect, children with an abnormal renal ultrasound are more likely to have an abnormal nuclear renal scan. Multiple studies demonstrate a strong correlation between the relative renal volume determined by ultrasound and the relative renal function determined by renal scintigraphy in children (Troell et al, 1984, 1988; Sargent and Gupta, 1993; Adibi et al, 2007; Weitz et al, 2013). However, the ultrasound has relatively poor sensitivity for identifying renal injury or scars compared to nuclear cortical renal scintigraphy, and it may miss more than 10% of renal scars (Christian et al, 2000; Moorthy et al, 2004; Massanyi et al, 2013). Despite this limitation, ultrasound may be useful in screening the children who would be most likely to benefit by further evaluation with DMSA scan.

Some authors question the usefulness of obtaining an ultrasound in all children with a febrile UTI. The NICE guidelines do not recommend obtaining an ultrasound in children between 6 months and 3 years of age after the first febrile UTI unless it is atypical. Part of this questioning is related to the limitations of routine ultrasonography. High-resolution ultrasonography has improved the sensitivity of the ultrasound for detection of acute renal involvement (Morin et al, 1999). It is also widely recognized that renal ultrasound includes a very low sensitivity for the detection of VUR, even with high grades of VUR (Nepple et al, 2011; Juliano et al, 2013; Supavekin et al, 2013; Suson and Mathews, 2014). In one large study of children less than 24 months of age after their first febrile UTI, the ultrasound failed to detect 73% of those patients considered to have urologic abnormalities that would require additional surgical or medical interventions (Wong et al, 2010). Others have demonstrated that a normal ultrasound was not associated with a decreased risk of recurrent pyelonephritis (Juliano et al, 2013).

Voiding Cystourethrogram

VCUG may be performed by the instillation of an iodinated contrast medium into the bladder and imaging with fluoroscopy, or with the instillation of nuclear imaging agents such as technetium-99m pertechnetate. When performed with contrast, the VCUG remains the gold-standard imaging technique for the detection and grading of VUR. Some have suggested that the sensitivity for the detection of VUR is higher with nuclear imaging because of the ability to image the bladder continuously; however, the anatomic resolution and ability for grading is significantly less than the contrast VCUG. Because of the decreased anatomic resolution, many prefer to use a contrast VCUG as the initial method and reserve the radionuclide cystogram for follow-up imaging. The contrast VCUG provides additional information aside from grade that may be significant in evaluating and treating a child with a history of UTI. It provides anatomic information about the bladder such as size and shape and the presence of trabeculations or diverticula. The voiding images, which are an essential component of the standard VCUG, provide information about the function of the urinary sphincters as well as any evidence of urethral obstruction. The images may also be evaluated for the stool pattern that could suggest constipation, which is frequently associated with UTIs and abnormal bladder function. In addition, the images might also demonstrate a spinal defect consistent with spina bifida occulta and might raise the possibility of a tethered spinal cord.

In evaluating the child with UTI, VCUG may be performed as soon as the urine is sterile and the child is asymptomatic and demonstrating typical voiding (Hoberman and Wald, 1999). A negative

VCUG does not completely eliminate the possibility of VUR. One study demonstrated that 30% of patients with a history of VUR and a single negative nuclear VCUG showed positive cystogram results 1 year later (Neel and Shillinger, 2000). A cyclic VCUG, in which the bladder is filled, the child voids, and the bladder is filled a second time and is followed by voiding, will increase the sensitivity for VUR detection as well as the detection of an ectopic ureter. Overfilling of the bladder beyond the expected bladder capacity has also been shown to increase the detection of VUR; however, the physiologic significance of VUR under such artificial circumstances would seem to be minimal and would potentially lead to significant overtreatment. It should be noted that at present there are no widely accepted technical performance standards for a VCUG. Factors such as the size of the catheter, how much contrast should be instilled and at what rate or height/pressure the contrast should be hung, as well as how many cycles should be performed vary significantly among institutions (Palmer et al, 2011).

The radiation reported from VCUG varies from 0.5 to 3.2 millisievert (mSv) with 1 mSv noted as a commonly accepted value (La Scola et al, 2013). One reported advantage of the radionuclide VCUG is lower radiation exposure; however, improved imaging techniques have significantly reduced radiation exposure with fluoroscopic VCUG (Kleinman et al, 1994). To avoid the radiation associated with VCUG, an ultrasound technique has been developed, which is called the voiding cystourethrosonography (Darge, 2010). This technique requires the instillation of sonographic contrast medium via catheter into the bladder, and further investigation remains to be undertaken to determine its sensitivity compared to the VCUG (De Palma and Manzoni, 2013).

^{99m}Tc-dimercaptosuccinic Acid

Cortical renal scan with DMSA combined with single-photon emission computed tomography (SPECT) is considered by many as the gold standard for identification of lesions in the renal parenchyma (Craig et al, 2000; De Palma and Manzoni, 2013). DMSA is injected intravenously and is taken up by the kidney, bound to the proximal renal tubular cells, and excreted very slowly in the urine, providing good and stable imaging of the renal cortex. The imaging is obtained 2 to 4 hours after injection. Of note, it has been shown with CT that DMSA may miss some lesions of APN; however, there are significant drawbacks to using CT in children with UTI (see later) (Lee et al, 2011). The radiation dose for DMSA scintigraphy has been estimated as 1 mSv (La Scola et al, 2013).

The maximum sensitivity of DMSA for detection of APN is within 1 week from the onset of symptoms (Zhang et al, 2014). A DMSA within the first 10 days of APN shows abnormal results in 49% to 79% of patients and this decreased to 30% by 1 month after a UTI (Supavekin et al, 2013). Therefore, the timing of DMSA for detection of kidney involvement with a UTI significantly impacts its sensitivity. Acute DMSA studies usually demonstrate uptake defects in the cortex. In addition, the overall size of the kidney may appear enlarged because of inflammation and edema. Assessment of irreversible renal damage and scar should not be performed earlier than 6 months after APN, and some suggest waiting up to 1 to 2 years for resolution of any reversible defects (De Palma and Manzoni, 2013). Many acute cortical lesions are transient, but about 15% of children with these lesions will develop evidence of renal scarring on repeated DMSA (Shaikh et al, 2010). Renal scars appear as regions of decreased uptake in the cortex, but they may be indistinguishable from regions of congenital renal dysplasia that are frequently associated with VUR.

Multiple studies demonstrate that the risk of an abnormal DMSA is increased in patients with dilating grades of VUR compared to those with nondilating or no VUR (Wong et al, 2010; Supavekin et al, 2013; Zhang et al, 2014). It is this finding that advocates of the TDA cite as advantageous for selecting children with clinically significant VUR to undergo subsequent VCUG. The degree of renal scarring has also been demonstrated to be worse with higher grades of VUR (Shaikh et al, 2010; Supavekin et al, 2013). In addition, abnormal DMSA scan has been demonstrated to decrease the

likelihood of spontaneous VUR resolution independent of the grade of VUR (Nepple et al, 2008a, 2008b; Sjöström et al, 2010). Most studies demonstrate that older children have a higher chance of renal cortical defects, which is a finding that is consistent with the cumulative nature of scars.

In addition to DMSA, other renal nuclear agents such as ^{99m}Tc -mercaptoacetyltriglycine (MAG3) may be used. Although it may not provide quite the level of detailed imaging of the renal cortex that is obtained with DMSA, it does have some advantages. This scan provides renal cortical imaging as well as imaging of the collecting system, which is useful in assessing obstruction of urinary flow. In a very hydronephrotic kidney, imaging of the collecting system may help reduce false-positive results that would be obtained with a DMSA. Because of its uptake and rapid excretion relative to DMSA, the duration of the study and the radiation dose to most organs, including the bladder and gonads, are reduced (Sfakianakis and Georgiou, 1997).

Computed Tomography

Although CT provides detailed anatomic imaging and excellent sensitivity for determination of kidney involvement with infection, the high degree of radiation, as well as potential problems with contrast media, severely limit any benefit of this imaging modality in a child with a UTI. The mean radiation dose for a pediatric abdominal/pelvic CT is 10 to 15 mSv (Miglioretti et al, 2013). One exception may be a noncontrast CT when there is a high index of suspicion for urolithiasis not identified by ultrasound. In addition, it may be useful for distinguishing inflammatory changes from the tumor at times when the acute ultrasound is suspicious for a renal mass. Typical findings associated with renal infection and inflammation include cortical regions of hypoattenuation, wedge-shaped defects, a loss of the corticomedullary differentiation, and striations. Although a renal abscess may show no function, it should be noted that a similar appearance can occur on the acute scans with an acute focal pyelonephritis, and delayed scans may be required to distinguish these entities.

Magnetic Resonance Imaging

MRI provides both excellent anatomic and functional renal imaging. However, the expense and potential need for sedation or anesthesia, as well as a limited availability of the procedure, all restrict the use of routine MRI in the child with febrile UTI. In addition, there is a risk of nephrogenic systemic fibrosis in some patients with impaired renal function related to paramagnetic contrast media (De Palma and Manzoni, 2013).

KEY POINTS: RADIOGRAPHIC IMAGING

- Various conflicting guidelines have been developed for imaging the child with a UTI; however, all fall short of being able to identify and test only those children who will benefit from the results of these tests.
- Ultrasound is noninvasive and free of radiation and is readily available, but it is unreliable at detecting VUR and will also miss some renal scars.
- VCUG is the most reliable method of detecting and grading VUR as well as imaging the bladder and urethra.
- DMSA remains the gold standard for renal cortical imaging and provides relative renal function.

MANAGEMENT OF PEDIATRIC URINARY TRACT INFECTION

Antibiotic Treatment

The goals of acute UTI management include eradicating the infectious agent, preventing renal scarring, and alleviating the child's

symptoms. With successful antibiotic treatment the urine usually becomes sterile after 24 hours (Beetz et al, 2002). As might be expected, early antibiotic treatment of febrile UTI is a significant factor in limiting both renal involvement and subsequent renal scarring (Winter et al, 1983; Smellie et al, 1994; Hiraoka et al, 2003; Doganis et al, 2007). One study of infants and young children with febrile UTI demonstrated that the incidence of acute scintigraphic renal lesions increased from 22% to 59% when the start of antibiotics went from 2 to 3 days from onset of symptoms (Oh et al, 2012). The rate of ultimate scar formation in this series also increased from 11% to 76.5% when the start of antibiotics went from 2 days to 6 days from the onset of symptoms, respectively. The role of anti-inflammatory agents such as dexamethasone or methylprednisolone in reducing renal inflammation and ultimate scar formation has been demonstrated in several studies and is currently under investigation (Pohl et al, 1999; Sharifian et al, 2008; Huang et al, 2011).

Because a UTI frequently presents in young children and neonates with nonspecific symptoms, and a definitive diagnosis based on urine culture may require a wait of 2 to 3 days, the clinician must maintain a high index of suspicion for UTI and must routinely begin antibiotics empirically. Surprisingly, although this empiric decision to begin antibiotics for a presumed UTI should be based on a urinalysis and subsequently confirmed and adjusted based on urine culture results, a review of more than 40,000 outpatient pediatric UTIs suggests that a urinalysis was obtained in only 75% of cases and a urine culture was obtained only a little more than half the time (Copp et al, 2013). This practice may lead either to over-treatment with antibiotics in children who do not have UTIs, or undertreatment and therapeutic delay for those who do have UTIs but have a resistant bacteria requiring a different antibiotic. The indiscriminate use of broad-spectrum antibiotics also leads to increased side effects and bacterial resistance.

Inpatient Versus Outpatient Management

Management of suspected UTI should be based on a combination of factors including likely uropathogen, clinical status, and the reliability of the patient and the family to comply with medical recommendations. Fewer than 1% of patients evaluated for UTI in the outpatient setting require admission (Copp et al, 2011). Infants older than 2 months and nontoxic children with suspected pyelonephritis can be treated as outpatients as long as compliance with and tolerance to oral antibiotics is not an issue (American Academy of Pediatrics, 1999; Hoberman et al, 1999; Hodson et al, 2007; Montini et al, 2007). Most antibiotics result in extremely high urine antibiotic levels relative to serum, and several randomized comparative studies of oral and intravenous antibiotics have demonstrated no significant differences in the time elapsed to clinical improvement or to the prevention of renal scars (Hoberman et al, 1999; Hodson et al, 2007; Montini et al, 2007; Bitsori and Galanakis, 2012).

Hospitalization and parenteral antibiotics might be required based on patient age and clinical status. A febrile UTI in newborns and young infants proceeds more frequently to urosepsis than it does in older children. Positive blood cultures are found in 20% of this age group and this group is also more likely to develop electrolyte abnormalities including hyponatremia and hyperkalemia. For these reasons newborns and young infants require hospitalization and parenteral antibiotics (Beetz et al, 2002; Brady et al, 2010). Indications for hospitalization include infants younger than 1 month of age, and, according to some, younger than 2 or even 6 months of age, toxic presentation or dehydration, intolerance to oral intake, and questionable compliance with antibiotics (Royal Children's Hospital Melbourne, 2011). Neonates require initial hospitalization and full septic evaluation along with parental antibiotics. After the diagnosis is confirmed by urine culture, the parental antibiotics may be changed to oral antibiotics depending on the clinical picture, which would include an improvement in symptoms. Significant clinical improvement including defervescence routinely takes at least 24 hours after

beginning antibiotics (Hoberman et al, 1999). Ninety percent of children will have a normal body temperature within 48 hours of the start of therapy, but if the child is not improving after 48 hours an RBUS should be strongly considered. In addition, if urine culture results are not yet available, consideration should be given to broadening antimicrobial therapy (see [Radiographic Imaging](#)).

Antibiotic Duration

In children, antibiotic treatment lasting 7 to 14 days is recommended for febrile UTI because shorter courses have been proven inferior (American Academy of Pediatrics, 1999; Keren and Chan, 2002; Michael et al, 2003). With severe infections, such as acute lobar nephronia, a longer course of antibiotics of at least 3 weeks is sufficient in most cases (Beetz et al, 2002; Cheng et al, 2006). In many cases, a renal abscess can also be treated with antibiotics; however, a lack of clinical response or resolution may require drainage. With less severe UTI, such as afebrile acute cystitis (lower UTI), a 2- to 4-day course has a reduced rate of recurrence compared

to a single dose or a 1-day course and no significant difference compared to a 7- to 14-day course (Michael et al, 2003).

Antibiotic Selection

If a urine Gram stain was obtained, it might help guide initial empiric antibiotic choice while awaiting urine culture results. *E. coli* remains the most common pediatric uropathogen (>80% of UTIs) (Edlin et al, 2013) (Table 127-4). TMP-SMX and amoxicillin are used in approximately 50% of outpatient UTI visits but these might be poor empiric choices because of high resistance rates of *E. coli* (Table 127-5). Nitrofurantoin or a first-generation cephalosporin is an appropriate narrow-spectrum antibiotic choice for many children with a UTI; however, the age of the child and comorbid conditions should also be considered when selecting antibiotics (Copp et al, 2011; Edlin et al, 2013). Uropathogen prevalence and resistance rates also vary by gender and visit setting as well as by previous exposure to antibiotics, so these factors must be considered when choosing empiric antibiotic therapy. **Empiric treatment of acute**

TABLE 127-4 Uropathogen Prevalence by Gender and Clinical Setting*

ORGANISM	MALE		FEMALE	
	OUTPATIENT	INPATIENT	OUTPATIENT	INPATIENT
<i>Escherichia coli</i>	50% (48-52)	37% (35-39)	83% (83-84)	64% (63-66)
<i>Enterobacter</i>	5% (5-6)	10% (8-11)	1% (1-1)	4% (4-5)
<i>Enterococcus</i>	17% (16-18)	27% (25-29)	5% (5-5)	13% (12-14)
<i>Klebsiella</i>	10% (9-11)	12% (10-13)	4% (4-5)	10% (9-11)
<i>Pseudomonas aeruginosa</i>	7% (6-8)	10% (8-11)	2% (2-2)	6% (5-7)
<i>Proteus mirabilis</i>	11% (10-12)	5% (4-6)	4% (4-4)	2% (2-3)

*Based on national data from The Surveillance Network. Prevalence will vary based on region.

Modified from Edlin RS, Shapiro DJ, Hersh AL, et al. Antibiotic resistance patterns of outpatient pediatric urinary tract infections. J Urol 2013; 190(1):222-7.

TABLE 127-5 Uropathogen Resistance Rates*

ANTIBIOTICS	PERCENT ANTIBIOTIC RESISTANCE					
	<i>E. COLI</i>	<i>ENTEROBACTER</i>	<i>ENTEROCOCCUS</i>	<i>KLEBSIELLA</i>	<i>P. MIRABILIS</i>	<i>P. AERUGINOSA</i>
NARROW-SPECTRUM						
TMP-SMX	24	18		15	11	94
Ampicillin	45	78	3	81	12	
Nitrofurantoin	<1	23	<1	17	94	0
Cephalothin	16	96		7	4	
Cefazolin	4	91		7	4	
Gentamicin	4	2		3	5	10
Vancomycin			<1			
BROAD-SPECTRUM						
Amoxicillin/clavulanic acid	5	91		4	1	
Cefuroxime	2	33		7	0	
Ceftriaxone	<1	12		2	<1	31
Ceftazidime	<1	15		2	<1	4
Ciprofloxacin	5	1	5	3	3	5
Piperacillin/tazobactam	1	7		3	<1	5
Imipenem	<1	<1		<1	2	3
Aztreonam	<1	13		3	<1	4

*Based on national data from The Surveillance Network. Resistance rates will vary based on region. Blanks indicate that testing was not performed for antibiotic to which uropathogens are known to be nonsusceptible.

E. coli, *Escherichia coli*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *P. mirabilis*, *Proteus mirabilis*; TMP-SMX, trimethoprim-sulfamethoxazole.

Modified from Edlin RS, Shapiro DJ, Hersh AL, et al. Antibiotic resistance patterns of outpatient pediatric urinary tract infections. J Urol 2013; 190(1):222-7.

TABLE 127-6 Details of Common Antibiotic Dosing

	DOSE	COMMON SIDE EFFECTS	COMMENTS
ORAL AGENTS			
Amoxicillin-clavulanate	20-40 mg/kg/day in 3 doses	Diarrhea, nausea/vomiting, rash	Contraindicated <6 wk of age
TMP-SMX	6-12 mg/kg/day of TMP in 2 doses	Diarrhea, nausea/vomiting, photosensitivity, rash	
Cefixime	8 mg/kg/day in 1 dose	Abdominal pain, diarrhea, flatulence, rash	
Cefpodoxime	10 mg/kg/day in 2 doses	Abdominal pain, diarrhea, nausea, rash	Contraindicated <3 mo of age or when GFR is <50% or in children with G6PD deficiency
Cefprozil	30 mg/kg/day in 2 doses	Abdominal pain, diarrhea, elevated LFTs, nausea	
Cephalexin	50-100 mg/kg/day in 4 doses	Diarrhea, headache, nausea/vomiting, rash	
Nitrofurantoin	3-5 mg/kg in 2 doses	Nausea, vomiting, bad taste	
PARENTERAL AGENTS			
Ceftriaxone	75 mg/kg/day in 1 dose		Single daily dosing acceptable (Gauthier et al, 2004)
Cefotaxime	150 mg/kg/day divided q6-8h		Single daily dosing acceptable alternative
Ceftazidime	100-150 mg/kg/day divided q8h		
Gentamicin	7.5 mg/kg/day divided q8h		
Tobramycin	5 mg/kg/day divided q8h		
Piperacillin	300 mg/kg/day divided q6-8h		

G6PD, glucose-6-phosphate dehydrogenase; GFR, glomerular filtration rate; LFTs, liver function tests; TMP-SMX, trimethoprim-sulfamethoxazole.

UTI should be based on local/regional antibiograms that are revised and published on an annual basis, because uropathogen prevalence and resistance patterns will vary regionally and will change with time ([Table 127-6](#)). [Table 127-6](#) lists common oral and parenteral antibiotics used for treatment of UTI along with common dosing and side effects.

In addition to *E. coli*, other common gram-negative bacterial uropathogens include *Klebsiella*, *Proteus*, *Enterobacter*, and *Citrobacter*. Gram-positive bacterial uropathogens include *Staphylococcus saprophyticus*, *Enterococcus*, and, rarely, *Staphylococcus aureus*. Neonates and young infants should be covered for *Enterococcus* species when choosing empiric antibiotics because the incidence of infections with this uropathogen is higher in early infancy than at a later age ([Beetz and Westenfelder, 2011](#)). *Enterococcus* is frequently sensitive to ampicillin and first-generation cephalosporins. A combination of ampicillin and a third-generation cephalosporin or aminoglycoside is considered a safe empiric choice for neonates and young infants receiving parenteral therapy. Aminoglycosides may be given in once-daily dosing and should be considered for patients at risk for *Pseudomonas* UTIs such as those with recent exposure to antibiotics or urinary tract abnormalities ([Beetz and Westenfelder, 2011](#); [Bitsori and Galanakis, 2012](#)). Parenteral antibiotics may be converted to oral therapy in most children after several days based on culture results and the child's clinical response, including defervescence.

Most uropathogens are susceptible to narrow-spectrum antibiotic agents such as first-generation cephalosporins and nitrofurantoin. However, nitrofurantoin has poor tissue penetration and should not be used for febrile UTI/pyelonephritis. Nitrofurantoin has also been associated with increased risk of hemolytic anemia in infants less than 3 months of age and should not be used in this population. Similarly, TMP is contraindicated in premature infants and newborns less than 6 weeks of age ([Beetz and Westenfelder, 2011](#)). Empiric broad-spectrum antibiotic prescription is appropriate in children at risk for resistant UTI such as those with a history of previous UTI, recent antibiotic exposure, recent

hospitalization, and presence of genitourinary anomaly ([Allen et al, 1999](#); [Cheng et al, 2008](#); [Paschke et al, 2010](#)). Broad-spectrum antibiotics include broad-spectrum penicillins (antipseudomonal penicillins and β -lactamase/ β -lactam inhibitor combination penicillins), macrolides, fluoroquinolones, second-, third-, or fourth-generation cephalosporins, lincosamides, and carbapenems.

Although fluoroquinolones are highly effective against most uropathogens, bacterial resistance has increased as a result of widespread use. Fluoroquinolones should not be a first-line choice but should be reserved for those with suspected or proven resistant uropathogens such as *Pseudomonas aeruginosa*. In addition, the safety of quinolones in children has been questioned and is under investigation ([Bradley et al, 2011](#)).

MANAGEMENT OF POST-URINARY TRACT INFECTION

Following treatment of initial UTI, management is aimed at preventing subsequent UTIs. Routinely repeating a urine culture in children treated with an antibiotic based on previous urine culture susceptibilities is not necessary ([Currie et al, 2003](#); [Oreskovic and Sembrano, 2007](#)). Approximately 10% to 30% of children will develop at least one recurrent UTI ([Winberg et al, 1975](#); [Nuutinen and Uhari, 2001](#); [Shaikh et al, 2008](#); [Peters et al, 2010](#)). The recurrence rate is highest within the first 3 to 6 months following a UTI, and the more frequent and more recurrent a child's UTIs, the more likely he or she is to experience a subsequent UTI ([Winberg et al, 1974](#); [Kasanen et al, 1983](#); [McCracken, 1984](#)). For boys younger than 1 year of age, 18% will develop a recurrent infection, usually within the following year. If the initial infection is in a boy more than 1 year of age, his risk of a reinfection increases to 32%. A similar trend is noted in girls less than and greater than 1 year of age, who have a recurrence risk of 26% and 40%, respectively ([Winberg et al, 1974](#)).

Parents should be counseled regarding the high risk of recurrent UTI and should be urged to seek prompt evaluation for

subsequent febrile illnesses, as prompt treatment from the time of onset of symptoms should help to reduce renal damage. Renal scarring increases with an increasing number of febrile UTIs, with the risk going from 5% to 10%, 20%, 40%, and 60% after the first, second, third, fourth, and fifth pyelonephritic episodes, respectively (Jodal, 1987). Children who have had a febrile UTI should routinely have their height, weight, and blood pressure monitored by their primary care provider.

Identification of the risk factors predisposing a patient to UTIs helps direct individualized patient management by treating or eliminating these risk factors. UTIs, like infections in other sites of the body, are more likely to occur with increased inoculum and duration of exposure to the pathogen as well as in situations that compromise local and/or systemic immunity. Relative to UTIs, factors thought to increase the inoculum and duration of exposure include those that create urinary stasis as well as constipation. Surgical correction of obstructive uropathies should help reduce stasis. Infrequent voiding and urinary retention, or high pressures as may occur with dysfunctional voiding or obstructive uropathies, may compromise the local immunity of the bladder. As noted, a history of a recent UTI also predisposes the child to subsequent UTIs. In some patients, the risk factors responsible for recurrent UTIs may not be identifiable or modifiable, and these patients may benefit from nonspecific preventive therapies.

Prophylactic Antibiotics

The use of prophylactic antibiotics may be considered a nonspecific approach to the prevention of recurrent UTIs. The efficacy of prophylaxis has been questioned, even in children with VUR, by several relatively small randomized series including children with low grades of VUR (Garin et al, 2006; Montini et al, 2008; Pennesi et al, 2008; Roussey-Kesler et al, 2008). Neither the AAP guidelines nor the NICE guidelines recommend routinely prescribing prophylactic antibiotics to infants and children following their first UTI. As might be expected, the benefit of prophylactic antibiotics is more easily demonstrated when used in specific populations known to be at high risk for recurrent UTI (Brandström et al, 2010a). In populations known to be at higher risk for recurrent UTI, such as girls with dilating VUR (i.e., greater than or equal to grade III), prophylactic antibiotics have proven effective (Craig et al, 2009; Brandström et al, 2010a). The following risk factors are associated with a low risk of recurrent UTI and therefore make it more difficult to demonstrate any benefit of prophylactic antibiotics: circumcised boys, no bowel or bladder dysfunction, no recent history of UTI, normal renal ultrasound or DMSA scan, a lack of anatomic abnormalities, and nondilating VUR (Peters et al, 2010). The prospective randomized intervention for vesicoureteral reflux (RIVUR) trial compared TMP-SMX prophylaxis to placebo in 600 children with grade I-IV VUR following UTI and demonstrated that those receiving prophylaxis had a significantly reduced risk of recurrent UTI. The risk reduction for recurrent UTI was greatest in those children with bowel and bladder dysfunction at baseline, a history of febrile UTI, or higher grades of VUR (RIVUR Trial Investigators et al, 2014).

Aside from a lack of efficacy, antibiotic resistance is another concern regarding the use of prophylactic antibiotics. Multiple studies confirm that exposure to antibiotics increases the likelihood that any subsequent UTIs will be caused by bacteria resistant to the previously prescribed antibiotics (Allen et al, 1999; Conway et al, 2007; Craig et al, 2009; Brandström et al, 2010a; Paschke et al, 2010). This relates to the fact that the fecal flora frequently becomes resistant to the treatment antibiotic. In general, the risk of resistance appears to be about 3 times greater following treatment with antibiotics. Thus, the prophylactic antibiotic chosen should be different than the therapeutic antibiotic used for the UTI.

The ideal antibiotic for prophylaxis would be effective against most uropathogens, be easily administered and tolerated without significant side effects, have high urinary concentrations and low serum concentrations, and make little impact on indigenous

bacterial flora and bacterial resistance (Beetz and Westenfelder, 2011). The dosage is usually one fourth the normal dose, and in toilet trained children it is routinely administered shortly before going to sleep in hopes of increasing the duration of antibiotic within the urinary bladder. Common choices for prophylactic antibiotics include TMP-SMX, TMP, nitrofurantoin, and first-generation cephalosporins. With increasing resistance of *E. coli* to TMP-SMX, its use in this manner is increasingly questionable. Sulfonamides may compete for bilirubin binding sites on albumin and cause neonatal hyperbilirubinemia and kernicterus, so TMP-SMX is avoided during the first 6 weeks of life.

Nitrofurantoin produces minimal effect on the fecal flora, and resistance rates have remained relatively low, making it an effective prophylactic antibiotic. Because serum levels with nitrofurantoin are low, it is not recommended for use with APN or urosepsis. In addition, it can cause hemolysis in children with glucose-6-phosphate dehydrogenase (G6PD) deficiencies by oxidizing hemoglobin to methemoglobin. This deficiency is found in about 1 0% of African-Americans, Sardinians, non-Ashkenazi Jews, Greeks, Eti Turks, and Thais. Long-term treatment has been associated with rare cases of pulmonary fibrosis.

Many unanswered questions exist regarding not only which patients benefit from prophylactic antibiotics but also the best therapeutic regimen. The ideal dosing and schedule, as well as the use of alternating antibiotics, remain to be defined. Patient non-compliance with a prescribed daily antibiotic is common, as demonstrated in a study by Daschner and Marget (1975) in which only about one third of children took the prescribed antibiotics on a regular basis and 19% did not take them at all.

Cranberry juice has been suggested to reduce UTIs. A meta-analysis that included adults and children demonstrated no UTI reduction for those using cranberry products as compared to placebo, water, or no treatment (Jebson and Craig, 2012). Several studies in children with neurogenic bladders also demonstrated no reduction on recurrent UTI (Foda et al, 1995; Schlager et al, 1999). However, several other studies in children did suggest a possible benefit of cranberry juice in reducing recurrent UTIs (Ferrara et al, 2009; Salo et al, 2012). At present, there does not appear to be enough evidence demonstrating conclusive benefit to warrant a recommendation for the routine use of cranberry juice or cranberry products in children for the prevention of UTIs.

Circumcision reduces the risk of UTIs in infants and toddlers (Wiswell et al, 1985). The risk reduction appears greatest in those with a history of recurrent UTIs and dilating VUR (Singh-Grewal et al, 2005). Some consider conditions that place boys at high risk for UTI as a relevant medical indication for circumcision. Such patients may have a history of recurrent febrile UTIs, obstructive uropathy, hydroureteronephrosis, or high-grade VUR. The benefit of prophylactic circumcision even in these patients is controversial.

Bladder and Bowel Dysfunction

Consideration and assessment of underlying bladder or bowel dysfunction as predisposing factors should occur with any pediatric UTI. There exists a well-recognized association between bladder dysfunction and UTI, and bladder dysfunction predisposes children to recurrent UTI and renal injury (Nijman, 2000; Hoebeke et al 2001). In particular, the risk of bladder colonization and UTI is increased in children with incomplete bladder emptying resulting from dysfunctional voiding or underactive bladder. In addition, there is an association between VUR and bladder dysfunction (Koff et al, 1998; Schulman et al, 1999; Hoebeke et al, 2001). It is thought that voiding against a closed sphincter can increase bladder pressure and may contribute both to the development and to the persistence of VUR (Yeung et al, 1998, 2006; Chandra and Maddix, 2000). Treatment of bladder dysfunction, particularly overactive bladder, has been shown to improve the spontaneous VUR resolution rate, further suggesting an etiologic component for overactive bladder in the genesis of reflux (Homsy et al, 1985; Koff et al, 1998; Willemssen and Nijman, 2000).

Anorectal and lower urinary tract function are interrelated, and constipation is often associated with bladder dysfunction. Reported frequency of constipation associated with pediatric bladder dysfunction ranges from 30% to 88% (O'Regan et al, 1986; Schulman et al, 1999; Burgers et al, 2013a, 2013b). This relationship between abnormal bowel and bladder function is referred to as bowel bladder dysfunction (BBD) or as the dysfunctional elimination syndrome (DES) (Koff et al, 1998; Feng and Churchill, 2001; Bower et al, 2005; Burgers et al, 2013b). Children with VUR and bowel and/or bladder dysfunction are at particularly high risk for developing recurrent pyelonephritis (Thompson et al, 2001; Hellerstein and Nickell, 2002; Leslie et al, 2010; Sillen et al, 2010). Recurrent UTI are estimated to occur in about 45% of these children as opposed to 15% without BBD (Peters et al, 2010). Treatment of constipation has been shown to reduce recurrent UTIs significantly and to improve bladder function (Loening-Baucke, 1997; Erickson et al, 2003).

Detailed information regarding treatment of pediatric bladder and bowel dysfunction is reviewed in Chapters 143 and 144. In general, the initial conservative therapeutic measures for treating the child with bladder dysfunction include voiding behavior modification with timed voiding schedules and treatment of constipation, if present (Erickson et al, 2003; Allen et al, 2007). In patients who fail conservative treatment, directed therapy is focused toward improving the specific cause of bladder dysfunction. In most cases, noninvasive uroflow studies and the determination of postvoid residual provide enough data to help direct therapy, but some children will benefit from further evaluation with formal urodynamic study. Targeted interventions may include pharmacologic therapy, biofeedback, electrical stimulation therapy, surgery, clean intermittent catheterization, or a combination of these therapies (Nelson et al, 2004; Van Arendonk et al, 2006a, 2006b; Malm-Buatsi et al, 2007). The choice of therapeutic interventions is also impacted by the underlying condition and severity of symptoms. For children with a neurogenic bladder on intermittent catheterization, increasing the frequency of catheterization has been associated with decreased rates of recurrent UTI.

Management of Vesicoureteral Reflux

Sterile VUR does not appear to cause renal injury, although it is now well recognized that it is associated with congenital dysplasia in the kidney. Regions of renal dysplasia demonstrate no function on a DMSA scan and may be identical in appearance to nonfunctional regions from a renal scar caused by UTI. A lack of recognition of the etiology of these areas as dysplasia, and not as scar, previously led to an overestimation of potentially preventable renal injury in all children with VUR by preventing UTI or surgical correction.

Despite the historical overestimation of VUR based on a child's risk of pyelonephritis and renal scars, it is important to note that VUR remains a risk factor for both recurrent pyelonephritis and renal scarring. The risk of both of these events increases with increasing grades of VUR and seems to become significant in most series with dilating VUR (i.e., \geq grade III) (Hellerstein and Nickell, 2002; Conway et al, 2007; Montini et al, 2008; Roussey-Kesler et al, 2008; Brandström et al, 2010a, 2010b; Holmdahl et al, 2010; Leslie et al, 2010; Shaikh et al, 2010; Oh et al, 2012). Intuitively, increasing grades of VUR lead to increases in bacterial inoculum and exposure to the kidney from bacteria in the bladder. Higher grades of VUR also add an element of urinary stasis and decreased mechanical washout of bacteria that likely contributes to an increased exposure of the urothelium to bacteria. At present, the only method to diagnose and grade VUR definitively and to characterize further this risk factor remains the VCUG. As previously noted, multiple studies have challenged the dogma that all children with a febrile UTI and reflux will benefit from the diagnosis of VUR and subsequent treatment of this condition by either continuous antibiotic prophylaxis or surgical correction (Reddy et al, 1997; Cooper et al, 2000; Thompson et al, 2001; Hellerstein and Nickell, 2002; Garin et al, 2006; Montini et al, 2008; Pennesi

et al, 2008; Roussey-Kesler et al, 2008; Leslie et al, 2010; Subcommittee on Urinary Tract Infection et al, 2011).

Almost paradoxically, as more studies provide additional information regarding VUR, determining the ideal management of a patient with VUR has become increasingly complex. It is apparent that risk factors for developing recurrent UTI and renal scars must be considered when evaluating the potential benefits of various treatment options. A child who has VUR and has a negligible risk of developing a recurrent febrile UTI is unlikely to benefit from daily antibiotics. In assessing risk, it is important to treat each patient as an individual needing personalized treatment. Because multiple factors affect an individual's risk, it is not possible to provide excellent health care by developing broad, sweeping guidelines that dictate management protocols based on one specific factor, such as grade of reflux. Rather, one must consider additional information, aside from grade of reflux, gender, and age, ultimately to provide tailored management. The patient's history, presenting symptoms, bowel or bladder dysfunction, likelihood of persistent VUR, and kidney status including function and scars should all be considered and factored into the determination of a child's individual risk for developing recurrent febrile UTIs and renal scars (Cooper, 2012). In addition to considering these factors, the physician must also consider the social situation of the child, which, although difficult to quantify, may be one of the greatest predictive factors for a child's risk of adverse outcome. Guidelines published by the American Urological Association are relatively nonprescriptive, and they permit a wide range of management options for most children with VUR (Peters et al, 2010). These options include observation, continuous antibiotic prophylaxis, endoscopic injection, or open operative correction.

SEQUELAE OF PEDIATRIC URINARY TRACT INFECTIONS

Renal Scarring

Pyelonephritic scarring occurs most commonly in the poles of the kidney and is associated with compound papillae (Hannerz et al, 1987). These papillae are fused with adjacent papillae and contain papillary ducts that open at right angles rather than oblique angles, permitting more pyelotubular backflow of bacteria (Ransley and Risdon, 1974). Children with pyelonephritis and VUR are at increased risk for renal scar development, and this risk increases with increasing grade of VUR (Oh et al, 2010; Shaikh et al, 2010; Lee et al, 2012). After the acute inflammatory phase, the ultimate scar involves a loss of tissue that is reflected on radiographic imaging as thinning of the renal parenchyma over the calyces. The calyces themselves may become blunted and deformed. As noted previously, it can be difficult or impossible to distinguish scar from regions of congenital dysplasia by radiographic imaging, although patients with a small kidney and diffusely decreased isotope uptake and decreased differential renal function are often considered to have renal dysplasia. Although it has been suggested by some that infants and young children have a higher incidence of developing a renal scar following pyelonephritis, conflicting data exist on this topic. Prompt antimicrobial treatment decreases the chance of permanent renal damage, as does the elimination of any subsequent episode of pyelonephritis. The use of anti-inflammatory agents to minimize renal injury and scar during the acute phase of pyelonephritis is under investigation (Pohl et al, 1999; Sharifian et al, 2008; Huang et al, 2011).

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis (XGP) is a specific form of chronic inflammatory kidney disease rarely seen in children that is usually associated with an element of obstruction and, most commonly, *Proteus* or *E. coli* (Rippentrop et al, 2002). Symptoms are often vague and nonspecific and may include fever, abdominal or flank pain or mass, and more nonspecific symptoms including weight loss and failure to thrive. Laboratory studies may demonstrate leukocytosis, anemia, and pyuria.

Imaging may demonstrate a mass-like lesion with focal or diffuse renal involvement as well as perinephric extension (Malek and Elder, 1978; Eastham et al, 1994; Cooper and Turner, 1997). This may be mistaken for a malignancy and requires a high index of suspicion (Nam et al, 2012; Inouye et al, 2013). CT images may demonstrate areas of low attenuation that do not enhance as well as dilated calyces. Renal calculi are present in 38% to 70% of patients (Anhalt et al, 1971; Malek and Elder, 1978).

Nephrectomy is the treatment of choice for the diffuse form, whereas partial nephrectomy or conservative medical therapy may be indicated to manage focal XGP (Cooper and Turner, 1997; Nam et al, 2012). Technically, these operative cases can be extremely difficult as the process may extend beyond the kidney, distorting and destroying normal anatomy as it involves and encases surrounding structures including the psoas muscle and, at times, even the great vessels (Malek and Elder, 1978; Loffroy et al, 2007).

Long-Term Sequelae

It is difficult to predict which children will develop long-term sequelae of pediatric UTI, including hypertension, preeclampsia, or chronic kidney disease (CKD), because of a lack of clear data establishing the long-term consequences following pediatric UTIs. A review of 23 papers including a total of 3573 children demonstrates that the majority of children with a history of febrile UTI develop no long-term sequelae (Toffolo et al, 2012). This seems to be true in particular if at birth the children had normal kidneys that were unaffected by significant renal dysplasia. Toffolo and colleagues estimated that only 0.4% of children with normal renal function at the start of follow-up experienced a decrease in renal function. This rate is consistent with that found in the prospective International Reflux Study in Children (Smellie et al, 1998) and in another series of 226 adults with a history of childhood UTI who were followed for 10 to 41 years, which noted that only two patients developed CKD that was attributed to UTIs (Jodal et al, 2006). Wennerstrom and coworkers (2000) demonstrated a decrease in mean GFR after 16 to 26 years of follow-up more frequently in children with bilateral renal scars but not unilateral scars compared to children without scars. This same group showed no significant difference in mean 24-hour ambulatory blood pressure between those with and without urographic renal scars. Two other studies with follow-up of 22 and 41 years demonstrated an increased prevalence of hypertension of 29% and 35%, respectively, in patients with scars, suggesting that scars are a risk factor for the development of hypertension (Jacobson et al, 1989; Bailey et al, 1992). The risk of hypertension appears to increase with the severity of renal scarring. It has also been demonstrated that during first pregnancies, hypertension was significantly more common in women with severe renal scarring (Martinell et al, 1996; Smellie et al, 1998).

Children with significant bilateral renal scars or reduction of renal function warrant long-term follow-up for assessment of hypertension, renal function, and proteinuria. Studies suggest that proteinuria may not only be a clinical feature of CKD but may hasten its progression. The use of renin-angiotensin antagonists may slow the progression of CKD in some of these patients (Wong et al, 2009).

UNCOMMON PEDIATRIC URINARY TRACT INFECTIONS

Viral Cystitis

Acute hemorrhagic cystitis in children has occasionally been related to UTIs caused by adenovirus-11. In a series from Mufson and coworkers (1973) that evaluated children suffering from hemorrhagic cystitis, adenovirus-11 was recovered from the urine in 14.5% of patients, adenovirus-21 was found in the urine of 9% of these children, and *E. coli* was present in 17.4% of the cohort. In the vast majority of the individuals, no infectious etiology was identified.

Viral cystitis has commonly been identified in individuals after bone marrow transplantation and in other immunosuppressed individuals. Without successful treatment, severe viral cystitis and

KEY POINTS: MANAGEMENT AND SEQUELAE

- Delay in antibiotic treatment of a febrile UTI increases the incidence of renal parenchymal involvement and ultimate scar formation.
- Newborns and young infants should be hospitalized because of a higher incidence of urosepsis than older children.
- A total of 7 to 14 days of antibiotic treatment is recommended for children with febrile UTI; a 2- to 4-day course is acceptable for afebrile cystitis.
- Empiric antibiotic selection should be guided by local/regional antibiograms because of changing uropathogen prevalence and resistance patterns.
- Nitrofurantoin should not be used for febrile UTI/pyelonephritis.
- A total of 10% to 30% of children will develop at least one recurrent UTI.
- Antibiotic prophylaxis has been demonstrated to decrease subsequent UTI in high-risk populations such as girls with dilating reflux.
- Bowel and bladder dysfunction increase the risk of recurrent UTI and should be evaluated and treated in any child with a UTI.
- Although the risk of long-term sequelae of pediatric UTIs is relatively low, children with significant bilateral renal scars or a reduction of renal function warrant long-term follow-up for the assessment of hypertension, renal function, and proteinuria.

associated hemorrhagic cystitis is associated with a 50% to 80% mortality rate in these children (Gavin and Katz, 2002). BK virus, a DNA virus of the polyomavirus genus, has also been found in the urine of immunosuppressed and especially bone marrow transplant patients, causing both symptomatic and asymptomatic infections (Apperley et al, 1987; Bedi et al, 1995).

Funguria

Fungal UTIs appear to be increasing in prevalence and are commonly associated with individuals who have recently received antibiotics or who have had indwelling urethral catheters. In one neonatal intensive care unit, funguria increased tenfold throughout a 10-year period (Kossoff et al, 1998). Predisposing factors in children include antibiotic use, prematurity, intravenous and umbilical artery catheterization, parental nutrition, and an immunocompromised state (Keller et al, 1977). The urinary tract may serve as a portal of entry and as a site of disseminated fungal infection. In children with disseminated candidiasis, the kidney is the most commonly involved organ (Keller et al, 1977). *Candida* species are the most common cause of fungal UTI, with *Candida albicans* being the most common species involved in these infections, followed by *Torulopsis glabrata*. It is important to recognize the infections caused by *Torulopsis glabrata*, as these are commonly resistant to fluconazole (Kauffman et al, 2000).

Fungal bezoars may also form in the renal pelvis and potentially create urinary obstruction in these children (Keller et al, 1977; Bartone et al, 1988). For this reason, renal ultrasound may be beneficial in evaluating these patients, especially if the funguria is persistent. Urinary alkalization and oral antifungal therapy may occasionally dissolve some fungal balls, but if the child is suffering from renal obstruction, percutaneous or surgical removal of these fungus balls is necessary. Percutaneous drainage may also be needed so that local antifungal therapy can be administered. In these individuals, local and systemic amphotericin B and/or oral fluconazole may be useful for treatment. If the fungal balls are shown to persist, endoscopic or open surgical removal may be necessary.

Deciding when to treat asymptomatic funguria that are related to indwelling urethral catheters continues to be debated. In individuals with funguria secondary to these foreign bodies,

progression to disseminated candidemia is rare (Kauffman et al, 2000). When repeated urine cultures grow greater than 10,000 to 15,000 CFU/mL, antifungal treatment is generally recommended. Stopping antibiotic therapy, changing or removing urethral catheters, and urinary alkalization may be helpful in some cases, but these do not always clear the fungus from the urine. Prospective studies with intravesical amphotericin B bladder irrigation and oral fluconazole show that both may clear the funguria (Gubbins et al, 1994, 1999). Fluconazole has been used successfully in children, although its use is contraindicated in children less than 6 months of age.

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The complete reference list is available online at www.expertconsult.com.

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Growth and Maturation

Perioperative Fluids

Pediatric Anesthesia and Analgesia

Surgical Preparation and Intraoperative Considerations

Postoperative Care

The maxim “children are not small adults” is a critically important concept that must be remembered when contemplating surgical intervention in the pediatric population. Children have unique anatomy, physiology, and emotional and psychological needs, all of which vary with the child’s age. In addition, we are increasingly involved in prenatal counseling and care, and therefore an understanding of fetal development and physiology is necessary. This chapter reviews the core principles of pediatric perioperative care, with which any pediatric surgeon must be familiar to ensure optimal surgical outcomes.

GROWTH AND MATURATION

Prematurity and Intrauterine Growth Restriction

A baby born before 37 weeks’ gestation is considered premature. The severity of prematurity may be indicated by the birth weight, although these two factors are not necessarily related. Infants weighing 2500 g or less at birth are considered low birth weight (LBW) in prematurity, but in an infant born full term this weight would indicate intrauterine growth restriction (IUGR). This is an important distinction because full-term neonates with IUGR usually have different problems than premature infants. In the United States, approximately 30% of LBW infants are born after 37 weeks’ gestation. Premature infants weighing 1500 to 2500 g are referred to as moderately low birth weight (MLBW), less than 1500 g are referred to as very low birth weight (VLBW) infants, and infants who weigh less than 1000 g are considered extremely low birth weight (ELBW) infants. MLBW infants account for 82% of premature infants, VLBW 12%, and ELBW 6%. In 2006, 12.8% of live births in the United States were premature, and 8.3% were LBW. Between 1996 and 2006, the rate of premature births in the United States increased more than 16%. With respect to race, the rate of prematurity in the United States is highest for black infants (18.3%), followed by Native Americans (14.1%), Hispanics (12.1%), whites (11.6%), and Asians (10.7%). **The clinical implications of prematurity are profound, and premature infants accounted for 16.6% of all infant deaths in the United States in 2005.** These implications are especially relevant to the VLBW and ELBW infants, who are surviving in increasing numbers because of remarkable advances in neonatal critical care. These infants account for a large proportion of neonatal deaths and long-term disability, and because of their extreme prematurity they are predisposed to hyaline membrane disease, chronic lung disease, retinopathy of prematurity, intraventricular hemorrhage, and necrotizing enterocolitis (Teitelbaum and Coran, 2003b; Pierro et al, 2006; Eichenwald and Stark, 2008; Goldenberg et al, 2008).

IUGR is defined on prenatal ultrasonography as a fetus whose estimated weight is below the 10th percentile for its gestational age. At term, a birth weight below 2500 g is considered a result of IUGR. Approximately 70% of infants with a birth weight that

qualifies for IUGR are constitutionally small, and in the remaining 30%, the cause of IUGR is pathologic. IUGR can be temporary, with a normal-sized baby at birth. General causes of IUGR include placental insufficiency, chronic maternal disease, abnormal placentation, genetic disorders, malformations, immunologic diseases, maternal infections, metabolic diseases, maternal substance abuse, and multiple gestations. IUGR is typically classified as symmetrical or asymmetrical. Symmetrical IUGR describes a fetus whose entire body is proportionally small, and this is considered the more severe form (Styne, 2004). Asymmetrical IUGR is related to processes that require the fetus to direct its energy to the maintenance of vital organs, usually the heart and the brain. Therefore the fetus with asymmetrical IUGR typically has a normal head circumference but a small abdominal circumference, small limbs, reduced skeletal muscle mass, and decreased subcutaneous and abdominal fat. Infants with asymmetrical IUGR more frequently exhibit catch-up growth than their symmetrical IUGR counterparts. However, of all infants with IUGR, 10% to 30% will have short stature as adults. Given the wide variety of causes, the management of IUGR is individualized and complex decisions are often required, weighing elective preterm delivery and the risks of prematurity against the risks associated with IUGR (Teitelbaum and Coran, 2003b; Pierro et al, 2006; Alberry and Soothill, 2007; Goldenberg et al, 2008).

Intrauterine Growth and Lung Development

Proper intrauterine growth and development are dependent on presence of normal amniotic fluid volume. Of particular relevance to urologists is lung development, which is dependent on amniotic fluid. Early in pregnancy, the placenta produces amniotic fluid. **At 10 to 12 weeks’ gestation, the fetal kidneys begin to produce urine, which from there onward comprises the majority of amniotic fluid.** Lung development is a highly complex orchestration of molecular processes, and it is divided into three stages: the embryonic, the fetal, and the postnatal or alveolar stages.

The embryonic stage begins with a ventral bud from the foregut at 3 weeks’ gestation. By 6 weeks, the lung bud divides sequentially into bronchopulmonary segments. These segments are poised for further division, and their embryonic components will ultimately differentiate into specialized epithelium, smooth muscle, cartilage, connective tissue, and blood vessels (Teitelbaum and Coran, 2003b; Wilson and DiFiore, 2006).

The fetal stage of lung development begins at 7 weeks’ gestation and proceeds to term. This stage is further subdivided into three phases: pseudoglandular (7 to 17 weeks), canalicular (16 to 25 weeks), and saccular (25 weeks to term). The pseudoglandular phase is of particular interest, as its timing coincides with the replacement of placenta-derived amniotic fluid with fetal urine-derived amniotic fluid. **By the end of the sixteenth week of gestation, all lung branching occurs resulting in the terminal bronchial airways.** After this time the only further growth that

occurs is elongation and widening of existing airways. A large body of experimental data indicates that these early and critical events in lung development are dependent on lung fluid dynamics, and any restrictive process including tracheal occlusion (e.g., atresia) or oligohydramnios results in pulmonary hypoplasia, which can be fatal at birth. The severity of the restrictive process is proportional to the degree of hypoplasia (Teitelbaum and Coran, 2003b; Wilson and DiFiore, 2006).

Postnatal Considerations

In the postnatal period, growth and development in children occurs at a rapid pace, especially in early childhood. A full-term newborn grows at a rate of 25 to 30 g/day during the first 6 months of life, leading to a doubling of the birth weight during this period. In the first 12 months of life, an infant's birth weight is typically tripled. By 3 years of age, birth weight is expected to quadruple, and by 10 years of age it will increase twentyfold from the birth weight. Body length increases by approximately 50% in the first year of life, and by threefold by 10 years of age (Teitelbaum and Coran, 2003c).

Cardiovascular

A detailed description of pediatric cardiovascular physiology and management is beyond the scope of this chapter, but a few principles are important for the urologist to consider. These include the basic differences between pediatric and adult cardiovascular physiology and an understanding of the common congenital heart defects that may affect our patients.

Compared with the adult heart, the neonatal and pediatric myocardium is stiffer and less compliant. This results in diminished preload reserve, which means that the point at which further increases in end-diastolic ventricular volume do not result in increased cardiac output occurs more quickly than in adults. In addition, infants and children have relatively higher resting heart rates. As a result, increasing the heart rate can rarely increase cardiac output in children. A reduction of a child's heart rate to that of a typical adult would result in a marked decrease in cardiac output. Finally, the pediatric heart is significantly less responsive to inotropic agents because it exhibits reduced intramyocardial calcium release (Hirschl and Coran, 2003a; Rocchini, 2006).

Congenital heart defects are common, occurring in approximately one of every 120 live births. In general, these defects are classified as hypoplastic, septal, cyanotic, or obstruction defects. The septal defects are the most common, of which ventricular septal defect (VSD) is most prevalent. Most infants with septal defects have no symptoms during the first month. However, after 4 to 6 weeks of life, pulmonary resistance reaches normal levels, and thus during the second month of life congestive heart failure can occur. Hypoplasia of the heart is rare, but it is the most serious form of congenital heart disease. These defects typically result in the failure of either the right ventricle or the left ventricle to develop adequately, leaving only one side of the heart capable of pumping blood to the body and lungs. In hypoplastic left heart syndrome, the presence of a patent ductus arteriosus is critical for the infant's ability to survive until emergency surgery can be performed. Without this pathway, blood cannot circulate to the body. In hypoplastic right heart syndrome, a patent foramen ovale serves the same function. Obstruction defects occur when heart valves, arteries, or veins are abnormally narrow or blocked. Common obstruction defects include pulmonary valve stenosis, aortic valve stenosis, and coarctation of the aorta, with other types such as bicuspid aortic valve stenosis and subaortic stenosis being comparatively rare. Any narrowing or blockage can cause enlargement of the heart or hypertension. Cyanotic heart defects are named as such because they result in cyanosis. These defects include persistent truncus arteriosus, total anomalous pulmonary venous connection, tetralogy of Fallot, transposition of the great vessels, and tricuspid atresia. From a noncardiac surgery perspective, it is important to remember that many children with complex cardiac anomalies are on medications such as aspirin and sildenafil, which predispose them to bleeding.

In addition, certain types of surgically induced circulation, for example Fontan, purposely increase systemic venous pressure, which can be problematic for postoperative bleeding. Careful consideration of these variables and planning with a pediatric cardiac anesthesiologist is obligatory (Hirschl and Coran, 2003a; Rocchini, 2006).

Immunologic

Neonates have increased susceptibility to bacterial infections, which is predominantly a result of deficiencies in neonatal host defense mechanisms. Premature infants are at even higher risk. This susceptibility stems from several factors related to the immaturity of neonatal leukocytes, including neutrophils, monocytes, T and B lymphocytes, and natural killer (NK) cells, and also from deficiencies in the complement activation system.

Although the number of neutrophils is near the adult level at term (approximately 60% of circulating leukocytes), neonates have a relative inability to increase their circulating levels in response to stress or infection. This is thought to be a result of a decreased neutrophil storage pool and a result of increased margination of neutrophils. Premature infants have the added problem of having a significantly lower neutrophil count at birth. Neonatal neutrophils are also less adhesive to activated endothelium, a process that is critical to chemotaxis and migration to sites of inflammation and infection. In addition, neonatal serum is deficient in opsonins, which are necessary for neutrophil phagocytosis. Therefore, even though neonatal neutrophils are fully competent to kill bacteria, they may do so less efficiently. Unlike a decreased neutrophil storage pool, the number of monocytes in neonates is equal or greater than in adults. For unclear reasons, however, the migration of monocytes to sites of inflammation and infection is significantly delayed (Hirschl and Coran, 2003b; Upperman and Ford, 2006).

T-lymphocyte function is also impaired in neonates, despite having a significantly greater number of circulating T cells compared with adults. In addition, unlike adults, there is a greater proportion of CD4⁺ T cells than CD8⁺ T cells. The impaired function is believed to be related to their naive phenotype that is due to their lack of exposure to foreign antigens and also related to the fact that they produce relatively limited amounts of key inflammatory cytokines. B-lymphocyte function is also impaired in neonates, which is because of their inability to differentiate into IgG- or IgA-secreting plasma cells. They are able to differentiate into IgM-secreting plasma cells, but rely on maternal placental transfer for essentially all IgG. This reliance continues until the third or fourth month of life, after which time the proportion of neonatal IgG overtakes maternal IgG. Although maternal IgG is adequate for protection against most infections, strains of bacteria such as *Escherichia coli* and *Salmonella* can elicit a different immunoglobulin subtype, leaving the fetus and neonate with suboptimal immune protection. Premature infants are at even greater risk, as they are born without sufficient levels of maternal IgG (Hirschl and Coran, 2003b; Upperman and Ford, 2006).

Another lymphocytic deficiency in neonates involves the NK cells, which play an important role in protection against intracellular pathogens by targeted cell lysis. At term, the proportion of NK cells is similar to that in adult circulation, but they are functionally and phenotypically immature. For unclear reasons, their lytic potential is only 50% of adult NK cells, and it is not until late infancy that they reach their full functional potential (Hirschl and Coran, 2003b; Upperman and Ford, 2006).

The relative deficiency of immunoglobulins in neonates results in the increased reliance on the alternative, that is, antibody-independent pathway of complement activation. However, in neonates there is a reduced number of classic and alternative complement activation pathway factors. Specifically, the level of C9 is diminished, which is critical for protection against gram-negative bacteria. Breastfeeding is believed to partially compensate for these intrinsic neonatal immunologic deficiencies. Human milk contains immunoglobulins including IgG, IgM, and secretory IgA, lymphocytes, macrophages, polymorphonuclear leukocytes, and

components of the complement cascade. Because of these and other benefits, the American Academy of Pediatrics recommends continuing breastfeeding for the first 12 months of life. **Although the neonatal period presents the highest risk of infection for children, the immune system is not fully competent until approximately 8 years of age** (Hirschl and Coran, 2003b; Upperman and Ford, 2006). How the relative immunodeficiency of neonates and young children impacts surgical practice is not clear, and, as is discussed later in this chapter, evidence-based guidelines for surgical antibiotic prophylaxis in pediatric surgery are not available.

Renal

A detailed discussion of renal development can be found in Chapter 123 of this text, and therefore this section presents a very brief synopsis. Renal function begins in utero, with the first functional nephrons appearing at 8 weeks' gestation. Nephrogenesis is complete by 34 weeks. Urine production begins between 10 and 12 weeks' gestation, coinciding with the start of glomerular filtration. In utero, renovascular resistance is high, which limits renal blood flow. Immediately following birth, the distribution of renal cortical blood flow changes, with increased perfusion of the outer cortex and increased reactivity of the renal vascular bed. Consequently, the glomerular filtration rate (GFR) rises quickly despite renal blood flow remaining unchanged. In addition, water and electrolyte homeostasis is difficult to predict. GFR and tubular function double by 1 month of age (Kaskel et al, 1987), and during the first 3 months of life, renovascular resistance continues to decrease, which results in further rises in GFR. Following this relatively rapid rise, GFR continues to increase more slowly toward adult levels, which are reached by 12 to 24 months of life. The maturation of renal tubular function lags behind the maturation of glomerular function, and therefore the neonate can concentrate urine only to approximately 50% of adult capability (Greco et al, 2002; Teitelbaum and Coran, 2003a; Pierro et al, 2006).

KEY POINTS: GROWTH AND MATURATION

- Infants with a history of prematurity and/or IUGR are at risk for adverse events and account for a large proportion of neonatal deaths and long-term disability.
- Proper intrauterine growth and development are absolutely dependent on the presence of normal amniotic fluid volume, the majority of which is comprised of urine after 10 to 12 weeks' gestation.
- Lung development, in particular, depends on fluid dynamics, and processes such as oligohydramnios result in pulmonary hypoplasia.
- Neonatal and pediatric myocardium is stiffer and less compliant than in an adult, resulting in significant differences in physiologic responses and cardiovascular care.
- Many children with complex cardiac anomalies are on medications that predispose them to bleeding such as aspirin and sildenafil. In addition, certain types of surgically induced circulation, for example Fontan, purposely increase systemic venous pressure, which can be problematic for postoperative bleeding.
- Neonates have increased susceptibility to bacterial infections because of deficiencies in host defense mechanisms, and the immune system is not fully competent until 8 years of age.
- The normalization of renal function is a rapidly evolving process at birth, and adult-level GFR is not reached until 12 to 24 months of life.

PERIOPERATIVE FLUIDS

Maintenance of hydration is a fundamental and critically important concept in pediatric care. For the pediatric urologist, administration of fluids is usually for maintenance therapy in the postoperative

period or for deficit therapy in the setting of postoperative dehydration. Appropriate intraoperative fluid therapy is critical to simplify postoperative fluid management and to optimize the postoperative course. This is increasingly important given the increase in ambulatory surgery and the shorter length of hospital stays. **Perioperative fluid therapy begins with a careful and complete estimation of fluid deficit by the anesthesia team. Accurate knowledge of when exactly a patient last ate or drank is necessary to avoid the low urine output that is often observed during open bladder surgery.** If possible, urine output should be carefully monitored for the duration of surgery, and in the setting of an open lower urinary tract, the urologist should provide feedback to the anesthesiologist to ensure that the patient remains well hydrated.

Maintenance fluid replaces two losses: insensible, or evaporative, losses and urinary losses. In the perioperative period, insensible losses can vary widely with the presence or severity of several variables including fever, tachypnea, and so forth. Insensible losses represent loss of free water and generally account for one third of maintenance fluids. Urine losses are calculated as 280 to 300 mOsm/kg of water with a specific gravity of 1.008 to 1.015, but this concentration can vary depending on the patient's ability to concentrate urine. Urinary losses account for two thirds of total maintenance fluids. **The total requirements for maintenance fluids can be calculated using the Holliday-Segar formula as shown in Table 128-1 (Holliday and Segar, 1957).** After calculating the fluid requirement, children usually receive either D5 $\frac{1}{4}$ normal saline (NS) + 20 mEq/L KCl or D5 $\frac{1}{2}$ NS 20 mEq/L KCl. Children less than 6 months of age are generally given the solution with $\frac{1}{4}$ NS because of their high water needs per kilogram. Children 6 months and older, however, should receive the solution with $\frac{1}{2}$ NS (Greenbaum, 2007).

In the setting of postoperative dehydration the severity is determined as described in Table 128-2 (Siker, 2002). **Generally, deficit replacement should begin with a balanced salt solution such as lactated Ringer (LR) solution or NS to increase circulating blood volume.** Typically, a bolus of 10 to 20 mL/kg is used, but a rate of up to 40 mL/kg during the first 1 to 2 hours is well tolerated (Carvajal, 1994). The type of fluid deficit can be estimated from the

TABLE 128-1 Daily Maintenance Fluid Requirements

WEIGHT (kg)	DAILY REPLACEMENT	HOURLY REPLACEMENT
0-10	100 mL/kg/day	4 mL/kg/hr
11-20	1000 mL/day + 50 mL/kg/day	40 mL/hr + 2 mL/kg/hr
>20	1500 mL/day + 25 mL/kg/day	60 mL/hr + 1 mL/kg/hr

From Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957;19:823-32.

TABLE 128-2 Estimation of Fluid Deficit

DEFICIT	CLINICAL FINDINGS
Mild (1%-5%)	Dry mucous membranes, poor skin turgor, irritability, decreased urination
Moderate (6%-10%)	No tears, tenting of skin, lethargy, oliguria
Severe ($\geq 11\%$)	Sunken eyes and fontanelles, cold skin, anuria, tachycardia and tachypnea, hypotension, coma

Modified from Siker D. Pediatric fluids, electrolytes, and nutrition. In: Gregory GA, editor. *Pediatric anesthesia*. New York: Saunders; 2002.

patient's history, physical examination findings, electrolyte values, and serum tonicity. Types of dehydration include isotonic (serum osmolality 270 to 300 mOsm/L, serum Na⁺ concentration 130 to 150 mEq/L), hypotonic (serum osmolality <270 mOsm/L, serum Na⁺ concentration <130 mEq/L), or hypertonic (serum osmolality >310 mOsm/L, serum Na⁺ concentration of >150 mEq/L). Patients with hypertonic dehydration require careful consideration of fluid type and rate, because complications, such as cerebral edema, may occur during rehydration (Friedman, 2005; Greenbaum, 2007).

KEY POINTS: PERIOPERATIVE FLUIDS

- Maintenance of appropriate hydration is a fundamental and critically important concept in pediatric care.
- Fluid therapy must begin with an assessment of fluid deficit.
- Replacement fluids should begin with a balanced salt solution such as LR or NS.
- Maintenance fluids can be calculated using the Holliday-Segar formula.
- For maintenance fluids, children usually receive either D5 ¼ NS + 20 mEq/L KCl or D5 ½ NS 20 mEq/L KCl depending on their age and weight.

PEDIATRIC ANESTHESIA AND ANALGESIA

Psychological and Emotional Preparation

The psychological state of a child and family as well as the clinical state of each child must be thoroughly understood before anesthesia and surgical intervention can commence. If the child is not treated in an age-appropriate manner, the entire perioperative experience will likely be compromised. Conversely, if the psychological and emotional aspects of a child's condition distract caregivers from the primary medical and surgical concerns, a successful outcome might be compromised. Therefore it is imperative that the entire health care team find the ideal balance between these two considerations (Ferrari, 2008).

It is well known that significant preoperative anxiety is associated with a difficult and often prolonged anesthetic induction (Kain et al, 1996a, 1996b). Factors including the temperament and age of the child as well as the situational distress of the parent and the outcome of previous medical experiences will affect the child's anxiety level. For many children, the immediate postoperative course is a mirror of the induction experience. Children who go to sleep peacefully generally awaken in the same manner and are known to have fewer difficulties in the postanesthetic care unit (PACU). It is therefore necessary to take the time to prepare the child for the anesthetic experience in an age-appropriate manner. There is consensus among anesthesiologists regarding the need for the treatment of a child's anxiety before surgery (McCann and Kain, 2001). The development of coping skills is considered the most effective preoperative intervention, followed by modeling, play therapy, an operating room (OR) tour, and printed material (Kain et al, 1996a; O'Byrne et al, 1997; Ferrari, 2008).

The level of maturity affects a child's understanding of and response to illness (Moynihan and Kurkar, 1999). Infants fear separation from their primary caregivers and exhibit stranger anxiety; therefore it is important that parental involvement in the perioperative experience be maintained. Toddlers fear loss of control, so enabling a child to make choices, such as asking if the child has a color preference for his or her hospital gown, will diminish anxiety. Preschool-age children fear injury; they may fear, for example, that a blood draw may result in not enough blood being left in their bodies. They tend to think in concrete terms and therefore may take statements literally, so one must be cautious when choosing the language used with this age group. The school-age child typically fears that he or she may not

meet the expectations of adults. They may nod with understanding and listen intently despite not grasping what the adult is saying. They are reluctant to ask questions for fear that they should already know the answer. It is therefore imperative that expectations are clearly explained. **Adolescents fear death and usually do not understand bodily functions.** They are often panic stricken preoperatively, but try to not show any sign of this. As a result, they might remain very quiet. It is the responsibility of the care team to anticipate this anxiety and reassure the adolescent without prompting (Ferrari, 2008).

Risk of Anesthesia

Most parents will express that they experience more anxiety about the anesthetic than the risks of the surgery. Fear of anesthesia among parents originates largely from a lack of information regarding modern anesthesia practice rather than from a high probability of risk. For many families, it may be helpful to discuss specific risks of anesthesia for their child (Olsson and Hallen, 1984; Ferrari, 2008). **For a healthy child undergoing uncomplicated surgery, the risk of an adverse event is approximately 1 in 200,000 (Eichhorn, 1993).** The risk of death under anesthesia is the most feared complication. This risk is 1 in 10,000 for all patients of any age undergoing any surgical procedure (Keenan and Boyan, 1985; Tired et al, 1986; Holzman, 1994). **However, the risk of death directly attributable to the anesthetic approaches zero, although the risk of cardiac arrests resulting from anesthesia remains approximately 4.5 in 10,000 (Gobbo Braz et al, 2006).** The incidence of anesthetic-related complications and death is highest during the first year of life at 43 in 10,000, but this decreases dramatically during the second year of life to 5 in 10,000 (Tired et al, 1988). **Anesthetic risks increase by a factor of 6 during emergency procedures in all age groups (Ferrari, 2008).**

Anesthesia-Induced Neurotoxicity

The effects of anesthesia on the developing central nervous system of infants has been studied and debated for decades. In the past several years, research efforts to study this critical question have intensified, coincident with the increasing suspicion that commonly used anesthetic drugs are deleterious to the developing brain. This suspicion is based on several large epidemiologic studies and a large volume of data derived from animal studies. However, most of the epidemiologic studies are retrospective, and it is therefore impossible to eliminate the significant confounders of underlying pathology and surgery (McCann and Soriano, 2012). The Victorian Infant Collaborative Study Group reported in a retrospective study that procedures in infants, who were 27 weeks' post-conception and who underwent surgery including patent ductus arteriosus ligation, inguinal herniorrhaphy, gastrointestinal procedures, neurosurgery, and tracheostomy, were associated with blindness, cerebral palsy, deafness, and neurocognitive scores that were three standard deviations below the mean (Victorian Infant Collaborative Study Group, 1996). However, a study on premature infants with tracheoesophageal fistula repaired at birth did not have different IQ scores from their normal cohort (Bouman et al, 1999). Some prospective data are available, and one large study of infants undergoing cardiopulmonary bypass showed lower academic achievement, fine and gross motor skills, visual spatial skills, memory, sustained attention, and higher-order language skills (Bellinger et al, 2003). Despite these compelling data, definitive answers will be difficult to ascertain, as it is ethically impossible to conduct a definitive prospective randomized trial involving anesthesia in infants.

Preclinical studies in fetal and neonatal animals including chicks, mice, rats, guinea pigs, swine, sheep, and rhesus monkeys have clearly demonstrated that commonly used anesthetic, sedative, and analgesic agents are associated with neuroapoptosis and neurobehavioral deficits (Lin et al, 2014). However, the mechanisms underlying the neurotoxic effects have not been elucidated. Moreover, how the effects documented in animal species relate to

possible effects in humans is not known. Much research remains to be performed to understand these processes better and to model better the timing of human brain development.

Considering the available data, it is most likely that the most vulnerable group of patients potentially susceptible to the effects of prolonged exposure to anesthetics and sedatives during an immature state of brain development are premature infants requiring neonatal intensive care and not pediatric patients who are otherwise healthy who are undergoing brief, elective surgical procedures (Lin et al, 2014).

Basic Preoperative Preparation

A complete medical history is always the first step in a thorough preoperative assessment. The history should include the prenatal course and neonatal period because events during pregnancy and delivery may influence the child's current state of health (Means, 1997). Any previous hospital admissions should be noted. A complete review of systems is performed to evaluate for medical comorbidity that could influence the choice or outcome of anesthesia (Cote et al, 2001). The presence of cough, asthma, or a recent upper respiratory infection (URI) might predispose the child to bronchospasm, atelectasis, or pneumonia. New-onset heart murmur, cyanosis, hypertension, exercise intolerance, or a history of rheumatic fever can suggest an evolving issue that could be exacerbated by an anesthetic or with a surgical procedure. Parents should be queried for the presence of vomiting, diarrhea, malabsorption, black stools, gastroesophageal reflux, or jaundice to interrogate for electrolyte imbalance, dehydration, hypoglycemia, anemia, or the need for a rapid-sequence induction. A history of seizures, head trauma, or difficulty swallowing may indicate a metabolic derangement, increased intracranial pressure, or sensitivity to muscle relaxants. Urinary tract abnormalities may impact the state of hydration and renal function, and the urologist should clearly communicate the significance of these. Abnormal development, alterations in serum glucose levels, or a history of chronic steroid use may indicate an endocrinopathy, diabetes mellitus, hypothyroidism, or adrenal insufficiency. Lastly, a history of anemia, bruising, or excess bleeding may suggest a transfusion requirement or coagulopathy (Ferrari, 2008).

The family history should be obtained with particular attention to anesthesia-related events. Specifically, a history of liver problems in family members after anesthesia is important to elicit, as certain anesthetic agents are known rarely to cause liver damage. Malignant hyperthermia is always a concern in the pediatric population. Although most pediatric anesthesiologists refrain from routinely using succinylcholine, a family history of prolonged paralysis or mechanical ventilation after general anesthesia should be obtained. Finally, families should be asked if there is a history of unexpected death, sudden infant death syndrome, genetic defects, or familial conditions such as muscular dystrophy, cystic fibrosis, sickle cell disease, bleeding tendencies, or human immunodeficiency virus (HIV) infection (Ferrari, 2008).

Obtaining a complete medication history is essential. This includes prescription medications, nonprescription medications, and herbal or alternative therapies. Many over-the-counter cold remedies contain aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or other compounds that may interfere with coagulation. Herbal and alternative therapies are known to include significant deleterious interactions with certain prescription medications, and these must be considered before administration of anesthesia and proceeding with surgery (Cupp, 1999).

The practice of body piercing is becoming increasingly common in adolescents and young adults. Metal objects in the skin during surgery and anesthesia increase the risk of burn injury if there is an intraoperative electrocautery malfunction. In addition, metal objects can become caught on equipment in the OR, resulting in tears of the skin and subcutaneous tissue. Tongue piercing may interfere with laryngoscopy and might make securing the airway unnecessarily challenging. Therefore, patients should be counseled to remove all metal objects and disclose any body

piercing that cannot be seen during the preoperative interview (Ferrari, 2008).

The physical examination of children must begin with simple observation from a distance because the infant or child may become frightened when approached directly. A great deal can be learned about relevant physical findings without touching the child. The color of the skin including the presence of pallor, cyanosis, rash, jaundice, unusual markings, or scars from previous surgery may indicate the presence of organ system dysfunction. Because congenital anomalies often occur in association with other anomalies, abnormal facies may indicate additional anomalies. The respiratory system examination should specifically address any signs of a URI. The cardiovascular examination specifically addresses the presence of heart murmurs, which must be accurately diagnosed as innocent versus pathologic. Lesions in which bacterial endocarditis prophylaxis or protection from paradoxical air embolism are required must be documented (Ferrari, 2008).

Routine diagnostic testing in preparation for surgery is rarely indicated in healthy children, and studies that are ordered should be selected based on the general medical health of the patient and the procedure being performed. In general, measurement of hemoglobin/hematocrit in a healthy child undergoing elective surgery is unnecessary (Steward, 1991). A hemoglobin/hematocrit should be measured if significant blood loss is anticipated or if the child is younger than 6 months of age or was born prematurely. Neither the routine measurement of a coagulation profile nor a history of "easy bruising" is reliable in predicting surgical bleeding (Burk et al, 1992). A history of a previous hematoma and excessive bleeding following circumcision or large bruises should prompt an appropriate hematologic evaluation. Routine preoperative urinalysis is not indicated in children, and serum chemistries should only be performed when an abnormality is suspected. Children who are treated with anticonvulsants should have these medication levels checked, and an electrocardiogram or chest radiograph should only be ordered if the general medical condition warrants. Routine pregnancy test is controversial, and the policy of one's medical facility should be followed (Ferrari, 2008).

Nulla per Os (NPO) Guidelines

It is no longer advisable or safe to restrict children to "NPO after midnight" (Cote, 1990). This outmoded restriction increases the child's chance of undergoing induction of anesthesia when dehydrated, hypoglycemic, and cranky, all of which lead to a suboptimal situation. The risk of pulmonary aspiration of gastric contents in healthy children undergoing elective surgery is only 0.04% (Warner et al, 1999). The American Society of Anesthesiologists (ASA) has proposed practice guidelines that may be followed when determining NPO restrictions in children (American Society of Anesthesiologists, 1999). **The ASA recommends fasting from clear fluids for 2 hours before anesthesia.** Clear liquids consist of water, nonparticulate juices (e.g., apple, white grape), Pedialyte, and Popsicles. **Fasting from breast milk for 4 hours and formula for 6 hours is recommended.** **The suggested fasting period for solid food is 6 hours for regular meals and 8 hours for fat-containing meals.** However, a large survey of pediatric institutions recommends fasting from all solids for at least 8 hours in all children (Ferrari et al, 1999). However, individual institutions may have specific practice guidelines that differ from those mentioned here.

Immunizations

The timing of vaccinations in the perioperative period has been a controversial topic. It is known that both anesthesia and surgery exert immunomodulatory effects, and some believe that these effects may exert additive or synergistic influences on vaccine efficacy and safety (Siebert et al, 2007). This risk, however, is theoretical and there are no guidelines that address the issue. Based on an exhaustive review of the literature, Siebert et al concluded that the immunomodulatory influence of anesthesia during elective

surgery is both minor and transient, lasting around 48 hours, and that the current evidence does not provide any contraindication to the immunization of healthy children scheduled for elective surgery. However, respecting a minimal delay of 2 days (inactivated vaccines) or 14 to 21 days (live attenuated viral vaccines) between immunization and anesthesia may be useful to avoid the risk of misinterpretation of vaccine-driven adverse events as postoperative complications (Siebert et al, 2007).

Special Circumstances

The Child with an Upper Respiratory Infection

Whether to proceed with an elective operation in a child with an active URI is one of the most difficult and fundamental questions in pediatric anesthesia (Hinkle, 1989). Children typically experience three to nine URI episodes per year, and the majority occur during the winter months (Van der Walt, 1995). The classic signs and symptoms include fever, irritability, restlessness, sneezing, nasal discharge, nasal obstruction, headache, malaise, and anorexia (Tait and Malviya, 2005). Children between the ages of 3 months and 3 years also experience fever early in the course of the illness, and in general younger children develop more severe infections than older children. It is likely that during the winter months a child has a cold, is just recovering from a cold, or is about to catch a new cold (Ferrari, 2008).

A cough is a sign of lower respiratory involvement and should be evaluated for origin (upper airway or bronchial) and quality (wet or dry). Most children will have clear breath sounds when auscultated during quiet respirations. It is during coughing and crying that rales and rhonchi will be best detected (Ferrari, 2008).

Definitive criteria for canceling surgery have not been established, and the decision is often subjective. Criteria that suggest that cancellation should be considered include the necessity for endotracheal intubation, parental observation that the child is acutely ill on the day of surgery, the presence of nasal congestion and cough, a history of secondary smoke exposure, and active sputum production (Cohen and Cameron, 1991; Parnis et al, 2001). Decisions to cancel surgery should be made in conjunction with the surgeon and based on the type of procedure, the urgency of the procedure, and the child's overall medical condition. Most authors agree that surgery may be scheduled after the acute symptoms have resolved and no sooner than 3 to 4 weeks after the initial evaluation (Ferrari, 2008). A suggested algorithm is provided in Figure 128-1 (Tait and Malviya, 2005; Zuckerberg and Maxwell, 2009).

Asthma

Asthma is one of the most common chronic pediatric illnesses and is characterized by bronchoconstriction, hypersecretion of mucus, mucosal edema, and desquamation of inflammatory cells. The

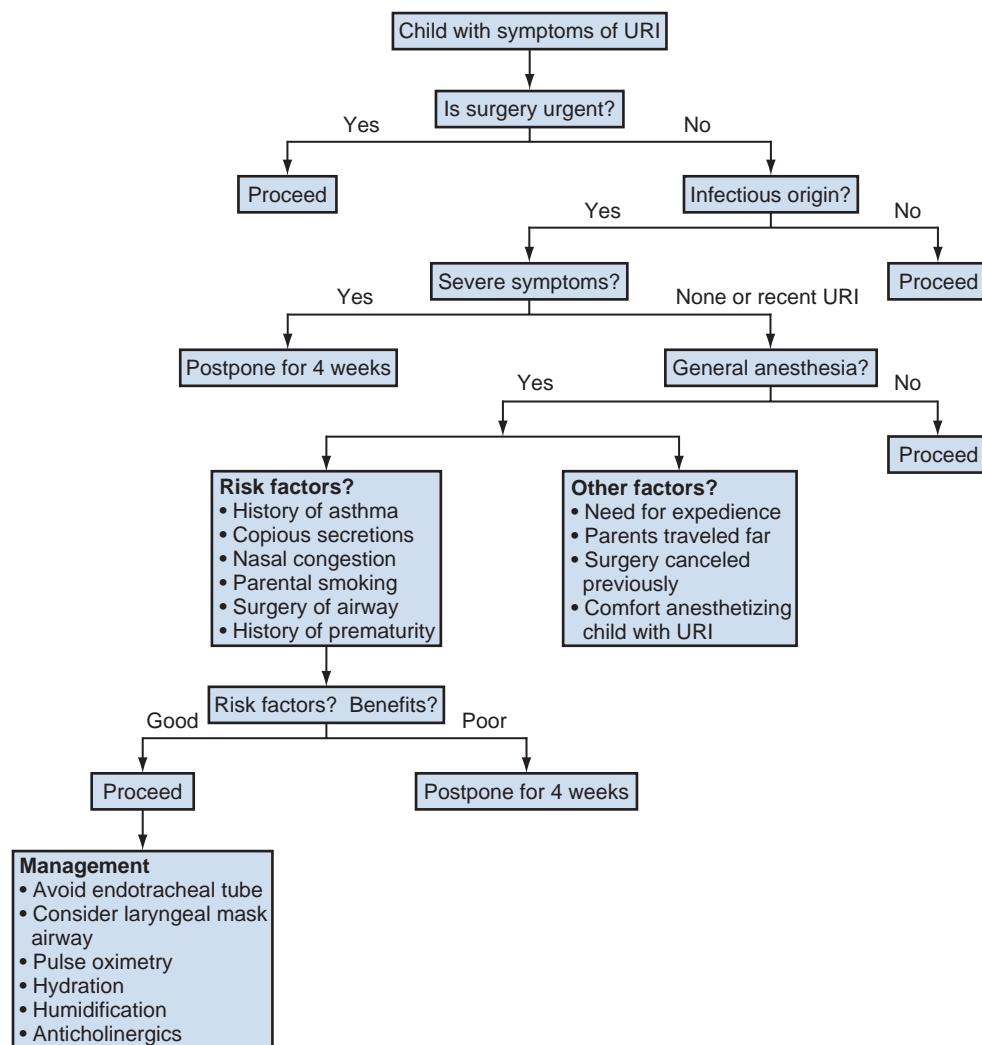


Figure 128-1. Preoperative decision making in children with upper respiratory infection (URI) symptoms. (From Tait AR, Malviya S. Anesthesia for the child with an upper respiratory infection: still a dilemma? *Anesth Analg* 2005;100:59–65.)

hyperactive airways are sensitive to stimulation, and endotracheal intubation is one of the most noxious. In preparing children with asthma for surgery, it is important to note whether a child is on maximal medical therapy and whether wheezing persists despite this. All asthma medications, both inhaled and oral, should be administered up to and including the morning of surgery. If children are not on maintenance therapy and only require treatment during acute exacerbations, this therapy should be administered for the 48 hours before anesthesia even if the child is asymptomatic. If performed, recent pulmonary function test (PFT) results should be available, and children as young as 5 years can cooperate with PFT (Ferrari, 2008).

The Former Premature Infant

Advances in neonatology have resulted in an increasing number of premature infants surviving. These infants generally have complex medical issues and often require surgery for a variety of reasons. Urgent urologic surgery in these babies, however, is rare. From a perioperative perspective, the major issue for these infants is the risk of apnea associated with bradycardia. Apnea is usually central and is the result of brainstem immaturity, which predisposes these infants to more significant apnea during the postoperative period (Kurth et al, 1987). This risk is less than 1% in a 35-week-old former premature infant if surgery is delayed until after 54 weeks' postconceptual age (Cote et al, 1995). If surgery cannot wait, then postanesthetic apnea monitoring is required for 24 hours. Postanesthetic apnea has also been reported in full-term infants younger than 4 weeks of age, and therefore similar monitoring is required (Noseworthy et al, 1989). In addition, a hematocrit less than 30 is associated with an increased risk of postanesthetic apnea in the former preterm infant, and therefore a preoperative hematocrit is warranted in all premature infants undergoing surgery (Welborn et al, 1991; Ferrari, 2008).

Spina Bifida

Spina bifida is one of the most common birth defects, and urologists should be involved in the care of these patients beginning immediately after birth. The average incidence of spina bifida in the United States is 0.7 per 1000 live births. The incidence is higher on the east coast of the United States than on the west coast, and it is higher in whites (1 case per 1000 live births) than in blacks (0.1 to 0.4 case per 1000 live births) (Lemire, 1988). These children are frequent visitors to the OR and require careful preoperative preparation because of their frequent comorbidities. There is a high incidence of sensitivity to latex-containing products, so all patients with spina bifida should be regarded as having a latex allergy. A significant number of children with spina bifida have ventriculo-peritoneal (VP) shunts to manage the hydrocephalus. At Children's Hospital Boston we have a mandatory protocol for elective surgery preparation in children with VP shunts to ensure that they are functional before the administration of anesthesia (Fig. 128-2).

Children with Cancer

Children with a current or previous malignancy should have all chemotherapy documented. Anthracyclines (doxorubicin [Adriamycin]) can cause myocardial dysfunction, and others such as mitomycin C and bleomycin can cause pulmonary dysfunction. Children who have been treated with anthracycline agents require echocardiography if the cumulative dose is greater than 150 mg/m² (Lipshultz et al, 1991). Any child with a history of congestive heart failure who has not had a postanthracycline echocardiogram or an echocardiogram within 2 years before the time of anesthesia requires a preoperative echocardiogram (Ferrari, 2008).

The Child of a Jehovah's Witness

Jehovah's Witnesses refuse blood transfusions because of the belief that the "life force" resides in their blood. Although adult Jehovah's

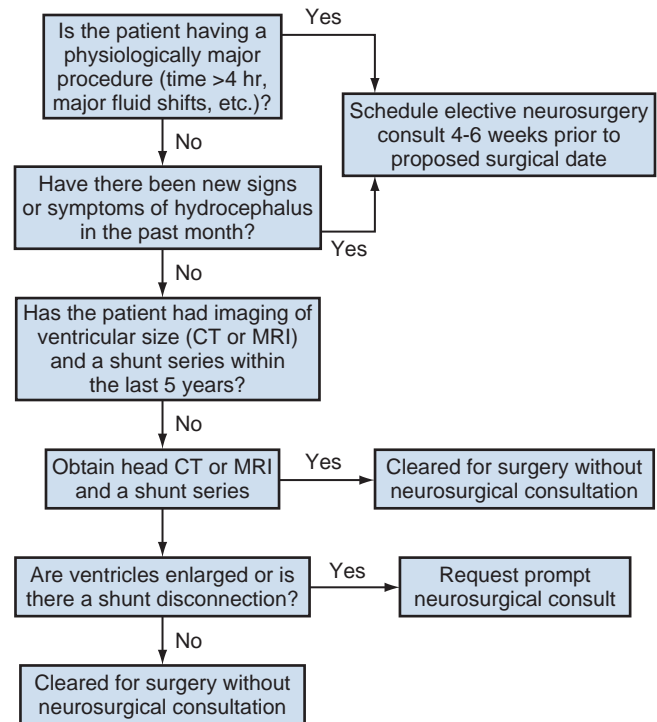


Figure 128-2. Preoperative assessment of patients with shunted hydrocephalus. CT, computed tomography; MRI, magnetic resonance imaging. (From Children's Hospital Boston, © 2008.)

Witness patients may choose to refuse lifesaving blood transfusions, pediatric patients, as minors, do not have that same right. It is therefore imperative that the surgical and anesthesia teams define a plan with the parents in the event that blood is required. Perioperative volume expanders such as albumin, hemodilution, and blood banking are acceptable to some individuals, depending on their interpretation of biblical passages (Benson, 1989). Most medical care providers agree that in an emergency it is unacceptable for a parent to make a conscious decision that could result in the loss of a minor child's life; in such cases, appropriate medical therapy, including transfusion of blood products, is administered against the wishes of the family (Swartz, 1985). In most circumstances, the courts have intervened to allow blood transfusions over the religious objections of the parents. No child of Jehovah's Witness parents should die for lack of transfused blood without a physician seeking a court order to provide blood (Waisel et al, 2001). Consultation with a pediatric hematologist may be helpful to optimize the preoperative preparation, which may include oral iron therapy 2 to 3 weeks before surgery.

Congenital Adrenal Hyperplasia

Pediatric urologists frequently treat patients with congenital adrenal hyperplasia (CAH), and the patients' condition requires careful perioperative preparation. The most common form of CAH is 21-hydroxylase deficiency, which results in an excess of progesterone and 17-hydroxyprogesterone. These hormones are then peripherally converted to androgens, which result in the virilization of affected girls. Approximately 75% of these patients are also salt-wasters because of impaired mineralocorticoid production. In addition, adrenal catecholamine production is deficient in patients with CAH. The cornerstone of the medical management of CAH is life-long hormonal replacement. Children are given hydrocortisone, and salt-wasting patients also require fludrocortisone and sodium chloride supplementation. Perioperatively, it is critical to clearly understand the nature of the child's CAH and how well and stably it is medically managed. Baseline parameters including

hydration status, blood pressure, and electrolytes are determined. The usual doses of hydrocortisone are inadequate to cover the physiologic stress of surgery, and thus CAH patients are typically administered 100 mg/m² hydrocortisone in 4 divided intravenous doses for the first 24 hours and then slowly tapered (Zuckerberg and Maxwell, 2009). A clear perioperative plan for hormonal supplementation should be developed in conjunction with the child's endocrinologist.

Regional Anesthesia

There has been increased interest in regional anesthesia in children mainly as a result of two general factors: decreased general anesthetic requirement and improved postoperative pain management. At Children's Hospital Boston, we routinely use two related types of regional anesthesia: single-shot caudal blocks and epidurals. Caudal blocks are typically used in patients undergoing bilateral groin surgery, those undergoing open ureteroneocystostomy, and in neonatal patients in whom we would like to limit the administration of narcotics. Epidural anesthesia is generally used in children undergoing renal surgery or extensive pelvic surgery.

Single-shot caudal blocks are one-time injections of local anesthetic agents into the epidural space, and these can provide analgesia in the T10 to S5 dermatome region. The most common local anesthetic used is bupivacaine 0.125% to 0.25% with epinephrine administered in volumes of 0.5 to 2 mL/kg (not to exceed toxic doses measured in mg/kg) (Kraemer and Rose, 2009). The addition of clonidine, 1 to 2 µg/kg to a maximum of 30 µg, may enhance the duration and intensity of the caudal block (Constant et al, 1998). In addition to the one-time injection, an angiocatheter may be left in place in the caudal region for additional postoperative local anesthetic administration. One of the most frequent complications with caudal blocks is the inadvertent needle placement into the vasculature, the intrathecal space, or even the bone in very young children; however, this rate is low (0.7 per 1000) (Kraemer and Rose, 2009).

Continuous epidural analgesia (CEA) provides excellent perioperative analgesia in infants and children undergoing thoracic, abdominal, pelvic, and perineal surgery. The epidural space may be accessed at any level, but it is most frequently approached at the lumbar or caudal region in children. If the epidural needle touches the spinal cord, the awake patient will react and spinal cord injury can thereby be avoided. However, the vast majority of epidural catheters in children are placed under general anesthesia because it is generally considered safer to place epidurals in children who are

not moving. The risk of neurologic injury with lumbar epidural catheter placement is exceedingly low, but thoracic placement does carry a higher risk of spinal cord injury should the needle be advanced too far. As such, direct thoracic placement under general anesthesia should be performed only by very experienced personnel and with careful consideration of the potential risks and benefits (Greco et al, 2002). In selected cases, catheters can be advanced to the thoracic level from a lumbar or caudal route under fluoroscopic guidance. The location of the catheter tip can be confirmed with a contrast epidurogram (Greco et al, 2002). Epidural drug selection is individualized and varies with site of surgery, location of the epidural, and patient-specific factors. In general, local anesthetics are infused in combination with opioids, clonidine, or both. Clonidine is used because of the same benefits as discussed for single-shot caudal blocks, and clonidine is used preferentially over opioids if possible, because it does not cause adverse effects typical of opioids including pruritus, nausea, ileus, urinary retention, or respiratory depression (Greco et al, 2002; Hirschl and Coran, 2003c). The risk of local anesthetic toxicity is one of the main concerns that require continuous monitoring during CEA. Hospitals should have a dedicated team of anesthesiologists and nurses immediately available to manage any emergent problems with pain control or adverse effects with CEA. The epidural site should be evaluated daily for signs of infection. Protocols and CEA order sets should include patient monitoring parameters and neurologic assessment every 4 hours (Kraemer and Rose, 2009).

Postoperative Pain Management

It is incumbent on pediatric care providers to make every attempt possible to assess their patients' pain, which may be challenging given the limited cognition and language skills of infants and children. Pain assessment tools are well established and widely available, but assessing pain in neonates, infants, and nonverbal or developmentally delayed children is still limited (Kraemer and Rose, 2009). In general, the younger the child, the less likely he or she can clearly delineate between levels of pain using pain scales. In general, however, children 8 years of age and older can reliably report pain on the visual analog scale used in adults. Children between the ages of 3 and 7 years can better report pain using a "faces" scale that presents a series of drawings depicting increasing levels of distress (Kraemer and Rose, 2009). Table 128-3 provides examples of some routinely used pediatric pain scales. In addition to the child, parents are often an excellent source of information regarding their child's pain.

TABLE 128-3 Pediatric Pain Scales

SCALE	TYPE	AGES	SCORING INDICATORS
PIPP	Behavioral and physiologic parameters Procedural pain	Term and preterm infants	Gestational age Behavioral state Heart rate, SpO ₂ Facial expression
CRIES	Behavioral and physiologic parameters Postoperative pain	32-60 wk	Crying, increased O ₂ Increased vital signs Expression Sleeplessness
FLACC	Behavioral parameters	<3 yr or unable to self-report	Face, legs, activity, cry, consolability
Faces	Self-report	3-12 yr	Happy face to saddest face yield numeric 0-10 score
VAS	Self-report	>7 yr	0 = no pain 10 = maximum pain

CRIES, crying, increased O₂, increased vital signs, facial expression, sleeplessness; FLACC, face, legs, activity, cry, consolability; PIPP, premature infant pain profile; VAS, visual analog scale.

Modified from Kraemer FW, Rose JB. Pharmacologic management of acute pediatric pain. *Anesthesiol Clin* 2009;27:241-68.

TABLE 128-4 Acetaminophen Dosing

ROUTE OF ADMINISTRATION	PRETERM INFANTS (28-32 wk)	PRETERM INFANTS (>32 wk)	FULL-TERM INFANTS AND CHILDREN <50 kg	CHILDREN >50 kg, ADOLESCENTS, AND ADULTS
Oral	12.5 mg/kg q6h PRN for 72 hr	12.5 mg/kg q4h PRN for 72 hr	12.5 mg/kg q4h PRN for 72 hr	325-975 q4h PRN for 72 hr
Rectal	20 mg/kg q12h PRN for 72 hr	15 mg/kg q8h PRN for 72 hr	15-20 mg/kg q4h PRN for 72 hr	325-975 q4h PRN for 72 hr
Intravenous	Not approved <2 yr old	Not approved <2 yr old	≥2 yr old: 15 mg/kg q6h or 12.5 mg/kg q4h	1000 mg q6h or 650 mg q4h
Maximum dose	50 mg/kg/day	90 mg/kg/day	Oral/rectal: 90 mg/kg/day (≤4 g/day) IV: 75 mg/kg/day (≤3750 mg/day)	4 g/day

Based on Boston Children's Hospital formulary.

Based on severity, pediatric pain management involves targeting several of the complex elements of pain transduction, transmission, modulation, and perception (Kraemer and Rose, 2009). Common multimodal plans include NSAIDs acting on the periphery, regional block of peripheral nerves, nerve roots, or spinal cord, and/or opiates acting centrally. A balanced approach such as this can minimize the adverse effects of each and can work synergistically to manage acute pain best.

For children who undergo nonambulatory surgery and who do not have CEA, patient-controlled analgesia (PCA) is an excellent option for treating moderate to severe pain. **Children as young as 5 years old have successfully used PCA with proper education and guidance, but PCA is routinely used in children aged 7 and older (McDonald and Cooper, 2001).** The use of PCA mandates institutional/departmental monitoring requirements that include respiratory rate, pulse oximetry, heart rate, blood pressure, pain assessment, and level of consciousness. When used with appropriate monitoring, PCA is safe, effective, and highly reliable. In younger children or those unable to control their PCA reliably, nurse- or parent-controlled analgesia can be used with similar success and efficacy.

Oral pain medications include nonopioid and opioid analgesics. Nonopioid options include acetaminophen and NSAIDs. **Acetaminophen is the most widely used antipyretic and analgesic medication in pediatrics, and it is commonly combined with opioids for patients with moderate to severe pain.** When dosed appropriately, acetaminophen can be used safely in neonates. It is normally metabolized in the liver primarily by glucuronidation and sulfation. Neonates and infants primarily conjugate by sulfation, and the mature ratio of glucuronidation/sulfation is reached at approximately 12 years of age. **The concerning feature of acetaminophen is that overdose can lead to liver necrosis and failure.** This is because in supranormal doses acetaminophen is metabolized by the oxidative cytochrome P450 pathway, which results in a highly hepatotoxic metabolite. Acetaminophen is available in several formulations including drops (80 mg/0.8 mL), elixir (160 mg/5 mL), chewable tablets (80 mg and 160 mg), dissolvable tablets (160 mg), tablets (325 mg and 500 mg), suppositories (80 mg, 120 mg, 325 mg, and 650 mg), and intravenous solution. The suggested dosing of acetaminophen is provided in Table 128-4.

NSAIDs are commonly used for postoperative pain because they provide excellent analgesia and are well tolerated. A review of short-term ibuprofen use in a large cohort of children showed no increase in renal or gastrointestinal adverse effects compared with acetaminophen (Lesko and Mitchell, 1995). NSAIDs are more similar than they are different. Adult clinical trials, outcome studies, and systematic reviews indicate that there is no NSAID that possesses uniquely greater analgesic effect than others and that the oral, rectal, and parenteral routes of administration are equally effective (Greco et al, 2002). Like acetaminophen, ibuprofen is available in several preparations including drops (50 mg/1.25 mL), elixir

TABLE 128-5 Opioid Dosing

OPIOID	ROUTE/AGE GROUP	DOSE/INTERVAL
Morphine	Intravenous bolus:	
	Full-term neonate	10-25 µg/kg q2-4h
	Preterm neonate	25-50 µg/kg q3-4h
	Infants and children	50-100 µg/kg q3-4h
	IV infusion:	
	Preterm neonate	2-5 µg/kg/hr
	Full-term neonate	5-10 µg/kg/hr
	Infants and children	15-30 µg/kg/hr
Codeine	Oral	0.5-1 mg/kg q4h
Oxycodone	Oral	0.05-0.15 mg/kg q4h

Modified from Kraemer FW, Rose JB. Pharmacologic management of acute pediatric pain. *Anesthesiol Clin* 2009;27:241-68.

(100 mg/5 mL), chewable tablets (50 mg and 100 mg), and tablets (200 mg, 400 mg, 600 mg, and 800 mg). Intravenous ibuprofen is available in the United States, but has not been approved for use in pediatric patients for the treatment of pain. Ibuprofen should be used routinely in children aged 6 months and older. For analgesia, a single dose of 15 mg/kg can be used. However, if repeated doses are anticipated or planned, dosing should be 4 to 10 mg/kg/dose every 6 to 8 hours, with a maximum daily dose of 40 mg/kg/day.

Ketorolac is the only parenteral NSAID (15 mg/mL and 30 mg/mL) available for use in the United States to treat pediatric pain, and it has been used as an adjuvant to opioids and a single agent for the treatment of postoperative pain. We routinely use ketorolac in children at least 6 months of age, but it is approved for use in children 2 years or older. **We have found that in addition to excellent analgesia, ketorolac significantly reduces the incidence and severity of bladder spasms (Park et al, 2000), and we routinely use ketorolac following bladder surgery.** However, significant adverse effects have been reported including acute renal failure, prolongation of bleeding times, and hypersensitivity reactions, and therefore caution is warranted (Kraemer and Rose, 2009). Because of this, we do not use ketorolac in patients with renal insufficiency, renal scarring, a solitary kidney, NSAID sensitivity, or in a patient in whom a risk of significant postoperative bleeding is feared. Dosing of ketorolac is 0.25 to 0.5 mg/kg every 6 hours with no loading dose requirement.

Opioids are commonly used for moderate to severe pain, and for the vast majority of children they provide excellent analgesia with a wide margin of safety. They affect analgesia by central nervous system neuronal inhibition. The commonly used opioids in the pediatric population are µ₁ agonists and include morphine, hydromorphone, methadone, fentanyl, codeine, oxycodone, and hydrocodone (Table 128-5). Opioids can be administered through

several routes, including orally, intravenously, intramuscularly, subcutaneously, rectally, transdermally, or transmucosally. Oral administration is usually the easiest route and provides relatively constant drug plasma levels. **Despite their general efficacy, there is substantial individual variation in opioid dose requirements. The adequate opioid dose is that which provides pain relief but does not result in excessive somnolence or respiratory depression.** Morphine is the standard opioid to which all others are compared (Greco et al, 2002; Kraemer and Rose, 2009). It is metabolized in the liver, the elimination half-life is longer, and the clearance is decreased in newborns. This difference is even more substantial in preterm neonates. Within 2 months of age, however, the elimination half-life and clearance reach adult levels. There is no established optimal morphine plasma concentration, and therefore the appropriate dose needs to be established for each patient while being carefully monitored for respiratory depression.

Codeine is available in elixir form and is the most common orally administered opioid in young children. It is often combined with acetaminophen (acetaminophen 120 mg with codeine 12 mg/5 mL), and in this form it is more effective. Dosing of codeine is 0.5 to 1 mg/kg every 4 hours, but the dose of acetaminophen needs to be carefully considered to avoid acetaminophen toxicity. The maximum dose based on acetaminophen content for children weighing less than 45 kg is acetaminophen 90 mg/kg/day and for children weighing more than 45 kg it is acetaminophen 4 g/day. **Codeine itself is a relatively weak opioid given its extremely low affinity for opioid receptors, and most of its analgesic effect is a result of the 10% that is metabolized to morphine.** The metabolism to morphine is predominantly via O-demethylation by the cytochrome P450 enzyme CYP2D6, which is known to show genetic polymorphism (Williams et al, 2001). **Therefore, variations in CYP2D6 will result in variable abilities to metabolize codeine.** In this way, individuals may be classified as poor metabolizers or ultrarapid metabolizers, depending on the phenotype of their CYP2D6 enzyme. A total of 3% of Caucasians and 40% of people of North African descent are ultrarapid metabolizers, resulting in dangerously high plasma levels of morphine (Gasche et al, 2004). Conversely, 7% to 10% of Caucasians are poor metabolizers of codeine, and receive little or no analgesia from codeine administration (Kraemer and Rose, 2009). The disastrous consequences of CYP2D6 variability is highlighted by the report of the death of a 2-year-old child who was given codeine at home following a routine tonsillectomy (Ciszkowski et al, 2009). Genotyping of the patient showed duplication of the CYP2D6 allele (ultrarapid metabolizer), and the plasma concentration of morphine was 32 ng/mL (>20 ng/mL results in respiratory depression). **Because of this risk, we use oxycodone exclusively, which appears to have less variable metabolism.**

Oxycodone is available in tablet and liquid form, and it is also commonly combined with acetaminophen. The combined preparation is commonly used in children, and it is available in solution (oxycodone 5 mg and acetaminophen 325 mg/5 mL) and in tablet form (oxycodone 2.5 to 10 mg and acetaminophen 300 to 650 mg). The initial dose is based on the oxycodone content, but the maximum daily dose is based on the acetaminophen content. Based on pain severity, the initial oxycodone dose is 0.05 to 0.3 mg/kg/dose. The maximum dose based on acetaminophen content for children weighing less than 45 kg is acetaminophen 90 mg/kg/day, and for children weighing more than 45 kg it is acetaminophen 4 g/day. A strategy that we commonly use for most outpatient surgical procedures is a scheduled regimen of alternating acetaminophen and ibuprofen every 3 hours for the first 48 hours after surgery. Plain oxycodone can then be used in addition if the acetaminophen and ibuprofen prove inadequate. This approach is commonly used in pediatrics for fever reduction and has been shown to be safe in the surgical setting (Bauer et al, 2010; Wong et al, 2013). Although we use plain oxycodone exclusively, its widespread availability appears to be limited, as many community pharmacies consider it a specialty item and do not keep it in regular stock. If this is the case, then a combined acetaminophen/oxycodone preparation is favored,

which will complicate the alternating scheme of acetaminophen and ibuprofen.

KEY POINTS: PEDIATRIC ANESTHESIA AND ANALGESIA

- Surgical preparation is a multifaceted endeavor that involves the consideration of the medical and psychological needs of children and their families, all of which vary with the child's age and developmental status.
- The risks associated with anesthesia in a healthy child undergoing uncomplicated surgery are extremely low. In addition, it is currently unknown whether anesthesia is neurotoxic to the developing brain.
- Routine diagnostic testing for surgery is rarely indicated in healthy children and studies that are ordered should be selected based on the general health of the patient and the procedure being performed.
- Children should not be kept "NPO after midnight"; the ASA has provided guidelines to optimize patient hydration and to minimize risk.
- URI is very common in childhood; elective surgery should be scheduled after the acute symptoms have resolved and no sooner than 3 to 4 weeks after the initial evaluation.
- Children with VP shunts should undergo evaluation to ensure proper shunt function before undergoing major surgery.
- Regional anesthesia plays an important role in several urologic surgeries, and the most commonly performed are the single-shot caudal block and continuous epidurals.
- Based on severity, pediatric pain management involves targeting several of the complex elements of pain transduction, transmission, modulation, and perception.
- Acetaminophen is the most widely used analgesic in pediatrics; ibuprofen is also commonly used and children are unlikely to experience adverse renal or gastrointestinal effects.
- Opioids are used for moderate to severe pain and there is substantial variation in individual opioid dose requirements.
- Codeine has highly variable efficacy because of genetic polymorphism of the CYP2D6 liver enzyme; patients may be poor metabolizers resulting in little or no analgesia or they might be rapid metabolizers resulting in dangerous levels of postmetabolism opioid plasma levels.

SURGICAL PREPARATION AND INTRAOPERATIVE CONSIDERATIONS

Surgical Preparation

Antimicrobial Prophylaxis

Because there are no available guidelines from any of the pediatric urologic or surgical societies, whether to use prophylactic antibiotics in children undergoing surgery remains an individual and non-evidence-based decision. This decision is generally not controversial for major surgery for which surgical antimicrobial prophylaxis (SAP) is routinely administered, but it is so for minor procedures such as orchidopexy, herniorrhaphy, and circumcision. The Centers for Disease Control and Prevention (CDC) provided guidelines for SAP (Mangram et al, 1999), but these were broad and general and did not specifically address urologic surgery. In 2001 the European Association of Urology published urology-specific guidelines, but pediatric procedures were not specifically addressed. The Japanese Urological Association published comprehensive SAP guidelines that included pediatric procedures (Matsumoto et al, 2007), but these were not evidence-based and were formulated based on the opinions and practice patterns of academic pediatric urologists. The

CDC surgical wound classification system of clean (class I), clean-contaminated (class II), contaminated (class III), and dirty/infected (class IV) can be applied to pediatric urologic procedures, and examples are provided in Table 128-6. In general, SAP is recommended for: (1) all surgery in neonates younger than 72 hours of age because of possible exposure to maternal pathogens and

particularly compromised immunologic capacity, (2) major class II surgery, and (3) all class III and class IV surgical procedures (2004). Antibiotic use in class I and minor class II operations is not studied, and this use remains based on individual surgeons' preferences. Recommendations for SAP are provided in Table 128-7. The timing of SAP administration is critically important, and the first dose should be administered from 30 minutes to 3 hours before incision to achieve bactericidal levels of the antibiotic at the site of incision.

TABLE 128-6 Wound Classification in Pediatric Urologic Surgery

WOUND CLASSIFICATION	PROCEDURES
Clean	Nephrectomy, adrenalectomy, retroperitoneal tumor resection, orchidopexy, herniorrhaphy
Clean-contaminated	Nephroureterectomy, partial nephrectomy, pyeloplasty, ureteral reimplant, other intravesical procedures, exstrophy closure, partial cystectomy, hypospadias repair, other genital surgery, cystoscopy, transurethral incision of ureterocele, transurethral ablation of posterior urethral valves
Contaminated	Bladder enterocystoplasty, continent urinary diversion
Dirty	Open trauma of the urinary tract, operations for infected kidney, ruptured bladder augmentation

Modified from Yamamoto S, Shima H, Matsumoto T. Controversies in perioperative management and antimicrobial prophylaxis in urologic surgery. *Int J Urol* 2008;15:467–71.

Thromboembolism Prophylaxis

Venous thromboembolic events (VTEs) in children are rare when compared with adults. The incidence of VTEs in children is estimated to be between 0.07 and 0.14 per 10,000 in the general population and 5.3 per 10,000 for pediatric hospital admissions (Andrew et al, 1994; van Ommen et al, 2001). In general, the frequency of VTEs in children is one tenth that of adults (Levy et al, 2004), and several factors are believed to contribute to this difference. These include lower levels of thrombin in childhood, enhanced levels of thrombin inhibitors in children, and significantly lower levels of various clotting factors at different times in childhood (Jackson and Morgan, 2008). Despite the rare incidence, it is believed to be increasing, most likely owing to increased awareness and diagnosis and improved life expectancy of children with serious prothrombotic diseases such as congenital heart disease, cancer, and extreme prematurity (Jackson and Morgan, 2008). The incidence of VTE in the pediatric population is bimodal, occurring most often in infants aged less than 1 year and in adolescents. These two age groups account for more than 70% of VTEs. Risk factors in infants include diminutive blood vessels, a unique hemostatic system, and the use of central venous catheters (CVCs). Risk factors in adolescents include smoking, contraception, and obesity (Sandoval et al, 2008). In general, the greatest risk factor is the presence of a CVC. There are no clear guidelines in pediatric surgery for the use of thromboprophylaxis, and individual institutions typically develop local policy. In general, for pediatric noncancer urologic surgery we use thromboprophylaxis for all peri- and postpubertal patients,

TABLE 128-7 Recommendations for Surgical Antimicrobial Prophylaxis

OPERATION	LIKELY PATHOGENS	PROPHYLACTIC ANTIBIOTICS	PREOPERATIVE DOSE
Neonatal (<72 hr old) surgery	Group B streptococci, enteric gram-negative bacilli, enterococci	Ampicillin + gentamicin	50 mg/kg ampicillin 2.5–3 mg/kg gentamicin
Class I (clean)	<i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i> , streptococci, gram-negative enteric bacilli	Cefazolin or Vancomycin (if MRSA or MRSE likely)	25 mg/kg 10 mg/kg
Class II (clean-contaminated)	Enteric gram-negative bacilli, enterococci	Cefazolin or Ampicillin + gentamicin	25 mg/kg 50 mg/kg ampicillin 2.5–3 mg/kg gentamicin
Class III (contaminated)	Gram-negative enteric bacilli, enterococci, anaerobes	Cefoxitin or Cefotetan	40 mg/kg 40 mg/kg
Class IV (dirty/infected)	Gram-negative enteric bacilli, enterococci, anaerobes	Cefoxitin or Cefotetan ± gentamicin or Gentamicin + clindamycin	40 mg/kg 40 mg/kg (±2 mg/kg gentamicin) 2 mg/kg gentamicin + 10 mg/kg clindamycin

MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

Modified from McInerney TK, Adam HM, Campbell DE, et al, editors. American Academy of Pediatrics textbook of pediatric care. Elk Grove Village (IL): American Academy of Pediatrics; 2009.

because it is assumed that the adult risk of VTE develops after sexual maturation. The extent of thromboprophylaxis, which can include compression stocking and/or sequential compression devices plus or minus subcutaneous enoxaparin, is made on a case-by-case basis based on the assessment of an individual child's risk factors.

Hair Removal

Peripubertal children and postpubertal adolescents may have a significant amount of hair at the sites of urologic procedures. The questions of appropriate timing and method of hair removal have been debated because they are thought to impact significantly the development of surgical site infections (SSIs). Data indicate that there is a higher risk of SSI when hair is removed on the day of or night before surgery and also with the use of razors. Lower rates of SSI are achieved by using clippers or depilatory agents immediately before surgery (Tanner et al, 2007). Based on this, our policy is to remove hair at the time of immediate presurgical preparation in the OR using clippers. Razors are no longer available in our ORs.

Intraoperative Considerations

Blood Loss and Transfusion Requirement

Blood volume in children varies with age, but estimates can be between 75 and 80 mL/kg (Linderkamp et al, 1977). In general, transfusion of packed red blood cells (PRBCs) is indicated for a hematocrit of less than 24% with signs and symptoms of anemia in the perioperative period or blood loss of more than 15% of the blood volume (Roseff et al, 2002). In cases of blood loss less than 15% of the blood volume, volume replacement with crystalloid is usually adequate. Massive bleeding involving the loss and replacement of 1 blood volume within 24 hours can lead to serious complications, and the mortality rate associated with this situation is approximately 40% (Radel, 2009). In an extreme situation, non-crossmatched O Rh-negative blood may be used, but all efforts should be made to use blood-type-specific blood products. In general, platelet transfusion is reserved for a platelet count of less than 50,000/mL. Fresh-frozen plasma is used if the prothrombin time or partial thromboplastin time is more than 1.5 times normal (Radel, 2009). In our experience, the pediatric urologic surgical case most likely to require transfusion of PRBCs has been newborn complete primary repair of bladder exstrophy, with 75% of boys and 29% of girls requiring intraoperative transfusion (Borer et al, 2005).

The risks associated with transfusion are minimal, but they are a consistent source of worry for parents. The elimination of paid donors, more thorough donor screening, and increasingly sophisticated donor blood testing have led to a significant decrease in the incidence of infection transmitted by transfusion (Zuckerberg and Maxwell, 2009). The incidence of transfusion-associated hepatitis B is 1 in 63,000, and the risk of transfusion-transmitted hepatitis C is 1 in 103,000 (Schreiber et al, 1996). The risk of transfusion-transmitted HIV is estimated to be between 1 in 450,000 and 1 in 600,000 (Schreiber et al, 1996). In addition to the risk of transmission of infection, transfusion reactions occur in 2% to 3% of cases. Of these, 41% are febrile and nonhemolytic, 58% are urticarial, and 1% are delayed hemolytic (American Medical Association, 1985).

Thermoregulation

Infants and children are more susceptible than adults to changes in ambient temperature because they have a relatively large body surface to mass ratio, less insulating tissue such as fat or hair, and limited energy reserves. Neonates are especially sensitive to cold exposure because they are unable to shiver, and they rely on brown adipose tissue for the generation of heat. Maintaining normal body temperature intraoperatively is important because hypothermia increases the incidence of intraoperative and post-

operative complications including bleeding, acidosis, impaired immune function, and delayed wound healing. During anesthesia, children are exposed to all the factors of heat loss, including convection, radiation, evaporation, and conduction. Measures including humidification and warming of inspired air, warmed fluids for intravenous administration, and the use of warming devices such as the BAIR hugger may be used as needed (Pierro et al, 2006; Wetzel, 2007).

KEY POINTS: SURGICAL PREPARATION AND INTRAOPERATIVE CONSIDERATIONS

- In general, SAP is recommended for (1) all surgery in neonates less than 72 hours of age because of possible exposure to maternal pathogens and particularly compromised immunologic capacity, (2) major class II surgery, and (3) all class III and IV surgical procedures; antibiotic use in class I and minor class II operations is based on individual surgeons' preferences.
- The timing of SAP administration is critically important, and the first dose should be administered 30 minutes to 3 hours before incision.
- VTEs in children are rare, but the incidence is believed to be increasing and is bimodal, occurring most often in infants less than 1 year of age and in adolescents.
- Lower rates of SSI are achieved by using clippers or depilatory agents for hair removal immediately before surgery.
- Blood volume in children varies with age, but it can be estimated at 75 to 80 mL/kg.
- The risks associated with blood transfusion are very low; the incidence of transmission of hepatitis B is 1:63,000, of hepatitis C is 1:103,000, and of HIV is 1:450,000 to 1:600,000.
- Infants and children are more susceptible than adults to changes in ambient temperature because they have a relatively large body surface to mass ratio, less insulating tissue such as fat or hair, and limited energy reserves.
- Maintaining normal body temperature intraoperatively is important because hypothermia increases the incidence of intraoperative and postoperative complications including bleeding, acidosis, impaired immune function, and delayed wound healing.

POSTOPERATIVE CARE

A majority of pediatric urologic operations are performed as outpatient procedures, and there continues to be a push to expand the number of these. Routine outpatient urologic procedures include orchidopexy, herniorrhaphy, circumcision, laparoscopic procedures for maldescended testes, and hypospadias repair. Some groups are also performing operations in this manner that were previously performed exclusively as inpatient surgery, such as unilateral extravesical ureteral reimplants (Palmer, 2008). Certainly outpatient surgery has many advantages including cost savings, lessened psychological trauma, fewer nosocomial infections, and faster recovery (Yaster et al, 1994). However, adequate perioperative patient and family education is vital to obtaining good outcomes, and this requires collaborative efforts from the surgeon, anesthesiologist, and nursing staff.

Complications

The vast majority of children who undergo urologic surgery are healthy, and in this population the incidence of serious complications is less than 1% (Hannallah, 1987). A detailed discussion of complications specific to various urologic procedures is beyond the scope of this chapter, but broad postoperative complications will be addressed instead.

TABLE 128-8 Common Causes of Postoperative Fever

SITE	ETIOLOGY	TIME	INCIDENCE	SIGNS/SYMPTOMS	THERAPY
Wind	Atelectasis	24-48 hr	Very common	Cough, shortness of breath, retractions	Cough, deep breathing, incentive spirometry
Wound	SSI	<24 hr-7 days	Rare	Pain, erythema, induration	Antibiotics, open drainage, and debridement
Water	UTI	3-5 days	Very rare in nonurologic surgery; needs to be considered in any surgery involving the urinary tract	Dysuria, hematuria	Remove indwelling catheter as early as possible, antibiotics
Walking	DVT	>3 days	Extremely rare	Swelling, lower extremity pain, superficial venous congestion, palpable cord	Bed rest, elevation, anticoagulation, thrombolytics

DVT, deep vein thrombosis; SSI, surgical site infection; UTI, urinary tract infection.

Modified from Maxwell LG. Postoperative care. In: McInerney TK, Adam HM, Campbell DE, et al, editors. American Academy of Pediatrics textbook of pediatric care. Elk Grove Village (IL): American Academy of Pediatrics; 2009. p. 552–63.

Although not a surgical complication per se, postoperative nausea and vomiting (PONV) is the most common early complication associated with the administration of anesthesia (Maxwell, 2009). PONV is the most common cause of delayed discharge from the PACU and unscheduled hospitalization following outpatient procedures, representing the cause of almost 25% of unplanned admissions (Patel and Hannallah, 1988; Blacoe et al, 2008). The cause of PONV is multifactorial, but some procedures are known to be associated with higher rates, including orchidopexy, which has been associated with a greater than 50% incidence of PONV (Maxwell, 2009). Another significant contributing factor is the use of opioids in the perioperative period. Several measures can be taken for limiting PONV, including avoiding opioids if possible, using antiemetics perioperatively, adequate intravenous hydration with glucose supplementation, and limiting oral intake postoperatively (Maxwell, 2009). The commonly used antiemetics include benzamides (metoclopramide [Reglan]), serotonin antagonists (ondansetron [Zofran]), phenothiazines (prochlorperazine [Compazine], promethazine [Phenergan]), and antihistamines (diphenhydramine [Benadryl]). We most commonly use ondansetron because it is the only antiemetic drug for children that does not routinely result in sedation. Ondansetron is contraindicated in children taking serotonin reuptake inhibitors for migraine headaches. The use of promethazine (Phenergan) in children is strongly discouraged, given the U.S. Food and Drug Administration warning issued in 2006 that warns that it should not be used in children less than 2 years of age because of the potential for fatal respiratory depression. In addition, it should be used with caution in children 2 years of age and older. In general, children in the PACU should not be forced fluids, and the administration of fluids should be based on the child's request. In the setting of PONV, forced fluids to encourage timely discharge will most likely be counterproductive.

Postoperative fever is a common early surgical problem, and its etiology is taught in the first days of medical-school surgery clerkships as the 4 Ws: wind, wound, water, walking. "Wind" refers to atelectasis, "wound" to an SSI, "water" to an infection in the urinary tract (UTI), and "walking" to fever caused by deep vein thrombosis (DVT) in the lower extremities. Fever, defined as greater than 38.5° C rectal temperature, is common within 24 hours of surgery, and fever is usually caused by atelectasis. Pulmonary toilet with deep breathing, coughing, and ambulation is usually effective in otherwise healthy children. In patients too young to participate in pulmonary toilet, measures such as blowing bubbles can be effective. UTI in the setting of urologic surgery is always a concern and needs to be considered. The other causes, SSI and DVT, are rare to extremely rare in the pediatric population. These common

causes are summarized in Table 128-8. In addition, other common causes of fever in children should be considered including URIs, gastroenteritis, and otitis media.

Postoperative SSIs were traditionally characterized as incisional (superficial) or deep, but this fails to consider the total operative site. The CDC has modified the definition of SSIs, which now are reported as Incisional SSI–Superficial versus Deep or Organ/Space SSI (Ziegler et al, 2003; Ashcroft et al, 2005). It is critically important to diagnose early and to intervene promptly to avoid morbidity and even mortality. The wound is examined for classic signs of infection and inflammation, including erythema, edema, tenderness, and warmth. If there appears to be an SSI, a Gram stain and culture should be obtained with a sterile swab. Treatment should be tailored according to the extent of the infection, and it may include oral or parenteral antibiotics, incision and drainage, or extensive debridement. The incidence of SSIs varies from 1% to 11% in clean wounds and from 6% to 21% in contaminated wounds (Ashcroft et al, 2005). In general, most SSIs occur between the fifth and tenth postoperative days. The rare exceptions are *β*-streptococcal, *Clostridium difficile*, and *Clostridium perfringens* (*welchii*) infections, which produce SSIs that can become clinically apparent within 24 to 48 hours postoperatively. Clostridial and streptococcal infections may be life threatening, and children with these develop high, spiking fevers (39° C to 41° C), become irrational, and may develop jaundice (Maxwell, 2009). Table 128-9 provides a summary of SSIs.

Significant postoperative bleeding is rare in pediatric urology. Persistent bleeding at the surgical incision for more than 6 to 8 hours postoperatively usually indicates inadequate hemostasis and is usually a result of a superficial skin artery. The two most common postoperative bleeding situations encountered in pediatric urology involve circumcisions and scrotal hematomas following herniorrhaphy/hydrocelectomy or orchidopexy, with rates of persistent bleeding of approximately 1% to 2% and 2% to 11%, respectively (Caruso et al, 2000; Brisson et al, 2002; Cathcart et al, 2006). Persistent bleeding following circumcision usually responds to direct digital pressure, and reoperation is exceedingly rare. Scrotal hematomas are usually self-limited, and they generally resolve during a period of 4 to 6 weeks. However, fever, erythema of the overlying scrotal skin, tenderness, and progressive enlargement may indicate close monitoring and surgical re-exploration. In patients with thrombocytopenia, prophylactic platelet transfusion is prudent for platelet counts less than 50,000/ μ L (Gmur et al, 1991).

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The complete reference list is available online at www.expertconsult.com.



TABLE 128-9 Postoperative Surgical Site Infections

ONSET (POSTOPERATIVE DAY)	USUAL PATHOGENS	WOUND APPEARANCE	OTHER SIGNS
1-3	<i>Clostridium welchii</i>	Brawny, hemorrhagic, cool Occasional gaseous crepitance Putrid dishwater exudate Intense local pain	High standard fever (39° C-40° C) Irrational behavior Leukocytosis (WBC count >15,000/mL) Occasional jaundice
2-3	<i>Streptococcus</i>	Erythematous, warm, tender Occasionally, hemorrhagic with blebs Serous exudate	High, spiking fever (39° C-40° C) Irrational at times Leukocytosis (WBC count >15,000/mL) Rare jaundice
3-5	<i>Staphylococcus</i>	Erythematous, warm, tender Purulent exudate	High, spiking fever (39° C-40° C) Irrational at times Leukocytosis (WBC count 12,000-20,000/mL)
>5	Gram-negative rods	Erythematous, warm, tender Purulent exudate	Sustained low-grade to moderate fever (38° C-40° C) Rational behavior Leukocytosis (WBC count 10,000-16,000/mL)
>5	Symbiotic (usually anaerobes plus gram-negative rods)	Erythematous, warm, tender Focal necrosis Purulent, putrid exudate	Moderate to high fever (38° C-40° C) Leukocytosis (WBC count >15,000/mL) Occasional jaundice Mentation variable

WBC, white blood cell count.

Modified from Maxwell LG. Postoperative care. In: McInerney TK, Adam HM, Campbell DE, et al, editors. American Academy of Pediatrics textbook of pediatric care. Elk Grove Village (IL): American Academy of Pediatrics; 2009. p. 552-63.

KEY POINTS: POSTOPERATIVE CARE

- PONV is the most common early complication associated with the administration of anesthesia.
- Certain procedures are associated with high rates of PONV; the rate approaches 50% following orchidopexy.
- Fever, defined as greater than 38.5° C rectal temperature, is common within 24 hours of surgery and, as in adults, is usually caused by atelectasis.
- In cases of SSI, it is critically important to diagnose early and to intervene promptly to avoid morbidity and even mortality.
- The incidence of SSIs varies from 1% to 11% in clean wounds and from 6% to 21% in contaminated wounds; most SSIs occur between the fifth and tenth postoperative days.

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General Applications of Laparoscopy

Advantages of Minimally Invasive Surgery

Disadvantages of Minimally Invasive Surgery

Team Development

Hemostatic Devices

Suturing

Anesthesia

The Different Approaches: Transperitoneal versus Retroperitoneal

Troubleshooting the Robotic Approach

Laparoendoscopic Single-Site Surgery

Potential Complications and Solutions

Outcomes

Conclusion

Laparoscopy was first performed in urology when a cystoscope was used to inspect the peritoneal cavity. This was done for the localization of nonpalpable undescended testes and inspection of the gonads in children with ambiguous genitalia (Cortesi et al, 1976). Although laparoscopy was initially used primarily as a diagnostic modality to identify a nonpalpable testis, it has now expanded to indications for many types of procedures and is currently considered safe. The ability to effectively treat children with minimally invasive surgery (MIS) has been fueled by improvements in instrumentation, robotics, and the creativity of minimally invasive surgeons. Laparoscopic surgery has gained widespread acceptance given the reliability and durability of outcomes. The proposed benefits of laparoscopic surgery over the standard open approach include better cosmesis, increased magnification improving visualization, reduced postoperative pain, and shorter hospital stays (Casale and Kojima, 2009). Complex laparoscopic surgery such as pyeloplasty, orchiopexy, nephrectomy, renal cyst decortication, pyelolithotomy, ureteral reimplantation, and bladder augmentation have all been performed safely and effectively with outcomes at least comparable to those of open techniques (Docimo, 1995; Law et al, 1997; Baker et al, 2001; Ismail et al, 2010).

The technical difficulty and steep learning curve of laparoscopic surgery has contributed to the growing popularity of robotic-assisted surgery (RAS). The da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) is the only currently available system approved by the U.S. Food and Drug Administration (FDA). It provides advantages such as precise exposure and simplification of suturing as a result of movement of the robotic arms in real time with increased degree of freedom and magnified three-dimensional (3D) view (Lendvay et al, 2008a). RAS has the potential to make laparoscopic surgery more accessible to pediatric urologists and to simplify complex upper-tract and reconstructive procedures (Olsen, 2004; Casale, 2009a, 2010). RAS, initially used for pyeloplasty (Casale and Lambert, 2010) and nephrectomy (Patel and Casale, 2007), can be used to perform ureteral reimplantation (Casale, 2011) and more complex reconstructive surgeries including bladder augmentation (Kojima and Casale, 2011) and antegrade continence enema (Gundeti et al, 2013).

One argued disadvantage of conventional pediatric laparoscopy and RAS is the need for multiple incisions that are significant in size in relation to patient size (Casale, 2009b; Tapscott et al, 2009).

Single-incision laparoscopic surgery (SILS) may be advantageous in children, but experience with these novel techniques remains in its infancy.

GENERAL APPLICATIONS OF LAPAROSCOPY

See Table 129-1 and Box 129-1.

ADVANTAGES OF MINIMALLY INVASIVE SURGERY

The goal and promise of MIS is to reduce the morbidity of surgery. The concept of reducing morbidity through MIS falls under four provisions. The first provision is reducing collateral damage to the body wall. Most genitourinary organs are retroperitoneal and hard to access. The incisional length, even total length, is often reduced. We can definitely state that there is nothing therapeutic in a body wall incision; therefore making them smaller will only help.

The second provision is to reduce scars. Port sites, particularly smaller ones, appear to anecdotally undergo wound contraction during the remodeling process so as to be unnoticeable in my experience. In a current study, we are comparing MIS incisions with open incisions over time. Larger linear scars are growing proportionally with the patient, whereas smaller incisions are contracting over time.

The third provision is to reduce the recovery and precautionary period. The advantage of a reduced recovery period is the principal driving force for laparoscopy in adults. This is harder to demonstrate for children, who tend to heal and recover remarkably quickly. Return to work, typically the reported end point of convalescence, is often not at issue; however, it is important to keep in mind that a child's convalescence frequently occupies one or both of the parents. Furthermore, the reduced disruption of the integrity of the body wall reduces the need for limited activity during wound healing—an advantage for the parent who otherwise would need to police the child's activity.

The fourth and final provision relates to speed and efficiency. Although the reputation of laparoscopy is for longer procedures, some of this might be attributed to an artifact of the learning curve. Once proficient, the laparoscopist is usually just as efficient with a minimally invasive approach as with an open approach.

TABLE 129-1 Current Nonexclusive Categories of Laparoscopic Procedures

CATEGORY	DESCRIPTION
Diagnostic	Examination of internal organs (e.g., evaluation of intersex, evaluation of nonpalpable testis, staging)
Extirpative	Removal of an organ when the surgical approach is through a series of port sites rather than an open incision (e.g., nephrectomy, adrenalectomy, orchiectomy)
Reconstructive	Alteration of the urinary tract to approach normal anatomic order or for function (e.g., pyeloplasty, augmentation, catheterizable channels)

BOX 129-1 Current List of Laparoscopic Procedures Performed in Practice

- Radical nephrectomy
- Partial nephrectomy
- Nephroureterectomy
- Heminephroureterectomy
- Antegrade continent enema
- Varicocelectomy
- Pyeloplasty
- Calyceal diverticulectomy
- Uterocalicostomy
- Pyelolithotomy
- Nephropexy
- Renal cyst ablation
- Renal denervation
- Neovagina
- Bladder diverticulectomy
- Partial cystectomy
- Appendicovesicostomy
- Undescended testis
- Autoaugmentation
- Adrenalectomy
- Extravesical reimplant
- Ureteroureterostomy
- Tapered reimplant
- Transvesical reimplant
- Ileocystoplasty
- Sigmoidocystoplasty
- Sacrocolpopexy
- Retroperitoneal lymph node dissection

DISADVANTAGES OF MINIMALLY INVASIVE SURGERY

The Learning Curve

The working environment is different and requires thinking regarding placement of incisions, different presentation of anatomy to the surgeon, and new equipment for the operating room staff to learn. Technical skills require mastery, and it is difficult for experienced surgeons to move from the comfort of the proficient master to join the ranks of the novice surgeon. For those in academic training centers, training residents and fellows can present an unfamiliar challenge, particularly if their exposure is otherwise limited. Tasian and colleagues (2013) showed that fellows can approach

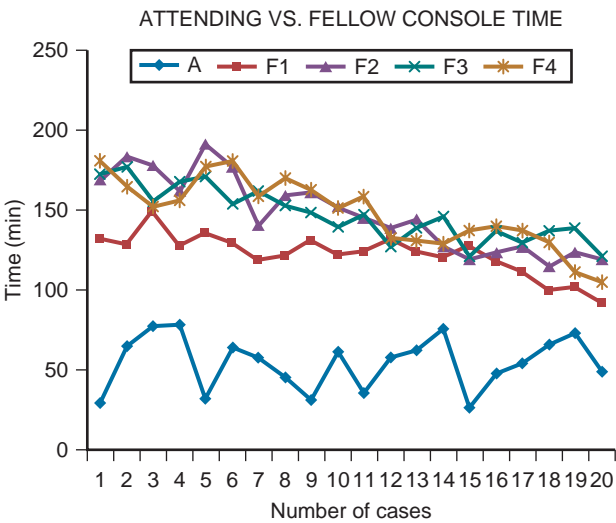


Figure 129-1. Fellow console time consistently decreased when more procedures were performed.

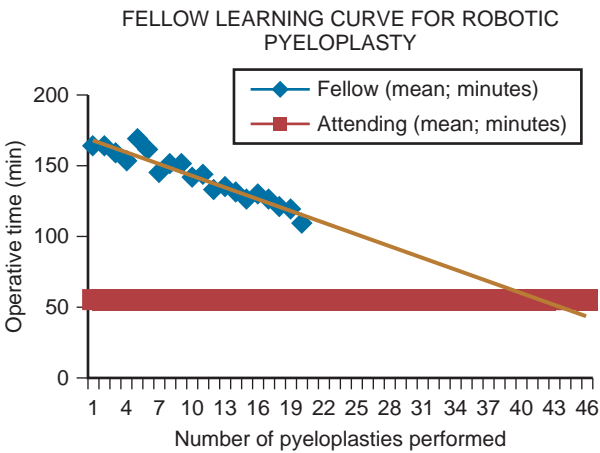


Figure 129-2. Extrapolated learning curve.

near-expert level within the 2-year timeframe of pediatric urologic fellowship. These researchers prospectively collected the surgical console times in 20 consecutive robotic pyeloplasty cases of four pediatric urology fellows who performed 75% or more of the console time. The console times were compared with 20 consecutive robotic pyeloplasty cases in which the attending surgeon alone performed 100% of the console time. They found that the operative times for the cases in which the fellow performed 75% of the procedure decreased with increasing number of procedures performed (Fig. 129-1). Assuming the trend of increasing efficiency continues at the same rate, operative times for fellows are projected to be equal to those of attending urologists once 42 procedures have been performed (Fig. 129-2). They concluded that with the appropriate exposure to robotics, the learning curve for robotic pyeloplasty would be overcome during a 2-year pediatric urology fellowship, enabling newly graduated fellows to be proficient in robotic surgery (Tasian et al, 2013). This of course would translate to other robotic procedures done by the fellows during training. Because the training is not done in a silo, the experience is additive, making the fellow proficient at many cases and truly experienced at robotics overall.

Cost

As a new field with constantly emerging new technology, institutional commitment to the purchase and upgrading of instrumentation is required. Although laparoscopic surgical procedures are

often criticized for higher costs, attention to selection of reusable over disposable instruments can substantially reduce costs (Yung et al, 2010). Behan and coworkers (2011) compared perioperative factors in patients who underwent robotic-assisted laparoscopic and open pyeloplasty, especially with regard to human capital changes, in an institutional cost analysis. Robotic-assisted laparoscopic pyeloplasty in children was associated with human capital gains, such as decreased lost parental wages, and lower hospitalization expenses. Although true cost is difficult to ascertain, we need a true cost analysis to help monitor expenses and ensure cost containment because the expense of delivering high-quality health care is constantly on the rise.

Contraindications to Minimally Invasive Surgery

Contraindications to laparoscopy in infants, children, and adolescents are the same as for any other surgical procedure, except for evidence of limited pulmonary reserve, which may be considered a relative contraindication. If the patient has sepsis, is in shock, or exhibits a coagulopathy, this should be corrected before MIS is contemplated. If surgery is deemed essential under these circumstances, then it probably should be performed using open techniques (Longdon, 2001).

Strong Contraindications

In the pediatric population there are strong contraindications to MIS. The strong contraindications are cardiopulmonary morbidity, uncorrected coagulopathy, and sepsis. The role of laparoscopy in malignant tumors is yet to be defined. Although laparoscopy may play a role in extirpative procedures for renal cell carcinoma or for retroperitoneal lymph node dissection, its role in the management of Wilms tumor or neuroblastoma has yet to be defined. Morcellation of specimens for extraction has raised concerns about accurate pathologic staging; hence, large tumors mandate an incision to retrieve them. In addition, the fragile consistency of the tumor makes it more prone to rupture, which may preclude the use of this technique (Holcomb, 1999).

Size of the Child

The smaller size of children presents a smaller working environment than found in adults after establishment of pneumoperitoneum. Whereas an adult pneumoperitoneum will typically provide a 5- to 6-liter working space, a 1-year-old boy will present a 1-liter intra-abdominal space (Casale, 2010). Furthermore, the limited volume and small working distance on the abdominal wall in a child can significantly limit the mobility of the laparoscopic and robotic instruments, and the chance of port site conflicts or collisions is greater. A difference of a few millimeters can greatly affect the safety and efficiency of the operation, making the location and placement of the robotic trocars critical in children and necessitating slight variations compared with placement in adults. The diminished thickness of the abdominal wall, especially in infants, makes maintenance of insufflation during instrument exchange challenging. Anchoring the trocar to the abdominal wall with a heavy suture will keep the abdominal wall in place if rapid desufflation should occur (Peters, 1996).

TEAM DEVELOPMENT

A consistent minimally invasive team is imperative to the success of any program, especially robotics. The program should be led by a "Surgeon Champion" who is both dedicated and knowledgeable regarding all instrumentation, credentialing, cost, and operating room flow related to the program. Currently there are no guidelines available for the training of nonphysician personnel involved in the program. Two basic principles should encompass a training program: The first is familiarity with the equipment

and troubleshooting, and the second is the ability to perform a specific surgical procedure safely and efficiently (Orvieto and Patel, 2012).

HEMOSTATIC DEVICES

Manual Ligation

Vessels may be ligated with laparoscopic devices that are available in 5- and 10-mm sizes. Laparoscopic tie assisting devices are also available if clips are not preferred. They typically require a 5-mm or larger cannula and either have a cinch knot technology or allow extracorporeal tying and knot placement with a pusher device. Freehand laparoscopic tying can also be performed but is time-consuming and does not seem to be beneficial with the current hemostatic devices available. Laparoscopic stapling devices are available for hemostasis. They are an excellent alternative for large vessels and for transecting thick tissue such as bowel mesentery. The laparoscopic stapling devices require a 10-mm or larger trocar for access and come in different lengths, deployment widths, and angulation capabilities. The tissue or vessel is transected as the staples are deployed. One must ensure that the device completely traverses the target before deployment; otherwise hemorrhage can occur, especially with large vessels or thick vascular tissue. Stapling devices have been routinely used for main organ vessels as well as mesentery with reproducible success. If dividing vascular structures, one must be certain that the device contains vascular and not gastrointestinal staples.

Energy Devices

Care should be taken when dividing tissue or establishing hemostasis with high-energy devices, because injury to adjacent structures is possible. A 3- to 5-mm, right-angled hook cautery is a useful device for dividing tissue and preventing hemorrhage. It is important to make contact with the tissue before activation of the monopolar electrode to avoid arcing of current, which may cause a delayed thermal injury to internal structures. Another form of electrosurgery that is available is use of a bipolar cautery forceps, which allows for greater control of the current than with standard monopolar devices owing to less dispersion of energy. Ultrasonic shear devices use high-frequency ultrasonic oscillation to heat the tissue, forming a coagulum. They come in 5-mm and 10-mm widths. Both the ultrasonic and bipolar vessel sealing devices can be used for vessels up to 5 to 7 mm in diameter. Mishra (2013) performed a meta-analysis of the literature comparing these devices. The analysis found that bipolar devices provided a more secure seal in up to 7-mm vessels; however, the ultrasonic devices had less thermal spread and used less surgical time. Based on the data, he concluded that the decision regarding which energy source to use for each particular part of a specific procedure was dependent on the surgeon's experience.

SUTURING

Intracorporeal suturing requires two needle holders or a needle holder and a grasping device. I favor a 10-cm length of suture with its curved needle directly passed through 5-mm trocars, but not through 3.5-mm trocar unless the curved needle is first straightened. The suture may also be passed through the abdominal wall to avoid the need for a 5-mm trocar if 3-mm or smaller trocars are being used. Laparoscopic extracorporeal assisted tying is possible but requires a large cannula at one of the port sites. There are various automatic suturing devices and suture assistants; however, it is important for the endoscopic surgeon to become proficient with unassisted suturing techniques. This is because suture-assist devices require larger trocars and are more costly than unassisted intracorporeal suturing. Furthermore, the majority of devices have a limited choice of suture material and size, and most are not acceptable for complex delicate reconstruction (Schwab and Casale, 2005).

An innovative technique for intracorporeal suturing for a procedure such as a pyeloplasty is to tie together the ends of two 5-cm segments of 6-0 Vicryl, one dyed and one undyed, both on a small taper needle, before insertion into the peritoneal cavity. The knot tied initially secures the first suture into the renal pelvis and both decreases trauma to the tissue and expedites the anastomosis. The color differentiation facilitates suturing and decreases any confusion and need for repetitive suturing (Farhat and Casale, 2009).

Robotics adds an element of dexterity; seven degrees of freedom are achieved to perform complex manipulation to aid in suturing and intracorporeal tying. The key to a successful robotic execution of suturing is twofold: (1) awareness of the limits in pitch and yaw of the robotic wrists, and (2) visual cues to realize when the suture is tied effectively without breaking it. The latter element comes with practice and experience with the currently available platforms.

ANESTHESIA

Induction and maintenance of anesthesia may be with either inhalational or intravenous agents or a combination of both. Nitrous gas increases bowel distention, potentially bringing the peritoneum closer to the area of dissection for retroperitoneal procedures and decreasing working space in transperitoneal procedures. Also, it is very important to communicate with the anesthesiologist to ensure that during induction, gastric distention with air is addressed immediately after intubation owing to the rapid gastric emptying time of children. This will decrease the amount of air in the small bowel. When the air is left in the stomach and passes to the small bowel, it causes what I call a "pufferfish effect" whereby the distended bowel occupies the majority of the peritoneal cavity, making laparoscopy difficult or impossible (Fig. 129-3).

Intraoperative monitoring should include routine electrocardiogram, noninvasive blood pressure, SpO₂, temperature, end-tidal CO₂, and inspired oxygen concentration (Tobias, 2002). Maintenance intravenous fluid is usually sufficient unless there is unanticipated bleeding. Finally, it is preferable to insert the intravenous line in the arm on the side of the surgery for a patient in the flank position for easy access.

Anesthesia Physiology

Patient positioning during laparoscopic surgery may potentiate the impact of gas insufflation. For instance, Trendelenburg position



Figure 129-3. Distended small stomach after induction of anesthesia. It is imperative to empty the stomach after intubation and before any other manipulation.

during laparoscopy will increase heart rate and vascular resistance while decreasing mean arterial pressure and cardiac output, whereas the opposite effect is seen in reverse Trendelenburg (Logsdon, 2001). In my experience, flank positioning adds further stress, with the left lateral decubitus position producing more significant hemodynamic and respiratory changes than the right flank position, which produces more than the supine position.

Pressure Effects

As gas is placed in the closed space of the operative field, the pressure rises and cardiovascular, pulmonary, and renal effects occur. The heart rate and mean arterial pressure increase while the venous return and cardiac output decrease. These parameters are seen even when pressure is set at a standard working level of 10 mm Hg. Above a level of 15 mm Hg, more profound hemodynamic alterations are anticipated to occur with further decrease in cardiac output. Furthermore, limitation of diaphragmatic mobility may cause respiratory restriction manifesting with increased airway pressure, requiring an increase in the peak end-inspiratory pressure to maintain a set tidal volume. In some cases this can lead to a pneumothorax. Finally, renal effects occur secondary to gas insufflation, manifesting with decreased glomerular filtration rate and urine output. Animal studies have shown that gas insufflation causes renal vein compression inducing decreased renal blood flow, decreased urine output, and diminished creatinine clearance (Holcomb, 1999; Peters, 2000). These effects do not appear to cause renal damage in humans, however.

Absorption Effects

Insufflated CO₂ is absorbed into the blood by diffusion that is limited and determined by many variables. Most important are the pressure differential and the cross-sectional area of the absorbing surface. The pulmonary effects are increased CO₂ retention and increased end-tidal CO₂, exacerbated by decreased functional residual capacity and decreased diaphragmatic excursion. The hemodynamic effects of hypercarbia are increased heart rate, vasodilation, increased cardiac contractility, and increased intracranial pressures. Although in healthy children there is little if any added cardiorespiratory risk from laparoscopic procedures, children with cardiopulmonary compromise require close and careful monitoring (Tobias, 2002) (see Table 129-1).

THE DIFFERENT APPROACHES: TRANSPERITONEAL VERSUS RETROPERITONEAL

Laparoscopic approaches provide exceptional exposure rivaled only by a complete abdominal laparotomy incision because the intraperitoneal space is large. Trocar selection is at the discretion of the surgeon and should be a balance of minimizing the incision without compromising the access needed for the correct size equipment to complete the procedure safely and efficiently. When deciding on making the incision for the trocar, the length of the incision is very important. Blinman (2010) described the wound tension of incisions, stating that tension rises nonlinearly with increasing wound length. The total tension across multiple incisions is less than the total tension for an incision of the same total length. For example, a 2-cm incision has 2.7 times more wound tension than three 5-mm incisions. Two 3-mm incisions have less than one 5-mm trocar. He also describes that the correct length of the incision of a trocar's width is half the circumference as with any cylinder. I use the angle at the tip of the trocar where it has its maximal open distance as the proper incision length because this angle causes the maximal length to closely approximate half of the trocar's circumference. This length allows the correct trocar incision where tension is minimized but still would hold the trocar in place without dislodgement (Fig. 129-4 and Table 129-2).

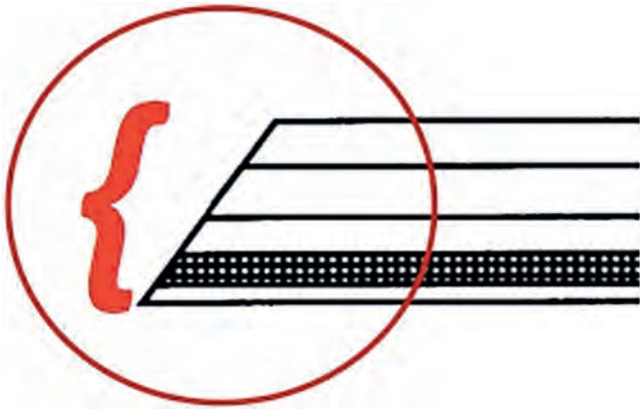


Figure 129-4. The distance between the widest portion of the angled opening of the trocar is an easy approximation of the length needed for half the circumference of the cylindric trocar to have an adequate incision with minimal tension and looseness.

TABLE 129-2 Comparison of Retroperitoneoscopy and Transperitoneoscopy

RETROPERITONEAL	TRANSPERITONEAL
Avoids need to retract intestines	Roll and Trendelenburg often all that is needed
Great vessels typically serve as the medial boundary	Intestines in working environment
Less traditional; lower acceptance	“Tried and true”
Lower incidence of port site problems	Higher incidence of port site–associated complications (e.g., hernia, enteric fistula)
Lower hernia risk	Higher hernia risk
Does not decrease risk for injury of organs such as colon	Quickest “exit” strategy for emergency
Steps to get to the retroperitoneum allow laparoscopic “warm-up” techniques	“Warm-up” exercises before the actual procedure are possible because of larger working space

Patient Preparation

I prefer to have the child take an age-appropriate dose of magnesium citrate 2 nights and 1 night before surgery. If the child cannot take magnesium citrate, then I prefer a liquid diet the day before surgery to help with any excess stool in the colon. True bowel preparations are not needed unless bowel is going to be used during the surgery. In that instance, admission the day before with a proper bowel cleanout would be recommended. Nonsteroidal anti-inflammatories should be avoided for 2 days before surgery and aspirin for 7 days. Taking more than 3 g of fish oils per day might keep blood from clotting and can increase the chance of bleeding, so fish oils should be discontinued 1 week before surgery.

Transperitoneal Approach

Positioning

For upper tract transperitoneal procedures, positioning the patient in a flank or modified flank position at the edge of the table is helpful, although these procedures can be performed with the patient supine with rotation of the operative table. Edge positioning

allows the surgeon full access to the abdominal cavity without limitations caused by the edge of the table. For the modified flank, a roll should be placed under the torso to provide a 60-degree patient angulation from the table. The patient should be secured so the table may be repositioned as necessary during the procedure. The main monitor should be placed on the lesion side of the operative table, with a slave monitor behind the surgeon. All cables, lines, and wires for the instruments should preferably go off the opposite side to the surgeon. This positioning is used for the majority of renal interventions such as nephrectomy, heminephrectomy, pyeloplasty, and other renal extirpative and reconstructive procedures. The transabdominal approach also allows access to the anatomic pelvis by placing the camera through the subcostal port and instruments through the umbilical and lateral ports.

For lower transperitoneal procedures in infants, it is most convenient to position the patient at the foot of the bed, across the bottom, and to stand at the side of the bed (at the patient's head) to operate (Holcomb, 1999). This is an optimal approach to the bladder. For older patients a midtable, supine position with a sacral roll to thrust the pelvis up is preferable. Usually the side opposite the lesion is chosen, and the telescope is placed centrally in or near the umbilicus. The instrument trocars are placed lateral to the rectus muscle usually at the level of the anterior superior iliac spine. The monitor should be at the foot end of the operative table. Only one monitor is necessary in this scenario. All cables, lines, and wires should be off the foot of the bed for optimal ergonomics. This approach is extremely helpful for gynecologic and urologic procedures in the pelvis.

The transvesical approach requires cannula fixation so that the bladder mucosa does not strip and dissect away from the detrusor muscle. One way to achieve this is to perform a cystostomy using cystoscopic visualization to ensure the mucosa is attached at the skin incision to help hold the bladder wall and mucosa to the anterior abdominal wall. A balloon-tipped cannula may also be helpful here, but the size of the balloon tip may impair instrument manipulation in a small child.

If a robot is being used, the room setup must allow the robot to approach the patient on the side of the target organ. For example, if the left kidney is to be operated on, the robot must come over the patient from the left. If the bladder is the target organ, the robot should come from the foot of the bed. For bladder procedures it can come directly at the foot of the bed or on an angle to the pelvis from the foot of the bed, aiming at the contralateral shoulder of the position. For example, if the robot is coming from the right foot of the bed, aim the robot at a 45-degree angle toward the left shoulder.

Laparoscopic Access Techniques

Transabdominal access is best achieved through the umbilicus with use of either a Veress or an open technique whereby the umbilicus is lifted using an Allis clamp, then with a No. 11 blade the skin and subcutaneous tissue are incised and the peritoneum is entered. Instruments can be placed directly through a stab wound without the need for a trocar if the surgeon does not anticipate repeatedly withdrawing and reinserting instruments through this site (Lobe, 1998; Holcomb, 1999; Peters, 2000; Tam, 2000; Telsey and Caldamone, 2001; Blinman, 2010).

In infants and thin children, the laxity of the abdominal wall might allow large trocars or heavy instruments to compress the abdominal wall, obscuring vision and limiting CO₂ distention. Once access has been attained, sometimes bowel, bladder, or other structures can obstruct the view. It can be helpful to pass one or more sutures through the abdominal wall, through the structure, and back out through the abdominal wall for retraction. These can be tied to a self-retaining retractor or can simply be tied at the distended abdominal wall if that is sufficient (Holcomb, 1999).

Step-by-Step Access Procedure

See Boxes 129-2 and 129-3.

BOX 129-2 Steps in Veress Access

1. Position patient.
2. Patient secured with tape for Trendelenburg and airplane roll of operating room table to 30 degrees each. Table should be moved through a full range of motion (table run to limits of motion), particularly with larger patients, to ensure they are stable in position.
3. Urethral catheter—if orchiopexy, varicocele ligation, or bladder manipulation, place on field after preparation. In male retroperitoneal cases, one can consider scrotal wrap to prevent pneumoscrotum.
4. Surgical preparation and drape, full access to abdomen (and perineum if Foley manipulation required, varicocele, or orchiopexy).
5. Assemble and test lens, camera (white balance), light source, monitor, insufflator, electrocautery generator. Secure cords to table. If a robot is being employed, ensure the team has checked the system.
6. Warm lens (I prefer a warming bath).
7. Supraumbilical or infraumbilical incision with a length determined by the trocar width as previously described. In infants (especially) and children, the peritoneum is not well affixed to the abdominal wall and therefore the access to the abdomen through a supraumbilical position, above the fixation point of the peritoneum to the umbilicus, reduces potential for preperitoneal insufflation.
8. Abdominal wall lifted at the umbilicus; in thicker-walled patients (e.g., a muscular adolescent), a towel clip or heavy suture or Kelly clamp can be used to lift the abdominal wall.
9. Veress held in “dart fashion” with thumb, index, and middle fingers; ball of hand on patient’s upper abdomen.
10. Forefingers and thumb advance Veress through stab wound and abdominal wall.
11. Confirm position with either pressure via insufflator (my preference) or a “drop test”—aspirate (no succus entericus, blood, urine), inject with 5 mL saline, withdraw (return of fluid suggests preperitoneal position), reinject 1 to 2 mL to break potential air locks, release syringe, fluid should “drop.”
12. Insufflate—confirm low pressure, switch to high flow and to pressure of 15 to 20 mm Hg. For initial port placement, 15 mm Hg in children, 20 mm Hg in adults.
13. Insert trocar with hand braced to prevent any uncontrolled advance of trocar.
14. Decrease pressure to 8 to 10 mm Hg. The right pressure is enough to see. Added pressure does not help visualization and will only add to the anesthetic effects of insufflation.
15. Insert lens.
16. Survey abdomen for injury.
17. Secure trocar—suture to abdominal wall.

Direct Access

Direct access offers another means of entry via an incision sized to the port made at the umbilicus. The abdominal wall is supported and lifted upward. The trocar is placed directly into the abdomen. Proponents argue that the use of a single blind step is preferable to two blind steps in Veress access. The access can be done blindly or under direct visualization through a trocar designed to traverse tissue with a camera inserted through its obturator.

Midline or off-midline visual trocar access employs various optical trocars, such as a VisiPort (Covidien, Norwalk, CT) or Opti-View (Ethicon, Cincinnati, OH), which range from 5 mm to

BOX 129-3 Steps for Open Access

- 1-8. Same as for Veress access
9. Periumbilical incision of 15 to 20 mm in length created with No. 11 blade. The incision should allow insertion of Sims retractors to visualize the fascia.
10. The subcutaneous tissue is spread and incised to the level of the fascia. Two stitches are placed in the fascia to secure it. The suture is cut to length to allow it to be tied, then lifted into the wound. The fascia is incised between the stitches.
11. The preperitoneal fat is spread and the peritoneum identified, elevated into the wound, and opened.
12. The port is inserted into the peritoneal cavity under vision. Blunt-ended trocars are typically used. One problem is that a 10- to 12-mm port, typically used in this setting, obscures the view into the “hole,” preventing clear vision of the actual insertion step. The use of a Step trocar and sheath system allows the surgeon to place the 2-mm sleeve into the cavity under direct vision then expand it to size.
13. The fascial sutures are snugged at the fascia and held in a Rommel fashion then secured to the port.
- 14-17. Same as for Veress access.

12 mm. These allow the tissue beneath the end of the trocar to be seen. Off midline, an incision is made in the skin typically overlying the rectus muscle, and the trocar is inserted. The muscle is observed as the trocar advances. When the port is placed through the rectus the posterior sheath is encountered just deep to the rectus. The port is advanced to a position just beyond the rectus, then insufflation is begun. The same is done through the umbilicus, but of course the layers are different. Once the rectus midline has been passed, the surgeon will visualize the peritoneal lining to enter the abdomen.

When the initial access is lateral to the rectus, the location of the port is followed through the orientation and layer number of the muscle fibers. It is important to remember that at the lateral border of the rectus all three muscle layers (external oblique, internal oblique, and transversus) may not be present. Familiarity with the orientation of the fibers is paramount for safe entry. Briefly, the external oblique courses from a superior lateral to inferior medial position, internal oblique from inferior lateral to medial, and transversus lateral to medial. A thorough understanding of this anatomy and variations likely to be encountered is needed for this access (Box 129-4).

Retroperitoneal Laparoscopic Approach (Box 129-5)**Advantages**

The retroperitoneal approach mimics the open urologic surgical procedure through the retroperitoneum. This is a direct approach to the organs of the genitourinary tract that requires less dissection of the colon or the spleen to expose the kidneys and adrenals and is a familiar region to the urologist. The landmarks are the same as in open retroperitoneal surgery. The retroperitoneal approach is also possible in the face of previous transperitoneal surgery done via either open or laparoscopic technique. It is my experience that the trocar sites have fewer postoperative hernias than do open incisions. Once retroperitoneal access is gained, the view of the posterior surface of the kidney, hence access to the renal hilum, is rapid.

Disadvantages

The disadvantage of retroperitoneal laparoscopy is that manipulation of instruments may be initially difficult owing to a restricted

BOX 129-4 Steps for Direct Access

1. Position patient.
2. Patient secured with tape for Trendelenburg and airplane roll of operating room table. Confirm full range of motion.
3. Surgical preparation and drape, full access to flank and back.
4. Assemble and test lens, camera (white balance), light source, monitor, insufflator, electrocautery generator. Secure cords to table.
5. Lens placed in VisiPort—refocus (lens effect of device).
6. Incision as described previously.
7. VisiPort placed in wound; orient blade parallel to anticipated muscle layer 8.
8. Advance to fascia; incise.
9. Incise and spread muscle.
10. If multiple layers of muscle, reorient blade for each sequential layer.
11. At end of “last layer” (transversalis for flank, lumbodorsal fascia prone), advance slightly with single activation.
12. Gently advance VisiPort; observe retroperitoneal fat or bowel.
13. Insufflate—low pressure.
14. Balloon or lens—dissect space if retroperitoneal.
15. Remove optical trocar piece, reinsert lens, refocus.
16. Survey for injury.
17. Secure trocar—suture to abdominal wall.

BOX 129-5 Relative Contraindications to Retroperitoneal Surgery

1. Prior retroperitoneal scar (kidney surgery, kidney biopsy, or pyeloplasty)
2. Previous infectious or inflammatory retroperitoneal process (xanthogranulomatous pyelonephritis) except for surgeons experienced with this approach

working space. For instance, in reconstructive surgery such as a pyeloplasty, suturing and knot tying may be difficult. In ablative surgery, the degree of technical difficulty increases in the presence of large specimens. Also, achieving anatomic orientation may initially be a challenge for the inexperienced laparoscopist.

Anatomic Considerations for Retroperitoneal Laparoscopy

An understanding of the retroperitoneal surgical anatomy is mandatory before embarking on retroperitoneoscopic surgery. The boundaries of the retroperitoneal space are as follows:

1. Posteriorly and laterally: the paraspinous, psoas, and quadratus lumborum muscles, which are anatomically fixed structures
2. Anteriorly: the mobile posterior parietal peritoneum and its contents
3. Superiorly: the diaphragm
4. Inferiorly: contiguous with the extraperitoneal portions of the pelvis

Step-by-Step Retroperitoneal Access Procedure

Patient Positioning. Although a retroperitoneoscopic approach may be accomplished with the patient prone, I prefer the flank position for renal cases because it increases the anteroposterior dimensions of the retroperitoneal space and displaces the peritoneal

reflection anteriorly, decreasing the chance of inadvertently opening it. The prone position for retroperitoneal access is used for retroperitoneal lymph node dissection only (Box 129-6).

Insert the trocar toward the area of dissection; if the trocar is advanced away from the site of dissection, this might result in the following:

1. Constant tension on the skin during surgery, making maneuvering difficult
2. Greater chance of gas leakage at the trocar site

In the event that more than three ports are required, laparoscopic guidance and bimanual palpation are recommended for accurate placement. The placement of this accessory port varies from case to case and patient to patient owing to the differences in the retroperitoneal space.

TROUBLESHOOTING THE ROBOTIC APPROACH**Robotic Port Placement (Box 129-7)**

Port placement for both robotic and pure laparoscopic procedures will vary with the anatomic organ. Laparoscopy adds an element of surgeon ergonomics whereby a triangulation of the trocars is typically easier on the posture of the surgeon. The robotic platform works better when the trocars are in a straight line with the ports at a minimum of 4 cm apart from one another. It is my experience that this configuration virtually eliminates collisions of the robotic arms. Figures 129-5 through 129-8 show my preferred port sites for the specified procedures. Patient positioning is the same for pure laparoscopic and robotic-assisted procedures.

Robotic Visualization

The visualization offered by the robotic platform is an advantage that is not possible with pure laparoscopy. It allows 3D visualization as well as digital zooming. However, because it is a more complex visual aid, it requires more troubleshooting than just the average laparoscope. The issues that arise from the camera fall into six distinct categories: restricted movement; restricted excursion; “fuzzy” vision; “cloudy” vision; dark fields; and inability to focus. Each is addressed in Box 129-8.

LAPAROENDOSCOPIC SINGLE-SITE SURGERY

Although in its infancy, laparoendoscopic single-site surgery (LESS or SILS) has the potential to minimize the number of incisions while maximizing intracorporeal access. The theoretical advantage of LESS is that an entire procedure can be done using an incision that would have been necessary for specimen removal in conventional laparoscopy. The umbilical location of the incision improves cosmesis; however, the advantages of LESS compared with conventional laparoscopic surgery have yet to be proved. It also is contrary to the current literature of wound tension and healing presented earlier. In most cases of LESS for the pediatric patient, an accessory port is used. Some argue that this form is just an awkward way to perform pure laparoscopy because the added trocar negates the LESS advantage. A limited number of case reports and small series have described the use of LESS surgery for pediatric urology procedures including nephrectomy (Lobe, 1998; Koh et al, 2010; Marietti et al, 2010; Vricella et al, 2010; Ham et al, 2011), nephroureterectomy (Koh et al, 2010; Ham et al, 2011), and pyeloplasty (Tugcu et al, 2010, 2011).

Access is obtained using an open Hasson technique by way of the umbilicus, and a single-port access device is deployed. Two commonly employed ports include the Olympus TriPort (Olympus, America, Melville, NY; Advanced Surgical Concepts, Wicklow, Ireland) and the Covidien SILS port (Covidien). The Olympus port includes an associated introducer, which allows for placement of the single port using a 10- to 15-mm umbilical incision. The SILS port can be placed through an incision as small as 15 mm, and it

BOX 129-6 Step-by-Step Retroperitoneal Access

1. The patient is positioned in the full 90-degree flank position as close to the posterior edge of the table as possible.
2. The table is flexed and the kidney rest elevated.
3. Pressure points are padded and an axillary roll is placed.
4. The patient should be taped to the table using 3-inch adhesive tape placed across the shoulder and the hips so that they will remain secured while the table is moved during the surgery.
5. I prefer to have the surgeon and assistant standing on the same side; therefore we use only one monitor to facilitate eye-hand coordination between assistant and performing surgeon.
6. Open (Hasson) technique provides visual guidance. Because children have a small retroperitoneal space and close proximity between the abdominal wall and the major vessels, the closed technique is not recommended. In addition, because there is no actual preexisting retroperitoneal space, the placement of a Veress needle is not precise and may cause injury to either the great vessels or the pneumoperitoneum.
7. Midaxillary line: a 1-cm long incision is made 1 to 2 cm below the tip of the 12th rib.
8. The muscles are split in the direction of their fibers, and then the lumbodorsal fascia is incised to enter the retroperitoneum.
9. Development of the retroperitoneal space using a blunt instrument or the balloon dissector is up to the surgeon. Although commercial balloon dissectors are readily available, an inexpensive balloon can be made using the finger of a surgeon's glove tied around a catheter. The balloon is inserted anterior to the psoas muscle and outside the Gerota fascia, and approximately 400 to 500 mL of air is used to inflate the balloon, creating the space. Another technique described by [Farhat and Casale \(2009\)](#) is to introduce a wet gauze close to the posterior muscular wall to create the retroperitoneal space.
10. Ensure the primary trocar is inserted in the correct space. If too far medial, it will result in peritoneal entry or colon injury; entering posteriorly in the quadratus or psoas muscles may cause bleeding.
11. Create the retroperitoneal space outside the Gerota fascia; dissect the peritoneum medially. I create the retroperitoneal space using blunt dissection. Through the primary incision and with the psoas muscle as a reference point, a 10-mm trocar with the laparoscope (0 degree) is inserted to confirm correct placement. Initially, the posteroinferior aspect of the Gerota fascia and the lower pole are visualized. Identification of the psoas muscle posteriorly is crucial. Anteriorly, the edge of the peritoneum is identified and swept medially to expose the underside of the transversalis fascia.
12. Avoid tearing the peritoneum by dissecting it medially with the laparoscope in a lateral-to-medial fashion close to the abdominal wall to expose the internal surface of the transversalis muscle.
13. Place the posterior secondary port approximately midway between the 12th rib and the iliac bone, and lateral to the border of the paraspinal muscles. With use of a grasper through this trocar, the peritoneum is further mobilized medially to create the pelvic extraperitoneal space.
14. Place the anterior secondary trocar at the anterior axillary line 2 cm superior to the iliac crest. The two secondary ports should be inserted as far apart as possible to improve ergonomics.

BOX 129-7 Nuances for Robotic Trocar Placement

- Place the umbilical trocar in the superior aspect of the umbilicus in smaller children.
- Mark ports 4 cm apart after the abdomen is insufflated (becomes extremely important in the infants).
- Anchor skin at port sites to trocar to prevent abdominal wall slippage off trocar during moments of desufflation.
- Always "burp" the camera and working ports. Burping the ports encompasses holding the trocar and pressing the set joint button on the robot while lifting both the arm and the trocar together to increase the distance between the trocar and target organ. This maneuver allows further excursion of the robotic instruments, which becomes important during procedures on infants.

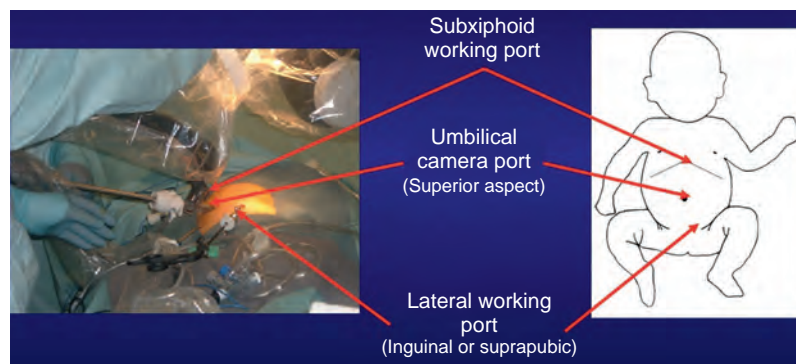


Figure 129-5. Schematic of renal port sites for robotic cases.

allows access for three 5-mm cannulas or two 5-mm cannulas and one 12-mm cannula. All ports are single-access multichannel laparoscopic ports. A combination of flexible forceps and scissors and conventional laparoscopic (straight) instruments can be used. Procedures are performed in similar fashion to conventional laparoscopy.

POTENTIAL COMPLICATIONS AND SOLUTIONS

Laparoscopic surgery always carries the risk of injuries. These are more common during the learning curve, and increasing experience may lead to a decrease in complication rates. The overall complication rate in laparoscopy has recently been shown by Peters and

colleagues to be 5.4%, with the rate of major complications being 1.2%, of which 0.4% necessitate surgical intervention (Passerotti et al, 2008). The group also concluded that the greatest predictor of complications was the surgeon's laparoscopic experience.

Vascular

If bleeding occurs, usually coagulation and pressure are sufficient for control during the procedure (Mishra, 2013). Severe vascular injuries are rare and may necessitate open conversion. However, not all vascular injuries occur during the laparoscopic portion of the operation. Great vessel injury may occur from laparoscopic access or dissection. In children the distance between the abdominal wall and the great vessels may be as little as 5 cm. To avoid vascular injury secondary to access, it is advisable to tailor the length of the trocars to the patient age and body habitus. During access, vascular injuries might manifest with either bloody return from the injury site or rapid deterioration of the hemodynamic status of the patient. Once extensive vascular injury is suspected, the trocar should be left in place and an open exploration should be performed. If a major vascular injury is encountered during dissection, laparoscopic compression should be maintained while gaining open access. If the vascular injury during dissection is minor, such as laceration to the gonadal vessels or adrenal vessels, hemostasis can potentially be achieved laparoscopically through the use of clips, staples, or ligation. Vascular entry of insufflation can be catastrophic. If vascular entry is noted after insufflation has started, the patient should be placed in reverse Trendelenburg position with right side up to trap the air embolus in the right atrium. The air can then be retrieved with catheterization aided by transesophageal ultrasound.

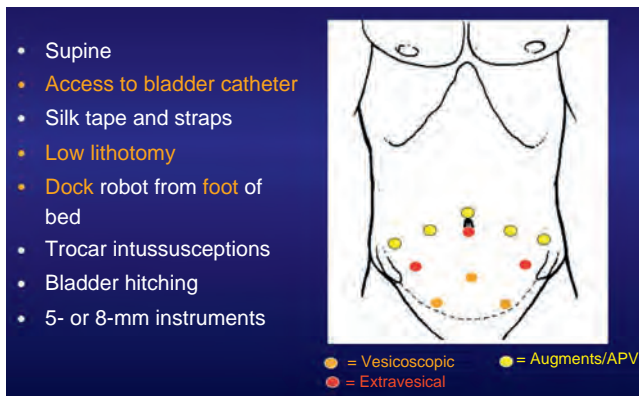


Figure 129-6. Robotic bladder access port sites. APV, appendicovesicostomy.

Organ Injury

Bowel injury is a risk of both transperitoneal and retroperitoneal laparoscopy. Because bowel is out of sight during retroperitoneal procedures, injuries may occur during trocar insertion, dissection secondary to lacerations, or thermal injuries from electrocautery.

If bowel injury is identified during laparoscopy, it is best dealt with at the time of occurrence. If the surgeon is laparoscopically skilled, the bowel may be repaired using a laparoscopic approach; otherwise a general surgery consultation is recommended. I believe that a contaminating small or large bowel injury is best handled by open repair with or without proximal fecal diversion. In addition, injuries to the liver or spleen may occur during laparoscopic retroperitoneal surgery. If the injuries are superficial, attempts to control the injury laparoscopically with gel foam or with an argon beam coagulator may be undertaken. Otherwise, open exploration is recommended. Because these injuries may go unnoticed, inspection of the peritoneal or retroperitoneal space on access and before exiting is of paramount importance. If a bowel injury goes unrecognized at the time of surgery it will usually manifest at 2 to 3 days postoperatively as a result of thermal injury with abdominal pain, particularly at the port sites, ileus, fever, and leukopenia. The physical examination findings are usually out of proportion to the pain. Causes are usually from cauterizing instruments, but injury can also arise from the heat generated by the camera.

Infection

Wound infection should occur in less than 5% of patients and is managed either by a 7- to 10-day course of antibiotics that cover common skin organisms or sometimes just by simple wound drainage. In my experience, the umbilicus appears more susceptible to infection than the other port sites.

Intraoperative urinary cultures should always be obtained in case a postoperative urinary tract infection develops. Postoperative urinary infections should be managed with 10 to 14 days of antibiotics once susceptibilities have returned. Urinary drainage might be indicated, because all these infections should be considered complicated and not simple urinary tract infections. If signs of sepsis continue despite proper urinary drainage and antibiotics, an abscess or infected urinoma should be assessed with an ultrasound and/or computed tomography (CT) scan. There are no current data available to determine whether or not prophylactic poststent antibiotics are beneficial.

Urine Leak

Because the urinary tract is manipulated, especially in reconstructive procedures, there is always a risk of urinary leakage from the target

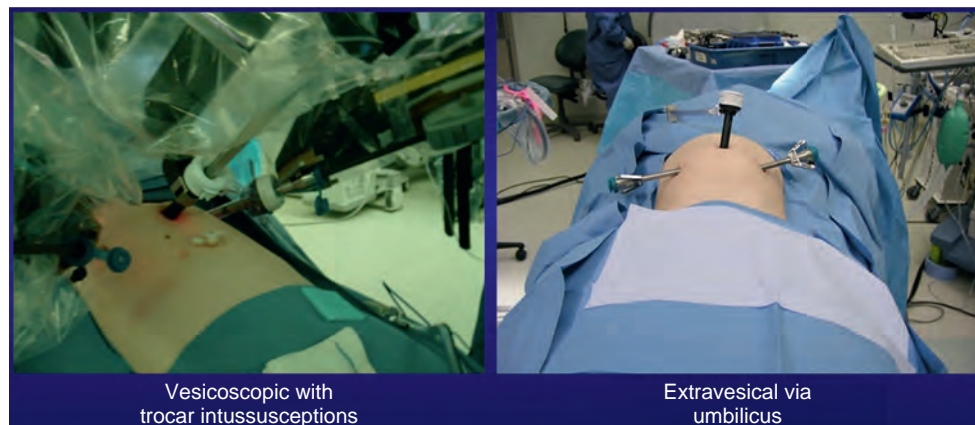


Figure 129-7. Extravesical ports and intravesical ports. The use of intussuscepted trocars might help with the intravesical approach because of the limited excursion of the instruments and camera resulting from limited working space of the pediatric bladder.

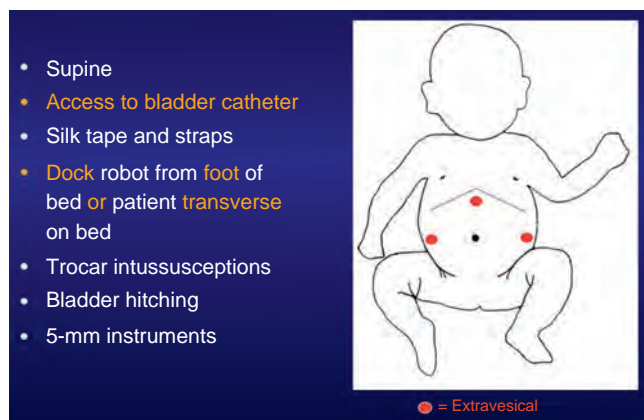


Figure 129-8. Infant port site positioning for bladder access.

organs. Intra-abdominal urine leak usually results in severe ileus, pain, and acute abdominal distention, which may include nausea and vomiting. The physical examination typically reveals a tense abdomen with tympanic bowel only on the anterior midline of the abdominal cavity. On abdominal x-ray examination, the bowel is usually centralized and surrounded by a ground-glass appearance, especially in the right and left colonic gutters. Urinary diversion is paramount, and, depending on the location of the leak, a stent, stent and bladder drainage, or percutaneous upper tract diversion with nephrostomy tubes might be necessary. Causes of urinary leakage can be from an anastomosis; an unrecognized kidney, bladder, or ureteral injury from dissection or cautery; or stent migration in the setting of pyeloplasty or ureteral reimplantation, for example. Stent migration can occur intraoperatively when the stent is not positioned correctly, or the stent can be dislodged with removal of the urethral catheter. It has been helpful in my experience to turn the urethral catheter just before removal to help dislodge a stent if it becomes entrapped in the eye of the catheter. If stent location is questioned, one can fill the bladder with methylene blue to see if it comes up the stent during upper tract surgery. However, if there truly is a concern, intraoperative imaging is paramount before waking the patient from general anesthesia.

Hernias

Typically, hernias at the port sites require operative intervention on an emergent basis. Port site hernias may manifest as a bulge or tenderness at one of the port sites, but initially can just be continuous leakage of serous fluid. If findings are not definitive on physical examination, ultrasound can help diagnose a hernia. The size of the trocar does not preclude hernia in children, and port site herniation may occur in 3-mm and 5-mm trocar sites. Most of the time, it is the omentum that herniates through the port site. A few published reports state that 3- and 5-mm trocar sites should be closed; however, no definitive algorithm exists. It is at the discretion of the surgeon whether closure of these wounds is warranted (Peters, 1996; Farhat and Casale, 2009). Nonetheless, because trocar site closure in the pediatric patient is relatively straightforward, one should consider it in order to prevent the potential complication of herniation (Farhat and Casale, 2009). Internal hernias are rare but could theoretically occur at the window in a mesenteric defect if inadvertently created when reflecting bowel, or from intra-abdominal adhesions.

OUTCOMES

The implementation of MIS in children, while at first met with reservations, is now becoming embraced by pediatric urologists (Lee et al, 2009; Koh et al, 2010; Tugcu et al, 2010; Vricella et al, 2010; Ham et al, 2011; Tugcu et al, 2011). The reason for this

BOX 129-8 Categories of Issues with Robotic Visualization

RESTRICTED MOVEMENT

- Camera is bumping into something such as the Mayo stand or another arm.
- It can be restricted by the plastic drape.
- In the standard systems, the camera mount may have come undone from the arm

LIMITED ZOOM

- Make sure the trocar is seated at the limit of the camera mount.
- Make sure the trocar is inserted appropriately at the fascia level. For an obese individual, the camera trocar might have to be inserted farther in than the guide markers.

“FUZZY” VISION: EDGES ARE NOT CRISP OR ARE OUT OF FOCUS

- Try closing one eye then the other to see if there is a difference. If not, then focus. If there is a difference then do the following:
 - Check for a smudge on the lens.
 - If both are not focused after cleaning, try calibrating again.
 - If one is focused but becomes out of focus when you focus the other eye, then you need a new scope.

“CLOUDY” VISION: A FILM ACROSS THE VISUAL FIELD

- First, clean the end of the lens.
- If still present, check for condensation between the lens and the camera.
- If it continues, check the surgeon console because cleaners can cause a film on the eyepiece in the surgeon console. Do not clean with alcohol. Use warm water and dry thoroughly.

DARK VISION

- From the outset:
 - Have the assistant look at the light coming out of the lens.
 - Check cord to see if it is bright. If not, you need a new cord. If yes, you need a new lens.
- During the procedure:
 - Make sure the light is turned up all the way.
 - Check the bulb life.
 - Make sure the cord is pushed in all the way.
 - In the standard model, confirm that the black balance was done.
 - Still dark despite all these efforts? Turn up the gain; this is not a long-term solution, and the problem should be addressed before the next case.

evolution might be the improved instrumentation, but the current armamentarium available is far from perfect for the pediatric patient. The instruments are adapted from the adult patient to be used in pediatrics, but pediatric-specific instrumentation is in its infancy. The true movement in this evolution is that despite some of the instrument deficiencies, pediatric urologists have been able to mimic the gold standard open success rates and operative times (Farhat and Casale, 2009). Table 129-3, from Tomaszewski and colleagues, summarizes some of the outcomes in the literature of minimally invasive procedures (Lee et al, 2009). One can infer from the data that it is at centers of excellence with surgeon champions where these outcomes are possible. However, because these are teaching institutions, if we perform our duty as mentors properly

TABLE 129-3 Current Robotic Series Outcomes

PROCEDURE	SERIES	n	MEAN/MEDIAN (RANGE) AGE (yr)	APPROACH	MEAN OR TIME (min)	MEAN LOS (day)	COMPLICATIONS (n)	SUCCESS RATE (%)
Pyeloplasty	Atug et al, 2005	7	13.0 (6-15)	TP	184 (165-204)	1.2	1	100
	Yee et al, 2006	8	11.5 (6.4-15.6)	TP	363 (255-522)	2.4	1	100
	Lee et al, 2006	33	7.9 (0.2-19.6)	TP (32), RP (1)	219 (133-401)	2.3	1	93.9
	Kutikov et al, 2006	9	0.5 (0.3-0.7)	TP	123	1.4	0	100
	Olsen et al, 2007	67	7.9 (1.7-17.1)	RP	143 (93-300)	2.0	12	94
	Franco et al, 2007	15	11.9 (4.0-18.0)	TP	223 (150-290)	NR	4	NR
Ureteral reimplantation	Peters and Woo, 2005	6	(5-15)	Vesicoscopic	NR	(2-4)	1	83.3
	Casale et al, 2008b	41	3.2 (1.3-6.8)	Extravesical	2.33 (1.4-3.2)	1.1 (0.8-1.4)	0	97.6
Partial nephrectomy	Pedraza et al, 2004a	1	4	TP	440	2	0	NR
	Olsen and Jorgensen, 2005	14	4.9 (0.5-20.2)	RP	176 (120-360)	1.0 (1.0-4.0)	3	NR
	Lee et al, 2009	9	7.2 (0.5-16.5)	TP	275 (170-417)	2.9 (1.9-4.8)	2	NR
Ureteroureterostomy	Kutikov et al, 2007	2	8.0 (6-10)	TP	NR	NR	0	100
	Passerotti et al, 2008	3	9.5 (4.7-14.3)	TP	244 (240-251)	3.5 (2.4-4.3)	0	100
Ureterocalicostomy	Casale et al, 2008a	9	6.5 (3-15)	TP	168 (102-204)	0.9 (0.7-1.1)	0	100
Appendicovesicostomy	Pedraza et al, 2004b	1	7	TP	360	4	0	NR
(+ augmentation + ileocystoplasty)	Gundeti et al, 2008	1	10	TP	600	5	0	NR
(+ ACE)	Thakre et al, 2008	1	10	TP	200	5	0	NR
(+ ACE)	Lendvay et al, 2008b	1	9	TP	480	5	1	NR
Pyelolithotomy	Lee et al, 2007	5	16.6 (10.2-23.2)	TP	315 (165-465)	3.8 (2.3-5.7)	1	75 (stone free)
Bladder neck sling	Storm et al, 2008	2	9.5 (9.0-10.0)	TP	189 (170-208)	3 (2-4)	0	100

ACE, antegrade continent enema; LOS, length of stay; NR, not recorded; OR, operating room; RP, retroperitoneal; TP, transperitoneal.

From Tomaszewski JJ, Casella DP, Turner RM 2nd, et al. Pediatric laparoscopic and robot-assisted laparoscopic surgery: technical considerations. J Endourol 2012;26(6):602-13.

KEY POINTS

- The proposed benefits of laparoscopic surgery over the standard open approach include better cosmesis, increased magnification improving visualization, reduced postoperative pain, and shorter hospital stays.
- In the pediatric population there are strong contraindications to MIS. The strong contraindications are cardiopulmonary morbidity, uncorrected coagulopathy, and sepsis. The role of laparoscopy in malignant tumors is yet to be defined.
- With regard to learning curve, assuming a trend of increasing efficiency continues at the same rate, operative times for fellows are projected to be equal to those of attending urologists after 42 robotic pyeloplasties have been performed. Because the training is not done in a silo, the experience is additive, making the fellow proficient at many cases and truly experienced at robotics overall.
- A successful minimally invasive program, especially if it includes robotics, should be led by a “surgeon champion” who is both dedicated and knowledgeable regarding all instrumentation, credentialing, cost, and operating room flow related to the program.
- With regard to anesthesia effects, the heart rate and mean arterial pressure increase while the venous return and cardiac output decrease. The renal effects occur secondary to gas insufflation manifested by decreased glomerular filtration rate and urine output.
- With regard to the different approaches (transperitoneal versus retroperitoneal):
 - The total tension across multiple incisions is less than the total tension for an incision of the same total length.
 - The correct length of the incision of a trocar’s width is half the circumference as with any cylinder.
- Issues related to complications include the following:
 - The overall complication rate in laparoscopy has recently been shown to be 5.4%, with the rate of major complications being 1.2%, of which 0.4% necessitate surgical intervention.
 - Vascular entry of insufflation can be catastrophic. If vascular entry is noted after insufflation has started, the patient should be placed in reverse Trendelenburg position with right side up to trap the air embolus in the right atrium. The air can then be retrieved with catheterization aided by transesophageal ultrasound.
 - If a bowel injury goes unrecognized at the time of surgery, it will usually manifest 2 to 3 days postoperatively as a result of thermal injury with abdominal pain, particularly at the port sites, ileus, fever, and leukopenia. The physical examination findings are usually out of proportion to the pain. Causes are usually from cauterizing instruments, but injury can also arise from the heat generated by the camera.
 - Intraoperative urinary cultures should always be obtained in case a postoperative urinary tract infection develops.
 - With regard to urinary leakage, the physical examination typically reveals a tense abdomen with tympanic bowel only on the anterior midline of the abdominal cavity. On abdominal x-ray examination, the bowel is usually centralized and surrounded by a ground-glass appearance, especially in the right and left colonic gutters.
 - Typically, hernias at the port sites require operative intervention on an emergent basis. Port site hernias may manifest as a bulge or tenderness at one of the port sites, but initially can just involve continuous leakage of serous fluid. If findings on physical examination are not definitive, ultrasound can help diagnose a hernia. The size of the trocar does not preclude hernia in children, and port site herniation may occur in 3-mm and 5-mm trocar sites.

we can disseminate the technique and ability to our trainees. This will allow MIS to become part of the mainstream of pediatric urology.

Outcomes for LESS are scant in the literature owing to its infancy in pediatric urology. Koh and colleagues performed LESS nephrectomy in 11 children ranging from infants to adolescents and compared them with a historical cohort with similar perioperative parameters (Koh et al, 2010). The mean operative time, hospital length of stay, and complications were not statistically different between the groups, with preliminary results showing it is a safe and effective modality. Other smaller series have reported similar results (Marietti et al, 2010; Tugcu et al, 2010; Vricella et al, 2010; Ham et al, 2011; Tugcu et al, 2011). Successful completion of LESS pyeloplasty has been reported in one series of 11 patients (Tugcu et al, 2011). Similar surgical parameters and a success rate of 100% were reported. Nonetheless, additional studies are necessary to determine whether a single umbilical incision in children is associated with improved operative outcomes, reduced pain medication requirements, shorter convalescence, and validated measures of postoperative cosmesis.

CONCLUSION

Minimally invasive procedures have revolutionized the way we do surgery in the pediatric urologic patient. The evolution has been through improvement in equipment and teaching technology such as simulation. The outcomes parallel our open surgical results with the benefit of smaller incisions and less manipulation of tissue during the procedures. Compared with conventional laparoscopy, use of robotics has enhanced MIS with increased dexterity, better visualization, and less fatigue, allowing greater precision. We have come a long way in pediatric urologic MIS, but it is still in its infancy.

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130 Anomalies of the Upper Urinary Tract

Ellen Shapiro, MD, and Shpetim Telegrafi, MD

Anomalies of Number

Anomalies of Ascent

Anomalies of Form and Fusion

Anomalies of Rotation

Anomalies of Renal Vasculature

Anomalies of the Collecting System

Congenital anomalies of the upper urinary tract comprise a group of abnormalities, ranging from complete absence of the kidney to aberrant location, orientation, and shape of the kidney, as well as aberrations of the collecting system and blood supply. These diverse entities are among the most common malformations in newborns. Advances in molecular genetics have provided the opportunity to hypothesize regarding the complex mechanisms of normal and abnormal development.

ANOMALIES OF NUMBER

Bilateral Renal Agenesis

Of all the anomalies of the upper urinary tract, bilateral renal agenesis (BRA) has the most profound effect on the fetus. Although Wolfstrigel first recognized BRA in 1671, it was not until Potter's extensive description of the constellation of associated defects that the full extent of the syndrome could be easily recognized (Potter, 1946a, 1946b, 1952). Owing to the myriad of complex molecular events that are required for normal renal development, there is probably no single etiology.

Incidence. The incidence of BRA is rare, with only about 500 cases reported in the literature. Potter (1965) estimated that BRA occurs once in 4800 births, whereas Stroup and colleagues (1990) detected an incidence of 3.5 per 100,000. A study in 8500 pregnancies in Poland documented a higher incidence of 0.25% (Forys et al, 2003). Almost 75% of affected individuals are males. Increasing maternal age may be a risk factor (Bianca et al, 2003), but complications of pregnancy or maternal disease do not appear to influence the incidence of BRA (Ruhland et al, 1998). An autosomal recessive inheritance pattern may exist (Dicker et al, 1984), although other investigators have suggested an autosomal dominant trait with variable penetrance (Kovacs et al, 1991; Murugasu et al, 1991; Moerman et al, 1994; Stella, 1998). When siblings and parents of an index child with BRA were screened, 4.5% had unilateral renal agenesis (URA) (Roodhooft et al, 1984) and 3.5% had BRA (McPherson et al, 1987). This is 1000 times higher than in the general population (Stroup et al, 1990). McPherson (2007) evaluated renal anomalies in families of individuals with congenital solitary kidneys including renal agenesis or a very poorly functioning kidney resulting from dysplasia/hypoplasia. The empirical risk of 7% for offspring, 4% for parents, and 2.5% for siblings may be an underestimation, because not all relatives underwent ultrasound screening. The incidence of BRA in offspring of congenital solitary

kidney probands was approximately 1%, which is significantly greater than the risk found in the general population but less than that for families with a history of BRA. Ultrasound screening has been recommended for parents and siblings of infants born with either URA or BRA or dysgenesis (Roodhooft, 1984). McPherson (2007) has recommended prenatal and/or postnatal ultrasound examination when either parent or another first-degree relative has a congenital solitary kidney.

Syndromic Associations. BRA has been detected in higher-than-expected proportions in esophageal atresia (Saing et al, 1998), cryptophthalmos or Fraser syndrome (Fryns et al, 1997), Klinefelter syndrome (Barroeta et al, 2004), and Kallmann syndrome (Colquhoun-Kerr et al, 1999).

Renal Embryology. The intermediate kidney, or mesonephros, develops and then regresses except for the mesonephric tubules (Uetani and Bouchard, 2009; Costantini and Kopan, 2010). In the male, these are the efferent ductules that serve as a link between the gonad and the mesonephric or wolffian duct (WD) structures (the body and tail of the epididymis and vas deferens). In the female, the mesonephric tubules link the ovary through the fimbriated end of the fallopian tube to the reproductive tract. The WD elongates caudally and fuses with the anterior cloaca. The definitive kidney differentiates from the metanephric blastema, which is a specialized region of the intermediate mesoderm termed the *metanephric mesenchyme* (MM).

This process requires the reciprocal induction between the metanephric blastema and the ureteral bud (UB). The metanephric blastema sends signals to the WD to initiate UB formation from its caudal end between 5 and 7 weeks' gestation. The UB evaginates and invades the metanephric blastema and branches repeatedly in a characteristic pattern to form the collecting duct system. The ureteral tips induce nephron differentiation in the adjacent mesenchyme, forming the mature metanephros (Uetani and Bouchard, 2009). The absence of a nephrogenic ridge on the dorsolateral aspect of the coelomic cavity, or the failure of a UB to develop from the WD, will result in renal agenesis. Therefore for BRA to occur, there must be an alteration in normal molecular development or a mutation that causes renal or ureteral maldevelopment on both sides of the midline (see *Molecular Mechanisms of Mammalian Kidney Organogenesis*).

Relationship of the Wolffian Duct to Müllerian Duct Formation. A review of the relationship of the WD to müllerian duct (MD) development is necessary to understand the genitourinary phenotype of individuals with renal anomalies, or more

specifically, renal agenesis (Kobayashi and Behringer, 2003). Gene fate mapping and lineage tracing experiments show that the WD does not contribute cells to the MD, and the MDs are derived from the coelomic epithelium (Guioli et al, 2007; Orvis and Behringer, 2007). A three-phase model of MD development has been proposed (Guioli et al, 2007; Orvis and Behringer, 2007). In the first phase, cells of the coelomic epithelium in the cervical region of the intermediate mesoderm are specified to become MD cells and have been noted to express *Lim1* (Kobayashi et al, 2005; Orvis and Behringer, 2007; Masse et al, 2009) (Fig. 130-1). After the process of specification is complete, the second phase is heralded by *Wnt4* expression from the mesonephros or coelomic epithelium, which induces these cells that are destined to become the MDs to invaginate (Kobayashi et al, 2004, 2005; Orvis and Behringer, 2007). The second phase of MD development is WD independent and ends when the MD extends caudally and contacts the WD (Carroll, 2005; Kobayashi et al, 2005; Orvis and Behringer, 2007). The third phase involves elongation of the MDs posteriorly until they are joined at the urogenital sinus (UGS). This process is WD dependent, requiring the MD epithelium at its posterior end to be in close physical contact with the WD epithelium, whereas the MDs are separated from the coelomic epithelium only by a basement membrane (Orvis and Behringer, 2007). This intimate relationship between the WD and MD is emphasized in experiments that interrupt the formation of the WD at a specific point and show that the MD could not grow beyond that point to complete its formation (Gruenewald, 1941). *Lim1* in the WD is critical for WD maintenance. Loss of *Lim1* in the WD by inactivation leads to WD loss. Because the MD is dependent on the WD in this third phase, the MDs are again incompletely formed (Kobayashi et al, 2005). This third phase is also dependent on the *Pax2* gene; mice mutants for this gene show cellular invagination but no elongation because the WDs have degenerated (Torres et al, 1995; Miyamoto et al, 1997). Studies have also shown that the WD not only acts as a physical guide but also plays a role in MD elongation through paracrine signaling. More specifically, *Wnt9b* is expressed by the WD epithelium, and gene

inactivation results in incomplete formation of the MDs (Carroll et al, 2005). Loss of *Wnt9b* expression did not affect the WD, per se, or the first two phases of MD development, but it did affect the caudal extension and elongation of the MDs, suggesting that WD signaling by *Wnt9b* is one of the critical factors in directing MD formation (Carroll et al, 2005). For a clinical correlation, see **Unilateral Renal Agenesis: Anomalies in the Female**.

Molecular Mechanisms of Mammalian Kidney Organogenesis. Several genes play a critical role in WD development, including *Pax2/8*, *Gata3*, and *Lim1*. Many of the same genes affecting renal development will also affect internal duct development. If there is gene inactivation of *Pax2/8*, *Gata3*, or *Lim1*, there will be no formation of the kidneys (BRA), ureters, or genital tract (Uetani and Bouchard, 2009). Reciprocal epithelial-mesenchymal inductive signaling between the UB epithelium and the MM regulates the pathway for mammalian kidney development (Yu et al, 2004). UB formation and the induction of its branching require glial cell line-derived neurotrophic factor (GDNF), a secreted growth factor expressed in the MM (Michos et al, 2007). The GDNF ligand activates the RET receptor, which is expressed in the WD epithelium and then around the UB tips as branching proceeds. *Eya1* and *Pax2* positively regulate *Gdnf* expression and localization (Michos, 2009). GDNF activation of RET requires the GDNF family receptor $\alpha 1$ (GFR $\alpha 1$) and is essential for induction of UB formation and initiation of outgrowth and branching (Chi et al, 2009). Most genes that are considered essential for UB formation are also regulators of *Gdnf* or *Ret* expression. Studies of murine kidney development show that *Gdnf*^{-/-} mice have renal agenesis, whereas *Ret*^{-/-} mice have renal agenesis or dysplastic kidneys (Pichel et al, 1996; Schuchardi et al, 1996).

Skinner and colleagues (2008) examined the association between abnormal kidney development and mutations of *RET*, *GDNF*, and *GFR $\alpha 1$* in 29 stillborn fetuses with BRA or URA. Mutations in *RET* were found in 7 of 19 fetuses with BRA and in 2 of 10 fetuses with URA. A mutation in *GDNF* was found in 1 fetus with URA who also had mutations in *RET*. No *GFR $\alpha 1$* mutations were observed. These data suggest that congenital renal agenesis results from *RET* mutations that prevent or impede the embryonic development of *RET*-dependent structures.

After the GDNF/GFR $\alpha 1$ complex binds to RET, the *Wnt11* gene is activated in the epithelial tips of the UB and is associated with UB branching (Majumdar et al, 2003). *Wnt11* is a member of the *Wnt* gene family, which is composed of structurally related genes encoding secreted signaling proteins. These proteins are likely involved in several processes, including regulation of cell fate and patterning during embryogenesis. WNT11 signaling is required for the propagation of mesenchymal GDNF signaling, which establishes the autoregulatory epithelial-mesenchymal GDNF/WNT11 feedback-signaling loop that controls the progression of metanephric branching morphogenesis after initiation of UB outgrowth (Majumdar et al, 2003; Michos et al, 2007).

Bone morphogenetic protein-4 (BMP4), a member of the transforming growth factor- α family, is expressed in the periureteral mesenchyme, and is essential for morphogenesis (Miyazaki et al, 2000, 2003; Michos et al, 2007). In wild-type mouse embryos, BMP4 is expressed by the mesenchyme surrounding the WD and UB. Mesenchymal cells that express BMP4 inhibit UB formation, in part by inhibiting *Wnt11* expression. BMP4 migrates to ectopic sites, thereby preventing ectopic UB formation. The BMP4 mesenchymal cells act in a similar fashion during UB branching by inhibiting side branching and permitting stems to lengthen. Mesenchymal cells that are devoid of BMP4 surround the tip, where further branching proceeds. Mice heterozygous for a null mutation in BMP4 (+/-) manifest anomalies, including hypoplastic/dysplastic kidney, hydroureter, ectopic ureter, ureteral duplication, megaureter, ureterovesical junction obstruction, and reflux (Miyazaki et al, 2000, 2003).

Mammalian Kidney Organogenesis: New Advances. Gremlin 1 (GREM1) is an extracellular BMP antagonist that is expressed in the mesonephric mesenchyme and in the MM (Michos et al, 2004) (Fig. 130-2). GREM1 is upregulated in the mesenchyme around the origin of the UB before the initiation of its outgrowth. BMP activity,

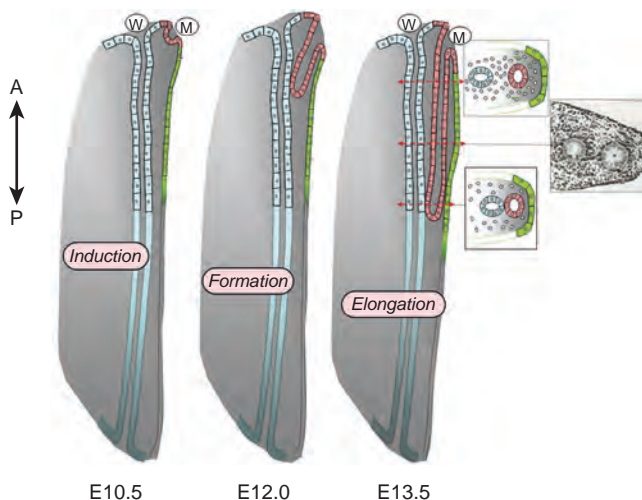


Figure 130-1. Model for müllerian duct (MD) development. At E11.75, after a subset of coelomic epithelium cells (green) are specified, they invaginate in the intermediate mesoderm. Then the invaginating cells form the MD (M, pink). Anteriorly the funnel is opened in the abdominal cavity, and caudally the growing tip extends to and contacts the wolffian ducts (WDs; W, blue) at E12.0. A phase of elongation allows the MD to elongate posteriorly in close contact with the WD. As soon as the MD growing tip has deposited cells and elongated caudally, the physical contact between the ducts is lost by the appearance of mesenchymal cells around the MD epithelium. At E13.5, the two MDs reach the urogenital sinus and fuse together. Developmental stages indicated in this figure correspond to mouse stages. (From Masse J, Watrin T, Laurent A, et al. The developing female genital tract: from genetics to epigenetics. *Int J Dev Biol* 2009;53:411–24.)

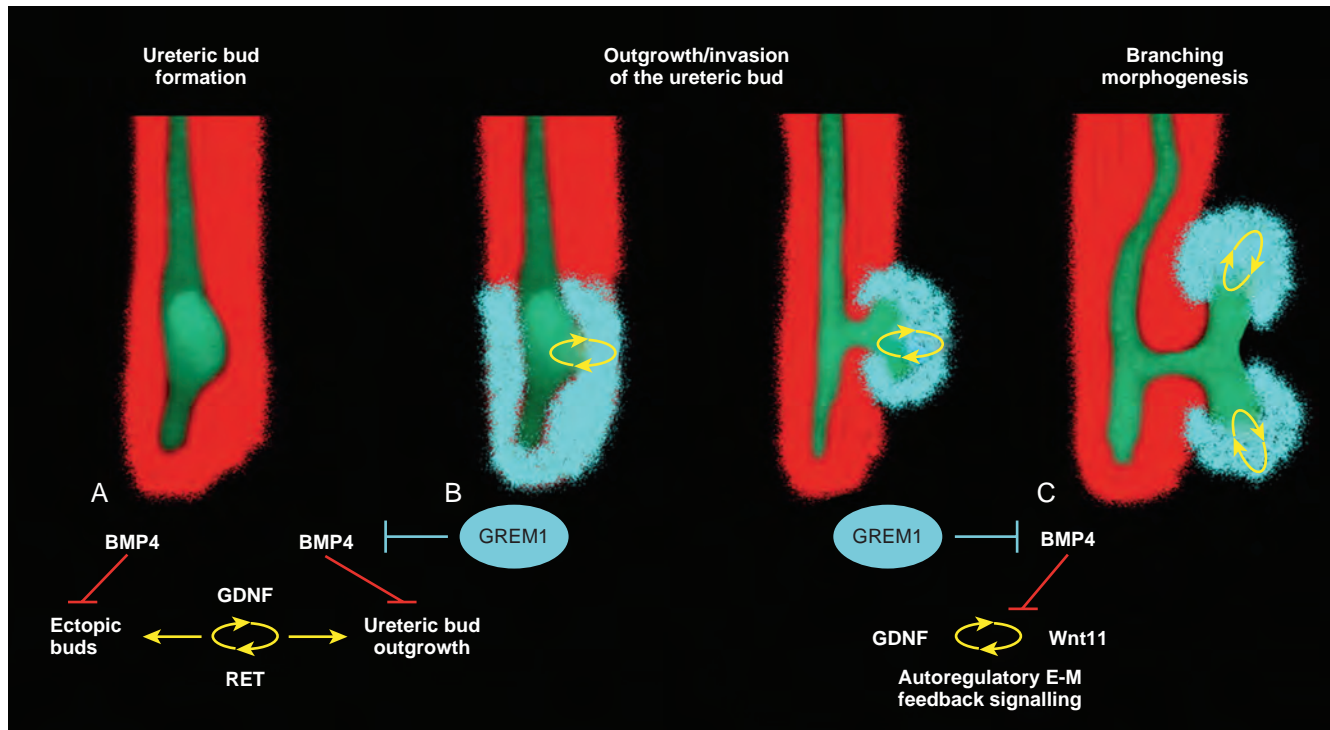


Figure 130-2. Reduction of bone morphogenetic protein-4 (BMP4) activity by gremlin 1 (GREM1) in the mesenchyme around the ureteric bud is essential to enable ureteric epithelial outgrowth, glial cell line–derived neurotrophic factor (GDNF)-RET– and WNT11-mediated epithelial-mesenchymal (E-M) feedback signaling, and branching morphogenesis. **A**, In mouse, the ureteric bud forms in the caudalmost part of the wolffian duct (WD) under the influence of GDNF-RET signaling. During this inductive period, *Bmp4* is expressed by the mesenchyme enveloping the WD. High levels of mesenchymal BMP4 activity inhibit the formation of ectopic epithelial buds and epithelial branching at this stage (prior to E11.0). At this early stage, only low levels of *Grem1* transcripts are detected (not shown). **B**, Expression of the BMP antagonist *Grem1* is upregulated in the mesenchyme around the nascent ureteric bud, thereby locally reducing BMP4 signal transduction (around E11.75-11.0). This reduction of BMP4 activity by GREM1 enables initiation of ureteric bud outgrowth and its invasion into the metanephric mesenchyme. **C**, GREM1 is required to maintain and propagate expression of *Wnt11* in the ureteric epithelial tip(s) and *Gdnf* in the mesenchyme by E-M feedback signaling. (From Michos O, Goncalves A, Lopez-Rios J, et al. Reduction of BMP4 activity by gremlin 1 enables ureteric bud outgrowth and GDNF/WNT11 feedback signaling during kidney branching morphogenesis. *Development* 2007;134:2397–405.)

at this time, is reduced locally. In the *Grem1*-deficient mouse embryo, metanephric development is disrupted at the stage of UB outgrowth initiation, resulting in BRA. This inhibition of UB outgrowth causes progressive loss of *Gdnf* expression, resulting in apoptosis of the MM.

To examine further the relationship of these various ligands and their effects on epithelial-mesenchymal interactions, Michos and colleagues (2007) cultured early *Grem1*-deficient mutant mouse kidney rudiments in a medium supplemented with recombinant GREM1. The addition of GREM1 restored UB outgrowth and induced supernumerary epithelial buds that invaded the MM and initiated branching morphogenesis. At the molecular level, GREM1 replacement activated *Wnt11* expression in the epithelial buds and upregulated *Gdnf* expression in the mesenchyme. Because genetic suppression of BMP4 activity in a *Grem1*-deficient mouse model completely restored kidney development, the local reduction of BMP4 activity by GREM1 was presumed to be critical to the initiation of UB outgrowth and kidney organogenesis.

Because BMP4 signaling by the mesenchyme surrounding the WD prevents the formation of supernumerary epithelial buds, successful initiation of UB outgrowth most likely requires both the antagonism of BMP4 by GREM1 in mesenchyme and the signaling by GDNF from the MM to RET in the ureteric epithelium (Michos

et al, 2007). In addition, autoregulatory feedback signaling between GDNF in the mesenchyme and WNT11 in the epithelial tips regulates branching morphogenesis. *Grem1* is essential for both upregulation of *Wnt11* in the ureteric epithelium and *Gdnf* expression in the mesenchyme and the establishment of epithelial-mesenchymal feedback signaling.

Reviews by Faa and colleagues (2012) and Chai and colleagues (2013) provide further insight into the molecular mechanisms involved in human kidney development. It is well known that the major signaling pathway for ureteral branching is the c-Ret receptor tyrosine kinase whose ligand and downstream target are GDNF and Wnt11, respectively (Faa et al, 2012). Increased Wnt11 expression induces GDNF in adjacent mesenchyme leading to ureteric bud tip cell proliferation, decreased bud tip cell apoptosis, and branching. Investigations examine the role of the renin-angiotensin system (RAS) in known mechanisms regulating UB branching that are essential to normal renal development (Yosypiv, 2014). Gene mutations of the RAS lead to a spectrum of congenital anomalies of the kidney and urinary tract (CAKUT) resulting from defects in UB morphogenesis. UB tips induce surrounding mesenchymal cells to undergo mesenchymal to epithelial transition, forming the glomerulus to the distal tubule. Therefore a decrease in UB branching efficiency will result in a significant decrease in nephron endowment.

Aberrant branching can result in abnormal nephrogenesis and renal hypodysplasia that may progress to chronic renal failure.

In the RAS, renin cleaves angiotensinogen to angiotensin I, which is converted to angiotensin II by the angiotensin-converting enzyme (ACE) (Yosypiv, 2014). Angiotensin II, the primary effector peptide growth factor of the RAS, acts through two major protein receptors: AT₁R and AT₂R. Angiotensin II acts through the AT₂R to stimulate UB branching by upregulating PAX2, a downstream regulator of GDNF that induces the expression of *GDNF/Ret/Wnt11* pathway genes. These genes promote proliferation in UB tip cells and stimulate UB branching. Angiotensin II might also act through the AT₁R to downregulate Spry1, an inhibitor of GDNF/Ret. In turn, this downregulation of Spry1 results in angiotensin II-induced UB branching. The critical role for the RAS in UB morphogenesis is observed when ACE inhibitors or AT₁R antagonists are administered during pregnancy. These inhibitors cause abnormal nephrogenesis, more specifically, renal tubular dysgenesis, which is characterized by absent or underdeveloped proximal tubules. In mice, gene inactivation of angiotensinogen, renin, ACE, or AT₁R results in renal pelvic dilation and hypoplastic papilla. Mutations in the AT₂R gene in mice result in downregulation of the *GNFR/Ret/Wnt11* pathway gene expression, decreased proliferation, and induction of apoptosis of the UB cells. Clinically, ureteral duplication and vesicoureteral reflux are associated with AT₂R gene mutations. These observations in receptor-deficient mice illustrate the need for a critical balance of cell proliferation and cell apoptosis in normal UB branching and nephrogenesis.

SOX genes are an essential component of the c-RET signaling pathway and are important developmental regulators expressed in the tips of the UB that are thought to direct UB branching. Further evidence for the critical role of the c-RET signaling pathway is found in SOX8/9 double mutants because they have abnormal nephrogenesis ranging from renal hypoplasia to renal agenesis (Reginensi et al, 2011).

Gross Pathologic Description of Retroperitoneal Findings

In an extensive autopsy analysis by Ashley and Mostofi (1960), the kidneys were completely absent on gross inspection of the entire retroperitoneum. Complete absence of the renal vessels was observed in about 25% of specimens. Complete ureteral atresia was observed in 39 of the 42 cases of BRA, and partial ureteral absence was noted in three cases. With complete absence of the ureter, a rudimentary kidney was discovered in only a few instances.

The adrenal gland may appear flattened ("lying down" sign) on ultrasonography but is rarely malpositioned or absent (Hoffman et al, 1992). A normally located adrenal gland is expected, because the adrenal cortex develops from primitive mesoderm medial to the urogenital ridge and the medulla develops from ectodermal neural crest cells, whereas the metanephros is derived from the intermediate mesoderm.

Fused and/or horseshoe-shaped glands have been noted on prenatal ultrasound screening (Strouse et al, 2002). Potter (1965) noted that fused glands were often found in the presence of spinal anomalies. In a small number of autopsies, the gonads were absent, indicating the insult occurred before the fifth week and affected the development of the urogenital ridge (Carpentier and Potter, 1959).

KEY POINTS: BILATERAL RENAL AGENESIS

- A total of 40% of the affected infants are stillborn.
- Most of the children who are born alive do not survive beyond 48 hours because of respiratory distress associated with pulmonary hypoplasia.
- The characteristic Potter facies and the presence of oligohydramnios are pathognomonic.
- The ureters are almost always absent, and the bladder is either absent or hypoplastic.
- The adrenal glands are usually positioned normally.
- MD anomalies are commonly observed.

In the Ashley and Mostofi series (1960), about 50% of cases of complete ureteral atresia showed complete absence of the bladder, and in the remainder, a hypoplastic bladder was found consisting only of a muscular tube with a minute lumen. In Potter's series (1965), the bladders were also hypoplastic and lacked ureteral orifices. A normally closed urachus was observed.

Abnormal development of the bladder is thought to be a result of the lack of stimulation by fetal urine production, which starts at 10 to 12 weeks' gestation. Alternatively, it has been postulated that UB and WD structures migrating into the ventral cloacal region are needed to initiate normal bladder development. The absence of the UB, and not the lack of urine, may arrest bladder development (Katz and Chatten, 1974). This theory is supported by the fact that, despite the absence of bladder filling in bladder exstrophy, many of these bladders are functional following surgical closure alone, whereas the bladders associated with bilateral ureteral ectopia (below the bladder neck) almost invariably require augmentation (Jayanthi et al, 1997; Gearhart and Matthews, 2007).

Phenotypic Features. Potter has extensively described phenotypic features associated with BRA. These infants have low birth weights, ranging from 1000 to 2500 g, and intrauterine growth retardation resulting in part from low iron stores in the liver (Georgieff et al, 1996). At birth, oligohydramnios is present. The characteristic facial appearance and deformity of the extremities distinguishes these neonates from normal newborns. The infants look prematurely senile and have "a prominent fold of skin that begins over each eye, swings down in a semicircle over the inner canthus and extends onto the cheek" (Potter, 1946a, 1946b). This facial feature is a sine qua non of nonfunctioning renal parenchyma and suggests that its absence confirms the presence of at least one kidney (Fig. 130-3). The nose is blunted, and a prominent depression exists between the lower lip and chin. The ears appear to be low set, are drawn forward, and are often pressed against the side of the head, making the lobes seem unusually broad and exceedingly large. Periauricular pits and tags have been noted (Wang et al, 2001). The skin can be excessively dry and appears too loose for the body. The hands are relatively large and clawlike. The legs are often bowed and clubbed, with excessive flexion at the hip and knee joints (Das et al, 2002). Occasionally the lower extremities are completely fused as seen with sirenomelia (Liatsikos et al, 1999). A lumbar meningocele with or without the Arnold-Chiari malformation and hydrocephalus is often observed (Ashley and Mostofi, 1960). In Potter's series (1965), anomalies of the gastrointestinal tract were found in 60% of fetuses.

Anomalies of the external genitalia include absence of the scrotum and clitoral hypertrophy. Penile development is usually normal, but in a few cases, penile agenesis or a rudimentary penis and scrotum have been reported (Potter, 1965; O'Connor et al, 1993). Hypospadias is rare and does not appear to be related to the presence or absence of the testes. The testes are undescended in 43% of cases (Carpentier and Potter, 1959). Ashley and Mostofi (1960) found testicular agenesis in 10% of cases. The vas deferens is normal in most cases, implying that the factor responsible for the renal agenesis influenced the UB only after it formed from a completely elongated WD or that the insult affected the induction of the MM.

There is a relatively high incidence of anomalies of the MD structures and ovaries (Carpentier and Potter, 1959). The ovaries are frequently hypoplastic or absent. The uterus is usually rudimentary or bicornuate but occasionally absent. The vagina is a short, blind-ending pouch or is completely absent.

Role of Amniotic Fluid Production and Pulmonary Development. The characteristic facial and limb features may result from deformations rather than malformations of structures as a result of the lack of "cushioning" from amniotic fluid (Thomas and Smith, 1974). This observation was confirmed by an experiment in nature in which one twin with BRA did not have the characteristic Potter facies because it shared the same amniotic sac with the second twin who had an adequate volume of amniotic fluid (Klinger et al, 1997). Fetal renal urine is the major source of amniotic fluid,



Figure 130-3. An anephric child who lived 2 days has the typical Potter facial appearance. **A,** Note the prominent fold and skin crease beneath each eye, blunted nose, and depression between lower lip and chin. **B,** The ears give an impression of being low set because lobes are broad and drawn forward, but actually the ear canals are located normally.

accounting for more than 90% of its volume by the third trimester (Chevalier and Roth, 2007).

Pulmonary hypoplasia and a bell-shaped chest are commonly associated findings that were thought to be caused by uterine wall compression of the thoracic cage as a result of oligohydramnios (Bain and Scott, 1960). Pulmonary airway branching occurs between 12 and 16 weeks' gestation (Reid, 1977). A reduction in the number of branches and a decrease in acini formation in fetuses with BRA imply interference with this process before 16 weeks' gestation (Hislop et al, 1979). They suggested that the anephric fetus fails to produce proline, which is a prerequisite for collagen formation in the bronchiolar tree. The kidney is the primary source of proline (Clemmons, 1977). Thus pulmonary hypoplasia may result from the absence of renal parenchyma and not from diminished amniotic fluid. This hypothesis is supported by the finding of normal lungs in two infants with prolonged leakage of amniotic fluid beginning at a time when pulmonary hypoplasia would have been expected if the amniotic fluid alone was responsible for the defect (Perlman et al, 1976; Cilento et al, 1994).

Peters and colleagues (1991a) proposed a two-step process in pulmonary development, with a primary "renal growth factor" influencing early lung development and an amniotic fluid volume-dependent phase influencing later gestational lung growth. Smith and colleagues (2006) studied early lung development using a murine knockout model of renal agenesis/dysgenesis and anuria. They found that pulmonary development occurred early in embryogenesis, and fetal anuria and hypoplastic lung development preceded oligohydramnios. These observations support the two-step model proposed by Peters (1991a). Alternatively, oligohydramnios resulting from experimentally induced urinary obstruction is associated with pulmonary hypoplasia in fetal sheep that initially showed normal renal function (Peters et al, 1991a, 1991b).

Restoring amniotic fluid volume only partially restores lung growth. Therefore, uropathy-associated pulmonary hypoplasia appears to be a result of oligohydramnios rather than renal dysfunction (Peters, 1991b).

Prenatal and Postnatal Diagnosis. BRA is being diagnosed by prenatal ultrasonography in the second and third trimesters, when severe oligohydramnios is noted and no renal parenchyma can be identified (Forys et al, 2003). Additional diagnostic findings include small lung volumes and chest diameter and abnormal adrenal gland appearance (Heling et al, 2001; Strouse et al, 2002). The characteristic Potter facies and the presence of oligohydramnios are pathognomonic. Amnion nodosum—small, white, keratinized nodules on the surface of the amniotic sac—have been considered a placental hallmark of severe oligohydramnios, but the condition is not pathognomonic and the finding should be interpreted with caution (Adeniran and Stanek, 2007).

In a study of 500 infants, every infant voided within the first 24 hours of life, regardless of the gestational age (Clarke, 1977). After the first 24 hours, anuria without distention of the bladder suggests BRA.

Postnatal Radiographic Evaluation. Renal ultrasonography is the most efficient way to identify the kidneys and bladder and to confirm the presence or absence of urine production. Power Doppler ultrasonography has been highly accurate in determining the status of the renal arteries, even in fetuses with suspected BRA (Sepulveda et al, 1998). A flattened orthotopic adrenal gland supports the diagnosis of an absent kidney (Hoffman et al, 1992). If abdominal ultrasonography is inconclusive, ^{99m}Tc -dimercaptosuccinic acid (^{99m}Tc -DMSA) scanning can be performed. The absence of uptake of the radionuclide in both renal fossae above background activity or in an ectopic location confirms the diagnosis of BRA.

Prognosis. About 40% of the affected neonates are stillborn. Of those neonates born alive, most do not survive beyond the first 24 to 48 hours because of respiratory distress.

Unilateral Renal Agenesis

Complete absence of one kidney occurs more frequently than BRA but is not easily detected on physical examination. The largest study to date of neonates with an isolated single umbilical artery did not find an increased incidence of URA or other malformations (Deshpande et al, 2009). URA may remain undetected unless examination of the external genitalia and/or radiographic evaluation of the female or male pelvis for other reasons shows an anomaly associated with renal agenesis. Since the mid-1990s, prenatal ultrasound examinations have been performed more routinely, and URA is detected with increased frequency (Sipek et al, 1997). A substantial number of cases thought to be URA were a dysplastic or multicystic dysplastic kidney (MCDK) that had involuted before birth (5%) (Hiraoka et al, 2002; Schreuder et al, 2009). MCDK has an incidence of 1 in 4300. Renal aplasia is found in 1 in about 1300 births, which is similar to the incidence of renal agenesis and may be the most common cause of congenital solitary kidney. Renal aplasia includes those units with rudimentary parenchyma and ureter. It is thought to be a result of early regression of the ureteric bud, altered metanephric differentiation, or defects in the branching ureteric duct and the metanephric blastema to “communicate” and to provide reciprocal induction. A plain film of the abdomen supports this diagnosis if the splenic or hepatic flexure of the bowel is in its normal location and not in the ipsilateral renal fossa, suggesting that a dysplastic kidney or MCDK may have formed in the renal fossa before involuting (Matsell, 1998). Curvilinear calcifications on a plain radiograph or computed tomography (CT) scan are another sign of a previous MCDK (Nakano et al, 1996). A flattened adrenal or the spleen (on the left) may be mistaken for a kidney on the 20-week structural ultrasound (Woolf and Hillman, 2006).

Incidence. Most autopsy series suggest that URA occurs once in 1100 births (Doroshov and Abeshouse, 1961). Ultrasound screening of 280,000 school children in Taipei showed the incidence of URA to be 1 in 1200 (Shieh et al, 1990). The high male predominance of BRA is not nearly as striking in the unilateral condition, with a male-to-female ratio of 1.8:1 (Doroshov and Abeshouse, 1961). Absence of a kidney occurs somewhat more frequently on the left side. A familial tendency has been noted (Cascio et al, 1999). McPherson and colleagues (1987) concluded the inheritance of URA was autosomal dominant with a 50% to 90% penetrance. Others who evaluated families with more than one affected individual have confirmed this inheritance pattern (Roodhooft et al, 1984; Battin et al, 1993). For screening recommendations, see *Bilateral Renal Agenesis: Incidence*.

Genetic/Syndromic and Other Associations. An absent kidney has been noted in a number of genetic disorders in which there is a deletion of several chromosomal loci: 8q13.3 (Pierides et al, 2002), 18q22.2 (Dowton et al, 1997), 22q11 (Stewart et al, 1999), as well as in X-linked and sporadic cases of Kallmann syndrome (Quinton et al, 2001). Several syndromes have been associated with URA, including Turner syndrome, Poland syndrome (Mace et al, 1972), Fraser syndrome (Fryns et al, 1997), branchio-oto-renal (BOR) syndrome (Pierides et al, 2002), and DiGeorge anomaly (when associated with maternal insulin-dependent diabetes mellitus) (Wilson et al, 1993; Novak and Robinson, 1994). Maternal diabetes is associated with a threefold increased risk of renal agenesis and dysplasia (Davis et al, 2010). Animal studies have shown that the developing kidney is adversely affected by a high glucose environment, causing dysmorphogenesis of the metanephros and ureteric bud and disruptions in the normal process of nephrogenesis resulting in a reduced population of nephrons (Kanwar et al, 2005; Cunha et al, 2008).

About 30% of children with the VACTERL association (vertebral, imperforate anus, cardiac, tracheo-esophageal atresia, renal, and limb anomalies) have URA (Kolon et al, 2000). Children with

supernumerary nipples (Urbani and Betti, 1996) and disorders of the ears with hearing loss, especially if it is congenital (Huang et al, 2001), and preauricular pits (Pierides et al, 2002) have been thought to have an increased incidence of URA. Studies have not shown a significant relationship between preauricular pits, minor ear tags, and URA (Arora and Pryce, 2004; Deshpande and Watson, 2006). A renal sonogram is recommended when these ear anomalies are found in the presence of other malformations. In addition, when more than one anomaly is present (e.g., ventricular septal defect and an undescended testis) a renal sonogram is prudent, but when specific complexes of anomalies associated with renal agenesis are present (e.g., VACTERL-associated anomalies), a comprehensive radiographic examination of all organ systems including the spine is mandatory.

Embryology. The embryologic basis for URA and BRA is thought to be similar and it is most likely caused by the UB, because increased *RET* mutations occur in humans with renal agenesis (Skinner et al, 2008; Chatterjee et al, 2012; Davis et al, 2014). Complete absence of a bud or aborted ureteral development prevents reciprocal induction, which is critical for the development of the metanephric blastema into the definitive adult kidney. The metanephros is not likely to be responsible for the majority of cases, because the ipsilateral gonad (derived from adjacent mesenchymal tissue) is rarely absent, malpositioned, or nonfunctioning (Ashley and Mostofi, 1960). The high incidence of absent or malformed proximal WD structures in the male and anomalies of the MD structures in the female suggest that the embryologic insult affects the UB primarily in its early development and influences the development of WD derivatives. The abnormality most likely occurs no later than 4 or 5 weeks' gestation, when the UB forms and the WD begins to develop into the ejaculatory duct, seminal vesicle, and vas deferens. The MD in the female begins its medial migration at this time, crossing over the WD (sixth week) during its differentiation into the fallopian tube, uterine horn and body, and proximal vagina (Yoder and Pfister, 1976).

Magee and colleagues (1979) proposed an embryologic classification to explain the association of URA and MD anomalies (Fig. 130-4 on the Expert Consult website). In type I URA, the insult occurs before the fourth week, and there is nondifferentiation of the urogenital ridge structures, including the MD and WD. If unilateral, a uterus consisting of a single MD (unicornate uterus) will form and will be associated with contralateral renal agenesis. In type II URA, the insult occurs early in the fourth week of gestation, affecting both the WD and the UB. Because it is critical that the MD maintains close contact with the WD for MD elongation and subsequent fusion, maldevelopment of the WD affects renal development, MD elongation, contact with the UGS, and subsequent fusion. Therefore a didelphys uterus will form with obstruction of the horn and vagina on the side of the URA (Fig. 130-5). Finally, in type III URA, the insult occurs after the fourth week, and the WD and MD elongation and differentiation proceed normally. In this case, only the UB and metanephric blastema are affected, thereby resulting in isolated URA.

Associated Genitourinary and Adrenal Anomalies. The ipsilateral ureter is absent in about 60% of cases (Ashley and Mostofi, 1960). In this series, 19 of 232 with URA had only a portion of the lower end of the ureter present. In most cases of complete absence of the ureters, the bladder showed no evidence of a ureteric orifice with failure of ipsilateral trigone development (Ashley and Mostofi, 1960). Cell lineage studies using a murine model show that the trigone has a UGS origin and should form normally (Viana et al, 2007; Mendelsohn, 2009). The trigone may not be distinguishable from the surrounding detrusor when the intramural ureter is absent. Therefore the endoscopic appearance of the trigone in this setting has led to the probable misnomer in the case of the “hemitrigone” (in association with complete ureteral agenesis) or “asymmetrical trigone” (in the presence of a partially developed ureter). Except for ectopia or malrotation, anomalies of the contralateral kidney are infrequent (Chow et al, 2005). However, abnormalities of the contralateral ureter are not uncommon, including ureteropelvic and ureterovesical junction obstruction in 11% and 7%, respectively

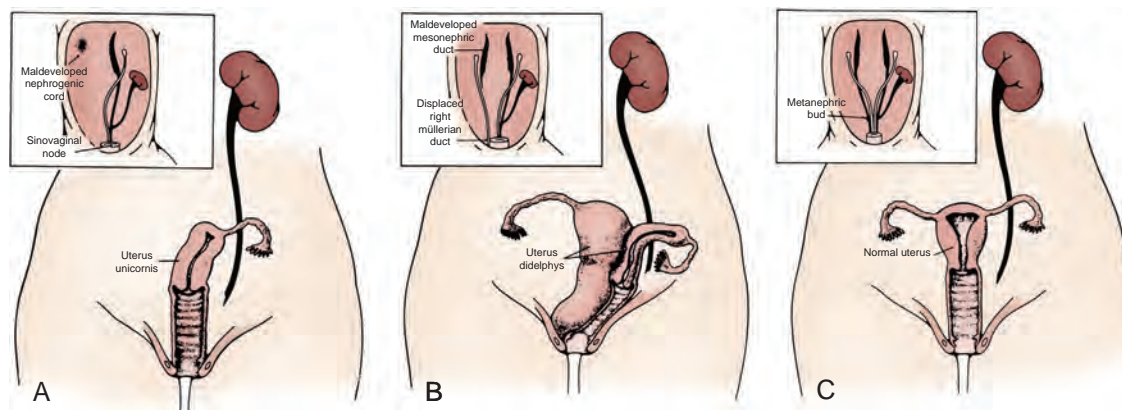


Figure 130-4. A to C, A proposed categorization of genital and renal anomalies in females. See text for details. (From Magee MC, Lucey DT, Fried FA. A new embryologic classification for uro-gynecologic malformations: the syndromes of mesonephric duct induced müllerian deformities. J Urol 1979;121:265–7.)

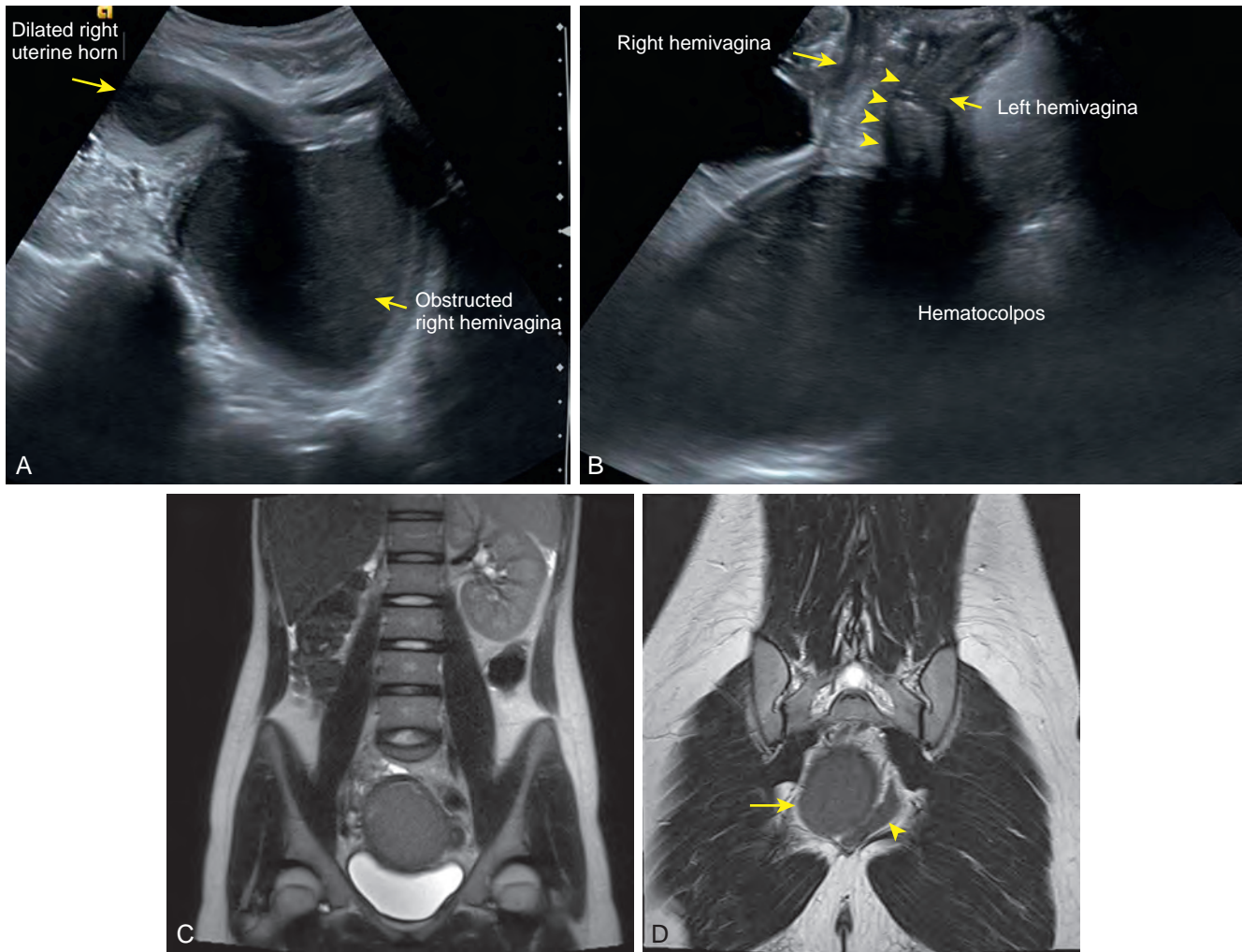


Figure 130-5. Fourteen-year-old girl with pelvic pain underwent a pelvic sonogram that shows (A) sagittal view of right hemipelvis with dilated uterine horn (arrow) and obstructed hemivagina (arrow). B, Translabial view of right hemipelvis and normal left hemivagina. A longitudinal vaginal septum is observed (arrowheads). C, Magnetic resonance imaging demonstrates coronal T2 image of right renal agenesis with bowel occupying the right renal fossa and hematocolpos. D, Coronal T2 image of right hemipelvis (arrow) and normal left hemivagina (arrowhead).

(Cascio et al, 1999), and reflux in 30% (Atiyeh et al, 1993; Cascio et al, 1999).

Although the ipsilateral adrenal gland may be flattened (Hoffman et al, 1992), adrenal agenesis occurs in fewer than 10% at autopsy (Ashley and Mostofi, 1960) and in 17% of individuals with URA undergoing a CT scan (Kenney et al, 1985) (Fig. 130-6).

Genital anomalies occur much more frequently. The incidence of a reproductive tract malformation for both genders varies from 20% to 40% (Thompson and Lynn, 1966). Despite the predominance of males with URA, reproductive tract abnormalities in females occur in at least 25% to 50% of cases compared with 10% to 15% in males. Regardless of sex, both gonads are usually normal. Therefore the different phenotypes that occur with URA may result from a primary urogenital ridge defect, which explains the finding of gonadal and adrenal agenesis in the minority of cases, or a primary defect in the development of the UB and WD, which leads to the more common cases of URA and frequently observed abnormalities of the WD, MD, and their derivatives.

Anomalies in the Male. The testis and head of the epididymis, which contain the efferent ductules derived from the mesonephric tubules, are invariably present; all structures proximal to

that point, which develop from the WD (the body and tail of the epididymis, vas deferens, seminal vesicle, ampulla, and ejaculatory duct), are absent in almost 50% (Ochsner et al, 1972). Donohue and Fauver (1989) reported 79% of adult males with an absence of the vas deferens have an absent ipsilateral kidney; left-sided lesions predominated with a ratio of 3.5:1. However, bilateral absence of the vas has been noted with URA (McCallum et al, 2001). Occasionally, the WD structures are rudimentary or ectopic rather than absent (Holt and Peterson, 1974). Ipsilateral cryptorchidism rarely occurs. A seminal vesicle cyst caused by obstruction (atresia) of the ejaculatory duct may be seen in association with ipsilateral renal agenesis, and it has been referred to as Zinner syndrome (Pereira et al, 2009). Six cases (5%) were noted among 119 boys found to have URA during ultrasound screening (Shieh et al, 1990). A pelvic sonogram or magnetic resonance imaging (MRI) in boys diagnosed with URA may demonstrate a seminal vesicle cyst (Van den Ouden et al, 1998; Seo et al, 2009) (see Fig. 130-6). In cases of seminal vesicle cysts and URA, the ureter may insert into the prostatic urethra or seminal vesicle. Cystic dysplasia of the rete testis is a rare benign condition, often associated with ipsilateral renal anomalies, most commonly URA, and it has been reported to regress spontaneously and can be

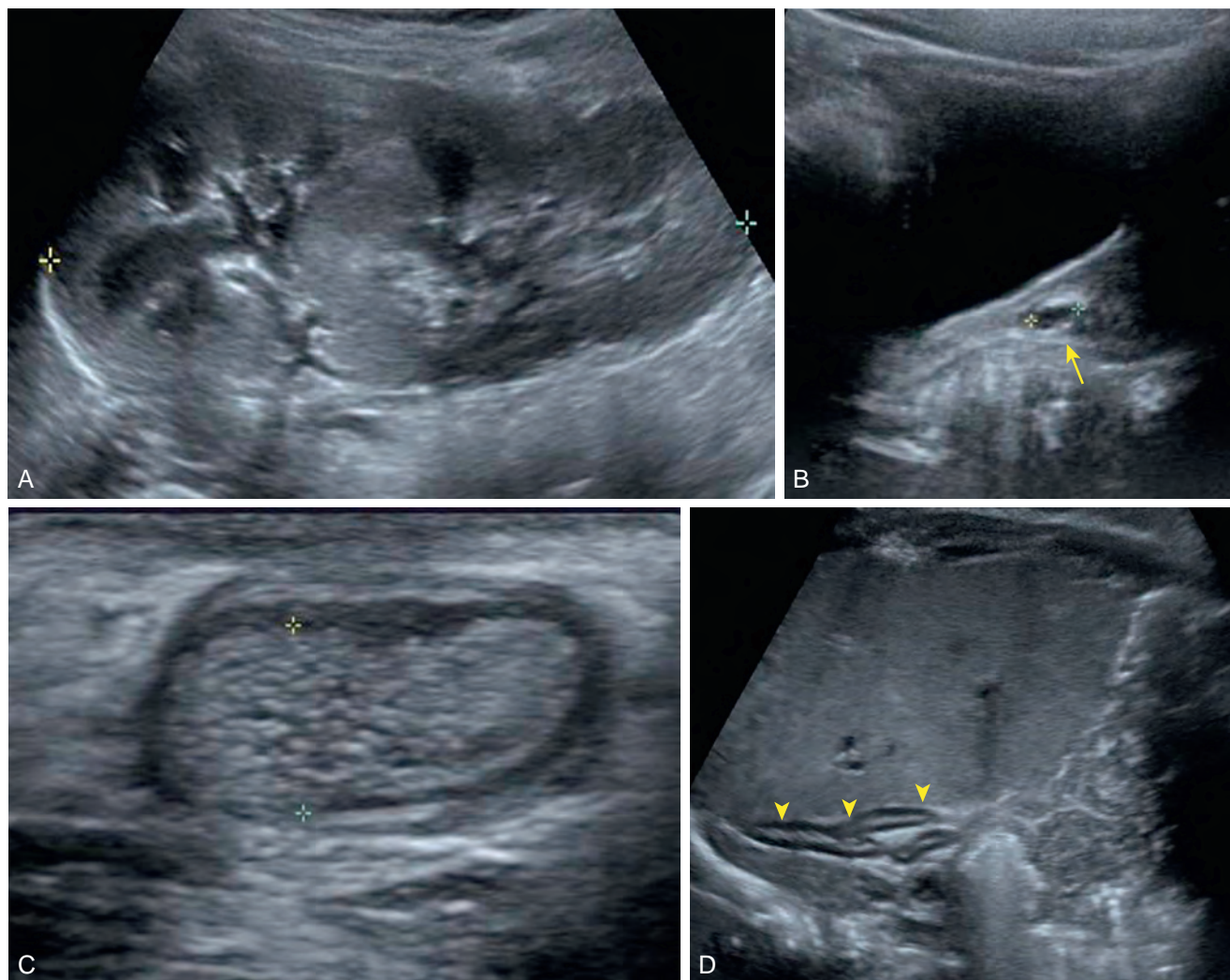


Figure 130-6. Four-year-old boy underwent left inguinal herniorrhaphy. No left vas deferens was present in the spermatic cord. **A**, Postoperative sonogram shows sagittal view of the solitary right kidney with duplicated collecting system. **B**, Sagittal view of the left seminal vesicle cyst (arrow). **C**, Sagittal view of left cystic dysplasia of the rete testis (between calipers). **D**, Sagittal view of an empty right renal fossa with a flattened or “lying down” adrenal gland in a neonate with right renal agenesis (arrowheads).

treated conservatively in the setting of WD defects (Jeyaratnam and Bakalinova, 2010) (see Fig. 130-6).

In males evaluated for infertility, the diagnosis of URA should be suspected when the vas deferens or body and tail of the epididymis are impalpable. In children, URA should be considered when vasal and/or epididymal anomalies are incidentally found at the time of scrotal ultrasonography, herniorrhaphy, or orchiopexy.

Anomalies in the Female. A variety of anomalies may result from incomplete MD formation because of alterations in normal WD development. Approximately one fourth to one third of women with URA have an abnormality relating to WD development (Thompson and Lynn, 1966; Heinonen, 2004). Conversely, 43% of women with genital anomalies have URA (Semmens, 1962; Heinonen, 1997). The most common MD anomalies are a unicornuate uterus with complete absence of the ipsilateral horn and fallopian tube or a bicornuate uterus with rudimentary development of the horn on the affected side (Candiani et al, 1997). The fimbriated end of the fallopian tube, however, is usually fully formed and is analogous to the head of the epididymis in the male (Shumacker, 1938). Partial or complete midline fusion of the MD may result in a double (didelphys) or septate uterus with either a single or a duplicated cervix. Complete duplication or separation of the vagina,

proximal vaginal atresia associated with a small introital dimple, and complete absence of the vagina have been reported (D’Alborton et al, 1981). Obstruction of one side of a duplicated system is not uncommon, and unilateral hematocolpos or hydrocolpos associated with a pelvic mass and/or pain has been described in pubertal girls and has been previously referred to as the Herlyn-Werner-Wunderlich syndrome (Yoder and Pfister, 1976; Tong et al, 2013). Smith and Laufer (2007) suggested the acronym OHVIRA to classify the syndrome of Obstructed Hemivagina and Ipsilateral Renal Anomaly (see Fig. 130-5). In rare instances, this anomalous condition has been mistaken for a large or infected Gartner duct cyst. Sometimes a Gartner duct cyst has been found in a prepubertal girl with an ectopic ureter that is blind ending proximally or one that is connected to a rudimentary kidney (Currarino, 1982). A total of 6% of girls with URA were found to have a Gartner cyst on mass screening of schoolchildren (Shieh et al, 1990). Infertility occurs in as many as 33% of affected women with renal agenesis and unicornuate uterus (Heinonen, 1997). When anomalies of the uterus, including congenital absence of the uterus, unicornuate uterus, and didelphys uterus, are found on ultrasonography or MRI, radiologic investigation of the urinary tract often demonstrates URA or other renal anomalies (Reichman and Laufer, 2010).

Another anomaly often associated with URA is the Mayer-Rokitansky-Küster-Hauser syndrome (MRKH), which is a complex of malformations occurring in 1 of 4500 newborn females (Guerrier et al, 2006; Oppelt et al, 2012; Pizzo et al, 2013). This syndrome includes not only renal anomalies, but also genital tract anomalies ranging from upper vaginal atresia to total müllerian agenesis in an otherwise phenotypically normal 46, XX female. There are two main subtypes. Type I is the typical form characterized by the finding of only symmetrical muscular buds or müllerian remnants and normal fallopian tubes. Type II, which is the more common but considered the atypical form, is characterized by asymmetrical hypoplasia of one or two buds with or without dysplasia of the fallopian tubes. Most importantly, the atypical form is often associated with renal anomalies, primarily URA, ectopia of one or both kidneys, or horseshoe kidney in about 40% to 60% (Guerrier et al, 2006). Duncan and colleagues (1979) reported on the most severe constellation of malformations and referred to this as the MURCS association or müllerian duct aplasia (96%), renal aplasia or ectopia (86%), and cardiothoracic somite dysplasia (two to four anomalous vertebrae between C5-T1 [80%]).

Anomalies of Other Organ Systems. Dursun and colleagues (2005) found that 44% of individuals with a congenital solitary kidney had various nonurologic anomalies including cardiovascular (15%), gastrointestinal (9%), neurologic (3%), and hematologic (6%).

KEY POINTS: UNILATERAL RENAL AGENESIS

- Unilateral agenesis occurs once in 1100 births.
- Males predominate with a ratio of 1.8:1.
- Absence of one kidney occurs somewhat more frequently on the left side.
- The ipsilateral ureter is completely absent in about half of the patients.
- Despite the predominance of males with URA, MD abnormalities occur in 25% to 50% of cases of females with URA compared with WD anomalies in 10% to 15% of males with URA.
- Approximately one fourth to one third of women with MD anomalies are found to have URA.
- Anomalies of other organ systems are found frequently in affected individuals. The more common sites involve the cardiovascular, gastrointestinal, and musculoskeletal systems.

Diagnosis and Radiographic Evaluation. About 90% of fetal kidneys associated with URA or MCDK undergo compensatory hypertrophy in utero from 20 weeks' gestation (Van Vuuren et al, 2012). Postnatally, a retroperitoneal ultrasonogram with color Doppler will show an absence of the kidney and ipsilateral renal vessels. The diagnosis of URA usually can be confirmed with a DMSA scan showing absent uptake of the isotope on one side, with the contralateral kidney often showing compensatory hypertrophy. A DMSA scan will also detect an ectopic (usually pelvic) or a crossed ectopic kidney in cases where the nonvisualized orthotopic kidney is thought to be absent (Volkan, 2003). In some cases, crossed fused ectopia may be difficult to distinguish from a congenital solitary kidney that has undergone compensatory hypertrophy or a solitary complete duplication. A small dysplastic kidney or MCDK may be misdiagnosed as URA when a kidney is not seen on ultrasonography (Mesrobian, 1993).

When a fetus with other suspected organ anomalies undergoes MRI, an absent kidney can be confirmed (Dell'Acqua et al, 2002). When URA is diagnosed especially in infants and young children, a voiding cystourethrogram should be performed, because there is a 28% incidence of contralateral reflux (Kaneyama et al, 2004). **Special Considerations.** The most common question many parents ask is "Will having only one kidney affect my child's

life, and will there be any restrictions on the child's activities?" Psooy (2009) summarizes several North American studies, which suggest that whereas bicycling, sledding, downhill skiing/snowboarding, and equestrian activities are the more common causes of injury, motor vehicle accidents as passenger and pedestrian result in more renal trauma than sports activities. In addition, these sports activities have more than a fivefold relative risk for head injury compared with renal injury. Psooy (2009) notes that children are generally not restricted from these activities just because they have "only one head." Rice and the Council on Sports Medicine and Fitness of the American Academy of Pediatrics (2008) advise that each athlete needs individual assessment for their particular sport and that wearing protective padding may reduce the risk of injury to the solitary kidney, thus allowing participation in most sports. Since those recommendations were proposed, Grinsell and colleagues (2012) used data from the National Athletic Trainers' Association High School Injury Surveillance Study, which calculated the rates for sport-specific injuries to select organs. Although more than 4.4 million athlete-exposures, defined as 1 athlete participating in 1 game or practice, and 23,666 injuries were reviewed, only 18 kidney injuries (3 lacerations and 15 contusions) occurred, none of which were catastrophic or required surgery.

Prognosis. In the past, there was no definitive evidence that having a congenitally solitary kidney predisposed to long-term problems when compared to outcomes of individuals undergoing nephrectomy for Wilms tumor or donor nephrectomy (Shapiro et al, 2003). It is now well recognized that the latter two groups represent completely different conditions compared to the congenitally solitary kidney group in which genetic or environmental events may have altered the development of both kidneys, impacting growth and function throughout life. The remaining kidney is thought to be healthy in living kidney donors who have lower rates of end-stage renal failure (ESRF) than the general population or those undergoing nephrectomy for tumor in childhood (Ibrahim et al, 2009).

Current Concepts Regarding Prognosis in Adults with Unilateral Renal Agenesis. Several studies examine the long-term outcome of children with a solitary functioning kidney (SFK) although there are no definitive conclusions. These studies are based on the "hyperfiltration hypothesis" of Brenner and coworkers (1996). In their rodent model, unilateral nephrectomy led to hyperfiltration of the remnant nephrons and altered sodium balance with subsequent glomerular hypertension. These hemodynamic changes resulted in glomerular damage with albuminuria and glomerulosclerosis. The hyperfiltration hypothesis may be extrapolated to individuals with SFK who have reduced nephron number especially when the solitary kidney is also affected by CAKUT (Westland et al, 2012, 2013b). CAKUT spectrum includes renal agenesis, renal hypo-/dysplasia, MCDK, ureteropelvic junction (UPJ) obstruction, megaureter, posterior urethral valves, and vesicoureteral reflux, and it occurs in 1 in about 600 births (Wiesel et al, 2005) and is found in 20% of those with chromosomal abnormalities (Game et al, 2009). About 10% of those with CAKUT have close relatives with renal abnormalities but most are asymptomatic (Bulum et al, 2013).

There is now evidence that subtle defects in UB branching can cause reduced nephron number, which may lead to renal disease later in life (Brenner and Mackenzie, 1997; Costantini and Shakya, 2006; Chevalier, 2009). In humans, there is an eightfold range in normal variation in the number of glomeruli, that is, from 200,000 to 1.8 million (Hughson, 2003). Therefore it is more likely for an individual with nephron numbers at the lower end of the spectrum to be at greater risk for renal insufficiency at any age and from any etiology. Luyckx and Brenner (2010; Luyckx et al, 2013) propose clinical surrogates for low nephron number and susceptibility to hypertension and renal disease in humans. They include low birth weight, preterm birth, short stature, reduced kidney volume by ultrasonography, low kidney mass by scintigraphy, glomerulomegaly by biopsy, gene polymorphisms (PAX2, RET), and infants of diabetic mothers.

Prenatal renal development may be affected by medications including ACE inhibitors, dexamethasone, antiepileptic medications, and aminoglycosides, as well as intrauterine growth restriction and maternal diabetes. Postnatally, nephrogenesis can affect the premature infant (age ≤ 28 weeks' gestation) when aminoglycosides and nonsteroidal anti-inflammatory agents are administered.

In the past, studies of the renal survival in children with CAKUT have been difficult to perform because they involve decades of follow-up, and the phenotypes of these disorders are not uniform (Pope et al, 1999). Sanna-Cherchi and colleagues (2009) evaluated the long-term functional outcomes in individuals with CAKUT, including those with URA from a single pediatric nephrology center. A total of 312 patients with CAKUT who had a known defect of the number or size of at least one kidney were followed up for as long as 20 years. Patients with isolated vesicoureteral reflux and duplications were excluded. Dialysis-free survival was evaluated, taking into consideration reflux, age at diagnosis, hypertension, proteinuria, and serum creatinine. Six subgroups were examined, including URA, unilateral and bilateral hypodysplasia, posterior urethral valves, MCDK, and horseshoe kidney. These investigators found that by 30 years of age, 19% of all patients were on dialysis, most of whom had posterior urethral valves, bilateral renal hypoplasia, or URA. Further analysis showed that patients with a solitary kidney had a 50% probability of requiring dialysis by 30 years of age. Notably, most of the patients with URA in this study were diagnosed during adolescence and had a normal creatinine level at the time of diagnosis. Interestingly, the patients diagnosed at birth had a slightly elevated creatinine level (0.68 mg/dL). These and other studies point to the fundamental differences in individuals with URA and adults who undergo unilateral nephrectomy. The number of nephrons in children with URA may be abnormally low, and those with fewer nephrons may be at greater risk for developing hypertension, albuminuria, and focal glomerulosclerosis.

The KIMONO (Kidney of Monofunctional Origin) study retrospectively evaluated 116 children with congenital or pSFK (primary solitary functioning kidney, 54 with URA and 62 with MCDK) and 90 children with sSFK (secondary after unilateral nephrectomy for CAKUT or tumor) (Westland et al, 2011). About 30% had ipsilateral CAKUT (the side of the SFK only) in both of these groups. Renal injury was defined as hypertension and/or albuminuria and/or the use of renoprotective medication. Of all children with SFK, 32% had renal injury at a mean age of 9.5 years. GFR declined as early as age 9, and microalbuminuria developed at about age 16. As expected, children with ipsilateral CAKUT, involving pSFK or sSFK, had more renal injury than those in either group without CAKUT. Although the results of the KIMONO study are similar to those of Sanna-Cherchi and colleagues, the study did not consider the different molecular origin(s) and clinical course of the different conditions of each patient. The estimates of renal injury and the proportion of patients who develop ESRF are most likely overestimated because of several factors including selection bias. These studies, however, underscore the importance of identifying those individuals who are more likely to progress to chronic renal failure in adulthood.

Current suggestions for children with SKF include annual assessments of blood pressure and microalbuminuria (first morning specimen) when there is no CAKUT and biannually when there is CAKUT, because hypertension and microalbuminuria (>30 mg/24 hr) are hallmarks of progressive decrease in glomerular filtration rate (Hegde and Coulthard, 2009; Westland et al, 2013a, 2014). Treatment with an ACE inhibitor may be indicated to slow the progression of renal injury (Puddu et al, 2009). Depending on the age of the patient, dietary changes may also be recommended, including limiting salt and avoiding excessive protein intake. Blood pressure, urinary albumin, and serum creatinine are monitored 2 to 4 times a year when the GFR <60 mL/min/1.73 m² or the individual is taking medication for hypertension or proteinuria (Westland et al, 2013a, 2014). In addition, periodic ultrasonography is performed for both pSFK and sSFK especially with CAKUT to assure appropriate compensatory hypertrophy and/

or growth into adolescence. For those with GFR greater than 60 mL/min/1.73 m² who are on no medication, serum creatinine can be performed every 5 years (Westland et al, 2014).

Supernumerary Kidney

The supernumerary kidney is truly an accessory organ with its own collecting system, blood supply, and distinct encapsulated parenchymal mass. Three separate kidneys can form with the third usually being smaller. The two main kidneys are commonly normal and equal in size. The supernumerary kidney may be either totally separate from the normal kidney on the same side or connected to it by loose areolar tissue (Geisinger, 1937). The ipsilateral ureters may be bifid or completely duplicated. The condition is not analogous to a single kidney with ureteral duplication in which the collecting systems drain portions of one parenchymatous mass surrounded by a single capsule.

Incidence. The true incidence of this anomaly cannot be determined because only about 100 cases have been reported (Macpherson, 1987). It affects males and females equally but has a higher predilection for the left side (N'Guessan and Stephens, 1983). Four cases of bilateral supernumerary kidneys have been reported (Oto et al, 2002).

Embryology and Molecular Mechanisms. A second UB or a branching from the initial UB appears as a necessary first step. Next, the nephrogenic anlage may divide into two metanephric tails, which separate entirely when induced to differentiate by the separate or bifid UBs (N'Guessan and Stephens, 1983). The two metanephroi develop only after being penetrated by the bifid or separate UBs.

Kidney development is initiated when a single UB forms from the WD in response to GDNF secreted by the adjacent MM. Posterior restriction of *Gdnf* expression is critical for the development of a UB in the normal position, whereas another intercellular signaling system, including SLIT2 or its receptor ROBO2, is also important in ensuring that a single UB forms in the appropriate location. Grieshammer and colleagues (2004) showed that mutant mice lacking either SLIT2 or its receptor ROBO2 develop supernumerary UBs that are correlated with abnormal maintenance of *Gdnf* expression in anterior MM. The SLIT2/ROBO2 intercellular signaling system restricts, directly or indirectly, the extent of the *Gdnf* expression and plays a critical role in precisely positioning the site of kidney induction.

Description and Associated Anomalies. The supernumerary kidney is a distinct renal mass that may be either completely separate or only loosely attached to the major kidney on the ipsilateral side. In about 60% of cases, it is located caudad to the dominant kidney, which is in its orthotopic position in the renal fossa. When a separate and distinct ureter is present, the supernumerary kidney is more likely to be cranial to the dominant kidney but caudal to the adrenal (Bernik et al, 2001) (Fig. 130-7).

KEY POINTS: SUPERNUMERARY KIDNEY

- The supernumerary kidney is a definitive accessory organ with its own collecting system, blood supply, and distinct encapsulated parenchyma.
- The supernumerary kidney may be either completely separate or loosely attached to the kidney on the ipsilateral side.
- The ureteral interrelationships on the side of the supernumerary kidney can be variable.

The supernumerary kidney is reniform but generally smaller than the main ipsilateral kidney. In almost half of reported cases, the collecting system is severely dilated with thin parenchyma suggesting obstruction. The ipsilateral and contralateral kidneys are usually normal.

The ureteral interrelationships on the side of the supernumerary kidney can be variable. Convergence of the ipsilateral ureters distally to form a common stem and a single ureteral orifice occurs

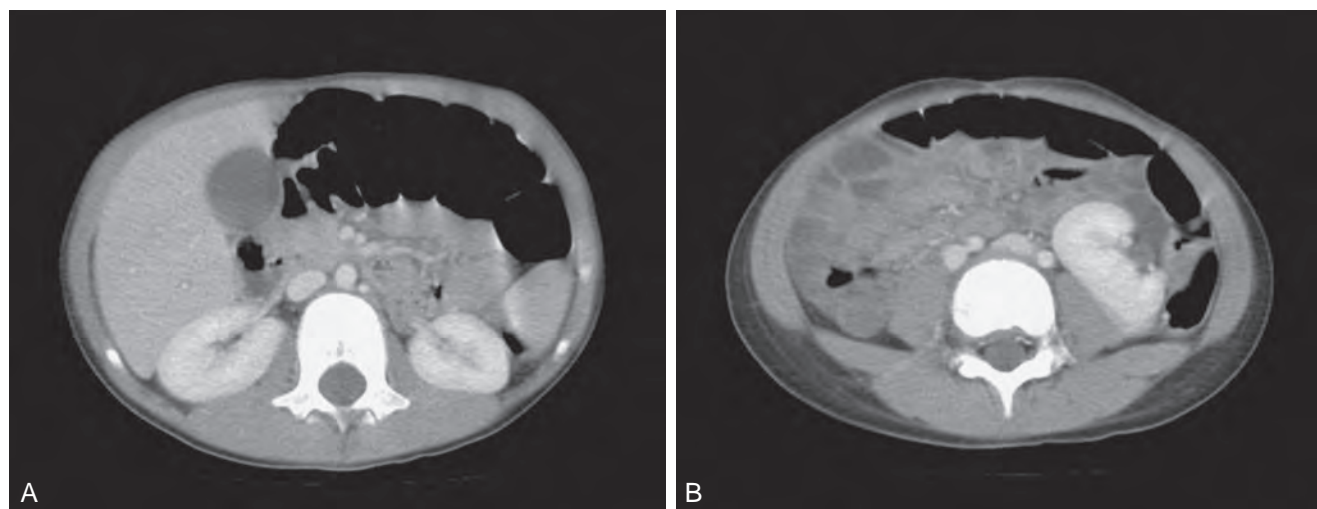


Figure 130-7. Contrast computed tomography scan showing (A) right and left orthotopic kidneys. B, Right midabdominal malrotated supernumerary kidney.

in 50% of the cases (N'Guessan and Stephens, 1983), which suggests "a bud off of a bud" situation. Two completely independent ureters, each with its own entrance into the bladder, are seen in the other 50% of cases. The Weigert-Meyer principle is usually followed, but in 10% of cases, the caudal kidney has a ureter that does not follow the rule and enters the trigone below the ipsilateral ureter (Tada et al, 1981) (Fig. 130-8 on the Expert Consult website). Individual case reports have described calyceal communications between the supernumerary and the dominant kidney, or fusion of the dominant kidney's ureter with the pelvis of the supernumerary kidney (Kretschmer, 1929) to create a single distal ureter that then enters the bladder (Fig. 130-9 on the Expert Consult website). The vascular supply to the supernumerary kidney is anomalous, depends on its position in relation to the major ipsilateral kidney, and should be separate to be considered a true supernumerary kidney (Kaneoya et al, 1989).

Symptoms. This anomaly is rarely symptomatic but it may become symptomatic in early adulthood. The average age at diagnosis was 36 years. Pain, fever, hypertension, and a palpable abdominal mass are the usual presenting complaints. Urinary infection, obstruction, or both, are the major conditions that lead to evaluation. Ureteral ectopia from the supernumerary kidney may produce urinary incontinence, but this is extremely rare. A palpable abdominal mass secondary to a carcinoma in the supernumerary kidney has been described in two patients. In 25% of all reported cases, the supernumerary kidney is discovered only at autopsy (Carlson, 1950).

Diagnosis. If the supernumerary kidney is normal and asymptomatic, it is usually diagnosed when radiographic studies are performed for other reasons. The kidney may be inferior and distant enough from the ipsilateral kidney so that it does not alter the position of the normal kidney (Conrad and Loes, 1987). If it is in close proximity, it may displace the predominant kidney or its ureter very slightly.

A supernumerary kidney may become symptomatic because of obstruction from a stone (Koureas et al, 2000). In this case, ultrasonography may demonstrate distortion of the normal ipsilateral kidney and ureter. If the collecting system is bifid, the dominant kidney on that side will usually be involved in the same disease process. If the ureters are separate, the ipsilateral kidney may show the effects of an abnormal supernumerary kidney. Magnetic resonance urography (MRU) and retrograde pyelography may be needed to delineate the anomaly. Radionuclide imaging provides information about relative function in the supernumerary and the normal kidneys (Conrad and Loes, 1987). Cystoscopy reveals one or two ureteral orifices on the ipsilateral side, depending on whether the ureters are completely duplicated. Ureteral ectopia may exist in or

outside of the bladder. Occasionally, a supernumerary kidney is not accurately diagnosed until the time of surgery or at autopsy, or it may mimic a duplication (Kaneoya et al, 1989).

ANOMALIES OF ASCENT

Simple Renal Ectopia

When the mature kidney fails to reach its normal location in the "renal" fossa, the condition is known as *renal ectopia*. The term is derived from the Greek words *ek* ("out") and *topos* ("place"), and it literally means "out of place." It is to be differentiated from renal ptosis, in which the kidney initially is located in its proper place (and has normal vascularity) but moves downward in relation to body position. The ectopic kidney has never resided in the appropriate location. An ectopic kidney can be found in one of the following positions: pelvic, iliac, abdominal, thoracic, and contralateral or crossed (Fig. 130-10 on the Expert Consult website).

Incidence. The actual incidence among autopsy series varies from 1 in 500 (Campbell, 1930) to 1 in 1200 (Bell, 1946a), with an average occurrence of about 1 in 900 with no significant difference between the sexes (Abeshouse and Bhisitkul, 1959). Clinically, renal ectopia is more commonly diagnosed in females because they are more apt to undergo urologic evaluation for urinary tract infection (UTI) and/or associated genital anomalies (Thompson and Pace, 1937).

The left side is favored slightly over the right. Pelvic ectopia has been estimated to occur in 1 of 2100 to 3000 autopsies (Stevens, 1937). A solitary ectopic kidney occurs in 1 of 22,000 autopsies (Delson, 1975). By 1973, only 165 cases of a solitary pelvic kidney had been recorded (Downs et al, 1973). Bilateral ectopic kidneys are more rarely observed and account for only 10% of all patients with renal ectopia (Malek et al, 1971) (see Fig. 130-10 on the Expert Consult website).

Embryology. The UB, arising from the WD at the end of the fourth week, grows craniad toward the urogenital ridge, acquiring a cap of metanephric blastema by the fifth week. The developing metanephric tissue and UB migrate cephalad, rotating medially on its long axis. The entire process is completed by 8 weeks' gestation. Factors that may prevent the orderly ascent and rotation of the kidneys include UB maldevelopment (Campbell, 1930), defective metanephric tissue that fails to induce ascent (Ward et al, 1965), genetic abnormalities, and maternal illnesses or teratogenic causes (Malek et al, 1971). A vascular barrier that prevents upward migration secondary to persistence of the fetal blood supply has also been postulated (Baggenstoss, 1951), but the existence of an "early" renal blood supply does not prevent the

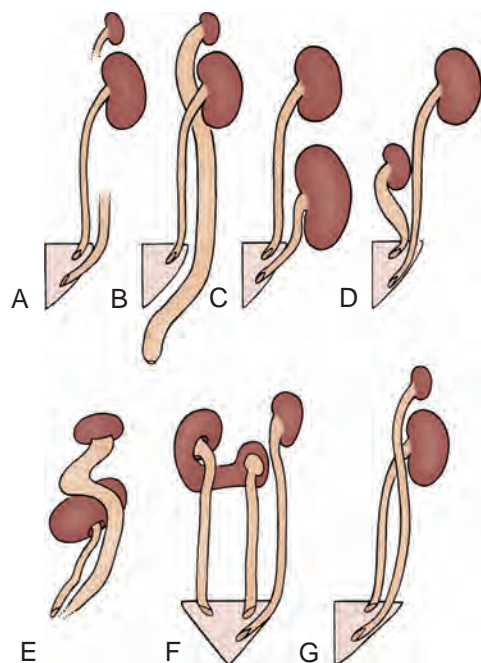


Figure 130-8. A to G, Various patterns of urinary drainage of supernumerary and ipsilateral kidneys when ureters are completely separated. All kidney positions are relative only and are depicted on the left side for ease of interpretation. *Dashed lines* indicate that detail was not defined. (From N'Guessan G, Stephens FD. Supernumerary kidney. *J Urol* 1983;130:649–53.)

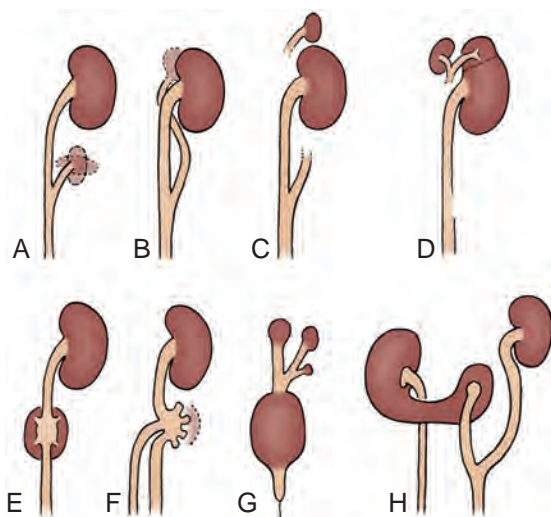


Figure 130-9. A to H, Various patterns of urinary drainage when ureters form a common stem. All kidney positions are relative only and are depicted on the left side for ease of interpretation. *Dashed lines* indicate that detail was not defined. (From N'Guessan G, Stephens FD. Supernumerary kidney. J Urol 1983;130:649–53.)

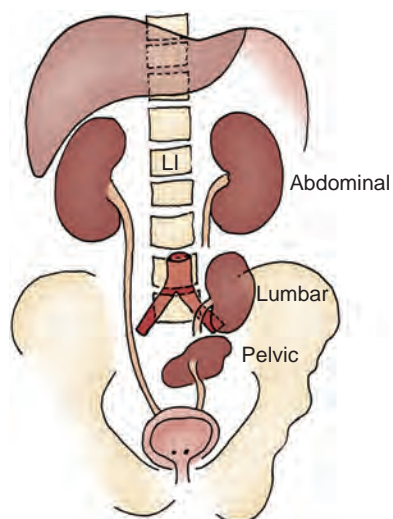


Figure 130-10. Incomplete ascent of kidney. The kidney may halt at any level of its ascent from the pelvis. (From Gray SW, Skandalakis JE. The kidney and ureter. In: Gray SW, Skandalakis JE, editors. Embryology for surgeons. Philadelphia: Saunders; 1972.)

affected kidney's movement to its ultimate position. This is probably the result, not the cause, of renal ectopia.

Description and Associated Anomalies. The classification of ectopia is based on the position of the kidney within the retroperitoneum. The pelvic kidney opposite the sacrum and the kidneys below the aortic bifurcation are the most common sites of ectopia; the lumbar kidney resides near the sacral promontory in the iliac fossa and anterior to the iliac vessels, and the abdominal kidney is above the iliac crest and is adjacent to the second lumbar vertebra (see Fig. 130-10 on the Expert Consult website).

The ectopic kidney is usually smaller, and because of fetal lobulations it may not conform to the usual reniform shape. The axis of the kidney is slightly medial or vertical, but it may be tilted as much as 90 degrees laterally so that it lies in a true horizontal plane. The renal pelvis is usually anterior (instead of medial) to the parenchyma, because the kidney has incompletely rotated. As a result, 56% of ectopic kidneys have a hydronephrotic collecting system. Half of these cases are a result of obstruction of the ureteropelvic or the ureterovesical junction (70% and 30%, respectively), 25% from reflux grade III or greater, and 25% from the malrotation alone (Gleason et al, 1994). Reflux has been found in 30% of children with ectopic kidneys (Guarino et al, 2004) (Fig. 130-11).

The length of the ureter usually conforms to the position of the kidney; the ureter is occasionally slightly tortuous but it is rarely redundant. The ureter usually enters the bladder on the ipsilateral side with its orifice positioned normally, except for those unusual cases with ectopic ureters (Borer et al, 1998). The arterial and venous network is anomalous and its vascular pattern depends on the ultimate position of the kidney (Anson and Riba, 1939). There may be one or two main renal arteries arising from the distal aorta or from the aortic bifurcation, with one or more aberrant arteries emanating from the common or external iliac or even the inferior mesenteric artery. The kidney may be supplied entirely by multiple anomalous branches, none of which arise from the aorta. In no instance has the main renal artery arisen from the level of the aorta that would be its proper origin if the kidney were positioned normally.

Although the contralateral kidney is usually normal, it is associated with a number of congenital defects. Malek and colleagues (1971) and Thompson and Pace (1937) reported the incidence of contralateral agenesis to be high (Chow et al, 2005). Bilateral ectopia occurs infrequently (10%) (see Fig. 130-11).

KEY POINTS: SIMPLE RENAL ECTOPIA

- The left side is affected slightly more than the right.
- Pelvic ectopia has been estimated to occur in 1 of 2100 to 3000 autopsies.
- Fifty-six percent of ectopic kidneys have a hydronephrotic collecting system. Half of these cases result from obstruction at the ureteropelvic or the ureterovesical junction (70% and 30%, respectively), 25% from reflux grade III or greater, and 25% from the malrotation alone.
- Vesicoureteral reflux has been found in 30% of children with ectopic kidneys.
- The incidence of genital anomalies in the patient with ectopia is about 15%.
- Most ectopic kidneys are clinically asymptomatic, except in cases of associated ectopic ureter.

The most striking feature of renal ectopia is the association of genital anomalies. The incidence varies from 15% (Thompson and Pace, 1937) to 45% (Downs et al, 1973). Twenty percent to 66% of females have one or more of the following abnormalities of the reproductive organs: bicornuate or unicornuate uterus with atresia of one horn (McCrea, 1942), rudimentary or absent uterus and proximal and/or distal vagina (D'Alborton et al, 1981), and duplication of the vagina. Among male patients, 10% to 20% have a recognizable associated genital defect; undescended testes, duplication of the urethra, and hypospadias are the most common

(Thompson and Pace, 1937). Fourteen percent of patients with a cloacal malformation have an ectopic kidney (Dursun et al, 2005).

Rarely is the adrenal gland absent or abnormally positioned. A total of 21% of individuals exhibit anomalies of other organ systems (Downs et al, 1973); most involve the skeletal or cardiac systems.

Diagnosis. With the increasing use of various imaging modalities, the incidence of ectopic kidneys is increasing although most ectopic kidneys are asymptomatic. Vague abdominal complaints or ureteral colic secondary to an obstructing stone are the most frequent symptoms leading to the diagnosis of an ectopic kidney. The abnormal position of the kidney results in a pattern of direct and referred pain that is atypical for colic and may be misdiagnosed as acute appendicitis or as pelvic inflammatory disease in female patients. Symptoms rarely occur because of organs that are adjacent to the ectopic kidney. Renal ectopia may also present with a UTI or a palpable abdominal mass. Seven cases of concomitant renal and ureteral ectopia presenting with urinary incontinence have been reported (Borer et al, 1998). Diagnosis may be difficult because of the diminished function of some ectopic kidneys. The kidneys may be very small and/or dysplastic with essentially no function, leading to the misdiagnosis of URA. Both DMSA scanning and/or MRU may be necessary to diagnose these unusual cases (Borer et al, 1998).

The diagnosis of an ectopic lumbar or pelvic kidney is made when the renal sonogram fails to show a kidney in its orthotopic location and when power color Doppler delineates the main renal artery and intrarenal vasculature of the ectopic kidney.

Cystoscopy, when performed, will demonstrate ureteral orifices that are invariably normal unless the ureteral orifice is also ectopic. If surgery is indicated on an ectopic kidney, MR arteriography may be useful preoperatively to define the anatomy of the renal vasculature, especially in cases of solitary ectopia.

Prognosis. The ectopic kidney is no more susceptible to disease than the orthotopic kidney, except for the development of hydronephrosis or stones (Gleason et al, 1994; Benchekroun et al, 2002). This may be a result of the anteriorly placed pelvis and malrotation of the kidney, which may impair drainage of urine from a high insertion of the ureter to the pelvis or anomalous vasculature that partially obstructs one of the major calyces or the upper ureter. In addition, there may be an increased risk of injury from blunt abdominal trauma, because the low-lying kidney is not protected by the rib cage.

Van den Bosch and colleagues (2010) examined the urologic and nephrologic consequences of both simple and crossed renal ectopia. They found no adverse effects on blood pressure or kidney function during childhood. They did note that although global renal function of these kidneys was normal, the relative function of the ectopic kidney on DMSA scan was 38%.

Anderson and Harrison (1965), in a review of pregnant women with renal ectopia, found no increased occurrence of maternal or fetal complications related to the ectopic kidney (Anderson and Harrison, 1965; Delson, 1975). Dystocia from a pelvic kidney is rare but may require cesarean section. Although three cases of cancer in an ectopic kidney have been reported, there is no increased risk for malignancy. Before modern imaging, in at least five instances solitary ectopic kidneys were mistaken for pelvic malignancies and were removed (Downs et al, 1973).

Cephalad Renal Ectopia

The kidney may be positioned more craniad than normal when there is an omphalocele (Pinckney et al, 1978). When the liver herniates into the omphalocele with the intestines, the kidneys continue to ascend until the diaphragm arrests their ascent. Both kidneys are ectopic and are positioned immediately beneath the diaphragm at the level of the 10th thoracic vertebra. The ureters were excessive in length but were otherwise normal. A color Doppler sonogram or MR arteriography demonstrates that the origin of each renal artery is more cephalad than normal. Patients usually have no symptoms caused by malposition, and urinary drainage is not impaired.

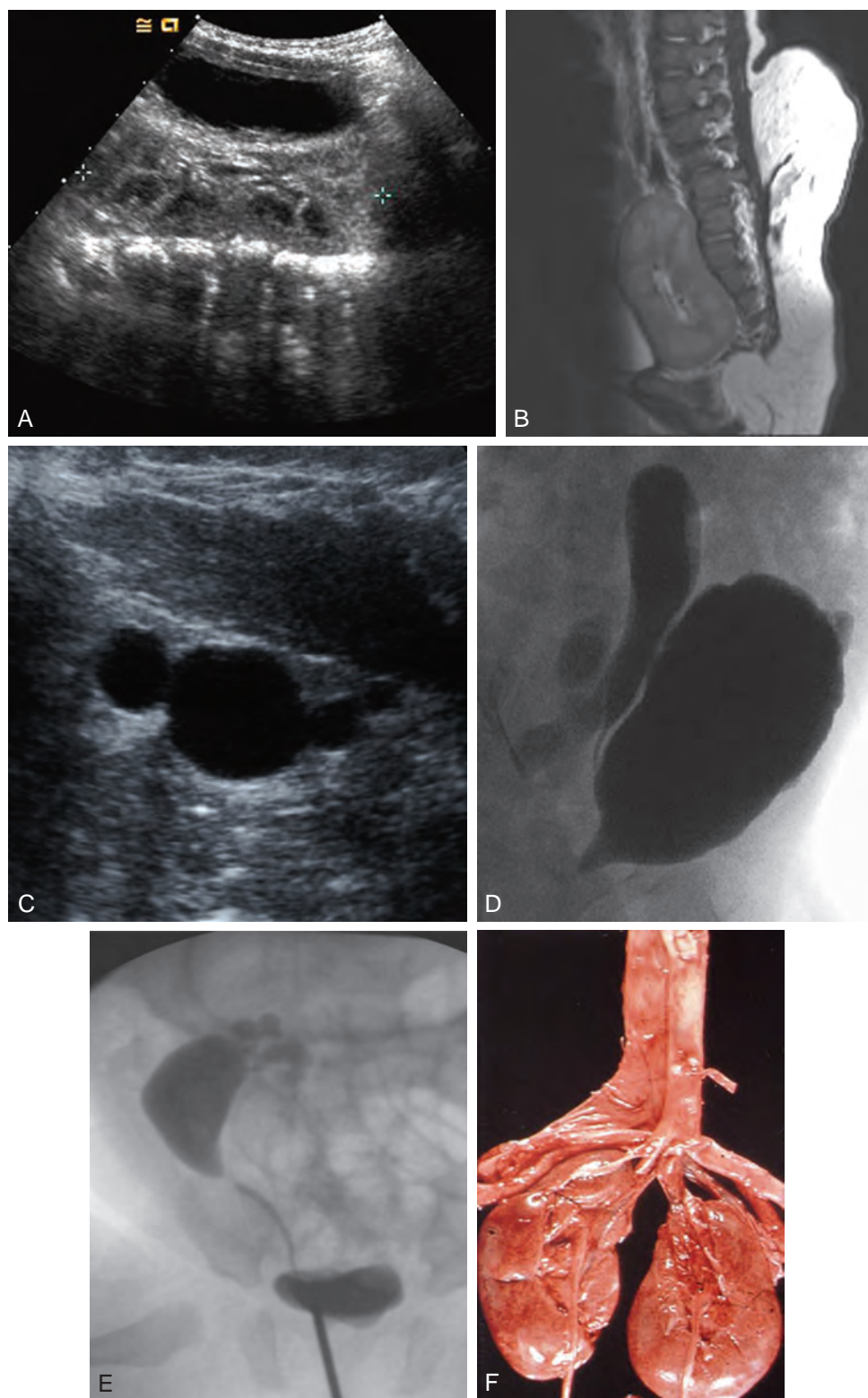


Figure 130-11. One-day-old boy with a right retrovesical pelvic kidney demonstrated on (A) transverse sonogram of right pelvis. B, Sagittal magnetic resonance image. Vertebral abnormalities and a portion of a lipomyelomeningocele are also observed. C, Longitudinal sonogram of left multicystic dysplastic pelvic kidney. D, Voiding cystourethrogram shows reflux into dilated, tortuous right megaureter. E, Right retrograde pyelogram shows malrotated ectopic kidney with ureteropelvic junction obstruction in another infant. F, Postmortem specimen from a different case showing bilateral pelvic ectopia, anterior orientation of renal pelves, and anomalous blood supply from the aortic bifurcation. (C, Courtesy Dr. Sara Milla; F, from Weiss MA, Mills SE. Atlas of genitourinary tract disorders. Philadelphia: JB Lippincott; 1988.)

Thoracic Kidney

Intrathoracic ectopia denotes either a partial or a complete protrusion of the kidney above the level of the diaphragm into the posterior mediastinum (Fig. 130-12). It is the rarest form of renal ectopia; fewer than 5% of patients with ectopia have an intrathoracic kidney, with an incidence of 1:13,000 at autopsy (Campbell, 1930).

Incidence. At least 200 patients with a thoracic kidney have been reported (Lacasta Garcia et al, 1999), four of whom had bilateral thoracic kidneys (Liddell et al, 1989). There appears to be a slight left-sided predominance of 1.5:1, and the sex ratio favors males by 2:1 (Lozano and Rodriguez, 1975). This entity has been found on prenatal ultrasonography (Masturzo et al, 2001) and in all age groups, but it is most commonly detected in adults undergoing chest radiography for other reasons (Drop et al, 2003) (see Fig. 130-12).

Embryology. The kidney reaches its final location by the end of 8 weeks' gestation. At this time, the diaphragmatic leaflets are formed as the pleuroperitoneal membrane separates the pleural from the peritoneal cavity. Mesenchymal tissues associated with this membrane eventually form the muscular component of the diaphragm. It is uncertain whether delayed closure of the diaphragmatic anlage allows for protracted renal ascent above the level of the future diaphragm or whether the kidney overshoots its usual position because of accelerated ascent before normal diaphragmatic closure (N'Guessan and Stephens, 1984). Delayed involution of mesonephric tissue has been proposed as a causative factor (Angulo et al, 1992), because intrathoracic kidneys occur in only 0.25% of patients with a diaphragmatic hernia (Donat and Donat, 1988). Renal angiography has demonstrated either a normal site (Lundius, 1975) or a more cranial origin (Franciskovic and Martincic, 1959) of the renal artery from the aorta supplying the thoracic kidney (see Fig. 130-12).

Description. The kidney is situated in the posterior mediastinum and usually has completed the normal rotation process. The renal contour and collecting system are normal. The kidney usually lies in the posterolateral aspect of the diaphragm in the foramen of Bochdalek. At this point, the diaphragm thins out and a flimsy membrane surrounds the protruding portion of kidney. Therefore the kidney is not within the pleural space (N'Guessan and Stephens, 1984). The lower lobe of the adjacent lung may be hypoplastic secondary to compression by the kidney mass. The renal vasculature and the ureter enter and exit from the pleural cavity through the foramen of Bochdalek.

Associated Anomalies. The ureter is elongated to accommodate the excessive distance to the bladder. N'Guessan and Stephens (1984) determined that the adrenal gland typically occupies its normal location and the contralateral kidney is usually normal. No consistent anomalies have been described in other organ systems.

Symptoms. The vast majority of affected individuals are asymptomatic. Flank pain was the presenting symptom in a case of UPJ obstruction in a thoracic kidney (Hampton and Borden, 2002). The case depicted in Figure 130-12 shows severe hydronephrosis of a previously normal thoracic kidney, presumably caused by intermittent obstruction by the muscular fibers of the diaphragm (Shapiro, personal communication, 2000).

Diagnosis. The diagnosis is commonly made after a routine chest radiograph shows the affected hemidiaphragm slightly elevated. A smooth, rounded mass is seen extending into the chest near the midline on an anteroposterior film and along the posterior aspect of the diaphragmatic leaflet on a lateral view (see Fig. 130-12). A thoracic kidney may be found at the time of thoracotomy for a suspected mediastinal tumor (DeNoronha et al, 1974). CT or MRU is currently the imaging modality of choice.

Prognosis. Neither autopsy series nor clinical reports suggest that a thoracic kidney will usually cause serious urinary or pulmonary complications.

ANOMALIES OF FORM AND FUSION

Crossed Renal Ectopia with and without Fusion

When a kidney is located on the side opposite that in which its ureter inserts into the bladder, the condition is known as *crossed ectopia*. Ninety percent of crossed ectopic kidneys are fused to their ipsilateral mate. Except for horseshoe kidney, they account for the majority of fusion defects. Fusion anomalies are usually diagnosed in children as part of a constellation of malformations, in young adults during evaluation for delayed menarche, and in the elderly as incidental findings (Glodny et al, 2008).

Fusion anomalies of the kidney were categorized as crossed ectopia with fusion, crossed ectopia without fusion, solitary crossed ectopia, and bilaterally crossed ectopia (McDonald and McClellan, 1957) (Fig. 130-13). The fusion anomalies have been designated as (1) unilateral fused kidney with inferior ectopia; (2) sigmoid, or S-shaped; (3) lump or cake; (4) L-shaped, or tandem; (5) disc, shield, or doughnut; and (6) unilateral fused kidneys with superior ectopia (Fig. 130-14 on the Expert Consult website).

Incidence. Abeshouse and Bhisitkul (1959) reported almost 500 cases of crossed ectopia with and without fusion that presented primarily with clinical symptoms. Glodny and colleagues (2008) reported on 24 crossed fused ectopia found on a CT scan performed for nonurologic indications.

Sixty-two patients with crossed ectopia without fusion have been reported (Winram and Ward-McQuaid, 1959). This represents approximately 10% of all crossed ectopic kidneys (Lee, 1949). The anomaly occurs more commonly in males with a ratio of 2:1, and left-to-right ectopia is seen three times more frequently than right-to-left ectopia (Lee, 1949).

Solitary crossed ectopia has been reported in 34 patients (Miles et al, 1985; Gu and Alton, 1991). Males predominate with a ratio of 2:1. The crossed ectopia involves migration of the left kidney to the right side with absence of the right kidney, rather than the reverse, with a ratio of almost 2:1 (Takei et al, 1976). In most cases, the kidney fails to ascend and rotate completely. The left-to-right crossed kidney is rarely a MCDK. Bilateral crossed renal ectopia has been described in five patients (Abeshouse and Bhisitkul, 1959) and is considered the rarest form. Abeshouse and Bhisitkul (1959) compiled 443 reports of crossed ectopia with fusion and estimated its occurrence at 1 in 1000 live births. This figure varies with the type of fusion anomaly; the **unilaterally fused kidney with inferior ectopia is the most common variety**, whereas fusion with superior ectopia is the least common. The autopsy incidence has been

Figure 130-12. One-year-old girl with febrile urinary tract infection. **A**, Intravenous pyelogram shows a right thoracic kidney (arrow) and left orthotopic kidney. She was found to have bilateral vesicoureteral reflux and underwent bilateral ureteral reimplants. At age 16, she developed right back pain and chest tightness. **B**, Chest radiograph demonstrates right diaphragmatic eventration and a right intrathoracic kidney (arrow). **C**, Magnetic resonance urogram shows coronal T1 fat saturation after contrast images of poorly functioning right hydronephrotic kidney located superior to the liver and inferior to the right lung with absence of the posterior right hemidiaphragm, permitting the colon to enter the right hemithorax. **D**, Angiographic sequence demonstrating right renal artery (arrow) arising from the aorta at the normal level of the left renal artery coursing superiorly to enter the right renal hilum. **E**, Intraoperative right retrograde pyelogram shows narrowing at the ureteropelvic junction. (A, Courtesy Dr. Terry Hensle.)

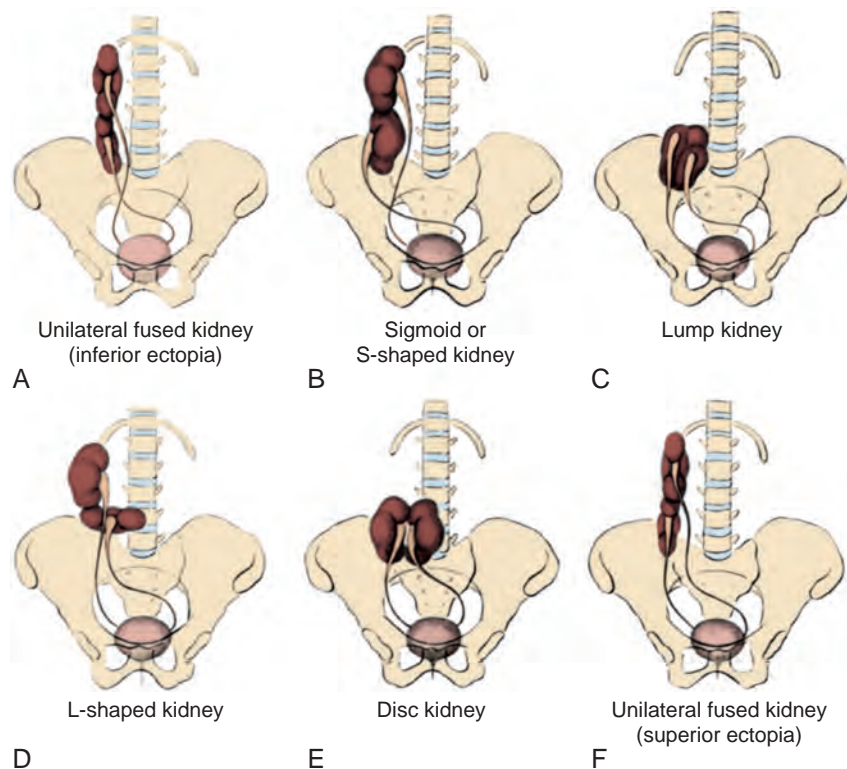
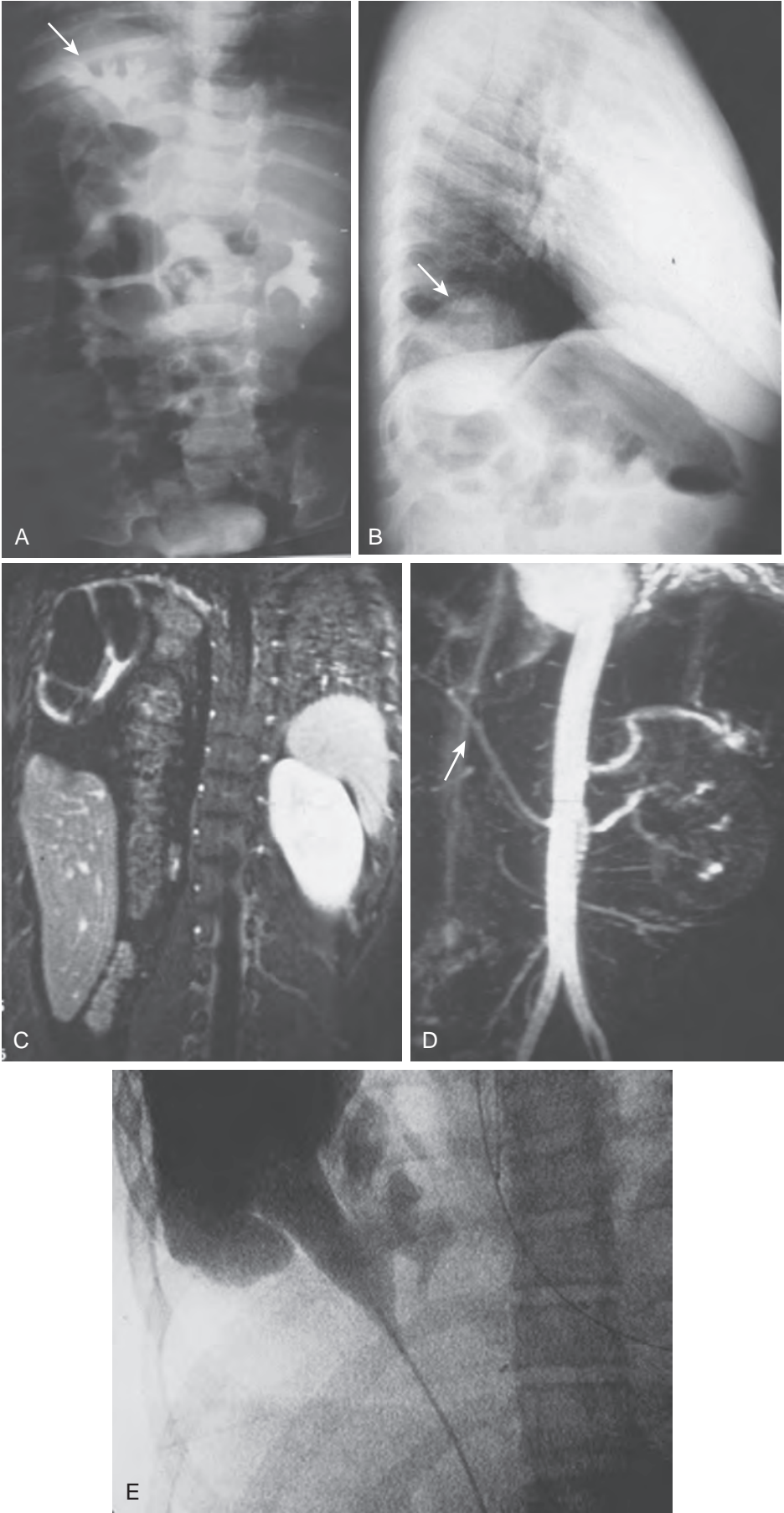


Figure 130-14. A to F, Six forms of crossed renal ectopia with fusion.



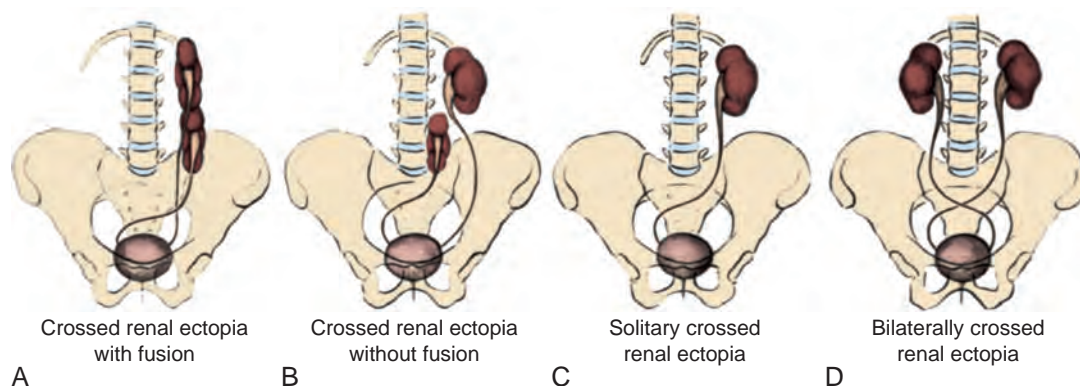


Figure 130-13. A to D, Four types of crossed renal ectopia.

calculated at 1 in 2000 (Baggenstoss, 1951). There is a slight male predominance (3:2), and a left-to-right crossover occurs somewhat more frequently than its counterpart.

Embryology. The UB enters the metanephric blastema adjacent to the anlage of the lumbosacral spine. During the next 4 weeks, the developing kidney is at the level of the L1-L3 vertebrae. Because the mechanisms responsible for complete ascent of the kidney are unknown, the cause of crossed ectopia is also unknown.

Cook and Stephens (1977) postulated that crossover is the result of malalignment and abnormal rotation of the caudal end of the developing fetus, with the distal curled end of the vertebral column being displaced to one side or the other. As a result, either the cloaca and WD structures lie to one side of the vertebral column, allowing one ureter to cross the midline and enter the opposite nephrogenic blastema, or the kidney and ureter are transplanted to the opposite side of the midline during "normal" renal ascent (Hertz et al, 1977; Maizels and Stephens, 1979).

Kelalis and colleagues (1973) implicated teratogenic factors after they noted an increased incidence of associated genitourinary and other organ system anomalies. Finally, genetic influences may play a role, because familial inheritance of crossed renal ectopia has been reported (Rinat et al, 2001).

Fusion of the metanephric masses may occur when the renal anlagen are still in the true pelvis before or at the start of cephalad migration, or it may occur during the latter stages of ascent. The extent of fusion is determined by the proximity of the developing renal anlagen to one another. After fusion, midline retroperitoneal structures, the aortic bifurcation, the inferior mesenteric artery, and the base of the small bowel mesentery impede the advancement of the kidneys toward their normal location (Joly, 1940).

Description. Fusion of a crossed ectopic kidney is related to the time it comes in contact with its mate. The crossed kidney usually lies caudad to its normal counterpart on that side. It is likely that migration of each kidney begins simultaneously, but ascent of the ectopic renal unit lags behind because of crossover time. Therefore it is the superior pole of the ectopic kidney that usually joins with the inferior aspect of the normal kidney. Ascent continues either until the uncrossed kidney reaches its normal location or until one of the retroperitoneal structures prevents further migration of the fused mass. The final shape of the fused kidneys depends on the time and extent of fusion and the degree of renal rotation that has occurred. No further rotation is likely after the two kidneys have joined. An anteriorly placed pelvis suggests early fusion, whereas a medially positioned renal pelvis indicates that fusion probably occurred after rotation was completed.

Ninety percent of crossed ectopic kidneys are fused with their mate. When they are not fused, the uncrossed kidney usually resides in its normal dorsolumbar location with proper orientation, whereas the ectopic kidney is inferior and is in either a diagonal or a horizontal position with an anteriorly placed renal pelvis. A variable distance usually separates the two kidneys, and its own capsule

of Gerota fascia surrounds each. In every case of crossed ectopia without fusion, the ureter from the normal kidney enters the bladder on the same side, and that of the ectopic kidney crosses the midline at the pelvic brim and enters the bladder on the contralateral side (Fig. 130-15).

In cases of solitary crossed ectopia, the kidney is usually located somewhat low but in the opposite renal fossa at the level of L1-L3 and is oriented anteriorly, having incompletely rotated on its vertical axis (Purpon, 1963). When the kidney remains in the pelvis or ascends only to the lower lumbar region, it may assume a horizontal lie with an anteriorly placed pelvis because it has failed to rotate fully (Trabisky and Bhisitkul, 1965). The ureter crosses the midline above the S2 vertebra and enters the bladder on the opposite side (Gu and Alton, 1991). The contralateral ureter, if present, is often rudimentary (Caine, 1956). Bilateral crossed ectopia may have normal-appearing kidneys and renal pelves, but the ureters cross the midline at the level of the lower lumbar vertebrae (Abeshouse and Bhisitkul, 1959).

KEY POINTS: CROSSED RENAL ECTOPIA WITH AND WITHOUT FUSION

- When a kidney is located on the side opposite that in which its ureter inserts into the bladder, the condition is known as crossed ectopia.
- Ninety percent of crossed ectopic kidneys are fused with their mate; the superior pole of the ectopic kidney usually joins with the inferior aspect of the normal kidney.
- In all the types of fusion anomalies, the ureter from each kidney is usually orthotopic.
- The highest incidence of associated anomalies occurs in children with solitary renal ectopia and involves both the skeletal system and genital organs.

Inferior Ectopic Kidney. Two thirds of all unilaterally fused kidneys involve inferior ectopia. Both renal pelves are anterior, so fusion probably occurs relatively early.

Sigmoid, or S-Shaped, Kidney. The sigmoid, or S-shaped, kidney is the second most common anomaly of fusion. The crossed kidney is inferior, with the two kidneys fused at their adjacent poles. Fusion of the two kidneys occurs relatively late, after complete rotation on the vertical axis has occurred. Therefore each renal pelvis is oriented correctly, and they face in directions opposite from one another. The lower convex border of one kidney is directly opposite the outer border of its counterpart, creating an S-shaped appearance to the entire renal outline. The ureter from the normal kidney courses downward anterior to the outer border of the inferior kidney, and

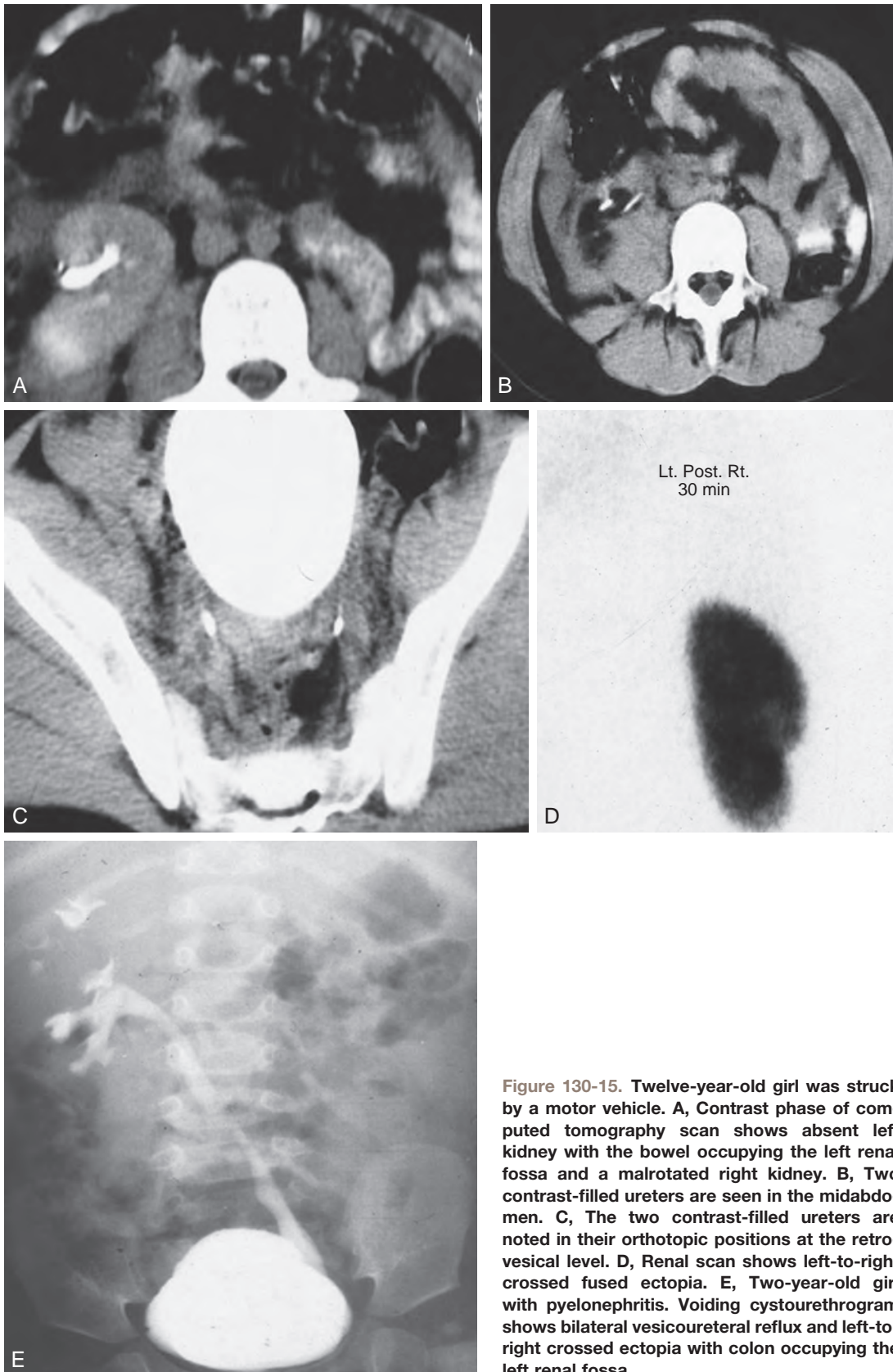


Figure 130-15. Twelve-year-old girl was struck by a motor vehicle. A, Contrast phase of computed tomography scan shows absent left kidney with the bowel occupying the left renal fossa and a malrotated right kidney. B, Two contrast-filled ureters are seen in the midabdomen. C, The two contrast-filled ureters are noted in their orthotopic positions at the retrovesical level. D, Renal scan shows left-to-right crossed fused ectopia. E, Two-year-old girl with pyelonephritis. Voiding cystourethrogram shows bilateral vesicoureteral reflux and left-to-right crossed ectopia with colon occupying the left renal fossa.

the ectopic kidney's ureter crosses the midline before entering the bladder.

Cake or Lump Kidney. The cake or lump kidney is a relatively rare form of fusion (Fig. 130-16). Extensive fusion has occurred over a wide margin of maturing renal anlage, resulting in one mass. The

total kidney is irregular and lobulated. Ascent usually progresses only as far as the sacral promontory, but in many instances the kidney remains within the true pelvis. Both renal pelvises are anterior, and they drain separate areas of parenchyma. The ureters do not cross. Only ten cases of pelvic cake kidney drained by a single ureter

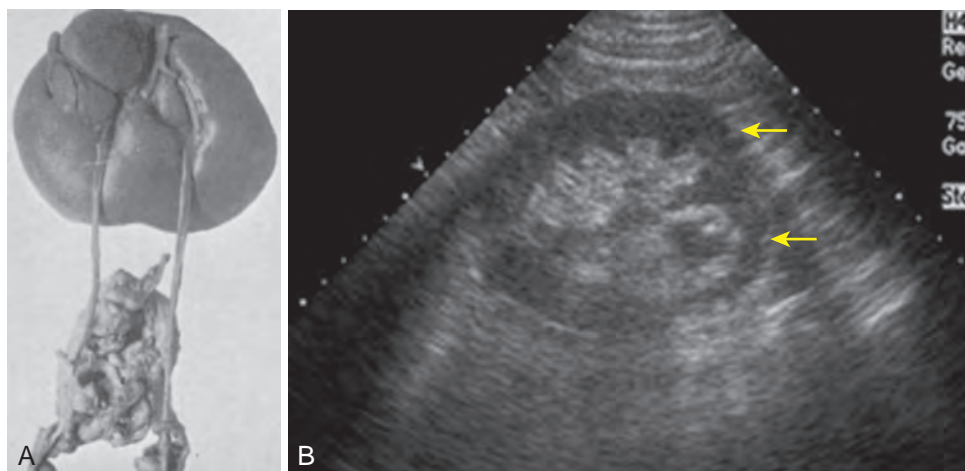


Figure 130-16. A, Lump or cake kidney showing the unusual anatomy, with the anterior blood supply coming from above and the ureters leaving from below. B, Sonogram of cake kidney in sagittal view (arrows). (A, Courtesy Dr. H. S. Altman.)

have been reported (Schwartz, 2010) with one case associated with a unicornuate uterus, and another associated with bilateral absence of the vas.

L-Shaped Kidney. The L-shaped, or tandem, kidney occurs when the crossed kidney assumes a transverse position at the time of its attachment to the inferior pole of the normal kidney. The crossed kidney lies in the midline or in the contralateral paramedian space anterior to the L4 vertebra. Rotation about the long axis of the kidney produces an inverted or a reversed pelvic position. The ureter from each kidney enters the bladder on its respective side.

Disc Kidney. Disc, shield, doughnut, or pancake kidneys are kidneys that have joined at the medial borders of each pole to produce a doughnut- or ring-shaped mass. More extensive fusion along the entire medial aspect of the kidneys creates a disc or shield shape. The lateral aspect of each kidney retains its normal contour. This type of fusion differs from the lump or cake kidney in that the reniform shape is better preserved owing to a less extensive degree of fusion (see Fig. 130-16). The pelves are anteriorly placed, and the ureters remain uncrossed. The collecting system drains each respective half of the kidney and does not communicate with the opposite side.

Superior Ectopic Kidney. The least common variety of renal fusion is the crossed ectopic kidney that lies superior to the normal kidney. The lower pole of the crossed kidney is fused to the upper pole of the normal kidney. The renal units retain a fetal orientation, with both pelves lying anteriorly, suggesting that fusion occurred very early.

Regardless of the type of fusion encountered, the vascular supply to the kidneys is variable. The crossed ectopic kidney is supplied by one or more branches from the aorta or common iliac artery (Rubinstein et al, 1976). The normal kidney frequently has an anomalous blood supply, with multiple renal arteries originating from various levels along the aorta. The solitary crossed ectopic kidney generally receives its blood supply from the aorta or iliac artery on the side where it is positioned (Tanenbaum et al, 1970).

Associated Anomalies. In all the types of fusion anomalies, the ureteral orifice associated with each kidney is usually orthotopic. Except for solitary crossed ectopia, most patients with crossed ectopia have a normal trigone (Yates-Bell and Packham, 1972). The incidence of an ectopic ureteral orifice from the crossed renal unit is about 3% (Abeshouse and Bhisitkul, 1959; Hendren et al, 1976). The ureter from the uncrossed renal segment of a fusion anomaly occasionally has an ectopic orifice or an associated ureterocele (Malek and Utz, 1970; Hendren et al, 1976). Vesicoureteral reflux is noted in 20% of crossed ectopia and in 71% of bilateral crossed ectopia (Kelalis et al, 1973; Guarino et al, 2004) (see Fig. 130-15).

Currarino and Weisbruch (1989) reported 10 cases of midline renal fusion in which a single ureter divided into two pelves that stretched across the midline to drain one respective half of the total parenchymatous mass. In 4 of the 10 cases, a second ureter was present that drained a separate duplex system on either the right or left side. Most of the affected individuals had an imperforate anus, an abnormal vertebrae, or both.

The ectopic kidney may have associated UPJ obstruction (29%), reflux (15%), or carcinoma (Abeshouse and Bhisitkul, 1959; Gleason et al, 1994). Only five tumors have been reported, all of which were renal cell carcinomas and one was in a solitary crossed ectopic kidney (Stimac et al, 2004; Grotas and Phillips, 2009).

The highest incidence of associated anomalies occurs in children with solitary renal ectopia and involves both the skeletal system and genital organs (Gleason et al, 1994). This may be related more to renal agenesis than to the ectopic anomaly, per se. Fifty percent and 40% of solitary crossed renal ectopia have a skeletal or genital abnormality, respectively (Gu and Alton, 1991). The most common genital anomalies are cryptorchidism or absence of the vas deferens and vaginal atresia or a unilateral uterine abnormality (Takei et al, 1976). Imperforate anus has also been observed in 20% of those with solitary crossed ectopia.

In general, the occurrence of an associated nonurologic anomaly in crossed renal ectopia, excluding solitary crossed ectopia, is low; the most frequent are imperforate anus (4%), orthopedic anomalies (4%), skeletal abnormalities, and cardiovascular septal defects.

Symptoms. Most individuals with crossed ectopic anomalies present no symptoms. These anomalies are often discovered incidentally at autopsy, during routine perinatal ultrasound, or after bone scanning. When symptoms occur, they usually develop in the third or fourth decades of life and they include vague lower abdominal pain, pyuria, hematuria, and UTI (Gleason et al, 1994). It is believed that the abnormal kidney position and the anomalous blood supply may impede drainage from the collecting system, creating a predisposition to UTI and calculus formation (Collura et al, 2004). Romans and colleagues (1976) observed that when a stone in a crossed ureter causes colic, the pain is lateralized to the anephric side or the side of the embryonic origin of the ureter, whereas when there is pyelonephritis or obstruction at the UPJ in the crossed kidney, the lumbar pain is on the side of the kidneys. These observations suggest ureteral, not renal, migration as a causative factor in crossed ectopia.

An asymptomatic abdominal mass is the presenting sign in one third of cases (Abeshouse and Bhisitkul, 1959; Nussbaum et al, 1987). Hypertension evaluation shows an ectopic fusion anomaly (Abeshouse and Bhisitkul, 1959).

Diagnosis. Ultrasonography and DMSA scanning have currently shown more asymptomatic cases (Volkan et al, 2003). Multidetector three-dimensional (3D) CT urography is excellent for delineating the renal parenchyma, collecting system, ureters, and vascular supply of the fused kidneys. The main limitation of this modality is the increased risk of significant radiation exposure, which is especially problematic for children, pregnant women, and individuals requiring repeat examinations (Türkvtan et al, 2009). MRU and magnetic resonance arteriography (MRA) should be performed in children undergoing extensive surgery on an ectopic kidney. Cystoscopy and retrograde pyelography can be useful in mapping the collecting system and pattern of drainage.

Prognosis. Most individuals with crossed renal ectopia have normal longevity. However, those with an obstructive-appearing collecting system are at risk for the development of UTI, renal calculi, or both (Kron and Meranze, 1949).

Horseshoe Kidney

The horseshoe kidney is the most common of all renal fusion anomalies. The anomaly consists of two distinct renal masses lying vertically on either side of the midline and connected at their respective lower poles by a parenchymatous or fibrous isthmus that crosses the midplane of the body (Natsis et al, 2014).

Incidence. Horseshoe kidney occurs in 0.25% of the population, or about 1 in 400 persons (Campbell, 1970). A review of more than 15,000 radiologic imaging studies showed an incidence of 1 in 666 individuals (Weizer et al, 2003). Horseshoe kidney is found more commonly in males with a ratio slightly greater than 2:1 (Weizer et al, 2003). The abnormality has been discovered in all age groups. In autopsy series, it is more prevalent in children (Segura et al, 1972). This early-age prevalence is related to the high incidence of multiple congenital anomalies associated with the horseshoe kidney, some of which are incompatible with long-term survival (Scott, 2002). Horseshoe kidneys have been reported in identical twins (Bridge, 1960) and among several siblings (David, 1974). It is doubtful that this anomaly represents a particular genetic predisposition, but it may be the result of a genetic expression with a low degree of penetrance (Leiter, 1972).

Embryology. The abnormality occurs between 4 and 6 weeks' gestation, after the UB has entered the renal blastema. In view of the ultimate spatial configuration of the horseshoe kidney, the entrance of the UB occurred before rotation and before renal ascent (Fig. 130-17).

Tripathi and colleagues (2010) investigated the role of axial structures, including the notochord and the floor plate of the neural tube in metanephric kidney development. The notochord, which is replaced by the vertebral column in higher vertebrates, is essential for the formation of the floor plate. In addition, the sonic hedgehog (*Shh*) gene exists in these structures and is thought to affect renal development. Using a murine model, these investigators disrupted the notochord and neural plate, which resulted in kidney fusions. Then they only inactivated *Shh* in the notochord and floor plate, which also resulted in kidney fusion. These findings suggest that the notochord is *not* necessary for nephrogenesis but is *required* for correct positioning of the metanephric kidney, whereas the axial SHH signal is critical for kidney positioning along the mediolateral axis. These studies provide insights into the molecular basis for horseshoe kidney formation and provide an explanation for the increased incidence of horseshoe kidneys in children with vertebral and neural tube defects (see [Associated Anomalies](#)).

Description. In 95% of cases, the kidneys join at the lower pole, which occurs before the kidneys have rotated on their long axes. The pelves and ureters of the horseshoe kidney are usually anteriorly placed, crossing ventrally to the isthmus (see Fig. 130-17). Very rarely, the pelves are anteromedial, suggesting that fusion occurred after some rotation occurred. In a small subset, an isthmus connects both upper poles (Love and Wasserman, 1975). In addition, migration is usually incomplete and it is thought that the inferior mesenteric artery prevents full ascent.

The isthmus is generally bulky and consists of parenchymatous tissue with its own blood supply (Glenn, 1959; Love and Wasserman, 1975). Occasionally it is just a flimsy midline structure composed of fibrous tissue that tends to draw the renal masses close together. The isthmus is located adjacent to the L3 or L4 vertebra just below the origin of the inferior mesenteric artery from the aorta. The isthmus most often lies anterior to the aorta and vena cava, but it has been reported to pass between the inferior vena cava and the aorta or even behind both great vessels (Dajani, 1966). In some instances, the anomalous kidneys are very low, anterior to the sacral promontory or even in the true pelvis behind the bladder (Campbell, 1970). Fused pelvic kidneys are observed in the *Foxd1* mouse mutant, which show defects in UB branching and nephron formation (Levinson et al, 2005).

The calyces are normal in number and are atypical in orientation. Because the kidney fails to rotate, the calyces point posteriorly, and the axis of each pelvis remains in the vertical or obliquely lateral plane (on a line drawn from the lower to the upper poles). The lowermost calyces extend caudally or even medially to drain the isthmus and may overlies the vertebral column (Strauss et al, 2000).

The ureter may insert high on the renal pelvis and lie laterally, probably as the result of incomplete renal rotation. It courses downward and has a characteristic bend as it crosses over and anterior to the isthmus (Strauss et al, 2000). The lower ureter enters the bladder normally and rarely is ectopic.

The blood supply to the horseshoe kidney can be variable. In 30% of cases it consists of one renal artery to each kidney (Glenn, 1959) (see Fig. 130-17). Duplicate or triplicate renal arteries may supply one or both kidneys. The blood supply to the isthmus and lower poles is also variable. The isthmus and adjacent parenchymal masses might receive a branch from each main renal artery, or they may have their own arterial supply from the aorta originating either above or below the level of the isthmus. Not infrequently, branches from the inferior mesenteric, common or external iliac, or sacral arteries supply this area (Kolln et al, 1972).

Associated Anomalies. About 30% of horseshoe kidneys are associated with other congenital anomalies (Boatman and colleagues (1972). The autopsy incidence of other anomalies is greater in children who die at birth or in early infancy than in those who reach adulthood (Scott, 2002). This implies that a horseshoe kidney occurs more often in association with other serious congenital anomalies. The organ systems most commonly affected include the skeletal, cardiovascular (primarily ventriculoseptal defects [Voisin et al, 1988]), and central nervous system. Horseshoe kidney is found in 3% of children with neural tube defects (Whitaker and Hunt, 1987). Anorectal malformations are frequently encountered in these patients. Horseshoe kidney is seen in 60% of females with Turner syndrome (Lippe et al, 1988).

KEY POINTS: HORSESHOE KIDNEY

- Horseshoe kidney occurs in 0.25% of the population, or about 1 in 400 persons.
- The isthmus is bulky and consists of parenchymatous tissue.
- The calyces, normal in number, are atypical in orientation. Because the kidney fails to rotate, the calyces point posteriorly, and the axis of each pelvis remains in the vertical or obliquely lateral plane.
- The blood supply can be variable.
- Horseshoe kidney is frequently found in association with other congenital anomalies.
- UPJ obstruction, causing significant hydronephrosis, occurs in as many as one third of individuals with horseshoe kidneys.
- Sixty percent of patients with horseshoe kidneys remained asymptomatic for an average of 10 years after discovery.

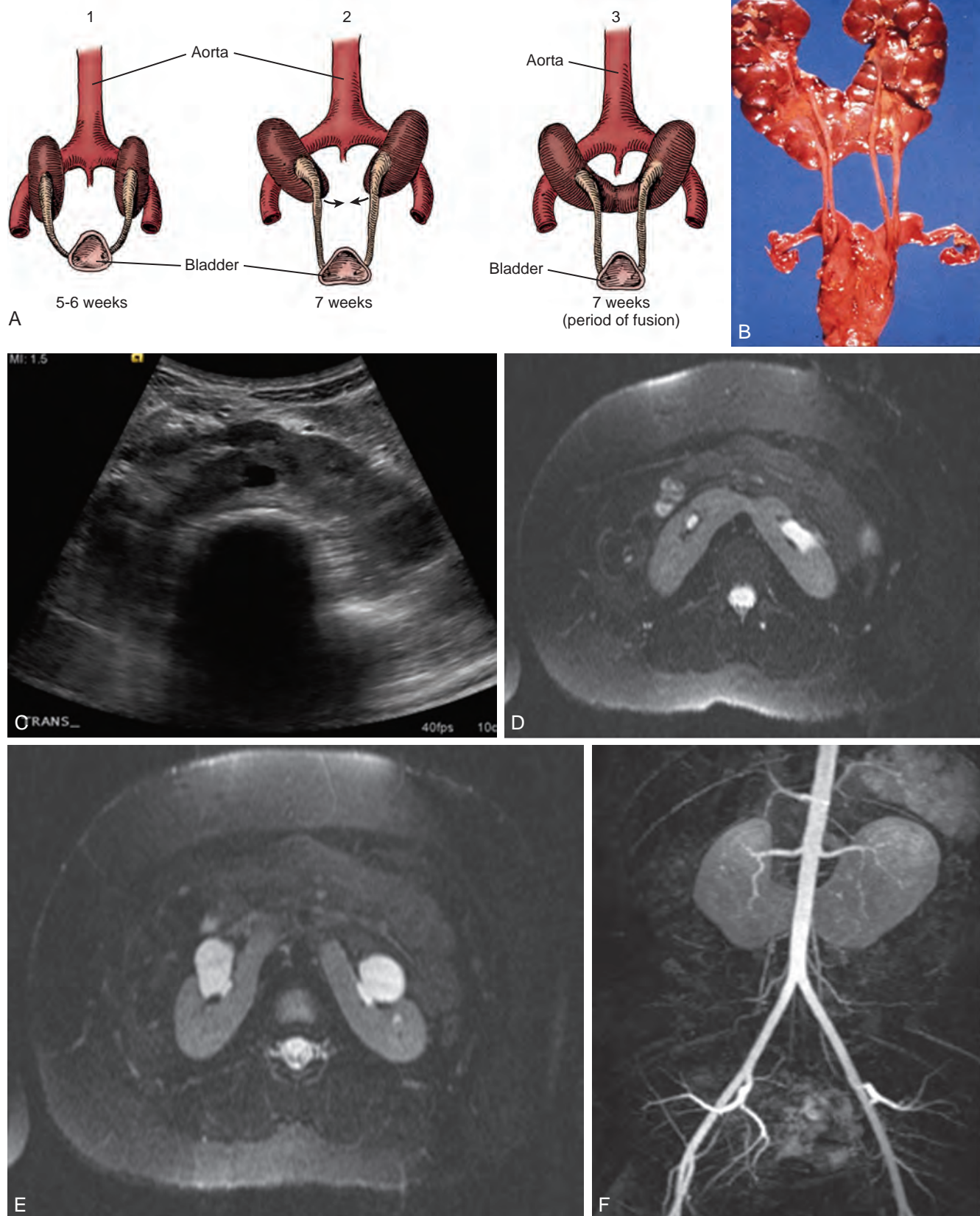


Figure 130-17. A, Embryogenesis of horseshoe kidney. The lower poles of the two kidneys touch and fuse as they cross the iliac arteries. Ascent is stopped when the fused kidneys reach the junction of the aorta and the inferior mesenteric artery. B, Postmortem specimen showing horseshoe kidney with bilateral duplicated ureters. C, Sonogram of horseshoe kidney at the level of the isthmus. D, Magnetic resonance (MR) urogram shows axial T2 fat-saturated image at the level of the isthmus. E, Axial T2 fat-saturated image demonstrates extrarenal pelves. F, Angiographic sequence shows variable blood supply to the kidney.

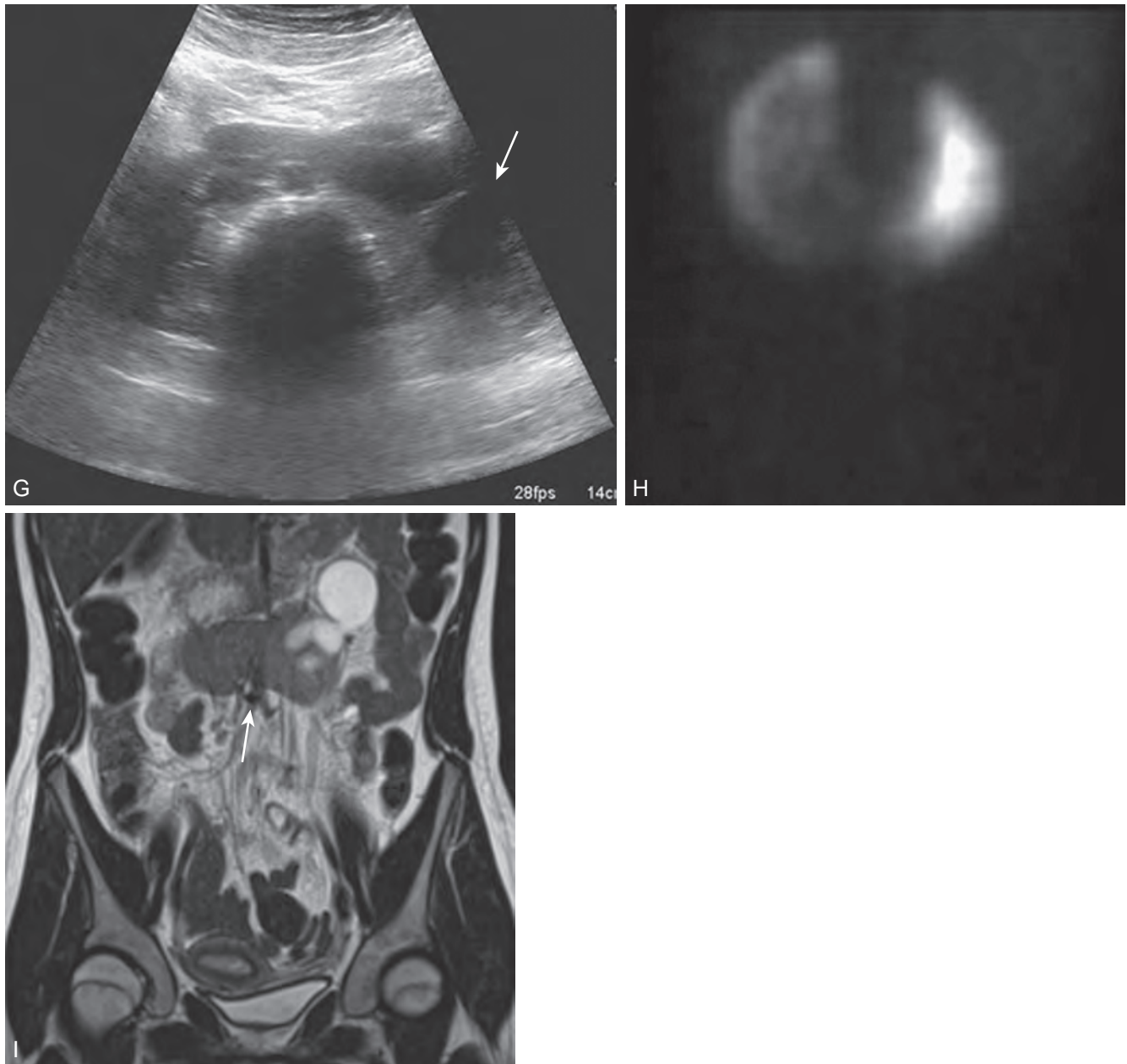


Figure 130-17, cont'd G, Transverse sonogram of 14-year-old girl with left flank pain found to have marked left hydronephrosis in a horseshoe kidney (*arrow*). H, MAG3 scan demonstrates left ureteropelvic junction obstruction. I, Coronal T2 images of MR urogram show the isthmus (*arrow*) and severe left hydronephrosis. (A, From Benjamin JA, Schullian DM. Observation on fused kidneys with horseshoe configuration: the contribution of Leonardo Botallo [1564]. *J Hist Med Allied Sci* 1950;5:315–26, after Gutierrez, 1931; B, from Weiss, MA, Mills, SE. *Atlas of genitourinary tract disorders*. Philadelphia: JB Lippincott; 1988.)

Boatman and his colleagues (1972) also discovered an increased occurrence of other genitourinary anomalies associated with a horseshoe kidney. Hypospadias and undescended testes occurred in 4% of males, and a bicornuate uterus, a septate vagina, or both, were noted in 7% of the females.

Duplication of the ureter occurs in 10% of cases (Boatman et al, 1972); in some cases this has been associated with an ectopic ureterocele (see Fig. 130-17). Vesicoureteral reflux has been noted in more than half (Cascio et al, 2002). Previously, up to one third with horseshoe kidney had hydronephrosis thought to be secondary to UPJ obstruction (Whitehouse, 1975; Das and Amar, 1984) (see Fig. 130-17). The high insertion of the ureter into the renal pelvis, its abnormal course anterior to the isthmus, and the anomalous blood supply to the kidney may individually or collectively contribute to

the hydronephrosis. In the modern era, horseshoe kidneys are frequently discovered incidentally, and their apparent hydronephrosis more often shows a nonobstructed pattern on radionuclide scanning.

Horseshoe kidneys are also incidentally observed on ^{99m}Tc bone scan as a result of renal uptake and excretion of the isotope (O'Brien et al, 2008). Back pain that prompts a bone scan may have resulted from UPJ obstruction (Shapiro, personal communication, 2013).

Cystic disease, including multicystic dysplasia in one half (the upper pole) of one side (Boullier et al, 1992) and the lower pole of one side (Shapiro, personal communication, 2004), and adult polycystic kidney disease have been reported with horseshoe kidney (Correa and Paton, 1976). DMSA scanning in 22 patients showed asymmetrical function in 63% (Kao et al, 2003). Stone formation

has been commonly seen in horseshoe kidney. Metabolic stone evaluation in 11 of 37 of these stone formers showed at least one abnormality, with an average of 2.68 abnormalities per 24-hour urine collection. Hypovolemia, hypercalciuria, and hypocitraturia were the most common metabolic defects (Raj et al, 2004).

Symptoms. At least 50% with horseshoe kidneys are asymptomatic, and in most instances the anomaly is an incidental finding at autopsy (Kolln et al, 1972; Pitts and Muecke, 1975). Symptoms are typically related to hydronephrosis, infection, or calculus formation. The most common symptom is vague abdominal pain that may radiate to the lower lumbar region. UTIs occur in 30% of patients, and calculi have been noted in 20% to 80% (Glenn, 1959; Kolln et al, 1972; Pitts and Muecke, 1975; Evans and Resnick, 1981; Sharma and Bapna, 1986; Benckekroun et al, 1998). Five percent to 10% of horseshoe kidneys are confirmed after palpation of an abdominal mass (Kolln et al, 1972).

Diagnosis and Radiographic Appearance. The classic radiologic features on a plain film of the abdomen include kidneys that are somewhat low lying and close to the vertebral column and that have a vertical or outward axis with the lower poles being more medial than in the normal kidney (O'Brien et al, 2008). The kidneys may be observed by the delineation of the perinephric fat. Prenatal ultrasonography detects most horseshoe kidneys (Sherer and Woods, 1992; Van Every, 1992). Postnatal ultrasonography detects the isthmus joining the two lower poles of the kidneys in the midline, unless the isthmus is only a thin fibrous band. Ultrasound diagnosis is made by scanning horizontally along the midline in a craniocaudal direction, especially in children and in thin patients. Radionuclide scanning demonstrates the abnormal axis of a horseshoe kidney. A continuous band across the midline is observed if the isthmus contains functioning parenchyma. CT and MRU can also be used to characterize the isthmus. MRA will delineate the vascular anatomy for preoperative planning (O'Brien et al, 2008).

Prognosis. Although Smith and Orkin (1945) believed that horseshoe kidneys are almost always associated with disease, Glenn (1959) observed patients with horseshoe kidneys for an average of 10 years after discovery and found that almost 60% of these remained asymptomatic. Only 13% had persistent urinary infection or pain, and 17% developed recurrent calculi.

Many disease processes have been described with a horseshoe kidney, but this likely reflects the relative frequency of the congenital defect. Kidney cancers have been reported in about 150 individuals with horseshoe kidney (Stimac et al, 2004). Renal cell carcinoma accounts for about half of these cases, although the incidence is no greater than that in the general population. Two cases of bilateral tumors have been reported (Romics et al, 2002). Renal pelvic tumors and Wilms tumor each accounted for about 25% of the total, with sarcoma and carcinoids occurring much less frequently. Overall, 41 of 8617 (0.48%) Wilms tumors in the National Wilms Tumor study occurred in horseshoe kidneys, primarily on the left side, rarely in the isthmus, and practically all with favorable histology (Neville et al, 2002). The incidence of Wilms tumor in horseshoe kidneys is 1.76 to 7.93 times higher than that expected in the general population (Mesrobian et al, 1985). Thirty-seven percent of these Wilms tumors were initially inoperable. However, with preoperative chemotherapy, most patients were salvaged, yielding a 75% preservation rate of renal parenchyma (Neville et al, 2002). Wilms tumor may originate in the isthmus (Beck and Hlivko, 1960), creating a bizarre radiologic picture (Walker, personal communication, 1977). Except for renal pelvic tumors, a surprisingly high number of renal cancers arise in the isthmus (Blackard and Mellinger, 1968). For this reason, it has been suggested that teratogenic factors are responsible for abnormal migration of nephrogenic cells to form an isthmus, which then leads to the horseshoe shape and the predisposition for the development of cancer in this portion of the kidney (Hohenfellner et al, 1992).

It has been suggested that the increased occurrence of chronic infection, obstruction, and stone formation explains the higher-than-expected incidence of renal pelvic tumors because the incidence exceeds that of the general population (Dische and Johnston,

1979). Survival from these tumors is related to the pathology and stage of the tumor at diagnosis and not to the renal anomaly (Murphy and Zincke, 1982). Surveillance for tumors in symptomatic horseshoe kidneys may be prudent.

Because a horseshoe kidney is located above the pelvic inlet, it should not adversely affect pregnancy or delivery (Bell, 1946b). The development of renal failure associated with adult polycystic kidney disease is not any greater in a horseshoe kidney (Correa and Paton, 1976). A worldwide review of horseshoe kidney transplant from the Netherlands noted that 23 whole and 57 split horseshoe kidneys have been transplanted with initial failure rates of only 4.3% and 13.4% for en bloc and for split transplants, respectively. An overall 80% graft survival rate has been reported at 5 years (Stroosma et al, 2001).

ANOMALIES OF ROTATION

The kidney, as it assumes its final position in the "renal" fossa, orients itself so that the calyces point laterally and the pelvis faces medially. When this alignment is not exact, the condition is known as *malrotation* and is often described in conjunction with other renal anomalies, such as ectopia with or without fusion or horseshoe kidney. This discussion centers on malrotation as an isolated renal entity.

Incidence. Campbell (1963) found renal malrotation in 1 of 939 autopsies, and Smith and Orkin (1945) noted 1 case per 390 hospital admissions. It is frequently observed in association with Turner syndrome (Gray and Skandalakis, 1972b). Males are affected twice as often as females, but there does not appear to be any predilection for side.

Embryology. It is thought that medial rotation of the collecting system occurs simultaneously with renal migration. The kidney starts to turn during the sixth week, just when it is leaving the true pelvis, and it completes this process by rotating 90 degrees toward the midline by the time ascent is complete at the end of 9 weeks' gestation.

In 1912, Felix postulated that rotation is actually the result of unequal branching of successive orders of the budding ureteral tree, with two branches extending ventrally and one dorsally during each generation or division. Each ureteral branch then induces differentiation of the metanephrogenic tissue. More parenchyma develops ventrally than dorsally, and the pelvis seems to rotate medially. Weyrauch (1939) accepted this theory of renal rotation as the result of excessive ventral versus dorsal branching of the ureteral tree and concluded that the fault of malrotation lies entirely with the ureter. A late-appearing UB may insert into an atypical portion of the renal blastema, leading to a lessened propensity for the developing nephric tissue to shift. Late appearance of the UB is almost always associated with an aberrant origin from the WD; this translates into ureteral ectopia at the level of the lower urinary tract. Mackie and colleagues (1975), however, did not describe any malrotation anomalies in their study of renal ectopia. The renal blood supply does not appear to be the cause nor does it appear to be a limiting factor in malrotation, but rather it follows the course of renal hyporotation, hyper-rotation, or reverse rotation.

KEY POINTS: ANOMALIES OF ROTATION

- The kidney and renal pelvis normally rotate 90 degrees ventromedially during ascent so that the calyces point laterally and the pelvis faces medially. When this alignment is not exact, the condition is known as malrotation.
- Malrotation is frequently associated with Turner syndrome.

Description. The kidney and renal pelvis normally rotate 90 degrees ventromedially during ascent. Weyrauch (1939), in a detailed study, categorized the various abnormal phases of medial and reverse rotation according to the position of the renal pelvis (Fig. 130-18 on the Expert Consult website).



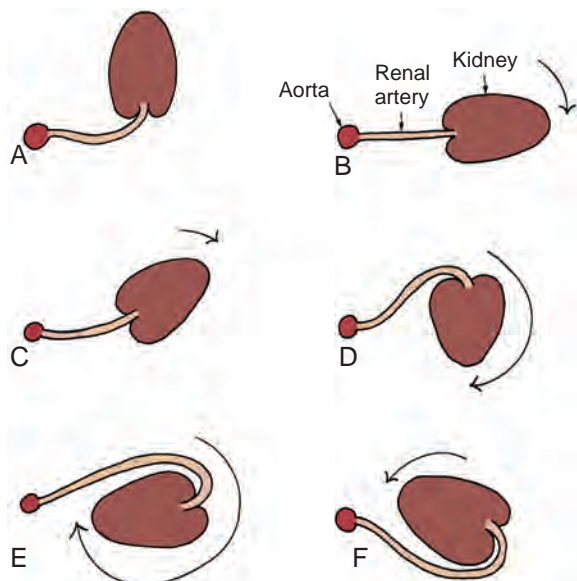


Figure 130-18. Rotation of the kidney during its ascent from the pelvis. The left kidney with its renal artery and the aorta are viewed in transverse section to show normal and abnormal rotation during its ascent to the adult site. A, Primitive embryonic position; hilus faces ventrad (anterior). B, Normal adult position; hilus faces mediad. C, Incomplete rotation. D, Hyper-rotation; hilus faces dorsad (posterior). E, Hyper-rotation; hilus faces laterad. F, Reverse rotation; hilus faces laterad. (From Gray SW, Skandalakis JE. *Embryology for surgeons*. Philadelphia: Saunders; 1972.)

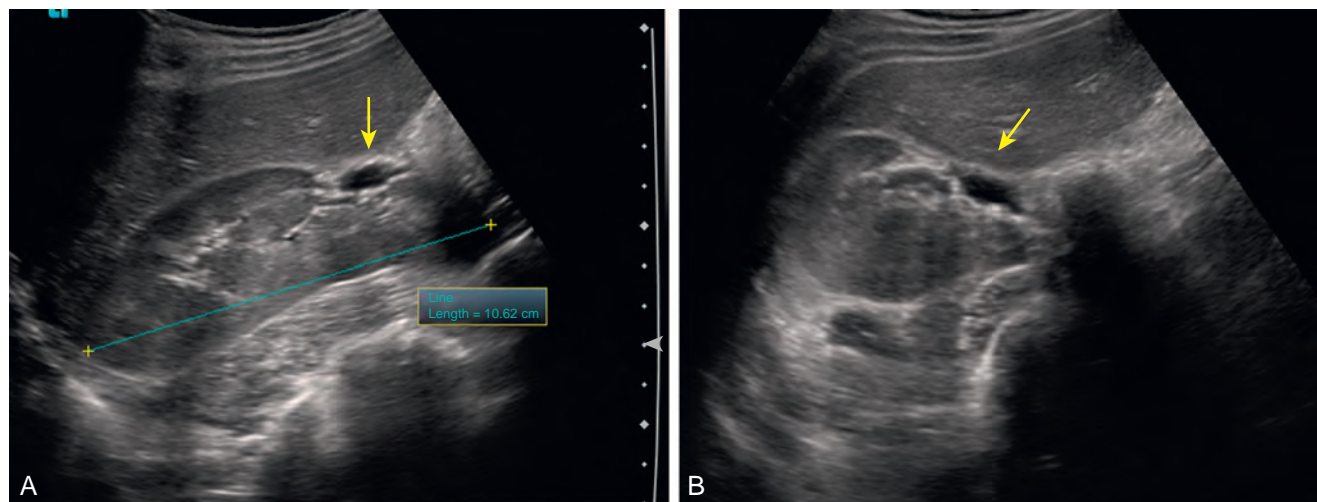


Figure 130-19. Sonogram showing (A) sagittal view of malrotated right kidney. B, Transverse view of malrotated right kidney. Note the anterior position of the renal pelvis (arrows).

Ventral Position. The pelvis is ventral and in the same anteroposterior plane as the calyces, which point dorsally because they have undergone no rotation at all. This is the most common form of malrotation (Fig. 130-19).

Ventromedial Position. The pelvis faces ventromedially because of an incompletely rotated kidney. Excursion probably stops during the seventh week of gestation when the kidney and pelvis normally reach this position. The calyces thus point dorsolaterally.

Dorsal Position. Renal excursion of 180 degrees occurs to produce this rarest position. The pelvis is dorsal to the parenchyma, and the vessels pass behind the kidney to reach the hilum.

Lateral Position. When the kidney and pelvis rotate between 180 degrees to 360 degrees, or when reverse rotation of up to 180 degrees occurs, the pelvis faces laterally and the kidney parenchyma resides medially. The renal vascular supply provides the only clue to the actual direction of excursion. Vessels that course ventral to the kidney to enter a laterally or dorsolaterally placed hilum suggest reverse rotation, whereas a path dorsal to the kidney implies excessive ventral rotation.

In cases of isolated malrotation, other characteristic features may be present. The kidney shape may be discoid, elongated, oval, or triangular, with flattened anterior and posterior surfaces. Fetal lobulations are invariably present and are accentuated beyond normal limits. A dense amount of fibrous tissue encases the hilar area, possibly even distorting and fixing the pelvis. The UPJ may be distorted as well. The upper ureter initially courses laterally, and it, too, may be encased in this fibrous matting. The pelvis is elongated and narrow, and calyces, especially the superior calyx, may be stretched. The blood supply may vary widely, depending on the direction and degree of rotation. The vasculature may consist of a single vessel with or without multiple additional branches entering the parenchyma along the course of the renal artery. There also may be a polar vessel in conjunction with the main renal artery. The vascular orientation around the kidney provides the only clue to the type and extent of renal rotation.

Symptoms. Rotation anomalies, per se, do not produce specific symptoms. The excessive amount of fibrous tissue encasing the pelvis, UPJ, and upper ureter, however, may lead to varying degrees of hydronephrosis. Vascular compression from an accessory or main renal artery or distortion of the upper ureter or UPJ may contribute to intermittent obstruction.

Diagnosis. The diagnosis should be considered when a renal calculus is detected in an abnormal location, but confirmation should be obtained from a renal sonogram, CT, MRU, or retrograde pyelogram. These studies show the abnormal orientation of the renal pelvis and calyces, a flattened and elongated pelvis, a stretched superior calyx with blunting of the remaining calyces, and a laterally

displaced upper third of the ureter. Bilateral malrotation is not uncommon and may suggest the diagnosis of a horseshoe kidney. However, careful inspection for an isthmus and observation of the lower pole renal outline should distinguish the two entities.

Prognosis. Malrotation does not impair renal function. Hydronephrosis resulting from impaired urinary drainage may lead to infection and calculus formation.

ANOMALIES OF RENAL VASCULATURE

Aberrant, Accessory, or Multiple Vessels

The kidney is divided into various segments, each supplied by a single “end” arterial branch that usually courses from one main renal artery. The correct term to describe any kidney supplied by more than one vessel is *multiple renal arteries*. The terms *anomalous vessels* or *aberrant vessels* should be reserved for those arteries that originate from vessels other than the aorta or main renal artery. The term *accessory vessels* denotes two or more arterial branches supplying the same renal segment.

Incidence. Between 71% (Merklin and Michele, 1958) and 85% (Geyer and Poutasse, 1962) of kidneys have one artery that supplies the entire renal parenchyma. A slightly higher percentage of right-sided kidneys have a single renal artery compared with left-sided organs (Geyer and Poutasse, 1962). True aberrant vessels are rare, except in cases with renal ectopia, with or without fusion, and in individuals with a horseshoe kidney (Degani et al, 2010).

Embryology. The renal arterial tree is derived from three groups of primitive vasculature that coalesce to form the mature vascular pattern for all retroperitoneal structures. The cranial group consists of two pairs of arteries dorsal to the suprarenal gland that shift dorsally to form the phrenic artery. The middle group is made up of three pairs of vessels that pass through the suprarenal area and retain the same lateral position, becoming the adrenal artery. Finally, the caudal group of four paired arteries cross ventral to the suprarenal area and become the main renal artery. Sometimes the most inferior pair from the middle group joins them (Guggemos, 1962). It is believed that during renal migration this network of vessels selectively degenerates, and the remaining adjacent arteries assume a progressively more important function. By a process of elimination, one primitive renal arterial pair eventually becomes the dominant vessel, the completed process being dependent on the final position of the kidney (Graves, 1956). Polar arteries or multiple renal arteries to the normally positioned kidney represent a failure of complete degeneration of all primitive vascular channels. The multiple vessel pattern that has been described for renal

ectopia should be considered as an arrested embryonic state for that particular renal position (Gray and Skandalakis, 1972a).

Description. Based on vascular supply, the renal parenchyma is divided into five segments: apical, upper, middle, lower, and posterior. The main renal artery divides initially into an anterior and posterior branch. The anterior branch almost always supplies the upper, middle, and lower segments of the kidney. The posterior branch invariably supplies the posterior and lower segments (Sampaio and Aragao, 1990a). The vessel to the apical segment has the greatest variation in origin; it arises from (1) the anterior division (43%), (2) the junction of the anterior and posterior divisions (23%), (3) the mainstem renal artery or aorta (23%), or (4) the posterior division of the main renal artery (10%) (Graves, 1954). Rarely the upper segment is supplied from a branch totally separate from the main renal artery (Merklin and Michele, 1958). Sampaio and Aragao (1990a, 1990b) beautifully depicted in endocasts the arterial and venous tree of the kidney and its relationship to the collecting system. These investigations showed that the least likely areas to encounter vessels when entering the collecting system, either endourologically or with open surgery, are directly end-on through a fornix or inferiorly on the posterior aspect of the pelvis. Shoja and colleagues (2008) studied the perihilar (extraparenchymal) branching patterns and morphologies of the renal artery. A “fork” pattern with a common branching point (usually duplicated) was the most commonly observed extrarenal division and branching pattern of the main renal artery. They conclude that perihilar branching of the main renal artery was highly variable, with predictable patterns in the majority of kidneys. This information is useful for the transplant surgeon when interpreting radiodiagnostics of the renal hilum.

The lower renal segment, however, is often supplied by an accessory vessel (Fig. 130-20). This vessel is usually the most proximal branch when it arises from the main renal artery or its anterior division (Graves, 1954). However, it may originate directly from the aorta near the main renal artery, or it may be aberrant, arising from the gonadal vessel. Merklin and Michele (1958) performed an extensive study of the variant renal and suprarenal blood supply. Sampaio and Aragao (1990b) have studied the venous drainage of the kidney, and they noted a close association between the inferior branch to the main renal vein and the anterior inferior aspect of the renal pelvis in 40% of kidneys.

Symptoms. Symptoms attributable to renal vascular anomalies are those that might result from inadequate urinary drainage. Multiple,

aberrant, or accessory vessels may constrict an infundibulum, a major calyx, or the UPJ (Yen et al, 2004). Pain and hematuria secondary to hydronephrosis, UTI, or calculus may result.

Diagnosis. Precise anatomic resolution of vascular variants and associated disease states can be obtained using 3D power Doppler ultrasonography, CT, or MRI (Degani et al, 2010).

Prognosis. Hydronephrosis secondary to a vascular anomaly such as a lower pole crossing vessel is a very rare finding, especially when one considers the relative frequency of all renal vascular variations. Hypertension is no more frequent in patients with multiple renal arteries than in those with a single vessel (Geyer and Poutasse, 1962).

Renal Artery Aneurysm

Aneurysmal dilation was the first disease process of the renal artery to be recognized (Poutasse, 1957) and was considered a rare occurrence until selective renal angiography became widely available. Since then, the overall incidence has been calculated as between 0.1% and 0.3%. Abeshouse (1951) classified renal artery aneurysms (RAAs) as follows: saccular, fusiform, dissecting, and arteriovenous. The saccular aneurysm, a localized outpouching that communicates with the arterial lumen by a narrow or wide opening, is the most common type, accounting for 93% of all aneurysms (Zinman and Libertino, 1982). When the aneurysm is located at the bifurcation of the main renal artery and its anterior and posterior divisions, or at one of the more distal branchings, it is considered to be congenital in origin and is called the fusiform type (Poutasse, 1957). The presence of similar aneurysms at branching points in the vasculature of other organ systems attests to this possible origin (Lorentz et al, 1984). Acquired aneurysms may be located anywhere and may result from inflammatory, traumatic, or degenerative factors. A localized defect in the internal elastic tissue and the media allows the vessel to dilate at that point. It is a true aneurysm, because its walls are composed of most of the layers that make up the normal artery (Poutasse, 1957). The outpouchings may vary in size from 1 to 2 cm up to 10 cm (Garritano, 1957), but 90% are smaller than 2 cm. There is no absolute predilection for side, but the right appears to be favored, and bilateral aneurysms are seen in 15% (Pfeiffer et al, 2003).

Almost half of RAAs are silent, especially in children (Sarker et al, 1991). Some produce symptoms at a later age, because the size of the aneurysm increases with time. Pain (15%), hematuria

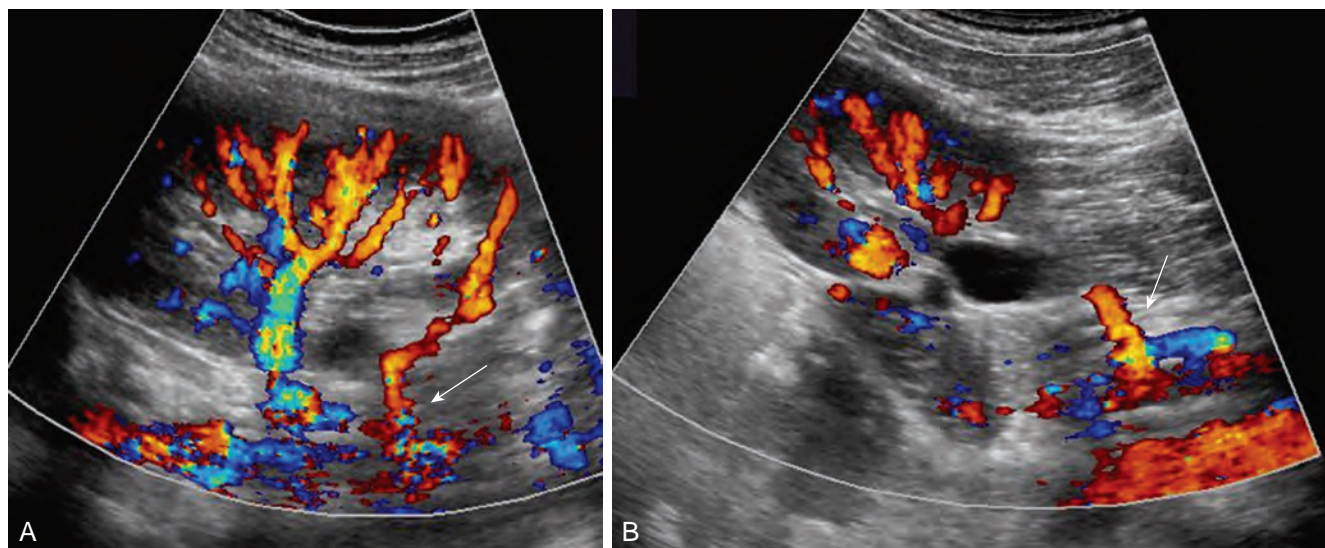


Figure 130-20. Nine-year-old girl with intermittent left flank pain, nausea, and vomiting. A, Color Doppler ultrasound study shows normal left renal artery and lower pole accessory vessel (arrow). B, Oblique sagittal view shows left lower pole accessory vessel (arrow) supplying the lower pole of the kidney, causing intermittent left ureteropelvic junction obstruction.

(microscopic and macroscopic) (30%), and hypertension (55%) secondary to compression of adjacent parenchyma or to altered blood flow within the vascular tree can occur (Bulbul and Farrow, 1992). The hypertension is renin-mediated and secondary to relative parenchymal ischemia (Lorentz et al, 1984). Thirteen cases of hydronephrosis secondary to an adjacent renal vessel aneurysm were noted (Miyagawa et al, 2001).

The diagnosis is suspected when a pulsatile mass is palpated in the region of the renal hilum or when a bruit is heard on abdominal auscultation. A wreathlike calcification in the area of the renal artery or its branches (30%) is highly suggestive (Silvis et al, 1956). RAAs can be evaluated with color Doppler sonography (Bunchman et al, 1991), spiral CT, 3D MRA, or digital subtraction arteriography (González et al, 2014).

Many asymptomatic RAAs come to light during a workup of uncontrolled hypertension (35%), whereas 26% are diagnosed when angiography is performed for other reasons (Hupp et al, 1992). The indications for treatment of RAAs remain controversial (González et al, 2014). It is generally agreed that treatment is indicated for those presenting with rupture or are at a high risk for rupture. High risk for rupture is associated with rapidly expanding RAAs and pregnant females or those who are considering pregnancy. More than 30 cases of a ruptured aneurysm during pregnancy have been reported (Lacroix et al, 2001). In addition, intervention is indicated for RAAs larger than 2.0 cm or for individuals with symptoms including uncontrolled hypertension from renal artery stenosis, flank pain, hematuria, or renal ischemia/infarction resulting from embolization from the aneurysm. Caution is advised because flank pain and hematuria may have alternative etiologies (González et al, 2014). The likelihood of spontaneous rupture (about 10%), with its dire consequences, dictates emergency treatment. Open surgical or endovascular techniques should be performed electively for those at high risk for rupture (González et al, 2014).

KEY POINTS: RENAL ARTERY ANEURYSM

- The overall incidence of RAA has been calculated to be between 0.1% and 0.3%.
- Most RAAs are silent, especially in children. Many asymptomatic RAAs are diagnosed during an evaluation of hypertension.
- The diagnosis may be suspected with a pulsatile mass in the region of the renal hilum or when an abdominal bruit is heard. A wreathlike calcification in the area of the renal artery or its branches (30%) is highly suggestive.

Renal Arteriovenous Fistula

Although rare, renal arteriovenous fistulas (AVFs) have been diagnosed with increasing frequency. Two types exist, congenital and acquired (Maldonado et al, 1964), with the latter (secondary to trauma, inflammation, renal surgery, or percutaneous needle biopsy) accounting for the increase in incidence. Only the congenital variant is discussed here.

Fewer than 25% of all AVFs are congenital, with only 91 reported cases (Takaha et al, 1980). They are identifiable by their cirroid configuration and multiple communications between the main or segmental renal arteries and the venous channels (Crummey et al, 1965; Cho and Stanley, 1978). Although congenital, they rarely present clinically before the third or fourth decade. Women are affected three times as often as men, and the right kidney is involved slightly more often than the left (Ishikawa et al, 2004). The lesion is usually located in the upper pole (45% of cases), but not infrequently it may be found in the midportion (30%) or in the lower pole (25%) of the kidney (Yazaki et al, 1976).

The condition is thought either to be present at birth or to result from a congenital aneurysm eroding into an adjacent vein (Thomason et al, 1972). The pathophysiology involved in the

shunting of blood, which bypasses the renal parenchyma and rapidly joins the venous circulation and returns to the heart, results in a varied clinical picture. The symptoms are based on the age and size of the AVF (Messing et al, 1976).

The hemodynamic derangement often produces a loud bruit in 75% of cases. Diminished perfusion of renal parenchyma distal to the fistulous site leads to relative ischemia and renin-mediated hypertension in approximately 50% (McAlhany et al, 1971). The increased venous return and high cardiac output with concomitant diminution in peripheral resistance may result in left ventricular hypertrophy and subsequent high-output cardiac failure in 50% of cases (Maldonado et al, 1964). Macroscopic and microscopic hematuria occurs in more than 75% of affected individuals because of the proximity of the collecting system (Montoya et al, 2004). Although flank or abdominal pain may be present, a mass is rarely palpable (10%).

Three-dimensional Doppler sonography and MRA are accurate and noninvasive tests (Mohaupt et al, 1999; Ishikawa et al, 2004), but selective renal arteriography or digital subtraction angiography is the most definitive method for diagnosing the lesion. A cirroid appearance with multiple small, tortuous channels; prompt venous filling; and an enlarged renal, and possibly gonadal, vein are pathognomonic for arteriovenous malformation (AVM) (DeSai and DeSautels, 1973).

The symptomatic nature of this lesion, which causes progressive alterations in the cardiovascular system, often dictates surgical intervention. The congenital variant rarely behaves like its acquired counterpart, which may disappear spontaneously after several months. Nephrectomy, partial nephrectomy, vascular ligation (Boijssen and Kohler, 1962), selective embolization (Bookstein and Goldstein, 1973), and balloon catheter occlusion (Bentson and Crandalls, 1972) have been used to obliterate the fistula.

ANOMALIES OF THE COLLECTING SYSTEM

Calyceal Diverticulum

A calyceal diverticulum is a cystic cavity within the kidney that is lined by transitional epithelium and communicates with a calyx or less commonly with the renal pelvis through a narrow isthmus (Estrada et al, 2009). This abnormality, first described by Rayer in 1841, may be multiple, with the upper calyx most frequently affected.

In the past, an incidence of 4.5 per 1000 had been reported (Timmons et al, 1975). A similar incidence was noted both in children and in adults, with no predilection for either side or gender. Most diverticula, labeled type I, occur adjacent to an upper or, occasionally, a lower pole calyx. Type II diverticula are larger, communicate with the renal pelvis, and tend to be symptomatic (Wulfsohn, 1980).

Congenital and acquired factors have been suggested to explain the formation of calyceal diverticula. The similar incidence in children and adults is consistent with an embryologic etiology (Middleton and Pfister, 1974). At the 5-mm stage of the embryo, ureteral branches of the third and fourth generation, which ordinarily degenerate, may persist as isolated branches, resulting in the formation of a calyceal diverticulum (Lister and Singh, 1973).

A localized cortical abscess draining into a calyx has also been postulated as an etiologic factor. Other proposed causes include obstruction from stones or infection within a calyx, progressive fibrosis of an infundibular stenosis, renal injury, achalasia, and spasm or dysfunction of one of the supposed sphincters surrounding a minor calyx (Siegel and McAlister, 1979; Patriquin et al, 1985). Vesicoureteral reflux has also been considered an etiologic factor. Amar (1975) postulated that calyceal tubular backflow of infected urine could result in abscess formation and parenchymal injury leading to diverticular formation. Small diverticula are usually asymptomatic and are found incidentally by ultrasonography, CT, or MRI. These diverticula tend to distend progressively with trapped urine (Amar, 1975; Siegel and McAlister, 1979; Patriquin et al, 1985). Infection, milk of calcium (Patriquin et al, 1985),

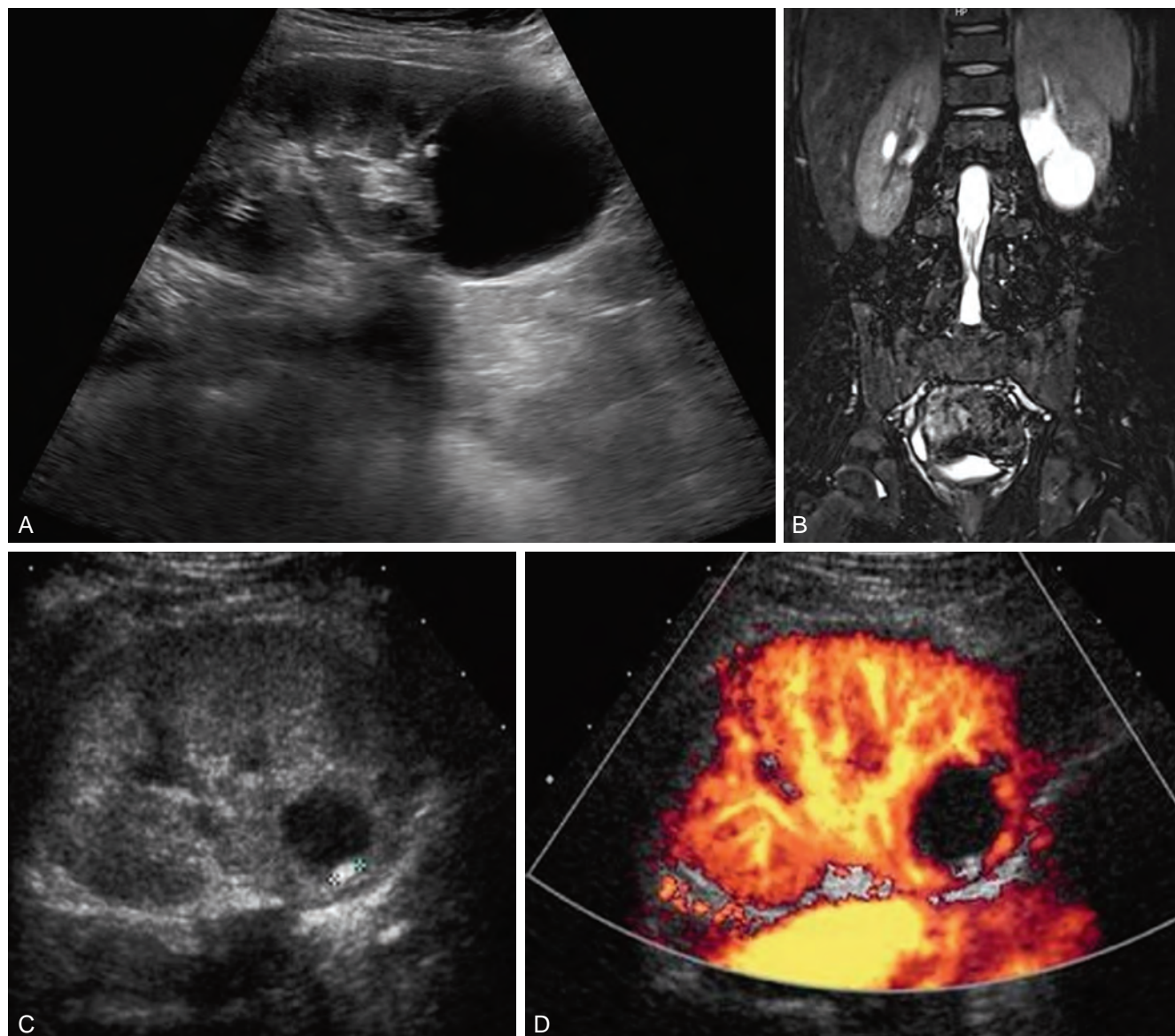


Figure 130-21. Lower pole calyceal diverticulum. A, Sagittal sonogram. B, Sequence of coronal T2 images. C, Sagittal sonogram shows small stone within a diverticulum. D, Color Doppler sonogram demonstrates absence of flow. (B, Courtesy Dr. Sara Milla.)

or true stone formation are complications of stasis or obstruction that can produce symptoms ([Lister and Singh, 1973](#); [Siegel and McAlister, 1979](#)) ([Fig. 130-21](#)). Hematuria, pain, and UTI may be seen in the presence of stones, which may be present in almost 40% of patients.

KEY POINTS: CALYCEAL DIVERTICULUM

- A calyceal diverticulum is a cystic cavity within the kidney that is lined by transitional epithelium and communicates with a calyx or, less commonly, with the renal pelvis through a narrow isthmus.
- The incidence based on excretory urography is about 4.5 per 1000.
- The diagnosis is best made by CT or MRU.
- Laparoscopy by a retroperitoneal approach for marsupialization of the diverticulum, fulguration of the epithelial lining, and percutaneous marsupialization/ablation are treatment options.

The diagnosis is suggested on ultrasonography but is confirmed on CT scan or MRU ([Estrada et al, 2009](#)) (see [Fig. 130-21](#)). Delayed films demonstrate pooling of contrast material in the diverticulum. Ultrasonography delineates a fluid-filled area more centrally located near the collecting system than a simple renal cyst (see [Fig. 130-21](#)). When it is filled with microcalculi, ultrasonography characteristically demonstrates a layering effect, within the diverticulum, between clear fluid above and echo-dense debris without shadowing below ([Patriquin et al, 1985](#)). Ultrasonography will image the milk of calcium within the diverticulum as the patient changes position.

Patients who are asymptomatic do not require treatment but should be followed periodically with ultrasonography. [Estrada and colleagues \(2009\)](#) reported 10 of 23 calyceal diverticula (43%) that required treatment at a mean of 27 ± 25 months after initial diagnosis. Most commonly, these children presented with febrile UTI. The indications for surgery included enlargement of the diverticulum associated with pain or infection, abscess formation, urosepsis, and symptomatic calculus formation. Percutaneous ablation of the communication and fulguration of the diverticular lining was used until 1995. Although percutaneous ablation remains a viable

treatment alternative, the availability of pediatric laparoscopic equipment has led to the retroperitoneal laparoscopic approach for marsupialization of the diverticulum and fulguration of the epithelial lining (Estrada et al, 2009). Ureteroscopy with enlargement of the diverticular communication and removal of the stones has also been reported (Baldwin et al, 1998).

Hydrocalycosis

Hydrocalycosis is a rare cystic dilation of a major calyx with a demonstrable connection to the renal pelvis (Fig. 130-22).

Dilation of the upper calyx resulting from obstruction of the upper infundibulum by vessels or stenosis has been described (Johnston and Sandomirsky, 1972). Cicatrization of an infundibulum may result from infection or trauma or without an obvious etiology (Williams and Mininberg, 1968). It has been postulated that achalasia of a ring of muscle at the entrance of the infundibulum into the renal pelvis causes a functional obstruction (Williams and Mininberg, 1968).

Mild upper calyceal dilation caused by partial infundibular obstruction is relatively common but usually asymptomatic. Although the most frequent presenting symptom is upper

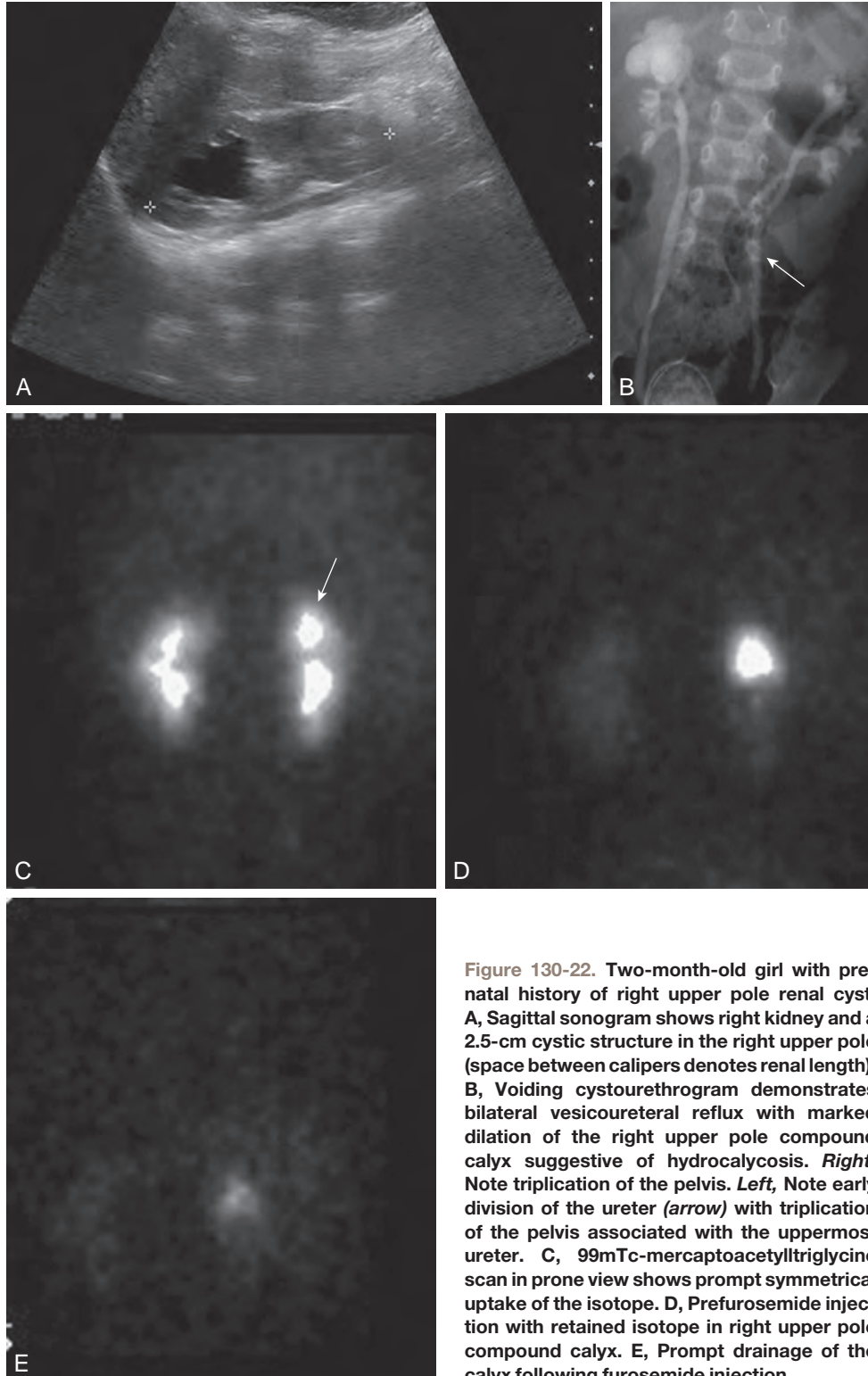


Figure 130-22. Two-month-old girl with pre-natal history of right upper pole renal cyst. **A**, Sagittal sonogram shows right kidney and a 2.5-cm cystic structure in the right upper pole (space between calipers denotes renal length). **B**, Voiding cystourethrogram demonstrates bilateral vesicoureteral reflux with marked dilation of the right upper pole compound calyx suggestive of hydrocalycosis. **Right**, Note triplication of the pelvis. **Left**, Note early division of the ureter (arrow) with triplication of the pelvis associated with the uppermost ureter. **C**, ^{99m}Tc -mercaptoacetyltriglycine scan in prone view shows prompt symmetrical uptake of the isotope. **D**, Prefurosemide injection with retained isotope in right upper pole compound calyx. **E**, Prompt drainage of the calyx following furosemide injection.

abdominal or flank pain, hydrocalycosis may be detected on prenatal ultrasonography (see Fig. 130-22). On occasion, a mass may be palpated. Stasis can lead to hematuria, urinary infection, or both.

Hydrocalycosis must be differentiated from multiple dilated calyces secondary to ureteral obstruction, calyceal clubbing as a result of recurrent pyelonephritis or medullary necrosis, renal tuberculosis, a large calyceal diverticulum, and megacalycosis.

Megacalycosis

Megacalycosis is defined as nonobstructive enlargement of calyces resulting from malformation of the renal papillae (Fig. 130-23). The calyces are generally dilated and malformed and may be increased in number (12 to 20) (Pieretti-Vanmarcke et al, 2009). The renal pelvis is not dilated, nor is its wall thickened, and the UPJ is normally funneled without evidence of obstruction. The cortical tissue around the abnormal calyx is normal in thickness. The medulla, however, is underdeveloped and assumes a falciform (crescent) or semilunar appearance instead of its normal pyramidal

shape. The collecting tubules are not dilated but are definitely shorter than normal, and they are oriented transversely rather than vertically from the corticomedullary junction (Puigvert, 1963). A mild disorder of maximal concentrating ability has been reported (Gittes and Talner, 1972), but acid excretion is normal after an acid load (Vela-Navarrete and Garcia Robledo, 1983). Other functions of the kidney such as glomerular filtration, renal plasma flow, and isotope uptake also are not altered (Gittes, 1984).

Megacalycosis is congenital and has been diagnosed prenatally (Vidal Company et al, 2001). It occurs predominantly in males with a ratio of 6:1 and has been found only in Caucasians. Bilateral disease has been seen almost exclusively in males, whereas segmental unilateral involvement occurs only in females (Cacciaguerra et al, 1996).

It was theorized by Puigvert (1964) and endorsed by Johnston and Sandomirsky (1972) that there is transient delay in the recanalization of the upper ureter after the branches of the UB hook up with the metanephric blastema. This produces transient obstruction when the glomeruli start producing urine. The fetal calyces may

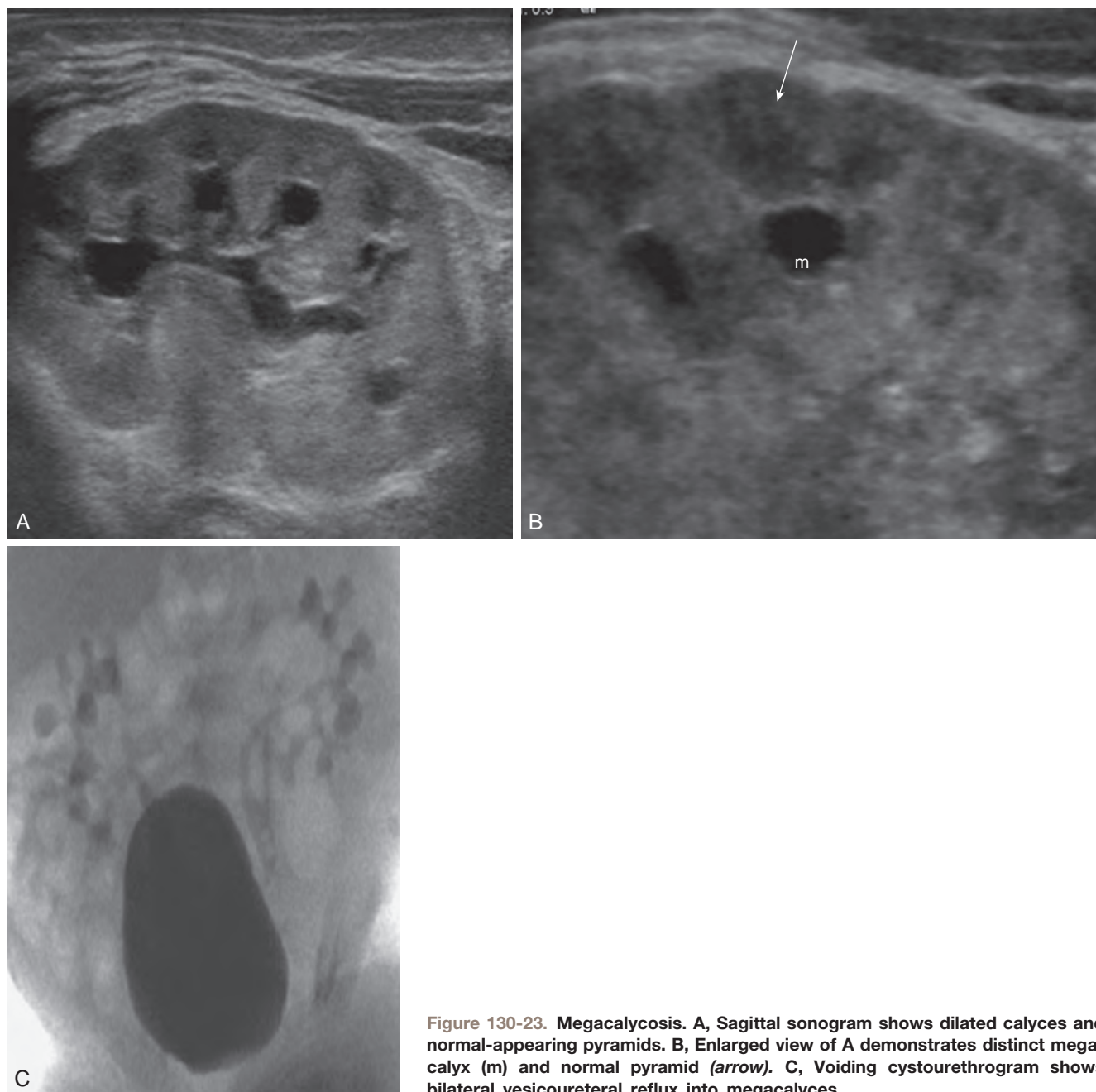


Figure 130-23. Megacalycosis. A, Sagittal sonogram shows dilated calyces and normal-appearing pyramids. B, Enlarged view of A demonstrates distinct megacalyx (m) and normal pyramid (arrow). C, Voiding cystourethrogram shows bilateral vesicoureteral reflux into megacalyces.

dilate and retain their obstructed appearance, despite the lack of evidence of obstruction in postnatal life (Gittes and Talner, 1972). The increased number of calyces may be an aborted response by the branching UB to the obstruction.

The abnormality is usually diagnosed during radiographic evaluation of a UTI or of other congenital anomalies (Arambasic et al, 2003). Adults frequently present with hematuria secondary to renal calculi.

The calyces are dilated and are usually increased in number, but the infundibuli and pelvis may not be enlarged. Although the UPJ does not appear obstructed, there may be segmental dilation of the distal third of the ureter (Kozakewich and Lebowitz, 1974). A normal-caliber ureter was interposed between the two entities. This anatomic picture may be mistaken for congenital ureteropelvic, ureterovesical junction obstruction, or infundibular stenosis (Pieretti-Vanmarcke et al, 2009). Diuretic renography shows a normal pattern for uptake and washout of the isotope (Gomez Tellado et al, 1997). Long-term follow-up of these patients does not show progression of the anatomic derangement or functional impairment of the kidney (Gittes, 1984).

KEY POINTS: MEGACALYCOSIS

- Megacalycosis is a nonobstructive enlargement of calyces resulting from malformation of the renal papillae.
- Megacalycosis occurs predominantly in males with a ratio of 6:1. Bilateral disease has been seen almost exclusively in males, whereas segmental unilateral involvement occurs only in females.
- Long-term follow-up of patients with this anomaly does not usually show progression of the anatomic or functional status of the kidney.

Pseudotumors of the Kidney

A renal pseudotumor is a prominence of normal renal parenchyma simulating a mass on radiographic studies. One such entity consists of cortical tissue situated between the infundibula of the upper and middle calyces, which splays or distorts the renal sinus and is called a hypertrophied column of Bertin (Fig. 130-24). These columns of Bertin have a similar echotexture to the surrounding parenchyma (Zwirewich and Rowley, 1997; Bhatt et al, 2007).

Another renal pseudotumor is termed *lobar dysmorphism*. This refers to a complete renal lobe that is seated deeply in the kidney and contains not only the renal cortex but a centrally located, well-formed calyx. Contrast studies show early opacification of the ectopic cortex, with sequential visualization of the medulla followed by the calyx. The sonographic finding of the posterior calyx and the echolucent pyramid is diagnostic for lobar dysmorphism (Zwirewich and Rowley, 1997).

Infundibulopelvic Stenosis

Infundibulopelvic stenosis most likely forms a link between cystic dysplasia of the kidney and the grossly hydronephrotic organ (Uhlenhuth et al, 1990). This condition includes a variety of radiographically dysmorphic kidneys with varying degrees of infundibular or infundibulopelvic stenosis that may be associated with renal dysplasia (Fig. 130-25). It is believed that this was the result of extensive dysgenesis of the pyelocalyceal system but with preservation of renal function.

Infundibulopelvic stenosis is usually bilateral and is commonly associated with vesicoureteral reflux, suggesting an abnormality of the entire UB (Kelalis and Malek, 1981). Patients usually present with urinary infection, hypertension, or flank pain. Sometimes, an asymptomatic child with multiple anomalies is found to have this condition. Despite extensively dysmorphic kidney features, the function is either normal or only slightly affected (Kelalis and Malek, 1981). In Husmann's study of 21 patients with the longest follow-up to date (median of 11 years), 90% had bilateral renal disease (Husmann et al, 1994). Ten patients had bilateral infundibulopelvic stenosis, six had a contralateral dysplastic renal unit, and three had contralateral URA. Renal insufficiency or end-stage renal disease (ESRD) developed in eight patients (37%), all of whom had bilateral kidney anomalies. Renal biopsies in those with ESRD demonstrated renal dysplasia proximal to the stenotic infundibuli and varying degrees of glomerulosclerosis of the glomeruli that were not involved in the regions with dysplasia. They proposed that the decreased total functional renal tissue leads to hyperfiltration injury. They suggested that endoscopic or percutaneous surgery should be considered for increasing hydronephrosis (see Fig. 130-25). More recently, Nurzia and colleagues (2002) recommend monitoring of renal function to include a baseline and yearly serum creatinine level, estimation of glomerular filtration rate, and urinalysis. Prevention of hyperfiltration injury with calcium channel blocking agents, ACE inhibitors, and dietary restriction of protein should be considered when a decline in renal function occurs (Puddu et al, 2009).

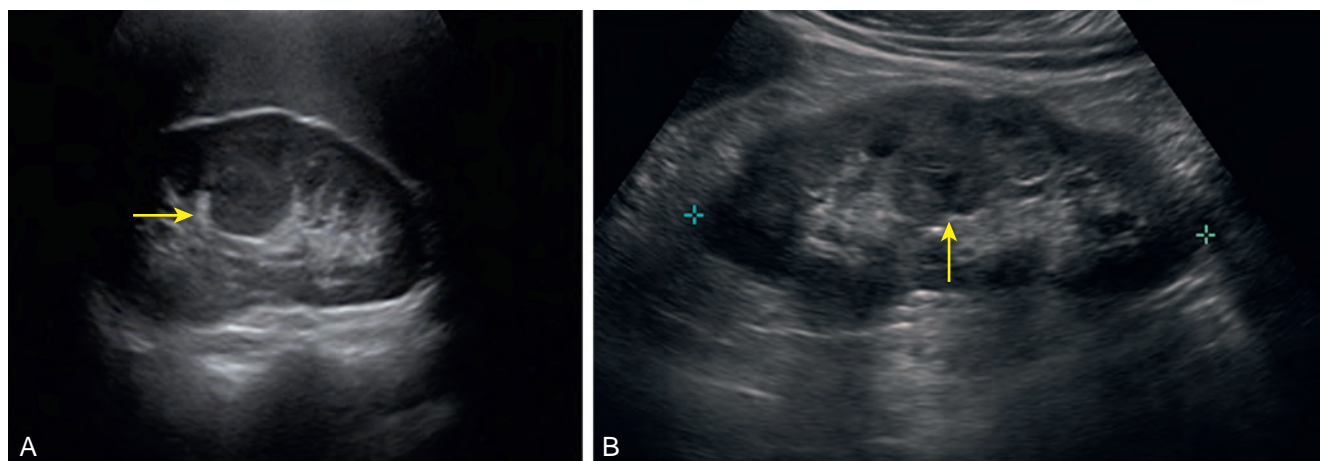


Figure 130-24. Sonogram of (A) sagittal view of right kidney with hypertrophied column of Bertin (arrow). B, Sagittal view of right kidney showing lobar dysmorphism resulting from malrotation of the renal lobe. The findings of a central echolucent pyramid and a posterior calyx (arrow) are diagnostic.

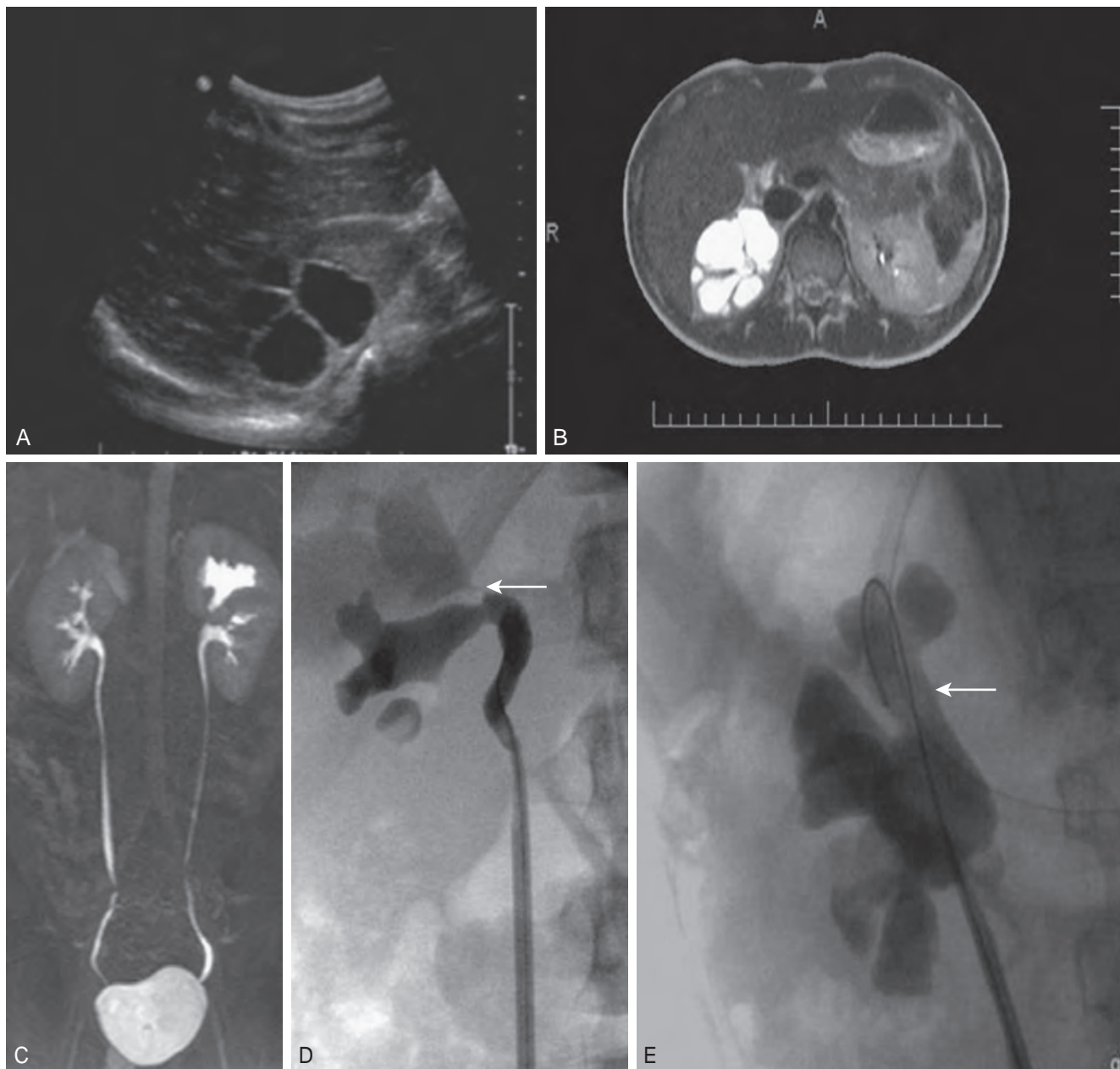


Figure 130-25. Infundibular stenosis of right upper pole calyx. A, Sagittal sonogram. B, Axial T2 images. C, Coronal magnetic resonance urogram. D, Right retrograde pyelogram shows no filling of the stenotic infundibulum (arrow). E, Right retrograde pyelogram following laser incision and balloon dilation of the infundibulum (arrow). (Courtesy Dr. Pasquale Casale.)

KEY POINTS: INFUNDIBULOPELVIC STENOSIS

- Infundibulopelvic stenosis most likely forms a link between cystic dysplasia of the kidney and the grossly hydronephrotic kidney.
- Infundibulopelvic stenosis is usually bilateral and is commonly associated with vesicoureteral reflux, suggesting an abnormality of the entire UB.

Bifid Pelvis

Approximately 10% of normal renal pelves are bifid, the pelvis dividing to form two major calyces first at, or just within, its entrance to the kidney. A bifid pelvis should be considered a normal variant.

If further division of the renal pelvis occurs, triplication of the pelvis may result, but this is extremely rare (see Fig. 130-22).

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The complete reference list is available online at www.expertconsult.com.



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Overview of Genetics

Renal Agenesis and Dysplasia

Hypoplasia and Hypodysplasia

Cystic Diseases of the Kidney

Autosomal Recessive (Infantile) Polycystic Kidney Disease

Autosomal Dominant (Adult) Polycystic Kidney Disease

Juvenile Nephronophthisis and Medullary Cystic Disease Complex

Other Inheritable Renal Cystic Diseases (Congenital Nephrosis)

Familial Hypoplastic Glomerulocystic Kidney Disease (Cortical Microcystic Disease)

Multiple Malformation Syndromes with Renal Cysts

Multicystic Dysplastic Kidney

Benign Multilocular Cyst (Cystic Nephroma)

Simple Cysts

Medullary Sponge Kidney

Sporadic Glomerulocystic Kidney Disease

Acquired Renal Cystic Disease

Calyceal Diverticulum (Pyelogenic Cyst)

Parapelvic and Renal Sinus Cysts

Congenital and acquired renal malformations constitute a wide spectrum of clinical entities. Ectopia and fusion anomalies are covered in another chapter. This chapter is devoted to those disorders that lead to dysgenesis of the kidney, cystic lesions of the kidney, or both.

Many of these conditions are related to maldevelopment of the kidney and urinary tract and are thus the result of anomalous genetic mechanisms, some of which are understood and others of which are not. A basic knowledge of molecular genetics is required to better understand normal renal development, absence of renal development, and the effects of genetic mutations and abnormal signaling proteins on renal maldevelopment and cystic diseases. Within this chapter, the relevant genetic processes are discussed as they relate to specific disease processes. Further discussion on the specific genes involved with renal development appears in Chapter 122 and in an article by [Glassberg in 2002](#).

OVERVIEW OF GENETICS

Genetic direction of kidney and urinary tract development results when a gene from a specific chromosomal area produces a protein product that then signals certain actions to occur within an individual cell or group of cells. This cellular differentiation is then responsible for the particular action of those cells. In general, when a gene is normal, its protein product is normal as well. When a gene is abnormal, it produces an abnormal protein that can lead to maldevelopment or disease. Obviously, with complex organogenesis, the process is not always this simple. Often, more than one gene can be responsible for a specific disease. For example, an abnormality of one of two genes is responsible for the entity tuberous sclerosis. One tuberous sclerosis gene, *TSC1*, is located on chromosome 9 and the second, *TSC2*, on chromosome 16.

Each gene within a cell is one of a set of two; each is called an *allele*. One defective allele may be the carrier for the defect. In [Knudson's \(1971\) two-hit theory](#), the first hit is an inherited mutation that is found in all cells of an individual (i.e., a

germline mutation). The second hit occurs when the wild-type, normal allele spontaneously mutates within a specific organ, although it may be a different mutation than in the primarily affected allele ([Knudson, 1971](#)). For example, the typical somatic cells in the kidney and all other cells of a patient with von Hippel-Lindau (VHL) disease typically are heterozygous for the *VHL* gene located on chromosome 3; that is, the mutant *VHL* allele is inherited and its mate is the normal wild-type allele. However, the configuration of wild-type *VHL* makes it prone to spontaneous mutation. If the wild-type allele develops a defect within the cells of a specific organ, those cells no longer are able to produce normal pVHL (VHL protein) with its suppressor properties. That organ then has the propensity to develop a tumor. The variability in manifestations of autosomal dominant polycystic kidney disease (ADPKD) may be related to a two-hit phenomenon as well. For example, ADPKD is a heterozygous condition in which one allele of the *PKD1* or *PKD2* set is responsible for the genetic transmission of the disease but may not be enough for cystogenesis. A spontaneous mutation of the wild-type allele may be responsible for cystogenesis or for other manifestations of the disease. [Qian and colleagues \(1996\)](#) suggested that the *PKD1* gene has an unusual genomic structure that makes it readily mutable for a second hit, and the timing of this second hit may account for the phenotypic variability within one family. The second hit itself may occur only in a few cells, possibly accounting for the fact that less than 1% of nephrons in ADPKD eventually develop cysts ([Qian et al, 1996](#)). Within a cyst, many but not all of the lining cells have lost their heterozygosity ([Brazier and Henske, 1997](#); [Qian et al, 1999](#)).

RENAL AGENESIS AND DYSPLASIA

There are many terms that can be used to describe anomalous development of the kidney. These terms are often used interchangeably and can result in great confusion. The definitions as adopted in 1987 by the American Academy of Pediatrics (AAP) Section on Urology ([Glassberg et al, 1987](#)) are used in this chapter.

Renal Agenesis

Renal agenesis, or absent kidney development, can result from anomalous development of the wolffian duct, ureteric bud, and/or metanephric blastema. Bilateral agenesis occurs in 1 of every 4000 births and has a male predominance (Potter, 1965). Fetal demise occurs secondary to the lack of fetal urine production and subsequent oligohydramnios. Affected infants are born with immature lungs and pneumothorax, Potter facies (hypertelorism, prominent inner canthal folds, and recessive chin), and orthopedic defects secondary to intrauterine compression. Most cases of bilateral agenesis are sporadic, and many are associated with other congenital anomalies, including urogenital sinus defects.

Unilateral agenesis is more common, with an incidence of 1 in 450 to 1000 births (Kass and Bloom, 1992). Again, a wolffian duct abnormality is often the cause, and associated other wolffian and müllerian abnormalities may also be present, such as malformation of the ipsilateral uterine horn, fallopian tube, or ovary in the female or absence of the ipsilateral testis, vas deferens, or seminiferous tubules in the male. Mayer-Rokitansky-Küster-Hauser syndrome refers to a group of associated findings that include unilateral renal agenesis or renal ectopia, ipsilateral müllerian defects, and vaginal agenesis. Of men with unilateral or bilateral congenital absence of the vas deferens, 26% or 11%, respectively, had renal agenesis. Congenital bilateral agenesis of the vas deferens is also an expected finding in male patients with cystic fibrosis. Cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutations frequently contribute to maldevelopment of the vas deferens, but vasal agenesis can occur without any evidence of *CFTR* defects. *CFTR* abnormalities are rarely detected in men with congenital absence of the vas deferens and renal anomalies (Schlegel et al, 1996).

Unilateral renal agenesis can also be associated with other urologic abnormalities in 48% of patients, including primary vesicoureteral reflux (28%), obstructive megaureter (11%), and ureteropelvic junction obstruction (UPJO) (3%) (Cascio et al, 1999). These findings are similar to those associated with unilateral multicystic kidney disease, suggesting the possibility that some absent kidneys represent involuted multicystic dysplastic kidneys (MCDKs).

Additional reading on renal agenesis may be found in Chapter 130.

KEY POINTS: RENAL AGENESIS

- Bilateral renal agenesis is associated with oligohydramnios and Potter facies (hypertelorism, prominent inner canthal folds, and recessive chin).
- Unilateral agenesis is often associated with other genitourinary anomalies, and these patients should be appropriately screened.

Dysplasia

Definition

Renal dysgenesis is defined as maldevelopment of the kidney that affects its size, shape, or structure. It is composed of two primary subtypes, the first of which is dysplasia. The term *dysplasia*, while literally and most simply is defined as “abnormal tissue,” specifically, as it relates to the kidney, can only truly be defined on the basis of histopathology. **Dysplasia is a histologic diagnosis made by the presence of embryonic, immature mesenchyme, and primitive renal components.** The differentiation of the metanephros into mature renal components halts at some point along the developmental pathway, often because of an error in the wolffian duct–ureteric bud–metanephric blastema interaction. Common histologic features include distortion of renal architecture, immature or primitive glomeruli, nephron precursors such as comma- and S-shaped bodies, and cartilage and tubules encircled by collars

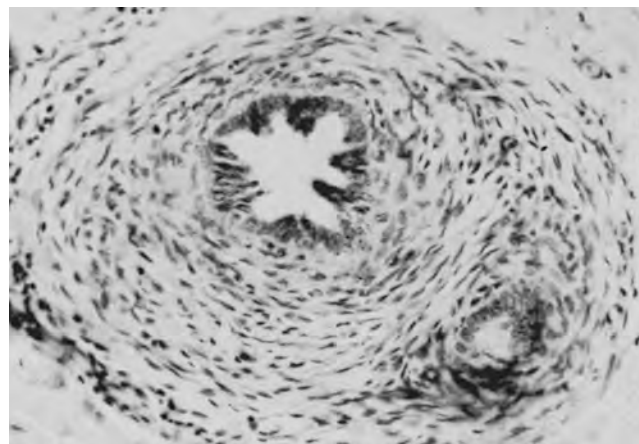


Figure 131-1. Primitive duct lined with columnar epithelial cells. Note concentric arrangement of spindle mesenchymal cells around the duct. Special staining is required to demonstrate smooth muscle cells.

of fibromuscular cells (referred to as *primitive ducts*) (Fig. 131-1). Ericsson and Ivemark (1958) considered these primitive ducts to be the sine qua non finding of all dysplasia. Cysts may or may not be present. The cause of the development of dysplasia appears to be twofold: (1) a primary, inherent abnormality in the differentiation of the nephron and collecting duct, often with an underlying genetic cause, and (2) a secondary cause resulting from congenital urinary tract obstruction.

KEY POINTS: DYSPLASIA

- The hallmark of dysplasia is the primitive duct, a duct encircled by a collar of fibromuscular cells.
- Dysplasia in its truest form is a histopathologic definition, not a clinical one.
- Dysplasia often is associated with ureteric bud anomalies and/or urinary tract obstruction.

Etiology

Renal dysplasia is the primary cause of childhood end-stage renal disease (ESRD), and two main theories have been considered in its pathogenesis: (1) a primary failure of ureteric bud activity and (2) a disruption in renal development produced by fetal urinary outflow impairment (obstruction). Mackie and Stephens (1975) described the ureteric bud theory, suggesting that ectopic (cephalad or caudal) ureteric bud formation leads to abnormal ureteric orifice location either laterally (often leading to vesicoureteral reflux) or distally (often leading to ureteral obstruction). Normal nephrogenesis is dependent on the ureteric bud meeting the center of the metanephric mesenchyme so that nephrogenesis is appropriately induced by the ureteric bud. However, an abnormally located ureteric bud would be expected to penetrate into a peripheral, degenerating area of the metanephric blastema. The result is a marginal (i.e., hypoplastic or dysplastic) kidney. In cases of dysplasia that are associated with an ectopic ureter, it is not clear if it is the obstruction, aberrant ureteric bud–metanephros interaction, or some other factor that leads to the dysplasia. Dysplasia associated with vesicoureteral reflux would also be included in this category.

Currently, there is no direct experimental evidence to prove that an abnormal ureteric bud site leads to ureteric bud penetration at a peripheral area of the blastema. However, there are substantial data to support the idea that defects in genetic and

apoptotic pathways can affect ureteric bud formation, branching morphogenesis within the metanephric blastema, and normal nephrogenesis (e.g., *RET*, *RAR*, *BMP4*, *SLIT2-ROBO2*, *COX-2*, *AT2*, *Fgfr2*) (Mendelsohn et al, 1994; Norwood et al, 2000; Pope et al, 2001; Grieshammer et al, 2004; Thomas et al, 2005; Bates, 2011). The genetic defect at each point may be the same, but the downstream pathway associated with the defect may vary for each process.

Animal studies of fetal urinary tract obstruction generate some but not all of the anatomic and histopathologic features of human renal dysplasia. Findings in these animal studies include dilation at various segments of the nephron and collecting duct, inhibition of nephron development in the nephrogenic zone, architectural disorganization, and the appearance of primitive glomeruli as well as S-shaped bodies and cysts. At times, obstruction in these animal models can even lead to de-differentiation of certain cells. An example is the conversion of renal epithelial cells back into mesenchymal cells and even of mesenchymal cells into myofibroblasts (Peters et al, 1992; Nguyen et al, 1999; Matsell and Tarantal, 2002). Dysplasia arising from obstruction typically appears at the periphery of the kidney, at the nephrogenic zone, and frequently with subcapsular cysts. This type usually develops later in gestation, as in the case of posterior urethral valves (PUVs) (Fig. 131-2).

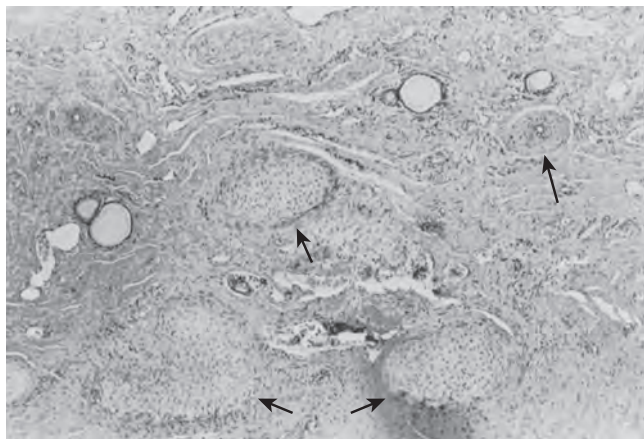


Figure 131-2. Histologic specimen of a nonfunctioning reflux kidney in a patient with posterior urethral valves. Note presence of nests of cartilage (short arrows). Primitive ducts are scattered throughout the specimen (long arrow) (100×). The findings are compatible with dysplasia.

Dysplasia is associated with numerous genetic syndromes (Fraser syndrome; branchio-oto-renal [BOR] syndrome; renal-coloboma syndrome; Kallmann syndrome; Simpson-Golabi-Behmel syndrome; Smith-Lemli-Opitz syndrome; hypoparathyroidism, sensorineural deafness, and renal dysplasia [HDR] syndrome, and Townes-Brocks syndrome, to name a few). The kidney, in association with these conditions, may be composed mostly of normal functioning parenchyma with areas of dysplasia, or, alternatively, the entire kidney may be dysplastic or entirely absent.

On rare occasions, renal agenesis, renal dysplasia, multicystic dysplasia, and renal aplasia may appear in family members but heterogeneously. One family member may have renal agenesis while another has renal dysplasia and still another has a multicystic dysplastic or aplastic kidney. When all or part of this group of anomalies is seen in one family, an encompassing term for these four entities is used: *familial renal adysplasia*.

Ultrasonographically, dysplastic kidneys have a distinct appearance. The kidney is typically small and is hyperechogenic when compared with the liver. There is loss of the typical corticomedullary differentiation, and there is minimal distinction of the renal parenchyma and the perirenal fat (Fig. 131-3A). Cysts can be seen in conjunction with parenchymal dysplasia (Fig. 131-3B). These cysts can also develop from either abnormal development of the metanephric blastema or from distal obstruction. Again, the exact cause of the cyst formation can be unclear. The important point is that not all cysts are a result of dysplasia and not all dysplasia is associated with cysts.

HYPOPLASIA AND HYPODYSPLASIA

Renal Hypoplasia

Another form of renal dysgenesis is hypoplasia, which is defined as the underdevelopment of a tissue or organ and which is usually caused by a deficiency in the number of cells. Renal hypoplasia is a condition in which there is a reduction in the size of the functioning renal mass. Use of the term *hypoplasia* should be restricted to kidneys that have less than the normal number of calyces and nephrons but are not dysplastic or embryonic. These are kidneys that are morphologically normal but have either a reduced number of nephrons or smaller nephrons, although a hypoplastic kidney may have a normal nephron density despite its small size. Hypoplasia may be bilateral or unilateral. In unilateral cases, the other kidney usually shows greater compensatory growth than is characteristic in patients with renal atrophy caused by acquired disease. Many have used the term *hypoplasia* to describe small kidneys associated with vesicoureteral reflux. These kidneys often do not function and have dysplastic elements histologically. The term *hypoplasia* is

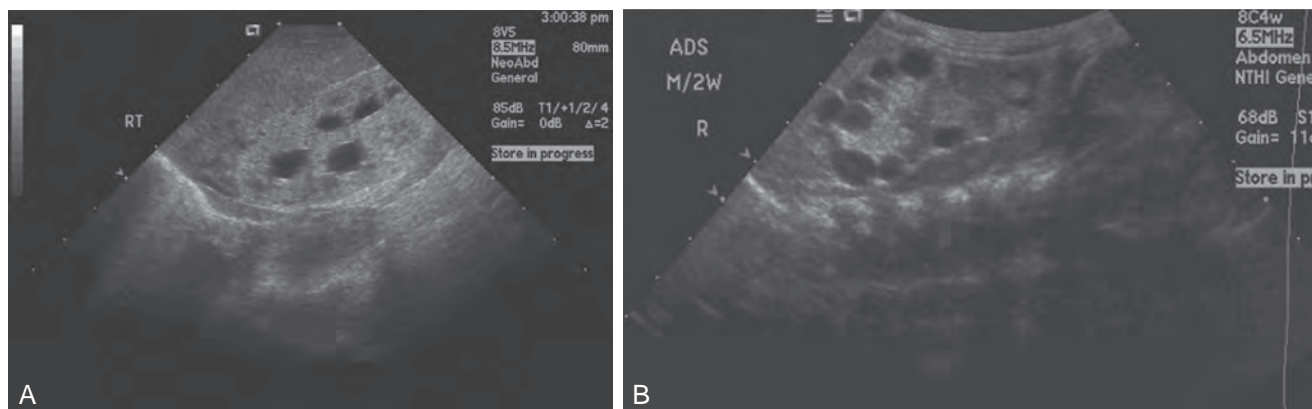


Figure 131-3. Ultrasonographic appearance of renal dysplasia. A, Classic dysplasia with hyperechogenic appearance of the kidney relative to the liver, a loss of normal corticomedullary differentiation, and dysmorphic calyces. B, Renal dysplasia accompanied by cysts. (Courtesy Marta Hernanz-Schulman, MD.)

thus technically incorrect, and a more appropriate term for these kidneys would be *congenital reflux nephropathy*. The terms *hypoplasia* and *congenital reflux nephropathy* should not, however, be used interchangeably. Small kidneys associated with reflux have been called *hypoplastic* in the past; however, now the term *reflux nephropathy* is used to describe the renal changes associated with reflux.

Hypodysplastic kidneys most often occur in conjunction with ectopic ureteric orifices, with the extent of dysplasia correlating with the degree of ectopia (Schwarz et al, 1981). However, hypodysplastic kidneys are seen in a few patients with normal ureteric orifices. In such patients, obstruction may or may not be present.

All forms of hypoplasia can be assessed by ultrasonography with measurement of the kidneys. The size will be reduced in all forms. Dilated calyces may also be seen. The collecting systems will be demonstrated by excretory urography if renal function is not sufficiently impaired to prevent this. Renal function is assessed biochemically and, if there is unilateral hypoplasia, by radionuclide studies.

Oligomeganephronia

First described in 1962 (Habib et al, 1962; Royer et al, 1962), oligomeganephronia is a type of renal hypoplasia that results from a quantitative defect of the renal parenchyma with a reduced number of nephrons and hypertrophy of each nephron. This condition differs histopathologically from simple hypoplasia in which the renal mass is reduced but the number of nephrons is normal. Oligomeganephronia may occur as a sporadic defect or in association with a number of syndromes. It is usually a bilateral condition, although a few instances of unilateral oligomeganephronia associated with contralateral renal agenesis have been reported (Griffel et al, 1972; Lam et al, 1982; Forster and Hawkins, 1994).

Etiology

Oligomeganephronia results from arrested development of the metanephric blastema at 14 to 20 weeks' gestation, with subsequent hypertrophy of glomeruli and tubules in the kidney. This hypertrophy and hyperfiltration results in further nephron injury and sclerosis. Eventually, this progressive loss of nephrons leads to ESRD. Although oligomeganephronia is associated with some genetic syndromes, most cases are sporadic. However, mutations in the paired-box transcription factor (*PAX2*) gene have been noted in persons with nonsyndromic oligomeganephronia (Salomon et al, 2001). Recently, mutations in the homeobox transcription factor (hepatocyte nuclear factor-1 β) have been described in association with oligomeganephronia (Bohn et al, 2003). It is interesting to note that the heterozygous mutation may be associated with development of the kidney lesion. Vascular abnormalities and accidents have been associated with this type of renal hypoplasia. The cause of most oligomeganephronia cases is unknown.

Clinical Features

Oligomeganephronia is a nonheritable congenital disorder, and boys appear to be affected more often than girls. It frequently is associated with low birth weight (2500 g). The condition is usually discovered within the first 2 years of life. In neonates, kidney disease is often suspected with spontaneous pneumothorax, feeding problems, or laboratory abnormalities. Oligomeganephronia typically manifests with anorexia, vomiting, dehydration, intense thirst, polyuria, and failure to thrive. It may also be incidentally diagnosed when renal anomalies are discovered in the evaluation of another illness. The creatinine clearance is abnormal (10 to 50 mL/min/1.73 m²), and the maximum specific gravity of the urine is 1.007 to 1.012. Moderate proteinuria may be present, but this is more likely to be a later finding. In neonates with oligomeganephronia, particular attention should be directed to diagnosis of associated syndromes, including BOR syndrome, acrorenal syndrome, and tapetoretinal dystrophy.

After the first year of life, individuals with oligomeganephronia most often have short stature, polyuria and polydipsia, or proteinuria. Renal function remains below normal (although stable) for many years. As the patient enters his or her teens, the creatinine clearance begins to drop rapidly. Marked proteinuria (2 g/24 hr) is common. Over a period of years, the kidney continues to atrophy with reduction in the number of tubules. Oligomeganephronia is a progressive disorder, and many patients go on to renal failure in the second decade.

Histopathology

Meticulous histologic examination of the kidney is the only way to establish an absolute diagnosis of oligomeganephronia. There is a reduced number of nephrons, which are all elongated (sometimes fourfold) and widened, particularly at the proximal end (Fig. 131-4). Immature glomeruli are often present. Existing glomeruli and tubules are enlarged. As the disease progresses, segmental sclerosis and hyalinosis of glomeruli are present. Tubular atrophy with interstitial fibrosis occurs. The renal artery is small.

Evaluation

Proteinuria is often the first laboratory manifestation of oligomeganephronia and precedes decline in renal function by several years. Other laboratory manifestations of renal failure are frequently present, including elevated blood urea nitrogen (BUN) and creatinine levels, hyponatremia, and metabolic acidosis. Advancing renal failure may result in secondary hyperparathyroidism and anemia as a result of erythropoietin deficiency. In terms of imaging studies, small kidney size depicted on renal ultrasonography (RUS) usually establishes the diagnosis of hypoplasia.

Treatment

In general, treatment is supportive and directed at maintaining normal biochemical balance, hemoglobin, and growth. High fluid intake and correction of salt loss and acidosis are the initial steps. Daily dietary protein should be limited to 1.5 g/kg during the stable phase (Royer et al, 1962). In addition, angiotensin-converting enzyme (ACE) inhibitors may be of benefit in slowing progression of renal failure, even if the patient has a normal blood pressure (BP). ESRD is managed by dialysis and transplantation. The allograft may come from a living related donor because the disease is not familial.

Ask-Upmark Kidney (Segmental Hypoplasia)

In 1929, Erik Ask-Upmark, a Swedish physician, described distinctive small kidneys in eight patients, seven of whom had malignant hypertension; six of these patients were adolescents. Subsequently, this problem was described histologically as focal renal hypoplasia resulting in a segmental renal scar. Segmental renal hypoplasia, or Ask-Upmark kidney, refers to situations of extreme acquired reflux nephropathy, and the patients (usually young women and girls) most frequently have hypertension. The lesions found in these kidneys are most likely acquired, possibly representing chronic atrophic pyelonephritis caused by vesicoureteral reflux, although some appear to be congenital. Segmental vascular (arterial) anomalies have also been cited as a possible cause for these lesions.

Clinical Features

Most patients are 10 years of age or older at diagnosis. The disease is associated with severe hypertension, sometimes with headaches, either alone or together with hypertensive encephalopathy (Rosenfeld et al, 1973) and with retinopathy in half of the patients (Royer et al, 1971).

Proteinuria and some degree of renal insufficiency may be present if the disease is bilateral. Approximately half of the patients

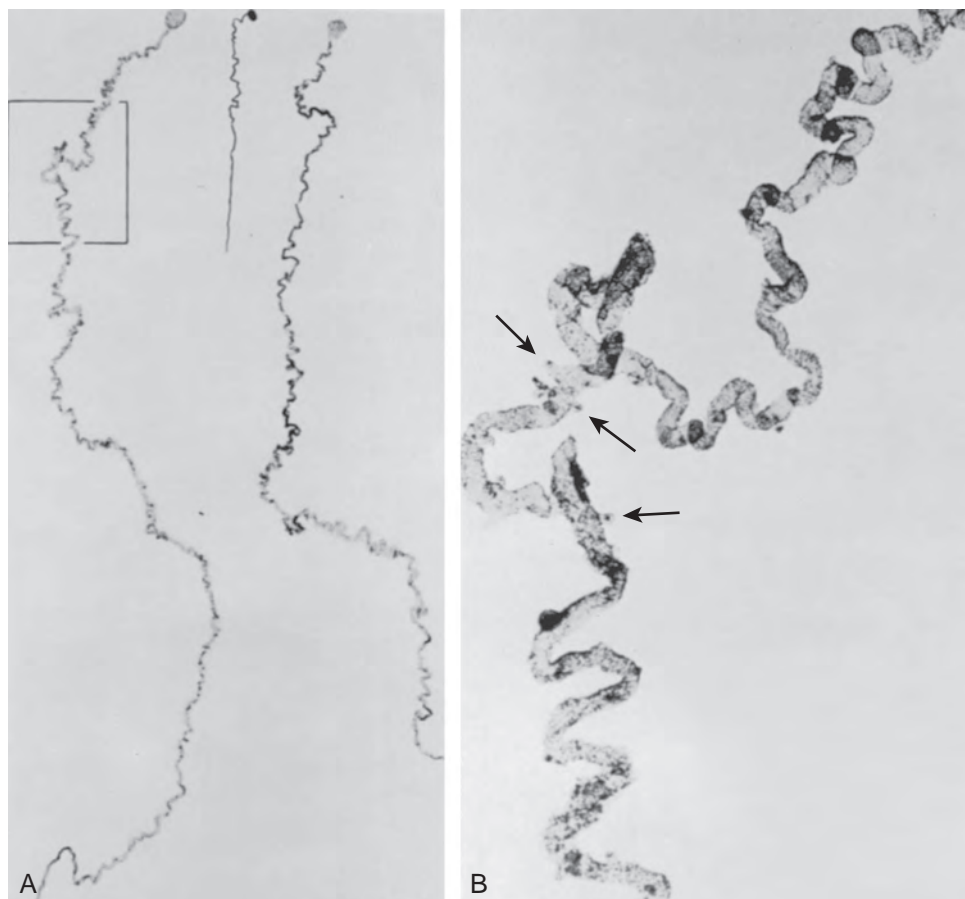


Figure 131-4. A, Mosaic photograph of two typical proximal tubules dissected from the kidney of a patient with oligomeganephronia. The silhouette in the top center is a diagrammatic representation to scale of an average proximal tubule from a kidney of an age-matched control. B, Enlargement of the inset in A showing the diverticula along the course of the nephron (arrows). (From Fetterman GH, Habib R. Congenital bilateral oligonephronic renal hypoplasia with hypertrophy of nephrons [oligomeganephronia]. *Am J Clin Pathol* 1969;52:199–207.)

in the series described by [Royer and colleagues \(1971\)](#) had these signs at diagnosis. The disorder is usually unilateral, producing a small kidney with deep, narrow, segmental scars (slit-scar) found in the midzone. These slit-scars are the classic radiographic finding. Although the scar can be detected with ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), the presence of a deep scar is often overlooked.

Histopathology

The Ask-Upmark kidney is smaller than normal—12 to 35 g ([Royer et al, 1971](#)). Its distinctive feature is one or more deep grooves on the lateral convexity, underneath which the parenchyma consists of tubules resembling those in the thyroid gland. Usually, the hypoplastic segments are easily distinguished from adjacent areas. The medulla consists of a thin band, and remnants of the corticomedullary junction and arcuate arteries are seen. Arteriosclerosis is common, and juxtaglomerular hyperplasia may be seen ([Bernstein, 1968](#); [Meares and Gross, 1972](#); [Kaufman and Fay, 1974](#); [Arant et al, 1979](#)) (Fig. 131-5).

Treatment

Abnormal renin secretion has been proposed as the cause of the hypertension; however, nephrectomy has been shown to normalize BP regardless of plasma renin activities ([Babin et al, 2005](#)). In

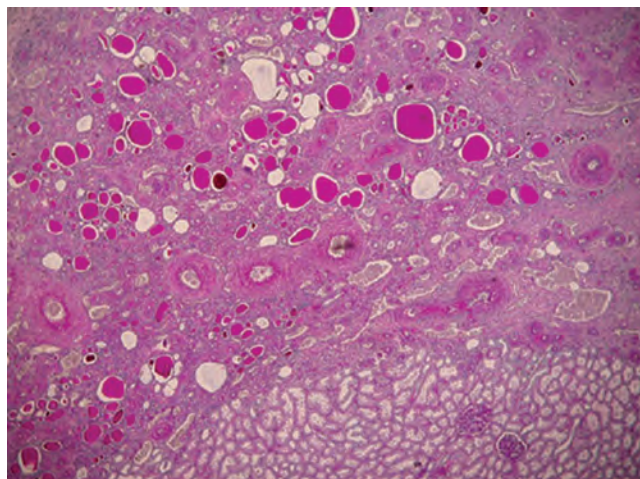


Figure 131-5. Typical microscopic pattern of segmental hypoplasia affecting the cortex with thyroid-like tubules, thick-walled arteries, and the absence of glomerulus. Note the sharp delineation from the surrounding normal kidney (bottom). Periodic acid-Schiff stain. (From Babin J, Sackett M, Delage C, et al. The Ask-Upmark kidney: a curable cause of hypertension in young patients. *J Hum Hypertens* 2005;19:315–6.)

patients with unilateral disease, partial or total nephrectomy may control the hypertension (Royer et al, 1971; Meares and Gross, 1972). Failure of this measure suggests an unrecognized scar or generalized arteriosclerosis in the remaining kidney (Arant et al, 1979). Bilateral disease with renal insufficiency usually is managed medically, although dialysis and transplantation may be needed. Correction of reflux may prevent further renal damage but probably will have no effect on the hypertension.

Renal Hypodysplasia

Hypodysplasia may be associated with a wide spectrum of urologic diseases, such as primary obstructive megaureter and UPJO, ureterocele, urethral obstruction, or prune-belly syndrome, to name a few. It has been previously mentioned that abnormal ureteric budding leads to abnormal renal development that often manifests as hypodysplasia. Lateral ureteral ectopia usually leads to vesicoureteral reflux and its associated forms of hypodysplasia—be it a developmental anomaly, the result of chronic pyelonephritis, or a combination of both. Medial ureteral ectopia, with or without the presence of a ureterocele, can often result in hypodysplasia as well. The renal cortex may be thin, secondary to hydronephrosis, or severely dysplastic, and perhaps with numerous small cysts.

According to Osathanondh and Potter (1964), PUVs may be associated with two types of renal hypodysplasia. In the less severe form, there are small, usually subcapsular cysts and nearly normal renal function. In the second form, the cysts are larger and more widely distributed, and numerous islands of cartilage are present. This form usually is associated with earlier onset and more severe obstruction and reflux (see Fig. 131-2).

The features of the prune-belly syndrome (absent abdominal musculature, triad syndrome) include grossly deformed kidneys, which may have various degrees of hypodysplasia. The ureters are wide and tortuous, often with large and laterally placed orifices. Urethral obstruction or atresia may be present in the most severe cases, but usually there is no lower urinary tract obstruction.

KEY POINTS: HYPOPLASIA AND HYPODYSPLASIA

- Hypoplasia and hypodysplasia often are associated with ectopic orifices and sometimes with obstruction.
- Oligomeganephronia is a condition with a reduced number of nephrons and hypertrophy of each nephron.
- Ask-Upmark kidneys have segmented dysplasia, are seen most frequently in association with reflux, and are often the cause of severe hypertension.

CYSTIC DISEASES OF THE KIDNEY

The kidney is one of the most common sites in the body for cyst formation. Renal cystic diseases encompass a broad spectrum of sporadic and genetically determined congenital or acquired conditions that have in common the presence of cysts in one or both kidneys. These diseases often require a multidisciplinary approach to evaluation and treatment.

Renal cysts are cavities derived primarily from tubules and are composed of a layer of partially de-differentiated epithelial cells enclosing a cavity filled with urine-like liquid or semisolid material. They may develop in any tubular segment between the Bowman capsule and the tip of the renal papilla, depending on the nature of the underlying disorder. Some cysts are saccular or fusiform structures that resemble diverticula. Other cysts may or may not communicate with a glomerulus, tubule, collecting duct, or calyx, or they may initially have communicated only to become isolated later. **Multicystic dysplasia is an exception in that it arises before formation of the nephron, from abnormal induction of metanephric development, from a primary abnormality**

of the nephrogenic blastema, or from obstruction occurring early in renal development. Another exception, benign multilocular cyst, represents a neoplastic growth.

The fundamental processes that are essential for the development and progressive enlargement of renal cysts include (1) proliferation of epithelial cells in segments of renal tubule, (2) accumulation of fluid within the expanding tubule segment, and (3) disturbed organization and metabolism of the extracellular matrix (Fig. 131-6).

An imbalance of the secretory and absorptive properties in proliferating epithelial cells leads to a net accumulation of fluid in otherwise normal renal tubules. Beyond the loop of Henle, tubule cells have the capacity to secrete solutes and fluid on stimulation with 3',5'-cyclic adenosine monophosphate (cAMP) (Wallace et al, 2001). This secretory flux operates in competition with the more powerful mechanism by which sodium (Na^+) is absorbed through apical epithelial Na^+ channels (ENaC). Under conditions in which Na^+ absorption is diminished, the net secretion of sodium chloride (NaCl) and fluid occurs.

Abnormalities of the extracellular matrix in and about renal cysts are seen in all cystic disorders. In the early stages of renal cyst development, changes in expression of collagen I and IV, metalloproteinase activators and inhibitors, integrins, and β -catenin may forecast a vital role for extracellular matrix remodeling in the pathogenesis of renal cysts. Recently, a hypomorphic mutation in the mouse laminin $\alpha 5$ gene was found to cause polycystic kidney disease (PKD) (Joly et al, 2006; Shannon et al, 2006).

Until recently, the mechanisms responsible for the abnormal differentiation and functional behavior of the epithelial cells that give rise to the cysts were largely unknown. Evidence now strongly suggests that a long-neglected structure, the primary cilium, is essential in maintaining epithelial cell differentiation. Structural and functional defects in the primary apical cilia of tubular epithelia may have a central role in determining cyst development and the abnormal differentiation and behavior of the cystic epithelium, and in various forms of human and rodent cystic diseases (Torres and Grantham, 2008). There have been several novel signaling pathways identified that are involved in the regulation of these epithelial cells and that are providing new opportunities for targeted therapies to slow and/or prevent cystogenesis (Blanco and Wallace, 2013; Choi et al, 2013; Mochizuki et al, 2013; Zhou et al, 2013).

Cystic kidneys of different causes may appear morphologically similar, whereas the same etiologic entity may cause a wide spectrum of renal abnormalities. For example, in ADPKD, tuberous sclerosis, VHL disease, and acquired renal cystic disease (ARCD), the cysts have a hyperplastic lining, sometimes with nodules of hyperplasia or polyps that project into the cyst lumen. However, these hyperplastic conditions are very different from one another. Another example of such similarities is the ectatic collecting ducts seen in two very different clinical entities, autosomal recessive polycystic kidney disease (ARPKD) and medullary sponge kidney.

Classification

In this chapter, the classification of renal cystic disease as outlined in 1987 by the Committee on Classification, Nomenclature, and Terminology of the AAP Section on Urology is used. **The primary distinction is between genetic (inheritable) and nongenetic (nonheritable) disease.** Box 131-1 gives an overview of characteristics associated with the various forms of cystic disease.

The terms multicystic and polycystic should not be confused, even though both terms literally mean “many cysts.” *Multicystic* typically refers to a dysplastic kidney resulting from aberrant renal development. *Polycystic* refers to renal units that developed in a normal fashion, all of which have no dysplasia and have nephrons throughout the kidney. The term *polycystic kidney disease* traditionally is used in reference to two conditions: ARPKD and ADPKD. Many of the PKD entities progress to renal failure as the nephrons become more diseased. In other conditions, such as tuberous sclerosis and VHL disease, there are hyperplastic cysts, and the

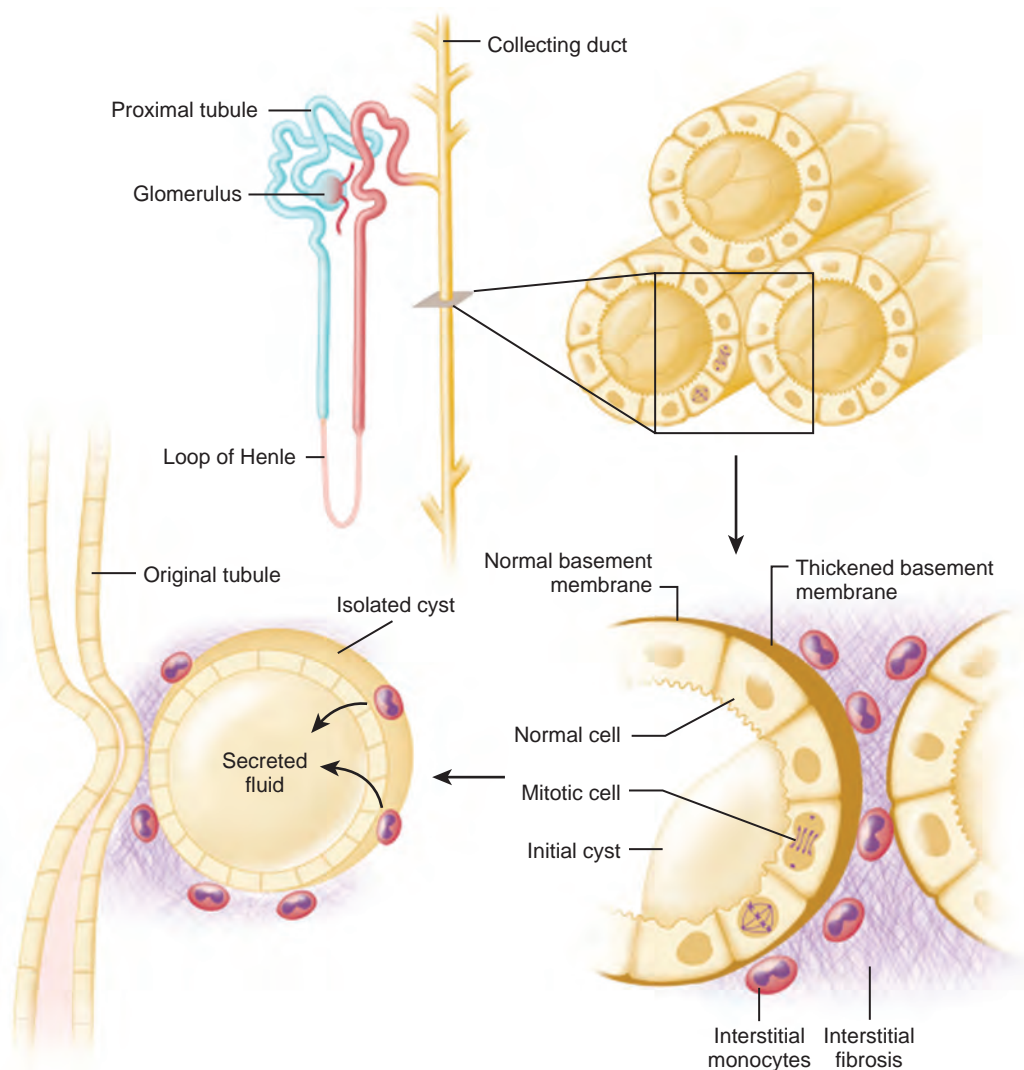


Figure 131-6. Evolution of cysts from renal tubules. Abnormal proliferation of tubule epithelium begins in a single cell after a “second-hit” process disables the function of the normal allele. Repeated cycles of cell proliferation lead to expansion of the tubule wall into a cyst. The cystic epithelium is associated with thickening of the adjacent tubule basement membrane and with an influx of inflammatory cells into the interstitium. The cystic segment eventually separates from the original tubule, and net epithelial fluid secretion contributes to the accumulation of liquid within the cyst cavity. (From Brenner BM, editor. *Brenner and Rector’s the kidney*. 8th ed. Philadelphia: Saunders; 2008. p. 1428.)

individual nephrons are normal. Only occasionally do the nephrons become compressed by the cysts or by associated tumors, and only in such situations does renal failure ensue.

Among the nonheritable cystic diseases, benign multilocular cysts, cystic renal cell carcinoma (RCC), and other variants are considered neoplasms. Medullary sponge kidney is a disease principally of dilated ectatic collecting ducts, with cysts playing a lesser role, although the size of the ducts by definition makes them cysts. The nephrons initially are normal.

Inheritable Cystic Disease

Genetic (inheritable) cystic diseases can be classified based on their mode of transmission: autosomal dominant, autosomal recessive, X-linked, and others. Some of these disorders are caused by a single gene defect, some by an X-linked gene defect, and others by chromosomal defects. The modes of inheritance of these diseases and the specific gene or gene locus, where identified, are summarized in Table 131-1.

AUTOSOMAL RECESSIVE (INFANTILE) POLYCYSTIC KIDNEY DISEASE

ARPKD is typified by relatively rapid, symmetrical, and bilateral enlargement of the kidneys in infants secondary to collecting duct cysts. It is invariably associated with some degree of congenital hepatic fibrosis (Zerres et al, 1988; Guay-Woodford and Desmond, 2003; MacRae Dell and Avner, 2003). ARPKD has been referred to as the “infantile” form in the past; however, the disease can occur in adolescents and young adults, although significantly less frequently. ARPKD has a spectrum of severity, with the most severe forms appearing earliest in life. If it is not apparent at birth, the disease will become apparent later in childhood (up to age 13 years or, rarely, up to age 20 years).

The reported incidence of ARPKD varies from 1 in 10,000 to 50,000 live births (Zerres et al, 1988; Kaplan et al, 1989a). However, as many as 50% of affected newborns die in the first few days of life, making for a significantly lower incidence among children who live for at least 1 year. Of those infants who survive the neonatal

BOX 131-1 Cystic Diseases of the Kidney**INHERITABLE**

Autosomal recessive (infantile) polycystic kidney disease
 Autosomal dominant (adult) polycystic kidney disease
 Juvenile nephronophthisis and medullary cystic disease complex
 Juvenile nephronophthisis (autosomal recessive)
 Medullary cystic disease (autosomal dominant)
 Congenital nephrosis (familial nephrotic syndrome) (autosomal recessive)
 Familial hypoplastic glomerulocystic disease (autosomal dominant)
 Multiple malformation syndromes with renal cysts (e.g., tuberous sclerosis, von Hippel-Lindau disease)

NONHERITABLE

Multicystic kidney (multicystic dysplastic kidney)
 Benign multilocular cyst (cystic nephroma)
 Simple cysts
 Medullary sponge kidney
 Sporadic glomerulocystic kidney disease
 Acquired renal cystic disease
 Calyceal diverticulum (pyelogenic cyst)

period, approximately 50% are alive at 10 years of age (Kaplan et al, 1989a).

Genetics

Once the diagnosis of ARPKD is strongly suspected, referral for genetic evaluation and counseling is appropriate. A detailed history should be taken of at least three generations. **Because the disease is transmitted as an autosomal recessive trait, siblings of either sex have a 1 in 4 chance of being affected.**

Despite the clinical variability of ARPKD, it appears that only mutations of a single gene, named *PKHD1* and located on chromosome 6 (6p12), are responsible for the disease. The gene produces a protein called *fibrocystin* (also known as *polyductin*) (Onuchic et al, 2002; Ward et al, 2002). This protein is a member of a larger family of proteins involved in regulation of cell proliferation and of cellular adhesion and repulsion. More specifically, dysfunction of this protein mediates cystogenesis through dysfunction of the primary cilia of renal epithelial cell. It is highly expressed in the kidney, with levels also present in the liver and pancreas. It is localized to the branching ureteric bud, collecting ducts of the kidney, and biliary ducts, consistent with the phenotype seen in ARPKD, and it is often absent in the patients with ARPKD (Wilson, 2004; Al-Bhalal and Akhtar, 2008).

Clinical Features

Affected children typically have enlarged, echogenic kidneys in utero. Oligohydramnios is common because of the lack of normal urine production by the fetus. The infant often displays Potter facies and deformities of the limbs and may have respiratory distress as a consequence of pulmonary hypoplasia. The affected newborn usually has enormous, kidney-shaped, nonbosselated flank masses that are hard and do not transilluminate. In some cases, the kidneys are large enough to impede delivery. The infant's serum creatinine and BUN concentrations are those of the mother's at birth but soon begin to rise. Thirty percent to 50% of the affected individuals die shortly after birth as a result of uremia or respiratory failure (Kaplan et al, 1989b; Capisonda et al, 2003; Guay-Woodford, 2003). The earlier the age at which the disease is identified, the

more severe the disease. **No matter what the severity of the renal disease, all patients with ARPKD have liver involvement in the form of congenital hepatic fibrosis and vary in the degree of biliary ectasia and periportal fibrosis** (Habib and Bois, 1973; Kissane and Smith, 1975).

Patients who survive the neonatal period have a milder form of the disease and are likely to survive into adulthood. Some diagnosed as neonates can live beyond age 3 or 4 years before going into renal failure (Cole et al, 1987; Avni et al, 2002). **Hypertension and renal insufficiency are the major manifestations in surviving children, with liver disease becoming more prevalent in older patients.** The exact cause of hypertension remains unclear. Consequences of chronic renal insufficiency (e.g., growth failure, anemia, osteodystrophy) become more apparent as the children age. Renal calcifications occur commonly in patients with ARPKD.

Patients whose disease appears later in life develop renal failure and hypertension more slowly. In general, their clinical problems are the consequence of liver disease rather than the renal disease, with hepatic fibrosis leading to portal hypertension, esophageal varices, and hepatosplenomegaly. Hepatocellular function is rarely abnormal, with liver enzymes typically remaining normal. The kidneys in these patients are often normal in appearance.

No association of ARPKD with renal neoplasms has been reported to date.

Histopathology

The kidneys are symmetrically enlarged (up to 20 times their normal size) and retain a reniform configuration. The parenchyma exhibits small subcapsular cysts, representing generalized fusiform dilations of the collecting tubules radiating from the medulla to the cortex with their long axis perpendicular to the renal surface (Bisceglia et al, 2006). Almost 100% of collecting ducts are affected in the most severe cases. The cortex is crowded with minute cysts (Fig. 131-7A). The renal pedicle is normal, as are the renal pelvis and ureter.

ARPKD affects both the kidneys and the liver in approximately inverse proportions (Torres and Grantham, 2008). The disease may be viewed as a spectrum ranging from severe renal disease and mild liver changes at one extreme to mild renal damage and severe liver disease at the other. The form with severe renal disease is the most common and the one typically seen at or near the time of birth. The form with less severe renal disease and more significant liver damage is present in older children. **All children with ARPKD have lesions in the periportal areas of the liver** (Habib and Bois, 1973; Kissane and Smith, 1975) (Fig. 131-7B). Congenital hepatic fibrosis is characterized by enlarged and fibrotic portal areas with apparent proliferation of bile ducts, absence of central bile ducts, hypoplasia of the portal vein branches, and sometimes prominent fibrosis around the central veins. Bulbar protrusions from the walls of dilated ducts also occur, and bridges sometimes form. This malformation has been found to occur occasionally as an isolated event (Caroli disease), but most often it is associated with ARPKD (Torres and Grantham, 2008).

Evaluation

The diagnosis may be suspected from in utero ultrasound examination and may be associated with oligohydramnios, a finding secondary to low urinary output. **In both fetus and newborn, ultrasonography identifies bilateral, very enlarged, diffusely echogenic kidneys, especially when compared with the echogenicity of the liver** (Fig. 131-8A). The increased echogenicity is due to the presence of numerous microcysts (created by tightly compacted, dilated collecting ducts) that result in innumerable interfaces. Compared with normal newborn kidneys, in ARPKD, the pyramids are hyperechogenic because they blend in with the rest of the kidney, and the kidneys typically have a homogeneous appearance (see Fig. 131-8A). In ADPKD, the cysts, if apparent in newborns, are usually diffuse and large (see Fig. 131-8B). Also included in the differential diagnosis is severe bilateral

TABLE 131-1 Characteristics of Major Inheritable and Nonheritable Cystic Kidney Diseases

DISEASE ENTITY	CHROMOSOMAL DEFECT	RENAL FINDINGS	EXTRARENAL MANIFESTATIONS
INHERITABLE			
Autosomal recessive polycystic kidney disease (ARPKD)	Chromosome 6	In newborn usually large, homogeneous, echogenic kidneys	Congenital hepatic fibrosis; biliary dysgenesis
Autosomal dominant polycystic kidney disease (ADPKD)	<i>PKD1</i> : chromosome 16 <i>PKD2</i> : chromosome 4 <i>PKD3</i> : not mapped	Renal cysts scattered throughout parenchyma; large kidneys	Diverticulitis; liver, spleen, pancreatic cysts; mitral valve prolapse; intracranial (berry) aneurysms
Juvenile nephronophthisis and medullary cystic disease complex Juvenile nephronophthisis (autosomal recessive) Medullary cystic disease (autosomal dominant)	Chromosome 2; not mapped	Cysts of corticomedullary junction; develop after onset of renal failure; always thickened tubular basement membrane	Retinitis pigmentosa (16%; also known as Senior-Loken syndrome); rarely skeletal abnormalities, hepatic fibrosis, Bardet-Biedl syndrome, ocular motor apraxia, and other neurologic defects
		Cysts of corticomedullary junction; develop before onset of renal failure; tubular basement membrane may not be thickened	None
Tuberous sclerosis (autosomal dominant)	<i>TSC1</i> : chromosome 9 <i>TSC2</i> : chromosome 16	Cysts and angiomyolipomas throughout kidney; cysts even present in utero; 3% incidence of RCC	Adenoma sebaceum; epilepsy; mental retardation; cranial tumors
von Hippel-Lindau disease (autosomal dominant)	Chromosome 3	Cysts, adenomas, and clear cell RCC (35%-38% of cases)	Cerebellar hemangioblastomas; retinal angiomas; pheochromocytomas; cysts of pancreas and epididymis
NONHERITABLE			
Multicystic dysplastic kidney	Renal maldevelopment with diffuse cysts and remnants of early metanephros; minimal, if any, nephron development; most frequent renal cystic disease in newborns		Unusual
Benign multilocular cyst	Benign cystic neoplasm of the kidney; remainder of kidney has normal nephrons that may be compromised by growing mass; present more often in males when younger than 4 yr and females when older than 30 yr		None
Simple cysts	Single or multiple cysts; normal nephrons throughout kidney; very common in normal kidneys with increasing age		None
Medullary sponge kidney	Ectatic collecting ducts; nephrons usually normal		None
Acquired renal cystic disease	Diffuse cysts; adenomas; occasionally RCC; increases with duration of ESRD		None

ESRD, end-stage renal disease; RCC, renal cell carcinoma.



Figure 131-7. Newborn with abdominal mass and pulmonary hypoplasia. Neither parent had a history of renal cysts. A, Renal histology demonstrates dilated ducts radiating out to the periphery of the kidney. B, On liver histology, ectatic biliary ducts are seen in the left half of the figure, and periportal fibrosis is seen at the upper edge. These findings confirm the diagnosis of autosomal recessive polycystic disease.

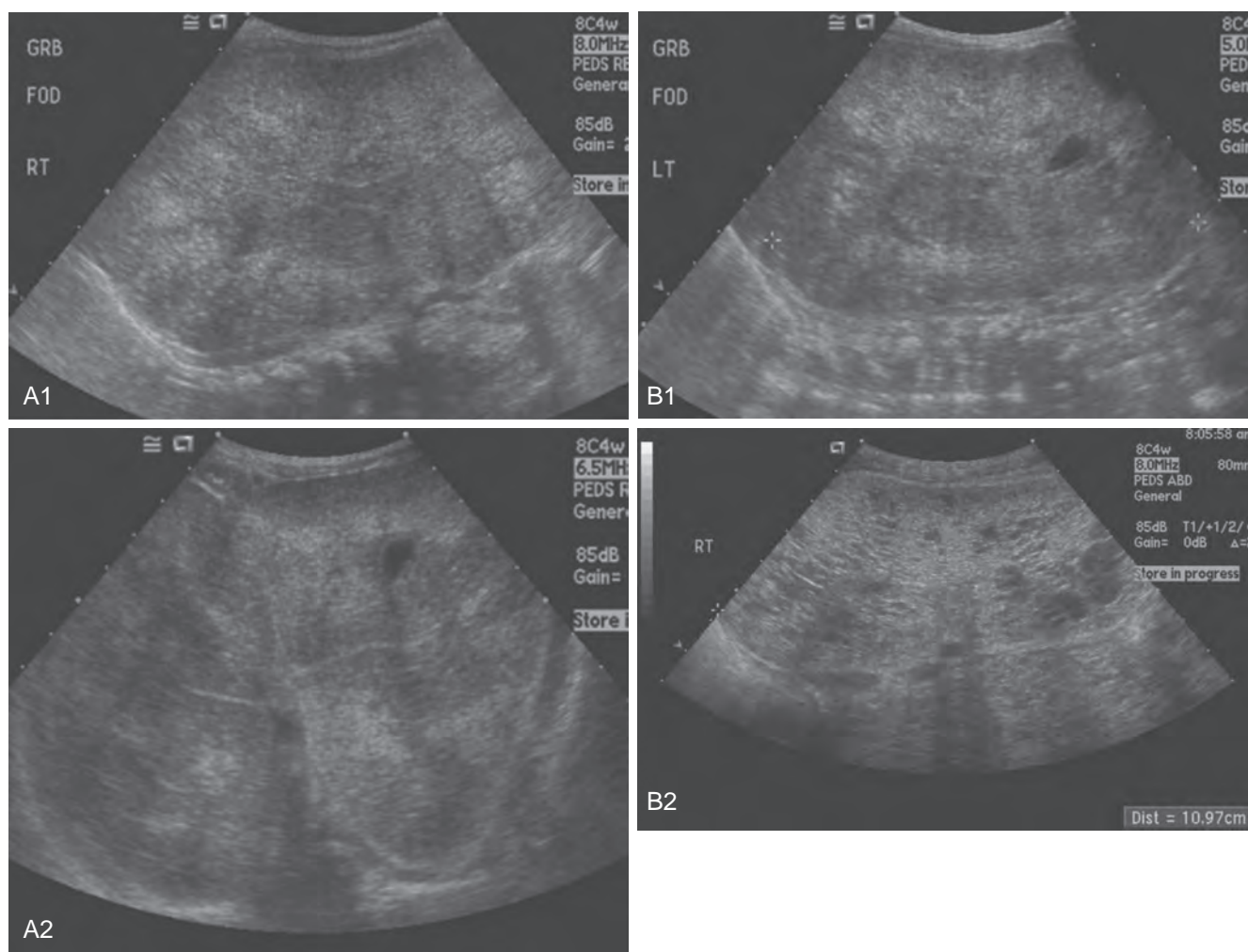


Figure 131-8. Ultrasonographic appearance of the kidneys in neonates with autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD) can be similar. A1 and A2, Newborn with ARPKD. Note the large size and hyperechoic, homogeneous appearance of the renal parenchyma. A2 is a cross-sectional cut of the baby's abdomen showing both kidneys to be quite large and occupying a large portion of the abdominal cavity. B1 and B2, Newborn with ADPKD. Again note the abnormal renal architecture and the hyperechoic appearance of the kidneys. The parenchyma consists of multiple tiny cysts, with some being slightly larger than others. (Courtesy Marta Hernanz-Schulman, MD.)

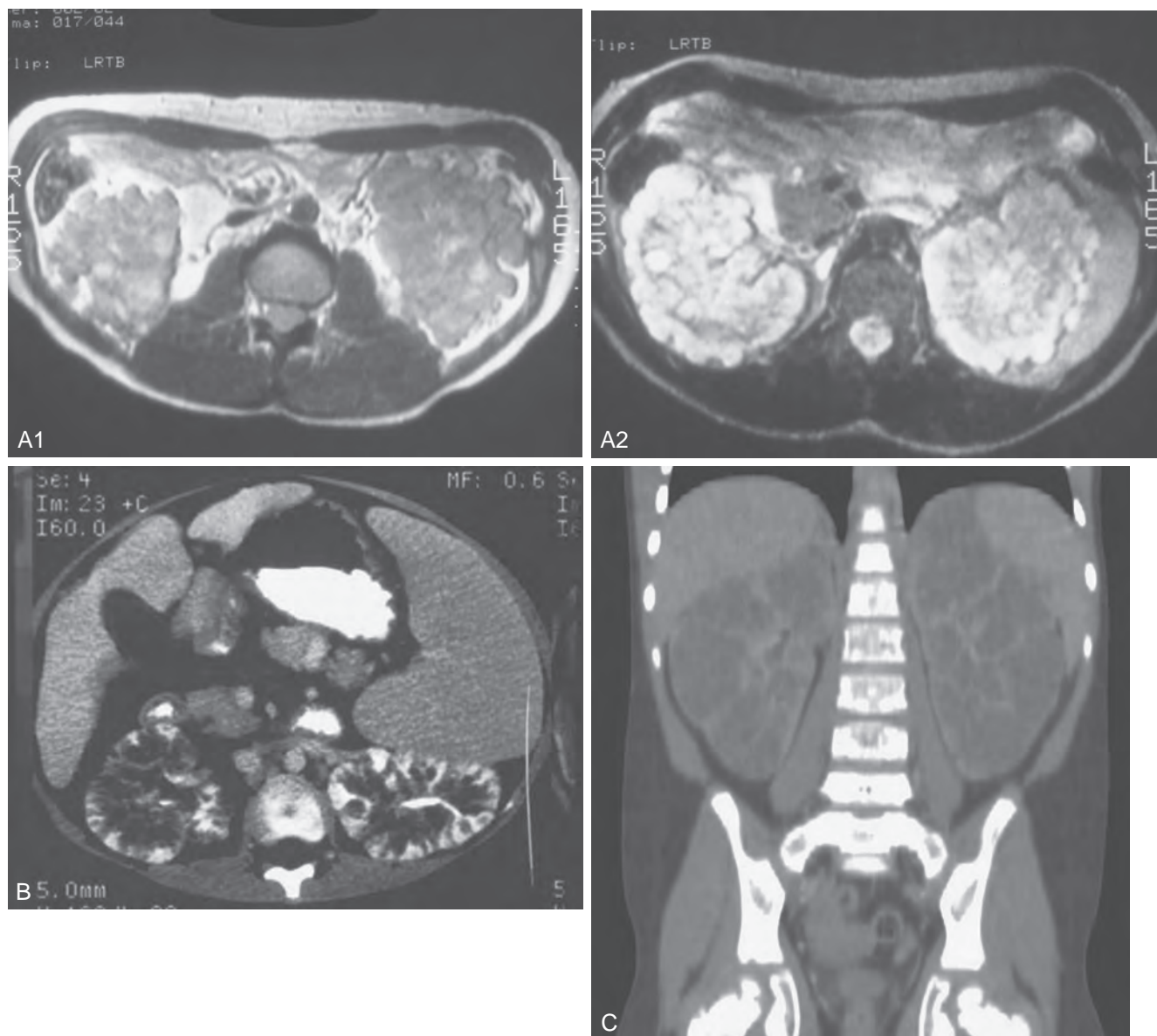


Figure 131-9. A1 and A2, Magnetic resonance images of an 8-month-old child with autosomal recessive polycystic kidney disease (ARPKD) demonstrating multiple renal cysts. A1, On T1-weighted image, fluid content of cysts appears dark. A2, On T2-weighted image, the fluid content appears white. B, Computed tomography scan of a child with ARPKD. Horizontal cuts showing contrast puddling in collecting ducts. C, Coronal cut. Note that the kidneys are enlarged and the enhancing renal parenchyma is effaced by nonenhancing cysts and represents the progression and normal history of the disorder. (A, Courtesy Walter Berdon, MD; B, courtesy Marta Hernanz-Schulman, MD.)

hydronephrosis (the kidneys are enlarged with hypoechogenic calyces), multicystic kidney (hypoechogenic cysts lie within a non-reniform mass that has very little parenchyma), sporadic glomerulocystic kidney disease (GCKD), bilateral mesoblastic nephroma, Wilms tumor, and bilateral renal vein thrombosis. If the diagnosis is in doubt, CT is valuable because it is more sensitive to inhomogeneity (and therefore to tumor) within abdominal masses.

Considerable overlap in clinical presentation and imaging findings can occur between ADPKD and ARPKD. Occasionally, a newborn with severe ADPKD can also have enlarged, homogeneously hyperechogenic kidneys. Age at onset can overlap, and typically, when ADPKD manifests at birth, cysts are apparent on the sonographic image. Macrocysts are rare in newborns with ARPKD but do increase in frequency as the child gets older, sometimes producing an appearance similar to that of the dominant disease.

Cysts less than 1 cm appear more often than large cysts (Avni et al, 2002) (Fig. 131-9). Hepatic fibrosis can rarely occur in patients with ADPKD, as can brain aneurysms with ARPKD (Cobben et al, 1990; Neumann et al, 1999). The correct diagnosis of ARPKD depends on the overall clinical data: a positive family history with a recessive mode of inheritance, a positive liver biopsy, and the lack of the extrarenal malformations often associated with other renal cystic diseases.

Treatment

No cure has been found for ARPKD. Respiratory care can ease or extend the child's life. Severely affected neonates may require unilateral or bilateral nephrectomy, because of respiratory and nutritional compromise. Patients who survive may require treatment for

hypertension, congestive heart failure, and renal and hepatic failure. Portal hypertension may be dealt with by decompressive procedures such as a splenorenal shunt. Esophageal varices may be managed, at least temporarily, by gastric section and reanastomosis. Endoscopic sclerotherapy is widely used in pediatric and adult patients with bleeding varices. Hemodialysis and renal transplantation must eventually be considered in many patients.

KEY POINTS: AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

- ARPKD is secondary to a mutation of the *PKHD1* gene on chromosome 6.
- The severe form manifests in utero or in infancy; milder cases can manifest later in childhood and rarely up to age 20.
- All affected individuals have some degree of congenital hepatic fibrosis.
- When it manifests early, it is associated most often with very large kidneys that are homogeneously hyperechogenic.
- Discrete cysts appear more often as the child gets older.
- RUS reveals bilateral, very enlarged, diffusely echogenic kidneys, and the increased echogenicity is a result of the presence of numerous microcysts (created by tightly compacted, dilated collecting ducts) that result in innumerable interfaces.
- Considerable overlap in clinical presentation and imaging findings can occur between ADPKD and ARPKD.

AUTOSOMAL DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE

ADPKD is by far the most common inheritable form of renal cystic disease, with an incidence of approximately 1 in 400 to 1000 live births (Iglesias et al, 1983; Grantham, 1996). It is an important cause of renal failure, accounting for 7% to 15% of patients who receive hemodialysis (Hildebrandt, 1995; Grantham, 1996; Wilson, 2004). The trait theoretically has a 100% penetrance, and, on average, because it is transmitted in an autosomal dominant fashion, 50% of an affected individual's offspring will likewise be affected. Although a positive family history is one of the major criteria for the diagnosis of ADPKD, 10% of cases occur sporadically. Ninety-six percent of affected persons will manifest the disease clinically by age 90 years (Gabow, 1991).

Although most cases are identified between the fourth and fifth decades of life, the condition has been reported in newborns and infants (Proesmans et al, 1982). All affected individuals manifest the disease (although not necessarily symptomatically) if they live long enough, but renal failure is seldom seen before the age of 40 years, unless the disease manifests during infancy, in which case it is much more aggressive.

A number of associated anomalies are common, including cysts of the liver, pancreas, spleen, and lungs; aneurysms of the circle of Willis (berry aneurysms); colonic diverticula; aortic aneurysms; and mitral valve prolapse (Table 131-2).

Genetics

There are two major genetic forms of ADPKD caused by mutation in the genes *PDK1* and *PDK2* (Reeders et al, 1985; Breuning et al, 1987; Ryyanen et al, 1987; Piek et al, 1989). *PDK1* has been localized to the short arm of chromosome 16, with its gene product being polycystin-1. Mutations in the *PDK1* gene account for 85% of ADPKD cases. These patients typically have a more rapidly progressive form of the disease, with cysts usually developing by the age of 20 years (64% of children have cysts by the age of 10 years and 90% by the age of 20 years) and ESRD occurring in their 50s (Chakraborty and McHugh, 2005). The *PKD2* gene

TABLE 131-2 Comparison of Autosomal Recessive and Autosomal Dominant Polycystic Kidney Disease

	AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE	AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE
Gene defect	Chromosome 6	Chromosome 4 and 16
Incidence	1:5000-40,000	1:500-1100
Usual age at clinical presentation	Perinatal	Third to fifth decades
Typical ultrasonographic appearance of kidneys	Symmetrically enlarged, homogeneous, hyperechogenic	Large, cystic kidneys, sometimes asymmetrical
Histology	Collecting duct ectasia; cysts derived principally from collecting duct	Microcysts and macrocysts derived from the entire nephron
Liver	Always with congenital hepatic fibrosis but of varying severity	Cysts, mostly in adults
Other organ system(s) involvement	None	Intracranial (berry) aneurysms, colonic diverticuli; mitral valve prolapse; cysts of other organs (seminal vesicle, arachnoid membrane, pancreas)

has been mapped to the long arm of chromosome 4 and it encodes the protein polycystin-2. *PDK2* mutations account for about 15% of ADPKD cases, and in these patients, the disease progresses more slowly. ESRD usually does not occur until these patients are in their 70s (Hateboer et al, 1999). The presence of a third locus (*PKD3*) is now accepted as the cause of disease in a very small percentage of patients who have been found to have neither a *PKD1* nor a *PKD2* gene defect (Dauost et al, 1993). When either the *PKD1* or the *PKD2* gene is abnormal, cystic kidneys can develop. Because defects of *PKD1* and *PKD2* manifest similarly, it has been suggested that the gene product of each is involved in the same pathway and that an abnormality of either product results in similar manifestations of the disease (Qian et al, 1996).

Every cell of the nephron and collecting duct has the *PDK1* or *PDK2* mutation; however, only 1% to 2% of these glomerular units are affected by cyst formation. Only those nephrons that undergo a disruption of a second allele undergo cystic enlargement. This is the "second hit" of the Knudson theory, which has been proposed to explain the focal nature of the cysts (Knudson, 1971). In this model, a mutated *PKD1* (or *PKD2*) gene is inherited from one parent, and a wild-type gene is inherited from the unaffected parent. During the lifetime of the individual, the wild-type gene undergoes a somatic mutation and becomes inactivated. Loss of heterozygosity caused by somatic mutations of the *PKD1* and *PKD2* genes has been identified in the cells lining the cysts in both the kidney and liver (Qian et al, 1996; Watnick et al, 1998). The phenomenon of

genetic anticipation is seen as well; it manifests with progressively earlier presentation and increased severity in subsequent generations of patients with ADPKD (Fick et al, 1994; Zerres et al, 1994). Genetic testing for *PDK1* and *PDK2* is commercially available through polymerase chain reaction amplification and direct DNA sequencing.

Occasionally, the classic ADPKD phenotype is seen in conjunction with tuberous sclerosis. This association is a classic example of a “contiguous gene syndrome,” which is a disorder caused by deletion of multiple gene loci that are adjacent to one another. Contiguous gene syndromes are characterized by multiple, apparently unrelated, clinical features caused by deletion of the multiple adjacent genes. Owing to the fact that the *PDK1* gene is immediately adjacent to the *TSC2* gene (the most important gene in tuberous sclerosis) on chromosome 16, large deletions in this area can involve both the *PDK1* and *TSC2* genes. Thus these patients have the classic features of tuberous sclerosis in addition to the renal cystic phenotype of ADPKD.

Pathogenesis

The *PDK1* and *PDK2* proteins, polycystin-1 (PC1) and polycystin-2 (PC2), are transmembrane proteins that in all likelihood form a functional complex. When working properly, PC1 and PC2 inhibit cell proliferation by several pathways. Polycystin-1 functions as a mechanoreceptor located on the primary cilium of renal tubular cells. These cilia project from the surface of the cell into the lumen of the ducts and tubules. Mutations that block the assembly of these cilia are known to cause many cystic diseases of the kidney. The products of the *ADPKD*, *ARPKD*, and *nephronophthisis* (NPH) genes are at least partially localized to these primary cilia. Polycystin-1 is linked to polycystin-2, which contains a calcium (Ca^{2+}) channel. When the mechanoreceptor of PC1 is stimulated by calcium-containing urine flowing through the tubule, the calcium channel of PC2 opens and calcium enters the cell (Nauli et al, 2003; Braun, 2009). This process regulates the proliferative state of the renal tubular cells through a variety of signaling pathways (e.g., cAMP, extracellularly regulated kinase [ERK], mammalian target of rapamycin [mTOR]). The cilia likely serve as organization centers for this signal transduction (Pazour, 2004).

In ADPKD, the polycystins do not function properly, and these proliferative pathways are unopposed and cyst formation occurs to varying degrees.

Increased levels of cAMP have been noted in multiple animal models of ADPKD, and biochemical processes that alter cAMP appear to affect the presence and size of renal cysts. For example, cAMP is broken down by phosphodiesterases. Caffeine and methylxanthine products, such as theophylline, interfere with phosphodiesterase activity, raise cAMP in epithelial cell cultures from patients with ADPKD, and increase cyst formation in canine kidney cell cultures (Mangoo-Karim et al, 1989; Belibi et al, 2002). The abnormal response to cAMP is directly linked to alterations in Ca^{2+} channel activity and results in the abnormal response of cyst-derived cells. This has also been shown to be regulated by cAMP stimulation of the mitogen-activated protein kinase/extracellularly regulated kinase (MAPK/ERK) signaling pathways, which leads to abnormal cellular proliferation of the PKD renal epithelial cells.

Upregulation of the vasopressin V_2 receptor has also been shown to increase cAMP levels. In genetically produced polycystic animals, two antagonists of the vasopressin V_2 receptor (VPV2R), OPC31260 and OPC41061 (tolvaptan), decreased cAMP and ERK, prevented or reduced renal cysts, and preserved renal function (Gattone et al, 2003; Wang et al, 2005). Not surprisingly, simply increasing water intake decreases vasopressin production and the development of PKD in rats (Nagao et al, 2006). Polycystic kidney (PCK) animals with no vasopressin activity had virtually no cAMP or renal cysts, whereas animals with increasing amounts of vasopressin had progressively larger kidneys with more numerous cysts. Administration of synthetic vasopressin to PCK rats that totally lacked vasopressin re-created the full cystic disease (Wang et al, 2008; Braun, 2009). Finally, the absence of polycystin permits excessive kinase

activity in the mTOR pathway and the development of renal cysts (Shillingford et al, 2006). The mTOR system can be blocked by rapamycin, which has been shown to slow PKD progression in rats (Wahl et al, 2006).

Clinical Features

Phenotypes associated with ADPKD are highly variable in penetrance. This variability related to the severity of renal disease can range from fetal demise and neonatal death to adequate renal function into old age. Characteristics of the associated liver disease and extrarenal manifestations can also be quite variable. *PDK1* and *PDK2* gene mutations are obviously critical, but intrafamilial variability also indicates that genetic background and environmental factors can also affect ultimate clinical expression of the disease (Rossetti and Harris, 2007). Now that the families of ADPKD patients are being screened by ultrasonography, large numbers of asymptomatic children with renal cysts are being identified before full-blown disease develops. Bilateral renal involvement is the usual presentation, but 17% of cases are asynchronous or asymmetrical, especially in children. These extreme forms of asymmetry are referred to as *unilateral ADPKD*, with the involvement in the contralateral kidney becoming apparent at a much older age (Strand et al, 1989; Bisceglia et al, 2006).

Typically, signs or symptoms first occur between the ages of 30 and 50 years (Glassberg et al, 1981). These include microscopic and gross hematuria, flank pain, gastrointestinal symptoms (perhaps secondary to renomegaly or associated colonic diverticula), renal colic (secondary either to clots or stones), and hypertension. Microscopic or gross hematuria is seen in 50% of patients, and in 19% to 35% it is the presenting sign (Milutinovic et al, 1984; Delaney et al, 1985; Zeier et al, 1988; Gabow et al, 1992). Because patients with ADPKD have increased renal mass, erythropoietin levels are increased, making anemia unusual even when ESRD is present (Gabow, 1993).

Pain (flank and/or abdominal) is the most common presenting symptom in adults. This results from a number of possible factors: mass effect (cysts impinging on abdominal wall or neighboring organs), bleeding into the cysts, urinary tract infection (including infected cysts), and nephrolithiasis. Twenty percent to 30% of patients with ADPKD develop stones (Fick et al, 1994), and these are treated by conservative means if possible (i.e., urine alkalization, spontaneous stone passage, extracorporeal shock wave lithotripsy). Uric acid stones and calcium oxalate stones are equally prevalent. The finding of hydronephrosis, which helps make the diagnosis of stones, may not be as useful in ADPKD patients because of the number of cysts camouflaging the findings (Choyke et al, 1995). Urinary tract infections are more frequent in female patients. Cyst aspiration for both diagnostic and therapeutic reasons should be considered in the setting of suspected cyst infection.

As BP screening has become more widespread, hypertension has become a very common form of presentation (Zeier et al, 1988). Hypertension is present in roughly 50% of patients 20 to 35 years old having ADPKD with normal renal function. Virtually 100% of patients with ESRD have hypertension (Kelleher et al, 2004). The hypertension seems to be renin mediated, secondary to stretching of the intrarenal vessels around cysts, causing distal ischemia (Gabow, 1993). Diagnosis and treatment of this hypertension is critical to slow the progression of renal failure, as well as to decrease morbidity and mortality from heart disease and cerebral aneurysms.

The development of renal failure is highly variable. Renal function is usually maintained, despite increasingly rapid cyst growth, until the fourth to sixth decade of life. Risk factors for earlier onset of ESRD include *PKD1* gene mutation, male gender, first episode of hematuria before age 30 years, onset of hypertension before age 35 years, hyperlipidemia, and sickle cell trait (Yium et al, 1994; Johnson and Gabow, 1997). There is a strong relationship between the decline in renal function and the size of the kidneys and cyst volumes. As the cysts, and thus the kidneys, become

larger, renal function declines proportionately (Gabow et al, 1990a). Hypertension and vascular remodeling secondary to cyst expansion also contribute to progressive renal failure.

Extrarenal Manifestations

Hepatic cysts, usually identified incidentally by ultrasonography, are the most common extrarenal manifestation of ADPKD. These cysts are associated with *PKD1* and non-*PKD1* genotypes. They are rare in children, and their frequency increases with age. They are present in virtually all ADPKD patients by the age of 50 years (Bae et al, 2006). Hepatic cysts are more prevalent and their size greater in females (Fick et al, 1994). Several studies have shown an estrogen effect on hepatic cyst growth (Gabow et al, 1990b; Sherstha et al, 1997). Hepatic cysts are usually asymptomatic but can occasionally cause symptoms owing to mass effect or from complicating infection or hemorrhage. In rare instances, enlargement of hepatic cysts leads to portal hypertension and bleeding esophageal varices (Campbell et al, 1958). When secondary portal hypertension appears, differentiating ADPKD from ARPKD can be difficult. In ARPKD, portal hypertension is seen much more frequently and is always secondary to congenital hepatic fibrosis. However, congenital hepatic fibrosis, on very rare occasions, may accompany ADPKD as well, particularly when the diagnosis is made perinatally.

Intracranial aneurysms (ICAs)—predominately aneurysms of the circle of Willis (berry aneurysm)—occur in 10% to 30% of patients, and approximately 9% of these patients die because of subarachnoid hemorrhages (Hartnett and Bennett, 1976; Grantham, 1979; Wakabayashi et al, 1983; Sedman and Gabow, 1984; Ryu, 1990). The most common symptom of subarachnoid hemorrhage is the sudden onset of a severe headache, frequently associated with nausea and vomiting. When this occurs, immediate medical evaluation is obviously imperative. Morbidity and mortality from these aneurysms are strongly influenced by positive family history and the *PDK1* genotype. Now, with MRI, even small berry aneurysms can be detected. These aneurysms, when diagnosed, average only 6.1 mm. Although small aneurysms (1 cm) have a lower risk of rupture, patients with small aneurysms have a greater risk of rupture when there is a positive family history of ruptured ICAs or the presence of ADPKD (Huston et al, 1993). Control of hypertension is critical to minimize the risk of aneurysm rupture. In some patients with ADPKD, hemorrhage follows the rupture of intracerebral arteries, which is the usual type of intracranial hemorrhage seen in patients with hypertension who do not have ADPKD.

Cysts may also occur in the seminal vesicles (40%), arachnoid membrane (8%), and pancreas (5%). Seminal vesicle cysts rarely cause infertility; however, many of these men may have problems with sperm motility. Arachnoid membrane and pancreatic cysts are typically asymptomatic. Other abnormalities associated with ADPKD are mitral valve prolapse and colonic diverticulosis (Scheff et al, 1980; Hossack et al, 1986; Kupin et al, 1987). Patients who have diverticulosis are more likely to have hepatic cysts and symptomatic berry aneurysms (Kupin et al, 1987).

Association with Renal Cell Carcinoma

The incidence of renal adenomas is almost as high in ADPKD as in ARCD associated with ESRD (i.e., one in four to five patients). However, whereas ESRD is associated with an increased incidence of RCC, especially when associated with ARCD (three to six times the incidence seen in the general population), the incidence of RCC in patients with ADPKD is no higher than that in the general population. However, there are certain findings considered typical of a predisposition to RCC that are seen more frequently in patients with ADPKD than in the general population. For example, RCC in ADPKD is often diagnosed at a younger age, is more often concurrently bilateral (12% vs. 1% to 5% in the general population), multicentric (28% vs. 6%), and

sarcomatoid in type (33% vs. 1% to 5%) (Keith et al, 1994). The diagnosis of RCC in the context of ADPKD can be quite difficult, because tumor may be masked by the complex cystic appearance of the kidney. In addition, cystic hemorrhage, degenerating blood clots, proteinaceous debris, and infection can also complicate the diagnosis.

Histopathology

ADPKD kidneys typically maintain their reniform shape, and their size can range from minimally enlarged in early disease to massive enlargement in more advanced disease. Both kidneys are usually equally affected, and the cysts range from a few millimeters to a few centimeters in diameter and appear diffusely throughout the cortex and medulla with communications at various points along the nephron (Kissane, 1974). The cysts appear to begin as focal tubular outpouchings, and as they enlarge they usually become detached from their tubule of origin. The first pathologic finding in fetuses is focal tubular dilation, which may occur anywhere along the nephron (Choyke et al, 1995) (Fig. 131-10).

Epithelial hyperplasia or even adenoma formation in the cyst wall is common, and the basement membrane of the wall is thickened. Arteriosclerosis is present in more than 70% of patients with preterminal or terminal renal failure, and interstitial fibrosis, with or without infiltrates, is common (Zeier et al, 1988). This fibrosis may be secondary to infection or to an inflammatory reaction set off by spontaneously rupturing cysts.

Up to 90% of adults with ADPKD have cysts of the liver (Bae et al, 2006). These cysts are lined by a single layer of epithelium resembling that of the biliary tract and contain fluid that resembles the bile salt-independent fraction of the bile. The electrolyte composition and osmolality are similar to those of serum, whereas the concentrations of phosphorus, cholesterol, and glucose are lower (Everson et al, 1990). They are derived by progressive proliferation and dilation of the biliary ductules and peribiliary glands and become detached as they grow so that macroscopic liver cysts usually do not communicate with the biliary system. Minimal to moderate dilation of the extrahepatic bile ducts is common (Torres and Grantham, 2008).

Evaluation

To make the diagnosis, it is important to have at least three generations of the patient's family history. Questions should be asked about renal disease, hypertension, and strokes. Patients and families should be counseled before any imaging or other testing is

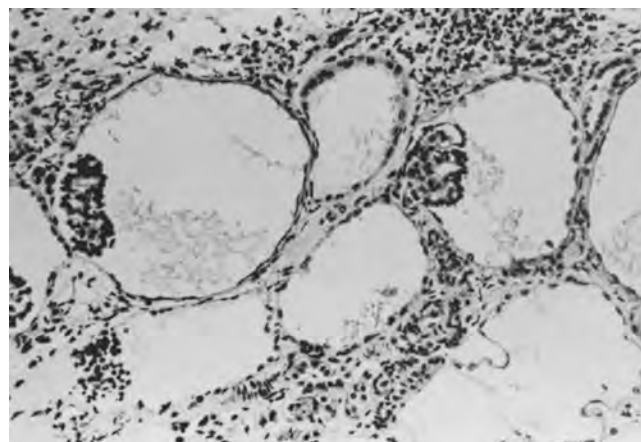


Figure 131-10. Glomerular cysts with a pattern compatible with autosomal dominant polycystic kidney disease in early childhood (190 \times). (From Bernstein J, Gardner KD Jr. Cystic disease and dysplasia of the kidneys. In: Murphy WM, editor. Urological pathology. Philadelphia: Saunders; 1989. p. 483–524.)

undertaken. Genetic testing can be used when the imaging results are equivocal and when a definite diagnosis is required. Benefits of testing include making a diagnosis that may affect family planning, early detection and treatment of disease complications, and selection of genetically unaffected family members for living donor-related renal transplantation. Disadvantages to testing include discrimination in terms of insurability and employment associated with a positive diagnosis, as well as the psychological stress of impending organ failure.

Abdominal ultrasonography may reveal renal cysts (Fig. 131-11) as well as cysts in other organs. Ultrasonographic diagnostic criteria for individuals at 50% risk for the disease include at least two unilateral or bilateral cysts in individuals younger than 30 years of age, two cysts in each kidney in individuals 30 to 59 years of age, and four cysts in each kidney in individuals 60 years of age or older (Ravine et al, 1994). The sensitivity of these criteria is nearly 100% for individuals 30 years or older and for younger individuals with *PKD1* mutations but only 67% for individuals with *PKD2* mutations younger than 30 years (Nicolau et al, 1999). When there is no family history to support a diagnosis of ADPKD, a presumptive diagnosis can be made if bilateral renal cysts are present and two or more of the following symptoms are present as well: bilateral renal enlargement, three or more hepatic cysts, cerebral artery aneurysm, and a solitary cyst of the arachnoid, pineal gland, pancreas, or spleen (Grantham, 1993).

CT or MRI (or both) may be helpful in some cases and often is superior to ultrasonography for detecting cysts in organs other than the kidney (Fig. 131-12A). CT is helpful in making the diagnosis of hemorrhage within a cyst. More acute hemorrhage has a higher density (50 to 90 Hounsfield units [HU]) than old hemorrhage (Choyke et al, 1995). MRI also may be helpful, particularly in patients with compromised renal function, because no contrast agent is needed (Fig. 131-12B).

When ADPKD manifests in utero or in infancy, 50% of affected kidneys are large with identifiable macrocysts (Pretorius et al, 1987). However, the kidneys may appear identical to those seen

in ARPKD, having no apparent macrocysts and showing only enlargement and homogeneous hyperechoic features. In such situations, one must look for a parent with ADPKD to confirm the diagnosis. With time, cysts often larger than 1 cm will develop in most children (Avni et al, 2002).

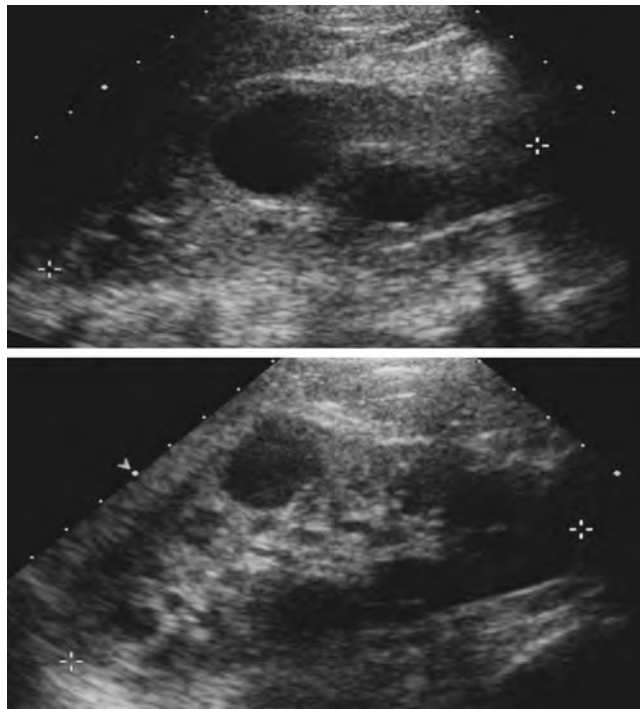


Figure 131-11. Renal ultrasonogram of 20-year-old patient newly diagnosed with autosomal dominant polycystic kidney disease. Note the presence of multiple cysts in both kidneys. (Courtesy Marta Hernanz-Schulman, MD.)

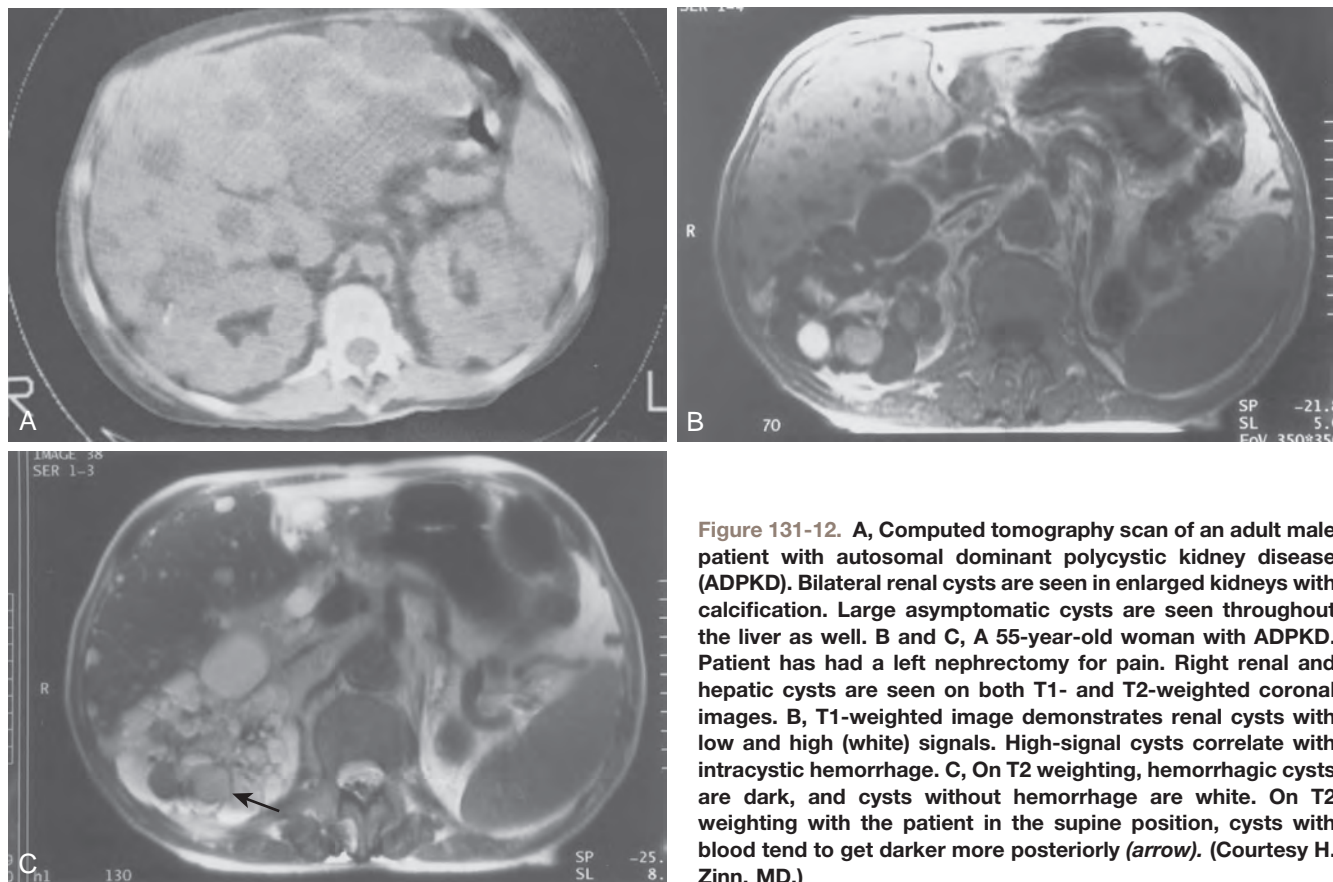


Figure 131-12. A, Computed tomography scan of an adult male patient with autosomal dominant polycystic kidney disease (ADPKD). Bilateral renal cysts are seen in enlarged kidneys with calcification. Large asymptomatic cysts are seen throughout the liver as well. B and C, A 55-year-old woman with ADPKD. Patient has had a left nephrectomy for pain. Right renal and hepatic cysts are seen on both T1- and T2-weighted coronal images. B, T1-weighted image demonstrates renal cysts with low and high (white) signals. High-signal cysts correlate with intracystic hemorrhage. C, On T2 weighting, hemorrhagic cysts are dark, and cysts without hemorrhage are white. On T2 weighting with the patient in the supine position, cysts with blood tend to get darker more posteriorly (arrow). (Courtesy H. Zinn, MD.)

Treatment and Prognosis

Current therapy is directed toward lessening the complications of ADPKD and delaying the onset of ESRD. There is no known cure at this time. More than 60% of patients with ADPKD who do not yet have renal impairment have hypertension (Gabow et al, 1984), which can worsen renal function, cause cardiac disease, and predispose the patient to intracranial hemorrhage. The complications of ADPKD can be reduced significantly by controlling the BP. There is no proven antihypertensive agent of choice; however, ACE inhibitors or angiotensin receptor antagonists would seem to be logical first-line choices. Not only does the hypertension associated with ADPKD appear to be renin mediated, but these drugs increase renal blood flow, have minimal side effects, and may have renoprotective properties beyond BP control. The optimum BP target is not clear. Ongoing studies will determine whether a low BP target is more protective of renal function than a standard BP target (<130/80) and whether combination drug therapy is more advantageous than single-drug therapy.

Chronic pain must be evaluated and entities such as infection, stone, and tumor treated accordingly. The use of chronic nephrotoxic analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs]) must be avoided. The use of narcotic analgesics should be limited to acute pain episodes, because patient dependence on narcotics is a significant risk in this patient population. When conservative measures fail, surgical management must be considered. Ultrasonography- or CT-guided cyst aspiration is a straightforward procedure and may be both diagnostic and therapeutic. Surgical unroofing of multiple or very large cysts can potentially alleviate symptoms of pain and can be performed either laparoscopically or through open flank or dorsal lumbar incisions (Elzinga et al, 1992; Lee and Lee, 2003; Lee and Clayman, 2004). The effect of laparoscopic unroofing in those patients with hypertension was quite variable. Surgical intervention appears only to improve symptomatology and does not appear to either accelerate the decline of renal function or preserve declining renal function. Nephrectomy is indicated for symptomatic patients with ESRD.

Upper urinary tract infections are common in patients with ADPKD, especially women, and must be treated appropriately. If a patient with suspected pyelonephritis does not respond to an appropriate antibiotic, one must consider whether the infection may be present in a noncommunicating cyst (Gabow, 1993). Actual cyst infections can be quite challenging to treat owing to poor cyst penetration of many antibiotics. Lipophilic antibiotics, such as trimethoprim-sulfamethoxazole, chloramphenicol, and fluoroquinolones, are the best choices (Schwab et al, 1987; Bennett et al, 1990). If appropriate antibiotic therapy fails, percutaneous or surgical drainage of infected cysts may be required. Complicating factors, such as urinary tract obstruction, renal or perinephric abscess, or urolithiasis, must be excluded.

Screening for asymptomatic berry aneurysms is not currently recommended unless the patient has a family history of aneurysm or subarachnoid hemorrhage, previous aneurysm rupture, need for screening in preparation for major elective surgery, high-risk occupation (e.g., airline pilot), or a high anxiety level over the possibility of ICA (Pirson et al, 2002). CT and magnetic resonance angiography are the imaging studies of choice, although the former requires intravenous contrast. Aneurysm rupture occurs most often in people with larger aneurysms and/or poorly controlled high BP. Screening of low-risk patients is not recommended because aneurysms are rare in this group, and most aneurysms that are found have a low risk of rupture. Conservative management is usually recommended for ADPKD patients with small (<7 mm) aneurysms detected by presymptomatic screening. Aneurysms that are larger than 7 to 10 mm have a higher risk of rupture (up to 2% per year for larger aneurysms). Cerebral aneurysms of this size and those that cause symptoms may be corrected with open surgical clipping or with endovascular procedures, placing a coil within the aneurysm. Smaller aneurysms that do not cause symptoms are much less likely to rupture and are not routinely corrected, except in patients with a history of a bleeding aneurysm.

Emerging Therapeutics

Changing the natural course of the disease by altering the course of cyst growth has received the most attention in recent years. The HALT PKD study is the largest treatment study ever performed on patients with PKD, and the National Institutes of Health (NIH) extended the study because of the valuable information being obtained. This study examined the role of BP control versus the impact of specific medications on the course of the disease and assessed whether combination ACE inhibitor (lisinopril) and angiotensin receptor blocker (ARB; telmisartan) therapy is more effective in slowing cyst progression than ACE inhibition alone. The study was completed in June 2014, and in a recent report by Schrier and colleagues (2014) showed that in early ADPKD, the combination of lisinopril and telmisartan did not significantly alter the rate of increase in total kidney volume. As compared with standard blood-pressure control (120-130/70-80), rigorous blood-pressure control (95-110/60-75) was associated with a slower increase in total kidney volume, no overall change in the estimated GFR, a greater decline in the left-ventricular-mass index, and greater reduction in urinary albumin excretion (Schrier et al, 2014). From this study, the investigators also hope to learn how to predict when renal insufficiency will occur in individual patients (Steinman, 2011).

Approaches have also been undertaken to reduce the levels of cAMP in the kidneys of ADPKD patients. A recent phase III trial showed that compared with placebo, tolvaptan, a selective vasopressin V₂-receptor antagonist, slowed the increase in total kidney volume and the decline in renal function over a 3-year period in these patients. It was, however, associated with a relatively high discontinuation rate as a result of adverse events, such as increased aquaresis (thirst, polyuria, nocturia, and polydipsia as a result of the excretion of electrolyte-free water) and liver function abnormalities. Serious adverse events associated with chest pain and headache were also slightly more frequent in the tolvaptan group (Torres, 2012).

Somatostatin, known to inhibit vasopressin-induced cAMP, has also been tested in humans and has shown substantial retardation of the increase in kidney volume (Chapman, 2007). Two studies have evaluated the efficacy of blocking mTOR with rapamycin and have shown a significant reduction in kidney cyst burden (Tao et al, 2005; Wahl et al, 2006). Other drugs shown to be effective in pre-clinical trials and of potential value for the treatment of human PKD include ErbB1 (epidermal growth factor receptor) and ErbB2 tyrosine kinase inhibitors, Src kinase inhibitors, MEK inhibitors, and cyclin-dependent kinase inhibitors. These drugs, which have been developed for the treatment of neoplastic diseases, may also be considered for the treatment of PKD (Sweeney et al, 2000; Bukanov et al, 2006; Omori et al, 2006; Wilson et al, 2006; Brenner, 2008).

JUVENILE NEPHRONOPHTHISIS AND MEDULLARY CYSTIC DISEASE COMPLEX

Juvenile NPH (first described by Fanconi and colleagues in 1951) and medullary cystic kidney disease (MCKD) (first reported by Smith and Graham in 1945) describe a group of genetic (inheritable) disorders with both similar and unique characteristics. Similarities include the gross and histopathologic appearance of the kidneys, with the hallmark being interstitial fibrosis. Distinguishing features are the mode of inheritance, the age of onset of ESRD, and the type of extrarenal organ involvement. Juvenile NPH is the more common condition and is responsible for 10% to 20% of cases of renal failure occurring in children and occurs in 1% to 5% of patients undergoing dialysis or transplantation (Cantani et al, 1986) (see Table 131-1).

Genetics

Although either condition can occur sporadically, juvenile NPH usually is inherited as an autosomal recessive trait. It is genetically heterogeneous, and 13 responsible genes have been identified

KEY POINTS: AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

- ADPKD is the most common inheritable form of renal cystic disease.
- ADPKD most often becomes clinically apparent after age 30 years but may manifest at any age, including in utero.
- Ninety-nine percent of affected individuals have a mutation either of the *PKD1* gene on chromosome 16 or, less often, of the *PKD2* gene on chromosome 4.
- The protein products of *PKD1* and *PKD2* are PC1 and PC2, and they inhibit cell proliferation through several pathways.
- Cysts can be identified sonographically before age 20 years in almost all affected individuals.
- ADPKD is associated with a high incidence of liver cysts that increases with age.
- Signs or symptoms first occur between the ages of 30 and 50 years and include hematuria, flank pain, gastrointestinal symptoms, renal colic, and hypertension.
- Hepatic cysts occur in virtually all patients with ADPKD by the age of 50 years and are rarely symptomatic.
- ICAs of the circle of Willis (berry aneurysm) occur in 10% to 30% of patients, and approximately 9% of these patients die because of subarachnoid hemorrhages.
- The incidence of RCC in ADPKD patients is no higher than that of the general population.
- Tight BP control, the use of ACE inhibitors and/or ARB BP medication, and the possible use of tolvaptan are the most current treatment options.

for various forms of NPH (Hildebrandt et al, 1997; Saunier et al, 1997; Olbrich et al, 2003; Otto et al, 2003; Mollet et al, 2005; Otto et al, 2005; Sayer et al, 2006; Loftus, 2013). The *NPHP1* gene encodes nephrocystin; *NPHP2/INVS*, inversin; *NPHP3*, nephrocystin-3; *NPHP4*, nephrocystin-4/nephroretinin; *NPHP5/IQCB1*, nephrocystin-5; and *NPHP6/CEP290*, nephrocystin-6. *NPHP1* mutations are found in approximately one half of the patients with NPH. The majority of patients are homozygous for an *NPHP1* deletion (Konrad et al, 1996). *NPHP1*, *NPHP4*, *NPHP5*, and *NPHP6* mutations may be associated with the Senior-Loken syndrome (a combination of NPH and retinitis pigmentosa).

MCKD usually is inherited in an autosomal dominant fashion (50% of all offspring will have the disease) and is caused by mutations in either the *MCKD1* or *MCKD2* gene. The *UMOD* gene encodes for uromodulin, the most abundant protein found in normal human urine. Mutations in this gene can also lead to MCKD type 2 (Loftus, 2013). Because patients with either condition theoretically can be fertile in their early childbearing years, the risk of transmitting the condition to offspring must be acknowledged: 1% for juvenile NPH and 50% for MCKD (Neumann et al, 1997).

Clinical Features

Juvenile NPH and MCKD both cause polydipsia and polyuria in more than 80% of patients, but not to the extent observed in patients with diabetes insipidus (Gardner and Evan, 1984; Cantani et al, 1986). The polyuria is caused by a renal tubular urinary concentrating defect that leads to salt wasting, and this process is resistant to vasopressin. Subsequently, a large dietary salt intake frequently is necessary. One major difference in the two entities is the presence of hypertension. There is no hypertension associated with juvenile NPH, whereas patients with MCKD can have significant hypertension. Rarer versions of NPH occur as well: infantile NPH (ESRD in patients 4 years of age or younger) results from a mutation in the *NPHP2/INVS* gene, and adolescent NPH (ESRD variable, occurring in patients ranging from 3 to 13 years old) results from a mutation in the *NPHP3* gene.

Renal failure usually ensues 5 to 10 years after initial presentation (Cantani et al, 1986). Another important difference between

the two entities is that renal failure develops in patients with NPH at a mean age of 13 years and almost always before 25 years (Neumann et al, 1997). MCKD is a milder disease when it manifests in early adulthood, but it will manifest in all patients by 50 years of age (Bernstein and Gardner, 1979). ESRD in patients with MCKD most often develops in the third or fourth decade. MCKD type 1 manifests as slowly progressive chronic renal disease. There is minimal proteinuria and hematuria, and hypertension and hyperuricemia become more common as the renal disease progresses. Hyperuricemia is characteristic of MCKD2, and gout is a common presentation in teenage males. Proteinuria is minimal (Bleyer, 2003; Loftus, 2013).

Twenty percent of juvenile NPH families have extrarenal manifestations, whereas MCKD usually affects only the kidneys (Neumann et al, 1997). Sixteen percent of patients with juvenile NPH have associated retinitis pigmentosa (Hildebrandt et al, 1993). When the two entities coexist, the condition is referred to as renal-retinal or Senior-Loken syndrome. More rarely, other conditions can also be present, such as skeletal abnormalities; hepatic fibrosis; Bardet-Biedl syndrome (combination of obesity, mental retardation, polydactyly, retinitis pigmentosa, and hypogenitalism); ocular motor apraxia (Cogan syndrome); and other neurologic defects varying from subtle cerebellar involvement to clear Joubert syndrome (JS) phenotypes, peripheral dysostosis (cone-shaped epiphyses), or truncal cerebellar ataxia (Hildebrandt and Orman, 2001).

Pathologically, NPH and MCKD are similar. Grossly, the kidneys are small to normal in size with multiple cysts at the corticomedullary junction. Histologically, there is a characteristic triad present that includes (1) irregular thickening and disintegration of the tubular basement membrane, (2) marked tubular atrophy with cyst development, and (3) interstitial cell infiltration with fibrosis.

Evaluation

Diagnosis of NPH and MCKD can be difficult early in the onset because of the relative vagueness and nonspecificity of symptoms; thus a high index of suspicion is required. Excretory urography and ultrasonography frequently fail to detect cysts because they are small (Chang and Udupa, 1989; Ala-Mello et al, 1998). Excretory urography may show inhomogeneous streaking in the medulla as a result of accumulation of contrast material in the collecting ducts. Ultrasonography may show smaller-than-normal kidneys in juvenile NPH. Cysts may be seen on imaging studies if they are large enough (Rosenfeld et al, 1977), but, early in the disease, cysts are rarely visible. The parenchyma may also appear hyperechogenic secondary to tubulointerstitial fibrosis (Resnick and Hartman,

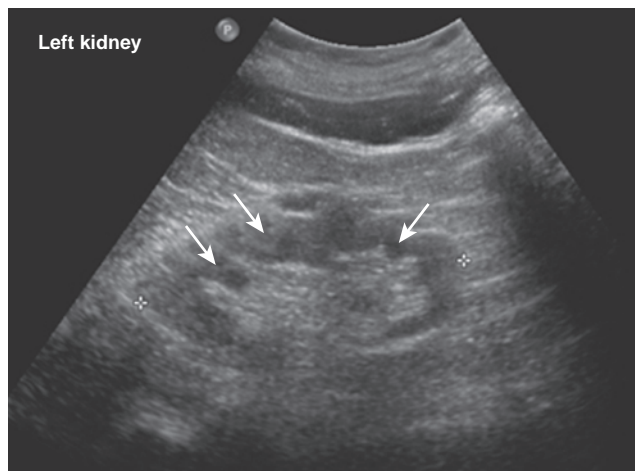


Figure 131-13. Features of medullary cystic kidney disease. Ultrasonogram demonstrating corticomedullary cysts, some of which are indicated by arrows. The hyperechogenicity is secondary to the tubulointerstitial fibrosis. (From Simms RJ, Eley L, Sayer JA. Nephropthisis. *Eur J Hum Gen* 2009;17:406-16.)

1990) (Fig. 131-13). Contrast-enhanced CT and MRI scans are more sensitive for detecting small corticomedullary and medullary cysts, but failure to detect cysts does not exclude the diagnosis.

Treatment

The treatment of NPH is supportive. Because of the tendency for sodium wasting, volume contraction, and renal azotemia, sodium replacement is indicated early in the course of the disease, and unnecessary sodium restriction or use of diuretics should be avoided. Later, dialysis and transplantation must be considered. Allografts apparently are not susceptible to the same process that destroyed the native kidney, because there is no evidence of serum antibodies to the basement membrane or other renal structural proteins (Cantani et al, 1986; Cohen and Hoyer, 1986). If kidneys from siblings are considered for transplant surgery, precautions should be taken to obtain them only from unaffected, older relatives, who should be subjected to meticulous diagnostic evaluation.

KEY POINTS: JUVENILE NEPHRONOPHTHISIS AND MEDULLARY CYSTIC DISEASE COMPLEX

- Juvenile NPH, an autosomal recessive disease, is responsible for 10% to 20% of cases of renal failure in children and leads to early ESRD (early teens).
- MCKD, an autosomal dominant disease, manifests in early adulthood.
- Polyuria, polydipsia, and hypertension are clinical hallmarks of these disease entities.
- Both have almost identical histology, with severe interstitial nephritis; many patients demonstrate cysts at the corticomedullary junction.

OTHER INHERITABLE RENAL CYSTIC DISEASES (CONGENITAL NEPHROSIS)

Congenital nephrosis is predominantly of two types. The more common variety is referred to as *congenital nephrotic syndrome of the Finnish type* (CNF) (Norio, 1966; Lanning et al, 1989) and is recessive. The second type is referred to as *diffuse mesangial sclerosis* (DMS), and one third are familial (Habib and Bois, 1973; Habib et al, 1989). These conditions are associated with dilation of the proximal convoluted tubules, and the patients have profound proteinuria. In infants with CNF, proteinuria is present in the first urinalysis. Without dialysis, half of the patients die by the age of 6 months, and the rest die before their fourth birthday (Huttunen, 1976). In DMS, the onset of symptoms is variable, and the diagnosis is usually made by the age of 1 year. All children have terminal renal failure by the age of 3 years. Approximately one third of DMS cases are associated with Drash syndrome (nephrotic syndrome and Wilms tumor with or without male pseudohermaphroditism) (Habib et al, 1989). Interstitial fibrosis is present in both conditions but is more pronounced in DMS (Norio and Rapola, 1989). After the kidneys have failed, transplantation is curative. Neither type of disease responds to corticosteroids.

FAMILIAL HYPOPLASTIC GLOMERULOCYSTIC KIDNEY DISEASE (CORTICAL MICROCYSTIC DISEASE)

Cortical microcystic disease is an autosomal dominant disorder described in several families and has been called *hypoplastic glomerulocystic disease* (Rizzoni et al, 1982) and cortical microcystic disease (Melnick et al, 1984; Kaplan et al, 1989a). The diagnosis of familial hypoplastic glomerulocystic disease requires four features: (1) stable or progressive chronic renal failure, (2) small or normal-sized kidneys with irregular calyceal outlines and abnormal papillae, (3)

presence of the condition in two generations of a family, and (4) histologic evidence of glomerular cysts.

MULTIPLE MALFORMATION SYNDROMES WITH RENAL CYSTS

Renal cysts are a feature of several syndromes characterized by multiple malformations (see Table 131-1). Tuberous sclerosis and VHL disease are autosomal dominant disorders and are the ones most likely to be encountered by urologists. Meckel syndrome, Jeune asphyxiating thoracic dystrophy, and Zellweger cerebrohepato renal syndrome are some of the more common autosomal recessive syndromes. Many of these conditions involve glomerular cysts, and some have cystic dysplasia as a feature.

Tuberous Sclerosis Complex

Bourneville described tuberous sclerosis in 1880. It is usually an autosomal dominant neurocutaneous disorder with an incidence of up to 1 in 6000 individuals (Webb et al, 1991; O'Hagan et al, 1996). It is characterized by benign growths called *hamartomas*, which can develop in nearly every organ of the human body.

Classically, tuberous sclerosis has been described as the triad of Bourneville phakomatosis (epilepsy) (80% of patients), mental retardation (60% of patients), and adenoma sebaceum (facial angiofibromata) (75% of patients) (Lagos and Gomez, 1967; Pampiglioni and Moynahan, 1976). It is also associated with autism and other neurocognitive and behavioral disabilities (Kohrman, 2012). Adenoma sebaceum consists of firm, discrete, red or brown telangiectatic papules located in the nasolabial folds, chin, and cheeks. They usually appear after the age of 2 years, gradually become more prominent with time, and persist throughout life. An earlier skin lesion that is a white papule in the shape of an ash leaf is sometimes identified (Shepherd et al, 1991). An examination of the skin with ultraviolet light may reveal cutaneous lesions earlier and should be part of a diagnostic evaluation.

Definitive diagnosis, however, is no longer dependent on this triad but rather on the presence of certain major and minor clinical features (Roach et al, 1998). The diagnosis of tuberous sclerosis complex (TSC) requires two major features (renal angiomyolipoma [AML], facial angiofibromas or forehead plaques, nontraumatic ungual or periungual fibroma, three or more hypomelanotic macules, shagreen patch, multiple retinal nodular hamartomas, cortical tuber, subependymal nodule, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis) or one major plus two minor features (multiple renal cysts, nonrenal hamartoma, hamartomatous rectal polyps, retinal achromic patch, cerebral white matter radial migration tracts, bone cysts, gingival fibromas, "confetti" skin lesions, multiple enamel pits).

The kidneys of these patients may be free of lesions (Stillwell et al, 1987) or may display cysts, AMLs, or both (Figs. 131-14 and 131-15).

Genetics

Although it is transmitted as an autosomal dominant trait in 25% to 40% of patients, in the remainder, tuberous sclerosis occurs either sporadically or as an example of the genetic condition with variable or incomplete penetrance. Because it is a heterogeneous genetic disorder with variable manifestations, it usually is referred to as *tuberous sclerosis complex*. It is caused by mutations in one of two genes. *TSC1* is located on chromosome 9 (9q34) and encodes the protein hamartin, and *TSC2* is on chromosome 16 (16p13) and encodes the protein tuberlin (Jones et al, 1999; Dabora et al, 2001; Sancak et al, 2005). Both of these genes are characterized as tumor suppressor genes, and the loss of function of either gene leads to hamartoma formation. Both hamartin and tuberlin function as a complex to inhibit the mTOR pathway. This pathway serves to modulate cell signaling pathways that are important in the regulation of cell growth and migration, as well as cell number and

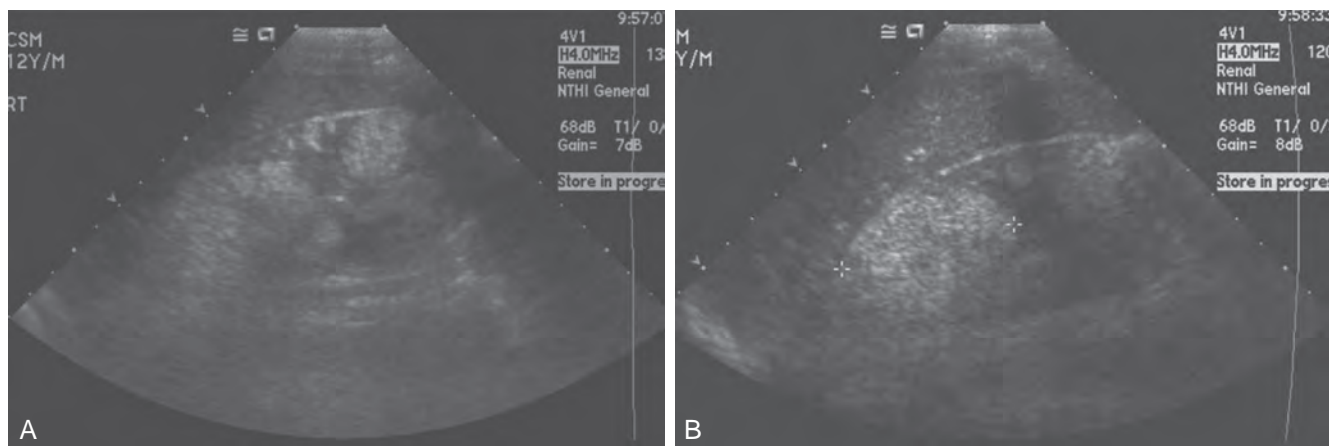


Figure 131-14. A and B, Renal ultrasonogram of 13-year-old patient with tuberous sclerosis. Multiple hyperechoic lesions of varying size are visible, consistent with angiomyolipomas. (Courtesy Marta Hernanz-Schulman, MD.)

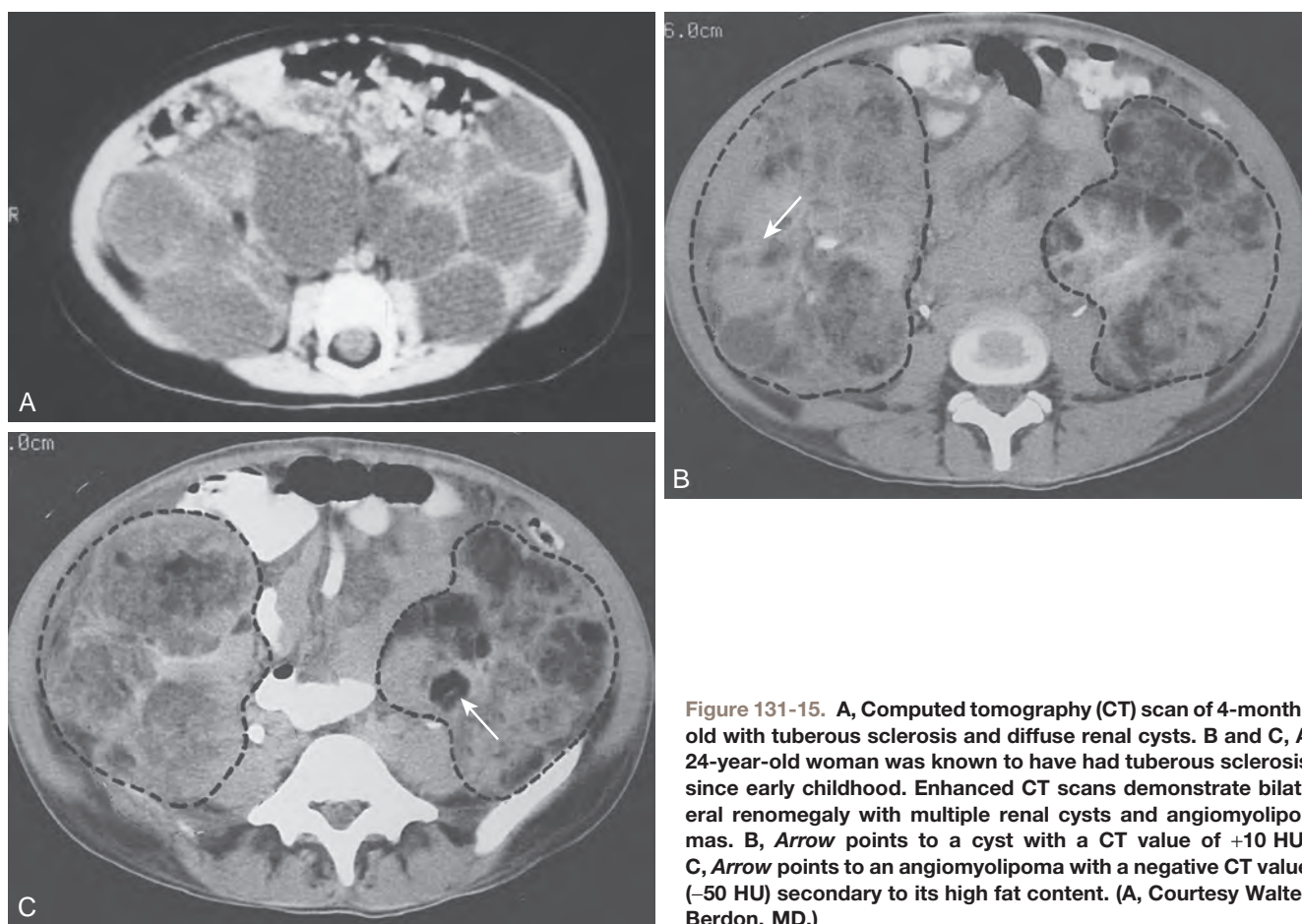


Figure 131-15. A, Computed tomography (CT) scan of 4-month-old with tuberous sclerosis and diffuse renal cysts. B and C, A 24-year-old woman was known to have had tuberous sclerosis since early childhood. Enhanced CT scans demonstrate bilateral renomegaly with multiple renal cysts and angiomyolipomas. B, Arrow points to a cyst with a CT value of +10 HU. C, Arrow points to an angiomyolipoma with a negative CT value (-50 HU) secondary to its high fat content. (A, Courtesy Walter Berdon, MD.)

organ size. Therefore a mutation of either gene will lead to similar clinical manifestations (Fig. 131-16).

Clinical Features

Renal involvement in TSC is second only to central nervous system abnormalities and includes predominately AML, renal cysts, and RCCs. AMLs are extremely common in TSC and are usually bilateral and multiple and affect both genders, whereas in the general

population they are uncommon, are usually single, and are found mainly in middle-aged women. Renal AMLs occur in 40% to 80% of patients with TSC (Chonko et al, 1974; Gomez, 1979). They are rarely identified before the age of 6 years but are common after age 10 years (Bernstein and Gardner, 1986). The primary risk of these lesions relates to their potential for hemorrhage or mass effect. Abdominal or flank mass and tenderness, hypertension, and renal insufficiency can also occur as a result of these lesions. By themselves, these lesions probably do not cause renal failure

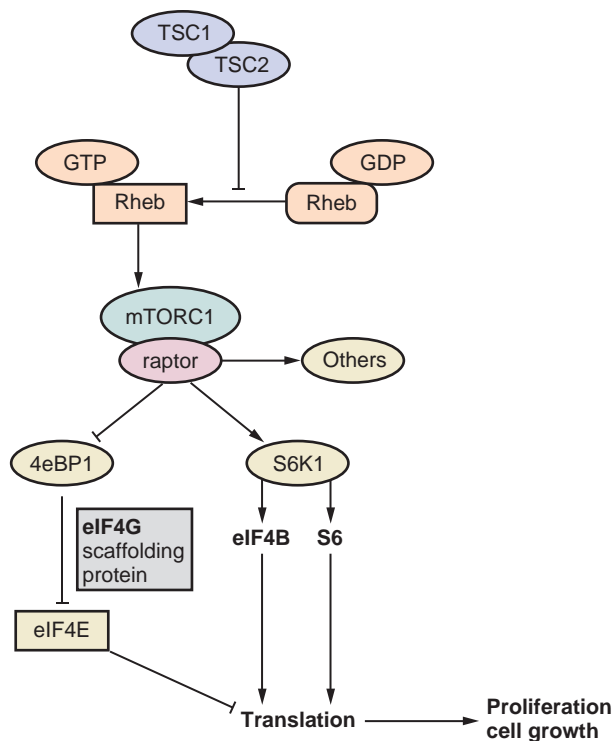


Figure 131-16. Features of signaling through the mammalian target of rapamycin complex 1 pathway (mTORC1) via the tuberous sclerosis 1/tuberous sclerosis 2 complex. 4EBP1, eukaryotic translation initiation factor 4E binding protein 1; eIF4B, eukaryotic translation initiation factor 4B; eIF4E, eukaryotic translation initiation factor 4E; eIF4G, eukaryotic translation initiation factor 4G; GDP, guanosine diphosphate; GTP, guanosine triphosphate; Rheb, Ras homolog enriched in the brain; S6, ribosomal protein S6; S6K1, ribosomal protein S6 kinase 1; TSC1, tuberous sclerosis complex 1 protein; TSC2, tuberous sclerosis complex 2 protein.

(Okada et al, 1982; Bernstein and Gardner, 1986). Also, belying their aggressive histologic appearance, which is characterized by pleomorphism and mitoses, no evidence of metastases has been presented.

Unlike AMLs, renal cysts may be present in the first year of life, and cystic disease may be the presenting manifestation of TSC. Renal cysts develop in approximately 20% of patients and most often manifest before 3 years of age; one third of children are younger than 1 year of age at presentation. Patients with large cysts or PKD may be identified by in utero ultrasonography or may demonstrate an abdominal mass and distended abdomen in the first year of life. Most patients with renal cysts do not develop any serious renal compromise, but when the disease is more widespread within the kidney and large cysts are present, renal failure may develop in the milder form with PKD. If any renal failure develops, it is uncommon before the fourth decade (Glazier et al, 1996).

TSC2 and PKD1 lie adjacent to each other in a tail-to-tail orientation on chromosome 16 at 16p13.3. Deletions inactivating both genes are associated with PCKs diagnosed during the first year of life or early childhood (TSC2/PKD1 contiguous gene syndrome) (Brook-Carter et al, 1994; Sampson et al, 1997). Therefore TSC should be considered in children with renal cysts and no family history of PKD. Rarely, TSC2/PKD1 contiguous gene syndrome can be diagnosed in adults (Martignoni et al, 2002). Patients with the contiguous gene syndrome usually reach ESRD at an earlier age than patients with ADPKD alone. Patients with TSC1 or TSC2 mutations without the contiguous gene syndrome also have an increased frequency of renal cysts. The combination of cystic kidneys and

AMLs has been said to be virtually pathognomonic for tuberous sclerosis.

Association with Renal Cell Carcinoma

The numerous reports of RCC in patients with tuberous sclerosis make it clear that this association is more than coincidental and may be as frequent as 2% (Bernstein and Gardner, 1986; Bernstein, 1993). However, the incidence of RCC is considerably less than that seen in VHL disease and ARCD of chronic renal failure. Compared with sporadic RCCs, there is a female predominance, earlier age of presentation, and increased bilaterality. Early detection is essential. RCC should be suspected in cases of enlarging lesions without demonstrable fat and in the presence of calcifications within the lesions.

Radiographic Evaluation

Sometimes both renal cysts and AMLs can be identified by ultrasonography in tuberous sclerosis, the former lesions being sonolucent and the latter having a fluffy, white appearance. When renal cysts are present without AMLs, the ultrasonographic appearance of the kidneys in tuberous sclerosis is very similar to that in ADPKD. Therefore it is not that unusual for a patient with cysts identified as typical of ADPKD to be diagnosed as having ADPKD, only to develop the stigmata of tuberous sclerosis a few years later. To help make the diagnosis, abdominal CT can be useful in demonstrating AMLs that may be present in the kidney or other organs (findings that are compatible with tuberous sclerosis) and in revealing cysts in other organs (compatible with ADPKD) (see Fig. 131-15). MRI or CT of the head may demonstrate the classic cranial calcifications associated with tubers or gliosis (Okada et al, 1982).

Treatment

Because more patients with tuberous sclerosis now survive their central nervous system lesions than in the past, the urologist is more likely to be asked to manage the renal problems (Stillwell et al, 1987). Shepherd and colleagues (1991) found that renal disease was the leading cause of death in these patients (11 of 40 deaths). Of these 11 patients, 2 died of metastatic RCC, 2 of massive hemorrhage associated with renal AMLs, and 6 of renal failure secondary to the cysts, AMLs, or both.

AMLs are benign lesions that usually are asymptomatic and do not require treatment. Large AMLs are more likely to bleed. van Baal and colleagues (1994) recommended careful monitoring of the size of AMLs and prophylactic embolization or surgical excision if they enlarge to greater than 4 cm. Annual surveillance with RUS or CT is necessary to assess for growth of the lesions and to detect the development of other complications. Renal-sparing surgery is indicated for symptoms such as pain and hemorrhage, growth of the lesions to the point at which they compromise renal function, and the inability to exclude RCC. Reports of hemorrhagic complications during pregnancy have led to the recommendation that patients with multiple or large AMLs be warned about the potential risk of pregnancy and estrogen administration.

Hypertension and renal failure must also be treated appropriately. Bilateral nephrectomy should be considered before transplantation owing to the risk of life-threatening hemorrhage and the development of RCC.

Finally, treatment in rodent models of TSC with rapamycin before the onset of disease reduces the development of renal tumors without affecting the number of precursor lesions (Kenerson et al, 2005). Clinical trials of the mTOR inhibitor rapamycin have demonstrated reduction in the size of tuberous sclerosis-associated renal, lung, and brain tumors. Sirolimus (rapamycin) and everolimus have demonstrated reduction in size of subependymal giant cell astrocytomas, reduction in seizure frequency, and inhibition of AML growth and even reduction of AML size in some reports (Kohrman, 2012). Larger-scale randomized controlled trials of mTOR inhibitors continue.

von Hippel-Lindau Disease

In 1904, Eugene von Hippel, a German ophthalmologist, first described retinal angiomas—angiomatic lesions of the retina that caused blindness in association with similar cerebellar tumors. One of his patients developed renal cancer, and this was reported in 1921. In 1926, Arvid Lindau, a Swedish pathologist, published a series about patients with retinal and cerebellar tumors, with four of his patients also having renal cysts and renal cancer. He was also the first to propose that these lesions had an inherited origin.

VHL disease is an autosomal dominant syndrome manifesting with cerebellar and retinal hemangioblastomas; cysts of the pancreas, kidney, and epididymis; epididymal cystadenoma; pheochromocytoma; and clear cell RCC. It is found in all ethnic groups, both sexes are affected, and it has an incidence ranging from 1 in 30,000 to 1 in 50,000 individuals. It has over 95% penetrance by the age of 65 years in affected individuals. It is grouped with the phakomatoses (Sturge-Weber-Krabbe syndrome, TSC, and neurofibromatosis), because they all have a common inheritance pattern and propensity for neoplasm.

Etiology

VHL disease is caused by a germline mutation in the tumor suppressor gene known as *VHL*, located on chromosome 3 (3p25) (Latif et al, 1993; Lesho, 1994; Kondo and Kaelin, 2001). A tumor suppressor gene is one in which both copies of the gene must be disabled for a cancer to develop. Seventy percent of patients will have a mutation of one *VHL* allele. As long as one copy of the *VHL* gene is producing functional VHL protein in each cell, tumors do not form. If a mutation occurs in the second copy of the *VHL* gene during a person's lifetime (another example of a second hit as proposed by Knudson's two-hit hypothesis (Knudson, 1971), the cell will have no working copies of the gene and will produce no functional VHL protein. A lack of this protein allows tumors characteristic of VHL syndrome to develop. The discovery and characterization of the *VHL* gene, and its role in cell regulation, is a prime example of how discoveries in the basic science arena can revolutionize treatment of human disease (Clark and Cookson, 2008).

The protein encoded by the *VHL* gene (pVHL) is a tumor suppressor and acts through multiple routes. It forms a complex of proteins that are involved with specific target proteins, typically hypoxia-inducible factors (HIFs), being "marked" for degradation. The most researched of these targets is hypoxia-inducible factor-1 α (HIF-1 α), a transcription factor that induces the expression of a number of angiogenesis-related factors (Czyzk-Krzeska and Meller, 2004). HIF1 α , when not suppressed, can stimulate the formation of hemangioblastomas and RCC. HIF targets specific genes that encode growth factors that seem to play a role in tumorigenesis, including platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), and vascular endothelial growth factor (VEGF), the last of which is particularly prominent in RCC. HIF1 α and pVHL are also involved in a transcriptional system that is a major regulator in oxygen homeostasis. HIF regulation in normoxia depends on VHL-mediated destruction. When the oxygen supply is reduced, the HIF pathway is activated. Together with activation of HIF in normoxia, VHL-deficient cells show a striking defect in extracellular matrix assembly. Thus altered oxygen tension in pathologic settings could have major effects on matrix behavior (Esteban et al, 2004). pVHL has also been shown to be a ciliary protein that controls ciliogenesis in kidney cells. Cilia play an important role in several biologic processes, including mechanosensation, photoperception, and osmosignaling. Loss of pVHL appears to impede the formation of cilia in renal cancer cells, whereas the expression of pVHL in VHL-negative renal cancer cells rescued the ciliogenesis defect (Schermer et al, 2006).

Clinical Features

The mean age at presentation is 35 to 40 years (Neumann et al, 1997). There is no sex preference for the disease or for RCC

development. Sporadic RCC in individuals without VHL disease occurs more often in males and usually after age 50 years. **Renal cysts, the most common and often earliest manifestation, are seen in 76% of patients (Levine et al, 1982).** The cysts are bilateral in 75% of affected persons and multifocal in 87% (Reichard et al, 1998). RCC occurs in approximately 50% of affected persons. The renal cysts, as well as the tumors, usually are asymptomatic, although large tumors may cause pain or a mass. Hematuria may occur after rupture of the tumor into the pelvicalyceal system. When cysts are present, typically they are large. Only rarely do images demonstrate ADPKD, and even less often do cysts cause renal failure.

Pheochromocytoma occurs in 10% to 17% of affected persons and appears to be confined to specific families (Horton et al, 1976; Levine et al, 1982). Patients may have seizures or dizziness secondary to hemangioblastomas of the central nervous system. **Cerebellar hemangioblastomas** usually become symptomatic between 15 and 40 years of age (Jennings and Gaines, 1988). These lesions are the most frequent, characteristic, and clinically specific tumors seen in VHL (Zbar et al, 1996; Shehata et al, 2008). Although benign tumors, they often result in major morbidity and mortality. They cause a mass effect because of their location, and, because of their vascular nature, they tend to rupture and bleed. **Retinal angiomas (hemangiomas)** frequently manifest early. Bleeding may cause blurred vision, retinal detachment, and blindness. Early diagnosis is important, because these tumors respond to laser therapy or cryotherapy. The pancreas is commonly involved with either cysts or true neoplasms. **Pancreatic cysts** can occur in up to 70% of patients with VHL but are usually asymptomatic and benign. Islet cell tumors occur in approximately 12% of VHL patients, and metastatic RCC of the pancreas is not unusual (Cheng et al, 1997; Kogire et al, 2000). Other clinical findings in patients with VHL can include **endolymphatic sac tumor, which is a papillary tumor of the petrous bone and can cause hearing loss; papillary cystadenomas of the epididymis; and the female counterpart, cystadenoma of the broad ligament (Zbar et al, 1996; Shehata et al, 2008).**

Because of the high incidence of RCC in patients with VHL disease, the urologist's primary role is careful surveillance so that small tumors can be identified and treated before they metastasize. Although central nervous system hemangioblastomas account for more than half of the deaths in these patients, metastatic RCC is also a major cause of mortality and in some accounts is the leading cause of death in this population (Maher et al, 1990; Reichard et al, 1998). Accordingly, annual or perhaps biannual CT examinations are advised.

Classification

Patients with VHL are subdivided into groups based on disease presentation, and each group has a specific *VHL* gene aberration. VHL type 1 is the most common form of the disease and is characterized by a tendency to develop tumors in the eyes, brain, spinal cord, kidney, and pancreas. VHL type 2 is less common. VHL type 2 differs from type 1 in that affected family members are at high risk to develop pheochromocytomas. VHL type 2 is further divided into types 2A, 2B, and 2C. Individuals in families with VHL type 2A develop pheochromocytomas but have a low risk for RCC (this type of VHL is uncommon). Those with VHL type 2B develop pheochromocytomas and have a high risk for RCC. Patients with type 2C VHL have familial pheochromocytoma without hemangioblastomas and clear cell RCCs (Zbar et al, 1996; Shehata et al, 2008) (Table 131-3).

Histopathology

When present, renal cysts and tumors often are multiple and bilateral. The cysts usually simulate simple benign cysts, with flattened epithelium that some investigators consider precancerous. In VHL patients, cysts larger than 2 cm are more likely than smaller cysts to have components of RCC (Poston et al, 1993). Frank cancer usually appears between the ages of 20 and 50 years (Jennings and Gaines, 1988). Others found that the hyperplastic

cells lining cysts frequently resembled the clear cell type of RCC, the most common type in these patients (Loughlin and Gittes, 1986). Ibrahim and colleagues (1989) studied the cysts adjacent to carcinomas and found, much as in tuberous sclerosis, that the karyotype resembled that of the tumors. This similarity is evidence that the hyperplastic cells of the cyst lining are precursors of the carcinomas.

Solomon and Schwartz (1988) believed that a spectrum of pathology is found within the kidneys of patients with VHL disease. At one extreme is a simple cyst with a single layer of bland epithelium. The next step is a typical proliferative cyst with layers of epithelial cells. In the ensuing step, there are complex neoplastic projections into the cyst lumen. If one agrees with the arbitrary distinction between adenoma and carcinoma on the basis of size, the next stage would be adenoma. Finally, there is full-blown RCC. All of these stages may be found within a single kidney (Solomon and Schwartz, 1988).

Evaluation

In patients with a known family history of VHL, the diagnosis can be made based on the presence of a single retinal or cerebellar hemangioblastoma, RCC, or pheochromocytoma (Melmon and Rosen, 1964; Couch et al, 2000). In such families, germline mutations may be present without clinical manifestations, and the patient should be screened for this mutation. For patients who do not have a family history, the diagnosis requires two or more cardinal manifestations, such as retinal or cerebellar hemangioblastomas, or a single hemangioblastoma and an additional characteristic lesion.

Ultrasonography is useful in diagnosing the typical benign renal cystic features of VHL disease: absence of internal echoes, well-defined margins, and acoustic enhancement. On CT, sharp thin walls are seen around homogeneous contents without enhancement after contrast medium injection. Because multiple lesions (cysts, tumors, or both) are often present, CT frequently is more useful than ultrasonography. CT often is useful in examining the adrenal glands for pheochromocytomas.

TABLE 131-3 Classification of von Hippel-Lindau Disease

TYPE	CLINICAL CHARACTERISTICS
1	Without pheochromocytoma
2	With pheochromocytoma
2A	Without renal cell carcinoma or pancreatic cysts
2B	With renal cell carcinoma and pancreatic cysts
2C	Familial pheochromocytoma without hemangioblastomas and clear cell renal cell carcinoma

When the lesions are small, it is impossible to distinguish tumors from cysts. In such cases, patients should have regular CT scans with narrow-screen collimation (Levine et al, 1982). With larger lesions, and whenever RCC is suspected, renal angiography with magnification or subtraction is advisable. This type of study helps to reveal any additional tumors and indicates the appropriateness of conservative surgery (Kadir et al, 1981; Loughlin and Gittes, 1986). Intra-arterial administration of epinephrine is sometimes helpful, because it causes vasoconstriction of the normal vessels but has no effect on tumor neovascularity.

MRI has not been very useful for small tumors of the kidney, unless the shape of the kidney is altered. The lesions on MRI have a signal intensity that is similar to that of normal renal parenchyma on T1- and T2-weighted images. However, gadolinium is useful because it enhances RCC. The heterogeneous nature of the larger tumors makes them more readily diagnosed (Rominger et al, 1992).

Screening

The genetic nature of VHL disease mandates careful screening. However, because of molecular genetic advances, the screening process for the disease in family members can now be more selective. Previously, asymptomatic relatives required routine ophthalmoscopic examination to rule out retinal angiomas, as well as frequent abdominal CT scans. Now only genetically affected family members require screening (Table 131-4).

Treatment

The treatment of patients with VHL requires a multidisciplinary approach, because the involvement of multiple organ systems and numerous medical problems is inherent to this disease. Because the tumors that characterize VHL disease are frequently multiple, bilateral, and recurrent, the goals of treatment for patients who have VHL disease are not as straightforward as the goals of treatment for patients who have sporadic tumors. Close surveillance and minimization of surgical procedures constitute the mainstay of treatment. For patients who have VHL disease, and all patients who have hereditary cancer syndromes, the goal of treatment is cancer control, not cancer cure, and preservation of functional parenchyma to avoid the morbidity associated with renal or adrenal loss. In patients who have VHL disease, surgical resection is performed with the understanding that microscopic disease probably is left behind. At present, open nephron-sparing surgery should be considered the standard of care for treating low-grade RCC in the setting of VHL disease. Patients with high-grade disease are still probably best served with bilateral nephrectomy. With the objective of sparing as much renal parenchyma as possible and preventing metastasis of the lesions already present, it is not curative surgery (Reed and Parekh, 2009). Although this approach does not reduce the risk of recurrence, reported to be 75% to 85%, the 10-year disease-specific survival rates are quite high (81% to 94%) (Malek

TABLE 131-4 Screening Protocol for Patients and Families with von Hippel-Lindau Disease

STUDY	AFFECTED PERSONS	RELATIVES AT RISK
Physical examination	Annual	Annual
24-Hour urine collection for metanephrines and normetanephrines	Annual	Annual
Funduscopy	Annual	Annual (age 10-60 yr)
Gadolinium MRI brain scan (or CT)	Every 3 yr from age 10-50 yr; every 5 yr thereafter	Every 3 yr from age 15-40 yr then every 5 yr until age 60 yr
Abdominal evaluation	Annual RUS with abdominal CT scan every 3 yr (more frequently if multiple renal cysts present)	Annual RUS with abdominal CT scan every 3 yr from age 20-65

CT, computed tomography; MRI, magnetic resonance image; RUS, renal ultrasonography.

From Maher ER, Yates JR, Harris R, et al. Clinical features and natural history of von Hippel-Lindau disease. *Q J Med* 1990;7:1151-63.

et al, 1987; Steinbach et al, 1995; Roupert et al, 2003; Ploussard et al, 2007). Classically, the survival rate after nephrectomy has been only 50%. Because most of these tumors are low grade, a nephron-sparing approach provides very good survival rates while avoiding the diminished quality of life that comes with bilateral nephrectomy and subsequent dialysis and transplantation. Laparoscopic and percutaneous image-guided ablative techniques, such as radiofrequency ablation and cryoablation, have also been used and are currently under investigation.

Given the high risk of multiple and bilateral pheochromocytomas in patients who have VHL disease, bilateral adrenalectomy can lead to the loss of all adrenal function. Preservation of normal adrenocortical function should be a primary surgical goal, because medical replacement therapy is associated with decreased quality of life (Telenius-Berg et al, 1989). Partial adrenalectomy can preserve normal adrenal function and avoid this morbidity. Identification of small pheochromocytomas may enable laparoscopic preservation of adrenal function and maintain quality of life in these complicated patients. The small size and lack of function of these tumors make them ideal for partial adrenalectomy; however, recurrences may develop in 15% of patients (Walther et al, 1999a, 1999b).

Papillary cystadenomas of the epididymis can be unilateral or bilateral and occur in approximately 10% to 26% of men who have VHL disease (Horton et al, 1976; Lamiell et al, 1989). They seem to have no malignant potential. Surgery is not performed for these lesions unless the patient experiences severe pain.

KEY POINTS: MULTIPLE MALFORMATION SYNDROMES

- Tuberous sclerosis complex is an autosomal dominant condition that includes the triad of epilepsy, mental retardation, and adenoma sebaceum. It is associated with renal cysts (20% of patients), renal AML (40% to 80%), and RCC (2%).
- There are two different gene mutations associated with tuberous sclerosis: *TSC1* on chromosome 9 and *TSC2* on chromosome 16.
- VHL disease is an autosomal dominant syndrome associated with cerebellar and retinal hemangioblastomas; cysts of the pancreas, kidney (76%), and epididymis; pheochromocytoma (10% to 12%); and clear cell RCC (50% incidence, and 30% to 40% incidence of death).
- VHL disease is associated with an inherited mutation of the *VHL* gene on chromosome 3.
- *VHL* is a tumor suppressor gene involved in regulation of HIF target genes, including *VEGF*; abnormal or absent *VHL* leads to increased tissue levels of specific growth factors and, in particular, *VEGF*, the most prominent growth factor in RCC.

MULTICYSTIC DYSPLASTIC KIDNEY

MCDK is a developmental anomaly resulting in multiple cysts of varying sizes, without identifiable normal renal parenchyma. These kidneys have no function by definition, and usually the contralateral kidney is normal and exhibits compensatory hypertrophy. Only unilateral involvement is compatible with life. The kidney often does not have a reniform appearance, and it is typically associated with an atretic ureter with no connection between glomerulus and calyces. Typically, the kidney has the appearance of a bunch of grapes, with little stroma between the cysts (Fig. 131-17). Renal size is highly variable, ranging from a small nubbin of tissue to a very large mass that fills most of the abdomen. In fact, MCDK is the second most common cause of an abdominal mass in a newborn, after hydronephrosis.

MCDK can be of two types: the infundibulopelvic type, with the atresia involving both the renal pelvis and the ureter, and the less common hydronephrotic type, in which only the upper ureter is atretic (Felson and Cussen, 1975). In both cases, the ureters are

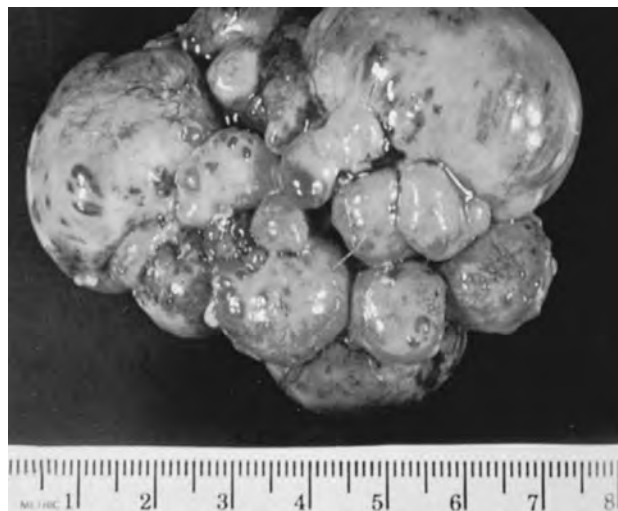


Figure 131-17. A typical multicystic dysplastic kidney having the appearance of a bunch of grapes. The kidney is composed almost entirely of cysts with very little stroma.

absent or atretic and the renal vessels are hypoplastic. MCDK can also rarely be secondary to ureterocele that have caused complete obstruction. It can rarely be seen in one half of a duplex kidney (usually the upper pole associated with an ectopic ureter) or in other abnormalities such as a horseshoe kidney.

Etiology

Many theories have been offered to explain the cause of MCDK. Clearly, it is a result of an error in renal development. Some have proposed that the multicystic kidney is an extreme form of obstructive hydronephrosis that occurs secondary to atresia of the ureter or renal pelvis. The fact that the left kidney is the one more often affected supports this view, because this is the kidney more often associated with primary obstructive megaureter (Glassberg, 1977) and UPJO (Johnston et al, 1977). Several investigators have attempted to establish an animal model of MCDK by ligating the ureter at various points in gestation (Beck, 1971; Tanagho, 1972; Fetterman et al, 1974). This approach is not effective in middle or late gestation; early ligation of the fetal lamb ureter produces renal dysplasia but not multicystic dysplasia (Beck, 1971). Similarly, other investigators have been able to induce dysplasia, but no one as yet has been able to induce an MCDK.

Another theory stems from the “ureteric bud theory” as proposed by Mackie and Stephens (1975). This theory hypothesizes that MCDK may result from abnormal interaction between the ureteric bud and metanephric mesenchyme. Mutations in genes such as *EYA1*, *SIX1*, *WNT*, *WT-1*, *GNF*, *AT2*, and *PAX2* are known to have important roles in ureteric bud development and have been identified in multiple human syndromes with renal dysplasia (Pope et al, 1999). These studies linking genetic mutations with renal dysplasia support the ureteric bud theory in the pathogenesis of MCDK and may also explain its frequent association with other urinary tract anomalies (Hains et al, 2009). In addition, Hildebrandt (1894) suggested that failure of the union between the ureteric bud and the metanephric blastema leads to cystic dilation in the latter; this hypothesis, like the obstructive view, is supported by the high incidence of concomitant ureteral atresia.

Although the ureteric bud theory and the obstruction theory may at some level go hand in hand, there is no question that there are several gene-mediated processes that go awry in the process of making a developmentally abnormal MCDK. These genes and their proteins are currently potential targets for both therapeutic intervention and research to further elucidate the mechanisms that cause MCDK.

Clinical Features

Multicystic dysplasia is the most common type of renal cystic disease and is the second most common cause of an abdominal mass in infants (Longino and Martin, 1958; Melicow and Uson, 1959; Griscom et al, 1975). Most cases in the current era are diagnosed by prenatal ultrasonography, and the incidence is 1 per 1000 to 4000 live births (Kalyoussef et al, 2006). There is a male preponderance (55% to 70%), and studies conflict as to whether MCDK is more common on the right or left side.

The contralateral system frequently is abnormal. For example, contralateral UPJO is found in 3% to 12% of infants with MCDK, and contralateral vesicoureteral reflux is seen in 18% to 43% of infants (Heikkinen et al, 1980; Atiyeh et al, 1992; Flack and Bellinger, 1993; Wacksman and Phipps, 1993; Al-Khaldi et al, 1994).

The natural history of MCDK is benign; the incidence of complications is extremely rare; and approximately 40% of MCDKs will spontaneously involute. Although anecdotal case reports exist, available large series data indicate that MCDK is not associated with an increased risk for hypertension or neoplasm (Wacksman and Phipps, 1993; Tilemis et al, 2003; Truong et al, 2003; Rabelo et al, 2004; Farnham et al, 2005; Narchi, 2005a, 2005b; Onal and Kogan, 2006). Although hypertension is a rare but recognized sequela of MCDK, it is reasonable to follow patients with MCDK conservatively. The primary care provider should monitor patients with MCDK for hypertension, abdominal mass, and urinary tract infection.

Histopathology

Multicystic kidneys with large cysts tend to be large with little stroma, whereas those with small cysts typically are smaller and more solid. Likewise, the blood supply is variable, ranging from a pedicle with small vessels to no pedicle at all (Parkkulainen et al, 1959). Usually the ureter is partly or totally atretic, and the renal pelvis may be absent. Griscom and colleagues (1975) referred to the form without a renal pelvis as *pyeloinfundibular atresia* and reported finding no evidence of communication between the cysts. However, others have shown distribution of contrast medium among the cysts by means of connecting tubules (Saxton et al, 1981). Microscopically, the cysts are lined by low cuboidal epithelium, are surrounded by collars of spindle cells, and are filled with proteinaceous or sanguineous fluid. They are separated by thin septa of fibrous tissue and primitive dysplastic elements, especially primitive ducts. Immature-appearing cartilage is often present in the tissue. Frequently, immature glomeruli are present, and on occasion a few mature glomeruli are seen (Fig. 131-18).

Evaluation

MDCK is most often identified by prenatal ultrasonography, and in newborns ultrasonography is usually repeated (once within the first few days of life and again 1 month later) to confirm the diagnosis and to evaluate the contralateral kidney and bladder. In a few cases, it is difficult to differentiate multicystic kidney disease from severe hydronephrosis (Gates, 1980; Hadlock et al, 1981). In general, the multicystic kidney has a haphazard distribution of cysts of various sizes without a larger central or medial cyst and without visible communications among the cysts. Frequently, very small cysts appear among the large cysts. By comparison, in UPJO, the cysts or calyces are organized around the periphery of the kidney; connections usually can be demonstrated between the peripheral cysts and a central or medial cyst that represents the renal pelvis; and there is an absence of small cysts among the larger cysts (Fig. 131-19).

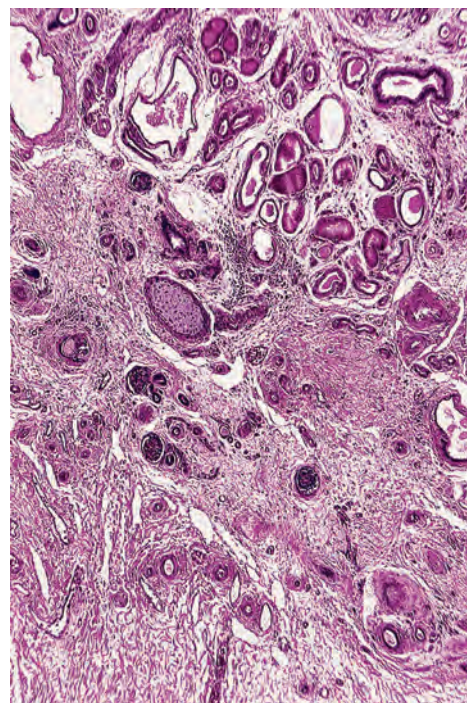


Figure 131-18. Disorganized development of kidney consistent with multicystic dysplastic kidney showing primitive glomeruli, tubules, and mesenchyme. (From Ordonez NG, Rosai J. Urinary tract. In: Rosai J, editor. Rosai and Ackerman's surgical pathology. 9th ed. Edinburgh: Mosby; 2004.)

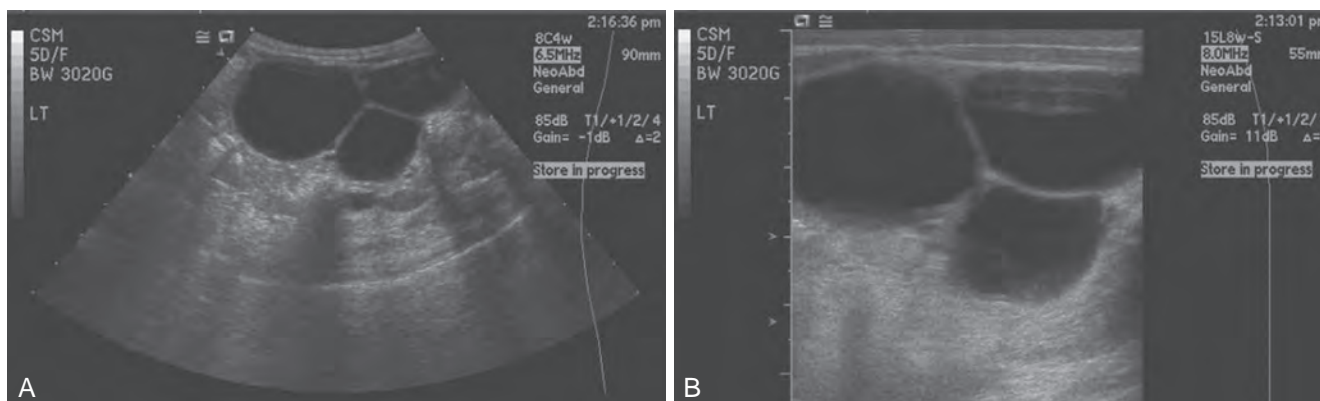


Figure 131-19. A and B, Renal ultrasonogram of large left multicystic dysplastic kidney. There are multiple large cysts. No definite renal cortex is seen.

In these difficult cases, radioisotope studies may be helpful. Hydronephrotic kidneys usually show some function on a dimercaptosuccinic acid (DMSA) or technetium-99m mercaptoacetyl-triglycine (^{99m}Tc -MAG3) scan, whereas renal uptake is seldom seen in multicystic kidneys (Fig. 131-20). Angiography reveals an absent or small renal artery in the multicystic kidney, but this study is rarely indicated. Cystoscopy may reveal a hemitrigone and absent ureteric orifice on the affected MCDK side; however, more often an orifice is present, but retrograde urography demonstrates ureteral atresia. Again, this study is seldom performed. As mentioned previously, a voiding cystourethrogram (VCUG) is usually indicated in the workup, because of the high incidence of reflux into the contralateral single functioning kidney. Some authors, however, have started to advocate that the VCUG is of little value if serial high-quality ultrasound findings are consistent with MCDK and

demonstrate a normal bladder and contralateral kidney. A VCUG is not necessary unless clinically indicated later in life (Ismaili et al, 2005; Welch and Wacksman, 2005; Onal and Kogan, 2006).

Treatment and Prognosis

It has often been stated that the multicystic kidney can be ignored unless its bulk is inconvenient (Pathak and Williams, 1964; Griscom et al, 1975), and attention should be directed instead to identifying any abnormalities of the contralateral urinary tract. Large MCDKs are known to interfere with respiratory and digestive function simply because of their mass effect. Intervention for these large masses may need to be undertaken to relieve these problems. Nephrectomy for MCDK may also be necessary to correct the rare cases of associated hypertension or if a cyst

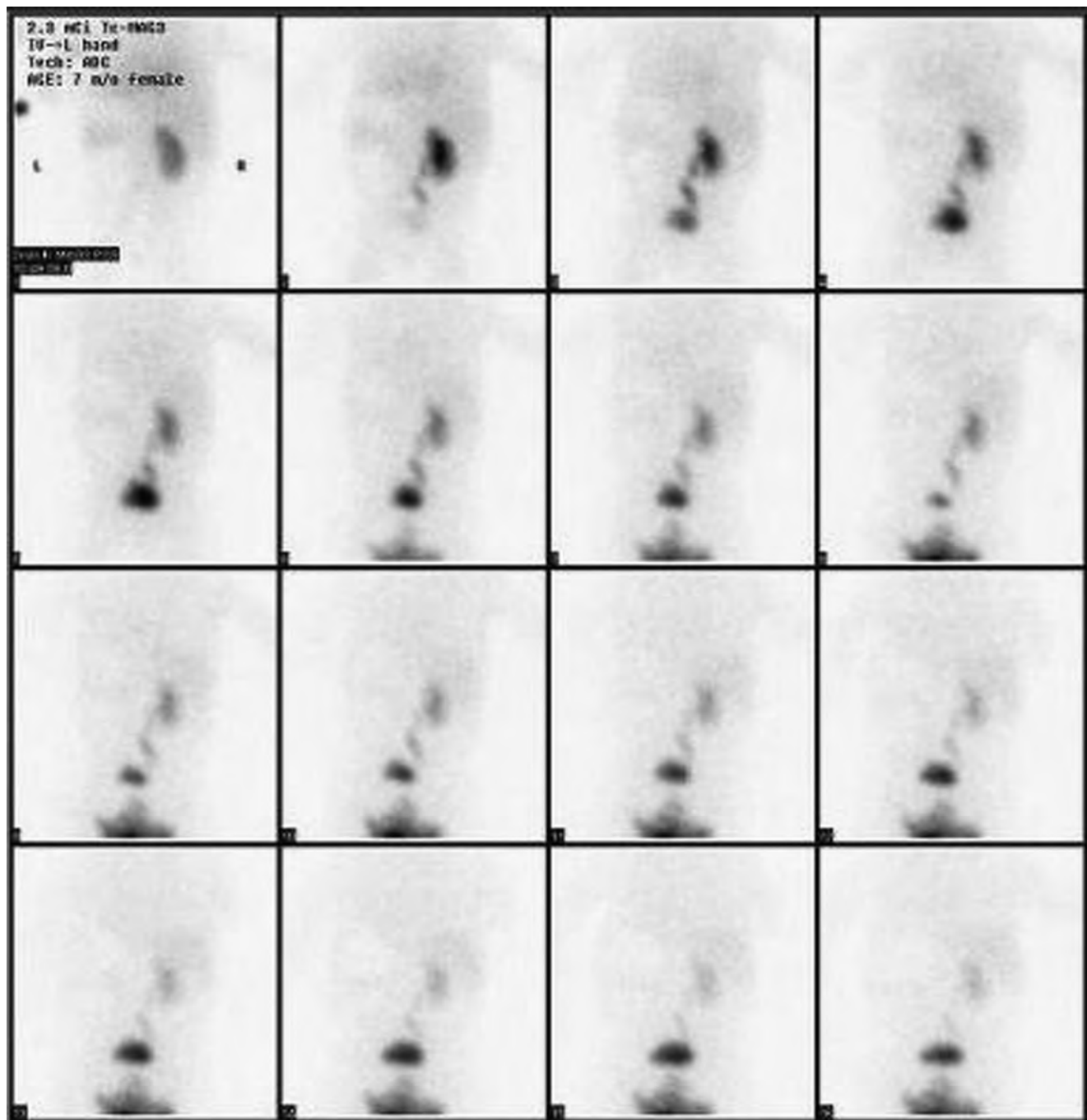


Figure 131-20. Technetium-99m mercaptoacetyl-triglyceride renogram revealing a normally functioning right kidney and no function on the left, which is consistent with a left multicystic dysplastic kidney.

has ruptured spontaneously or secondary to trauma (to relieve pain or hemorrhage).

A nonfunctioning hydronephrotic kidney could be mistaken for a multicystic kidney, although complete nonfunction on a nuclear medicine study is unusual in kidneys affected by UPJO. Fortunately, if the correct diagnosis is missed in such a case, there are unlikely to be significant consequences, because a totally nonfunctioning hydronephrotic kidney is rarely salvageable and probably will cause no problems other than a predisposition to infection or hypertension.

The probability of malignant transformation is estimated to be extremely low and believed by many to be nonexistent (Avni et al, 1987; Gordon et al, 1988; Wacksman and Phipps, 1993; Narchi, 2005b). Fewer than 15 cases of malignant degeneration have been reported in MCDK. Roughly half have been identified as RCC and half as Wilms tumor, and there has been one reported mesothelioma. Recommendations for addressing this risk range from early nephrectomy of the MCDK to minimal follow-up with no imaging and only periodic abdominal examination by the primary care physician (PCP). Many pediatric urologists will perform ultrasound surveillance every 3 to 12 months, but there has been no conclusive evidence that this is beneficial or cost-effective (Perez et al, 1998; Onal and Kogan, 2006).

There has also been much debate in contemporary series regarding hypertension in MCDK. The various case reports and small series that have been reviewed offer conflicting data on the issue. An additional confounding factor is that MCDK is often associated with contralateral abnormalities, such as UPJO and reflux. Thus groups have had difficulty determining if hypertension is associated with contralateral abnormalities or with MCDK. Several small series have reported patients with MCDK and hypertension who were cured with nephrectomy (Javadpour et al, 1970; Suskind et al, 1989; Angermeier et al, 1992; Webb et al, 1997; Snodgrass, 2000). Although these reports demonstrate that hypertension can occur with MCDK, most large series support the rarity of hypertension in association with MCDK. Several studies, including the report from the Multicystic Kidney Registry in 1993, have demonstrated the incidence of hypertension in patients with MCDK and long-term follow-up to be less than 1% (Wacksman and Phipps, 1993; Gough et al, 1995; Perez et al, 1998; Farnham et al, 2005). One study, however, demonstrated a much higher incidence of hypertension than the other MCDK series (Seeman et al, 2001). This could be a result of the more stringent measurement of BP applied, although

these patients were examined at a much later age than in other series, which may also have contributed to the higher detected incidence of hypertension. Two of those four patients with hypertension had concomitant abnormalities; thus it was concluded that increased BP is mainly associated with contralateral kidney damage regardless of the presence or absence of the dysplastic kidney (Seeman et al, 2001). In summary, hypertension is a rare but recognized sequela of MCDK. However, there is a suggestion that with more diligent monitoring, its incidence would increase. Therefore it is reasonable to follow patients with MCDK conservatively, realizing that hypertension can exist and should be assessed periodically. Because hypertension can be discovered on an examination by the PCP, the potential for this problem does not require urologic follow-up, only an informed PCP and family (Farnham et al, 2005).

KEY POINTS: MULTICYSTIC DYSPLASTIC KIDNEY

- MCDK is a developmental anomaly resulting in multiple cysts of varying sizes, is without identifiable normal renal parenchyma, is associated with active expression of genes involved with nephrogenesis, and has a changing morphology.
- Kidneys usually get smaller or disappear from view on imaging studies (i.e., renal aplasia), very occasionally increase in size, and very rarely are associated with Wilms tumor.
- There is no clear indication for removal of the kidney, unless an increased amount of solid tissue is identified.
- Large series data indicate that MCDK is not associated with an increased risk for hypertension or neoplasm.
- Fifteen percent of patients have associated contralateral reflux, and debate exists regarding whether or not to obtain a VCUG in all or only in those with some degree of fullness in the contralateral collecting system.

BENIGN MULTILOCLAR CYST (CYSTIC NEPHROMA)

Benign multilocular cyst (multilocular cystic nephroma) is a multilocular cystic neoplastic lesion in the kidney that falls in a spectrum of diseases along with multilocular cyst with partially differentiated Wilms tumor, a multilocular cyst with nodules of Wilms tumor, or cystic Wilms tumor (Fig. 131-21). These four

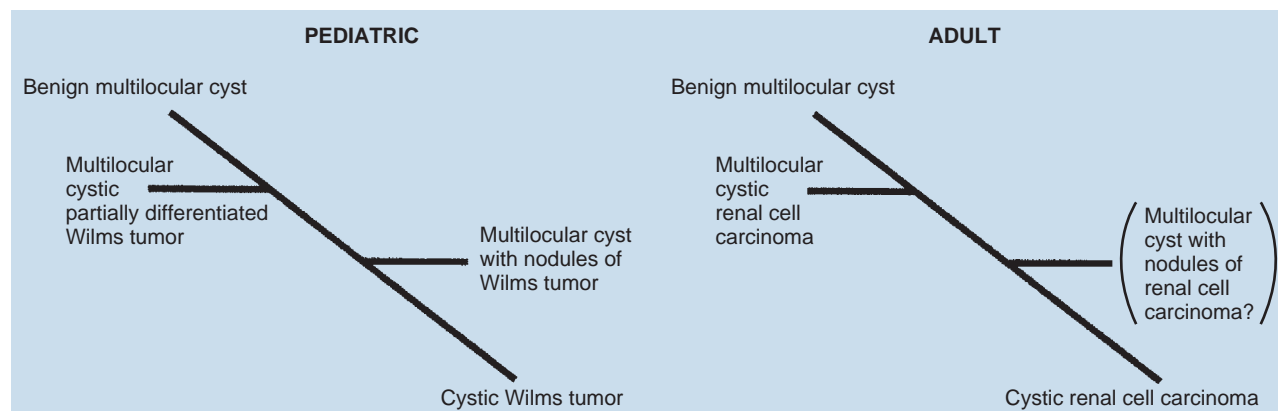


Figure 131-21. The spectrum of multilocular cystic lesions in children and adults. There is no evidence that one lesion can convert into the other. Benign cystic partially differentiated Wilms tumor and multilocular cystic renal cell carcinoma act as benign lesions. When nodules of tumor are present, the lesion should be considered malignant, although the prognosis of this lesion, as well as cystic Wilms tumor and cystic renal cell carcinoma, seems to be better than that of the corresponding solid lesions. It is not clear whether clinical examples of “multilocular cyst with nodules of renal cell carcinoma” actually exist, but this entity is placed in the spectrum for consideration. For simplicity, the multilocular-appearing lesions of other cystic tumors (e.g., cystic oncocyoma, cystic hamartoma of the renal pelvis) are not included in the figure.

lesions form a spectrum, with benign multilocular cyst at the most benign extreme and cystic Wilms tumor at the most malignant extreme. There has been some debate as to whether these lesions represent a spectrum of one disease with a common cause.

A multilocular cyst is not a renal segment affected by multicystic kidney disease; these conditions differ clinically, histologically, and radiographically. However, controversy continues about whether the multilocular cyst is a segmental form of renal dysplasia (Powell et al, 1951, Osathanondh and Potter, 1964; Johnson et al, 1973), a hamartomatous malformation (Arey, 1959), or a neoplastic disease (Boggs and Kimmelsteil, 1956; Christ, 1968; Fowler, 1971; Gallo and Penchansky, 1977). The confusion arises in part from the variability of the histologic picture: the appearance of the primitive stroma; the maturity of tubular and even on occasion of muscle elements; and the degree of epithelial atypia that differs not only from patient to patient but also within the same lesion.

Clinical Features

The great majority of cases (95%) manifest before the age of 4 years or after 30 years. If younger than 4 years, the patient is twice as likely to be male; if older than 30 years, the patient is eight times as likely to be female (Eble and Bonsib, 1998).

The signs and symptoms differ according to the age at presentation. In children, an asymptomatic flank mass is the most common finding, whereas most adults have a flank mass, abdominal pain, or hematuria. The bleeding is felt to be secondary to herniation of the cyst through the transitional epithelium into the renal pelvis (Uson and Melicow, 1963; Aterman et al, 1973; Madewell et al, 1983).

Seven cases of bilateral benign multilocular cysts of the kidney have been described (Castillo et al, 1991), and recurrence after excision has been rarely described (Geller et al, 1979). There are also at least two instances in which multilocular cysts arose in kidneys known to have been normal previously (Uson and Melicow, 1963; Chatten and Bishop, 1977). Such cases support a neoplastic theory of the origin of this lesion.

Histopathology

These lesions are bulky and are circumscribed by a thick capsule. Normal renal parenchyma adjacent to the lesion frequently is compressed by it. The lesion may extend beyond the renal capsule into the perinephric space or renal pelvis. The loculi, which range from a few millimeters to centimeters in diameter, do not communicate. They contain clear, straw-colored or yellow fluid and are lined by cuboidal or low columnar epithelial cells. In some cases, eosinophilic cuboidal cells project into the cyst lumen, creating a hobnail appearance (Madewell et al, 1983). The septa of a benign multilocular cyst are composed of fibrous tissue in which well-differentiated tubules may be present, but poorly differentiated tissues and blastemal cells are not present (Joshi and Beckwith, 1989).

In children, although there may be a continuum from benign multilocular cyst to cystic Wilms tumor, and although all of these lesions may be derived from similar cells or tissues, no evidence suggests that one entity transforms into another. Furthermore, none of the genetically determined conditions associated with Wilms tumor (e.g., hemihypertrophy, aniridia) has accompanied a benign multilocular cyst (Banner et al, 1981).

In adults, there also is a spectrum of multilocular cystic lesions. Multilocular cystic RCC in adults falls in the spectrum between a benign multilocular cyst and a cystic malignant tumor, such as a multilocular cystic RCC, a cystic RCC, a cystic oncocyoma, or a cystic hamartoma of the renal pelvis (Eble and Bonsib, 1998; Kirsh et al, 1999). The cystic component of the tumor at the carcinomatous end of the spectrum in both children and adults (i.e., cystic Wilms tumor and cystic RCC) improves the prognosis of the malignant lesion (Kirsh et al, 1999). In adults, as in children, there is no evidence that one lesion can convert into another (Fig. 131-22).

Evaluation

A number of tests may be useful, including ultrasonography, CT, MRI, cyst puncture with aspiration and double-contrast cystography, and arteriography. Ultrasonography and CT can distinguish multicystic kidneys from multilocular cysts, but neither study is sufficiently reliable to distinguish among multilocular cysts, multilocular cysts with foci of Wilms tumor or adenocarcinoma, mesoblastic nephromas, cystic Wilms tumors, and clear cell sarcomas. Typically, the septa are highly echogenic with sonolucent loculi, although if there is debris in a loculus, it may appear more solid. On CT the septa are less dense than normal parenchyma. Calcification is rarely visible in such lesions in children (Madewell et al, 1983).

Treatment

The treatment for any multilocular cystic lesion, even the most benign variant, is nephrectomy. If the lesion is localized enough and there is well-preserved normal tissue, excision of the lesion or partial nephrectomy is feasible. Children who have a multilocular cyst with nodules of Wilms tumor or a cystic Wilms tumor should be treated as for Wilms tumor, according to the National Wilms Tumor Study (NWTs) recommendations for the appropriate stage of disease, recognizing the generally favorable outlook. Similarly, cystic RCC in adults should be managed as a malignant lesion, again recognizing its better prognosis. In adults, benign multilocular cysts more often are associated with larger amounts of normal renal tissue, making partial nephrectomy more often feasible.

If enucleation or partial nephrectomy is chosen, recurrence is possible. However, with more Wilms tumors being treated by local excision, the case for enucleation or partial nephrectomy combined with close follow-up by ultrasonography and CT is stronger, even if malignancy is found within the lesion. By comparison, if a clear cell sarcoma is found after enucleation, the remaining ipsilateral renal tissue should be removed because of the aggressiveness of this cancer. The recurrence of a multilocular cyst not containing malignancy probably reflects inadequate excision of the initial lesion.

KEY POINTS: BENIGN MULTILOCULAR CYST

- A benign multilocular cyst is a benign, nondysplastic, neoplastic lesion that occurs most commonly either before the age of 4 years, most frequently in males, or after the age of 30 years, predominantly in females.
- The only way to determine the diagnosis of a multilocular cystic lesion identified on imaging studies, in either a child or an adult, is by surgical excision.
- Benign multilocular cyst is thought to fall at the benign end of a spectrum of the same disease process that also includes multilocular cyst with partially differentiated Wilms tumor, multilocular cyst with nodules of Wilms tumor, or cystic Wilms tumor at the most malignant end of the spectrum.

SIMPLE CYSTS

Simple cysts are the most common cystic lesions found in the human kidney. They are usually oval to round; may be solitary or multiple, unilateral or bilateral; and are filled with plasma-like clear or straw-colored fluid (Nahm and Ritz, 2000; Terada et al, 2002). They are not connected to any part of the nephron, although they may originate initially from a portion of the nephron.

Simple cysts may manifest at any time in utero and have been diagnosed as early as 14 weeks of gestation. Ultrasonography done on 29,984 fetuses in succession revealed 0.09% of 11,000 pregnancies to have renal cysts (Blazer et al, 1999). Between birth and 18 years of age, the incidence of simple renal cysts is fairly stable,

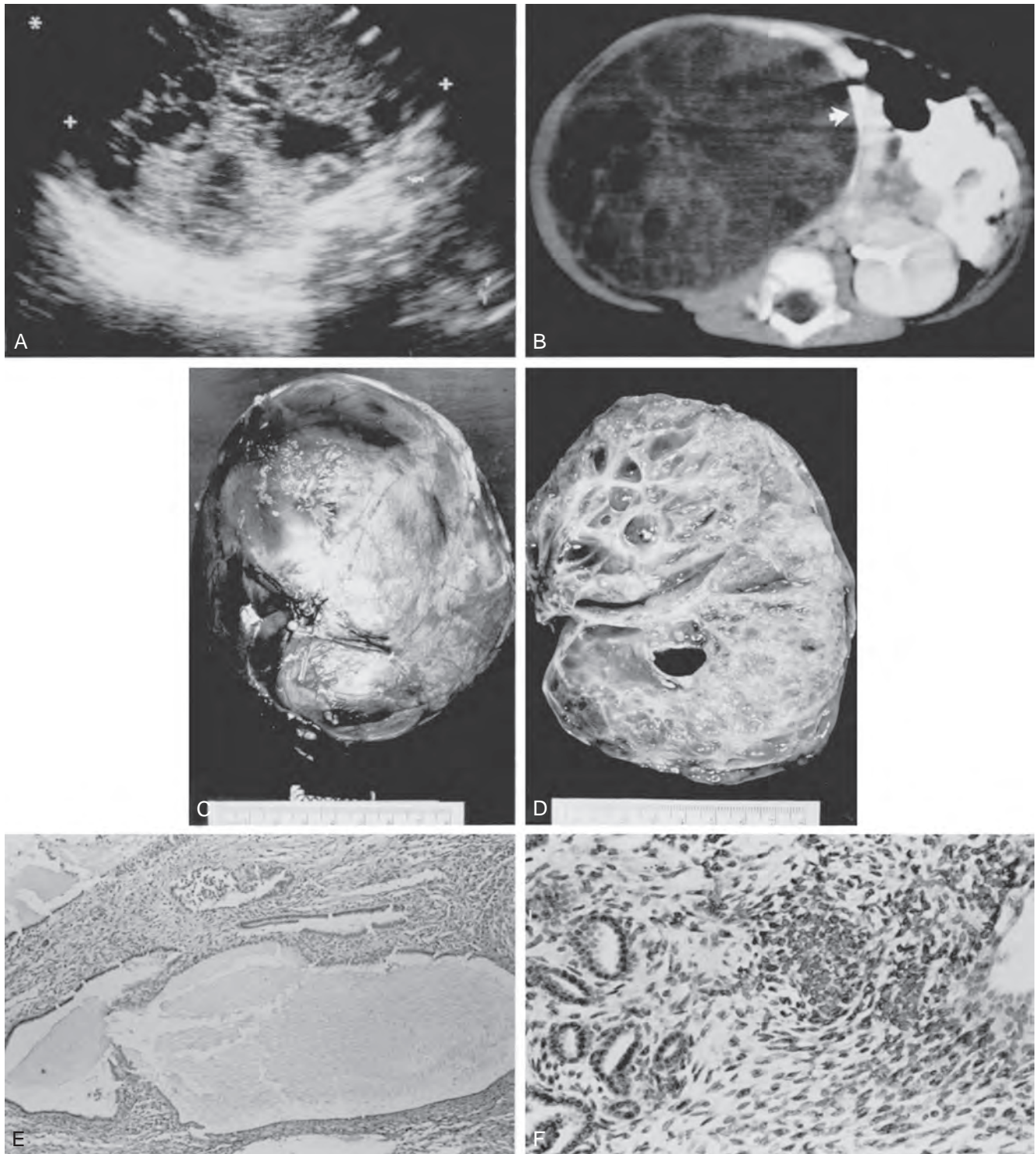


Figure 131-22. A 4-year-old girl with a right-sided abdominal mass. **A**, Renal ultrasonogram shows multiple cysts throughout the left kidney. **B**, On contrast medium-enhanced computed tomography scan, a large, smoothly outlined left renal mass is seen with fine septa throughout the mass. Residual preserved parenchyma and the pelvicalyceal system are compressed medially and pushed to the contralateral side (arrow). **C**, Uncut gross specimen reveals a smooth-walled, encapsulated renal mass. **D**, Cross section of mass reveals multiple noncommunicating loculations. **E**, On histology, a hypocellular cystic area is seen with monotonous stroma (100 \times). **F**, Between loculi, nests of blastemal cells are visualized along with tubular elements (left), making the diagnosis of multilocular cyst with partially differentiated Wilms tumor (200 \times).

ranging from 0.1% to 0.45%, with an average incidence of 0.22% (McHugh et al, 1991). However, in adults the frequency rises with age, with an incidence of 20% by age 40 years and as high as 50% after age 60 years (Kissane and Smith, 1975; Laucks and McLachlan, 1981). Most reports show no gender predilection; however, in at least two studies, men were affected more frequently than women (Bearth and Steg, 1977; Tada et al, 1983).

Clinical Features

In both children and adults, cysts rarely call attention to themselves. Instead, they are discovered incidentally on ultrasonography, CT, or urography. However, cysts can produce an abdominal mass or pain, hematuria secondary to rupture into the pelvicalyceal system, and hypertension secondary to segmental ischemia (Rockson et al, 1974; Lüscher et al, 1986; Papanicolaou et al, 1986). Cysts can cause calyceal or renal pelvic obstruction as well (Wahlqvist and Grumstedt, 1966; Evans and Coughlin, 1970; Hinman, 1978; Barloon and Vince, 1987). They may or may not increase in size with time.

Cysts can rupture into the pelvicalyceal system, maintain a communication, and become a pseudocalyceal diverticulum. The reverse is also possible: Closure of the communication of a diverticulum can create a simple cyst (Mosli et al, 1986; Papanicolaou et al, 1986). These two sequences of events can be distinguished only by histologic examination. Theoretically, diverticula should have linings of transitional epithelium, whereas simple cysts should be lined by a single layer of flattened or cuboidal epithelium.

Histopathology

Simple cysts vary considerably in size, ranging from less than 1 cm to greater than 10 cm. The majority are less than 2 cm in diameter, however (Tada et al, 1983). The wall is fibrous and of varying thickness and has no renal elements. The cyst lining is glistening and usually smooth and histologically is a single layer of flattened or cuboidal epithelium, and the cysts are filled with a clear, serous fluid. Because cysts are increasingly common with age, they have been considered an acquired lesion. Some cysts may be trabeculated by partial septa that divide the cavity into broadly interconnecting loculi. These septated simple cysts should not be confused with multilocular cysts. The cysts are often cortical and distort the renal contour, but they may be deep cortical or apparently medullary in origin. They do not communicate with the renal pelvis. The walls typically are thin and transparent but may become thickened, fibrotic, and even calcified, possibly from earlier hemorrhage or infection (Torres and Grantham, 2008).

Evaluation

Most simple cysts are identified incidentally. One can safely make the diagnosis of a classic benign simple cyst by ultrasonography when the following criteria are met: (1) absence of internal echoes, (2) presence of a sharply defined, thin, distinct wall with a smooth and distinct margin, (3) good transmission of sound waves through the cyst with consequent acoustic enhancement behind the cyst, and (4) a spheric or slightly ovoid shape (Goldman and Hartman, 1990). If all of these criteria are satisfied, the chance that malignancy is present is negligible (Fig. 131-23) (Lingard and Lawson, 1979; Livingston et al, 1981).

When some of these criteria are not met (e.g., when there are septations, irregular margins, calcifications, or suspect areas), further evaluation by CT, or perhaps needle aspiration or MRI, is indicated (Bosniak, 1986). A cluster of cysts is another indication for further study, because they may be hiding a small carcinoma. CT is better than ultrasonography in defining such a camouflaged lesion (Bosniak, 1986). Peripelvic cysts often require CT confirmation, because they frequently are interspersed among structures of the collecting system and hilum, which can create artificial echoes (Bosniak, 1986).

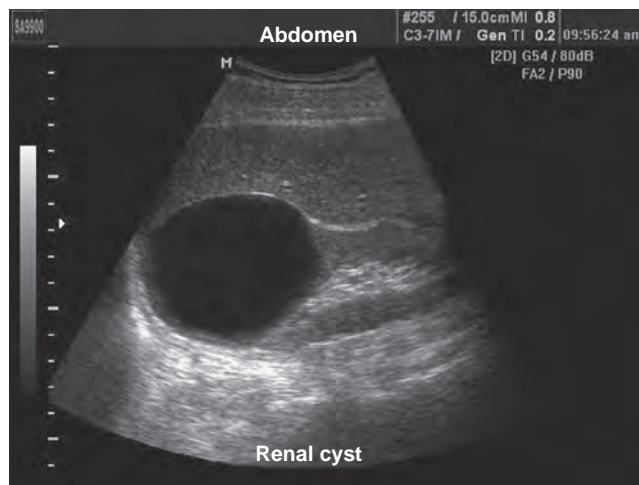


Figure 131-23. Ultrasonographic appearance of a 4-cm simple renal cyst. This meets the definition of a true simple cyst: (1) absence of internal echoes; (2) sharply defined, thin, distinct wall with a smooth and distinct margin; (3) good transmission of sound waves through the cyst with consequent acoustic enhancement behind the cyst; and (4) spheric or slightly ovoid shape.

The CT criteria for a simple cyst are similar to those used in ultrasonography: (1) a sharp, thin, distinct, smooth wall and margin, (2) a spheric or ovoid shape, and (3) homogeneous content. When these criteria are respected, the accuracy of diagnosis of a simple cyst by CT approaches 100% (Fig. 131-24) (McClellan et al, 1979). The density ranges from -10 to +20 HU, similar to the density of water, and no enhancement should occur after the intravenous injection of contrast medium.

When the cyst fluid is hyperdense (i.e., between 20 and 90 HU), the cyst still is likely to be a simple cyst if no enhancement occurs when intravenous contrast agent is injected and if the other criteria of CT and ultrasonography are met. Hyperdense cysts must be evaluated with narrow window settings to make sure that they are homogeneous. Other criteria that must be met to avoid further evaluation of hyperdense cysts (e.g., cyst puncture or exploration) include size (the lesion should be 3 cm or smaller) and location (at least one fourth of the cyst's circumference should extend beyond the renal contour so that the smoothness of a good portion of the cyst can be evaluated) (Bosniak, 1991; Hartman et al, 1992). Because cysts have no blood vessels and do not communicate directly with nephrons, they should not enhance; enhancement therefore implies vascular tissue or contrast medium mixing with fluid. Enhancement of any nodular areas on the wall of the cyst or of a thickened septum within the cyst is taken as proof of vascularity within the lesion, and thus there should be a high index of suspicion for neoplasm.

When ultrasonographic or CT criteria are not met, conditions other than a simple cyst must be considered, such as complicated cysts (i.e., those containing blood, pus, or calcification) and cystic neoplasms. Cyst puncture and aspiration with or without contrast medium injection has been popular in the past, but with current imaging modalities the need for cyst puncture is very rare. The remaining indications for cyst puncture are (1) suspected infection, in which case puncture may be therapeutic as well as diagnostic, (2) the presence of low-level echoes on ultrasonography but a classic cyst on CT, and (3) a borderline lesion in a poor surgical candidate.

Two percent of simple cysts and 10% of RCCs contain calcium deposits, but calcification in simple cysts appears to be peripheral, whereas in tumors it is more central. When the cysts are numerous and bilateral, differentiation from ADPKD may be difficult if liver cysts are not also found. Because of the obvious implications, it is important to avoid a diagnosis of ADPKD in questionable cases

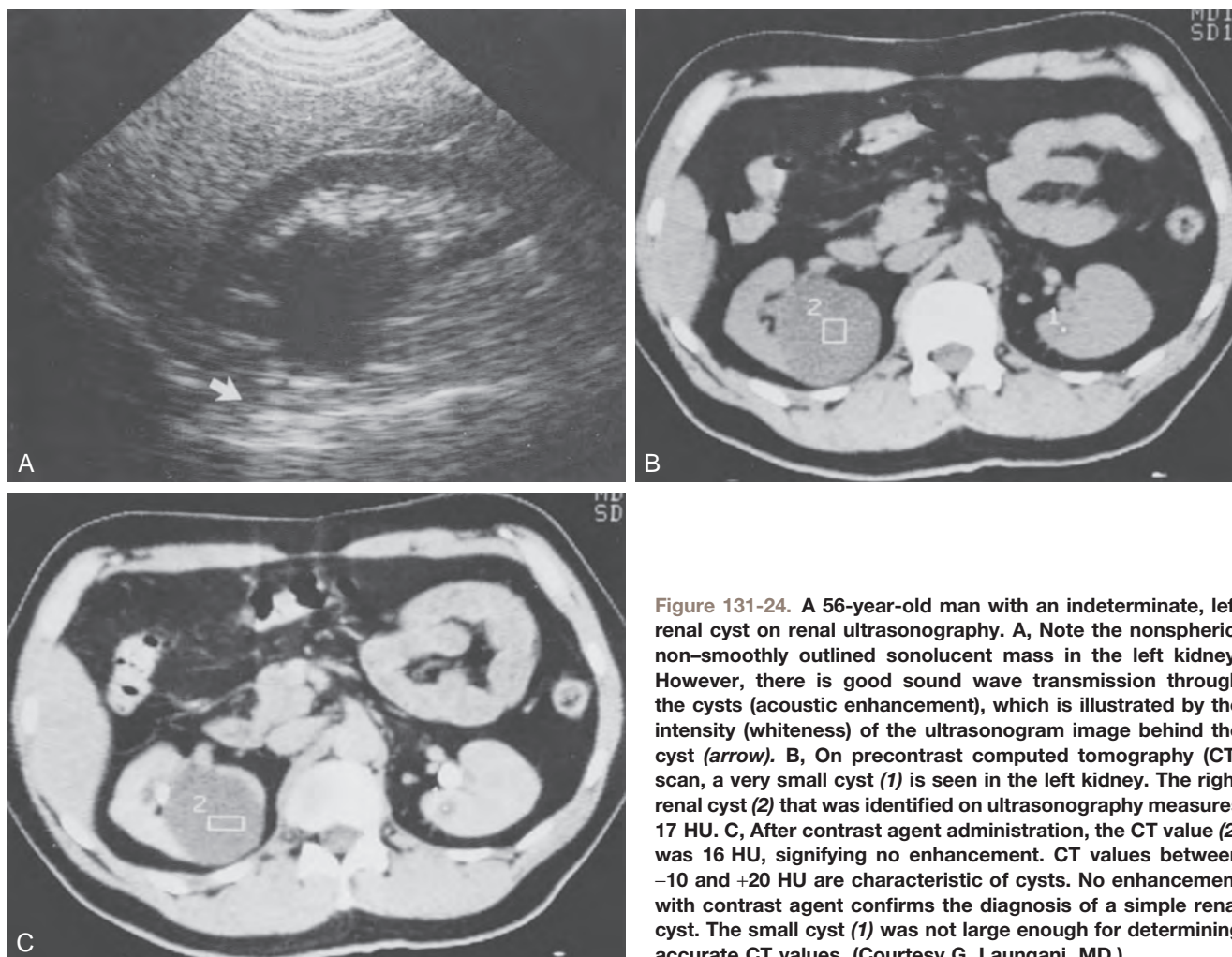


Figure 131-24. A 56-year-old man with an indeterminate, left renal cyst on renal ultrasonography. **A**, Note the nonspherical, non-smoothly outlined sonolucent mass in the left kidney. However, there is good sound wave transmission through the cysts (acoustic enhancement), which is illustrated by the intensity (whiteness) of the ultrasonogram image behind the cyst (arrow). **B**, On precontrast computed tomography (CT) scan, a very small cyst (1) is seen in the left kidney. The right renal cyst (2) that was identified on ultrasonography measures 17 HU. **C**, After contrast agent administration, the CT value (2) was 16 HU, signifying no enhancement. CT values between -10 and $+20$ HU are characteristic of cysts. No enhancement with contrast agent confirms the diagnosis of a simple renal cyst. The small cyst (1) was not large enough for determining accurate CT values. (Courtesy G. Laungani, MD.)

unless a familial history consistent with autosomal dominant transmission can be documented or the diagnosis confirmed by genetic testing.

MRI offers little information beyond that available from ultrasonography and CT, although it is more specific in identifying the nature of the cyst fluid. Marotti and colleagues (1987) found that if the fluid has low signal intensity (similar to that of urine) on T1-weighted images, the cyst is benign even if the wall is thick or septa are present. If this report is substantiated by additional studies, MRI may prove valuable in deciding which indeterminate cysts are benign and which should be considered for exploration. The T2-weighted images identify bloody fluid with an extremely bright image.

Classification

In an attempt to better categorize surgical and nonsurgical cysts in the kidney, Bosniak suggested a classification in 1986 that was clarified further in 1997 and modified by Israel and Bosniak in 2003 (Box 131-2). In addition, Wallis and colleagues (2008) suggested a modified Bosniak classification that can be used as a guideline to direct the need for surgical intervention in the pediatric population. They propose that in the absence of change or symptoms Bosniak class II cysts may be safely followed with periodic ultrasound imaging. Patients with Bosniak class III and class IV cysts have a significant chance of harboring malignancy, and surgical resection should be considered (Wallis et al, 2008).

Category I cysts are the typical benign cysts. Category II cysts are benign cystic lesions that are minimally complicated, such as by septations, small calcifications, infection, or high density, and do not require surgery. For example, when all the criteria for

BOX 131-2 Bosniak's Classification of Simple and Complex Cysts

CATEGORY I

Simple benign cyst with (1) good through-transmission (i.e., acoustic enhancement), (2) no echoes within the cyst, (3) sharply margined smooth wall; requires no surgery.

CATEGORY II

Looks benign with some radiologic concerns, including septation, minimal calcification, and high density; requires no surgery.

CATEGORY II F

Although calcification in wall of cyst may even be thicker and more nodular than in category II, the septa have minimal enhancement, especially those with calcium; requires no surgery.

CATEGORY III

More complicated lesion that cannot confidently be distinguished from malignancy, having more calcification, more prominent septation of a thicker wall than a category II lesion; more likely to be benign than malignant; requires surgical exploration and/or removal.

CATEGORY IV

Clearly a malignant lesion with large cystic components, irregular margins; solid vascular elements; requires surgical removal.

a simple cyst are met, except that a fine line of calcification or a short segment of slightly thickened calcification is seen in the wall or septa, the lesion should be considered a benign cyst, and exploration is not required. Another example is the cyst with fine traversing strands, perhaps containing calcium. In this case, exploration is not required unless the septa are numerous, irregular, or thick.

Category II F cysts (Israel and Bosniak, 2003) are complex cysts that cannot be classified as either category II or III. These lesions may contain increased calcification. The calcification may even be thicker and nodular, but although the septa may have minimal enhancement those septa with calcium do not enhance. Calcification seems to represent a less significant finding in making a lesion suspicious as a malignancy than previously thought. More focus is placed on tissue enhancement. There is little concern if calcification increases with time but much concern if the wall or septa becomes thicker or irregular. **Category II F cysts do not require surgical exploration** (Israel and Bosniak, 2003) (Fig. 131-25).

Category III cysts are more complicated lesions with radiologic features that are also seen in malignancy. One example is the lesion with more extensive calcification, especially if the wall is not pencil-point thin or is irregular. Other category III cysts are those with septations, suggesting a multilocular cystic lesion, or chronic infection with a thickened wall. These lesions are more problematic and require a surgical approach that is individualized. In some cases, one might consider violating the Gerota fascia to expose the kidney for examination of the lesion or partial nephrectomy.

Bosniak category IV lesions are cystic malignant tumors and are dealt with as such, namely, by radical nephrectomy.

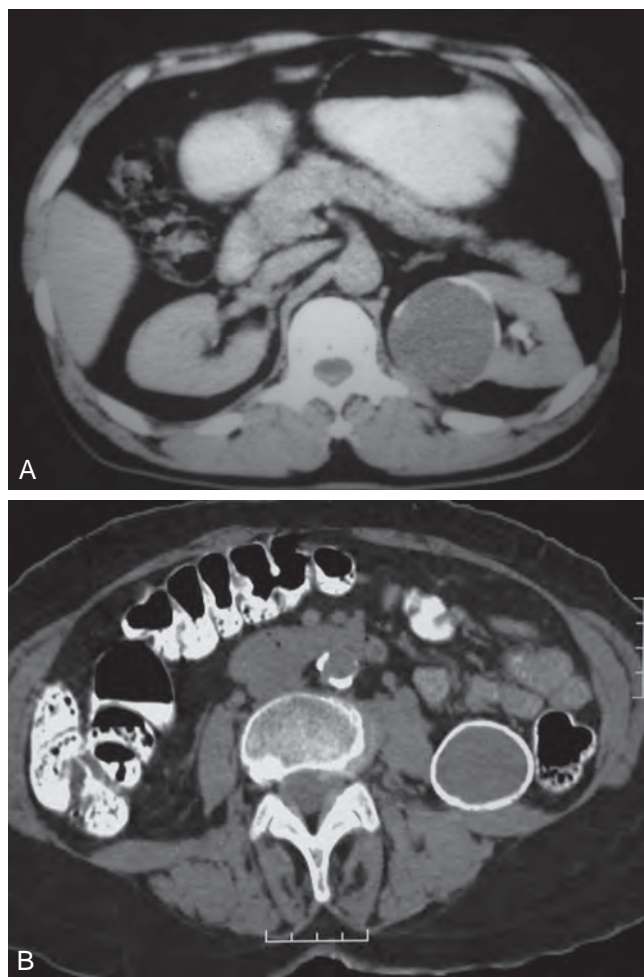


Figure 131-25. A and B, Two examples of Bosniak category II F cysts with diffuse calcification but no enhancement of septa on computed tomography. (Courtesy Jeffrey Newhouse, MD.)

Treatment and Prognosis

Once malignancy has been ruled out, surgical intervention for an asymptomatic cyst is not indicated (Gordon et al, 1979; Bartholomew et al, 1980; Ravden et al, 1980; Siegel and McAlister, 1980). Large renal cysts may cause abdominal or flank pain, although this pain may be caused by a coexisting problem (e.g., nephrolithiasis), and other sources of pain should be ruled out. Other symptoms that may arise as a result of simple cysts are pain resulting from hemorrhage into the cyst or calyceal or infundibular obstruction caused by cyst impingement. In rare cases, hypertension may occur, presumably from cyst compression causing segmental renal ischemia of the surrounding renal parenchyma. Cyst infection is a rare but potentially severe complication, with patients demonstrating fever, flank pain, and often a sympathetic pleural effusion (Torres and Grantham, 2008). Most of these patients are women, the most common pathogen is *Escherichia coli*, and urine cultures can often be negative.

Treatment of the simple cyst must thus be directed to the symptomatology. When a benign simple cyst causes pyelocalyceal obstruction or hypertension, the problem may be corrected either surgically, by unroofing the cyst, or percutaneously, by aspirating the fluid and perhaps injecting a sclerosing agent, particularly if fluid has reaccumulated after an earlier aspiration. Several sclerosing agents have been used, including glucose, phenol, iophendylate (Pantopaque), bismuth phosphate, and absolute ethanol, but none has been sufficiently impressive for its use to become dominant (Holmberg and Hietala, 1989). Infected cysts must be drained and appropriate antibiotics given. Percutaneous resection, intrarenal marsupialization (Hubner et al, 1990; Hulbert and Hunter, 1990; Meyer and Jonas, 1990), and laparoscopic unroofing (either transperitoneally or retroperitoneally) are all reasonable options for the treatment of symptomatic simple cysts.

Unilateral renal cystic disease is characterized by cysts of varying size appearing side by side, often more numerous at one pole. Except for its unilateral location, lack of extrarenal cyst formation, and the fact that these patients show no genetic background or progressive deterioration in renal function, the gross and histologic findings are indistinguishable from those of asymmetrical ADPKD (Lee et al, 1978; Kossow and Meek, 1982). It is important not to overdiagnose unilateral simple cyst disease, because the entity itself is rare, and when first identified in an individual it is more likely to represent a unilateral asymmetrical presentation of ADPKD. Because the entity seems to represent nothing more than multiple simple cysts lying side by side within a kidney, it seems reasonable to consider it as a variation of the presentation of simple cysts. Now that genetic studies are becoming available for ADPKD, tuberous sclerosis, and VHL disease, the diagnosis of unilateral renal cystic disease can more readily be confirmed (Fig. 131-26).

KEY POINTS: SIMPLE CYSTS

- Simple cysts are seldom seen in children; in adults, simple cysts are seen increasingly more frequently with age.
- For diagnosis of a benign simple cyst on ultrasonography, it should (1) have no internal echoes, (2) have a sharply defined, thin, distinct smooth wall, (3) be spheric or oval with no internal echoes, and (4) have good transmission of sound waves with acoustic enhancement behind the cyst. When these criteria are not met, CT with contrast enhancement must be performed.
- Relevant guidelines for determining when to explore or remove a complex cyst are often based on the Bosniak CT classification (see Box 131-2).

MEDULLARY SPONGE KIDNEY

The condition known as *medullary sponge kidney* (MSK; also known as *precalleal canalicular ectasia*) was recognized by Beitzke in 1908, and its radiographic features were described by Lenarduzzi in 1939.



Figure 131-26. Unilateral renal cystic disease. Diffuse simple cysts were evident in one kidney. There was no discrete mass or evidence of multiple malformation syndrome. (Courtesy Jeffrey Newhouse, MD.)

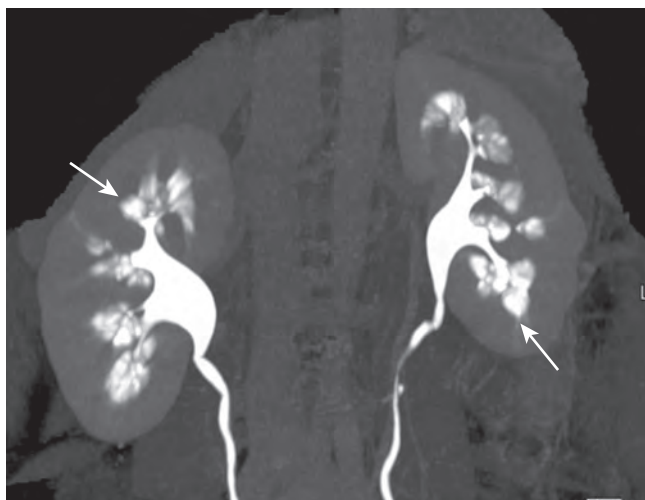


Figure 131-27. Contrast-enhanced maximum intensity projection three-dimensional image from multidetector-row computed tomography (CT) urogram shows characteristic papillary blush (arrows) associated with scattered calculi within the dilated collecting tubules. The CT demonstration is equivalent to the well-documented intravenous pyelography findings. (From Maw AM, Megibow AJ, Grasso M, et al. Diagnosis of medullary sponge kidney by computed tomographic urography. *Am J Kid Dis* 2007;50:146–50.)

The name of this disorder dates from a 1949 publication by Cacchi and Ricci. It is characterized by tubular dilation of the distal portion of the collecting ducts with numerous associated cysts and diverticula strictly confined to the medullary pyramids. These dilated ducts have the appearance of the bristles on a brush and often are more ectatic and filled with calcifications, giving an appearance suggestive of a bouquet of flowers. In general, classic intravenous urography is more sensitive than CT in detecting mild cases of MSK; however, three-dimensional (3D) volume-rendered imaging acquired during the urographic phase of a multidetector CT urogram can also establish the diagnosis (Fig. 131-27). The current literature suggests that single-slice helical CT, ultrasonography, and MRI are not able to detect findings specific to MSK. However, CT urography with 3D volume-rendered imaging is comparable to intravenous pyelography (IVP) for the diagnosis of MSK (Maw, 2007).

A significant number of patients with MSK are asymptomatic, and their condition is never diagnosed. As a result, the true incidence of the condition is unknown. Among patients undergoing intravenous urography for various indications, 1 in 200 were found to have MSK (Palubinskas, 1961; Myall, 1970). MSK is more common in calcium stone formers. It is usually regarded as a non-hereditary disease, and the small number of reported cases in children implies that this is an acquired rather than a congenital disease. There has been some recent evidence, however, that some forms of the disease are inherited in an autosomal dominant-type fashion. This evidence supports the hypothesis that MSK is caused by a disruption at the ureteric bud–metanephric blastema or RET/GDNF interface (Gambaro, 2013).

Clinical Features

MSK is usually a benign process, and it may remain asymptomatic and undetected for life. Clinical presentation usually occurs after age 20 years, with the most common presentation being renal colic (50% to 60%), followed by urinary tract infection (20% to 33%) and gross hematuria (10% to 18%) (Kuiper, 1976). The incidence of MSK in stone formers differs widely in the reported series, ranging from 2.6% to 21%. The incidence appears to be higher in female than in male stone formers (Palubinskas, 1961; Lavan et al, 1971; Parks et al, 1982; Sage et al, 1982; Wikstrom et al, 1983; Vagelli et al, 1988; Yendt, 1990). Urinary tract infections, likewise, seem to be more common in female patients with MSK (Parks et al, 1982).

One third to one half of the patients with MSK have hypercalciuria (Ekstrom et al, 1959; Harrison and Rose, 1979; Parks et al, 1982; Yendt, 1990). Incomplete distal renal tubular acidosis may be found in as many as 30% to 40% of these patients (Torres and Grantham, 2008). In the absence of infection, the stones passed by patients with MSK are composed of calcium oxalate, either alone or in combination with calcium phosphate. MSK has also been reported in association with rare congenital anomalies, such as hemihypertrophy, Beckwith-Wiedemann syndrome (macroglossia, omphalocele, and gigantism), Ehler-Danlos syndrome, anodontia, and Caroli disease.

Three different clinical pictures of MSK have been described: the typical form characterized by recurrent calcium nephrolithiasis and a number of concomitant tubular defects, including renal acidosis and metabolic bone disease; an indolent form with no or few renal stones and no tubular defects; and a rare but very severe condition dominated by intractable excruciating renal pain (Gambaro, 2013).

Histopathology

The principal finding is dilated intrapapillary collecting ducts and small medullary cysts, which range in diameter from 1 to 8 mm and give the cross-sectioned kidney the appearance of a sponge. The renal size is usually normal or slightly enlarged. The precalyceal canaliculi ectasia may involve one or more renal papillae in one or both kidneys. The lesions are bilateral in 70% of cases. The cysts are lined by collecting duct epithelium (Bernstein, 1990) and usually communicate with the collecting tubules. The cysts and the dilated collecting ducts may have concretions mostly made of pure apatite (calcium phosphate) and, less frequently, apatite and calcium oxalate (Ekstrom et al, 1959). The cysts contain a yellow-brown fluid and desquamated cells or calcified material.

Diagnosis

The urographic features of the disorder are as follows: (1) enlarged kidneys, sometimes with calcification, particularly in the papillae; (2) elongated papillary tubules or cavities that fill with contrast medium; and (3) papillary contrast blush and persistent medullary opacification (Gedroyc and Saxton, 1988). Calcium deposits within the tubules may appear as renal calculi or nephrocalcinosis.

In rare cases, MSK can mimic the radiographic appearance of ADPKD. In these instances, the liver should be evaluated before a

diagnosis is made. In addition, the absence of family history and a CT showing the absence of cortical cysts help confirm the diagnosis.

When nephrocalcinosis is found, other hypercalciuric states, such as hyperparathyroidism, sarcoidosis, vitamin D intoxication, multiple myeloma, tuberculosis, and milk alkali syndrome, must be ruled out. In these conditions, the calcium deposits are in collecting ducts of normal caliber, whereas in MSK the calcifications occur in dilated ducts (Levine and Grantham, 1990).

Treatment and Prognosis

It is the complications of MSK, calculus formation, and infection that require management. Given the frequent presence of hypercalciuria and hypocitraturia (possibly caused by incomplete renal tubular acidosis), treatment with potassium citrate is effective in reducing the rates of calciuria and stone recurrence (Gambaro, 2013). In addition to liberal fluid intake and a low-sodium diet, **thiazides are effective for lowering hypercalciuria and limiting stone formation.** If thiazides cannot be used, **inorganic phosphates may be appropriate;** however, they should not be used in patients with urinary tract infections caused by urease-producing organisms, because of the risk of struvite stones. **For patients with renal lithiasis, thiazides should be administered even if hypercalciuria is not present.**

Because infections are not unusual in patients with MSK, especially if stones are present, cultures should be obtained frequently, and long-term prophylaxis should be considered in some cases. Infections by coagulase-positive staphylococci are common in patients with stones and should be treated even when the colony count in the cultures is less than 100,000/mL (Yendt, 1990). Repeated investigations for hematuria should be avoided. When stones require surgical therapy, standard procedures, such as extracorporeal lithotripsy and percutaneous nephrolithotomy, may be used.

KEY POINTS: MEDULLARY SPONGE KIDNEY

- MSK is usually a nonheritable condition associated with dilated collecting ducts that appear as bristles on a brush on IVP, and the ducts are sometimes filled with calcifications.
- There are high incidences of renal colic (50% to 60%), urinary tract infections (20% to 33%), gross hematuria (10% to 18%), and hypercalciuria (33%).

SPORADIC GLOMERULOCYSTIC KIDNEY DISEASE

GCKD is a specific entity, but the term has often been used to include all conditions in which there are glomerular cysts, regardless of cause. The term *glomerulocystic* means that cysts of the glomeruli or Bowman space are present diffusely and bilaterally. However, cysts of the glomeruli are present in many forms of renal cystic disease, and they may or may not be the predominant pathology. The specific disease entity, glomerulocystic disease (or "sporadic" glomerulocystic disease), is a nonheritable condition producing bilaterally enlarged kidneys containing small cysts, predominantly of the Bowman space. The clinical significance of this disease process is that it is often **indistinguishable from other conditions in which glomerular cysts are present, namely, autosomal dominant polycystic disease, familial hypoplastic glomerulocystic disease, and juvenile NPH.** Characteristically, with sporadic GCKD, no other family members are affected and no associated anomalies are typically present.

ACQUIRED RENAL CYSTIC DISEASE

ARCD, also known as *acquired cystic kidney disease* (ACKD), is defined as bilateral cystic renal change in patients with ESRD from

causes other than inherited renal cystic disease. A minimum of three cysts in each kidney is required for diagnosis. This disease entity was first described in 1977 in **patients receiving hemodialysis; however, it soon became apparent that the disorder is almost as common in patients receiving peritoneal dialysis** (Dunhill et al, 1977; Thomson et al, 1986). It is now known that dialysis is not a prerequisite of ARCD, and it is likely that the uremic state causes the pathologic changes seen; dialysis merely prolongs patient survival and the amount of time available for the cystic changes to occur (Fisher and Horvath, 1972; Ishikawa et al, 1980; Kutcher et al, 1983; Miller et al, 1989; Truong et al, 2003).

The prevalence and severity of this disease increase with the duration of azotemia and the subsequent need for dialysis. Acquired cysts are found in roughly 10% of patients with ESRD before dialysis. The incidence increases to 44% within 3 years after initiation of dialysis, to 60% at 5 years after initiation of dialysis, and to greater than 90% if the patient is on dialysis for 10 or more years. ARCD is three times more common in men than in women and is generally thought to be unrelated to age or the cause of renal failure. African-Americans and perhaps Japanese are more prone than Americans of European descent to develop ARCD (Reichard et al, 1998). ARCD can occur in children as well (an incidence of approximately 23% has been reported) (Hakim et al, 1994). A successful renal transplant was previously thought to delay or even reverse the cystic changes, but this is not supported by more recent data (Heinz-Peer et al, 1995; Doublet et al, 1997; Kliem et al, 1997).

Etiology

Several etiologic theories have been proposed for ARCD, although the exact cause has not been identified. One theory suggests that tubular obstruction resulting from fibrosis, oxalate crystals, vascular occlusion, or ischemia leads to cyst formation. Various other findings suggest a role for toxins. First, the cysts, adenomas, and carcinomas usually are multiple and bilateral, as are the carcinomas induced experimentally in rats by toxins. Second, there is often a regression of the cysts after successful transplantation (Ishikawa et al, 1983), suggesting that some cystogenic or carcinogenic toxin of uremia is being eliminated by the allograft. Third, if transplantation fails and dialysis is resumed, the cysts return even in chronically rejected transplanted kidneys. Another hypothesis suggests that the accumulation of growth factors, such as epidermal growth factor (EGF), and other stimulatory chemicals (present with uremia) leads to the development of cysts (Bisceglia et al, 2006). Yet another theory suggests that loss of functioning renal tissue leads to the production of renotrophic agents that induce hyperplasia of remaining glomeruli, cyst development, and in extreme cases renal tumors (Harris et al, 1983; Yamamoto et al, 1983).

Clinical Features

Most patients with ARCD are asymptomatic. **The majority of clinical manifestations result from spontaneous bleeding into one or more of the cysts, making the most common presentation loin pain, hematuria, or both conditions. Bleeding occurs in as many as 50% of patients** (Levine, 1996). When significant bleeding occurs, it may cause a subcapsular or retroperitoneal hematoma and may be secondary to renal cysts or to RCC. This bleeding may be complicated by coagulation defects induced by uremia or heparinization during dialysis. Other, much less common complications are cyst infection, urolithiasis, and a rapid rise in hematocrit, which is probably related to increased renal synthesis of erythropoietin (Shalhoub et al, 1982; Ratcliffe et al, 1983; Mickisch et al, 1984). Patients with microscopic hematuria (more than 5 red blood cells per high-power field), both dialysis patients and transplant recipients, should be radiographically evaluated because of the increased risk of tumor formation in these groups (Kim, 2010).

Renal neoplasms, principally adenomas, occur in 10% of patients receiving chronic hemodialysis, and, when ARCD is present, the

incidence of neoplasms is even higher, ranging from 20% to 25% (Gardner and Evan, 1984; Schwarz, 2007). The overall prevalence of RCC in hemodialysis patients is approximately 1%. Carcinoma is 3 times more likely in the presence of ARCD and 6 times more common in large cystic kidneys than in small cystic kidneys (Torres and Grantham, 2008). Overall, the incidence of renal malignancy in dialysis patients is 5 to 50 times greater than in the general population (Resseguie et al, 1978; Port et al, 1989; Levine et al, 1991; Ishikawa, 1993; Truong et al, 1995).

Compared with the sporadic form, RCC associated with ARCD is characterized by younger patient age, male predominance, frequent multicentricity and bilaterality, and less aggressive behavior (Gronwald et al, 1999; Denton et al, 2002; Truong et al, 2003). Approximately 20% of ARCD-associated RCC metastasizes versus 50% for sporadic RCC. The risk factors for tumor development include male gender, duration of dialysis, and kidney weight, but not type of dialysis. Children on dialysis can also develop RCC, despite its rarity in the general pediatric population. Most tumors (86%) are asymptomatic, and the symptomatic ones are related mostly to bleeding from tumor. Many manifest exclusively as persistent hematuria and are not seen by any available imaging techniques. Nephrectomy is recommended for tumors larger than 3 cm or for smaller ones that are associated with persistent hematuria or rapid growth (Truong et al, 1995; Ishikawa, 2000).

Histopathology

Both kidneys are usually smaller than normal, and the cysts are multiple and bilateral. The cysts develop predominantly in the cortex, although the medulla may be affected, especially later in the disease process (Fig. 131-28). The cysts average 0.5 to 1.0 cm in diameter, but some have been reported to reach 5.0 cm (Miller et al, 1989). Larger cysts, a frequent feature of ADPKD, are rare. The cysts are unilocular and contain clear, straw-colored, or gelatinous fluid, with frequent bleeding and/or neoplastic transformation.

Most cysts are lined by a single layer of epithelium composed of flat nondescript cells, cells with abundant cytoplasm and hyaline droplets, or small cuboidal cells resembling those from distal tubules or collecting ducts. Cysts usually show secondary changes, including luminal deposition of degenerated blood, hemosiderin, or calcium oxalates (Hughson et al, 1986; Ishikawa, 1991; Truong et al, 1995). The nuclei of the epithelial cells in these cases are round and regular, without prominent nucleoli (Hughson et al,

1980). However, some cysts (atypical or hyperplastic) are lined by epithelial cells with larger, irregular nuclei that contain prominent nucleoli and may show mitotic activity. This hyperplastic lining is thought by some to be a precursor of renal tumors. Moreover, some hyperplastic cysts have papillary projections, and to some observers the distinction between cyst and neoplasm becomes blurred when papillary hyperplasia predominates.

Differentiating renal tumors into adenomas and carcinomas is arbitrary at times. Most renal nodules that are smaller than 1 cm in diameter are adenomas, and most that are larger than 3 cm in diameter are carcinomas. Tumors between 1 and 3 cm in diameter must be considered equivocal. It is not clear whether renal adenomas undergo malignant transformation. It is believed that atypical hyperplastic epithelium occurs even without cyst formation and that these cells are the precursors of both atypical cysts and adenomas (Hughson et al, 1986). It is thus possible that either hyperplastic cysts or adenomas can become RCCs. Therefore one must not ignore the native kidney left in situ during a renal transplantation. Hyperplastic cyst epithelium has also been considered a possible precursor of RCC in other cystic diseases (VHL disease and tuberous sclerosis) (Fayemi and Ali, 1980).

Evaluation

Ultrasonography is the modality most commonly used to diagnose and monitor patients with ARCD. CT and MRI identify more cysts, and MRI is probably better at demonstrating and characterizing small lesions in particular (Heinz-Peer et al, 1998). Ultrasonography usually shows small, hyperechoic kidneys with cysts of various sizes. Cyst wall calcification may be visible, but it is more readily seen on CT. CT with and without contrast is better for distinguishing kidneys with a few simple cysts from those with multiple acquired cysts and is the most useful for detecting neoplasms. In patients with ESRD not yet on dialysis, however, the use of CT contrast should be avoided for fear of causing further deterioration of renal function. Ultrasonography and MRI with gadolinium enhancement are better alternatives to contrast-enhanced CT in these patients. A word of caution, however: Nephrogenic systemic fibrosis (NSF) is a rare but serious and life-threatening disorder observed in patients with renal impairment and is associated with the infusion of gadolinium as an MRI contrast agent in patients with ESRD. Caution should be used when using gadolinium in these patients.

In uremic patients with fever, one should consider the diagnosis of ARCD and the possibility of an infected cyst (Bonai et al, 1987). Infection should be suspected if ultrasonographic examination shows internal echoes or a thickened wall. Cyst puncture can be used to confirm the diagnosis and to identify the infecting microorganism. CT examination may identify cyst wall thickening in patients with infection.

In the differential diagnosis of ARCD, the etiology of the renal failure must be considered and, in particular, the possibility of ADPKD. Usually, patients with ARCD have smaller kidneys and smaller cysts and are free of the extrarenal manifestations of ADPKD. In patients receiving hemodialysis, kidneys affected by ARCD usually are smaller than 300 g; ADPKD kidneys usually are larger than 800 g (Feiner et al, 1981).

Treatment

Bleeding episodes are often treated conservatively with bed rest and symptom control. Persistent bleeding and pain, however, may require nephrectomy or renal embolization. If heparinization is associated with hematuria during hemodialysis, peritoneal dialysis may be substituted. Because the risk of undetected RCC is high in patients with retroperitoneal hemorrhage, nephrectomy is recommended when carcinoma cannot be ruled out. If a few larger cysts are associated with flank pain, percutaneous aspiration (with cytologic examination) is a reasonable temporizing measure, because ARCD may regress after successful renal transplantation (Torres and Grantham, 2008). For an infected cyst, percutaneous drainage



Figure 131-28. Bilateral multiple renal cysts and diffuse calcification in enlarged kidneys in a patient undergoing chronic hemodialysis. The findings simulate those of ADPKD. However, cystic disease was not the cause of the uremia, and the diagnosis of acquired renal cystic disease was made. (Courtesy D. Gordon, MD.)

may be effective. When it is not, surgical drainage or nephrectomy should be considered.

Although small renal tumors may metastasize, it is known that those smaller than 3.0 cm in diameter rarely do so (Bell, 1935; Talamo and Shonnard, 1980). Thus it is currently recommended that renal masses larger than 3 cm detected in patients with ACKD be treated by surgical excision. For tumors smaller than 3 cm, some advise nephrectomy for the acceptable surgical candidate, whereas others recommend annual CT follow-up with resection only if the tumors enlarge. Although metastases are statistically less likely to occur from small than from large tumors, small tumor size is not a guarantee against metastasis. Laparoscopic bilateral radical nephrectomy in patients with ESRD, ACKD, and suspicious tumors has been proposed as a more desirable alternative to traditional open surgery (Ghasemian et al, 2005).

It has been recommended that patients who have been receiving hemodialysis for longer than 3 years be screened by ultrasonography and CT and then monitored by ultrasonography every 6 months if the kidneys are without cysts and tumors or by both ultrasonography and CT on the same schedule if cysts or tumors smaller than 2 cm are identified (Sarasin et al, 1995). The benefit of screening in this population continues to be the subject of much debate. It has been proposed that screening be restricted to patients younger than 55 years who have been on dialysis for at least 3 years and are in good general health (Sarasin et al, 1995). Others have suggested that screening of patients should be considered when known risk factors exist, such as prolonged dialysis, presence of ARCD, and male gender (Reichard et al, 1998).

A number of investigators have found that the cysts of ARCD regress after renal transplantation (Ishikawa et al, 1983; Kutcher et al, 1983; Thomson et al, 1986). Therefore it was considered that the incidence of RCC might fall after transplantation as well. Unfortunately, 18% of patients developed new cysts after transplantation, and renal carcinoma can occur in the native kidney 3 to 8 years after transplantation (Ishikawa, 1991; Levine and Gburek, 1994). It appears that the malignant potential of ARCD may persist for many years after transplantation, especially in older transplantation patients and in men (Heinz-Peer et al, 1995). Finally, it must be remembered that immunosuppression in and of itself makes these patients vulnerable to carcinoma. Native kidneys account for 4.5% of all malignancies in renal transplantation recipients (Penn, 1979). After renal transplantation for ESRD, the risk for developing RCC is more than 15-fold increased (Kasiske, 2004). RCCs of native kidneys and RCCs of the allografts can be distinguished, with more than 70% of the tumors occurring in native kidneys (Tsaur, 2010; Klatte, 2011). It also appears that the clinical significance of RCC in patients undergoing chronic hemodialysis must be questioned because in this population, RCCs rarely cause metastases or death. In contrast, renal cancer in the transplant population behaves quite aggressively and warrants aggressive evaluation both before and after renal transplantation (Pope, 1994).

KEY POINTS: ACQUIRED RENAL CYSTIC DISEASE

- ARCD is associated with chronic renal failure and is most often seen in patients on long-term hemodialysis and peritoneal dialysis.
- ARCD consists of hyperplastic renal cysts and frequently adenomas; either can progress to RCC.
- The incidence of renal malignancy in dialysis patients is 5 to 50 times greater than in the general population. If RCC develops, it mostly does so before 10 years of dialysis.
- The cysts usually regress with transplantation. Even when this occurs, there still is some suggestion that the risk of developing RCC still persists, but at a much lower incidence.

CALYCEAL DIVERTICULUM (PYELOGENIC CYST)

A calyceal diverticulum is an outpouching of the collecting system into the corticomedullary region of the kidney, and it usually arises from the fornix of a calyx. It is a transitional epithelial-lined, smooth-walled, spheric cavity that communicates with the pelvicalyceal system by a thin channel or neck, typically in the upper or lower pole. It is sometimes known as a *pyelogenic cyst*, especially if it arises from the renal pelvis. The size of such lesions can range from a few millimeters to several centimeters. Most diverticula are presumed to be congenital; however, similar lesions may occur as a result of blunt renal trauma or obstruction of a calyceal infundibulum. Diverticula are usually asymptomatic but may occasionally develop calculi. The calculi may be a single larger stone or multiple tiny stones. Occasionally, milk of calcium may be present. Passage of a stone through the narrow channel into the calyx may cause pain and hematuria.

Radiographically, these diverticula are seen as a spheric collection of contrast medium adjacent to a papilla on IVP; however, the connecting channel is often too narrow to be demonstrated. On upright films, the urine and contrast media form a fluid level. Calyceal diverticula can also be seen on CT, MRI, and ultrasonography, but the distinction between an obstructed calyx and a renal cyst may be difficult unless contrast is administered (Fig. 131-29).

This entity is discussed in more depth in Chapter 130.

PARAPELVIC AND RENAL SINUS CYSTS

Parapelvic cysts, renal sinus cyst, peripelvic cyst, pelvic cyst, parapelvic lymphatic cysts, hilus cysts, cysts of the renal hilum, and parapelvic lymphangiectasia are all terms used to describe cysts that are adjacent to the renal pelvis or within the hilum. Although some peripelvic cysts are simple cysts that arise from the renal parenchyma and impinge on the renal pelvis, true cysts derived from the renal sinus have no parenchymal cause. Thus the terms *parapelvic* and *peripelvic* are terms better used to describe the location of parenchymal cysts, and the term *renal sinus cyst* more accurately describes all other cysts in the hilum that are not derived from the renal parenchyma but rather from the other structures of the renal sinus, such as arteries, lymphatics, and fat. These are all benign lesions found in 15% to 20% of patients at autopsy. With modern imaging techniques, they can easily be distinguished from more serious lesions of the renal pelvis or renal parenchyma (Fig. 131-30).

The predominant type of renal sinus cyst appears to be a result of dilation of lymphatics; however, the mechanism responsible for these changes is not known. Most often these cysts are multiple, and often they are bilateral. Other renal sinus cysts are caused by fluid replacing adipose tissue in the renal sinus as the kidney becomes affected by local vascular disease and atrophy.

Patients are usually in their fifth or sixth decades and are almost always asymptomatic. These cysts are usually discovered incidentally in the course of evaluation for other conditions, such as urinary tract infections, nephrolithiasis, hypertension, and prostatism. There are rare instances of obstruction of a collecting system from these cysts. Ultrasonography will show multiple echo-free areas in the region of the renal sinus. Differentiation from hydronephrosis may be difficult. A diagnosis of hydronephrosis is established without question when dilated calyces are seen to communicate with a dilated renal pelvis. On CT, renal sinus cysts have the attenuation value of water, and they can often be seen within the renal sinus as they displace the calyces peripherally. On nonenhanced scans, multiple renal sinus cysts resemble a dilated renal pelvis and thus mimic hydronephrosis. Differential diagnosis should include renal sinus lipomatosis (fat density), lymphoma, hemorrhage, and urinoma. The therapeutic approach to renal sinus cysts should be conservative.

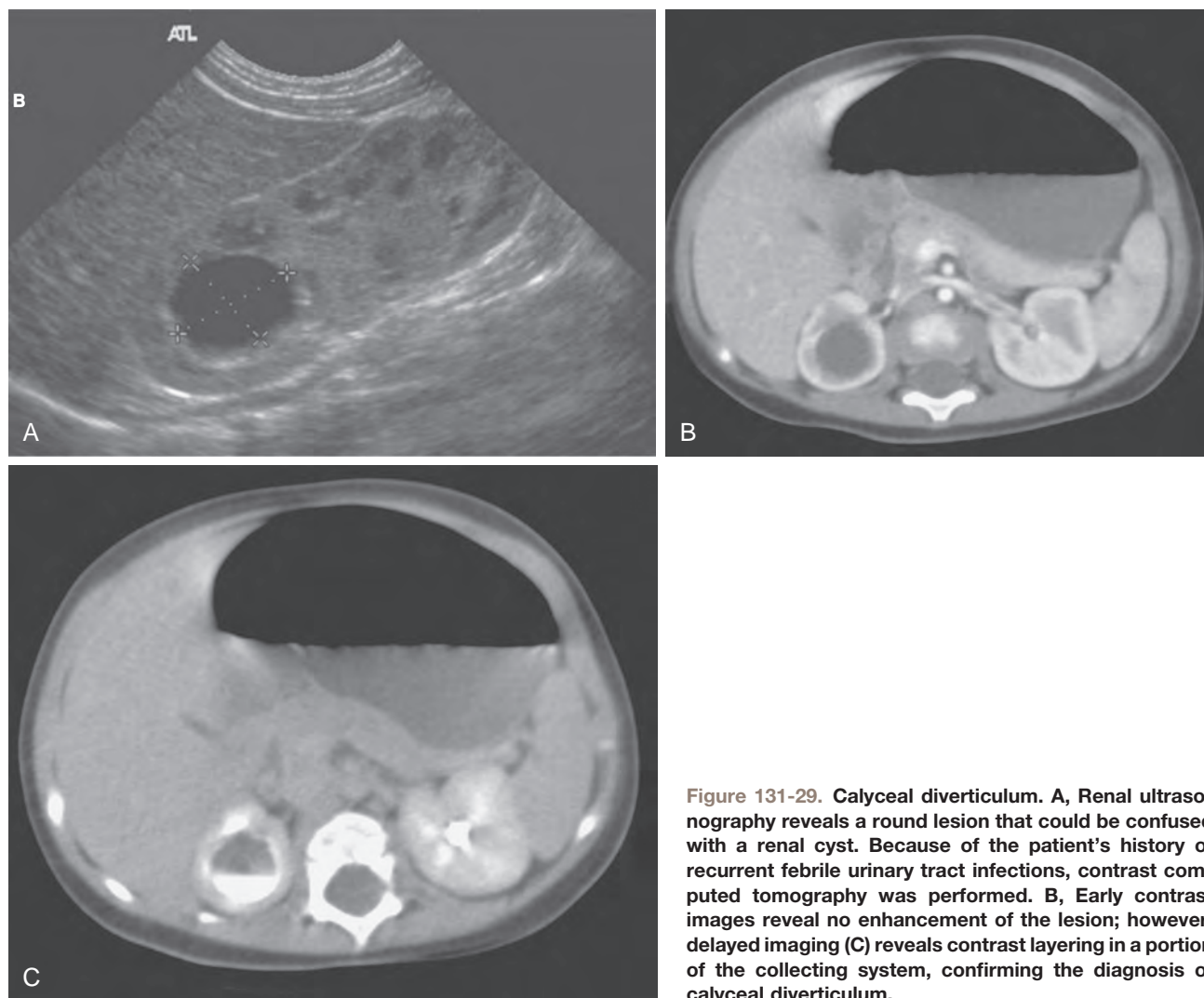


Figure 131-29. Calyceal diverticulum. A, Renal ultrasonography reveals a round lesion that could be confused with a renal cyst. Because of the patient's history of recurrent febrile urinary tract infections, contrast computed tomography was performed. B, Early contrast images reveal no enhancement of the lesion; however, delayed imaging (C) reveals contrast layering in a portion of the collecting system, confirming the diagnosis of calyceal diverticulum.

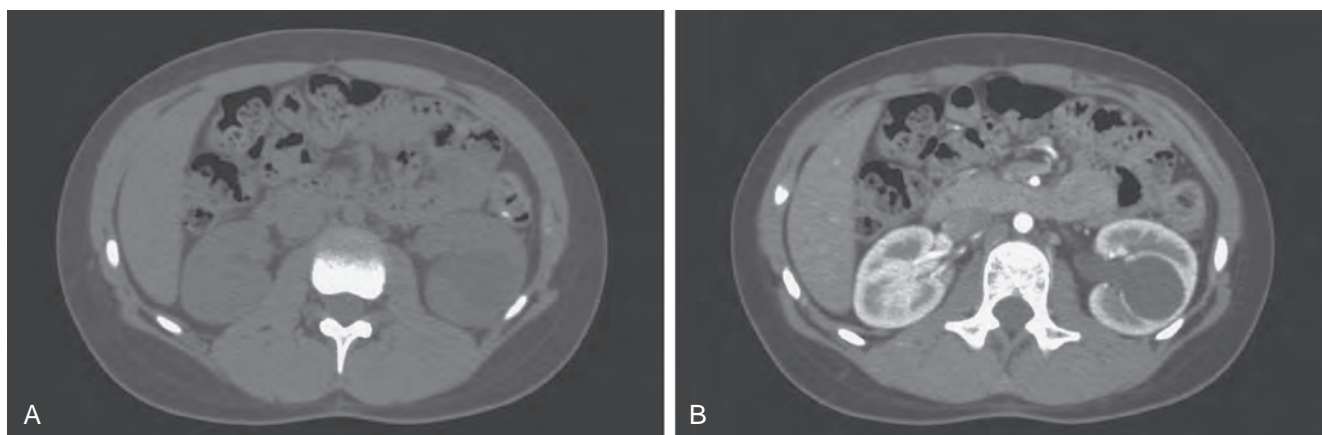



Figure 131-30. Parapelvic cyst. A, A hypoechoic, well-circumscribed, round focus in the peripelvic region of the kidney. B, There is no delayed enhancement after the administration of intravenous contrast. There is no hydronephrosis or hydroureter. Note contrast within the ureter on the contrasted images.

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 Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

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Clinical Context

Clinical Presentation of Obstruction

Progressive Renal Dysfunction

Definition of Obstruction

Patterns of Congenital Obstructive Nephropathy

Reversal of Congenital Obstruction

Approach to Clinical Cases

Prognosis and Management Strategies

CLINICAL CONTEXT

The spectrum of urinary obstruction in children is one of the most common conditions affecting the urinary tract and it includes substantial health consequences. Obstructive nephrouropathies constitute the single largest entity leading to renal insufficiency in male children younger than 1 year of age, and renal insufficiency is the largest single cause of renal failure needing transplantation, occurring in about 23% of children undergoing transplant (Benfield et al, 2003; Seikaly et al, 2003). A large number of children are affected by lesser degrees of obstruction and may undergo years of clinical monitoring and imaging studies.

The wide spectrum of obstructive changes constitutes one of the major challenges in the clinical management of these conditions in that there is no definitive dividing line between obstruction that warrants intervention and obstruction that does not (Peters, 1995). The presence of an obstructive lesion is readily determined with current imaging, but the criteria for intervention remain controversial. This is largely due to the absence of effective markers of the patterns and progression of obstruction as well as limited information regarding the natural history of differing degrees of obstruction (Chevalier, 2004). We are left with few guideposts along the spectrum of obstruction by which clinical decisions may be made.

This chapter will review the current state of knowledge regarding the pathophysiology of congenital urinary obstruction, how it may be correlated with clinical scenarios, and its distinction from post-natal obstruction. It is anticipated that with increasing understanding of the mechanisms of congenital urinary obstruction, we will become better able to discriminate between children requiring therapeutic interventions from those in whom this would be unnecessary.

CLINICAL PRESENTATION OF OBSTRUCTION

Prenatal ultrasonographic diagnosis has radically altered the clinical presentation of obstructive conditions and today most are detected before birth, and many have no apparent clinical signs. Those with clinical manifestations are often severe obstructive conditions such as posterior urethral valves or massive hydronephrosis. Children are still found with clinical signs of obstruction, usually infection or pain, and rarely hypertension. In the child with obstruction of the entire urinary tract, even when the obstruction is relieved, the functional abnormalities inform us of the effects of obstruction on developing kidneys. Reduced filtration function resulting from glomerular injury can cause a rising serum creatinine concentration, acidosis is due to tubular injury, and nephrogenic diabetes insipidus is secondary to collecting-duct abnormalities. In extreme cases, these may all be present, but on

occasion they are noted in isolation and may persist after relief of the obstruction (Hutcheon et al, 1976). Obstructive hypertension appears to be renin mediated (Riehle and Vaughan, 1981; Urata et al, 1985; Mizuiri et al, 1992) and may be reversible with surgical repair (de Waard et al, 2008).

The pathologic correlates of these functional alterations have been described in the congenitally obstructed kidney to varying degrees (Elder et al, 1995; Stock et al, 1995; Han et al, 1998; Poucell-Hatton et al, 2000; Zhang et al, 2000; Huang et al, 2006). The pathologic changes associated with lesser degrees of obstruction have been less thoroughly investigated, and a spectrum of qualitatively similar alterations has been described. In the absence of overt functional alterations and in unilateral conditions, determining the state of the one affected kidney becomes a clinical challenge. This challenge is often tied to the question of whether surgical intervention is appropriate, and much controversy has emerged from this question. Clinical imaging studies are currently the only widely used modality to make this assessment and their interpretation is variable. The natural history of many conditions in the spectrum of obstruction is not well described, yet it is the essence of the clinical question. It should be clearly seen that the spectrum of obstruction is wide, involves conditions that do not require intervention as well as others that produce profound renal injury, and may change with age and persistence of the obstruction.

PROGRESSIVE RENAL DYSFUNCTION

A major concern regarding obstructive conditions in the urinary tract is the potential for a progressive situation leading to ever-increasing loss of renal function. Progression may be seen in two forms, one with the uncorrected partially obstructive lesion (i.e., ureteropelvic junction obstruction [UPJO]), and the second with the previously obstructed, but corrected obstruction that has produced some degree of renal damage (i.e., posterior urethral valves). In the first, renal function may initially appear intact on imaging tests, yet in time there will be progressive loss of absolute and relative function of the kidney affected by the obstruction. If this were known prospectively, intervention would be appropriate and should be performed early. The challenge is in predicting this situation, and few markers are available to do this. The frequency of progressive deterioration in unilateral asymptomatic obstruction likely ranges from 20% to 40%, but duration of follow-up will affect this rate significantly. Every prospective study of obstructive conditions has documented the potential for progressive loss (Parkhouse et al, 1988; Koff and Campbell, 1992; Palmer et al, 1998; Koff, 2000; Thorup et al, 2003; Ross et al, 2011).

The second situation reflects the fact that the damaged kidney does not have the functional reserve of a normal kidney by which

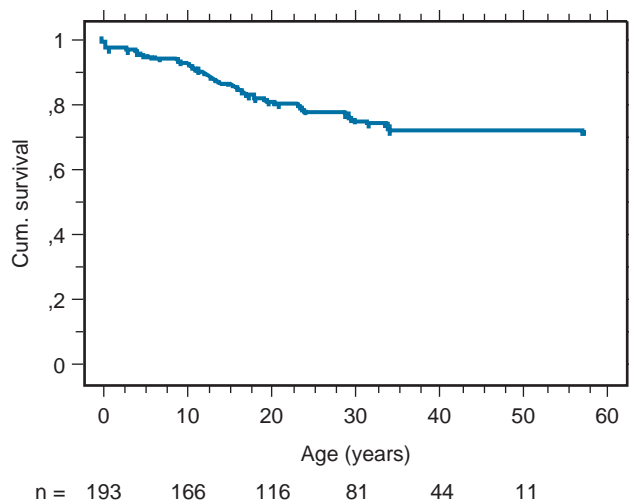


Figure 132-1. Graph depicting the progressive deterioration in renal function and progression to end-stage renal disease in children with posterior urethral valves. (From Heikkilä J, Holmberg C, Kyllönen L, et al. Long-term risk of end stage renal disease in patient with posterior urethral valves. *J Urol* 2011;186:2392–6.)

it may maintain its absolute function throughout time. These kidneys will demonstrate a steady decline in function with time, and this is usually evident only in bilateral obstruction. The mechanism may be hyperfiltration of remnant renal units and clinically this is most often seen with posterior urethral valves (Parkhouse et al, 1988; Nguyen and Peters, 1999; Heikkilä et al, 2011). These children may show adequate renal function early in life yet demonstrate a delayed and inexorable progression into renal failure in adolescence (Fig. 132-1). Whether earlier intervention would have protected their renal function is uncertain, but that possibility cannot be neglected. Ultimately, specific therapeutic interventions could be targeted toward prevention of this progressive process.

Predictors of ongoing progression of renal injury secondary to either ongoing or previous renal obstruction are of critical importance, yet there are few on which to rely. The most evident predictor is altered absolute renal function as clinically indicated by a creatinine clearance or serum creatinine. This is relatively insensitive in early stages of progression. Radionuclide imaging may be helpful in some cases, but there is no gold standard as to the best interpretation of potentially progressive disease. Urinary biomarkers have been extensively investigated, yet none are commonly used (Madsen et al, 2011).

KEY POINTS: CLINICAL CONTEXT

- Obstruction is the single largest entity leading to renal insufficiency in boys younger than 1 year and is the largest single cause of renal failure requiring transplantation.
- Progression of obstructive renal dysfunction may be seen in two forms, one with an uncorrected, partially obstructive lesion and the other with a previously obstructed but corrected lesion that has produced some degree of renal damage.
- The second situation reflects the fact that the damaged kidney does not have the functional reserve of a normal kidney by which it may maintain its absolute function with time.
- Elevated creatinine indicates altered absolute renal function but is relatively insensitive in the early stages of progression.

DEFINITION OF OBSTRUCTION

Although it may not be difficult to diagnose the potentially obstructed urinary tract, usually by ultrasonographic identification of hydronephrosis, the determination of whether this particular

condition requires surgical intervention to protect renal function and development is much more difficult. The frequently quoted definition of congenital obstruction (Koff, 1987), that of “a condition producing a restriction of urinary flow that will lead to deterioration in renal function,” seems too limited. In the growing child, renal function is expected to increase significantly, initially in excess of body mass and subsequently in parallel to it. If this increase in function does not occur, renal functional potential is lost, which may be of greater consequence than losing absolute function. Therefore the impairment of renal functional development should be considered as a determinant of obstruction that warrants intervention (Peters, 1995).

If this is the case, then an obstructive or hydronephrotic condition that has already resulted in less than normal function should be considered as being likely obstructive and warranting intervention. The child with significant hydronephrosis, with a kidney contributing significantly less than the anticipated 50% on a radionuclide renal scan, has already suffered an impairment of functional potential and should perhaps be considered as having sufficient obstruction to warrant intervention to limit further impairment. The ability to recover function that has not yet been achieved is unpredictable, however.

A critical element of congenital obstructive uropathy (COU) is the recognition that it is distinct from acquired obstruction in the mature animal (or mature kidney). The fact that obstruction develops while the kidney is in the process of formation creates an entirely different paradigm for COU as compared to obstruction of the mature kidney (Peters, 1997). The patterns of renal development are affected by obstruction and this produces the ultimate functional effects. The mechanisms for these alterations are therefore wholly distinct from mature obstruction. Although there is likely to be some overlap in the critical mechanisms of change, many mechanisms will be different. It cannot be assumed that the principles relevant to mature obstruction are applicable to congenital obstruction. This will clearly impact our interpretation of experimental data in the postnatal and mature animal, as well as the selection and application of experimental systems.

One of the frustrations in the management of clinical congenital obstruction is the dichotomy between therapeutic options, which are currently limited to either observation or surgery. Although the surgical options have expanded somewhat, the large gap between these divergent options creates a great deal of tension in the minds of the patient and family, as well as in physicians. The absence of any medical or pharmacologic therapy to ameliorate or prevent the complications of obstruction has been a major factor in the controversy between those who choose to correct a problem and those who believe it is better to await spontaneous resolution or unambiguous evidence of obstructive injury. The horizon holds promise for medical therapies that might prevent renal injury in various ways, but it will be essential to understand more completely the nature of COU to permit such specific treatment.

PATTERNS OF CONGENITAL OBSTRUCTIVE NEPHROPATHY

General Observations

In an attempt to understand the pathophysiology of COU, examination of obstructed renal tissues has shown disorganization of structure with primitive forms of renal tissues, pathologically defined as dysplasia. Although there is not universal agreement regarding the definition of dysplasia, evidence of altered renal development in association with obstruction is frequently reported (Bernstein, 1971; Matsell, 1998; Tarantal et al, 2001; Matsell and Tarantal, 2002; Matsell et al, 2002). Dysplasia is often considered an embryonic process that is irreversible, yet this is not proven. It is clear that some dysplasias are a result of very early abnormalities of renal development (Winyard and Chitty, 2008) and are unrelated to obstruction, but it is equally clear that obstructive processes can produce dysplasia. Whether there are subtle differences between

these patterns is unclear, but it should not be difficult to understand that several underlying etiologies may produce similar outcomes when renal developmental patterns are disrupted.

In some cases, however, usually in lesser degrees of obstruction, there is no dysplasia (Bonsib, 1998; Zhang et al, 2000). In such cases, the mechanisms of obstructive effect may be similar but to a lesser degree, or they may be qualitatively very different. It is important to recognize the variability of the patterns of response to obstruction.

If obstruction can produce dysplasia or abnormal developmental patterns, the particular mechanisms of obstructive effects may be identifiable. These include the fundamental processes of renal development, the character of which may provide insights into the critical mechanisms of obstructive nephropathy. **Development is the controlled process of growth and differentiation of tissues in the formation of an organ or tissue. The factors that regulate these processes are likely targets of obstructive effects.**

Structural alterations with obstruction are obviously evident with hydronephrosis, but this is largely a distortion of normal architecture and relative alterations in the amounts of elements of renal tissues. There may be subtle changes, however, that are functionally important. Other alterations include fibrosis and increased interstitial tissues, as well as the presence of abnormal tubules and glomeruli. The normal layered organization of the kidney with the cortical and medullary areas with inner and outer stripes is often distorted or absent (Zhang et al, 2000). Less obvious will be changes in the differentiation of the individual renal cell types that make up the nephron (Huang et al, 2006). Cells are unlikely to perform their normal functions, including communicating with neighboring cells in an integrated fashion. Function will therefore be disrupted.

Closely tied with these altered patterns of structure are distortions of normal growth regulation with either increased or decreased growth of specific structures. In some cases, obstructed kidneys are markedly smaller than normal, and in a developmental context this does not represent atrophy but rather hypoplasia. The distinction is important in that renal tissue mass has not been lost, but has never been formed. This is growth failure, not atrophy, and the mechanisms are likely distinct.

These observations are supported by both clinical and experimental work. Several biopsy studies have shown patterns indicative of altered differentiation and growth in various levels of obstruction, including both upper (UPJO) (Elder et al, 1995; Stock et al, 1995; Zhang et al, 2000; Huang et al, 2006) and lower (posterior urethral valves) (Poucell-Hatton et al, 2000; Haecker et al, 2002). These variations are not well explained, and correlation with clinical parameters is often imperfect. Experimental studies, however, have shown similarly that obstruction during development will produce changes in patterns of renal differentiation and in growth regulation (Beck, 1971; Steinhardt et al, 1988; Gonzalez et al, 1990; Peters et al, 1992; Wen et al, 2002; Cachat et al, 2003; Mure et al, 2006b). These can be seen to vary depending on the time of onset in experimental models, as well as the severity of obstruction (Fig. 132-2) (Chevalier et al, 1988, 1999c; Thornhill et al, 2005; Klein et al, 2011a; Truong et al, 2011). The latter is difficult to measure accurately. The validity of any of these model systems must be considered conditional, however, until we have more definite correlations. Nonetheless it is clear that induced obstruction can produce such severe abnormalities of differentiation as to be considered dysplasia and it can produce clear disruptions of growth regulation (Peters et al, 1992). It is therefore reasonable to examine the specific patterns observed and the potential mechanisms of those changes, all of which are likely contributing factors in the development of obstructive nephropathy.

Patterns of Effect

The effects of obstruction on the developing kidney may be summarized as producing alterations in the regulation of growth, tissue differentiation, extracellular matrix (ECM) and fibrosis, and in altering the functional integration of the kidney

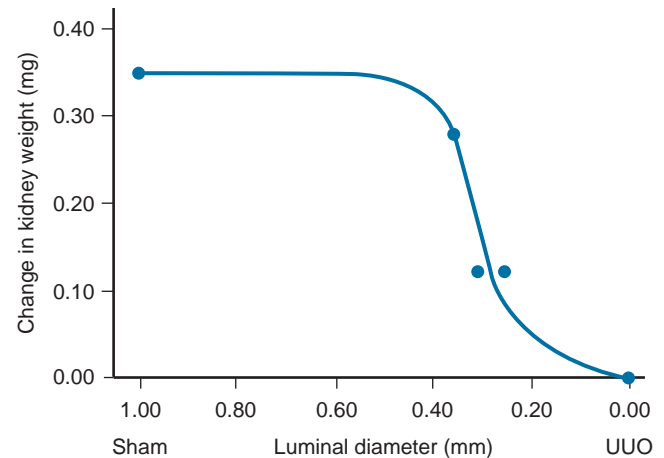


Figure 132-2. Interval change in kidney weight between 2 and 4 weeks of age in rats subjected to experimental unilateral ureteral obstruction (UUEO) at birth. The sharp drop in weight with decreasing luminal diameter of the ureter suggests a threshold effect on the obstructive effects on renal growth regulation. (Modified from Thornhill BA, Burt LE, Chen C, et al. Variable chronic partial ureteral obstruction in the neonatal rat: a new model of ureteropelvic junction obstruction. *Kidney Int* 2005;67:42–52.)

(Fig. 132-3). The latter is largely a result of the first three major factors and refers to the mechanisms producing vascular, neural, and humoral homeostasis and in the regulation of inflammatory cascades. Understanding the mechanisms by which these systems are dysregulated by obstruction will permit a better understanding of the outcomes of obstruction, which should improve our diagnostic, prognostic, and therapeutic abilities.

KEY POINTS: PATTERNS OF CONGENITAL OBSTRUCTIVE NEPHROPATHY

- Impairment of renal functional development should be considered a determinant of obstruction that warrants intervention.
- COU is distinct from acquired obstruction in a mature kidney.
- Obstructed renal tissues show disorganization of structure with primitive forms of renal tissues, called *dysplasia*.
- Structural alterations caused by obstruction are evident in hydronephrosis as a distortion in normal architecture and relative alterations in the amount of renal tissue elements. Subtle changes are functionally important and include fibrosis and increased interstitial tissue, as well as abnormal tubules and glomeruli.
- The effects of obstruction on the developing kidney vary with the time of onset, as well as the severity of obstruction.
- Obstruction of a developing kidney produces alterations in the regulation of growth, tissue differentiation, and ECM and fibrosis, as well as alterations in functional integration of the kidney.

Growth

Growth regulation is a critical part of development, and the obstructed kidney may evidence impaired or accelerated growth. It is important to recognize that the small, obstructed kidney is not atrophic as might be seen in the adult, but is hypoplastic. The growth it should have experienced never occurred. This can be readily seen by prenatal ultrasound and has been shown repeatedly

experimentally (Peters et al, 1992; Mandell et al, 1994). This seems usually to be a generalized impairment of all parts of the kidney, with both reduced numbers of nephrons as well as smaller nephrons. Differential growth impairment within the nephron segments may be present as well (Cachat et al, 2003; Huang et al, 2006). The functional effects of significant growth impairment are obvious as there are fewer and smaller nephron units. There may be compensatory responses to these changes, and it is difficult to assess their long-term impact. Reduced renal mass can be associated with hypertension as well as reduced filtration function, and loss of tubular mass will affect electrolyte and acid-base homeostasis, as well as water balance.

Growth acceleration can be seen in the larger-than-normal hydronephrotic kidney, although this is difficult to prove in humans, as few of those kidneys are removed. In animal experiments, fetal partial obstruction can increase renal mass (Gobet et al, 1999a; Ayan et al, 2001). This is not seen with dysplastic changes and is not a product of edema, as the total protein and DNA are increased

as well. The factors that predict altered growth appear to be the severity of obstruction and timing of the obstructive effect, although the latter is difficult to ascertain in human situations. The functional consequences of accelerated growth are not known, and this may correlate with the occasional hyperfunction measured on renal scans that is seen in some patients with hydronephrosis (Moon et al, 2003; Maenhout et al, 2005). Compensatory responses to obstruction may not be benign; growth enhancement of the glomeruli occurs in early diabetes and is later associated with glomerular sclerosis.

Growth Regulation of the Kidney. Regulation of renal growth is extremely complex and dynamic throughout development. A variety of growth factors are known to influence kidney growth at various stages of renal development and act at different loci of the nephron. Obstructive conditions have been shown to alter expression of growth-regulatory genes as well as the presence of the proteins coded by these genes (Chevalier, 1996). Table 132-1 lists some of the factors reported as altered in renal obstruction (not all in early

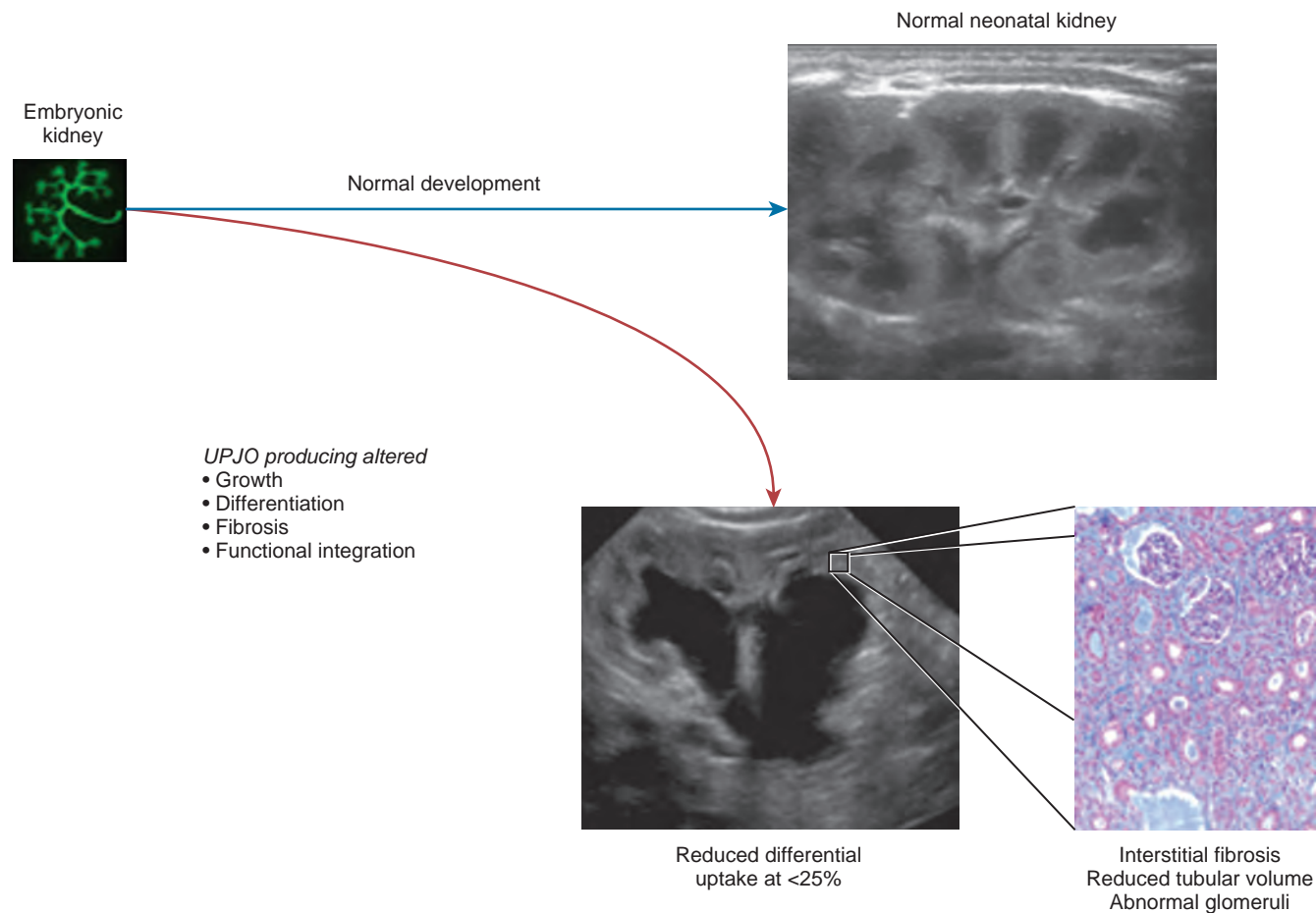


Figure 132-3. Diagram of the key patterns of effect due to obstruction during fetal life. UPJO, ureteropelvic junction obstruction.

TABLE 132-1 Key Factors in Congenital Obstructive Uropathy

APOPTOSIS ACTIVATION	APOPTOSIS INHIBITION
GROWTH TGF-β1 (Medjebeur et al, 1997; Ayan et al, 2001)	BMP7 (Klahr and Morrissey, 2003) HGF (Liu, 1999)
RAS (Eskild-Jensen et al, 2007a): AT1 receptor TNF-α/NF-κB (Misseri et al, 2005; Meldrum et al, 2006) BAD, Bax (Liapis et al, 2000)	Angiotensin AT2 receptor (Ma et al, 1998; Liapis, 2003) STAT6 (Yukawa et al, 2005a) Bcl-2 (Manucha et al, 2007; Manucha and Valles, 2008)

TABLE 132-1 Key Factors in Congenital Obstructive Uropathy—cont'd

APOPTOSIS ACTIVATION	APOPTOSIS INHIBITION
GROWTH—cont'd ROS (Ricardo et al, 1997) DAPK (Yukawa et al, 2004) Tubular stretch (Nguyen et al, 2000; Cachat et al, 2003) p53 caspases (Choi et al, 2001; Misseri et al, 2005; Nguyen et al, 2006; Guerin et al, 2008) FAS (Choi et al, 2000) NHE1 downregulation (Manucha et al, 2007)	Catalase, SOD (Kinter et al, 1999; Truong et al, 2011) CD44 (Rouschop et al, 2004) EGF (Chevalier et al, 1999a; Bartoli et al, 2000; Grandaliano et al, 2000; Bartoli et al, 2011) P21 (Silverstein et al, 2003) HO-1 (Kim et al, 2006; Li et al, 2012) HB-EGF (Nguyen et al, 2000) IGF (Kiley et al, 2003) Osteopontin (Yoo et al, 2006) PAX2 (Cohen et al, 2007) SS-31 (Mizuguchi et al, 2008)
EMT INDUCTION	EMT INHIBITION
DIFFERENTIATION TGF- β 1/Smad2/Smad3 (Inazaki et al, 2004; Chevalier, 2008) Snail-1 (Yoshino et al, 2007) PAI-1 (Zhang et al, 2007) Leukocytes (Lange-Sperandio et al, 2007) Angiotensin (Topcu et al, 2007)	BMP7 (Klahr and Morrissey, 2003) ALK TGF- β 1R inhibitor (Galarreta et al, 2013)
PROFIBROTIC	ANTIFIBROTIC
FIBROSIS TIMPs (Ayan et al, 2001; Mure et al, 2006b) TGF- β 1 (Yang et al, 2001a; Silverstein et al, 2003; Lange-Sperandio et al, 2007) Smad2/Smad3 (Inazaki et al, 2004) RAS: AT1 receptor (Manucha et al, 2004) Ischemia, hypoxia, ROS (Cachat et al, 2003) TNF- α (Meldrum et al, 2007) Osteopontin (Yoo et al, 2006) PAI-1 (Zhang et al, 2007) PDGF (Liapis et al, 1994; Seseke et al, 2004), CTGF (Yokoi et al, 2004) DAPK (Yukawa et al, 2005b)	MMPs (Gobet et al, 1999a) HGF (Mizuno et al, 2001; Yang et al, 2003a), BMP (Klahr and Morrissey, 2003) Smad7 (Lan et al, 2003; Fukasawa et al, 2004; Chung et al, 2009) Angiotensin AT2 receptor (Yoo et al, 1997), bradykinin B2 receptor (Vari et al, 1993) iNOS (Ito et al, 2004), eNOS (Chang et al, 2002) Decorin (TGF- β inhibitor) (Diamond et al, 1997; Silverstein et al, 2003) ALK5 TGF- β 1R inhibitor (Moon et al, 2006) Losartan (Manucha et al, 2004) Rosuvastatin (Mazzei et al, 2012)
PROINFLAMMATORY	ANTI-INFLAMMATORY
INFLAMMATION MCP-1 (Silverstein et al, 2003; Pittock et al, 2005; Bartoli et al, 2011; Madsen et al, 2012) NF- κ B (Seseke et al, 2004) Classically activated macrophage (Liu et al, 2008) TNF- α /NF- κ B (Valles et al, 2003; Meldrum et al, 2006) Krox 24 (Silverstein et al, 2003) Integrins, selectins, ICAM-1 (Lange-Sperandio et al, 2006) CCR1 (Eis et al, 2004), CCR2 (Kitagawa et al, 2004) Chemokines (RANTES, MIP-1 β , MIP-1 α) (Lange-Sperandio et al, 2007)	Candesartan (AngRec inhibitor) (Topcu et al, 2007) I κ B (Tashiro et al, 2003) Alternatively activated macrophage Adenosine A2A receptor/PDE4 (Lange-Sperandio et al, 2005)

ALK, activin receptor-like kinase; AT1, angiotensin type 1; AT2, angiotensin type 2; BAD, Bcl-2 associated death; Bcl-2, B-cell lymphoma 2; BMP, bone morphogenetic protein; BMP7, bone morphogenetic protein-7; CCR1, chemokine receptor type 1; CCR2, chemokine receptor type 2; CTGF, connective tissue growth factor; DAPK, death-associated protein kinase; EGF, epidermal growth factor; EMT, epithelial-to-mesenchymal transition; eNOS, endothelial nitric oxide synthase; FAS, fatty acid synthase; HB-EGF, heparin-binding epidermal growth factor; HGF, hepatocyte growth factor; HO-1, heme oxygenase-1; ICAM-1, intercellular adhesion molecule-1; IGF, insulin-like growth factor; I κ B, inhibitor of kappa B; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; MIP-1 α , macrophage inflammatory protein-1 α ; MIP-1 β , macrophage inflammatory protein-1 β ; MMPs, matrix metalloproteinases; NF- κ B, nuclear factor- κ B; PAI-1, plasminogen activator inhibitor-1; PDE4, phosphodiesterase type 4; PDGF, platelet-derived growth factor; RANTES, regulated on activation normal T cell expressed and secreted; RAS, renin-angiotensin system; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF- β , transforming growth factor- β ; TGF- β 1, transforming growth factor- β 1; TGF- β 1R, transforming growth factor- β 1 receptor; TIMPs, tissue inhibitors of metalloproteinases; TNF, tumor necrosis factor; TNF- α , tumor necrosis factor- α .

or fetal models) and also shows potentially important mechanistic determinants. Epidermal growth factor (EGF) has been shown to reduce some of the growth effects of obstruction when administered exogenously (Kennedy et al, 1997; Chevalier et al, 1998, 1999a; Wen et al, 2009). Many studies have focused on specific growth factors, but it is evident from the complexity of renal development and growth regulation that the interactions of multiple factors and their signaling pathways will be of greater relevance.

Apoptosis Regulation. A critical component of growth in the developing kidney is apoptosis, which is described as regulated cell death. The early fetal kidney is extremely active in terms of new cell formation as well as turnover (Carr et al, 1995). This permits remodeling during development, as well as providing a control system over unregulated growth. Small increases in the rate of apoptosis, even with normal ongoing growth, would lead to significant reductions in renal mass with time. The role of apoptosis in congenital obstruction has become more firmly established in recent years, including cellular patterns characteristic of apoptosis and enhanced expression of apoptosis-regulating molecules (Yang et al, 2001b; Yoo et al, 2006; Eskild-Jensen et al, 2007a; Campbell et al, 2008; Klein et al, 2011a). The changes may be seen heterogeneously, and the precise means by which these alterations occur remains incompletely defined, although apoptotic activity is regulated by cytokines (Cohen et al, 2007; Manucha et al, 2007; Campbell et al, 2008; Manucha and Valles, 2012) as well as mechanical factors (Nguyen et al, 2000; Hsieh and Nguyen, 2005). Inappropriate apoptosis may also be related to interstitial fibrosis as well (Docherty et al, 2006a). An important aspect of understanding the role of apoptosis in congenital obstruction is that the mediators may be measurable in the urine or blood, and they may permit therapeutic manipulation (Mizuguchi et al, 2008).

Differentiation

Differentiation is the process of cells attaining specific functional traits to permit specialized functions and organization into tissues, and it is the basis for the many functions of the kidney. Obstruction affects these finely tuned patterns by gross structural disruption as seen in a severely obstructed dysplastic kidney. More subtle effects may require assessment of tubular or glomerular function, but all are a result of altered differentiation. Disruption of differentiation may begin as early as induction of the nephron, or later in development with injury to renal collecting duct cells that regulate urinary concentrating ability. Some of these changes may be reversible, but it is usually presumed that many are not, in that some cells will undergo terminal differentiation, and if that does not occur at a particular time in development, there will not be another opportunity for it to occur. Disruption of normal differentiation of renal elements is unique to congenital obstruction, and it does not occur in a major way in adult obstruction. Abnormal epithelial-to-mesenchymal transition (EMT) is one alteration in differentiation that does occur in the adult and it can be reversible (Hay and Zuk, 1995; Yang et al, 2005; Docherty et al, 2006b; Forino et al, 2006; Higgins et al, 2007; Ivanova et al, 2008). A variety of mediators of EMT have been described, including transforming growth factor- β (TGF- β), plasminogen (Zhang et al, 2007), and leukocytes (Lange-Sperandio et al, 2007), as well as inhibitors such as hepatocyte growth factor (HGF) (Yang et al, 2005) (Fig. 132-4). EMT is likely to be an important factor in fetal obstruction as well, although little is known about its role. Most adult cells may be injured and lose their differentiated capacity, but the cell types rarely change their behavior after they are differentiated. Understanding the patterns of altered differentiation and its regulators is critical to understanding congenital obstructive nephropathy.

Induction Process. Renal differentiation begins with induction and from then on is exquisitely sensitive to various outside effects that may disrupt the normal sequence of cellular changes that occurs in the development of a kidney. When these changes may be disturbed by obstruction is unclear, but it can be presumed that some of the variation in the spectrum of obstruction is a result of different times of onset of the obstructive effect and also of different

degrees of severity. The pattern of effect is likely to reflect the time of onset and to be reflected in the number of nephron generations and the degree of dysplastic transformation. Controversy remains as to whether obstruction can produce dysplasia, and it is often stated that if dysplasia is present, then it was due to abnormal induction and not obstruction. Abnormal induction and nephrogenesis might be produced by various factors, including genetic ones, or might be a result of cellular disruption from mechanical forces with subsequent cellular responses. The study of Maizels and Berman is often cited to indicate that dysplasia in the chick kidney (a mesonephric kidney) was only produced with mechanical disruption of the mesenchyme and not hydronephrosis. It should be noted that the production of "obstruction" in that elegant study was by necessity rather crude, and several of the preparations were not obstructed. It is unclear whether all of the obstructions were to a sufficient degree. It also suggests that mechanical forces can, in fact, disrupt nephronogenesis enough to produce dysplasia and there is no inherent reason to believe that this cannot be a result of obstruction as well. Later mammalian studies in fetal sheep have shown dysplastic changes produced by obstruction (Steinhardt et al, 1988; Peters et al, 1992; Matsell et al, 1996), and this has been shown in rodent studies as well (Thomasson et al, 1970).

The critical determinant of dysplasia in animal studies has been complete obstruction early in gestation. In the fetal sheep, dysplasia was only seen when the obstruction was induced before 50% of gestation (70 days in most sheep species, which have a gestation period from 140 to 145 days). Obstruction induced after that point only produces hydronephrotic changes, albeit severe (Beck, 1971). Partial obstructions produced hydronephrosis only, without apparent disruption of the renal architecture. The reason for this is presumably the altered sensitivity of the developing nephrons to obstructive effects at this point. Alternatively, the particular signaling systems that are active in the early phases of renal development begin to fade with ongoing development. It is possible that the pathways sensitive to obstruction that would inherently alter the pattern of development have run their course of expression and activity by midgestation. The expression of recognized mediators of renal development has been affected in models of fetal obstruction, including WT-1 (Liapis, 2003), Wnt gene family (Nguyen et al, 1999), and PAX2 (Attar et al, 1998; Mure et al, 2006b; Cohen et al, 2007; Fenghua et al, 2009).

One of the histologic hallmarks of renal dysplasia is fibromuscular collars surrounding tubular structures, so-called primitive ducts. These have a characteristic appearance, and the smooth muscle surrounding the tubules stains for α -smooth muscle actin (α -SMA) (Fig. 132-5). This pattern suggests an abnormality in the regulation of EMT (Butt et al, 2007; Baum et al, 2008). The mesenchymal structures of the primitive nephrogenic blastema and the epithelium of the ureteral bud processes interact, and there is differentiation from epithelial phenotypes to mesenchymal phenotypes and the reverse. It is uncertain whether the presence of the primitive tubules suggests persistence of mesenchyme that should have transformed to epithelium, or whether it represents inappropriate epithelial-to-mesenchymal transformation. Understanding the signaling pathways involved in these processes (Roberts et al, 2006; Bani-Hani et al, 2008) will directly impact our understanding of obstructive processes. Persistent expression of α -SMA can be seen in partial obstruction without dysplastic patterns, so this may be important at several levels of severity (Gobet et al, 1999a; Mure et al, 2006b). TGF- β 1, linking these two proteins to growth as well as to fibrotic changes, regulates α -SMA expression.

Development of the glomerulus is a tightly regulated process that involves interaction of the mesenchyme and epithelium with a very specific pattern of growth and formation of intermediate structures such as the S-shaped body. In general, primitive glomeruli are not evident in obstructive changes, but markedly abnormal glomeruli are seen as well as hypoplastic glomerular structures (Matsell et al, 2002). In some cases, glomeruli may be enlarged in obstruction, suggestive of the changes seen in hyperfiltration that lead to glomerulosclerosis. Dissociation of the glomerulus from the tubules can be seen in early neonatal rodent obstruction (Thornhill

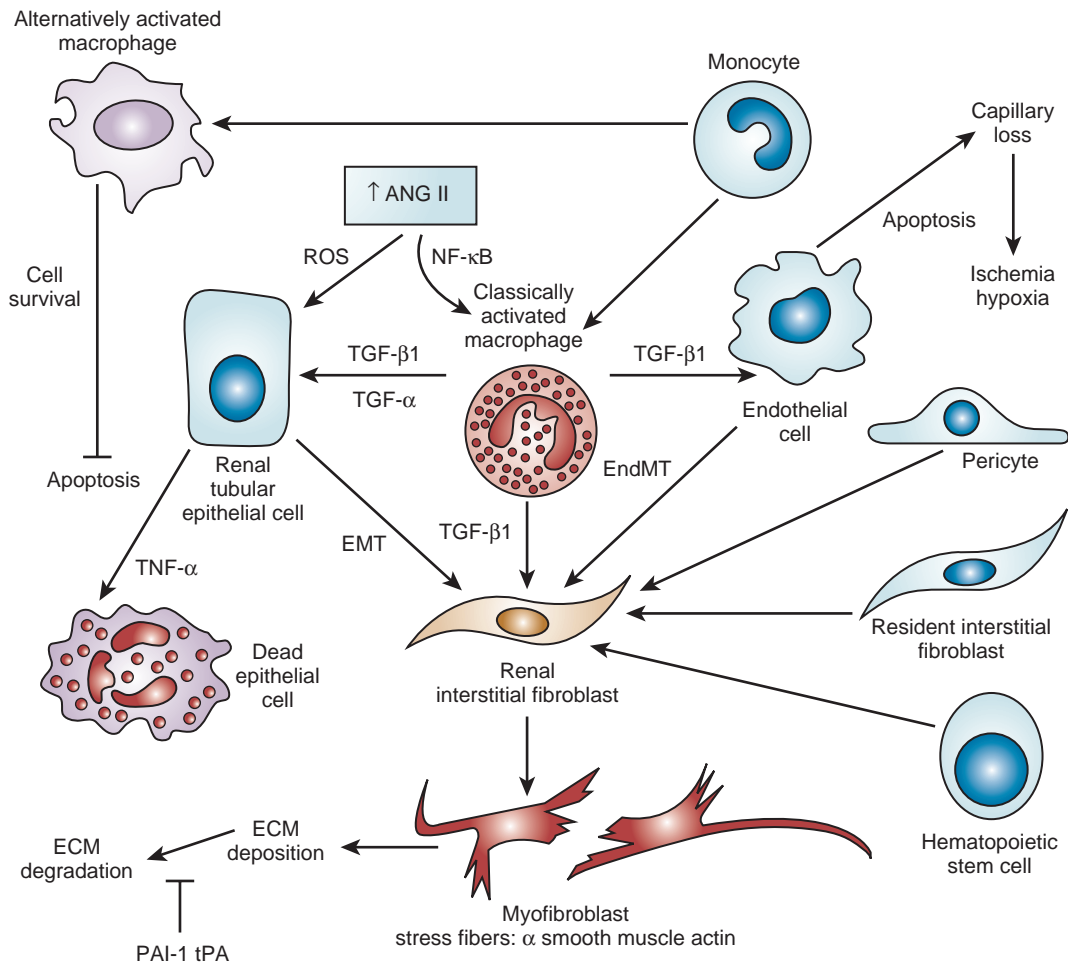


Figure 132-4. Renal cellular interactions in obstructive nephropathy. The interstitium is infiltrated by monocytes, which are “classically” activated to macrophages that release cytokines such as transforming growth factor- β 1 (TGF- β 1) and tumor necrosis factor- α (TNF- α). In turn, TGF- β 1 promotes a phenotypic response of tubular epithelial cells either to undergo apoptosis (leading to tubular atrophy) or to undergo epithelial-to-mesenchymal transition (EMT), becoming fibroblasts that migrate to the interstitium. Angiotensin II (ANG II), produced by the activation of monocytes, stimulates the production of nuclear factor- κ B (NF- κ B), which leads to the recruitment of more macrophages, as well as to the production of reactive oxygen species (ROS), which aggravates renal tubular injury. In contrast, alternatively activated macrophages can enhance tubular cell survival and proliferation. Endothelial cells can undergo endothelial-to-mesenchymal transition (EndMT) or apoptosis, which leads to capillary loss and to secondary renal ischemia and hypoxia. Resident pericytes and infiltrating hematopoietic stem cells can also differentiate into fibroblasts. Under the stimulus of cytokines such as TGF- β 1 produced by macrophages or other cells, fibroblasts synthesize stress fibers and undergo further differentiation to become myofibroblasts. The myofibroblasts are contractile and augment the deposition of extracellular matrix (ECM), leading to progressive interstitial fibrosis. This process is augmented by a decrease in ECM degradation, mediated by plasminogen activator-inhibitor-1 (PAI-1) and tissue-type plasminogen activator (tPA). (From Chevalier RL, Forbes MS, Thornhill BA. Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. *Kidney Int* 2009;75:1145–52.)

et al, 2007), suggesting severe disruption of the developmental program.

Fibrosis

A universal characteristic of obstructive nephropathy appears to be renal fibrosis, although it is a nonspecific pattern seen in a variety of pathologic conditions affecting the kidney (Eddy, 2000; Klein et al, 2011b). It is seen as infiltration of the interstitium with abnormal amounts of ECM, including collagens, fibronectin, and other connective tissue proteins. Their presence disrupts the

normal interconnections between cells that permit functional integration of the renal tissues. Tubular cells may be disrupted and inadequately regulated. Cell:cell signaling by direct connection or paracrine messengers may be disrupted. Tissue oxygenation may be impaired. Fibrosis is a histopathologic hallmark of many renal diseases.

The ECM is essential to normal function of the kidney as well, in terms of providing structural integrity and contributing to normal signaling systems. When abnormally expressed, however, this matrix becomes detrimental. ECM homeostasis is a complex balance of synthesis and breakdown. Synthetic regulation is controlled by

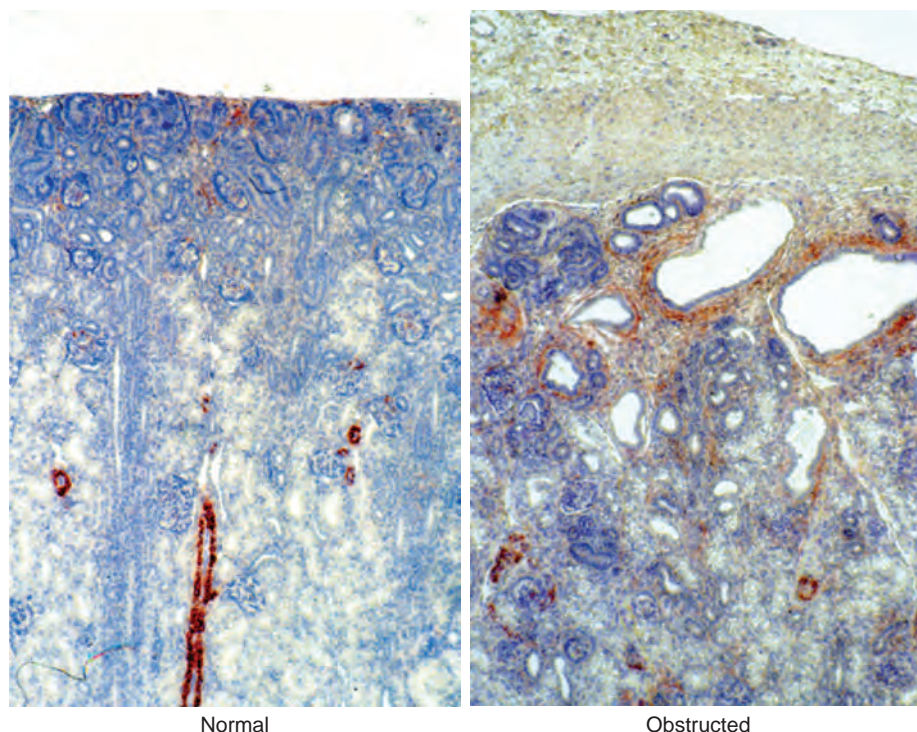


Figure 132-5. Histologic view of normal and obstructed full-term sheep showing the abnormal structural pattern of the kidney, increased interstitial fibrosis and cells, as well as abnormally persistent α -smooth muscle actin (brown stain). (From Gobet, Bleakley J, Cisek L, et al. Fetal partial urethral obstruction causes renal fibrosis and is associated with proteolytic imbalance. *J Urol* 1999;162:854–60.)

KEY POINTS: GROWTH AND DIFFERENTIATION

- The effects of growth impairment include fewer nephron units and delayed nephron maturation.
- Obstructive conditions have been shown to alter the expression of growth-regulating genes, as well as the presence of proteins coded by these genes.
- Congenital obstruction increases apoptosis and cellular patterns characteristic of apoptosis, with enhanced expression of apoptosis-regulating molecules.
- The ultimate cellular effects of such stimuli, however, depend on the summation of competing pro-apoptotic signals and antiapoptotic signals, as well as growth stimulation.
- Alteration in the differentiation of cells is unique to congenital obstruction and does not occur in a major way in adult obstruction.
- The critical determinant of dysplasia in animal studies has been complete obstruction early in gestation.

various mechanisms, including growth factors and signaling systems that are just recently being discerned. Mechanical forces contribute to these signals in various conditions, including hypertension and hydronephrosis. ECM breakdown is tightly regulated and represents the product of degradative enzymes, the matrix metalloproteinases (MMPs), and their endogenous inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). This product is the proteolytic balance and is regulated by various cytokines, hormones, and mechanical forces. This balance has been studied vigorously in renal disease and to a limited degree in congenital obstruction (Engelmyer et al, 1995; Ayan et al, 2001; Mure et al, 2006b). In a neonatal murine model of partial obstruction, the degree of fibrosis and contralateral hypertrophy did not correlate with the degree of hydronephrosis in

the affected kidney (Botto et al, 2011). The interaction of these systems is complex, and various compensatory pathways are likely to be present (Kim et al, 2001; Chevalier et al, 2009).

Oxidative stress in the developing kidney is a probable contributor to both fibrotic and inflammatory pathways in obstructive uropathy. The ability of the immature kidney to mount an appropriate response to increased oxidative stress may define the degree of functional and developmental impairment suffered (Manucha and Valles, 2008; Rinaldi Tosi et al, 2010; Chevalier et al, 2014).

Modulation of renal fibrosis may be a significant potential target for managing obstructive nephropathy, but the delicate balance of these factors needs to be understood to a greater degree than it is at present (Eddy, 2005).

Evidence and Patterns

Increased interstitial connective tissue is a hallmark of various renal pathologic processes (Eddy, 1996), including obstruction. Although it is unclear whether the mechanisms of fibrotic change are universal, they are believed to interfere with intercellular signaling and therefore with functional integration (Fig. 132-6). The most likely causes of excessive connective tissue include abnormal accumulation resulting from imbalance of synthesis and breakdown. This condition may also represent abnormal inductive signaling that produces excessive conversion of epithelium to mesenchymal tissue and connective tissues that accompany this (Bascands and Schanstra, 2005; Burns et al, 2007; Zhang et al, 2007). These processes may be normal developmental sequences that persist because of the obstructive effect.

Abnormal accumulation may simply represent excessive synthesis with no change in ECM breakdown. Increased collagen synthesis has been shown by upregulation of collagen gene expression in obstructive models (Liapis et al, 1994; Fu et al, 2006). Collagen synthesis is regulated in part by various cytokines, including TGF- β and the renin-angiotensin system (RAS). Reduced fibrosis may be

Nephron segment cytokines

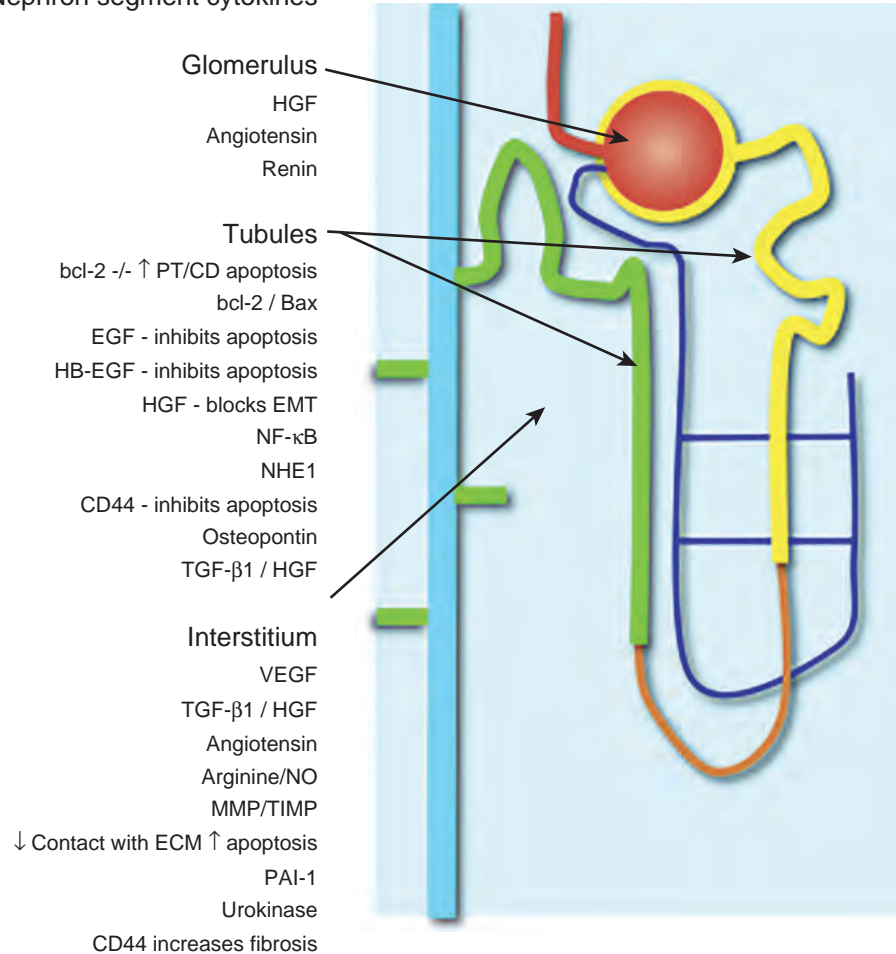


Figure 132-6. Diagram illustrating the various cytokines with reported effects on specific nephron segments. See text for details and references. Bcl-2, B-cell lymphoma 2; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-to-mesenchymal transition; HB-EGF, heparin-binding epidermal growth factor; HGF, hepatocyte growth factor; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NHE1, sodium/hydrogen exchanger-1; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PT/CD, proximal tubule/collecting duct; TGF-β1, transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinase; VEGF, vascular endothelial growth factor.

seen when angiotensinogen activity is downregulated in an obstructed system (Fern et al, 1999; Kellner et al, 2006). Similar approaches have been demonstrated in nonobstructive fibrosis as well.

The role of TGF-β is complex and context dependent, yet inhibition of activity will produce less fibrosis as well (Isaka et al, 2000; Miyajima et al, 2000; El Chaar et al, 2007). There is evidence that TGF-β interacts and regulates the activity of the RAS, as well as regulating cellular growth dynamics. Fetal obstruction induces increased expression of TGF-β1 (Medjebeur et al, 1997; Ayan et al, 2001; Yang et al, 2001a). Upregulation of the principal TGF-β receptors, TGF-βRI and RII, have been demonstrated in ureteral obstruction in fetal sheep (Yang et al, 2001a). As reviewed earlier, TGF-β1 regulates EMT, thereby contributing to renal dysplasia (Yang et al, 2000). There is considerable interest in the role of TGF-β1 in promoting EMT of differentiated renal tubular epithelial cells in response to chronic ureteral obstruction. As shown in Figure 132-4, renal interstitial fibroblasts, through transformation to myofibroblasts, play a pivotal role in the deposition of ECM in a hydronephrotic kidney. TGF-β1 has also been shown to play a role in glomerular response to injury, because receptor inhibition protects glomerular integrity in the obstructed neonatal mouse model (Galarreta et al, 2013).

There is growing evidence that in addition to proliferation of resident interstitial fibroblasts and transformation of hematopoietic

stem cells, renal tubular epithelial cells can undergo EMT and migrate to the interstitium to contribute to the pool of fibroblasts (Iwano et al, 2002). TGF-β1 regulates many of the steps involved in the transformation of tubular epithelial cells; these steps include loss of cell adhesion, expression of α-SMA, disruption of tubular basement membrane, and cell migration to the interstitium (Liu, 2004). Signaling by TGF-β1 is mediated in part by Smads, which are both profibrotic (Smad2 and Smad3) and inhibitory (Smad7). Thus targeted deletion of Smad3 reduces apoptosis and fibrosis in mice with ureteral obstruction, whereas gene therapy with Smad7 also reduces fibrosis (Lan et al, 2003; Sato et al, 2003). TGF-β1 also acts through downregulation of transcriptional corepressors of the Smads: SnoN and Ski (Yang et al, 2003b). In contrast, HGF blocks EMT by blocking Smad2 and Smad3, and gene therapy with HGF reduces fibrosis in rats with ureteral obstruction (Gao et al, 2002; Yang and Liu, 2003). HGF also acts by upregulating the Smad corepressors SnoN and Ski, countering the action of TGF-β1 (Yang et al, 2005). These complex networks of counterbalancing factors provide many potential opportunities for therapeutic intervention to prevent the progression—or even promote the reversal—of interstitial fibrosis resulting from obstructive nephropathy (Fogo, 2003).

Nitric oxide (NO) was also shown to regulate the development of obstructive fibrosis in postnatal animals and it might play a similar role prenatally (Huang et al, 2000; Felsen et al, 2003;

Manucha and Valles, 2008; Yoo et al, 2010). Increased NO generation reduces the degree of interstitial fibrosis (Ito et al, 2004), and, in animals without the gene to produce NO synthase, unilateral ureteral obstruction (UUO) produces a greater degree of fibrosis than in those animals with this enzyme intact (Hochberg et al, 2000). Data suggest a greater potential role for NO derived from endothelial nitric oxide synthase (eNOS) than inducible nitric oxide synthase (iNOS) (Huang et al, 2000; Chang et al, 2002).

Hypoxia may be a factor in the development of tissue fibrosis as well, in response to induction of hypoxia-inducible factor-1 (HIF-1) and hypoxia-inducible factor-2 (HIF-2) (Higgins et al, 2008). In vitro stimulation of renal epithelia with HIF-1 increases EMT, which is known to induce fibrosis. Genetic models that do not express HIF-1 α develop less fibrosis and inflammatory infiltration in response to ureteral obstruction in postnatal models (Higgins et al, 2007). The role in prenatal obstruction remains undefined, but it is potentially relevant.

Altered regulation of ECM breakdown, the proteolytic balance, is a potential mechanism for interstitial fibrosis of obstruction as well, although this is less explored. Connective tissue breakdown is controlled by the MMPs, of which there are at least 15 having specific activity toward particular connective tissue proteins. MMP-1, for instance, is a collagenase (Pardo and Selman, 2005), whereas MMP-2 specifically degrades gelatin. Their expression and activity are both subject to close regulation, as this is crucial to appropriate ECM homeostasis. Too much activity will degrade the tissues, whereas too little permits accumulation of abnormal amounts of ECM. These pathologic alterations have been described in a variety of disease states, including arthritis and pulmonary fibrosis (Corbel et al, 2002; Vincenti and Brinckerhoff, 2002). One of the means by which their activity is regulated is through endogenous TIMPs. These are less varied and may have less specific activity over the MMPs in their environment, and they serve to check the degradative activity of the MMPs. Their expression and activity are closely regulated and their net activity is the proteolytic balance. The role of the proteolytic balance in a wide variety of disease states has been the subject of active research (Diamond et al, 1998; Vincenti, 2001).

Altered activity and regulation of the MMPs and TIMPs have been studied in the kidney (Eddy, 1996) in several conditions, and it is clear that they are important regulators of the state of the ECM. Their expression has been shown in the developing kidney as well and in postnatal obstruction, and they are altered in activity. In prenatal obstruction, increased expression (Ayan et al, 2001; Mure et al, 2006b) and activity (Gobet et al, 1999a) have been shown as well as in congenital reflux-related fibrosis (Gobet et al, 1998). The precise regulators of the MMPs and TIMPs in development and obstruction are not well defined, but they are likely to be an important element in the development of pathologic fibrosis. There is some evidence of regulation by the RAS and TGF- β as well, which opens therapeutic options for the treatment of fibrosis (Diamond et al, 1998; Ding et al, 2005; Bolbrinker et al, 2006; Yang et al, 2007).

Fibrosis is clearly a major component of the pathophysiology of congenital obstruction. Understanding the role and activities of the various components of this system may permit more specific diagnosis through urinary biomarkers reflecting the elements of the system. These elements may also be relevant targets of therapeutic intervention to modulate ECM homeostasis.

KEY POINTS: FIBROSIS

- One of the histologic hallmarks of renal dysplasia is the presence of fibromuscular collars around tubular structures, so-called primitive ducts.
- A universal characteristic of obstructive nephropathy appears to be renal fibrosis.
- Breakdown of ECM is tightly regulated and represents the product of degradative enzymes (MMPs and their endogenous inhibitors [TIMPs]).

Functional Integration

Renal function is regulated at numerous levels, including vascular, neural, and hormonal factors, and inflammatory processes may significantly affect this function. **Congenital obstruction alters both the ongoing functional integration of the kidney as well as the development of the mechanisms that are intrinsic to this regulation. It can change the regulatory mechanisms themselves.** For example, hypertension is well recognized as a potential consequence of obstruction, and it might have effects beyond the kidney. More subtle effects on the normal regulatory systems of the kidney may be more difficult to detect.

Inflammation appears to be a common consequence of obstruction in the postnatal human or animal model. Much attention has been paid to this in acquired obstruction, but it is surprisingly absent in congenital obstruction. Biopsies of human kidneys with obstruction but no history of infection have sparse inflammatory infiltrates (Huang et al, 2006). Models of fetal obstruction show little evidence of inflammation (Peters et al, 1992). The reason for this marked difference is unclear, but it suggests fundamentally distinct mechanisms. It is another indication that congenital obstruction is distinct in many ways from postnatal acquired obstruction.

Vascular. The developing vascular tree plays a critical role in renal development and any disruption could be associated with a wide variety of abnormalities, ranging from lack of development of the glomerulus to aberrant regulation of renal blood flow. Sensitivity to humoral and neural regulation of blood flow may be altered as well, which may be a permanent effect.

Expression of renal renin is increased in the obstructed kidney (el Dahr et al, 1993; Gobet et al, 1999b; Ayan et al, 2001) and decreased in the contralateral. Renin-secreting renal cortical cells appear to be recruited with obstruction as well (Norwood et al, 1994). Expression of receptors for the RAS is altered in specific patterns in neonatal obstruction. AT1, which mediates vasoconstriction (as well as growth alterations) (Chung et al, 1995; Yoo et al, 1998) increases whereas the levels of angiotensin receptor type 2 (AT2), which act in a contrary manner, are decreased. These alterations suggest a role for a local renal RAS in obstruction-mediated vasoconstriction and are independent of the systemic RAS.

Altered sensitivity of both kidneys to renin-mediated vasoconstriction has been shown to occur with unilateral obstruction. Interaction with NO has been seen as important in the regulation of both glomerular and tubular function in early obstruction (Eskild-Jensen et al, 2007b). Following the release of obstruction, sensitivity to angiotensin-II mediated vasoconstriction was reduced in the obstructed kidney but increased in the contralateral (Chevalier and Gomez, 1988). These observations indicate the sensitivity of renal vascular regulation to obstruction as well as the importance of recognizing the interaction of the two developing kidneys. The role of renal counterbalance in obstruction has been recognized, but it has been investigated only to a limited degree. A possible mechanism for these observations is through neural regulation of renin expression (Chevalier and Thornhill, 1995a).

Neural. Renal innervation is an important regulator of vascularity and perfusion and is associated with expression of renin in the kidney (el Dahr et al, 1991). Sympathetic denervation, both mechanical and chemical, has been shown to reduce the expected increase in renin expression in the setting of obstruction (Chevalier and Thornhill, 1995b). A more primitive pattern of renin gene expression appears to persist with congenital obstruction and may cause a persistence of fetal patterns of neural and vascular regulation.

Hormonal. The major hormones regulating renal functional development are in the RAS, and these are significantly affected by COU. This results in a variety of effects, including growth alterations, fibrosis, as well as altered blood flow. The sensitivity of the kidney to elements of the RAS changes during development, presumably to permit transition from a fetal state, with reduced oxygen tension and limited need for renal perfusion, to the postnatal environment. Postnatally, all filtration must be through the

kidneys rather than through the placenta as occurred prenatally. This is thought to be related to the shift in expression of the angiotensin receptors as one aspect of this system. In fetal life, AT2 is predominant in expression, has a vasodilating effect, and may promote growth, whereas AT1 (type 1) is less active until postnatally, which permits regulation of renal perfusion in the postnatal environment (Robillard et al, 1995). Altered developmental regulation of these receptors has been induced with fetal obstruction as well (Gobet et al, 1999b). Activity of the RAS is balanced in the developing kidney by NO, and alterations in this balance have been demonstrated in the developing kidney subjected to obstruction (Bogaert et al, 1996), perhaps explaining the observed preservation of renal blood flow despite ongoing fetal bladder obstruction (Bogaert et al, 1995; Nguyen and Kogan, 1998). In contrast, with complete fetal UO, renal blood flow was not maintained, indicating thresholds of obstructive severity for certain renal responses (Mure et al, 2006a). Targeting these specific alterations may provide information about the impact of obstruction as well as the possibility of therapeutic value (Topcu et al, 2007). Improved diagnostics may be developed if imaging can be linked to hormonal activity that shows distinct patterns in obstruction. For example if COU induces a balance of the RAS that favors the more fetal pattern of receptor subtypes, perfusion renography or imaging coupled with pharmacologic inhibition or stimulation of this system, as in a captopril renogram, might permit identification of this pattern (Bajpai et al, 2002). It is important to recognize that the integrity of the RAS is critical to normal renal development, and inhibition may produce negative effects on normal renal function or might even exacerbate obstructive effects (Coleman et al, 2007).

Aldosterone may be a potentially useful target for therapy, as it has been shown to contribute to cardiac and renal fibrosis in various pathologic situations (Xu et al, 2008; Ku and Campese, 2009; Lea et al, 2009). Inhibition using spironolactone, a receptor antagonist, has been shown experimentally to limit the amount of interstitial fibrosis in a juvenile rodent model of complete obstruction (Trachtman et al, 2004). This raises the potential for therapeutic interventions using familiar pharmacologic tools, yet it also indicates the complexity of the interaction in the kidney's responses to obstruction.

Tubular Function. Although glomerular filtration and renal plasma flow are the most commonly measured elements of renal function, renal tubular function is equally important, yet is often ignored in obstructive uropathy. Tubular function regulates acid-base homeostasis, electrolyte balance, and urinary concentration as well as vitamin D homeostasis. When bilateral, defects in these various functions are major clinical problems. When unilateral, they are often compensated by the contralateral kidney, and are therefore difficult to measure accurately and noninvasively. There are reports of persisting tubular dysfunction in various congenital obstructions (Hutcheon et al, 1976), but it is uncommon for this to be a clinical problem.

Congenital obstruction can be shown experimentally to produce several functional effects on the renal tubules, including acid/base, sodium, and water homeostasis. Specific downregulation of sodium transporters (Norregaard et al, 2005; Eskild-Jensen et al, 2007b) in the tubules as well as reduction in the expression and protein levels of the aquaporins have been demonstrated in neonatal obstruction in rats and juvenile piglets (Frokjaer et al, 1996, 1997, 2003; Jensen et al, 2006). Downregulation of acid-base transporters in the tubular epithelium has been demonstrated in juvenile rats (Wang et al, 2009). Evidence also exists to demonstrate that some of these transporters may also act as signaling systems affecting tubular apoptosis (Manucha et al, 2007). Although a normal contralateral kidney may compensate for these functional defects, limiting the clinical impact of the defects, alterations in urinary levels of these proteins may serve as markers for significant obstructive effects (Madsen et al, 2011).

The mechanisms of injury are likely to be a combination of the effects described earlier, and therapeutic interventions targeted toward those mechanisms may limit tubular dysfunction. Measur-

ing abnormal tubular function may be possible using more sensitive measures and imaging technology.

Inflammatory Mediators

Although inflammatory changes do not appear to be a major factor in early postnatal COU (Misseri et al, 2004), it is likely that they begin to play a greater role with age. It will be necessary to confirm the pattern and role of these factors of COU in humans, as many animal systems demonstrate significant inflammation postnatally, although fetal systems do not (Peters et al, 1992). Human pathologic material has not shown large amounts of inflammation (Huang et al, 2006), except when complicated by infection (Bartoli et al, 2000; Kiratli et al, 2008). If there were a subset of patients with inflammatory changes in the face of obstruction, it would seem an important target for investigation to improve both diagnostic and therapeutic capability (Meldrum et al, 2006, 2007). The various inflammatory cascades that have been investigated postnatally are manipulable pharmacologically and this may permit important therapeutic regulation of renal injury (Cale et al, 2000). Inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor- α (TNF- α), regulated on activation normal T cell expressed and secreted (RANTES), and others may be measurable in the urine as well, as has been shown in experimental systems (Crisman et al, 2001; Silverstein et al, 2003; Madsen et al, 2012).

KEY POINTS: FUNCTIONAL INTEGRATION

- Angiotensin is a key modulator of many of the inflammatory responses to ureteral obstruction.
- Expression of renal renin is increased in the obstructed kidney and decreased in the contralateral one. Renin-secreting renal cortical cells appear to be recruited with obstruction as well.
- The activity of the RAS is altered with obstruction, which affects renal functional development by a variety of changes including growth, fibrosis, and blood flow.

REVERSAL OF CONGENITAL OBSTRUCTION

An important element in the understanding of congenital obstruction is the potential for reversal of renal functional and developmental impairment with correction of the obstructive lesion. This is clinically relevant when making decisions regarding the use of intervention either postnatally or prenatally. In the latter, the potential for reversal has great significance in determining whether the risks associated with fetal intervention are warranted. Improvement in function is also important in the expectation of response to relief of obstruction.

In the fetal obstructed kidney, Glick and colleagues showed that the functional salvageability of a unilaterally obstructed kidney was dependent on the duration of obstruction and gestational age (Glick et al, 1984). A direct relationship between progression of nephronogenesis and reversibility can be demonstrated (Edouga et al, 2001; Fenghua et al, 2009). Similar observations have been made in early postnatal models, with the recognition that complete reversal of the damage is seldom achieved (Claesson et al, 1987; Chevalier et al, 1988, 1999b, 2002; Eskild-Jensen et al, 2003; Shi et al, 2004; Dissing et al, 2008; Thornhill and Chevalier, 2012). Mediators of improvement have not been explored. The severity of obstruction is also a critical determinant (Bussieres et al, 1993), but it is challenging to measure in any meaningful way. Biomarkers of salvageability have been developed and were first used clinically in accordance with the work of Glick and Adzick in obstructed fetal sheep (Adzick et al, 1985). From these basic parameters emerged the clinical prognostic factors currently used, with modification, in fetal obstruction (Harrison et al, 1982; Glick et al, 1985). Measures of urinary sodium, chloride, osmolarity, and

calcium have correlated with fetal renal functional potential (Muller et al, 1993; Johnson et al, 1995; Dommergues et al, 2000; Biard et al, 2005). When fetal urine approaches the character of serum, irreversible damage appears to have occurred in the developing kidney. Other markers have been explored in the fetus, including α_1 -microglobulin in amniotic fluid and β_2 -microglobulin in urine and serum (Burghard et al, 1987; Freedman et al, 1997; Nicolini and Spelzini, 2001; Craparo et al, 2007).

The mechanisms of functional recovery may be similar to the mechanisms of injury, but they may also be unique and the potential may exist for enhancing recovery if these mechanisms can be understood and used. In part, the pathway of recovery includes normal developmental pathways that had been impaired because of obstruction (Chevalier et al, 1988). As a consequence of urinary tract obstruction, nephron injury is heterogeneous, with some nephrons undergoing adaptive growth and hyperfiltration and others being destroyed. Thus, 1 month after relief of 5 days of UUU in the neonatal rat, the glomerular filtration rate (GFR) of the postobstructed kidney was normal despite a 40% reduction in the number of glomeruli (Chevalier et al, 1999b). However, 1 year after relief of the obstruction, the GFR of the postobstructed kidney had decreased by 80% (Chevalier et al, 2000). Even though there had been no further loss of nephrons during this interval, the remaining glomeruli had undergone progressive sclerosis (Chevalier et al, 2000). Although relief of temporary UUU did not lead to nephron loss in the adult rat, there was a reduction in glomeruli after relief of temporary UUU in the period immediately following nephrogenesis, as well as during nephrogenesis (Chevalier et al, 2002). This underscores the susceptibility of the developing kidney to obstructive injury not only during nephrogenesis but also during subsequent nephron maturation.

KEY POINTS: REVERSAL OF CONGENITAL RENAL OBSTRUCTION

- The functional salvageability of a unilateral obstructed fetal kidney is dependent on the duration of obstruction and the gestational age.
- Measures of urinary sodium, chloride, osmolarity, and calcium have been correlated with fetal renal functional potential.
- When fetal urine approaches the character of serum, irreversible damage appears to have been done to the developing kidney.

APPROACH TO CLINICAL CASES

General Approach

The clinical challenge of COU reflects the clinical spectrum of the condition itself. A determination must be made as to which patients need intervention to protect renal functional development. Some will clearly need such intervention, whereas many others will do well without. Given the wide spectrum, it is extremely difficult to determine a clinically practical dividing line between those in whom intervention is appropriate and those in whom it is not needed. This question is relevant to the largest number of patients with some form of COU. The ultimate determination of the need for intervention may come as a single diagnostic test, or it might be the determination based on a pattern of change, or the lack thereof, throughout time. In this situation we wish to be sensitive but will accept being less specific. We would rather not miss a large number of patients with COU needing intervention, recognizing that some patients may undergo further evaluation or intervention when they might not have needed it.

The second challenge in COU is with the patients at the extreme end of the spectrum in whom renal functional impairment has already occurred and poses the threat of permanent and progressive

renal insufficiency. In the face of obstruction, what is our best approach to preserve the maximal amount of renal function? Even with successful surgical intervention, we are often confronted with an inexorable progression to renal failure in these children, yet it would seem reasonable to ask if we can prevent renal demise. As yet there has been no clinically applicable approach, but as our understanding of the pathophysiologic mechanisms of COU improves, we may be able to alter specifically the critical components of the system to regulate better the mechanisms affecting renal response to obstruction.

Diagnosis

General Issues

The challenge in diagnosing "obstruction" has been made more difficult because of disagreement regarding the definition of obstruction. Although the concept that obstruction is an "impairment of urine flow that will produce a reduction in function if left uncorrected" is logical, it misses several important elements in the context of congenital obstruction. One is that the developing kidney should be increasing its function, not remaining static. It also does not provide any insight into the interpretation of a kidney that presents with reduced function when diagnosed. Strictly interpreted, this kidney is already affected by having had its normal potential function limited, and by definition it is "obstructed." This interpretation has not been widely used, however, and it is only on prospective follow-up that a decrease from normal is thought to be indicative of "obstruction." A more useful definition might be that any condition that has or will limit ultimate functional potential should be considered as clinically significant obstruction. It should also be recognized that "obstruction" does not mean surgical therapy is required. Obstruction may be mild and clinically insignificant. The exclusion of these patients from the diagnosis of "obstruction" has tended to force people to create convoluted descriptions of hydronephrotic kidneys.

Ultimately a determination of the potential risk to a kidney will have to be made clinically, and a judgment must be made as to whether a particular child would benefit from intervention. It would seem reasonable and cautious to assume that any hydronephrotic kidney is obstructed until proven otherwise and to assess the degree of risk. Understanding the pathologic mechanisms of obstructive nephropathy will permit more specific examination of the kidney to determine its response. It should be the renal response primarily that is used to make the determination of obstructive effect. The fluid dynamics of the upper urinary tract, although obviously relevant to the renal effect, should not be the primary focus. This may explain why many drainage studies, including diuretic renography and pressure-perfusion tests, are imperfect predictors of the renal response. We have seen that the obstructed kidney is undergoing altered growth regulation, abnormal differentiation, and increased fibrosis, all mediated through a variety of molecular, cellular, and renal homeostatic mechanisms. These patterns of change are likely to be reflected in altered expression of proteins and chemicals, which may be assayed in the urine. There may be systemic alterations that are detectable in the blood as well. The search for these biomarkers has been active, yet few have been firmly linked to the pathologic progression of obstructive nephropathy (Chevalier, 2006; Madsen et al, 2011).

Biomarkers

Biomarkers of renal obstruction may reflect the response of the kidney in a direct manner, such as in the expression of growth factors that contribute to fibrosis or are associated with increased apoptosis in renal epithelium. They may also be downstream effects reflecting specific alterations mediated by other cytokines, which in themselves are not directly relevant but are indicative of the level and pattern of the obstructive effect. A broad approach that is emerging uses assessment of changes in overall protein expression in the urine: proteomics. Normal developing kidneys

have an evolving protein fingerprint, which can be defined (Lee et al, 2008) and which is altered with obstruction. If particular elements of the alteration can be identified and associated with clinical outcomes, these patterns may be diagnostic of functionally significant obstruction. Such patterns may reflect a single protein, which may be an element of a response pattern or might be a downstream consequence. It may be that a particular pattern of protein expression that involves several factors will be the best indicator of obstruction (Decramer et al, 2006, 2008; Stodkilde et al, 2013). Such studies will require development in animal systems and validation in the human. It will be necessary to set limits for what is and is not clinically significant “obstruction” and to correlate this with clinical and functional outcomes of relevance. These changes will need to be correlated with histopathologic changes in the developing kidney as well, as our ability to measure some functional alterations remains imperfect.

An alternative approach to diagnosis may be to assess response to stimulus. This is the basis of the captopril renogram, in which radionuclide uptake in the face of obstruction is reduced when the RAS is inhibited by the angiotensin-converting enzyme inhibitor captopril, but is not reduced in the dilated, nonobstructed system (Bajpai et al, 2002). The underlying rationale for this test is that in the obstructed kidney, function is dependent on increased activity of the RAS, as suggested earlier. In reducing the capacity of this system to support function by the administration of captopril, a decrease is detected in the postcaptopril study. The concept is reasonable, but problems with definitions of true “obstruction” continue to thwart its broad applicability. Alternative pharmacologic manipulations are needed to address more specifically one or more functional factors in the potentially obstructed kidney. The production of various cytokines in the face of a stimulus might provide the ability to distinguish the kidney at risk for injury from the kidney not at risk.

At present, we are limited to the conventional imaging modalities of ultrasound, diuretic renography, and an increasing use of magnetic resonance imaging.

Clinical Evaluation

Presentation

The mode of presentation of obstructive uropathy will often determine the clinical management. Those presenting with symptoms will require a careful anatomic and functional assessment that will likely include surgical intervention. Those in the less discrete category are more challenging, including patients with UPJO and ureterovesical junction obstruction (UVJO) who present without symptoms. If posterior urethral valves, ureterocele, or ectopic ureter is detected, even if asymptotically, intervention is almost always appropriate. Very mild versions might be considered candidates for an observational approach if no evidence of bladder or renal dysfunction is present.

Symptomatic presentation of UPJO and UVJO almost always will be managed with surgical intervention. The timing is unpredictable for such a symptom episode to recur, but the likelihood of recurrence is high even though the probability of recurrence has never truly been determined. Infection is uncommon with UPJO, but not with UVJO, and these children can become very ill because of the combination of infection and obstruction. It seems as if the severity of the obstruction may be exacerbated by the reaction to the infection. Marked increases in hydronephrosis have been reported in association with an acute infectious episode, likely resulting from the effect of bacterial toxins (Pais and Retik, 1975). A pattern of apparent aldosterone resistance has been seen in several children with UVJO and urosepsis, manifested by dangerously low serum sodium levels and presumably resulting from transient resistance to aldosterone caused by bacterial endotoxins (Vaid and Lebowitz, 1989; Levin et al, 1991). Subsequent resolution should not falsely suggest an insignificant process.

Stone development is another form of clinical presentation, often with hematuria or pain. Although the two conditions are

linked, it cannot be assumed that a treatable metabolic disorder is not possible (Husmann et al, 1996). Appropriate evaluation is warranted. Conversely, a stone impacted in the UPJ can create the appearance of a congenital UPJO on routine imaging.

The classic presentation of acute episodes of flank pain and nausea because of UPJO is termed Dietl crisis when bilateral (Dietl, 1864). It can more often occur unilaterally and is often thought to be a gastrointestinal disorder with subsequent misdirected evaluation (Alagiri and Polepalle, 2006). These children can present at any age, although the condition is rarely recognized in early childhood. The pattern is often one of increasingly frequent and severe episodes of acute onset abdominal or flank pain with nausea and vomiting. These episodes may last for minutes to several hours and often occur in the evening. Only occasionally is the episode obviously triggered by fluid intake. Some children will report that leaning over a chair can help reduce the discomfort. Little can reduce their discomfort otherwise, yet when the episode has passed, they seem fully recovered. The repetitive and consistent nature of the episodes, particularly with a nonrevealing gastrointestinal workup, should prompt consideration of a renal cause and the obtaining of an ultrasound. Further evaluation with diuretic renography can usually define the etiology (Sparks et al, 2013). Diagnoses given to these episodes before being accurately identified have included abdominal migraines, cyclic vomiting syndrome, food allergies, musculoskeletal problems, and emotional disturbances. In a most extreme example, a girl received ongoing diagnoses of more and more food allergies while her kidney became progressively nonfunctional, which occurred because of an early evaluation that was misinterpreted.

Imaging

To define both the nature and extent of any potentially obstructive condition, it is necessary to obtain an anatomic and functional assessment of the kidneys, ureters, bladder, and urethra. Performing this in a logical sequence will usually permit an appropriately selective workup. The details of the specific imaging tests, their interpretation, and limitations are presented in Chapter 126.

KEY POINTS: APPROACH TO CLINICAL CASES

- Congenital urinary obstruction may best be defined as urinary flow impairment that has limited or may potentially limit normal renal development.
- Not all hydronephrosis represents obstruction that requires surgical correction.
- Biomarkers for renal obstruction should reflect changes in normal development, as well as specific alterations caused by obstruction.
- Although most clinical cases of congenital obstruction are asymptomatic, the condition in children is still detected by pain, a mass, hematuria, and hypertension.

PROGNOSIS AND MANAGEMENT STRATEGIES

The assessment of possible outcomes for an obstructed kidney is important in terms of determining the value of an intervention and in providing a clinical prediction of possible failure of the kidney. These predictions will serve to guide therapy and to assess the risk/benefit balance in treatment. As yet there are few studies to suggest any accuracy either in unilateral obstruction or bilateral obstruction. Use of renal biopsies in obstruction has shown some loose correlations but none that are clinically practical. It is likely that this ability will follow as a result of more accurate diagnostic ability.

Can any of our current incomplete understanding of COU be used in developing a clinical management strategy for these patients? Several factors seem to emerge from the many conflicting and incomplete studies of congenital obstruction. Obstruction can be

very harmful to the developing kidney, to an extent far beyond that seen in the mature kidney. The effects of obstruction may not be reversible because of the alteration of the actual structure and functional characteristics of the kidney, which does not occur in the mature kidney. There seems to be a limited window of time to permit reversal of obstruction and to anticipate clinically relevant recovery of functional potential. It is clear that the developing kidney, as with the mature kidney, is able to compensate in the face of obstruction and to appear as healthy. Yet most biologic compensation mechanisms are ultimately limited in their ability to maintain homeostasis, and these might mask eventual significant functional derangements. The clinical threshold for intervention may therefore be better set lower than in the mature patient.

The response to obstruction in the developing kidney is extremely complex, and multiple factors are involved in various aspects of this response. Although this may seem to be a significant impediment to understanding and clinically managing these problems, it should be seen as providing multiple opportunities to develop biomarkers of these responses that may eventually facilitate our decision making.

It is clear that not all children with dilated kidneys will suffer ill effects from this condition; it is equally evident that the potential for obstructive nephropathy is significant and has severe clinical implications. As our understanding of these conditions and the mechanisms of renal response to obstruction in development improves, determining which kidneys are at risk for developmental impairment will become more accurate.

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The complete reference list is available online at www.expertconsult.com.

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Ureteropelvic Junction Obstruction

The first part of this chapter will focus on open surgical repair of ureteropelvic junction obstruction (UPJO), including retrocaval ureters, midureteral strictures, and UPJO in duplex systems. Because of the evolving interest in minimally invasive procedures such as laparoscopy, retroperitoneoscopy, and robotic procedures, these procedures also are discussed. The second part will deal with surgery of the congenital megaureter.

URETEROPELVIC JUNCTION OBSTRUCTION

Definition

Hydronephrosis in children, defined by an anteroposterior intrarenal pelvis diameter of 12 mm (Dhillon, 1998), differs from that seen later in life and is not necessarily synonymous with true obstruction. Available diagnostic tools are imprecise, leaving the definition by Koff as the only gold standard prognosticator of obstruction. Koff (1987) defined obstruction as "any restriction to urinary outflow that if left untreated will lead to progressive kidney damage." Working by this definition, indications for surgery are often amassed retrospectively and at the cost of losing irrevocably valuable renal function. In an attempt to circumvent use of such diagnostics, numerous guidelines have been published; however, in the absence of precise diagnostic tools, indications for surgery always will be debatable (Chertin et al, 2006).

Evidence

Obviously there are two entities in UPJO in children. First of all, the prenatally detected hydronephrosis, which, if unilateral, is assessed 5 to 10 days after birth by ultrasonography. This is due to the fact that the kidney in the newborn has to become functional during the first days of life. Indeed, the case is different in bilateral hydronephrosis when infravesical obstruction is suspected, which may require immediate diversion by a suprapubic or urethral catheter.

Clinical Presentation

In many countries antenatal ultrasound scans are offered at approximately 20 weeks of gestation. Of the malformations identified, urogenital anomalies are dominant and dilatations, in the form of hydronephrosis or hydroureteronephrosis, are most common. Postnatal diagnosis is made by ultrasound, incidentally or in conjunction with the workup for a child presenting with urinary tract infections (UTIs). Febrile infections often are sufficiently treated with antibiotics, with only a minority of patients needing nephrostomy tube diversion in the case of concomitant finding of hydronephrosis or hydroureteronephrosis. Most often, the UPJO in newborns and infants is caused by an *intrinsic* narrowing of the UPJ (Fig. 133-1). The typical finding is a narrowed segment of the UPJ with an interruption in the development of the circular muscular fibers. This leads to a functional discontinuity of the muscular contractions and ultimately to insufficient emptying of the renal pelvis. UPJO in childhood and adolescence is often

Megaureter

caused by an accessory vessel to the lower pole of the kidney (Fig. 133-2), with the ureter kinking over the lower pole vessel (Lowe and Marshall, 1984) (*extrinsic*) giving rise to loin pain, nausea, and vomiting. However, it is unclear whether an intrinsic factor in conjunction with a lower pole vessel is the reason for the symptomatic hydronephrosis (Stephens, 1982). Hydronephrosis is more often seen in boys (Williams and Karlaftis, 1966; Kelalis et al, 1971; Johnston et al, 1977; Olsen et al, 2007), especially in the infant and toddler age groups (Robson et al, 1976; Williams and Kenawi 1976; Johnston et al, 1977; Olsen et al, 2007). UPJO predominates on the left side and is bilateral in 10% to 40% (Nixon, 1953; Uson et al, 1968; Robson et al, 1976; Lebowitz and Griscom, 1977; Karnak et al, 2008). There also might be an increased incidence in family members (Cohen et al, 1978).

Secondary Ureteral Pelvic Junction Obstruction

In some cases of high-grade vesicoureteral reflux (VUR) with a tortuous dilated ureter, kinking or narrowing of the UPJ can be present. Whether this resolves spontaneously or needs surgical correction of both the VUR and the UPJO is not always clear (Lebowitz, 1984; Bomalaski et al, 1997). This condition is specific to high-grade reflux, in which surgical correction of the VUR by injectable biomaterials is doubtful; therefore contemplating concomitant reimplantation and dismembered pyeloplasty is discouraged because there are concerns this may compromise ureteral blood supply. Thus a conservative approach or operation in two stages is advisable, despite the lack of convincing evidence.

Lower Pole Ureteral Pelvic Junction Obstruction

In uncommon cases of duplex kidneys, a UPJO of the lower moiety is seen (Privett et al, 1976) (Fig. 133-3). In cases of incomplete duplication a ureteropelvic anastomosis of the upper pole ureter to the lower pole pelvis is possible, either side to side or end to side. In cases of complete duplication a standard dismembered pyeloplasty is done, depending on the function of both the upper and lower moiety and the length of the stenosis (Joseph et al, 1989). A nonfunctioning or minimally functioning moiety (i.e., $\leq 5\%$ to 10% of the overall kidney function on nuclear scan) should prompt partial nephrectomy rather than any attempts at repair.

Associated Anomalies

Congenital renal malformations are commonly seen in association with UPJO. Up to 50% of the affected infants have another urologic abnormality (Uson et al, 1968; Robson et al, 1976; Lebowitz and Griscom, 1977; Lebowitz and Blickman, 1983; McGrath et al, 1987). Contralateral UPJO is the most common anomaly, seen in 10% to 40% of cases, followed by renal dysplasia, multicystic dysplastic kidneys, and renal agenesis (Williams and Karlaftis, 1966; Robson et al, 1976; Williams and Kenawi, 1976). Horseshoe kidneys are rare but are in some cases associated with UPJO, both with a genuine stricture and accessory vessels (Glenn, 1959; Blanc et al, 2014). VATER syndrome (vertebrae, anus, trachea, esophagus,

renal) also has some association with UPJO (Kolton et al, 2000). Furthermore, VUR is seen in up to 40% of children with UPJO, albeit with a high degree of spontaneous resolution (Williams and Kenawi, 1976; Lebowitz and Blickman, 1983).

Indications for Surgery

Only approximately one third of affected children will need surgical intervention (Dhillon, 1998). The widely accepted indications for surgery are an increasing anteroposterior diameter on ultrasound, low or decreasing differential renal function, breakthrough infections while on prophylactic antibiotics, or symptoms such as pain in older infants and children. In infants, UPJO can be a cause of failure to thrive, feeding difficulties, and constipation.

However, most cases resolve with time and do not proceed to surgery. Hematuria is seen in some cases and is believed to result from disruption or rupture of mucosal vessels in the dilated pelvis (Kelalis et al, 1971; Williams and Kenawi, 1976). UPJO also has been shown to be a rare cause of hypertension most likely the result of renal functional deterioration and activation of the renin-angiotensin axis (Belman et al, 1968; Squitieri et al, 1974; Munoz et al, 1977; Grossman et al, 1981).

Surgical Repair

When indicated, surgical intervention can be performed by open surgery or laparoscopic and robot-assisted procedures. In infants, open access is the preferred procedure because the incision required

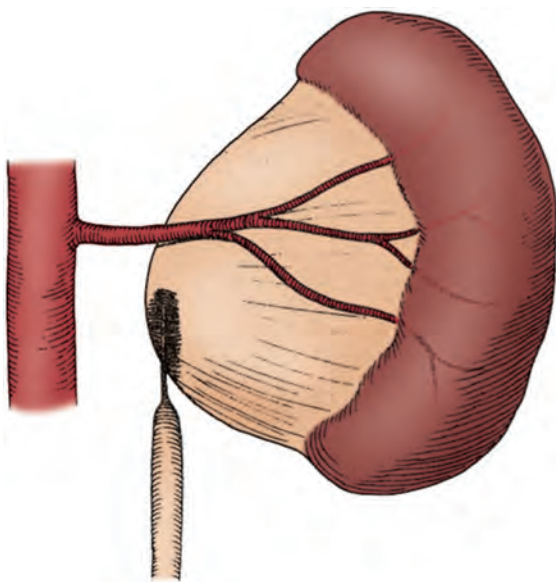


Figure 133-1. Intrinsic narrowing of upper ureter contributing to ureteropelvic junction obstruction.

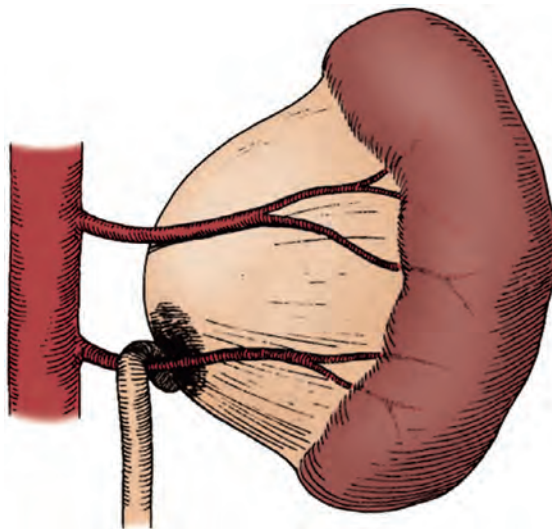
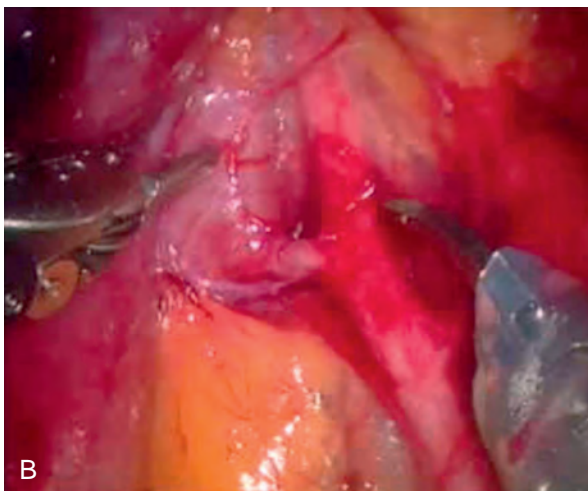
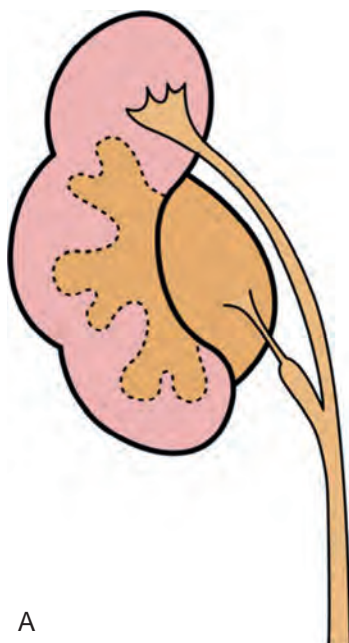


Figure 133-2. A lower pole crossing vessel contributes to significant kinking at ureteropelvic and resultant intermittent obstruction. Often, when the ureter is mobilized, no evidence of intrinsic narrowing is found. However, dismembering and moving of the ureter anteriorly to the vessel prevents recurrence of the symptoms.



A

B

Figure 133-3. A and B, Duplex kidney with stenosis of the lower ureteropelvic junction. A V-plasty can resolve the problem.

does not differ significantly from what is necessary for laparoscopic or robotic access. Debate is ongoing on whether minimally invasive procedures should be conducted through the transperitoneal or retroperitoneal routes even though the majority of pediatric urologists prefer retroperitoneal access when performing an open procedure. However, no proper randomized studies have yet been published comparing either the transabdominal or the retroperitoneal laparoscopic routes. The main argument for laparoscopic transperitoneal access is that the procedure is easier and familiar anatomic landmarks assist in orientation. However, ease should not stand alone as an argument for any kind of surgical access; other variables that need to factor in are potential risk for damage to intra-abdominal organs, postoperative urine leakage, and subsequent prolonged hospital stay, all of which tip the balance toward the retroperitoneal approach. Despite a longer learning curve and a more time-consuming procedure needed for retroperitoneoscopic pyeloplasty, we have preferred and advocated the use of retroperitoneoscopic pyeloplasty because the advantages seem to outweigh many of the potential difficulties encountered during the learning phase (Olsen and Jorgensen, 2004; Olsen, 2006; Olsen et al, 2007; Olsen and Rawashdeh, 2012).

Dismembered Pyeloplasty

Regardless of access, the Anderson-Hynes dismembered pyeloplasty technique is the preferred procedure for most surgeons and the gold standard against which all other interventions are compared (Anderson and Hynes, 1949). Originally developed for the repair of an obstruction in a retrocaval ureter, the procedure has since gained widespread acceptance as the standard UPJO repair, with a success rate of approximately 95% (Douville, 1953; Poulsen et al, 1987; O'Reilly, 1989; MacNeily et al, 1993; Shaul et al, 1994; Salem et al, 1995; McAleer and Kaplan, 1999; Austin et al, 2000; Casale et al, 2004; Bonnard et al, 2005). The initial concerns of compromising the blood supply and innervation of the proximal ureter have since been disclaimed (Douville, 1953). The advantage

of dismembering the UPJ is that a vessel crossing the lower pole can be preserved, the adynamic part of the ureter excised, and redundant pelvic tissue reduced (Fig. 133-4). In case of a long dysplastic segment of the upper ureter, complete mobilization of the kidney can bridge the distance between pelvis and ureter for several centimeters. In addition, a horizontal incision in the lower part of the pelvis can give further length and facilitate tension-free anastomosis (Fig. 133-5). Irrespective of access, the main steps of the Anderson-Hynes dismembered pyeloplasty are as follows (Fig. 133-6): after opening the Gerota fascia the anterior or posterior aspect of the UPJ is dissected (depending on the access used). The lower pole of the kidney is freed to avoid overlooking an accessory vessel, especially with the retroperitoneoscopic access. Electrocautery should be used with caution to minimize damage to the blood supply of both the pelvis and the ureter, with preference given to bipolar diathermy. A stay suture is placed in the pelvis proximal to the anticipated line of dismemberment; another stay suture can be placed in the ureter at the level of the stenosis. The UPJ is dismembered, and the pelvis reduced if indicated. A tensely dilated pelvis should be decompressed with a 21-gauge needle before dismembering, to avoid excessive pelvic reduction. The ureter is then spatulated along its lateral border, well beyond the dysplastic stenotic segment and carried through adequately into healthy ureteral tissue. At this stage, the stenotic part of the ureter should not be removed, because it can serve as a handle that minimizes ureteral tissue manipulation while performing the anastomosis, reducing the risk for mucosal edema. The anastomosis can be completed with interrupted or continuous suturing according to surgeon preference. Suture size depends on the prevailing anatomy, but most often a 6-0 or 5-0 resorbable monofilament suture on a round needle is used. Care should be taken at the tip of the V of the anastomosis, which has to be assembled precisely and in a tension-free manner. Placing inadvertent excessive tension on the stay sutures while aligning the anastomosis should be avoided because it can lead to kinking of the ureter once tension is relieved. Just before completing the anastomosis, the stenotic part of the

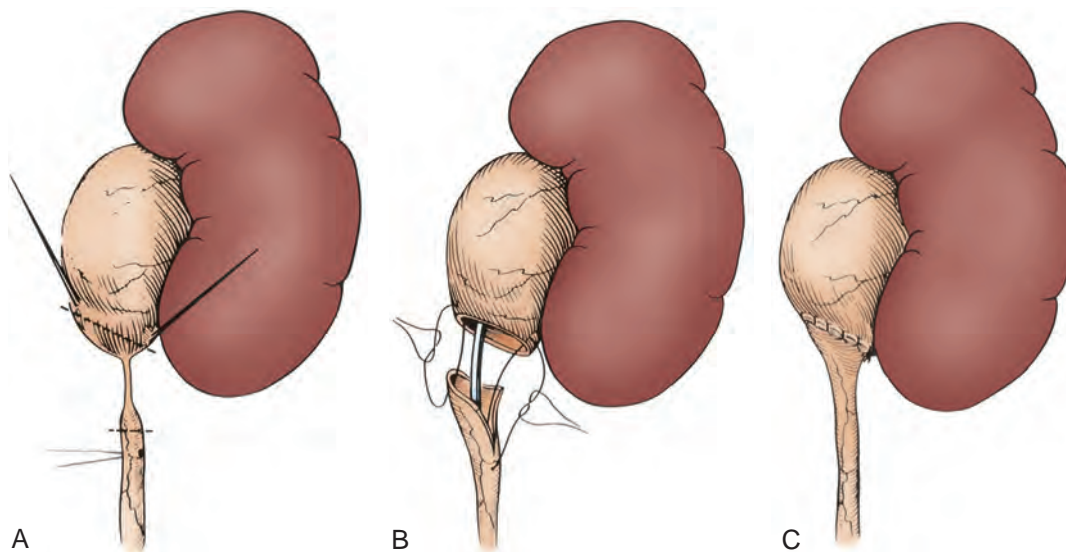


Figure 133-4. Anderson-Hynes dismembered pyeloplasty. A, Traction sutures are placed on the medial and lateral aspects of the dependent portion of the renal pelvis in preparation for dismembered pyeloplasty. A traction suture is also placed on the lateral aspect of the proximal ureter below the level of the obstruction. This suture will help maintain proper orientation for the subsequent repair. B, The ureteropelvic junction is excised. The proximal ureter is spatulated on its lateral aspect. The apex of this lateral, spatulated aspect of the ureter is then brought to the inferior border of the pelvis, and the medial side of the ureter is brought to the superior edge of the pelvis. C, The anastomosis is performed with fine interrupted or running absorbable sutures placed full thickness through the ureteral and renal pelvic walls in a watertight fashion.

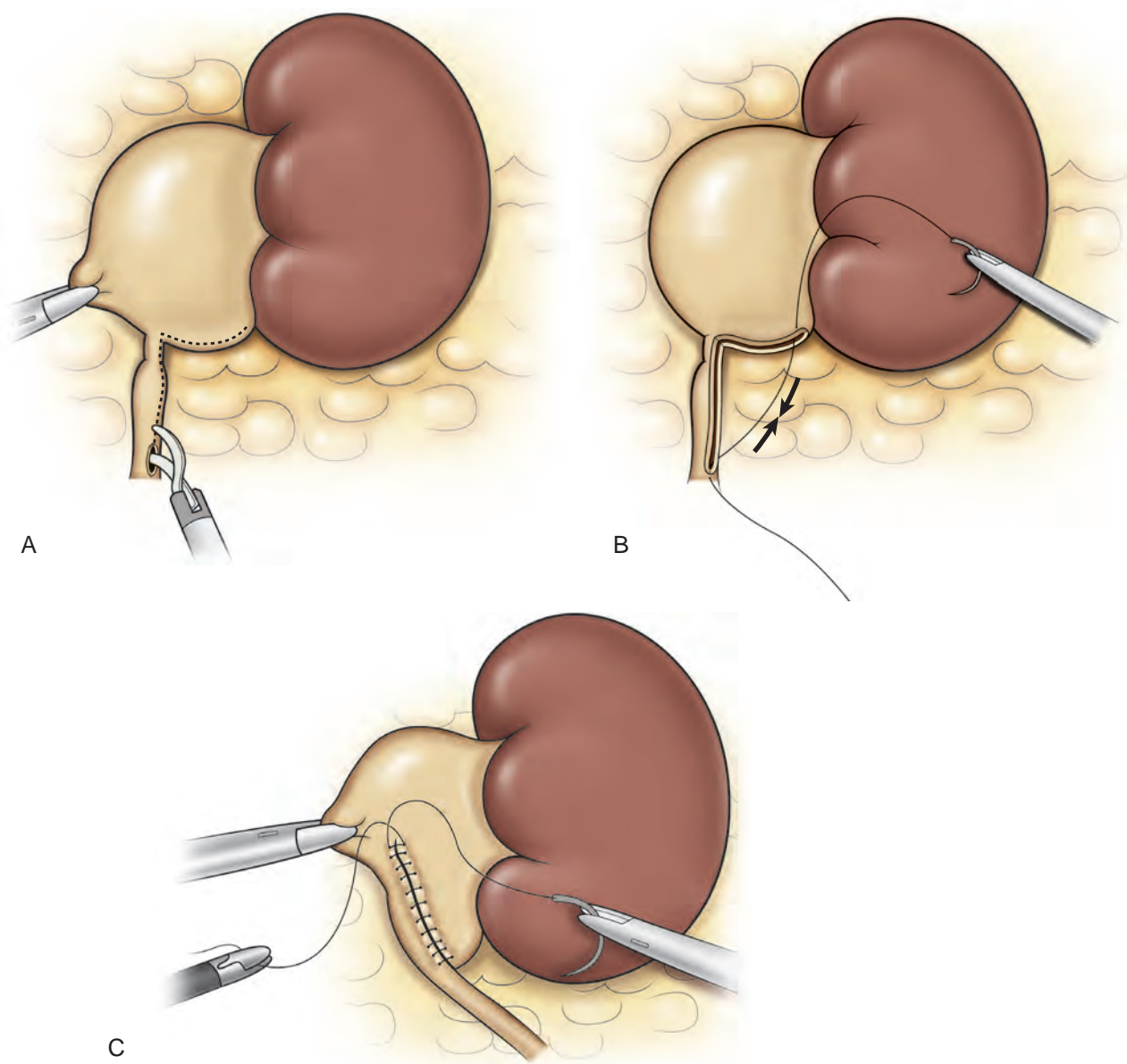


Figure 133-5. A-C, The schematic represents a modified “bypass” pyeloplasty in which a side-to-side anastomosis of the ureter and renal pelvis is performed without transecting the stenotic ureteropelvic junction (UPJ). This allows the new UPJ to be configured within 1 cm of the lower pole parenchyma. It also keeps the ureter oriented by keeping it anchored to the pelvis during reconstruction, encouraging a “no touch” technique.

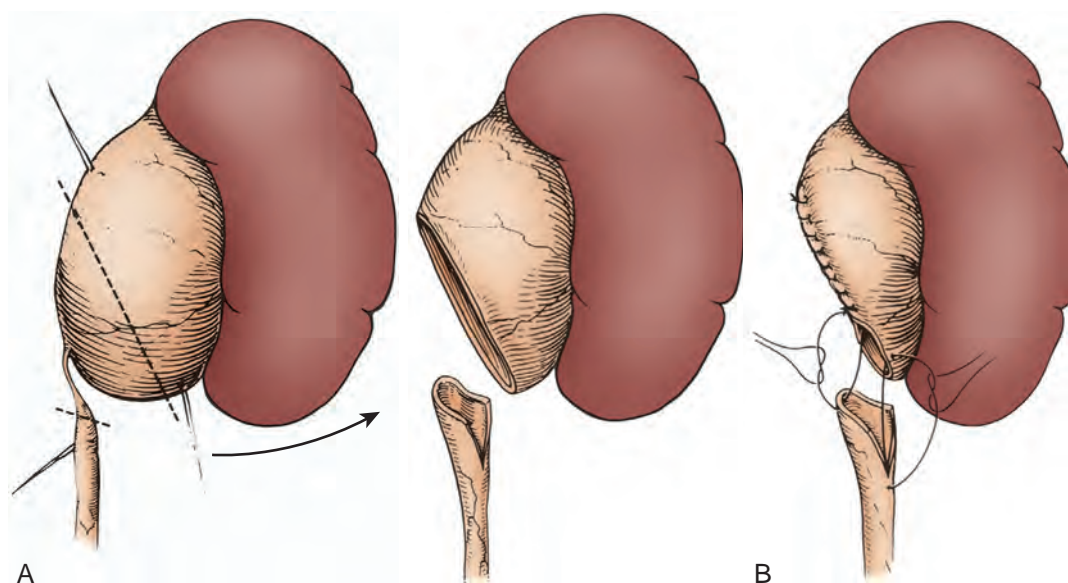


Figure 133-6. A, For a large or redundant pelvis, a reduction pyeloplasty is performed by excising the redundant portion between traction sutures. B, The cephalad aspect of the pelvis is then closed with running absorbable sutures down to the dependent portion. The dependent aspect of the pelvis is anastomosed to the proximal ureter as described in [Figure 133-4](#).

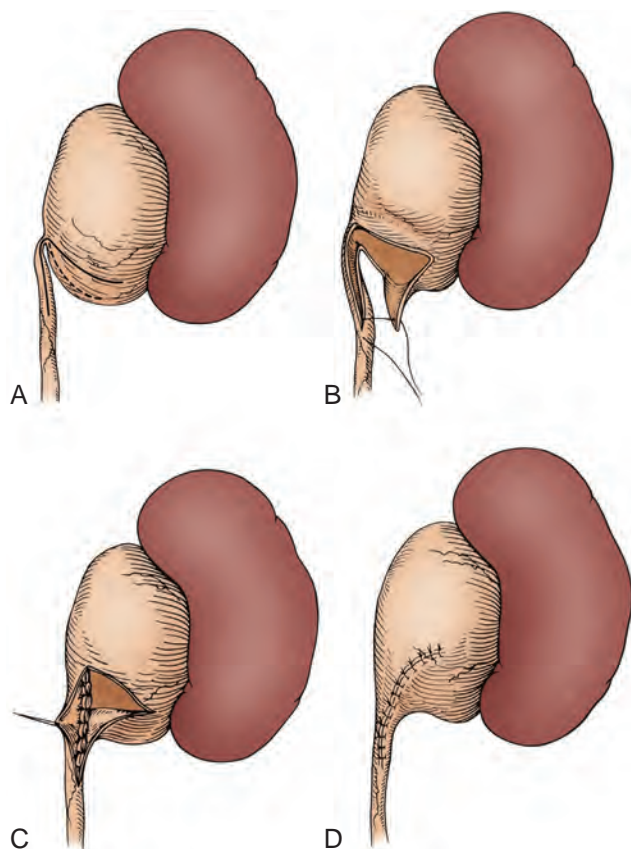


Figure 133-7. A, A Foley Y-V plasty is best applied to a ureteropelvic junction (UPJ) obstruction associated with a high insertion of the ureter. The flap is outlined with tissue marker or stay sutures. The base of the V is positioned on the dependent, medial aspect of the renal pelvis and the apex at the UPJ. The incision from the apex of the flap, which represents the stem of the Y, is then carried along the lateral aspect of the proximal ureter well into an area of normal caliber. B, The flap is developed with fine scissors. The apex of the pelvic flap is brought to the most inferior aspect of the ureterotomy incision. C, The posterior walls are approximated using interrupted or running fine absorbable sutures. D, The anastomosis is completed with approximation of the anterior walls of the pelvic flap and ureterotomy.

ureter is removed and the pelvis is irrigated with saline to avoid blood clots obstructing the ureter. Stenting the anastomosis and the nature of the stent used is a matter of choice that differs across surgeons and institutions. The kidney is brought back to its native position, and the anastomosis can be covered with perinephric fat if available. Usually the use of external drainage in the form of a Penrose is not indicated.

Nondismembered Pyeloplasty

Several techniques have been described for nondismembered pyeloplasty. Casale and colleagues (2004), in a comparative series of 26 children using the laparoscopic approach, showed that dismembered pyeloplasty gives results superior to those of nondismembered pyeloplasty of the Heineke-Mikulicz fashion. A feasible alternative is the Foley Y-V plasty, especially in cases with a high insertion of the ureter and no accessory vessels (Fig. 133-7). In a prospective randomized study, Szydelko and associates (2012), compared the outcome of Anderson-Hynes pyeloplasty and the Foley Y-V plasty with success rates of 95% and 86%, respectively, although the difference did not reach statistical significance. A vertical (Fig. 133-8) or spiral flap (Fig. 133-9) technique may be an option in cases of severe hydronephrosis with a long stenotic

ureteral segment, which makes tension-free primary anastomosis impossible. The bypass pyeloplasty (see Fig. 133-5) might be a feasible alternative although a systematic review of this technique is not available.

Surgical Approach to the Ureteropelvic Junction Obstruction

Posterior Lumbotomy

This approach should be reserved for infants and toddlers, because the increasing dorsal musculature with age can make this access difficult if not impossible (Fig. 133-10). In prone position, after a vertical incision has been made, the lumbodorsal fascia is incised and retracted laterally. The Gerota fascia is opened, giving direct access to the UPJ. The renal pelvis and the proximal ureter are then stabilized with stay sutures, and the UPJO repair is performed as previously described.

Flank Approach

In the supine position the affected side is supported by a gel roll. A small horizontal incision is made at the level of the tip of the 11th to 12th rib. The fascial and muscle layers are separated in a muscle-splitting fashion. Currently, and because pyeloplasties in older children are mostly performed laparoscopically, division of the muscle fibers is deemed unnecessary. The peritoneum is liberally loosened from the abdominal wall muscles and swept medially, thus giving access to the Gerota fascia. The fascia is opened vertically and pushed medially. The UPJ is dissected and stabilized with stay sutures in the pelvis and proximal ureter. The pyeloplasty is then performed as described previously.

Minimally Invasive Techniques

Endoscopic Approach

The antegrade and retrograde endoscopic approach to the UPJO was popularized in the late 1980s and 1990s with varying results. The reported success rate on long-term follow-up of balloon dilatation in patients younger than 18 years of age was 25% (Osther et al, 1998), and the ureteral cutting balloon catheter showed a success rate of 78% in adults (Kim et al, 1998), including two patients requiring embolization of a lower pole vessel because of gross postoperative hematuria. They recently reported a review of their 25 years of experience with endopyelotomy and found a success rate of 62% in primary UPJO, whereas the success rate in secondary UPJOs resulting, for example, from scarring was as high as 94% (Kim et al, 2012). Antegrade pyelotomy should be reserved for older children and adolescents with moderate hydronephrosis (Figenshau and Clayman, 1998). However, preoperative screening for accessory vessels is required by computed tomography (CT), magnetic resonance imaging (MRI), or transluminal ultrasound, so as to avoid vascular injury. Additionally, fluoroscopy is needed during the procedure, which leads to significant radiation exposure and makes this approach less attractive in pediatrics. However, endopyelotomy may have a place in the management of failed primary open or laparoscopic procedures (Fig. 133-11), followed by the placement of a double-pigtail catheter for 6 weeks. In these cases, the precise anatomy is known from the primary procedure in which absence of an accessory vessel is documented. However, patients should be carefully selected and a repeat pyeloplasty, either open or laparoscopically, is the best choice in most cases.

Laparoscopic Pyeloplasty

The first cases of laparoscopic pyeloplasty were reported in 1993 (Kavoussi and Peters, 1993; Schuessler et al, 1993). Tan and Roberts (1996) reported the first preliminary results of the transabdominal approach, and Yeung and colleagues (Yeung et al, 2001) described

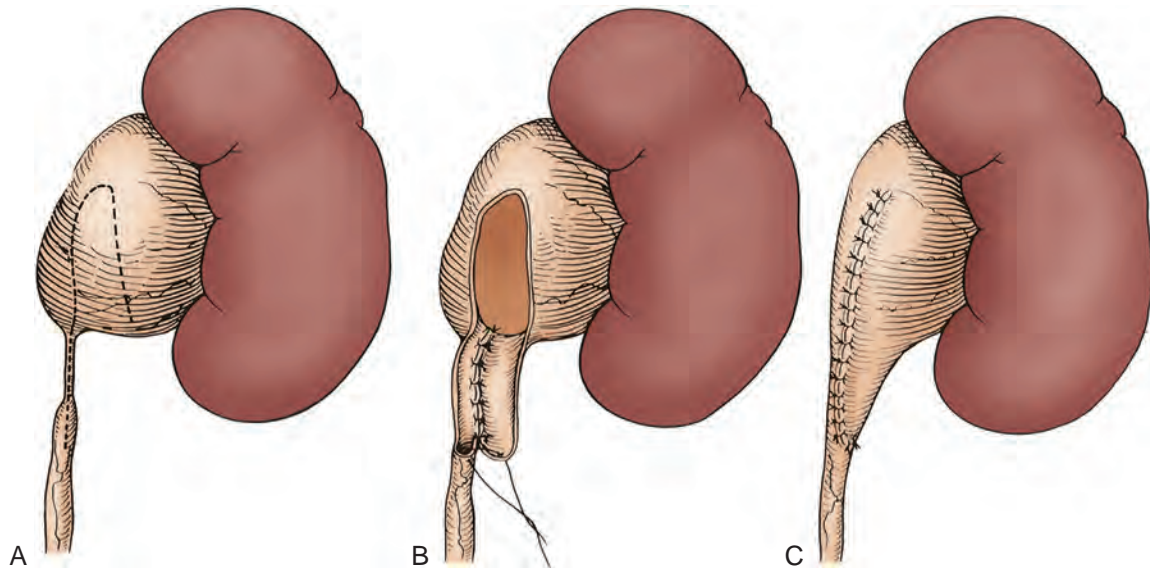


Figure 133-8. A, Vertical flap technique may be used when a dependent ureteropelvic junction (UPJ) is situated at the medial margin of a large, box-shaped extrarenal pelvis. In contrast to the spiral flap, the base of the vertical flap is situated more horizontally on the dependent aspect of the renal pelvis, between the UPJ and the renal parenchyma. The flap itself is formed by two straight incisions converging from the base vertically up to the apex on either the anterior or posterior aspects of the renal pelvis. As for the spiral flap, the position of the apex determines the length of the flap, which should be a function of the length of proximal ureter to be bridged. The medial incision of the flap is carried down the proximal ureter completely through the strictured area into normal-caliber ureter. B, The apex of the flap is rotated down to the most inferior aspect of the ureterotomy. C, The flap is closed by approximating the edges with interrupted or running fine absorbable sutures.

the retroperitoneal approach in infants and children. The evolution of both instruments and video equipment has made the laparoscopic approach widely accepted, and it has become the method of choice at many centers (Bonnard et al, 2005; Metzelder et al, 2006; Sweeney et al, 2011; Blanc et al, 2013).

Transperitoneal or Retroperitoneal Approach. From a theoretical point of view, the retroperitoneal approach should be safer and is the route of choice in open surgery. However, only few studies have compared retroperitoneal with transperitoneal access and without noting any significant differences in the outcome and/or complications. Abuanz and associates (2010) found a higher rate of conversion to open surgery in adults when using the retroperitoneal approach compared to the transabdominal route. This might reflect a more technically challenging procedure in the retroperitoneum. Canon and colleagues (2007) reported a longer operative time for the retroperitoneal approach. Larger randomized studies have not been published so far.

Robot-Assisted Pyeloplasty. In the beginning of this century, the first publications on robotic pyeloplasty in children emerged (Olsen and Jorgensen 2004; Kutikov et al, 2006; Lee et al, 2006). The transperitoneal approach has gained wide acceptance, whereas the retroperitoneal approach seems to have attracted fewer proponents, undoubtedly because of a more technically challenging procedure in children with the confined working space, difficult orientation, and relatively large instruments that need to be maneuvered (Olsen et al, 2007). Robotic-assisted pyeloplasty has a shorter and more efficient learning curve compared to that of laparoscopy because of advanced visualization through three-dimensional vision and the dexterity of the instruments provides for easier manipulation, precise dissection, and suturing. Recently Barbosa and associates (2013) compared open and robot-assisted pyeloplasty in a larger series and found comparable outcomes but a faster resolution rate in the robotic group. Others (Lee et al, 2006; Dangle et al, 2013) found similar results. Peters (2011) describes the robot-assisted transperitoneal technique, and Olsen

and Rawashdeh (2012) describe the robot-assisted retroperitoneal technique in detail.

Technique of Laparoscopic or Robotic-Assisted Pyeloplasty. With the patient in a 45- to 60-degree flank position, port placement of the transperitoneal approach is shown in Figure 133-12. The caudal port can be placed more medially in cases of large hydronephrosis or in small children. The primary access for the camera port is established using the open technique, and instrument ports are placed under visual guidance. On both sides, retrocolic access is feasible. However, most surgeons prefer a transmesenteric approach on the left side (Lee et al, 2006; Gupta et al, 2009; Sedlacek et al, 2010; Khan et al, 2011; Shadpour et al, 2012) because of the shorter operating time, lower morbidity, reduced hospital stay, and no difference in outcome compared to the retrocolic approach. If the pelvis cannot be identified through the mesocolon, the ureter should be identified and followed to the UPJ with attention paid to the possible presence of any accessory vessel (Peters, 2011). The UPJO can then be stabilized by a stay suture, and surgery is performed as detailed earlier. Essentially, there is no difference in port placement between a laparoscopic transabdominal or robot-assisted approach.

For the retroperitoneal approach, port placement varies in accordance with the use of laparoscopic or robotic instruments (Fig. 133-13). In both cases, the patient is placed in an 80- to 90-degree flank position. A small gel roll is placed under the contralateral iliac crest, and the upper leg is stretched (Fig. 133-14). The table should not be flexed, because this will diminish the anteroposterior diameter of the retroperitoneal space. During the retroperitoneoscopic procedure with standard instruments, the surgeon is placed behind the patient (dorsally) (see Fig. 133-13A) (Bonnard, 2005), providing better ergonomics. Small children might even be placed diagonally on the table, exposing the instruments in a right angle to the surgeon. In the robot-assisted procedure, the robot is docked from a cranial position and, contrary to the case in laparoscopy, camera position is relatively fixed and

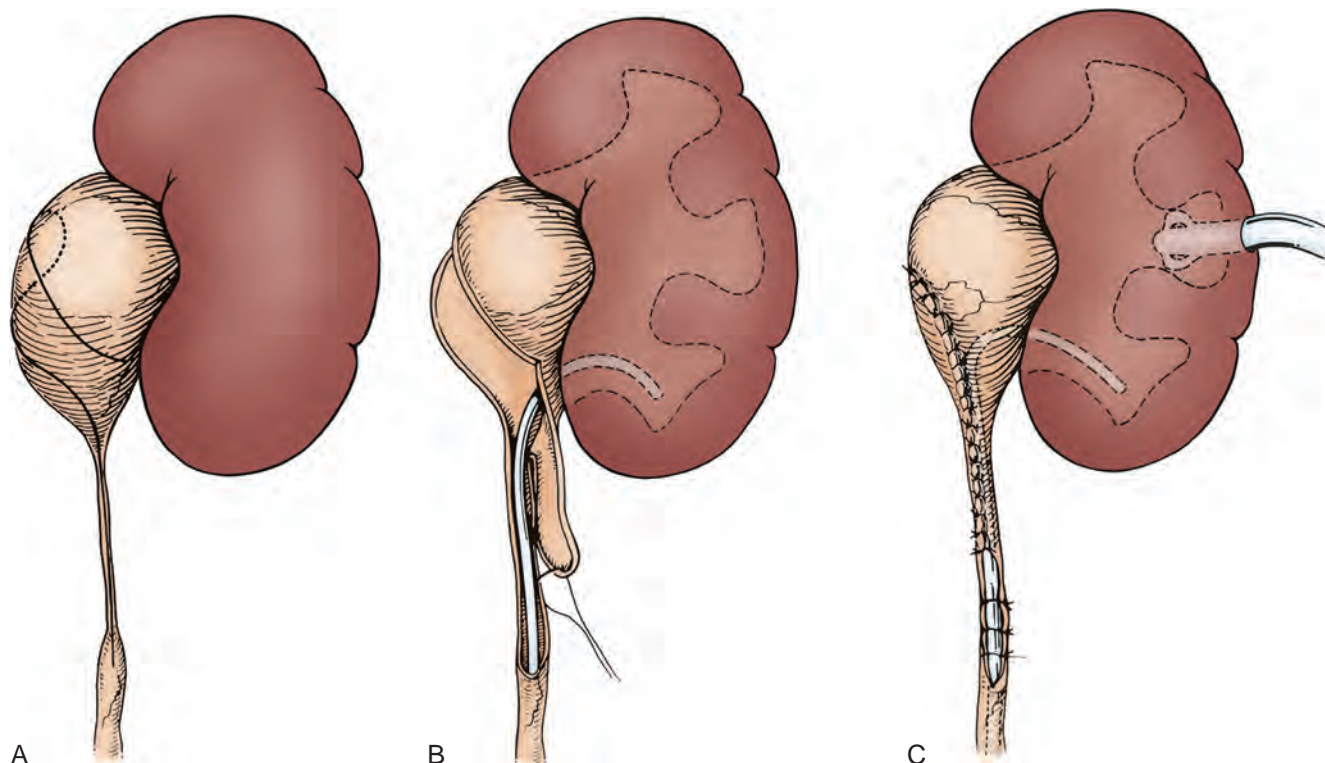


Figure 133-9. A, Spiral flap may be indicated for relatively long areas of proximal ureteral obstruction when the ureteropelvic junction (UPJ) is already in a dependent position. The spiral flap is outlined with the base situated obliquely on the dependent aspect of the renal pelvis. The base of the flap is positioned anatomically lateral to the UPJ between the ureteral insertion and the renal parenchyma. The flap is spiraled posteriorly to anteriorly or vice versa. The anatomically medial line of incision is carried down completely through the obstructed proximal ureteral segment into normal-caliber ureter. The site of the apex for the flap is determined by the length of the flap required to bridge the obstruction. The longer the segment of proximal ureteral obstruction, the farther away is the apex, because this will make the flap longer. To preserve vascular integrity to the flap, however, the ratio of flap length to width should not exceed 3:1. B, Once the flap is developed, the apex is rotated down to the most inferior aspect of the ureterotomy. C, The anastomosis is completed, usually over an internal stent, using fine absorbable sutures.

cannot easily be changed during the procedure. In both cases a muscle-splitting dissection is carried out at the camera port site and the lumbodorsal fascia is opened. The retroperitoneal space is then developed into a 200- to 300-mL working space, depending on the size of the patient. This is done with either a homemade balloon using a 12-Fr catheter with the finger of a latex surgical glove secured to its tip or a commercially available balloon. The latter can be difficult to use in small children because of the large size of these dilators. Additional ports are placed under digital or visual guidance. Use of an extra 5-mm assistance port in the iliac fossa is recommended to facilitate suture delivery and suction during the procedure, because removing and replacing robotic instruments for that same purpose is much more cumbersome and time-consuming. After opening the Gerota fascia the UPJ and the pelvis are dissected. A stay suture in the pelvis brought intracorporeally through the abdominal wall provides needed tension and alignment. The pyeloplasty is then performed as described earlier. In case of a UPJO in a horseshoe kidney, the retroperitoneal approach is not advisable because the pelvis is approached from behind. This advice applies for the retroperitoneal approach in the rare case of a retrocaval ureter, at least for the robot-assisted procedure. Even with standard laparoscopic equipment, retroperitoneal access in these cases is difficult. On the other hand, retroperitoneal access to a UPJO of a lower moiety in a duplex system with the subsequent challenging repair is a perfect case for the robot (see Fig. 133-3).

Stones and Congenital Hydronephrosis. Occasionally, pelvic/renal stones are found with congenital hydronephrosis. Regardless of whether open or laparoscopic/robotic access is used, the treatment of choice is with a flexible cystoscope. In minimally invasive surgery the cystoscope can be brought in through either a laparoscopic or a robotic port. Alternatively a flexible ureteroscope can be used. However, the latter makes stone removal more cumbersome. Standard techniques for stone removal are used as described elsewhere in this text.

Vascular Hitch. Originally described by Hellström and associates (Autorino et al, 2014), the vascular hitch technique (Fig. 133-15) has regained acceptance among laparoscopic surgeons, probably because it is easier to perform than pyeloplasty (Sakoda et al, 2011). However, the technique is feasible only in cases of an anterior lower pole vessel without any intrinsic obstruction of the UPJ. Gundeti and colleagues (2008) conclude that the vascular hitch should be reserved for cases with “moderate hydronephrosis with no calyceal dilatation and a well-preserved cortex, poor renal drainage with preserved split function and lower pole crossing vessels. Intraoperative criteria included a normal ureter and ureteropelvic junction with peristalsis.” Long-term results are lacking (Gundeti et al, 2008; Schneider et al, 2013), and one can speculate whether this technique of embedding the vessel in the pelvic tissue can lead to hypertension later in life.

Stenting. Most surgeons prefer stenting the UPJ, both in open and minimally invasive surgery (Austin et al, 2000). This decreases the

risk for leakage from the anastomosis and subsequent urinoma formation or, if the transperitoneal route is chosen, bowel paralysis resulting from urinary ascites. Stentless anastomoses have been advocated by some authors (Liss et al, 2013). This mandates extra careful tissue handling to avoid edema and subsequent obstruction



Figure 133-10. Positioning of patient for left posterior lumbotomy incision. An oblique incision is made from the angle of the 12th rib down to the iliac crest at a point one third the distance from the anterior superior iliac spine to the spinal processes.

and leakage from the reconstructed UPJ in the postoperative period. Stenting with double-pigtail catheters in children consigns the patient to another anesthesia for stent removal and adds significant time to the procedure when done in connection with the pyeloplasty. Use of a stent with an extraction string and placed retrograde can be a feasible alternative. Antegrade preoperative stenting with double-pigtail catheters also can pose difficulties in passing the ureterovesical junction, which can be quite narrow in small infants. For purposes of confirming stent position in the bladder, instillation of methylene blue into the bladder has been advocated. Retrograde stenting immediately before the procedure might make the anastomosis more difficult, and if done days to weeks before surgery as in cases in which emergent diversion is necessary because of obstruction, anastomosis might be more challenging as a result of local tissue inflammation caused by the catheter traversing the UPJ. It is our experience to divert with a nephrostomy tube in the rare patient with hydronephrosis who needs emergent diversion in close temporal proximity to definitive surgery, because the inflammation caused by a nephrostomy is less severe at the UPJ.

We prefer using a transanastomotic ureteropyelostomy tube, the so-called BLUE stent (Helmy et al, 2011), brought out through the renal parenchyma through a middle calyx or directly through the upper part of the anastomosis and the lateral abdominal wall (Fig. 133-16). This externalized stent is kept open for 24 to 48 hours, after which it is knotted and kept in situ for 7 to 14 days and simply pulled out without the need for anesthesia. In cases of obstruction, infection, or postoperative pain, the knot is released and the transanastomotic ureteropyelostomy drains the system acting as a nephrostomy tube.

It is customary to leave the bladder drained by Foley catheter for up to 24 to 48 hours postoperatively. Although dogmatic and not based on hard evidence, it makes perfect sense when the anastomosis is stented by a double-pigtail catheter because VUR will be present, transferring bladder pressure unhindered to the

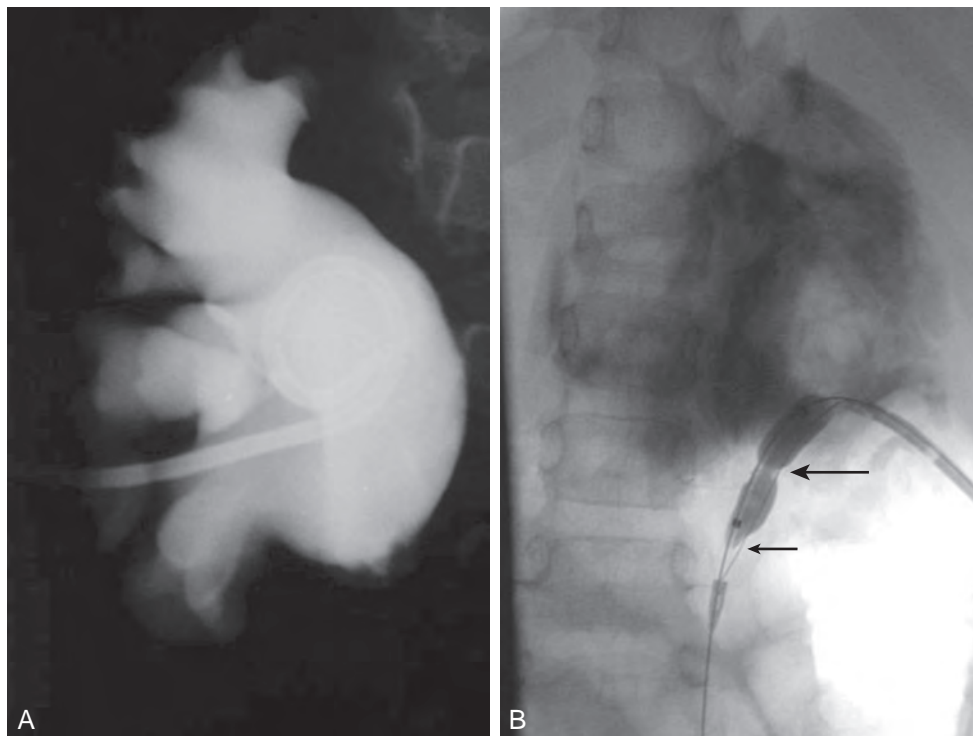


Figure 133-11. A, Right antegrade nephrostogram performed 2 months after dismembered pyeloplasty, demonstrating persistent obstruction at the ureteropelvic junction (UPJ). A nephrostomy tube was placed 2 weeks after surgery, after the patient developed flank pain, fever, and *Staphylococcus aureus* urinary tract infection. B, Acuise balloon being inflated across the UPJ narrowing. Note waist present in balloon (upper arrow) and cutting wire positioned laterally (lower arrow).

renal pelvis. However, it is unnecessary when using an externalized transanastomotic ureteropyelostomy tube because the lower end of the stent is removed before placement and does not traverse the ureterovesical junction.

Surgical Outcome and Complications

In general, pyeloplasty is a safe procedure with few complications and a high success rate between 90% and 100% (Poulsen et al, 1987; O'Reilly, 1989; MacNeily et al, 1993; Shaul et al, 1994; Salem et al, 1995; McAleer and Kaplan, 1999; Austin et al, 2000; Houben et al, 2000; Casale et al, 2004; Bonnard et al, 2005; Peters, 2011; Olsen and Rawashdeh, 2012; Autorino et al, 2014). However, the definition of *success* is wide ranging and covers everything from cessation of symptoms to improvement or at least stability of function of the affected kidney to decreasing anteroposterior diameter of the hydronephrosis on ultrasound, and more rigidly *failure* as the need for reoperation or reintervention. This

makes the comparison among different outcome studies difficult if not impossible.

Perioperative complications include bleeding from ureteral or pelvic vessels, which can be handled preferably by bipolar diathermy in most cases. Bleeding is the most commonly reported reason for conversion in minimally invasive procedures, followed by lack of progression or difficulties dissecting the UPJ. Postoperatively, infection, pain, and increasing dilatation might be early signs of a failed reconstruction (Lindgren et al, 2012). However, blood clots and edema may be the cause and usually will resolve within a few days, but may require temporary diversion by nephrostomy tube. In the long term, decreasing kidney function and increasing dilatation may indicate the need for further intervention, initially by balloon dilatation/incision of the stenotic UPJ (see Fig. 133-11) and stenting for 4 to 6 weeks, but may ultimately require a repeat pyeloplasty. In such cases, retroperitoneal access can be cumbersome because of scarring and a transperitoneal approach is preferred. If scarring of the ureter is severe and mobilization of the kidney and ureter does not allow for an appropriate length to perform a tension-free anastomosis, a ureterocalicostomy should be considered. This can be done openly or with laparoscopic or robotic-assisted procedures (Fig. 133-17).

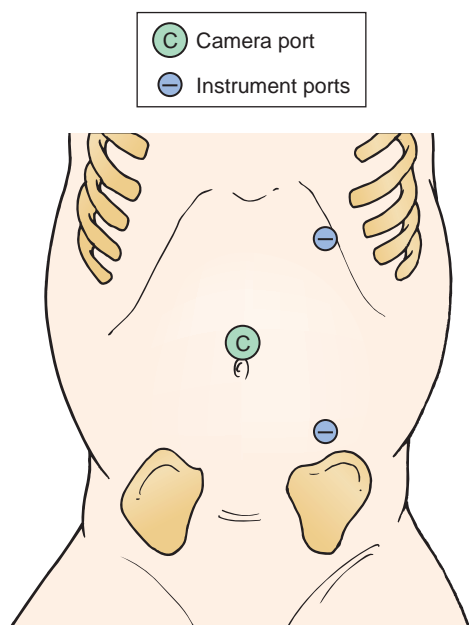


Figure 133-12. Port placement in transabdominal laparoscopic or robotic-assisted pyeloplasty.

MEGAURETER

Definition

The term *megaureter* is a descriptive one denoting dilatation of the ureter irrespective of cause. Originally coined by Caulk in 1923 as megaloureter, other synonyms in use include wide ureter and hydroureter and in general refer to a ureter that has a diameter of 7 mm or greater based on the studies of Cussen (1967) and Hellström (1985), which defined the upper limit of the range of normal ureteral diameters in children up to 16 years of age as being 0.50 to 0.65 mm. The cause of megaureters is either primary, representing a condition intrinsic to the ureter itself, or secondary to bladder pathologic processes, such as neurogenic bladder dysfunction, bladder outlet obstruction, and/or infection. Megaureters have been subclassified into four categories based on causality; obstructed, refluxing, nonobstructed nonrefluxing, and refluxing with obstruction (Smith 1977; King 1980). In circumventing the refluxing type, which is easily diagnosed and is dealt with elsewhere in this book, distinguishing between obstructed megaureters and those that are nonobstructed, nonrefluxing can be challenging. For, as is the case with hydronephrosis, the mere presence of ureteral

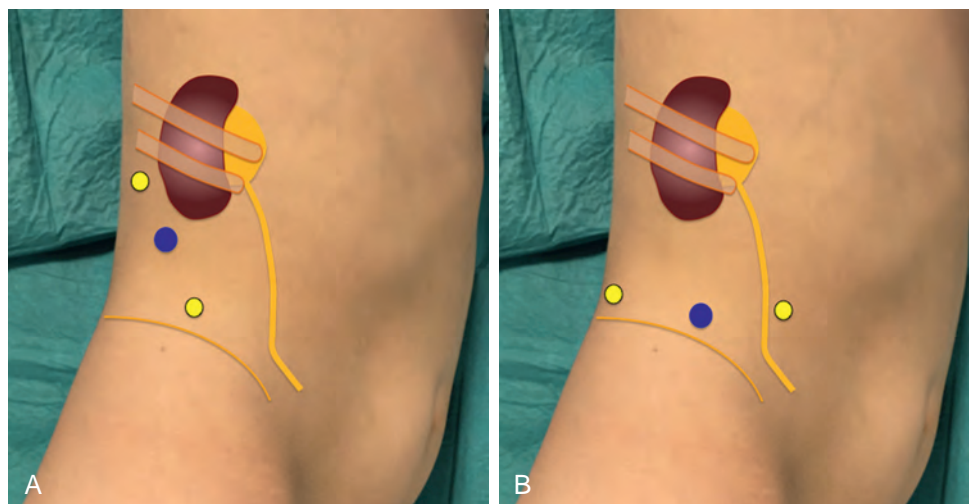


Figure 133-13. Port placement in retroperitoneal approach. A, Approach with standard laparoscopic instruments. B, Approach with robotic-assisted instruments.

KEY POINTS: PYELOPLASTY

- UPJO typically is due to either an intrinsic narrowing in which the ureteral segment has an interruption in the development of the circular musculature of the UPJ, an alteration in collagen fibers in and around the muscular cells, or an extrinsic obstruction that is seen in association with aberrant, accessory, or early branching lower pole vessel that passes anteriorly to the UPJ or proximal ureter and contributes to mechanical obstruction.
- Congenital renal malformations can be commonly seen in association with a UPJ, with a contralateral UPJO being the most common anomaly, followed by renal dysplasia and multicystic dysplastic kidneys.
- The surgical approach favored in the repair of a UPJO obstruction is the dismembered pyeloplasty, which has been shown to be effective because of its broad applicability, means of allowing excision of the pathologic segment in question, and facilitation of a reduction pyeloplasty when necessary.
- Laparoscopic pyeloplasties provide excellent visualization of the anatomy, enhance cosmesis, and duplicate the results of open pyeloplasties with short-term follow-up. The technical challenges of this approach have been facilitated by the use of a robotic-assisted procedure that improves the anastomotic repair.
- Complications from a pyeloplasty include prolonged urinary drainage postoperatively, lack of improvement in renal function or improvement in washout, and, occasionally, worsening hydronephrosis and diminished renal function postoperatively. Such a situation may lend itself to a repair using endoscopic procedures or a repeat dismembered pyeloplasty.

dilatation, which at times can be quite alarming on imaging, does not necessarily indicate significant obstruction. **The challenge is in the balance between early identification and management of the obstructed ureters, to prevent renal functional deterioration, and that of not consigning ureters with balanced stable dilatations to unnecessary intervention.**

Cause, Occurrence, and Presentation

The pathophysiology of primary obstructed megaureters (POM) has not been fully ascertained, but there is general agreement that obstruction results from the presence of an abnormal adynamic segment at the terminal end of the ureter near or at the ureterovesical junction (UVJ). Insufficient peristalsis at the UVJ leads to obstruction and upstream dilatation. Fetal animal studies by [Tanagho \(1973\)](#) and [Pirker and associates \(2007\)](#) demonstrated that the ureteral muscular layers develop in a craniocaudal direction, leaving the juxtavesicular part of the ureter to develop last, with maturation of this terminal part continuing postnatally. This corresponds well with studies in human fetuses that showed a

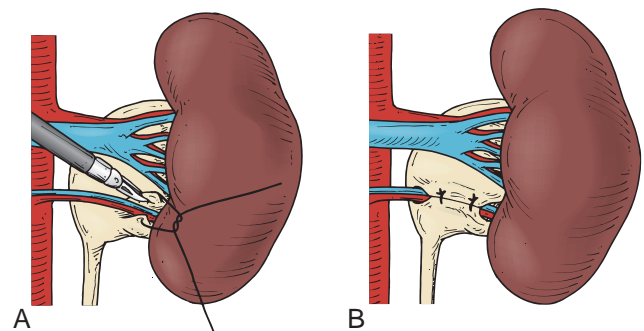


Figure 133-15. A and B, Vascular hitch in cases with crossing vessels and without intrinsic obstruction of the ureteropelvic junction (UPJ). After the removal of all adhesences between the UPJ and the vessel, the latter is moved cranially on the pelvis and then embedded into pelvic tissue with nonresorbable sutures.



Figure 133-14. Patient positioning for the retroperitoneoscopic examination. The contralateral iliac crest is supported by a gel roll. The table is not flexed, to avoid a reduction of the anteroposterior diameter in the retroperitoneal space. The upper leg is stretched, and the lower leg is bent. This positioning is not advisable for adult patients.

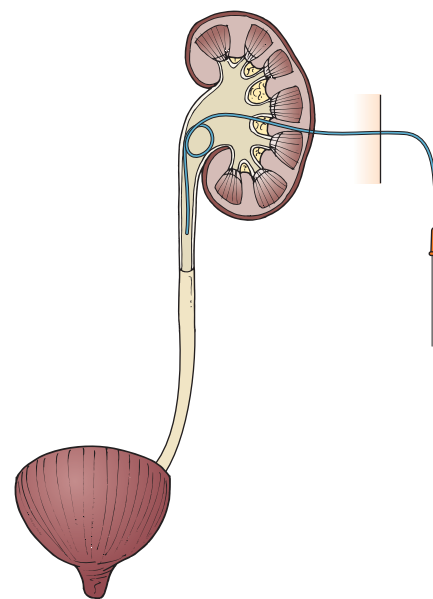


Figure 133-16. Transanastomotic ureteropyelostomy BLUE Stent. The lower coil is removed, and the upper end is brought out to the skin, through either the anastomosis or the renal parenchyma. The stent is left open for 24 to 48 hours and then knotted. It can easily be removed after 7 to 14 days without the need for anesthesia.

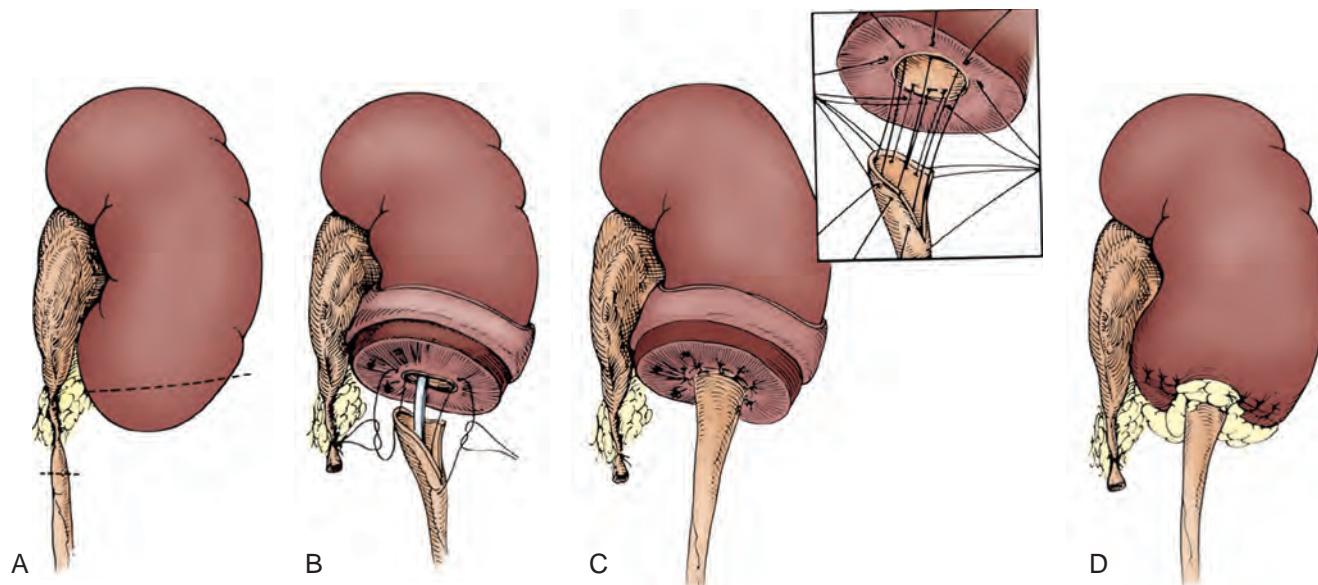


Figure 133-17. Ureterocalicostomy. A, The ureter is identified in the retroperitoneum and dissected proximally as far as possible. The kidney is mobilized as much as necessary to gain access to the lower pole and subsequently perform the anastomosis without tension. A lower pole nephrectomy is performed, removing as much parenchyma as necessary to widely expose a dilated lower pole calyx. B, The proximal ureter is spatulated laterally. The anastomosis subsequently should be performed over an internal stent and consideration given to leaving a nephrostomy tube. The initial suture is placed at the apex of the ureteral spatulation and the lateral wall of the calyx, with another suture placed 180 degrees from that. C, The anastomosis is completed in an open fashion, placing each suture circumferentially but not securing them until the anastomosis has been completed. D, The renal capsule is closed over the cut surface of the parenchyma whenever possible. However, the capsule should not be closed close to the anastomosis itself because that may compromise the lumen by extrinsic compression. Instead, the anastomosis should be protected with a graft of perinephric fat or with a peritoneal or an omental flap.

similar directional maturation with typical fetal circular muscular fibers first maturing to the double muscle layer of the full-term infant well past delivery, a fact that may explain transient dysfunctions at the UVJ and the spontaneous resolution of some POMs with age (Matsuno et al, 1984; McLellan et al, 2002). Other studies point to the presence of excessive and abnormal collagen deposition at the narrow part of the ureter (Notley, 1968; Gosling and Dixon, 1978) or presence of a thick enveloping sleeve of muscle surrounding the muscle bundles of the terminal ureter (Dixon et al, 1998). Most recently Kang and colleagues (2009) demonstrated abnormalities in the interstitial cells of Cajal in POM, cells whose primary function is related to smooth muscle contractility, pacemaker activity, and ultimately peristalsis.

The true incidence of POM is not known but is thought to average 10% to 23% of antenatally detected upper urinary tract dilatations (Brown et al, 1987; Gokce et al, 2012). The anomaly has a predilection for boys and the left side. It is bilateral in 25% of cases and is associated with contralateral dysplasia or obstruction in 10% to 15% of cases (Joseph, 2007). Most POMs are detected by antenatal ultrasound screening, with the vast majority being asymptomatic. Brown and colleagues (1987) clearly demonstrated the impact of prenatal ultrasound in that the majority (79 %) of patients with POM—constituting 23% of antenatally detected dilatations—were detected antenatally as opposed to the era before ultrasound, when only 8% of patients presenting symptomatically and consequently found to have upper urinary tract dilatation were diagnosed with POM (Brown et al, 1987). When present, symptoms include those of UTI, abdominal pain, and microscopic hematuria, even in the absence of infection. This is believed to result from the disruption of urothelial microvasculature because of distention or calculi. In rare instances, previously undiagnosed patients can

present with an abdominal mass, although this is more a feature of the era before the ultrasound era, as is the current very infrequent manifestation with signs and symptoms of renal impairment (Shokeir and Nijman, 2000).

Surgical Indications

By historical account it can be deduced that the majority of non-refluxing megaureters run a benign course and resolve spontaneously within the first few years of life (Matsuno et al, 1984; Brown et al, 1987; McLellan et al, 2002; Shukla et al, 2005). This has been confirmed in a prospective observational study by Ranawaka and Hennayake (2013), who were able to show that complete resolution and time to resolution were inversely related to ureteral diameter with minimal complications or febrile episodes during follow-up for those with a ureteral diameter less than 10 mm while maintained on antibiotic prophylaxis and virtually none proceeded to surgery. On the other hand, patients with ureteral diameters greater than 10 mm were more prone to complications such as recurring febrile UTIs, stone formation, and abdominal pain, with only 17% resolving completely and an overall 21% requiring surgical intervention. Persistence of dilatation therefore warrants continued close follow-up of these patients with periodic ultrasound examinations supplanted with functional studies when deemed necessary until resolution or stability of dilatation is confirmed. The role of extended follow-up into early adulthood also has been advocated based on worsening of some previously stable megaureters at or beyond puberty (Shukla et al, 2005).

Therefore a steady trend toward nonoperative management of patients with megaureters has occurred during the last 25 years. An increased understanding of the pathophysiology of this condition

combined with advances in minimally invasive procedures also has shifted management in a more minimally invasive direction. Surgery in the case of POM is to be considered when patients are symptomatic or have recurring UTIs, progressive unremitting dilatation on ultrasound, differential renal function less than 40%, and/or significant decreases in differential renal function of 5% or greater on sequential “comparable” renal nuclear functional studies (Farrugia et al, 2014). Several studies cite prolonged washout or drainage curves on diuretic renograms as being an indication to intervene, because prolongation of half-life is equated with significant obstruction. However, relying on renographic washout curves as a measure of obstruction is problematic and can be misleading, because it has been shown that washout curves in neonates and infants can be affected by many factors other than restriction of flow: renal function and the ability to respond to diuretic stimulation, hydration status, posture, distensibility, and volume of the collecting system, in addition to matters related to procedural and technical aspects, such as the timing of diuretic administration and curve interpretation. Collectively, these variables limit the usefulness of drainage curves, as has been documented in a study that reported false-positive results in up to 44% of renographies (O'Reilly, 1989; Shokeir and Nijman, 2000; Amarante et al, 2003).

Surgical Management

Basic principles of megaureter correction are simple and straightforward; the surgical procedure can be quite demanding, however, and should be reserved for the pediatric urologist with experience in bladder and ureteral surgery and in whose hands good results

can be achieved. In summary, the stenotic distal part of the ureter is excised, the megaureter is straightened, then tapered to facilitate reimplantation in a nonrefluxing fashion with adequate length-to-diameter ratio of 5:1 so as to improve coaptation of the ureteral lumen whereby effective peristalsis and urine transportation are achieved (Paquin, 1959). Several eponymous procedures have been described for ureteral remodeling and its reimplantation, and with time numerous modifications and refinements have emerged. As the laparoscopic and robotic envelopes continue to be pushed, the same basic principles are increasingly being achieved by laparoscopic and robot-assisted techniques, albeit at a limited number of centers.

If prompt decompression of a POM is necessary, this can be achieved by nephrostomy tube diversion; however, nephrostomy tubes are difficult to maintain in infants for prolonged periods and carry the risk for leakage, infection, and displacement. A better temporizing option in this case would be distal cutaneous ureterostomy. This simple technique allows rapid decompression of the dilated and potentially infected system and allows a delay in definitive reconstruction, which is usually warranted in infants in whom incongruity between the small bladder and the severely dilated ureter does not allow for a safe nonrefluxing reimplantation and the general reluctance to perform reimplantations in infants for fear of inducing bladder dysfunction, a claim that may be overstated according to a study by de Kort and colleagues (2002). The ureter can be approached through a small oblique inguinal incision, carried through muscle-splitting dissection to the perivesical space (Fig. 133-18). The dilated tortuous ureter is identified and picked up by nontraumatic forceps or a noncrushing Allis clamp. Peritoneal adhesions may have to be swept off using a

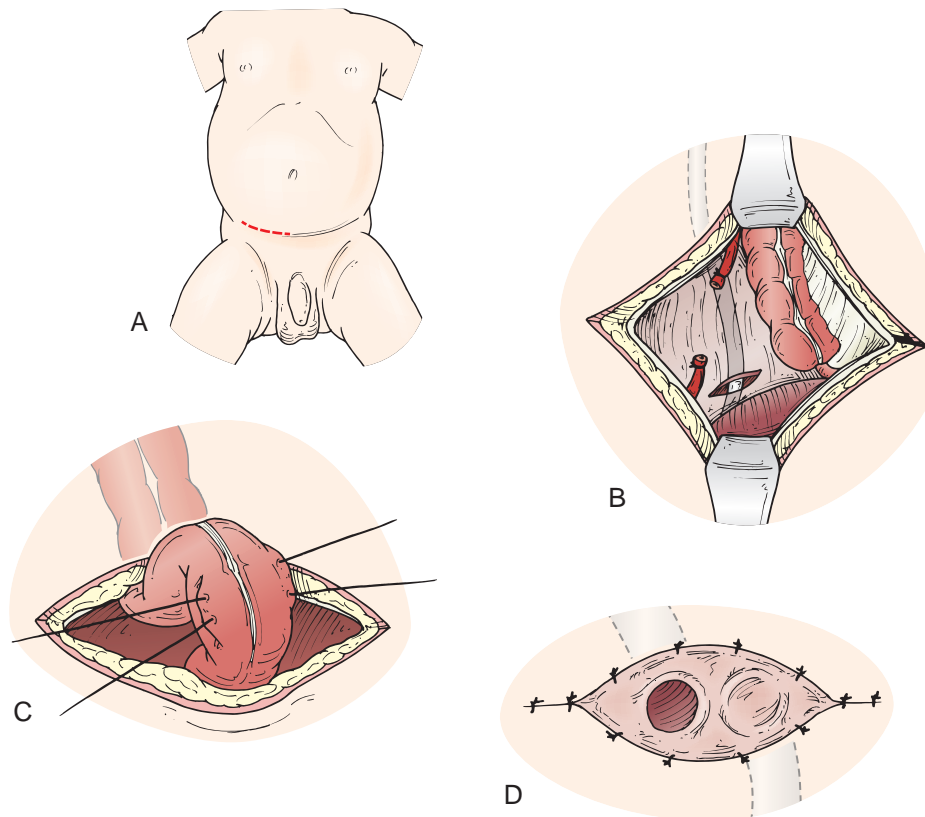


Figure 133-18. Diversion with ureterostomy. A, A small oblique or transverse inguinal incision is made. B, Muscles are separated bluntly, and the perivesical space is accessed. The dilated tortuous ureter is identified, the obliterated umbilical artery being divided and ligated if necessary. C, The ureter is mobilized and brought out as a loop to the incision, where it is fixed to the fascia, and the incision is approximated to the ureteral wall. D, The ureter is now opened, and the edges are everted and fixed to the skin with fine resorbable monofilament interrupted sutures.

pledget. A vascular loop is pulled under the ureter to allow atraumatic handling. The ureter can now be pulled out into the incision as a loop and secured to the fascia with several resorbable monofilament 5-0 sutures, whereafter the fascia is approximated to the distended ureter with the same suture. The ureter can now be opened transversely and the edges everted and secured to the skin using 5-0 or 6-0 resorbable monofilament sutures. A drainage catheter can be left in situ for the first 24 to 48 hours to aid in drainage and decompression of the redundant dilated system. Because of the dimensions of the ureter, stenosis of the stoma is a rare occurrence (Rabinowitz et al, 1977; Kitchens et al, 2007). Another temporizing procedure that is gaining acceptance in the infant is that of internal diversion by means of a refluxing reimplantation. The dilated ureter is transected proximal to the stenotic terminal part and is anastomosed directly in a freely high-grade refluxing fashion

whereby “dangerous” obstruction is converted into the “lesser evil” of VUR. Preliminary studies have shown promising results of this temporizing procedure; however, long-term outcomes with regard to effect of reflux on renal function are awaited (Lee et al, 2005; Farrugia et al, 2014; Kaefer et al, 2014).

Definitive reconstruction entails remodeling and reimplanting the ureter in a nonrefluxing fashion. The bladder is accessed through a low transverse Pfannenstiel incision; in redo cases a vertical lower abdominal incision might be preferable because it allows more extensive cranial mobilization of the ureters (Fig. 133-19). The bladder is opened in the midline between stay sutures, and the index ureteral orifice is identified and cannulated with a baby feeding tube of appropriate size—usually 5 or 6 Fr—and secured to the mucosa with a 5-0 monofilament resorbable suture. This aids in the dissection of the ureter and provides an invaluable handle

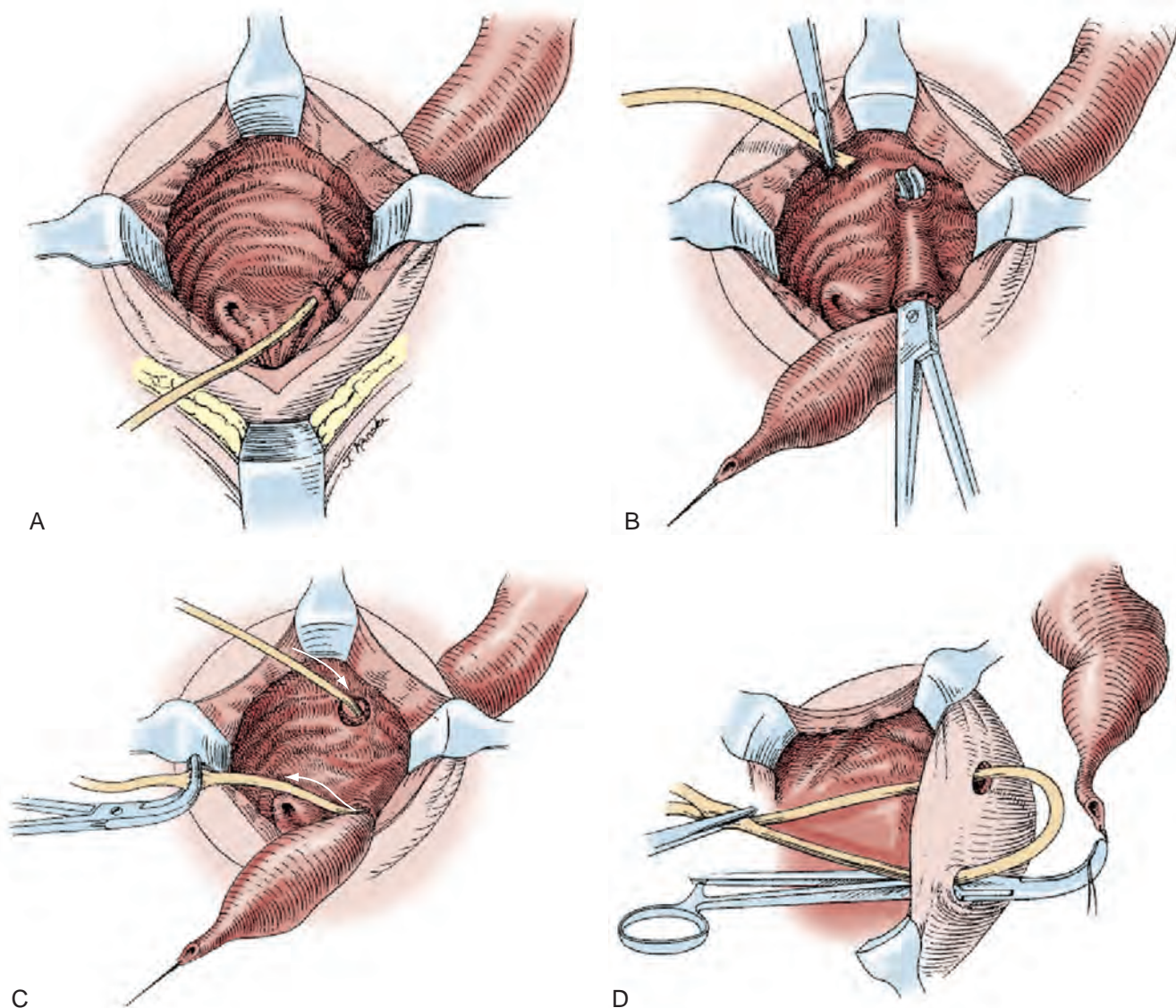


Figure 133-19. Remodeling and reimplantation of primary obstructed megaureter. A, A 5-Fr feeding tube typically passes up a normal-caliber intravesical segment of primary obstructive megaureter. B, After the megaureter is freed from its intravesical and extravesical attachments, a blunt right-angle clamp is used to clear the peritoneum from the posterior and base of the bladder. If extravesical dissection is necessary, it is advisable to make the new hiatus before moving outside the bladder. A right-angle clamp is incised upon and spread. C, A vascular loop marks the new hiatus by being pulled from within the bladder to the outside and then through the old hiatus. D, A right-angle clamp is guided from within the bladder to the perivesical space, where it is identified and incised upon. The ureter is brought extravesically by grasping the traction suture in the ureter.

for traction. The dilated ureter can now be mobilized into the bladder by dividing its intravesicular and extravesicular attachments. Care must be taken to preserve the blood supply to the distal ureter, which usually emanates medially. Once the ureter is mobilized within the bladder, the technique of reimplantation and remodeling must be decided on, because they dictate the next steps. In the case of an intravesicular repeat implant, such as the Cohen transtrigonal or the Politano-Leadbetter, work can be continued from within the bladder. However, it is advisable to move outside the bladder in cases of a very large ureter or to perform the whole dissection, transection, and remodeling of the ureter extravesically and proceed with an extravesicular form of reimplantation especially if the discrepancy between ureteral diameter and bladder is significant, so as to avoid excessive bladder dissection and creation of a very large hiatus in the trigone area (Perovic, 1994). Should the Politano-Leadbetter procedure be chosen (see Fig. 133-19), an appropriate site for the new hiatus superiomedially is identified and a blunt right-angled clamp is carefully passed

through the original hiatus, which may need to be widened, and the clamp is probed toward the new planned hiatus while taking care to sweep off the peritoneal attachments from the posterior aspect of the bladder. Once the clamp is in position and palpable digitally from inside the bladder, the clamp's right angle is pushed inward, opened slightly, and the jaws of the right angle clamp are incised upon the branches, thereby creating the new hiatus, which then can be widened appropriately. A vascular loop is passed from within the bladder from the new to the old hiatus, thereby traversing extravesically. The dilated ureter is now guided out of the bladder, allowing further mobilization and release. After remodeling (Fig. 133-20), the ureter is brought back into the bladder through the new hiatus guided by the vascular loop. The original hiatus is closed with a 4-0 monofilament resorbable suture, and a new submucosal tunnel is created toward the new hiatus. The ureter is now pulled through and shortened adequately to the length of the tunnel; the ureteral orifice is hitched to the detrusor with a 5-0 monofilament resorbable suture at the 6 o'clock position, and the

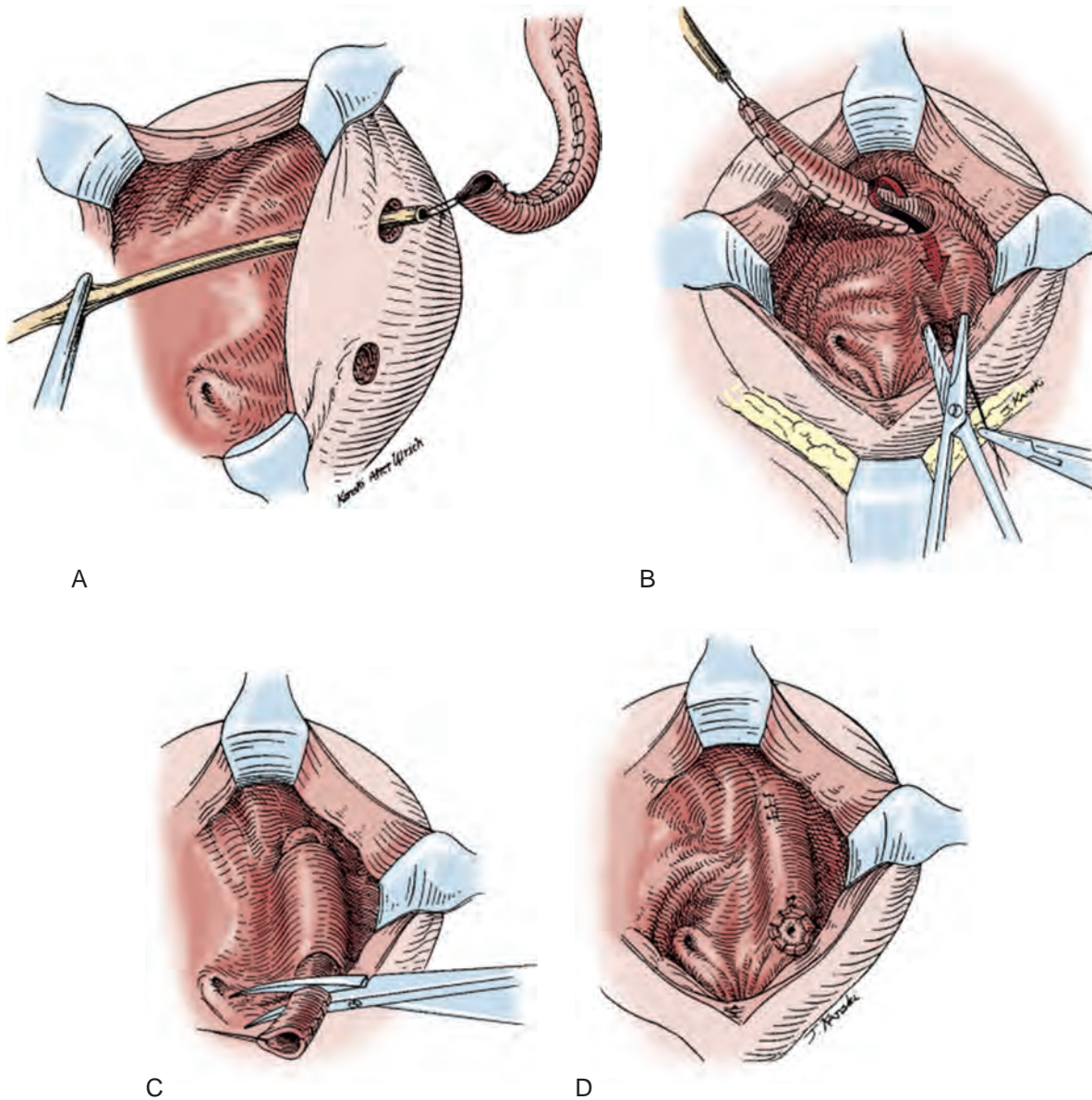


Figure 133-20. Remodeling and reimplantation of primary obstructed megaureter completed. **A,** The tailored ureter is brought back into the bladder through the new hiatus. **B,** After closing the original hiatus, a new submucosal tunnel is made to the new hiatus. **C,** The distal portion of ureter is resected to match the length of the tunnel. **D,** The revised ureter is anastomosed to the bladder with fine interrupted sutures.

mucosa is adapted circumferentially to the bladder mucosa in the new position with 6-0 interrupted monofilament resorbable sutures. Postoperatively the bladder is decompressed with a Foley catheter for a few days.

Tailoring of the ureter can be achieved by one of two basic ways: plication or excisional tapering. With plication the mega-ureter is imbricated or folded around an 8- or 10-Fr catheter, depending on patient age. Ureteral redundancy is marked by brief placement of atraumatic Allis clamps around the ureter containing the medialized catheter. After removing the clamps the Starr plication technique (Fig. 133-21) dictates imbricating the redundant lateral edge of the dilated ureter by multiple interrupted 5-0 monofilament resorbable sutures in the Lembert fashion along the clamp impressions (Starr, 1979). Whereas in the Kalicinski plication

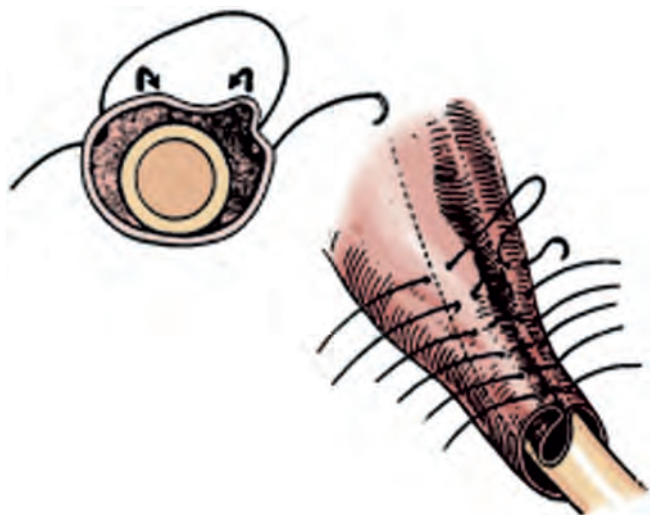


Figure 133-21. Starr plication. Ureteral plication is performed over the appropriate catheter, with interrupted 5-0 monofilament resorbable sutures placed in Lembert fashion (after Starr). (From Keating MA, Retik AB. Management of failures of ureteroneocystostomy. In: McDougal WS, editor. Difficult problems in urologic surgery. Chicago: Year Book Medical; 1989. p. 131.)

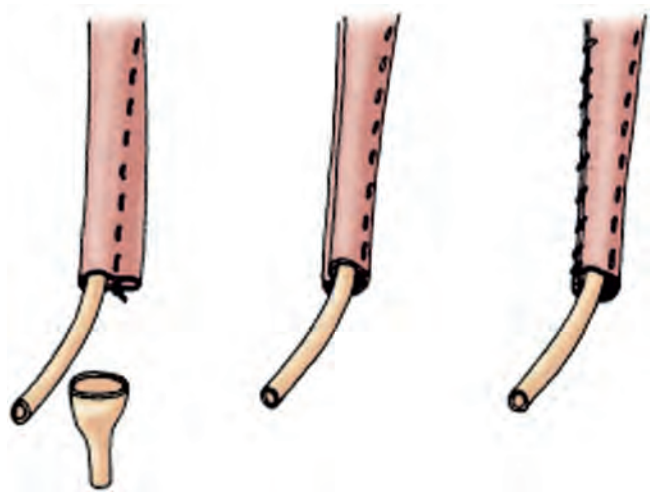


Figure 133-22. Kalicinski folding technique. Ureteral folding technique. A running suture is longitudinally woven through the mega-ureter to create two lumens. This isolates the best-vascularized portion as a functional ureter (catheter within) and excludes redundancy. The redundant portion is then folded, and the two are tacked together with interrupted sutures. (From Kalicinski ZH, Kansy J, Kotarbinska B, et al. Surgery of megaureters: modification of Hendren's operation. J Pediatr Surg 1977;12:183.)

(Fig. 133-22) a 6-0 monofilament resorbable suture is woven in a continuous fashion craniocaudally through the ureteral wall along the clamp impressions, thereby defunctionalizing the redundant lateral aspect, which in turn is folded back and fixed along the catheterized lumen with multiple 6-0 interrupted sutures (Kalicinski et al, 1977). In plication techniques the blood supply to the ureter is preserved as the ureteral walls are kept intact, thereby decreasing the risk for ischemia and stenosis (Bakker et al, 1988). Folding techniques, however, are suitable only for the moderately dilated ureter (<1.75 cm in diameter) (Fretz et al, 2004) because a diameter that is too large will result in a bulky remodeled ureter that is difficult to reimplant and significantly increases complications and failure rates (Parrott et al, 1990). In general, good results have been reported with folding techniques, with success rates of 90% to 95% (Ehrlich 1985; Perdzynski and Kalicinski, 1996; Daher et al, 1999; Fretz et al, 2004). Postoperatively stents in the form of baby feeding tubes or double-pigtail catheters are left in situ for 7 days and 4 weeks, respectively, for drainage purposes. Follow-up pyelography via stentograms is not indicated at stent removal.

Excisional tapering as originally described by Hendren (1969) was the forerunner for the later modifications of folding techniques, because it is thought and has been shown that excisional tapering may jeopardize ureteral vasculature with all its attendant complications (Bakker et al, 1988; Whitmore and Ehrlich 1988; Parrott et al, 1990). Nonetheless, the Hendren procedure has advantages, especially when dealing with massively dilated ureters that are not amenable to folding, and when performed with care the risk for vascular compromise should be minimal.

The procedure (Fig. 133-23) follows the same principal steps of defining the redundant less vascular lateral part of the ureter around an 8- to 10-Fr catheter. Instead of folding, the excess ureteral tissue is excised and closed with a running locking 6-0 resorbable monofilament suture along the proximal two thirds of the ureteral length to be remodeled; the distal third is closed by interrupted sutures of the same kind to allow for appropriate shortening of the ureter at reimplantation without violating the integrity of the running anastomosis (Hendren, 1969). The same postoperative regimen is followed as with the folding techniques. Although success rates with this method have generally been excellent,

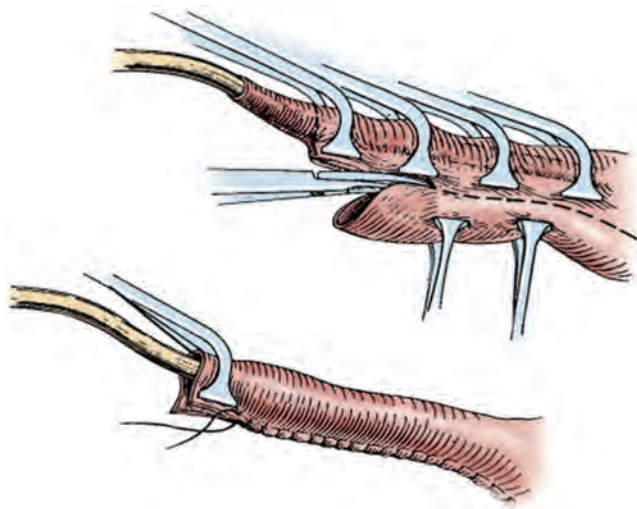


Figure 133-23. Excisional tapering. Tapering is done over an 8-Fr red rubber catheter in infants or a 10-Fr catheter in older children and adults. After vascularity is defined, special atraumatic clamps are placed over the catheter. Baby Allis clamps help retract the portion of ureter to be resected, which is usually lateral. It is important not to resect too much ureter. Running 5-0 monofilament resorbable suture is used to reapproximate the proximal two thirds of the ureter. Its distal third is closed with interrupted sutures to allow for shortening.

exceeding 90% in many studies (Hendren, 1969; Parrott et al, 1990; DeFoor et al, 2004), refinements aimed at preserving vasculature by limiting excision to the mucosal and muscular parts of the redundant ureter, and leaving behind the vascular rich adventitial layers may even improve on these outcomes by lowering the risk for ischemia (Ossandon et al, 2005). It is pertinent for all types of ureteral remodeling that tapering be gradual so as not to cause an abrupt change in ureteral caliber, which may cause a form of obstruction.

Laparoscopic ureteral remodeling and reimplantation follows the same general principles set for open techniques. An increasing number of reports are demonstrating the feasibility and success of these minimally invasive techniques with excellent short- to medium-term outcomes fully comparable with those of open procedures (Bi and Sun, 2012; Abraham et al, 2012; Bondarenko, 2013). Extravesicular reimplantations seem to dominate because technical limitations impede tapering from within the bladder (Abraham et al, 2012; Bondarenko, 2013) notwithstanding that a recent report has shown pneumovesicular laparoscopic excisional tapering and transtrigonal reimplantation achievable (Bi and Sun, 2012). Robot-assisted reimplantations for VUR in children are well established but have yet to develop for POM (Marchini et al, 2011; Smith et al, 2011).

Outcomes

In general, techniques of ureteral remodeling and reimplantation for POM have stood the test of time, producing excellent and durable results of over 90% success rates in several studies. Interestingly, outcomes for patients with POM have generally been better than those for patients with refluxing megaureters, a fact that may be explained by histologic changes in the ratios of collagen to smooth muscle in the UVJ of refluxing ureters, which may result in a stiffer, less compressible ureter (Lee et al, 1998; DeFoor et al, 2004). Worse outcomes also have been reported in patients with dysfunctional voiding, neurogenic bladders, and other concomitant lower urinary tract pathologic conditions such as posterior urethral valves and obstructed flow (DeFoor et al, 2004; Carr and Casale, 2012). The main reported complications are obstruction, vesicoureteric reflux, and persistent dilatation. Obstruction is initially managed by stenting because in some cases it is the result of postoperative edema. It also can be the result of ischemic structuring—especially after excisional tapering. In this case repeat ureteroneocystostomy is indicated, with the attendant risks associated with revision surgery. Conservative management of vesicoureteric reflux is warranted especially with the lower grades, because reflux has a tendency to resolve spontaneously in many cases. However, successful management with subureteric injection has been reported with minimal complication (DeFoor et al, 2004; Kitchens et al, 2006). Should subureteric injections fail, especially in cases of recurrent febrile UTIs, proceeding to revision surgery may be the only available option. A transureteroureterostomy may offer a valuable management option for repeat cases in unilateral affliction in which there is severe ureteral scarring or concerns regarding compromised blood supply.

Dilatation and Stenting

Endoscopic dilatation and stenting of the UVJ in POM has garnered increasing interest during the last decade or so. The method is less invasive than formal open or laparoscopic surgical intervention, with short- to medium-term success rates in the vicinity of 70% in most studies (Angerri et al, 2007; Carroll et al, 2010; Farrugia et al, 2011). However, the procedure is not without complications; stent migration, infection, hematuria, and stone formation have been reported in up to 31% of cases in one series (Farrugia et al, 2011). Furthermore, the need for repeat stenting, stenting by open surgical access in difficult cases, and ureteral injuries requiring emergent reimplantation may limit widespread use before long-term outcomes are documented (Carroll et al, 2010; Farrugia et al, 2011). In essence the ureteral orifice of the POM is accessed

endoscopically and dilated by a ureteral catheter or high-pressure balloon under fluoroscopic guidance until the indentation or waist-ing on the balloon disappears. Thereafter a double-pigtail catheter is left for 2 to 6 months before removal. Persistent dilatation or renal function deterioration at follow-up has successfully been treated by repeat stenting in some patients, whereas others have required reimplantation (Farrugia et al, 2014). Because long-term outcomes still are pending, patients need to be followed into adolescence (Christman et al, 2012).

Ureteral Strictures

Congenital ureteral strictures are rare anomalies that have been described causing hydroureteronephrosis. Dilatation is detected antenatally, but because of their extreme rarity these patients are usually misdiagnosed as having hydronephrosis or megaureter. Postnatal diagnostics with ultrasound, MRI, and retrograde pyelography subsequently usually confirm the diagnosis as being the result of a midureteral stricture. Management entails excision of the stenotic ureteral segment and reanastomosis by ureteroureterostomy; excised segments range in length from 1 to 3 cm and histologically are characterized by increased collagen deposition and muscular hypertrophy (Hwang et al, 2005; Brugnara et al, 2007).

Ureteral Polyps

Ureteral polyps are another rare anomaly that may lead to obstruction and dilatation. The polyps are most frequently seen in the upper third of the ureter and usually lead to UPJO. They are more common in males and on the left side, can be single or multiple, and can reach a size of several centimeters in diameter. Although they may cause antenatal dilatation, they tend to manifest symptomatically with pain and hematuria later in childhood because they exhibit slow growth and are benign. Diagnosis can be made by ultrasound, contrast-based CT scan, and MR urography. Confirmation usually is attained by retrograde pyelography or ureteroscopy. Management options include dismembered pyeloplasty with resection of the afflicted part of the ureter when polyps are near the UPJ or ureteral resection and ureteroureterostomy by open and even laparoscopic surgery. In cases of smaller polyps, ureteroscopic excision might be a feasible alternative. Histologically, they are classified as fibroepithelial benign polyps (Kanamori et al, 2010; Bian et al, 2011; Shive et al, 2012).

KEY POINTS: MEGAURETER

- The term *megaureter* is a descriptive one denoting dilatation of the ureter irrespective of cause.
- Megaureters have been subclassified into four categories based on causality: obstructed, refluxing, nonobstructed nonrefluxing, and refluxing with obstruction.
- The challenge is to prevent renal functional deterioration with either conservative or surgical treatment.
- Surgery is indicated in recurring UTIs, progressive unremitting dilatation on ultrasound, differential renal function less than 40%, and/or significant decreases in differential renal function of 5% or greater on sequential “comparable” renal nuclear functional studies.
- During the surgical procedure the stenotic distal part of the ureter is excised; the megaureter is straightened and then tapered to facilitate reimplantation in a nonrefluxing fashion with adequate ratio of length to diameter of 5:1 to improve coaptation of the ureteral lumen, whereby effective peristalsis and urine transportation are achieved.
- Most surgeons advocate temporary postoperative stenting.

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The complete reference list is available online at www.expertconsult.com.



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Classification and Anatomic Description

Clinical Presentation

Evaluation

Clinical Management

Other Ureteral Anomalies

CLASSIFICATION AND ANATOMIC DESCRIPTION

General Patterns

Abnormalities of ureteral development, including ectopic ureters and ureteroceles, represent a large component of clinical urology and continue to challenge clinical management, despite their wide recognition and well-defined surgical strategies. The wide spectrum of involvement and the variable patterns of presentation underlie the clinical challenge and require a thorough understanding of both normal and abnormal embryology of the lower urinary tract. This chapter presents the clinical manifestations, embryologic pathology, and evaluation and management strategies for ectopic ureters and ureteroceles as well as other less common ureteral anomalies of formation. Obstructive ureteral pathologies including ureteropelvic junction obstruction (UPJO) and ureterovesical junction obstruction are reviewed in Chapter 132.

Although ectopic ureter and ureterocele are typically presented as distinct entities, it is apparent that they share many common features and may well have the same underlying developmental mechanisms, with slight variations that induce the very obvious differences in their appearances. In many ways, they may be approached in a similar manner, with slight variation in management because of their particular differences. It is also apparent that clinical cases may represent manifestations that lie between the two entities, suggesting a continuum of embryologic development.

Ectopic Ureter

By definition, an ectopic ureter is any ureter, single or duplex, that does not enter the trigonal area of the bladder. In a duplex system this is inevitably the upper pole ureter, presumably because of its budding from the mesonephric duct later than the lower pole with later incorporation into the developing urogenital sinus. If it is simply near the bladder neck, it is not technically ectopic, which requires entry at the level of the bladder neck or distal. In females, the ectopic ureter may enter anywhere from the bladder neck to the perineum and into the vagina, uterus, and even rectum (Fig. 134-1). It may be associated with a cyst of the Gartner duct, the remnant of the wolffian duct from which the ureter buds, and may include cystic dilation of the duct. The duct typically runs parallel to the vagina (the müllerian structure), and with rupture of the cystic ductal structure, communication with the vagina is established. This is the basis for incontinence, the frequent presentation of an ectopic ureter in females. In males, the ectopic ureter always enters the urogenital system above the external sphincter or pelvic floor, and usually into the wolffian structures, including vas deferens, seminal vesicles, or ejaculatory duct (Fig. 134-2; also see Fig. 134-1). Presentation in male patients does not involve incontinence, but

rather infection and pain of the affected organs (testicles and epididymis).

Single-system ectopic ureters and ureteroceles may manifest in a similar fashion but may also be associated with an apparently absent kidney. This usually reflects an inability to identify the kidney on typical imaging and has led to the use of computed tomography (CT) imaging with contrast to detect small, poorly functioning renal units associated with an ectopic ureter (Borer et al, 1998). Either single or duplex systems with an ectopic ureter may cause severe hydronephrosis reflecting distal obstruction. This may have impaired normal renal development to the point that the affected segment is nonfunctional, which needs to be clinically assessed.

The rare entity of bilateral single-system ectopic ureters may be associated with a hypoplastic bladder and bilateral renal abnormalities, typically dysplasia (Koyanagi et al, 1977; Noseworthy and Persky, 1982; Johnin et al, 2007). Some of these children may be considered to have bladder agenesis owing to the absence of a recognizable bladder structure, presumably because of the absence of bladder work in utero.

KEY POINTS: ECTOPIC URETER

- An ectopic ureter is any ureter, single or duplex, that does not enter the trigonal area of the bladder.
- In a duplex system the ectopic ureter is inevitably the upper pole ureter owing to its budding from the mesonephric duct later (more cephalad) than the lower pole ureteral bud.
- In females, the ectopic ureter may enter anywhere from the bladder neck to the perineum and into the vagina, uterus, and even rectum. One of the classic symptoms is continuous wetting.
- In males, the ectopic ureter always enters the urogenital system above the external sphincter or pelvic floor and usually into the wolffian structures, including vas deferens, seminal vesicles, or ejaculatory duct. Clinical presentation is not incontinence but infection.

Ureterocele

Ureteroceles represent a version of the ectopic ureter with a cystic dilation of the distal aspect of the ureter that is located either within the bladder or spanning the bladder neck and urethra. As with the ectopic ureter, ureteroceles may be associated with a single or duplex system, and in duplex systems are associated with the upper pole (Fig. 134-3). Ureteroceles can extend into the urethra but do not form entirely within the urethra, nor do they attach to the wolffian ductal structures.

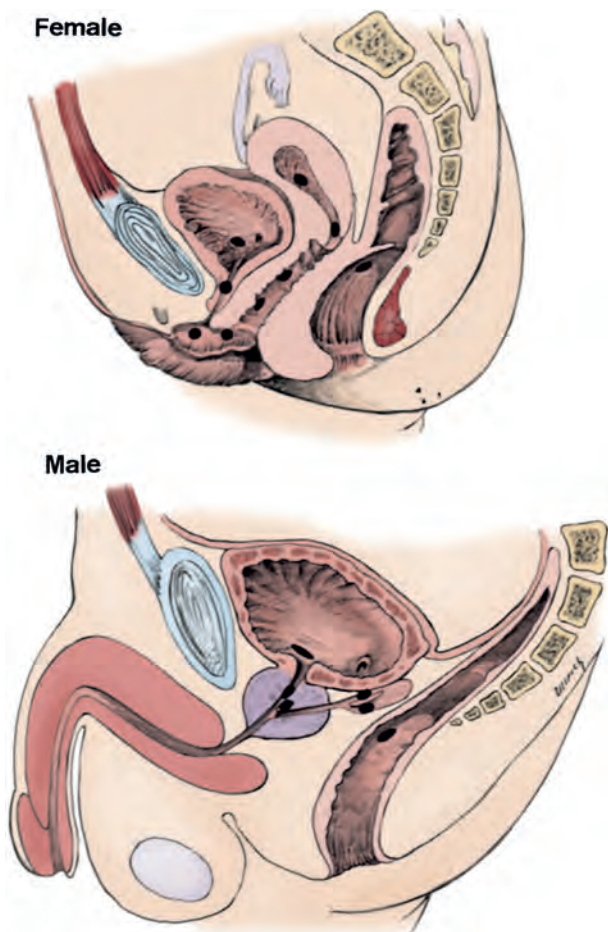


Figure 134-1. Sites of ectopic ureteral orifices in the male and female.

Several classification systems exist for ureteroceles, but the most useful one for clinical practice separates intravesical from extravascular ureteroceles. The intravesical ureterocele is entirely within the bladder and above the bladder neck. This would include a “simple” ureterocele that may be seen in the adult with minimal dilation and mild to no upper tract dilation. This term, however, should be discouraged; the term *single intravesical ureterocele* should be used (Glassberg et al, 1984). An ectopic ureterocele includes those “in which some portion of the ureterocele is situated permanently at the bladder neck or urethra” (Glassberg et al, 1984). The orifice may be in the bladder, at the bladder neck, or in the urethra. This should be distinguished from an intravesical ureterocele that prolapses into the urethra with voiding.

Further descriptive subdivision of ureterocele types has been published, particularly by Stephens (Stephens, 1971; Stephens et al, 1996). These include cecoureterocele and stenotic, sphincteric, sphincterostenotic, blind, and nonobstructed ureteroceles (Fig. 134-4). From a clinical perspective, the most important subgroup to recognize is the cecoureteroceles. In these cases, the orifice of the affected ureter is within the bladder but the cavity of the ureterocele extends beyond the bladder neck into the urethra. These may not be readily identified preoperatively (Smith and Parrott, 1994), and their complexity may create surgical challenges, particularly with endoscopic incision (see later).

An unusual but diagnostically challenging ureterocele variant is the nonobstructive ureterocele with duplication (Bauer and Retik, 1978) or “ureterocele disproportion” (Share and Lebowitz, 1989) (Fig. 134-5). These are associated with a duplex kidney, but the affected upper pole is nondilated and typically dysplastic to such a degree that it is not readily detected on most imaging and the affected ureter is not dilated beyond the bladder. A typical appearing ureterocele is seen in the bladder, but the ipsilateral kidney appears completely normal.

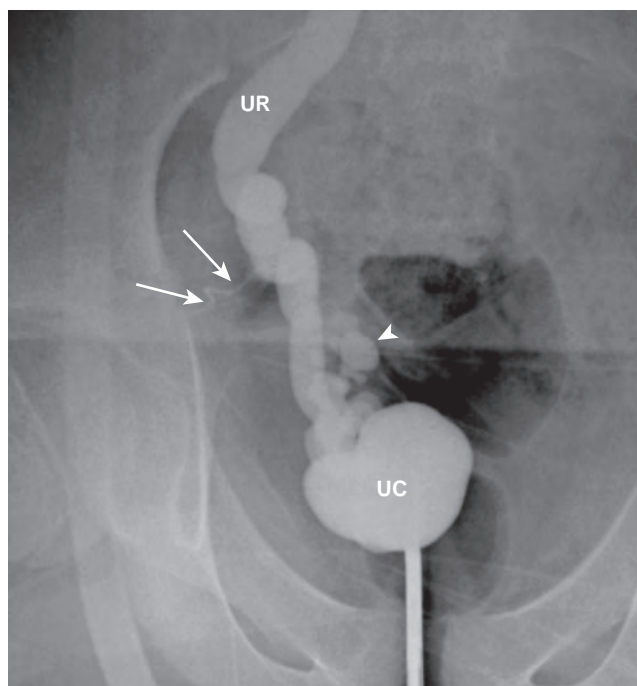


Figure 134-2. Retrograde injection study of a boy with abdominal pain and a ureterocele associated with a hypoplastic right kidney. The intravesical ureterocele (UC) is being injected and demonstrates communication with the right seminal vesicle (arrowhead) and vas deferens (arrows), with the ureter (UR) leading to the dysplastic kidney. At surgical resection, the ureter and vas joined just above the seminal vesicles.

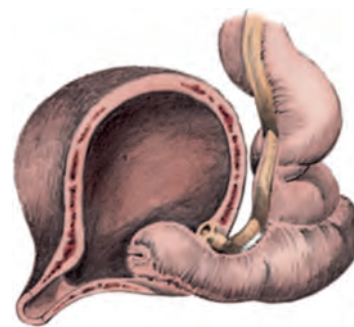


Figure 134-3. Diagram of intravesical ureter with stenotic orifice just proximal to the bladder neck.

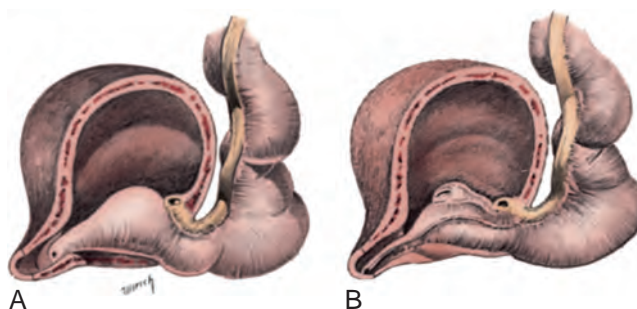


Figure 134-4. A, Sphincterostenotic ectopic ureterocele. B, Cecoureterocele lumen extends distal to the orifice as a long tongue beneath the ureteral submucosa. The orifice communicates with the lumen of the bladder and is large and incompetent.



Figure 134-5. Ureterocele disproportion demonstrated via retrograde pyelography. Note the disparity between the large ureterocele and the thin ureter and nondilated collecting system.

There is some association of ureterocele type with outcomes of various therapeutic measures, but these have not proven to be as predictable as initially reported. Churchill and colleagues proposed a classification system based on the impact of the ureterocele on the upper urinary tract, including all renal units (Churchill et al, 1992). This functional system separates those in which the upper pole only is in jeopardy, those in which an entire ipsilateral kidney is threatened, and those in which the contralateral system is also at risk because of reflux or bladder outlet obstruction. The last group comprised 26% of the reported cases.

KEY POINTS: URETEROCELE

- Ureteroceles represent a version of the ectopic ureter with a cystic dilation of the distal aspect of the ureter that is located either within the bladder or spanning the bladder neck and urethra.
- Several classification systems exist for ureteroceles, but the most useful one for clinical practice separates intravesical from extravesical ureteroceles.
- In a cecoureterocele, the orifice of the affected ureter is within the bladder but the cavity of the ureterocele extends beyond the bladder neck into the urethra.

Embryology and Etiology

The specific mechanisms responsible for ectopic ureters and ureteroceles remain undefined, but our emerging understanding of normal and abnormal ureterotrigonal development, with new investigational tools, is likely to provide valuable insights (Mendelsohn, 2009). These molecular mechanisms will be of scientific importance, but they will also permit potential separation among variants of these conditions with therapeutic relevance, as well as ultimately permitting early detection (i.e., in utero) and intervention. The last is a distant but not implausible horizon. At present, we remain uncertain as to fundamental mechanisms yet need to

know which ureteroceles and ectopic ureters may be associated with bladder neck and trigonal maldevelopment sufficient to cause functional disturbances such as incontinence. These children will require more aggressive therapy to achieve continence. Early identification may permit earlier and more effective surgical therapies.

Clinical Relevance

Understanding the potential relationships of the abnormal ureter associated with ectopia or a ureterocele, which occurs because of aberrations in normal development of wolffian and müllerian ducts, ureteral bud, urogenital sinus, and bladder, can facilitate clinical interpretation of these conditions. Knowledge of the sites of ectopic insertion may be useful in planning imaging and surgical correction. Recognition of the possible effects of abnormal ureteral development on bladder and urethral development is essential in determining reconstructive strategies, and an awareness of the possible coexistence of ureteral and müllerian abnormalities is important.

Ureteral-Trigonal-Renal Development

The pathogenesis of ureteral ectopia with or without ureterocele results in renal maldevelopment caused by defective ureterotrigonal connections. At present, a growing number of genetic pathways have been identified that are critical in humans and rodents for establishing distal ureter connections, and studies in mouse models have led to a better understanding of the process by which proper distal ureter connections are generated.

Function of the urinary tract depends on patent ureterobladder connections and an antireflux mechanism that prevents backflow of urine to the ureter and kidneys. The antireflux valve is formed by intersecting ureteral and bladder muscle fibers, hence malpositioned ureters that do not follow a precise trajectory through the bladder wall or terminate outside the normal insertion site in the trigone can cause obstruction or vesicoureteral reflux (VUR). Renal defects associated with ureteral ectopia, ureterocele, or VUR can be caused by obstruction that damages renal cell types (see Chapter 132) or mutations in genes that are required independently for normal kidney development and ureter insertion, including *Ret*, *Fgfr2*, *Gata3* and a number of others (Chia et al, 2011; Liu et al, 2011; Hoshi et al, 2012).

Classic understanding of ureterotrigonal development suggests that the trigone originates from the mesodermal common nephric duct (CND), as do the mesonephric duct and ureter, and is distinct from the urogenital sinus, which is of endodermal origin. According to this model, proper ureterobladder connections depend on expansion of the CND and its subsequent insertion into the urogenital sinus epithelium (UGE), both separating the CND and ureter and producing a mature insertion site in the bladder (Wesson, 1920; Tanagho and Pugh, 1963; Woodburne, 1965). However, the observation that the CND degenerates during ureter maturation suggests that it may not give rise to the trigone as previously thought (Batourina et al, 2002, 2005; Viana et al, 2007; Chi et al, 2009; Mendelsohn, 2009; Uetani et al, 2009; Tanaka et al, 2010). Consistent with this, lineage studies and tissue recombination studies in mice suggest that the trigone is formed by interconnections between the detrusor and fibers surrounding the intravesical ureter (Viana et al, 2007).

With ureteral bud formation, the mesonephric duct becomes the CND caudally towards the insertion into the urogenital sinus. Studies in animal models indicate that establishing a mature ureterobladder connection depends on a process of ureteral maturation, a complex series of events driven by cellular rearrangements and apoptosis of the CND. Ureteral maturation begins when the most distal portion of the CND begins to merge with the urogenital sinus and undergoes apoptosis, which occurs over the course of several days. This first round of apoptosis results in removal of the most distal portion of the CND and formation of a loop composed of the remaining CND and distal ureter. The loop makes contact with the dorsal UGE, an event that sets the position of the future

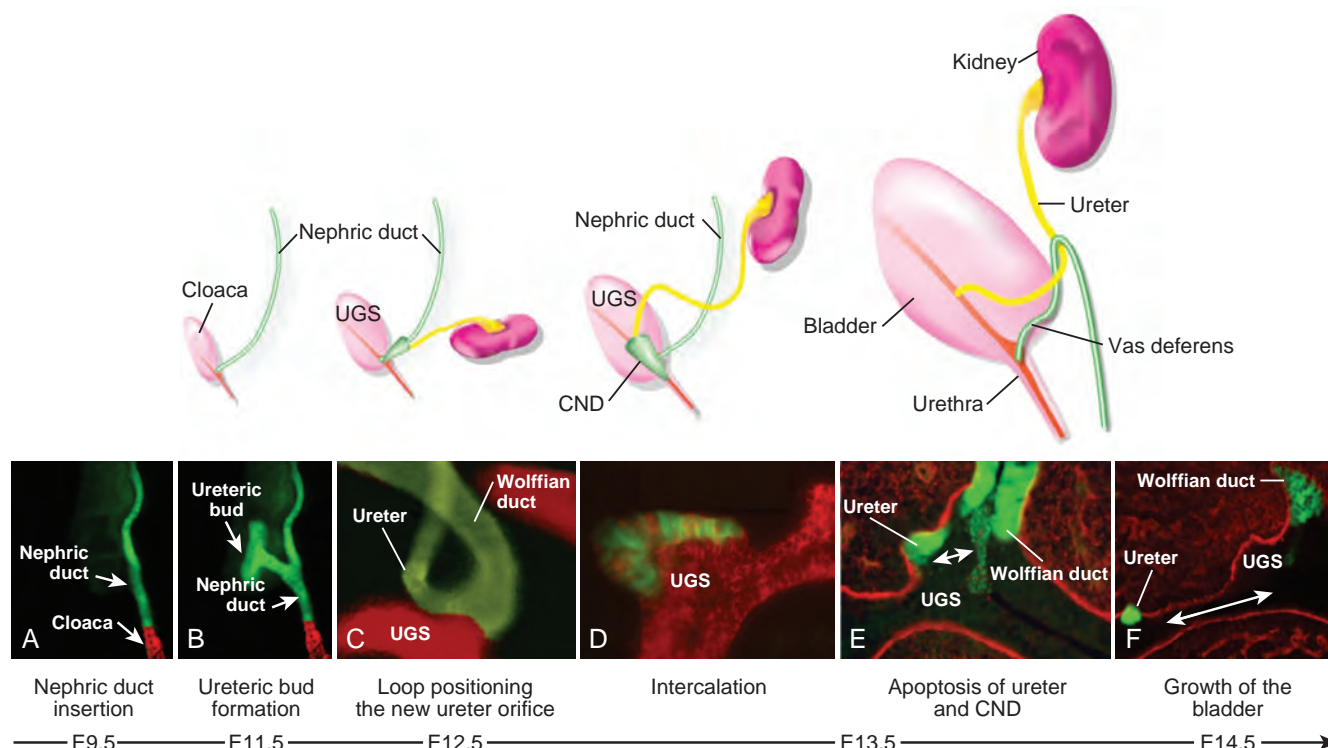


Figure 134-6. *Top*, Schematic drawing showing a revised model of ureter maturation. *Bottom*, Images of *Hoxb7-GFP* expressing embryos showing different stages of urinary tract morphogenesis. In the lower urinary tract, the *Hoxb7-GFP* transgene is localized in the ureter, mesonephric (wolffian) duct, and common nephric duct (CND) (Srinivas et al, 1999). **A**, Whole mount urogenital tract from an E9 *Hoxb7-GFP* embryo counterstained with E-cadherin to reveal the mesonephric duct (green) inserting into the primitive bladder (red). **B**, A whole mount urogenital tract from an E11 *Hoxb7-GFP* embryo counterstained with E-cadherin (red). The CND lies below the primary ureteric bud branch, which at this stage has invaded the kidney blastema (not visible). **C**, Whole mount urogenital tract from an E12 *Hoxb7-GFP* embryo (green) stained with cytokeratin (red). Apoptosis of the CND has brought the caudal-most ureter into close contact with the bladder, where it aligns, setting the position of the future ureteral orifice. **D**, A vibratome section from an E13 *Hoxb7-GFP* urogenital tract stained with E-cadherin (red). Cells from the most distal ureter epithelium have now merged with the bladder epithelium, where they will undergo apoptosis, creating a new ureteral bud connection. **E**, A whole mount urogenital tract from an E13.5 *Hoxb7-GFP* embryo stained with laminin to reveal the basement membrane of the bladder epithelium (red). The ureter orifice is now inserted in the epithelium and is separated from the mesonephric duct by a short distance. **F**, Expansion and elongation of the bladder has moved the ureter orifice farther away from the mesonephric (wolffian) duct. UGS, urogenital sinus.

ureter orifice. Merger of the loop with the UGE and removal of the remaining CND by apoptosis generates a patent connection between the ureter and bladder, which at this stage is at the level of the verumontanum (Fig. 134-6). Subsequent growth and expansion of the bladder and urethra further separate the mesonephric duct and distal ureter. The ureter is initially occluded by cells that undergo apoptosis shortly before birth (Mendelsohn, 2009). These cells may correspond to the Chwalle membrane, which in humans is thought to be important for generating a patent ureterobladder connection, which if abnormal, can result in ureterocele (Chwalle, 1927).

Studies in mouse models suggest that ectopic ureters can arise from defects that cause misalignment of the loop with the dorsal side of the urogenital sinus, altering the position where the ureteral orifice inserts. Potential events include delayed or defective nephric duct insertion into the cloaca, sprouting of the primary ureteric bud from an abnormally high or low position on the nephric duct relative to the urogenital sinus, and defective ureteral maturation. A ureter that inserts in the proper site but is obstructed may reflect failure in regression of the Chwalle membrane. The revised model of ureteral maturation provides possible mechanisms for ureteral ectopia and ureterocele formation. Abnormal apoptosis may maintain the connection between the ureter and the wolffian duct and

prevent incorporation of the ureter and the urogenital sinus. This defect would produce a ureter attached to the wolffian remnants in girls (Gartner duct) or to the vas deferens or ejaculatory system in boys. Alternately, partial CND regression may result in ureters that join the bladder at an abnormally posterior site, close to or in the urethra.

In duplicated systems, upper pole kidneys derived from ureteric bud branches that formed at an abnormally high position on the mesonephric duct tend to be obstructed, whereas distal ureteral obstruction is rare in lower-pole renal moieties that arise from ureteric bud branches that sprout from the mesonephric duct at the appropriate site. This upper pole defect may reflect incomplete CND remodeling, a suggestion supported by observations from mouse models with duplicated systems. In this case, CNDs associated with ureters that form at an abnormally anterior site on the mesonephric duct persist, resulting in obstruction, whereas CNDs associated with ureters that form at the proper site, close to the urogenital sinus, undergo regression. These observations together suggest that signals from the urogenital sinus may normally regulate ureteral maturation by controlling CND remodeling.

These observations suggest that the final position of the ureter depends in large part on the extent of CND remodeling, which can

be disrupted by defects in cell movements or apoptosis. If there is no remodeling, the ureter will remain joined to the sex duct (ectopic vas deferens or Gartner duct in girls). Partial CND remodeling could produce a different defect. In this case, distal ureters will be joined to the urogenital sinus at a site that is closer to the nephric duct, which joins at the level of the verumontanum or sinus ridge. Very similar defects are observed in mouse models, including mutants lacking *Ret*. Mutations in *RET* in humans cause Hirschsprung disease, renal abnormalities, VUR, and hydronephrosis. Studies in *Ret*-mutant mice indicate that *Ret* controls ureteric bud formation as well as mesonephric duct insertion and CND regression, suggesting that conserved genetic pathways may be required at independent sites and at different stages for generating a normal urinary system.

Obstruction is unlikely to be a major, and certainly not the only, factor producing ureteral dilation as seen with ureteroceles. Ureteroceles with large orifices and no apparent obstruction are well recognized clinically. Ectopic ureters with insertion into the bladder neck are dilated, but do not have the disproportionate distal dilation characteristic of the ureterocele. Obstruction plays some role in ureterocele pathophysiology, however, as is evident in the frequent occurrence of decompression with ureterocele puncture. Whether this is determined by the degree of muscularization of the ureterocele is undefined. Recent studies support the idea that degeneration of the Chwalle membrane (Chwalle, 1927) is important for generating a patent connection between the ureter orifice and the bladder (Mendelsohn, 2009). These studies suggest that the Chwalle membrane, which has been thought to form from the urogenital sinus, may in fact be derived from luminal cells in the ureter that undergo apoptosis at a relatively late stage, before the onset of renal function, which may be important for generating a patent connection between the distal ureter and bladder.

KEY POINTS: EMBRYOLOGY

- In contrast to the classic model in which the CND forms the trigone, the revised model includes regression of the CND in the normal animal through apoptosis and formation of the trigone from the endoderm, like the bladder.
- The classic explanation of ureterocele formation is that of Chwalle, who postulated that distal ureteral expansion is produced by failure of rupture of a distal membrane at the ureteral orifice (Chwalle membrane).
- Because the ureteral bud derives from the wolffian duct, the ectopic ureter will not insert directly into the müllerian structures (vagina, cervix, uterus), but will be associated with them through the remnant of the wolffian duct, the Gartner duct, that runs alongside the mature müllerian structures.
- The Weigert-Meyer rule describes the inverse relationship of the duplex ureteral orifices, in which the ectopic ureter or ureterocele associated with the upper pole is caudal to the lower pole ureteral orifice.

CLINICAL PRESENTATION

Imaging

Prenatal Detection

The majority of ureteroceles and ectopic ureters are detected through prenatal ultrasound imaging, even if the specific diagnosis is not made. The abnormality prompts postnatal imaging, which will invariably determine the specific cause, lead to further studies, and permit an adequate characterization of the condition. The prenatal imaging patterns are identical to those seen postnatally on ultrasound imaging, yet may be misinterpreted. While these are described in the chapter on prenatal diagnosis (Chapter 124), several elements should be emphasized.

The identification of a duplex system prenatally may be difficult except when one of the moieties is dilated. The report of an upper pole “cyst” in a fetus should be interpreted as being upper pole

hydronephrosis until proven otherwise. Minor degrees of hydronephrosis may not be as readily identified, although changes over time may prompt recognition. The expected ureteral dilation may not be readily detected but can be traced to the bladder. The bladder must be inspected in all such cases to identify a ureterocele, but it may be required to await bladder filling to make this observation. A large ureterocele can fill a bladder and mask its presence.

The character of the renal parenchyma of the upper pole should be noted, both thickness and echogenicity. The findings should never be used alone to determine salvageability of the upper pole but may be useful in making clinical decisions.

The ectopic ureter can appear identical to a ureterocele except at the bladder level, with a dilated upper pole, tortuous ureter, but no intravesical component. On occasion, a large ectopic ureter may impinge on the bladder and appear as an intravesical structure, termed a *pseudoureterocele* (Sumfest et al, 1995). These patterns are identical to the postnatal appearance, but their recognition does require an experienced maternal-fetal ultrasonographer.

With a tentative diagnosis of a ureterocele or ectopic ureter, careful evaluation of the other renal units and bladder should be made. Ipsilateral lower pole or contralateral dilation suggests reflux or less commonly obstruction from the ureterocele or the dilated ectopic ureter. Bladder outlet obstruction by a ureterocele can occur and manifest as hydronephrosis of all renal units (Ogunyemi, 2001; Quintero et al, 2001; Godinho et al, 2013). Although it is very unusual to identify bladder obstruction from a ureterocele to the extent to produce oligohydramnios, this can occur. Contralateral renal dysplasia may be evident and associated with reduced amniotic fluid. The need for prenatal intervention or early delivery is exceptional and unlikely to provide any significant benefit.

A single-system ureterocele or ectopic ureter will be evident with dilation of the entire kidney as well as ureter. It may be impossible to differentiate this from an obstructive megaureter or severe reflux, but this will have little immediate prenatal clinical impact.

Incidental

When significant hydronephrosis is present with either an ectopic ureter or ureterocele, an incidental diagnosis will occasionally be made. In some cases, however, this may result from a search for an explanation of general abdominal pain that was not considered to have a renal cause. It is also possible that the dilated ureter may not be recognized as such, and cases of presumed ovarian cysts have been seen that were actually markedly dilated ureters (Mason et al, 2012).

Infection

Infection remains a significant reason for clinical presentation of both ectopic ureters and ureteroceles, which may occur at any age and have a highly variable pattern.

Clinical Patterns: Highly Variable

Although there is great variability in the presentation of either ectopic ureter or ureterocele, there are several patterns that may be anticipated. In either case, generalized urosepsis may be the presenting clinical scenario, and a renal bladder ultrasound will usually provide the diagnosis. It has been reported that an acute ultrasound study is unnecessary if a child has a febrile urinary tract infection (UTI) and a history of a normal prenatal ultrasound examination after 30 to 32 weeks (Hoberman et al, 2003). The extreme variability of quality of prenatal imaging makes this recommendation tenuous, and it would seem prudent that an ultrasound study be obtained in all children with urosepsis. In those with a febrile UTI, there is rarely urgency if they are clinically responding. The value of early detection is the potential for early treatment, which may be a simple drainage procedure. If the child is recovering rapidly, imaging may be elective.

In the acute setting, with evidence of an ectopic ureter or ureterocele, initial clinical response will determine the timing of

intervention (discussed later). Certainly the child with sepsis who is not responding rapidly to appropriate therapy may require urgent transurethral incision (TUI) of an infected ureterocele, or percutaneous or open drainage of an ectopic ureter. Open drainage in this setting is often an end ureterostomy as described later.

Ectopic ureters will frequently manifest with a less acute pattern evidenced by ongoing low-grade fever with periodic spikes. In some cases, a negative urine culture will be present simply because the infected ectopic system is not draining into the bladder. Parents may describe a purulent discharge from the perineum ([See and Mayo, 1991](#)). This clinical pattern should prompt an ultrasound study, which will usually reveal a dilated upper pole or entire system. It is rare for the unobstructed ectopic ureter to manifest with infection, but it is associated with incontinence.

In boys, a similar generalized subacute pattern of infection may be present, but more often these boys have epididymitis on presentation. Although this may be an unusual subset of young boys with an acute scrotum, they will have a true bacterial epididymitis and may or may not have infected urine. In the setting of a suspicion for epididymitis in a young boy, it is prudent to perform a brief ultrasound examination of the upper tracts to ensure no abnormality ([Rajfer et al, 1978](#); [Umeyama et al, 1985](#); [Chu et al, 2012](#)). Older males will also present in this manner, although it is unclear why it may be so delayed. Some have had recurrent episodes of epididymitis before the underlying cause is detected.

Incontinence

Clinical Patterns

Urinary incontinence may be caused by an ectopic ureter in a girl, but not in a boy. Untreated ureteroceles are not associated with incontinence. The toilet-trained girl with verified continuous urinary leakage must be evaluated for an ectopic ureter. Imaging studies may not immediately detect this condition because the affected renal moiety may not be dilated, and the level of suspicion must be guided by a careful history and occasionally physical examination. Before toilet training it may be difficult to detect continuous incontinence, although some parents will note persistent dribbling during changing. In early training, the wetting may be falsely attributed to lack of motivation. Persistence will usually prompt evaluation, and the characteristic history can be obtained. This is usually one of persistent low-volume dampness at all time. When asked if the child can be dry for 30 to 60 minutes, the parent will usually say no. It is important to be cautious in questioning, because some parents with children who wet for other reasons may state, "She is always wet," when in fact the child can be dry for periods of time. The dampness associated with an ectopic ureter typically occurs throughout the day and does not relent. It may seem to be worse with activity in some. In rare patients it has been intermittent, perhaps caused by intermittent leakage through a membrane of Gartner duct.

In older children in whom the diagnosis has not been recognized, attribution of the symptoms may be to dysfunctional voiding, laziness, and even sexual abuse ([Lane, 1962](#); [Carrico and Lebowitz, 1998](#)). During the history taking, signs of typical voiding dysfunction such as voiding postponement, posturing, and constipation should be sought to assess likelihood of these being an explanation for the wetting.

Pain

Pain is uncommonly associated with either an ectopic ureter or a ureterocele. The exceptions are acute infection, and also episodic obstruction of the ectopic ureter or bladder pain caused by an obstructing ureterocele. Occasional cases of intermittent drainage of an ectopic ureter in older children have been experienced and are characterized by abdominal pain followed by perineal drainage of urine or purulent material. It is presumed that this reflects accumulation of urine in a system that is obstructed at the level of the orifice with subsequent drainage and relief of symptoms.



Figure 134-7. A prolapsed ureterocele presented as an interlabial mass in a 3-week-old girl.

Prolapse

Ureterocele prolapse is an unusual but distinctive presenting sign that may still confuse the clinician. These are usually smooth, congested mucosal-covered intralabial masses, and the child may be experiencing difficulty voiding. The mass protrudes from the urethra, distinct from the vagina, and is not circumferential as a urethral prolapse would be. It is not lobulated as a sarcoma botryoides would appear. An ultrasound examination of the bladder will usually confirm the diagnosis, and kidney images will further support this ([Fig. 134-7](#)).

Late Presentation

Presentation of both ectopic ureters and ureteroceles in the teen or adult has been reported, usually associated with infection or abdominal pain and rarely incontinence ([Idbohrn and Sjostedt, 1954](#); [Abrahamsson et al, 1981](#); [Amitai et al, 1992](#); [Westesson and Goldman, 2013](#)). The nonobstructing ureterocele, often associated with a single system, is well recognized in the adult, often with a stone in the small ureterocele ([Singh, 2007](#); [Mizuno et al, 2008](#)). Vaginal wall prolapse has also been associated with an ectopic ureter ([Chai et al, 2014](#)). In most cases of late presentation, upper pole nephrectomy may be the most appropriate management because there is usually little to no function associated with the affected renal moiety ([Brehmer et al, 2007](#); [Mason et al, 2012](#)).

KEY POINTS: CLINICAL PRESENTATION

- The majority of ureteroceles and ectopic ureters are detected through prenatal ultrasound imaging, even if the specific diagnosis is not made until after birth.
- Ectopic ureters will frequently manifest with a less acute pattern evidenced by ongoing low-grade fever with periodic spikes. In some cases, urine cultures will be negative because the infected ectopic system is not draining into the bladder.
- In boys, a similar subacute pattern of infection may be present, but more often these boys have epididymitis.
- Urinary incontinence may be caused by an ectopic ureter in a girl but not in a boy.
- The toilet-trained girl with verified continuous urinary leakage must be evaluated for an ectopic ureter.
- Ureterocele prolapse is an unusual but distinctive presenting sign; these are usually smooth, congested mucosa-covered intralabial masses, and the child may be experiencing difficulty voiding.

EVALUATION

Management of ectopic ureter or ureterocele is based on a thorough assessment of the affected anatomy and the functional implications of the condition. This may usually be obtained readily but in some cases will require more involved imaging such as magnetic resonance urography.

Anatomic Assessment

Physical Examination

With both ectopic ureter and ureterocele, physical findings may facilitate diagnosis. The prolapsed ureterocele is diagnostic and dramatic, but unusual. Further study of the detailed anatomy is necessary. It is unusual to be able to detect an ectopic perineal ureteral orifice in a child, but this will provide much information as to the character of the situation and best treatment (Fig. 134-8). A search for the perineal orifice in a child with continuous wetting or a

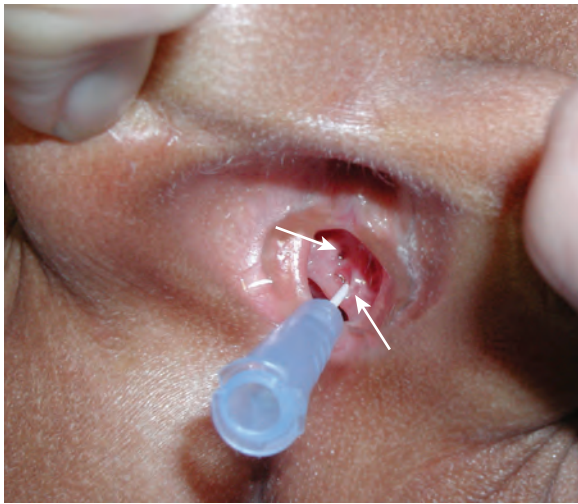


Figure 134-8. Perineal ectopic ureteral orifice (*bottom arrow*) cannulated with an angiocatheter, situated between the urethral orifice (*top arrow*) and the vagina, just to the left of midline.

known leaking ectopic ureter is worthwhile. Rarely, the dilated Gartner duct cyst may be detected on careful perineal examination (Fig. 134-9). These orifices or cystic structures may then be imaged by injection of contrast.

The dilated upper pole of either an ectopic ureter or ureterocele may be palpable in the relaxed infant, but this is difficult in the older child.

Ultrasound

The ultrasound image will usually provide the anatomic diagnosis and permit inference of functional assessment. **The typical findings are as with the prenatal imaging of a dilated upper pole with ureteral dilation or a dilated single system.** The character of the renal parenchyma will be more readily seen postnatally and if it appears healthy, the true need for functional upper tract imaging can be questioned. Depending on the chosen treatment algorithm, it may be argued that this is unnecessary, as it will not change treatment. The difference between functioning upper poles and those with little to no function is usually apparent (Figs. 134-10 and 134-11).

There are no characteristics that permit differentiation between a dilated ectopic ureter and ureterocele above the bladder. **The bladder images therefore become critically important because management is very different.**

Bladder views should be diagnostic to differentiate ureterocele from ectopic ureter by revealing a thin-walled, cystic dilation within the bladder and not extending beyond its walls (Fig. 134-12). The laterality of the ureterocele is usually apparent but may appear midline if large. A lobulated ureterocele may appear as two structures, but careful examination should show communication. It is difficult to visualize extension of a cecoureterocele into the bladder neck, so nonvisualization is not diagnostic.

Several ultrasound patterns may produce confusion in diagnosis. A large ureterocele may completely fill a bladder with no urine in the bladder itself. A full bladder with an effaced ureterocele may be mistakenly considered an ectopic ureter. Observation of the bladder over time will usually avoid these errors. A very dilated ectopic ureter may produce an impression on the bladder and appear as a ureterocele, as noted in fetal diagnosis, but the wall will be bilaminar and much thicker than typically seen with a ureterocele (Fig. 134-13). Furthermore, the lumen of the ectopic ureter will extend well outside the bladder walls.

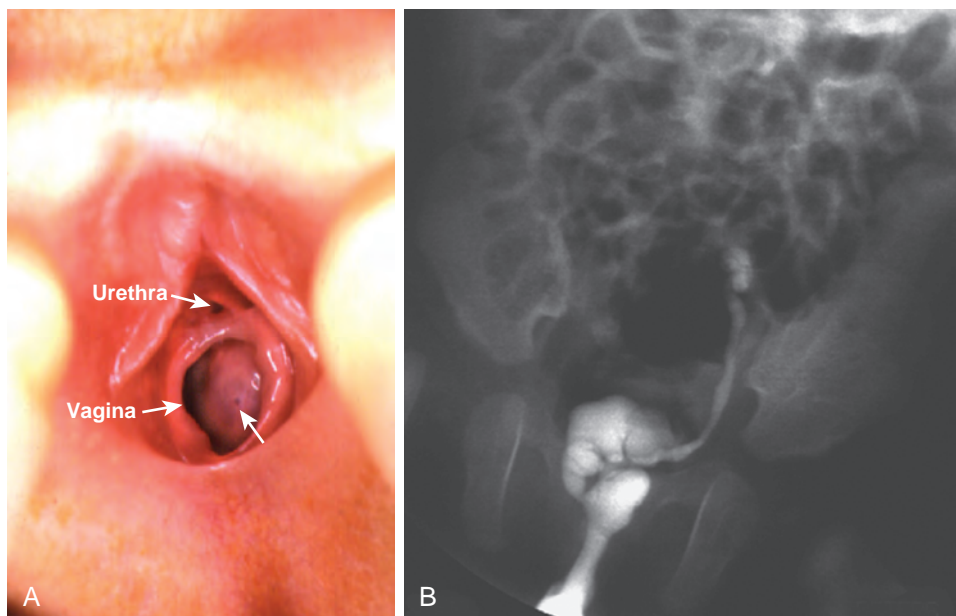


Figure 134-9. A, Gartner duct cyst (*bottom right arrow*) in newborn with a left multicystic dysplastic kidney. B, Injection of the cyst communicated with the ureter and dysplastic kidney.

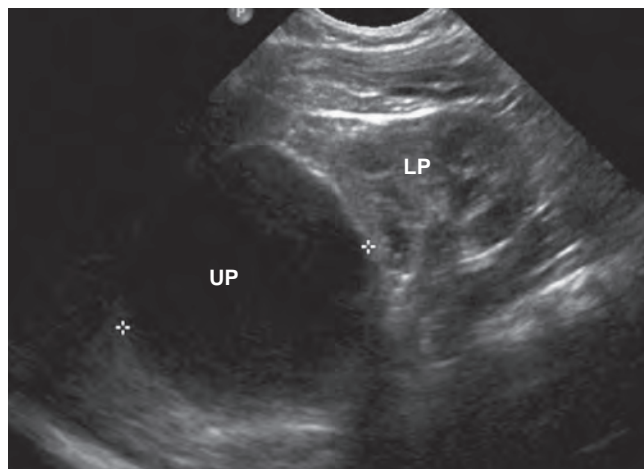


Figure 134-10. Ultrasound image of dilated upper pole (UP) associated with a ureterocele, demonstrating limited renal parenchyma (same patient as in Fig. 134-34). LP, lower pole.

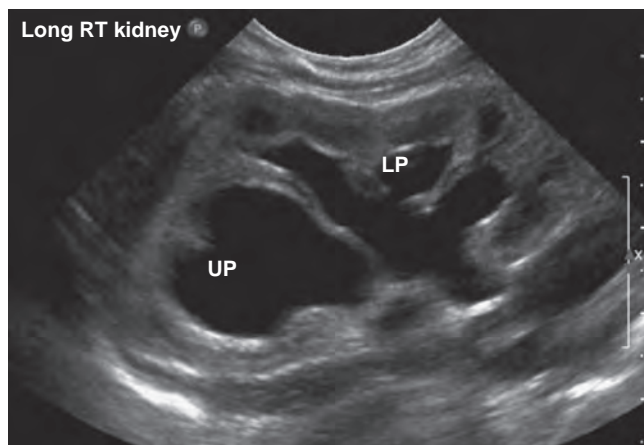


Figure 134-11. Ultrasound demonstrating dilated upper pole (UP) and lower pole (LP) associated with a ureterocele. The upper pole has evident renal parenchyma. The lower pole is dilated because of compression of the dilated upper pole ureter on the lower pole system, creating a partial obstruction.



Figure 134-12. Ultrasound image of an intravesical ureterocele at the bladder level.

Magnetic Resonance Imaging

Magnetic resonance urography can provide the most detailed images of an affected urinary tract, as a whole with functional information, yet is rarely useful to provide data that may be obtained with less expensive methods not requiring sedation. Eventually, magnetic resonance imaging (MRI) is likely to become the modality of choice, however. At present its value rests with patients in whom other imaging cannot define complex anatomy. This may occur with massive dilation in which the existence of duplication may be uncertain, or in which anatomic relationships are significantly distorted (Fig. 134-14). If this type of anatomic delineation is needed, MRI offers the addition of functional information that is an equally important aspect of evaluation. The sensitivity of MRI may also be useful in detecting the occult duplication with an ectopic ureter (Fig. 134-15).

Functional Assessment

Functional urinary assessment in association with an ectopic ureter or ureterocele is the foundation for both initial management and postoperative care. Both renal and bladder function are affected by the developmental abnormalities of ureteral formation and may ultimately require complex surgical interventions.

Renal Function

Nuclear Imaging. Radionuclide renal imaging remains the gold standard for renal functional assessment, and this is usually best afforded by dimercaptosuccinic acid (DMSA) imaging. (Fig. 134-16) The function of the affected upper pole is the principal focus, but the health of the other renal moieties must be determined as well, particularly if there is lower pole reflux or hydronephrosis of any unit. Although there have been some attempts to define what the “normal” function of an upper pole associated with an ectopic ureter or ureterocele should be, there are no criteria to define this. The clinical impact comes with the decision to preserve the upper tract or not, yet there are no objective parameters to determine what level of functional contribution should be preserved. The functional assessment therefore offers the dichotomy of some function versus no function, and this may or may not determine clinical management (see later). In general, this is clear, but there will always be ambiguous cases. Preoperative assessment is further confused by the lack of ability to predict the effect of decompression.

The assessment of drainage function for ureteroceles in which an observational approach may be considered is best accomplished with a diuretic renal scan (Han et al, 2005), which would then replace the DMSA scan. This provides both functional and drainage measurements. This has been shown to be of some clinical value in ureteroceles in which drainage is adequate, and ultimate resolution of the hydronephrosis has been reported (Han et al, 2005). A dilated ectopic ureter is only rarely suitable for observational management, so the value of an assessment of obstruction is limited.

Intravenous Pyelogram. In unusual situations the intravenous pyelogram (IVP) may offer adequate functional information with anatomic delineation without the complexities of an MRI. Functional assessment is only qualitative, however, and the IVP is a less useful baseline study except when the anatomy is uncertain or there is uncertainty about an ectopic ureter with no dilation in the setting of incontinence (Fig. 134-17).

Bladder Function

Although the bladder is not the principal focus of clinical attention in the evaluation of the ectopic ureter or ureterocele, the potential for impaired bladder function cannot be ignored. This may be caused by bladder outlet obstruction from a ureterocele, or impaired continence resulting from inadequate bladder neck function with an ectopic ureter or ureterocele. In the extreme case of bilateral single-system ectopic ureters, bladder development may be severely impaired because of the absence of fetal bladder filling.

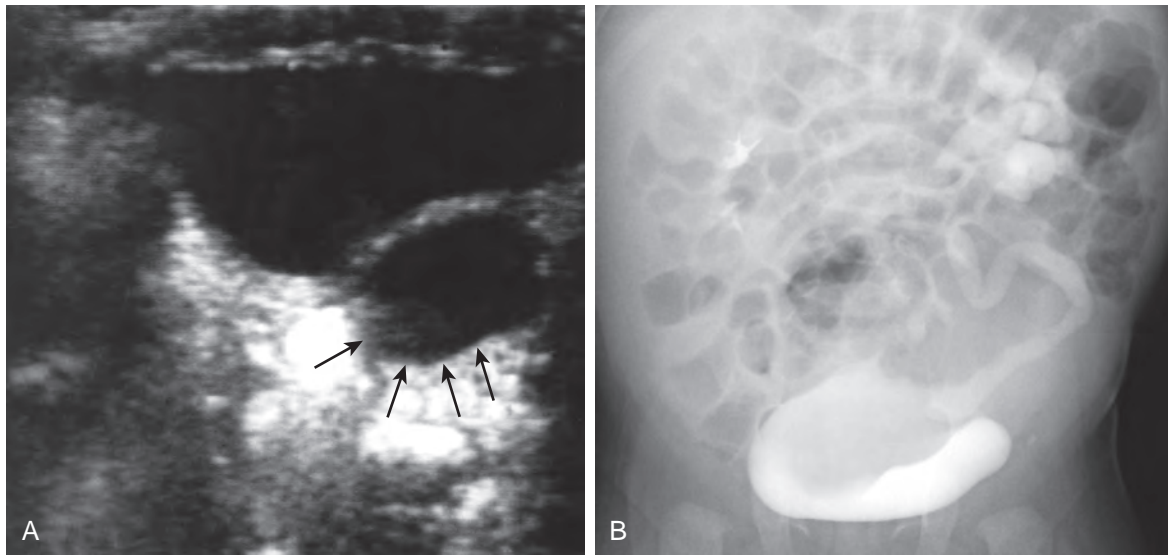


Figure 134-13. A, Ultrasound image of bladder in a child with an ectopic ureter extending into the bladder. The wall of the ureter is thicker than a ureterocele, and the lumen of the ureter extends well outside the bladder lumen, indicating that this is an ectopic ureter rather than a ureterocele. B, Voiding cystourethrogram of a large ectopic ureter pushing inward on the back of the bladder and appearing as a filling defect in the bladder (pseudoureterocele). (B, Courtesy Dr. Jeanne Chow, Assistant Professor of Radiology, Harvard Medical School and Children's Hospital Boston.)

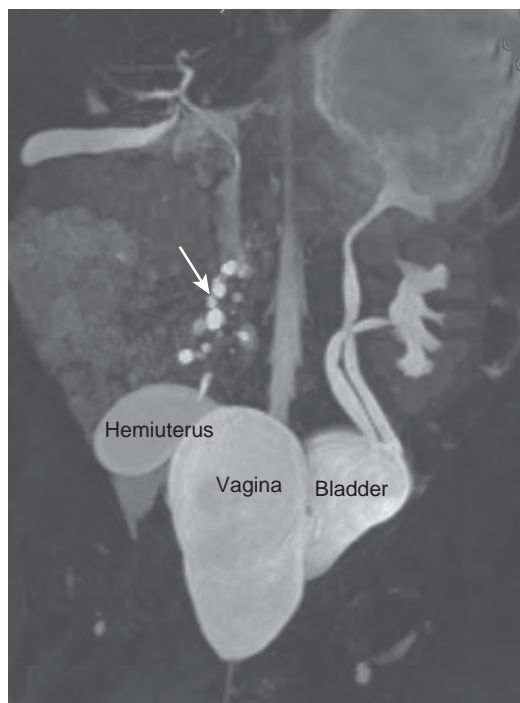


Figure 134-14. Use of magnetic resonance imaging to define the complex anatomy of a child with an ectopic ureter associated with a right dysplastic, cystic kidney (arrow) draining into an obstructed hemivagina and producing urinary dilation of the right hemiuterus. Initial therapy constituted creating a distal window between the two vaginae. Subsequently she underwent right nephrectomy.

Ultrasound Imaging Interpretation

A simple bladder ultrasound image may be very useful in completing the functional evaluation of these patients. Perhaps requiring some patience, waiting for bladder filling and emptying will yield information on bladder capacity emptying efficiency and bladder



Figure 134-15. Magnetic resonance urography demonstrating the presence of an occult upper pole associated with an ectopic ureter producing incontinence. The left upper pole ureter is marked by the arrow at the level of the lower pole pelvis.

wall thickness (indicative of possible outlet obstruction). The character, location, and size of the ureterocele can usually be assessed as well (see Fig. 134-12). In some cases, the ectopic nature of a dilated ureter may be identified ultrasonographically.

Voiding Cystourethrogram

The voiding cystourethrogram (VCUG) provides the most definitive evaluation of the bladder and distal ureters, as well as the urethra in ureteroceles and ectopic ureters, and is an obligatory imaging test (Fig. 134-18). This should almost always be obtained before any intervention to define the baseline situation. The unusual situation in which a VCUG may not be obtained would be if decompression of a ureterocele producing bladder outlet obstruction or severe bilateral upper tract obstruction in an infant is urgently indicated. It is unlikely that the findings on VCUG would alter treatment, which would nearly always be transurethral puncture.

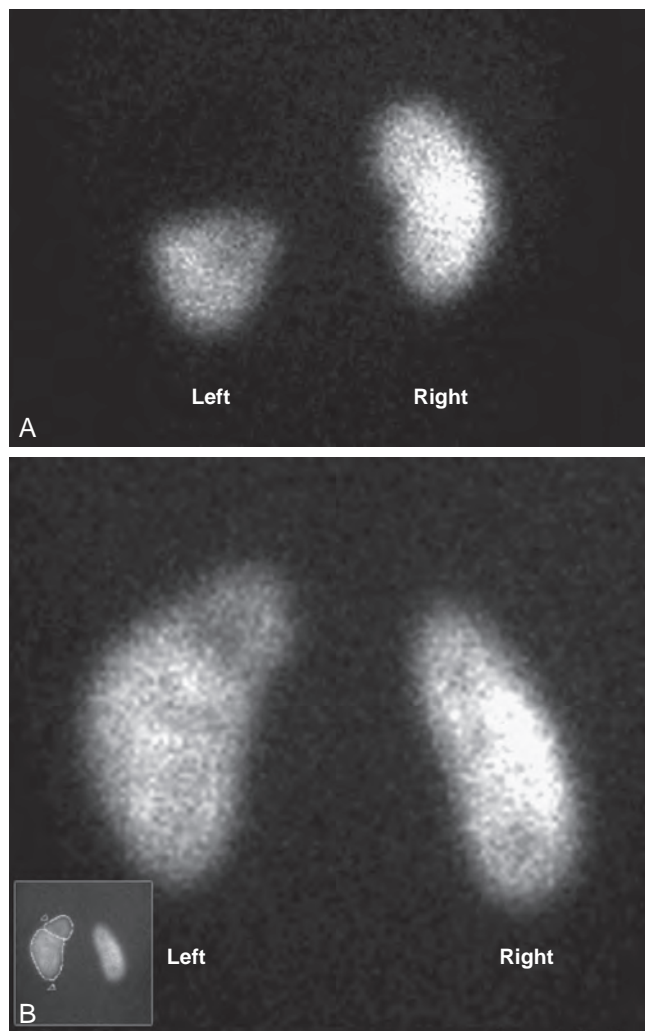


Figure 134-16. A, Dimercaptosuccinic acid renal scan in a child with a left ureterocele demonstrating no function in the affected upper pole. B, Dimercaptosuccinic acid renal scan in a child with a ureterocele with evidence of upper pole function after transurethral incision to decompress the ureterocele. The upper pole was separately assessed as contributing approximately 18% of total renal function.

Reflux

The presence of reflux may determine initial treatment for some practitioners and is an important parameter in clinical management after initial decompression of the ureterocele. In the setting of an ectopic ureter, ipsilateral lower pole reflux is unlikely to resolve spontaneously and will determine definitive treatment options.

After incision of a ureterocele, the presence of reflux either ipsilaterally or contralaterally will be critical in therapeutic decision making.

Ureterocele and Bladder Outlet

The appearance of the bladder base with filling and voiding demonstrated on VCUG will also be useful in therapeutic decisions, because significant eversion indicates a weak trigonal floor that may be more likely to require surgical repair. Prolapse of a ureterocele into the urethra or demonstration of a cecoureterocele is an important factor in planning and performing a TUI and may be more predictive of the subsequent need for secondary surgery. The usual descriptive terms in the context of a ureterocele include *prolapse*, which is movement of the ureterocele into the urethra, *eversion*, or *diverticulum-like protrusion* of the bladder base and trigone



Figure 134-17. Intravenous pyelogram image of a 10-year-old child with lifelong wetting and evidence of ureteral duplication (*black arrow—upper pole*) with no hydronephrosis. The distal ureter (*white arrow*) can be seen passing by the bladder and bladder neck and inserting into the urethra near the perineum.



Figure 134-18. Voiding cystourethrogram image of child with a ureterocele appearing as a filling defect within the bladder and massive ipsilateral lower pole reflux.

with filling and voiding (Fig. 134-19), and *intussusception*, or protrusion of the ureterocele back into its ureter (Fig. 134-20).

Although it is difficult to predict continence at initial presentation, the ureterocele or ectopic ureter associated with a patulous bladder neck may be complicated by later urinary incontinence.

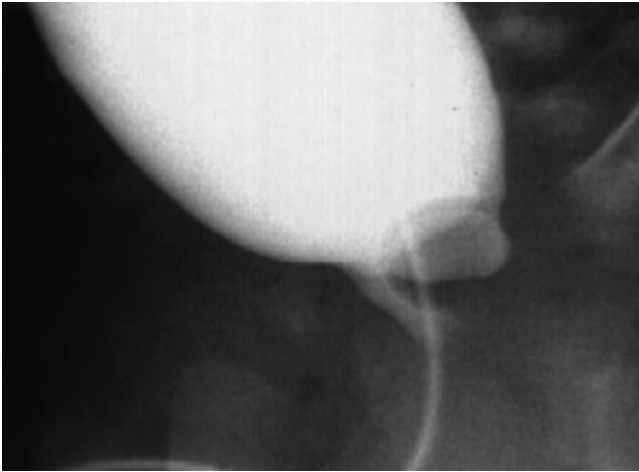


Figure 134-19. Voiding cystourethrogram of child with ureterocele and evidence of prolapse of the ureterocele into the bladder neck with voiding. This is distinct from a cecoureterocele, in which the ureterocele is part of the urethra. This pattern of prolapse can cause bladder outlet obstruction.

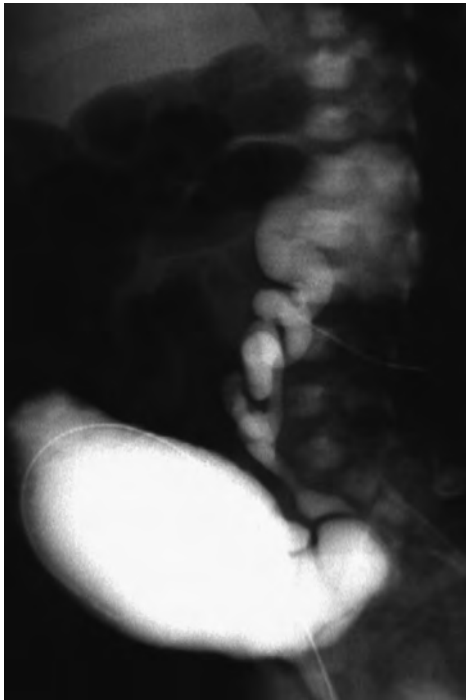


Figure 134-20. Voiding cystourethrogram in a child with a ureterocele and evidence of ureterocele eversion with voiding. The apparent diverticulum is the ureterocele extending outside the bladder wall with increased intravesical pressure. This pattern may be seen with the ureterocele everting or intussuscepting into its dilated ureter. There is lower pole reflux as well.

Cecoureteroceles are of particular risk, but we have also observed bladder neck ectopic ureters with wide-open bladder necks and later incontinence after resection of the distal ectopic ureter and external bladder neck reinforcement (Fig. 134-21). These patients may benefit from more aggressive bladder neck tightening at the time of definitive resection of the ureterocele or ectopic ureter; however, this entails some risk of disturbing what may be normal bladder neck function. Video-urodynamic evaluation may be helpful in such patients.

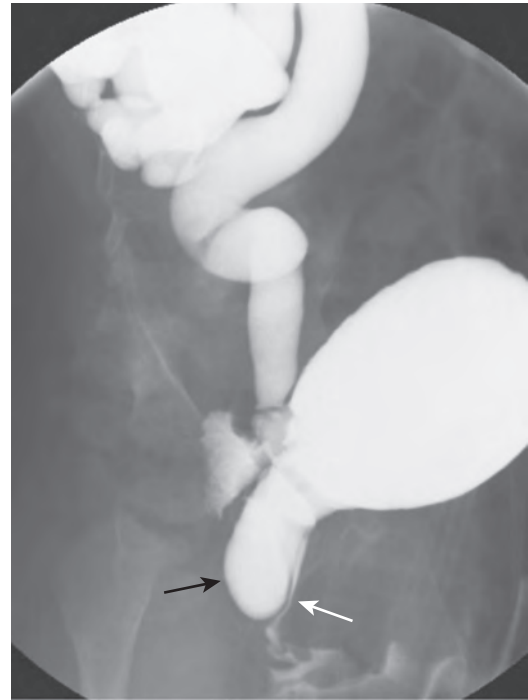


Figure 134-21. Voiding cystourethrogram image of a cecoureterocele where the ureterocele (black arrow) is attached to the urethra (white arrow) and the lumen extends into the urethra. These are the most challenging ureteroceles owing to the involvement of the bladder neck and urethra.

Endoscopic Evaluation

The final element of evaluation of a ureterocele or ectopic ureter can be endoscopic. Although this is not always essential, most cases of both ureterocele and ectopic ureter will come to operative intervention, and concurrent endoscopic evaluation is important if not essential. Certainly when endoscopic incision is to be performed, this is a critical element and should be performed thoroughly before incision to permit selection of the most effective site.

Endoscopy should take note of the character of the urethra, bladder neck, and trigone relative to the ureterocele or ectopic ureter. The location of the other ureteral orifices should be documented. The orifice of the affected ureter should be sought but may not be identified. The urethra is examined carefully for the orifice if not seen in the bladder. The appearance of the ureterocele will vary with bladder filling, and it is best to start with little filling and slowly increase bladder volume (Fig. 134-22). The ureterocele will be seen to slowly flatten. Its true limits are best appreciated with limited bladder filling; this will expose the lowest portion, which is probably the best site for incision. Extension of the ureterocele into the urethra, indicative of a cecoureterocele, may be detected, and this would indicate the need to make sure this section does not cause obstruction with incision. Retrograde contrast injection can confirm the presence of ureterocele disproportion, as there will be only a narrow proximal ureter and no filling of an upper pole segment (see Fig. 134-5). Unusual connections with the genital ducts may also be demonstrated as in the example of a boy with a ureterocele and communication among the ureter, vas deferens, and seminal vesicles (see Fig. 134-2).

An ectopic ureteral orifice may be very difficult to find endoscopically, but if in the bladder neck it is often patulous (Fig. 134-23). The anatomic connections of the ectopic ureter may be demonstrated using retrograde contrast studies. We have identified ectopic ureters that appear to have a very thin layer of tissue separating them from the urethra, looking much more like a ureterocele than an ectopic ureter (Fig. 134-24A and B). These may be associated with defects in the bladder neck and incontinence

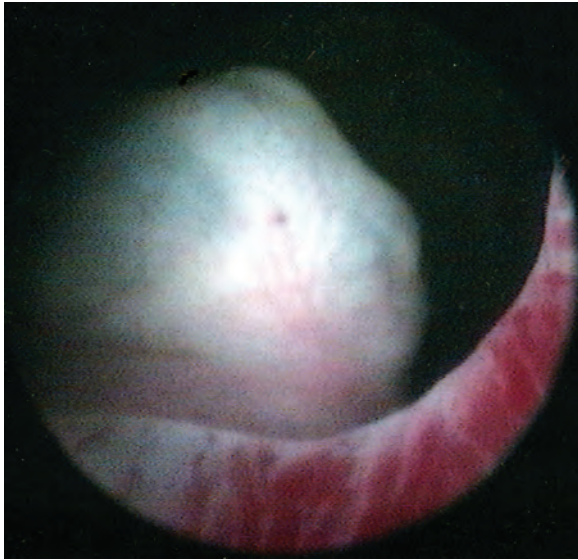


Figure 134-22. Endoscopic image of an intravesical ureterocele just inside the bladder neck.

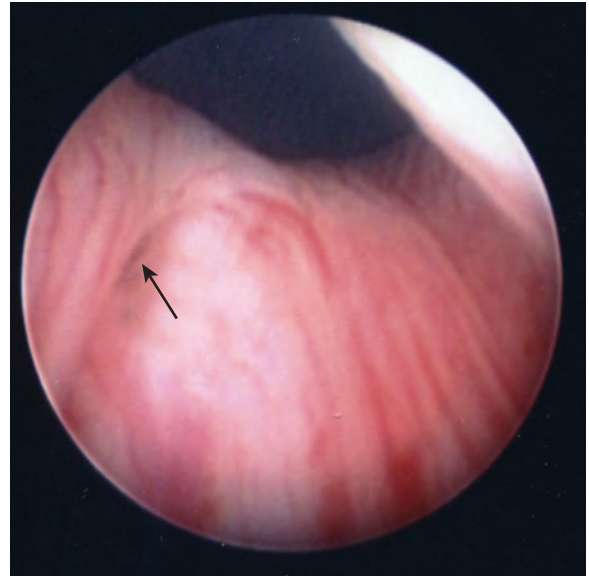


Figure 134-23. Endoscopic views of the bladder neck and the ectopic ureteral orifice marked by the *arrow*. Bladder neck ectopic ureteral orifices are often patulous but do not always reflux.

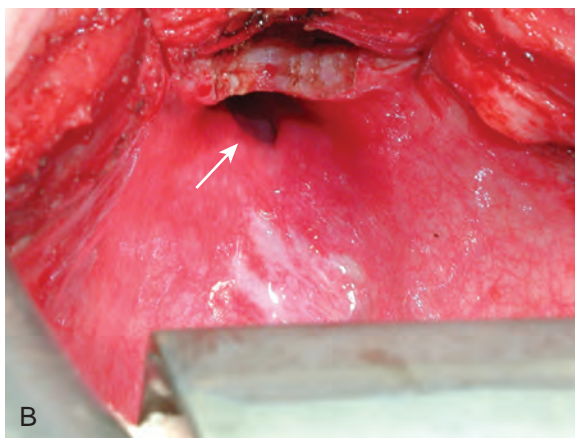
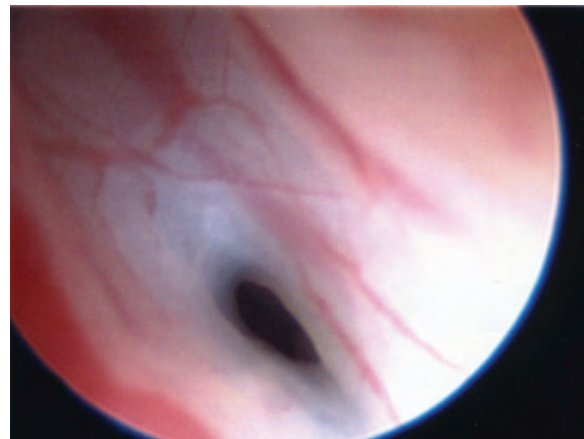
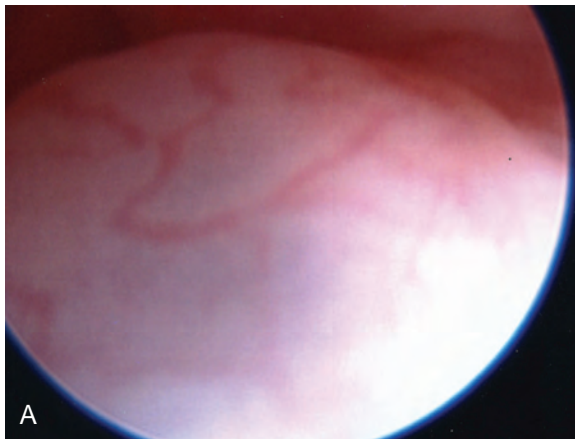


Figure 134-24. **A,** Endoscopic images of the bladder neck orifices of an ectopic ureter with an appearance similar to that of a ureterocele without the dilated intravesical portion. The membrane overlying the orifice was thin and fluttered with irrigation, just as a ureterocele would be. **B,** At open surgery, these bladder neck ectopic ureters can have the appearance of a defect in the bladder neck (*arrow*) and be associated with incontinence. It remains unclear how these ectopic ureters are related to ureteroceles.

(Fig. 134-24C). Consideration for more extensive removal of these patulous segments with reconstruction of the bladder neck may be part of the clinical decision, and their endoscopic appearance can facilitate this decision.

KEY POINTS: EVALUATION OF ECTOPIC URETERS AND URETEROCELES

- The ultrasound image will usually provide the anatomic diagnosis of an ectopic ureter or ureterocele and permit an inference of renal function.
- The typical findings are of a dilated upper pole with ureteral dilation or a dilated single system.
- The ureterocele is characterized by a thin-walled, cystic dilation within the bladder and not extending beyond its walls.
- A very dilated ectopic ureter may produce an impression on the bladder and appear as a ureterocele.
- Radionuclide renal imaging remains the gold standard for renal functional assessment, and this is usually best provided by DMSA imaging.
- The function of the affected upper pole is the principal focus, but the health of the other renal moieties must be determined as well.
- VCUG provides the most definitive evaluation of the bladder and distal ureters, as well as the urethra.
- The appearance of the bladder base with filling and voiding demonstrated on VCUG will also be useful in therapeutic decisions, as massive eversion indicates a weak trigonal floor that may be more likely to require surgical repair.
- Endoscopy should take note of the character of the urethra, bladder neck, and trigone relative to the ureterocele or ectopic ureter.

CLINICAL MANAGEMENT

Management Goals

It should once again be stressed that, before any surgical intervention for ectopic ureters or ureteroceles, the surgeon must obtain as much information as possible regarding the patient's altered anatomy and physiology. Only then can a rational treatment plan be devised. Although specific and definitive management for ectopic ureters and ureteroceles differs in some individuals, the goals of management are the same, and in many cases the approaches are identical.

The goals of therapy should be clearly defined and factored into the clinical decisions. These goals are **preservation of renal function; elimination of infection, obstruction, and reflux; and maintenance of urinary continence**. Minimizing surgical morbidity is a goal that must be included in this consideration. Although the goals of treatment are generally agreed on, the means to achieving those goals remain controversial. One area of at least partial agreement is that early institution of daily prophylactic antibiotics can reduce the risk of UTIs in those patients in whom there is significant hydronephrosis.

Relieve Obstruction, Prevent Reflux, Maintain Continence

For both ectopic ureter and ureterocele associated with a duplicated system, a primary concern is the preservation of functional renal parenchyma if at all possible. This goal is achieved by **correcting obstruction and preventing reflux with its risks of renal parenchymal damage from infection** (Churchill et al, 1992). At times it is necessary to balance one against the other, because relieving the obstruction of an ectopic ureter or ureterocele may induce reflux in either or both poles of the involved kidney. In other instances, the same action may cause existing lower pole reflux to resolve. Several means of achieving these goals are available.

For an ectopic ureter, this can mean common sheath reimplantation or ureteroureterostomy, either low or proximal near the renal pelvis. For a ureterocele, this can be accomplished by TUI as well as ureterocele excision and common sheath reimplantation or ureteroureterostomy. In both cases, acute decompression may be necessary owing to sepsis and the age of the child. For the ectopic ureter, acute decompression is best achieved with an end ureterostomy near the bladder, whereas for a ureterocele, TUI is usually effective.

The decision making for renal parenchymal preservation is largely empirical, and there are few objective criteria to indicate how much residual function is worth preserving. The presence of VUR into either of the ureters must be considered as well, and every effort should be made to correct this with the drainage procedure.

Ectopic ureters and ureteroceles are overwhelmingly dealt with postnatally. Although one might reason that a prenatal diagnosis could lead to earlier relief of obstruction and presumably a greater chance of recovery of upper pole function, the evidence in the literature seems to show that there is a limited recovery of function, even with early decompression. The observations by Tank using early endoscopic puncture demonstrated function that had not been detected before drainage (Tank, 1986). Impaired function of the upper pole occurs equally in those diagnosed prenatally and postnatally (Upadhyay et al, 2002). In most instances, the upper pole contributes little to overall renal function, but as discussed earlier, there are no criteria for what should be normal upper pole function.

KEY POINTS: CLINICAL MANAGEMENT—GOALS OF TREATMENT

- The goals of therapy are preservation of renal function; elimination of infection, obstruction, and reflux; and maintenance of urinary continence.
- Minimization of overall procedural morbidity is also a goal of treatment.
- For both ectopic ureter and ureterocele associated with a duplicated system, a primary concern is the preservation of functional renal parenchyma.
- Decision making for renal parenchymal preservation is largely empirical, and there are few objective criteria to indicate how much residual function is worth preserving.
- For an ectopic ureter, this can mean common sheath reimplantation or ureteroureterostomy, either low or proximal near the renal pelvis.
- For a ureterocele, this can be accomplished by TUI, as well as ureterocele excision and common sheath reimplantation or ureteroureterostomy.
- Observational management of ureteroceles in carefully selected patients is a reasonable option, with the potential for spontaneous decompression.

Historical Perspective

Initial management for ureterocele and ectopic ureter focused on the same goals as today, and ureterocele excision using open surgery was described in the early 1950s (Gross and Clatworthy, 1950; Campbell, 1951). Total reconstruction was presented as a viable option in the mid 1950s and again became popular in the 1970s with the reports of Hendren and Perlmuter (Hendren and Monfort, 1971; Kroovand and Perlmuter, 1979). The upper tract approach for ureteroceles, with upper pole partial nephrectomy to decompress the ureterocele, became the standard approach in the 1980s (King et al, 1983). Endoscopic incision of the ureterocele, initially as a salvage approach in the septic child, gained widespread favor in the 1990s (Tank, 1986; Rich et al, 1990), but its use is now more selectively applied based on imaging criteria. Observational management has emerged more recently, although this remains controversial.

Ectopic ureter has been usually managed surgically in nearly all patients. An early description of the clinical presentation and management of the ectopic ureter focused on removal of the associated renal unit in patients with incontinence (Aldred and Higgins, 1951). Presentation in most cases was relatively late, and residual renal function was usually limited. Excision was commonly the best option. With prenatal detection, salvage of the affected renal moiety has become a common option, usually with an upper to lower drainage procedure in duplicated systems.

Observational Management

Coplen and Austin described a subset of patients with ureteroceles and multicystic dysplastic kidneys in the associated upper tract segment (Coplen and Austin, 2004). This group had either low-grade or no reflux and no ureteral dilation. These prenatally diagnosed patients were managed nonoperatively and had a benign clinical course. Other groups have reported nonoperative management of ureteroceles meeting criteria of no obstruction of the ipsilateral lower pole or contralateral kidney and limited reflux to the lower pole (grade III or less) (Shankar et al, 2001; Direnna and Leonard, 2006), no function of the upper pole, or no obstruction on diuretic renography (Han et al, 2005). In these small cohorts, reflux (including grade IV) into the lower pole was seen to resolve in 50% to 100% without intervention. Clearly some children will do well for a period of time without intervention, and in some patients resolution of upper pole dilation and lower pole reflux has been reported. It is challenging to know how to counsel families regarding this approach, as the potential for later, unpredictable acute presentation is real. For that individual, even if with a low statistical incidence, it is very significant clinically. The long-term risk and relative balance of morbidities of this strategy and the robustness of clinical predictors have yet to be determined. Carefully considered, observational management of children with ureteroceles can be an appropriate strategy with careful selection and parental education.

Total Reconstruction

Total reconstruction of both upper and lower tracts has been advocated by some authors as being the most definitive procedure for ureteroceles (Hendren and Mitchell, 1979; Kroovand and Perlmutter, 1979). **Upper pole nephrectomy with ureterocele excision and reimplantation of the lower pole ureter is definitive but is an extensive operation performed with two incisions.** Although the reported success rates are good, it remains uncertain if this is appropriate in most children when long-term relief from obstruction and reflux may be achieved with one or at most two lesser procedures. No clear clinical situations have been reported to be such that two procedures are always required, and if TUI is the first procedure, it is not comparable to either an upper or lower tract procedure. The older child with a massive ureterocele and no function of an upper pole with significant lower pole reflux might be reasonably treated with upper pole nephrectomy and ureterocele excision and bladder reconstruction. At present, the partial nephrectomy would be reasonably performed laparoscopically with a lower Pfannenstiel incision for the bladder reconstruction and reimplantation. This is an unusual clinical scenario.

Upper Pole Partial Nephrectomy

Upper pole removal using a partial nephrectomy or heminephrectomy of a duplex system is typically the preferred treatment when there is clearly no function in the upper pole and if there is concern about how effective a drainage procedure may be because of massive dilation. There are numerous series advocating one or another approach with variable results dependent on factors such as degree of reflux, age, and underlying pathology, but there are no clear data to indicate that one approach is so definitively better as to be the universal choice.

The surgical methods for partial nephrectomy have been described and remain useful and similar whether being used with open surgery, conventional laparoscopy, or robotic laparoscopy. These apply to both ectopic ureters and ureteroceles in duplex systems.

Open Partial Nephrectomy or Heminephrectomy

Heminephrectomy is a standardized procedure with relatively little recent evolution (Mor et al, 1994), but several technical points deserve emphasis (Fig. 134-25). A flank approach for heminephrectomy usually offers better exposure to the upper pole vessels. The procedure may be performed through a dorsal lumbotomy approach, which is both effective and less morbid than a muscle-dividing flank incision. In older children this exposure can become less effective, however.

In an upper pole nephrectomy, the primary concern is to avoid damaging the viable lower pole. The kidney should be retracted gently so as not to cause any vascular injury through traction and spasm of small vessels. Transecting the upper pole ureter and placing a traction stitch on the proximal portion of this ureter affords the surgeon a good method of retraction and manipulation of the upper pole. Once at the pedicle, dissection of the ureter both below and above the vessels allows for easier, safer freeing of the ureter. The ureter is passed behind the main renal vessels. The dissection *around* the renal vessels should be done carefully to avoid damage to the lower pole. The upper pole vessels (most often two or three in number) are sequentially ligated. Demarcation of the upper pole parenchyma becomes apparent after the upper pole vessels are ligated.

During upper pole nephrectomy, atraumatic clamping of the renal pedicle can be used, enabling work in a bloodless field. Administration of an intravenous osmotic diuretic (e.g., mannitol) moments before and after clamping of the pedicle helps prevent acute tubular necrosis. Topical vasodilating agents (e.g., papaverine) should be available in case vasospasm occurs. In general, vascular control is not essential in upper pole partial nephrectomy because the polar vessels may be identified and controlled. Resection of the upper pole renal tissue can then be carried out with electrocautery or another cutting device. Stripping the capsule off the upper pole in continuity allows it to be used in the closure. Several mattress sutures incorporating a pedicle of retroperitoneal fat are used for closure.

When performing the upper pole ureterectomy, it is of utmost importance to maintain the dissection immediately on the wall of the upper pole ureter as much as possible to preserve the blood supply to the remaining lower pole ureter.

If in addition to obstruction there is concomitant reflux into the ectopic ureter, some recommend a second incision (i.e., a Gibson incision) to resect the ureter in its entirety. Care must be taken to avoid injury to the vas deferens in male patients. To prevent complications that may arise from dissection within a common sheath of two ureters (especially distally), the back wall of the upper pole ureter can be left attached to the lower pole ureter. The remainder of the upper pole ureter should be removed (Fig. 134-26). Such a maneuver prevents damage to the lower pole ureteral blood supply, which courses between both ureters. Resection is carried out to the level of the bladder, where several sutures are placed to close the upper pole ureteral hiatus.

Other surgeons are comfortable ligating the distal refluxing ureteral stump and leaving it in situ, with few subsequent problems attributed to the small volume of reflux into that stump (Cain et al, 1998; Kim et al, 2001). The refluxing, obstructed ectopic ureter raises the most concern regarding a later infection, and as much of the ureter should be removed as is possible without injury to the bladder neck.

A Penrose drain (brought through a separate stab wound or at the edge of the incision) is placed in such a fashion as to drain the renal fossa and the area of the ureteral dissection. **Postoperative evaluation is best performed with a Doppler sonogram to demonstrate normal postoperative anatomy, absence of a urinoma,**

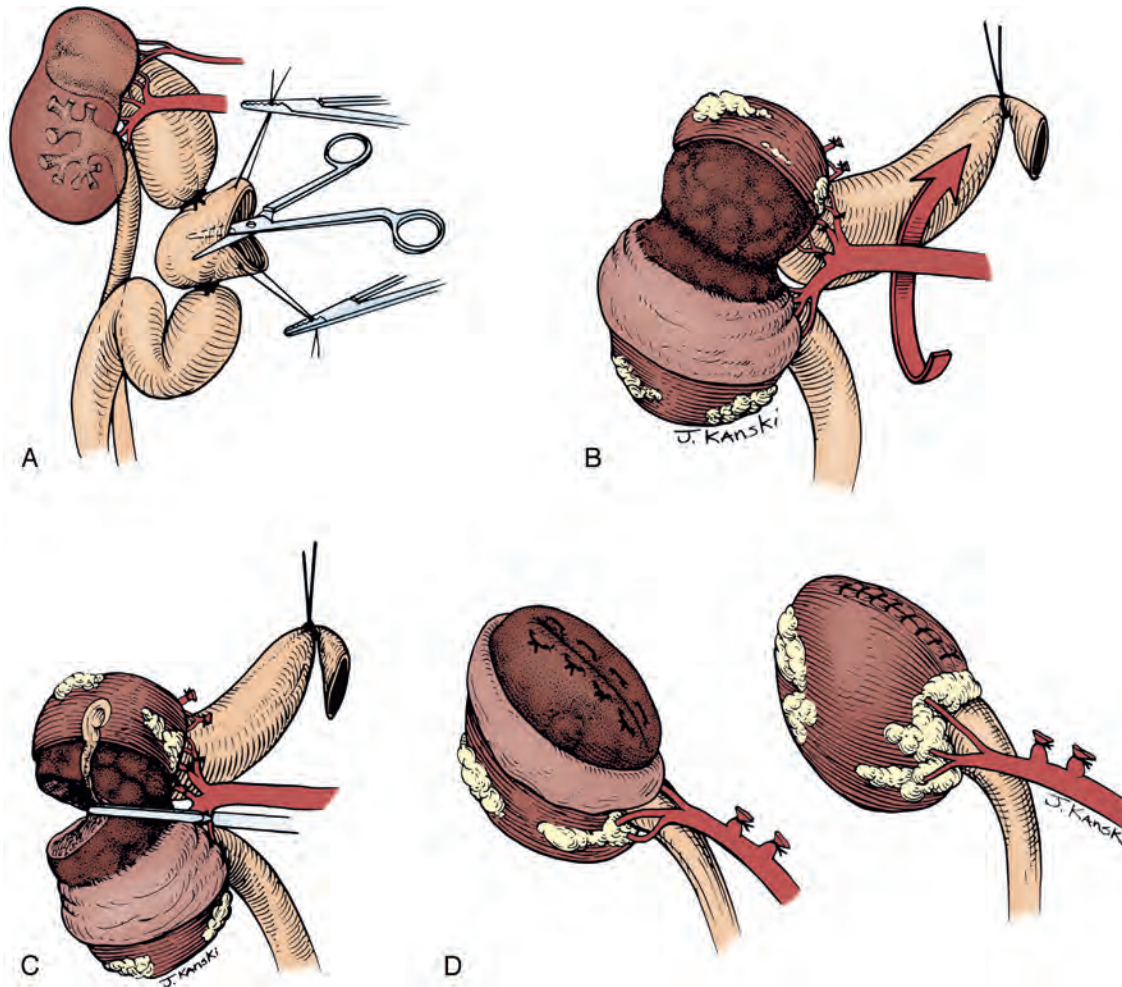


Figure 134-25. Technique of upper pole nephrectomy. **A**, The upper pole ureter is usually dilated and tortuous and can be identified readily at the lower pole of the kidney. It is separated carefully from the lower pole ureter, divided, and used to improve access to the upper pole moiety. **B**, The upper pole ureter is passed beneath the hilar renal vessels and retracted upward. Small feeding vessels to the upper pole are individually ligated and divided. Any larger vessels that may be supplying the upper pole can be temporarily clamped to determine the extent of their distribution. The capsule of the upper pole is bluntly stripped away, exposing the often coarse and cystic parenchyma of the upper pole. This can usually be distinguished from the smooth texture of the normal lower pole. Often, an indented demarcation is seen between the two poles. **C**, While traction is applied to the lower pole ureter, the upper pole is excised with the use of electrocautery. Vascular control is achieved by temporary clamping of the lower pole vessels. This may also be accomplished by gentle finger compression of the lower pole. Individual vessels are identified and ligated during this part of the procedure. **D**, The parenchyma of the lower pole is approximated at the site of removal of the upper pole with the use of broad mattress sutures. The redundant capsule is then brought over the site of repair and sewn together with a running suture.

and normal blood flow to the lower pole. Optionally, a functional study such as a nuclear renal scan may be performed if there is concern regarding viability of the lower pole.

Laparoscopic Partial Nephrectomy

Another surgical option is laparoscopic nephrectomy or heminephrectomy. This can be done by either a transabdominal or a retroperitoneal approach, and robotic assistance is now available. Laparoscopic procedures may offer reduced morbidity with less postoperative pain, earlier return of gastrointestinal function, earlier discharge home, and presumably a quicker return to work for the parents (Jordan and Winslow, 1993; Janetschek et al, 1997; El-Ghoneimi et al, 1998; Wang et al, 2004; Lee et al, 2005; Wallis et al, 2006; Lee et al, 2009; You et al, 2009). Other advantages

include enhanced visualization and increased magnification of the operative field, improved cosmesis, and avoidance of a second incision that is often needed for the distal ureterectomy of a nephroureterectomy.

Laparoscopic heminephrectomy can be performed in very small infants, and the operative time has decreased as experience and skill have increased (El-Ghoneimi et al, 2003; Wang et al, 2004; Lee et al, 2005; Sydorak and Shaul, 2005; Piaggio et al, 2006). Newer energy devices allow for resection of the upper pole in a bloodless field (LigaSure [Valleylab, Boulder, CO]; Harmonic scalpel [Ethicon EndoSurgery, Cincinnati, OH]; Thunderbeat [Olympus, Tokyo, Japan]).

Some authors believe that cystoscopic placement of a ureteral catheter allows for easier identification of the ureter at the time of laparoscopy (Yao and Poppas, 2000).

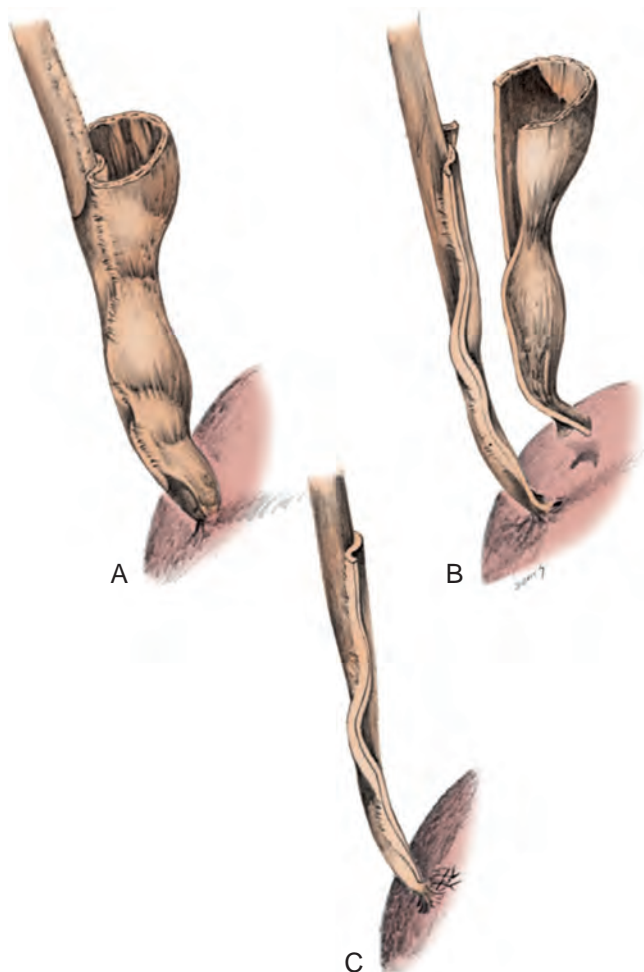


Figure 134-26. Surgical management of the refluxing ureteral stump. A, It is difficult to completely separate the distal 2 to 3 cm of the upper pole ureter from the lower pole ureter. The ectopic ureter is excised to this point. B, The outer wall of the ectopic ureter is excised to the bladder level. C, A transfixing suture obliterates its lumen, with care being taken not to injure the orthotopic ureter.

Laparoscopic heminephroureterectomy performed transperitoneally begins similarly to the open procedure in that the pathologic ureter is grasped as a handle and dissected closely to its wall to avoid compromise of the blood supply to the normal ureter. The upper pole ureter is passed behind the vessels and used to facilitate dissection of the upper pole. The polar renal vessels are then ligated with clips or divided with electrocautery; this allows for a more discernible demarcation of the affected upper pole (Fig. 134-27A). The plane between the upper pole collecting system and the upper parenchyma of the lower pole is developed bluntly to facilitate identifying and transecting the upper pole attachments to the lower pole (Fig. 134-27B). After the polar element is removed with electrocautery, one can check for collecting system leakage with intravenous injection of methylene blue (Yao and Poppas, 2000). Janetschek and colleagues place fibrin glue and hemostatic agents on the cut surface and then cover it with Gerota fascia to aid in hemostasis (Janetschek et al, 1997). We have not used these agents but have closed the defect over a pedicle of local fatty tissue (Fig. 134-27C).

In performing a partial nephrectomy, robotic-assisted laparoscopy offers advantages over standard laparoscopy (Lee et al, 2009). The magnification is augmented and the dexterity of the robotic instruments allows for greater precision when working around the renal pedicle and controlling the upper pole vessels, in addition to the visual advantages of a three-dimensional image. Patient and

port positioning are the same as for pyeloplasty. Vascular control may be by absorbable or metal clips or even with suture ties. The latter may be preferable by reducing the risk of avulsing a clip during later dissection. The defect is usually closed with a tongue of retroperitoneal fat laid into the defect, which is then closed with two or three mattress sutures of 3-0 polydioxanone suture (PDS) or Vicryl.

Laparoendoscopic single-site surgery (LESS) nephrectomy has been described for a single-system ectopic ureter. This technique represents the newest horizon for minimally invasive surgery because only one 22-mm multitrocar port site (recessed in the umbilicus) is used to perform the entire surgical procedure (Park et al, 2009).

Outcomes

Results of upper pole removal for ectopic ureters and ureteroceles are, in general, very good. The residual stump is rarely problematic in cases of an ectopic ureter. In cases of ureteroceles in which lower pole reflux is present, resolution may be expected in up to 20% (Husmann et al, 1999), and new reflux may be seen in 15% to 50% of patients in whom no reflux was present preoperatively. The overall secondary surgery rate after primary upper pole nephrectomy for ureterocele is 40% to 50% based on the literature. The difficulty in interpreting the literature rests in variable indications for secondary surgery. In some cases, reflux was simply followed and within the short follow-up did not cause any problems, whereas in others it was felt that removal of a nonfunctioning upper pole was necessary. Neither of these approaches has been validated by long-term data.

Complications. The most significant complication related to heminephrectomy is loss of lower pole function (Mandell et al, 1980; Wallis et al, 2006; You et al, 2009). Loss of function may be a long-term issue and may not be recognized immediately. Clinical signs of fever, increasing pain, and hematuria may be evident in the first week after surgery. Development of a postoperative upper pole urinoma has been reported in up to 20% of laparoscopic and robotic cases but is rarely of clinical significance (Valla et al, 2003; You et al, 2009). Urinomas have been reported mostly in series in which there is no formal closure of the polar defect. Whether these urinomas are caused by injury to the lower pole or remnant upper pole is unclear. Urinomas, if causing no symptoms and not expanding, can be observed. Other less common problems can include inferior vena cava laceration, duodenal perforation, total nephrectomy, and peritoneal tears (if the procedure is done retroperitoneally).

KEY POINTS: UPPER POLE NEPHRECTOMY

- In an upper pole nephrectomy, the primary concern is to avoid damaging the viable lower pole.
- Postoperative evaluation is best performed with a Doppler sonogram to demonstrate normal postoperative anatomy, absence of a urinoma, and normal blood flow to the lower pole.
- Definitive cure by partial nephrectomy for ectopic ureters is usually successful, as the residual stump is rarely problematic.
- In ureteroceles in which lower pole reflux is present, resolution may be expected in up to 20%, and new reflux may be seen in 15% to 50% of those where no reflux was present preoperatively.
- Complications related to heminephrectomy include loss of lower pole function and development of a postoperative upper pole urinoma.
- Separation of the duplicated ureters during intravesical dissection should be discouraged because it can lead to injury of the common blood supply running longitudinally between the two ureters.

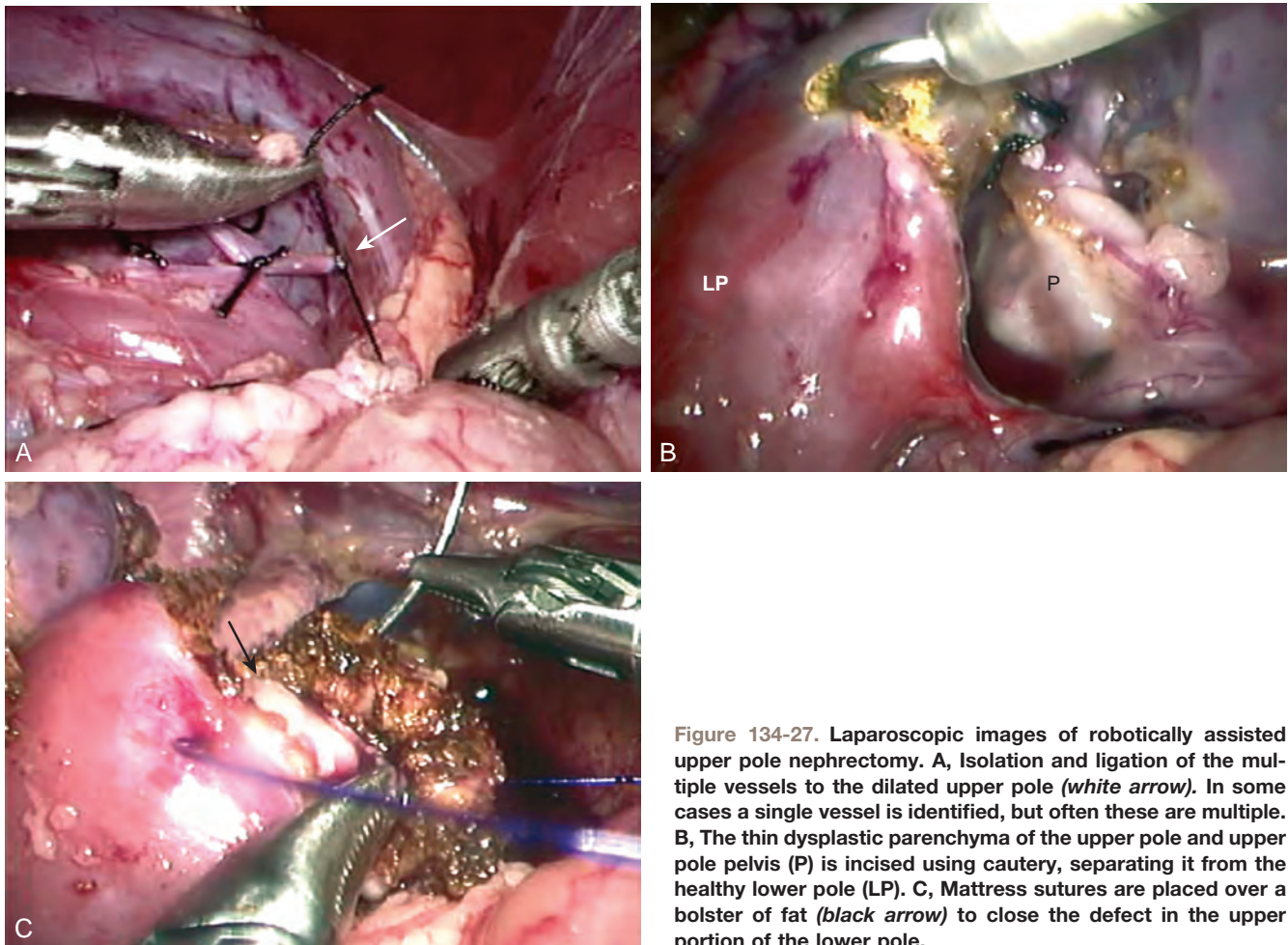


Figure 134-27. Laparoscopic images of robotically assisted upper pole nephrectomy. **A**, Isolation and ligation of the multiple vessels to the dilated upper pole (*white arrow*). In some cases a single vessel is identified, but often these are multiple. **B**, The thin dysplastic parenchyma of the upper pole and upper pole pelvis (P) is incised using cautery, separating it from the healthy lower pole (LP). **C**, Mattress sutures are placed over a bolster of fat (*black arrow*) to close the defect in the upper portion of the lower pole.

Lower Tract Reconstruction

A definitive reconstruction at the bladder is suitable for both the ectopic ureter and ureterocele. This approach has the advantage of relieving obstruction as well as correcting reflux. The disadvantages, however, are the potential for injury to the bladder neck and vagina and the complexity of the procedure. If clinically significant reflux persists after other procedures, lower tract reconstruction may be necessary.

Ureterocele Excision and Common-Sheath Reimplantation

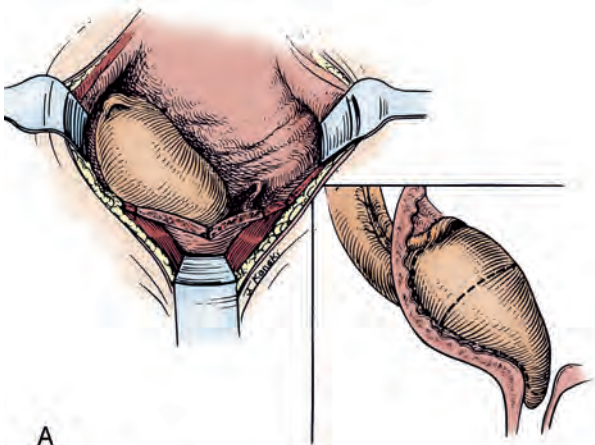
The intravesical approach to the ureterocele begins with a transverse incision of the ureterocele between two stay sutures (Figs. 134-28A to C and 134-29A). Proximally, a plane is obtained between the ureterocele wall and the wall of the bladder. The ureterocele is dissected off the bladder to the point at which it joins the lower pole ureter. Then the two ureters are dissected as a unit, the upper pole ureter is tapered as needed, and both ureters are reimplanted submucosally. The distal portion of the ureterocele is dissected in the same plane (Figs. 134-28D and 134-29B) to the level of the bladder neck, where it is resected. The detrusor muscle is plicated if it is attenuated and it appears that it may offer insufficient backing. Bladder mucosal flaps are raised to cover the area of the removed ureterocele (Figs. 134-28E and F and 134-29C).

Once again, several technical points regarding ureterocele excision and common sheath reimplantation deserve mention. **Separation of the duplicated ureters during intravesical dissection should be discouraged, because it can lead to injury of the common blood supply running longitudinally between the two**

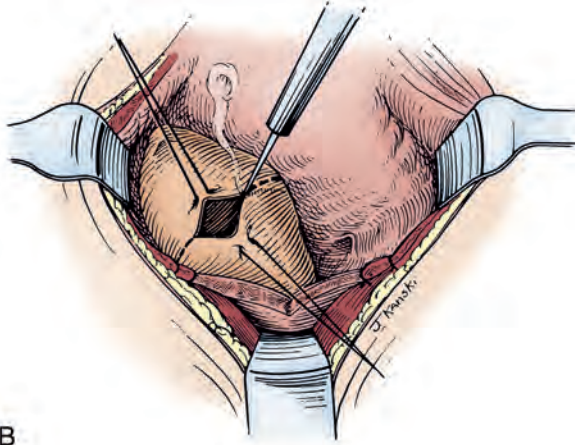
ureters. Plication of the detrusor muscle underlying the ureterocele may be necessary to reinforce any areas of muscle deficiency. Furthermore, the distal portion of the ureterocele may extend below the bladder neck. Extreme care must be taken in this part of the dissection to avoid injury to the sphincter mechanisms. If the entire ureterocele cannot be excised, it can be fulgurated carefully and closed over with two layers.

Cecoureteroceles present a unique challenge in ureterocele excision and reimplantation in that the distal aspect of the ureterocele can create an obstructive flap-valve with voiding, acting like a windsock behind the urethra. Options include resection by gentle retraction of the ureterocele if it is not very large, closure of the opening with two layers of tissue, or fulguration of the lumen to cause collapse and closure. Careful postoperative assessment is needed in any case to identify what can be progressive voiding dysfunction if the remnant cecoureterocele creates obstructive voiding (Fig. 134-30).

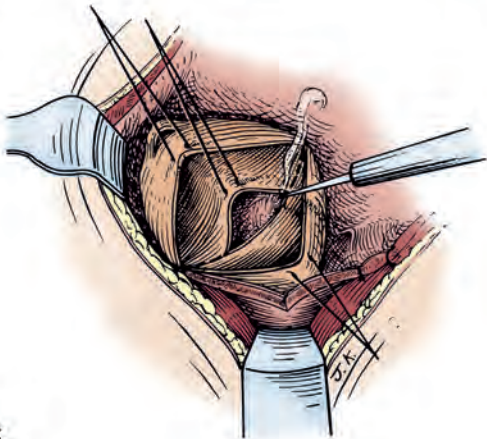
An alternative approach to ureterocele resection is marsupialization, in which the thin intravesical aspect is removed and the edge is sutured. No attempt is made to reinforce the back wall, based on the empirical observation that this is not always needed. Reported results have been satisfactory (Scherz et al, 1989; Lewis et al, 2008). Although this eliminates the need to dissect out the ureterocele and avoids injury to the underlying vagina, it is our impression that this approach has inherent risks that can be avoided by a controlled and predictable surgical approach of trigonal reconstruction. A major problem with marsupialization may be uncommon, but it seems preferable to definitively correct the anatomic and functional defect as certainly as possible on the first open operation when needed.



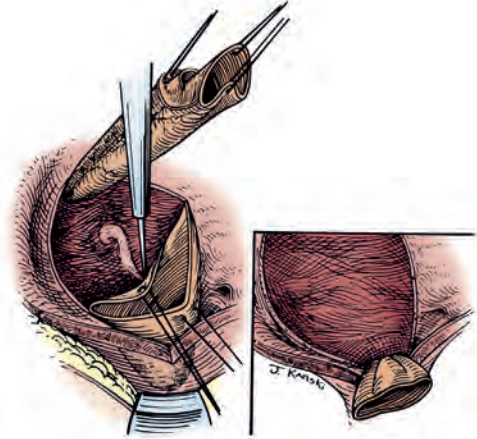
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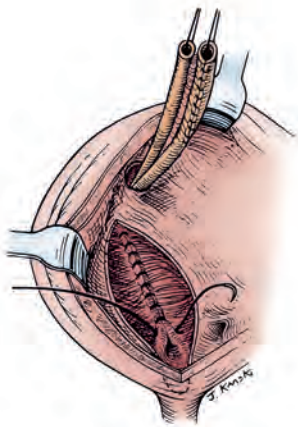
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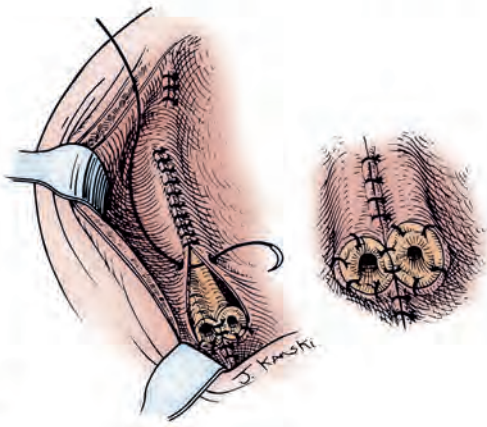
C



D



E



F

Figure 134-28. Technique for excision of ectopic ureterocele and common sheath reimplantation of upper and lower pole ureters. **A**, Appearance of right-sided ureterocele with open bladder, viewed from below. Note proximity of the contralateral ureteral orifice. *Inset*, Cutaway side view demonstrating the close association of the two polar ureters with a common vascular supply. The *dotted line* indicates the planned initial incision of the ureterocele. **B**, After stay sutures are placed, the ureterocele is incised with electrocautery in a transverse direction, exposing the inner cavity of the ureterocele. **C**, The posterior mucosal wall of the ureterocele is incised transversely, revealing the often thinned posterior muscular wall of the bladder. This incision will then be continued around the bladder mucosal edge of the ureterocele including the orifice of the lower pole ureter. Stay sutures are important to provide adequate exposure. **D**, The upper and lower pole ureters have been mobilized and are retracted into the bladder. The distal aspect of the ureterocele is being mobilized in a similar fashion. The bladder mucosal surface will also be incised around the edge of the ureterocele to permit complete removal of the ureterocele. *Inset*, The fully mobilized distal ureterocele is retracted caudally, revealing its narrowing attachment at the bladder neck. **E**, The dilated upper pole ureter associated with the ureterocele has been tapered and remains in continuity with the lower pole ureter. Both have been brought into the bladder through a newly formed muscular hiatus to provide adequate tunnel length for the ureteral reimplantation. The thinned-out posterior bladder wall has been repaired with multiple interrupted sutures to provide adequate muscular backing for the ureters. The bladder mucosa surrounding the ureterocele defect has been mobilized to permit covering of the ureters. **F**, *Left*, The ureters have been reimplanted into the new ureteral tunnel, have been sutured distally after spatulation, and are being covered with bladder mucosa. The lower pole orifice is medial. *Right*, Final appearance of the ureteral tunnel after completion of the reimplantation.

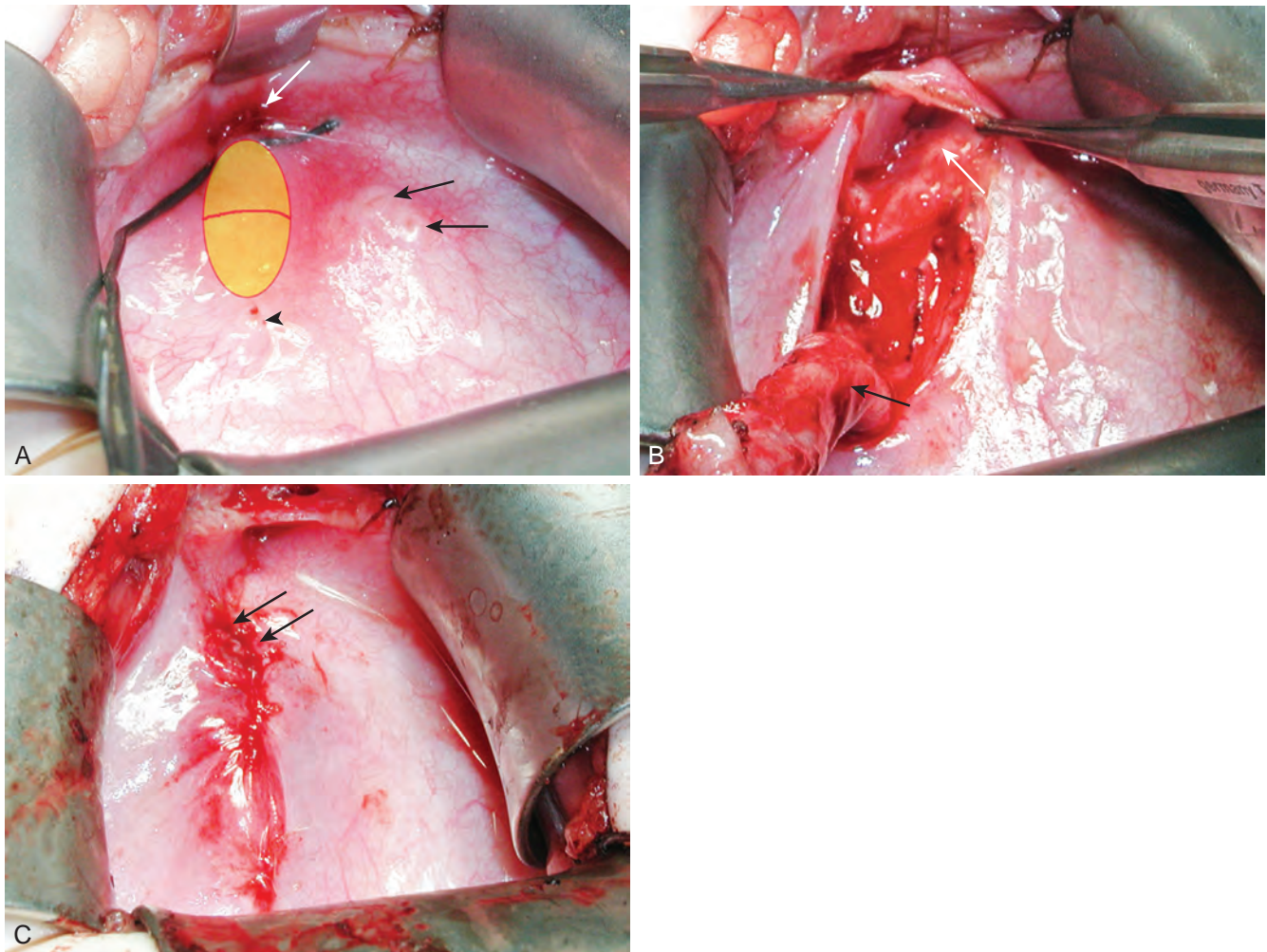


Figure 134-29. Operative view of ureterocele excision and common sheath reimplantation. **A**, View of the decompressed ureterocele (*yellow ellipse*) after incision (*white arrow* marks site of incision and the bladder neck orifice) and marking of extent of the ureterocele and the lower pole orifice (*black arrowhead*). The contralateral duplicated ureteral orifices are indicated by the *black arrows*. **B**, The ureterocele has been divided and the lower aspect is visible (*white arrow*), going to the bladder neck. This will be excised and the trigonal floor imbricated. The two ureters have been mobilized and are seen being retracted cephalad (*black arrow*). **C**, Completed appearance of the reimplanted two ureters (*arrows*).

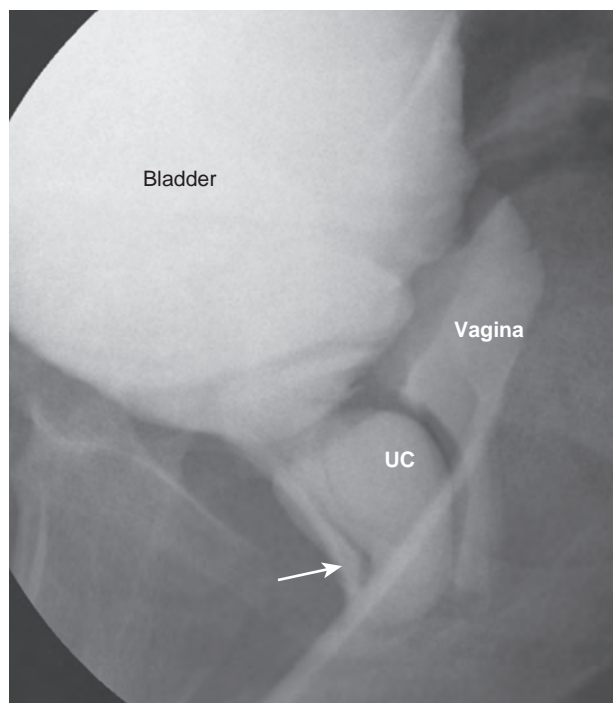


Figure 134-30. Voiding cystourethrogram appearance of a large cecoureterocele (UC) extending down the urethra and causing bladder outlet obstruction with voiding. The ureterocele fills, acting like an obstructive windsock. The lumen of the urethra is marked with the arrow.

Reported results of ureterocele excision and common sheath reimplantation are very good, although persisting reflux can be an issue in 5% to 10% of patients. This may be more common when ureteral tapering is needed. Whereas in some reports it is claimed that these patients do not require surgery, persisting reflux in this context must be viewed with caution.

KEY POINTS: URETEROCELE EXCISION AND REIMPLANTATION

- Cecoureteroceles present a unique challenge in ureterocele excision and reimplantation in that the distal aspect of the ureterocele can create an obstructive flap-valve with voiding, acting like a windsock behind the urethra.
- An alternative approach to ureterocele resection is marsupialization, in which the thin intravesical aspect is removed and the edge is sutured.
- The results of ureterocele excision and common sheath reimplantation are very good, although persisting reflux can be an issue in 5% to 10% of patients.
- Total reconstruction including upper pole nephrectomy with ureterocele excision and reimplantation of the lower pole ureter is definitive but is an extensive operation performed with two incisions.

Pyeloureterostomy and Ureteroureterostomy

When the upper pole of either an ectopic ureter or ureterocele is to be maintained owing to function or surgeon preference, pyeloureterostomy or ureteroureterostomy may be carried out. Both proximal and distal approaches may be used, and these have been described with open and laparoscopic techniques.

Open Procedure

Ureteroureterostomy can be performed distally to create an anastomosis between the upper pole ureter and the lower pole ureter in an end-to-side fashion. This can be done at the distal ureter via an inguinal, open approach (Huisman et al, 1987; Lashley et al, 2001; Chacko et al, 2007; Prieto et al, 2009). It is critically important in this type of procedure to correctly identify the recipient lower pole ureter, and it is strongly recommended to cystoscopically place a stent into the lower pole ureter at the start of the procedure.

Other options to achieve this goal are the proximal anastomotic technique of ureteroureterostomy or pyeloureterostomy. This results in the upper pole system's draining into the lower pole system. Such high anastomoses may be preferable to a distal ureteroureterostomy with a dilated upper pole, because the latter may result in more urinary stasis with a distal anastomosis. Whether the "yo-yo" phenomenon is clinically significant remains uncertain, but we prefer a proximal anastomosis when there is a significant mismatch in ureteral size.

When performing upper tract anastomoses, dissection should be limited to an absolute minimum, especially medially, to prevent disruption of either ureter's blood supply. The upper pole ureter may be considerably larger than the lower pole ureter. A generous longitudinal pyelotomy or ureterotomy is made in the lower recipient pole to overcome such disproportion, and the anastomosis is performed in an end-to-side fashion. The distal portion of the upper pole ureter should be aspirated with a feeding tube to decompress it. The distal upper pole ureter is resected as far inferiorly as possible, with care taken to stay directly on this ureter's wall and avoid the vasculature of the adjacent lower pole ureter. If there is no reflux, the resection is taken as distally as possible and the remnant lower portion of ureter may be left open. If reflux is present in an ectopic ureter, it should be taken as close to the bladder neck as possible. If associated with a ureterocele, it may be possible to avoid resection of the ureterocele as long as it is well decompressed.

Laparoscopic Procedure

Both ureteroureterostomy and pyeloureterostomy can be readily performed laparoscopically (Gonzalez and Piaggio, 2007; Steyaert et al, 2009), which is aided with robotic control (Kutikov et al, 2007; Smith et al, 2009). A stent is placed in the recipient ureter only and not across the anastomosis (Fig. 134-31).

Transurethral Incision for Ureterocele

The simplest means to decompress the obstructed upper pole or single system ureterocele is TUI. Reported rates of relief of obstruction range from 78% to 97% (Rich et al, 1990; Jayanthi and Koff, 1999; Di Renzo et al, 2010; Adorisio et al, 2011; Palmer et al, 2011; Castagnetti et al, 2013). A comparison between TUI and multiple punctures (watering can technique) showed no difference in decompression rates, although multiple punctures induced less reflux into the affected ureter. In the setting of acute sepsis, TUI is the most appropriate intervention, although a percutaneous nephrostomy would be a viable option as well.

Although TUI can reliably relieve obstruction, it carries the risk of inducing reflux into the affected ureter, which may then cause upper tract infection and the need for reconstruction. The balance between the minimal morbidity of TUI and its uncertainty is the basis for the clinical controversy as to its usefulness.

Our preferred method of incising the ureterocele is similar to the one described by Rich and colleagues (1990): a transverse incision through the full thickness of the ureterocele wall using the cutting current. Making the incision as distally on the ureterocele and as close to the bladder floor as possible lessens the chance of postoperative reflux into the ureterocele. One can use either a Bugbee electrode or an angled-tip wire. We favor the latter instrument because it has a finer tip and allows for more precision and the angle allows for easier manipulation. In older children, the

resectoscope with the Collins hot knife may be used to make the incision. Laser incision has been reported with equivalent results (Marr and Skoog, 2002; Jankowski and Palmer, 2006). Cold knife incision has been used as well.

The ureterocele should be incised deeply because ureteroceles may be thick walled. Adequacy of ureterocele incision is confirmed either by the escape of a jet of urine from the ureterocele or by viewing the urothelium on the inside of the ureterocele (Fig. 134-32). For the ectopic ureterocele that extends into the urethra, adequate drainage may be achieved by either a longitudinal incision that extends down from the intravesical portion into the urethral portion or two separate punctures, one in the intravesical portion

of the ureterocele and one in the urethral portion of the ureterocele.

No bladder catheter is left in place, and most children are treated as outpatients. A follow-up ultrasound is performed in 4 to 6 weeks to assess the degree of decompression (Fig. 134-33). A voiding cystogram is performed in 2 to 3 months to determine the status of lower pole reflux and whether new reflux has been created into the ureterocele (Fig. 134-34).

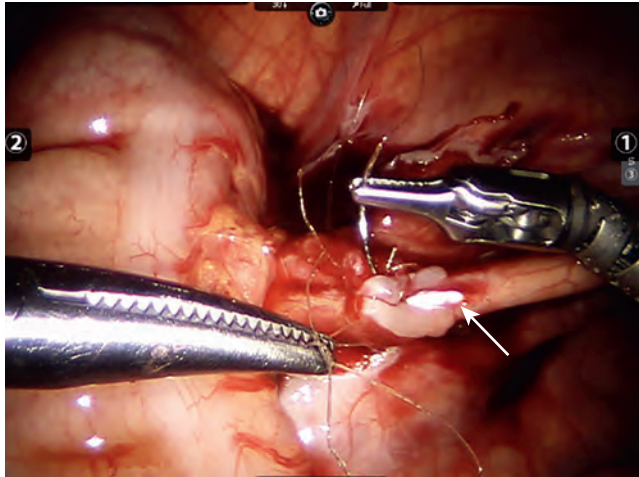


Figure 134-31. Operative view of robotic ureteroureterostomy for ectopic ureter presenting with incontinence. The procedure is being performed at the level of the iliac vessels. The arrow indicates the ureteral stent in the recipient (lower pole) ureter.

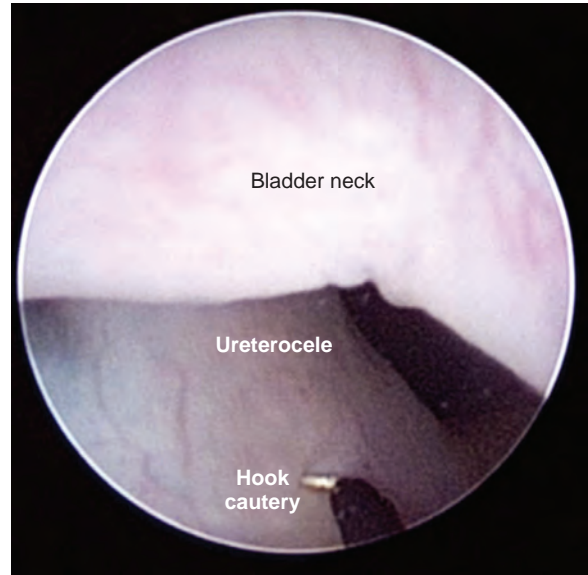


Figure 134-32. Endoscopic image of a ureterocele about to be incised with a hook cautery. The incision should be made inferiorly and medially to limit the risk of reflux, but the key goal is decompression. The ureterocele should be incised with the bladder partially filled, but not so much as to efface the ureterocele.

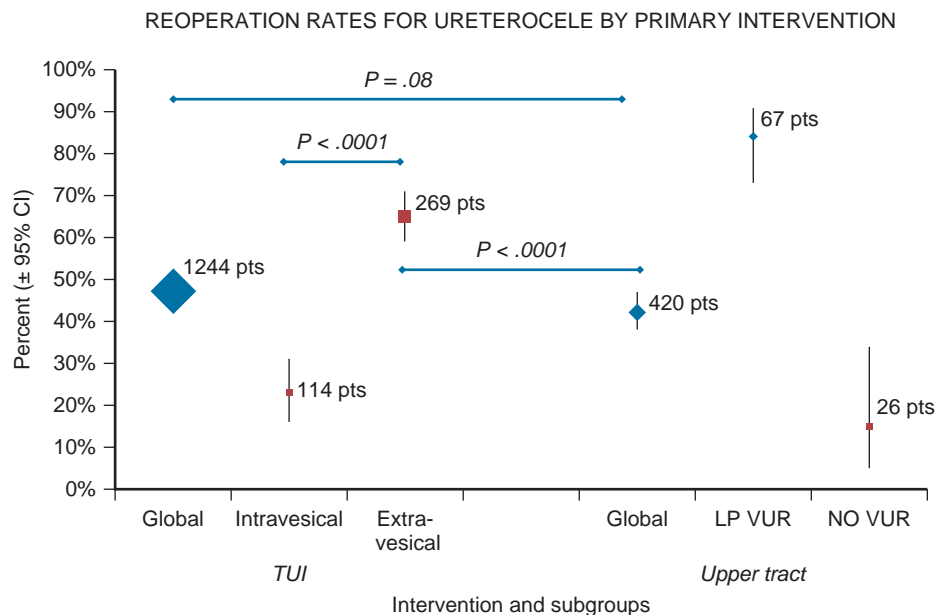


Figure 134-33. Chart indicating incidence of secondary surgery after either transurethral incision (TUI) or upper tract approach (partial nephrectomy or ureteroureterostomy) based on data from multiple sources. The number of patients (pts) is indicated adjacent to the data points. Statistical differences are indicated between selected groups based on two-tailed Fisher exact. CI, confidence interval; LP, lower pole; VUR, vesicoureteral reflux.

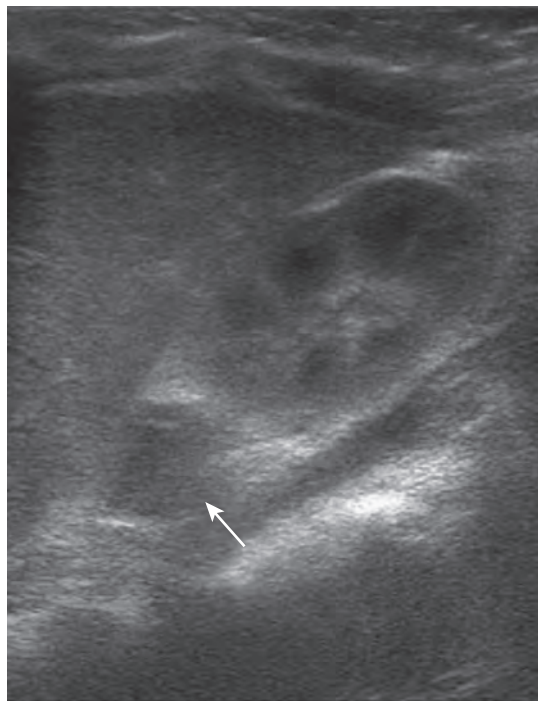


Figure 134-34. Appearance of the decompressed upper pole (arrow) from Figure 134-10, following endoscopic incision of the ureterocele.

The reported incidence of new reflux ranges from 0% to 50%. The risk of reflux may be dependent on the method used for incision (Tank, 1986; Rich et al, 1990; Blyth et al, 1993; Jelloul et al, 1997; Dahm and King, 1998; Husmann et al, 1999; Jayanthi and Koff, 1999; Shekarriz et al, 1999; Cooper et al, 2000; Singh and Smith, 2001; Upadhyay et al, 2002; Chertin et al, 2007). Some authors favor puncture instead of incision, but no data are available that demonstrate a clear difference. The type of ureterocele is a clear determinant of the outcomes of TUI, with intravesical ureteroceles having the highest likelihood of achieving all therapeutic goals with only the incision. Decompression with no reflux can be achieved in 70% to 80% of patients. Extravesical ureteroceles, however, are more likely to have persisting or new reflux and may require secondary surgery based on the presence of reflux in 70% by some series. In the meta-analysis by Byun and Merguerian, the presence of lower pole reflux and the location of the ureterocele are similar in their impact on outcomes (Byun and Merguerian, 2006). In this analysis, the relative risk of reoperation was 1.74 times greater in the presence of reflux than without, and 2.78-fold times higher if extravesical. These factors did not seem to be additive, suggesting they represented similar underlying causes. In comparison with an open approach of any modality, however, the simplicity of ureterocele incision coupled with the potential for definitive cure, even if not in a large fraction, is appealing. TUI also acts to better prepare the patient for a secondary major surgery if needed, by decompressing dilated ureters.

Reflux Outcomes after Transurethral Incision

The natural history of lower pole reflux after TUI is incompletely defined. In some series an observational approach has been taken, and resolution has been reported in a few series with variable follow-up (Jesus et al, 2011). The usefulness of observing these patients will be dependent on occurrence of infection as well as parental preferences.

Ureterostomy for Ectopic Ureter

The ectopic ureter in a neonate with sepsis or with massive dilation may be best managed with a temporary end ureterostomy

KEY POINTS: TRANSURETHRAL INCISION OF URETEROCELE AND DRAINAGE PROCEDURES

- The reported incidence of new reflux after TUI of a ureterocele ranges from 0% to 60% and may be dependent on the method used for incision.
- The type of ureterocele is a clear determinant of the outcomes of TUI, with intravesical ureteroceles having the highest likelihood of achieving all therapeutic goals with only the incision.
- TUI also acts to better prepare the patient for a secondary major surgery, if needed, by decompressing dilated ureters.
- Persisting reflux into the upper or lower poles is typically an indication for ureterocele excision and reimplantation, but resolution has been reported.
- In general, it has not been possible to predict with any accuracy how an individual might respond to TUI based on clinical parameters.
- The ectopic ureter in a neonate with sepsis or with massive dilation may be best managed with a temporary end ureterostomy.
- Ureteroureterostomy can be performed distally or proximally to create an anastomosis between the upper pole ureter and the lower pole ureter in an end-to-side fashion.

(el Ghoneimi et al, 1996). This has the advantage of permitting acute decompression to manage sepsis and permit later assessment of any function in the affected renal unit before definitive management. By performing an end ureterostomy, the ureter can decompress and it is in position to be reimplanted if the renal unit is felt to be salvageable. No resection of redundant ureter is performed because this will shorten in time and some length will be needed to perform the reimplantation. The stoma should be positioned at what would be the lateral end of a Pfannenstiel incision. Percutaneous ureterostomy has been reported as well (Bilen et al, 2006). Assessment of functional status is performed shortly before definitive surgery, usually in 4 months or after age 6 months. DMSA scanning is probably the most efficient means, but differential urine collection is an option as well. If there is no function appreciable, partial or total nephrectomy is performed with removal of the entire ureter to the stoma.

Summary of Clinical Decision Making

For ectopic ureters, clinical decision making is much more straightforward than for ureteroceles and rests on whether to maintain the upper pole of a duplex system. If this is chosen, then the surgical approach depends on the presence of reflux in the lower pole; if present, a common sheath reimplantation or a lower pole reimplantation with distal upper to lower pole ureteroureterostomy is performed. If there is no lower pole reflux, either proximal or distal ureteroureterostomy is performed. If the degree of function is ambiguous, a temporary end ureterostomy can be used to permit assessment out of the acute setting, particularly with a massively dilated ureter. Also, if reflux is present, the need for lower surgery to correct the reflux may influence the choice to avoid upper tract surgery. If removal of the upper pole is chosen based on degree of dilation or the preference for removal of nonfunctioning, dysplastic tissue, an upper pole nephrectomy is performed. For the single-system ectopic ureter, preservation or removal is also based on degree of function and surgeon preference. There are no objective outcome data to advocate clearly for one or another approach.

For a ureterocele in a duplex system, the availability of endoscopic incision creates more options (Table 134-1 and Fig. 134-35). It is important to recognize that although TUI is an operation, it is of a totally different nature than either an upper pole nephrectomy or a lower tract reconstruction. It is inappropriate to equate them as operations in a comparative manner. In general, it has not been possible to predict with any accuracy how an individual might

TABLE 134-1 Options for Ureterocele Management

PROCEDURE	IDEAL INDICATIONS	ADVANTAGES	LIMITATIONS
Transurethral incision	Infant Large ureterocele with VUR	Outpatient procedure Effective decompression Occasionally definitive	May produce reflux into ureterocele segment, necessitating bladder surgery
Upper pole nephrectomy	Older patient Large nonfunctioning upper pole No VUR	May be definitive Removes pathology Avoids bladder level surgery	May not be definitive Significant surgery Risk to lower pole May still require lower surgery in bladder
Ureteroureterostomy or ureteropyelostomy	Older patient Functioning upper pole No VUR	Drains obstructed segment with little risk of obstruction or UTI	Leaves ureterocele in bladder May develop reflux
Ureterocele excision and common sheath reimplantation	Reflux Functioning upper pole without significant dilation	Eliminates obstruction and reflux, removes ureterocele No renal risk	Complex surgery Risk to vagina and bladder neck May require ureteral tapering

UTI, urinary tract infection; VUR, vesicoureteral reflux.



Figure 134-35. Voiding cystourethrogram demonstrating reflux into the upper pole of a duplex system after ureterocele incision. This type of reflux will rarely resolve spontaneously. Although the clinical risk is uncertain, the reflux is most often repaired.

respond to TUI based on clinical parameters. Because in some patients significant lower pole reflux and upper tract dilation may be treated with a brief outpatient procedure with documented long-term results, it would seem reasonable to offer that option before moving directly to a more complex upper or lower tract reconstruction. Even if half of those patients may need subsequent surgery, it can be safely deferred until the child is older. There is also the further appeal of TUI in that it may make a subsequent surgical procedure less complex by decompressing a dilated upper pole ureter. Reimplantation may be much more effective and not require excisional tapering. This lessens overall morbidity, another goal of management. The appeal of TUI may therefore be less in the older child with a massive upper pole in whom removal may be preferable and definitive surgery can be performed at diagnosis.

Voiding Dysfunction after Ureterocele Repair

Voiding dysfunction after lower urinary tract reconstruction for ureterocele has been reported in some series (Abrahamsson et al, 1998; Sherman et al, 2003; Lewis et al, 2008), but with a low incidence. In other series there was no evidence of incontinence or significant bladder dysfunction (de Jong et al, 2000; Vereecken and Proesmans, 2000; Beganovic et al, 2007). Abrahamsson and colleagues reported infrequent voiding with the possibility of infection in 19 of 36 patients, whereas 3 of 36 demonstrated incontinence (Abrahamsson et al, 1998). A similar observation was made with a lower incidence by Vereecken after complex bladder surgery for duplication anomalies (Vereecken and Proesmans, 2000). Abrahamsson suggested that the bladder dysfunction was the result of an intrinsic bladder abnormality rather than the surgical procedures.

In the child with either recurrent infections or incontinence after surgical repair of a ureterocele, one must consider the type of surgery and if there was the possibility of inadequate trigonal support. This can lead to a weak bladder base, ballooning of the trigone posterior to the bladder neck, and an obstructive process. This can also occur after transurethral incision of a ureterocele with a urethral component. Inadequate bladder emptying and infection as well as upper tract dilation can result.

A VCUG may be needed to assess the bladder anatomy with voiding, and video-urodynamics may be needed. It would be important to recognize the need for lateral views during voiding to identify the bladder pathology. We have also used antegrade cystoscopy via a suprapubic puncture to better assess the bladder neck. Recurrent VUR may occur, particular if there is obstructed voiding, and may require repeat VCUGs in the setting of febrile UTIs.

Managing bladder dysfunction after ureterocele repair will depend on the cause and may include bladder and trigonal reconstruction or bladder neck repair, intermittent catheterization, or, if there is evidence of bladder neck incompetence, endoscopic injection of bulking agents.

OTHER URETERAL ANOMALIES

Anomalies of Number

Bifid Ureters

Ureteral duplication may be associated with ectopia or a ureterocele but is also compatible with a normally functioning renal system if both ureters enter orthotopically or if there is partial duplication. Ureteral duplication is a common condition, described in

approximately 1 in 125 people (0.8%) based on autopsy series, which tend to be less selective (Nation, 1944; Kaplan and Elkin, 1968; Timothy et al, 1971; Privett et al, 1976). There is a slightly higher incidence in females, estimated to be approximately 1.6:1. Duplication is unilateral six times more frequently than bilateral; however, it is clinically prudent to carefully look for contralateral duplication when unilateral duplication is documented. This may be critical in the setting of nonhydronephrotic upper poles and ureteral ectopy causing incontinence. Right and left sides appear to be affected similarly with unilateral duplication.

A bifid renal pelvis includes only a single ureter, but with confluence of the upper and lower ureters lower than the ureteropelvic junction (UPJ) constitutes partial duplication of the ureter or bifid ureter.

An increased incidence of ureterorenal pathology has been documented with duplication anomalies. The clinical implication of duplication depends largely on the ureteral insertion. A useful clinical approach is to consider that conditions that routinely affect the single-system kidney are those that affect the lower pole, including UPJO and VUR. The upper pole is more likely affected by conditions resulting from abnormal ureteral formation, including ectopic and ureterocele as previously discussed.

Lower pole UPJO evaluation and management are similar to those for a single-system UPJ obstruction. Lower pole UPJO may be identified with partial and complete ureteral duplication. Recognition of the presence of the duplication may be challenging with massive hydronephrosis, but in most cases the normal upper pole will be identified on functional imaging such as a renal scan, even if not detected on ultrasound. Lower pole UPJ obstruction may resolve spontaneously, just as a single system with comparable severity of dilation. Repair may be optionally accomplished with a pyeloureterostomy of the dilated renal pelvis of the lower pole to the normal upper pole ureter.

Upper pole UPJ obstruction has been reported, including in association with lower pole UPJ obstruction, but is exceptionally rare (Ho et al, 1995; Ng, 1999).

Hydronephrosis of the lower pole moiety may also represent VUR, and this is often of high grade. The presence of a dilated ureter on ultrasonographic evaluation will usually be present. This rarely represents ureterovesical obstruction and more often indicates VUR. Lower pole VUR is often associated with significant functional reduction in the lower pole, which is usually congenital but may also be associated with prior infection. Evaluation and management are similar to reflux into a single system, but spontaneous resolution may be more delayed (Afshar et al, 2005). Common sheath ureteral reimplantation and endoscopic injection are surgical options, as well as low ureteroureterostomy of the refluxing lower pole ureter to the upper pole ureter.

TriPLICATION

TriPLICATION of the ureter, either complete or partial, is very rare. These conditions typically have manifested with infection or wetting. The classification by Smith remains useful, in which triplex ureters are divided into four types (Smith, 1946). Type 1 constitutes three entirely separate ureters with unique attachment to the bladder or distally and accounts for 35% of triPLICATIONs. Type 2 is an incomplete separation with two ureteral orifices, occurring in 21%. Type 3 is a trifid ureter with a single ureteral orifice, seen in 31%. Type 4 describes two ureters with three orifices. This occurs with an inverted-Y bifurcation, similar to that described for duplicated ureters. The positioning of the ureteral orifices typically follows the Weigert-Meyer law (Zaontz and Maizels, 1985).

The ureters may be associated with ureteroceles (Park, 2008) and may be ectopic to the bladder neck, urethra, or vagina (Engelstein et al, 1996; Patel et al, 2001). Lower pole and mid-pole (Sivrikaya et al, 2007) UPJ obstruction may be present, as well as ureterovesical obstruction (Merlini, 1983). VUR is also described (Ander et al, 1997), as well as contralateral duplication (Srivastava et al, 1996). Fusion anomalies may be present in some (Pode et al, 1983; Golomb and Ehrlich, 1989).

Quadruple Ureters

Even more rare is ureteral quadruplication, with only eight cases reported. Most have been in adults, but three recent cases included four ureters draining into a large ureteral cyst and connecting to the bladder through a single ureter (Klinge et al, 2001; Vicentini et al, 2007; Koszutski et al, 2008). One report of a young adult with incontinence describes three of the four ureters merging and entering the bladder orthotopically, and the fourth ureter drained to the perineum. This ectopic ureter was associated with the lower mid-calyx, contrary to what the Weigert-Meyer law would predict.

Fibroepithelial Polyps

Polyps of the ureter may manifest clinically with flank pain or hematuria or by incidental detection of hydronephrosis. The most common site of attachment is at the UPJ, although they may originate from any part of the ureter. As a cause of UPJO, they are very uncommon, reported as 0.5% of all UPJ patients undergoing pyeloplasty (Adey et al, 2003; Kojima et al, 2011). A very large majority of patients were male (89%) and a majority of polyps occurred on the left side (78%). They are uncommonly bilateral, but this has been reported with clinical effects on both kidneys (Bartone et al, 1990; Lavelle et al, 1997; Bhalla et al, 2002; Adey et al, 2003; Romesburg et al, 2009). In a recent series, two of nine patients had bilateral clinically obstructive UPJ polyps. They may also be multiple. We have seen one case in which the polyp protruded from the urethra and produced severe voiding symptoms and was ultimately found to originate from the proximal third of the ureter.

Smaller polyps may not be evident on modern imaging and in a recent series were detected in 22% of patients before surgery for UPJO (Adey et al, 2003). Ultrasound may be useful in detecting these polyps (Wang et al, 2012). They would usually be seen on intravenous pyelography but may be mistaken for ureteral blood clots, particularly in the setting of hematuria (Fig. 134-36). Filling

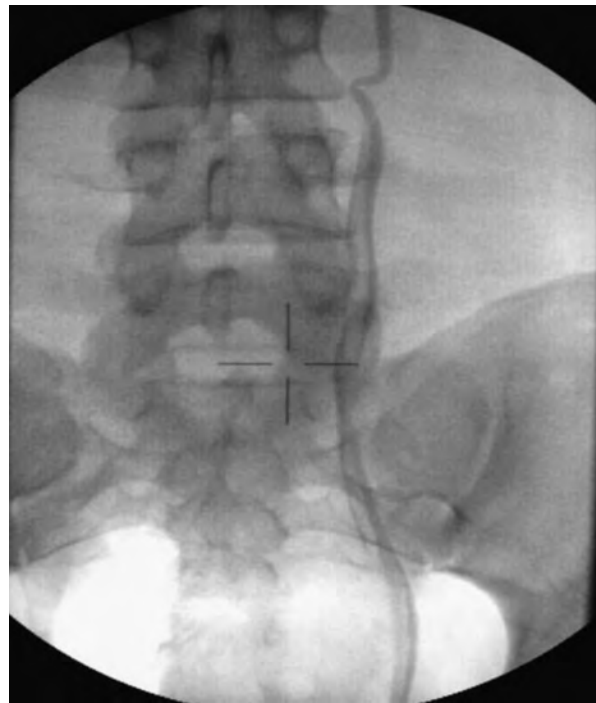


Figure 134-36. Retrograde ureterogram of adolescent with a history of hematuria, dysuria, and a fleshy mass protruding from her urethra. The distal segment had been resected by an outside physician. The long-filling defects are typical of fibroepithelial polyps but may be confused for blood clots.

defects on retrograde pyelography in anticipation of a pyeloplasty should trigger a search for the polyps. It is unlikely that this would alter the surgical approach unless the polyp was significantly distal to the UPJ.

The cause of fibroepithelial polyps is unclear, although progressive traction resulting from ureteral peristalsis may promote edema and growth. We have seen one in which the ureter was being intussuscepted into itself owing to traction on the polyp in the mid-ureter. Histologically, they are considered benign neoplasms with fibroepithelial and vascular elements, with overlying normal to hypertrophied urothelium. There is usually a fibrovascular core with significant stromal edema. Little inflammation is seen.

Management of the polyp is dictated by the presentation and location. For polyps at the UPJ, most have undergone pyeloplasty, although the question of whether simple endoscopic resection might suffice is not settled, as there are too few cases. Ureteroscopic removal of ureteral polyps is the recommended therapy away from the UPJ, based on combined adult and pediatric reports (Minevich et al, 2005; Childs et al, 2009; Iwatsuki et al, 2010). Earlier reports advocated sleeve resection and reanastomosis of the ureter to prevent recurrence, yet the persisting success with ureteroscopic resection would suggest that to be unnecessary. Even earlier reports recommended nephrectomy, which cannot be justified.

KEY POINTS: OTHER URETERAL ANOMALIES

- Ureteral duplication is compatible with a normally functioning renal system if both ureters enter orthotopically or if there is partial duplication.
- It is clinically prudent to look for contralateral duplication when unilateral duplication is documented.
- An increased incidence of ureterorenal pathology has been documented with duplication anomalies.
- Conditions routinely affecting a single system kidney are those that affect the lower pole, including UPJO and VUR; the upper pole is more likely affected by conditions resulting from abnormal ureteral formation, including ectopia and ureterocele.
- Polyps of the ureter may manifest clinically with flank pain or hematuria or by incidental detection of hydronephrosis.
- The most common site of attachment of a fibroepithelial polyp is at the UPJ, although they may originate from any part of the ureter.
- UPJ polyps are best treated with pyeloplasty, although the question of whether endoscopic resection might suffice is not settled.
- Ureteroscopic removal of ureteral polyps is the recommended therapy away from the UPJ.

Anomalies of Position

Vascular Anomalies Involving the Ureter

A variety of vascular lesions can cause ureteral obstruction. With these lesions, the vascular system rather than the urinary system is anomalous. With the exception of accessory renal blood vessels, all of these lesions are relatively uncommon, although all have clinical relevance.

Preureteral Vena Cava

Anatomy. Preureteral vena cava is commonly known to urologists as *circumcaval* or *retrocaval* ureter, terms that are anatomically descriptive but misleading with regard to development (Lerman et al, 1956; Dreyfuss, 1959). The term *preureteral vena cava* emphasizes that the circumcaval ureter results from altered vascular, rather than ureteral, development. This is the more accurate term.

This disorder involves the right ureter, which typically deviates medially behind (dorsal to) the inferior vena cava, winding

about and crossing in front of it from a medial to a lateral direction, to resume a normal course, distally, to the bladder. The renal pelvis and upper ureter are typically elongated and dilated in a J or fishhook shape before passing behind the vena cava. The collecting system is not inevitably obstructed. Circumcaval ureters can be classified into two clinical types (Bateson and Atkinson, 1969; Kenawi and Williams, 1976). The more common type I has hydronephrosis and a typically obstructed pattern demonstrating some degree of fishhook-shaped deformity of the ureter to the level of the obstruction. Type II has a lesser degree of hydronephrosis or none at all. Here, the upper ureter is not kinked but passes behind the vena cava at a higher level, with the renal pelvis and upper ureter lying almost horizontal before encircling the vena cava in a smooth curve. In type I, the obstruction appears to occur at the edge of the iliopsoas muscle, at which point the ureter deviates cephalad before passing behind the vena cava.

Embryology. The definitive inferior vena cava develops on the right side from a plexus of fetal veins (Fig. 134-37). Initially, the venous retroperitoneal pathways consist of symmetrically placed vessels, both central and dorsal. The posterior cardinal and supracardinal veins lie dorsally, and the subcardinal veins lie ventrally. These channels, with their anastomoses, form a collar on each side through which the ascending kidneys pass. Normally the left supracardinal veins and the lumbar portion of the right posterior cardinal vein atrophy. The subcardinal veins become the internal spermatic veins. The definitive right-sided inferior vena cava forms from the right supracardinal vein. If the subcardinal vein in the lumbar portion fails to atrophy and becomes the primary right-sided vein, the ureter is trapped dorsal to it.

When the definitive vena cava forms normally and the ventral portion of the primitive ring also persists, a double right vena cava is formed because of the persistence of both the right subcardinal vein dorsally and the right subcardinal vein ventrally. This double vena cava traps the right ureter between its limbs (Sasai et al, 1986).

Although bilateral vena cava or left-sided vena cava can occur (Clements et al, 1978; Mayo et al, 1983), a bilateral circumcaval ureter has been described in a case of situs inversus (Brooks, 1962). In cases of bilateral vena cava associated with a circumcaval ureter, the circumcaval ureter has been reported only on the right side, denoting that the right vena cava developed abnormally from a persistent subcardinal vein, whereas the left vena cava developed from the left supracardinal vein but otherwise normally (Pick and Anson, 1940).

Incidence. The incidence of preureteral vena cava at autopsy is about 1 in 1500 (Heslin and Mamonas, 1951), and the anomaly is three to four times more common in male than in female cadavers, although a literature review reported a ratio of 114:41 male to females (2.8:1) (Kenawi and Williams, 1976).

The symptoms of preureteral vena cava are those of obstruction. Although the lesion is congenital (Soundappan and Barker, 2004; Acharya et al, 2009), presentation in most patients does not occur until the third or fourth decade of life (Kenawi and Williams, 1976).

Diagnosis. Clinically, patients may have symptoms of flank or abdominal pain or infection, or the disorder may be discovered incidentally during other radiologic tests. Excretory urography often fails to visualize the portion of the ureter beyond the J hook (i.e., extending behind the vena cava), but retrograde ureteropyelography demonstrates an S curve to the point of obstruction with the retrocaval segment lying at the level of L3 or L4 (Kenawi and Williams, 1976). Cavography is no longer a necessary diagnostic test.

Ultrasound (Murphy et al, 1987) and CT or MRI also have been useful in defining the vascular malformation. CT urography may be the procedure of choice to confirm the diagnosis and avoid retrograde ureteropyelography (Sasai et al, 1986; Kellman et al, 1988). Nuclear renal furosemide scanning can categorize the anomaly as obstructed or nonobstructed (Pienkny et al, 1999). MRI can demonstrate the course of a preureteral vena cava and may be a more detailed and less invasive imaging modality when compared with CT and retrograde pyelography (Uthappa et al, 2002).

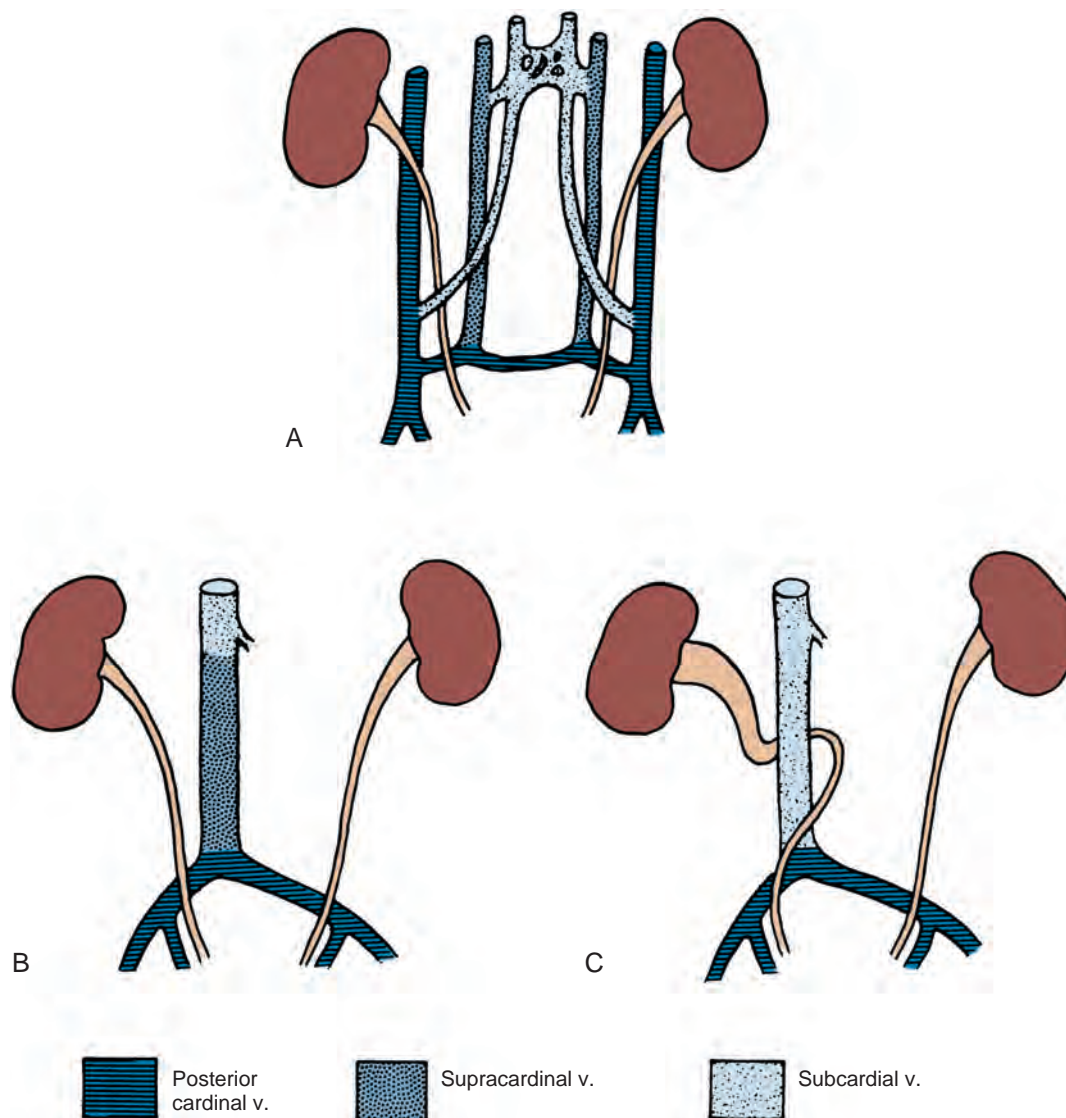


Figure 134-37. Fetal venous ring (A), normal vena cava (B), and preureteral vena cava (C). (Redrawn from Hollinshead WH. *Anatomy for surgeons*, vol 2. New York: Hoeber Medical Division of Harper and Row; 1956.)

Treatment. Surgical correction involves ureteral division, with relocation and ureteroureteral or ureteropelvic reanastomosis, usually with excision or bypass of the retrocaval segment, which can be aperistaltic. It is important to be mindful of the ureter's blood supply from the renal artery and aorta superiorly and the iliac vessels inferiorly. As stated earlier, the preferred approach for the obstructed ureter is ureteral division and relocation. Laparoscopic (Miyazato et al, 2002; Ramalingam and Selvarajan, 2003; Tobias-Machado et al, 2005; Fernandez-Fernandez and Pachano-Arenas, 2008) and robotic (Gundet et al, 2006; Smith et al, 2009) reconstruction of the ureter in a preureteral vena cava via both the transperitoneal and retroperitoneal approaches in children has been described.

Other Anomalies of Position

Several instances of horseshoe kidney have been reported (Cukier et al, 1969; Cendron and Reis, 1972; Heffernan et al, 1978; Taguchi et al, 1986). Anomalies include a variety of left renal anomalies, such as agenesis, hydronephrosis, malrotation, and hypoplasia (Kenawi and Williams, 1976). An obstructing branch of the right spermatic vein and a lumbar vein have mimicked circumcaval

ureteral obstruction (Dreyfuss, 1959; Psihramis, 1987), as has an anomalous tendon of the iliopsoas muscle (Guarise et al, 1989). **Preureteral Iliac Artery (Retroiliac Ureter).** A ureter coursing behind the common iliac artery is rare (Corbus et al, 1960; Seitzman and Patton, 1960; Hanna, 1972; Radhkrishnan et al, 1980). Either side can be involved; in two cases, the condition was bilateral (Hanna, 1972; Radhkrishnan et al, 1980). Obstruction occurs at the level of L5 or S1 as the ureter is compressed behind the artery. Coexisting anomalies are common (Nguyen et al, 1989), particularly valsal anomalies. (Seitzman and Patton, 1960; Radhkrishnan et al, 1980).

Like the preureteral cava, the preureteral iliac artery is considered to be of vascular origin without definitive proof. Normally, the primitive ventral root of the umbilical artery is replaced by development of a more dorsal branch between the aorta and the distal umbilical artery. Persistence of the ventral root as the dorsal root fails to form traps the ureter dorsally.

Ureteral or mesonephric duct ectopia is often present (Nguyen et al, 1989). The case of Seitzman and Patton involved an ectopic ureter that emptied, along with the ipsilateral vas deferens, via a persistent common mesonephric duct into the proximal posterior urethra (Seitzman and Patton, 1960). In the case of Radhkrishnan

and colleagues, bilateral retroiliac ureters also involved bilateral ectopic termination of the vasa deferentia into the ureters (Radhkrishnan et al, 1980). Luchtman and associates described ectopic vaginal termination of the involved ureter, with urometrocolpos from an imperforate hymen (Luchtman et al, 1980).

Taibah and coworkers reported the unusual finding of left ureteral obstruction from a retrointernal iliac artery ureter in an otherwise normal young woman (Taibah et al, 1987).

Vascular Obstruction of the Distal Ureter. Obstruction of the distal ureter from uterine, umbilical, obturator, and hypogastric vessels close to the bladder has been described (Campbell, 1936; Young and Kiser, 1965; Scultety and Varga, 1975). However, it is not always clear that vascular impressions on a dilated ureter are the cause of the obstruction. At times, these findings may be an artifact, as when a dilated ureter from an intrinsic obstruction is secondarily compressed against the adjacent vessel. Judging from the paucity of contemporary reports describing this lesion, it is likely that primary terminal ureteral obstruction by vascular lesions is a rare occurrence.

Herniation of the Ureter. Herniation of the ureter is another extremely rare condition. Dourmashkin searched the literature and tabulated a series of inguinal, scrotal, and femoral herniations of the ureter (Dourmashkin, 1937). Most of these were paraperitoneal—that is, a loop of herniated ureter extended alongside a peritoneal hernial sac. Only a minority were extraperitoneal (i.e., with no hernial sac present). In paraperitoneal ureteral hernias, the ureteral loop is always medial to the peritoneal sac. Of six scrotal hernias, four did not have peritoneal sacs. When the ureter extended into the scrotum, it was more likely to be dilated, causing upper tract obstruction.

In children, herniated ureters have manifested with hydronephrosis, associated with megaureters and with persistent hydronephrosis after posterior urethral valve ablation (Jewett and Harris, 1953; Powell and Kapila, 1985; Burgu et al, 2009).

Internal hernias of the ureter are even more exceptional. Reports have been published of a sciatic hernia containing a ureter (Oyen et al, 1987; Witney-Smith et al, 2007; Tsai et al, 2008; Hsu et al,

2010), herniation between the psoas muscle and iliac vessels (Page, 1955), and lumbar triangle herniation (Cabello et al, 2008). Ureteral herniation with obstruction has been reported as a rare complication of renal transplantation (Ingber et al, 2007).

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The complete reference list is available online at www.expertconsult.com.



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KEY POINTS: PREURETERAL VENA CAVA (CIRCUMCAVAL URETER, RETROCAVAL URETER)

- Preureteral vena cava involves the right ureter, which typically deviates medially behind (dorsal to) the inferior vena cava, winding about and crossing in front of it from a medial to a lateral direction, to resume a normal course to the bladder.
- If the subcardinal vein in the lumbar portion fails to atrophy and becomes the primary right-sided vein, the ureter is trapped dorsal to it.
- The preureteral cava may manifest with symptoms of flank or abdominal pain or infection, or the disorder may be discovered incidentally.
- Surgical correction involves ureteral division, with relocation and ureteroureteral or ureteropelvic reanastomosis, usually with excision or bypass of the retrocaval segment, which can be aperistaltic.

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Endourologic Management

Evaluation

Conservative Management

Shock Wave Lithotripsy

Ureteroscopic Management of Upper Urinary Tract Calculi

Percutaneous Nephrolithotomy

Laparoscopic and Robotic-Assisted Pyelolithotomy

Percutaneous Cystolithotripsy for Bladder Stones

Determination of Stone-Free Status

Conclusions

Before 1990, nephrolithiasis was responsible for 1 in 1000 to 1 in 7600 hospital admissions annually throughout the United States (Nimkin et al, 1992). However, a dramatic increase in pediatric urolithiasis has been observed in more recent years (Srivastava and Alon, 2005), especially among adolescents without known metabolic disturbances. A large retrospective multihospital analysis of emergency department visits confirmed this observation finding an almost 90% increase in admission rate for pediatric patients with renal colic from 1999 to 2008 (Kairam et al, 2013). The highest risk group appears to be white, adolescent girls. It has been speculated that diets rich in sodium and carbohydrates may contribute to the etiology of urolithiasis in this cohort of children, but as yet no clear evidence supports any one etiologic theory. Metabolic risk factors are more likely to be identified in younger patients, such as patients with Dent disease, primary hyperoxaluria, or Lesch-Nyhan syndrome (Sas, 2011). In addition, diabetes and hypertension appear to be risk factors for the development of nephrolithiasis in children younger than 6 years old (Matlaga et al, 2010). Although obesity is a major health care issue among children and adolescents, an increased body mass index (defined as 25 to 29.9 kg/m²) does not predispose this cohort to increased risk of stone formation (Kieran et al, 2010). To date, there is no uniform strategy to manage pediatric stone disease (Clayton and Pope, 2011).

A complete metabolic blood profile and a 24-hour urine collection often are obtained when a stone is confirmed by imaging. There are no accepted standard reference ranges for 24-hour urine analyses in the stone-forming pediatric patients. Many pediatric urologists use adult standards to direct medical treatment because specific referenced ranges are not readily available or require additional complicated calculations. However, there are significant differences between the normal ranges of urine chemistries in children and adults (Battino et al, 2002; DeFoor et al, 2006). In addition, conflicting reports exist regarding the commonality of metabolic disturbances in the presence of calcium-based stones (Lande et al, 2005).

In the preliminary evaluation of pediatric stone disease, it is common to obtain 24-hour urine values for creatinine, sodium, calcium, oxalate, uric acid, and citrate. The cumbersome nature of a 24-hour urine collection often limits its accuracy in pediatric patients, and random urine spot sample ratios have been used. For example, urine calcium/urine creatinine ratios have been used with sensitivities and specificities of 90% and 84%, respectively, in the evaluation of hypercalciuria, a known risk factor for urolithiasis (Mir and Serdaroglu, 2005). However, such a test is limited to one

urinary metabolite and cannot be relied on to monitor responses to various medical treatments. Also, it is unreasonable to rely solely on urinary calcium excretion values as an indication of overall metabolic disturbances.

It has been suggested that measurement of urinary supersaturation products (calcium oxalate, urate) may help to improve identification of children at risk for stone formation. DeFoor and colleagues (2006) determined that supersaturation levels of calcium oxalate and calcium/creatinine ratios were significantly higher in children with stones compared with control subjects. However, this difference may have been reflective of differences found in urinary volumes. Lande and associates (2005) demonstrated that low urine volumes in children often negate the benefit of pursuing urine supersaturation products in a stone workup. Because of such conflicting data, clinicians are often confused about what urinary evaluation to pursue in the workup and management of pediatric stone disease.

Stone disease in pediatric patients has genetic, metabolic, dietary, and anatomic causes. There are numerous genetic causes of hypercalciuric nephrolithiasis alone that contribute to pediatric stone disease (Stechman et al, 2009). In this regard, medical treatment always accompanies endourologic management. To treat the pediatric patient with stone disease completely, there must be a focus on prevention through diet and medication monitoring. For this reason, the pediatric nephrologist is a critical player in the management and surveillance of these children. Details regarding the metabolic workup and medical treatment of pediatric stone disease are beyond the scope of this chapter; however, metabolic abnormalities are most often present, and hypocitruria is most common (Kovacevic et al, 2012). Numerous pediatric nephrology resources are available. Alon (2009) provides an excellent pediatric nephrology review including medication dosing by weight. Litholink (www.litholink.com) can provide parents and pediatric urologists with valuable information.

ENDOUROLOGIC MANAGEMENT

The management of upper urinary tract calculi has evolved dramatically in adults and children in the last two decades. Progress in the management of pediatric stone disease has been motivated by surgeon prowess of adopting and applying adult endourologic methods. The most important catalyst in the evolution of surgical advancement has been the expansion of minimally invasive surgery in general with development of smaller and more durable

endoscopic equipment. This advance has allowed easier endourologic treatment in children at an earlier age (Onal et al, 2013).

Extracorporeal shock wave lithotripsy (ESWL) transformed the management of pediatric upper tract calculus disease when it was introduced in the 1980s, and it remains very useful today. Other modalities of treatment, including ureteroscopy, percutaneous nephrolithotomy (PCNL), and combination treatment protocols allow for flexibility in management. However, a consensus has not been reached as to the most effective and safe technique for upper tract urolithiasis, especially between ESWL and ureteroscopy. Despite the lack of compelling scientific data comparing these treatment methods in children, ureteroscopy is the first-line treatment in many centers.

Pediatric stone disease has always been more prevalent in underdeveloped countries. Melamine-tainted milk has been associated with bilateral renal calculi in children 6 to 18 months old (Wen et al, 2010, 2011). The observation that pediatric stone disease is becoming more prevalent in the Western hemisphere is concerning. Many pediatric patients with urolithiasis have metabolic abnormalities (Jayanthi et al, 1999). There has been an increased demand on pediatric urologists to manage simple and complex urolithiasis in all pediatric age groups.

EVALUATION

Imaging

Radiographic assessment of a child with calculus disease must be accurate, economical, and safe. **Goals include determination of stone location, size, and density and urinary tract anatomy.** Children in whom radiographic assessment is indicated include children with a suspected calculus with acute symptoms and children with known calculus disease requiring follow-up evaluation to determine either stone burden or recurrence. Radiographic evaluation also is important in children with abnormal urinary tract anatomy that may predispose to calculus formation requiring eventual surgical management.

Radiographic imaging in children is similar to imaging in adult patients. The workup begins when the diagnosis of a calculus is suspected, and the radiographic study is determined by factors such as acuity of presentation and treating hospital practices. Many, if not most, children with renal colic present to an emergency department, and **unenanced helical computed tomography (CT) is the most accurate and efficient first choice in initial imaging.** Typically, a thin-slice helical protocol is defined by narrow collimation (≤ 5 mm). CT not only is able to visualize the entire urinary tract for the tiniest calculus, but it also potentially can rule out alternative diagnoses. Unenhanced helical CT of the abdomen and pelvis to evaluate urinary tract calculi was first described in 1995 and is the mainstay for imaging of calculi in adolescents and adults replacing more traditional studies such as intravenous pyelogram, kidney-ureter-bladder (KUB) radiograph, and ultrasound scan (Smith et al, 1995). With increased usage and familiarity with the technique, the application of unenhanced helical CT has expanded to include pediatric patients with similar advantages. These advantages include high sensitivity and specificity, ready availability, and speed in assessment; also an intravenous contrast agent is not necessary. Because children are at significant lifetime risk for recurrence of urolithiasis, judicious use of unenhanced helical CT is necessary to limit radiation exposure, particularly gonadal exposure, because of concerns of potential increased risk of future malignancy. There are ongoing efforts to monitor radiation exposure in children treated in the inpatient setting with the intention of mitigating future cancer risk. Kuhns and associates (2011) estimated the lifetime calculated cancer risk in children who underwent a single CT scan for stone disease workup to be increased to 2 in 1000 to 3 in 1000 compared with naturally occurring pediatric malignancies.

CT is highly accurate in stone assessment with greater than 96% sensitivity and specificity independent of the location of the calculus (Smith et al, 1996; Hamm et al, 2001; Heneghan et al, 2003; Palmer et al, 2005). CT also is helpful in demonstrating second-

ary signs of acute obstruction, such as hydroureteronephrosis, renal enlargement, and perinephric or periureteric stranding; however, the latter findings may be less obvious or absent in pediatric patients because of comparably less retroperitoneal fat (Smith et al, 1996; Smergel et al, 2001; Strouse et al, 2002).

Progress has been made in developing unenhanced CT protocols that minimize the radiation dosage without compromising diagnostic information (Heneghan et al, 2003; Cody et al, 2004; Singh et al, 2009). Experimental protocols using anthropomorphic pediatric phantoms have been used in numerous studies to determine specific organ doses, calculate effective dose, and determine the lifetime attributable risk for cancer incidence and relative risk of cancer induction from a single scan under standard-dose and low-dose modes (Brisse et al, 2009; Kim et al, 2010). Computer-simulated dose reduction has been useful in determining diagnostic thresholds in children. Compared with standard protocols, halving the dose to 40 mAs for children weighing 50 kg or less does not significantly affect the diagnosis of pediatric renal stones (Karmazyn et al, 2009). Spielmann and colleagues (2002) found excellent detectability of calculi measuring between 2 and 8 mm using much lower amperage with an almost threefold decreased estimated radiation dose compared with standard protocols. Perhaps most importantly, radiation exposure can be reduced effectively by reducing the number of CT examinations performed for poor clinical indications, scanning only the anatomic region of interest, and not performing both unenhanced and contrast-enhanced scanning unless absolutely necessary (Cohen, 2009).

Ultrasonography has a more limited role in assessment of urolithiasis compared with CT but has the distinct advantage of no associated ionizing radiation. Ultrasonography should be considered as a screening tool in the workup for nonemergent abdominal or flank pain. Although useful in the evaluation of renal calculi or hydronephrosis, ultrasonography is technically limited for use in diagnosis of a ureteral stone with the possible exception of the very distal ureter or bladder. Especially in the acute setting (i.e., symptomatic presentation with renal colic or hematuria), ultrasonography is less useful in detecting or directing management of urolithiasis. One group demonstrated that ultrasonography was nondiagnostic in 41% of children compared with 5% with CT and failed to detect ureteral calculi in 62% of pediatric patients (Palmer et al, 2005). Similar results were reported in adults confirming that ultrasonography is of limited value in the workup of urolithiasis (Fowler et al, 2002). Ultrasonography and a KUB radiograph alone may suffice in symptomatic children with a known history of renal urolithiasis or children on observation protocols, limiting exposure to ionizing radiation. It has been demonstrated in children and adults at high risk for nephrolithiasis that an initial ultrasound scan was not associated with significant differences in complications, serious adverse events, pain scores, return emergency department visits, or hospitalizations compared with patients undergoing an initial CT scan (Johnson et al, 2011; Smith-Bindman et al, 2014).

Fluoroscopy has an important role in the real-time detection and management of urolithiasis in children, and the same important safety concerns as with CT exist with respect to radiation exposure. C-arm fluoroscopy is used in the surgical setting to assist in antegrade percutaneous access of the upper urinary tract and retrograde access of the lower urinary tract. Manipulation of endoscopic instruments in vivo often requires fluoroscopic monitoring. Fluoroscopy also is used during ESWL to assist in stone localization and to monitor the effectiveness of treatment. Urologists must have a working understanding of the principles of fluoroscopy and be aware of the intraprocedure fluoroscopy time and energy settings to limit radiation exposure to the pediatric patient and the operative staff.

CONSERVATIVE MANAGEMENT

Conservative management of pediatric nephrolithiasis is considered first-line treatment, provided that there is no evidence of an

KEY POINTS: EVALUATION OF STONE DISEASE

- There has been a dramatic increase in the incidence of pediatric urolithiasis, especially among white, adolescent girls.
- Evaluation of pediatric stone disease must include genetic, metabolic, dietary, and anatomic causes.
- Goals of pediatric stone disease evaluation include determination of stone location, size, and density and urinary tract anatomy.
- A complete metabolic workup including a 24-hour urinalysis should include creatinine, sodium, calcium, oxalate, uric acid, and citrate measurements.
- Although unenhanced helical CT scan is the most accurate and efficient imaging study for stone disease, judicious use is necessary to limit radiation exposure; ultrasonography should be considered as a screening tool in the workup of nonemergent renal colic.

obstructing stone harboring an infection or a child is failing to thrive as a result of stone disease. Clinical scenarios including anorexia for more than 24 hours, persistent nausea and vomiting, and pain refractory to conservative measures should prompt endourologic intervention. In the case of a stone-bearing solitary kidney, early intervention is favored over conservative treatment. **In managing stone disease in pediatric patients, renal calculi smaller than 3 mm are likely to pass spontaneously, and stones 4 mm or larger in the distal ureter are likely to require endourologic treatment** (Van Savage et al, 2000). This information should be relayed to caregivers and parents. If a ureteral stent is placed acutely in children for the clinical circumstances described earlier, definitive endourologic therapy is delayed 4 to 6 weeks to allow for decompression, ureteric orifice dilation, resolution of edema, and proper treatment and clearance of any infection if necessary.

Many studies in adults have evaluated the efficacy of medical expulsive therapy to facilitate distal stone passage. Use of α antagonists, calcium channel blockers, and steroids has been shown to be effective. Based on efficacy demonstrated in adult patients (Porpiglia et al, 2004), α -receptor antagonists such as tamsulosin may be offered on an individualized basis as adjunctive therapy to facilitate ureteral expulsion in children. To date, however, published data to prove superiority of these agents over standard pain medication in pediatric patients are lacking. For example, a Turkish study demonstrated that daily administration of 0.03 mg/kg of the α antagonist doxazosin versus analgesic alone did not show superior expulsive results with regard to distal ureteral stones measuring up to 10 mm in children 2 to 14 years old (Aydogdu et al, 2009).

Pediatric Considerations

Special considerations in the endourologic management of stone disease in children include preservation of renal development and function, prevention of radiation exposure, and minimizing need for re-treatment. Despite advances in endourologic equipment and technique, controversy remains regarding the contribution of shock wave lithotripsy (SWL) to future development of diabetes or hypertension and whether ureteric orifice dilation during ureteroscopy leads to ureteral stricture formation or development of vesicoureteral reflux. International consensus is lacking as to the most effective surgical management of pediatric stone disease because of a lack of prospective randomized trials comparing treatment modalities and disparity in the access to emerging technologies. **Regardless of treatment modality, the presence of residual stone fragments (RFs) is associated with adverse clinical outcome** (Afshar et al, 2004), and every attempt should be made to achieve a stone-free status. Surgeon experience is paramount to facilitate complete stone clearance and minimize re-treatment rates. The decision regarding the most efficacious primary treatment modality must be individualized to the child based on age, anatomy, location, and composition of stone burden.

Antibiotic Use

In line with the 2008 American Urologic Association best practice statement on antibiotic prophylaxis, 24 hours or less of perioperative antibiotics is indicated in all patients undergoing upper tract instrumentation (Wolf et al, 2008). In children, appropriate agents include trimethoprim-sulfamethoxazole, first-generation and second-generation cephalosporins, and ampicillin in combination with an aminoglycoside. A urine culture is mandatory before all upper tract procedures to determine if the urine is sterile, and culture results are used to guide preoperative antibiotic therapy, particularly for patients undergoing percutaneous procedures, patients with high-grade obstruction, or patients with an indwelling stent (Wu and Docimo, 2004). In our practice, children with a negative urine culture undergoing uncomplicated SWL and ureteroscopy procedures receive perioperative cefazolin, and all children undergoing a percutaneous procedure or who have a preexisting ureteral stent or nephrostomy tube receive a fluoroquinolone or ampicillin/gentamicin. Use of postoperative antibiotics is controversial and is determined on an individual basis for each child, especially with more recent data demonstrating an increased risk of developing resistant bacterial strains with prolonged use of antibiotic prophylaxis (Conway et al, 2007).

SHOCK WAVE LITHOTRIPSY

The emergence of SWL during the early 1980s revolutionized minimally invasive treatment of adult urolithiasis. Since the initial report on successful SWL use in children in 1986 (Newman et al, 1986), large series have reported complication, safety, and stone-free rates comparable to adult cohorts (Table 135-1) (Myers et al, 1995; Elsobky et al, 2000; Ather and Noor, 2003; Muslumanoglu et al, 2003; Rizvi et al, 2003; Aksoy et al, 2004; Raza et al, 2005; Demirkesen et al, 2006). When used as a primary treatment option for upper tract calculi, SWL efficacy ranges from 68% to 84% (Myers et al, 1995; Rizvi et al, 2003; DeFoor et al, 2005). SWL has been a preferred treatment modality for uncomplicated renal and proximal calculi 15 mm or smaller in pediatric patients. In a contemporary series of 216 children (mean age of 6.6 years) with a mean stone size of 14.9 mm undergoing SWL with the Dornier HM3 lithotripter, Landau and colleagues (2009) reported a 3-month stone-free rate of 80%, demonstrating that stone-free rates can be achieved efficaciously in appropriate candidates. **Complications are minimal and range in severity from hematuria and ecchymosis to obstruction with sepsis** (Farhat and Kropp, 2007).

Although well tolerated in children, current stone-free rates with SWL are difficult to interpret from the existing body of data because of discrepancies between studies with regard to type of lithotripter, number of shocks administered, and re-treatment rates. **Data suggest that stone-free rates in children with a history of a urologic condition or urinary tract reconstruction are quite low (12.5%); with alternative surgical techniques available, such children may be better served with ureteroscopy or PCNL** (Nelson et al, 2008). Despite encouraging results, SWL has not been approved by the U.S. Food and Drug Administration for use in children, although it is a widely accepted treatment modality.

Shock Wave Lithotripsy Technique in Children

General anesthesia is administered in most smaller children to avoid patient and stone motion and the need for repeated repositioning. With modern lithotripters, intravenous sedation has been successfully employed in some older children (Aldridge et al, 2006). Bowel preparation is seldom used to avoid dehydration and electrolyte imbalance postoperatively. The number of shocks delivered and the kilovoltage used vary per lithotripter, but the current consensus is that low power settings (17 to 22 kV) be used to prevent stone migration during the procedure, with 3000 shock waves per session (<2000 in very young children) (Farhat and Kropp, 2007). A report assessed and compared the number and intensity of shock

TABLE 135-1 Outcomes with Large Series of Shock Wave Lithotripsy in Children

STUDY	CHILDREN/ RENAL UNITS	LITHOTRIPTER	MEAN AGE (yr)	STONE LOCATION (%)	MEAN SIZE (mm)	RE-TREATMENT RATE (%)	STONE-FREE (%)	COMPLICATIONS (%)
Myers et al, 1995	446	Siemens Lithostar	13.7 R 14.1 U	53.4 R 46.6 U	12.3 R 7.3 U	10.7 R 3.5 U	67.9 R 91.1 U	Sepsis—0.2
Elsobky et al, 2000	148	Dornier MFL 5000 (106); Echolith MedTech (42)	11.2	92.6 R 7.4 U	10.2	64	86	Steinstrasse—0.7
Muslumanoglu et al, 2003	344	Siemens Lithostar Plus	8.7	57.1 R 42.9 U	N/A	53.9	73.3	Overall—9.6 Steinstrasse—7.8 UTI—1.2 Colic—2.9
Rizvi et al, 2003	262	EDAP LT02 Technomed	N/A	67.6 R 32.4 U	N/A	29.5	84.2 R 54.1 U	Colic—10.1 Fever—8.5 Steinstrasse—1.1 Hematuria—11.3
Ather and Noor, 2003	105	Dornier MPL 9000	5.6	100 R	15	N/A	95	Colic—2.9 Steinstrasse—1.9 UTI—2.9
Aksoy et al, 2004	129/134	Dornier MPL 9000	8.7	84.4 R 15.6 U	15.7	N/A	85	Overall—14.7 Steinstrasse—5.4 UTI—7.8 Hematoma—0.8
Raza et al, 2005	122/140	Piezolith 2300; Dornier Compact Delta	7.7	N/A	17.9	N/A	69	Fever—2.9 Colic—7.2 Steinstrasse—2.4
Demirkesen et al, 2006	126/151	Siemens Lithostar	8 (median)	66.9 R 33.1 LP	10 R 6 LP	40	71.5	Overall—7.2 Fever—0.8 Steinstrasse—6.4

LP, lower pole; NA, not available R, renal; S, staghorn; U, ureteral; UP, upper pole; UTI, urinary tract infection.

waves required for stone fragmentation in 44 children (mean age of 5.9 years) and 562 adults (mean age of 40.9 years). With an equivalent number of sessions (1.1 vs. 1.1), the mean number of shock waves (950 vs. 1262, $P < .001$) and kilovoltage required (11.8 kV vs. 12.4 kV, $P < .001$) were significantly reduced in the pediatric cohort (Kurien et al, 2009).

Whether or not to place a ureteral stent before ESWL in children is controversial and a matter of personal preference. It is unclear if placement of a ureteral stent before SWL facilitates fragment passage and improves stone-free outcomes. Although rates of stent placement before SWL are inconsistent across series, **current relative indications include solitary kidneys, staghorn calculi, large ureteral calculi, obstruction, or abnormal anatomy and are not based on total stone burden.** Ureteral catheters with retrograde opacification are occasionally employed by some clinicians to aid in the localization of radiolucent calculi.

Stone Size, Location, Composition, and Patient Age

Although early series focused primarily on the feasibility, safety, and efficacy of SWL in children, more recent efforts have centered on identifying demographic, anatomic, and stone-related prognostic factors for treatment success. SWL is considered the primary treatment for upper tract calculi 15 mm or smaller in children (Farhat and Kropp, 2007), but evidence to support this stone size cutoff is lacking. Ather and Noor (2003) analyzed the correlation between stone size and clearance in 105 children younger than 14 years old. They reported an overall stone-free rate of 95% after a mean of 1.7 SWL treatments; 5% of patients required additional procedures as adjuncts to SWL. In this cohort, mean stone size in the treatment success group was 14 mm compared with 16 mm in the treatment failure group (Ather and Noor, 2003). In contrast, Elsobky and coworkers (2000) reported a 91% stone-free rate for mean stone diameter less than 10 mm versus 75% stone-free rate for mean stone diameter greater than 10 mm. Shouman and colleagues (2009) reported on a series of 24 children with a mean stone size of 31 mm undergoing SWL with the Dornier DoLi S device. In 53 sessions requiring a mean number of 3489 shock waves per session, stone-free and complication rates were 83.3% and 25%, respectively (Shouman et al, 2009). Although it is possible to treat very large stone burdens with SWL, concerns include the need for more shock treatments, more frequent re-treatment sessions, and increased risk of postoperative obstruction. Further study delineating a clear size cutoff for uncomplicated upper tract stone burden is required to counsel parents regarding the most effective first-line therapy for renal calculi between 1 and 1.5 cm.

Stone attenuation is an important predictor of success of stone fragmentation. McAdams and colleagues (2010) reported a stone attenuation of less than 1000 HU to be a significant predictor of SWL success in children, and El-Assmy and associates (2013) more recently reported that stone attenuation of 600 HU or less and stone length of 12 mm or less were the only significant predictors of success.

Renal anatomy and stone location has been a subject of more recent interest. The most effective management of lower pole calculi, a subject of frequent debate in adult patients, has yet to be determined in children. Stone-free rates from initial small retrospective SWL series range from 56% to 61% (Ozgur Tan et al, 2003; Onal et al, 2004) with re-treatment rates of 40% (Onal et al, 2004). SWL failure and re-treatment rates were associated with increased mean stone burden (Onal et al, 2004), increased infundibular length (Ozgur Tan et al, 2003), and infundibulopelvic angle greater than 45 degrees (Ozgur Tan et al, 2003).

Staghorn calculi are uncommon in children and represent a management challenge. Although monotherapy success rates are low in adults, acceptable stone-free rates in children have been achieved with SWL. In 23 children stratified by age with a mean stone burden of 1.6 cm, Lottmann and coworkers (2001) reported an overall stone-free rate of 82.6% with only one case of symptomatic obstruction. A ureteral stent was placed in 22% of children, and the authors reported an 88% stone-free rate in children younger

than 2 years old compared with 71% in children 6 to 11 years old (Lottmann et al, 2001). In 42 children with a mean stone burden of 3.2 cm stratified by ureteral stent placement, Al-Busaidy and colleagues (2003) reported an overall stone-free rate of 79%. Although stent placement did not affect stone-free rates, stent placement significantly reduced the major complication rate (Al-Busaidy et al, 2003). **The superior success rates with SWL monotherapy in children compared with adults have been attributed to softer stone composition, smaller relative stone volume, increased ureteral compliance to accommodate RFs, and smaller body volume to facilitate shock transmission.**

SWL safety and efficacy have been demonstrated even in very young children. McLorie and colleagues (2003) treated 34 children younger than 3.5 years old (mean age of 23 months) and reported an 86% overall stone-free rate (66% after one treatment) without major complications. Treatment of proximal ureteral stones has achieved similar success rates to renal stones in most pediatric series, although ureteral stenting is more commonly employed to aid in stone localization and clearance (Myers et al, 1995). Treatment of mid-ureteral to distal ureteral calculi historically has been avoided in children because of difficulties with localization over the sacroiliac joint and concern regarding possible injury to developing reproductive systems. The greater and lesser sciatic foramen has been explored as a potential blast path to treat distal stones in children.

SWL success by stone composition is similar between adult and pediatric patients. Cystine stones are uniquely challenging owing to their durability and high recurrence rates. Although SWL monotherapy has demonstrated variable results in adults, there are few reports in pediatric patients. In a small series, Slavkovic and associates (2002) reported a 50% stone-free rate in six children with cystine stone burden ranging from 0.2 to 2.5 cm. Although stone-free rates were low, fragmentation was achieved in 100% of patients, and stone dissolution was achieved with medical therapy in the remaining children after SWL (Slavkovic et al, 2002). Other authors have proposed that cystine stones formed within 2 years of therapy may be more easily fragmented with SWL and that stone number and not diameter may be more predictive of success (Farhat and Kropp, 2007).

Limitations and Concerns

In children, there is currently no consensus regarding the maximum size of RFs that are considered clinically significant (Wu and Docimo, 2004; Farhat and Kropp, 2007), and as a result there is no clear definition as to what constitutes "stone-free" status. Although children have been shown to have a greater capacity to clear RFs than adults (Gofrit et al, 2001), the presence of RFs has been correlated with an adverse clinical outcome (Afshar et al, 2004). Afshar and associates followed 26 renal units with RFs 5 mm or smaller and reported that although 31% were asymptomatic with no RF growth, 69% had adverse clinical outcomes, including RF growth or clinical symptoms. Patients with RFs had a significant increase in adverse clinical outcomes compared with stone-free subjects, and the presence of metabolic disorders was associated with RF growth (Afshar et al, 2004). For these reasons, metabolic evaluations are now routinely performed in children with a history of calculi, and every attempt should be made to achieve stone-free status.

Although SWL is well tolerated in children with few complications, stone-free rates after single-session monotherapy may be only 44% (Muslumanoglu et al, 2003). As a result, children are subjected to multiple treatments requiring general anesthesia (Aldridge et al, 2006). The need for multiple treatment sessions is concerning because the effects of shock waves on renal tissue are unclear. A growing body of evidence in adults indicates that shock waves result in renal vessel vasoconstriction and that renal tubular injury and subcapsular hematoma from cavitation and shear forces are dependent on the kilovoltage applied (Lingeman et al, 2003). In a large series of 340 adult patients with a mean follow-up period of 19 years after SWL, Krambeck and colleagues (2006)

reported an increased risk of hypertension and diabetes mellitus related to bilateral treatment, number of administered shocks, and treatment intensity. Although these results are concerning, differences between pediatric and adult populations and limitations inherent to a questionnaire-based retrospective study make application of these data in children difficult.

Retrospective studies with limited follow-up in children reported that SWL and PCNL do not cause renal morphologic or functional alteration as measured by glomerular filtration rate and serial dimercaptosuccinic acid functional studies (Wadhwa et al, 2007); however, long-term data to date are unavailable. To eliminate confounding variables and address fully the risks of chronic renal damage from SWL, long-term prospective data in children are required.

KEY POINTS: CONSERVATIVE MANAGEMENT AND SHOCK WAVE LITHOTRIPSY

- Calculi less than 3 mm are likely to pass spontaneously, whereas stones 4 mm or larger in the distal ureter are likely to require endourologic treatment.
- Surgical treatment should be predicated on achieving a stone-free status because the presence of RFs is associated with adverse clinical outcomes.
- Although complication rates with SWL are low, stone-free rates are difficult to interpret in children.
- SWL failure and re-treatment rates were associated with increased mean stone burden, increased infundibular length, and infundibulopelvic angle greater than 45 degrees.
- Children with urologic conditions or a history of urinary tract reconstruction may be better served with other surgical approaches because SWL stone-free rates are undesirably low.

URETEROSCOPIC MANAGEMENT OF UPPER URINARY TRACT CALCULI

The indications for primary ureteroscopic management of upper tract calculi in children have significantly expanded. In combination with new endourologic instrumentation and holmium:YAG laser, access and treatment of calculus disease throughout the entire pediatric urinary tract is effective, safe, and readily available in the acute setting. Adoption of ureteroscopy in the treatment of pediatric upper tract calculus disease lagged behind the adult experience because of concerns regarding large ureteroscope caliber size in children. However, evolving experience with ureteroscopy and more recent large, single-center retrospective series reporting comparable stone-free and complication rates of SWL in children validate the growing application of ureteroscopy in children.

Indications

Since the mid 1980s, with the acceptance of SWL as primary therapy for upper tract calculi smaller than 1.5 cm, ureteroscopy historically has been used for calculi below the iliac crests and for upper tract calculi after SWL failure (Wu and Docimo, 2004). Ureteroscopy was not considered primary therapy for upper tract stones in children because of complications from ureteral ischemia, perforation, stricture formation, and development of vesicoureteral reflux as a result of dilation of small-caliber ureteric orifices.

With significant improvements in the miniaturization and the durability of endoscopic equipment and the acceptance of the holmium laser, ureteroscopy has become a more attractive option in young children. Early series using rigid ureteroscopy for distal stones reported stone-free rates ranging from 86% to 100% with minimal complications (Table 135-2) (Ritchey et al, 1988; Van Savage et al, 2000; Schuster et al, 2002; Rizvi et al, 2003; De Dominicis et al, 2005; Minevich et al, 2005; Tan et al, 2005). Among

children randomly assigned to either ureteroscopy or SWL as primary therapy for distal ureteral stones, the children treated with ureteroscopy were reported to have a significantly higher stone-free rate after one treatment (94% vs. 43%) (De Dominicis et al, 2005). Another group reported experience using 4.5-Fr, 6-Fr, and 8-Fr rigid ureteroscopy to treat proximal ureteral stones in children with a mean age of 10.7 years. Ureteral dilation was not performed in any of the cases, and 100% of children were rendered stone-free (Lesani and Palmer, 2006). The results of these retrospective studies have helped to refute the notion that dilation of the pediatric ureter results in vesicoureteral reflux or the development of ureteral strictures. In a systematic review of the literature encompassing 221 pediatric ureteroscopies, Schuster and colleagues (2002) noted only two ureteral strictures and a low incidence of vesicoureteral reflux. Newer 4.5-Fr semirigid ureteroscopes with working ports that accommodate 2.4-Fr endosurgical instrumentation extend the versatility of managing distal ureteral calculi in most pediatric patients without predilation.

Standardization in the treatment of distal calculi in children led many centers to expand ureteroscopy to the treatment of upper tract calculi (see Table 135-2). Comparable stone-free rates approaching 100% with complication rates similar to the adult population have been reported (Minevich et al, 2005; Lesani and Palmer, 2006; Cannon et al, 2007; Corcoran et al, 2007; Smaldone et al, 2007). Smaldone and colleagues (2007) reported a 91% stone-free rate with a mean follow-up period of 10 months in a series of 100 children with a mean stone diameter of 8.3 mm, 52% of whom had upper tract calculi. Staged procedures were performed in 9% of these children. The authors reported a 4.2% perforation rate managed with ureteral stenting and one distal ureteral stricture requiring open neocystostomy (Smaldone et al, 2007). Corcoran and associates (2007) reviewed a cohort of 47 children (mean age of 9.4 years) with upper tract calculi managed with flexible ureteroscopy and holmium laser lithotripsy. An 88% stone-free rate with a mean stone burden of 10.2 mm was reported with 26% requiring staged procedures. These authors concluded that because of improved ureteroscopic access to the pediatric upper tract, calculi measuring 15 mm were as safely and effectively treated in children as in adults (Corcoran et al, 2007). Even with outstanding pediatric ureteroscopic technology, pediatric ureters may require a period of stenting before embarking on endoscopic treatment. For example, a smaller caliber ureter, resistant to instrumentation, may be passively dilated with an indwelling stent over 6 to 8 weeks (Fig. 135-1).

Adoption of techniques used in adult patients, most notably sequential coaxial and balloon dilation of the ureteric orifice and use of ureteral access sheaths, has further facilitated access to the pediatric urinary tract. Initially described in 8 children by Singh and coworkers (2006), ureteral access sheaths have been shown to facilitate repetitive upper tract access, reduce intrarenal pressures, decrease operative time, and improve stone-free rates in adults. Access for the treatment of lower pole calculi is possible with the use of ureteral access sheaths and 6.9-Fr flexible ureteroscope; this stone location previously would have required SWL or PCNL. Cannon and associates (2007) reported a 76% stone-free rate in 21 children with lower pole calculi and a mean stone diameter of 12.2 mm. After a mean of 11.4 months, no major complications were observed (Cannon et al, 2007). With the transition from SWL to ureteroscopy as a primary treatment modality at our institution, current relative contraindications to ureteroscopic management include staghorn stones in recurrent stone formers more amenable to PCNL, anatomic anomalies making retrograde access difficult, and previous endoscopic failure.

Equipment

Having an updated and well-stocked system that is familiar to the operative staff is vital to efficient management. It usually falls on the nursing staff to care for the delicate instruments and maintain them in working condition so that the instruments are operational when needed; maintenance is often needed after 20 to 30 uses. A

TABLE 135-2 Outcomes with Large Series of Rigid and Flexible Ureteroscopy in Children

STUDY	NO. CHILDREN/ NO. PROCEDURES	MEAN AGE (yr)	STONE SIZE (mm)	STONE LOCATION (%)	URETERIC ORIFICE DILATION (%)	STONE- FREE (%)	STAGED (%)	POST OPERATIVE STENTING (%)	COMPLICATIONS (%)
RIGID URETEROSCOPY FOR MID-URETERAL TO DISTAL URETERAL CALCULI									
Al-Busaidy et al, 2003	43/47	6.2	12.6	100 U	N/A	93	N/A	N/A	Ureteral perforation—4 Ureteral stricture—2 Fever/VUR—12
Bassiri et al, 2002	66/66	9	8	100 U	37.9	88	N/A	N/A	Renal colic—1.5 Gross hematuria—16.7 Pyelonephritis—4.5
Raza et al, 2005	35/52	5.9	9.4	100 U	3.9	79.3	28.6	N/A	Ureteral stricture—2 Fever—10 Ureteral perforation—6
RIGID AND FLEXIBLE URETEROSCOPY FOR UPPER TRACT AND RENAL CALCULI									
Minevich et al, 2005	58/65	7.5	N/A	64.6 U 35.4 P	30	98	N/A	85	Ureteral stricture—1.3
Smaldone et al, 2007	100/115	13.2	8.3	52 R 48 U	70	91	9	75	Ureteral perforation—4.2 Ureteral stricture—1
Cannon et al, 2007	21/21	15.1	12.2	100 LP	81	76	14	71	0
Corcoran et al, 2007	47/61	9.4	10.2	100 R	91	88	26	70	Ureteral perforation—9

HL, holmium laser; LP, lower pole; N/A, not available; P, proximal; R, renal; U, ureteral; VUR, vesicoureteral reflux.

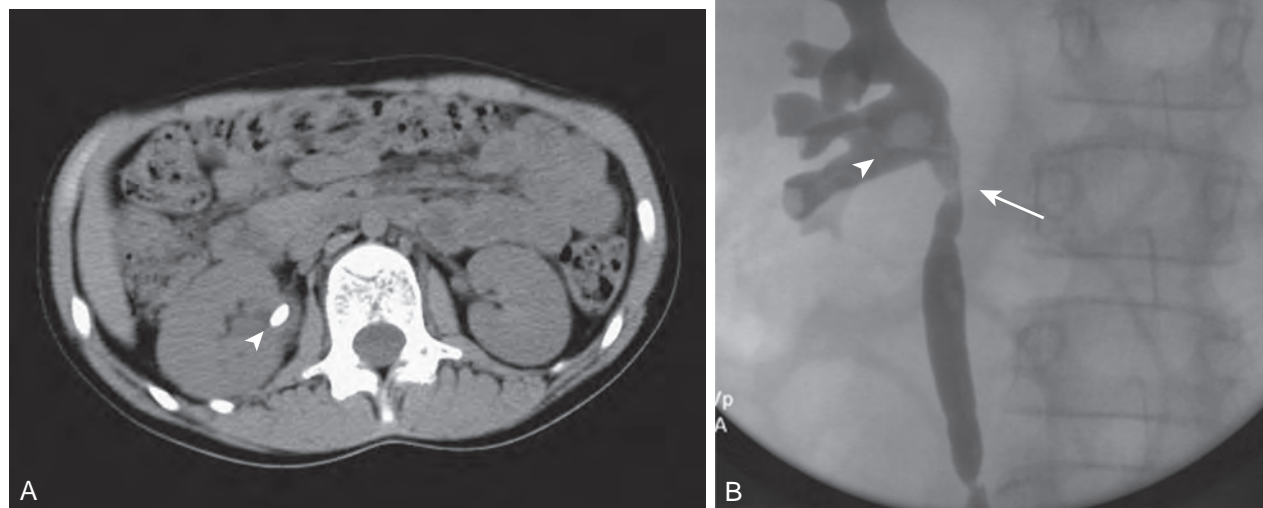


Figure 135-1. Computed tomography scan (A) and retrograde pyelogram (B) in a 10-year-old girl with glucose transport deficiency demonstrating a 9-mm renal pelvic stone (*arrowheads*). Nephrolithiasis was secondary to profound hypocitruria and hypercalciuria. Primary ureteroscopy could not be accomplished because of a narrowed segment of proximal ureter (*arrow*). After 8 weeks of ureteral accommodation with an indwelling stent, flexible ureteroscopy with laser lithotripsy and stone basketing was performed.



Figure 135-2. Pediatric semirigid self-dilating ureteroscopes may be used for rigid ureteroscopy in toddlers. A 4.5-Fr distal beak allows easier passage to facilitate dilation with the 6.5-Fr proximal component. (Photo provided by Richard Wolf; © Richard Wolf, all rights reserved.)

“basic” ureteroscopic kit is listed here; however, variation exists based on manufacturers. Various semirigid and flexible pediatric ureteroscopes in addition to ureteral access sheaths are available from numerous companies (Buscarini and Conlin, 2008). In general, semirigid ureteroscopes usually have a 2.4-Fr to 3.5-Fr working port, and flexible ureteroscopes have a 1.8-Fr to 3.5-Fr working port. With flexible ureteroscopes, distal tip deflection up to 270 degrees facilitates access to most lower pole stones (Figs. 135-2 and 135-3). However, smaller working areas and difficulties in exchanging instruments through the working element of a deflected ureteroscope may limit this treatment modality in some cases (Fig. 135-4).

The contents of a basic ureteroscopic kit are as follows:

Ureteroscopes:

- 6.9-Fr flexible ureteroscope
- 4.5-Fr and 6.5-Fr semirigid ureteroscope

Endourologic equipment:

- Guidewires: 0.035-inch Sensor GW, 0.018- to 0.025-inch Glidewire
- Basket devices: Zero-tip
- 8/10-Fr coaxial ureteral dilators
- Ureteral access sheaths (9.5-Fr and 11-Fr internal diameter)
- Double-J ureteral stent array: 3 Fr, 4.8 Fr, and 6 Fr

Ureteroscopic Technique in Children

All ureteroscopic procedures are performed under general anesthesia with paralysis to prevent patient movement and minimize the risk of ureteral perforation. When clinically appropriate, a sterile urine culture should be confirmed before surgery. Following broad-spectrum antibiotic prophylaxis, patients are placed in the lithotomy position, and rigid cystoscopy (7.5 Fr, 11 Fr, or 18 Fr) is performed to obtain a retrograde pyelogram and place a safety or working wire under fluoroscopic guidance. Initial ureteric orifice dilation is performed under C-arm fluoroscopic guidance with 8/10-Fr coaxial dilators in ureters that have not been stented beforehand or when the rigid/flexible ureteroscope cannot be advanced easily. We generally do not use balloon dilation of the ureteric orifice because of less control and cognitive “feel” during active dilation as well as concern for development of ureteral stricture from ischemia. If we encounter difficulty passing the 8/10-Fr dilator easily, we prefer to place a stent and return for a second procedure rather than dilate more aggressively.

The decision to use a flexible (6.9-Fr) or semirigid (7.5-Fr) ureteroscope is determined based on size and location of the stone, anatomic factors, and individual surgeon preference. Rigid or

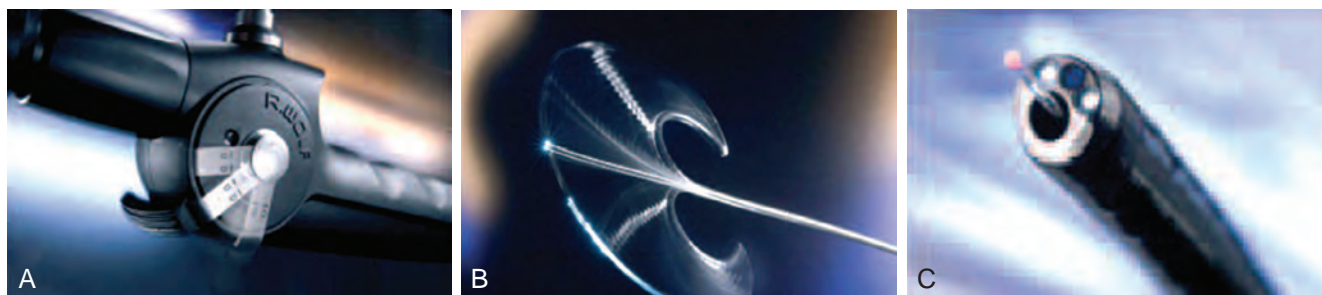


Figure 135-3. Flexible ureterscopes offer thumb control (A) for biplanar 270-degree deflection (B). Working channels from 1.8 Fr to 3.6 Fr can accommodate working elements such as a holmium:YAG laser fiber (C). (Photos provided by Richard Wolf; © Richard Wolf, all rights reserved.)

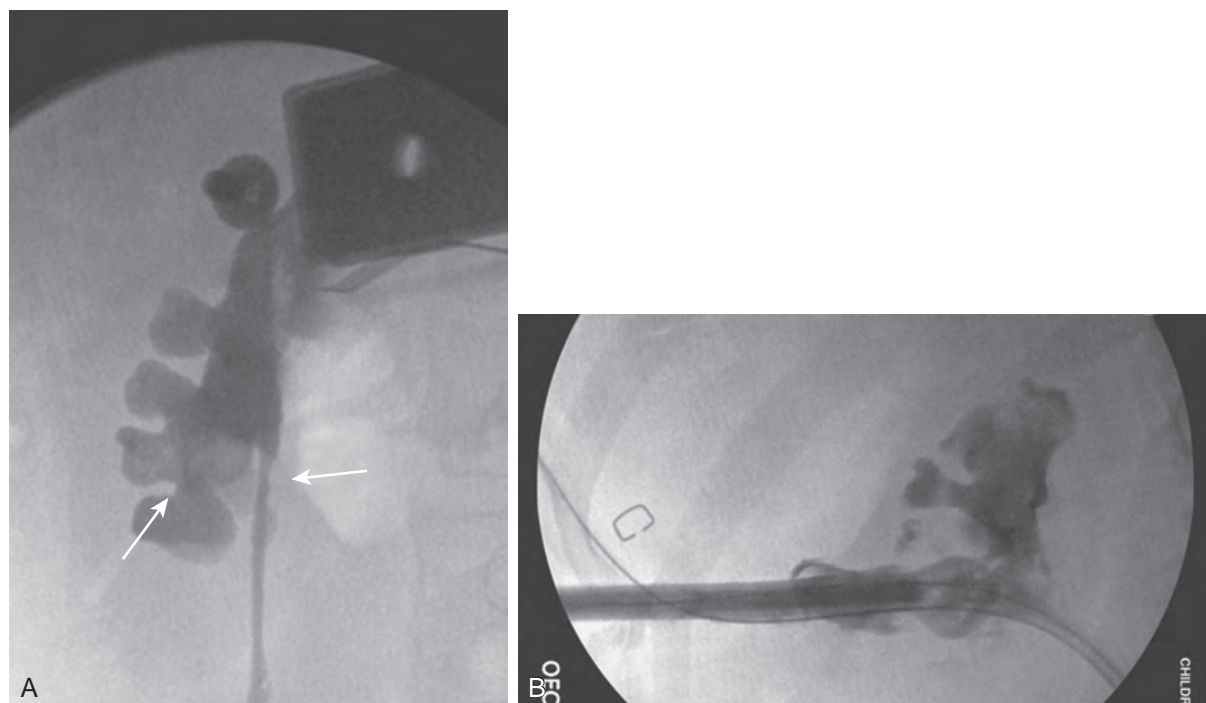


Figure 135-4. A, A 7-year-old boy with two separate 7- to 9-mm stones within lower pole calyces (left arrow). A ureteroscopic approach was attempted, but a lower pole infundibular-ureteropelvic junction angle greater than 270 degrees (right arrow) limited ureteroscopic access and visibility. B, A percutaneous nephrolithotomy was subsequently performed, clearing all stones in one sitting.

semirigid ureteroscopy for ureteral calculi is routinely performed with a safety wire in place, and flexible ureteroscopy is performed with a safety wire and a working wire in place. Ureteral access sheaths (internal diameter of 9.5 Fr) are routinely used to facilitate flexible ureteroscopy, especially in cases of large proximal ureteral stones and heavy renal pelvis stone burdens. Access sheaths also may facilitate flexible ureteroscopy when altered anatomy or tortuous ureters are encountered (Fig. 135-5).

Irrigating fluid, which may be used under pressure, should be isotonic and body temperature to avoid hyponatremia and hypothermia. Calculi are basket extracted when feasible or fragmented using a holmium:YAG laser to facilitate removal. The decision to place a ureteral stent postoperatively is based on the duration of the procedure, the number of passes with the ureterscope, and the degree of visible ureteral trauma or edema at the conclusion of the procedure. If the child can tolerate leaving a urethral string in place for 3 days to 1 week, the patient's parents are asked to remove the stent at home, otherwise the stent is removed under brief anesthetic after 7 days.

Limitations and Complications

As ureteroscopy is becoming more prominent in the armamentarium of the pediatric endourologist, complications need to be anticipated, and unanswered questions need to be addressed. **The most common complications involve unrecognized ureteral injury including mucosal flaps and tears, perforation, false passage, and partial to complete avulsion.** Mitigating the damage by early recognition and temporizing with immediate discontinuation of the procedure and passage of a ureteral stent may avoid complications related to shear force injury on the ureter, ischemic damage, and extravasation of irrigant or urine. Injury can occur during introduction of the ureterscope or either antegrade or retrograde passage of instrumentation (guidewires, baskets, dilators), especially in the area of an impacted ureteral calculus. Attempting to withdraw a basket-entrapped calculus too large for the ureter to accommodate can result in any of the above-mentioned injuries. In postpubertal children with an adult body mass, ureteroscopic access is technically similar to in adults. However, in prepubertal children, whether

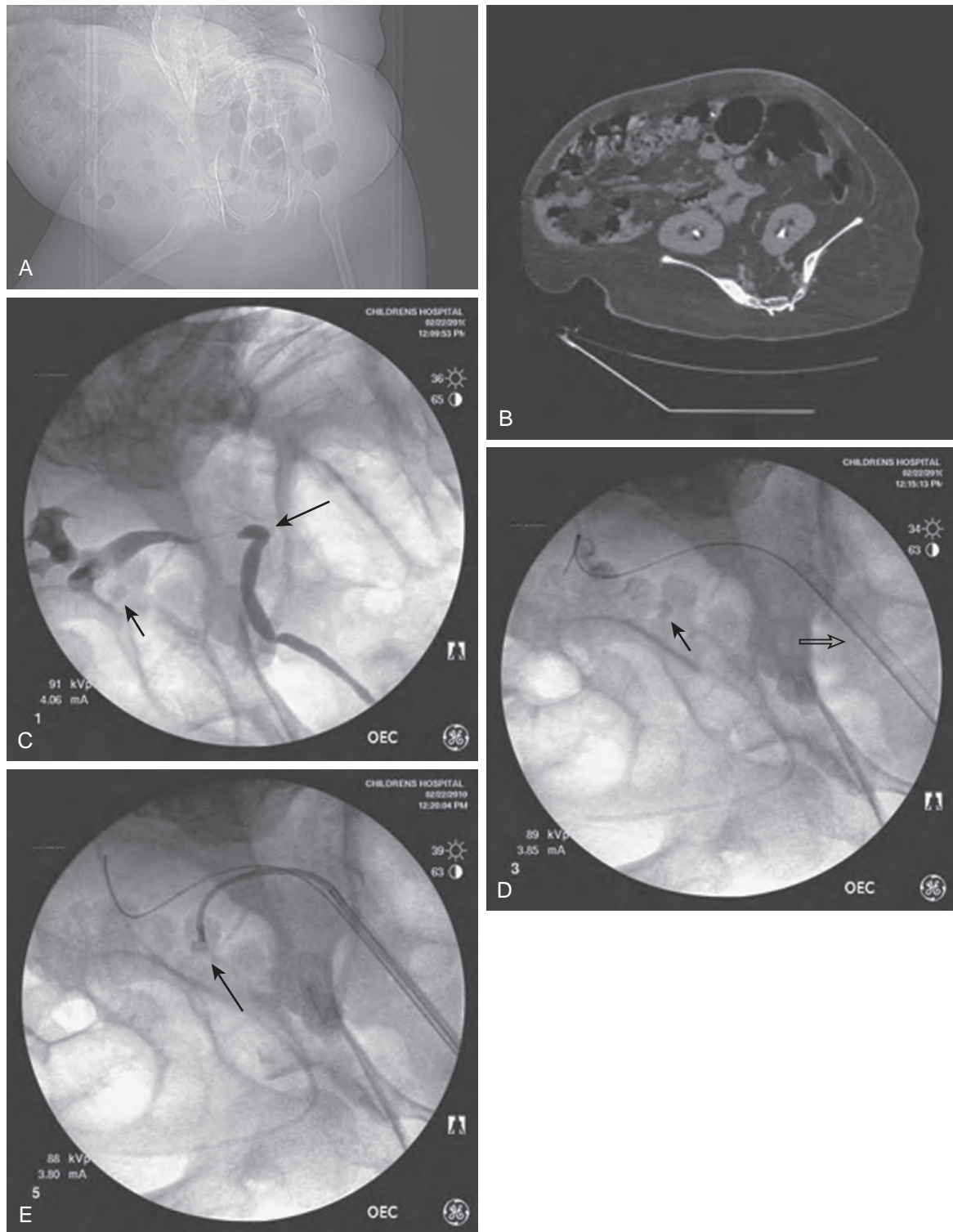


Figure 135-5. Altered anatomy in a 17-year-old boy with spina bifida who underwent a high thoracic myelomeningocele closure at birth (A). A computed tomography scan performed for a gross hematuria workup revealed bilateral nephrolithiasis in pelvic kidneys (B). The right retrograde pyelogram (C) demonstrated the lower pole stone (*short arrow*) and a tortuous ureter almost taking a perpendicular course (*long arrow*). Placement of a ureteral access sheath (D) straightened the ureter (*open arrow*). This allowed easier access to address the stone (*short arrow* in D) with a flexible ureteroscope (E).

or not to attempt primary treatment without ureteric orifice dilation, perform dilation at the time of definitive therapy, or place a stent and allow the ureter to passively dilate before definitive therapy remains uncertain. [Herndon and colleagues \(2006\)](#) performed semirigid ureteroscopy (4.5 Fr and 6.5 Fr) in 29 children with a mean age of 11 years for distal ureteral calculi. With no ureter actively dilated and only 14% of children receiving a stent beforehand, the ureter was accessed in 100% of cases for a stone-free rate of 96% ([Herndon et al, 2006](#)). We can further validate this report with our own institutional experience using 6.9-Fr flexible and 4.5-Fr and 6.5-Fr semirigid ureteroscopy; however, we prefer to perform sequential dilation with the 8/10-Fr coaxial dilator even in very young children. If we encounter difficulty, we place a stent rather than dilate more aggressively. This approach appears to minimize the immediate risks and potential long-term complications, particularly in the management of upper tract calculi; however, it increases the number of children who require a second anesthetic and procedure to achieve stone-free status. Reports suggest that 40% of pediatric patients require at least two procedures to treat upper tract calculi, which indicates that the likelihood of achieving a stone-free status after one ureteroscopic procedure may not be significantly better than with SWL ([Corcoran et al, 2007](#)). Performance of additional procedures was reported in more than half of the stones 6 mm or larger ([Tanaka et al, 2008](#)).

The necessity of placing a stent after ureteroscopy in all children is also debated. Although the tendency in large series was to leave a stent in place after ureteroscopic manipulation in most children ([Smaldone et al, 2007](#)), several authors reported no acute or long-term sequelae despite leaving a postoperative stent in less than 20% of cases ([Herndon et al, 2006](#)). In our experience, the decision to place a stent after ureteroscopy is made on an individual patient basis and depends on surgeon experience and degree of visible ureteral trauma at the conclusion of the procedure.

KEY POINTS: URETEROSCOPIC MANAGEMENT OF UPPER TRACT CALCULI

- The combination of endoscopic miniaturization and durability with the adoption of adult ureteral access systems and techniques to the pediatric upper tract has allowed calculi measuring 15 mm to be treated effectively and safely.
- Irrigating fluid, which may be used under pressure, should be isotonic and body temperature to avoid hyponatremia and hypothermia.
- Postoperative stenting, although not clearly necessary in most uncomplicated ureteroscopic procedures, is based on the duration of the procedure, number of passes with the ureteroscope, and degree of visible ureteral trauma or edema at the conclusion of the procedure.
- The most common complications involve unrecognized ureteral injury, including mucosal flaps and tears, perforation, false passage, and partial to complete avulsion.

PERCUTANEOUS NEPHROLITHOTOMY

The safety and efficacy of percutaneous nephrolithotomy for large stone burdens have been well established in adults. Urologists initially were reluctant to perform PCNL in children because of concerns regarding the use of large instruments in pediatric kidneys and parenchymal damage and the associated effects on renal function, radiation exposure with fluoroscopy, and the risks of major complications including sepsis and bleeding. Also, a deterrent to performing PCNL in children was the potential resultant sequelae of hypothermia (i.e., coagulopathy) from prolonged exposure to irrigation. However, with significantly accumulated experience, PCNL is used at the present time as monotherapy and in combination with SWL (sandwich therapy) in children achieving stone-free rates ranging from 68% to 100% ([Table 135-3](#)) ([Rizvi et al,](#)

[2003](#); [Mahmud and Zaidi, 2004](#)). Although there is no current international consensus, relative indications for PCNL as a primary treatment modality in children include large upper tract stone burden (>1.5 cm), lower pole calculi larger than 1 cm, concurrent anatomic abnormality impairing urinary drainage and stone clearance, or known cystine or struvite composition ([Wu and Docimo, 2004](#); [Farhat and Kropp, 2007](#)).

The earliest pediatric PCNL series were performed using standard adult-sized instruments. [Woodside and associates \(1985\)](#) first reported a series of seven patients (age range, 5 to 18 years) who were rendered stone-free without complications using adult percutaneous techniques and equipment. [Mor and colleagues \(1997\)](#) subsequently reported another pediatric PCNL series using adult-sized instruments. These early series avoided performing PCNL in very small children (<5 years old) because of concerns regarding parenchymal damage. In contrast to these concerns, multiple series used adult-sized instruments and reported high efficacy rates with acceptable complication rates even when dilating tract size as much as 30 Fr ([Zeren et al, 2002](#); [Salah et al, 2004](#); [Samad et al, 2006](#); [Bilen et al, 2007](#)). More recent data suggested that PCNL is possible in very young children using adult-sized equipment ([Nouralizadeh et al, 2009](#)). Investigations regarding the risk of renal damage in pediatric patients treated with PCNL revealed that there is no significant risk of renal functional loss. [Mor and colleagues \(1997\)](#) performed radioisotope scans on 10 children before and after PCNL and found no change in differential function and no evidence of significant scarring.

Despite successful use of adult equipment, early efforts focused on developing technology to minimize percutaneous tract size without affecting PCNL efficacy. [Jackman and associates \(1998\)](#) developed a novel percutaneous access technique ("mini-perc") using a 13-Fr peel-away vascular access sheath and reported an 85% stone-free rate for 11 procedures in 7 children with a mean age of 3.4 years and an average stone burden of 1.2 cm² ([Fig. 135-6](#)). With this technique, PCNL could now be performed in preschool-age children. The benefits of minimal tract dilation included increased maneuverability, decreased blood loss, and shorter hospital stay. However, theoretical limitations including prolonged operative times and impaired visualization from bleeding suggest that this technique may be inadequate for very large stone burdens.

Advancements in instrumentation such as smaller nephroscopes (15 to 18 Fr), more efficient energy sources for intracorporeal lithotripsy including holmium:YAG laser, and smaller pneumatic lithoclast and ultrasound probes have greatly facilitated percutaneous treatment techniques in pediatric patients ([Fig. 135-7](#)). As a result, PCNL has replaced open surgery as the treatment of choice for large stone burdens in all children.

Planning for Percutaneous Nephrolithotomy in Children

Much planning is required before performing PCNL in children. Films must be reviewed scrupulously to determine if stones are amenable to a percutaneous procedure. For example, nephrocalcinosis in children may be confused with staghorn calculi, but the etiology and treatment are very different ([Fig. 135-8](#)). Infection is the most common causative agent in the formation of a staghorn calculus, and PCNL is a first-line treatment. The most frequent causes of nephrocalcinosis are hereditary tubulopathies and vitamin D intoxication ([Ammenti et al, 2009](#)). Medullary sponge kidney is a renal malformation characterized by cystic anomalies of precalyceal ducts that is frequently associated with nephrocalcinosis and stone formation ([Gambaro et al, 2006](#)). Nephrocalcinosis is most often not amenable to endourologic treatment because calculi are intraparenchymal and outside the collecting system. Management is often medical and aimed at prevention of further nephrocalculi, a cause of worsening renal function.

The risks of PCNL must be reviewed with the consenting parent or guardian. It must be understood that a percutaneous procedure carries risks that include, but are not limited to, bleeding requiring transfusion, delayed renal hemorrhage requiring

TABLE 135-3 Outcomes with Large Series of Percutaneous Nephrolithotomy in Children

STUDY	NO. CHILDREN/ RENAL UNITS	MEAN AGE (yr)	EQUIPMENT	STONE SIZE (mm)	TRANSFUSION (%)	STONE- FREE (%)	SANDWICH HERAPY (%)	COMPLICATIONS (%)
Badawy et al, 1999	60	6	US	N/A	3.3	90	1.7	Fever—8.3 Colon injury—1.7 Urine leak—3.3 Open conversion—5
Zeren et al, 2002	55/62	7.9	US, EHL	16.8	23.9	86.9	1.6	Fever—29.8 Open conversion—1.6
Rizvi et al, 2003	62	N/A	US	47	25.3	67.7	27.4	Open conversion—4.8 Fever—46.8 Urine leak—6.4 Hydrothorax—1.6
Desai et al, 2004	56	9.1	EHL	18.4	14.3	89.8	5.4	Urine leak—5.4
Salah et al, 2004	135/138	8.9	US	22.5	0.7	98.6	0	Urine leak—8
Holman et al, 2004	138	8.9	US	22.5	.4	98.5	0	Fever—1.1 Urine leak—8
Samad et al, 2006	169/188	8.2	N/A	27.2	4	59.3	34.5	Fever—42.8 Hyponatremia—0.1 Obstruction—0.1
Shokeir et al, 2006	75/82	6.6	US	14.4	1.2	95.1	4.8	Urine leak—1.2

EHL, electrohydraulic lithotripsy; HL, holmium laser; N/A, not available; US, ultrasonography.

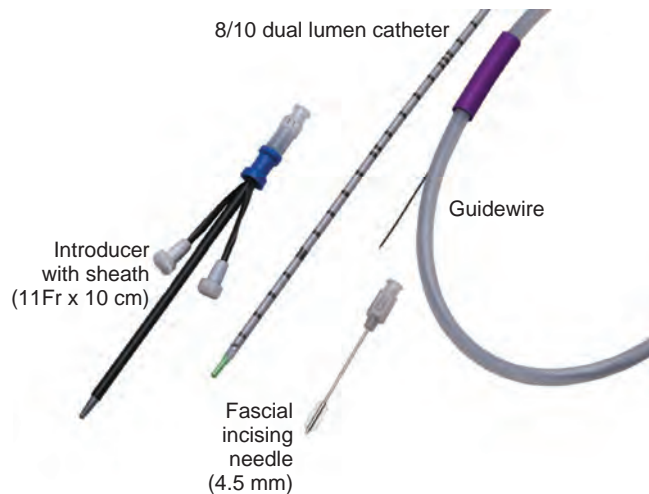


Figure 135-6. The mini-perc set uses an 11-Fr to 13-Fr peel-away vascular access sheath to accommodate a ureteroscope or cystoscope, serving as a nephroscope, to perform percutaneous nephrolithotomy in children of preschool age.

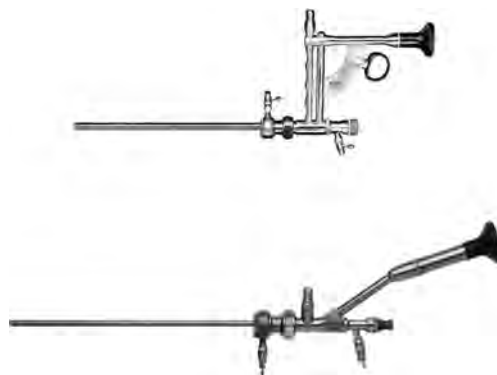


Figure 135-7. Smaller caliber nephroscopes (15 to 18 Fr) with offset lenses have greatly facilitated standard percutaneous treatment techniques in pediatric patients. (From Wolf JS Jr, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. J Urol 2008;179:1379-90.)

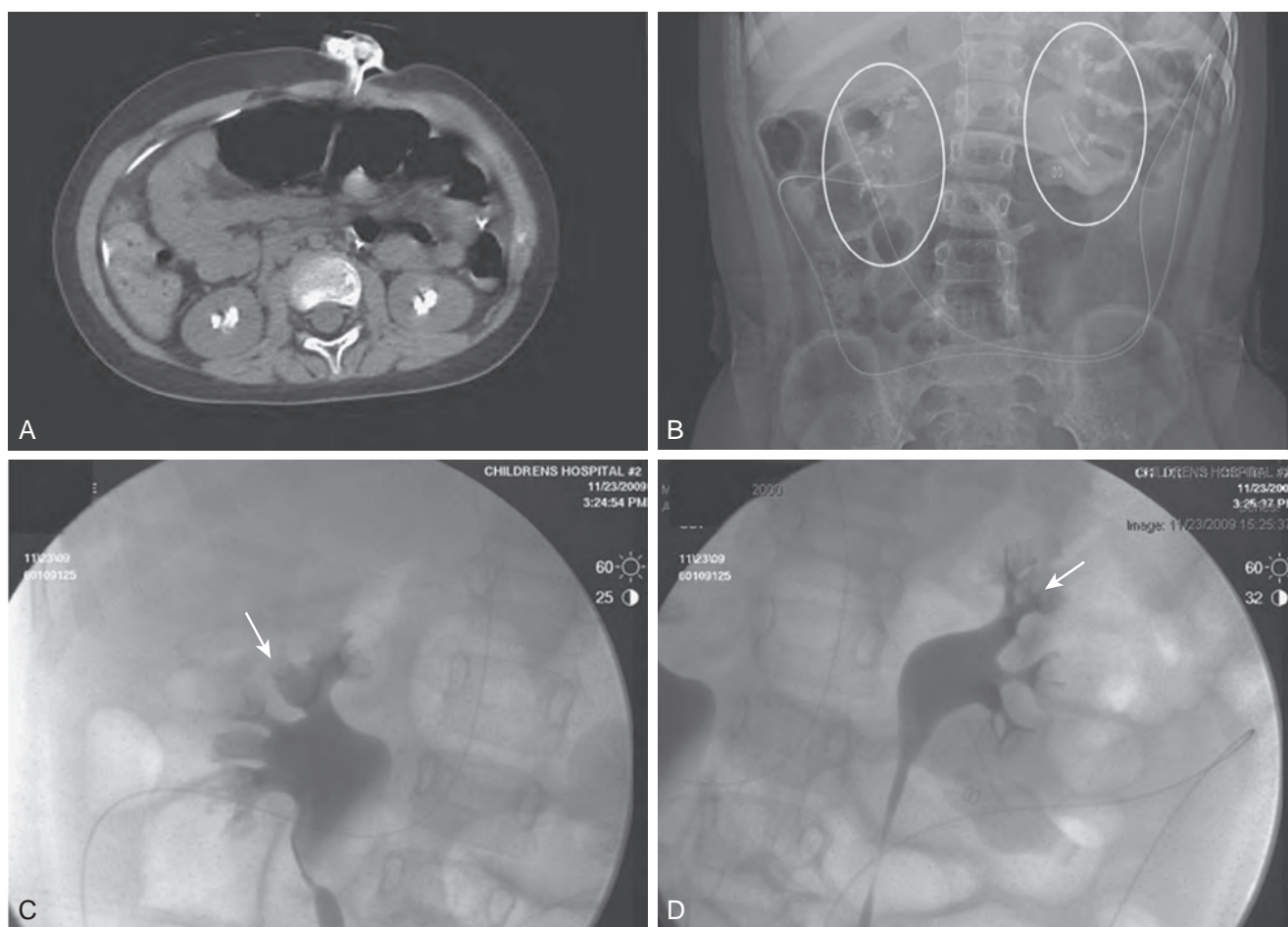


Figure 135-8. A 9-year-old boy with cerebral palsy and gross hematuria. Computed tomography scan demonstrated bilateral nephrolithiasis (A) thought to be staghorn calculi. Plain radiograph (B) and bilateral retrograde pyelograms (C and D) correlate to show nephrocalcinosis (white circles in B and arrows in C and D) reflective of medullary sponge kidney disease. Subsequent metabolic workup revealed renal tubular acidosis with hypercalciuria.

angioablation, sepsis, pneumothorax, hemothorax, urothorax, incomplete stone treatment, and injuries to organs adjacent to each respective kidney.

Every attempt should be made to treat a urinary tract infection and/or minimize bacteriuria before the procedure. A urine culture, with antibiotic sensitivities, should be checked 3 weeks before the procedure. A positive culture requires a full course of antibiotics and repeat culture to confirm. A 3- to 5-day course of prophylactic antibiotics is recommended before the procedure, even with a negative preoperative culture. Broad-spectrum intravenous antibiotics (i.e., ampicillin and gentamicin) should be given at the time of the procedure.

All percutaneous procedures are performed using general anesthesia. A warm operating room, warmed isotonic irrigation solution, short operative times (not to exceed 1.5 hours), proper draping, and monitoring of body temperature should decrease the incidence of hypothermia and hyponatremia. After induction of anesthesia with the patient in the lithotomy position, a retrograde pyelogram is obtained to outline the collecting system, and an occlusive balloon or a 5-Fr open-ended ureteral catheter is left in situ to opacify the collecting system during percutaneous access. The patient is repositioned in prone with the torso elevated 30 degrees from the table surface with a towel roll (Farhat and Kropp, 2007).

Circumstances that require special consideration involve children with spinal cord injuries and congenital anomalies such as spina bifida. In these patients, positioning can be a challenge because of existing spinal hardware and limb contracture (Fig. 135-9) (Ost and Lee, 2006). Patients who have had prior spinal surgery consisting of vertebral fusion or Harrington rod placement have restricted spinal mobility, spinal curvature, or atrophic or contracted extremities (Fig. 135-10). Renal anatomy is altered secondary to scoliosis, lordosis, or kyphosis. As a consequence, the risk of injuries to adjacent organs (i.e., pneumothorax) during percutaneous procedures increases. Assessing the degree of mobility in the trunk and extremities is crucial in planning for PCNL in these patients (Fig. 135-11). These patients must be placed in the most comfortable position possible without excessive contortion or flexion of the joints. Special attention must be paid to latex precautions in patients with myelomeningocele, and as in all cases, proper padding of pressure points is mandatory.

Percutaneous Nephrolithotomy Technique in Children

After selection of the desired calyx, a 16-gauge or 18-gauge spinal needle is placed with the assistance of fluoroscopy in the 30-degree position. The ideal tract is one that provides the shortest and most direct access to the stone. For complex calculi occupying multiple calyces including the lower pole, a supracostal posterior access is preferred to provide visualization of the superior calyx and pelvis, access to the pelvis and ureter, and straight access to the inferior calyces allowing easier manipulation of the working instruments and minimizing torque on the collecting system (El-Nahas et al, 2008). After the initial puncture, no attempt should be made to redirect the needle while it is located within the cortex of the kidney to avoid trauma. With the C-arm in the 90-degree plane, the depth and medial extension of the needle are checked. After access is confirmed with urine or irrigation return, a flexible guidewire is placed into the collecting system through the needle and directed down the ureter into the bladder. A small skin incision is made with a No. 11 scalpel and 8-Fr and 10-Fr coaxial dilators are passed over the guidewire into the collecting system. Once in place, an Amplatz Super Stiff guidewire is placed as a working wire.

Tract dilation can be performed by several techniques. The most common technique employed is serial dilation with Amplatz dilators over working wires and subsequent sheath placement under fluoroscopic guidance. For smaller children and lower stone burdens, an 11-Fr to 13-Fr peel-away sheath (Docimo Mini-Perc; Cook Urological Inc., Spencer, IN) and trocar are passed over the wire and through the calyx under fluoroscopic guidance. For balloon dilation, either the Bard X-Force or the NephroMax High Pressure Nephrostomy Balloon Catheter (Boston Scientific, Marlborough, MA) may be used. Both catheters facilitate dilation of a 30-Fr tract at a pressure of 17 atm. This technique permits dilation and sheath placement in a single step, minimizing potential parenchymal trauma and bleeding from sequential dilation with rigid dilators. The decision to proceed with mini-perc or dilation is individualized based on the child's age, anatomy, and stone burden; however, familiarity with all of the above-described techniques facilitates complete access with minimal morbidity (Fig. 135-12A and B).

Once access is obtained, nephroscopy and nephrolithotomy can be performed with a variety of energy sources for stone

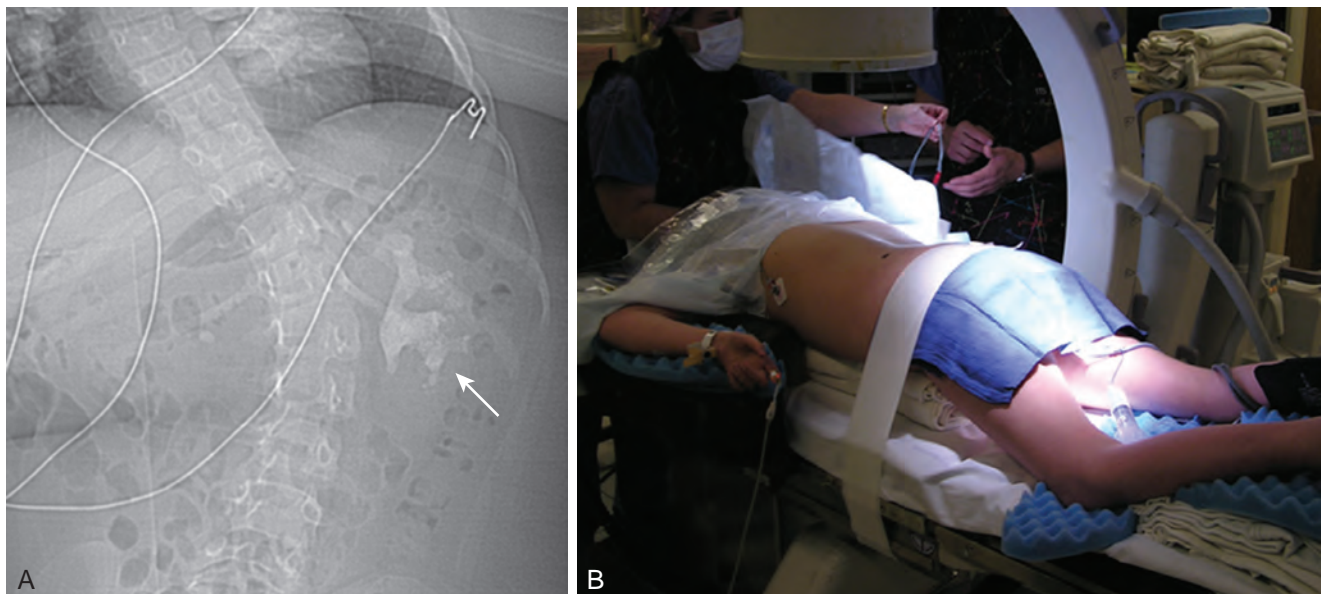


Figure 135-9. A, Severe scoliosis and complete staghorn calculus (arrow) in a 10-year-old patient with partial quadriplegia. B, Spinal curvature and limb contractures (left arm) prevented optimal prone positioning. Care is taken to pad all joints in the prone position.

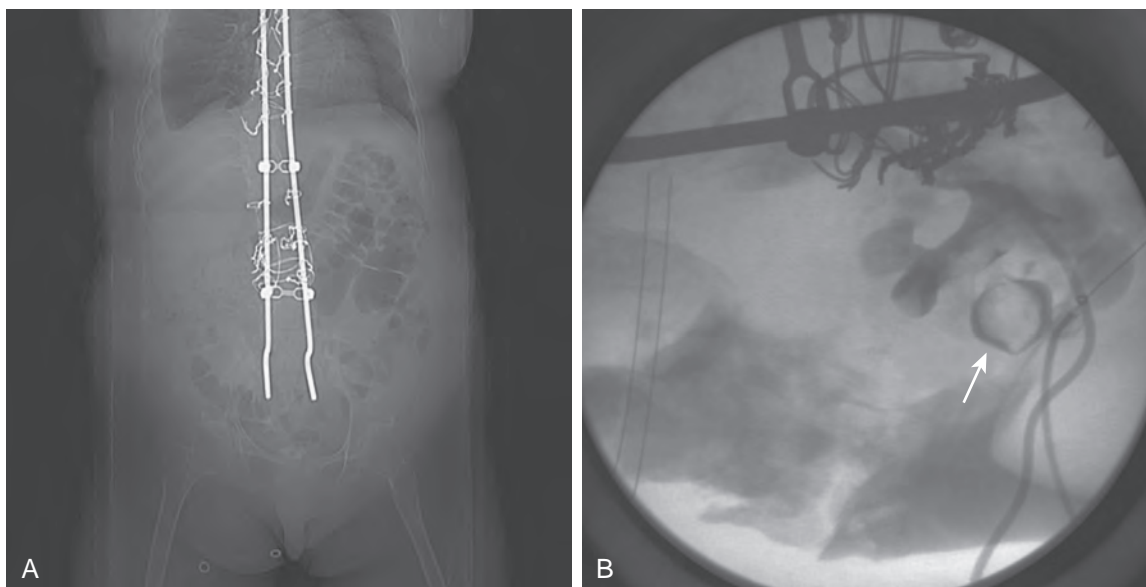


Figure 135-10. A, Harrington spinal rods in a 16-year-old patient with spina bifida. B, Prone view of right collecting system showing midpole calyceal stone as filling defect (arrow). Hardware obscured the proximal ureter and impeded access to this calyx when the C-arm was in the 30-degree position.

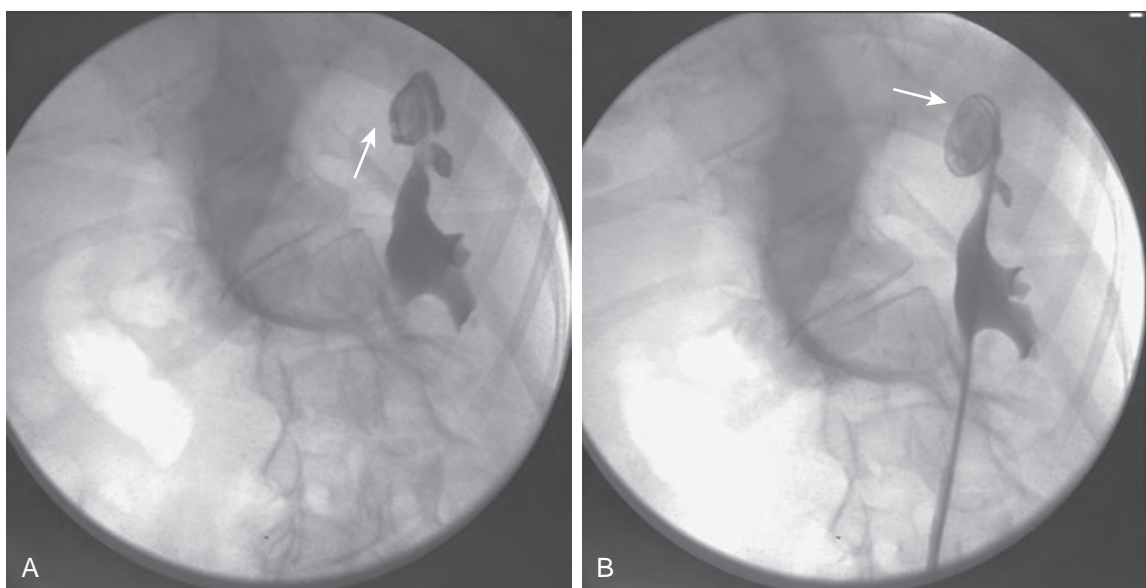


Figure 135-11. A, A 14-year-old boy with spina bifida and scoliosis with a left upper pole partial staghorn calculus (arrow). B, Altered spinal anatomy had deflected renal anatomy cephalad (arrow). Intercostal access between the 10th and 11th rib increases the risk of pneumothorax considerably.

fragmentation. The outer diameter of nephroscopes ranges from 15 to 26 Fr. A 15-Fr flexible nephroscope with a 6-Fr working channel also has been developed. In addition, 7-Fr and 8-Fr offset cystoscopes with 5-Fr working ports and 7- to 9-Fr flexible ureteroscopes can be used through an 11-Fr access sheath with enough clearance to allow low-pressure irrigation (Wu and Docimo, 2004). Energy sources used include ultrasonic lithotripsy, electrohydraulic lithotripsy (EHL), and the holmium laser, although individual preference is determined by availability and surgeon experience. Postoperative stenting and placement of a nephrostomy tube are patient and surgeon dependent and vary among series. Similar to adult procedures, tubeless PCNL has theoretical advantages,

including decreased postoperative pain and short hospital stay, but data are limited in pediatric patients (Khairy Salem et al, 2007).

Percutaneous Nephrolithotomy Outcomes

Large retrospective series of PCNL monotherapy have demonstrated high efficacy rates approaching 90% (see Table 135-3) (Zeren et al, 2002; Desai et al, 2004; Bilen et al, 2007). In 56 children (mean age of 9.1 years) with a mean stone burden of 337.5 mm², Desai and colleagues (2004) reported a stone-free rate of 89.8% using EHL through a 14-Fr nephroscope and a 20- to 24-Fr sheath. Of these procedures, 61% required multiple tracts, and 45%

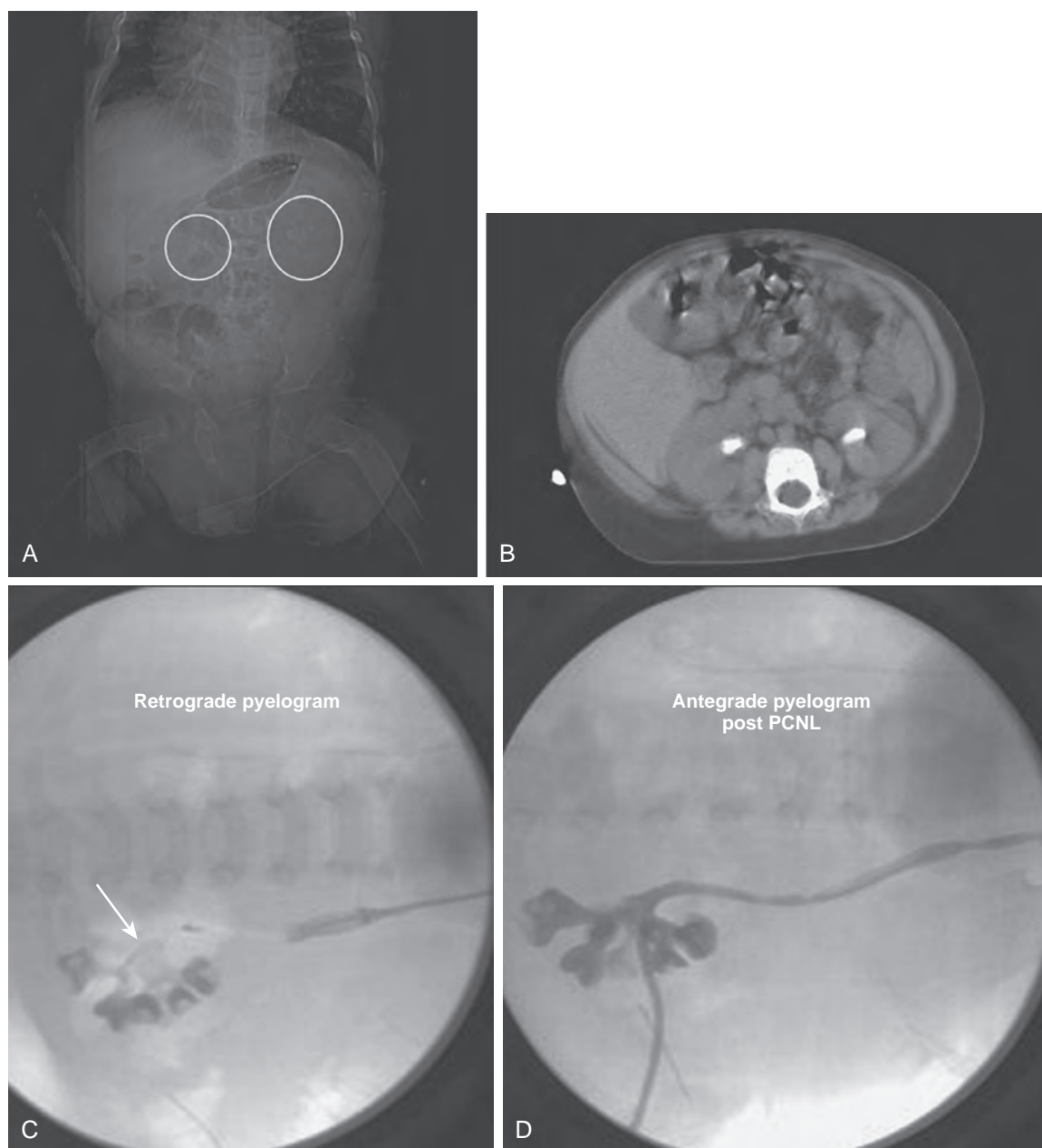


Figure 135-12. A 22-month-old boy with intractable diarrhea of infancy from tufting enteropathy who awaited a small bowel transplant. Risks for nephrolithiasis included dependency on total parenteral nutrition, osteomalacia, chronic dehydration, hypocitruria, and hyperoxaluria. **A**, Kidney-ureter-bladder film demonstrated mildly radiopaque stones. **B**, Subsequent computed tomography scan confirmed bilateral staghorn calculi. **C**, Prone view of left retrograde pyelogram of child in **A**, demonstrating staghorn calculi as a filling defect (*arrow*). A mini-perc technique was used to address the stones. **D**, Prone view of the antegrade nephrostogram through a 6-Fr nephrostomy tube demonstrating “stone-free” status. PCNL, percutaneous nephrolithotomy.

were staged procedures. Findings demonstrated that the number and size of tracts were significantly associated with postoperative hemoglobin decrease (mean 1.9 g/dL) and overall transfusion rate (14%) (Desai et al, 2004). In 52 children with a mean age of 7.9 years and a mean stone burden of 282 mm², Zeren and coworkers (2002) reported an 87% stone-free rate using ultrasonography and EHL for fragmentation and tract dilation from 18 Fr to 30 Fr. Complications included postoperative fever (30%) and need for transfusion (24%). Transfusion was associated with operative time, sheath size, and stone burden (Zeren et al, 2002). In 135 children with a mean age of 8.9 years and a mean stone burden of 507 mm², Salah and associates (2004) reported a 98.5% stone-free rate using

ultrasonography through a 26-Fr nephroscope. Complications were low (8% urine leak rate and .7% transfusion rate), with only one patient requiring a second procedure (Salah et al, 2004). In a series of 46 children with a mean stone burden of 332 mm², Bilen and coworkers (2007) reported an 88% stone-free rate using EHL, ultrasonography, and the holmium laser. When stratified by tract size (14 Fr, 20 Fr, and 24 Fr), efficacy rates were similar in all groups, but there were no complications or transfusions in the 14-Fr tract group (Bilen et al, 2007). A large multicenter study demonstrated that the most significant determinants affecting complication rates were operative time, sheath size, midcalyceal puncture, and partial staghorn formation (Onal et al, 2014).

In an effort to reduce the number of tracts and associated morbidity, some centers follow primary PCNL with adjunctive SWL therapy to clear RFs. In a small series of 29 children with a mean age of 3.8 years and a mean stone burden of 2.4 cm, [Mahmud and Zaidi \(2004\)](#) reported a 60% stone-free rate after PCNL monotherapy using EHL through a 17-Fr angled nephroscope. Only one tract was used in all patients, and after SWL sandwich therapy, the stone-free rate increased to 100% ([Mahmud and Zaidi, 2004](#)). In a larger series of 169 children with a mean stone burden of 3.1 cm, [Samad and colleagues \(2006\)](#) reported a 59% monotherapy stone-free rate with 96% of cases performed through a single tract. Approximately one third (34.5%) of primary failures were treated with SWL; the cumulative stone-free rate in all patients was 93.8% with a 3.6% transfusion rate ([Samad et al, 2006](#)). When stratified by age, anatomy, bilaterality, and renal function, stone-free outcomes were equivalent in all groups. The decision to follow PCNL with SWL is related to operator experience with percutaneous technique and available technology. **We prefer to perform a second-look nephroscopy through the original tract to ensure stone-free status during the initial hospital admission rather than progress to SWL sandwich therapy.** Endoscopic surveillance during the initial procedure can determine the need for second-look nephroscopy without relying on additional imaging and the associated risks of radiation exposure ([Roth et al, 2009](#)). With continued improvement in technology and technique, the indications for PCNL in children are expected to continue to increase. PCNL is technically challenging, and surgeon experience with PCNL is paramount in developing individualized treatment plans to optimize efficacy with minimal morbidity.

KEY POINTS: PERCUTANEOUS NEPHROTHOTOMY

- Relative indications for PCNL as a primary treatment modality in children include large upper tract stone burden (>1.5 cm), lower pole calculi larger than 1 cm, concurrent anatomic abnormality impairing urinary drainage and stone clearance, and known cystine or struvite composition.
- A urine culture before PCNL is required, and prophylactic antibiotics 3 to 5 days before the procedure are recommended despite a negative preoperative culture to minimize bacteriuria.
- Despite efficacy rates approaching 90%, PCNL is associated with risks including bleeding, delayed renal hemorrhage, sepsis, pneumothorax, hemothorax, urothorax, incomplete stone treatment, and injuries to organs adjacent to each respective kidney.

LAPAROSCOPIC AND ROBOTIC-ASSISTED PYELOLITHOTOMY

Treatment of large stone burdens in children is technically challenging and often requires multiple procedures. Laparoscopy and robotic-assisted laparoscopy have been used successfully in adults for treatment of calculi during the concomitant treatment of ureteropelvic junction obstruction and in the primary treatment of staghorn calculi. Small series using these techniques in children have been described only more recently. In eight children (mean age of 4 years) with a mean stone burden of 2.9 cm undergoing transperitoneal laparoscopic pyelolithotomy, [Casale and coworkers \(2004\)](#) reported a 100% success rate, a mean hospital stay of 2.15 days, and a mean operative time of 1.6 hours with no major complications. In the first report of robotic-assisted laparoscopic pyelolithotomy, [Lee and associates \(2007\)](#) described their experience in five patients: four with cystine staghorn calculi refractory to PCNL and SWL and one with calcium oxalate calculi and concurrent ureteropelvic junction obstruction. Of these cases, four were completed robotically, with one patient having a residual 6-mm lower pole stone and one patient requiring conversion to an open procedure. Mean operative time in this series was 315 minutes, mean estimated

blood loss was less than 20 mL, and the mean hospital length of stay was 3.8 days ([Lee et al, 2007](#)). These early experiences demonstrate that laparoscopic pyelolithotomy is feasible, safe, and efficacious as an alternative to open pyelolithotomy in children and warrants further study. However, because of their demanding technical nature, these procedures are likely to be limited to endourologic management failures in academic centers with abundant expertise in laparoscopic and robotic pediatric surgery.

PERCUTANEOUS CYSTOLITHOTRIPSY FOR BLADDER STONES

Bladder stones are found more often in children from developing countries and are thought to be related endemically to malnutrition. It is thought that diets low in animal protein and phosphorus (breast milk as opposed to cow's milk) in addition to vitamin A deficiency are contributory ([Kancha and Anasuya, 1992](#)). **Bladder stones from children in these developing countries are most often composed of ammonium acid urate.** In contrast, among children from industrialized nations, bladder stones are most often found in children with spinal cord injuries and/or congenital abnormalities such as spina bifida. These children often have undergone augmentation cystoplasty and/or manage their bladders by clean intermittent catheterization. **It has been reported that 50% of those children with reconstructed bladders develop bladder stones in their lifetime** ([Palmer et al, 1993](#)). Urinary stasis, bacterial colonization or infection with urea-splitting organisms, retained mucus, and foreign bodies all can contribute to the formation of bladder stones, most of which are struvite.

Open cystolithotomy has been the traditional modality to treat bladder stones. Transurethral cystolithotripsy is an alternative, although it is not ideal in pediatric patients. In children, a smaller caliber urethra limits effective treatment of large bladder stone burdens. However, percutaneous cystolithotripsy is used worldwide with the advantage of shorter hospital stays, smaller scars, and less indwelling catheter time postoperatively ([Al-Marhoon et al, 2009](#)). At the present time, percutaneous cystolithotripsy is the preferred method to treat bladder stones that have formed in reconstructed bladders ([Paez et al, 2007](#)). In developing countries, percutaneous lithotripsy has become the first-line treatment modality to address bladder stones in bladders that have not been augmented. For example, [Salah and colleagues \(2005\)](#) reported on their experience with cystolithotripsy in 155 children from Pakistan and Yemen with a mean age of 4.5 years and average bladder stone burden of 2.3 cm (range, 0.7 to 4 cm). All children were treated safely and successfully using a 26-Fr nephroscope through a 30-Fr sheath placed through a 1-cm suprapubic incision ([Salah et al, 2005](#)).

Percutaneous cystolithotripsy has been used effectively in infants younger than 1 year to clear bladder stones. [Gan and colleagues \(2010\)](#) reported on their experience using a 16-Fr peel-away sheath with a ureteroscope to treat bladder stones with an average size of 1.4 cm in 15 boys with a mean age of 8.2 months.

Percutaneous cystolithotripsy in children may be performed under ultrasound or fluoroscopic guidance and is most often an outpatient procedure. With either modality, the bladder is first filled to capacity with water or contrast material. The child is placed in Trendelenburg position to minimize the risk of bowel injury during access and tract dilation/formation. An 18-gauge needle is placed into the distended bladder midline, one to two fingerbreadths above the pubic bone. When proper placement is confirmed with return of fluid, a wire is passed through the needle into the bladder. A tract may then be established reflective of stone diameter and child size. Most often, a tract is established with a balloon dilator to accompany a 30-Fr sheath. Amplatz dilators also may be used. A 26-Fr nephroscope is used to extract stones smaller than 1 cm with a rigid stone forceps, or an ultrasonic lithotripter may be used to fragment stones larger than 1 cm. At the conclusion of a percutaneous cystolithotripsy procedure, a Foley catheter is left per urethra or per continent catheterizable stoma for 1 week. The rectus fascia defect is closed with a 2-0 Vicryl suture ([Fig. 135-13](#)).

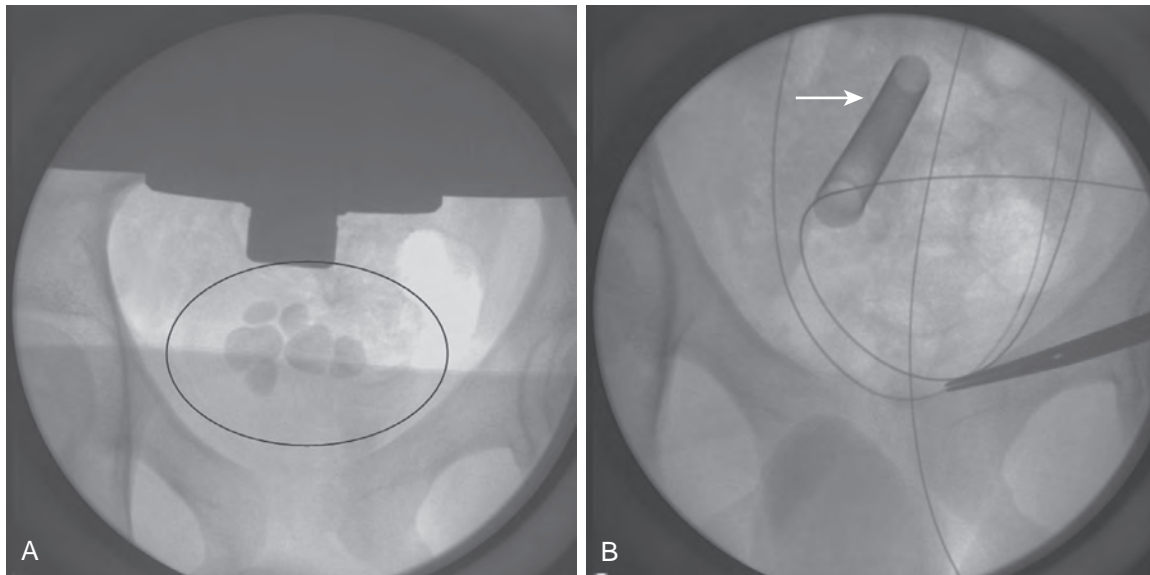


Figure 135-13. A 12-year-old boy with spina bifida with an augmented bladder (ileocystoplasty) found to have multiple sizeable bladder stones (A) on a workup for recurrent *Proteus mirabilis* infections. B, Percutaneous cystolithotripsy with an ultrasonic lithotripter was performed through a 30-Fr access sheath (arrow), clearing all stones from the augmented bladder.

KEY POINT: BLADDER STONES

- Of children with reconstructed bladders, 50% develop bladder stones in their lifetime. Urinary stasis, bacterial colonization or infection with urea splitting organisms, retained mucus, and foreign bodies all can contribute to the formation of bladder stones, most of which are struvite.

DETERMINATION OF STONE-FREE STATUS

As the surgical management of pediatric stone disease evolves, the lack of a consistent definition of “stone-free” after definitive therapy is an issue that remains unaddressed. Although controversial, in select adult patients, all RFs can be considered clinically significant and can lead to stone recurrence (Krambeck et al, 2008). Likewise, the presence of RFs in children has been associated with poor outcomes (Afshar et al, 2004), and any size RF in a young stone former may result in the need for repeat surgical procedures. RFs smaller than 4 mm in children require a high reintervention rate; 40% of these children become symptomatic, and 20% experience stone regrowth (Dincel et al, 2013). However, these RFs often are not detected on ultrasound scan or KUB film necessitating reliance on CT imaging in select children.

Balancing the risks of radiation exposure for post-treatment stone detection and the risks of anesthesia for secondary procedures is a challenging dilemma for contemporary pediatric endourologists. Newer, high-speed helical CT scanners reduce radiation exposure and rarely require intravenous sedation. In addition, maximizing intraoperative fragment detection by direct visualization in ureteroscopy and PCNL and continued development of high-resolution real-time fluoroscopy may result in less reliance on postoperative imaging and decrease the need for second-look nephroscopy/ureteroscopy, SWL, or sandwich therapy (Ost and Lee, 2006). Until the risks of radiation exposure in children are more clearly defined, surveillance in these children will be individualized based on age, anatomy, stone burden, and underlying metabolic abnormalities.

CONCLUSIONS

Evolution of technique and miniaturization of instruments have changed the management of pediatric stone disease. However, despite encouraging results, concern remains regarding safety of endourologic treatment in smaller patients and its subsequent effects on the growing kidney. Although SWL is still considered first-line therapy for upper tract calculi smaller than 1.5 cm, evidence is accumulating that ureteroscopy with laser lithotripsy and stone basketing may be more efficacious in treating upper tract stone disease in children. PCNL remains the most effective technique for large upper tract stone burdens; however, there are reports of laparoscopic and robotic-assisted laparoscopic pyelolithotomy in major pediatric academic centers with extensive laparoscopic and robotic experience. Prospective studies designed to determine the “preferred” endourologic approach to upper tract calculi in children would be helpful, albeit difficult to conduct. In this regard, individual surgeon experience and comfort level weigh heavily in choosing a treatment modality. Familiarity of pediatric urologists with percutaneous renal access and the full spectrum of endourologic equipment and techniques will continue to facilitate efficacious, minimally invasive approaches to the entire pediatric urinary tract.

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SECTION D Lower Urinary Tract Conditions

136 Development and Assessment of Lower Urinary Tract Function in Children

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Normal Lower Urinary Tract Function in Infants and Children

Epidemiology and Terminology of Lower Urinary Tract Dysfunction in Children

Bladder and Bowel Dysfunction

Clinical Assessment of Lower Urinary Tract Conditions in Children

Summary

Our increasing understanding and recognition of non-neurogenic lower urinary tract (LUT) dysfunction as a cause of various urologic disorders in childhood has had a profound influence on our management strategies over the last decade. What was known as primary or idiopathic, such as primary vesicoureteric reflux or primary nocturnal enuresis, is often associated with underlying LUT dysfunctions (LUTDs) evident on urodynamics and resolves with successful correction of the bladder physiology (Koff and Murtagh, 1983; Homsy et al, 1985; Watanabe et al, 1994; Yeung et al, 1998, 1999). Conversely, failure of recognition and treatment of the associated problem can result in persistence or even further deterioration.

The understanding of the spectrum of dysfunction of the LUT and even of normal LUT physiology in infants and young children is complex. Not only are the dynamics and functional disturbances of the LUT very different from those in adults, but the evolution in normal bladder-sphincteric function during growth and maturation in children poses continuous changes (Yeung et al, 1995a, 1995b; Sillen et al, 1996; Holmdahl, 1997). More confusingly, one type of LUTD often may progress with time and evolve imperceptibly into another, without a sharp distinction between the different stages. This is further confounded by a lack of age- and sex-specific normal reference values for various urodynamic parameters, especially for the very young age groups (Yeung et al, 1995b).

Recent advances and development in the use of urodynamic techniques specially designed for infants and young children have allowed more accurate assessment of LUT function and provided much better understanding of LUT pathophysiology. This has allowed for better recognition of functional disorders and provided a scientific basis for therapy (Hjalmas, 1988; Perez et al, 1992; Bauer, 1997; Norgaard et al, 1998). In view of the important association of LUT dysfunctions with various common urologic disorders, urologists should be acquainted with the spectrum of dysfunction and the techniques to facilitate proper diagnosis and treatment.

NORMAL LOWER URINARY TRACT FUNCTION IN INFANTS AND CHILDREN

Anatomy of Bladder

The bladder is a unique organ of the human body in that not only does it carry a dual function of both storage and emptying of urine but it also has a complex innervation of voluntary and involuntary control of function. Understanding of the functional anatomy of the LUT stems from extensive postmortem studies carried out over decades (Gosling et al, 1981; Gosling, 1985; DeLancey, 1988; de Groat, 1993; Zvara et al, 1994).

The bladder is an abdominal organ and when full can be readily palpable in infants and young children because of a shallow pelvis (Wiegel, 1990). The bladder wall consists of three layers: mucosa, detrusor, and adventitia. The detrusor consists of a meshwork of smooth muscle fibers arranged into a single functioning unit with an ability to elicit nearly maximum active tension over a wide range of length. This allows the bladder to fill with urine from the upper tract at low pressures (compliance) (Mattiasson, 1994). The ability of the bladder to store urine (reservoir function) is determined by the concomitant activity of the detrusor muscle and the bladder outlet (consisting of the bladder neck, proximal urethra, and striated muscle of the pelvic floor) (de Groat, 1993).

The bladder sphincter (external and internal) plays a major role in urinary continence by closure of the bladder neck and proximal urethra. The anatomy of the external urinary sphincter consists of a cylindric structure, which is accentuated anteriorly and thinned or actually absent posteriorly, thus giving a characteristic horseshoe or ω shape on cross section. It has an inner layer of smooth muscle and an outer layer of striated muscle, extending from the apex of the prostate to invest the length of the membranous urethra in males. In females this is less well developed and extends from the bladder neck to the mid-urethra. The internal sphincter, however,

has not been well delineated anatomically. It has generally been accepted that it consists of smooth muscle fibers continuing from the bladder base and trigone that traverse inferiorly through the bladder neck to extend toward the proximal urethra. Its existence has been better delineated on radiologic and urethral pressure measurement studies. During micturition, the bladder base, bladder neck, and proximal urethra can be shown to contract simultaneously as a unit, producing a funneling effect that opens up the bladder outlet with initiation of voiding.

Little, too, is known about the natural course of development or maturation of the structure and function of the sphincter mechanism. The literature suggests that immature detrusor-sphincter coordination, manifested as detrusor hypercontractility and interrupted voiding, commonly occurs in the first 1 to 2 years of life, causing some degree of functional bladder outflow obstruction (Sillen et al, 1992; Yeung et al, 1998). In a postmortem study of the ontogeny of the external urinary sphincter in human fetuses, infants, and young children, Kokoua and colleagues (1992) found significant age-related differences in the histologic structure of the sphincter compared to that in adults. Striated muscle fibers of the sphincter first appeared at approximately 20 weeks of gestation, then became arranged in a concentric pattern as a closed ring, fused posteriorly to form a tail-like structure that was directed to the perineal body. Posterior splitting of the striated sphincter, starting first caudally and progressively in a cephalad manner occurred during the first year of life, coinciding in parallel with gradual resorption of the "tail," eventually giving way to a mature ω -shaped structure (Kokoua et al, 1992). Because a complete closed ring of striated sphincteric muscle was present up to 1 year of age in over 40% of cases, it may be conjectured that this could be related to the high intravesical pressures and interrupted voiding that are commonly observed

during urodynamic studies in infants (Sillen et al, 1992; Yeung et al, 1995b, 1998).

Innervation of Bladder

Activation, coordination, and integration of various parts of the bladder-sphincteric complex involves both the central somatic and autonomic nervous systems through three sets of peripheral nerves: sacral parasympathetic (pelvic nerve), thoracolumbar sympathetic (hypogastric nerves and sympathetic chain), and sacral somatic nerves (primarily the pudendal nerve) (de Groat, 1993; Mattiasson, 1994) (Fig. 136-1).

Parasympathetic nerve fibers run in the pelvic nerve (S2 to S4) to supply the pelvic and vesical plexuses before entering the bladder. Parasympathetic ganglia are found within these plexuses and in the bladder wall. Sympathetic nerves arise from segments T10 to L2 of the spinal cord and go to the inferior mesenteric ganglion through the sympathetic trunk. From the inferior mesenteric ganglion the nerve fibers pass to the pelvic plexus and bladder through the hypogastric nerves. There is also sympathetic innervation originating from T10 to L2 supplying the detrusor and urethral sphincter (Bradley et al, 1974). The somatic nervous system (pudendal nerve) supplies the periurethral pelvic floor musculature (Mattiasson, 1994). The sensory and motor nerve fibers carried by all three nerves innervate both the bladder and urethral sphincter. They originate from parasympathetic ganglia located in the second, third, and fourth segments of the sacral spinal cord (Bradley et al, 1974). Within the spinal cord, information from bladder afferents is integrated with that from other viscera and somatic sources and projected to the brainstem centers that coordinate the micturition cycle (Harrison and Abrams, 1994).

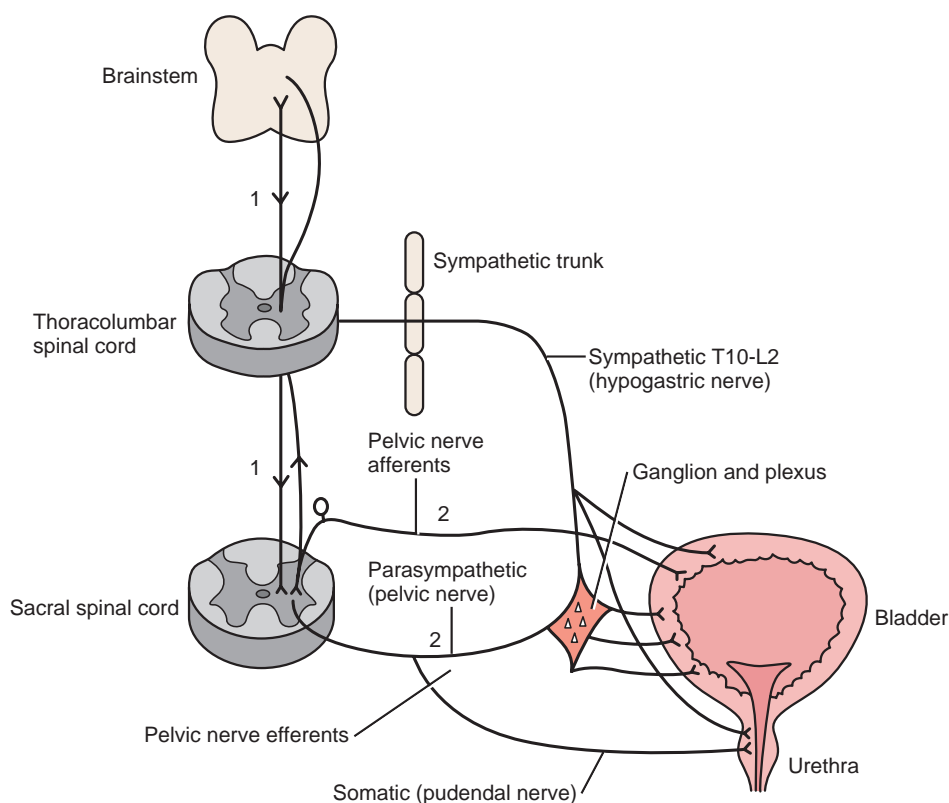


Figure 136-1. Diagram to illustrate the innervation of the bladder-sphincter complex. (From Yeung CK, Barker GM, Läckgren G. Pathophysiology of bladder dysfunction. In: Gearhart JP, Rink RC, Mouriquand PDE, editors. Pediatric urology. 2nd ed. Philadelphia: Saunders; 2010. p. 353–65.)

Development of Normal Lower Urinary Tract Function and Micturition Control

Urodynamic studies on normal infant bladders have shown that LUT function in young children is very different from that in adults. During the first 2 to 3 years of life there is progressive development from an initially indiscriminate infantile voiding pattern to a more socially conscious and voluntary or adult type of micturition. This is achieved through an active learning process whereby the child acquires the ability to voluntarily inhibit or initiate voiding at socially convenient times. This natural evolution of bladder control entails an intact nervous system and depends on at least three main events occurring in parallel: (1) a progressive increase in bladder functional storage capacity, (2) maturation of voluntary control over the urethral striated muscle sphincter, and, perhaps most importantly, (3) development of direct volitional control over the bladder-sphincteric unit so that the child can voluntarily initiate or inhibit the micturition reflex. This process also can be influenced by an awareness of the accepted social norms in families during toilet training (Yeung, 2001).

Change in Lower Urinary Tract Functional Parameters

Voiding Frequency. During the third trimester of pregnancy, the fetus is voiding at the rate of approximately 30 times every 24 hours (Goellner et al, 1981). However, immediately after birth, this drops dramatically for the first few days of life, only to increase again after the first week to reach a peak by week 2 to 4 to an average of once per hour. Subsequently this rate declines again to approximately 10 to 15 times per day between 6 to 12 months and to about 8 to 10 times per day by 2 to 3 years (Goellner et al, 1981; Yeung et al, 1995b; Holmdahl et al, 1996). This reduction in voiding frequency observed during the first few years of life appears to be related mainly to an increase in bladder volume in parallel to body growth, which is proportionately greater than simultaneous increase in urine volume production (Yeates, 1973; Koff, 1997). By the age of 12, the voiding pattern is very similar to that in an adult and usually comprises 4 to 6 voids per day (Fig. 136-2).

Bladder Volume and Emptying Efficiency. The increase in bladder volume with the growth of the child is a crucial step in the development of bladder function and urinary continence. An adequate reservoir function for urine storage is necessary to meet the increased rate of urine production and decreased voiding frequency in the growing child.

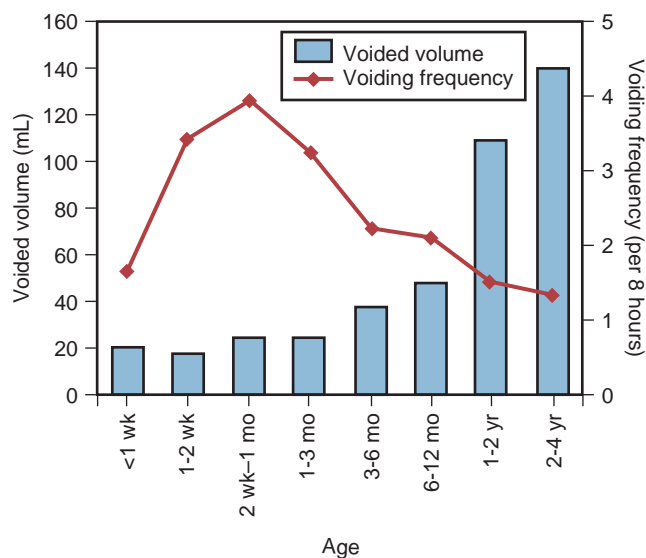


Figure 136-2. Changes in voided volume and micturition frequency from neonates to early infancy.

Several studies have shown that the age-related expected bladder capacity—that is, the maximum voided volume at a certain age—can be accurately estimated and expressed as a function of age with no difference in sex. For young infants it can be expressed as follows (Holmdahl et al, 1996):

$$\text{Expected bladder capacity (mL)} = 38 + 2.5 \times \text{Age (months)}.$$

For older children, the most widely accepted formulas include Koff's formula (Koff, 1983):

$$\text{Expected bladder capacity (mL)} = [\text{Age (years)} + 2] \times 30.$$

Or, similarly, Hjalmas' formula (Hjalmas, 1976, 1988):

$$\text{Expected bladder capacity (mL)} = 30 + [\text{Age (years)} \times 30].$$

In parallel to the increase in bladder volume, the mean voided volume of each micturition increases with age. Of note, urodynamic studies have shown that a significant proportion of infants with incomplete maturation of detrusor-sphincter coordination before the age of 1 year are still able to achieve satisfactory bladder emptying (>80% efficacy) (Yeung, 1995; Yeung et al, 1995b, 1998; Holmdahl et al, 1996; Bachelard et al, 1999; Sillen et al, 2000).

Detrusor Pressure at Voiding. Limited studies have been done on detrusor pressures at voiding in normal infants, because of the technical difficulties involved in performing urodynamic studies in young infants and an ethical consideration in justifying doing so. From the data we have in a natural filling cystometric study of infants with normal LUTs (as indicated by a normal micturating cystourethrogram) and who had undergone either dismembered pyeloplasty for pelviureteral junction obstruction or nephrectomy for dysplastic kidney, we have documented significantly higher maximum detrusor pressures with micturition ($P_{\text{det,max}}$) than in normal adults. It was also noted that male infants voided with significantly higher pressures than females (mean $P_{\text{det,max}}$: 118 vs. 75 cm H_2O , respectively, $P < .03$) (Yeung et al, 1995a, 1995b, 1998). Similar findings were reported in healthy, asymptomatic infant siblings of children with vesicoureteral reflux (Bachelard et al, 1999).

Studies also have shown that these high detrusor pressures noted during micturition were mainly observed only during the first year of life and decreased progressively with age. Furthermore, an interrupted or "staccato" type of urinary stream was noted in over half of the patients (Yeung et al, 1995a, 1995b, 1998). This was demonstrated by fluctuations of the detrusor pressure when it reached maximum during voiding and resumption of urinary stream in conjunction with a sharp fall in the detrusor pressure. The high detrusor pressures during voiding are thought to represent variations among individual infants in the maturation process of detrusor and sphincter coordination during the first 1 to 2 years of life (Yeung et al, 1995a, 1998; Holmdahl et al, 1996; Bachelard et al, 1999; Sillen et al, 2000).

We have further confirmed this finding using video-cystometry under fluoroscopy combined with natural fill urodynamics and perineal electromyography (EMG) in infants with a history of urinary tract infections (UTIs). Periods of increase in perineal or sphincteric EMG activities were noted during voiding and associated with a sudden cessation of urinary flow with a simultaneous isometric rise or high peak of detrusor pressure. In contrast, resumption of urinary flow was associated with relaxation of the external urinary sphincter and a paradoxical drop in detrusor pressure. Also, the detrusor pressure associated with the initiation of urinary flow was usually significantly lower than the maximal detrusor pressure during micturition ($P_{\text{det,max}}$) and the $P_{\text{det,max}}$ was significantly higher than those recorded in normal adults (Fig. 136-3).

Evolution of Normal Micturition Control

Traditionally, it has been assumed that micturition in newborns and young infants occurs automatically with a full bladder by a simple

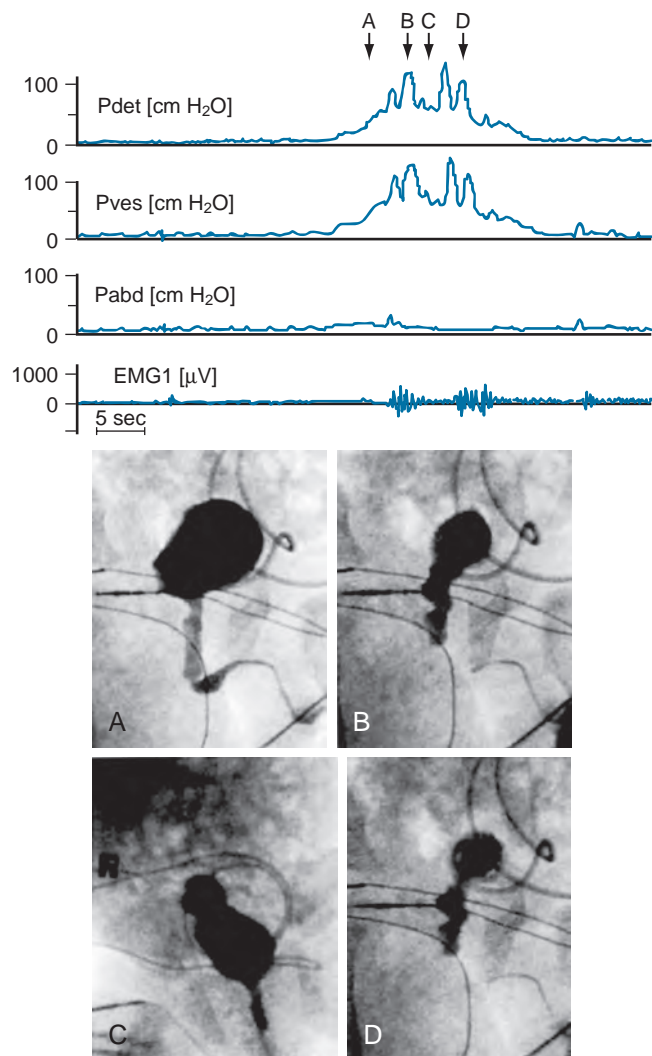


Figure 136-3. Interrupted voiding pattern due to detrusor-sphincter discoordination as revealed by urodynamic study with simultaneous perineal electromyographic (EMG) monitoring and video-cystourethrography. Arrows in top figure (graph) correspond to urethrograms at bottom. A, Urinary flow started. B, Premature sphincteric contraction and urethral closure as evidenced by the urethrogram and increase in sphincteric EMG activities, leading to a sharp spike of detrusor pressure (isometric increase) associated with a paradoxical abrupt cessation of urinary flow. C, Urinary flow resumed in parallel with sphincter relaxation. D, Repeated sphincteric contraction leading to another sharp increase in detrusor pressure and paradoxical interruption of urinary flow. Pabd, abdominal pressure; Pdet, detrusor pressure; Pves, intravesical pressure. (From Yeung CK, Barker GM, Läckgren G. Pathophysiology of bladder dysfunction. In: Gearhart JP, Rink RC, Mouriquand PDE, editors. Pediatric urology. 2nd ed. Philadelphia: Saunders; 2010. p. 353–65.)

spinal cord reflex, with little or no mediation by the higher neural centers and that with progressive maturation, voluntary inhibition of the bladder emptying reflex is achieved by adulthood. A delay in the normal maturation of bladder control was attributed to certain conditions such as primary nocturnal enuresis and hence the traditional belief that all enuretics would get better with age (Nash, 1949). However, more recent studies have indicated that this is an oversimplification of what actually occurs. Even in full-term fetuses and newborns, it has been shown that micturition is modulated by higher centers. Ohel and associates (1995) showed that intra-uterine micturition almost exclusively occurs while the fetus is awake rather than randomly distributed over various behavioral (sleep/arousal) states. Furthermore, it has been observed that mic-

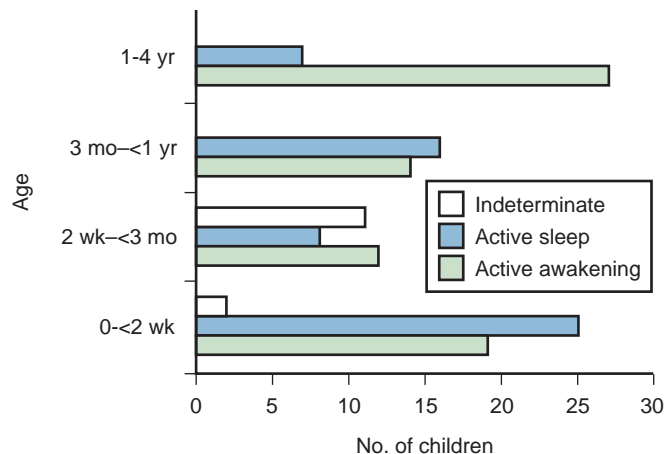


Figure 136-4. Incidence of micturition during different sleep states, according to age group.

turition in a full-term fetus can be elicited by vibroacoustic stimulation, all of which indicate that the micturition reflex is probably under higher neural control even at near gestational term (Zimmer et al, 1993). Further extensive modulation occurs during the post-natal period.

Studies on normal neonates using ambulatory bladder monitoring techniques in conjunction with polysomnographic recordings have shown that even in newborns, micturition does not occur during sleep (Yeung et al, 1995b). During sleep the bladder is normally quiescent and stable with lack of facilitation of detrusor contractions, whereas during wakefulness marked detrusor overactivity is observed. Clear electroencephalographic evidence of cortical arousal or actual awakening occurs in response to bladder distention, and sleeping infants are noted to wake up before bladder activity returns and voiding occurs. However, this arousal period often may be transient, with the infant crying or moving for a brief period, micturating, and then going back to sleep without being noticed to have awakened. This waking response to bladder distention probably involves more complicated neural pathways and higher centers than has been appreciated until now (Fig. 136-4).

These results also correlate with recent animal studies showing a sophisticated integration of preexisting central and peripheral neural pathway in micturition control at birth with remodulation occurring in the early postnatal period (Maggi et al, 1986; Thor et al, 1989). Extensive studies by de Groat and colleagues (de Groat, 1993; de Groat et al, 1998; Sugaya and de Groat, 1994; Araki and de Groat, 1997; Sugaya et al, 1997) using experimental animals have indicated that early postnatal maturation of bladder function probably occurs at different levels: (1) changes in the properties of detrusor muscle; (2) developmental modifications in the peripheral innervation of the bladder; and (3) alterations in central synaptic circuitry and neuroplasticity in the parasympathetic reflex pathways to the bladder. Recordings of spontaneous activity in bladder smooth muscle in neonatal rats showed much larger amplitude and more synchronous rhythmic contractions compared to those observed in adult rats (Sugaya and de Groat, 1994). This suggests that there is a progressive reduction in intercellular communication between detrusor smooth muscle cells, resulting in less spontaneous activities and hence more efficient urine storage during early postnatal development. In addition, peripheral and central neural mechanisms also change extensively during this period. In cats (and some other species) micturition during the newborn period depends on an exteroceptive somatovesical reflex triggered when the mother licks the perineum of the kittens (de Groat et al, 1993, 1998; Araki and de Groat, 1997). This somatovesical reflex, processed in the sacral spinal cord, disappears in older animals but may reappear after spinal cord injury. Further neuroanatomic studies have indicated that spinal bladder reflexes are mediated by interneurons

located immediately adjacent to, and synapsing with, the sacral preganglionic neurons (Sugaya et al, 1997). This interneuron–preganglionic neuron synaptic transmission is very efficient immediately after birth but is very abruptly downregulated during the third postnatal week when the mature supraspinal micturition reflexes start to appear (Araki and de Groat, 1997). Transection of the spinal cord prevents this downregulation, indicating that the higher neural centers play an important role in this synaptic remodeling, which contributes to postnatal development of micturition reflexes.

During the second or third year of life there is progressive development toward a socially conscious continence and a more voluntary or adult type of micturition control. The child becomes more aware of the sensation of bladder distention and the urge to urinate, as well as the social norm and embarrassment associated with urinary incontinence. Through an active learning process, the child acquires the ability to voluntarily inhibit and delay voiding until a socially convenient time and then actively initiate urination even when the bladder is not very full and allow it to proceed to completion. This natural evolution of micturition control mechanisms depends on an intact neural pathway and awareness of social norms, as well as multiple factors, including the gradual increase in functional bladder capacity, maturation of detrusor-sphincter coordination and progressive development of voluntary control over the whole bladder-sphincter-perineal complex. The final steps are usually achieved at approximately 3 to 4 years of age, when most children have developed the adult pattern of urinary control and will be dry both day and night. The child has learned to inhibit a micturition reflex and postpone voiding and to voluntarily initiate micturition at socially acceptable and convenient times and places. This development of continence and voluntary micturition also depends on behavioral learning and can be influenced by toilet training, which in turn depends on the cognitive perception of the maturing urinary tract. It is understandable therefore that this series of complex events is highly susceptible to the development of various types of dysfunctions.

Neurologic control of normal micturition occurs at different levels of the central nervous system, from the spinal cord with the sacral micturition center to the brainstem with the pontine micturition center, the cerebellum, basal ganglia, limbic system, thalamus and hypothalamus, and cerebral cortex (Blaivas, 1982; McLorie and Husmann, 1987; de Groat, 1993; Fernandes et al, 1994). It should be noted that the bladder is unique among visceral organs in that its function is under the control of both the somatic and the autonomic nervous systems. Besides acetylcholine and norepinephrine, various other neurotransmitters, including prostaglandin substance P, opioid peptides, vasoactive intestinal peptide, and neuropeptide Y, are involved during bladder stimulation (Fernandes et al, 1994). Simple manipulation of adrenergic and cholinergic receptors may abolish only partially the effect of neural stimulation, which explains why pharmacologic blockage of the classic neurotransmitters (acetylcholine and norepinephrine) alone may fail to elicit the expected full clinical response.

Transitory Detrusor-Sphincter Discoordination in Infancy

Studies have shown that in making the transition from an infantile to an adult pattern of micturition control, all children may transiently display some degree of abnormal bladder-sphincter function (Koff, 1997). For instance, it has been clearly shown that a significant proportion of normal infants exhibit prominent detrusor-sphincter discoordination and interrupted voiding during the first 1 to 2 years of life. This is manifested by a disordinated and interrupted urine flow that even may be brought to a complete stop for 1 to 2 minutes before restarting, producing a pattern of repeated small voidings in quick succession (Yeung et al, 1995a, 1995b, 1998). Urodynamic findings show association with high voiding pressures and interruption of flow but no impairment of overall bladder emptying. However, this type of dysfunction resolves with a period of successful toilet training and is only transitory or intermittent and does not persist. One must there-

fore be very cautious in the assessment of young children with apparent voiding dysfunctions and able to resist the temptation to overinterpret intermittent or transient symptoms as pathologic and hence overinvestigate. However, if voiding dysfunctions are persistent well beyond the period of toilet training, especially if associated with urinary complications such as recurrent urosepsis, the possibility of underlying anatomic and neurologic causes must be considered and duly evaluated.

EPIDEMIOLOGY AND TERMINOLOGY OF LOWER URINARY TRACT DYSFUNCTION IN CHILDREN

Epidemiology and Prevalence

Non-neuropathic LUTD in children is probably more common than what meets the eye, but many times present to us only when UTI, vesicoureteral reflux, or urinary incontinence is manifested. It has been reported that 15% of 6-year-old children have this condition (Hoebeke, 2002). Various conditions have been described under the category of non-neuropathic LUTD, but it must be emphasized that these conditions should not be viewed rigidly as separate and distinct entities but rather as transitional phases of a complex sequence of events. For instance, a girl with dysfunctional voiding may start with having detrusor overactivity associated with sphincter and pelvic floor overactivity, then gradually evolve to develop fractionated voiding with increasing post-micturition residues, and finally develop bladder decompensation and the “lazy bladder” syndrome (van Gool et al, 1992). It also must be emphasized that use of the term *non-neuropathic* is based purely on the fact that no obvious and neurologic lesions can be identified. However, conditions such as the urofacial syndrome complex (Ochoa syndrome) and the Hinman syndrome (severe bladder and bowel dysfunction) behave almost identically to the typical neuropathic bladder-sphincter dysfunctions. It is indeed conceivable that they do have an organic underlying neurologic cause, although the exact neuroanatomic lesion has not yet been identified. Hence, the distinction between neuropathic and non-neuropathic bladder-sphincter dysfunctions may not be as clear as traditionally thought. This chapter will focus on the discussion of non-neuropathic LUTD. Details of neuropathic LUTD will be discussed in Chapter 137.

In adults, LUT function has been well understood, and standardization of terminology has been established by a committee working under the International Continence Society (ICS) since the early 1970s (Bates et al, 1976a, 1976b, 1979). In contrast, neural control over the bladder-sphincter unit in children is age-dependent and is much more variable and complex. Definitions of normal versus abnormal LUT function therefore have been far less standardized. Various classifications for bladder dysfunctions in children have been described over the past few decades (Lapides, 1970; Bellinger, 1996; Wein, 1998). To avoid confusion, in 1998 the International Children's Continence Society (ICCS) proposed a standardized set of terminology and definitions for different LUT symptoms and dysfunctions (Norgaard et al, 1998). This was subsequently revised in 2006 and most recently in 2014 (Nevés et al, 2006; Austin et al, 2014). Terminology used in this chapter will adhere to the standard terminology as recommended by the ICCS except where specifically noted (Norgaard et al, 1998; Nevés et al, 2006; Austin et al, 2014).

Terminology of Lower Urinary Tract Symptoms

LUT symptoms (LUTS) and LUTDs are best classified according to their relation to the storage and/or emptying phase of bladder function (Norgaard et al, 1998; Nevés et al, 2006; Austin et al, 2014). Because quantitative data defining symptomatic terms are often lacking, especially in children, the ICCS standardized terminology for LUTS has focused on a descriptive rather than a quantitative language (Nevés et al, 2006; Austin et al, 2014). ICCS uses 5 years of age as the reference for LUTS, because this

age is used by the *Diagnostic and Statistical Manual Fifth Edition* (DSM-5) and the *International Classification of Disease-10* (ICD-10) to characterize urinary incontinence disorders (Chase et al, 2010). It must of course be realized that there may be significant variability in the maturation of LUT function among different children, and hence the LUTS terminology may be selectively applicable to younger cohorts of children who have already achieved good voluntary control of LUT function before 5 years of age. Of note, because symptoms are variable, the duration of any manifesting symptom is crucial in the understanding of the underlying LUTD. In addition, other variables that may have an impact on LUT function and continence, including the developmental level of the child as well as any coexisting behavioral disorders, need to be considered. For functional bowel dysfunction the minimum age is 4 years. As a result of the intricate relationship between the bladder and bowel, concomitant bladder and bowel functional disturbances are very common and these have been labeled as **bladder and bowel dysfunction (BBD)**. BBD is a comprehensive term that can further be subcategorized into LUTD and bowel dysfunction.

BLADDER AND BOWEL DYSFUNCTION

BBD is a new term presented in the third ICCS standardization document on terminology for LUT function (Austin et al, 2014) published in 2014; this enhances previous ICCS documents (Norgaard et al, 1998; Abrams et al, 2002; Nevéus et al, 2006; Dannaway et al, 2013).

The commonality of bowel emptying issues with bladder function is reflected in this new terminology. Older terms such as *Hinman bladder*, *non-neurogenic neurogenic bladder*, *occult neurogenic bladder*, and *dysfunctional elimination syndrome* have become obsolete. By this new term the close relationship between bowel and bladder function is acknowledged. Thus the importance of bowel-related terms in relation to bladder function is emphasized.

The rectum and urinary bladder have close anatomic proximity, and they share innervation from parasympathetic S2 to S4 and sympathetic L1 to L3 nerve roots. Because of this close relationship, concomitant bladder and bowel disturbances have been labeled BBD. BBD is recommended as a more descriptive comprehensive term of a combined bladder and bowel disturbance that does not explain pathogenesis but rather encompasses this parallel dysfunction. BBD is an umbrella term that can be subcategorized into LUTD and bowel dysfunction.

BBD is prevalent. Almost 40% of referrals to pediatric urologists are related to LUTD, and 30% of referrals to pediatric gastroenterologists are related to bowel dysfunction. Up to 50% of patients seen at a pediatric urology clinic have combined LUTS and functional constipation (Burgers et al, 2013a, 2013b).

Patients with BBD represent a homogeneous group having more psychological difficulties, such as attention problems and oppositional behavior. These patients would potentially benefit from a multidisciplinary treatment approach involving urology, gastroenterology, and psychology professionals (Wolfe-Christensen et al, 2013).

CLINICAL ASSESSMENT OF LOWER URINARY TRACT CONDITIONS IN CHILDREN

The tools used for assessment of LUT conditions in children are given in **Box 136-1**. The assessment of children with LUT conditions should consist of a detailed and structured history, a frequency/volume chart, and a physical examination (Nevéus et al, 2006). Uroflowmetry and ultrasonography (US) can be added.

After screening the wet child by this means, those patients who will benefit from further urodynamic studies can be selected. Furthermore, patients with other conditions such as neuropathic bladder, structural anomalies of the LUT, or UTIs should be identified after this screening.

BOX 136-1 Assessment of Functional Voiding Disorders

ESSENTIAL

History
Clinical examination
Urinalysis
Frequency voiding chart
Uroflowmetry

SELECTIVE

Video-urodynamics
Magnetic resonance imaging of lumbosacral spine
Cystoscopy
Somatosensory evoked potential and electromyography

History

Medical History and Questionnaires and Scoring Systems

Literature on this topic is sparse. There are only some brief comments in the recent standardization reports of the ICCS (Nevéus et al, 2006; Austin et al, 2014). History taking in children with LUTDs should be detailed and structured. This should include relevant questions to exclude neurologic and congenital abnormalities. Bowel dysfunction can coexist in the form of encopresis, constipation, and fecal impaction and should be noted during obtaining the history. The urinary history should focus on symptoms related to both the storage and evacuation of urine. If possible, the history is obtained from both the child and the parents/guardians. Information from the child can then be checked and completed with parents' information. The majority of children with non-neuropathic LUTD typically present after toilet training with symptoms of either nighttime or daytime urinary incontinence, or both. Occasionally they can be recognized at an earlier age when the child presents for investigation of UTIs or vesicoureteral reflux (VUR).

Incontinence should be assessed after the standardization criteria of the ICCS. Clear distinction should be made between continuous and intermittent incontinence and between nighttime and daytime urine loss. Quantification of urine loss is subjective, and, if necessary, a pad test may help to make it more objective.

The medical history should start with an obstetric history asking for possible fetal distress, anoxia, birth trauma, prenatal hydronephrosis, and oligohydramnios. Developmental milestones should be evaluated. Any associated stool problems can raise suspicion for neurogenic impairment. Information on toilet training and ages at which continence was obtained during day and night can be useful to distinguish those children at risk for having developed LUTD. Early toilet training and early continence are sometimes considered risk factors for developing LUTD. Furthermore, voiding frequency, urine loss frequency, urge, and reactions to urge should be assessed. These data should be controlled by the data obtained from the voiding chart.

Toilet behavior and subjective quantification of the urinary stream are important parameters. Is urinary flow in one stream or interrupted? Staccato voiding is difficult to distinguish by the patient; however, fractionated voiding is well recognized. Does the child have to strain during voiding. How is the urinary stream? Especially in girls, one should ask for deviations of urinary stream or eventual compensations in toilet posture. Many girls with an anterior deflection of the urinary stream take a forward bent position on the toilet. Urge and reactions to urge should be assessed. Most parents will tell that their child waits too long to go to the toilet. Instead, however, it is the child's bladder that contracts too early. Some children hold urine while squatting, closing the urethra with the heel, the so-called Vincent's curtsy sign (Fig. 136-5).



Figure 136-5. Vincent's curtsy sign.

Previous UTIs and relevant surgery should be queried. Bowel function (obstipation, soiling) as well as menstrual and, if applicable, sexual function should be assessed. Familial history, which often is positive in pediatric LUTDs also should be included. General history taking includes questions relevant to neurologic and congenital abnormalities. All diagnostic and therapeutic interactions that have been performed previously should be assessed.

Scoring systems for pediatric incontinence are not popular among pediatric urologists, despite the fact that scoring systems in general provide a more standardized assessment of voiding pathologic conditions. Because LUTD became recognized as a clinical entity affecting many children, two scoring systems have been published. The first scoring system was used by the International Reflux Study in Children group and described by Jan van Gool and colleagues (1992). This scoring system, developed to interpret data obtained from the International Reflux Study, was not validated and has never been used in daily practice. A more recently published scoring system devised by Akbal and associates (2005) is based on this scoring system. A second scoring system, from the Toronto group, was published in 2000 (Farhat et al, 2000). It is a validated questionnaire consisting of 10 questions with good sensitivity and specificity for diagnosing dysfunctional voiding. The same group published a manuscript on the use of their scoring system to predict outcome of reflux after treatment of dysfunctional voiding (Upadhyay et al, 2003).

The main advantage of using a scoring system is to help people with limited experience. Practitioners that deal with children with LUTD on a daily basis often have the skills, learned through experience, to diagnose these conditions. For the less experienced, a scoring system can indicate that an LUTD might be present and that further investigations, such as a voiding diary and uroflowmetry, are needed. In addition to aiding diagnosis, a scoring system is a tool to measure LUTD during therapy, allowing comparison of the effectiveness of different therapies and thus helping provide the best therapy to our patients, based on evidence.

Recently questionnaires and scoring systems for BBD have been developed. They are found to be valid and reliable (Afshar et al, 2009; Drzewiecki et al, 2012). A validated bladder/bowel dysfunction questionnaire is a useful tool in the pediatric urology clinical

setting that correlates well with physician assessment. It can help patients and their families to better define their bladder/bowel symptoms before their visit; however, it should be noted that some families will not be able to fill out the questionnaire appropriately.

Frequency Volume Chart or Voiding Diary and Bowel Diary

The frequency/volume chart is a diary recording fluid intake and urine output over 24-hour periods. Episodes of urgency and urine loss also can be recorded. Urine loss is quantified by recording if clothing had to be changed after the urine loss (= important urine loss) or not. The chart gives information about fluid intake, number of voidings, voided volume, and urine loss. It can be used for diagnostic and therapeutic purposes (Olbing, 1992). For diagnostic purposes the chart should cover at least 3 days of registration. In therapy it is important that the child takes the responsibility to fill out the chart, because this enhances motivation and participation to training.

A lot of information can be obtained from these charts, as follows:

- Voiding frequency
- Total voided volume in 24 hours
- Average voided volume
- Largest and smallest voided volume
- Distribution of urine volume over day and night
- Urine loss
- Fluid intake

The close relationship between bladder and bowel function requires careful screening of the bowel function to rule out BBD. The recommended workup for bowel dysfunction in the context of BBD is outlined in the ICCS guideline on the management of functional constipation in children with LUT symptoms (LUTS) (Burgers et al, 2013b). Briefly, a 7-day bowel diary is advisable and includes the Bristol Stool Form Scale. The diagnosis of functional constipation in children is controversial, and the Rome-III criteria are the most commonly accepted guideline for diagnosis (Rasquin et al, 2006).

Physical Examination

Besides a general pediatric examination, which pays special attention to abdominal palpation looking for fecal impaction, perianal and perineal sensation, anal sphincter tone, and bulbocavernosus reflex should be assessed. The perineal region is supplied by the sacral segments S1 to S4, which also supply part of the bladder and the urethral sphincter.

Complete evaluation of the back with special attention for cutaneous manifestations of an underlying occult spinal dysraphism (lipoma, skin discoloration, hair growth) is necessary to rule out any underlying neurogenic cause (Mandell et al, 1980). Examination of lower extremities can show lesions compatible with neurogenic diseases affecting the lumbar cord. Muscle atrophy, foot deformities, and any asymmetry of the lower extremities must draw our attention. Genital examination, which comprises inspection of the introitus in girls with special attention to the position of the urethral meatus, appearance of the hymen, and inspection of the penis and the meatus urethrae in boys, should be done (Hoebeke et al, 1999).

Urinalysis and Other Laboratory Investigations

Urinalysis may provide information that could be missed by the clinical assessment. Asymptomatic bacteriuria is sometimes observed in the wet child. Infection can be the consequence of the dysfunctional voiding because turbulence in the urinary stream can milk-back bacteria from the urethra to the bladder. On the other hand, infection can be the origin of some irritative bladder symptoms. The presence of glucose or proteins in urine can detect metabolic or nephrologic diseases that can interfere with bladder function.

Ultrasonography

All children with LUTD should receive a screening ultrasound study. In most instances this should be the first-line investigation in children with non-neuropathic LUTD because it is a simple, readily available, and noninvasive tool that can provide information both on anatomic and functional problems when performed by experienced pediatric radiologists. Evaluation of the bladder after voiding can show the amount of residual urine.

Ultrasonography also has been used in the study of the pelvic floor musculature. In boys, the external sphincter, puborectalis, and bulbocavernosus have been observed on US to contract during a hold maneuver. In girls, lengthening of the urethra and movement of the bladder neck in the direction of the symphysis is seen. However, in patients with non-neuropathic bladder-sphincter dysfunction, approximately one third of the children were unable to elicit movement of the pelvic floor or had paradoxical movement. The clinical significance of this remains unclear, but when introduced to a period of urotherapy, marked improvement of symptoms had been reported. Similarly US has been employed in the study of bladder neck mobility. Studies have shown that in a proportion of girls with hyperlaxity of joints, coughing or straining would result in a wide opening of the bladder neck and urethra. In this group of girls, urotherapy would prove difficult and occasionally some would go on to require surgery to the bladder neck (de Jong et al, 2006, 2007).

More recently, US has been used to measure bladder parameters, including bladder wall thickness, and these can be used in calculating a bladder volume and wall thickness index (BVWI). This BVWI can be classified into normal, thick, or thin according to the measured parameters. **Bladder wall thickness measured by US has been correlated with LUTD with good specificity, and this can act as a reliable tool to guide for further invasive investigations (Yeung et al, 2004).** Furthermore, US can detect structural anomalies of the urinary tract. Upper tract dilation, which can signify VUR or obstruction either at the vesicoureteral or the ureteropelvic junction, can be detected. The advantage of US in children is that it is a completely noninvasive and nonpainful examination without risk for irradiation as in other imaging modalities.

Other Imaging Studies

Radiologic examination of the spine may be necessary to rule out any neurogenic causes of bladder-sphincter dysfunction. A voiding cystourethrogram may be performed in patients to rule out VUR. Information on bladder emptying efficiency may be obtained, and the status of the urethra can be assessed to exclude any outflow obstruction.

Urodynamic Studies

Urodynamic studies are employed to evaluate the physiologic parameters involved in the bladder mechanics during filling and voiding. Uroflowmetry, postvoid residual (PVR) urine, sphincter EMG, and 4-hour voiding observation are noninvasive tests and can be used as first-line investigative tools for LUT function. Detrusor activity, bladder sensation, bladder compliance and capacity, and urethral function during both the filling and the voiding phases of cystometry can be recorded during the urodynamic study (UDS) and then used as reference for classification of LUTD. Video-urodynamic study incorporating images during storage and the voiding phase can provide better insight of LUT function.

Uroflowmetry and Postvoid Residual

Uroflowmetry is indicated in toilet-trained children with LUTS and/or UTI (Fig. 136-6). Although there is no specific contraindication for these tests, they are usually not recommended in children with acute illness or active UTI. Before the tests, the uroflowmeter should be calibrated and the scale of interpretation sheet should be adjusted

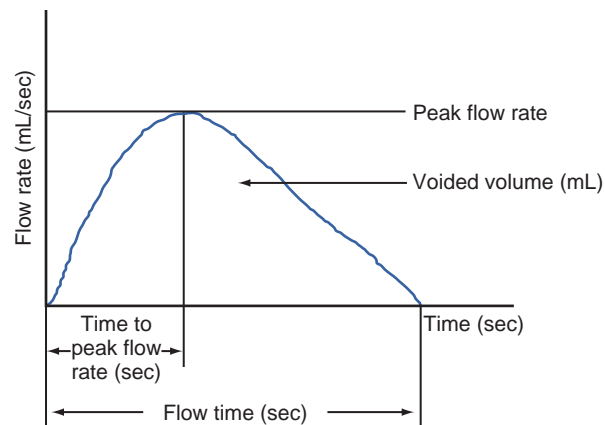


Figure 136-6. Parameters in a bell-shaped uroflowmetry curve.

to a 1 : 1 ratio for flow rate (mL/sec) versus time (sec). The uroflowmeter should be placed in a quiet and private place that makes the child feel comfortable and relaxed. The child micturates at normal desire to void. Any artifact (sharp peak in flow curve with duration less than 2 seconds) should be corrected before interpreting the uroflowmetry results.

Expected Bladder Capacity and Optimal Bladder Capacity

The most relevant parameters for interpretation of uroflowmetry are voided volume, Qmax, and uroflow patterns. Because these parameters depend on bladder capacity (voided volume + PVR), ICCS defines expected bladder capacity (EBC) as $(\text{age in years} + 1) \times 30 \text{ mL}$, which is useful for comparisons among children of variable ages. Voided volume of less than 50 mL is regarded as irrelevant for interpretation (Norgaard et al, 1998), whereas bladder capacity greater than 115% EBC or voided volume above 100% EBC are associated with frequent abnormal uroflow patterns and elevated PVRs (Yang and Chang, 2008; Chang et al, 2011). Thus optimal bladder capacity—that is, bladder capacity between 50% and 115% of EBC—is recommended as adequate for interpretation (Yang et al, 2003; Hoebeke et al, 2010). If abnormal parameters occur in the situation of bladder overdistention, uroflowmetry should be repeated.

Peak Flow Rate

Peak flow rate (Qmax) is defined as the maximal flow rate during voiding with duration of more than 2 seconds. Qmax is regarded by the ICCS as the most relevant variable when assessing the status of bladder outflow resistance (Nevés et al, 2006). Several nomograms for Qmax are published in the literature (Yang and Chang, 2012; Gupta et al, 2013; Yang et al, 2014). Yang and colleagues used the ranking method to construct a Qmax nomogram (Fig. 136-7). Minimally acceptable Qmax, approximately the 5th to 10th percentile of the nomogram, is defined as 11.5 mL/sec in children 4 to 6 years of age and 15.0 mL/sec in children 7 to 12 years (Yang and Chang, 2012; Yang et al, 2014).

Uroflow Patterns

Under some conditions, detrusor contractility in children is so good that it can overcome bladder outlet resistance, which makes Qmax less reliable in the evaluation of bladder outlet resistance. Therefore some consider uroflow pattern to be a more important parameter than Qmax. The uroflow pattern may provide a clue to the possible underlying cause of LUTD in children. The ICCS suggests that uroflow patterns could be classified as bell-shaped, interrupted, staccato, tower, and plateau types. Only the bell-shaped curve is regarded as normal. Interrupted flow (Fig. 136-8A) is defined as flow rate that reached zero during voiding, which may imply

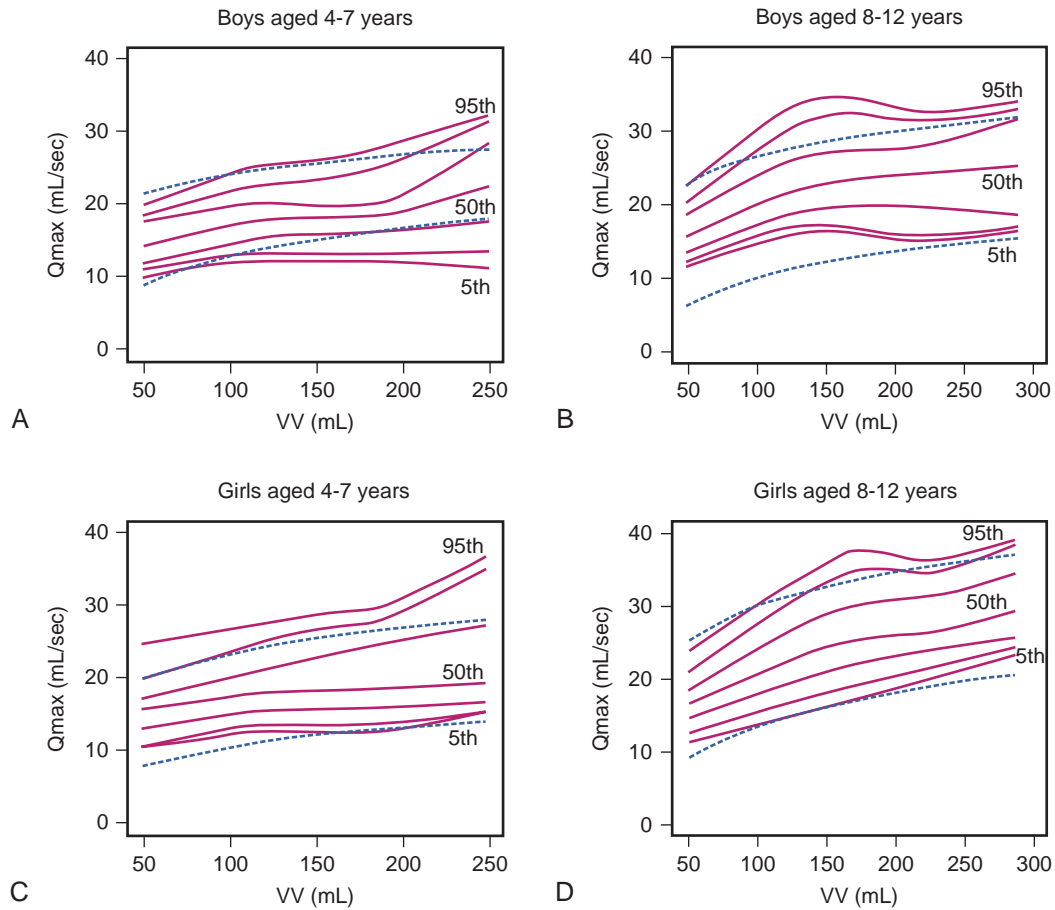


Figure 136-7. A-D, Peak flow rate nomograms (the lines of percentiles were 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles, respectively, from the bottom up) in boys and girls aged 4 to 7 and 8 to 12 years. The 5th and 95th percentile line of the Miskolc nomogram (*dashed lines*) were plotted on the figures for comparison. VV, voided volume.

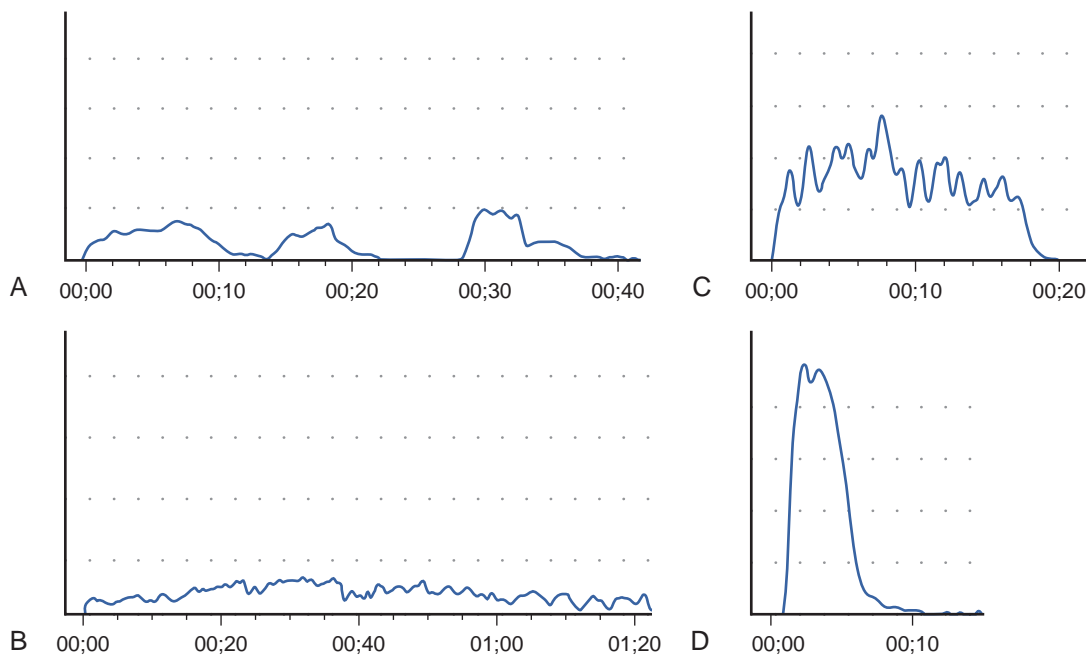


Figure 136-8. Patterns of uroflowmetry curves. A, Interrupted curve. B, Plateau curve. C, Staccato curve. D, Tower curve.

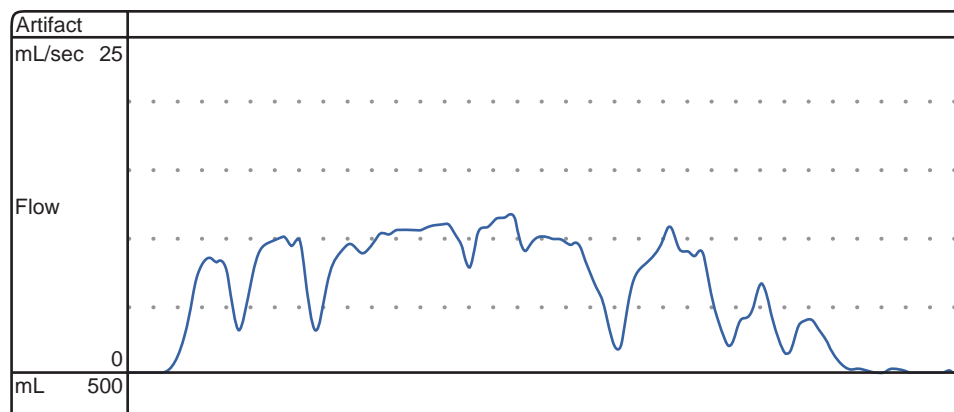


Figure 136-9. A uroflow pattern in a 12-year-old boy with anterior urethral valve fits criteria of both staccato and plateau patterns.

detrusor underactivity or pelvic flow overactivity during voiding. Plateau curve (Fig. 136-8B) is defined as continuous, low-amplitude, and flattened flow. Peak flow rate less than the age-specific minimally acceptable Qmax and lasting for 4 seconds could be two useful parameters to define plateau curve, which implies bladder outlet mechanical obstruction or tonic sphincter contraction. Staccato flow pattern (Fig. 136-8C) is defined as an irregular and fluctuated flow curve, and the fluctuations between peak and trough should be larger than the square root of Qmax. The cause of the staccato flow curve is assumed to be sphincter overactivity. The tower-shaped curve (Fig. 136-8D) is defined as sudden and high-amplitude flow, which is suggestive of detrusor overactivity. Time to peak flow rate is usually less than 2 seconds, and the left arm of the uroflowmetry curve is almost perpendicular to the x-axis. Peak flow rate more than age-specific 95th percentile of Qmax nomogram may be regarded as high amplitude.

In healthy children, the proportion of non-bell-shaped curves ranges widely from 2.8% to 37%, whereas only 3.8% of healthy children had repetitive non-bell-shaped curves, which can be defined as abnormal (Mattsson and Spangberg, 1994; Bower et al, 2004; Yang and Chang, 2008; Yang et al, 2014). Because subjective uroflowmetry patterning is liable to personal bias (Kanematsu et al, 2010) and substantial interobserver disagreement existed in classifying specific abnormal patterns (Chang and Yang, 2008), arguing that a specific type of abnormal flow pattern is present may be not clinically relevant. In addition, some abnormal uroflow patterns may fit criteria in two types of flow patterns (Fig. 136-9). Simply classifying uroflow pattern into normal and abnormal may be sufficient for clinical practice (Yang and Chang, 2012). Uroflowmetry should be repeated in cases with any abnormal flow pattern, with invasive UDS reserved for cases with repeated abnormal flow patterns.

Electromyography during Uroflowmetry

The use of EMG during pediatric uroflowmetry is controversial. EMG may help diagnose detrusor and sphincter/pelvic floor dys-synergy in cases with a staccato or interrupted uroflow pattern (Wenske et al, 2012). However, the perianal surface EMG may be compromised by artifact and may not really reflect urinary sphincter activity.

Postvoid Residual

PVR should be checked with transabdominal US within 5 minutes after voiding. Although urethral catheterization may be more accurate, possible complications of UTI and associated discomfort prevent its wide acceptability as screening tests. Until recently, first PVR nomograms were generated from 1128 children (Chang et al, 2013) (Fig. 136-10). For children 4 to 6 years of age, a single PVR greater than 30 mL or greater than 21% of bladder capacity, or

repetitive PVR above 20 mL or greater than 10% of bladder capacity can be regarded as elevated. For children 7 to 12 years, a single PVR greater than 20 mL or 15% of bladder capacity or repetitive PVR greater than 10 mL or 6% of bladder capacity can be defined as elevated (Chang et al, 2013; Austin et al, 2014). Because of the high variability of PVR tests, repetitive testing for PVR is warranted when the first PVR is high (Chang and Yang, 2009). The nomograms serve as a reference value for clinical practice; there is no existing clear cutoff point of PVR that is at higher risk for UTIs.

Four-Hour Voiding Observation

Four-hour voiding observation is a validated technique used for the evaluation of LUT function in infancy and pre-toilet-trained children. The method involves continuous observation of the freely moving infant with frequent ultrasound measurement of bladder filling and residual urine after each voiding. Voided volumes also may be measured by the weighing of diapers (Austin et al, 2014). This observation identified infants with LUTD, which affected the treatment outcomes of UTI and VUR (Sillen et al, 2010).

Conventional Fill Urodynamic Studies

This involves more sophisticated instruments and becomes more invasive to the patient, requiring a bladder catheter introduced transurethral or suprapubically. The use of suprapubic catheterization has been suggested as a better alternative to transurethral catheterization. Although it may be considered more invasive, it is much more physiologic than to try to void with a catheter in the urethra, particularly in young children. Not only is it obstructive to flow, but the trauma of placing the catheter just before the investigation may cause significant discomfort. For suprapubic catheterization, a 6-Fr double-lumen catheter is placed suprapubically under sedation and left in situ for 24 hours before commencement of the UDS.

The suprapubic catheter is connected to a computer system and used to measure intravesical pressure. Another catheter is placed in the rectum to measure intra-abdominal pressure surrounding the bladder. By subtracting the latter from the intravesical pressure, the detrusor pressure can be calculated. Sphincteric activity also can be measured with simultaneous perineal EMG recordings. All the measured data are directly fed into a computer for analysis and display of graphical measurements. The UDS looks at both the filling and voiding phases of the bladder. Bladder filling and storage are described according to bladder sensation, detrusor activity, bladder compliance, and bladder capacity. Pressure flow studies are carried out during the voiding phase (Fig. 136-11).

Traditionally, the bladder is filled artificially with normal saline at a rate of 10% EBC per minute to speed up the procedure. The child is asked to indicate his or her desire to void (if old enough to do so) and then void into a specially designed seat with a uroflowmeter attached. The investigator observing the study also should

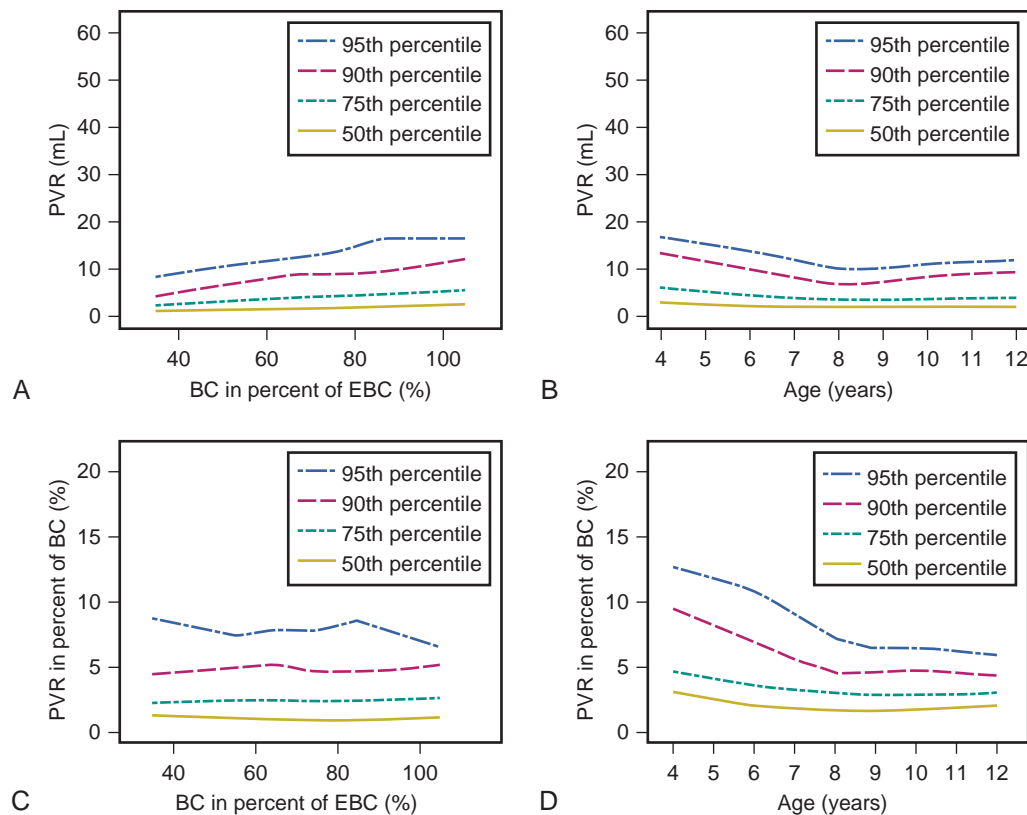


Figure 136-10. Postvoid residual (PVR) nomogram is constructed by using the lower value of two consecutive tests: PVR in milliliter (A and B) and PVR in percent of bladder capacity (BC), (C and D) over varied age and BC/expected bladder capacity (EBC). The lines of 50th, 75th, 90th, and 95th percentiles were plotted separately in the nomograms.

make note of any events occurring during the study (e.g., any large movements of the patient, coughing, or in particular any urinary dribbling).

Video-Urodynamic Study. By combining cystometry with fluoroscopy, video-urodynamics can be performed, capturing fluoroscopic images of the bladder, bladder neck, and urethra (Fig. 136-12). Conventional fill urodynamics is performed in the usual manner with the child sitting in a specially designed chair with a uroflowmetry device in the fluoroscopy suite. Fluoroscopic images are taken during filling and voiding. This has the added advantage of being able to observe the shape of the bladder during filling and voiding, observing for signs of VUR, as well as the configuration of the urethra and pelvic floor. In institutes where video-urodynamics is not available, conventional urodynamics plus voiding cystography can be an alternative for video-urodynamics.

Natural Fill Urodynamic Studies

More recently, studies have shown that the nonphysiologic filling of the bladder during conventional urodynamics, even at low filling rates, can lead to misrepresentations of true bladder activity during normal situations. Therefore natural filling urodynamic studies may be performed in which the child is asked to drink to allow the bladder to fill at its own rate. Urodynamic studies in children with an overactive bladder usually reveal detrusor overactivity associated with a small bladder capacity but occasionally may be normal, with incontinence only barely perceptible, particularly if conventional cystometry rather than natural filling cystometry is used. It appears that the artificial filling may inhibit the detrusor response and attenuate its maximum contractile potential, rendering detrusor instability much less pronounced and undetectable. Therefore natural filling cystometry is the preferred technique in children; better still, the combined use of artificial and natural filling urodynamic studies

is helpful to accurately delineate the underlying bladder dysfunction (Yeung et al, 1995a, 2010).

Ambulatory Urodynamic Studies

The unfamiliar hospital and urodynamic laboratory environment, as well as the presence of a urodynamics investigator, can sometimes cause significant distress, particularly to young children. To overcome this, an ambulatory UDS (AUDS) may be performed. The major advantages of AUDS were in natural filling of the urinary bladder; therefore this can be applied in children who are refractory to standard urotherapy and cannot tolerate a conventional UDS or with noncontributory results with conventional UDS. However, the labor-intensive and time-consuming nature of AUDS prevented its widespread use in children. Additionally, some children still suffered from distress and discomfort and were unable to void because of AUDS (Deshpande et al, 2012).

The AUDS system converts digital pressure signals through modulated infrared wave or Bluetooth (Luna [Nokia], MMS). The evaluation time varied from 45 minutes to 24 hours. During the investigation the infant or child can conduct normal activities, be totally mobile, and be accompanied by one or both of the parents undisturbed in a private place. A diary including activities, urinary dribbling, incontinence, urgency, and micturition should be recorded continuously. Overall, it allows for a continuous monitoring of bladder function under near-natural conditions for the child. For toilet-trained children, uroflowmetry may be performed with a uroflowmeter.

Limited studies have been undertaken with a small number of children enrolled. Care should be taken during interpretation of AUDS results. AUDS can yield more detrusor contractions, lower voided volume, and greater voiding pressure than conventional UDS (Yeung et al, 1995a; Deshpande et al, 2012). High end-filling

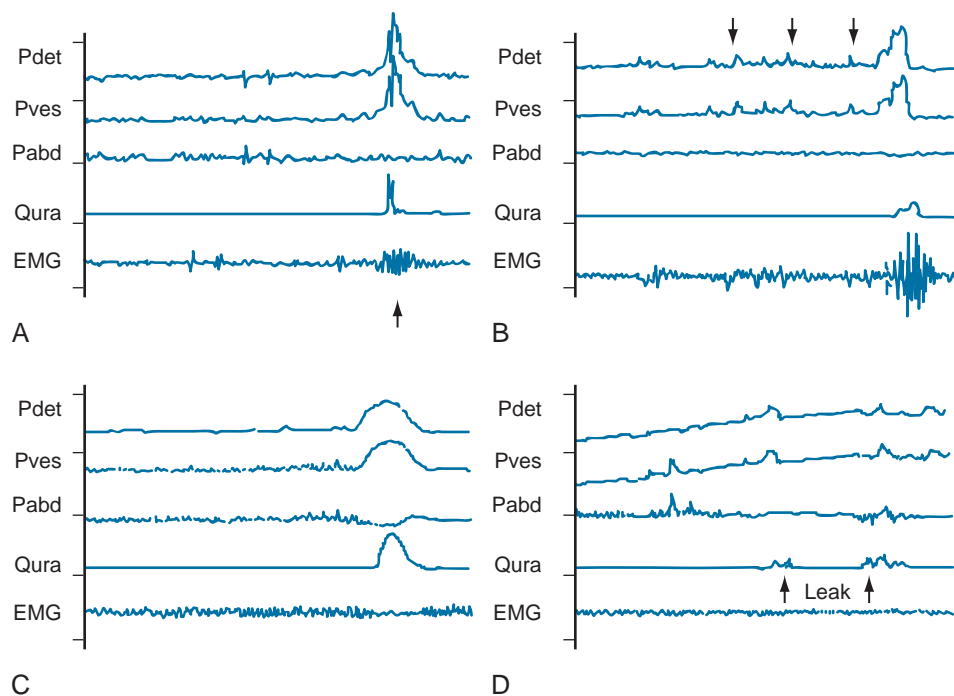


Figure 136-11. Various bladder functional patterns. A, Dyssynergic patterns with an increase in sphincteric electromyographic activities during micturition (arrow), leading to an interrupted urinary flow. B, Overactive bladder, characterized by frequent unstable detrusor contractions (arrows) during the filling phase. C, Normal female micturition pattern; note the pelvic floor relaxation as evidenced by a drop in abdominal pressure during micturition. D, Bladder with low (poor) compliance as evidenced by a rapid increase in intravesical pressure during filling, often associated with urinary leakage (arrows). EMG, electromyogram; Pabd, abdominal pressure; Pdet, detrusor pressure; Pves, intravesical pressure; Qura, uroflow. (From Yeung CK, Barker GM, Läckgren G. Pathophysiology of bladder dysfunction. In: Gearhart JP, Rink RC, Mouriquand PDE, editors. Pediatric urology. 2nd ed. Philadelphia: Saunders; 2010. p. 353–65.)

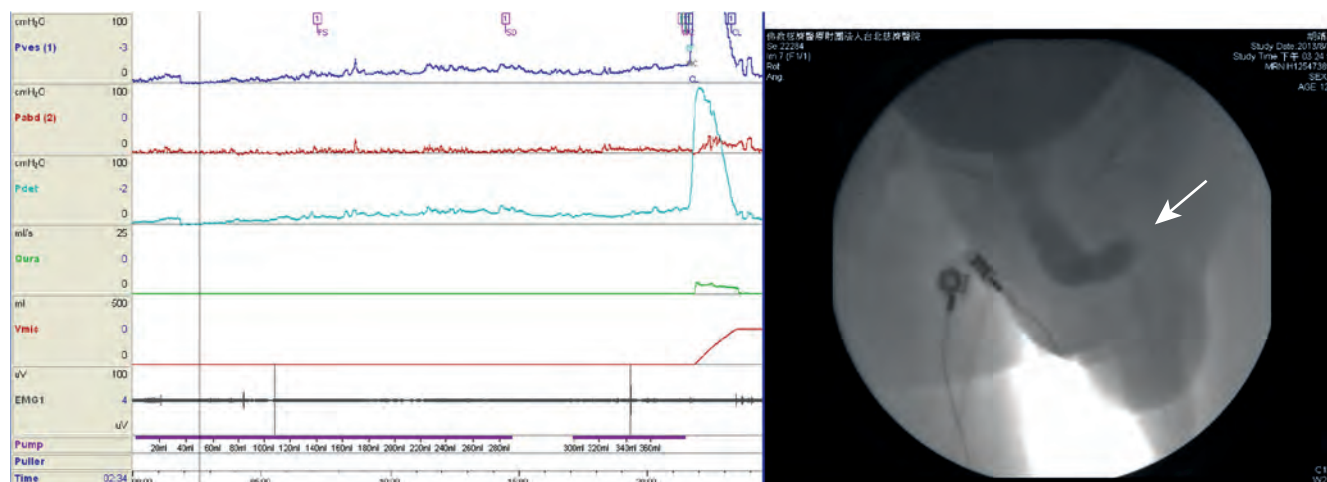


Figure 136-12. Video-urodynamic study in a 13-year-old boy with overactive bladder and bilateral hydronephrosis. High detrusor pressure with low uroflow rate is shown in the pressure flow study, and simultaneous image depicts stenosis at the level just distal to bulbar urethra (arrow) with proximal dilatation.

KEY POINTS

- LUT function in young children is very different from that in adults. Infants void with significantly higher maximum detrusor pressures than in normal adults, and male infants void with significantly higher pressures than females.
- The high detrusor pressures during micturition were mainly observed only during the first year of life and decreased progressively with age. They most probably represent variations between individual infants in the maturation process of detrusor and sphincter coordination during the first 1 to 2 years of life.
- During the first 2 to 3 years of life there is progressive development from an initially indiscriminate infantile voiding pattern to a more socially conscious and voluntary or adult type of micturition.
- Micturition control is achieved through an active learning process whereby the child acquires the ability to voluntarily inhibit or initiate voiding at socially convenient times.
- The natural evolution of bladder control entails an intact nervous system and depends on at least three main events occurring in parallel: (1) a progressive increase in bladder functional storage capacity; (2) maturation of voluntary control over the urethral striated muscle sphincter; and, perhaps most importantly, (3) development of direct volitional control over the bladder-sphincteric unit so that the child can voluntarily initiate or inhibit the micturition reflex.
- LUTS and LUTDs are best classified according to their relation to the storage and/or emptying phase of bladder function
- It is now well recognized that LUTD often has associated bowel dysfunction, and together this is known as BBD.
- BBD is prevalent. Almost 40% of referrals to pediatric urologists are related to LUTD.
- VUR may be secondary to underlying LUTD, particularly in girls.
- An adequate history should include congenital abnormalities, voiding and wetting patterns (including a voiding diary), and assessment of bowel function. Structured questionnaires can be useful.
- Abnormalities of the lower spine should be sought specifically to exclude the possibility of an occult spinal dysraphism.
- Ultrasonography is useful to assess bladder function and wall thickness, as well as pelvic floor function.
- Normal uroflow pattern is bell shaped. Age- and gender-specific peak flow rate and PVR can be helpful in detecting pediatric LUTD.
- UDS looks at both the filling and voiding phases of the bladder.
- Artificial filling may inhibit the detrusor response and attenuate its maximum contractile potential, rendering detrusor instability much less pronounced and undetectable.

pressure during conventional UDS was not observed in AUDS. In addition, the artifacts can make interpretation more difficult. The standard AUDS procedures and reference parameters generated from ambulatory UDS need more investigation. With the advance in technology, hopefully, we may evaluate the urinary bladder in children in a more natural way.

SUMMARY

Despite extensive clinical and animal research, it is perhaps embarrassing to admit that the exact neurologic mechanisms of the development of micturition control from newborn to infancy and later childhood, as well as the pathophysiologic pathways that are involved in various types of LUTD, have as yet remained largely unclear. However, it is clear that the bladder and the brain are in constant communication from as early as in utero, and there are extremely rapid and extensive changes and modulation of micturition reflexes during the early postnatal period, leading to abundant potential for developmental errors and voiding dysfunctions. Over the last decade we have learned that both normal and abnormal LUT function is much more dynamic than we had previously believed. New investigative tools and research have allowed us to study in much greater detail and precision the various components, including neurologic, muscular, urodynamic, and hormonal mechanisms, that may intricately interact to produce different patterns of LUTDs, and their relentless, dynamic changes.

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The complete reference list is available online at www.expertconsult.com.



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Historical Perspective

Demographics

Inheritance and Genetics

Embryology of the Uterovesical Junction

Functional Anatomy of the Antireflux Mechanism

Cause of Vesicoureteral Reflux

Lower Urinary Tract Infection and Reflux

Grading of Reflux

Diagnosis and Evaluation of Vesicoureteral Reflux

Assessment of the Lower Urinary Tract

Assessment of the Upper Urinary Tract

Cortical Defects

Associated Anomalies and Conditions

Natural History and Management

Surgical Management

Intravesical Procedures

Suprahiatal Tunnels

Infrahiatal Tunnels

Extravesical Procedures

Postoperative Evaluation

Complications of Ureteral Reimplantation

Long-Term Complications

Redo Reimplantation

Endoscopic Treatment of Vesicoureteral Reflux

Nonautologous Materials

Autologous Materials

Laparoscopic Surgical Procedures

Vesicoureteral reflux (VUR) represents the retrograde flow of urine from the bladder to the upper urinary tract. VUR is a common clinical entity. Its clinical challenges arise from the fact that it is usually asymptomatic. When it is not, however, it is responsible for pyelonephritic scarring and can be associated with congenital renal dysmorphism. There are many unresolved issues regarding the cause, diagnosis, and management of VUR. This chapter attempts to reconcile some of these areas by interpreting the best available information in the literature. Some areas, however, continue to await more rigorous study. Some may remain unresolved for quite some time.

HISTORICAL PERSPECTIVE

VUR has a unique distinction of having evolved from an anatomic curiosity around the 1st century AD into one of the most contentious and complex areas of urology today. Galen and da Vinci made the first references to VUR by Western medicine when they alluded to the ureterovesical junction (UVJ) as a mediator of unidirectional flow of urine from the kidneys to the bladder. Although VUR was first demonstrated to be a normal finding in dogs and rabbits (Semblinow, 1907), it was a gynecologic misadventure that revealed that VUR in human adults may not be a normal state (Pozzi, 1893). Sampson, in 1907, suggested that the oblique course of the ureter through the bladder wall created a locking mechanism at the UVJ and also was the first to imply that VUR might lead to renal

infection (Sampson, 1903). Although it was not possible to uniformly demonstrate VUR in all people in cadaveric studies (Young, 1898), it was not until the UVJ had been more clearly dissected that it was realized the incidence of VUR varied with the length of the ureter's obliquity in the bladder and the formation of the trigone (Gruber, 1929).

Pivotal discoveries occurred when Hutch (1952) reported on a relationship between VUR and chronic pyelonephritis in paraplegic patients and Hodson (1959) observed that urinary tract infection (UTI) and renal scarring carried a high likelihood of VUR in children.

Two seminal bodies of work defined the modern era of VUR. The first, the work of Ransley and Risdon (1979), defined the pathophysiology of reflux nephropathy by demonstrating the relationship among infection, reflux, and pyelonephritic scarring. Second, these observations complemented the clinical studies of Smellie (1991) and colleagues, who galvanized the related concepts inherent in clinical UTI, bacterial pyelonephritis, renal scarring, and VUR. In 1985 a consensus system for the grading of reflux was published by Lebowitz and colleagues (1985) on the basis of the International Reflux Study Group's deliberations.

Until recently, the virtues of medical therapy to avert infections and surgical therapy to correct reflux have been evenly debated for more than 20 years. However, the recent introduction of the biodegradable cross-linked polysaccharide dextranomer and stabilized hyaluronic acid for use in injectable endoscopic correction of reflux, as well as re-examination of the basis for medical therapy and the

risks for reflux, have initiated a re-examination of virtually all aspects of reflux. From the age-related impact of reflux, through use of antibiotics for medical prophylaxis, invasiveness of cystography, and traditional indications for surgery, the impact of reflux and its management are being openly explored. Although the fundamental biologic importance of reflux disease is not in question, many facets of how reflux diagnosis and management are approached may take new shape in the coming decade.

DEMOGRAPHICS

Prevalence

The tendency for VUR to resolve spontaneously on the one hand or persist beyond its natural resolution rate because of abnormal bladder dynamics makes it difficult to confidently generalize the true prevalence of reflux from a given population. In one meta-analysis of studies of children undergoing cystography for various indications (Sargent, 2000), the prevalence of reflux was estimated to be approximately 30% for children with UTI and 17% without infection. **In contrast, reflux may be present in up to 70% of infants who present with UTI (Baker et al, 1966).** In a population of 157 adults investigated for incidental hypertension without any evidence of renal abnormality, the prevalence of VUR was estimated to be 19%, with high-grade reflux in more than half of the refluxing group (Barai et al, 2004). Reflux is relatively uncommon in adult men (Chapple et al, 1990). In asymptomatic infants followed for antenatal hydronephrosis, the prevalence of reflux ranges from 15% in infants with absent or mild hydronephrosis on postnatal ultrasonography (Phan et al, 2003) to 38% in a group of neonates with various postnatal upper tract sonographic anomalies, including hydronephrosis, renal cysts, or renal agenesis (Zerin et al, 1993).

Gender

Differences in reflux rates between males and females may suggest a sexual dichotomy in the function of the lower urinary tract, bladder outlet, and urethra. In one study of 117 infants assessed for reflux after fetal upper tract dilation, 76% of refluxing infants were male (Ring et al, 1993). In later life, the likelihood of having reflux if presenting with a UTI is higher if male than female (Shopfner, 1970), even though the great majority (85%) of prevailing reflux in older children is in females. A confounding factor in understanding true gender differences in reflux between males and females is the gender-driven predisposition to UTI. Uncircumcised male infants show a 12-fold greater risk for UTI than circumcised males, as well as a greater propensity for harboring periurethral uropathogenic flora (Wiswell et al, 1988; Wiswell and Hachey, 1993). The greater incidence of UTI will necessarily invite more frequent evaluation and therefore detection of VUR in this population. It is not known whether the incidence of reflux detection would rise in females if they were to be incidentally evaluated for reflux as often as infant males. In a related finding, only 10% of patients entered into the International Reflux Study in Children from the United States were boys compared with 24% entered from Europe. The circumcision rate in the latter group was only 5% compared with 62% in the U.S. group ($P < .001$) (Weiss et al, 1992b).

Reflux in the Fetus

Most studies of fetal reflux do not in fact detect reflux per se in the fetus but relate fetal hydronephrosis parameters to reflux in the neonatal period. However, fetal hydronephrosis is common, often resolves, and has low specificity for postnatal VUR. Nevertheless, fetal hydronephrosis is commonly associated with postnatally detected reflux. Zerin and associates (1993) described a 38% detection rate of reflux in 130 neonates with prenatal hydronephrosis. In 19% the reflux was bilateral. It is suggested that the lower the threshold for defining hydronephrosis (in millimeters of pelvic diameter) in the fetus, the more often reflux will be detected postnatally (Anderson et al, 1997). This leads to speculation as to

TABLE 137-1 Incidence of Reflux in Patients with Urinary Tract Infections

AGE (yr)	INCIDENCE (%)
<1	70
4	25
12	15
Adults	5.2

From Baker R, Maxted W, Maylath J, et al. Relation of age, sex, and infection to reflux: data indicating high spontaneous cure rate in pediatric patients. *J Urol* 1966;95:27.

whether reflux is a normal variant in the population but becomes clinically relevant only in some because of a predisposition to UTI, a conclusion supported by the observation that reflux without infection is of questionable clinical significance. Boys appear to harbor postnatal reflux more commonly—a 6:1 male-to-female ratio was reported in one study of 27 cases (Marra et al, 1994). The highest grades of reflux are most commonly associated with renal scintigraphic abnormalities. In many cases, even in the absence of any infection history from birth, the presence of a small kidney with globally reduced scintigraphic function may indicate that such renal scintigraphic abnormalities may be associated with a developmental ureteric bud abnormality associated with high-grade reflux or secondary to the reflux itself (Oliveira et al, 1998; Stock et al, 1998).

Age

As stated previously, because the natural history of reflux involves spontaneous resolution over time, it is self-evident that less primary reflux would be prevalent in older children compared with infants (Table 137-1). Even in the presence of infection or asymptomatic bacteriuria, reflux is more common in younger patients (Smellie, 1991).

Race

Little is known about racial predisposition to reflux worldwide because reflux studies have generally been restricted to Western countries. **One difference established over several studies is the relative 10-fold lower frequency of reflux in female children of African descent (Skoog and Belman, 1991; Chand et al, 2003).** In addition, reflux resolved sooner in this population ($P < .005$). In a series of non-Caucasian children with a 4:1 male-to-female ratio, 58% of whom were younger than 1 year of age presenting with UTI (72%), voiding difficulties (10%), or other malformations (14%), reflux was present in only 10% (West and Venugopal, 1993). Even in follow-up of antenatal hydronephrosis, reflux was found in 17.6% of 51 nonblack versus 0% of 58 black infants (Horowitz et al, 1999). Such differences may involve a delay in maturation of the antireflux mechanism in Caucasian patients as the race-associated frequency of reflux becomes equal regardless of race after 10 years of age (Melhem and Harpen, 1997).

KEY POINTS: DEMOGRAPHICS

- The younger the child with UTI, the greater is the likelihood of discovering reflux.
- VUR is relatively rare in children of African descent.

INHERITANCE AND GENETICS

Sibling Reflux

A recent meta-analysis of sibling reflux studies suggests the prevalence of VUR in siblings to be approximately 32% (Hollowell and Greenfield, 2002). However, the prevalence may be as low as 7% in

older siblings (Connolly et al, 1996) or as high as 100% in identical twin siblings (Kaefer et al, 2000). **The latter finding undeniably supports the notion that VUR can be an inherited condition** and that the genetic mode of transmission may in some cases be autosomal dominant. Although a heightened prevalence of reflux exists in siblings of refluxing index patients, the natural history of reflux would suggest that siblings who are older harbor reflux less often compared with relatively younger siblings because of spontaneous reflux resolution (Connolly et al, 1996). However, none of the existing sibling studies rigorously state whether the prevalence of sibling reflux depends on whether the sibling is younger or older than the index patient. By virtue of its detection by screening, sibling reflux is usually asymptomatic at the time of diagnosis. Furthermore, the tendency for reflux to have resolved before any renal changes such as focal scarring detected by imaging can be reliably ascribed to the reflux itself further complicates the management of reflux in siblings. These clinical features underscore the difficulties inherent in formulating meaningful recommendations for the management of sibling reflux detected by screening.

Much of the concern for sibling reflux detected by screening stems from reports of renal abnormalities detected by ultrasonography or nuclear scintigraphy in these patients.

In one retrospective study of 123 screened siblings, 44 (36%) demonstrated VUR on voiding cystography (Houle et al, 2004). Of these patients, 37 underwent renal imaging. Ultrasonography was abnormal in 30% and renal scintigraphy, when used, was abnormal in 28%. However, in siblings older than 2 years, renal scintigraphic abnormalities were twice as common as in the entire group of siblings. The authors concluded that renal damage is therefore progressive in the older siblings and proposed earlier screening of siblings of refluxing index patients. However, this study fails to address the fact that renal damage or aberrant formation may have occurred very early and over time (beyond 2 years of age), renal growth may have exaggerated the appearance of such scintigraphic abnormalities. Scintigraphic results may become exaggerated by normal cortical growth surrounding a scarred region that has failed to grow or by compensatory hypertrophy of a contralateral kidney. **The missing link is a prospective scintigraphic or sonographic follow-up of asymptomatic refluxing infant sibling children from birth onward.** Finally, the reporting of scintigraphic results by many sibling reflux studies is confounded by failing to differentiate between aberrant renal development often associated with higher grades of reflux and true scarring secondary to infection and inflammation. Moreover, the ability to modulate the course of the processes that mediate congenital dysplasia is not possible presently, as it is with scarring. In the absence of such data and faced with the invasive nature of the gold standard test for reflux, the cystogram, one is left with the following questions.

Is asymptomatic reflux in a sibling of clinical concern? If the propensity for UTI, with or without VUR, could be reliably determined to be genetically regulated, it would strengthen the case for screening for reflux in a sibling. Because biologic infection propensity cannot be presently determined in either an index patient or his or her sibling, the likelihood of developing a UTI cannot be used to support screening siblings for reflux. Therefore the aggregate clinical information available must be relied on for the sibling in question. **Because it is renal consequences of reflux that are at issue, rather than reflux itself, siblings may be better served by noninvasively screening for cortical abnormalities first, and screening for reflux if history of compounding factors such as UTI or bowel and bladder dysfunction are manifested.** The intensity of renal assessment, using ultrasonography for general screening or a nuclear scan for highest accuracy, could then be tempered by clinical factors, including family history, patient and family compliance with follow-up, blood pressure, a history of UTIs and fevers, and voiding dysfunction. The absence of renal imaging abnormalities would allow the clinician to conclude that reflux, if present, has not yet been of any renal structural consequence.

Should screening depend on sibling age? Because the risk for new renal scarring after pyelonephritis is lower in children older than 5 years of age, older siblings would likely suffer fewer conse-

quences from a recent reflux-induced pyelonephritis and therefore stand to benefit less from confirming a diagnosis of reflux and instituting antibiotic prophylaxis than an infant or younger sibling. Nevertheless, a history of untreated febrile infections would support a decision to consider renal assessment or even obtain a cystogram in an older sibling.

Thus, by imaging the kidneys first, followed by assessing the integrity of the UVJs, a rational top-down approach to sibling reflux screening emerges. Such an approach helps strike a balance between the invasive nature of reflux detection and classic commitment to prophylaxis versus first detecting existing renal cortical abnormalities that might be the result of past or ongoing reflux. If consideration of age and renal integrity is combined, a possible graded approach to screening can be developed for siblings older or younger than 5 years of age, with or without renal structural abnormalities. The proximate urologic and voiding history also must play a deciding role in whether a sibling is ultimately screened by cystography for VUR. Thus, in siblings 5 years or older with normal kidneys, little would be gained from detecting reflux that could not be addressed by responding to a febrile UTI in the usual fashion as for the general pediatric population. Indeed, the knowledge that the index patient has VUR might heighten the attention to family or self-reporting regarding urinary symptoms in the older sibling. In siblings 5 years or older with renal abnormalities, the suggestion would be of past or continuing reflux. Ruling the diagnosis in or out by cystography could then depend on prevailing voiding habits and proximate urologic history. The sibling younger than 5 years of age with normal kidneys would be managed on the basis of clinical judgment regarding likelihood for infection rather than an immediate need to diagnose reflux. The sibling younger than 5 years with cortical renal defects would have the most to lose by a febrile infection in the face of reflux and the attendant risk for additional cortical loss after reflux-induced pyelonephritis triggered by an infection (Hunziker et al, 2014). In this case, aggregate knowledge of the potentially higher prevalence of reflux in siblings combined with a fever history, either unexplained or with UTI, or significant bowel dysfunction would support select consideration of cystography. In any sibling, if reflux is diagnosed, the indications for reflux correction remain the same as for the general refluxing pediatric population.

Genes Involved

In addition to sibling reflux, a prospective screen of progeny of patients with reflux revealed a 66% rate of reflux in the offspring (Noe et al, 1992), which further strengthens the notion of an autosomal dominant component to the genetic mechanism of reflux. The substantially higher rate of reflux in siblings and progeny of index patients than in the general population defines these patients as susceptible to renal morbidity. Previous segregation and linkage analyses have implicated a number of loci in the pathogenesis of VUR, though no specific gene product or functional role for these loci in reflux has yet been identified (Chapman et al, 1985; Feather et al, 2000). Several studies used a morphogenetic approach to search for candidate genes that may underlie VUR. The original ureteric budding studies of Mackie and Stephens (1975), which correlate the position of ureteric budding from the mesonephric (wolffian) duct with that of the final ureteric orifice, provide a modern basis for a genetic interpretation of VUR. Several genes have been observed to regulate these developmental processes and, by extension, are believed to serve as potential regulators of UVJ integrity, though their specific connection to VUR is clinically unproved. Indeed, genetic misregulation of ureteric budding is believed to underlie many congenital anomalies of the kidney and urinary tract (often referred to as CAKUT) (Miyazaki and Ichikawa, 2003). *Pax2* is a transcription factor regulating kidney, central nervous system, and ocular development in mice. It is necessary for ureteric budding in mice (Keller et al, 1994). *PAX2* is located on human chromosome 10q, and mutations have been reported in human syndromes involving colobomas and renal anomalies, including hypoplasia, dysplasia, glomerulonephritis, and VUR (Sanyanusin et al, 1995). However, *PAX2* has not been shown to be a major determinant of

primary VUR (Choi et al, 1998; Cunliffe et al, 1998). Glial-derived neurotrophic factor (*Gdnf*) and its receptor *RET* show strong involvement in UVJ formation in mice (Yu et al, 2004). Overexpression of *RET* in mice leads to abnormal placement of the ureteric bud and is associated with a 30% incidence of VUR at birth compared with 4% in wild-type mice. Nevertheless, the *Gdnf*-*Ret* signaling complex has been found to not mediate VUR in humans (Shefelbine et al, 1998). One reason for the conflicting studies in the literature on reflux genetics is that clusters of specific populations with their own inherent genetic backgrounds occasionally amplify a putative gene association for VUR that does not apply to all populations. This was recently reported for *RET*, which showed a very high-frequency *RET* polymorphism in patients with primary VUR from Quebec, Canada, but not in a similar cohort of patients with primary VUR from Ireland (Darlow, 2009). Another fascinating animal model of VUR is observed after deletion of the uroplakin III gene (Hu et al, 2000). However, no structural uroplakin III gene alterations have been noted in human cohorts with VUR (Giltay et al, 2004; Jiang et al, 2004). One explanation for this finding may be that major uroplakin mutations are developmentally lethal in humans. Finally, members of the renin-angiotensin family of proteins have been implicated in several renal and ureteral developmental anomalies, including uteroperic junction obstruction (UPIO) and megaureter (Hohenfellner et al, 1999). Although associations between angiotensin receptor-2 (*Agtr2*) (Yoneda et al, 2002) and angiotensin-converting enzyme (*ACE*) (Liu et al, 2004) genes with VUR have been sought, no definitive etiologic link with VUR has been found. Similarly, a more recent study of specific insertion/deletion polymorphisms of *ACE* in children with and without renal scarring failed to confirm a previously suspected association between homozygous *ACE* deletion polymorphism and scarring, even when stratified for age or VUR (Sekerli et al, 2009). Notwithstanding an observed pattern of autosomal dominant inheritance in some families, the failure to identify any strong genetic mechanism in primary VUR in humans despite the presence of convincing animal genetic models of reflux argues for a more complex polygenetic mechanism of disease in humans. Indeed, in the largest whole-genome linkage and association scan for primary nonsyndromic reflux done to date, no clear overlap involving previously reported gene candidates was found (Cordell, 2010). Specifically, this study did not detect any association with *AGTR2*, *HNF1B*, *PAX2*, *RET*, *ROBO2*, or uroplakin III. The authors concluded that major gene loci may not exist for common VUR in the populations tested.

KEY POINTS: SCREENING, INHERITANCE, AND GENETICS

- The prevalence of reflux is higher in siblings.
- There is a tendency for an autosomal dominant pattern of inheritance.
- Probably many genes are involved.
- It cannot be assumed that all cortical abnormalities in refluxing siblings are acquired. The lack of prospective studies should temper the notion of mass screening of siblings.

EMBRYOLOGY OF THE URETEROVESICAL JUNCTION

A full discussion of the embryology of the trigone and ureteric orifice is found elsewhere in the text. In brief, two events proceed simultaneously to govern the ultimate position and integrity of the UVJ. At one point, the embryonic ureter buds from the mesonephric or wolffian duct to define the metanephric duct or early fetal ureter. The wolffian duct (early vas deferens) and early ureter can be thought of as forming the two upper arms of a Y with the distal mesonephric duct as the stem of the Y. While budding is occurring, the distal mesonephric duct is being drawn and incorporated into the region of the urogenital sinus (UGS), which later becomes the bladder. Incorporation continues until the entire stem is absorbed, leaving the two arms of the Y to enter the bladder separately—one

as the ureter and the other as the vas and ejaculatory duct in the male prostatic urethra (or the vestigial Gartner duct in the female vagina). The two arms of the Y also rotate relative to each other once they contact the UGS/bladder wall, resulting in the ureteric orifice being proximal to the ejaculatory duct orifice. If the ureteric bud reaches the UGS too soon (thought to be due to early budding), over-rotation draws it high and lateral in the bladder wall, leading to inadequate incorporation, insufficient intramural length in the bladder wall, and reflux (Mackie et al, 1975). If the ureteric bud reaches the UGS too late (because of budding late), insufficient rotation occurs, resulting in an ectopic ureter that is drawn distally and medially, often obstructing in the bladder neck region or elsewhere. Furthermore, early or late budding is also thought to mistarget the contact between bud epithelium and the metanephros, leading to renal malformations, dysplasia, hypoplasia, or even agenesis.

FUNCTIONAL ANATOMY OF THE ANTIREFLUX MECHANISM

The phenomenon of VUR represents a balance of several factors. Abnormality in any of these factors alone or in combination will allow or cause the retrograde flow of urine from the bladder up the ureter and ultimately to the renal pelvis and tubules. These factors include the functional integrity of the ureter, the anatomic composition of the UVJ, and the functional dynamics of the bladder.

First, for purposes of reflux prevention, the ureter represents a dynamic conduit, which adequately propels the urine presented to it in a bolus fashion, antegrade, by neuromuscular propagation of peristaltic activity. In so doing, reflux is actively opposed. Moreover, if reflux were to occur, depending on its degree and timing, antegrade flow might be expected to keep refluxing urine from reaching the renal pelvis. The second component is the anatomic design of the UVJ. At the heart of this unique mechanism lies an intramural portion of ureter that travels within the detrusor muscle as it traverses the bladder wall (Fig. 137-1) (Elbadawi, 1972). At the extravascular bladder hiatus, the three muscle layers of the ureter separate. The outer ureteral muscle merges with the outer detrusor muscle to form the Waldeyer sheath, which contributes to formation of the deep trigone. The intramural ureter remains passively compressed by the bladder wall during bladder filling, preventing urine from entering the ureter. Adequate intramural length and fixation of the ureter between its extravascular and intravesical points is required to create this antirefluxing compression valve. Paquin's (1959) early dissections of the UVJ in children revealed an approximately 5:1 ratio of tunnel length to ureteral diameter in nonrefluxing junctions compared with a 1.4:1 ratio in refluxing UVJs (Table 137-2 on the Expert Consult website). Intravesically, the inner muscle of the ureter merges with detrusor muscle to contribute to the superficial trigone. Some of these inner ureteral fibers pass medially to contribute to the intraureteric ridge (Mercier bar). The cellular and molecular details that characterize normal and refluxing UVJs are still unknown. However, it is likely that in addition to architectural deficiencies of tunnel length, abnormalities in uterovesical smooth muscle and extracellular matrix composition and neural function may contribute to reflux (Oswald et al, 2004).

Opening of the UVJ is achieved by active contraction of the longitudinal muscles within the tunnel. This draws the extravascular and intravesical points of the intramural ureter closer together, shortening and widening the tunnel, and allows passage of the urine bolus into the bladder. Indeed, when viewed cystoscopically, a lateral displacement of the ureteric orifice accompanies the classic jet of urine into the bladder. Although such lateral displacement is functionally normal and necessary to permit urine to pass, permanent lateral displacement by virtue of a constitutively short tunnel characterizes the cystoscopic position of the refluxing ureteric orifice. Closure of the UVJ results both from compression of the intramural ureter and a return to its full tunnel length as the ureteral muscle relaxes. Thus active and passive mechanisms dynamically reconfigure the tunnel as needed to allow antegrade passage of

TABLE 137-2 Mean Ureteral Tunnel Length and Diameter in Normal Children

AGE (yr)	INTRAVESICAL URETERAL LENGTH (mm)	SUBMUCOSAL URETERAL LENGTH (mm)	URETERAL DIAMETER AT THE URETEROVESICAL JUNCTION (mm)
1-3	7	3	1.4
3-6	7	3	1.7
6-9	9	4	2.0
9-12	12	6	1.9

From Paquin AJ. Ureterovesical anastomosis: the description and evaluation of a technique. J Urol 1959;82:573.

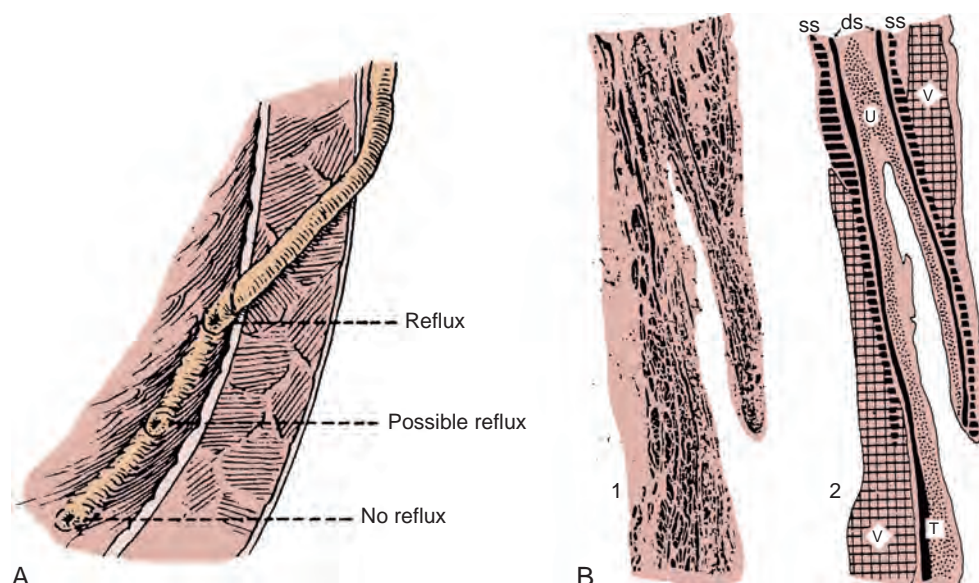


Figure 137-1. A, A refluxing ureterovesical junction has the same anatomic features as a non-refluxing orifice, except for inadequate length of the intravesical submucosal ureter. Some orifices with marginal submucosal tunnels may reflux intermittently. B, Ureterovesical junction in longitudinal section. 1, Photomicrograph; 2, diagrammatic representation. The ureteral muscularis (U) is surrounded by superficial (ss) and deep (ds) periureteral sheaths that extend in the roof of the submucosal segment and continue beyond the orifice into the trigonal muscle (T). The relationship of the superficial sheath to the vesical muscularis (v) is clearly seen. Transverse fascicles in the superior lip of the ureteric orifice belong to the superficial and deep sheaths. No true space separates ureter from bladder. (A, From Glenn J. Urologic surgery. 2nd ed. New York: Harper & Row; 1975; B, from Elbadawi A. Anatomy and function of the urethral sheath. *J Urol* 1972;107:224.)

urine while preventing retrograde flow. Finally, the existence of local efferent and afferent neuromuscular coordination between the UVJ and the periureteral bladder wall is suggested by neurophysiologic studies that induce elevation or decrease in intraluminal UVJ pressure during bladder filling (Shafik, 1996).

KEY POINTS: FUNCTIONAL ANATOMY

- Integrity of the antireflux mechanism depends on balancing the anatomic and functional relationships between the ureter and the bladder.
- Secondary reflux may be of an anatomic or functional origin in the UVJ, bladder, or bladder outlet.

CAUSE OF VESICoureTERAL REFLUX

As mentioned previously, the occurrence of VUR represents a balance of several factors. The degree to which each contributes to the pathologic processes largely defines whether reflux is considered primary or secondary. In general, reflux is considered primary if the main reason for it is a fundamental deficiency in the function of the UVJ antireflux mechanism while the remaining factors (bladder and ureter) remain normal or relatively noncontributory. Secondary reflux, then, implies reflux caused by overwhelming the normal function of the UVJ. Bladder dysfunction of a congenital, acquired, or behavioral nature is often the root cause of secondary reflux. It is also accepted that reflux is often considered secondary if its absence was documented at some point before its detection.

Primary Reflux

As stated earlier, primary reflux represents a congenital defect in the structure and therefore function of the UVJ. Reflux occurs despite

an adequately low-pressure urine storage profile in the bladder. The length-to-diameter ratio of the intramural ureteral tunnel is almost always less than that described by Paquin (1959). Although inadequate tunnel length rather than excessive ureteral diameter usually underlies primary reflux, the dilated ureter often poses a challenge when a nonrefluxing ureterovesicostomy is required. This has traditionally prompted both long tunnels (>5 cm) or reduction of ureteral diameter by tapering, plication, or both to reconstruct a successful antireflux mechanism. On the other hand, construction of a new tunnel with a full 5:1 length-to-diameter ratio may not be absolutely required to correct reflux.

Secondary Reflux

Any number of obstructing bladder pathologic processes can create hostile and excessive storage and emptying pressures that eventually overwhelm a normal antirefluxing intramural flap-valve mechanism. Such abnormalities can be functional or anatomic.

The natural history of reflux to resolve suggests the length-to-diameter ratio of the ureter at the UVJ gradually evolves toward functional competency. However, reflux more likely represents a balance between dynamic storage and voiding characteristics of the bladder and the architectural competency of the UVJ to resist reflux. By this reasoning, it may be suggested that most reflux indeed may be secondary at any given point during the development and chronology of a child's competence with elimination functions.

The most common anatomic obstruction of the bladder in the pediatric population is posterior urethral valves (PUVs). Reflux is present in 48% to 70% of patients with PUV patients (Reuter and Lebowitz, 1985; Puri and Kumar, 1996; Hassan et al, 2003; Priti et al, 2004). Relief of PUV obstruction appears responsible for resolution of reflux in about one third of the patients. In one of these series, 78% of reflux resolved within 6 months of valve ablation (Priti et al, 2004). Such observations argue for the secondary nature of reflux as a result of elevated voiding pressures in PUV bladders.

Even prostatic enlargement and its relief are associated with VUR and its resolution, respectively (Morita, 1987). In females, anatomic bladder obstruction is rare. The most common structural obstruction is from a ureterocele that prolapses into the bladder neck (Merlini and Lelli Chiesa, 2004). In such cases, reflux in a contralateral ureter is likely due to the ensuing outlet obstruction and often resolves with decompression of the ureterocele. In general, then, if relief of the obstruction results in rapid reflux resolution, the reflux was likely secondary.

In contrast to anatomic obstruction, neurofunctional causes of elevated bladder pressures also predispose to VUR. In particular, neurogenic bladder associated with spina bifida is at risk for reflux (Bauer et al, 1982). This fact must be borne in mind during evaluation of the child with UTI. Special attention to the potential for occult spinal dysraphism, including sacral dimple or hairy patch, gluteal cleft abnormality, diminished rectal tone, or significant constipation or encopresis, should prompt consideration of investigation for coexistent spinal cord abnormalities.

Urodynamic extremes that predispose to reflux in the absence of overt neurologic pathologic processes also may exist. Some studies suggest that a secondary aspect to neonatal reflux is a peculiarity of male infants. In a study by Yeung and colleagues (1998), 22 of 24 infants with reflux showing urodynamic evidence of instability (overactivity), inadequate, or obstructive voiding patterns were males. Normal or immature voiding patterns were observed in all infants in the nonrefluxing control group, of which 16 of 21 were male. In infants, higher voiding pressures are associated with reflux, particularly in boys (Chandra et al, 1996), and may contribute to the male preponderance of reflux in infants. Urodynamic evaluation suggests these elevated infant bladder pressures may be due to inadequate sphincter relaxation (Chandra and Maddix, 2000) during this stage of development. However, detrusor activity in such infants is largely normal during filling, with slightly diminished bladder capacities in some (Podesta et al, 2004), though uninhibited activity during filling has been observed, again predominantly in male infants (Yeung et al, 1998). Considering that the high prevalence for reflux in infants coexists with urodynamic evidence of elevated voiding pressures, these observations suggest that infant voiding patterns may be a part of normal development. Thus, even though the UVJ likely matures with age, the interplay between the UVJ and infant voiding patterns may predispose to a form of secondary reflux that resolves with normalization of urodynamic parameters as these infants grow older.

In older children, acquired abnormalities in bladder and bowel function commonly known as *bladder and bowel dysfunction (BBD)* have been associated with reflux. The precise cause of voiding dysfunction is variable but may evolve from a persistence of the expected early attempts to suppress bladder contractions during the toilet training months by volitional contraction of the external sphincter (Allen, 1985). If this behavior becomes prolonged or intensifies, often driven by the child's overwhelming desire for continence, bladder voiding pressures increase. Continence is gradually exchanged for incomplete emptying, resulting in a higher UTI risk. Although investigation of UTI might necessarily diagnose some patients with persistence of primary reflux, the elevated bladder pressures gradually distort bladder and UVJ architecture and may create (secondary) reflux (Koff and Campbell, 1992). Structural failure of the UVJ is likely a critical determinant because high voiding pressures of approximately 100 cm H₂O are common in normal bladders and structurally intact nonrefluxing UVJ. Indeed, with structural failure of the UVJ, reflux occurs easily and at low voiding pressures or during early filling and is a poor prognostic factor for reflux resolution (Koff and Campbell, 1992; Hinman et al, 2002). Uninhibited bladder contraction is the most common urodynamic abnormality associated with reflux in neurologically normal children. In one study of 37 girls with primary reflux, 75% had overactive detrusor contractions (Taylor, 1982). However, the observation that treatment of such patients with oxybutynin can eliminate reflux in up to 80% of refluxing ureters strongly argues that an overactive bladder frequently can be responsible for reflux, by either causing secondary reflux or perpetuating primary reflux

(Koff and Murtagh, 1983; Homsy et al, 1985; Seruca, 1989). Thus it is apparent that primary and secondary reflux may not always be mutually exclusive or that what is perceived as primary reflux in some children may, in fact, be secondary to BBD.

Clinical Correlates

The previous discussion clearly suggests that multiple opportunities exist for modifying the course of reflux if secondary causes are appreciated, identified, and treated. Van Gool and coworkers (1992) identified that 18% of children enrolled in the European arm of the International Reflux Study in Children harbored voiding dysfunction associated with more frequent UTI and greater persistence of reflux compared with those subjects without voiding dysfunction. Similar findings were reported from the recent Swedish Reflux Trial in which a cohort of children 1 year of age to younger than 2 years of age with grade 3 and 4 reflux were assessed and followed for 2 years for lower urinary tract dysfunction prevalence and type (Sillen et al, 2010). Twenty percent of children harbored some form of dysfunction at entry. This dysfunction prevalence increased to 34% at 2 years of follow-up. A negative correlation was found between dysfunction at follow-up and reflux improvement ($P = .002$). In addition, scintigraphic renal abnormalities (defined in Brandström et al, 2010a) at study entry and at follow-up also were associated with dysfunction ($P = .001$). Failure to address voiding abnormalities can adversely affect outcome of antireflux surgery (Koff et al, 1998).

Indeed, meta-analytic evidence recently compiled by the American Urological Association (AUA) Panel on VUR Guidelines now suggests that BBD is by far one of the most critical and modifiable variables that affect VUR management and attendant UTIs. Composite study analysis now indicates that BBD is associated with a higher incidence of UTIs while on antibiotic prophylaxis, as well as after surgical correction of VUR, with less VUR resolution at 24 months from diagnosis and with reduced success of endoscopic surgery. In the studies selected by the panel that qualified as having acceptable levels of evidence, BBD did not appear to reduce the success of open surgical reflux correction (Fig. 137-2).

Thus, although BBD is discussed in detail elsewhere in the text, a thorough evaluation of the toilet-trained child with reflux must recognize dribbling, urgency, or incontinence as signs of coexisting voiding disorders. Girls also will exhibit procrastination about voiding or demonstrate curtsying behavior, and boys may squeeze the penis, in attempts to suppress bladder contractions. The close proximity of the bladder and anal outlets often leads to sympathetic contraction of the anal sphincter as well, resulting in the frequent association of constipation and encopresis with reflux and UTI, in what is probably a mutually aggravating pattern (O'Regan and Yazbeck, 1985; O'Regan et al, 1986; Chase et al, 2004). Constipation must be recognized and eliminated as much as possible to establish optimal conditions for successful spontaneous or surgical resolution of reflux. The initial report of McGuire and colleagues (1981) suggested that pressures in excess of 40 cm H₂O measured at full capacity are associated with reflux and upper tract deterioration. Treatments to maintain pressures below this value result in significant reflux resolution (Flood et al, 1994).

LOWER URINARY TRACT INFECTION AND REFLUX

Reflux is not a general cause of UTI. In the absence of bladder symptoms or inflammation, reflux is most readily considered a clinical accelerant of bacteriuria, by mechanically delivering infected urine to the renal pelvis. Infection-related cystitis is expected to incite bladder irritability and dysuria, upsetting the voiding pattern and lowering the threshold for reflux in a given UVJ. However, animal studies differ on whether infection can perpetuate ureterovesical reflux. In primate studies, surgically created reflux followed by introduction of pathogenic bacteria into the bladder was associated with reflux persistence (Roberts et al, 1988),

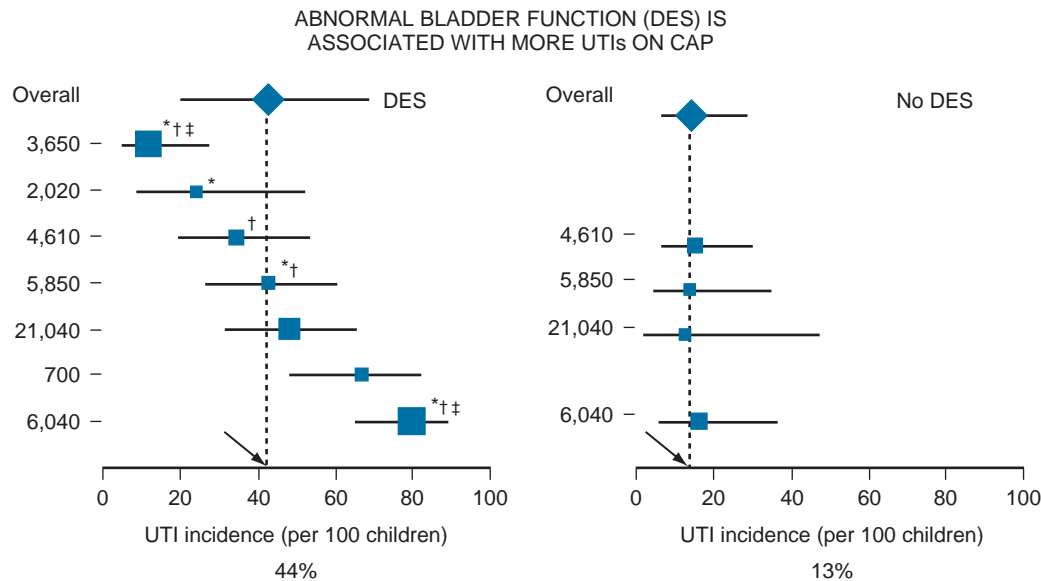


Figure 137-2. Dysfunctional elimination syndrome (DES) and urinary tract infection (UTI). CAP, continuous antibiotic prophylaxis. (From Peters CA, Skoog SJ, Arant BS, et al. Summary of the AUA guideline on management of primary vesicoureteral reflux in children. J Urol 2010;184: 1134–44.)

compared with spontaneously occurring primary reflux in the presence of chronic infection (Lewis and Roberts, 1986) in which infection did not delay reflux resolution.

Significant hydroureter and hydronephrosis associated with high-grade reflux could, in theory, act as a reservoir for the repeat antegrade reintroduction of pathogenic organisms to the bladder. Colonized urine might then cyclically reflux retrograde to the upper tracts. Similarly, ureteral atony secondary to the effects of endotoxin could fail to expel infected urine from the upper tracts, but this does not appear to reduce the ultimate resolution of reflux (Roberts and Riopelle, 1978). Indeed, the dilated upper tracts seen in high-grade reflux explored in the randomized prospective controlled Swedish Reflux Trial were associated with a higher rate of recurrent febrile UTI in patients on surveillance without antibiotic prophylaxis (57%) (Brandström et al, 2010b). Reflux correction or antibiotic prophylaxis reduced the recurrent infection rate to approximately 20% ($P = .0001$). Interestingly, the finding was restricted to girls, which may reflect an anatomic predisposition to bacterial colonization of the bladder in girls versus boys; the febrile nature of the infection was likely due to reflux washing of bacteria to the upper tracts and renal parenchyma.

KEY POINTS: LOWER URINARY TRACT INFECTION AND REFLUX

- Reflux is not a general cause of UTI.
- Reflux facilitates pyelonephritis.

GRADING OF REFLUX

Grading systems generally exist to help prognosticate the behavior of the disease they classify. In 1981 the International Reflux Study Committee proposed a system of five grades of reflux that remains in current use today in North America (Duckett and Bellinger, 1982; Lebowitz et al, 1985). Five grades of reflux are currently used to depict the appearance of the ureter, renal pelvis, and calyces as seen on the radiographic contrast images generated by the voiding cystourethrogram (VCUG) (Table 137-3; Fig. 137-3). Using such a system serves several purposes. Grading standardizes the description of the degree of reflux for clinical management of

TABLE 137-3 International Classification of Vesicoureteral Reflux

GRADE	DESCRIPTION
1	Into a nondilated ureter
2	Into the pelvis and calyces without dilation
3	Mild-to-moderate dilation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices
4	Moderate ureteral tortuosity and dilation of the pelvis and calyces
5	Gross dilation of the ureter, pelvis, and calyces; loss of papillary impressions; and ureteral tortuosity

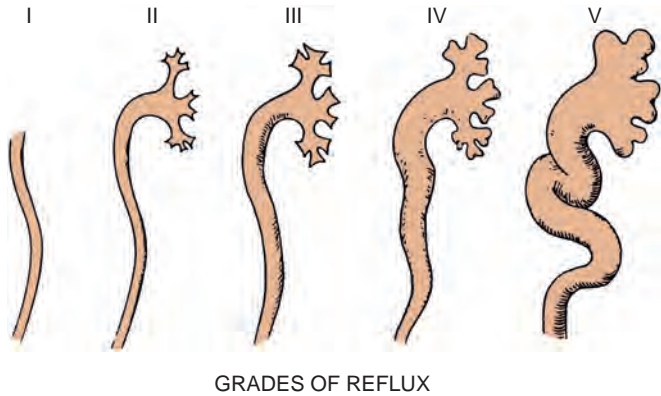


Figure 137-3. International classification of vesicoureteral reflux.

the individual patient and is used for grouping research subjects in the design of clinical studies and trials. Grading facilitates documenting the natural history of the reflux process in the individual patient. It also permits establishing quantitative associations between reflux and other clinical parameters, to determine whether such associations hold clinical relevance. Most importantly, description of initial grade in primary reflux is the most significant parameter associated with prediction of reflux resolution (see later).

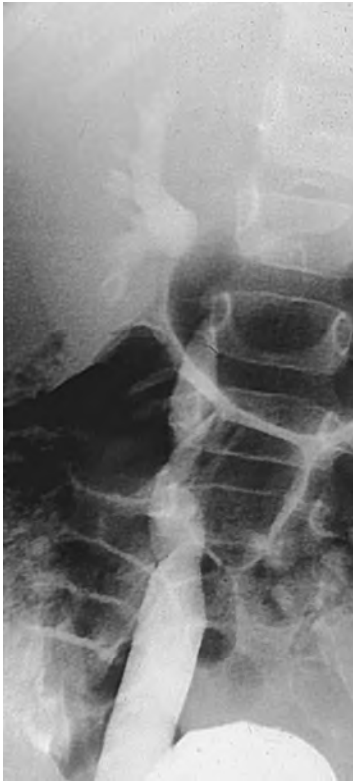


Figure 137-4. A refluxing ureter with significant dilation of the lower segment but no distortion of the collecting system may be different from the typical system with grade 2 reflux.

Despite the widespread use of the five-point grading system, several shortcomings exist. For example, the expected concordance between ureteral and calyceal dilation does not always occur (Fig. 137-4). Either the ureter or the calyces may demonstrate dilation out of proportion to the calyces or ureter, respectively. Whether this reflects an anomaly in the biomechanical tissue properties or peristaltic activity of the excessively dilated structure, as compared with the typical refluxing upper tract is unknown. Nevertheless, such anatomy is difficult to grade using the current system. Similarly, it is unknown whether the propensity to either scarring in the face of infection or reflux resolution is altered in such systems.

Attempts also have been made to grade reflux using radionuclide cystography (RNC). Because RNC does not provide discrete images of the ureteral and calyceal architecture required to assign reflux grade, classifying reflux by RNC is difficult. Alternative RNC grading has been proposed (Zhang et al, 1987). This provides reasonable concordance to the objectives of the classic grading system by collapsing grades 2 and 3, as well as grades 4 and 5, into low-grade and high-grade reflux, respectively (Fig. 137-5). The impact of the reduction in grading detail from 5 grades (1 to 5) to 2 (low and high) on understanding reflux pathophysiology and on the design of clinical studies has yet to be determined.



For further details, please see the Expert Consult website.

DIAGNOSIS AND EVALUATION OF VESICoureTERAL REFLUX

Confirmation of Urinary Tract Infection

Because preventable reflux nephropathy is predicated on the combined effects of UTI and reflux, confirming and documenting true UTI is paramount in the appropriate management of the patient with reflux. Many variables are responsible for the accurate assessment and interpretation of UTI in the context of reflux. These include clinical history and presence of fever; age of the patient; circumcision status; method of urine specimen collection, storage,



Figure 137-5. Nuclear voiding cystography showing right-sided reflux. Radionuclide tracer can be quantitated (from left to right) as grade 1 (grade I of the international grading system), grade 2 (grades II to III of the international grading system), and grade 3 (grades IV to V of the international grading system).

and delivery; and the results of urine dipstick and microscopic analyses. Although confirming true pyuria by dipstick or microscopic analysis, in addition to the presence of bacteriuria, will help to differentiate infection from colonization, colonization alone in the presence of reflux still may pose a threat to the upper tracts. Attention to these details cannot be overemphasized because major management decisions, including operative intervention for correction of reflux, often rest solely on a diagnosis of UTI. Conversely, confirming microbial growth in a urine specimen is of little value if the mode of collection is highly suspect and likely to harbor contamination. Confirmation of UTI begins with collection of the urine specimen. If storage is necessary, specimens should be maintained at 4° C until transfer to the laboratory.

For further details, please see the Expert Consult website.



Evaluating Urinary Tract Infection

Numerous factors support a search for reflux in the patient with UTI. The probability of finding VUR in children with a UTI is 29% to 50% (Anonymous, 1981). Furthermore, in some patients, higher grades of reflux may be associated with various degrees of existing renal parenchymal maldevelopment (see earlier section on embryology) (Nakai et al, 2003). In addition, because reflux tends to resolve over time, it is reasonable that UTI is more commonly associated with reflux in younger patients (Smellie et al, 1981b), whose renal parenchyma is at more risk for scarring after pyelonephritis than that of an older child. Smellie and colleagues also suggest that the presence of reflux does not usually provide any unique clinical features in the patient with a UTI. Thus, as with the search for sibling reflux, radiologic investigation of the patient with UTI is tailored to patients who are placed at greatest renal functional risk from the presence of VUR. For this reason, radiographic investigation for VUR until recently has generally been directed to children younger than 5 years of age, all children with a febrile UTI, and any male child with a UTI regardless of age or fever, unless sexually active. More recent guidelines specifically for children under 2 years of age from the American Academy of Pediatrics (AAP) tighten the recommendation for voiding cystography to follow a second rather than the initial febrile UTI, with infection based on stricter culture criteria (see later discussion).

The high repeat UTI rate after a first UTI has prompted a recommendation for some form of VUR workup (Fig. 137-6). However, the current state of the VUR debate makes it difficult to know which patients, by such evaluations, might harbor clinically significant reflux, given how common UTI is in children. Some reassurance can be provided when a voiding study is negative for VUR. However, the parental concern over the invasiveness of the cystogram may first limit the evaluation to ultrasonography only, to rule out any existing gross structural defects. Thus taking the appropriate voiding, fever, and family histories into account, a sonographic study of the bladder and kidneys can be considered a reasonable minimum evaluation in the infant or child after a UTI, concordant with the present AAP guidelines. Even the detection of reflux after treatment for UTI could be of questionable significance if the child is older and/or no fever accompanies the UTI. On the other hand, the presence of structural renal anomalies or significant asymmetry would

Although grading is purely a classification of the appearance of contrast in the upper tract, ascribing an absolute value to the grade has the potential to cast the reflux in unequivocal terms, to the exclusion of other factors that modulate reflux at the time the images are acquired. Inherent bladder dynamics, the bladder outlet, and even ipsilateral UVJ obstruction all influence the degree of reflux at any given assessment (Lebowitz, 1992). Grade, reflux detection, and reflux resolution are all interrelated and are influenced by the degree of bladder filling, the voiding cycle, the number of filling cycles during the contrast cystogram, and whether the reflux occurs during filling or only during voiding. None of these parameters is built into the grading system for reflux used currently. However, given the principal role of a reflux grading system is to help prognosticate reflux resolution, future incorporation of other parameters may provide additional clinical acumen. Finally, it must be remembered that reflux grade is still presently determined by an imaging study that requires invasion of a sensitive anatomic region. For a given reflux grading result, the variables of bladder dynamics, filling, and voiding cannot necessarily be replicated with certainty in a given patient each time he or she is studied. It is reasonable to speculate that reflux grade could easily vary up or down by at least one grade if sequential studies were performed in a given patient. Thus the entire reflux literature, which historically reports results in terms of five separate grades, must be considered with some circumspection because the veracity of grade at the time of the contrast study may be, to some extent, arbitrary.

In infants, specimen collection often will entail the placement of an adhesive urine collection bag over the genitalia. Although topical cleansing of the area is reasonable to reduce contamination and false-positive cultures, care must be taken to avoid introducing the disinfection agent into the specimen. Unfortunately, routine practice is so variable that such guidelines are often difficult to follow or confirm and **microbial contamination of bagged specimens is common. Conversely, this method is most useful if the resulting urine culture is negative.** Although fevers are common in infants, UTI comprises only 5% of children presenting with fever (Hoberman and Wald, 1997). Thus the ability to easily rule out a UTI in the febrile infant with reflux facilitates management. If there is a high clinical suspicion for UTI in an infant, the more accurate method is to obtain a catheterized specimen. Even this method may prove suspect in the uncircumcised infant whose preputial skin is not yet retractable to easily reveal the urethral meatus. In this and other instances in which the urethral route is difficult or compromised in patients of any age, a suprapubic needle aspiration of bladder urine provides the most accurate method of obtaining a urine sample. In the younger child, however, repeated catheterization for specimen acquisition and radiographic assessment (see later discussion) should be considered carefully. This routine practice is coming under greater scrutiny as the long-term sequelae of this invasive maneuver become appreciated (Stashenko and Goldberger, 1998) and could become a factor in patient compliance with follow-up (and therefore management decisions for reflux).

In patients who can void spontaneously, a clean voided mid-stream catch specimen is preferred. The initial urine is discarded because it is rich in periurethral organisms.

The previously mentioned guidelines pertain to patients with both unknown and known reflux status. In the former, the decision to look for reflux will depend on the propensity for acquired reflux nephropathy in the individual patient. In the patient known to have reflux, the prevailing propensity for acquired reflux nephropathy and compliance with proper voiding habits, antibiotic prophylaxis, and timely reporting will influence further management (see later discussion).

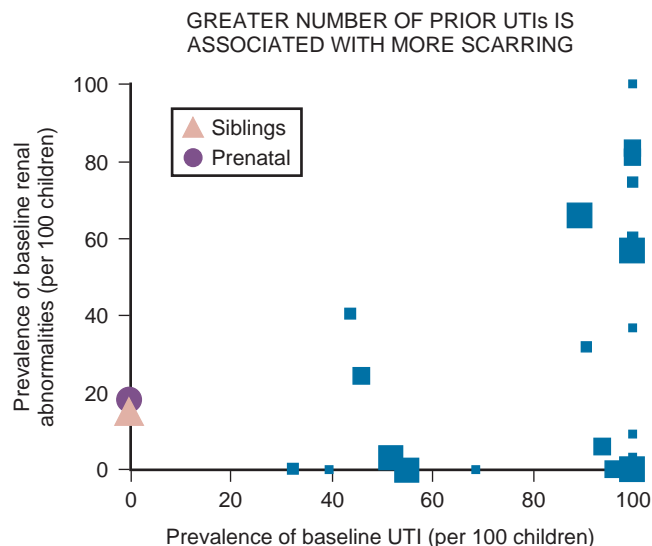


Figure 137-6. Urinary tract infection (UTI) history. (From Peters CA, Skoog SJ, Arant BS, et al. Summary of the AUA guideline on management of primary vesicoureteral reflux in children. *J Urol* 2010;184:1134–44.)

support proceeding with a cystogram. More recent studies of racial predilection for reflux have supported a lower prevalence in children of African origin (Askari and Belman, 1982; Horowitz et al, 1999), but the prevalence in children of Hispanic origin (Pinto, 2004) is similar to that of Caucasians.

The advent of prenatal ultrasonography has likely augmented the detection of asymptomatic reflux in newborns, as a result of mass surveillance for persistent postnatal hydronephrosis and the ensuing performance of cystography in these infants. It must be remembered that the sonographic finding of hydronephrosis is generally much more common than hydronephrosis because of a renal moiety actively refluxing at the time of the sonogram. Indeed, there is little correlation between the degree of antenatal hydronephrosis and the existence of reflux (Farhat et al, 2000). A corollary study also demonstrated normal postnatal sonograms in 25% of patients with VUR and antenatal hydronephrosis (Lebowitz, 1993).

ASSESSMENT OF THE LOWER URINARY TRACT

Cystographic Imaging

The basis of reflux detection lies in demonstrating the retrograde passage of an imaging contrast material from the bladder to the ureter and renal pelvicalyceal system. The currently available methodologies require a source of contrast agent in the bladder. Two approaches, the indirect and direct cystograms, can be performed depending on whether the contrast enters the bladder indirectly after excretory urography or directly, usually by urethral catheterization. Indirect cystography, although avoiding the invasive nature of urethral catheterization, is prone to false-positive interpretation as a result of contrast that does not originate from the bladder, remaining in the ureter or pelvis after filtration and antegrade passage, and false-negative results in lower grades of reflux (Conway et al, 1975). However, it has been suggested that the value of indirect cystography may lie in ruling out the presence of VUR (Carlsen et al, 1986).

The VCUG and radionuclide cystogram are the two common forms of direct cystography and constitute the present-day gold standard approaches to reflux detection. More recently, to eliminate the need for ionizing radiation, some studies have demonstrated a growing interest in sonographic detection of reflux using either color Doppler imaging (Haberlik, 1997; Oak et al, 1999; Galia et al, 2004) or echo-enhancing contrast agents (Berrocal et al, 2001; Darge et al, 2001; Darge and Troeger, 2002; McEwing et al, 2002; Tasic and Todorovska, 2003; Valentini et al, 2004; Vassiou et al,

2004; Darge et al, 2005). Direct imaging of reflux is affected by several parameters. These include bladder contraction during voiding, the fluid volume instilled into the bladder, and presence of infection and therefore inflammation of the UVJ mucosa. Reflux may occur during filling or only during the active bladder contraction associated with voiding. Consequently, if a patient is unable to void in the artificial setting of the radiography suite, false-negative results may ensue. More importantly, even during voiding, reflux may not be demonstrated on a single filling-voiding cycle. Several studies have demonstrated a roughly 12% to 20% greater detection rate for VUR if a cyclic study is performed (Paltiel et al, 1992; Papadopolou et al, 2002; Novljan et al, 2003). A cyclic VCUG involves a second or third cycle of bladder filling and emptying under fluoroscopic observation. A similar cyclic strategy is commonly employed for the RNC as well (Fettich and Kenda, 1992). Reflux also may be demonstrated during catheter filling of the bladder. Because filling assumes far lower intravesical pressure than that of voiding, reflux during filling, or passive reflux, is generally considered a poor prognostic sign for reflux resolution and suggests the presence of a fixed decompensation of the UVJ. This is a common finding in patients with acquired or neurogenic voiding dysfunction, wherein high-resistance voiding gradually remodels the bladder wall and UVJ, leading to complete failure of the latter's antireflux mechanism and immediate reflux at virtually any volume of the filling phase (Koff, 1992). This is in contrast to reflux that occurs only during the higher pressure milieu of bladder emptying and contraction. Thus technical inconsistencies in the ratio of instilled volume-to-bladder capacity during the radiographic technique can lead to variations in rates of reflux detection: if the bladder is overfilled or underfilled for a given degree of progressive UVJ incompetency, reflux may be overdetected or underdetected, respectively.

One difficult dilemma in the performance of voiding studies involves cystography during active infection. On one hand, some UVJs maintain only borderline antireflux mechanisms, which are competent in a sterile milieu but become incompetent from edema and inflammation associated with mucosal inflammation during cystitis. Such patients may have VCUG studies negative for reflux in the absence of infection but suffer from repeated pyelonephritic episodes. Cystograms in such patients may demonstrate reflux if obtained during clinically active infection, whereas cystogram obtained in the presence of positive urine cultures alone may not (Gross and Lebowitz, 1981). On the other hand, evoking reflux during an active cystitis, by definition, will transmit bacteria to the upper urinary tract and renal pelvis and risks iatrogenic pyelonephritis. Nevertheless, the general consensus has been to delay the voiding study for at least a week or longer to allow for adequate recovery from the acute infection episode (Craig et al, 1997). Only if it is imperative to make the diagnosis of reflux in children with a history of recurrent pyelonephritis and repeatedly negative voiding studies in the intercurrent periods should cystography during UTI be considered.

The VCUG is a fluoroscopic study that provides information on both the functional dynamics and structural anatomy of the urinary tract. The detailed technique of the VCUG is discussed more fully elsewhere in the text. Bladder contrast is instilled by gravity after urethral catheterization. Bladder capacity is recorded when contrast influx ceases. Static images record bladder contour, presence of diverticula or ureteroceles, grade of reflux, configuration and blunting of calyces, and intrarenal reflux. Passive or active reflux is demonstrated dynamically during fluoroscopy while filling and voiding, respectively. In addition, bladder neck anatomy, funneling or dilation, and urethral patency are parameters derived from the VCUG. Delayed or postvoid films are crucial in documenting clearance of contrast from the upper tracts because retained contrast, particularly with dilated pelvicalyceal systems, could signify the presence of a concomitant UPJ obstruction (UPJO), either primarily or secondarily as a result of distortion of the UPJ by massive retrograde filling of the pelvis by the reflux (Hollowell et al, 1989). If both the UPJ and UVJ meet criteria for operative repair, the UPJ should be repaired first to avoid the incipient obstruction that may ensue if resistance is added to the UVJ when reflux is

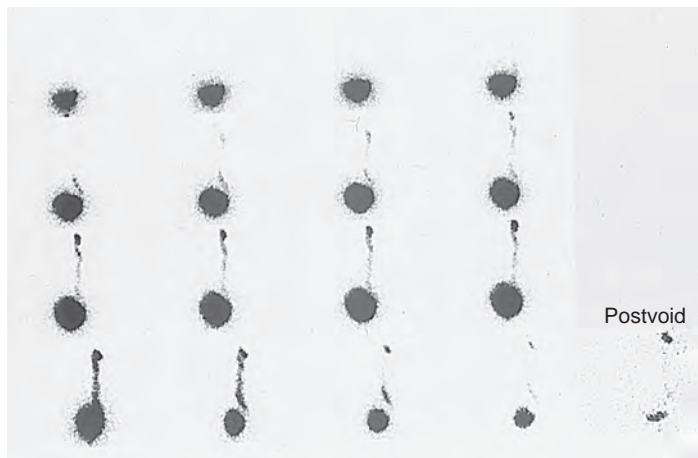


Figure 137-7. Radionuclide cystogram showing right-sided reflux that worsens with bladder filling. The upper collecting system drains fully with voiding.

corrected (Hollowell et al, 1989). With care, both processes may be repaired simultaneously when it is clear that they are independent significant problems.

The RNC has historically enjoyed a reputation for requiring approximately 1% the radiation exposure generated by the VCUG (Blaufox et al, 1971; Diamond et al, 1996a). Presently, the reduced radiation requirements of modern digital techniques have significantly narrowed the difference between fluoroscopy and RNC. Although little anatomic detail is afforded by the RNC, it is ideal as both a screening modality and for monitoring the natural history or surgical follow-up of reflux. In contrast to the VCUG, the instilled bladder contrast material, usually technetium-99m pertechnetate, is the radiation source. Reflux is detected on scintigraphic gamma camera images (Fig. 137-7). Lack of confounding imaging densities typical of fluoroscopy, as well as the ability to obtain prolonged exposures, allow for greater sensitivity of the RNC in grade 2 to 5 reflux. Ironically, grade 1 reflux into the distal ureter is often poorly detected because of the overlying exposure generated by contrast within the bladder. Thus RNC and VCUG imaging can be used complementarily, balancing radiation exposure with the need for dynamic information and anatomic detail. Notwithstanding the previous discussion, modern digital fluoroscopic equipment has further reduced the radiation exposure of conventional fluoroscopy, thereby narrowing the difference in radiation exposure between the two modalities.

Another modality gaining popularity in some centers is ultrasonic cystography to detect reflux. Modern transducers coupled with the use of echo-enhancing contrast agents can image reflux well in older children (Novljan et al, 2003; Riccabona et al, 2003; Tasic and Todorovska, 2003; Galia et al, 2004), but the technique remains of limited use in neonates (McEwing et al, 2002). Furthermore, although radiation exposure is eliminated, bladder catheterization remains a necessary feature with this approach.

Diagnostic Controversies: Challenging the Assessment of Reflux

The well-recognized distress of the family and patient associated with urethral catheterization, particularly in children, coupled with the advent of low-morbidity outpatient correction of reflux using endoscopic approaches appears to be challenging conventional reflux management and therapy. All aspects of VUR, including modern incidence of renal scarring and failure, peak ages of renal susceptibility, and indications for reflux correction, including the assumption that permanent correction of reflux is an absolute necessity, are coming under scrutiny. This has given rise to added pressure to avoid bladder catheterization. The cystogram can have

traumatic after effects in young patients (Stashinko and Goldberger, 1998; Elder, 2005) and must be approached with sensitivity and awareness of the developmental stage of the patient. Sedation (Stokland et al, 2003), topical urethral anesthetic (Gerard et al, 2003), and more recently hypnosis (Butler et al, 2005) have all been effective in mitigating the deleterious psychological effects of cystography. Nevertheless, it is clear that parental perception of the nature of the medical modalities involved in reflux management will influence their choice of therapy for their children (Ogan et al, 2001). This should in no way be construed as license for the abandonment of conventional observational therapy, including antibiotic prophylaxis and periodic cystography in favor of immediate reflux correction in all patients (Aaronson, 2005). Rather, the evolution of less invasive imaging modalities for reflux detection and reduced morbidity of reflux correction should be encouraged in parallel.

Uroflowmetry

Evaluation of the lower urinary tract during clinical assessment of VUR cannot rely solely on imaging. Because reflux is a dynamic phenomenon, the prevailing functional status of the bladder also must be considered. Although full pressure-volume urodynamic studies of the bladder are not required in all patients with reflux, a minimal survey of bladder emptying characteristics can be obtained by uroflowmetry. The details of uroflowmetry technique are discussed elsewhere in the text. In patients with reflux, it is important to establish whether the bladder outlet is functioning relatively normally or harbors more resistive characteristics that are highly prevalent in younger patients. Elements of the uroflow such as lack of smoothness of the flow-velocity curve suggest incomplete relaxation of the bladder outlet during voiding. This implies the existence or development of relatively higher pressures during voiding, which could delay the natural history of reflux resolution or even perpetuate reflux. An increased postvoid residual volume may be a risk factor for UTI. In the setting of passive reflux, carrying infected postvoid residual urine also can lead to ascending infection and pyelonephritis.

Top-Down Approach

The top-down approach is an interesting concept based on the notion that only clinically relevant reflux with potential to cause renal injury is worthy of uncovering, with the critical assumption that VUR in the absence of scintigraphic renal abnormality is unlikely to cause future renal damage. Only a dimercaptosuccinic acid (DMSA) renal scan is obtained after a febrile UTI, with cystography reserved only for patients with abnormal scintigraphy findings. Children with a negative DMSA scan undergo no further evaluation unless they develop recurrent UTI, in which case a VCUG should be obtained.

Hansson and colleagues (2004) retrospectively reviewed 303 children younger than 2 years of age who had undergone evaluation by DMSA and VCUG within 3 months of their first UTI. Although 82% of these infections were febrile, VUR was found in only 26% of the children (80 in 303), 66% of whom had abnormal DMSA scans, and no abnormalities were detected in the remaining 27 patients. An approach based on identifying renal cortical abnormalities before obtaining a VCUG would have identified the 66% of children with VUR presumably at risk for further scarring, and it would have excluded 120 children (40%) without VUR or renal abnormalities from an unnecessary VCUG.

Implementation of a top-down approach would obviously not have detected 34% (27 in 80) of the cases of VUR. However, the patients in Hansson's study did receive prophylaxis, because the top-down approach was being studied only from a theoretic viewpoint. In applying the top-down approach, these infants would not have been started on antibiotic prophylaxis and potentially might have been at risk to develop recurrent UTI. However, in 74% (27 in 80) of these patients, VUR was low grade and the remaining 7 cases (grade 3 to 5 VUR) either resolved or improved significantly during

TABLE 137-4 American Academy of Pediatrics Clinical Practice Guideline on Febrile Urinary Tract Infection in Febrile Infants and Young Children: Key Updates

AREA OF MANAGEMENT	UPDATES FROM THE 1999 GUIDELINE
Diagnosis	Both an abnormal urinalysis result and a positive urine culture result are needed to confirm inflammation A positive culture result is defined as at least 50,000 colony-forming units per milliliter, rather than the previous criterion of at least 100,000 colony-forming units per milliliter Guidance is added for using clinical criteria to establish a threshold to decide whether to obtain a urine specimen
Treatment	Oral treatment is as effective as parenteral treatment
Imaging	Voiding cystourethrography is not recommended routinely after the first febrile urinary tract infection; ultrasonography should include the bladder and kidneys
Follow-up	Emphasis is on urine testing with subsequent febrile illnesses, rather than on regularly repeated urine cultures after treatment

NOTE: The guideline applies to infants and children 2 to 24 months of age with unexplained fever.

Data from Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011;128:595–610.

a 2-year follow-up period, with one of them developing a renal scar on repeat DMSA scintigraphy.

In a follow-up study from the same institution, [Preda and colleagues \(2007\)](#) prospectively confirmed these observations in 290 children younger than 1 year of age with UTI (79% febrile) with VCUG and DMSA renal scans. Of the patients, 51% had positive scans, including 85% (44 in 52) of the children later found to have VUR. Of the 8 cases of VUR with normal DMSA scans, 7 were low grade, with the remaining boy having grade 3 VUR with no acquired renal scars in follow-up despite an episode of breakthrough UTI.

The potential ability to detect children with significant VUR who are at risk for renal scarring while avoiding invasive evaluation and unnecessary treatment of those who are not is clearly appealing. However, a recent meta-analysis has shown the top-down approach to perform poorly at detecting high-grade VUR with a sensitivity and specificity of only 79% and 53%, respectively ([Mantadakis et al, 2011](#)). These data underscore the importance of further prospective analysis with longer follow-up to establish the validity and safety of the top-down approach.

National Institutes for Clinical Excellence Guidelines

In an attempt to streamline the investigations and treatment in infants and children presenting with UTI, the National Institutes for Clinical Excellence (NICE) in the United Kingdom proposed a set of guidelines aimed at reducing morbidity, antibiotic usage, and cost ([Baumer and Jones, 2007](#)). Investigations are limited to a sonogram of the urinary tract, with cystography reserved for infants younger than 6 months and in older infants when dilation is observed by ultrasonography. They do not recommend early DMSA renal scans to confirm or exclude renal involvement and rely solely on ultrasonography in sicker patients to determine the need for further investigation. The major criticism to this approach lies in the poor correlation between the appearance of the kidneys on ultrasonography and the presence of renal parenchymal changes or the presence and grade of VUR. The NICE committee did not provide any clinical outcomes to validate these guidelines, and until confirmation of the safety of this approach is established prospectively, it cannot be recommended for general clinical use.

American Academy of Pediatrics Guidelines for Febrile Urinary Tract Infection Diagnosis and Management in Young Children

In 2011 the AAP released revised guidelines for the diagnosis and management of UTI in children 2 to 24 months of age ([Roberts](#)

[et al, 2011](#)). The guidelines were based on a rigorous review of the literature and six new randomized controlled trials of antibiotic prophylaxis to prevent recurrent UTI. The guidelines are summarized in [Table 137-4](#).

To establish the diagnosis, stricter infection criteria were suggested, including a lowered threshold for urine culture colony-forming units per milliliter (50,000 from 100,000) as well as the additional requirement of an abnormal urinalysis result. Oral and parenteral antibiotic treatments are now considered equally efficacious. The use of renal-bladder sonography retains its traditional and important role in structural assessment. However, the most important deviation from past practice is the AAP recommendation to forgo a VCUG after the *first* febrile UTI. Emphasis is now placed on this familiar cystographic imaging study and on follow-up after a *second* or subsequent febrile UTI. This essentially shifts the potential burden of postinfection injury after a single isolated febrile UTI, which may never recur, to one or more subsequent febrile UTI episodes. This position also does not account for preexisting VUR-related developmental renal abnormalities that were not sustained by UTI per se.

However, the recommendation to forgo VCUG after initial febrile UTI is qualified. If hydronephrosis, sonographic indications of possible renal scarring or dysmorphism, or other findings that suggest high-grade VUR or obstructive uropathy are present, the VCUG should be obtained. Similarly, any complex or clinically atypical scenario supports obtaining the VCUG after a first febrile UTI. It should be remembered that a positive finding of VUR by VCUG does not occur in many patients after a first febrile UTI. Thus this newer recommendation would seem to balance the incidence of first febrile UTI in infants with the attendant invasiveness, radiation exposure, and patient and family trepidation surrounding a VCUG. Notwithstanding these developments, at least one study has suggested that even with vetting of the decision to proceed with a VCUG using sonographic evidence of renal abnormality after initial febrile UTI, a clinically significant VUR diagnosis still may be delayed or missed because scintigraphic renal abnormalities may exist even in the presence of a normal renal ultrasonography. The crux of this concern lies in details of the degree and significance of such nuclear imaging abnormalities, which were not discussed in the study ([Suson and Mathews, 2014](#)).

Cystoscopy and the Positioning of the Instillation of Contrast Cystogram

Modern management of reflux does not include routine cystoscopy. It is rare for cystoscopy to add any information that will alter

management of a patient with reflux, either at the time of initial diagnosis or during follow-up. Its routine use, especially in children with UTI or reflux, should be considered an anachronism. Similarly, the appearance and configuration of the ureteric orifices and intramural tunnel length that are afforded by cystoscopy and once considered useful parameters have over time provided little correlation with either the diagnosis or grade of reflux (Duckett, 1983). Cystoscopy can provide useful information immediately before open surgery, such as confirmation of orifice position and duplication and the proximity of diverticula to the orifice, and clarify urethral patency if indicated. Similarly, such cystoscopic parameters will become immediately available in all patients at the time of endoscopic reflux correction.

A recently developed, although still controversial (Elder, 2005), cystoscopic modality termed *positioning of the instillation of contrast at the ureteric orifice (the PIC technique)* purports to detect reflux under general anesthesia in patients with a history of febrile UTIs but a normal VCUG. The technique of PIC cystography (Edmondson et al, 2006) involves cystoscopy using a 9.5- or 14-Fr rigid cystoscope. With the bladder empty, the cystoscope beak is positioned close to and facing the ureteric orifice. Contrast is instilled at the ureteric orifice using the irrigation port of the cystoscope from a height of 1 meter above the bladder. Fluoroscopic spot imaging is done simultaneously with the instillation. PIC-VUR is confirmed if retrograde flow of contrast into the ureter/kidney pelvis is observed. The bladder is emptied before the procedure is repeated on the contralateral side.

It is conceivable that antireflux mechanisms may be barely functional in some patients with recurrent UTI. The unique but unphysiologic nature of the PIC technique may then reveal reflux in such cases. Furthermore, PIC cystography does not allow for age-adjusted instillation pressures; some pressures may be too high in younger patients and may be creating iatrogenic reflux rather than unmasking relevant, physiologically borderline reflux.

A multi-institutional study by the PIC Cystography Group (Hagerty et al, 2008) examined the clinical significance of reflux discovered by PIC in 118 children with a history of febrile UTIs and negative VCUGs. VUR diagnosed by PIC was treated by surgery (endoscopic injection in 104 patients, reimplantation in 3) or by antimicrobial prophylaxis (11 patients). In the 98 evaluable patients, VUR grade was 1 to 3 and was unilateral in 34 patients and bilateral in 64 patients. Treating occult VUR identified by PIC cystography, with either antibiotics or surgery, reduced the incidence rate of febrile UTI by 20-fold (from 0.161 per patient per month before PIC-VUR treatment to 0.008 per patient per month after treatment).

It is generally believed that VUR does not cause UTI; however, in this nonrandomized study (with the patients acting as their own controls), PIC cystography provides some evidence and rationale for antireflux therapy in a new subset of patients, particularly because endoscopic correction could theoretically and easily follow the fluoroscopy at the same time. However, **the urologist must exercise caution in this approach until prospective studies randomizing patients with PIC-VUR to treatment or observation confirm its clinical importance.**

ASSESSMENT OF THE UPPER URINARY TRACT

Rationale for Serial Assessment of Upper Tracts

The known effects of VUR on the upper tracts are largely what direct the need for reflux diagnosis and correction. Pyelonephritis propagated by reflux causes renal scarring, impedes attainment of full renal growth potential, and increases risk for renovascular hypertension. Therefore imaging of the upper tracts is directed at assessing renal structure and function, with attention to the aforementioned parameters. A fundamental goal in upper tract imaging with VUR is to ascertain whether abnormalities are due to ongoing or resolved reflux and differentiate them from intrinsic developmental disturbances, medical renal disease, or antegrade flow resistance. Almost always, particularly in the youngest patients in whom VUR has the

greatest potential to adversely affect renal function, these goals are best achieved through serial imaging of the kidneys over a period of months to years.

However, a meta-analysis of 63 studies assessing the value of routine diagnostic imaging after initial UTI in children for the prevention of renal damage found no accurate evidence to support this practice (Dick and Feldman, 1996). Many observational studies raised concern for the sequelae of UTIs and highlighted the potential for successful intervention. The reason to image the upper tracts after a UTI may occur with or without knowledge of the reflux status of the lower tract. Reflux status may be known, suspected, or completely unknown. These three considerations, coupled with the age of the patient, gender, race, family history of reflux, and bladder functional status serve as a guide to selective imaging, which attempts to balance intensity of imaging studies with propensity for renal damage.

Renal Sonography

The mainstay of renal imaging in VUR management is ultrasonography. As a nonionizing, noninvasive imaging platform, coupled with its ability to assess renal vasculature, it is ideally suited to serial follow-up of renal growth and development. Ultrasonography has supplanted routine excretory urography as the imaging modality of choice to monitor renal status over time.

Ultrasonography lends itself well to quantitative assessment of renal dimensions (Rodriguez et al, 2001; Chen et al, 2002), which then can be used to follow renal growth over time. Renal growth can be referenced to standard renal growth curves. In reflux diagnosed in the neonatal period, baseline renal dimensions are obtained and appropriate renal growth can be monitored over time. The impact of any intercurrent febrile urinary infection can be gauged by observing the effects on renal growth. Similarly, if the UTI history between follow-up visits for reflux is unclear, serial assessment of renal dimensions can help the urologist advise on the need for further assessment of renal function by scintigraphy or on the need for reflux correction. Indeed, in the presence of reflux, modern postnatal renal sonography provides excellent correlation between renal length and scintigraphic hypoplasia (Farhat et al, 2002a).

Ultrasonography also images the degree of corticomedullary differentiation in the kidney. Loss of corticomedullary differentiation, or an increase in the overall echogenicity of the kidney, is associated with some degree of renal functional impairment. In neonates in particular, these parameters can be useful in assessing overall status of a renal unit in the context of higher grades of reflux, even before any history of UTI or pyelonephritis has occurred. Coupled with a relatively smaller ipsilateral kidney, loss of corticomedullary differentiation or increased echogenicity suggests a degree of intrinsic renal dysplasia that developmentally accompanies high-grade reflux. In the neonate with no infection history, such findings should not be confused with renal scarring, which is the direct sequela of inflammation and infectious pyelonephritis. In general, the routine sonogram is noninvasive, is performed relatively quickly, and does not require intravenous access for contrast agents.

Notwithstanding the value of renal sonography, it must be remembered that a single ultrasound study cannot reliably diagnose VUR. Although it is tempting to speculate on the presence of reflux in the presence of postnatal hydronephrosis on sonography, particularly of higher grades, there is no significant correlation between a normal sonogram and the absence of reflux (Farhat et al, 2000; Zamir et al, 2004). Similarly, renal sonography is limited in its ability to visualize renal cortical abnormalities. Sonography is better suited to the noninvasive detection of larger cortical defects or renal size asymmetry (Merguerian et al, 1999).

Modern enhancements in ultrasound technology permit imaging of perfusion abnormalities in tissue. In reflux nephropathy using color Doppler ultrasonography, renal resistive index measurements derived from blood flow in interlobar and arcuate arteries are significantly increased in higher grades of reflux and correlate positively with scintigraphic findings from the same renal unit (Radmayr et al, 1999). Resistive indices are also higher in patients with bona



Figure 137-8. Dimercaptosuccinic acid renal scintigraphy. Pinhole images show a normal left kidney and a right kidney with multiple cortical defects.

fide pyelonephritis confirmed by nuclear scintigraphy compared with patients with lower UTI alone (Ozcelik et al, 2004). Animal studies also have demonstrated that contrast-enhanced harmonic ultrasonography can detect histologically confirmed regions of reflux-induced pyelonephritis with great sensitivity and more than 80% positive and negative predictive values (Farhat et al, 2002b).

Renal Scintigraphy

The gold standard for imaging functioning renal parenchyma is scintigraphy using ^{99m}Tc -labeled DMSA. The radiotracer is taken up only by functioning proximal tubular tissue mass, where it binds for several hours. The uptake of DMSA provides a good proportional representation of glomerular filtration (Taylor et al, 1982). Because pyelonephritis impairs tubular uptake of radiotracer, these areas will fail to radioemit photons and appear as unexposed or underexposed regions in the resultant renal cortical images (Fig. 137-8). Although many such affected areas in the kidney resolve, especially if prompt medical treatment is possible (Fernández-Menéndez et al, 2003), when they persist, irreversible renal damage or scarring is said to have occurred (Rushton and Majd, 1992). In a study of 79 children followed for 1 to 4 years, DMSA scanning provided 98% sensitivity and 92% specificity for scar detection (Merrick et al, 1980). Although Rushton's study suggested that subsequent scarring was independent of the presence or absence of VUR (Rushton and Majd, 1992), a more recent meta-analysis found that reflux conferred an approximately three-fold increased risk for detecting renal cortical abnormalities after infection (Faust et al, 2009). Indeed, considering the overall incidence of pyelonephritis in children, VUR is present in 22% to 39% of such patients (Hoberman et al, 2003; Lin et al, 2003). Nonetheless, the importance of VUR lies in the realization that it remains a spontaneously resolving or surgically treatable cause for this ascending group of renal infections (Majd et al, 1991).

One advance in nuclear scintigraphy of the kidneys is single-photon emission computed tomography (SPECT imaging). This approach reconstructs three-dimensional (3D) images of the renal cortical architecture, which can be viewed in any aspect in 360 degrees of rotation. Although SPECT images provide slightly higher sensitivity for detection of cortical defects, they do not add appreciably to standard pinhole DMSA images in the clinical management of reflux (Majd et al, 1996).

Despite the well-established guidelines for renal cortical scintigraphy from the Society of Nuclear Medicine (Mandell et al, 2003), investigators in the Randomized Intervention in Vesicoureteral Reflux (RIVUR) study reported a significant degree of interinstitutional variability in how DMSA scans are performed with 17% of RIVUR DMSA scans rejected because of poor quality (Ziessman and Majd, 2009).

Much has been written in the literature on the role of DMSA scanning in the management of VUR, as an indirect entrée to the diagnosis of reflux itself, for the detection of reflux-associated renal damage and acute pyelonephritic changes, and for follow-up of

reflux. However, no consensus exists on the precise use of DMSA scanning in reflux management. For example, growing concern over the nature and frequency of voiding studies has prompted some to propose cystography after UTI only in children with persistent postinfection renal lesions on DMSA scan, citing that only a minority of post-UTI cystograms are positive for reflux (Hansson et al, 2004). DMSA and ultrasonography are often used complementarily, particularly when knowledge of relative renal function is desired (Riccabona et al, 1993). As a general rule, the utility of scintigraphy can best be appreciated in the context of the data it provides relevant to reflux: imaging cortical defects and relative renal function. The usefulness of this information will depend on which associated clinical and radiology data are at hand. If reflux and infection history are unclear or unknown in a new patient referred for evaluation after UTI, scintigraphy can provide the gold standard for demonstration of cortical defects for any reason and help with counseling on additional studies. If the significance or febrile nature of a potential pyelonephritis is unclear, particularly in a younger patient, a follow-up DMSA scan 4 to 6 months after UTI can rule out subsequent scarring, particularly if a normal scan exists from a prior evaluation. DMSA scanning can be particularly useful if the diagnosis of pyelonephritis is unclear during an acute infection. Confirmation of photopenic radioemission and acute pyelonephritis can help ensure that adequate antimicrobial therapy is provided. If surgical intervention is planned and significant renal asymmetry exists on ultrasonography, quantification of relative function by scintigraphy can help in the decision between reflux correction and nephrectomy.

DMSA scanning also has demonstrated that congenital cortical maldevelopment can exist, particularly in high-grade reflux, even in the absence of any history of UTI or outlet obstruction (Wallin and Bajc, 1994; Nguyen et al, 2000). This underscores the fact that cortical defects detected by DMSA scanning are not always the by-product of infection; all DMSA defects are not necessarily scars. The distinction is an important one in the design of clinical studies and interpretation of the reflux literature, where congenital cortical defects may be erroneously construed and evaluated as if they were due to postinfection scarring. One corollary to this observation is that scintigraphic renal defects detected for the first time in a child in whom the reflux history from birth cannot be confidently known could be secondary to reflux-associated pyelonephritic scarring, even though the reflux has resolved by the time of the study. Failure to appreciate that reflux often resolves in early childhood before scanning detects cortical defects for the first time makes it difficult to know whether these defects were associated with reflux.

CORTICAL DEFECTS

Congenital Defects versus Acquired Scar

The term *scar* is defined as fibrous tissue replacing normal tissues destroyed by injury or disease. In a renal context, the term is most accurately used to describe the fibrous, contracted regions of the kidney that have been destroyed by infection. This scar tissue often appears as a smaller and photopenic area by scintigraphy or, when larger, as hyperechoic and shrunken areas on sonographic images. The importance of such scars lies in the realization that they are the preventable complication of pyelonephritis, the latter being directly influenced by VUR in the presence of a bladder infection.

However, VUR, particularly of higher grades, may result in renal maldevelopment that often appears scintigraphically or sonographically identical to postinfection pyelonephritic scars (Murer et al, 2007; Peters and Rushton, 2010). Thus, over time in the literature and in clinical practice, the terminology of scarring, which is ideally defined to describe an end product of infection, has become contaminated by the inclusion of reflux-associated congenital dysmorphism. However, until such time that primary reflux can be averted prenatally (Gobet et al, 1998) or during the early postnatal phase of continued renal development, dysmorphism will remain a non-preventable developmental sequela of reflux. Failure to appreciate

this important distinction has tainted and confused study design and interpretation in the reflux literature.

Reflux-Associated Renal Dysmorphism

The association of renal maldevelopment with the highest grades of reflux is expected by the theory of [Mackie and Stephens \(1975\)](#), which suggests that an abnormal origin of the ureteric bud will interact suboptimally with the metanephric blastema ([Fig. 137-9](#) on the Expert Consult website). The latter process is currently believed to be the likely cause of renal dysmorphism associated with reflux. Several studies have confirmed the association between VUR and a smaller than normal ipsilateral kidney, an overall reduced relative renal function, and global ([Najmaldin et al, 1990](#); [Burge et al, 1992](#)) or focal ([Risdon, 1993](#)) areas of poor uptake by scintigraphy. These infants tend to be males, and the preponderance of refluxing renal units are grade 4 or 5 ([Marra et al, 1994, 2004](#)) ([Table 137-5](#); [Fig. 137-10](#)). Indeed, boys tend to be spared an infectious cause of reflux-associated scarring because they have a lower incidence of recurrent UTIs ([Wennerstrom et al, 2000](#)).

Renal dysplasia is not unique to primary isolated VUR but also may occur in a variety of urologic settings. Duplex renal moieties ([Mackie et al, 1975](#)), prune-belly syndrome ([Manivel et al, 1989](#)), and posterior valves may exhibit reflux-associated renal dysmorphism, particularly when the grade of reflux has been high.

Requirement for Urinary Microorganisms

It is now firmly established that nephropathy from primary VUR requires the colonization of urine with pathogenic bacteria in the face of normal voiding dynamics. Indeed, the basis of current expectant medical management of reflux is to maintain urinary sterility while allowing reflux to resolve naturally. In the absence of infection, sterile urinary reflux is insufficient to cause renal damage. This concept has been most definitively demonstrated by the elegant series of experiments by [Ransley and Risdon \(1981\)](#). Reflux was induced experimentally in a pig model by unroofing the intravesical ureteral tunnel. Only if the urine was subsequently infected could pyelonephritis and reflux nephropathy be induced. Without urine infection, no nephropathy could be created ([Ransley and Risdon, 1981](#)). Large clinical studies have reiterated these experimental findings, demonstrating new reflux-associated scarring only in children with recurrent UTIs ([Smellie et al, 1975](#); [Huland and Busch, 1984](#)). These observations conflict somewhat with earlier animal studies by [Hodson and colleagues \(1975\)](#), which induced reflux with sterile urine. However, bladder outflow obstruction also was included in this model, leading to a finding of atrophic pyelonephritis similar to obstructive nephropathy. Scarring was nevertheless intensified by the presence of urinary microorganisms. Thus abnormal hydrodynamic bladder characteristics may modulate even sterile reflux, but reflux is unlikely to be of any clinical significance in the absence of

TABLE 137-5 Congenital Renal Scarring

GRADE OF VESICoureTERAL REFLUX	NO. PATIENTS NORMAL (%)	SLIGHT DAMAGE (%)	SEVERE DAMAGE (%)
1-3	13 (100)	—	—
4	8 (53)	5 (34)	2 (13)
5	2 (15)	5 (38)	6 (46)

Modified from Marra G, Barbieri G, Dell'Agnola CA, et al. Congenital renal damage associated with primary vesicoureteric reflux. *Arch Dis Child Fetal Neonatal* Ed 1994;70:F147.

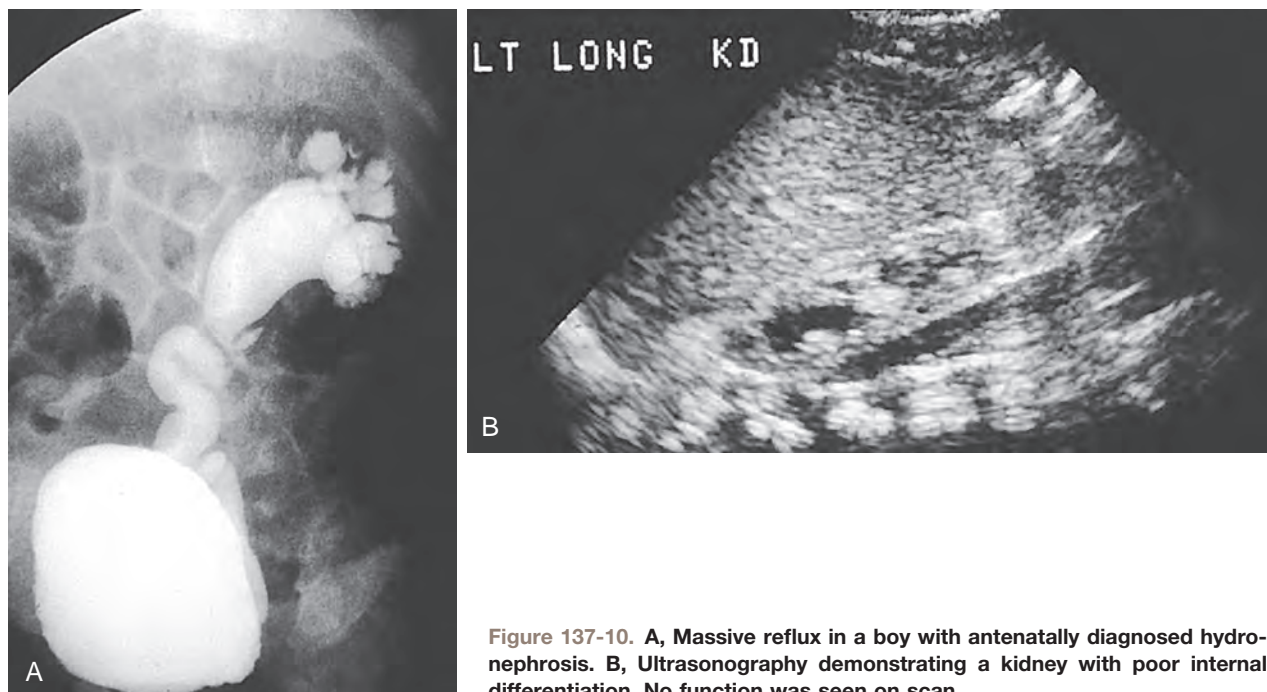


Figure 137-10. A, Massive reflux in a boy with antenatally diagnosed hydronephrosis. B, Ultrasonography demonstrating a kidney with poor internal differentiation. No function was seen on scan.

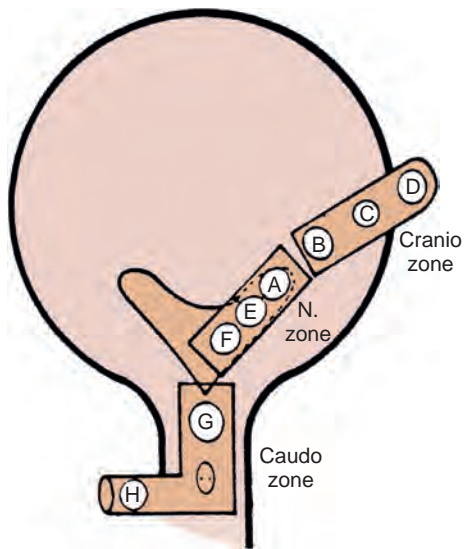


Figure 137-9. Classification of ureteric orifice position. Obstruction usually occurs in the caudo zone, and ureters positioned in the cranio zone are likely to result in reflux. Ureters positioned in the normal (N.) zone are associated with normal kidneys. Because of ureteric bud abnormality, renal dysplasia occurs with ureters projecting from both abnormal positions. (From Mackie GC, Stephens FD. Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice. *J Urol* 1975;114:274.)

infection with relatively normal bladder function. These earlier observations of Hodson, however, underscore the importance of normalizing bladder and bowel function while awaiting reflux resolution.

KEY POINTS: DIAGNOSIS AND EVALUATION OF VESICoureTERAL REFLUX

- The method of urine collection and the presence of pyuria are of utmost importance in the diagnosis of UTI to avoid false-positive culture results.
- Radiologic studies should be tailored to age, gender, and mode of manifestation (i.e., fever).
- The gold standard study for the diagnosis of reflux requires bladder catheterization.
- Nuclear cystograms, though more sensitive, provide much less anatomic detail than does a VCUG.
- Parental perceptions of reflux management must be considered when treating a child with reflux.
- Routine cystoscopy is **contraindicated** in reflux management.
- Upper tract assessment is based on serial studies.
- The intensity of upper tract studies should be proportional to the propensity for renal damage.
- The challenge in imaging is to differentiate congenital reflux-associated renal dysmorphism from scarring acquired after infection.

Pathophysiology of Acquired Scarring

Renal scarring is a sequela of infectious pyelonephritis. A full discussion of the pathophysiology of renal scarring is covered elsewhere in the text. However, VUR exploits several conditions that predispose to scarring. Most importantly, **reflux provides a mechanical hydrodynamic mechanism that facilitates the ascension of microorganisms from the bladder to the kidneys. Thus reflux may be considered an accelerant for renal tissue infection after bacterial colonization of the bladder.** This principle has been confirmed by studies showing an increased incidence of pyelonephritis in higher grade reflux compared with lower grade reflux (Majd et al, 1991). Furthermore, the frequency of scarring itself appears to be directly proportional to the grade of reflux with which it is associated (Winter et al, 1983; Weiss et al, 1992a). This principle is also supported by observations after reflux correction. In one study of 74 patients in whom preoperative and postoperative scintigraphy studies were available, more than 90% of renal units corrected for reflux showed no new scars during a mean follow-up period of 19 months, despite asymptomatic bacteriuria in 47% of the patients during follow-up (Choi et al, 1999).

Age

The kidney's predilection for postpyelonephritic scarring is inversely proportional to age. This point is a guiding principle that must be considered in all decisions regarding reflux diagnosis and choice of therapy. The greatest risk for postinfectious renal scarring occurs within the first year of life (Winberg, 1992). Similarly, patients younger than 4 years are more prone to developing scarring after a single UTI than older children (Smellie and Normand, 1985), though scarring may still occur beyond 5 years of age (Smellie and Normand, 1985; Benador et al, 1997). Indeed, although younger patients are the most vulnerable to scarring, scarring in older children is often the result of late diagnosis, delayed or inadequate treatment of infection, and social factors that often interfere with patient management. Thus, in older children with reflux in whom relinquishing care from the urologist back to the family physician is being considered, it is vital that fundamental principles of an adequate clinical index of suspicion for UTI and

prompt UTI management be reiterated before transfer (Coulthard, 2002; Coulthard et al, 2009).

The seminal studies of Ransley and Risdon (1981) proposed a "big bang" theory for the origin of scars after infant pyelonephritis. They observed that most of the scarring to which the kidney is ultimately susceptible occurs after the initial bout of pyelonephritis and that further scarring in the absence of repeated pyelonephritic episodes is unlikely to occur. Consequently, the assumption is that little change in the initial scarring pattern is to be expected in follow-up scintigraphic imaging. However, the uncertainties introduced by such factors as (1) the weakly substantiated assumption that a relatively greater scarring propensity exists in younger kidneys, (2) the reports of new follow-up scarring in the landmark reflux studies (see later discussion), (3) the failure to differentiate between postpyelonephritic imaging defects resulting from infection versus intrinsic developmental dysmorphism associated with reflux, (4) the changing appearance of such imaging defects with renal growth over time, and (5) the limited ability to compare disparate imaging modalities in the reflux literature (urograms vs. nuclear scans) together must challenge the notion that the greatest postinfection parenchymal loss occurs after the first infection.

KEY POINTS: CORTICAL DEFECTS

- Sterile reflux is considered benign.
- The youngest patients are at greatest risk for postpyelonephritic renal scarring.
- Most parenchymal abnormalities are detected after the first episode of pyelonephritis.
- Somatic growth is an accurate reflection of renal cortical integrity.

Papillary Anatomy

Another factor governing renal susceptibility to scarring is the configuration of the papillae as their ducts open to the calyces. Papillae with a concave architecture (compound papillae) present their ducts at right angles, whereas more convex papillae possess ducts that end obliquely, producing a valvular effect that guards against backflow of urine into the medullary collecting ducts (Fig. 137-11). The more polar calyces are composed preferentially of compound papillae compared with the middle calyces. The former are more commonly the site of intrarenal reflux (reflux into the ducts) and are the prime regions of susceptibility to scarring. Furthermore, necropsy studies have determined that reflux into compound papillae occurs at lower pressures than into simple papillae (Funston and Cremin, 1978). Intrarenal reflux can occur with as little as 2 mm Hg pressure in the neonate (Fig. 137-12). By 1 year of age, the pressure required is one order of magnitude greater (Funston and Cremin, 1978) and helps explain the relative infrequency of intrarenal reflux in older children.

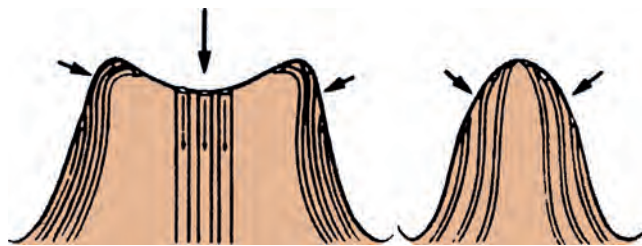


Figure 137-11. Papillary configuration in intrarenal reflux. A convex papilla (right) does not reflux because the crescentic or slitlike openings of its collecting ducts open obliquely onto the papilla. In contrast, a concave (left) or flat papilla refluxes because its collecting ducts open at right angles onto a flat papilla. (From Ransley PG, Risdon RA. Reflux and renal scarring. *Br J Radiol* 1978;14[Suppl.]:1.)

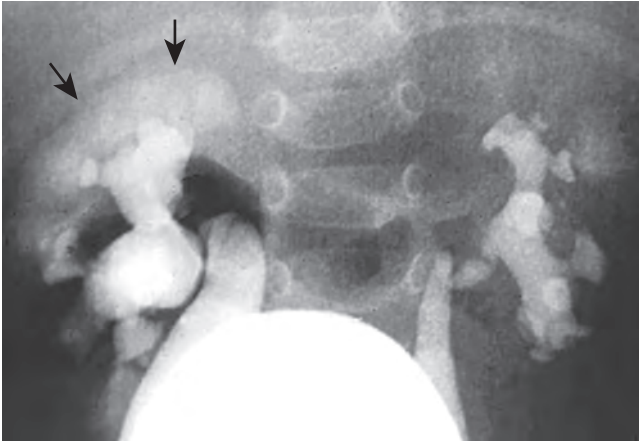


Figure 137-12. Intrarenal reflux (arrows) shown on a voiding cystourethrogram.

Bacterial Virulence



Please see the Expert Consult website for details.

Host Susceptibility and Response



Please see the Expert Consult website for details.

Hypertension

VUR has long been held as the primary cause of significant hypertension in children. Arterial derangements in the renin-angiotensin system and sodium-potassium adenosine triphosphatase activity (Goonasekera and Dillon, 1998) may be involved, though the precise pathophysiologic process is not clear. Although methodologic flaws (Farnham et al, 2005) taint many studies of hypertension in the pediatric urology population, one study using continuous ambulatory blood pressure monitoring revealed some correlation between progression to hypertension and more severe reflux nephropathy in children (Lama et al, 2003). A recent adult review of 157 patients with hypertension, but no evidence of abnormal renal parameters, discovered by cystography that latent VUR was present in 20% of the subjects, demonstrating that a significant association between reflux and hypertension exists in adulthood (Barai et al, 2004). The striking association between VUR diagnosed for the first time only in adulthood and arterial hypertension continues to underscore the importance of remaining vigilant about untreated infections in the reflux population (Kohler et al, 1997). Nevertheless, it remains unclear whether it is the nephropathy associated with postinfection scarring, congenital dysmorphism associated with reflux, or some combination of both that predisposes to hypertension (Wolfish et al, 1993). This latter observation questions, then, whether prevention of postinfection scarring per se in the management of VUR will specifically help offset future hypertensive risk in cases in which congenital renal dysmorphisms are already present. There is obvious potential for the cause of reflux-associated hypertension to rest with deranged renal microvascular mechanisms associated with parenchymal defects. This suggests that successful correction of reflux alone is unlikely to ameliorate blood pressure (Wallace et al, 1978). Indeed, removal of renal segments verified by selective renal vein sampling of arteriolar or segmental vessel renin levels has provided durable normalization of blood pressure in carefully selected patients (Tash et al, 2003). On occasion, complete removal of a small unilateral congenitally dysmorphic or globally scarred and shrunken kidney also may correct renovascular hypertension (Dillon and Smellie, 1984), because such kidneys are clearly not amenable to partial nephrectomy for any discrete segment.

Renal Growth

Several studies have attempted to demonstrate that correction of reflux will restore retarded renal growth associated with reflux, particularly when the growth defect is in a unilaterally affected kidney. However, reflux correction is a poor predictor of catch-up growth in such kidneys (Hagberg et al, 1984; Shimada et al, 1988). A significant factor governing growth of an ipsilateral kidney is the function of its contralateral mate. Although forestalling infection in the presence of VUR will maintain the normal trajectory of renal growth in most cases (Smellie et al, 1981a), it must be remembered that compensatory hypertrophy of the contralateral kidney will magnify the perceived impact of infection on renal growth because the contralateral developing kidney will assume the required renal function whenever the ipsilateral kidney is unable to contribute optimally to function. When reflux correction has been associated with improved renal growth, it is likely this is due to removal of the propensity for ascending infection rather than the elimination of the reflux per se (Willscher et al, 1976a, 1976b).

Renal Failure and Somatic Growth

Today, renal failure resulting from primary VUR-associated infection should be an anachronism, although it is still seen. This is largely due to the virtual paradigm shift in reflux management championed by Smellie and colleagues during their pivotal studies of reflux and infection in children during the 1970s and 1980s. Over the past 30 years, chronic pyelonephritis as a primary cause of end-stage renal disease has fallen from 15% to 25% (Advisory Committee to the Renal Transplant Registry, 1975) to less than 2% (North American Pediatric Renal Transplant Cooperative Study, 2004). Reflux nephropathy in all its forms, however, was the fourth most common primary diagnosis in nonblack pediatric transplant recipients (North American Pediatric Renal Transplant Cooperative Study, 2004). The medical renal disease (Hinchliffe et al, 1994) that accompanies renal scarring can include hyperfiltration, concentrating defects, proteinuria, microalbuminuria (Lama et al, 1997), renal tubular acidosis (Guizar et al, 1996), and increased fractional excretion of sodium and magnesium. Although all of these parameters are likely the direct result of tubular and parenchymal damage or dysmorphism, concentrating defects and increased concentrations of tubular enzymes (Carr et al, 1991) have been reported in the presence of sterile reflux, independent of any history of infection per se (Walker et al, 1973). The concentrating defect is proportional to reflux grade and improves after reflux cessation. These observations have suggested that a relative flow resistance may be created by retrograde nature of reflux and raises the possibility of a functionally obstructive parameter in reflux pathogenesis. However, the precise relationship between antegrade flow, retrograde flow, and bladder dynamics in this theoretic mechanism has not been more fully articulated.

One of the best global parameters of renal function in children is the somatic growth curve. Many children with VUR fall below the normal age-adjusted growth curve, particularly in patients with bilateral reflux and some degree of renal damage. Furthermore, successful suppression of pyelonephritis through either medical prevention of infection or surgical correction of reflux itself can result in catch-up growth, both for height and weight (Polito et al, 1996, 1997). Although a clear superiority has yet to be demonstrated between medical and surgical therapy to affect growth improvement or subsequent renal scarring after an initial pyelonephritic insult, surgical correction of reflux can benefit somatic growth when recurrent breakthrough infection indicates failure of antibiotic prophylaxis (Sutton and Atwell, 1989).

ASSOCIATED ANOMALIES AND CONDITIONS

Ureteropelvic Junction Obstruction

VUR and UPJO are two of the most common pathologic conditions in pediatric urology. Thus it is not unusual that these two conditions

Bacteria possess phenotypes that provide infective advantage when exposed to the lumen of the urinary tract. Chief among these is the ability to adhere to uroepithelium. Adherence is mediated by interaction between specific molecules or ligands located on bacterial fimbriae and specific receptors on host uroepithelial cells. A full discussion of the mechanism of action of uropathogenic bacteria is found elsewhere in the text. Once bacteria bind to host epithelium, specific biologic responses are activated in both the microorganism and host cell. Bacterial responses are designed to facilitate their survival and proliferation, as well as inhibit host defenses. These include release of endotoxin and reduction of ureteral peristalsis, which may lead to urinary stasis and reduced antegrade flow of urine. The host inflammatory response perpetuates the classic symptoms of UTI. Although a more systematic understanding of bacterial-host interactions in the propensity for reflux-associated renal scarring is not yet available, it appears that bacteria responsible for postpyelonephritic scars in the presence of reflux often express fewer than three virulence factors (Lomberg et al, 1984). Ironically, then, less virulent bacteria are most often sufficient to produce scarring in the presence of reflux.

Nonhematogenous bacterial access to the urinary tract rests essentially with periurethral organisms. Thus the type and number of vaginal and preputial organisms will determine individual propensity for bladder colonization. Local factors such as hygiene and bowel habits also will influence the bacterial load presented to the perineal surface from the intestinal tract, the latter being the principal repository for organisms that infect the urinary tract. The functional diversity of the host receptors for bacterial adherence also plays a role in the success or failure of bacteria to gain entry to the bladder. In one study, girls with recurrent UTI harbored far heavier periurethral colonization than a control group of girls who were infection free, suggesting a variation in the function of antibacterial defenses in susceptible females (Bollgren and Winberg, 1976a). Furthermore, such factors may exhibit both gender- and age-related dimorphism (Bollgren and Winberg, 1976a). The great majority of UTIs in both sexes younger than 6 months of age is confined to uncircumcised boys (Rushon et al, 1992) and is consistent with the observation that *Escherichia coli* colonization is dense in infant boys but sparse in girls (Bollgren and Winberg, 1976b).

Perhaps the greatest tangible factor in promoting susceptibility to UTI is urinary dwell time. The postvoid urine volume is traditionally singled out as being suspect in providing sanctuary for ascending urethral organisms. Perhaps more important, however, is the overall dwell time between voids, which provides the greatest advantage to bacterial proliferation. **When the average doubling time for *E. coli* is measured in minutes, it is self-evident that a quantity of microorganisms sufficient for clinical infection can easily incubate exponentially in a bladder that is not emptied for several hours.**

Advances also have been made in understanding the renal epithelial response to pathogens. The classic components of the innate immune response to infection include activation of the complement system; recruitment of neutrophils and macrophages with scavenging ability; and production of a variety of cytokines, chemokines, and defensins (antimicrobial peptides). One family of receptors, the Toll-like receptors (TLRs), responds to highly constant antigens expressed in bacteria (Chowdhury et al, 2004). The best studied of these, TLR4, detects lipopolysaccharide (LPS). A breakthrough in understanding renal infection came with the demonstration that mutations encoding the *TLR4* gene were responsible for LPS hyporesponsiveness (Hoshino et al, 1999). Nevertheless, molecules accessory to TLR4 are important to its response to LPS. Similarly, molecules such as CXCR1 and CXCR2 are receptors for interleukin-8, the principal renal epithelial secreted chemokine responsible for neutrophil migration (Godaly et al, 2000). Deficiencies of CXCR expression and function may underlie human susceptibility to pyelonephritis (Freundt et al, 2000, 2001). Such advances placed into the context of VUR provide interesting and powerful opportunities to modify the natural history of the condition.

As well as orchestrating the assembly of the phagosome for bacterial clearance, **the fallout of these renal epithelial processes that is the inflammatory response leads to local tissue damage and scarring.** Hallmarks of the response include capillary congestion, ischemia and reperfusion injury, and free oxygen radical and inflammatory cytokine release (Roberts, 1990, 1992). Microabscess formation later coalesces into scar tissue typical of the histologic changes of chronic pyelonephritis (Roberts, 1995). Although limiting the inflammatory response to reduce scarring may appear logical, no specific pyelonephritis anti-inflammatory pharmacotherapy is yet available. Traditional nonspecific anti-inflammatory agents, both steroidal and nonsteroidal, are not currently indicated in the treatment of pyelonephritis; in their current formulations the latter poses a threat to renal function (Schaller and Kaplan, 1998). Nevertheless, the concept has been demonstrated experimentally in animals (Huang et al, 1999). A full understanding of the specific pathways involved in reflux-associated pyelonephritis could provide key strategies to limiting specific renal inflammatory fallout without limiting bacterial clearance. Until then, antimicrobial therapy instituted in a timely fashion, usually within 24 to 48 hours, is the single most effective pharmacologic strategy to date to limit the scarring consequences of pyelonephritis in both young and older children (Ransley and Risdon, 1981; Smellie et al, 1985).

coexist. Whether the concomitant presence of these two conditions is a random event or is causally related remains unclear. It has been speculated that a developmental ureteric bud anomaly may be responsible for the imperfect formation of both the UVJ and the UPJ (Bomalaski et al, 1997a).

The incidence of VUR associated with UPJO ranges from 9% to 18% (Lebowitz and Blickman, 1983; Maizels et al, 1984; Hollowell et al, 1989; Bomalaski et al, 1997a; Kim et al, 2001). When the two conditions were primarily present, most of the patients in these studies had reflux that was coincidentally discovered, was of low grade, and resolved spontaneously with time. Such patients typically exhibited a significant discrepancy between the minimal degree of ureteral dilation and the significantly dilated renal pelvis. Thus the apparent grade of reflux may be overestimated, and management decisions based on the grade of reflux are inaccurate at best.

Conversely, the incidence of UPJO in patients with reflux ranges from 0.75% to 3.6% (Lebowitz and Blickman, 1983; Bomalaski et al, 1997a), with high-grade reflux being five times more likely to be associated with UPJO than lower grades of reflux (Lebowitz and Blickman, 1983; Bomalaski et al, 1997a). Indeed, in one study of children with reflux and hydronephrosis, 50% of high-grade sonographic hydronephrosis, commonly associated with the highest grades of reflux, showed an obstructive pattern on furosemide (Lasix) scintigraphy (Stauss et al, 2003).

Three radiology signs might suggest the existence of UPJO in the setting of reflux. First, if the pelvis shows little or no filling, while the ureter is dilated by contrast, this may indicate a point of kinking secondary to reflux or from a primary UPJO (Fig. 137-13). Second, contrast that does enter the pelvis may be poorly visualized because of dilution in a large pelvic volume and exhibits a markedly reduced radiodensity compared with the ureter or bladder. Finally, a large

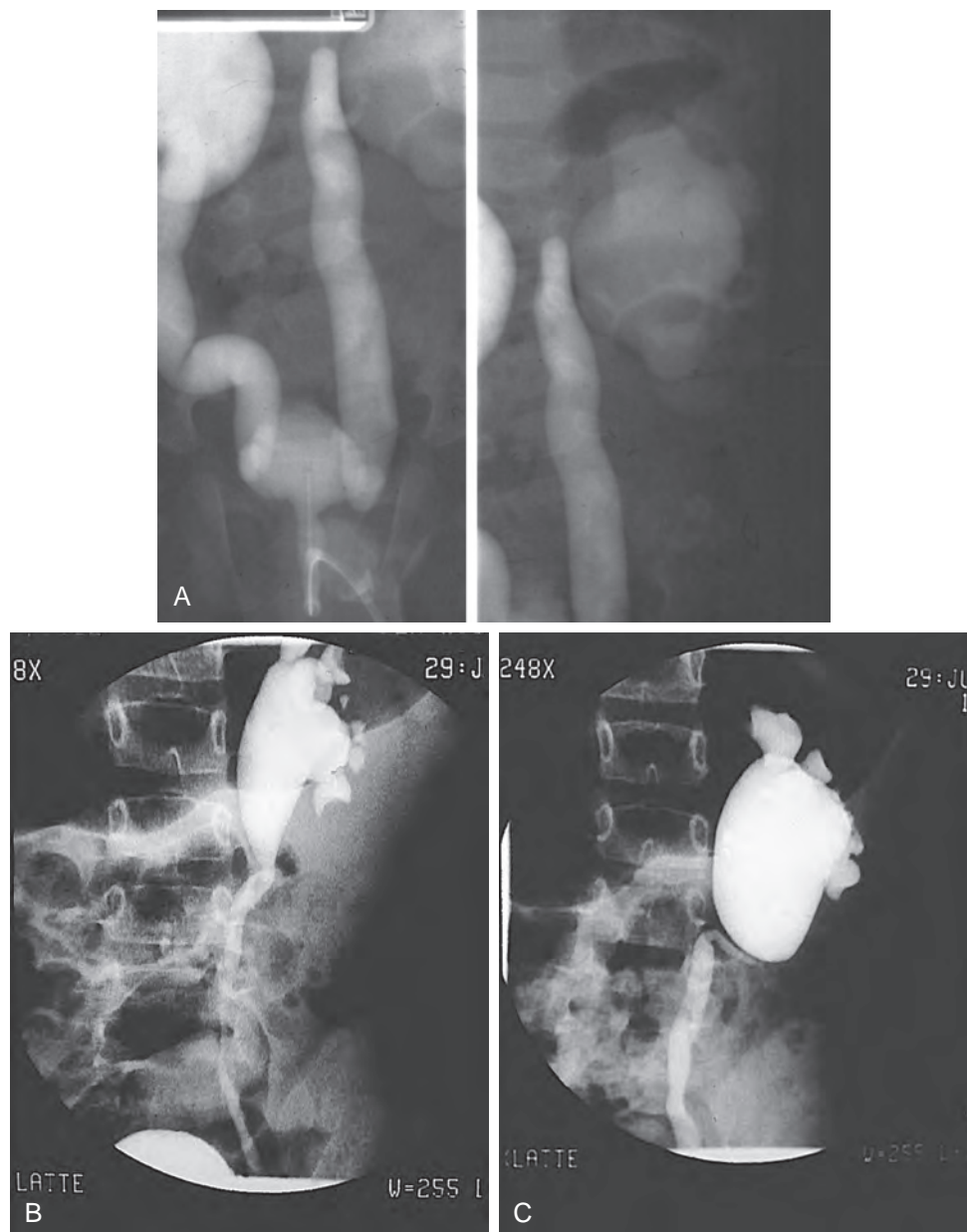


Figure 137-13. Reflux and ureteropelvic junction (UPJ) obstruction. A, Significant reflux fills the left ureter to the level of the UPJ. Minimal filling of the pelvis can be a sign of obstruction at this level. B, In a different patient, reflux is seen as the bladder fills. C, Significant kinking of the UPJ occurs with voiding.

pelvis that fails to exhibit prompt drainage but retains contrast is also suggestive of UPJO.

Radiographic studies of UPJO associated with VUR may indicate true anatomic obstruction or simply dilation associated with pelvic-ureteral dilation from higher grades of reflux. [Hollowell and colleagues \(1989\)](#) referred to three clinical categories of concomitant obstruction and reflux. Group 1 had primary UPJO and incidental low-grade reflux, and group 2 had secondary UPJO from high-grade reflux. These two groups represent true anatomic obstruction for which pyeloplasty is recommended. Group 3 represents only significant dilation of the upper tracts, which is confirmed by documenting good drainage images by cystography or renal scintigraphy.

The cause of secondary UPJO is unclear. Several factors are thought to predispose or even aggravate a potential narrowing at the level of the UPJ. High-grade reflux may result in kinking of the upper ureter and adjacent pelvic junction. The chronic effects of reflux also may stretch the renal pelvis so that atonicity and an inability to propel urine through the UPJ may occur ([Whitaker, 1973](#)). In the setting of UTI propagated to the upper tracts by reflux, inflammation and ureteritis also can contribute to transient or chronic obstruction at the UPJ.

The convergence of two ureteral anomalies in the same patient raises additional management questions in the situation in which treatment of one anomaly may affect the natural history of the other. Nevertheless, the guiding therapeutic principle is the preservation of renal function. Although sterile reflux may be observed, obstruction even in the absence of infection may jeopardize renal function. Therefore, in the presence of reflux, if scintigraphy with catheter drainage confirms obstruction, pyeloplasty should be performed. The secondary insult to the UPJ from reflux is an evolving process that cannot be efficiently or adequately corrected by surgical repair of the reflux itself. Furthermore, reflux correction alone risks amplifying upper tract dilation during the phase of postoperative edema in the lower ureter, as well as risks introducing infection to a renal pelvis still harboring obstruction at the UPJ.

The simultaneous open correction of UPJO and reflux has always raised a concern over surgical manipulation of both the upper and lower ureter at the same time, as well as its potential negative impact on ureteral vascularity. However, the advent of endoscopic injection raises the possibility of correcting reflux at the time of pyeloplasty for secondary or primary UPJO. The indications for reflux correction are being re-evaluated since the advent of endoscopic therapy and are discussed in the later section on endoscopic management.

Ureteral Duplication

VUR is the most common abnormality associated with complete ureteral duplications. The embryologic origin of the duplicated ureter supports the observation that reflux occurs most commonly into the lower pole. This relationship is based on the studies of [Weigert \(1877\)](#) and [Meyer \(1946\)](#), who documented the more lateral and proximal insertion of the lower pole ureter associated with a shorter intramural ureter at the UVJ ([Fig. 137-14](#) on the Expert Consult website).

The incidence of reflux is increased in patients with complete ureteral duplication ([Privett et al, 1976](#)). Earlier studies provide a limited view of whether reflux in a duplex moiety carries increased patient risk because of lack of control groups, arbitrary patient selection, and short follow-up. There has been some tendency to correct reflux on the basis of the existence of the duplication anomaly itself. Even in the absence of obstruction from a ureterocele or ureteral ectopia, duplication with low-grade reflux may take longer to resolve than in single-system reflux ([Estrada et al, 2009](#)), though it carries no heightened risk for increasing grade, breakthrough infection, or scarring ([Ben-Ami et al, 1989](#); [Husmann and Allen, 1991](#)). The most recent series supports this finding in low-grade reflux but notes that high-grade reflux into lower pole ureters in females is more prone to breakthrough infection and scarring and therefore may warrant more aggressive management ([Afshar, 2005](#); [Estrada et al, 2009](#)).

Bladder Diverticula

A full discussion of bladder diverticula is found elsewhere in the text. The outpouching of mucosa between detrusor muscle bundles, which lacks any true muscle backing itself, commonly defining a bladder diverticulum, has the theoretic potential to affect the natural history of VUR in two ways. Most commonly, if the UVJ is distorted by the so-called paraureteral diverticulum, which shares an anatomic point of origin at or near the UVJ, it is theoretically possible that the configuration of the diverticulum could compromise the antireflux configuration of the UVJ to cause reflux ([Fig. 137-15](#) on the Expert Consult website). Second, and more rarely, a large paraureteral diverticulum could expand within the Waldeyer fascia to cause ureteral obstruction or project forward into the bladder to obstruct the bladder outlet, much as a ureterocele, and incite secondary reflux ([Boechat and Lebowitz, 1978](#)). Although the latter would require cystoscopic confirmation, neither cystoscopy nor imaging is predictive of whether paraureteral diverticula truly compromise the resolution of reflux, as has been commonly believed. [Hutch \(1961\)](#) was the first to recognize that bladder diverticula were congenital abnormalities that occurred primarily in smooth-walled normal bladders in children. A 40-year review of the literature from 1966 to 2004 fails to provide any objective case-control or cohort studies to support the routine repair of reflux where the sole indication was the presence of a paraureteral or Hutch diverticulum. However, a contemporary retrospective cohort analysis of 84 patients with paraureteral diverticula and reflux showed no significant difference in spontaneous resolution rates (60%, 39%, and 22% for grades 1 to 2, 3, and 4 to 5 reflux with paraureteral diverticulum vs. 52%, 28%, and 33% in a matched control group of 95 patients with reflux without diverticulum). Rates of UTI and scarring were similar in both groups. Multivariate analysis revealed reflux grade to be the only predictor of resolution in both groups ([Afshar, 2005](#)). Thus reflux associated with paraureteral diverticula resolves at rates similar to that of primary reflux and should be managed according to the prevailing indications for the reflux itself, irrespective of the diverticulum. However, when a refluxing ureter enters a diverticulum, the latter is no longer paraureteral. With no muscular support to the UVJ, reflux is not expected to resolve. In a given patient, indications for repair require the combined consideration of the potential impact of unresolved reflux, if any, along with whether the diverticulum itself is of sufficient size or conformation to incite complications.

Renal Anomalies

By definition, primary reflux represents a dysfunction of the UVJ. Because the development of both the UVJ and the kidney itself are linked to the origin and fate of the ureteral bud, it is reasonable to consider the existence of reflux whenever an anomaly of renal form or number is present. The cardinal renal anomalies associated with reflux are multicystic dysplastic kidney (MCDK) and renal agenesis, and the presence of either condition mandates a VCUG. In the largest series to date, 75 patients with MCDK showed a prevalence of contralateral reflux of 26% (19 patients) and half of these were low grade (1 to 2) ([Miller et al, 2004](#)). Spontaneous resolution occurred in a mean of 4.4 years, regardless of grade. Only one patient had reflux corrected surgically. In a small series of ureteral ectopia, one patient with MCDK had the contralateral ureter enter into the ductus deferens ([Wunsch et al, 2000](#)), further underscoring the importance of documenting the contralateral kidney's ureteral conformation in patients with MCDK. Although contralateral renal growth often displays compensatory hypertrophy, one study observed somewhat less compensatory hypertrophy by 1 year of age ([Zerin and Leiser, 1998](#)) than may be expected if contralateral reflux is absent (5.1 vs. 6.2 cm median renal lengths, $P < .001$).

Renal agenesis is associated with an even higher prevalence of contralateral VUR. In a retrospective study of 46 children with solitary renal agenesis, the rate of contralateral renal pathology was 46%. VUR was by far the most common contralateral defect (28%) ([Cascio et al, 1999](#)) with UVJ and UPJO seen in 11% and 7%,



Figure 137-14. Reflux into both ureters of a complete duplication, as shown here, is less common than reflux into the lower pole ureter alone.

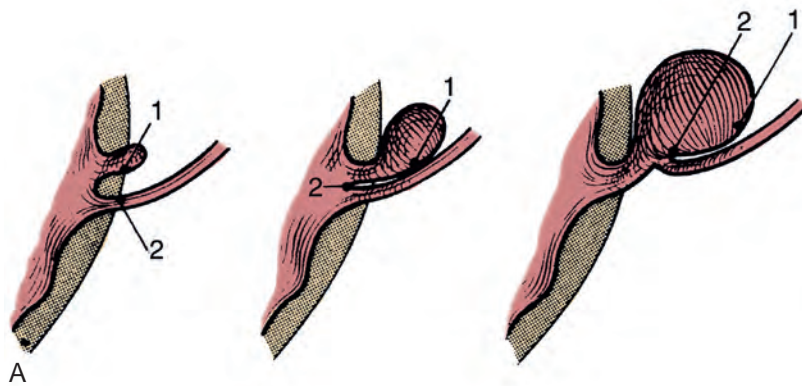


Figure 137-15. A, Schematic representation of a bladder diverticulum (2). A small amount of mucosa initially herniates through a congenital defect in the bladder musculature. The defect enlarges with voiding. Finally, the ureteric orifice (1) is incorporated into the diverticulum. B, Reflux into a right-sided paraureteral diverticulum and ureter seen on voiding cystography. (A, From Hernanz-Schulman M, Lebowitz RL. The elusiveness and importance of bladder diverticula in children. *Pediatr Radiol* 1995;15:399–402.)

respectively. Both UPJ and reflux were present in 1 patient. In another study, 19 cases of contralateral reflux were observed in 51 patients with ipsilateral renal agenesis (Song et al, 1995). Reflux repair or persistence was documented in 9 and 7 patients, respectively, with spontaneous resolution observed in only 3 patients. Whether renal agenesis represents one extreme on a continuum that includes MCDK is unclear. Nevertheless, these data suggest that contralateral reflux associated with renal agenesis may show less tendency to spontaneous resolution than that associated with MCDK.

Megacystis-Megaureter Association

Massive bilateral VUR can cause a gradual remodeling of the entire upper urinary tract. The gross inefficiency of the bladder that expels urine to both the exterior and the upper tracts results in gradual bladder dilation as the refluxed urine returns to the bladder. This perpetuates marked ureteral dilation, leading to the radiographic appearance of massive hydroureter and a thin-walled enlarged bladder (Burbige et al, 1984). The phenomenon is referred to as the megacystis-megaureter association or syndrome. This configuration is even discernable in utero (Mandell et al, 1992). It is more frequent in males, and the differentiation from posterior valves is crucial (Kaefer et al, 1997). Although the latter is due to an obstructive lesion, megacystis-megaureter is a nonobstructive condition akin to cardiac dilation by regurgitation from incompetent valves. Voiding studies will readily demonstrate an open posterior urethra and differentiate megacystis-megaureter from posterior valves or prune-belly syndrome. The persistent large residual urine volume is a significant risk factor for recurrent UTI. Vesicostomy can temporize by eliminating the residual urine volume and establishing safe drainage of the upper tracts until ureteral reimplantation can be performed. Given the propensity for reflux to exacerbate the effects of bacteriuria and the fact that UVJ dysfunction is the primary factor perpetuating the syndrome, surgical correction for the reflux is indicated. Treatments aimed at improving an already patent bladder outlet are contraindicated, risk infection, and fail to correct the primary cause. A period of bladder rehabilitation by strict attention to emptying in the postoperative period (Koefoot et al, 1981) usually will result in a return to normal bladder volume and contractile behavior. This suggests that potentially normal underlying bladder physiology can be realized if the propensity for reflux is corrected.

Other Anomalies

VUR also has been described in association with a number of congenital conditions and syndromes. No precise common genetic insult has been determined to explain such associations. A complete survey of the Online Mendelian Inheritance in Man Database developed by Johns Hopkins University, maintained by the National Center of Biotechnology Information, reveals more than 40 different syndromes in which VUR has been described (<http://www.ncbi.nlm.nih.gov/Omim/getmap.cgi?193000>). These include the VACTERL association (Vertebral, Anal, Cardiac, TracheoEsophageal, Renal, and Limb anomalies), CHARGE syndrome (Coloboma, Heart disease, Atresia choanae, Retarded development, Genital hypoplasia, and Ear anomalies), and imperforate anus. In cases in which VUR is anticipated, a VCUG is the initial study of choice to disclose both dysfunction at the UVJ and overall bladder and bladder outlet anatomy.

Pregnancy and Reflux

The morphology of the urinary tract is altered with the onset of pregnancy and increases throughout gestation (Beydoun, 1985). Bladder tone decreases because of edema and hyperemia, changes that predispose the patient to bacteriuria. In addition, urine volume increases in the upper collecting system as the physiologic dilation of pregnancy evolves. The slower drainage that results can enhance the growth of organisms and increase the

propensity to develop pyelonephritis. It seems logical to assume that during pregnancy the presence of VUR in a system already prone to bacteriuria would lead to increased morbidity. A number of studies have been conducted to examine this relationship.

The presence of active reflux appears to present a risk factor for the affected mother. In 1958, Hutch described a higher incidence of pyelonephritis during pregnancy in 23 women with a history of reflux and recurrent bacteriuria (Hutch, 1952, 1961). Heidrick and colleagues (1967) evaluated 321 women with cystography either during the last trimester or within 30 hours after delivery. The incidence of pyelonephritis was 33% in women with reflux compared with less than 5% in women without reflux. Finally, cystograms performed 4 to 6 months postpartum in 100 women with a history of asymptomatic bacteriuria during pregnancy showed reflux in 21%. Bacteriuria was easier to clear in patients without reflux (67%) than in those with reflux (33%) (Williams and Hulme-Moir, 1970).

Maternal history also becomes a factor if past reflux, renal scarring, or a tendency to UTIs is included. Martinell and colleagues (1990) compared the outcome of pregnancy in matched controls with that in 41 women with and without renal scarring after childhood UTIs. They found that women with a history of prior infections had a high incidence of bacteriuria during pregnancy, whereas those with renal scarring and persistent reflux were more prone to develop acute pyelonephritis. In a similar study, the outcome of pregnancy was assessed in 88 women with previous bacteriuria. Women with known scars had a 3.3-fold increased incidence of hypertension, a 7.6-fold increased risk for preeclampsia, and a higher rate of obstetric interventions. Women with normal kidneys and reflux also had an increased risk for hypertension during the last trimester (McGladdery et al, 1992). Pregnant women with bilateral renal scars were also shown to have a higher incidence of preeclampsia than those with unilateral scarring (24% vs. 7%, respectively) (El-Khatib et al, 1994), and those with creatinine elevation are also at risk (Jungers et al, 1987). In a large study of 158 women with reflux nephropathy, pregnancy was uneventful in patients with normal blood pressure and renal function, whereas the risks for fetal demise and accelerated maternal renal disease were increased in women with impaired renal function (Jungers, 1996).

The implications of reimplantation surgery were studied by Austenfeld and Snow (1988), who found an increased risk for UTI and fetal loss in 31 women who had undergone ureteral reimplantation as children, despite correction of the anomaly. In a follow-up study comparing these patients with a new cohort of historical controls, women with UTIs and reflux who underwent reimplantation (suggesting an initially higher degree of reflux and increased renal scarring) were still at significant risk for UTI during pregnancy (Mansfield et al, 1995). However, they were not at a higher risk for miscarriage than the general population. In a larger study of 77 pregnancies in 41 women whose ureters had been reimplanted, Bukowski (1998) and colleagues reported that the incidence of pyelonephritis during pregnancy was slightly higher than in the general population but that the fetus and mother were at significant risk when renal scarring or hypertension was present. Although these studies may at first suggest a limited benefit to reimplantation during a subsequent pregnancy, several factors must be borne in mind. None of these studies document any associated BBD in these women, which may have existed in childhood and continued unrecognized into the fertility years. Also, bladder dynamics change during pregnancy as a result of increasing uterine size. Although it is assumed that reflux remains absent during pregnancy after correction in childhood, radiologic verification that the surgically corrected UVJ remains competent (reflux free) is not feasible and such data are not available. Finally, it is not known whether formerly refluxing renal units in such adult patients carry a latent predisposition or heightened susceptibility to pyelonephritis during the pregnancy as a consequence of previous postinfection damage during childhood and/or any inherent reflux-associated dysmorphism, both of which would persist despite surgery at the bladder level. Nevertheless, in keeping with the more recent emphasis on preexisting renal status when considering reflux management, at least one meta-analysis of the

significance of a pregnancy and reflux association also suggests that the presence of renal scarring, and not the presence or absence of reflux, is the principal factor driving morbidity during pregnancy in such women (Hollowell, 2008). When combined with the known physiologic renal and bladder changes during pregnancy, it is reasonable to speculate that such kidneys may carry a heightened predisposition to pyelonephritis.

In summary, the majority of studies examining the effects of VUR on pregnancy suggest that women with a history of reflux have increased morbidity during pregnancy because of infection-related complications, whether the reflux has been corrected or not. **Women with hypertension and an element of renal failure are particularly at risk.** Those with uncorrected reflux appear to be particularly at risk and should have their reflux corrected before pregnancy to minimize maternal and fetal morbidity. The morbidity during pregnancy of women with persistent reflux without renal scarring remains poorly defined, but the tendency to UTI seems to be increased. Because of the difficulty in predicting an outcome for this subset of patients, most clinicians recommend surgical correction for girls with reflux that persists beyond puberty, although there has been a trend toward discontinuation of prophylactic antibiotics in older girls with active reflux. Long-term follow-up studies of these patients through puberty are unavailable (see later discussion).

KEY POINTS: PREGNANCY AND REFLUX

- Physiologic changes in the ureter and bladder during pregnancy may influence the propensity for reflux-associated pyelonephritis in pregnant patients with reflux.
- In the absence of definitive studies to the contrary, correction of reflux may be considered before pregnancy.

NATURAL HISTORY AND MANAGEMENT

Spontaneous Resolution

The one feature of VUR that provides the greatest relief to parents and caregivers but at the same time creates confusion in reflux study design and literature interpretation is spontaneous resolution. Indeed, the basis of contemporary medical therapy is predicated on an expected rate of spontaneous resolution. At birth, the probability of spontaneous resolution of primary reflux is roughly inversely proportional to the initial grade. If a patient is encountered at a later age, resolution from any point in time forward will depend on initial grade of reflux, if it is known, and age at presentation. For example, unilateral grade 3 reflux at birth should resolve in 70% of cases by age 5. However, if a 6-year-old with normal bladder function presents with grade 3 reflux, it is much less likely to resolve. Given a growing tendency among some clinicians to reassess females for persistent reflux and possible endoscopic correction after a holiday period without follow-up (between 5 years and the teenage years), it is possible new information remains to be learned about reflux resolution. Reflux likely resolves spontaneously as a result of remodeling of the UVJ over time, with progressive elongation and consolidation of the intravesical ureter and antireflux mechanism, as well as stabilization of bladder dynamics. Conversely, failure of the latter likely accounts for reflux persistence beyond the statistical norms in many patients. Indeed, inability to strictly understand bladder dynamics may have skewed earlier determinations of absolute reflux resolution rates but in doing so provided a real-world picture of spontaneous resolution.

Resolution by Grade

Most cases of low-grade reflux (grade 1 and 2) will resolve. Several studies have documented this high rate of spontaneous resolution. However, the variance in reported resolution rates for low-grade reflux was 63% of grade 2 (Duckett, 1983), 80% of grade 2 (Arant,

1992), and 85% of grade 2 (Edwards et al, 1977). This belies the fact that lower urinary tract dynamics may also play a role in mitigating spontaneous resolution.

Grade 3 reflux will resolve in approximately 50% of cases (Duckett, 1983; McLorie et al, 1990). Very few cases of higher grade reflux (grades 4 and 5, and bilateral grade 3) will resolve spontaneously. Analyses from several sources, including the International Reflux Study in Children, support a uniformly low prevalence of resolved high-grade reflux with no more than 25% (Weiss et al, 1992b) and as little as 9% (Skoog et al, 1987) of patients demonstrating spontaneous resolution. It is possible no real difference exists in resolution rates in high-grade reflux (Tamminen-Mobius et al, 1992). Considering the fact that any given reflux grade is assigned on the basis of a dynamic voiding study, the possibility for variability by at least one grade, especially in assigning higher grades to reflux, is quite real. Thus attempting to discriminate true differences in resolution rates for grades 3 and higher reflux may not be particularly clinically relevant.

Resolution by Age

The age at which reflux begins or is first encountered will play a more potent role in the management of the patient with reflux than the grade itself. It is self-evident that if reflux is a congenital disorder with an inherent tendency to resolve spontaneously over time, it will (1) be most prevalent in neonates and young children, and (2) demonstrate the greatest tendency to resolve in this group. Conversely, in any analysis, if reflux is truly primary, is encountered in an older child, and has been present since birth, it already has demonstrated a propensity to persist and therefore is self-selected for reflux, which is unlikely to resolve (Skoog et al, 1987). The 1997 AUA guidelines data provide a synthesis of large numbers and reasonable statistical estimates of resolution rates segregated by age and grade (Elder et al, 1997) (Fig. 137-16). Interpretation of more recent follow-up studies (Connolly et al, 2001) suggest that diagnosis at age 5, as well as in infancy, is associated with a similar resolution rate (20% per year), regardless of age. However, as stated at the outset, it must be remembered that resolution 5 years after age 5 implies reflux has required 10 years to resolve versus resolution 5 years after birth. Moreover, the observation by McLorie and colleagues (1990) that high-grade reflux in patients presenting after birth showed no difference in resolution rates between subjects younger and older than 1 year of age may reflect the generally poor resolution rate of high-grade reflux to begin with. Thus persistence in early life will imply persistence when older. These principles likely underlie the observation that when reflux resolves, it often does so within the first few years of life. The study by Skoog and colleagues (1987) observed that 30% to 35% of subjects resolved their reflux each year. Reflux in younger patients (<12 months old) resolved more quickly (1.44 vs. 1.85 years, $P < .02$), with grade 3 requiring slightly more time than grade 2 to resolve (1.56 vs. 1.97 years, $P < .04$).

The traditional period of observation for resolution is 5 years, probably because the greatest proportion of growth and anatomic remodeling of the UVJ is complete. In the study by McLorie and coworkers (1990), 92% of resolved grade 3 reflux occurred within 4 years. There is a tendency to ascribe a benefit to the observation of interval reduction in grade. Such a finding could herald progression to resolution, but in the end it still carries the same risk for escalating a UTI to pyelonephritis and so should be interpreted with caution when counseling families. The resolution rates for VUR followed into the teenage and adult years remain unknown. **Clearly then, what constitutes reflux resolution depends on the period over which resolution is sought.**

Principles of Management

The medical and surgical therapy for reflux has purported to offer similar benefit to patients (Table 137-6 on the Expert Consult website). This has fueled the debate between fundamental choices of therapy for decades. The tension embedded in decision making



TABLE 137-6 Outcomes of Medical and Surgical Therapy for Children with Primary Vesicoureteral Reflux and Renal Scarring

REGISTRANT	NO. PATIENTS	NEW SCARS (%)	THINNING (%)
EUROPE			
Medical	155	19 (12)	11 (7)
Surgical	151	20 (13)	15 (10)
UNITED STATES			
Medical	66	14 (20)	9 (13)
Surgical	64	16 (25)	2 (3)

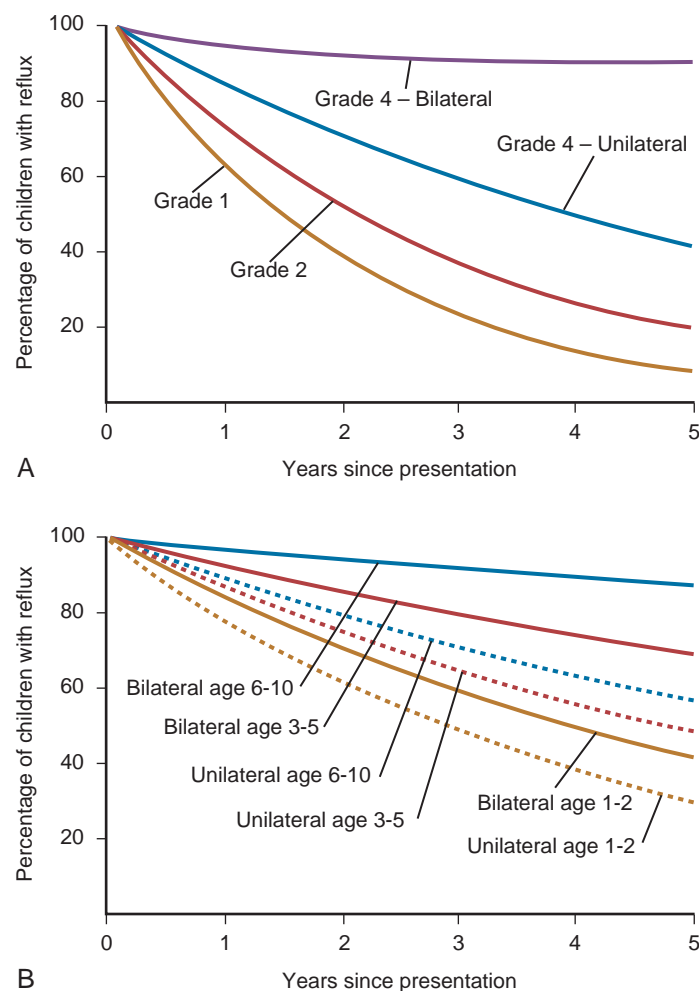


Figure 137-16. A, Percent chance of persistence of grades 1, 2, and 4 reflux for 1 to 5 years after initial evaluation. B, Percent chance of persistence of grade 3 reflux by age for 1 to 5 years after initial evaluation. (From American Urological Association. Report on the management of vesicoureteral reflux in children. Baltimore: American Urological Association, Pediatric Vesicoureteral Reflux Clinical Guidelines Panel; 1997.)

for reflux management stems from the almost perfect results attainable by surgical correction of reflux, now commonly successful in more than 98% of cases. However, traditional practice in reflux management has held that the end does not justify the means: Reflux correction is not indicated merely because it can be corrected easily and reliably. As stated earlier, almost 80% of low-grade and half of grade 3 reflux will resolve spontaneously. Walker (1994) summarized the essential tenets of reflux management as follows:

1. Spontaneous resolution of reflux is very common.
2. High-grade reflux is less likely to resolve spontaneously.
3. Sterile reflux is benign.
4. Extended use of prophylactic antibiotics is benign.
5. Success of (open) surgical correction is very high.

Rather than providing strict guidelines for treatment, these principles provide ample room to individualize treatment on the basis of the particular preferences and tolerances of physicians, families, and patients for the various burdens each of the principles entails. The classic approach has been to offer daily low-dose prophylactic antibiotic suppression of infections as the first line of treatment under the principle that every case of reflux should be offered time to resolve spontaneously, despite grade. Clearly, age at presentation and grade will factor into predicting when and if resolution is likely to occur. In addition, in patients diagnosed after

one or more episodes of pyelonephritis, the presence of scarring on renal scintigraphy may temper a decision for extended prophylaxis and observation, particularly if scarring is extensive, the reflux is high grade, renal function is already globally depressed, or congenital dysmorphism of one or both kidneys is present. In such cases, tolerance for yet another infection despite the presence of prophylaxis may be low, or simple disquiet with the notion of ongoing reflux may invite strong consideration for reflux correction.

As stated previously, it is not clear how long to wait for reflux resolution in the individual patient. In newborn patients, it is reasonable to wait until approximately 5 years of age assuming no intercurrent breakthrough infections occur. Beyond this age, it is commonly believed that the kidneys become less prone to scarring after pyelonephritis (Olbing et al, 2003), although the previously mentioned limitations in the interpretation of imaging inherent in the reflux literature should be remembered. Thus some practitioners are withdrawing prophylaxis as the child approaches the age of 5. After this age, boys with asymptomatic reflux will require little or no formal follow-up as long as lifelong attention to good bladder habits is reinforced, and they are counseled to seek prompt medical attention if a pyelonephritis were to occur in the future, as well as reassessment of their reflux status. Nevertheless, disagreement would remain as to whether to correct asymptomatic bilateral high-grade reflux with normal renal parenchyma and function in an older boy despite the thought that sterile reflux is benign. Girls have traditionally undergone open surgical correction, even for asymptomatic reflux that fails to resolve by the age of 5, on the premise that it will reduce maternal and fetal morbidity during a future pregnancy. Using the rationale of antibiotic withdrawal in the older child, one study demonstrated that less than 10% of patients will subsequently develop recurrent febrile UTIs mandating surgical correction of reflux (Cooper et al, 2000), albeit with limited clinical follow-up and using only ultrasound imaging to assess renal health. Clinical guidelines for reflux management in children are presented in Table 137-7 on the Expert Consult website.

Adult patients who present with nonobstructive flank pain, febrile UTIs, or pyelonephritis and are found to have VUR have traditionally been offered antireflux surgery. Endoscopic correction of uncomplicated adult reflux also should be possible (Arce et al, 2009).

Emerging Role for Endoscopic Correction of Reflux

Please see the Expert Consult website for details.

Medical Management: Watchful Waiting

Although some reports have suggested the existence of “water-hammer” renal damage from high-grade reflux of sterile urine against the renal papillae (Hodson et al, 1975; Hagen and Klevmark, 1991), no such clinical entity has been predictably demonstrated. Because it is not reflux per se that is actually being managed, the hallmark of observational therapy in reflux disease can be more accurately termed “watchful waiting” while maintaining urinary sterility through the judicious use of single daily low-dose antimicrobial prophylaxis. Often, antibiotics are given as oral suspensions once per day and preferably at night. Nighttime dosing allows for antibiotic concentration in the bladder urine over the longest period of expected physiologic retention, when infection is most likely to develop. For children younger than 2 months of age, the most commonly used medications are trimethoprim and amoxicillin.

For further details, please see the Expert Consult website.

Breakthrough febrile UTIs or pyelonephritis while on antibiotic prophylaxis are generally considered an indication for termination of watchful waiting and correcting the reflux. However, individual documentation and verification of true breakthrough infection varies widely. Thus it is likely that instances of premature reflux correction (false positive) and failure to proceed with reflux correction (false negative) are to be expected. This possibility underscores the importance of proper antibiotic dosing, patient and parental

TABLE 137-7 Treatment Recommendations for Boys and Girls with Primary Vesicoureteral Reflux*

VUR GRADE AND LATERALITY	CLINICAL MANIFESTATION AGE (yr)	INITIAL (ANTIBIOTIC PROPHYLAXIS OR OPEN SURGICAL REPAIR) GUIDELINE	FOLLOW-UP† (CONTINUED ANTIBIOTIC PROPHYLAXIS, CYSTOGRAPHY, OR OPEN SURGICAL REPAIR) PREFERRED OPTION	REASONABLE OPTION	GUIDELINE	PREFERRED OPTION	NO CONSENSUS‡
FOR CHILDREN WITHOUT SCARRING AT DIAGNOSIS							
1-2, unilateral or bilateral	<1 1-5 6-10	Prophylaxis Prophylaxis Prophylaxis					Boys and girls Boys and girls Boys and girls
3-4, unilateral or bilateral	<1 1-5 6-10	Prophylaxis Unilateral: Prophylaxis Unilateral: Prophylaxis	Bilateral: Prophylaxis Unilateral: Prophylaxis		Bilateral: Surgery if persistent\$ Unilateral: Prophylaxis Bilateral: Surgery	Unilateral: Surgery if persistent\$ Surgery if persistent\$ Surgery if persistent\$	
5, unilateral or bilateral	<1 1-5 6-10	Surgery	Prophylaxis Bilateral: Prophylaxis Unilateral: Prophylaxis	Bilateral: Prophylaxis Unilateral: Surgery	Surgery if persistent\$ Surgery if persistent\$		
FOR CHILDREN WITH SCARRING AT DIAGNOSIS							
1-2, unilateral or bilateral	<1 1-5 6-10	Prophylaxis Prophylaxis Prophylaxis					Boys and girls Boys and girls Boys and girls
3-4, unilateral	<1 1-5 6-10	Prophylaxis Prophylaxis	Prophylaxis		Girls: Surgery if persistent\$ Girls: Surgery if persistent\$ Surgery if persistent\$	Boys: Surgery if persistent\$ Boys: Surgery if persistent\$ Surgery if persistent\$	
3-4, bilateral	<1 1-5 6-10	Prophylaxis Surgery	Prophylaxis	Surgery	Surgery if persistent\$ Surgery if persistent\$		
5, unilateral or bilateral	<1 1-5 6-10	Bilateral: Surgery Surgery	Prophylaxis Unilateral: Surgery	Surgery	Surgery if persistent\$ Surgery if persistent\$	Surgery if persistent\$	

Guidelines: Treatments selected by 8 or 9 of 9 panel members, given the strongest recommendation language.

Preferred options: Treatments selected by 5 to 7 of 9 panel members.

Reasonable alternatives: Treatments selected by 3 to 4 of 9 panel members.

No consensus: Treatment selected by no more than 2 of 9 panel members.

*Recommendations were derived from a survey of preferred treatment options from 36 clinical categories of children with reflux. The recommendations are classified as follows:

†For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.

‡No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.

\$See the text regarding the length of time that clinicians should wait before recommending surgery.

From American Urological Association. Report on the management of vesicoureteral reflux in children. Baltimore: American Urological Association, Pediatric Vesicoureteral Reflux Clinical Guidelines Panel; 1997.

Endoscopic management is discussed in greater detail later. In North America the relative ease and low morbidity of endoscopic correction has begun to transform the indications for unresolved reflux correction in females. Indeed, although open antireflux surgery is more technically demanding, as well as more taxing on the older female patient, endoscopic correction can be easily performed well into the teenage years and beyond. Between the age of 5 and mid-to-late teens, girls with asymptomatic reflux may be treated in the same fashion as boys and have their antibiotic prophylaxis withdrawn and follow-up imaging suspended for several years, in the absence of any febrile UTI. This also will afford the opportunity for a new cohort of older patients to provide longer term resolution rates on a systematic basis. Girls may then return for a final cystogram. If reflux is still present, endoscopic injection is performed followed by a postinjection cystogram. Formal prospective trials of this proposition will be required to validate the principle.

Moreover, studies of parental preference in reflux management are revealing that endoscopic treatment may sometimes be preferred over either antibiotic prophylaxis or open surgery depending on the perceived duration for reflux resolution (Ogan et al, 2001; Capozza et al, 2003). However, such studies must be interpreted with caution in that any therapy that combines low morbidity and technical ease can become a seductive choice, especially because endoscopic therapy was preferred despite an acknowledged lower success rate than that of open surgery and potential for more than one anesthetic. Alternatively, others may tolerate only definitive open surgical correction.

Notwithstanding the ethical considerations of proffering endoscopic treatment for reflux correction, endoscopic indications have a wider theoretic potential than open surgery. For example, even if the durability of endoscopic correction is not indefinite, recognizing that the prime age for postpyelonephritic scarring is younger than 5 years, one could conceive of temporary reflux correction by endoscopy for the early years, obviating the need for several years of prophylaxis in either males or females. Beyond 5 years, postinjection recurrence of asymptomatic reflux in males, were it to occur, would be of little clinical consequence. Males would require reevaluation only if pyelonephritis were to occur after the age of 5 years. In females, demonstration of durability of injection therapy extending from infancy to at least the end of the childbearing years would be required. One recent long-term study documents only a 5- to 7-year durability of 80% (Dodat et al, 2004); thus in one fifth of patients, reflux recurs. Moreover, these results represent the brand of injectable agent called Macroplastique (Uroplasty, Minnetonka, MN). Similar data are as yet unavailable for Deflux (Salix Pharmaceuticals, Raleigh, NC). Nevertheless, regardless of the substance injected and the uneven durability reported to date compared with open reflux correction, the endoscopic approach to reflux management has gained favor over the past several years in both Europe (Puri et al, 2003; Lendvay et al, 2006) and the United States.

Children younger than 2 months of age possess relative hepatic immaturity and are unable to clear sulfamethoxazole efficiently; the drug displaces fetal bilirubin and leads to jaundice. After 2 months of age, the antibiotic of choice becomes trimethoprim-sulfamethoxazole (TMP-SMX; Septra, Bactrim). Like virtually any drug, some mild side effects should be kept in mind and include gastrointestinal upset and allergy. Although transient leukopenia has been reported with TMP-SMX, it is rare, resolves with discontinuation of the drug, and is not believed to be significant enough to warrant regular monitoring of white blood cell counts in all children taking the drug. The other drug most commonly used is nitrofurantoin (Macrochantin). Nitrofurantoin may minimize the development of resistance to fecal organisms, the latter being the largest reservoir for urine infectivity. This drug is known to cause pulmonary fibrosis and, rarely, interstitial pneumonia. However, oral tolerance is less than with TMP-SMX because of taste and gastrointestinal symptoms are subjectively worse. A comprehensive literature review of the use of these drugs by Karpman and Kurzrock (2004) in children revealed a low incidence of significant hepatic (five patients) or pulmonary (nine patients) involvement, almost always associated with full-dose rather than once-daily low-dose therapy. Finally, a growing literature on the use of probiotics (live microorganisms such as strains of *Lactobacillus*, which may displace and suppress the growth of uropathogenic bacteria) is addressing UTI prophylaxis in children (Bruce and Reid, 2003; Reid and Devillard, 2004; Salvini et al, 2004). The mechanisms that underlie the demonstrated benefit of probiotic use are now emerging (Reid and Bruce, 2006; Storm et al, 2011). Further studies will be required to define the use of this attractive approach in the medical treatment of patients with reflux.

acceptance and compliance with the chosen therapy, and meticulous attention to proper collection and handling of urine culture specimens (see earlier discussion). Although the interaction between host defenses and bacterial virulence factors is what ideally dictates breakthrough infection, [Smellie \(1991\)](#) has provided useful interpretations surrounding practical causes of breakthrough infection: (1) If the organism is sensitive to the prescribed prophylactic antibiotic, the child or parent has likely not been compliant or the dose is too low. (2) If the organism is resistant to the prescribed antibiotic, either the residual bladder volume is too high too often or the dose is too high ([Smellie, 1991](#)). Indeed, many referrals for definitive reflux correction result from breakthrough UTI following full-dose antibiotic usage for extended periods.

Once the radiographic resolution of reflux has been documented, antibiotic prophylaxis is terminated, usually a few days after the cystogram. However, because reflux resolution will likely herald a tapering or discharge from regular urologic follow-up, this also is the precise time for reinforcing a lifelong adoption of good toileting and bladder behaviors.

In keeping with the notion of reflux resolution, recent studies have conducted multivariate analyses to construct predictive models for reflux resolution ([Knudson et al, 2007](#); [Estrada et al, 2009](#)). The assumption is that when reflux is less likely to resolve, the likelihood of ensuing complications is ever present and may sway management toward earlier or more proactive consideration for reflux correction in the individual patient. However, the converse also is true in that lifelong reflux, including persistent reflux per se may never be the cause of any morbidity. However, any standard instrument for the prediction of such morbidity is presently lacking. It appears that the factors associated with reflux resolution have become conflated with the more important factors that may be associated with its complications. Recent observations on the stratification of risk factors for reflux complications, in this case, breakthrough UTI, used a logistic regression model combining both reflux grade and clinical patient characteristics (gender, mode of reflux diagnosis, bowel/bladder dysfunction) to derive low-, intermediate-, and high-risk predictions for a breakthrough UTI within 2 years of follow-up ([Hidas et al, 2013](#)). This and subsequent tools that may follow show an advantage for counseling practitioners and families on more direct indications for both reflux intervention or relaxing follow-up, including a reconsideration of the ongoing need for prophylactic antibiotics. It is the consequences of reflux that pose the greatest threat; the ability to predict them rather than predict reflux persistence or resolution may be more clinically relevant.

Landmark Studies

The efficacy of medical management rests with a few key studies that came to define and establish watchful waiting as a cornerstone of therapy for reflux disease. Smellie and colleagues led a series of studies that repeatedly demonstrated the ability of low-dose prophylactic antibiotics to prevent infection and renal scarring while reflux resolved in a significant majority of children ([Edwards et al, 1977](#)). Since then two additional large-scale prospective studies validated this approach and helped to further define the natural history of VUR.

International Reflux Study in Children

The International Reflux Study in Children was a North American ([Weiss et al, 1992a](#)) and European ([Tamminen-Mobius et al, 1992](#)) cooperative study that randomized children younger than 9 years of age with high-grade reflux to watchful waiting with prophylaxis or corrective open surgery (see [Table 137-6](#)). Although surgery was complicated by temporary postoperative obstruction in some patients, it was more effective than prophylaxis in reducing, but not eliminating, the occurrence of pyelonephritis. Nevertheless, the incidence of UTI (38%) was the same with both modalities. Furthermore, the modalities were equally effective in reducing, but not eliminating, new scar formation. Only the European arm

stratified data for the effect of dysfunctional voiding behaviors (18%) ([van Gool et al, 1992](#)). When untreated, voiding dysfunction was associated with more UTIs, more persistent cases of reflux, and greater grade variation during follow-up.

Birmingham Reflux Study

Medical and surgical management was prospectively compared in a randomized cohort of 104 patients with high-grade reflux ([Birmingham Reflux Study Group, 1987](#)) over a 5-year period. Again, the incidence of new scars was the same using either treatment modality. Although more than half the patients continued to reflux at 5 years, all cases of new scarring occurred within the first 2 years, consistent with the “big bang” concept of postinfectious renal injury mentioned previously.

Additional Prospective Studies

Medical management alone was assessed in 59 patients (84 refluxing ureters, grades 1 to 3) by the Southwest Pediatric Nephrology Group ([Arant, 1992](#)). Resolution occurred in 67%, breakthrough infection in 33%, and new scarring in 10% of the low-grade and 28% of the patients with grade 3. [Scholtmeijer \(1993\)](#) demonstrated resolution in 57% of 47 cases of grade 3 to 4 reflux followed by watchful waiting and prophylaxis for 5 years. Interestingly, 15 cases underwent surgical correction after breakthrough infection and 6 of these subsequently developed new scars, whereas 2 of the patients managed medically developed new scars.

Randomized Intervention for the Management of Vesicoureteral Reflux Study

Despite the long-standing standard of care regarding medical management of VUR using prophylactic antibiotics, there exist mounting countervailing concerns over the long-term use of low-dose antimicrobials. These concerns are likely fueled at least in part by the documented abundant use of antibiotics both within the medical arena and in the food chain, as well as the rising incidence of antimicrobial resistance ([Cheng et al, 2008](#); [Alam et al, 2009](#)). Furthermore, newer prospective studies are beginning to question the ability of daily antibiotic prophylaxis to reliably reduce the incidence of UTI (see later). Reflux management is being further challenged by discordant and seemingly random recommendations variously for watchful waiting with or without antibiotic prophylaxis or first-line endoscopic, laparoscopic, or open correction of the reflux, depending on the individual consultant. The lack of appropriate (placebo) controls or observational arms in prior retrospective reflux studies has further called their conclusions into question. If daily low-dose antimicrobial prophylaxis is to maintain any position as a first-line treatment, its true efficacy will require greater scrutiny. One major study to address this question is termed the Randomized Intervention for the Management of Vesicoureteral Reflux (RIVUR study). RIVUR is a National Institutes of Health multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate the effectiveness of antimicrobial prophylaxis in children found to have reflux after an initial UTI. Fifteen collaborating centers enrolled approximately 600 children with grade 1 to 4 reflux after an initial or second febrile or symptomatic UTI. Study participants were randomized to oral placebo versus oral TMP-SMX antibiotic prophylaxis. The primary outcome measure was the development of recurrent febrile or symptomatic UTI ([Chesney et al, 2008](#); [Greenfield et al, 2008](#); [Keren et al, 2008](#); [Mathews et al, 2009](#); [RIVUR Trial Investigators et al, 2014](#)). Results suggested that antibiotic prophylaxis reduced recurrent UTI risk by 50% (39 of 302 antibiotic vs. 72 of 305 prophylaxis subjects), particularly in subjects with febrile UTI or bowel/bladder dysfunction at baseline. However, renal scarring findings appeared unaffected by prophylaxis (11.9% vs. 10.2% in antibiotic vs. prophylaxis groups, respectively). Several limitations reiterate the significant challenges in conducting such studies. The compliance figures showed that

approximately 75% of antibiotic subjects took the drug only 75% of the time, almost a third discontinued the drug and were withdrawn from analysis, and 2% in each group reported adverse drug reaction. Using more stringent criteria for treatment failure (multiple UTI recurrences, \pm fever, \pm symptoms, etc.), twice as many placebo subjects suffered treatment failure (9.5% vs. 5% of antibiotic subjects). However, the converse is that 90% treatment success was achieved with placebo alone. Finally, 484 (83%) of baseline nuclear scans in both groups were obtained 1 to 4 months after the index infection event. However, the scan data cannot conclude whether positive baseline scan findings were a result of the index infection or were related to renal dysmorphism coincident with the genesis of reflux itself. Despite these limitations, this study nevertheless highlights the importance of balancing the consequences of UTI and its prevention in a reflux background (5% with prophylaxis vs. 9.5% with placebo) for both the patient and family as a whole (significant illness, hospitalization, loss of work) versus absence of any perceived benefit to the refluxing renal units per se. Greater attention to patient selection should help identify the specific subset of children who stand to benefit clinically from prophylaxis.

Antibiotic Controversies and Potential New Approaches

The principal rationale for antibiotic use in the management of reflux is in the prevention of urinary infection, principally febrile pyelonephritis, which may lead to permanent postinfection renal scarring. Driving this rationale in part is the belief that the first febrile UTI, in the presence of reflux, will create the greater proportion of clinically significant postinfection scarring, despite the fact that this concern is based on models of postinfection scarring in experimentally induced reflux in animals with a priori normal renal development (Torres et al, 1985). This belief, in turn, spawned the now routine and widespread sonographic follow-up of prenatal hydronephrosis for evidence of postnatal hydronephrosis, which, if present, then triggers the documentation of reflux by cystography to prevent the first febrile UTI by instituting immediate antibiotic prophylaxis if reflux is found.

However, several recent prospective studies have brought into question the ability of chronic low-dose antibiotic prophylaxis to prevent UTI in children. For example, in children with grade 2 to 4 reflux, after an initial UTI, randomization of 50 patients each to antibiotic prophylaxis versus no-treatment groups showed no difference in the rate of subsequent UTI or renal scarring (Pennesi et al, 2008). One multicenter trial of 225 children with reflux aged 1 to 3 years, randomizing subjects to antibiotic prophylaxis versus no treatment, found no statistical overall reduction in UTI incidence with prophylaxis, although subset analysis did suggest some benefit in boys with grade 3 reflux (Roussey-Kesler et al, 2008). As a corollary, patients with ongoing reflux in whom prophylactic antibiotics have been withdrawn have not suffered any increased incidence of UTI when compared with age-matched refluxing control patients who remain on prophylaxis (Leslie et al, 2009). Similarly, patients who have failed endoscopic reflux correction that remains uncorrected fail to show any increased incidence of UTI regardless of whether they remain on prophylaxis (Moore et al, 2009).

Such studies are plagued with a host of important shortcomings, including small patient numbers, high dropout rates, inaccurate urine collection methods (i.e., bags), no placebo controls, routine screening rather than evaluation in response to symptoms including screening bagged sample collections in uncircumcised infants, and lack of distinction between febrile and nonfebrile UTIs. Many of these shortcomings are being addressed in the large RIVUR study. Nevertheless, despite their limitations, these studies have succeeded in casting new doubt on the true and precise effectiveness and role of antibiotic prophylaxis in reflux management. However, in the recent Swedish Reflux Trial (Brandström et al, 2010c) girls 1 to 2 years old with grade 3 to 4 VUR prospectively randomized to antibiotic prophylaxis had a significantly lower incidence of new renal scars compared with those randomized to surveillance (no antibiotics) and endoscopic treatment. New scars were more prevalent after

febrile UTIs (11 of 49 [22%]). In contrast, only 4 of 152 (3%) of nonfebrile UTIs were associated with new renal damage ($P < .0001$). The rate of new renal damage was low in boys (observed in 2 of 75 males enrolled). These data support the use of antibiotic prophylaxis in girls younger than 2 years of age with grade 3 to 5 VUR.

Endoscopic correction of VUR did not reduce the incidence of new renal scars or febrile UTIs. However, the relatively low success rate of endoscopic treatment in this study (54% complete resolution with an additional 17% downgraded to grades 1 to 2) may have negated any potential benefit of endoscopic correction.

When added to the underlying concern for the long-term use of antibiotics in general, studies that bring into question the efficacy of antibiotic prophylaxis are giving rise to reflux management alternatives. Where low-dose antibiotic prophylaxis may be of questionable value, the effectiveness of appropriate full-dose antibiotic treatment of UTI by eliminating fever and symptoms of acute illness, as well as eradicating the infection, is not in question. Therefore one alternative is close observation for UTI symptoms without prophylaxis, coupled with precise treatment of culture-proved UTI. However, two recent pediatric nephrology studies of UTI (Doganis et al, 2007; Hewitt et al, 2008) suggest that early (within 24 hours) versus later (within 4 to 7 days) antibiotic treatment does not necessarily reduce the incidence of postpyelonephritic scarring if the kidneys become involved in the UTI, though early treatment may reduce initial renal involvement (Doganis et al, 2007). Moreover, in both studies, reflux was not found to be a significant variable affecting scarring incidence. In both studies, limitations such as precise knowledge of timing of UTI onset and the previously mentioned limitations of DMSA scanning in differentiating preexisting renal dysmorphism from true postinfection renal scarring (none of the foregoing study subjects had preinfection scans) remain.

With regard to endoscopic correction of reflux, the aforementioned chemoprophylaxis and invasive imaging concerns, the ease of endoscopic therapy, and parental preference for endoscopic correction despite knowledge of a lower success rate versus open surgery (Ogan et al, 2001) may be among the factors driving the resurgence and ever-increasing use of endoscopic correction of reflux. If this trend continues without rigorous prospective analysis, it could erode equipoise, to potentially position this technique as another first-line therapy after reflux diagnosis. Although studies of primary endoscopic therapy are emerging from South America and Europe (Nortes Cano et al, 2008), no North American studies endorsing this as a primary approach for low-grade reflux management are yet available. One uncontrolled retrospective study has suggested that endoscopic correction may reduce incidence of subsequent UTI, similar to the conclusion of the International Reflux Study, though endoscopic correction was not primary therapy (Wadie et al, 2007). More importantly, the durability of endoscopic reflux correction is in question, with the recent studies documenting 20% and 27% delayed recurrence of reflux after initial successful reflux correction (Sedberry-Ross et al, 2008; Holmdahl et al, 2010). Thus the indications for primary endoscopic correction of reflux will require carefully designed prospective randomized trials taking into account patient age and concomitant stage of renal development and renal susceptibility to scarring. In addition, other patient factors known to modify surgical outcomes such as preexistence or subsequent onset of elimination dysfunction must be considered. Finally, given the high incidence of incidental and clinically silent reflux in the normal population, as well as the high propensity for reflux to resolve over time, primary endoscopic correction of reflux without knowing which patients will benefit physiologically and clinically will likely result in both unnecessary correction of reflux destined to resolve naturally and/or correction of reflux with no clinical benefit.

Antibiotic prophylaxis is not a panacea—this approach is destined to fail without adequate teaching and periodic review of perineal hygiene techniques, timely bladder emptying habits, and anticonstipation measures. Similarly, family compliance with the antibiotic administration and follow-up visits for imaging may vary widely (Wan et al, 1996). Careful discussion of obligations and

expectations should take place to assess whether watchful waiting is appropriate in each case. Given the need for strict compliance with such an approach, alternative regimens such as alternate-day dosing of prophylactic antibiotics or early aggressive treatment of UTI with full-dose antibiotics with no prophylaxis otherwise, while conceptually attractive, will be at risk for decreasing compliance, especially when new opportunities for relaxing a daily routine and awareness are introduced into the management profile. If families or patients are willing but unable to maintain all the elements of a watchful waiting treatment regimen, then consideration for open or endoscopic correction of VUR may be relatively indicated.

KEY POINTS: NATURAL HISTORY AND MANAGEMENT

- Reflux has a natural tendency to resolve spontaneously.
- The likelihood of resolution is inversely proportional to grade.
- Maintaining urine sterility (through both prophylactic antibiotics and strict attention to bladder and bowel management) is the cornerstone of watchful waiting medical management.
- Continuous antibiotic prophylaxis results in a modest reduction in UTIs, but does not reduce renal scarring or chronic kidney disease.
- Prophylactic antibiotics are more likely to benefit patients with higher grade reflux, baseline bladder dysfunction, febrile UTI bowel and bladder dysfunction, or initial presentation with febrile UTI.

SURGICAL MANAGEMENT

Starting with Hutch's initial report on the successful correction of VUR in seven out of nine patients with paraplegia (Hutch, 1952), multiple surgical techniques have been described to effectively correct VUR. Currently, the principles from these techniques have been incorporated into a handful of procedures with excellent results. The choice of procedure is individualized according to surgeon experience and patient condition.

Surgical Principles of Reflux Correction

The principles of surgical correction of reflux include the following:

- Exclusion of causes of secondary VUR
- Adequate mobilization of the distal ureter without tension or damage to its delicate blood supply
- Creation of a submucosal tunnel that is generous in caliber and satisfies the 5:1 ratio of length to width recommended by Paquin (1959)
- Attention to the entry point of the ureter into the bladder (hiatus), the direction of the submucosal tunnel, and the ureteromucosal anastomosis to prevent stenosis, angulation, or twisting of the ureter
- Attention to the muscular backing of the ureter to achieve an effective antireflux mechanism
- Gentle handling of the bladder to reduce postoperative hematuria and bladder spasms

The surgical procedures can be classified on the basis of the approach to the ureter as *intravesical*, *extravesical*, or *combined*. Furthermore, they can be classified on the basis of the position of the submucosal tunnel in relation to the original hiatus into *suprahiatal* or *infrahiatal*.

The following components apply to all of the various surgical techniques. The surgeon is free to select the appropriate components tailored to the patient's anatomy to achieve a successful ureteral reimplant. Prophylactic antibiotics may be administered with induction of anesthesia. The patients are generally admitted the

morning of the surgery unless there are specific reasons requiring preoperative admission. Enemas are reserved for only select cases because all issues related to dysfunctional elimination should be addressed when the diagnosis of VUR is made.

Cystoscopy

Historically, many centers performed cystoscopy after the diagnosis of VUR with the premise that it offers a predictive assessment of the likelihood of spontaneous resolution of VUR. Parameters such as shape (except for the golf hole orifice associated with high-grade reflux) and location of the ureteric orifice and the submucosal tunnel length were subsequently found not to have a predictive value (Duckett and Bellinger, 1982). Therefore cystoscopy in the course of conservative management of VUR is indicated only to confirm or manage abnormalities found on other imaging modalities (Ferrer et al, 1998).

Some surgeons choose to perform cystoscopy at the time of ureteral reimplantation surgery after induction of anesthesia. This is helpful in identifying subtle anomalies not detected on preoperative imaging, particularly if an extravesical technique is employed and the bladder is not opened. Preoperative cystoscopy may uncover inflammatory changes, trabeculation, duplication anomalies, or anatomic anomalies at the UVJ such as small ureteroceles or diverticula.

The bladder should be examined as it is distending, because a paraureteral diverticulum may not be apparent until the bladder is moderately to fully distended. Some authors suggest the use of hydrodistention of the ureteric orifice (Kirsch et al, 2004), particularly of the contralateral ureter, as a predictor of which ureters will develop contralateral reflux after surgery. PIC cystography (Rubenstein et al, 2003) also has been recommended for the detection of occult reflux in children who have had febrile UTI and a negative VCUG. In both of these techniques the tip of the cystoscope is positioned at the ureteric orifice and the irrigating fluid flow (with or without radiographic contrast) is directed at the ureter. The elevation of the anterior wall of the ureter, allowing visualization of the ureteral lumen, and/or the retrograde flow of contrast detected by fluoroscopy is considered to be indicative of an incompetent UVJ that might reflux during a UTI or after contralateral surgery but remains to be validated.

At the completion of cystoscopy the bladder is left half full if an intravesical technique is contemplated. If an extravesical technique will be used, a Foley catheter connected to a three-way adapter can be inserted to allow bladder distention to facilitate the dissection of the detrusor flaps.

Positioning

The child is positioned supine. To facilitate exposure of the bladder, especially in older children and adolescents, a rolled towel may be placed at the level of the upper sacrum or a slight break in the table is used to raise the lower pelvis and hips. All pressure points are appropriately padded, and a wide surgical preparation is performed. The hips are abducted slightly to allow access to the urethra in girls if required; in boys the penis is prepared and draped in the field.

Incision

A Pfannenstiel skin incision, along a skin crease, is made approximately 2 cm above the symphysis pubis to the lateral edges of the rectus muscles. If the child is exceptionally overweight, the classic Pfannenstiel can be extended. The anterior rectus fascia is opened in a transverse fashion and elevated superiorly to just below the umbilicus and inferiorly to the symphysis pubis. The pyramidalis muscles attach between the pubic bone and the anterior rectus sheath. Thus they should not be separated from the rectus sheath. The bellies of the recti are then separated in the midline exposing the bladder. Alternatively, after the skin and Scarpa fascia are incised, the skin can be mobilized off the anterior rectus sheath and the linea alba can be opened in the midline vertically.

INTRAVESICAL PROCEDURES

Approaching the Ureters

The peritoneum is gently swept off the dome of the bladder. This is easier with a moderately full bladder. The bladder is opened in the midline down to approximately 2 cm proximal to the bladder neck. Figure-of-eight stay sutures, using 3-0 Prolene, are placed at the junction of the lateral edges with the bladder dome and at the inferior apex of the incision to prevent extension of the incision into the bladder neck. A Denis Brown retractor provides excellent exposure. Saline-soaked sponges are folded and gently packed into the dome of the bladder and also placed along the lateral edges of the bladder incision. Three blades of the retractor are used to retract the lateral walls of the bladder and the dome. The retractor blades should be placed with the utmost care, and minimal touching, suctioning, or rubbing of the bladder mucosa are recommended to prevent edema or inflammation of the mucosa, which can lead to bleeding and difficult mucosal dissection and may aggravate the bladder spasms in the postoperative period.

Intravesical Mobilization of the Ureter

The ureter(s) is cannulated with a 3- or 5-Fr Silastic feeding tube that is sutured to the bladder mucosa at the inferior edge of the ureteric orifice with 5-0 Prolene. This serves to maintain orientation of the ureter during all phases of the procedure and is used to handle the ureter and apply gentle traction. Before ureteral mobilization, some surgeons inject epinephrine 1:200,000 submucosally to reduce the bleeding. Using needle-point cautery, a circumscribing incision is made in the bladder mucosa approximately 1 to 2 mm away from the ureteric orifice. With gentle traction on the feeding tube, the ureter can be mobilized into the bladder. Mobilization of the ureter is best started at the 6 o'clock position by spreading the blades of the tenotomy scissors gently in a posterior direction initially. Once the correct plane is entered, the dissection is carried out circumferentially. The adventitia of the ureter must not be violated to prevent ischemic injury to the ureter. The ureter is freed from its attachments to the bladder using a fine right-angle clamp and electrocautery. This is aided by gentle traction on the feeding tube. Dissection of the ureter is continued until it can reach the contralateral bladder wall without tension. At that point the surgeon is ready to develop the submucosal tunnel using the same ureteral hiatus or a suprahiatal technique, depending on experience and preference.

SUPRAHIATAL TUNNELS

Politano-Leadbetter Technique

The principle behind this technique, which was originally described by Politano and Leadbetter (1958), is to bring the ureter in through a new hiatus superior to the original insertion. A submucosal tunnel is created in the direction of the trigone, medial to the original orifice. The advantage of this technique is that a long tunnel can be created, which is valuable in the higher grades of reflux. This anti-reflux mechanism can be further supported by a psoas hitch.

Technique

After completion of the ureteral mobilization intravesically, the location of new hiatus is selected in a **straight line superior to the original orifice** (Fig. 137-17). With the bladder open and the lateral walls retracted, the inexperienced surgeon might be inclined to position the new hiatus too laterally on the posterior wall. Once the bladder is closed and full, the ureter enters on the anterolateral wall and then hooks back posteriorly toward the trigone, creating the classic "hooking," which is an important cause for postoperative ureteral obstruction. In the original description of the Politano-Leadbetter technique, the new hiatus was created blindly by passing a right-angle clamp from the original hiatus behind the bladder to

puncture through the posterior wall of the bladder at the new hiatal opening. This blind maneuver must be discouraged because it is the cause of significant complications that may be associated with this procedure, such as routing the ureter intraperitoneally, injury to bowel, vas deferens, vagina, or other nearby structures. The current approach is to retract the superior lip of the original hiatus with a stay suture or a vein retractor and clear the back wall of the bladder bluntly under direct vision. A right-angle clamp is then used to create a new hiatus through which the ureter enters the bladder. The submucosal tunnel is created in the direction of the trigone, medial to the original orifice. The length of the tunnel depends on the diameter of the ureter. A 5:1 ratio (length to width) as suggested by Paquin (1959) is a helpful guide. It is important to lift the mucosa off the detrusor at the point of entry of the ureter into the bladder so that the mucosa can be closed properly over the new hiatus. The tunnel should be capacious enough to prevent constriction of the ureter. The ureter is pulled through the tunnel, and the feeding tube is removed.

Ureteral Anastomosis

The ureter is spatulated ventrally (at the 6 o'clock position), and the edges are freshened if necessary. Three interrupted sutures of 5-0 polyglactin placed relatively close to each other anchor the ureter to the trigone by suturing it to the bladder muscle and mucosa. The anchoring sutures should be placed carefully because the apex of the spatulation is the narrowest point of the ureter. The remainder of the ureteral anastomosis is carried out with interrupted 5-0 polyglactin sutures at the 3-, 9-, and 12-o'clock positions. The 12-o'clock suture also may be used to evert the anterior wall of the ureter, thus creating a small cuff. Although a 5-Fr feeding tube passed up the ureter confirms patency and absence of kinks, the most reassuring sign that the ureteral reimplant is not obstructed is to see the jet of urine emerging from the orifice. It is thus important to communicate to the anesthesiologist the importance of adequate fluid administration throughout the case. The mucosa overlying the new hiatus is closed with a running 5-0 polyglactin suture. The bladder is closed in two layers using a 3-0 polyglactin suture. A Foley catheter is used to drain the bladder for 48 hours; drains and stents are only employed for the more complex cases.

Paquin Technique

Please see the Expert Consult website for details.



INFRAHIATAL TUNNELS

Glenn-Anderson Technique

In 1967 Glenn and Anderson described their technique of ureteral reimplantation (Fig. 137-18). By using the same hiatus and advancing the ureter distally toward the bladder neck, the potential complications associated with the Politano-Leadbetter technique, specifically kinking of the ureter, are avoided. The ureter is mobilized as described earlier. A submucosal tunnel is created toward the bladder neck using tenotomy scissors. The distance from the hiatus to the bladder neck limits the length of the tunnel. Glenn and Anderson (1978) later described a modification that allows creation of a longer tunnel by incising the detrusor proximally at the original hiatus. The detrusor edges are then reapproximated distal to the ureter. With advancement of the ureter toward the bladder neck, the distal anastomosis of the ureter could be challenging with this technique. As with the other procedures, the results with this technique are excellent, with a 98% success rate (Gonzales et al, 1972).

Cohen Cross-Trigonal Technique

Cohen's technique (1975) overcomes the limitation of the tunnel length in the Glenn-Anderson technique by directing the tunnel across the trigone toward the contralateral bladder wall (Figs. 137-19

Paquin described this combined extravesical/intravesical technique in 1959 (Paquin, 1959). The new ureteral hiatus is created from outside the bladder, thus avoiding the difficulties associated with this maneuver in the Politano-Leadbetter technique. As with most of the other open techniques, a success rate greater than 95% for primary VUR is achieved with this method (Woodard and Keats, 1973).

The ureter in the Paquin technique can be approached extravesically (see Extravesical Procedures) before opening the bladder. A right-angle clamp is applied at the UVJ, the ureter is divided, and a 3-0 polyglactin suture is used to suture ligate the original hiatus. The bladder is then opened in the midline, and a new hiatus is created, located cephalad to the prior position. The peritoneum is carefully cleared off the back wall of the bladder at the site of the new hiatus. A right-angle clamp is passed from inside the bladder under direct vision, and one end of a 5-mm Penrose drain is pulled into the bladder. A mosquito snap is applied to the Penrose drain, which acts as a holder and facilitates the creation of the submucosal tunnel. The mucosa is dissected off the detrusor circumferentially at the new hiatus. The length of the submucosal tunnel is governed by the diameter of the ureter, and a 5:1 ratio is usually achievable. In more complex cases a psoas hitch may be required to achieve a longer tunnel length. The tunnel is developed by carefully lifting the mucosa off the detrusor using tenotomy scissors. Countertraction on the mucosa is helpful, especially in cases that must be redone and when the bladder wall is trabeculated. Once the tunnel is developed the remainder of the reimplants is similar to the Politano-Leadbetter procedure.

The modified Paquin technique is particularly suited for dilated ureters and complex (El-Sherbiny et al, 2002) and failed reimplants (Mesrobian et al, 1985) because of the versatility offered by the combined extravesical/intravesical approach to the ureter and the ability to achieve longer submucosal tunnel lengths.

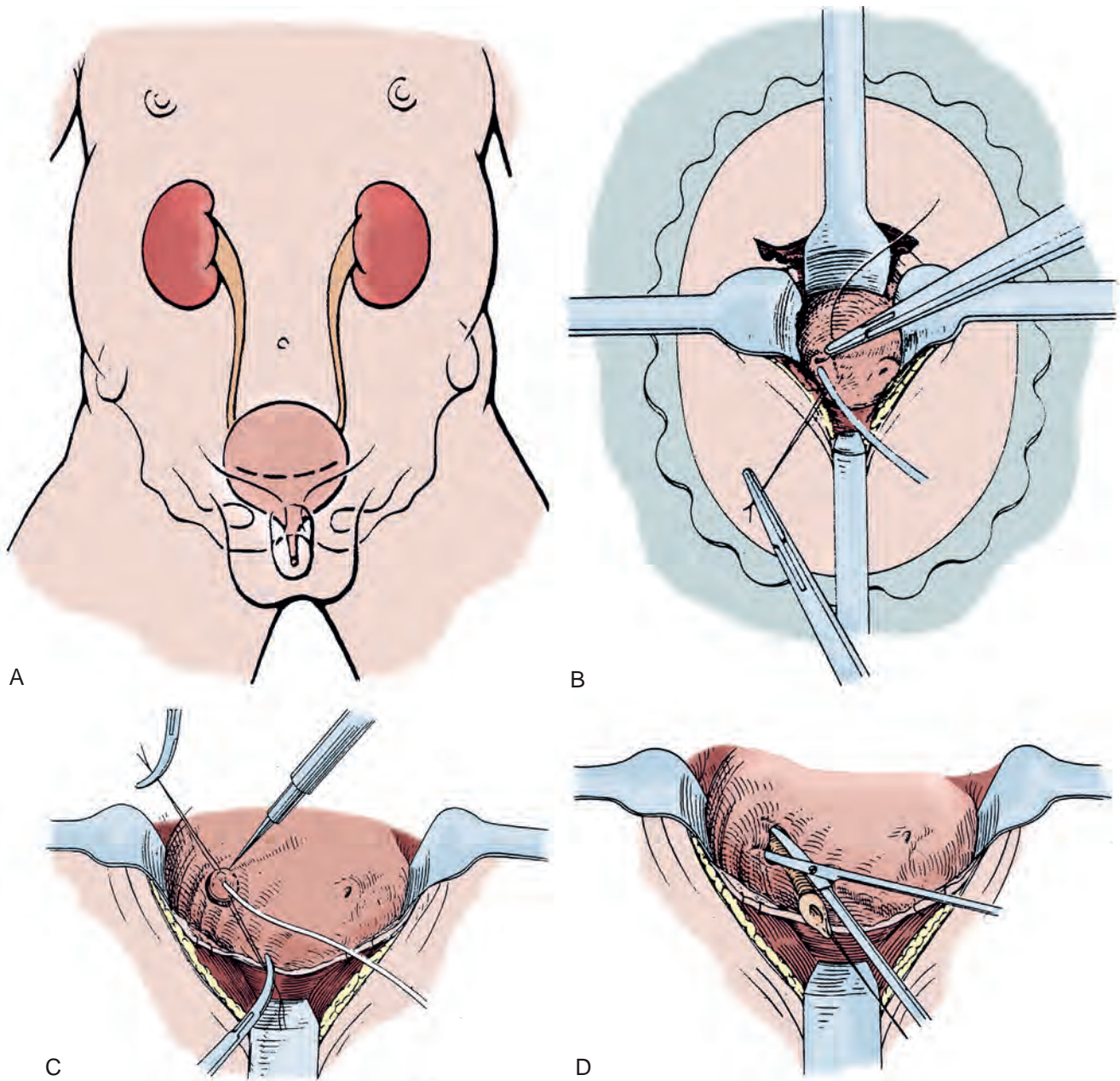


Figure 137-17. Politano-Leadbetter technique. A, Typical approach to the bladder for reimplantation. A transverse, lower abdominal incision (*dashed line*) is made along a skin crease one or two fingerbreadths above the symphysis pubis. B, Fine sutures are placed above and below the ureteric orifice for handling. A feeding tube in the ureter aids in the initial dissection. C, A needle-tip cautery outlines a circumferential incision around the orifice. D, Tenotomy scissors initially establish the plane of dissection inferiorly, where ureteral damage can be avoided. The plane is then carried around the ureter.

Continued

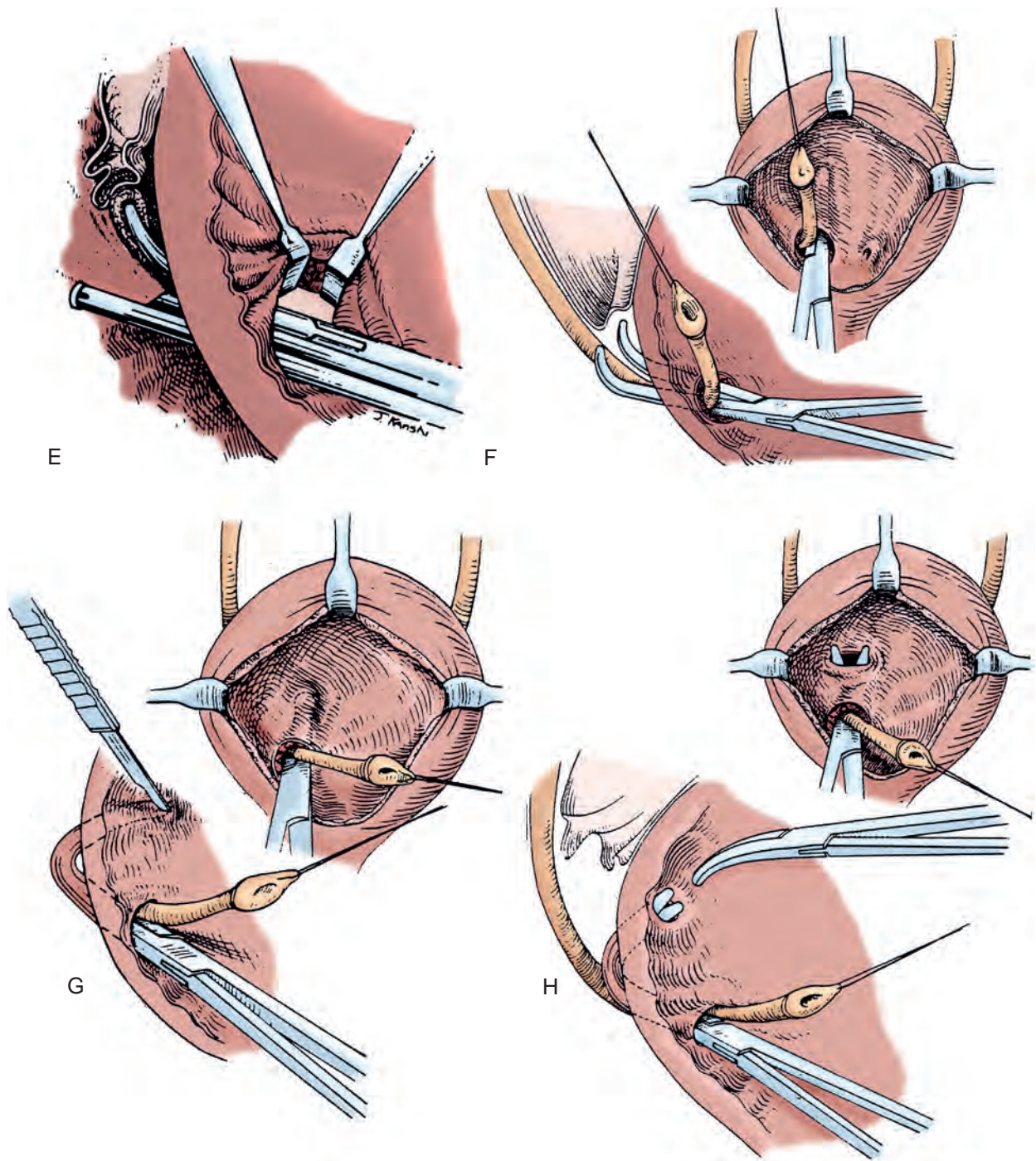


Figure 137-17, cont'd E, With the aid of a lighted suction tip and two Senn retractors, a fine gauze dissector is used to sweep the peritoneum from the posterior bladder wall. F, After sweeping the peritoneum away, a blunt right-angle clamp indents the bladder from behind at a new hiatus approximately 2.5 cm superior and somewhat medial to the original hiatus. G, The clamp is incised on from within and generously spread to make certain that the new hiatus is wide enough. H, A second right-angle clamp follows the first from within the bladder to the original hiatus.

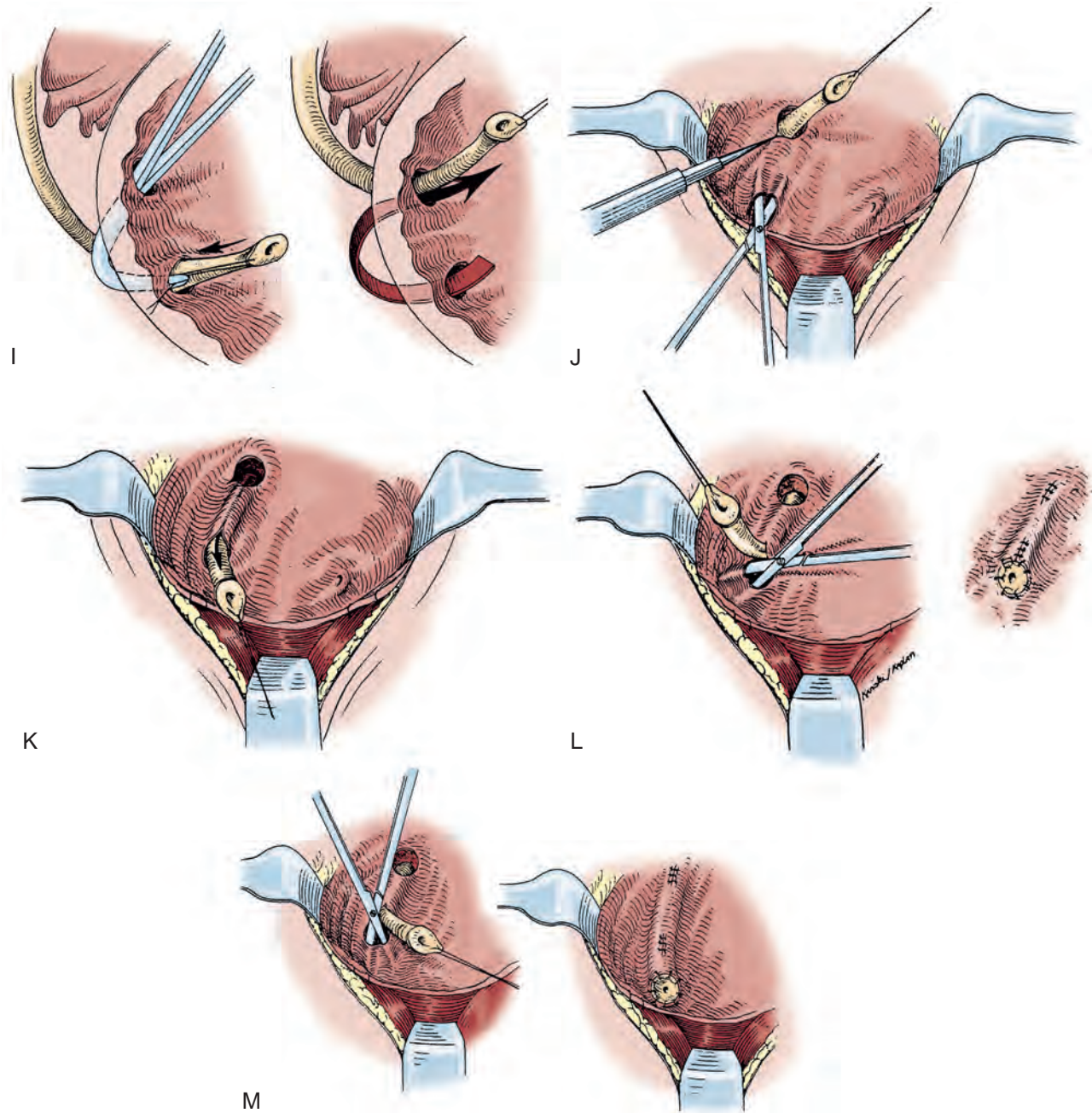


Figure 137-17, cont'd I, The right-angle clamp grasps the stay suture, and the ureter is pulled through the new hiatus. J, The inferior lip of muscle at the new hiatus is divided for a few millimeters to eliminate any ureteral angulation at its entrance to the submucosal tunnel that is created with scissors. K, The ureter is brought through the new tunnel to the original hiatus. L, The ureter is anastomosed to the original hiatus in the classic Politano-Leadbetter technique. Proximal mucosa can be closed over the ureter to give the tunnel additional length. M, Ureteral advancement is also helpful, especially if the original hiatus is laterally positioned. A second submucosal tunnel can be created toward the bladder neck to place the new orifice in a more inferior position and gain additional length for the reimplant. (A to D and F to M, from Retik AB, Colodny AH, Bauer SB. *Pediatric urology*. In: Paulson DF, editor. *Genitourinary surgery*, vol. 2. New York: Churchill Livingstone; 1984. p. 757-63; E, from Keating MA, Retik AB. *Management of failures of ureteroneocystostomy*. In: McDougal WS, editor. *Difficult problems in urologic surgery*. Chicago: Year Book; 1989. p. 121.)

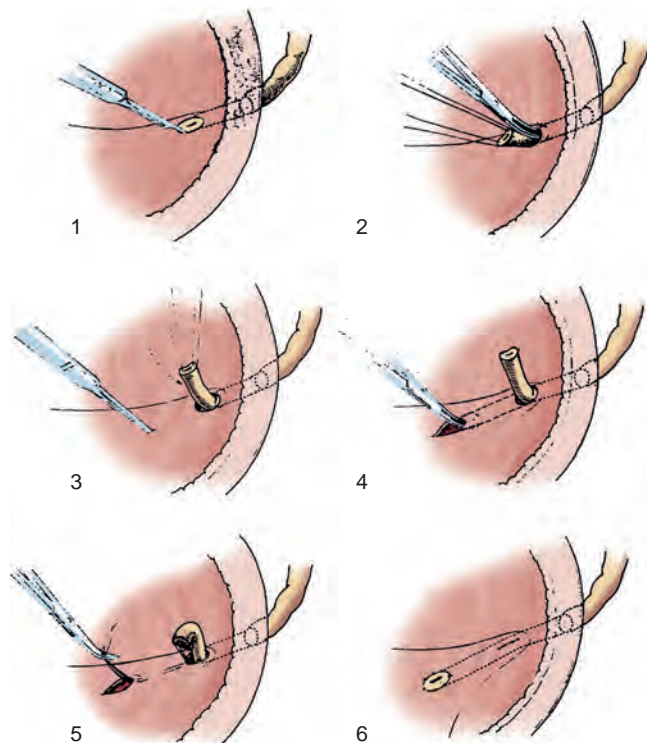


Figure 137-18. Glenn-Anderson technique. The ureter is mobilized and advanced beneath a new submucosal tunnel. (From Glenn JF, Anderson EE. Distal tunnel ureteral reimplantation. *J Urol* 1967;97:623.)

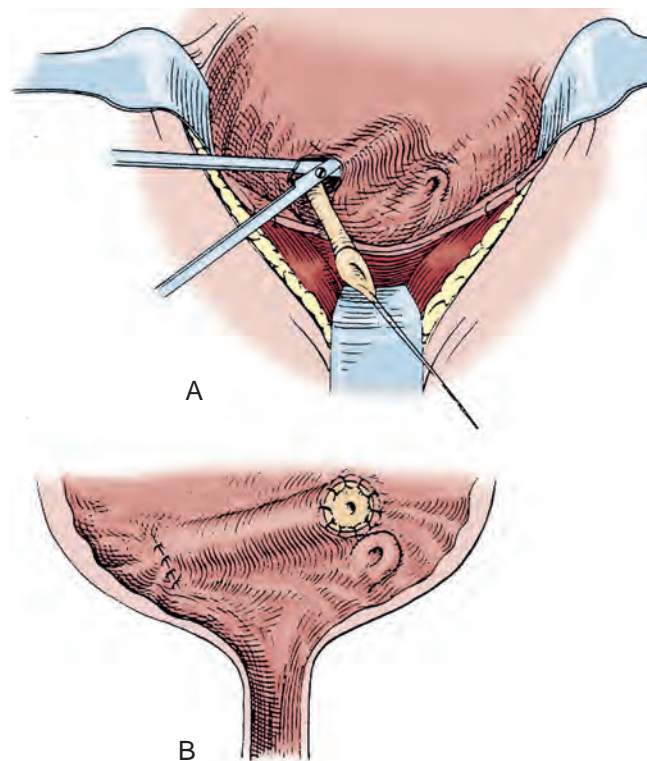


Figure 137-19. Cohen cross-trigonal technique, unilateral reimplantation. After the ureter is freed (A), a submucosal tunnel is made, with the new mucosal hiatus just above the contralateral ureteral orifice (B). (From Retik AB, Colodny AH, Bauer SB. *Pediatric urology*. In: Paulson DF, editor. *Genitourinary surgery*, vol. 2. New York: Churchill Livingstone; 1984. p. 764.)

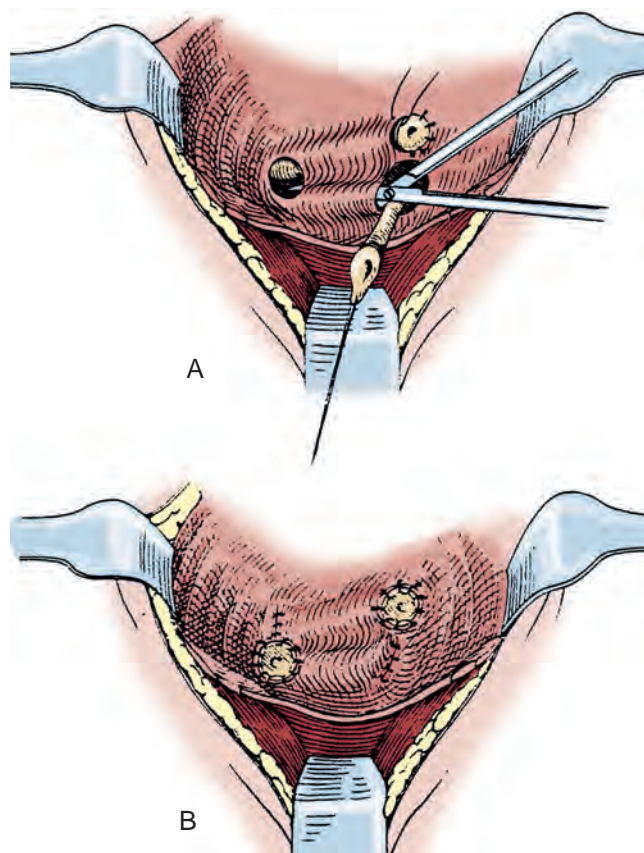


Figure 137-20. Cohen cross-trigonal technique, bilateral reimplant. A, The more superior ureter is tunneled transversely, with its new orifice just above the contralateral orifice. B, The other ureter is tunneled inferiorly, with its new orifice located at the inferior-most portion of the contralateral hiatus. (From Retik AB, Colodny AH, Bauer SB. *Pediatric urology*. In: Paulson DF, editor. *Genitourinary surgery*, vol. 2. New York: Churchill Livingstone; 1984, p. 765.)

and 137-20). The difficulty with the distal anastomosis in the Glenn-Anderson technique is also eliminated.

Cohen's technique is particularly suited for small or thick-walled bladders (PUV or neuropathic) because the ureteral advancement across the back wall of the bladder rarely results in kinks or obstruction. The cross-trigonal reimplant is also the procedure of choice in conjunction with bladder neck reconstructive procedures because the superior displacement of the ureters provides room for adequate elongation of the bladder neck.

As a result of its simplicity and reliable results (up to 99% [Glassberg et al, 1985; Kennelly et al, 1995; McCool and Joseph, 1995; El-Ghoneimi et al, 1999]), Cohen's procedure has become the most commonly employed intravesical reimplant.

Critics of this technique cite the difficulty of retrograde catheterization of the superolaterally positioned ureteral orifice for radiographic studies, insertion of stents, and management of ureterolithiasis as significant disadvantages. Suggested approaches to overcome this include suprapubic cystostomy by trocar (Lamesch, 1981) or 14-gauge, 5-cm intravenous cannula in conjunction with cystoscopy to direct the ureteral catheter into the ureter or by using a curved-tip vascular access catheter and an angle-tipped glide wire with a torque device (Wallis et al, 2003) or the use of a flexible ureteroscope.

Method

1. The technical methods of the Cohen and Glenn-Anderson procedures are similar in many aspects.
2. The ureter is approached and mobilized using the standard intravesical approach.

3. A hiatal groove may be created on the medial side of the ureter to reduce the angulation of the ureter as it crosses transversely, especially when the bladder wall is thickened. If the hiatus is excessively patulous, it can be reapproximated with one or more interrupted 3-0 polyglactin sutures to avoid diverticulum formation (Ahmed and Tan, 1982). The hiatus should easily accommodate the tips of a large right-angle clamp alongside the ureter to avoid obstruction of the ureter.
4. The submucosal tunnel is developed using the tenotomy scissors as previously described. When only one ureter is reimplanted, the tunnel is directed superior to the contralateral ureteric orifice. If both ureters are reimplanted, the tunnel for the more laterally displaced ureter is directed superior to the contralateral orifice. The second tunnel is directed toward the inferior edge of the orifice of the laterally displaced ureter. A common submucosal tunnel has been used successfully for bilateral reimplants (Androulakakis et al, 2003).
5. The ureter is spatulated and anastomosed to the bladder mucosa as described in the Politano-Leadbetter technique. The mucosa over the old hiatus is closed with 5-0 polyglactin sutures.
6. Alternatively, the mucosal cuff of the ureteric orifice may be preserved and anastomosed to the bladder mucosa without spatulation.
7. The ureter is catheterized with a 5-Fr feeding tube to ensure patency, although the continuous efflux of urine from the orifice provides the best assurance of patency.
8. Closure of the bladder and drainage is completed as described previously.

EXTRAVESICAL PROCEDURES

Lich and colleagues (1961) in the United States and Gregoir (1964) in Europe independently described the extravesical approach to ureteral reimplantation (Fig. 137-21). The technique became more popular after the modifications described by Daines and Hodgson (1971), and Zaontz and colleagues (1987) popularized anchoring the ureter with advancement sutures. These modifications allow for a combined advancement of the ureter and lengthening the tunnel proximally. In addition, anchoring sutures fix the ureter distally and thus maintain stability of the tunnel. The advantage of the extravesical technique is that the bladder is not opened; thus postoperative hematuria and bladder spasms are minimized. The technique is simple to learn and is readily taught.

The main concern with this technique has been the development of transient voiding inefficiency that is seen in up to 20% (Fung et al, 1995; Lapointe et al, 1998; Lipski et al, 1998; Barrieras et al, 1999; Marotte and Smith, 2001) of children who undergo bilateral extravesical reimplants. The mechanism is thought to be due to disruption of the nerves to the bladder bilaterally, possibly resulting from excessive use of cautery during the detrusorotomy. The population most at risk appears to be boys younger than 3 years of age with bilateral high-grade reflux (Barrieras et al, 1999).

Leissner and colleagues (2001) used human cadavers to study the topography of the pelvic plexus in an effort to understand the mechanism of injury to the plexus resulting from extravesical reimplant surgery. They demonstrated that the main portion of the pelvic plexus is located approximately 1.5 to 2 cm dorsal and medial to the UVJ in adult cadavers. Smaller branches travel along the medial aspect of the ureter, outside the thin layer of tissue (the mesoureter) that surrounds the ureter. On the basis of their anatomic description, injury to the branches of the pelvic plexus is avoided if dissection of the distal ureter is carried out between the mesoureter and ureteral adventitia. Yucel and Baskin (2003) further refined the description of the neuroanatomy of the distal ureter and UVJ using immunohistochemical analysis and 3D imaging techniques in normal human fetuses (21 to 40 weeks of gestation). They confirmed the localization of the nerves along the medial aspect of the ureter just outside the Waldeyer sheath. At the UVJ the nerves surround the ureter in a network-like fashion; distally, once the ureter enters the bladder, the nerves localize on the detrusor muscle

distal and lateral to the ureter. From these two studies it is suggested that the incidence of voiding inefficiency observed after bilateral extravesical reimplants depends on the surgical technique. The injury is limited to the smaller nerve branches rather than the actual pelvic plexus, which is located medially and posteriorly. The neural damage may be due to transection of the nerves, electrocautery, or neuropraxia caused by surgical trauma. Injury to the nerves may be prevented by limiting the dissection to the correct plane, just outside the ureteral adventitia, reducing the use and power of electrocautery, restricting the incision of the detrusor distal to the UVJ, and gentle handling of the tissues (David et al, 2004).

Patients who develop urinary retention, requiring insertion of a Foley catheter or intermittent catheterization, are able to void within 1 to 2 weeks (Minevich et al, 1998a; Barrieras et al, 1999), indicating the reversibility of the neurologic lesion.

Approaching the Ureters

A Pfannenstiel incision is used as described earlier. It is best to have the bladder somewhat distended to this point to facilitate dissection of the peritoneum of the lateral bladder wall. The obliterated umbilical artery is identified. The ureter crosses medial to the point of origin of the obliterated umbilical artery from the internal iliac artery. This is an excellent anatomic reference point for identification of the distal ureter. Dividing the obliterated umbilical artery facilitates dissection and mobilization of the ureter. Some authors were concerned that the injury to the bladder innervation occurs when the obliterated umbilical artery is divided. However, Lipski and colleagues (1998) demonstrated that there was no difference between two groups of patients regardless of whether the obliterated umbilical artery was divided. The peritoneum is meticulously reflected off the anterior surface of the ureter. To avoid injury to any of the branches of the pelvic plexus, it is recommended that the surgeon stay right on the ureter during its dissection while being careful not to injure blood vessels running in the ureteral adventitia. A vessel loop is passed around the ureter and used as a handle. Dissection and mobilization of the ureter is carried distally to the point where it tunnels under the detrusor muscle.

Creation of the Extravesical Tunnel

With the bladder in its normal anatomic position, the course of the ureter along the posterior wall of the bladder is identified and marked for a distance of 5 cm. The bladder is reflected medially; a Denis Brown retractor is quite helpful for this procedure. The outlined course of the ureter is inspected. The peritoneal reflection may need to be gently lifted off the wall of the bladder. With the bladder retracted, the tunnel direction will appear to be pointing toward the anterior abdominal wall. It is important to have the bladder full and somewhat tense but not overstretched. The detrusor is incised using low-current electrical cautery (15 W) to create the new submucosal tunnel. After that, tenotomy scissors are used to divide the detrusor fibers along the same line of the initial incision down to the bladder mucosa. Care should be taken to incise the detrusor fibers along one line, without wandering sideways, to facilitate lifting the detrusor off the mucosa with minimal disruption to the detrusor muscle and its innervation. Blood vessels are easily seen as one incises the detrusor fibers, and these are cauterized selectively with bipolar cautery. It is critical that all detrusor muscle bundles are divided before elevation of the detrusor flaps. When the last detrusor bundles have been divided, a **uniform** mucosal dome bulges out. This provides the surgeon with an excellent point of reference that the tunnel has been established in the correct plane.

The detrusor is dissected off the mucosa on either side of the incision, for a width slightly larger than the circumference of the ureter. This dissection is best carried out from proximal to distal, leaving the dissection around the ureter as the final step of the tunnel creation.

There is a definite **avascular** plane between the muscle and the mucosa. The most efficient method to realize this dissection is to

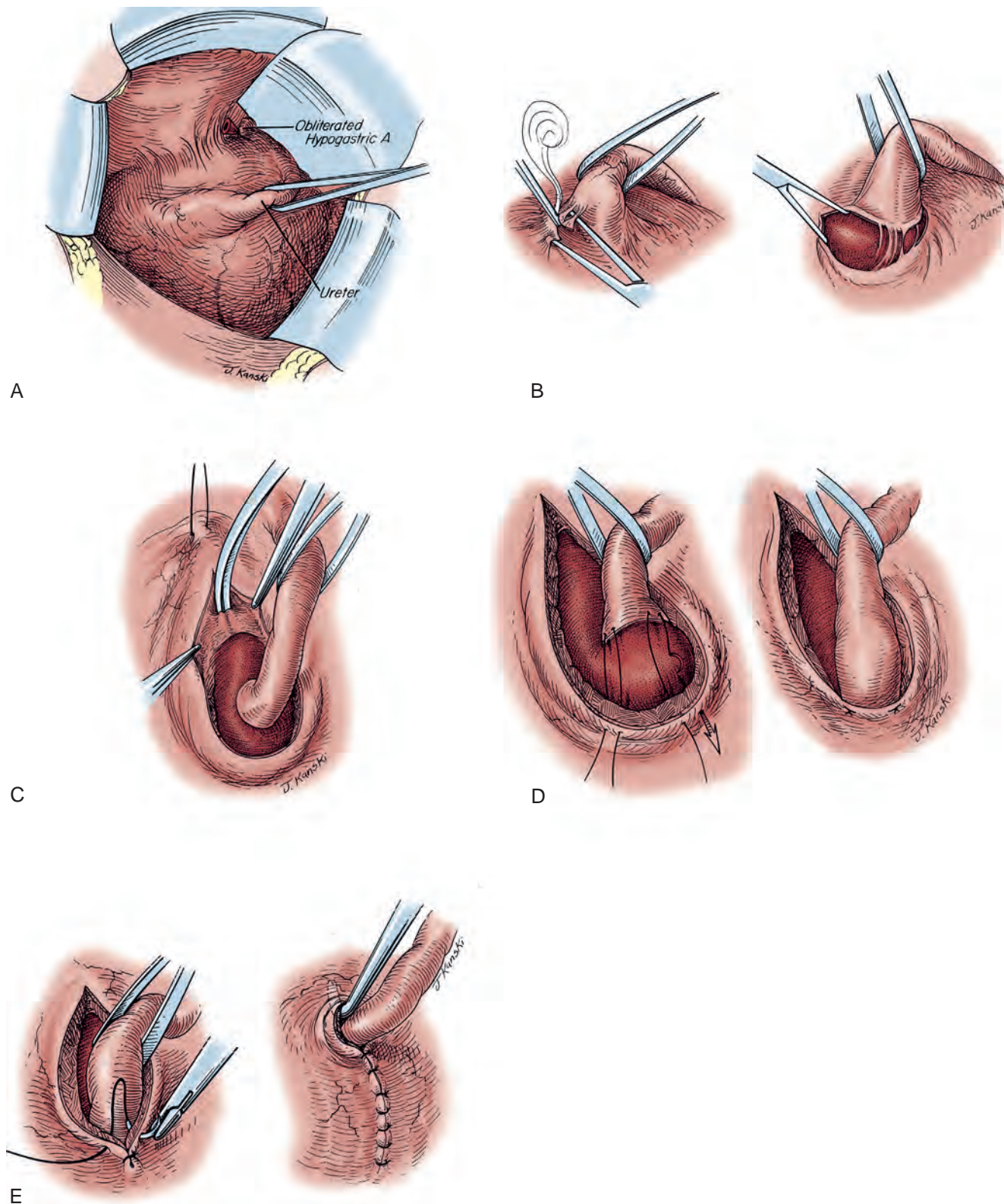


Figure 137-21. Modified Lich-Gregoir/detrusorrhaphy technique. A, The ureter is identified and gently grasped after ligation of the obliterated hypogastric artery. B, The ureter is circumferentially mobilized at its intersection with the bladder by incising the detrusor at the level of the ureteral hiatus. C, The serosal and muscular layers of the bladder (4 to 5 cm) are opened along a straight course cephalad and lateral from the ureterovesical junction to create the trough for reimplantation. A tacking suture aids in orientation. D, The bladder mucosa is elevated off muscle wall, and vest-type sutures are placed from the detrusor at the distal limit of dissection to the proximal ureteral adventitia and back again through the same tissue planes. Tying of the vest sutures advances and anchors the ureter onto the trigone. E, Reapproximation of the detrusor creates a long submucosal tunnel and completes the repair. (From Peters C, Retik AB. Ureteral reimplantation including megaureter repair. In: Marshall FF, editor. Textbook of operative urology. Philadelphia: Saunders; 1996. p. 868–70.)

have the assistant grasp the detrusor bundles closest to the mucosa with two forceps, elevating the muscle off the mucosa. The surgeon gently depresses the mucosal bulge with one hand and uses the tenotomy scissors to sharply separate the muscle bundles off the mucosa, on either side, along the length of the tunnel. Injury to the mucosa during dissection of the tunnel is quite avoidable unless the bladder is thick walled and trabeculated. Inadvertent injury to the mucosa could be closed with a 6-0 polyglactin figure-of-eight suture. It is not necessary to create a wide tunnel unless the ureter is very dilated.

Particular attention is necessary when dissecting around the ureter. The detrusor fibers attached to the ureter are carefully divided, staying close to the ureter to avoid injury to any of the terminal nerve branches entering the bladder. The dissection is carried out along the lateral and medial attachments of the ureter but is not extended distally.

The original modification described by [Zaontz and colleagues \(1987\)](#) for the extravesical procedure included incision of the detrusor distal to the ureteric orifice for 5 to 10 mm with advancement of the ureter using two vest sutures. [Leissner and colleagues \(2001\)](#) demonstrated that this particular aspect of the procedure may be responsible for injury to the bladder innervation at the trigonal area and may be the lead cause of urinary retention in bilateral extravesical reimplants. Therefore, to avoid damage to the nerves, this maneuver should be avoided unless there is a paraureteral diverticulum that requires repair simultaneously ([Jayanthi et al, 1995](#)). In those cases, dissection of the detrusor distal to the ureter should be carried out in a limited fashion.

Once creation of the submucosal tunnel is complete, the bladder is decompressed before reapproximation of the detrusor. The ureter is positioned in the new tunnel, and the detrusor reapproximated using interrupted 3-0 polyglactin sutures. To achieve alignment of the tunnel, it is best to place the most proximal suture first at the new ureteral hiatus and to leave it untied and tagged on a mosquito snap. Tension applied to this suture straightens and elevates the detrusor flaps, allowing the surgeon to reapproximate the detrusor without risk for injury to the ureter or the mucosa. The suturing commences at the most distal portion. The adventitia of the ureter may be incorporated in one or two of these sutures to stabilize the tunnel and prevent a diverticulum from forming at the most distal or proximal portion of it. At the completion of the suture line, the caliber of the hiatus should be tested with a right-angle clamp to ensure absence of any constriction or compression of the ureter.

The bladder is refilled and the retractor is removed. The course of the ureter is reinspected to ensure absence of any kinks in the retroperitoneum or any bulging of the mucosa at either end of the tunnel.

A Foley catheter is left for 24 to 48 hours; some authors recommended not leaving a catheter at all ([Marotte and Smith, 2001](#)). If an epidural caudal catheter is inserted for postoperative analgesia, it should be discontinued 6 to 12 hours before removal of the Foley catheter.

If the child is observed to void without problems, he or she is discharged, to return for a follow-up sonogram and a VCUG usually 3 months postoperatively.

POSTOPERATIVE EVALUATION

In expert hands the success rate for ureteroneocystostomy in patients with low-grade primary VUR approaches 100%. As a result of these outstanding outcomes, several centers have evaluated the need for postoperative invasive imaging. Most agree that a sonogram is necessary at 6 to 12 weeks postoperatively. In a large study by [Barrieras and colleagues \(2000\)](#), 723 renal units were evaluated. At 1 year postoperatively there was a significant difference between children who had undergone surgery for low-grade primary VUR (99% resolution) versus those with high-grade reflux (94%). Thus, in patients who initially had low-grade primary reflux, in whom the preoperative and postoperative ultrasound examinations were normal and do not have voiding dysfunction or recurrent UTIs ([Lavine et al,](#)

[2001](#)), the success rate with uncomplicated ureteroneocystostomy approaches 100% ([Bisignani and Decter, 1997](#); [Bomalaski et al, 1997b](#); [El-Ghoneimi et al, 1999](#); [Barrieras et al, 2000](#); [Grossklauss et al, 2001](#)). On the basis of these reports, it has been suggested that the postoperative VCUG can be avoided in this group of patients. This recommendation should be individualized on the basis of the family situation and the expertise of the center performing the surgery. Some families have followed reflux for several years and are anxious to know with certainty that the reflux has resolved. In other families, the children are quite reluctant to undergo another VCUG, and in this situation it may be reasonable not to perform a postoperative study unless the child has a dysfunctional bladder or develops postoperative hydronephrosis or UTIs. However, the lower success rate for high-grade reflux would still support complete postoperative studies in most cases.

After ureteroneocystostomy, the presence of minimal ureteral dilation and low-grade hydronephrosis on early postoperative ultrasonography is not unusual ([Bomalaski et al, 1997b](#); [Barrieras et al, 2000](#)). Indeed, this common finding should argue against performing such studies too early after surgery. On the other hand, persistence of this dilation beyond 3 months or its progression should be further investigated ([Aboutaleb et al, 2003](#)). Additionally, the development of new renal scars on late follow-up ultrasonography, a discrepancy in renal growth, or recurrent UTIs may warrant complete radiologic re-evaluation of the patient.

As discussed previously, children with renal scarring should have their blood pressure measured at every visit with their family physician.

COMPLICATIONS OF URETERAL REIMPLANTATION

Early Complications

Persistent Reflux

Early reflux after ureteroneocystostomy usually is not a significant clinical problem and commonly resolves by 1 year on repeat cystography. In the report by [Barrieras and colleagues \(2000\)](#), 49 of 723 renal units had reflux at 3 months, 11 of which were contralateral. At 12 months' follow-up, reflux resolved spontaneously in 20 of the 38 ipsilateral and in 8 of the 11 contralateral ureters. Persistent reflux at 1 year was more common in patients who had high-grade reflux preoperatively. In their study 30% of patients undergoing surgery had high-grade reflux. Two thirds of those with persistent reflux at 1 year (12 of 18) were from that group. Thus the majority of low-grade postoperative reflux detected in the initial VCUG at the 3-month follow-up point disappeared spontaneously, likely because of the resolution of the bladder inflammation and improvement in bladder dysfunction that may be present in the early postoperative period.

Contralateral Reflux

The issue of contralateral reflux has been the subject of several reports in the literature over the past 15 years, most of which are retrospective ([Hubert et al, 2014](#)). [Minevich and colleagues \(1998b\)](#) and [Burno and colleagues \(1998\)](#) noted a low incidence of contralateral reflux after unilateral extravesical detrusorrhaphy in 5.6% and 11.6% of their patients, respectively. [Diamond and colleagues \(1996b\)](#), in a multicenter trial of 141 patients, reported an 18% incidence of contralateral VUR. These patients were analyzed according to grade of initial reflux, presence of a Hutch diverticulum or duplex system, and the surgical technique employed to correct the reflux. No difference was noted among the various surgical techniques, but there was a significant trend toward development of contralateral reflux with the higher grades of ipsilateral corrected reflux and correction of reflux in duplex systems. They concluded that the distortion of the contralateral hemitrigone was not a responsible factor for contralateral reflux but rather the severity (grade 5) of reflux, and the presence of a duplex system put patients at risk for development of contralateral reflux postoperatively. Conversely,

Kumar and Puri (1997) reported on 495 children with unilateral reflux who had undergone subureteral Teflon injections. New contralateral reflux was diagnosed in only 37 children (7%). They were unable to find any correlation between the grade of preoperative ipsilateral reflux and postoperative contralateral reflux and suggested that low incidence of new contralateral VUR may be due to a relative noninterference with the contralateral trigone afforded by endoscopic compared with open reflux correction. They refuted the existence of the pop-off mechanism accounting for new contralateral reflux in their series because the risk for new contralateral reflux did not correlate with the preoperative reflux grade (grades 4 and 5). Sparr and colleagues (1998) reviewed a series of 143 patients on conservative management and initially diagnosed with unilateral reflux but subsequently developed metachronous contralateral reflux. Contralateral reflux appeared in 33%, suggesting a different cause for the appearance of contralateral reflux unrelated to surgical correction. They speculated that the contralateral reflux was in fact synchronous (i.e., bilateral) but missed on initial cystogram or that the natural history of unilateral or bilateral reflux may involve intermittent appearance and disappearance of VUR on one side.

Prophylactic bilateral reimplantation for unilateral reflux, to avoid contralateral reflux, is not warranted on the basis of the high spontaneous resolution rates (Burno et al, 1998). Recommendations for management of contralateral reflux range from observation in the majority of cases to intervention for control of clinical pyelonephritis episodes. In asymptomatic children, younger than 4 to 5 years of age, prophylactic antibiotics are warranted for postoperative contralateral reflux, particularly if one is to be consistent with the medical therapy for the previous ipsilateral reflux. If the child remains asymptomatic and infection free, repeat VCUGs may not be necessary because contralateral reflux resolves spontaneously in the majority of children. In girls around the age of puberty, controversy persists as to whether a VCUG and correction of reflux at that point become necessary. In a recent report by Hubert and colleagues (2014) from Boston, new contralateral reflux was observed in 10% of the children (18% grade 1, 70% grade 2, and 12% grade 3). Younger age (<6 years) and low observed bladder capacity (<50% of predicted capacity) were significant predictors of contralateral reflux on multivariable analysis. Follow-up cystography documented resolution of contralateral reflux in almost 80% at a median of 21.5 months, confirming the benign nature of this vexing problem.

Obstruction

It is not unusual to detect a mild-to-moderate degree of hydronephrosis in the early postoperative period by ultrasonography (see earlier discussion). This should resolve spontaneously with time. Acute postoperative obstruction may be related to technical issues such as twisting or kinking of the ureter in its new tunnel, intramural blood clots, or extramural compression by submucosal hematoma or edema at the site of anastomosis. Progressive, significant obstructions usually become apparent in the first 2 weeks after surgery. The children typically present with symptoms of acute ureteral obstruction, including acute abdominal pain, nausea, and vomiting. Although infection is less common, if it occurs it is quite significant in the obstructed system. The diagnosis is readily made on ultrasonography, and the severe hydroureteronephrosis is confirmed by delayed function and excretion on renal scintigraphy. In the more significant cases, drainage of the system either by retrograde insertion of a double-J stent or a percutaneous nephrostomy tube may be necessary. The nephrostomy tube should be internalized as early as possible to avoid a dry reimplant. Many of these cases resolve without requiring additional surgery.

LONG-TERM COMPLICATIONS

Obstruction

Progressive dilation of the ureter and kidney after reimplantation surgery can be due to several factors and can be classified on the basis of the location of the obstructive lesion.

Suprahiatal

Twists of the ureter and ischemia result from poor handling of the ureter and are the most common causes of suprahiatal obstruction.

Hiatus

At the point of entry into the new hiatus, angulation of the ureter occurs, most commonly as a result of a hiatus that is positioned too lateral or anterior such that when the bladder fills, the ureter becomes carried laterally and anteriorly, resulting in the "high reimplant" phenomenon. These ureters drain better when the bladder is empty. This situation may resolve spontaneously but on occasion requires stenting or repeat surgery.

Tunnel

A submucosal tunnel that is not adequately developed can lead to compression of the ureter causing obstruction within the tunnel. The submucosal tunnel is obviously more difficult to develop in an abnormal bladder such as the valve or neuropathic bladder. Developing a smooth, capacious, submucosal tunnel can be quite challenging because of the irregularities created by the muscular hypertrophy, trabeculation, and cellulite formation. Ischemia to the ureter and the submucosal tunnel is another important factor that results from improper handling of the ureter, leading to its devascularization. Significant obstruction in the submucosal tunnel can be overcome by balloon dilation and stenting for a time. If conservative measures are unsuccessful, reimplantation is required.

Orifice

The anastomosis of the ureter to the bladder and the new hiatal position is an important technical aspect of the reimplant procedure. The most vulnerable point for obstruction is the apex of the ureteral spatulation. The apical sutures must be placed with the utmost care to ensure an adequate orifice caliber. Stenosis also can occur as a result of ischemic changes. Isolated obstruction of the orifice can be managed by dilation and stenting. If the submucosal tunnel is of adequate length, endoscopic unroofing of the distal few millimeters, including the orifice, may relieve the obstruction while maintaining the antireflux mechanism.

Recurrent or Persistent Reflux

Failure of antireflux procedures in primary low-grade reflux is extremely rare. Most failures are due to either high-grade reflux or an inadequate ratio of tunnel length to ureteral diameter. Development of a short tunnel and failure to taper the excessively wide ureter are obvious important factors. Another significant cause of persistent or recurrent reflux is failure to recognize secondary reflux, especially associated with neurogenic bladders and PUV bladders. **Reflux in these situations is secondary to the poor storage or emptying characteristics of the bladder. These issues need to be addressed and optimized before reimplant surgery is attempted.** In most situations, improving bladder storage and/or emptying with a combination of an anticholinergic agent and intermittent self-catheterization results in spontaneous resolution of secondary reflux (Agarwal et al, 1997). Proceeding with reimplantation surgery in the presence of an abnormal bladder results only in worsening of the ureteral dilation and deposition of scar tissue in the pelvis, which would render future attempts at correcting the reflux even more difficult.

REDO REIMPLANTATION

Redo reimplantation is technically more challenging and requires careful attention to detail and meticulous surgical technique. Dissection of the ureter and extensive mobilization are required to achieve an adequate submucosal tunnel. Careful dissection of the ureter is best accomplished by a combination of extravesical and

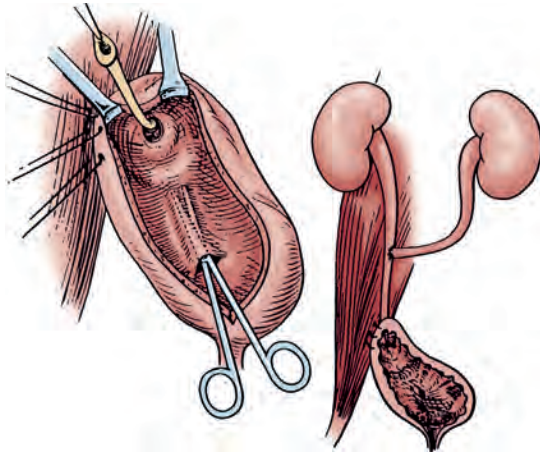


Figure 137-22. A psoas hitch can be used to effectively bridge significant ureteral defects. Its combination with transureteroureterostomy is ideal when both ureters are addressed in a reoperative setting. (From Keating MA, Retik AB. Management of failures of ureteroneocystostomy. In: McDougal WS, editor. Difficult problems in urologic surgery. Chicago: Year Book; 1989. p. 140.)

intravesical mobilization as needed. The ureter should be carefully evaluated and ischemic segments excised. Free bleeding from the divided distal end should be observed in addition to peristaltic activity, ensuring normal musculature and blood supply. It is preferable to create a new hiatus and submucosal tunnel. If the ureter is shorter, a psoas hitch (Fig. 137-22) can be used to facilitate the creation of the antireflux mechanism. The psoas hitch should be carried out with nonabsorbable suture before creation of the submucosal tunnel. The bladder is fixed to the psoas muscle sheath on either side of the iliac vessels, providing a stable posterior bladder wall. In children, the bladder can be mobilized sufficiently to bring it up almost to the bifurcation of the common iliac vessels. This may provide adequate bridging for a distal ureteral defect. A psoas hitch can be achieved only on one side. Attempting a psoas hitch on both sides will not provide adequate length on either side and thus should be avoided. If both ureters are shortened, consider a psoas hitch on one side to achieve a satisfactory antireflux mechanism with a transureteroureterostomy for the other ureter.

Other techniques to consider for the short ureter include the Boari flap, in which a flap extending from the dome to the anterior wall of the bladder based on the posterior wall can be rotated proximally. The flap should be wide enough to allow creation of a submucosal tunnel and tubularization of this flap. In the short ureter a nipple valve can be created in association with a short submucosal tunnel. The nipple valve is particularly useful in dilated ureters and is fashioned by spatulating the ureter and folding it back onto itself.

In situations in which the ureter is significantly foreshortened, it can be replaced using a reconfigured segment of bowel as described by Pope and Koch (1996). The colon or ileum is reconfigured similar to the Monti procedure. This technique offers important advantages over the classic tapered ileal ureter, allowing a long tube to be created from a short segment of colon without tapering, thus eliminating the metabolic consequences; additionally, the mesentery is in the center of the tube, which facilitates creation of the submucosal tunnel.

ENDOSCOPIC TREATMENT OF VESICoureTERAL REFLUX

(See Fig. 137-23.)

Matouschek (1981) first described the injection of polytetrafluoroethylene (PTFE) paste at the ureteral orifice to correct VUR. O'Donnell and Puri (1986) popularized the technique when they

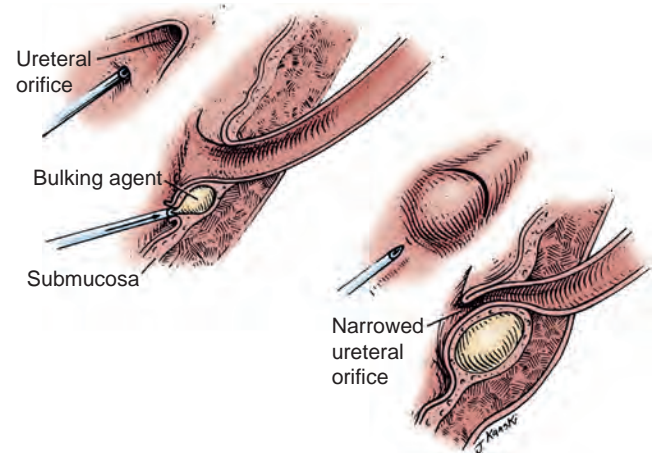


Figure 137-23. Principle of endoscopic treatment of reflux. A bulking agent is injected beneath the ureteral orifice with a needle. The buttress that is provided helps coapt the distal end of the ureter.

published their initial report on the successful endoscopic correction of primary VUR in 103 ureters with a success rate of 75% after one injection. They coined the term *STING* (Subureteric Teflon Injection). This procedure became popular in many countries but never achieved widespread use in the United States because of lack of U.S. Food and Drug Administration (FDA) approval over concerns regarding the potential migration of PTFE particles (Malizia et al, 1984a, 1984b; Aaronson et al, 1993). The ability to correct reflux in a large proportion of patients (the more recent studies report success rates approaching 90% after one injection of Deflux in low-grade primary reflux [Kirsch et al, 2004]) on an outpatient basis using a simple procedure with minimal morbidity prompted the search for safer materials. One caveat when evaluating the reported results of endoscopic correction is to interpret with caution reports in which the authors regard downgrading of reflux to grade 1 or 2 (Sweden) as a successful outcome. Because this would not be acceptable to most surgeons performing open surgery, the definition of success should be applied uniformly.

Because of the minimal morbidity of the procedure, the benefit of endoscopic injection in newly diagnosed patients has been evaluated using computer modeling with a view to reduce the morbidity and cost of repeated VCUGs and long-term antibiotics (Kobelt et al, 2003). Rigorous comparisons of various treatment approaches need to be undertaken, and until the outcomes of such studies are available, the indications for correction of reflux should remain unchanged, whether reflux is corrected by open surgery, endoscopy, or laparoscopy.

Two key challenges with endoscopic treatment of reflux are reproducibility and durability of the results. Long-term follow-up will determine whether endoscopic therapy, with the currently available materials, will stand the test of time or if open surgery with its 95% to 99% success rate will remain the most cost-effective way of permanently correcting reflux.

Technique of Endoscopic Injection

The classic STING technique was described by O'Donnell and Puri (1984) (Fig. 137-24). Prophylactic antibiotic is usually administered with induction of anesthesia. A cystoscopy should be carried out before opening the materials in case the procedure is canceled because of inflammatory changes in the bladder. If a rigid needle is used, an offset lens injection scope should be used. If a flexible needle is used, a standard 0- or 30-degree lens cystoscope can be used. The size of the needle varies depending on the viscosity of the material and ranges from 3.7 to 5 Fr. The viscosity of the material also determines whether injecting the material can be carried out using a regular syringe or requires a ratcheted metal syringe holder. A 3-Fr ureteral catheter may be introduced to lift up the anterior

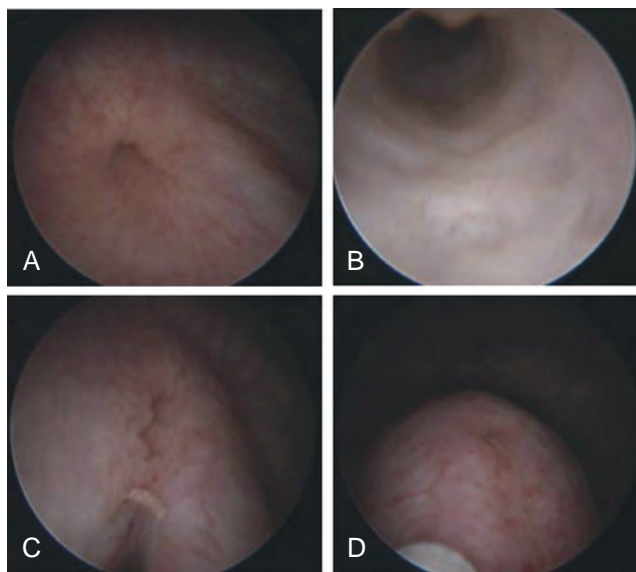


Figure 137-24. The classic subureteral Teflon injection (STING) technique. **A**, Appearance of the orifice before hydrodistention (**B**). **C**, The entry point of the needle is 2 mm distal to the 6-o'clock position. **D**, Appearance of the mound after completion of the injection.

wall of the ureter and identify the axis of the tunnel. The needle is inserted with the bevel facing up at the 6 o'clock position. The original description by O'Donnell and Puri suggested entering the mucosa 2 to 3 mm distal to the UVJ and advancing the needle in the submucosal plane for a distance of 4 to 5 mm. For high-grade reflux and ureters without submucosal tunnel, the Dublin group suggested inserting the needle directly inside the ureter to increase the length of the intravesical ureter (Chertin et al, 2002, 2003). Kirsch and colleagues (2004) popularized this approach (submucosal implantation within the intramural ureter) and reported improved results with all grades of reflux compared with the classic technique (92% vs. 79% of ureters). They further modified the technique with addition of a second injection inside the orifice and named it the double hydrodistention implantation technique (HIT), resulting in further improvement (93%) in intermediate and long-term results (Kalisvaart et al, 2012).

The accuracy of the needle entry point and needle placement is an important component for success of the procedure (Fig. 137-24). An improper puncture may not result in the desired mound formation and thus may not provide adequate support for the UVJ. If the needle requires repositioning, the implanted material may leak out of the first puncture site, resulting in failure of the procedure.

Injection should be carried out slowly. If the needle is positioned in the submucosal plane, the mound becomes apparent with the initial injection of 0.1 to 0.2 mL. This is a key point in the procedure; unsatisfactory mound formation and location after this initial injection is an indicator that the tip of the needle is not in the proper position. Repositioning of the needle by withdrawing it slowly and then advancing it while injecting, in addition to rotating the bevel gently (depending on the lateral location of the mound), should help achieve the desired effect. Once a volcano appearance with the ureteral meatus on top of the mound is achieved, additional volume is injected until the ureteric orifice becomes crescent or slit shaped. The shape of the achieved mound was found to be a significant predictor of a successful outcome. Achieving a volcano-shaped mound was associated with an 87% success rate, whereas other morphologies were associated with only a 53% successful rate (Lavelle et al, 2005). For most materials, the needle should be kept in place for 1 minute at the end of the injection to reduce extrusion of the material at the injection site. With Deflux this step is not essential. The bladder is emptied, and the mound is inspected with an empty and a full bladder to ensure that adequate support of the

BOX 137-1 Agents Used for Endoscopic Correction of Vesicoureteral Reflux

NONAUTOLOGOUS MATERIALS

Polytetrafluoroethylene (PTFE)
Cross-linked bovine collagen
Polydimethylsiloxane
Dextranomer hyaluronic copolymer (Deflux)
Coaptite

AUTOLOGOUS MATERIALS

Chondrocytes
Fat
Collagen
Muscle

ureter is persistent. Rarely, bleeding occurs at the puncture site. This is best dealt with by emptying the bladder and applying gentle pressure with the tip of the scope until the bleeding stops. Cauterizing the area is not advisable because it results in sloughing of the mucosa and extrusion of the injected material. At the end of the procedure, lidocaine gel may be instilled in the urethra; catheter drainage is not necessary. In general the child spends a brief amount of time in the recovery room, followed by discharge. All activities can be resumed immediately.

There is a significant learning curve with endoscopic correction of VUR (Kirsch et al, 2003). In a study by Herz and colleagues (2001) the importance of the learning curve was highlighted. In the first 6 months of their study the success rate was 46% in 18 children with 28 refluxing ureters. In the remaining 18 months of that study, the overall correction rate was 93% in 56 children with 84 refluxing ureters after a single endoscopic injection. Although the technique is quite simple once learned, there are some technical nuances and details that require specific attention.

Follow-Up

The child is maintained on antibiotics for 3 months when a follow-up sonogram and VCUG are obtained. If reflux is persistent, a repeat injection can be considered 6 months after the initial injection. If there is still no resolution, open surgery is recommended.

Most reports to date have not indicated any additional difficulty with open surgery after endoscopic correction using Deflux (Herz et al, 2001; Lackgren et al, 2001), but some have experienced difficulty with other substances. At open surgery the injected material is either not seen at all or is found well encapsulated but in an incorrect plane or location inside or outside the bladder. The material is easily removed en bloc, and the open reimplant procedure carried out without difficulty.

Materials Used for Endoscopic Correction of Reflux

For an injectable biomaterial to be ideal, it must be nontoxic and stable without migration to vital organs. It should cause minimal local inflammation, while at the same time be well encapsulated by normal fibrous tissue and fibrocytes. The material should be easy to inject through a long needle that passes easily through most standard endoscopic instruments. It must be viscous enough to prevent leakage from the puncture site and maintain its injected volume and the mound shape after the normal process of exchange and excretion of any carrier molecules.

Several agents have been used for endoscopic correction of VUR. These materials can be classified as **particulate or degradable and autologous or nonautologous** (Box 137-1).

The concern with the particulate agents is migration and with degradable agents is durability. Distant migration can occur by two mechanisms. The first is expansion of the injected bolus, which

may lead to disruption of the small vessels in the area of the distal ureter and trigone, resulting in the material gaining intravascular access. Particles smaller than 50 μm may bypass the pulmonary vascular bed and thus access the systemic circulation and reach other organs in the body. The second migration mechanism is by phagocytosis of the injected particles by tissue macrophages or blood-borne monocytes. The particle size determines whether phagocytosis can occur, because it is generally agreed that phagocytosis requires a particle less than 80 μm in diameter.

NONAUTOLOGOUS MATERIALS

Polytetrafluoroethylene Paste (Teflon Paste)

PTFE has been in use as a component of many biomaterials and injectable agents for many years. It has been used for the manufacturing of vascular grafts, cardiac valves/implants, surgical sutures, cosmetic surgery, and patches for hernia repairs (Monaghan and Meban, 1991; Godin et al, 1995; Sayers et al, 1998; Briguori et al, 2001). Teflon paste also was used as an injectable agent for embolization of vessels (Weingarten and Kauffman, 1977), for injection of vocal chords (Kasperbauer, 1995), and as a bulking agent for urinary incontinence (Politano, 1992).

Matouschek (1981) first reported on the use of Teflon paste as a bulking agent for correction of reflux. O'Donnell and Puri (1984) and Chertin and Puri (2002) popularized this technique and reported on its use in hundreds of patients with long-term follow-up (Puri, 1995; Chertin and Puri, 2002). A large European multicenter survey reported on 6216 ureters and 4166 children with 10 years of follow-up and demonstrated a cure rate of 86% after one to four injections (Puri et al, 1995). The longest follow-up is available from Dublin; 247 patients treated with Teflon paste with 11 to 17 years of follow-up demonstrated a sustained success rate of 95% with a 5% recurrence rate (Chertin and Puri, 2002).

Teflon paste is relatively inexpensive; it is viscous and requires a ratcheted syringe for injection. Despite its widespread use in Europe, Teflon paste never gained FDA approval in the United States because of concerns regarding distant migration of the PTFE particles. Malizia demonstrated in experimental studies that the particles can migrate to regional lymph nodes and to distant organs, including the lung and the brain (Malizia et al, 1984a, 1984b). Malizia's findings were substantiated by several clinical reports confirming particle migration (Claes et al, 1989; Aaronson et al, 1993; Dewan and Fraundorfer, 1996; Steyaert et al, 2000). Particle migration is thought to be related to the small size of the Teflon paste particles, which range from 4 to 100 μm , with 90% of the particles less than 40 μm .

With the availability of other, presumably, safer injectable agents, PTFE has fallen totally out of favor and been all but abandoned.

Cross-Linked Bovine Collagen



Please see the Expert Consult website for details.

Polydimethylsiloxane



Please see the Expert Consult website for details.

Dextranomer and Hyaluronic Copolymer

Dextranomer/hyaluronic copolymer (DX/HA) (Deflux) is formed of cross-linked dextranomer microspheres (80 to 250 μm in diameter) suspended in a carrier gel of stabilized sodium hyaluronate. DX/HA is biodegradable, the carrier gel is reabsorbed, and the dextranomer microspheres capsulated by fibroblast migration and collagen ingrowth. DX/HA loses approximately 23% of its volume beyond 3 months of follow-up (Stenberg and Lackgren, 1995).

Deflux was first introduced by the Swedish group of Stenberg and Lackgren (1995) and received FDA approval in 2001. Since then several clinical reports from Europe and the United States have documented success rates ranging from 68% to 89% (Lackgren

et al, 2001; Puri et al, 2003; Kirsch et al, 2004; Lavelle et al, 2005). The introduction of the double HIT by the Atlanta group has resulted in higher reflux resolution rates in 90% of 336 children (Kaye, 2012).

In a long-term follow-up study by Lackgren and colleagues (2001), 68% of 221 children injected using the classic STING technique and followed for a mean of 5 years maintained grade 1 VUR or less at the last VUCG. No significant long-term adverse effects were noted. Salvage ureteral reimplantation after failed endoscopic correction with DX/HA can be accomplished, usually without difficulty. The implant bolus is frequently observed in the periureteral space outside the bladder and is well encapsulated, with mild inflammatory changes (Sparks, 2011).

The appeal of DX/HA is that it is a natural product that is easily administered without a ratcheted syringe through a smaller gauge needle. It is currently the preferred agent for endoscopic correction in most centers; however, the durability of correction of VUR with DX/HA remains to be proved.

Calcium Hydroxyapatite

Calcium hydroxyl apatite (CaHA) (Coaptite; Bioform Medical, San Mateo, CA) is synthetic bone material. The particles have a uniform spherical shape and range in size from 75 to 125 μm . The material injects easily through a 21-gauge needle without the need for a ratcheted syringe. Mevorach and colleagues (2002) presented the initial results in a clinical trial including 98 patients and 155 ureters with grade 2 to 4 reflux. Reflux resolved in 67% of the patients and 75% of the ureters. In a recent consecutive case series from Stanford University the success rate per ureter was lower for CaHA (52%) than for DX/HA (78%) (Ngo et al, 2013).

AUTOLOGOUS MATERIALS

Fat, collagen, muscle, and chondrocytes have been evaluated as bulking agents. The key advantage of these agents is that they are not foreign materials, but the obvious disadvantage is the observed volume loss (up to 100% in the case of fat [Matthews et al, 1994]) and that they need to be harvested and expanded (in the case of chondrocytes and muscle) before injection. Autologous materials behave as a free graft at the injection site, so reabsorption of the material is worrisome and may be responsible for the inconsistent results.

Other Injectable Substances

Please see the Expert Consult website for details.



Recurrence of Vesicoureteral Reflux after Endoscopic Correction

The true incidence of recurrent VUR after successful endoscopic correction with any specific material is difficult to determine because a repeat VCUG is not obtained beyond the initial negative study except in the context of a research protocol.

Only a handful of series have reported long-term follow-up with repeat VCUG beyond the initial negative study. Chertin and colleagues (2002) reported a 5% recurrence rate using Teflon paste with follow-up up to 17 years. In the Swedish Reflux Trial, 20% of previously successfully treated children had a recurrence after 2 years of follow-up (Holmdahl et al, 2010).

The higher recurrence rate with Deflux, an absorbable agent, is not unexpected. However, in the absence of UTIs, the significance of confirming the long-term absence of VUR is less important. Furthermore, even if absorbable bulking materials were to lose volume or reabsorb completely over time, VUR resolution may be maintained by growth of the child and maturation of the UVJ. The injectable agent may just have bought time for this process to conclude. The implication of recurrent reflux in young adulthood

Apart from concerns regarding allergy to bovine collagen in 3% of the population, this material is otherwise safe and causes minimal local inflammatory changes (Leonard et al, 1990). It is easily injectable through a 25-gauge needle with standard endoscopic equipment. The downside to cross-linked collagen is the fact that the results are not durable because of the variable degree of ingrowth of native fibroblasts and replacement of the injectable collagen with native collagen (Leonard et al, 1990, 1991; Frey et al, 1992). Despite the odd report of sustained effect (Reunanen, 1995), the inconsistency, and questionable durability of cross-linked collagen (Haferkamp et al, 2000a, 2000b), most centers have abandoned its use for correction of reflux.

Polydimethylsiloxane (PDS) (Macroplastique) is a solid silicone elastomer that has been used as a soft tissue bulking agent. The injectable material is composed of soft, flexible, highly textured implants of heat-vulcanized PDS suspended in a bioextractable carrier gel. The carrier gel is a water-soluble low-molecular-weight polyvinylpyrrolidone hydrogel (Povidone). The carrier gel is absorbed and replaced with host fibroblasts that subsequently deposit collagen, encapsulating the implant. The implant retains its size and shape. To minimize the risk for migration, PDS is engineered to create an elastomer, instead of the less cross-linked silicone gels or non-cross-linked silicone oils. Although 76% of particles are greater than 100 μm in diameter, 7% are less than 50 μm in diameter. The smaller particles (Henley et al, 1995) and possible intramuscular injection of the agent are responsible for migration of particles to the lungs, kidneys, brain, and lymph nodes demonstrated in animal models. Unlike Teflon paste, Macroplastique does not cause an intense local inflammatory response. In patients requiring open surgery after failed injection with Macroplastique, the injectable bolus was found encapsulated and easily removed without adherence to the ureter or bladder (Herz et al, 2001). Histologic examination of the bladder muscle biopsies and pelvic lymph nodes at the time of open surgery revealed a mild inflammatory reaction with no evidence of PDS particle migration in either the wall of the bladder or the draining lymph nodes.

The efficacy of PDS as a bulking agent for correction of reflux is well documented. Dodat and colleagues (2004) reported on the long-term outcomes of Macroplastique injections for correction of VUR. Results in 590 refluxing ureters in 389 patients who were injected with a minimum follow-up of 5 years revealed a sustained success rate of 79.4%. Herz and colleagues (2001) demonstrated a reflux resolution rate of 81% after a single injection and 90% after a second injection with a 12-month follow-up. Similarly, van Capelle and colleagues (2004) reported an 82.3% success rate in 311 ureters in 195 children over a 10-year period from two European centers.

The main advantage of PDS is that it is a permanent material that remains well encapsulated, causing minimal local inflammatory changes. A recent report, however, draws attention to the development of Macroplastique bolus calcification occurring in 3 of 232 children injected between 1998 and 2004. Patients presented with worsening hydronephrosis, hematuria, and irritative lower urinary tract symptoms 5 to 9 years after injection. At time of surgery the calcified material was extracted after unroofing the overlying eroded mucosa (Lorenzo et al, 2010). This report underscores the importance of long-term monitoring after the injection of foreign bodies in growing children. Despite its demonstrated long-term track record, PDS has yet to achieve FDA approval for correction of VUR in the United States, possibly because of concerns regarding migration, particularly particles that are smaller than 80 μm , and the negative connotations associated with silicone implants.

Chondrocytes

Atala and colleagues (1993, 1994) described the harvesting and expansion of chondrocytes in vitro and successful correction of VUR in animal models. Subsequently, human trials using chondrocytes harvested from the posterior auricular cartilage were conducted (Diamond and Caldamone, 1999; Caldamone and Diamond, 2001). The chondrocytes were grown in culture for 6 weeks, quantitated, concentrated, and then suspended in a mixture of sodium alginate and calcium sulfate solution for injection. At 3-month follow-up, reflux was corrected in 55% (27 of 47) of the ureters. This improved to 86% after one or two repeat injections. At 1-year follow-up, reflux correction was maintained in 70% (32 of 46) of the ureters and 60% (19 of 29) of the patients. At subsequent endoscopy, failures were attributable to volume loss and shifting of the subureteral mounds.

Polyacrylate Polyalcohol Copolymer (Vantris)

Polyacrylate polyalcohol copolymer (PPC) (Vantris; Promedon, Córdoba, Argentina) belongs to the family of acrylics, which are nonbiodegradable agents of synthetic origin. PPC particles average 320 μm and are highly deformable by compression and thus may be injected using a 23-gauge needle. After implantation of particles, a fibrotic capsule of up to 70 μm forms around the implant providing stability and presumed long-term permanence. Recently published results demonstrate a promising reflux correction rate of 92.7% per ureter in 109 children and 165 ureters after a single injection (Chertin et al, 2013). To date PPC has yet to receive FDA approval.

for these patients is inadequately defined at present. More recent evidence suggests that children undergoing endoscopic correction with a preinjection history of multiple febrile UTIs, BBD, and renal scarring are at a higher risk for recurrent infections and late recurrence of VUR despite initial negative VCUG (Sedberry-Ross et al, 2008).

Endoscopic correction of VUR is a reasonable alternative for children being considered for surgical correction; however, families should be informed of the varied success rates across centers and that outcomes may not be durable.

Laparoscopy as Applied to Correction of Reflux

The laparoscopic approach to ureteral reimplantation should theoretically provide the success rate and durability of open surgery while avoiding its morbidity. Three procedures have been attempted laparoscopically: the extravesical reimplant, the Gil-Vernet procedure, and the Cohen cross-trigonal reimplant.

In addition to the long operative times and steep learning curve, the initial experience with laparoscopic reimplantation identified significant technical challenges in the creation of the submucosal tunnel while maintaining an intact bladder urothelium and with the suturing aspects of the procedures. The enhanced dexterity and outstanding visualization offered by the robot facilitates the laparoscopic reimplantation; however, the current port size required is still not ideal for smaller children. The continued refinement of open reimplantation surgery, more recently dispensing with the use of both postoperative bladder catheters and the need for overnight hospital stays, will place even greater onus on the proponents of the laparoscopic approach to better define the ideal candidates for minimally invasive technique.

LAPAROSCOPIC SURGICAL PROCEDURES

Gil-Vernet Procedure

In this procedure the trigonal mucosa is incised vertically and the two ureters are approximated into the midline with a single submucosal suture. This procedure has been accomplished laparoscopically transvesically with limited success. Okamura and colleagues (1999) and Cartwright and colleagues (1996) reported success rates of 59% and 62.5%, respectively. The recurrence of reflux is thought to be due to splitting of the trigone and lateral displacement of the ureters. This procedure is the least successful amongst the three described laparoscopic techniques and is all but abandoned.

Laparoscopic Extravesical Reimplant

In 1994 Ehrlich and associates first described the extravesical Lich-Gregoir technique through a transperitoneal approach (Ehrlich et al, 1994). This is the most commonly used procedure for laparoscopic correction of reflux. The technique has a steep learning curve; initial experiences described challenges with exposure of the ureter, trauma to the ureter, difficulty developing the extravesical tunnel without injuries to the urothelium, and long operative times.

Separation of the urothelium from the detrusor is difficult laparoscopically because the adequately distended bladder protrudes into the limited pelvic working space and hinders the laparoscopic dissection. Additionally, the ability to adequately retract the incised detrusor edges to create a wider trough is limited because of the exposure and the angles at which the instruments enter the abdomen.

Several modifications of the technique have been described by Lakshmanan and Fung (2000), leading to a more effective procedure with shorter operative time and results that approximate those of open surgery.

Trocar Placement

A 5-mm, 0-degree laparoscope is inserted through the umbilicus. Three additional working ports are inserted in the lower abdomen

along the lines of a Pfannenstiel incision in the middle and on either end.

Ureteral Dissection

The ureter is best identified at the pelvic brim and followed distally. The overlying peritoneum is incised transversely. Ureteral catheters placed cystoscopically may aid in identification of the ureter in the older patient. Once the ureter is identified, it can be grasped with Babcock forceps and freed from the surrounding tissues. In males the incision of the peritoneum should be carried out caudal to the vas deferens so that the vas can be reflected with the peritoneum in a cephalad direction. A vessel loop or a Diamond-Flex retractor can be passed around the ureter and used as a holder.

Creation of the Tunnel

It is important to mark the direction of the tunnel with electrocautery while the bladder is semidistended in its normal position. A 4-0 Prolene traction suture is applied at the proximal end of the detrusor tunnel. This suture is passed through the abdominal wall on a straight needle and used to hitch the bladder, and then the needle is passed out again, providing external control to achieve the desired tension and elevation of the detrusor. The incision of the detrusor is carried out starting from proximal to distal. The serosa is scored with cautery, but most of the dissection should be carried out using scissors to prevent injury to the bladder innervation, as described in the discussion of open extravesical reimplant earlier in the chapter. Elevation of the detrusor flaps is more difficult in the laparoscopic procedure, and therefore a trough as wide as that developed with open surgery may not be achievable. The incision is continued distally around the ureter, leaving the distal attachments intact. The mucosal bulge is also not as obvious as in open surgery because the bladder is not as distended and is also compressed by the peritoneal insufflation.

Closure of the Myotomy (Detrusorrhaphy)

The ureter is placed in the new tunnel, and a 3-0 polyglactin suture is placed at the most proximal end to stabilize the ureter and facilitate reclosure of the detrusor with interrupted sutures starting at the ureteral orifice distally. Anchoring sutures are not required because the distal attachments of the ureter are left intact.

After completion of the detrusorrhaphy, the bladder retraction suture is released and the bladder is filled. The ureter is observed in its new tunnel to confirm the absence of angulation or kinking. A catheter may be left in the bladder for 12 to 24 hours postoperatively.

The largest published series is that of Lakshmanan and Fung (2000) in which 71 ureters were reimplanted laparoscopically. Early on in that series, three ureteral injuries required open reimplantation in two and stenting in one to drain a urinoma. The remaining patients are free of reflux and obstruction.

Robotic Approach

Despite the initial successful reporting of the laparoscopic approach, its widespread use was limited by the significant technical demands and long operative times. In 2004, Peters was first to describe the initial experience with robotic-assisted laparoscopic ureteral reimplantation (RALUR) in the pediatric population (Peters, 2004). The major advantages of the robot over pure laparoscopic techniques are the 10× visual magnification and 3D visualization, in addition to reducing the technical challenges of fine suturing in the small spaces. The surgeon also benefits from the improved ergonomics of the robot console where the surgeon sits during the procedure; this is particularly helpful for longer or bilateral procedures (Lendvay, 2008).

In the most recent series, the reported results of robotic extravesical reimplantation closely approximate the success rates of the open procedure. Casale and colleagues (2008) reported a 97.6%

success rate in 41 patients using a transperitoneal robotic-assisted approach. An update of their experience was recently published (Kasturi et al, 2012) documenting a 99.3% reflux resolution rate in 150 patients with grade 3 or greater bilateral VUR. The one failure was a patient with bilateral grade 5 VUR that was downgraded to unilateral grade 2 VUR that was subsequently corrected with a sub-ureteral injection therapy after an episode of pyelonephritis. More significantly, in this group of 150 toilet-trained children, no patient experienced de novo voiding dysfunction. In a comparative study, RALUR was reported to demonstrate a reduction in length of stay and use of postoperative opioids relative to open surgery (Smith et al, 2011).

The current advantages of RALUR over the laparoscopic approach are anticipated to be enhanced by further equipment refinement and reduction in port and instrument size. However, the cost of the console, instruments, and disposables associated with RALUR are significantly higher and may remain a critical limitation in many countries.

Endoscopic Cross-Trigonal Reimplant

To avoid transgressing the peritoneum and the challenges associated with the small pelvis in the child, other groups have developed a transvesical approach, similar to the Cohen cross-trigonal reimplant, using carbon dioxide insufflation of the bladder (pneumovesicum).

Yeung and colleagues (2005) initially described the procedure using standard laparoscopic instruments. Peters and Woo (2005) followed with a report describing a robotically assisted technique to facilitate the creation of the submucosal tunnel and the ureteral anastomosis.

Port Placement

The patient is positioned supine with the legs separated to allow access to the urethra for cystoscopy and bladder catheterization intraoperatively. Cystoscopy is carried out, and the bladder is distended with saline. A traction suture is passed percutaneously at the level of the bladder dome under cystoscopic vision to anchor the bladder wall to the abdomen and prevent it from pulling away when the camera port incision is made at the dome. Yeung and colleagues (2005) described the placement of a U-hitch stitch, tightened over a short piece of rubber tubing outside the abdomen, to prevent port dislodgement and gas leakage into the extravescical space. After that, a 5-mm port is inserted under cystoscopic vision. The cystoscope is removed, and a urethral catheter is inserted. Carbon dioxide insufflation to 10 mm Hg pressure is started, and a 5-mm, 30-degree lens is inserted. Two additional 3-mm working ports are inserted on either side of the bladder under direct vision.

Dissection of the Ureter

A 5-cm segment of a 5-Fr feeding tube is inserted in the ureter and secured with a 4-0 Prolene suture. The catheter facilitates handling and dissection of the ureter as described in the open Cohen procedure. The ureteral mobilization begins with the usual circumscissoring incision using the hook electrocautery. The 3-mm endoscopic scissors are used to develop the plane of dissection starting on the distal aspect of the ureter. The dissection is carried out circumferentially for a distance of 2 to 3 cm. The muscular defect in the ureteral hiatus is repaired before creation of the tunnel to reduce gas leak, using 4-0 absorbable sutures.

Creation of the Submucosal Tunnel

An incision is made using the hook cautery at the site of the new ureteric orifice across the back wall of the bladder. The submucosal tunnel is started from the old hiatus toward the new hiatus using fine endoscissors. A fine grasper is then inserted through the new hiatus, and the feeding tube is used to pull the ureter through the tunnel.

Ureteral Neocystostomy

The ureter is spatulated at the 6-o'clock position and anastomosed at the new location using 6-0 interrupted sutures. Peters and Woo (2005) described using the robot to facilitate the delicate suturing laparoscopically and improve the efficiency of the procedure. The port sites in the bladder are closed, and an indwelling urethral catheter is maintained for 24 hours. Reflux resolution was demonstrated in 15 of 16 patients in series reported by Yeung and colleagues (2005) and in 5 of 6 patients in the series reported by Peters and Woo (2005). Providing a detailed description of the nuances of the vesicoscopic technique, Jayanthi and Patel (2008) reported a 94% success rate in a larger series of 103 patients, 10 of whom failed endoscopic injection. Three patients were converted to open surgery early in their experience. Of the 77 patients who underwent postoperative cystograms, reflux resolution was confirmed in 72 of 77 (94%). The failures were all in the first 30 patients of the series, with no reported failures in the last 47 patients.

Although open surgical correction of reflux is still the gold standard against which the endoscopic and laparoscopic approaches are compared, the technical advances and improved results achieved using minimally invasive techniques are gradually becoming more enthusiastically endorsed.

KEY POINTS: SURGICAL MANAGEMENT

- Exclude secondary reflux.
- The success rate of open surgical correction is very high.
- Adequate ureteral mobilization and protection of the ureteral blood supply are essential.
- A generous submucosal tunnel should be fashioned.
- Attention should be directed to avoid angulation and twisting.
- Attention to muscular backing is important.
- Bladder mucosa must be handled gently.
- Always consider bladder and bowel function preoperatively, as well as in all cases of persistent or recurrent reflux.
- Until appropriate prospective studies prove otherwise, indications for correction of reflux are the same regardless of whether the planned approach is open, endoscopic, laparoscopic, or robotic.

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The complete reference list is available online at www.expertconsult.com.



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Bladder and Urachal Development

Classification of Bladder Anomalies

Conclusion

Although anomalies of the urogenital tract are among the most commonly diagnosed antenatal malformations, the incidence of all congenital bladder anomalies is low (Carrera et al, 1995). Additionally, bladder anomalies are often a reaction to infravesical obstruction or part of a more serious disorder rather than a true isolated structural malformation. Bladder anomalies can be severe, cause urinary obstruction, and even lead to renal failure. Early detection and intervention are crucial to prevent future decompensation of the genitourinary tract. Anomalies can be detected prenatally or postnatally using ultrasound, but often require voiding studies for definite diagnosis. This chapter reviews congenital bladder abnormalities in the prenatal and postnatal periods and focuses on malformations not caused by infravesical obstruction. This chapter includes a discussion of the initial manifestation, diagnosis, and current treatment options for the different entities and a classification based on the prenatal and postnatal manifestations of bladder anomalies.

BLADDER AND URACHAL DEVELOPMENT

A comprehensive understanding of the embryologic development of the bladder and urachus is mandatory to correctly interpret the prenatal and postnatal findings and to counsel the parents toward optimal management.

Between the 4th and 6th weeks of gestation, the urorectal septum divides the endodermal cloaca into a ventral urogenital sinus and a dorsal rectum. The cranial part of the urogenital sinus is continuous with the allantois and develops into the bladder and pelvic urethra. The caudal portion gives rise to the phallic urethra in males and the distal vagina in females. Unlike in males, the entire female urethra is derived from the pelvic part of the urogenital sinus. The allantois develops as an extraembryonic cavity from the yolk sac and connects with the cranioventral portion of the cloaca, the future bladder. Around the 4th to 5th month of gestation, the allantoic duct and ventral cloaca involute as the bladder descends into the pelvis. The descent causes the allantoic duct to elongate because it does not grow with the embryo. This epithelialized fibromuscular tube continues to become narrower until it obliterates into a thick fibrous cord, the urachus (Moore, 1982). The obliterated urachus becomes the median umbilical ligament and connects the apex of the bladder with the umbilicus (Nix et al, 1958).

Normal Antenatal Sonographic Findings of the Bladder

The fetal bladder manifests as an elliptical structure filled with anechoic fluid within the pelvis. It is bordered laterally by the umbilical arteries. The pubic bones mark the anterior border and the rectosigmoid the posterior border. The bladder wall thickness should not exceed 3 mm, and the mucosa and musculature have an echogenicity similar to that of other structures in the pelvis

(McHugo and Whittle, 2001). The bladder can be visualized in approximately 50% of cases in the fetal pelvis at the 10th week of gestation, concurrent with the onset of urine production (Green and Hobbins, 1988). The detection rate increases with fetal age to 78% at 11 weeks, 88% at 12 weeks, and almost 100% at 13 weeks (Rosati and Guariglia, 1996). Compared to abdominal ultrasound, transvaginal ultrasound increases the quality of the obtained images as well as the detection rate. The fetal bladder empties every 15 to 20 minutes; therefore a second ultrasound in the same setting is mandatory in case of nonvisualization of the bladder. The bladder's diameter increases during the first trimester but should not be more than 6 to 8 mm.

The fetal sex, the amount of amniotic fluid, and the appearance of the umbilical cord become increasingly important in the interpretation and differential diagnosis of abnormal bladder findings. Fetal sex is difficult to determine before week 14 and should not be based on the presence or absence of a phallus but on visualization of the testes (Efrat et al, 1999). The measurement of amniotic fluid as an indicator of fetal urine production is a critical portion of every antenatal ultrasound. Until 16 weeks of gestation, the amniotic fluid is mainly consistent with placental transudate, at which time it changes to predominantly fetal urine (Takeuchi et al, 1994). The umbilical cord should contain two arteries and one vein without evidence of a fluid-filled urachus (Bronstein et al, 1990).

CLASSIFICATION OF BLADDER ANOMALIES

Bladder anomalies can manifest either as abnormal findings during prenatal ultrasound or postnatally as symptoms or in an unrelated workup.

It is difficult to classify bladder anomalies because of the large variety of possible malformations, the relatively low incidence of the anomalies, and the common association with other congenital anomalies. Therefore it seems reasonable to classify the different presentations into the following two main groups:

- Prenatally detected
 - Dilated
 - Nondilated
- Postnatally detected
 - Urachal abnormalities
 - Bladder diverticulum
 - Bladder duplication
 - Other bladder anomalies

Prenatally Detected Bladder Anomalies

The fetal bladder can appear dilated, hypoplastic, or absent on ultrasound. If the bladder is dilated, the condition can be due to obstruction or caused by incomplete emptying of the bladder without evidence of a mechanical obstruction. In nondilated

conditions, the bladder is either completely absent or is unrecognizable as a fluid-filled structure because of incomplete formation.

Dilated Fetal Bladder

In the first trimester, the fetal bladder is considered dilated if larger than 7 mm on ultrasound. If, on subsequent ultrasounds, the bladder continues to retain urine and shows no evidence of urine cycling, concern regarding obstruction should be raised. If the amniotic fluid does not increase, this may indicate the progression to oligohydramnios. **Determination of the sex of the child is very important because of the male gender predominance of certain conditions and diseases such as posterior urethral valves or prune belly syndrome.** It can be difficult to distinguish in utero if the dilation is due to obstruction. In a retrospective study, [Kaefer and coworkers \(1997\)](#) described 15 patients with marked bladder dilation in utero, 8 with and 7 without obstruction. All of the patients with obstruction presented with moderate-to-severe oligohydramnios and a marked increase in renal echogenicity, whereas all but one of the nonobstructed bladders had normal amniotic fluid levels and regular renal echogenicity. Therefore fetuses with nonobstructive dilation appear to pass enough urine to maintain renal function and adequate amniotic fluid levels throughout the pregnancy ([Mandell et al, 1992](#)).

Dilation Caused by Obstruction

Urethral Anomalies and External Bladder Outlet Obstruction. Dilations of the fetal bladder caused by anatomic obstructions are mostly due to urethral anomalies or external obstruction. Urethral anomalies include congenital urethral strictures, anterior and posterior urethral valves, and urethral atresia. Compression of the bladder outlet region can be due to obstructing syringoceles, a sacrococcygeal teratoma or pelvic neuroblastoma, an anterior sacral myelomeningocele, or rectum anomalies. The observed bladder changes are due to mechanical obstruction and affect bladder development at a critical time, which can lead to bladder wall hypertrophy and remodeling ([Pagon et al, 1979](#); [Beasley et al, 1988](#); [Stephens and Gupta, 1994](#)).

Dilation in Nonobstruction

Prune Belly Syndrome and Neurogenic Bladder Disease. Affected patients do not demonstrate any sign of obstruction on postnatally performed voiding studies or cystoscopic evaluations, except when urethral atresia is also present. In this case the presentation is similar to that in patients with posterior urethral valve. However, it is possible that the largely distended bladder, as in prune belly syndrome, is caused by a transient obstruction in utero, and in some cases the presence of urethral atresia has been noted with prune belly syndrome. Another possibility for the distention is the presence of neurologic disorders leading to an inability to empty the bladder in utero.

Congenital Megacystis

The term *megacystis* is often used to describe any condition leading to a distended fetal bladder in utero, without referring to the cause of the dilation. Historically, congenital megacystis was thought to be caused by bladder neck obstruction, leading to massive bilateral vesicoureteral reflux (VUR) and a thin bladder wall ([Williams, 1957](#); [Paquin et al, 1960](#)). Even the describing authors recognized that surgical interventions at the bladder neck level did not change the future outcome. [Harrow \(1967\)](#) revisited the subject and recognized that all patients had normal urethras and complete emptying of their bladders on voiding cystourethrography (VCUG). **Therefore the observed reflux is not an after effect of obstruction but rather the cause of the bladder dilation from continuous recycling of the urine between the upper tract and bladder** ([Harrow, 1967](#)). Congenital megacystis is defined currently as a dilated, thin-walled bladder with a wide and poorly developed trigone. The



Figure 138-1. Megacystis. Vesicoureterogram image of congenital megacystis with associated reflux.

wide-gaping ureteral orifices are displaced very laterally, causing massive reflux ([Fig. 138-1](#)). Bladder contractility is normal, although a majority of the urine refluxes into the ureters with each void. No neurogenic abnormalities are described. Most patients are recognized prenatally and should be placed on prophylactic antibiotics after birth ([Mandell et al, 1992](#)). **Correcting the reflux often restores normal voiding dynamics and should be performed after 6 months of age.** Reduction cystoplasty can be performed but is usually unnecessary ([Burbige et al, 1984](#)). Although the bladder is large enough to accommodate the tapered ureters even in a young infant, the operation can be very difficult because of the bladder wall's thinness. Anterior urethral valves also have been associated with megacystis, with improvement after valve resection ([Confer et al, 2010](#)).

Congenital megacystis has been recognized in association with microcolon-intestinal hypoperistalsis syndrome. This syndrome is a rare congenital disorder characterized by a dilated, nonobstructive urinary bladder and hypoperistalsis of the gastrointestinal (GI) tract. The syndrome can be identified on antenatal ultrasound by the appearance of a largely dilated bladder. It has been reported mostly in females and is usually considered lethal ([Srikanth et al, 1993](#); [Lashley et al, 2000](#)). So far only 10 patients have lived beyond the first year of life, and almost all need total parental nutrition. Once identified after birth, the distended bladder requires drainage by intermittent catheterization or vesicostomy placement. Long-term data concerning the urinary tract are not available because of the short life span of the patients ([Bloom and Kolon, 2002](#)).

Nondilated or Absent Fetal Bladder

To truly diagnose an absent fetal bladder on ultrasound, the examination has to be repeated after 15 to 20 minutes to rule out that the fetus has not simply emptied the bladder.

Cloacal and Bladder Exstrophy. Bladder exstrophy conditions are characterized by the presence of a bladder template only. Therefore it can be suspected in the absence of regular bladder filling during fetal ultrasound. Bladder exstrophy can be distinguished from bladder agenesis by the bladder template on the lower abdominal wall, which, along with the amniotic fluid level,

remains normal throughout the pregnancy (Mirk et al, 1986; Gearhart et al, 1995).

Bladder Hypoplasia. The bladder can be hypoplastic as a result of inadequate filling or storing of urine during fetal life. Although the bladder is formed during fetal development and can be detected on antenatal ultrasound throughout pregnancy, it never reaches an adequate capacity. Conditions caused by inadequate bladder outlet resistance (e.g., severe epispadias), separation defects (e.g., urogenital sinus abnormalities), abnormalities of renal development (e.g., bilateral renal dysplasia or agenesis), or urine bypassing the bladder (e.g., ureteral ectopia), all can lead to underdevelopment of the fetal bladder. Some of these bladders grow once the malformation is corrected; however, later bladder augmentation is often required to reach adequate capacity (Gearhart, 2002).

Bladder Agenesis. Embryologic development of bladder agenesis remains difficult to explain. The division of the cloaca into the urogenital sinus and the anorectum apparently is regular, because the hindgut is usually normal. Therefore the defect can be due to either atrophy of the cranial part of the urogenital sinus or failure to incorporate the mesonephric ducts and ureters into the trigone (Krull et al, 1988). The absence of the bladder is often associated with neurologic, orthopedic, or other urogenital anomalies such as renal dysplasia or agenesis or absence of the prostate, seminal vesicles, penis, and vagina (Aragona et al, 1988). It is a very rare anomaly; only 16 live births have been reported in the 45 known cases in the English literature. All but 2 were female (Adkes et al, 1988; Gopal et al, 1993; Di Benedetto et al, 1999). The defect is compatible with life only if the ureters drain ectopically into normally developed müllerian structures in the female or in the rectum in males. In surviving infants, the diagnosis can be confirmed by retrograde ureteronephrograms via the ectopic openings. Renal function can be preserved after creation of a ureterosigmoidostomy or external stoma (Glenn, 1959; Berrocal et al, 2002).

KEY POINTS: PRENATALLY DETECTED BLADDER ANOMALIES

- Prenatally detected bladder anomalies can be categorized into dilated and nondilated anomalies.
- Dilated bladders can be caused by anatomic or functional obstruction. They are commonly associated with severe anomalies, are often the cause for oligohydramnios, and can require fetal or immediate postnatal intervention to prevent fetal demise.
- Nondilated anomalies are associated with the most severe forms of congenital urologic malformations, such as bladder and cloacal exstrophy. Usually normal amniotic fluid levels are found.
- Bladder agenesis is compatible with life only if the ureters drain ectopically.

Postnatally Detected Bladder Anomalies

The malformations in this group can be diagnosed by antenatal ultrasound. However, most patients are diagnosed postnatally because of symptomatic disease or during workup for a nonrelated disease. Malformations listed in the prenatally detected group usually severely affect fetal development, are often associated with other malformations, and require prenatal or postnatal interventions. Postnatally detected defects, on the other hand, usually do not affect fetal development and generally can be treated with conservative measures or a single surgical intervention. Bladder anomalies in the infant or child are suspected in cases of urinary tract infections, hematuria, voiding difficulties, anatomic malformations and masses, or umbilical site drainage.

Urachal Anomalies

Understanding the embryologic development of the urachus and its unique location is the key to understanding congenital urachal



Figure 138-2. Urachal anatomy. (From Cullen TS. *Embryology, anatomy and diseases of the umbilicus*. Philadelphia: Saunders; 1916.)

anomalies. The urachus is located pre-peritoneally in the center of a pyramid-shaped space. This space is lined by the obliterated umbilical arteries, with its base on the anterior dome of the bladder and the tip directed toward the umbilicus (Fig. 138-2). The urachal length varies from 3 to 10 cm. It has a diameter of 8 to 10 mm and can connect with one or both obliterated umbilical arteries. Microscopically, three layers can be identified. An inner layer consists of either transitional or cuboidal epithelial cells surrounded by a layer of connective tissue. A smooth muscle layer in continuity with the detrusor muscle composes the outer layer. Because the urachus is surrounded by the umbilicovesical fascia, disease processes usually remain contained inside the pyramid-shaped space (Hammond et al, 1941). The urachus can remain either completely open or obliterate partially, leading to the formation of cystic structures at any site throughout its course.

Ashley and associates (2007) examined the medical records of 176 patients diagnosed with a urachal anomaly, and urachal remnants were found in 46 children and 130 adults. Children mostly presented with umbilical drainage or on physical examination, and 74% underwent excision. Of the adults, 66% had hematuria or pain and 90% underwent excision. Surgical treatment in children consisted of simple excision, whereas over 50% of adults required partial or radical cystectomy because of malignancy. They concluded that urachal anomalies manifest and progress differently in

pediatric and adult populations and recommended urachal excision in early childhood to prevent later problems or cancer formation. There was no reported evidence that a persistent urachal remnant in childhood was the cause of later cancer development (Ashley et al, 2007). Galati and colleagues (2008) reported 23 children with urachal remnants, of which 10 underwent excision because of symptomatic problems. In their treatment protocol, asymptomatic remnants are managed with physical and sonographic examination. They found that spontaneous resolution with nonoperative management is likely with remnants in patients younger than 6 months. However, if symptoms persist or the remnant fails to resolve after age 6 months, they recommend excision. The following four different urachal anomalies have been described (Fig. 138-3):

1. Patent urachus (50%)
2. Umbilical-urachus sinus (15%)
3. Urachal cyst (30%)
4. Vesicourachal diverticulum (3% to 5%)

Patent Urachus

Patent urachus is explained by nondescent of the bladder or, more commonly, failure of the epithelial-lined urachal canal to obliterate (Gearhart, 2002). Bladder obstruction during fetal development has been blamed for the urachus remaining tubular. The fact that urachal patency is often absent with severely obstructed bladders in utero, however, casts doubt on this theory. Additionally, only up to 14% of patients with a patent urachus have postnatal confirmation of in utero bladder obstruction (Schrenck and Campbell, 1972; Mesrobian et al, 1997). It seems possible that obliteration of the urachus may be independent from the level of bladder distention. Therefore retubularization, rather than primary patency, might be the cause for urinary drainage from the umbilicus. This theory is supported by reports of umbilical urinary fistulas in acquired

bladder obstructions later in life (Schubert et al, 1983; Berman et al, 1988).

A patent urachus is suspected in the neonatal period by continuous or intermittent drainage of fluid from the umbilicus. The most common organisms cultured from the umbilical drainage include *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus*, *Citrobacter*, and, rarely, *Proteus* species (Mesrobian et al, 1997). Additional manifestations include an enlarged or edematous umbilicus and delayed healing of the cord stump (Razvi et al, 2001; Schiesser et al, 2003). The diagnosis is confirmed by demonstration of the fluid-filled canal on longitudinal ultrasound or contrast filling on retrograde fistulogram or VCUG (Fig. 138-4) (Mesrobian et al, 1997). Computed tomography (CT) scans can aid in the diagnosis but usually depend on the bladder's filling status. It is important to differentiate the condition from a patent omphalomesenteric duct. The presence of both anomalies in the same patient is rare (Mendoza et al, 1968).

Management of an infected urachus with abscess formation includes initial drainage under antibiotic coverage. Once the infection has subsided, complete excision of the patent urachus, including a bladder cuff, is required (Nix et al, 1958). It is important to remove all anomalous tissue. This avoids recurrences or stone formation and prevents the rare event of later transformation into a malignant adenocarcinoma (Blichert-Toft and Nielson, 1971; Sheldon et al, 1984; Goldman et al, 1988; Upadhyay and Kukkady, 2003).

Traditionally, the patent urachus is surgically excised using a transverse or midline infraumbilical incision. Before surgery, a balloon catheter is used to distend the bladder. In infants, a small transverse subumbilical incision is often possible because the bladder dome is still high. A feeding tube or small catheter is placed into the patent urachus for better intraoperative identification. The urachus can be incised circumspectly, without removing

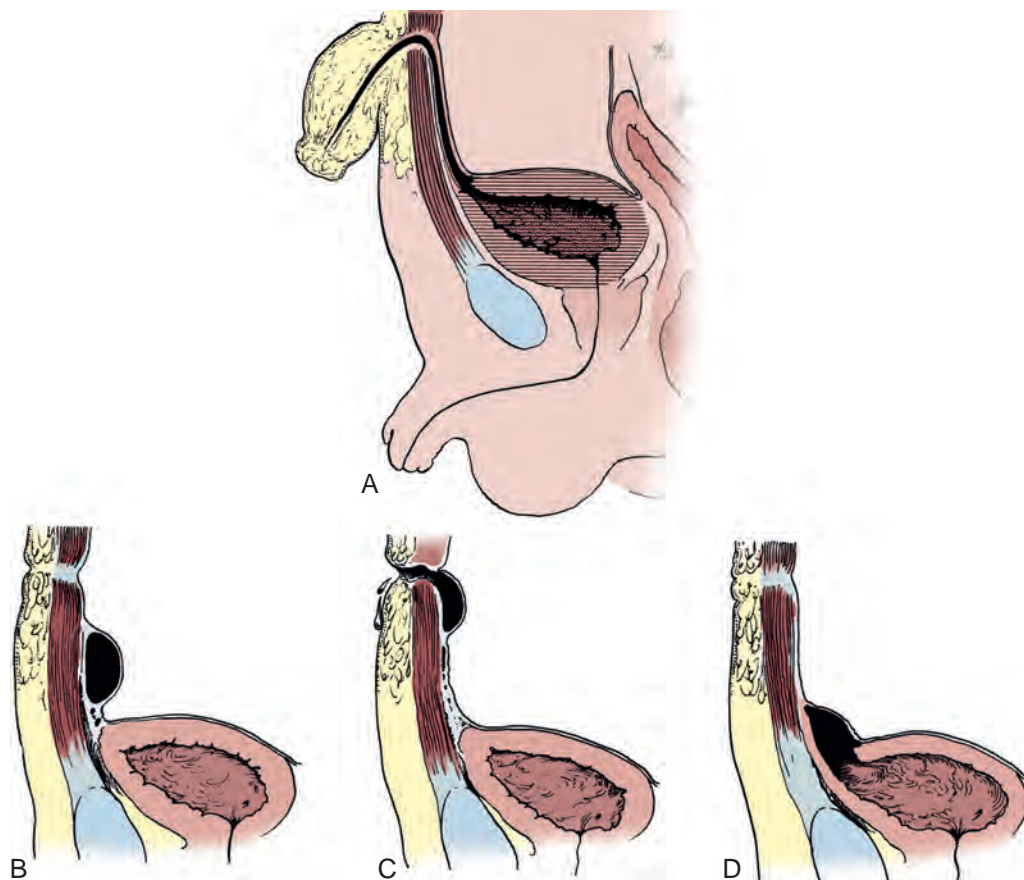


Figure 138-3. Urachal anomalies. A, Patent urachus. B, Urachal cyst. C, Umbilical-urachus sinus. D, Vesicourachal diverticulum.

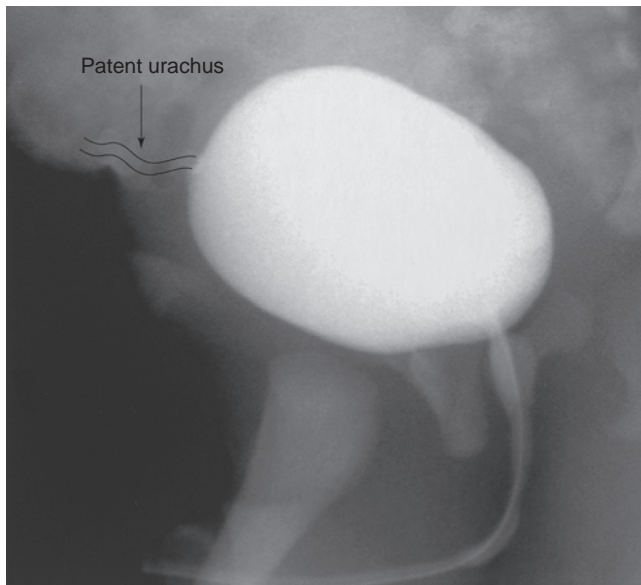


Figure 138-4. Patent urachus. Vesicoureterogram image of patent urachus in a newborn. Retrograde contrast filling of patent canal with contrast pooling in umbilicus.

the umbilicus for cosmetic reasons. The rectus fascia is incised in a longitudinal fashion, muscles spread apart, and the dome of the distended bladder identified. The urachus is identified and isolated, and a vessel loop is placed. The dissection continues extraperitoneally toward the umbilicus until the previously incised umbilical portion is free and can be pulled into the surgical field. It is then removed. A bladder cuff including the urachal insertion is marked and excised using electrocautery. The bladder is closed watertight in two layers. The catheter can be left in place overnight and removed the following morning.

Alternatively, urachal remnants can be removed laparoscopically. This can be done even in children younger than 6 months of age (Fahlenkamp et al, 1995; Cadeddu et al, 2000; Khurana and Borzi, 2002). Khurana and Borzi (2002) described their laparoscopic experience with 4 children between 5 months and 10 years and found the procedure to be safe in children of all ages. Technically, they suggested a three-port approach, with the camera port in the midline between the umbilicus and the xiphoid and two working ports on either side in the upper quadrant. Turial and colleagues (2007) reported 27 children with a median age of 4.7 years. Early in their series they inserted the camera port at the umbilicus with working ports into the right and left upper abdomen. Later they preferred to place the camera into the left lower abdominal wall, with 2-mm working ports at the left lower and upper abdomen for better visualization of the urachus at the umbilicus. They reported no intraoperative or postoperative complications, no recurrences, and a median operating time of 35 minutes. The advantage of the laparoscopic technique is the good visualization of the course of the urachus and the bladder dome. However, the laparoscopic techniques require an intra-abdominal approach and pose the potential risk for spilling infected or malignant material into the abdominal cavity. Robotic-assisted removal and single-port laparoscopy also have been suggested.

Umbilical-Urachus Sinus

In the umbilical-urachus sinus, the urachus obliterates at the bladder level but remains open at the umbilical site, causing a continuously draining sinus. The manifestation is similar to that of the patent urachus. The diagnosis is made by sinugram. The caudal part of the urachus is filled with desquamated epithelial cells, and no connection to the bladder can be identified. The presence of a persistent omphalomesenteric duct has to be considered. This

would manifest as a Meckel diverticulum connected to the umbilicus. These structures can be very difficult to differentiate from an umbilical-urachus sinus because no connection to the bladder or bowel can be seen on sinugram. However, the surgical approach to both anomalies requires the complete excision of all tissue. Unlike urachal structures, omphalomesenteric remnants can show gastric or small bowel mucosa on histologic examination.

Urachal Cyst

There is no communication of the cyst with the bladder or umbilicus. However, the fluid-filled cyst can drain through the umbilicus or into the bladder intermittently. Urachal cysts are found more commonly in the distal part of the urachus and manifest more commonly in adults than in infants or children (Cilento et al, 1998). The cyst material consists of desquamated epithelial cells. These cells can become infected; *Staphylococcus aureus* has been identified as the most common organism (Mesrobian et al, 1997).

Once infected, urachal cysts can manifest as umbilical abscess formation or bladder infections. Additional symptoms include localized lower abdominal pain, voiding symptoms, or even a painful and palpable mass. The diagnosis is confirmed by ultrasound, demonstrating the localized cyst between the anterior abdominal wall and the peritoneum. In a case of massive infection or difficult manifestation, a CT scan can clarify the anatomy and extent of disease (Berrocal et al, 2002). If unrecognized, the infected cyst can perforate into the bladder (Maruschke et al, 2003) or peritoneal cavity. This can cause peritonitis and formation of an enteric fistula (Ohgaki et al, 2003; Quek et al, 2003). Treatment consists of draining the infected cyst, followed by complete excision of the urachal remnant structures.

Vesicourachal Diverticulum

The urachus obliterates almost completely, except at the level of bladder apex. Here it forms a diverticulum of varying size. These lesions are usually nonsymptomatic and found incidentally on nonrelated radiographic workups. Although the diverticulum can enlarge in the case of urinary obstruction, this rarely causes problems because they tend to have a large opening and drain into the bladder well. Stone formation and urinary tract infections have been reported, especially in the case of a narrowed neck causing the need for intervention.

KEY POINTS: URACHAL ANOMALIES

- Urachal anomalies are usually detected postnatally because of umbilical drainage.
- Infected urachal remnants are initially treated with drainage and antibiotics, followed by surgical excision. Conservative treatment with observation is justified in asymptomatic cases because of possible spontaneous resolution.
- Imaging possibilities include ultrasound, CT, and VCUG.
- Nonresolved urachal remnants should be excised because of the increased risk for later adenocarcinoma formation.

Bladder Diverticulum

Bladder diverticula are caused by infravesical obstruction, iatrogenic after bladder surgery, or as a congenital defect. Independent from the cause, all diverticula develop as herniation of bladder mucosa between defects of bladder smooth muscle fibers. The neck of the resulting diverticulum depends on the size of the muscular defect. The incidence is reported to be low, with 1.7% in a selected pediatric population of children undergoing radiographic evaluation for symptomatic disease (Blane et al, 1994). In adult males the incidence tends to be much higher because of the higher occurrence of infravesical obstruction. The

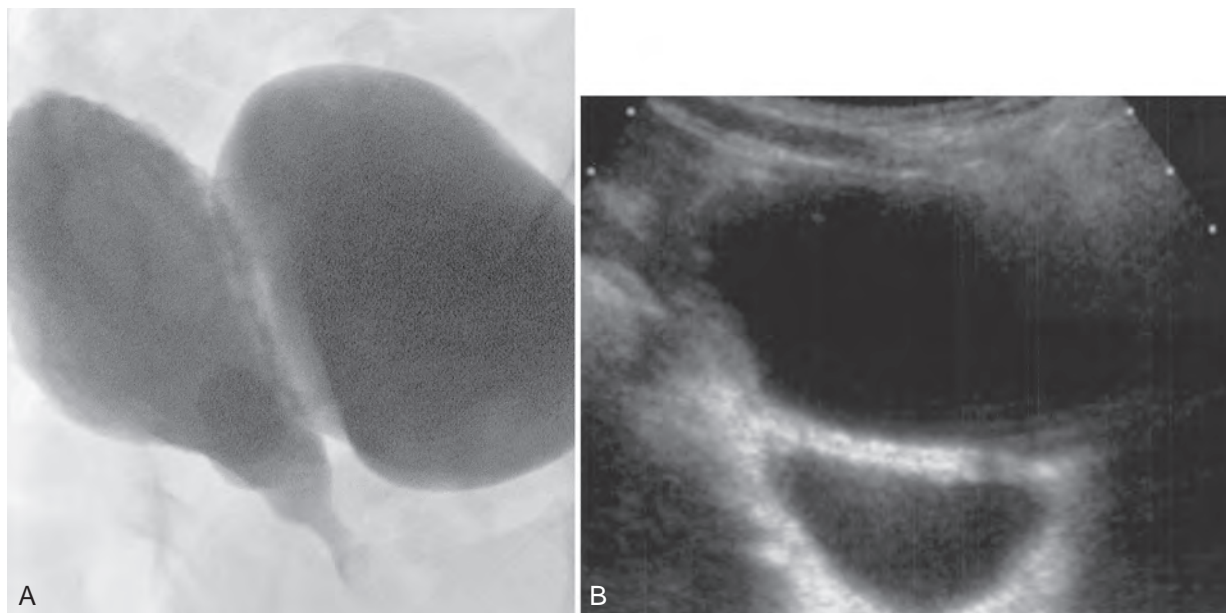


Figure 138-5. Primary paraureteral diverticulum. A, Vesicoureterogram image of large primary paraureteral diverticulum. B, Ultrasound image of the same diverticulum.

true incidence in children is difficult to evaluate, because many of the congenital diverticula remain asymptomatic and are probably never detected.

In his landmark article from 1961, Hutch describes the following two kinds of diverticula at the ureteral hiatus:

- **Primary paraureteral diverticula** are seen in smooth-walled bladders, occur isolated with no other diverticula, are intermittent in manifestation, and happen in children with no infravesical obstruction.
- **Secondary paraureteral diverticula** are found in trabeculated bladders as one of many diverticula in the bladder, are always present, and are caused by infravesical obstruction.

Primary diverticula arise as a localized herniation of bladder mucosa through the ureteral hiatus between the intravesical ureter and the roof of the ureteral hiatus. These primary diverticula are also known as *congenital diverticula* and are most likely caused by a congenitally deficient bladder wall (Fig. 138-5). Some authors have implied an isolated defect in the Waldeyer sheet; however, congenital diverticula often occur on one side only and a unilateral defect seems unlikely (Stephens, 1963). Congenital diverticula are often found in children with generalized connective tissue diseases such as Ehlers-Danlos, Williams elfin-facies, or Menkes syndrome (Babbitt et al, 1979; Daly and Rabinovitch, 1981; Levard et al, 1989). These diverticula can be resected if symptomatic; however, because of the impaired healing in patients with connective tissue disease, recurrence and wound healing complications are more common.

Secondary paraureteral diverticula are acquired and develop as a result of existing infravesical obstruction. The resulting increased infravesical pressure forces the bladder mucosa to bulge between the muscle fibers. These diverticula are usually just one of many pop-off mechanisms that can occur throughout the bladder. These diverticula also can be caused by weakening in the bladder muscle by infection (Barrett et al, 1976) or development of a muscular defect after bladder surgery (Sheu et al, 1998).

In both types of paraureteral diverticula, the Waldeyer sheet eventually becomes damaged as the diverticulum expands in size. The increasing diverticulum pulls the intravesical ureter out of its anchored position, causing dysfunction of the ureterovesical junction. Eventually, the enlarged diverticulum can become responsible for ureteral obstruction. This even has been associated with renal dysplasia (Amar, 1972; Livne and Gonzales, 1985).

Paraureteral diverticula or diverticula located in the lower part of the bladder can become so large that they compress the bladder

neck or posterior urethra. The resulting bladder outlet obstruction starts a vicious circle by continuously filling and expanding the diverticulum. This increases the obstructing and subsequently causes complete urinary retention (Sheldon and Essig, 1994; Zia-Ul-Miraj, 1999).

Bladder diverticula can be detected on prenatal ultrasound (Gaudet et al, 1999), but are mostly discovered during workup for infection, hematuria, incontinence, or obstruction. They can be suspected during ultrasound examination, especially if the bladder is viewed in different filling stages. The gold standard remains VCUG, which will reveal possible accompanying VUR. If no VUR is present, an intravenous pyelogram (IVP) with oblique views can help determine the relationship of the ureter with the diverticulum if there is hydronephrosis. Alternatively, nuclear renal studies can be used to obtain information concerning anatomy, kidney function, and ureteral obstruction. It is important to remember that congenital diverticula can have a dynamic nature and might not be present on every study. Radiographic studies may need to be repeated in cases of continuous clinical suspicion.

Small, asymptomatic congenital diverticula detected during unrelated workups can be treated conservatively with regular observation. Many surgeons tend to recommend excision of paraureteral diverticula if they are accompanied by VUR. Girls will show spontaneous resolution of their diverticula in association with VUR more frequently than boys. In his review of 304 patients with VUR, Amar (1972) confirmed the lesser resolution rate in boys. He attributed it to higher voiding pressures even without the presence of infravesical obstruction.

In acquired bladder diverticula, the infravesical obstruction has to be eliminated first. After bladder outlet resistance is normalized, the bladder can reshape and diverticulectomy might become unnecessary. If symptomatic, the diverticulum should be excised. The ipsilateral ureter should be reimplanted if it is near or included in the diverticulum. This traditionally has been performed intravesically; however, the procedure can be safely performed by an extravesical approach (Jayanthi et al, 1995; Yu, 2002). Laparoscopic excision also has been successfully performed in a 6-year-old child (Kok et al, 2000). Endoscopic subureteral injection of dextranomer/hyaluronic acid (Deflux) has been used for the correction of VUR, even in the presence of a primary paraureteral diverticulum (Perez-Brayfield et al, 2004). Robotic-assisted diverticulectomy in 14 patients was reported and described as a safe alternative to open surgery (Christmas and Casale, 2012).

KEY POINTS: BLADDER DIVERTICULUM

- Bladder diverticula can be detected on prenatal ultrasound, but the gold standard remains VCUG, which will reveal possible accompanying VUR.
- Primary diverticula arise as a localized herniation of bladder mucosa at the ureteral hiatus and are most likely caused by a congenitally deficient bladder wall.
- Secondary paraureteral diverticula are acquired and develop as a result of existing infravesical obstruction.
- Symptomatic diverticula, especially in conjunction with VUR, should be treated surgically.

Bladder Duplication

Duplication of the bladder and urethra can be complete or incomplete. It can occur in either the coronal or sagittal plane. [Abrahamson \(1961\)](#) attempted to classify the various bladder duplication anomalies and found complete duplication in the sagittal plane the most common. In incomplete duplications, the two bladder halves communicate and are usually drained by a single urethra. In complete duplications, the two bladders are fully separated entities with normal mucosa and a full-thickness musculature wall divided by a peritoneal fold ([Fig. 138-6](#)). Although the size and quality of each entity can be different, they are usually supplied with their own ureter and are drained by an individual urethra and external meatus ([Esham and Holt, 1980](#)). In rare cases, one bladder can lack a urethra. This leads to ipsilateral renal dysplasia via complete obstruction ([Cheng and Maizels, 1996](#)). Both bladders may possess a sufficient continence mechanism, or one side may be compromised, causing incontinent episodes.

Associated duplication anomalies of the external genitalia have been reported in up to 90% of cases; associated duplication anomalies of the lower GI tract have been reported in up to 42% of cases ([Kossow and Morales, 1973](#)). Duplicated vaginas can be connected to a separate unicornuate uterus. Duplicated penises are supplied with an individual urethra. Additional urologic abnormalities such as VUR, renal ectopia, or dysplasia are commonly found. Association with other nonurologic congenital anomalies are more frequent in sagittal than coronal duplications. Multiple manifestations have been described, including GI malformations,

duplications of the spine, spina bifida conditions, and various fistula formation between the urogenital and GI tract ([Berrocal et al, 1999](#)). In duplication variations of the classic cloacal-bladder exstrophy complex, patients present with an exstrophic bladder and urethra in addition to a closed regular intra-abdominal bladder ([Perren and Frey, 1998](#)).

The embryologic development of the various duplication anomalies remains poorly understood. Complete duplication of the bladder and hindgut is thought to occur as a result of partial twinning of the tail portion of the embryo ([Ravitch and Scott, 1953](#)). It also is suggested that the development of a sagittal fissure on the cloacal plate occurs when the urorectal septum separates the urogenital from the digestive sinus ([Bellagha et al, 1993](#)).

The wide range of anatomic manifestations of duplicate bladders explains the different time points and modes of manifestation. With associated malformations of the GI tract or external genital tract, the diagnosis is often made in the newborn period. However, many children are not diagnosed until recurrent infections or incontinence initiates a urologic workup. Although similarities exist, each case is different and warrants individual management. Complete preoperative diagnostic evaluations with karyotype, ultrasound, IVP, videourodynamic studies, genitogram, and GI tract imaging are useful to determine the anatomic situation. VCUG and nuclear renal scans can supply additional information regarding VUR and renal function. Complete understanding of the various anomalies can be very difficult. Often the final treatment plan has to be deferred until the time of endoscopic and surgical exploration of the malformation. **Initial treatment is directed toward renal preservation and prevention of infections by relieving possibly obstructed genitourinary tracts.** Long-term goals include achieving continence and reconstructing the internal and external genitalia. Incomplete duplications may not require surgical procedures if both bladder halves are sufficiently drained by a common urethra. In complete duplications, the two bladders can be combined into one. If both sphincter complexes are competent, the distal urethras are connected. If one is incompetent, the corresponding bladder neck can be closed and the connected urethra excised. Duplicated vaginas are combined in the midline, and a vulvoplasty is performed. The urogenital duplications also can be left uncorrected if the patient is asymptomatic; [Gastol and associates \(2000\)](#) reported two successful pregnancies in a 26-year-old woman. Because of the rarity of the disease and the large variety of manifestations, the surgeries must be individualized and should be performed in centers experienced in complex urogenital reconstruction.

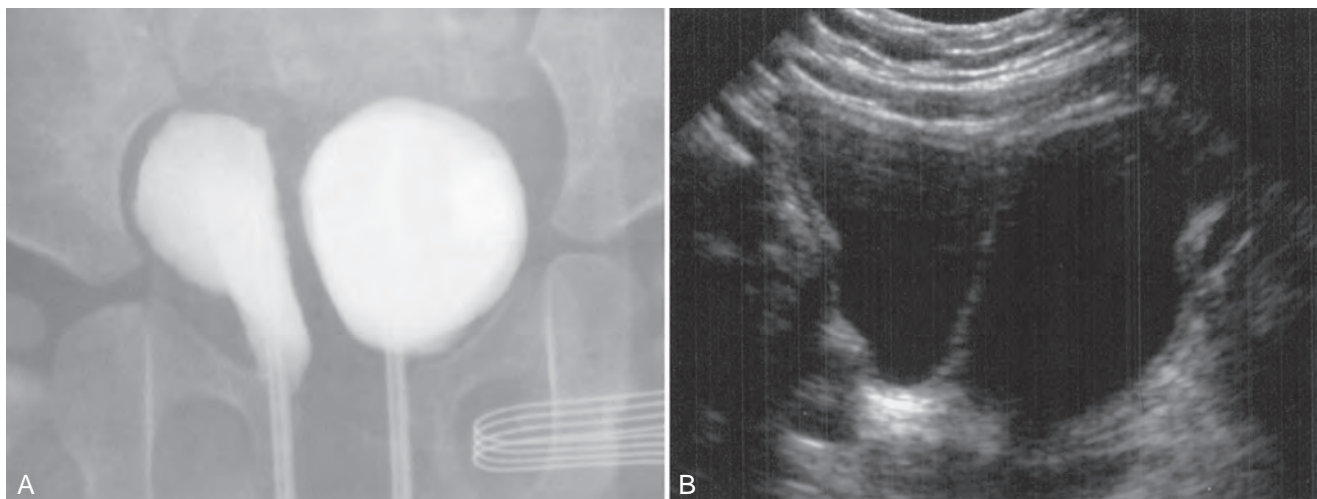


Figure 138-6. Complete bladder duplication. A, Vesicoureterogram image of complete bladder duplication with catheters inserted into each individual urethra. Note the size discrepancy. B, Ultrasound image of the same patient.

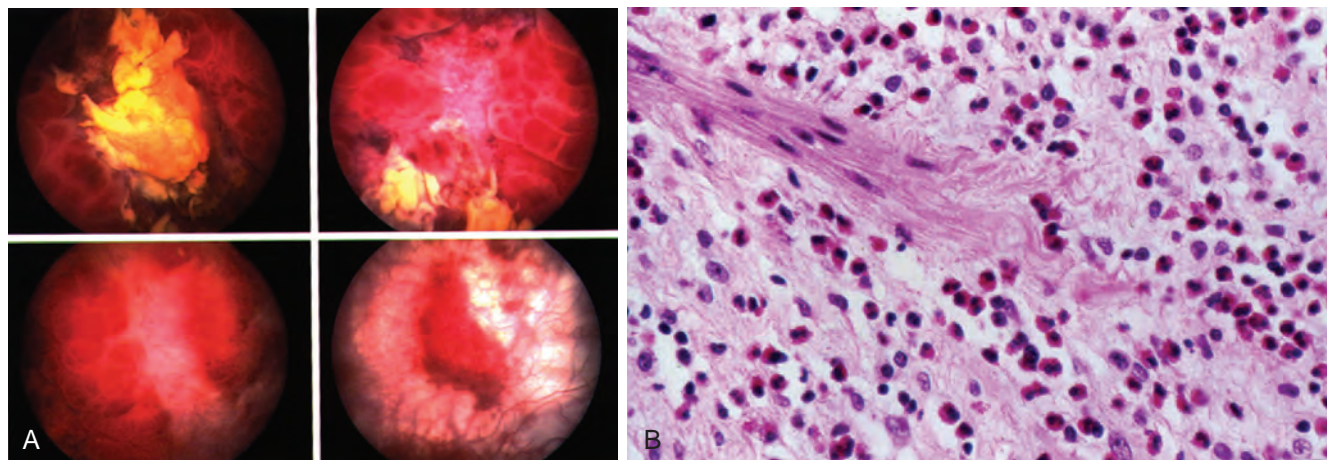


Figure 138-7. Eosinophilic cystitis. A, Cystoscopic views of lesion detected as mass on ultrasound in teenage male with severe dysuria and gross hematuria. B, Biopsy of mucosal lesion demonstrating eosinophilic infiltrate and no evidence of malignancy.

KEY POINTS: BLADDER DUPLICATION

- Bladder duplication is often associated with duplication anomalies of the external genitalia and lower GI tract.
- Initial treatment is directed toward renal preservation and prevention of infections by relieving possibly obstructed genitourinary tracts.
- Long-term goals include achieving continence and reconstructing the internal and external genitalia.
- Because of the rarity of the disease and the large variety of manifestations, the surgeries must be individualized.

Other Bladder Anomalies

Nephrogenic Adenoma

Nephrogenic adenoma of the urinary bladder is a rare benign tumor mostly found in adults. Sporadic case reports in children describe the lesion as a reaction to infection, lithiasis, or trauma or in response to surgery. [Heidenreich and coworkers \(1999\)](#) found a significant predominance of girls compared to boys (5:1), typically presenting with hematuria or irritative bladder symptoms. The diagnosis is established after cystoscopy with biopsy. Treatment consists of transurethral fulguration or resection and can be combined with long-term antibiotic prophylaxis. Although malignant transformation was not reported, tumor recurrence developed in 80% of the children, with a latency period of 4 years. Resection of nephrogenic adenoma followed by successful long-term resolution using ibuprofen and trimethoprim-sulfamethoxazole also has been described ([Voss and Peppas, 2013](#)).

[Hungerhuber and colleagues \(2008\)](#) reported a rare case of an adenocarcinoma in a 25-year-old patient who developed a nephrogenic bladder after a car accident. He subsequently developed a nephrogenic adenoma, which was resected several times. Although the initial pathologic finding was benign, a moderately differentiated adenocarcinoma was found after several resections. He underwent a radical cystectomy and remained tumor-free.

[Kao and associates \(2013\)](#) reviewed 21 cases of nephrogenic adenomas from urinary bladder biopsies. Most patients had a history of bladder augmentation with recurrent stone formation and infections. The immunohistochemical profile suggested that nephrogenic adenomas are derived from distal tubular cells.

Eosinophilic Cystitis

Eosinophilic cystitis in children is sporadically described in case reports with a predominance in boys. **The cause remains unclear,**

and the histopathologic examination includes inflammatory cells with numerous eosinophils throughout all layers of the bladder wall ([Tsakiri et al, 2004](#)). Manifesting symptoms include dysuria, hematuria, suprapubic pain, and urinary retention. It can be detected on ultrasound, but the diagnosis is made by cystoscopy with transurethral biopsy of the lesion ([Fig. 138-7](#)). Immunologic diseases and allergies have been suggested to be causative for the development of the lesions. In his large review of 135 cases, van den [Ouden \(2000\)](#) found transurethral resection combined with corticosteroids, antihistaminics, or antibiotics to be most successful for all age groups. In neonates and young children the disease can be self-limited and observation is justified ([Al-Omar et al, 2005](#)). In a case series of 4 patients between 5 days and 18 years, all were diagnosed by biopsy after clinical suspicion and were successfully treated with a combination of steroids, antihistamines, and antibiotics ([Sparks et al, 2013](#)).

Bladder Hemangioma

These benign vascular tumors are mostly seen in association with Klippel-Trenaunay syndrome and can be solitary or in multiple locations throughout the bladder. The leading symptom is macrohematuria and the vascular tumors are found during cystoscopy. Treatment consists of neodymium:yttrium-aluminum-garnet (Nd:YAG) laser irradiation of the affected areas ([Kato et al, 2000](#)).

Bladder Hernia

In rare cases the bladder has been found in hernia sacs during a routine hernia repair. It can be suspected in an unusual large hernia sac, urine drainage during or after surgery, or the new onset of hematuria postoperatively. [Manatt and associates \(2006\)](#) reported a bladder hernia in a premature infant found during a cystogram performed because of hydronephrosis. The bladder was reduced during hernia repair, and no further problems were encountered.

CONCLUSION

Isolated congenital bladder anomalies are very rare. Most published information relies on case reports of various malformations and their individualized management. Many of the detected anomalies are due to infravesical obstruction or are part of a syndrome affecting other parts of the genitourinary or nonurologic systems. Prenatal ultrasound allows early detection of bladder changes and has vastly influenced the prenatal and postnatal management of the described malformations. However, because of the rarity of the various manifestations, large series with adequate follow-up are

missing. Management and treatment remain individualized. Severe anomalies are often difficult to understand, and treatment should be centralized in specialized centers.

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The complete reference list is available online at www.expertconsult.com.

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139 Exstrophy-Epispadias Complex

John P. Gearhart, MD, and Ranjiv Mathews, MD

Exstrophy-Epispadias Complex

Classic Bladder Exstrophy

Surgical Reconstruction of Bladder Exstrophy

Modern Initial Repair of Bladder Exstrophy: Outcomes and Results

Other Modern Exstrophy Repairs: Continence Outcomes

Exstrophy Reconstruction Failures and Complications

Adolescents and Adults with Exstrophy-Epispadias Complex

Continence

Sexuality

Fertility

Quality of Life

Long-Term Adjustment Issues

Epispadias

Cloacal Exstrophy

Surgical Reconstruction of Cloacal Exstrophy

Long-Term Issues in Cloacal Exstrophy

EXSTROPHY-EPISPADIAS COMPLEX

The exstrophy-epispadias complex of genitourinary malformations can be as simple as a glanular epispadias or an overwhelming multisystem defect such as cloacal exstrophy (Fig. 139-1). This chapter provides a comprehensive overview of the entire bladder exstrophy-epispadias-cloacal exstrophy spectrum. In addition, all modern methods of exstrophy management and their complications and outcomes are discussed.

Historical Aspects

In older texts, the first account of bladder exstrophy was ascribed to Assyrian-Babylonian sources dating from the first and second millennia BCE. At that time, birth anomalies in both humans and animals were carefully recorded on tablets for their importance as omens, based on their interpretation by divination experts. Feneley and Gearhart (2000) examined Assyrian-Babylonian descriptions of congenital anomalies from cuneiform texts at the British Museum in London. Although references to anomalies involving the external genitalia were frequent (e.g., hermaphroditism, absence of external genitalia, unilateral and bilateral undescended testes), references to renal and bladder anomalies were few and difficult to interpret medically. Duplication and laterality of anomalies were described in detail owing to their distinct significance, but malformations in combination were not recorded. On the basis of these studies performed with a prominent Assyriologist, a definitive description of bladder or cloacal exstrophy was not corroborated. The first described case of epispadias is attributed to the Byzantine emperor Heraclius (610-641 CE), and the first description of cloacal exstrophy to Schenck in 1595 (Feneley and Gearhart, 2000).

Incidence and Inheritance

Data from the International Clearinghouse for Birth Defects monitoring system estimated the incidence to be 2.2 cases in 100,000 live births (Siffel et al, 2011). The male-to-female ratio of bladder exstrophy derived from multiple series is 2.3:1 (Shapiro

et al, 1984). However, two series reported a 5:1 to 6:1 male-to-female ratio of exstrophy births (Ives et al, 1980; Lancaster, 1987).

The risk of recurrence of bladder exstrophy in a given family is approximately 1 in 100 (Ives et al, 1980). Shapiro and colleagues (1985) in a questionnaire identified the recurrence of exstrophy and epispadias in only 9 of approximately 2500 indexed cases. Lattimer and Smith (1966) cited a set of identical twins with bladder exstrophy and another set of twins in whom only one child had exstrophy. Shapiro's series identified five sets of male and female nonidentical twins in whom only one twin was affected with exstrophy; five sets of male identical twins in whom both twins were affected; one set of identical male twins in whom only one twin was affected; and three sets of female identical twins in whom only one twin had the exstrophy anomaly (Shapiro et al, 1984). Reutter and coworkers (2003) have demonstrated six families with two occurrences of the exstrophy-epispadias complex, one in which the proband was the product of a consanguineous union and four discordant twin pairs. Also, Boyadjiev and colleagues (2004a) found four multiplex families (2.7%) in a cohort of 151 families with the exstrophy-epispadias complex. There were three twin pairs, two of which were monozygotic, and concordance was present in only one of the twin pairs. Consanguinity was present in one family. Bladder exstrophy or epispadias was not reported until the 1980s in the offspring of parents with the exstrophy-epispadias complex. Shapiro and colleagues (1984) determined that the risk of bladder exstrophy in the offspring of individuals with bladder exstrophy and epispadias is 1 in 70 live births, a 500-fold greater incidence than in the general population. Boyadjiev and colleagues (2004a) studied sibling data from 200 families and found 259 unaffected children in addition to the probands with exstrophy. Twenty-six probands had first-, second-, or third-degree relatives with congenital anomalies unrelated to the exstrophy-epispadias complex, most of which were midline defects and oral clefts. Four probands had a total of seven biologic children who were unaffected. New data from Boyadjiev and coauthors (2004a) indicates that the average maternal age for exstrophy mothers was 34 years and the average paternal age was 32 years. In addition, 49% of probands were born from first pregnancies. This may represent

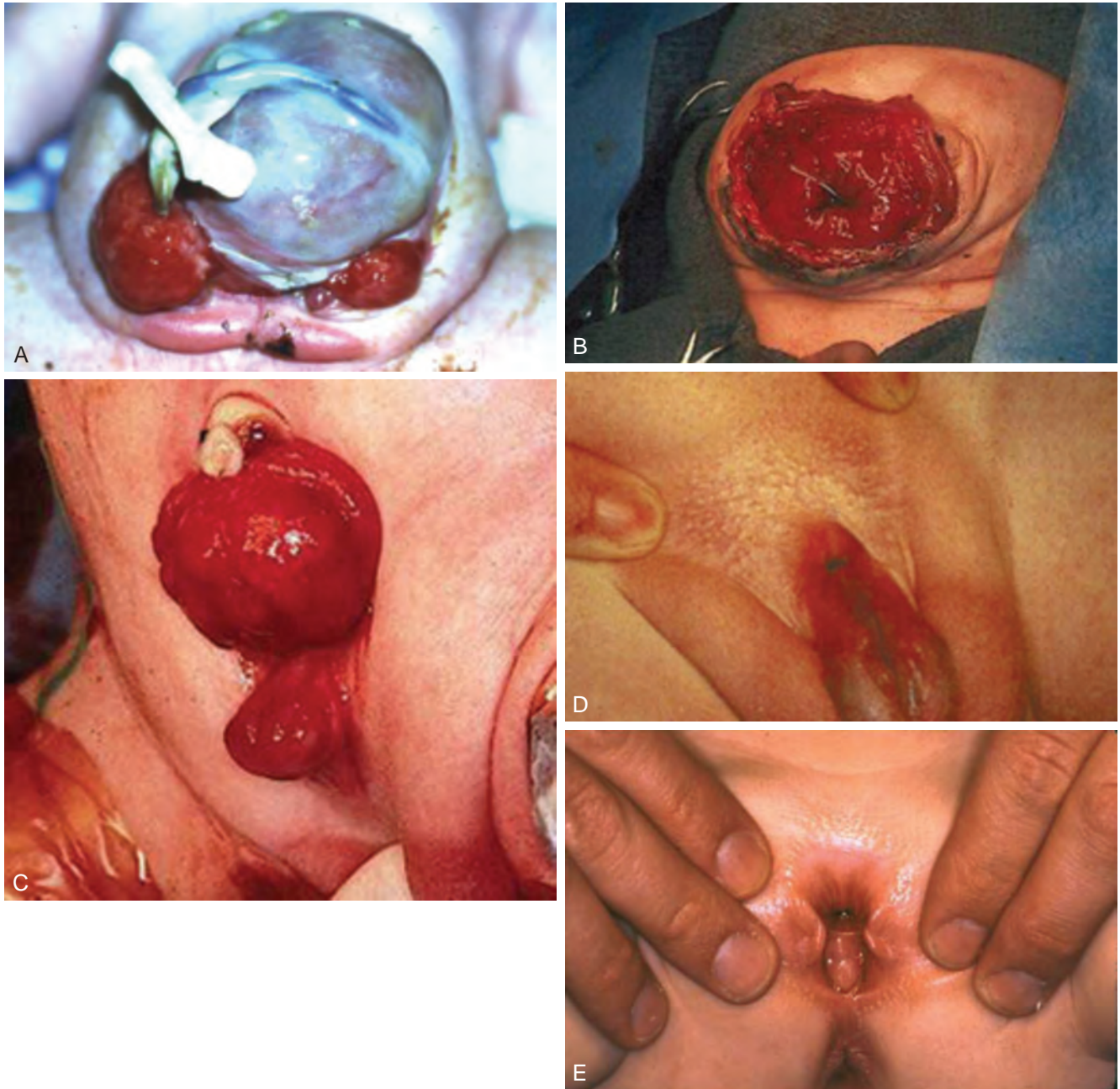


Figure 139-1. Entities that constitute the exstrophy-epispadias complex. **A,** Cloacal exstrophy. **B,** Superior vesical fissure. **C,** Classic bladder exstrophy. **D,** Male epispadias. **E,** Female epispadias.

societal changes indicating advancing maternal age for first pregnancies and increased risk of exstrophy when assisted reproductive techniques are used (Wood et al, 2003).

A recent (2011) multi-institutional study from North America and Europe involving an analysis of 441 families divided the study into mild epispadias ($n = 43$), intermediate-classic exstrophy ($n = 366$), and severe (cloacal) exstrophy ($n = 31$). Males were over-represented in all groups. Cleft lip and cleft palate were seen in a high prevalence. Maternal smoking during the first trimester was associated closely with cloacal exstrophy, and maternal preconception folic acid supplementation was associated with the mildest phenotype (epispadias) (Reutter et al, 2011).

Exploration of possible causes for the exstrophy-epispadias complex continues. A report from Israel indicated a 10-fold increase in exstrophy births to mothers who had received large doses of progesterone in the early part of the first trimester.

Wood and colleagues (2003) reported on a sizable series of children with exstrophy conceived using assisted reproductive techniques. A 7.5-fold increase in incidence was noted when in vitro fertilization was used. These two reports indicate a role for hormonal changes in the etiology of the exstrophy-epispadias complex. In a large series of 214 females, no association with parental age, maternal reproductive history, or preconception maternal exposure to alcohol, drugs, radiation, or infections was found (Gambhir et al, 2008). However, preconception maternal exposure to smoking was significantly more common in patients with cloacal exstrophy than in the combined group of patients with classic exstrophy-epispadias.

Genetic studies to identify a genetic locus for the exstrophy-epispadias complex are underway. Boyadjiev and coauthors (2004b) have reported finding a breakpoint disruption in the 5' region of the *CASPR3* gene on chromosome 9. This observation is the first to suggest a possible genetic basis for development of

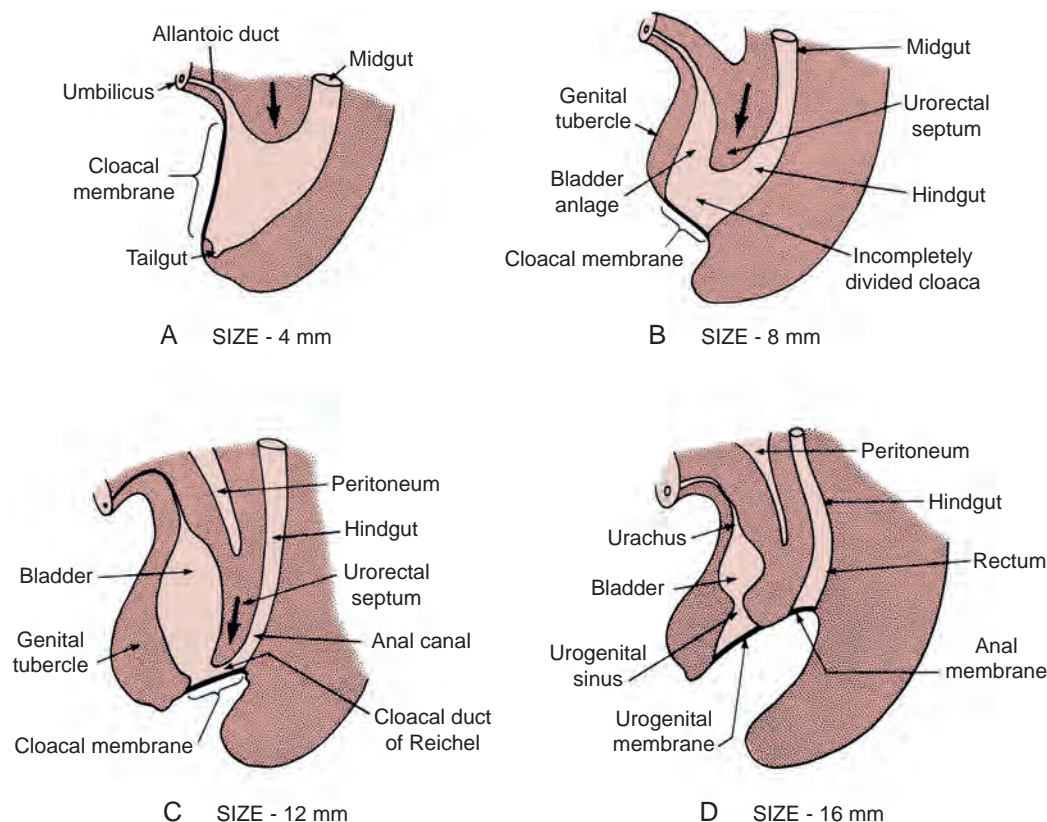


Figure 139-2. A-D, Development of the cloaca and cloacal membrane in the 4- to 160-mm embryonic stages. Caudal growth of the urorectal septum leads to separation of the anterior urogenital sinus from the posterior rectum.

the exstrophy-epispadias complex. In another recent study by Ludwig and colleagues (2009), risk loci for the exstrophy spectrum were found in seven separate chromosomes, with susceptibility genes in several regions.

Qi and colleagues (2011) used genome wide expression profiling to identify 162 bladder exstrophy-epispadias complex candidate genes that had twofold or higher expression differences between exstrophic and normal bladder smooth muscles in mouse and human embryologic bladder tissues. They also found 16 candidate genes that are expressed in the infraumbilical endoderm and mesoderm. Most of these genes have functions related to cellular assembly, musculoskeletal system development, and connective tissue morphology. Specifically, 30% of these genes were related to the desmosomal structure and cytoskeleton assembly, of which 69% were underexpressed in exstrophic bladders. In this study, the two most downregulated genes in exstrophic bladders, desmin and desmuslin, encode muscle-specific proteins that interact with desmoplakin, the sixth most overexpressed gene in exstrophic bladders. New data from Ching and colleagues (2010) and Qi and colleagues (2013) has shown significant dysregulation of p63 in tissue from newborns with bladder exstrophy.

Embryology

Bladder exstrophy, cloacal exstrophy, and epispadias are variants of the exstrophy-epispadias complex (see Fig. 139-1). The cause of this complex is thought to be the failure of the cloacal membrane to be reinforced by ingrowth of mesoderm (Muecke, 1964). The cloacal membrane is a bilaminar layer situated at the caudal end of the germinal disk that occupies the infraumbilical abdominal wall. Mesenchymal ingrowth between the ectodermal and endodermal layers of the cloacal membrane results in formation of the lower abdominal muscles and the pelvic bones. The cloacal membrane is subject to premature rupture, and, depending on the extent of the infraumbilical defect and the stage of development during which

the rupture occurs, bladder exstrophy, cloacal exstrophy, or epispadias results (Ambrose and O'Brien, 1974).

After mesenchymal ingrowth occurs, the urorectal septum grows in a caudal direction and divides the cloaca into a bladder anteriorly and a rectum posteriorly (Fig. 139-2). Distally, the septum meets the posterior remnant of the bilaminar membrane, which eventually perforates and forms the urogenital and anal openings. The paired genital tubercles migrate medially and fuse in the midline, cephalad to the dorsal membrane before perforation.

The theory of embryonic maldevelopment in exstrophy held by Marshall and Muecke (1968) is that the basic defect is an abnormal overdevelopment of the cloacal membrane during the 4th week of gestation, which prevents medial migration of the mesenchymal tissue and proper lower abdominal wall development. The timing of the rupture of this defective cloacal membrane determines the variant of the exstrophy-epispadias complex that results. Classic exstrophy accounts for more than 50% of the patients born with this complex (Muecke, 1964; Marshall and Muecke, 1968). Martinez-Frias and coworkers (2001), using epidemiologic factors of low birth weight, twinning, single umbilical artery, and associated defects, postulated that cloacal exstrophy and exstrophy of the bladder are two different expressions of a primary developmental field defect, with cloacal exstrophy being an early defect. It has been postulated that one or both of the lateral body wall folds fails to move far enough ventrally to meet its counterpart in the midline (Sadler and Feldkamp, 2008). Thus, if closure fails in the abdominal and pelvic region, cloacal exstrophy results, and if failure occurs in the pelvis alone, classic exstrophy occurs.

Other plausible theories concerning the cause of the exstrophy-epispadias complex exist. Abnormal development of the genital hillocks caudal to the normal position, with fusion in the midline below rather than above the cloacal membrane, has been embraced by other investigators (Patton and Barry, 1952; Ambrose and O'Brien, 1974). Another interesting hypothesis that remains controversial describes an abnormal caudal insertion of the body stalk,

which results in a failure of interposition of the mesenchymal tissue in the midline (Mildenberger et al, 1988). As a consequence of this failure, translocation of the cloaca into the depths of the abdominal cavity does not occur. A cloacal membrane that remains in a superficial infraumbilical position represents an unstable embryonic state with a strong tendency to disintegrate (Johnston and Kogan, 1974), which has been supported by the laboratory work of Thomalla and colleagues (1985).

Maldevelopment of the bony pelvis rather than soft-tissue defects has been suggested to be the inciting issue for the development of exstrophy. Beaudoin and colleagues (1997) have suggested that lack of "rotation" of the pelvic ring primordium prevents structures attached to the pelvic ring from joining in the midline, allowing herniation of the bladder to occur. The cause of this inadequate rotation remains elusive.

CLASSIC BLADDER EXSTROPHY

Anatomic Considerations

Exstrophy of the bladder is part of a spectrum of anomalies involving the urinary tract, the genital tract, the musculoskeletal system, and sometimes the intestinal tract. In classic bladder exstrophy (CBE), most anomalies are related to defects of the abdominal wall, bladder, genitalia, pelvic bones, rectum, and anus. Because of the involved nature of this defect, the deficits are described here as they affect each system.

Skeletal Defects

Formerly, CBE was thought only to show the characteristic widening of the pubic symphysis caused by malrotation of the innominate bones with an outward rotation or eversion of the pubic rami at their junction with the iliac bones. However, modern imaging using three-dimensional (3D) computed tomography (CT) has demonstrated previously unknown rotational and dimensional abnormalities (Sponseller et al, 1995). Rotational anomalies include (1) external rotation of the posterior pelvis/iliac wings; (2) external rotation of the anterior pelvic segment; (3) coronal rotation of the sacroiliac joint; (4) acetabular retroversion; (5) convergence of iliac wings; and (6) femoral retroversion. Dimensional anomalies include (1) increased pubic diastasis; (2) shortened anterior pubic segment; and (3) increased intertriradiate cartilage distance.

Sponseller and associates (1995), using CT of the pelvis with 3D reconstruction, were the first to accurately characterize the exact bony defect associated with both CBE and cloacal exstrophy. In reviewing a large group of patients with exstrophy of the bladder, using pelvic CT scans and age-matched controls, Sponseller and coworkers (1995) found that patients with CBE have a mean external rotation of the posterior pelvis of 12 degrees on each side, along with retroversion of the acetabulum, and a mean 18 degrees of external rotation of the anterior pelvis, along with 30% shortening of the pubic rami, in addition to the previously described diastasis of the symphysis pubis (Fig. 139-3). In long-term follow-up there was a foot progression angle of 20 to 30 degrees of external rotation beyond the normal limits seen in early childhood, which improves with age. Likewise, patients with cloacal exstrophy not only had pelvic deformities to a greater degree but also had asymmetry of the preceding parameters between the right and left sides of the pelvis, malformation of the sacroiliac joints, and occasional dislocations of the hip (Sponseller et al, 1995).

Data from Stec and associates (2001a), who used 3D models from CT scans, found the sacroiliac joint angle (before closure) was 10 degrees larger than controls in the exstrophy pelvis, being 10 degrees more toward the coronal plane than sagittal (Fig. 139-4); the exstrophy pelvis had 14.7 degrees more inferior rotation than controls. In addition, the sacrum in exstrophy patients has a 42.6% larger volume and 23.5% more surface area than in controls.

These rotational deformities of the pelvic skeletal structures contribute to the short, pendular penis seen in bladder exstrophy.

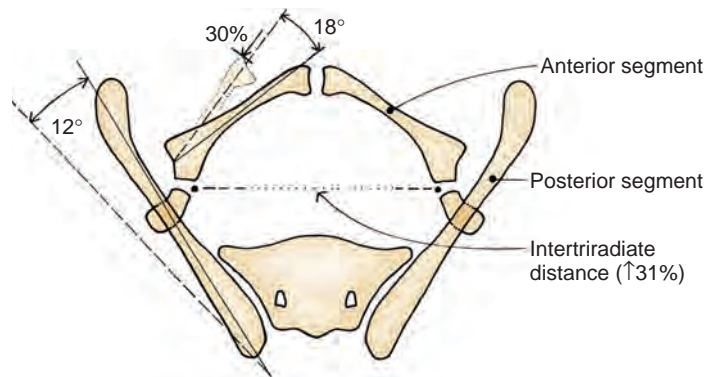


Figure 139-3. Pelvic bone abnormalities noted in classic bladder exstrophy. The posterior bone segment is externally rotated (12 degrees mean on each side), but the length is unchanged. The anterior segment is externally rotated (18 degrees mean on each side) and shortened by 30%. The distance between the triradiate cartilage is increased by 31%.

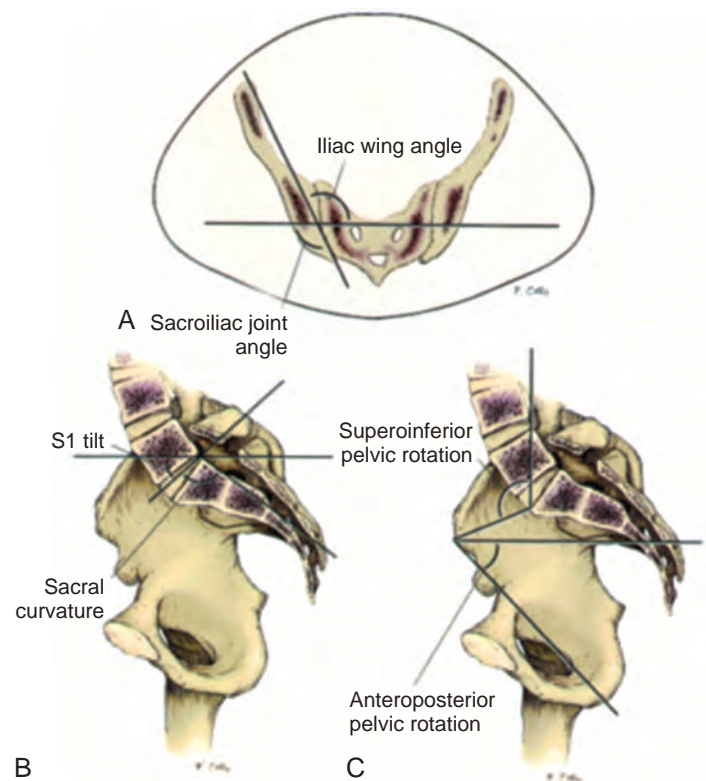


Figure 139-4. Sacroiliac joint angles before closure in children with classic exstrophy are 10 degrees larger than normal controls. The bony pelvis has 14.7 degrees of inferior rotation compared with lack of rotation. (From Stec AA, Pannu HK, Tadros YE, et al. Evaluation of the bony pelvis in classic bladder exstrophy using 3D-CT: further insights. *Urology* 2001;58:1030-5.)

Outward rotation and lateral displacement of the innominate bones also accounts for the increased distance between the hips, waddling gait, and outward rotation of the lower limbs in these children, which in itself causes little disability and usually corrects to some degree over time. The 30% shortage of bone in the exstrophy pelvis has largely gone unexplained. Studies by Stec and colleagues (2003) using sections from the bony pelvis in fetal exstrophy specimens and normal aborted fetuses found that the ultrastructure, bone development, microscopic growth patterns, and endochondral ossification were absolutely the same. Thus,

restoration of the physiologic shape of the pelvis may lead to more normal bone growth, decreased shortage of bone, and a more appropriate distribution of the mechanical and developmental forces on a more closed, normally functioning pelvic ring.

The incidence of spinal anomalies in exstrophy has not been well studied. A single study of 299 children with bladder exstrophy indicated spinal variations without clinical significance (spina bifida occulta, lumbarization or sacralization of vertebrae) in 11%, uncomplicated scoliosis in 2.7%, and spinal dysraphism in 4%, including myelomeningocele, lipomeningocele, scimitar sacrum, and hemivertebrae, but only 1 patient demonstrated any evidence of neurologic dysfunction (Cadeddu et al, 1997).

Pelvic Floor Defects

Stec and colleagues (2001b), using 3D models created from CT scans of children with CBE and normal age-matched controls, found that the puborectal slings were supporting two times more body cavity area than normal. The levator ani group is positioned more posteriorly in exstrophy patients, with 68% located posterior to the rectum and 32% anterior (vs. 52% posterior and 48% anterior in healthy controls) (Fig. 139-5). The levators are also rotated outward 15.5 degrees, and in the coronal aspect the levators are 31.7 degrees more flattened than normal. This deviation from normal makes the exstrophy puborectal sling more flattened than its normal conical shape. There was no significant difference in the length or

thickness of these muscles between patients with exstrophy and controls.

A comparison of 3D magnetic resonance imaging (MRI) in children with exstrophy before closure and normal controls indicated that the levator ani group was less dome shaped and more irregular in those with exstrophy (Williams et al, 2004). Also, there was no relationship between the amount of pubic diastasis and the extent of disproportionate curvature of the levator ani group. In addition, Halachmi and coauthors (2003) reported on the postoperative appearance of the pelvic floor with 3D MRI. In 2 patients who had some degree of continence, the intrasymphyseal distance was shortest, the angle of the levator ani divergence more normal, and the bladder neck most deeply positioned in the pelvis. Gargollo and colleagues (2005), reporting on a mixed group of patients, noted that the puborectalis angle in those with dry intervals was decreased compared with that before closure. These two studies correlate well with earlier findings of Gearhart and coworkers (1993c) showing that in the adult patients who were dry, the puborectalis angle was less than 65 degrees. Recent data, again from Stec and colleagues (2012b), used 3D MRI to evaluate the pelvis before and after primary closure. Of the 19 patients, 12 had closure as newborns without osteotomy and 7 had closure outside of the newborn period with an osteotomy. The preoperative and postoperative MRIs revealed that closure (1) reshapes the pelvis from a boxlike configuration to a more inwardly rotated hammock; (2) redistributes a significant portion of the levator group into the

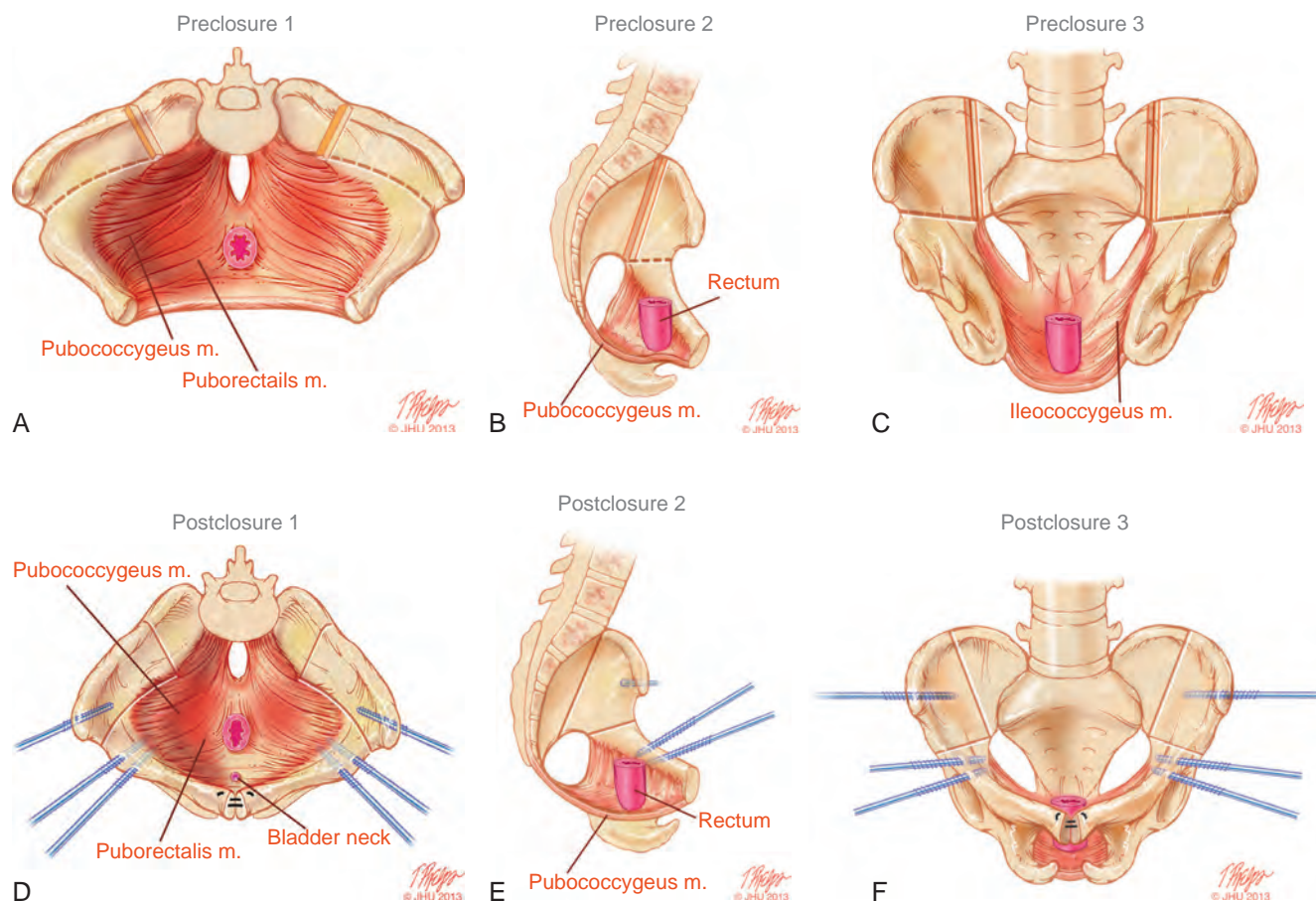


Figure 139-5. A, Pelvic floor anatomy before closure of exstrophy. Osteotomy incisions marked. B, Lateral view of pelvic floor anatomy showing postdisplacement of pelvic floor muscles behind rectum. C, Head-on view of pelvic floor musculature showing paucity of anterior pelvic floor musculature. D, Pelvic floor anatomy after pelvic bony closure with intrafragmentary pins placed and bony apposition. E, Lateral view of pelvic floor anatomy after closure showing new anterior distribution of pelvic floor musculature and pin placement. F, Head-on view of pelvic floor musculature showing new anterior distribution of muscle and bony apposition. (Used with permission of Brady Urological Institute.)

anterior compartment; and (3) facilitates a smooth uniform contouring of the pelvic floor. These data reinforce the necessity for aggressive dissection and posterior placement of the posterior vesicourethral unit into the pelvis and the role of pelvic osteotomy and pelvic fixation.

Abdominal Wall Defects

The triangular defect caused by the premature rupture of the abnormal cloacal membrane is occupied by the exstrophied bladder and posterior urethra. The fascial defect is limited inferiorly by the intrasymphyseal band, which represents the divergent urogenital diaphragm. This band connects the posterior vesicourethral unit to the pubic ramus on anatomic study. The anterior sheath of the rectus muscle has a fanlike extension behind the urethra and bladder neck that inserts into the intrasymphyseal band. Investigations into the relationship of the rectus muscle and fascia to the urogenital diaphragm (Wakim and Barbet, 2002) have found no gross or histologic evidence of the presence of the striated sphincter. However, clear evidence of bladder musculature extending laterally to the pubis was found where it interdigitates with fibers from the rectus fascia, forming the fibrous urogenital diaphragm (Wakim and Barbet, 2002). Gearhart and colleagues (1991) have shown the importance of radical incision of these fibers lateral to the urethral plate down to the level of the inferior pubic ramus and levator hiatus, and data from failed exstrophy closures show these fibers to be intact in many patients at the time of reclosure.

At the upper end of the triangular fascial defect is the umbilicus. In bladder exstrophy, the distance between the umbilicus and the anus is foreshortened. Because the umbilicus is situated well below the horizontal line of the iliac crest, there is an unusual expanse of uninterrupted abdominal skin. If an umbilical hernia is present, it is usually of insignificant size. The umbilical hernia is repaired at the time of the initial exstrophy closure. Omphaloceles frequently seen in cloacal exstrophy are rare in exstrophy and are usually small and closed at the time of bladder closure.

The frequent occurrence of indirect inguinal hernias is attributed to a persistent processus vaginalis, large internal and external inguinal rings, and lack of obliquity of the inguinal canal. Connolly and colleagues (1995), in a review of 181 children with bladder exstrophy, reported inguinal hernias in 81.8% of boys and 10.5% of girls. At the time of closure of the bladder exstrophy, these hernias should be repaired by excision of the hernial sac and repair of the transversalis fascia and muscle defect to prevent recurrence or a direct inguinal hernia. The contralateral side should also be explored because the incidence of synchronous or asynchronous bilaterality is 81.8% (Connolly et al, 1995). Recent data by Lavien and colleagues (2014) in a large group of 136 exstrophy closures clearly demonstrated that if pelvic osteotomy is used for the closure, the incidence of development of a hernia is lower and the risk of recurrence after repair is lower.

Anorectal Defects

The perineum is short and broad and the anus is situated directly behind the urogenital diaphragm; it is displaced anteriorly and corresponds to the posterior limit of the triangular fascial defect. Recent data from Stec and colleagues (2011) found in a series of 678 patients with classic exstrophy an incidence of colorectal anomalies of 1.8%. The most common anomaly was imperforate anus, second was rectal stenosis, and third was congenital rectal prolapse. Although the incidence is low, it is a 72-fold increase compared with the general population.

The divergent levator ani and puborectalis muscles and the distorted anatomy of the external sphincter contribute to varying degrees of anal incontinence and rectal prolapse. Anal continence is usually imperfect at an early age. Rectal prolapse frequently occurs in untreated exstrophy patients and is usually transient and easily reduced. Prolapse disappears after bladder closure and pubic apposition. The appearance of prolapse in an infant is an indication to proceed with definitive management of the exstrophied bladder. If



Figure 139-6. Newborn male with classic bladder exstrophy. Note the dorsal chordee, short urethral plate, and flattening of the scrotum.

rectal prolapse occurs at any time after exstrophy closure, posterior urethral or bladder outlet obstruction should be suspected, and immediate evaluation of the outlet tract by cystoscopy should be performed (Baker and Gearhart, 1998).

Male Genital Defect

The male genital defect is severe and is the most troublesome aspect of the surgical reconstruction (Fig. 139-6). Formerly, it was thought that the individual corpora cavernosa were of normal caliber but appeared shorter because of the wide separation of the crural attachments, the prominent dorsal chordee, and the shortened urethral groove. However, Silver and colleagues (1997b) described the genital defect for the first time in exacting detail. MRI was used in adult men with bladder exstrophy and compared with results for age- and race-matched controls. It was found that the anterior corporeal length of male patients with bladder exstrophy was almost 50% shorter than that of normal controls (Fig. 139-7). However, although the posterior length of the corporeal body was the same as in age-matched controls, the diameter of the anterior corporeal segment was 30% greater than normal. Also, on MRI, although the diastasis of the symphysis pubis increased the intra-symphyseal and intercorporeal distances, the angle between the corpora cavernosa was unchanged because the corporeal bodies were separated in a parallel fashion. Therefore the penis appears short not only because of the diastasis of the pubic symphysis but also because of marked congenital deficiency of anterior corporeal tissue (Silver et al, 1997b). In a recent surgical anatomic study by Perovic and Djinojic (2008), precise description of the penile defect included (1) corporeal bodies separated and triangular in shape; (2) a long convex ventral surface and a short wedge-shaped dorsal surface; and (3) neurovascular bundle length determined by its lie on the individual corporeal bodies.

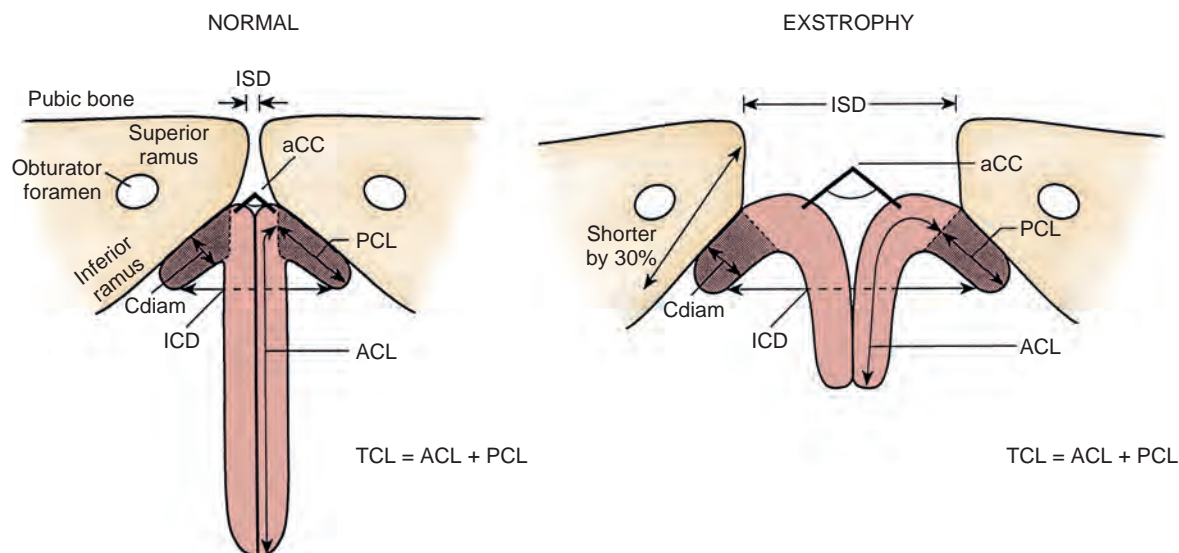


Figure 139-7. Separation of the pubic bones in men with classic exstrophy combined with the congenital deficiency of the anterior corporeal tissue leads to the shorter appearance of the penis. aCC, corpora cavernosa suspended angle; ACL, anterior corporeal length; Cdiam, corpus cavernosum diameter; ICD, intercorporeal distance; ISD, intersymphyseal distance; PCL, posterior corporeal length; TCL, total corporeal length.

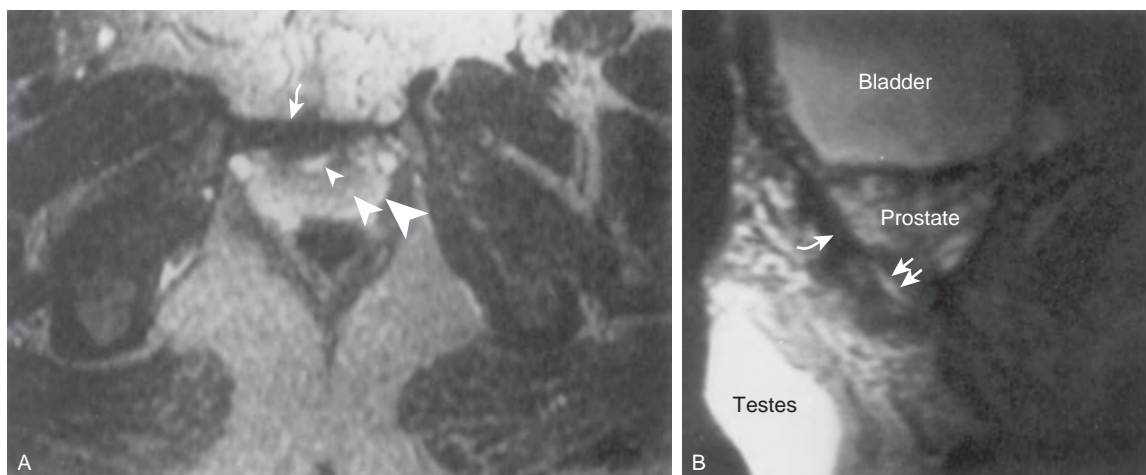


Figure 139-8. A, Axial T2-weighted image of the mid-prostate in a 20-year-old continent patient with bladder exstrophy. Small arrowhead, lumen of the urethra; medium arrowhead, transitional zone; large arrowhead, peripheral zone. Curved arrow, fibrous band of the intersymphyseal bar. B, Sagittal T2-weighted image through the mid-prostate gland shows anterior urethra (double arrows) and posterior prostate gland. Intersymphyseal fibrous band (curved arrow) extends along the entire length of the prostate.

In a study by Gearhart and associates (1993c), 13 adult men born with bladder exstrophy were evaluated with MRI of the pelvis to evaluate the size and configuration of the prostate and accessory sex organs. The volume, weight, and maximum cross-sectional area of the prostate appeared normal compared with published control values (Fig. 139-8). In none did the prostate extend circumferentially around the urethra, and the urethra was anterior to the prostate in all patients. Silver and coworkers (1997a) reported free and total prostate-specific antigen (PSA) levels for a group of adult men with exstrophy. Although the levels were measurable, they were below the upper limits of established age-specific reference ranges for normal men. The vas deferens and ejaculatory ducts are normal in the exstrophy patient, and the mean seminal vesicle length in men is normal compared with published controls.

Autonomic innervation of the corpus cavernosum is provided by the cavernous nerves. These autonomic nerves are displaced laterally in patients with exstrophy (Schlegel and Gearhart, 1989). These nerves are preserved in almost all exstrophy patients because potency is preserved after surgery. However, retrograde ejaculation may occur after bladder closure and/or bladder neck reconstruction.

Testis function has not been studied in a large group of postpubertal exstrophy patients, and it is generally believed that fertility is not impaired by testicular dysfunction. The testes frequently appear undescended in their course from the widened separated pubic tubercles to the flat, wide scrotum. Most testes are retractile and have an adequate length of spermatic cord to reach the scrotum without the need for orchiopexy.



Figure 139-9. Newborn girl with classic bladder exstrophy. Notice the open urethral plate, bifid clitoral halves, and anterior displacement of the vaginal orifice.

Female Genital Defects

Reconstruction of the female genitalia presents a less complex problem than in the male (Fig. 139-9). The vagina is shorter than normal, hardly greater than 6 cm in depth, but of normal caliber. The vaginal orifice is frequently stenotic and displaced anteriorly, the clitoris is bifid, and the labia, mons pubis, and clitoris are divergent. The cervix enters the vagina superiorly so that it lies in the anterior vaginal wall near the introitus. The fallopian tubes and ovaries are normal. The clitoral halves should be joined and the two ends of the labia minora joined to make a fourchette at the time of primary closure. Vaginal dilation or episiotomy may be required to allow satisfactory intercourse in the mature female. Prior data by [Stec and colleagues \(2001b\)](#) and recent 3D ultrasound data by [Ebert and colleagues \(2009\)](#) show that although the levator hiatus has a normal anteroposterior length, it is almost two times wider than normal. This defective pelvic floor may predispose mature females to the development of uterine prolapse, making uterine suspension necessary. This usually occurs after childbirth but can occur even in the nulliparous patient. When studied in a large adult female population, 10 of 56 women developed uterine prolapse at a mean age of 16 years. Six patients had been managed with reconstruction that included a posterior iliac osteotomy ([Mathews et al, 2003a](#)). Mean age at the time of osteotomy was 2.1 years. Formerly, it was thought that osteotomy in the newborn or during early childhood would be protective against the development of uterine prolapse in adult life. However, new data from [Anusionwu and colleagues \(2013\)](#) in a large group of women with exstrophy showed that the width of the adult diastasis was the only factor on univariate analysis to predict adult prolapse.

Urinary Defects

At birth, the bladder mucosa usually appears normal; but often hamartomatous polyps may be present on the bladder surface. The bladder mucosa should be frequently irrigated with saline and protected from trauma by some form of protective membrane before closure, so that cystic or metaplastic changes in the mucosal surface do not occur.

The size, distensibility, and neuromuscular function of the exstrophied bladder, as well as the size of the triangular fascial defect to which the bladder muscles attach, affect the decision to attempt repair. In the past several years, multiple basic science studies have been published that further delineate the exact nature of the exstrophied bladder in the newborn. One of the first papers to characterize the neuromuscular function of the bladder was published by [Shapiro and colleagues \(1985\)](#). In their work, muscarinic cholinergic receptor density and binding affinity were measured in control subjects and in patients with CBE. The

density of the muscarinic cholinergic receptors in both the control and exstrophy groups were similar, as was the binding affinity of the muscarinic receptor. Therefore, the neurophysiologic composition of the exstrophied bladder is not grossly altered during its anomalous development. Studies have investigated both the neural innervation of the newborn exstrophy bladder and its muscle and collagen content. [Lee and coworkers \(1996\)](#) looked at bladder biopsy specimens obtained from 12 newborns with bladder exstrophy, compared them with age-matched controls, and found an increase in the ratio of collagen to smooth muscle. Using anticollagen antibodies, they evaluated various types of collagen in these bladders and found there was no statistical difference in the amount of type I collagen in the bladders of newborns with exstrophy at initial closure, but there was a threefold increase in type III collagen. [Peppas and associates \(1999\)](#) found, in patients who gained adequate bladder capacities and were awaiting bladder neck reconstruction, that the ratio of collagen to smooth muscle decreased markedly after a successful closure and infection-free follow-up. [Lais and coworkers \(1996\)](#) reported similar findings and found that the ratio of smooth muscle to collagen increased after a successful closure.

In an extension of the studies just cited, [Mathews and coworkers \(1999b\)](#) looked at the number of myelinated nerves per field in the bladders of normal newborn subjects and those with exstrophy. The average number of myelinated nerves per field was significantly reduced in the exstrophy bladders compared with controls. This reduction in nerve fibers appears to be the result of a lack of small fibers with preservation of larger nerve fibers. In light of the findings, it is believed that bladder exstrophy in a newborn represents an earlier stage of bladder development and differentiation.

In a large study by [Rosch and colleagues \(1997\)](#), multiple immunocytochemical and histochemical markers were examined in patients with epispiadias or CBE. These studies involved indirect immunocytochemistry for vasoactive intestinal polypeptide (VIP), neuropeptide Y (NPY), substance P (SP), calcitonin gene-related peptide (CGRP), protein gene product (PGP) 9.5, and nicotinamide adenine dinucleotide phosphate diaphorase (NADPHd). No evidence of bladder muscle dysinnervation was found morphologically in any cases of CBE. Therefore, although a newborn with bladder exstrophy may have a maturational delay in bladder development, these bladders have the potential for normal development after a successful initial closure.

When the bladder is small, fibrosed, inelastic, and covered with polyps, functional repair may be impossible (Fig. 139-10). [Novak and colleagues \(2005\)](#) investigated the pathology and malignant potential of the polyps found in these small bladders. Two types of polyps were observed, with some overlap in findings: fibrotic and edematous. Both were associated with overlying squamous metaplasia in approximately 50% of cases. Varying degrees of von Brunn nests, cystitis cystica, and cystitis glandularis were noted. Cystitis glandularis was noted in a higher percentage of secondary closures. Because of the potential risk of adenocarcinoma associated with cystitis glandularis, future surveillance of these patients with urine cytology and cystoscopy as they enter adulthood is recommended. The more normal bladder may be invaginated or it may bulge through a small fascial defect, indicating the potential for satisfactory capacity after successful initial closure. **Not until examination under anesthesia can the true defect be adequately evaluated because the depth of this bladder extension into the pelvis cannot be appreciated unless the patient is under anesthesia.**

Bladder function was assessed in a group of continent exstrophy patients with normal reflexive bladders. Normal cystometrograms were obtained in 70% to 90% of patients ([Toguri et al, 1987](#)). [Diamond and associates \(1999\)](#), looking at 30 patients with bladder exstrophy at various stages of reconstruction, found that 80% of patients had compliant and stable bladders before bladder neck reconstruction. After bladder neck reconstruction, approximately half of the patients maintained normal bladder compliance and a lesser number maintained normal stability. The authors believed that compliance and stability were impaired after bladder neck reconstruction and that 25% of patients with exstrophy may



Figure 139-10. A, Small bladder template covered with polyps; unsuitable for closure. B, Extremely small bladder template in newborn; unsuitable for closure.

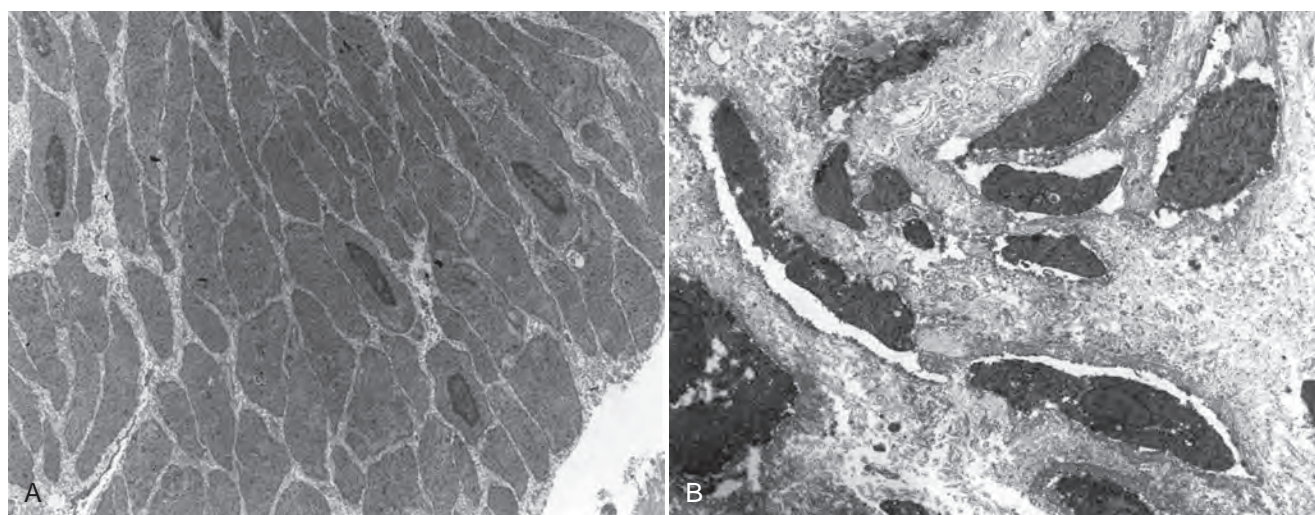


Figure 139-11. Ultrastructural changes noted in the exstrophic bladder. A, Normal muscle and nerve profiles in the newborn bladder. B, After failure of prior closure, significant deterioration is noted with increased intercellular collagen and degenerating muscle in an immunohistologic study. (From Mathews R, Gosling JA, Gearhart JP. Ultrastructure of the bladder in classic exstrophy: correlation with development of continence. *J Urol* 2004;172:1446–9.)

maintain normal detrusor function after reconstruction. In an earlier paper by [Hollowell and colleagues \(1993\)](#), 13 of 21 children revealed involuntary contractions and only 4 revealed stable bladders before bladder neck reconstruction. Also, 7 of 21 had increased pressures (greater than 10 cm H₂O), suggesting decreased compliance. The difference in findings between these two urodynamic studies is difficult to explain from an experimental perspective. However, standardized methods of bladder neck repair do not exist, and these differences may be reflected in the different urodynamic findings after bladder neck repair in these two groups of patients.

Several interesting aspects of the microstructure of the bladder in children with bladder exstrophy were noted by [Mathews and coauthors \(2004\)](#), who used specimens obtained from children with bladder exstrophy at various stages of reconstruction (newborn

bladder closure, bladder neck reconstruction, augmentation cystoplasty). At the cellular level, important differences were noted. Caveolae, which are important intracellular structures involved in cell-cell signaling, were found to be normal in the patients with a successful closure and improvement in bladder capacity and significantly lacking in the patients who required eventual augmentation cystoplasty ([Fig. 139-11](#)). In addition, the ultrastructure of cells in the patients in whom closure failed was noted to be abnormal. In a recent study by [Suson and colleagues \(2012\)](#) an attempt was made to further identify similarities and differences between exstrophy smooth muscle and normal bladder muscle. More than 95% of exstrophy and control smooth muscle cells stained positive for actin and myosin. Intracellular calcium concentration was lower in exstrophy smooth muscle than controls. More exstrophy cells migrated than control cells, although

it is not known if this movement is organized or directional. There were no differences in cell proliferation between the two groups. In a second study, [Suson and colleagues \(2012\)](#) showed that enhanced exstrophy smooth muscle cell migration was a result of excess transforming growth factor- β 1 signaling but was independent of increases in intracellular calcium concentration.

The upper urinary tract is usually normal, but anomalous development does occur. In a recent report by [Stec and colleagues \(2012a\)](#), 674 patients were reviewed; 462 were found to have had ultrasound examination. In this large review, 13 of 462 (2.8%) had a renal anomaly. The most common malformation was a duplicated collecting system (6); others included hypoplastic or absent kidney (3), pelvic kidney (2), ureteropelvic junction obstruction (1), and multicystic dysplastic kidney. This is a higher incidence than the 0.57% seen after 2 to 4 years of follow-up by antenatal screening ([Rosen-dahl, 1990](#)). The ureters have an abnormal course in their termination. The peritoneal pouch of Douglas between the bladder and the rectum is enlarged and unusually deep, forcing the ureter down laterally in its course across the true pelvis. The distal segment of the ureter approaches the bladder from a point inferior and lateral to the orifice, and it enters the bladder with little or no obliquity. Therefore, reflux in the closed exstrophy bladder occurs in 100% of patients, and reimplantation surgery is required at bladder neck reconstruction. If excessive outlet resistance is gained at the time of either initial closure or combined epispadias and bladder exstrophy closure, and recurrent infections are a problem even with suppressive antibiotics, ureteral reimplantation or Deflux injections are required before bladder neck reconstruction.

Exstrophy Complex and Variant

In addition to the three main presentations of the bladder exstrophy-epispadias complex—CBE, cloacal exstrophy, epispadias—many variations in anatomy and types of defects have been noted. Because there is probably a common embryologic origin for all of these defects, they all share many or some of the defects noted in the three major components of the complex—skeletal, urinary, and genital. The presence of a characteristic musculoskeletal defect of the exstrophy anomaly with no major defect in the urinary tract has been named *pseudoexstrophy* ([Marshall and Muecke, 1968](#)). Predominant characteristics include an elongated, low-set umbilicus and divergent rectus muscles that attach to the separated pubic bones. In this variant, the mesodermal migration has been interrupted in its superior aspect only, thus wedging apart the musculoskeletal elements of the lower abdominal wall without obstructing the formation of the genital tubercle.

In the superior vesical fissure variant of the exstrophy complex, the musculature and skeletal defects are exactly the same as those in classic exstrophy; however, the persistent cloacal membrane ruptures only at the uppermost portion, and a superior vesical fistula results that actually resembles a vesicostomy. Bladder extrusion is minimal and is present only over the normal umbilicus (see [Fig. 139-1B](#)).

In a large review of an exstrophy database of over 815 patients, [Lowentritt and colleagues \(2005\)](#) reported 25 exstrophy complex variants, of which six were cloacal exstrophy variants. Continence rates after bladder neck repair were compatible with classic exstrophy. Three cases were reported by [Arap and Giron \(1986\)](#) in which the patients had classic musculoskeletal defects, and two of the three were continent. Of the two male patients, one had an associated complete epispadias and the other had a completely normal penis. Therefore the external genital manifestations in exstrophy variants can be quite variable.

In addition to pseudoexstrophy, superior vesical fissure, and duplicated exstrophy, isolated occurrences of a fourth entity, covered exstrophy, have been reported ([Cerniglia et al, 1989](#)). This has also been referred to as *split symphysis variant*. A common factor in these patients is the presence of musculoskeletal defect associated with classic exstrophy but no significant defect of the urinary tract. [Chandra and associates \(1999\)](#) reported a covered exstrophy with incomplete duplication of the bladder. However, in cases of covered

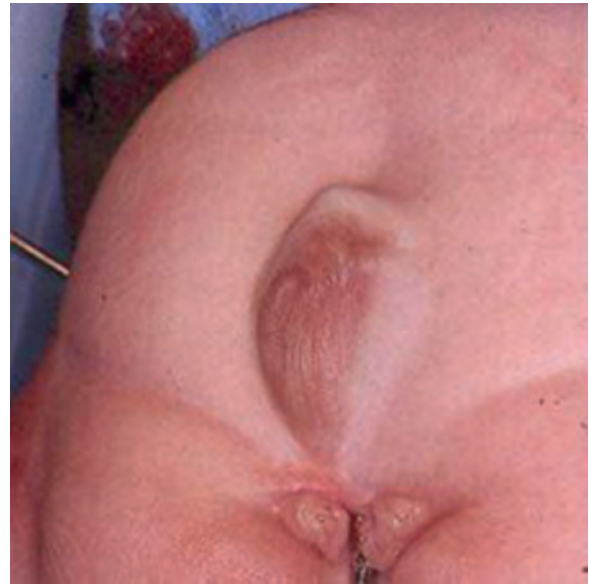


Figure 139-12. Skin-covered exstrophy in a female patient. Note urethral sound in the bladder and the subcutaneous position below the skin of the abdominal wall. No bowel is sequestered on the abdominal wall, as has been reported in some patients with this variant.

exstrophy ([Narasimharao et al, 1985](#); [Cerniglia et al, 1989](#)), there has been an isolated ectopic bowel segment present on the inferior abdominal wall near the genital area, which can be either colon or ileum with no connection with the underlying gastrointestinal tract and only epispadias in the male. A patient seen at our institution had the standard appearance of most split symphysis variants, and one could actually see the bladder through a thin membrane of lower abdominal skin ([Fig. 139-12](#)); all of the classic musculoskeletal defects of exstrophy were present. These patients should all undergo formal exstrophy closure at birth.

There are two different forms of bladder duplication: anteroposterior duplication and side-by-side duplication. The former form is considered a duplicate exstrophy with a patch of everted bladder mucosa on the anterior abdominal wall and a second bladder lying in the pelvis. The ureters attach to the closed bladder, rendering the superficial mucosa dry ([Fig. 139-13](#)). The mainstay of treatment has been resection of the ectopic mucosa and closure of the abdominal wall defect. The other form of duplication involves patients who have two separately formed bladder halves in a left-right orientation with a midline septum between the bladders containing muscle. Each bladder has its own ureter and an intact sphincter. Often there is diastasis of the pubis and rectus muscle.

The bladder exstrophy-epispadias-cloacal exstrophy complex has a wide range of presentations. Variants are rare, but it is important to recognize the different appearances at birth, because the initial treatment will greatly influence the long-term outcome. Two patient groups had better outcomes than those with classic presentations—superior vesical fissure and skin-covered cloacal exstrophy. Because the sphincter is intact, patients with superior vesical fissure went through regular toilet training and became continent without the need for a later bladder neck procedure. Many reports of exstrophy variants include these patients, leading to the wrong belief that all patients with variants perform better than those with bladder exstrophy. [Lowentritt and colleagues \(2005\)](#) suggest that other than superior vesical fissure, all variants should be managed with formal exstrophy closure at birth and followed in the same manner as their classic presentations.

Prenatal Diagnosis

Even with modern ultrasound modalities, the prenatal diagnosis of bladder exstrophy is often difficult to delineate. Frequently, a

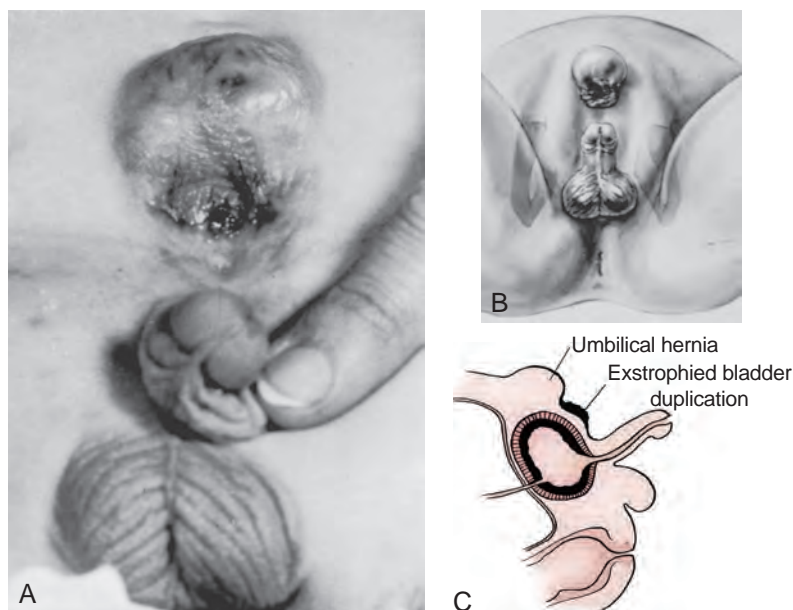


Figure 139-13. A-C, Duplicate exstrophy in a boy with an intact lower urinary tract.

diagnosis of omphalocele or gastroschisis is made and the exstrophy condition is overlooked. Ultrasound evaluation of the fetus by means of high-resolution real-time units allows a thorough survey of the fetal anatomy, even during routine obstetric ultrasound examinations (Gearhart et al, 1995a). Several groups have outlined important criteria for the diagnosis of CBE prenatally. In these reviews, the absence of a normal fluid-filled bladder on repeated examinations suggested the diagnosis, as did a mass of echogenic tissue on the lower abdominal wall (Mirk et al, 1986; Verco et al, 1986). In a review of 25 prenatal ultrasound examinations with the subsequent birth of a newborn with CBE, Gearhart and colleagues (1995a) made several observations: (1) absence of bladder filling, (2) a low-set umbilicus, (3) widening pubis ramus, (4) diminutive genitalia, and (5) a lower abdominal mass that increased in size as the pregnancy progressed and as the intra-abdominal viscera increased in size (Fig. 139-14).

The application of 3D ultrasonography and fetal MRI has only somewhat improved the antenatal diagnosis of bladder and cloacal exstrophy, because only 25% of cases of bladder exstrophy-epispadias complex are diagnosed prenatally (Goyal et al, 2012). In our practice, fetal MRI is reserved for patients in whom 3D ultrasonography is not sufficient to differentiate satisfactorily between classic and cloacal exstrophy, or when other severe anomalies are suspected. The main reason for the prenatal diagnosis of bladder exstrophy is so that the parents can be counseled regarding the risks and benefits and other aspects of the condition. After appropriate counseling, arrangements can be made for delivery of the baby in a specialized exstrophy center where immediate reconstruction of the exstrophy can occur. Delivery in a specialized exstrophy center allows the parents to be exposed to the expertise of multiple disciplines, including the all-important psychological support these parents need when a child with a birth defect of this magnitude is delivered.

SURGICAL RECONSTRUCTION OF BLADDER EXSTROPHY

Sweetser and associates (1952) initially described a staged surgical approach for bladder exstrophy. Four to 6 days before bladder closure, bilateral iliac osteotomies were performed. Epispadias repair was performed as a separate procedure. The continence procedure was limited to freeing the fibers from the intrasymphyseal band and wrapping this band around the urethra at the time of closure to increase outlet resistance.

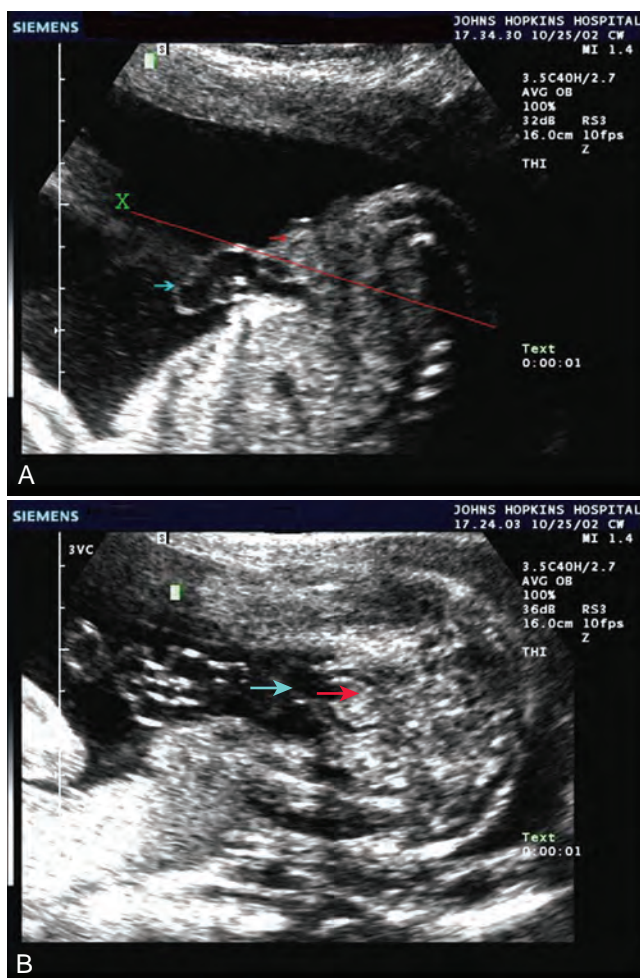


Figure 139-14. Prenatal ultrasound scan demonstrating bladder exstrophy. A, Longitudinal view showing the low-set umbilicus (cyan arrow), lack of intra-abdominal bladder, and lower abdominal mass (red arrow). B, Transverse view through the plane (X) in A shows presence of the umbilicus (cyan arrow) and the upper edge of the bladder plate that appears hyperechoic (red arrow).

The initial staged approach to functional bladder closure included three separate stages: bladder and abdominal wall closure; bladder neck reconstruction and antireflux procedure; and later epispadias repair. This approach was recommended for most cases of exstrophy reconstruction beginning in the early 1970s (Cendron, 1971; Jeffs et al, 1972; Williams and Keaton, 1973). Although this procedure was successful, it has been modernized in the last 15 years to include bladder closure, abdominal wall closure, and posterior urethral closure well onto the penis in the newborn period with bilateral innominate and vertical iliac osteotomy, if indicated; epispadias repair at 6 months to 1 year of age; and bladder neck reconstruction along with antireflux procedure at age 4 to 5 years, when the child has achieved an adequate bladder capacity for bladder neck reconstruction and is motivated to participate in a postoperative voiding program (Gearhart and Jeffs, 1998).

Other methods of treatment of the newborn with bladder exstrophy have been offered. Grady and Mitchell (1999) proposed combining bladder exstrophy closure with penile repair in the newborn period. Baka-Jakubiak (2000) recommended newborn exstrophy closure alone and combined bladder neck reconstruction and epispadias repair when the child reaches a satisfactory age for participation in a voiding program. Kelly (1995) has recommended a staged repair in which no osteotomy is used and a second-stage “radical soft-tissue mobilization” is performed before later urethral repair. Schrott and colleagues (1984) recommended bladder closure, ureteral reimplantation, epispadias repair, and bladder neck reconstruction in the newborn period. Lastly, Stein and coworkers (1999) recommended ureterosigmoidostomy in the newborn period with abdominal wall and bladder closure.

Evaluation and Management at Birth

At birth, although the bladder mucosa is usually smooth, pink, and intact, it is also sensitive and easily denuded. In the delivery room the umbilical cord should be tied with 2-0 silk close to the abdominal wall so that the umbilical clamp does not traumatize the delicate mucosa and cause excoriation of the bladder surface. The bladder can then be covered with a nonadherent film of plastic wrap (e.g., Saran Wrap) (Fig. 139-15) to prevent sticking of the bladder mucosa to clothing or diapers. In addition, each time the diaper is changed the wrap should be removed, the entire bladder surface irrigated with sterile saline, and clean wrap placed over the bladder surface area.

The parents typically need reassurance at this stage. Counseling of the parents and decisions regarding eventual therapy should begin prenatally if the condition is diagnosed by prenatal ultrasonography. The parents should be educated by a surgeon with a

special interest and experience in managing the exstrophy spectrum. An exstrophy support team should be available and should include a pediatric orthopedic surgeon, pediatric anesthesiologist, social workers, nurses with special interest in bladder exstrophy, and a child psychiatrist or psychologist with expertise and experience in genital anomalies. The Association for the Bladder Exstrophy Community is available and has a website for parents and family members to obtain further information about the bladder exstrophy condition.

Cardiopulmonary and general physical assessment measures can be carried out in the first few hours of life. Well-done ultrasound studies are usually sufficient to provide evidence of renal structure, function, and drainage, even in the first few hours of life before the patient undergoes closure of the exstrophy defect.

Circumstances may be less than ideal at birth. A thorough neonatal assessment may have to be deferred until transportation to a major children's medical center can be arranged. In these days of modern transportation, no child is ever more than a few hours away from a neonatal center with full diagnostic and consultative services. During travel the bladder should be protected by a plastic membrane, as in the nursery, to prevent damage to the delicate newborn bladder mucosa.

Selection of Patients for Immediate Closure

Successful treatment of exstrophy with functional closure demands that the potential for success in each child be carefully considered at birth by an experienced exstrophy surgeon. The size and the functional capacity of the detrusor muscle are important considerations for the eventual success of functional closure. Correlation between apparent bladder size and the potential bladder capacity must not be confused. In minor grades of exstrophy that approach the condition of complete epispadias with incontinence, the bladder may be small yet may demonstrate acceptable capacity, either by bulging when the baby cries or by indenting easily when touched by a sterile gloved finger in the operating room with the child under anesthesia. **Sometimes a good bit of previously unappreciated bladder can be discovered behind the fascia on examination with anesthesia** (Gearhart and Jeffs, 1998). Once the bladder is relieved of surface irritation and repeated trauma, the small bladder can enlarge and increase in capacity with the absence of sphincter activity and with minimal outlet resistance.

Small Exstrophy Bladder Unsuitable for Newborn Closure

A small, fibrotic bladder patch that is stretched between the edges of the small triangular fascial defect without elasticity or contractility cannot be selected for the usual closure procedure (Gearhart and Jeffs, 1998) (see Fig. 139-10A). Examination with the patient under anesthesia is often required to assess the bladder adequately, particularly if considerable edema, excoriation, and polyp formation have developed between birth and the time of assessment. **Decisions regarding the suitability of bladder closure or the need for waiting should be made only by surgeons with a great deal of experience in the exstrophy condition** (Gearhart and Jeffs, 1998). Some conditions preclude primary closure, including penoscrotal duplication, ectopic bowel within the extruded bladder (a relative contraindication), a hypoplastic bladder, and significant bilateral hydronephrosis.

In a paper submitted by Lakshmanan and colleagues (2008) of an exstrophy database of 1248 classic exstrophies, it was found on initial judgment that the bladder was too small for closure in 46 patients evaluated at birth. There were 36 boys and 10 girls who underwent delayed closure at a mean age of 13.2 months. Osteotomy was performed on 41 (89%). All had a successful delayed primary closure. Eighteen boys had a simultaneous epispadias repair. Sixty-one percent developed sufficient capacity for bladder neck reconstruction, and 39% are continent. Compared with data by Novak and colleagues (2010), these rates are more than double the continence rates seen in bladder neck repair after failed primary closure and successful secondary closure.



Figure 139-15. Use of plastic wrap to keep bladder plate moist before closure.

Thus, waiting for the bladder template to grow for 6 to 12 months in the child with a small bladder is not as risky as submitting a small bladder template to closure in an inappropriate setting, resulting in dehiscence and possible future incontinence. If the bladder does not grow to sufficient size for closure after 6 to 12 months, other options include excision of the bladder and a non-refluxing colon conduit or ureterosigmoidostomy.

Osteotomy

Children born with bladder exstrophy have not only an exposed bladder but a wide diastasis of the pubic rami (average 4.8 cm), resulting in an open pelvic ring. In addition, the larger the bladder template, the wider the resultant diastasis and the greater the need for osteotomy. The musculoskeletal function of the hip and lower extremity appears to be normal throughout childhood; however, the gait is characterized by external foot rotation, which lessens with growth as lower extremity muscle function strengthens, even if osteotomy is not performed.

Several types of pelvic osteotomies have been developed to help to close the pelvic ring, decrease the stress on the abdominal wall during initial exstrophy closure, and improve the outcome of future genitourinary reconstruction. Shultz (1958) was the first, as far as we know, to describe bilateral posterior iliac osteotomy as part of a two-stage repair of bladder exstrophy. Bilateral posterior iliac osteotomy was performed, and 1 to 3 weeks later exstrophy closure was accomplished. This early osteotomy was shown to lower rates of wound dehiscence and to help achieve a more secure and better genitourinary reconstruction.

Patients may undergo pelvic osteotomy at any stage of exstrophy repair if the diastasis prevents attainment of these urologic goals. **In general, we do not routinely perform osteotomy on newborns unless the diastasis is over 4 cm or the malleability of the pelvis is poor.** The laxity of the sacroiliac ligaments usually allows closure of the defect without undue tension in the first 48 to 72 hours of age. We make this decision with the patient under anesthesia at the time of primary closure with our pediatric orthopedic colleagues.

Types of osteotomies that have been used include bilateral osteotomy of the superior pubic ramus, diagonal osteotomy of the iliac wing, and anterior innominate osteotomy with or without vertical iliac osteotomy. The more commonly used combined anterior innominate and vertical osteotomy was developed for several reasons: (1) the osteotomy is performed with the patient in the supine position as for the urologic repair, avoiding the need to turn the patient; (2) the anterior osteotomy also allows placement of an external fixator and intrafragmentary pins under direct vision; (3) a greenstick-type closing-wedge osteotomy of the ilium is also performed adjacent to the sacrum in most patients, creating two large bony fragments that are easily movable; (4) the cosmetic appearance of this osteotomy is superior to that of a posterior iliac osteotomy (Gearhart et al, 1996b); and (5) the superior pelvic bone malleability and ease of apposition of the pubic bone without tension.

After failure of initial closure in children with significant pubic diastasis, as seen in large bladder templates and cloacal exstrophy, osteotomy is always required. Pubic approximation may not be possible in a single step at the time of abdominal closure when the diastasis is extreme (>6 cm). The use of staged closure of the pelvis after osteotomy has been used successfully in this circumstance. This technique has been used for the treatment of children with extreme diastasis, even in younger patients, and the cloacal exstrophy condition.

Pelvic osteotomy performed at the time of initial closure confers several advantages, including (1) easy approximation of the symphysis with diminished tension on the abdominal wall closure and elimination of the need for fascial flaps; (2) placement of the posterior vesicourethral unit deep within the pelvic ring, enhancing bladder outlet resistance; and (3) bringing the large pelvic floor muscles near the midline, where they can support the bladder neck and aid in eventual urinary control

(Fig. 139-16). After pubic approximation with osteotomy, some patients show the ability to stop and start the urinary stream, experience dry intervals, and in some cases become completely continent (Gearhart and Jeffs, 1991a). In a review of a large number of patients referred to our institution after failed exstrophy procedures, it was found that a majority of the patients who had partial or complete dehiscence of the bladder or major bladder prolapse had not undergone an osteotomy at the time of initial bladder closure (Gearhart et al, 1993b). We recommend performing bilateral transverse innominate and vertical iliac osteotomy when bladder closure is performed after 72 hours of age (Fig. 139-17). In addition, if the pelvis is not malleable or if the pubic bones are more than 4 cm apart at the time of initial examination under anesthesia, osteotomy should be performed, even if closure is done before 72 hours of age. A well-coordinated surgery and anesthesia team can perform osteotomy and proceed to bladder closure without undue loss of blood or risk of prolonged anesthesia in the child. However, it must be realized that osteotomy together with posterior urethral and bladder closure and abdominal wall closure is a 5- to 7-hour procedure in these infants.

If the patient is younger than 72 hours and examination under anesthesia reveals that the pubic bones are malleable and able to be brought together easily in the midline by medial rotation of the greater trochanters, the patient can undergo closure without osteotomy. No chances should be taken with a decision of this magnitude, and if any doubt exists, an osteotomy should be performed.

The most frequently used osteotomy today is the bilateral anterior innominate and vertical iliac osteotomy, popularized by Gearhart and colleagues in 1996 (Gearhart et al, 1996b). This approach improves the ease of symphyseal approximation in the patient with exstrophy compared with posterior approaches. In our experience, this osteotomy is superior to the pubic mobilization seen with simple bilateral transverse anterior innominate osteotomy or even pubic ramotomy. **With the ease of approximation obtained with this combined osteotomy, tension on the midline abdominal closure is lessened and the rates of bladder dehiscence and bladder prolapse are markedly decreased (Gearhart and Jeffs, 1998).** In addition, pelvic closure allows anterior movement of the levator ani to strengthen the puborectalis sling. This helps position the bladder neck and posterior urethra deep within the pelvic ring and improved continence rates. This also moves the pelvic floor muscles into a more anterior position, thus providing more support for the anterior pelvic organs.

Combined osteotomy is performed by placing the patient in the supine position, preparing and draping the lower body below the costal margins, and placing soft absorbent gauze over the exposed bladder. The pelvis is exposed from the iliac wings inferiorly to the pectineal tubercle and posteriorly to the sacroiliac joints. The periosteum and sciatic notch are carefully elevated, and a Gigli saw is used to create a transverse innominate osteotomy exiting anteriorly at a point halfway between the anterior superior and anterior inferior spines (see Fig. 139-17). This osteotomy is created at a slightly more cranial level than that described for a Salter osteotomy to allow placement of external fixator pins in the distal segments. In addition to the transverse osteotomy, the posterior ilium may be incised from the anterior approach in an effort to correct the deformity more completely. For this part of the osteotomy, an osteotome is used to create a closing wedge osteotomy vertically and just lateral to the sacroiliac joints. The proximal posterior iliac cortex is left intact and used as a hinge (see Fig. 139-17). This combination osteotomy easily corrects the abnormalities in both the anterior and posterior segments of the pelvis.

Two fixator pins are placed in the inferior osteotomized segment, and two are placed in the wing of the ilium superiorly. Radiographs are obtained to confirm pin placement, soft tissues are closed, and the urologic procedure is performed (see Fig. 139-16). At the end of the procedure, the pelvis is closed with a suture between the two pubic rami. The external fixators are then applied between the pins to hold the pelvis in a correct position. In a newborn with less than optimal amounts of cancellous bone, only one pin is placed

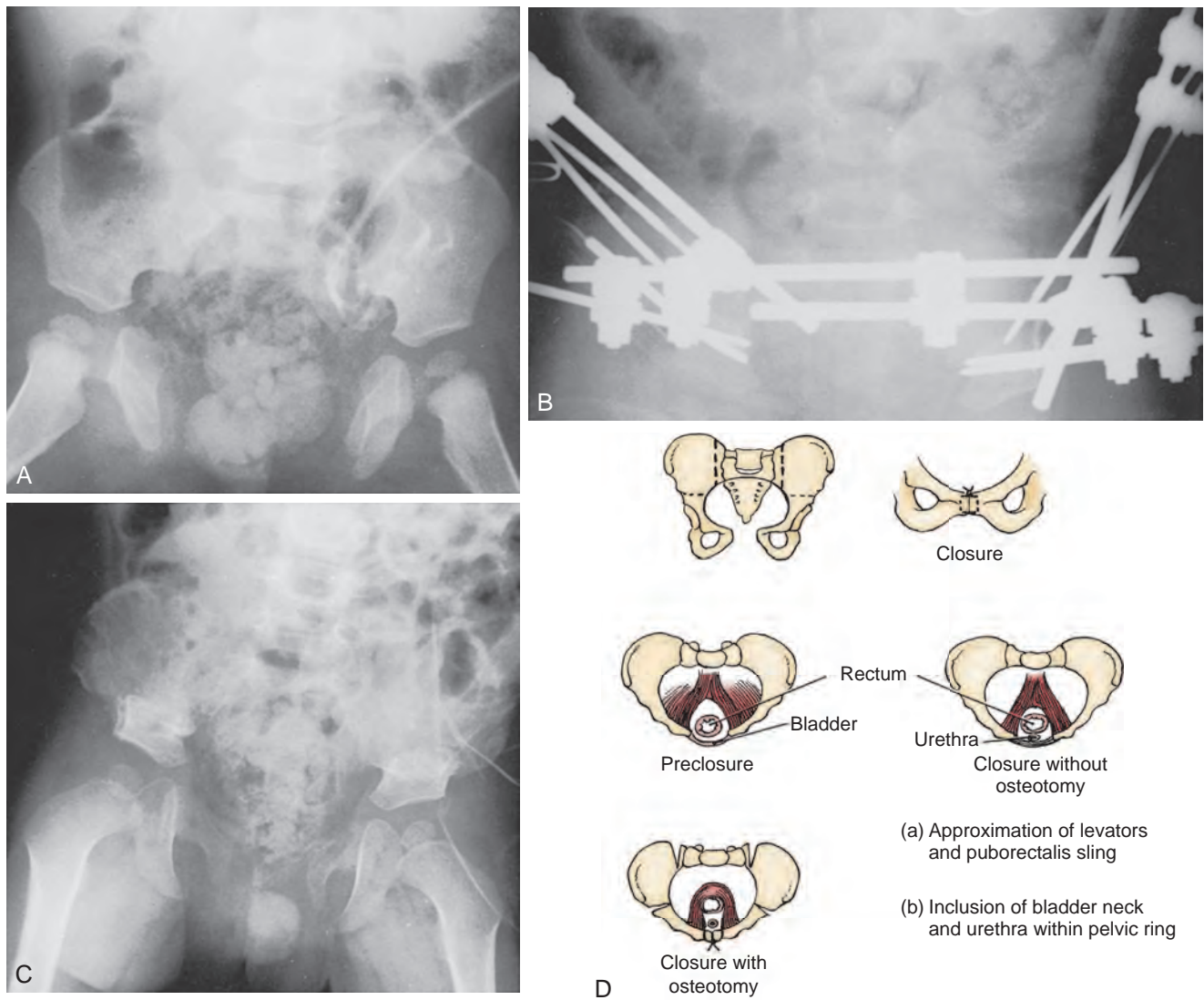


Figure 139-16. A, Eight-month-old patient with classic bladder exstrophy closed at birth without osteotomy with complete dehiscence. Patient was initially seen at 8 months of age. B, Patient after having undergone anterior innominate and vertical iliac osteotomy and placement of intrafragmentary pins and external fixator. C, The same patient 4 months after removal of external fixator and pins. Successful closure was achieved. D, The technique of combined osteotomy showing incision sites.

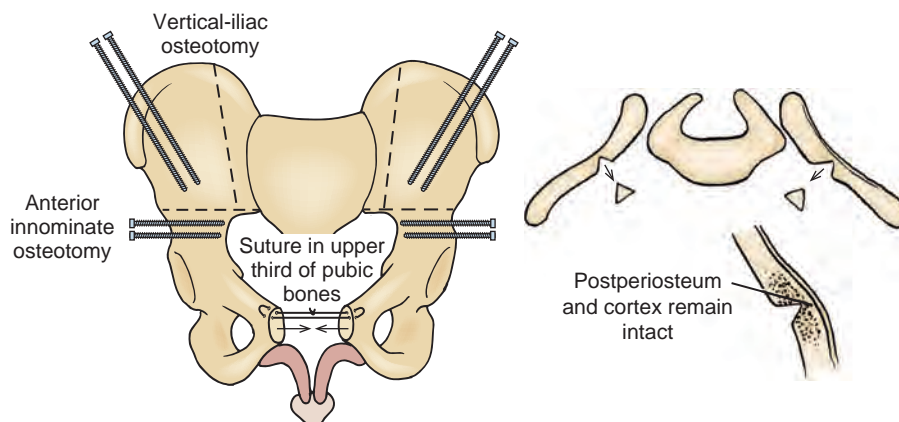


Figure 139-17. Technique of combined osteotomy showing bony incision sites and pin placement.



Figure 139-18. Fifteen-month-old patient after reclosure of bladder exstrophy with external fixator in place and modified Buck traction.

inferiorly and superiorly in the wing of the ileum, instead of two as in older children.

Radiographs are taken 7 to 10 days after surgery to look for complete reduction of the symphyseal diastasis. If this diastasis has not been completely reduced, the right and left sides can be gradually approximated by means of the fixator bars over several days. Longitudinal skin traction is used to keep the legs still (Fig. 139-18). The patient remains supine in traction for approximately 4 weeks to prevent dislodgement of tubes and destabilization of the pelvis. The external fixator is kept on for 4 to 6 weeks, until adequate callus is seen at the site of the osteotomy (see Figs. 139-16B and 139-17). Postoperatively, in newborns who undergo closure without osteotomy in the first 48 to 72 hours of life, the baby is immobilized in modified Bryant traction in a position in which the hips have 90 degrees of flexion. When modified Bryant traction is used, the traction is used for 4 weeks. A horizontal mattress suture of No. 2 nylon is placed between the fibrous cartilage of the pubic rami and tied anteriorly to the pubic closure at the time of bladder closure. Evidence obtained by [Sussman and associates \(1997\)](#) from biomechanical testing in an intact piglet pelvic model revealed that all methods of pubic approximation were weak compared with the intact symphysis. However, the best technique with the strongest load-to-failure ratio was a No. 2 nylon horizontal mattress suture.

Complications of Osteotomy and Immobilization Techniques

Complications of inadequate immobilization can include failure of the closure, bladder prolapse, loss of suprapubic tubes, and ureteral stents. Closely related to inadequate immobilization is inadequate pain and movement control. With tunneled epidural catheters for 2 to 3 weeks, pain and movement are well controlled while the pelvic bone callus formation increases in the osteotomy wound and the wound stabilizes.

Some centers still prefer to use spica casts and mummy wraps. In a series from Seattle, the authors preferred spica casts with or without osteotomy over other techniques and felt this allowed earlier discharge from the hospital ([Shnorhavorian et al, 2010](#)). However, in a large series of 86 failed exstrophy closures, [Meldrum and colleagues \(2003\)](#) found that most had been immobilized with a mummy wrap or spica cast. Successful closure was noted in 97% of those immobilized with an external fixator and modified Buck traction.

[Sponseller and colleagues \(2001\)](#) reported on a total of 86 combined bilateral anterior innominate and vertical iliac osteotomies performed in 88 children. Ten children had cloacal exstrophy and

72 bladder exstrophy with at least 2 years of clinical follow-up (mean 4.8 years). Complications included seven cases of transient left femoral nerve palsy, which resolved fully by 12 weeks after surgery. There were no cases of right femoral nerve palsy, although the same surgeon performed the same technique on both sides. Patients with transient femoral nerve palsy were on bed rest for the first 6 to 8 weeks; a knee immobilizer was needed for the remaining 6 weeks until resolution. Other complications included three cases of delayed ileal union, one case of superficial infection of the ileal femoral incision that required irrigation and debridement, one case of transient right thigh abductor weakness, one infection of the ileum around a pin site requiring irrigation and debridement, and one case of transient right peroneal palsy. Almost all patients had skin inflammation around the pins, particularly those in the proximal (iliac crest) segments. This was always controlled with the use of oral antibiotics. In a paper by [Satsuma and colleagues \(2006\)](#), comparisons were made between patients who underwent posterior iliac or combined osteotomy. Pubic approximation was better and the mean recurrence far less in the combined transverse innominate and vertical iliac osteotomy. Thus, the combined approach corrected and maintained the pelvic ring with fewer complications than a posterior pelvic osteotomy.

When good callus formation is seen on radiography, the fixating device and pins are removed at the bedside with the patient under light sedation. The age of the patient plays a role in the amount of correction of the diastasis that is maintained over time. On review of the previously described types of osteotomy, both classic and cloacal exstrophy patients gained approximation, although the former group gained greater correction toward normal ([Gearhart et al, 1996b](#)). Greater preoperative diastasis as well as less optimal bone density in the newborn contributes to the greater difficulty in obtaining and maintaining closure of the pelvic bone deformity over time.

It is our impression that partial recurrence of diastasis occurs in classic exstrophy by two mechanisms, even after osteotomy. First, the pelvis may partially derotate owing to early loosening of pins before the time of osteotomy healing; this is seen mostly in infants. In the older child, increased bone density allows more rigid external fixation and thus better maintenance of the corrected position. Second, there is long-term undergrowth of the ischiopubic segment, which has been shown to be 33% smaller than normal in the adult with exstrophy, as the pelvis grows. Pubic diastasis increases with growth in the patient with uncorrected exstrophy. Therefore, even with some loss of approximation, significant correction remains in comparison to the unoperated state. **We regard the main role of osteotomy to be relaxation of tension on the bladder, posterior urethra, and abdominal wall repair during healing.** Therefore, we

use osteotomy less in newborns and young infants because ligament laxity allows the pelvis to be closed without tension if the diastasis is reasonable and pubic bones are malleable. However, it becomes essential in the older child with a failed exstrophy repair, in the patient with cloacal exstrophy, and in a newborn with a wide diastasis and excellent bladder template. In patients undergoing combined exstrophy closure and epispiadias repair, osteotomy allows the pubis to be joined, making it easier for the corpora to be brought over the closed proximal urethra (Gearhart et al, 1998). In a large series of failed exstrophy reclosures (mean age 23.2 months), 56 patients were found who underwent repeat pelvic osteotomy (Nelson et al, 2006). All of the reclosures were successful, and 95% of the patients had a normal gait after reoperative osteotomy. There were no femoral or sciatic nerve palsies, and only five local pin site infections, which were easily treated. Repeat pelvic osteotomy is safe with low complications in experienced hands.

Whichever type of osteotomy is used, pelvic ring closure not only allows midline approximation of the abdominal wall structures but also allows the levator ani and puborectalis muscles to lend potential support to the bladder outlet, thus increasing resistance to urinary outflow (see Fig. 139-16D) (Sponseller et al, 1991; Gearhart et al, 1993b, 1996b; Schmidt et al, 1993; McKenna et al, 1994). Furthermore, a continence procedure can be performed later on the bladder neck and urethra deep within the closed pelvic ring at a distance from the surface without independent movement of the two halves of the pubis. The urethra and bladder neck are set more deeply in the true pelvis, in a more normal relationship than when acutely angulated.

Surgical Options in the Newborn with Classic Bladder Exstrophy

Although modern staged repair of exstrophy (MSRE) currently enjoys widespread popularity, other methods have been described for the primary reconstruction of exstrophy and are used in good centers. This section discusses the other types of repair and their use and application. The outcomes and complications are discussed in separate sections, as many are similar and their correction the same.

Warsaw Approach

First described by Baka-Jakubiak in 2000, the Warsaw procedure involves closing the bladder, posterior urethra, pubis, and abdominal wall at the time of primary closure with or without osteotomy but always with appropriate immobilization. Osteotomy is used in all patients older than 72 hours or in any with a diastasis greater than 5 cm. A spica cast is used for 3 weeks and an elastic bandage for 3 additional weeks. When the bladder has achieved suitable capacity (more than 70 mL) and the child is interested in continence, bladder neck repair is performed along with epispiadias repair. Baka-Jakubiak used this approach in over 100 patients with classic exstrophy and complete epispiadias. The intersymphyseal band is routinely divided to allow better visualization of the bladder neck and posterior urethra region. An additional proposed benefit of this procedure is that the bladder neck and posterior urethral unit is straighter at the second procedure, and this allows easier catheterization and cystoscopy after reconstruction. A 10% complication rate, mainly urethral fistula or stricture, is noted with this procedure.

Kelly Repair

The radical soft-tissue mobilization procedure was developed by Kelly in the late 1980s and early 1990s as a means to improve on the technique described by Ansell (1983) and to obviate pelvic osteotomies that were often required to obtain a tension-free closure. It is a multistage repair that includes (1) closure of the bladder dome and hernia repair at birth, followed at age 3 to 6 months by (2) reconstruction of the proximal urethra with

associated sphincteric tissue with penile lengthening and creation of a penoscrotal urethroostomy in boys, and (3) repair of the resulting penoscrotal hypospiadias at around 3 years of age. The unique aspects relate to the second stage, in which a more radical mobilization of the pelvic floor muscles is performed. Specifically, the dissection includes the periosteum of the ischium and pubis where one encounters the attachment of the voluntary and involuntary sphincter muscles, as well as the pudendal nerves and vessels. The muscles are then wrapped around the reconstructed proximal urethra in an attempt to provide a continence mechanism. The neourethra itself is constructed from the urethral plate on the dorsum of the penis after it is dissected from the corporeal bodies much as in the penile disassembly technique. However, unlike the penile disassembly technique, the meatus is always brought to the penoscrotal junction and later is brought distally.

Complete Repair

Developed by Mitchell, the complete repair combines the standard bladder closure with the “penile disassembly” technique for epispiadias repair in an effort to decrease the number of procedures required for reconstruction and potentially provide continence without the need for formal bladder neck reconstruction (Grady and Mitchell, 1999).

This technique of penile repair was developed by Mitchell and Bägli (1996). It has now been incorporated in the complete primary repair of exstrophy (CPRE) for primary closure in the newborn.

The penis is dissected into three components—the right and left corpora with their associated hemiglans and the urethral wedge (urethral plate with its associated spongiosa) (Fig. 139-19). The dissection as in the Cantwell-Ransley repair begins on the ventral aspect of the penis. The dissection moves medially just above the Buck fascia but is taken down to the tunica albuginea of the corpora. Care is taken to preserve the spongiosum with the urethral wedge, and this dissection is carried posteriorly to the area of the bladder neck. The penis is then separated into the three aforementioned components. Several authors have found problems getting the reconstructed urethra back to the tip of the glans and have recommended interrupted suturing of the urethral plate or leaving the most distal part of the urethral plate attached to the glans as in the Cantwell-Ransley repair. Others have found the need to make the patients hypospiadiac and then perform a later hypospiadias repair because of a shortened urethral plate. The rate of hypospiadias created has been reported to be from 30% to 70% of cases. If the urethra can be brought up to each hemiglans, an orthotopic meatus is configured. The glans is brought together using interrupted mattress sutures of polydioxanone suture (PDS) followed by horizontal mattress sutures of 7-0 nonfilament suture to bring the glanular epithelium together. The urethra is matured to the glans with interrupted sutures of 7-0 braided polyglactin sutures. The corpora are then brought over the reconstructed urethra with interrupted sutures. Skin closure is similar to that of standard hypospiadias repair with fine absorbable sutures. If concomitant exstrophy closure is to be done, the dissection then moves proximally into the pelvis to be able to move the structures into the pelvis. Another part of the complete repair is bladder neck “tailoring” to provide some outlet resistance after closure in the newborn (see Fig. 139-19).

Mitchell emphasizes the importance of dissecting the perineal membrane from the pubis, allowing the bladder and posterior urethra to be set deep into the pelvis. This feature is common to all properly performed exstrophy reconstructions and helps ensure success. The dissection of the urethral plate from the corpora leaves 60% to 75% of patients with hypospiadias (Hafez and El-Sherbiny, 2005), and 50% of children require urethral reimplantation in the first year of life (Grady and Mitchell, 1999).

Mainz Repair

Hohenfelner and colleagues first began using ureterosigmoidostomy for both failed exstrophy patients and for patients with small

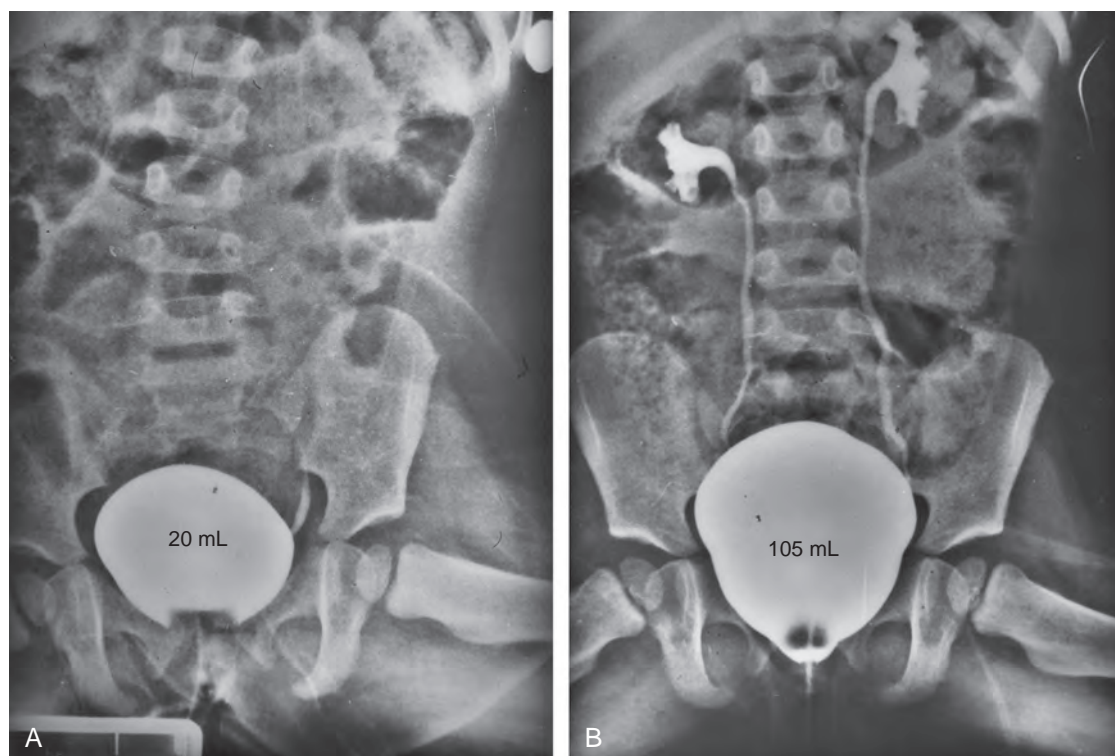


Figure 139-19. A, Initial cystogram under anesthesia showing small bladder capacity after bladder closure. B, Improvement in bladder capacity noted after urethroplasty.

bladder templates, which led to its use as a technique in primary exstrophy closures. Beginning in 1964, this was begun in all newborns with exstrophy, irrespective of bladder template size at birth. At the age of 2, the patient undergoes ureterosigmoidostomy. Some of the remnant bladder is made into a small seminal receptaculum and the penis is reconstructed during the same procedure. In girls, the external genitalia are reconstructed and anterior fixation of the uterus is performed. In both boys and girls, cosmetic correction is usually needed later. However, this usually means only one further operation. In 1996, Fisch and colleagues reported long-term results with the Mainz Sigma pouch (Fisch et al, 1996). This was designed to reduce intracolonic pressures and to maintain better fecal continence. Most of the patients are immediately started on oral alkalinization.

Erlangen Approach

The Erlangen approach is clearly the most evolved of any of the primary closure techniques. In the Erlangen approach, developed by Schrott and popularized by Rosch, if the bladder template is deemed of adequate size, the "total" repair is done at 8 weeks of age. If the template is too small at birth, the bladder only is closed with bilateral groin exploration, closure of the pubis, epispadias repair, and no osteotomy. In the classic Erlangen total repair, the bladder is closed along with bilateral reimplantations, bladder neck plasty, bilateral groin exploration, epispadias repair, pubic closure, no osteotomy, and an epidural catheter for 5 days. Osteotomy is only done in cloacal exstrophy and reoperative closures. Thus, the Erlangen repair is truly a complete repair, encompassing all phases of exstrophy repair in one setting (Schrott et al, 1984).

Regardless of the method of exstrophy reconstruction chosen for the newborn, certain surgical principles remain: (1) radical mobilization of the posterior vesicourethral unit from surrounding tissue; (2) combined closure with epispadias repair in only carefully selected patients; (3) tension-free closure of the abdominal

wall and pelvic bones with adjunctive osteotomy if needed; and (4) definition of strict criteria for selection of newborns to undergo closure.

Modern Reconstruction of Bladder Exstrophy

The primary objective in functional closure is to convert the bladder exstrophy into a complete epispadias with the urethra well up onto the proximal shaft or midshaft of the penis with combined complete epispadias repair in only highly select patients. The resultant incontinence with balanced posterior outlet resistance not only preserves renal function but also stimulates bladder growth. Typically, epispadias repair is now performed at around 6 months of age, after testosterone stimulation. Bladder neck repair usually occurs when the child is 4 to 5 years of age, has an adequate bladder capacity, and, most important, is ready to participate in a postoperative voiding program. Many repairs such as the Erlangen, Kelly, and CPRE were purported to establish continence without the need for bladder neck repair, but recent reports have shown the need for an outlet procedure in almost all patients (Gearhart et al, 2005, 2007; Shoukry et al, 2009; Gargollo et al, 2011).

Bladder, Posterior Urethral, and Abdominal Wall Closure

Various steps in primary bladder closure are illustrated in Figure 139-20A to H. A strip of mucosa 2 cm wide, extending from the distal trigone to well below the verumontanum in the male and to the level of the vaginal orifice in the female, is outlined for prostatic and posterior urethral reconstruction in the male and adequate urethral closure in the female. The male urethral groove may be adequate, in which case no transverse incision of the urethral plate need be performed for urethral lengthening (Fig. 139-20A). We tend not to incise a urethral plate unless the length of the urethral groove from the verumontanum to the urethral glans is so short that it interferes with eventual penile length and produces dorsal

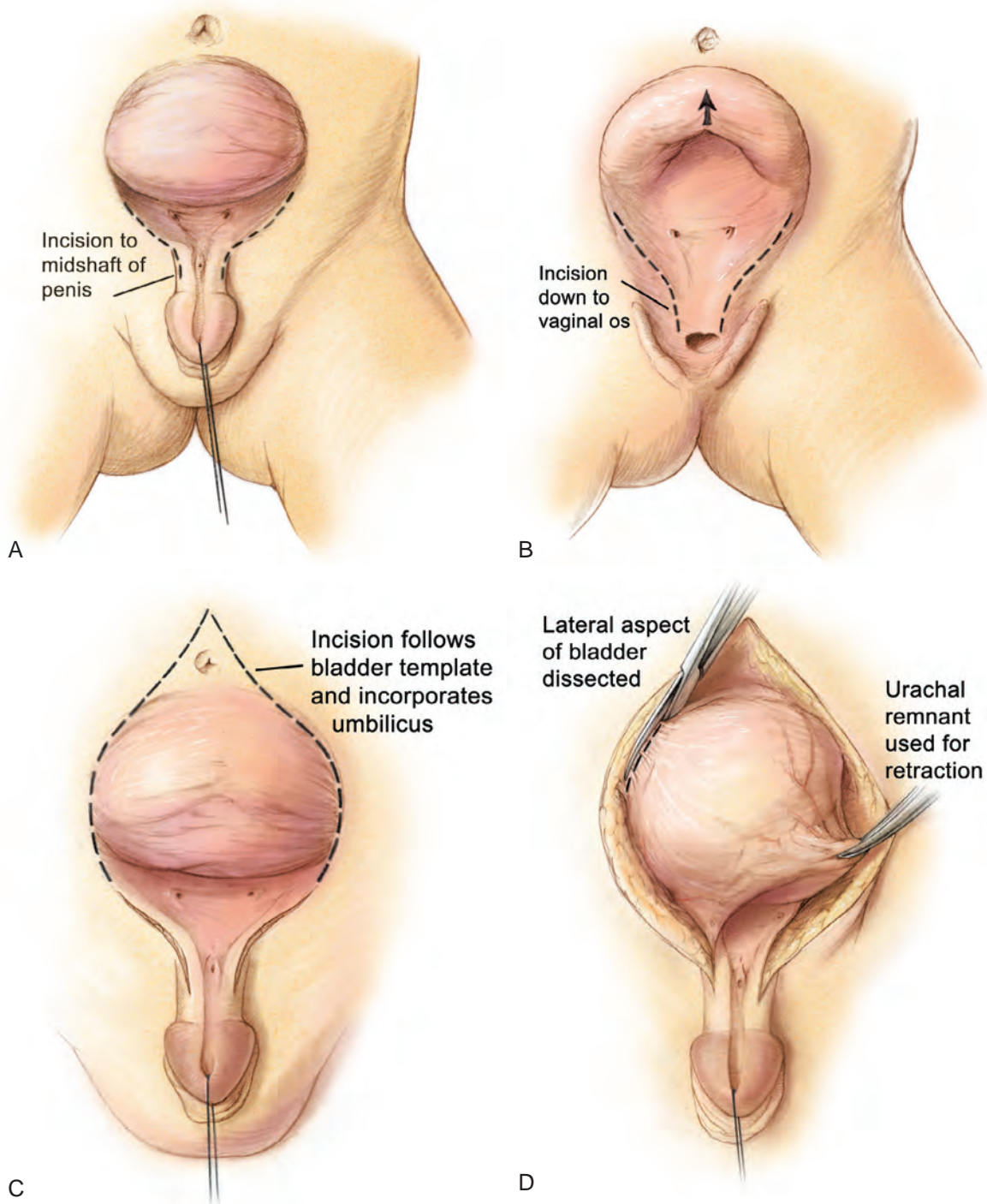


Figure 139-20. Steps in the initial closure of the bladder and posterior urethra with or without osteotomy. The bladder plate is dissected off the anterior abdominal wall. A, Initial incision around the bladder plate in the male. B, Initial incision around the bladder plate in the female. C, Incision follows the bladder template and includes the umbilicus. D, Dissection of the lateral aspect of the bladder from the abdominal wall.

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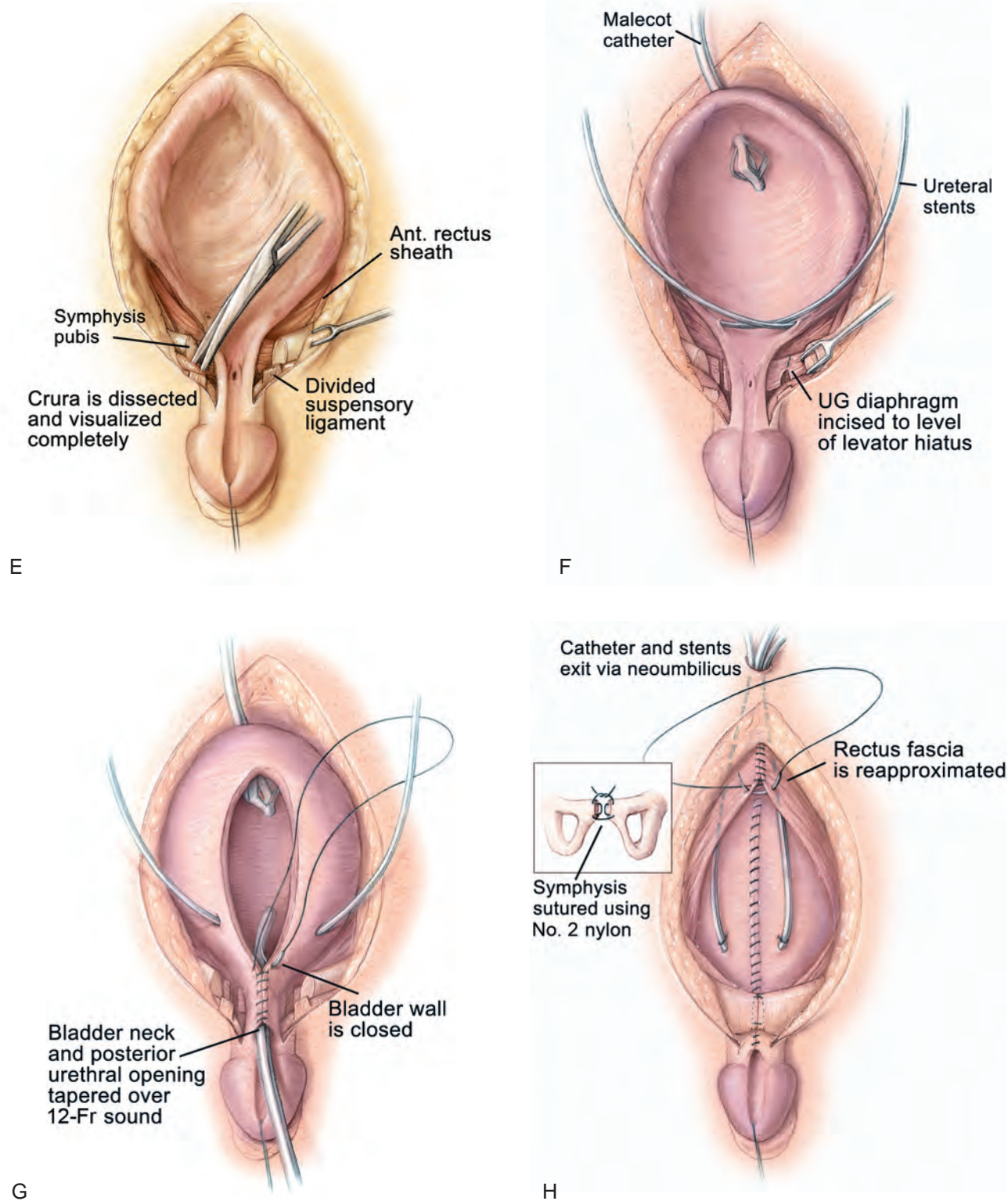


Figure 139-20, cont'd E, Dissection of the crura from the symphysis pubis. **F,** Division of the urogenital (UG) diaphragm fibers. Note stents and suprapubic tubes in place in the bladder. **G,** Initial layer of the bladder closure. Urethral meatus is calibrated to 14-Fr size. Stents are brought out of the bladder. **H,** Pubic approximation is performed with No. 2 nylon mattress suture (see inset). Abdominal wall closure is completed. Suprapubic tube and stents are brought out through the neumbilicus. (© Brady Urological Institute.)

angulation. If so, the urethral groove is lengthened after the manner of Johnston (1974) or Duckett (1977). The drawings in Figure 139-20B and C show marking of the incision just above the umbilicus, down the junction of the bladder and paraexstrophy skin, to the level of the urethral plate.

An appropriate plane is entered just above the umbilicus, and a plane is established between the rectus fascia and the bladder (Fig. 139-20D). The umbilical vessels are doubly ligated and incised and allowed to fall into the pelvis. The peritoneum is taken off the dome of the bladder at this point so that the bladder can be placed deep into the pelvis at the time of closure. The plane is continued caudally down between the bladder and rectus fascia until the urogenital diaphragm fibers are encountered bilaterally. The pubis is encountered at this junction, and a double-pronged skin hook can be inserted into the bone at this time and pulled laterally to accentuate the urogenital diaphragm fibers and help the surgeon radically incise these fibers between the bladder neck, posterior urethra, and pubic bone (Fig. 139-20E). Gentle traction on the glans at this point shows the insertion of the corporeal body on the lateral inferior aspect of the pubis. These urogenital diaphragm fibers are taken down sharply with electrocautery down to the levator hiatus in the pelvic floor in their entirety (Fig. 139-20F). If this maneuver is not performed adequately, the posterior urethra and bladder will not be placed deeply into the pelvis, and when the pubic bones are brought together, the posterior vesicourethral unit will be brought anteriorly into an unsatisfactory position for later Cantwell-Ransley epispadias repair. If the urethral plate is left in continuity, it must be mobilized up to the level of the prostate to create as much additional urethral and penile length as possible. Further urethral lengthening can be performed at the time of epispadias repair.

Penile lengthening is achieved by exposing the corpora cavernosa bilaterally and freeing the corpora from their attachments to the suspensory ligaments on the anterior part of the inferior pubic rami. However, because Silver and colleagues (1997b) showed that there is a 50% shortage of length of the corporeal bodies in exstrophy versus normal controls, any penile length that is obtained is through correction of chordee and change in angulation of the penis rather than true penile lengthening. The wide band of fibers and muscular tissue representing the urogenital diaphragm is detached subperiosteally from the pubis bilaterally (Fig. 139-20E). Reluctance to free the bladder neck and urethra well from the inferior ramus of the pubis moves the neobladder opening cephalad should any separation of the pubis occur during healing, thus increasing the chance of bladder prolapse. The mucosa and muscle of the bladder, bladder neck, and urethra are then closed well onto the penis in the midline anteriorly (Fig. 139-20G). This posterior vesicourethral unit should be tapered over a 12-Fr sound. The purpose of this tapering is to slightly narrow and elongate this unit to allow it to be placed deeply into the pelvis. The size of the opening should allow enough resistance to aid in bladder adaptation and to prevent prolapse but not enough outlet resistance to cause upper tract changes. The posterior urethra and bladder neck are buttressed with a second layer of local tissue if possible. The bladder is drained by a suprapubic nonlatex Malecot catheter for a period of 4 weeks. The urethra is not stented to avoid necrosis with accumulation of secretions in the neourethra. Stents provide drainage during the first 10 to 14 days after closure, because swelling caused by the pressure of closure of a small bladder can obstruct the ureters and give rise to obstruction and transient hypertension. If there are no problems with the stents during healing, we leave the stents in for as long as 2 to 3 weeks.

When the bladder and urethra have been closed and the drainage tubes placed, pressure over the greater trochanters bilaterally allows the pubic bones to be approximated easily in the midline. Horizontal mattress sutures are placed in the pubis and tied with a knot away from the neourethra (Fig. 139-20H). Often we are able to use another stitch of No. 2 nylon at the most caudal insertion of the rectus fascia onto the pubic bone. This maneuver adds to the security of the pubic closure. A V-shaped flap of abdominal skin at a

point corresponding to the normal position of the umbilicus is tacked down to the abdominal fascia, and a drainage tube exits this orifice. The method described by Hanna (1986) is our most commonly performed procedure. Before and during the procedure, the patient is given broad-spectrum antibiotics in an attempt to convert a contaminated field into a clean surgical wound.

In the very short penis at birth, the urethral groove must be transected. As described by Duckett (1977), the groove is then cut distal to the verumontanum with continuity maintained between the thin, mucosal, paraexstrophy non-hair-bearing skin adjacent to the posterior urethra and bladder neck and the skin and mucosa of the penile skin and glans. Flaps in the area of the thin skin are subsequently moved distally and rotated to reconstruct the urethral groove, resurfacing the penis dorsally. The corporeal bodies are not brought together at this juncture because later Cantwell-Ransley repair is planned.

Combined Bladder Closure and Epispadias Repair

MSRE has yielded consistently good cosmetic and functional results, and the use of osteotomy has improved the potential for successful initial closure and later continence. In an effort to decrease costs, decrease the morbidity associated with multiple operative procedures, and possibly affect continence, there has been interest in performing single-stage reconstruction or combining procedures in appropriately selected patients. This technique was first described by Lattimer and Smith (1966) but was abandoned in the 1970s because of high complication and failure rates. The technique was revisited by Gearhart and Jeffs (1991a) for failed exstrophy closures and more recently by Grady and Mitchell for newborn patients (1999). In the combined exstrophy and epispadias repair, bladder closure is combined with the modified Cantwell-Ransley epispadias repair (Gearhart and Mathews, 2000; Baird et al, 2005c). This technique can be applied to both delayed primary closure and failed closures. This method does not require making the patient hypospadiac.

Results have now emerged in groups of boys undergoing single-stage reconstruction (bladder closure and epispadias repair) in infancy (Gearhart et al, 1998; Baird et al, 2005c). In our opinion, this technique should be limited to boys of older age (older than 6 months) because of evidence indicating that potential complication of these combined procedures is significant loss of penile and corporeal tissue that makes further reconstruction problematic (Cervellione et al, 2010). Patients should be carefully selected, and use of these extensive procedures by the occasional exstrophy surgeon is not recommended. Selection should take into account phallic size and length, depth of the urethral groove, and size of the bladder template in those with delayed primary closures, as well as perivesical and urethral scarring in those who have undergone a prior failed closure (Gearhart and Jeffs, 1991a; Gearhart et al, 1998; Baird et al, 2005c).

Management after Primary Closure

The initial step of the MSRE converts a patient with exstrophy into one with penile shaft epispadias and incontinence. Before removal of the suprapubic tube, 4 weeks after surgery the bladder outlet is calibrated by a urethral catheter or a urethral sound to ensure free drainage. A complete ultrasound examination is performed to ascertain the status of the renal pelvis and ureters, and appropriate urinary antibiotics are administered because all patients have reflux after closure. Residual urine is estimated by clamping the suprapubic tube, and specimens for culture are obtained before the patient leaves the hospital and at subsequent intervals to detect infection and ensure that the bladder is empty. If the initial ultrasound examination shows good drainage, upper tract imaging by ultrasonography is repeated 3 months after discharge from the hospital and at intervals of 6 months to 1 year during the next 2 to 3 years to detect any upper tract changes caused by reflux, infection, or obstruction. Prophylactic antibiotics should be continuous because all patients with bladder exstrophy, once it has been closed,

have vesicoureteral reflux. If a useful continence interval has resulted from the initial closure, a further operation for incontinence may not be required; however, this situation is quite unusual. After the conversion from exstrophy to complete epispadias with incontinence, the bladder gradually increases in capacity as inflammatory changes in the mucosa resolve.

Concerns have been raised about delaying the initial exstrophy closure because of late referrals, small templates, or purposeful delay, as practiced at some centers in which the CPRE repair is used to prevent penile ischemia and soft-tissue loss. In a recent large series of 82 patients reported by [Baradaran and colleagues \(2012a\)](#), 33 delayed closures were compared with 59 primary closures in the neonatal period. Longitudinal analysis of bladder capacities demonstrated that compared with neonatal closures, bladder capacities were on average 36 mL smaller in repairs delayed because of small templates and 29 mL smaller in late referrals. However, the rate of bladder growth was the same in all three groups.

Cystoscopy and cystography at yearly intervals are used to evaluate the degree of reflux noted in almost 100% of patients and to provide an estimate of bladder capacity ([Gearhart and Jeffs, 1998](#)). Even in a completely incontinent patient, bladder capacity gradually increases to a point at which the bladder can be distended at cystography to its true capacity. This must be done under anesthesia in young children because the values obtained differ markedly from those obtained when trying to fill the bladder of a crying, squirming infant on an x-ray table ([Gearhart and Jeffs, 1998](#)). If the bladder has not achieved a capacity of at least 30 mL by 1 to 2 years, concern must be voiced to the parents about the overall ability of the bladder to undergo a continence procedure. Currently, the best parameters available to predict overall success are the size of the bladder template at birth and a successful primary closure with absence of infections.

Should bladder outlet resistance be such that urine is retained within the bladder and reflux and ureteral dilation develop with infected urine, it may be necessary to dilate the urethra or to begin intermittent catheterization ([Baker et al, 1999](#)). Sometimes the posterior urethral obstruction can be such that it requires a transurethral incision of the stricture to maintain an adequate posterior urethral outlet. If bladder outlet resistance persists and infections continue, an antireflux procedure may be required as early as 6 months to 1 year after initial closure ([Mathews and Gearhart, 2003](#)). After primary CPRE repair, 50% of patients will require ureteral reimplantation in the first year after closure. Because of this problem, some units are trying ureteral reimplantation at the time of bladder closure, but the numbers of patients treated in this fashion is small ([Braga et al, 2010](#)). If severe upper tract changes occur, surgical revision of the bladder outlet by advancing skin flaps into the orifice or even patching the stricture may be necessary to prevent scarring and further obstruction. As mentioned previously, transurethral incision of the urethral stricture to obtain a balanced outlet should be tried before surgical revision.

Judgment is required to know when to avoid attempts at functional closure and to know when to turn to urinary diversion as a means to preserve renal function. This change of plan is seldom necessary if an adequate outlet has been constructed at the initial closure and if careful attention has been paid to the details of follow-up of the bladder and posterior urethra. An important caveat is that if there are recurrent urinary tract infections (UTIs) and the bladder is distended on ultrasonography, cystoscopy should be performed. The posterior urethra should be carefully examined anteriorly for erosion of the intrapubic stitch, which may be the cause of the recurrent infections ([Baker et al, 1999](#)). If the intrapubic stitch is seen in the posterior urethra, a small suprapubic incision should be made and the stitch should be removed, or, if it can be grasped, it should be removed transurethrally. [Husmann and colleagues \(1990\)](#) have shown very acceptable levels of upper tract function after primary closure as long as prophylactic antibiotics were used after initial closure and elevated urinary residuals were kept below 50 mL. In a recent study by [Schaeffer and colleagues \(2013\)](#), glomerular filtration rate (GFR) was measured before closure and 1

year after bladder neck reconstruction and was found to be no worse or higher than normal values.

Selected Technical Aspects of Other Methods of Closure

Kelly Repair

The multiple-stage Kelly repair begins when the bladder is closed up to the level of the posterior urethra with no attempt to bring the pubic bones into apposition. The second step of the Kelly repair, which differs from other types of repair, is the radical soft-tissue mobilization. This is accomplished by making an incision around the old bladder closure and by making parallel incisions on the urethral plate extending proximally to halfway between the ureteric orifices and the verumontanum. This maneuver helps expose the corpora laterally as they move over toward their insertion onto the pubis. The mucosa lateral to the urethra is excised, as is some of the mucosa of the bladder ([Fig. 139-21A and B](#)). The initial lateral extension of the incision exposes the dorsal nerves of the penis and the attachment of the corpora to the pubis ([Fig. 139-21B](#)). The urethral plate is mobilized from the corporeal bodies and moved to below them to create a penoscrotal hypospadias.

Laterally, the extraperitoneal space behind the rectus is entered and the vas retracted ([Fig. 139-21C](#)). An incision is made in the superior aspect of the pubis downward, creating a “flake” to which medially is attached the corpora of the penis and remnants of the urogenital diaphragm ([Fig. 139-21D](#)). The incision is then taken deeper to the superior aspect of the levator ani. The incision is carried through the levator muscles both deeply and anteriorly to where the levators insert on the back of the pubis. The pudendal vessels and nerves are freed from any attachments. When it appears the entire course has been determined, the flake of the pubis is incised totally and the urethral and bladder neck area and muscles are brought together without tension.

Mitchell Repair

The Mitchell repair, as in all closures, is best performed in the newborn period. The main difference is that the urethra is separated from its attachments to the underlying corporeal bodies and pelvic diaphragm during the first stage of the procedure. Mitchell purports that this allows better posterior positioning of the bladder neck and posterior urethra into the pelvis. This combined bladder closure with penile repair was originally thought to be sufficient for the patient to achieve urinary continence, but this has been found not to be the case in that most of these patients require bladder neck repair ([Gearhart et al, 2005](#); [Shoukry et al, 2009](#); [Gargollo et al, 2011](#)).

The closure is begun in the standard fashion, but the incision is carried out onto the urethral plate, taking care to preserve its blood supply and avoiding corporeal injury. The penis is then disassembled into three components—the right corpus, left corpus, and urethral wedge ([Fig. 139-22A](#))—because it is believed that each corpora has its own blood supply. However, the urethral plate draws blood from spongiosa so there can be ischemia. The dissection moves cranially and the intersymphysal band is incised. This is also accomplished as in the MSRE procedure by going medial to the inferior aspect of the pubis and cutting these fibers from their posterior urethral attachment all the way down to the levator hiatus ([Gearhart et al, 2007](#)). During standard closure of the bladder, the bladder neck is tailored and the urethra is closed in an attempt to move the urethra to the tip of the penis ([Fig. 139-22B](#)). If it does not reach the tip of the penis, the urethra is taken to the base of the penis in a hypospadiac position in a majority (70%) of patients ([Fig. 139-22D](#)).

The repair is very similar in the female patient, with care taken to mobilize the bladder neck, urethra, and vagina as a single unit. Unlike the Kelly repair but similar to MSRE, an osteotomy is used in both sexes if the child is older than 3 years or the diastasis is judged to be excessive.

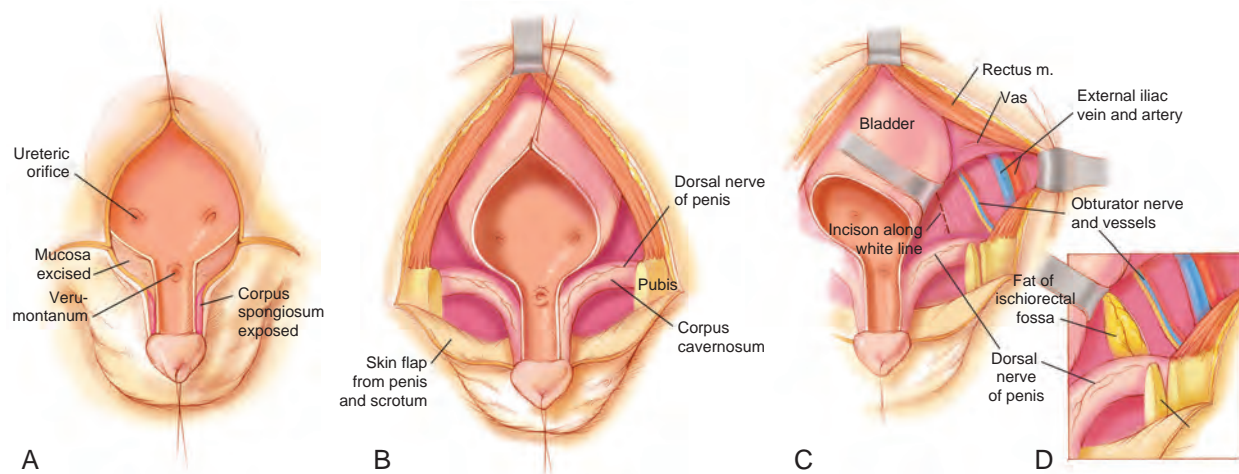


Figure 139-21. Kelly repair. A, The penis has been degloved and pulled down over the scrotum. The corpora are exposed with their attachments to the pubis. The dorsal nerves of the penis are identified emerging from the pelvis superior to the attachment of the corpus to the pubis. B, The extraperitoneal plane behind the left rectus muscle has been opened. The vas is identified and retracted with peritoneum. The external iliac vessels and obturator vessels and nerves are identified. The initial incision is made into the pubis to create a flake of bone, taking care to go down only to the level of the emergence of the dorsal nerve of the penis. C, The pelvic floor is opened, and the bladder and rectum retracted medially. An incision is made through the levator medial to the white line. This incision is taken out to the wall of the pelvis so the attachment of the levator to the back of the pubis will be moved with the bone flake. D, Deeper, the ischiorectal fossa is encountered where the pudendal vessels are identified and freed up. Once the vessels and bone flake are totally free, the tissues of the penis, bladder neck, and urethra are reconstructed. (A and B, Redrawn from Kelly with permission.)

Penile and Urethral Closure in Exstrophy

Epispadias Repair

Historically, bladder neck reconstruction was performed before penile and urethral reconstruction. An increase in bladder capacity in patients with extremely small bladder capacities after epispadias repair prompted a change in the management program (Gearhart and Jeffs, 1989a) (see Fig. 139-19). In a group of patients with a small bladder capacity after initial closure, there was a mean increase of 55 mL in males only 22 months after epispadias repair. However, with MSRE, the epispadias repair is now performed at about 6 to 10 months of age in all patients. Recent data by Kufner and colleagues (2010) clearly demonstrated better eventual overall bladder capacity in patients in whom the epispadias repair was completed before 12 months of life. With this modification, possibly all patients can achieve an appropriate capacity by the time they are physically and mentally ready to undergo bladder neck reconstruction. Because most boys with exstrophy have a somewhat small penis and a shortage of available penile skin, all patients undergo testosterone stimulation before urethroplasty and penile reconstruction (Gearhart and Jeffs, 1987).

Many techniques have been described for reconstruction of the penis and urethra in patients with CBE. Current methods of epispadias repair in bladder exstrophy are the Cantwell-Ransley repair (1989), the modified Cantwell-Ransley repair (1995), and the penile disassembly technique described by Mitchell and Bāgli (1996).

Regardless of the surgical technique chosen for reconstruction of the penis in bladder exstrophy, four key concerns must be addressed to ensure a functional and cosmetically pleasing penis. These concerns are (1) correction of dorsal chordee, (2) urethral reconstruction, (3) glanular reconstruction, and (4) penile skin closure.

Although it is possible to achieve some penile lengthening and release of chordee at the time of initial closure, it is always necessary

to perform formal penile elongation with release of chordee at the time of urethroplasty in exstrophy patients. Data of Silver and associates (1997b) clearly showed that this is more of an apparent lengthening of the penis than a true lengthening because the anterior corporeal bodies in exstrophy patients have 50% less length than age-matched controls. All remnants of the suspensory ligaments and old scar tissue from the initial bladder closure must be excised. Further dissection of the corpora cavernosa from the inferior pubic ramus can be achieved. It is often surprising how little is accomplished in freeing the corporeal bodies from the pubis at the time of initial exstrophy closure (Gearhart, 1991).

Lengthening of the urethral groove is also essential. In the penile disassembly technique described by Mitchell and Bāgli (1996), the urethral plate is dissected completely from the glans; in over 70% of patients it is not long enough to reach the tip of the penis, and as a result hypospadias is present, with further reconstruction needed at another time (Hafez and el-Sherbiny, 2005).

Chordee

Besides lengthening of the urethral groove, dorsal chordee must be addressed. To release dorsal chordee, one may lengthen the dorso-medial aspect of the corpora by incision and anastomosis of the corpora themselves (Gearhart et al, 1992). Also, length can be gained by placement of a dermal graft to allow lengthening of the dorsal aspect of the corpora (Woodhouse, 1986). However, most of these techniques, especially grafting, are reserved for patients who are seen in adolescent and adult years for epispadias surgery with the need for some increased penile length and correction of residual chordee.

Urethral Reconstruction

Urethral reconstruction is an important aspect of external genital reconstruction in exstrophy. This can be accomplished by many

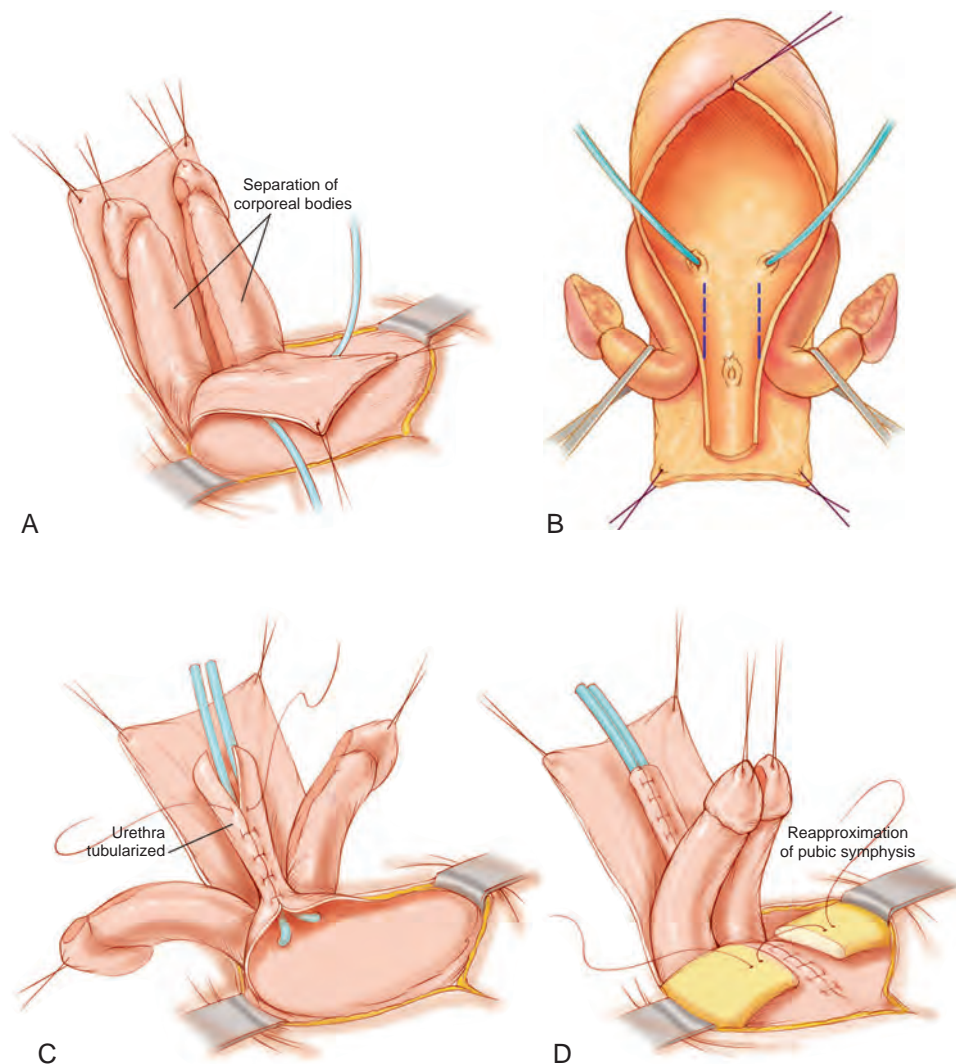


Figure 139-22. Mitchell repair. A, Corporeal separation with dissection of urethral plate to complete penile disassembly. B, Tailoring of bladder neck in complete primary repair of exstrophy procedure. C, Urethral plate tubularization done with interrupted sutures in an attempt to lengthen it. D, Reapproximation of pubic symphysis with medial rotation of the corpora and placement of tubularized urethra underneath corpora either on or below glans in a hypospadiac position. (A, C, and D, Redrawn from Grady with permission.)

previously reported methods, most of which have been abandoned: (1) tubularization of dorsal urethral groove; (2) free grafts of genital and extragenital skin; (3) ventral transverse island flaps; and (4) double-faced ventral island flaps. Most modern techniques of epispadias repair associated with bladder exstrophy use tubularization of the urethral plate, moving the urethral plate under the corporeal bodies after closure to lessen the incidence of urethrocutaneous fistula, to give the penis a more downward deflection, and to make a more easily catheterizable urethral channel (Surer et al, 2000). With the penile disassembly technique, interrupted sutures are often used to try and get the urethra to the tip of the penis again after it is completely detached, with resultant hypospadias in many. Although some authors have described the ease and success of hypospadias repair after penile disassembly (Shnorhavorian et al, 2008), a good-sized European study (Berrettini et al, 2011) found quite the opposite with a 50% complication rate. Patients who did well underwent a two-stage repair and placement of a graft before urethroplasty.

Our preference for urethroplasty and penile reconstruction, if the urethral groove has adequate length, is the modified Cantwell-Ransley repair (Gearhart et al, 1992, 1995c, 2005) (Fig. 139-23).

Currently, in the modern applications of the staged reconstruction of bladder exstrophy, epispadias repair is performed when the child is 6 to 10 months of age. At the time of primary closure the urethra is closed well up on the penile shaft.

The modified Cantwell-Ransley procedure is begun by placing a transverse stitch through the glans as a traction stitch. Incisions are made over two parallel lines marked previously on the dorsum of the penis that outline an 18-mm-wide strip of urethral mucosa, extending from the prostatic urethral meatus to the tip of the penis (Fig. 139-24A). For this procedure, a deep vertical incision is made in the urethral plate distally. The incision is then closed with 6-0 polyglycolic sutures in a transverse fashion (Fig. 139-24B to D). This procedure flattens the distal urethral plate and advances the urethra to the tip of the phallus so that it will be in excellent glanular position when the glanular wings are closed over the reconstructed urethra. Glanular mucosal areas of the dorsal glans are excised adjacent to the urethral strip, and thick glanular flaps are constructed bilaterally (Fig. 139-24F). Lateral skin flaps are mobilized and undermined. A Z incision of the suprapubic area permits wide exposure and division of the suspensory ligaments and old scar tissue from initial exstrophy closure (Fig. 139-24F).

Ventral penile skin is taken down to the level of the scrotum (Fig. 139-24E). Care is taken to preserve the mesentery to the urethral plate, which arises proximally and extends upward between the corporeal blood supply to the urethral plate. Dissection of the corpora is begun ventrally with dissection on the surface of Buck fascia covering the corporeal bodies. The plane is followed closely until one exits on the dorsum of the penis between the corpus spongiosum and the corporeal body, first on one side and then on the other (Fig. 139-24F and G). Vessel loops are placed around the corporeal bodies, and the dissection is extended proximally on the corpora to dissect the urethral plate free from the corporeal bodies up to the level of the prostate. Although one might expect difficulties when dissecting proximally where the paraexstrophy skin flaps had been sutured to the urethral plate, this has not been encountered

in our experience, and dissection is kept just on the corporeal bodies while proceeding proximally. The urethral plate is also dissected distally past the level of the junction of the glans with the corporeal bodies. In this manner, adequate mobilization is obtained, and it is not difficult to bring the corporeal bodies over the urethra at the level of the corona. This separates the penis into three components: the two corpora and the urethral plate (Fig. 139-24F). Complete penile disassembly is not undertaken, because the most distal 1-cm attachment of the mucosa plate to the glans is left intact (Surer et al, 2000).

The neurovascular bundles, situated between Buck fascia and the corporeal wall, are typically left intact in young patients if rotation of the corporeal bodies over the urethra effectively straightens the penis. If not, the neurovascular bundles are dissected free from the

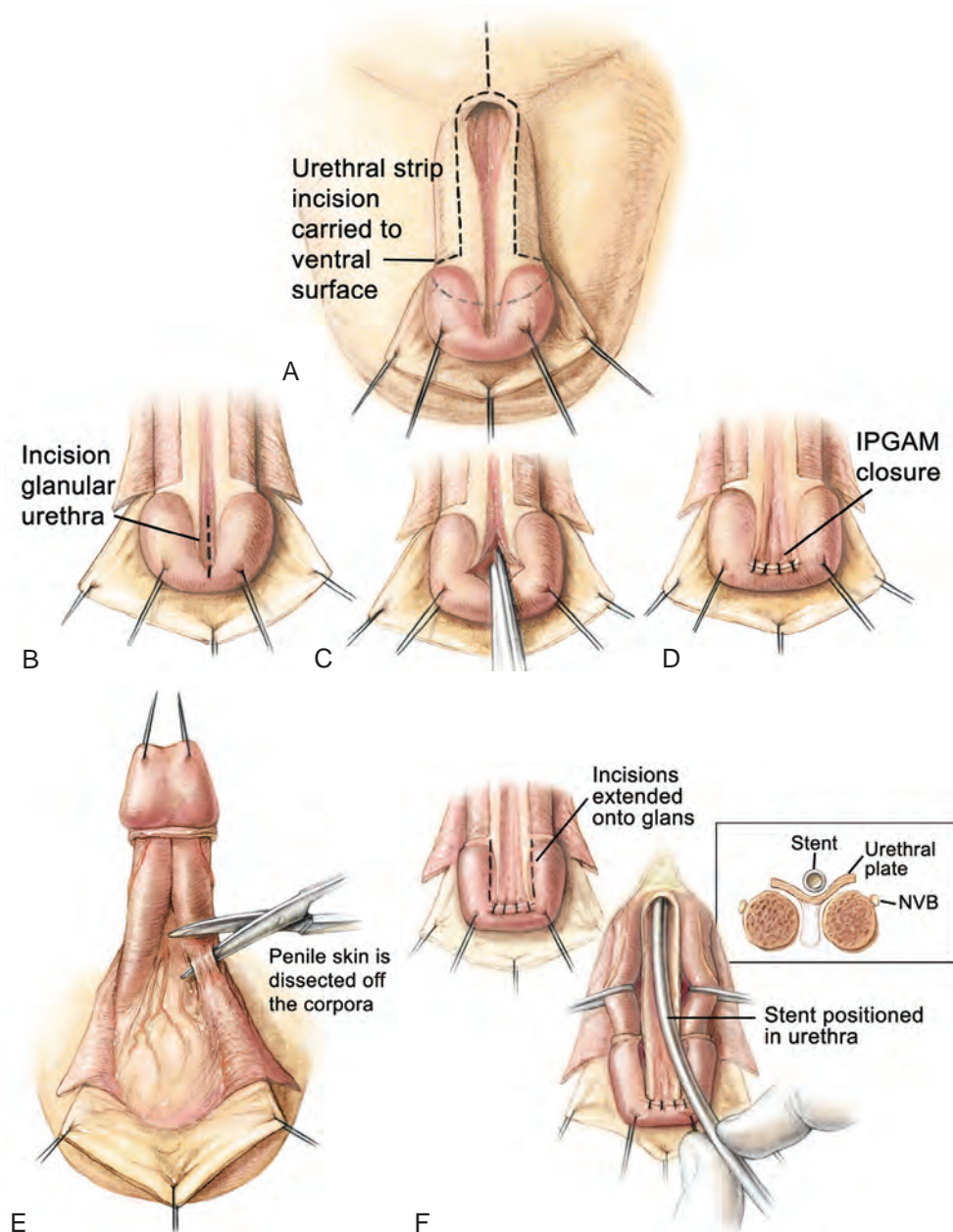


Figure 139-23. Modified Cantwell-Ransley epispadias repair. A, Initial incision line extending around the urethral plate and the coronal sulcus. B to D, Performance of the reversed meatal advancement and glanuloplasty procedure to bring the urethral meatus to the tip of the glans. E, Dissection of the foreskin on the ventral aspect of the penis. F, The corpora are dissected off the urethral plate, and parallel incisions are made into the glans to create glans wings. Note the lateral position of the neurovascular bundles (NVB) (inset).

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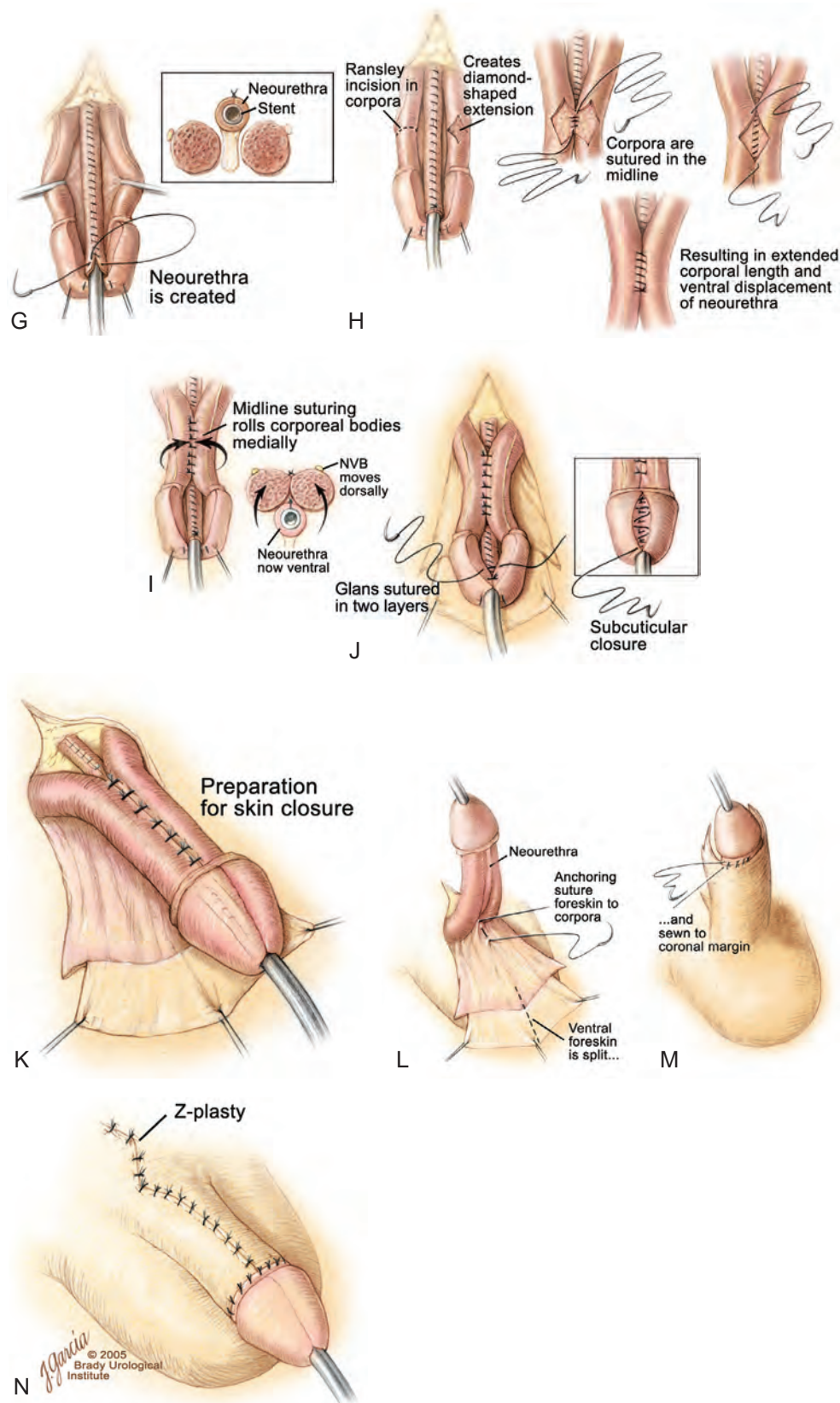


Figure 139-23, cont'd **G**, The urethra is tubularized using a continuous running suture. **H**, Approximation of the corpora using the incisions in the corpora if indicated. **I**, Corpora approximated above the urethra to provide an anatomically ventral location of the urethra (see *inset*). **J**, Glans is reconstructed in two layers. **K**, Preparation for skin closure. **L**, Suture is placed at the base of the penis to locate the foreskin on the shaft of the penis as well as to provide an area of distinction between the penis and the scrotum. **M**, Foreskin is sewn to the coronal sulcus. **N**, Completion of the repair with resurfacing of the penis and use of a proximal Z-plasty incision to provide downward penile deflection. (© Brady Urological Institute.)

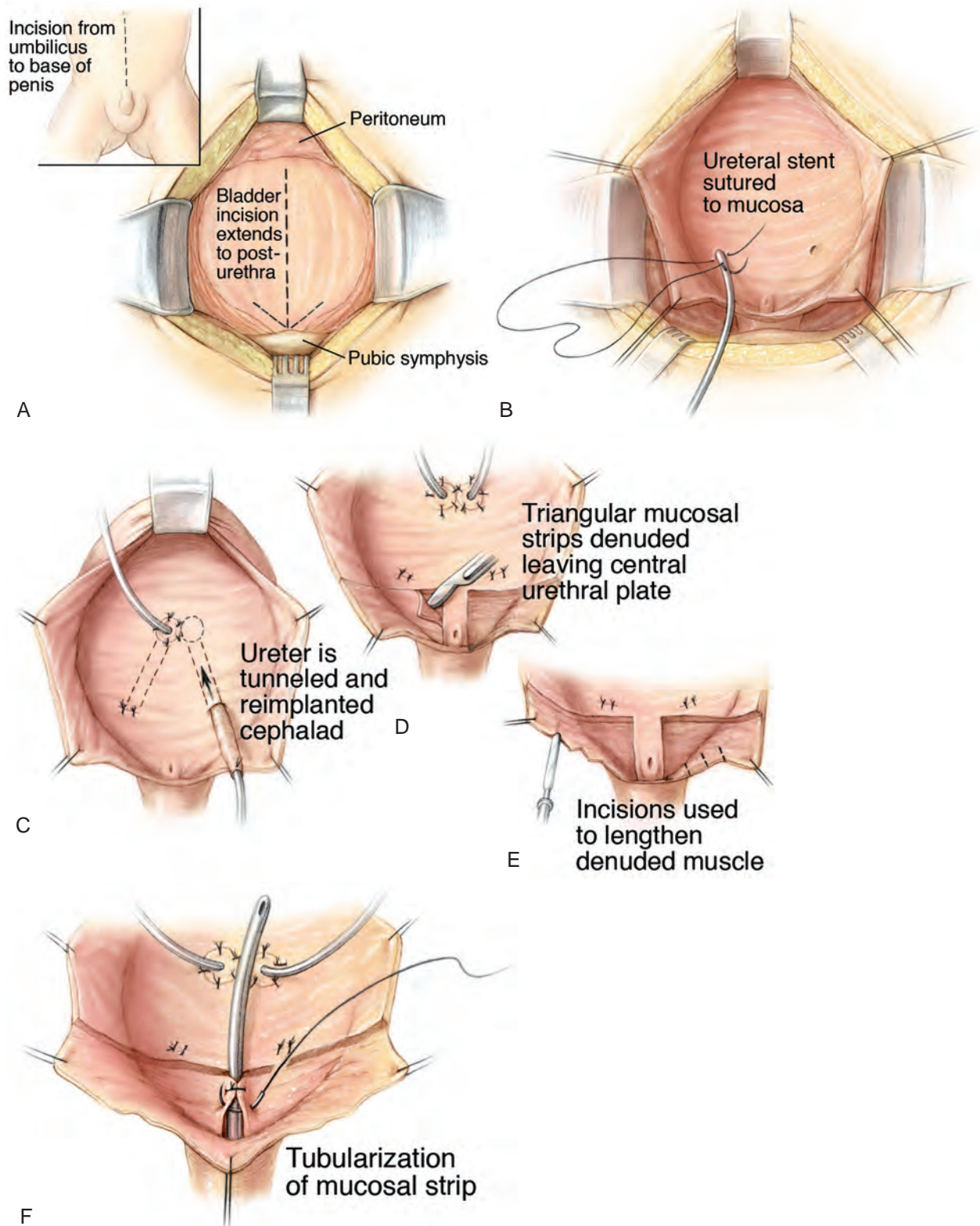


Figure 139-24. Modified Young-Dees-Leadbetter bladder neck reconstruction. A, Vertical bladder incision with distal transverse extension where the bladder and posterior urethra are under the pubic bar. B and C, Ureters are identified, mobilized, and reimplanted in a cephalotrigonal position. D and E, Segments of mucosa are excised from either side of a median strip (1.5×3 cm) that will form the neourethra. Short incisions in the muscle will permit extension of the bladder neck. F, Urethra is tubularized using a continuous running suture.

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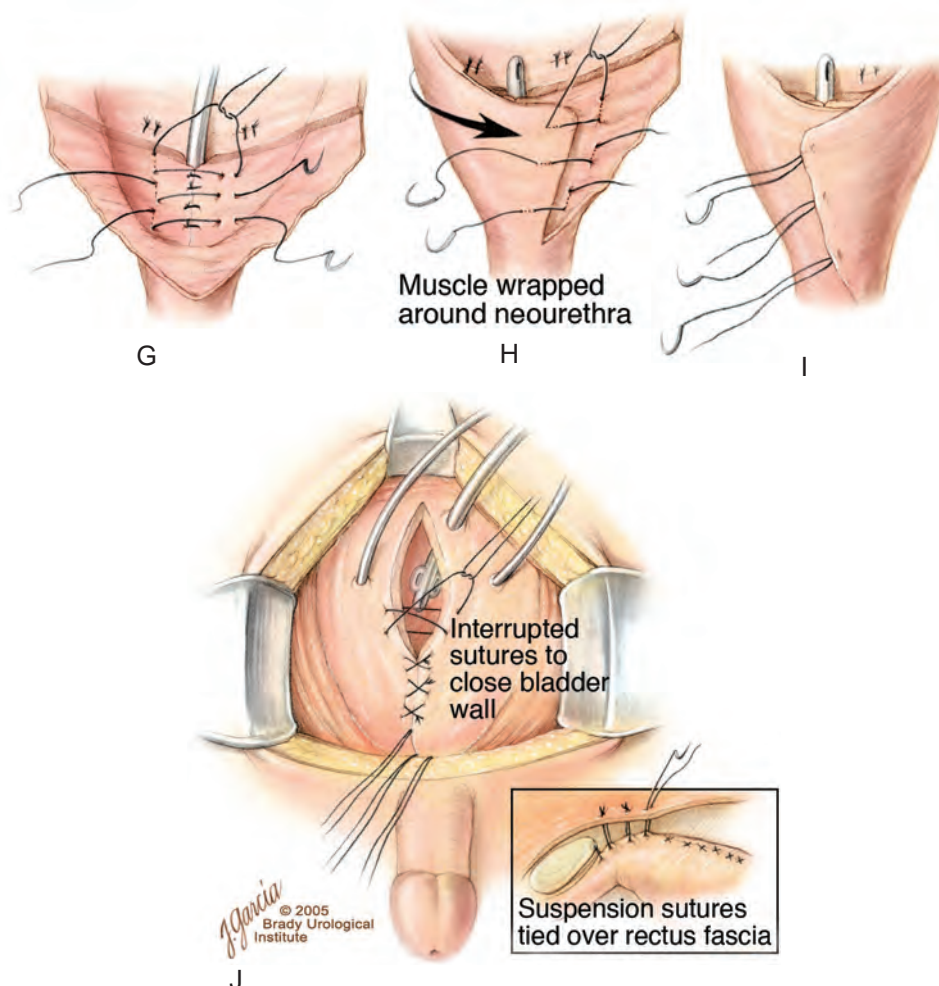


Figure 139-24, cont'd G, Posterior urethra and bladder neck are reconstructed. H and I, Bladder muscle is brought together in a double-breasted fashion over the neourethra. J, Bladder closure is completed and the distal suspensory sutures are tied over the abdominal wall (see inset). Suprapubic tube and stents are left in place; however, the urethra is left unstented. (© Brady Urological Institute.)

corporeal bodies, with vessel loops being placed around these structures so that the neurovascular bundles will not be compromised when incisions are made in the corpora and the corpora are rotated medially over the neourethra (Fig. 139-24H). After the corporeal bodies are incised or rotated over the urethra, the urethral strip is closed in a linear manner from the prostatic opening to the glans over an 8-Fr silicone stent with 6-0 polyglycolic acid sutures. After this is accomplished, incisions are made in the corporeal bodies at the point of maximum curvature, opening a diamond-shaped defect in the erectile tissue (Fig. 139-24H). The corpora are then closed over the neourethra with two running sutures of 5-0 PDS, and the diamond-shaped defects in the adjacent area of the corpora are sutured to each other. This procedure effectively displaces the urethra ventrally in a normal position. This not only causes the downward deflection of the penis but also allows some additional length by dorsal rotation and approximation of the corporeal bodies over the neourethra. After the urethra has been transferred to the ventrum, further sutures of 4-0 polyglycolic acid are placed between the corporeal bodies to bury the urethra further, especially at the level of the junction of the glans and the corporeal bodies at the corona (Fig. 139-24I).

The glans wings are then closed over the glanular urethra using subcuticular sutures of 5-0 polyglycolic acid, and the glans epithelium is closed with 6-0 polyglycolic acid sutures (Fig. 139-24I). The ventral skin is then brought up and sutured to the ventral edge of the corona, and the flaps are fashioned to provide adequate

coverage and lengthening of the dorsum of the penis. The skin is reapproximated with interrupted 5-0 or 6-0 polyglycolic acid sutures (Fig. 139-24K to M). A Z-plasty at the base of the penis is closed with interrupted 5-0 or 6-0 polyglycolic acid sutures. A silicone stent is left indwelling in the neourethra to provide drainage for 10 to 12 days (see Fig. 139-24).

Penile Skin Closure

If skin closure continues to be a problem in genital reconstruction owing to the paucity of skin associated with this condition, a Z-plasty incision and closure at the base of the penis prevents skin contraction and upward tethering of the penis. The ventral foreskin can be split in the midline and brought to the dorsum as lateral preputial flaps for coverage of the penile shaft. If the flaps are a bit asymmetrical, a staggered dorsal suture line results, with less upward tethering. Alternatively, a buttonhole can be created in the ventral foreskin and simply transposed to the dorsum for additional penile skin coverage. All patients in our series are given testosterone enanthate 2 mg/kg intramuscularly 5 weeks and 2 weeks before repair.

Postoperative Problems

Postoperative pain and bladder spasms after extensive external genital reconstructive surgery require a combined effort of the

pediatric anesthesia pain service and the surgical service. Controlling bladder spasms is paramount because they are associated with urinary extravasation and fistula formation. All of our patients have a caudal epidural catheter placed at the time of surgery, and oxybutynin is started immediately after surgery to decrease the incidence of bladder spasms and enhance the patient's comfort. At the time of discharge, the plastic dressing on the penis is left intact and the child is discharged with narcotics, antispasmodics, and appropriate broad-spectrum antibiotic coverage.

Female Exstrophy

The principles of repair of female and male exstrophy are similar. However, in the female patient we recommend the following: (1) radical dissection of the bladder and urethra from surrounding structures while connection to the vagina is maintained; (2) dissection of the lateral aspects of the posterior vesicourethral and vaginal unit from their attachments to the pelvic floor; (3) tension-free closure of the abdomen, bladder-urethra, and external genitalia; and (4) judicious use of osteotomy and proper immobilization of the pelvis and extremities.

As in the male patient, if the pelvic bones are separated over 4 cm or are not malleable under anesthesia, an osteotomy is then performed. The transverse innominate osteotomy along with vertical iliac osteotomy is commonly used in our practice. Interfragmentary pins are placed and the fixator is applied after the soft-tissue surgery has been completed. An interesting finding in over 1287 exstrophies in our institutional-approved database is that even with a large bladder template the diastasis tends to be narrower in female than in male patients. Thus, closure in female exstrophy patients is easier to perform, and female patients do not require an osteotomy as commonly as male patients.

The vagina is prepared with an iodine preparation so that if it is violated during the dissection it can simply be closed. In the closure, we start our dissection along the medial aspect of the clitoral or corporeal halves and move deeply into the pelvis. Pinpoint electrocautery at a low setting is used to limit both bleeding and tissue injury. The dissection of the vagina proceeds laterally and posteriorly. The urethrovaginal septum is left intact to preserve its blood supply. As in the male patient, the dissection proceeds posterior and downward until the levator hiatus is reached, with the urogenital diaphragm fibers lateral and posterior to the vesicourethral plate and vaginal incision. This maneuver allows placement of the unit deeply into the pelvis and, more important, keeps it from being displaced anteriorly when the pelvic bones are brought together.

The bladder is closed with a single figure-of-eight layer of 3-0 polyglactin suture to maximize postclosure bladder volume. The urethra is closed with a single layer of 4-0 to 5-0 polyglactin depending on the thickness of the tissue. An indwelling suprapubic tube is brought out through the dome of the bladder along with two small feeding tubes that act as stents and are left in place for 4 full weeks. These exit the neoumbilicus as described by Hanna (1986). No tubes are brought out through the neourethra because this can be associated with wound infection and prolapse or dehiscence. A No. 2 nylon suture in a horizontal mattress fashion is used to bring the pubic bones into apposition. Once the pubic bones are brought together, a routine subcutaneous and skin closure are performed. A mons plasty is then performed, and the subcutaneous tissue of the clitorides are brought together with 5-0 polyglactin and the epithelium with 6-0 polyglactin sutures. If needed a Y-V labioplasty is performed for better exteriorization of the vaginal introitus.

If an osteotomy has been performed, the external fixator is then placed and a pelvic x-ray study obtained. If pin and fixator placement are optimal, then the infant is placed in modified Buck traction for 4 weeks. If an osteotomy was not performed, the infant is placed in Bryant traction for 4 weeks. Postoperative care is the same as in the male patient, with an indwelling epidural catheter and bladder spasms controlled by both the epidural and oral oxybutynin.

Continence and Antireflux Procedure

Although some modern exstrophy repair methods are claimed to establish suitable continence without formal bladder neck repair, many patients are referred to our unit still incontinent after only prior newborn repair or after newborn repair and multiple injections of various substances into the bladder neck area. Likewise, other groups have reported their outcomes with newborn repair, and most have recommended some sort of outlet procedure. In our unit each child has a cystoscopy and gravity cystogram under anesthesia yearly after newborn closure to assess bladder growth. Prior data by Gearhart and Jeffs has shown that after newborn exstrophy closure there should be an average increase in bladder capacity of 54 mL in 24 months (Gearhart and Jeffs, 1989b). Chan and colleagues (2001) found that in selected exstrophy patients who underwent closure, epispadias repair, and bladder neck reconstruction at our institution, a median bladder capacity of 100 mL was more common in the group of patients who were completely dry after bladder neck reconstruction. Most of these children were 5 to 7 years of age and were ready emotionally, maturationally, and intellectually to participate in a postoperative voiding program. An intense pre-bladder neck repair program is conducted by a senior urology nurse practitioner, senior clinical nurses, and a child psychologist well versed in voiding issues. These sessions are begun for both child and parents at least 6 months before an outlet procedure. Successful completion of the program is required before surgery is scheduled.

Continence and antireflux procedures performed at our institution are illustrated in Figure 139-23. The bladder is opened through a transverse incision at the bladder neck with a vertical extension. The later midline closure of this incision is the width of the bladder neck and enlarges the vertical dimension of the bladder, which in exstrophy is often short (see Fig. 139-23A). A Cohen transtrigonal ureteral reimplantation or a cephalotrigonal reimplantation is performed to move the ureter across the bladder, above the trigone, or to direct the ureter cephalad up onto the edge of the trigone (see Fig. 139-23B and C) (Canning et al, 1992). If the ureters are low on the trigone and there is a need to move the ureteral hiatus higher, the hiatus is simply cut in a cephalad direction, and cross-trigonal reimplants are performed at the upper aspect of the trigone (see Fig. 139-23C).

The continence procedure is begun by selecting a posterior strip of mucosa 15 mm wide and 30 mm long that extends distally from the mid-trigone to the prostate or posterior urethra (see Fig. 139-23D). Bladder muscle lateral to the mucosal strip is denuded from the mucosa. It is often helpful at this juncture to use one or two epinephrine-soaked sponges to aid in the control of bleeding and the visualization of the denuded area. Tailoring of the denuded lateral muscle triangles is aided by multiple small incisions on the free edge bilaterally that allow the area of the reconstruction to assume a more cephalad position (see Fig. 139-23E). These muscle flaps not only are smaller but also are not incised transversely at their cephalad extent as described in the original Young-Dees procedure to prevent denervation and ischemia. The basic premise is to create a mucosa-lined tube inside a muscular funnel that narrows from its junction with the floor of the bladder that extends caudally. The edges of the mucosa and underlying muscle are closed with interrupted sutures of 4-0 polyglycolic acid (see Fig. 139-23F). The adjacent denuded muscle flaps are overlapped and sutured firmly in place with a 3-0 PDS to provide reinforcement of the bladder neck and urethral reconstruction (see Fig. 139-23G to I). An 8-Fr urethral stent may be used as a guide during posterior urethral and bladder neck reconstruction but is removed after the repair is completed. After the bladder neck repair is completed, the repair is suspended to the rectus fascia (see Fig. 139-23J, inset).

Very radical dissection of the bladder, bladder neck, and posterior urethra is required, not only within the pelvis but also from the posterior aspect of the pubic bar to provide enough mobility for the bladder neck reconstruction. This maneuver allows adequate bladder neck narrowing and tightening of the bladder neck repair and subsequent anterior suspension of the newly created posterior urethra and bladder neck. In patients who are presented after CPRE repair in the newborn period and who had

a vesicocutaneous fistula after closure, great care must be taken anteriorly during mobilization of the bladder neck because the tissues are more adherent to the back of the intrasymphyseal bar. If visualization of the posterior urethra is problematic, the intrasymphyseal bar can be cut, thus providing a widened field of exposure. The intrasymphyseal bar is approximated with 2-0 sutures of PDS. If the intrasymphyseal bar is cut, abduction of the lower extremities should be restricted in the postoperative period to allow proper healing of the intrasymphyseal bar.

Postoperative Care

Ureteral stents are placed in the reimplanted ureters and brought out through the wall of the bladder, and the bladder is drained by suprapubic tube, which is left indwelling for a 3-week period. At the end of 3 weeks the suprapubic tube is clamped and the patient is allowed to attempt to void. Initially, the tube should not be clamped for more than 1 hour. If voiding does not occur, the child is given an anesthetic and an 8-Fr Foley catheter is placed. This is left in place for 5 days, then removed, and another voiding trial is begun. This part of the postoperative period is most demanding on the patient and family. Some children require several catheter placements before voiding is initiated. If the child can empty the bladder satisfactorily, the suprapubic tube is removed. Frequent bladder and renal ultrasound examinations are required in the first few months after bladder neck repair.

MODERN INITIAL REPAIR OF BLADDER EXSTROPHY: OUTCOMES AND RESULTS

The use of functional reconstruction in bladder exstrophy has resulted in dramatic improvement in the success of reconstruction. Several series (Purves et al, 2008; Shnorhavorian et al, 2008) have demonstrated the success and applicability of early newborn closure with or without pelvic osteotomy. Important older series have shown acceptable continence rates with preservation of renal function in a majority of patients treated in early life.

Two of the most reliable predictors of eventual urinary continence are the size of the bladder template at birth and a successful primary closure. Regardless of the technique used, a complication-free newborn closure of the abdomen, pelvis, bladder, and proximal or complete urethra paves the way for an optimal long-term result. A very large series by Surer and colleagues (2001) demonstrated in a large group of exstrophy patients who underwent early closure the importance of a successful primary closure. Sixty-eight patients (57 male and 11 female patients) were referred for bladder neck reconstruction after primary closure at other centers. Twenty percent had concomitant pelvic osteotomy at the time of closure. The majority of patients underwent closure within the first 72 hours of life. Mean capacity at the time of bladder neck repair was 121 mL. Eighty-three percent are continent and voiding per urethra. This application of early successful closure and follow-up reconstruction by a second surgeon shows convincingly that a successful primary closure is one of the most important determinants of eventual bladder capacity and continence regardless of who originally performed the repair.

Initial Closure

Long-term data on all modern types of exstrophy repair can be difficult to obtain. Nonetheless, this section will deal with what has been gleaned from the recent literature. Most data come from the MSRE and CPRE groups. In a large series reported by Hernandez and colleagues (2008), clinical information from 189 patients who had undergone primary closure between 1988 and 2004 was extracted from our exstrophy database. The records of 131 patients (95 males) who underwent MSRE with a modified Cantwell-Ransley repair by a single surgeon in 1988 to 2004 were reviewed with a minimum 5-year follow-up. The importance of a successful initial closure is emphasized by Oesterling and Jeffs (1987) and Husmann

and colleagues (1989a), who found that the onset of continence was quicker and the continence rate higher in those who underwent a successful primary closure with or without osteotomy. In addition, Novak and colleagues (2010) reported on patients with bladder exstrophy who underwent more than one attempt at primary closure. If a patient underwent two closures, the chance of having an adequate bladder capacity for bladder neck repair was 60% and the chance of voided continence was 17% overall. Patients who underwent three closures had only a 50% chance of an adequate capacity and less than a 16% chance of voided continence. In an evaluation of this select group, it was found that at the time of primary closure, 80% of patients had no form of pelvic osteotomy. Thus, the chance of achieving an adequate bladder capacity and eventual continence after more than one exstrophy closure is markedly diminished. These very poor results underline the paramount importance of a secure abdominal, bony pelvis and posterior vesicourethral unit in the newborn with exstrophy.

Also, compared with many of the other repairs, data are available from several units on their results with the CPRE repair. In a series by Shnorhavorian and colleagues (2008), 2 of 39 patients had dehiscence of the fascia and 9 of 39 developed a vesicocutaneous fistula. Complications seen in the CPRE repair are as much as those seen in MSRE. However, some are particular to this repair. A large series of vesicocutaneous fistulae was reported from a single institutional study; some patients had an osteotomy, and others did not (Shoukry et al, 2009). In addition, several series have reported the need for early ureteral reimplantation after closure and the occurrence of significant upper tract changes in many patients (Grady and Mitchell, 1999). This has prompted the call for ureteral reimplantation at the time of exstrophy closure by one group (Braga et al, 2008).

Although many earlier published series were small, the incidence of bladder prolapse and dehiscence is reported to be low. However, in a recent large series of primary CPRE repairs by Shoukry and colleagues (2009), the incidence of major prolapse and dehiscence was 15.8% even with the use of osteotomy. In this author's series we have seen a number of referred patients with complete dehiscence and major bladder prolapse after newborn CPRE repair. However, the other complicating factors we have seen, in addition to the aforementioned, have been significant losses of soft tissue including partial or complete loss of the penile glans in 9 patients and the loss of the urethrovaginal septum in 2. In a series by Hamouda (2003), 5 of 42 patients had ischemic loss of glans tissue after CPRE repair. Thus, the complications of closure between CPRE and MSRE are similar, but much more serious if soft-tissue loss occurs.

Baka-Ostrowska and colleagues from Warsaw (2013) reported on 100 primary closures. Complete dehiscence occurred in 31 patients, of whom 24 had no osteotomy and 7 a posterior iliac osteotomy only. Of those who were newborns and underwent closure at less than 72 hours ($n = 47$) and in whom no osteotomy was performed, dehiscence occurred in 13 patients. All were immobilized with a modified spica "chair" cast for 3 weeks and then an elastic bandage for 3 weeks. These authors now recommend osteotomy for all newborns with a diastasis greater than 5 cm and in those undergoing closure after 72 hours.

In a recent publication of the Erlangen repair by Rosch and colleagues of 100 closures, the complications in general were mild, with urethrocutaneous fistulae in 2%, minimal hydronephrosis in 20%, and severe hydronephrosis requiring further surgery in 3% (Rosch et al, 2001). There were no incidents of bladder prolapse or dehiscence. Osteotomy was not used in any patient, but a very sophisticated coaptation technique involving the obturator foramen was used in all patients.

In a report by Kelly and colleagues (2008) of 26 patients undergoing Kelly repair, there was a reported incidence of bladder prolapse requiring treatment in 25%. Soft-tissue loss of glanular tissue was noted in 2 of 26 patients.

Interest in the outcomes of exstrophy closure has expanded to interest in the economic outcomes of the treatment of this major birth defect and who should be doing these types of operations

in the newborn. In a paper by [Nelson and colleagues \(2005\)](#), high-volume hospitals (those closing more than five exstrophies per year) had lower overall costs per patient than low-volume hospitals (fewer than five exstrophies per year). In addition, [Nelson and colleagues \(2008\)](#) found that a successful newborn closure had overall markedly lower inflation-adjusted hospital charges than reclosures owing to shorter operating times and shorter length of stay.

A corollary to these papers was one from [Meldrum and colleagues \(2005\)](#), who found that when exstrophy closures failed and the exstrophy had to be reclosed, the success rates and ultimate continence were better in patients of fellowship-trained pediatric urologists than those of other surgeons (general urologists, non-fellowship-trained pediatric urologists, and general pediatric surgeons).

In the evaluation of this group of selected exstrophy patients, it was found that at the time of initial closure, 19 of 23 patients had no osteotomy. Six of the patients had obtained bladder capacity suitable for bladder neck reconstruction; three were dry, and three were incontinent. Bladder size was inadequate in 9 patients who had been monitored for bladder growth. The chance of achieving an adequate bladder capacity and eventual continence after more than one closure attempt is markedly diminished. Lastly, the importance of early initial closure was emphasized by [Husmann and colleagues \(1989a\)](#), who showed that only 10% of the patients who undergo bladder closure before 1 year of age but 40% of those who undergo the procedure at a later age require eventual augmentation.

Epispadias Repair

Although urinary incontinence remains the most significant problem for patients with CBE and epispadias, anxiety about inadequate and unattractive genitalia still poses the greatest concern to male patients. We began using the modified Cantwell-Ransley repair in patients with classic exstrophy or epispadias in 1988 and have reported our early experience ([Gearhart et al, 1992, 1995c](#)).

Since 1988, the modified Cantwell-Ransley repair has been performed for 129 male patients with either CBE (97 patients) or epispadias (32 patients) ([Baird et al, 2005b](#)). At the time of surgery, the patients' ages ranged from 1 to 18 years with an average age of 19 months. Of the 97 patients with bladder exstrophy, 31 had a short urethral groove requiring paraexstrophy skin flaps for penile lengthening at the time of initial bladder exstrophy closure. Of the 32 epispadiac patients, 26 had penopubic and 6 had penile epispadias at presentation.

This technique was used for primary urethroplasty in 106 patients with bladder exstrophy and 32 with epispadias. The modified Cantwell-Ransley repair was used as a secondary procedure after failed urethroplasty in 15 patients with exstrophy and 8 with epispadias and was combined with reclosure of bladder exstrophy in 18 patients. Early epispadias repair was performed when the patients were 6 months to 1 year of age. However, because of concerns about getting the urethra deeper under the corpora at the glanular level, beginning in 1994 we further modified the Cantwell-Ransley repair by detaching the mucosal plate from the corona except for the distal 0.5 to 1 cm of the plate inside the glans.

One hundred twenty patients had a horizontal or downward-angled penis while standing. The incidence of urethrocuteaneous fistula in the immediate postoperative period was 16%, and at 3 months it was 12%. Nine patients developed a urethral stricture of the proximal anastomotic site, and 12 had minor skin separation of the dorsal skin closure. Cystoscopy with catheterization in 120 patients revealed an easily negotiable channel in all. Eight patients required further penile straightening surgery. Fifteen patients older than 16 years had engaged in satisfactory intercourse, and all reported orgasms and ejaculation with a straight penis on erection. One patient reported that his penis was shorter after surgery.

Modern penile reconstructive techniques should create a straight and functional penis with a glanular meatus, an easily catheterizable neourethral channel (if needed), and an acceptable cosmetic appearance. Many adolescents considered their odd-appearing

genitalia with a short, widened penis upwardly deviated to be a greater psychosocial problem than incontinence, and therefore every effort should be made to restore the penis to a normal condition. In 1989, Ransley and associates introduced a concept to release dorsal chordee by incision and anastomosis of the dorso-medial aspect of the corpora over the urethra and urethral meatotomy at the distal end of the glans, to move the meatus to a more normal position and secure good direction of the urinary stream (reverse MAGPI [meatal advancement and glansplasty incision]) ([Ransley et al, 1989](#)). Ransley's group has reported its long-term experience with 95 patients in whom the modified Cantwell-Ransley repair was used: fistula occurred in only 4% of patients, and a urethral stricture in only 5% ([Kajbafzadeh et al, 1995](#)).

Dissection of the urethral strip to inside the glans penis provides a ventral position of the urethra and the glans and submerges the urethra well below the corpora at the glans level. This approximation of raw surface of glanular tissues dorsally over the urethra is clearly why the incidence of fistula in the area of the corona is very rare compared with the Young repair. Fistulae in our patients usually appear at the base of the penis, where the urethra comes up proximally between the corporeal bodies. In modern exstrophy reconstructive techniques, most surgeons try to preserve the urethral plate at the time of exstrophy closure. Because the use of paraexstrophy skin flaps has been noted to be associated with the development of strictures, the use of these flaps is limited to selected patients in whom penile lengthening cannot be achieved with standard techniques.

Papers from several institutions have reported their results with the Mitchell-Bagli penile disassembly technique. Complications are very similar to those of other methods of epispadias repair (i.e., fistula and urethral stricture) ([Zaontz et al, 1998](#); [Kibar et al, 2009a](#)). Although not a complication, a high percentage are made hypospadiac as the completely dissected urethral plate fails to reach the tip of the glans. The rate of being made hypospadiac has been reported as 38% to 83%. ([Mitchell and Bagli, 1996](#); [El-Sherbiny and Hafez, 2005](#)).

As mentioned in the prior section on exstrophy closure, ischemic loss of the glans, urethral plate, and corpora have been reported by [Hammouda \(2003\)](#) and [Husmann and Gearhart \(2004\)](#) after penile disassembly. [Cervellione and colleagues \(2010\)](#) have reported the largest series of penile ischemic injury in the exstrophy-epispadias spectrum. Most occurred at the time of exstrophy closure, and 19 of 24 did not have a pelvic osteotomy. The suggested explanation by the authors was compression of the pudendal vessels owing to tension after pelvic apposition and/or direct injury to the pudendal vessels. Stopping the closure and doing an immediate osteotomy while the vessels had time to regain flow was the recommended course of action.

Repair of the hypospadias in these patients has been reported by the Seattle group as not difficult or associated with major complications. However, data from [Hafez and El-Sherbiny \(2005\)](#) and [Gearhart and Baird \(2005\)](#) shows that difficulties can be associated with these repairs. In an attempt to deal with the issues and prevent them, [El-Sherbiny and Hafez \(2005\)](#) and [Perovic and colleagues \(1999\)](#) have modified the Mitchell repair to resemble the modified Cantwell-Ransley repair ([Gearhart and Baird, 2005](#)) by keeping the urethral plate attached to the distal glans to obviate the need for making the child hypospadiac at the time of isolated epispadias repair or when associated with CPRE.

In our opinion, none of the current epispadias repairs offers any significant gain in penile length by removal of the entire urethral plate from the glans or even the use of a free graft. Data reported by [Silver and colleagues \(1997b\)](#) clearly showed that although anterior corporeal length is significantly less in patients with exstrophy, posterior corporeal length is normal. These findings suggest that penile lengthening procedures at the time of epispadias repair improve apparent penile length and straighten the penis but do not transfer additional tissue (i.e., length) to the corporeal bodies. We have observed that the modified Cantwell-Ransley repair effectively corrects corporeal chordee and adds some penile length, and it can be hoped that dorsal penile curvature,

TABLE 139-1 Urinary Continence after Functional Bladder Closure

	MOLLARD ET AL (1994)	MCMAHON ET AL (1996)	LOTTMANN ET AL (1998)	BAIRD ET AL (2007)	PURVES ET AL (2008)	SCHAEFFER ET AL (2011)
No. of closures evaluated	73	33	57	67*	41†	27‡
Patients confirmed dry day >3 hr; dry hr§	69%	70%	67%	70%	74%	56%

*All male.

†All female.

‡Young-Dees-Leadbetter procedure after complete primary repair of exstrophy as newborn.

§Patients reported that they were dry for more than 3 hours during the daytime.

often seen at puberty, will be lessened. In our significant experience with adolescent exstrophy males with significant dorsal chordee, we agree with [Perovic and colleagues \(1999\)](#) that movement of the neurovascular bundles along with incision and grafting of the resultant defect gives better results long term than incision and corpora cavernostomy. Typically in our experience, incision and rotation are used only for older patients with marked chordee. In the patients in whom corporeal rotation is used without corporeal incision and anastomosis, the neurovascular bundle is left intact and not dissected from its bed. Although review of findings reveals that almost all penises are straight or deflected downward, many of these patients are still young children. The long-term assessment of penile and urethral reconstruction in exstrophy patients by the modified Cantwell-Ransley repair has shown that in patients with bladder exstrophy and epispadias there is some increase in penile length, and a relatively straight penis with an adequate urethral caliber, which is adequate to void and ejaculate through, can be achieved with minimal morbidity. Long-term reports with the penile disassembly technique have also demonstrated a reasonably straight penis ([Grady, 2003](#)).

Bladder Neck Repair

Bladder neck reconstruction results in the exstrophy population have been reported by several groups. Some extensive experiences have come from the European groups in Lyon and Paris. [Mouriquand and associates \(2003\)](#) reported on 80 children with bladder exstrophy and 25 with incontinent epispadias. Follow-up ranged from 1 to 11 years. Forty-five percent of the group with exstrophy and 52% of those with epispadias had a dry interval longer than 3 hours. Although the continence rate was low, many of the exstrophy patients did not undergo closure until 6 to 12 months of age. Many underwent epispadias repair after bladder neck reconstruction, a factor known to influence both eventual capacity and continence. [Lottmann and colleagues \(1998\)](#) presented a long-term follow-up study of Cendron's exstrophy patients who underwent complete reconstruction. With the Young-Dees repair, [Lottman and coworkers \(1998\)](#) were able to achieve urinary continence in 71% of male patients and 53% of female patients. Overall continence was 65% with a mean follow-up of 12 years after bladder neck repair. Series from North America using mainly the classic Young-Dees-Leadbetter repair reported continence rates ranging from 60% to 82% ([Husmann et al, 1989a; Mergurian et al, 1991; Perlmutter et al, 1991; Franco et al, 1994; McMahon et al, 1996; Chan et al, 2001; Cole et al, 2003](#)) (Table 139-1). The most important long-term factor gleaned from a review of all these series is the fact that bladder capacity at the time of bladder neck reconstruction is the most important determinant of eventual success.

Records of 95 patients who underwent all stages of MSRE by a single surgeon at our institution between 1988 and 2004 were reviewed by [Baird and colleagues \(2007\)](#). Sixty-seven patients with bladder neck reconstruction and minimum 5-year follow-up were available for analysis. The current voiding status of each patient was obtained from parental or patient interview or direct observation by the nursing and physician staff. The patients were categorized as spontaneous voiding not on intermittent catheterization and were

TABLE 139-2 Urinary Continence after 67 Initial Bladder Neck Reconstructions

RESULT	AVERAGE DRY INTERVAL	NO. OF PATIENTS	% OF PATIENTS
Continent	3 Hours	47	70%
Social continence (dry daytime, occasional wet nights)	3 Hours	7	10%
Wet	<3 Hours	13	19%

assigned a status of (1) completely dry—day and night; (2) socially continent—dry at least 3 hours during the day with occasional wet nights; or (3) wet—dry for less than 3 hours during the day and wet at night (Table 139-2).

Of the 67 male patients who underwent bladder neck repair, the mean age for primary closure was 4 months (range 6 hours to 4 months). The mean age at bladder neck repair was 4.8 years (range 40 to 60 months), and these patients had a mean bladder capacity before repair of 98 mL (range 75 to 185 mL). Of the 67 patients, 47 (70%) are continent and voiding urethrally without the need for augmentation or intermittent catheterization. Seven patients (10%) had social continence with occasional wet nights. The renal units of all patients who underwent bladder neck repair were evaluated by intravenous pyelography or ultrasound postoperatively on multiple occasions to assess preservation of renal function after the outlet procedure. One patient had reflux and hydronephrosis after the outlet procedure and bilateral reimplantation and developed left pyelonephritis with resultant mild scarring. Dimercaptosuccinic acid (DMSA) scanning revealed nearly normal bilateral function. Conservative follow-up revealed resolution of the reflux with time. One patient developed ureteral obstruction and required reoperative reimplantation. Prolonged outlet obstruction required cystoscopy and placement of an 8-Fr catheter in 19 patients, and prolonged suprapubic drainage was required in 13 patients. Thirteen (19%) failed bladder neck repair completely; 6 have undergone continent diversion, and 7 await further surgery. The mean time to daytime continence was 14 months (range 4 to 23 months), and the mean time to nighttime dryness was 23 months (range 11 to 34 months). No correlation was found between age at bladder neck reconstruction and age at achievement of continence.

The findings in this series were that continence was more likely in patients who underwent primary exstrophy closure before 72 hours of age or after 72 hours of age with an osteotomy. These results coincide with those of [Husmann and colleagues \(1989a\)](#), who found that patients who underwent delayed closure without osteotomy showed a continence rate of only 10%. There was another very revealing factor in this study. Bladder capacity at the time of bladder neck repair gave a strong indication not only of who would be dry but also who would be dry sooner. If the patients were

divided into those with a preoperative bladder capacity greater than or less than 100 mL, results showed that the group with the larger capacity had a high rate of continence: 42 of 50 dry and voiding versus 5 of 17 in the lower-capacity group. In addition, the mean times to dryness in the higher- and lower-capacity groups were 10 months and 21 months, respectively (14 months in the group overall).

In a similar series by [Purves and colleagues \(2008\)](#), the results in females mirrored those of the male group, with a slightly higher continence rate of 74% (dry day and night) and social continence again in 10%. Again, patients with capacity greater than 100 mL had better outcomes. In a phenomenon not seen in the males, 6 patients (20%) became continent after bladder and pelvic closure alone.

A continence procedure should be delayed until the bladder reaches a capacity of 100 mL and the child is motivated to be dry and participate in a postoperative voiding program. The vast majority achieve daytime dryness within 12 months after bladder neck repair. A few patients gain a longer daytime dry interval during the second year after their outlet procedure. However, patients who are not dry within 2 years are considered incontinent, and the procedure is considered to have failed. The onset of nighttime continence varies from 2 to 3 years and takes longer than the time needed for daytime continence. [Caione and colleagues \(1999\)](#) showed that use of desmopressin acetate (DDAVP) can increase the onset and number of dry nights in these patients. In the series by [Baird and colleagues \(2007\)](#), 25% of patients required either DDAVP or oxybutynin to establish nighttime dryness.

Urodynamic evaluation by [Dave and colleagues \(2001\)](#) showed that patients with good continence after bladder neck repair had high cystometric bladder capacity and compliance compared with those who were incontinent. However, unstable contractions were seen in both groups. Also, higher end filling pressures were reported, and those patients had a high incidence of nonobstructive hydronephrosis. These findings, in addition to those of [Bolduc and others \(2002\)](#), indicate that careful lifelong follow-up is essential in these patients after successful childhood reconstruction.

OTHER MODERN EXSTROPHY REPAIRS: CONTINENCE OUTCOMES

Warsaw Approach

The long-term reported outcomes of this repair include 36 patients with classic exstrophy and 37 with epispadias. Eighty-nine percent of patients with epispadias were continent during the day, but more than 40% were still wet at night. Seventy-five percent of patients with classic exstrophy had daytime continence, but nine had occasional wet nights. Eleven boys required short-term intermittent catheterization, which was easily performed by the patient and family. All but 2 began voiding within 3 to 5 months, and only 2 have continued with intermittent catheterization. Ureteral reimplantation was not performed at the time of bladder neck reconstruction and epispadias repair, but many patients required later reimplantation for gradually worsening hydronephrosis.

Compared with this experience, [Mathews and coauthors \(2003b\)](#) reported on a group of patients who had ureteral reimplantation performed at the time of bladder neck reconstruction and epispadias repair. None of these patients developed reflux or worsening hydronephrosis. [Baka-Jakubiak \(2000\)](#) recommends performance of this combined procedure if the bladder capacity is documented to be above 100 mL and the penis is large enough for epispadias repair. Follow-up urodynamic studies demonstrated the presence of normal detrusor function in most, although some patients developed high voiding pressures and some had poor detrusor contractility. If poor detrusor contractility was noted, prolonged intermittent catheterization was required and high voiding pressures were managed with anticholinergic therapy. Most patients were managed later in life, and the standard addition of ureteral reimplantation at the time of reconstruction should probably be universally performed.

Erlangen Approach

[Rosch and colleagues \(2001\)](#) have reported on 100 patients, using this technique in both newborns and failed closures. Ninety-one children with exstrophy (69 boys and 22 girls) and 9 with complete epispadias (7 boys and 2 girls) have had this procedure performed. The complete single-stage repair was performed in 47 children and included pelvic closure without osteotomy, bladder neck reconstruction, an antireflux procedure, and epispadias repair using the Cantwell-Ransley technique. An additional 53 patients underwent primary reconstruction elsewhere and then had bladder neck reconstruction and epispadias repair performed. Continence was defined as dryness for more than 3 hours and no nocturnal enuresis. Partial continence was defined as dryness for 1 to 3 hours, or for longer than 3 hours with occasional stress incontinence or wet nights. Patients dry for less than 1 hour were considered incontinent. Among the patients undergoing single-stage repair, 34 of 39 are dry (72%) and voiding per urethra, 2 of 39 are on clean intermittent catheterization (CIC), and 3 of 39 are on CIC after augmentation. Four patients are partially continent and 2 are dry on desmopressin. Four patients are incontinent and 3 have undergone continent diversion. Of 53 patients who underwent primary closure elsewhere, 55% are continent and 7 have been augmented. Fourteen are partially continent and 10 are incontinent, 4 of whom have undergone continent diversion.

Complete Repair

Various series have been published about outcomes, including the need for ureteral reimplantation in the first year of life, the number of patients requiring hypospadias repair after this procedure, and the complication rates of this procedure. However, little has been published about the long-term continence results or the need for bladder neck reconstruction in this group of patients. [Borer and colleagues \(2005\)](#) reported that ultimately almost 65% to 70% of patients undergoing CPRE in the newborn period will require a bladder outlet procedure. In an updated series, [Gargollo and colleagues \(2011\)](#) found that 80% of patients with long-term follow-up required bladder neck repair. In a series by [Hafez and colleagues \(2005\)](#) with some patients who had delayed or failed primary closures, 84% of males and 50% of females required bladder neck repair to be dry. Some of these required concomitant bladder augmentation to be dry. In another very large series by [Shoukry and colleagues \(2009\)](#), no patients were continent after CPRE alone and most required augmentation to be dry. More important, early dry intervals did not translate into later continence.

Mitchell and Grady (2008) reviewed their experience with 39 patients over 19 years with CPRE. Daytime voided continence was achieved in 74% of males and females with 4 years of follow-up. However, only 20% and 43% of boys and girls, respectively, achieved continence without the need for bladder neck repair. Eighteen percent achieved dryness with bladder neck injection only. In a recent series of CPRE patients referred for reclosure or after successful closure for bladder neck reconstruction, the results were very interesting ([Schaeffer et al, 2011](#)). All patients were operated on by an experienced senior surgeon who does not do CPRE in newborns. None of the 14 referred patients who underwent successful CPRE in the newborn period was continent for any appreciable interval after closure. Of the 19 patients who underwent bladder neck reconstruction after complications with their newborn closure, only 25% were voiding from the urethra and continent. In the group with a successful primary closure ($n = 14$), 57% were dry day and night and 28% were dry during the day only ([Schaeffer et al, 2011](#)). Of major interest, all patients who were dry after bladder neck reconstruction had a successful primary closure with pelvic osteotomy and hypospadias repair before 1 year of age, and none required ureteral reimplantation before bladder neck repair. These data clearly show that in the majority of cases "complete repair" patients will need to undergo bladder neck repair. However, as in all of the major repairs, a successful primary closure with fewer bladder violations and

interval surgeries will increase the chance for bladder growth and voided continence.

Other methods have combined epispadias repair with bladder exstrophy closure in the male patient. In a series of 38 boys with classic exstrophy, [Baird and colleagues \(2005c\)](#) evaluated patients with either failed or delayed primary closures. The complications were those seen with routine exstrophy repairs including urethrocutaneous fistula, urethral strictures, and so on. Three boys were dry with combined closure alone. Nineteen boys went on to modified Young-Dees-Leadbetter bladder neck repair. Twelve (63%) of these 19 were totally dry both day and night. These data as well as the data of Mitchell and Grady clearly show that epispadias repair and exstrophy closure can be combined with acceptable results. However, the complications are real and can portend the loss of any chance at volitional voiding, and the procedures should be performed only by experienced exstrophy surgeons and not the occasional surgeon.

Kelly Repair

There are not many papers with long-term follow up of the Kelly technique. However, a recent presentation by the Melbourne group gives the best and most current results that can be found with this repair ([Jarzebowski et al, 2009](#)). Data were collected in children older than 4 years. Complete continence was defined as dryness for longer than 3 hours day and night (with two or fewer wet nights per month). Partial continence was dryness for 2 or more hours during the day and 3 or more wet nights per month and/or stress incontinence. Twenty-four of 31 Kelly patients void spontaneously and 17 of 31 void in an unaided fashion (without intermittent catheterization or augmentation). Overall continence was 71%, with 3 of 17 (18%) voiding in an unaided fashion and having complete continence and 9 of 17 (53%) having partial continence. The 18% dry and voiding rate compares favorably to that recently reported for CPRE. Another study from Italy ([Berrettini et al, 2009](#)) showed that in 5 of 9 boys, continence was achieved with a Mainz pouch in 1, intermittent catheterization in 2, and by voiding in 2. One of 9 experienced glans loss ([Berrettini et al, 2009](#)).

EXSTROPHY RECONSTRUCTION FAILURES AND COMPLICATIONS

Failed Closure

After any form of repair, failures can manifest as complete bladder dehiscence, bladder prolapse, neourethral stricture and obstruction, soft-tissue loss, and vesicocutaneous fistula ([Massanyi et al, 2013](#)). [Meldrum and associates \(2005\)](#) reported on a select group of children in whom exstrophy reconstruction had failed before referral to a tertiary care facility. In the cohort of 101 children, 51 had primary surgical management performed by a fellowship-trained pediatric urologist, 18 by a general urologist, 6 by a pediatric surgeon, and 9 by an unknown surgeon. After successful reclosure, 38 patients eventually developed adequate bladder capacity for bladder neck reconstruction, and only 26% (10) eventually achieved dryness. These data emphasize the need for initial successful reconstruction and suggest that individuals undertaking this reconstruction should be comfortable with the complexity of repair. It is prudent for the surgeon who may see only a few patients with this condition to consider referral of these complex management situations to a center where special expertise and experience exist.

In a recent large series by [Schaeffer and colleagues \(2008\)](#), 185 patients who underwent closure by one of two surgeons were reviewed for both major and minor complications ([Table 139-3](#)). Sixty-three underwent osteotomy at the time of primary closure. There were 14 major complications (11%) and 27 minor complications (14%). Major urologic complications included bladder prolapse or dehiscence in 6 male patients (3%), all of whom underwent successful reclosure. Major orthopedic complications, including nonunion in two patients, leg-length inequality in 1, and persistent

TABLE 139-3 Urologic, Orthopedic, and Neurologic Complications in 185 Primary Bladder Closures

UROLOGIC COMPLICATIONS	NO.
Bladder prolapse and dehiscence	6
Postoutlet obstruction	4
Suprapubic tube removal	2
Intrapubic stitch erosion	4
Febrile urinary tract infection	6
Wound infection	3
Bladder calculi	5
ORTHOPEDIC COMPLICATIONS	
Nonunion osteotomy	2
Leg-length inequity	1
Persistent joint pain	1
Pelvic osteomyelitis	1
Pin site infection	3
Pressure sore	1
NEUROLOGIC COMPLICATION	
Femoral nerve palsy	4

joint pain in 1, developed in 4 of 63 patients (6%) who underwent osteotomy. Major neurologic complications included femoral nerve palsy in 4 of the 185 patients (2%). There were 21 minor urologic complications (11%) including posterior bladder outlet obstruction in 4 patients, urethrocutaneous fistula in 2, suprapubic tube removal in 2, intrapubic stitch erosion in 4, febrile UTI in 6, and surgical site infection in 3. Six patients (3%) had minor orthopedic complications including pelvic osteomyelitis in 1, pin site infection in 3, and a pressure sore from immobilization in 1.

Dehiscence, which may be precipitated by incomplete mobilization of the pelvic diaphragm and inadequate pelvic immobilization postoperatively, wound infection, abdominal distention, or urinary tube malfunction, necessitates a 4- to 6-month recovery period before a second attempt at closure can be made ([Gearhart and Jeffs, 1991a](#); [Gearhart et al, 1993b](#)) ([Fig. 139-25A1](#)). Dehiscence and prolapse after CPRE have also been reported and may be associated with glans, corporeal, urethral plate, and other major soft-tissue loss ([Fig. 139-25B and C](#)). Tension-free reclosure with osteotomy and immobilization are important factors in initial and subsequent closures. Unfortunately, the chance of obtaining adequate bladder capacity for bladder neck plasty and eventual continence after multiple closures is markedly diminished ([Gearhart et al, 1996a](#); [Novak et al, 2010](#)). Similarly, bladder prolapse is considered a failure and requires bladder reclosure or revision. In a recent series from a single institution of 122 patients who underwent reclosure with a mean follow-up of 14 years, the voided continence rate was 16% ([Novak et al, 2010](#)). In a patient with significant bladder prolapse or dehiscence, at the time of secondary closure we combine epispadias repair with bladder, posterior urethral, and abdominal wall closure ([Gearhart et al, 1998](#)). The patient is given testosterone enanthate intramuscularly 5 weeks and 2 weeks before surgical repair and undergoes an osteotomy with concomitant bladder, urethral, and abdominal wall closure. Major soft-tissue loss that is seen after CPRE necessitates extensive preoperative planning; use of buccal mucosal or full-thickness grafts and tissue expansion may be required before definitive surgery ([Gearhart and Baird, 2005](#)).

[Baird and coauthors \(2005c\)](#) reported on 38 boys undergoing combined exstrophy closure and epispadias repair along with osteotomy; in 30, prior reconstruction had failed. Complications in this group were limited to urethrocutaneous fistulae and urethral strictures. Although the results after reclosure are not as good as those obtained with a successful primary closure, they are respectable and may obviate the need for bladder augmentation.

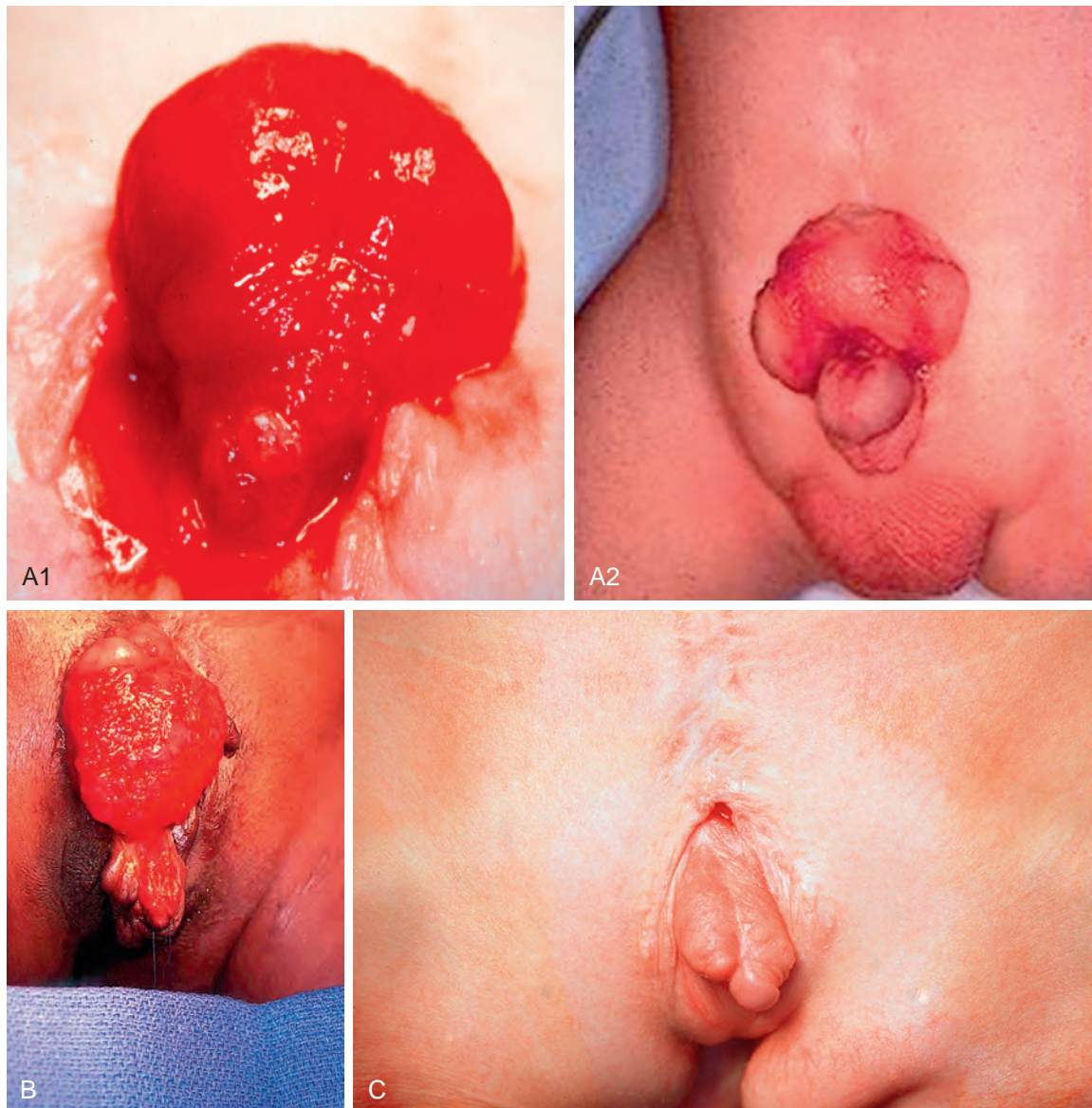


Figure 139-25. A1, Failed female newborn closure. A2, Major bladder prolapse after complete primary repair of exstrophy (CPRE) without osteotomy. B, Complete dehiscence and loss of right glans and partial loss of corpora after CPRE. C, Loss of right glans and urethra after penile disassembly in newborn (under testosterone stimulation before placement of full-thickness skin graft).

Neourethral stricture is often associated with paraexstrophy skin flap use, pubic suture reaction, erosion, or the use of urethral stents. This may be somewhat subtle; however, warning signs consist of UTIs, detectable increased bladder volumes on ultrasonography, bladder stones, prolonged dry intervals, and unexplained rectal prolapse. In a review by [Baker and colleagues \(1999\)](#), posterior urethral obstruction was found in 41 patients. Most episodes occurred within 60 days after primary closure. If diversion was used for longer than 6 months, the ultimate fate of the bladder was augmentation. If diversion was used for less than 6 months, most reconstructions were ultimately bowel free. The authors have also seen outlet obstruction including complete obliteration after both the CPRE and Kelly repair ([Hernandez et al, 2008](#)). Whether this is a result of ischemic damage to the urethral plate or technical error is unclear. Regardless, because there is a paucity of long-term data from these two repairs, the outlet must be monitored carefully as with all exstrophy patients after primary closure. Ultimately, posterior urethral obstruction after exstrophy closure markedly decreases

the success of any repair. This complication presents a significant risk to the upper urinary tract and should be detected early.

Although all closed exstrophy bladders have vesicoureteral reflux, upper tract deterioration is the ultimate fate of significant outlet obstruction. At this point the management includes urethral dilation (incision), open urethroplasty, or upper tract diversion. If renal function is compromised, the choice must achieve unquestionable free drainage to allow the upper tracts and kidneys to recover fully. Further bladder neck or urethral reconstruction should not be performed until the posterior urethral stricture is clearly repaired and free drainage has been achieved. After CPRE repair, up to 50% of patients will require bilateral ureteral reimplantation during the first year after surgery because of UTIs and increasing hydronephrosis.

[Massanyi and colleagues \(2012\)](#) found that a high number of patients with a vesicocutaneous fistula after primary closure actually have a failed closure. On evaluation 13 of 18 patients referred because of vesicocutaneous fistulae were found to have a failed closure

represented by (1) a fistulous tract in the lower abdominal midline; (2) a pubic diastasis increased from preclosure measurements; and (3) cystoscopic evidence of an anteriorly positioned bladder just under the abdominal skin.

Despite satisfactory closure, some bladders never achieve adequate capacity to act as functional bladders. [Baradaran and colleagues \(2011\)](#) presented a large series of patients including those with failed primary bladder closures ($n = 62$) who underwent successful secondary closure; these patients were evaluated and compared with another group of patients with successful primary closures ($n = 48$). Both groups were followed over 5 years. Bladders in patients who had had a successful primary closure had a significantly larger cystographic capacity than the group with failed closure. Bladders grew at a significantly slower rate in the group with failed procedures and had significantly lower bladder capacities over time. These data underscore the importance of a successful primary closure. It has become clear that multiple bladder closures, bladder prolapse, dehiscence, bladder calculi, recurrent infections, and vesicostomy have a negative impact on the potential of the exstrophy bladder ([Silver et al, 1997b](#)).

Unsuccessful primary closures regardless of the method of repair really calls into question the ability of the bladder to grow, undergo an eventual bladder neck reconstruction, and be continent of urine. [Schaeffer and colleagues \(2011\)](#) reported on a large series of patients with failed CPRE procedures who were referred for further treatment. Of the 23 male patients, only half obtained a capacity sufficient for a bladder neck procedure, and only 25% were voiding and continent. [Novak and colleagues \(2010\)](#) reported a very large series of 122 patients with a failed primary or secondary closure of whom 94 underwent a successful repeat closure. Only 38 were candidates for bladder neck repair and only 17 of the 94 (18%) were voiding and continent. Thus, regardless of the type of repair, a failed closure portends significant implications for long-term surgical outcomes.

We have used transurethral injection of collagen and dextranomer around the bladder neck to increase outlet resistance and stimulate the bladder to grow. However, in our hands this has not been as successful as reported by [Caione and colleagues \(1993a, 1993b\)](#). If the bladder does not grow to a sufficient size for bladder neck reconstruction, bladder augmentation is recommended in this situation. If the bladder neck or urethra or both are problematic, a catheterizable continent stoma with or without bladder neck plasty or transection is performed, along with augmentation ([Gearhart et al, 1995b](#)).

Failed Bladder Neck Repair

Even with experienced exstrophy surgeons, missteps can occur, and there remains a subgroup of children with urinary incontinence after bladder neck reconstruction secondary to (1) inadequate outlet resistance; (2) a small bladder capacity (lack of growth after bladder neck reconstruction); (3) decreased compliance; or (4) a combination of these factors.

If urinary continence, defined as a 3-hour dry interval, is not achieved within 2 years after bladder neck reconstruction, failure to achieve dryness has resulted. Occasionally the dry interval is nearly acceptable for daytime dryness (i.e., longer than 2 hours). In these situations urethral bulking agents have been used in an attempt to avoid further major reconstructive procedures ([Burki et al, 2006](#)). Formerly, collagen was the bulking agent of choice, but often multiple injections were required ([Ben-Chaim et al, 1995a](#)). In a large series from Paris, [Lottmann and colleagues \(2006\)](#) reported on the use of a dextranomer-based bulking agent in childhood with incontinence from multiple causes. Twenty-six patients had the exstrophy-epispadias syndrome. Of the 9 exstrophy patients, 4 achieved success; in the epispadias group the success rate was much higher (longer than 3 hours dry by intermittent catheterization or voiding).

In a recent very large series of specifically exstrophy-epispadias patients ([Shah et al, 2014](#)) with a median follow-up of 8 years, 41 underwent injection before bladder neck reconstruction and 25 after bladder neck reconstruction. Injection before bladder neck

reconstruction did result in 50% developing an adequate capacity for bladder neck reconstruction, but only 9 (22%) became dry. Bladder capacity was the most predictive variable of a successful bladder neck reconstruction after bladder neck injection. In the group of 25 patients with prior bladder neck surgery of whom 16 were partially dry (1 to 3 hours), all were rendered socially continent (dry for longer than 3 hours) after bladder neck injection. Of the 9 dry for less than 1 hour, bladder neck injection was not helpful at all. Thus, outlet injection after a failed bladder surgery is more successful if a reasonable dry interval has been achieved with open bladder neck surgery. In recent data from [Alova and colleagues \(2012\)](#), bladder neck surgery after prior dextranomer bladder neck injection was not found to be more difficult and success rates were quite acceptable with long-term follow-up. However, repeated dextranomer injections after a prior failure did not result in success.

Some successes have been seen with repeated Young-Dees-Leadbetter repair if the bladder neck is patulous, the bladder capacity is adequate, and urodynamic evaluation reveals a stable bladder ([Gearhart et al, 1991](#)). In that series only 50% of patients with a failed prior bladder neck reconstruction were candidates for reoperative surgery. In this highly select group, continence rates were acceptable after reoperative bladder neck reconstruction. All of these patients had excellent bladder capacity (>100 mL) and were stable on urodynamics before the redo repair. A majority of bladder neck failures require eventual augmentation or continent diversion ([Burki et al, 2006](#)). The artificial urinary sphincter has been used with some success in patients who have a good bladder capacity. However, in most of these failures the bladder capacity is small and augmentation is required. At the time of reoperative surgery, either the bladder neck is transected proximal to the prostate with a Mitrofanoff substitution or a continence procedure, such as creation of an artificial sphincter, is performed. In our extensive experience with failed bladder neck reconstructions, most of the patients have had several surgeries of the bladder neck area and are desperate to be dry. In a recent large series of 31 patients who had undergone prior bladder neck reconstruction, [Novak and colleagues \(2009\)](#) found that most patients had undergone multiple prior repairs to achieve continence. Bladder neck transection along with enterocystoplasty was performed with initial continence achieved in 86%. Seven patients underwent further bladder neck surgery, and 90% achieved dryness by intermittent catheterization. One renal unit was lost, nonobstructive hydronephrosis developed in 8, and bladder stones occurred in 30%.

Delayed urinary continence has been reported at the onset of puberty in some males, and this has been attributed to prostatic growth. On MRI, the prostate of exstrophy patients is cloverleaf shaped and absent anteriorly, and its mean weight and maximal cross section and volume are normal ([Gearhart et al, 1992](#)). Therefore, it is doubtful that growth of this abnormally configured prostate can have much impact on urinary continence after failed bladder neck repair, and improved continence at puberty may be a result of changes in the pelvic floor with maturity.

Failed Genitourethral Reconstruction

Common complications of modern epispadias repair include urethrocutaneous fistula formation. This has been reported in as few as 4% and as many as 19% of cases ([Kajbafzadeh et al, 1995](#); [Surer et al, 2000](#)). Urethral tortuosity with difficult catheterization or strictures are uncommon with modern epispadias repair. Since the application of the penile disassembly for epispadias reconstruction, newer, more significant complications have been noted ([Hammouda, 2003](#)). [Gearhart and Baird \(2005\)](#) have reported loss of the glans, corpora, or both in addition to loss of penile skin and the urethral plate (see [Fig. 139-25C](#)). Whether this is secondary to surgical misadventure, vagaries in the blood supply of the penis, or the intrinsic difficulties in the procedure remains a topic of debate. Reconstruction of these complications has required additional techniques including tissue expansion, full-thickness skin grafting, buccal mucosal grafting, and other complex techniques. In some patients with significant losses, neophalloplasty may eventually provide the

material for final cosmetic reconstruction. Recent data by [Massanyi and colleagues \(2012\)](#) shows the applicability of radial forearm phalloplasty in patients who have lost glans, corpora, and other soft tissue as a consequence of epispadias repair or in cloacal exstrophies where penile tissue hardly exists. This alternative allows a sensate cosmetic neophallus for this special group of exstrophy failures.

At an older age, unsightly penile scars and a short phallus may prompt further surgical intervention. Scar excision can be closed in a plastic fashion if enough penile skin is available. Otherwise, flaps or full-thickness skin grafts can be used. In severe cases, tissue expanders can be placed under the penile skin and gradually inflated over 6 weeks to allow more penile skin and obviate the need for grafting. Freeing all scar tissues and suspensory ligament tissue can maximize available penile length. A dorsal dermal corporeal graft or ventral corporeal plication or rotation may also help lengthen as well as correct any chordee. However, it must be recognized that the exstrophy penis, when compared with age- and race-matched controls, is congenitally deficient in anterior corporeal tissue as assessed by MRI ([Silver et al, 1997b](#)). Therefore, overly aggressive attempts at penile lengthening may result only in corporeal denervation and devascularization without additional lengthening.

Alternative Techniques of Reconstruction

Not all children with bladder exstrophy are candidates for primary repair at initial evaluation because of a small bladder plate or significant hydronephrosis. Additional reasons for seeking other methods of treatment include failure of initial closure with a small remaining bladder or failure of continence surgery, or both. Excluding the patients in whom initial treatment fails, this discussion deals with options available when modern repair is not chosen by the surgeon or for other reasons has not been suitable.

Ureterosigmoidostomy

Whichever urinary diversion is chosen, the upper tracts and renal function are initially normal. This allows the reimplantation of normal-sized ureters in a reliable, nonrefluxing manner into the colon or other suitable reservoir. Historically, ureterosigmoidostomy was the first form of diversion to be popularized for patients with exstrophy. Although the initial series was associated with multiple metabolic problems, results improved markedly with newer techniques of reimplantation ([Zarbo and Kay, 1986](#); [Koo et al, 1996](#)). Ureterosigmoidostomy is favored by some because of the lack of an abdominal stoma. **However, this form of diversion should not be offered until one is certain that anal continence is normal and after the family has been made aware of the potential serious complications, including pyelonephritis, hyperkalemic acidosis, rectal incontinence, ureteral obstruction, and delayed development of malignancy** ([Spence et al, 1979](#); [Duckett and Gazak, 1983](#)). More recently, ureterosigmoidostomy has been proposed again as an initial treatment of bladder exstrophy with acceptable continence and renal preservation on follow-up of 10 years or longer. In a long-term Swiss study by [Gobet and colleagues \(2009\)](#) of 42 patients, 50% had their ureterosigmoidostomy in place and were fecally continent at 50 years of age. One had developed a colonic malignancy and 60% had normal renal function. Another good-sized study from Sweden by [Pettersson and colleagues \(2013\)](#) found a higher rate of colorectal cancer than the Swiss study and a higher rate of rediversion. The mean time from ureterosigmoidostomy was 38 years. Almost all of the malignancies were poorly differentiated adenocarcinoma. The difference in the results of these two European studies is unclear but underscores the need for lifelong vigilance for early detection of cancer.

[Stein and associates \(1999\)](#) treated a group of 128 patients with bladder exstrophy-epispadias with the Mainz technique for ureterosigmoidostomy. The Mainz Sigma pouch is constructed and the ureters reimplanted in a nonrefluxing manner. The abdominal wall is reconstructed and the bladder is closed as a seminal receptacle above the prostate. The penis is then reconstructed at a later date. [D'elia and coauthors \(2004\)](#) reported on 26 patients with the

exstrophy-epispadias complex who showed excellent continence rates with long-term upper tract preservation when compared with standard ureterosigmoidostomy. Continence was achieved in 95% of patients with a rectal reservoir. Their recommendation for treatment in a number of patients with severely impaired renal function was that a colonic conduit was the best method of choice for diversion. In the patients with a normal or slightly dilated upper tract and intact anal sphincters, a Mainz rectal reservoir was recommended. Although the group from Mainz reported no cancer in a long-term follow-up study of patients who underwent ureterosigmoidostomy, the risk for malignancy still exists. Patients who have had mixing of urine and feces at any time during reconstruction remain at high risk for the development of cancers ([Smeulders and Woodhouse, 2001](#)). Bladder exstrophy patients in whom an initial reconstruction has failed and who have polyposis at the time of repeated closure may also be at higher risk for the later development of malignancy ([Novak et al, 2005](#)). This is especially true in today's very mobile society, in which careful long-term follow-up may be difficult to guarantee. All patients with a ureterosigmoidostomy should have a yearly renal ultrasound and colonoscopy in adult life.

Continent Urinary Diversion in the Exstrophy Patient

In modern pediatric urology there is usually very little need for incontinent urinary diversion in the patient with bladder exstrophy. In a young child with a bladder that is too small to close, or in a failed closure where the bladder template is too small to reclose, we recommend a nonrefluxing colon conduit. This protects the kidneys from vesicoureteral reflux, and undiversion can be performed when clinically indicated at an older age.

Advances in the reconstruction of the lower urinary tract in the past several years have been applied to the patient with exstrophy. ([Cervellione et al, 2008](#)). Most commonly, further reconstruction is required in the patient in whom bladder neck reconstruction has failed. If a patient does not meet the criteria for bladder neck reconstruction (i.e., inadequate bladder capacity or inability to conform to a voiding regimen), deferring surgery is advisable. Patients in whom bladder neck reconstruction fails are most often destined to augmentation cystoplasty and continent urinary diversion. [Surer and colleagues \(2003\)](#) reported on 91 patients with the exstrophy-epispadias complex who underwent continent urinary diversion. The majority had undergone prior failed bladder neck reconstruction (n = 62). Seventy-nine patients (87%) had exstrophy closure before referral, 53 had also undergone bladder neck reconstruction, and 29 patients had never reached adequate capacity for bladder neck reconstruction. Ten of the 53 patients had undergone one prior attempt, 35 had undergone two prior attempts, and 8 had undergone three prior attempts at bladder neck reconstruction. A combined augmentation cystoplasty, continent urinary diversion, and bladder neck closure was performed in 59 patients (65%), and reaugmentation and continent urinary diversion was performed in 18 children. Ileocystoplasty was used in 41 patients, and sigmoid cystoplasty was performed in 30 patients. The appendix was used as the continent channel in 67 patients. Continence using intermittent catheterization through the stoma was achieved in 93% of children with the most common complication reported being that of bladder stones, noted in 26%. Although infrequent, failures can occur with continent urinary diversion in exstrophy ([Frimberger et al, 2003](#)). The most common modes of failure were a detrusor intussusception of a nipple valve, inadequate tunnel for an appendiceal channel, or continued bladder neck incompetence. The vast majority of these complications can be successfully repaired. Equally successful outcomes have been reported by [Baird and colleagues \(2005a\)](#) in adolescents who had undergone a mean of eight prior procedures before their definitive repair.

Occasionally, urinary diversion must be established at a very young age (5 years or younger). The need for early diversion in exstrophy is mainly driven by upper tract changes and social factors and can be safe in younger children with a favorable continence outcome. In a recent offering by [Baradaran and colleagues \(2012b\)](#), 19 patients underwent early diversion (14 continent, 5 incontinent).

Of the group who underwent early continent diversion, 7 had an early desire to be dry; 4 had persistent severe hydronephrosis; 1 had severe recurrent pyelonephritis; 1 underwent a repeat continent urinary diversion; 1 had inaccessible proper follow-up; and only 2 had a successful primary closure. Three patients had neobladder creation, 10 had augmentation with a continent stoma, and 2 had ureterosigmoidostomy. Currently, all patients with stomas are dry on intermittent catheterization. Continence can be achieved in most patients with exstrophy after failure of bladder neck reconstruction and is typically obtained through augmentation cystoplasty and closure of the bladder neck. If a patient is unlikely to develop adequate capacity for eventual bladder neck reconstruction, moving early to continent urinary diversion is preferable. One long-term concern has been the risk of malignancy in patients with continent urinary diversion. Recent data by [Husmann and Rathbun \(2008\)](#) revealed that the overall rate of malignancy is low unless associated with coexisting carcinogenic stimuli (prolonged tobacco, chronic immunosuppression) or the inherent risk associated with bladder exstrophy.

ADOLESCENTS AND ADULTS WITH EXSTROPHY-EPISPADIAS COMPLEX

As children with exstrophy grow into adulthood, there is an increasing need to address long-term functional and psychological aspects of dealing with a multiorgan birth defect. Some aspects such as sexuality and continence are common to all forms of the exstrophy-epispadias complex; however, in cloacal exstrophy there are additional neurologic and orthopedic aspects that can lead to significant disability.

A mainstay of the functional reconstruction of the exstrophy-epispadias complex is the preservation of renal function. Functional reconstruction of the exstrophy-epispadias complex has been associated with good preservation of renal function ([DeMaria et al, 1980](#); [Schaeffer et al, 2013](#)). Renal function, however, can be compromised after urinary diversion ([Husmann et al, 1988](#)). Although urinary diversion has been used successfully as a temporary modality for providing upper tract decompression ([Baradaran et al, 2012b](#)), most children will eventually undergo undiversion to continent urinary pouches. Long-term urinary diversion is now infrequently used in the exstrophy-epispadias complex.

CONTINENCE

Early surgical management of patients with bladder exstrophy included initial cystectomy and replacement with an ileal conduit or ureterosigmoidostomy. The use of ureterosigmoidostomy has fallen into disfavor owing to an increased identification of lethal colonic cancer ([Gobet et al, 2009](#)). Renal function, however, was preserved in the majority of patients with ureterosigmoidostomy. Some institutions have been using continent catheterizable pouches for bladder management ([Nerli et al, 2008](#)). More recently, however, use of augmentation cystoplasty with bladder neck reconstruction or closure has been used successfully to provide continence in the majority of patients ([Novak et al, 2009](#); [Kavanagh et al, 2012](#)). Long-term concerns about augmentation cystoplasty continue to be raised. [Fontaine and colleagues \(2000\)](#) evaluated 53 patients who had undergone augmentation cystoplasty and had at least 10 years of follow-up. In 80% of patients, there was no reduction in GFR noted. Remediable causes were found to account for the reduction in GFR noted in the remaining 20% of patients, leading the researchers to conclude that augmentation cystoplasty was effective in providing urine storage without compromising long-term renal function. Owing to the long-term potential for carcinogenesis in patients who had undergone ureterosigmoidostomy, concerns were raised regarding tumor formation in children with augmentation cystoplasty. [Husmann and Rathbun \(2008\)](#) reviewed their experience with 153 patients who had undergone augmentation cystoplasty; 38 of these patients had bladder exstrophy, of whom 3

developed multifocal adenocarcinoma, which suggests that there may be an inherent risk for long-term carcinogenesis in patients with bladder exstrophy who undergo augmentation. Exposure to cigarette smoking increased the potential for the development of cancers in patients with augmentation cystoplasty, as did the use of immunosuppression for post-transplant management. Endoscopic surveillance beginning 5 years after reconstruction has been suggested; however, identification of early lesions can be difficult in the augmented bladder. Fecal incontinence has recently been noted in patients with bladder exstrophy and appears to persist into adulthood ([El-Hout et al, 2010](#)). Although this has not been noted by other investigators, ongoing evaluation for this psychologically debilitating problem seems appropriate.

SEXUALITY

Male Concerns

The most often expressed male concerns relate to the length, appearance, and the axis deviation (chordee) of the penis noted with exstrophy. Functional penile length can be gained by degloving the penis and resecting all of the residual scar tissue and releasing any remnants of the suspensory ligaments. Skin coverage can be a significant problem after penile lengthening procedures. Use of tissue expansion will permit local skin to be used for coverage; however, this will require preplanning. Placement of a tissue expander and subsequent expansion can take 4 to 6 weeks. If the penile skin is not ideal for expansion, full-thickness grafting is a suitable alternative ([Hernandez et al, 2008](#)). Residual dorsal chordee from childhood reconstruction is not uncommon. Grafts (dermal grafts, tunica vaginalis, human AlloDerm) can be used to lengthen the dorsal aspect of the penis. Our preference is human AlloDerm because it is readily available, durable, and easy to use. Because of its anatomy, the penis must be opened dorsally for one half of its circumference as described by [Perovic and Djinic \(2008\)](#) to both lengthen and straighten the penis. Early measurements and determinations from artificial erections must be adequate because after grafting, the artificial erections can leak saline through the suture lines and give misleading information about the adequacy of correction.

In the cloacal exstrophy patient, the corporeal structures can be very small, and the only option for a functional phallus would be reconstruction with flap phalloplasty (see earlier). Retention of all of the present corporeal and glanular tissue will permit a location for anchorage of the neophallus ([Ballaro et al, 1999](#)).

Sexual function and libido in exstrophy patients are normal ([Woodhouse, 1998](#)). The erectile mechanism in patients who have undergone epispadias repair appears to be intact because 87% of boys and young men in the Hopkins series experienced erections after repair of epispadias ([Surer et al, 2000](#)). [Woodhouse \(1998\)](#), [Ben-Chaim and colleagues \(1996\)](#), and [Ebert and coworkers \(2008\)](#) reported satisfactory orgasmic function in most patients. In the men who had participated in sexual intercourse, female partners also expressed sexual satisfaction. In the series by Ben-Chaim, the only patients who had no ejaculation were 2 patients who had undergone cystectomy. A report from Castagnetti and colleagues (2010) of 19 men with bladder exstrophy evaluated via the International Index of Erectile Function questionnaire and compared with normal men indicated a higher incidence of erectile dysfunction (58%) as compared with the normal controls (23%). Erectile function was worse in those who had undergone multiple surgeries for treatment of incontinence. Orgasmic function was also noted to be lower in men with exstrophy. It is interesting to note that no difference in sexual desire, sexual satisfaction, or overall satisfaction was indicated, leading the authors to conclude that men with bladder exstrophy seem to lead a sexual life that is as satisfactory as that of their peers. Overall, it seems from the reports of many investigators that most men with exstrophy are able to achieve normal erectile function and are sexually satisfied.

As men grow into adulthood, additional concerns are now becoming evident and require transition of care to adult urology

specialists. Men with bladder exstrophy will increasingly be seeking evaluation for prostatic hyperplasia and prostate cancer (Berkowitz et al, 2008). Silver and colleagues (1997a) reported on the ability to identify PSA in men with exstrophy. PSA was noted to be below the upper age-specific limit of norms, indicating that PSA changes could be muted in men with exstrophy. Routine digital rectal examination and PSA screening should become part of the standard follow-up for men with bladder exstrophy as with age-related screenings for normal men.

Female Concerns

The three main female concerns are the appearance of the external genitalia, adequacy of the vaginal opening, and uterine prolapse. Although initial correction of the female external genitalia defect is performed at birth, sometimes “touch-up” surgery needs to be performed at puberty. The appearance of the external genitalia is compromised owing to the recurrence of the pubic diastasis, which leads to widening of the inferior abdominal scar and separation of the pubic hair. In addition, separation of the clitoral halves may be noted. To repair this in adolescence, mons flaps are raised laterally and brought to the midline and sewn to the fascia and themselves easily. In extreme cases with an extremely scarred flat mons veneris, tissue expanders can be placed laterally and gradually inflated over 6 weeks. These flaps are moved medially and used to reconstruct the mons. The pseudocapsules are rolled together in the midline to give the mons a more elevated appearance. Mobilizing lateral mons veneris flaps brings the clitoral halves closer to the midline and makes them easier to reconstruct into a single entity. Topical estrogen cream is used three times daily for 2 weeks before any external genital surgery to soften scars, increase skin viability, and improve local vascularity. The vaginal orifice is more vertical and somewhat stenotic in exstrophy compared with normal females (Cervellione et al, 2010). Insertion of tampons and sexual intercourse can therefore be difficult. Rotating an inverted U-flap of perineal skin into the incised posterior vaginal wall will permit widening of the vaginal os (Stein et al, 1995). Uterine prolapse may be noted more frequently in women who have had vaginal wall cutback (Mathews et al, 2003a). After vaginal reconstruction, if the patient is not sexually active a vaginal dilator is used once daily until sexual activity occurs.

Uterine prolapse has been noted more frequently and at younger ages in girls with exstrophy-epispadias complex (Mathews et al, 2003a). Woodhouse (1999) reported prolapse in a number of patients, and it is a considerable problem to correct. Seven patients had total prolapse, one of whom had never had intercourse or a pregnancy. Woodhouse believes that prolapse may occur in up to half of patients after pregnancy. In a report from Mathews and coauthors (2003a), vaginal and uterine prolapse was noted commonly and even quite early in life (mean age 16 years). Uterine suspension provided only modest success for the prevention of recurrent prolapse. Stein and colleagues (1995), in a large exstrophy series from Germany, found that uterine fixation was required to correct prolapse in 13 patients with long-term follow-up of more than 25 years. The anterior displacement of the vaginal os and the marked posterior displacement of the puborectalis sling with its deficient anterior component were postulated as reasons for prolapse. Use of osteotomy has not been shown to reduce the incidence of uterine prolapse; however, the degree of pubic diastasis has been shown to be significant (Anusionwu et al, 2012). The degree of prolapse depends on the degree of pubic bone divergence and the diameter of the opening in the levator hiatus for the vagina and rectum (Miles-Thomas et al, 2006). We suspend the uterus to the sacrum with human AlloDerm or Pelvicol pubovaginal sling. The suspensory substance is sewn to the uterus from the cervix and dome of the uterus so that it can be snugly suspended to the ligaments on the front of the uterus. Regardless of the method of repair, the uterus must be anchored in such a way that it is fixated in the pelvis and less susceptible to prolapse.

Prophylactic suspension of the uterus in adolescent girls with exstrophy undergoing urinary reconstruction should be considered

to prevent prolapse (Stein et al, 1999). Woodhouse (1999) believed that although prophylactic surgery may be helpful, once prolapse occurs, anterior fixation is insufficient to correct uterine prolapse in the exstrophy patient. Woodhouse recommends fixing both sides of the uterus from the cervix to the top of the uterus bilaterally to the presacral ligaments.

Mathews and coauthors (2003a) reported on a large series of girls and women with the exstrophy complex. All girls older than 18 years indicated that they had normal sexual desire, and many were sexually active. Mean age for commencement of sexual activity was 19.9 years. Although a few patients complained of dyspareunia, most indicated normal orgasms. Some patients indicated that they restricted sexual activity because of the cosmetic appearance of their external genitalia. Mons plasty is therefore very important to obtain a cosmetically pleasing appearance either in infancy or in adolescence because hair-bearing skin and fat should be used to cover the midline defect. As mentioned earlier, we perform this procedure at the time of initial closure. It certainly can be done in adolescence with the use of rhomboid flaps, as popularized by Kramer and colleagues (1986).

FERTILITY

The Male Patient

Reconstruction of the male genitalia and preservation of fertility were not primary objectives in early surgical management of bladder exstrophy. Sporadic instances of pregnancy or the initiation of pregnancy by males with bladder exstrophy have been reported. In two large exstrophy series, male fertility was documented. Only 3 of 68 men in one study (Bennett, 1973) and 4 of 72 in another (Woodhouse et al, 1983) had successfully fathered children. Milking the urethra in an antegrade fashion from proximal to distal has provided pregnancy in some cases (Woodhouse, 1999). In a large series of 2500 patients with exstrophy and epispadias (Shapiro et al, 1985), there were 38 males who had fathered children.

Hanna and Williams (1972) compared semen analyses in men who had undergone primary closure and ureterosigmoidostomy. A normal sperm count was found in only 1 of 8 men after functional closure and in 4 of 8 men with diversion. The difference in observed fertility potential is probably attributable to iatrogenic injury to the verumontanum during functional closure or bladder neck reconstruction. Retrograde ejaculation may also account for low sperm counts after functional bladder closure. In a long-term study from our institution, Ben-Chaim and associates (1996) found that 10 of 16 men reported they ejaculated a few cubic centimeters of volume, 3 ejaculated only a few drops, and 3 had no ejaculation. Semen analysis was obtained in 4 patients: 3 had azoospermia and 1 had oligospermia. The average ejaculated volume of the patients who had sperm counts was 0.4 mL. In another large series by Stein and colleagues (1994) from Germany, the authors found that none of the patients who had reconstruction of the external genitalia could ejaculate normally, nor had they fathered children. Five patients who did not undergo reconstruction had normal ejaculation, and 2 had fathered children. The conclusion was that male patients with genital reconstruction and closure of the urethra demonstrated high risk of infertility. In a large study of successful primary closure from a large exstrophy center by Ebert and colleagues (2008), sperm parameters were poor in 18 of 21 patients and follicle-stimulating hormone was increased in 25% of patients (Ebert et al, 2009). Ebert and colleagues (2010) reported on 17 adult men with bladder exstrophy undergoing the Erlangen approach single-stage procedure. At a mean follow-up of 19 years, 15 had bladder preservation and 12 were voiding per urethra. 16 men had proven ejaculation and 3 had normal sperm counts, 7 had oligoasthenospermia, and 6 had azoospermia. The potential for normal sperm counts was greater in patients who underwent only a single bladder neck procedure.

Assisted reproductive techniques have been applied to the exstrophy population (D'Hauwers et al, 2008). Regardless of the

method of reconstruction of the external genitalia and bladder neck, newer techniques such as gamete intrafallopian transfer (GIFT) or intracytoplasmic sperm injection (ICSI) can be used to assist these patients in their goal of achieving pregnancy. Use of GIFT or ICSI in 21 men with exstrophy led to successful pregnancy with no instances of exstrophy in any of the offspring.

The Female Patient

Krisiloff and colleagues (1978) reported on 45 women with bladder exstrophy who successfully delivered 49 normal offspring. The main complication after pregnancy was cervical and uterine prolapse, which occurred frequently. Burbage and coworkers (1986) described 40 women ranging from 19 to 36 years of age who were treated in infancy for bladder exstrophy; 14 pregnancies in 11 of these women resulted in 9 normal deliveries, 3 spontaneous abortions, and 2 elective abortions. Uterine prolapse occurred in 7 of the 11 patients during pregnancy. All had undergone prior permanent urinary diversions. Spontaneous vaginal deliveries were performed in those women, and cesarean sections were performed in women with functional bladder closures to eliminate stress on the pelvic floor and to avoid traumatic injury to the urinary sphincter mechanism (Krisiloff et al, 1978). With modern reconstructive techniques, successful pregnancies have been reported in female patients who have undergone continent urinary diversion (Kennedy et al, 1993). Giron and colleagues (2011) reported on 14 women who had undergone successful reconstruction and had 22 pregnancies. Seventeen pregnancies resulted in healthy newborns, 1 premature delivery of an infant who did well, 4 spontaneous abortions caused by genital prolapse, and 1 postpartum demise. After delivery, 3 mothers had temporary urinary incontinence, 1 mother had a vesicocutaneous fistula, and 7 women (50%) had genital prolapse. In a larger report on 52 women with bladder exstrophy, Deans and colleagues (2012) reported on reproductive outcomes. Of those who attempted conception, 66% were successful; 19 patients conceived and there were 3 sets of twins—a total of 57 pregnancies. There were 34 of 57 live births (56%), 21 of 57 miscarriages (35%), 1 termination, and 4 stillbirths. There were 4 major complications related to delivery including 1 ureteral transection, 1 fistula formation, and 2 postpartum hemorrhages. Deans and colleagues (2012) stress that pregnancy in women with bladder exstrophy remains high risk for both the mother and the fetus and stress the need for referral to a tertiary care center for successful outcomes. In the majority of cases, planned cesarean section appears to be the safest mode for delivery.

QUALITY OF LIFE

Overall and health-related quality of life (QoL) have become increasingly important as reconstructive techniques have improved and survival has become universal. Most groups have limited their studies to those with CBE. The preliminary results of the QUALEX (Quality of Life of Bladder Exstrophy) study (Jochault-Ritz et al, 2010) suggest that after reconstruction patients had reduced QoL. Adolescents reported a superior QoL score as compared with adults and children. Another report from Wittmeyer and colleagues (2010) of 47 patients (9 women and 16 men) also showed that QoL scores were less than norms; however, these reductions were mainly based on health concepts including limitation of physical activity and general health perception. Dodson and colleagues (2010) reported that overall adolescent QoL was comparable to norms, but parents reported significantly impaired adolescent general health and family activity and increased parental emotional distress. Schaeffer and colleagues (2013) confirmed that adolescents with bladder exstrophy appear to have good QoL scores when compared with norms; although incontinent patients had a tendency to have lower QoL scores, the sample size evaluated was inadequate to demonstrate statistical significance.

LONG-TERM ADJUSTMENT ISSUES

Interest has increased in long-term adjustment issues in patients with bladder exstrophy. Children with exstrophy undergo multiple reconstructive surgeries and have potential problems with respect to urinary incontinence and sexual dysfunction. However, the ultimate outcome would be better measured by how these children adjust overall in society. The severe nature of the exstrophy disorder could predict that this birth defect could have substantial psychological implications. Parental reaction to the child's medical condition may change the way the parents interact with the child. Incontinence may have a negative impact on social function and self-esteem. Multiple hospitalizations may interfere with the ability to be like other children. Concerning the potential medical and psychological implications of this anomaly, children born with exstrophy may be at increased risk for difficulties.

Formerly, there was a limited amount of information in the literature concerning this condition and its treatment and whether or not it has a deleterious effect on children and their families. Montagnino and coworkers (1998) evaluated younger children who performed more poorly and had disturbed behavior, specifically in skills related to function in school. Children who achieved continence after the age of 5 years were more likely to have problems with acting-out behavior. There were no differences in adjustment based on male or female sex, bladder versus cloacal exstrophy, type of continence strategy, or gender reassignment versus no reassignment. The conclusions of this long-term study were that children with exstrophy do not have clinical psychopathology (Montagnino et al, 1998). There was acting-out behavior rather than depression or anxiety, suggesting that improved outcomes may be achieved through a focus on normal adaptation rather than potential psychological stress. In addition, earlier achievement of continence through reconstructive efforts is potentially of psychological benefit. This work was further supported by Catti and colleagues (2006), who found that QoL in adults was better in those who were continent with a good body image. Reiner (1999) studied 42 children with exstrophy and presented preliminary results suggesting that these patients tend to have more severe behavioral and developmental problems than children with other anomalies, significant body distortion, and self-esteem problems. Reiner has recommended early intervention with the exstrophy patient and family and continuation with long-term psychiatric support into adult life. In a study from Europe, Feitz and associates (1994) found a more positive picture when they evaluated 11 women and 11 men with exstrophy, of whom 9 women (82%) and 10 men (91%) did not manifest any clinical levels of psychological stress. The authors concluded that these adults had a positive attitude toward life. With the use of structured instruments and appropriate evaluation and interviews, Reiner and Gearhart (2006) indicated that all 20 patients evaluated met criteria for at least one anxiety disorder. Older patients experienced waning of anxiety associated with peer discovery of incontinence after successful surgical reconstruction, and all noted intensified sexual activity with age. Data from Reiner and colleagues (2008) from a large series of male patients revealed that 14% experienced suicidal ideation. As they became older, 31% experienced this phenomenon; a few attempted adolescent or early adulthood suicide, and 1 succeeded. These findings underline the importance of screening patients for psychopathology as they age.

In an important study by Lee and colleagues (2006), females were found to have more close friendships, fewer disadvantages in relation to healthy peers, and more partnerships than males. There were no gender differences in adjustment within educational and professional careers, which overall were very good. Ebert and colleagues (2005) reviewed by questionnaire a group of 100 exstrophy adolescents. Education and social integration were high. All patients were heterosexual and almost 50% were sexually active, but almost 60% expressed anxiety about sexual activity. The most important finding was that 94% of patients expressed an interest in psychological assistance, underlining the importance of early childhood intervention.

Being born with exstrophy per se does not result in childhood psychopathology. Children with exstrophy exhibit some tendency toward increased problems with acting out or lack of attainment of age-appropriate adaptive behavior (Montagnino et al, 1998; Reiner, 1999). Therefore, early counseling should be part of the standard management strategy for all children with the exstrophy-epispadias complex. In addition, patients and families should be encouraged to continue with psychological support as the child grows into adulthood.

KEY POINTS: BLADDER EXSTROPHY—PRIORITIES IN MANAGEMENT

- Size and quality of bladder template
- Extent of pubic diastasis and malleability of the pelvis
- Need for osteotomy
- Length and width of urethral plate
- Penile size
- Associated anomalies

EPISPADIAS

Epispadias varies from a mild glanular defect in a covered penis to the penopubic variety with complete incontinence in males or females. It is most commonly noted as a component of bladder and cloacal exstrophy.

Male Epispadias

Isolated male epispadias is a rare anomaly, with a reported incidence of 1 in 117,000 males. Most male epispadias patients (about 70%) have complete epispadias with associated incontinence (Gearhart and Jeffs, 1998). Epispadias consists of a defect in the dorsal wall of the urethra. The normal urethra is replaced by a broad, mucosal strip lining the dorsum of the penis extending toward the bladder, with potential incompetence of the sphincter mechanism. The displaced meatus is free of deformity, and occurrence of urinary incontinence is related to the location of the dorsally displaced urethral meatus (Gearhart and Jeffs, 1998). The displaced meatus may be found on the glans, on the penile shaft, or in the penopubic region. All types of epispadias are associated with varying degrees of dorsal chordee (Fig. 139-26). In penopubic or subsymphyseal epispadias, the entire penile urethra is opened and the bladder outlet may be large enough to admit the examining finger, indicating obvious gross incontinence (see Fig. 139-1D). To a lesser extent than in those with CBE, patients with epispadias have



Figure 139-26. Complete male epispadias.

a characteristic widening of the symphysis pubis caused by outward rotation of the innominate bones. This separation of the pubis causes divergent penopubic attachments that contribute to the short, pendular penis with dorsal chordee. Therefore, the penile deformity is virtually identical to that observed in bladder exstrophy. The reported male-to-female ratio of epispadias varies between 3:1 (Dees, 1949) and 5:1 (Kramer and Kelalis, 1982a).

Kramer and Kelalis (1982a) reviewed their experience with 82 male patients with epispadias. Penopubic epispadias occurred in 49 patients, penile epispadias in 21, and glanular epispadias in 12. Urinary incontinence was observed in 46 of 49 patients with penopubic epispadias, in 15 of 21 patients with penile epispadias, and in no patient with glanular epispadias. The goals of the treatment of complete male epispadias include creation of normal urinary control and establishment of a straight, cosmetically acceptable penis of adequate length that is functional for sexual intercourse.

Associated Anomalies

Anomalies associated with complete epispadias are usually confined to deformities of the external genitalia, diastasis of the pubic symphysis, and deficiency of the urinary continence mechanism. The only renal anomaly observed in 11 cases of epispadias was agenesis of the left kidney (Campbell, 1952). In a review by Arap and associates (1988), 1 case of renal agenesis and 1 ectopic kidney occurred among 38 patients.

The ureterovesical junction is inherently deficient in complete epispadias, and the incidence of reflux has been reported in a number of series to be between 30% and 40% (Kramer and Kelalis, 1982a; Arap et al, 1988). In a review by Ben-Chaim and colleagues (1995b) of a series of 15 patients with complete male epispadias treated at our institution, a lower rate of vesicoureteral reflux was noted compared with male patients with CBE (100% versus 82%, respectively); the rate of inguinal hernias (33%) was also significantly lower. A possible explanation for the lower incidence of reflux in complete male epispadias is that the pouch of Douglas is not as enlarged and deep. Therefore, the distal ureter enters the bladder in a more oblique fashion than in classic exstrophy (Gearhart and Jeffs, 1998).

Surgical Management

The objectives of repair of penopubic epispadias include achievement of urinary continence with preservation of the upper urinary tracts and the reconstruction of cosmetically acceptable genitalia. The surgical management of incontinence in penopubic epispadias is virtually identical to that in closed bladder exstrophy.

Young (1922) reported the first cure of incontinence in a male patient with complete epispadias. Since this initial report, continence after surgical reconstruction has progressively improved (Burkholder and Williams, 1965; Kramer and Kelalis, 1982a; Arap et al, 1988; Peters et al, 1988; Mollard et al, 1998). In patients with complete epispadias and good bladder capacity, epispadias and bladder neck reconstruction can be performed in a single-stage operation. Urethroplasty formerly was performed after bladder neck reconstruction (Kramer and Kelalis, 1982a; Arap et al, 1988). However, improvements in bladder capacity in the small bladder associated with exstrophy (Gearhart and Jeffs, 1989a) and that associated with epispadias (Peters et al, 1988) have led us to perform urethroplasty and penile elongation before bladder neck reconstruction. A small, incontinent bladder with reflux is hardly an ideal situation for bladder neck reconstruction and ureteral reimplantation. Before bladder neck reconstruction there was an average increase in bladder capacity of 95 mL within 18 months after epispadias repair in the patients with an initial small bladder capacity and a continence rate of 87% after the continence procedure (Peters et al, 1988). In a series by Ben-Chaim and colleagues (1995b) composed exclusively of patients with complete male epispadias, bladder capacity increased by an average of 42 mL within 18 months after urethroplasty. Nine (82%) of 11 patients were dry day and night after an average of 9 months.

In epispadias, as in bladder exstrophy, bladder capacity is the predominant indicator of eventual continence (Ritchey et al, 1988). Arap and coworkers (1988) reported higher continence rates in patients who had an adequate bladder capacity before bladder neck reconstruction than in those with inadequate capacity (71% vs. 20%, respectively). In addition, in Arap's group of patients with complete epispadias, most obtained continence within 2 years, similar to results in patients with CBE.

A firm intrasymphyseal band typically bridges the divergent symphysis, and an osteotomy is not usually performed. The Young-Dees-Leadbetter bladder neck plasty, Marshall-Marchetti-Krantz suspension, and ureteral reimplantation are performed when the bladder capacity reaches approximately 100 mL, which usually occurs between 4 and 5 years of age when the child is ready to be dry. Genital reconstruction procedures in epispadias and exstrophy are similar. The following reconstructive maneuvers must take place: release of dorsal chordae and division of the suspensory ligaments; dissection of the corpora from their attachments to the inferior pubic ramus; lengthening of the urethral groove; and lengthening of the corpora, if needed, by incision and anastomosis or grafting or by medial rotation of the ventral corpora in a more downward direction.

Urethral reconstruction in complete epispadias has been performed in many ways. A transverse island flap was used by Monfort and colleagues (1987). The urethra, once reconstructed, can be positioned between and below the corpora (Cantwell, 1895; Ransley et al, 1989; Gearhart et al, 1992, 1995c). Mitchell and Bāgli (1996) reported their experience with a complete penile disassembly technique, and a multicenter experience was reported in a total of 17 patients from four institutions (Zaontz et al, 1998). Chordee was reliably corrected, erectile function was preserved, the urethra was eventually situated in a cosmetic fashion, and satisfactory cosmesis was achieved. Caione and Capozza (2001) reported on their experience with the use of penile disassembly and reapproximation of the perineal muscle complex for the management of boys with epispadias, indicating the ability to achieve continence without the need for additional bladder neck reconstruction. A recent small series by Kibar and colleagues (2009a) of patients with complete epispadias showed that complications with use of the disassembly repair were in the acceptable range. Unlike the use of this in the exstrophy group, there was no ischemia of the glans or corpora. However, most patients required additional surgery because hypospadias was created in a number of patients. Repair of this hypospadias can be challenging and can have high complication rates (Berrettini et al, 2011). Cervellione and colleagues (2010) did report on 4 patients who underwent penile disassembly or radical soft-tissue mobilization (Kelly procedure) who had significant corporeal loss after surgery. Ransley and Surer and associates reported excellent results using the modified Cantwell-Ransley procedure, saving cavernocavernostomy for patients with very severe chordee and especially those in the older age group (Kajbafzadeh et al, 1995; Surer et al, 2000). For detailed description of the surgical reconstruction, see the previous discussion in the section on bladder exstrophy.

It was formerly thought that the effect of urethral lengthening and prostatic enlargement might be significant in complete epispadias by increasing outlet resistance if continence was not perfect as the child became older. Earlier in a series by Arap and associates (1988), the establishment of continence had no relation to puberty and usually occurred within 2 years, usually preceding puberty by several years. In the series reported by Ben-Chaim and coworkers (1995b), as stated previously, all patients obtained daytime continence at a mean of 9 months after bladder neck reconstruction, and 9 (82%) of 11 patients attained total day and night continence. All patients voided spontaneously. After a mean follow-up of 7 years, all patients maintained normal upper tracts and kidney function. All of them had cosmetically pleasing genitalia, as judged by parents, patients, and physicians, and experienced normal erections. A 36-year-old patient was married and had fathered three children. Many of the patients were younger than 16 years and had not yet become sexually active. Results of urethroplasty in epispadias have been reported in a number of publications (Mesrobian et al, 1986;

Ransley et al, 1989; Kajbafzadeh et al, 1995; Zaontz et al, 1998). In a modern series of modified Cantwell-Ransley repairs reported by Surer and colleagues (2000), the incidence of postoperative fistula in the 3-month period after surgery was 19%, and the incidence of urethral stricture formation was less than 10%. Catheterization and cystoscopy could easily negotiate the neourethral channel in all patients who underwent a modified Cantwell-Ransley epispadias repair. In another modern series reported by Mollard and coworkers (1998), the continence rate was 84% and the fistula rate was less than 10%. In Mollard's series with long-term follow-up, patients had normal erections; the vast majority had regular sexual intercourse, and most had normal ejaculation or had fathered children. Most of Surer's patients were quite young, and assessment of genital reconstruction must be deferred until these patients are sexually mature and active (Surer et al, 2000). Hafez and Helmy (2011) reported on three patients with isolated penopubic epispadias who underwent postpubertal reconstruction using penile disassembly, indicating good cosmesis with a meatus at the tip.

Although many methods of epispadias repair exist, meticulous follow-up of the urethra, appropriate selection of patients, and surgical experience remain the milestones of success. Lastly, Ransley and colleagues (Kajbafzadeh et al, 1995) obtained very good results using a modified Cantwell-Ransley repair in a large number of patients with epispadias. The fistula rate was 4%, and the urethral stricture rate was 5.3%. Baird and colleagues (2005b) reported on 129 boys who underwent a modified Cantwell-Ransley repair. Of this group, 32 had penopubic epispadias. Twenty-four procedures were primary repairs and eight were secondary repairs. Urethrocavitaneous fistula occurred in 13% of primary and 25% of secondary repairs. A urethral stricture occurred in one patient.

Achievement of urinary continence in patients with isolated epispadias is summarized in Table 139-4. A majority of these patients underwent reconstruction by means of a modified Young-Dees-Leadbetter bladder neck plasty. Urinary continence was obtained in 82% of male patients (Ben-Chaim et al, 1995b). As in the exstrophy population, repair of the epispadiac deformity results in an increase of outlet resistance and possible increase in bladder capacity before bladder neck reconstruction. Although both complete epispadias and bladder exstrophy patients achieve improvement in bladder capacity after epispadias repair, the mean increase in overall capacity is higher in those with complete epispadias. This increase in bladder capacity may account for increased continence in this group compared with the CBE population. Clinically, these bladders are more supple, easier to mobilize, and more amenable to bladder neck reconstruction. Ben-Chaim and colleagues (1995b) reported that the mean time to initial continence after bladder neck reconstruction was 90 days in patients with complete male epispadias compared with 110 days in those with bladder exstrophy. These results suggest that for patients with complete epispadias, bladder capacity before reconstruction and the rate of achieving continence afterward are better than in exstrophy. The reason might be that the bladder is not exposed in utero and does not have any scarring from prior closure; therefore its potential for expansion is higher.

In a different approach to the treatment of incontinence associated with epispadias reported by Duffy and Ransley (1998), 12 boys aged 3 to 7 years underwent endoscopic submucosal injection of plastic microspheres. All patients had undergone a modified Cantwell-Ransley epispadias repair before injection. The procedure was performed 24 times, with a total volume of 83 mL of material injected into 59 sites in the posterior urethra. Mean follow-up was 10.8 months. Three patients (25%) were rendered completely dry, the degree of incontinence was improved in 6, and there was no change in 3. The authors offered this approach as an alternative to bladder neck reconstruction in patients with primary epispadias. Ben-Chaim and coworkers (1995a) reported that submucosal injection of collagen in the bladder neck area can have a role in improving stress incontinence when the patient with complete epispadias has incomplete urinary control or as an adjunct after bladder neck reconstruction. In a recent study by Kibar and colleagues (2009b) of complete epispadias, 1 patient out of 12 was continent after bladder neck injection.

TABLE 139-4 Urinary Continence after Bladder Neck Reconstruction (BNR) in Patients with Complete Epispadias

	BEN-CHAIM ET AL (1995b)	GEARHART ET AL (1993a)	KRAMER AND KELALIS (1982a)	ARAP ET AL (1988)	BURKHOLDER AND WILLIAMS (1965)	BRAGA ET AL (2008)
No. of patients	15	11	53	38	27	17
MALES						
Treated with BNR	11		32*	21	17	17
Surgically corrected incontinence	9		22	15	8	13
Percent with surgically corrected incontinence	82%		69%	71%	47%	76%
FEMALES						
Treated with BNR	0	9	12	9	10	
Surgically corrected incontinence	0	8	10	7	7	
Percent with surgically corrected incontinence	0%	87%	83%	77%	70%	

*All complete female epispadias cases.

Kramer and associates (1986) reported the success of genital reconstruction in epispadias, with good long-term follow-up ending with a straight penis angled downward in almost 70% of patients, with normal erectile function. Of this group, 80% had satisfactory sexual intercourse, and of 29 married patients, 19 had fathered children. These results were mirrored in the long-term follow-up study of [Mollard and associates \(1998\)](#).

A carefully constructed and well-planned approach to the management of urinary incontinence in genital deformities associated with complete epispadias should provide a satisfactory cosmetic appearance, normal genital function, and preservation of fertility potential in most patients.

Female Epispadias

Female epispadias is a rare congenital anomaly; it occurs in 1 of every 484,000 female patients ([Gearhart and Jeffs, 1998](#)) ([Fig. 139-27](#)). We use the classification of [Davis \(1928\)](#), which describes three degrees of epispadias in female patients ([Fig. 139-28A to D](#)). In the least severe degree of epispadias, the urethral orifice simply appears patulous. In intermediate epispadias, the urethra is dorsally split along most of the urethra. In the most severe degree of epispadias, the urethral cleft involves the entire length of the urethra and sphincteric mechanism and the patient is rendered incontinent ([Fig. 139-28](#)). The genital defect is characterized by a bifid clitoris. The mons is depressed in shape and coated by a smooth, glabrous area of skin. Beneath this area, there may be a moderate amount of subcutaneous tissue and fat, or the skin may be closely applied to the anterior and inferior surface of the symphysis pubis. The labia minora are usually poorly developed and terminate anteriorly at the corresponding half of the bifid clitoris, where there may be a rudiment of a preputial fold. These external appearances are most characteristic: on minimal separation of the labia, one sees the urethra, which may vary considerably, as mentioned previously. The symphysis pubis is usually closed but may be represented by a narrow fibrous band. The vagina and internal genitalia are usually normal. Because the external appearance changes may be minimal, some children are identified only because of persistent incontinence ([Yeni et al, 2004](#); [Shetty et al, 2011](#)).



Figure 139-27. Complete female epispadias.

Associated Anomalies

The ureterovesical junction is inherently deficient in patients with epispadias, and the ureters are often laterally placed in the bladder with a straight course so that reflux occurs. The incidence of reflux is reported to be 30% to 75% ([Kramer and Kelalis, 1982b](#); [Gearhart et al, 1993a](#)). Because there is no outlet resistance, the bladder is small and the wall is thin. After initial reconstruction, the urethral resistance that is created allows the bladder to grow and develop to an acceptable capacity for bladder neck reconstruction.

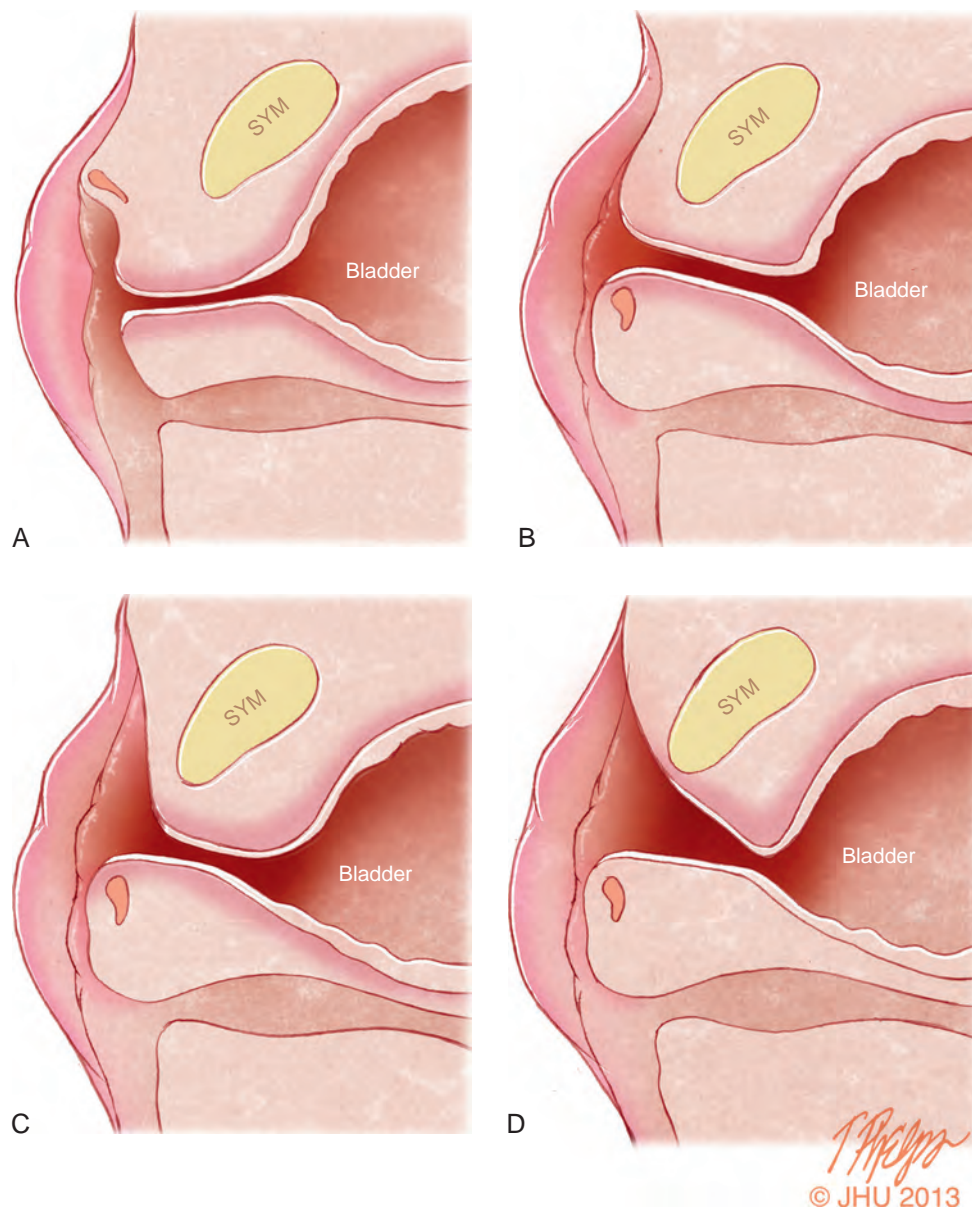


Figure 139-28. A, Normal female anatomy. B, Vesicular epispadias—urethra mainly normal but relation to clitoris altered. C, Subsphyseal epispadias—defect in anterior wall of urethra for about one half its length. D, Retrosymphyseal epispadias—defect in anterior wall of entire urethra. Sphincter is usually involved. SYM, symphysis. (Used with permission of Brady Urological Institute.)

Surgical Objectives

Objectives for repair of female epispadias parallel those devised for male patients: (1) achievement of urinary continence, (2) preservation of the upper urinary tracts, and (3) reconstruction of functional and cosmetically acceptable external genitalia.

Operative Techniques

With the patient in the lithotomy position, the defect of the female epispadias with incontinence is apparent (Fig. 139-29A). The two halves of the clitoris are widely separated, and the roof of the urethra is cleft between the 9 o'clock and 3 o'clock positions. The smooth mucosa of the urethra tends to blend cephalad with the thin, hairless skin over the mons. The urethral incision is begun at the cephalad extent of the vertical incision at the base of the mons and is brought inferiorly through the full thickness of the urethral wall at the 9 o'clock and 3 o'clock positions

(Fig. 139-29B). Sutures can be placed in the urethra to permit downward traction on the urethra so that the roof of the urethra is excised to a level near the bladder neck (Fig. 139-29C). Often, one finds the dissection proceeding under the symphysis. An inverting closure of the urethra is then performed over a 10-Fr Foley catheter. Suturing is begun near the bladder neck and progresses distally until closure of the neourethra is accomplished (Fig. 139-29D). Attention is then given to denuding the medial half of the bifid clitoris and the labia minora so that proper genital coaptation can be obtained.

After this is done, fat from the mons and subcutaneous tissue can be used to cover the suture line and obliterate the space in front of the pubic symphysis (Fig. 139-29E and F). The two halves of the clitoris and labia minora are brought together using interrupted sutures of 6-0 polyglycolic acid. The corpora may be partially detached from the anterior ramus of the pubis to aid in the urethral closure. Also, bringing these tissues together may contribute by adding resistance to the urethra. Mons closure is further aided by

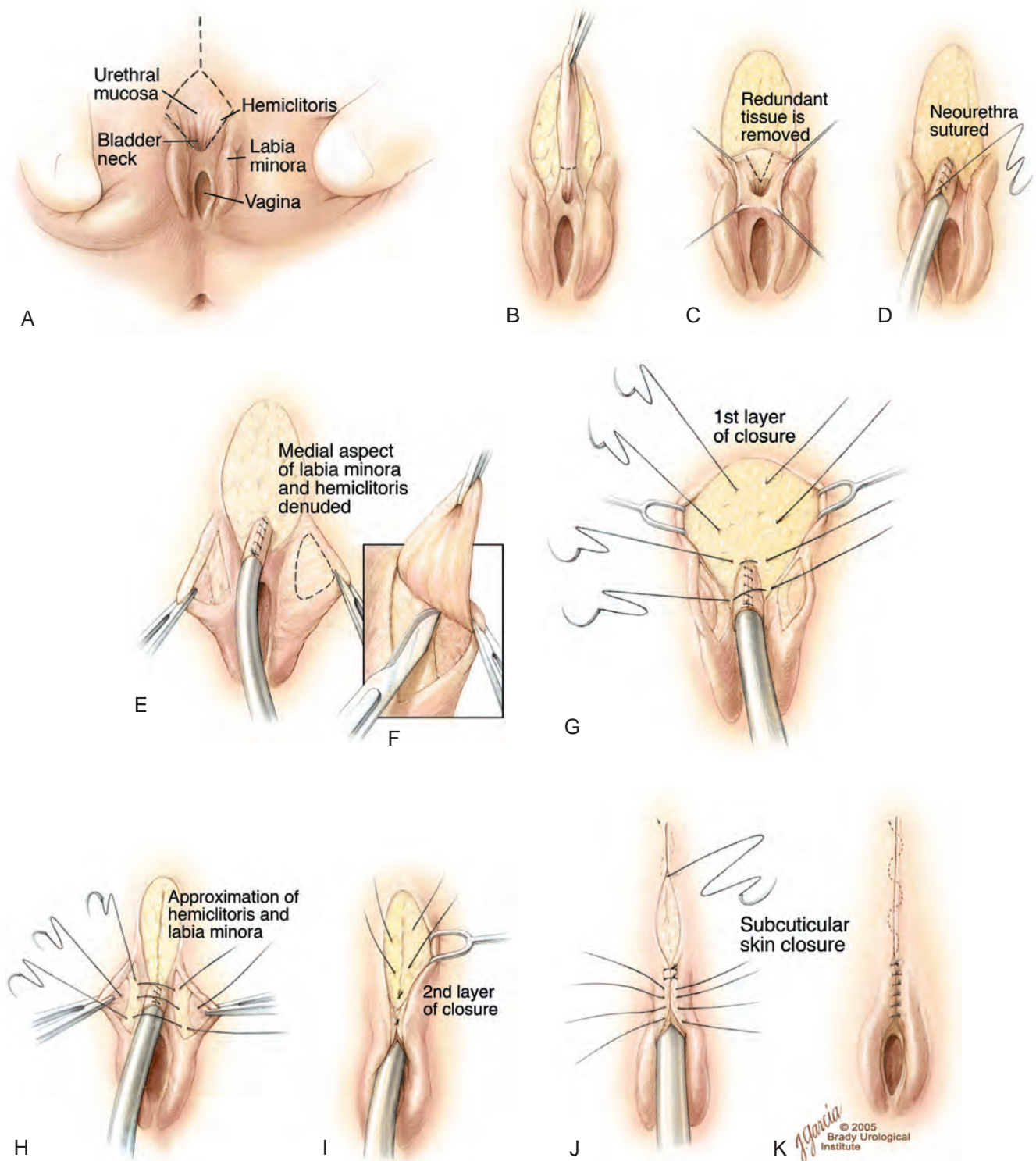


Figure 139-29. A, Typical appearance of female epispadias with initial incisions outlined. B, Excision of the glabrous skin of the mons. C, Tapering of the urethra with a dorsal resection of a wedge of tissue. D, Reconstruction of the urethra over a catheter with running suture. E and F, Medial aspect of the labia minora and clitoris. G, Initial layer of mons closure. H, Approximation of the labia minora over the urethral reconstruction. I, Second layer of mons closure. J, Creation of clitoral hood. K, Completion of mons closure. (© Brady Urological Institute.)

mobilizing subcutaneous tissue laterally and bringing it medially to fill any prior depression that remains (Fig. 139-29G). The subcutaneous layer is closed with 4-0 polyglactin suture in an interrupted fashion (Fig. 139-29H). The skin is closed with interrupted sutures of 6-0 polypropylene (Fig. 139-29I to K).

A 10-Fr catheter is left indwelling for 5 to 7 days. Should the patient undergo simultaneous bladder neck reconstruction, a Foley catheter is not left in the urethra and the patient is placed in the supine position for the abdominal part of the procedure.

Achievement of a satisfactory cosmetic appearance of the external genitalia and urinary continence in the female child with epispadias represents a surgical challenge. Many operations have been reported to control continence in the epispadias group, but the results are disappointing. These procedures include transvaginal plication of the urethra and bladder neck, muscle transplantations, urethra twisting, cauterization of the urethra, bladder flap, and Marshall-Marchetti vesicourethral suspension (Stiles, 1911; Davis, 1928; Marshall et al, 1949; Gross and Kresson, 1952). These procedures may increase urethral resistance, but they do not correct incontinence or the malformed anatomy of the urethra, bladder neck, and genitalia.

The challenge of the small bladder in the female epispadias patient is comparable to a situation seen in patients with a closed exstrophy. The small, incontinent bladder, with or without reflux, is hardly an ideal setting for a successful bladder neck reconstruction and ureteral reimplantation. A third of all incontinent epispadias patients have a bladder capacity of less than 60 mL, in our experience and that of Kramer and Kelalis (1982b). Bladder augmentation, injection of polytetrafluoroethylene (Teflon) in the bladder neck area, and simultaneous bladder neck reconstruction and bladder neck augmentation have been offered as a solution to this challenge. However, primary closure of the epispadiac urethra in children with closed exstrophy was found to increase bladder capacity without causing hydronephrosis, and this approach has been applied to male and female patients with epispadias (Peters et al, 1988; Gearhart and Jeffs, 1989a; Ben-Chaim et al, 1995b). Although we typically perform urethral and genital reconstruction at 6 months to 1 year of age, we advocate delaying bladder neck reconstruction until the child is 4 to 5 years old. Not only does this delay allow the bladder to increase in capacity, it also allows the child to accept essential instructions for toilet training, which is critical to achieving satisfactory continence in the postoperative state. Data from de Jong and colleagues (2000) combined a standard exterior genitoplasty plus urethroplasty with a percutaneous bladder neck suspension. The authors felt the suspension moved the bladder neck into an intra-abdominal position. In this small series, one patient was dry and voiding, two required bladder neck bulking agents, and one was on CIC. In another small series from India, Bhat and colleagues (2008) performed a urethroplasty and the perineal musculature was double-breasted over the urethral closure from the bladder neck distally. Bhat and coauthors reported impressive results with two totally continent, one partially continent, and one continent patient after bladder neck reconstruction.

Surgical Results

The continence rate of 87.5% in our female patients is comparable to that of Hanna and Williams (1972), who found a 67% continence rate in female patients with good bladder capacity, and that of Kramer and Kelalis (1982b), who reported an 83% continence rate in patients with adequate bladder capacity. All of our patients seen for primary treatment have achieved a capacity in excess of 80 mL (see Table 139-4).

Hendren (1981) and Kramer and Kelalis (1982b) showed that genitourethral reconstruction can be accomplished with satisfactory results. At our institution, patients who underwent prior urethral and genital reconstruction had a mean bladder capacity at bladder neck reconstruction of 121 mL, making the bladder suitable for the reconstruction and eventual continence without the use of augmentation cystoplasty or need for intermittent catheterization.

The time interval to achieve continence in our patients was a mean of 18 months for those who underwent genitourethral and bladder neck reconstruction in one procedure and 23 months for those who underwent preliminary urethroplasty and genital reconstruction after bladder neck reconstruction. In a series by Klauber and Williams (1974), the mean interval to acceptable continence was 2.25 years. Also, in a series by Kramer and Kelalis (1982b), some patients became continent within a short period, whereas complete continence was delayed for several years in others. The time delay for achieving continence may represent increased pelvic muscular development, as suggested by Kramer and Kelalis (1982b). In regard to the interval to continence, no advantage appears to be gained by preliminary urethroplasty. However, we believe that the advantage gained by increased bladder capacity at the time of bladder neck reconstruction outweighs any advantage gained by a combined approach. Suson and colleagues (2013) compared 22 girls with complete female epispadias to 23 girls with CBE. Although girls with female epispadias had reconstruction at a later age than those with CBE, bladder growth rate did not differ between the two groups. Neither group had any difference in number of surgical procedures, development of continence with or without the need for bladder neck reconstruction, or eventual need for continent urinary diversion.

CLOACAL EXSTROPHY

Cloacal exstrophy includes a spectrum of abnormalities but is primarily an anterior abdominal wall defect. A reported incidence of 1:200,000 to 1:400,000 makes this one of the rarer urologic abnormalities (Hurwitz et al, 1987). Although prior reports have suggested a male-to-female ratio of 2:1 (Gearhart and Jeffs, 1998), a large study by Boyadjiev and colleagues (2004a) indicated that the sex ratio may be 1:1. Most cases are sporadic, and isolated incidences of unbalanced translocations have been reported to be potentially causative (Thauvin-Robinet et al, 2004); however, one report noted recurrence in siblings, perhaps indicating a more multifactorial etiology. Recent reports have indicated a greater incidence of cloacal exstrophy associated with maternal exposure to cigarette smoke (Gambhir et al, 2008). It is interesting to note that mothers of infants with cloacal exstrophy were more compliant with preconceptional folate use. Associated defects of the neurospinal axis, intestinal tract, and urogenital and skeletal systems are frequently noted. When neurospinal defects and omphalocele coexist with cloacal exstrophy, the term *OEIS complex* (omphalocele, exstrophy, imperforate anus, spinal defects) has been used (Keppler-Noreuil, 2001). Advances in the care of critically ill children has resulted in most infants with cloacal exstrophy surviving into adulthood. The focus of management has therefore shifted to improving QoL (Mathews et al, 1998).

Anatomic Considerations

The classic constellation of anomalies that are noted in children with cloacal exstrophy includes exstrophy of the bladder, complete phallic separation, wide pubic diastasis, exstrophy of the terminal ileum between the two halves of the bladder, a rudimentary hindgut, imperforate anus, and the presence of an omphalocele. Many children have associated spinal defects, and various lower extremity malformations may be noted (Loder and Dayioglu, 1990; Jain and Weaver, 2004). The urogenital anomalies in cloacal exstrophy are similar to those seen with CBE (see earlier), although they are typically of greater severity.

Neurospinal Abnormalities

Abnormalities of the spinal cord or vertebral column or both have been noted in 85% to 100% of children with cloacal exstrophy (Appignani et al, 1994; McLaughlin et al, 1995). Although most patients have lumbar myelodysplasia (80%), thoracic defects may be noted in 10%, with the remaining having sacral defects. In a large

series of 34 patients from a single center with cloacal exstrophy and associated spinal defects, Mathews and coworkers (1998) noted lipomeningocele in 17, myelomeningocele in 8, and spina bifida and isolated cord tethering in 7 and 2 patients, respectively. The nearly universal incidence of spinal abnormalities has led some authors to suggest MRI for all patients with a diagnosis of cloacal exstrophy (Cohen, 1991). Spinal ultrasound evaluation, which is easily performed, has been noted to be comparable to MRI for the diagnosis of spinal anomalies in infants with cloacal exstrophy (Dick et al, 2001). Karrer and colleagues (1988) noted that only 1 in 5 children with spinal dysraphism noted on ultrasonography had a sacral abnormality visible on the skin surface.

The embryologic basis for the neurospinal defects associated with cloacal exstrophy has been postulated to be secondary to disruption of the tissue of the dorsal mesenchyme rather than failure of neural tube closure (McLaughlin et al, 1995). Alternatively, it has been suggested that the defects that lead to the formation of cloacal exstrophy may lead to the developing spinal cord and vertebrae being pulled apart (Cohen, 1991). Functional deficits can range from patients who have almost normal sensation of the pelvis and lower extremity to patients who are wheelchair bound. The presence of a clinically significant neurologic anomaly was found to negatively affect the development of continence (Husmann et al, 1999). Only 1 of 13 neurologically impaired patients in this series developed voided continence.

The neuroanatomic dissections performed by Schlegel and Gearhart (1989) further indicate that the neuroanatomic landmarks in the infant with cloacal exstrophy are different from those in the normal newborn, with the autonomic bladder innervation being derived from a more medial location (Fig. 139-30). This potentially

puts the nerve supply in jeopardy during initial bladder dissection and reconstruction and can potentially leave the bladder neuropathic after reconstruction (Husmann et al, 1999). Innervation to the duplicated corporeal bodies arises from the sacral plexus, travels in the midline, perforates the pelvic floor, and courses medially to the hemibladders (Schlegel and Gearhart, 1989). Innervation abnormalities were also noted at a histologic level in the studies by Rosch and colleagues (1997). When compared with those in patients with bladder exstrophy, the neural elements identified on immunohistochemical evaluation were found to show significant structural abnormalities.

Skeletal System Abnormalities

Anomalies of the skeletal system are universally noted in children with cloacal exstrophy. The pubic diastasis noted in the exstrophy-epispiadias complex are seen at their most extreme with cloacal exstrophy. Sponseller and associates (1995), studying patients with the exstrophy complex, noted that the posterior segment of the pelvis in children with cloacal exstrophy was angled farther posteriorly and there was a greater likelihood of asymmetry between the two sides. Similarly, the anterior segment of the pelvis had more severe degrees of external rotation. The actual length of the bone segments, however, was similar between those with cloacal and classic exstrophy. The interpubic distance (diastasis) in children with cloacal exstrophy was noted to be almost twice that in children with CBE. Malformation of the sacroiliac joints and side-to-side asymmetry were also noted. Most children with cloacal exstrophy therefore require osteotomy for successful reconstruction. Stec and colleagues (2003) noted that microscopically the bones in

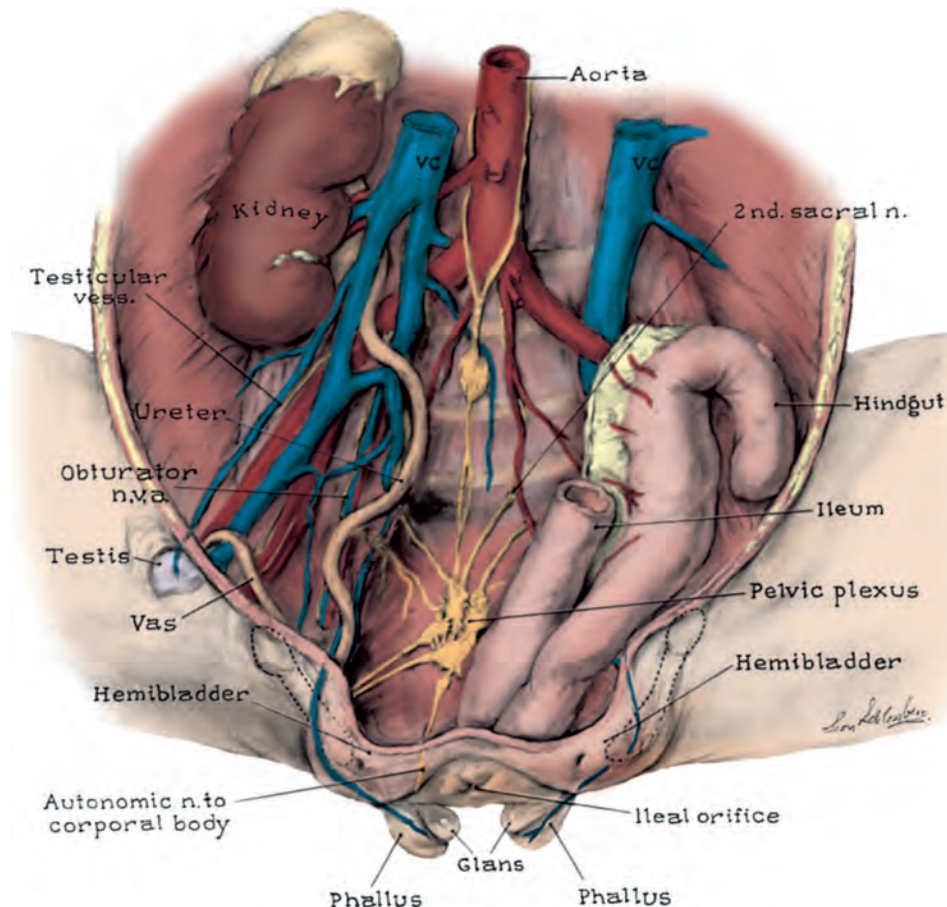


Figure 139-30. Internal view of a patient with cloacal exstrophy. Pudendal vessels, nerves, and other vessels and autonomic innervations of the corporeal bodies are demonstrated. Internal structures of the pelvis along with duplication of the vena cava in this dissected specimen are also shown.

children with cloacal exstrophy were similar to those in normal controls and were developing at a similar rate, indicating that the potential for growth was also similar.

Vertebral anomalies not associated with myelodysplasia were noted in 8 of 37 children with cloacal exstrophy (Mathews et al, 1998). Loder and Dayioglu (1990) noted vertebral anomalies in 3 of 5 children with cloacal exstrophy. Absence or shortening of limbs was also noted, as were clubfoot malformations. Skeletal and limb anomalies were also reported by Diamond (1990) in 12% to 65% of patients. The vast majority were clubfoot deformities, although absence of feet, severe tibial or fibular deformities, and congenital hip dislocations were commonly noted in this group of patients. A similar high incidence of foot abnormalities and greater than normal abduction of the hips was noted in a study by Greene and coworkers (1991).

Intestinal Tract Abnormalities

Gastrointestinal tract anomalies occur in virtually all patients with cloacal exstrophy. In Diamond's series (1990), the incidence of omphalocele was 88%, and most other series report an incidence of 95% or greater. In the series reported by Mathews and colleagues (1998), 100% of patients had an omphalocele. Omphaloceles do vary in size and usually contain small bowel or liver or both. Immediate closure of the omphalocele defect in the newborn period is advised to prevent subsequent rupture.

Hurwitz and colleagues (1987), in a large review of cloacal exstrophy patients, reported a 46% incidence of associated gastrointestinal tract anomalies, with malrotation, duplication anomalies, and anatomically short bowel occurring with equal frequency. A hindgut remnant of varying size is also noted in most patients. Hurwitz noted a 23% incidence of short gut syndrome, which is compatible with the 25% incidence reported by Diamond (Hurwitz et al, 1987; Diamond, 1990). It now seems well accepted that short gut syndrome may occur in the presence of normal small bowel length, suggesting absorptive dysfunction and emphasizing the absolute need to preserve as much large bowel as possible. If not used for incorporation into the fecal stream, the hindgut remnant may be preserved for use in urogenital tract reconstruction (Mathews et al, 1998). Modern techniques have reduced the incidence of short gut syndrome in the majority of patients (Sawaya et al, 2010).

Genitourinary Abnormalities

Müllerian anomalies have been frequently noted in conjunction with cloacal exstrophy. The most commonly reported müllerian anomaly was uterine duplication, seen in 95% of patients (Diamond, 1990). The vast majority of these patients had partial uterine duplication, predominantly a bicornate uterus. Vaginal duplication occurred in 65% of patients, and vaginal agenesis was seen in 25% to 50% of patients. In a report by Hurwitz and colleagues (1987), cases of complete duplication of the uterus and fallopian tubes associated with both vaginal duplication and vaginal agenesis were noted. Gearhart and Jeffs (1991b) recommended preservation of all müllerian duplication anomalies for possible use in reconstructing the lower urinary tract.

Upper urinary tract anomalies occurred in 41% to 60% of patients in Diamond's review (1990). The most common anomalies were pelvic kidney and renal agenesis, both occurring in up to one third of patients. Hydronephrosis and hydroureter were common, occurring in one third of patients. Multicystic dysplastic kidneys and fusion anomalies were seen less frequently. Ectopic ureters draining to the vasa in the male and into the uterus, vagina, or fallopian tubes in the female were also reported (Diamond, 1990). A similar incidence of upper tract defects was noted by Mathews and colleagues (1998). Ureteral duplication, congenital stricture, and megaureter were also reported.

Genital anomalies in the male have typically included complete separation of the two phallic halves and accompanying separation of the scrotal halves. Asymmetry of these structures can also be seen and can provide additional challenges to successful reconstruction.

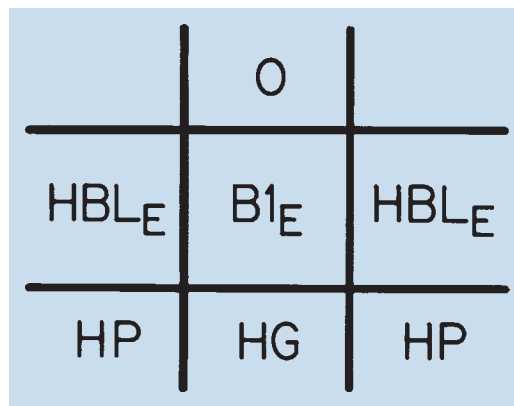


Figure 139-31. Coding grid used to describe cloacal exstrophy and its variants. B1_E everted bowel; O, omphalocele; HBL_E, hemibladder; HG, hindgut; HP, hemiphallus. (From Manzoni GA, Ransley PG, Hurwitz RS. Cloacal exstrophy and cloacal exstrophy variants: a proposed system of classification. *J Urol* 1987;138:1065-8.)

Testes may be noted in the scrotum but are frequently noted to be undescended, and associated inguinal hernias are a common finding. Girls typically have widely divergent clitoral halves.

The lower urinary tract is typically composed of two exstrophied hemiblasters flanking the exstrophied intestinal segment. Each bladder half usually drains the ipsilateral ureter and is closely related to the ipsilateral phallic segment. Variations of anatomy, however, are frequently seen, and every patient has unique anatomic features.

Additional System Anomalies

Life-threatening cardiovascular and pulmonary anomalies are rarely seen in cloacal exstrophy. Reported cases included two patients with cyanotic heart disease and one with aortic duplication. A bilobed lung was reported in two patients and an atretic right upper lung in one. Also, Schlegel and Gearhart (1989) reported caval duplication in their anatomic dissection of a patient with cloacal exstrophy.

Because of the complexity and the multisystem nature of cloacal exstrophy, Hurwitz and coauthors (1987) have devised a grid for the clarification of anatomy in each patient and to permit planning for reconstruction (Fig. 139-31). This permits the standard form of cloacal exstrophy to be separated from variants and allows the soft-tissue components of the defect to be described systematically.

Cloacal Exstrophy Variants

Cloacal exstrophy usually includes an open and everted intestinal segment situated between two hemiblasters, an omphalocele, and a blind-ending tailgut with an imperforate anus. The pubic symphysis and the rectus muscles are widely separated. The phallus is bifid, and the scrotum or labia are split and laterally displaced. In girls the vagina is bifid with two uteri. Given that cloacal exstrophy encompasses abnormalities of the genitourinary, gastrointestinal, and musculoskeletal systems, and often the neurologic system, it is not surprising that a wide range of variants from the classic presentation have been reported. The treatment of cloacal exstrophy has evolved from palliation of an almost universally fatal disorder into complex genitourinary and gastrointestinal reconstruction and a near-normal life span.

Of six cases reported by Lowentritt and colleagues (2005) with cloacal variants, five were skin covered and one involved duplication of the bowel and hemiblasters. Cases of cloacal exstrophy are challenging in their surgical management, and the variations of the complex add to the difficulties of initial diagnosis and management. Only by using a combination of genitograms, retrograde ureterograms, and bowel continence studies was it possible to

understand the complex anatomy of the patients in these groups. It is interesting to note that three patients had no spinal abnormalities and one had spina bifida occulta. Three patients in this group had innervation of the pelvic floor, enabling successful Pena procedures in two, with the third patient awaiting the procedure. Cloacal variants have a lower incidence of spinal abnormalities and a higher rate of fecal continence compared with their classic presentations. Overall, these patients had a low incidence of severe comorbid conditions. Therefore, appropriate treatment of these genitourinary malformations can significantly affect and improve QoL.

Prenatal Diagnosis

Since the initial description of cloacal exstrophy in the early 1980s, further refinements in its prenatal ultrasound diagnosis have occurred (Meizner and Bar-Ziv, 1985). These authors indicated that the three main criteria used to identify the diagnosis were a large midline infraumbilical anterior abdominal wall defect, lumbosacral myelomeningocele, and failure to visualize the urinary bladder. Chitrit and colleagues (1993) reported the diagnosis of monozygotic twins with cloacal exstrophy detected during antenatal ultrasound screening. Since these initial reports, there have been only occasional case reports of prenatal diagnosis of cloacal exstrophy, and only 15% of patients with this anomaly have been diagnosed by prenatal ultrasonography, according to the literature. With the marked improvements in survival of patients with cloacal exstrophy in the last 20 years and the common application of fetal ultrasonography, early diagnosis may permit appropriate prenatal counseling for parents and expedite postnatal care.

Austin and colleagues (1998) reviewed 20 patients with this abnormality, expanded on the diagnostic findings, and proposed major and minor criteria for the prenatal ultrasound diagnosis of cloacal exstrophy, based on the frequency of occurrence rather than the severity of individual findings. A criterion was considered major if it was present in more than 50% of cases. The gestational age at diagnosis of cloacal exstrophy ranged from 15 to 32 weeks (mean, 22 weeks). Major diagnostic criteria included nonvisualization of the bladder in 91%, a large midline infraumbilical anterior wall defect or a cystic anterior wall structure in 82%, an omphalocele in 77%, and a myelomeningocele in 68%. Minor criteria included lower extremity defects in 23%, renal anomalies in 23%, ascites in 41%, widened pubic arches in 18%, narrow thorax in 9%, hydrocephalus in 9%, and a single umbilical artery in 9%. Hamada and coauthors (1999) reported a single case in which ultrasonography revealed a wavy cordlike segment of soft tissue protruding from the anterior abdominal wall of the fetus below the umbilicus. This was found to be prolapsed terminal ileum, which resembled the trunk of an elephant. The authors suggested that this sonographic image be added to the criteria described by Austin and associates (1998) for making a prenatal diagnosis of cloacal exstrophy.

MRI has been used successfully for the prenatal evaluation of cloacal exstrophy (Chen et al, 2008). In conjunction with ultrasonography, excellent definition of anatomy can now be obtained. MRI was found to be superior to ultrasonography when a normal bladder is not identified (Calvo-Garcia et al, 2013). In addition, MRI was able to definitively identify the omphalocele, gender ambiguity, and spinal defect that were not easily defined with ultrasonography (Goto et al, 2012).

Antenatal diagnosis now permits parental counseling and postnatal management. Extensive parental counseling regarding the significant anatomic anomalies that constitute the complex is appropriate in conjunction with psychological support. Prenatal identification of cloacal exstrophy should permit planned maternal-fetal transfer to a center with subspecialty experience for perinatal management (Keppler-Noreuil et al, 2007).

SURGICAL RECONSTRUCTION OF CLOACAL EXSTROPHY

The initial successful reconstruction of cloacal exstrophy was reported by Rickham and Johnston (Rickham, 1960). Survival in

BOX 139-1 Modern Functional Reconstruction of Cloacal Exstrophy

IMMEDIATE NEONATAL ASSESSMENT

Evaluate associated anomalies
Decide whether to proceed with reparative surgery

FUNCTIONAL BLADDER CLOSURE (SOON AFTER NEONATAL ASSESSMENT)

One-Stage Repair (Few Associated Anomalies)

Excision of omphalocele
Separation of cecal plate from bladder halves
Joining and closure of bladder halves and urethroplasty
Bilateral anterior innominate and vertical iliac osteotomy
Terminal ileostomy and colostomy
Genital revision if needed

Two-Stage Repair

First Stage (Newborn Period)

Excision of omphalocele
Separation of cecal plate from bladder halves
Joining of bladder halves
Gonadectomy in male with unreconstructible phallus
Terminal ileostomy and colostomy

Second Stage

Closure of joined bladder halves and urethroplasty
Bilateral anterior innominate and vertical iliac osteotomy
Genital revision if needed

ANTI-INCONTINENCE AND REFLUX PROCEDURE (AGE 4 TO 5 YEARS)

Bladder Capacity ≥ 100 mL (Small Select Group of Patients)

Young-Dees-Leadbetter bladder neck reconstruction
Bilateral Cohen ureteral reimplantations
Bowel and/or stomach segment used to augment bladder, or
Continent diversion with abdominal or perineal stoma

VAGINAL RECONSTRUCTION

Vagina constructed or augmented using colon, ileum, of full-thickness skin graft

the 1970s remained at about 50%; however, the institution of intensive postnatal care led to improvement in survival in the 1980s to almost 100%. Where access to subspecialty care is limited, survival can be severely compromised.

Evaluation and Management at Birth

Immediate management is directed to the medical stabilization of the infant. Complete physical examination and determination of the various anatomic defects present allow short- and long-term management strategies to be created (Box 139-1). This initial planning stage should include decisions about gender assignment. The bowel and bladder segments are kept moist with protective plastic dressings as with bladder exstrophy (Gearhart and Jeffs, 1998). Presence of neurospinal abnormalities requires immediate neurosurgical evaluation. Consultations from social work, pediatric orthopedic surgery, and other disciplines should be obtained. Evaluation of the genitalia and gender assignment should be made by a gender assignment team, including a pediatric urologist, pediatric surgeon, pediatrician, pediatric endocrinologist, and child psychologist or psychiatrist. Gender assignment decisions should be made in conjunction with appropriate parental counseling and



Figure 139-32. A 46,XY child with cloacal exstrophy with a dominant right hemiphallus. This child underwent reconstruction and was reared as male.

involvement. In a large medical center with experience in dealing with complex malformations, these multiple consultations should be done in a short period of time. If there are medical concerns or the bladder segments are too small for closure, delayed closure after initial intestinal diversion is appropriate (Mathews et al, 1998).

Gender Assignment

Because of the significant separation of the corpora of the penis and scrotum and the reduction in corporeal size noted in boys with cloacal exstrophy, early reports had recommended universal gender reassignment of boys (46,XY) with cloacal exstrophy to functional females (Tank and Lindenaur, 1970). To this end, bilateral orchiectomy was combined with phallic reconstruction as a functional clitoris and early or delayed vaginoplasty. Reiner and Gearhart (2004) have reported on 29 males with cloacal exstrophy who had gender reassignment to female. Psychosexual evaluation indicated that all of these patients had a marked male shift in psychosexual development despite having no pubertal hormonal surges. Mirheydar and colleagues (2009) reported a case of masculinization in a 46,XY gender-converted patient secondary to an ectopic testis. A comparison of patients with cloacal exstrophy and other cloacal anomalies at the Great Ormond Street Hospital for Sick Children, however, indicated no difference in social or behavioral competence or psychological problems. Gender assignment was not associated with childhood psychological, emotional, or behavioral problems (Baker Towell and Towell, 2003). Schober and coauthors (2002), reporting on 14 children who had undergone early gender reassignment, indicated that although patients had masculine childhood behavior, they had a feminine gender identity. Currently, however, most authors recommend assigning gender that is consistent with karyotypic makeup of the individual if at all possible (Fig. 139-32). A recent survey of pediatric urologists indicated that two thirds of respondents favored gender-congruent assignment (Diamond et al, 2006). This policy can be supported by a report indicating that the histology of the testis at birth is normal (Mathews et al, 1999a). Furthermore, with evolution of techniques for phallic reconstruction, a functional and cosmetically acceptable phallus can now be constructed (Husmann et al, 1989b; Massanyi et al, 2012).

Immediate Surgical Reconstruction

Cloacal exstrophy patients should undergo carefully planned and individualized reconstructions (Ricketts et al, 1991; Lund and Hendren, 1993; Mathews et al, 1998). For infants with spinal dysraphism and myelocystocele, neurosurgical consultation should be obtained and closure undertaken as soon as the infant's condition is medically stable. After closure of the myelocystocele, long-term

follow-up is mandatory to evaluate for subtle changes in the neurologic evaluation that could herald cord tethering. Symptomatic spinal cord tethering can be seen in up to 33% of children (McLaughlin et al, 1995). A more recent series evaluating neuro-orthopedic manifestations in cloacal exstrophy indicated that 57 of 68 children had spina bifida (Suson et al, 2010). Of 62 children who were of walking age, 37 were able to ambulate completely, 17 ambulated with devices, and 8 were wheelchair bound.

Neonatal omphalocele closure is recommended to prevent untimely rupture and is typically combined with intestinal diversion. Formerly, initial attempts focused on ileostomy with resection of the hindgut remnant. Since the recognition of the metabolic changes that occur in patients with ileostomy, an attempt is always made to use the hindgut remnant to provide additional length of bowel for fluid absorption (Husmann et al, 1989a; Mathews et al, 1998). Tubularization of the cecal plate with end colostomy has been shown to be beneficial in reducing the incidence of short gut syndrome (Sawaya et al, 2010). Enlargement of the hindgut remnant and increased water absorption have been noted in children who have had the hindgut remnant incorporated into construction of a fecal colostomy (Taghizadeh et al, 2009). The hindgut segment may be anastomosed in an isoperistaltic or retroperistaltic fashion to increase motility and generate formed stool. Children who have anal stenosis and not imperforate anus may have the capability for later continence and may be treated with a pull-through procedure (Ricketts et al, 1991). If the hindgut remnant is not used for bowel reconstruction, it should be left as a mucous fistula to be used for later bladder augmentation or vaginal reconstruction (Lund and Hendren, 1993; Mathews et al, 1998). If gastrointestinal reconstruction is combined with bladder closure, approximation of the pubis, usually with osteotomies, is beneficial in reconstruction of the pelvic ring and increases the potential for successful bladder and abdominal wall closure (Mathews et al, 1998). Some authors have suggested that gastrointestinal reconstruction after initial fecal diversion be delayed for 1 to 2 years of observation (Soffer et al, 2000). After this time, radiographic evaluation is performed to determine residual colonic length. If near-normal colonic length is noted, a pull-through procedure is performed. If there is short colon but the patient is able to make solid stool, the patient may still be a candidate for pull-through procedures. A number of patients who can make solid stool are now able to be managed with pull-through procedures in conjunction with bowel management strategies to help them stay clean (Levitt et al, 2008). Bowel-lengthening procedures have also been used to improve absorptive function and benefit nutritional outcomes (Figueroa-Colon et al, 1996). Children who are unable to make solid stool are typically managed with a permanent fecal stoma.

At the initial stage of omphalocele closure, if it is determined that bladder and abdominal wall closure may not be accomplished, the bladder halves are approximated in the midline without further dissection and the defect is converted to a bladder exstrophy (Ricketts et al, 1991; Mathews et al, 1998). This permits abdominal distention to allow enlargement of this bladder plate for later closure. If the hindgut segment is not used in the initial reconstruction of the bowel, it is left as a mucous fistula.

Urinary Reconstruction

Modern Staged Reconstruction

The staged management of the urinary tract follows that used for the management of bladder exstrophy (Gearhart and Jeffs, 1991b). Once the bladder halves have been approximated posteriorly, the lateral edges are separated from the abdominal wall and brought together in the midline. As in the patient with classic exstrophy, placement of the bladder and posterior urethra deep into the pelvis remains a key factor in the successful surgical reconstruction of the urinary tract. Use of an AlloDerm patch to reduce the incidence of erosion of the interpubic stitch and prevent penopubic fistulization has been shown to be beneficial (Henderson et al, 2010). Inguinal hernias that are noted should be repaired at the time of closure. In

genetic females and in genotypic male subjects undergoing gender reassignment, reconstruction should be performed to improve the appearance of the genitalia. Recent reports by [Thomas and colleagues \(2007\)](#) in a series using a staged approach found successful results in a series of seven patients, all with tethered cords.

Reconstruction of the external genitalia in the immediate postnatal period is performed to make the infant's appearance more congruent with the gender assigned. The psychiatric studies of children who have had gender assignment have fueled interest in male gender assignment if adequate unilateral or bilateral corporeal tissue is present ([Reiner, 2004](#)). Histologic studies indicate normal histology in the testes of male subjects who have had gender reassignment despite the presence of cryptorchidism ([Mathews et al, 1999a](#)). Past results of phallic reconstruction in male patients with limited penile tissue have been disappointing. Penile replacement with phalloplasty has now permitted successful reconstruction to be performed and allows most if not all genotypic males to be raised with a congruent sex ([Lumen et al, 2008](#)). Multiple flaps have been used successfully for phallic reconstruction ([Bluebond-Langner and Redett, 2012](#); [Massanyi et al, 2012](#)). If male-to-female reassignment is deemed necessary, initial female genital reconstruction should bring the phallic halves together in the midline as a clitoris.

However, in instances with adequate corporeal tissue, either unilaterally or bilaterally, epispiadias repair can be performed at around age 1 using the standards identified for the staged reconstruction. Vaginal reconstruction can be performed early in the genetic female patient. In gender-converted male patients who require reconstruction of a neovagina, delayed reconstruction is appropriate. Reconstruction may be performed by using a preserved hindgut segment or expanded perineal skin ([Belloli et al, 1997](#)). Long-term dilation of the neovagina may be required.

Pubic approximation permits abdominal wall closure and usually requires osteotomy and fixation with postoperative traction. External fixation and traction are typically maintained for 6 to 8 weeks to permit healing.

Role of Osteotomy

Infants who are medically stable may be considered for urinary tract reconstruction in the immediate postnatal period. **Osteotomy is indicated in all children with cloacal exstrophy at the time of bladder closure because of the wide diastasis that is invariably present** ([Mathews et al, 1998](#)). Osteotomy allows the pelvic ring, bladder, and abdominal wall to be closed without undue tension on the closure. Reduction in dehiscence and postoperative ventral hernias has been noted in patients treated with osteotomy. In a large series reported by [Ben-Chaim and associates \(1995c\)](#), significant complications occurred in 89% of patients who underwent closure of the cloacal exstrophy without osteotomy but in only 17% of patients who underwent osteotomy at the time of initial cloacal exstrophy closure. It is interesting to note that the patients who underwent osteotomy and those who did not were similar in terms of size of the omphalocele, presence of myelomeningocele, and time of primary closure. However, it is not surprising that osteotomy had no effect on eventual continence of patients with cloacal exstrophy.

Currently, combined bilateral anterior innominate and vertical iliac osteotomies are routinely used at our institution ([Silver et al, 1999](#)). This approach does not require the patient to be repositioned on the operating table before commencement of bladder and abdominal wall closure. In addition, this method obviates the use of a posterior approach and any complication of the procedure related to the spinal or back closure. In a series of five patients with extreme pubic diastasis greater than 10 cm, [Silver and colleagues \(1999\)](#) described initial pelvic osteotomy and gradual pelvic closure of the fixator for 1 to 2 weeks, followed by abdominal wall and bladder closure. Closure was successful in all patients without technical problems or complications. This technique of staged pelvic closure may provide reliable initial secondary repair in patients with cloacal exstrophy in whom one-stage pelvic closure is not feasible, even with pelvic osteotomy. An interpubic titanium bar has been



Figure 139-33. Pubic apposition using titanium plate in cloacal exstrophy with extreme preoperative diastasis (8 cm) now with complete pelvic reduction.

added to permit stabilization of the pubic approximation and maintain the reduction in diastasis ([Fig. 139-33](#)) ([Mathews et al, 2006](#)). Because of the possible asymmetry that can be noted in the pelvic bones, care must be used when performing osteotomies and fixation. In patients who have lower extremity abnormalities, providing postoperative traction can also be challenging.

Failure of urinary reconstruction in children with exstrophy can lead to lack of growth of the bladder and may require loss of the bladder template. Recently [Shah and colleagues \(2014\)](#) identified potential causes for failure of the urinary reconstruction in a large series of children with cloacal exstrophy undergoing reconstruction at a tertiary medical center. They compared 26 patients (6,XY males, 8,XX females, and 12,XY gender-converted females) in whom prior urinary reconstruction had failed and who had been referred for reconstruction, with 34 patients (17,XY males, 12,XX females, and 5,XY gender-converted females) who underwent successful primary closure, to identify potential risk factors for failure.

It is interesting to note that 77% of patients with failed procedures had undergone closure in the first week of life, compared with 26% of those having undergone successful closure. In addition, only 31% of patients in whom closure had failed had osteotomy, compared with 82% of those who had undergone successful closure. In the patients with failed closure, 76% were immobilized with spica casts or mummy wraps. Among those in whom closure was successful, 56% were immobilized using modified Buck traction and external fixation, and an additional 20% were immobilized using Bryant traction with or without external fixation. Intersymphyseal plates to prevent separation of the pubis were used in 30% of patients with successful closure and in 50% of patients with successful reclosure. Ninety-two percent of patients with successful reclosure had osteotomy. Use of a technique that staged the closure over a 2- to 3-week period after performance of the osteotomy by gradually cranking the fixator medially was also shown to be of benefit in providing a successful primary or secondary closure ([Mathews et al, 2006](#)).

Single-Stage Reconstruction

[Grady and Mitchell \(1999\)](#) have reported using a single-stage reconstruction in cloacal exstrophy—a procedure similar to that done for bladder exstrophy. Delay in urinary tract reconstruction has also been advised by these authors if there is a large omphalocele or other medical instability. In this situation, the conversion to a bladder exstrophy and subsequent reconstruction of the bladder

and penis as a single step is performed. Lee and colleagues (2006) presented a limited experience in seven children with cloacal exstrophy who underwent reconstruction performed using a single-stage approach. There was one mortality before reconstruction. Six children who underwent reconstruction had dry intervals before toilet training. Some patients have required bladder neck injection to enhance continence. One child is voiding spontaneously and one child has undergone augmentation cystoplasty.

Techniques to Create Urinary Continence

Urinary continence is possible in most children but usually requires bladder augmentation and the use of intermittent catheterization. Multiple series by Gearhart and Jeffs (1991b), Mitchell and associates (1990), and Hendren (1992) have shown the applicability of modern techniques for lower tract reconstruction to help these patients achieve urinary continence. Enhancement of bladder capacity may be performed using a hindgut segment, if available; ileum; or stomach. Continence appears to be more difficult to achieve in male patients who undergo gender reassignment, and a continent stoma may be most applicable in this special group of patients (Mathews et al, 1998). In genetic female patients, successful continence has been achieved after Young-Dees-Leadbetter bladder neck reconstruction, but the vast majority of patients have required intermittent catheterization (Husmann et al, 1999). Similar findings were reported in a series by Mitchell and associates (1990). Husmann and colleagues (1999) reported that the success rate of Young-Dees-Leadbetter bladder neck reconstruction in the cloacal exstrophy population was closely related to the presence of coexisting neurologic abnormalities.

Urinary continence can be achieved in these individuals in many ways. An orthotopic urethra can be constructed from local tissue, vagina, ileum, stomach, or ureter. A catheterizable stoma can be constructed from ileum when enough bowel is present and fluid loss is not a problem. The bladder may be augmented with unused hindgut, ileum, or stomach. However, surgery to provide a continent urinary reservoir should be delayed until a method of evacuation can be taught and the child is old enough to participate in self-care. The choice between a catheterizable urethra and an abdominal stoma depends on the adequacy of the urethra and bladder outlet, interest and dexterity of the child, and orthopedic status regarding the spine, hip joints, braces, and ambulation. A more recent evaluation of a large cohort of children with cloacal exstrophy (Suson et al, 2010), indicates that over 50% of children (35 of 61) were able to achieve continence, 30 of 35 using intermittent catheterization through a continent stoma and the rest voiding or catheterizing via the urethra. An innovative approach is required to find a suitable solution for each individual patient according to the patient's bladder size and function and mental, neurologic, and orthopedic status.

LONG-TERM ISSUES IN CLOACAL EXSTROPHY

Because survival has become almost universal, the focus has changed in cloacal exstrophy to improving QoL. Improvement in functional outcomes has become the mainstay of improving the QoL. It must be stressed that although broad management strategies can be suggested, the management of patients with cloacal exstrophy must be individualized to maximize functional outcomes.

The factor most likely to lead to long-term disability is the level of the neurologic defect. Early aggressive evaluation and management of the neurologic issues with long-term close follow-up to evaluate for signs of cord tethering are critical to make sure that function can be preserved (McLaughlin et al, 1995).

Further management is most determined by the degree of neurologic deficit. When neurologic issues are minimal or absent, bowel pull-through and voided continence would be ideal. Ricketts and associates (1991) have presented a continence score that can be used in this group of children. Using a six-point scoring system to determine bowel and bladder continence (6 = best; 0 = worst),

they evaluated 12 patients who had been managed over time. They had 7 patients with a continence score of 1 (colostomy and incontinent bladder) and only 1 patient who had a score of 5 (enema program and a continent bladder), attesting to the difficulties presented with surgical reconstruction.

Some children have required permanent ileostomy for management of their gut. Husmann and colleagues (1999) noted that patients undergoing permanent ileostomy, in comparison with terminal colostomy, had greater initial morbidity; however, bowel adaptation appeared to occur by age 3 years with resolution of the short gut syndrome in most. If patients with terminal ileostomy were aggressively managed with hyperalimentation, growth characteristics in the two groups were very similar. As noted earlier, bowel reconstructive techniques have permitted most children to avoid the long-term debility associated with short gut syndrome.

Attempts at phallic reconstruction in the past had minimal success because of the diminutive nature of the corpora in boys and the wide pubic separation. Modern reconstructive surgical techniques may allow some boys to have complete phallic reconstruction performed with forearm or other grafts. Fertility appears to be universally compromised in boys, but girls have normal fertility, and pregnancy has been reported. Girls have higher degrees of cervical prolapse when compared with their counterparts with bladder exstrophy.

Summary

Evolution in management of cloacal exstrophy has permitted near-universal survival with significant improvement in cosmetic and functional outcomes. Debate continues regarding the issue of gender reassignment, and long-term data are still accruing on the best strategy for management. Continence can be achieved with appropriate reconstruction and the use of intermittent catheterization. Despite the extensive malformations noted, many patients have gone on to live fruitful lives.

KEY POINTS: CLOACAL EXSTROPHY—PRIORITIES IN MANAGEMENT

- Medical stabilization
- Gender assignment
- Colonic functionalization
- Separation of bladder from the gastrointestinal tract
- Functional genital reconstruction

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Genetics

Embryology

Clinical Features

Presentation

Evaluation and Management

Long-Term Outlook

Pruno-belly syndrome (PBS) represents a constellation of anomalies with variable degrees of severity. The three major findings are a deficiency of the abdominal musculature, bilateral intra-abdominal testes, and an anomalous urinary tract. The urinary tract is characterized by variable degrees of hydronephrosis, renal dysplasia, dilated tortuous ureters, an enlarged bladder, and a dilated prostatic urethra. Additional associated anomalies involve the respiratory tract, gastrointestinal tract, cardiac system, and musculoskeletal system. There is a broad spectrum of severity of the syndrome, with some children not surviving the newborn period and others being minimally affected. The single most important determinant of long-term survival is usually the severity of the urinary tract anomaly, in particular, the degree of renal dysplasia.

Frolich (1839) first described the characteristic abdominal wall, and the full triad of anomalies was described by Parker (1895). Osler's vivid description of the abdominal wall of an infant with the characteristic findings led to the term *prune-belly syndrome* (Osler, 1901). Other names that have been applied to this syndrome include *triad syndrome*, *Eagle-Barrett syndrome*, and *abdominal musculature syndrome* (Eagle and Barrett, 1950; Greskovich and Nyberg, 1988).

The incidence of PBS has been reported as 1 in 29,000 to 1 in 40,000 live births, similar to that of bladder exstrophy (Williams and Burkholder, 1967), with 95% occurring in males (Wheatley et al, 1996). Females with PBS exhibit the abdominal wall deficiency and urinary tract dysmorphism without any gonadal anomaly (Rabinowitz and Schillinger, 1977; Reinberg et al, 1991b). A higher incidence is noted in twins, blacks, and children born to younger mothers. In developed countries, the incidence appears to be declining because of prenatal diagnosis and a decision to terminate the pregnancy. In a review reported by Routh and coworkers (2010) of the Kids' Inpatient Database (United States based), which evaluated newborns with PBS during their initial hospitalization between 2000 and 2006, the weighted incidence estimate was 38 cases per 100,000 live births (Routh et al, 2010).

GENETICS

The high male-to-female ratio, occasional occurrence in male siblings and cousins, and increased occurrence in twins suggest a genetic basis for PBS. Yet most cases are sporadic and have a normal karyotype. One in 23 children with PBS is the product of a twin pregnancy (Ives, 1974). However, the majority of reported twins have been discordant for PBS, which is evidence against a genetic etiology. It has been suggested that the etiology in twins may be a result of an uneven distribution of mesenchymal tissue at a critical time of primitive streak development during the third week of

embryogenesis (Coplen et al, 1996). There is a reported association with Turner syndrome, monosomy 16, trisomy 13, and trisomy 18 (Amacker et al, 1986; Hoagland and Hutchins, 1987). A variety of inheritance patterns have been proposed including X-linked recessive (Frydman et al, 1993), a two-step autosomal dominant mutation (Riccardi and Grum, 1977), and polygenetic transmission (Garlinger and Ott, 1974; Lockhart et al, 1979; Adeyokunnu and Familusi, 1982). A report by Ramasamy and colleagues (2005) suggested a sex-influenced autosomal recessive mode of inheritance in familial PBS. The consensus, however, remains that an associated chromosomal abnormality is the exception rather than the rule because most have a normal karyotype. Other reports have noted an association between PBS and Beckwith-Wiedemann syndrome (Silengo et al, 2002; Sinico et al, 2004).

EMBRYOLOGY

Several theories about the embryogenesis of PBS have been proposed. However, because there is no experimental model that can be used to test these theories, the exact mechanism remains elusive. The four chief theories are as follows: (1) early in utero posterior urethral obstruction resulting in severe dilation of urinary tract and possible fetal ascites and oligohydramnios (Strumme, 1903; Pagon et al, 1979; Beasley et al, 1988; Wheatley et al, 1996); (2) primary defect in the lateral plate mesoderm, which is the precursor of the ureters, bladder, prostate, urethra, and gubernaculum (Ives, 1974; Gonzalez et al, 1990); (3) an intrinsic defect of the urinary tract leading to ureteral dilation and fetal ascites (Symonds and Driscoll, 1974; Monie and Monie, 1979; Smythe, 1981; Nakayama et al, 1984; Cazorla et al, 1997); and (4) a yolk sac defect (Stephens, 1983; Stephens and Gupta, 1994). None of these theories has universal acceptance, and there is some overlap among them.

CLINICAL FEATURES

Genitourinary Anomalies

Kidneys

A spectrum of renal abnormalities extends from normal renal parenchyma to dysplasia (Figs. 140-1 and 140-2). The more severely dysplastic kidneys are generally associated with bladder outlet obstruction in which there has not been decompression through a patent urachus (Potter, 1972). Dysplasia is present in 50% of cases; however, it may vary in degree and laterally (Rogers and Ostrow, 1973; Stephens, 1983). Renal dysplasia in PBS of the Potter type II and type IV varieties is seen. The Potter type II variety

with few nephrons and parenchymal disorganization is more indicative of a renal mesenchymal defect, whereas the Potter type IV with cortical and tubular cysts is associated with outlet obstruction (Wigger and Blanc, 1977).

The renal collecting system is characteristically dilated, often to a severe degree. The degree of dilation, however, does not correlate with the degree of renal dysplasia. Calyceal morphology may be well preserved, even in the presence of massively dilated ureters and renal pelves (Berdon et al, 1977). Some patients may present with one severely dysplastic or dilated kidney, with the contralateral having only mild abnormalities. Ureteropelvic junction obstruction can occur on a primary or secondary basis; however, nonobstructive hydronephrosis is the rule (Woodard and Parrott, 1978b). It is renal

infection rather than obstruction that poses the greatest risk to renal function.

Ureters

The ureters are typically dilated, tortuous, and redundant (Fig. 140-3). The proximal (upper) portions of the ureters are usually less abnormal than the distal segments, although massive dilation and stenosis can occur at all levels. It is noteworthy that in many patients the severity of the urinary tract abnormalities is not proportional to the flaccidity of the abdominal wall. Histologic sectioning demonstrates a lack of smooth muscle cells and an increase in fibrous connective tissue. Generally there are more normal-appearing smooth muscle cells in the proximal segments (Palmer and Tesluk, 1974; Stephens, 1983). This fact is critical when ureteral reconstruction is undertaken. The ratio of collagen to smooth muscle cells in prune-belly ureters has been noted as elevated, especially in refluxing ureters (Gearhart et al, 1995). A decreased number of thick and thin myofibrils noted on ultrastructural examination is thought to contribute to the poor peristalsis (Berdon et al, 1977; Stephens, 1983).

Vesicoureteral reflux (VUR) is present in 75% of children with PBS (Berdon et al, 1977; Fallat et al, 1989) (Fig. 140-4). Obstruction is not common but has been reported at both the ureteropelvic and ureterovesical junctions (Wigger and Blanc, 1977; Moerman et al, 1982; Manivel et al, 1989).

These large ureters may have ineffective peristalsis because of poor ureteral wall coaptation. The ureteral conduction wave reaches a reduced smooth muscle cell population of poor contractile potential related to reduced myofibrils, often separated by patches of collagen with a resulting bolus of urine reaching more dilated ureteral segments as it progresses toward the bladder (Woodard and Smith, 1998). This can be seen fluoroscopically as ineffective peristalsis, resulting in upper tract stasis, which may lead to infection (Nunn and Stephens, 1961; Williams and Burkholder, 1967).



Figure 140-1. Ultrasound scan of a kidney of a newborn with prune-belly syndrome demonstrating markedly echogenic renal parenchyma and cortical cysts indicative of renal dysplasia.

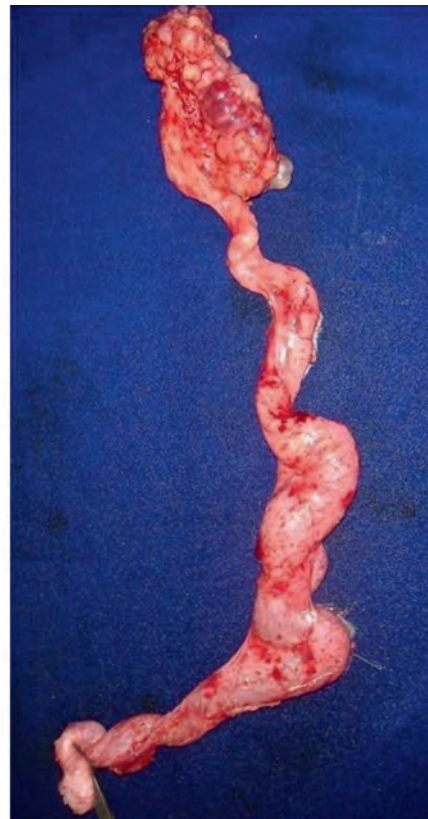


Figure 140-2. Unilateral renal dysplasia with dilation and tortuosity of the ureter in a patient with prune-belly syndrome.

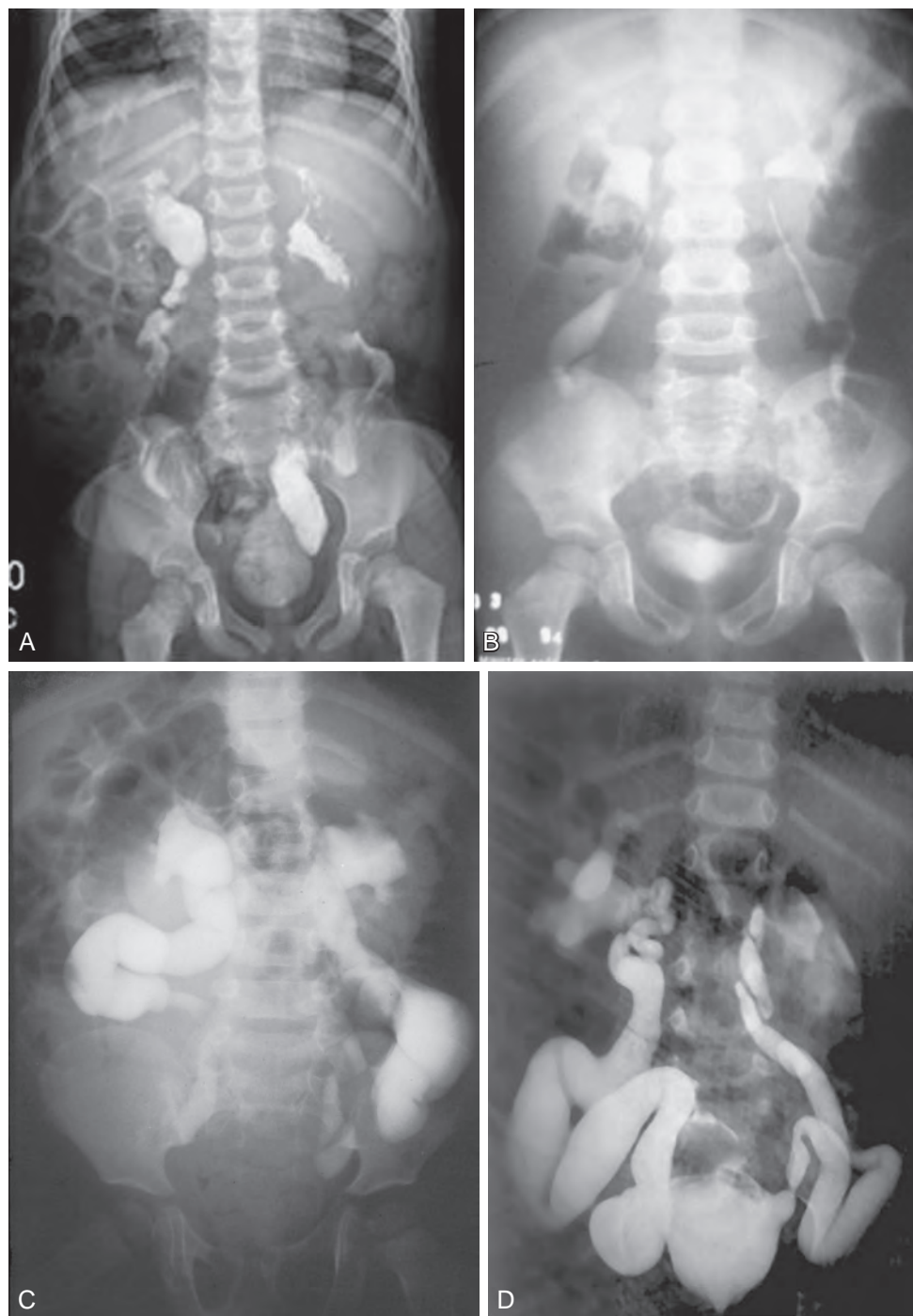


Figure 140-3. Excretory urogram (A to C) demonstrating the variability in the degree of hydro-ureteronephrosis in prune-belly syndrome. Note the preservation of calyceal architecture, despite severe ureteral dilation in C. D, Dilated tortuous refluxing ureters as seen on a voiding cystourethrogram.

Bladder

The bladder usually appears as massively enlarged with a pseudodiverticulum at the urachus (Fig. 140-5). The urachus is patent at birth in 25% to 30% of children (Lattimer, 1958; Wigger and Blanc, 1977; Stephens and Gupta, 1994). Despite being very thick, the bladder wall is smooth, unlike that seen in obstructed bladders. Histologically, the bladder has an increased ratio of collagen to muscle fibers in the absence of obstruction (Workman and Kogan, 1990). Smooth muscle hypertrophy can be seen, however, in the obstructed prune bladder (Perlmutter, 1976). The pelvic distribution of ganglion cells has been shown as normal (Nunn and

Stephens, 1961; Burke et al, 1969); however, a decrease in α_1 -adrenoceptor immunostaining intensity has been documented (Schneider-Monteiro et al, 2010). Stephens demonstrated that the trigone is splayed with the ureteric orifices displaced laterally and superiorly, possibly contributing to the high incidence of reflux (Williams and Burkholder, 1967).

On voiding, the bladder neck opens widely into a dilated prostatic urethra (see Fig. 140-5). Urodynamic assessment generally shows normal compliance; however, there is a delayed first sensation to void and there is a large capacity (Snyder et al, 1976). The ability to empty the bladder is variable, with some emptying well and others carrying a significant postvoid residual. This is thought

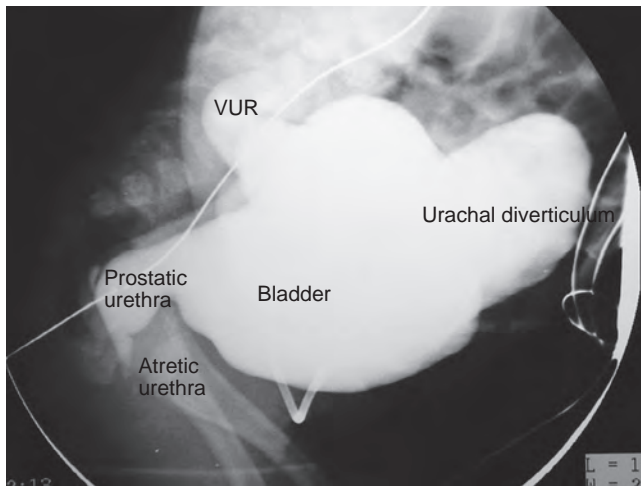


Figure 140-4. Voiding cystourethrogram of a child with prune-belly syndrome demonstrating urethral atresia, urachal diverticulum, and vesicoureteral reflux (VUR).

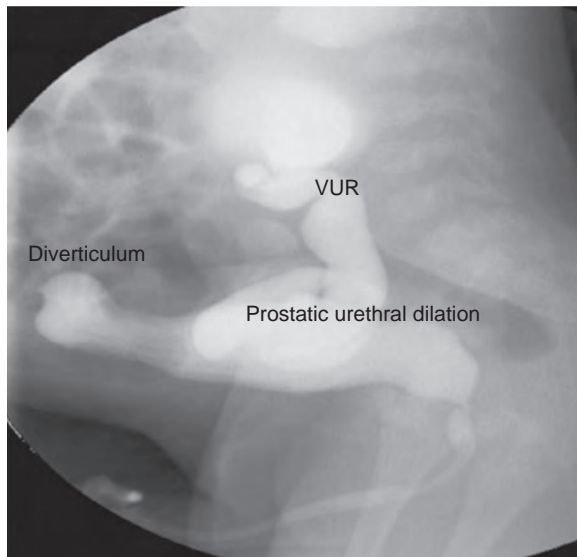


Figure 140-5. Voiding cystourethrogram of a child with prune-belly syndrome demonstrating prostatic urethral enlargement related to a hypoplastic prostate and also demonstrating a urachal diverticulum. VUR, vesicoureteral reflux.

to be a result of a relative outlet obstruction and the ability of the bladder to generate sufficient pressure with a detrusor contraction. When the relative outflow resistance prevents effective bladder emptying, the term *unbalanced voiding* is used (Snyder et al, 1976; Kinahan et al, 1992). Despite these limitations, about 50% of prune-belly patients void spontaneously with normal voiding pressures, normal flow rates, and low postvoid residuals (Nunn and Stephens, 1961; Kinahan et al, 1992). However, as Kinahan and colleagues (1992) demonstrated, deterioration of balanced voiding can occur, resulting in significant postvoid residuals and emphasizing the need for periodic assessment.

Prostate and Accessory Sex Organs

The dilation of the posterior urethra is caused by prostatic hypoplasia, probably related to abnormal mesenchymal-epithelial development (Stephens and Gupta, 1994). Histologically, there are few

prostatic cellular elements with a reduction of both epithelial and smooth muscle cells and an increase in connective tissue cells (Moerman et al, 1982; Popek et al, 1991; Stephens and Gupta, 1994). Various obstructive lesions of the distal posterior urethra have been described—urethral atresia, valves, urethral stenosis, urethral membrane, and urethral diverticulum—and are thought to occur in 20% of cases (Hoagland and Hutchins, 1987). Stephens (1983) described an angulation of the urethra during voiding, referred to as *type IV valves*, which results from a lack of prostatic parenchymal tissue. Prostatic hypoplasia, the etiology of which is controversial, is thought to be a factor in the ejaculatory failure of PBS patients (Volmar et al, 2001). The vas deferens and seminal vesicles are often atretic, although either may be dilated or thickened (Stephens and Gupta, 1994). The epididymis may be poorly attached to the testis, as is seen commonly in abdominal undescended testes. There may also be a lack of continuity between the efferent ductules and the rete testis. Ejaculation is usually in a retrograde fashion because of an incompetent bladder neck.

Anterior Urethra

Although the anterior urethra of the PBS child is usually normal, several anomalies of the anterior urethra have been reported, with the most common being urethral atresia or hypoplasia and megalourethra (Kroovand et al, 1982; Perrotin et al, 2001). Unless it is associated with a patent urachus, urethral atresia is often lethal (see Fig. 140-4). It has been postulated that urethral atresia or hypoplasia occur because the urethra is unused rather than malformed. Spontaneous bladder rupture with fistula formation has also been reported (Reinberg et al, 1993).

PBS is associated with two variations of megalourethra (Shrom et al, 1981; Mortensen et al, 1985). The fusiform type is a deficiency of the corpus cavernosum, as well as the spongiosum, and the scaphoid variety is a deficiency of the spongiosum only with preservation of the glans and corpora cavernosa (Fig. 140-6). With the scaphoid variety, the ventral urethra dilates with voiding, whereas with the fusiform variety the entire phallus dilates with voiding. The fusiform variety is thought to result from a mesenchymal deficiency of the urethral folds, whereas the scaphoid variety results from a mesenchymal deficiency of the urethral supportive tissues (Dorairajan, 1963). Megalourethra is more commonly seen in PBS than any other syndrome (Appel et al, 1986). Transient in utero obstruction of the junction between the glanular and penile urethra has been proposed as a cause of megalourethra.

Testes

Bilateral intra-abdominal testes lying over the iliac vessels and adjacent to the dilated ureters are the most typical findings. Although mechanical forces such as a distended bladder and intra-abdominal pressure have been implicated in maldescent of the testes (Kaplan et al, 1986; Hutson and Beasley, 1988), the fact that some patients with the typical urinary tract and abdominal musculature anomalies (termed *pseudoprune patients*) may have descended testes raises some doubt about the pure mechanical factors.

Pak and colleagues (1993) compared the histology of the testes in PBS patients with that of non-prune-belly intra-abdominal testes and that of age-matched control subjects. They found no difference in germ cell counts, Ad spermatogonia, and Leydig cells between PBS testes and non-PBS intra-abdominal testes. However, because germ cell counts in PBS patients younger than 1 year are similar to those of age-matched controls, the implication is that the environmental state of the abdomen is a major factor in their later spermatogenic potential (Nunn and Stephens, 1961; Coplen et al, 1996). This mirrors findings of Nunn and Stephens (1961) of normal germinal epithelium of fetal and newborn PBS testes. Alternatively, Orvis and colleagues (1988) noted decreased numbers of spermatogonia and Leydig cell hyperplasia in fetal PBS testes, implying an intrinsic testicular abnormality. Azoospermia was found in adult PBS patients, and no PBS patient has been reported as having fathered a child (Woodhouse and Snyder, 1985). The



Figure 140-6. Scaphoid megalourethra and prostatic urethral dilation.

infertility is thought to be caused by a combination of testicular histologic abnormalities, structural defects of the ducts, and prostatic abnormalities (Tayakkanonta, 1963). More recently, paternity with normal live births was documented in adult patients with classic PBS, achieved by sperm retrieval techniques and intracytoplasmic sperm injection (Kolettis et al, 1999; Fleming et al, 2013). Normal pregnancy with assisted vaginal delivery was also described in a female patient with the syndrome (Hillman et al, 2012).

Three cases of testis tumor have been reported (Woodhouse and Ransley, 1983; Sayre et al, 1986; Massad et al, 1991; Parra et al, 1991). Massad and colleagues (1991) described histologic testicular patterns similar to those in intratubular germ cell neoplasia in three infants. Although the risk of malignancy may be relatively low considering the lack of germinal epithelium (Uehling et al, 1984), it is clear that placement of the testis in the scrotum and long-term follow-up are necessary to reduce the risk of testicular malignancy and to enhance detection.

Extragenitourinary Abnormalities

Of all children with PBS, 75% have non-urinary tract abnormalities (Geary et al, 1986). After the obvious abdominal wall defect, the most common abnormalities are cardiac, pulmonary, and orthopedic (Table 140-1). In addition to these organ-specific morbidities, nearly 50% of children with PBS are born premature, which significantly contributes to comorbidities.

Abdominal Wall Defect

The most characteristic feature of PBS in newborns is the appearance of the abdominal wall (Fig. 140-7). Although in some cases the musculature of the abdominal wall may be totally absent (Manivel et al, 1989), most commonly there is uneven involvement, with the medial and inferior musculature typically most deficient (Mininberg et al, 1973; Randolph, 1977). The appearance at birth is that of wrinkled, redundant skin with an abdomen that bulges in the flanks. One may be able to discern intra-abdominal organs through the thinned abdominal wall. The most severely affected areas may have skin, subcutaneous fat, and a single fibrous layer on the peritoneum (Mininberg et al, 1973; Baird and Sadovnick, 1987). Randolph conducted electromyographic mapping and demonstrated that the inferior and medial segments are the most consistently affected (Randolph et al, 1981a). Electron microscopy has demonstrated a nonspecific pattern of myofilament disarray, Z-line disorganization, and mitochondrial proliferation (Afifi et al, 1972; Randolph et al, 1981b; Woodard and Smith, 1998). The fact that normal spinal anterior horn cells have

TABLE 140-1 Nonurologic-Associated Abnormalities in Children with Prune-Belly Syndrome

COMORBID CONDITION	PATIENTS WITH PBS (%)
Cardiovascular	25
Dermatologic	2
Gastrointestinal	24
Head, eyes, ears, nose, and throat	5
Hematologic	4
Immunologic/inflammatory	5
Metabolic/endocrine	22
Musculoskeletal	23
Neurologic	5
Other syndrome	6
Prematurity	43
Weight (g):	
<2000	26
2000-2500	30
>2500	42
Respiratory	58
Sepsis/infectious disease	14

PBS, prune-belly syndrome.
Modified from Routh JC, Huang L, Retik AB, et al. Contemporary epidemiology and characterization of newborn males with prune belly syndrome. *Urology* 2010;76:44-8.

been shown rules out a neuropathic etiology for the muscular deficiency (Nunn and Stephens, 1961). The muscular deficiency, however, is typically inconsistent and patchy and, as mentioned earlier, may be disproportional to the abnormalities of the urinary tract.

As the child grows older, the abdomen becomes less wrinkled and takes on more of a pot-bellied appearance (Fig. 140-8). Gait is usually not affected, although it may be delayed, and the children tend to roll to their sides and use their arms to sit from a supine position. The poor support of the lower chest wall results in flaring of the costal margin (Woodard and Smith, 1998). These children are more vulnerable to respiratory illness because their cough effectiveness is compromised. In spite of these abdominal wall issues, Woodard and Smith (1998) reported good wound healing without a tendency toward infections or incisional hernias.



Figure 140-7. The variability of the abdominal wall defect in patients with prune-belly syndrome.

Cardiac Anomalies

Cardiac anomalies such as patent ductus arteriosus, atrial septal defect, ventricular septal defect, and tetralogy of Fallot occur in 10% of children with PBS (Adebonojo, 1973). Cardiac abnormalities at birth may take precedence over urologic issues.

Pulmonary

Pulmonary difficulties can be observed at any age in patients with PBS. Pulmonary hypoplasia can result from severe oligohydramnios related to renal dysplasia or severe bladder outlet obstruction and may result in newborn demise. In addition, pneumothorax and pneumomediastinum can be seen with or without pulmonary hypoplasia (Skooog, 1992). Significant pulmonary difficulties have been reported in 55% of PBS survivors (Geary et al, 1986; Routh et al, 2010). In nearly half of PBS newborns, intubation and

mechanical ventilatory support will be required with its attendant morbidities (Routh et al, 2010).

The lack of ability to generate significant intra-abdominal pressure may contribute to pneumonia and lobar atelectasis (Alford et al, 1978; Ewig et al, 1996). Acute respiratory illnesses or an anesthetic procedure can easily lead to respiratory insufficiency in the PBS patient, who may have underlying chronic bronchitis from repeated respiratory illnesses. Many patients demonstrate significant restrictive lung disease secondary to musculoskeletal abnormalities such as scoliosis, rib cage abnormalities, and compromised abdominal musculature (Coplen et al, 1996).

Gastrointestinal Abnormalities

In at least 30% of cases, gastrointestinal anomalies are observed. The majority of the anomalies result from incomplete rotation of the midgut, giving way to a wide mesentery, which results in

increased bowel mobility with intestinal malrotation, volvulus, atresias, and stenosis (Silverman and Huang, 1950; Wright et al, 1986). Splenic torsion related to abnormal mesenteric fixation has also been reported (Heydenrych and Du Toit, 1978; Teramoto et al, 1981; Tran et al, 2013). Omphalocele, gastroschisis, and anorectal abnormalities have been reported (Petersen et al, 1972; Morgan et al, 1978; Wilbert et al, 1978; Short et al, 1985; Walker et al, 1987). With a limited ability to generate intra-abdominal pressure, constipation becomes a lifelong problem and leads to acquired megacolon (Woodard and Smith, 1998).

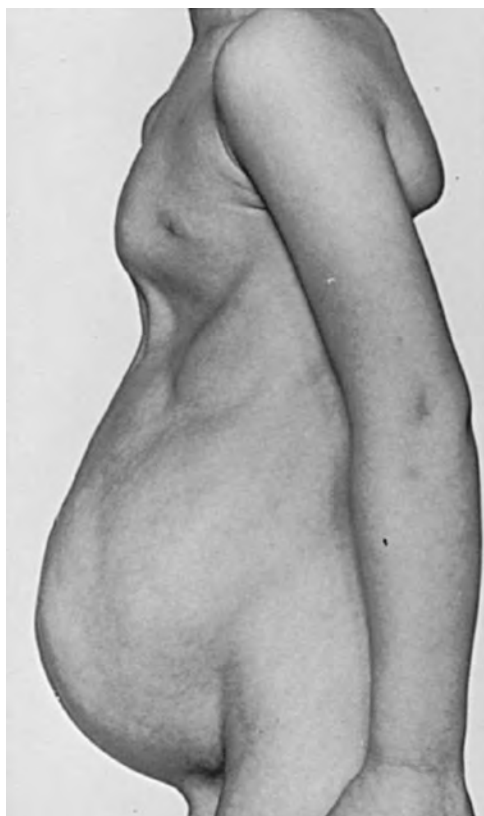


Figure 140-8. Older child with prune-belly syndrome, showing the absence of wrinkling, the “potbelly” appearance, and the consequent deformity of the lower ribs.

Orthopedic

Orthopedic abnormalities, ranging in incidence from 30% to 45%, are second in frequency to those of the genitourinary tract and abdominal wall. Many of these abnormalities result from the compressive effects of oligohydramnios. Some consider the musculoskeletal defects to result from the abnormal mesenchymal development at 6 weeks of gestation (Loder et al, 1992). Green and colleagues (1993), however, pointed out that because many of the deformities are unilateral, oligohydramnios is the most likely etiology. Dimpling of the lateral aspect of the knees is a common finding in oligohydramnios. Oligohydramnios may also result in talipes equinovarus (26%), hip dysplasia (5%), and congenital scoliosis (4%) (Woodard and Smith, 1998). It has been proposed that a distended bladder that may impinge on the external iliac vessels may compromise the blood supply to the lower extremities, and in severely affected cases it may result in lower extremity hypoplasia, absence, or amputation (Smith, 1913; Green et al, 1993).

Oral. There are reports on oral manifestations of the syndrome, including dental and bone abnormalities (Basso et al, 2012; Pessoa and Galvão, 2013).

KEY POINTS: CLINICAL FEATURES

- Hydroureteronephrosis is often present to a severe degree; however, the calyceal morphology may be well preserved.
- The proximal portion of the ureters has more normal muscle than the distal portions.
- The bladder is large with a pseudodiverticulum at the urachus and a wide bladder neck opening into a dilated prostatic urethra.

PRESENTATION

Prenatal Diagnosis and Management

Prenatal ultrasonography has played a major role in the identification of congenital genitourinary abnormalities. Fetal hydronephrosis can be diagnosed accurately in the second trimester and is present in approximately 1% of all pregnancies. However, the etiology of the hydronephrosis cannot be accurately determined in all cases. Elder (1990) estimated that the accuracy of determining the etiology of fetal hydronephrosis varies from 30% to 85%.

In particular, PBS presents prenatally with findings similar to those of other causes of bladder outlet obstruction (Fig. 140-9), as in posterior urethral valves, or megacystis megaureter syndrome (Kramer, 1983). Although an accurate diagnosis of PBS has been made as early as 11 to 14 weeks of gestation (Shimizu



Figure 140-9. Prenatal sonogram of a fetus with prune-belly syndrome. A, Massively dilated bladder that fills most of the abdominal cavity. Note the lack of amniotic fluid. B, The cephalic portion of the bladder reaching the level of both kidneys with hydronephrosis and renal parenchyma noted. C, A dilated bladder with a urachal diverticulum (arrow) and an elongated and dilated posterior urethra. (Courtesy C. Peters.)

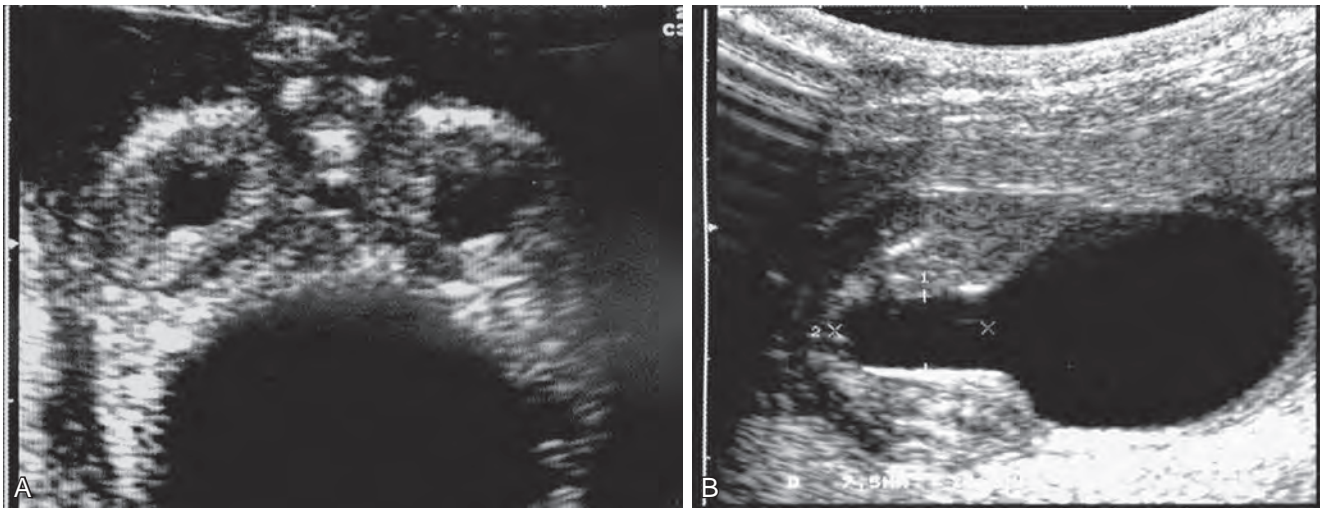


Figure 140-10. A, Fetus with prune-belly syndrome demonstrating distended bladder with hydronephrotic echogenic kidneys. B, Distended bladder with dilated prostatic urethra indicative of outlet obstruction from urethral atresia. (Courtesy E. Ruiz.)

et al, 1992; Yamamoto et al, 2001) (Fig. 140-10), the classic findings of hydronephrosis, a distended bladder, and an irregular abdominal circumference are not consistently seen at 30 weeks (Okulski, 1977; Bovicelli et al, 1980; Christopher et al, 1982; Shih et al, 1982). Early fetal ascites has been suggested to correlate with PBS (Scarborough et al, 1988). It is imperative to remember that the majority of patients with PBS do not experience demonstrable urinary obstruction and that the degree of hydronephrosis does not correlate with the postnatal renal function (Gadziala et al, 1982).

Whereas some have recommended in utero intervention for relief of urinary tract dilation and oligohydramnios (Gadziala et al, 1982; Glazer et al, 1982; Nakayama et al, 1984; Scarborough et al, 1988; Estes and Harrison, 1993; Leeners et al, 2000), others have recommended termination of pregnancy (Pescia et al, 1982). It is difficult to justify the advocacy of pregnancy termination in light of our inability to diagnose precisely the etiology of prenatal hydronephrosis and the inability to predict postnatal renal function on the basis of the degree of urinary tract dilation, except in rare cases of early and severe oligohydramnios. Prenatal intervention has been applied to PBS with no proven benefit in terms of postnatal renal function (Elder et al, 1987; Sholder et al, 1988; Freedman et al, 1999; Biard et al, 2005; Blaicher et al, 2005). The only circumstances in which prenatal intervention may be justified are the rare situations of urethral atresia with progressive oligohydramnios (Steinhardt et al, 1990; Reinberg et al, 1993; Perez-Brayfield et al, 2001) or cases in which decompression of the urinary tract is necessary to prevent dystocia (Gadziala et al, 1982).

Neonatal Presentation

The way that the abdominal wall appears immediately suggests a diagnosis of PBS (see Fig. 140-7) whether or not the diagnosis was suspected prenatally. It should be remembered that other associated abnormalities, such as cardiac or pulmonary, should often take precedence over the urinary tract, because, in the absence of true bladder outlet obstruction as seen with urethral atresia, the hydronephrosis is not life threatening.

Spectrum of Disease

With the number of variable anomalies present in PBS, it is understandable that there is a wide spectrum of clinical presentations. As described by Woodard (1985), there are three major categories of presentation in the neonatal period (Table 140-2).

TABLE 140-2 Spectrum of Prune-Belly Syndrome

CATEGORY	CHARACTERISTICS
I	Renal dysplasia Oligohydramnios Pulmonary hypoplasia Potter features Urethral atresia
II	Full triad features Minimal or unilateral renal dysplasia No pulmonary hypoplasia May progress to renal failure
III	Incomplete or mild triad features Mild to moderate uropathy No renal dysplasia Stable renal function No pulmonary hypoplasia

Category I consists of neonates who have experienced marked oligohydramnios as a result of renal dysplasia or severe bladder outlet obstruction with resultant pulmonary hypoplasia and skeletal abnormalities. Most infants with urethral atresia fall into this category. The exceptions to this are patients with urethral atresia and a patent urachus (Rogers and Ostrow, 1973). Those in this category who are not stillborn commonly succumb within a few days of life to pulmonary hypoplasia or later to renal failure. Approximately 20% of newborns with PBS die in the perinatal period (Woodard and Parrott, 1978b; Burbige et al, 1987; Fallat et al, 1989). It would be unusual for any urologic intervention in this category of patients to alter the course of events. Simple catheter drainage is all that is justifiable.

Category II demonstrates the full spectrum of the disorder with moderate or unilateral renal insufficiency and moderate to severe hydronephrosis. Pulmonary hypoplasia is not a prominent feature of this group of patients. The clinical course is that of stabilization of renal function at or somewhat below normal or progressive azotemia. Significant controversy regarding management exists in this group of patients (Waldbaum and Marshall, 1970; Randolph, 1977; Woodard and Parrott, 1978b).

Category III consists of patients with mild features of the triad or incomplete forms of PBS. This category comprises the majority of PBS patients in whom hydronephrosis is present to some degree but renal function is well maintained (Woodhouse et al, 1982; Woodard, 1998). There is no evidence of pulmonary insufficiency. There is little controversy that urologic intervention in the group is reserved for patients who demonstrate repeated urinary tract infections, probably related to urinary stasis, VUR, or the development of upper tract deterioration (Woodard and Smith, 1998). As previously noted, there is poor correlation between the extent of abdominal wall deficit and the degree of hydronephrosis or renal dysplasia, or both. This is also apparent in other variants of the syndrome. Some children have markedly dilated urinary tracts with minimal or no dysplasia and therefore normal renal function. Therefore the appearance of the abdominal wall or the degree of hydronephrosis may have little bearing on the long-term prognosis of children with PBS.

Incomplete Syndrome

These are male patients who may not have all the features of the triad syndrome but share other features. Most typically, these incomplete forms of the syndrome would lack the typical abdominal wall features but have the common uropathy and cryptorchidism. Many of these patients may eventually experience renal failure and they therefore require close observation, monitoring, and selective intervention. Bellah and colleagues (1996) reported a relatively high (8 of 15) tendency to progressive renal failure in a population of pseudoprune patients. This may be partially attributed to a delay in diagnosis in the absence of the obvious abdominal musculature deficiency and therefore a tendency to present with recurring urinary tract infections (Bellah et al, 1996).

Adult Presentation

Patients with incomplete forms of PBS and those specifically who lack the abdominal wall features may present as late as adulthood with symptoms of renal failure and hypertension (Lee, 1977; Kerbl and Pauer, 1993). Although there have been isolated reports of adults with no history of urinary tract infections, most others who present in adulthood eventually develop urinary tract infections from the chronic urinary stasis associated with the syndrome (Culp and Flocks, 1954).

Female Syndrome

Five percent of PBS patients are female, most of whom have the abdominal wall deficiency and the abnormal urinary tract (Reinberg et al, 1991b). Rabinowitz and Schillinger (1977) reported female patients with the typical abdominal wall deficit and a normal urinary tract. In the series of Reinberg and colleagues (1991b), bladder outlet obstruction was commonly seen along with a 40% occurrence of anorectal anomalies similar to the statistics for the male; 40% did not survive the newborn period.

EVALUATION AND MANAGEMENT

The initial evaluation of the newborn with PBS requires a team consisting of a neonatologist, a nephrologist, and a urologist. As dictated, other specialists may be indicated, particularly a cardiologist. Early orthopedic evaluation is also warranted. The major initial concern is that of management of cardiac and respiratory issues. An immediate chest radiograph is necessary to exclude commonly associated pulmonary abnormalities such as pneumothorax, pneumomediastinum, and pulmonary hypoplasia that is commonly a result of oligohydramnios (Perlman and Levin, 1974). Early urologic intervention is indicated only for neonates with evidence of bladder outlet obstruction, in whom a percutaneous suprapubic tube can be inserted while the newborn is in the neonatal intensive care unit.

Initial evaluation of renal function and the urinary tract status is important but must be tempered by transitional neonatal physiology. Although an initial creatinine level is important in establishing a baseline, it may be more reflective of the mother's renal function, and therefore the trend in creatinine levels throughout the course of the early postnatal days or weeks is much more predictive of long-term renal function.

KEY POINTS: INITIAL MANAGEMENT

- A neonatology, nephrology, and urology team is necessary, including members from other specialties such as cardiology.
- A voiding cystourethrogram (VCUG) is indicated in the neonatal period, only after antibiotic prophylaxis, especially if there remains renal insufficiency or evidence of bladder outlet obstruction.
- A chest radiograph to evaluate for pneumothorax, pneumomediastinum, and pulmonary hypoplasia is necessary.
- Baseline assessment of renal function should include renal and bladder ultrasonography, blood urea nitrogen (BUN), creatinine, and electrolytes.
- Circumcision is advisable in the absence of a structural penile abnormality.
- Early intervention is indicated for evidence of bladder outlet obstruction and preferably with a percutaneous suprapubic tube.

Serum, BUN, and electrolytes are necessary to assess for the potential systemic acidosis and electrolyte imbalances that may be seen in renal insufficiency. It has been shown in multiple reports that a baseline creatinine level less than 0.7 mg/dL is predictive of adequate renal function through childhood, in the absence of repeated insults from pyelonephritis (Geary et al, 1986; Reinberg et al, 1991a; Noh et al, 1999).

Early renal and bladder ultrasonography, after the newborn is stabilized, is necessary to assess the renal parenchyma for its thickness, density, and presence or absence of cortical cysts and degree of urinary tract dilation (see Fig. 140-1).

Avoidance of urinary tract infection is essential in light of the urinary stasis and often compromised baseline renal function. Circumcision is advisable in the absence of a structural penile abnormality to reduce the risk of infant urinary tract infections. Similarly, prophylactic antibiotic therapy is recommended, especially before urinary tract instrumentation, including the initial VCUG. Although instrumentation without a defined purpose, which may alter management, should be avoided, a VCUG to assess the bladder outlet and bladder emptying ability, especially in the presence of renal insufficiency, is warranted (Woodard and Smith, 1998). The VCUG is necessary in neonates with renal insufficiency to rule out as the etiology bladder outlet obstruction versus urinary stagnation. In up to 70% of children with PBS, VUR is diagnosed (Berdon et al, 1977; Fallat et al, 1989). Any instrumentation should be performed with strict attention to a sterile technique to reduce the risk of inoculation of a static urinary system. One can avoid an early VCUG in the presence of normal renal function and evidence of adequate bladder drainage per urethra or per a patent urachus.

As noted, neonates can be categorized based on their spectrum of disease (see Table 140-1). There is little disagreement on the management of category I PBS patients. There is no evidence that anything beyond supportive care is justifiable; in particular, intervention in the urinary tract is not indicated beyond simple bladder drainage because the results of these interventions cannot be altered (Woodard and Smith, 1998).

At the other end of the spectrum, category III patients rarely require early urologic intervention for the urinary tract because they are in a balanced state of hydronephrosis with good, if not normal, renal function. Children in this category require regular monitoring

of urinary tract dilation (ultrasonography) and renal function (serum creatinine), as well as urinary tract infection. However, their cryptorchidism requires correction during the first year of life. Some of these patients have persistent vesicoureteral reflux that may require surgical treatment on midterm to long-term follow-up, if symptomatic. Others will also benefit from abdominoplasty, as they may have significant flaccidity that persists or worsens during childhood.

Category II patients require individualization of evaluation and management based on the fact that within this category there are variable degrees of severity of each facet of PBS. There is, however, much controversy regarding their management. Evaluation of renal function, renal drainage, or both, is required in those with renal insufficiency. Excretory urography, although providing dramatic images of the urinary tract (see Fig. 140-3), does not provide sufficient information on comparative function. Renal parenchymal function is best assessed by a technetium-99m (^{99m}Tc) dimercaptosuccinic acid renal scan at 4 to 6 weeks of age to prevent difficulties in interpretation related to transitional neonatal physiology. Renal outflow obstruction is best assessed by ^{99m}Tc mercaptoacetyltriglycine, which also provides an assessment of comparative renal function with massive hydronephrosis and resultant stasis. In the presence of poor renal function, assessment of renal outflow obstruction by nuclear scan techniques may be limited; therefore selective use of the Whitaker antegrade perfusion test may help.

Controversies in Management of Category II Prune-Belly Syndrome

Aggressive surgical intervention was initially derived from early observations of the poor prognosis for category II infants as a group. Compilation of the cases reported in the literature between 1950 and 1970 by Waldbaum and Marshall (1970) showed that 86% of the 56 accurately traceable patients had died, with or without surgical intervention. The obvious implication was that a more aggressive approach was necessary to improve the fate of the infant with PBS. With the recognition that infection and progressive renal insufficiency are the factors that most often pose the greatest threat to quality of life and survival, surgical reconstruction to normalize the anatomy and function of the genitourinary tract was advocated. Early retailoring of the urinary system to reduce stasis and to eliminate reflux or obstruction has included ureteral shortening, infolding, and vesicoureteral reimplantation and reduction cystoplasty. Although very rare, eventual dysplastic or hydronephrotic kidneys with severely reduced function may require removal if they are symptomatic. Reconstruction is best delayed until the child is at least 3 months of age to allow for pulmonary maturation. This approach has been successful in achieving anatomic and functional improvement as evidenced by stable radiographic studies, stable creatinine values, and a reduced occurrence of infection (Waldbaum and Marshall, 1970; Jeffs et al, 1977; Woodard and Parrott, 1978b; Randolph et al, 1981b). Early urinary tract reconstruction can be performed in conjunction with orchiopexy, abdominoplasty, and circumcision, without increasing the morbidity of the procedure. In one of our personal reconstructive experiences (E.T.D.), 34 patients who have undergone urinary tract reconstruction have maintained normal creatinine levels, whereas four demonstrated moderate to severe renal insufficiency and two required renal transplantation, in a follow-up ranging from 1 to 27 years.

An alternative approach to limited surgical intervention has also been applied. Proponents advocate close surveillance with medical management of bacteriuria and surgical intervention only in patients with proven obstruction or intractable infection. Opinions vary about the management of VUR in the PBS population, although there is no reason to believe that reflux in this population is any less important, and correction of high-grade reflux seems prudent. Success with minimal surgical intervention has been reported (Woodhouse et al, 1979; Duckett et al, 1980; Tank and McCoy, 1983; McMullin et al, 1988). Woodhouse and colleagues (1979)

reviewed a series of patients with PBS who were managed conservatively. Nine of these 11 patients, who were monitored from infancy for periods of up to 24 years, remained well except for a few urinary tract infections. They were said to have normal voiding patterns and normal renal function. Thus patients in category III are candidates for this type of management.

The paucity of long-term data for category II patients, the probable variation in assignment of disease severity in treatment groups, and the variable natural history of the disease make comparisons of these retrospective studies difficult. Spontaneous improvement in ureteral appearance and function may occur with normal growth and elongation of the ureters (Duckett et al, 1980). Also, some patients with gross abnormalities of the urinary collecting system have survived for decades without medical attention (Asplund and Laska, 1975; Lee, 1977; Texter and Koontz, 1980). Yet progressive uropathy is also known to occur, and many patients with PBS ultimately require renal transplantation (Reinberg et al, 1989). Controversy will persist regarding category II patients until accurate application of a medical or surgical approach is possible on the basis of distinct clinical features. Dénes and colleagues (2004) emphasize the individualization of care in their 17-year experience with 32 patients.

Surgical Management of the Prune-Belly Syndrome Patient

Surgical management of children with PBS can be divided into three categories: urinary tract reconstruction, abdominal wall reconstruction, and orchidopexy. Urinary tract reconstruction is generally reserved for children with progressive or severe hydroureteronephrosis, recurrent upper tract infections, true obstructive uropathy, and progressive renal failure. Temporary urinary diversion also plays a role in the very young or the very ill child.

Supravesical Urinary Diversion

In certain instances the occurrence of repeated upper tract infections or deterioration of renal function dictates temporary urinary diversion. Although cutaneous vesicostomy usually provides adequate upper tract drainage and decompression, in rare instances more proximal diversion is indicated because of ureteropelvic or ureterovesical junction obstruction. Here a cutaneous pyeloplasty is advocated rather than proximal ureterostomy because it provides the best upper tract drainage and avoids sacrificing a normal proximal ureter that might be useful in later reconstruction.

Cutaneous Vesicostomy

Urinary diversion may be necessary as a temporary measure in children with acute renal failure, urinary sepsis, or bladder outlet obstruction from urethral atresia with limited patency of the urachus (Fig. 140-11) (Teramoto et al, 1981; Joseph, 1999). When temporary urinary diversion is indicated, a cutaneous vesicostomy is the procedure of choice. This is best performed by the Blocksom technique as described by Duckett (1974, 1986) and colleagues. If there is a large urachal diverticulum, it can be excised at that time. It is advisable to create a larger than normal stoma in the PBS patient because stenosis is common, probably because of the decreased intra-abdominal pressure (Snow and Duckett, 1987).

Internal Urethrotomy

The normal resistance of the urinary sphincter has been implicated in "unbalanced" urethrovesical function contributing to large postvoid residuals. Snyder and Cukier proposed lowering urethral resistance by internal urethrotomy to improve bladder emptying (Snyder et al, 1976; Cukier, 1977). In patients who were studied by urodynamic flow rate profilometry, improved flow rates with reduced residual urine and improvement in the radiographic appearance of the upper tracts were found (Snyder et al, 1976; Woodhouse et al, 1979). Although sustained long-term success has not been demonstrated, internal urethrotomy can be considered in PBS children

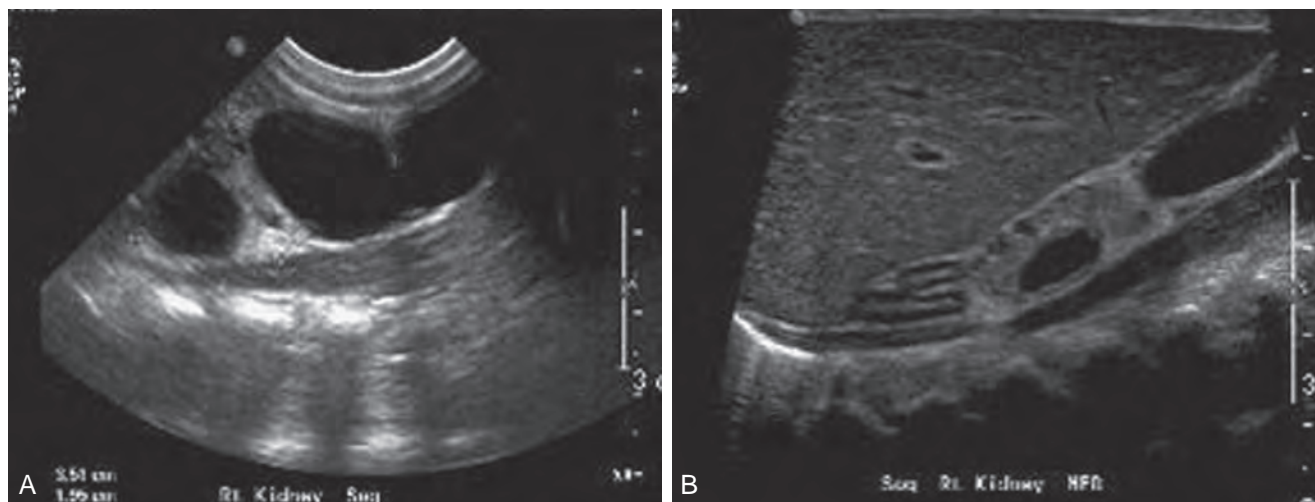


Figure 140-11. A, Prevesicostomy ultrasonography of the right kidney demonstrating massive hydronephrosis with echogenic parenchyma. B, Postvesicostomy ultrasonography demonstrating a decompressed kidney with echogenic parenchyma and cortical cysts. (Courtesy C. Peters.)

with high postvoid residuals, increasing hydroureteronephrosis, or VUR with recurrent upper tract infections. Williams (1979) advocated using an Otis urethrotome achieving a No. 24-Fr to 30-Fr caliber with one or two incisions made anteriorly or anterolaterally; however, direct visual urethrotomy would seem preferable and should be performed at the distal end of the prostatic urethra (Smith and Woodard, 2002). It is interesting to note that internal urethrotomy does not result in incontinence in this population.

Reduction Cystoplasty

In many PBS patients, poor bladder contractility leads to incomplete and infrequent emptying from the complicating urinary stasis and VUR issues. This leads to the concept of reducing the size of the bladder and remodeling it into a more spherical shape to direct better the contractible forces (Perlmutter, 1976). A variety of approaches have been proposed, from simple excision of the urachal diverticulum to the excision of redundant mucosa with the creation of an overlap between flaps to improve contractibility (Williams and Parker, 1974; Woodard and Trulock, 1986). With time, however, high bladder capacity and residual volumes seem to recur (Bukowski and Perlmutter, 1994). It seems therefore that reduction cystoplasty would be justified only to remove the larger urachal diverticulum or as part of a more extensive internal reconstruction. In some patients, intermittent catheterization through the urethra or through an appendicovesicostomy channel is likely to afford better long-term bladder emptying with reduction of residual urinary volumes until the patient is able to achieve better voiding pressures with age or as a result of abdominoplasty (Joseph, 1999).

Anterior Urethral Dilatation or Reconstruction

Urethral maldevelopment may be present as urethral atresia or hypoplasia (see Fig. 140-4). Patients with this abnormality may survive without any intervention, but they frequently require some form of treatment to improve bladder emptying. Passerini-Glazel and colleagues (1988) reported on progressive gentle urethral dilation with good success. This technique may be used in situ or through and through in cases in which a vesicostomy has been performed (Fig. 140-12). As reported by Reinberg and colleagues (1993), however, urethral dilation is not uniformly successful, and one may require a more formal urethroplasty with skin flaps, grafts, or both. Kajbafzadeh and colleagues (2010) reported significant improvement of the urethral caliber after one to three sessions of hydrodistention in patients with urethral hypoplasia.

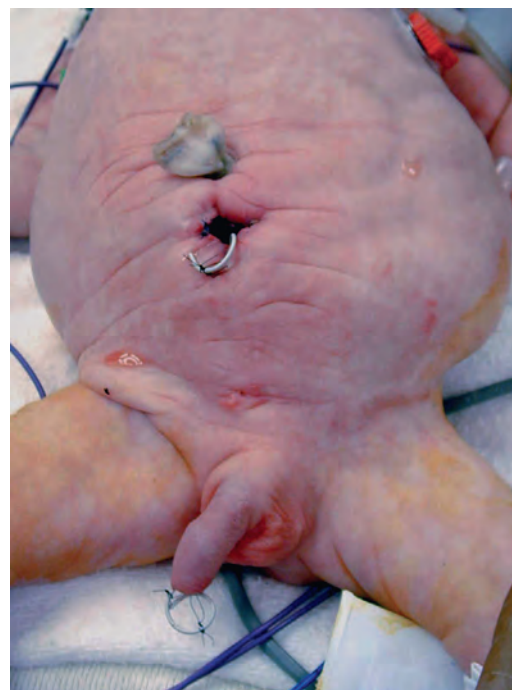


Figure 140-12. Prune-belly syndrome patient with urethral atresia. Note vesicostomy and double-J stent through the urethra for progressive urethral dilation.

Megalourethra in PBS may be either fusiform or scaphoid (Appel et al, 1986). This is best approached with a circumferential subcoronal incision and penile degloving (Fig. 140-13A to F). The redundant urethra can be excised or infolded to provide support, and can be reconstructed over an appropriately sized catheter. Alternatively, some of the urethra can be used to reinforce the urethroplasty because in either form of megalourethra the spongiosum is deficient.

Ureteral Reconstruction

Ureteral remodeling remains controversial. It is best undertaken in children who demonstrated repeated nonsuppressible upper urinary tract infections or in those with progressive upper tract

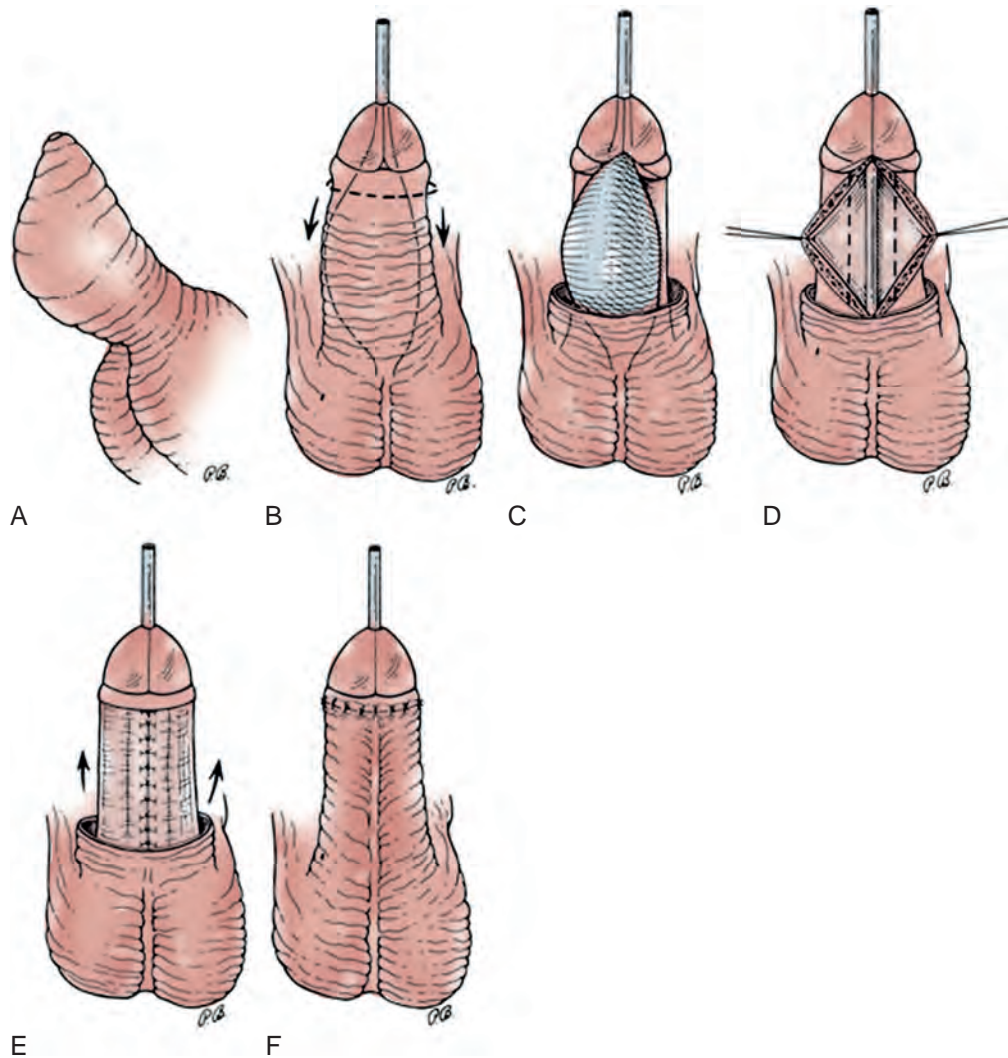


Figure 140-13. Repair of megalourethra. A, The prepuce is reduced, and a circumcising incision is made, preserving a mucosal collar. B, With a catheter in place to assist with identification of the urethra, the penis is degloved along the subdartos plane. C, The involved segment of the urethra is opened longitudinally, and the redundant urethral wall is excised to allow tapering of the urethra over a catheter of appropriate size. D, The urethra is closed with absorbable running sutures and is bolstered with a second layer of sutures placed in an interrupted fashion if possible. E, The penile skin is brought forward, the excess foreskin is removed with a second circumferential incision, and the penile shaft skin is approximated to the mucocutaneous border (F).

deterioration. The goal of remodeling is to reduce urinary stasis. The key to success relies on a meticulous surgical technique and the preservation of the upper few centimeters of proximal ureter, which are less dilated, for reconstruction. Even then, tailoring or infolding of these segments may be necessary for adequate reimplantation into the abnormal bladder. This step can be difficult, in that the creation of a submucosal tunnel can be challenging (Woodard and Trulock, 1986).

In cases with associated secondary ureteropelvic junction obstruction, proximal ureterolysis without compromising ureteral vascularization may decompress the renal pelvis. In those with true mechanical obstruction, a nondismembered ureteropyelostomy between the dilated pelvis and a normal upper ureteral segment might normalize urinary drainage.

Woodard and his colleagues have demonstrated excellent success in this population when these procedures were performed in the neonatal period or in the older child (Woodard and Parrott, 1978b; Woodard and Zucker, 1990). They no longer, however, recommend such extensive reconstructive surgery before the age of 3 to 6

months. Fallat and colleagues (1989), as well as Dénes and colleagues (2004), have reported excellent results of extensive surgery including the reconstruction of the upper and lower urinary tracts, abdominoplasty, and orchiopexy in a single procedure in large groups of patients; both of these surgeons have more than 17 years' experience.

Orchidopexy

The timing of orchidopexy is dictated by our current understanding of the need for early treatment of the undescended testis in non-PBS patients along with individual PBS patients' needs for either temporary or reconstructive surgery. Although it is known that the fertility potential of the PBS patient is compromised, germ cells are present in the testes of infants with PBS. In addition, the prognosis for normal hormonal function at puberty is excellent. These factors, along with the potential risk for testicular carcinoma (Uehling et al, 1984; Massad et al, 1991), would justify early orchidopexy. Because the testes are uniformly located in the abdomen, most commonly

KEY POINTS: SURGICAL RECONSTRUCTION

- Upper urinary tract reconstruction is controversial but clearly indicated for evidence of declining renal function in the presence of hydronephrosis, recurrent upper tract infections, or progression of the hydronephrosis.
- Orchidopexy is best performed early in life because this affords the most likely prospect of a successful single-stage procedure.
- Abdominal wall reconstruction has demonstrated improved bladder emptying, a more effective cough, and improved defecation in addition to psychosocial benefits.
- Comprehensive surgery that includes all of the abovementioned points, as well as circumcision, are feasible in most patients.

on a broad mesorchium overlying the iliac vessels (Coplen et al, 1996), standard inguinal approaches are not usually successful in achieving a satisfactory scrotal position. Four alternative approaches may be considered.

Transabdominal Orchidopexy. Woodard, Parrott, and other researchers noted that if an orchidopexy is performed in the neonatal period and up to 6 months of age using a transabdominal approach, adequate spermatic vessel mobilization can usually be achieved for scrotal placement (Woodard and Parrott, 1978a, 1978b; Randolph et al, 1981a; Fallat et al, 1989). Transabdominal bilateral orchidopexy at about 6 months of age is currently considered the approach of choice (Fig. 140-14). This approach is often used in conjunction with other abdominal surgeries, such as vesicostomy, urinary tract reconstruction, or abdominal wall reconstruction. In the absence of the need for other abdominal surgeries, this procedure can be accomplished laparoscopically (Philip et al, 2011).

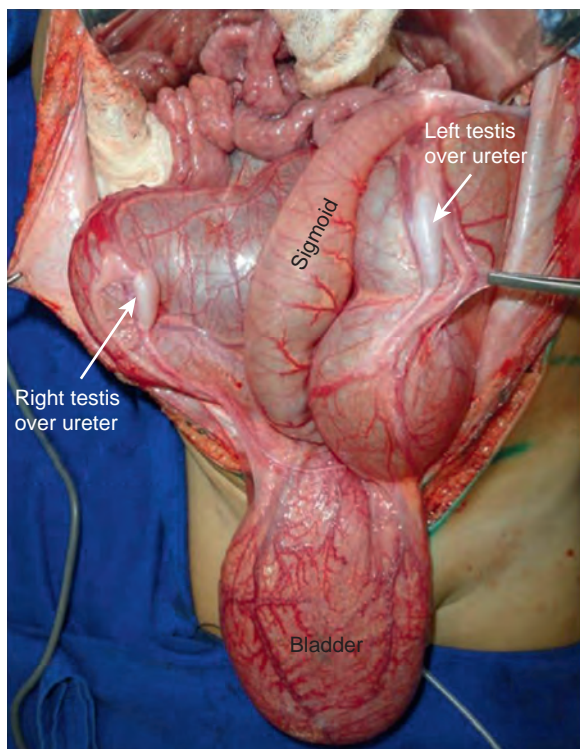


Figure 140-14. Intra-abdominal testes (arrows) overlying massively dilated ureters.

Spermatic Vessel Ligation. When successful transabdominal orchidopexy cannot be accomplished in the first few months of life, other options that may be considered include (1) Fowler-Stephens orchidopexy (Fowler and Stephens, 1959; Gibbons et al, 1979; Boddy et al, 1991; Kirsch et al, 1998), (2) staged Fowler-Stephens orchidopexy (Fig. 140-15) (Ransley et al, 1984; Bloom, 1991; Caldamone and Amaral, 1994; Docimo, 1995; Yu et al, 1995), and (3) microvascular autotransplantation (MacMahon et al, 1976; Wacksman et al, 1980; Boddy et al, 1991). A meta-analysis report by Docimo (1995) indicated comparative success rates of 67% and 77% for standard and staged Fowler-Stephens techniques, respectively. In a multi-institutional report of laparoscopic orchidopexy, Baker and colleagues (2001) noted a success rate of 81% for a standard Fowler-Stephens approach compared with 90% for a staged approach. In a long-term follow-up report, Patil and colleagues (2004) reported a satisfactory outcome for PBS with a one- or two-stage Fowler-Stephens orchidopexy. Some authors have recommended several technical adjustments during laparoscopic orchidopexy in children with PBS, particularly port placement, because there is little resistance to cannula placement in these children (Saxena and Brinkmann, 2007).

Reconstruction of the Abdominal Wall

Children with mild degrees of abdominal muscular deficiency may show improvement in the abdominal wall laxity as they mature. However, most others with moderate to severe degrees of abdominal wall laxity are left with a potentially psychologically crippling defect (Ehrlich et al, 1986; Parrott and Woodard, 1992). An elasticized corset can improve the external appearance when the wearer is fully clothed; however, the corset is inconvenient to use. There is general agreement about the cosmetic benefit of abdominal wall reconstruction. However, whether or not it improves bladder, bowel, and pulmonary function is controversial (Smith et al, 1998; Woodard, 1998). Smith and colleagues demonstrated improved bladder emptying following abdominal wall reconstruction; however, some of their reconstructed patients underwent concomitant urinary tract remodeling as well. Potential effects include a more effective cough and improvement in defecation. The timing of abdominal wall reconstruction should be dictated by the need for other surgical interventions, particularly if upper urinary tract remodeling is necessary. If upper tract remodeling is not anticipated, the abdominal wall can be addressed at any time and has been undertaken in patients as young as 6 months of age along with transabdominal orchidopexy (Smith and Woodard, 2002). If the procedure is done in infancy, however, one must be prepared to place the infant on a respirator postoperatively for a period of time. The following techniques have been described:

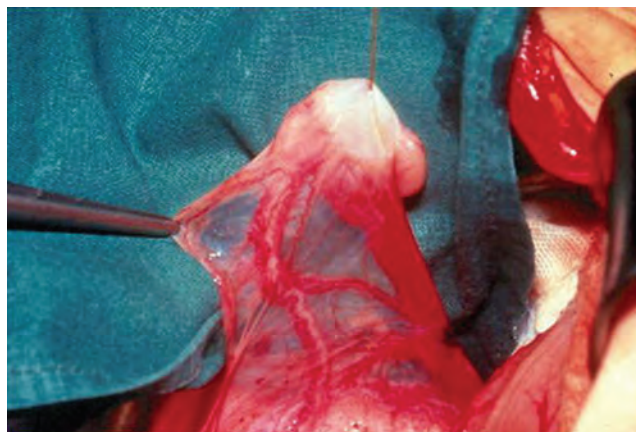


Figure 140-15. Operative photograph showing increased vascularity along vas deferens 4 months after first-stage Fowler-Stephens orchidopexy.

Randolph Technique

Randolph and colleagues (1981a) first popularized a technique for abdominal wall reconstruction based on electromyographic mapping, which indicated that the most severely affected area of the abdomen includes the infraumbilical regions, and the lateral and supraumbilical regions are generally least affected. This technique makes a transverse incision from the 12th rib to the pubic symphysis to the opposite 12th rib with a full-thickness removal of the skin, lower abdominal musculature, and peritoneum. The healthy fascia is then approximated to the anterior iliac spines, pubic tubercle, and inferior fascia. Although this technique is successful in establishing a waistline, lateral abdominal bulging often persists. Of the 16 patients reported, nine experienced excellent cosmetic results, and there was some residual protuberance in seven (Fallat et al, 1989).

Ehrlich Technique

The technique described by Ehrlich used a vertical midline incision and allowed the preservation of the umbilicus on a vascular pedicle

from the inferior epigastric artery (Ehrlich et al, 1986; Ehrlich and Lesavoy, 1993). The skin and subcutaneous tissues are elevated off the muscle and fascial layers, and an overlapping, vest-over-pants advancement of each side to the contralateral flank is performed, preserving the less affected lateral muscles and fascia. Excellent long-term follow-up of this technique has been reported (Lesavoy et al, 2012).

Monfort Technique

Monfort described a technique that is vertically oriented similar to that of Ehrlich's approach; however, an elliptically oriented incision is used to isolate the redundant skin (Monfort et al, 1991). The incision extends from the tip of the xiphoid to the pubis. A second incision is made around the umbilicus to preserve it in situ (Fig. 140-16A to J). The skin and subcutaneous tissue are dissected off the attenuated fascia and muscle with the dissection extending laterally to the anterior axillary line. Vertical fascial incisions are made lateral to the superior epigastric arteries, leaving a central fascial bridge. If intra-abdominal surgery is necessary, excellent exposure to the urinary tract or abdominal testes is afforded through these lateral fascial

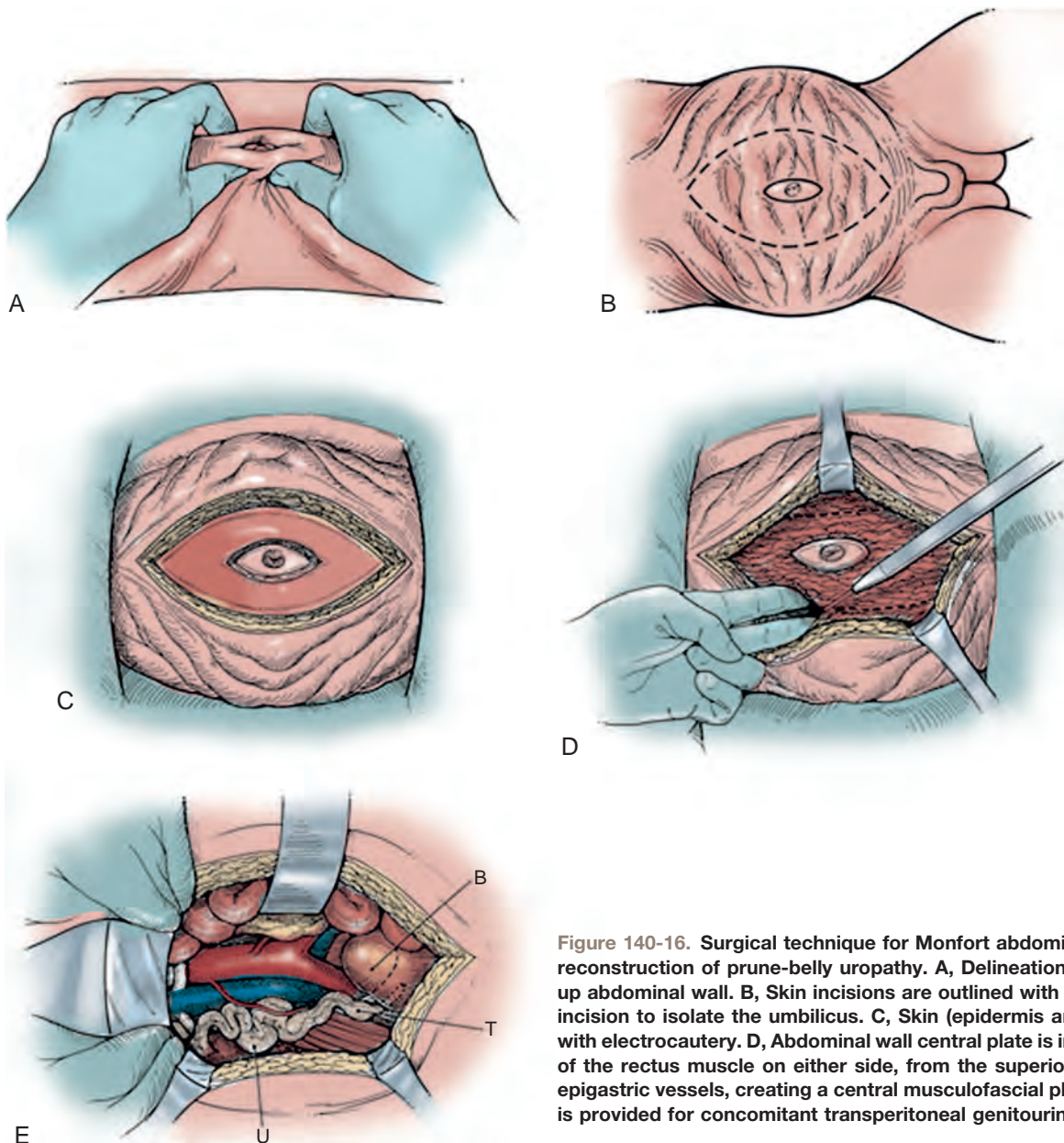


Figure 140-16. Surgical technique for Monfort abdominoplasty and concomitant reconstruction of prune-belly uropathy. A, Delineation of redundancy by tenting up abdominal wall. B, Skin incisions are outlined with a separate circumscribing incision to isolate the umbilicus. C, Skin (epidermis and dermis only) is excised with electrocautery. D, Abdominal wall central plate is incised at the lateral border of the rectus muscle on either side, from the superior epigastric to the inferior epigastric vessels, creating a central musculofascial plate. E, Adequate exposure is provided for concomitant transperitoneal genitourinary procedures.

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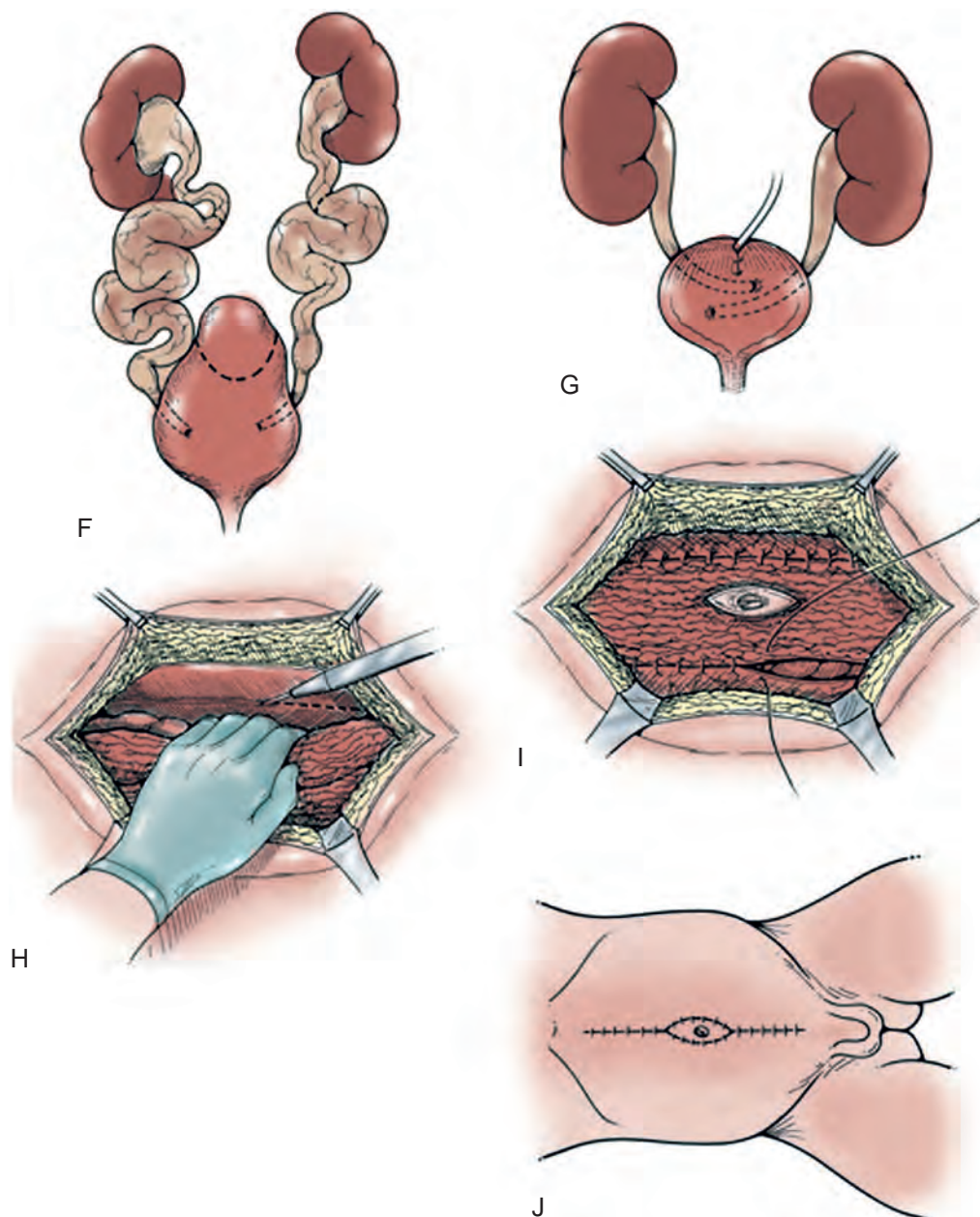


Figure 140-16, cont'd F, Only the more normal proximal ureter is preserved for vesicoureteral reimplantation, and the urachal diverticulum is excised. G, Transtrigonal ureteral reimplantation is performed with or without ureteral tapering as needed. The bladder is closed in two layers, and ureteral stents (not shown) and a cystostomy tube are used. H, Completion of abdominoplasty by scoring of the parietal peritoneum overlying the lateral abdominal wall musculature with electrocautery. I, The edges of the central plate are sutured to the lateral abdominal wall musculature along the scored line. J, Lateral flaps are brought together in the midline, with closed suction drains placed between the lateral flaps and the central plate. Skin is brought together in the midline, enveloping the previously isolated umbilicus. B, bladder; T, testis; U, ureter. (From Woodard JR, Perez LM. Prune-belly syndrome. In: Marshall FF, editor. Operative urology. Philadelphia: Saunders; 1996.)

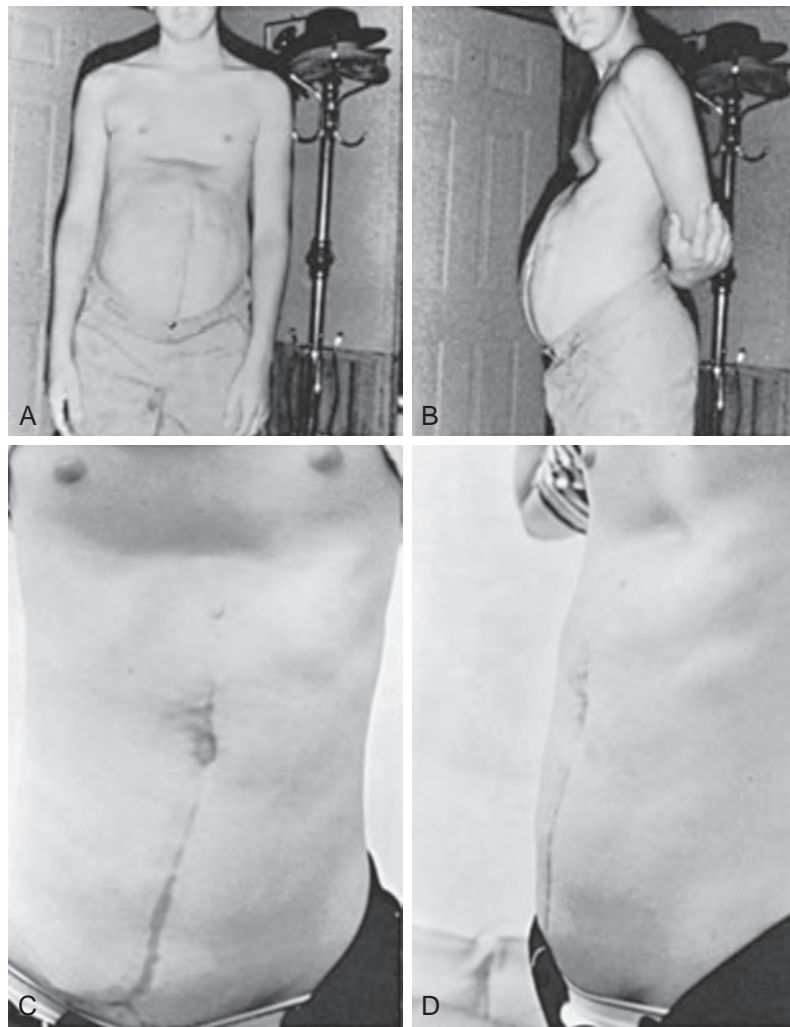


Figure 140-17. A and B, Anterior and lateral views of the abdomen of a 14-year-old boy who underwent major surgical remodeling of the urinary tract during early infancy with good results. Note typical abdominal configuration. C and D, Anterior and lateral views of the same boy 1 month after undergoing abdominoplasty with the technique described by Monfort.

incisions. The lateral fascial is then advanced over the central fascial bridge from both sides, alleviating the redundancy and increasing the thickness of the abdominal wall (Fig. 140-17).

A modification of the Ehrlich and Monfort technique was reported, in which, after the fusiform longitudinal resection of the midabdominal skin and subcutaneous tissue with preservation of the musculoaponeurotic fascia and umbilicus, one elliptical xiphopubic incision is made in the more flaccid side of the fascia, producing one wide and one narrow fascial flap, with the umbilicus being kept intact in the wide flap. Closure is made by suturing the wide flap laterally to the inner side of the narrow flap, followed by a vest-over-pants suture of this flap over the wide, now “inner” flap, with a buttonhole exposing the umbilicus, which is then fixed in place. After slight undermining of the skin edges, they are approximated and sutured with the incorporation of the umbilicus (Dénes et al, 2014) (Figs. 140-18, 140-19, and 140-20).

Furness and colleagues (1998) described a modified midline approach with less abdominal wall dissection, which avoids entering the peritoneum and which may be useful if intra-abdominal surgery is not planned. A modification of the Monfort technique uses laparoscopy to protect the abdominal contents (Franco, 2005).

LONG-TERM OUTLOOK

The nadir creatinine value during infancy has proven useful as a predictor of long-term renal function. If the nadir value is less than 0.7 mg/dL, renal function tends to be stable during childhood unless there is further renal compromise by pyelonephritis (Geary et al, 1986; Reinberg et al, 1991b; Noh et al, 1999). The importance of urinary tract monitoring by periodic cultures and prompt treatment of urinary tract infections cannot be overemphasized. Unfortunately the risk of infection is constant in the setting of urinary tract dilation and stasis. Up to 30% of patients, generally those with impaired renal function at initial evaluation, develop chronic renal failure during childhood or adolescence (Geary et al, 1986). Renal transplantation is necessary for these patients to ensure normal growth and development, and success with transplantation in PBS patients can be expected to equal that in other age-matched groups (Reinberg et al, 1989). Fusaro and colleagues (2004) have published a report of five boys with PBS who underwent renal transplantation. The 5-year graft survival rate was 66.7%, with all patients maintaining their native urinary tracts. Normal growth can be expected in most of the patients with normal renal function, although growth retardation in the absence of renal compromise

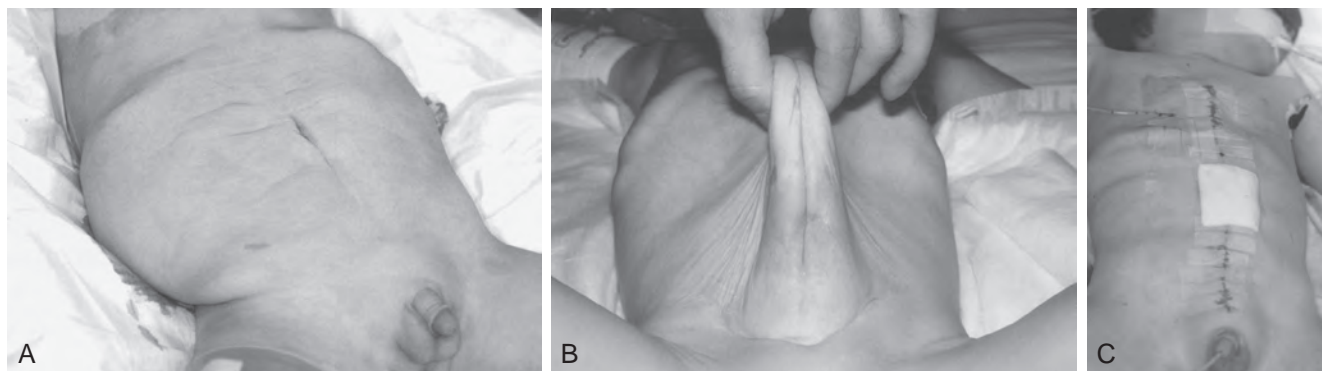


Figure 140-18. Prune-belly syndrome patient demonstrating preoperative appearance of abdominal wall (A), estimated extent of abdominal wall resection (B), and immediate postoperative appearance (C).

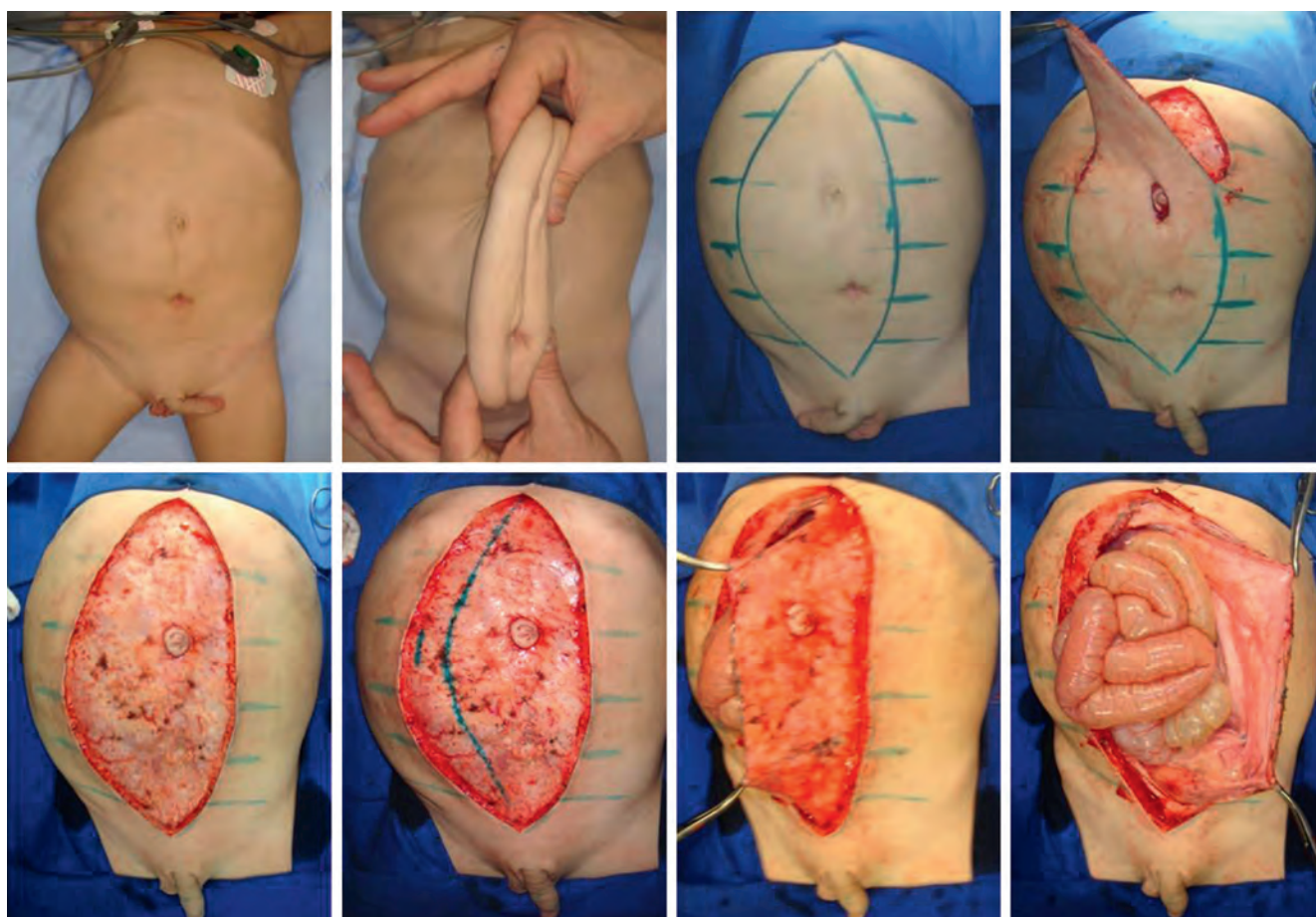


Figure 140-19. Abdominoplasty: elliptical excision of skin and subcutaneous tissue with preservation of umbilicus. An eccentric elliptical incision of the musculoaponeurotic fascia is made on the more flaccid side, creating broad and narrow flaps.

was observed in one third of patients in one series (Geary et al, 1986). A normal pattern of secondary sexual development can be expected (Woodhouse and Snyder, 1985). Although primary fertility is not expected in the PBS population, fertility with assisted reproductive techniques may be feasible for those experiencing successful early orchidopexy.

The overall outlook for the PBS patient, both for survival and for quality of care, has improved considerably, largely through advances in medical, surgical, and urodynamic management. However, despite these advances in care for children of PBS, there continues to be a high

perinatal mortality rate, largely resulting from associated prematurity and pulmonary complications (Routh et al, 2010). The key to management of the PBS patient is individualization of care, because some require major urologic reconstruction, and others require little if any reconstruction. Long-term surveillance of the urinary tract is essential because functional dynamics can change with time.

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The complete reference list is available online at www.expertconsult.com.



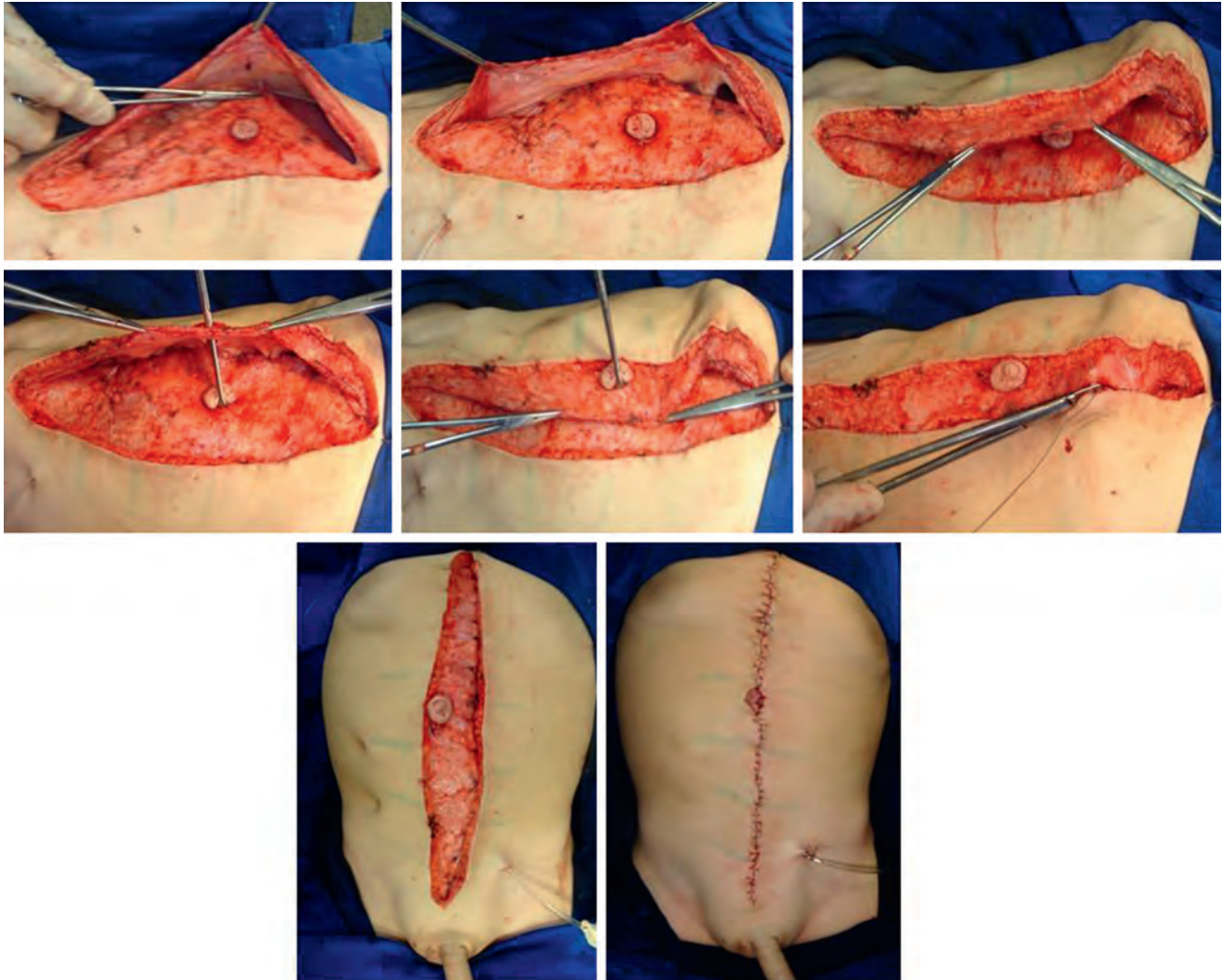


Figure 140-20. Abdominoplasty closure: suturing of broad flap to inner side of narrow flap, followed by a pants-over-vest fixation of narrow flap over broad flap (now inner flap), with a buttonhole for umbilicus.

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Description

Epidemiology

Pathophysiology of Posterior Urethral Valves

Diagnosis

Clinical Presentation and Initial Management

Surgical Intervention

Management of Vesicoureteral Reflux

Bladder Dysfunction and Valve Bladder Syndrome

Antenatal Management

Prognostic Indicators for Renal Function

Transplantation in Posterior Urethral Valve Patients

Quality of Life with Posterior Urethral Valves

Other Urethral Anomalies

Few afflictions of the newborn male share the irony of a relatively simple diagnosis and initial surgical intervention but significant long-term consequences characteristic of posterior urethral valves. As the most common cause of bladder outlet obstruction in infants, the presentation of posterior urethral valves is often antenatal, and pathognomonic findings on postnatal imaging confirm the diagnosis. Although an endoscopic ablation or urinary diversion will address the immediate uropathy, the embryologic insults to the bladder and kidneys manifest to varying extents, requiring that these boys remain under the extended care of urologists and nephrologists.

DESCRIPTION

A congenital obstruction of the posterior urethra ascribed to valve-like leaflets was recognized as early as 1769 by Morgagni, then confirmed by Langenbeck in 1802, both based on postmortem dissections. It was Hugh Hampton Young, however, who described the first endoscopic diagnosis of a urethral obstruction that was termed *posterior urethral valves* (Young et al, 1919). Despite the rudimentary nature of the early endoscopic instruments, Randall carried out the first endoscopic resection of valves in 1920, providing a description that remarkably encapsulates the visual findings of the posterior urethra even today:

The prostatic urethra is markedly dilated. The vesical neck raised and bladder orifice relaxed. Deep pittings penetrate down into either lateral wall of the prostatic urethra and at the extremity the verumontanum is seen a fine frenulum which extends distally for about 1 cm, and in dividing, forms what is apparently a definite valve on either side of the urethra, rising from the floor to each side wall. (Randall, 1921)

Young and colleagues (1919) were the first to propose a classification system for the lesion, based on an initial 12 patients, that remains a widely used contemporary nomenclature (Fig. 141-1). The type 1 lesion, pertinent to 95% of cases, is theorized as a hypertrophied variant of the inferior urethral crest formed by the insertion of the distal ends of the wolffian ducts into the anterolateral walls of the cloaca (Stephens, 1983). The urethral valves are actually leaflets that arise from the verumontanum, take an

anterior course, and then fuse in the midline just proximal to the external striated urethral sphincter. Some argue that the cleft seen in the midline—the “two forklike processes” as Young and coworkers described, or the leaflets fanning out from the verumontanum—are actually iatrogenic and created by retrograde instrumentation in the perinatal period (Dewan et al, 1994).

The type 2 valve of Young and colleagues, described as arising from the verumontanum and extending posteriorly and superiorly to the bladder neck, is not obstructing and has not been reported definitively since early reports. Stephens (1983) reported seeing no type 2 valves in 210 boys with posterior urethral valves examined with cystoscopy and suggested that the description was that of the secondary effects at the bladder neck of more distal obstruction.

The type 3 valve is similarly contentious as a diagnosis, but is most commonly described as an annular ring similar to that seen with a congenital urethral stricture. Young and colleagues (1919) described a complete obstruction “attached to the entire circumference of the urethra, there being a small opening in the center.” The embryologic origin for this variant affecting 5% to 10% of cases of outlet obstruction is thought to be a persistence of the urogenital membrane after the urorectal septum divides the cloacal membrane (Stephens et al, 2002).

A consensus view on the embryologic origins of posterior urethral valves remains elusive, though various mechanisms have been proposed. The earliest theory held that hypertrophy of the urethral mucosal folds was the cause of obstruction, which was furthered later to suggest cloacal remnants caused the appearance of valves after division by the urogenital membrane (Krishnan et al, 2006). Lowsley placed the origin of posterior urethral valves in an abnormal development of the wolffian and müllerian ducts based on an autopsy study in 1914 (Lowsley, 1914), but a more recent autopsy study corroborates the presence of a congenital obstructing posterior urethral membrane, consistent with a persistent oblique urogenital membrane that is punctured at the time of catheter or feeding tube placement by the medical practitioner in the immediate postpartum period (Dewan et al, 1994; Krishnan et al, 2006).

EPIDEMIOLOGY

Congenital anomalies of the urinary tract affect up to 1 in 500 pregnancies, and obstructive uropathy accounts for most of these cases

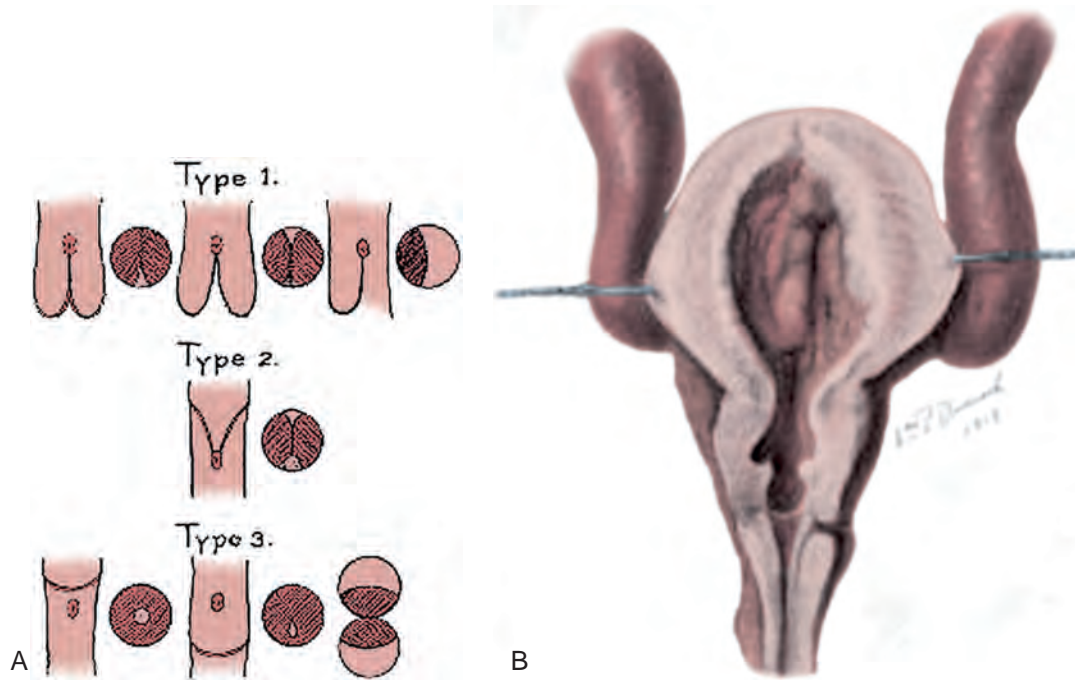


Figure 141-1. A, Young and colleagues' original figures from their 1919 article describing three types of posterior urethral valves. B, Illustration by William P. Didusch of the pathognomonic findings associated with posterior urethral valves: the thickened bladder with elevated bladder neck, the dilated prostatic urethra, and the valve leaflets commonly ascribed to type 1 valves. The ureters are shown to be dilated. (From Young HH, Frontz WA, Baldwin JC. Congenital obstruction of the posterior urethra. *J Urol* 1919;3:289.)

(Lissauer et al, 2007; Ruano, 2011). A large population-based registry study from the United Kingdom demonstrated that lower urinary tract obstruction (LUTO) has an incidence of 2.2 per 10,000 births, of which the most common pathology was posterior urethral valves (1.4 per 10,000 births), followed by urethral atresia and the prune-belly syndrome (Anumba et al, 2005). Since birth incidence requires the often inaccurate count of early spontaneous pregnancy loss, a later study following a similar cohort based in the West Midlands between 1995 and 2007 calculated a prevalence ratio of posterior urethral valves—number of affected births divided by the total number of live and stillbirths—of 2.10 per 10,000 births (Malin et al, 2012). This prevalence was also significantly higher in black and minority ethnic groups when compared with white Europeans.

A review of the Kids' Inpatient Database—a national database of inpatient pediatric hospitalizations in the United States—found 578 newborn males diagnosed with posterior urethral valves between 1997 and 2009. When divided by 10.0 million live male births in hospitals over that interval, this gave a weighted prevalence rate of 1.6 per 10,000 in-hospital live male births (Lloyd et al, 2013).

Considering that the United States alone may expect 300 to 500 new cases of infants with posterior urethral valves born annually—of which one third will go on to end-stage renal failure (Heikkilä et al, 2011)—the economic repercussions in terms of dialysis and renal transplantation arising from this congenital anomaly are enormous.

PATHOPHYSIOLOGY OF POSTERIOR URETHRAL VALVES

Although the initial treatment of posterior urethral valves—cystoscopy and valve ablation—is a relatively simple and reproducible procedure with adequate training, the bladder outlet obstruction during early fetal development creates downstream consequences that afflict an individual, often for a lifetime (Table 141-1). The long-term sequelae of valvular disease can be correlated to bladder dysfunction, renal dysplasia, polyuria, and multiple other anatomic and physiologic factors. Simply put, the bladder exposed to

KEY POINTS: DESCRIPTION AND EPIDEMIOLOGY

- Type 1 valves are the most common variant of posterior urethral valves, and appear as leaflets that arise from the verumontanum and fuse anteriorly just proximal to the external urethral sphincter.
- Type 3 valves present as a congenitally obstructing membrane that is likely perforated at the time of the initial post-natal catheterization.
- The incidence of posterior urethral valves is between 1.6 and 2.1 per 10,000 births.

developmental obstruction becomes hypertrophied, and empties well during the compensated phase. Over time, however, polyuria caused by renal dysplasia and continuing glomerular and tubular damage leaves the bladder without adequate periods of bladder emptying, leading to decompensation. This phase leads to increased bladder residuals that are causally linked to exacerbation of hydronephrosis and further renal damage.

Lower Urinary Tract

It cannot be overstated that the potential comorbidities arising from posterior urethral valves—renal dysfunction, urine reflux, worsening hydronephrosis—are due to bladder dysfunction. Mitchell (1982) coined the term *valve bladder syndrome* when he described 11 patients in whom bladder filling and emptying were noted to be intricately related to extent of renal pelvocaliectasis and overall renal function and dysfunction. This concept was subsequently illustrated as a “vicious cycle” leading to the valve bladder syndrome. Bladder hypertrophy secondary to the fetal obstruction results in higher voiding pressures that maintain complete bladder emptying in the compensated phase. The increased voiding pressures lead to gradual remodeling of the bladder wall, further increasing voiding pressures, and ultimately to higher postvoid residuals as emptying begins to fail. The rise in urine

TABLE 141-1 Damage Caused by Posterior Urethral Valves

ORGAN	EFFECT	NATURAL HISTORY
Lung	Pulmonary hypoplasia	May be fatal in newborns; if infant survives, there are few long-term problems
Kidney		
Glomerular injury		
Obstructive uropathy	Reversible renal insufficiency	Usually improves with initial treatment but can recur with bladder dysfunction
Dysplasia	Irreversible renal insufficiency	Permanent level of renal damage that limits growth; leads to progressive renal failure and hypertension
Tubular injury	Inability to limit sodium and water loss	Progressive with age; nephrogenic diabetes insipidus
Bladder	Poor sensation, hypercontractility, low compliance, and eventual myogenic failure all may contribute to incontinence and poor emptying	Bladder problems are lifelong and change with age
Ureters	Poor contractility and inability to coapt and transport urine	Most will improve initially, but most have chronic hydronephrosis

output with normal growth and development combined with the latent polyuria of existing renal dysplasia and increased glomerular pressure caused by poor bladder emptying conspire to increase urine volumes stored in the upper urinary tract. As this bolus of urine fills the bladder even as the bladder empties partially, a lack of extended periods of an empty, relaxed bladder pushes the compensated bladder toward decompensation. This, of course, leads to even greater postvoid residuals, overflow incontinence, and further renal damage (Close et al, 1997).

The storage and voiding of urine at high pressures has been simulated in fetal sheep and rabbit models in vitro to simulate and then investigate the cascade of events effectuating bladder smooth muscle alterations. Increased bladder dilation is seen following partial bladder outlet obstruction (Kirsch et al, 2003), and the dilated, poorly contracting bladders (simulating the decompensated bladder) lead to more upper tract dilation. Thus increased bladder dilation places the upper urinary tract at risk. This model and the work of other researchers confirmed that extracellular matrix elements line the detrusor smooth muscle cells of the bladder after obstruction—as noted in valve bladders (Workman and Kogan, 1990). Importantly, the pathologically significant elevated storage pressures must be distinguished from the neonatal and infantile elevated voiding pressures that are a normal feature of bladder development (Sillén et al, 1992).

There remains some controversy as to whether the changes in bladder morphology in the valve-affected bladder are reversible, as opposed to the phenotypic changes in neurogenic bladders that are more permanent (Keating, 1994; Hutcheson et al, 2004).

The deposition in the extracellular matrix causes altered contraction and passive relaxation of the bladder, which may cause multiple intracellular changes ranging from a reduction in detrusor blood flow causing ischemia to free radical toxicity. These changes alter the phenotype of detrusor muscle myosin bundles and actin-associated filaments (Ghafar et al, 2002; Shukla et al, 2004; Levin et al, 2005).

The valvular obstruction will also lead to marked dilation of the posterior urethra, hypertrophy of the bladder neck, and a flattening of the verumontanum with dilation of the ejaculatory ducts—the pathognomonic findings of this diagnosis on voiding cystourethrogram (Fig. 141-2 and Fig. 141-3). These changes seem to return to a more normal appearance following valve ablation as the offending distal obstruction is removed.

Upper Urinary Tract

A bladder exposed to posterior urethral valves undergoes a cascade of changes that alter the organ's normal function in storing and emptying urine. This bladder dysfunction manifests in varied ways

during infancy and later, and is discussed in a later section. What is apparent is that a sustained increase in intravesical storage pressures over prolonged time intervals transmits that pressure to the ureter, the renal pelvis, and ultimately the glomerular units—causing architectural and functional changes at each ascending structure (Koff et al, 2002). These architectural changes can be inferred clinically by the severe hydroureteronephrosis that is often seen in the setting of posterior urethral valves. Increased echogenicity, parenchymal thinning with cortical cysts, and lack of corticomedullary differentiation similarly imply significant renal dysplasia (Fig. 141-4A).

Ureteral dilation occurs as a direct transmission of pressure from the dysfunctional bladder, as well as the vesicoureteral reflux that is seen in up to 70% of patients with posterior urethral valves (Puri and Kumar, 1996; Sarhan et al, 2011). Polyuria caused by progressive renal damage and congenital renal dysplasia compound ureteral dilation as well (Smyth et al, 1991). The chronicity of ureteral dilation is classically believed to cause ureteral wall thickening, loss of peristalsis, and loss of mucosal coaptation, increasing the risk of urine stasis, infection, and increased pressures in the renal units (Fig. 141-4B) (Parkhouse et al, 1988; Glassberg, 2001).

The elevated renal pelvic pressures secondary to the bladder and ureteral pressure increases lead to significant alterations in renal morphology and function. The renal dysfunction seen in posterior urethral valves has two specific etiologies: (1) obstructive uropathy and (2) renal dysplasia.

Obstructive uropathy causing renal damage is a well-known phenomenon in various models. Fetal sheep ureteral obstruction models clearly demonstrate that, although hydronephrosis occurs rapidly after obstruction, irreversible dysplastic changes in the renal architecture are seen by term, and these changes were confirmed after outlet obstruction in the same model (Peters et al, 1992; Chevalier, 2004). Apoptosis and increased oxidative stress in mouse kidneys with ureteral obstruction are also seen in the face of bladder outlet obstruction (Kawada et al, 1999; Chevalier, 2004).

The increased pressure from obstruction damages luminal cells in the renal tubules and will also lead to poorly concentrated urine production (Li et al, 2004; Nguyen et al, 2005a). Obstruction may also affect urinary concentration by reducing blood flow to the medulla, causing a loss in the medullary concentration gradient that results in significant polyuria and even in the postobstructive diuresis seen after catheter placement in an infant with posterior urethral valves (Dinneen et al, 1995).

Although some debate whether the entirety of renal damage seen in posterior urethral valves is actually a secondary phenomenon resulting from obstruction, the observation that even early prenatal intervention does not necessarily forestall long-term

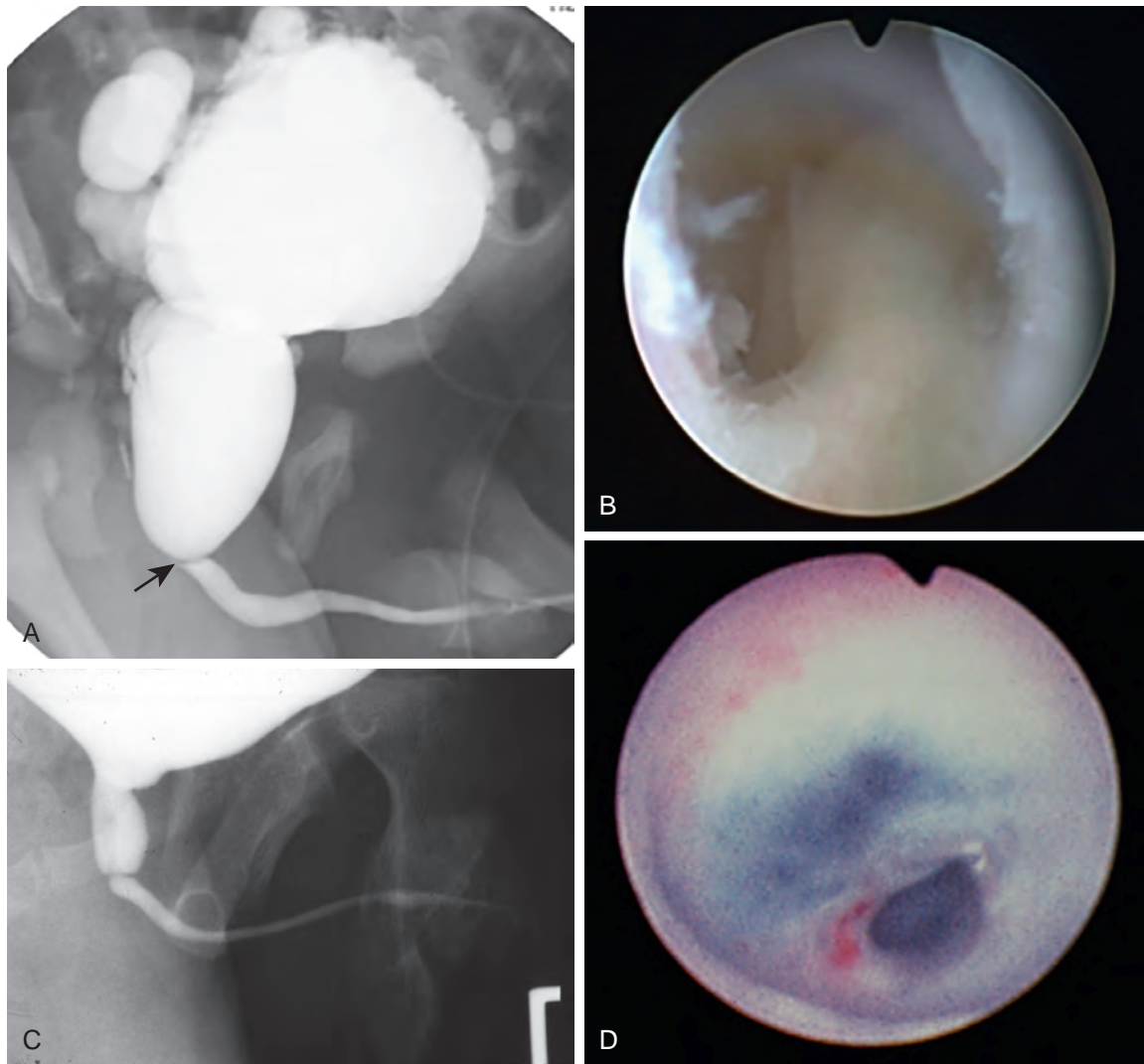


Figure 141-2. A, Voiding cystourethrogram image shows a bladder affected by multiple diverticuli and a dilated posterior urethra narrowing at the site of valvular obstruction. B, Cystoscopic image corresponding to the point of obstruction in A. Arrows indicate valve leaflet that would be fulgurated at the time of valve ablation. The urethral valves are seen as leaflets arising from the verumontanum and fusing in the midline, just proximal to the striated sphincter. The verumontanum is noted just proximal to the valve leaflets. C, Voiding cystourethrogram image shows an elevated bladder neck and dilated posterior urethral funneling to a point of obstructed flow. These are typical radiologic findings of posterior urethral valves. D, Cystoscopic image corresponding to point of obstruction in C. The concentric narrowing is classically associated with a type 3 valve but is also considered consistent with the congenital obstructing posterior urethral membrane that may have been perforated at the time of initial catheter placement.

renal disease posits that renal dysplasia may be concurrent with—rather than a consequence of—posterior urethral valves (Haecker et al, 2002). Others have demonstrated known primary dysplastic malformations of fetal cartilage tissue or dysplastic glomeruli and tubules in posterior urethral valves that affected renal tissue at the time of nephrectomy (Haecker et al, 2002).

A correlation between severe renal hypodysplasia and decreased activity of the renin-angiotensin system that modulates renal development has been noted in posterior urethral valves, as well as a decrease in the angiotensin receptor type 1 genetic polymorphisms (Peruzzi et al, 2005). Bajpai and associates (2005) found that plasma renin activity increases precede common clinical findings of renal damage such as rising serum creatinine, renal scars, and lowering glomerular filtration rate. Although angiotensin II contributes to renal damage by hemodynamic alterations in glomerular flow, it also induces profibrogenic actions and inflammation through the induction of transforming growth factor- β_1 and tumor necrosis

factor- α (Kagami et al, 1994; Furness et al, 1999; MacRae Dell et al, 2000). These cytokines are considered potential biomarkers that seem to decrease with improvement in renal function after valve ablation, whereas elevations imply worsening outcomes.

Institution of an angiotensin-converting enzyme inhibitor (ACEI) showed therapeutic potential in experimental studies by reducing fibrosis (Yu et al, 2004; Gagliardini and Benigni, 2006), and seemed to reduce expression of biomarkers such as transforming growth factor- β_1 and tumor necrosis factor- α in another clinical study, suggesting a potential role in selected children with posterior urethral valves (Mandelia et al, 2013). Further corroborating the hypothesis that renal damage in valves is due, in part, to dysplasia and not only obstruction is the finding that the *ACE1* gene is expressed significantly more, and the angiotensin receptor gene (*ATR*) less, in patients with posterior urethral valves compared to those with other dysplasias and controls (Peruzzi et al, 2005; Laksmi et al, 2010).

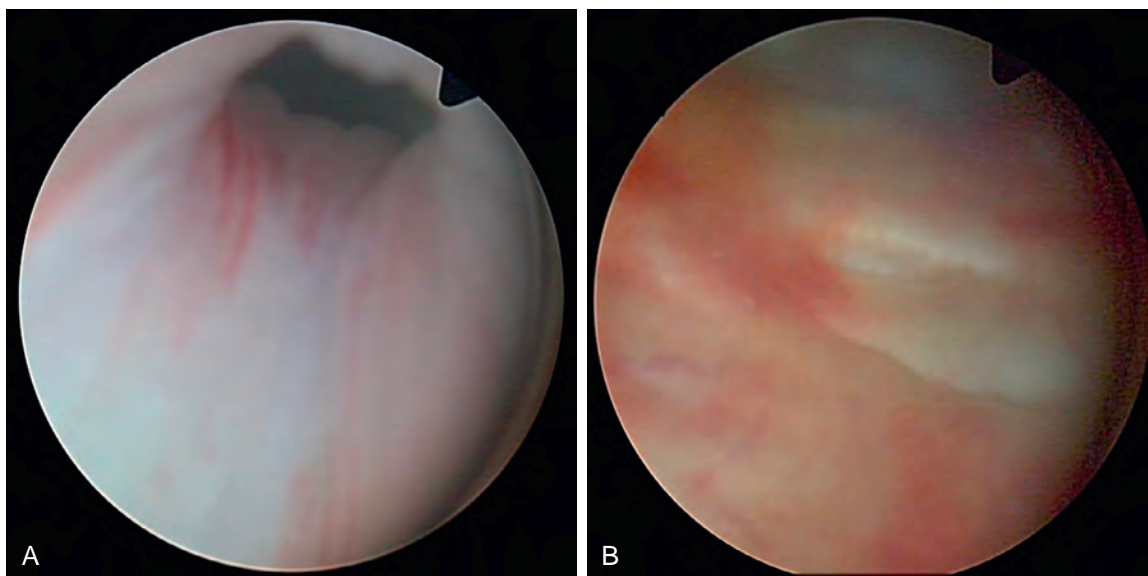


Figure 141-3. Cystoscopic views in an infant with posterior urethral valves of (A) elevated bladder neck and (B) trabeculations in affected bladder consistent with obstructive uropathy.

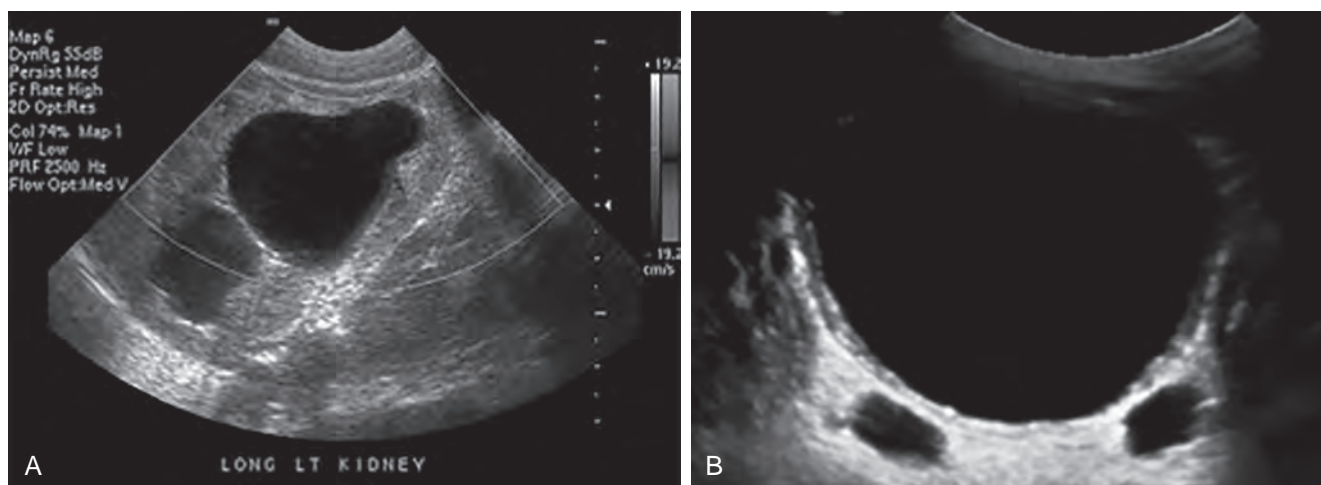


Figure 141-4. A, Left renal sonogram in a newborn with posterior urethral valves shows severe pelvocaliectasis with thinning of the parenchyma with increased echogenicity and loss of corticomedullary differentiation. B, Pelvic view of same patient, not yet catheterized, shows a distended bladder with dilation of bilateral distal ureters.

Vesicoureteral Reflux and Dysplasia

Hoover and Duckett (1982) observed that the high-grade vesicoureteral reflux seen in children with posterior urethral valves was usually into an ipsilateral poorly functioning renal unit, whereas the contralateral renal unit appeared to have preserved renal function (Fig. 141-5). They hypothesized that the reflux served as a pop-off mechanism in which the dysplastic kidney with reflux served as a pressure reservoir mitigating damage to the contralateral kidney, and coined the term *vesicoureteral reflux and dysplasia* (VURD). This relationship, in that original series, was found in 13% of patients with posterior urethral valves, and the theory that these children would have better long-term renal function as a result of the pop-off phenomenon was widely accepted.

Longer-term studies have confirmed, however, that the VURD syndrome does not improve renal prognosis. Fifteen years after the VURD syndrome was first described, Cuckow and colleagues (1997) found that, whereas 67% of patients affected by VURD during year 2 of life had a normal serum creatinine, only 30% of these children had normal values between ages 8 and 10 years. The glomerular filtration rate, importantly, was already abnormal in

75% of these same patients even in the first 2 years of life. Another observation that even the contralateral, nonrefluxing renal unit in VURD patients carries a high risk of congenital renal cortical damage—implying poorer long-term prognosis—means that VURD should never be allowed to create a false sense of security, and close follow-up as with any other cohort with posterior urethral valves is mandatory (Narasimhan et al, 2005).

KEY POINTS: PATHOPHYSIOLOGY OF POSTERIOR URETHRAL VALVES

- The renal dysfunction, vesicoureteral reflux, and voiding dysfunction seen in children with posterior urethral valves are mediated by a dysfunctional bladder.
- Renal impairment in posterior urethral valve patients is due to renal dysplasia and obstructive uropathy.
- The VURD syndrome confers no protective benefit on long-term renal prognosis.



Figure 141-5. Massive, dilating vesicoureteral reflux is seen on the left side on this voiding cystourethrogram and, in this case, is typically associated with a poorly functioning kidney on the ipsilateral side, referred to as the vesicoureteral reflux with dysplasia syndrome.

DIAGNOSIS

Ultrasonography

With widespread access to antenatal sonography, posterior urethral valves and other LUTOs such as urethral atresia or stenosis are increasingly detected during the fetal period. Posterior urethral valves are detected in approximately 1 in 1250 ultrasound screenings, accounting for 10% of significant antenatally detected genitourinary disease and afflicting one third of surviving infants with bilateral renal disease (Thomas and Gordon, 1989; Gunn et al, 1995). The pathognomonic ultrasound findings of a thickened, dilated bladder along with bilateral hydroureter and pelvocaliectasis do carry a high sensitivity (95%) and specificity (80%), and oligohydramnios and the dilated posterior urethra displaying the “keyhole sign” further corroborate the presence of LUTO (Figs. 141-6 and 141-7) (Peters, 1998; Robyr et al, 2005). Renal echogenicity will be increased in posterior urethral valves, and is a reliable indicator to infer renal damage as well.

However, although LUTO may be diagnosed prenatally, differentiating valves from urethral atresia or prune-belly syndrome, high-grade vesicoureteral reflux, or bilateral primary obstructing megaureters is much more problematic, reducing the accuracy of diagnosing posterior urethral valves with prenatal sonography alone to as low as 50% (Abbott et al, 1998). Still, the antenatal finding of a thickened, enlarged bladder and bilateral ureterectasis with pelvocaliectasis with or without oligohydramnios in a male infant requires an early postnatal sonogram and voiding cystourethrogram prior to the infant’s discharge from the postpartum unit (Lee et al, 2006; Herndon, 2012; St. Aubin et al, 2013).

Fetal magnetic resonance imaging (MRI) is an adjunct in prenatal diagnosis and increasingly available at major centers. As with ultrasonography, fetal MRI is used to distinguish the degree of obstruction based on urethral dilation, distended bladder size with thickening, and reduced amniotic fluid levels (Fig. 141-8). Lung hypoplasia and cystic changes in renal parenchyma are also appar-

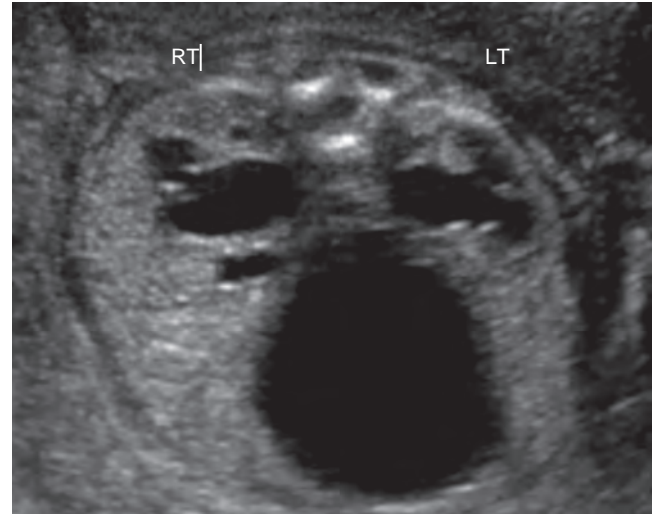


Figure 141-6. Antenatal ultrasound examination demonstrates bilateral severe pelvocaliectasis with dilated bladder in fetus. LT, left kidney; RT, right kidney. (Courtesy Dr. Mark P. Johnson, Children’s Hospital of Philadelphia.)

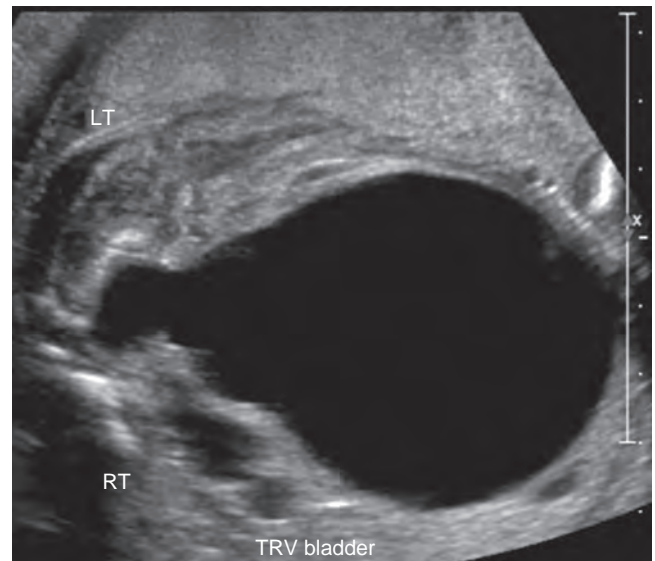


Figure 141-7. Sonogram of fetal bladder shows a thickened bladder with dilated posterior urethra below, suggesting the “keyhole sign.” LT, left kidney; RT, right kidney; TRV, transverse. (Courtesy Dr. Mark P. Johnson, Children’s Hospital of Philadelphia.)

ent on MRI, though the rate of renal dysplasia does not necessarily correlate with micro- or macrocystic changes (Chauvin et al, 2012). One study of fetal MRI in early gestations showed that the modality altered the initial sonographic diagnosis in 30% of the cases (Poutamo et al, 2000). However, although MRI does provide added analysis of causes of obstruction in select cases, the utility of MRI is limited, as with sonography, in diagnosing the actual cause of LUTO (Miller et al, 2002).

Voiding Cystourethrogram

Voiding cystourethrogram (VCUG) remains the definitive radiologic study in confirming the diagnosis of posterior urethral valves. This study should be completed in the early postnatal period after renal and bladder sonography, and as soon as an infant with suspected prenatal findings of valves is hemodynamically stabilized and able to undergo the contrast study.

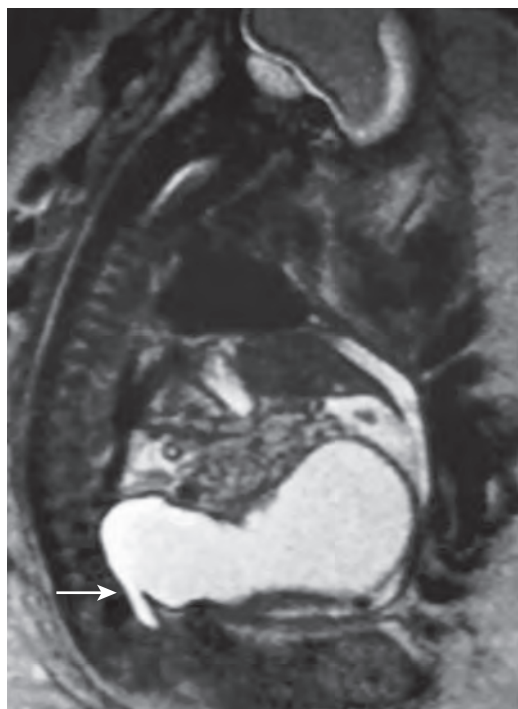


Figure 141-8. Fetal magnetic resonance imaging demonstrating lower urinary tract obstruction that was postnatally diagnosed as posterior urethral valves. A dilated bladder funneling to a visible posterior urethra (arrow) is seen on this T2 image.

The bladder often appears thickened and trabeculated with multiple diverticuli, mimicking the appearance of a neuropathic bladder. High-grade vesicoureteral reflux may be seen in approximately 50% of patients with valves at the time of diagnosis (Hassan et al, 2003). Images obtained during the voiding phase will show contrast traveling across a hypertrophied, elevated bladder neck and grossly dilated posterior urethra (Fig. 141-9). The urethra funnels abruptly at a transverse membrane, or cusp, representing the obstructing valve leaflets seen at cystoscopy. These are the pathognomonic signs for posterior urethral valves.

The study commences with the insertion of a 6- or 8-Fr feeding tube into the urethra. This tube may curl within the capacious posterior urethra or hypertrophied bladder neck, requiring the use of a coude catheter to advance into the bladder. Often a catheter may already be in place at the time of the study, and it is important that the catheter be withdrawn gradually distal to the posterior urethra during the voiding phase of the study to offer unobstructed views of that segment.

Radionuclide Renal Scan

The radionuclide renal scan offers quantification of differential renal function, and cortical deficits seen on the study may imply renal dysplasia when completed in the neonatal period. Mercaptoacetyl triglycine is a useful agent to evaluate renal functional contribution, though delayed emptying of nuclear tracer from the often dilated collecting systems should not be necessarily interpreted as ureterovesical junction obstruction requiring intervention. Placement of a urinary catheter is essential in a patient with vesicoureteral reflux to minimize error in the calculation of renal function.

Laboratory Evaluation

Laboratory evaluation of a newborn with a diagnosis of posterior urethral valves will, as with any newborn, reflect maternal values and must be interpreted with caution. After 48 hours, the maternal blood mediated through the placenta should clear, and the infant's baseline laboratory values may be monitored. The nadir creatinine

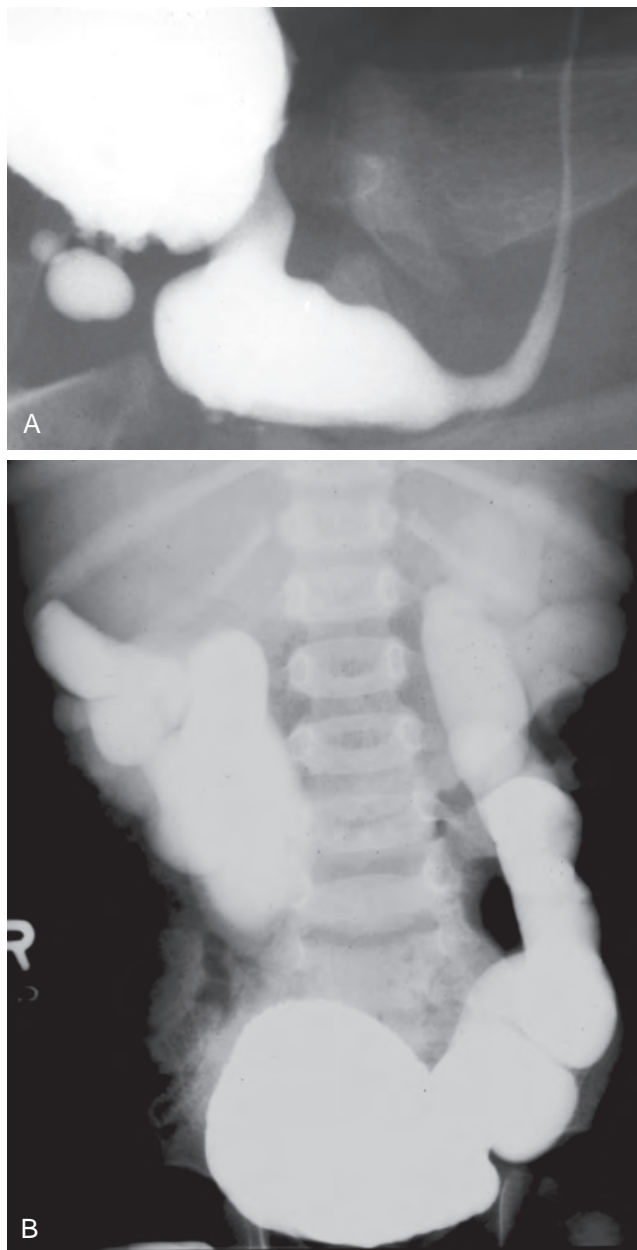


Figure 141-9. A, Voiding cystourethrogram image demonstrates a dysmorphic, elongated bladder with dilated posterior urethra and classic appearance of posterior urethral valves. B, Dilating vesico-ureteral reflux is seen bilaterally.

value at 1 year of age is considered an important diagnostic tool—and this value may be plotted to evaluate immediate response to treatment in the neonatal period. However, the serum creatinine plateau even in unaffected children may not be seen until days 65 to 220 of life (DeFoor et al, 2008, Boer et al, 2010).

CLINICAL PRESENTATION AND INITIAL MANAGEMENT

An infant affected by posterior urethral valves may be affected by serious comorbidities such as pulmonary hypoplasia and physical stigmata of oligohydramnios, including Potter facies, clubfeet and deformed hands, and poor abdominal muscle tone, and require intensive initial management. The infant may be noted to have difficulty with voiding, and the urinary stream may be weak or intermittent. A 5- or 7-Fr feeding tube, or similar caliber urinary catheter, should be inserted per urethra in an infant presenting to the

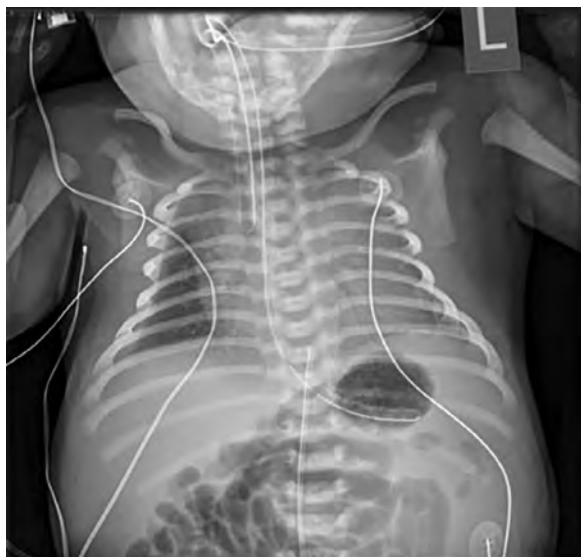


Figure 141-10. Plain radiograph of a 5-day-old infant with posterior urethral valves and bronchopulmonary dysplasia, requiring airway support, shows reduced lung volume and left upper and lower lobe atelectasis.

neonatal intensive care unit with a presumed diagnosis of LUTO. Catheter placement into the bladder may be impeded by the hypertrophied and often elevated bladder neck and curling of the catheter within the dilated posterior urethra. In such cases, a coude-tipped catheter or, alternatively, using a stylet to curl the tip of the feeding tube dorsally will facilitate bladder drainage. Minimizing any type of catheter balloon filling is important to prevent inducing bladder spasms in the small, hypertrophic bladder and potentially occluding the ureteric orifices (Jordan and Hoover, 1985). Placement of the catheter within the bladder may be confirmed by bladder sonography or, in some instances, a one-shot cystogram.

Pulmonary Hypoplasia

Whereas the focus in posterior urethral valves is too often on the lower urinary tract and kidneys, the most profound complication and cause of perinatal mortality in infants affected by severe LUTO remains pulmonary hypoplasia. The frequently cyanotic baby requires complex ventilatory support, and this is often the factor delaying definitive surgical intervention to address the valves. Pulmonary hypoplasia seen in the infant with a history of antenatally detected oligohydramnios may be the contributing factor to perinatal mortality in these children, requiring intensive and rapid supportive treatment (Pinar, 2004).

The association between posterior urethral valves, oligohydramnios, and pulmonary hypoplasia is recognized (Fig. 141-10), but the etiology of hypoplasia is unclear and likely multifactorial. It is recognized that the reduced expansion of alveoli because of hypoplasia adversely affects the development of the fetal pulmonary tree, which requires intraluminal pressure, volume, and flow while providing cellular signaling to the developing alveoli (Husain and Hessel, 1993; Laudy et al, 2002).

Although the concept that grossly hydronephrotic kidneys and a dilated bladder, combined with increased uterine pressure on the developing fetus resulting from oligohydramnios, reduce diaphragmatic expansion and affect lung volume and growth seems logical, it is an insufficient explanation for the clear correlation between pulmonary hypoplasia and oligohydramnios. Rather, the finding that abnormal pulmonary development commences in early embryogenesis indicates that pulmonary hypoplasia may actually precede uropathy (Smith et al, 2006). Peters and associates (1991) proposed a two-stage relationship with early pulmonary develop-



Figure 141-11. Sonographic image of left kidney in a newborn diagnosed with posterior urethral valves shows a large urinoma. The urinoma compresses the renal parenchyma inferiorly and is contained within the renal capsule.

ment being controlled by a “renal growth factor,” whereas lung growth and maturation in the later fetal period was more susceptible to the variations in amniotic fluid volume.

Urinomas

A urinoma is associated with posterior urethral valves in 3% to nearly 10% of cases (Fig. 141-11) (Greenfield et al, 1982; Patil et al, 2003). The introduction of renal ultrasonography in 1979 increased the detection of urinomas to 15% in one study (Heikkilä et al, 2011). Forniceal rupture will appear on renal ultrasonography as distorted renal parenchyma resulting from fluid trapped within the renal capsule, whereas transperitoneal transudation of fluid or bladder rupture will present as neonatal ascites (Greenfield et al, 1982). Although VCUG or radionuclide cystography may delineate the site of leakage for ascites, the cause is often difficult to determine (Patil et al, 2003).

Urinomas are usually addressed by restoring urinary flow and treating the proximate cause of LUTO, allowing the fluid to be reabsorbed. It is only in cases in which the ascites is causing respiratory distress, severe abdominal distention, or other clinical symptoms that percutaneous drainage or tapping of ascites becomes necessary; these interventions are uncommon.

There is some debate as to whether a urinoma heralds better or worse renal function for the affected side. Numerous studies have postulated that the urinoma serves as a pop-off mechanism, thereby reducing renal dysplasia on a given side, and some studies demonstrate globally preserved renal function, including an index of long-term renal severity (Rittenberg et al, 1988; Wells et al, 2010). Other studies hold that the urinoma, especially one retained within the renal capsule and compressing the kidney, impairs ipsilateral renal function and is a harbinger for worsened renal prognosis or has no bearing at all on long-term renal function (Patil et al, 2003; Kleppe et al, 2006; Heikkilä et al, 2011).

Delayed Presentation

In the age of extensive antenatal ultrasonography, delayed postinfancy presentation of posterior urethral valves is assumed to be less common. Still, Engel and colleagues (2011) reported that 141 of 228 children (62%) undergoing valve ablation presented with posterior urethral valves with a clinical presentation other than prenatal hydronephrosis or oligohydramnios. Up to 64% of these children had a normal prenatal ultrasonography and most presented with urinary tract infections, voiding complaints, and acute renal failure

in 10% (Engel et al, 2011). Another recent study at the Children's Hospital of Philadelphia followed a cohort of 138 patients presenting with posterior urethral valves between 1988 and 2011, of whom 60 (43%) presented after 6 months of life (Pulido et al, 2013). A high degree of suspicion for posterior urethral valves is therefore still warranted in boys presenting with lower urinary tract symptoms, especially recurrent urinary tract infections but also overflow incontinence, gross hematuria, renal dysfunction, and less commonly ejaculatory dysfunction (Bomalaski et al, 1999; Schober et al, 2004). A renal sonogram in these patients often detects the telltale bladder wall thickening and distal ureteral dilation that requires a voiding cystourethrogram for confirmation.

KEY POINTS: DIAGNOSIS, CLINICAL PRESENTATION, AND MANAGEMENT

- Antenatal finding of a thickened bladder and bilateral ureterectasis should be evaluated with early postnatal ultrasonography and voiding cystourethrogram.
- VCUG in a posterior urethral valve patient will show bladder wall irregularity, hypertrophied and elevated bladder neck, and dilated and elongated posterior urethra.
- The most common cause of early mortality in infants with posterior urethral valves is pulmonary hypoplasia.

SURGICAL INTERVENTION

Valve Ablation

Today, cystoscopy with ablation of the valves is considered the preferred initial surgical option in any neonate diagnosed with posterior urethral valves. The treatment goal is to restore flow of urine through the urethra and enable normal cyclic filling and emptying of the bladder, which is superior to urinary diversion and passive urine drainage (Smith et al, 1996; Close et al, 1997). Experimental models corroborate clinical evidence of the importance of bladder cycling, and one model of urinary diversion and undiversion demonstrated the changes that occur in a diverted bladder prevented from cycling (Chun et al, 1989). A fetal sheep model developed an increase in expression of extracellular matrix elements and apoptosis following a high diversion (Chun et al, 1989).

There are several approaches to valve ablation, which has historically been successfully completed even with a crochet hook passed retrograde into the urethra and feeling the hook catch the obstructing tissue. Innes Williams first described the engagement of valves with a hook, and Whitaker and Sherwood (1986) modified the hook by insulating the wire except for the very distal portion of the hook, which measures 6 to 7 Fr and could be passed at the bedside without general anesthesia while applying a small amount of diathermy when ablating the valves.

With the miniaturization of endoscopes in the age of fiberoptic and now digital technology, cystoscopy can be accomplished in even the smallest neonate and endoscopic valve ablation is the preferred approach at most centers today. Availability of a 7.5- or 9-Fr infant cystoscope with an offset lens facilitates passage of a variety of ablating devices, including a Bugbee electrode that can be used to incise the valves at the ventral 5 o'clock and 7 o'clock positions with or without an incision at the dorsal 12 o'clock position. Alternatively, the valves may be incised at the 12 o'clock position alone. A wire bent at the tip and passed through a 3-Fr ureteral catheter is another option, as is the visually guided Fogarty embolectomy catheter (Soliman, 2009). In an infant with a normal-caliber urethra, the 9.5-Fr resectoscope may be used with a Collins knife working element (Fig. 141-12).

Posterior urethral valves are thin and associated with minimal vascularity, and aggressive resection should be avoided. Use of a hot loop resectoscope for valve ablation, primarily in older children

in whom a resectoscope can be readily inserted, seems to be associated with a higher risk of urethral stricture and caution should be exercised with its use (Sarhan et al, 2010).

A urethral catheter is typically placed for at least 24 hours after the procedure. It is not necessary, though it is not uncommon, for the catheter to be left in for a longer period while the infant continues to be monitored for improvements in renal parameters or respiratory issues, often in an intensive care environment. A VCUG must be repeated after valve ablation within 1 month to ensure that the valves are no longer visible. It is not uncommon to see immediate signs of diminished bladder pressures, including some improvement in renal dilation and in the volume of vesicoureteral reflux.

Bladder neck hypertrophy and the subsequent elevation of the bladder neck dorsal to the posterior urethra, along with the incomplete emptying that seems to persist on imaging in some boys after valve ablation, prompted an interest in transurethral incision of the bladder neck during or after primary valve ablation (Androulakakis et al, 2005; Kajbafzadeh et al, 2007). Although some studies confirm that the bladder neck incision benefits emptying in children with neurogenic bladder, concerns of retrograde ejaculation and the lack of improvement compared to controls in even short-term pilot studies have limited the adoption of this technique until longer-term data are available (Christensen et al, 1985; Sarin and Sinha, 2013).

Vesicostomy

With miniaturization of endoscopic technology, vesicostomy is reserved primarily for the very low-birth-weight infant whose urethra cannot accommodate an endoscope, as well as a child with continued impaired renal function, high bladder urine volumes, and upper tract deterioration after valve ablation or urethral catheterization. The vesicostomy does reduce bladder storage pressures and may optimize glomerular filtration rate in some cases (Kim et al, 1997). The argument that the vesicostomy defunctionalizes the bladder and leads to decreased compliance in the long term has been refuted, since a properly created vesicostomy allows bladder filling and preserves contractile function because urine must be expelled through the stoma, albeit at a reduced leak point pressure (Hutcheson et al, 2001). The vesicostomy is best seen as a temporary diversion in children with posterior urethral valves because it does not alter clinical outcomes as compared to primary ablation, nor does it prevent a bladder from acting as an adequate reservoir for a renal transplant (Fine et al, 2011).

The vesicostomy is classically created with a 2-cm midline transverse incision made midway between the pubic symphysis and the umbilicus (Fig. 141-13). The rectus muscles are separated, the bladder is exposed with traction sutures, and the peritoneum is mobilized cephalad and away from the posterior wall and dome of the bladder. The bladder dome is identified by isolating the urachus, which is ligated so that the dome can be exposed through the fascial incision. The urachus and a small portion of the bladder dome are excised and the detrusor is then sutured to the fascia 1 cm below the edge of the cystostomy. The key operative step in creation of the vesicostomy is to ensure that the posterior wall of the bladder is taut—accomplished by bringing the dome of the bladder to the skin—to prevent prolapse of the back wall of the bladder through the incision (Hutcheson et al, 2001).

Upper Tract Diversion

Proponents of supravescical urinary diversion hold that direct decompression of the kidney by a cutaneous ureterostomy or pyelostomy will produce direct, low-pressure urinary drainage, allowing optimization of renal function (Fig. 141-14). High diversion, when renal dilation and biochemical markers of renal function fail to improve despite maximal bladder drainage, historically was believed to protect the upper urinary tract from ureterovesical junction obstruction caused by a tortuous intramural ureter passing through a thickened valve-affected bladder. In those cases, a loop

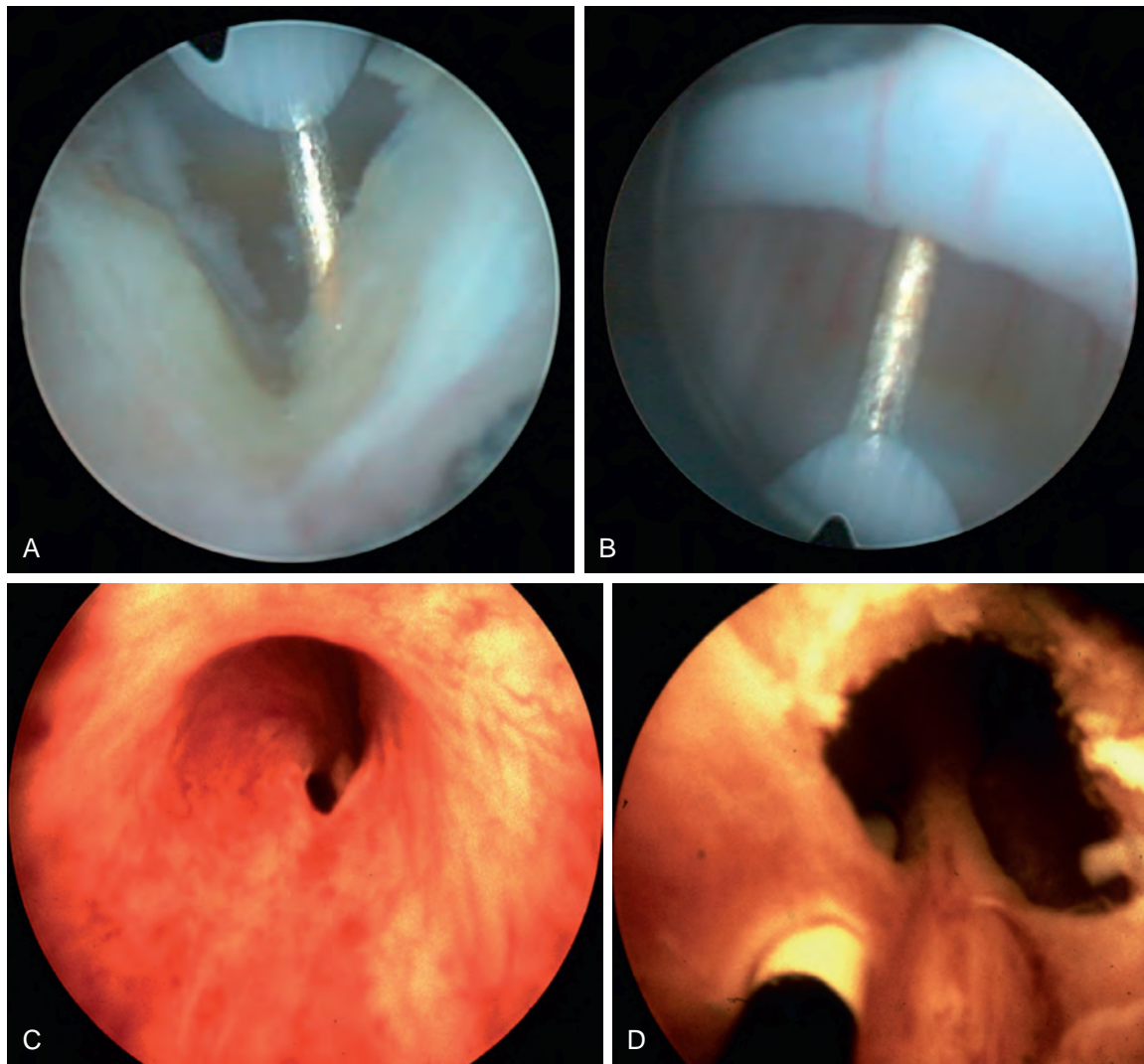


Figure 141-12. Cystoscopic images of incision of posterior urethral valves. A and B, Incision with a Collins knife being made at the 5 o'clock position (A) and at the dorsal 12 o'clock position (B). C and D, Before (C) and after (D) incision with Bugbee wire. The ureteral catheter has been passed through a perforation in the valve leaflet.

diversion of the ureter or renal pelvis, for example, also allows bladder filling and bladder cycling, mitigating the concern of defunctionalizing the bladder (Pinto et al, 1978; Churchill et al, 1990; Kim et al., 1997).

Contemporary studies and long-term follow-up of these patients, however, failed to detect a long-term renal protective benefit of high diversion, which necessarily requires an often complicated undiversion procedure as the child matures (Smith et al, 1996). Moreover, the finding that renal biopsies taken at the time of high urinary diversion uniformly show renal dysplasia, while the diversion does not seem to protect from renal failure, suggest that renal dysplasia occurring in early fetal development is the primary mediator of renal outcome, rather than any type of complex surgical undertaking in the neonate (Tietjen et al, 1997).

Upper urinary tract diversion may be considered in an infant with complete decompression of the lower urinary tract but worsening renal function, increasing upper tract dilation, and possibly a clinical picture of sepsis. Whether upper urinary tract diversion or vesicostomy preserves renal function better than valve ablation alone cannot be definitively concluded because of the lack of controlled comparative studies or other available studies. Still, upper urinary tract diversion will require secondary surgery, and the bladder may be exposed to a potentially extended period of defunctionalization with attendant risks of impairment

in compliance and contractility (Close et al, 1997). The preferred initial surgical intervention for infants with posterior urethral valves is endoscopic valve ablation. The clinician should be prepared to create a properly constructed vesicostomy or upper urinary tract diversion when primary valve ablation is impossible, or bladder decompression is not achieved by urethral catheterization or valve ablation alone.

Circumcision

A urinary tract infection can quickly progress to pyelonephritis and sepsis in an infant with posterior urethral valves because of the associated morbidities of vesicoureteral reflux, incomplete bladder emptying, and severe upper urinary tract dilation. The overall risk of urinary tract infection in children with posterior urethral valves is 50% to 60%—several magnitudes greater than the 1% risk for unaffected boys (Mukherjee et al, 2009; Bader and McCarthy, 2013). Circumcision reduces that risk of urinary tract infection by 83% to 92%, a reduction to a level of risk similar to that for unaffected boys (Wiswell et al, 1988; Mukherjee et al, 2009). It is recommended that a circumcision be strongly considered as a prophylactic measure for any boy diagnosed with posterior urethral valves, and it should certainly be completed before giving any consideration to a ureteral reimplant in a scenario

of frequent febrile urinary tract infections despite conservative measures.

Nephroureterectomy

Nephroureterectomy was historically considered an appropriate intervention for posterior urethral valve patients manifesting elements of the VURD syndrome discussed previously. The nonfunctioning renal unit in association with dilating urinary reflux was long considered a potential source for infections and sepsis, and prophylactic excision was considered appropriate. In contemporary practice, a focus on proper bladder emptying and circumcision has decreased the incidence of urinary tract infections sufficiently that

nephroureterectomy is rarely considered. Indeed, renal preservation is appropriate for even poorly functioning renal units contributing moderate polyuria, which is easier to manage than anuria. If frequent urinary tract infections localizing to the nonfunctioning renal unit necessitate a nephrectomy, preserving the ureter for potential subsequent reconstruction, such as a ureteral augmentation, is recommended (Husmann et al, 2004).

MANAGEMENT OF VESICoureTERAL REFLUX

A voiding cystourethrogram will reveal vesicoureteral reflux (see Fig. 141-9) in 50% to 80% of infants undergoing a workup for posterior

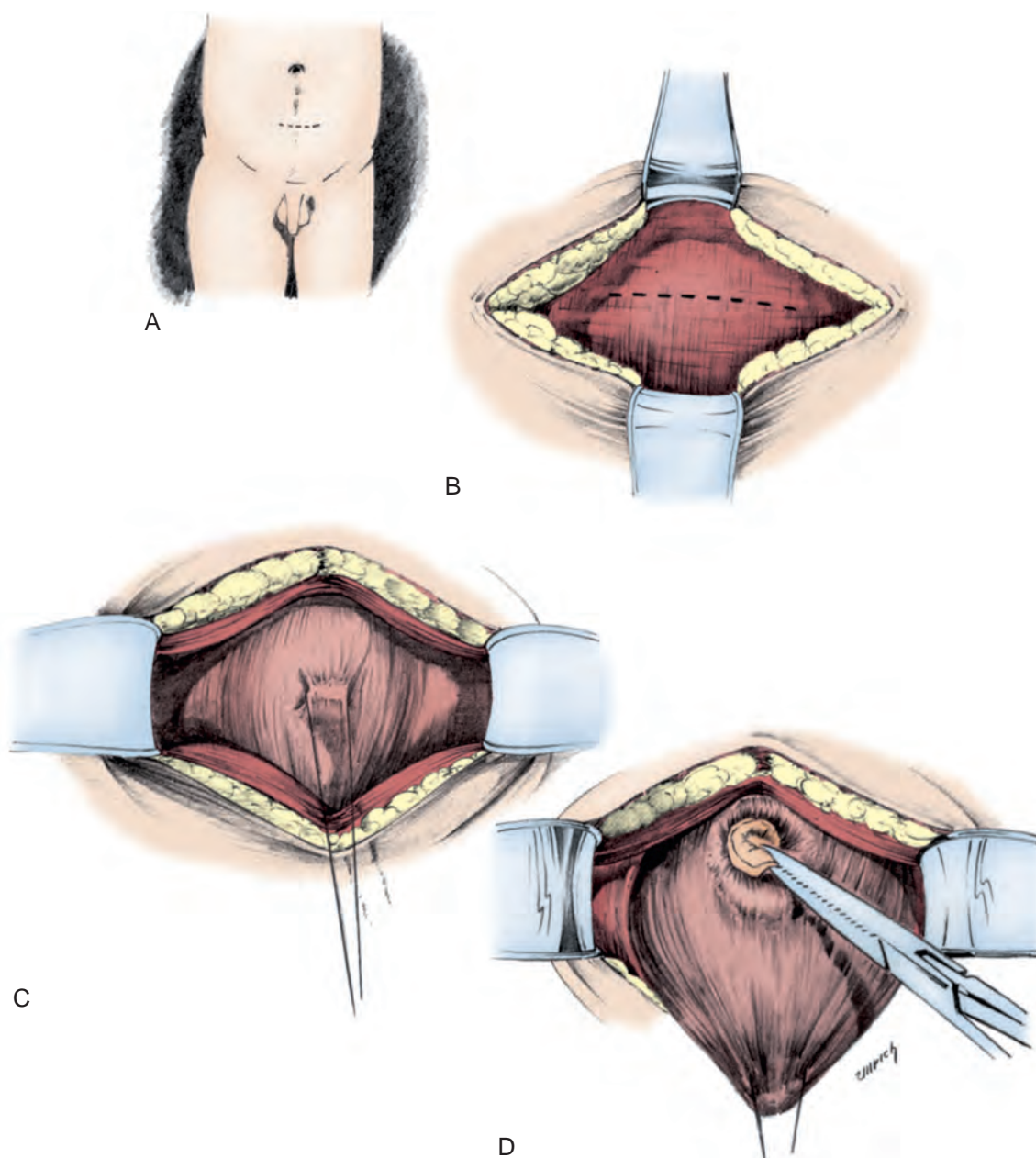


Figure 141-13. Blocksom technique for performance of cutaneous vesicostomy. A, An incision is made at a point midway between the umbilicus and pubis that corresponds to the upper limit of the filled bladder. B, A transverse incision is made in the rectus fascia and the bladder detrusor muscle is exposed. C, Stay sutures or noncrushing clamps are used to mobilize the bladder while dissecting the peritoneum away from the bladder dome. D, The dome of the bladder is identified by ligating the urachal remnant.

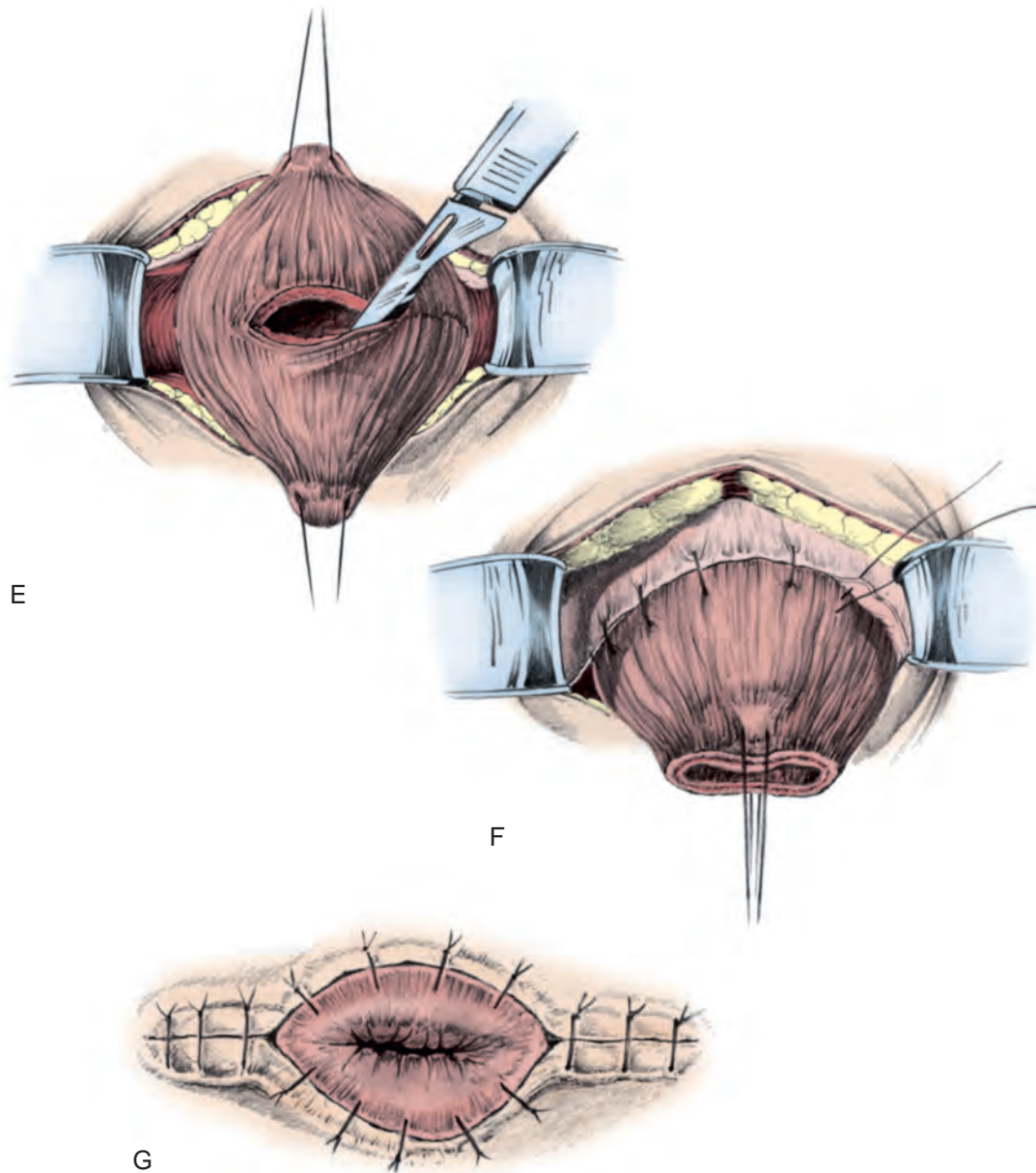


Figure 141-13, cont'd E, A transverse incision is then made in the dome of the bladder. F, The bladder detrusor is sutured to the rectus fascia, placing these sutures 1 cm away from the edge of the bladder incision. G, The bladder opening is sutured to the skin. (From Gonzales ED. Posterior urethral valves and other ureteral anomalies. In: Walsh PC, Retik AB, Vaughan ED, et al, editors. *Campbell's urology*. 8th ed. Philadelphia: Saunders; 2002.)

KEY POINTS: SURGICAL INTERVENTION

- Cystoscopy with valve ablation is the preferred initial treatment for posterior urethral valves.
- Vesicostomy does not inhibit bladder cycling, because the bladder continues to contract, but is reserved for select cases in which valve ablation is not possible.
- High urinary diversion offers no renal protective benefit and requires a complex secondary procedure to reverse the diversion.
- Circumcision should be encouraged as a prophylactic measure for a child with posterior urethral valves, and especially any boy with a history of urinary tract infection.

urethral valves (Puri and Kumar, 1996; Tournchi et al, 2014). Infants with valves are also at an increased risk for urinary tract infections as discussed in the previous section, and the coexistence of reflux and valves presents a clinical scenario that may suggest a role for ureteral reimplantation. However, understanding that reflux in these infants is a consequence of obstruction and the secondarily elevated bladder pressures is critical to management, and should render the ureteral reimplantation an option in atypical cases in which urinary tract infections continue despite maximal bladder therapy. Indeed, ablation of the valves or vesicostomy alone will resolve ureteral reflux in 25% to 40% of patients with urinary reflux prior to ablation (Hassan et al, 2003; Tournchi et al, 2014).

Hassan and colleagues (2003) found that the presence of urinary reflux did not correlate with renal outcomes, underscoring that the presence of reflux alone should not be seen as an indication for intervention. All efforts in a symptomatic posterior urethral valve

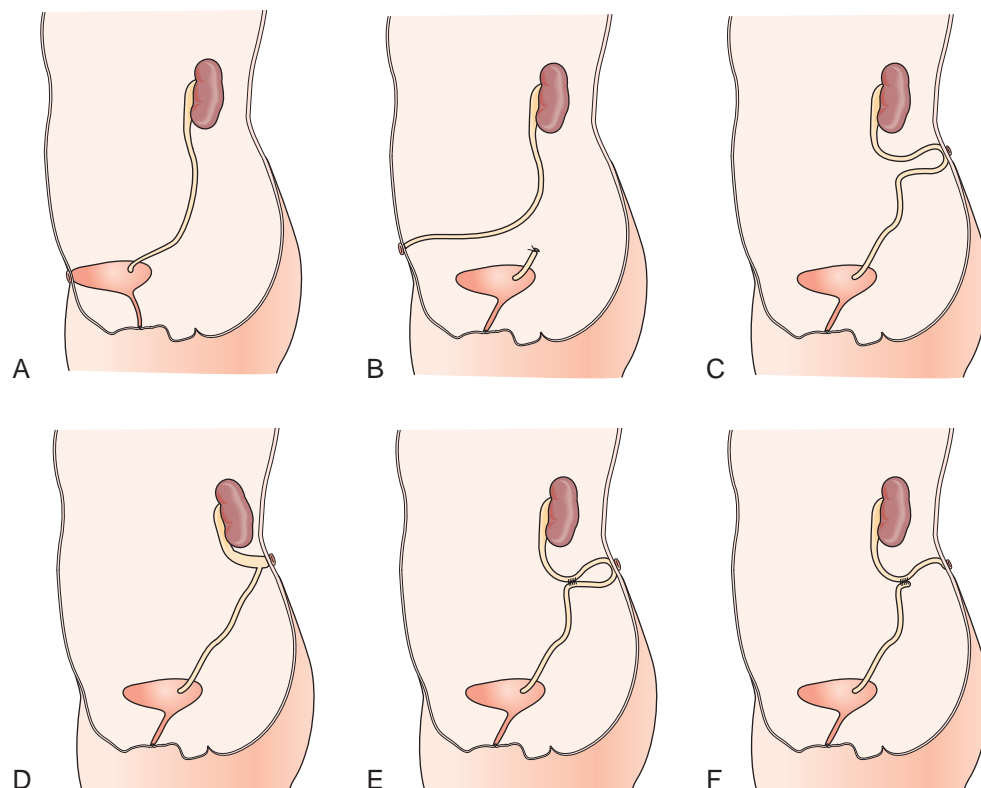


Figure 141-14. The variety of urinary tract diversions useful in posterior urethral valves. **A**, Vesicostomy. **B**, Distal ureterostomy. **C**, Proximal loop ureterostomy. **D**, Cutaneous pyelosotomy. **E**, Ring ureterostomy. **F**, Sober Y ureterostomy. (From Glassberg KI, Horowitz M. Urethral valves and other anomalies of the male urethra. In: Belman AB, King LR, Kramer SA, editors. *Clinical pediatric urology*. 4th ed. London: Martin Dunitz; 2002. p. 899–945.)

patient with vesicoureteral reflux must focus on addressing any persistent bladder outlet obstruction, reducing intravesical pressures by considering anticholinergic treatment, and treating underlying bladder dysfunction that is common in bladders exposed to fetal bladder outlet obstruction. Urodynamic evaluation may help guide management in this regard (Kim et al, 1997).

In the rare event that a clinical scenario of recurrent urinary tract infections mandates intervention in a child with posterior urethral valves, bladder management in advance of intervention is a critical component in ensuring favorable surgical outcomes (Hunziker et al, 2012).

Consideration of surgical correction for reflux must also recognize the higher complication rate of stricture and persistent reflux associated with reimplanting dilated ureters into thick-walled bladders that are not properly rehabilitated prior to surgery (Coleman and McGovern, 1978; Atwell, 1983). Indeed, any treatment of urinary reflux in a child with profound bowel dysfunction—as commonly seen in boys with posterior urethral valves—potentially puts an already compromised renal unit at risk for further deterioration (Sillén et al, 2010; Tekgül et al, 2012). Endoscopic correction of reflux seems to carry less of the risks of myogenic disruption and renal deterioration seen with ureteroneocystotomy in children with valves, but the overall surgical success rate is lower than that for children without valves (Puri and Kumar, 1996; Tourni et al, 2014).

BLADDER DYSFUNCTION AND VALVE BLADDER SYNDROME

Consequent to exposure to obstruction from its earliest development, the bladder is necessarily the focus of management and rehabilitation throughout the life of a boy diagnosed with posterior

urethral valves (Parkhouse et al, 1988). The extent of remodeling and subsequent functional compromise may vary, but the bladder and its dysfunction begin a cascade of pathophysiologic changes, including voiding dysfunction, urinary reflux, and worsening of renal dysplasia and obstructive uropathy. The ultimate manifestation of this dysfunction is the valve bladder syndrome.

Urodynamics plays an important role in monitoring an affected child's progression through various well-described changes in bladder function throughout childhood. The bladder evolves through three distinct contractility patterns through childhood: (1) detrusor hyperreflexia in infancy and early childhood; (2) decreasing intravesical pressures and improved compliance bladder in childhood; and (3) increased capacity bladder with hypocontractility and atony in adolescence (Peters et al, 1990; De Gennaro et al, 2000). Holmdahl and coworkers (1995) stressed that the patterns outlined here overlap in most children, emphasizing that the patterns are not arbitrary but rather are useful guideposts in monitoring and managing children over the long term.

Mitchell (1982) conceptualized a vicious circle in voiding dysfunction wherein the outlet obstruction begins a cascade of events leading to the end-stage bladder, or valve bladder. Bladder outlet obstruction leads to detrusor hypertrophy, which increases the voiding pressures initially as the bladder strives to complete emptying. As further remodeling of the bladder occurs, however, the post-void residual begins to increase as the urine output increases. Ultimately, the bladder cannot meet the demand of emptying and the detrusor decompensates.

Bladder dysfunction, even when not detected on clinical history alone, must always be suspected in children with a history of valve ablation. One systematic review of 34 studies describing renal function, vesicoureteral reflux, and urodynamic findings after endoscopic valve ablation in 1474 patients found that, whereas the self-reported history of incontinence ranged

widely between 0% and 70%, the mean incidence was 19%. However, when urodynamic outcomes were examined, the incidence of bladder dysfunction rose to a mean of 55% (Hennus et al, 2012). Reliance on clinical examination or patient questionnaires alone may grossly underestimate bladder dysfunction, and obtaining a uroflow and checking postvoid residuals should be a routine part of follow-up in toilet-trained children with a history of posterior urethral valves. Upper tract assessment with renal ultrasonography can also be a useful, simple tool to detect dangerous bladder dysfunction and monitor response to therapy (Lopez Pereira et al, 2013).

Bladder Management

The typical follow-up for children with posterior urethral valves after ablation for bladder dysfunction has focused on observation, clinical history, and urodynamics. Education of parents and growing children is a critical component of bladder management and the success of any prescribed behavior modifications. Families are counseled to not aggressively push an affected child toward toilet training and to expect a lag compared to the normal population. Daytime incontinence is not uncommon, ranging from 7% to 35%, and nocturnal enuresis is expected in 1 of 4 children with a history of valve ablation (Hennus et al, 2012). Once toilet training is achieved, children and caregivers are educated to ensure adequate fluid intake, to void on a timed regimen, and to practice double voiding. Biofeedback therapy and home pelvic floor exercises have also been shown to be useful (Ansari et al, 2008).

The role of adjunctive medications is unclear. The preferred intervention is predicated also on varying proposed etiologies of voiding dysfunction after valve ablation: (1) functional obstruction at the bladder neck as a result of hypertrophy and external sphincter hyperreflexia, or (2) bladder wall thickening caused by detrusor wall thickening from increased collagen deposition. One study suggests the use of α -adrenergic blockade to relieve sphincteric hypertonicity and relax the bladder neck in children with high postvoid residuals, finding a significant reduction in residual volumes (Abraham et al, 2009). In contrast, Casey and coworkers (2012) administered oxybutynin at 0.1 mg/kg twice daily in 18 consecutive infants undergoing urodynamic assessments at 3 months after valve ablation and showing high voiding pressures or small bladder capacity. Although the study found that both of these parameters improved significantly with oxybutynin, the lack of a control group in both afore-

mentioned studies and the reality that detrusor hypercontractility and elevated voiding pressures are normal findings in neonates necessitate more rigorous prospective studies (Sillén et al, 1992; Casey et al, 2012). If oxybutynin is chosen, its use must be closely monitored for effect, and if a growing child begins to demonstrate higher bladder residual volumes and capacity, oxybutynin should be stopped. Therapy was stopped in 4 of 18 patients in the Casey and coworkers (2012) study, and another study found that myogenic failure required intermittent catheterization (Kim et al, 1997). It is unclear whether the myogenic failure was a consequence of evolving bladder dysfunction inherent to posterior urethral valves or secondary to oxybutynin, but caution nevertheless should be exercised during the treatment period.

Valve Bladder Syndrome

The term *valve bladder syndrome* was coined by Mitchell in 1982 after reviewing his experience with 11 patients in whom hydronephrosis and renal function continued to worsen despite no clinical evidence of residual bladder outlet obstruction (Lloyd et al, 2013). Mitchell's concept, which is illustrated in Figure 141-15 and was described earlier, holds that although the bladder initially compensates for outlet obstruction by generating high voiding pressures, it begins to experience higher volumes of urine as a result of increasing urine production as the child grows. The polyuria caused by nephrogenic diabetes insipidus secondary to evolving renal impairment augments the urine volumes entering a bladder that is increasingly unable to empty completely. As the postvoid residuals increase, the bladder no longer enjoys periods of complete relaxation, and the detrusor fibers are continuously in a state of partial or complete stretch, beginning a cascade of gene expression and phenotypic changes that further impair contractility of the bladder (Kirsch et al, 2003; Hutcheson et al, 2004; Shukla et al, 2004). When the bladder does empty partially, the urine already stored in the hydronephrotic kidneys quickly empties into the bladder once again, denying the detrusor muscle periods of relaxation. The impaired contractility and increasing postvoid residuals then transmit the increasing bladder pressures to the kidneys, potentially worsening the already impaired renal function.

In sum, then, three processes contribute toward the devolution of a bladder into a valve bladder in a cohort of patients with posterior urethral valves: (1) polyuria. (2) poor bladder

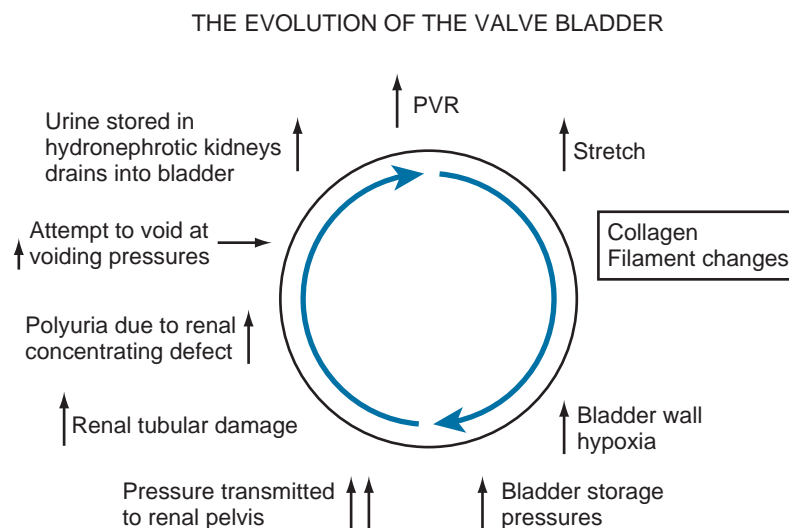


Figure 141-15. The valve bladder “vicious cycle.” An affected bladder will lead to increasing postvoid residuals (PVR). The sustained stretch will cause increasing collagen deposition and other changes that cause increased pressures to be transmitted to the renal pelvis. Subsequent renal tubular injury causes polyuria and increased volume in the bladder that already empties poorly, and the cycle continues, leading to additive damage.

compliance with high-pressure voiding and elevated wall tension bladder, and (3) residual urine volume. These three factors conspire to sustain the bladder overdistention that is the original insult leading to the valve bladder (Koff et al, 2002).

Although the goal of intensive management of bladder dysfunction is to arrest the progression toward full expression of late-term manifestations of valve bladder syndrome, *valve bladder syndrome* is actually a broad term describing a continuum of symptoms of bladder dysfunction. As described in the previous section, monitoring urine postvoid residuals, flow rates, and voiding pressures, along with timed voiding, double voiding, and anticholinergics or α -blockers, comprises the mainstay of treatment. Clean intermittent catheterization (CIC) becomes necessary if myogenic failure progresses.

Overnight bladder drainage is an important adjunct in therapy, and increasingly adopted as a standard intervention in children with classic evidence of developing a valve bladder syndrome (Koff et al, 2002; Nguyen et al, 2005b). Nocturnal bladder drainage is instituted if ureteral dilation and hydronephrosis do not respond to behavior modification, or an affected child develops worsening renal function or recurrent urinary tract infections. The continuous bladder drainage achieved by leaving a urinary catheter in the bladder over a 7- to 10-hour period allows an extended period of bladder decompression even as the kidneys empty urine without encountering the increased voiding or resting bladder pressures they face during the day. This simple step interrupts the “vicious cycle” of bladder remodeling and consequent renal effects resulting from chronic bladder distention. Koff and colleagues (2002) and Nguyen and associates (2005a) both noted significant improvements in hydronephrosis, continence, and urinary tract infections after instituting overnight bladder drainage.

When CIC or overnight bladder drainage is difficult because of an elevated bladder neck or sensate urethra, an appendicovesicostomy utilizing the Mitrofanoff principle (Mitrofanoff, 1980) presents a useful option. Minimally invasive techniques to create this catheterizable channel, utilizing both laparoscopic and robotic-assisted approaches, are increasingly being adopted at many centers (Mitrofanoff, 1980; Hsu and Shortliffe, 2004; Nguyen et al, 2009; Famakinwa and Gundeti, 2013; Famakinwa et al, 2013). The robotic-assisted approach potentially limits the field of dissection and could, in older children, make it difficult to mobilize the appendix and perform bladder mobilization with anastomosis of the appendix through a single robot docking. In such situations, a pure laparoscopic approach could be used to mobilize the appendix, followed by docking of the robot with standard triangulation of port sites focused on the pelvic midline for anastomosis of the appendix.

Augmentation cystoplasty is rarely utilized for a valve bladder in the contemporary era, perhaps because of improved understanding of bladder dysfunction, behavior modification, and timely institution of overnight bladder drainage. However, when faced with a small-capacity, high-pressure, thick-walled valve bladder with worsening upper tract anatomy refractory to conservative measures, augmentation may be considered. Ureteral augmentation is preferred in children with posterior urethral valves because it reduces the risks of mucus production, acidosis, and stones that are common to ileal augmentation. Moreover, severe ureteral dilation or unilateral VURD seen in boys with posterior urethral valves offers an ideal clinical scenario wherein the ureter can be detubularized and patched on a bisected bladder without bowel manipulation. Johal and coworkers (2008) reported lasting benefits of increased capacity and decreased filling pressures at a mean follow-up of 4.5 years after ureteral augmentation.

ANTENATAL MANAGEMENT

Antenatal intervention in cases of suspected LUTO was popularized in the mid 1990s as advances in fiberoptics and endoscopic miniaturization enabled even complex fetal procedures. Intervention is considered in some centers when antenatal sonography detects

KEY POINTS: MANAGEMENT OF VESICoureTERAL REFLUX, BLADDER DYSFUNCTION, AND VALVE BLADDER SYNDROME

- The focus of management for vesicoureteral reflux in a child with posterior urethral valves should be centered on the bladder, and ureteral reimplantation is rarely offered.
- The bladder evolves through three patterns in boys with posterior urethral valves: (1) detrusor hyperreflexia in infancy and early childhood, (2) decreasing intravesical pressures and improved compliance bladder in childhood, and (3) increased bladder capacity with hypocontractility and atony in adolescence.
- Overnight bladder drainage is considered in the scenario of increasing postvoid residuals, urinary tract infections, or worsening hydronephrosis and renal function.

evidence of oligohydramnios, a dilated bladder, and severe hydronephrosis—without renal cortical cystic lesions—in a fetus with a normal karyotype (Ruano, 2011). A fetal urine sample can also be obtained after 20 weeks' gestational age, and favorable prognosis is suggested by a urinary sodium less than 100 mEq/L, chloride less than 90 mEq/L, osmolarity less than 200 mEq/L, and β_2 -microglobulin less than 6 mg/L (Nicolini and Spelzini, 2001).

Vesicoamniotic shunting to treat oligohydramnios offers potential ameliorative effects on pulmonary function and represents the first stage in fetal intervention, with several hundred shunt procedures reported in the literature (Ruano, 2011). This approach is corroborated by fetal sheep models demonstrating that restoration of amniotic fluid volume prevents lung hypoplasia, though the lack of controlled studies in the literature constrains conclusions as to its effectiveness (Kitagawa et al, 2006). Also, although a systematic review published a survival advantage in infants having undergone vesicoamniotic shunting, randomized trials were lacking (Clark et al, 2003). The Percutaneous vesicoamniotic shunting versus conservative management for Lower Urinary Tract Obstruction (PLUTO) trial attempted to fill this void but was limited by poor recruitment and pregnancy terminations, with only 12 live births in each group studied. The results showed a trend toward improved survival at 28 days in the shunted group but overall survival was very poor in both groups, with only 2 infants surviving to 2 years of age with normal renal function. There was a high mortality owing to pulmonary hypoplasia. There was also a greater risk of pregnancy loss in the shunt group because of procedure-related complications and early rupture of membranes (Morris et al, 2013).

Biard and colleagues (2005) reported a mean 5.83 years of follow-up on 20 pregnancies with a singleton male fetus that underwent vesicoamniotic shunting for clear evidence of isolated LUTO and good or borderline urinary sampling parameters. This study found an overall 1-year survival of 91%, and health-related quality-of-life parameters were similar to those in the unaffected, healthy child population. Vesicoamniotic shunting, in contemporary practice, is utilized as a potential intervention in the rare case of LUTO with oligohydramnios but should be limited to experienced centers with multidisciplinary capabilities.

No studies similar to the PLUTO trial have been attempted for even more complex fetal interventions such as fetal cystoscopy with valve ablation, or even fetal surgery. Fetal cystoscopy, performed using a 1.0-mm fetoscope, is carried out in an antegrade fashion by a transuterine percutaneous incision into the bladder. When the posterior urethra is entered through the bladder neck, a Nd:YAG laser or cauterizing wire is used to perforate the obstructing membrane (Quintero et al, 1995, 2000; Ruano, 2011). Holmes and coworkers (2001) reported a series of 14 fetal surgical procedures for posterior urethral valves, including antenatal valve ablation, vesicoamniotic shunting, cutaneous ureterostomy, and vesicostomy.

Six infants died as a result of premature delivery and respiratory failure and 5 of 8 surviving children at a mean 11.6 years of follow-up were in renal failure. The 43% fetal mortality rate for fetal surgery must be an essential part of any prenatal counseling prior to considering fetal intervention that offers potential, though yet unproven, benefits for a very select group of pregnancies.

PROGNOSTIC INDICATORS FOR RENAL FUNCTION

Despite numerous advances in antenatal diagnosis and intervention, and rapid postnatal evaluation and treatment, the lifetime prevalence of end-stage renal disease in boys with posterior urethral valves is between 20% and 50% (Parkhouse et al, 1988; Smith et al, 1996; Sarhan et al, 2011). Risk factors known to affect the prognosis of an infant diagnosed with posterior urethral valves include age at diagnosis, renal dysplasia with or without vesicoureteral reflux, nadir creatinine during 1 year of life, recurrent urinary tract infections, and bladder dysfunction.

Nadir creatinine has long been considered a relatively easy method of predicting long-term renal outcome in affected children. The nadir creatinine value measured at 1 year of life appears to be more accurate as a predictive tool than the value obtained at 1 month of age (Drozd et al, 1998; Lal et al, 1999; Heikkilä et al, 2011). A serum creatinine of less than 0.8 mg/dL appears to indicate a minimal risk, whereas a value greater than 1.2 mg/dL at 1 year of age predicts a higher risk of developing end-stage renal failure (Drozd et al, 1998; DeFoor et al, 2008). In those studies suggesting that a 1-month post-treatment serum creatinine is a more accurate predictor of renal function, again the value of less than 0.8 mg/dL at 1 month after treatment seems to indicate better long-term outcomes (Rittenberg et al, 1988).

Age at diagnosis remains an unclear predictor of future renal outcomes. The assumption that antenatal diagnosis would lead to more rapid diagnosis of posterior urethral valves and therefore forestall renal injury has not been sustained. Indeed, Heikkilä and associates (2011) found that patients diagnosed in the pre-sonography era (before 1982) had a risk of end-stage renal disease of 16.8%, as compared to 36.6% developing renal failure if diagnosed during the post-sonography era. Another review found a similar variation with 41% of those presenting before 1 year of age having poor long-term renal outcome compared to 15% of those presenting after 1 year of age (Parkhouse et al, 1988). This difference in outcomes may be explained by the assumption that the critically ill infants in the pre-sonography era likely died before diagnosis was complete, and early interventions, including fetal measures, in the current era increased survival dramatically. These infants born after 1982 may previously have died and tended to have more severe manifestations of valve disease and related comorbidities contributing to worse renal outcomes.

Another common assumption, not corroborated, was that the later-presenting children likely had a milder variant of valve disease, allowing them to go undetected for some years before presenting with more vague symptoms of voiding dysfunction. However, some reports found much worse outcomes in children presenting outside of the neonatal period with posterior urethral valves, with delayed presentation associated with a significantly higher risk of azotemia, higher serum creatinine, and worse long-term renal outcomes (El-Sherbiny et al, 2002; Ziylan et al, 2006; Sarhan et al, 2011).

Quantifying renal dysplasia without a renal biopsy requires reliance on available imaging technology, including renal sonography and nuclear scintigraphy. Hyperechogenic kidneys, cystic changes in the cortex, and loss of corticomedullary differentiation are considered to portend a poor prognosis (Robyr et al, 2005). Pulido and colleagues (2013) examined the association of the renal parenchymal area—defined as the area of the kidney minus the area of the pelvicaliceal system on the first postnatal sonogram—with end-stage renal disease. Reviewing the first postnatal ultrasound images of 60 patients followed for 393 person-years, the authors found that, for infants with a serum creatinine between 0.8 and 1.1 mg/dL at 1 month of life, each 1-cm² increase in renal parenchymal area

was associated with a lower risk of end-stage renal disease (Pulido et al, 2013). The study highlights that there is a need for novel ways of predicting renal outcomes in children with posterior urethral valves, and certainly more definitive and powerful predictive tools may lie in the elucidation of genetic and biochemical markers (Farrugia et al, 2006).

TRANSPLANTATION IN POSTERIOR URETHRAL VALVE PATIENTS

The prevalence of end-stage renal disease in boys with a history of posterior urethral valves is up to 50%, and the 2006 annual report of the North American Pediatric Renal Trials and Collaborative Studies listed obstructive uropathy as the second most common cause for transplantation, accounting for 1424 of 8990 transplantation cases (15.8%) since 1987 (Smith et al, 2007).

Patients with posterior urethral valves comprise an especially difficult cohort for receiving a renal transplant. These boys are likely to have several comorbidities, including high-grade vesicoureteral reflux into native nonfunctioning kidneys and valve bladder syndrome with a thick-walled, poorly contractile or hypercontractile bladder. A pediatric urologist must be a critical component of the transplantation team and should carefully examine the prospective recipient as part of the pretransplantation evaluation. Transplant recipients in whom bladder dysfunction is incompletely managed or the bladder reservoir is not optimized have significantly higher complication rates and graft loss rates (Sheldon et al, 1994; Mendizabal et al, 2005).

Outcomes after renal transplantation in children with posterior urethral valves have been mixed. The thickened bladder wall of posterior urethral valve patients may contribute to the significantly increased incidence of ureteral obstruction on univariate and multivariate analysis compared to a non-posterior urethral valve transplantation cohort, but recent studies saw no risk of increased graft loss or patient death despite ureteral obstruction, stenting, or dilation (Indudhara et al, 1998; DeFoor et al, 2003; Smith et al, 2010; Fine et al, 2011). Fine and colleagues (2011) reported on 59 valve patients who underwent renal transplantation with 8-year follow-up and found that outcomes were similar whether a boy underwent an initial valve ablation, vesicostomy, or supravescical diversion; also, though bladder dysfunction increased the risk of graft failure, the effect did not reach significance.

Video-urodynamics should be obtained for transplant candidates to determine the safe storage pressures and contractile function of the future reservoir. Overnight bladder drainage or CIC may be initiated prior to transplantation to optimize the reservoir and establish proper bladder management skills that will be essential for graft success after transplantation. Pretransplantation nephrectomy is rarely required and only considered in cases in which proteinuria or severe polyuria is creating hemodynamic challenges.

If augmentation is believed necessary based on unsafe storage pressures in the bladder, this reconstruction can be considered before or after transplantation. Whereas previous dogma suggested that a pretransplantation augmentation is preferable to prevent the undertaking in an immunocompromised child or one too young to take responsibility for catheterization and pouch management, recent experience argues that transplantation into even a vesicostomy is a safe alternative until the child grows to an appropriate age for cystoplasty and the attendant reliance on CIC (Rigamonti et al, 2005; Christman et al, 2013).

QUALITY OF LIFE WITH POSTERIOR URETHRAL VALVES

It must be emphasized that posterior urethral valves have lifetime repercussions. Understanding these long-term risk factors and their impact on quality of life is necessary for counseling, preparing, and treating valve patients as they reach adulthood.

The evolution of the valve bladder and the associated comorbidities of renal transplantation that many valve patients face are

associated with well-known risks, including erectile dysfunction and infertility. The lower urinary tract symptoms that affect children with valves also affect them as adults two to three times more often than those symptoms affect the general population (Tikkinen et al, 2011). A survey of 67 adult patients with posterior urethral valves found that the overall rate of erectile dysfunction or infertility was not different than that in the general population (Taskinen et al, 2012). However, a subgroup analysis of these same patients with urinary incontinence or renal insufficiency showed that valve patients had the greatest evidence of impaired quality of life, underscoring the necessity of long-term follow-up and active treatment well into adulthood (Jalkanen et al, 2013). Indeed, the chronicity of bladder dysfunction, risk of urinary tract infections, and sequelae of renal dysfunction require communication between pediatric and adult urologists, even as the adult urologist should be knowledgeable of the pathophysiology of posterior urethral valves and well prepared to provide care to these patients after their transitions into adulthood.

KEY POINTS: ANTENATAL MANAGEMENT, PROGNOSTIC INDICATORS FOR RENAL FUNCTION, AND TRANSPLANTATION IN VALVE PATIENTS

- An antenatal vesicoamniotic shunt can be considered in selected patients with bladder wall thickening, hydronephrosis, and oligohydramnios. Although it may reduce the severity of pulmonary hypoplasia, the procedure confers limited protection from renal impairment.
- A nadir serum creatinine at 1 year of less than 0.8 mg/dL confers a significantly decreased risk of developing end-stage renal disease.
- Transplantation into a valve-affected bladder may carry a higher risk of ureteral obstruction, but there is no increased risk of graft loss compared to controls.

OTHER URETHRAL ANOMALIES

Anterior Urethral Valves

Anterior urethral valves are the most common congenital obstructive lesion of the anterior urethra, but are 25 to 30 times less common than posterior urethral valves (Confer et al, 2010). Since the condition is often found in association with a large anterior urethral diverticulum, the valve itself is variously described as an obstruction resulting from a wall of the diverticulum obstructing flow or a semilunar fold draping down from the wall of the anterior urethra and interrupting urinary flow (Tank, 1987; Paulhac et al, 2003). The embryology of anterior urethral valves is not clear, but abortive corpus spongiosum over the affected portion of the anterior urethra indicates a place on the hypospadias spectrum or a faulty union between urethral mucosa and the epithelium of the fossa navicularis. A rupture of dilated bulbourethral glands has also been suggested as an etiology (McLellan et al, 2004). The valves may be located at the bulbar urethra, the penoscrotal junction, or the penile urethra (Firlit et al, 1978).

Patients present with anterior urethral valves at different ages based on the severity of the obstructive process. Symptoms may consist of postvoid dribbling and mild incontinence, significant bulging of the distal penis, palpable bladder with obstruction or even renal insufficiency, and urinary tract infections (Cruz-Diaz et al, 2013). Diagnosis requires a careful examination of the external genitalia, and compression of the distal shaft may result in expressing of urine as seen in a diverticulum. A voiding cystourethrogram is required to confirm the diagnosis and may demonstrate a dilated anterior urethra with proximal signs of chronic obstruction, including bladder diverticula and massive vesicoureteral reflux.

The treatment approach to anterior urethral valves varies according to age of presentation, extent of upper tract damage, and extent of anterior urethral deformity. In a premature or small infant, a vesicostomy may be required to facilitate relief of obstruction until the infant can accommodate a cystoscope or undergo further reconstruction. In the majority of cases, cystoscopy with valve ablation using a Bugbee electrode or laser is possible as an initial treatment, and when successful, no further surgery of the urethra is required (Cruz-Diaz et al, 2013). In more severe cases in which a gross urethral diverticulum is seen, surgical reconstruction over a urethral catheter may be required.

Up to 80% of children with anterior urethral valves will develop bladder dysfunction, and bladder instability, hyperreflexia, and diminished compliance and capacity will be seen on urodynamics (Kajiwaru et al, 2007). As with posterior urethral valves, long-term renal function is contingent upon preoperative creatinine and glomerular filtration rate. Routh and colleagues (2010) performed a multivariate analysis of data available from 97 studies including 229 patients with anterior urethral valves and found that pretreatment azotemia, vesicoureteral reflux, and urinary tract infection together increased the risk of poor renal outcome 25-fold. Still, because of the milder and more subtle presentation, the overall incidence of preserved renal function in anterior urethral valves is better than that in posterior urethral valves, with 78% of patients having normal renal function after treatment (Routh et al, 2010).

Urethral Atresia

Urethral atresia or congenital urethral stricture is a rarely described entity, likely because of its high associated mortality. When an infant survives—because the obstruction is incomplete or because there was decompression owing to an antenatal shunt placement or a patent urachus—the outcome can be similar to that of a child with obstructing posterior urethral valves (González et al, 2001). An obstructing membrane is typically seen at the distal end of the prostatic urethra and the urethra distal to that point may be hypoplastic. As a part of the LUTO spectrum seen in antenatally detected anomalies of the lower urinary tract, the obstruction is confirmed after birth with cystoscopy (Fig. 141-16) and a vesicostomy is usually required (Freedman et al, 1999).



Figure 141-16. Cystoscopic image on the second day of life in a neonate with a prenatal history of lower urinary tract obstruction. Cystoscopy demonstrates a near-complete urethral obstruction in the mid-bulbar urethra most consistent with urethral atresia.

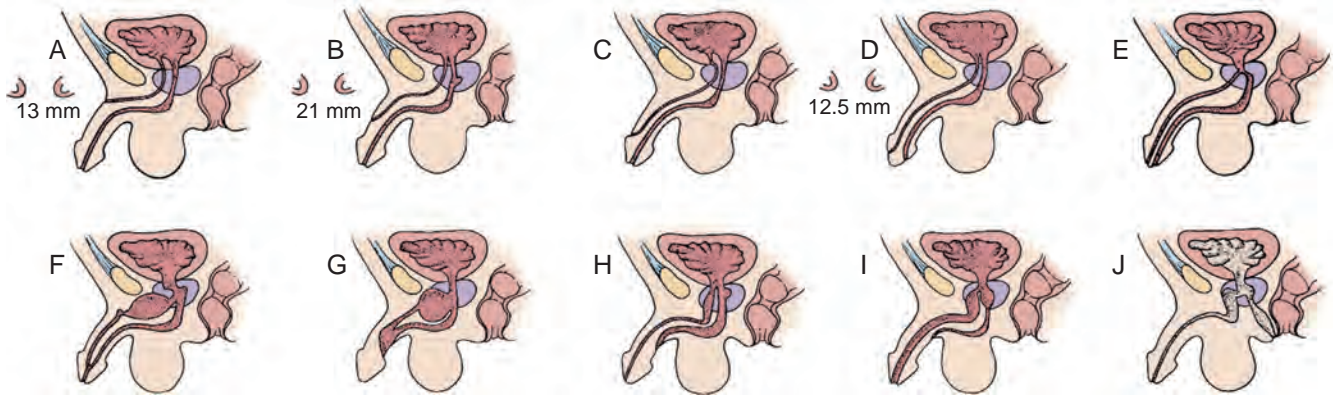


Figure 141-17. A to J, Variations of urethral duplications shown in the sagittal plane. Each of these drawings shows the ventral urethra as the functional one as it passes through the prostate and sphincter. (From Colodny A. Urethral lesions in infants and children. In: Gillenwater JT, Howards SS, Duckett JW, editors. *Adult and pediatric urology*. 2nd ed. St. Louis: Mosby; 1991. p. 2013.)

Whether urethral atresia is a precipitating factor for development of prune-belly syndrome in certain cases remains controversial, but infants with urethral atresia or congenital urethral stricture often will present with oligohydramnios, bilateral hydroureteronephrosis, and weak abdominal wall musculature. The progressive augmentation by dilating the urethra anterior (PADUA) procedure is considered a safe alternative for restoring urethral continuity in selected cases without complex reconstructive surgery (Passerini-Glazel et al, 1988; Stalberg and González, 2012).

Urethral Duplication

Urethral duplication is another rare anomaly of the urethra with several known anatomic variants. The duplication may begin at the bladder neck or within the more distal urethra. Whereas one urethra usually terminates on the glans near its orthotopic position, another urethra may end in a meatus placed on the glans or more ventrally along the shaft of the penis. In the most severe cases, the duplicated urethra may even be as proximal as the anal sphincter. The duplication occurs in a sagittal plane, with the ventral urethra usually the functional meatus containing the sphincteric complex and verumontanum.

Effmann and associates (1976) are credited with the most widely used classification system for urethral duplications. Broadly, the type I abnormality includes a blind incomplete urethral duplication or accessory urethra. Type II is a complete patent urethral duplication with four subtypes and type III refers to urethral duplication as a component of partial or complete caudal duplication (Fig. 141-17). The Y-type duplication refers to a type IIA2 in which the duplicated urethra arises from the first urethra but diverges away to open into a second meatus that opens as ventral as the rectum.

Diagnosis is readily made in some cases when two distinct meatal openings are seen on the glans, but in other cases requires a high index of suspicion when examining what appears to be an atypical case of proximal hypospadias with a patent-appearing opening on the glans. A voiding cystourethrogram will confirm the diagnosis during the voiding phase in many cases, though a retrograde injection of the distinct urethra can also be accomplished (Fig. 141-18) (Hoekstra and Jones, 1985; Podesta et al, 1998).

Surgical management is complex and may require a variety of single or multiple-stage repairs. Whereas the small, blind-ending accessory urethra may be treated expeditiously with simple coagulation of the mucosal tract with a Bugbee electrode, a patent duplicated urethra connected to the bladder with a distinct bladder neck will require a planned reconstruction. When two urethral openings

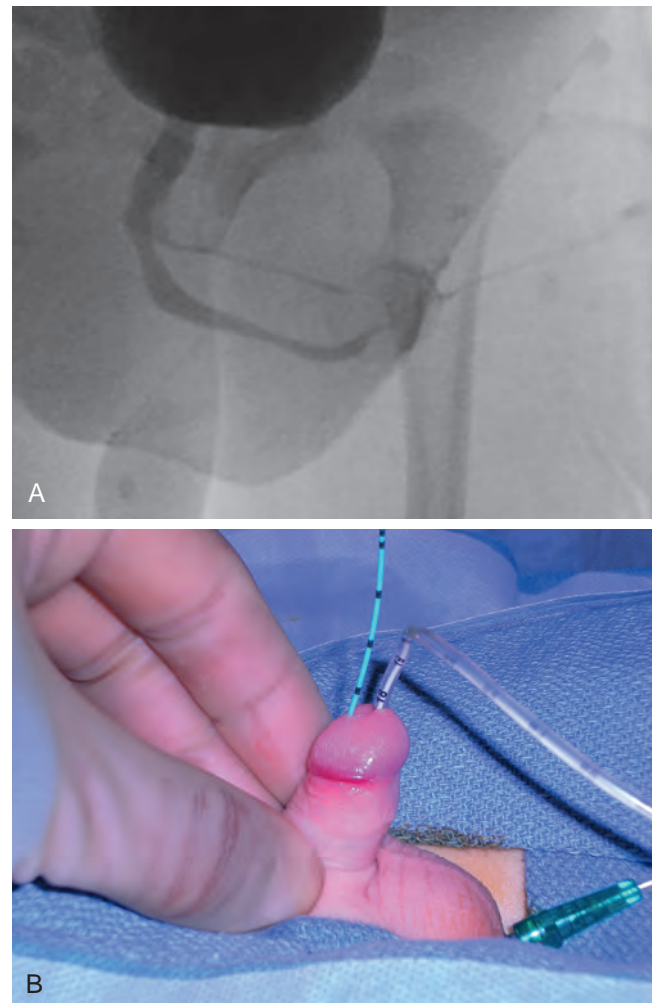


Figure 141-18. A, Voiding cystourethrogram image demonstrates a type IIA2 urethral duplication with two noncommunicating urethral channels passing through the urogenital diaphragm. B, Intraoperative photo of same patient showing two distinct urethral openings that were noted on the glans penis and are cannulated separately.

are found on the glans, the more dorsal urethra may mimic the appearance of a distal epispadias. [Alanee and colleagues \(2012\)](#) recently described a technique by which the septum between the two urethral channels is incised and the dorsal defect is repaired with reverse glans wings to cover a dorsal urethroplasty. In cases in which the urethral openings are separated by the Y-type arrangement, a staged reconstruction using preputial or buccal mucosa flaps is often required to bring the more ventral, but functional, meatus to the glans penis where it can be insinuated into the dorsal, usually atretic, urethra. The anterior sagittal trans-ano-rectal approach (ASTRA) is also recommended as a means to mobilize the meatus placed in the anal sphincter ([Macedo et al, 2012](#)).

Urethrorrhagia

Urethrorrhagia, usually referred to as idiopathic urethrorrhagia, describes a spotting of blood on the underwear after urination, or voiding of clear urine followed by a few drops of blood. The visible blood tends to raise alarm within families, but the condition is typically considered benign and self-limited. Urethrorrhagia is most commonly seen in boys.

The etiology of urethrorrhagia is unclear, though various hypotheses have been offered. Meatal stenosis and dysfunctional elimination syndrome have been suggested as inciting factors ([Herz et al, 2005](#)). Proponents of voiding dysfunction as the etiology of urethrorrhagia hold that increased voiding pressures caused by incomplete relaxation of the external urethral sphincter lead to turbulent flow that creates a negative intraluminal urethral pressure. That negative pressure causes an engorgement of the sinuses of the urethral mucosa and a small extravasation of blood ([Docimo et al, 1998](#); [Herz et al, 2005](#)). Meatal stenosis is similarly proposed as a cause of increased voiding pressures.

Adult urologists consider cystoscopy and upper urinary tract evaluation a necessary step for the evaluation of hematuria, but the high rate of spontaneous resolution of urethrorrhagia in symptomatic adolescent males—up to 92%—means that routine cystoscopy is not necessary. Rather, evaluation should focus on a detailed history of bowel and bladder function, renal and bladder ultrasonography, and an office evaluation of urinary flow rate and postvoid residual. If urethrorrhagia becomes atypical—accompanied by symptoms of urethral stricture or increased urethral bleeding—then cystoscopy should be performed.

Although the majority of cases of urethrorrhagia will have an idiopathic origin, urethral strictures are diagnosed during evaluation in 14% to 60% of patients ([Dewan and Wilson, 1996](#); [Poch et al, 2007](#)). This strong association has led to some debate as to whether cystoscopy itself, in traversing abnormal inflamed epithelium, initiates stricture formation. [Poch and associates \(2007\)](#), in a review of 66 boys with urethrorrhagia, found that cystoscopy in atypical cases of urethrorrhagia identified varying levels of bulbar urethral inflammation, with 24% of patients having a white membranous exudate noted at cystoscopy subsequently being diagnosed with a urethral stricture over a mean of 5 years. In the same cohort, 12% had a stricture found on cystoscopy without any prior history of instrumentation. These findings seem to support a perspective that, although cystoscopy is benign in most cases, the procedure may exacerbate the inflammation of an already inflamed urethra in a small population that cannot readily be distinguished by any radiologic modality. A careful analysis of voiding habits and baseline uroflow is therefore imperative before cystoscopy is considered ([Poch et al, 2007](#)).

Urinary Fistula in Boys with Anorectal Malformation

The vast majority of boys born with anorectal malformation will have a rectal fistula to the urinary tract ([Hong et al, 1992](#)). Since the initial diverting colostomy is completed during the neonatal period, the fistula tract is usually seen on distal colostogram during subsequent workup prior to anorectoplasty (Fig. 141-19).



Figure 141-19. Voiding cystourethrogram in a male infant with an anorectal malformation demonstrates passage of contrast into the rectum via a patent, though small, urethrorectal fistula visualized on the voiding phase of the study.

Pediatric urologists are an integral part of any multidisciplinary team caring for children with anorectal malformations. Because associated genitourinary anomalies range from 25% to 50%, routine diagnostic imaging to determine the presence of renal anomalies and vesicoureteral reflux is recommended ([Hoekstra et al, 1983](#)). A recent analysis of 190 patients with anorectal malformations found that 31 (16.3%) developed a febrile urinary tract infection; of these, 51.6% had a diagnosis of vesicoureteral reflux. On multivariate analysis the presence of genitourinary malformations was associated with a urinary tract infection, but the association did not reach statistical significance ([Sanchez et al, 2014](#)).

When definitive surgical repair is planned in association with general pediatric surgeons, a posterior sagittal approach is preferred to address the rectourethral fistula concurrently. Care must be taken to properly identify the fistula tract and ensure that the tract is excised adjacent to the urethra as well as the rectum, to ensure complete removal of excess tissue that could become a diverticulum if not resected completely.

A urologist is present at the time of anorectoplasty and fistula repair, and the procedure begins with cystoscopy with an attempt to pass an open-ended ureteral catheter through the fistula tract. A guidewire may also be passed if the caliber of the fistula is small. A urethral catheter is then placed into the bladder, across the urethra. Once the child is placed prone, and posterior sagittal anorectoplasty begins, the rectum is adequately mobilized away from the urethra using the previously placed catheter as a guide to location. The fistula tract is excised completely, and the urethral defect is approximated as close to the urethra as possible, reducing the risk of a urethral diverticulum. The rectal defect may be closed primarily, but if redundant intestinal tissue is available, then the fistulous portion of intestine is excised. Healthy adjacent tissue is interposed and the catheter is left in place for at least 1 week to ensure healing of the urethroplasty.

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The complete reference list is available online at www.expertconsult.com.



KEY POINTS: ANTERIOR URETHRAL VALVES, URETHRAL ATRESIA, URETHRAL DUPLICATION, URETHRORRHAGIA, AND ANORECTAL MALFORMATION

- Anterior urethral valves and urethral atresia are less common causes of LUTO, and outcomes can be similar to those of posterior urethral valves if the neonate survives.
- Dysfunctional voiding causing a turbulent urinary flow may lead to urethrorrhagia.
- Treatment for urethrorrhagia should focus on improving voiding habits and conservative management, reserving cystoscopy for refractory cases and when there is significant straining during voiding.
- An infant diagnosed with anorectal malformation should undergo renal ultrasonography as well as VCUG because of the high risk of associated genitourinary anomalies.

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Neural Tube Defects

Principles of Management of Neuromuscular Dysfunction of the Lower Urinary Tract

Management of Vesicoureteral Reflux in Neuropathic Dysfunction of the Lower Urinary Tract

Lipomeningocele and Other Spinal Dysraphisms

Sacral Agenesis

Conditions of the Pelvis

Central Nervous System Insults

Conditions of the Brain (Tumors, Infarcts, Encephalopathies)

Conditions of the Spinal Cord

Neuromuscular dysfunction of the lower urinary tract (LUT) may be either congenital or acquired. The most common cause of congenital dysfunction encountered by the urologist is the condition of neural tube defect (NTD) (Box 142-1). Before 1960, the outcome of children with NTDs was poor, with less than 10% surviving infancy (Rinck et al, 1989). Improvements in neurosurgical and urologic care have resulted in a significant improvement in the survival rate such that by the mid 1990s, more than 85% of children survived infancy (Rinck et al, 1989). Survival has plateaued at this level (Kancherla et al, 2014). The most important intervention in this population was the institution of clean intermittent catheterization (CIC) for the prevention of upper urinary tract deterioration (Lapides et al, 1971). A longitudinal cohort study revealed that one third of children die before 5 years of age, and a further one quarter die before the age of 40 years (Oakeshott et al, 2010). The risk of death correlates with a higher level of neurologic deficit (Oakeshott et al, 2010). As these patients live longer, renal failure becomes an important cause of mortality and thus necessitates lifelong monitoring and management of the urinary tract in infancy (Singhal and Mathew, 1999; McDonnell and McCann, 2000; Mitchell, 2005). For children who survive, challenges persist for the achievement of bowel and bladder continence (Bomalaski et al, 1995; Metcalfe et al, 2011) and sexual function (Lassmann et al, 2007).

NEURAL TUBE DEFECTS

Epidemiology of Neural Tube Defects

The most common cause of neurogenic bladder dysfunction in children is abnormal development of the spinal canal and intervertebral spinal cord. See Figure 142-1 for an example of an open myelomeningocele (MMC). Formation of the spinal cord and vertebral column begins at about the 18th day of gestation. Closure of the canal proceeds in a caudal direction from the cephalad end and is complete by 35 days. The exact mechanism that results in closure and what produces a dysraphic state have yet to be elucidated, but numerous factors have been implicated. NTDs have a worldwide incidence of 0.3 to 4.5 per 1000 births (de Jong et al, 2008). Based on data from 2004 to 2006, the estimated national prevalence of spina bifida (SB) (without encephalocele) in the United States when adjusted for maternal race and ethnicity is 3.50 per 10,000 live births (Parker et al, 2010). This correlates to an estimated 1460 cases annually (Parker et al, 2010). Children born to women of

Hispanic descent have the highest likelihood of an NTD (4.17 per 10,000 births). Non-Hispanic white children have a risk of 3.22 per 10,000 births. The risk for children of non-Hispanic black or African-American descent is the lowest at 2.64 per 10,000 births (Boulet et al, 2008). There is geographic and temporal variation in the incidence of NTDs (Olney and Mulinare, 1998, 2002).

Women with low levels of folic acid and impairment of folate-mediated pathways or antibodies to folate are known to be at increased risk of NTDs (Botto and Mulinare, 1999). Folic acid supplementation in prospective randomized trials resulted in a 50% to 70% decrease in the prevalence of NTDs (Prevention of neural tube defects, 1991; Czeizel and Dudás, 1992; Botto and Mulinare, 1999). In 1992 the U.S. Public Health Service recommended that women of childbearing age take a folic acid supplement (400 µg daily) (Recommendations for the use of folic acid, 1992). The neural tube develops early in gestation, before most women realize that they are pregnant (Botto and Mulinare, 1999). Thus, it is suggested that the optimal time for folic acid supplementation is at least 4 weeks before and during the first month of pregnancy (Czeizel and Dudás, 1992; Dawson et al, 2001). However, only one third of women take a folic acid supplement as recommended (Honein et al, 2001). Therefore, governments regulated the fortification of flour and pasta with folic acid in the late 1990s (Food and Drug Regulations, 1998). Fortification of grains with folic acid has resulted in a 20% to 50% decrease in the prevalence of NTDs (Honein et al, 2001; Godwin et al, 2008).

Risk Factors for the Development of Neural Tube Defects

There is a strong familial risk for NTDs. A mother with one affected child has a 20 to 50 times increased risk of having another child with an NTD, and for an individual with myelodysplasia the risk is 40 times greater than for normal individuals (Scarff and Fronczak, 1981; Stein et al, 1982).

Other well-documented risk factors include young and advanced maternal age (Vieira and Castillo Taucher, 2005); maternal obesity (Stothard et al, 2009); maternal diabetes (Soler et al, 1976); maternal fever or flu (Lynberg et al, 1994); maternal caffeine consumption (Schmidt et al, 2009); specific maternal occupational exposures (Blanco Muñoz et al, 2005); maternal low educational level and socioeconomic status (Blanco Muñoz et al, 2005); maternal passive smoking (Wang et al, 2013); maternal periconceptual stressful event (Li et al, 2013); low maternal weight gain (Shaw et al, 2001);

BOX 142-1 Causes of Neuromuscular Dysfunction of the Lower Urinary Tract**CONGENITAL**

Neural tube defect
Occult forms of neural tube defect (lipomeningocele and other spinal dysraphisms)
Sacral agenesis
Anorectal malformations

ACQUIRED

Extensive pelvic surgery
Central nervous system insults
 Cerebral palsy
 Conditions of the brain (tumors, infarcts, encephalopathies)
Spinal cord insults
 Trauma
 Transverse myelitis



Figure 142-1. Typical appearance of an open myelomeningocele in a neonate.

maternal use of folic acid antagonists such as valproic acid and/or carbamazepine (Lammer et al, 1987; Hernández-Díaz et al, 2001); preceding history of maternal miscarriage (Blanco Muñoz et al, 2006) or other birth defect (Yin et al, 2010); and higher birth order (Vieira, 2004).

Owing to the complex needs of these patients with neurologic, musculoskeletal, gastrointestinal, and developmental challenges, their care is best managed by a dedicated multidisciplinary team.

Pathogenesis

Almost all infants born with MMC have the Arnold-Chiari malformation, which includes hindbrain herniation, brainstem abnor-

TABLE 142-1 Spinal Level of Myelomeningocele

LOCATION	INCIDENCE (%)
Cervical–high thoracic	2
Low thoracic	5
Lumbar	26
Lumbosacral	47
Sacral	20

malities, low-lying venous sinuses, and a small posterior fossa (Adzick et al, 2011). This malformation is also associated with hydrocephalus and developmental brain abnormalities (Adzick et al, 2011). This affects motor, cranial nerve, and cognitive functioning. Hydrocephalus has traditionally been managed by diverting cerebral spinal fluid to the peritoneal cavity with a surgically placed shunt (Adzick et al, 2011). Endoscopic third ventriculostomy combined with choroid plexus cauterization effectively manages hydrocephalus in more than 70% of patients with MMC, avoids the need for placement of a ventriculoperitoneal (VP) shunt, and has similar neurocognitive outcomes as the VP shunt (Warf and Campbell, 2008; Warf et al, 2009).

The neurologic lesion produced by the MMC can be variable, depending on what neural elements, if any, have everted with the meningocele sac. The bony vertebral level often provides little or no clue to the exact neurologic level or lesion produced. The height of the bony level may differ from the highest extent of the neurologic lesion for one to three vertebrae in either direction (Bauer et al, 1977). Therefore, the neurologic lesion produced by this condition influences LUT function in a variety of ways and cannot be predicted just by looking at the spinal abnormality or the neurologic function of the lower extremities. Table 142-1 notes the distribution of spinal levels affected in MMC.

Perinatal Concerns

Antenatal ultrasonography suggests that the insult to the central and peripheral nervous systems of a fetus with MMC is progressive, such that lower limb movement may be lost and hindbrain herniation and hydrocephalus may worsen during gestation (Korenromp et al, 1986; Sival et al, 1997). Animal studies have demonstrated that prenatal coverage of SB-like lesions can preserve neurologic function and limit hindbrain herniation (Meuli et al, 1995). It is postulated that the ultimate neurologic deficit in SB is the result of two “hits”: (1) the initial failure of neural tube formation and (2) ongoing injury to the exposed neural tissue in the intrauterine environment that results from mechanical and chemical trauma (Meuli et al, 1995; Adzick et al, 2011). Thus, it is suggested that in utero intervention may improve outcomes for children with SB.

To further evaluate this theory, a randomized trial of prenatal surgery before 26 weeks of gestation or standard postnatal repair of MMC, the Management of Myelomeningocele Study (MOMS), was completed. The primary outcome (a composite of fetal or neonatal death or the need for a cerebrospinal fluid shunt) was reduced in the prenatal surgery group (relative risk of 0.70). However, 40% of the prenatal closure group still required shunting, and not all experienced improved neuromotor function or complete resolution of hindbrain herniation. The second primary outcome (a composite score of mental development and motor function at 30 months) was also better in the prenatally treated group. No maternal deaths were noted. Fetal and neonatal deaths did not differ between the two groups. However, pregnancy complications, including oligohydramnios, chorioamniotic separation, placental abruption, need for transfusion at the time of delivery, and spontaneous membrane rupture, were more common in the prenatal group. One third of women with prenatal surgery had an area of dehiscence or a very thin uterine surgical scar at the time of delivery. Those fetuses that underwent prenatal surgery were much more likely to be preterm, with an average gestational age of 34.1 weeks (with 13% delivered

before 30 weeks) compared with 37.3 weeks of gestation in the postnatal surgery group (with none delivered before 30 weeks). In addition, infants in the prenatal surgery group underwent more procedures for delayed spinal cord tethering and had a much higher rate of respiratory distress syndrome and a lower birth weight (Adzick et al, 2011).

Bladder Function after Prenatal Closure of Myelomeningocele

Several early studies of a small number of children who underwent closure of the NTD in utero found that urodynamic parameters were similar to those published in the literature for children undergoing standard postnatal closure (Holzbeierlein et al, 2000; Holmes et al, 2001). A case-control series found that those with prenatal closure had a higher incidence of complete denervation of the external urinary sphincter and detrusor overactivity compared with those with postnatal closure (Koh et al, 2006). Larger studies with a comparative postnatal closure group confirmed that there is no difference in the need for CIC, bladder capacity, detrusor overactivity (Clayton et al, 2011; Lee et al, 2012b), incontinence between catheterizations, antimuscarinic use, antibiotic use, detrusor-sphincter dyssynergia (DSD) (Lee et al, 2012b), incidence of detrusor leak point pressure exceeding 40 cm H₂O, vesicoureteral reflux (VUR), need for a bowel regimen, or need for surgery including augmentation cystoplasty, catheterizable channel, or Malone antegrade continence procedure (Clayton et al, 2011).

In summary, prenatal closure of MMC appears to improve neuromotor function and decrease the need for ventriculo-peritoneal shunting. However, this advantage comes with an increased risk of maternal morbidity and preterm labor with its resultant complications. In addition, there is clear evidence that bowel and bladder function are not improved and in some cases may be hindered with prenatal closure of MMC when compared with postnatal closure.

Initial Postnatal Management

Ideally, it would be best to perform urodynamic testing immediately after the infant is born, but the risk of spinal infection and the need for prompt spinal closure have not made this a viable option. It was accomplished in one study, however, and the results showed that 1 in 30 children (3.3%) experienced a change in neurologic status as a result of the spinal canal closure (Kroovand et al, 1990). Therefore, **renal ultrasonography and measurement of residual urine are performed as early as possible after birth**, either before or immediately after the spinal defect is closed. Residual urine may be measured by ultrasound or catheterization after the child voids or leaks urine with a Valsalva maneuver (Bauer et al, 2012). Urodynamic studies are delayed until it is safe to transport the child to the urodynamic suite and place him or her on the back or side for the test. If the infant cannot empty the bladder after a spontaneous void, CIC is begun even before urodynamic studies are conducted. The normal bladder capacity in the newborn period is 10 to 15 mL; therefore a residual urine volume of less than 5 mL is acceptable. Other tests that should be performed in the neonatal period include urinalysis and culture, serum creatinine determination (if indicated after the first week of life when it reflects the child's renal function) (Bauer et al, 2012), and a careful neurologic examination of the lower extremities.

Once the spinal closure has healed sufficiently, a renal ultrasonogram is performed to assess upper urinary tract architecture and function. If hydronephrosis, ureteral dilation, renal size or contour discrepancy, or increased bladder wall thickness is noted, a voiding cystourethrogram (VCUG) is recommended (Bauer et al, 2012). Abnormalities on the initial urodynamic study that warrant further investigation with a VCUG include detrusor overactivity, poor compliance, elevated leak point pressure, or DSD (Bauer et al, 2012). **These studies meet several objectives: They provide baseline information about the radiologic appearance of the upper urinary tract and LUT as well as the condition of the sacral spinal cord and the central nervous system (CNS); they provide infor-**

mation that can be compared with findings of subsequent assessments, so that early signs of deterioration of urinary tract function and drainage, or of progressive neurologic denervation, can be detected; they help to identify infants at risk for urinary tract deterioration as a result of a poorly compliant or overactive detrusor or outflow obstruction from DSD, which predetermines the need to initiate prophylactic measures before any deterioration in upper urinary tract architecture and function actually takes place; and they help the physician to counsel parents about the child's future bladder and sexual function (McGuire et al, 1981; Bauer, 1984a, 1984b; Sidi et al, 1986; Lais et al, 1993). If an abnormality is detected on renal ultrasonography or VUR is demonstrated, a dimercaptosuccinic acid (DMSA) renal scan is recommended.

KEY POINTS: EVALUATION OF THE NEWBORN WITH NEUROGENIC BLADDER DYSFUNCTION

- Renal ultrasonography and measurement of residual urine are performed as early as possible after birth.
- Initial evaluation can be compared with findings on subsequent assessments, so that early signs of deterioration of urinary tract function and drainage, or of progressive neurologic denervation, can be detected.
- Infants at risk for urinary tract deterioration as a result of a poorly compliant or overactive detrusor or outflow obstruction from DSD need to be identified.
- This determines the need to initiate prophylactic measures before any deterioration in upper urinary tract architecture and function take place.
- Three categories of LUT dynamics may be detected: synergic (26%), dyssynergic with and without poor detrusor compliance (37%), and complete denervation (36%).

Findings

Five percent to 10% of newborns have an abnormal urinary tract on radiologic examination when first evaluated (Bauer, 1985); 3% have hydronephrosis secondary to spinal shock, probably from the spinal canal closure (Chiaramonte et al, 1986), and 15% have abnormalities that developed in utero as a result of abnormal LUT function in the form of outlet obstruction (Bauer, 2003).

Urodynamic studies in the newborn period have shown that 63% of infants have bladder contractions. This is also true for an equivalent number of children with upper lumbar or thoracic lesions in whom the sacral spinal cord is spared, 50% of whom have detrusor overactivity (Pontari et al, 1995). Thirty-seven percent have an acontractile detrusor with compliance during filling that is either good (20%) or poor (17%) in this subgroup (Bauer et al, 1984; Bauer, 2003). Electromyographic assessment of the external urethral sphincter demonstrates an intact sacral reflex arc with no evidence of lower motor neuron denervation in 40% of newborns; partial denervation is seen in 24%; and complete loss of sacral cord function is noted in 36% (Lais et al, 1993; Bauer, 2003).

Prediction of Risk of Upper Urinary Tract Deterioration

A combination of bladder contractility and external sphincter activity results in **three categories of LUT dynamics: synergic (26%), dyssynergic with and without poor detrusor compliance (37%), and complete denervation (36%) (Figs. 142-2 and 142-3) (Sidi et al, 1986; Bauer, 2003).** DSD occurs when the external sphincter fails to decrease or actually increases its activity during a detrusor contraction or a sustained increase in intravesical pressure as the bladder is filled to capacity (Blaivas et al, 1981). Frequently, a poorly compliant bladder with high intravesical pressure occurs in conjunction with a dyssynergic sphincter, resulting in a bladder that empties only at high intravesical pressure (Sidi et al, 1986).

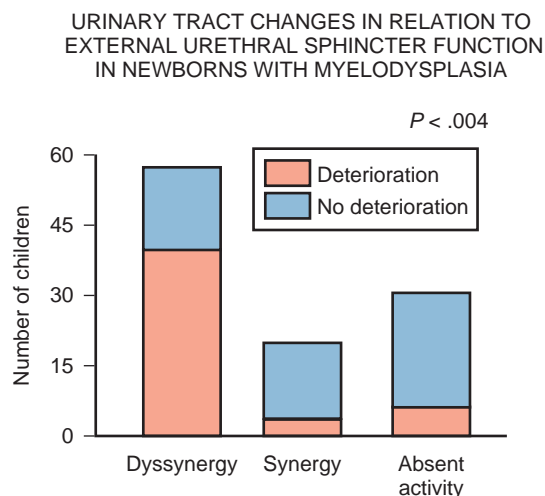


Figure 142-2. Urinary tract deterioration is related to outflow obstruction and is most often associated with dyssynergy. Children with synergy converted to dyssynergy, and patients with complete denervation developed fibrosis with a fixed high outlet resistance in the external sphincter, before any changes occurred in the urinary tract. (From Bauer SB. Early evaluation and management of children with spina bifida. In: King LR, editor. Urologic surgery in neonates and young infants. Philadelphia: Saunders; 1988. p. 252–64.)

(Fig. 142-4). Synergy is characterized by complete silencing of the sphincter during a detrusor contraction or when capacity is reached at the end of filling. Voiding pressures are usually within the normal range. Complete denervation is noted when no bioelectric potentials are detectable in the region of the external sphincter at any time during the micturition cycle or in response to sacral stimulation or a Credé maneuver.

Categorizing LUT function in this way has been extremely useful because it reveals which children are at risk for urinary tract changes, which should be treated prophylactically, and which need close surveillance. Within the first 3 years of life, 71% of newborns with DSD had urinary tract deterioration on initial assessment or subsequent studies, whereas only 17% of synergic children and 23% of completely denervated individuals developed similar changes (see Fig. 142-2). Infants in the synergic group who showed deterioration did so only after they converted to a dyssynergic pattern of sphincter function. Among the infants with complete denervation, the ones who showed deterioration were those who had increased levels of urethral resistance, presumably caused by fibrosis of the skeletal muscle component of the external sphincter. Therefore it appears that bladder outlet obstruction is a major contributor to the development of urinary tract deterioration in these children. Poor detrusor compliance plays an important role in this regard, especially when outlet resistance exceeds 40 cm H₂O (McGuire et al, 1981; Landau et al, 1994; Tanaka et al, 1999). Detrusor compliance seems to be worse in children with high levels of outlet resistance (Ghoniem et al, 1989).

It may be that detrusor filling pressures need to be looked at in a more critical way to determine whether they are an important factor in upper urinary tract deterioration. Landau and colleagues developed the concept of low detrusor filling pressure (less than 30 cm H₂O) at specific volumes adjusted for age, and not at maximal capacity (Landau et al, 1994). Applying this idea, they noted significantly improved sensitivity in predicting upper urinary tract deterioration.

Early Intervention in Children with Myelodysplasia

The concept of early intervention for children with DSD, poor compliance, high bladder pressures, and outflow obstruction was introduced in the early 1990s (McGuire et al, 1981; Bauer et al, 1984; Sidi et al, 1986). Early intervention is herein defined as CIC

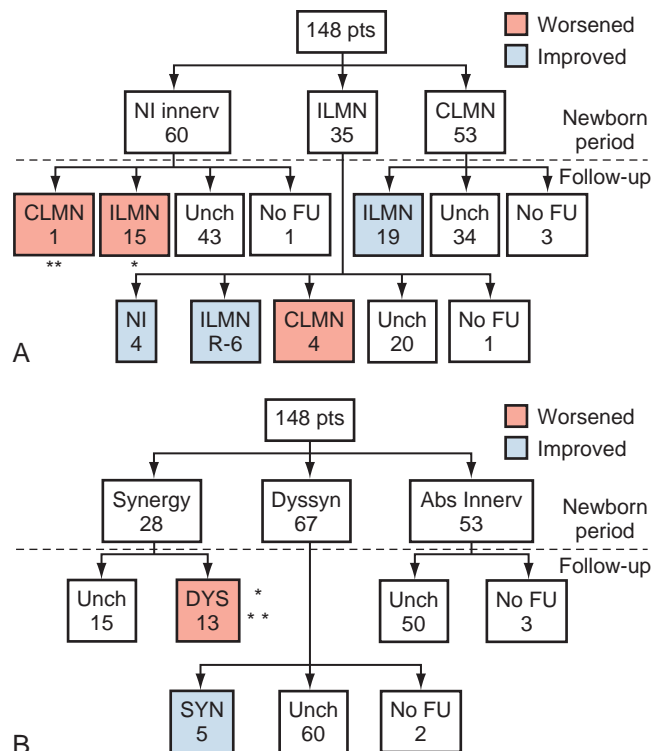


Figure 142-3. Changes in innervation of the purely sacral (A) and pontine-sacral (B) reflex arc pathways that occurred in a group of children with myelodysplasia who were monitored with sequential urodynamic studies beginning in the newborn period. A, The double asterisk indicates 1 patient changed from synergy to dyssynergy, and the single asterisk indicates 4 of 15 patients so changed. B, The single asterisk indicates 1 patient changed from normal to partial and then complete denervation, and the double asterisk indicates 4 patients changed from normal to partial denervation. CLMN, complete lower motor neuron lesion; DYS, dyssynergy; FU, follow-up; ILMN, incomplete lower motor neuron lesion; NI, normal innervation; SYN, synergy; Unch, unchanged. (From Lais A, Kasabian NG, Dyro FM, et al. Neurosurgical implications of continuous neuro-urological surveillance of children with myelodysplasia. J Urol 1993;150: 1879–83.)

and antimuscarinic therapy. There has been some controversy about the benefit of early intervention in children with myelodysplasia; however, there is a plethora of data that document its beneficial effects on outcomes in this population.

Effect of Early Intervention on Bladder Function

In one study of 26 newborns with DSD and high bladder pressures treated with CIC and oxybutynin, this drug was noted to eliminate overactive contractions in 2 of 14 children and lowered peak contractile pressure in the remaining 12 children (Fig. 142-5). It was also noted to lower bladder filling pressure at capacity in all 12 patients with poor compliance (Kasabian et al, 1992). Minimal side effects were noted from its use, and none from CIC (Kasabian et al, 1992). Early intervention also results in improved continence (Kaefer et al, 1999). One study found that up to 44% of children treated with early intervention were dry at age 6 years (Dik et al, 2006).

Early Initiation of Clean Intermittent Catheterization Decreases the Rate of Urinary Tract Infection

Studies of expectant management document urinary tract infection (UTI) in 50% of children by the age of 15 months and 81% by the

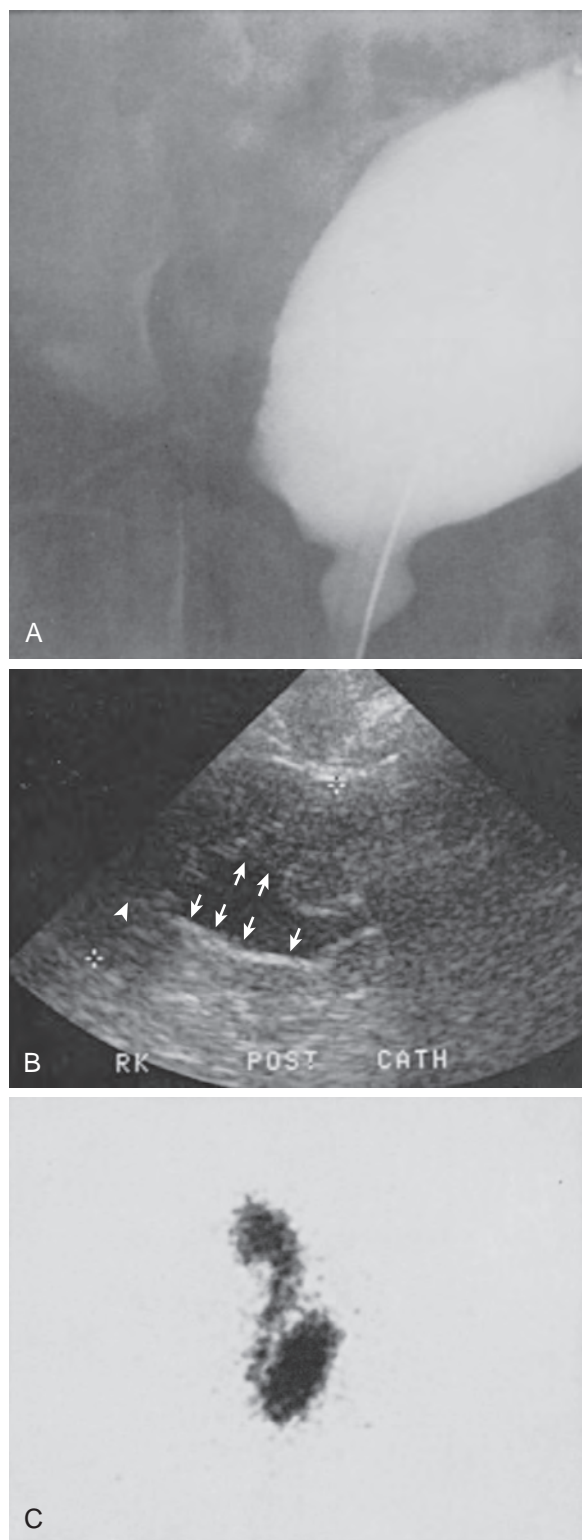


Figure 142-4. A, A voiding cystourethrogram in a female neonate with dyssynergy and elevated voiding pressures demonstrates no reflux and a smooth-walled bladder. Her initial renal echogram was normal. She was started on clean intermittent catheterization and oxybutynin chloride (Ditropan) but did not respond. Within 1 year she developed right hydronephrosis (B, arrows) and severe reflux, evident on a radionuclide cystogram (C).

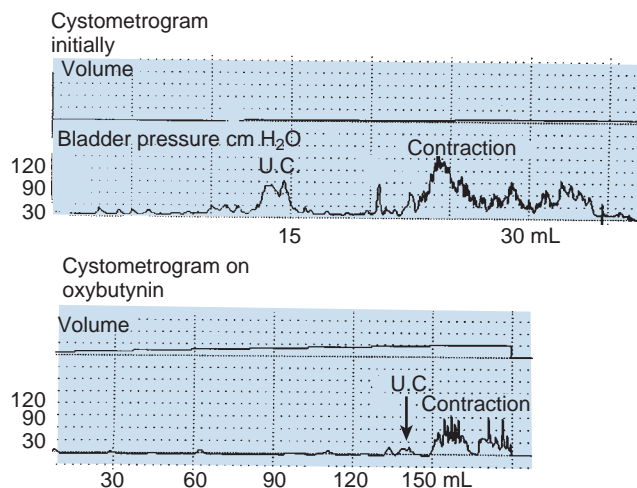


Figure 142-5. Oxybutynin is a potent anticholinergic agent that dramatically delays detrusor contractions and lowers contraction pressure, as demonstrated on these two graphs. U.C., uninhibited contraction.

age of 15 years. In addition, recurrent UTIs are common, with over 44% of children having 5 episodes and almost 10% having more than 20 episodes of UTI (Filler et al, 2011), whereas in children with early institution of CIC, the mean number of infections is 0.3 per year (Wide et al, 2012). Several studies have demonstrated a decreased rate of UTI when CIC is used, either within the same patient (Olandoski et al, 2011) or in contrast to a comparative group (Kari et al, 2009).

Early Intervention Decreases Upper Urinary Tract Deterioration

The potential for the development of hydroureteronephrosis in children with high-risk bladders including DSD is well established. In one study, 72% of children with dyssynergia later developed hydronephrosis (Bauer et al, 1984). Other studies note hydroureteronephrosis in children with high-risk bladders treated expectantly in 18% to 80% (Geraniotis et al, 1988; Edelstein et al, 1995; Kaefer et al, 1999; Kochakarn et al, 2004). The development of hydroureteronephrosis is much less common in trials of early intervention, ranging from 0% to 15% (Geraniotis et al, 1988; Edelstein et al, 1995; Kaefer et al, 1999; Dik et al, 2006).

Early Intervention Reduces Rate of Vesicoureteral Reflux

Studies of expectant management of children with myelodysplasia and high-risk bladders identify VUR in up to 50% of patients by the age of 9 years (Filler et al, 2011). In children managed with CIC from birth, the development of VUR is much less common (28%) (Wide et al, 2012). Another study also found that children treated with CIC early had a much lower incidence of VUR than those who were not on therapy or were noncompliant with therapy (62% vs. 92%) (Kari et al, 2009).

Early Intervention Decreases the Need for Surgery

Several studies comparing early intervention with expectant therapy have noted a lower need for surgical intervention in children with high-risk bladders. Up to 11% of children treated expectantly may require urinary diversion (Filler et al, 2011). Comparatively, no children required renal protective surgery in a group of 41 children treated with early intervention. In fact, only 1 child in this group required surgery for incontinence, and 6 received injection of botulinum toxin (Wide et al, 2012). Others have documented an 18% to 24% reduction in the need for bladder augmentation when early

intervention is compared with expectant management (Kaefer et al, 1999; Kochakarn et al, 2004).

Early Intervention Decreases the Incidence of Renal Scarring and End-Stage Renal Disease

Early intervention does not appear to be advantageous for children who can empty their bladder spontaneously (Torre et al, 2011). Studies of historical cohorts document evidence of renal scarring in 27% to 50% of children (Lewis et al, 1994; Müller et al, 2002; Filler et al, 2011). The rate of renal scarring in children treated with early intervention is much lower, ranging from 4% to 12% (Dik et al, 2006; Torre et al, 2011; Wide et al, 2012). As anticipated, the decrease in renal scarring related to a decreased incidence of end-stage renal disease (ESRD) in children treated with early intervention (0% to 1.6%) (Dik et al, 2006; Torre et al, 2011; Malakounides et al, 2013) compared with those managed expectantly (30%) (Rickwood et al, 1984).

Assessment of Renal Function in Children with Neuromuscular Dysfunction of the Lower Urinary Tract

Although serum creatinine is a widely used marker of glomerular filtration rate (GFR), it is known to be a poor marker of renal function in children with neurogenic bladder dysfunction. Creatinine is produced from the nonenzymatic degradation of creatinine derived from muscle. It is freely filtered and secreted by the kidney (Perrone, 1992). Its serum level is dependent on age, gender, height, and muscle mass (Pham-Huy et al, 2003). Individuals with reduced muscle mass may demonstrate a low endogenous creatinine release that may not result in an elevated creatinine level despite a decrease in GFR (Quan et al, 1997). Numerous studies have confirmed that serum creatinine is not an accurate reflection of GFR in children with myelodysplasia, who often have diminished muscle mass (Quan, 1997; Filler and Lepage, 2003; Pham-Huy et al, 2003). **The gold standard for measuring GFR is the renal scan, which is invasive and exposes the patient to radiation.** Thus, it is preferable to have a serum marker that would closely reflect GFR in this specific population, at high risk of renal functional impairment.

Small molecular weight proteins, such as cystatin C, have been suggested as alternative markers of GFR for children with neuromuscular dysfunction of the urinary tract (Pham-Huy et al, 2003). Cystatin C is a 13-kDa cysteine proteinase inhibitor, produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus, not secreted from the renal tubule, and almost entirely catabolized at the proximal tubule (Grubb, 2000). Thus, the serum concentration of cystatin C is determined primarily by glomerular filtration. When compared with commonly accepted gold standards for the measurement of GFR in children with SB, serum cystatin C levels correlate more closely with GFR than when estimated by the Schwarz formula or other low-molecular-weight proteins (Pham-Huy et al, 2003; Abrahamsson et al, 2008). However, at early stages of renal functional impairment, cystatin C may not be as reliable as a full clearance study (Filler and Lepage, 2003; Abrahamsson et al, 2008). A formula for estimating GFR from serum creatinine in children has been proposed, $\log(\text{GFR}) = 1.962 + [1.123 \times \log(1/\text{cystatin C})]$ (Filler and Lepage, 2003). A recent meta-analysis in a diverse population of adults revealed that cystatin C more accurately predicts the risk of ESRD and death than creatinine (Shlipak et al, 2013).

Thus, serum cystatin C is superior to serum creatinine for estimating GFR in this population; however, when mild renal functional impairment is suspected, a full nuclear medicine clearance study may be required.

Kidney Size in Children with Spina Bifida

Sutherland and colleagues (1997) noted that children with SB had smaller kidneys than their normal peers and generated a nomogram for renal size in this population. The finding of small renal size in

some children with SB has been confirmed by others (Del Gado et al, 2003; Montaldo et al, 2014). It was initially suggested that a potential cause could be low levels of growth hormone, but this has been excluded by the demonstration of normal levels of insulin-like growth factor-1 (Del Gado et al, 2003; Montaldo et al, 2014). A study of newborns with SB found those with small kidneys as well as their mothers to have high serum levels of homocysteine. These infants also had a higher incidence of intrauterine growth retardation. As hyperhomocysteinemia has been linked to placental vasculopathy, it has been suggested that the mechanism for small renal size in children with SB might be related to abnormal placental function (Montaldo et al, 2014). Small renal size in children with SB has been associated with decreased renal function (Del Gado et al, 2003).

Renal Dysfunction in Myelodysplasia

Several studies have identified that surrogate markers of renal dysfunction in children with SB are frequently abnormal. For example, 54% and 19% of children referred to nephrologists for recurrent UTI were noted to have microalbuminuria and metabolic acidosis, respectively (Olandoski et al, 2011). The rate of hypertension in myelodysplastic children ranges from 12% to 41% (Rickwood et al, 1984; Mazur et al, 2011; Olandoski et al, 2011). This is significantly higher than national age-matched control groups (3%) (Mazur et al, 2011). The risk of hypertension is positively correlated with maximum body mass index (Mazur et al, 2011). Hypertension is more frequently noted after puberty and in those with renal scarring (Rickwood et al, 1984).

Some degree of renal dysfunction has been noted in 30% to 50% of children with SB (Müller et al, 2002; Malakounides et al, 2013). Historical studies noted an incidence of ESRD in 18% of children before and 30% of children after puberty (Rickwood et al, 1984). Others have found that ESRD is noted in 15% of those with SB (Cy, 2010). More contemporary studies assessing early intervention with CIC and antimuscarinics note much lower rates of renal dysfunction (6%) and ESRD (0% to 1.6%) (Dik et al, 2006; Torre et al, 2011; Malakounides et al, 2013).

Determinants of Risk of Renal Dysfunction in Myelodysplasia. There has been much investigation regarding the determinants of renal functional loss in children with myelodysplasia. In most studies, renal deterioration or dysfunction is defined as altered renal function as measured by creatinine or creatinine clearance or renal scarring noted on DMSA renal scans. Urodynamic findings that are associated with increased incidence of renal deterioration such as hydronephrosis, VUR, and renal scarring include DSD (Bauer et al, 1984; Ozel et al, 2007); high detrusor pressures (Arora et al, 2007; Ozel et al, 2007; Wide et al, 2012); and detrusor overactivity (Ozel et al, 2007). The association between history of febrile UTI and renal scarring in this population is well documented (Ozel et al, 2007; Shiroyanagi et al, 2009). Hydronephrosis (Arora et al, 2007; DeLair et al, 2007; Ozel et al, 2007; Torre et al, 2011) and VUR (Arora et al, 2007; DeLair et al, 2007; Ozel et al, 2007; Torre et al, 2011) are also associated with renal scarring, although one study using a multivariate analysis demonstrated that a high-pressure bladder and hydronephrosis, in the absence of VUR, were not associated with renal cortical loss (DeLair et al, 2007). Lack of compliance with recommended therapy has also been shown to be an important factor in the development of renal scarring in this population (Kari et al, 2009; Wide et al, 2012).

Sexual Function

Sexuality in this population is becoming an increasingly important issue as more individuals reach adulthood and want to marry or to have intimate relationships (Cromer et al, 1990). Many psychosocial factors play a role in the development and sexual maturation of children with SB. Parents and health care workers are often reluctant to discuss sexual development with adolescents (Sandler et al, 1996; Joyner et al, 1998; Woodhouse, 1998). In addition, teens with SB often experience social isolation (Dorner, 1977;

KEY POINTS: EARLY INTERVENTION AND RENAL FUNCTION IN NEURAL TUBE DEFECTS

- Early intervention with CIC and antimuscarinics improves urodynamic parameters and decreases the rate of UTI, VUR, upper urinary tract deterioration, and the incidence of ESRD.
- Cystatin C is superior to serum creatinine to monitor renal function in children with NTDs. Renography is the gold standard for estimating GFR.
- Determinants of risk of renal dysfunction in myelodysplasia include DSD, high detrusor pressures, detrusor overactivity, febrile UTIs, and VUR. These entities should be actively managed to minimize risk of renal functional decline.

Joyner et al, 1998). This is supported by studies showing that children with MMC are less likely than those without MMC to have their peers act as the main source of sexual education (Dorner, 1977; Decter et al, 1997). Some children with MMC are dependent on others for their activities of daily living and therefore often live with their parents or an alternative caregiver (Börjeson and Lagergren, 1990). Young men with MMC reported better erectile function and intercourse satisfaction when they lived independently (Gamé et al, 2006). Parents of children with SB tend to be more overprotective than parents of normal children and are less willing to grant autonomy to them for adequate peer and sexual development (Holmbeck et al, 2002). When asked about sexual function, many teens with MMC report they find their parents are overprotective or too restrictive (Dorner, 1977). Parental permissiveness in social participation and age-appropriate treatment by parents contribute positively to high self-esteem in these adolescents (Wolman et al, 1994). In a study of life satisfaction of Dutch young adults with SB, the highest proportion of dissatisfaction was found for partnership relations (49%) and sex life (55%). More than 50% of young adults with SB report that they are dissatisfied with their current sex life (Verhoef et al, 2005a). Males with SB were much more dissatisfied with their sex life than females (Barf et al, 2007).

Boys reach puberty at an age similar to the age for normal males, whereas breast development and menarche tend to start as much as 2 years earlier than usual in myelodysplastic females compared with normal girls. In 15% of girls with myelodysplasia, the average age at menarche varies from 10.9 to 11.4 years (Trollman et al, 1998). The cause of this early hormonal surge is uncertain, but it may be related to changes in pituitary function in girls secondary to hydrocephalus (Hayden et al, 1979).

Sexual education specific to individuals with SB should be provided. Latex-free condoms are necessary for those with latex allergy or those adhering to latex avoidance recommendations. The use of estrogen and progestin contraceptives may increase the risk of thromboembolic events in those with decreased mobility, and the use of intrauterine devices for contraception is unsafe owing to pelvic infections (Jackson and Mott, 2007).

The degree of sexuality is inversely proportional to the level of neurologic dysfunction (Joyner et al, 1998; Palmer et al, 1999; Gatti et al, 2009). In addition, lower occurrence of sexual activity seemed to be noted in populations with greater rates of incontinence and more severe disability (Börjeson and Lagergren, 1990; Sandler et al, 1996; Verhoef et al, 2005a; Cardenas et al, 2008; Gatti et al, 2009). Those with the lowest lesion levels are most likely to form partnerships (Gatti et al, 2009). Increasing age is associated with increased likelihood of having a partner; those older than 26 years were 2.1 times more likely to have a partner than those aged 18 to 25 years (Gatti et al, 2009). The absence of hydrocephalus is a positive predictor of sexual activity (Verhoef et al, 2005a). This effect is more pronounced for women than for men (Cardenas et al, 2008). Females are more likely than males to be sexually active (Sawyer and Roberts, 1999; Verhoef et al, 2005a; Cardenas et al, 2008). **Females with SB are at risk of sexual abuse.** Unwanted sexual attention was reported by 37% and unwanted sexual

touching was noted by 30% of women with SB in one study (Sawyer and Roberts, 1999). Four percent of men with SB have experienced improper sexual touching (Sawyer and Roberts, 1999).

In several studies, researchers interviewed groups of teenagers with MMC and reported that 28% to 40% of them had had one or more sexual encounters and almost all of them had a desire to marry and ultimately to bear children (Cromer et al, 1990; Palmer et al, 1999). Seventy percent of those with SB desired sexual contact (Verhoef et al, 2005a). Common features of studies evaluating sexual function in adolescents and young people with MMC include low participation rates resulting from patient or parental refusal and elimination of patients with severe physical disabilities and/or severely compromised intellectual function. This results in a very selected population in which only highly functioning individuals are studied. Five of six studies found that more than 70% of young men with MMC are able to obtain an erection (range 70% to 92%) (Cass et al, 1986; Diamond et al, 1986; Börjeson and Lagergren, 1990; Sandler et al, 1996; Decter et al, 1997). The ability to ejaculate has been found to range from approximately 40% to 75% (Cass et al, 1986; Börjeson and Lagergren, 1990; Sandler et al, 1996; Decter et al, 1997). In some cases, retrograde ejaculation was noted (Sandler et al, 1996). Self-report of sexual activity varied greatly with different study populations, ranging from 8% to 83% for males (Laurence and Beresford, 1975; Cass et al, 1986; Börjeson and Lagergren, 1990; Sandler et al, 1996; Decter et al, 1997) and 23% to 69% for females (Cass et al, 1986; Börjeson and Lagergren, 1990).

Studies reveal that 70% to 80% of myelodysplastic women were able to become pregnant and to have an uneventful pregnancy and delivery, although urinary incontinence in the latter stages of gestation was common in many, as was delivery by cesarean section (Laurence and Beresford, 1975; Cass et al, 1986; Bomalaski et al, 1995; Arata et al, 2000). In the same studies, 17% to 39% of male subjects claimed that they were able to father children, and another 25% had a good prognosis for fathering them (Laurence and Beresford, 1975; Bomalaski et al, 1995; Decter et al, 1997). Both females and males with SB have an increased risk of having a child with SB, compared with individuals without SB (3.7% incidence of SB in offspring) (Bong and Royner, 2007). This effect is more pronounced in females (Chatkupt et al, 1992). If both parents have SB, the risk of having a child with SB increases to 15% (Cameron and Moran, 2009). To reduce this risk, women with SB should be counseled about taking 4.0 to 5.0 mg of folic acid supplement daily before even contemplating getting pregnant (Visconti et al, 2012). It is more likely that men will have problems with erectile and ejaculatory function because the sacral spinal cord is frequently involved, whereas reproductive function in women, which is under hormonal control, is not affected. Men with neurologic lesions at S1 or lower are likely to have normal or adequate reproductive sexual function, but only 50% of those with lesions above that level have adequate function (Woodhouse, 1994, 2005). Poor semen quality (Reilly and Oates, 1992) and Sertoli cell-only histology on testis biopsy (Glass and Soni, 1999) have been reported as reasons (in addition to erectile dysfunction) for infertility in males with SB.

One study used a validated questionnaire, the International Index of Erectile Function (IIEF) to evaluate sexual function in men older than 18 years with MMC (Gamé et al, 2006). Overall, 75% of the men had erectile dysfunction. Of the 16 men who had recently had sexual intercourse, 4 had no erectile dysfunction, 3 had mild dysfunction, 4 had mild-to-moderate dysfunction, and 5 had severe dysfunction. Erectile function was directly related to the ability to maintain erections and the presence of a sacral nerve root lesion (Gamé et al, 2006). The role of intact pelvic parasympathetic reflex activity has been demonstrated to be a positive correlate in men with MMC (Diamond et al, 1986; Sandler et al, 1996).

Medical therapy for erectile dysfunction has been shown to be effective in this population. Sildenafil improved erectile function in 80% of men with MMC in a randomized, double-blind, placebo-controlled trial (Palmer et al, 1999). Some promise has been shown with attempts to restore penile sensation in men with SB by connecting the sensory ilioinguinal nerve

microsurgically to the ipsilateral dorsal nerve of the penis in men with normal groin sensation (Jacobs et al, 2013; Overgoor et al, 2013). Preliminary results in small case series showed increased sensation of the ipsilateral glans penis, better overall sexual function, and increased satisfaction (Overgoor et al, 2013), but these findings await long-term studies.

Management of Neurogenic Bowel Dysfunction in Myelomeningocele

Options for the management of constipation traditionally include dietary modification, digital stimulation, laxatives, enemas, and biofeedback therapy. Management in children with neurogenic bowel must be tailored to the individual's ability to address mobility and balance, ability for self-care, manual dexterity, and anal sphincter tone.

Two thirds of children aged 6 and older and one third of children and young adults aged 16 to 25 years with SB report fecal incontinence, which has a substantial impact on their quality of life (Krough et al, 2003; Verhoef, et al, 2005b). Most recommend a **graduated approach** to the management of constipation in this population (Vande Velde et al, 2007; Burgers et al, 2013; Choi et al, 2013a, 2013b). Initially, treatment is directed toward high dietary fiber and osmotic laxatives (Vande Velde et al, 2007; Choi et al, 2013b). Polyethylene glycol has been shown to be more effective in this population than lactulose (Rendeli et al, 2006). An option for those who are unable to sit on the toilet is **controlled constipation with manual evacuation of stool** because large-volume enemas cannot easily be delivered in these children (Vande Velde et al, 2007). In those who are able sit independently, with some anal sphincter activity, a regular postprandial toilet sitting regimen three times daily after meals has been effective, as it employs the gastrocolic reflex to initiate a bowel movement (Vande Velde et al, 2007). When continence is not achieved by defecation, **digital stimulation** is suggested (Vande Velde et al, 2007). If manual evacuation fails or if the anal sphincter is nonfunctioning, **retrograde enemas** (tap water with irrigation cone) followed by kneading of the abdomen or alternative transanal irrigation devices (Ausili et al, 2010) are instituted (Shandling and Gilmour, 1987; Vande Velde et al, 2007). Initially enemas are given daily, and, if successful, the frequency can be decreased to every second day. Initial enema volume is 500 mL and increased to 1 L if required. If fecal incontinence persists at this point, the **antegrade continence enema (ACE)** is considered the next step in management. Antegrade continent enemas are begun on a daily basis and reduced to 4 to 5 times per week as needed over time, if successful. Volumes used range from 1 to 2 L (Vande Velde et al, 2007). This stepwise approach to fecal pseudocontinence was successful in 69% of patients with MMC; 10% achieved fecal continence. Of those who were pseudocontinent, 16% used manual evacuation, 10% used a toileting scheme, 42% used retrograde enemas, and 32% used ACE (Vande Velde et al, 2007). The addition of polyethylene glycol (GoLYTELY), mineral oil, polyethylene glycol 3350 (MiraLAX), or glycerin to tap water enemas has successfully increased the continence rate for ACE regimens (Bani-Hani et al, 2008).

ACE delivered through a surgically placed appendicostomy or cecostomy was first described in children with SB or anorectal malformations by Malone and colleagues (1990). Use of ACE has been shown to significantly improve fecal continence, not increase the amount of time dedicated to bowel care, and improve quality of life (Ok and Kurzrock, 2011). Anal plugs may be effective for some patients during specific activities, such as swimming (Vande Velde et al, 2007). Long-term studies indicate that approximately 40% of children discontinue use of their surgically created cecostomies after a median of 11 years. Reasons for nonuse include lack of effectiveness, complications, psychological issues, and poor compliance (Yardley et al, 2009). In those who continue using the cecostomy, their level of satisfaction is very high (Yardley et al, 2009). Placement of percutaneous cecostomy under fluoroscopic guidance for delivery of the ACE in children with SB was described by Shandling

and colleagues (1996); it provides the advantage of avoiding laparotomy or laparoscopy.

Initial Diagnostic Evaluation and Follow-Up of Congenital Neuropathic Dysfunction in Children

The initial diagnostic evaluation of neuropathic bladder dysfunction will be discussed as it relates to specific pathologic processes throughout the chapter. The International Children's Continence Society (ICCS) has recently published general recommendations for the follow-up of congenital neuropathic bladder that are a compilation of best practices as a result of a paucity of high-level evidence (Bauer et al, 2012). These recommendations are based on developmental stages and associated growth spurts in the first 2 years of life and adolescence that may increase the risk of spinal cord tethering and are summarized in Table 142-2. An example of the magnetic resonance imaging (MRI) findings in a patient with spinal tethering is shown in Figure 142-6. A recent study has noted that in adulthood, patients followed at a multidisciplinary SB clinic had developed a urologic issue at a median of 12 months and 40% had an asymptomatic urologic issue at 36 months. This suggests that a follow-up period of 12 to 18 months in adulthood may be prudent (Duplisea et al, 2014).

PRINCIPLES OF MANAGEMENT OF NEUROMUSCULAR DYSFUNCTION OF THE LOWER URINARY TRACT

The primary principle in management of neuromuscular dysfunction of the LUT is preservation of renal function. Secondary goals include attaining urinary and fecal continence, avoidance of UTI, and facilitation of sexual function and fertility. **Preservation of renal function is best achieved by maintaining low bladder pressures, avoiding hydronephrosis, and actively managing VUR if recurrent UTIs occur.** Initial efforts to reduce bladder pressures include minimally invasive therapy to reduce bladder pressures such as CIC and antimuscarinic therapy. If this is unsuccessful, overnight indwelling catheter drainage has been shown to improve or resolve hydronephrosis, increase bladder capacity, and decrease the frequency of UTI (Koff et al, 2005). Those who have failed conservative management require surgical intervention. When choosing a surgical intervention, consideration must be given to the patient's ambulatory status, body habitus, manual dexterity, compliance with therapy, and capacity to provide self-care.

The normal bladder functions by storing urine at low pressures and empties by coordinating decreased outlet resistance with a bladder contraction. In neuropathic dysfunction, incontinence may result from failure of proper storage, emptying, or both. Storage may be compromised by low compliance, low capacity, overactive bladder contractions, and low bladder outlet resistance. Emptying may be compromised by inadequate bladder contractions or DSD. Tables 142-3 and 142-4 indicate some possible options to address the failure of storage (Table 142-3) and emptying (Table 142-4) in neuropathic dysfunction of the LUT in children. The specific medical and surgical treatment options are described in the following sections.

Medical Management of Neuropathic Dysfunction of the Lower Urinary Tract

Antimuscarinic drugs are the first-line treatment for detrusor overactivity (Hood and Andersson, 2013). The detrusor smooth muscle has M₂ and M₃ receptors. M₂'s predominate in number; however, M₃ receptors mediate the direct contractile effects of acetylcholine in the detrusor (Hegde and Eglen, 1999). Initial response rates are good; however, adverse effects and decreasing efficacy result in dwindling long-term compliance (Hood and Andersson, 2013). Use of antimuscarinics in children with detrusor overactivity results in increased bladder capacity, increased volume to first detrusor

TABLE 142-2 Summary of the International Children's Continence Society Recommendations for the Diagnostic Evaluation and Follow-up of Congenital Neuropathic Bladder and Bowel Dysfunction in Children

AGE GROUP	TYPE OF INVESTIGATION	RECOMMENDED FREQUENCY OF INVESTIGATION	INDICATION FOR INVESTIGATION
Newborn to toddler	Ultrasound Urodynamic studies DMSA renal scan	Every 6 mo until age 2 yr Every 12 mo When indicated	High risk of tethering with rapid growth UTIs or lower extremity changes Consider if VUR on initial VCUG/RNC or febrile UTIs
Toddler to adolescent	Ultrasound Urodynamic studies DMSA renal scan	Every 12 to 24 mo When indicated When indicated	Low risk of tethering with slower growth Change in ambulation or lower extremity function Febrile UTIs
Adolescent to adult	Ultrasound Urodynamic Studies VCUG/RNC	Every 12 mo When indicated When indicated	Low risk of tethering with slower growth; may decrease to every 24 mo once growth velocity has decreased Development of hydronephrosis, more frequent CIC required for continence, new wetting, recurrent UTI Recurrent UTI
Adult	Ultrasound Urodynamic studies	Every 36 mo When indicated	Low risk of tethering without ongoing somatic growth Development of hydronephrosis, more frequent CIC required for continence, new wetting, recurrent UTI

CIC, clean intermittent catheterization; DMSA, dimercaptosuccinic acid; RNC, radionuclide cystogram; UTI, urinary tract infection; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

KEY POINTS: MANAGEMENT OF NEUROPATHIC DYSFUNCTION OF THE LOWER URINARY TRACT

- The primary goal of management is preservation of renal function.
- Secondary goals of management include urinary and fecal continence, avoidance of UTI, and facilitation of sexual function and fertility.
- Preservation of renal function is achieved by maintaining low bladder pressures and active management of VUR and avoidance of UTI.
- The ICCS recommendations for follow-up are based on developmental stages and the relative risk for secondary spinal cord tethering.
- Minimally invasive therapies should precede the use of more invasive therapies to address failure of the bladder to store or empty.

contraction, decreased number of incontinence episodes, and decreased number of catheterizations (Ellsworth et al, 2005; Nijman et al, 2005; Christoph et al, 2007; Reddy et al, 2008; Alloussi et al, 2010; Bolduc et al, 2010). Common adverse events include dry mouth, constipation, blurred vision, facial flushing, dizziness, and headache (Ellsworth et al, 2005; Nijman et al, 2005; Christoph et al, 2007; Reddy et al, 2008; Alloussi et al, 2010; Bolduc et al, 2010). There have been some concerns about potential cognitive effects of antimuscarinics, but a prospective, randomized, double-blind trial showed no negative effect of antimuscarinic medications on attention or memory (Giramonti et al, 2008).

The most commonly used antimuscarinic agent in children is oxybutynin. It may be delivered orally, transcutaneously (Cartwright et al, 2009), or intravesically (Guerra et al, 2008). Oral administration is usually done at 0.2 mg/kg/dose given up to three times daily. Oral preparations include tablets, syrup, and extended-release tablets. All three have been shown to be safe and effective



Figure 142-6. Magnetic resonance image of a 9-year-old girl who developed a tethered cord after myelomeningocele repair reveals the conus opposite the L3-4 vertebrae (arrow).

TABLE 142-3 Strategies to Address Inadequate Bladder Storage in Children with Neurogenic Bladder Dysfunction

CAUSE OF INADEQUATE STORAGE	MINIMALLY INVASIVE TREATMENT OPTIONS	MORE INVASIVE TREATMENT OPTIONS
Low compliance	CIC Antimuscarinic therapy Overnight catheter drainage	Intravesical botulinum toxin Augmentation cystoplasty Urinary diversion
Low capacity	Antimuscarinic therapy Overnight catheter drainage	Intravesical botulinum toxin Augmentation cystoplasty Urinary diversion
Overactive bladder contractions	CIC Antimuscarinic therapy Overnight catheter drainage	Intravesical botulinum toxin Augmentation cystoplasty Urinary diversion
Low bladder outlet resistance	Sympathomimetic therapy	Bladder neck sling Bladder neck procedure Injection of bulking agents into bladder neck

CIC, clean intermittent catheterization.

TABLE 142-4 Strategies to Address Inadequate Bladder Emptying in Children with Neurogenic Bladder Dysfunction

CAUSE OF INADEQUATE EMPTYING	MINIMALLY INVASIVE TREATMENT OPTIONS	MORE INVASIVE TREATMENT OPTIONS
Inadequate bladder contractions	CIC Overnight catheter drainage	Neuromodulation
Detrusor sphincter dyssynergia	CIC Antimuscarinic therapy Overnight catheter drainage	Intravesical and/or sphincteric botulinum toxin Augmentation cystoplasty Urinary diversion Neuromodulation

CIC, clean intermittent catheterization.

in children (Franco et al, 2005). The transdermal dose is 3.9 mg daily (Cartwright et al, 2009). Transdermal oxybutynin has been shown to be a well-tolerated and effective alternative to oral oxybutynin in children with neurogenic detrusor overactivity. Skin irritation is noted in some patients, which leads to discontinuation of treatment in 20% of children (Cartwright et al, 2009; Gleason, et al, 2014). A systematic review noted a low level of evidence for the intravesical use of oxybutynin, which is thought to result in fewer side effects by avoiding first-pass metabolism. It did increase maximum bladder capacity and decrease bladder pressure with lower side effects than oral administration; however, 9% of children discontinued its use because of side effects and 22% because of other issues such as inconvenience of administration (i.e., crushing pills to prepare the solution) (Guerra et al, 2008).

Fesoterodine is an oral antimuscarinic. Its active metabolite, 5-hydroxymethyl tolteridene, is the same as tolteridene, but fesoterodine has less pharmacokinetic variability (Malhotra et al, 2011). It has been shown to be safe and tolerable in children at daily doses of 4 mg and 8 mg (Malhotra et al, 2012). Its main benefit is the fact that a methyl group has been added that bypasses the cytochrome oxidase enzymes that convert tolterodine to its active form, leading to a more effective antimuscarinic drug (Chapple et al, 2007).

Solifenacin is a once-daily antimuscarinic that has been shown to increase urodynamic bladder capacity, decrease overactive contractions, and improve continence with acceptable tolerability and safety in an open-label study of children with neurogenic and non-neurogenic detrusor overactivity who were recalcitrant to oxybutynin or tolterodine therapy (Bolduc et al, 2010). In this study, 21% had mild side effects, 4% had moderate side effects, and 5% withdrew because of intolerable adverse effects.

Tolteridene (antimuscarinic) has been noted to inhibit nonvoiding bladder activity, as well as to reduce the amplitude of voiding

contractions (Gillespie et al, 2012). In children with neurogenic detrusor overactivity, tolteridene was shown to be well tolerated, with minimal treatment-related adverse events; to increase functional bladder capacity in children younger than 10 years; and to decrease the mean number of incontinence episodes with long-term (12-month) use (Reddy et al, 2008).

Mirabegron is a novel β_3 -adrenergic receptor antagonist that decreases the number of micturitions and improves continence (Yamaguchi et al, 2014). It works by stimulating β_3 receptors located throughout the bladder that, when stimulated, elicit relaxation of the detrusor muscle by activating adenylyl cyclase, causing increases in the intracellular levels of cyclic adenosine monophosphate (cAMP) and calcium (Chapple et al, 2014). It is effective in adults but has not yet been approved by the U.S. Food and Drug Administration (FDA) for use in children.

Sympathomimetic Agents (Fig. 142-7)

Examples of sympathomimetic agents include ephedrine hydrochloride (0.5 to 1.0 mg/kg/day tid) and pseudoephedrine (0.4 mg/kg bid to 0.9 mg/kg tid). If incontinence results from inadequate urethral resistance, sympathomimetic agents act to increase tone at the bladder neck where the concentration of α -adrenergic receptors is highest, thereby raising outlet resistance and improving continence. It is hard to predict which children might respond to these drugs, which potentially increase bladder outlet resistance by stimulating receptors in the trigone and bladder neck, but in some patients there is a dramatic increase leading to continence between CICs (Bauer, personal communication, 2014). Regular use of sympathomimetic agents, however, may be limited by their side effects, including dizziness, nausea, nervousness, insomnia, loss of appetite, headache, mood changes, and urinary retention.

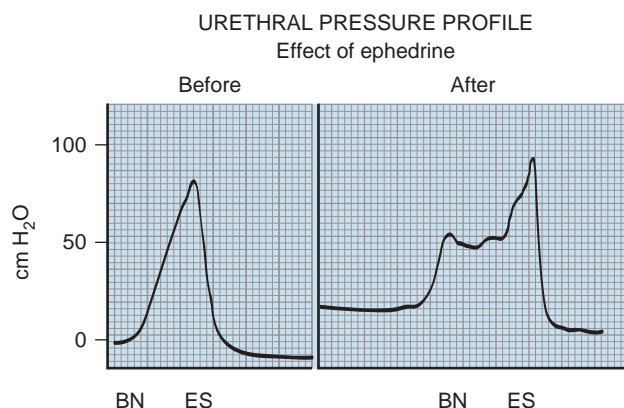


Figure 142-7. α -Sympathomimetic agents potentially have their greatest effect in the bladder neck region, where the highest concentration of α -adrenergic receptor sites exists. They can raise outlet resistance and improve continence in many individuals. BN, bladder neck; ES, external sphincter.

Surgical Treatment Options for Neuropathic Dysfunction of the Lower Urinary Tract

Botulinum Toxin

An alternative option for detrusor overactivity in neurogenic bladder is the intravesical injection of botulinum A toxin (BTA). BTA is a neurotoxin protein produced by the gram-positive bacterium *Clostridium botulinum*; it acts by inhibiting acetylcholine release, resulting in muscle paralysis. BTA has also been found to inhibit the release of other neurotransmitters including adenosine triphosphate and neuropeptides such as substance P, and to down-regulate the expression of purinergic and capsaicin receptors on afferent neurons within the bladder (Apostolidis et al, 2006; Chapple and Patel, 2006). The first use of BTA to treat neurogenic detrusor was in adults with spinal cord injury (Dykstra and Sidi, 1990). The first use in children with neuropathic bladder was documented in 2002 (Schulte-Baukloh et al, 2002). A systematic review of the use of BTA in children with neurogenic detrusor overactivity found that the most commonly injected dose is 10 IU/kg, with a maximum total dose of up to 300 IU. Most studies use 30 injection sites, sparing the trigone with rigid cystoscopy and using general anesthesia. Sixty-five percent to 87% of children in whom conservative medical management and CIC have failed have achieved dryness with a BTA injection (Riccabona et al, 2004). Improvements in urodynamic parameters include decreased maximum detrusor pressure (33% to 57%); increased maximum cystometric capacity (34% to 165%); and improved compliance (121% to 183%). The duration of response ranges from 6 to 10.5 months (Gamé et al, 2009). The most common minimal age for injection was 2 years, which corresponds to that approved by the FDA for the treatment of cerebral palsy (Gamé et al, 2009).

Overall, patient and caregiver satisfaction with this treatment exceeds 70% (Figuerola et al, 2014). Injection of BTA may allow approximately 25% of patients to discontinue antimuscarinic therapy after the first injection and an additional 10% after a second injection (Figuerola et al, 2014). Side effects from BTA are infrequently reported by patients (Kask et al, 2013). Side effects of intravesical BTA injection include urinary retention, UTI, hematuria, transient muscle weakness, dysuria, and pain (Duthie et al, 2011). It appears that repeated injections continue to be effective, with the interval between repeated injections increasing with each series of injections (Schulte-Baukloh et al, 2005; Altaweel et al, 2006). A reduction of dose in repeat injections (300 IU to 200 IU) was associated with recurrence of symptoms, which resolved with reinstitution of the original regimen (Figuerola et al, 2014). Injection of

intradetrusor BTA avoided bladder augmentation in close to 90% of children in whom first-line treatment with CIC and antimuscarinics had failed in one study (Figuerola et al, 2014). Serial injections of BTA show additional, significant improvement in urodynamic parameters, suggesting that tachyphylaxis, neutralizing antibody formation, or progressive fibrosis are not considerations with repeat BTA injections (Figuerola et al, 2014). This finding is supported by histopathologic examination of the detrusor. One study found no significant difference in edema, inflammation, or fibrosis when comparing children with neurogenic dysfunction before their first injection with those having had an intradetrusor injection of BTA previously. Repeated injections were associated with a significant decrease in the amount of fibrosis compared with those with no history of injection (Pascali et al, 2011).

Children who respond poorly to BTA intradetrusor injection have preexisting poor bladder compliance (Kask et al, 2013). Complete lack of a response to BTA injection has been linked to the presence of BTA antibodies (Schulte-Baukloh et al, 2008). One study compared injection of BTA in the detrusor to injection in both the detrusor and external urinary sphincter in 60 children with neurogenic dysfunction in whom CIC and antimuscarinic therapy had failed. More than 90% of the study population had DSD documented before injection of BTA. The researchers found that those with sphincter injection had a significant improvement in postvoid residual urine measurement and the presence of DSD on follow-up urodynamic studies; clinical parameters including constipation and incontinence trended toward improvement in the group with injections into the external urethral sphincter, although it was not a statistically significant difference (Safari et al, 2010). A larger study is required to confirm these preliminary findings.

Thus, intradetrusor injection of BTA is associated with improved continence and urodynamic parameters and may avoid reconstructive surgery in those in whom conservative management has failed. Serial injections are not associated with fibrosis or a decreased treatment effect.

For a thorough discussion of the surgical management of neurogenic bladder in children including augmentation, autoaugmentation, urinary diversion, bladder neck procedures, and the artificial urinary sphincter (AUS), please see the Expert Consult website.

Neuromodulation

Electrostimulation

Most studies of electrostimulation in pediatric neurogenic bladder involve a small sample size, often lack a control group, and have varied methods of electrostimulation and different outcome measures. Although some studies have shown improvement in clinical and urodynamic parameters, larger, prospective, randomized trials are required (Godec and Cass, 1978; Dexter et al, 1992, 1994; Balcom et al, 1997; Marshall and Boston, 1997; Han et al, 2004; Cirović et al, 2009; Kajbafzadeh et al, 2009, 2010; Choi et al, 2013a).

Sacral Neuromodulation

Sacral neuromodulation has been used extensively in children with non-neurogenic bladder dysfunction. Its use in children with neurogenic dysfunction has been limited. One prospective, randomized study of 42 children with SB comparing standard conservative management and sacral neuromodulation found that urodynamic variables did not differ between the two groups with the exception of better functional bladder capacity in the control group and lower leak point pressure in the neuromodulation group (Guys et al, 2004). Some of those in the implant group noted improved intestinal transit, resolution of UTI, and better sensation of a persistently full bladder (Guys et al, 2004). Seven percent of the neuromodulation group required revision surgery (Guys et al, 2004). Thus, sacral neuromodulation in this population appears to be safe with some limited benefits over standard therapy, but a larger study is required to determine its efficacy.

Surgical Management of Neuropathic Dysfunction of the Lower Urinary Tract

Augmentation

A persistent poorly compliant, small-capacity, or overactive detrusor may be treated with enterocystoplasty (Mitchell and Piser, 1987; Sidi et al, 1987). It is estimated that in the early 2000s, approximately 5.4% of children with SB underwent augmentation cystoplasty (Lendvay et al, 2006). Sigmoid, cecum, stomach, and small intestine have been used to enlarge the bladder. The ileocecal segment is avoided in children with myelodysplasia because removing it might aggravate the bowel dysfunction in these children (Bauer, personal communication, 2014). Detubularization of the bowel is needed to minimize the intrinsic contractions of the intestinal segment and prevent it from causing intractable incontinence once it has been added to the bladder (Goldwasser et al, 1987; Hinman, 1988).

Most studies evaluating outcomes for augmentation cystoplasty have patient populations with mixed causes (primarily neurogenic bladder but also other etiologies such as exstrophy-epispadias, posterior urethral valves, and so on), and augmentation cystoplasty is performed with and without concomitant procedures such as continent catheterizable channels, antireflux surgery, and bladder outlet procedures. Thus there are limited data that reflect the outcomes specifically in those with neurogenic bladder treated with augmentation cystoplasty in isolation. Continence is achieved in 90% or more (Shekarriz et al, 2000; Husmann and Cain, 2001; Quek and Ginsberg, 2003; Veenboer et al, 2013). Increased mean bladder capacity (Krishna et al, 1995; Quek and Ginsberg, 2003), improved compliance (Veenboer et al, 2013), and safe storage pressures (Krishna et al, 1995; Quek and Ginsberg, 2003) are achieved in most patients. Preexisting hydronephrosis resolves in up to 92% (Krishna et al, 1995).

Postoperative urodynamic studies may reveal regular phasic contractions (Robertson et al, 1991). It is unclear if these contractions arise from the bowel segment or the remaining bladder. These contractions are usually of low-amplitude activity (<40 cm H₂O), and are volume dependent, occurring only at volumes above 200 mL (Quek and Ginsberg, 2003). Zero to 29% of patients require antimuscarinics after augmentation (Mitchell et al, 1986; Luangkhot et al, 1991; Herschorn and Hewitt, 1998; Chartier-Kastler et al, 2000; Quek and Ginsberg, 2003).

Complications of Augmentation Cystoplasty. The complication rate of augmentation cystoplasty is approximately 30% (Metcalf et al, 2006b; Schlomer et al, 2013). Approximately half of those are considered to be major complications (Schlomer et al, 2013). Complications include small bowel obstruction (Schlomer et al, 2013), bleeding requiring transfusion (Schlomer et al, 2013), fistula (Schlomer et al, 2013), bladder perforation (Metcalf et al, 2006b), and recurrent UTIs or pyelonephritis (Flood et al, 1995; Bertschy et al, 2000; DeFoor et al, 2004). The need for further surgery is estimated to be 0.04 operations per patient per year. Further surgery may include surgical intervention for stones (11% to 63%) (Flood et al, 1995; DeFoor et al, 2004; Metcalf et al, 2006a), laparotomy for bowel obstruction (3.2% to 4%) (Flood et al, 1995; Metcalf et al, 2006a), closure of bladder perforation (4% to 13%) (Bauer et al, 1992; Flood et al, 1995; Krishna et al, 1995; Bertschy et al, 2000; Shekarriz et al, 2000; DeFoor et al, 2003; Metcalf et al, 2006b), and revision of or repeat augmentation (9.4% to 16%) (Flood et al, 1995; Metcalf et al, 2006a).

Risk factors for the development of stones in augmented bladders include excessive mucus production from enteric segments (Hensle et al, 2004), use of the ileal segment (DeFoor et al, 2004; Metcalf et al, 2006b), the presence of an abdominal stoma (Hensle et al, 2004), and an immobile patient with sensory impairment (Hensle et al, 2004). Stone formation is recurrent in up to 30% of patients (Flood et al, 1995; DeFoor et al, 2004). Regular irrigation with water or saline is recommended to decrease the rate of stone formation related to mucus (Hensle et al, 2004).

Bladder perforation is a life-threatening complication of bladder augmentation and requires prompt diagnosis and treatment. In some individuals it is a recurring problem (Metcalf et al, 2006b). Presenting symptoms include abdominal distention and pain, septic shock, and shoulder pain related to diaphragmatic irritation from extravasated urine (Bauer et al, 1992). Sepsis resulted in death in 25% of patients with bladder perforation in one series (Bauer et al, 1992). Those with a history of bladder outlet procedures seem to be at increased risk (Bauer et al, 1992; Metcalf et al, 2006b). It appears that those with a catheterizable abdominal stoma are at lower risk of perforation (Metcalf et al, 2006b), perhaps because of increased compliance with catheterization schedules (Horowitz et al, 1995). There is controversy about which bowel segment is at highest risk of rupture; some studies have identified the sigmoid colon as the most likely to perforate, although most of the sigmoid segments in this series were not detubularized (Metcalf et al, 2006b), whereas others have found that ileum is the most likely to rupture (Bauer et al, 1992). Because of the risk of sepsis and death, diagnosis and treatment should be prompt. Cystography (either fluoroscopic or with computed tomography [CT]) is diagnostic in most but not all cases (Bauer et al, 1992; Slaton and Kropp, 1994). It is postulated that overdistention and relative ischemia related to bowel detubularization are important in the pathophysiology of rupture (Bauer et al, 1992). The gold standard approach to management of this problem is exploratory laparotomy and closure of the perforation; however, conservative management with drainage of the urinary reservoir and percutaneous drainage of abdominal urinoma in patients without hemodynamic instability or worsening symptoms has been described (Slaton and Kropp, 1994; Leyland and Masters, 2003).

Long-term metabolic complications are also common with augmentation cystoplasty. Concerns have surfaced about gastric segments because they can cause hyponatremic hypochloremic metabolic alkalosis (Gosalbez et al, 1993) or the hematuria dysuria syndrome (Castellan et al, 2012). Except for children with progressive or end-stage renal failure, gastrocystoplasty is not recommended currently as a routine form of augmentation (Chadwick Plaire et al, 2000; Leonard et al, 2000). Augmentation cystoplasty with any segment of the gastrointestinal tract can lead to long-term consequences in acid-base balance, vitamin B₁₂ deficiency, fat absorption, renal function changes, aberrant bone metabolism, and growth retardation (Gilbert and Hensle, 2005).

It has been suggested that patients with SB are at increased risk for bladder cancer (Austin et al, 2007). Proposed risk factors for the development of malignancy in SB include chronic UTI, stone disease, repeated catheterization, and incorporation of enteric segments (Mehan et al, 2011). Early reports suggested that intestinal and gastric bladder augmentation were associated with an increased risk of bladder cancer. The largest study found that bladder cancer developed in 0.6% of patients undergoing augmentation (Metcalf et al, 2006a). Most studies note a 10-year minimum lag time between the augmentation and presentation of disease. Presenting symptoms are often atypical and may include vague abdominal pain, gross hematuria, urosepsis, renal failure, difficult catheterization, increasing frequency of UTI, new-onset hydronephrosis, and bladder wall thickening (Austin et al, 2007; Castellan et al, 2007; Vemulakonda et al, 2008; Veenboer and Kort, 2011). Age at presentation is younger than is typical for bladder cancer (Austin et al, 2007; Veenboer and Kort, 2011). One study found that almost 90% of patients had locally advanced disease or lymph node metastases at presentation (Austin et al, 2007). Urothelial cell carcinoma accounts for close to 60% of the tumors, followed by squamous cell carcinoma in 21%, adenocarcinoma in 16%, and signet cell tumor of the gastric augment in 5% (Austin et al, 2007). Some studies have disputed the association of enteric augmentation and an increased risk of malignancy. For example, there have also been reports of malignancy in those with autoaugmentation without incorporation of enteric segments (Mehan et al, 2011; Veenboer and Kort, 2011). In addition, several studies have found that enteric augmentation in this group does not result in a greater risk of

developing malignancy than in a comparable group of patients without augmentation (Austin et al, 2007; Higuchi et al, 2010). Most of these studies are compromised owing to relatively small study numbers and confounding factors, such as smoking history, exposure to known carcinogens, and family history, all of which are not addressed. Thus it is clear that patients with neurogenic bladder affected by bladder malignancy have a younger age at presentation, atypical symptoms, and advanced disease. Some, including the ICCS, have recommended annual surveillance cystoscopy and cytology starting 5 to 10 years after augmentation (Soergel et al, 2004; Castellán et al, 2007; Vemulakonda et al, 2008; Rawashdeh et al, 2012). However, there is insufficient evidence to determine the efficacy of screening for bladder cancer in this population (Kokorowski et al, 2011). In fact, four of six patients diagnosed with bladder cancer had no discernible mass noted on routine cystoscopic surveillance (Castellán et al, 2007; Vemulakonda et al, 2008). In addition, hypothetical models predict that screening for bladder cancer after augmentation cystoplasty is not cost-effective (Kokorowski et al, 2011).

Alternatives to standard augmentation cystoplasty have been sought to avoid the short- and long-term complications associated with this procedure. Although initial reports of autologous tissue-engineered bladder augmentation were promising (Atala et al, 2006), a recent phase II study showed that bladder capacity and compliance were not improved and the incidence of serious adverse events was unacceptable (Joseph et al, 2014).

Autoaugmentation

Because augmentation with enteric segments has a significant risk for short- and long-term complications, some have advocated for autoaugmentation or detrusorrectomy (with or without demucosalized enteric segments) to treat small and poorly compliant neurogenic bladders (Cartwright and Snow, 1989a; 1989b). Although some series have shown short-term improvement in bladder capacity, compliance, and maximum detrusor pressures (Hansen et al, 2013), when compared with enteric augmentation, those who have had autoaugmentation are more apt to be incontinent, use antimuscarinics, and have worse compliance (Marte et al, 2002; MacNeily et al, 2003; Veenboer et al, 2013). The incidence of de novo hydronephrosis (30%) (MacNeily et al, 2003) and VUR (Marte et al, 2002) in autoaugmentation is unacceptably high. The failure rate of autoaugmentation and need for subsequent augmentation cystoplasty ranges from 15% to 45% (Marte et al, 2002; MacNeily et al, 2003; Hansen et al, 2013; Veenboer et al, 2013). The lack of long-term improvement in urodynamic parameters and continence, combined with the high failure rate, make autoaugmentation an undesirable option.

Urinary Diversion

Urinary diversion, once considered a panacea for children with myelodysplasia, has turned out to be a Pandora's box of new clinical problems (Schwarz and Jeffs, 1975; Shapiro et al, 1975). Pyelonephritis and renal scarring, urinary tract calculi, ureterointestinal obstruction, strictures of the conduit, and stomal stenosis are often encountered in children who are monitored on a long-term basis. In recent times, urinary diversion is rarely performed unless accompanied by a continent catheterizable stoma.

Incontinent Urinary Diversion. Button vesicostomy using a gastrostomy button was first described in 1996 (de Badiola et al, 1996). It has the advantage of being readily reversible and can be used as a temporary measure. The incidence of minor complications such as transient leakage, wound infection, and overgranulation are expected in 40%, with 17% requiring removal or replacement of the device because of infection, device failure, and significant leakage (Bradshaw et al, 2014).

Vesicostomy drainage (Duckett, 1974; Mandell et al, 1981) is rarely required today but is reserved for those infants (1) who have such severe reflux that CIC and antimuscarinic medication fail to improve upper urinary tract drainage, (2) whose parents cannot

adapt to the catheterization program, or (3) who are not good candidates for augmentation cystoplasty (Morrisroe et al, 2005). It has been shown to improve renal function, hydronephrosis, and VUR in almost all patients undergoing the procedure (Queipo Zaragozá et al, 2003). Complications include bladder stomal prolapse, stomal stenosis, peristomal irritation, and vesical lithiasis (Queipo Zaragozá et al, 2003).

Ileovesicostomy is suggested to be advantageous over vesicostomy because an external appliance can be applied to the stoma that eliminates the need for diapers (Ching et al, 2014). Although short-term results look promising (Ching et al, 2014), long-term follow-up reveals that over half of children require reoperation or additional procedures (Tan et al, 2008; Hellenthal et al, 2009).

Urethral Dilation. External urethral dilation (up to 36 Fr in infants or up to number 18 Hegar dilators in older children) under general anesthesia has been described to address elevated leak point pressures in select children with neurogenic bladder dysfunction who have not responded to CIC and antimuscarinic therapy (Bloom et al, 1990). The mean number of dilations needed per patient is 1.6 (Park et al, 2001). The dilation in males can be achieved via perineal urethrostomy (Bloom et al, 1990; Miller et al, 2003). Durable (mean follow-up of 8 years) improvement has been demonstrated in mean leak point pressure, capacity, and initial and terminal compliance (Bloom et al, 1990; Park et al, 2001). Those with an elevated leak point pressure and good initial compliance seem to have the most long-lasting results from the procedure. However, upper urinary tract deterioration was noted in 20% by about 9.5 years after the dilation (Park et al, 2001). Approximately 43% have improvement in VUR and 64% have improvement or resolution of hydronephrosis (Kiddoo et al, 2006). Thus, urethral dilation may benefit a select group of children with neurogenic bladder in whom initial conservative measures fail but long-term follow-up is compulsory.

Bladder Neck Procedures

Artificial Urinary Sphincter. In children with low bladder outlet resistance, the AUS provides increased outlet resistance while maintaining the ability to catheterize per urethra. In children, the sphincter may be placed at the bladder neck or bulbar urethra (in males). The procedure is often performed in conjunction but not simultaneously with other procedures, such as augmentation cystoplasty to address poor compliance and low bladder volumes. Continence rates range from 63% to 86% (Simeoni et al, 1996; Spiess et al, 2002; Herndon et al, 2003; Catti et al, 2008). The need for revision ranges from 16% to 61% (Simeoni et al, 1996; Spiess et al, 2002; Catti et al, 2008), with erosion of the cuff noted in 16% to 20% (Simeoni et al, 1996; Castera et al, 2001; Catti et al, 2008). Worsening of bladder function is noted in 4% to 30% (Simeoni et al, 1996; Castera et al, 2001; Catti et al, 2008). This is seen more commonly in those with a preexisting poorly compliant or overly contractile bladder. Long-term surveillance is required in all patients because they may develop bladder hypertonicity after outlet resistance is increased, which can lead to upper urinary tract changes eventually causing renal failure (Castera et al, 2001). Patients with an AUS are less likely to void spontaneously if the sphincter is implanted before puberty or in conjunction with an augmentation cystoplasty (Catti et al, 2008). Mean operational life of the AUS ranges from 4.6 to 12.7 years (Simeoni et al, 1996; Castera et al, 2001; Spiess et al, 2002). Better continence outcomes are noted in those without a history of a prior bladder neck procedure (Castera et al, 2001).

Bladder Neck Slings. It is difficult to compare published data concerning the effectiveness of bladder neck slings in the treatment of bladder outlet incompetence, because most published series include patients with varied preoperative bladder function and previous or concurrent procedures, such as augmentation cystoplasty, bladder neck reconstruction, and continent catheterizable channels. As well, there is no standardized definition of continence. In addition, varied materials are used to perform the sling including rectus fascia (Bauer et al, 1989; Walker et al, 1995), bladder wall (Alboust et al, 2007), and small intestinal submucosa (Colvert et al,

2002; Misseri et al, 2005a). Success rates for continence appear to be similar with the varied sling materials, although rectus fascia is used most commonly. Both U-shaped and 360-degree type slings are described (Bauer et al, 1989; Snodgrass et al, 2007). And again, similar continence rates are noted. In those with decreased bladder compliance or hypercontractility, bladder neck slings are usually done in conjunction with augmentation cystoplasty, yielding continence rates of 30% to 93%, with most studies noting success in excess of 70% (Barthold et al, 1999; Dik et al, 1999; Walker et al, 2000; Albouy et al, 2007; Churchill et al, 2010). Continence rates for females tend to be better than for males treated with a bladder neck sling (Barthold et al, 1999; Colvert et al, 2002). Most studies note that bladder neck slings do not lead to difficulty with catheterization (Albouy et al, 2007; Dean and Kunkle, 2009; Churchill et al, 2010). Some have advocated for the use of a bladder neck sling alone, without augmentation, in children with neurogenic sphincter deficiency, bladder underactivity, and a detrusor leak point pressure below 25 cm H₂O (Snodgrass et al, 2007). Continence, defined as two or fewer wet pads per day, is noted in 83% (Snodgrass et al, 2007). However, as noted in those with increased outlet resistance after placement of an AUS (Bauer et al, 1986), these patients are at risk for developing hypercontractility and decreased bladder compliance. Approximately one third of patients treated with a tight 360-degree bladder neck sling develop increased bladder pressures and/or overactive detrusor contractions (Snodgrass et al, 2007; Snodgrass and Barber, 2010). Most of these children responded to antimuscarinic treatment, although augmentation cystoplasty was required in 2 of 37 patients (5%) (Snodgrass and Barber, 2010; Snodgrass et al, 2010). Therefore if a bladder neck sling procedure is done in isolation, long-term surveillance is

required to monitor for changes in bladder function to prevent upper urinary tract deterioration. When compared with those who had a bladder neck sling without augmentation, those with augmentation had a longer interval between catheterizations, required less antimuscarinic medication, and scored higher on a health-related quality-of-life survey for achieving independence for self-directed care (Snodgrass et al, 2009). For children who do not achieve continence with a bladder neck sling, placement of an AUS is more likely to be effective than injection of periurethral bulking agents (Barthold et al, 1999).

Injection of Periurethral Bulking Agents

Over time, the type of material injected to increase outlet resistance at the bladder neck has changed; currently the most commonly used agent is dextranomer/hyaluronic acid (Alova et al, 2012; DaJusta et al, 2013). Success rates for achieving complete continence with retrograde, transurethral injection of the bladder neck are low, ranging from 7% to 50%, with deterioration in results over time (Guys et al, 2001; Godbole et al, 2003; Misseri et al, 2005b; Guys et al, 2006; Lottmann et al, 2006; De Vocht et al, 2010; Alova et al, 2012; DaJusta et al, 2013). Repeat injections do not appear to be beneficial (De Vocht et al, 2010; Alova et al, 2012). Success in those with antegrade injection of bulking agents and suprapubic catheter drainage postinjection is much better, ranging from 70% to 78% (Dean et al, 2007; Kaye et al, 2010; Alova et al, 2012). Thus, although the success rates are low, bladder neck injection of bulking agents does achieve dryness for some children with neurogenic sphincter deficiency. Antegrade injection has superior success rates compared with retrograde injection.

Artificial Somatic-Autonomic Reflex Pathway Procedure

The artificial somatic-autonomic reflex pathway is a promising new therapeutic approach to restore bladder function in children with SB. The procedure involves a limited laminectomy and a lumbar ventral root to S3 ventral root microanastomosis. The L5 dorsal root is left intact as the afferent branch of the somatic-autonomic reflex pathway after axonal regeneration (Xiao et al, 2005). In a series of 20 children with SB, 17 developed satisfactory bladder control and continence within 12 months of the procedure. Those children with DSD and overactivity demonstrated nearly normal storage and synergic voiding on follow-up urodynamic studies (Xiao et al, 2005). A recent study at an independent center confirmed early favorable results with improved continence, bowel function, and spontaneous voiding in 30% of the SB patients (median age 8 years) who underwent intradural lumbar to sacral motor root microanastomosis. Postoperative complications included prolonged wound drainage, ipsilateral footdrop, and temporary lower extremity muscle weakness (Peters et al, 2010). Others have found variable results and in some cases no improvement in bladder function (Nouhaud et al, 2011; Tuite et al, 2013). Thus this novel approach appears to have promising results when performed by experts. The long-term results and general application of the procedure have yet to be determined.

KEY POINTS: MEDICAL AND SURGICAL TREATMENT OPTIONS

- Antimuscarinic therapy and CIC are the mainstays of therapy.
- Bladder pressures should be maintained below 30 cm H₂O as much as possible to prevent urinary tract deterioration.
- Intravesical injection of botulinum toxin is well tolerated and avoids the need for more invasive treatment options in a high proportion of children, with minimal side effects.
- Enterocystoplasty is an effective option to prevent deterioration of upper tracts but comes with a high risk of complications.
- Patients undergoing isolated bladder neck procedures (AUS and bladder neck sling) may develop hypercontractility and poor compliance that lead to upper tract deterioration, mandating close follow-up.

MANAGEMENT OF VESICoureTERAL REFLUX IN NEUROPATHIC DYSFUNCTION OF THE LOWER URINARY TRACT

VUR occurs in 3% to 5% of neonates with myelodysplasia, usually in association with poor detrusor compliance, detrusor overactivity, and/or DSD (Flood et al, 1994). It is rare to find reflux in any neonate without these urodynamic findings (Bauer, 1984; Geraniotis et al, 1988; Edelstein et al, 1995). If left untreated, the incidence of reflux in these infants at risk increases with time until 30% to 40% are affected by 5 years of age (Bauer, 1984; Seki et al, 1999). In children with reflux grades I to III (International Classification) who void spontaneously or have a complete lesion with little or no bladder outlet resistance and who empty the bladder completely, management consists solely of prophylaxis with antibiotics to prevent recurrent infection. In children with high-grade reflux (grade IV or V), CIC is begun to ensure complete emptying. Children who cannot empty the bladder spontaneously, regardless of the grade of reflux, are treated with CIC to empty the bladder efficiently.

Children with poor detrusor compliance with or without hydro-ureteronephrosis are also started on antimuscarinic agents to lower intravesical pressure and ensure adequate upper urinary tract decompression (Flood et al, 1994). When reflux is managed in this manner there has been a dramatic response, with reflux resolving in 30% to 55% of individuals (Kass and Koff, 1981; Bauer, 1984;

Joseph et al, 1989; Flood et al, 1994; Agarwal et al, 1997; Hopps and Kropp, 2003). Although bacteriuria can occur in as many as 56% of children on CIC, it is not harmful except in the presence of high-grade reflux, because symptomatic urinary infection and renal scarring rarely occur with lesser grades of reflux (Kass and Koff, 1981; Cohen et al, 1990).

Credé voiding should be avoided in children with reflux, especially those with a reactive external urethral sphincter. In this circumstance, the Credé maneuver results in a reflex response in the external sphincter that increases urethral resistance and raises the pressure needed to expel urine from the bladder (Barbalias et al, 1983) (Fig. 142-8). This has the effect of aggravating the degree of reflux and accentuating its water hammer effect on the kidneys.

The indications for antireflux surgery in this group of children are not very different from those applicable to children with normal bladder function. They include recurrent symptomatic (febrile) urinary infection while the child is receiving adequate antibiotic therapy and appropriate catheterization techniques; persistent hydronephrosis despite effective emptying of the bladder and lowering of intravesical pressure; and severe reflux with an anatomic abnormality at the ureterovesical junction.

Jeffs and colleagues were the first to show that antireflux surgery can be very effective in children with neurogenic bladder dysfunction as long as it is combined with measures to ensure complete bladder emptying (Jeffs et al, 1976). Before this observation was made, the results of ureteral reimplantation were so dismal that most physicians treating these children advocated urinary diversion as a means of managing reflux (Smith, 1972; Cass, 1976). Since the advent of CIC, success rates for antireflux surgery have approached 95% (Kass and Koff, 1981; Woodard et al, 1981; Kaplan and Firlit, 1983). Bilateral surgery for unilateral disease need not be done, because contralateral reflux does not occur postoperatively (Bauer, 1984a).

In patients with low-grade reflux who are undergoing augmentation cystoplasty, most clinicians have found acceptable resolution

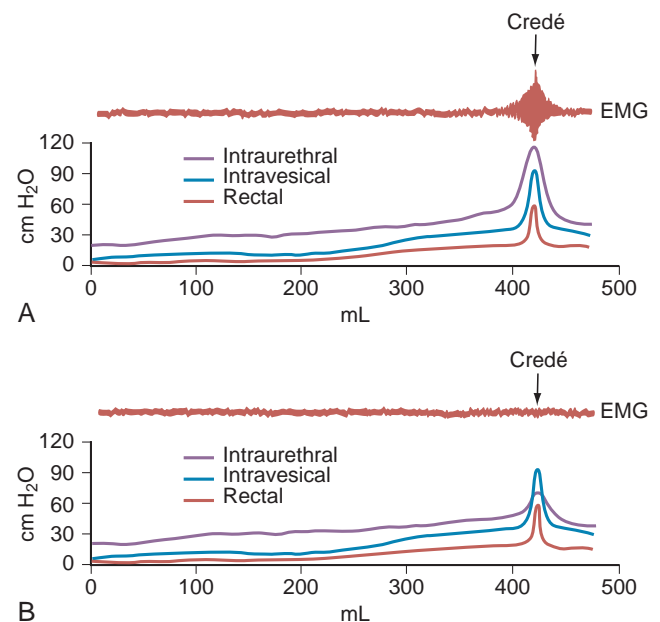


Figure 142-8. When the external sphincter is reactive (A), a Credé maneuver produces a reflex increase in electromyographic (EMG) activity of the sphincter and a concomitant rise in urethral resistance, resulting in high voiding pressure. A child whose sphincter is denervated and nonreactive (B) will not have a corresponding rise in EMG activity, urethral resistance, or voiding pressure. A Credé maneuver here will not be detrimental. (From Bauer SB. Early evaluation and management of children with spina bifida. In: King LR, editor. Urologic surgery in neonates and young infants. Philadelphia: Saunders; 1988. p. 252–64.)

rates of VUR without ureteral reimplantation (Morioka et al, 1998; López Pereira et al, 2001; Helmy and Hafez, 2013). However, for those with high-grade reflux (grades III and greater) treated with augmentation cystoplasty alone, persistence of VUR ranges from 20% to 47% (Morioka et al, 1998; Wang et al, 2011; Helmy and Hafez, 2013). Thus, children with high-grade reflux undergoing augmentation cystoplasty should have concurrent ureteral reimplantation (Morioka et al, 1998; Wang et al, 2011; Helmy and Hafez, 2013).

The endoscopic injection of various materials has altered the management of reflux in children with MMC (Schlussel, 2004). Success rates of 73% with one injection and 91% with two injections have been reported for the endoscopic management of VUR in those with neurogenic bladder dysfunction (Misra et al, 1996; Estornell Moragues et al, 2008). It has been suggested that success rates of endoscopic therapy in children with neurogenic bladder do not differ from those with a normal bladder (Routh et al, 2008). Higher success rates approaching 95% have been noted when endoscopic treatment of VUR is paired with intravesical injection of botulinum toxin (Neel et al, 2008; Neel, 2010).

However, the durability of this approach has been questioned, with one study showing that 40% of those with initial success with endoscopic management had VUR recur at a mean of 4.5 years after the initial treatment (Polackwich et al, 2012). Studies comparing the effectiveness of open surgical to endoscopic management in this population show a significantly greater success rate for traditional open procedures (84.3% to 95.5% vs. 61% to 72.5%) (Engel et al, 1997; Granata et al, 1999). Thus, the endoscopic approach is a reasonable alternative to ureteroneocystotomy; however, long-term outcomes raise concerns about the durability of this approach in those with neurogenic bladder dysfunction.

KEY POINTS: MANAGEMENT OF VESICoureTERAL REFLUX

- Low-grade reflux in those who are emptying well without outlet resistance can be managed with antibiotic prophylaxis alone.
- Patients with high-grade reflux or who are not emptying well also require CIC.
- Those with poor compliance with or without hydronephrosis should be started on antimuscarinics.
- The Credé maneuver is contraindicated in reflux.
- Indications for surgery for reflux are similar to those for children without neurogenic bladder. Success rates are similar if effective bladder emptying is addressed.

LIPOMENINGOCELE AND OTHER SPINAL DYSRAPHISMS

Presentation

There is a group of congenital defects that affect the formation of the spinal column but do not result in an open vertebral canal (James and Lassman, 1972) (Box 142-2). They occur once in 4000 live births, but with the ease of MRI screening of children with

suspected lesions, the detected incidence of these defects is increasing (Bruce and Schut, 1979). The incidence of lipomeningocele in families was calculated to be 0.043% (Sebold et al, 2005). These lesions can be very subtle and have no obvious outward signs, but in more than 90% of children there is a cutaneous abnormality overlying the lower spine (Anderson, 1975; Pierre-Kahn et al, 1997). This varies from a small dimple or skin tag to a tuft of hair, a dermal vascular malformation, a very noticeable subcutaneous lipoma, or an asymmetrically curving gluteal cleft (Fig. 142-9). In addition, on careful inspection of the legs, one may note a high arched foot or feet; hammer toes or claw toes; a discrepancy in muscle size, leg length, and decreased strength in one leg compared with the other, typically at the ankle; and/or a gait abnormality, especially in older children (Dubowitz et al, 1965; Weissert et al, 1989; Jindal and Mahapatra, 2000). Absent perineal sensation, back pain, and secondary incontinence after a period of dryness are common symptoms in older children and young adults (Linder et al, 1982; Yip et al, 1985; Weissert et al, 1989). LUT function is abnormal in 40% to 90% of affected older individuals, with the incidence of an abnormality increasing proportionately with age (Mandell et al, 1980; Koyanagi et al, 1997; Pierre-Kahn et al, 1997; Sarica et al, 2003). The child may experience difficulty with toilet training, urinary incontinence after an initial period of dryness once toilet trained (especially during the pubertal growth spurt), recurrent urinary infection, and/or fecal soiling. Occasionally, some patients without an obvious back lesion escape detection until they develop urinary (66%) or lower extremity (19%) symptoms or back pain (14%) after puberty, caused by delayed traction on the spinal cord (Satar et al, 1995).

When these children are evaluated in the neonatal period or early infancy, a majority have perfectly normal neurologic examination findings (Atala et al, 1992). Urodynamic testing, however, reveals abnormal LUT function in about one third of infants younger than 18 months (Keating et al, 1988) (Fig. 142-10). Such studies may provide the only evidence of a neurologic injury involving the lower spinal cord (Keating et al, 1988; Foster et al, 1990; Atala et al, 1992; Satar et al, 1995; Nogueira et al, 2004). When present, the most likely abnormality is an upper motor neuron lesion characterized by an overactive detrusor and/or hyperactive sacral spinal cord reflexes (Fone et al, 1997; Pierre-Kahn et al, 1997); mild forms of DSD are rarely noted. Lower motor neuron signs with denervation potentials in the sphincter or an acontractile detrusor occur in only 10% of young children.

In contrast, practically all individuals older than 3 years who have not been operated on or in whom an occult dysraphism has been belatedly diagnosed have either an upper or a lower motor neuron lesion or a combination thereof on urodynamic testing (92%) (see Fig. 142-10) or neurologic signs of lower extremity dysfunction (Yip et al, 1985; Kondo et al, 1986; Keating et al, 1988; Atala et al, 1992; Satar et al, 1995; Nogueira et al, 2004). When such children were observed expectantly from infancy after the diagnosis was made, 58% experienced deterioration of their disorder within 2 years (Andar et al, 1997; Cornette et al, 1998). There does not seem to be a preponderance of one type of lesion over another (i.e., upper vs. lower motor neuron), and often the child shows signs of both (Hellstrom et al, 1986; Kondo et al, 1986). In one study of children older than 3 years, 43% had denervation in the sphincter and 52% had an acontractile detrusor, with a total of 81% having an abnormality (Satar et al, 1995).

Pathogenesis

Various occult spinal dysraphic lesions produce different neurourologic findings. When they do cause an abnormality, lipomas of the cauda equina invariably cause an upper motor neuron lesion (70%), alone or in combination with a lower motor neuron deficit (30%) (Satar et al, 1995). The split cord syndrome results in an isolated upper or lower motor neuron lesion in 25% each or a combined lesion in 50% (Proctor et al, 2000).

The reason for this difference in neurologic findings may be related to (1) compression of the cauda equina or sacral nerve

BOX 142-2 Types of Occult Spinal Dysraphisms

Lipomeningocele
Intradural lipoma
Diastematomyelia
Tight filum terminale
Dermoid cyst or sinus
Aberrant nerve roots
Anterior sacral meningocele
Cauda equina tumor

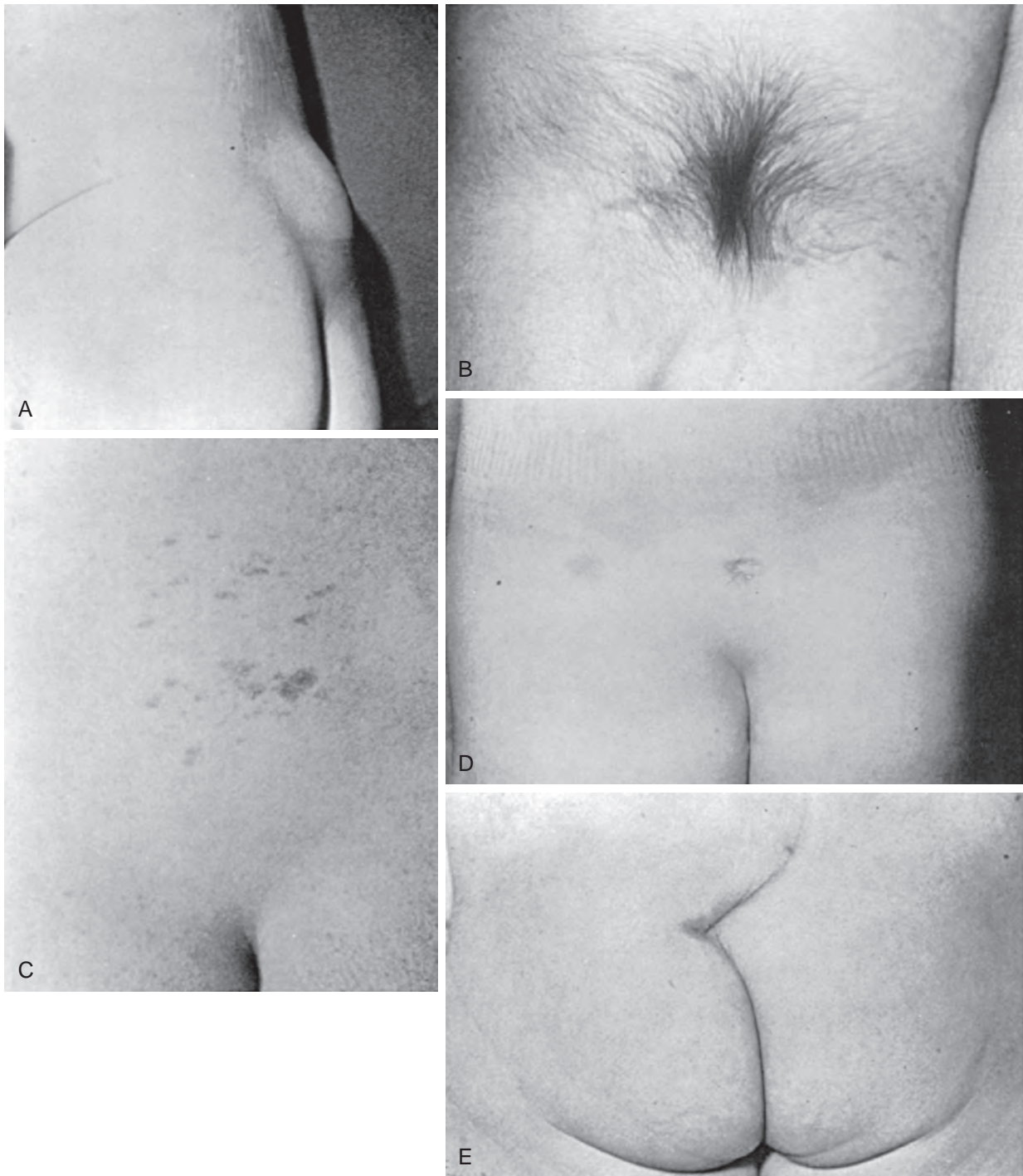


Figure 142-9. Cutaneous lesions occur in 90% of children with various occult dysraphic states. These lesions vary from a small lipomeningocele (A) to a hair patch (B), a dermal vascular malformation (C), a dimple (D), or an abnormal gluteal cleft (E).

roots by an expanding lipoma or lipomeningocele (Yamada et al, 1983), (2) tension on the spinal cord from tethering secondary to differential growth rates in the bony vertebrae and neural elements while the lower end of the cord is held in place by the lipoma or by a thickened filum terminale (Dubowitz et al, 1965), or (3) fixation of the split lumbosacral cord by an intravertebral bony spicule or fibrous band (Pang, 1992; Pang et al, 1992; Andar et al, 1997). The overt stretching that invariably occurs when there is a forcible flexion and/or extension of the spinal cord with normal movement leads to changes in oxidation and reduction of cytochrome oxidase, most notably in the lumbosacral spinal neurons when there is no intraspinal pathologic process (Yamada et al,

1983; Henderson et al, 2005). Under normal circumstances the conus medullaris ends just below the L2 vertebra at birth and recedes upward to T12 by adulthood (Barson, 1970). When the cord does not “rise” or is fixed in place owing to one of these lesions, ischemic injury may ensue (Yamada et al, 1981, 2004). Correcting the lesion in infancy has resulted not only in stabilization but also in improvement in the neurologic picture in many instances (Koyanagi et al, 1997; Cornette et al, 1998; Proctor et al, 2000) (Fig. 142-11). Sixty percent of infants with abnormal urodynamic findings preoperatively revert to normal postoperatively, with improvement noted in 30%; 10% become worse with time. In older children there is a less dramatic change after surgery, with only 27%

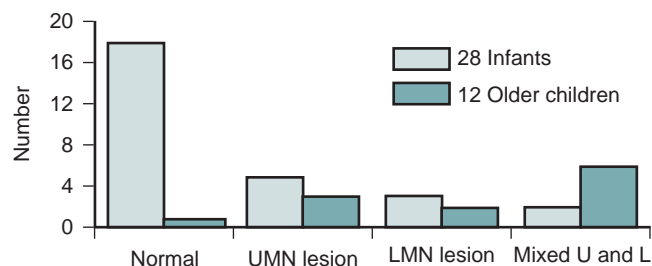


Figure 142-10. Most neonates with an occult spinal dysraphism have normal lower urinary tract function, whereas older children tend to have both upper motor neuron (UMN) and lower motor neuron (LMN) lesions.

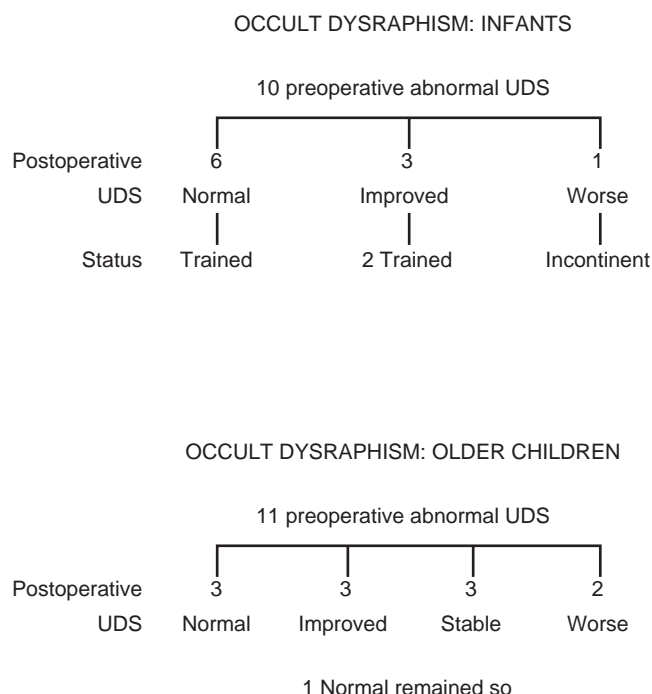


Figure 142-11. The potential for recoverable function is greatest in infants (6 of 10, 60%) and less so in older children (3 of 11, 27%). The risk of damage to neural tissue at the time of exploration in those with normal function is small (2 of 19, 11%). UDS, urodynamic study.

becoming normal, 27% improving, 27% stabilizing, but 19% actually becoming worse with time (see Fig. 142-11) (Keating et al, 1988; Satar et al, 1995). Older children with an overactive detrusor tend to improve, whereas those with acontractile bladders do not (Flanigan et al, 1989; Hellstrom et al, 1986; Kondo et al, 1986). Finally, 5% to 27% of children operated on in early childhood develop secondary tethering when observed for several years, suggesting that early surgery has both beneficial and sustaining effects in patients with this condition (Satar et al, 1995; Pierre-Kahn et al, 1997; Proctor et al, 2000).

As a result of these findings, it is apparent that urodynamic testing may be the only way to document that an occult spinal dysraphism is actually affecting lower spinal cord function (Keating et al, 1988; Khoury et al, 1990; Pierre-Kahn et al, 1997; Sarica et al, 2003). The serial use of electromyography (EMG) of the external urethral sphincter using a needle electrode to monitor individual motor unit action potentials provides a precise mechanism for measuring changes in innervation that may occur over time. Some investigators have shown that posterior tibial somatosensory evoked potentials are an even more sensitive indicator of tethering and should be an integral part of the urodynamic evaluation (Roy et al, 1986). The implication of these findings lies in the fact that early

detection and early intervention can either reverse or at least stabilize the progression of the lesion, which does not happen in older children (Yamada et al, 1983; Kaplan et al, 1988) and offers a degree of protection from subsequent tethering (Satar et al, 1995; Pierre-Kahn et al, 1997; Proctor et al, 2000), which seems to be a frequent occurrence when the lesion is not dealt with expeditiously in infancy (Chapman, 1982; Seeds and Jones, 1986) (see Fig. 142-11). Improvement of urodynamic parameters is most likely to occur in those undergoing neurosurgical repair for lipomeningocele in the first 12 months of life, compared with those aged 12 to 36 months. Those children undergoing surgery after 36 months of age were least likely to have improvement in their urodynamic findings (Rendeli et al, 2007). Thus, early intervention provides better outcomes for motor and bladder function.

Specific Recommendations

In addition to MRI studies (Tracy and Hanigan, 1990), urodynamic testing including EMG of the external urethral sphincter should be performed in every child who has a questionable cutaneous or bony abnormality of the lower spine, especially if there is a radiologic abnormality of the spinal cord (Packer et al, 1986; Campobasso et al, 1988; Hall et al, 1988; Meyrat et al, 2003). This test provides the most accurate measure of sacral spinal cord function at diagnosis and provides a basis for comparison with subsequent studies when the children are either operated on or carefully observed. In children younger than 3 months of age, the vertebral bones have not ossified; thus a window of opportunity exists for ultrasonography to be a useful screening tool in visualizing the spinal canal (Fig. 142-12) (Raghavendra et al, 1983; Scheible et al, 1983). At this age there is good correlation between the ultrasound imaging and MRI findings; however, if a spinal cord abnormality is identified, MRI provides a better definition of the spinal cord lesion. Consequently, ultrasonography should not be used as the definitive imaging modality (Hughes et al, 2003). Older children with an occult spinal cord lesion may have urologic symptoms in 20% of cases (Hsieh et al, 2006), and 50% to 60% may have abnormal urodynamic findings preoperatively (Guerra et al, 2006). Resolution of the abnormal urodynamic parameters is noted in 50% to 60% of patients after detethering (Guerra et al, 2006; Hsieh et al, 2006). Therefore, urodynamic study is recommended for all children with an occult spinal dysraphism before and after spinal cord detethering procedures. In addition to urodynamic studies, all children should have a renal and bladder ultrasound at presentation (Bauer et al, 2012).

In the past, most of these conditions were treated by excising the superficial skin lesion, without dissecting further into the spinal canal to remove or repair the entire abnormality. Currently, most neurosurgeons advocate laminectomy and removal of the intraspinal process as completely as possible without injuring the nerve roots or cord to release the tether and prevent further injury with subsequent growth (Linder et al, 1982; Kondo et al, 1986; Kaplan et al, 1988; Foster et al, 1990; Atala et al, 1992; Pierre-Kahn et al, 1997; Proctor et al, 2000). Long-term urologic follow-up is recommended, according to the guidelines put forth by the ICCS, summarized in Table 142-2 (Bauer et al, 2012).

SACRAL AGENESIS

Presentation

Sacral agenesis has been defined as the absence of part or all of two or more lower vertebral bodies. The presentation is bimodal, with more than three fourths of children being detected in early infancy and the remainder discovered between 4 and 5 years of age (Wilmschurst et al, 1999). With the increased use of prenatal ultrasonography, it is being diagnosed with increased frequency before birth. Sacral vertebral bony ossification begins at 15 weeks, so it is possible to detect the lesion after 18 weeks of gestation on an ultrasound examination and then to confirm it by fetal MRI (De Biasio et al, 2003). When not detected prenatally or at birth, the

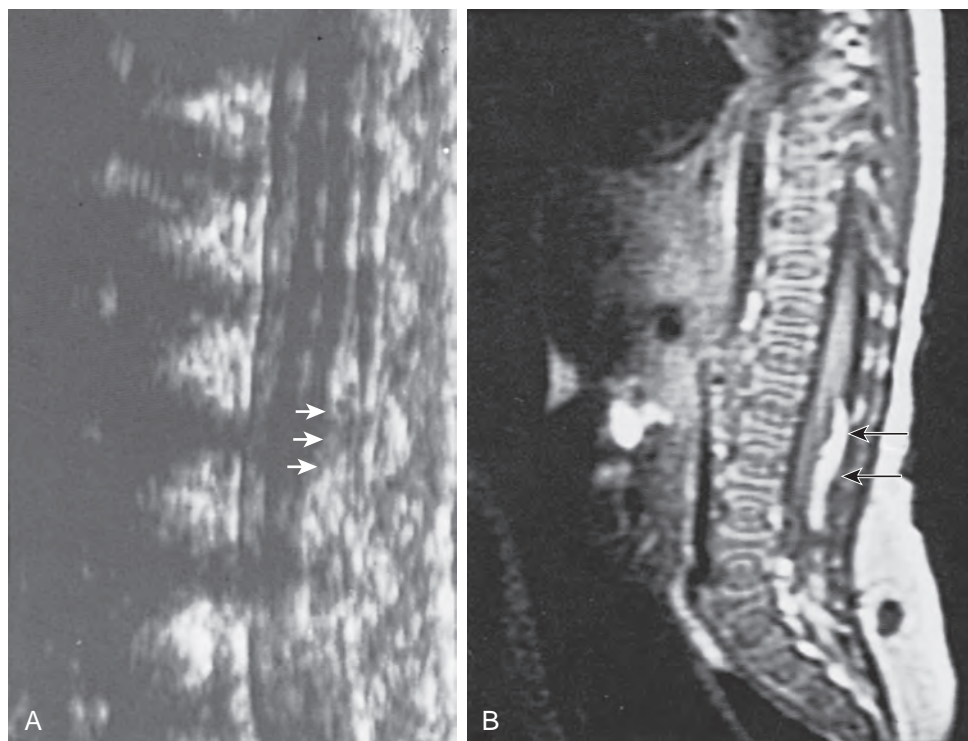


Figure 142-12. A, During the first few months of life, ultrasonography can clearly demonstrate intravertebral anatomy because the posterior arches have not completely ossified. Note that the spinal cord along with its central canal is displaced anteriorly (*white arrows*) beginning at L3 because of an intradural lipoma. B, The magnetic resonance image is juxtaposed to confirm the ultrasound findings. The longitudinal white intraspinal mass (*black arrows*) is the lipoma; the longitudinal gray mass is the spinal cord.

KEY POINTS: LIPOMENINGOCELE AND OTHER SPINAL DYSRAPHISMS

- Children with an occult NTD often are presented after age 3 or 4 years with incontinence or constipation. They may have new urologic symptoms after a growth spurt, related to tethering of the spinal cord. Most have a cutaneous abnormality overlying the spine.
- Radiologic examination of the spine, MRI, and renal ultrasound are indicated in the initial evaluation. A spinal ultrasound may be used as a screening investigation before MRI in those younger than 3 months.
- Urodynamic studies should be done before and after spinal cord detethering.
- Intervention with spinal cord detethering early in life is associated with better outcomes than when done later.

diagnosis is often delayed until failed attempts at toilet training bring the child to the attention of a physician. Presenting urinary symptoms in those aged 4 years and older include urinary incontinence or constant dribbling in 85% and recurrent UTI in 74%. VUR may be seen in up to 65% (Emami-Naeini et al, 2012). Sensation, including that in the perianal dermatomes, is usually intact, and lower extremity function is normal (Koff and Deridder, 1977; Capitanucci et al, 1997). Because these children have normal sensation and little or no orthopedic deformity in the lower extremities (although high arched feet or claw toes or hammer toes may be present), the underlying lesion is often overlooked. In fact, 20% escape detection until the age of 3 or 4 years (Guzman et al, 1983). The only clue, besides a high index of suspicion, is flattened buttocks with a low, short gluteal cleft (Bauer, 1990) (Fig. 142-13). Palpation of the coccyx is helpful in detecting the absent vertebrae

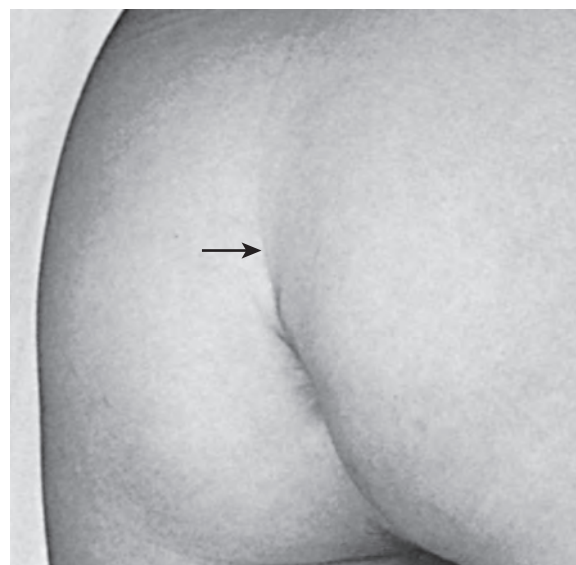


Figure 142-13. Characteristically, in sacral agenesis the gluteal crease is short and is seen only inferiorly (*below arrow*) because of the flattened buttocks.

(White and Klauber, 1976). The diagnosis is most easily confirmed with a lateral film of the lower spine, because this area is often obscured by the overlying gas pattern on an anteroposterior projection (White and Klauber, 1976; Guzman et al, 1983) (Fig. 142-14). MRI has been used to visualize the spinal cord in these patients; it reveals a sharp cutoff of the conus at T12 as a consistent finding (Pang, 1993; Diel et al, 2001) (Fig. 142-15).

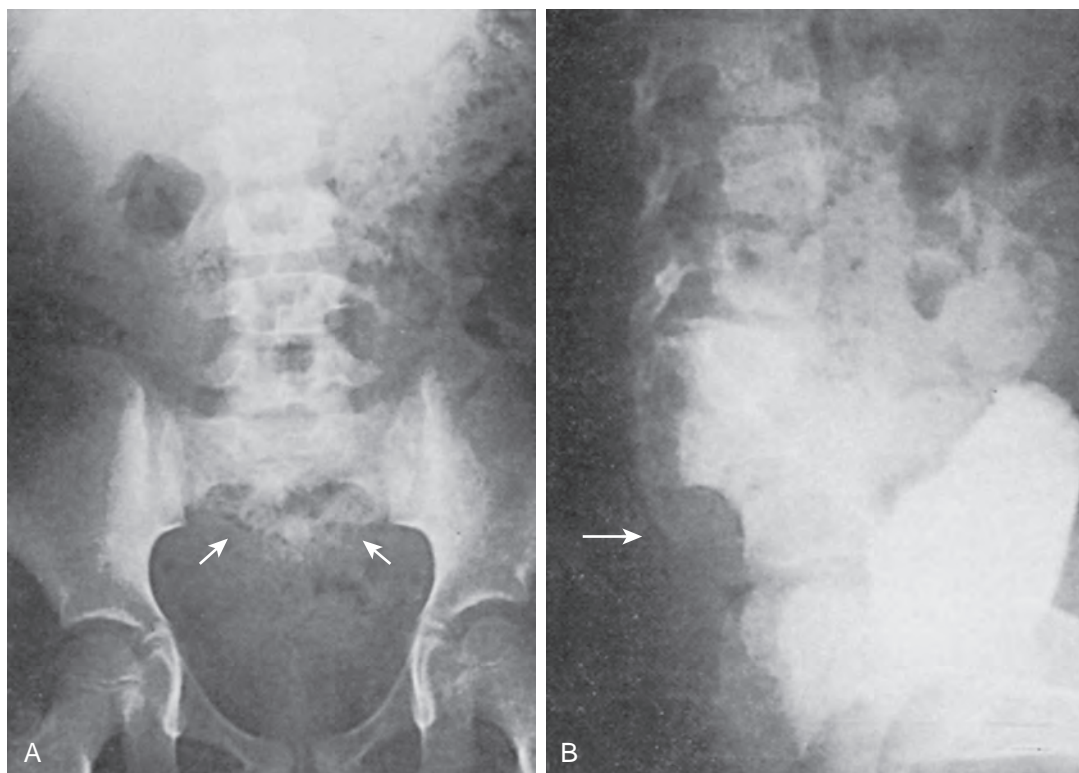


Figure 142-14. The diagnosis of partial or complete sacral agenesis (arrows) is easily confirmed on an anteroposterior (A) or lateral (B) radiograph of the spine if bowel gas obscures the sacral area. (From Bauer SB. Early evaluation and management of children with spina bifida. In: King LR, editor. Urologic surgery in neonates and young infants. Philadelphia: Saunders; 1988. p. 283–310.)

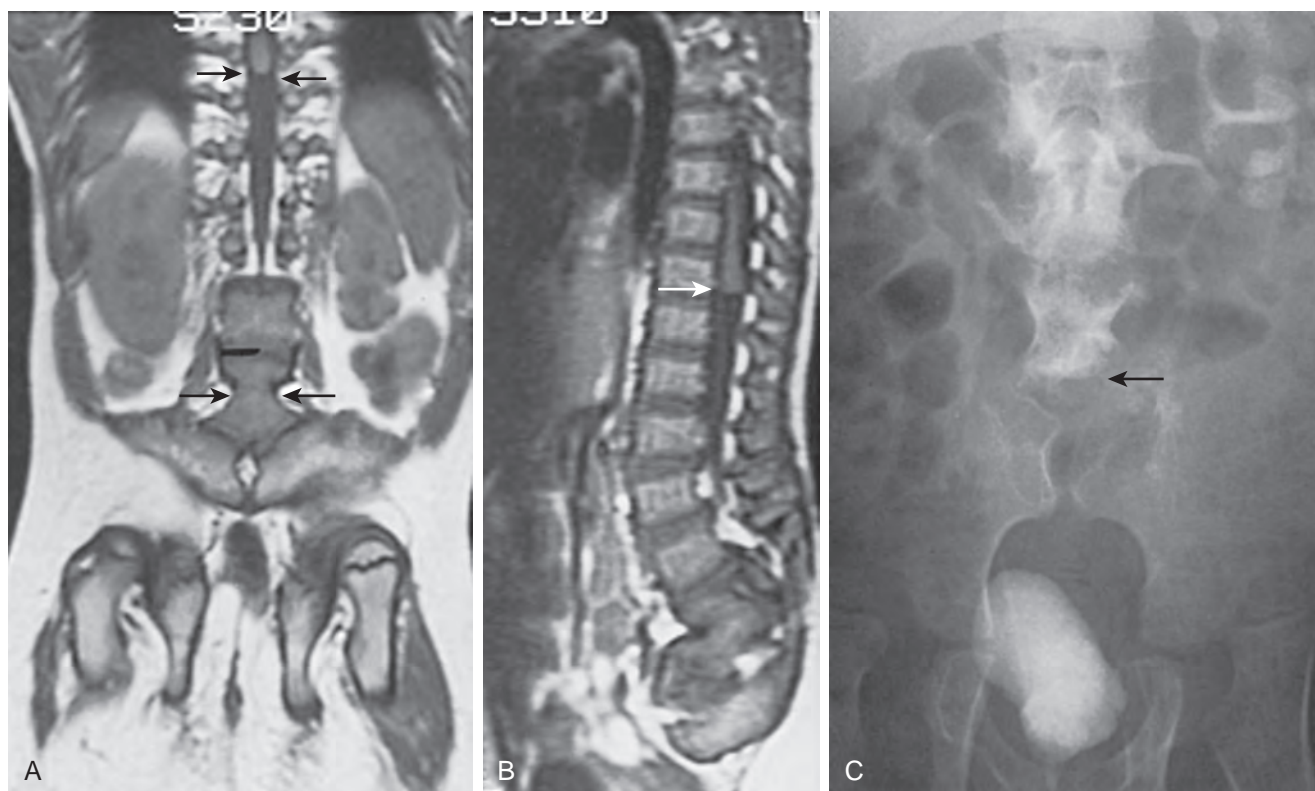


Figure 142-15. Coronal (A) and sagittal (B) magnetic resonance images in a 10-year-old boy with sacral agenesis beginning at L5. Note the squared lower limit of the cord adjacent to T11 (A, upper arrows; B, white arrow) and the two sacroiliac joints (A, lower arrows), which are in the midline because of absence of the sacrum. C, An anteroposterior radiograph from an excretory urogram shows no vertebral bodies below L4 (arrow).

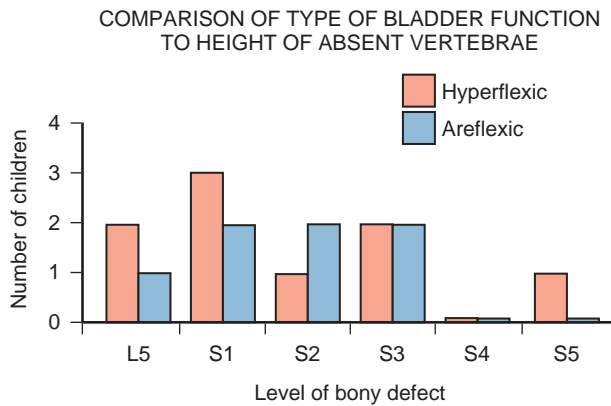


Figure 142-16. Bladder contractility is unrelated to the number of absent vertebrae. (From Bauer SB. Early evaluation and management of children with spina bifida. In: King LR, editor. Urologic surgery in neonates and young infants. Philadelphia: Saunders; 1988. p. 283–310.)

On urodynamic evaluation an almost equal number of individuals manifest either an upper or a lower motor neuron lesion (35% vs. 40%, respectively); 20% to 25% have no sign of denervation (Guzman et al, 1983; Boemers et al, 1994a). The number of affected vertebrae does not seem to correlate with the type of motor neuron lesion present (Boemers et al, 1994a) (Fig. 142-16). The injury appears to be stable and rarely shows signs of progressive denervation as the child grows. Sacral sensation is relatively spared, even in the presence of extensive sacral motor deficits (Boemers et al, 1994a). UTI may be detected in 75% of children over time, with VUR diagnosed in 37%. Reflux is most likely to occur in those with an upper (75%) (irrespective of whether they have synergy or dyssynergy) versus a lower (40%) motor neuron lesion (Wilmschurst et al, 1999).

Pathogenesis

The cause of this condition is still uncertain, but teratogenic factors may play a role, because insulin-dependent diabetic mothers have a 1% chance of giving birth to a child with this disorder. Conversely, 16% or more of children with sacral agenesis have a mother who is insulin dependent with diabetes mellitus (Passarge and Lenz, 1966; Guzman et al, 1983; Wilmschurst et al, 1999). Often the mothers have only gestational insulin-dependent diabetes. The disease has been reproduced in chicks by exposing embryos to insulin (Landauer, 1945; White and Klauber, 1976). Maternal insulin-antibody complexes have been noted to cross the placenta, and their concentration in the fetal circulation is directly correlated with macrosomia (Menon et al, 1990). It is possible that a similar cause-and-effect phenomenon occurs in sacral agenesis. There is evidence that a deletion of the seventh chromosome (7q36) leading to the absence of a transcription factor may be responsible for this anomaly (Papapetrou et al, 1999). In addition, maternal drug exposure (i.e., minoxidil) has been reported to cause sacral agenesis (Rojansky et al, 2002).

In familial cases of sacral agenesis associated with the Currarino syndrome (presacral mass, sacral agenesis, and anorectal malformation), deletions in chromosome 7 (7q) resulting in *HLXB9* genetic mutations have been found (Ross et al, 1998). A mutation in *HLXB9*, a homeodomain gene of a 403-amino acid protein that appears to be responsible for neural plate infolding, has been identified in 20 of 21 patients with familial cases and in 2 of 7 sporadic cases of Currarino syndrome (Hagan et al, 2000; Köchling et al, 2001). Heterozygote carriers within these families have also been identified (Lynch et al, 2000). Thus, sacral agenesis may represent one point on a spectrum of abnormalities that encompasses sacral meningoceles and anorectal malformations (Bernbeck et al, 2004).

Specific Recommendations

Because most children who are diagnosed with this condition have a neurologic deficit, urodynamic testing is mandatory at the time of diagnosis. Renal ultrasonography and nuclear or conventional cystography should be included as part of the evaluation process, especially if the child has a history of UTI or findings of an upper motor neuron lesion on urodynamic testing. Additional imaging studies may be required based on the child's history and findings from baseline studies.

Management depends on the specific type of neuromuscular dysfunction seen on urodynamic testing. Antimuscarinic agents should be given to children with upper motor neuron findings of detrusor overactivity, whereas CIC and α -sympathomimetic medications may have to be given to individuals with lower motor neuron deficits who cannot empty their bladders or stay dry between catheterizations. When antimuscarinic medication is ineffective in controlling the overactive detrusor, augmentation cystoplasty may be required to attain an adequate organ for urinary storage. Failure of α -sympathomimetic agents may necessitate either endoscopic injection of bulking agents or even AUS implantation to increase bladder outlet resistance. The bowels manifest a similar picture of dysfunction and need as much characterization and treatment as the LUT. Anorectal manometry has identified abnormalities in the internal anal sphincter and in voluntary anal sphincter squeeze pressure, leading to weakness of the muscle and concomitant fecal incontinence (Morera and Nurko, 2003). It is important to identify these individuals as early as possible so that they can become continent and out of diapers at an appropriate age, thus avoiding the social stigma of fecal or urinary incontinence.

KEY POINTS: SACRAL AGENESIS

- The index of suspicion for sacral agenesis should be high in children with incontinence or UTIs with a short gluteal cleft and/or flattened buttocks.
- The children of diabetic mothers or mothers with gestational diabetes are at increased risk.
- Initial investigation includes urodynamics, renal ultrasound, and nuclear cystogram.
- Long-term follow-up is required.

CONDITIONS OF THE PELVIS

Anorectal Malformation

Presentation

Anorectal malformations encompass a wide spectrum of diseases involving the distal anus and rectum as well as the urinary and genital tracts. The abnormalities may be minor with an excellent prognosis or very complex with poor functional outcomes (Levitt and Peña, 2007). This malformation occurs in approximately 1 in every 5000 live births (Levitt and Peña, 2007). The International (Krackenbeck) Classification of anorectal malformations separates entities into major clinical groups according to the location of fistula and rare or regional variants (Box 142-3) (Holschneider et al, 2005). Urinary tract abnormalities have been noted in 26% to 52% of affected children, with renal agenesis (primarily left-sided) and VUR as the most common associated findings (Parrott, 1985). The highest incidence of an abnormality is in those children with a high (70%) (supralelevator insertion of fistula) versus a low (infralelevator) (35%) lesion (Shaul and Harrison, 1997; Emir and Söylet, 1998), with boys more prone than girls to having an anomaly (50% vs. 29%) (Metts et al, 1997).

Spinal bony abnormalities range in incidence from 30% to 44%, but patients with a high lesion are more likely to be affected (48% to 54%) than those with a low lesion (15% to 27%) (Carson et al, 1984; Tsakayannis and Shamberger, 1995; Long et al, 1996). Spinal

BOX 142-3 International (Krackenbeck) Classification of Anorectal Malformations)**MAJOR CLINICAL GROUPS**

Perineal (cutaneous fistula)
 Rectourethral fistula
 Prostatic
 Bulbar
 Retrovesical fistula
 Vestibular fistula
 Cloaca
 No fistula
 Anal stenosis

RARE OR REGIONAL VARIANTS

Pouch colon
 Rectal atresia or stenosis
 Rectovaginal fistula
 H fistula
 Others

cord abnormalities including a tethered cord, thickened or fatty filum terminale, and lipoma have been noted in 18% to 50% of patients, with the incidence varying proportionately in relation to the height of the rectal lesion (Shaul and Harrison, 1997). Neurogenic bladder dysfunction is a frequent finding (Kakizaki et al, 1994), usually manifesting as incontinence, but its occurrence is rare when no spinal cord malformation exists (Hulthén de Medina et al, 2004) (Fig. 142-17). It often manifests when the child is older and the parents have difficulty with toilet training.

Anorectal malformations may be nonsyndromic or may occur in conjunction with many different syndromes (Levitt and Peña, 2007). Important examples of syndromic anorectal malformations include VACTERL syndrome (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb abnormalities), MURCS (müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia), OEIS (omphalocele, exstrophy, imperforate anus, and spinal defects), and Currarino syndrome (anorectal malformation, sacrococcygeal defect, presacral mass) (Currarino et al, 1981; Levitt and Peña, 2007).

The most common finding on urodynamic testing is an upper motor neuron lesion with an overactive detrusor and/or DSD (Boemers et al, 1994b; Taskinen et al, 2002; Borg et al, 2009), but a lower motor neuron lesion with an acontractile detrusor and a denervated sphincter may be seen as well (see Fig. 142-17) (Greenfield and Fera, 1991; Taskinen et al, 2002). Leak point pressures in excess of 40 cm H₂O, decreased compliance, and low bladder capacity have been noted (De Filippo et al, 1999; Stathopoulos et al, 2012). Normal urodynamic studies do not exclude a vertebral anomaly or myelodysplasia (Stathopoulos et al, 2012).

Children with Currarino syndrome are noted to have a tethered spinal cord in more than 80% of cases (Lee et al, 2012a). Postoperative voiding complaints including urgency, frequency, incontinence, and UTI are noted in approximately 80% (Lee et al, 2012a). Upper urinary tract changes such as hydronephrosis and VUR are not uncommon (Lee et al, 2012a). Surgical untethering of the spinal cord results have variable outcomes for urodynamic abnormalities, with some showing improvement, worsening, or no change (Lee et al, 2012a). Urodynamic abnormalities include small capacity, poor compliance, detrusor overactivity, DSD, and high voiding pressure (Lee et al, 2012a).

Pathogenesis

The cause of anorectal malformations remains unclear. It is most likely multifactorial, with some genetic component (Levitt and Peña, 2007). Although evidence for risk factors in the development

of anorectal malformations is limited, paternal smoking, maternal obesity, and maternal pregestational and gestational diabetes are associated with increased risk (Zwink et al, 2011). The cause of neurogenic bladder in these children is most commonly associated with a spinal cord abnormality. The posterior sagittal anorectoplasty (PSARP) approach espoused by Peña (1986) minimizes the chances of injuring the pelvic nerves that innervate the pelvic floor muscles and does not appear to result in iatrogenic neurogenic bladder dysfunction (De Filippo et al, 1999; Borg et al, 2009). Eighteen percent to 35% of those with anorectal malformations are noted to have neurogenic bladder (Mosiello et al, 2003a; Borg et al, 2009; Stathopoulos et al, 2012). Almost all have abnormal urodynamic findings before PSARP (Borg et al, 2009) and are usually (Borg et al, 2009) but not always (De Filippo et al, 1999; Stathopoulos et al, 2012) associated with a spinal cord abnormality.

Specific Recommendations

Initial evaluation in the neonatal period should include a careful inspection of the perineum looking for a fistulous site from the bowel, an examination of the upper and lower extremities, and an assessment of the spine and spinal cord (Carson et al, 1984; Mosiello et al, 2003a). Because of the high rate of associated genitourinary abnormalities, renal-bladder ultrasound is indicated in all children with an anorectal malformation (Levitt and Peña, 2007). Abnormalities on the renal ultrasound such as hydronephrosis and renal asymmetry should be further investigated with a VCUG.

Not all patients with a spinal cord abnormality have a bony defect, so intraspinal imaging in all children with anorectal malformations is recommended to ensure the presence of a normal spinal cord (Rivosecchi et al, 1995; Mosiello et al, 2003a; Miyasaka et al, 2009). Ultrasonography of the spine is recommended if the child is younger than 3 months because the vertebral bodies have not ossified, or a spinal MRI to rule out any abnormal intraspinal process is recommended in those older than 3 months (see Figs. 142-12 and 142-17) (Barnes et al, 1986; Tunell et al, 1987; Emir and Söylet, 1998; Mosiello et al, 2003a).

Urodynamic studies are reserved for those children with a bony abnormality of the spine, a spinal cord defect, or the telltale signs of dysfunction on VCUG or renal ultrasonography (Taskinen et al, 2002; Mosiello et al, 2003a). These studies should be conducted early in infancy before the child has had any definitive surgery for the imperforate anus and again after a pull-through operation has been performed on the rectum to determine, respectively, the true incidence of neurogenic bladder dysfunction and any changes that might have occurred as a result of the surgery (Borg et al, 2009). The presence of an abnormality on urodynamic testing in early infancy may warrant either intervention at that time to correct a spinal cord defect or watchful waiting to determine whether the lesion is progressive. Urodynamic studies are repeated subsequently or performed for the first time if secondary urinary or fecal incontinence ensues (Taskinen et al, 2002). Long-term follow-up reveals that ESRD is rare, but it may occur in just under 2% of children with anorectal malformation (Giuliani et al, 2013). Thus, if neurogenic bladder dysfunction is noted, long-term follow-up with annual ultrasound and repeat urodynamic or other imaging studies as specified in Table 142-2 is recommended.

Pelvic Surgery**Presentation**

In children, exenterative pelvic surgery for sacrococcygeal teratoma (Ozkan et al, 2006), pelvic rhabdomyosarcoma or other pelvic neoplasms (Yeung et al, 1994), and Hirschsprung disease (Holschneider et al, 1982) are well known to have deleterious effects on bladder function.

Children who have surgical resection of sacrococcygeal teratomas are noted to develop neurogenic bladder dysfunction in 35% to 45% of cases (Gabra et al, 2006; Le et al, 2011). Common presenting symptoms include UTI and incomplete bladder emptying

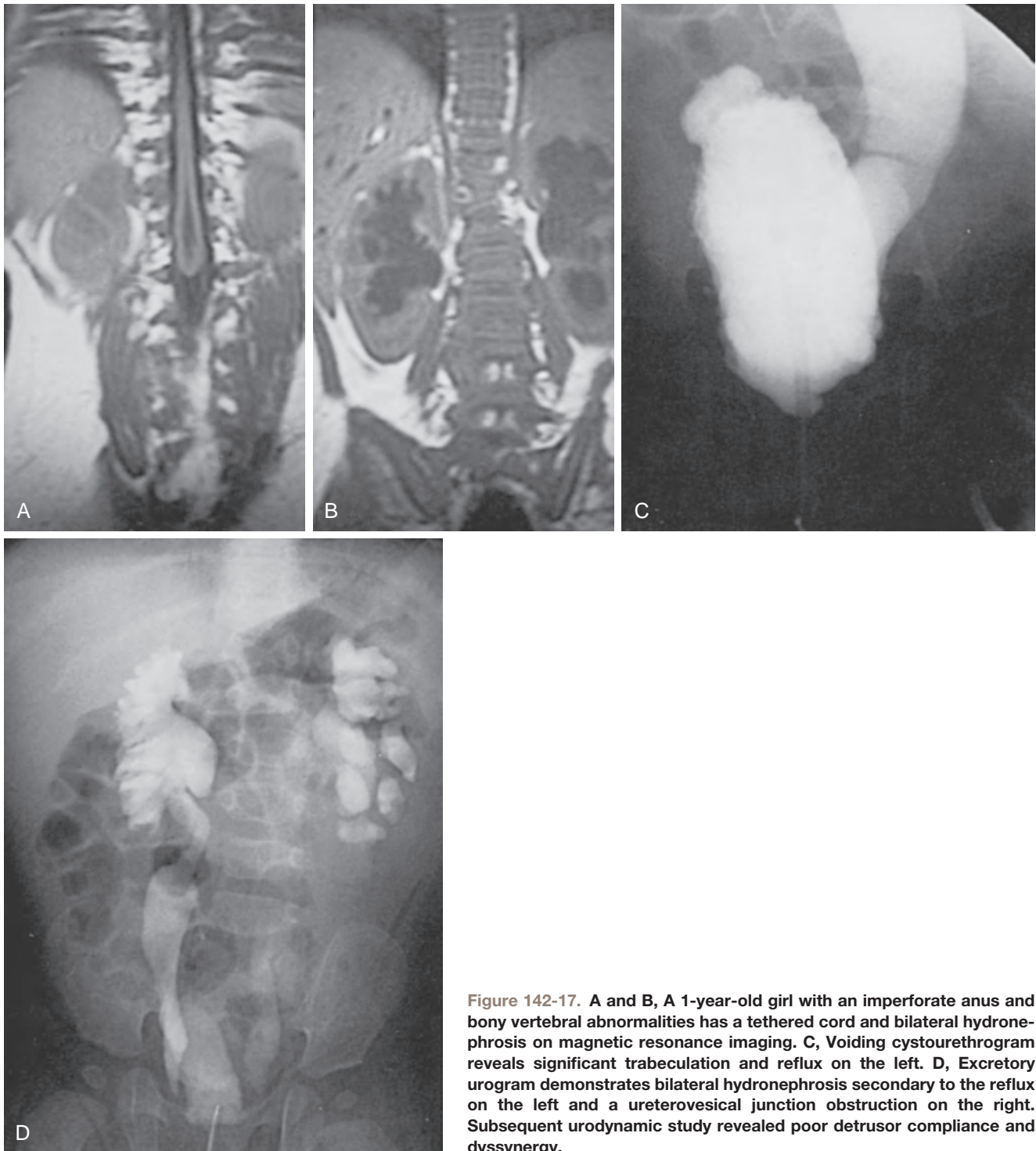


Figure 142-17. A and B, A 1-year-old girl with an imperforate anus and bony vertebral abnormalities has a tethered cord and bilateral hydronephrosis on magnetic resonance imaging. C, Voiding cystourethrogram reveals significant trabeculation and reflux on the left. D, Excretory urogram demonstrates bilateral hydronephrosis secondary to the reflux on the left and a ureterovesical junction obstruction on the right. Subsequent urodynamic study revealed poor detrusor compliance and dyssynergy.

(Ozkan et al, 2006). Urodynamic profiles reveal normal findings in 28% (Ozkan et al, 2006), detrusor overactivity in 57% to 81% (Boemers et al, 1994a; Ozkan et al, 2006), detrusor underactivity in 14% to 27% (Boemers et al, 1994a; Ozkan et al, 2006), poor compliance (Le et al, 2011), and DSD in 18% to 38% (Boemers et al, 1994a; Ozkan et al, 2006). Upper urinary tract deterioration may include renal scarring or decreased GFR (25%) (Le et al, 2011), VUR (25% to 50%) (Ozkan et al, 2006; Le et al, 2011), and hydronephrosis (30% to 43%) (Ozkan et al, 2006; Le et al, 2011). A tethered spinal cord can contribute to the neurogenic bladder abnormality in a small proportion of patients with sacrococcygeal teratoma (Boemers et al, 1994a; Mosiello et al, 2003b).

Children with genitourinary rhabdomyosarcomas in the past were uniformly treated with cystectomy. Currently, bladder preser-

vation is attempted when feasible (Raney et al, 2006). Children treated for pelvic neoplasms are noted to have normal bladder function postoperatively in 27% to 40% of cases (Mosiello et al, 2003b; Arndt et al, 2004; Hishiki et al, 2013). Those whose LUT dysfunction is symptomatic have nocturnal enuresis (26%) (Raney et al, 2006), daytime incontinence (14% to 27%) (Raney et al, 2006), urinary urgency (Soler et al, 2005), suprapubic pain with bladder filling (Soler et al, 2005), and UTIs (55%) (Raney et al, 2006). Urodynamic studies reveal markedly reduced functional bladder capacity (Yeung et al, 1994; Soler et al, 2005), detrusor overactivity (Mosiello et al, 2003b; Soler et al, 2005), detrusor underactivity (Mosiello et al, 2003b), and DSD (Mosiello et al, 2003b). Those children treated with bladder preservation strategies for pelvic rhabdomyosarcoma, especially those who receive radiation therapy,

are at high risk for LUT symptoms and upper urinary tract deterioration (Yeung et al, 1994; Soler et al, 2005; Raney et al, 2006). Abnormal renal function has been noted in one third, and hydronephrosis in 15% (Raney et al, 2006). Urinary tract reconstruction or diversion was ultimately required in close to 20% in one large series (Raney et al, 2006).

Up to 45% of children with Hirschsprung disease will have unstable detrusor contractions, which often resolve after the abnormal bowel is resected (Boemers et al, 2001). Transient urinary retention is noted in up to 7% of children undergoing surgery for Hirschsprung disease (Ateş et al, 2007). From 0% to 6% of children are noted to have urinary incontinence postoperatively with long-term follow-up (Holschneider et al, 1982; Boemers et al, 2001). Approximately one third of these children will have normal urodynamic findings postoperatively (Boemers et al, 2001). Two thirds have an increased maximum cystometric capacity (Boemers et al, 2001), and a high postvoid residual urine volume is noted in 55% to 78% (Boemers et al, 2001; Ateş et al, 2007). Poor compliance is rarely noted (Boemers et al, 2001). Different surgical approaches are noted to have varying effects on bladder function (Ateş et al, 2007).

Pathogenesis

Surgery of the pelvic viscera can result in damage to the pelvic splanchnic nerves, the hypogastric nerves, or the pelvic nerve plexus, resulting in autonomic denervation. Parasympathetic denervation (injury to the pelvic splanchnic nerves) may result in an acontractile bladder. Sympathetic denervation (injury to the hypogastric nerves) may cause a loss of bladder compliance and incompetence of the bladder neck. Mixed patterns of bladder dysfunction may be seen with injury to the pelvic plexus (Woodside and Crawford, 1980; Blaivas and Barbalias, 1983; Chang and Fan, 1983; Yalla and Andriole, 1984; Leveckis et al, 1995).

Specific Recommendations

The risk for upper urinary tract deterioration in those undergoing resection of pelvic sacrococcygeal teratomas is high; therefore preoperative and postoperative urodynamic studies are recommended for all (Ozkan et al, 2006; Le et al, 2011). Long-term urologic follow-up is required with annual ultrasound and clinical review in those who demonstrate urodynamic abnormalities or symptoms. Those who are asymptomatic and/or demonstrate normal postoperative investigations do not require long-term further evaluation unless symptoms arise.

As the risk of upper tract deterioration in those undergoing surgery for pelvic rhabdomyosarcomas is relatively high, it is recommended that all survivors, particularly those who had radiation therapy, be carefully monitored for upper urinary tract and LUT dysfunction (Yeung et al, 1994). It is recommended that screening be carried out with a frequency volume chart (Yeung et al, 1994), with urodynamic and ultrasound investigation limited to those with dysfunction. Long-term urologic follow-up is required with annual ultrasound and clinical review in those who demonstrate urodynamic abnormalities or symptoms. Those who are asymptomatic and/or demonstrate normal postoperative investigations do not require long-term further evaluation unless symptoms arise.

Because children undergoing surgery for Hirschsprung disease are usually symptomatic if bladder function is altered, routine postoperative urodynamic testing is not recommended for everyone. However, all patients should be screened clinically preoperatively and postoperatively for abnormal LUT function and undergo ultrasonographic examination of the urinary tract (Boemers et al, 2001). Those who are symptomatic preoperatively should undergo urodynamic studies before surgery. Those who are symptomatic after surgery should have urodynamic studies completed 6 months after surgery to allow resolution of temporary neuropathia (Boemers et al, 2001). Long-term urologic follow-up is required with annual ultrasound and clinical review in those who demonstrate urody-

namic abnormalities or symptoms. Those who are asymptomatic and/or demonstrate normal postoperative investigations do not require long-term further evaluation unless symptoms arise.

CENTRAL NERVOUS SYSTEM INSULTS

Presentation

Cerebral palsy is the most common physical disability in childhood. A recent study in the United States found that approximately 3.3 of 1000 8-year-old children have a variable degree of cerebral palsy. Its prevalence varies by region. It is more common in black and white children than in those who are Hispanic and is 1.2 times more common in boys than girls (Kirby et al, 2011). Cerebral palsy is a disorder of the development of movement and posture causing limitations in activities and is the result of nonprogressive disturbances of the fetal or infant brain. Sensation, perception, cognition, communication, and behavior may also be affected (Richards and Malouin, 2013). The Gross Motor Function Classification System—Expanded and Revised (2007; GMFCS-E & R; <http://motorgrowth.canchild.ca/en/GMFCS/resources/GMFCS-ER.pdf>) is based on self-initiated movement, with emphasis on sitting, transferring, and mobility. This is a 5-level scale that ranges from 1 (walks without limitations) to 5 (transported in a manual wheelchair). Specific descriptions with relevant age band categories exist for each level.

Affected children will often achieve urinary continence, although later than their age-adjusted normal peers (Roijen et al, 2001). In general, daytime continence is achieved first, followed by nighttime continence within the next year. Overall, 14% (Silva et al, 2009) to 34% of children (Richardson and Palmer, 2009) are continent of urine. The median age for achieving continence in those with high intellectual capacity and diplegia or hemiplegia is 3.6 to 4.1 years. For those with low intellectual capacity and tetraplegia, this milestone is achieved much later (10.1 to 13.2 years) (Roijen et al, 2001). Most studies do not correlate mobility (or GMFCS level) with the achievement of continence (Ersoz et al, 2009; Silva et al, 2009; Murphy et al, 2012). One study of 97 children evaluated with a standardized dysfunction voiding symptom survey found that 1 of 4 who were able to walk had LUT dysfunction compared with 3 of 4 who were unable to do so ($P < .001$) (Silva et al, 2009). LUT symptoms were more prevalent as the children aged (Silva et al, 2009; Murphy et al, 2012).

The incidence of urinary symptoms in children with cerebral palsy varies among studies, ranging from 16 (Murphy et al, 2012) to 94% (Gündoğdu et al, 2013). Females are more likely than males to have LUT symptoms (Ersoz et al, 2009; Silva et al, 2009). The most common symptom is incontinence, occurring in 23% to 94%; most have noted a prevalence of 35% to 45% (Roijen et al, 2001; Richardson and Palmer, 2009; Murphy et al, 2012; Gündoğdu et al, 2013). Urgency and frequency have also been reported (Murphy et al, 2012). Monosymptomatic enuresis is seen in 3% (Richardson and Palmer, 2009) to 13% (Silva et al, 2009). UTI is also variable, occurring in 5% to 57% (Ersoz et al, 2009; Silva et al, 2009, 2010; Gündoğdu et al, 2013). On evaluation, constipation is detected in 33% to 66% (Silva et al, 2009, 2010; Gündoğdu et al, 2013). Upper urinary tract deterioration, defined primarily as hydronephrosis, is uncommon, occurring in less than 5%, with a range of 0.5% to 12% (Silva et al, 2009, 2010; Murphy et al, 2012; Gündoğdu et al, 2013). Other parameters of deterioration include asymmetric renal size, VUR, and microlithiasis (Silva et al, 2009; Murphy et al, 2012; Gündoğdu et al, 2013). Factors raising the risk of upper urinary tract deterioration include increasing age, clinical symptoms of DSD (retention, interrupted voiding, hesitancy), and recurrent UTI (Gündoğdu et al, 2013).

Pathogenesis

The cause of urinary tract symptoms in children with cerebral palsy may be related to abnormal LUT function rather than to decreased mobility or ability to communicate.

Normal urodynamic studies are found in one third of children with cerebral palsy (Silva et al, 2009). Detrusor overactivity is noted in approximately 30% (Murphy et al, 2012; Gündoğdu et al, 2013) to 61% (Decter et al, 1987). Detrusor underactivity is documented in 6% (Murphy et al, 2012). Bladder capacity is less than expected in 42% to 93% (Ersoz et al, 2009; Silva et al, 2009; Gündoğdu et al, 2013). DSD is found in approximately 12% (Decter et al, 1987; Gündoğdu et al, 2013).

Thirteen percent may have an elevated postvoid residual urine volume (Silva et al, 2009). Uroflow patterns include a bell-shaped curve in 63%, staccato pattern in 17%, intermittent pattern in 13%; plateau-shaped pattern in 3%, and tower-shaped pattern in 3% (Ersoz et al, 2009).

Specific Recommendations

Although many affected children may have LUT symptoms, upper urinary tract deterioration is rare. Therefore most can be managed initially with minimal investigation and conservative management. In those with frequency, urgency, and/or incontinence, initial investigation should include a urinalysis and culture to rule out UTI, and a minimally invasive uroflow and postvoid residual urine measurement. Conservative measures such as timed voiding with or without antimuscarinic therapy may be instituted. If these measures fail, further investigation with urodynamic studies may be indicated. In addition, children with factors known to be associated with upper urinary tract deterioration—that is, recurrent UTIs or clinical symptoms of DSD (urinary retention, interrupted voiding, hesitancy)—should receive a more aggressive investigation including renal and bladder ultrasound and urodynamic studies. VCUG is indicated in the presence of UTI or DSD.

CONDITIONS OF THE BRAIN (TUMORS, INFARCTS, ENCEPHALOPATHIES)

Presentation

Children with neurogenic bladder resulting from CNS tumors most commonly have urinary incontinence and urinary retention (Soler and Borzyskowski, 1998; Nguyen et al, 2010). Other presenting symptoms include UTI, straining or difficulty voiding, hydronephrosis, or urinary urgency (Soler and Borzyskowski, 1998; Nguyen et al, 2010). In some children, development of bladder symptoms heralds progression or recurrence of the disease (Soler and Borzyskowski, 1998).

Pathogenesis

Urodynamic studies of children with neurogenic bladder resulting from CNS tumors demonstrate poor compliance, inability to void, high voiding pressures, detrusor overactivity, and postvoid residual urine; on EMG, sphincter action potentials were both absent and present (Soler and Borzyskowski, 1998; Nguyen et al, 2010). There was no correlation between tumor location and any specific urodynamic parameter. Nor was there a difference in urodynamic findings in patients with intracranial versus extracranial tumors or in those with suprasacral versus sacral involvement (Nguyen et al, 2010).

There is little literature related to neurogenic dysfunction that arises from other brain conditions such as encephalopathies and infarcts in children. One study noted that the voided volume and rate of consciousness with voiding were significantly lower in newborns with hypoxic ischemic encephalopathy (HIE) than in those without HIE (Wen et al, 2012). Those with HIE had significantly higher postvoid residual urine volumes and voiding frequencies (Wen et al, 2012).

Specific Recommendations

Various types of storage and voiding dysfunction may occur independent of tumor location; routine urologic investigation including

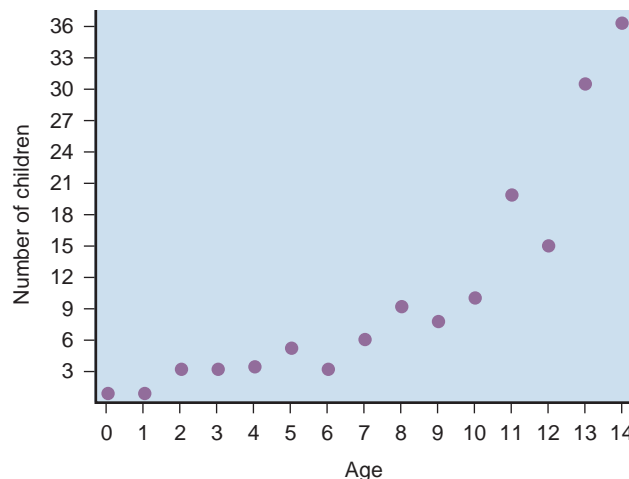


Figure 142-18. Increasing frequency of spinal injury with age. (From Anderson JM, Schutt AH. Spinal injury in children: a review of 156 cases seen from 1958 through 1980. *Mayo Clin Proc* 1980;55:499–504.)

renal ultrasound and urodynamic studies in all children with CNS tumors is recommended (Soler and Borzyskowski, 1998; Nguyen et al, 2010). Children with encephalopathy may be at risk of bladder dysfunction and should be screened with clinical history. Those who are symptomatic should undergo investigation with renal ultrasound and urodynamic studies.

CONDITIONS OF THE SPINAL CORD

Traumatic Injuries

Presentation

Despite increased exposure to and the potential for traumatic spinal cord injuries, such injuries are rarely encountered in children. The incidence in Sweden is 2.6 cases per million children per year (Augutis and Levi, 2003). The incidence tends to increase geometrically with age (Anderson and Schutt, 1980) (Fig. 142-18). When an injury does occur, it is more likely to happen in a boy than a girl, and it is usually the result of a motor vehicle or bicycle accident (24% to 52%), a fall from a high place, a gunshot wound, or a diving or sports incident (Cass et al, 1984; Hadley et al, 1988; Decter and Bauer, 1993; Brown et al, 2001; Augutis and Levi, 2003; Cirak et al, 2004). The type of causative injury varies with age, with infants more prone to an injury from a motor vehicle accident (71%), toddlers and children more likely to be injured secondary to a fall (48% and 34%, respectively), and adolescents more likely to have a sports-related injury (29%) (Cirak et al, 2004). An injury may also occur iatrogenically after surgery to correct scoliosis, kyphosis, or other intraspinal processes or congenital aortic anomalies or after ligation of a patent ductus arteriosus (Cass et al, 1984; Batista et al, 1995). Neonates are particularly prone to a hyperextension injury during a high forceps delivery (Adams et al, 1988; Lanska et al, 1990). Among younger children, girls are affected as often as boys (Ruge et al, 1988).

Pathogenesis

Spinal cord injuries in children are intrinsically different from those in adults because of a variety of factors, including the mechanism of injury and the difference in configuration of the brainstem and spinal cord in children compared with adults. In addition, the horizontal versus vertical orientation of the facet joints in vertebral bodies that predisposes to anteroposterior subluxation in children, the delayed supportive effect of the paraspinous musculature and ligaments, and the relative heaviness of the

head, which causes a fulcrum of maximal flexion of the upper cervical region in infants and young children all contribute to a high degree of hypermobility that places the child's spinal cord at risk for ischemic necrosis (Decter and Bauer, 1993).

Specific Recommendations

The LUT dysfunction that ensues is not likely to be an isolated event but is usually associated with loss of sensation and paralysis of the lower limbs. Radiologic investigation of the spine may not reveal any bony abnormality, although momentary subluxation of osseous structures resulting from the elasticity of the vertebral ligaments can result in a neurologic injury (Pollack et al, 1988). This condition has been seen only in children (usually younger than 8 years) and has been designated *spinal cord injury without radiologic abnormality* (SCIWORA) (Pang and Wilberger, 1982; Pang and Pollack, 1989). Overall, SCIWORA can account for up to 38% of spinal cord injuries in children (Brown et al, 2001). Myelography and CT show swelling of the cord below the level of the lesion (Adams et al, 1988; Lanska et al, 1990). Often, what appears to be a permanent lesion initially turns out to be a transient phenomenon with time. Although sensation and motor function in the lower extremities may be restored relatively quickly, the dysfunction involving the bladder and rectum may persist considerably longer.

During the acute phase of the injury the bladder is often acontractile and the urethral sphincter nonreactive, although normal-appearing bioelectric potentials can be recorded on sphincter EMG (spinal shock). Over a variable period of time, detrusor contractility and sphincter reactivity return as spinal cord edema subsides. With this return of function, an overactive detrusor and bladder-sphincter dyssynergy develop if the lateral reticulospinal cord pathways to and from the brainstem have been disrupted. When the lesion affects the cauda equina, there is probably little to no return of bladder or urethral sphincter function. Sacral sensation and peripheral reflexes are not good indicators of ultimate LUT function (Shenot et al, 1998). Over time, the predominant urodynamic pattern in patients with a thoracic-level lesion is an overactive detrusor with DSD, high voiding pressures, eventual hydronephrosis, and VUR. Often children exhibit a highly compliant bladder for a portion of bladder filling but then have C-fiber-mediated, small, ineffective rhythmic contractions of the detrusor with simultaneous waxing and waning of external urethral sphincter activity. Some urinary leakage may occur with these contractions, but in general the bladder does not empty with them. Patients with an upper thoracic or cervical lesion are likely to exhibit autonomic dysreflexia with a spontaneous discharge of α_1 -stimulants during bladder filling and with contractions of the detrusor. Monitoring of blood pressure and availability of α -antagonists are mandatory during VCUG or urodynamic studies (Perkash, 1997; Vaidyanathan et al, 1998).

If urinary retention occurs immediately after the injury, an indwelling Foley catheter is passed into the bladder and left in place for as short a time as possible, until the patient's condition is stable and aseptic intermittent catheterization can be started safely on a regular basis (Guttmann and Frankel, 1966; Barkin et al, 1983). There is no difference in the incidence of urinary infection or in the development of stones in patients using sterile versus clean catheterization techniques to empty the bladder (Prieto-Fingerhut et al, 1997; Van Hala et al, 1997). Rates of infection range as high as 60% to 80% (Biering-Sørensen et al, 1999), and stone formation occurs in 1.5% to 3% within the first 5 years after the trauma (Donnellan and Bolton, 1999; McKinley et al, 1999). When the child starts to void again, the timing of catheterization can be regulated so that it is used as a means of measuring the residual urine after a spontaneous void. Residual urine volumes of 25 mL or less are considered safe enough to allow reducing the frequency or even stopping the catheterization program (Barkin et al, 1983). After 4 to 6 weeks, if there is no improvement in LUT function, urodynamic studies are conducted to determine whether the condition is the result of spinal shock or an actual nerve root or spinal cord injury. An acontractile detrusor is not uncommon under these

circumstances (Iwatsubo et al, 1985). On the other hand, EMG of the sphincter often reveals normal motor units without fibrillation potentials but absent sacral reflexes and a nonrelaxing sphincter with bladder filling, a sign that transient spinal shock has occurred (Iwatsubo et al, 1985). The outcome of this situation is guarded but good, because most cases resolve completely as edema of the cord in response to the injury subsides, leaving no permanent damage (Iwatsubo et al, 1985; Fanciullacci et al, 1988).

If and when bladder function returns and emptying is incomplete, it has been shown in the cat (Xiao et al, 1999) that peripheral L7 dermatome stimulation initiates a micturition reflex without DSD. In a preliminary study of 15 adults with spinal cord injury, detrusor overactivity, and DSD, the creation of an artificial somatic/CNS/autonomic reflex pathway resulted in satisfactory bladder control in 67% of patients. Follow-up urodynamic study revealed a change to almost normal storage and synergic voiding without DSD (Xiao et al, 2003). A more recent study showed satisfactory bladder control in 75% of patients with complete suprasacral spinal cord injury within 6 to 12 months. However, the mean and median time after the injury was 9 months, so the time from injury may have been a factor in this study (Lin et al, 2009). Incomplete emptying may be enhanced by the judicious use of α -sympatholytic agents (Al-Ali et al, 1999). The goal is balanced voiding at pressures lower than 40 cm H₂O, which reduces the 30% risk for urinary tract deterioration seen in poorly managed patients (Giannantoni et al, 1998; Kim et al, 1998). If this cannot be achieved, then CIC is continued. Antimuscarinics, either orally or intravesically (Vaidyanathan et al, 1998; Wein, 1998), or capsaicin (an inhibitor of C-fiber stimulation) (Wiart et al, 1998) have been added and are effective in reducing an overactive detrusor, but at the cost of significant side effects. Alternative treatments that have been effective to ensure complete emptying at low pressure include external urethral sphincterotomy (Kim et al, 1998), urethral stent placement (Chancellor et al, 1999), or injection of BTA into the external sphincter (Schurch et al, 1997; Kuo, 2003). In some cases, a continent catheterizable abdominal urinary stoma may be created to facilitate self-catheterization in patients with low cervical or upper thoracic lesions who cannot easily catheterize themselves (Sylora et al, 1997).

Most permanent traumatic injuries involve either the upper thoracic or the cervical spinal cord, but some affect the cauda equina region. The sacral cord injury most likely produces a lower motor neuron deficit of the striated urethral sphincter that usually leads to low-pressure bladder emptying with little risk of upper urinary tract deterioration. However, it probably necessitates medical and/or surgical therapy to achieve continence. On the other hand, upper spinal cord injuries produce an upper motor neuron-type lesion with an overactive detrusor and DSD. The potential danger from this outflow obstruction is obvious (Donnelly et al, 1972). Substantial residual urine volumes, high-pressure reflux, urinary infections, and their sequelae are the leading causes of long-term morbidity and mortality in patients with spinal cord injury (Giannantoni et al, 1998). Even patients who voluntarily urinate and are continent or who involuntarily but spontaneously void to completion are not immune to urinary tract changes (Decter and Bauer, 1993). Urodynamic studies are imperative to identify which patients are at risk (Barkin et al, 1983). These studies should be performed within 2 to 3 months after the injury, again 6 to 9 months later, and possibly at 2 years after the trauma to determine the stability of LUT function and the need for continued CIC and whether adjuvant drug or surgical therapy should be added (or continued) to achieve good long-term success. When these measures are employed judiciously, effective management can be achieved (Pannek et al, 1997). Renal ultrasonography early in the course and VCUG if signs of bladder outlet obstruction are present on urodynamic testing or if recurrent urinary infection ensues are also recommended. Radionuclide cystography is indicated if the patient has repeated UTI or develops hydronephrosis (Phillips et al, 1997). Because stone formation can be insidious, periodic imaging of the kidneys and bladder is necessary. Early identification and proper management may prevent the signs and effects of bladder outlet

obstruction before they become apparent on radiographic examination of the urinary tract (Pearman, 1976; Ogawa et al, 1988).

Transverse Myelitis

Presentation

Transverse myelitis is a clinical syndrome caused by an immune-mediated inflammatory process that affects the spinal cord (DaJusta et al, 2008). Approximately 1400 new cases are diagnosed in the United States annually, and 28% of affected individuals are children (Krishnan et al, 2004). The incidence peaks between 10 and 19 years of age and again in the third decade of life (Krishnan et al, 2004). Males and females have an equal incidence (DaJusta et al, 2008). The diagnosis of transverse myelitis is made by accepted criteria, including sensory, motor, or autonomic dysfunction attributable to the spinal cord, bilateral neurologic signs and/or symptoms, a clearly defined sensory level, and inflammation in the spinal cord as demonstrated by cerebrospinal fluid pleocytosis or an increased T2 signal on MRI (Fig. 142-19) (Krishnan et al, 2004).

Transverse myelitis usually manifests with sudden lower back pain or lower extremity muscle weakness that rapidly progresses to paralysis and often to urinary retention (Knebusch et al, 1998). Bladder dysfunction may occur simultaneously with the motor dysfunction or more commonly follows it (DaJusta et al, 2008). Bowel dysfunction is also likely to occur at presentation (DaJusta et al, 2008). In the acute stage of transverse myelitis there may be a varying period of spinal shock that may persist for up to 6 weeks (Guttmann, 1970) and that gradually progresses to spasticity. The segment of the spinal cord affected by the disease determines the motor deficit (DaJusta et al, 2008). During the acute phase of the disease, treatment options include steroids, plasma exchange, and intravenous immunoglobulin G (IgG) (DaJusta et al, 2008). Recovery from the disease usually commences within 2 weeks to 3 months after the onset of symptoms. The most significant recovery occurs within the first 6 months (DaJusta et al, 2008), but sometimes improvement continues up to 2 years after the event (Krishnan et al, 2004).

Pathogenesis

It is well documented that the most common urinary symptom in children with transverse myelitis is **urinary retention**; in fact,

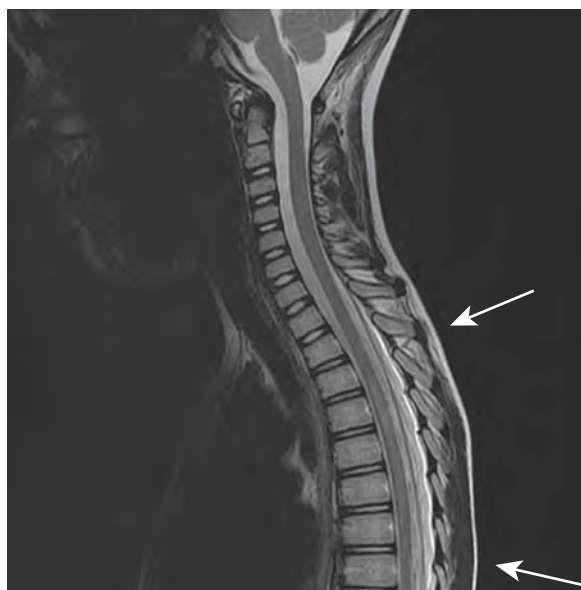


Figure 142-19. Sagittal T2-weighted magnetic resonance image of the spine of an 8-year-old boy with lower extremity weakness and urinary retention. Increased signal intensity of the spinal cord is noted from T3 to T8 (arrows).

more than 95% of affected children have urinary retention during the acute phase of the disease (Gatti et al, 2001; Kalita et al, 2002; DaJusta et al, 2008). The most common urodynamic finding in the acute phase is areflexia or detrusor underactivity, found in close to 70% (Kalita et al, 2002). Detrusor overactivity is noted in the acute phase in approximately 13%; 30% have decreased compliance, and 20% may have DSD (Kalita et al, 2002). After resolution of spinal shock, the urodynamic patterns identifiable are detrusor overactivity (59% to 90%), decreased compliance (47%), DSD (17% to 80%), and detrusor leak point pressure greater than 40 cm H₂O (12% to 33%). Detrusor underactivity is noted rarely after resolution of the acute phase of the disease (Ganesan and Borzyskowski, 2001; Kalita et al, 2002; Tanaka et al, 2006).

Approximately one third of children will be able to void spontaneously after the acute phase (Tanaka et al, 2006; DaJusta et al, 2008). Some children (57% to 73%) will require CIC to empty their bladder (Tanaka et al, 2006; DaJusta et al, 2008). Antimuscarinic medications are needed to manage symptoms of detrusor overactivity in 14% to 64% (Ganesan and Borzyskowski, 2001; Tanaka et al, 2006; DaJusta et al, 2008). For children whose incontinence is not resolved with CIC and antimuscarinics owing to small capacity, poor compliance, or unremitting overactivity, injection of botulinum toxin and bladder augmentation have been helpful (Tanaka et al, 2006). Up to 77% may have persistent bowel dysfunction; consequently, most require active bowel management (Tanaka et al, 2006).

Although some reports have not correlated recovery of LUT function with recovery of motor function (Ganesan and Borzyskowski, 2001; Tanaka et al, 2006), other larger studies have demonstrated an association (Dunne et al, 1986; Kalita et al, 2002; DaJusta et al, 2008). One study found that children with full motor recovery were likely to also have full recovery of LUT function—that is, normal voiding with continence and no requirement for antimuscarinic medication. It was also noted that partial recovery of motor function was associated with partial recovery of LUT function, meaning that children could void spontaneously but required antimuscarinics for incontinence. Children with no motor recovery or those who were wheelchair dependent were likely to require CIC and possibly antimuscarinics (DaJusta et al, 2008).

Profound urologic complications have been noted infrequently in children with transverse myelitis including UTI (DaJusta et al, 2008), VUR (Tanaka et al, 2006), hydronephrosis (Tanaka et al, 2006), chronic renal insufficiency (Tanaka et al, 2006), bladder calculi (Kalita et al, 2002), and bladder diverticula (Kalita et al, 2002). One study documented an association between late initiation of CIC and an increased risk of decreased bladder compliance and upper urinary tract deterioration (Tanaka et al, 2006). In this series, upper urinary tract deterioration, where hydronephrosis or VUR was noted, occurred in 5% of children (Tanaka et al, 2006). In this series, neither neurologic examination nor urinary symptoms were able to predict the risk of upper urinary tract deterioration. In addition, ambulatory status did not correlate with urodynamic findings (Tanaka et al, 2006).

Specific Recommendations

Urodynamic studies and a baseline renal and bladder ultrasound once the acute phase of the neurologic injury has stabilized are suggested to identify those patients who may have DSD. Children with bladder underactivity and/or DSD will benefit from the early introduction of CIC and antimuscarinic therapy, respectively (Tanaka et al, 2006). Urodynamic studies should be performed again after resolution of the acute phase (at approximately 6 months) to guide therapy for incontinence and preservation of the upper urinary tract. Voiding or radionuclide cystography is indicated in the presence of DSD or UTIs. Because these children are at risk for upper urinary tract deterioration, annual follow-up evaluation including renal ultrasonography is recommended as outlined in Table 142-2. Urodynamic studies are advisable if there is a change in LUT symptoms or in sonographic images.

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The complete reference list is available online at www.expertconsult.com.

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Clinical Significance

Epidemiology

Self-Esteem and Quality-of-Life Issues

Comorbidities

Terminology

Daytime Urinary Incontinence and Bladder Dysfunction

Enuresis

CLINICAL SIGNIFICANCE

Functional disorders of the lower urinary tract (LUT) encompass abnormalities in the filling and/or emptying phases of the bladder and include a broad spectrum of clinical entities that vary in their cause and prognosis. These are functional disorders in that children do not have a readily identifiable neurologic or anatomic abnormality but rather the disorder is thought to originate from behavioral factors that affect toilet training and inhibit the development of normal urinary control. *LUT dysfunction (LUTD)*, *bladder and bowel dysfunction*, and the antiquated *dysfunctional elimination syndrome*, are terms that describe the common array of symptoms that include overactive bladder (OAB), voiding postponement, underactive bladder, dysfunctional voiding, primary bladder neck dysfunction, giggle incontinence, vaginal reflux, pollakiuria, and enuresis.

Evidence-based medicine lends support to the hypothesis that LUTD can predispose children to recurrent urinary tract infections (UTIs) and vesicoureteral reflux (VUR) with a potential for significant impact on subsequent LUT and renal function. Beyond these largely urologic sequelae, however, the impact of symptoms such as daytime incontinence are profound and can affect the behavioral, emotional, and social aspects of a child's daily life. Timely diagnosis and a coherent therapeutic approach are therefore paramount in the successful treatment of these physically and emotionally distressing disorders.

EPIDEMIOLOGY

LUTD is commonly encountered in daily practice, accounting for up to 40% of pediatric urology clinic visits annually (Feldman and Bauer, 2006). Cross-sectional studies confirm that functional LUT problems are prevalent, with 22% of school-age children reporting at least one LUT symptom. The most common urinary symptoms cited included holding maneuvers (19.1%) and urgency (13.7%) (Vaz et al, 2012).

United States

Daytime incontinence is estimated to affect up to 7 million children in the United States 6 years of age or older (Franco, 2012). OAB is the most commonly encountered LUT disorder in children and appears to have a peak incidence between 5 and 7 years of age, although its true prevalence is difficult to determine (Franco, 2007). To date, studies have focused primarily on daytime versus nighttime incontinence and have not attempted to differentiate the type of daytime incontinence. Chandra (1998) reported the responses to

583 questionnaires completed by families of children between 5 and 9 years of age and found that urinary urgency and pelvic tightening maneuvers to postpone voiding and prevent incontinence were the voiding issues most frequently reported. Urge incontinence was present in 7% of girls and 3% of boys (Chandra, 1998).

International

A study by Hellström and colleagues of 7-year-old Swedish children entering school revealed that 21% of girls and 18% of boys had moderate-to-severe urinary urgency. Daytime urinary incontinence occurred once weekly in 3.1% of girls and 2.1% of boys. A Japanese study of 6917 school-age children demonstrated an overall prevalence rate of 17.8% for OAB (Kajiwarara et al, 2006). Interestingly, this epidemiologic survey found a nearly equal prevalence of OAB between boys and girls of 19.1% and 16.6%, respectively. An Australian study addressed the frequency of voiding disorders in school-aged children (Sureshkumar et al, 2009). This study of 2856 students reported that 19.2% of children had experienced at least one episode of daytime incontinence in the previous 6 months, with 16.5% having experienced more than 1 wetting episode and only 0.7% experiencing wetting on a daily basis. Independent risk factors for daytime incontinence included nocturnal enuresis, female sex, history of UTI, and encopresis (Sureshkumar et al, 2009).

A large cross-sectional study of over 19,000 children between the ages of 5 and 13 was performed in the Republic of Korea and evaluated the prevalence of OAB by parental questionnaire (Chung et al, 2009). The overall prevalence of OAB was 16.6% and decreased with age from 23% to 12% by age 13 years (Chung et al, 2009). Compared with other children, those with OAB had a greater prevalence of nocturnal enuresis, constipation, fecal incontinence, UTI, delayed bladder control, and poor toilet facilities.

Gender and Age-Related Demographics

Robson (1997) and associates found that daytime incontinence varies with both age and gender. This group reported that the prevalence of daytime wetting at least once every 2 weeks was 10% in 5- to 6-year-old children, 5% from 6 to 12 years of age, and 4% from 12 to 18 years of age. In a population survey of 1192 individuals aged 1.5 to 27 years, daytime incontinence occurred in 13% of children aged 4 years, 7% of children aged 5 years, 10% of children aged 6 years, and 5% of children aged 7 years (Bloom et al, 1993). Studies on the prevalence of voiding disorders in school-age children indicate that daytime urinary incontinence is 2 to 5 times more common in girls (Sureshkumar et al, 2009). Hellström

and colleagues (1990) found that daytime incontinence was more common in girls (6.7%) than in boys (3.8%) and that most children with incontinence had other LUT symptoms (LUTS).

SELF-ESTEEM AND QUALITY-OF-LIFE ISSUES

Multiple epidemiologic and cross-sectional studies demonstrate that between 5% and 20% of children suffer with daytime incontinence (Hellström et al, 1990; Kajiwarra et al, 2004; Joinson et al, 2006; Sureshkumar et al, 2009). The reported incidence of incontinence ranges from 1.2% daily to 3.6% at least twice a week (Hellström et al, 1990). Remarkably, the majority of parents surveyed did not seek medical attention for their child's incontinence, and teachers recognized only 3% of the children in their classroom who actually suffered from daytime wetting (Sureshkumar et al, 2009). These statistics would make it appear that LUTD and its sequelae are of nominal consequence in the daily lives of young children. Various studies examining the impact of symptoms like urinary incontinence on self-esteem and quality of life in children would suggest otherwise.

Given the emerging recognition of patient perspectives in health care over the last decade, quality-of-life assessment is an important part of incontinence research. Measurement of quality of life in children with urinary incontinence gives a child-centric estimate of the impact that incontinence makes in daily life. In a survey study of 1185 children, both in the United States and Australia, school-age children were asked to grade the severity of 20 different stressful life events (Ollendick et al, 1989). Of the different situations examined, "Wetting pants in class" was rated as the third most stressful, which underscores the importance of urinary control in school-age children and their peers.

A recent article by Thibodeau and associates (2013) prospectively studied 40 children (10 males and 30 females), between 5 and 11 years of age with non-neurogenic daytime wetting. The Dysfunctional Voiding Symptom Score (DVSS), originally put forth by Farhat and colleagues (2000) was used to quantify the severity of LUTS and was completed by both parents and children. Parents and their children also completed the Pediatric Urinary Incontinence Quality of Life Score tool (PIN-Q), originally developed by Bower and coworkers (2006b), which measures the emotional impact that urinary incontinence has on a child. There was no statistically significant difference between parent and child scores for symptoms (DVSS) and quality of life (PIN-Q), indicating that parents were very aware of the child's symptoms and the impact they had. DVSS and PIN-Q responses were positively correlated (i.e., as DVSS scores increased the PIN-Q showed a corresponding rise).

COMORBIDITIES

Urinary Tract Infections

A clear and consistent relationship has been repeatedly demonstrated in multiple studies between LUTD and UTIs. What is unclear, however, is whether a causal relationship exists. This most likely is related to study design and interpretation. Bauer (2002) suggested that UTIs are not only an effect of dysfunctional voiding but also may precipitate the development of LUTD, specifically OAB.

Hellström and associates (1990) disseminated a questionnaire to analyze the micturition habits and UTI history to more than 3500 school-age children. Girls with daytime wetting, urgency, and emptying difficulties had a higher prevalence of a UTI history than those without symptoms. Hoebeke and colleagues (2001a) prospectively studied 1000 children during a 4-year study period with video-urodynamics to ascertain the cause and epidemiology of LUTD. The incidence of UTI was significantly higher in girls than in boys. In addition, boys with LUTD had no greater risk for UTI. In girls with underactive bladder there was a significantly higher incidence of UTI.

Chen and colleagues (2004) performed a multivariate analysis on 2759 children to elucidate the relationships among dysfunctional elimination, UTI, and VUR. Their data demonstrated a higher rate of LUTD in girls (43.7%) than in boys (23.8%), with 44% of children who had a history of UTIs also having concomitant LUTD. Interestingly, they observed no association of UTI or VUR individually, but rather found that LUTD was noted only when both UTI and VUR were present. This study challenges the contemporary paradigm espousing an independent association between UTI and LUTD.

In a recent retrospective review, Van Batavia and coworkers (2013) determined how many children who initially presented with LUTD had a history of UTIs. Of 623 children diagnosed with LUTD, one third had a history of UTIs, with the prevalence rate being significantly higher in girls than boys. When stratified by specific LUT conditions, girls with underactive bladder and dysfunctional voiding had the highest UTI rates. Not surprisingly, the association between UTIs and LUTD was most often noted for LUT conditions in which urinary stasis occurs.

Vesicoureteral Reflux

There is a known association between LUTD and VUR. Whether VUR is secondary to the LUT condition is controversial. Lapides and Diokono (1970) first described the association between dysfunctional voiding and VUR (Lapides and Diokono, 1970). Since that time a number of authors have expanded on the description and nature of the association. In the late 1970s, Koff and associates (1979) demonstrated that voiding against a closed sphincter can increase bladder pressure and may contribute to the development and persistence of VUR. The incomplete bladder emptying that occurs in children with LUTD can lead to urinary stasis with subsequent UTI causing inflammatory changes in the bladder wall that stimulate hypertrophy and overactivity. This is particularly true in older children who manifest with febrile UTIs after toilet-training has been completed. It has been theorized that detrusor hypertrophy can alter the closure mechanism at the ureterovesical junction, leading to reflux (Yeung et al, 1998).

One of the first studies to systematically address the relationship between LUTD and VUR was performed by Van Gool and associates (1992), who distributed a questionnaire to all children enrolled in the European arm of the International Reflux Study in Children. Extrapolating from the questionnaire results, the prevalence of dysfunctional voiding was approximately 18%. A strong association was observed between recurrent UTI and LUTD, and in those children with spontaneous resolution of their reflux, the prevalence of dysfunctional voiding was much lower.

Koff and associates (1998) reported their experience on 143 children with primary VUR who either resolved spontaneously or were surgically treated. LUTD was present in 66 (43% of the cohort), with 54 (82%) of these children having a breakthrough UTI and undergoing reimplantation compared to only 18% without LUTD. Of 70 children who had a breakthrough UTI, LUTD was present in 54 children (77%); in 73 patients who did not have a breakthrough infection, dysfunction was present in only 12 (16%) children. Additionally, if VUR resolution did occur, the time for resolution increased by 1.6 years in those with dysfunction compared to those without LUTD. Finally, unsuccessful surgical outcomes involving persistent, recurrent, and contralateral reflux occurred only in children with elimination disorders.

The association between LUTD and treatment failure after surgical correction for reflux has been borne out in a number of clinical studies. Regardless of surgical treatment modality (i.e., endoscopic vs. open reimplantation) ongoing LUTD has been shown to be associated with a higher failure rate. Capozza and colleagues (2002) treated a total of 320 children between 3 and 11 years of age with subureteral injection for grades II to IV VUR. They found untreated LUTD to be highly associated with endoscopic treatment failure at 6-month follow-up.

Targeted treatment for LUTD has been demonstrated to improve spontaneous resolution rates for VUR (Willemsen and

Nijman, 2000; Fast et al, 2013). In a recent study by Fast and coworkers (2013) patients diagnosed and treated for LUTD who had concomitant VUR at or near the time of diagnosis underwent targeted treatment for their specific dysfunction along with antibiotic prophylaxis. VUR was monitored with serial voiding cystourethrogram or video-urodynamics. After a mean of 3.1 years of treatment, VUR resolved with targeted therapy in 26 of 58 ureters. All of these patients had a history of UTIs before starting targeted intervention. Interestingly, they found that resolution rates for VUR were similar regardless of VUR grade. Resolution or significant improvement of reflux was greater in patients with dysfunctional voiding (70%) compared to those with OAB (38%) or underactive bladder (40%).

Psychological Associations

Recently, there has been an emerging awareness of the strong association that exists between neuropsychiatric comorbidities and LUTD in children. In fact, functional causes of LUTD are believed by many to originate from behavioral issues that evolve from personal stressors and/or adverse events that occurred around the time of toilet-training (Feldman and Bauer, 2006). If the LUTD is not addressed, this behavioral or learned response often will perpetuate itself. Limiting free access to a restroom or, worse, discouraging voiding in response to urgency in a child who has not developed complete cortical inhibition of voiding may alter normal coordination between bladder and sphincter (McKenna and Herndon, 2000).

Between 20% and 40% of children with daytime urinary incontinence are affected by comorbid behavioral disorders (von Gontard et al, 1998b; Joinson et al, 2006). Additionally, a number of epidemiologic studies have reported clinically significant behavioral problems in up to one third of children with enuresis (Hirasing et al, 1997; Liu et al, 2000). This is 2 to 4 times higher than children without enuresis and is comparable with rates of psychosocial problems in other pediatric chronic illness groups. Other studies have investigated the psychological problems associated with specific syndromes responsible for daytime urinary incontinence. These investigators found a higher rate of behavior problems in children with voiding postponement compared to those with urge incontinence as their major complaint (Lettgen et al, 2002; von Gontard et al, 2011a). Moreover, some have suggested that voluntary holding with postponement of voiding is acquired and may be reflective of ongoing behavioral issues (von Gontard et al, 1999).

Recently, Oliver and associates (2013) explored the prevalence of psychosocial comorbidities and their relationship to children presenting with LUTD (Oliver et al, 2013). Data were prospectively collected on patients 6 to 17 years of age. Parents completed a 21-question LUTS score based on a validated questionnaire and a psychosocial questionnaire that screened for stressful life events and psychological diagnoses. Of the 358 patients examined, 32% had a recent life stressor and 23% had a comorbid psychiatric disorder. Younger age correlated with a higher LUTS score. Children with a recent life stressor, psychiatric disorder, or the two comorbidities had a significantly higher LUTS score than children without comorbidities. This study lends support to the recommendation for screening of psychosocial comorbidities during the evaluation of pediatric LUTD.

In perhaps one of the largest epidemiologic studies to look at the association between daytime urinary incontinence and neuropsychiatric issues in children, researchers found a significantly increased rate of psychological problems among children who wet themselves compared to those who were dry (Joinson et al, 2006). Of the over 8000 children between 7.5 and 9 years of age who were studied, those with daytime wetting had significantly increased rates of attention-deficit/hyperactivity disorder (ADHD) (24.8%), conduct disorders (11.8%), separation anxiety (11.4%), and oppositional behavior (10.9%). The increased vulnerability to psychological problems in children with daytime urinary incontinence underscores the importance of parents seeking early intervention for the condition to help prevent later psychological problems. Moreover, clinicians should be cognizant of the association with

disorders such as ADHD in children with daytime wetting, because this is likely to interfere with treatment success.

Bowel Dysfunction

It has long been recognized that an intimate association exists between both hindgut and LUT function. Indeed, LUTS are seen in approximately 30% of children who present with constipation (Belman and Loening-Baucke, 1998). Previous reports have indicated a significant overlap in these conditions in the primary care setting, with nearly one quarter of children with functional fecal retention also reporting daytime urinary incontinence (Loening-Baucke, 2004). As one would expect, the prevalence of these comorbid conditions is even higher at tertiary care centers. Burgers and associates (2013a) recently reported that nearly half of patients seen at their pediatric urology clinic for LUTS also met criteria for functional constipation.

The relationship between abnormal bowel and bladder activity is termed *bowel-bladder dysfunction (BBD)* and is part of an entity originally described by Koff and colleagues (1998) as the *dysfunctional elimination syndrome*. The International Children's Continence Society discourages using the term *dysfunctional elimination syndrome* as this connotes a particular abnormality or condition (Austin et al, 2014). BBD is a more descriptive comprehensive term that does not necessarily explain pathogenesis but rather encompasses this parallel dysfunction. In any event, Koff recognized the significance of bowel dysfunction; if present, its clear identification and management were paramount if treatment of the LUT condition was to be successful. Koff and colleagues (1998) recommended that each LUT condition be treated specifically while at the same time addressing any concomitant bowel dysfunction, often before treatment of the LUT condition.

Although an exact pathophysiologic basis for BBD has not been clearly elucidated, a number of different theories have been put forth. One theory espouses that rectal distention from fecal retention puts direct pressure on the posterior bladder wall and that this constant force in turn leads to detrusor instability, which can precipitate bladder overactivity and impair efficient bladder emptying (Lucanto et al, 2000). A second theory assumes that both the urethral and anal sphincters share a common neural input. With chronic contraction of the anal sphincter from rectal stool impaction, the pelvic floor musculature similarly contracts inappropriately, leading to secondary detrusor-external urinary sphincter dyssynergia. This vicious cycle of discoordination is what is thought to induce bladder overactivity, urinary incontinence, recurrent UTIs, and VUR (O'Regan et al, 1985).

Please see the Expert Consult website for further details.



KEY POINTS: EPIDEMIOLOGY, SELF-ESTEEM AND QUALITY-OF-LIFE ISSUES AND COMORBIDITIES

- LUTD is commonly encountered in daily practice.
- Daytime incontinence varies with both age and gender in school-age children and seems to be more common in girls.
- There is a clear and consistent relationship between LUTD and UTIs, especially when urinary stasis occurs.
- There is a known association between LUTD and VUR. Continued LUTD is a risk factor for treatment failure after surgical correction for reflux. Targeted treatment for LUTD has been demonstrated to improve spontaneous resolution rates for VUR.
- Clinicians should be cognizant of the association between neuropsychiatric disorders and LUTD. Failure to adequately address these comorbidities is likely to interfere with treatment success.
- The relationship between abnormal bowel and bladder activity is termed *bowel-bladder dysfunction (BBD)*, and, if present, its clear identification and management is paramount if treatment of the LUT condition is to be successful.

In a recent study by [Burgers and colleagues \(2013a\)](#), researchers assessed the prevalence of functional defecation disorders in children referred to a tertiary pediatric urology outpatient clinic for LUTS. They analyzed the records of 113 patients between 4 and 17 years of age who presented with LUTS. Rome III criteria for functional constipation and functional nonretentive fecal incontinence were fulfilled by 47% and 11% of patients with LUTS, respectively. Not surprisingly, children with dysfunctional voiding were more likely to fulfill the criteria for functional constipation, while children with urge incontinence more often fulfilled the criteria for nonretentive fecal incontinence. This last point is intriguing in that it supports the notion that children with fecal incontinence and urge urinary incontinence often will not respond to a standard bowel program, which could potentially exacerbate the situation. Perhaps these children would be better served by a centrally acting agent to aid in suppression of overactivity or lack of inhibition. Clearly, there continues to be a void in our understanding of the bowel and bladder interaction in higher cortical centers and the spinal cord.

In a similar study by [Combs and associates \(2013\)](#), researchers sought to better illuminate the relationship between LUT and bowel dysfunction by studying 368 consecutive children who presented with LUTD. In a secondary analysis, they also sought to determine if constipation and encopresis, which are often presumed to coexist, also coexisted for their specific cohort. Overall, children with dysfunctional voiding had the highest incidence of bowel dysfunction, with constipation alone being the most frequently observed form. Somewhat surprisingly, nearly 50% of patients reporting encopresis did not have associated constipation. The majority of patients with encopresis with or without associated constipation had idiopathic detrusor overactivity, and those with the worst urgency were the ones reporting encopresis. Interestingly, in children with encopresis, severe urgency was commonly reported and after initiation of anticholinergic therapy the encopresis frequently resolved even before the urgency had fully subsided. This finding is similar to the results of [Burgers and colleagues \(2013a\)](#), and perhaps may be secondary to an overactivity of the detrusor and the rectal wall musculature, or a lack of inhibition of detrusor and rectal muscular activity. Whether this is a centrally mediated phenomenon is unclear.

TERMINOLOGY

The International Children's Continence Society (ICCS) is a global, multidisciplinary organization of clinicians involved in the care of children with LUTD (Austin et al, 2014). Perhaps one of the most significant impacts of the ICCS on the pediatric LUT function community was its initial terminology document (Névéus et al, 2006). Before the publication of this document, the nomenclature used in LUTD had been endemic with transposable terms that in some cases were not completely accurate and were often confusing. Moreover, this fostered uncertainty and made it rather difficult to compare research and study outcomes among different groups. The standardization of the nomenclature for pediatric and adolescent LUT function is thus critical in providing a platform for optimal comprehension and more effective interaction and treatment among multiple health care providers who care for these patients. Recently the ICCS revised the original terminology document to provide a current and consensus update reflecting refinement and current advancement of knowledge on pediatric and adolescent LUT function (Austin et al, 2014).

The terminology used for LUTS focuses on descriptive (as opposed to quantitative) language because quantitative data are currently lacking. Of particular relevance is the age of the child when applying terminology to describe pediatric LUT function. The reference point used by the ICCS is 5 years old or greater (4 years of age for bowel dysfunction), because this age is used by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-V) (American Psychiatric Association, 2013) and the International Classification of Diseases 10 (ICD-10) to characterize urinary incontinence disorders (World Health Organization, 2008). The ICCS terminology document authors do stipulate, however, that there is variability and maturational aspects that certainly will affect LUT function and that there are, in fact, children who have voluntary control over LUT function under 5 years of age. As a result, it is at the discretion of the provider to selectively apply these terms in younger cohorts of children. (See "Terminology Document" by Austin and associates, 2014, for specific terms and their definition.)

DAYTIME URINARY INCONTINENCE AND BLADDER DYSFUNCTION

Evaluation

Evaluation of the child or adolescent with suspected voiding dysfunction commences with a detailed and thorough history and physical examination. The goals of evaluation are first and foremost to determine whether the patient has a filling or emptying (or both) phase abnormality. If an abnormality is found, the evaluation should then be directed toward determining the underlying cause and distinguishing whether the dysfunction stems from an anatomic or functional issue. This last point is critical because the management strategy will depend on the cause.

History

A thorough history is going to be invaluable in ascertaining whether and what type of bladder dysfunction is present. In general, the history should be taken from the child if possible (as opposed to caregivers) and tailored to the maturational age and stage of development of bladder and bowel control. Our approach has been to first focus on the identification of a possible anatomic or neurologic source to explain a patient's current symptomatology and, once this has been ruled out, to distinguish which form of bladder dysfunction is present. Vital components of the history often will include voiding schedule, symptomatology, bowel habits, family history, maternal prenatal history, perinatal history, developmental milestones, toilet training, neuropsychiatric comorbidities, medical/surgical history, social history, diet, and previous UTIs.

Bladder and Bowel Diaries

Perhaps one of the most helpful diagnostic tools in the armamentarium of providers who care for children with LUTD is the voiding diary. Its usefulness stems from the fact that this log is an objective record of the child's bowel habits and urinary voiding pattern. The diary should include voided volumes, timing of each void and incontinent episode, timing of each bowel movement and fecal soiling episode, and fluid intake.

In the evaluation of LUTD, the frequency/volume chart is a diary recording fluid intake and urine output during a 24-hour period (Bower et al, 1997; Hoebeke et al, 2010). It can be used for both diagnostic and therapeutic purposes. For diagnostic purposes, the chart should cover at least 48 hours and not necessarily recorded on 2 consecutive days (Austin et al, 2014). Episodes of urgency and urine loss also should be recorded. Urine loss is quantified by recording if clothing had to be changed after the urine loss (significant urine loss) or not. The chart gives information about fluid intake, number of voids, voided volume, and urine loss (Fig. 143-1). We also employ a 7-day bowel diary that uses the Bristol Stool Form scale (Lane et al, 2011) in ruling out BBD. Although controversy surrounds the best way to diagnose functional constipation in children, the ICCS recommends the use of the Rome III criteria (Rasquin et al, 2006).

Questionnaires

Questionnaires in the evaluation of LUT function have emerged as useful tools to more objectively translate somewhat subjective complaints into semiquantitative data (Akbal et al, 2005). These scoring systems not only allow providers to more accurately gauge the extent of LUTD but also provide a method of monitoring outcomes during treatment (Afshar et al, 2009). The two main types of questionnaires that have emerged for pediatric LUTD are measurements of LUT function and psychological screening.

Dysfunctional Voiding Symptom Score

In 2000, Farhat and colleagues (2000) reported on the creation of the DVSS based on the International Prostate Symptom Score for benign prostatic hyperplasia. The DVSS was the first scoring system of its kind and has been used in a variety of clinical settings. There are 10 quantitative and qualitative urologic parameters translated into age-appropriate questions for children regarding urinary symptoms, such as urinary incontinence, voiding habits, urgency, posturing, bowel habits, and stressful life conditions. The 10 questions were assigned scores of 0 to 3 according to incidence in the month before responding to the questionnaire and responses are weighted equally, giving a maximum possible score of 30 (Fig. 143-2).

Pediatric Urinary Incontinence Quality of Life Score

The Pediatric Urinary Incontinence Quality of Life Score (PIN-Q), developed by Bower and colleagues (2006b) measures the emotional impact that urinary incontinence has on a child. This cross-cultural urinary incontinence quality-of-life tool has been found to have excellent test-retest reliability and validity (Bower et al, 2006a). It consists of 20 questions related to urinary incontinence quality of life that are graded on a scale of 0 to 4 (0 = No, 1 = Hardly ever, 2 = Sometimes, 3 = Often, 4 = All the time) with a total possible score of 80. The total score indicates the impact urinary incontinence has on the child's quality of life, with the higher score indicating a more significant effect. Both the PIN-Q and DVSS questionnaire have been found to be complementary and provide a clinically appropriate picture of LUTD and its impact on a child's quality of life (Thibodeau et al, 2013).

Psychological Screening

It is well documented that children with BBD have a high rate of comorbid behavioral and emotional disorders. In several

PATIENT NAME:
HOSPITAL NUMBER:
REASON FOR REFERRAL:
DATE:

Over the last month	Almost never	Less than half the time	About half the time	Almost every time	Not available
1. I have had wet clothes or wet underwear during the day.	0	1	2	3	NA
2. When I wet myself, my underwear is soaked.	0	1	2	3	NA
3. I miss having a bowel movement every day.	0	1	2	3	NA
4. I have to push for my bowel movements to come out.	0	1	2	3	NA
5. I only go to the bathroom one or two times each day.	0	1	2	3	NA
6. I can hold onto my pee by crossing my legs, squatting, or doing the "pee dance."	0	1	2	3	NA
7. When I have to pee, I cannot wait.					
8. I have to push to pee.	0	1	2	3	NA
9. When I pee it hurts.	0	1	2	3	NA
10. Parents to answer. Has your child experienced something stressful like the example below?	NO (0)			YES (3)	
TOTAL					

- New baby.
- New home.
- New school.
- School problems.
- Abuse (sexual/physical).
- Home problems (divorce/death).
- Special events (birthday).
- Accident/injury.
- Others.

Figure 143-2. Dysfunctional Voiding Symptom Score questionnaire. (Modified from Farhat W, Bagli DJ, Capolicchio G, et al. The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. J Urol 2000;164:1011.)



Figure 143-3. Occult spina bifida in a child with a sacral dimple. (Courtesy Elaine Fonseca, MD.)

(Fig. 143-3). These include an asymmetrical gluteal cleft, a presacral dimple, a lipoma, a hair tuft, a dermal sinus tract, and a dermal vascular malformation. In general, these lesions should be evaluated with magnetic resonance imaging of the lumbar and sacral spine.

Genital Examination

In boys, the examination necessarily includes inspection of the urethral meatus to detect possible meatal stenosis. Although direct inspection of the meatus may be sufficient, our preference has been to observe the urinary stream directly during voiding to note its caliber and direction because this entity is not a true stenosis but rather a ventral urethral membrane that deflects the urinary stream upward (Fig. 143-4). Almost invariably, meatal stenosis is seen in circumcised boys because the prepuce is thought to protect the meatus from chronic irritation and subsequent epithelialization of this ventral meatal web of tissue. Epididymoorchitis sometimes can be seen in males with dyssynergic voiding. The theory is that increased bladder pressures can lead to retrograde reflux of caustic urine into the ejaculatory ducts, leading to inflammation along the course of the vas deferens, epididymis, and testes.

In girls, deformities of the urethral meatus also have been noted to be associated with LUT voiding dysfunction (Hoebeke et al, 1999; Klijn et al, 2012). The theory is that girls with certain anomalies of the urethral meatus (i.e., a ventral web of tissue akin to meatal stenosis in males) predispose to an anterior deflected urinary stream and so they cannot void in the ideal toileting position. This then results in lower success rates for behavioral training programs. Hoebeke and colleagues (1999) demonstrated that young females with meatal deformities were diagnosed with more severe forms of dysfunctional voiding on urodynamic investigation compared to a control group. They also showed improved micturition patterns and fewer symptoms after surgical correction. This finding



Figure 143-4. Meatal stenosis with an inferior web of tissue that results in an upward urinary deflection.

was corroborated in a second study by [Klijn and associates \(2012\)](#), who found that 39% of female patients with dysfunctional voiding reported an anteriorly deflected urinary stream. After surgical correction, they found that half of these girls were free of all related symptoms and required no further behavioral training. Examination of the labia and vaginal introitus is performed to detect any evidence of labial adhesions. Although labial adhesions are often purported to be a cause of bladder outlet obstruction (BOO), this has rarely been the case in our experience, unless they are dense enough to require surgical division. More often, as the labia minora adhere (usually from posterior to anterior) the resultant pouch sequesters small amounts of urine that may dribble into the underwear between voids, depending on the child's posture. The stagnant urine in the pouch predisposes to asymptomatic bacteriuria and UTI ([Leung and Robson, 2004](#)). The problem is usually self-limited at around the time of puberty because the presence of estrogen has a protective effect ([Leung and Robson, 2004](#)). Areas of skin excoriation or redness may be present and are often a sign of continuous or severe urinary leakage with chronic inflammation and less often secondary to fungal infection.

Neurologic Examination

A focused neurologic examination should include assessing lower extremity strength and deep tendon reflexes, gait, perineal and anal sensation, and rectal tone. The anocutaneous reflex (i.e., "anal wink") and bulbocavernosus (Osinski) reflex should be assessed to denote any interruption of the sacral reflex arcs (S2 to S4). Any abnormality of the neurologic examination may be indicative of a neurologic lesion that also affects the function of the bladder and should be assessed with proper spinal imaging.

Investigative Tools

Urinalysis

The single most important and perhaps only laboratory test that should be performed in all children who present with LUTD is the urinalysis. This screening test will invariably aid in deciphering whether the child's symptomatology is due to a bona fide UTI or is merely dysuria associated with BBD. **Particularly important elements of the urinalysis include specific gravity and the presence of white or red blood cells, bacteria, protein, and glucose.** A low specific gravity may be secondary to a renal concentrating defect and often will lead to polyuria. White blood cells (WBCs) suggest infection and/or inflammation. Red blood cells (RBCs) generally denote infection when found with WBCs; however, isolated RBCs can be found in children with LUTD secondary to storage and

voiding dynamics. Isolated proteinuria is common in children and may represent a benign condition or a serious underlying renal disease or systemic disorder. Depending on the degree of proteinuria, consideration should be given to obtaining a serum creatinine level to estimate the glomerular filtration rate. Significant glucosuria clinches the diagnosis of diabetes mellitus and often will lead to significant polyuria.

Urine Culture and Sensitivity

A urine culture sample should be obtained if there is evidence of a bona fide UTI. We generally would not recommend performing urine cultures reflexively on all patients, because this practice will undoubtedly identify patients with simple bacterial colonization and has the potential to foster bacterial resistance and infection with more virulent organisms if treated.

Uroflowmetry

Uroflow studies consist of measuring the velocity of urinary flow (volume voided per unit time) and examining the pattern during urination into a uroflowmeter. The child voids into a collection device that produces a urinary flow curve providing the maximum (Qmax) and average (Qavg) urinary flow rates, voided volume, flow time, and shape of urine flow. Uroflowmetry may be done concomitantly with electromyography (EMG) testing of the pelvic floor musculature and external urethral sphincter by affixing pads to the perineum. **The advantage of combining EMG with uroflowmetry is the ability to appreciate synergy or dyssynergy between the bladder and the pelvic floor-sphincter complex.**

Qmax is the most relevant quantitative variable when assessing bladder outflow. Sharp peaks in the curve are usually artifacts, so maximum flow rate should be registered only when a peak level has a duration of longer than 2 seconds ([Szabo et al, 1995](#)). In studies of normal children and adults, a linear correlation has been found between maximum flow and the square root of voided volume ([Chang et al, 2013](#)). If the square of the maximum flow rate ($[mL/s^2]$) equals or exceeds the voided volume (milliliters), the recorded maximum flow is most likely normal.

There are a few caveats that should be mentioned. **First, to obtain an interpretable uroflow, a child must be toilet-trained.** **Second, uroflowmetry provides information regarding the emptying phase of the bladder only and gives no information about what is happening during filling.** **Third, it is important that the volume of voided urine is adequate, because curves change when the voided volume is less than 50% of expected bladder capacity for age** ([Austin et al, 2014](#)). Finally, it is critical to obtain more than one curve to improve the accuracy, reliability, and interpretation of the test.

Uroflowmetry provides readily useful information regarding the pattern or shape of urine flow curve that often can be diagnostic of an underlying cause. In fact, obtaining an adequate uroflow pattern along with a coherent history and physical examination often can obviate the need to pursue more invasive urodynamic testing, which should be performed only when the diagnosis is unclear. The precise shape is determined by detrusor contractility and influenced by abdominal straining, coordination with the bladder outlet musculature, and any anatomic obstruction. The ICCS has developed categories for what is considered normal and abnormal, with five types of urine flow patterns identified ([Fig. 143-5](#)). Each specific pattern is no guarantee of an underlying diagnostic abnormality but rather serves as a guide to the existence of a specific condition.

Bell-Shaped Curve. The urinary flow curve of a healthy child should register as a smooth *bell-shaped* curve regardless of gender, age, and voided volume.

Tower-Shaped Curve. The tower-shaped curve is a sudden, high-amplitude curve of short duration that suggests an OAB produced by an explosive voiding contraction. It should be noted, however, that children with OAB may have a bell-shaped curve because this LUTD is mainly related to the filling phase of the bladder.

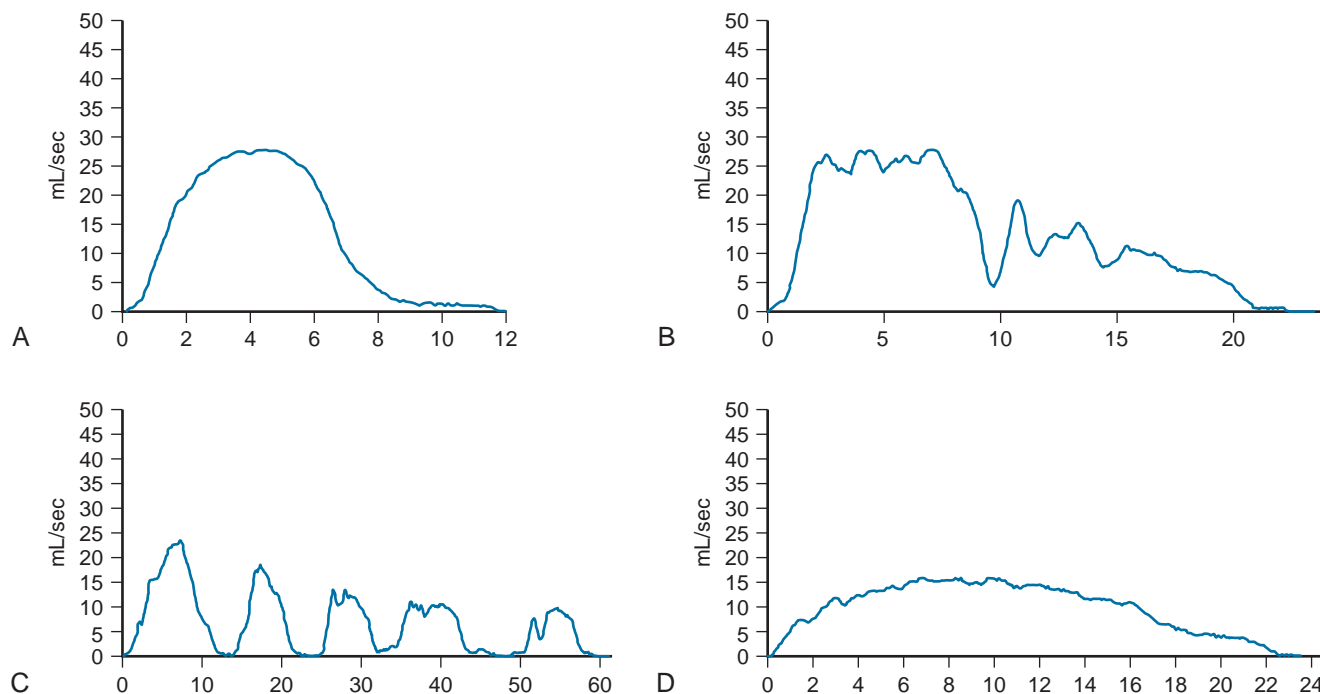


Figure 143-5. Common uroflow patterns. A, Bell shaped. B, Staccato. C, Interrupted. D, Plateau. (From Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society. *J Urol* 2014;191:1863-5.)

Staccato-Shaped Curve. The staccato-shaped pattern is irregular and fluctuating throughout voiding, but the flow is continuous and never reaches zero during voiding. This pattern suggests intermittent sphincter overactivity during voiding and is often associated with dysfunctional voiding. It will be seen as sharp peaks and troughs in the flow curve. To qualify for a staccato label, the fluctuations should be larger than the square root of the maximum flow rate.

Interrupted-Shaped Curve. This flow curve will display discrete (albeit low amplitude) peaks similar to a staccato-shaped curve; however, there will be segments where the flow rate is zero with complete cessation of urinary flow between these peaks. This flow pattern suggests an underactive bladder because each peak represents abdominal muscle straining (i.e., Valsalva) creating the main force for urine evacuation. In between each strain, the flow ceases as a result of an absent or weak detrusor contraction. It is possible this flow pattern can be seen with dyssynergy between the bladder and external urethral sphincter, and a concomitant EMG and/or pressure flow study often will be useful to distinguish between the two.

Plateau-Shaped Curve. The plateau-shaped curve is a flattened, low-amplitude prolonged flow curve that is suggestive of BOO. The BOO can be anatomic (e.g., posterior urethral valves or urethral stricture) or dynamic (e.g., continuous, tonic sphincter contraction). Flow EMG may differentiate among BOO subtypes. A plateau-shaped curve may be seen with an underactive bladder during a long continuous abdominal strain. Abdominal pressure monitoring during the uroflow can help delineate an underactive bladder condition.

Pelvic Ultrasound

Pelvic ultrasound is a key tool in the evaluation of pediatric LUT function and is used in the initial evaluation of all children with suspected BBD at our institution (Fig. 143-6). In addition to giving objective information about the voiding pattern of the child in question, it can be readily used to monitor progress over time.

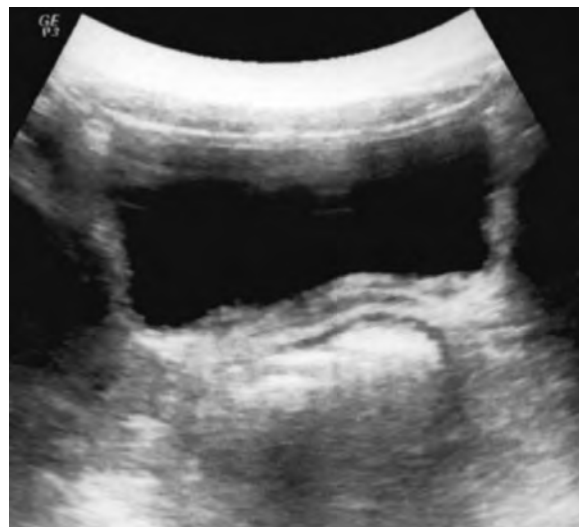


Figure 143-6. Pelvic ultrasound demonstrating a thickened bladder wall and a large amount of stool in the rectum.

Ultrasonography can calculate bladder volume and thus is useful in measuring prevoid and postvoid residual (PVR) urine volume and anatomic details of the bladder and rectum (e.g., bladder wall thickness, stool, rectal distention).

Postvoid Residual

PVR measurements in neurologically intact children are highly variable with significant intraindividual variability. Chang and Yang (2009) suggested that abnormal PVR urine volume could be defined as a PVR greater than 20 mL (as opposed to >10% of estimated bladder capacity) on repeat micturitions without bladder

overdistention. Recently, investigation of 1128 healthy Taiwanese children between 4 and 12 years of age with a bell-shaped uroflow pattern and a voided volume of greater than 50 mL support the following normative 95th percentile values for an abnormally elevated PVR (Chang et al, 2013):

- **Children 4 to 6 years:** Single PVR greater than 30 mL or greater than 21% of bladder capacity (BC), where BC is determined as voided volume (VV) + PVR and expressed as percent of the expected bladder capacity ($EBC = [age\ (yr) + 1] \times 30\ mL$). It is recommended that a repeat PVR be performed with dual measurements; a repetitive PVR greater than 20 mL or greater than 10% BC is considered significantly elevated.
- **Children 7 to 12 years:** A single PVR greater than 20 mL or 15% BC or repetitive PVR greater than 10 mL or 6% BC is considered elevated.

According to Chang and colleagues (2013), standard conditions should be applied to measuring PVR; the bladder should not be underdistended (<50%) nor overdistended (>115%) in relation to the EBC; PVR must be obtained immediately after voiding (<5 minutes). Further validation is needed for these nomograms in similar cohorts across cultures.

Bladder Wall Thickness

In daily clinical practice a thickened bladder wall should alert the clinician to long-standing problems with urine storage and emptying. The bladder wall is normally less than 3 mm when full and less than 5 mm when relatively empty (Jequier and Rousseau, 1987). A thickened bladder wall is suggestive of an anatomic or functional outlet obstruction causing detrusor hypertrophy; however, the most common diagnosis associated with a thickened bladder wall was found to be OAB (Yeung et al, 2007). Bladder wall thickness can be measured with either a full or an empty bladder and is inversely proportional to the degree of bladder filling.



Please see the Expert Consult website for further details.

Rectal Distention

Although there is insufficient evidence to support the notion that the transverse diameter of the rectum alone can be used as a predictor of constipation and fecal impaction, a number of authors have made several observations on this subject (Fig. 143-7). Klijn and associates (2004) measured the diameter of the rectum on bladder ultrasonography in a constipated group of patients with dysfunc-



Figure 143-7. Pelvic ultrasound showing a dilated rectum filled with stool compressing posterior wall of bladder.

tional voiding and compared this diameter in a control group of patients with a normal defecation pattern. Not surprisingly, in the group of constipated patients with dysfunctional voiding, the diameter of the rectum was significantly larger than in the control group.

Please see the Expert Consult website for further details.



Bristol Stool Scale

The Bristol Stool Scale or Bristol Stool Chart is a useful guide designed to classify the form of human feces into seven distinct categories. Sometimes referred to in the United Kingdom as the Meyers scale, it was developed at the University of Bristol in 1997 (Lewis and Heaton, 1997). The seven types of stool (ranging from most firm in type 1 to loosest in type 7) are as follows (Fig. 143-8):

- **Type 1:** Separate hard lumps, like nuts (difficult to pass because stool has not retained any water)
- **Type 2:** Sausage-shaped, but lumpy; represents multiple type 1 stools congealed into a single mass, typical for functional constipation
- **Type 3:** Like a sausage but with cracks on its surface
- **Type 4:** Like a sausage or snake, smooth and soft, typical for someone who has a daily bowel movement
- **Type 5:** Soft blobs with clear-cut edges, passed easily, usually multiple times per day
- **Type 6:** Fluffy pieces with ragged edges, a mushy stool, urge to defecate can be difficult to control
- **Type 7:** Watery, no solid pieces, entirely liquid

We prefer to use it as a clinical communication aid with our patients and their families in terms of what to strive for and to facilitate titration of supplemental fiber or laxative administration.

BRISTOL STOOL SCALE		
Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely liquid

Figure 143-8. Bristol Stool Chart. (Modified from Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920-4.)

In 2004, Yeung and colleagues reported on their evaluation of a special bladder ultrasound protocol for the assessment of LUTD compared with urodynamic findings and for the prediction of treatment outcome in children with enuresis (Yeung et al, 2004b). The bladder volume wall thickness index (BVWI) was a ratio of bladder volume to wall thickness, and they found statistically significant correlations between BVWI and enuresis treatment response. In addition, there was a high predictive value of normal bladder function as evaluated by urodynamics with a normal BVWI. Although it is intuitive that bladder wall thickness would correlate with LUTD, not all groups have come to the same conclusion (Mostafavi et al, 2012).

Recently, Burgers and colleagues (2013b) took a group of 84 children with a median age of 9 years (range 6 to 11) and performed both transabdominal ultrasound and digital rectal examination (DRE) under anesthesia. A rectal mass was found on transabdominal ultrasound and DRE in 32% and 41% of all children, respectively, with agreement between the two tests in 82.5%. The median diameter of the rectum was 3.3 cm in children with a full rectum and 2.5 cm and 2.0 cm in patients with a half-filled and empty rectum, respectively. They concluded that transabdominal ultrasound was a noninvasive and reliable alternative to assess the rectal filling state and might replace DRE in the evaluation of children with constipation.

KEY POINTS: EVALUATION OF DAYTIME URINARY INCONTINENCE AND BLADDER DYSFUNCTION

- The goals of evaluation are to determine whether the patient has a filling or emptying (or both) phase abnormality. If an abnormality is found, the evaluation then should be directed toward determining the underlying cause and distinguish whether the dysfunction stems from an anatomic or functional issue.
- Vital components of the history include voiding schedule, symptomatology, bowel habits, family history, maternal prenatal history, perinatal history, developmental milestones, toilet training, neuropsychiatric comorbidities, past medical/surgical history, social history, diet, and previous UTIs.
- The voiding diary is one of the most helpful diagnostic tools in the armamentarium of providers who care for children with LUTD.
- During physical examination, special attention should be paid to the lower back for cutaneous manifestations of occult spinal dysraphism.
- All children presenting with LUTD should provide a urinalysis with important elements of the urinalysis, including the specific gravity and the presence of white or red blood cells, bacteria, protein, and glucose.
- Uroflowmetry provides readily useful information regarding the pattern or shape of urine flow curve that can often be diagnostic of an underlying cause. Qmax is the most relevant quantitative variable when assessing bladder outflow.
- Ultrasonography can calculate bladder volume and thus is useful in measuring prevoid and PVR urine volume and can provide useful anatomic details of the bladder and rectum (e.g., bladder wall thickness, stool presence, rectal distention).

Treatment

The ICCS has published treatment guidelines on various LUT conditions and their associated comorbidities (Chase et al, 2010; Hoebeke et al, 2010; Franco et al, 2013; Burgers et al, 2013c; Austin et al, 2014). The management of a child or adolescent who suffers from LUTD is primarily directed at improving symptoms (e.g., urinary and/or fecal incontinence, recurrent UTIs) and protecting the upper urinary tract from permanent damage. Methods for treating children with BBD must be tailored to the specific LUTD and the child's symptomatology. Therapeutic considerations include the underlying cause, patient age, motivation and maturity level, symptom severity and duration, prior interventions, and potential risk factors for upper urinary tract damage (i.e., elevated intravesical storage pressures, VUR, recurrent UTIs).

We use a stepwise approach to the treatment of children presenting with symptoms concerning for BBD (Thom et al, 2012). Our algorithm generally moves from least to most invasive with conservative measures (e.g., treatment of constipation, behavioral modification) exhausted before initiating medications, physical therapy, biofeedback, neuromodulation, or surgical intervention.

According to the ICCS, researchers and/or clinicians should recognize three basic principles of treatment outcomes (Austin et al, 2014). First, the symptom frequency during baseline and after treatment should each be documented. Second, the assessment of treatment response must be based on pretreatment baseline registration symptom frequency. Third, the response during treatment should be noted, as well as the response after cessation of treatment for a specified period; and these two responses may not be the same. This has been outlined as follows:

- **Initial success** (based on symptom frequency)
 - No response: Less than 50% reduction
 - Partial response: 50% to 99% reduction
 - Complete response: 100% reduction

- **Long-term success**

- Relapse: More than one symptom recurrence per month
- Continued success: No relapse in 6 months after cessation of treatment
- Complete success: No relapse in 2 years after cessation of treatment

Urotherapy

Urotherapy is conservative-based therapy and treatment of LUTD that rehabilitates the LUT and encompasses a very wide field of health care professionals (Austin terminology document [Austin, 2014]). It primarily involves behavioral modification of voiding (i.e., timed voiding schedules), lifestyle modifications, and treatment of constipation. Although there are no randomized, controlled trials comparing the efficacy of conservative intervention to other therapies, several retrospective studies suggest a reduction in symptoms of up to 70% with a strictly conservative approach (Wiener et al, 2000; Allen et al, 2007).

Urotherapy can be divided into standard therapy and specific interventions. **Standard components** include the following:

1. *Information and demystification.* It is often helpful to explain normal LUT function to parents and children and how the particular child deviates from normal.
2. *Instruction* on how to resolve LUTD (i.e., behavioral modification, timed voiding, treatment of constipation).
3. *Lifestyle advice.* Encompasses balanced fluid intake and diet modification; diminished dietary irritants such as caffeine, carbonation, citrus, chocolate, and spicy foods; regular bladder and bowel emptying patterns; and skin care for those with perineal irritation from incontinence. It is also helpful to review optimal posture during voiding (i.e., sitting in the middle of the toilet with heels flat on the ground or supported on a footstool). One useful aid to teach correct upright posture is to have children straddle the toilet seat and face the toilet bowl during voiding, because this spreads the legs apart (preventing holding maneuvers such as forcefully crossing the legs) and forces them to straighten the back as they balance themselves on the toilet seat. This maneuver also can be used to successfully correct vaginal reflux.
4. *Registration* of symptoms and voiding habits, using bladder diaries or frequency-volume charts and potentially mobile applications.
5. *Support and encouragement* via regular follow-up with the caregiver.

Specific interventions of urotherapy include various forms of pelvic floor muscle retraining (i.e., biofeedback), neuromodulation, and intermittent catheterization.

Conservative Management

Bowel Dysfunction

One of our first steps is to decipher whether concomitant bowel dysfunction exists based on history, physical examination, and pelvic ultrasound. As mentioned previously, anorectal and LUT function are closely interrelated. If evidence of bowel dysfunction is indeed present (as is often the case), we generally initiate a bowel regimen that includes high fiber and increased fluid intake. Our rule of thumb for daily fiber intake is age in years + 15 to 20 for total number of grams to be ingested. Parents are reminded that without concurrent increased fluid intake, increased fiber could actually make matters worse by allowing smaller stool balls to bind together and subsequently increase the severity of their child's constipation.

If increased fiber is not a feasible solution, we usually recommend titrating polyethylene glycol such that children are eventually having daily Bristol type 4 stools. In severe cases, we recommend a complete bowel cleanse (i.e., chemical disimpaction) consisting of what we term "magic mousse" supplementing with tap water enemas to relieve any distal obstruction by impacted stool in the

rectal vault. Magic mousse consists of three simple ingredients: 1 cup ice cream, 1 cup prepared pudding, 6 oz. mineral oil, that are mixed and frozen (Campigotto, personal communication, 2014). Children younger than 6 years of age are given 4 T twice daily and those 6 years of age or older get double the dose twice daily. This is generally done over a weekend for children who are in school or daycare because this routine is fairly intense and children may have multiple, somewhat unpredictable bowel movements. **It is imperative that the bowel regimen be continued throughout the treatment course to both maximize therapeutic efficacy for the bladder dysfunction component and counteract the constipating side effect of anticholinergic medications.**

The importance of addressing constipation in those with BBD is substantiated by the findings of a large retrospective study of 234 chronically constipated and encopretic children who were treated for constipation and reassessed at least 12 months after initiation of therapy (Loening-Baucke, 1997). Of these children, 29% complained of daytime urinary incontinence and 34% had enuresis. UTI was present in 11% of the cohort and was more common in girls. **Relief of constipation resulted in disappearance of daytime urinary incontinence in 89% and enuresis in 63% of patients. There were no reported UTIs in any patient who had no anatomic abnormality of the urinary tract.**

Behavioral Modification

The ultimate goal of any structured behavioral modification program is to return the child to normal micturition habits. With this goal in mind, it is important to set an individualized voiding regimen to establish a consistent voiding routine. **The classic regimen entails timed voiding with frequent voids scheduled every 2 hours during the day.** This strategy is crucial in aiding to avoid bladder overactivity and urge symptoms, which can occur as the bladder fills and begins to reach the critical volume that triggers the urge to void. We recommend wristwatch alarms to all patients because these can readily assist older, more independent children to comply with timed voiding (Hagstroem et al, 2010). The use of a vibratory watch is also a good option because it does not disturb peers, with only the patient knowing that it has indicted the set time. Regardless of what regimen is used, children are encouraged to urinate before they have a sense of urgency, empty their bladders completely, and avoid abdominal straining.

The timed voiding regimen is often linked to a positive reinforcement program using a diary in which the child tracks the number of times voided during the day. It has been demonstrated that the establishment of a reward system can significantly improve the child's self-esteem and compliance (Allen et al, 2007). Specifically, the incentive scheme should focus on rewarding the child for following the recommended program (e.g., stickers each time the child voids during the day) as opposed to "not wetting" themselves. Not surprisingly, behavioral modification has been shown to be more successful in older children (older than 8 years of age), who, in general, will be more motivated by peer pressure and are mature enough to respond to and follow instruction (Curran et al, 2000; Heilenkötter et al, 2006).

Biofeedback

Biofeedback is a treatment modality that uses electronic or mechanical instruments to relay perceptual evidence to assist a person in gaining control over a physiologic process or function (Liberati, 2005). This method has been used for over three decades in the urologic setting and employs noninvasive urodynamic instrumentation to measure, record, and provide direct, instantaneous information to the child about voiding function (Maizels et al, 1979). Real-time uroflowmetry allows the patient to observe the urine flow rate. Concurrent placement of adhesive pads on the perineum measures sphincter and/or pelvic floor activity. Abdominal EMG also can be performed if desired. Each session lasts approximately 45 minutes with a trained practitioner overseeing therapy. The visual and auditory feedback allows the child to become aware of and gain

control over LUT function by teaching them how to voluntarily relax their sphincter and pelvic floor musculature during voiding, thus preventing detrusor-sphincter dyscoordination. In fact, many biofeedback programs have been tailored to children by using interactive computer games controlled by pelvic floor contraction and relaxation along with urinary flow rate (McKenna et al, 1999). This system has facilitated the training process and lowered the age at which children can be successfully treated; however, one should bear in mind that most children under 5 years of age are typically incapable of receiving biofeedback regularly.

A number of observational studies have documented the utility of biofeedback therapy in reducing the symptoms associated with LUTD (Yamanishi et al, 2000; Chin-Peuckert and Salle, 2001; Nelson et al, 2004; Klijn et al, 2006), expediting the resolution of VUR (Palmer et al, 2002; Kibar et al, 2007), and eliminating recurrent UTIs (Nelson et al, 2004). Recently, a systematic review evaluated the efficacy of biofeedback in the treatment of children with BBD (Desantis et al, 2011). The review included 27 studies (1 randomized controlled trial and 26 case-series). The pooled estimate showed an 83% and 80% improvement in UTI and daytime urinary incontinence, respectively. The only included randomized study favored biofeedback over standard urotherapy (relative risk [RR] 1.4, 95% confidence interval [CI] 0.98 to 2), but this was not statistically significant. On analysis of all included studies, there also was improvement in constipation (18% to 100%), frequency (67% to 100%), urgency (71% to 88%), and VUR (21% to 100%).

Clean Intermittent Catheterization

Lapides and colleagues (1972) first introduced the concept of clean intermittent catheterization (CIC) as a method of emptying the bladder in neurologically impaired patients. Since its initial description, this treatment strategy has gradually been employed in neurologically intact individuals with various types of LUTD. In the setting of dysfunctional voiding and in children who postpone micturition, the detrusor muscle stretches and the bladder becomes chronically overdistended. This repeated action over time can lead to underactive bladder with the end result of myogenic failure. In these cases, bladder emptying is often incomplete, resulting in large PVR urine volumes, urinary incontinence, and recurrent UTIs from stasis. CIC is a safe, effective, and well-tolerated treatment strategy to attain continence and reduce the rate of recurrent UTI in children with LUTD (Pohl et al, 2002). It is particularly crucial to discuss the merits of this intervention with sensate patients and their families to maximize adherence.

Pharmacotherapy

Pharmacologic intervention in the treatment of children with LUTD has traditionally encompassed anticholinergic agents and α -adrenergic receptor antagonists (i.e., α -blockers) to enhance bladder filling and emptying, respectively. We will generally initiate one or both of these two medications once all other conservative measures have been exhausted. In some instances we will start α -blockers concomitantly with biofeedback, and this management decision is ultimately left up to the discretion of the provider.

Anticholinergic Agents

Anticholinergics (i.e., antimuscarinics) are the current gold standard in the treatment of patients with symptoms referable to OAB. Muscarinic receptors are found in the human detrusor muscle, and bladder contractions are initiated by stimulation of these receptors with the release of acetylcholine from cholinergic nerves. The main action of anticholinergics is on the M1 and M3 receptor subtypes, which are thought to be responsible for the pathogenesis of detrusor overactivity (Chapple et al, 2002). **These agents act by reducing the frequency and intensity of uninhibited detrusor contractions during the filling phase of the bladder, resulting in an increase in the functional bladder capacity and compliance (Nijman, 2004; Finney et al, 2006).** The clinical efficacy depends

on various factors such as receptor affinity, pharmacokinetics, and the specificity for the bladder.

Oxybutynin was among the first generation of modern antimuscarinic medications available for treating incontinence in children. Five anticholinergic agents are currently approved in the United States for the treatment of OAB (darifenacin, oxybutynin, solifenacin, tolterodine, and trospium), with only two of these (oxybutynin and tolterodine) having formally achieved approval for use in children. Oxybutynin has antimuscarinic, antispasmodic, and analgesic properties. It causes the antispasmodic effect by acting as a calcium channel blocker. The analgesic and antispasmodic properties make the medication particularly attractive; however, these effects occur only with supraphysiologic doses that would render them useless secondary to side effect profile (Chapple, 2000).

The nonselective pattern of activity and penetration of the blood-brain barrier are known to induce systemic and central side effects, respectively. The longer acting extended-release formulation (Oxybutynin XL) is also approved by the U.S. Food and Drug Administration (FDA) for use in children and uses a novel delivery system resulting in absorption in the large intestine (Youdim and Kogan, 2002). This avoids the first-pass metabolism in the liver, leading to a decrease in the active metabolite *N*-desethyloxybutynin, thought to be responsible for many of the adverse effects associated with the use of oxybutynin. **The main side effects include constipation, dry mouth, blurred vision, reduced sweating, flushing, and altered behavior and cognition.** Oxybutynin is lipid soluble and therefore likely to cross the blood-brain barrier and in adults has been reported to interfere with cognition. However, in a non-randomized trial of 25 children, Sommer and colleagues (2005) found that treatment with oxybutynin was not associated with cognitive impairment. Additionally, in a recent study by Veenboer and associates (2013), no significant differences in behavior were found between children with spinal dysraphism with and without long-term use of antimuscarinics.

Other methods of delivery of oxybutynin are intravesical and transdermal. The intravesical method of delivery avoids the first-pass effect and leads to increased amounts of oxybutynin available compared to immediate-release oral oxybutynin. Its use in the non-neurogenic, sensate population is limited, however, because of the need for catheterization. **The transdermal patch is as efficacious as the immediate-release oral form but with nearly half the incidence of dry mouth (Davila et al, 2001).** Local skin erythema and pruritus are side effects unique to this route of administration that can be seen in over one third of patients (Gleason et al, 2014).

α-Adrenergic Receptor Antagonists (α-Blockers)

α-Adrenoreceptors have been demonstrated in the LUT, with a large concentration located at the bladder neck and urethra (Ek, 1978). **α-Adrenergic blockade results in smooth muscle relaxation and decreased bladder outlet resistance.** Limitations of early α-blockers included their side effect profile with hypotension and dizziness. With subsequent development of more “selective” α-blockers in the 1980s that targeted α_{1a}-receptors rather than both α_{1a}- and α_{1b}-adrenergic receptors, these side effects were greatly diminished. Examples of selective α-blockers include alfuzosin, doxazosin, prazosin, silodosin, tamsulosin, and terazosin.

Currently, α-blockers are a mainstay drug used to facilitate bladder emptying in the adult population, particularly in adult males with benign prostatic hyperplasia. Early work on the benefits of α-blockers on pediatric LUTD by Austin and colleagues (1999) pioneered the introduction of α-blockers into the armamentarium of drugs that can be used to treat voiding issues in children. In this pilot report, there was an 82% improvement in the measured parameters of 17 patients treated with α-blocker therapy. In a follow-up of their initial study, the group continued to see improvement in multiple LUTS, daytime incontinence episodes, and PVR measurements in 55 children treated with doxazosin for dysfunctional voiding (Cain et al, 2003).

Please see the Expert Consult website for further details.

α-Blocker treatment selection of children with LUTD is done through a comprehensive treatment program that involves an escalating treatment paradigm (Chase et al, 2010; Thom et al, 2012) or by identifying patients with characteristic uroflow abnormalities (Van Batavia et al, 2010). The uroflow finding of a prolonged “EMG lag time” is associated with bladder neck and internal urethral sphincter discoordination and may be used to select patients for α-blocker therapy (Van Batavia et al, 2011, 2014). The EMG lag time is the time duration after the external sphincter relaxes and the flow of urine. A prolonged lag time of greater than 6 seconds is suggested as a reliable indicator of tailoring LUTD treatment with α-blocker therapy (Van Batavia et al, 2014). Further validation is needed to investigate the reliability and reducibility of these uroflow findings.

Botulinum Toxin

A relatively recent investigational pharmacologic approach in refractory cases of LUTD is botulinum-A toxin (BTX-A). The toxin acts by inhibiting acetylcholine (ACh) release at the presynaptic neuromuscular junction. Inhibited ACh release results in regionally decreased muscle contractility and atrophy at the injection site. The chemical denervation that ensues is a reversible process, and eventually the toxin is inactivated and removed. Clinical effects begin within 5 to 7 days of injection with maximal effects reached within 4 to 6 weeks (Game et al, 2009). The duration of induced paralysis varies depending on the type of muscle treated, with duration of treatment effect lasting between 3 and 12 months (Riccabona et al, 2004).

Clinically, BTX-A injections have been used safely in the treatment of a number of clinical disorders (Maria et al, 2005), including neurogenic LUTD (Game et al, 2009). BTX-A has been subsequently applied to non-neurogenic LUTD, and there are a number of reports of BTX-A used to treat children with OAB and dysfunctional voiding (Steinhardt et al, 1997; Hoebeke et al, 2006; Mokhless et al, 2006; Radojicic et al, 2006; Franco et al, 2007; Petronijevic et al, 2007; Vricella et al, 2014). BTX-A is directly injected into the detrusor muscle (in patients with OAB) or external urinary sphincter (in patients with dysfunctional voiding) under cystoscopic guidance. One of the main drawbacks of this therapeutic modality is the need for re-treatment given the reversible nature of this chemical denervation secondary to synaptic terminal resprouting within 6 months of injection. Fortunately, preliminary studies suggest that repeated BTX-A injections are safe in children and do not induce additional fibrosis in the bladder wall (Pascali et al, 2011).

Neuromodulation

During the last two decades electrical nerve stimulation, also known as neuromodulation, has been applied to the treatment of non-neurogenic LUTD in children (Table 143-1). Several of the reported changes after treatment with neuromodulation include significantly increased bladder capacity, decreased severity of urgency, improved continence, and decreased UTIs (Bower et al, 2001; Hoebeke et al, 2001b; Roth et al, 2008). A significant improvement in urodynamic parameters of bladder compliance, number of involuntary contractions, and bladder volume at first detrusor contraction also have been noted (De Gennaro et al, 2004).

In neuromodulation, electrical stimuli are exerted in a noninvasive manner to alter the existent neural transmission pattern and modulate detrusor activity. The putative mechanism involves acting centrally by rebalancing excitatory and inhibitory information and returning the neural drive toward a more neutral status. A number of modalities have been studied in children, including sacral neuromodulation, pudendal nerve stimulation, and tibial nerve stimulation. Although preliminary results have been promising, electrical nerve stimulation's role in children with non-neurologic LUTD nevertheless remains controversial because of the lack of controlled trials and largely obscure mechanism of action.

With transcutaneous electrical nerve stimulation (TENS) superficial electrodes are placed on each side of the S3 and S2 spinal cord



Kramer and colleagues (2005) conducted the first randomized, placebo-controlled study of selective α -blocker therapy in children with dysfunctional voiding. Thirty-eight children were randomized to either placebo or 0.5 mg of doxazosin. Unlike in previous studies, they found no significant difference in the PVR and uroflow measurements between the treatment groups. There was a trend toward a significant improvement in urinary incontinence (4 vs. 14 incontinent episodes per week from a median baseline of 18 weekly episodes) and the DVSS parental survey in the α -blocker group compared to the placebo group. There was a significant difference in parental satisfaction, with a higher parental satisfaction in the children treated with α -blockade.

Vanderbrink and colleagues (2009) reported an observational study of 23 children with bladder neck dysfunction who were treated for an average of 10 months with tamsulosin. The number of incontinent episodes decreased from over 5.5 to less than 1 episode on average per day. In addition, increases in Qavg and Qmax and a reduction in PVR urine and abnormal uroflow patterns were observed during therapy. The safety profile for α -blockade in this pediatric population also was assessed, and the results were consistent with those in other reports using selective α -blockers in children. Although orthostatic hypotension was not formally evaluated, the authors did not find any significant alterations of blood pressure measurements and there were no reports of any symptomatology suggestive of hypotension.

TABLE 143-1 Studies Evaluating Neuromodulation in Treatment of Children with Lower Urinary Tract Dysfunction

REFERENCE	ES TYPE	LUTD	NO. PTS	TREATMENT SCHEME	FREQUENCY/AMPLITUDE	TREATMENT PERIOD	FOLLOW-UP (mo)	OUTCOME (%)
Hoebeke et al, 2001b	TENS	OAB	41	S3: 2 hr/day	2 Hz/not stated	6 mo	12	56 cured, 20 improved
Bower et al, 2001	TENS	OAB	14	Suprapubic/ S2-3: 1 hr, 2 times/day	10 or 150 Hz/ not stated	1 mo	1	50 cured, 23 improved
Barroso et al, 2006	TENS	OAB	19	S3: 20 min, 3 times/wk	10 Hz/6-42 mA	1 mo	14	63 cured, 32 improved
Hagstroem et al, 2009	TENS	OAB	25	S2-3: 2 hr/day	10 Hz/37.5 mA	1 mo.	1	0 cured, 61 improved
Malm-Buatsi et al, 2007	TENS	OAB	18	S2-3: 20 min, 2 times/day	100 Hz/0-60 mA	8 mo	13	13 cured, 60 improved
Lordêlo et al, 2010	TENS	OAB	37	S2-3: 20 min, 3 times/wk	10 Hz/not stated	7 wk	16	62 cured, 90 improved
Hoebeke et al, 2002	PTNS	DV	31	30 min, wkly	20 Hz/not stated	10 wk	3	Urgency: 25 cured, 36 improved Incontinence: 17 cured, 52 improved
De Gennaro et al, 2004	PTNS	OAB DV	10 7	30 min, wkly	20 Hz/0-10 mA	12 wk	3	OAB: 56% cured, 80% improved DV: 50 cured, 71 improved
Capitanucci et al, 2009	PTNS	OAB DV	14 14	30 min, wkly + maintenance (once/mo)	20 Hz/0-10 mA	12 wk	24	OAB: 36 cured, 86 improved DV: 86 cured, 100 improved
Humphreys et al, 2006	SNM	BBD	23	S3	Not stated	13 mo	13	UI: 16 cured, 68 improved UR: 33 cured, 60 improved Bladder pain/urgency/ frequency: 67/75/73 improved Constipation: 80 improved
Roth et al, 2008	SNM	BBD	20	S3	Not stated	27 mo	27	UI: 75 cured, 88 improved UR: 25% cured Urgency/frequency: 83 cured/78 cured/89 improved Constipation: 41 cured, 59 improved
Stephany et al, 2013	SNM	BBD	14	S3	Not stated	6 mo	6	Significant improvements in quality-of-life (psychosocial, total) scores and LUTD scores

BBD, bowel-bladder dysfunction; DV, dysfunctional voiding; ES, electrical stimulation; LUTD, lower urinary tract dysfunction; OAB, overactive bladder; PTNS, percutaneous tibial nerve stimulation; SNM, sacral nerve modulation; TENS, transcutaneous electrical nerve stimulation; UI, urinary incontinence; UR, urinary retention.

segments. In general, therapy consists of 20-minute sessions three times per week. Percutaneous tibial nerve stimulation (PTNS) is performed with a 34-gauge stainless steel needle inserted approximately 5 cm cephalad to the medial malleolus and a grounding pad placed just posterior to the medial malleolus. Proper needle placement in children is confirmed by observing ipsilateral plantar and/or toe flexion or fanning. Although the purported mechanism of action differs somewhat, neuromodulation by PTNS is based on the traditional Chinese practice using the Sanyinjiao acupuncture point, which overlies the posterior tibial nerve (van Balken et al, 2004). The posterior tibial nerve is a mixed sensory and motor nerve originating from the L4 to S3 spinal roots that also contributes to sensory and motor control of the bladder, urinary sphincter, and pelvic floor musculature. Therapy has been invariably applied once weekly, usually for 30-minute outpatient treatment sessions.

Since its initial description, a significant number of reports have been generated on sacral nerve root stimulation via implantable electrodes. In the last decade sacral nerve modulation (SNM) has gained widespread recognition in adults and was approved by the FDA for use in urology for urinary urgency/frequency, urge incontinence, pelvic floor dysfunction, and nonobstructive urinary retention. Despite off-label use, a number of groups have reported on their experience with SNM in children with non-neurogenic LUTD (Tanagho, 1992; Humphreys et al, 2006; Roth et al, 2008; McGee et al, 2009; Stephany et al, 2013).

Before sacral implantation can be performed, percutaneous transforaminal access to the S3 spinal nerve must be achieved. Once the correct responses are obtained, the quadripolar tined lead of the neurostimulator device can be implanted. This lead can then be connected to an external neurostimulator device via a tunneled subcutaneous extender for programming and trial assessments. If this is successful, the patient undergoes a second procedure to implant the permanent neurostimulator device into a subadipose pocket in the upper gluteal region. Complications commonly cited with implantable SNM devices are device and/or wound infection, electrode migration, loss of effect, and lead fracture. Revision rates range between 7% and 18%, secondary to lead migration, faulty connection, and infection.

Special Conditions of Lower Urinary Tract Dysfunction and Their Treatment

Giggle Incontinence (Enuresis Risoria)

Enuresis risoria is an uncommon form of daytime incontinence classically seen in school-aged females. Typically, moderate-to-large amounts of urinary leakage are triggered by laughing alone. The accepted theory is that of a central nervous system (CNS) inactivation (i.e., cataplexy) in association with laughter resulting in urinary incontinence (Sher and Reinberg, 1996). It should be emphasized that the incontinence episodes are invariably significant and often the entire bladder volume is drained. Daytime urinary incontinence in conjunction with laughter is also seen in children with OAB and is more common than true giggle incontinence. It is a diagnosis of exclusion and is usually established on history and is supplemented by the absence of other voiding symptoms and normal investigations. Giggle incontinence has a significant adverse effect on the social life, and this is often why medical assistance is sought. Currently, available treatment strategies include biofeedback or methylphenidate (Berry et al, 2009; Richardson and Palmer, 2009).

Pollakiuria (Extraordinary Daytime Urinary Frequency)

This is a disorder characterized by a very high daytime frequency of micturition (sometimes as high as 50 times per day). A key aspect of this syndrome, which differentiates it from OAB and often can clinch the diagnosis, is that the symptoms are limited only to the daytime. It is seen in early childhood (4 to 6 years of age) in both genders and associated with a history of recent death or life-threatening event in the family. Usually, it runs a benign, self-

KEY POINTS: MANAGEMENT OF DAYTIME URINARY INCONTINENCE AND BLADDER DYSFUNCTION

- The management of a child or adolescent with LUTD is primarily directed at improving symptoms (e.g., urinary and/or fecal incontinence, recurrent UTIs) and protecting the upper urinary tract from permanent damage.
- In general, a stepwise approach is used with an algorithm that progresses from least to most invasive with conservative measures (e.g., treatment of constipation, behavioral modification) exhausted before initiating medications, physical therapy, biofeedback, neuromodulation, or surgical intervention.
- In one large study, relief of constipation alone resulted in the disappearance of daytime urinary incontinence in 89% and enuresis in 63% of patients studied (Loening-Baucke, 1997).
- Anticholinergics are the current gold standard in the treatment of patients with symptoms referable to OAB. These agents act by reducing the frequency and intensity of uninhibited detrusor contractions during the filling phase of the bladder, resulting in an increase in the functional bladder capacity and compliance. The main side effects include constipation, dry mouth, blurred vision, reduced sweating, flushing, and altered behavior and cognition.
- α -Adrenergic blockade results in smooth muscle relaxation and decreased bladder outlet resistance to facilitate bladder emptying.
- In neuromodulation, electrical stimuli are exerted in a non-invasive manner to alter the existent neural transmission pattern and modulate detrusor activity. The putative mechanism involves acting centrally by rebalancing excitatory and inhibitory information and returning the neural drive toward a more neutral status. A number of modalities have been studied in children, including SNM, pudendal nerve stimulation, and tibial nerve stimulation.

limited course over a period of approximately 6 months (Bergmann et al, 2009). No specific treatment, apart from reassurance, is necessary. Children presenting with frequency, however, merit clinical investigation to exclude other pathologic causes.

Underactive Bladder

As the name suggests, underactive bladder describes a child who is required to raise intra-abdominal pressure to initiate, maintain, and complete voiding. Once a functional or anatomic cause for BOO has been ruled out, there are two main approaches to this entity. The first is with timed voiding and double voiding to more efficiently empty the bladder and lower the ultimate PVR volume of urine. If this treatment strategy fails to achieve the desired effect, we often recommend CIC with frequency dependent on symptom severity. Obviously, this requires appropriate counseling and thoughtful guidance of both patient and caregiver, especially in the child who is neurologically intact.

Vaginal Reflux (Vaginal Entrapment and Vaginal Voiding)

Vaginal reflux is characterized by incontinence after normal voiding in the absence of other LUTS. It is commonly seen in prepubertal girls, and the typical history is that of wetting of undergarments approximately 10 to 15 minutes after a normal void. It often can be associated with labial adhesions as a result of chronic irritation and inflammation from skin exposure to relatively caustic urine. Reassurance and postural modification to ensure complete vaginal emptying is the only treatment required.

ENURESIS

Over the last several decades, much has changed in our understanding of enuresis. Previous notions of voluntary control have been replaced by an appreciation of genetic and pathophysiologic mechanisms. What is known with certainty is that enuresis is a common medical condition in children (Shreeram et al, 2009). It affects millions of children throughout the world and is associated with significant negative impacts on self-esteem and health-related quality of life (Wolfe-Christensen et al, 2013).

Terminology and Background

The term *enuresis* is synonymous with *nocturnal enuresis* and is defined as discrete episodes of urinary incontinence during sleep in children over 5 years of age in the absence of congenital or acquired neurologic disorders. The term *diurnal enuresis* has been eliminated completely. The child who wets during the day and night can be said to have daytime urinary incontinence and enuresis or non-monosymptomatic enuresis.

Enuresis is categorized as monosymptomatic (MSE) or non-monosymptomatic (NMSE). MSE is defined as enuresis in children without any other LUTS and without a history of bladder dysfunction. MSE is further subdivided into *primary* and *secondary* forms. Children who have *never* achieved a satisfactory period of nighttime dryness (~80% of enuretic children fit this definition) have primary MSE (Friman and Warzack, 1990). Children who develop enuresis after a dry period of at least 6 months are said to have secondary enuresis (von Gontard and Nevés, 2006). Secondary enuresis often is ascribed to an unusually stressful event (e.g., parental divorce, birth of a sibling, sexual abuse) or an organic (e.g., UTI, diabetes, obstructive sleep apnea, neurogenic bladder) or psychological cause (e.g., ADHD or conduct disorder) at a time of vulnerability in a child's life. These children are more likely to have NMSE (see next) and respond less well to treatment. The exact cause of secondary MSE, however, remains largely unknown. The clinical presentations of children with primary and secondary MSE are otherwise similar, which suggests a common pathogenesis (Robson et al, 2005). Moreover, large family studies have demonstrated that secondary MSE is usually no different etiologically from primary MSE, with undue emphasis on their difference being unwarranted (Schaumburg et al, 2008).

Enuresis with any daytime LUTS is defined as NMSE (Franco et al, 2013). Daytime LUTS suggesting NMSE include daytime incontinence (not obligatory), frequency, genital or LUT pain, and holding maneuvers (i.e., strategies to postpone voiding). A careful history is often required to elicit these symptoms, which usually indicate either OAB (i.e., a storage issue) such as urgency or dysfunctional voiding (i.e., emptying problems) such as hesitancy, straining, weak stream, intermittency or a feeling of incomplete emptying.

The pathogenesis, evaluation, and treatment of MSE and NMSE overlap considerably (Nevés et al, 2010). Approximately 15% to 30% of enuretic children experience daytime LUTS; however, these reported numbers are likely grossly underestimated (Järvelin et al, 1988; Gumus et al, 1999). In fact, most experts in the field would estimate the proportion of children with enuresis that are truly monosymptomatic to represent fewer than half of all bedwetting children (Franco et al, 2013).

Our initial approach to NMSE is nearly identical to our approach for children with LUTD. Obviously one begins with a thorough history and physical examination, along with the appropriate laboratory and imaging studies. In terms of NMSE therapy, we also begin by identification and treatment of constipation. As we have previously seen, effective treatment of bowel problems can lead to the spontaneous remission of daytime incontinence (Loening-Baucke, 1997). We also will treat the underlying LUTD symptoms first, because effective treatment of OAB (or dysfunctional voiding) can lead to cessation of the enuresis entirely (Franco et al, 2013). If comorbid behavioral disorders are present, these should be addressed by an appropriate provider. If enuresis persists after the

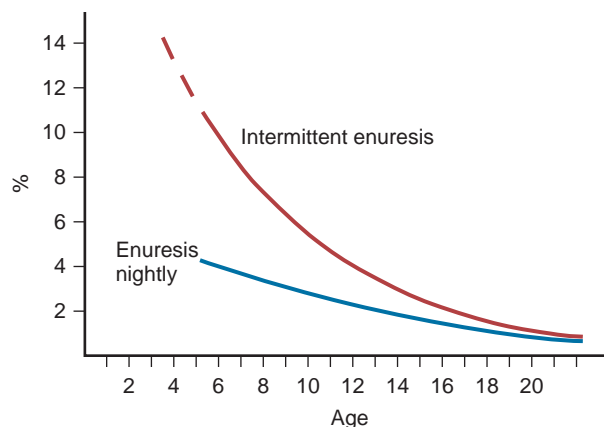


Figure 143-9. Prevalence rate of enuresis from childhood through young adulthood. (From Austin PF, Nevés T. Evaluation and management of enuresis. AUA Update Series, Vol. XXI, 2012.)

previously mentioned interventions, standard treatment for MSE can follow. The remaining section of this chapter will focus specifically on MSE and its epidemiology, cause, evaluation, and treatment strategies.

Epidemiology and Natural History

Enuresis is a common problem, with an estimated 7 million children in the United States alone with this condition. According to a recent large longitudinal study in the United Kingdom, at least 20% of children in the first grade occasionally wet the bed and 4% wet the bed two or more times per week (Butler and Heron, 2008). Prevalence varies with age, suggesting an immaturity of the LUT and nervous system (Fig. 143-9). In a study of almost 11,000 children in the United States, the prevalence of enuresis in boys at 7 and 10 years of age was 9% and 7%, respectively, and in girls at those ages, 6% and 3%, respectively (Byrd et al, 1996). It is currently generally accepted that in the West approximately 15% of children will have some degree of nighttime wetting at 5 years of age, with a spontaneous resolution rate of approximately 15% per year (Forsythe and Redmond, 1974). Consequently, at 15 years of age only 1% to 2% of teenagers will still wet the bed (Klackenberg, 1981). It has also been shown that the longer the enuresis persists, the lower the probability is that it will resolve spontaneously (Forsythe and Redmond, 1974; Bakker et al, 2002).

Enuresis seems to be more common in boys than in girls, with most reports revealing a 2:1 ratio. Although this finding has been disputed by other groups, it is well accepted that by adolescence the prevalence in both males and females reaches equipoise (Yeung et al, 2004b).

Enuresis is also known to be common in children with comorbid behavioral issues such as ADHD, oppositional defiant disorder, conduct disorder, anxiety, and depression (Baeyens et al, 2004; von Gontard et al, 2011). It is estimated that 20% to 30% of children with enuresis have comorbid clinical behavioral disorders that fulfill the criteria for the DSM-V psychiatric disorders and may subsequently have a negative impact on compliance and ultimate outcome if left untreated (von Gontard et al, 2011).

Genetics

Enuresis has a complex and multifactorial pathophysiology with a strong genetic underpinning (von Gontard et al, 1998a; Schaumburg et al, 2008). When one or both parents have a history of prolonged nighttime wetting, approximately 43% and 77%, respectively, of the offspring are affected (Bakwin, 1973). When neither parent has a history of nocturnal enuresis, only 15% of offspring are affected (Bakwin, 1973). Moreover, the concordance among

monozygotic twins is almost twice that among dizygotic twins (68% vs. 36%) (Bakwin, 1971). Linkage of enuresis to markers on chromosomes 12, 13, and 22 has been reported, with autosomal dominant inheritance and high penetrance suggested; however, a major gene locus has yet to be identified (Eiberg et al, 1995, Eiberg 1998; Arnell et al, 1997). Family and twin studies suggest locus heterogeneity and poor phenotype-genotype correlation (von Gontard et al, 2011b). The identification of these genes certainly lifts the burden of guilt from children who have enuresis and helps to dispel the theory that enuresis is behavioral in origin and completely under their control.

Pathophysiology

It is generally accepted that enuresis stems from a maturational delay in the ultimate development of bladder control (Järvelin, 1989; Light, 1998). This contention is rooted in the fact that most children eventually attain nocturnal dryness regardless of what intervention is used and even if enuresis is left untreated. The hypothesis that there is a difference in the CNS maturation in children with primary enuresis compared with controls is supported by neurophysiologic data (Isacan et al, 2002). Many children who have enuresis are noted to have progressive maturation of bladder stability in conjunction with electroencephalography (EEG) findings that suggest increased CNS recognition of bladder fullness and the ultimate ability to suppress the onset of bladder contraction (Watanabe and Azuma, 1989). This would further lend credence to the premise that delayed maturation of the bladder control plays a role in MSE.

Put very simply, the three organ systems implicated in the pathogenesis of enuresis include the bladder (i.e., a reduced nocturnal bladder capacity) (Yeung et al, 2004a), the kidney (i.e., nocturnal polyuria) (Nørgaard et al, 1989a; Vande Walle et al, 2007), and the brain (i.e., a disorder affecting arousal from sleep) (Watanabe and Azuma, 1989; Isacan et al, 2002). Enuresis is logically thought to result from a disruption or maturational lag in one or more of these critical domains (Fig. 143-10).

Bladder Overactivity and Reduced Nocturnal Bladder Capacity

There seems to be a subset of children with primary MSE who have nocturnal bladder overactivity regardless of amount of urine production (Yeung et al, 1999). Yeung and associates found that nearly half of treatment failures with standard therapy (i.e., desmopressin or moisture alarm) had normal daytime bladder function but marked detrusor overactivity during sleep that resulted in enuresis. Almost none of these children had nocturnal polyuria.

When urodynamic studies are performed during sleep, the only difference between children with and without MSE is the increased rate of bladder contractions that occur in association with the enuretic episode (Nørgaard et al, 1989b). In addition, urodynamic

studies during sleep demonstrate a relationship between nocturnal enuresis and pelvic floor activity. When pelvic floor activity increased in association with detrusor contractions, wetting was usually avoided, and patients often would awaken subsequently to void. In contrast, when pelvic floor activity did not increase, the detrusor contraction usually was associated with a wetting episode (Nørgaard et al, 1989b).

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Nocturnal Polyuria

Increased nighttime urine output appears to play an important role in nocturnal enuresis (Nevéus et al, 2010). In children and adolescents without enuresis, the diurnal pattern of urine production results in a relative reduction in nocturnal diuresis to approximately 50% of daytime levels (Rittig et al, 1995, 2010). The prevailing mechanism for how this occurs is thought to result from a nocturnal circadian peak of antidiuretic hormone (ADH) release from the posterior pituitary gland that regulates free water excretion. Other purported mechanisms for increased nocturnal urine production may include increased fluid intake before bedtime (Robson, 2001), a blunted response to ADH, increased evening dietary solute load with high nocturnal urine osmolality (Dehoorne et al, 2006), abnormal renal sodium handling (related to release of angiotensin II, aldosterone, and natriuretic peptide), abnormal circadian rhythm of glomerular filtration rate (De Guchteneere et al, 2007), abnormal sodium and calcium excretion (Raes et al, 2006), and obstructive sleep apnea/hypoventilation (Su et al, 2011).

Regardless of the mechanism, urine production that normally decreases at night secondary to these circadian systems fails to do so and will subsequently result in nocturnal polyuria, which can exceed the functional capacity of the bladder and result in an enuretic episode. Proof of this concept was demonstrated by Rasmussen and colleagues (1996), who were able to actually induce enuresis in normal healthy children by increasing nocturnal urine output. Despite this seemingly simple causal relationship, however, it is clear that nocturnal polyuria and ADH responsiveness are highly complex phenomena, because not all children with enuresis have nocturnal polyuria and, in those who do, nocturnal ADH may be normal (Steffens et al, 1993). In fact, it has been observed that the urine osmolality of children with and without MSE is similar and that early morning osmolality tends to increase with age (Kawauchi et al, 1996). This suggests that the ADH secretion response may be a maturational one and lend further support to the maturation hypothesis.

Arousal and Sleep

Regardless of whether the child has detrusor overactivity and/or nocturnal polyuria, neither observation explains why a child with enuresis is unable to awaken from sleep to void before a wetting episode. Given that both bladder distention and detrusor contractions are robust arousal stimuli (Koyama et al, 1998), it is curious that an enuretic child will not wake up during the night to the sensation of a full or contracting bladder. Parents invariably describe their children with enuresis as excessively deep sleepers (Wille, 1994; Nevéus et al, 1999a). This situation is often experienced by family members of patients exposed to alarm therapy as parents awaken from sleep while their enuretic child will sleep through the alarm. Nevéus and colleagues (1999a) obtained questionnaire data from 1413 schoolchildren between the ages of 6 and 10 years and noted that enuresis was associated with subjectively high threshold arousal and significant confusion on awakening from sleep. Wolfish and coworkers (1997) performed a laboratory study of 33 boys aged 7 to 12 years (15 with enuresis and 18 age-matched controls) and found that attempts at arousal were more often successful in control subjects than in boys with enuresis (40% vs. 9%, respectively).

A subjectively deep sleep, however, is not the same as an objectively deep sleep, as measured by EEG. Freitag and associates (2006) studied brainstem evoked potentials in 37 children with MSE and compared these children to 40 age-matched controls. They found

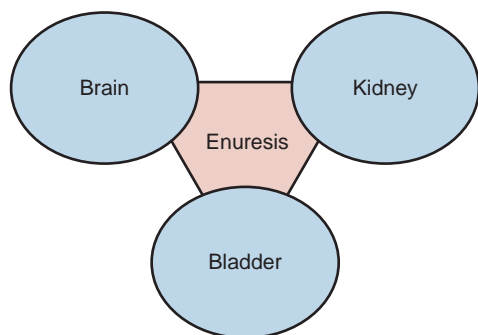


Figure 143-10. Organ system involvement in pathogenesis of enuresis.

Children with enuresis (even those without daytime symptoms) have been noted to have a smaller bladder capacity than age-matched children controls (Starfield, 1967). The reduced bladder capacity appears to be functional rather than anatomic. This was illustrated by a study in which bladder capacity was measured in the awake state as well as under general anesthesia in children with enuresis and compared with functional bladder capacity among controls (Troup et al, 1971). Compared with control children, the average volume of urine voided by enuretic children in the awake state was reduced. However, when volumes were measured during general anesthesia, enuretic children had similar mean bladder volumes to awake controls. In a somewhat contradictory study, Kawauchi and colleagues (2003) found that the maximal endurable bladder capacity during the daytime was similar between children with enuresis and controls. However, among children with enuresis, the maximal voided volume during the night (measured using a diaper and enuresis alarm) was significantly smaller than the maximal daytime bladder capacity. They concluded that inability to hold urine during sleep may be an important factor in MSE. A number of trials have noted functional bladder capacity to be a strong predictor of response to desmopressin in MSE (Rushton et al, 1996; Eller et al, 1998). As a result, a refractory response to desmopressin may suggest either unrecognized nocturnal OAB or that the decreased nocturnal urine production elicited by desmopressin continues to overwhelm a functionally undersized bladder. Whether this situation is a result of reduced nocturnal functional bladder capacity or nocturnal detrusor overactivity, however, may not be critical because the treatment strategy employed would largely be the same (i.e., anticholinergic medications).

that interpeak latencies of the brainstem evoked potentials were increased in children with MSE, suggesting a maturational defect of the brainstem to account for this finding. Other sleep studies, however, show that sleep patterns among children with and without enuresis are similar (Ritvo et al, 1969; Bader et al, 2002). These studies indicate that enuretic episodes may occur at random throughout the night, but primarily during nonrapid eye movement (non-REM) sleep (Nevéus et al, 1999b) and when the bladder is at a volume equivalent to the maximal daytime functional capacity (Mikkelsen et al, 1980; Nørgaard et al, 1989b). A study of 35 children with therapy-resistant MSE in Hong Kong demonstrated that although appearing to be heavy sleepers, these children had, in fact, more overall light sleep (stage I/II non-REM) with sleep fragmentation, rather than deep sleep (stage III/IV non-REM). The cerebral cortex received afferent input of sleep OAB with frequent cortical arousals that failed to wake the children, which was presumed to be a paradoxical elevation in the conscious awakening threshold. OAB-associated cortical arousals may cause a shift from deep to light sleep but not to complete awakening, perhaps because of long-term overstimulation of the sleep arousal center by signals from the bladder. In summary, these studies suggest that children who wet the bed sleep normally (i.e., the distribution and proportion of the various stages of sleep are within normal limits) but are unable to awaken in response to nocturnal detrusor contractions or bladder fullness.

Evaluation

The basic evaluation of the child with MSE includes **history, physical examination, and urinalysis. The history, including a voiding diary, is the mainstay of the evaluation** (Robson, 2009; Nevéus et al, 2010). As previously discussed, the voiding diary is an objective means of documenting the voiding pattern (see section on *Bladder and Bowel Diaries*). This is especially useful when the history is unclear. A voiding diary kept by the parents should help assess the times at which a child voids; the relationship between voiding and common events such as meals, breaks at school, and play activities; the occurrence of urgency or incontinence; and voided volume. **The principal objective of the evaluation is to rule out BBD or enuresis as a manifestation of an underlying medical disease (e.g., posterior urethral valves, spinal dysraphism, diabetes mellitus) and to identify that the enuresis is truly monosymptomatic.** If BBD is present, it should be treated as described previously before initiating therapy for MSE (Franco et al, 2013).

Once MSE is confirmed, it is often helpful to characterize the enuresis further, such as frequency and volume. Distinguishing between primary and secondary MSE should be attempted, mainly for prognostic purposes because treatment is generally the same. One important point to ask about is the presence of nocturia; this would suggest that the child is not extremely difficult to arouse from sleep. The social history is also particularly germane because somatic and psychological comorbid conditions are more common in children who were previously dry than in those with primary MSE (Robson et al, 2005). A family history of enuresis is often helpful in establishing a genetic pattern. Interventions the family has already tried also should be determined.

The physical examination should be focused and is similar in scope to that described in the prior section on LUTD. Briefly, examination should include palpation of the abdomen to screen for constipation, examination of the lower spine for cutaneous stigmata of spinal dysraphism, examination of the genitalia to screen for meatal stenosis, introital erythema or damp/wet underwear, assessment of the sacral reflex arc, and evaluation of the motor strength, tone, reflexes, and sensation in the legs for evidence of a neurogenic bladder.

In terms of laboratory testing, a simple urinalysis should be performed to detect any possible glucosuria, proteinuria, hematuria, pyuria, and/or bacteriuria. Neither radiologic imaging nor urodynamics has a role in the evaluation of MSE. If based on history and physical examination the patient is suspected to have NMSE, we would recommend evaluation following the previously

described protocol for children with LUTD (i.e., pelvic ultrasound and uroflowmetry).

Treatment

Conventional therapies for enuresis include behavioral modification, the enuresis “moisture” alarm, and pharmacologic therapy (e.g., desmopressin, anticholinergics, imipramine). The evidence for the efficacy of much of the care that we provide to children with enuresis is weak (Nevéus et al, 2010). Given the self-limiting nature of enuresis, one treatment option is to observe and allow the natural history to follow its predetermined course. However, enuresis that occurs as infrequently as once per month is associated with reduced self-esteem and treatment has been reported to improve self-worth, regardless of the type or the success of therapy (Hägglöf et al, 1998; Longstaffe et al, 2000).

The decision about when to start treatment generally should be guided by the degree of concern and motivation on the part of the child rather than the parents. For the child, nocturnal enuresis usually becomes significant when it interferes with his or her ability to socialize with peers (e.g., sleepovers, summer camps) (Jalkut et al, 2001). **It is important to determine whether the child is mature enough to assume responsibility for treatment.** Treatment probably should be delayed if it seems that the parents are more interested in treatment than the child and the child is unwilling or unable to assume some responsibility for the treatment program. The child must be highly motivated to participate in a treatment program that may take months to achieve successful results. Although general advice should be given to all bedwetting children, active treatment should usually not be started before 6 years of age (Nevéus et al, 2010). However, age should not be the only criterion for initiation of active treatment.

Behavioral Therapy

Data from randomized trials on the efficacy of behavioral therapy are lacking (Pennesi et al, 2004; Caldwell et al, 2013), but clinical experience (i.e., level 4 evidence) suggests that this approach is beneficial (Nevéus et al, 2010). Likewise, although the influence of the clinician's behavior has not been formally studied, clinical experience suggests that the ability to establish a rapport with the child and to engender and sustain motivation is important for successful behavioral therapy. **The fundamental goal of behavioral therapy is much like the treatment of daytime urinary incontinence and centers around the practice of good bladder and bowel habits.**

Children should attempt to void regularly during the day and just before going to bed for a total of six to seven times daily. High-sugar and caffeine-based drinks should be avoided, particularly in the evening hours. Daily fluid intake should be concentrated in the morning and early afternoon, and both fluid and solute intake should be minimized during the evening. Isolated nighttime fluid restriction, without compensatory increase in daytime fluid consumption, may prevent the child from meeting his or her daily fluid requirement and is usually unsuccessful.

In practice, compliance improves when parents and children understand normal bladder function and the pathogenesis of enuresis. **Children should be reassured that enuresis is not their fault, and children should not be punished for bedwetting, because this practice is often counterproductive** (van Londen et al, 1993). An individualized program with a series of realistic goals between appointments and monthly follow-up to sustain motivation improves the outcome (Glazener and Evans, 2004). A personalized calendar for recording daytime incontinence and enuresis episodes and the frequency and timing of bowel movements aids the family and child to follow their progress.

When initiating active treatment for primary MSE, there is level 1 evidence to support the use of the enuresis alarm (Glazener et al, 2005), **desmopressin** (Glazener and Evans, 2009), **anticholinergics** (Austin et al, 2008), and **tricyclic antidepressants (e.g., imipramine)** (Glazener and Evans, 2000), either alone or in combination. Generally, in addition to behavioral therapy, the two

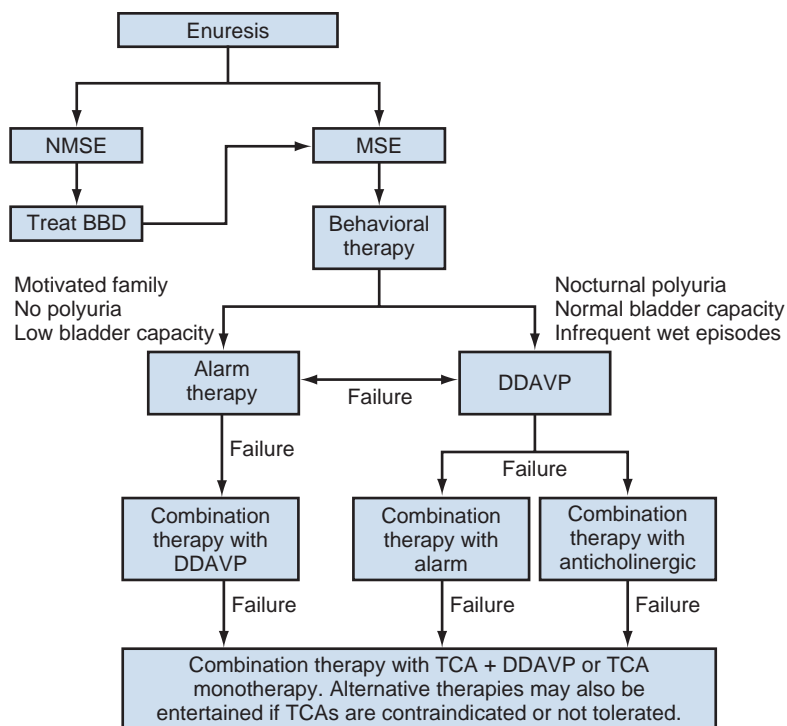


Figure 143-11. Algorithm of the evaluation and treatment of a pediatric patient with enuresis. BBD, bowel-bladder dysfunction; DDAVP, 1-deamino-8-D-arginine vasopressin (desmopressin); MSE, monosymptomatic enuresis; NMSE, nonmonosymptomatic enuresis; TCA, tricyclic antidepressant.

contemporary first-line therapies for MSE include the enuresis alarm and desmopressin. They are both valid treatment options, but patient, caregiver, and disease-related parameters exist that may aid in offering prognostic information in terms of which therapeutic modality should be first entertained (Fig. 143-11). The enuresis alarm seems best fit for motivated families and for children without polyuria but with low voided volume (Nevéus et al, 2010). Desmopressin seems best suited for children with nocturnal polyuria and normal bladder reservoir function (Hunsballe et al, 1998), those with infrequent wet episodes, and for families in whom alarm treatment has failed or who have refused alarm treatment (Nevéus et al, 2010). Children in whom one first-line treatment has failed should be offered the other, and for those in whom both have failed, second- and third-line treatments can be tried, either alone or in combination (e.g., desmopressin plus oxybutynin).

Enuresis Alarm

Alarm training has been shown to be the most effective long-term therapeutic modality in the treatment of MSE (Glazener et al, 2005). Alarms have been used since the 1930s and represent classic pavlovian conditioning techniques, but exactly how the alarm works remains somewhat of a mystery because, strictly speaking, classical conditioning mechanisms should not be functional during sleep. Proposed mechanisms include suppression of bladder emptying during sleep, increasing nocturnal bladder volume (Hansen and Jørgensen, 1997), and waking to void by signaling when they urinate. Interestingly, most children who become dry with the use of the enuresis alarm actually sleep through the night and do not necessarily wake to void. The response is more gradual and sustained than for desmopressin, with approximately two thirds of children becoming dry during active treatment and nearly half remaining dry after treatment completion (Glazener et al, 2005). Enuresis alarms are activated when a sensor, placed in the undergarments or on a bed pad, detects moisture, with both types demon-

strated to be equally effective (Butler and Robinson, 2002). The arousal device is usually an auditory alarm and/or a vibrating belt.

The family should be instructed that the child is in charge of the alarm. After the alarm goes off, only the child should turn off the alarm, get up, and finish voiding in the toilet. We often remind parents that at the initiation of therapy, the child may fail to awaken and that parents should wake the child when the alarm sounds. The child being fully awake and cognizant of what is happening is critical to the success of alarm therapy. The child should then return to the bedroom, change the bedding and underwear, replace the sensor, and reset the alarm before returning to sleep. A diary should be kept of wet and dry nights, with positive reinforcement given for dry nights as well as successful completion of the sequence of events. Approximately 30% of patients discontinue enuresis alarms for various reasons, including skin irritation, disturbance of other family members, and/or failure to wake the child (Schmitt, 1997). Adverse effects of alarms include alarm failure, false alarms, disruption of the lives of other family members, and lack of adherence because of difficulty using the alarm (Glazener et al, 2005).

Alarm treatment should be continued until the child has had a minimum of 14 consecutive dry nights (Nevéus et al, 2010). Children who do not continue to improve after 6 weeks of alarm training are unlikely to become completely dry with this technique (Taylor and Turner, 1975), and alternative interventions may be warranted. Therapy with the alarm can be reinitiated for relapse (more than two wet nights in 2 weeks). Children who relapse after discontinuation of the alarm usually can achieve a rapid secondary response because of preconditioning as a result of the first treatment program (Tuncel et al, 2008). During this refractory treatment period, the chance of long-term cure can be increased by a technique called *overlearning* (Morgan, 1978). In overlearning, additional fluids are given at bedtime while alarm training is continued after dryness has been achieved (Young and Morgan, 1972). In alarm training without overlearning, the child trains to inhibit urination without necessarily learning to wake to void. A systematic review indicated that overlearning trains the child to wake in

response to the sense of a full bladder and reduces relapse when alarm treatment is stopped (Glazener et al, 2005).

Pharmacotherapy

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) is a synthetic analogue of ADH released by the posterior pituitary gland that reduces urine production by increasing water reabsorption by the collecting tubules. DDAVP has been used to treat enuresis for the past 40 years. Desmopressin is fairly easy to administer and its clinical effects appear immediately, with a serum half-life of approximately 2 to 3 hours when taken in oral form (the duration of pharmacodynamic action approximates the average duration of sleep for a child in the age range for elementary school). It is available in the United States in oral (crushable) tablets and in sublingual and intranasal spray formulations. The main safety issue is the risk for water intoxication with resultant hyponatremic seizures should the drug be taken with excessive fluids. This risk seems to be somewhat higher with the intranasal form, which has a prolonged half-life, and thus use of the spray is discouraged (Robson et al, 2007). Treatment should be interrupted during episodes of fluid and/or electrolyte imbalance (e.g., fevers, vomiting or diarrhea, vigorous exercise, or other conditions associated with increased water consumption).

The usual starting dose is 0.2 mg orally 1 hour before bedtime, and the drug can be titrated up incrementally by 0.2 mg to a maximum dose of 0.6 mg at bedtime. Children are instructed to void directly before going to bed. Fluid intake is reduced to a maximum of one 8-oz glass at the time of ingestion, with absolutely no more fluids until morning, decreasing the risk for significant hyponatremia to virtually zero (Glazener and Evans, 2009).

Desmopressin is most efficient in children with nocturnal polyuria (defined by the ICCS as nocturnal urine production >130% of expected bladder capacity for age) and normal bladder reservoir function (maximum voided volume >70% of expected bladder capacity for age) (Rushton et al, 1996; Hunsballe et al, 1998; Austin et al, 2014). There is a wide range of efficacy among studies, most likely because of heterogeneous patient populations (MSE vs. NMSE), differences in concomitant behavioral therapy recommendations, and differences in the dosage or formulation of DDAVP, without taking into account nocturnal urine volume. Overall, approximately 30% of patients achieve total dryness and another 40% exhibit a significant decrease in nighttime wetting (Nevéus et al, 2010). However, the relapse rate after discontinuation is high (60% to 70%) (Wille, 1986). In a systematic review of 47 randomized trials (3448 children), researchers noted that compared with placebo, children treated with desmopressin were more likely to become dry and had a reduction in bedwetting by 1.34 nights per week (Glazener and Evans, 2009). In contrast to the enuresis alarm, however, treatment effects were not sustained after discontinuation of therapy, with a relapse rate of 65% versus 46% with DDAVP versus the alarm, respectively (Glazener and Evans, 2009).

The response to desmopressin should be assessed within 2 weeks (Schmitt, 1997). Treatment should be continued if there is a positive response (e.g., smaller wet patches, fewer wetting episodes). If enuresis improves or remits with desmopressin, the family and child can determine whether to use it every night or just for special occasions (e.g., sleepovers, summer camp). When DDAVP is administered daily, we generally give patients regular scheduled drug holidays of approximately 1 week every 3 to 6 months to assess whether the medication is still needed.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have been demonstrated to decrease the amount of time spent in rapid eye movement (REM) sleep, stimulate ADH secretion, and relax the detrusor muscle via weak anticholinergic properties. Its antienuretic effect has been theorized

to be less likely because of its action at the kidney or bladder level and more likely a result of noradrenergic stimulation at the brainstem, specifically the locus coeruleus (Gepertz and Nevéus, 2004). Given the efficacy and safety of enuresis alarms and DDAVP, TCAs (e.g., imipramine, amitriptyline, and desipramine) are considered a third-line treatment for therapy-resistant MSE (Nevéus et al, 2010).

Level 1 evidence demonstrates that compared to placebo, TCAs are more effective at reducing the number of wet nights and at achieving 14 consecutive dry nights (i.e., cure) but essentially become ineffective once treatment is discontinued.

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Although other TCAs are effective, imipramine is used most often in the treatment of enuresis. Imipramine is available in 10-, 25-, and 50-mg tablets. The initial dose is 10 to 25 mg 1 hour before bedtime; it may be increased by 25 mg if there is no response after 1 week (Schmitt, 1997). On average, the bedtime dose is 25 mg for children 5 to 8 years of age and 50 mg for older children. The dose should not exceed 50 mg in children between 6 and 12 years of age and 75 mg in children older than 12 years of age (Glazener and Evans, 2000).

The response to imipramine should be assessed after 1 month. If there is no improvement after 3 months, it should be discontinued as a gradual taper (as is done with other TCAs). As is the case with other pharmacotherapy for enuresis, we give patients a drug holiday every 3 to 6 months, gradually tapering the dose over a 2-week period (Gepertz and Nevéus, 2004).

Adverse effects of TCA therapy are relatively uncommon. Approximately 5% of children treated with TCAs develop neurologic symptoms, including nervousness, personality change, and disordered sleep. TCAs (as with other antidepressants) are required by the FDA to carry a black box warning regarding the possibility of increased suicidality, particularly in individuals with preexisting depressive symptoms. The most serious adverse effects of TCAs involve the cardiovascular system: cardiac conduction disturbances and myocardial depression, particularly in cases of overdose (Swanson et al, 1997). Before initiation of therapy with a TCA, a thorough cardiac history (e.g., palpitations, syncope) and family cardiac history (e.g., arrhythmias, sudden cardiac death) should be obtained with a baseline electrocardiogram to rule out a prolonged QT interval if history or physical examination raises suspicion.

Anticholinergics

Monotherapy with anticholinergic drugs, such as oxybutynin or tolterodine, has been demonstrated not to be effective as a first line of treatment for MSE (Lovering et al, 1988; Persson-Jünemann et al, 1993). Although evidence of efficacy from randomized trials is lacking, uncontrolled studies do show improvement in some children with NMSE, presumably because many of these children have a reduced functional bladder capacity (Caione et al, 1997; Nevéus, 2001). There is also some evidence that nocturnal detrusor overactivity (especially without nocturnal polyuria) plays a role in the pathogenesis of enuresis and therefore makes anticholinergics an attractive pharmacotherapeutic option (Nevéus, 2001).

Where anticholinergics clearly do have a role is combination therapy in the treatment of children who are refractory to DDAVP monotherapy. In the first randomized, placebo controlled study of combination therapy with anticholinergics, Austin and colleagues (2008) studied 34 children with primary MSE who failed maximal-dose DDAVP monotherapy and assigned them, in a double-blind manner, to receive either extended-release tolterodine or placebo while all children continued to take DDAVP. Patients were reassessed after 1 month of therapy with a 1-week nocturnal record. They found a significant reduction in the mean number of wet nights in the combination therapy group compared to the placebo group. With a generalized estimating equation approach, there was a significant 66% reduction in the risk for a wet episode compared with the placebo group. Recently, Montaldo and associates (2012) reported their results in 206 children with MSE refractory to DDAVP monotherapy who were randomized to 5 mg of oxybutynin or placebo and followed for 1 month. As predictive factors, bladder

In a recent systematic review, treatment with TCAs was associated with a reduction of approximately one wet night per week compared to placebo ([Glazener and Evans, 2000](#)). Approximately 20% of children became dry during therapy versus 5% with placebo. The rate of relapse was 96% after discontinuation of therapy. In an observational study of children who were refractory to first-line therapy, researchers found that approximately one third of children became dry on monotherapy, one third became dry after adding DDAVP, and the remaining third were nonresponders ([Gepertz and Nevéus, 2004](#)).

volume and wall thickness index, nocturnal polyuria, and voiding latency were considered. Corroborating the original study by Austin and associates, the oxybutynin group showed a higher rate of full and partial responses than the placebo group. The responders to combined oxybutynin and desmopressin had a significantly lower bladder volume and wall thickness index than nonresponders.

Combination Therapy

The efficacy of the enuresis alarm plus desmopressin combination has been investigated in a number of studies (Sukhai et al, 1989; Bradbury, 1997; Leebeek-Groenewegen et al, 2001; Fai-Ngo et al, 2005).



Please see the Expert Consult website for further details.

A reduction in the number of wet nights is consistently observed when using combination therapy of desmopressin and the moisture alarm compared to monotherapy. Enuresis relapse, however, is noted in some patients with long-term follow-up.

Alternative Therapies

Other drugs, including indomethacin, ephedrine, atropine, furosemide, and diclofenac, have been tried in the treatment of enuresis. A recent systematic review of randomized trials of drugs other than TCAs and DDAVP found that although indomethacin, diclofenac, and diazepam were better than placebo in reducing the number of wet nights, none of the drugs was better than desmopressin (Deshpande et al, 2012). A second recent review of complementary approaches such as hypnosis, psychotherapy, and acupuncture found limited evidence from small trials with methodologic limitations to support the use of such modalities for the treatment of enuresis (Huang et al, 2011).

KEY POINTS: ENURESIS

- The majority of children who present with enuresis have the nonmonosymptomatic form.
- The spontaneous resolution rate of enuresis is approximately 15% annually, such that only approximately 1% of teenagers will continue to be afflicted.
- Enuresis stems from a maturational delay in the ultimate development of bladder control, with three organ systems implicated in its pathogenesis: the bladder, the kidney, and the brain.
- The basic evaluation of the child with MSE includes history (including a voiding diary), physical examination, and urinalysis. The principal objective of the evaluation is to rule out BBD or enuresis as a manifestation of an underlying medical disease (e.g., posterior urethral valves, spinal dysraphism, diabetes mellitus) and to identify that the enuresis is truly monosymptomatic.
- Conventional therapies for enuresis include behavioral modification, the enuresis moisture alarm, and pharmacologic therapy (e.g., desmopressin, anticholinergics, imipramine).

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The complete reference list is available online at www.expertconsult.com.



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Sukhai and colleagues (1989) reported a crossover trial of 28 children with primary MSE who were blindly allocated at random to a combination of enuresis alarm plus 20 µg intranasal DDAVP or alarm plus placebo for 2 weeks. Patients received the other therapy after a 2-week treatment-free period. The combined treatment of desmopressin plus enuresis alarm resulted in significantly more dry nights per week during the 2 weeks of observation than placebo plus the alarm. Although there was a significant difference between groups, the treatment period of 2 weeks was most likely too short for alarm therapy to contribute significantly to the outcome variable.

Bradbury compared the efficacy of enuresis alarm monotherapy to alarm treatment in combination with 40 µg DDAVP nasal spray (Bradbury, 1997). At the end of the treatment period, children receiving combination therapy had more dry nights per week (mean: 6.1) than children using an alarm alone (mean: 4.8). In addition, more children achieved an initial success (4 weeks of dryness) after combination treatment (27 children [75%]) compared with alarm monotherapy (16 children [46%]). Interestingly, this improvement was most pronounced in children with severe wetting (>5 nights per week), family problems, or behavioral problems.

In a placebo-controlled study containing 93 patients with MSE, Leebeek-Groenewegen and colleagues (2001) compared 9 weeks of desmopressin plus alarm therapy with alarm monotherapy. They showed a significant decrease in the number of wet nights per week with combination therapy. After 6 months of follow-up, however, they reported that there was no significant difference between the two treatment groups regarding the efficacy and number of children who relapsed.

In a recent multicenter randomized controlled trial, Fai-Ngo et al (2005) compared the efficacy of the enuresis alarm, oral DDAVP, and combined treatment in children with primary MSE. They assigned 105 children equally among groups to receive treatment for 12 weeks, and patients were then followed for 12 weeks after treatment. They found that the mean number of wet nights per week was significantly lower in the combination group than in the other groups at the conclusion of therapy. Desmopressin produced an immediate effect but relapses were most common in the DDAVP monotherapy and combination therapy groups (60% and 40%, respectively). Alarms took several weeks to produce a benefit, but this was sustained on follow-up (20% relapse rate).

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Clinical Significance

Epidemiology

Self-Esteem and Quality-of-Life Issues

Comorbidities

Terminology

Daytime Urinary Incontinence and Bladder Dysfunction

Enuresis

CLINICAL SIGNIFICANCE

Functional disorders of the lower urinary tract (LUT) encompass abnormalities in the filling and/or emptying phases of the bladder and include a broad spectrum of clinical entities that vary in their cause and prognosis. These are functional disorders in that children do not have a readily identifiable neurologic or anatomic abnormality but rather the disorder is thought to originate from behavioral factors that affect toilet training and inhibit the development of normal urinary control. *LUT dysfunction (LUTD)*, *bladder and bowel dysfunction*, and the antiquated *dysfunctional elimination syndrome*, are terms that describe the common array of symptoms that include overactive bladder (OAB), voiding postponement, underactive bladder, dysfunctional voiding, primary bladder neck dysfunction, giggle incontinence, vaginal reflux, pollakiuria, and enuresis.

Evidence-based medicine lends support to the hypothesis that LUTD can predispose children to recurrent urinary tract infections (UTIs) and vesicoureteral reflux (VUR) with a potential for significant impact on subsequent LUT and renal function. Beyond these largely urologic sequelae, however, the impact of symptoms such as daytime incontinence are profound and can affect the behavioral, emotional, and social aspects of a child's daily life. Timely diagnosis and a coherent therapeutic approach are therefore paramount in the successful treatment of these physically and emotionally distressing disorders.

EPIDEMIOLOGY

LUTD is commonly encountered in daily practice, accounting for up to 40% of pediatric urology clinic visits annually (Feldman and Bauer, 2006). Cross-sectional studies confirm that functional LUT problems are prevalent, with 22% of school-age children reporting at least one LUT symptom. The most common urinary symptoms cited included holding maneuvers (19.1%) and urgency (13.7%) (Vaz et al, 2012).

United States

Daytime incontinence is estimated to affect up to 7 million children in the United States 6 years of age or older (Franco, 2012). OAB is the most commonly encountered LUT disorder in children and appears to have a peak incidence between 5 and 7 years of age, although its true prevalence is difficult to determine (Franco, 2007). To date, studies have focused primarily on daytime versus nighttime incontinence and have not attempted to differentiate the type of daytime incontinence. Chandra (1998) reported the responses to

583 questionnaires completed by families of children between 5 and 9 years of age and found that urinary urgency and pelvic tightening maneuvers to postpone voiding and prevent incontinence were the voiding issues most frequently reported. Urge incontinence was present in 7% of girls and 3% of boys (Chandra, 1998).

International

A study by Hellström and colleagues of 7-year-old Swedish children entering school revealed that 21% of girls and 18% of boys had moderate-to-severe urinary urgency. Daytime urinary incontinence occurred once weekly in 3.1% of girls and 2.1% of boys. A Japanese study of 6917 school-age children demonstrated an overall prevalence rate of 17.8% for OAB (Kajiwarara et al, 2006). Interestingly, this epidemiologic survey found a nearly equal prevalence of OAB between boys and girls of 19.1% and 16.6%, respectively. An Australian study addressed the frequency of voiding disorders in school-aged children (Sureshkumar et al, 2009). This study of 2856 students reported that 19.2% of children had experienced at least one episode of daytime incontinence in the previous 6 months, with 16.5% having experienced more than 1 wetting episode and only 0.7% experiencing wetting on a daily basis. Independent risk factors for daytime incontinence included nocturnal enuresis, female sex, history of UTI, and encopresis (Sureshkumar et al, 2009).

A large cross-sectional study of over 19,000 children between the ages of 5 and 13 was performed in the Republic of Korea and evaluated the prevalence of OAB by parental questionnaire (Chung et al, 2009). The overall prevalence of OAB was 16.6% and decreased with age from 23% to 12% by age 13 years (Chung et al, 2009). Compared with other children, those with OAB had a greater prevalence of nocturnal enuresis, constipation, fecal incontinence, UTI, delayed bladder control, and poor toilet facilities.

Gender and Age-Related Demographics

Robson (1997) and associates found that daytime incontinence varies with both age and gender. This group reported that the prevalence of daytime wetting at least once every 2 weeks was 10% in 5- to 6-year-old children, 5% from 6 to 12 years of age, and 4% from 12 to 18 years of age. In a population survey of 1192 individuals aged 1.5 to 27 years, daytime incontinence occurred in 13% of children aged 4 years, 7% of children aged 5 years, 10% of children aged 6 years, and 5% of children aged 7 years (Bloom et al, 1993). Studies on the prevalence of voiding disorders in school-age children indicate that daytime urinary incontinence is 2 to 5 times more common in girls (Sureshkumar et al, 2009). Hellström

and colleagues (1990) found that daytime incontinence was more common in girls (6.7%) than in boys (3.8%) and that most children with incontinence had other LUT symptoms (LUTS).

SELF-ESTEEM AND QUALITY-OF-LIFE ISSUES

Multiple epidemiologic and cross-sectional studies demonstrate that between 5% and 20% of children suffer with daytime incontinence (Hellström et al, 1990; Kajiwarra et al, 2004; Joinson et al, 2006; Sureshkumar et al, 2009). The reported incidence of incontinence ranges from 1.2% daily to 3.6% at least twice a week (Hellström et al, 1990). Remarkably, the majority of parents surveyed did not seek medical attention for their child's incontinence, and teachers recognized only 3% of the children in their classroom who actually suffered from daytime wetting (Sureshkumar et al, 2009). These statistics would make it appear that LUTD and its sequelae are of nominal consequence in the daily lives of young children. Various studies examining the impact of symptoms like urinary incontinence on self-esteem and quality of life in children would suggest otherwise.

Given the emerging recognition of patient perspectives in health care over the last decade, quality-of-life assessment is an important part of incontinence research. Measurement of quality of life in children with urinary incontinence gives a child-centric estimate of the impact that incontinence makes in daily life. In a survey study of 1185 children, both in the United States and Australia, school-age children were asked to grade the severity of 20 different stressful life events (Ollendick et al, 1989). Of the different situations examined, "Wetting pants in class" was rated as the third most stressful, which underscores the importance of urinary control in school-age children and their peers.

A recent article by Thibodeau and associates (2013) prospectively studied 40 children (10 males and 30 females), between 5 and 11 years of age with non-neurogenic daytime wetting. The Dysfunctional Voiding Symptom Score (DVSS), originally put forth by Farhat and colleagues (2000) was used to quantify the severity of LUTS and was completed by both parents and children. Parents and their children also completed the Pediatric Urinary Incontinence Quality of Life Score tool (PIN-Q), originally developed by Bower and coworkers (2006b), which measures the emotional impact that urinary incontinence has on a child. There was no statistically significant difference between parent and child scores for symptoms (DVSS) and quality of life (PIN-Q), indicating that parents were very aware of the child's symptoms and the impact they had. DVSS and PIN-Q responses were positively correlated (i.e., as DVSS scores increased the PIN-Q showed a corresponding rise).

COMORBIDITIES

Urinary Tract Infections

A clear and consistent relationship has been repeatedly demonstrated in multiple studies between LUTD and UTIs. What is unclear, however, is whether a causal relationship exists. This most likely is related to study design and interpretation. Bauer (2002) suggested that UTIs are not only an effect of dysfunctional voiding but also may precipitate the development of LUTD, specifically OAB.

Hellström and associates (1990) disseminated a questionnaire to analyze the micturition habits and UTI history to more than 3500 school-age children. Girls with daytime wetting, urgency, and emptying difficulties had a higher prevalence of a UTI history than those without symptoms. Hoebeke and colleagues (2001a) prospectively studied 1000 children during a 4-year study period with video-urodynamics to ascertain the cause and epidemiology of LUTD. The incidence of UTI was significantly higher in girls than in boys. In addition, boys with LUTD had no greater risk for UTI. In girls with underactive bladder there was a significantly higher incidence of UTI.

Chen and colleagues (2004) performed a multivariate analysis on 2759 children to elucidate the relationships among dysfunctional elimination, UTI, and VUR. Their data demonstrated a higher rate of LUTD in girls (43.7%) than in boys (23.8%), with 44% of children who had a history of UTIs also having concomitant LUTD. Interestingly, they observed no association of UTI or VUR individually, but rather found that LUTD was noted only when both UTI and VUR were present. This study challenges the contemporary paradigm espousing an independent association between UTI and LUTD.

In a recent retrospective review, Van Batavia and coworkers (2013) determined how many children who initially presented with LUTD had a history of UTIs. Of 623 children diagnosed with LUTD, one third had a history of UTIs, with the prevalence rate being significantly higher in girls than boys. When stratified by specific LUT conditions, girls with underactive bladder and dysfunctional voiding had the highest UTI rates. Not surprisingly, the association between UTIs and LUTD was most often noted for LUT conditions in which urinary stasis occurs.

Vesicoureteral Reflux

There is a known association between LUTD and VUR. Whether VUR is secondary to the LUT condition is controversial. Lapides and Diokono (1970) first described the association between dysfunctional voiding and VUR (Lapides and Diokono, 1970). Since that time a number of authors have expanded on the description and nature of the association. In the late 1970s, Koff and associates (1979) demonstrated that voiding against a closed sphincter can increase bladder pressure and may contribute to the development and persistence of VUR. The incomplete bladder emptying that occurs in children with LUTD can lead to urinary stasis with subsequent UTI causing inflammatory changes in the bladder wall that stimulate hypertrophy and overactivity. This is particularly true in older children who manifest with febrile UTIs after toilet-training has been completed. It has been theorized that detrusor hypertrophy can alter the closure mechanism at the ureterovesical junction, leading to reflux (Yeung et al, 1998).

One of the first studies to systematically address the relationship between LUTD and VUR was performed by Van Gool and associates (1992), who distributed a questionnaire to all children enrolled in the European arm of the International Reflux Study in Children. Extrapolating from the questionnaire results, the prevalence of dysfunctional voiding was approximately 18%. A strong association was observed between recurrent UTI and LUTD, and in those children with spontaneous resolution of their reflux, the prevalence of dysfunctional voiding was much lower.

Koff and associates (1998) reported their experience on 143 children with primary VUR who either resolved spontaneously or were surgically treated. LUTD was present in 66 (43% of the cohort), with 54 (82%) of these children having a breakthrough UTI and undergoing reimplantation compared to only 18% without LUTD. Of 70 children who had a breakthrough UTI, LUTD was present in 54 children (77%); in 73 patients who did not have a breakthrough infection, dysfunction was present in only 12 (16%) children. Additionally, if VUR resolution did occur, the time for resolution increased by 1.6 years in those with dysfunction compared to those without LUTD. Finally, unsuccessful surgical outcomes involving persistent, recurrent, and contralateral reflux occurred only in children with elimination disorders.

The association between LUTD and treatment failure after surgical correction for reflux has been borne out in a number of clinical studies. Regardless of surgical treatment modality (i.e., endoscopic vs. open reimplantation) ongoing LUTD has been shown to be associated with a higher failure rate. Capozza and colleagues (2002) treated a total of 320 children between 3 and 11 years of age with subureteral injection for grades II to IV VUR. They found untreated LUTD to be highly associated with endoscopic treatment failure at 6-month follow-up.

Targeted treatment for LUTD has been demonstrated to improve spontaneous resolution rates for VUR (Willemsen and

Nijman, 2000; Fast et al, 2013). In a recent study by Fast and coworkers (2013) patients diagnosed and treated for LUTD who had concomitant VUR at or near the time of diagnosis underwent targeted treatment for their specific dysfunction along with antibiotic prophylaxis. VUR was monitored with serial voiding cystourethrogram or video-urodynamics. After a mean of 3.1 years of treatment, VUR resolved with targeted therapy in 26 of 58 ureters. All of these patients had a history of UTIs before starting targeted intervention. Interestingly, they found that resolution rates for VUR were similar regardless of VUR grade. Resolution or significant improvement of reflux was greater in patients with dysfunctional voiding (70%) compared to those with OAB (38%) or underactive bladder (40%).

Psychological Associations

Recently, there has been an emerging awareness of the strong association that exists between neuropsychiatric comorbidities and LUTD in children. In fact, functional causes of LUTD are believed by many to originate from behavioral issues that evolve from personal stressors and/or adverse events that occurred around the time of toilet-training (Feldman and Bauer, 2006). If the LUTD is not addressed, this behavioral or learned response often will perpetuate itself. Limiting free access to a restroom or, worse, discouraging voiding in response to urgency in a child who has not developed complete cortical inhibition of voiding may alter normal coordination between bladder and sphincter (McKenna and Herndon, 2000).

Between 20% and 40% of children with daytime urinary incontinence are affected by comorbid behavioral disorders (von Gontard et al, 1998b; Joinson et al, 2006). Additionally, a number of epidemiologic studies have reported clinically significant behavioral problems in up to one third of children with enuresis (Hirasing et al, 1997; Liu et al, 2000). This is 2 to 4 times higher than children without enuresis and is comparable with rates of psychosocial problems in other pediatric chronic illness groups. Other studies have investigated the psychological problems associated with specific syndromes responsible for daytime urinary incontinence. These investigators found a higher rate of behavior problems in children with voiding postponement compared to those with urge incontinence as their major complaint (Lettgen et al, 2002; von Gontard et al, 2011a). Moreover, some have suggested that voluntary holding with postponement of voiding is acquired and may be reflective of ongoing behavioral issues (von Gontard et al, 1999).

Recently, Oliver and associates (2013) explored the prevalence of psychosocial comorbidities and their relationship to children presenting with LUTD (Oliver et al, 2013). Data were prospectively collected on patients 6 to 17 years of age. Parents completed a 21-question LUTS score based on a validated questionnaire and a psychosocial questionnaire that screened for stressful life events and psychological diagnoses. Of the 358 patients examined, 32% had a recent life stressor and 23% had a comorbid psychiatric disorder. Younger age correlated with a higher LUTS score. Children with a recent life stressor, psychiatric disorder, or the two comorbidities had a significantly higher LUTS score than children without comorbidities. This study lends support to the recommendation for screening of psychosocial comorbidities during the evaluation of pediatric LUTD.

In perhaps one of the largest epidemiologic studies to look at the association between daytime urinary incontinence and neuropsychiatric issues in children, researchers found a significantly increased rate of psychological problems among children who wet themselves compared to those who were dry (Joinson et al, 2006). Of the over 8000 children between 7.5 and 9 years of age who were studied, those with daytime wetting had significantly increased rates of attention-deficit/hyperactivity disorder (ADHD) (24.8%), conduct disorders (11.8%), separation anxiety (11.4%), and oppositional behavior (10.9%). The increased vulnerability to psychological problems in children with daytime urinary incontinence underscores the importance of parents seeking early intervention for the condition to help prevent later psychological problems. Moreover, clinicians should be cognizant of the association with

disorders such as ADHD in children with daytime wetting, because this is likely to interfere with treatment success.

Bowel Dysfunction

It has long been recognized that an intimate association exists between both hindgut and LUT function. Indeed, LUTS are seen in approximately 30% of children who present with constipation (Belman and Loening-Baucke, 1998). Previous reports have indicated a significant overlap in these conditions in the primary care setting, with nearly one quarter of children with functional fecal retention also reporting daytime urinary incontinence (Loening-Baucke, 2004). As one would expect, the prevalence of these comorbid conditions is even higher at tertiary care centers. Burgers and associates (2013a) recently reported that nearly half of patients seen at their pediatric urology clinic for LUTS also met criteria for functional constipation.

The relationship between abnormal bowel and bladder activity is termed *bowel-bladder dysfunction (BBD)* and is part of an entity originally described by Koff and colleagues (1998) as the *dysfunctional elimination syndrome*. The International Children's Continence Society discourages using the term *dysfunctional elimination syndrome* as this connotes a particular abnormality or condition (Austin et al, 2014). BBD is a more descriptive comprehensive term that does not necessarily explain pathogenesis but rather encompasses this parallel dysfunction. In any event, Koff recognized the significance of bowel dysfunction; if present, its clear identification and management were paramount if treatment of the LUT condition was to be successful. Koff and colleagues (1998) recommended that each LUT condition be treated specifically while at the same time addressing any concomitant bowel dysfunction, often before treatment of the LUT condition.

Although an exact pathophysiologic basis for BBD has not been clearly elucidated, a number of different theories have been put forth. One theory espouses that rectal distention from fecal retention puts direct pressure on the posterior bladder wall and that this constant force in turn leads to detrusor instability, which can precipitate bladder overactivity and impair efficient bladder emptying (Lucanto et al, 2000). A second theory assumes that both the urethral and anal sphincters share a common neural input. With chronic contraction of the anal sphincter from rectal stool impaction, the pelvic floor musculature similarly contracts inappropriately, leading to secondary detrusor-external urinary sphincter dyssynergia. This vicious cycle of discoordination is what is thought to induce bladder overactivity, urinary incontinence, recurrent UTIs, and VUR (O'Regan et al, 1985).

Please see the Expert Consult website for further details.



KEY POINTS: EPIDEMIOLOGY, SELF-ESTEEM AND QUALITY-OF-LIFE ISSUES AND COMORBIDITIES

- LUTD is commonly encountered in daily practice.
- Daytime incontinence varies with both age and gender in school-age children and seems to be more common in girls.
- There is a clear and consistent relationship between LUTD and UTIs, especially when urinary stasis occurs.
- There is a known association between LUTD and VUR. Continued LUTD is a risk factor for treatment failure after surgical correction for reflux. Targeted treatment for LUTD has been demonstrated to improve spontaneous resolution rates for VUR.
- Clinicians should be cognizant of the association between neuropsychiatric disorders and LUTD. Failure to adequately address these comorbidities is likely to interfere with treatment success.
- The relationship between abnormal bowel and bladder activity is termed *bowel-bladder dysfunction (BBD)*, and, if present, its clear identification and management is paramount if treatment of the LUT condition is to be successful.

In a recent study by [Burgers and colleagues \(2013a\)](#), researchers assessed the prevalence of functional defecation disorders in children referred to a tertiary pediatric urology outpatient clinic for LUTS. They analyzed the records of 113 patients between 4 and 17 years of age who presented with LUTS. Rome III criteria for functional constipation and functional nonretentive fecal incontinence were fulfilled by 47% and 11% of patients with LUTS, respectively. Not surprisingly, children with dysfunctional voiding were more likely to fulfill the criteria for functional constipation, while children with urge incontinence more often fulfilled the criteria for nonretentive fecal incontinence. This last point is intriguing in that it supports the notion that children with fecal incontinence and urge urinary incontinence often will not respond to a standard bowel program, which could potentially exacerbate the situation. Perhaps these children would be better served by a centrally acting agent to aid in suppression of overactivity or lack of inhibition. Clearly, there continues to be a void in our understanding of the bowel and bladder interaction in higher cortical centers and the spinal cord.

In a similar study by [Combs and associates \(2013\)](#), researchers sought to better illuminate the relationship between LUT and bowel dysfunction by studying 368 consecutive children who presented with LUTD. In a secondary analysis, they also sought to determine if constipation and encopresis, which are often presumed to coexist, also coexisted for their specific cohort. Overall, children with dysfunctional voiding had the highest incidence of bowel dysfunction, with constipation alone being the most frequently observed form. Somewhat surprisingly, nearly 50% of patients reporting encopresis did not have associated constipation. The majority of patients with encopresis with or without associated constipation had idiopathic detrusor overactivity, and those with the worst urgency were the ones reporting encopresis. Interestingly, in children with encopresis, severe urgency was commonly reported and after initiation of anticholinergic therapy the encopresis frequently resolved even before the urgency had fully subsided. This finding is similar to the results of [Burgers and colleagues \(2013a\)](#), and perhaps may be secondary to an overactivity of the detrusor and the rectal wall musculature, or a lack of inhibition of detrusor and rectal muscular activity. Whether this is a centrally mediated phenomenon is unclear.

TERMINOLOGY

The International Children's Continence Society (ICCS) is a global, multidisciplinary organization of clinicians involved in the care of children with LUTD (Austin et al, 2014). Perhaps one of the most significant impacts of the ICCS on the pediatric LUT function community was its initial terminology document (Névéus et al, 2006). Before the publication of this document, the nomenclature used in LUTD had been endemic with transposable terms that in some cases were not completely accurate and were often confusing. Moreover, this fostered uncertainty and made it rather difficult to compare research and study outcomes among different groups. The standardization of the nomenclature for pediatric and adolescent LUT function is thus critical in providing a platform for optimal comprehension and more effective interaction and treatment among multiple health care providers who care for these patients. Recently the ICCS revised the original terminology document to provide a current and consensus update reflecting refinement and current advancement of knowledge on pediatric and adolescent LUT function (Austin et al, 2014).

The terminology used for LUTS focuses on descriptive (as opposed to quantitative) language because quantitative data are currently lacking. Of particular relevance is the age of the child when applying terminology to describe pediatric LUT function. The reference point used by the ICCS is 5 years old or greater (4 years of age for bowel dysfunction), because this age is used by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-V) (American Psychiatric Association, 2013) and the International Classification of Diseases 10 (ICD-10) to characterize urinary incontinence disorders (World Health Organization, 2008). The ICCS terminology document authors do stipulate, however, that there is variability and maturational aspects that certainly will affect LUT function and that there are, in fact, children who have voluntary control over LUT function under 5 years of age. As a result, it is at the discretion of the provider to selectively apply these terms in younger cohorts of children. (See "Terminology Document" by Austin and associates, 2014, for specific terms and their definition.)

DAYTIME URINARY INCONTINENCE AND BLADDER DYSFUNCTION

Evaluation

Evaluation of the child or adolescent with suspected voiding dysfunction commences with a detailed and thorough history and physical examination. The goals of evaluation are first and foremost to determine whether the patient has a filling or emptying (or both) phase abnormality. If an abnormality is found, the evaluation should then be directed toward determining the underlying cause and distinguishing whether the dysfunction stems from an anatomic or functional issue. This last point is critical because the management strategy will depend on the cause.

History

A thorough history is going to be invaluable in ascertaining whether and what type of bladder dysfunction is present. In general, the history should be taken from the child if possible (as opposed to caregivers) and tailored to the maturational age and stage of development of bladder and bowel control. Our approach has been to first focus on the identification of a possible anatomic or neurologic source to explain a patient's current symptomatology and, once this has been ruled out, to distinguish which form of bladder dysfunction is present. Vital components of the history often will include voiding schedule, symptomatology, bowel habits, family history, maternal prenatal history, perinatal history, developmental milestones, toilet training, neuropsychiatric comorbidities, medical/surgical history, social history, diet, and previous UTIs.

Bladder and Bowel Diaries

Perhaps one of the most helpful diagnostic tools in the armamentarium of providers who care for children with LUTD is the voiding diary. Its usefulness stems from the fact that this log is an objective record of the child's bowel habits and urinary voiding pattern. The diary should include voided volumes, timing of each void and incontinent episode, timing of each bowel movement and fecal soiling episode, and fluid intake.

In the evaluation of LUTD, the frequency/volume chart is a diary recording fluid intake and urine output during a 24-hour period (Bower et al, 1997; Hoebeke et al, 2010). It can be used for both diagnostic and therapeutic purposes. For diagnostic purposes, the chart should cover at least 48 hours and not necessarily recorded on 2 consecutive days (Austin et al, 2014). Episodes of urgency and urine loss also should be recorded. Urine loss is quantified by recording if clothing had to be changed after the urine loss (significant urine loss) or not. The chart gives information about fluid intake, number of voids, voided volume, and urine loss (Fig. 143-1). We also employ a 7-day bowel diary that uses the Bristol Stool Form scale (Lane et al, 2011) in ruling out BBD. Although controversy surrounds the best way to diagnose functional constipation in children, the ICCS recommends the use of the Rome III criteria (Rasquin et al, 2006).

Questionnaires

Questionnaires in the evaluation of LUT function have emerged as useful tools to more objectively translate somewhat subjective complaints into semiquantitative data (Akbal et al, 2005). These scoring systems not only allow providers to more accurately gauge the extent of LUTD but also provide a method of monitoring outcomes during treatment (Afshar et al, 2009). The two main types of questionnaires that have emerged for pediatric LUTD are measurements of LUT function and psychological screening.

Dysfunctional Voiding Symptom Score

In 2000, Farhat and colleagues (2000) reported on the creation of the DVSS based on the International Prostate Symptom Score for benign prostatic hyperplasia. The DVSS was the first scoring system of its kind and has been used in a variety of clinical settings. There are 10 quantitative and qualitative urologic parameters translated into age-appropriate questions for children regarding urinary symptoms, such as urinary incontinence, voiding habits, urgency, posturing, bowel habits, and stressful life conditions. The 10 questions were assigned scores of 0 to 3 according to incidence in the month before responding to the questionnaire and responses are weighted equally, giving a maximum possible score of 30 (Fig. 143-2).

Pediatric Urinary Incontinence Quality of Life Score

The Pediatric Urinary Incontinence Quality of Life Score (PIN-Q), developed by Bower and colleagues (2006b) measures the emotional impact that urinary incontinence has on a child. This cross-cultural urinary incontinence quality-of-life tool has been found to have excellent test-retest reliability and validity (Bower et al, 2006a). It consists of 20 questions related to urinary incontinence quality of life that are graded on a scale of 0 to 4 (0 = No, 1 = Hardly ever, 2 = Sometimes, 3 = Often, 4 = All the time) with a total possible score of 80. The total score indicates the impact urinary incontinence has on the child's quality of life, with the higher score indicating a more significant effect. Both the PIN-Q and DVSS questionnaire have been found to be complementary and provide a clinically appropriate picture of LUTD and its impact on a child's quality of life (Thibodeau et al, 2013).

Psychological Screening

It is well documented that children with BBD have a high rate of comorbid behavioral and emotional disorders. In several

Patient name

INTAKE AND VOIDING DIARY

Instructions: Begin recording as soon as you wake in the morning and continue for 24 hours. Choose 2 full days to complete this record—note that they DO NOT need to be consecutive, but just days that you can be sure to record EVERY void. Please measure voided volumes in the hat provided in 'cc' and fluid intake in 'oz.' Please record approximate times for all events, and try to note the severity of urinary leakage and if there is any associated urgency.

[illegible]

Figure 143-1. Daytime frequency and volume chart for 48 hours.

representative studies 20% to 30% of children with enuresis, 20% to 40% with urinary incontinence, and 30% to 50% with fecal incontinence are affected by comorbid behavioral disorders (Tekgul et al, 2009; von Gontard et al, 2011). The principle behind psychological screening is that the same care used by the provider to exclude organic causes of LUTD should be applied to the assessment of behavioral aspects. Therefore all health care professionals who work with children with BBD should possess a basic understanding of psychological principles to treat their young patients adequately.

Child Behavior Checklist

The Child Behavior Checklist (CBCL) is a parental questionnaire on which children are rated on various behavioral and emotional problems (Achenbach and Ruffle, 2000). It has been one of the most widely used standardized measures in child psychology for evaluating maladaptive behavioral and emotional problems in preschool subjects aged 18 months to 5 years and in subjects between the ages of 6 and 18 years. The preschool checklist contains 100 questions and the school-age checklist contains 120 questions, with responses recorded on a Likert scale. It assesses internalizing (i.e., anxious, depressive) and externalizing (i.e., aggressive, hyperactive) behaviors. Several subareas are also measured, including somatic complaints, anxiety, depression, destructive behavior, social problems, thought problems, attention problems, aggressive behavior, and delinquent behaviors.

Short Screening Instrument for Psychological Problems in Enuresis

The Short Screening Instrument for Psychological Problems in Enuresis (SSIPPE) is a brief instrument derived from seven items of the Internalizing scale of the CBCL and six items of the Attention Deficit Hyperactivity Disorder scale of the Disruptive Behavior Disorders Rating scale (Van Hoeckel et al, 2007). At a minimum, a short validated screening questionnaire such as the SSIPPE (or CBCL)

should be completed by every parent of a child who presents with LUTD. If no problem items are checked and no obvious behavioral problems have become apparent during the initial assessment, the recommendation is to concentrate on treatment of BBD only. If more than two "Yes" items per section (SSIPPE) are checked, parents should fill out a long validated questionnaire such as the CBCL. Should the CBCL demonstrate a significant behavioral or emotional issue, a full child psychological assessment ought to follow.

Physical Examination

The physical examination is focused on genitourinary anatomy and neurologic function. Related to anatomy and critical in the initial evaluation of children with suspected BBD is the appearance of their undergarments. For instance, yellow stains in the underwear may be an indicator of urge or overflow incontinence or postvoid dribbling. Stool soiling of the underwear is also important and can denote a spectrum of gastrointestinal dysfunction, from functional constipation to encopresis.

Abdominal Examination

As previously stated, constipation is one of the most common signs of bowel dysfunction in children and adolescents presenting with BBD. Examination of the abdomen is critical in determining whether stool is present in the colon. In a child with constipation, the abdominal examination may detect tenderness of the left upper and lower quadrants resulting from colonic distention secondary to fecal impaction and/or gaseous distention.

Back and Spinal Examination

In the overwhelming majority of cases, examination of the lower back and spine will reveal a normal-appearing back and anocutaneous folds. Regardless of the incidence, however, **special attention should always be paid to the lower back for cutaneous manifestations of an occult spinal dysraphism or sacral agenesis**

PATIENT NAME:
HOSPITAL NUMBER:
REASON FOR REFERRAL:
DATE:

Over the last month	Almost never	Less than half the time	About half the time	Almost every time	Not available
1. I have had wet clothes or wet underwear during the day.	0	1	2	3	NA
2. When I wet myself, my underwear is soaked.	0	1	2	3	NA
3. I miss having a bowel movement every day.	0	1	2	3	NA
4. I have to push for my bowel movements to come out.	0	1	2	3	NA
5. I only go to the bathroom one or two times each day.	0	1	2	3	NA
6. I can hold onto my pee by crossing my legs, squatting, or doing the "pee dance."	0	1	2	3	NA
7. When I have to pee, I cannot wait.					
8. I have to push to pee.	0	1	2	3	NA
9. When I pee it hurts.	0	1	2	3	NA
10. Parents to answer. Has your child experienced something stressful like the example below?	NO (0)			YES (3)	
TOTAL					

- New baby.
- New home.
- New school.
- School problems.
- Abuse (sexual/physical).
- Home problems (divorce/death).
- Special events (birthday).
- Accident/injury.
- Others.

Figure 143-2. Dysfunctional Voiding Symptom Score questionnaire. (Modified from Farhat W, Bagli DJ, Capolicchio G, et al. The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. J Urol 2000;164:1011.)



Figure 143-3. Occult spina bifida in a child with a sacral dimple. (Courtesy Elaine Fonseca, MD.)

(Fig. 143-3). These include an asymmetrical gluteal cleft, a presacral dimple, a lipoma, a hair tuft, a dermal sinus tract, and a dermal vascular malformation. In general, these lesions should be evaluated with magnetic resonance imaging of the lumbar and sacral spine.

Genital Examination

In boys, the examination necessarily includes inspection of the urethral meatus to detect possible meatal stenosis. Although direct inspection of the meatus may be sufficient, our preference has been to observe the urinary stream directly during voiding to note its caliber and direction because this entity is not a true stenosis but rather a ventral urethral membrane that deflects the urinary stream upward (Fig. 143-4). Almost invariably, meatal stenosis is seen in circumcised boys because the prepuce is thought to protect the meatus from chronic irritation and subsequent epithelialization of this ventral meatal web of tissue. Epididymoorchitis sometimes can be seen in males with dyssynergic voiding. The theory is that increased bladder pressures can lead to retrograde reflux of caustic urine into the ejaculatory ducts, leading to inflammation along the course of the vas deferens, epididymis, and testes.

In girls, deformities of the urethral meatus also have been noted to be associated with LUT voiding dysfunction (Hoebeke et al, 1999; Klijn et al, 2012). The theory is that girls with certain anomalies of the urethral meatus (i.e., a ventral web of tissue akin to meatal stenosis in males) predispose to an anterior deflected urinary stream and so they cannot void in the ideal toileting position. This then results in lower success rates for behavioral training programs. Hoebeke and colleagues (1999) demonstrated that young females with meatal deformities were diagnosed with more severe forms of dysfunctional voiding on urodynamic investigation compared to a control group. They also showed improved micturition patterns and fewer symptoms after surgical correction. This finding



Figure 143-4. Meatal stenosis with an inferior web of tissue that results in an upward urinary deflection.

was corroborated in a second study by [Klijn and associates \(2012\)](#), who found that 39% of female patients with dysfunctional voiding reported an anteriorly deflected urinary stream. After surgical correction, they found that half of these girls were free of all related symptoms and required no further behavioral training. Examination of the labia and vaginal introitus is performed to detect any evidence of labial adhesions. Although labial adhesions are often purported to be a cause of bladder outlet obstruction (BOO), this has rarely been the case in our experience, unless they are dense enough to require surgical division. More often, as the labia minora adhere (usually from posterior to anterior) the resultant pouch sequesters small amounts of urine that may dribble into the underwear between voids, depending on the child's posture. The stagnant urine in the pouch predisposes to asymptomatic bacteriuria and UTI ([Leung and Robson, 2004](#)). The problem is usually self-limited at around the time of puberty because the presence of estrogen has a protective effect ([Leung and Robson, 2004](#)). Areas of skin excoriation or redness may be present and are often a sign of continuous or severe urinary leakage with chronic inflammation and less often secondary to fungal infection.

Neurologic Examination

A focused neurologic examination should include assessing lower extremity strength and deep tendon reflexes, gait, perineal and anal sensation, and rectal tone. The anocutaneous reflex (i.e., “anal wink”) and bulbocavernosus (Osinski) reflex should be assessed to denote any interruption of the sacral reflex arcs (S2 to S4). Any abnormality of the neurologic examination may be indicative of a neurologic lesion that also affects the function of the bladder and should be assessed with proper spinal imaging.

Investigative Tools

Urinalysis

The single most important and perhaps only laboratory test that should be performed in all children who present with LUTD is the urinalysis. This screening test will invariably aid in deciphering whether the child's symptomatology is due to a bona fide UTI or is merely dysuria associated with BBD. **Particularly important elements of the urinalysis include specific gravity and the presence of white or red blood cells, bacteria, protein, and glucose.** A low specific gravity may be secondary to a renal concentrating defect and often will lead to polyuria. White blood cells (WBCs) suggest infection and/or inflammation. Red blood cells (RBCs) generally denote infection when found with WBCs; however, isolated RBCs can be found in children with LUTD secondary to storage and

voiding dynamics. Isolated proteinuria is common in children and may represent a benign condition or a serious underlying renal disease or systemic disorder. Depending on the degree of proteinuria, consideration should be given to obtaining a serum creatinine level to estimate the glomerular filtration rate. Significant glucosuria clinches the diagnosis of diabetes mellitus and often will lead to significant polyuria.

Urine Culture and Sensitivity

A urine culture sample should be obtained if there is evidence of a bona fide UTI. We generally would not recommend performing urine cultures reflexively on all patients, because this practice will undoubtedly identify patients with simple bacterial colonization and has the potential to foster bacterial resistance and infection with more virulent organisms if treated.

Uroflowmetry

Uroflow studies consist of measuring the velocity of urinary flow (volume voided per unit time) and examining the pattern during urination into a uroflowmeter. The child voids into a collection device that produces a urinary flow curve providing the maximum (Qmax) and average (Qavg) urinary flow rates, voided volume, flow time, and shape of urine flow. Uroflowmetry may be done concomitantly with electromyography (EMG) testing of the pelvic floor musculature and external urethral sphincter by affixing pads to the perineum. **The advantage of combining EMG with uroflowmetry is the ability to appreciate synergy or dyssynergy between the bladder and the pelvic floor–sphincter complex.**

Qmax is the most relevant quantitative variable when assessing bladder outflow. Sharp peaks in the curve are usually artifacts, so maximum flow rate should be registered only when a peak level has a duration of longer than 2 seconds ([Szabo et al, 1995](#)). In studies of normal children and adults, a linear correlation has been found between maximum flow and the square root of voided volume ([Chang et al, 2013](#)). If the square of the maximum flow rate ($[mL/s^2]$) equals or exceeds the voided volume (milliliters), the recorded maximum flow is most likely normal.

There are a few caveats that should be mentioned. **First, to obtain an interpretable uroflow, a child must be toilet-trained.** **Second, uroflowmetry provides information regarding the emptying phase of the bladder only and gives no information about what is happening during filling.** **Third, it is important that the volume of voided urine is adequate, because curves change when the voided volume is less than 50% of expected bladder capacity for age** ([Austin et al, 2014](#)). Finally, it is critical to obtain more than one curve to improve the accuracy, reliability, and interpretation of the test.

Uroflowmetry provides readily useful information regarding the pattern or shape of urine flow curve that often can be diagnostic of an underlying cause. In fact, obtaining an adequate uroflow pattern along with a coherent history and physical examination often can obviate the need to pursue more invasive urodynamic testing, which should be performed only when the diagnosis is unclear. The precise shape is determined by detrusor contractility and influenced by abdominal straining, coordination with the bladder outlet musculature, and any anatomic obstruction. The ICCS has developed categories for what is considered normal and abnormal, with five types of urine flow patterns identified ([Fig. 143-5](#)). Each specific pattern is no guarantee of an underlying diagnostic abnormality but rather serves as a guide to the existence of a specific condition.

Bell-Shaped Curve. The urinary flow curve of a healthy child should register as a smooth *bell-shaped* curve regardless of gender, age, and voided volume.

Tower-Shaped Curve. The tower-shaped curve is a sudden, high-amplitude curve of short duration that suggests an OAB produced by an explosive voiding contraction. It should be noted, however, that children with OAB may have a bell-shaped curve because this LUTD is mainly related to the filling phase of the bladder.

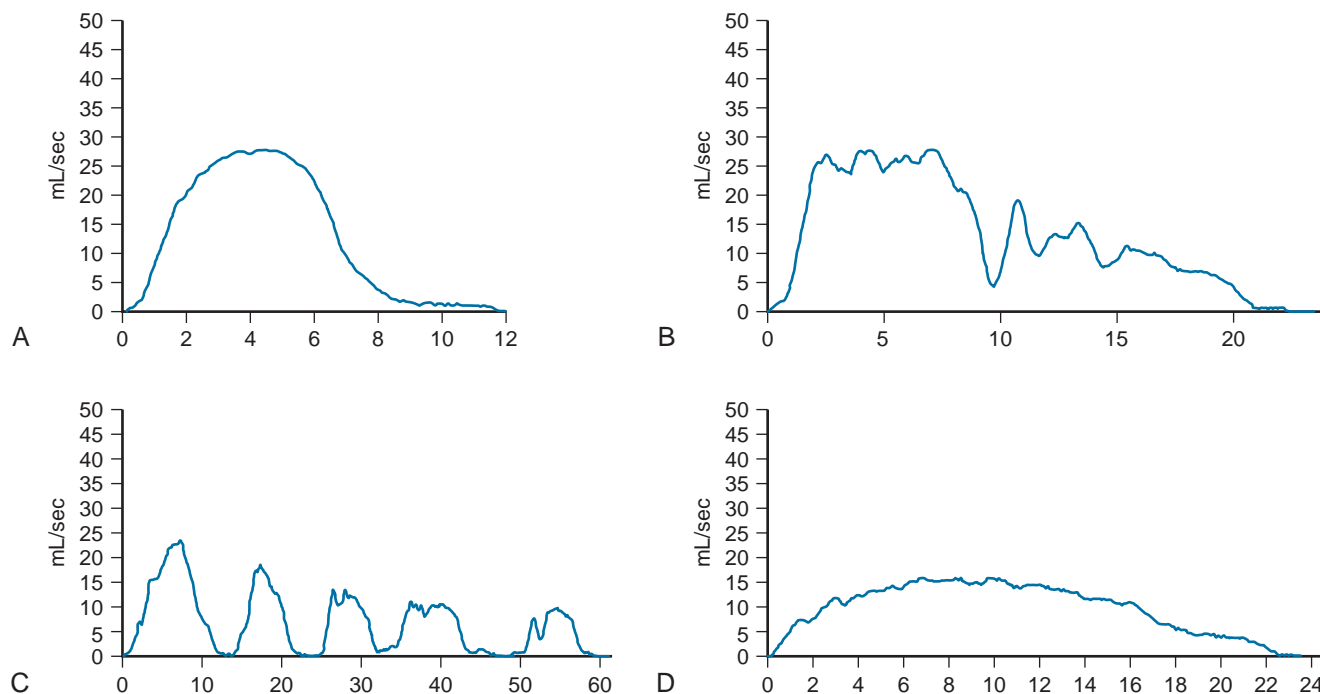


Figure 143-5. Common uroflow patterns. A, Bell shaped. B, Staccato. C, Interrupted. D, Plateau. (From Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society. *J Urol* 2014;191:1863-5.)

Staccato-Shaped Curve. The staccato-shaped pattern is irregular and fluctuating throughout voiding, but the flow is continuous and never reaches zero during voiding. This pattern suggests intermittent sphincter overactivity during voiding and is often associated with dysfunctional voiding. It will be seen as sharp peaks and troughs in the flow curve. To qualify for a staccato label, the fluctuations should be larger than the square root of the maximum flow rate.

Interrupted-Shaped Curve. This flow curve will display discrete (albeit low amplitude) peaks similar to a staccato-shaped curve; however, there will be segments where the flow rate is zero with complete cessation of urinary flow between these peaks. This flow pattern suggests an underactive bladder because each peak represents abdominal muscle straining (i.e., Valsalva) creating the main force for urine evacuation. In between each strain, the flow ceases as a result of an absent or weak detrusor contraction. It is possible this flow pattern can be seen with dyssynergy between the bladder and external urethral sphincter, and a concomitant EMG and/or pressure flow study often will be useful to distinguish between the two.

Plateau-Shaped Curve. The plateau-shaped curve is a flattened, low-amplitude prolonged flow curve that is suggestive of BOO. The BOO can be anatomic (e.g., posterior urethral valves or urethral stricture) or dynamic (e.g., continuous, tonic sphincter contraction). Flow EMG may differentiate among BOO subtypes. A plateau-shaped curve may be seen with an underactive bladder during a long continuous abdominal strain. Abdominal pressure monitoring during the uroflow can help delineate an underactive bladder condition.

Pelvic Ultrasound

Pelvic ultrasound is a key tool in the evaluation of pediatric LUT function and is used in the initial evaluation of all children with suspected BBD at our institution (Fig. 143-6). In addition to giving objective information about the voiding pattern of the child in question, it can be readily used to monitor progress over time.

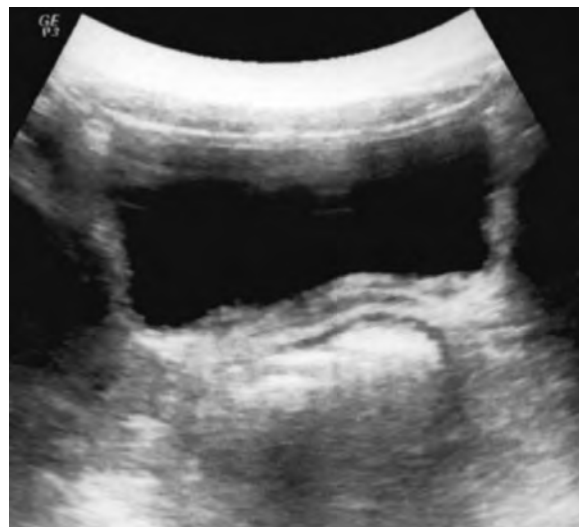


Figure 143-6. Pelvic ultrasound demonstrating a thickened bladder wall and a large amount of stool in the rectum.

Ultrasonography can calculate bladder volume and thus is useful in measuring prevoid and postvoid residual (PVR) urine volume and anatomic details of the bladder and rectum (e.g., bladder wall thickness, stool, rectal distention).

Postvoid Residual

PVR measurements in neurologically intact children are highly variable with significant intraindividual variability. Chang and Yang (2009) suggested that abnormal PVR urine volume could be defined as a PVR greater than 20 mL (as opposed to >10% of estimated bladder capacity) on repeat micturitions without bladder

overdistention. Recently, investigation of 1128 healthy Taiwanese children between 4 and 12 years of age with a bell-shaped uroflow pattern and a voided volume of greater than 50 mL support the following normative 95th percentile values for an abnormally elevated PVR (Chang et al, 2013):

- **Children 4 to 6 years:** Single PVR greater than 30 mL or greater than 21% of bladder capacity (BC), where BC is determined as voided volume (VV) + PVR and expressed as percent of the expected bladder capacity ($EBC = [age\ (yr) + 1] \times 30\ mL$). It is recommended that a repeat PVR be performed with dual measurements; a repetitive PVR greater than 20 mL or greater than 10% BC is considered significantly elevated.
- **Children 7 to 12 years:** A single PVR greater than 20 mL or 15% BC or repetitive PVR greater than 10 mL or 6% BC is considered elevated.

According to Chang and colleagues (2013), standard conditions should be applied to measuring PVR; the bladder should not be underdistended (<50%) nor overdistended (>115%) in relation to the EBC; PVR must be obtained immediately after voiding (<5 minutes). Further validation is needed for these nomograms in similar cohorts across cultures.

Bladder Wall Thickness

In daily clinical practice a thickened bladder wall should alert the clinician to long-standing problems with urine storage and emptying. The bladder wall is normally less than 3 mm when full and less than 5 mm when relatively empty (Jequier and Rousseau, 1987). A thickened bladder wall is suggestive of an anatomic or functional outlet obstruction causing detrusor hypertrophy; however, the most common diagnosis associated with a thickened bladder wall was found to be OAB (Yeung et al, 2007). Bladder wall thickness can be measured with either a full or an empty bladder and is inversely proportional to the degree of bladder filling.



Please see the Expert Consult website for further details.

Rectal Distention

Although there is insufficient evidence to support the notion that the transverse diameter of the rectum alone can be used as a predictor of constipation and fecal impaction, a number of authors have made several observations on this subject (Fig. 143-7). Klijn and associates (2004) measured the diameter of the rectum on bladder ultrasonography in a constipated group of patients with dysfunc-



Figure 143-7. Pelvic ultrasound showing a dilated rectum filled with stool compressing posterior wall of bladder.

tional voiding and compared this diameter in a control group of patients with a normal defecation pattern. Not surprisingly, in the group of constipated patients with dysfunctional voiding, the diameter of the rectum was significantly larger than in the control group.

Please see the Expert Consult website for further details.



Bristol Stool Scale

The Bristol Stool Scale or Bristol Stool Chart is a useful guide designed to classify the form of human feces into seven distinct categories. Sometimes referred to in the United Kingdom as the Meyers scale, it was developed at the University of Bristol in 1997 (Lewis and Heaton, 1997). The seven types of stool (ranging from most firm in type 1 to loosest in type 7) are as follows (Fig. 143-8):

- **Type 1:** Separate hard lumps, like nuts (difficult to pass because stool has not retained any water)
- **Type 2:** Sausage-shaped, but lumpy; represents multiple type 1 stools congealed into a single mass, typical for functional constipation
- **Type 3:** Like a sausage but with cracks on its surface
- **Type 4:** Like a sausage or snake, smooth and soft, typical for someone who has a daily bowel movement
- **Type 5:** Soft blobs with clear-cut edges, passed easily, usually multiple times per day
- **Type 6:** Fluffy pieces with ragged edges, a mushy stool, urge to defecate can be difficult to control
- **Type 7:** Watery, no solid pieces, entirely liquid

We prefer to use it as a clinical communication aid with our patients and their families in terms of what to strive for and to facilitate titration of supplemental fiber or laxative administration.

BRISTOL STOOL SCALE		
Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely liquid

Figure 143-8. Bristol Stool Chart. (Modified from Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920-4.)

In 2004, Yeung and colleagues reported on their evaluation of a special bladder ultrasound protocol for the assessment of LUTD compared with urodynamic findings and for the prediction of treatment outcome in children with enuresis (Yeung et al, 2004b). The bladder volume wall thickness index (BVWI) was a ratio of bladder volume to wall thickness, and they found statistically significant correlations between BVWI and enuresis treatment response. In addition, there was a high predictive value of normal bladder function as evaluated by urodynamics with a normal BVWI. Although it is intuitive that bladder wall thickness would correlate with LUTD, not all groups have come to the same conclusion (Mostafavi et al, 2012).

Recently, Burgers and colleagues (2013b) took a group of 84 children with a median age of 9 years (range 6 to 11) and performed both transabdominal ultrasound and digital rectal examination (DRE) under anesthesia. A rectal mass was found on transabdominal ultrasound and DRE in 32% and 41% of all children, respectively, with agreement between the two tests in 82.5%. The median diameter of the rectum was 3.3 cm in children with a full rectum and 2.5 cm and 2.0 cm in patients with a half-filled and empty rectum, respectively. They concluded that transabdominal ultrasound was a noninvasive and reliable alternative to assess the rectal filling state and might replace DRE in the evaluation of children with constipation.

KEY POINTS: EVALUATION OF DAYTIME URINARY INCONTINENCE AND BLADDER DYSFUNCTION

- The goals of evaluation are to determine whether the patient has a filling or emptying (or both) phase abnormality. If an abnormality is found, the evaluation then should be directed toward determining the underlying cause and distinguish whether the dysfunction stems from an anatomic or functional issue.
- Vital components of the history include voiding schedule, symptomatology, bowel habits, family history, maternal prenatal history, perinatal history, developmental milestones, toilet training, neuropsychiatric comorbidities, past medical/surgical history, social history, diet, and previous UTIs.
- The voiding diary is one of the most helpful diagnostic tools in the armamentarium of providers who care for children with LUTD.
- During physical examination, special attention should be paid to the lower back for cutaneous manifestations of occult spinal dysraphism.
- All children presenting with LUTD should provide a urinalysis with important elements of the urinalysis, including the specific gravity and the presence of white or red blood cells, bacteria, protein, and glucose.
- Uroflowmetry provides readily useful information regarding the pattern or shape of urine flow curve that can often be diagnostic of an underlying cause. Qmax is the most relevant quantitative variable when assessing bladder outflow.
- Ultrasonography can calculate bladder volume and thus is useful in measuring prevoid and PVR urine volume and can provide useful anatomic details of the bladder and rectum (e.g., bladder wall thickness, stool presence, rectal distention).

Treatment

The ICCS has published treatment guidelines on various LUT conditions and their associated comorbidities (Chase et al, 2010; Hoebeke et al, 2010; Franco et al, 2013; Burgers et al, 2013c; Austin et al, 2014). The management of a child or adolescent who suffers from LUTD is primarily directed at improving symptoms (e.g., urinary and/or fecal incontinence, recurrent UTIs) and protecting the upper urinary tract from permanent damage. Methods for treating children with BBD must be tailored to the specific LUTD and the child's symptomatology. Therapeutic considerations include the underlying cause, patient age, motivation and maturity level, symptom severity and duration, prior interventions, and potential risk factors for upper urinary tract damage (i.e., elevated intravesical storage pressures, VUR, recurrent UTIs).

We use a stepwise approach to the treatment of children presenting with symptoms concerning for BBD (Thom et al, 2012). Our algorithm generally moves from least to most invasive with conservative measures (e.g., treatment of constipation, behavioral modification) exhausted before initiating medications, physical therapy, biofeedback, neuromodulation, or surgical intervention.

According to the ICCS, researchers and/or clinicians should recognize three basic principles of treatment outcomes (Austin et al, 2014). First, the symptom frequency during baseline and after treatment should each be documented. Second, the assessment of treatment response must be based on pretreatment baseline registration symptom frequency. Third, the response during treatment should be noted, as well as the response after cessation of treatment for a specified period; and these two responses may not be the same. This has been outlined as follows:

- **Initial success** (based on symptom frequency)
 - No response: Less than 50% reduction
 - Partial response: 50% to 99% reduction
 - Complete response: 100% reduction

- **Long-term success**

- Relapse: More than one symptom recurrence per month
- Continued success: No relapse in 6 months after cessation of treatment
- Complete success: No relapse in 2 years after cessation of treatment

Urotherapy

Urotherapy is conservative-based therapy and treatment of LUTD that rehabilitates the LUT and encompasses a very wide field of health care professionals (Austin terminology document [Austin, 2014]). It primarily involves behavioral modification of voiding (i.e., timed voiding schedules), lifestyle modifications, and treatment of constipation. Although there are no randomized, controlled trials comparing the efficacy of conservative intervention to other therapies, several retrospective studies suggest a reduction in symptoms of up to 70% with a strictly conservative approach (Wiener et al, 2000; Allen et al, 2007).

Urotherapy can be divided into standard therapy and specific interventions. **Standard components** include the following:

1. *Information and demystification.* It is often helpful to explain normal LUT function to parents and children and how the particular child deviates from normal.
2. *Instruction* on how to resolve LUTD (i.e., behavioral modification, timed voiding, treatment of constipation).
3. *Lifestyle advice.* Encompasses balanced fluid intake and diet modification; diminished dietary irritants such as caffeine, carbonation, citrus, chocolate, and spicy foods; regular bladder and bowel emptying patterns; and skin care for those with perineal irritation from incontinence. It is also helpful to review optimal posture during voiding (i.e., sitting in the middle of the toilet with heels flat on the ground or supported on a footstool). One useful aid to teach correct upright posture is to have children straddle the toilet seat and face the toilet bowl during voiding, because this spreads the legs apart (preventing holding maneuvers such as forcefully crossing the legs) and forces them to straighten the back as they balance themselves on the toilet seat. This maneuver also can be used to successfully correct vaginal reflux.
4. *Registration* of symptoms and voiding habits, using bladder diaries or frequency-volume charts and potentially mobile applications.
5. *Support and encouragement* via regular follow-up with the caregiver.

Specific interventions of urotherapy include various forms of pelvic floor muscle retraining (i.e., biofeedback), neuromodulation, and intermittent catheterization.

Conservative Management

Bowel Dysfunction

One of our first steps is to decipher whether concomitant bowel dysfunction exists based on history, physical examination, and pelvic ultrasound. As mentioned previously, anorectal and LUT function are closely interrelated. If evidence of bowel dysfunction is indeed present (as is often the case), we generally initiate a bowel regimen that includes high fiber and increased fluid intake. Our rule of thumb for **daily fiber intake** is **age in years + 15 to 20 for total number of grams to be ingested**. Parents are reminded that **without concurrent increased fluid intake, increased fiber could actually make matters worse by allowing smaller stool balls to bind together and subsequently increase the severity of their child's constipation**.

If increased fiber is not a feasible solution, we usually recommend titrating polyethylene glycol such that children are eventually having daily Bristol type 4 stools. In severe cases, we recommend a complete bowel cleanse (i.e., chemical disimpaction) consisting of what we term "magic mousse" supplementing with tap water enemas to relieve any distal obstruction by impacted stool in the

rectal vault. Magic mousse consists of three simple ingredients: 1 cup ice cream, 1 cup prepared pudding, 6 oz. mineral oil, that are mixed and frozen (Campigotto, personal communication, 2014). Children younger than 6 years of age are given 4 T twice daily and those 6 years of age or older get double the dose twice daily. This is generally done over a weekend for children who are in school or daycare because this routine is fairly intense and children may have multiple, somewhat unpredictable bowel movements. **It is imperative that the bowel regimen be continued throughout the treatment course to both maximize therapeutic efficacy for the bladder dysfunction component and counteract the constipating side effect of anticholinergic medications.**

The importance of addressing constipation in those with BBD is substantiated by the findings of a large retrospective study of 234 chronically constipated and encopretic children who were treated for constipation and reassessed at least 12 months after initiation of therapy (Loening-Baucke, 1997). Of these children, 29% complained of daytime urinary incontinence and 34% had enuresis. UTI was present in 11% of the cohort and was more common in girls. **Relief of constipation resulted in disappearance of daytime urinary incontinence in 89% and enuresis in 63% of patients. There were no reported UTIs in any patient who had no anatomic abnormality of the urinary tract.**

Behavioral Modification

The ultimate goal of any structured behavioral modification program is to return the child to normal micturition habits. With this goal in mind, it is important to set an individualized voiding regimen to establish a consistent voiding routine. **The classic regimen entails timed voiding with frequent voids scheduled every 2 hours during the day.** This strategy is crucial in aiding to avoid bladder overactivity and urge symptoms, which can occur as the bladder fills and begins to reach the critical volume that triggers the urge to void. We recommend wristwatch alarms to all patients because these can readily assist older, more independent children to comply with timed voiding (Hagstroem et al, 2010). The use of a vibratory watch is also a good option because it does not disturb peers, with only the patient knowing that it has indicted the set time. Regardless of what regimen is used, children are encouraged to urinate before they have a sense of urgency, empty their bladders completely, and avoid abdominal straining.

The timed voiding regimen is often linked to a positive reinforcement program using a diary in which the child tracks the number of times voided during the day. It has been demonstrated that the establishment of a reward system can significantly improve the child's self-esteem and compliance (Allen et al, 2007). Specifically, the incentive scheme should focus on rewarding the child for following the recommended program (e.g., stickers each time the child voids during the day) as opposed to "not wetting" themselves. Not surprisingly, behavioral modification has been shown to be more successful in older children (older than 8 years of age), who, in general, will be more motivated by peer pressure and are mature enough to respond to and follow instruction (Curran et al, 2000; Heilenkötter et al, 2006).

Biofeedback

Biofeedback is a treatment modality that uses electronic or mechanical instruments to relay perceptual evidence to assist a person in gaining control over a physiologic process or function (Liberati, 2005). This method has been used for over three decades in the urologic setting and employs noninvasive urodynamic instrumentation to measure, record, and provide direct, instantaneous information to the child about voiding function (Maizels et al, 1979). Real-time uroflowmetry allows the patient to observe the urine flow rate. Concurrent placement of adhesive pads on the perineum measures sphincter and/or pelvic floor activity. Abdominal EMG also can be performed if desired. Each session lasts approximately 45 minutes with a trained practitioner overseeing therapy. The visual and auditory feedback allows the child to become aware of and gain

control over LUT function by teaching them how to voluntarily relax their sphincter and pelvic floor musculature during voiding, thus preventing detrusor-sphincter dyscoordination. In fact, many biofeedback programs have been tailored to children by using interactive computer games controlled by pelvic floor contraction and relaxation along with urinary flow rate (McKenna et al, 1999). This system has facilitated the training process and lowered the age at which children can be successfully treated; however, one should bear in mind that most children under 5 years of age are typically incapable of receiving biofeedback regularly.

A number of observational studies have documented the utility of biofeedback therapy in reducing the symptoms associated with LUTD (Yamanishi et al, 2000; Chin-Peuckert and Salle, 2001; Nelson et al, 2004; Klijn et al, 2006), expediting the resolution of VUR (Palmer et al, 2002; Kibar et al, 2007), and eliminating recurrent UTIs (Nelson et al, 2004). Recently, a systematic review evaluated the efficacy of biofeedback in the treatment of children with BBD (Desantis et al, 2011). The review included 27 studies (1 randomized controlled trial and 26 case-series). The pooled estimate showed an 83% and 80% improvement in UTI and daytime urinary incontinence, respectively. The only included randomized study favored biofeedback over standard urotherapy (relative risk [RR] 1.4, 95% confidence interval [CI] 0.98 to 2), but this was not statistically significant. On analysis of all included studies, there also was improvement in constipation (18% to 100%), frequency (67% to 100%), urgency (71% to 88%), and VUR (21% to 100%).

Clean Intermittent Catheterization

Lapides and colleagues (1972) first introduced the concept of clean intermittent catheterization (CIC) as a method of emptying the bladder in neurologically impaired patients. Since its initial description, this treatment strategy has gradually been employed in neurologically intact individuals with various types of LUTD. In the setting of dysfunctional voiding and in children who postpone micturition, the detrusor muscle stretches and the bladder becomes chronically overdistended. This repeated action over time can lead to underactive bladder with the end result of myogenic failure. In these cases, bladder emptying is often incomplete, resulting in large PVR urine volumes, urinary incontinence, and recurrent UTIs from stasis. CIC is a safe, effective, and well-tolerated treatment strategy to attain continence and reduce the rate of recurrent UTI in children with LUTD (Pohl et al, 2002). It is particularly crucial to discuss the merits of this intervention with sensate patients and their families to maximize adherence.

Pharmacotherapy

Pharmacologic intervention in the treatment of children with LUTD has traditionally encompassed anticholinergic agents and α -adrenergic receptor antagonists (i.e., α -blockers) to enhance bladder filling and emptying, respectively. We will generally initiate one or both of these two medications once all other conservative measures have been exhausted. In some instances we will start α -blockers concomitantly with biofeedback, and this management decision is ultimately left up to the discretion of the provider.

Anticholinergic Agents

Anticholinergics (i.e., antimuscarinics) are the current gold standard in the treatment of patients with symptoms referable to OAB. Muscarinic receptors are found in the human detrusor muscle, and bladder contractions are initiated by stimulation of these receptors with the release of acetylcholine from cholinergic nerves. The main action of anticholinergics is on the M1 and M3 receptor subtypes, which are thought to be responsible for the pathogenesis of detrusor overactivity (Chapple et al, 2002). **These agents act by reducing the frequency and intensity of uninhibited detrusor contractions during the filling phase of the bladder, resulting in an increase in the functional bladder capacity and compliance (Nijman, 2004; Finney et al, 2006).** The clinical efficacy depends

on various factors such as receptor affinity, pharmacokinetics, and the specificity for the bladder.

Oxybutynin was among the first generation of modern antimuscarinic medications available for treating incontinence in children. Five anticholinergic agents are currently approved in the United States for the treatment of OAB (darifenacin, oxybutynin, solifenacin, tolterodine, and trospium), with only two of these (oxybutynin and tolterodine) having formally achieved approval for use in children. Oxybutynin has antimuscarinic, antispasmodic, and analgesic properties. It causes the antispasmodic effect by acting as a calcium channel blocker. The analgesic and antispasmodic properties make the medication particularly attractive; however, these effects occur only with supraphysiologic doses that would render them useless secondary to side effect profile (Chapple, 2000).

The nonselective pattern of activity and penetration of the blood-brain barrier are known to induce systemic and central side effects, respectively. The longer acting extended-release formulation (Oxybutynin XL) is also approved by the U.S. Food and Drug Administration (FDA) for use in children and uses a novel delivery system resulting in absorption in the large intestine (Youdim and Kogan, 2002). This avoids the first-pass metabolism in the liver, leading to a decrease in the active metabolite *N*-desethyloxybutynin, thought to be responsible for many of the adverse effects associated with the use of oxybutynin. **The main side effects include constipation, dry mouth, blurred vision, reduced sweating, flushing, and altered behavior and cognition.** Oxybutynin is lipid soluble and therefore likely to cross the blood-brain barrier and in adults has been reported to interfere with cognition. However, in a non-randomized trial of 25 children, Sommer and colleagues (2005) found that treatment with oxybutynin was not associated with cognitive impairment. Additionally, in a recent study by Veenboer and associates (2013), no significant differences in behavior were found between children with spinal dysraphism with and without long-term use of antimuscarinics.

Other methods of delivery of oxybutynin are intravesical and transdermal. The intravesical method of delivery avoids the first-pass effect and leads to increased amounts of oxybutynin available compared to immediate-release oral oxybutynin. Its use in the non-neurogenic, sensate population is limited, however, because of the need for catheterization. **The transdermal patch is as efficacious as the immediate-release oral form but with nearly half the incidence of dry mouth (Davila et al, 2001).** Local skin erythema and pruritus are side effects unique to this route of administration that can be seen in over one third of patients (Gleason et al, 2014).

α-Adrenergic Receptor Antagonists (α-Blockers)

α-Adrenoreceptors have been demonstrated in the LUT, with a large concentration located at the bladder neck and urethra (Ek, 1978). **α-Adrenergic blockade results in smooth muscle relaxation and decreased bladder outlet resistance.** Limitations of early α-blockers included their side effect profile with hypotension and dizziness. With subsequent development of more “selective” α-blockers in the 1980s that targeted α_{1a}-receptors rather than both α_{1a}- and α_{1b}-adrenergic receptors, these side effects were greatly diminished. Examples of selective α-blockers include alfuzosin, doxazosin, prazosin, silodosin, tamsulosin, and terazosin.

Currently, α-blockers are a mainstay drug used to facilitate bladder emptying in the adult population, particularly in adult males with benign prostatic hyperplasia. Early work on the benefits of α-blockers on pediatric LUTD by Austin and colleagues (1999) pioneered the introduction of α-blockers into the armamentarium of drugs that can be used to treat voiding issues in children. In this pilot report, there was an 82% improvement in the measured parameters of 17 patients treated with α-blocker therapy. In a follow-up of their initial study, the group continued to see improvement in multiple LUTS, daytime incontinence episodes, and PVR measurements in 55 children treated with doxazosin for dysfunctional voiding (Cain et al, 2003).

Please see the Expert Consult website for further details.

α-Blocker treatment selection of children with LUTD is done through a comprehensive treatment program that involves an escalating treatment paradigm (Chase et al, 2010; Thom et al, 2012) or by identifying patients with characteristic uroflow abnormalities (Van Batavia et al, 2010). The uroflow finding of a prolonged “EMG lag time” is associated with bladder neck and internal urethral sphincter discoordination and may be used to select patients for α-blocker therapy (Van Batavia et al, 2011, 2014). The EMG lag time is the time duration after the external sphincter relaxes and the flow of urine. A prolonged lag time of greater than 6 seconds is suggested as a reliable indicator of tailoring LUTD treatment with α-blocker therapy (Van Batavia et al, 2014). Further validation is needed to investigate the reliability and reducibility of these uroflow findings.

Botulinum Toxin

A relatively recent investigational pharmacologic approach in refractory cases of LUTD is botulinum-A toxin (BTX-A). The toxin acts by inhibiting acetylcholine (ACh) release at the presynaptic neuromuscular junction. Inhibited ACh release results in regionally decreased muscle contractility and atrophy at the injection site. The chemical denervation that ensues is a reversible process, and eventually the toxin is inactivated and removed. Clinical effects begin within 5 to 7 days of injection with maximal effects reached within 4 to 6 weeks (Game et al, 2009). The duration of induced paralysis varies depending on the type of muscle treated, with duration of treatment effect lasting between 3 and 12 months (Riccabona et al, 2004).

Clinically, BTX-A injections have been used safely in the treatment of a number of clinical disorders (Maria et al, 2005), including neurogenic LUTD (Game et al, 2009). BTX-A has been subsequently applied to non-neurogenic LUTD, and there are a number of reports of BTX-A used to treat children with OAB and dysfunctional voiding (Steinhardt et al, 1997; Hoebeke et al, 2006; Mokhless et al, 2006; Radojicic et al, 2006; Franco et al, 2007; Petronijevic et al, 2007; Vricella et al, 2014). BTX-A is directly injected into the detrusor muscle (in patients with OAB) or external urinary sphincter (in patients with dysfunctional voiding) under cystoscopic guidance. One of the main drawbacks of this therapeutic modality is the need for re-treatment given the reversible nature of this chemical denervation secondary to synaptic terminal resprouting within 6 months of injection. Fortunately, preliminary studies suggest that repeated BTX-A injections are safe in children and do not induce additional fibrosis in the bladder wall (Pascali et al, 2011).

Neuromodulation

During the last two decades electrical nerve stimulation, also known as neuromodulation, has been applied to the treatment of non-neurogenic LUTD in children (Table 143-1). Several of the reported changes after treatment with neuromodulation include significantly increased bladder capacity, decreased severity of urgency, improved continence, and decreased UTIs (Bower et al, 2001; Hoebeke et al, 2001b; Roth et al, 2008). A significant improvement in urodynamic parameters of bladder compliance, number of involuntary contractions, and bladder volume at first detrusor contraction also have been noted (De Gennaro et al, 2004).

In neuromodulation, electrical stimuli are exerted in a noninvasive manner to alter the existent neural transmission pattern and modulate detrusor activity. The putative mechanism involves acting centrally by rebalancing excitatory and inhibitory information and returning the neural drive toward a more neutral status. A number of modalities have been studied in children, including sacral neuromodulation, pudendal nerve stimulation, and tibial nerve stimulation. Although preliminary results have been promising, electrical nerve stimulation's role in children with non-neurologic LUTD nevertheless remains controversial because of the lack of controlled trials and largely obscure mechanism of action.

With transcutaneous electrical nerve stimulation (TENS) superficial electrodes are placed on each side of the S3 and S2 spinal cord



Kramer and colleagues (2005) conducted the first randomized, placebo-controlled study of selective α -blocker therapy in children with dysfunctional voiding. Thirty-eight children were randomized to either placebo or 0.5 mg of doxazosin. Unlike in previous studies, they found no significant difference in the PVR and uroflow measurements between the treatment groups. There was a trend toward a significant improvement in urinary incontinence (4 vs. 14 incontinent episodes per week from a median baseline of 18 weekly episodes) and the DVSS parental survey in the α -blocker group compared to the placebo group. There was a significant difference in parental satisfaction, with a higher parental satisfaction in the children treated with α -blockade.

Vanderbrink and colleagues (2009) reported an observational study of 23 children with bladder neck dysfunction who were treated for an average of 10 months with tamsulosin. The number of incontinent episodes decreased from over 5.5 to less than 1 episode on average per day. In addition, increases in Qavg and Qmax and a reduction in PVR urine and abnormal uroflow patterns were observed during therapy. The safety profile for α -blockade in this pediatric population also was assessed, and the results were consistent with those in other reports using selective α -blockers in children. Although orthostatic hypotension was not formally evaluated, the authors did not find any significant alterations of blood pressure measurements and there were no reports of any symptomatology suggestive of hypotension.

TABLE 143-1 Studies Evaluating Neuromodulation in Treatment of Children with Lower Urinary Tract Dysfunction

REFERENCE	ES TYPE	LUTD	NO. PTS	TREATMENT SCHEME	FREQUENCY/AMPLITUDE	TREATMENT PERIOD	FOLLOW-UP (mo)	OUTCOME (%)
Hoebeke et al, 2001b	TENS	OAB	41	S3: 2 hr/day	2 Hz/not stated	6 mo	12	56 cured, 20 improved
Bower et al, 2001	TENS	OAB	14	Suprapubic/ S2-3: 1 hr, 2 times/day	10 or 150 Hz/ not stated	1 mo	1	50 cured, 23 improved
Barroso et al, 2006	TENS	OAB	19	S3: 20 min, 3 times/wk	10 Hz/6-42 mA	1 mo	14	63 cured, 32 improved
Hagstroem et al, 2009	TENS	OAB	25	S2-3: 2 hr/day	10 Hz/37.5 mA	1 mo.	1	0 cured, 61 improved
Malm-Buatsi et al, 2007	TENS	OAB	18	S2-3: 20 min, 2 times/day	100 Hz/0-60 mA	8 mo	13	13 cured, 60 improved
Lordêlo et al, 2010	TENS	OAB	37	S2-3: 20 min, 3 times/wk	10 Hz/not stated	7 wk	16	62 cured, 90 improved
Hoebeke et al, 2002	PTNS	DV	31	30 min, wkly	20 Hz/not stated	10 wk	3	Urgency: 25 cured, 36 improved Incontinence: 17 cured, 52 improved
De Gennaro et al, 2004	PTNS	OAB DV	10 7	30 min, wkly	20 Hz/0-10 mA	12 wk	3	OAB: 56% cured, 80% improved DV: 50 cured, 71 improved
Capitanucci et al, 2009	PTNS	OAB DV	14 14	30 min, wkly + maintenance (once/mo)	20 Hz/0-10 mA	12 wk	24	OAB: 36 cured, 86 improved DV: 86 cured, 100 improved
Humphreys et al, 2006	SNM	BBD	23	S3	Not stated	13 mo	13	UI: 16 cured, 68 improved UR: 33 cured, 60 improved Bladder pain/urgency/frequency: 67/75/73 improved Constipation: 80 improved
Roth et al, 2008	SNM	BBD	20	S3	Not stated	27 mo	27	UI: 75 cured, 88 improved UR: 25% cured Urgency/frequency: 83 cured/78 cured/89 improved Constipation: 41 cured, 59 improved
Stephany et al, 2013	SNM	BBD	14	S3	Not stated	6 mo	6	Significant improvements in quality-of-life (psychosocial, total) scores and LUTD scores

BBD, bowel-bladder dysfunction; DV, dysfunctional voiding; ES, electrical stimulation; LUTD, lower urinary tract dysfunction; OAB, overactive bladder; PTNS, percutaneous tibial nerve stimulation; SNM, sacral nerve modulation; TENS, transcutaneous electrical nerve stimulation; UI, urinary incontinence; UR, urinary retention.

segments. In general, therapy consists of 20-minute sessions three times per week. Percutaneous tibial nerve stimulation (PTNS) is performed with a 34-gauge stainless steel needle inserted approximately 5 cm cephalad to the medial malleolus and a grounding pad placed just posterior to the medial malleolus. Proper needle placement in children is confirmed by observing ipsilateral plantar and/or toe flexion or fanning. Although the purported mechanism of action differs somewhat, neuromodulation by PTNS is based on the traditional Chinese practice using the Sanyinjiao acupuncture point, which overlies the posterior tibial nerve (van Balken et al, 2004). The posterior tibial nerve is a mixed sensory and motor nerve originating from the L4 to S3 spinal roots that also contributes to sensory and motor control of the bladder, urinary sphincter, and pelvic floor musculature. Therapy has been invariably applied once weekly, usually for 30-minute outpatient treatment sessions.

Since its initial description, a significant number of reports have been generated on sacral nerve root stimulation via implantable electrodes. In the last decade sacral nerve modulation (SNM) has gained widespread recognition in adults and was approved by the FDA for use in urology for urinary urgency/frequency, urge incontinence, pelvic floor dysfunction, and nonobstructive urinary retention. Despite off-label use, a number of groups have reported on their experience with SNM in children with non-neurogenic LUTD (Tanagho, 1992; Humphreys et al, 2006; Roth et al, 2008; McGee et al, 2009; Stephany et al, 2013).

Before sacral implantation can be performed, percutaneous transforaminal access to the S3 spinal nerve must be achieved. Once the correct responses are obtained, the quadripolar tined lead of the neurostimulator device can be implanted. This lead can then be connected to an external neurostimulator device via a tunneled subcutaneous extender for programming and trial assessments. If this is successful, the patient undergoes a second procedure to implant the permanent neurostimulator device into a subadipose pocket in the upper gluteal region. Complications commonly cited with implantable SNM devices are device and/or wound infection, electrode migration, loss of effect, and lead fracture. Revision rates range between 7% and 18%, secondary to lead migration, faulty connection, and infection.

Special Conditions of Lower Urinary Tract Dysfunction and Their Treatment

Giggle Incontinence (Enuresis Risoria)

Enuresis risoria is an uncommon form of daytime incontinence classically seen in school-aged females. Typically, moderate-to-large amounts of urinary leakage are triggered by laughing alone. The accepted theory is that of a central nervous system (CNS) inactivation (i.e., cataplexy) in association with laughter resulting in urinary incontinence (Sher and Reinberg, 1996). It should be emphasized that the incontinence episodes are invariably significant and often the entire bladder volume is drained. Daytime urinary incontinence in conjunction with laughter is also seen in children with OAB and is more common than true giggle incontinence. It is a diagnosis of exclusion and is usually established on history and is supplemented by the absence of other voiding symptoms and normal investigations. Giggle incontinence has a significant adverse effect on the social life, and this is often why medical assistance is sought. Currently, available treatment strategies include biofeedback or methylphenidate (Berry et al, 2009; Richardson and Palmer, 2009).

Pollakiuria (Extraordinary Daytime Urinary Frequency)

This is a disorder characterized by a very high daytime frequency of micturition (sometimes as high as 50 times per day). A key aspect of this syndrome, which differentiates it from OAB and often can clinch the diagnosis, is that the symptoms are limited only to the daytime. It is seen in early childhood (4 to 6 years of age) in both genders and associated with a history of recent death or life-threatening event in the family. Usually, it runs a benign, self-

KEY POINTS: MANAGEMENT OF DAYTIME URINARY INCONTINENCE AND BLADDER DYSFUNCTION

- The management of a child or adolescent with LUTD is primarily directed at improving symptoms (e.g., urinary and/or fecal incontinence, recurrent UTIs) and protecting the upper urinary tract from permanent damage.
- In general, a stepwise approach is used with an algorithm that progresses from least to most invasive with conservative measures (e.g., treatment of constipation, behavioral modification) exhausted before initiating medications, physical therapy, biofeedback, neuromodulation, or surgical intervention.
- In one large study, relief of constipation alone resulted in the disappearance of daytime urinary incontinence in 89% and enuresis in 63% of patients studied (Loening-Baucke, 1997).
- Anticholinergics are the current gold standard in the treatment of patients with symptoms referable to OAB. These agents act by reducing the frequency and intensity of uninhibited detrusor contractions during the filling phase of the bladder, resulting in an increase in the functional bladder capacity and compliance. The main side effects include constipation, dry mouth, blurred vision, reduced sweating, flushing, and altered behavior and cognition.
- α -Adrenergic blockade results in smooth muscle relaxation and decreased bladder outlet resistance to facilitate bladder emptying.
- In neuromodulation, electrical stimuli are exerted in a non-invasive manner to alter the existent neural transmission pattern and modulate detrusor activity. The putative mechanism involves acting centrally by rebalancing excitatory and inhibitory information and returning the neural drive toward a more neutral status. A number of modalities have been studied in children, including SNM, pudendal nerve stimulation, and tibial nerve stimulation.

limited course over a period of approximately 6 months (Bergmann et al, 2009). No specific treatment, apart from reassurance, is necessary. Children presenting with frequency, however, merit clinical investigation to exclude other pathologic causes.

Underactive Bladder

As the name suggests, underactive bladder describes a child who is required to raise intra-abdominal pressure to initiate, maintain, and complete voiding. Once a functional or anatomic cause for BOO has been ruled out, there are two main approaches to this entity. The first is with timed voiding and double voiding to more efficiently empty the bladder and lower the ultimate PVR volume of urine. If this treatment strategy fails to achieve the desired effect, we often recommend CIC with frequency dependent on symptom severity. Obviously, this requires appropriate counseling and thoughtful guidance of both patient and caregiver, especially in the child who is neurologically intact.

Vaginal Reflux (Vaginal Entrapment and Vaginal Voiding)

Vaginal reflux is characterized by incontinence after normal voiding in the absence of other LUTS. It is commonly seen in prepubertal girls, and the typical history is that of wetting of undergarments approximately 10 to 15 minutes after a normal void. It often can be associated with labial adhesions as a result of chronic irritation and inflammation from skin exposure to relatively caustic urine. Reassurance and postural modification to ensure complete vaginal emptying is the only treatment required.

ENURESIS

Over the last several decades, much has changed in our understanding of enuresis. Previous notions of voluntary control have been replaced by an appreciation of genetic and pathophysiologic mechanisms. What is known with certainty is that enuresis is a common medical condition in children (Shreeram et al, 2009). It affects millions of children throughout the world and is associated with significant negative impacts on self-esteem and health-related quality of life (Wolfe-Christensen et al, 2013).

Terminology and Background

The term *enuresis* is synonymous with *nocturnal enuresis* and is defined as discrete episodes of urinary incontinence during sleep in children over 5 years of age in the absence of congenital or acquired neurologic disorders. The term *diurnal enuresis* has been eliminated completely. The child who wets during the day and night can be said to have daytime urinary incontinence and enuresis or non-monosymptomatic enuresis.

Enuresis is categorized as monosymptomatic (MSE) or non-monosymptomatic (NMSE). MSE is defined as enuresis in children without any other LUTS and without a history of bladder dysfunction. MSE is further subdivided into *primary* and *secondary* forms. Children who have *never* achieved a satisfactory period of nighttime dryness (~80% of enuretic children fit this definition) have primary MSE (Friman and Warzack, 1990). Children who develop enuresis after a dry period of at least 6 months are said to have secondary enuresis (von Gontard and Nevés, 2006). Secondary enuresis often is ascribed to an unusually stressful event (e.g., parental divorce, birth of a sibling, sexual abuse) or an organic (e.g., UTI, diabetes, obstructive sleep apnea, neurogenic bladder) or psychological cause (e.g., ADHD or conduct disorder) at a time of vulnerability in a child's life. These children are more likely to have NMSE (see next) and respond less well to treatment. The exact cause of secondary MSE, however, remains largely unknown. The clinical presentations of children with primary and secondary MSE are otherwise similar, which suggests a common pathogenesis (Robson et al, 2005). Moreover, large family studies have demonstrated that secondary MSE is usually no different etiologically from primary MSE, with undue emphasis on their difference being unwarranted (Schaumburg et al, 2008).

Enuresis with any daytime LUTS is defined as NMSE (Franco et al, 2013). Daytime LUTS suggesting NMSE include daytime incontinence (not obligatory), frequency, genital or LUT pain, and holding maneuvers (i.e., strategies to postpone voiding). A careful history is often required to elicit these symptoms, which usually indicate either OAB (i.e., a storage issue) such as urgency or dysfunctional voiding (i.e., emptying problems) such as hesitancy, straining, weak stream, intermittency or a feeling of incomplete emptying.

The pathogenesis, evaluation, and treatment of MSE and NMSE overlap considerably (Nevés et al, 2010). Approximately 15% to 30% of enuretic children experience daytime LUTS; however, these reported numbers are likely grossly underestimated (Järvelin et al, 1988; Gumus et al, 1999). In fact, most experts in the field would estimate the proportion of children with enuresis that are truly monosymptomatic to represent fewer than half of all bedwetting children (Franco et al, 2013).

Our initial approach to NMSE is nearly identical to our approach for children with LUTD. Obviously one begins with a thorough history and physical examination, along with the appropriate laboratory and imaging studies. In terms of NMSE therapy, we also begin by identification and treatment of constipation. As we have previously seen, effective treatment of bowel problems can lead to the spontaneous remission of daytime incontinence (Loening-Baucke, 1997). We also will treat the underlying LUTD symptoms first, because effective treatment of OAB (or dysfunctional voiding) can lead to cessation of the enuresis entirely (Franco et al, 2013). If comorbid behavioral disorders are present, these should be addressed by an appropriate provider. If enuresis persists after the

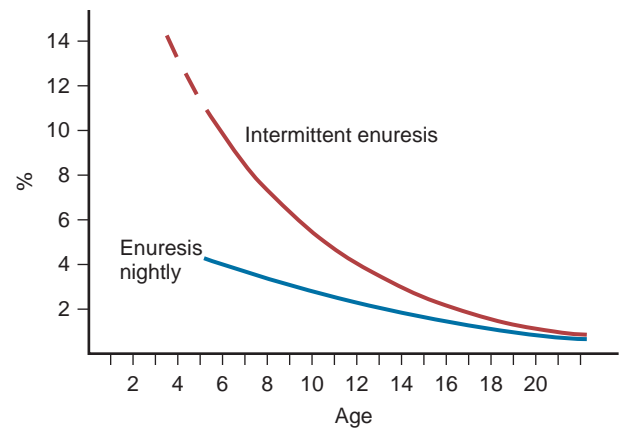


Figure 143-9. Prevalence rate of enuresis from childhood through young adulthood. (From Austin PF, Nevés T. Evaluation and management of enuresis. AUA Update Series, Vol. XXI, 2012.)

previously mentioned interventions, standard treatment for MSE can follow. The remaining section of this chapter will focus specifically on MSE and its epidemiology, cause, evaluation, and treatment strategies.

Epidemiology and Natural History

Enuresis is a common problem, with an estimated 7 million children in the United States alone with this condition. According to a recent large longitudinal study in the United Kingdom, at least 20% of children in the first grade occasionally wet the bed and 4% wet the bed two or more times per week (Butler and Heron, 2008). Prevalence varies with age, suggesting an immaturity of the LUT and nervous system (Fig. 143-9). In a study of almost 11,000 children in the United States, the prevalence of enuresis in boys at 7 and 10 years of age was 9% and 7%, respectively, and in girls at those ages, 6% and 3%, respectively (Byrd et al, 1996). It is currently generally accepted that in the West approximately 15% of children will have some degree of nighttime wetting at 5 years of age, with a spontaneous resolution rate of approximately 15% per year (Forsythe and Redmond, 1974). Consequently, at 15 years of age only 1% to 2% of teenagers will still wet the bed (Klackenberg, 1981). It has also been shown that the longer the enuresis persists, the lower the probability is that it will resolve spontaneously (Forsythe and Redmond, 1974; Bakker et al, 2002).

Enuresis seems to be more common in boys than in girls, with most reports revealing a 2:1 ratio. Although this finding has been disputed by other groups, it is well accepted that by adolescence the prevalence in both males and females reaches equipoise (Yeung et al, 2004b).

Enuresis is also known to be common in children with comorbid behavioral issues such as ADHD, oppositional defiant disorder, conduct disorder, anxiety, and depression (Baeyens et al, 2004; von Gontard et al, 2011). It is estimated that 20% to 30% of children with enuresis have comorbid clinical behavioral disorders that fulfill the criteria for the DSM-V psychiatric disorders and may subsequently have a negative impact on compliance and ultimate outcome if left untreated (von Gontard et al, 2011).

Genetics

Enuresis has a complex and multifactorial pathophysiology with a strong genetic underpinning (von Gontard et al, 1998a; Schaumburg et al, 2008). When one or both parents have a history of prolonged nighttime wetting, approximately 43% and 77%, respectively, of the offspring are affected (Bakwin, 1973). When neither parent has a history of nocturnal enuresis, only 15% of offspring are affected (Bakwin, 1973). Moreover, the concordance among

monozygotic twins is almost twice that among dizygotic twins (68% vs. 36%) (Bakwin, 1971). Linkage of enuresis to markers on chromosomes 12, 13, and 22 has been reported, with autosomal dominant inheritance and high penetrance suggested; however, a major gene locus has yet to be identified (Eiberg et al, 1995, Eiberg 1998; Arnell et al, 1997). Family and twin studies suggest locus heterogeneity and poor phenotype-genotype correlation (von Gontard et al, 2011b). The identification of these genes certainly lifts the burden of guilt from children who have enuresis and helps to dispel the theory that enuresis is behavioral in origin and completely under their control.

Pathophysiology

It is generally accepted that enuresis stems from a maturational delay in the ultimate development of bladder control (Järvelin, 1989; Light, 1998). This contention is rooted in the fact that most children eventually attain nocturnal dryness regardless of what intervention is used and even if enuresis is left untreated. The hypothesis that there is a difference in the CNS maturation in children with primary enuresis compared with controls is supported by neurophysiologic data (Isacan et al, 2002). Many children who have enuresis are noted to have progressive maturation of bladder stability in conjunction with electroencephalography (EEG) findings that suggest increased CNS recognition of bladder fullness and the ultimate ability to suppress the onset of bladder contraction (Watanabe and Azuma, 1989). This would further lend credence to the premise that delayed maturation of the bladder control plays a role in MSE.

Put very simply, the three organ systems implicated in the pathogenesis of enuresis include the bladder (i.e., a reduced nocturnal bladder capacity) (Yeung et al, 2004a), the kidney (i.e., nocturnal polyuria) (Nørgaard et al, 1989a; Vande Walle et al, 2007), and the brain (i.e., a disorder affecting arousal from sleep) (Watanabe and Azuma, 1989; Isacan et al, 2002). Enuresis is logically thought to result from a disruption or maturational lag in one or more of these critical domains (Fig. 143-10).

Bladder Overactivity and Reduced Nocturnal Bladder Capacity

There seems to be a subset of children with primary MSE who have nocturnal bladder overactivity regardless of amount of urine production (Yeung et al, 1999). Yeung and associates found that nearly half of treatment failures with standard therapy (i.e., desmopressin or moisture alarm) had normal daytime bladder function but marked detrusor overactivity during sleep that resulted in enuresis. Almost none of these children had nocturnal polyuria.

When urodynamic studies are performed during sleep, the only difference between children with and without MSE is the increased rate of bladder contractions that occur in association with the enuretic episode (Nørgaard et al, 1989b). In addition, urodynamic

studies during sleep demonstrate a relationship between nocturnal enuresis and pelvic floor activity. When pelvic floor activity increased in association with detrusor contractions, wetting was usually avoided, and patients often would awaken subsequently to void. In contrast, when pelvic floor activity did not increase, the detrusor contraction usually was associated with a wetting episode (Nørgaard et al, 1989b).

Please see the Expert Consult website for further details.



Nocturnal Polyuria

Increased nighttime urine output appears to play an important role in nocturnal enuresis (Nevéus et al, 2010). In children and adolescents without enuresis, the diurnal pattern of urine production results in a relative reduction in nocturnal diuresis to approximately 50% of daytime levels (Rittig et al, 1995, 2010). The prevailing mechanism for how this occurs is thought to result from a nocturnal circadian peak of antidiuretic hormone (ADH) release from the posterior pituitary gland that regulates free water excretion. Other purported mechanisms for increased nocturnal urine production may include increased fluid intake before bedtime (Robson, 2001), a blunted response to ADH, increased evening dietary solute load with high nocturnal urine osmolality (Dehoorne et al, 2006), abnormal renal sodium handling (related to release of angiotensin II, aldosterone, and natriuretic peptide), abnormal circadian rhythm of glomerular filtration rate (De Guchteneere et al, 2007), abnormal sodium and calcium excretion (Raes et al, 2006), and obstructive sleep apnea/hypoventilation (Su et al, 2011).

Regardless of the mechanism, urine production that normally decreases at night secondary to these circadian systems fails to do so and will subsequently result in nocturnal polyuria, which can exceed the functional capacity of the bladder and result in an enuretic episode. Proof of this concept was demonstrated by Rasmussen and colleagues (1996), who were able to actually induce enuresis in normal healthy children by increasing nocturnal urine output. Despite this seemingly simple causal relationship, however, it is clear that nocturnal polyuria and ADH responsiveness are highly complex phenomena, because not all children with enuresis have nocturnal polyuria and, in those who do, nocturnal ADH may be normal (Steffens et al, 1993). In fact, it has been observed that the urine osmolality of children with and without MSE is similar and that early morning osmolality tends to increase with age (Kawauchi et al, 1996). This suggests that the ADH secretion response may be a maturational one and lend further support to the maturation hypothesis.

Arousal and Sleep

Regardless of whether the child has detrusor overactivity and/or nocturnal polyuria, neither observation explains why a child with enuresis is unable to awaken from sleep to void before a wetting episode. Given that both bladder distention and detrusor contractions are robust arousal stimuli (Koyama et al, 1998), it is curious that an enuretic child will not wake up during the night to the sensation of a full or contracting bladder. Parents invariably describe their children with enuresis as excessively deep sleepers (Wille, 1994; Nevéus et al, 1999a). This situation is often experienced by family members of patients exposed to alarm therapy as parents awaken from sleep while their enuretic child will sleep through the alarm. Nevéus and colleagues (1999a) obtained questionnaire data from 1413 schoolchildren between the ages of 6 and 10 years and noted that enuresis was associated with subjectively high threshold arousal and significant confusion on awakening from sleep. Wolfish and coworkers (1997) performed a laboratory study of 33 boys aged 7 to 12 years (15 with enuresis and 18 age-matched controls) and found that attempts at arousal were more often successful in control subjects than in boys with enuresis (40% vs. 9%, respectively).

A subjectively deep sleep, however, is not the same as an objectively deep sleep, as measured by EEG. Freitag and associates (2006) studied brainstem evoked potentials in 37 children with MSE and compared these children to 40 age-matched controls. They found

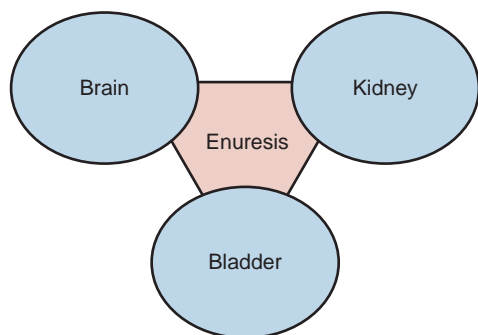


Figure 143-10. Organ system involvement in pathogenesis of enuresis.

Children with enuresis (even those without daytime symptoms) have been noted to have a smaller bladder capacity than age-matched children controls (Starfield, 1967). The reduced bladder capacity appears to be functional rather than anatomic. This was illustrated by a study in which bladder capacity was measured in the awake state as well as under general anesthesia in children with enuresis and compared with functional bladder capacity among controls (Troup et al, 1971). Compared with control children, the average volume of urine voided by enuretic children in the awake state was reduced. However, when volumes were measured during general anesthesia, enuretic children had similar mean bladder volumes to awake controls. In a somewhat contradictory study, Kawauchi and colleagues (2003) found that the maximal endurable bladder capacity during the daytime was similar between children with enuresis and controls. However, among children with enuresis, the maximal voided volume during the night (measured using a diaper and enuresis alarm) was significantly smaller than the maximal daytime bladder capacity. They concluded that inability to hold urine during sleep may be an important factor in MSE. A number of trials have noted functional bladder capacity to be a strong predictor of response to desmopressin in MSE (Rushton et al, 1996; Eller et al, 1998). As a result, a refractory response to desmopressin may suggest either unrecognized nocturnal OAB or that the decreased nocturnal urine production elicited by desmopressin continues to overwhelm a functionally undersized bladder. Whether this situation is a result of reduced nocturnal functional bladder capacity or nocturnal detrusor overactivity, however, may not be critical because the treatment strategy employed would largely be the same (i.e., anticholinergic medications).

that interpeak latencies of the brainstem evoked potentials were increased in children with MSE, suggesting a maturational defect of the brainstem to account for this finding. Other sleep studies, however, show that sleep patterns among children with and without enuresis are similar (Ritvo et al, 1969; Bader et al, 2002). These studies indicate that enuretic episodes may occur at random throughout the night, but primarily during nonrapid eye movement (non-REM) sleep (Nevéus et al, 1999b) and when the bladder is at a volume equivalent to the maximal daytime functional capacity (Mikkelsen et al, 1980; Nørgaard et al, 1989b). A study of 35 children with therapy-resistant MSE in Hong Kong demonstrated that although appearing to be heavy sleepers, these children had, in fact, more overall light sleep (stage I/II non-REM) with sleep fragmentation, rather than deep sleep (stage III/IV non-REM). The cerebral cortex received afferent input of sleep OAB with frequent cortical arousals that failed to wake the children, which was presumed to be a paradoxical elevation in the conscious awakening threshold. OAB-associated cortical arousals may cause a shift from deep to light sleep but not to complete awakening, perhaps because of long-term overstimulation of the sleep arousal center by signals from the bladder. In summary, these studies suggest that children who wet the bed sleep normally (i.e., the distribution and proportion of the various stages of sleep are within normal limits) but are unable to awaken in response to nocturnal detrusor contractions or bladder fullness.

Evaluation

The basic evaluation of the child with MSE includes **history, physical examination, and urinalysis. The history, including a voiding diary, is the mainstay of the evaluation** (Robson, 2009; Nevéus et al, 2010). As previously discussed, the voiding diary is an objective means of documenting the voiding pattern (see section on *Bladder and Bowel Diaries*). This is especially useful when the history is unclear. A voiding diary kept by the parents should help assess the times at which a child voids; the relationship between voiding and common events such as meals, breaks at school, and play activities; the occurrence of urgency or incontinence; and voided volume. **The principal objective of the evaluation is to rule out BBD or enuresis as a manifestation of an underlying medical disease (e.g., posterior urethral valves, spinal dysraphism, diabetes mellitus) and to identify that the enuresis is truly monosymptomatic.** If BBD is present, it should be treated as described previously before initiating therapy for MSE (Franco et al, 2013).

Once MSE is confirmed, it is often helpful to characterize the enuresis further, such as frequency and volume. Distinguishing between primary and secondary MSE should be attempted, mainly for prognostic purposes because treatment is generally the same. One important point to ask about is the presence of nocturia; this would suggest that the child is not extremely difficult to arouse from sleep. The social history is also particularly germane because somatic and psychological comorbid conditions are more common in children who were previously dry than in those with primary MSE (Robson et al, 2005). A family history of enuresis is often helpful in establishing a genetic pattern. Interventions the family has already tried also should be determined.

The physical examination should be focused and is similar in scope to that described in the prior section on LUTD. Briefly, examination should include palpation of the abdomen to screen for constipation, examination of the lower spine for cutaneous stigmata of spinal dysraphism, examination of the genitalia to screen for meatal stenosis, introital erythema or damp/wet underwear, assessment of the sacral reflex arc, and evaluation of the motor strength, tone, reflexes, and sensation in the legs for evidence of a neurogenic bladder.

In terms of laboratory testing, a simple urinalysis should be performed to detect any possible glucosuria, proteinuria, hematuria, pyuria, and/or bacteriuria. Neither radiologic imaging nor urodynamics has a role in the evaluation of MSE. If based on history and physical examination the patient is suspected to have NMSE, we would recommend evaluation following the previously

described protocol for children with LUTD (i.e., pelvic ultrasound and uroflowmetry).

Treatment

Conventional therapies for enuresis include behavioral modification, the enuresis “moisture” alarm, and pharmacologic therapy (e.g., desmopressin, anticholinergics, imipramine). The evidence for the efficacy of much of the care that we provide to children with enuresis is weak (Nevéus et al, 2010). Given the self-limiting nature of enuresis, one treatment option is to observe and allow the natural history to follow its predetermined course. However, enuresis that occurs as infrequently as once per month is associated with reduced self-esteem and treatment has been reported to improve self-worth, regardless of the type or the success of therapy (Hägglöf et al, 1998; Longstaffe et al, 2000).

The decision about when to start treatment generally should be guided by the degree of concern and motivation on the part of the child rather than the parents. For the child, nocturnal enuresis usually becomes significant when it interferes with his or her ability to socialize with peers (e.g., sleepovers, summer camps) (Jalkut et al, 2001). **It is important to determine whether the child is mature enough to assume responsibility for treatment.** Treatment probably should be delayed if it seems that the parents are more interested in treatment than the child and the child is unwilling or unable to assume some responsibility for the treatment program. The child must be highly motivated to participate in a treatment program that may take months to achieve successful results. Although general advice should be given to all bedwetting children, active treatment should usually not be started before 6 years of age (Nevéus et al, 2010). However, age should not be the only criterion for initiation of active treatment.

Behavioral Therapy

Data from randomized trials on the efficacy of behavioral therapy are lacking (Pennesi et al, 2004; Caldwell et al, 2013), but clinical experience (i.e., level 4 evidence) suggests that this approach is beneficial (Nevéus et al, 2010). Likewise, although the influence of the clinician's behavior has not been formally studied, clinical experience suggests that the ability to establish a rapport with the child and to engender and sustain motivation is important for successful behavioral therapy. **The fundamental goal of behavioral therapy is much like the treatment of daytime urinary incontinence and centers around the practice of good bladder and bowel habits.**

Children should attempt to void regularly during the day and just before going to bed for a total of six to seven times daily. High-sugar and caffeine-based drinks should be avoided, particularly in the evening hours. Daily fluid intake should be concentrated in the morning and early afternoon, and both fluid and solute intake should be minimized during the evening. Isolated nighttime fluid restriction, without compensatory increase in daytime fluid consumption, may prevent the child from meeting his or her daily fluid requirement and is usually unsuccessful.

In practice, compliance improves when parents and children understand normal bladder function and the pathogenesis of enuresis. **Children should be reassured that enuresis is not their fault, and children should not be punished for bedwetting, because this practice is often counterproductive** (van Londen et al, 1993). An individualized program with a series of realistic goals between appointments and monthly follow-up to sustain motivation improves the outcome (Glazener and Evans, 2004). A personalized calendar for recording daytime incontinence and enuresis episodes and the frequency and timing of bowel movements aids the family and child to follow their progress.

When initiating active treatment for primary MSE, there is level 1 evidence to support the use of the enuresis alarm (Glazener et al, 2005), **desmopressin** (Glazener and Evans, 2009), **anticholinergics** (Austin et al, 2008), and **tricyclic antidepressants (e.g., imipramine)** (Glazener and Evans, 2000), either alone or in combination. Generally, in addition to behavioral therapy, the two

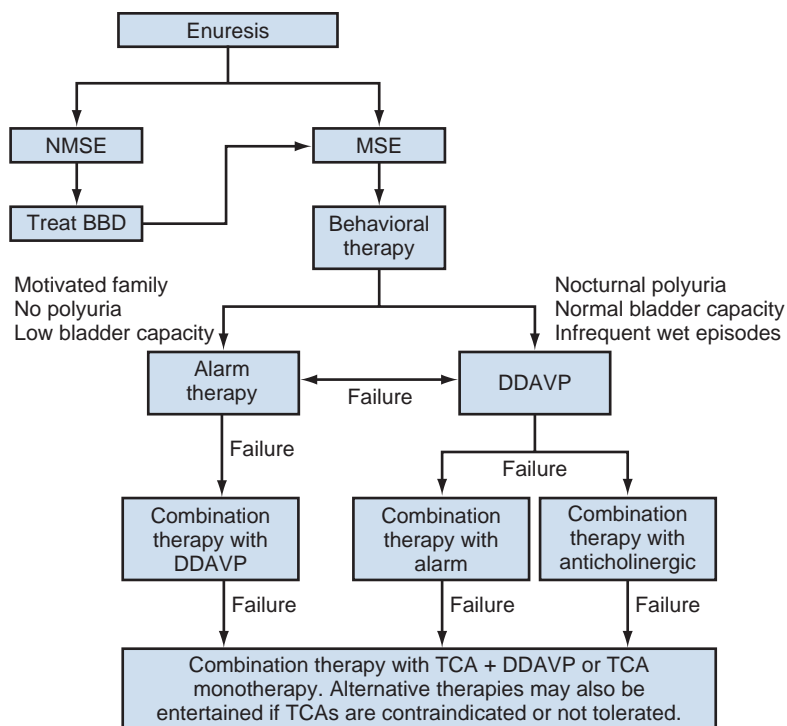


Figure 143-11. Algorithm of the evaluation and treatment of a pediatric patient with enuresis. BBD, bowel-bladder dysfunction; DDAVP, 1-deamino-8-D-arginine vasopressin (desmopressin); MSE, monosymptomatic enuresis; NMSE, nonmonosymptomatic enuresis; TCA, tricyclic antidepressant.

contemporary first-line therapies for MSE include the enuresis alarm and desmopressin. They are both valid treatment options, but patient, caregiver, and disease-related parameters exist that may aid in offering prognostic information in terms of which therapeutic modality should be first entertained (Fig. 143-11). The enuresis alarm seems best fit for motivated families and for children without polyuria but with low voided volume (Nevéus et al, 2010). Desmopressin seems best suited for children with nocturnal polyuria and normal bladder reservoir function (Hunsballe et al, 1998), those with infrequent wet episodes, and for families in whom alarm treatment has failed or who have refused alarm treatment (Nevéus et al, 2010). Children in whom one first-line treatment has failed should be offered the other, and for those in whom both have failed, second- and third-line treatments can be tried, either alone or in combination (e.g., desmopressin plus oxybutynin).

Enuresis Alarm

Alarm training has been shown to be the most effective long-term therapeutic modality in the treatment of MSE (Glazener et al, 2005). Alarms have been used since the 1930s and represent classic pavlovian conditioning techniques, but exactly how the alarm works remains somewhat of a mystery because, strictly speaking, classical conditioning mechanisms should not be functional during sleep. Proposed mechanisms include suppression of bladder emptying during sleep, increasing nocturnal bladder volume (Hansen and Jørgensen, 1997), and waking to void by signaling when they urinate. Interestingly, most children who become dry with the use of the enuresis alarm actually sleep through the night and do not necessarily wake to void. The response is more gradual and sustained than for desmopressin, with approximately two thirds of children becoming dry during active treatment and nearly half remaining dry after treatment completion (Glazener et al, 2005). Enuresis alarms are activated when a sensor, placed in the undergarments or on a bed pad, detects moisture, with both types demon-

strated to be equally effective (Butler and Robinson, 2002). The arousal device is usually an auditory alarm and/or a vibrating belt.

The family should be instructed that the child is in charge of the alarm. After the alarm goes off, only the child should turn off the alarm, get up, and finish voiding in the toilet. We often remind parents that at the initiation of therapy, the child may fail to awaken and that parents should wake the child when the alarm sounds. The child being fully awake and cognizant of what is happening is critical to the success of alarm therapy. The child should then return to the bedroom, change the bedding and underwear, replace the sensor, and reset the alarm before returning to sleep. A diary should be kept of wet and dry nights, with positive reinforcement given for dry nights as well as successful completion of the sequence of events. Approximately 30% of patients discontinue enuresis alarms for various reasons, including skin irritation, disturbance of other family members, and/or failure to wake the child (Schmitt, 1997). Adverse effects of alarms include alarm failure, false alarms, disruption of the lives of other family members, and lack of adherence because of difficulty using the alarm (Glazener et al, 2005).

Alarm treatment should be continued until the child has had a minimum of 14 consecutive dry nights (Nevéus et al, 2010). Children who do not continue to improve after 6 weeks of alarm training are unlikely to become completely dry with this technique (Taylor and Turner, 1975), and alternative interventions may be warranted. Therapy with the alarm can be reinitiated for relapse (more than two wet nights in 2 weeks). Children who relapse after discontinuation of the alarm usually can achieve a rapid secondary response because of preconditioning as a result of the first treatment program (Tuncel et al, 2008). During this refractory treatment period, the chance of long-term cure can be increased by a technique called *overlearning* (Morgan, 1978). In overlearning, additional fluids are given at bedtime while alarm training is continued after dryness has been achieved (Young and Morgan, 1972). In alarm training without overlearning, the child trains to inhibit urination without necessarily learning to wake to void. A systematic review indicated that overlearning trains the child to wake in

response to the sense of a full bladder and reduces relapse when alarm treatment is stopped (Glazener et al, 2005).

Pharmacotherapy

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) is a synthetic analogue of ADH released by the posterior pituitary gland that reduces urine production by increasing water reabsorption by the collecting tubules. DDAVP has been used to treat enuresis for the past 40 years. Desmopressin is fairly easy to administer and its clinical effects appear immediately, with a serum half-life of approximately 2 to 3 hours when taken in oral form (the duration of pharmacodynamic action approximates the average duration of sleep for a child in the age range for elementary school). It is available in the United States in oral (crushable) tablets and in sublingual and intranasal spray formulations. The main safety issue is the risk for water intoxication with resultant hyponatremic seizures should the drug be taken with excessive fluids. This risk seems to be somewhat higher with the intranasal form, which has a prolonged half-life, and thus use of the spray is discouraged (Robson et al, 2007). Treatment should be interrupted during episodes of fluid and/or electrolyte imbalance (e.g., fevers, vomiting or diarrhea, vigorous exercise, or other conditions associated with increased water consumption).

The usual starting dose is 0.2 mg orally 1 hour before bedtime, and the drug can be titrated up incrementally by 0.2 mg to a maximum dose of 0.6 mg at bedtime. Children are instructed to void directly before going to bed. Fluid intake is reduced to a maximum of one 8-oz glass at the time of ingestion, with absolutely no more fluids until morning, decreasing the risk for significant hyponatremia to virtually zero (Glazener and Evans, 2009).

Desmopressin is most efficient in children with nocturnal polyuria (defined by the ICCS as nocturnal urine production >130% of expected bladder capacity for age) and normal bladder reservoir function (maximum voided volume >70% of expected bladder capacity for age) (Rushton et al, 1996; Hunsballe et al, 1998; Austin et al, 2014). There is a wide range of efficacy among studies, most likely because of heterogeneous patient populations (MSE vs. NMSE), differences in concomitant behavioral therapy recommendations, and differences in the dosage or formulation of DDAVP, without taking into account nocturnal urine volume. Overall, approximately 30% of patients achieve total dryness and another 40% exhibit a significant decrease in nighttime wetting (Nevéus et al, 2010). However, the relapse rate after discontinuation is high (60% to 70%) (Wille, 1986). In a systematic review of 47 randomized trials (3448 children), researchers noted that compared with placebo, children treated with desmopressin were more likely to become dry and had a reduction in bedwetting by 1.34 nights per week (Glazener and Evans, 2009). In contrast to the enuresis alarm, however, treatment effects were not sustained after discontinuation of therapy, with a relapse rate of 65% versus 46% with DDAVP versus the alarm, respectively (Glazener and Evans, 2009).

The response to desmopressin should be assessed within 2 weeks (Schmitt, 1997). Treatment should be continued if there is a positive response (e.g., smaller wet patches, fewer wetting episodes). If enuresis improves or remits with desmopressin, the family and child can determine whether to use it every night or just for special occasions (e.g., sleepovers, summer camp). When DDAVP is administered daily, we generally give patients regular scheduled drug holidays of approximately 1 week every 3 to 6 months to assess whether the medication is still needed.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have been demonstrated to decrease the amount of time spent in rapid eye movement (REM) sleep, stimulate ADH secretion, and relax the detrusor muscle via weak anticholinergic properties. Its antienuretic effect has been theorized

to be less likely because of its action at the kidney or bladder level and more likely a result of noradrenergic stimulation at the brainstem, specifically the locus coeruleus (Gepertz and Nevéus, 2004). Given the efficacy and safety of enuresis alarms and DDAVP, TCAs (e.g., imipramine, amitriptyline, and desipramine) are considered a third-line treatment for therapy-resistant MSE (Nevéus et al, 2010).

Level 1 evidence demonstrates that compared to placebo, TCAs are more effective at reducing the number of wet nights and at achieving 14 consecutive dry nights (i.e., cure) but essentially become ineffective once treatment is discontinued.

Please see the Expert Consult website for further details.

Although other TCAs are effective, imipramine is used most often in the treatment of enuresis. Imipramine is available in 10-, 25-, and 50-mg tablets. The initial dose is 10 to 25 mg 1 hour before bedtime; it may be increased by 25 mg if there is no response after 1 week (Schmitt, 1997). On average, the bedtime dose is 25 mg for children 5 to 8 years of age and 50 mg for older children. The dose should not exceed 50 mg in children between 6 and 12 years of age and 75 mg in children older than 12 years of age (Glazener and Evans, 2000).

The response to imipramine should be assessed after 1 month. If there is no improvement after 3 months, it should be discontinued as a gradual taper (as is done with other TCAs). As is the case with other pharmacotherapy for enuresis, we give patients a drug holiday every 3 to 6 months, gradually tapering the dose over a 2-week period (Gepertz and Nevéus, 2004).

Adverse effects of TCA therapy are relatively uncommon. Approximately 5% of children treated with TCAs develop neurologic symptoms, including nervousness, personality change, and disordered sleep. TCAs (as with other antidepressants) are required by the FDA to carry a black box warning regarding the possibility of increased suicidality, particularly in individuals with preexisting depressive symptoms. The most serious adverse effects of TCAs involve the cardiovascular system: cardiac conduction disturbances and myocardial depression, particularly in cases of overdose (Swanson et al, 1997). Before initiation of therapy with a TCA, a thorough cardiac history (e.g., palpitations, syncope) and family cardiac history (e.g., arrhythmias, sudden cardiac death) should be obtained with a baseline electrocardiogram to rule out a prolonged QT interval if history or physical examination raises suspicion.

Anticholinergics

Monotherapy with anticholinergic drugs, such as oxybutynin or tolterodine, has been demonstrated not to be effective as a first line of treatment for MSE (Lovering et al, 1988; Persson-Jünemann et al, 1993). Although evidence of efficacy from randomized trials is lacking, uncontrolled studies do show improvement in some children with NMSE, presumably because many of these children have a reduced functional bladder capacity (Caione et al, 1997; Nevéus, 2001). There is also some evidence that nocturnal detrusor overactivity (especially without nocturnal polyuria) plays a role in the pathogenesis of enuresis and therefore makes anticholinergics an attractive pharmacotherapeutic option (Nevéus, 2001).

Where anticholinergics clearly do have a role is combination therapy in the treatment of children who are refractory to DDAVP monotherapy. In the first randomized, placebo controlled study of combination therapy with anticholinergics, Austin and colleagues (2008) studied 34 children with primary MSE who failed maximal-dose DDAVP monotherapy and assigned them, in a double-blind manner, to receive either extended-release tolterodine or placebo while all children continued to take DDAVP. Patients were reassessed after 1 month of therapy with a 1-week nocturnal record. They found a significant reduction in the mean number of wet nights in the combination therapy group compared to the placebo group. With a generalized estimating equation approach, there was a significant 66% reduction in the risk for a wet episode compared with the placebo group. Recently, Montaldo and associates (2012) reported their results in 206 children with MSE refractory to DDAVP monotherapy who were randomized to 5 mg of oxybutynin or placebo and followed for 1 month. As predictive factors, bladder

In a recent systematic review, treatment with TCAs was associated with a reduction of approximately one wet night per week compared to placebo ([Glazener and Evans, 2000](#)). Approximately 20% of children became dry during therapy versus 5% with placebo. The rate of relapse was 96% after discontinuation of therapy. In an observational study of children who were refractory to first-line therapy, researchers found that approximately one third of children became dry on monotherapy, one third became dry after adding DDAVP, and the remaining third were nonresponders ([Gepertz and Nevéus, 2004](#)).

volume and wall thickness index, nocturnal polyuria, and voiding latency were considered. Corroborating the original study by Austin and associates, the oxybutynin group showed a higher rate of full and partial responses than the placebo group. The responders to combined oxybutynin and desmopressin had a significantly lower bladder volume and wall thickness index than nonresponders.

Combination Therapy

The efficacy of the enuresis alarm plus desmopressin combination has been investigated in a number of studies (Sukhai et al, 1989; Bradbury, 1997; Leebeek-Groenewegen et al, 2001; Fai-Ngo et al, 2005).



Please see the Expert Consult website for further details.

A reduction in the number of wet nights is consistently observed when using combination therapy of desmopressin and the moisture alarm compared to monotherapy. Enuresis relapse, however, is noted in some patients with long-term follow-up.

Alternative Therapies

Other drugs, including indomethacin, ephedrine, atropine, furosemide, and diclofenac, have been tried in the treatment of enuresis. A recent systematic review of randomized trials of drugs other than TCAs and DDAVP found that although indomethacin, diclofenac, and diazepam were better than placebo in reducing the number of wet nights, none of the drugs was better than desmopressin (Deshpande et al, 2012). A second recent review of complementary approaches such as hypnosis, psychotherapy, and acupuncture found limited evidence from small trials with methodologic limitations to support the use of such modalities for the treatment of enuresis (Huang et al, 2011).

KEY POINTS: ENURESIS

- The majority of children who present with enuresis have the nonmonosymptomatic form.
- The spontaneous resolution rate of enuresis is approximately 15% annually, such that only approximately 1% of teenagers will continue to be afflicted.
- Enuresis stems from a maturational delay in the ultimate development of bladder control, with three organ systems implicated in its pathogenesis: the bladder, the kidney, and the brain.
- The basic evaluation of the child with MSE includes history (including a voiding diary), physical examination, and urinalysis. The principal objective of the evaluation is to rule out BBD or enuresis as a manifestation of an underlying medical disease (e.g., posterior urethral valves, spinal dysraphism, diabetes mellitus) and to identify that the enuresis is truly monosymptomatic.
- Conventional therapies for enuresis include behavioral modification, the enuresis moisture alarm, and pharmacologic therapy (e.g., desmopressin, anticholinergics, imipramine).

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The complete reference list is available online at www.expertconsult.com.



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Sukhai and colleagues (1989) reported a crossover trial of 28 children with primary MSE who were blindly allocated at random to a combination of enuresis alarm plus 20 µg intranasal DDAVP or alarm plus placebo for 2 weeks. Patients received the other therapy after a 2-week treatment-free period. The combined treatment of desmopressin plus enuresis alarm resulted in significantly more dry nights per week during the 2 weeks of observation than placebo plus the alarm. Although there was a significant difference between groups, the treatment period of 2 weeks was most likely too short for alarm therapy to contribute significantly to the outcome variable.

Bradbury compared the efficacy of enuresis alarm monotherapy to alarm treatment in combination with 40 µg DDAVP nasal spray (Bradbury, 1997). At the end of the treatment period, children receiving combination therapy had more dry nights per week (mean: 6.1) than children using an alarm alone (mean: 4.8). In addition, more children achieved an initial success (4 weeks of dryness) after combination treatment (27 children [75%]) compared with alarm monotherapy (16 children [46%]). Interestingly, this improvement was most pronounced in children with severe wetting (>5 nights per week), family problems, or behavioral problems.

In a placebo-controlled study containing 93 patients with MSE, Leebeek-Groenewegen and colleagues (2001) compared 9 weeks of desmopressin plus alarm therapy with alarm monotherapy. They showed a significant decrease in the number of wet nights per week with combination therapy. After 6 months of follow-up, however, they reported that there was no significant difference between the two treatment groups regarding the efficacy and number of children who relapsed.

In a recent multicenter randomized controlled trial, Fai-Ngo et al (2005) compared the efficacy of the enuresis alarm, oral DDAVP, and combined treatment in children with primary MSE. They assigned 105 children equally among groups to receive treatment for 12 weeks, and patients were then followed for 12 weeks after treatment. They found that the mean number of wet nights per week was significantly lower in the combination group than in the other groups at the conclusion of therapy. Desmopressin produced an immediate effect but relapses were most common in the DDAVP monotherapy and combination therapy groups (60% and 40%, respectively). Alarms took several weeks to produce a benefit, but this was sustained on follow-up (20% relapse rate).

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Epidemiology and Classification of Disorders of Defecation

Normal versus Abnormal Bowel Function

Evaluation of Abnormalities of Defecation

Imaging Studies

Management

Prognosis

Surgical Management

At first glance, a bowel management chapter may appear out of place in a textbook discussing urology. However, clinical experience has called attention to a deep interrelation between urinary and bowel function. Indeed the past decade has witnessed a greater understanding of the pelvic floor, seeing it as working as a functional unit blending the artificial barriers set by specialty training. The lower gastrointestinal and genitourinary tracts share embryological origin, anatomic location, innervation (both motor and sensory), volitional control with normal development, and sphincteric mechanisms. On clinical grounds this is evidenced during careful history and examination, with frequent dual dysfunction in neurologic conditions (neuropathic bladder and bowel in disease processes of the lower spinal cord), bladder capacity compromise resulting from a distended rectum (Fig. 144-1), and dysfunctional elimination rarely affecting only one system (instead often seeing concurrent urinary and bowel symptomatology in affected children). Thus understanding of urinary tract dysfunction is incomplete without taking into account and addressing all aspects of elimination, including defecation.

Anomalies of the bowel and urinary tract frequently coexist, whether functional, anatomic, and/or neuropathic. Constipation and rectal distention might adversely impact bladder function (Burgers et al, 2010), leading to low functional bladder capacity, incontinence, and predisposition for urinary tract infections, and constipation and rectal distention might also trigger or exacerbate vesicoureteral reflux (Fig. 144-2 on the Expert Consult website) (Yazbeck et al, 1987, Loening-Baucke, 1997). In addition, constipation is a common side effect of medications used to manage lower urinary tract symptoms (anticholinergics). Because of this common association, pediatric urologists during the past few decades have become comfortable with assessing and managing bowel problems in the everyday care of children and adolescents who have genitourinary complaints. In particular, contemporary management of children with dysfunctional elimination calls for routine simultaneous assessment of the gastrointestinal and genitourinary tract. Good understanding of both medical and surgical options is also warranted, as it is often the urologist who is in position to manage both urinary and fecal problems synchronously (Burgers et al, 2013).

EPIDEMIOLOGY AND CLASSIFICATION OF DISORDERS OF DEFECATION

Defecation disorders are common throughout life, and childhood is not an exception. In children, these are most often manifested

KEY POINTS: INTRODUCTION

- The bladder is not an isolated organ. On the contrary, it works in close functional and anatomic relationship with surrounding structures, including the lower gastrointestinal tract.
- Constipation is common yet hard to ascertain just by asking children or parents.
- Neurologic problems can affect both systems, as evident in patients with neuropathic bladder dysfunction.
- Medications commonly used for bladder management have an adverse impact on bowel function (most notably anticholinergics).
- Based on the referral pattern, pediatric urologists are in a privileged position to address bowel function effectively and to produce a positive impact on the child's well-being and quality of life.

as infrequent bowel movements without a specific underlying organic etiology; thus these are labeled as “functional” constipation. Reported prevalence in the pediatric population ranges between 0.7% and 29.6%, with no significant difference in rates for boys and girls (van den Berg et al, 2006). This condition is a frequent reason for evaluation by family medicine health care providers, pediatricians, pediatric gastroenterologists, pediatric surgeons, and—because of associated lower urinary tract symptoms—pediatric urologists. Common presenting symptomatology includes infrequent defecation, abdominal bloating or distention, painful bowel movements, abdominal pain, and fecal incontinence (Nurko and Scott, 2011). Although there are multiple potential etiologies (Box 144-1), most children have a negative assessment for associated conditions. Nevertheless, concerns regarding an organic cause often trigger an overtly extensive, occasionally invasive, and expensive workup. In essence, functional constipation is a diagnosis of exclusion, defined as a defecation disorder not associated with congenital or acquired abnormalities or specific medications.

Of all the functional gastrointestinal disorders of childhood—irritable bowel syndrome (IBS), functional bloating, functional constipation, and functional diarrhea (Longstreth et al, 2006)—constipation is the condition most frequently encountered by pediatric urologists, and this demands expertise in management along with ruling out other pathologies that require specialized assessment and treatment. Thus modern management in specialized centers should include health care providers who are comfortable with addressing common elimination disorders.

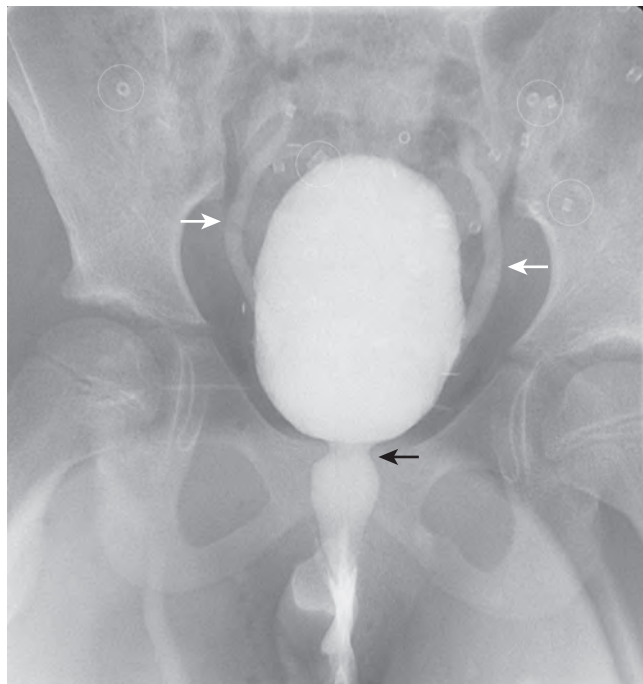


Figure 144-2. Voiding cystourethrogram in a patient with dysfunctional elimination and recurrent episodes of pyelonephritis. Note the presence of bilateral vesicoureteral reflux (*white arrows*) and “spinning top” deformity of the bladder neck during voiding (*black arrow*). Patient previously underwent a motility study because of persistent constipation despite stool softeners (note encircled radiopaque markers).

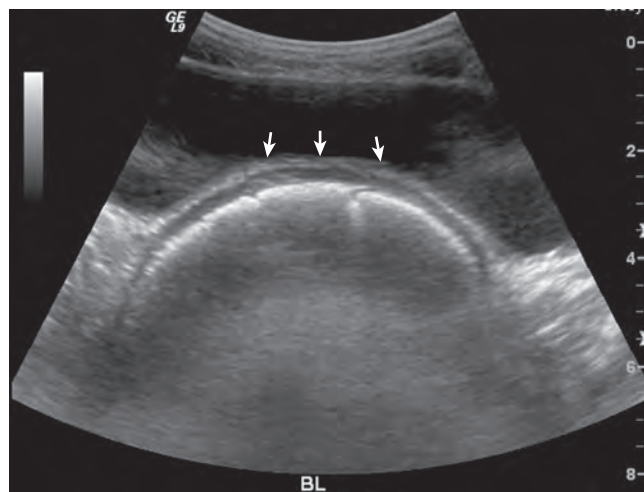


Figure 144-1. Pelvic ultrasound demonstrates anterior displacement of the bladder wall with decrease in functional bladder capacity as a result of a large amount of fecal material in the rectum (arrows).

BOX 144-1 Differential Diagnosis of Chronic Constipation

- Idiopathic or functional
- Behavioral: Dysfunctional elimination resulting from defecation avoidance, intellectual disability, psychological problems, adverse life event(s)
- Poor dietary habits: Low fluid and fiber intake
- Structural defects: Anorectal malformation, anal stenosis, Hirschsprung disease, extrinsic compression by pelvic mass, deficient abdominal musculature (most notably, prune-belly syndrome)
- Neurologic disorders: Isolated to spinal cord (myelomeningocele, tethered cord, trauma, transverse myelitis, postsurgical, tumors), cerebral palsy, muscular dystrophy, neurodegenerative disorders
- Endocrine disorders associated with chronic dehydration (such as diabetes insipidus) and electrolyte disorders (most notably hypercalcemia and hypokalemia), hypothyroidism, hypervitaminosis D
- Cystic fibrosis
- Celiac disease
- Connective tissue disorders (such as Ehlers-Danlos syndrome)
- Food intolerance (cow's milk) and other food allergies
- Medications: Anticholinergics, opioid analgesics, anticonvulsants, antidepressants and antipsychotics, iron and calcium supplements, antispasmodics, diuretics
- Other bowel motility disorders: Colonic dysmotility, chronic pseudo-obstruction

NORMAL VERSUS ABNORMAL BOWEL FUNCTION

The definition of normal bowel function has to be framed within the context of age, developmental issues, and cultural expectations. Although seemingly simple, normal bowel function is often difficult to define and ascertain. There is expected variation in toilet-training age; nevertheless, children are generally expected to begin to experiment at age 2 and to gain control of the defecation process completely by age 3 (Wald et al, 2009). After this age, frequency varies from three stools per week to three stools per day (under normal circumstances), with the majority of normal children 5 to 8 years of

BOX 144-2 Rome III Diagnostic Criteria for Functional Constipation

In the absence of organic pathology, ≥ 2 of the following must occur:

- A. For a child with a developmental age <4 yr (Criteria fulfilled for at least 1 mo)
 1. ≤ 2 defecations per wk
 2. At least 1 episode of incontinence per wk after the acquisition of toileting skills
 3. History of excessive stool retention
 4. History of painful or hard bowel movements
 5. Presence of a large fecal mass in the rectum
 6. History of large-diameter stools that may obstruct the toilet

Accompanying symptoms may include irritability, decreased appetite, and/or early satiety, which may disappear immediately following passage of a large stool.
- B. For a child with a developmental age ≥ 4 yr with insufficient criteria for irritable bowel syndrome (Criteria fulfilled at least once per wk for at least 2 mo before diagnosis)
 1. ≤ 2 defecations in the toilet per wk
 2. At least 1 episode of fecal incontinence per wk
 3. History of retentive posturing or excessive volitional stool retention
 4. History of painful or hard bowel movements
 5. Presence of a large fecal mass in the rectum
 6. History of large-diameter stools that may obstruct the toilet

age having a bowel movement daily or every other day without straining or withholding (Fontana et al, 1989; Wald et al, 2009). Unfortunately, children with irregular, incomplete, and/or infrequent defecation may not report symptoms; parents are often surprisingly unaware of their child's bowel routine. To aid with assessment, the presence of constipation should be ascertained with standardized diagnostic tools such as the Rome III criteria (Box 144-2) (Hyman et al, 2006; Rasquin et al, 2006). These criteria take into account three important considerations: absence of an organic underlying cause, developmental age, and duration of symptoms.

EVALUATION OF ABNORMALITIES OF DEFECATION

A good history and physical examination are the cornerstones of evaluation and they may suffice for the diagnosis and initial management of most children. A detailed previous medical history is clearly relevant. Critical information to actively gather includes age of onset of symptoms, failure to toilet-train within an age-appropriate and developmental timeframe, frequency of bowel movements, stool consistency (assessed by appearance and preferably recorded with existing stool scales, such as the Bristol Stool Form scale [Lewis and Heaton, 1997; Longstreth et al, 2006] [Fig. 144-3] or the scale's pediatric modifications [Chumpitazi et al, 2010; Lane et al, 2011]), pain with defecation, bleeding per rectum, presence and characteristics of associated abdominal pain, fecal incontinence, holding behaviors, dietary history, changes in appetite, nausea or vomiting, weight loss, growth pattern (including height and weight), developmental delay, and failure to thrive. The age of onset of symptoms is one of the easiest and most important pieces of information to obtain, as it can be an important indicator for underlying pathology (Box 144-3). A detailed previous surgical history is also of great value, and attention should be paid to previous correction of anorectal malformations, resection of sacrococcygeal teratomas or other pelvic tumors, closure of spinal dysraphism, spinal cord untethering, and genitourinary reconstruction for conditions such as prune-belly syndrome.








Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely liquid

Figure 144-3. The Bristol Stool Form scale.

BOX 144-3 Warning Signs and Symptoms

- Constipation, fecal impaction that predates bowel training, particularly in the first year of life*
- Chronic or recurrent respiratory problems†
- Need for medications or rectal stimulation in the first year of life, particularly breast-fed infants
- Bloody stools
- Alternating constipation and diarrhea
- Severe or constant abdominal pain
- History of bowel obstruction
- Associated weight loss, growth retardation, failure to thrive‡
- Hypotonia, developmental delay§
- Decreased appetite, early satiety
- Bilious vomiting
- Ribbon-like stools
- Fecal and urinary incontinence beyond age of toilet training
- Associated neurologic symptoms, particularly in the lower extremities (weakness, gait abnormalities, muscle atrophy, sensory abnormalities)
- Lower back abnormalities (sacral dimple, lipoma, hair tuft, gluteal cleft deviation)
- Explosive stool and air from rectum after stimulation (digital, suppository) or following rectal examination

*Onset of symptoms in infants younger than 1 month old or delayed passage of meconium by 48 hours in a term neonate should raise suspicion for an organic condition, specifically Hirschsprung disease (Ghosh and Griffiths, 1998), and ruling out the diagnosis with a rectal biopsy should be considered.

†Suspect cystic fibrosis.

‡Suspect celiac disease, hypothyroidism, and Hirschsprung disease.

§Associated with hypothyroidism and trisomy 21.

Critical components of physical examination include appearance of the perianal region and perineum, abdominal examination (including presence of palpable masses, muscle tone, distention, pain on examination), presence of a cremasteric and anal reflex, gluteal cleft and sacral region assessment (for hair tufts, deviated gluteal cleft [Fig. 144-4 on the Expert Consult website], sacral dimples [Fig. 144-5 on the Expert Consult website], flat buttocks [Fig. 144-6 on the Expert Consult website]), and lower extremity examination (weakness, coordination, muscle atrophy, decreased muscle strength, abnormal deep tendon reflexes, gait abnormalities). Although prune-belly syndrome is often an obvious diagnosis on physical examination, the presence of cryptorchidism (or previous bilateral orchidopexies for intra-abdominal gonads), lax abdominal wall, and lower urinary tract problems should raise concern for prune-belly syndrome, and abdominoplasty should be assessed appropriately and considered as a means for addressing the difficulty in generating increased intra-abdominal pressure for defecation.

Physical examination should also include weight and height (parameters graphed against normal growth curves) and inspection of the anal region (anal position, stool present around the anus or on the underwear, signs of trauma, anal fissures, sensation). Although potentially considered an integral part of a complete physical examination, digital rectal examination should not routinely be conducted in children. It is reserved for difficult-to-treat cases and should be performed by health care professionals comfortable with interpreting features of anorectal anatomic abnormalities (Mugie et al, 2011) to evaluate specifically for anal stenosis, a large fecal mass, or an empty rectum. Extreme fear during anal inspection, fissures, or signs of trauma should raise suspicion for sexual abuse.

Assessment of patients with functional constipation should be reassuringly normal. The expected findings are those of a generally well-appearing child, with weight and height within normal limits, normal appearance of anus and surrounding area, a soft abdomen (occasionally distended or with a palpable fecal mass in the left lower abdominal quadrant), normal appearance of the skin and anatomic structures of lumbosacral/gluteal regions, normal gait, normal tone strength, and normal lower limb reflexes. In addition, these patients should not exhibit clinical manifestations until at least a few months of life, having a history of normal passage of meconium (within the first 24 to 48 hours after birth). Presentation will sometimes coincide or worsen with precipitating factors, such as change in diet (e.g., transitioning out of breastfeeding), new medications (such as anticholinergics for management of urinary frequency), or psychosocial stressors (i.e., moving, starting or changing school, parents separating, new sibling, major illness in family, travel).

Aside from abnormalities on physical examination, based on history and ancillary tests there are selected children who should undergo a specific workup for organic conditions that manifest themselves or are associated with elimination problems. These include cystic fibrosis, hypothyroidism, celiac disease, dietary allergies, Hirschsprung disease or colonic aganglionosis, anal stenosis, and trisomy 21. Laboratory evaluation in refractory cases or in cases with associated worrisome findings includes celiac screening and thyroid function tests (TSH, T₄). In older children and teenagers, other conditions should be added to the differential, such as mental health issues (depression), eating disorders, sexual abuse, and IBS (Longstreth et al, 2006). IBS, a functional bowel disorder, presents with abdominal pain associated with defecation or a change in bowel habits, and diagnosis depends on key temporal relationships: recurrent abdominal discomfort for at least 3 days per month in the last 3 months that is associated with improvement with defecation, and onset or worsening with a change in frequency or stool form (appearance).

IMAGING STUDIES

Although of modest clinical value, along with exposure to a very low dose of radiation, abdominal radiographs are commonly used



Figure 144-4. Deviated gluteal cleft in a child with neuropathic bladder and bowel dysfunction secondary to cord tethering and occult dysraphism.



Figure 144-5. Sacral dimple (*arrow*).

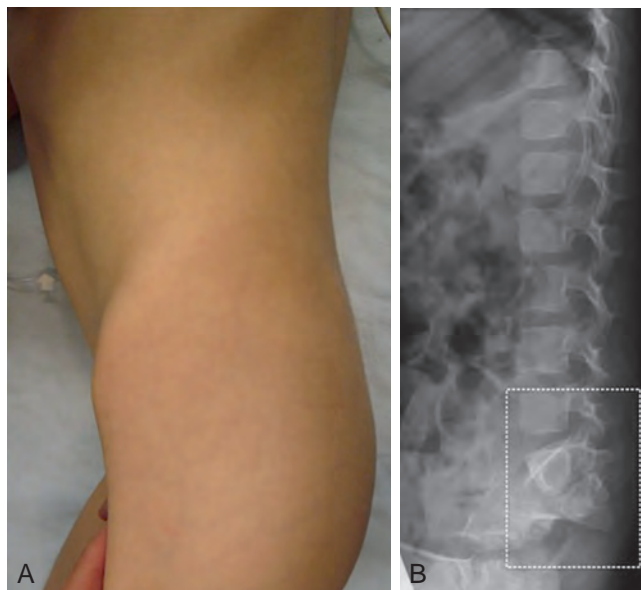


Figure 144-6. Sacral agenesis. A, Findings on physical examination, including a “flat” appearance of the buttocks, associated with neuropathic bladder and bowel. B, Lateral-view lumbosacral radiograph with bony defects of the lower spine consistent with sacral agenesis (or caudal regression syndrome).



Figure 144-7. Abdominal radiograph demonstrating fecal loading throughout the colon (asterisks) in a child, resulting in abdominal distention, encopresis, and urinary frequency.



Figure 144-8. Abdominal radiograph with evidence of fecal impaction (asterisks) in a child who presented with acute urinary retention (note placement of suprapubic tube for bladder management).

in the diagnosis and management of defecation disorders, particularly constipation. The sensitivity and specificity of abdominal radiography in diagnosing childhood constipation is far from optimal, ranging from 60% to 80% and 40% to 90%, respectively (Reuchlin-Vroklage et al, 2005; Mugie et al, 2011). The test is clearly subjective to interpretation, and findings depend on the time since the child's last evacuation. Nevertheless, scales have been devised to help standardize evaluations, based on estimated bowel dilation, as well as the pattern, amount, and distribution of feces in the colon, and these scales provide scores that can be useful for diagnosis, monitoring, and research (Barr et al, 1979; Blethyn et al, 1995; Leech et al, 1999; van den Bosch et al, 2006). Proponents who favor routine radiologic assessment argue that the study can demonstrate clearly the amount of fecal loading, can delineate stool distribution throughout the colon and rectum (Fig. 144-7), as well as can help ascertain the presence of fecal impaction (which includes important therapeutic implications) (Fig. 144-8). In addition, it may also show associated pathologies, such as bony abnormalities indicative of occult spinal dysraphism or sacral agenesis (Fig. 144-9 on the Expert Consult website), and might help provide a visual aid for family and patient recognition of stool retention despite a history of regular defecation. In turn, this can be useful to maximize adherence to treatment in cases where there is disagreement or disbelief regarding the presence of constipation (particularly if patient is consulting solely for lower urinary tract symptoms or urinary tract infections). Serial examinations may also provide an objective means to monitor response to disimpaction and/or maintenance treatment (taking "as low as reasonably achievable" radiation exposure principle into account), although many would contend that the consideration of symptomatic improvement alone is sufficient. In some circumstances, the study can be replaced or enhanced by conducting ultrasound evaluation of the lower abdomen and pelvis, which assesses fecal loading behind the bladder as an alternative or adjunct marker for constipation (Klijn et al, 2004; Joensson et al, 2008) (Fig. 144-10). Ultimately, if constipation and fecal impaction or loading is obvious on history and

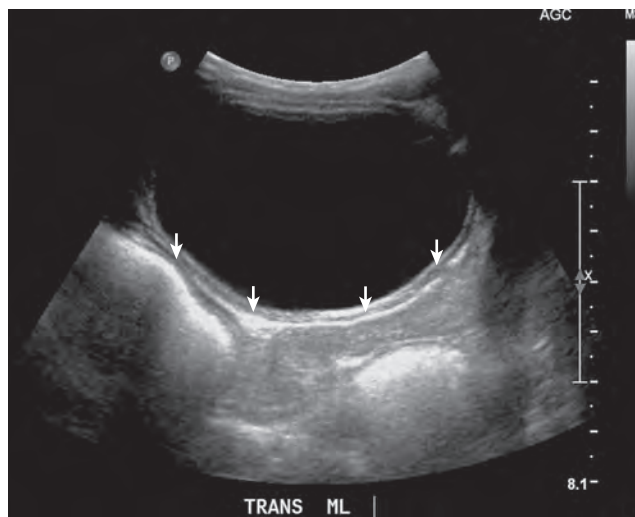


Figure 144-10. Assessment of fecal load in rectum during pelvic ultrasound. Stool is seen behind the bladder (arrows). Note bladder distention caused by incomplete emptying and infrequent voiding resulting from toilet avoidance secondary to pain with defecation.

physical examination, management based on clinical grounds without imaging studies is reasonable and is recommended in routine practice (Tabbers et al, 2014).

Colonic transit time studies, which evaluate the progression of radiopaque markers along the gastrointestinal tract with serial radiographs, are not recommended for routine diagnosis of functional constipation. However, in difficult-to-treat or unresponsive cases this study may have some value, as a normal evaluation in the setting of fecal incontinence would suggest either nonretentive

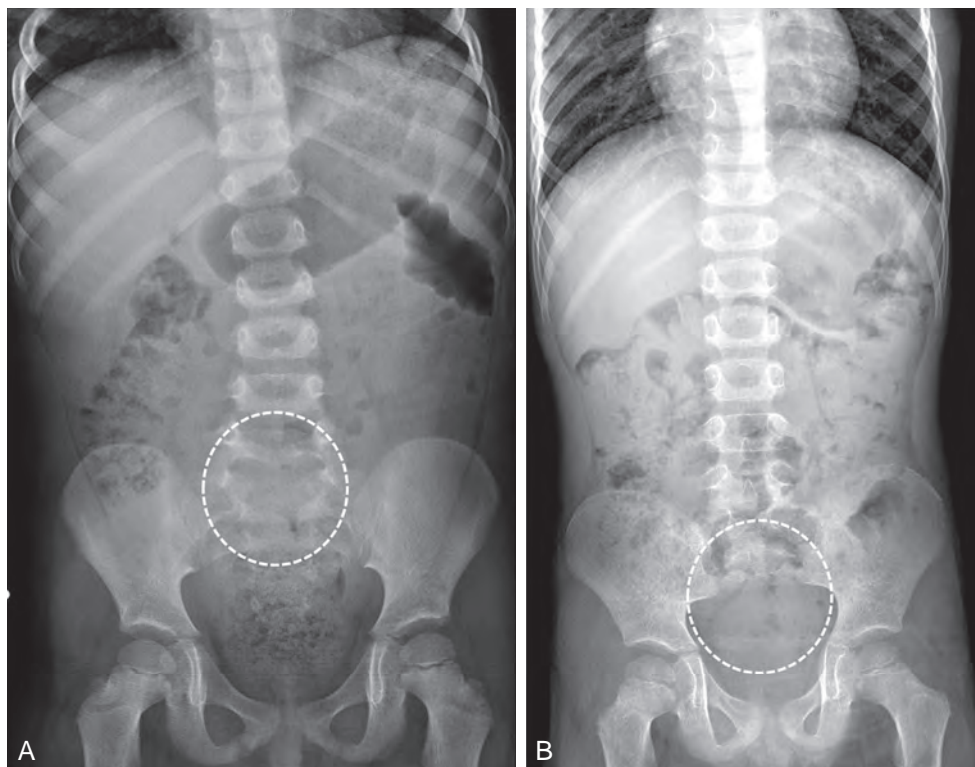


Figure 144-9. Bony abnormalities detected on abdominal radiograph during assessment of difficult-to-treat constipation. **A,** Lumbar bony defects consistent with occult spinal dysraphism. **B,** Absent sacrum, suggestive of sacral agenesis.

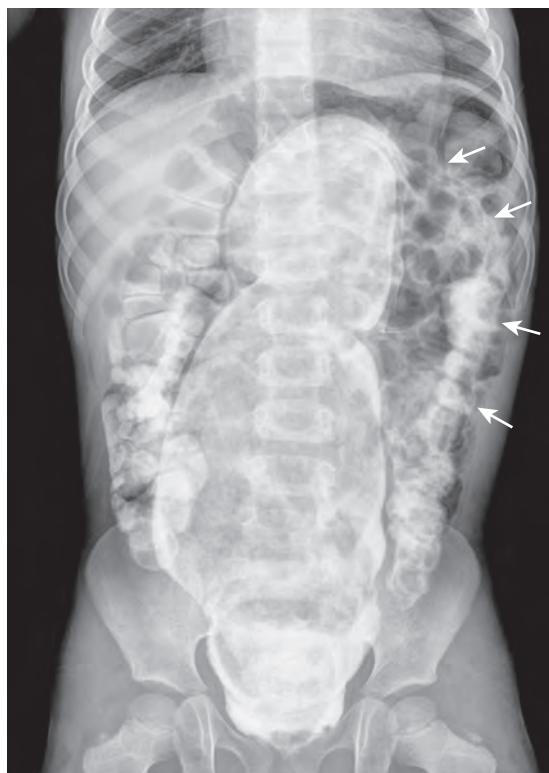


Figure 144-11. Soluble contrast enema for evaluation of child with defecation problems since birth. Findings suggestive of Hirschsprung disease, including massively distended colon and rectum that can progress toward more normal-appearing large bowel (arrows). This child was subsequently assessed with a rectal biopsy to confirm the diagnosis.

defecation disorder or an unreliable medical history. Additional studies are selectively obtained based on suspicion for an underlying condition. A contrast enema series can be of value in evaluating children with characteristics suggestive of Hirschsprung disease (Reid et al, 2000; Langer, 2013) (Fig. 144-11) and repaired congenital anatomic abnormalities (i.e., anorectal malformation); concern for a neuropathic process and/or lower spine stigmata should be evaluated with a spine ultrasound (if detected before calcification of the vertebral bodies in the first 3 to 6 months of life) (Fig. 144-12 on the Expert Consult website) or lumbosacral magnetic resonance imaging in older children (Fig. 144-13 on the Expert Consult website), and suspicion for sacral agenesis should be further assessed with a lateral-view lower spine/pelvis radiograph (see Fig. 144-6 on the Expert Consult website).

If Hirschsprung disease or colon aganglionosis is suspected, a deep suction biopsy (including submucosal) should be obtained (Langer, 2013), favoring a transanal approach and aiming at a location 2 to 3 cm from the dentate line. Diagnosis is supported by the absence of ganglion cells, by hypertrophied nerve fibers, and by an increase in acetylcholinesterase activity in the lamina propria and muscularis mucosa. Anorectal manometry is useful only in selected cases (Noviello et al, 2009), such as suspected Hirschsprung disease and internal sphincter achalasia. In these conditions, the rectoanal relaxation reflex is absent. Nevertheless, in patients suspected of having functional constipation, manometry adds little to the diagnosis or therapeutic strategy (van Ginkel et al, 2001).

MANAGEMENT

As is the case with many other conditions, careful thought and consideration must be first directed toward more conservative, non-operative management alternatives (Fig. 144-14). A medical plan,

KEY POINTS: EPIDEMIOLOGY AND CLASSIFICATION OF DISORDERS OF DEFECATION

- The Rome III criteria are recommended for diagnosis of functional constipation in children.
- The diagnosis of functional constipation should be mostly based on a good medical history and physical examination.
- The presence of alarm signs or symptoms or intractable constipation should trigger a focused assessment to diagnose underlying medical conditions.
- Routine use of abdominal radiographs is of limited value and should be reserved for selected cases, such as suspected fecal impaction and difficult or unreliable history and physical examination.

consisting of behavioral interventions, dietary changes, stool softeners and laxatives, and judicious use of retrograde enemas, is often sufficient to manage most patients with chronic constipation. In addition, education about defecation and demystification of toilet training (in children with a developmental age of at least 4 years) are crucial, and these are often overlooked as components of successful management (van der Plas et al, 1997). Clearly, whether a functional problem or a problem associated with an organic underpinning—especially considering the spectrum of associated urologic disorders—an individualized approach to patients is preferred.

Treatment of constipation is often started within the context of lower urinary tract symptoms. The association between the two has gained acceptance, and simultaneous assessment is part of the comprehensive evaluation offered in many pediatric urology practices, often run by nurse practitioners and other health care providers. The concept's popularity is based on data from a landmark study by Loening-Baucke (1997), who reported on 234 consecutive patients with constipation and encopresis and associated urinary incontinence and urinary tract infections. Successful relief of constipation in 52% of patients was associated with the resolution of daytime urinary incontinence in 89%, the resolution of nocturnal enuresis in 63%, and a resolution of infections. Although supported by experience and other subsequent case series—demonstrating improvement in incontinence episodes, voided volume, and post-void residuals (Erickson et al, 2003)—the value of the universal use of laxatives in children presenting for treatment of overactive bladder symptoms has been called into question in a randomized control trial (Bush et al, 2013). Nevertheless, if constipation is suspected, treatment should be recommended, as highlighted by the Standardization Committee of the International Children's Continence Society (Burgers et al, 2013).

Nonpharmacologic Interventions

If screening and imaging studies are negative, thus restricting the diagnosis to a functional elimination problem and/or slow colonic transit time, medical management follows a stepwise process that begins with medical therapy coupled with behavioral modifications; this process includes adequate fluid and fiber intake, regular defecation, scheduled postmeal attempts to take advantage of an increase in colon motility in response to gastric distention and the digestive process (so-called gastrocolic reflex), relaxation techniques and proper positioning in the toilet (with good foot support and forward leaning to flex thighs closer to the abdomen and to generate better an increase in abdominal pressure). Obviously, in cases where an underlying organic etiology is suspected, specific therapy should be sought following a directed workup.

Behavioral and dietary recommendations are often implemented first and may suffice as a stand-alone strategy or as an adjunct to medical or surgical interventions. The impact of these is difficult to measure because of wide differences in the protocols used, a high placebo response rate in some subgroups (Bush et al, 2013),

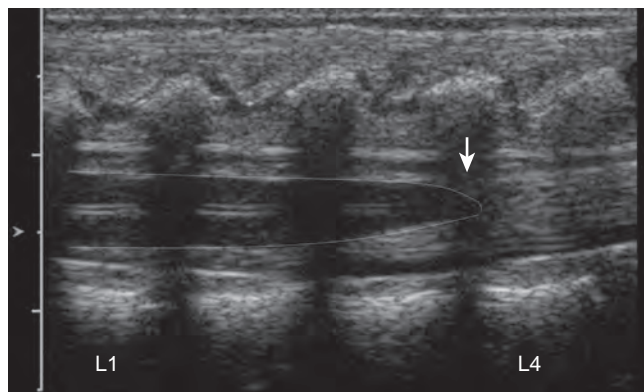


Figure 144-12. Spine ultrasound performed in a child with a sacral dimple, demonstrating a low-lying conus (at L4 level) (*arrow*). Note shadow by bony component of vertebral bodies.



Figure 144-13. Magnetic resonance imaging of lumbosacral region in a child with abnormal lower back examination during initial assessment of constipation and urinary frequency. Note presence of lipoma extending into the spinal canal (*arrows*).

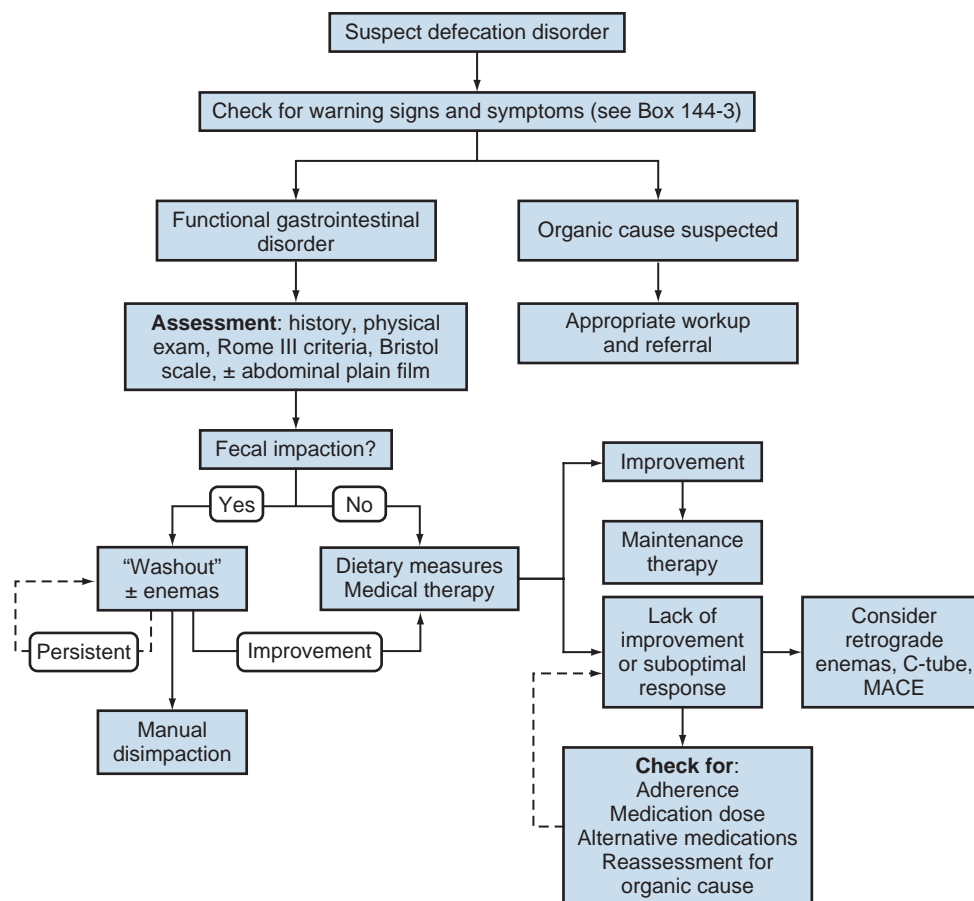


Figure 144-14. Management algorithm for childhood defecation disorders seen in a pediatric urology practice. Lack of improvement or intractable constipation should be diagnosed based on worsening response, absence of response, or suboptimal response to adequate medical treatment for at least 3 months. C-tube, cecostomy tube; MACE, Malone antegrade continence enema procedure.

and attrition (patient lost for follow-up). Nevertheless, a lack of benefit is often based on limited data; families commonly attempt therapeutic trials without recommendation or supervision by a health care provider, parents often favor nonpharmacologic strategies despite unproven benefit, and side effects are often mild or negligible. Thus the expectation is that early on, children will be asked to implement generous fluid intake (in accordance with expectations for children with lower urinary tract symptoms), to optimize diet (including liberal fiber intake in the form of fruits and vegetables), to establish a bowel routine taking advantage of gastrocolic reflex, to ensure active lifestyle (promoting physical activity and avoid sedentary tendencies), and to consider the use of prebiotics and/or probiotics (Chmielewska and Szajewska, 2010; Korterink et al, 2013), additional fiber intake (Staiano et al, 2000; Loening-Baucke et al, 2004; Castillejo et al, 2006; Chmielewska et al, 2011), or biofeedback (van der Plas et al, 1996a, 1996b). Unfortunately any positive effect on functional constipation is difficult to propose based on high-quality data (Tabbers et al, 2011), and treatment algorithms tend to be based on opinion rather than evidence (Pijpers et al, 2010).

The chronic nature of defecation disorders, in combination with fears of adverse effects or irreversible reliance on daily medication use, contributes to the search for some form of alternative treatment in approximately 40% of children with functional constipation (Vlieger et al, 2008). Many of these, aside from having unknown effectiveness, can be associated with important complications or discomfort (hypnotherapy, acupuncture, homeopathy, osteopathic or chiropractic musculoskeletal manipulations, transcutaneous nerve stimulation), and should be avoided or only

used under a research setting until confirmed by well-designed studies. In particular, phytotherapy (favored by parents who equate “natural” with safety) can elicit severe adverse reactions because of contamination, inability to quantify active compounds, unknown adulteration, or direct toxic effects.

Disimpaction and Large Bowel/Rectum Washout

Decreasing fecal load in the large intestine and rectal vault is the first step toward establishing an optimal medical regimen. Impaction is defined as the presence of a hard mass in the lower abdomen and/or left lower quadrant, or a dilated rectum filled with a large amount of stool as determined by rectal examination, pelvic ultrasound, or abdominal radiography, irrespective of the ability to produce bowel movements. The child may be able to pass some stool without effectively emptying, and on occasion may have loose bowel movements that can be paradoxically (and erroneously) labeled or treated as diarrhea. Approximately 30% of children with long-lasting functional constipation present with fecal impaction, which is frequently associated with stool incontinence (Mugie et al, 2011; Nurko and Scott, 2011). The presence of fecal impaction demands attention before the initiation of maintenance medical management; otherwise treatment will fail or paradoxically worsen the gastrointestinal symptoms.

Disimpaction and bowel washout, as the names imply, attempt to address the problem in a relatively short time, accepting the need for enemas or stimulants, and tolerating temporary worsening of fecal incontinence, abdominal distention, and discomfort. In stark contrast to maintenance therapy, enemas and suppositories are

acceptable as routine interventions during this period and may facilitate evacuation of a large/hard fecal load in the rectum. Although subject to variability based on the amount of fecal material, distribution within the colon, child's age, tolerance for medication administration per anus, provider experience, and cultural barriers, common programs include "high-dose" polyethylene glycol (PEG, 1 to 1.5 g/kg/day for 3 to 6 days) with or without sodium chloride, sodium phosphate, or mineral oil enemas (daily for 3 to 6 days) (Tabbers et al, 2014). The ultimate goal is to produce soft, watery bowel movements with correction of abdominal distention, palpable fecal mass on abdominal or rectal examination, and clearance of fecal load as determined by abdominal plain film or pelvic ultrasound.

In rare circumstances clearance can only be achieved with more aggressive medication administration that is conducted while admitted to the hospital and aided by nasogastric tube delivery and intravenous fluids to prevent dehydration (similar to local protocols for preoperative bowel preparation). If this treatment fails, is not tolerated, or is associated with severe pelvic pain resulting from difficulty in passing a hard, large rectal "fecaloma," digital disimpaction under anesthesia may be required. Subsequent outpatient management requires regular (often daily) visits, and consists of monitoring response while modifying the volume and content of the retrograde enemas to suit the individual needs of each patient. Normal saline is commonly used as the solution for enemas, with additives used based on preference and familiarity with use (glycerin, soap, or phosphate). Commercial sodium phosphate formulations (such as the Fleet enema) can be added in difficult cases, but these should be used with caution in children with renal impairment. Dosage is adjusted by age: 30 mL for children less than 4 years old, 60 mL for children 4 to 10 years old, and 120 mL for children older than 10 years. The total volume of the enema must be tailored to effect, with constipated patients often requiring up to 500 to 1000 mL. Management is considered successful when the underwear remains clean for 24 hours.

Maintenance Therapy

Before beginning any maintenance protocol, the provider should verify that the rectosigmoid is not impacted again, despite what was thought to be an adequate washout. Failure to do so means that management is bound to fail, paradoxically leading to overflow fecal incontinence or triggering pain and cramping with oral medications. In contrast to the management of fecal impaction, routine rectal administration of medications is avoided as first-line maintenance therapy. Although tolerated by some children, the use of enemas instead of optimal oral medical therapy does not appear to provide added benefit (Bongers et al, 2009). There is, however, limited place for routine use of enemas, suppositories, or rectal stimulation except for in severe, difficult-to-treat cases.

Osmotic laxatives—such as lactulose, milk of magnesia, and PEG—are usually sold as solutions or powders to be dissolved in water, thus making them relatively easy to administer to children and making them the preferred agents. They act as poorly absorbed hyperosmolar molecules, increasing stool water content (making feces softer and easier to pass), and increasing colonic peristalsis. Stimulant laxatives (sodium picosulfate, senna, and bisacodyl), which act directly on the intestinal mucosa, increase water and electrolyte secretion and are often reserved for second-line or adjunct (intermittent) protocols, used only in selected (otherwise refractory) circumstances.

With the introduction of PEG into routine clinical practice, tolerance of medical management has improved, and it is currently the preferred agent in many centers. PEG is better tolerated and easier to administer than alternative medications such as lactulose, mineral oil, and milk of magnesia (magnesium hydroxide) (Gordon et al, 2012, 2013). Maintenance PEG dose is 0.2 to 0.8 g/kg/day, further adjusted based on clinical response, and administered with fluids either once or twice daily. It is virtually tasteless and dissolves easily within seconds. The most common side effect, watery stools or diarrhea, can be easily addressed by

scaling back the dose administered daily. As an alternative if PEG is not available, lactulose (1 to 2 g/kg, once or twice daily) can be used (Tabbers et al, 2014).

New medications are being introduced in the therapeutic armamentarium. These have been mostly studied in the adult population, yet they are expected to transition slowly into pediatrics. New molecules include lubiprostone, linaclotide, and prucalopride (Tabbers et al, 2014). Prucalopride, an oral selective high-affinity 5-HT₄ receptor antagonist with gastrointestinal prokinetic activities, shows particular promise and may represent a reasonable choice for children who fail to respond to more conservative measures (Winter et al, 2013).

Maintenance treatment should continue for at least 2 months, and symptoms should completely resolve for at least 1 month before attempting gradual slow discontinuation. If the child is in the process of toilet training, medication should only be stopped after this developmental milestone has been completely achieved without evidence of defecation problems. Lack of improvement or worsening should alert the provider to the possibility of reimpaction, lack of adherence with the prescribed medications, insufficient dose, or the introduction of new medications that may worsen constipation. The development of new symptoms, new findings on physical examination, or failure to improve should also raise again consideration for underlying organic causes. Refractory cases are most commonly characterized by recurrent fecal impaction, likely resulting from retentive posturing, anal sphincter dyssynergia, and abnormal rectal motility or function (Youssef and Di Lorenzo, 2002; Voskuijl et al, 2006; Bongers et al, 2009).

PROGNOSIS

Functional constipation can be a difficult-to-treat and long-lasting problem for some children. Nevertheless, with adequate management nearly 50% of patients monitored for 6 to 12 months can recover and successfully discontinue medications, whereas in up to 80% the condition can be adequately controlled with routine interventions (Pijpers et al, 2010). Unfortunately, **subsequent recurrences are fairly common, with up to 50% of children experiencing an episode in the first 5 years after successful treatment** (Loening-Baucke, 1993; van Ginkel et al, 2003). There is a paucity of data on reliable prognostic factors—such as defecation frequency—that could identify patients at risk (Pijpers et al, 2010). Reported figures are clearly impacted by the included patient population, and specialized referral centers may evidence lower cure rates despite intensive medical and behavioral therapy, with some children experiencing persistent symptoms beyond puberty, particularly those with older age of onset and initial delay in treatment (Bongers et al, 2010). Importantly, approximately 80% of children adequately managed early in their course recover without the need

KEY POINTS: MANAGEMENT AND PROGNOSIS

- Adequate fluid and fiber intake, nonsedentary physical activity, education, and guidance for toilet training should be presented as first-line interventions for all children of adequate developmental age.
- Although of debatable value, interventions with low risk for adverse effects, such as behavioral therapy or biofeedback, can be considered for interested families.
- PEG should be considered as first-line treatment for constipation (both for initiation and maintenance).
- Enemas are of value in the short-term management of children with fecal impaction, but are not recommended for routine maintenance treatment.
- Treatment can be gradually discontinued in patients who remain symptom free for at least 1 to 2 months, with vigilance required regarding recurrence.

for medications at 6-month follow-up, compared with only 30% who experience a delay in treatment (i.e., initial medical treatment postponed for >3 months) (Pijpers et al, 2010). Ultimately, data clearly suggest that constipation without treatment does not improve with time or after puberty (van Ginkel et al, 2003). Early adequate therapeutic interventions are beneficial and may contribute to a successful long-term outcome while improving the child's quality of life.

SURGICAL MANAGEMENT

A small group of children fail medical management, and they may be considered candidates for surgical options. Surgical management of difficult-to-treat defecation disorders is not a new concept, and it has progressed from diversion (colostomy) for the most severe cases to liberal use of enemas and aggressive colon evacuation. With the introduction of the antegrade continence enema (ACE) or the Malone antegrade continence enema (MACE) procedure in 1989, in an attempt to treat the intractable fecal incontinence associated with spina bifida, a new and highly successful option became available (Malone et al, 1990). Koyle subsequently introduced the technique in North America in 1991 (Koyle et al, 1995). The concept behind this procedure is elegant and simple, which is to provide access to the colon (often at the level of the cecum) to allow regular emptying by means of antegrade instillation of fluid (so-called bowel "washout") (Fig. 144-15).

In essence, the MACE combines three well-recognized surgical principles familiar to pediatric urologists and surgeons: (1) complete colonic emptying can achieve bowel continence, (2) antegrade colonic emptying is feasible, and (3) the Mitrofanoff principle of continent cutaneous access to the bladder or bowel is highly successful and reproducible. Based on these, continent intermittent catheter access to the colon for the administration of antegrade enemas while the patient sits on the toilet produces colonic emptying and fecal continence. Success with this approach has been reported in numerous series, and it is now a procedure commonly practiced around the world (Squire et al, 1993; Griffiths and Malone, 1995; Koyle et al, 1995; Malone, 1995; Dick et al, 1996; Gerharz et al, 1997a; Schell et al, 1997; Peeraully et al, 2014).

The initial series described excising the appendix on its pedicle and then reimplanting it into the teniae of the cecum, as popularized with the Penn pouch continent urinary reservoir. Modifications have progressed to point of leaving the appendix in situ and retroverting it so that the serosa of the colon can be imbricated around it in an antirefluxing fashion, which can be achieved in an open, laparoscopic, or robotic-assisted fashion (Fig. 144-16).

Patient Selection and Preparation

For those children in whom conservative measures fail, retrograde enema compliance becomes an issue, and in those who experience successful bowel management through rectal enemas but desire or require a more convenient means of administration, surgical MACE might be considered an option. Although fecal continence is comparable whether enemas are administered rectally versus antegrade (Matsuno et al, 2010), procedural independence is often optimal for patients performing antegrade enemas. As such, the MACE procedure should be seen as an option that allows patient independence and avoids rectal instrumentation. The underlying

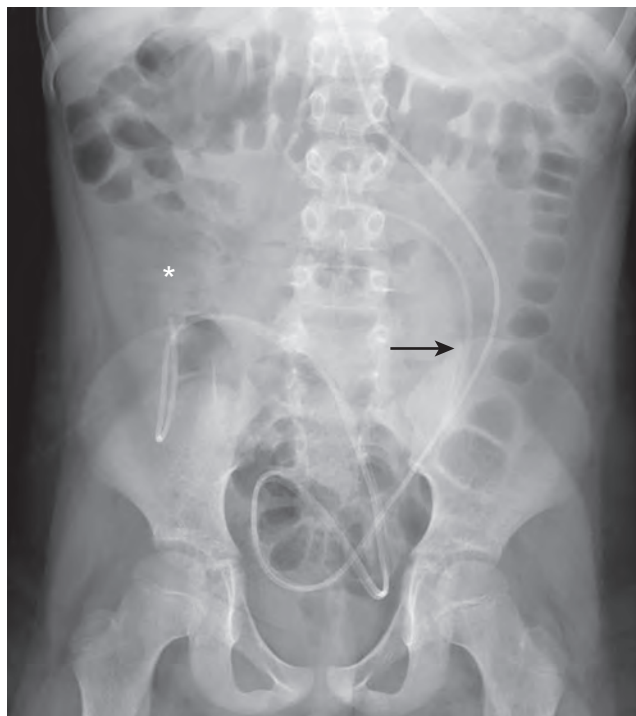


Figure 144-15. Clearance of large bowel contents with antegrade enemas. Abdominal radiograph taken 12 hours after washout, demonstrating absent fecal material except for early accumulation in the cecum and ascending colon (asterisk). Note presence of a ventriculoperitoneal shunt (arrow).

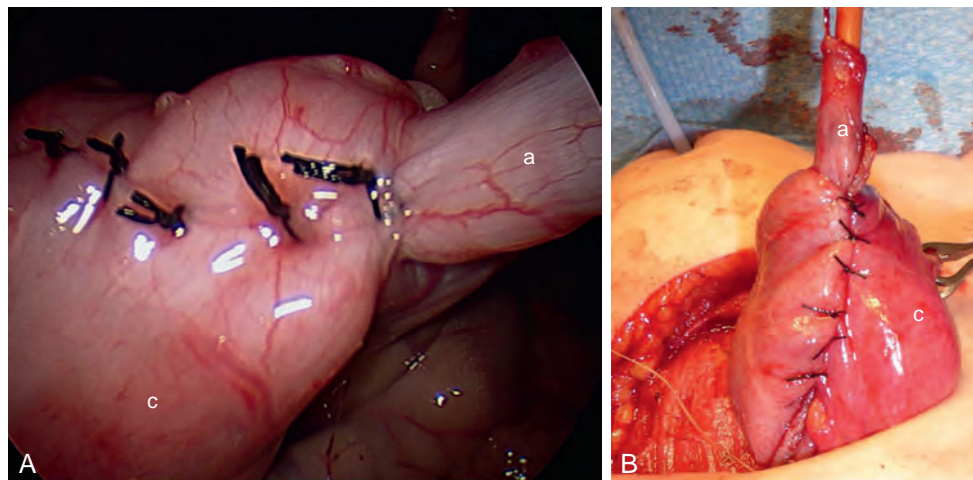


Figure 144-16. Cecal wrap performed during laparoscopic (A) and open (B) Malone antegrade continence enema procedure. Note appendix in situ, retroverted with colon serosa imbricated around it in an antirefluxing fashion. a, appendix; c, cecum.

diagnosis is important as it influences the success rate. Other issues that might be considered include the presence, length, and quality of the appendix, the need and timing of urinary tract reconstruction, patient age and potential intellectual capacity, as well as dexterity, ambulatory status, and body habitus.

Patients with a neuropathic bowel and anorectal malformations seem to fare better than those with chronic idiopathic constipation (Curry et al, 1998). Nevertheless, with increasing experience modest success rates appear to improve (Curry et al, 1999; Kokoska et al, 2001). Age at operation is also important, with failures more commonly seen in younger patients irrespective of the diagnosis (Curry et al, 1998). This may reflect the inability of young children to sit on a toilet for up to 1 hour before emptying is complete or the lack of drive to achieve continence (as seen in older children because of school and peer pressure). Favorable outcomes appear to decrease again after puberty (Gerharz et al, 1997b; Christison-Lagay et al, 2010). This may reflect the impact of changes in body habitus associated with transferring issues in those with neurologic conditions, combined attempts at independence with less caregiver support, and compliance issues with the washout regimen.

Similar to any other catheterizing protocol, ensuring understanding and reinforcing information to the patient and to their caregivers are essential. The importance of ongoing detailed counseling and continued support cannot be overemphasized, both preoperatively and postoperatively (ideally provided by a well-trained dedicated member of the team, such as a nurse practitioner). These are essential to ensure adequate and continued motivation, without which the procedure is set for failure. The ideal patient for a MACE procedure should be between the ages of 5 and 12 years, have a diagnosis of neuropathic bowel, anorectal malformation, or Hirschsprung disease, be well motivated with a dedicated family, and have tried and failed all conservative measures.

Operative Technique

Although preoperative bowel preparation might facilitate the initiation of postoperative enemas, an aggressive cleanout is not necessary for the purpose of performing the procedure. Appropriate prophylactic antibiotics are always administered perioperatively, and these might be adjusted based on any concurrent urinary tract reconstruction. In most instances where coincidental urinary tract surgery is to be performed, a lower midline or Pfannenstiel incision is selected, depending on the patient's body habitus, scars from previous surgeries, and surgeon preference. Laparoscopy allows for identification of the appendix and mobilization of the colon, being particularly useful when the right colon is located high in the abdomen, close to the liver (Fig. 144-17). In such cases (often spina bifida patients with previous abdominal incisions and ventriculoperitoneal shunts), a large incision is avoided. In addition, the presence and status of the appendix itself can be confirmed. If only a MACE channel is to be performed, a pure laparoscopic or robotic approach, or an open appendectomy incision, can be used depending on the individual situation and the surgeon's experience and comfort.

In most descriptions of the ACE procedure an "antireflux" valve mechanism is fashioned to prevent leakage of bowel contents via the cutaneous stoma. Because the tendency is to maintain the appendix in situ, this is achieved by wrapping it with the cecal wall, as in the adaptation by Koyle that follows the principle of the Nissen fundoplication (Koyle et al, 1995). This can be performed in a minimally invasive way (Webb et al, 1997; Nanigian and Kurzrock, 2008; Lawal et al, 2011). To reduce the risk of compromising blood supply to the appendix, its mesentery is fenestrated to allow the passage of sutures and tissue without entrapping the vessels (Fig. 144-18). The colon can also be sutured to the posterior aspect of the anterior abdominal wall to ensure that the catheterizable conduit is not lying free in the peritoneal cavity, preventing kinking and difficulties with catheterization. It has been suggested that it is not necessary to construct an antireflux mechanism, and some have advocated avoiding this step and simply mobilizing the appendiceal-cecal unit to the abdominal stoma site, which is a procedure that

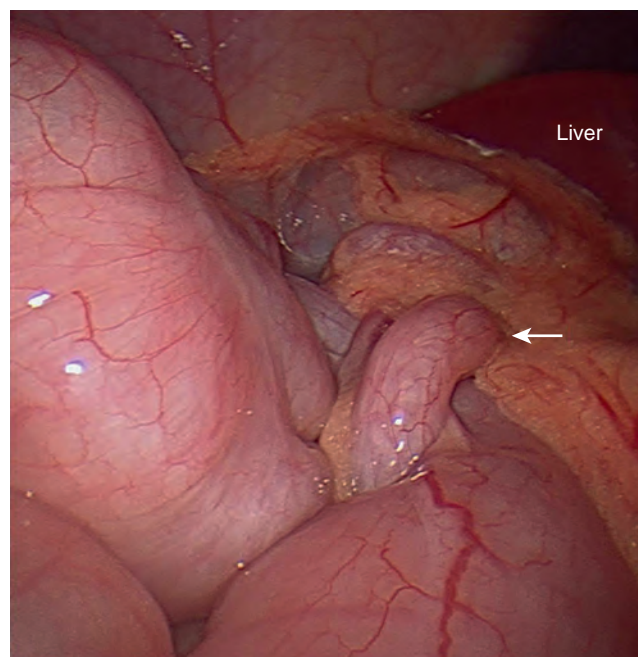


Figure 144-17. Diagnostic laparoscopy as the initial step to laparoscopic or laparoscopic-assisted Malone antegrade continence enema procedure. Presence, quality, and location of the appendix can be easily determined. Note location of cecum and appendix (arrow) close to the liver in a child with spinal dysraphism.

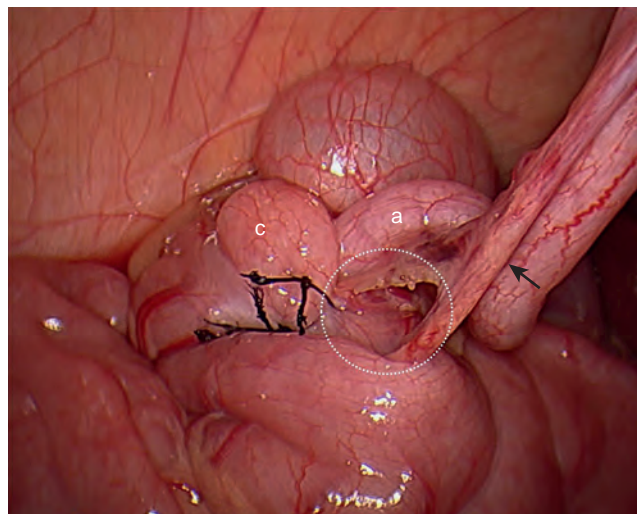


Figure 144-18. Fenestration of the appendix mesentery during laparoscopic Malone antegrade continence enema procedure, allowing passage of suture and creation of a cecal wrap without compromise of the blood supply (arrow). a, appendix; c, cecum.

is amenable to a purely laparoscopic or robotic-assisted approach (the so-called laparoscopic antegrade continence enema) (Webb et al, 1997; Thakre et al, 2008) (Fig. 144-19). Thus far, data appear to support no increase in stomal bowel incontinence based on retrospective reviews comparing MACE with and without cecal wrap (Koivusalo et al, 2006; Nanigian and Kurzrock, 2008).

If the patient requires synchronous bladder reconstruction, simultaneous MACE and Mitrofanoff urinary diversion offer patients the chance for complete dual fecal and urinary continence (Roberts et al, 1995; Wedderburn et al, 2001; Casale et al, 2006). The technique needs to be modified if both MACE and

appendicovesicostomy procedures are being considered. If the appendix is long enough and the vascular anatomy is suitable, it is possible to split the appendix (Fig. 144-20). If the appendix is not suitable to be split or is absent, alternative options must be considered. In these cases tubularized colon flaps (Fig. 144-21) or cecal extension of the appendiceal stump with a surgical stapler (Fig. 144-22) can be performed with relative ease, achieving good results with acceptable complication rates (Kiely et al, 1994; Herndon et al, 2005). The Monti-Yang procedure can also be employed as an alternative conduit (Monti et al, 1997) following the Mitrofanoff flap valve principle to implant in the bowel wall.

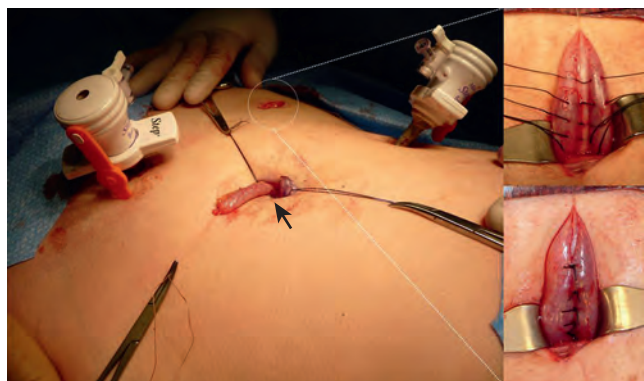


Figure 144-19. Laparoscopic-assisted cecostomy tube (C-tube) takedown and creation of Malone antegrade continence enema channel with appendix. Open imbrication through C-tube scar allows creation of “antireflux” mechanism. Note tip of appendix delivered through camera port at umbilicus (arrow).

Some advocate this option as the procedure of choice when the appendix is not available (Sugerman et al, 1998), and it can be particularly advantageous in very obese patients, as the use of a spiral or two segments of bowel will produce a conduit that is long enough for virtually all patients.

Another option worthy of consideration is the use of either a cecostomy tube (C-tube) or cecal button. Since the description by Chait and coworkers (1997a, 1997b), the technique for percutaneous placement of a cecal tube that can be regularly exchanged as a permanent, low-profile cecal button (similar to a gastrostomy button) has been refined. The C-tube option is favored when it is known that the appendix is absent (i.e., post-appendectomy), when the patient refuses to perform intermittent bowel



Figure 144-20. Long appendix with robust blood supply, amenable to split for simultaneous Malone antegrade continence enema channel and appendicovesicostomy.

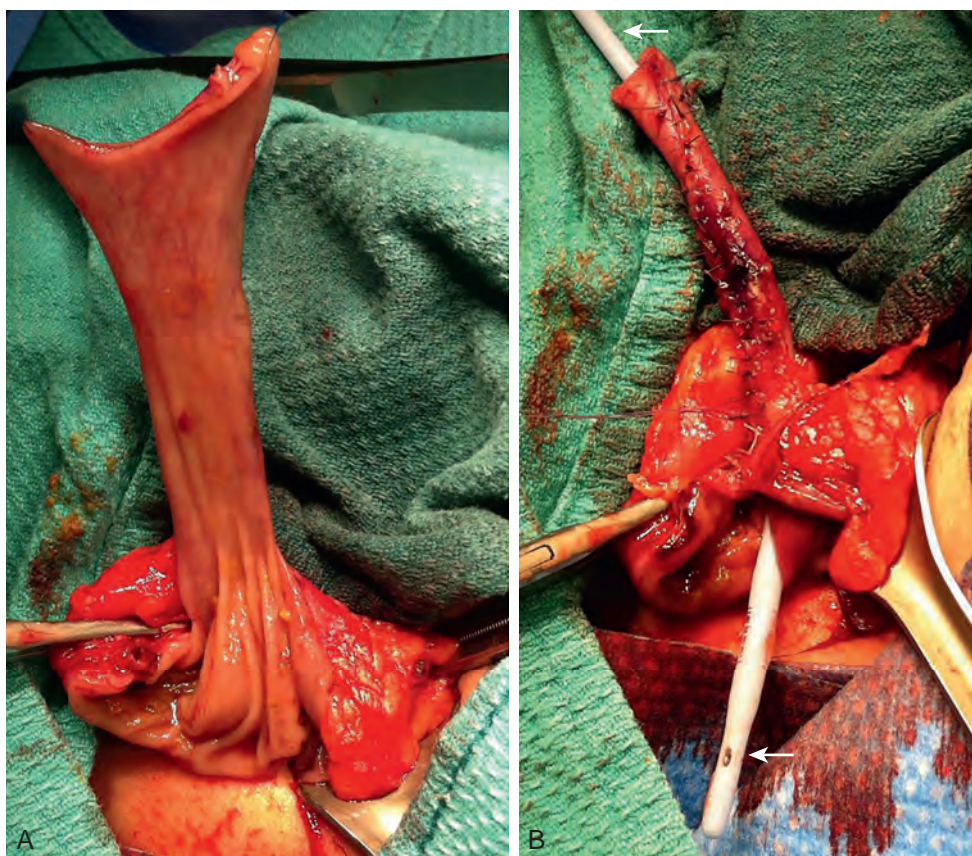


Figure 144-21. Creation of access with a colon flap (A), tubularized and subsequently imbricated (B). This is suitable for catheterization for flushes to the left or right colon. Note flap tubularization over catheter (arrow).

catheterization, for patients who develop stomal complications such as stenosis (as an alternative to revision of the MACE channel), as a temporary therapeutic challenge to determine response to antegrade enemas or to determine whether the ideal placement of a permanent MACE should be in the right or left colon, and as a permanent option in cases where a nonoperative access is favored. Long-term outcomes reported by Chait and coworkers (1997a), who performed the procedure percutaneously under fluoroscopic guidance, show successful placement in a large number of children with satisfactory outcomes, certainly similar to other approaches (Chait et al, 2003). The tube can also be placed open or under laparoscopic guidance at the time of concomitant appendicovesicostomy (Lorenzo et al, 2007). The main drawback is that the tube entry site can become unsightly, with granulation tissue and occasional fecal leakage (Fig. 144-23). In these cases patients may opt for subsequent formal conversion to a bowel-based MACE, either laparoscopic or open (Fig. 144-24). Regardless, the tube or button can always be converted to a formal ACE with time, thus providing a reasonable initial option and a bailout in complicated cases.

A problem occasionally encountered, particularly in children and adolescents with severe constipation and a redundant colon, is the length of time needed for the washout to work. This issue

can lead to frustration, failure, and abandonment of the irrigations (Griffiths and Malone, 1995). In an attempt to rectify this problem, some have advocated placing the conduit in the left colon, rather than in the cecum. By doing so, the length of bowel that has to be washed through is reduced and, theoretically, so is the time needed for successful enema completion. Results using this approach have been encouraging, with similar outcomes and complication rates compared to traditional MACE (Liloku et al, 2002; Churchill et al, 2003; Meyer et al, 2008; Sinha et al, 2008; Blackburn et al, 2012), yet with less enema fluid requirements and shorter transit times (Sinha et al, 2008). A left MACE should be considered strongly in patients suffering from severe constipation. The decision between left or right access might be a difficult one, and it can be settled by temporarily placing a cecostomy or percutaneous colostomy tube. If equivalent or better on the right, then the *in situ* appendix is the simpler option.

The Enema Regimen

Although protocols differ, the first enema is commonly administered via the indwelling catheter or percutaneously placed tube following a progressive irrigation protocol that is initiated after the postoperative ileus resolves. Considering individual patient needs

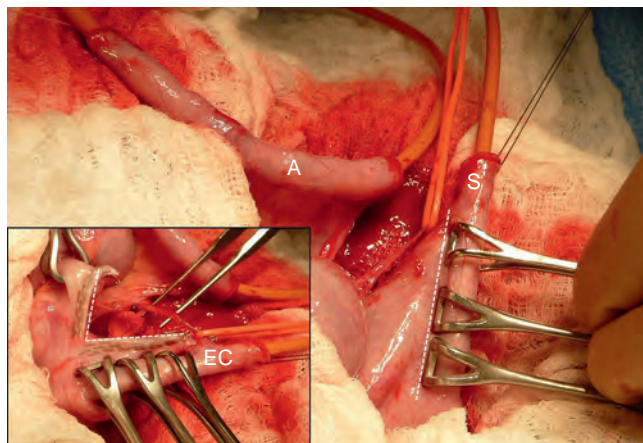


Figure 144-22. Technique for cecal elongation of appendiceal stump with a surgical stapler effectively lengthening the channel, which is subsequently imbricated to prevent leakage. A, distal segment of appendix preserved for appendicovesicostomy; EC, elongated cecum; S, appendiceal stump.



Figure 144-23. Granulation tissue (black arrows) and leakage (white arrow) around cecostomy tube. Unsightly appearance and soiling can occur with time, which can lead to removal or conversion to a Malone antegrade continence enema channel.

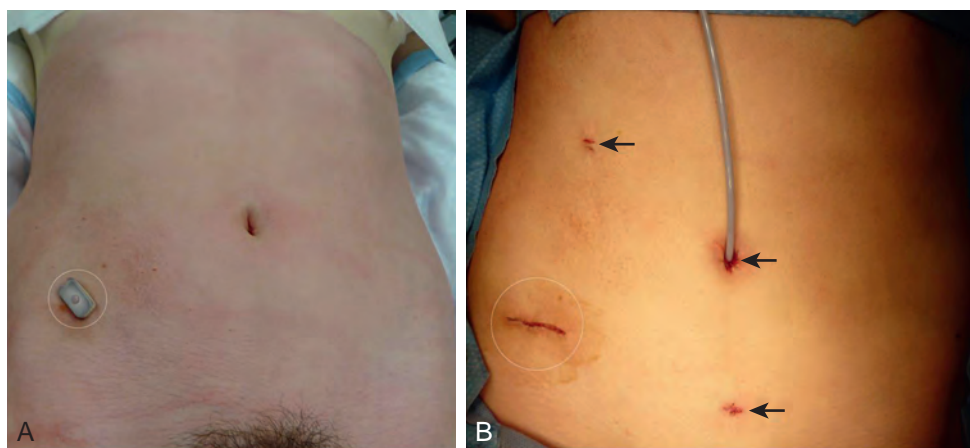


Figure 144-24. Port placement (arrows) and cosmetic outcome of cecostomy tube takedown and laparoscopic-assisted Malone antegrade continence enema creation. A, Preoperative view. B, View immediately post-operation.

and variable responses, there is much trial and error involved. One of the most important points, especially in the early weeks and months after surgery, is to advise patients not to expect immediate success, because early disappointment can lead to frustration and failure. In fact many children might not achieve a steady state or a reliable enema routine for a period of up to 6 months (Curry et al, 1998). Patients may also experience a degree of rectal leakage within the first few hours after the washout, but this does not appear to be a long-term problem. Although the washout regimen is being established outside the hospital, it is vital to maintain regular contact with the nurse specialist who helps manage the process.

Enema protocols differ among centers, and patients and families will frequently modify them to suit their own particular needs. Initially, daily washouts with 20 cc/kg of solution are encouraged, but after the patient is comfortable with the process and a routine has been established he or she may attempt to decrease frequency to alternate days. The time of day that the enema is administered is patient dependent, although most families prefer to administer the enema during the early evening hours after dinner. This time is chosen to allow a sufficient interval to achieve the desired result before bedtime. Rarely, others learn that twice-daily cleanouts are necessary and they adjust their frequency accordingly. Washout times range between 30 and 60 minutes. Because patients must sit on the toilet for a long period, buttock pressure sores may develop, and this is a complication that can be minimized with the use of padded toilet seats. Purges can be performed with a large volume of tap water (Koyle et al, 1995; Yerkes et al, 2001) or saltwater, with the judicious mix of additives such as glycerin, bisacodyl, phosphate, magnesium citrate, mineral oil, or PEG. Although uncommon, and depending on the solution used, water intoxication and/or electrolyte abnormalities may occur (Hunter et al, 1993; Schreiber and Stone, 1999). Changes and experimentation should only be performed under supervision to minimize this risk. After a steady state is achieved, there is little benefit from dramatically interfering or modifying the regimen.

Several difficulties can be experienced during enema infusion. The most common problem is pain or discomfort during instillation (Curry et al, 1998). In the majority of patients, this is a transient phenomenon that subsides during the first 3 months. Persistence beyond this time can contribute to discontinuation. Warming the solution, lowering additive concentration, reducing the rate of the infusion, using an antispasmodic before administering the enema, or using a licorice root solution can be attempted in these cases. It is always important to assure that the pain is not a result of distal fecal impaction (Fig. 144-25), which can occur despite regular washouts. These patients might require occasional retrograde cleanouts or might be candidates for repositioning the location of the access channel in the colon (cecum vs. right colon) (Liloku et al, 2002; Churchill et al, 2003).

Surgical Outcomes

In a survey of 300 ACE procedures performed by members of the British Association of Paediatric Surgeons, Curry and coworkers (1999) reported that success rates were dependent on the original diagnosis (Table 144-1). This large national series reported an overall full and partial success rate of 79%, with complication rates that were lower than in earlier historical series. In particular, stomal stenosis rates were reduced to 30%.

Standardized tools have been used to reflect improvements in quality of life (Shankar et al, 1998), self-esteem, psychosocial function (Aksnes et al, 2002), and fecal incontinence-related and constipation-related quality of life (including anxiety and family worry) (Ok and Kurzrock, 2011). Nonvalidated questionnaires have shown high satisfaction rates, with a majority of respondents recommending the procedure to others who have intractable defecation disorders (Hoekstra et al, 2011).

For patients undergoing synchronous bladder reconstruction and ACE procedures, a high percentage of fecal and urinary continence should be expected, with variable complication rates (Kajbafzadeh and Chubak, 2001; Wedderburn et al, 2001) and no

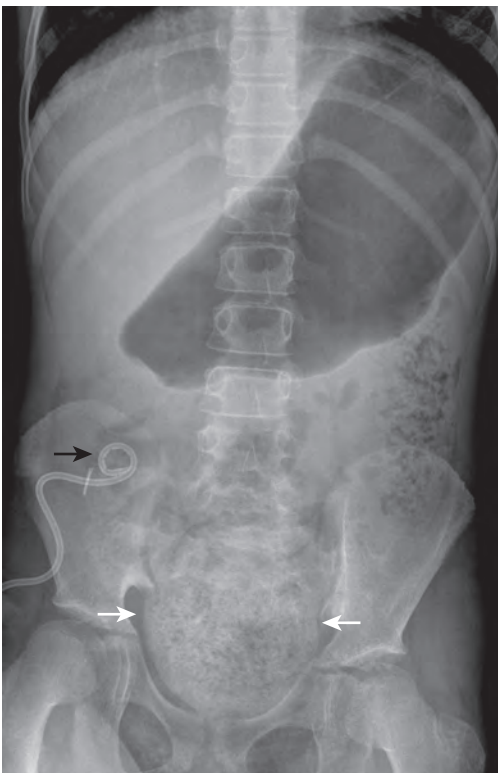


Figure 144-25. Presence of a large amount of fecal material in the distal colon and rectum (white arrows). This patient became impacted while doing infrequent antegrade enemas through a cecostomy access (black arrow). Attempts at clearing this fecal load with antegrade flushes only led to abdominal pain, lack of tolerance, and poor response. Improvement was achieved with disimpaction and retrograde enemas followed by diligent, regular antegrade flushes to achieve complete washout.

TABLE 144-1 Malone Antegrade Continence Enema Procedure Success and Failure* Based on Underlying Condition

DIAGNOSIS	FULL SUCCESS (%)	PARTIAL SUCCESS (%)	FAILURE (%)
Spinal bifida	63	21	26
Anorectal malformation	72	17	11
Hirschsprung disease	82	9	9
Idiopathic constipation	52	10	38
Other	44	25	31

*Surgical results have been classified as follows:
Full success: totally clean or minor rectal leakage on the night of washout.
Partial success: clean but significant rectal leakage, occasional major leak, still wearing protection, but improvement perceived by the parent or child.
Failure: regular soiling or constipation persists, no perceived improvement, and the irrigations are abandoned.

adverse impact compared to patients undergoing staged reconstruction (Casale et al, 2006). Stomal complications and difficulty catheterizing the conduits remain the most important postoperative problems (Barqawi et al, 2004). For example, Curry and coworkers (1998) reported an incidence of 55% for stomal complications. Ransley’s VQZ flap has been advocated as a technique to reduce the incidence of stenosis when the MACE is directed to a position other

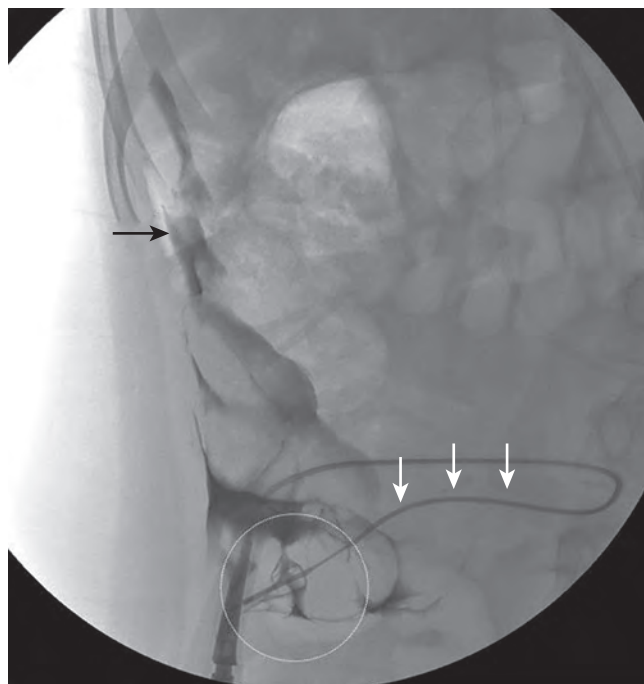


Figure 144-26. Water-soluble contrast study through catheter placed in Malone antegrade continence enema channel (white arrows) to evaluate possible perforation (black arrow).

KEY POINTS: SURGICAL MANAGEMENT

- Surgical management of defecation disorders has been revolutionized with the concept of antegrade enemas, delivered through a catheterizable channel (MACE) or a C-tube. This enables the patient to evacuate the colon at regular intervals, avoiding impaction and reducing fecal incontinence.
- Patient selection is critical, and candidates should have failed maximal conventional measures before proceeding to invasive options.
- Although individual variations are expected, patients commonly perform washouts on a regular basis (daily or every other day) to achieve continence.
- Concurrent reconstruction of the gastrointestinal and genitourinary tract is feasible in most cases, with adaptations to fashion access to the bladder and bowel using available bowel segments.
- Surgical options include open, laparoscopic, robotic-assisted, and percutaneous techniques.

than the umbilicus (Malone et al, 1998; McAndrew and Malone, 2002; Landau et al, 2008). Conduit perforation and intraperitoneal enema instillation occurs rarely (3.7% during a 13-year period), but it can result in significant morbidity and the need for emergency surgical exploration (Defoor et al, 2005). If suspected, a contrast study through the channel may help establish the diagnosis (Fig. 144-26).

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The “Functional” Urinary Tract

Patient Evaluation

Patient Preparation

Antireflux

Bladder Neck Reconstruction

Augmentation Cystoplasty

Continent Urinary Diversion

Summary

Although children with anomalies affecting the bladder and outlet are managed with a primary goal of minimizing the need for operative intervention, the basic functions of a “normal” lower urinary tract—to protect renal function, avoid urinary tract infection, and eventually provide urinary continence—must be achieved. Surgical reconstruction remains an important and effective tool for some children. When reconstruction is considered, it is imperative that the patient be thoroughly evaluated. Each child is unique, and their particular pathophysiology must be understood so that surgical techniques available may be used thoughtfully to optimize results while minimizing morbidity.

The scope of this chapter is large. Augmentation cystoplasty is reviewed in detail. In few areas of urology have intestinal segments been used as extensively. Complex patients with bladder dysfunction may also have bladder neck and external sphincteric problems, and this chapter covers techniques that increase bladder neck and external urinary sphincter resistance in the pediatric population. Perhaps the single most important contribution affecting lower urinary tract reconstruction was the introduction of clean intermittent catheterization (CIC) by [Lapides and colleagues \(1972, 1976\)](#) based on the work of [Guttmann and Frankel \(1966\)](#). Because many pediatric patients with bladder and sphincteric dysfunction will not void adequately after reconstruction, creation of a reliable means to easily catheterize may be essential; ways to do so are presented, along with related results in children.

Most pediatric lower tract reconstructive procedures are undertaken primarily to correct hostility in the native lower urinary tract unresponsive to medical management. Children with bladder and sphincteric dysfunction are among the most complex seen in pediatric urology, and those with spina bifida make up the majority of patients requiring this type of surgical intervention. The results discussed herein will therefore focus on the neurogenic population. Children with diagnoses such as exstrophy, persistent cloaca and urogenital sinus, posterior urethral valves, bilateral single ectopic ureters, and prune-belly syndrome may undergo similar reconstruction.

The most important factor influencing the outcome of urinary tract reconstruction in children is the commitment of the patient and family to achieving good care. Determining that commitment may at times be difficult, but its importance should not be underestimated.

THE “FUNCTIONAL” URINARY TRACT

Bladder physiology can be characterized in two dynamic phases, passive and active. During the passive storage phase, the bladder

functions as a reservoir allowing for urine to be stored at low pressure without leakage. In the active voiding phase, the bladder contracts and efficiently eliminates urine.

Basic Bladder Function

Passive: Storage

Urinary storage requires a reservoir that is compliant and of age-appropriate capacity. Age-based capacity may be estimated using formulas proposed by Koff (volume in milliliters = $30[\text{age in years} + 2]$) or Kaefer and colleagues (volume in milliliters = $32[2 \times \text{age in years} + 2]$ for children younger than 2 years, and volume in milliliters = $30[\text{age in years} + 2 + 6]$ for children older than 2 years) ([Koff, 1983](#); [Kaefer et al, 1997c](#)). Compliance is defined as the change in bladder volume divided by the change in pressure. Normally the bladder is a highly compliant vesicle in that it will accommodate an increasing volume of urine without a corresponding increase in intravesical pressure. Multiple factors contribute to this property. Initially the bladder is in a collapsed state, which allows for the storage of urine at low pressure by simple unfolding. As it expands, detrusor properties of elasticity and viscoelasticity engage. Elasticity allows the detrusor muscle to stretch without an increase in tension until it reaches a critical volume greater than the expected bladder capacity. The viscoelastic property allows for a subtle continuous pressure change during bladder filling. This small rise in pressure is balanced by a corresponding rapid pressure decay ([Zinner et al, 1976](#); [Wagg and Fry, 1999](#)). With slow natural bladder filling there is no net change in bladder pressure until capacity is reached. The viscoelastic bladder property is defined as stress relaxation and can be overcome when the rate of bladder filling exceeds normal parameters ([Mundy, 1984](#); [Finkbeiner, 1999](#)). This artifact of testing is often noted when urodynamic assessment is performed at an excessive filling rate for the child's age or size ([Joseph, 1992](#)). Properties of elasticity and viscoelasticity will eventually be overcome in every child; at that point, the bladder pressure rapidly rises. Favorable dynamics for appropriate urine storage include a thin bladder wall with an appropriate composition of muscle and collagen allowing for expression of normal elastic and viscoelastic properties. Factors adversely affecting normal compliance include detrusor hypertrophy, fibrosis, outlet obstruction, and recurrent urinary infections ([Mundy, 1984](#); [Joseph, 1994](#)).

Continence during urinary storage requires a closed bladder neck and external urinary sphincter. Fixed outlet obstruction, neurogenic dysfunction, and chronic inflammation can affect passive parameters, resulting in resting bladder hostility and clinical

manifestations of poor compliance, upper tract deterioration, and incontinence (Brading, 1997).

Active: Voiding

Under normal conditions the active phase of voiding requires the bladder to contract after descent of the bladder neck (Morrison, 1997). Reflexive opening of the bladder neck and sequential relaxation of the external urinary sphincter allow for low pressure balanced voiding and complete elimination of urine. Again, obstruction, neurogenic dysfunction, and chronic infection can cause physiologic changes preventing coordinated function of the detrusor, bladder neck, and external sphincter defined as dyssynergy (Mundy et al, 1985). A poorly functioning external sphincter from denervation fibrosis may also prevent appropriate relaxation, causing elevated voiding pressure against a fixed outlet. Finally, detrusor pathophysiology may prevent a sustained, coordinated bladder contraction and full elimination of all urine.

Dysfunction

Upper Urinary Tract

It is critical to understand the dynamics of the entire urinary tract before any major reconstructive procedure. In the presence of hydronephrosis, upper tract obstruction must be excluded. Upper tract obstruction may be secondary to severe, long-standing bladder hostility involving poor bladder compliance and emptying. Nuclear renography with a urethral catheter may be useful to rule out a primary upper tract obstruction. Upper tract obstruction, if present, should be corrected at the time of bladder and sphincter reconstruction.

Vesicoureteral reflux in the presence of bladder hostility may be primary or secondary, and differentiating the two may be difficult. If reflux was not present during earlier evaluation, new onset is likely secondary to bladder hostility. Reflux in children with neurogenic dysfunction is often secondary in nature. Previous work has suggested that reflux secondary to bladder hostility may not need surgical correction if the bladder is adequately managed. Neurogenic bladder requiring augmentation in children who did not undergo reimplantation for secondary reflux resolved with augmentation alone (Nasrallah and Aliabadi, 1991; Morioka et al, 1998; López Pereira et al, 2001; Soylet et al, 2004; Juhasz et al, 2008). It is interesting to speculate whether reflux is even a significant problem if a large, compliant bladder is achieved (Soylet et al, 2004). Bacteria may ascend with or without reflux after reconstruction, and certain forms of continent diversion have not shown an increased risk of pyelonephritis in the absence of any antireflux mechanism when compliance is adequate (Gonzalez and Reinburg, 1987; Helal et al, 1993; Pantuck et al, 2000). We agree that most secondary reflux will likely resolve with adequate reconstruction of the bladder but will correct high-grade reflux if present. Caution must be taken when considering the treatment of chronically dilated and scarred ureters. Correcting reflux in that setting is appropriate but can result in obstruction if overly aggressive tapering or tunneling is performed (Hendren, 1998).

Dysfunction in the upper urinary tract usually manifests with hydronephrosis, pyelonephritis, or impairment of renal function. When such problems are present in patients with lower tract dysfunction, thoughtful evaluation and treatment are necessary. All problems should be addressed before and at the time of reconstructive surgery to achieve the best result.

Bladder Dysfunction

Bladder dysfunction is a composite of physiologic abnormalities, and it is helpful to assess each component of passive and active bladder function independently. **Elevated passive filling pressure becomes clinically pathogenic when a pressure greater than 40 cm H₂O is chronically reached** (McGuire et al, 1981; Wang et al, 1988; Weston et al, 1989). Pressures at this level sustained

over a period of time impair ureteral drainage that may result in pyelocalyceal changes, hydroureteronephrosis, and decreased glomerular filtration rate. In addition, persistent elevation in filling pressure can result in acquired vesicoureteral reflux (Sidi et al, 1986a; Cohen et al, 1990).

Pharmacologic management can play a role in decreasing filling pressure, particularly when overactive detrusor contractions are present. A combination of medications and intermittent catheterization have a positive impact, particularly in children with neurogenic dysfunction (Rink and Mitchell, 1984; Aslan and Kogan, 2002; Verpoorten and Buyse, 2008). When compliance is unaffected by medical management, augmentation cystoplasty may be required to improve the storage characteristics. After reconstruction, the likelihood of efficient detrusor contractions and effective emptying of the bladder is diminished. Intermittent catheterization should be taught and accepted by the patient and caretaker preoperatively. CIC allows the reconstructive surgeon to aggressively correct storage problems through augmentation. Spontaneous voiding, while a goal, is not imperative because CIC can be used for emptying.

Urinary incontinence is a prominent sign of bladder dysfunction. Continence requires outflow resistance generated by the bladder neck and external urinary sphincter. Outflow resistance must remain greater than bladder pressure during storage throughout normal daily activity. When outflow resistance is diminished because of an abnormal bladder neck and external urinary sphincter, incontinence often will occur. Pharmacologic management with α -adrenergic agents can enhance outflow resistance, but more commonly operative reconstruction is required.

When incontinence occurs during the filling phase because of poor outlet resistance, it is essential to evaluate not only the bladder neck and external urinary sphincter, but also detrusor characteristics. Clinical experience has shown that once appropriate resistance is achieved at the bladder neck through operative intervention, adverse detrusor characteristics may become unmasked and result in high pressure urinary storage or uninhibited contractions not previously documented (Bauer et al, 1986; Churchill et al, 1987; Dave and Salle, 2008). For that reason, provocative urodynamic assessment with occlusion of the bladder neck is important before any bladder neck reconstruction in an attempt to identify children who will be at risk.

Normal synergistic voiding occurs when the bladder neck descends, relaxes, and opens, followed by relaxation of the external urinary sphincter and subsequent detrusor contraction resulting in low pressure voiding. Dysfunctional voiding during this active bladder phase occurs as a result of uncoordinated activity of the bladder neck, external urinary sphincter, and detrusor. With such dyssynergy, high-pressure voiding results that chronically can negatively affect the bladder and upper urinary tract (Mundy et al, 1982; Bauer et al, 1984). A similar clinical situation occurs with a fixed, fibrotic external sphincter. Initial treatment involves pharmacologic management and CIC in an attempt to bypass the abnormal voiding mechanics.

Other Considerations

Renal function should be assessed in any patient undergoing bladder reconstruction, particularly if hydronephrosis or severe renal scarring is present. Demos (1962) and Koch and McDougal (1985) have demonstrated that urinary solutes, particularly chloride, are absorbed from urine in contact with the mucosa of small and large bowel. For patients with normal renal function, the kidneys are able to handle the reabsorbed load of chloride and acid without obvious difficulty. Patients with decreased renal function, however, may develop significant metabolic acidosis secondary to such reabsorption. If acidosis exists preoperatively, it will invariably worsen if urine is stored in small or large intestinal segments (Mitchell and Piser, 1987). The first component of renal function to deteriorate after obstruction or infection is concentrating ability. Patients with compromised function may generate enormous volumes of urine. **The bladder volume achieved through bladder reconstruction must accommodate the patient's urinary**

output for an acceptable period of time, usually 4 hours. Patients with renal failure or other medical problems may conversely develop oliguria. Low urinary output may affect an augmented bladder or bladder reservoir with greater collection and inspissation of mucus.

Abnormal function of other organ systems also influences the risk of bladder reconstruction using intestinal segments. Reabsorption of ammonia by large or small intestinal segments in contact with urine may be dangerous for patients with hepatic failure (McDougal, 1992a). Some medications excreted in urine may be reabsorbed by bowel mucosa (Savauagen and Dixey, 1969). Therefore, liver function tests and arterial blood gas studies may be appropriate. Careful history should be taken regarding the patient's preoperative bowel function; this is particularly true of patients who may have acquired or secondary gastrointestinal problems. Short gut syndrome is a concern among children with cloacal extrophy, prior bowel resections, or a history of significant radiation. A history of chronic diarrhea or fecal incontinence preoperatively should signal concern about use of the ileocecal valve in urinary reconstruction.

A critical factor to consider is the commitment of the patient and family. Urinary incontinence, at times, protects some patients from infection and upper tract deterioration. Effective storage can put the patient at risk for problems if emptying is not accomplished on a regular basis. All must be aware of the responsibility that goes along with bladder reconstruction and urinary continence.

The timing of surgical intervention varies dramatically among patients. It might be necessary to perform reconstruction early when the upper tracts and renal function are threatened. This situation may occur in the presence of high outflow resistance and poor bladder compliance. Although work has suggested that augmentation cystoplasty to correct bladder hostility may slow deterioration of renal function even when renal insufficiency resulting from secondary upper tract damage is already established (Ivancic et al, 2010), early intervention to prevent such damage is preferable. More commonly, reconstruction is undertaken later to achieve urinary continence. The age at which urinary incontinence, or the presence of a urinary stoma after temporary diversion, becomes socially unacceptable varies among patients and families.

It is beneficial for the patient and family to wait for bladder reconstruction until all needs of the child are identified. This is not always possible when intervening because of infection or hydronephrosis. When reconstruction is undertaken to achieve continence, it is most efficient to identify all reconstructive issues and address them with one operation. Urodynamic assessment is usually necessary to determine whether a procedure to increase outflow resistance is necessary in addition to bladder augmentation or replacement. Introducing CIC preoperatively is mandatory in that it allows the patient to demonstrate the ability and desire to continue on a regular basis. It is also helpful in determining whether a continent abdominal wall stoma may be required to improve the reliability of catheterization and increase the patient's independence. Likewise in the neurogenic population, it is advantageous to identify the child who may benefit from an antegrade colonic enema. It is certainly better for the patient and surgeon to address all of these issues at one time rather than with sequential procedures that may add morbidity.

PATIENT EVALUATION

Each patient should have upper tract imaging before bladder reconstruction; most will have had routine ultrasonography as part of their surveillance. **When hydronephrosis is present, imaging should be performed to assess for obstruction or vesicoureteral reflux.** Nuclear renography with a catheter in the bladder is usually adequate to rule out primary upper tract obstruction. Reflux should be excluded with an independent voiding study or as part of video urodynamics. In the presence of hydronephrosis, patients should have baseline levels of serum electrolytes, blood urea nitrogen (BUN), and serum creatinine obtained. Patients with elevation of

the serum creatinine or significant hydronephrosis benefit from nephrologic evaluation and a 24-hour urine collection for creatinine clearance and urine volume.

Special attention must be given to patients after prior urinary diversion. Permanent intestinal diversions in children are now typically confined to patients requiring cystectomy for cancer. Most urinary diversions performed today are temporary in nature. **The key to urinary undiversion is to understand the original pathology that led to diversion.**

Urodynamics

Bladder Dynamics: Capacity and Compliance

Urodynamic testing of the lower urinary tract plays an essential role when considering bladder reconstruction. Results in infants and children are reproducible but require meticulous attention to detail (Joseph, 1994). Several mechanical factors adversely influence urodynamic data, creating artifacts that, if not recognized, can have a negative impact on the validity of the evaluation. Testing is typically performed with transurethral catheter placement. The size of the catheter can influence the measured leak point pressure, voiding pressure, and ability to empty completely, particularly in infants and young boys (Dexter and Harpser, 1992). Suprapubic catheter placement circumvents this problem but is not practical in most cases. The testing medium and infusion rate can influence the results. Carbon dioxide is not as reliable as fluid infusion, particularly when evaluating bladder compliance and capacity. Most commonly, saline or iodinated contrast is used at body temperature to provide reproducible results (Joseph, 1993, 1996). End filling pressure, and therefore bladder compliance, can be dramatically affected by simply changing the filling rate (Joseph, 1992). Bauer (1979) suggested that the cystometrogram be performed at a fill rate of no greater than 10% of the predicted bladder capacity per minute.

Special nuances may be necessary after diversion by vesicostomy. Any bladder is likely to show small capacity in that setting. A repeated study after several days of bladder cycling by occlusion of the vesicostomy may be more predictive of bladder function; the bladder may respond to cycling quickly (McGuire, personal communication, 1996; Errando et al, 2005). Temporary occlusion of the ostomy with a gastrostomy button may be informative (de Badiola et al, 1995).

Sphincter Dynamics: Outflow Resistance

The bladder neck and external urinary sphincter work in synergy, but only one is required for maintenance of urinary continence. Neurogenic dysfunction often leads to abnormalities of the bladder neck and external urinary sphincter, resulting in diminished outlet resistance during storage and/or dyssynergic function with voiding. Monitoring of external urinary sphincter electrical activity is required for evaluation of coordinated voiding and dyssynergic detrusor sphincter activity. Perineal surface electrodes, abdominal wall sensors, anal plugs, vaginal monitors, electrical wires, and concentric needle electrodes have all been used for electromyography (Joseph, 1996). In children with neurogenic dysfunction, a concentric needle electrode or dual needle electrodes placed through a 25-gauge needle increase accuracy when measuring sphincter activity (Blaivas et al, 1977; Joseph, 1996).

The functional length of the external urinary sphincter also plays a role in outflow resistance, and its measurement can be undertaken with urethral pressure profilometry (UPP). Unfortunately, the short length and small diameter of the pediatric urethra makes this study technically challenging because the mechanical pulling device is not practical for pediatric use. To perform UPP, a constant infusion of testing medium at a rate of 2 mL/min using a continuous Harvard pump is required (Joseph, 1996), eliminating pressure wave artifacts noted with the standard roller ball infusion pumps. Hand withdrawal of the catheter is used, marking every 5 mm on the recording strip. With experience and a cooperative patient, reliable measurements can be obtained. There is limited value comparing

specific UPP results for a patient against standard nomograms; however, preoperative UPP for a given patient provides baseline information that can be beneficial when assessing the intraoperative and postoperative functional urethral length.

Some surgeons use leak point pressure to evaluate outflow resistance during passive filling and Valsalva. It should be recognized that the leak point pressure may be artifactually elevated by the urodynamics catheter in a small male urethra (Decter and Harpster, 1992). Work remains to determine how well such measurable parameters correlate. Khoury and associates (2008) suggest that the presence of bladder trabeculation often predicts that outlet resistance is adequate and that such patients are likely to do well with augmentation cystoplasty alone.

Bladder Emptying

The patient's ability to empty the bladder before reconstruction should be assessed carefully. Parameters influencing bladder emptying include synergistic relaxation of the external sphincter on electromyography, urinary flow rates, and residual postvoid urine. Neurologically intact patients able to empty their bladder well preoperatively are much more likely to do so after reconstruction than are patients with neurogenic dysfunction. **No test ensures that a patient will be able to void spontaneously and empty well after bladder augmentation or other reconstruction.** Therefore all patients must be prepared to perform CIC postoperatively. The native urethra should be examined for the ease of catheterization. Ideally, the patient should learn CIC and practice it preoperatively until the patient, family, and surgeon are comfortable that catheterization can and will be done reliably. Physical and psychosocial limitations of the patient must be considered with regard to the ability to self-catheterize and perform independent care. **Failure to catheterize and empty reliably after bladder reconstruction may result in upper tract deterioration, urinary tract infection, or bladder perforation despite a technically perfect operation.** Most patients who may catheterize per native urethra or an abdominal wall stoma will overwhelmingly prefer the latter (Horowitz et al, 1995).

PATIENT PREPARATION

Bladder and sphincter reconstructive procedures remain challenging. The patient's general status should be optimized to afford the best chance to achieve a good result with the least risk of morbidity. General nutritional and hydration status should be determined and corrected, if necessary, before surgery. Coexisting medical problems, particularly cardiac and pulmonary issues, should be well managed preoperatively.

Bowel Preparation

Each patient undergoes preoperative bowel preparation to minimize the potential risk of surgery if the use of any bowel is required. Even when ureterocystoplasty or other alternatives are planned, intraoperative findings may dictate the need for use of a bowel segment. Two days of a clear liquid diet before bowel preparation aid in clearing of solid stool. The patient should then undergo full mechanical bowel preparation the day before surgery. Such bowel preparations have usually been done in the hospital (O'Donnell, 2007); however, recent trends find this changing to an outpatient setting. Major reconstructive procedures often require many hours of operative time with large fluid shifts. It is critical that the patient be well hydrated at the time of surgery even if it necessitates the use of intravenous fluids during the preoperative day. The use of oral antibiotics in bowel preparation, once dogma, is now a matter of personal preference. Special attention must be paid to the bowel preparation of patients with neurogenic dysfunction. Most of these patients have chronic constipation, and effective bowel cleansing can be difficult in such patients. Several days of oral cathartics at home may be helpful before formal preparation. Children with

renal insufficiency should be observed carefully during bowel preparation for dehydration and electrolyte disturbances.

Theoretically, gastric contents are sterile, and administration of parenteral antibiotics or a routine bowel preparation is not necessary before gastrocystoplasty. Gundeti and associates (2006) suggested that routine bowel preparation may not be necessary before ileocystoplasty in children.

Urine Culture

All patients should have a urine culture performed several days before bladder reconstruction. Any patient with a positive preoperative urine culture should undergo treatment with either oral or intravesical antibiotics and have a second culture documenting sterile urine before the procedure. Many pediatric patients undergoing augmentation cystoplasty have spina bifida and a ventriculoperitoneal shunt. With a negative urine culture and good bowel preparation, the incidence of shunt infection or problems should be very low (Yerkes et al, 2001; Hayashi et al, 2008).

Cystoscopy

Preoperative cystoscopy may be the final step in evaluating the native bladder, outflow, or ureteral orifices in pediatric patients. Endoscopy, if done, should be performed immediately before bladder reconstruction under the same anesthetic. Based on history, an occasional patient may warrant endoscopic or radiographic gastrointestinal evaluation preoperatively.

KEY POINTS: EVALUATION AND PREPARATION

- Evaluation for renal function, upper tract obstruction, and vesicoureteral reflux should be performed if hydronephrosis is present, although most such changes are secondary to the bladder dysfunction.
- Careful urodynamic evaluation is critical to understand all problems that may contribute to the dysfunction.
- The patient will likely require CIC to empty after reconstruction and must be capable of performing it on a reliable basis.
- Commitment of the patient and family is essential.
- Basic preoperative preparation includes sterile urine and thorough bowel cleansing.

ANTIREFLUX

Ureteral reimplantation into bladder, whether the ureter is dilated or not, is a standard procedure familiar to all pediatric urologists and reconstructive surgeons. The long-term success rate is good and complications rare. Such reimplantation is certainly preferable and usually possible during lower tract reconstruction. Special attention must be given to chronically scarred, short ureters sometimes found after urinary diversion. In Henden's extensive experience with urinary undiversion (1998), most complications were related to those ureters.

Transureteroureterostomy and Single Ureteral Reimplant

Occasionally, the urinary bladder is so small that it is inadequate for bilateral reimplantation, and alternatives must be considered. It is preferable to reimplant both ureters separately, although if the native urinary bladder is small and adequate for only a single ureteral tunnel, transureteroureterostomy (TUU) and a single reimplant may be helpful (Fig. 145-1). Typically, the better ureter should be implanted into the bladder. The crossing ureter should be mobilized to swing gently across the abdomen to the recipient side in a smooth course without tension. It should be carefully mobilized with all of its adventitia and as much periureteral tissue

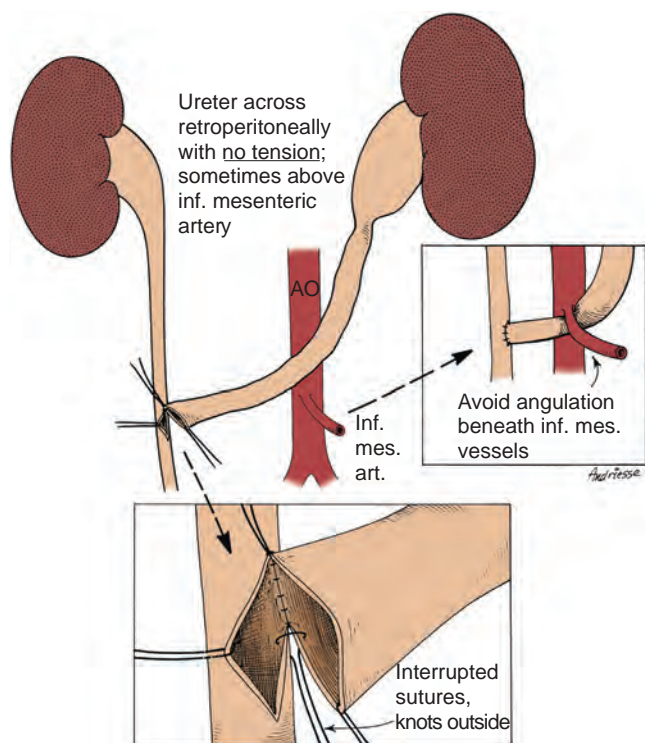


Figure 145-1. Technique for transureteroureterostomy. AO, aorta; inf. mes. art., inferior mesenteric artery. (Courtesy W. Hardy Hendren.)

as possible to preserve blood supply. Care must be taken not to angulate the crossing ureter immediately beneath the inferior mesenteric artery. The crossing ureter is widely anastomosed to the posteromedial aspect of the recipient ureter. The recipient is not mobilized or brought medially to meet the end of the other ureter. TUU when fashioned appropriately is successful and carries minimal risk for leakage or obstruction (Hodges, et al, 1963; Hendren and Hensle, 1980; Noble et al, 1997; Mure et al, 2000; Iwaszko et al, 2010). A history of previous calculi remains a relative contraindication to TUU.

The manner in which the bladder is opened may optimize its use for a single reimplant. Rather than incising the bladder in the anterior midline, a wide, anterior U-shaped incision based cephalad can be made. This potentially elongates the bladder as a posterior plate that can be brought to one side or the other to meet a single ureter. For ureteral reimplantation after such an incision, a psoas hitch of the bladder fixes the bladder in position for a long, straight ureteral tunnel. Incision of the bladder in this way may also be useful in placing a continent catheterizable stoma to the umbilicus.

Psoas Hitch

Fixation of the bladder to the psoas muscle allows for precise control of both the length and direction of a ureteral reimplant. A psoas hitch should prevent any angulation of the ureter with bladder filling. Such angulation may be particularly problematic or obstructive with a dilated and scarred ureter. The bladder should be secured to the psoas muscle and fascia using nonabsorbable sutures. Those sutures must not enter the bladder lumen or stones will occur. Broad, shallow purchases of the psoas muscle and fascia should be used to hold long term without trapping the sciatic nerve. The hitching sutures should not be tied so tightly that they cut through either bladder or psoas muscle. The contralateral bladder pedicle may be divided to increase bladder mobility and the length of the hitch on occasion. Although Hendren and Hensle (1980) suggested that the ureteral reimplant is more easily performed before the bladder hitch (Fig. 145-2), the steps should be performed

in whichever order allows each to be done precisely with good visualization.

Antireflux with Intestinal Segments

Necessity of ureteral reimplantation into an intestinal segment may occasionally determine the segment to be used for bladder augmentation or replacement. Long experience with ureterosigmoidostomy and colon conduit diversion has established an effective means of creating antireflux into a colonic segment; a flap valve mechanism can be created by tunneling the ureter beneath a tenia. Principles learned from ureterosigmoidostomy include a direct mucosal-to-mucosal anastomosis and a submucosal tunnel of adequate length. This technique has provided favorable long-term results since the 1950s (Nesbit, 1949; Goodwin et al, 1953; Leadbetter and Clarke, 1954) and is based on the initial work of Coffey (1911). Implantation may be done from within the reservoir or from without after the intestinal segment has been completely reconfigured and closed.

If a gastric segment is used for bladder augmentation or replacement, ureters may be reimplanted into the stomach in a manner remarkably similar to that used in the native bladder. The same principles for choosing the length of tunnel relative to the width of the ureter are used as with bladder. Creating an effective antireflux mechanism into an ileal segment is more difficult. The split nipple technique described by Griffith may prevent reflux at least at low reservoir pressure (Turner-Warwick and Ashken, 1967; Patil et al, 1976; Stone and MacDermott, 1989; Sagalowsky, 1995). A short longitudinal incision is made in the distal ureter, and the ureteral wall is turned back on itself. The nipple should be at least twice as long as the width of the ureter. The cuff is stabilized by suturing the ureter to itself. The adventitia of the ureter immediately proximal to the cuff is then approximated to the full thickness of the ileal wall at the hiatus so that the cuff protrudes into the lumen. Le Duc et al, (1987) described a technique in which the ureter is brought through a hiatus in the ileal wall. From that hiatus, the ileal mucosa is incised and the edges are mobilized so as to create a trough for the ureter. The spatulated ureter is laid into the trough and approximated to the mucosa at the distal end. The ileal mucosa is sutured to the lateral edges of the ureter and should eventually grow over it. Long-term results with these two techniques have been conflicting but in general have not proven as reliable as a tunneled uretero-colonic anastomosis in preventing reflux (Patil et al, 1976; Le Duc et al, 1987; Rowland, 1996; Bihrlé, 1997), with one exception (Lugagne et al, 1997). It is also possible to create an antirefluxing, serosally lined tunnel between two limbs of ileum as described by Abol-Enein and Ghoneim (1999; Soygur et al, 2005).

Reinforced nipple valves of ileum have been used extensively for antireflux with the Kock pouch (Skinner et al, 1989). After several modifications by Skinner, good long-term results have been achieved. His technique requires a relatively long segment of ileum and use of permanent staples. Attempts have been made to secure the nipple long term without staples or mesh (Hanna and Blois, 1987; Gosalbez and Gousse, 1998; Tsuchiya et al, 2004). Maintenance of the intussuscepted cuff is the key to a successful result. The same forces that compress the nipple to achieve antireflux or continence tend to evert or destabilize it. An ileal nipple valve may be particularly useful with short, dilated ureters; an isoperistaltic segment of ileum may be left with the nipple to replace a short ureter. The antireflux mechanism is based on the ileal segment and not the ureter. In some neobladders, an isoperistaltic limb of ileum is positioned between the reservoir and ureters to discourage reflux, at least at low pressures (Studer and Zingg, 1997).

KEY POINTS: ANTIREFLUX

- Ureteral reimplantation into native bladder is preferable when necessary; the initial bladder incision may facilitate such a procedure.
- An antireflux mechanism can be created with any bowel segment but is most challenging with ileum.

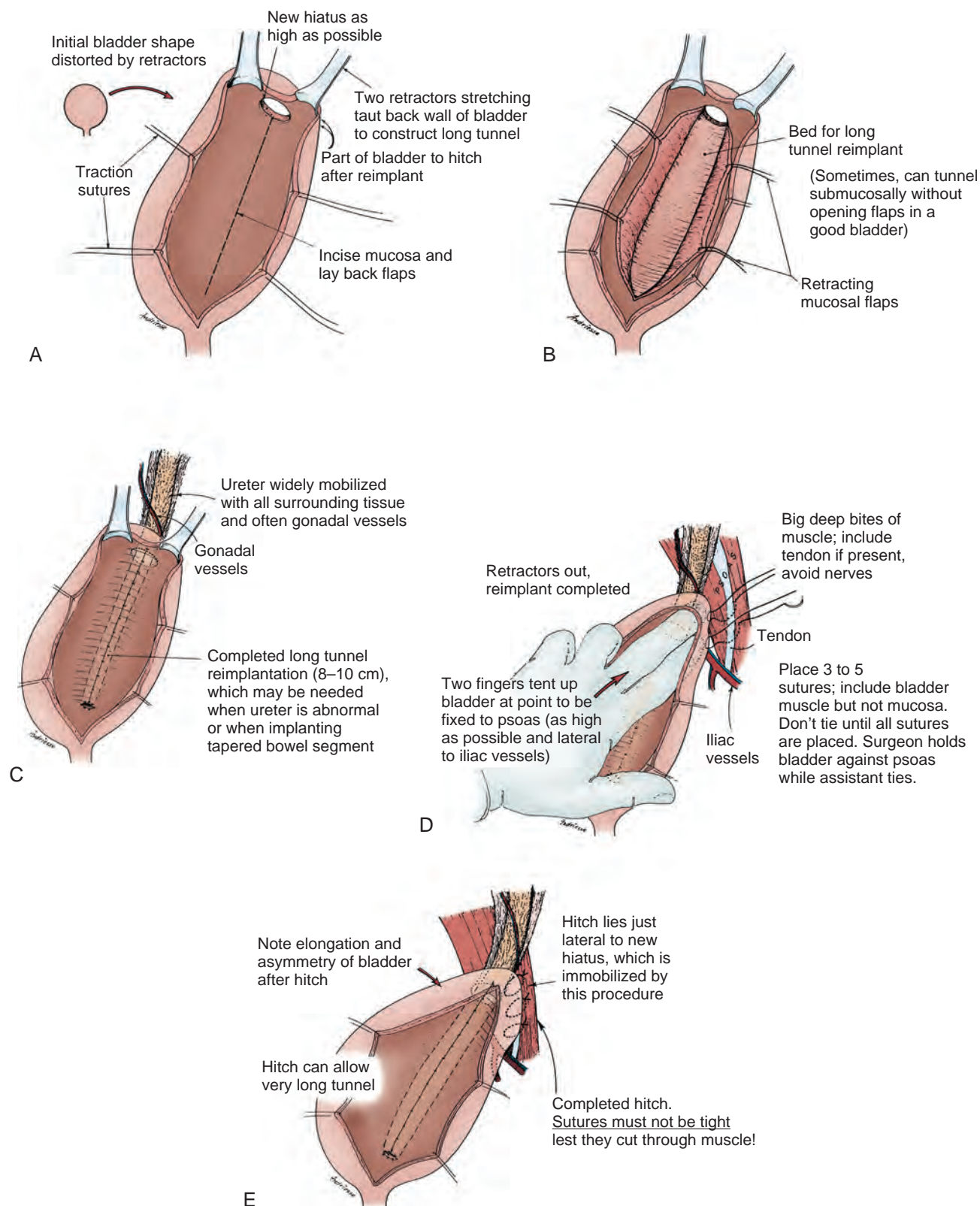


Figure 145-2. Technique for psoas hitch, which allows the construction of a long reimplantation tunnel and prevents angulation of the ureter or tapered bowel segment when the bladder fills. Monofilament nonabsorbable suture material is used to fix the bladder to psoas muscle. Care must be taken to avoid entering the bladder, which might cause stone formation on a suture. (Courtesy W. Hardy Hendren.)

BLADDER NECK RECONSTRUCTION

One of the greatest technical challenges facing the surgeon regarding bladder reconstruction is reliably providing adequate outflow resistance to achieve continence. The cause of bladder neck dysfunction may be neurogenic in origin or anatomic as noted with exstrophy, bilateral ectopic ureters, or ureteroceles. Each unique problem must be considered when addressing outlet resistance. Many operative techniques have been described for bladder neck reconstruction, indicating that no single option is best for all patients (Kryger et al, 2000; Cole et al, 2003; Lemelle et al, 2006). **It cannot be overstated that preoperative evaluation and thorough knowledge of the patient's specific physiologic limitations are required.**

The capability for a sustained bladder contraction to result in complete emptying by voiding or the absence of hyperreflexic contractions influences the technique selected for gaining outlet resistance. All operative techniques that create an increase in outlet resistance do so at the expense of detrusor contractility. For reasons not clearly defined, increasing outlet resistance can result in a noncompliant hostile detrusor environment (Bauer et al, 1986; Burbige et al, 1987; Churchill et al, 1987). Provocative cystometry may uncover only some patients at risk, and close postoperative observation is mandatory (Kronner et al, 1998b).

Multiple techniques are available to tighten the bladder neck and include creation of a flap valve mechanism, placement of artificial or autologous bulking agents, slings, and the artificial urinary sphincter (AUS). **The selected option is individualized to the patient's pathologic process, needs, goals, and desire for independence.**

An important consideration is the patient's ability to empty well before reconstruction and the likelihood that he or she will be able to do so afterward. Many of the repairs prohibit spontaneous voiding. Some patients with neurogenic dysfunction will require bladder augmentation and an increase in bladder outflow resistance, resulting in the need for CIC. Other diagnoses, especially when augmentation cystoplasty is not necessary, may allow for spontaneous voiding.

The following section covers operative techniques used to achieve urinary continence through bladder neck and external urinary sphincter reconstruction. Most of the results are based on experience in individuals with spinal dysraphism, but the techniques are used in children with other pathogenic conditions. All techniques have a learning curve that necessitates careful analysis of results and forthright reporting. An evidence-based review of operative bladder neck procedures found assessment of results to be limited by several factors, including the lack of a true, consistent definition of "success" and "continence," consideration of patients with and without concomitant bladder augmentation, and consideration of small patient populations with mixed pathologic conditions (Joseph et al, 2003).

Young-Dees-Leadbetter Repair

The Young-Dees-Leadbetter bladder neck reconstruction is one of the most recognized operative techniques to increase outlet resistance. The original Young procedure has evolved and remains of primary consideration when reconstructing the exstrophic bladder neck (Ferrer et al, 2001).

Technique

Young's initial description (1919) of excising a portion of the bladder neck and tightening the bladder neck over a silver probe was modified by Dees (1949), who extended the length of excised tissue through the trigone. Leadbetter (1964) followed by elevating the ureters off the trigone and placing them in a more cephalad position on the bladder floor. This allowed for tubularization of the trigone and enhanced lengthening of the urethra. A detailed description and illustrations are found in the chapter on bladder exstrophy.

Results

Reports of success with the Young-Dees-Leadbetter bladder neck reconstruction in children with neurogenic sphincter dysfunction are limited, not only in the number of patients but also in overall improvement. Tanagho (1981) and Leadbetter (1985) independently reviewed their long-term results and showed minimal success in individuals with neurogenic dysfunction. They speculated that the outcomes were the result of a lack of muscle tone and activity in the wrapped muscle related to the underlying neurogenic problem. Many patients in the early series did not undergo bladder augmentation, possibly compromising the continence achieved. Contrary to the results reported in exstrophy patients, most individuals with neurogenic deficiency of the bladder neck require bladder augmentation and intermittent catheterization. Sidi and colleagues (1987b) documented a 4-hour continence interval in 7 of 11 patients after such repair, although 10 required catheterization and nine augmentation. Five of the 7 needed a second surgery to achieve continence. This small series is one of the more recent showing long-term results of the Young-Dees-Leadbetter reconstruction in children with neurogenic dysfunction, as it has largely fallen out of favor. In an attempt to enhance the Young-Dees-Leadbetter procedure, Mitchell and Rink (1983) described the addition of external support and compression achieved through the placement of a silicone sheath around the reconstructed bladder neck. This was done to establish a plane for future placement of an artificial sphincter cuff, if necessary. The sheath improved the function of the repair by either increasing coaptation or maintaining the repair in a better anatomic position. Unfortunately, most of the thicker Silastic sheaths eventually eroded into the bladder or urethra (Kropp et al, 1993). Quimby and colleagues (1996) used a thinner Silastic sheath with interposed omentum and reported less risk of erosion. The authors noted improved continence and felt placement of an artificial sphincter cuff was easier when needed.

Donnahoo and colleagues (1999) reviewed one of the largest series of this repair used in neurogenic incontinence (38 children, 25 of whom were girls). A primary repair was performed in 24 children, a secondary procedure in 6, and a primary repair in conjunction with a silicone sheath in 8. Partial continence was achieved after the initial repair in 26 children (68%). All children with the silicone sheath were initially continent, but erosion occurred in 5. In addition, 35 (92%) of the children required augmentation cystoplasty in order to become continent without hostile detrusor characteristics. The authors found that although continence could be achieved with this technique, it was at the expense of augmentation cystoplasty and multiple procedures. Their results are similar to those reported by Cole and associates (2003).

Fascial Sling

Sling procedures were developed in an attempt to increase resistance at the bladder neck. Both artificial tissue and autologous fascia have been used. Continence is based on coaptation and elevation of the bladder neck that approximates opposing epithelial surfaces and increases outlet resistance greater above resting bladder pressure and the pressure reached during stressful activity or Valsalva behavior. With sling coaptation, the bladder neck remains fixed, and although a strong detrusor contraction can establish a voiding pressure leading to urinary flow, it rarely allows adequate bladder emptying in the face of anatomic or neurologic problems. The majority of pediatric patients who undergo a sling procedure must be prepared for CIC. The resistance achieved with bladder neck slings can potentially be overcome by overactive bladder contractions or elevated pressure caused by diminished bladder compliance. Therefore, simultaneous bladder augmentation has again been reported in 55% to 100% of patients who achieve urinary continence after a sling procedure (Bauer et al, 1989; Elder, 1990; Decter, 1993; Kakizaki et al, 1995; Perez et al, 1996a; Dik et al, 1999; Walker et al, 2000; Bugg and Joseph, 2003; Cole et al, 2003; Dik et al, 2003; Godbole and Mackinnon, 2004).

Only Snodgrass and colleagues have reported good results of bladder neck reconstruction without augmentation cystoplasty in these patients (Snodgrass et al, 2007, 2010; Snodgrass and Barber, 2010). However, long-term assessment from 2000 to 2014 of 109 patients from this group found that 70% required an additional continence procedure, 30% have required augmentation, 50% developed upper tract changes, and 20% developed chronic kidney disease (Grimsby et al, 2015). Alternatives to fascia, such as an expanded fluorocarbon polymer (Gore-Tex) have been used in a similar fashion, although early continence has not been maintained (Godbole and Mackinnon, 2004). Good early results have been noted with some biodegradable scaffolds (Colvert et al, 2002).

Technique

The bladder neck is exposed by clearing fatty tissue overlying the bladder neck and the lateral endopelvic fascia. An incision is made within the endopelvic fascia for approximately 2 cm. The junction between the bladder neck and proximal urethra can be identified by placing a transurethral catheter into the bladder and gently pulling down on the catheter to lodge the balloon at the bladder neck. Using blunt dissection, a plane between the posterior bladder neck and vagina in girls or rectal wall in boys is developed. The proper plane may be more easily developed from the cul-de-sac by dissecting behind the bladder and ureters from above (Lottmann et al, 1999; Badiola et al, 2000). If the landmarks are not easily defined, as in a secondary repair, the dissection becomes difficult. It may be appropriate to open the bladder to help prevent inadvertent dissection into the urethra or posterior structures. Dik and colleagues (2003) proposed use of a transvaginal approach, eliminating the need to open the bladder or dissect between the bladder neck and anterior vagina.

When fascial tissue is used, the technique is based on that described by McGuire and Lytton (1978) for stress urinary incontinence. Rectus abdominus fascia 1 cm in width and of an appropriate length is harvested. This fascia can be taken either in vertical or horizontal fashion depending on the initial skin incision. Fascia from other sites has been used in a similar fashion but requires a second incision. Cadaveric tissue or biodegradable scaffolds may also be used (Colvert et al, 2002; Misseri et al, 2005; Albouy et al, 2007). All are usually secured to the anterior rectus fascia on either side. Autologous fascial tissue has been used combining the benefits of a compressive wrap and suspension of the proximal urethra and bladder neck. Several variations of fascial placement and configuration have been described (Woodside and Borden, 1982; McGuire et al, 1986; Elder, 1990; Perez et al, 1996a; Bugg and Joseph, 2003; Dik et al, 2003). When fascial slings and wraps are used for neurogenic sphincter incontinence, there is not as much concern for creating a wrap or sling that is too tight because most patients are preferentially managed with CIC. Placement of a bladder neck sling using laparoscopic and robotic assistance is currently being explored by minimally invasive surgeons (Storm et al, 2008; Mattioli et al, 2010; Bagrodia and Gargollo, 2011). Magnification and access to the bladder neck in the deep pelvis appear to aid in the dissection and placement.

Results

Fascial slings have been used more extensively and with better results in girls with neurogenic sphincter incompetence, although recently some success has been reported in boys. Overall, long-term success with fascial slings in the neurogenic population has varied greatly from 40% to 100% (Kryger et al, 2000). A variation thought to contribute to a higher success includes a circumferential fascia wrap around the bladder neck. A circumferential wrap may equalize the compressive pressure over a greater surface area of bladder neck and posterior urethra (Walker et al, 1995; Strang et al, 2006). With the wrap, simultaneous suspension has also been used (Bugg and Joseph, 2003). Success rates have varied so

much that it is difficult to determine whether any modification of the sling accounts for an increase in continence. Most patients who have undergone a fascial sling or wrap have also had simultaneous bladder augmentation. **Success of the sling, as with most repairs, appears to be improved with augmentation cystoplasty in this patient population by almost all reports (Castellan et al, 2005).** Perez and associates (1996a) reviewed the outcome of sling cystourethropexy in 39 children, 15 of whom were boys. One of four various techniques was performed. When evaluating postoperative continence based on age, sex, underlying diagnosis, preoperative urodynamics, surgical technique, and enterocystoplasty, only concomitant enterocystoplasty was predictive of a successful outcome. This was not the experience of Snodgrass, who reported successful outcome of bladder neck sling without the need for enterocystoplasty. Snodgrass and colleagues (2010) reported manageable bladder hostility in their determination, but no need for augmentation, in 26 patients who underwent a sling only. They achieved continence in 46% of 35 patients undergoing a sling alone and 82% of 17 patients undergoing a sling combined with a Leadbetter-Mitchell bladder neck repair (Snodgrass and Barber, 2010).

Unlike with the Silastic sheath, erosion rarely occurs with fascial slings. Gormley and colleagues (1994) reported a revision rate with fascial slings of 15%. Placement of a fascial sling does not eliminate the possibility of later placement of an AUS (Decter, 1993; Barthold et al, 1999). It is not unreasonable to consider placing a fascial sling in a child with a marginally competent bladder neck and deficient external sphincter if the child is undergoing augmentation cystoplasty and already requires intermittent catheterization.

Bladder Neck Bulking Agents

Vorstman and colleagues (1985) reported one of the initial descriptions of injection therapy with a bulking agent into the bladder neck of incontinent children. The initial enthusiasm for use of polytetrafluoroethylene was quickly tempered because of concern over migration of particles to regional and distant sites including pelvic nodes, lungs, brain, kidney, and spleen found in animal models (Malizia et al, 1984). The technique remains of interest, and several alternatives to polytetrafluoroethylene have been assessed, including glutaraldehyde cross-linked collagen, dextranomer/hyaluronic acid copolymer, and polydimethylsiloxane (Leonard et al, 1990a; Guys et al, 2006; Knudson et al, 2006; Lottmann et al, 2006; Dean et al, 2007; Alova et al, 2012a). Bovine collagen should not be used in latex-sensitive children with spina bifida because the product is not latex free (Kryger et al, 2000). In an attempt to achieve an ideal substance for injection, investigation is ongoing using autologous cartilage cells harvested from a separate site then grown in an alginate matrix for endoscopic implantation (Bent et al, 2000). Preliminary results show a positive effect in women with stress incontinence. Whether this or other materials will be appropriate alternatives for neurogenic sphincter incontinence in children is yet to be seen.

To alleviate the risks of injecting a foreign biologic product, alternatives to collagen and bovine have been investigated. Polydimethylsiloxane is one such agent. It is composed of sterile solid textured silicone particles, with an average size of 200 µg, suspended in a biologic hydrogen carrier. The large size of the particles should virtually eliminate lymphatic and distant migration (Beisang and Ersek, 1992; Guys et al, 1999; Halachmi et al, 2004; Guys et al, 2006). Contemporary reports favor the use of dextranomer/hyaluronic acid (Lottmann et al, 2006; Dean et al, 2007; Dyer et al, 2007; Kitchens et al, 2007; Kaye et al, 2010; Alova et al, 2012a).

Technique

Endoscopic exposure is used for localizing the proximal urethra and bladder neck. Injection can be done directly through the working channel of the endoscope, often one with an offset lens system.

Ideal placement of the material is in a subepithelial space mobilizing the epithelium toward the lumen of the bladder neck. When completed in a circumferential fashion, adequate epithelial coaptation may occur, which can raise outlet resistance. Alternatively, periurethral injection in women through a long needle placed from the perineum or via a suprapubic approach has been used. [Dean and colleagues \(2007\)](#) advocate a combined antegrade and retrograde approach. Evidence is lacking regarding whether the exact approach affects success, but accurate placement is important and transurethral injection is usually preferred.

Results

The durability and success of bladder neck and proximal urethral injection remain in doubt for the pediatric population, particularly those with neurogenic dysfunction. True continence, as defined by a 4-hour dry period between voidings or catheterizations, has been reported to be at most 78% and has ranged as low as 5% ([Leonard et al, 1990a](#); [Capozza et al, 1995](#); [Bomalaski et al, 1996](#); [Perez et al, 1996b](#); [Sundaram et al, 1997](#); [Silveri et al, 1998](#); [Guys et al, 2001](#); [Godbole et al, 2003](#); [Halachmi et al, 2004](#); [Dean et al, 2007](#); [Kitchens et al, 2007](#); [De Vocht et al, 2010](#); [Kaye et al, 2010](#); [Alova et al, 2012a](#); [Dajusta et al, 2013](#)). Several factors play a role in the outcome, one of which is a history of any previous operative bladder neck repair. Success is enhanced by elevation of the epithelium of the bladder neck, which may be compromised by scarring from previous operative procedures. **The concept of a minimally invasive operation used to enhance a marginal result gained from a more formal bladder neck repair is enticing; unfortunately, the data are lacking to show that bladder neck injection is of lasting value or that repeat treatments are warranted in that setting** ([De Vocht et al, 2010](#); [Alova et al, 2012a](#); [Dajusta et al, 2013](#)).

[Sundaram and colleagues \(1997\)](#) reported on the efficacy and durability of glutaraldehyde cross-linked bovine collagen in 20 children, 12 of whom had neurogenic sphincter dysfunction. Over half of the children required two or three independent injections. Success was achieved in only 1 patient (5%) who was considered dry; 5 had some improvement, and 10 had either no change or transient improvement for only 2 to 90 days. In the hands of these researchers, collagen therapy only delayed the ultimate need for bladder neck reconstruction. Submucosal bladder neck injection of bovine dermal collagen was used by [Perez and colleagues \(1996b\)](#) in 32 patients. Continence was achieved after a single injection in only 20% of the children with neurogenic dysfunction. The authors concluded that even though their success was limited, the low morbidity and ease of placement justified a trial of submucosal injection in selected children.

[Guys and associates \(2006\)](#) treated 49 children with polydimethylsiloxane, 41 of whom had neurogenic bladder neck and sphincter incontinence. The level of continence deteriorated through 18 months after the procedure, then stabilized. After an average follow-up of 73 months, success had been achieved in 16 (33%), and 7 (14%) were improved. [Godbole and associates \(2003\)](#), [Halachmi and colleagues \(2004\)](#), and [Dyer and coworkers \(2007\)](#) independently came to the conclusion that regardless of the material injected (polytetrafluoroethylene, collagen, polydimethylsiloxane, dextranomer/hyaluronic acid), short-term success is not long lasting. [Alova and colleagues \(2012b\)](#) determined that failure after 1 year using dextranomer and hyaluronic acid was primarily caused by neurogenic bladder dysfunction and deterioration. However, failure after injection therapy does not preclude a successful outcome when it is salvaged by more invasive measures ([Alova et al, 2012b](#)).

The cost of the bulking agents can be excessive, and there does not appear to be any financial benefit over a formal repair ([Kryger et al, 2000](#)). At present, bulking agents play a limited role for increasing outlet resistance and should be reserved for a very select group of patients. **The exact criteria that define that group have not been well established.** Patients with marginal native outflow resistance are probably better candidates than those with minimal preoperative function.

Artificial Urinary Sphincter

The AUS has been recognized as a device that can result in prompt continence in select children while preserving their ability to void spontaneously. The AUS was introduced by [Scott and colleagues \(1974\)](#). The general concept and design of the initial model have been retained; however, improvements and enhancements have evolved that have a positive impact on the long-term success of the AUS. The current AS800 model includes a seamless, pressurized balloon reservoir, nonkink tubing, and changes in the cuff that facilitate its placement and effectiveness with coaptation of the bladder neck and proximal urethra ([Light and Reynolds, 1992](#); [Barrett et al, 1993](#); [Ruiz et al, 2006](#); [Lai et al, 2007](#); [Catti et al, 2008](#)). Alternatives to the AS800 model have also been explored ([Vilar et al, 2004](#); [Farrugia et al, 2012](#)).

Technique

Placement of the cuff should be at the level of the bladder neck in all females and prepubertal boys ([Fig. 145-3](#)). It is also the most desirable and effective location in pubertal and adult males with neurogenic sphincter incompetence. The bulbar urethra can be used as an alternative site in men with mature spongiosum. [Levesque and colleagues \(1996\)](#) have indicated that age is not a factor regarding placement of the cuff around the bladder neck. They found that children do not outgrow the AUS as they progress through puberty and that replacement of the cuff is not routinely necessary. The AUS cuff can be positioned around intestinal segments used in total urinary reconstruction but are more prone to erosion there. Several authors have described the successful placement of the cuff around a bowel segment, particularly when omentum is interposed between the cuff and the segment ([Burbige et al, 1987](#); [Weston et al, 1991](#); [Light et al, 1995](#)).

Placement of an AUS in children is the same as that described for adults. Development of the proper plane for the cuff is virtually identical to that described for a fascial sling. The cuff should be sized snugly, but not tightly, around the bladder neck. Obviously a sterile environment is critical when considering placement of the AUS to avoid infection. For that reason, preoperative antibiotics are a necessity, and confirmation of sterile urine required. With those precautions, there is freedom to open the bladder when dissecting around the bladder neck. This often will facilitate the dissection and ensure proper placement. The AS800 model has a locking mechanism in the pump that permits the AUS to be deactivated and activated without a second operative procedure. Experience has shown that leaving the unit deactivated with the cuff deflated after placement allows formation of a pseudocapsule around the cuff and decreases the risk of erosion ([Furlow, 1981](#); [Hanna, 1981](#); [Sidi et al, 1984](#)). The noncycled AUS occasionally may provide enough resistance for continence, eliminating the disadvantages of activation ([Herndon et al, 2004](#)).

Results

There are substantial short- and long-term data regarding continence after placement of the AUS, with the largest series presented by [Herndon and associates \(2003\)](#). **In investigation of continence, it must be placed in context of the cost experienced by the patient, defined by mechanical malfunctions resulting in secondary operative procedures and more catastrophic complications such as device infection or erosion.** Dramatic improvement regarding the need for secondary procedures has occurred because of the technical refinements in the device. Ten- to 15-year long-term follow-up of the AUS in children has been reported ([Levesque et al, 1996](#); [Kryger et al, 1999](#); [Castera et al, 2001](#); [Kryger et al, 2001](#); [Hafez et al, 2002](#); [Herndon et al, 2003](#); [López Pereira et al, 2006](#); [Ruiz et al, 2006](#)). All groups report an impressive continence rate of 80% and a functioning sphincter in 95% of patients. These reports are consistent with older series in children that reported continence rates of 75% to 90% and a functioning sphincter in 85% to 97% ([Nurse and Mundy, 1988](#); [Gonzalez et al, 1989a](#); [Bosco](#)

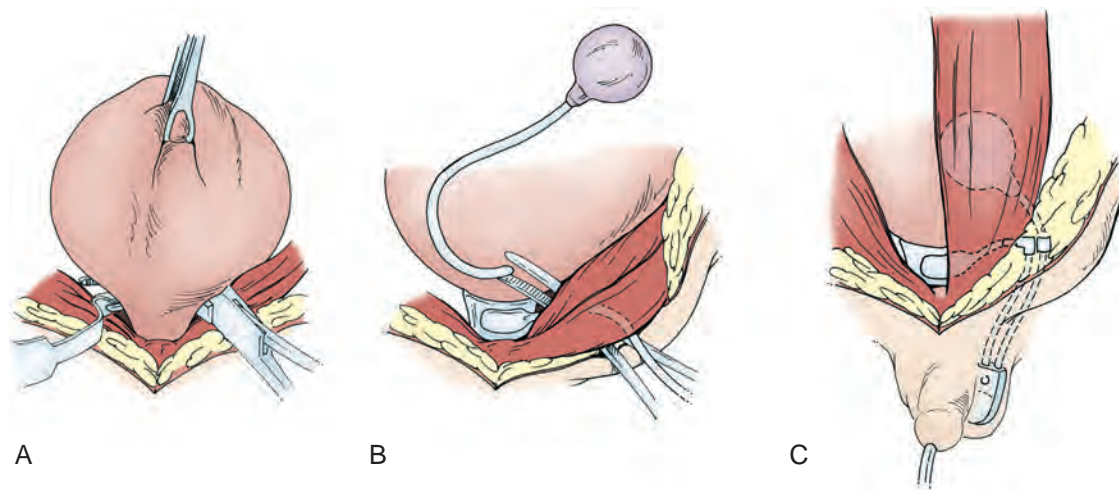


Figure 145-3. Artificial urinary sphincter placement in children. A, The cuff is placed around the bladder neck in prepubertal children. Dissection may be facilitated by palpation of a urethral catheter and balloon or by a posterior approach. If dissection is difficult, the bladder can be opened. B, The reservoir is placed beneath the rectus muscle. C, A tunnel is then made into the scrotum or labia for positioning of the pump on the same side as the reservoir. Tubing connections are made ventral to the rectus fascia, and the device is initially left deactivated.

et al, 1991; O'Flynn and Thomas, 1991; Aprikian et al, 1992; Simeoni et al, 1996; Singh and Thomas, 1996; Ruiz et al, 2006; Catti et al, 2008). Herndon and associates (2003) present the most comprehensive long-term data. They achieved overall continence in 86% of 142 patients with an average follow-up of 10 years. Age at implementation does not appear to affect continence (Kryger et al, 2001).

Although the AUS is one of the few surgically created continence mechanisms that does not negatively affect spontaneous voiding, CIC remains an important adjunct in approximately 75% of children with neurogenic sphincter incompetence and can be performed successfully through the cuff (Diokno and Sonda, 1981; Gonzalez et al, 1995; Levesque et al, 1996; Kryger et al, 1999; Castera et al, 2001; Kryger et al, 2001; Hafez et al, 2002; Herndon et al, 2003; Ruiz et al, 2006; Catti et al, 2008). As boys approach puberty, spontaneous voiding may become progressively inadequate. It has been speculated that growth of the prostate causes an increase in native outlet resistance. Kaefer and colleagues (1997a) evaluated increases in cuff size to facilitate spontaneous voiding in boys. In their limited series, they did not find that upsizing restored the ability to void spontaneously. Jumper and colleagues (1990) reported on prostatic development and sexual function in pubertal boys with spinal dysraphism who had been treated with the AUS. They found that the artificial sphincter did not alter sexual development, prostatic growth, or morphology.

Herndon and associates (2003) reported device malfunction with 64% of the pre-AS800 model and 30% with the AS800. Sphincter erosion was similar for the pre-AS800 and AS800, occurring at 19% and 16%, respectively, in their experience, similar to the reports of others (Ruiz et al, 2006; Bauer, 2008). Fastidious attention to detail and sterile technique diminish the risk of infection but do not eliminate it. When infection occurs without erosion, the unit can be removed and later replaced (Nurse and Mundy, 1988). Infections are minimized by sterilizing the urine preoperatively, meticulously cleaning the wound site, using a preoperative bowel preparation, administering perioperative parenteral antibiotics, and performing copious antibiotic wound irrigation. Newer cuff design and a 6-week delay in activation of the device help formation of a thickened pseudocapsule that substantially decreases bladder neck and proximal urethral erosion. Kryger and colleagues (1999) indicated that erosion can be virtually eliminated when the cuff is placed as the primary treatment for bladder neck incompetence.

They and others (Aliabadi and Gonzalez, 1990; Gonzalez et al, 1995; Levesque et al, 1996; Simeoni et al, 1996; Castera et al, 2001; Hafez et al, 2002; Herndon et al, 2003) noted that the risk of erosion is substantially increased after previous failed repairs, with only Ruiz and colleagues (2006) noting results to the contrary. Identifying the correct plane between the bladder neck and vagina in females or rectum in males preserves the vascularity of the bladder neck and proximal urethra and may decrease the rate of erosion (Aliabadi and Gonzalez, 1990). Initial exposure via a posterior bladder approach may be helpful (Hanna, 1981; Lottmann et al, 1999). Shankar and colleagues (2001) suggested that there is an advantage to exposure of the bladder neck with a transperitoneal approach by decreasing the potential of bleeding from the prostatic venous plexus and improving visualization of the rectal wall.

Levesque and associates (1996) evaluated the long-term outcome of the AUS based on date of insertion and location of the placement. Before 1985 the AUS was inserted in 36 children. From 1985 to 1990, an additional 18 children underwent placement. In the original group, 24 of the 36 sphincters were in place and 22 functional. Twelve had required at least one revision. The mean survival of the device was 12.5 years. Success rates at 5 and 10 years were 75% and 72%, respectively. In the group that underwent implantation after 1985, 78% retained a functioning sphincter. The overall continence rate in both groups was 59%; sphincter survival probability at 10 years was approximately 70%. There was no difference found between failure rates in males and those in females, with the exception that female patients who had previously undergone bladder neck surgery were more likely to develop erosion. The ability to void independently without the use of CIC was retained in 36 (67%) children. Those findings are supported by contemporary series (Levesque et al, 1996; Kryger et al, 1999; Castera et al, 2001; Kryger et al, 2001; Hafez et al, 2002; Herndon et al, 2003; Ruiz et al, 2006; Catti et al, 2008; Bar-Yosef et al, 2011). A meta-analysis of 585 children who had undergone AUS placement was reviewed by Bauer (2008). He reported that 80% of patients with a retained sphincter were continent, with approximately 32% spontaneously voiding. Secondary surgery was required in 28%; 19% had erosion involving the bladder neck, 50% of whom had undergone prior bladder neck surgery. It appeared that use of a low-pressure balloon reservoir (61% to 70% cm H₂O) had been advantageous. Placing only the cuff during bladder augmentation

may provide effective continence with decreased complications as reported by [Viers and colleagues \(2014\)](#).

Upper urinary tract changes including hydronephrosis have been reported to occur in up to 15% of children after placement of the AUS ([Light and Pietro, 1986](#); [Churchill et al, 1987](#); [Gonzalez et al, 1995](#); [Levesque et al, 1996](#); [Kryger et al, 1999](#)). In extreme cases, renal insufficiency has resulted. It is now recognized that occlusion of the bladder neck in children with neurogenic sphincter incompetence can result in the unmasking or development of detrusor hostility manifesting with a decrease in bladder compliance or increase in detrusor overactivity ([Bauer et al, 1986](#); [Bauer, 2008](#)). Careful preoperative urodynamic assessment helps to identify only some of the children who are at risk ([Kronner et al, 1998b](#); [Dave et al, 2008](#)). When hostile bladder characteristics are found preoperatively, anticholinergic medications can be beneficial for hyperreflexic contractions, but augmentation cystoplasty is usually required for diminished compliance. [Churchill and associates \(1987\)](#) showed that favorable parameters can be maintained after placement of the AUS; however, close observation is still recommended in any child undergoing bladder neck reconstruction to identify any early deterioration in bladder dynamics before upper tract changes.

Some children undergoing sphincter placement need bladder augmentation as well, and the timing of the two procedures may be questioned owing to the concern for AUS infection. [Light and colleagues \(1995\)](#) reported a 50% infection rate with simultaneous augmentation compared with 9.5% when the procedures were staged. To the contrary, a contemporary review by [Miller and coworkers \(1998\)](#) found infection necessitating removal of the device occurred in only 2 of 29 such patients (7%). This low rate is similar to that noted by others ([Gonzalez et al, 1989b](#); [Strawbridge et al, 1989](#)). Several reports have evaluated various factors and found that the intestinal segment selected for augmentation appeared to be the only parameter affecting results; gastric augmentation was the least offensive regarding infection ([Ganesan et al, 1993](#); [Miller et al, 1998](#); [Holmes et al, 2001](#)). [Gonzalez and colleagues \(2002\)](#) reported an alternative technique using a seromuscular colocolostomy and simultaneous placement of the AUS. They achieved continence in 89% without the need for additional procedures and with no deterioration of the upper urinary tract. Although infection of the AUS is a concern, placement can be successfully undertaken when bowel is simultaneously used for total continent reconstruction of the bladder and bowel ([Bar-Yosef et al, 2011](#)).

The AS800 is the subject of most reviews when discussing the AUS, but alternative devices have been reported. [Lima and associates \(1996\)](#) and [de O Vilar and colleagues \(2004\)](#) reported on the combined use of enterocystoplasty and a "new type" of AUS. The new device is a one-piece adjustable cuff connected to an inflatable port. The cuff provides static, fixed resistance that enhances continence and allows for intermittent catheterization. The injection port is placed subcutaneously and made available for percutaneous access to adjust the fluid volume and pressure of the cuff needed to maintain continence. It is particularly convenient for individuals with limited ability to actively pump the AS800. [Farrugia's group \(2012\)](#) in particular has reported good early results with the alternative device.

The ultimate benefits of the AUS lie in its ability to achieve a high rate of continence while maintaining the potential for spontaneous voiding. For practical purposes, when intermittent catheterization is required along with augmentation cystoplasty, use of native tissue for continence eliminates the long-term concern for infection or erosion and the risk of mechanical failure.

Urethral Lengthening

[Young's original description of bladder neck reconstruction \(1919\)](#) consisted of two components: excision of a segment of anterior urethral bladder neck tissue and narrowing of the adjacent remaining posterior portion. This, however, ultimately led to failure because the tubularized segment remained unsupported within the

bladder. Refinements by [Dees \(1949\)](#) and [Leadbetter \(1964\)](#) maximized good muscle tone at the bladder neck and extension of the urethral tube through the trigone.

[Tanagho \(1981\)](#) described a cephalad-based anterior detrusor wall tube. Closure of the tubularized bladder neck created circularly oriented muscle fibers, which Tanagho described as a sphincter mechanism. He, however, cautioned against the use of this technique in the neurogenic population. Because of potential breakdown of that tubularized bladder neck and poor results, other techniques have been developed based on the concept of a flap valve mechanism for urinary retention. [Kropp and Angwafo \(1986\)](#) described urethral lengthening and creation of a flap valve for neurogenic bladder neck and sphincter dysfunction. The technique is based on an anterior detrusor wall tube that is kept in continuity with the urethra, tubularized, and implanted into a submucosal tunnel within the trigone. Conceptually this is effective; however, difficulty with catheterization is a common problem and significant concern.

Technique

A Foley catheter is placed intravesically and the bladder filled to capacity. The bladder is exposed through either a midline or low transverse abdominal incision. The bladder neck is then identified with application of gentle catheter traction. A 6- × 2-cm rectangular flap based on the bladder neck and urethra is then isolated. Stay sutures are placed, and the flap is mobilized in continuity with the proximal urethra. The detrusor musculature at the bladder neck is divided, separating the bladder and urethra, or the muscle may be left intact at the 5 and 7 o'clock positions. In girls the anterior vaginal wall is exposed; in boys, the seminal vesicles. The rectangular strip based on the urethra is tubularized posteriorly around the urethral catheter with a continuous absorbable suture. The distal portion of the tubularized strip should be approximated in an interrupted fashion to facilitate excision of excessive tissue without jeopardizing the suture line. A capacious submucosal tunnel through the trigone is then created posteriorly for the neourethra ([Fig. 145-4](#)). A wide tunnel is required in order to prevent kinking at the level of the bladder neck, which would impede catheterization. It is important to eliminate dead space at the entrance of the urethra into the bladder; this can be accomplished by placing lateral anchoring sutures in the region of the bladder neck. The detrusor tube must be pulled straight through the tunnel without curve or deviation to facilitate catheterization. [Waters and colleagues \(1997\)](#) and [Kropp \(1999\)](#) have not found it necessary to reimplant all ureters in a cephalic location; they now typically reimplant only refluxing ureters ([Kropp, 1999](#)). When closing the bladder, the lateral wings in the region of the bladder neck are approximated and incorporate adventitia of the tubularized urethra. This enhances a watertight closure and is continued for 2 to 3 cm anteriorly, often up to the area of augmentation. The tubularized neourethra should be long enough to reach the true lumen of the bladder, where it is exposed to pressure as an effective flap valve.

Because of the difficulties with catheterization, modifications of the Kropp bladder neck procedure have been described. [Belman and Kaplan \(1989\)](#) suggested a simplified approach. They harvested a rectangular strip from the anterior bladder wall similar to that described by Kropp. The lateral and posterior musculature at the bladder wall, however, is not incised, and the proximal urethra and bladder are not separated. The flap is tubularized over an 8-Fr catheter. The epithelium on the floor of the bladder is incised contrary to the tunnel made by Kropp. The tube is placed within the trough with the proximal meatus secured on the floor of the bladder. The epithelial edges of the trough are then secured to the lateral aspect of the tube. As with the initial description, the suture line for tubularization of the urethra lies posteriorly against trigonal muscle. Closure of the bladder begins with reapproximation of the lateral walls of the bladder to the tube until the bladder edges meet. The remaining portion of the bladder is covered by an augmentation. Regardless of any modification to the Kropp bladder neck procedure, catheterization potentially remains problematic, and

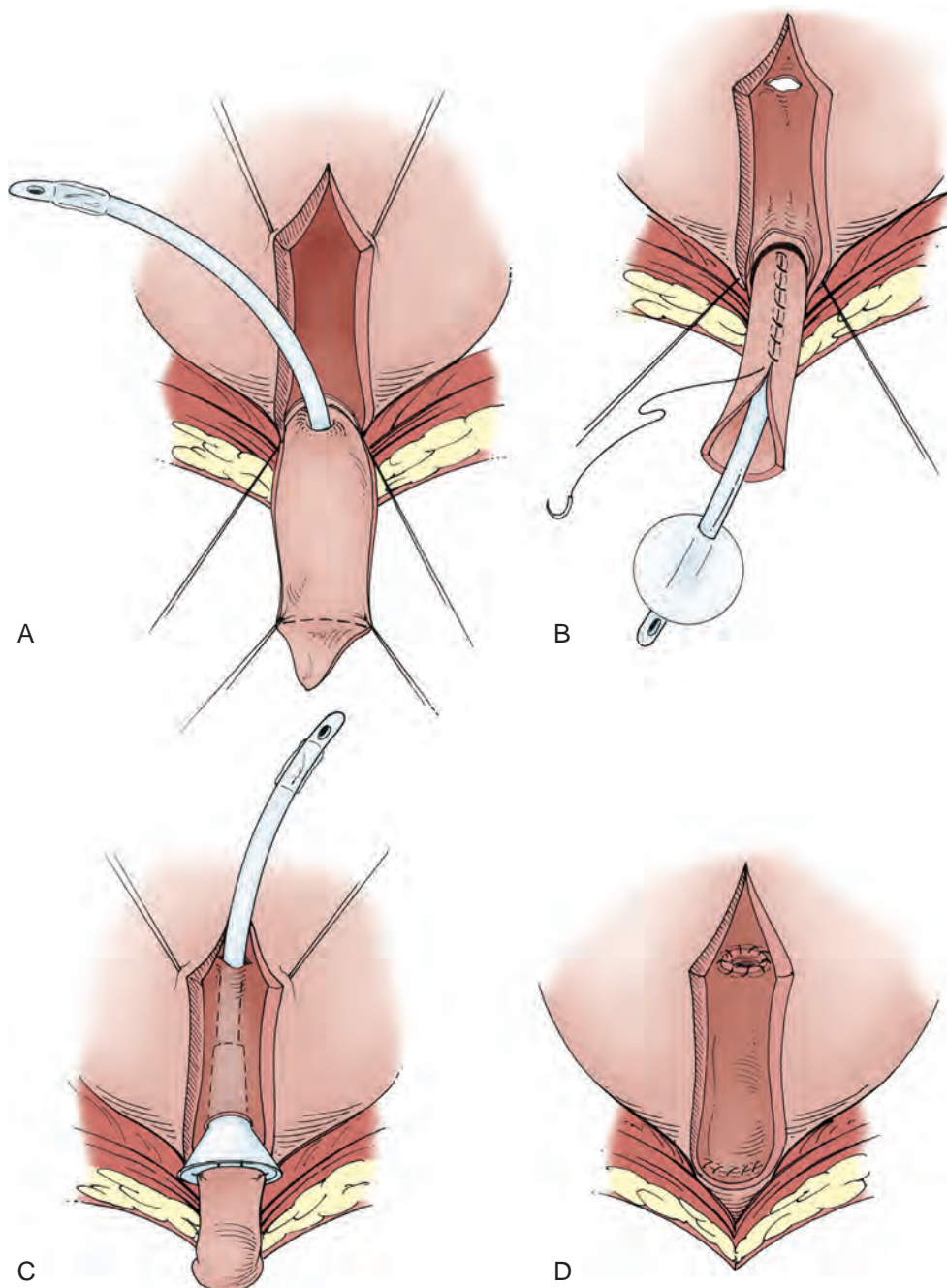


Figure 145-4. Kropp anterior detrusor tube. **A**, An anterior flap of bladder (2 cm wide \times 5 to 6 cm long) is developed in continuity with the urethra. **B**, The anterior flap is tubularized over a catheter. A tunnel beneath the mucosa of the trigone is made between the ureteral orifices for the length of the tube. **C**, The tubularized flap is brought through the tunnel. **D**, The detrusor tube is secured to the floor of the trigone with interrupted absorbable suture in a straight course.

therefore the patient should be prepared for a catheterizable abdominal-vesicle channel.

An innovative trial by [Chrzan and colleagues \(2013\)](#) was undertaken in 18 patients, using laparoscopic techniques that allowed for "vesicoscopic" exposure of the bladder neck. Chrzan and coworkers were able to lengthen the urethra by creating a U incision around the bladder neck and onto the epithelial surface of the bladder dome. This prevented interference of the ureteral orifices and could be undertaken in patients in whom other bladder neck procedures had failed. Unfortunately, a long-term benefit has not been achieved.

Results

[Snodgrass \(1997\)](#) examined the results in 23 children, 22 of whom had neurogenic sphincter incompetence, and noted continence in over 90% of the children. The most common complication was difficult catheterization, particularly in boys. Less than half of the boys in Snodgrass's series catheterized through the native urethra; the majority did so via an abdominal wall stoma. Postoperative vesicoureteral reflux was identified in 9 of 18 children, and Snodgrass speculated this was because of lateral retraction of the ureters. Their recommendation was made to leave the posterior bladder wall

open and flat when receiving the augmentation in order to prevent this distortion. Kropp (1999) has not had as much difficulty with catheterizations in his patients and likewise has achieved a high rate of continence without a high incidence of new reflux.

Some patients with an effective flap valve mechanism created by urethral lengthening will virtually never leak per urethra. This potentially puts them at risk for upper tract deterioration or bladder rupture, particularly if they do not or cannot catheterize reliably. Snodgrass (1997) thought that his modification was beneficial in that it resulted in a shorter intravesical tunnel for the neourethra, allowing for leakage per urethra with overfilling.

Pippi Salle Procedure

In an attempt to maximize the benefits of the Kropp technique and decrease problems with catheterization, Salle and associates (1994) reported an anterior bladder onlay flap. With this technique, the posterior wall of the neourethra is intact, theoretically providing less potential hang-up during catheterization. Since the first report, modifications have been made to improve flap viability, minimize fistula formation, and extend the indications for the procedure beyond that of the neurogenic bladder (Salle et al, 1997).

Technique

An anterior, full-thickness bladder wall flap 5×1 cm is mobilized to the bladder neck with 0.1 cm of its epithelial edges excised to avoid overlapping suture lines. Two parallel incisions down to the level of the muscle are made in the mucosa of the trigone from the native bladder neck. The anterior flap is secured to the midline strip of trigone mucosa to create a tube or lengthened urethra using absorbable suture. The muscle on either side of the posterior epithelial strip may be incised superficially to provide an edge to which the muscle of the anterior flap may be approximated with a second layer of suture in an effort to avoid fistula (Fig. 145-5). The more lateral mucosa of the trigone is mobilized and closed over the midline urethra. Distally, the muscle of the bladder neck is wrapped tightly around the urethra with closure. Proximally, the lengthened urethra should extend well into the lumen of the bladder.

Results

Initial complications of this procedure included persistent incontinence, urethrovesical fistula, and partial necrosis of the intravesical neourethra. Widening the base of the urethra at the level of the bladder neck may minimize these problems. Children who have previously undergone bladder surgery can have a secondary Salle repair if the anterior bladder flap is lateralized slightly to avoid any old midline suture line.

Salle and coworkers (1997) found that continence was achieved in 12 of 17 patients (71%) for more than 4 hours. Catheterization difficulties occurred in only 3 of 17 children, 1 of whom subsequently underwent an appendicovesicostomy. Fistula formation at the base of the flap between the proximal, intravesical urethra and bladder occurred in 2 children and resulted in recurrent incontinence. This problem appears to be diminished by creating a wider base to the flap and generously trimming the epithelial edges there. Jawaheer and Rangecroft (1999) reported a diurnal continence rate of 61% for 3 or more hours with the Salle procedure. However, only 44% of their patients were dry through the night. Less trouble with catheterization has occurred relative to the Kropp technique and rarely remains a problem. Continence rates have not been quite as high in most series (Rink et al, 1994; Mouriquand et al, 1995; Cole et al, 2003).

Canales and associates (2006) used a miniature intravesical lengthening of shorter length (3 cm) and radius (8 Fr) with the intent of enhancing resistance, minimizing the use of bladder, and avoiding need for ureteral reimplantation. After 2.5 years of follow-up, 8 of 9 children were continent and had an average leak point pressure of 71 cm H₂O.

Bladder Neck Division

The ultimate procedure to increase bladder outlet resistance is to divide the bladder neck so that it is no longer in continuity with the urethra. It must be accompanied by creation of a continent abdominal wall stoma and should be performed only in patients who will reliably catheterize. If effective, it prevents any leakage or pop-off per urethra and increases the risk for upper tract deterioration or bladder rupture if emptying is not performed. Division is seldom performed as a primary procedure but may be considered if the previously mentioned repairs fail (Khoury et al, 1999; Bergman et al, 2006; Landau et al, 2009; De Troyer et al, 2011; Baradaran et al, 2012; Kavanagh et al, 2012).

Closing the bladder neck moves the reconstructive effort into the realm of continent urinary diversion. The bladder neck is abandoned from a physiologic standpoint, although the bladder may be used as part of the reservoir. Effective division of the bladder neck is not a simple procedure. The bladder must be aggressively mobilized away from the urethra. The bladder should be closed distally in several layers after the posterior lip of bladder neck and trigone are rolled anteriorly and widely separated from the distal urethra. Omentum has usually been interposed, as has rectus abdominus muscle (Smith et al, 2010). Without these steps, fistulization and leakage per urethra can occur (Khoury et al, 1999; Nguyen and Baskin, 2003). With aggressive mobilization, the fistula rate can be low (Thomasch et al, 2009). Although eliminating secondary access to the bladder creates a concern, long-term follow-up indicates that a successful outcome is achieved in almost all patients (Landau et al, 2009; De Troyer et al, 2011; Kavanagh et al, 2012).

KEY POINTS: BLADDER NECK RECONSTRUCTION

- Any repair other than placement of an AUS, particularly if combined with cystoplasty, is likely to make spontaneous voiding inadequate.
- Young-Dees-Leadbetter repair in the spina bifida population has variable success related to the underlying neurogenic dysfunction.
- Fascial slings have been used more extensively and with better results in girls than boys with neurogenic dysfunction, although those results vary widely.
- Experience does not yet suggest that injection of bladder neck bulking agents has a lasting effect on severe neurogenic sphincter incompetence.
- A functioning, well-positioned artificial sphincter provides good resistance and is best reserved for patients who can empty adequately with spontaneous voiding.
- Urethral lengthening procedures use a flap valve mechanism for continence that disrupts any chance of voiding and may make catheterization per urethra difficult.
- The success of most bladder neck repairs in the neurogenic population improves if combined with augmentation cystoplasty.
- Bladder neck repair may unmask or result in new bladder hostility; careful follow-up is mandatory.

AUGMENTATION CYSTOPLASTY

The initial approach to the patient for augmentation cystoplasty is similar regardless of the bowel segment to be used. Cystoscopy may be performed preoperatively to identify any unsuspected anatomic abnormalities that may affect the surgery or postoperative care. If other bladder procedures such as ureteral reimplantation are to be performed, the bladder is left full after cystoscopy. If not, the bladder is emptied to allow easy access to the peritoneal cavity.

As a general rule, a midline incision is preferred for intestinal cystoplasty, although these procedures can be performed through a lower transverse incision if there has been no previous

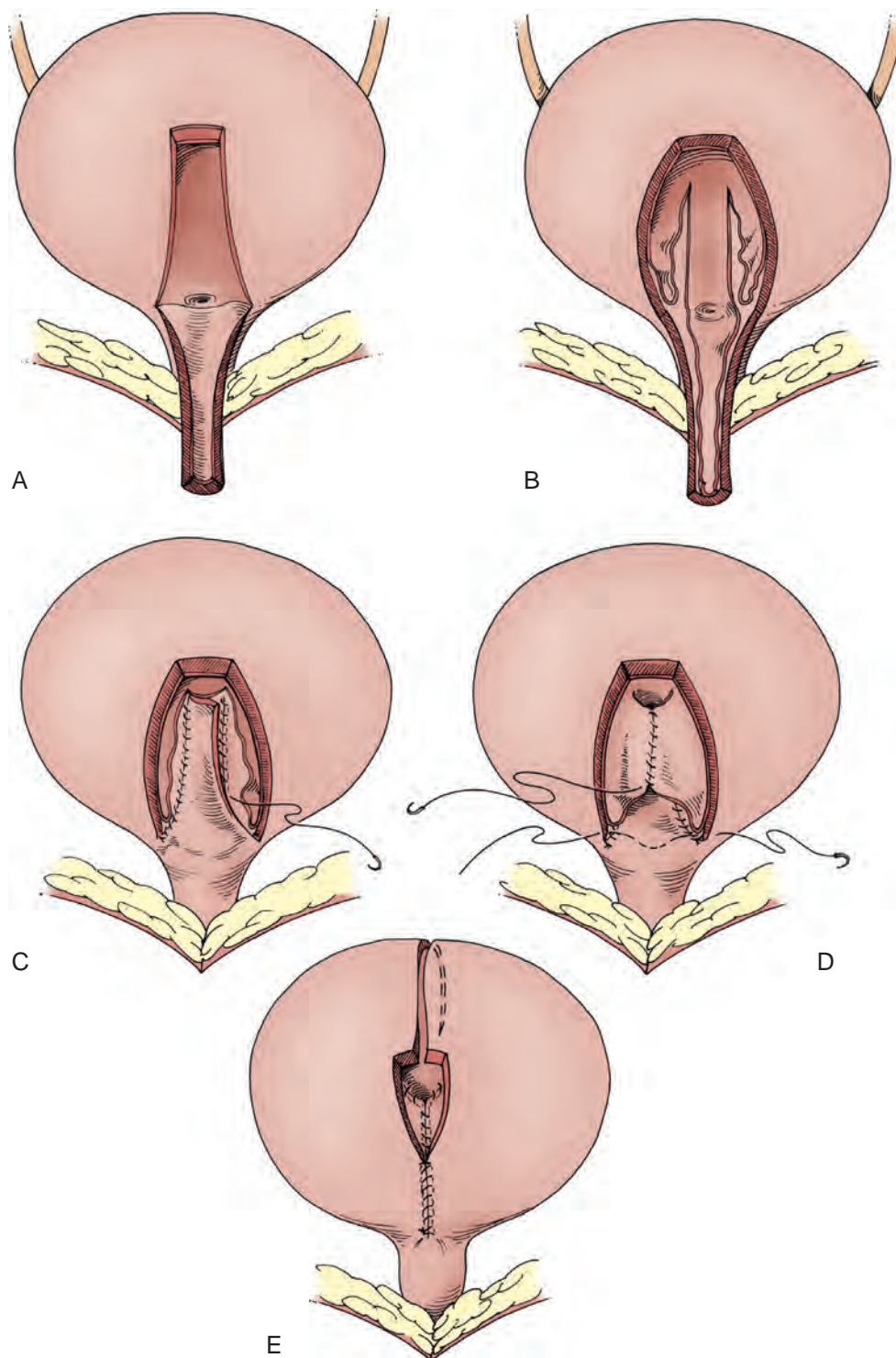


Figure 145-5. Pippi-Salle anterior detrusor tube only. A, An anterior detrusor tube (1 cm × 4 to 5 cm) is mobilized to the level of the bladder neck. B, A central strip on the floor of the bladder is developed by incision of the epithelium on either side. C, The anterior detrusor flap is secured to the strip in a two-layer fashion, approximating the epithelium with the first layer and muscle with the second. D, The lateral mucosa of the trigone is mobilized and secured over the lengthened urethra. Distally, the bladder is closed to itself and should incorporate a portion of the anterior detrusor flap to ensure a watertight seal. E, After distal closure the remaining portion of the bladder is left open if augmentation cystoplasty is necessary.

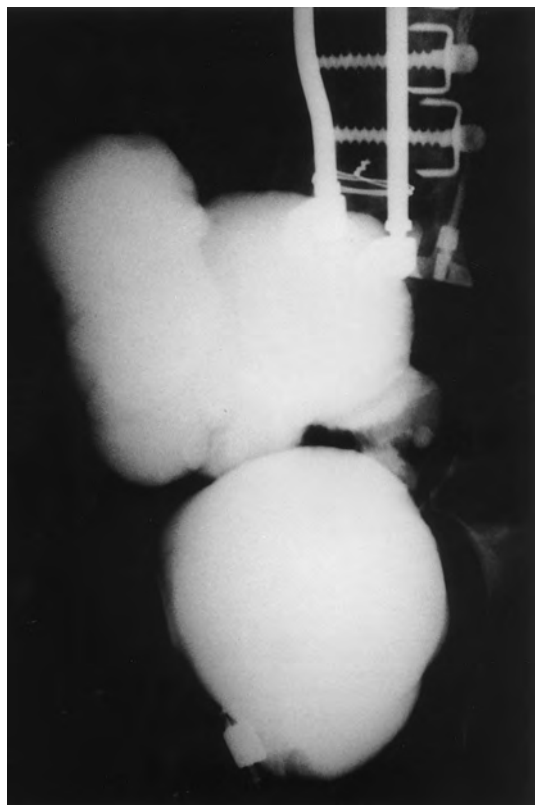


Figure 145-6. Cystogram after augmentation demonstrates a narrow anastomosis of the bowel segment to bladder. The segment behaves like a diverticulum.

abdominal surgery. Laparoscopic assistance with mobilization of the intestine may allow augmentation through a smaller, lower incision (Hedican et al, 1999). Associated bladder procedures should be performed before opening the peritoneal cavity to minimize third space fluid loss. For gastrocystoplasty, the incision extends from the pubis to the xiphoid to allow more cephalad exposure. Augmentation cystoplasty may be performed completely by laparoscopy with or without use of a robotic system (Lorenzo et al, 2007; Wang et al, 2007; Passerotti et al, 2008). For such cases, a 12-mm camera port is placed periumbilically or supraumbilically, and up to four 5- to 8-mm working ports are used; one working port should be larger if an endostapler is to be used. Assistant ports are optional, and the use of the fourth robotic arm may aid with retraction or passage of sutures (Gundeti et al, 2008).

Management of the Native Bladder

In the past, it had been recommended that the majority of the “diseased” bladder be excised in preparation for augmentation. This meant removal of the supratrigonal bladder, leaving only a small cuff for anastomosis to the intestinal segment. Despite the cuff, a relatively small area was left for anastomosis to the bowel segment; most of the bowel was approximated to itself. Most surgeons now preserve the native bladder as long as it is widely opened to prevent a narrow-mouthed anastomosis, which can result in the augmentation segment behaving as a diverticulum (Fig. 145-6). A sagittal incision to bivalve the bladder is generally useful (Fig. 145-7). The incision is carried from a point several centimeters cephalad to the bladder neck anteriorly to a position just above the trigone posteriorly. Such an incision allows a technically easier anastomosis to the bowel segment and leaves the native bladder to add to the overall capacity. A greater circumference for the anastomosis can be provided if need be, by opening the bladder in a stellate fashion with a second transverse incision into the two bladder halves. There have been reports of penile or perineal pain

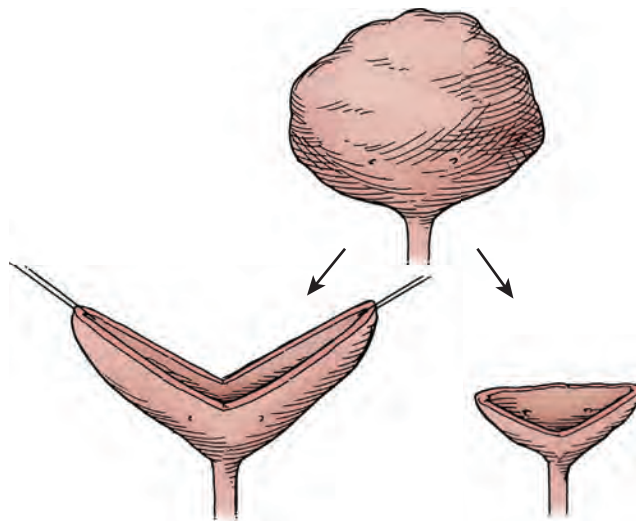


Figure 145-7. The native bladder can be managed by supratrigonal excision of the diseased bladder. More typically, the bladder is opened widely in a sagittal plane (left).

in sensate boys after augmentation with preservation of the native bladder (Phelps and Malone, 2004). Although four such patients required secondary removal of bladder, similar problems have not been frequent enough to warrant routine excision at the time of augmentation.

Management of Intestinal Segments

Hinman (1988) and Koff (1988) demonstrated the advantages of opening a bowel segment on its antimesenteric border with subsequent detubularization and reconfiguration of that intestinal segment. Reconfiguration into a spheric shape provides multiple advantages, including maximization of the volume achieved for any given surface area, blunting of bowel contractions, and improvement of overall capacity and compliance. All intact, tubular intestinal segments have been noted to generate pressures of 60 to 100 cm H₂O with contractions (Kock, 1969; Light and Engelmann, 1985; Fowler, 1988; Camey et al, 1991). Detubularization lowered the maximal contractile pressure from 63 to 42 cm H₂O in the right colon and 81 to 28 cm H₂O in ileum (Goldwasser et al, 1987). Furthermore, a shorter intestinal segment can be used to achieve the same capacity than when left in tubular form. Detubularization and reconfiguration should always be performed during augmentation cystoplasty.

Mathematical models based on the length and width of the bowel segment used may predict the volume needed but are cumbersome (Rink and Mitchell, 1990). Depending on the volume needed, 20 to 40 cm of ileum or approximately 20 cm of colon are typically used for cystoplasty. This somewhat depends on the volume of the native bladder being augmented. If the cystoplasty is being done on a bladder of moderate volume that generates high pressure by uninhibited contractions, less bowel is necessary than for one that is tiny in capacity. Unless otherwise contraindicated, the surgeon should err by making the bladder too large rather than too small. Appreciation of the patient's urinary volumes also should influence the size of the bladder required. Patients with upper tract damage may make huge volumes of urine and require a larger capacity.

Ileocystoplasty

Goodwin and associates (1959) were among the first to demonstrate the numerous ways to anastomose a patch of ileum to the native bladder after the ileum was detubularized and reconfigured to achieve the most spheric shape possible.

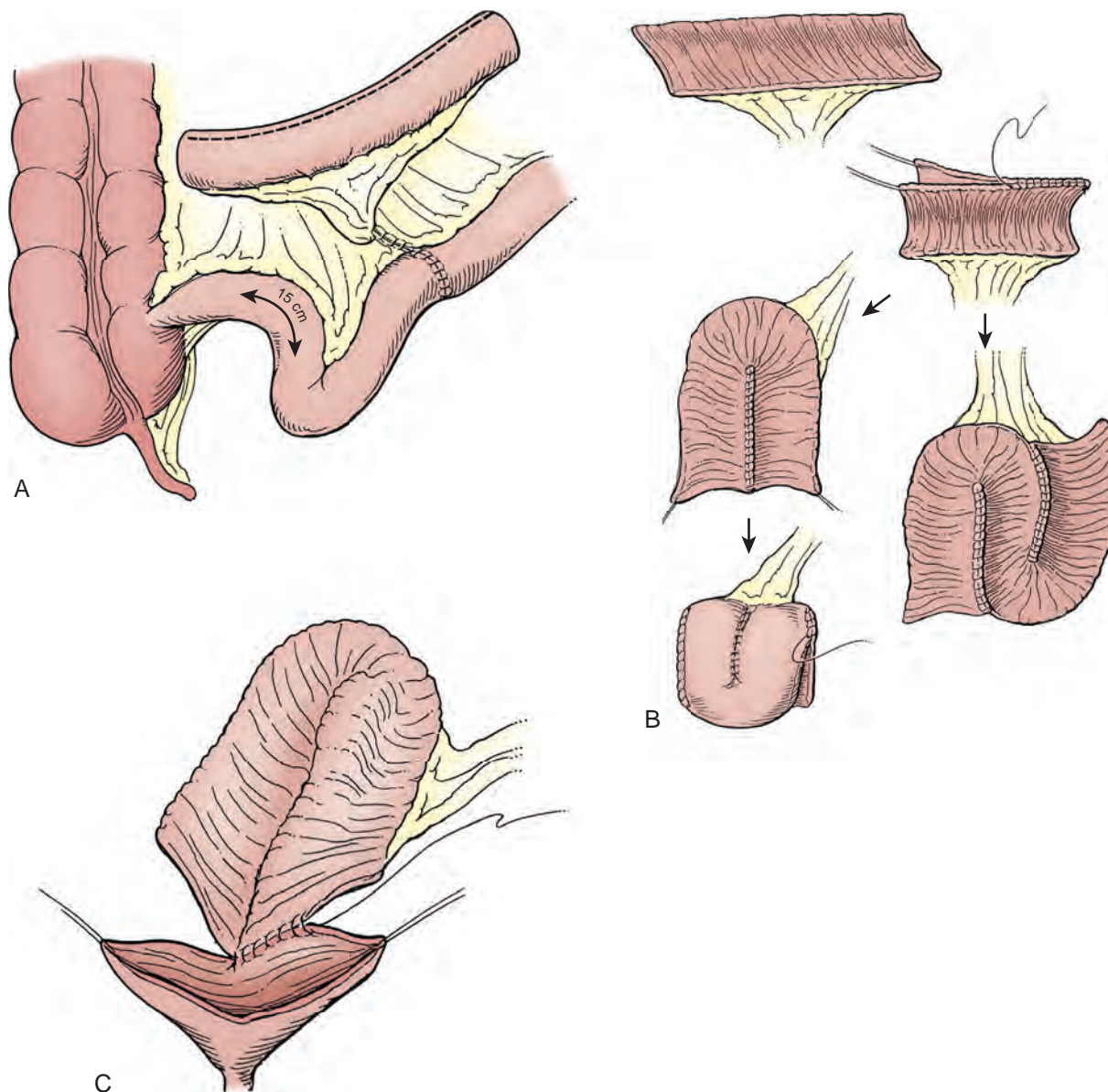


Figure 145-8. A, Ileocystoplasty. A 20- to 40-cm segment of ileum at least 15 cm from the ileocecal valve is removed and opened on its antimesenteric border. Ileoileostomy reconstitutes the bowel. B, The opened ileal segment should be reconfigured. This can be done in a U, S, or W configuration. It can be further folded as a cup patch. C, The reconfigured ileal segment is anastomosed widely to the native bladder.

Technique

A segment of ileum at least 15 to 20 cm proximal to the ileocecal valve should be selected. The distal portion of terminal ileum is unique from a physiologic standpoint and should be avoided. The isolated segment should be 20 to 40 cm in length depending on patient size, native bladder capacity, and the desired final capacity. With short ureters, an extra tail of isoperistaltic ileum can be useful to reach the foreshortened ureters. This would require creation of an ileal nipple valve to prevent reflux as in the Kock or hemi-Kock pouch; this type of construction may require up to 60 cm of small intestine. **The segment to be used should have an adequate mesentery to reach the native bladder without tension.** After selection of the appropriate segment, the mesentery is cleared from the bowel at either end for a short distance to create a window. The bowel is divided at those ends, and a hand-sewn ileoileostomy or stapled anastomosis is performed. The mesenteric window at the bowel anastomosis is closed to prevent an internal hernia. The harvested

ileal segment is irrigated clear with 0.25% neomycin solution and opened on its antimesenteric border (Fig. 145-8A). The ileum is folded in a U shape most commonly, although longer segments can be folded further into an S or W configuration. The ileum is anastomosed to itself with running absorbable sutures (Fig. 145-8B). The suture line should approximate the full thickness of ileum to ileum while inverting the mucosa. The anastomosis of the ileum to native bladder is easily done when started posteriorly. The anastomosis may be done in a one- or two-layer fashion, always using absorbable suture and inverting the mucosa to the lumen (Fig. 145-8C). Permanent sutures should never be used for any cystoplasty because they serve as a nidus for stone formation. A suprapubic tube is brought through the native bladder when possible and secured. The anterior aspect of the anastomosis is then completed. A drain is placed near the bladder and brought out of the pelvis through a separate stab incision. It should be removed promptly if not draining urine, particularly in neurogenic patients with a ventriculoperitoneal shunt.

Cecocystoplasty and Ileocecocolostomy

Couvelaire (1950) described the use of the cecum for augmentation cystoplasty, and numerous reports followed. Presently, cecocystoplasty is an uncommon operative procedure and will not be discussed because it has largely been replaced by various forms of ileocecocolostomy. With this technique, the cecum is opened, reconfigured, and used to augment the bladder alone, leaving a segment of ileum to reach the ureters or create a continent abdominal wall stoma. Conversely, the ileal segment can be opened and used as a patch on the cecal segment before augmentation cystoplasty.

Technique

Many modifications of the technique exist, but all start with mobilization of the cecum and right colon by incising the peritoneum along the white line of Toldt up to the hepatic flexure. Fifteen to 30 cm of the terminal ileum are used. The length of the ileal segment depends on the technique used. As with all intestinal cystoplasties, before division of the bowel segment, it should be noted that it will reach the bladder without tension (**Fig. 145-9A**).

The isolated ileocecal segment is irrigated clear with neomycin solution and opened on its antimesenteric border through the ileocecal valve for its entire length. In the typical ileocecal augmentation, the ileal and cecal segments are of equivalent length such that the borders of the open segment can be anastomosed and then folded on themselves to form a cup cystoplasty (**Fig. 145-9B**). The anastomosis of the reconfigured segments is done in either a one- or two-layer closure with absorbable suture. The opening should be left large enough to provide a wide anastomosis to the bivalved bladder. If more volume is necessary, the ileal segment can be significantly longer, allowing it to be folded before anastomosis to the cecum. The Mainz ileocecocolostomy uses an ileal segment twice the length of the cecal segment. The compound ileocecal patch is then anastomosed to the bladder (**Fig. 145-10**). The mesenteric window is closed, and a suprapubic tube is placed through the native bladder and secured through the abdominal wall.

Appendix

One potential advantage of ileocecocolostomy is the presence of the appendix. Particularly in children, the appendix is useful in

creation of a reliable continent abdominal wall stoma. The appendix may be removed with a small cuff of cecal wall and tunneled into the native bladder or a tenia of the cecal segment to provide a continence mechanism. Likewise, it may be left in situ and the base safely tunneled beneath a tenia. If the appendix is not to be used, an appendectomy is performed with standard ileocecocolostomy.

Ileocecal Valve

The ileocecal segment has been used extensively in the adult population undergoing reconstruction and bladder replacement. It has been used less frequently in children because the majority of patients undergoing augmentation cystoplasty do so for neurogenic dysfunction affecting both bladder and bowel. Removal of the ileocecal valve in such children can result in intractable diarrhea (**Gonzalez and Cabral, 1987; King, 1987**). Use of the ileocecal valve in such patients should be avoided unless other advantages of the segment outweigh the risk of diarrhea and fecal incontinence.

There are potential advantages to the use of the ileocecal segment. Antireflux tunnels can easily be performed into the tenia of the cecum when necessary. Again for the short ureter, a tail of ileum can be left intact to bridge the gap and the imbricated ileocecal valve used for antireflux. The same imbrication technique can be used to create a continent abdominal wall stoma similar to that used in the Indiana Pouch (**Cain and Husmann, 1994; Cain et al, 1999**).

Sigmoid Cystoplasty

Use of the sigmoid colon for augmentation cystoplasty was first reported by Lemoine in 1912 (**Charghi et al, 1967**), and it continues to be used commonly. Because of the strong unit contractions of the sigmoid, it is imperative to detubularize and reconfigure the segment to provide maximal compliance and disruption of contractions.

Technique

Fifteen to 20 cm of sigmoid colon are identified and mobilized. The mesentery is transilluminated to identify the vascular arcade to the segment. After identification of this blood supply, the surgeon must ensure that the segment can reach the bladder without tension. The bowel segment is divided between clamps, and a colocolostomy performed (**Fig. 145-11A**). The remainder of the abdominal cavity

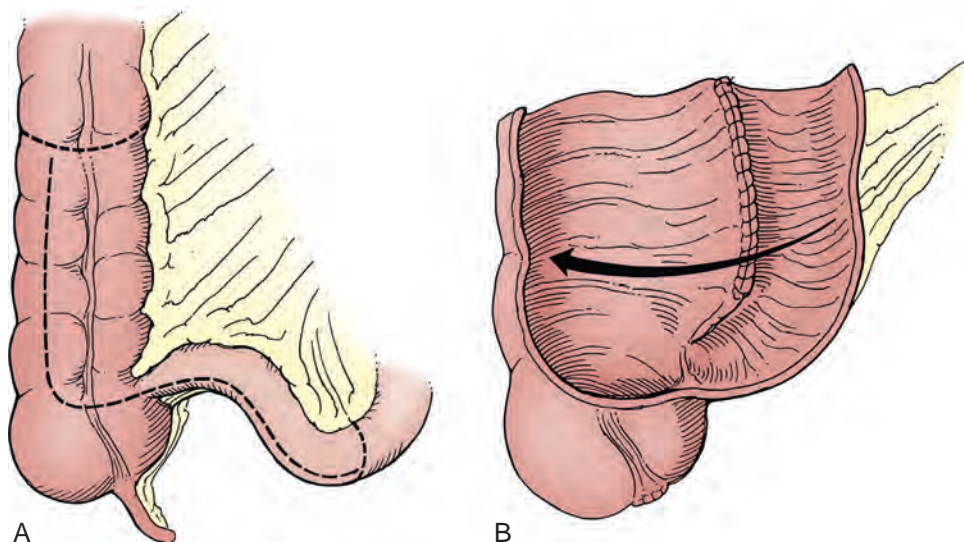


Figure 145-9. Ileocecocolostomy. A, An ileocecal segment is selected. The length of segment chosen depends on the technique used. After removal, it is opened on the antimesenteric border (dashed lines). B, The opened ileal and cecal segments are anastomosed to form a cup in the standard ileocecal cystoplasty.

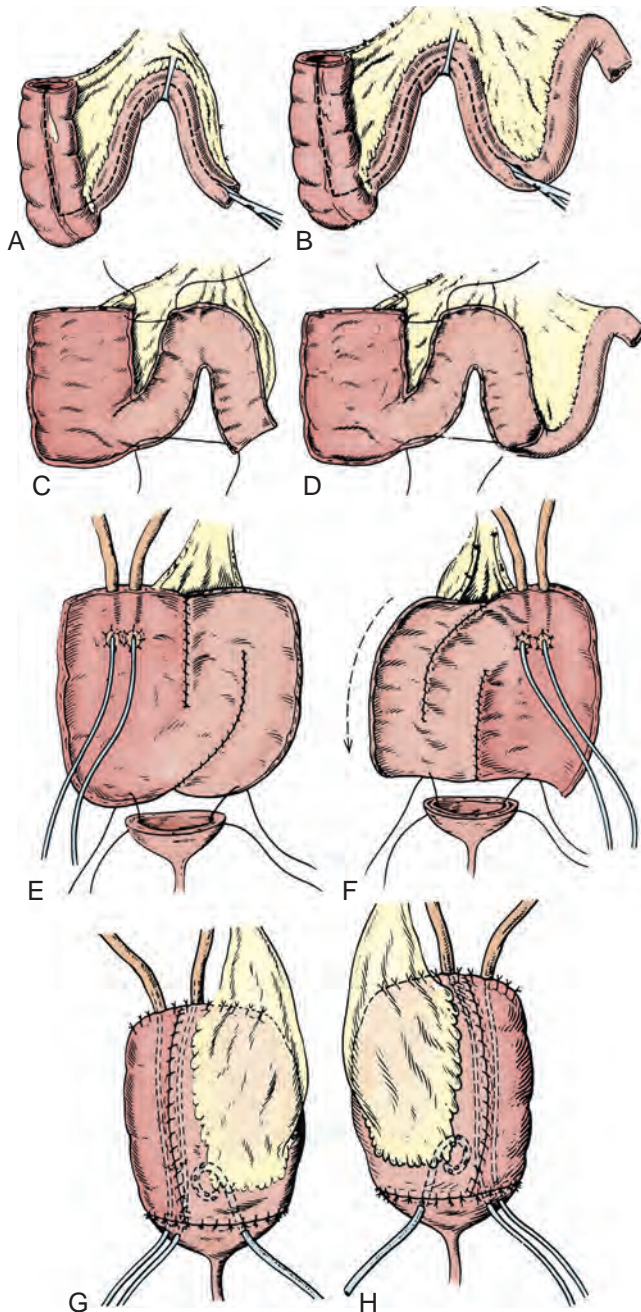


Figure 145-10. The Mainz ileocecostoplasty. A and B, The ileal segment is twice the length of the cecal segment. C and D, It is opened on the antimesenteric border. E and F, The ureters can be reimplanted into the opened cecal segment if necessary. G and H, The ileocecal segment is anastomosed to the native bladder. (From Thuroff JW, Alken P, Hohenfellner R. The Mainz pouch (mixed augmentation with ileum and cecum) for bladder augmentation and continent diversion. In: King LR, Stone AR, Webster GD, editors. *Bladder reconstruction and continent urinary diversion*. Chicago: Year Book; 1987. p. 252.)

should be carefully packed to prevent contamination from the open sigmoid segment. Detubularization and reconfiguration is done in a fashion determined by the surgeon's preference. The sigmoid patch is anastomosed to the bivalved bladder in a manner similar to that previously described for ileocystoplasty. Again, a large suprapubic tube is brought out through the native bladder and secured to the bladder and skin exit sites.

Reconfiguration of Sigmoid. In general, sigmoid colon segments are reconfigured in one of two ways. Mitchell (1986) suggested

closing the two ends and then opening the segment longitudinally opposite its blood supply. The segment easily fits on the bivalved bladder in either the sagittal or coronal plane (Fig. 145-11B). More radical reconfiguration, and perhaps breakup of unit contractions, may be achieved by folding the sigmoid segment in a U shape similar to that described for ileocystoplasty (Sidi et al, 1987a) (Fig. 145-11C). A slightly longer segment of sigmoid may be necessary for effective reconfiguration in this manner.

Gastrocystoplasty

Two basic techniques exist for use of stomach in bladder augmentation.

Technique Using Antrum

Leong and Ong (1972) described the use of the entire gastric antrum with a small rim of body for bladder replacement. With their technique, the left gastroepiploic artery is always used as a vascular pedicle. If the right gastroepiploic artery is dominant and the left vessel ends high of the greater curvature, a strip of body along the greater curvature from the left gastroepiploic artery to the antrum is maintained and provides adequate blood supply (Leong, 1988). Continuity of the upper gastrointestinal tract is restored with a Billroth I gastroduodenostomy.

Technique Using Body

A gastric wedge based on the midportion of the greater curvature may be used (Adams et al, 1988) (Fig. 145-12A). The gastric segment used in this technique is made up mainly of body and consequently has a higher concentration of acid-producing cells. The right or left gastroepiploic artery may be used as a vascular pedicle to this segment. The right artery is commonly dominant and thus more frequently used. The wedge-shaped segment of stomach includes both the anterior and posterior wall. The segment used may be 10 to 20 cm along the greater curvature depending on patient age and size as well as the needed volume (Fig. 145-12B). The incision into the stomach is stopped just short of the lesser curvature to avoid injury to branches of the vagus nerve controlling the gastric outlet. Branches of the left gastric artery just cephalad to the apex of this incision are suture ligated in situ before incision to avoid significant bleeding. Parallel atraumatic bowel clamps are placed on either side of the gastric incisions to avoid excessive bleeding or spillage of gastric contents. The native stomach is closed in two layers using permanent sutures on the outer seromuscular layer.

Branches of the gastroepiploic artery to the antrum on the right or to the high corpus on the left are divided to provide mobilization of the gastroepiploic pedicle. In order that the eventual pedicle is long enough to reach the bladder, the appropriate segment may be higher on the greater curvature if the right vessel is used as a pedicle or lower if based on the left. The vascular pedicle should not be free floating through the abdomen. The segment and pedicle may be passed through windows in the transverse mesocolon and mesentery of the distal ileum and carefully secured to the posterior peritoneum. Despite consideration for an adequate pedicle length, on occasion the gastric segment initially may not reach the bladder without tension. Either gastroepiploic artery may be mobilized closer to its origin for further length. The first few branches from the gastroepiploic artery to the isolated gastric segment may also be divided. Because of the rich submucosal arterial plexus in the stomach, devascularization of the isolated segment does not result. Rarely, it may be necessary to approximate some of the isolated gastric segment to itself in one corner. The gastric segment should be approximated to the native bladder using one or two layers of absorbable sutures, taking care to invert the mucosa (Fig. 145-12C).

Raz and colleagues (1993) and Lockhart and associates (1993) have described the use of a much longer, narrower segment of stomach based along the greater curvature. Use of this segment, which includes both body and antrum, somewhat narrows the

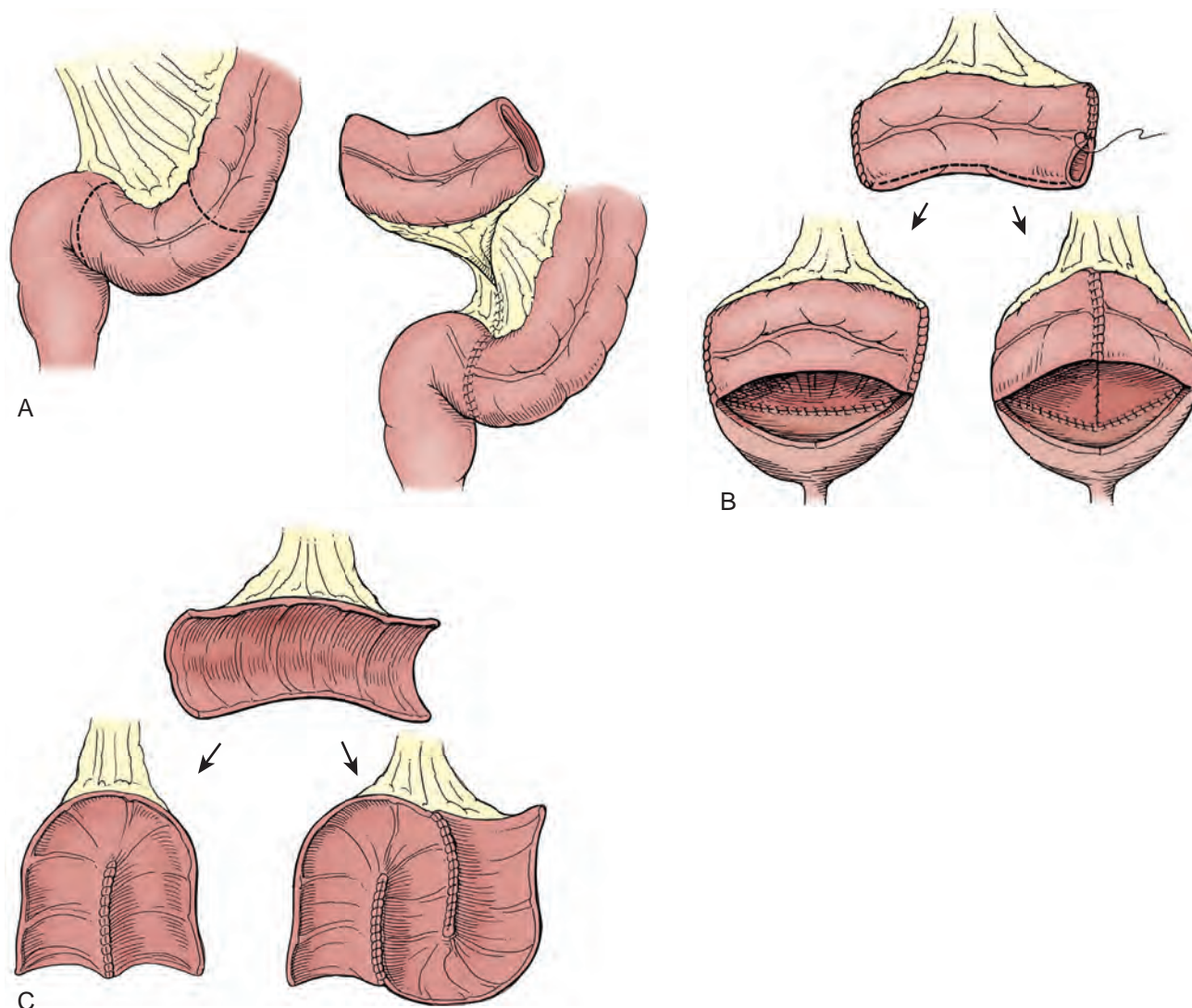


Figure 145-11. Sigmoid cystoplasty. A, A sigmoid segment of adequate length is removed from the gastrointestinal tract, and a colocolostomy is performed. B, In the Mitchell technique the two opened ends are closed. The antimesenteric border is incised, and the segment is anastomosed to the bivalved bladder. It may be rotated 180 degrees to allow an easy fit. C, The opened sigmoid segment can be reconfigured into a U or S configuration, which may lower pressure.

lumen of the stomach along its entire length except at the fundus and pylorus. Raz and colleagues have isolated this segment using a GI stapler so that the native stomach is never open. Postoperative bladder and gastric drainage is no different than that described for intestinal cystoplasty. H₂ blockers are given in the early postoperative period to promote healing (Rink et al, 2000).

Postoperative Management

Early Management

Care of patients after cystoplasty is similar regardless of the segment used in the procedure. Typically, all patients have been maintained on nasogastric decompression until bowel function recovers, although two studies (Gundeti et al, 2006; Erickson et al, 2007) have suggested that nasogastric suction may not be necessary after ileocystoplasty. Attention to fluid and electrolyte management is important because third space losses may be significant after extensive reconstructive surgery. Continuous drainage of the bladder is achieved by suprapubic cystostomy. Mucus production from small or large bowel may be excessive and

can potentially occlude the drainage catheter. **The suprapubic tube should be irrigated at least three times daily and whenever drainage is slowed by mucus.** Extravesical drains may be removed after several days, if drainage of urine is not apparent. The drains are usually removed more promptly in patients with a ventriculoperitoneal shunt to minimize risk of infection. Some surgeons prefer to perform a cystogram before patient discharge; others wait approximately 3 weeks for the study before clamping the suprapubic tube. All patients should begin CIC every 2 to 3 hours during the day and one or two times at night initially. The suprapubic tube is removed after regular catheterization is successfully underway. The duration between catheterizations is gradually increased over several weeks but should not exceed 4 to 5 hours during the day. Patients without neurologic impairment may eventually attempt to void spontaneously. All should check postvoid residual volumes and continue catheterizations if the residuals are significant.

Late Management

Routine radiographic surveillance of the upper urinary tract is indicated at 6 weeks, 6 months, and 1 year after augmentation

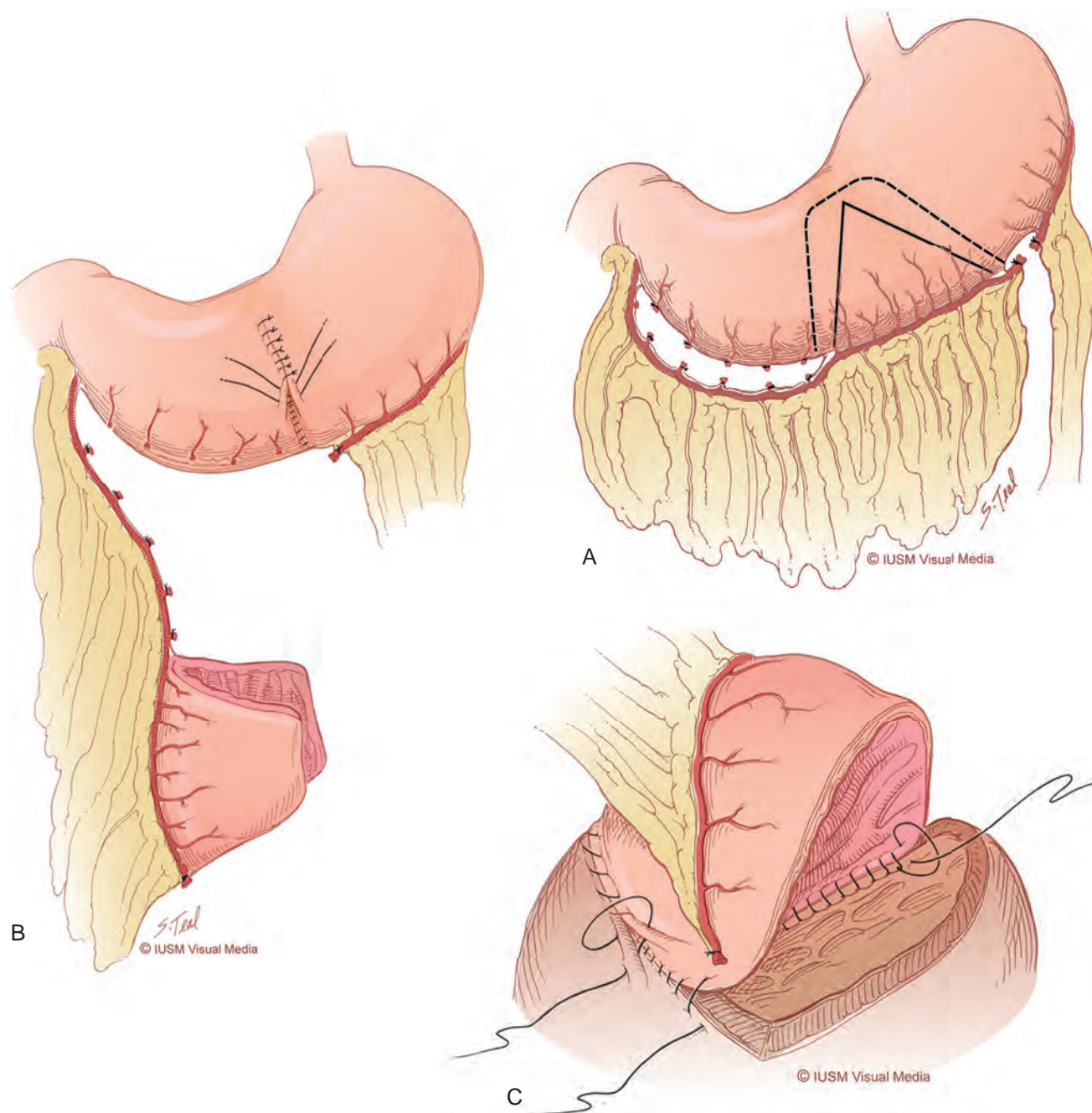


Figure 145-12. Gastrocystoplasty with use of the body. A, Gastric segment of body is mobilized on the right gastroepiploic artery. The left vessel may also be used; neither vessel as a pedicle should be free floating through the peritoneum. B, A longer gastric segment along the greater curvature with wider apex provides more surface area for augmentation. C, The gastric segment is anastomosed to the bivalved bladder with the mucosa inverted. (© Indiana University Medical Illustration Department.)

cystoplasty. Most such surveillance may be done with ultrasonography. Serum electrolytes, BUN, and creatinine levels along with urine cultures are performed several times in the first year after surgery. All positive urine cultures need not be treated in patients on CIC. Certainly symptomatic cystitis or infections involving urea-splitting organisms should be cleared. Evaluation by ultrasonography and serum chemistries is then appropriate once a year. Eventually, yearly endoscopy for tumor surveillance may be performed. No consensus exists about the timing or frequency of cystoscopic examination. Higuchi and coworkers (2010) have suggested that surveillance may

be of greater yield in patient populations at greater risk such as valve patients who are on immunosuppression after transplantation or exstrophy patients with their inherent increased risk for bladder adenocarcinoma. After the report of Castellan and coworkers (2012), surveillance may be of higher yield after gastrocystoplasty. It should be noted that there is no experience that demonstrates that routine surveillance is cost-effective or successful in this population (Higuchi et al, 2011; Kokorowski et al, 2011), and the Mayo Clinic group has gone so far as to suggest that such surveillance be discontinued (Higuchi et al, 2011).

Results and Complications of Augmentation Cystoplasty

The effect of cystoplasty on the patient should be considered in two ways. One must first consider the effect of removing a relatively small portion of the gastrointestinal tract for use in urinary reconstruction. Any more than rare development of gastrointestinal problems would be prohibitive, even if results were perfect from the standpoint of the urinary bladder. Second, the effect of augmentation cystoplasty on the urinary bladder must be reviewed. The primary goal of augmentation is to provide a compliant urinary reservoir. Therefore the main considerations after augmentation are the storage pressure and capacity that are achieved. Any other effects on the urinary bladder are side effects or complications that exist because bowel is not a perfect physiologic substitute for native bladder. It is clear that approximately one third of patients will require further surgery after augmentation cystoplasty because of various problems (Metcalfe et al, 2006; Kispal et al, 2011).

Gastrointestinal Effects

Postoperative bowel obstruction is uncommon after augmentation cystoplasty, occurring in approximately 3% of patients after augmentation (Gearhart et al, 1986; King, 1987; Mitchell and Piser, 1987; Hollensbe et al, 1992; Rink et al, 1995a). The rate of obstruction is equivalent to that noted after conduit diversion or continent urinary diversion (McDougal, 1992b). Delicate handling of tissues, closure of mesenteric windows, and elimination of sites of internal herniation help to avoid obstruction. Occasional series have suggested differing rates of bowel obstruction depending on the segment used. These differences have not been consistent in most series and are therefore likely not significant.

Reports of chronic diarrhea after bladder augmentation alone have been rare. Diarrhea can occur after removal of large segments of ileum from the gastrointestinal tract, although the length of the segments typically used for augmentation rarely is problematic unless other problems coexist. The use of a typical colonic segment for augmentation only rarely results in a change in bowel function. Removal of a segment from the gastrointestinal tract including the ileocecal valve is more likely to cause diarrhea. Some children with neurogenic impairment depend on constipation for fecal continence. Removal of the ileocecal valve from the gastrointestinal tract may significantly decrease bowel transit time. Loss of the valve can also allow bacterial backflow into the ileum, and the organisms may interfere with fat and vitamin B₁₂ metabolism. Studies have noted chronic diarrhea in 10% to 23% of patients with neurogenic dysfunction after displacement of the ileocecal valve (King, 1987; Roth et al, 1995), although the risk may be lower for carefully selected patients (Husmann and Cain, 1999).

Ileum is the sole site of vitamin B₁₂ absorption. Removal of the distal ileum from the gastrointestinal tract may therefore result in vitamin B₁₂ deficiency and megaloblastic anemia. The terminal 15 to 20 cm of ileum should not be used for augmentation, although problems may arise even if that segment is preserved (Steiner and Morton, 1991; Racioppi et al, 1999). Again, the risk is greater if longer segments of ileum are used as with continent diversion. Thirty-five percent of patients followed over 5 years after a Kock pouch procedure were found to be deficient in vitamin B₁₂ in one series (Akerlund et al, 1989). In general, the length of ileum used for augmentation is less than one half that used for a Kock pouch, so vitamin B₁₂ deficiency seems unlikely after routine bladder augmentation. Canning and associates evaluated 26 patients after bladder augmentation or replacement and found no patients with either fat malabsorption or vitamin B₁₂ deficiency (Canning et al, 1989). Only three patients, however, were followed for longer than 3 years, and longer observation is necessary because existing body vitamin B₁₂ storage may last considerably longer (Stein et al, 1997a). VanderBrink and associates (2010) found low or low-normal B₁₂ levels in 41% of patients evaluated a mean of 83 months after ileocystoplasty and were able to increase those levels by giving the oral vitamin.

Early satiety may occur after gastrocystoplasty but usually resolves with time. Disorders of gastric emptying should be extremely rare, particularly when gastric body is used.

Bladder Compliance after Augmentation

An early lesson of past clinical experience with augmentation cystoplasty has been the value of detubularization and reconfiguration of the bowel segment (Hinman, 1988; Koff, 1988). Some surgeons with extensive experience in augmentation cystoplasty have concluded that ileum is superior to other segments in terms of compliance after augmentation, although controlled experimental examination of similarly sized bowel segments is lacking (Goldwasser and Webster, 1986; Rink and McLaughlin, 1994; Studer and Zingg, 1997). On the contrary, one report has suggested superior results with colon compared with ileum (Shekariz et al, 2000) when a longer colonic segment reconfigured in a U shape was used. Good results have been achieved with all segments in most cases, and it is more important to use a bowel segment well than to choose a particular bowel segment for every patient.

Occasional problems with pressure after augmentation cystoplasty occur from uninhibited contractions, apparently in the bowel segment. It is extremely rare not to achieve an adequate capacity or flat tonus limb unless a technical error has occurred with use of the bowel segment. When pressure contractions occur in the bladder after augmentation, they are often noted in a rhythmic or sinusoidal pattern, occasionally with increasing amplitude (Fig. 145-13). Contractions that begin at low amplitude later in filling and progress only near capacity may be of no clinical significance. Early contractions of higher pressure may result in persistent incontinence, delayed perforation, hydronephrosis, or vesicoureteral reflux. If patients have such clinical problems after augmentation, repeat urodynamic testing is indicated because one cannot assume the bladder is compliant after augmentation. Rhythmic contractions have been noted postoperatively with all bowel segments, although ileum seems the least likely to demonstrate remarkable urodynamic abnormalities, and stomach the most.

After bladder augmentation or replacement, some urodynamic evaluation has suggested that colonic segments, whether cecum or sigmoid, still generate more pressure than ileum despite detubularization (Berglund et al, 1987; Jakobsen et al, 1987; Thuroff et al, 1987; Lytton and Green, 1989; Studer and Zingg, 1997), although other work has suggested that pressure contractions from the colon decrease with time (Hedlund et al, 1984; Sidi et al, 1986b). Goldwasser's review of enterocystoplasty demonstrated contractions greater than 15 cm H₂O in 42% of patients after ileocystoplasty versus in 60% of those after colocystoplasty (Goldwasser et al, 1987). Significant contractions, defined as those above 40 cm H₂O at a volume below 200 mL, were not noted in any of the ileal augmentations but persisted in 10% of cystoplasties. Their work agreed with that of Berglund and colleagues (1987) and Studer and Zingg (1997) in suggesting that ileal reservoirs have lower basal pressures and less motor activity. It must be noted that none of these studies critically controlled for the size of the bowel segment or the technique in which they were used. In fact, a canine model of partial bladder replacement using identically sized segments failed to demonstrate in vitro or in vivo differences between the gastrointestinal segments (Nelson et al, 2005).

Rhythmic contractions after gastrocystoplasty have been noted in up to 62% of patients (Adams et al, 1988; Atala et al, 1993; Gosalbez et al, 1993a; Roth et al, 2000). The segment of stomach initially described for augmentation using the body was much smaller in size than segments of ileum or colon commonly used. Use of a larger gastric segment that is longer along the greater curvature results in improved urodynamics after augmentation with less prominent contractions (Adams et al, 1995; Kurzrock et al, 1998; Koraitim et al, 1999; DeFoor et al, 2003a). Leong (1988) has suggested that an antral segment of stomach is less likely to demonstrate such contractions.

In perhaps the most extensive experience with pediatric bladder augmentation, Hollensbe and associates at Indiana University

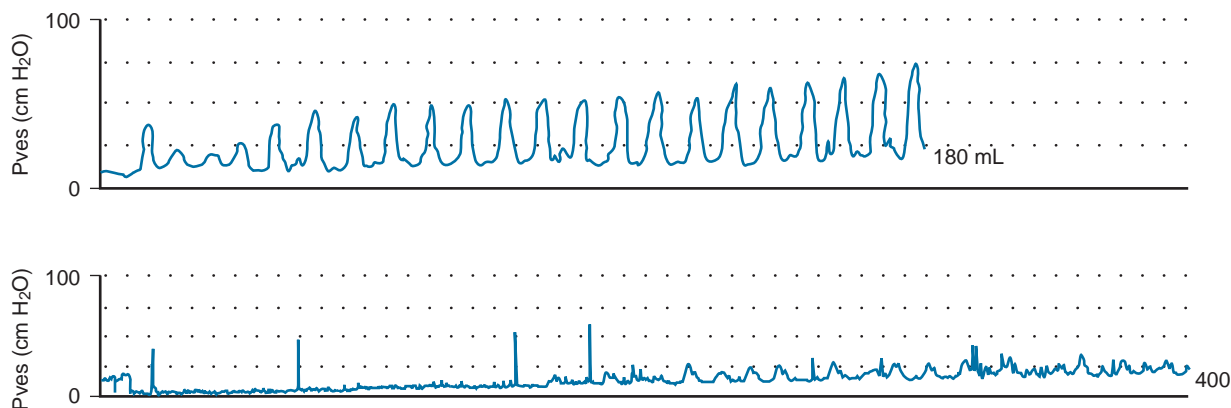


Figure 145-13. Rhythmic, sinusoidal contractions (*top*) may occur after bladder augmentation, in this case with stomach. Contractions of significant amplitude early in filling occasionally require secondary augmentation. After secondary augmentation with ileum (*bottom*), urodynamics show that contractions still occur but are much lower in pressure and occur later in filling.

found that approximately 5% of patients had significant uninhibited contractions after augmentation cystoplasty causing clinical problems (Hollensbe et al, 1992). Pope and Rink (1999) found that 6% of over 300 patients required secondary augmentation of a previously augmented bladder for similar problems. With longer follow-up, the same group has eventually performed reaugmentation in 9% of patients (Metcalf et al, 2006). These secondary augmentations represent true failures of the cystoplasty to achieve their primary objectives, capacity and compliance. In that series, sigmoid colon followed by stomach and then ileum were more likely to require reaugmentation. It should be noted that a colonic segment closed at the ends and not reconfigured otherwise was typically used in that experience. Other studies have suggested that stomach is more likely than colon to require secondary intervention (El-Ghoneimi et al, 1998; Castellan et al, 2012).

Metabolic Complications

Chloride Absorption and Acidosis. The first recognized metabolic complication related to storage of urine within intestinal segments was the development of hyperchloremic metabolic acidosis after ureterosigmoidostomy (Ferris and Odel, 1950). Patients with this metabolic derangement were noted to have fatigue, weakness, anorexia, and polydipsia. Koch and McDougal (1985) demonstrated the mechanisms by which acid is absorbed from urine in contact with intestinals mucosa. Resorption in the form of ammonium results in chronic acid loading. Patients with normal renal function are usually able to handle the resorbed load of chloride and acid without frank acidosis. Mitchell and Piser (1987) noted that essentially every patient after augmentation with an intestinal segment had an increase in serum chloride and a decrease in serum bicarbonate level, although full acidosis was rare if renal function was normal. Acidosis and electrolyte disturbances requiring treatment have been reported despite normal renal function (Schmidt et al, 1973; Whitmore and Gittis, 1983). Such derangements may be debilitating to the patient if not recognized and treated (Heidler et al, 1979). Hall and colleagues noted that there is an increase in the urinary acid load with wasting of bony buffers even in the absence of frank acidosis (Hall et al, 1991). Such wasting may result in bone demineralization and could potentially cause retarded growth in children after augmentation cystoplasty (Abes et al, 2003; Hafez et al, 2003; Vajda et al, 2003). Patients with acidosis should receive bicarbonate therapy. Nurse and Mundy (1989) have suggested that arterial blood gas values may be more sensitive than serum bicarbonate or chloride levels for detecting acidosis. Stein and associates (1998) felt that measurements of arterial blood gas for base deficit allowed early treatment

of acidosis and avoidance of bone demineralization. In severe cases of acidosis, chloride transport can be blocked with chlorpromazine and nicotinic acid.

Although jejunum is rarely used for bladder reconstruction, storage of urine in this segment results in a unique metabolic pattern of hyponatremic, hypochloremic, and hyperkalemic metabolic acidosis. The problem is often associated with significant hypovolemia.

Gastric mucosa is a barrier to chloride and acid resorption and, in fact, secretes hydrochloric acid (Piser et al, 1987). This difference was the primary factor in the initial consideration of stomach for use in the urinary tract. This secretory nature was shown to be of benefit in azotemic animals during acid loading (Piser et al, 1987; Kennedy et al, 1988). Serum chloride does decrease and serum bicarbonate increase slightly after gastrocystoplasty whether antrum or body is used in patients with normal and impaired renal function (Adams et al, 1988; Ganesan et al, 1991; Kurzrock et al, 1998). In 21 patients with renal insufficiency, serum bicarbonate improved in all patients except 1 after gastrocystoplasty, and many patients requiring oral bicarbonate therapy before cystoplasty did not do so after gastrocystoplasty (Ganesan et al, 1991). A similar benefit was noted in a group of patients with renal failure (Sheldon and Gilbert, 1991).

Patient Growth. Delayed or slowed growth in some children after intestinal cystoplasty has previously been recognized (Wagstaff et al, 1991; Mundy and Nurse, 1992; Wagstaff et al, 1992). A delay in linear growth was noted in 20% of almost 200 pediatric patients without any gross biochemical abnormalities. However, no control patients were included in that series. Body habitus and growth are difficult to predict in children with myelodysplasia, who make up the majority in most series of augmentation cystoplasty. Gros and colleagues (2000) evaluated growth in exstrophy patients. Patients requiring augmentation were matched retrospectively with a similar group not requiring bladder augmentation. Only 1 patient was noted to have acidosis in either group. Other factors that might affect growth, such as urinary tract infection, were not controlled. Of 17 patients with adequate measurements before and after cystoplasty, 14 (82%) had a decline in percentile height postoperatively. The decline corresponded to a 1½-inch decrease in expected height. The pattern of growth was significantly different between patients with and without augmentation in the series. That series is small, and no evaluation of familial growth patterns or ultimate height was possible; however, the findings are worrisome, particularly because Feng and colleagues (2002) noted similar differences in exstrophy patients. In the absence of any serum abnormalities, the exact mechanism of delayed growth was not evident, although it seems likely to be related to subclinical acidosis (Koch and

McDougal, 1988; Bushinsky, 1989; Hochstetler et al, 1997). It should be noted that Taskinen and colleagues (2008) found no adverse effect on longitudinal growth after bladder augmentation in the exstrophy population.

Three recent series did show effect of bowel cystoplasty on bone mineral density in some patients (Abes et al, 2003; Hafez et al, 2003; Vajda et al, 2003), whereas two others did not (Mingin et al, 2002; Haas et al, 2012). One must be careful to determine whether any such changes are the result of augmentation cystoplasty or the underlying pathology (Boylu et al, 2006; Taskinen et al, 2007; Haas et al, 2012). Better analysis of subtle metabolic alterations after enterocystoplasty may establish better understanding of the effect on growth, minimize changes, or aid in early treatment to avoid the complication (Brkovic et al, 2004).

Alkalosis. The secretory nature of gastric mucosa may at times be detrimental to the patient and can result in two unique complications of gastrocystoplasty. Episodes of hypokalemic, hypochloremic metabolic alkalosis after acute gastrointestinal illnesses were noted in 5 of 37 patients following gastrocystoplasty (Hollensbe et al, 1992). The episodes were significant enough to require hospitalization in all patients and were recurrent in 2 patients. Three of the 5 patients who developed the complication had renal insufficiency and would not have been good candidates for augmentation with other segments owing to acidosis. Ganesan and associates noted similar episodes of alkalosis in 5 of 21 patients with renal insufficiency after gastrocystoplasty (Ganesan et al, 1991). Patients with the primary indication for consideration of gastrocystoplasty may be the ones at greatest risk for this unusual complication. It has been proposed that the alkalosis results from ongoing chloride loss from the gastric segment in the bladder in the face of decreased oral intake. Gosalbez and associates (1993b) demonstrated persistently increased fractional excretion of chloride despite profound hypochloremia, suggesting that inappropriate gastric secretion is likely the primary mediator. One patient in their series eventually required resection of three quarters of the gastric segment in the bladder because of recurrent problems with alkalosis, and several required therapy with H₂ blockers or H⁺/K⁺ ion pump inhibitors. All patients and families should be made aware of this potential problem because it has been reported to occur intermittently in 3% to 24% of patients. A composite reservoir of stomach and ileum or colon may provide a more metabolically neutral reservoir (McLaughlin et al, 1995; Austin et al, 1997, 1999, 2001), although these have typically been constructed in only very complex patients or circumstances.

Hematuria-Dysuria Syndrome. Acid secretion by gastric mucosa may result in another unique problem after gastrocystoplasty, the hematuria-dysuria syndrome. Mitchell's group characterized this syndrome well (Nguyen et al, 1993; Plaire et al, 1999). Virtually all patients after gastrocystoplasty with normal sensation have occasional hematuria or dysuria with voiding or catheterization beyond what is expected with other intestinal segments (Leonard et al, 1999). All patients should be warned of this potential problem, although in most patients these symptoms are intermittent and mild and do not require treatment. The problem led one group to recommend avoiding gastrocystoplasty in patients with bladder exstrophy (El-Ghoneimi et al, 1998). The dysuria is not as problematic in patients with neurogenic dysfunction. In the experience of Nguyen and colleagues (1993), 36% of patients developed signs or symptoms of the hematuria-dysuria syndrome after gastrocystoplasty. Fourteen percent of patients required treatment with medications, including 9% on a regular basis. Patients who are incontinent or have decreased renal function are at increased risk. Others have noted a similar requirement for short-term and chronic medical therapy (Hollensbe et al, 1992; Adams et al, 1995; Castellan et al, 2012). The symptoms of the hematuria-dysuria syndrome do respond well to H₂ blockers and hydrogen ion pump blockers. Bladder irrigation with baking soda may also be effective. It has been demonstrated that urinary pH may decrease remarkably after meals in patients who have undergone gastrocystoplasty (Bogaert et al, 1995). The signs and symptoms of the hematuria-dysuria syndrome are most likely secondary to acid irritation. Work has

suggested that *Helicobacter pylori* may play a role in this complication (Celayir et al, 1999). Such problems can occur but are less frequent after antral cystoplasty because there is a smaller load of parietal cells (Ngan et al, 1993).

Acid in the urine may also cause external irritation. Leong first noted glanular excoriation after gastrocystoplasty in a patient with voiding symptoms (Ngan et al, 1993). Nguyen and associates noted skin excoriation in 8 of 57 patients following gastrocystoplasty; all 8 patients had some element of urinary incontinence (Nguyen et al, 1993). It is imperative to achieve reliable urinary continence in patients undergoing gastrocystoplasty because urinary leakage may result in the exposure of the skin to gastric secretions and in gastric secretions that are poorly diluted. Dilution is important; Reinberg and coworkers reported a perforation of a gastric segment in a defunctionalized bladder after gastrocystoplasty (Reinberg et al, 1992). They evaluated the influence of urine on gastrocystoplasties in dogs (Castro-Diaz et al, 1992). The animals developed marked inflammation of the gastric segment and native bladder after creation of a dry gastrocystoplasty; three of nine dogs developed ulceration and perforation. Use of H₂ blockers resulted in some protection for the animals; however, such a clinical situation should certainly be avoided. Rare perforations and ulcerations have been noted clinically without defunctionalization (El-Ghoneimi et al, 1998; Mingin et al, 1999a).

Mucus

Intestinal segments continue to produce mucus after placement in the urinary tract. The material can potentially impede bladder drainage during voiding or CIC, particularly in pediatric patients in whom the use of small-caliber catheters is necessary. Mucus may serve as a nidus for infection or stone formation when it remains in the bladder for long periods of time. Mucus production often increases after cystoplasty in the presence of cystitis. Kulb and associates (1986) showed experimentally in dogs that colonic segments produce more mucus than ileum and that gastric segments produce the least amount. This has been noted clinically as well; most patients do not require any routine bladder irrigations for mucus after gastrocystoplasty. Villous atrophy in the ileum has been documented after placement in the urinary tract. It has been suggested that such atrophy may result in decreased mucus production (Gearhart, 1987), although laboratory demonstration of any decrease in production with time has not been evident (Murray et al, 1987). Hendren and Hendren (1990) noted a decrease in mucus production from colonic segments over years; however, others have not been impressed with such changes (Rink et al, 1995a). Glandular atrophy in colonic mucosa has not been noted histologically (Mansson et al, 1984). Routine use of daily bladder irrigations to prevent mucus buildup may minimize complications of enterocystoplasty such as urinary tract infection and calculi (Hensle et al, 2004).

Urinary Tract Infection

Bacteriuria is common after intestinal cystoplasty, particularly in patients requiring intermittent catheterization (Gearhart et al, 1986; Hendren and Hendren, 1990; King, 1991). Recent experience with bowel neobladders has demonstrated that patients who are able to spontaneously void to completion often maintain sterile urine. It appears that use of CIC is a prominent factor in the development of bacteriuria in patients who have undergone augmentation cystoplasty. Bacteriuria has been noted even when patients are maintained on daily oral antibiotics or antibiotic irrigation (Gearhart et al, 1986; Casale et al, 1999). In Hirst's (1991) experience, persistent or recurrent bacteriuria occurred in 50% of patients augmented with sigmoid colon versus 25% of those following ileocystoplasty. Hollensbe and coworkers noted bacteriuria much more commonly in patients requiring CIC regardless of the segment considered (Hollensbe et al, 1992). The incidence of symptomatic cystitis after cystoplasty likely depends on the length of follow-up and the diligence with which symptoms are sought.

All patients and families should be told to expect some signs or symptoms of cystitis. Recurrent episodes of symptomatic cystitis requiring treatment occurred in 23% of patients after ileocystoplasty, 17% of patients after sigmoid cystoplasty, 13% after cecocystoplasty, and 8% after gastrocystoplasty at Indiana University (Hollensbe et al, 1992). Febrile urinary tract infections occurred in 13% of those 231 patients after augmentation. The same trend among different bowel segments was noted for febrile infections, although there was no statistically significant difference among the various segments. **The incidence of pyelonephritis after augmentation cystoplasty, as long as upper tract problems are corrected, is quite similar to that noted for conduit diversion, whether refluxing or not (McDougal, 1992b).** Infections may occasionally be more problematic in an immunocompromised patient (Alfrey et al, 1997), but that has not always proven to be the case (Traxel et al, 2011).

Not every episode of asymptomatic bacteriuria requires treatment in patients performing CIC. Bacteriuria should be treated in the presence of significant symptoms such as incontinence or suprapubic pain and may be treated if hematuria, foul-smelling urine, or remarkably increased mucus production occurs. **Bacteriuria should be treated if the urine culture demonstrates growth of a urea-splitting organism that may lead to stone formation.** To minimize infection, patients requiring CIC must perform it on a regular basis to avoid increased reservoir pressures and must work to empty the bladder completely. Special care must be taken by patients catheterizing through a continent abdominal wall stoma. Such patients may have more difficulty completely emptying the bladder from a nondependent stoma. Most can do so with effort (Ludlow et al, 1995). Although catheterization is not routinely a sterile technique, use of proper clean technique should be emphasized.

Calculi

Another long-term complication of augmentation cystoplasty is bladder calculus formation. In the early 1990s, several series reported calculi in 18% of patients after augmentation cystoplasty (Hendren and Hendren, 1990; Hirst, 1991). Blyth and associates noted calculus formation in 30% of such patients; they found that patients catheterizing through an abdominal wall stoma have the highest risk, likely because of incomplete emptying (Blyth et al, 1992). Palmer and colleagues (1993) noted urolithiasis in 52% of patients after augmentation cystoplasty. Metcalfe and colleagues (2006) noted a 15% rate of bladder stone formation in 500 patients with long-term follow-up after enterocystoplasty; the reasons for these remarkable differences are not clear. **Most bladder stones in this patient population are struvite in composition, and bacteriuria is an important risk factor.** Any infection with a urea-splitting organism should therefore be treated. All patients requiring CIC, particularly those who have already formed stones, should make every effort to empty the bladder completely with each catheterization. If stones are found in patients voiding spontaneously after augmentation, the adequacy of emptying should be re-evaluated. The association of urinary stasis with stone formation is well established. Routine bladder irrigations to avoid buildup of inspissated mucus may remove a nidus for stone formation. The group at Indiana and others have stressed irrigations and asked patients and families to routinely irrigate the bladder several times a day after augmentation (Rink et al, 1995a; Hensle et al, 2004). Stones have been noted after the use of all intestinal segments with no significant difference noted between small and large intestine. Struvite stones are less likely after gastrocystoplasty (Kaefer et al, 1998; Kronner et al, 1998a), likely because of decreased mucus production and acid that minimizes bacteriuria. Uric acid calculi have been noted in the bladder after gastrocystoplasty (Kaefer et al, 1998). Clearly, any foreign body will serve as a nidus for stone formation; the use of permanent sutures or staples in the urinary tract should be avoided during enterocystoplasty. Khoury and associates (1997) looked for metabolic problems in patients after augmentation and noted low urinary citrate levels in patient with and without stones.

They thought that poor emptying and mucus were more significant factors.

Tumor Formation

A well-recognized complication of ureterosigmoidostomy has been the development of tumors, primarily adenocarcinoma, at the ureterocolonic anastomotic site. In Husmann and Spence's (1990) review of reported tumors after ureterosigmoidostomy, the latency for development of such tumors averaged 26 years and ranged from 3 to 53 years. Adenocarcinomas were the prominent tumors that developed, but benign polyps and other types of carcinoma were also found. Eraklis and Folkman (1978) estimated that the risk for developing such tumors is increased by 7000-fold over age matched controls after ureterosigmoidostomy. Pettersson and colleagues (2013) reviewed their experience with 24 patients who had undergone ureterosigmoidostomy from 1944 to 1961; most had eventually been undiverted. Invasive colorectal adenocarcinoma developed in 7 patients, 5 of whom died as a result. The risk for tumor formation was 42 times that of the general Swedish population.

The basis for the increased risk is unknown; however, *N*-nitroso compounds thought to originate from a mixture of urine and feces may be carcinogenic. These compounds have been noted in the urine of patients with conduit diversion and augmentation (Treiger and Marshall, 1991). Husmann and Spence (1990) suggested that those compounds are more likely enhancing agents rather than a lone cause for tumor development. It has been proposed that inflammatory reaction at the anastomotic site may induce growth factor production, which, in turn, increases cellular proliferation. Filmer and Spencer (1990) identified 14 patients who have developed adenocarcinoma in an augmented bladder, and several more have been reported since then. Nine of those tumors occurred after ileocystoplasty, and 5 after colcystoplasty. One study has noted a relatively high incidence of tumor after gastrocystoplasty (Castellan et al, 2007). Experimental work in the rat demonstrated hyperplastic growth in the augmented bladder using all intestinal segments, with no segment showing any particular increased risk (Klee et al, 1990; Buson et al, 1993; Spencer et al, 1993; Little et al, 1994; Kispal et al, 2012). The long latency noted for tumor development after ureterosigmoidostomy suggests that short-term follow-up after augmentation cystoplasty is not adequate to evaluate tumor formation. The earliest reported tumor after augmentation was found only 4 years after cystoplasty (Carr and Hershow, 1997). **Patients undergoing augmentation cystoplasty should be made aware of a potential increased risk for tumor development.** Yearly surveillance of the augmented bladder with endoscopy may eventually be performed; the latency period until such procedures are necessary is not well defined (Vajda et al, 2002; Higuchi et al, 2011). Transitional cell carcinoma, hyperplasia, and dysplasia have also been noted near the anastomosis in humans (Gregoire et al, 1993; Barrington et al, 1997; Soergel et al, 2004). Transitional cell carcinomas associated with augmentation cystoplasty have been aggressive; often the patients have metastatic disease at presentation (Metcalfe et al, 2006; Higuchi et al, 2010). Urothelium adjacent to the anastomosis was demonstrated to be genetically unstable on biopsy in one study (Appanna et al, 2007). Castellan and associates (2012) noted a sobering experience with three cases of fatal adenocarcinoma within the gastric segment among only 29 patients who had undergone gastrocystoplasty. A benign lesion, nephrogenic adenoma, may actually be the most common tumor found after cystoplasty (Franke et al, 2011).

Delayed Spontaneous Bladder Perforation

Another disturbing complication of augmentation cystoplasty is delayed bladder perforation. Patients with spontaneous perforation after augmentation cystoplasty are typically quite ill with abdominal pain, distention, and fever. Sepsis has been common. Nausea, decreased urine output, and shoulder pain from diaphragmatic irritation have also been noted. Perforations have been found in

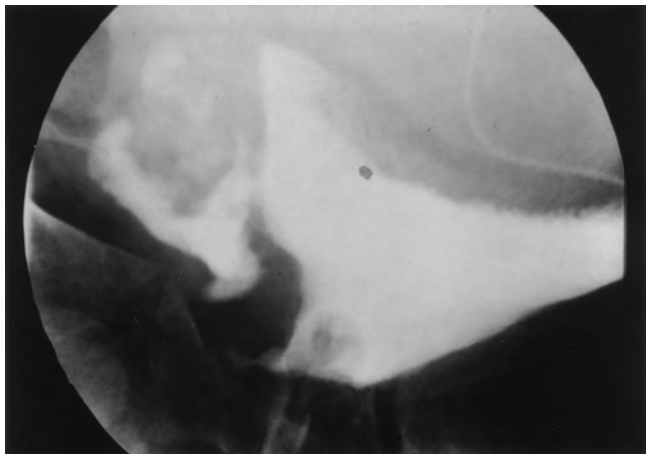


Figure 145-14. After complete filling, a sagittal view on the cystogram demonstrates a spontaneous bladder perforation on the post-drain view.

evaluation of asymptomatic pelvic masses (Pope et al, 1999) (Fig. 145-14). Patients with neurogenic dysfunction often have impaired lower abdominal sensation and are seen later in the course of the illness; severe sepsis and death have occurred. Patients with perforation after gastrocystoplasty often seek care promptly because of acid irritation. A high index of suspicion for perforation is necessary. Contrast cystography is diagnostic in most cases (Braverman and Lebowitz, 1991; Rosen and Light, 1991; Bauer et al, 1992) (see Fig. 145-14). Thorough technique is important to identify as many true positives as possible with cystography (Braverman and Lebowitz, 1991). Some reports have noted a significant false-negative rate on cystography (Rushton et al, 1988; Sheiner and Kaplan, 1988; Pope et al, 1999) and suggested that ultrasonography and computed tomography improve diagnostic accuracy. They recommended that one of those studies be done in any child suspected to have a perforation if the initial cystogram is negative.

Etiology. The cause of delayed perforations within a bowel segment is unknown. It has been suggested that some perforations might be secondary to traumatic catheterization (Elder et al, 1988; Rushton et al, 1988). Perforation of a bladder not previously augmented has been recognized after CIC (Reisman and Preminger, 1989). It seems unlikely that catheterization trauma is the lone cause in most patients. The location of the perforations has been variable among patients and even in a single patient with multiple perforations. Perforations have occurred in patients after augmentation who did not catheterize at all. Other authors have suggested that trauma to the bowel because of fixed adhesions resulting in sheering forces with emptying and filling may result in perforation (Elder et al, 1988). Transmural infection of the bladder wall has also been proposed as a cause. Histologic examination of areas of perforation has noted necrosis, vascular congestion, hemorrhage, and hemosiderin deposition compatible with chronic bowel wall ischemia (Crane et al, 1991). Chronic over distention of the bladder might result in such ischemia. Decreased perfusion in dog bowel used for augmentation can be induced experimentally with high intravesical pressure (Essig et al, 1991); changes were noted more prominently at the antimesenteric border of the bowel. Anderson and Rickwood (1991) have reported perforations occurring in bladders with significant uninhibited contractions after augmentation, as have others (Pope et al, 1998). High outflow resistance may maintain bladder pressure rather than allowing urinary leakage and venting of the pressure, potentially increasing ischemia (Martinez del Castillo et al, 2005). Hyperreflexia alone is likely not a solitary cause of perforation; the complication was not recognized in the era before bowel detubularization and reconfiguration when persistent pressure contractions were more

common. Once bowel is reconfigured, however, it may be more prone to ischemia if high pressure does persist. Failure to perform CIC on a regular basis when needed to empty may exacerbate such issues (DeFoor et al, 2003b; Martinez del Castillo et al, 2005).

The majority of patients who develop perforations after augmentation cystoplasty have had myelodysplasia. The incidence of perforation has been lower in series of patients with other diagnoses requiring bladder reconstruction (Hendren and Hendren, 1990). The role of neurogenic dysfunction in the cause of these perforations is unclear. No matter what the cause, there is likely some field effect on the entire segment. Once a patient has sustained a spontaneous perforation, the chance of recurrence is significant (Hollensbe et al, 1992; Martinez del Castillo et al, 2005), perhaps occurring in one quarter of patients (Metcalf et al, 2006). Consideration must eventually be given to removal of the original segment and replacement with another after repeated perforation.

Incidence. Early postoperative leaks from the bowel-to-bowel or bowel-to-bladder anastomoses after augmentation cystoplasty are rare and represent a technical error or problem with early healing. Delayed perforations more commonly occur within the bowel segment itself and represent a problem with long-term storage of urine within an intestinal segment. There may be no particular increased risk of one intestinal segment over another. At Indiana University, perforations were noted in 43 of 500 patients (8.6%) undergoing cystoplasty (Metcalf et al, 2006) an average of 4.3 years after augmentation. Analysis of this experience suggested that the use of sigmoid colon was the only significantly increased risk factor. Several other large series of patients with sigmoid cystoplasty have noted a low incidence of delayed perforation (Sidi et al, 1987a; Hendren and Hendren, 1990; Shekarriz et al, 2000). At Children's Hospital (Boston), the incidence of perforation after augmentation was reportedly highest in ileum (9.3%) and less frequent in ileocecal, sigmoid, and gastric segments (Bauer et al, 1992). With inconsistent differences across multiple large series, it is unlikely that any given enteric segment is at significantly increased risk for perforation and that multiple factors influence the risk for the complication. The highest rate of perforation noted was 16.6% in one relatively small series (Martinez del Castillo et al, 2005); however, it is reasonable to present an expected risk of about 9% to patients and families based on experience at Indiana University (Metcalf et al, 2006).

Treatment. The standard treatment of spontaneous perforation of the augmented bladder is immediate surgical repair. There are reported series of conservative management for suspected perforation (Slaton and Kropp, 1994). Conservative management including catheter drainage, antibiotics, and serial abdominal examinations was successful in 87% of patients, although only 2 of the 13 patients with suspected ruptures had x-ray documentation unequivocally identifying a perforation. Even patients who do well with conservative management during the acute episode often require eventual surgical intervention (Pope et al, 1999). Such management may be a consideration in a stable patient with sterile urine, but there should be a very low threshold for surgical repair. Most patients with perforations have myelodysplasia and are seen late in the course of the disease owing to impaired sensation. Increasing sepsis and death of the patient may result from a delay in diagnosis or treatment.

Pregnancy

Limited information exists regarding the outcome of pregnancy in women who have undergone augmentation cystoplasty. Three issues are raised in the context of pregnancy after bladder reconstruction: how the expanding uterus will affect the pedicle of the reconstruction; how to manage bacteriuria in the setting; and whether cesarean section is necessary in all or some patients.

Hatch and colleagues (1991) and Schumacher and colleagues (1997) noted that the mesenteric pedicle to bladder augmentations did not appear to be stretched at the time of cesarean section. In those cases the pedicle was not located near the exposed anterior uterus but deflected laterally. Schilling and colleagues

(1996) recognized similar deflection away from the uterus after urinary diversion but did occasionally find the uterus covered by the vascular pedicle after bladder augmentation. Neither process prevented the rise of the uterus during pregnancy. Those authors speculated that the mesentery underwent changes that enabled deflection or stretch without any adverse effect on circulation. Loss of the augmentation from a mechanical effect on the pedicle from the enlarging uterus has not been reported. Pregnancy itself has not been reported to have a detrimental effect on the augmentation other than temporary incontinence in some patients, particularly during the last trimester.

Urinary tract infections may be problematic during pregnancy in women who have undergone urinary reconstruction including bladder augmentation. Ureteral dilation, increased residual urine, and diminished tone to the upper tract may all be important risk factors (Hill et al, 1990; Hatch et al, 1991). Asymptomatic bacteriuria is usually treated immediately in pregnant women because of an increased rate of progression to symptomatic infection and pyelonephritis and because of the potentially significant consequences of pyelonephritis. There is little consensus about the role of antibiotics and the risk of asymptomatic bacteriuria in women on CIC after cystoplasty once pregnant (Thomas and Adams, 2009). Antibiotics, if used, must not be teratogenic.

Successful pregnancy with spontaneous vaginal delivery has been observed in some patients with bladder augmentations (Quenneville et al, 2003) and other forms of urinary reconstruction (Pedlow, 1961; Asif and Uehling, 1969). Schumacher and colleagues (1997) reviewed their experience with pregnancy and delivery in patients who had undergone continent catheterizable ileocecal diversion and found no major complications. This would likely be true for other forms of reconstruction (Wren et al, 2003). Late difficulty with catheterization has been noted with Kock continent ileostomies (Ojerskog et al, 1988) and can occur with any continent abdominal wall stoma (Greenwell et al, 2003).

The need for cesarean section is likely not universal after bladder reconstruction. Flaccid, distensible pelvic tissues, perhaps necessary for progression to spontaneous vaginal delivery, may not be present after extensive pelvic surgery. It is not known if tissues fixed from previous operative repairs can undergo the trauma of delivery and resume the same level of function found before the pregnancy. Our bias would be that woman having undergone extensive bladder neck repair should consider cesarean delivery, particularly if the progression toward spontaneous vaginal delivery is slowed or difficult at all. Although there are reports of spontaneous vaginal delivery in the presence of an AUS (Fishman and Scott, 1993; Creagh et al, 1995), the presence of such a prosthetic device raises a concern for erosion with a long, difficult delivery.

If cesarean section is required or selected, it is imperative to protect the augmentation or continent stoma and its vascular pedicle. The anterior uterus can typically be exposed atraumatically, although some time and patience may be required to protect the bladder. Such exposure may be more difficult if multiple abdominal stomas are present. The reconstructive urologist familiar with the patient and her anatomy should be present during cesarean section.

Choice of Segment and Approach

Enterocystoplasty improves bladder capacity and compliance in most cases when medical management fails. It is obvious from the previous discussion that there is no one single bowel segment that is perfect for augmentation in all patients. All gastrointestinal segments have been used and continue to be used with good results. Unremitting medical problems are relatively rare after augmentation cystoplasty if used appropriately in well-selected patients. No one bowel segment has a clear advantage over others when all such problems are considered. Patient diagnosis, anatomy, and physiology may suggest that one bowel segment is preferable for a particular patient. Each surgeon interested in augmentation cystoplasty should be familiar with the advantages and disadvantages of each segment in different settings.

In many routine cases, any gastrointestinal segment may be chosen for cystoplasty based purely on the personal preference and familiarity of the surgeon. The surgeon's experience and confidence in using a segment are important. **We believe that no one bowel segment is the best choice in all patients and that optimal results are achieved when the bowel segment is chosen based on the needs of the particular patient. The segment must then be used correctly.** Ileum is preferred if there is no clear advantage or reason to use another segment. Stomach is reserved for very select children with renal insufficiency and acidosis, short gut syndrome, and heavy irradiation; even then, the potential complications of gastrocystoplasty must be considered (Castellan et al, 2012). Sigmoid cystoplasty is used in select patients without reservation; good results can be expected for most patients with any segment if it is used properly.

The use of laparoscopy, usually with robotic assistance, to achieve augmentation cystoplasty evolved from early work on auto-augmentation to full intracorporeal enterocystoplasty (Ehrlich and Gershman, 1993; Docimo et al, 1995; Lorenzo et al, 2007; Gundeti et al, 2008). Intraoperative times vary greatly among these reports and are related to surgeon experience and inherent patient factors such as prior surgery, working space availability, and whether a pure laparoscopic or robotic-assisted approach is used. Outcomes have been similar to those of open reconstruction in early follow-up (Traxel et al, 2010; Gundeti et al, 2013). Potential advantages of a minimally invasive approach include faster recovery and improved cosmesis (Hasan et al, 2011). Experience with these approaches is already accumulating rapidly, and thorough evaluation will be needed to determine if a minimally invasive approach is cost-effective, particularly in the neurogenic population.

A Decreasing Necessity?

Although augmentation cystoplasty works well for most patients who require it and although work on alternatives to bowel cystoplasty may lower morbidity for the patient, a primary goal for every pediatric urologist is to minimize the number of patients needing cystoplasty. Newer medical regimens, botulinum toxin A injections (Schulte-Baukloh et al, 2005; Altaweel et al, 2006; Game et al, 2009; Stoehrer et al, 2009; Pascali et al, 2011), and neuromodulation may prove effective for some patients who at present do not respond to conservative measures (Aslan and Kogan, 2002; Lansen-Koch et al, 2012). Xiao and others (2005; Peters et al, 2010) continue to refine an artificial somatic-autonomic reflex pathway in children with neurogenic dysfunction. No matter what the diagnosis, earlier and more aggressive treatment of bladder dysfunction may minimize the insult to the bladder and maximize recovery as well as ultimate bladder function. Early urodynamic evaluation of boys with posterior urethral valves may identify treatable bladder problems and improve the prognosis from the standpoint of the kidneys and bladder (Misseri et al, 2002; Casey et al, 2012). Grady and associates (2003) suggested that complete primary repair of bladder exstrophy results in early bladder cycling that improves eventual bladder function and decreases the likelihood of augmentation cystoplasty.

With perhaps the most compelling evidence to date, Kaefer and colleagues (1999a) found that only 17% of patients with hostile neurogenic bladder dysfunction treated immediately on diagnosis required augmentation cystoplasty as compared with 41% of similar patients treated expectantly. Although the series included no collaborative urodynamic data and might be subject to lag time bias, the authors felt that there was a significant difference in the outcomes for the two groups. Because there are no prospective, randomized trials evaluating early evaluation and treatment of pediatric bladder dysfunction, suggestions that expectant treatment may lower the necessity for augmentation cystoplasty (Bauer, 2003; Mitchell, 2003) remain unproven. On early examination, early bladder management had not decreased the rate of augmentation cystoplasty (Lendvay et al, 2006); however, more recent re-evaluation (Schlomer et al, 2013) suggested that augmentation rates have fallen by 25% in the past decade. Critical, prospective evaluation of

such treatment is needed and will hopefully demonstrate how to successfully manage these patients. It is likely that such improvements will minimize the need for cystoplasty but not completely remove it (Cain and Rink, 2010).

Improving Quality of Life?

Reconstruction to achieve continence has been assumed to improve health-related quality of life. Early evaluation of small numbers of patients undergoing reconstruction including augmentation cystoplasty does not always show improved status on objective questionnaires compared with preoperative studies or control patients without surgery despite what generally would be considered to be good clinical results (MacNeily et al, 2005; Parekh et al, 2006). Assessment of the social impact of using a catheterizable channel instead of urethra is limited (Kari et al, 2013). Patient-reported scores also do not always correlate with those noted by their parents. Most evaluation of surgical techniques to date has focused on results and complications from the perspective of surgeons. Future evaluation should include objective, patient-reported consideration. Tools to acquire that information must be validated for longitudinal study of these patients and their disease processes.

KEY POINTS: AUGMENTATION CYSTOPLASTY

- Any gastrointestinal segment should be reconfigured and widely anastomosed to the bladder to maximize capacity and compliance.
- Failures to achieve adequate compliance are rare (5% to 10%) and are usually related to rhythmic pressure contractions.
- Gastrointestinal effects are rare, although chronic diarrhea may occur if the ileocecal segment is used in the neurogenic population.
- Ammonium resorption can cause metabolic acidosis, particularly among patients with renal insufficiency.
- Bacteriuria is common after cystoplasty and does not always require treatment.
- Bladder calculi occur in 10% to 30% of patients after augmentation.
- Aggressive adenocarcinomas have been reported as early as 4 years after augmentation but thus far have not occurred with the frequency noted after ureterosigmoidostomy.
- Delayed perforation of the bowel segment can be expected in 5% of patients after augmentation. It has occurred most frequently in colonic segments used in the neurogenic population.
- Good early care for underlying bladder dysfunction may lower the need for augmentation cystoplasty.

Alternatives to Gastrointestinal Cystoplasty

Largely because of the complications just reviewed, alternative methods that can achieve a large-capacity, compliant reservoir remain attractive. Efforts have covered the spectrum from synthetic materials and autologous grafts through creation of a bladder diverticulum (autoaugmentation) to various forms of neural stimulation. Some of these alternatives appear to hold promise, but none have stood the test of time in comparison to intestinal cystoplasty.

An ideal tissue for increasing capacity and improving compliance would have transitional epithelium so as to be relatively impermeable and avoid metabolic changes. The lining would also not produce mucus and would carry no increased potential for tumor development. Two such alternative procedures are ureterocystoplasty and autoaugmentation. With ureterocystoplasty, there is good muscle backing to transitional epithelium, whereas collagen eventually backs the transitional mucosa of an autoaugmentation.

Ureterocystoplasty

It has been noted for years that in patients with posterior urethral valves, unilateral reflux may behave as a pop-off valve to lower intravesical pressures and protect the contralateral upper tract (Hoover and Duckett, 1982; Rittenberg et al, 1988; Kaefer et al, 1995). It was a logical extension to use ureteral tissue in that setting to augment the bladder.

Technique. Ureterocystoplasty may be performed through a midline, intraperitoneal incision. This incision provides access to the intestine should mobilization of the ureter for augmentation be unsatisfactory. Bellinger (1993), Dewan and colleagues (1994), and Reinberg and colleagues (1995) have shown that ureterocystoplasty can be done through two incisions, remaining completely extraperitoneal. The general technique is the same. A standard nephrectomy is performed with great care to preserve the renal pelvic and upper ureteral blood supply. All adventitia and periureteral tissue are swept from the peritoneum toward the ureter during mobilization to protect the ureteral blood supply. Proximally, this blood supply typically arises medially. As the ureter enters the true pelvis, the blood supply arises posterior and laterally. After mobilization of the ureter into the pelvis, the bladder is opened in the sagittal plane. Posteriorly, this incision has typically been carried off-center directly into and through the ureteral orifice of the ureter used for cystoplasty. The ureter is *not* detached from the bladder but is opened longitudinally along its entire length, taking care to avoid its main blood supply (Fig. 145-15). The incision in the bladder and distal ureter should avoid branches of the superior vesical artery, which serves as an important blood supply to the mobilized ureter. The ureter is folded on itself, and the ureter-to-ureter and ureter-to-bladder anastomosis is performed with running absorbable suture. A suprapubic tube is left indwelling through the native bladder for 3 weeks during healing. After cystography documents the absence of leakage, CIC is started. Any patient attempting to void must prove that he or she can empty adequately through a check of postvoid residuals.

Alternatively, the bladder incision can be stopped approximately 2 cm from the orifice, and a similar length of distal ureter left in situ and intact without incision. The resulting small loop of intact ureter does not create clinical problems or adversely affect the end volume in a significant manner (Adams et al, 1998). This modification of technique is easier and may be safer in that it avoids potential injury to the blood supply of the ureter.

Results. Early experience with the procedure noted that the entire renal pelvis could be preserved, allowing more tissue for cystoplasty (Churchill et al, 1993; Landau et al, 1994; McKenna and Bauer, 1995; Reinberg et al, 1995). As with intestinal cystoplasty, folding the ureter into a more spheric configuration maximizes the volume to be achieved. If a massively dilated ureter drains a functioning kidney, the distal ureter alone may be used for augmentation, with the proximal ureter either reimplanted into the bladder or anastomosed to the contralateral ureter (Bellinger, 1993). Numerous series have reported good results after augmentation using ureter, some with follow-up as long as 8 years. The upper tracts have remained stable or improved in virtually all patients. Complications have been uncommon. Landau and colleagues (1994) compared age-matched and diagnosis-matched children undergoing ureterocystoplasty or ileocystoplasty. The total mean bladder capacity was 470 mL in the ureterocystoplasty group and 381 in the ileocystoplasty group. Bladder volumes at 30 cm H₂O were 413 mL and 380 mL after ureterocystoplasty and ileocystoplasty, respectively. Ureter effectively enhanced both volume and compliance. There was one failure in the group, which occurred in a child in whom the distal ureter did not provide enough volume. Work has shown that one dilated ureter typically is enough for cystoplasty (Zubieta et al, 1999; Kajbafzadeh et al, 2010).

The main disadvantage to ureterocystoplasty is the limited patient population with a nonfunctioning kidney draining into a megaureter. McKenna and Bauer (1995) reported the use of a normal-sized ureter. The ultimate success of ureterocystoplasty using normal ureter requires further follow-up, particularly because

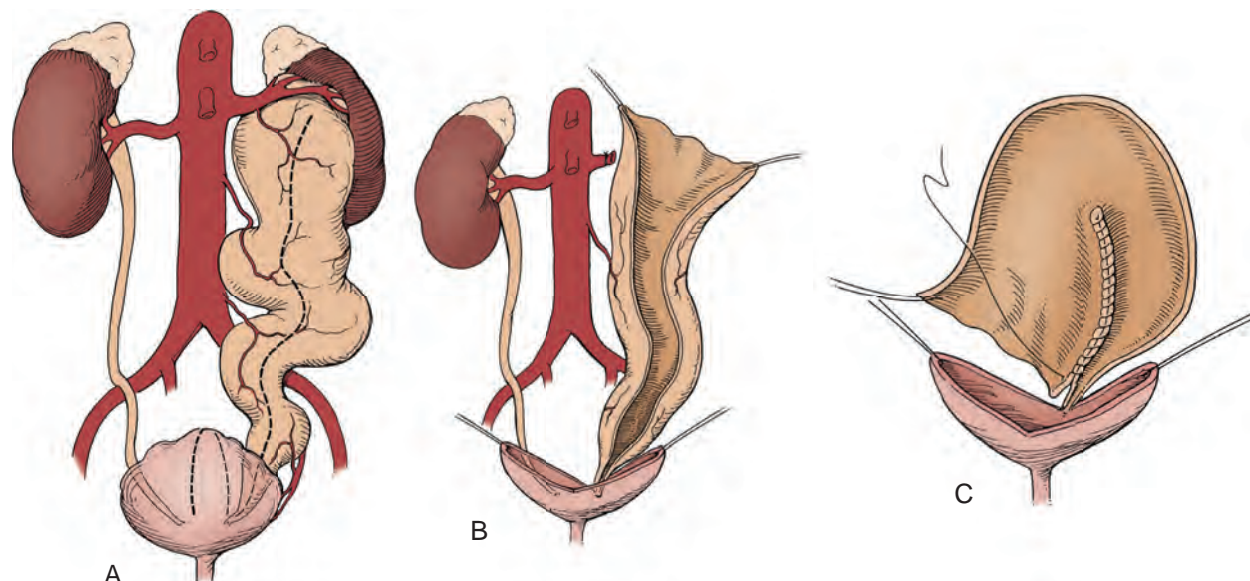


Figure 145-15. Ureterocystoplasty. A, After nephrectomy, the bladder is bivalved, with the posterior aspect of the incision carried off the midline to enter the ureteral orifice. The ureter is not detached from the bladder. B, The ureter is opened opposite its main blood supply. C, The ureter is reconfigured as in intestinal cystoplasty before anastomosis to the bladder.

Gonzalez (1999) stated that in one quarter of his patients with posterior urethral valves, ureterocystoplasty with a dilated ureter has failed owing to their huge urinary volume. Husmann and colleagues (2004) noted even worse results if the ureter used was less than 1.5 cm in diameter. Atala and colleagues (1994) presented an experimental technique to slowly dilate a normal ureter for later use. Work continued in porcine models (Stifelman et al, 1998; Desai et al, 2003); however, the principle has not yet proven to be clinically feasible.

Autoaugmentation

Techniques and Results. Cartwright and Snow (1989a, 1989b) described a method to improve bladder compliance and capacity through use of native urothelial tissue. In their procedure, known as *autoaugmentation*, they excised the detrusor muscle over the dome of the bladder, leaving the mucosa intact to protrude as a wide-mouthed diverticulum. Initially they made a midline incision through the bladder muscle (Fig. 145-16A). With the bladder distended with saline so that mucosa bulged from the incision, the muscle was then mobilized and excised laterally in each direction (Fig. 145-16B). The lateral edges of the detrusor muscle were then secured to the psoas muscle bilaterally to prevent collapse of the diverticulum (Fig. 145-16C). Their early experience noted improved compliance in most and increased capacity in some patients (Cartwright and Snow, 1989a).

This procedure has since been modified by a number of surgeons, each applying a different name for the procedure depending on whether the detrusor muscle was simply incised or was excised to create the diverticulum. In an effort to determine if incision or excision provided superior results, Johnson and colleagues performed 16 vesicomytomies and 16 vesicomytectomies in rabbits after previously reducing bladder capacity (Johnson et al, 1994). Functional bladder capacity in the animals increased by 43.5%, and there was no statistical difference between the two techniques. They then performed vesicomytomies (incision) in 12 patients with neurogenic bladder dysfunction and demonstrated a mean increase in capacity of 40% (Stothers et al, 1994). They concluded that detrusor excision offered no advantage over incision. All patients demonstrated some increase in capacity (15% to 70%),

and no patient in early follow-up clinically deteriorated and required enterocystoplasty.

Detrusorectomy, leaving a small cap of muscle at the dome through which a suprapubic tube can be placed, was proposed by Landa and Moorehead (1994). They were concerned that although these procedures usually improve compliance, increase in volume is “modest at best,” a concern shared by others (Snow and Cartwright, 1996; Cartwright and Snow, personal communication, 1998). In a report of 12 detrusorectomies, 5 patients were considered to have excellent results and 2 to have acceptable results, and 1 was lost to follow-up. Failures occurred in 4 patients, of whom 3 underwent conventional augmentation (Landa and Moorehead, 1994). In a combined series at those two institutions, only 52% of patients had a good result with autoaugmentation, whereas 20% had a poor outcome (Snow and Cartwright, 1996). Reoperative enterocystoplasty was not hampered by the prior detrusorectomy. The urothelial diverticulum at the time of augmentation cystoplasty was noted to be thick and fibrous, similar to a leather bag.

In general, complications from the procedures are uncommon. Perforation, a major concern after intestinal cystoplasty, has not been reported. Inadvertent opening of the mucosa during the procedure can make subsequent mobilization more difficult and may promote prolonged postoperative extravasation. Such extravasation usually stops with bladder drainage (Landa and Moorehead, 1994; Stothers et al, 1994). Prolonged drainage, however, may result in compromised results owing to collapse of the diverticulum. Rocha and coworkers (2011) suggested that early use of a silicone balloon to maintain distention may improve results. If concomitant ureteral reimplantation or bladder neck surgery is necessary, various authors have recommended that it be done first and the bladder then closed before detrusorectomy (Stothers et al, 1994).

Ehrlich and Gershman (1993) first reported laparoscopic myotomy (incision). A laparoscopic approach uses a smaller incision and perhaps shortens postoperative hospitalization; it may allow effective fixation of the detrusor muscle in an open fashion to make good bulging more difficult.

Concerns. The main disadvantage of autoaugmentation is a limited increase in bladder capacity such that adequate preoperative volume may be the most important predictor of success (Landa and Moorehead, 1994). If the maximum capacity and the

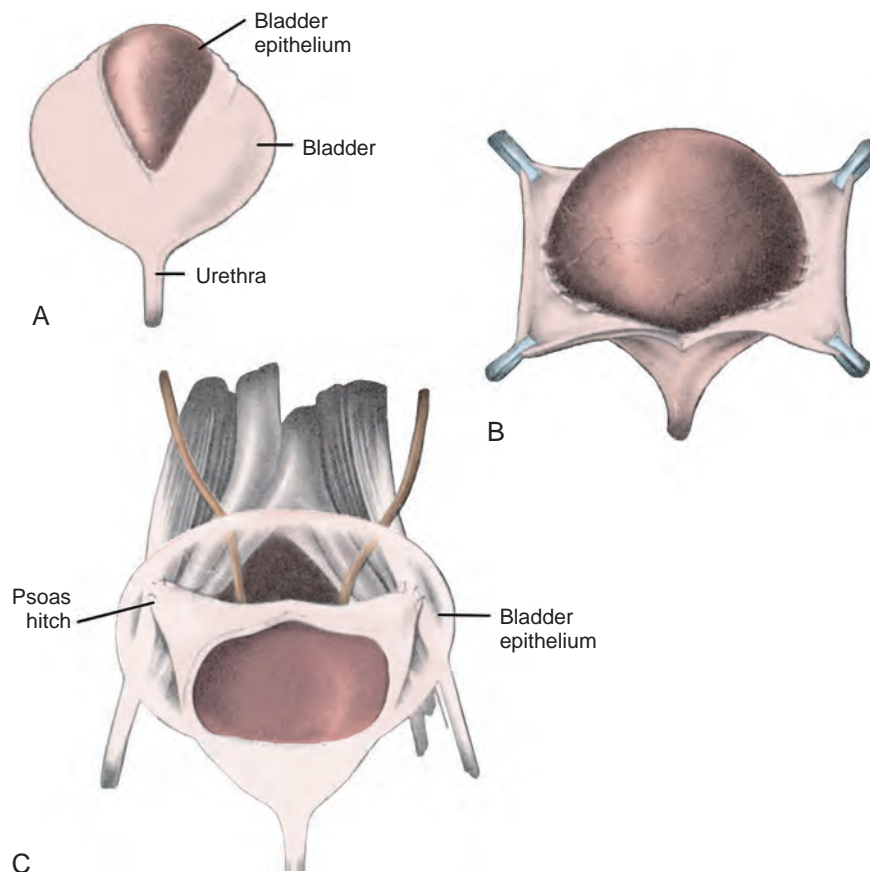


Figure 145-16. Autoaugmentation. A, The detrusor is incised. B, Detrusor is stripped and excised from mucosa. C, The detrusor muscle is anchored bilaterally so that the mucosa bulges with bladder filling. (From Cartwright PC, Snow BW. Bladder autoaugmentation: early clinical experience. *J Urol* 1989;142:505.)

volume of urine held at 40 cm H₂O are similar, the patient may be better served by immediate intestinal cystoplasty. It is of note that some patients have demonstrated clinical improvement after these procedures without a significant change in urodynamics. The reason for improvement in that setting is unknown.

In most series of autoaugmentation, no matter what the technique, occasional patients have been noted or concern has existed at the time of the initial procedure that adequate expansion was not achieved. In most such cases it was elected to proceed with enterocystoplasty immediately at the time (Landa and Moorehead, 1994). The patient and surgeon must be prepared for such an event on occasion. Stoehrer's group (1999) as well as Leng and associates (1999) reported good results with the technique among patients with hyperreflexia. In terms of capacity, even if adequate expansion is achieved initially, there is concern that any improvement may not persist long term (Dewan et al, 1994). In animals, the surface area of the autoaugmentation site was noted to decrease approximately 50% by 12 weeks. Progressive thickening and contracture of the site have been noted because of collagenous infiltrate (Johnson et al, 1994). Milam (personal communication, 2000) noted that almost one half of his adult patients with hyperreflexia who had a good early result after autoaugmentation failed with longer follow-up. Similar delayed failures have been noted in pediatric patients (Lindley et al, 2003) including one series with very poor results (MacNeily et al, 2003). To the contrary, Hansen and associates (2013) found that early decreases in capacity improvement may reverse with longer follow-up.

At this point, autoaugmentation should likely be considered only in patients who have reasonable capacity but poor compliance owing to uninhibited contractions. If a significant increase in capacity is needed, autoaugmentation may not be definitive.

Seromuscular Enterocystoplasty

Based on concerns about collagen deposition and contraction around autoaugmentation, efforts have been made to cover the bulging urothelium with demucosalized enteric segments. Use of bowel segments stripped of their mucosa within the bladder is not new. If exposed submucosa was left facing the bladder lumen, re-epithelialization with urothelium was noted in animals. Despite re-epithelialization, patch contracture often occurred (Oesch, 1988; Salle et al, 1990). Several series evaluated demucosalized augmentation in humans, with care taken to preserve the submucosa. Some encouraging results were noted (Lima et al, 1998; Dayanc et al, 1999; de Badiola et al, 1999; Lima et al, 2004), although regrowth of metaplastic enteric mucosa was found in the second study. Early placement of a silicone balloon or mold may help prevent contracture (Lima et al, 2004).

Technique and Results. To avoid contracture, a combination of autoaugmentation after detrusorectomy and coverage with a demucosalized enteric segment has now been used. Buson and colleagues (1994) used reconfigured, demucosalized sigmoid colon placed over the urothelium (seromuscular colocolocystoplasty lined with urothelium [SCLU]). They, and others, noted that the intestinal submucosa should be preserved to avoid contracture (Buson et al, 1994; Vates et al, 1997) (Fig. 145-17). This procedure has been performed clinically with early reports of good results in most patients (Gonzalez et al, 1994). Postoperative bladder capacity increased an average of 2.4-fold (139 to 335 mL) in 14 of 16 patients, and end filling pressure decreased from an average of 51.6 to 27.7 cm H₂O. In 2 patients the procedure failed, ileocystoplasty was required; their urodynamic data were excluded. Two other patients developed an hourglass deformity (Gonzalez et al, 1994).

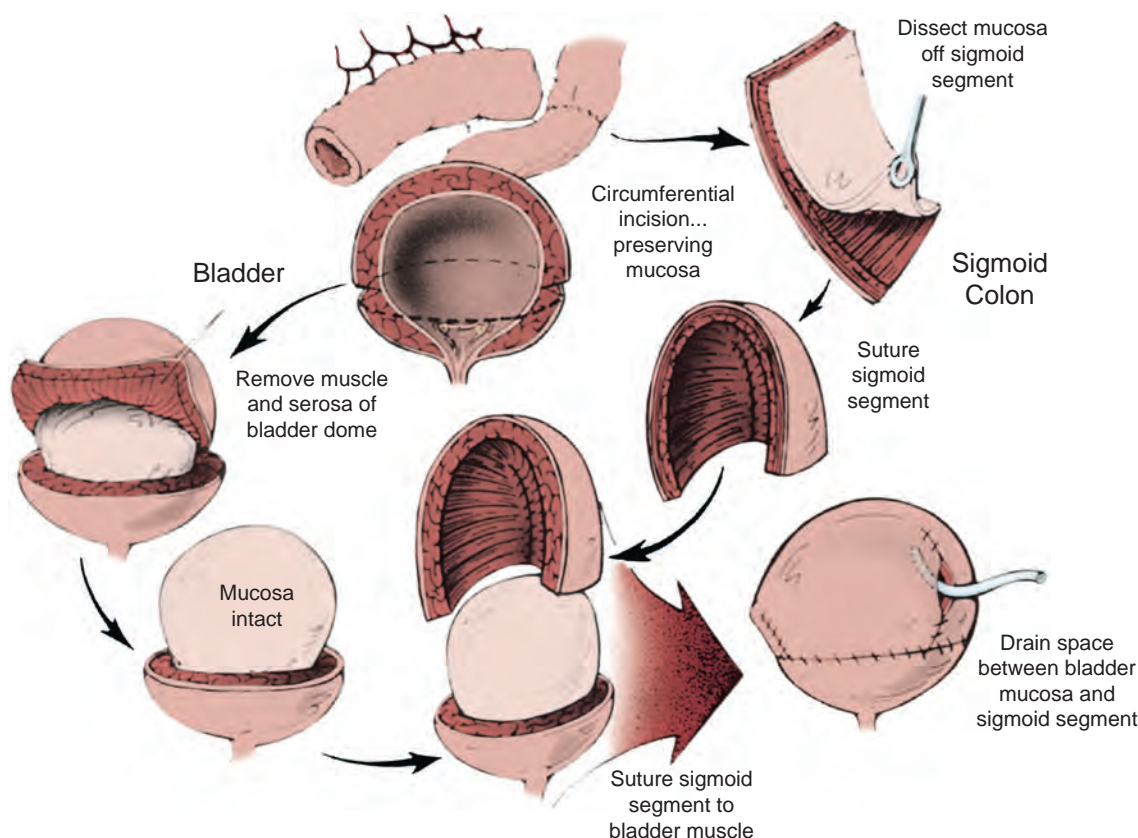


Figure 145-17. Seromuscular enterocystoplasty with use of sigmoid colon. Detrusor incision is performed as in autoaugmentation; however, the bulging mucosa is covered with a demucosalized segment of sigmoid colon. (From Buson H, Manivel JC, Dayanc M, et al. Seromuscular colocolocystoplasty lined with urothelium: experimental study. *Urology* 1994;44:745.)

Endoscopic biopsy of the segments has been interesting. Of 10 biopsy specimens, 1 was noted to contain urothelium with islands of colonic mucosa, whereas 2 others were found to contain only colonic mucosa. Removal of all of the enteric mucosa is important when using sigmoid to prevent mucoceles or overgrowth of intestinal mucosa (Gonzalez et al, 1994; Lutz and Frey, 1994). Dewan and associates (1997) felt preservation of the submucosa eventually promoted regrowth of bowel mucosa. The interaction of the two different tissues will be interesting to follow. The long-term effects on the urothelium by the seromuscular segment and vice versa are unknown. Work has shown that persistent transitional lining will protect from metabolic problems and mucus production (Denes et al, 1997).

Dewan and Byard (1993) and Close and colleagues (2004) alternatively used demucosalized stomach to cover an autoaugmentation, first in sheep and then in patients. Early results showed improved bladder function both clinically and by urodynamics (Horowitz and Mitchell, 1993; Dewan and Stefanek, 1994; Horowitz et al, 1994; Robinson et al, 1994), although long-term results are not as encouraging (Carr et al, 1999). These procedures are technically more demanding than simple augmentation or autoaugmentation and are associated with more blood loss and a longer operative time (Gonzalez et al, 1994; Horowitz et al, 1994). Increased bleeding is particularly true when stomach is used. These urothelial-lined, seromuscular augmentations are theoretically attractive. Thus far, the failure and reoperation rate after such procedures remains higher than that noted for standard enterocystoplasty (Vates et al, 1997; Carr et al, 1999; Shekarriz et al, 2000; Jung et al, 2012). The best results have been reported with use of colon (Shekarriz et al, 2000; Jung et al, 2012). Early results may be partially attributed to the learning curve with a new, complex procedure. Longer follow-up and more experience are necessary to

determine whether the complication rate will decrease with experience or increase because of problems with the combination.

Bladder Regeneration

Efforts to find alternatives to intestinal cystoplasty in the 1950s included the use of alloplastic materials for bladder substitution (Gleeson and Griffith, 1992; Kropp et al, 1995b, 2004; Kanematsu et al, 2007; Lewis and Cheng, 2007; Yamzon et al, 2008; Roth et al, 2011). Early research efforts met with very limited success owing to foreign body complications but provided a foundation for regenerative medicine. This led to focus on biodegradable, collagen-rich tissues serving as scaffold with and without cell "seeding" for bladder regeneration (Kelami, 1971; Fishman et al, 1987; Atala et al, 1992; Kambic et al, 1992; Kropp et al, 1995a; Zhang et al, 2004; Harrington et al, 2008). Atala and coworkers (2006) provided the first reported data regarding use of a seeded biodegradable construct for augmentation in the neurogenic population. This work led to an industry-supported prospective multi-institution investigation using a neobladder construct (Joseph et al, 2009). Unfortunately, compliance improved in only four patients after 12 months and in five at 36 months, but in none to a clinically or statistically significant degree. Capacity did not improve either (Joseph et al, 2014).

Using autologous tissue from a neuropathic source may result in lower yield of cells for use (Subramaniam et al, 2011) or could potentiate growth of abnormal tissue; an alternate cell source for regenerative tissue such as stem cells might circumvent those concerns. The use of stem cells carries its own set of obstacles (Aboushwareb and Atala, 2008; Aitken and Bāgli, 2009; Soler et al, 2009; Chen et al, 2011). Further investigation into the clinical applicability of regenerative tissue engineering is required, but this technology remains poised to alter the field of reconstructive bladder surgery.

KEY POINTS: ALTERNATIVES TO GASTROINTESTINAL CYSTOPLASTY

- Ureterocystoplasty avoids complications associated with bowel segments but may not provide adequate volume if the ureter is not remarkably dilated.
- Autoaugmentation seldom adds significant capacity and may not always improve compliance long term.

CONTINENT URINARY DIVERSION

The frequency with which continent urinary diversion is performed in children is dependent on one's definition of continent diversion. Tumors resulting in cystectomy among children are much less common than in adults. It is in that setting, and the occasional child in whom the bladder is congenitally absent or so small as to be virtually useless, that a pure continent urinary diversion in the classic sense of an Indiana or Kock pouch might be performed. Very good results with continent diversion in children have been achieved, equivalent to those reported in adults (Stein et al, 2005). Orthotopic neobladders in children are performed very infrequently because neurogenic or anatomic problems at the outlet prevent spontaneous voiding in many cases. Occasionally a child with neurogenic dysfunction may be a candidate for orthotopic bladder substitution (Stein et al, 2000, 2005), but it is not clear how many of those patients with neurogenic dysfunction can be expected to void adequately.

Some authors have defined combinations of bladder augmentation, continent abdominal wall stoma, and some procedure at the outlet as continent diversions (Kaefer et al, 1997b). Division and closure of the bladder neck to prevent incontinence per native urethra has typically meant inclusion. These procedures typically have been performed in complex patients with multiple problems that must be addressed, often after numerous previous surgeries.

Considerations

The amount of bowel used in continent urinary diversion may vary depending on the patient. Total bladder replacement requires much more intestine than simple augmentation. Typically a 40-cm segment of small bowel is used for an ileal reservoir in a Kock pouch compared with the 20 cm often used for augmentation. Likewise, the entire right colon with the hepatic flexure may be used in an Indiana pouch, whereas only 15 to 20 cm of colon are needed for colocolostomy. Because of the potential morbidity associated with use of a larger intestinal segment, the native bladder is often used in children if it provides any significant volume. To do so, however, may require repair of the outlet if outflow resistance is low.

Imbrication of the ileocecal valve and terminal ileum has proven to be a simple and reliable means for construction of an effective efferent limb in continent diversion among adults and children. Despite reports to the contrary in select patients (Husmann and Cain, 1999), concern about fecal incontinence secondary to use of the ileocecal valve persists for patients with neurogenic dysfunction. The flap valve continence mechanism provides numerous alternatives for those surgeons with such concerns in continent diversion. Good results achieved with use of the appendix or tapered intestinal segments have led to their increased use.

Whereas maintenance of the native urethra for catheterization is ideal, it may not be appropriate or possible in all individuals. Urethras after reconstructive bladder neck procedures are often subject to difficulty with catheterization. Children with neurogenic sphincter incompetence may have associated neurologic limitations that prevent easy access to the native urethra. This is particularly true for the wheelchair-bound child. For children without neurologic deficits, normal sensation in the native urethra can prevent compliance with a routine catheterization

schedule because of discomfort. For these reasons, a continent catheterizable stoma provides an adequate and sometimes a more reliably useful alternative.

Continence Mechanisms and Catheterizable Stoma***Ureterosigmoidostomy and Its Variants***

Ureterosigmoidostomy can be an effective form of continent urinary diversion in some patients. Its advantage is the spontaneous evacuation of urine with stool. The significant complications of hyperchloremic acidosis, infection, hydronephrosis, and colonic malignancies have led to disfavor and disuse, particularly in the United States. Although good results with standard ureterosigmoidostomy have been reported in some children, the procedure is rarely performed as originally described. The morbidity of acidosis and upper tract changes may increase with time, making those complications particularly worrisome for children with a long life expectancy. The significant risk of adenocarcinoma commits the patients to a lifetime of close surveillance for an avoidable tumor. It is unlikely that ureterosigmoidostomy, as classically described, will regain acceptance for children.

Several modifications of ureterosigmoidostomy have been developed in an attempt to decrease the significant complication rate. The most basic of the modifications is the sigma rectum or the Mainz II pouch. The colon is incised along the antimesenteric border for 6 cm both proximal and distal to the rectosigmoid junction. The ureters are implanted in an antirefluxing fashion, and that portion of colon is then reconfigured and closed. This is done to create a rectosigmoid reservoir of lower pressure to protect the upper tracts. The Mainz II pouch has been used in children with bladder exstrophy (Stein et al, 1997a). Continence in appropriately selected patients is good, although acidosis is still a significant problem owing to exposure of the entire colon to urine (Fisch et al, 1996; Gerharz et al, 1999; Mingin et al, 1999b). The risk for development of adenocarcinoma is unaltered with this technique. Long-term follow-up is necessary to determine if the reconfiguration of the sigmoid in the area of ureteral implantation is truly effective for protection of the upper tracts. Stricture at the ureterocolonic anastomosis has been the most common complication in relatively short follow-up (Fisch et al, 1996).

In an effort to control the amount of colon to which urine is exposed, Kock and associates (1988) described creation of a colorectal valve to confine urine distally. The intussuscepted nipple valve was stabilized with permanent staples. The distal rectal segment was opened and patched with ileum to lower pressure. With short-term follow-up, the valve was effective in that no necessity for sodium bicarbonate or potassium citrate therapy was noted (Kock et al, 1988; Mahran et al, 1999). Urodynamic evaluation revealed low pressure in the rectal reservoir (Kock et al, 1988), but long-term follow-up in children is needed to see if it is truly less morbid in terms of infection and upper tract deterioration.

If placement of a colorectal valve avoids most complications of metabolic acidosis from ureterosigmoidostomy and creation of a reservoir with lower pressure better protects the upper tracts, the last remaining major concern about ureterosigmoidostomy is tumor development. The concern is significant; of 94 children followed in Boston after ureterosigmoidostomy, 7 developed adenocarcinoma, of whom 4 died of the tumor (Rink and Retik, 1991). Kock and colleagues (1988), followed by Skinner and associates (1989), used a hemi-Kock pouch to augment the distal rectal segment. A colorectal valve was created to isolate urine to the distal colonic reservoir. The afferent nipple valve kept stool away from the ureteroileal anastomoses, perhaps lowering the risk for tumor development. Simoneau and Skinner (1995) reported their results with the procedure in 15 patients, including 4 children. Their complication rate, both early and late, was relatively high. This is not surprising, considering the relatively complex nature of the procedure. They did think that pediatric patients were better suited for the procedure. Rink and Retik (1991) suggested that the rectum could be augmented with a nonrefluxing ileocecal conduit in a similar fashion.

Before any variant of ureterosigmoidostomy is considered, competence of the anal sphincter must be ensured. Tests used to assess sphincter integrity include manometry, electromyography, and practical evaluation of the ability to retain an oatmeal enema in the upright position for a period of time without soilage. Incontinence of a mixture of stool and urine results in foul soilage and must be avoided. Most patients with neurogenic dysfunction who are incapable of fecal continence in the presence of diarrhea are not candidates for these procedures. Procedures that separate the fecal and urinary streams within the rectal sphincter have been described but have not been widely used in children.

Nipple Valves

The most extensive experience with nipple valves used to achieve urinary continence has been with the Kock pouch. Skinner and associates (1989) made a series of modifications to aid in maintenance of the efferent nipple. Despite experience and use of these modifications, a failure rate of 15% or higher can be expected (Benson and Olsson, 1998) (Fig. 145-18). Several authors have reported a reoperative rate of approximately 33% with the Kock pouch, most frequently related to the efferent nipple (deKernion et al, 1985; Waters et al, 1987). Equivalent results with the nipple valve and a Kock pouch have been achieved in children (Hanna and Bloiso, 1987; Skinner et al, 1988; Kaefer et al, 1997b; Abd-El-Gawad et al, 1999). The last report noted a significant incidence of hyperchloremic acidosis and new hydronephrosis, although those complications were likely related to the complex nature of the patients rather than the particular continent diversion used.

Intussuscepted nipple valves have also been used with colonic and ileocolonic reservoirs, particularly the Mainz I pouch. Evolution of the nipple valve in the Mainz pouch also occurred over time (Thuroff et al, 1986; 1988; Hohenfellner et al, 1990; Stein et al, 1995). Most recently, the intussuscepted ileum was fixed with staples, passed through the intact ileocecal valve, and fixed again. Much as with the Kock pouch, the incidence of incontinence decreased with experience and modifications. The Mainz I pouch has been used in children with good results and low rates of incontinence using the latest modifications (Stein et al, 1995, 1997a; Steiner et al, 1998; Stein et al, 2000). Maintenance of normal upper tracts has been good, and metabolic problems rare (Stein et al, 1997b).

Flap Valves and the Mitrofanoff Principle

Mitrofanoff (1980) described a continence mechanism using the appendix and ureter to create a flap valve. He recognized that any

tubular structure could be implanted effectively into a low-pressure reservoir. This continence mechanism circumvents many of the secondary potential complications associated with harvesting the ileocecal valve or using other gastrointestinal segments.

The foundation for the success of the Mitrofanoff principle is based on creating a submucosal tunnel for a supple, small-diameter conduit. As the reservoir fills, the rise in intravesical pressure is transmitted through the epithelium and to the implanted conduit, coapting its lumen (Fig. 145-19). The appendix is an ideal tubular structure that can be safely removed from the gastrointestinal tract without significant morbidity. The small caliber of the appendix facilitates creation of a short functional tunnel within the bladder wall. Experience has shown that continence can be achieved with only a 2-cm appendiceal tunnel (Kaefer and Retik, 1997). Whether implanted into a bowel segment or native bladder, the appendix has been used as an efferent limb with very good results (Jayanthi et al, 1995; Kaefer et al, 1997b; Mollard et al, 1997; Cain et al, 1999; VanderBrink et al, 2011). The appendix has been particularly useful in children because it is relatively longer and the abdominal wall generally thinner. The flap valve is likely the most reliable of all of the surgically constructed continence mechanisms. Some patients with a flap valve virtually never leak per stoma; this potentially puts them at risk for upper tract deterioration or spontaneous rupture of the bladder or reservoir if catheterization is not routinely performed.

If the appendix is used in situ as a continence mechanism in a continent urinary reservoir, the reservoir by necessity will include the right colon. Duckett and Snyder (1986, 1987) used the right colon and appendix with good results in children. The mesoappendix, in most cases, allows mobilization of the appendix for use in the native bladder or virtually any reservoir.

Technique. In most children good exposure to the appendix and reservoir can be achieved through a low midline or a transverse incision. On occasion, the cecum may be high in the abdomen, and mobilization of the ascending colon along the line of Toldt may be required to gain access to the appendix and its mesentery. Cadeddu and Docimo (1999) have used laparoscopy to aid in the mobilization of the ascending colon and cecum. Once the cecum has been mobilized, the base of the appendix is amputated, leaving a small cuff of cecum with the appendix. Use of the cecal cuff at the stoma may decrease the risk of stenosis. The cecum is closed in a fashion similar to an open appendectomy. If the length of the appendix is marginal, a greater portion of the cecum can be harvested to effectively increase the functional length of the appendix (Cromie et al, 1991; Bruce and McRoberts, 1998).

After harvesting, a location is selected for implantation of the appendix into the bladder. The location is based on the length of

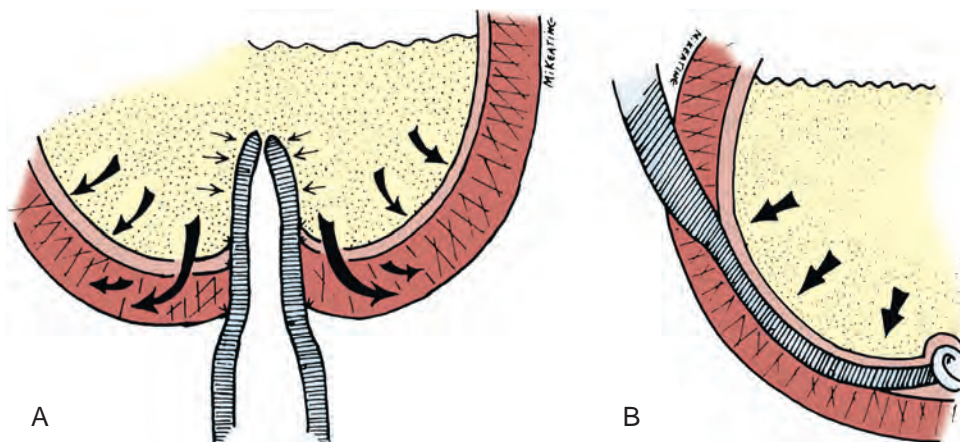


Figure 145-18. Continence mechanisms. A, The same pressures that create continence tend to efface nipple valves. B, This is not true of flap valves, which have been more reliable in pediatric reconstruction.

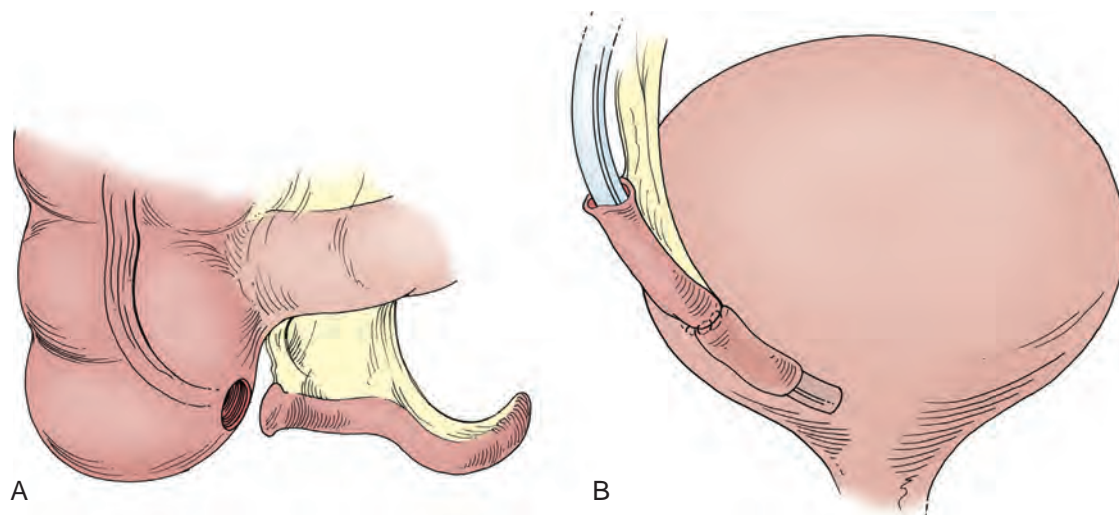


Figure 145-19. Appendicovesicostomy. A, The appendix is harvested with a cuff of cecum on a wide pedicle based on the appendiceal artery. A flap of cecum can be harvested in continuity with the appendix and tubularized to increase the length. B, The distal appendix is tunneled into the bladder to provide continence after the end is amputated. The proximal end of the appendix, the cecal cuff, is brought to the umbilicus or right lower quadrant as a catheterizable stoma.

the appendix, the mobility of the bladder, and the location for the appendiceal stoma. Typically the distal end of the appendix is tunneled into a posterolateral position within the bladder (see Fig. 145-19), although an anterior site may be useful as well. Creating a tunnel is easily done whether the bladder is opened or not (VanderBrink et al, 2011). Successful continence has also been achieved by developing an extravesical trough with or without a serosal base and then covering the channel with laterally mobilized serosa (Elshal et al, 2011; Baradaran et al, 2013).

The base of the appendix is brought to the abdominal wall in a location chosen preoperatively to suit the patient. It should be brought up to reach the skin without tension. Care must be taken not to twist the pedicle or occlude it as it passes through the abdominal wall fascia. The base of the appendix can often be hidden within the umbilicus, which allows for elimination of a small but obvious abdominal stoma. Because of the small circular diameter of the appendiceal base, stomal stenosis is common, and techniques have been described to prevent this problem. Various flaps have been described as a method for avoiding stomal stenosis (Keating et al, 1993; Kajbafzadeh, et al, 1995; Kaefer and Retik, 1997; Frane-Guimond et al, 2006; Berrettini et al, 2008; Landau et al, 2008). Weikert and associates (2012) described a rotational umbilical flap to enhance mobility and decrease tension when anastomosing to a channel with a short mesentery. Regardless of the technique, stomal stenosis remains the most common of complications. Chronic nighttime use of a stent through the channel may decrease that risk (Mickelson et al, 2009).

For prevention of kinking and problems with catheterization, it is advisable to maintain as short a conduit as possible. Securing the appendix and bladder wall to the peritoneum beneath the fascia will help diminish the problem of conduit kinking with reservoir filling. When appendix or any catheterizable stoma is used, it is advisable to repeatedly catheterize the channel after each step in reconstruction to confirm easy passage. If the catheter does not pass easily into the reservoir, the prior step needs to be revised. Problems with catheterization by the surgeon during the operative procedure usually result in more difficulty for the patient afterward. It is also beneficial to catheterize at variable reservoir volumes to confirm proper fixation of the reservoir and the absence of any kinking. The basic principles used for open reconstruction of a catheterizable channel can be used laparoscopically and with robotic assistance to achieve the same level of success (Hsu and

Shortliffe, 2004; Wille et al, 2011; Badawy et al, 2013; Famakinwa et al, 2013; Rey et al, 2013).

A 6-Fr to 12-Fr stent is typically left for 10 to 14 days within the efferent catheterizable channel during the healing process. It is then advisable for the surgeon to personally catheterize the efferent limb before the patient or family members do so. Catheterization should be repeated at least every 4 hours during the day for reservoir drainage, maintenance of patency, and minimalization of the risk of stomal stenosis.

The appendix may not be available for use in all patients owing to previous appendectomy, its location or length, congenital absence, involvement with adhesions, or its use for continence enemas. Histologic abnormalities of the appendix have been reported to occur in as many as 30% of patients (Liebovitch et al, 1992) and to increase with age. They rarely are of enough clinical significance to preclude use (Mulvihill et al, 1983).

Results. Several papers have reviewed large series of patients after appendicovesicostomy (Kaefer et al, 1997b; Cain et al, 1999; Harris et al, 2000; Thomas et al, 2006; Welk et al, 2008; VanderBrink et al, 2011). Inability to use the appendix, other than because it was needed for use in situ for antegrade continence enemas, has been rare. The results, in terms of continence, have been superb, usually above 95% (Kaefer and Retik, 1997; Mor et al, 1997; Suzer et al, 1997; Gerharz et al, 1998; Gosalbez et al, 1998; Cain et al, 1999; Castellan et al, 1999; Liard et al, 2001; Elshal et al, 2011; VanderBrink et al, 2011; Baradaran et al, 2012). Incontinence is a rare event with the Mitrofanoff principle and may result from inadequate length of the flap valve mechanism or persistently elevated reservoir pressure. Urodynamic evaluation is required to evaluate the cause of the incontinence. Injection of a bulking agent is a possible treatment for inadequate outflow resistance, with success reported up to 50% in the short term (Welk et al, 2008). A more formal approach with takedown and revision of the leaking Mitrofanoff valve is often required (Kaefer and Retik, 1997). The most common complication has been stomal stenosis, which in general has occurred in 6% to 10% of patients (Thomas et al, 2006; Welk et al, 2008; Leslie et al, 2011; Ardel et al, 2012). Stenosis resulting in difficult catheterization may occur early in the post-operative course and require formal revision (Harris et al, 2000). Mickelson and coworkers (2009) have described the successful use of an "L stent" with topical steroid cream as an effective noninvasive treatment. Another recognized complication has been appendiceal

perforation. Most problems with stomal stenosis and creation of a false passage (perforation) occur in the first few years after reconstruction, but long-term problems do occur, resulting in the need for lifelong monitoring (Thomas et al, 2006; Leslie et al, 2011). Benign fibroepithelial polyps and inflammatory granulomatous tissue have recently been reported in all types of catheterizable channels. Groth and associates (2013) reported an incidence of polyps occurring in 20% of their patients at a 7-year follow-up, with 50% being symptomatic and 45% having a recurrence after resection. Stricture and necrosis, particularly of cecal extensions of the appendix, have occurred rarely. Abdominal stomas may be associated with a higher risk of reservoir calculi owing to the potential for incomplete emptying.

Follow-up in the recent series has averaged approximately 4 years. Patients from Mitrofanoff's early experience (1980) now have follow-up of over 30 years, suggesting that the appendix may provide a durable alternative for pediatric patients, a finding also noted by others (Cain et al, 1999; Harris et al, 2000; Liard et al, 2001). Similar outcomes have been achieved in smaller series of adults (Gowda et al, 2008; Van der Aa et al, 2009; Ardel et al, 2012).

Alternatives. When the appendix is unavailable for use, other tubular structures can provide a similar mechanism for catheterization and continence. Mitrofanoff (1980) described a similar technique using ureter (Kaefer et al, 1997b). Care must be taken to preserve the distal blood supply to prevent ischemia. Refluxing ureters have even been used after extravesical reimplantation (Ashcraft and Dennis, 1986; Duel et al, 1996; Kaefer et al, 1997b). Stomal stenosis seems to be more problematic with use of the ureter compared with the appendix, possibly because of compromised blood supply. In addition, distention of the ureter from catheter passage has caused discomfort in some individuals (Duckett and Lofti, 1993).

Woodhouse and MacNeily (1994) used the fallopian tube, which can accommodate catheterization. Stenosis again appears to be a significant problem with the fallopian tube. The effect on fertility should be considered when there is a normal ipsilateral gonad. Ileum has been tapered to create a similar uniform tube of adequate length (Adams et al, 1992). By narrowing the ileal segment longitudinally along the mesenteric border using permanent staplers in series, a surrogate was constructed that was easy to catheterize and provided good continence. Others (Woodhouse and MacNeily, 1994; Hampel et al, 1995) have shown similar success with tapered ileum. The catheterizable channel must be long enough to reach from the reservoir to skin without tension, but kept as short and straight as possible to facilitate easy catheterization. An unnecessarily long, mobile catheterizable channel can kink and result in difficult catheterization or perforation.

Yang and Monti have been credited with a novel modification of the tapered intestinal segment that can be reimplanted according to the Mitrofanoff principle (Yang, 1993; Monti et al, 1997). A very short (1 to 2 cm) segment of small bowel is opened longitudinally along the antimesenteric border and then closed transversely (Fig. 145-20). By this reconfiguration, the initial circumference of the segment is converted to length and the original length to circumference. A very uniform tube is created with a small mesentery toward the center. The two ends are devoid of mesentery, making them very easy to tunnel into bladder and bring through the abdominal wall. If the first incision is made directly at the antimesenteric border, both limbs are of equal length. Because the incision is made off of midline and to one side, one limb may be created much longer than the other. Experience has shown that a long tunnel in the bladder or reservoir is not needed to achieve continence with such a small-diameter channel, and the longer limb has typically been used to reach the skin through a thick abdominal wall.

Very good results have been achieved using the Yang-Monti channel as a catheterizable stoma, and it is certainly an efficient use of bowel (Leslie et al, 2011; VanderBrink et al, 2011; Nerli et al, 2013). Some surgeons have suggested that it may be easier to catheterize than an ileal segment tapered longitudinally because circular mucosal folds are redirected longitudinally in the direction of

catheter passage. Stomas created with ileum may have a lower rate of stenosis than those created with appendix (Kaefer et al, 1999b). The one potential disadvantage of the Yang-Monti channel is that it remains relatively short and may not reach the skin without tension in obese patients. Despite extensive use of skin flaps, such tension may lead to stomal stenosis. Two separate reconfigured channels can be anastomosed together for increased length (Kaefer and Retik, 1997). Casale (1999) used an initial segment that was twice as long that was partially split in the middle and then opened in a spiral fashion on opposite sides to create a longer strip that could be tubularized in continuity. Narayanaswamy and associates (2001) noted difficulty with catheterizations through Yang-Monti channels in 28% of a large series of patients as a result of "pouch-like dilatation." Such a problem, to that degree, has been avoidable in most series. Excessive length of the limb may make such dilation more problematic.

Ileocecal Valve

Use of the ileocecal valve as a continence mechanism began with Gilchrist and colleagues (1950) and was popularized by the Indiana group (Rowland et al, 1985; Bihrlé, 1997). Various modifications have been developed. In general, a short segment of terminal ileum, whether imbricated or tailored, is used as an efferent limb. This segment should be kept as short and straight as possible to facilitate easy intermittent catheterization. Continence is based on the imbricated ileocecal valve, not the length of the efferent limb. The imbrication is usually secured with interrupted, permanent sutures, involving the very distal ileum and ileocecal valve, and the imbrication is carried onto the cecum.

The Indiana pouch has been used in children with excellent results as in adults. Besides the appendix, this continence mechanism is perhaps the simplest and has the shortest learning curve to achieve reliable results. Continence rates have been reported as high as 95% with preservation of normal upper tracts (Rowland et al, 1985; Lockhart et al, 1990; Rink and Bihrlé, 1990; Hensle and Ring, 1991; Rowland, 1995; Kaefer et al, 1997b). One report noted a higher rate of incontinence (Canning, 1998). Husmann and Cain (1999) have used the cecal segment for bladder augmentation and the efferent limb to construct a continent catheterizable stoma with good results. They noted a very low incidence of detrimental effect on gastrointestinal function in a select group of patients with neurogenic dysfunction.

Hydraulic Valves

Benckroun (Benckroun, 1982; Benckroun et al, 1989) developed a hydraulic valve as a continence mechanism that was modified by Guzman and colleagues (1989). Urine from the reservoir and generated pressure is allowed to enter a sleeve of ileum around the catheterizable channel. Compression of the inner tube theoretically provides continence, and early experience was encouraging. Initial continence rates approached 75% and then 90% with a single revision (Benckroun et al, 1989). Others have been unable to duplicate those results (Sanda et al, 1988; Leonard et al, 1990b). Koff and associates (1989) added a similar hydraulic sleeve around the efferent limb of an Indiana pouch, but the use of such valves has largely been abandoned.

Continent Vesicostomy

Yachia (1997) described creation of a bladder tube fashioned from a wide flap of the anterior bladder wall. An attempt to provide a continence mechanism was fashioned by weaving the bladder tube through the rectus muscle for compression and continence. Continence in their small, short-term series was reported to be 100%, but this has not been duplicated.

Hanna and associates (1999) described a continence mechanism based on either a flap of bladder or intestinal tissue fashioned after prior enterocystoplasty and used it on a very small series of patients. A rectangular flap in continuity with the bladder is tubularized over

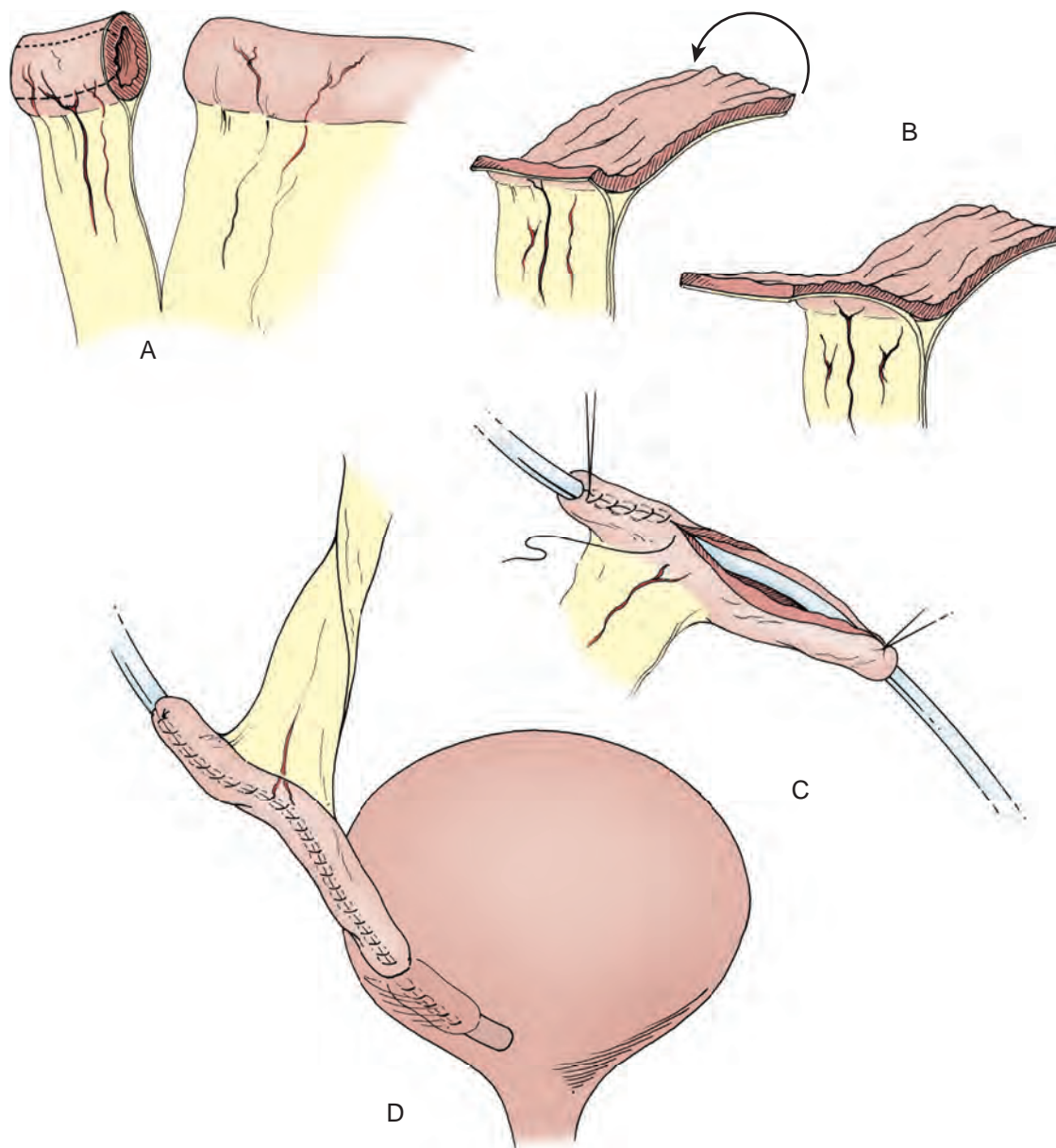


Figure 145-20. Yang-Monti technique to efficiently construct a catheterizable tube. A, A 2-cm length of ileum is harvested either independently or next to a segment for augmentation cystoplasty. The segment is opened horizontally and tubularized in a longitudinal fashion. B, If the segment is opened directly on the antimesenteric border, two equal-length limbs result with a central mesenteric pedicle. Initial incision may be made to one side to form a shorter limb for implantation in the bladder and a longer one to be brought through the abdominal wall. C, The reconfigured ileal segment is tubularized over a 12-Fr catheter in a two-layer technique with absorbable sutures. D, A continent catheterizable stoma is constructed.

a 14-Fr to 16-Fr catheter. The bladder is plicated around the proximal 3 cm of the tube using nonabsorbable suture to create a type of nipple similar to gastric fundoplication. [Macedo and Srougi \(2000\)](#) described a similar continence mechanism created at the time of initial augmentation. They achieved acceptable continence in eight of their first nine patients. Their technique is potentially appealing for patients requiring augmentation and having no appendix because of the simplicity; however, continence is based on a type of nipple valve that historically has been difficult to keep fixed. The same forces that create continence tend to efface the continence mechanism.

[Casale \(1991\)](#) has described a form of continent vesicostomy in which the continence mechanism is based on a flap valve created from a tubularized strip of bladder mucosa. It is particularly

suitable when the bladder is compliant and of large capacity. An anterior detrusor strip is used to create a catheterizable limb.

Technique. Parallel incisions 3 cm apart are made into the anterior bladder and used to create a long rectangular flap. The abdominal wall should be measured to ensure that the strip is long enough to reach the skin without tension. The full-thickness strip is tubularized down to the bladder, in two layers. The muscle portion is left broad to come around without tension and provide good blood supply. The mucosa may be trimmed in width before tubularization to avoid redundancy. A strip of mucosa within the bladder, 2 to 3 cm in length and 1.5 cm in width, is incised in a direct line and in continuity with the mobilized bladder tube. The edges of this strip are mobilized until it can be tubularized along its entire length. It may be beneficial to mobilize only one edge over to the other side

to avoid overlapping suture lines. Casale (1991) originally incised the mucosa transversely at the end of the intravesical strip to be tubularized; Rink and colleagues (1995b) then suggested that it could be left intact (Fig. 145-21). The bladder mucosa from either side of the channel is then mobilized and closed over the mucosal

tube to create a flap valve. More extensive mobilization of the side opposite that mobilized for the inner tube allows closure without overlapping suture lines, which may help avoid fistula formation and incontinence. A stent is left in the channel for 3 weeks to prevent stenosis. It does tend to stricture if not catheterized

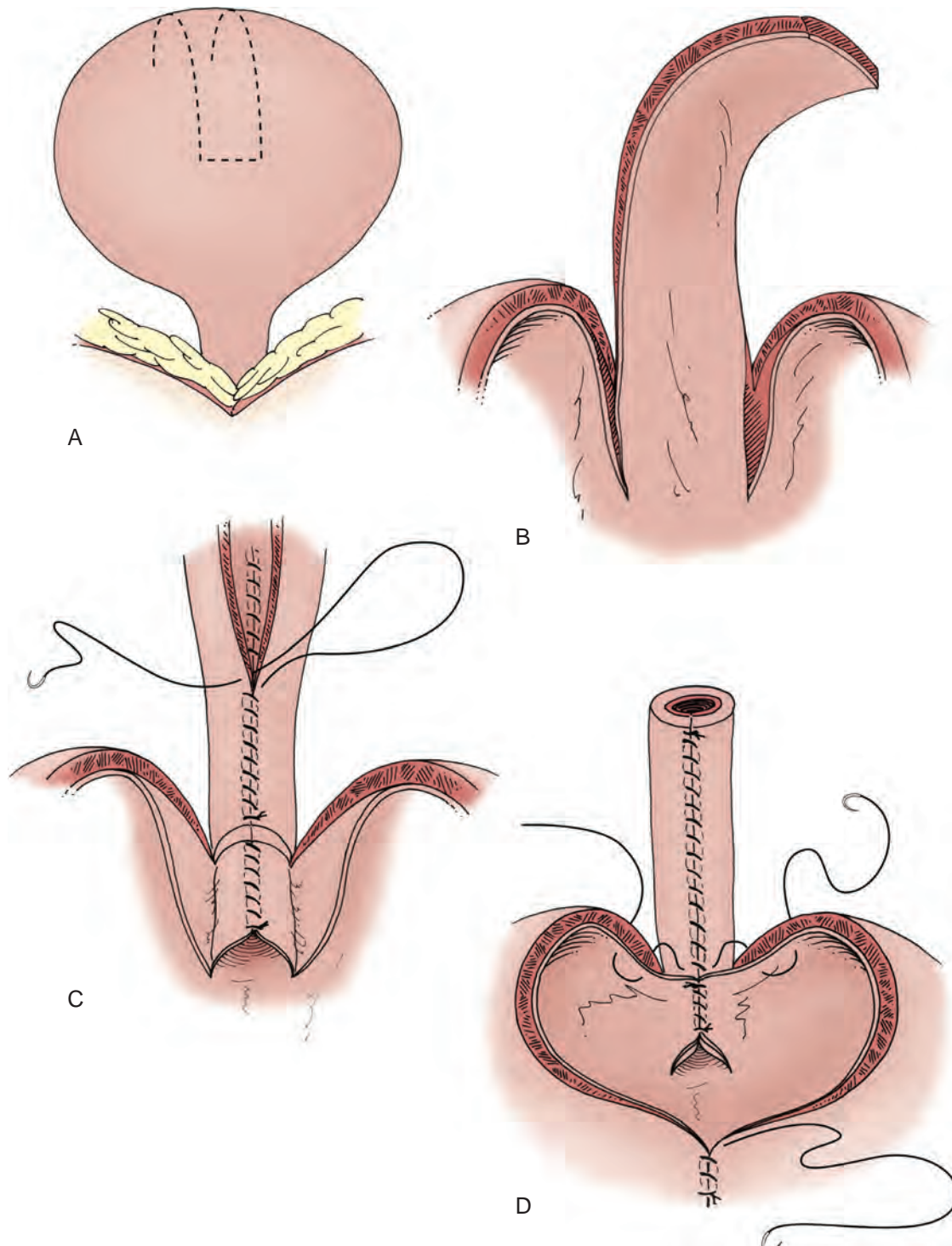


Figure 145-21. Casale continent catheterizable stoma. A, Parallel incisions are made in the bladder dome, forming a full-thickness bladder strip. B, The epithelium of the bladder is then incised for an additional 2.5 cm. The edges of the epithelium are mobilized, allowing tubularization. C, The epithelium is tubularized from the bladder out to the tip of the strip with an absorbable suture. The muscle of the bladder strip is then tubularized with an absorbable suture. D, The lateral edges of the epithelium within the bladder are reapproximated over the tubularized bladder segment with absorbable suture. The bladder is then closed with absorbable suture, incorporating the bladder tube with the initial sutures to prevent kinking.

regularly—more so than other catheterizable channels (Cain et al, 2002; Thomas et al, 2005).

Results. Continence rates have been good, as with most flap valves (Cain et al, 1999, 2002). Stomal stenosis remains a significant problem, 45% in the experience at Indiana University (Cain et al, 2002). Skin flaps and avoidance of tension to reach the skin may minimize this risk but not eliminate it. Advantages include avoidance of an intraperitoneal procedure and bowel anastomosis; the appendix can be reserved for use with enemas. It does use some bladder and decrease capacity, which may not be appropriate for many patients.

Results with Pediatric Continent Diversion

The most challenging aspect of continent diversion in children remains construction of an efferent limb that provides reliable continence and easy catheterization (Ardelt et al, 2012). The continence mechanism most familiar to pediatric urologists is the flap valve. The appendix is simple to use, suitable for most children, and associated with very good continence rates. If the appendix is not present or is to be used for antegrade colonic enemas, tapered intestinal segments provide a nice alternative. Nipple valves are the most complex continence mechanism and therefore have a longer learning curve. Continence rates approaching 85% can be expected with stapled nipple valves (Kaefer et al, 1997b; Benson and Olsson, 1998) after extensive experience. With use of the other efferent limbs, continence rates above 90% and approaching 95% have been reported in children (Duckett and Snyder, 1986; Hensle and Ring, 1991; Kaefer et al, 1997b; Surer et al, 2003; Ardelt et al, 2012).

Children undergoing continent diversion have a long life expectancy. With proper patient selection and appropriately performed continent diversion, postoperative hydronephrosis in children is rare and is not increased when compared with conduit diversion (Stein et al, 2000). If catheterization is not performed reliably, however, new hydronephrosis has been reported (Abd-El-Gawad et al, 1999). The incidence of complications after continent diversion will undoubtedly increase with longer follow-up. These patients will be subject to the same complications seen with bladder augmentation. All of those complications, including infection, hydronephrosis, calculi, spontaneous perforation, and tumor, have been reported after continent diversion in adults if not in children. These are largely a function of the use of intestine as a urinary reservoir. Because more intestine is usually required in continent diversion than bladder augmentation, the incidence of complications may ultimately be higher than with simple augmentation. Already, serum changes of increased chloride, decreased bicarbonate, and acidosis have been noted in some patients after continent diversion (Allen et al, 1985; Ashken, 1987; Thuroff et al, 1987; Boyd et al, 1989; McDougal, 1992a). Spontaneous perforation has occurred in up to 1.5% of patients (Mansson et al, 1997).

The most common complication in pediatric continent diversion, thus far, has been stomal stenosis. Stenosis occurs more commonly at the umbilicus with use of appendix compared with tapered ileal segments (Fichtner et al, 1997; Kaefer et al, 1999b). Various skin flaps may be placed into the terminal end of the appendix or intestinal segment to lower the rate of stenosis but do not eliminate it (Kajbafzadeh et al, 1995; Landau et al, 2008). Ardelt and associates, after extensive review (2012), found no consensus that a single type of efferent limb is superior and suggested that the choice of technique should be individualized according to the case.

SUMMARY

Every effort should be made to treat pediatric bladder dysfunction, no matter what the cause, early and aggressively to minimize the number of patients requiring reconstructive surgery for bladder and sphincter dysfunction. Some such surgery will still be necessary, and the patients must be carefully evaluated so that all problems are identified and addressed. The surgeon should then be flexible and prepared to use the bowel segments and techniques that best fit


KEY POINTS: CONTINENT URINARY DIVERSION

- “Pure” continent diversions have been used in children with good results similar to those expected in adults.
- Flap valves provide a reliable continence mechanism with appendix or reconfigured intestinal segments.
- The efferent limb should always be kept as short and straight as possible to facilitate catheterization.
- Stomal stenosis is the most common complication of pediatric continent diversion.

each patient. Although a given surgeon's results using any technique may improve with experience and confidence, each patient's unique problems and anatomy may make some choices better than others. Forcing one procedure to fit every patient should be avoided.

Preoperative evaluation should identify upper tract obstruction or vesicoureteral reflux. Such problems should be corrected at the time of surgery, although low-grade secondary reflux will usually resolve spontaneously with correction of bladder dysfunction. It is imperative to provide the patient with an adequate bladder or reservoir, one capable of holding at low pressure a urinary volume that will be produced between voidings or catheterizations. This can be accomplished by either augmentation or construction of a continent reservoir using any gastrointestinal segment. Each has its own set of advantages and disadvantages that should be considered. If adequate outflow resistance is lacking, it should be created at the bladder neck to prevent incontinence. Any patient undergoing reconstructive surgery for bladder or sphincter dysfunction must be prepared and capable of performing intermittent catheterization on a reliable basis; most will require it routinely. This is particularly true of those patients with neurogenic dysfunction.

As much of the patient's native urinary tract as possible should be preserved in pediatric urologic reconstruction. The urothelial lining avoids much of the morbidity associated with intestinal segments. If necessary, however, virtually any portion of the lower urinary tract may be reconstructed or replaced using intestine. Unfortunately, occasional complications do occur when intestinal segments are used in that manner. They are not perfect physiologic substitutes. Patients after reconstruction require a lifetime of follow-up, and that observation should include careful evaluation of their true quality of life. The most important factor in avoiding problems with such complex pediatric patients is the motivation of the patient and family to achieve a successful outcome. Assessment of that commitment is critical.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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146 Management of Abnormalities of the External Genitalia in Boys

Lane S. Palmer, MD, FACS, FAAP, and Jeffrey S. Palmer, MD, FACS, FAAP

Normal Male External Genitalia	Hernia and Hydroceles
Penile Anomalies	Acute Scrotum
Scrotal Anomalies	Varicocele
Vascular Lesions of the Genitalia	Epididymal and Vasal Anomalies

The normal anatomy of the penis includes the prepuce (foreskin), glans, urethral meatus, coronal sulcus, and penile shaft. The ventral surface of the penile shaft has the median raphe contiguous with the scrotal raphe. Anomalies of the penis and scrotum are common and may be congenital, acquired, or iatrogenic. The congenital anomalies may result from a disorder of sexual differentiation, genital differentiation, or genital growth and may be associated with other syndromes (Table 146-1 on the Expert Consult website) or organ systems. For example, up to 50% of children with congenital anorectal malformations also have an associated urologic malformation.

Although ultrasonographic technology has evolved in the past decade, permitting earlier fetal sex determination (Efrat et al, 2006), it is inaccurate and is not recommended before 12 weeks of gestation (Odeh et al, 2009). However, ultrasonography after 13 weeks of gestation is accurate in sex determination in 99% to 100% of cases without malformed external genitalia (Odeh et al, 2009) (Fig. 146-1 on the Expert Consult website). In utero ultrasonography has identified abnormal male genitalia including ambiguous genitalia and penoscrotal transposition (Cheikhelard et al, 2000; Vijayaraghavan et al, 2002; Pinette et al, 2003). More recent ultrasonographic technology, including three-dimensional (3D) ultrasonography, is being used to evaluate the fetal external genitalia, but there are no definitive results suggesting this as an enhanced diagnostic modality (Verwoerd-Dikkeboom et al, 2008; Abu-Rustum and Chaaban, 2009).

The understanding of the normal anatomy and embryologic development of the male external genitalia is essential to recognizing and treating penile and scrotal anomalies. Most genital abnormalities noted in neonates do not result in an ambiguous appearance but rather more common conditions such as inconspicuous penis or abnormal penile orientation. The American Academy of Pediatrics (AAP) Committee on Genetics and Sections on Endocrinology and Urology (2000) published a guide to the normal embryology of the external genitalia and the altered embryology, evaluation, and management of ambiguous genitalia.

NORMAL MALE EXTERNAL GENITALIA

Embryology

Normal embryogenesis of the male genitalia involves the formation of the penis and scrotum. The early development of the external genitalia in the two sexes is similar before the 9th week of gestation (Ammini et al, 1997). Understanding factors and sequential steps in normal embryogenesis is fundamental in understanding the pathogenesis of male genital anomalies. These factors include testosterone synthesis by the fetal testis and its enzymatic conversion into dihydrotestosterone by 5 α -reductase and the presence of androgen receptors able to recognize the androgenic hormones. The influence of dihydrotestosterone on the androgen receptors results in the differentiation of the genital tubercle, genital (labioscrotal) folds, and genital swelling at 9 to 13 weeks of gestation into the male structures of the glans penis, penile shaft, and scrotum, respectively.

The male develops in a proximal-to-distal manner. As the penis forms from the elongation and enlargement of the phallus, the lateral walls of the urethral groove form from the ventrally located genital folds, which then fuse in the midline. The glanular urethra forms from the ingrowth of surface epithelium, but this long-held theory has been challenged with evidence suggesting that it is a result of the fusion of the urethral plate (Glenister, 1921; Ammini et al, 1997). The scrotum forms through the inferomedial migration and midline fusion of the genital folds as delineated by the scrotal raphe. In females and in males with abnormalities in testosterone and/or dihydrotestosterone production, 5 α -reductase deficiency, or androgen-receptor insufficiency, the genital tubercle, genital folds, and genital swellings passively become the clitoris, labia minora, and labia majora, respectively.

Penile Length and Tanner Classification

Penile length significantly increases with gestational age (6 mm at 16 weeks to 26.4 mm at 38 weeks) (Johnson and Maxwell, 2000;

TABLE 146-1 Male Genital Anomalies That Commonly Occur in Various Syndromes (Microphallus, Hypospadias, Ambiguous Genitalia, and Bifid Scrotum)

ANOMALY	FEATURES
Anencephaly Aniridia–Wilms tumor association	WAGR syndrome: Wilms tumor, aniridia, genitourinary abnormalities or gonadoblastoma, and mental retardation
Bladder exstrophy Börjeson–Forssman–Lehmann syndrome Carpenter syndrome CHARGE association	Microcephaly, mental retardation, large ears Acrocephaly, polydactyly and syndactyly of feet, congenital heart disease Coloboma, heart malformation, atresia choanae, retarded growth and development, genital anomalies, ear anomalies and/or deafness
Cloacal syndrome Fraser syndrome Johanson–Blizzard syndrome	Cryptophthalmos, mental retardation, ear anomalies Hypoplastic alae nasi, hypothyroidism, mental retardation, pancreatic insufficiency, deafness
Meckel–Gruber syndrome	Occipital encephalomeningocele, micrognathia, polydactyly, cystic renal dysplasia
Noonan syndrome Opitz syndrome Pallister–Hall syndrome Popliteal pterygium syndrome Prader–Willi syndrome Rapp–Hodgkin ectodermal dysplasia syndrome Rieger syndrome Robinow syndrome	Webbed neck, pectus excavatum, pulmonic stenosis, short stature Hypertelorism, hypospadias, mild-to-moderate mental retardation Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus Popliteal web, cleft palate, lower lip pits Hypotonia, obesity, small hands and feet, mild to moderate mental retardation Hypohidrosis, oral clefts, dysplastic nails Iris dysplasia, hypodontia “Fetal face syndrome”; flat facial profile, hypertelorism, short forearms, thoracic hemivertebrae
Schinzel–Giedion syndrome	Growth deficiency, mental retardation, widely patent fontanelles, short forearms and legs, renal anomalies
Smith–Lemli–Opitz syndrome	Ptosis of eyelids, syndactyly of second and third toes, microcephaly, failure to thrive with short stature, mental retardation
Triploidy syndrome Trisomy 4p, 9p, 18, 20p, 21, 22, 9p, 10q, 11p, or 15q deficiency XXY, XXXXY	

From Jones KL. Smith's recognizable patterns of human malformation. 5th ed. Philadelphia: Saunders; 1997.



Figure 146-1. Fetal ultrasonogram of male genitalia. P, penis; S, scrotum.

Zalel et al, 2001) and during the first 3 months of life. The latter growth is a result of an increase in Leydig cell production of testosterone caused by the loss of the inhibitory effect of maternal estrogens on the fetal pituitary at birth, thereby causing a surge in gonadotropins. During the remainder of childhood, penile length increases more slowly until adolescence, when the length extensively increases again until the final size is reached. The normal penile size in a full-term male neonate is 3.5 ± 0.7 cm in the stretched length and 1.1 ± 0.2 cm in diameter compared with 13.3 ± 1.6 cm at adulthood. The penile stretched lengths from birth to adulthood are listed in Table 146-2. Sharony and colleagues demonstrated a positive correlation between prenatal penile length measurements and postnatal measurements (Sharony et al, 2012).

Tanner stages are a set of recognizable changes that occur to pubic hair, penis, and testes during puberty that are helpful in evaluating patients (Table 146-3). The stages range from preadolescent penis and testes with no pubic hair (stage 1) to adult-size penis and scrotum with adult pubic hair distribution (stage 5).

PENILE ANOMALIES

Prepuce (Foreskin)

Phimosis and Paraphimosis

At birth, a physiologic phimosis (Fig. 146-2A) with either partial or complete inability to retract the prepuce exists owing to natural adhesions between the glans and inner preputial skin and/or due to a preputial ring. Two factors are involved in the separation of the prepuce from the glans: (1) epithelial debris, referred to as smegma, accumulates under the prepuce during the first 3 to 4 years of age, and (2) intermittent penile erections. Preputial retractability increases with age, with 90% of uncircumcised boys 3 years of age

TABLE 146-2 Stretched Penile Length (cm) in Normal Male Subjects

AGE	MEAN \pm SD	MEAN $- 2.5$ SD
Neonate, 30-wk gestation	2.5 ± 0.4	1.5
Neonate, 34-wk gestation	3.0 ± 0.4	2.0
0-5 mo	3.9 ± 0.8	1.9
6-12 mo	4.3 ± 0.8	2.3
1-2 yr	4.7 ± 0.8	2.6
2-3 yr	5.1 ± 0.9	2.9
3-4 yr	5.5 ± 0.9	3.3
4-5 yr	5.7 ± 0.9	3.5
5-6 yr	6.0 ± 0.9	3.8
6-7 yr	6.1 ± 0.9	3.9
7-8 yr	6.2 ± 1.0	3.7
8-9 yr	6.3 ± 1.0	3.8
9-10 yr	6.3 ± 1.0	3.8
10-11 yr	6.4 ± 1.1	3.7
Adult	13.3 ± 1.6	9.3

SD, standard deviation.

Data from Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. *J Pediatr* 1975;86:895; Schonfeld WA, Beebe GW. Normal growth and variation in the male genitalia from birth to maturity. *J Urol* 1987;30:554; and Tuladhar R, Davis PG, Batch J, et al. Establishment of a normal range of penile length in preterm infants. *J Paediatr Child Health* 1998;34:471.

TABLE 146-3 Tanner Classification of Sexual Maturity Stages in Boys

STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Preadolescent	Preadolescent
2	Scanty, long	Slight enlargement; slightly pigmented	Enlarged scrotum, pink, texture altered
3	Darker, starts to curl, small amount	Longer	Larger
4	Resembles adult type but less in quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

Modified from Tanner JM. *Growth at adolescence*. 2nd ed. Oxford (UK): Blackwell Scientific Publications; 1962.



Figure 146-2. Conditions associated with the uncircumcised penis. A, Phimosis caused by a preputial ring. B, Paraphimosis with associated entrapped prepuce behind the glans penis.

with completely retractable prepuces and less than 1% by 17 years of age with phimosis (Oster, 1968; Kayaba et al, 1996). Thus, primary phimosis commonly resolves during childhood. Secondary phimosis may result from several causes, including forceful retraction and balanitis xerotica obliterans (BXO). Forceful preputial retraction should be discouraged to avert cicatrix formation.

Conditions associated with the uncircumcised penis include paraphimosis, infection, urinary tract infection (UTI), and cancer. Paraphimosis (Fig. 146-2B), the entrapment of the prepuce behind the glans penis, can result in gangrene if not reduced in a timely fashion by manipulation, dorsal slit procedure, or circumcision. Severe edema of the foreskin occurs within several hours, depending on the tightness of the tip of the foreskin, making reduction more difficult. In most cases, manual compression of the glans with placement of distal traction on the edematous foreskin allows reduction of the paraphimotic ring. Other treatments include application of an iced glove for 5 minutes, application of granulated sugar for 1 to 2 hours, and placement of multiple punctures in the edematous skin (Mackway-Jones and Teece, 2004).

Indications to enhance preputial retractability include persistent primary phimosis, secondary phimosis, balanitis, posthitis (i.e., inflammation of the prepuce), BXO, and UTIs. Several topical corticosteroid creams with different regimens have been successfully used to treat phimosis with a relatively small number of side effects. Palmer and Palmer (2008) compared the efficacy of two different topical betamethasone (0.05%) treatment regimens (twice daily for 30 days or three times daily for 21 days) and found an 84.5% and 87% response rate, respectively. Only one child had an untoward effect (candidal dermatitis).

Circumcision

Circumcision dates back more than 6000 years, with the oldest documented evidence thought to date to sixth dynasty (2345-2181 BCE) tomb artwork in Egypt. Since that time, different religions, countries, and cultures have adopted various views on circumcision (Palmer, 2009a). Many theories have been proposed regarding the origin of circumcision, including as a religious sacrifice, a rite of passage, an aid to hygiene, a way to differentiate cultural groups, and a method to discourage masturbation.

Elective circumcision in the neonate remains controversial. The AAP has historically weighed in on this subject. In 1989 the AAP concluded that neonatal circumcision offered potential medical benefits and advantages as well as disadvantages and risks, which should be explained to parents (AAP Task Force on Circumcision, 1989). In 1999, the AAP updated its policy statement (AAP Task Force on Circumcision, 1999; Lannon et al, 2000) emphasizing the importance of local anesthesia for the procedure. Most recently the AAP stated, "Although health benefits [significant reductions in the risk of UTI, risk of heterosexual acquisition of human immunodeficiency virus, and the transmission of other sexually transmitted infections] are not great enough to recommend routine circumcision for all male newborns, the benefits of circumcision are sufficient to justify access to this procedure for families choosing it and to warrant third-party payment for circumcision of male newborns" (AAP Task Force on Circumcision, 2012).

There are several techniques and devices for neonatal circumcision, including the Gomco clamp, Mogen clamp, and Plastibell device. There should be complete separation of the prepuce from the glans and complete inspection of the meatus and the corona to confirm the absence of anomalies, including hypospadias. When neonatal circumcision is performed, local anesthesia is recommended. Available options include the topical application of a cream containing eutectic mixture of local anesthetic (EMLA; lidocaine and prilocaine), a dorsal penile nerve block, and a penile ring block (Hardwick-Smith et al, 1998). Randomized controlled trials demonstrate the superiority of a dorsal penile nerve block to EMLA cream (Howard et al, 1999; Taddio et al, 2000), and prilocaine in the EMLA cream poses a low risk for methemoglobinemia (Couper, 2000). Typically, older infants and children are circumcised under general anesthesia, rather in the office, using freehand resection techniques.

Circumcision should not be performed in neonates with other penile conditions that require surgical correction. These conditions include hypospadias, penile curvature, dorsal hood deformity, buried penis, and webbed penis (see the corresponding sections). Other conditions commonly seen in neonates that should be taken into consideration are a large hydrocele or inguinal hernias, which are more likely to develop secondary phimosis, buried penis, and trapped penis. A patient with a coagulopathy is another contraindication.

Circumcision has several potential benefits, including the prevention of penile cancer, UTIs, sexually transmitted diseases including human immunodeficiency virus (HIV) infection, and phimosis, as well as lessening of the risk of balanitis. Although some have alleged that neonatal circumcision can lead to sexual dysfunction, this is not supported by long-term studies (Fink et al, 2002; Bleustein et al, 2005). Schoen and associates (2006) determined that neonatal circumcision has a cost benefit compared with postneonatal circumcision, including procedure charges and reduction in future health care costs.

Carcinoma of the penis develops almost exclusively in men who are not circumcised at birth. Phimosis is a significant risk factor (Tsen et al, 2001). Schoen and coworkers (2000b) reported that of 89 men in a large health maintenance organization with invasive penile cancer, only 2 (2%) had been circumcised at birth. Furthermore, of 116 men with penile carcinoma in situ, 16 (14%) had had a neonatal circumcision.

Uncircumcised neonates and infants are predisposed to UTIs (Singh-Grewal et al, 2005). In a study of 100 neonates with a UTI, Ginsburg and McCracken (1982) found that only 3 (5%) of the 62 boys who developed a UTI were circumcised. Subsequently, Wiswell and colleagues (1985) studied more than 2500 male infants and found that 41 had symptomatic UTIs; 88% of these infants were uncircumcised. Uncircumcised boys were almost 20 times more likely than circumcised neonates to develop a UTI. Other studies of larger groups of infants confirm these reports (Wiswell, 2000; Zorc et al, 2005) and demonstrate that neonatal circumcision is less costly than treating UTIs in uncircumcised boys (Schoen et al, 2000a). The increased risk seems to affect boys at least through 5 years of age (Craig et al, 1996), and the incidence of epididymitis is reduced (Bennett et al, 1998). The increased risk of UTIs can be attributed to colonization of the prepuce by urinary pathogens (Gunsar et al, 2004; Bonacorsi et al, 2005). It has been calculated that it takes 111 neonatal circumcisions to prevent one UTI (Singh-Grewal et al, 2005). However, Shim and colleagues (2009) evaluated 190 infants with confirmed normal urinary systems and diagnosed with their first febrile UTI for recurrent UTI during the following year. Thirty-four percent of infants with persistent nonretractile prepuces developed recurrent UTI, compared with 17.6% of infants with retractile prepuces.

Whether circumcision reduces the risk of sexually transmitted diseases has been controversial. Several recent reports of a large population of men have demonstrated reduced incidence of HIV infection among men, with a protective effect of 60% (Bailey et al, 2007; Gray et al, 2007). However, a recent study compared HIV transmission to HIV-uninfected female partners among 922 uncircumcised, HIV-infected, asymptomatic men, of whom 474 underwent immediate circumcision and 448 remained uncircumcised (Wawer et al, 2009). After 24 months of follow-up, 18% and 12% of women acquired HIV, respectively, concluding that circumcision of HIV-infected men did not reduce HIV transmission to female partners. It has been reported that circumcision may reduce the risk of ulceration, bacterial vaginosis, and trichomoniasis in female partners (Gray et al, 2009).

Several clinical trials of the effect of circumcision on the prevention of human papillomavirus (HPV) infection, herpes simplex virus type 2 (HSV-2) infection, and other sexually transmitted diseases (Auvert et al, 2009; Nielson et al, 2009; Tobian et al, 2009) have been done. Tobian and associates (2009) evaluated 5534 HIV-negative, uncircumcised males, with 3393 being HSV-2 seronegative at enrollment. Of the 3393 men, 1684 underwent immediate circumcision and 1709 were not circumcised, to evaluate HSV-2 and HPV transmission. At 24 months' follow-up, HSV-2 seroconversion was 7.8% and 10.3%, respectively, whereas prevalence of high-risk (carcinogenic) HPV genotypes was 18.0% and 27.9%, respectively.

This study underscores the benefit of circumcision in reducing the incidence of HSV-2 infection and the prevalence of HPV infection.

Circumcision Complications

The risk of complications after circumcision is 0.2% to 5% (Baskin et al, 1996; Christakis et al, 2000; Ben Chaim et al, 2005). Complications can occur immediately or months to years after a circumcision. The most common complication is bleeding, which occurs in 0.1% and is more common in older children. Bleeding is usually localized from the frenulum or, less frequently, from a large blood vessel on the penile shaft, or from a skin edge between the suture. The bleeding is usually self-limiting or may require compression. Occasionally cautery with an ophthalmic cautery or silver nitrate stick or a suture may be necessary. Wound infection is a rare complication, but antibiotic ointment (e.g., bacitracin) use after circumcision usually prevents its development. Penile degloving caused by excess skin removal or the edges of the penile skin not adhering to the mucosal collar can occur after circumcision. The penile shaft will usually epithelize, bridging the defect without any intervention other than the use of antibiotic ointment to the denuded region and warm baths to prevent eschar formation. Immediate suturing of the skin edges and skin grafting are not recommended to bridge the gap.

Penile Skin Complications. The amount of penile skin excised can also lead to complications after circumcision. Insufficient or asymmetrical prepuce excision can result in a cosmetic and social dilemma for the parents and child, especially as the child gets older (Fig. 146-3A). Unlike neonatal circumcision, circumcision revision requires general anesthesia. Several techniques have been described (Redman, 1995; Brisson et al, 2002; Ching and Palmer, 2008a). Excessive skin excision can result in penile chordee, torsion, and lateral deviation. These conditions, if necessary to repair, may require penile skin flaps or Z-plasty for closure. Excessive skin removal can also result in a trapped penis from a cicatricial scar. The trapped penis can be managed with betamethasone (Palmer et al, 2005), vertical relaxation incision, and formal repair. The use of 0.05% betamethasone in conjunction with manual retraction in children with a trapped penis resulting from a dense cicatrix of the residual foreskin distal to the glans has a 79% success rate in softening of the cicatrix with easy exposure of the glans or mild persistence of the cicatrix amenable to vertical relaxation incision (Palmer et al, 2005). Surgical correction includes excision of the cicatrix with possible need for penile skin flaps or Z-plasty for closure.

Glanular Adhesions and Skin Bridges. Glanular adhesions and skin bridges, attachments of the glans and penile shaft, are common complications associated with circumcision and are usually noticed

by the caregiver or primary medical provider. Both can occur in the well-circumcised penis and are usually the result of the physiologic retraction of the penis caused by a suprapubic fat pad and diaper irritation of the penis. Glanular adhesions are attachments between the inner prepuce or circumcision incision line attaching to the glans, with an incidence decreasing with age owing to epithelial separation of the adhesions (71% of infants, 28% of 1- to 5-year-olds, 8% of 1- to 9-year-olds, and 2% of children older than 9 years) (Van Howe, 1997; Ponsky et al, 2000). Persistent adhesions can be lysed in the office with the application of a topical analgesic such as EMLA cream or Pain Ease (Gebauer Company, Cleveland, OH) (1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane) (Palmer, 2009b). Use of low-dose corticosteroids has been relatively unsuccessful in lysing adhesions. Skin bridges (Fig. 146-3B) are epithelized adhesions that can lead to penile chordee and torsion, which can be excised in the office with the application of an analgesic (Palmer, 2009b) or in the operating room when the bridges are broad or thick and may require suturing of the glanular and shaft defects.

Meatal Stenosis. Meatal stenosis occurs in children almost only after circumcision during infancy (Fig. 146-4A). It can be congenital, occurring primarily in neonates with hypospadias, or acquired. The normal urethral meatus is 10 Fr before 4 years of age, 12 Fr from 4 to 10 years of age, and 14 Fr after 10 years of age (Litvak et al, 1976); this can be calibrated with a bougie à boule or sound. There are several proposed causes of secondary meatal stenosis. One theory is that after disruption of the normal adhesions between the prepuce and glans and removal of the foreskin, a significant inflammatory reaction occurs, resulting in a severe meatal inflammation and cicatrix formation. Other theories are frenular devascularization or chronic meatitis from diaper irritation of the exposed, unprotected meatus (Persad et al, 1995; Hensle, 1996). BXO is another cause of meatal stenosis (see later). A relatively small percentage of children will develop symptomatic meatal stenosis after neonatal circumcision. Symptoms include (1) typical urinary stream deviation in an upward direction resulting from a meatal baffle (Fig. 146-4B) or ventral web located at the inferior of the meatus, (2) a narrow, high-velocity stream, and (3) penile pain at the initiation of micturition. Urinary tract imaging usually does not reveal any obstructive changes in the urinary tract without other urologic issues but may be indicated for associated UTI or urinary incontinence. Meatotomy or meatoplasty to treat secondary meatal stenosis can be performed in the office with the use of topical lidocaine and prilocaine (EMLA) (Cartwright et al, 1996) or with general anesthesia by making a ventral incision long enough to create a normal meatal caliber. The suturing of the urethral mucosa to the glans with fine,

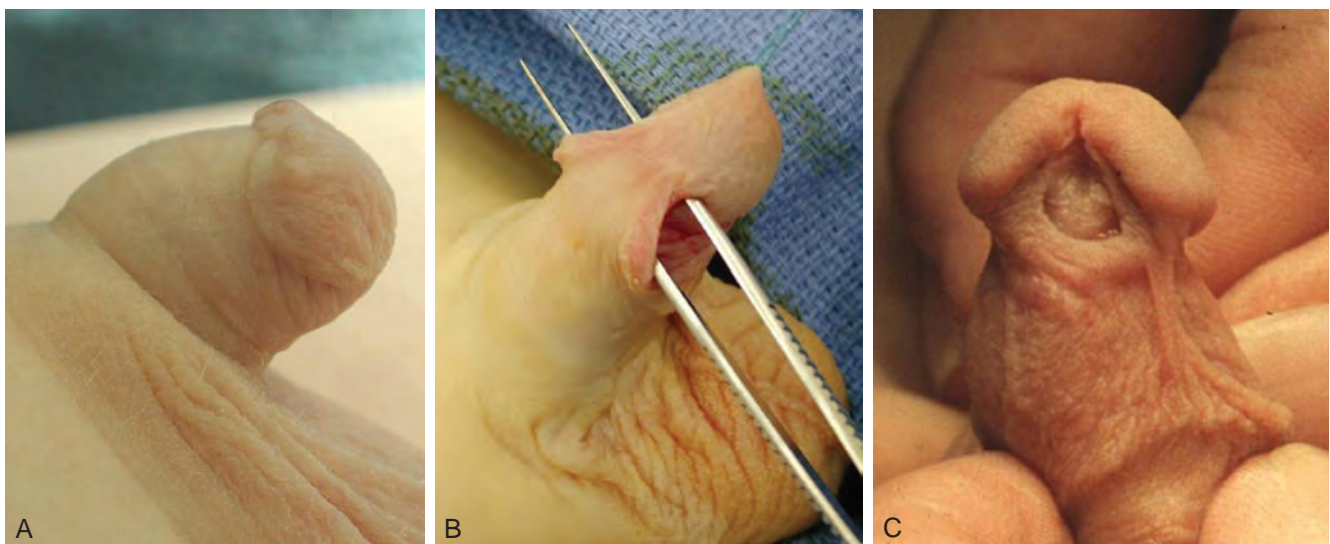


Figure 146-3. Complications associated with circumcision. A, Asymmetrical redundant penile skin. B, Penile skin bridge. C, Urethral and glanular resection.

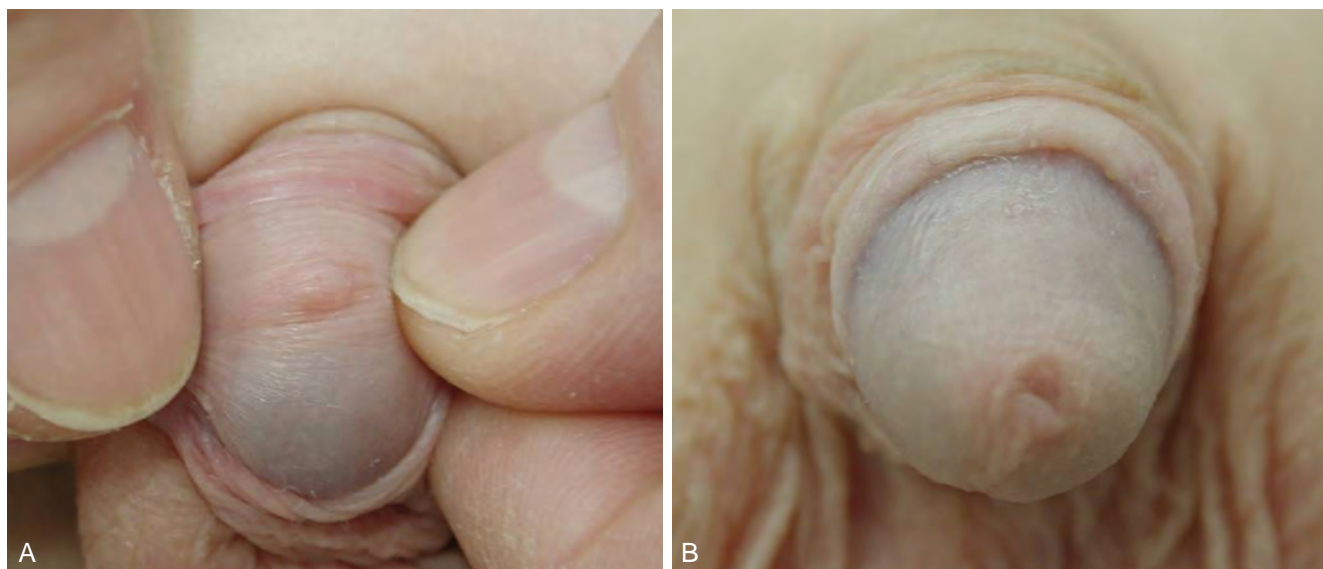


Figure 146-4. Meatal complications associated with circumcision. A, Meatal stenosis. B, Meatal baffle.

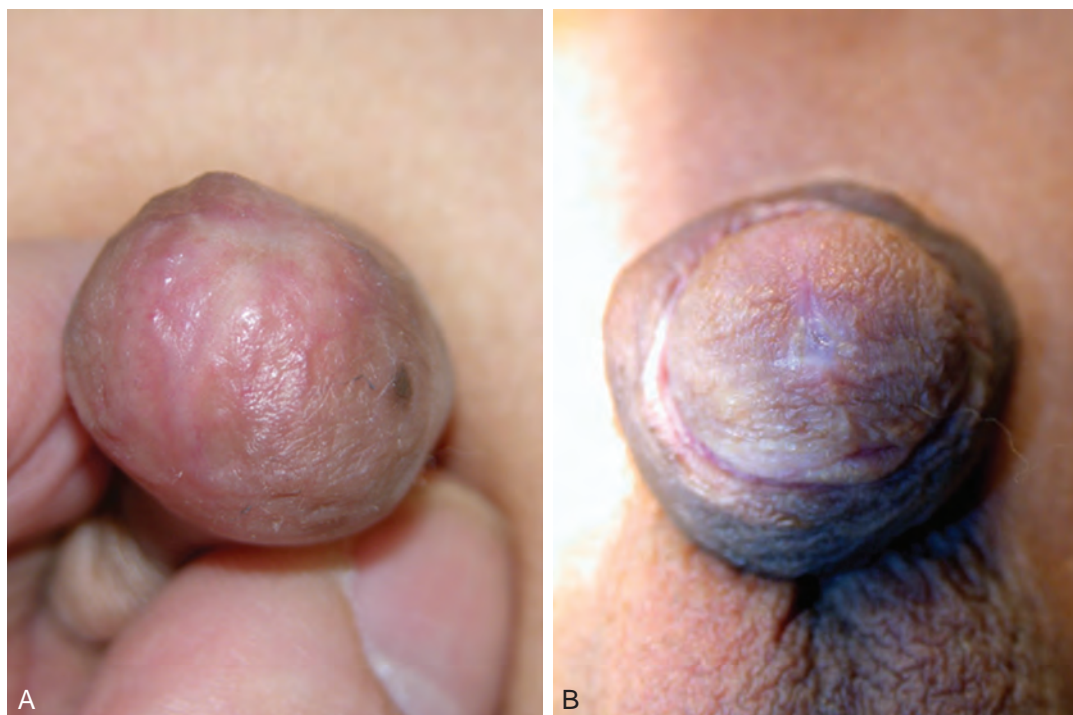


Figure 146-5. Balanitis xerotica obliterans of the prepuce (A) and meatus (B). (Courtesy Warren Snodgrass, MD.)

rapidly absorbable sutures tends to reduce the risk of recurrence. An alternative but equally efficacious technique involves meatal tailoring using clamps without the need for suture (Cubillos et al, 2012). **Penile Trauma.** The most serious complications associated with circumcision are penile trauma, including urethral injury, excision of the glans and/or penile shaft, and penile necrosis (see Fig. 146-3C). Urethral injury requires urethroplasty, with the technique dependent on the severity of the excision. Excision of the glans can be repaired by suturing the excised tissue back to the penis, often without the need for microscopic repair (Sherman et al, 1996), yielding good results if performed within 8 hours. Penile necrosis can result from thermal injury from several causes, including cautery contacting the metal ring applied to the prepuce being excised or

the inappropriate use of lasers to perform a circumcision. Several options are available without ideal outcomes, including penile reconstruction and female gender reassignment with bilateral orchiectomy (Gearhart and Rock, 1989; Bradley et al, 1998). Although the cosmetic and functional results of phallic reconstruction have advanced, they are still being refined (De Castro et al, 2007; Monstrey et al, 2009). The issues with gender reassignment can include these children growing up with a male identity believed to result from in utero and neonatal androgen imprinting (Reiner, 1996; Diamond and Sigmundson, 1997; Diamond, 1999). **Balanitis Xerotica Obliterans.** Lichen sclerosus et atrophicus, or BXO, is a chronic infiltrative and cicatrizing skin condition resulting in pathologic phimosis (Chalmers et al, 1984) (Fig. 146-5).

BXO can affect the glans and meatus, as well as the urethra. The inability to retract the prepuce is the common presentation at puberty and is rare in children younger than 5 years of age (Oster, 1968). Other presenting symptoms include local infection, irritation, discomfort after micturition, bleeding, and occasionally acute urinary retention or urinary incontinence (Bale et al, 1987). Older patients and those with BXO involving the meatus may have a more severe clinical course (Gargollo et al, 2005). The cause of BXO remains unknown without an identified viral or bacterial cause or a familial predisposition. The association of BXO and penile cancer in children is also not established.

Treatment of BXO includes medical and surgical management. The use of topical corticosteroids has had limited benefit to treat mild BXO of the prepuce with minimal scar formation (Vincent and Mackinnon, 2005). Circumcision is the preferred treatment along with meatotomy or meatoplasty if there is meatal involvement. Children with meatal involvement should be observed postoperatively because of the risk of recurrent meatal stenosis. An approach that spares the prepuce was described by Wilkinson and colleagues on 104 uncircumcised boys for whom triradiate preputial incisions and injection of triamcinolone intralesionally were performed. This resulted in 81% having a fully retractile prepuce without macroscopic evidence of BXO; 13% developed recurrent symptoms or BXO requiring circumcision or repeat foreskin preputioplasty. The development of meatal stenosis occurred in significantly fewer boys than in those who underwent initial circumcision (Wilkinson et al, 2012).

Abnormal Penile Number

Aphallia

Penile agenesis results from failure of development of the genital tubercle (Roth et al, 1981) (Fig. 146-6). The disorder is rare, with an estimated incidence of 1 in 10 million to 30 million births. The karyotype almost always is 46,XY, and the usual appearance is that of a well-developed scrotum with descended testes and an absent penile shaft. The anus is usually displaced anteriorly. The urethra often opens at the anal verge adjacent to a small skin tag or may open into the rectum. The incidence of stillbirth or neonatal death is approximately one in three cases (Gilbert et al, 1990).

Associated malformations are common and include cryptorchidism, vesicoureteral reflux, horseshoe kidney, renal agenesis, imperforate anus, and musculoskeletal and cardiopulmonary abnormalities (Skoog and Belman, 1989; Evans et al, 1999). The

connection between the genitourinary and gastrointestinal tract is variable. Skoog and Belman (1989) reviewed 60 reports of aphallia and found that the more proximal the urethral meatus, the greater the likelihood of neonatal death and the incidence of other anomalies. Sixty percent of patients had a postsphincteric meatus located on a peculiar appendage at the anal verge; these patients had the highest survival rate (87%) and the lowest incidence of other anomalies (1.2 per patient). Twenty-eight percent of patients had pre-sphincteric urethral communications (prostatorectal fistula), and there was a 36% neonatal mortality rate. Twelve percent had urethral atresia and a vesicorectal fistula for drainage. This group had the highest incidence of other anomalies and a 100% mortality rate.

Children with this lesion should be evaluated immediately with a multidisciplinary approach. Testing should include a karyotype and other appropriate studies to detect associated malformations of the urinary tract or other organ systems. Magnetic resonance imaging (MRI) may be beneficial in determining the severity of the defect (Lapointe et al, 2001).

Consequently, the recommendation to perform gender reassignment should be made carefully and only after full evaluation by an ambiguous genitalia assessment team and parental counseling. Some of these patients have a male gender identity despite reconstruction as a female, presumably because of in utero or postnatal sex steroid imprinting (Reiner, 1996; Diamond and Sigmundson, 1997; Diamond, 1999). As a male, the patient would potentially be fertile; although current advances in phalloplasty and urethroplasty allow for sexual and voiding function (De Castro et al, 2013; Garaffa et al, 2014), reproductive function is unknown. Gender reassignment involves orchiectomy and feminizing genitoplasty in the neonatal period (Bruch et al, 1996; Gluer et al, 1998) and neovagina at a later age. Urinary tract reconstruction with simultaneous construction of an intestinal neovagina through a posterior sagittal and abdominal approach in patients with penile agenesis has been described (Hensle and Dean, 1992; Hendren, 1997).

Diphallia

Duplication of the penis is a rare anomaly with an incidence of 1 in 5 million live births (Hollowell et al, 1977) and has a range of appearances from a small accessory penis to complete duplication (Gyftopoulos et al, 2002). In some cases each phallus has only one corporal body and urethra, whereas others seem to be a variant of twinning, with each phallus having two corpora cavernosa and a urethra. The penises are usually unequal in size and situated

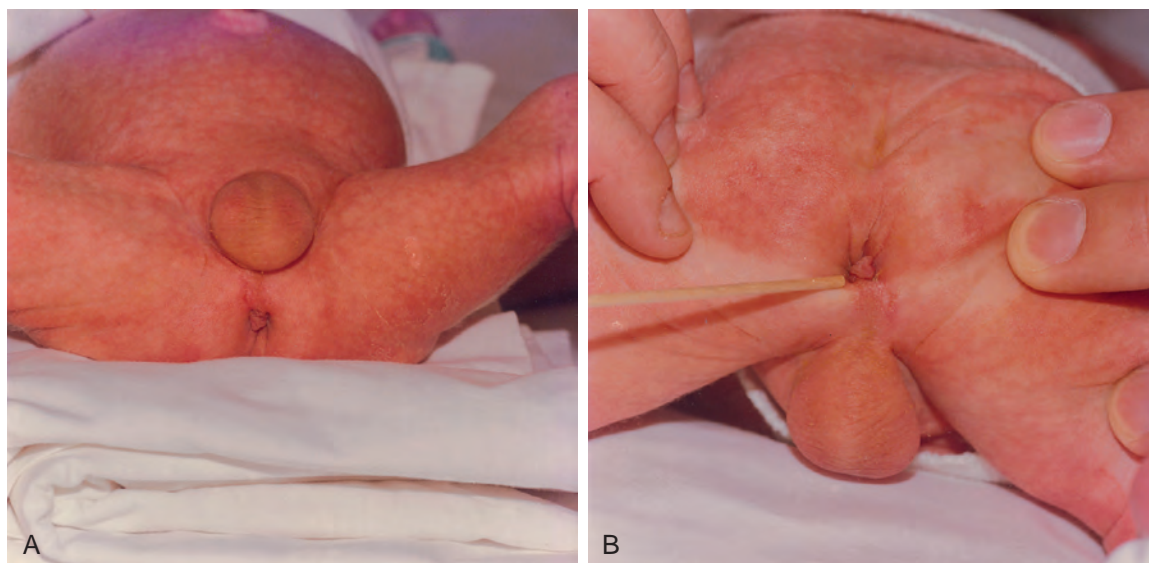


Figure 146-6. A, Neonate with aphallia. B, Urethral meatus at skin tag on anal verge.

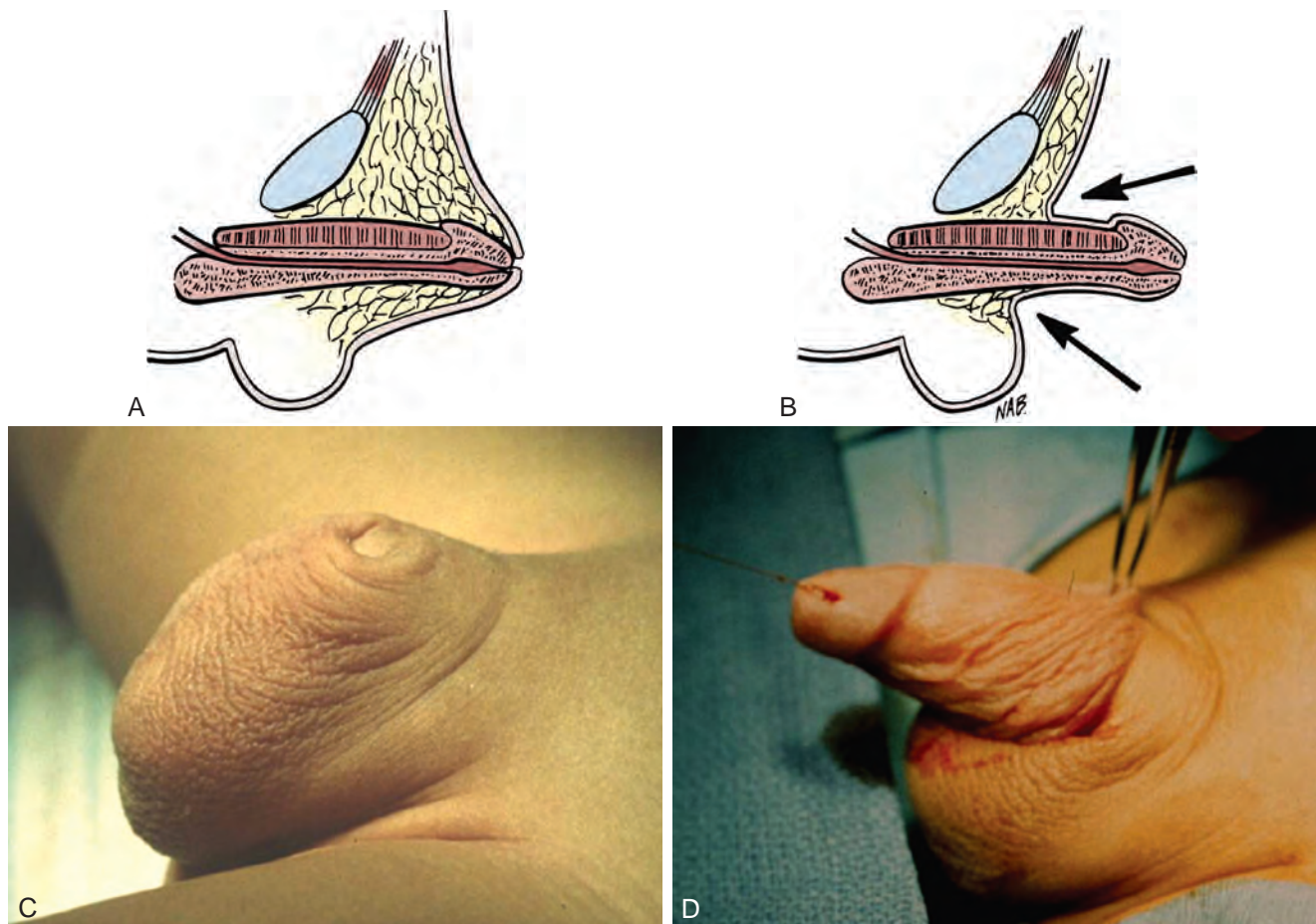


Figure 146-7. Buried penis (A and C), which may be visualized by retraction of the skin lateral to the penile shaft (B and D).

adjacently. Other associated anomalies are common, including hypospadias, bifid scrotum, bladder duplication, renal agenesis or ectopia, and diastasis of the pubic symphysis (Maruyama et al, 1999). Anal and cardiac anomalies are also common. Evaluation should include imaging of the entire urinary tract, including a renal ultrasonogram and voiding cystourethrogram. Ultrasonography and MRI can also be done to assess penile development (Marti-Bonmati et al, 1989; Lapointe et al, 2001). The cause has not been delineated. Treatment must be individualized, with consideration of the associated anomalies with the goal of attaining a satisfactory functional and cosmetic result (Dean and Horton, 1991).

Inconspicuous Penis

An inconspicuous penis is one that appears to be small but with normal stretched penile length measured from the pubic symphysis to the tip of the glans (see Table 146-2) and normal diameter of the penile shaft (Bergeson et al, 1993). This condition can be congenital or acquired and is usually of great concern for parents. Several entities are included in this disorder, including buried penis, trapped penis, and webbed penis (Palmer and Kogan, 1995). These conditions must be differentiated from micropenis, in which the penis is abnormally small. When an infant has an inconspicuous penis, prompt evaluation is necessary for proper treatment and the family must be informed as to whether the penis is or is not normal.

Buried Penis

A buried penis, also referred to as a *hidden* or *concealed* penis, is a form of inconspicuous penis (Cromie et al, 1998). A buried penis

is a normally developed penis that is hidden away by the suprapubic fat pad. This condition can be classified into three categories based on cause of the concealment (Maizels et al, 1986; Casale et al, 1999): (1) poor penopubic fixation of the skin at the base of the penis, (2) obesity, and (3) a trapped penis from cicatricial scarring after penile surgery, typically a circumcision.

The congenital form of buried penis is believed to result from the inelasticity of the dartos fascia, which normally allows the penile skin to slide freely on the deep layers of the shaft, with restricted extension of the penis because the penile skin is not anchored to the deep fascia (Fig. 146-7). The acquired form from obesity typically seen in older children and adolescents is caused by abundant fat on the abdominal wall hiding the penile shaft. The other acquired form, a trapped penis, results from embedding of the penis in the suprapubic fat pad from scar formation over the glans. This deformity may occur after neonatal circumcision in an infant with significant scrotal swelling as a result of a hernia or hydrocele or after routine circumcision in an infant with a webbed penis. Also, in some neonates the penile shaft seems to retract naturally into the scrotum; and if circumcision is performed in this situation, the skin at the base of the penis may form a cicatrix over the retracted phallus. This condition should be differentiated from a transient buried penis resulting from a large suprapubic fat pad noted in early childhood that resolves with increased age and ambulation (Eroglu et al, 2009).

On examination, a buried penis must be differentiated from a micropenis with an abnormal penile stretched length. The clinician should determine whether the glans can be exposed by retracting the skin covering the glans (see Fig. 146-7). If so, it remains the surgeon's judgment whether correction is warranted.

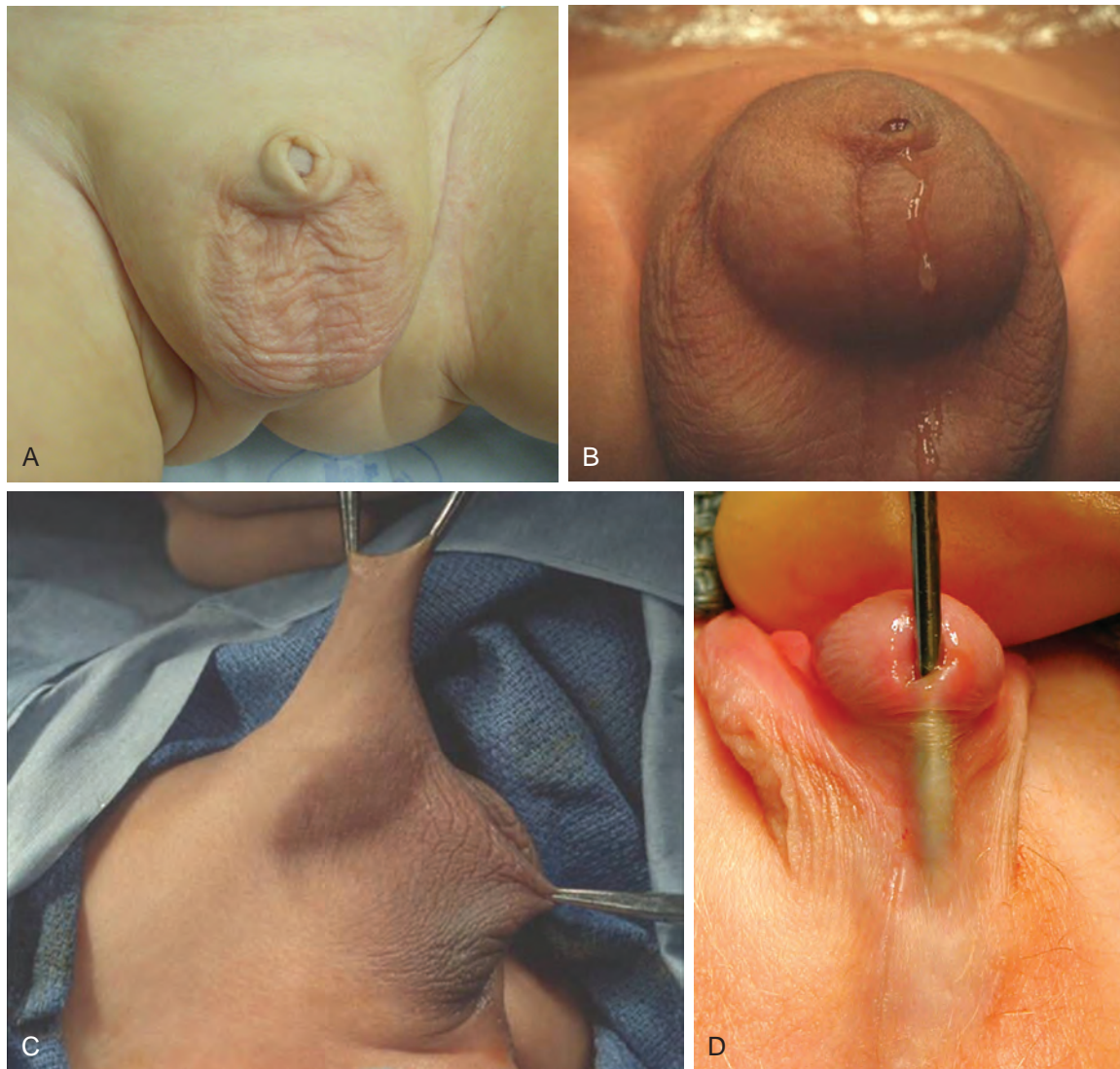


Figure 146-8. Inconspicuous penis. A, Trapped penis by cicatricial scarring resulting from neonatal circumcision. B, Urine pooling caused by cicatricial scarring, increasing susceptibility to urinary tract infections. C, Penoscrotal web resulting in a webbed penis. D, Webbed penis with hypoplastic distal urethra.

However, if the penis is trapped by physiologic phimosis in the uncircumcised or cicatricial scarring (Fig. 146-8A) in the circumcised penis, this increases the chance of difficulty voiding, maintaining proper hygiene, balanitis, UTIs, and psychosocial issues (Fig. 146-8B) (Kon, 1983).

The treatment options for children with buried penis are based on the cause. Patients with buried penis secondary to obesity should have the underlying condition treated with referral back to the primary care provider for a weight loss and exercise program, which is essential; surgery may no longer be necessary. Young children with secondary cicatricial scarring after penile surgery can be managed with forceful dilation of the cicatrix with a fine hemostat in the office after the application or injection of analgesic. Another option is the combination of topical betamethasone and manual retraction (Palmer et al, 2005), which yielded complete resolution in the majority of boys or released the closing cicatrix, allowing for a simple incision of the phimotic ring; this reduced the need for formal surgical repair by 79%. If topical corticosteroid application is ineffective, correction under general anesthesia is necessary, with the usual recommendation of elective repair when the child is at least 6 months of age. The surgical technique is similar to that for the congenital buried penis.

A number of surgical techniques have been described to correct the buried penis (Maizels et al, 1986; Casale et al, 1999; Elder, 2001; Frenkl et al, 2004; Gillett et al, 2005; Borsellino et al, 2007; Karapetian and Palmer, 2007). The indications and timing for reconstructive surgery are controversial. In moderately severe cases the dysgenic bands of tissue, which are located primarily on the proximal dorsal surface of the shaft of the penis, must be removed. The prepuce should be unfurled and used for ventral skin coverage. In addition, the subcutaneous tissue on the dorsal aspect of the penis should be fixed to the pubic fascia, and then the subcutaneous tissue of the scrotum should be fixed to the ventral aspect of the base of the penile shaft. During correction one must be careful to avoid injury to the neurovascular bundles (Baskin, 1999; Baskin et al, 2000). Skin coverage can also be accomplished by penoscrotal Z-plasty, lateral penile shaft Z-plasty, island pedicle of ventral preputial skin, or a skin graft. Rarely, in the most severe cases the suspensory ligament of the penis must be divided, the suprapubic fat excised, and the spermatic cords protected. Liposuction has been reported to be helpful in severe cases (Maizels et al, 1986; Shenoy et al, 2000). However, this technique should be reserved for adolescent boys because prepubertal boys may lose their fat pad with somatic growth.

Webbed Penis

Webbed penis, also known as *penoscrotal fusion*, is a congenital or acquired condition resulting from the scrotal skin extending onto the ventrum of the penis. The congenital form of a penoscrotal web represents an abnormality of the attachment between the penis and the scrotum, whereas the penis, urethra, and remainder of the scrotum are normal (Fig. 146-8C). The acquired condition results from circumcision or other penile surgery, as a result of excessive removal of ventral penile skin.

Although the penoscrotal web is usually asymptomatic, the appearance is often unacceptable. There are several surgical techniques to correct this condition. Similar to the treatment of a buried penis, one technique involves the fixation of the subcutaneous tissue of the scrotum to the ventral aspect of the base of the penile shaft. On occasion, this condition may be corrected by incision of the web transversely, separation of the penis from the scrotum, and closure of the skin vertically. In other cases a circumferential incision is made 1.5 cm proximal to the coronal sulcus, a Byar preputial skin flap is transferred to the ventral surface of the penis, and the redundant foreskin is excised. In rare cases the distal urethra is hypoplastic, necessitating urethral reconstruction (Fig. 146-8D).

Micropenis

Micropenis is a normally formed penis that is at least 2.5 standard deviations (SD) below the mean size in stretched length for age (Aaronson, 1994) (Fig. 146-9). The ratio of the length of the penile shaft to its circumference is usually normal, but occasionally the corpora cavernosa are severely hypoplastic. The testes are usually small and frequently cryptorchid, whereas the scrotum is usually fused and often diminutive.

Stretched penile length correlates more closely with erectile length than does the relaxed penile length and should be compared with standards for penile length (see Table 146-2). Stretched penile length is determined by measuring the penis from its attachment to the pubic symphysis to the tip of the glans. The suprapubic fat pad must be depressed completely for an accurate measurement to be obtained, especially in an obese infant or child. In general, the penis of a full-term neonate should be at least 1.9 cm long. One must differentiate buried penis or webbed penis from the micropenis, with the former having a normal penile shaft.



Figure 146-9. Micropenis resulting from hypogonadotropic hypogonadism.

Micropenis results from a hormonal abnormality that occurs after 14 weeks of gestation. Differentiation of the male external genitalia is complete by the 12th week of gestation and requires a normal testis producing testosterone, stimulated by maternal human chorionic gonadotropin (hCG). During the second and third trimesters, growth of the penis occurs under the direction of fetal androgen, which is controlled by the secretion of fetal luteinizing hormone (LH). An abnormality in the production or use of testosterone results in a small penis and hypospadias, whereas a true micropenis often seems to be a consequence of a deficiency of gonadotropic hormones.

The causes of micropenis are many (Box 146-1 on the Expert Consult website) and include isolated gonadotropin defects and generalized endocrinopathies that may be associated with central nervous system defects. The most common causes of micropenis are hypogonadotropic hypogonadism, hypergonadotropic hypogonadism (primary testicular failure), and idiopathic (Lee et al, 1980b). Micropenis is often associated with major chromosomal defects, including Klinefelter syndrome (47,XXY) and other X polysomy syndromes, deletions, translocations, and trisomy involving chromosomes 8, 13, and 18 (Aaronson, 1994).

The most common cause of micropenis is hypogonadotropic hypogonadism, that is, failure of the hypothalamus to produce adequate quantities of gonadotropin-releasing hormone (GnRH). This condition may result from hypothalamic dysfunction, which can occur in Prader-Willi syndrome, Kallmann syndrome (genital-olfactory dysplasia), Laurence-Moon-Biedl syndrome (Walsh et al, 1978; Danish et al, 1980), and the CHARGE association (Ragan et al, 1999). Other causes include an associated growth hormone deficiency or neonatal hypoglycemia secondary to congenital hypopituitarism, congenital pituitary aplasia, and midline brain defects, such as agenesis of the corpus callosum and occipital encephalocele.

Primary testicular failure hypergonadotropic hypogonadism is another cause of micropenis and may result from rudimentary testes syndrome or gonadal dysgenesis. It also occurs in Robinow syndrome (Lee et al, 1980b). The test most frequently used to identify this subgroup is the failure of serum testosterone concentration to rise appropriately after stimulation by hCG. However, in patients with Kallmann syndrome and cryptorchidism, the serum testosterone level may not increase after the administration of hCG. Rarely, a patient with partial androgen insensitivity syndrome has micropenis, but sexual ambiguity is more common. Micropenis may also result from improper timing or delayed onset of gonadotropin stimulation in the fetus (Lee et al, 1980a). These patients have an idiopathic form of micropenis and a normal hypothalamic-pituitary-testicular axis.

The initial evaluation of a child with micropenis should include a thorough medical history, physical examination, and a karyotype at birth. Accurate measurement of the penile length, palpation of the corporal bodies, and evaluation for cryptorchidism are important elements of the physical examination. Consultation with a pediatric endocrinologist assists in determining the cause of the micropenis (central or testicular), assessing for other abnormalities, and helping to determine penile growth potential. Testicular function is assessed by measuring serum testosterone levels before and after hCG stimulation. Primary testicular failure produces an absent response and elevated basal concentrations of LH and follicle-stimulating hormone (FSH). In some cases, a GnRH stimulation test is also performed. Anterior pituitary screening tests include serial measurements of serum glucose, sodium, and potassium; serum cortisol concentrations; and thyroid function tests. MRI of the head assesses the anatomic integrity of the hypothalamus, anterior pituitary gland, and midline structures of the midbrain.

Before extensive evaluation of the hypothalamic-pituitary-testicular axis, androgen therapy should be administered to determine the end-organ response. In general, intramuscular testosterone enanthate is given for 3 months. Although prolonged treatment might advance skeletal maturation, short courses of treatment do not affect height. Transdermal testosterone also has been

BOX 146-1 Etiology of Micropenis**DEFICIENT TESTOSTERONE SECRETION**

Hypogonadotropic hypogonadism

- Isolated, including Kallmann syndrome
- Associated with other pituitary hormone deficiencies (e.g., CHARGE association)
- Prader-Willi syndrome
- Laurence-Moon syndrome
- Bardet-Biedl syndrome
- Rud syndrome

Primary hypogonadism

- Anorchia
- Klinefelter syndrome and poly X syndrome
- Gonadal dysgenesis (incomplete)
- Luteinizing hormone receptor defects (incomplete)
- Genetic defects in testosterone steroidogenesis (incomplete)
- Noonan syndrome
- Down syndrome
- Robinow syndrome
- Bardet-Biedl syndrome
- Laurence-Moon syndrome

DEFECTS IN TESTOSTERONE ACTION

- Growth hormone/insulin-like growth factor 1 deficiency
- Androgen receptor defects (incomplete)
- 5 α -Reductase deficiency (incomplete)
- Fetal hydantoin syndrome

DEVELOPMENTAL ANOMALIES

- Aphallia
- Cloacal exstrophy

IDIOPATHIC

- Associated with other congenital malformations

Modified from Bin-Abbas B, Conte FA, Grumbach MM, et al. Congenital hypogonadotropic hypogonadism and micropenis: effect of testosterone treatment on adult penile size—why sex reversal is not indicated. *J Pediatr* 1999;134:579.

used in these patients (Choi et al, 1993). If androgen treatment in a neonate successfully increases the penis so that its size falls within the normal range, the effects at puberty have not been clearly delineated. In a mouse model of hypogonadotropic hypogonadal micropenis, significant prepubertal exposure of the penis to androgens reduced the ultimate growth response to androgens (Husmann and Cain, 1994; McMahon et al, 1995). Bin-Abbas and coworkers (1999) described eight boys with micropenis treated with androgens both at birth and at puberty. The final penile stretched length averaged 10.3 cm and was in the normal range in all cases. Therefore, exogenous stimulation at birth and at puberty with testosterone enanthate seems most reasonable (Tietjen et al, 1998) and is recommended until longer-term studies are available.

If the penis does not respond to testosterone, gender reassignment is an option but is controversial. Previously, gender reassignment was recommended, but this position has come under criticism owing to the implication that biologic factors during the prenatal period may affect gender identity. One such factor is testosterone-induced male brain imprinting (Diamond and Sigmundson, 1997). The lack of long-term data regarding the risks and benefits of reassigning these patients to a female gender (Calikoglu, 1999; Diamond, 1999) has resulted in a conservative use of this treatment option. Husmann (2004) described 20 adult men born with micropenis who had a suboptimal response to testosterone therapy and were raised as males. At adulthood, 90% had a micropenis and all had a male gender identity; 5 were undergoing psychiatric counseling for fear of rejection, and 8 had not been sexually active.

Several studies demonstrate that although ultimate penile size may be below the normal range, men born with micropenis have male gender identity and most have satisfactory sexual function. Reilly and Woodhouse (1989) described 20 patients with a primary diagnosis of micropenis in infancy. Almost all had received androgen therapy during childhood, but as adults none had a penis within the normal range of size. All of the boys stood to void. Parents of patients in the prepubertal group considered their children to be normal boys with a satisfactory penile appearance but did express concern about penile size and future sexual function. All of the patients in the adult group had a strong male identity, and 9 of the 12 patients were sexually active. In a study of 22 men born with micropenis, Lee and Houk (2004) had similar findings. Wisniewski and Migeon (2002) reported that their patients had a male gender identity but in general were dissatisfied with their genital appearance and function.

Abnormal Penile Orientation

Penile Curvature

Curvature of the penis may occur along the vertical (i.e., ventral or dorsal direction) or horizontal (i.e., lateral direction) plane of the penis. Penile curvature may be congenital or acquired after penile surgery (circumcision, hypospadias repair) or trauma and has consequences related to cosmesis and body image as well as future sexual difficulties. The indications for surgical repair include known associated sexual dysfunction, concurrent penile surgery, and surgeon's discretion regarding the likelihood of future sexual dysfunction with worsening curvature associated with penile growth.

Penile curvature is most commonly in the ventral direction, referred to as *chordee*, and is commonly associated with hypospadias. However, isolated chordee may occur with or without a dorsal hood of prepuce (Fig. 146-10) and is commonly associated with a deficiency of the ventral skin (Cendron and Melin, 1981). Ventral curvature in boys without hypospadias can usually be corrected by degloving of the penis, excision of fibrous tissue that is usually confined to the region superficial to Buck fascia, and development of Byar flaps for penile skin coverage, as necessary. In more severe cases, simple dorsal plication, Nesbit dorsal excision, or corporal rotation may be necessary. Urethral catheterization may be helpful in averting urethral injury during degloving. In the most severe cases the urethra is short and urethral reconstruction must be performed. Intraoperative artificial erection with injectable saline



Figure 146-10. Penile chordee and dorsal hood of foreskin without hypospadias.

confirms complete chordee correction. Some cases of chordee may be aggravated by a prominent frenulum, resulting in distal penile chordee with ventral glanular deflection. In these cases, the addition of frenulotomy will improve or correct the chordee.

Congenital dorsal penile curvature may be an isolated condition with or without asymmetrical penile skin or associated with epispadias and a ventral hood of prepuce. Some individuals may have hypospadias. Surgical repair of this condition without associated urethral anomalies is similar to chordee correction, involving degloving of the penis, excision of fibrous tissue that is usually confined to the region superficial to the Buck fascia, and development of skin flaps for penile skin coverage, as necessary. During correction, one must be careful to avoid injury to the neurovascular bundles (Baskin, 1999; Baskin et al, 2000). More severe cases involve plication and/or excision of ellipses from the ventral corporal bodies. Intraoperative artificial erection aids in determining the apex of the curvature and confirming chordee correction.

Lateral penile curvature is usually congenital and caused by overgrowth or hypoplasia of one corporal body. However, asymmetrical penile skin excision or postoperative scarring after circumcision or other penile surgery may also be a secondary cause. Lateral penile curvature may be unrecognized until later in childhood because the penis is normal when flaccid and only recognized as being curved when erect. Surgical repair of congenital lateral penile curvature involves degloving the penis and performing a plication and/or excision of ellipses from the corporal bodies from the area of maximum curvature to allow straightening of the penis. Secondary lateral penile curvature follows the same principles as for vertical curvature, with degloving of the penis, excision of fibrous tissue that is usually confined to the region superficial to the Buck fascia, and development of skin flaps for penile skin coverage as necessary. Intraoperative artificial erection may be necessary as described earlier.

Penile Torsion

Penile torsion is a rotational deformity of the penile shaft, usually in the counterclockwise direction (i.e., to the left side) (Fig. 146-11). In most cases, penile size is normal and the condition is unrecognized until circumcision is performed or until the foreskin is retracted. Penile torsion may also be associated with hypospadias, chordee, and other abnormalities involving the penile skin shaft, such as dorsal hood deformity without a urethral abnormality. In most cases the median raphe spirals obliquely around the shaft and inserts atypically rather than at the base of the glans in line with the urethral meatus. The cause of penile torsion has not been clearly delineated but may be the result of an anomalous arrangement of penile shaft skin.

Most forms of penile torsion are less than 60 degrees. If surgical repair is being considered, neonatal circumcision is discouraged

and then performed at the time of penile detorsion. Although the glans may be directed more than 90 degrees from the midline, the orientation of the corporal bodies and the corpus spongiosum at the base of the penis is normal. In mild forms of penile torsion, correction typically involves degloving the penile skin, rotating the glans in the direction opposite to the defect (i.e., clockwise rotation for a counterclockwise abnormality), and suturing the glans to the penile skin, resulting in a glans in a normal configuration (Bar-Yosef et al, 2007). In some instances the median raphe may take a serpentine course that prevents restoration to a normal position; this is not critical as long as the meatus has a normal configuration. However, in boys with penile torsion of 90 degrees or more, simple shaft skin rearrangement is insufficient. Instead, the base of the penis must be mobilized so that dysgenic bands of fibrous tissue can be identified and incised. If the penis still remains rotated, correction may be accomplished by placing nonabsorbable anchoring sutures at the base of the corpora cavernosa (Pomerantz et al, 1978;

Slawin et al, 1992; Elder, 2001). Other surgical techniques have been described, including the use of a dorsal dartos flap (Bauer and Kogan, 2009) and mobilization of the urethral plate and urethra (Bhat et al, 2009).

Penile Masses

Penile cysts, congenital or acquired, are the most common penile masses in children. A history of onset, previous surgery, and changes in appearance or size are important in the evaluation of these lesions.

Parameatal Urethral Cyst

The parameatal urethral cyst is a rare anomaly and appears as a small blister in proximity to the urethral meatus (Fig. 146-12A). Shiraki (1975) suggested that these cysts may result from occlusion of paraurethral ducts or in other cases from faulty preputial separation from the glans along the coronal sulcus. The cyst wall may consist of transitional and squamous or columnar epithelium. Treatment is complete excision of the cyst with the patient under anesthesia, with care taken not to cause meatal stenosis.

Inclusion Cysts

The most common acquired cystic lesion of the penis is entrapped smegma under the unretractable prepuce. The mass may appear yellow because of smegma. The prepuce usually does not need to be retracted because it almost always retracts on its own with time.

Epidermal inclusion cysts may form after penile surgery, including circumcision and hypospadias repair, owing to islands of epithelium within the subcutaneous tissue (Fig. 146-13). Excision of the epidermal inclusion is recommended.

Cyst of the Median Raphe

Congenital epidermal cysts tend to form along the median penile raphe on the glans or penile shaft, scrotum, or perineum (see Fig. 146-12B and C) (Little et al, 1992; Krauel et al, 2008). These congenital lesions may result from epithelial rests that become buried during the urethral infolding process or represent a mono-dermal teratoma. Rare cases of cysts enlarging and extending into the pelvis are reported (Huang et al, 1999). Excision with the use



Figure 146-11. Penile torsion. Patient also has redundant penile skin after a neonatal circumcision.



Figure 146-12. Penile cysts. A, Parameatal urethral cyst appearing as a small blister. B, Cyst of the penoscrotal junction raphe. C, Cysts of the perineal raphe.

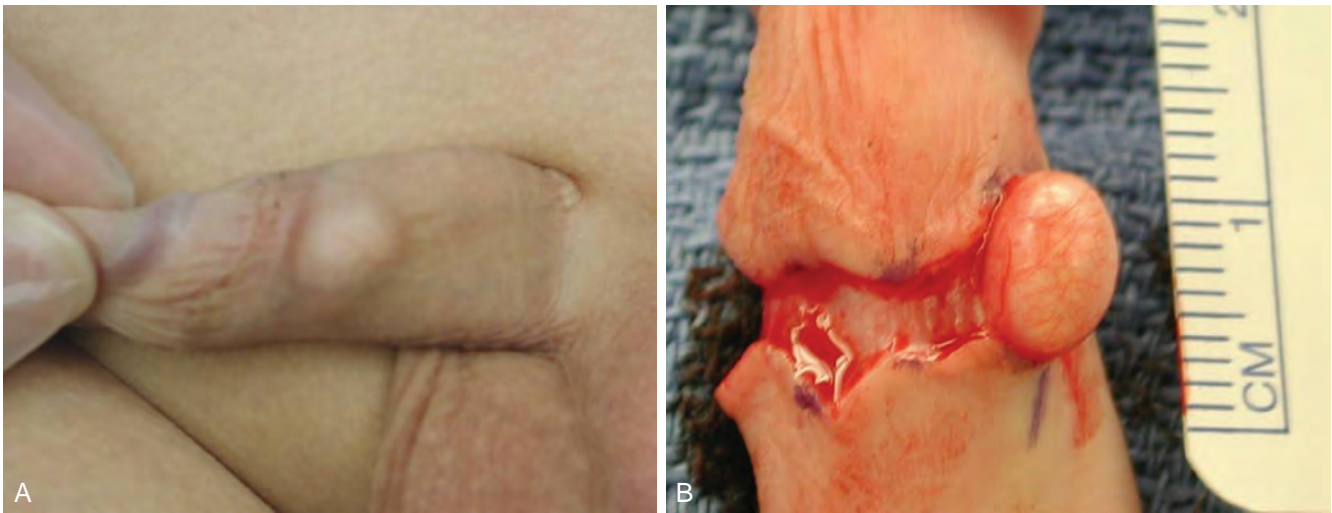


Figure 146-13. A, Epidermal inclusion cyst acquired after neonatal circumcision. B, Cyst exposed and excised intact through an incision of the circumcision scar.



Figure 146-14. Congenital penile nevus on the penile shaft.

of general anesthesia is recommended unless the cysts are small and asymptomatic.

Congenital Penile Nevi

Congenital penile nevi are pigmented lesions that can form on the glans and penile shaft (Fig. 146-14). Nevi can be classified based on the location of melanocytes: dermal (involving only the dermis), junctional (involving only the dermal-epidermal junction), and compound (involving the dermis and dermal-epidermal junction). They tend to be superficial and benign and should be excised (Papali et al, 2008).

Juvenile Xanthogranuloma

Juvenile xanthogranuloma is an uncommon benign, self-limiting lesion of the penis predominantly seen in infancy or early childhood. These lesions appear as solitary or multiple pigmented (yellow, orange, gold, brown, or red) nodules of rapid onset. They measure 2 to 20 mm in diameter and are well demarcated, firm, and rubbery. These lesions can affect the penis (Hautmann and Bachor, 1993; Bradford and Choudhary, 2009) or scrotum (Goulding and Traylor, 1983; Dehner, 2003), with as many as 20% being

present at birth. The lesion is often self-limited, and a period of 1 year of expectant monitoring is advised to avoid potentially unnecessary ablative genital surgery.

Accessory Urethral Openings

Congenital Urethral Fistula

Congenital urethral fistula is a condition whereby the urethra and meatus are normal and a urethrocutaneous fistula is present, typically located in the coronal or subcoronal position. This abnormality is usually an isolated deformity (Tennenbaum and Palmer, 1994), but may be associated with imperforate anus or ventral chordee (Ritchey et al, 1994). In a series of 14 such cases, 4 patients had distal hypospadias and 2 had chordee (Caldamone et al, 1999). The cause is unknown but may involve a focal defect in the urethral plate preventing the urethral folds from fusing. The diagnosis is made after circumcision in some cases (Caldamone et al, 1999), raising the possibility that the fistula is instead an iatrogenic injury. Surgical correction may require circumscription of the fistula and closure in multiple layers, similar to a urethrocutaneous fistula after hypospadias repair; or if the glans bridge is thin, the ventral glans can be opened through the distal urethra and then repaired by Thiersch-Duplay tubularization and incision of the urethral plate as needed.

Urethral Duplication

Urethral duplication is a rare congenital anomaly, with roughly 200 reported cases (Salle et al, 2000; Slavov et al, 2007). The duplication most commonly occurs in the sagittal plane with one urethra located ventrally and the other dorsally (Fig. 146-15). Collateral urethral duplication in which urethral duplication occurs in the same horizontal plane is extremely rare (Ching and Palmer, 2008b). In a series by Salle and colleagues (2000), sagittal plane duplication accounted for 94% of urethral duplication. Usually the dorsal urethra is considered the accessory urethra with or without a urinary stream, whereas the ventral urethra carries the urine stream and the anatomic landmarks such as the external sphincter and verumontanum. The most commonly used classification of urethral duplication is that of Effman (Fig. 146-16), which describes three types: types I and II distinguish between partial and complete urethral duplication; type III describes urethral duplication as part of bladder duplication (Effman et al, 1976). The embryology of urethral duplication is not well established, with explanations including ischemia (Woodhouse and Williams, 1979; Podesta et al,



Figure 146-15. Urethral duplication with catheters through meatus at tip of the glans penis and at perineum.

1998) and abnormal müllerian duct termination (Das and Brosman, 1977). Effman and coworkers (1976) suggested that caudal duplication may be related to division of the notochord with subsequent formation of two hindguts, allantoises, and cloacae.

Associated genitourinary, gastrointestinal, and musculoskeletal anomalies may be present. In the review by Podesta and colleagues (1998), six of seven patients with urethral duplication had other associated anomalies, with vesicoureteral reflux being the most common. Other anomalies included renal agenesis, bilateral cryptorchidism, sacral agenesis, imperforate anus, radial hypoplasia, and tracheoesophageal fistula. There appears to be an association with other midline defects such as duplicated bladder, duplicated colon, imperforate anus and anorectal agenesis, bifid glans, thoracic hemivertebrae, and partial sacral agenesis (Woodhouse and Williams, 1979; Fenster et al, 1980; Kennedy et al, 1988; Salle et al, 2000).

The most common presentation of urethral duplication is a double meatus and double urinary stream (Kennedy et al, 1988; Urakami et al, 1999; Salle et al, 2000). Incontinence and recurrent UTIs are other common presentations. Less common conditions include penile chordee and urinary obstruction secondary to a mucosal flap at the urethral bifurcation acting as an occluding valve during voiding (Effman et al, 1976; Das and Brosman, 1977; Salle et al, 2000). The presence of incontinence is dependent on the site of origin of the accessory urethra; the more proximal the site of urethral duplication, the higher the incidence and the greater the degree of incontinence (Farrell and Sparnon, 1987).

Patient evaluation should include a voiding cystourethrogram, retrograde urethrogram, and direct visualization of the anatomy during cystourethroscopy. Evaluation of the other associated anomalies should also be undertaken. Treatment of urethral duplication is usually reserved for the symptomatic child (Urakami et al, 1999). Cosmesis alone, however, has been advocated by some as a valid indication for intervention (Middleton and Melzer, 1992). The accessory urethra should not be used as the primary urethra secondary to being hypoplastic with the risk of inadequate urine flow (Salle et al, 2000). Surgical repair includes complete accessory tract excision, electrofulguration or injection of sclerosing agents into the accessory tract, septotomy if the septum between the two urethras is thin, and urethrourethrostomy of the accessory tract into the functional urethra. Management is dependent on the anatomy

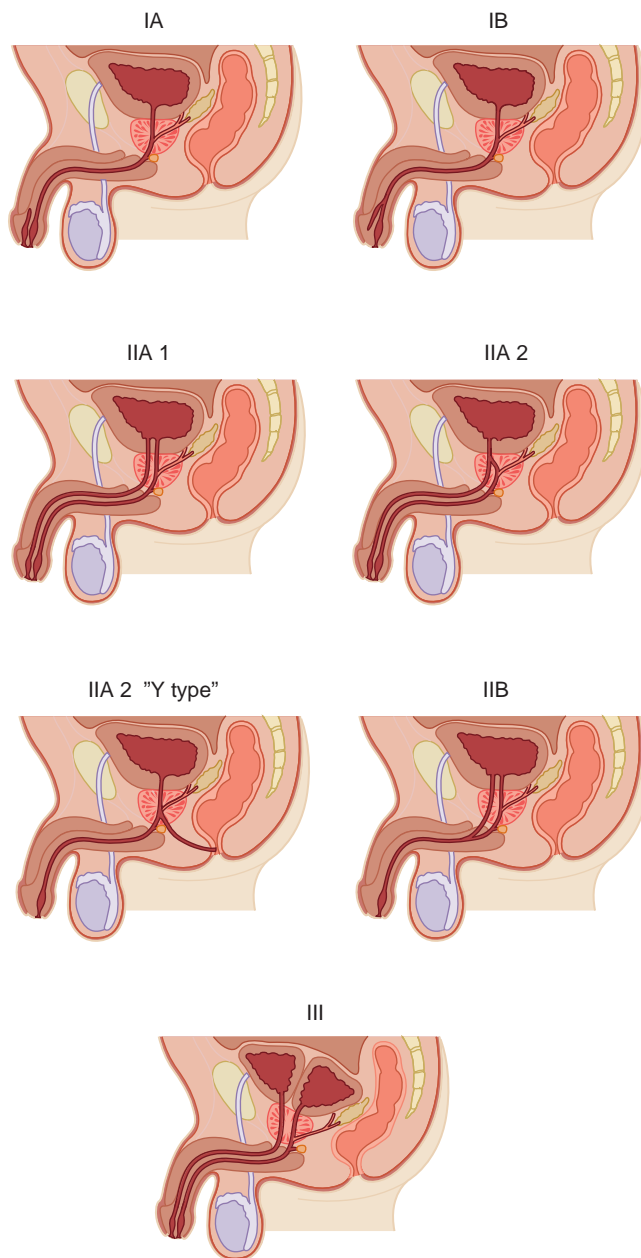


Figure 146-16. Effman classification.

of the urethral duplication (Farrell and Sparnon, 1987; Podesta et al, 1998).

Genital Lymphedema

Lymphedema of the genitalia, congenital or acquired, is a disfiguring disorder characterized by impaired lymphatic drainage that causes progressive penile or scrotal swelling. Congenital lymphedema may be sporadic (85%) or inherited (15%) and can be expressed at various ages (McDougal, 2003). Milroy disease is an autosomal dominant inherited trait, whereas Meige disease is probably autosomal dominant with variable penetrance and occurs in the first or second decade (Wheeler et al, 1981). If the genital lymphedema occurs at puberty and is sporadic, it is termed *lymphedema praecox*. Approximately 80% of patients with congenital lymphedema demonstrate onset of the disease at puberty (McDougal, 2003). The lymphedema may involve the penis, the scrotum, or both. Congenital lymphedema has been associated with several syndromes, including Turner, Noonan, Klinefelter, and intestinal

lymphangiectasia syndromes. Lower extremity involvement may also occur.

Initial management involves observation, but surgical therapy is necessary if the lymphedema remains significant or progresses. The goal of surgical treatment is to remove all involved tissue. On the penile shaft, the penis is degloved and all tissue between the Buck fascia and the skin as well as redundant penile skin must be excised. If the patient is uncircumcised, the prepuce may be unfurled to provide coverage of the penile shaft (Shenoy et al, 2001). If the scrotum is involved, the scrotal skin must be excised, with the exception of the posterior skin, and the spermatic cords and testes should be preserved (Ross et al, 1998). The penis may be covered with local skin flaps, and the scrotal contents may be covered with uninvolved posterior skin flaps (Bolt et al, 1998; Ross et al, 1998). Split-thickness skin flaps may be needed to cover the penis and scrotum if inadequate healthy skin is available (McDougal, 2003). Parents should be counseled that lymphedema in adjacent areas may recur after definitive surgical therapy.

Priapism

Priapism, a prolonged penile erection sustained for longer than 4 hours with the absence of both physical and psychological stimulation, is commonly painful. Tumescence is usually restricted to the corpora cavernosa (Montague et al, 2003), and in some cases the corpus spongiosum involves the glans. Priapism can be categorized into three types:

1. Ischemic (veno-occlusive, low-flow) priapism is characterized by little or no cavernous blood flow, and cavernous blood gases are hypoxic, hypercapnic, and acidotic. The corpora are rigid and tender to palpation.
2. Nonischemic (arterial, high-flow) priapism is caused by unregulated cavernous arterial inflow. Typically, the penis is neither fully rigid nor painful. There is often a history of antecedent trauma resulting in a cavernous artery or corpora cavernosa fistula.
3. Stuttering (intermittent) priapism is a recurrent form of ischemic priapism with painful erections with intervening periods of detumescence.

Low-flow priapism is most commonly secondary to homozygous sickle cell disease, which is characterized by predominance of sickle hemoglobin (HbS). Other causes include leukemia, other hemoglobinopathies, and local malignancy (Dewan et al, 1989; Friedman, 1998). Sickle cell–induced priapism occurs in 2% to 29% of males with the disease (Tarry et al, 1987; Hamre et al, 1991; Miller et al, 1995; Mantadakis et al, 1999). The priapism associated with sickle cell disease is generally related to sickling of red blood cells within the sinusoids of the corpora cavernosa during normal erection, resulting in venous stasis. The resulting decreased pH and local oxygen tension potentiates further stasis and sickling (Bruno et al, 2001). Priapism typically occurs during sleep, when mild hypoventilatory acidosis depresses oxygen tension and pH in the corpora or as a result of oxyhemoglobin desaturation (Roizenblatt et al, 2012). The pain that is experienced is a sign of ischemia.

Transient prolonged erections lasting less than 2 hours, stuttering priapism, is more common than prolonged erections in the patient with sickle cell disease. Pseudoephedrine, an oral α -adrenergic agent, given at bedtime promotes muscle contraction within the erectile tissue. If this treatment is unsuccessful, other agents can be used, including an oral β agonist. Recently, preliminary findings have suggested that the use of continuous, long-term oral phosphodiesterase type 5 (PDE5) inhibitor therapy may prevent recurrent priapism based on the hypothesis that PDE5 dysregulation may be involved in priapism (Burnett et al, 2006; Burnett, 2008).

The initial treatment of low-flow priapism resulting from sickle cell disease is conservative, with hydration, oxygenation, alkalinization, analgesia, and exchange transfusion aimed at reducing HbS concentration (Seeler, 1973; Hamre et al, 1991; Miller et al, 1995). Evacuation of blood and irrigation of the corpora cavernosa along with intracavernous injections of α -adrenergic

sympathomimetic agents, such as phenylephrine or epinephrine solution, can be a concurrent therapy (Montague et al, 2003). Surgical shunt procedures to facilitate corporal drainage are indicated in the absence of response to medical therapy (Tarry et al, 1987; Miller et al, 1995; Chakrabarty et al, 1996). Surgical shunting bypasses the veno-occlusive mechanism of the corpora cavernosa and thereby enhances blood drainage. Shunt procedures include distal cavernoglanular shunt (Winter, Ebbehøj, and Al-Ghorab shunts) (Ebbehøj, 1974; Winter, 1976; Ercole et al, 1981), proximal cavernospongiosal shunt (Quackels and Sacher shunts) (Quackels, 1964; Sacher et al, 1972), or saphenous vein anastomosis to one of the corpora cavernosa (Grayhack shunt) (Grayhack et al, 1964). Parents should be educated on the potential side effects from intervention, including cavernosal fibrosis and erectile dysfunction.

High-flow priapism is usually a result of perineal trauma, such as a straddle injury. Other causes include Fabry disease and sickle cell anemia (Ramos et al, 1995; Callewaert et al, 1998; Volkmer et al, 2001). Corporal irrigation is diagnostic and therapeutic. Typically, the aspirated blood is bright red and the aspirate is similar to arterial blood on blood gas analysis. Color Doppler ultrasonography (CDUS) often will demonstrate the fistula. The initial management is observation (Montague et al, 2003) because spontaneous resolution may occur. Superselective embolization of cavernous and penile arteries (Callewaert et al, 1998; Volkmer et al, 2001; Montague et al, 2003; Kuefer et al, 2005) is the next line of therapy.

A fourth type of priapism is a spontaneously resolving form observed in neonates (Walker and Casale, 1997). Causes may include idiopathic factors, birth trauma, and polycythemia. No intervention is necessary because the priapism usually resolves in 2 to 6 days without adverse results.

Penoscrotal Transposition (Scrotal Engulfment)

Penoscrotal transposition may be partial or complete (Fig. 146-17), with its less severe forms having been termed *bifid scrotum*, *doughnut scrotum*, *prepenile scrotum*, and *shawl scrotum*. The embryologic cause may result from incomplete or failed inferomedial migration of the labioscrotal swellings. The use of 2D and 3D ultrasound during gestation has been successful in identifying the condition in utero (Wang et al, 2011). Frequently, it occurs in conjunction with perineal, scrotal, or penoscrotal hypospadias with chordee (Pinke et al, 2001). Penoscrotal transposition has also been associated with caudal regression (Lage et al, 1987), sex chromosome abnormalities (Yamaguchi et al, 1989), and Aarskog syndrome (Shinkawa et al, 1983). As many as 75% of patients with complete penoscrotal transposition and a normal scrotum have a significant urinary tract abnormality, including renal agenesis and dysplasia (MacKenzie et al, 1994; Parida et al, 1995), and other nongenitourinary anomalies have been reported. These patients



Figure 146-17. Penoscrotal transposition.

should be evaluated with renal ultrasonography and voiding cystourethrography.

Surgical repair is usually performed during hypospadias or other penile repair. Several scrotoplasty techniques have been described (Glenn and Anderson, 1973; Ehrlich and Scardino, 1982; Levy et al, 1997) with the goal of freeing the penis from the scrotum, developing skin flaps, relocating the scrotum to a dependent position, and moving the penis superiorly. When scrotal engulfment is associated with severe hypospadias, hypospadias repair is often accomplished by a transverse preputial island flap in conjunction with Thiersch-Duplay tubularization of the proximal urethra. To minimize the possibility of devascularization of the preputial flap, correction of the scrotal engulfment is usually done as a second-stage procedure 6 months later (Elder and Duckett, 1990; Germiyanoglu et al, 1994). If the penis is normal, scrotoplasty can be accomplished when the child is 6 to 12 months of age.

Scrotoplasty is performed by circumscribing the superior aspects of each half of the vertical aspect of the scrotum and extending these incisions laterally to include at least half of the scrotum (Fig. 146-18). The medial aspects of the incision are joined on the ventral aspect of the penis, and the incision is carried down the midline along the median raphe. The injection of a solution of lidocaine with epinephrine into the subcutaneous tissue can be used to develop tissue planes and also help to diminish bleeding. Care must be taken not to injure the tunica vaginalis and spermatic cord during deeper dissection. The scrotal wings are rotated medially under the penis and sutured together in the midline in an everted manner. Although in most cases there is no deficiency of the ventral penile shaft skin, in more severe cases of penoscrotal transposition dorsal interposition flaps may be necessary, allowing caudal advancement of the skin of the abdominal wall (Pinke et al, 2001).

An alternative technique is to identify the correct position for the penis and make a buttonhole by excising a plug of epidermis, dermis, and suprapubic fat (Kolligian et al, 2000). The penis is then degloved, and the penile shaft is brought through the buttonhole. The penile shaft skin remains behind, is split down the ventrum, and is mobilized superiorly to the penile shaft. A window of the dartos pedicle is made, and the penile shaft is brought through this window. The degloved penis is then resurfaced with shaft skin.

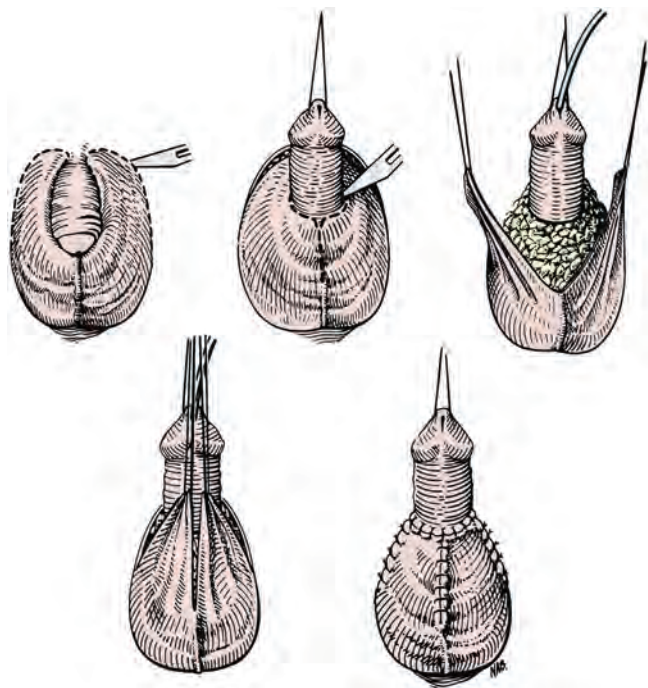


Figure 146-18. Repair of penoscrotal transposition (see discussion in text).

SCROTAL ANOMALIES

Bifid Scrotum

Bifid scrotum refers to the deformity in which the labioscrotal folds are completely separated and without a median raphe. This anomaly is most often associated with proximal hypospadias. Surgical repair is usually performed during hypospadias repair. The technique is similar to that used for repair of penoscrotal transposition. An alternative is the use of single or multiple Z-plasty procedures to correct the defect (Mokhless et al, 2011) (Fig. 146-19).

Ectopic Scrotum

Ectopic scrotum (Fig. 146-20), the anomalous position of one hemiscrotum along the inguinal canal, is a rare condition. The location can be suprainguinal (most common), infrainguinal, or perineal (Lamm and Kaplan, 1977; Elder and Jeffs, 1982). This anomaly has been associated with cryptorchidism, inguinal hernia, and bladder exstrophy as well as with the popliteal pterygium syndrome (Cunningham et al, 1989). In one review, 70% of boys with a suprainguinal ectopic scrotum exhibited ipsilateral upper urinary tract anomalies, including renal agenesis, renal dysplasia, and ectopic ureter (Elder and Jeffs, 1982). Another study indicated that an associated perineal lipoma was found in 83% of these children; 68% of those with a lipoma had no associated anomalies, whereas 100% of those without a lipoma had associated genital or renal malformations (Sule et al, 1994). Because the embryology of the gubernaculum and of the scrotum are intimately related chronologically and anatomically, the ectopic scrotum may result from a defect in gubernacular formation that prevents migration of the labioscrotal swellings (Hoar et al, 1998). **Patients with an ectopic scrotum should undergo upper urinary tract imaging with ultrasonography.** Scrotoplasty and orchiopexy may be performed at 6 to 12 months of age or earlier if other surgical procedures are necessary for associated anomalies.

Scrotal Hypoplasia

Scrotal hypoplasia, the underdevelopment of one or both sides of the scrotum, occurs most commonly in boys with an undescended testis and in infants with genital ambiguity. The deformity may result from lack of gubernacular swelling of the labioscrotal folds.

Scrotal Agenesis

The absence of the scrotum or hemiscrotum is rare (Fig. 146-21 on the Expert Consult website). There are seven reported cases of scrotal agenesis, all of which included XY karyotype and bilateral undescended testes; the presence of the median raphe; and other anomalies such as cognitive impairment, bilateral nystagmus, cleft palate, and syndactyly (Silay et al, 2013). Two cases of hemiscrotal agenesis have been reported. In one case, multiple anomalies were found; in the second case an isolated hemiscrotal agenesis was reported. In both cases the penis and contralateral hemiscrotum and contents were normal. In addition, the testes on the affected side were in what would have been the normal location (Flum et al, 2012; Yilmaz et al, 2013).

Scrotochisis

Meconium peritonitis may occasionally cause genital manifestations, including meconium hydrocele (Ring et al, 1989) and congenital rupture of the scrotum, termed *scrotochisis* (Gongaware et al, 1991; Salle et al, 1992; Chun and St-Vil, 1997; Kojori and Demaria, 2007; Premkumar et al, 2009). This can result in one or both testes being extruded from the scrotal sac. When scrotochisis is detected the clinician should suspect meconium peritonitis and proceed with the appropriate evaluation. Treatment involves scrotal exploration with orchiopexy and primary closure of the scrotal wall defect (Fig. 146-22 on the Expert Consult website).



Figure 146-21. Congenital agenesis of the scrotum. (From Silay MS, Yesil G, Yildiz K, et al. Congenital agenesis of scrotum and labia majora in siblings. *Urology* 2013;81:421–3.)



Figure 146-22. Congenital scrotoschisis and exposed testis. (From Shukla RM, Mandal KC, Roy D, et al. Scrotoschisis: an extremely rare congenital anomaly. *J Indian Assoc Pediatr Surg* 2012;17:176–7.)

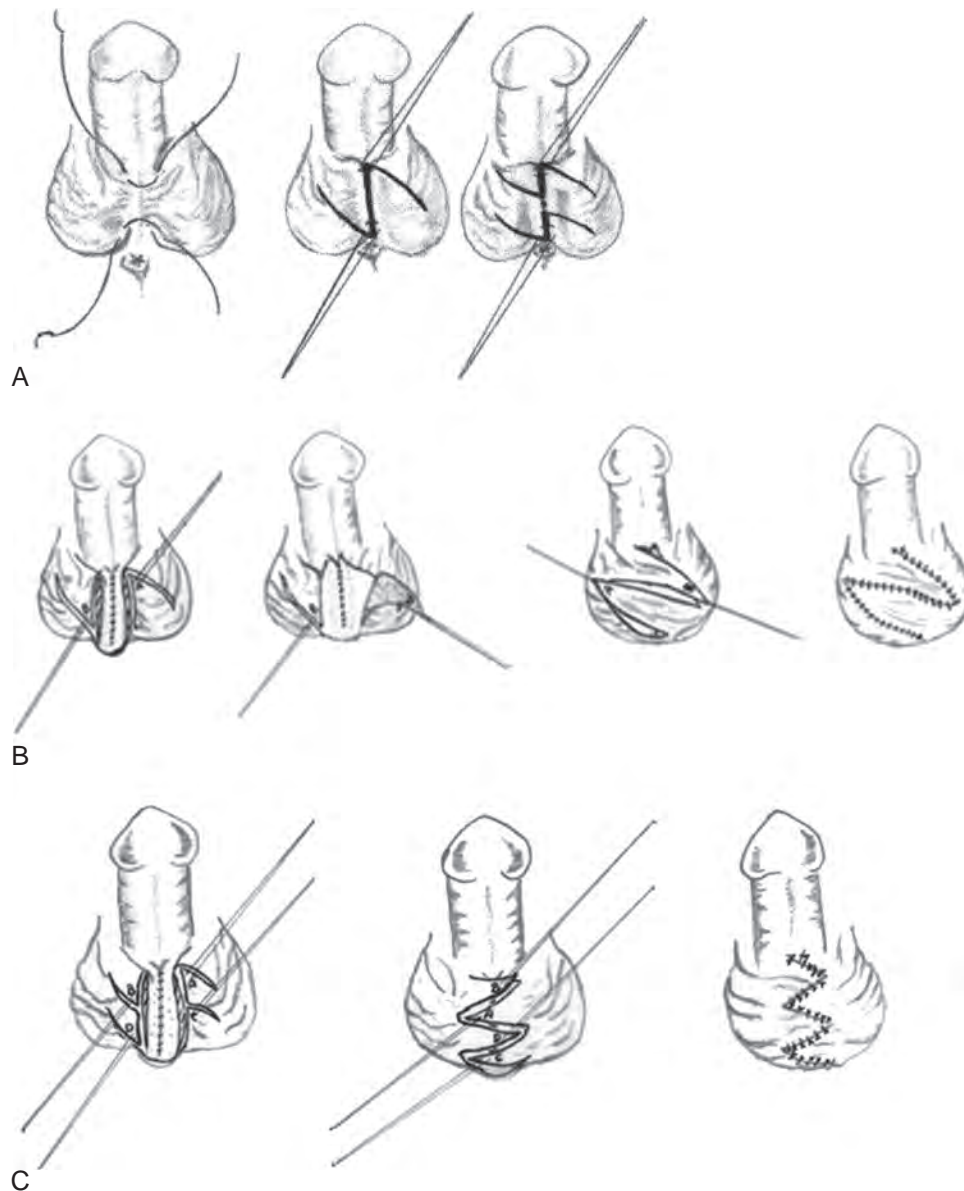


Figure 146-19. Use of Z-plasties to correct the bifid scrotum. **A,** The placement of initial stay sutures (*left*) and drawing lines of simple (*middle*) or multiple Z's (*right*). The development of the flaps and their rearrangement are seen for a simple Z-plasty (**B**) and multiple Z's (**C**). (From Mokhless I, Youssif M, Eltayeb M, et al. Z-plasty for sculpturing of the bifid scrotum in severe hypospadias associated with penoscrotal transposition. *J Pediatr Urol.* 2011 7:305-9.)

VASCULAR LESIONS OF THE GENITALIA

Vascular lesions of the genitalia are uncommon without a consensus on classification, etiology, and treatment. These deformities include hemangiomas and vascular malformations. **Hemangiomas are on the skin**, are often congenital, and may show significant growth in the postnatal period followed by slow involution. **Vascular malformations are present at birth in the subcutaneous tissues** and tend to persist or to enlarge, which can occur secondary to trauma, sepsis, or hormonal changes (Ramos et al, 1999). **Vascular malformations can be subdivided into either slow-flow (capillary, lymphatic, venous) or fast-flow (arterial, arteriovenous) types.**

Congenital Hemangiomas

Congenital hemangiomas are common and affect the genitalia in approximately 1% of all hemangiomas (Alter et al, 1993). The origin of these lesions and the mechanisms regulating their growth and

involution are controversial (Ritter et al, 2007). Strawberry hemangiomas are the most common type and result from proliferation of immature capillary vessels. These are also categorized as cutaneous hemangiomas because they occur on the skin. Although the lesions may undergo a period of rapid growth lasting 3 to 6 months, gradual involution is common, and most lesions require no treatment (Casale and Menashe, 1989; Girard et al, 2006). If ulceration develops, intervention is necessary to prevent complications from bleeding. The most popular form of therapy is short-term oral corticosteroid therapy. Treatment with laser therapy allows selective photothermolysis and destruction of superficial blood vessels (Kennedy et al, 1993; Ward et al, 1998). In some cases, surgical excision is necessary.

Subcutaneous Hemangiomas

Subcutaneous hemangiomas, also referred to as *cavernous hemangiomas*, are much less common than the cutaneous variety (Sule et al, 1993; Ferrer and McKenna, 1995) and are probably more appropriately



Figure 146-20. Ectopic scrotum.

classified as a vascular malformation. They may be detected at birth or later in life. In contrast to cutaneous hemangiomas, which tend to involute, cavernous hemangiomas tend to enlarge gradually and should be treated with care. Physical examination reveals a “bag of worms” sensation similar to that of a varicocele, although the lesions tend to be firm and do not decompress when the patient is recumbent. Ultrasonography with color Doppler imaging, computed tomography (CT), or MRI is recommended to delineate the size of the hemangioma (Aizenstein et al, 1996) because examination does not disclose the extent of the lesion. Definitive treatment by en bloc resection is advised, and preoperative angioembolization may reduce the size of the mass and the risk of bleeding.

Klippel-Trénaunay-Weber Syndrome

Klippel-Trénaunay-Weber syndrome is a triad of cutaneous vascular malformation, most commonly nevus flammeus, in combination with soft tissue and bone hypertrophy. The anomaly manifests at birth, usually involving a lower extremity, but it may also involve the trunk or face. These vascular lesions have a propensity to bleed. In a review of 214 patients from a single institution, Husmann and colleagues (2005) found that 30% had genitourinary cutaneous or visceral involvement. Of the 48 (22%) who had cutaneous genital involvement, 29% developed intractable bleeding. Excision of the hemangiomas was associated with significant blood loss.

Vascular Malformations

The penis may also be affected by vascular malformations. These lesions are congenital but are usually not diagnosed until the teenage years or young adulthood. The lesions are characterized as a faint blue patch or a soft blue mass. Careful excision is effective (Kaufman et al, 2010) but if the lesion affects the glans penis, the neodymium:yttrium-aluminum-garnet laser may yield a better result (Ramos et al, 1999).

HERNIA AND HYDROCELES

Embryology

Patients with inguinoscrotal pathology, namely inguinal hernias and hydroceles, are commonly referred to pediatric urologists for

diagnostic confirmation and management. The processus vaginalis forms during the third month of gestation as the peritoneum bulges into the inguinal canal just before the onset of testicular descent. On completion of testicular descent, the processus vaginalis obliterates and the portion adjacent to the testes becomes the tunica vaginalis. Obliteration of the processus vaginalis continues postnatally, and its failure to obliterate accounts for nearly all inguinoscrotal abnormalities seen in infancy and childhood. In an autopsy series, Mitchell found closure of the processus vaginalis in 18% of full-term infants at birth (Mitchell, 1939). Among 1965 children undergoing unilateral inguinal hernia repair, Rowe identified a patent contralateral processus vaginalis in 63% of patients younger than 2 months and about 40% of those 1 to 2 years of age, with similar frequency up until age 16 years (Rowe et al, 1969). The incidence of incidental patency observed in older children and adults at autopsy or laparoscopy is about 20% (Ajmani and Ajmani, 1983; van Wessem et al, 2003).

Definitions (Fig. 146-23)

Indirect inguinal hernia: a widely patent processus vaginalis extending beyond the internal inguinal ring containing abdominal contents (bowel, omentum, gonads) which may pass into the inguinal canal, labia, or scrotum

Communicating hydrocele: a patent processus vaginalis extending beyond the internal inguinal ring containing peritoneal fluid alone, which extends to the testis, with fluid within the tunica vaginalis

Hydrocele of the spermatic cord: fluid contained within a segment of patent processus vaginalis with obliterated processus distally and proximally

Scrotal hydrocele: fluid contained within the tunica vaginalis surrounding the testis without communication proximally

Abdominoscrotal hydrocele: a large scrotal hydrocele that extends proximally across the internal inguinal ring into the abdomen without communication with the peritoneum

Epidemiology and Pathogenesis

Inguinal Hernia and Communicating Hydrocele

Inguinal hernias develop in 1% to 5% of children. The incidence is 5 to 10 times more common in boys and significantly more common among premature infants (13% of babies born before 32 weeks and nearly 30% of babies weighing less than 1 kg). The propensity for the right side (3:1) is attributed to the later descent of the right testicle. (Jones et al, 1998; Brandt, 2008). Female gender, prematurity, age younger than 1 year, and history of cryptorchidism are risk factors for bilaterality (Ein et al, 2006; Brandt, 2008). One study suggests a protective effect of breastfeeding against the development of inguinal hernias (Pisacane et al, 1995). Whereas hernias may occur at any time during childhood, the average age at presentation is 3 to 4 years, with nearly one third of cases manifesting before age 6 months (Kapur et al, 1998). Concomitant hydroceles are frequently seen; 19% of 6361 cases were found by Ein and colleagues (2006) (70% scrotal, 26% cord, and 4% both) (Ein et al, 2006).

The majority of new hydroceles occurring after birth and before puberty are associated with a patent processus vaginalis. In an observational study, 59% of 302 newly identified hydroceles in patients 1 to 18 (mean 4.4) years of age were clinically communicating (clear history of fluctuation), and 6% were spermatic cord hydroceles (Christensen et al, 2006). Seventy (65%) of the apparently noncommunicating and 5 (29%) of the cord hydroceles were followed, and spontaneous resolution was noted in 39 and 3, respectively. Among boys undergoing hydrocele repair, complete obliteration of the processus vaginalis was noted in 0% to 22% of cases (Elder, 1992; Barthold and Redman, 1996; Han and Kang, 2002).

Noncommunicating Hydroceles

Hydroceles that spontaneously resolve during infancy or appear during or after puberty are more commonly noncommunicating.

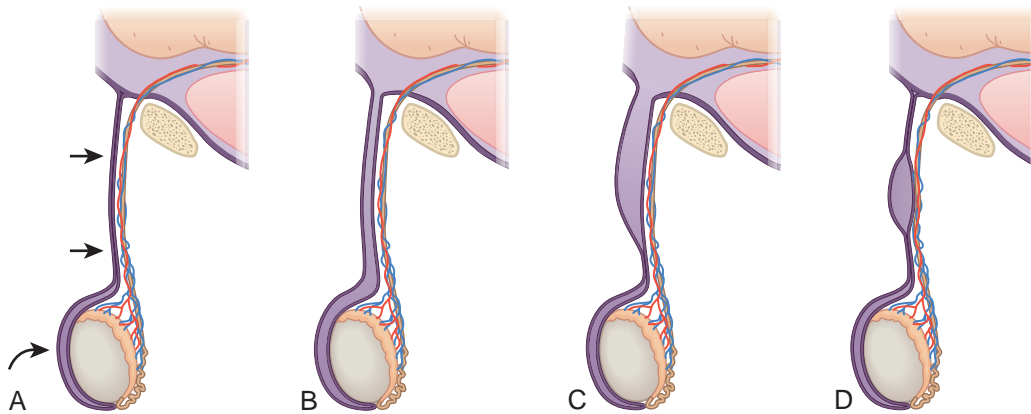


Figure 146-23. Anatomy of the processus vaginalis in hydrocele. A, Normal closure of the processus vaginalis; *straight arrows* indicate the funicular process; *curved arrow* is the tunica vaginalis. B, Communicating hydrocele with complete patency of the processus vaginalis. C, Funicular hydrocele with distal closure of the processus vaginalis; communication with the peritoneal cavity may also result in hernia. D, Encysted hydrocele of the spermatic cord. (From Martin LC, Share JC, Peters C, et al. Hydrocele of the spermatic cord: embryology and ultrasonographic appearance. *Pediatr Radiol* 1996;26:528–30.)

These form from delayed fluid absorption or abnormal fluid dynamics within the tunica vaginalis or less commonly in response to tumor, trauma, or inflammation. Simple scrotal hydroceles occur in at least 5% of male neonates (Osifo and Osaigbovo, 2008) and are typically bilateral, and resolve with fluid reabsorption.

Genetics and Associated Conditions



Please see the Expert Consult website.

Diagnosis

Signs and Symptoms

Inguinal hernias and communicating hydroceles typically manifest as a painless bulge found in the groin or extending along the cord to the scrotum. The bulge may be present only during periods of increased intra-abdominal pressure (crying or bowel movements); the supine position facilitates reduction of peritoneal fluid and intra-abdominal contents. **The presence of an intermittent bulge helps to distinguish a reducible inguinal hernia and communicating hydrocele from a scrotal hydrocele or hydrocele of the spermatic cord.** The child with an incarcerated inguinal hernia will be irritable or inconsolable and have a persistent or larger bulge without spontaneous reduction and may have decreased appetite and signs of bowel obstruction (abdominal distention, vomiting, and lack of flatus or stool).

The scrotal hydrocele may be seen as a chronic or acute scrotal swelling after an inflammatory, infectious, or traumatic event. The hydrocele size is typically stable but may decrease over time. The hydrocele of the spermatic cord is also usually painless and variable in size. It may be confused for the testis because of its round-oval shape.

Physical Examination

Physical examination starts with a child standing, if age appropriate, otherwise supine. Inspection proceeds from the lower abdominal skin crease and along the inguinal canal to the scrotum. If the child is crying, the bulge should be assessed to emerge or increase in size and then improve or disappear when the child is consoled. Techniques to increase intra-abdominal pressure may induce protrusion of the bulge (immobilizing the extremities to induce crying in infants, and jumping, coughing, laughing, blowing bubbles, or

blowing up balloons in older children) (Brandt, 2008). If a bulge is not elicited at the time of examination, photographs of the bulge taken by family members are diagnostically reliable (Kawaguchi and Shaul, 2009).

Palpation proceeds craniocaudally from superior-lateral to the pubic tubercle down to the scrotum to determine the proximal and distal extent of the swelling. Communicating hydroceles and hernias start at the level of the internal ring and end variably. The silk-stocking sign (sensation of rubbing silk together), sought by rubbing the cord structures side to side near the pubic tubercle, implies thicker cord structures. A hydrocele of the spermatic cord may be confused with a testis, but normal cord structures are palpable above and below and a testis will also be palpated. Scrotal hydroceles may elicit a blue hue through the scrotal skin. Normal cord structures are palpable superior to the hydrocele but may be difficult to distinguish if it extends up to or across (abdominoscrotal) the internal ring, in which case abdominal examination should reveal a ballotable mass. The hydrocele fluid surrounding the testicle should transilluminate; however, neonatal bowel may also transilluminate. The testis should be palpable within a soft scrotal hydrocele but may be difficult to discern within a tense hydrocele.

Radiologic Imaging

Imaging is often of limited usefulness. Ultrasonography may identify a large elongated echolucent area from the groin extending anteromedially in the spermatic cord; omentum or bowel with peristalsis can be found in a large hernia sac (Fig. 146-24). **In the presence of a presumed hydrocele, a sonogram can aid in identifying an unpalpable testicle surrounded by hydrocele fluid (Fig. 146-25).**

Surgical Repair

Inguinal Hernia

Inguinal hernias require surgical repair shortly after diagnosis, given the significant risk of associated complications. Outpatient surgery can be performed within a few weeks in easily reducible hernias or communicating hydroceles and more urgently if there is moderate difficulty in reducing the hernia contents. Parental counseling regarding the signs and symptoms of incarceration should occur. An irreducible hernia requires immediate exploration. Hernias in premature infants can be repaired before hospital

A genetic predisposition to developing inguinal hernias exists, and potential genome sites have been identified. Among probands, there is a 28% risk in other family members and a higher relative risk in first-degree relatives (6.9), particularly female siblings (17.8) of affected girls (Gong et al, 1994; Jones et al, 1998). Genetic transmission appears to be autosomal dominant with reduced penetrance. Zheng has implicated DNA sequence variants (DSVs) within T-box transcription factor 1 (TBX1) and TBX2 as rare causes (Zhang et al, 2014a, 2014b). Sezer identified polymorphisms of the collagen type I $\alpha 1$ (COL1A1). The Sp1 binding site was associated with a higher risk of developing inguinal hernias (Sezer et al, 2014).

Hernias are associated with other diseases and anomalies. These include bladder exstrophy, epididymal anomalies, connective tissue disorders, cystic fibrosis, and posterior urethral valves. Inguinal hernia is also a component of over 200 syndromes, many of which have known specific genetic alterations (Winter-Baraitser Dysmorphology Database, www.lmddatabases.com). Other genital anomalies such as polyorchidism, transverse testicular ectopia with or without persistent müllerian ducts, and splenogonadal fusion may be seen at the time of hernia repair. Abnormal epididymal-testicular attachment correlates with degree of closure of the processus vaginalis (Elder, 1992; Barthold and Redman, 1996). Finally, the presence of abdominal ascites or a ventriculoperitoneal shunt increase the chances of developing an inguinal hernia (Grosfeld et al, 1991).

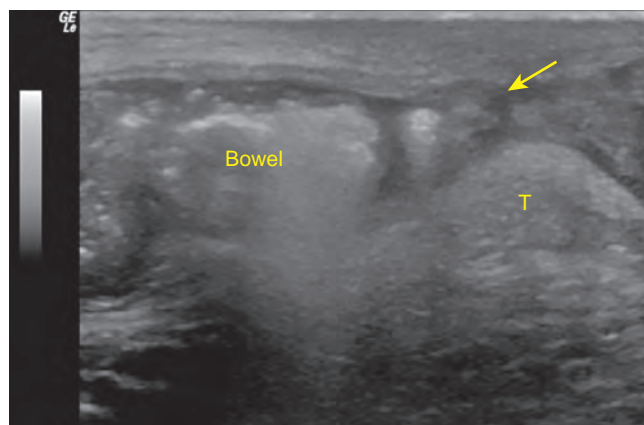


Figure 146-24. Sagittal image of a scrotal ultrasound in a 4-year-old boy with an inguinoscrotal bulge. Bowel is seen within the hernia sac that ends (arrow) superior to the testis (T) in the scrotum.



Figure 146-25. Sagittal (SAG) image from a scrotal sonogram of an 8-month-old boy with tense scrotal swelling and indiscernible testis on palpation. Sonogram demonstrates hypoechoic fluid (hydrocele) surrounding the normal testis.

discharge, but repair may need to be delayed in extremely low-birth-weight (<1500 g) infants or those with congenital heart disease, pulmonary disease, sepsis, or metabolic disease because of the increased risk of anesthesia. Some authors recommend delaying surgery until 50 to 52 weeks postconception rather than performing it before hospital discharge (Stylianios et al, 1993; Chen et al, 2009).

Hydroceles

Hydroceles in infants have the potential to resolve spontaneously. If the hydrocele persists by age 1 or if the hydrocele enlarges during the period of observation, then surgery is indicated. Hydroceles of the spermatic cord do not tend to resolve spontaneously but rarely require urgent surgery and can also be corrected after age 1 year.

Standard Inguinal Hernia Repair

The traditional surgical approach to repairing an indirect inguinal hernia or communicating hydrocele, high ligation of the hernia sac at the level of the internal inguinal ring, carries high success rate, low morbidity, limited postoperative pain, and good cosmesis. A small incision is made in the Langer lines at the skin crease superolateral to the pubic tubercle (Kogan, 2007). The Scarpa fascia is incised to expose the external oblique fascia, which is then cleared laterally and caudally to the external inguinal ring. The external oblique fascia is opened in the direction of its fibers, with care taken to avoid injuring the ilioinguinal nerve. In young infants, the internal and external inguinal rings are in close proximity, providing adequate access without opening of the external oblique fascia (Mitchell-Banks technique) (Kurlan et al, 1972). The cremaster

muscle fibers are separated perpendicular to the cord to expose the hernia sac anteromedially. The sac is elevated and separated from the rest of the cord and then divided between clamps. The proximal side is elevated and separated from the cord proximally to the internal ring, where it is ligated to avoid risk of recurrence (Grosfeld et al, 1991). If there are obvious contents present or if the sac is large or thickened, it should be opened before ligation to confirm the absence of any tissue or to reduce bowel, omentum, or a sliding component. The internal ring should be tightened medially in cases of significant widening (Ein et al, 2006; Brandt, 2008). When the distal sac is short, it may be left in place, and when long, the anterior aspect can be excised. A hydrocele should be excised and any appendages removed.

In peripubertal boys with hydrocele, an inguinal approach is preferred if there is clinical evidence of a communicating hydrocele; otherwise a trans-scrotal hydrocele repair is performed as in adults and an inguinal incision made only if a proximal communication is identified. In a retrospective study, Wilson and colleagues recorded the intraoperative findings of children undergoing hydrocele repair and found hydroceles were noncommunicating in 82.1% of children older than 10 years and in 86.4% of children older than 12 years. Age was significantly associated with a patent processus vaginalis (Wilson et al, 2008).

Complications

Early postoperative complications, including bleeding and infection, are rare after standard hernia repair. The rate of recurrent inguinal hernia after uncomplicated open repair is 0.5% to 1% (Farrow and Thompson, 1963; Grosfeld et al, 1991; Zhang and Li, 1993; Wright, 1994; Vogels et al, 2009) and rises to 2% for premature infants (Krieger et al, 1994; Misra et al, 1994) and 3% to 6% after repair of an incarcerated hernia (Clatworthy et al, 1954; Farrow and Thompson, 1963). Recurrence typically occurs within 1 year for 50% of the patients and by 2 years for more than 75% (Grosfeld et al, 1991; Wright, 1994). The causes of recurrent hernias include failure to properly identify or ligate the sac during the original procedure; a tear in the sac, leaving a strip of peritoneum along the cord; damage to the floor; or a missed direct hernia at the original exploration. Surgical repair of recurrent hernias can usually be accomplished inguinally with ligation of an indirect sac at the level of the internal inguinal ring and/or repair of the floor of the inguinal canal for a direct hernia.

The incidence of complications related to the genital tract, secondary cryptorchidism, testicular atrophy, and vasal injury is not well defined. If a testis is incompletely descended or retractile, orchidopexy should be performed at the time of herniorrhaphy. Iatrogenic cryptorchidism is avoidable (Kaplan, 1976; Puri et al, 1984) by confirming proper testis position on completing the herniorrhaphy. The risk of testicular atrophy was 0.3% in the large single center series (Ein et al, 2006) but ranged from 4% to 12% in other series (Clatworthy et al, 1954; Rowe and Clatworthy, 1970), with higher rates among the irreducible cases (Fasching and Hollwarth, 1989). The causes include compression of the gonadal vessels by the irreducible hernia or vascular damage incurred during surgical repair. Young infants are at higher risk with infarction rates of 30% to 33% (younger than 2 or 3 months) (Slowman and Mylius, 1958; Fasching and Hollwarth, 1989). Portions of vas deferens are found in 0.13% to 0.3% of cases, although embryonal remnants not representing true ductal structures are much more common (1.5% to 2.9%) (Popek, 1990; Partrick et al, 1998; Steigman et al, 1999). The risk of vasal injury may be higher in young infants and/or cases of incarceration. Vasal injury without transection may manifest as vasal obstruction and infertility later in life (Sheynkin et al, 1998).

Persistence of a hydrocele is very rare after decompression at the time of hernia repair (0.1% in the series by Ein and associates [2006]) and should be observed for spontaneous resolution for at least 1 year. If persistent, secondary scrotal hydrocele repair is indicated, or reoperative hernia repair if fluctuation suggests a recurrent hernia.

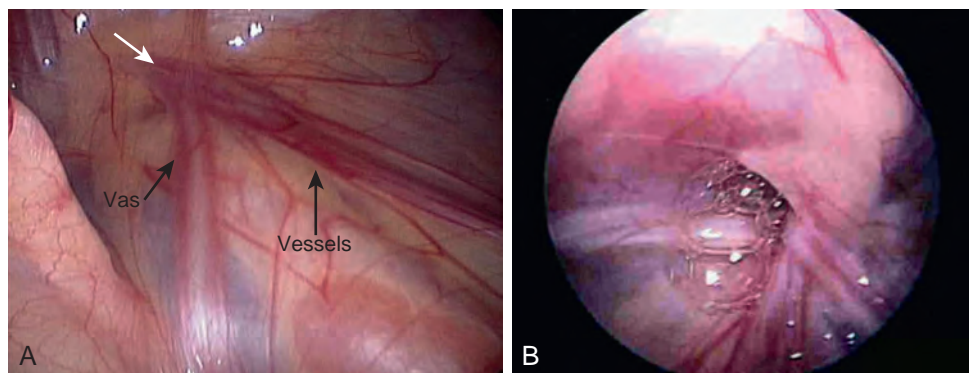


Figure 146-26. Transinguinal laparoscopic views of (A) a closed (white arrow) and (B) an open contralateral internal inguinal ring. Note the bubbles emanating from the air pushed back through the open ring. (Courtesy Israel Franco, MD.)

Scrotal Approach to Inguinal Hernia Repair

Concurrent with reports advocating a scrotal approach to orchidopexy, some authors suggest a similar approach to inguinal hernia and communicating hydrocele (Lais and Ferro, 1996; Fearne et al, 2002; Gokcora and Yagmurcu, 2003). For bilateral inguinal hernias, Shih described a median raphe approach (Shih and Uen, 2012). Initial data suggest no major differences in success rate or morbidity using the scrotal approach compared with standard inguinal surgery. Fearne and colleagues (2002) ligated the processus vaginalis at the level of the external inguinal ring in 195 boys and saw 1 recurrence (mean follow-up, 13 months). Issues related to the level of sac ligation and patient age have not been fully addressed (Wilson et al, 2008) and deserve longer-term follow-up.

Laparoscopic Inguinal Hernia Repair

Laparoscopic hernia repair using two major techniques—peritoneal closure of the defect (Schier, 2006) and an extraperitoneal approach (Takehara et al, 2006; Endo et al, 2009)—has gained interest. Alzahem performed a meta-analysis of 10 comparative studies of laparoscopic versus open inguinal hernia repair in 2699 infants and children. Laparoscopic techniques were associated with a trend toward higher recurrence rate, longer operative time for unilateral repairs, and shorter operative time for bilateral repairs. There was a significant reduction in development of a contralateral metachronous inguinal hernia in the laparoscopic group (Alzahem, 2011). Surgery can be performed efficiently but the recurrence risk remains higher (up to 4%) than with open repair, although it may decrease with increasing experience (Saranga Bharathi et al, 2008). Conflicting literature exists regarding levels of pain and operative time after laparoscopic repair (Chan et al, 2005; Koi-vusalo et al, 2009).



Please see the Expert Consult website for further details.

Assessment of the Contralateral Internal Ring

The need to assess the patency of the contralateral processus vaginalis or of the internal inguinal ring in children with a unilateral hernia remains controversial. The goal of contralateral assessment is avoidance of metachronous hernia development and its attendant risks and costs. Historically, routine contralateral exploration was performed, and then more selectively in patients considered at high risk for metachronous hernia based on age, prematurity, gender, or associated disease. In a survey, 51% of pediatric general surgeons stated that they routinely perform contralateral exploration in premature infants; 40% perform exploration in boys younger than 2 years, and 13% in boys ages 2 to 5 years (Levitt et al, 2002).

In contrast to older methods, transperitoneal diagnostic laparoscopy offers a rapid, direct, and accurate inspection of the

contralateral internal inguinal ring (Fig. 146-26). A meta-analysis of 964 laparoscopic evaluations identified a sensitivity of 99.4% and specificity of 99.5%. The incidence of an open contralateral internal ring among boys younger than 1 year without a clinical hernia is 10% undergoing laparoscopic orchidopexy (Palmer and Rastinehad, 2008). Among those undergoing unilateral inguinal hernia repair, the incidence of a contralateral patent processus vaginalis ranges from 57% to 68% during open exploration and 39% to 61% during laparoscopic hernia repair (Tepas and Stafford, 1986; Zona, 1996; Miltenburg et al, 1998; Saad et al, 2011). The incidence is inversely related to age; Chin and colleagues (1995) found an open contralateral ring in 41% of infants younger than 1 year, in about 30% of toddlers aged 2 to 5 years, and in 19% of children older than 10 years. The incidence in adults at autopsy is 20% (Ajmani and Ajmani, 1983).

The incidence of metachronous development of an inguinal hernia is low. A meta-analysis by Miltenburg and colleagues (1997) of studies including patients in whom the patency status of the contralateral ring was unknown reported a 7% risk of developing a metachronous contralateral hernia, with 90% developing within 5 years of the initial repair. A systemic review by Ron and associates (2007) confirmed this incidence. Among 1291 children whose contralateral ring was deemed closed by transinguinal laparoscopy, 2.5% had a metachronous contralateral hernia 12.2 months (median) later (Juang et al, 2012), and at the time of unilateral laparoscopic hernia repair 3.1% of 293 children at a median of 24 months of age (range, 6 to 42 months) (Tam et al, 2013). Unfortunately, these studies offer indirect insight into the natural history of an open internal ring, and the question of the natural history of such a ring will remain unanswered until a prospective study of known open contralateral internal inguinal rings is conducted.

Abdominoscrotal Hydrocele

Abdominoscrotal hydroceles are uncommon, accounting for 1.25% of all hydroceles in a large series (Avolio et al, 2000), and are bilateral in about 30% of cases (Ferro et al, 1995; Nagar and Kessler, 1998; Belman, 2001; Bayne et al, 2008; Cozzi et al, 2008). These noncommunicating scrotal masses are tense and extend into the abdomen, where they may be palpable. Ultrasound may aid in defining the proximal extent (Belman, 2001). Abdominoscrotal hydroceles usually manifest in infancy as such or as scrotal hydroceles that enlarge over time (Celayir et al, 2001; Cuervo et al, 2009), improve (Cozzi et al, 2008), or resolve spontaneously (Upadhyay et al, 2006). Associated diagnoses include cryptorchidism, contralateral hernia, hydrocele, or vanishing testis.

The most likely cause is enlargement and extension of a scrotal hydrocele into the retroperitoneal or properitoneal space after closure of the processus. Bayne and associates (2008) found that abdominoscrotal hydrocele fluid was exudative and theorized that

Despite the aforementioned considerations, efforts have been made to reduce the size (Turial et al, 2011b) and number of ports and to apply the techniques to younger and more complex patients. Whereas the standard laparoscopic approach uses three ports, some authors report similar outcomes using two ports (Xu et al, 2013) or even a single port (Shen et al, 2010). Turial and associates (2011a) reviewed their experience in 147 infants who weighed 5 kg or less using either a 5-mm scope or a microlaparoscope and 2-mm instruments. The median operative time for the bilateral hernia was 20 minutes. Hernias recurred in 2%, with a higher risk for those with an American Society of Anesthesiologists (ASA) score of 3 or more. No cases of testicular atrophy occurred, and high testes requiring surgery occurred in 4%, which was inversely related to body weight. Esposito and associates (2010) performed outpatient laparoscopic inguinal hernia repair on 50 children younger than 1 year. After division of the sac distal to the ring, the peritoneum was closed using a purse-string suture of a nonabsorbable material. The median operating time was 22 minutes (unilateral, 7 to 30; bilateral, 12 to 42) with one recurrence. Recurrence rates may be lower in those younger than 1 year than in older children (Choi et al, 2012). Esposito and colleagues (2013) reported their experience with 46 patients with an incarcerated hernia (1 month to 8 years), of which over one half were irreducible. There were no conversions and two recurrences (4.3%) after a minimum follow-up of 14 months. They purport three main advantages of the laparoscopic approach: aversion of edematous tissue by bypassing the cord structures; bowel reduction performed under direct visual control; and inspection of the incarcerated organ at case end.

increasing size and pressure would lead to lymphatic obstruction and progression. Massive enlargement could extend into the upper abdomen and be associated with hydroureteronephrosis, lower extremity edema, or appendicitis (reviewed by [Cuervo et al, 2009](#)). [Chamberlain and colleagues \(1995\)](#) first reported dysmorphic elongation of the testis; this was subsequently confirmed ([Bayne et al, 2008](#)) but found to be reversible in most cases ([Cozzi et al, 2008](#)).

The traditional surgical approach is an inguinal incision with proximal dissection of the sac from its abdominal attachments and distal complete or partial mobilization, with or without orchidopexy. Some authors advocate orchidopexy to avoid iatrogenic cryptorchidism ([Nagar and Kessler, 1998](#); [Bayne et al, 2008](#)). Aspiration of the scrotal component may facilitate the proximal dissection ([Cuervo et al, 2009](#)). Alternative approaches include a midline abdominal approach for large bilateral cases ([Serels and Kogan, 1996](#)) or laparoscopic decompression of the abdominal component followed by inguinal excision ([Abel et al, 2009](#)). To avert injury to the spermatic cord or vas, a strip of the lining of the sac may be left along the cord ([Ferro et al, 1995](#); [Cuervo et al, 2009](#)). Tightening of a patulous internal ring is described, but may be unnecessary because the processus vaginalis is invariably closed.

[Belman \(2001\)](#) described a primary scrotal approach with drainage and extensive plication with limited dissection; excision is performed. [Cozzi and colleagues \(2008\)](#) reported reduced morbidity and similar efficacy for the scrotal (5 patients) approach compared with the inguinal approach (13 patients). Persistent scrotal swelling, hematoma, and undescended and/or hypoplastic testis was reported in 11 inguinal cases and infection in 2 scrotal cases.

ACUTE SCROTUM

Acute scrotum refers to the constellation of new onset of pain, swelling, and/or tenderness of intrascrotal contents. There is a limited differential diagnosis ([Box 146-2](#)) with considerable overlap of signs and symptoms, which may affect the ability to make a definitive diagnosis; some reliable clinical features exist, and adjunct use of scrotal imaging is helpful in making a diagnosis. **Torsion of the appendix testis is the most common diagnosis** (40% to 60%), followed by spermatic cord torsion (20% to 30% excluding neonates), epididymitis (5% to 15%), and other or no pathology (10%) ([Anderson and Giacomantonio, 1985](#); [Sidler et al, 1997](#); [Van Glabeke et al, 1999](#); [Mushtaq et al, 2003](#); [Murphy et al, 2006](#); [Mäkelä et al, 2007](#)). Although all of these diseases can occur at any time during childhood, appendage torsion is typically most common after infancy and before puberty, whereas epididymitis and spermatic cord torsion are most common in the perinatal and pubertal periods. Torsion of an appendage and epididymitis are managed conservatively with limited consequence; prompt surgical exploration for testicular torsion is imperative because the gonad is at considerable risk of ischemic damage or loss, particularly when there is a delay in presentation, evaluation, or management.

Spermatic Cord Torsion

Acute Intravaginal Spermatic Cord Torsion

Predisposing Factors. Intravaginal torsion is commonly attributed to excess mobility of the testis within a “bell-clapper deformity” wherein the tunica vaginalis abnormally fixes proximally on the cord. Although found in 12% of males at autopsy ([Caesar and Kaplan, 1994a](#)), the prevalence of torsion is much lower: 8.6 per 100,000 males aged 10 to 19 per year in the United States ([Mansbach et al, 2005](#)). There is evidence for a familial predisposition ([Cunningham, 1960](#); [Collins and Broecker, 1989](#); [Cubillos et al, 2011](#)) for which the transmission is unknown. [Cubillos and colleagues \(2011\)](#) found a family history (various relatives) in 10% of probands, including one family with three generations of torsion. **The inciting event for torsion is unknown** but may include cold temperature ([Srinivasan et al, 2007](#); [Lyronis et al, 2009](#); [Chiu et al, 2012](#)) or a change in temperature ([Chen et al, 2013](#)) activating the

BOX 146-2 Differential Diagnosis of Pediatric Adolescent Acute Scrotal Pain

Appendage torsion
Appendix testis
Other appendage (epididymis, paradidymis, vas aberrans)
Spermatic cord torsion
Intravaginal, acute or intermittent
Extravaginal
Epididymitis
Infectious
Urinary tract infection
Sexually transmitted disease
?Viral
Sterile or traumatic
Scrotal edema or erythema
Diaper dermatitis, insect bite, or other skin lesions
Idiopathic scrotal edema
Orchitis
Associated with epididymitis with or without abscess
Vasculitis (e.g., Henoch-Schönlein purpura)
Viral illness (mumps)
Trauma
Hematocoele or scrotal contusion or testis rupture
Hernia or hydrocele
Inguinal hernia with or without incarceration
Communicating hydrocele
Encysted hydrocele with or without torsion
Associated with acute abdominal pathology (e.g., appendicitis, peritonitis)
Varicocele
Intrascrotal mass
Cystic dysplasia or tumor of testis
Epididymal cyst, spermatocele or tumor
Other paratesticular tumors
Musculoskeletal pain from inguinal tendonitis or muscle strain
Referred pain (e.g., ureteral calculus or anomaly)

cremasteric reflex, and/or rapid testicular growth at puberty; yet torsion may occur at rest or at sleep. Cryptorchid testes are at increased risk of torsion and difficult to assess because of the high position. Torsion after previous orchidopexy may be related to failure of suture (absorbable or nonabsorbable suture) to fix the testis in place ([Redman and Barthold, 1995](#); [Frank and O'Brien, 2002](#); [Mor et al, 2006](#)).

Clinical Presentation. Intravaginal testicular torsion may occur at any age, but the vast majority of cases occur after age 10 years with a peak at 12 to 16 years ([Anderson and Giacomantonio, 1985](#); [Sidler et al, 1997](#); [Mushtaq et al, 2003](#); [Mansbach et al, 2005](#); [Murphy et al, 2006](#); [Mäkelä et al, 2007](#)). The prevalence of testicular torsion is 1 in 4000 ([Williamson, 1976](#)) with left-sided predominance and rare bilaterality. Classically, boys complain of acute, severe scrotal pain that occurs at rest (even sleep), or with physical activity or after trauma. **A history of prior episodes may be elicited.** Alternatively, patients may have milder, less acute, or even absent scrotal pain or may have inguinal or abdominal pain. Nausea and vomiting occur in 10% to 60% of boys ([Williamson, 1976](#); [Knight and Vassy, 1984](#); [Jefferson et al, 1997](#); [Sessions et al, 2003](#); [Mäkelä et al, 2007](#)). Scrotal edema and erythema may be present, depending on the duration or degree of torsion. Dysuria and fever are uncommon.

The most common physical findings are generalized testicular tenderness, abnormal orientation of the testis, and absent cremasteric reflex. Inspection may identify the high-riding testis from a

foreshortened cord and horizontally oriented testis. The genitofemoral reflex arc, normally present after age 2 years (Caesar and Kaplan, 1994b), is elicited by scratching the inner thigh with resultant testis elevation. Some studies report reduced or absent reflex in all cases of testicular torsion (Caldamone et al, 1984; Rabinowitz, 1984; Kadish and Bolte, 1998), but it was intact in up to 10% of proven cases of torsion in other series (Hughes et al, 2001; Nelson et al, 2003; Karmazyn et al, 2005; Murphy et al, 2006). The presence of a cremasteric reflex correlates with intact testicular blood flow but does not unequivocally indicate normal testicular perfusion, especially if the clinical presentation is otherwise suggestive of torsion. Although anterior epididymal position, thickening of the cord, testicular induration, loss of boundaries between the testis and epididymis, scrotal edema, and/or erythema may be present, landmarks become obliterated and the examination less reliable as the duration of torsion increases.

Several efforts have been made to offer a better clinical assessment of testicular torsion in patients with the acute scrotum. Using a standardized history and physical examination form, Srinivasan and colleagues (2011) found that absence of ipsilateral cremasteric reflex, nausea or vomiting, and scrotal skin changes on multivariate analysis were predictive of testicular torsion. According

to use of a decision tool, patients with acute (<72 hours) scrotal pain and all of the following had no risk of testicular torsion (100% sensitivity and negative predictive value): normal testicular lie, lack of nausea and vomiting, and age 0 to 10 years (Shah et al, 2013). Barbosa and colleagues (2013) developed a scoring system based on testicular swelling, hard testicle, absent cremasteric reflex, nausea or vomiting, and high-riding testis that needs further validation.

Diagnostic Studies. Urinalysis is of limited usefulness in cases of testicular torsion but is used to identify pyuria and/or bacteriuria associated with epididymitis, or hematuria, implicating a urinary tract calculus. Before the advent of reliable and rapid scrotal imaging, immediate scrotal exploration was routine. Radionuclide imaging carried about 90% sensitivity and specificity but was lengthy, was not readily available, and used ionizing radiation and is currently rarely used. Ultrasound offered a rapid, available, and safe modality to assess testicular architecture, intraparenchymal blood flow, and other anatomic details (hydrocele, scrotal thickening).

CDUS findings consistent with testicular torsion include reduced or absent Doppler color or waveforms and parenchymal heterogeneity compared with the contralateral testis (Fig. 146-27). Kaye and

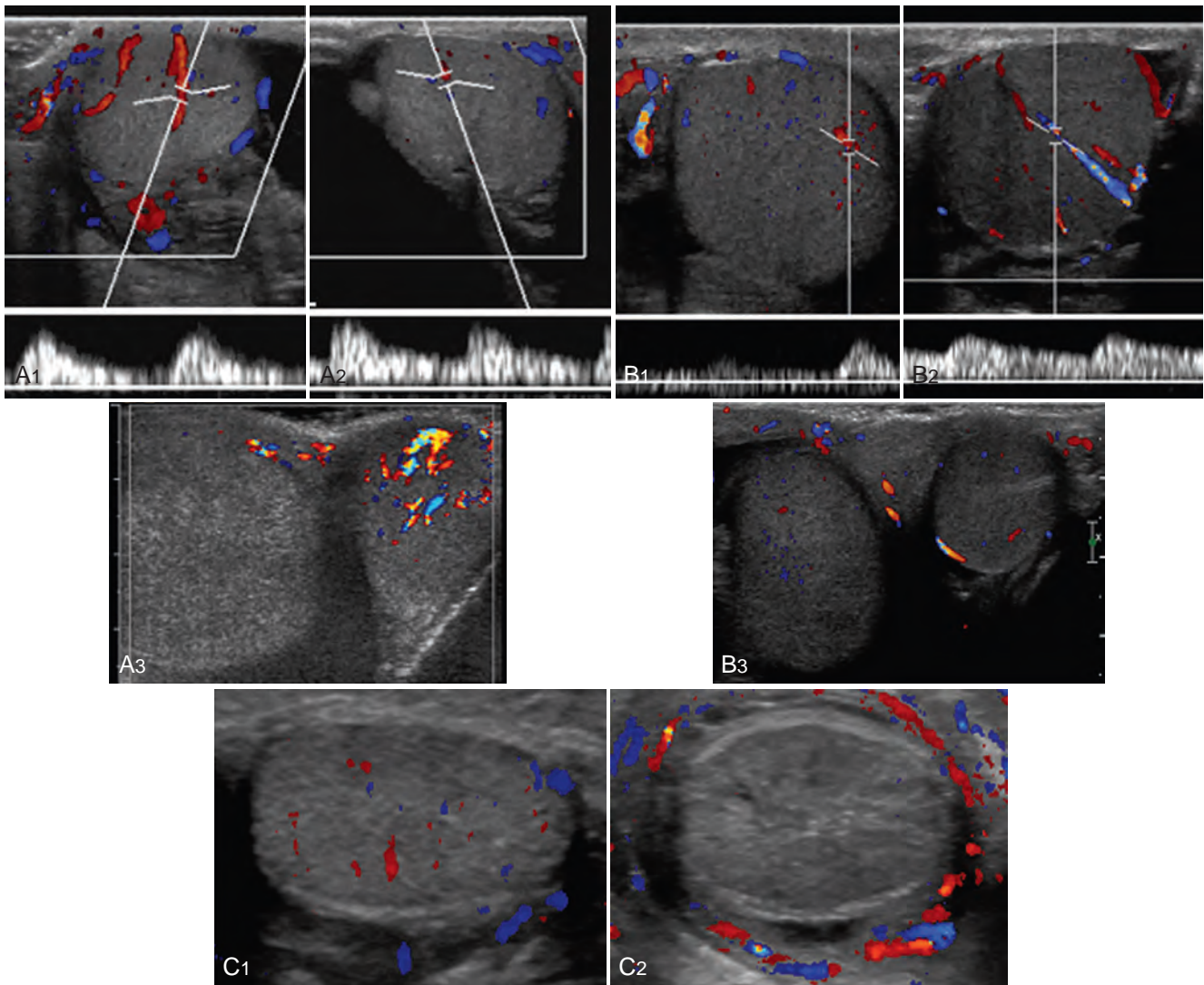


Figure 146-27. Imaging of intravaginal spermatic cord torsion. **A**, Intermittent torsion. Color Doppler ultrasonography (CDUS) demonstrates preserved arterial flow to testis with 12 hours of pain and then loss of flow and parenchymal heterogeneity when child returned later with worsening pain. **B**, Acute torsion with reduced arterial flow. **C**, Prolonged torsion. CDUS shows heterogeneous testis without arterial or venous flow and a hyperechoic parenchymal ring.

colleagues (2008b) and later Chmelnik and colleagues (2010) found that all testes with heterogeneous echogenicity were necrotic, whereas homogeneous echogenicity predicted a lower risk of orchiectomy. Lack of demonstrable intratesticular flow on CDUS is 86% sensitive, 100% specific, and 97% accurate in the diagnosis of torsion and ischemia in painful scrotum (Burks et al, 1990) and its use spread (Kass et al, 1993b), and even current studies reflect the accuracy of this approach. Altinkilic and colleagues (2013) prospectively assessed the diagnostic value of CDUS in patients with clinical suspicion of torsion who were explored by a surgeon blinded to the CDUS results. The sensitivity, specificity, and positive and negative predictive values of CDUS for detecting testicular torsion were 100%, 75.2%, 80.4%, and 100%, respectively. The authors concluded that routine surgical exploration was unnecessary if CDUS reveals normal intratesticular perfusion. However, in other studies the sensitivity in confirming decreased or absent blood flow in proven cases of spermatic cord torsion was only 63% to 90%, possibly because of enhanced detection of flow with newer equipment and/or user-dependent characteristics (Steinhardt et al, 1993; Stehr and Boehm, 2003; Bentley et al, 2004; Kalfa et al, 2004; Karmazyn et al, 2005). Cassar and colleagues (2008) evaluated Doppler waveforms in cases of torsion with decreased or preserved testicular flow and observed subtle waveform abnormalities, including increase or decrease in amplitude relative to the normal testis and reversal of diastolic flow. Increased epididymal size and/or echogenicity and altered epididymal vascularity, usually absent or reduced but occasionally increased, may provide additional support for the diagnosis of torsion (Nussbaum Blask and Rushton, 2006).

High-resolution (10- to 20-MHz probe) ultrasonography (HRUS) of the length of the spermatic cord may enhance the ability to diagnose torsion. Using HRUS to directly image the cord proximal to the testis, Kalfa and colleagues (2004) visualized the cord twist as a 1- to 3-cm snail-shaped mass in 43 patients and a completely linear cord in nontorsion cases. In a multi-institutional retrospective series of 919 cases of acute scrotum with cord imaging by HRUS, a cord twist was seen in 96% of cases of surgically proven torsion, and HRUS carried 99% specificity when the cord was linear (Kalfa et al, 2007). However, Karmazyn and coworkers (2005) observed normal testicular blood flow and no visible spermatic cord twist in 2 of 41 boys with partial or intermittent torsion.

Potentially useful diagnostic modalities include contrast-enhanced pulse-inversion ultrasonography (CEUS), infrared thermography, and scrotal MRI. Pulse-inversion imaging in a rabbit model showed superior quantitative assessment of perfusion of the experimentally torse testis as compared with conventional CDUS (Paltiel et al, 2006). CEUS was performed in 50 patients with acute scrotal pain or trauma in whom testicular lesion of undefined nature was found at CDUS. Sensitivity and specificity were 76% and 45% for CDUS and 96% and 100% for CEUS, respectively (Valentino et al, 2011). Infrared thermography showed significant reduction in scrotal temperature by 1 hour after 720-degree torsion and prompt normalization with detorsion in a sheep model (Capraro et al, 2008). MRI has been used in small series of testicular torsion and may have a role in difficult diagnostic cases with use of dynamic contrast-enhanced MRI, which requires gadolinium (Mäkelä et al, 2011), or diffusion-weighted imaging with findings of a lower testicular apparent diffusion coefficient (ADC) without need for contrast (Maki et al, 2011).

Management and Surgical Treatment

Testicular torsion is a true surgical emergency because testis viability is inversely related to duration of torsion. Visser and Heyns (2003) amassed data from published series including 1140 patients and found the risk of orchiectomy was approximately 5%, 20%, 40%, 60%, 80%, and 90% at 0 to 6, 7 to 12, 13 to 18, 19 to 24, more than 24, and more than 48 hours after onset of pain, respectively. The degree of torsion may provide incomplete vascular occlusion, helping to explain the variability of these data. Orchiectomy after surgical detorsion occurs in 30% to 70% in large

studies (Sessions et al, 2003; Murphy et al, 2006; Mäkelä et al, 2007; Kaye et al, 2008b) and in 32% to 42% in database reviews (Mansbach et al, 2005; Cost et al, 2011; Zhao et al, 2011). Sessions and associates (2003) found that the median degree of rotation was 540 degrees in orchiectomy testes and 360 degrees when the testis was salvaged, with a range of 180 to 1080 degrees in both groups. The risk of delayed atrophy after orchidopexy was less than 10%, 40%, and 75% after less than 12, 12 to 24, and more than 24 hours of pain, respectively (Visser and Heyns, 2003). Partial (<25%) testicular atrophy may occur after operative detorsion even after 4 hours after the onset of pain (Krupar, 1978; Anderson and Williamson, 1986; Tryfonas et al, 1994; Sessions et al, 2003). Preoperative manual cord detorsion may relieve symptoms and allow delayed orchidopexy but may incompletely untwist the cord. Sessions and associates (2003) found that lateral twisting (rather than medial untwisting) occurred in 33% and manual detorsion failed to completely relieve torsion in 32% of orchidopexy cases.

There are two management approaches to the acute scrotum. One is to avoid delay and perform exploration in virtually all boys to confirm absence of torsion; this implies many unnecessary surgeries (Anderson and Giacomantonio, 1985; Watkin et al, 1996; Sidler et al, 1997; Mushtaq et al, 2003; Mäkelä et al, 2007). The other approach is more selective of patients for surgical exploration (Caldamone et al, 1984; Kass et al, 1993b; Kalfa et al, 2004; Lam et al, 2005) based on the history, physical examination, and CDUS findings, which may lead to testis loss because of atypical presentation and/or false-negative imaging. **When findings support or raise suspicion for spermatic cord torsion, emergent scrotal exploration is indicated and should not be delayed.**

Surgical exploration of the testis through a hemiscrotal transverse (dartos pouch) or midline raphe incision should first address the affected side. The testis is delivered and the tunica vaginalis opened to note the color of the testis, the number of rotations, and the anatomy of the tunica vaginalis. The testis is untwisted, wrapped in warm soaked gauze, and observed for improvement in color while the contralateral testis is fixed with nonabsorbable suture to reduce the risk of metachronous torsion. The affected testis is re-examined for potential viability, and the largely subjective decision for orchidopexy or orchiectomy is made. A Doppler flow probe or incision of the tunica albuginea (Arda and Ozyaylali, 2001) with assessment of bleeding may document intratesticular flow after detorsion; however, the reliability of these assessments lacks validation. If the testis is to be retained, it is fixed either via dartos pouch or directly to the dartos with nonabsorbable suture. Kutikov and colleagues (2008) have suggested that a compartment syndrome contributes to testicular injury based on the improved appearance and lower intraparenchymal pressures seen after detorsion and tunica albuginea incision in three cases. A patch of vascularized tunica vaginalis was placed in the tunica albuginea defect to maintain lower intraparenchymal pressure and to reduce the likelihood of ongoing ischemia. Figueroa and colleagues (2012) applied this technique to 11 of 28 testes deemed nonsalvageable at surgery and found that 55% recovered. The long-term outcome of these patients is not available; however, in a rat model of testicular torsion, no significant histologic differences were found between a detorsion group and detorsion with tunica vaginalis flap group after 4 weeks, despite reduction of intratesticular pressure in both groups (Oktar et al, 2013).

Risk factors for orchiectomy include young age, African-American race, and being on Medicaid or lacking insurance (Cost et al, 2011; Zhao et al, 2011). Zhao and colleagues (2011) identified surgery at a children's unit to increase the risk of orchiectomy. This may reflect the transfer of patients, which delayed treatment by 75 minutes in the study by Bayne and colleagues (2010). Orchiectomy is performed by dividing the cord into segments, each of which is ligated with nonabsorbable suture. In cases of orchiectomy, prosthesis placement is usually offered after complete healing or later in puberty; however, Bush and Bagrodia (2012) demonstrated the feasibility of performing concurrent prosthetic placement and orchiectomy.

Prognosis

Although the impact of testicular torsion on fertility is poorly understood given the inherent difficulty of long-term follow-up in these patients, the few available studies suggest that subtle abnormalities of semen quality are common. **Semen density is often within the normal range but correlates with shorter duration of torsion and reduced atrophy** (Puri et al, 1985; Fisch et al, 1988; Anderson et al, 1992; Brasso et al, 1993; Arap et al, 2007). The observation that increasing duration of torsion inversely correlates with semen quality and limited contralateral testicular biopsy data suggest that global testicular dysfunction may exist after torsion (Visser and Heyns, 2003). The hypothesis of an autoimmune phenomenon (Anderson and Williamson, 1990) was dispelled by analysis of antisperm antibodies in individuals with torsion (Puri et al, 1985; Anderson et al, 1992; Brasso et al, 1993; Arap et al, 2007). Available animal and human data support a role for ischemia-reperfusion injury after release of testicular torsion (Kehinde et al, 2003; Turner et al, 2004). Additional clinical data are needed to determine long-term outcome after testicular torsion and the efficacy of any adjunctive treatment. Romeo and colleagues (2010) assessed serum levels of FSH and LH (before and after GnRH stimulation), testosterone, and inhibin B in 20 patients 5 years (mean) after testicular torsion and in 15 age-matched controls. Twelve patients were treated with detorsion and orchidopexy, and 8 underwent orchidectomy. Serum FSH, LH, and testosterone were within the reference range. Inhibin B levels were significantly reduced in the two torsion groups compared with the controls but not between each other.

Intermittent Intravaginal Spermatic Cord Torsion

Episodes of self-limited acute scrotal pain precede acute testicular torsion in 30% to 50% of patients (Williamson, 1976; Stillwell and Kramer, 1986). These episodes, single or multiple, typically begin and resolve acutely with durations of minutes to hours. Hayn and associates (2008) observed that the frequency of these episodes correlated with the risk for eventual persistent torsion and testicular loss; 71% of patients were previously diagnosed with epididymitis or appendage torsion, and 53% had acute or delayed testicular loss. Nausea and/or vomiting or notation of scrotal swelling may or may not be present. A normal vertical testicular orientation is most common (Hayn et al, 2008), but a horizontal lie may be present (Schulsinger et al, 1991). Physical findings consistent with torsion depend on whether the testis is twisted at the time of the examination. This includes the degree of tenderness and cremasteric reflexes. Eaton and colleagues (2005) reported absent cremasteric reflex in 3 of 15 patients and reduced or absent intratesticular blood flow by CDUS in only 5 of 12 patients. A whirlpool sign or an abnormal boggy cord and pseudomass formation below the twisted spermatic cord may also signify intermittent torsion (Munden et al, 2013).

There are challenges to confirming the diagnosis of intermittent torsion. **The diagnosis requires a high index of suspicion unless the testis is noted to untwist during an examination or an ultrasound study shows absent or decreased flow before and normal to increased flow after marked improvement of symptoms.** Once the condition is confirmed or highly suspected, **elective bilateral orchidopexy is indicated** to avert torsion and possible organ loss. Patients and parents should know that absolute confirmation of the diagnosis may not be possible and that symptoms may persist postoperatively.

Extravaginal Spermatic Cord Torsion (Perinatal Testicular Torsion)

Perinatal spermatic cord torsion is a term applied to infants regardless of whether the event occurred prenatally (hours, days, weeks, months), during delivery, or postpartum. Torsion of the entire cord occurs before fixation of the tunica vaginalis and dartos within the scrotum (extravaginal). This event most commonly occurs well

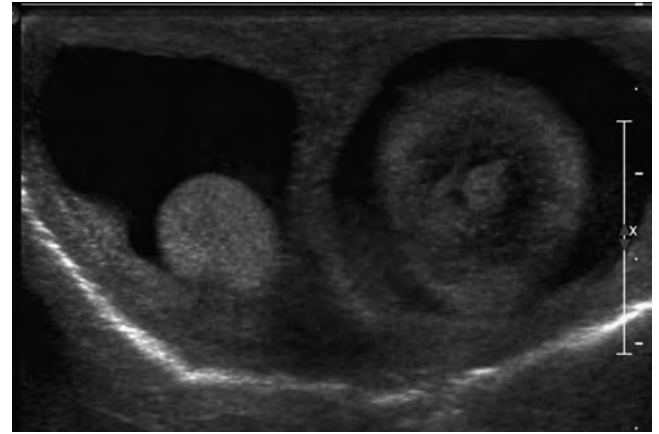


Figure 146-28. Extravaginal spermatic cord torsion in a neonate. Transverse ultrasound image demonstrates enlarged and heterogeneous left testis and bilateral hydroceles.

before delivery, yielding a “vanishing” testis or a hemosiderin-containing nubbin in the scrotum or less commonly in the inguinal canal. The testis that sustains loss of blood supply close to delivery is a hard, painless testis fixed to the overlying erythematous or dark scrotal skin with or without edema. A coexisting hydrocele complicates the examination. The estimated incidence is 6.1 per 100,000 births (John et al, 2008), and familial cases are reported (Castilla et al, 1975). Predisposing factors such as high birth weight and/or difficult delivery are suggested (John et al, 2008; Kaye et al, 2008a) but unconfirmed by controlled studies. In a minority of cases, symptoms occur after a documented normal scrotal examination. Rarely, neonatal intravaginal torsion occurs or infarction occurs without torsion (John et al, 2008). Bilateral torsion was noted in 5% and 22% in two series (Yerkes et al, 2005; Baglaj and Carachi, 2007) and may occur concurrently or metachronously. Several series indicate that bilateral metachronous torsion may occur in boys in whom the primary event occurs prenatally or postnatally (Beasley and McBride, 2005; Yerkes et al, 2005; Al-Salem, 2007; John et al, 2008).

Scrotal imaging may be obtained in cases of suspected perinatal torsion, but its usefulness and reliability are questionable. Prenatal ultrasonography may show torsion (Herman et al, 2002). Postnatal ultrasound may reveal parenchymal heterogeneity, calcification, and absent blood flow (Fig. 146-28) (Arenas et al, 2006). Reported cases of testicular blood flow suggest that postnatal CDUS may be unreliable (Yerkes et al, 2005; Al-Salem, 2007; Cuervo et al, 2007; John et al, 2008). Ultrasound helps to differentiate tumors from torsion (Kaye et al, 2008a), but its reliability in this has also been challenged (Calonge et al, 2004; Al-Salem, 2007).

There is no consensus as to the best treatment of perinatal testicular torsion (Snyder and Diamond, 2010). One side advocates elective exploration because of the unsalvageability in most cases, the rarity of metachronous torsion, and the increased anesthetic risk (Das and Singer, 1990; Brandt et al, 1992; Stone et al, 1995; Kaye et al, 2008a). Others advocate for immediate exploration to offer possible partial or complete testicular salvage (Sorensen et al, 2003; Al-Salem, 2007; Cuervo et al, 2007) and point to cases of unexpected contralateral torsion or atrophy found at exploration (Yerkes et al, 2005; Al-Salem, 2007; Baglaj and Carachi, 2007; John et al, 2008; Roth et al, 2011). Among 110 pediatric surgeons and urologists surveyed in the United Kingdom and Ireland, few (10.9%) used Doppler ultrasound to guide management or to exclude tumor. Although most (74.5%) performed ipsilateral orchiectomy and contralateral orchidopexy (71.9%), few operated emergently because a viable testis was seldom found (10%) and bilateral torsion was even rarer (7 cases). Some (21.8%) avoided contralateral orchidopexy owing to concern for iatrogenic injury (Rhodes et al, 2011). If torsion is suspected after a normal postnatal scrotal examination, then prompt exploration should be performed as

for intravaginal torsion. Some surgeons use a scrotal approach, whereas others advocate an inguinal approach to ligate a patent processus vaginalis and avoid the theoretic risk of trans-scrotal surgery if a tumor is found.

Torsion of the Appendix Testis and Epididymis

Appendage torsion is the most common cause of acute scrotum in prepubertal children. The appendix testis and appendix epididymis are vestiges of embryologic development without known function. The appendix testis (from the müllerian duct) and appendix epididymis (from the wolffian duct) are present in 76% to 83% and 22% to 28% of testes, respectively (Dresner, 1973; Jacob and Barteczko, 2005). The appendix testis, located at the cranial testicular pole or in the groove between the testis and epididymis, and the appendix epididymis, located along the caput, may be sessile or pedunculated. Although the sessile type may be more common (Jacob and Barteczko, 2005), the pedunculated type may be more prone to torsion (Jones, 1962). The cause of torsion is unknown but may be related to anatomy, trauma, and/or prepubertal enlargement.

The peak age at occurrence is 7 to 12 years (mean 8 to 9 years) (Anderson and Giacomantonio, 1985; Mushtaq et al, 2003; Lyronis et al, 2009), but the condition may occur at any age. Symptoms vary with sudden or insidious onset of pain, which may be mild or severe and intermittent with physical activity. Similarly, physical findings depend on the severity of inflammation and duration of symptoms (Rakha et al, 2006). Early on, a “blue dot sign” (Dresner, 1973), a discoloration at the upper pole of the testis representing the ischemic appendage, may be seen through stretched scrotal skin in 0% to 52% of patients (Caldamone et al, 1984; Van Glabeke et al, 1999; Karmazyn et al, 2005; Murphy et al, 2006; Lyronis et al, 2009). Murphy reported a false-positive blue dot sign in a patient with testicular torsion (Murphy et al, 2006). Other early signs include a tender nodule superior to the testis with limited testicular tenderness and symmetrical cremasteric reflexes. However, with longer duration and progressive inflammation, increased swelling and tenderness, lack of distinction between testis and epididymis, and marked scrotal wall edema and erythema may make it difficult to distinguish it from testis torsion or epididymitis.

CDUS rarely demonstrates an abnormal appendage but commonly shows hyperperfusion of the epididymis (Baldiasserotto et al, 2005). The normal appendix testis contains no internal blood flow (Yang et al, 2005), whereas the twisted appendage may appear as an ovoid hyperechoic, hypoechoic, or heterogeneous nodule without blood flow (Fig. 146-29). Park and colleagues (2011) found significant differences in the echogenicity correlated with the duration of symptom: hypoechoic in all 17 boys assessed within 24 hours of symptom onset and hypoechoic (6), isoechoic (4), or hyperechoic (8) after 24 hours.

Because torsion of an appendage is a self-limited process (Koff and De Ridder, 1976), surgery is rarely indicated. Treatment is aimed at reducing inflammation using ice packs and oral anti-inflammatory agents, and limiting physical activity. Surgical exploration is limited to cases in which torsion of the testis is not excluded or, rarely, there is prolonged and severe pain or recurrent episodes.

Epididymitis

Epididymitis, infectious or noninfectious, is a broad category causing an acute scrotum. The incidence is poorly defined (Lau et al, 1997; Merlini et al, 1998; Cappele et al, 2000; Somekh et al, 2004; Al-Taheini et al, 2008; Sakellaris and Charissis, 2008), perhaps because children with a torsed appendage may be diagnosed with epididymitis (Kadish and Bolte, 1998; Lam et al, 2005; Lyronis et al, 2009). In many series, peaks in prevalence occur in infancy and at puberty (Sidler et al, 1997; Mushtaq et al, 2003; Mäkelä et al, 2007).

Classically, the symptoms have a more insidious onset than torsion of the cord or an appendage but may be present rapidly. Fever and dysuria may or may not be present, and nausea is rare. A history of UTIs, urethral discharge, sexual activity, intermittent catheterization (Thirumavalavan and Ransley, 1992), dysfunctional voiding (Bukowski et al, 1995), urethral abnormalities (Karmazyn et al, 2009), or congenital anomalies of the ejaculatory duct (Pimpalwar et al, 2002; Yanai et al, 2005) may be present. There is a continuum on examination from localized epididymal enlargement and tenderness to massively swollen and erythematous hemiscrotum without distinct landmarks. The cremasteric reflex should be intact. Associated pyuria and/or bacteriuria is reported in 20% to 40% of cases (Anderson and Giacomantonio, 1985; Sidler et al, 1997; Mushtaq et al, 2003; Murphy et al, 2006; Mäkelä et al, 2007). CDUS shows increased epididymal size and blood flow as well as in the testis in some cases.

The management goal is to relieve inflammation and any associated infection. Efforts to reduce the inflammation include the use of ice packs, nonsteroidal anti-inflammatory agents, scrotal elevation, and rest to avoid traumatic exacerbation. In the absence of UTI, symptoms improve spontaneously without antibiotics (Lau et al, 1997). In the presence of pyuria, broad-spectrum antibiotics with gram-negative coverage should be used (Siegel et al, 1987), and in some cases intravenous antibiotics and hospitalization may be required. Treatment for sexually transmitted diseases should be considered, as appropriate, in adolescents.

The need to image the urinary tract has become more selective. Siegel and colleagues (1987) found that 47% of prepubertal boys had anomalies (urethral anomalies, ureteral ectopia) on imaging. Other clinical series have documented a low risk of urinary tract

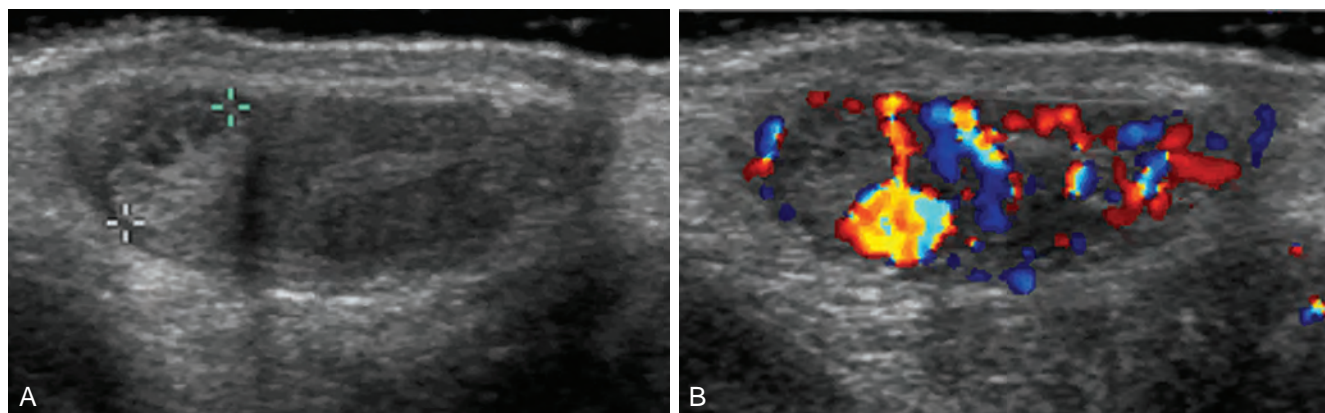


Figure 146-29. Torsion of testicular appendage. Color Doppler ultrasonography demonstrates (A) enlarged and heterogeneous appendage and (B) absent flow despite increased flow to the epididymis and testis.

anomalies in boys with epididymitis, although infants may be at higher risk (Merlini et al, 1998; Sakellaris and Charissis, 2008). Although some findings (pyelectasis, low-grade vesicoureteral reflux) may not directly contribute to epididymitis, other findings (urethral or ureteral obstruction, ejaculatory duct, or vasal anomalies) are important to detect. Some authors recommend renal ultrasonography only (Al-Taheini et al, 2008) or imaging only in recurrent cases (Cappele et al, 2000). However, in a prepubertal child with a positive urine culture, renal ultrasonography and voiding cystourethrography are indicated. In recurrent cases, endoscopy may reveal ejaculatory duct abnormalities undetected on voiding cystourethrography (Pimpalwar et al, 2002; Yanai et al, 2005). Recurrent epididymo-orchitis in these cases may require excision of a utricle or ejaculatory duct cyst with vasovasostomy or vasectomy.

Other Causes of Acute Scrotal Pain

Idiopathic scrotal edema manifests in prepubertal boys with unilateral or bilateral scrotal swelling with minimal or no pain (Klin et al, 2002; Lee et al, 2009). Associated findings may include local spread of erythema or edema to the inguinal or perineal region, inguinal lymphadenopathy, leukocytosis, and/or eosinophilia. The last suggests an allergic origin, although the cause is currently idiopathic. Distinctive characteristics include minimal or no pain, isolated scrotal tenderness, and thickening of the scrotal wall. Because the process is self-limited, no treatment is needed, except perhaps for antihistamines.

Henoch-Schönlein purpura is a systemic vasculitis affecting the skin, joints, gastrointestinal tract, and kidneys. The scrotum is involved in 2% to 38% of cases in the form of tenderness, edema, erythema; testicular hematoma, torsion, or infarction; or cord thrombosis or epididymitis (Turkish et al, 1976; Diana et al, 2000; Ioannides and Turnock, 2001). The typical purpuric rash of the buttocks, perineum, and lower limbs is usually present but may not precede the scrotal findings. Urgent scrotal exploration is indicated if clinical findings suggest concomitant testicular torsion.

Cystic dysplasia of the rete testis may present as acute scrotal swelling and pain (Noh et al, 1999; Smith et al, 2008; Jeyaratnam and Bakalnova, 2010). Rarely, an associated ureteral anomaly may lead to chronic testicular pain (McGee et al, 2009). Ipsilateral renal dysplasia, agenesis, or ureteral anomalies are present in the majority of cases and likely represent maldevelopment of the wolffian duct. Ultrasound will reveal multiple small cysts centrally located in the testis. Treatment is conservative enucleation, which may be associated with recurrence, or observation, which is associated with regression in some cases.

Testicular rupture from trauma may cause acute scrotal pain and swelling and hematocele. CDUS is sensitive in diagnosing testicular fracture. Surgical intervention may be indicated (Adams et al, 2008), or a conservative approach may be considered (Cubillos et al, 2010), reserving surgery for cases of expanding hematoma, symptomatic hydrocele, intractable pain, absent blood flow, or abscess. In their series, Cubillos and colleagues reported excellent outcomes and testis salvage; slow resumption of all physical activities was reported by a minority of patients in this small cohort.

VARICOCELE

Varicocele, an abnormal dilation and tortuosity of the internal spermatic veins within the pampiniform plexus, is common among adolescents and may contribute significantly to the risk of subfertility in adulthood. Its effect on paternity is less clear because about 85% of men with varicocele in population-based studies have fathered children (Pinto et al, 1994; Safarinejad, 2008; Bogaert et al, 2013).

Epidemiology and Pathogenesis

The prevalence of clinically diagnosed varicoceles in adolescents is 8% to 16%, which is similar to the 15% prevalence rates in

adults (Niedzielski et al, 1997; Skoog et al, 1997; Akbay et al, 2000; Stavropoulos et al, 2002; Kumanov et al, 2008; Zampieri and Cervellione, 2008). Thus, the group of adolescents identified as having a varicocele is presumed to be the same group identified as adults, because varicoceles are not known to resolve spontaneously and rarely manifest in older adults.

The frequency and severity of varicoceles vary with age, method of diagnosis, and Tanner development stage. Most varicoceles appear after 10 years of age, progress through puberty, and peak at Tanner stage 3 (Kumanov et al, 2008). Although historically varicoceles were predominantly left sided, recent reports indicate that identification of right-sided varicoceles in boys is increasing. Bilateral palpable varicoceles were repaired in one third of 10- to 24-year-old males by Decastro and colleagues (2009), and CDUS identified subclinical left or bilateral varicoceles in 7% to 17% of cases (Akbay et al, 2000; Pfeiffer et al, 2006; Cervellione et al, 2008). Woldu and associates (2013) identified retrograde blood flow in the right side of 40.3% of 503 adolescents with palpable left-sided varicoceles, of which 44% were subclinical. The clinical implication of these subclinical right-sided varicoceles is unclear. In adults, bilaterality is reported in 15% to 50% of cases (Zini and Boman, 2009).

The pathophysiology of the adolescent varicocele is likely to be multifactorial. The primary factors are believed to be increased venous pressure in the left renal vein, collateral venous anastomoses, and valvular incompetence of the left internal spermatic vein at its junction with the left renal vein. Varicocele progression may be related to continuous or spontaneous rather than Valsalva-induced spermatic venous reflux (Pfeiffer et al, 2006; Cervellione et al, 2008; Zampieri and Cervellione, 2008). The “nutcracker phenomenon” (compression of the left renal vein between the aorta and superior mesenteric artery) may account for the varicocele in some boys (Coolsaet, 1980; Kim et al, 2006). The reports by Sakamoto and Ogawa of higher peak and antegrade flow and venous diameter in the prostatic venous plexus of men with bilateral varicoceles versus controls and men with unilateral varicoceles (Sakamoto and Ogawa, 2008) and those showing increased risk of saphenofemoral junction incompetence (Karadeniz-Bilgili et al, 2003) and varicose veins (Kilic et al, 2007) reflect a more generalized venous abnormality in cases of varicocele. Genetic factors may contribute to the risk; the presence of a varicocele was fourfold to eightfold higher among first-degree relatives of men undergoing vasectomy or male kidney donors, and the incidence was especially high in brothers (Raman et al, 2005; Mokhtari et al, 2008). A tall, thin body habitus (low body mass index [BMI]) is associated with varicoceles in adolescents and adults (Handel et al, 2006; May et al, 2006b; Nielsen et al, 2006; Kumanov et al, 2008; Tsao et al, 2009), perhaps because of increased spermatic vein length and/or hydrostatic pressure, or perhaps resulting from difficulty in identification during physical examination.

Diagnosis and Classification

The vast majority of varicoceles in children and adolescents are identified incidentally by a primary care practitioner. On presentation, some adolescents have made the identification of an abnormality on self-examination or, less commonly (2% to 11%), have concerns regarding discomfort (Zampieri et al, 2008a).

The patient should be examined in both the supine and standing positions. The scrotum is inspected for visible swelling, followed by palpation of the spermatic cord at rest and during the Valsalva maneuver. The clinical grading system defines varicoceles as *grade 0* (subclinical), nonpalpable and visualized only by CDUS; *grade 1*, palpable only with Valsalva maneuver; *grade 2*, easily palpable but not visible; and *grade 3*, easily visible. The veins should decompress in the supine position; failure to do so, particularly on the right side, warrants evaluation (CT or sonogram) for an abdominal or pelvic mass (Roy et al, 1989). Testicular consistency should be assessed; the affected testis may be soft. Measurement of testicular volume is important because it may predicate surgical

TABLE 146-4 Testicular Volumes Based on Tanner Stage

TANNER STAGE	DANIEL ET AL, 1982				ZACHMANN ET AL, 1974	
	LEFT TESTIS (cm ³)		RIGHT TESTIS (cm ³)		TOTAL (mL)	
	MEAN	SD	MEAN	SD	MEAN	SD
1	4.8	2.8	5.2	3.9	6.0	2.6
2	6.4	3.2	7.1	3.9	6.8	3.6
3	14.6	6.5	14.8	6.1	9.3	3.8
4	19.8	6.2	20.4	6.8	12.6	4.2
5	28.3	8.5	30.2	9.6	16.3	4.6
6					18.9	4.0

SD, standard deviation.

intervention. The volumes should be assessed based on Tanner stage (Table 146-4). Volume can be determined using the Prader orchidometer (chain of 12 solid wooden ellipsoids of increasing volumes that are visually compared with the size of each testis), the Takihara orchidometer (15 elliptical rings with inner dimensions corresponding to ellipsoid volumes placed over the widest testis circumference), or by ultrasound (measure length, width, and depth and use one of several formulas). All three techniques are reliable, but **ultrasound is more sensitive in determining differences in left and right testicular size** (Costabile et al, 1992; Chipkevitch et al, 1996; Diamond et al, 2000). In a canine study, the use of ultrasound and the Lambert formula provided the most accurate and precise testicular volume estimates (Paltiel et al, 2002).

The ultrasound criteria for diagnosing a varicocele—spermatic vein diameter and retrograde blood flow—are controversial in adults and more so in adolescents. Niedzielski and colleagues (1997) measured spermatic vein diameter in the standing position and spermatic venous reflux with Valsalva maneuvers in 625 boys with varicoceles and 50 normal controls. They found normal spermatic vein diameter (<2 mm in normal boys) in 95%, 70%, and 4% of boys with grades 1, 2, and 3 varicocele and spermatic venous blood reflux in two thirds of boys with grade 2 or 3 varicoceles; flow velocity measured while the patient was standing correlated with varicocele grade and sperm motility. Kozakowski and associates (2009) found that spermatic venous diameter measured in the supine position was a poor criterion for clinical varicocele and did not predict risk of testicular volume loss, but that peak retrograde spermatic vein flow with Valsalva maneuvers that exceeded 38 cm/sec strongly correlated with testicular volume asymmetry.

Associated Pathologic Processes

There is abundant evidence that a varicocele may alter testicular growth, spermatogenesis, and fertility potential. The cause of testicular injury is presumed to be related to increased scrotal temperature, but the pathogenesis remains poorly understood.

Testicular Hypotrophy

In the absence of sufficient direct insight into the potential for subfertility (i.e., semen analysis) associated with varicoceles in adolescents, most attention has been on testicular hypotrophy as a harbinger of pathology and indirect marker surgical success. A decrease in testicular volume has long been associated with varicoceles (Lipshultz and Corriere, 1977). Steeno and colleagues (1976) confirmed the finding in adolescents with grade 2 (34.4% had decreased volume) and 3 (81.2%) varicoceles. The correlation between varicocele grade and left testicular hypotrophy has been confirmed in some studies (Thomas and Elder, 2002; Zampieri

et al, 2008b) but not others (Alukal et al, 2005; Kolon et al, 2008). Because ipsilateral volume loss may improve or resolve after varicocele repair, it was inferred that hypotrophy reflects significant testicular injury (Lyon et al, 1982; Kass and Belman, 1987). The global impact, and by extension damage, of varicocele was noted by Kass and colleagues (2001), who found significantly reduced right testicular size compared with control values in Tanner stage 4 or 5 boys with grade 3 left varicoceles. Okuyama and coworkers (1988) reported right testicular hypotrophy in 22% of patients with grade 2 or 3 left varicoceles, and lower sperm densities among those with bilaterally small testes. Mean right testicular volume increased significantly after left varicocele repair but not in untreated control groups in several other studies (Laven et al, 1992; Yamamoto et al, 1995; Paduch and Niedzielski, 1997).

Significant hypotrophy is variably defined as a 10%, 15%, 20%, or 2- or 3-mL relative difference in testicular size and is found in 10% to 77% of patients (Lyon et al, 1982; Okuyama et al, 1988; Akbay et al, 2000; Thomas and Elder, 2002; Diamond et al, 2004b; Kolon et al, 2008; Preston et al, 2008). This variability is related to the mode of measurement (see later), referral patterns, and the formula used to determine percent differences. Rapid increases in testicular size may occur as early as 10 years of age and persist until age 19, depending on Tanner stage of pubertal development (see Table 146-3) (Schonfeld, 1943; Rundle and Sylvester, 1962; Zachmann et al, 1974; Daniel et al, 1982; Matsuo et al, 2000). Because size variability can vary widely in individuals (Marshall and Tanner, 1970), longitudinal measurements over several years may more accurately define hypotrophy than isolated measurements, particularly in early puberty.

“Catch-up” growth, defined as normalization of left relative to right testicular size, occurs in 32% to 83% of patients after varicocele repair (Cayan et al, 2002; Greenfield et al, 2002; Yaman et al, 2006; Castagnetti et al, 2008; Feber and Kass, 2008; Decastro et al, 2009; Poon et al, 2009; Zampieri et al, 2009) and in 55% to 70% of boys in various series (Barroso et al, 2009). The hypothesis that postoperative resolution of left testicular hypotrophy reflects improved testicular function is challenged by observations that testicular size differential may improve spontaneously in untreated patients (Paduch and Niedzielski, 1997; Kolon et al, 2008). In contrast, others report worsening or development of significant hypotrophy in 10% to 26% of boys over time (Thomas and Elder, 2002; Zampieri and Cervellione, 2008; Kozakowski et al, 2009). Finally, Diamond and colleagues (2004b) reported no statistical difference in either direction in a longitudinal study. Kocvara and colleagues (2003) posited that lymphatic ligation contributes to increased postoperative testicular volume after lymphatic and arterial ligation, but this was disproved by reports showing no difference in rates of catch-up growth based on lymphatic (Poon et al, 2009) and/or arterial (Barroso et al, 2009) preservation. Laven and associates (1992) noted that varicocele repair increased the volume of small but not normal-sized testes. Postoperative left testicular hypertrophy (>10% size differential relative to the right testis) is attributed to non-lymphatic-sparing procedures or to a rebound effect on spermatogenesis in the affected testis (Gershbein et al, 1999; Cayan et al, 2002; Kocvara et al, 2005).

Significant discrepancy between left and right testicular size remains the primary indication for varicocele correction. Unfortunately, the currently available data are unclear as to the direct relationship between this discrepancy and testicular function with or without correction. **Prospective, randomized studies are needed to clearly establish whether unilateral and/or bilateral testicular hypotrophy or catch-up growth accurately predicts fertility potential in adolescent varicocele.**

Testicular Histology

The histologic effect of varicoceles is better known in adults but is largely absent and inconsistent in adolescents. In adults (reviewed by Hienz et al, 1980), histology findings vary from normal on light

and electron microscopy in all men (Fideleff et al, 2000) or even those with severe hypospermatogenesis (Kass et al, 1987; Aragona et al, 1994) to degenerative tubular changes, altered Leydig cell number, and/or proliferative lesions of the vasculature (Hienz et al, 1980). Hadziselimovic and associates (1995) found abnormal tubular maturation and Leydig cell number in a small series of young men who had testicular biopsies at the time of adolescent varicocele repair; these data failed to correlate with ultimate sperm quality in adulthood.

Hormonal Function

The use of hormonal profiles as a proxy to determine if varicoceles are deleterious to testicular function has been inconclusive. Baseline LH and FSH levels are not consistently different in the presence or absence of varicocele in adolescents (Laven et al, 1992; Yamamoto et al, 1995; Cayan et al, 2005; Ku et al, 2005). Basal and stimulated gonadotropin levels were not consistently different in varicocele patients when compared with controls and did not improve after surgery (Fideleff et al, 2000). GnRH stimulation led to an exaggerated LH and FSH response in about 30% of boys with varicoceles but did not correlate with testicular hypotrophy (Kass et al, 1993a). Inhibin B measurements failed to consistently correlate with testicular size or semen parameters in adolescents (Carrillo et al, 1999; Turkyilmaz et al, 2006; Romeo et al, 2007; Basar et al, 2010). Guarino and coworkers (2003) observed increased LH, FSH, and simulated FSH levels in 20 boys with varicoceles and abnormal semen parameters compared with 56 with normal semen, but this was confounded by 30% of boys with bilateral varicoceles, a history of inguinal surgery, or cryptorchidism.

Semen Quality

Semen quality is considered the most useful indicator of fertility potential despite many variables associated with collection and interpretation in adolescents. **Progressive improvement in sperm quality may parallel testicular growth and sexual maturation, and so semen analyses may be best obtained at stabilization of testicular growth, which may not depend on age.** In a study of 194 boys aged 12 to 19 years, Janczewski and Bablok (1985a, 1985b, 1985c, 1985d) found that ejaculation began at a bone age of 13 years (within 16 months of the onset of puberty), and normospermia was achieved by a bone age of 17. There were boys at Tanner stage 5 with asthenozoospermia and occasional oligozoospermia. Mean testicular size increased with progression in semen quality but showed a large SD in boys achieving normospermia; LH and FSH levels significantly declined with attainment of normospermia.

Reliable standards for semen quality based on Tanner stage or age do not exist, and, therefore, recent studies evaluating semen quality among adolescents with varicoceles depend on comparison with adult standards. In the majority of these studies, at least two semen samples were obtained and World Health Organization criteria were used; however, Tanner stage 5 was not always specified. Christman and associates (2013) recently advocated a single semen analysis, because they found sufficient reproducibility of total mobile count (more variability among other parameters) in adolescents at risk for subfertility (varicocele or cryptorchidism). In two randomized studies comparing treated and untreated patients with controls, no differences were found in semen quality at initial or follow-up analysis between groups, except for a significant postoperative increase in sperm concentrations in the treated group (Laven et al, 1992; Yamamoto et al, 1995), hypothesized to be a rebound in spermatogenesis. Correlations between left or total testicular volume and semen parameters were noted by some investigators (Haans et al, 1991; Paduch and Niedzielski, 1996; Diamond et al, 2007) but not others (Guarino et al, 2003). Recently, Christman and colleagues (2014) reported on 73 patients followed for 2.7 years (median) by serial scrotal ultrasound evaluating testicular size and semen analysis at Tanner 5, around age 18 years. A low total motile count was found

in 48 patients (66%). Testicular volume differential could not predict normal semen volume, density, sperm motility, or total motile count. Total testicular volume from the final ultrasound predicted total motile count. Investigators were unable to correlate postoperative increases in left testicular volume or varicocele grade with semen analysis data in controlled (Laven et al, 1992) and uncontrolled (Cayan et al, 2002; Diamond et al, 2007; Zampieri and Cervellione, 2008) studies. **The available data suggest that trends toward poorer sperm quality may be limited to a subset of affected males with varicocele, but that grade and postoperative testicular catch-up growth do not reliably predict ultimate semen quality.**

Intratesticular Varicocele

In 1% to 2% of adolescents, a varicocele may include an intratesticular component found on CDUS (Diamond et al, 2004a; MacLachlan et al, 2013). The diagnosis is made by identifying venous flow in anechoic structures greater than 2 mm in diameter near the mediastinum testis that increases during Valsalva maneuvers (Bucci et al, 2008). MacLachlan and colleagues (2013) found worsening testicular asymmetry that responded to surgical correction and progressed in one patient who refused surgery; they concluded that surgery was indicated in adolescents with intratesticular varicoceles and testicular asymmetry.

Treatment

Observation remains the approach of choice for the majority of adolescents with varicocele until a surgical indication is present. **Despite the aforementioned limitations regarding testicular hypotrophy, the main indications for surgical intervention remain significant left ($\geq 20\%$) or bilateral testicular hypotrophy, pain, or abnormal semen analysis findings; the last is most reliable in boys of Tanner stage 5 and/or at least 18 years of age.** Pain is a rare indication for surgery, reported in only 2% to 10% of patients in most series, and is relieved by the procedure in 68% to 88% of patients (Zampieri et al, 2008a).

Surgical Repair of Varicocele

Several approaches exist to correct the adolescent varicocele: inguinal or subinguinal, laparoscopic or retroperitoneal, or venographic. The surgical decision revolves around (1) whether to spare the testicular artery and/or lymphatics using the available approaches, and (2) the effect on the rate of recurrence and hydrocele formation (Table 146-5) (Poddoubnyi et al, 2000; Misseri et al, 2001; Greenfield et al, 2002; Esposito et al, 2004; Cayan et al, 2005; Kocvara et al, 2005; Schiff et al, 2005; Yaman et al, 2006; Castagnetti et al, 2008; Feber and Kass, 2008; Glassberg et al, 2008; Barroso et al, 2009; Diamond et al, 2009; Tong et al, 2009). Long-term outcome data are lacking to support any particular approach because the length of postoperative follow-up may be insufficient to identify potential recurrences (Glassberg et al, 2008) or sequelae such as a hydrocele, which may require 2 years or more to develop (Misseri et al, 2001; Esposito et al, 2004; Feber and Kass, 2008). Whereas many hydroceles may resolve spontaneously, up to one half may require formal scrotal repair (Misseri et al, 2001; Esposito et al, 2004; Feber and Kass, 2008; Diamond et al, 2009) or aspiration (Esposito et al, 2004) because of large size or symptoms.

Subinguinal or Inguinal Microsurgical Varicocelectomy

The *subinguinal microscopic approach* provides the advantages of facilitated artery and lymphatic sparing, high rate of success, and low risk of hydrocele but may be time-consuming and requires microscopic surgical skills. The procedure used in children is similar to that used in adults as originally published (see Chapter 25). Use of lower degrees of magnification in adolescents (e.g., loupes) may yield inferior results (Greenfield et al, 2002; Cayan et al, 2005;

TABLE 146-5 Results of Adolescent Varicocele Repair

PROCEDURE	RECURRENCE OR PERSISTENCE	HYDROCELE	TESTICULAR ATROPHY
Open suprainguinal (Palomo)	2%-4%	0%-30% (10%)*	
Laparoscopic:			
Nonlymphatic or artery sparing	0%-9%	11%-32% (7%)*	
Artery and/or lymphatic sparing	1%-7%	0%-4%	
Microscopic subinguinal	0%-10%	0%-6%	Rare
Nonmicroscopic inguinal	7%-33%	8%-14%	
Sclerotherapy	6%-35%	Occasional	Rare

*Number in parentheses refers to meta-analysis of Barroso et al, 2009.

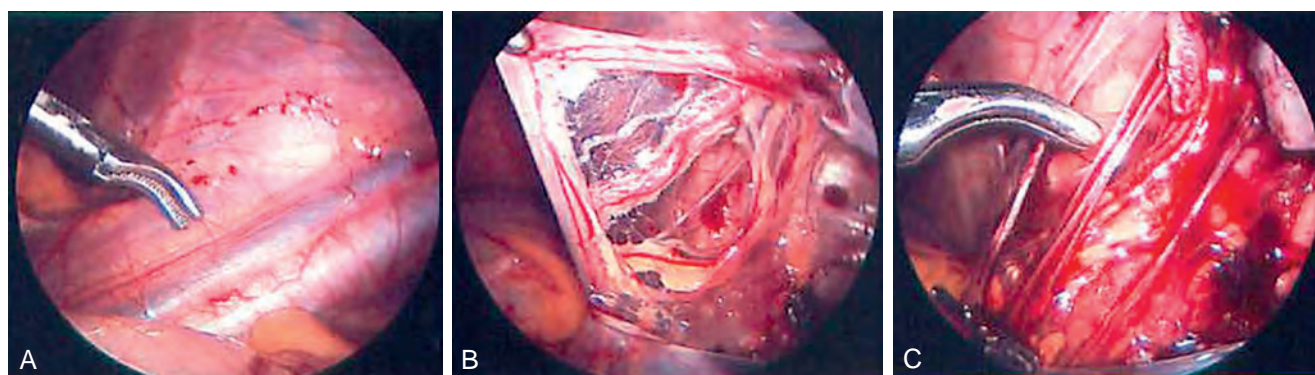


Figure 146-30. Images from a lymphatic sparing laparoscopic varicocelectomy. **A**, Laparoscopic dissector approaches internal spermatic vessels under posterior peritoneum. **B**, Vessels have been isolated and elevated off the posterior abdominal wall. **C**, Individual lymphatic channels have been teased out and will be spared and the veins divided. (Courtesy Israel Franco, MD.)

(Diamond et al, 2009) than use of an operating microscope. The subinguinal approach is associated in rare cases with testicular atrophy (necrosis), which has not been reported for suprainguinal procedures (Diamond et al, 2009).

Retroperitoneal and Laparoscopic Varicocelectomy

The ligation of the internal spermatic vessels above the level of the internal inguinal ring is a simple procedure performed by open or laparoscopic approaches with high success rates but higher rates of hydrocele formation. Mass ligation as described by Palomo (1949), offers a highly successful and efficient surgical result. Although potentially more difficult to isolate the arterial and lymphatic vessels, lymphatic- and/or artery-sparing techniques may reduce the incidence of postoperative hydroceles but have an impact on success rate (Kass and Marcol, 1992) and may not benefit catch-up growth (Fast et al, 2014). Zampieri and associates (2007a, 2007b) reported that sparing the artery was associated with improved semen quality; however, randomized prospective data are lacking that clearly define the effect of artery sparing on testicular function. In theory, testis atrophy may follow spermatic artery ligation in patients with prior inguinal surgery (Skoog et al, 1997) but did not occur after laparoscopic Palomo procedures in a small series (Barqawi et al, 2002). Similarly, testis atrophy may occur after non-artery-sparing varicocelectomy and subsequent surgery that compromises the vasal artery or vein (hernia repair, vasectomy).

The Palomo open procedure is performed through a muscle-splitting incision medial to the anterior superior iliac spine. The peritoneum is mobilized medially to expose the bundle of spermatic

vessels, which are isolated, clipped, or suture ligated and left as such, or the vessels are divided, according to surgeon preference. To reduce the risk of postoperative hydrocele formation, a microscopic lymphatic-sparing procedure through this incision was described by Wong and colleagues, without recurrence (Wong et al, 2009).

Laparoscopic varicocele repair is performed using three ports. The two working ports are placed in variable locations: left midclavicular line inferior to the umbilicus and lower midline/right lower quadrant, or both lower quadrants, or both on the right side at the lateral rectus margin. The peritoneum above the internal ring is opened and the vascular bundle and surrounding tissue are mobilized. To help identify the artery, a laparoscopic Doppler probe or papaverine can be used. The magnification provided by the laparoscope helps to identify lymphatic channels as clear tubular structures accompanying the artery and veins (Fig. 146-30). The use of vital dyes injected into the paratesticular tissue to identify lymphatics has potential technical challenges and risks if the dye is inadvertently injected into the testis (Schwentner et al, 2006; Makari et al, 2007). The vessels may be ligated using permanent sutures or clips and transected using the harmonic scalpel or vessel-sealing devices. To avoid recurrence, vein(s) accompanying the artery should be identified and ligated. Cimador and colleagues (2008) used CDUS to search for dilated, refluxing deferential veins in the iliac fossa, which were also ligated. Injury to the genitofemoral nerve has been reported in a limited number of adolescent and adult series and may be more commonly associated with use of electrocautery (Muensterer, 2008). This complication manifests as postoperative paresthesias along the proximal anterior thigh that slowly resolve over weeks or months.

Sclerotherapy or Embolotherapy

The published experience with intravascular injection of sclerosant or thrombotic material to occlude varicoceles in adolescents has been limited and mainly applied to cases of recurrent or persistent varicoceles (Fig. 146-31 on the Expert Consult website). The benefit of this approach is to identify and classify the venous collateralization as possible routes of outflow and reflux. The agents (3% sodium tetradecyl sulfate or polidocanol, with or without intravascular coils or balloons) can be injected in either a retrograde (Reyes et al, 1994; Mazzoni et al, 1999; Alqahtani et al, 2002; Sivanathan and Abernethy, 2003; May et al, 2006a; Beutner et al, 2007; Granata et al, 2008; Reiner et al, 2008) or antegrade fashion. The benefits of the procedure lie in its minimally invasive approach through a transfemoral venous puncture done under local anesthesia (with or without sedation). However, the procedure has generally inferior success rates compared with surgical (open or laparoscopic) procedures, involves significant radiation exposure, and is unfeasible for technical reasons in 5% to 22% of cases. The follow-up is short in available literature (rarely more than 1 or 2 years), with recurrence rates of 6% to 35%. Self-limiting complications include pain, epididymo-orchitis, phlebitis, or scrotal swelling; partial testicular atrophy and hydrocele occur rarely. Antegrade techniques entail use of a small subinguinal or upper scrotal incision, isolation of a vein or veins amenable to cannulation with or without fluoroscopic confirmation of antegrade flow into the internal spermatic vein, and injection of a sclerosant followed by ligation of the vein (Zaupa et al, 2006; Carmignani et al, 2009). Success rates are reported to be 4% to 12%, lower than for retrograde sclerotherapy, with similar complications.

EPIDIDYMAL AND VASAL ANOMALIES

Congenital anomalies of accessory testicular structures are often associated with primary diseases affecting testicular descent and genital development but may occur as isolated anomalies or as part of syndromes that do not primarily affect the genitalia.

Epididymal cysts are simple cystic structures that may be palpable by the patient or examining physician or found incidentally by ultrasonography (Homayoon et al, 2004). Posey found that over an 8-year period, 14.4% of all boys who underwent scrotal ultrasound had epididymal cyst with increasing incidence with age (35.3% among boys >15 years) (Posey et al, 2010). Epididymal cysts may be clinically indistinguishable from spermatoceles except that the latter occur postpubertally and contain sperm. The pathophysiology of epididymal cysts is unknown but may be related to an altered hormonal environment because they are linked to diethylstilbestrol (DES) exposure (Palmer et al, 2009). These lesions are different ultrasonographically and pathologically from the multicystic, solid epididymal cystadenomas that occur in von Hippel-Lindau disease (Choyke et al, 1997). Homayoon and associates (2004) observed spontaneous resolution of many cysts in their pediatric series, and surgical intervention is rarely needed.

Congenital absence of the vas deferens (CAVD) is in most cases associated with specific mutations of the cystic fibrosis gene *CFTR* (cystic fibrosis transmembrane regulator) that are less severe than those encountered in patients with cystic fibrosis (Kolettis and Sandlow, 2002). The disease can be bilateral (CBAVD) or unilateral (CUAVD) with a normal or obstructed contralateral vas and may be associated with renal agenesis or ectopia and/or partial or complete agenesis of the epididymis and seminal vesicles. *CFTR* mutations are more common in males with CBAVD, and renal anomalies are more common in cases of CUAVD. These patients typically have infertility. Abnormal vasal development may also result in a **persistent mesonephric duct** anomaly that is associated with ipsilateral renal and seminal vesicle agenesis and vasoureteral fusion (Kajbafzadeh and Payabvash, 2006). Reflux into the fused wolffian remnants results in UTI and epididymo-orchitis. Other associated anomalies

may include imperforate anus, hypospadias, tracheoesophageal fistula, tetralogy of Fallot, or coarctation of the aorta.

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The complete reference list is available online at www.expertconsult.com.

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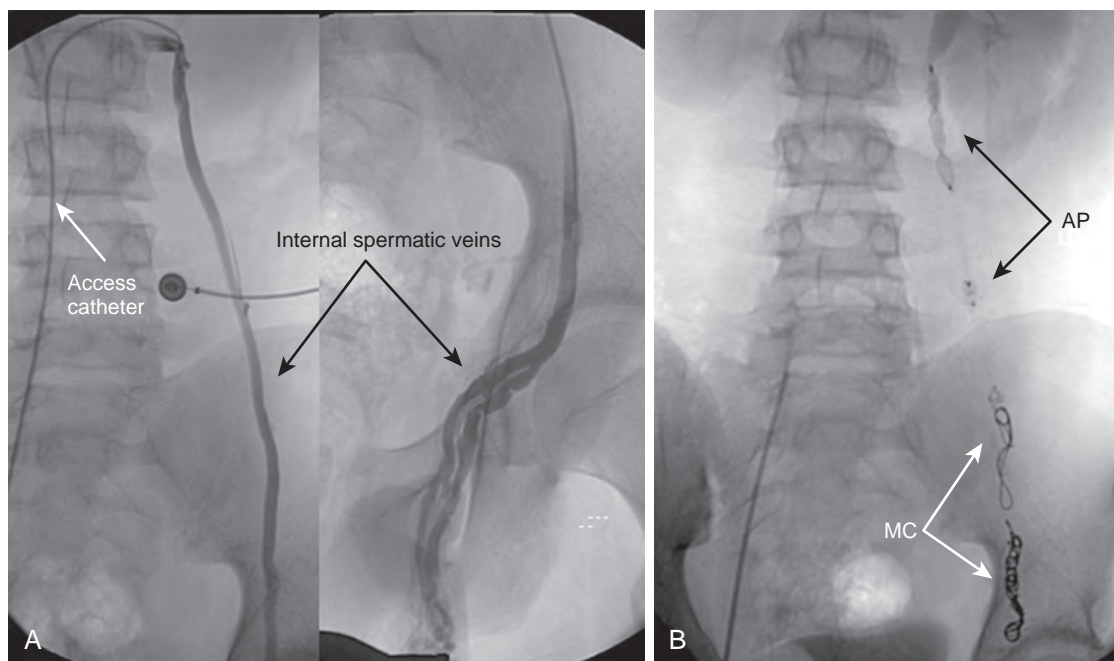


Figure 146-31. Antegrade varicocele embolization. A, The left internal spermatic veins are accessed via the right femoral vein, and venography demonstrates the dilated veins. B, Postembolization images with two levels of microcoils (MC) and two Amplatzer plugs (AP), representing the typical four levels of embolization. (Courtesy Ardeshtir Rastinehad, DO.)

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147 Hypospadias

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Preoperative Assessment and Management

Intraoperative Assessment and Management

Postoperative Management

Outcomes Assessment

Complications

Hypospadias Reoperations

Adult Outcomes after Prepubertal Repair

Improving Outcomes

Hypospadias refers to a urethral opening proximal to the normal glanular location. The defect is commonly considered arrested development, even though embryo penises do not exhibit a similar-appearing phase. Correction is surgical and includes not only urethroplasty but also straightening ventral penile curvature, circumcision or prepuceioplasty, and scrotoplasty with the goal to restore as normal function and appearance as possible.

We discuss hypospadias from a surgical perspective in this chapter, with sections discussing preoperative assessment, intraoperative decision making and management, postoperative care, and complications and their reoperations. Given that complications from initial surgery increase the risk for subsequent complications, we have described operative techniques in detail, emphasizing key steps to reduce the likelihood that additional surgery will be needed. Within each section we briefly recount the best studies available and summarize this evidence in bold type.

PREOPERATIVE ASSESSMENT AND MANAGEMENT

Diagnosis

Hypospadias is diagnosed by physical examination. Typically preputial development is asymmetrical, with a dorsal “hood” and ventral deficiency that exposes the glans and proximal meatus (Fig. 147-1). Other abnormal ventral findings potentially include downward glans tilt, deviation of the median penile raphe, ventral curvature (VC), scrotal encroachment onto the penile shaft, midline scrotal cleft, and penoscrotal transposition.

The main differential diagnosis is *chordee without hypospadias*, which refers to asymmetrical preputial development with a normal glanular meatus. The term implies ventral penile curvature, although in the majority of cases apparent downward bending is corrected simply by degloving the ventral skin. This categorization has included patients with a glanular meatus but deficient corpus spongiosum and a thin distal urethra that others consider a hypospadias variant. To end confusion, boys with a hooded prepuce and bending should be diagnosed with congenital VC if the urethra is grossly normal, or otherwise with hypospadias (Snodgrass, 2008).

Some hypospadias variants present with a normal foreskin concealing a glanular to distal shaft meatus. These generally have a deeply grooved urethral plate, which sometimes extends laterally under the skin edge creating a phenotype known as the megameatus with intact prepuce (Fig. 147-2). The diagnosis of these variants is made after circumcision or when the foreskin becomes retractable.

Prevalence and Inheritance

Hypospadias occurs in 1 in 300 males (0.3%). Recurrence risk is approximately 13 times greater in first-degree relatives (brothers, fathers, offspring).

Several birth registries suggested an increasing prevalence in the 1990s, possibly linked to environmental toxins, but changes in reporting criteria and accuracy of the diagnosis potentially account for these observations.

Three case-control studies of births in Denmark, France, and Italy reported prevalence of hypospadias in 0.3% to 0.45% of male births. The relative risk for recurrence in first-degree relatives was 13 times greater, found in 9% to 17% of brothers and 1% to 3% of fathers. Risk in same-sex twins was 50%. Recurrence risk in offspring was the same as in first-degree relatives (Calzolari et al, 1986; Stoll et al, 1990; Schnack et al, 2008).

Isolated versus Syndromic Hypospadias

Approximately 90% of hypospadias cases are isolated penile defects.

Case-control studies indicate that in most patients hypospadias is an isolated anomaly (Calzolari et al, 1986; Stoll et al, 1990). Syndromic hypospadias is suspected with development delay, dysmorphic facies, and/or anorectal malformation. Examples include:

- **Smith-Lemli-Opitz syndrome**—results from an autosomal recessive mutation of the *DHCR7* gene on chromosome 11q13 coding for 7-dehydrocholesterol reductase. Affected individuals have mental retardation, facial dysmorphism, microcephaly, and syndactyly.
- **WAGR syndrome (Wilms tumor, aniridia, genital anomalies, mental retardation)**—results from a deletion in chromosome 11p13.
- **G syndrome (Opitz G/BBB syndrome)**—occurs from X-linked mutations in the midline-1 gene or autosomal dominant deletions in chromosome 22q11. The resultant phenotype includes hypertelorism, tracheoesophageal defects, cleft lip/palate, and mild mental retardation.
- **Wolf-Hirschhorn syndrome**—derives from deletions in chromosome 4p resulting in mental retardation, seizures, abnormal facies, and midline defects.
- **13q deletion syndrome**—characterized by mental retardation, facial dysmorphism, imperforate anus, and hypospadias with penoscrotal transposition.
- **Hand-foot-uterus syndrome**—an autosomal dominant condition caused by mutations in the *HOXA13* gene on chromosome 7p14-15, resulting in bilateral thumb and great toe hypoplasia.

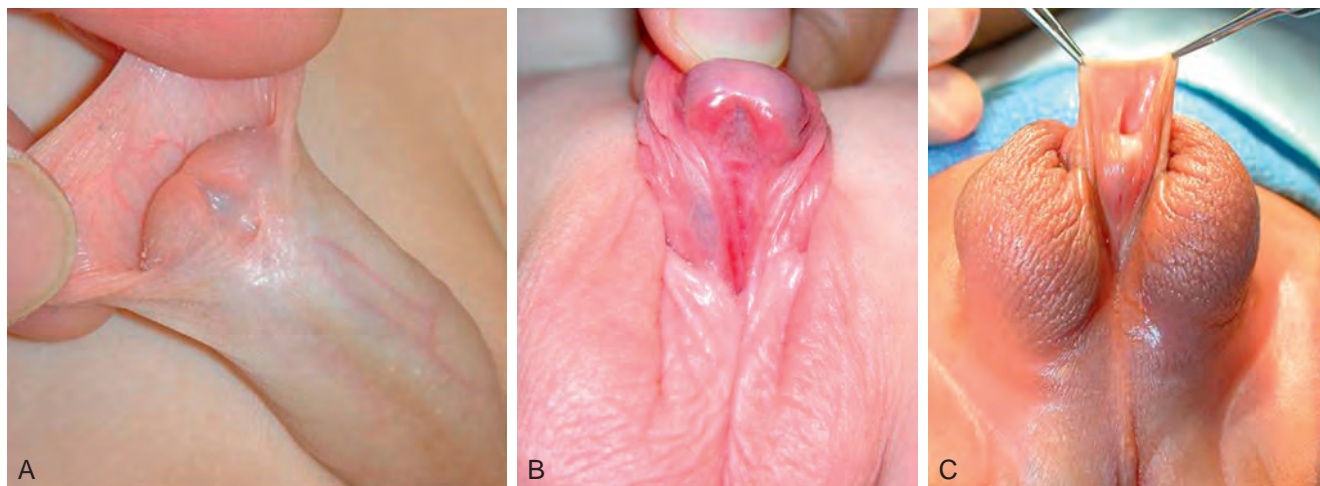


Figure 147-1. Spectrum of hypospadias. A, Coronal hypospadias. B, Penoscrotal hypospadias. C, Perineal hypospadias with scrotal transposition.

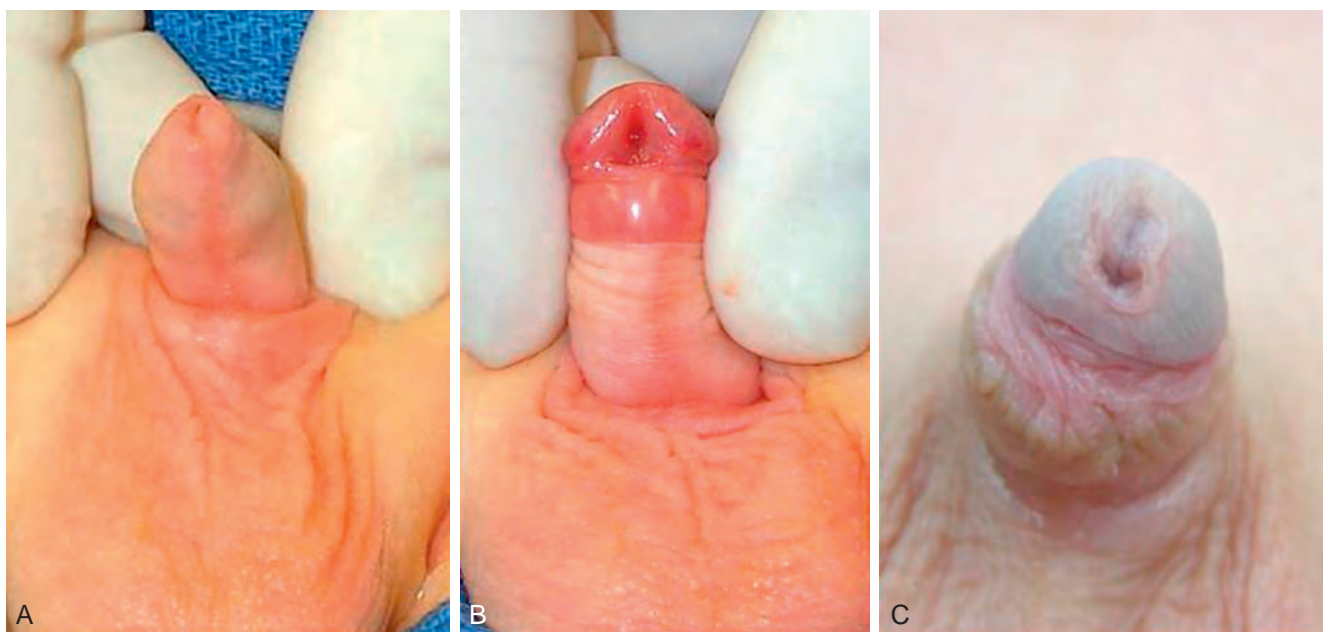


Figure 147-2. Hypospadias variants with a normal prepuce. A, Apparently normal penis with complete foreskin. B, Foreskin retracted, revealing a coronal hypospadias. C, Glanular mega-meatus intact prepuce discovered after circumcision.

Disorders of Sex Development

Disorders of sex development (DSDs) are possible in phenotypic boys with both hypospadias and undescended testes, which is considered an indication for karyotyping. The most common diagnosis is mixed gonadal dysgenesis, followed by ovotesticular DSD.

Isolated hypospadias is not considered a DSD. The coexistence of hypospadias with undescended testes may indicate a DSD, especially when there is proximal hypospadias and a nonpalpable testis, although the prevalence is difficult to determine from published reports, which are all retrospective and subject to selection bias for evaluation. Reasons for evaluating some but not other patients with hypospadias and undescended testes were not described in the articles summarized here.

For example, a review by [Kaefer and colleagues \(1999\)](#) identified 79 male-appearing patients with both hypospadias and undescended

testes of whom only 54 (68%) were evaluated by karyotyping. Of the 79 patients, 23 (29%) were diagnosed with a DSD, comprising mixed gonadal dysgenesis ($n = 11$), ovotesticular DSD ($n = 5$), 5α -reductase deficiency ($n = 2$), Klinefelter syndrome ($n = 2$), and partial androgen resistance ($n = 3$).

Two other studies concerning hypospadias with undescended testes similarly reported karyotyping in 42% and 57% of patients, finding either autosomal or sex chromosome anomalies in 17% and 24%, respectively. Of the total of 157 patients represented in these two reports, mixed gonadal dysgenesis occurred in 5 and ovotesticular DSD in 1 ([McAleer and Kaplan, 2001](#); [Cox et al, 2008](#)).

We harvest tunica vaginalis to cover the neourethra in all primary proximal and staged reoperative repairs, and have occasionally encountered an ovotestis fully descended in the scrotum in phenotypic boys with 46,XY karyotype. In such cases we remove the ovarian tissue and explore the contralateral testis then or subsequently.

Imaging

Isolated hypospadias, regardless of severity, is not considered an indication for urinary tract imaging.

One prospective study in Saudi Arabia obtained intravenous pyelography and voiding cystourethrography in patients less than 2 years of age, reporting results in 153 boys with glanular to perineal hypospadias over an 11-year period ending in 1983. Of these, 36 (24%) had abnormal findings, including vesicoureteral reflux ($n = 18$) and a variety of upper urinary tract conditions, including horseshoe kidney, solitary kidney, ureterovesical junction obstruction, and ureteral duplication. Surgery was thought to be indicated in 18 of the 36 patients (12%) (Moore, 1990).

Two retrospective series obtained intravenous pyelography or renal sonography in 41% and 72% of patients, both reporting 18% to be abnormal. Possibly significant findings of hydronephrosis occurred in 4% and 1% (Lutzker et al, 1977; Friedman et al, 2008). Voiding cystourethrography in 163 cases, of which 47% were penoscrotal, diagnosed vesicoureteral reflux in 6 patients (4%) and bladder diverticulum in 2. There was no mention of prostatic utricle (Friedman et al, 2008).

We do not obtain either renal sonography or voiding cystourethrography in boys with nonsyndromic hypospadias, regardless of its severity.

Age for Surgery

Hypospadias repair can be performed as an outpatient procedure in otherwise healthy full-term babies 3 months of age or older.

Considerations in determining the timing of operation include anesthetic risks, psychosexual factors, and the potentially varying risk for urethroplasty complications at different ages.

Anesthetic Risks

Bush and colleagues (2012) reported no unplanned hospital admissions for anesthetic complications in 230 babies 3 to 5 months of age, in whom bronchospasm was documented in the anesthetic record in 5 cases (2%). Preterm babies can undergo outpatient surgery after 56 gestational weeks.

Psychosexual Risks

The American Academy of Pediatrics recommended surgery be completed by age 18 months to limit psychosexual stress ("Timing of elective surgery," 1996). However, a study that used questionnaires and a standardized interview by a psychologist to compare patients ages 6 to 17 years operated before versus after 18 months found no differences in health-related quality of life, psychological adjustment, gender-role behavior, or penile self-perception (Weber et al, 2009).

Urethroplasty Complications

Various reports suggest urethroplasty complications increase with increasing patient age, although the time at which this increased risk occurs is not clear. In contrast, our data question if age is an independent risk factor for complications. This subject is discussed later under Risk Factors in the section on Complications.

Preoperative Androgen Stimulation

Androgens increase penile length and glans circumference, with varying duration of effect after stimulation ends. Only two studies concern the impact of preoperative androgen therapy on urethroplasty complications, one finding a significant reduction in those treated and the other reporting complications remained increased in those stimulated to increase glans size versus those having the same glans size without treatment.

Androgens are documented to increase penile length and glans circumference. However, only one published trial reports the impact

of therapy on urethroplasty complications. Otherwise, most series used subjective criteria in selecting patients for stimulation, used empirical treatment regimens, and had no objective end point.

We (Bush et al, 2013; Snodgrass et al, 2014b) found that urethroplasty complications increased in patients with glans width less than 14 mm, and based on that observation instituted a protocol using testosterone cypionate intramuscular injections to increase width to 15 mm or greater. Of 62 consecutive boys with midshaft and proximal hypospadias, 5 of 15 (33%) and 29 of 47 (60%), respectively, were treated. Initially testosterone 2 mg/kg was given for two or three injections, with all midshaft cases but only 43% of proximal cases achieving the desired glans width, indicating relative androgen resistance. The protocol was changed to administer an escalating dose of testosterone from 2 to 32 mg/kg per injection based on remeasurement 1 month after each injection.

Next Bush and colleagues (2013) analyzed urethroplasty complications in patients who received adjuvant testosterone injections versus those with glans 14 mm or greater who did not. Mean glans width before stimulation was 12 mm, increasing to a mean of 16.5 mm with testosterone injections. Untreated patients had a mean glans width of 15.4 mm. Urethroplasty complications occurred in 34% with versus 11% without adjuvant androgens ($P < .0001$). Because the goal of therapy was to reduce complications, we stopped preoperative testosterone stimulation.

In contrast, a trial by Kaya and coworkers (2008) randomized 75 consecutive boys of mean age 33 months (range 10 to 159) to preoperative topical dihydrotestosterone (2.5% to glans and shaft daily for 3 months) versus no therapy. Treated versus control patients had coronal (70% vs. 84%), penile (24% vs. 16%), and penoscrotal (5% vs. 0%) hypospadias, and all underwent tubularized incised plate (TIP) urethroplasty. Chi-square analysis reported fewer urethroplasty complications in those patients receiving adjuvant stimulation (1 of 37 vs. 9 of 38, $P = .01$).

Hypospadias Encountered During Newborn Circumcision

Caregivers desiring newborn circumcision should be assured that the newborn with a normal prepuce can undergo the procedure without concern for a concealed hypospadias, and that circumcision should not be stopped if hypospadias is encountered.

Original descriptions of the megameatus intact prepuce variant warned that circumcision should be avoided when this variant is discovered, although a review of the literature found no case mentioned in which the prepuce was needed for repair. We have been referred infants whose circumcision was stopped when the practitioner erroneously thought there was a urethral defect, requiring general anesthesia to complete the procedure. An evaluation of concealed hypospadias repair in those with versus without prior circumcision found no difference in urethroplasty complications. Therefore there is no reason to stop circumcision in a newborn with a normal prepuce even if a concealed hypospadias is suspected (Snodgrass and Khavari, 2006).

INTRAOPERATIVE ASSESSMENT AND MANAGEMENT

General Aspects of Surgical Repair

Sutures

There is no evidence that suture materials impact urethroplasty complications.

Guarino and associates (2009) compared primary distal TIP fistula rates for two types of sutures, randomizing 100 boys to either polyglytone (rapid absorption) or polydioxanone (slow absorption). All operations were done by one surgeon, performing urethroplasty in two layers using running subepithelial stitches. Follow-up assessment was blinded to suture type. At 2 years after repair there was no difference in the fistula rates: 4 of 50 (8%) with polyglytone versus 6 of 50 (12%) with polydioxanone.

We prefer 7-0 polyglactin for urethroplasty because the TG-140 needle is significantly smaller than the needle available on 7-0 polydioxanone.

Perioperative Antibiotics

There are no trials concerning preoperative antibiotics before hypospadias surgery. A single trial reported that febrile urinary tract infection (UTI) was reduced by postoperative oral antibiotics.

Meir and Livne (2004) randomized 101 patients undergoing TIP urethroplasty to intraoperative intravenous cefonicid versus intraoperative cefonicid plus postoperative oral cephalexin 3 times daily for 8 days during urinary diversion. Urethroplasty complications were the same, but febrile UTI occurred less often in those treated with oral antibiotics (3 of 52 vs. 12 of 49, $P < .05$).

We do not use preoperative antibiotics except when harvesting oral mucosa, in which case we administer intravenous cefazolin. Patients with postoperative urinary diversion are given trimethoprim-sulfamethoxazole during catheterization.

Nerve Blocks

One randomized controlled trial (RCT) reported penile block to be superior to caudal nerve block for distal hypospadias repair. Penile engorgement was more likely after caudal blocks.

A double-blind RCT by Kundra and colleagues (2012) allocated 54 boys ages 4 to 12 years with distal hypospadias to either penile or caudal nerve block using 0.25% bupivacaine after induction of general anesthesia. Duration of surgery was similar in both groups at 68 ± 15 minutes. A significant mean arterial pressure increase occurred after surgical incision in the caudal versus penile block groups, although only 1 patient was considered to have a failed block. Duration of block was significantly (82 minutes) longer in the penile versus caudal group (302 ± 25 minutes vs. 220 ± 23 minutes, $P = .00$) and there was 43% less postoperative morphine use after penile block. Penile engorgement was determined by measuring stretched penile length and midshaft circumference before and 10 minutes after block. Mean penile volume increased 27% with caudal versus 2.5% with penile block ($P < .001$) (Kundra et al, 2012).

For distal hypospadias we use a dorsal penile nerve block supplemented by a second midline scrotal injection, because infrapubic blocks do not reach sensory branches innervating the ventral midline penis and scrotal and perineal area (Kundra et al, 2012). Caudal nerve blocks are used in proximal cases. When a caudal block cannot be performed, penile and scrotal blocks are used, with a wider area of infiltration at the scrotal base and an additional region of injection superolateral to the scrotum on the side where tunica vaginalis will be harvested.

Urethral Plate Assessment

One study found poor agreement between surgeons judging urethral plate suitability for TIP urethroplasty from photographs. Three studies reported that designation of the urethral plate groove as flat, intermediate, or deep did not predict urethroplasty complications.

Perhaps inevitably, some surgeons wish to rate urethral plate "quality" as a factor in their selection of surgical technique. When done, such subjective assessment makes comparisons between series difficult because various surgeons likely would characterize the plates differently. Supporting this concern was a study by El-Hout and colleagues (2009) involving 21 pediatric urologists who were asked to review photographs and rate the suitability of the urethral plate for TIP urethroplasty using a Likert scale. The authors found poor to slight agreement between the responses regardless of meatal location (distal, midshaft, proximal) or years of surgical experience ($\kappa = 0.06$).

Three studies characterized the urethral plate groove as flat, intermediate, or deep, finding no differences in distal TIP urethroplasty

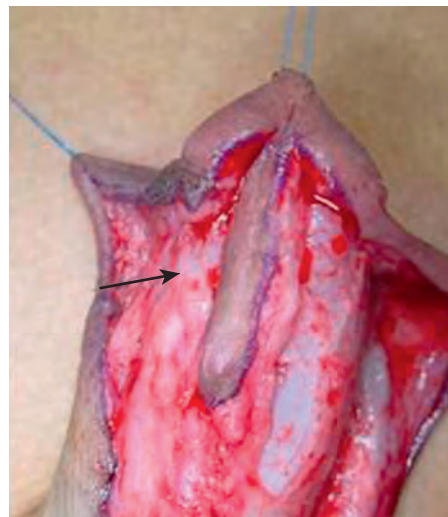


Figure 147-3. Urethral plate unsuitable for tubularization. The arrow indicates unilateral absence of the corpus spongiosum. Tubularized incised plate urethroplasty was considered a poor option without the usual subepithelial tissues comprising the urethral plate.

complications (Holland and Smith, 2000; Sarhan et al, 2009; Snodgrass et al, 2010). Two of these studies reported that urethral plate preincision width less than 8 mm predicted increased urethroplasty complications. In one the final neourethra calibrated to less than 6 French in 19% of cases (Holland and Smith, 2000), which we suspect indicates inadequate midline TIP incision. In the other both distal and midshaft patients were included (Sarhan et al, 2009), but the results were not adjusted for meatal location, which also impacts outcomes. We are currently measuring urethral plate width at its widest point under stretch and find that only 10% are greater than 8 mm. If TIP urethroplasty is contraindicated by width less than 8 mm, reported complications should be much greater.

Snodgrass and colleagues (2010) reported outcomes in 551 consecutive boys presenting with distal hypospadias. Only TIP urethroplasty was done, with no contraindication encountered. Similarly we have used TIP urethroplasty for nearly all proximal cases with VC less than 30 degrees regardless of the appearance of the urethral plate. In 7% of proximal cases there was intraoperative recognition of rigidity or deficient subepithelial tissues for tubularization (Fig. 147-3) (Snodgrass and Bush, 2011). Admittedly this is subjective, so we emphasize our intention to use TIP urethroplasty in all primary proximal hypospadias cases in which the urethral plate is not transected to achieve penile straightening.

Ventral Curvature

Prevalence

Only 10% of distal hypospadias cases have VC that is less than 30 degrees after degloving. Approximately 50% of proximal hypospadias cases have either no VC or VC less than 30 degrees after degloving, whereas the other 50% have greater than 30 degrees after degloving.

Preoperative assessment cannot accurately predict either the extent of curvature or the means required for straightening. Apparent bending may improve or resolve as the skin is degloved, so the common maneuver of compressing penopubic and penoscrotal tissues at the base of the penis to better visualize the penile shaft may falsely suggest or exaggerate VC by traction on deficient ventral skin. The finding that skin adjacent to the meatus may retract as far as the penoscrotal junction during degloving provides additional proof that relatively short ventral skin contributes to curvature.

Snodgrass and colleagues (2010) performed artificial erection in 440 boys with distal hypospadias after degloving, finding VC that was less than 30 degrees in 11% and lateral bending in another 2%.

In no case was bending greater than 30 degrees by visual estimation. Snodgrass and Prieto (2009) studied 70 consecutive boys with proximal shaft to perineal hypospadias. Nineteen percent had no VC and 31% had less than 30 degrees bending after the penis was degloved and scrotal attachments were dissected. The other 50% had curvature greater than 30 degrees.

These reported degrees of curvature were derived by visual estimation without objective measurement, which we have found cumbersome to perform. Few publications regarding VC report using protractors to accurately determine degrees of bending.

Significance

Several studies of men with Peyronie disease or congenital curvature report that those desiring surgical straightening had 25 degrees or greater bending (Savoca et al, 2000; Gholami and Lue, 2002; Greenfield et al, 2006).

Artificial Erection

Heparinized saline injected into the corpora was first described by Gittes and McLaughlin (1974) to create an erection intraoperatively in men with Peyronie disease, and subsequently was adapted for use in boys with hypospadias.

We perform artificial erection during hypospadias repair after degloving, dissection of ventral dartos, and release of the corpus spongiosum wings from the underlying corpora cavernosa and glans wings in proximal hypospadias because shortened ventral shaft skin, dartos, and spongiosum can contribute to apparent VC. Normal saline is injected into a single corpora using a 23-gauge butterfly needle until erection is achieved. We do not use a tourniquet because occasionally it can mask curvature if positioned at the point of bending. If compression is needed to slow fluid outflow and obtain erection, manual pressure is applied below the base of the penis, pressing the corpora against the crura.

Criticisms of saline injection include supraphysiologic or subphysiologic intracorporeal filling that would over- or underestimate curvature. Vasoactive drugs have also been injected to induce erection during hypospadias repair (Perovic et al, 1997; Kogan, 2000), with the proposed advantage of being a more physiologic assessment in contrast to saline injection. We have no experience with this method.

Means for Correction

VC less than 30 degrees is straightened by dorsal plication. VC greater than 30 degrees after degloving, dissection of ventral dartos and scrotal attachments, and division of the corpus spongiosum wings near their fusion with the glans wings next leads to urethral plate transection and dissection to the meatus. Persistent VC greater than 30 degrees can be corrected by ventral corporotomies with or without grafting.

We correct VC less than 30 degrees with a single midline dorsal plication using either 5-0 or 6-0 polypropylene. Should plication fail, this extent of VC is unlikely to hinder sexual activity. We do not use multiple plications to straighten VC greater than 30 degrees out of concern that results may not be durable into adulthood. Rather, when VC greater than 30 degrees persists after the penis is degloved, ventral dartos dissected, and corpus spongiosum released from the corpora and its fusion to glans wings, the urethral plate is transected at the corona and freed proximally to the meatus. Then artificial erection is done and persisting VC less than 30 degrees is corrected by dorsal plication, whereas VC greater than 30 degrees leads to three transverse corporotomies through the area of greatest bending.

Although single corporotomy with grafting can also be done for ventral lengthening when VC exceeds 30 degrees, this limits urethroplasty options to flaps because a urethroplasty graft placed onto a corporal graft may not take. Because we choose not to perform flap urethroplasties, we lengthen the shortened ventral tunica albuginea of the corpora using three corporotomies without grafting.

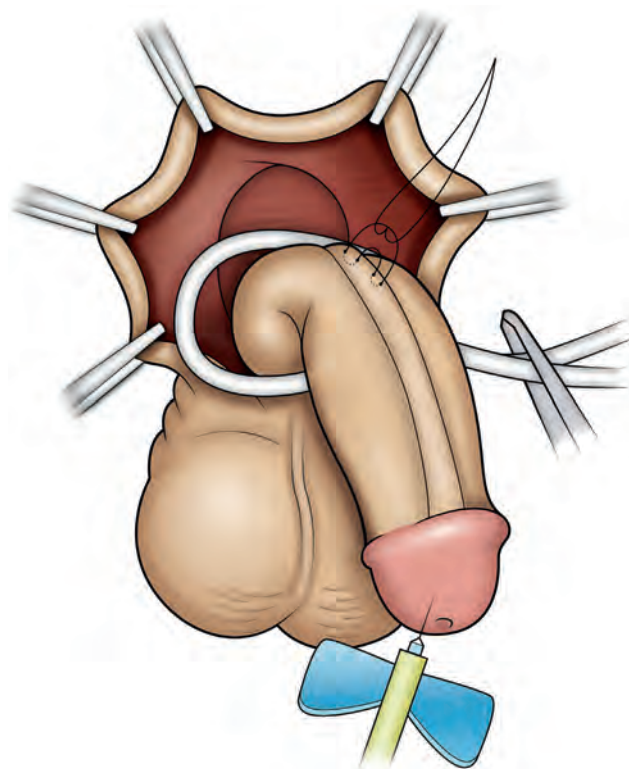


Figure 147-4. Midline dorsal plication. The surface of the corpora cavernosa is exposed in the midline opposite the region of curvature, avoiding the dorsal veins, and then polypropylene suture is placed, burying the knot.

Surgical Technique

Dorsal Plication. Midline plication is illustrated in Figure 147-4. Artificial erection identifies the point of greatest bending, and the Buck fascia is incised there longitudinally to expose the underlying tunica albuginea. A single 6-0 or 5-0 polypropylene stitch plicates the midline septum of the corpora, burying the knot. Repeat erection confirms straightening. We do not perform multiple plications.

Results. Recurrent VC was reported in two series in 7% of patients. One stated that all recurrences occurred in plications done for VC greater than 30 degrees. Penile shortening less than 0.5 cm occurred in adults having a mean of three plications.

Two retrospective studies using 5-0 (one also used 4-0) polypropylene both reported recurrent VC in 7% of patients during median follow-up of 16 months (Chertin et al, 2004) and 6 years (Bar Yosef et al, 2004). Chertin and colleagues (2004) did not state the extent of VC, whereas Bar Yosef and associates (2004) used one or two midline plications for VC estimated as less than 30 degrees in 47%, from 30 to 45 degrees in 44%, and greater than 45 degrees in 9% of patients. All patients with recurrent VC had greater than 30 degrees initially, including two of four with VC greater than 45 degrees (Bar Yosef et al, 2004).

One retrospective study involved 154 men with either Peyronie disease or congenital curvature who had objective measurement of both curvature and penile length before and after straightening (Greenfield et al, 2006). Mean curvature determined intraoperatively using papaverine and saline injection and measured using a protractor was 45 degrees (range 25 to 105) for Peyronie disease and 57 degrees (range 25 to 90) for congenital curvature. An average of three plications (range one to six) was done. Mean penile length loss was 0.36 cm (range 0 to 2.5). Although it is frequently stated that dorsal plication shortens the penis, this study suggests that any loss in length is likely subclinical.

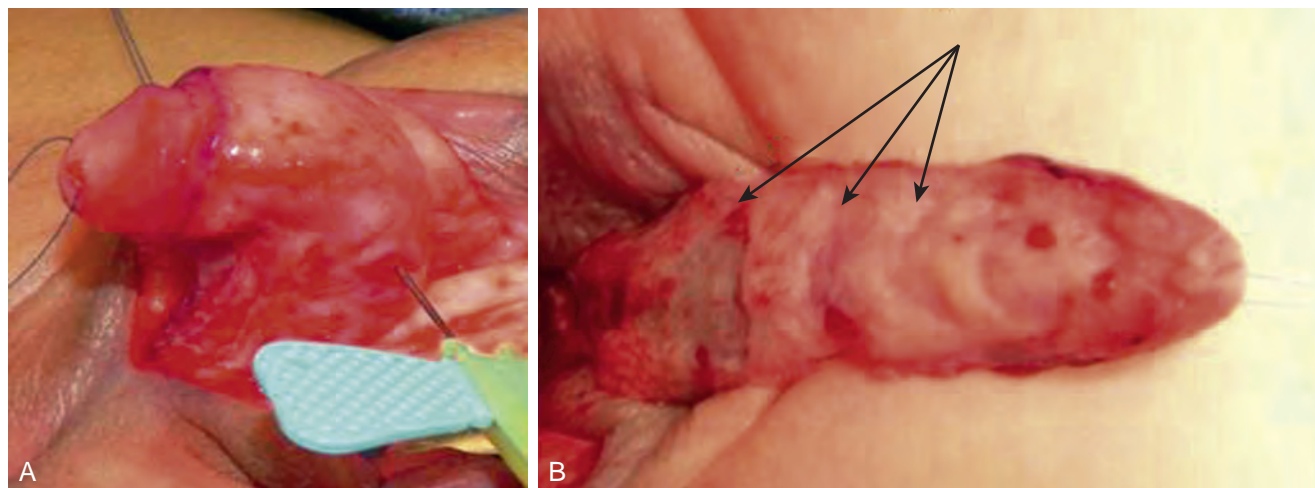


Figure 147-5. A, Ventral corporotomies to straighten curvature greater than 30 degrees. B, Three transverse corporotomies are made just through the tunica albuginea from 4 to 8 o'clock (arrows). Then the urethroplasty graft is placed over these incisions.

Ventral Corporal Lengthening. There are two methods for ventral corporotomy. Results appear equivalent, but options for subsequent urethroplasty are impacted by which technique is used.

A single ventral corporotomy can be made from 3 to 9 o'clock though the area of greatest bending. The opening in the tunica albuginea is patched using a graft. Reported materials for grafting include dermis from the groin (hernia-like incision), small intestine submucosa, and tunica vaginalis (as either a graft or flap). Incision with grafting requires flap urethroplasty because a graft urethroplasty would involve placing the urethroplasty graft onto the corporal graft, which likely would not adequately revascularize.

Alternatively, the ventral corpora can be incised from 4 to 8 o'clock beginning through the point of greatest curvature and then making similar incisions approximately 4 mm distally and proximally for a total of three (Fig. 147-5). These incisions through the tunica albuginea are not grafted, and so a urethroplasty graft can be placed directly over them.

Results. Retrospective studies all find recurrent curvature in less than 10% of patients following ventral lengthening by single corporotomy with grafting. One study reported no difference in outcomes from single corporotomy with grafting versus three corporotomies without grafting. One adult with corporotomy plus grafting before puberty reported erectile dysfunction requiring vasoactive drugs.

Snodgrass and Prieto (2009) reported outcomes in 18 consecutive boys with proximal hypospadias, the first 7 having corporotomy with dermal grafting and the next 11 having three transverse corporotomies without grafting. There was no recurrent curvature with either method during follow-up of 27 and 19 months, respectively. This observation demonstrates that corporotomies for ventral lengthening do not require grafting.

Results of single corporotomy with grafting suggest there is little difference in recurrent curvature regardless of the material used to graft the defect. For example, three reviews concerning dermal grafts reported no recurrent curvature requiring additional straightening during follow-up of 2 to 10 years (Pope et al, 1996; Caesar and Caldamone, 2000; Badawy and Morsi, 2008). Badawy and Morsi (2008) studied 16 postpubertal men after prepubertal corporotomy with dermal grafting and stated that one of the three who reported sexual activity needed vasoactive drug corporal injections to maintain a sufficient erection. To our knowledge there are no other reports of erectile dysfunction after incision with grafting, and the authors stated that this individual recovered natural erections after their publication (Badawy, personal communication).

Both single-ply and 4-ply small intestine submucosa have been used for corporal grafting. Of three reports, two observed no recurrent VC during follow up of 1.5 to 3 years (Weiser et al, 2003;

Elmore et al, 2007). A third review after 4-ply grafting stated that 17% of patients had either recurrent VC or a palpable fibrotic mass deemed necessary to excise (Soergel et al, 2003).

Three studies found recurrent VC in 10% or less of patients following grafting using tunica vaginalis (Perlmutter et al, 1985; Ritchey and Ribbeck, 2003; Kajbafzadeh et al, 2007). One other study used tunica vaginalis as a flap with similar results (Braga et al, 2007).

The "Thin" Urethra

The urethra proximal to the meatus may appear "thin" for a varying distance owing to absent or deficient dartos and corpus spongiosum covering (Fig. 147-6). Management depends in part on whether a surgical plane can be established to separate the overlying shaft skin from the urethra, and also on the extent of VC when present. Most often the "thin" segment is only a few millimeters long and the shaft skin can be separated from it. In that circumstance urethroplasty is not influenced except that spongioplasty can be done to cover the thin-appearing region. When shaft skin cannot be separated from the urethra, the "thin" urethra is split down the midline proximally until normal spongiosum is encountered, and then the still-attached skin is incorporated into the neourethra. In the presence of VC greater than 30 degrees after degloving, the urethral plate and the "thin" urethra are excised as part of the straightening process.

Algorithm for Hypospadias Urethroplasty

Figure 147-7 shows the algorithm for hypospadias repair based on tubularization of the urethral plate or a neoplate substitute. All hypospadias can be repaired using either of two operative techniques: TIP and two-stage graft urethroplasty. Inlay graft procedures are a variation on TIP urethroplasty. Two-stage grafts use prepuce or oral mucosa depending on clinical circumstances (discussed later).

Flap options are shown in Figure 147-7 with dashed lines. A comparison of flaps versus grafts is summarized later. We choose to not use flaps because cosmetic results appear to be inferior to these other alternatives.

Distal Hypospadias Repair

Tubularized Incised Plate Urethroplasty

Indications. Snodgrass and colleagues (2010) used TIP urethroplasty as the only repair for 551 consecutive patients with distal

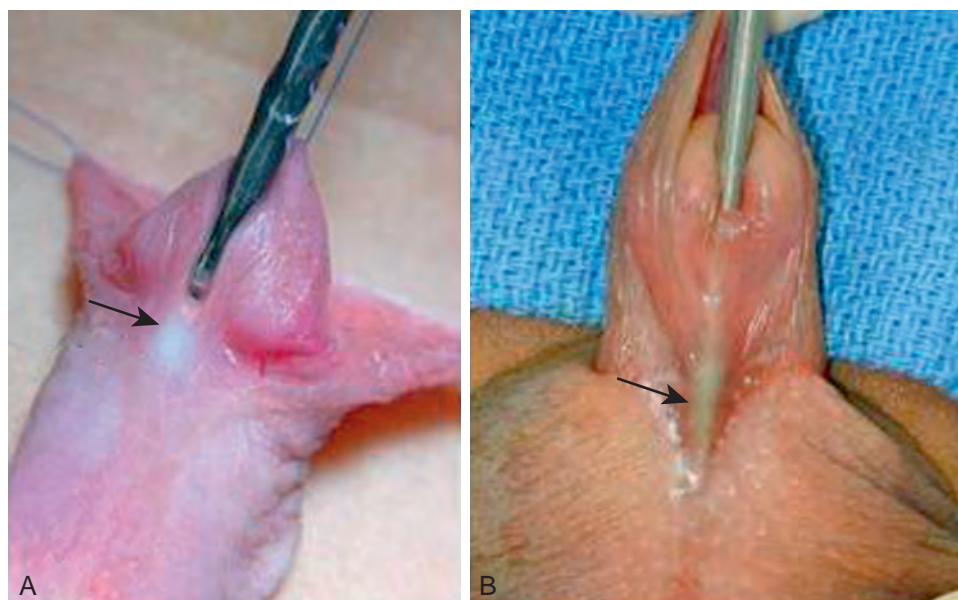


Figure 147-6. Sounding the distal urethra. A, Adequate subepithelial tissues between the shaft skin and urethra (arrow). Initial skin incision can be made 2 mm proximal to the meatus. B, Deficient subepithelial dartos and spongiosum between shaft skin and urethra (arrow). Initial U-shaped skin incision should be made lateral and proximal to the visible urethra.

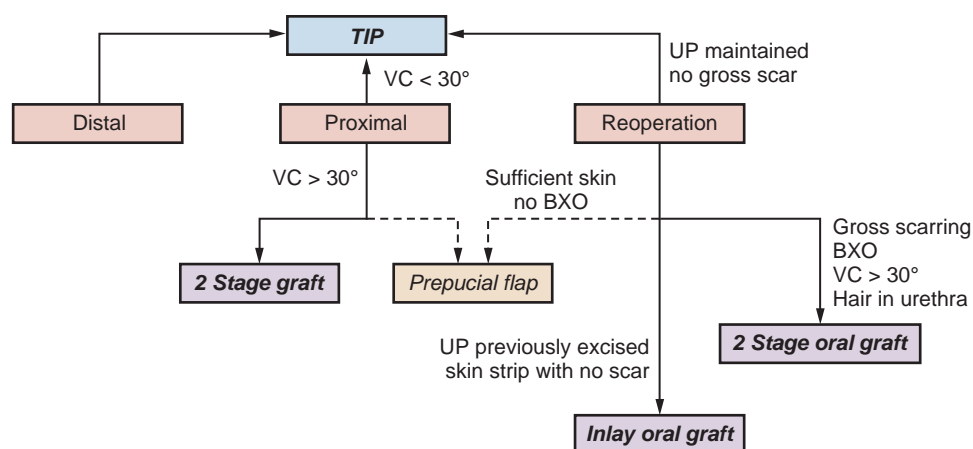


Figure 147-7. Algorithm for hypospadias urethroplasty. BXO, balanitis xerotica obliterans; TIP, tubularized incised plate; UP, urethral plate; VC, ventral curvature.

hypospadias, finding no contraindication to the technique. As discussed in the earlier [Urethral Plate Assessment](#) section, three studies reported no difference in TIP outcomes whether the groove was deep, intermediate, or flat (Holland and Smith, 2000; Sarhan et al, 2009; Snodgrass et al, 2010). Two of these stated that a narrow plate (<8 mm) increased complications (Holland and Smith, 2000; Sarhan et al, 2009), but we believe this indicated failure to adequately incise the plate.

Surgical Technique (Fig. 147-8). Skin management varies according to family preference for circumcision versus prepucioplasty. Because most request circumcision in the United States, we illustrate that method in this section and describe prepucioplasty separately later.

The glans width is determined at its widest point using calipers (Fig. 147-9) and then a 5-0 polypropylene stay stitch is placed. The corners of the dorsal prepuce are held and the line for incision is marked. Ventrally the incision is approximately 2 mm below the meatus, or more proximal if the distal urethra is found by sounding to appear “thin” from deficient underlying dartos and corpus

spongiosum (Fig. 147-10). For glanular cases without fusion of the glans wings, the incision is made a few millimeters below the corona. The oblique dorsal incision is made to preserve sufficient inner prepuce to transfer ventrally and create a uniform “collar” resembling a normal circumcision (Firlit, 1987).

Degloving is done in different planes: dorsally along the Buck fascia and ventrally just under the shaft skin, preserving available dartos. Dissection continues to the penopubic and penoscrotal junctions. Artificial erection is done, and if curvature less than 30 degrees is demonstrated it is corrected by dorsal plication as described earlier.

Next a tourniquet is placed at the base of the penis and the visible junctions of the glans wings to the urethral plate are marked. These lines are injected with 1:100,000 epinephrine and incised using a Beaver 69 blade (Beaver-Visitec International, Waltham, MA). Dissection continues down to the surface of the corpora and then laterally on each side to approximately 3 and 9 o'clock. If the glans width is less than 14 mm, or if there is tension on glans wings approximation after this “standard” mobilization, then additional

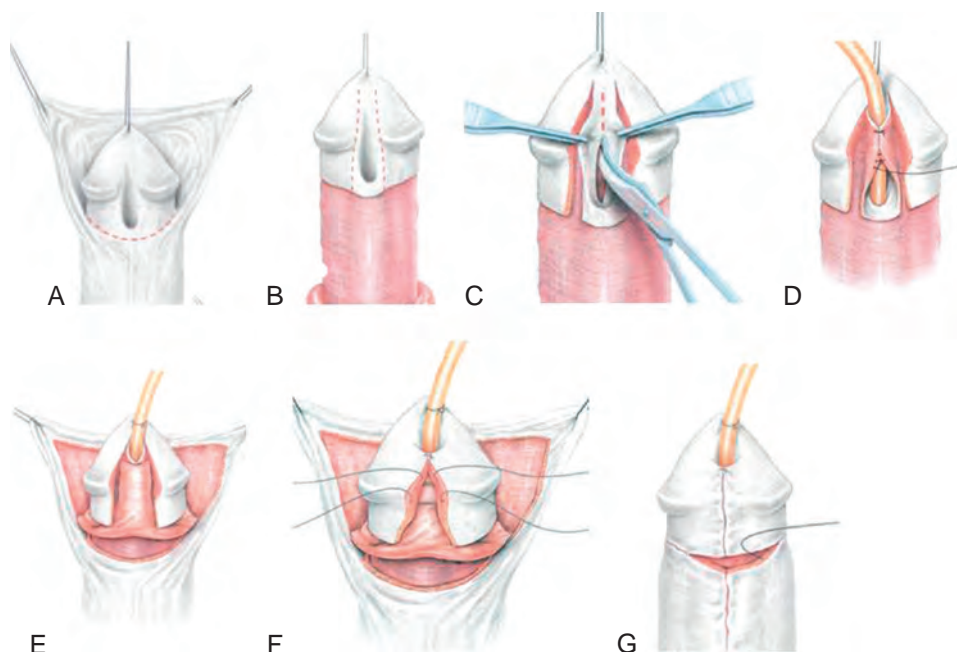


Figure 147-8. Distal tubularized incised plate repair. **A**, Circumscribing skin incision. **B**, Incisions along the visible junction of the glans wings to the urethral plate. **C**, Incision of the urethral plate extending to near the underlying corpora. **D**, Tubularizing the urethral plate from distally to proximally. Note that the first stitch is about 3 mm proximal to the end of the plate, creating an oval opening. **E**, The neourethra is covered with a dartos flap. **F**, Glansplasty creating the neomeatus and continuing down to the corona. **G**, Repair and circumcision completed. (From Snodgrass WT. Snodgrass technique for hypospadias repair. *BJU Int* 2005;95:683–93.)



Figure 147-9. Measuring glans width. Glans width less than 14 mm predicts increased urethroplasty complications.

“extended” dissection is next done at 3 and 9 o’clock, further releasing the wings for a distance of approximately 4 mm distally (Fig. 147-11).

The urethral plate is held on either side and gently stretched laterally using 0.5 Castroviejo forceps. Tenotomy scissors incise the midline from within the meatus to the tip of the plate down to the

surface of the underlying corpora. Depth of incision varies according to the preexistent plate groove; a flat plate requires a deeper dissection than an already deeply grooved plate. Distal plate incision may leave a small shelf at the glans junction but should not extend into the glans, which is distinguished by its more dull and granular appearance (Fig. 147-12).

A 6-Fr stent is passed into the bladder and tied to the glans traction suture. Urethral plate tubularization is done in two subepithelial layers using 7-0 polyglactin on a TG-140 needle. The first stitch is placed distally approximately 3 mm below the end of the plate to create an oval, not a rounded, opening. Suturing further distally increases risk for iatrogenic meatal stenosis. Continuous stitching proceeds proximally to the meatus where it is tied, and then the same suture returns distally for the second layer. Next a ventral dartos flap is raised, split into two longitudinal segments when possible, and crossed over the neourethra to provide two-layer coverage. We tack this into place using 9-0 polyglactin.

Glansplasty approximates the wings with 6-0 polyglactin subepithelial interrupted stitches, beginning distally and continuing to the corona proximally. Most often three stitches are placed. It is not necessary to additionally suture the epithelium, which could leave visible marks. If there is tension on this closure after usual glans wings mobilization, the stitches are removed and an extended mobilization is done as described previously. The glans wings are not sutured to the underlying neourethra even though there is a gap between the tubularized end of the urethral plate and the first distal stitch of the glans that creates the neomeatus (Fig. 147-13). This gap heals spontaneously.

Residual ventral shaft skin attached to the inner prepuce is then excised and the “collar” approximated using 7-0 polyglactin interrupted subepithelial stitches (see Fig. 147-10C and D), and usually a single epithelial 9-0 polyglactin stitch at the corona. The dorsal prepuce is split in the midline to the edge of the inner preputial collar and then fixed in the midline using a 7-0 polyglactin subepithelial stitch. The ventral midline skin is closed to re-create a median raphe, and remaining excess skin laterally on either side is excised

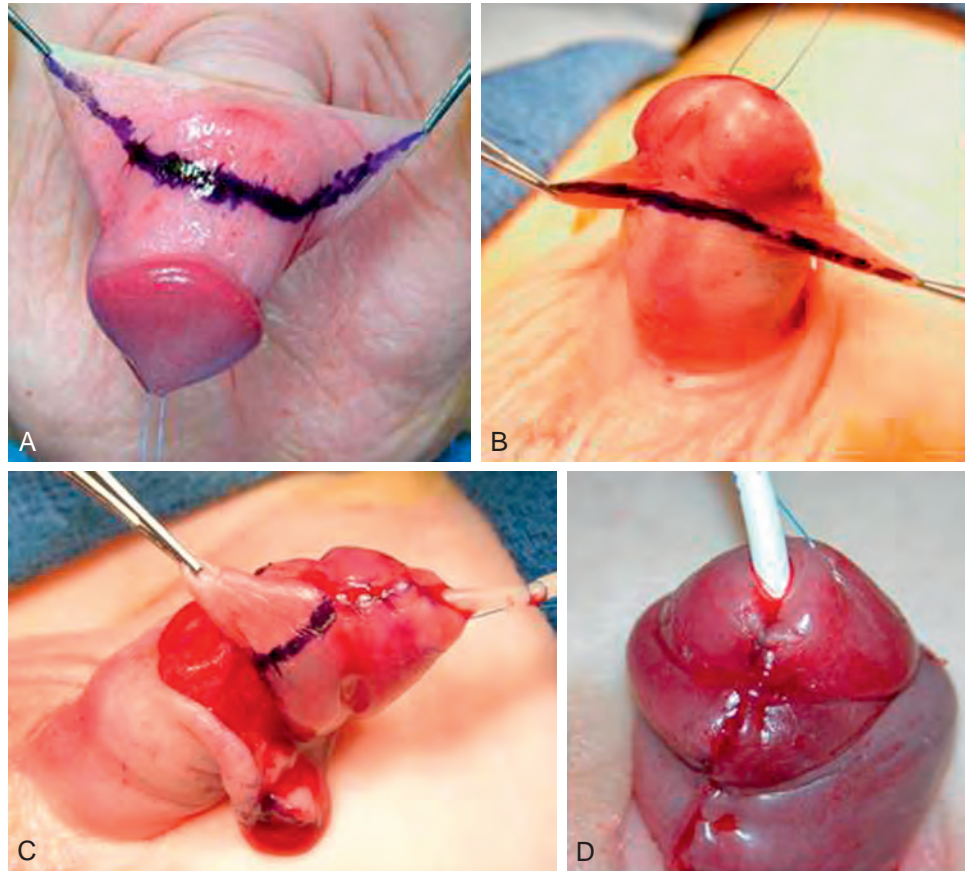


Figure 147-10. Skin incision for circumcision. A, Dorsal line. B, Ventral line. C, Perimeatal shaft skin to be excised before the inner preputial “collar” is made ventrally. D, Completed repair with circumcision demonstrating preputial collar.

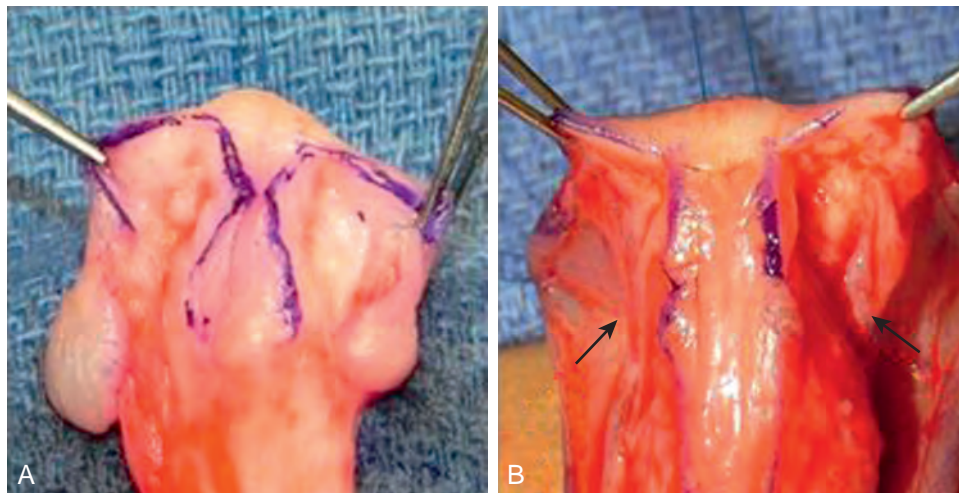


Figure 147-11. Glans wings dissection. A, “Standard” mobilization along the corpora from the urethral plate medially toward 3 and 9 o’clock laterally. B, “Extended” mobilization with additional dissection at 3 and 9 o’clock for about 4 mm distally along the corpora. The arrows indicate the surface of the corpora exposed by this further mobilization.

to complete circumcision. All skin edges are closed with subepithelial stitches. We use urinary diversion into diapers for approximately 1 week.

Alternative Methods. Multiple methods have been described for distal hypospadias that remain in use in various centers. Descriptions

are available elsewhere. The most common include the meatal advancement and glanuloplasty incorporation (MAGPI) and Mathieu or flip-flap techniques.

The MAGPI procedure is an operative technique for glanular and coronal hypospadias in which the urethral plate is cut in the dorsal

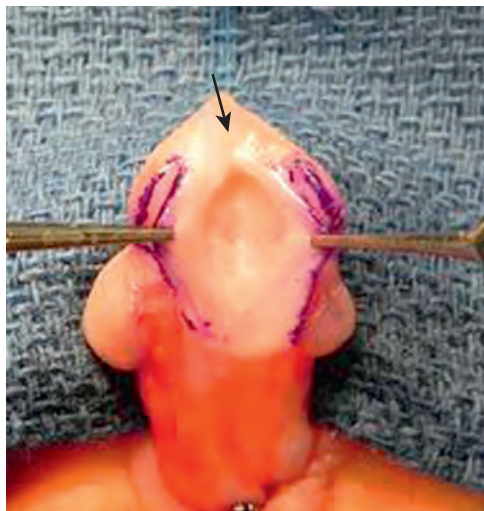


Figure 147-12. Urethral plate incision extends deeply to near the corpora, from within the meatus to the end of the plate distally (arrow).

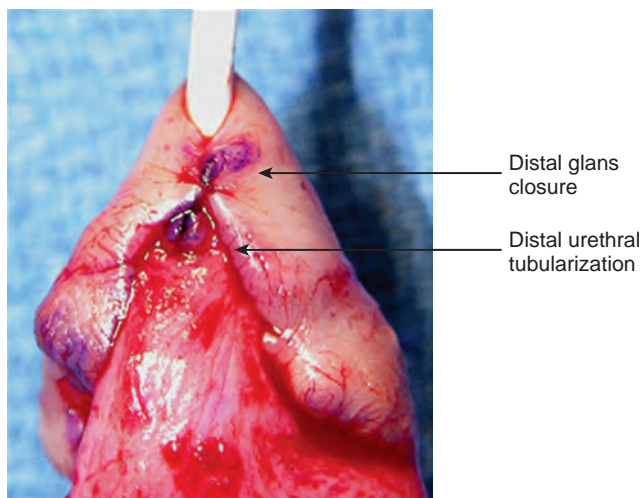


Figure 147-13. Tubularized incised plate (TIP) glansplasty. The most distal stitch approximating glans wings, creating the neomeatus, usually is beyond the most distal stitch of the tubularized urethral plate. It is not necessary to suture the glans wings to the urethral plate in TIP repair.

midline and then the dorsal meatus is advanced distally and sutured. Next the ventral lip of the meatus is pulled distally and the glans closed beneath it (Duckett, 1981).

The Mathieu procedure, or flip-flap, is an operative technique for distal hypospadias in which a rectangular flap is outlined proximally from the meatus on the ventral penile shaft, and then elevated and sutured distally to the urethral plate (Mathieu, 1932). This repair is typically stented for a short period.

Results. Most articles report complications in less than 10% of cases after distal TIP urethroplasty.

Snodgrass and colleagues (2010) reported outcomes in 426 boys a mean of 8 months after distal TIP repair had been performed by Snodgrass. Assessment included calibration, uroflowmetry, and/or urethroscopy done in 279 patients (65%). Urethroplasty complications occurred in 19 patients (4%), including nine fistulas, nine glans dehiscences, and one meatal stenosis that developed later from balanitis xerotica obliterans (BXO). There were no strictures or diverticula.

A systematic literature review by Wilkinson and associates (2012) included 15 articles on distal TIP urethroplasty from 1994 through 2009, comprising 1872 boys. The authors reported 4% fistulas and 3% meatal stenoses with no urethral strictures. Glans dehiscence was not reported.

Snodgrass (2011) also reviewed 36 articles on distal TIP urethroplasty published in English between 1994 and 2009. Reported complications ranged from none to 24%, with 25 of the articles reporting 10% or less, mostly fistulas and meatal stenoses.

Proximal Hypospadias Repair

Decision Making

Choice of technique for proximal hypospadias repair is largely determined by the extent of VC after degloving and excision of any scrotal extensions onto the penile shaft. Options for urethroplasty when there is curvature less than 30 degrees include TIP repair and onlay preputial flap. Curvature greater than 30 degrees resulting in transection of the urethral plate for straightening limits urethroplasty options to single-stage tubularized preputial flaps, two-stage preputial flaps, or two-stage preputial graft repairs.

Tubularized Incised Plate Urethroplasty

Indications. Proximal TIP urethroplasty can be done when there is VC less than 30 degrees. Greater curvature prompts urethral plate transection and so precludes TIP repair. As discussed in the earlier [Urethral Plate Assessment](#) section, in approximately 7% of cases the plate lacks sufficient subepithelial tissues to tubularize, or is subjectively rigid and therefore unsuitable to fashion the neourethra.

Surgical Technique (Fig. 147-14). Proximal TIP urethroplasty can be done with either circumcision or prepucioplasty. In this section we describe the operation as performed when circumcision is requested by the family; prepucioplasty is discussed later.

The glans width is first measured and then a 5-0 polypropylene stay stitch is placed. The dorsal line for incision extends adjacent to the corona approximately 3 mm proximally, preserving most of the inner prepuce for use as a graft should there be either VC greater than 30 degrees or a urethral plate not suitable for TIP urethroplasty. Ventrally the incision runs in a U shape alongside the plate, avoiding visible hair follicles, and then continues down the midline of the scrotum. The ventral incision lines adjacent to the urethral plate are injected with 1 : 100,000 epinephrine to minimize bleeding from underlying corpus spongiosum. The penis is degloved to the penopubic and penoscrotal junctions. All ventral dartos and scrotal attachments are dissected off to the base of the penis.

Next the glans wings are marked along their junction with the urethral plate and also injected with 1 : 100,000 epinephrine before incision. The glans wings are dissected laterally along the surface of the corpora cavernosa to 3 and 9 o'clock. In patients with a glans width less than 14 mm or with tension of glans wings approximation, dissection is extended along the corporal bodies distally for about 4 mm (see Fig. 147-11). The attachments of the corpus spongiosum wings to the ipsilateral glans wings on either side are divided. The spongiosum on either side of the urethral plate is further dissected off the corpora cavernosa for subsequent spongioplasty.

Artificial erection is done and VC is addressed as discussed earlier. When the penis is straight and the urethral plate conserved, the plate is incised dorsally from the meatus to its distal end extending to near the underlying corporal bodies. A 6-Fr stent is passed into the bladder and tubularization is done in two subepithelial layers, the first using an interrupted 7-0 polyglactin stitch and the second a continuous 7-0 polydioxanone stitch.

Spongioplasty approximates the corpus spongiosum wings over the neourethra. Then a hemiscrotum is entered and the testis exposed. The tunica vaginalis is opened transversely and stay stitches are placed into its distal corners. A stay is also placed in the adventitia near the inferior pole of the testis for countertraction. A tunica vaginalis flap is created by dissecting along the spermatic cord to near the external ring. Fatty scrotal tissues are excluded

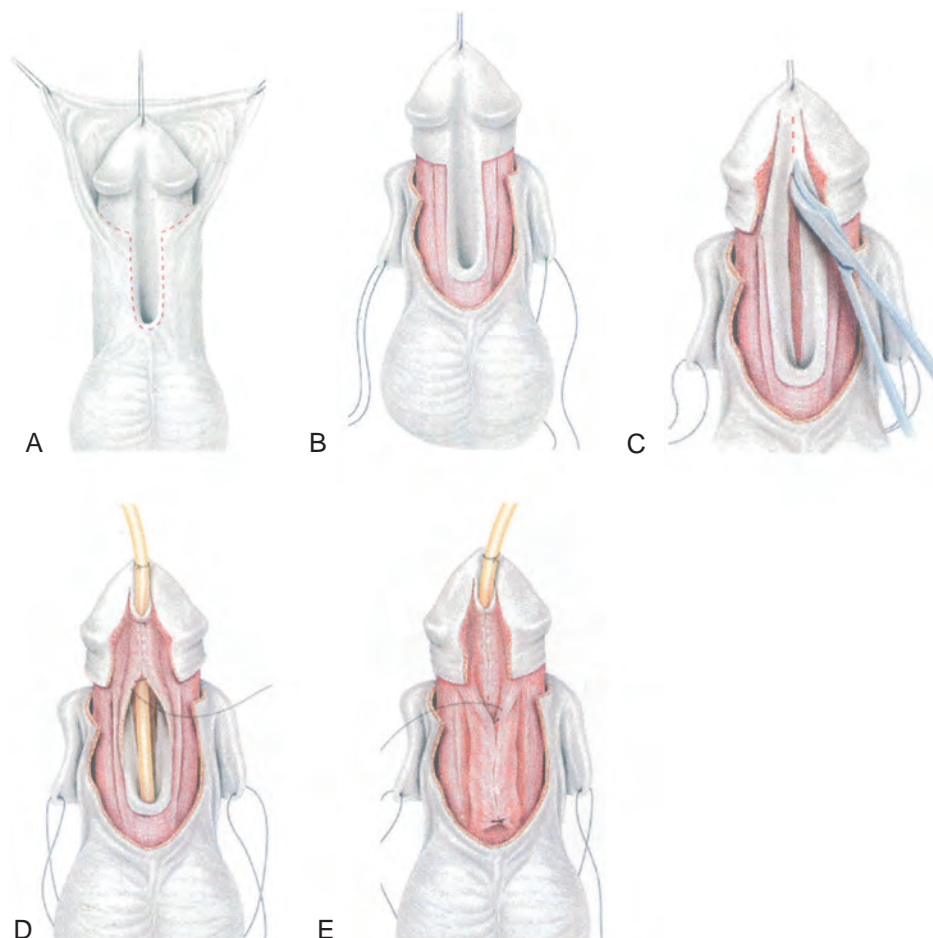


Figure 147-14. Proximal tubularized incised plate repair. A, Circumscribing incision preserves urethral plate in patient desiring circumcision. B, After degloving, glans wings are separated from the urethral plate. Corpus spongiosum is dissected from the cavernosal bodies and released distally from the glans wings for later spongioplasty. At this point artificial erection is performed and ventral curvature straightened as discussed in the text. C, Midline urethral plate incision. D, Two-layer urethral plate tubularization using interrupted subepithelial 7-0 polyglactin followed by running 7-0 polydioxanone. E, Spongioplasty approximates divergent corpus spongiosum over the neourethra, before a tunica vaginalis barrier flap is added. (From Snodgrass WT. Snodgrass technique for hypospadias repair. *BJU Int* 2005;95:683–93.)

(Fig. 147-15). The testis is returned to its normal position and suture pexed into place, and then its compartment is closed. The flap is brought over the neourethra, shiny surface down, and tacked with 7-0 polydioxanone.

Glansplasty is done in one layer using 6-0 interrupted subepithelial polyglactin, usually with three stitches from distal to the corona. As described for distal TIP urethroplasty, the glans wings are not sutured to the neourethra.

Shaft skin attached to the inner prepuce ventrally is excised (see Fig. 147-10C) and the preputial collar is completed using interrupted subepithelial 7-0 polyglactin and one epithelial 9-0 polyglactin suture at the corona. Then the dorsal prepuce is divided in the midline to the level of the preputial collar and sutured there using 7-0 subepithelial polyglactin. Ventrally the penoscrotal junction typically is incised to approximately 3 and 9 o'clock and then the scrotum near these points is sutured to the corpora on either side of the true penoscrotal junction with 5-0 polydioxanone, moving the tunica vaginalis flap aside to do so. In nearly all cases this maneuver corrects penoscrotal transposition without need for scrotal flaps and the visible scars those produce (Fig. 147-16).

Excess preputial skin is excised to complete the circumcision and the ventral skin is closed, creating a median raphe. All skin stitches are subepithelial. We use urinary diversion into diapers for 2 weeks.

An example of the final cosmetic appearance is shown in Figure 147-17.

Results. Urethroplasty complications have been reported in from 15% to over 50% of cases. One report described technical modifications in the urethroplasty that reduced complications.

Snodgrass and Bush (2011) reported outcomes in 59 consecutive patients, with urethroplasty complications occurring in 53% of the initial 15 cases, 25% of the next 20, and 13% of the last 24. Most of these were fistulas or glans dehiscences, and various technical changes were made specifically to reduce fistula occurrence, including a change from single-layer to two-layer urethroplasty, epithelial to subepithelial suturing, and 7-0 chromic catgut to polyglactin and polydioxanone. All of the first 35 patients had a dartos flap placed over the neourethra. The final 24 had tunica vaginalis rather than dartos flaps. There were no fistulas in the final cohort. Glans dehiscence is now our most common complication, and is discussed in detail later in this chapter.

A report by Ghanem and Nijman (2010) concerned 49 patients with proximal TIP repair in which urethroplasty was done in one layer using continuous subepithelial 6-0 polyglactin covered by dartos. During mean follow-up of 3 years there were urethroplasty complications in 12% of patients that included four fistulas, one meatal stenosis, and one glans dehiscence.

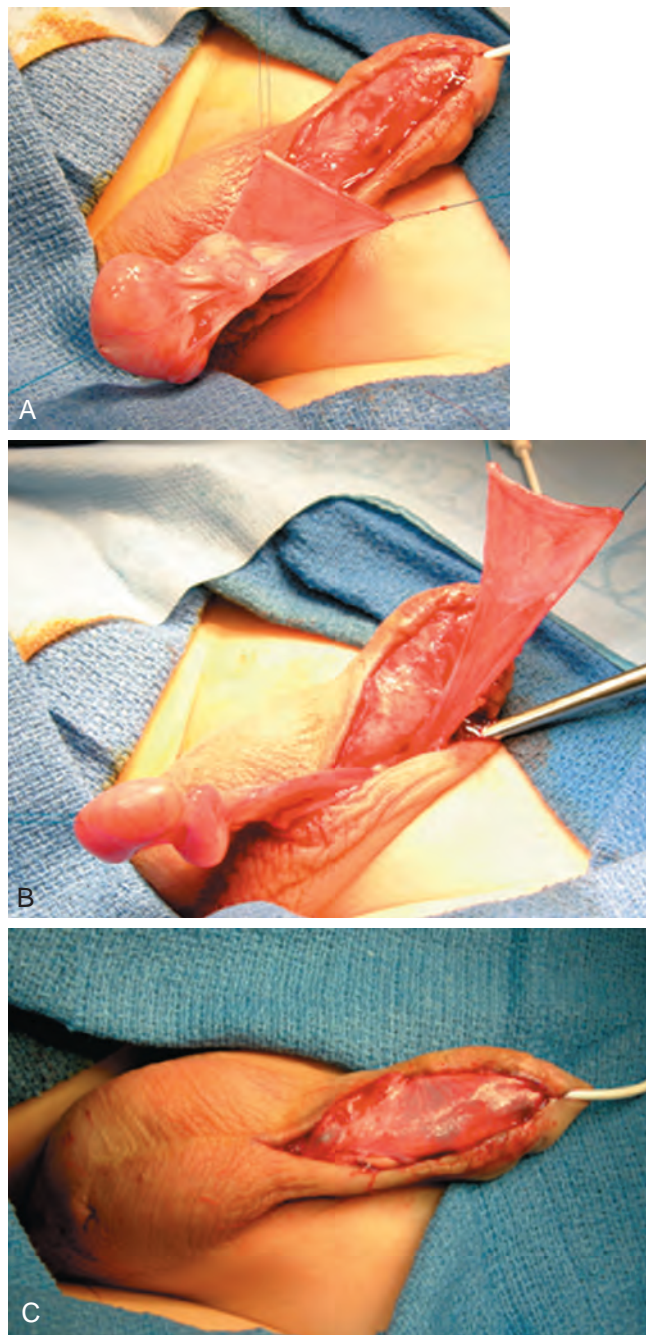


Figure 147-15. Tunica vaginalis barrier flap. A, Testicle delivered and tunica vaginalis opened transversely. B, Tunica vaginalis flap dissected to near the external ring to avoid tension on either the testicle or the penis. C, Flap covers the entire neourethra. Testicle is pexed into its scrotal compartment.

A retrospective review by Braga and associates (2008) compared 35 proximal TIP repairs to 40 onlay preputial flap repairs with mean follow-up of 3 years. There was no significant difference in urethroplasty complications: 60% for TIP and 45% for onlays.

Two-Stage Graft

Indications. The main indication for a two-stage graft repair is VC greater than 30 degrees after degloving and excision of ventral dartos and scrotal attachments to the penis. The urethral plate is transected as part of the straightening maneuvers, and either preputial or oral labial graft is used to bridge from the native urethra to the glans tip. The choice of graft is determined by the family's

preference for either circumcision or prepucioplasty. When circumcision is done the discarded prepuce is used for urethroplasty, whereas oral mucosa from the lower lip is taken when prepucioplasty is desired.

Surgical Technique

First Stage. The initial skin incision is the same as described earlier for proximal TIP urethroplasty, maintaining most of the inner prepuce for a graft if needed. The operation proceeds as described for proximal TIP urethroplasty to the point that artificial erection demonstrates VC greater than 30 degrees.

Urethral plate transection is done distally at the coronal level, and then the plate is excised from the corpora, moving proximally to the meatus and beyond toward the membranous portion. The native urethra is then gently stretched distally and anchored at intervals to the corpora using 6-0 polydioxanone. This maneuver moves the urethrostomy distally, reducing the length of graft needed. The native urethral mucosa is sutured to the corpora using 7-0 polyglactin at 10, 12, and 2 o'clock. Proximal urethroplasty is completed by suturing the native urethra to penile skin or scrotum at 4, 6, and 8 o'clock with 7-0 polyglactin.

Stay stitches are placed into the corners of the dorsal prepuce and the underlying dartos is excised. Typically the graft is mostly inner prepuce with less outer preputial skin, with the width determined by the lower edge of the subcoronal collar (Fig. 147-18).

The dorsal shaft skin is sutured to the preputial collar using interrupted subepithelial 7-0 polyglactin. Then the graft is placed into the ventral defect and first stitched to the glans, which has been opened widely, at the level of the corona with 7-0 polyglactin. Additional stitches secure the graft to the distal end of the glans, placed subepithelially to avoid marks where the neomeatus will be created during the second procedure. The graft is gently stretched proximally and sewn to the shaft skin on either side using interrupted 7-0 polyglactin. The proximal end is split in the midline to extend graft to either side of the urethrostomy, which is sutured at the 2, 10, and 12 o'clock positions medially and to the shaft skin or scrotum laterally. A preputial graft harvested as described in Figure 147-28 (see later) will fill the defect from the glans tip to deep within the scrotum.

Next the graft is quilted onto the corpora at 1-cm intervals using 6-0 polyglactin on an RB-1 needle, which easily penetrates the graft and adheres it to the underlying tunica albuginea (Fig. 147-19). A catheter is placed in the bladder. Then a rolled Vaseline gauze (Conopco, Englewood Cliffs, NJ) is laid onto the graft and held firmly, but not tightly, by 5-0 polypropylene stay stitches tied over the gauze. This tie-over bandage further immobilizes the graft and helps prevent seroma or hematoma accumulation beneath it. The catheter and tie-over bandage are maintained for 7 days. Physical activity is not limited in infants and young children. No special care is needed for the graft after the bandage is removed during the interval before the second stage. We always wait 6 months before second-stage repair.

Second Stage. An incision is marked along the glans wings and shaft skin adjacent to the now revascularized graft, moving into the urethrostomy ventrally to remove the penile or scrotal skin that was sutured there from 4 to 8 o'clock. The glans wings are injected with 1:100,000 epinephrine and incised and dissected laterally, as is the remainder of the marked incision. If the glans width is less than 14 mm, extended dissection is done as described earlier to reduce tension on the subsequent approximation of its wings.

A 6-Fr stent is passed into the bladder and secured to the glans traction stitch. Preputial grafts are very thin and can be tubularized in two layers similarly to the urethral plate in proximal TIP repair using 7-0 polyglactin and polydioxanone. Then a tunica vaginalis flap is created and placed over the entire neourethra. Glansplasty is completed as described earlier for proximal TIP urethroplasty.

A subepithelial 5-0 polydioxanone suture secures the scrotum to the corpora on either side of the neourethra to establish the penoscrotal junction, and then penile and scrotal skin are closed in the midline using subepithelial sutures. Urine is diverted for 2 weeks.

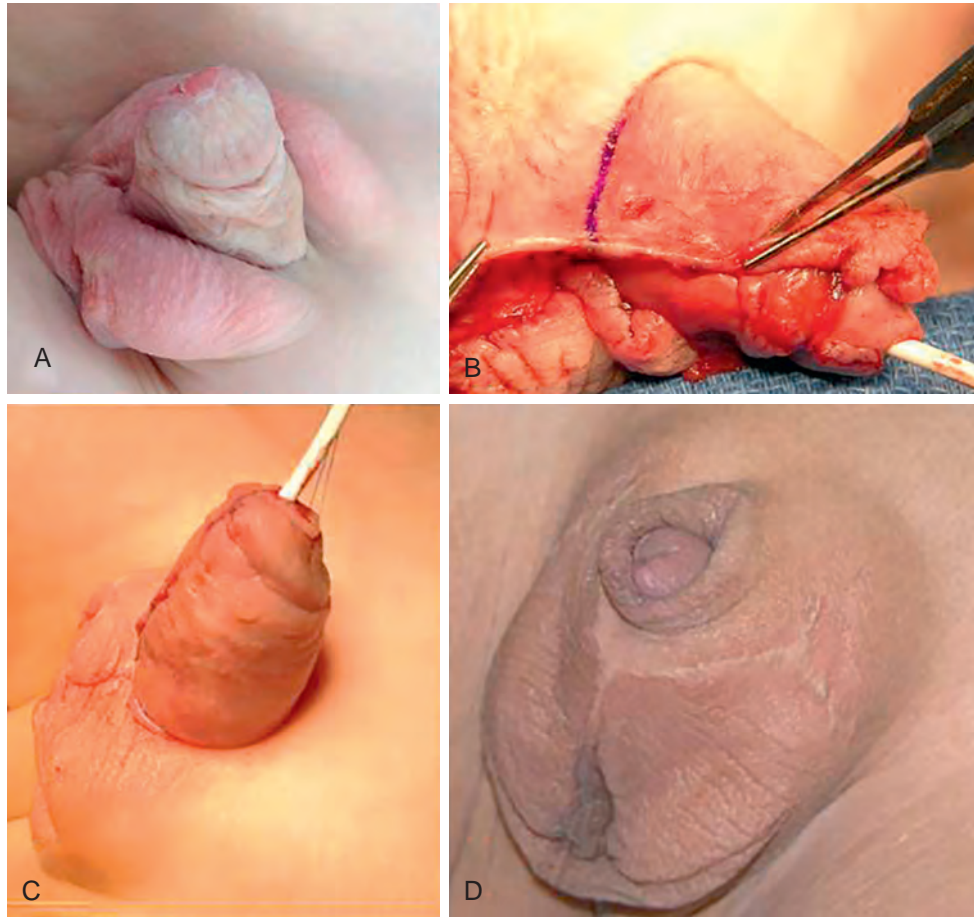


Figure 147-16. Scrotoplasty without scrotal flaps. A, Penoscrotal transposition. B, Ventral incisions at the penoscrotal junction extending to approximately 3 and 9 o'clock to allow the scrotum to be pulled downward and secured to the corpora on either side of the urethra. C, Correction of transposition without rotational scrotal flaps. D, Scars after rotational flaps. These are not always later concealed by pubic hair.

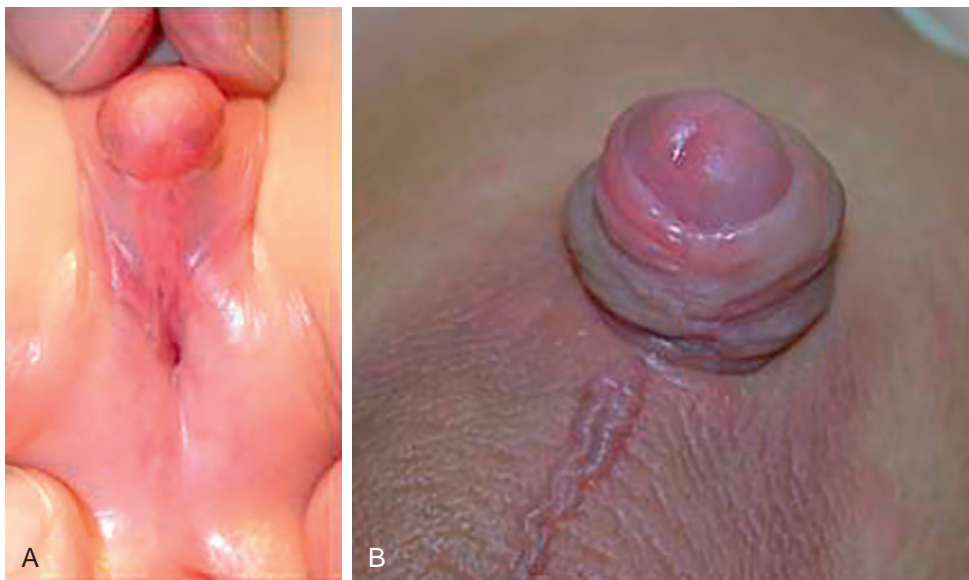


Figure 147-17. A and B, Appearance after proximal tubularized incised plate repair.

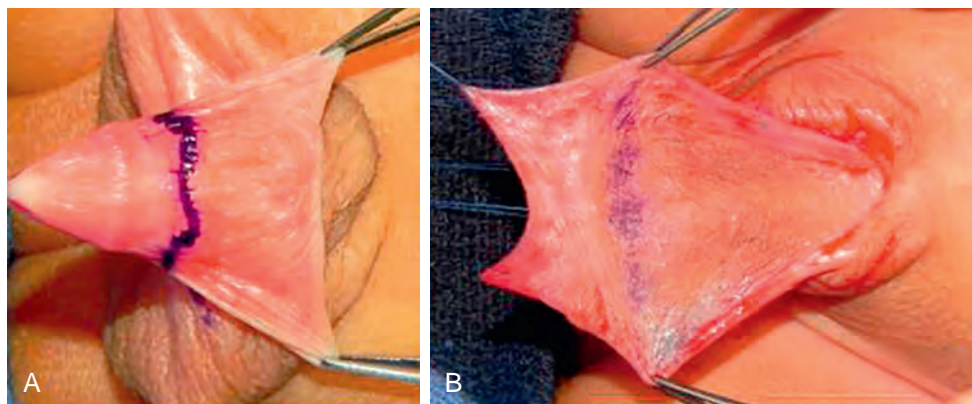


Figure 147-18. Preputial graft harvest. A, Initial degloving incision runs a few millimeters proximal to the corona, preserving as much inner prepuce as possible for the graft. B, Lower line of incision for graft harvest.

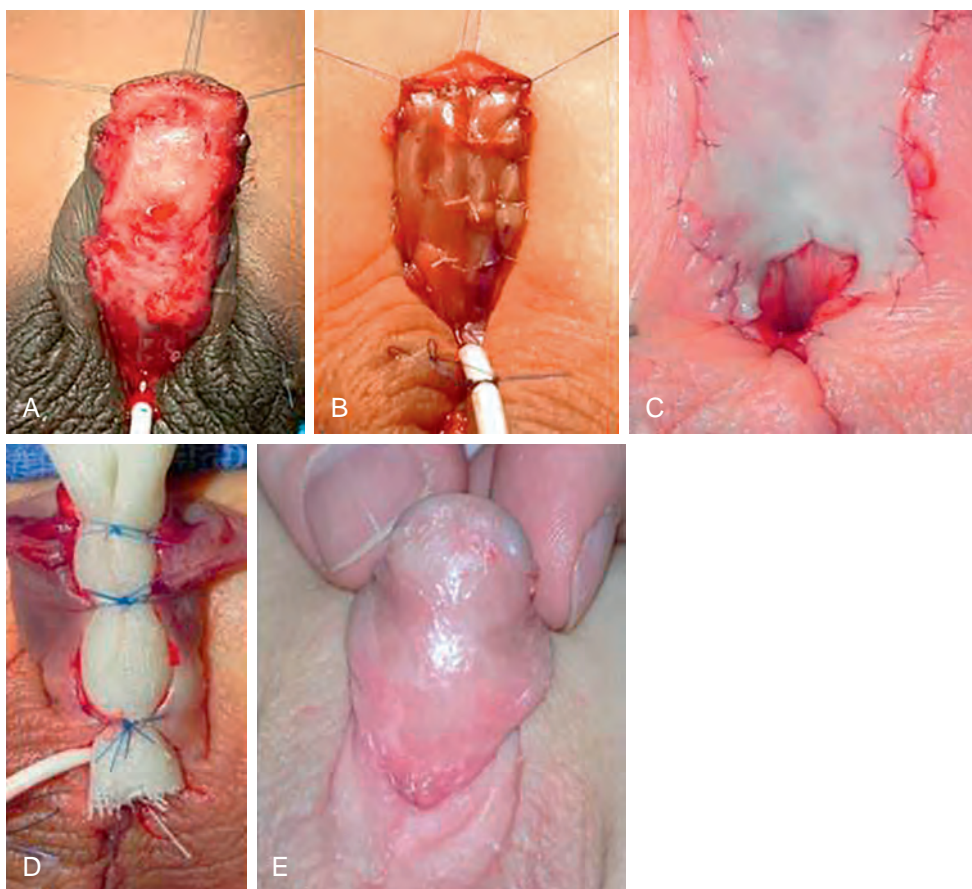


Figure 147-19. Preputial graft quilting and final result. A, Defect to be grafted after the urethral plate has been excised, glans wings developed, and proximal urethrostomy created. B, Graft secured to glans, shaft skin, and scrotum at the perimeter of the defect and then quilted to the corpora first along the midline and then to either side at approximately 1-cm intervals. C, Detail showing the graft extending to either side of the urethrostomy before quilting. D, Tie-over dressing gently compresses the graft to reduce possibility for seroma or hematoma to accumulate beneath it. E, Healed graft.

Results. There are few published results for two-stage primary graft repairs, with urethroplasty complications reported in from 25% to 50% of patients.

A retrospective review of 34 patients with proximal shaft to perineal hypospadias operated using two-stage preputial grafts reported urethroplasty complications in 26%, comprising four glans dehiscences,

two fistulas, one diverticulum, and one neourethral stricture (Ferro et al, 2002).

We currently have unpublished follow-up results in 24 patients with proximal shaft (n = 3), penoscrotal (n = 6), scrotal (n = 7), and perineal (n = 8) hypospadias. Ventral lengthening using transverse corporotomies without corporal grafting was needed after

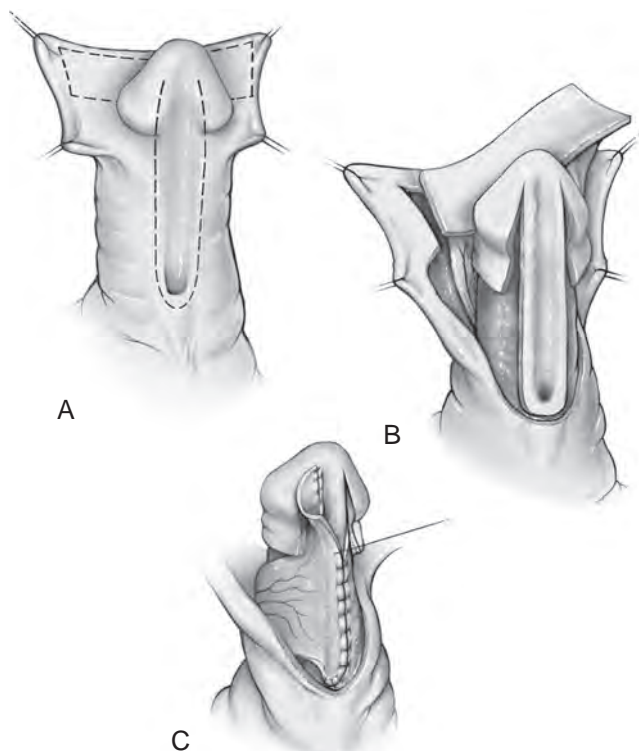


Figure 147-20. Onlay preputial flap. A, Lines of incision to create the preputial flap and preserve the urethral plate. B, Preputial flap mobilized on its vascular pedicle. C, Flap sewn to the urethral plate.

urethral plate transection in 20 (83%). Three patients (12.5%) had graft contracture requiring regrafting as a separate procedure, two involving lip grafts and one after preputial grafting. Urethroplasty complications occurred in 12 patients (52%): 11 glans dehiscences and 2 fistulas. Mean glans diameter for the entire group, measured in 22 patients, was 12 mm, with 15 (68%) less than 14 mm. Extended glans wings mobilization was not used in any of these patients because we had not yet started using this technique.

Preputial Flaps

Indications. Onlay and tubularized preputial flaps are single-stage alternatives to TIP and two-stage graft repairs, respectively.

Surgical Technique

Onlay Flap. The technique for onlay preputial flaps is illustrated in Figure 147-20. The initial lines of incision, degloving and release of dartos and scrotal attachments, and development of glans wings are the same as described earlier for proximal TIP urethroplasty. Artificial erection demonstrates 30 degrees or greater VC, straightened by dorsal plication when present.

The corners of the dorsal prepuce are held with stay stitches and a 10-mm-wide strip of its inner surface is harvested, preserving the underlying dartos vascular supply. Dissection of the pedicle extends to the penopubic junction to prevent tension when the flap is moved ventrally either around the side of the penis or via a buttonhole incision over the glans.

A 6-Fr stent is passed into the bladder. The flap is then sewn to the urethral plate using subepithelial 7-0 polyglactin, gently stretching it distally and trimming it as needed to maintain uniform dimensions. The dartos pedicle is used to cover the suture lines. Next, glansplasty first secures the glans wings to the flap edges using interrupted subepithelial 7-0 polyglactin. Proximally the wings are approximated together with interrupted subepithelial 6-0 polyglactin. Circumcision and skin closures are done as described for proximal TIP urethroplasty.

Tubularized Flap. The technique for tubularized preputial flaps is illustrated in Figure 147-21. When artificial erection finds VC greater

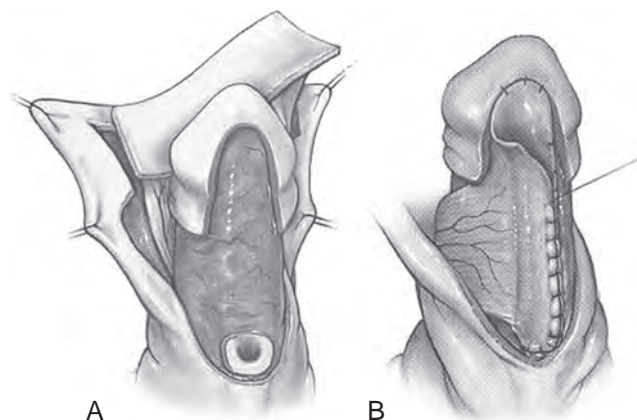


Figure 147-21. Tubularized preputial flap. A, After degloving and release of ventral dartos, persisting ventral curvature greater than 30 degrees led to excision of the urethral plate. An inner preputial flap approximately 10 mm wide is dissected on its dartos vascular pedicle and transposed ventrally. This flap can be tubularized, with the proximal end anastomosed to the spatulated native urethra and the distal end to the glans wings. B, Alternatively, one edge of the flap can be fixed with interrupted sutures to the corpora cavernosa from the proximal meatus distally into the glans. Then the flap is trimmed and the opposite edge sutured along the first to create a tube with uniform caliber. Glansplasty and skin closure are similar to that described for onlay preputial flaps.

than 30 degrees, the urethral plate is transected and additional straightening maneuvers as described earlier are performed as needed.

The corners of the dorsal prepuce are held with stay stitches and a flap 12 to 15 mm wide is outlined horizontally on its inner portion. The flap is released and its pedicle dissected to the penopubic junction. The flap can then be tubularized over a 6-Fr stent in two layers, the first using a running subepithelial 7-0 polyglactin followed by several more interrupted stitches. This tube is moved ventrally, sewn to the spatulated native urethral meatus, and then stretched distally with the suture line down against the corpora. The flap is sewn to the glans wings using interrupted subepithelial 7-0 polyglactin. Remaining glans wings are approximated using subepithelial interrupted 6-0 polyglactin.

Alternatively, the flap can be brought ventrally before its tubularization and sewn to the native urethra dorsally. Then it is stretched distally and one edge is sewn to the underlying corpora to create a pseudoplate. Excess flap skin is excised and the remaining free end is sewn to the lateral edge to complete a tube.

Results. Urethroplasty complications after proximal preputial flap repairs have been reported in 27% to 45% of onlay flaps and in 14% to 33% of tubularized flaps. Two articles suggested that complications are fewer with tubularized flaps when they are first secured to the corpora along one edge to create a pseudoplate and then fashioned into a tube.

Onlay flap repair for proximal hypospadias was reported in 126 patients with mean follow-up to 22 months. Urethroplasty complications developed in 27%, with 18 fistulas, 13 glans dehiscences, 2 strictures, 1 diverticulum, and 4 flap prolapses through the meatus (de Mattos e Silva et al, 2009). Another retrospective review described outcomes for penoscrotal onlay flaps in 75 cases with postoperative follow-up to a mean of 39 months. Complications were encountered in 45%: eight fistulas, two dehiscences, two strictures, one meatal stenosis, and five patients with recurrent VC after dorsal plication (Braga et al, 2007).

Tubularized preputial flap outcomes for penoscrotal or more proximal hypospadias were described for 27 cases with median 9 months of follow-up. Of these, 33% developed urethroplasty complications, including seven fistulas, one stricture, and one meatal stenosis (Powell et al, 2000).

Two reports described outcomes from tubed preputial flaps in which tubularization was accomplished after first suturing the flap to the corpora. In one, 12 patients with penoscrotal or scrotal hypospadias had postoperative follow-up to a mean of 24 months, during which time 2 (17%) had complications: one fistula and one meatal stenosis with diverticulum (Shukla et al, 2004). In the other, 22 boys with proximal hypospadias had a similar repair and subsequent follow-up also to an average of 24 months. There were complications in three (14%) patients: one fistula and two meatal stenoses (Aoki et al, 2008).

Byars Flaps

Byars flap refers to a two-stage operation in which the urethral plate is excised during penile straightening in the initial operation. The dorsal prepuce is split down its midline and the two parts are transferred ventrally with their dartos vascular pedicles and sutured into the defect from the meatus to the glans. At the second operation the previously transferred prepuce is tubularized (Byars, 1955).

This technique has been used following corporotomy with grafting by those who prefer a two-stage urethroplasty rather than a single-stage tubularized preputial flap. However, there are few reported outcomes. The largest, with 58 patients, only mentioned postoperative fistulas among all the possible urethroplasty complications (Retik et al, 1994). Another three studies had fewer patients. Shukla and colleagues (2004) reported results in only 10 patients with an average 43 months of follow-up, noting urethroplasty complications in 70%, including seven fistulas, three meatal stenoses, and one diverticulum. Gershbaum and colleagues (2002) had 11 patients with follow-up of "5 to 15" years, with complications in 18% (one fistula and one diverticulum), although the authors stated that 2 more patients had a "subterminal meatus or skin irregularities" that potentially increased the rate to 36%. In addition, they stated that 37% had abnormal voiding and spraying.

I (W.S.) used the operation in 9 patients with a 100% complication rate, with two fistulas, five diverticula, one stricture, and two glans dehiscences. Although fistulas and glans dehiscence are common in proximal hypospadias repair, it was diverticula, and the stricture that resulted when a less wide skin strip was tubularized to try to prevent a diverticulum, that prompted me to abandon this technique. We no longer perform Byars flaps or recommend their use.

Flaps versus Grafts

There are no trials randomizing patients with proximal hypospadias and VC greater than 30 degrees to tubularized flap versus two-stage

graft repair. Proponents of flaps state that their vascularity is assured from the pedicle, whereas that of grafts is less reliable because they must revascularize. However, Duckett once commented that fluorescein showed devascularized edges to his flaps that had to be excised, although he never published these observations in a clinical series (Duckett, unpublished comment to Hodgson, 1981).

Graft take was successful in all 43 cases reported by Ferro and colleagues (2002) using prepuce. We encountered contracture resulting in an additional procedure to partially or totally regraft in 4 of 65 (6%) patients, without a difference between prepuce and oral mucosa (Snodgrass and Bush, 2015). Our series differs from that of Ferro and colleagues in that we straightened VC in 26 (90%) of these cases using transverse corporotomies, which was done in 3 of the 4 patients with contracture. No patient has required more than one regrafting.

Urethroplasty complications that potentially indicate impaired vascularity include meatal stenosis and strictures. Tubularized flap outcomes described earlier reported meatal stenosis and/or stricture in approximately 8% (Powell et al, 2000; Shukla et al, 2004; Aoki et al, 2008), whereas 3% of two-stage grafts developed a stricture (Ferro et al, 2002). None of our patients has had either meatal stenosis or stricture.

There are also few data regarding cosmetic results. Patients we have evaluated who were operated elsewhere with flaps, an admittedly potentially biased group, most often have had glans dehiscence and a less cylindrical shape to the penis (Fig. 147-22). This glans dehiscence may be protective against diverticulum, but at the potential cost of urinary spraying.

Currently there are insufficient functional or cosmetic data to establish the best practice and determine if benefits of a two-stage repair outweigh the need for two operations.

Prepucioplasty

Prepucioplasty can be done in nearly all patients, with both distal and proximal hypospadias, whose caregivers request it (Fig. 147-23). In 1% of cases a patient has a large glans and small dorsal hood that prevent prepucioplasty. When prepucioplasty is done for proximal hypospadias in which urethral plate transection is needed for VC straightening, two-stage repair uses an oral labial mucosa graft.

Indications. Foreskin reconstruction is indicated in any primary hypospadias repair when caregivers prefer it to circumcision. We simply ask if newborn circumcision was anticipated and, if not, offer prepucioplasty.

Surgical Technique. Stay sutures are placed into the corners of the dorsal prepuce (see Fig. 147-23A). Initial incision extends from these points, lateral to the glans, and then to a point approximately



Figure 147-22. Appearance after flap and graft repair for proximal hypospadias. **A**, Tubularized flap repair with a pyramidal shape of the penis. **B**, The same patient, who appears to have a slit meatus, is noted instead to have glans dehiscence with a coronal meatus. **C**, Cylindrical penile shape and slit meatus with well-healed glansplasty after two-stage preputial graft repair.

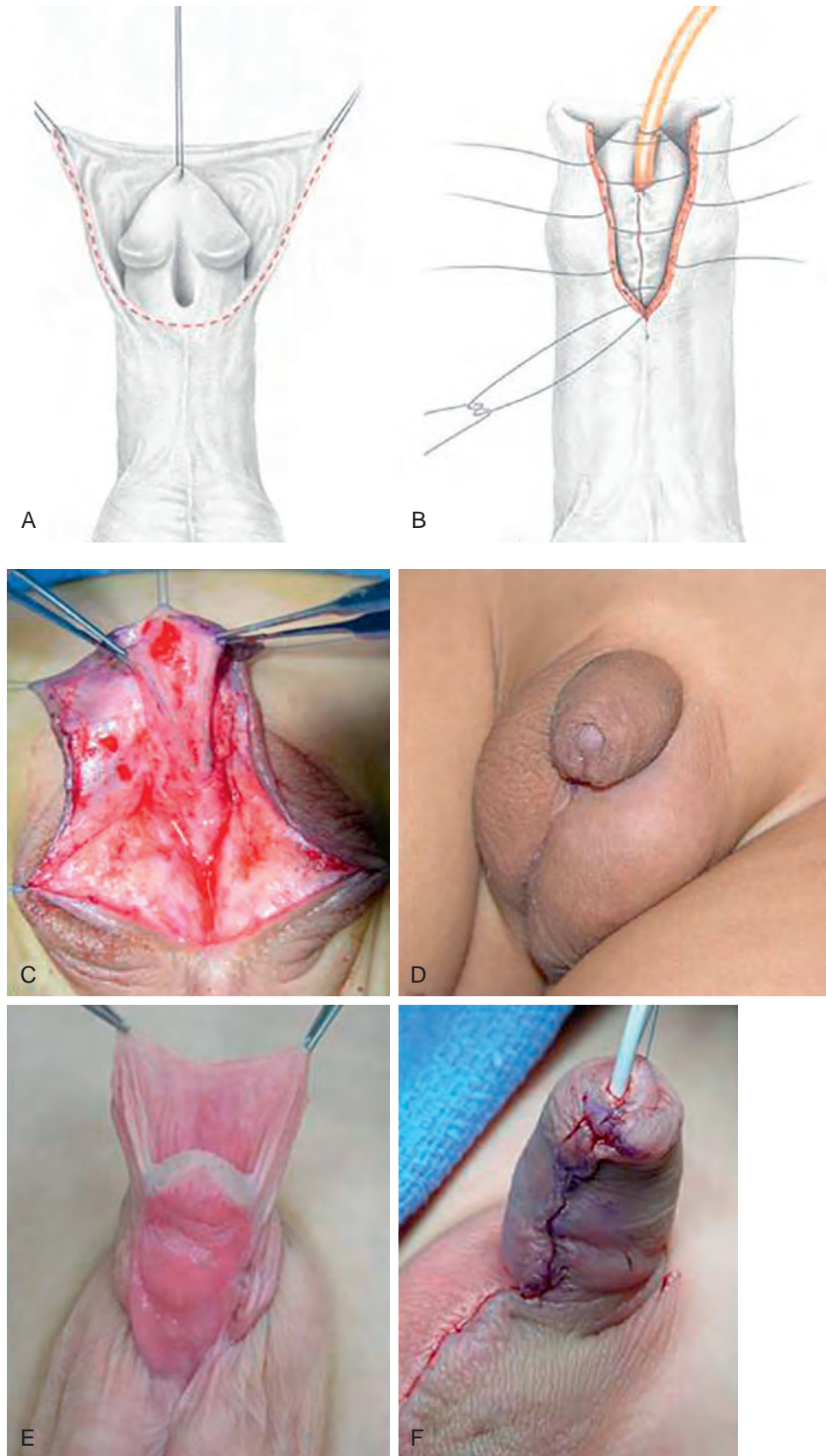


Figure 147-23. Prepuceplasty. A, V-shaped incision from the corners of the dorsal prepuce extending ventrally to below the meatus. B, Skin closure. C and D, Proximal tubularized incised plate urethroplasty with prepuceplasty. Note the excellent ventral exposure gained without degloving the penis. E and F, Two-stage proximal repair using oral mucosa graft.

2 mm below the meatus. The penis is not degloved, and ventrally dissection is done immediately under the skin to preserve dartos for a barrier flap until normal tissues are encountered, generally near the penoscrotal junction.

Urethroplasty and glansplasty are done as already described for distal or proximal TIP or two-stage graft repairs.

After glansplasty the foreskin stays are pulled down below the glans and the inner prepuce is approximated using subepithelial 7-0 polyglactin. Then the stays are pulled distal to the glans. These corners are approximated together also using subepithelial 7-0 polyglactin. Previously we adjusted the position of this initial stitch to allow the foreskin to readily retract back and forth over the glans. However, this sometimes leaves the prepuce visibly deficient ventrally, and so today we suture it to achieve the best appearance and are not concerned about its retractability, given that normal boys the same age as those undergoing hypospadias repair often have similarly nonretractable foreskin. The remainder of the incision is closed using interrupted 7-0 polyglactin. Caregivers are instructed not to retract the foreskin.

Results. Urethroplasty and skin complications are the same after distal or proximal TIP or two-stage graft repairs, whether circumcision or prepucioplasty is done.

Suoub and coworkers (2008) compared 25 distal TIP repairs with prepucioplasty to an age- and time-matched cohort of 49 distal TIP repairs with circumcision, reporting no difference in either urethroplasty or skin complications. The only urethroplasty complications were fistulas, occurring in 12% and 8%, respectively. One patient with "recalcitrant" phimosis had secondary circumcision after prepucioplasty versus two with "redundant skin" after circumcision who had circumcision revision (Suoub et al, 2008).

Snodgrass and colleagues (2013) also reported a case-cohort study of 428 consecutive distal TIP urethroplasties of which 85 had prepucioplasty. There were no intraoperative conversions to circumcision. Urethroplasty complications developed in 8% after prepucioplasty and 9% after circumcision. Two percent of each group had subsequent skin revision, which included one circumcision for BXO 5 years later and one excision of an unsightly dorsal whorl without circumcision following prepucioplasty.

Snodgrass and Bush (2011) did prepucioplasty during proximal TIP urethroplasty in 21% of cases (all who requested it), with none having postoperative urethroplasty or skin complications. Prepucioplasty was also done in 25% of those undergoing two-stage graft repair (all who requested it), with none having recurrent curvature or urethroplasty or skin complications (unpublished data).

Because prepucioplasty does not increase either urethroplasty or skin complications, the choice between it and circumcision should be mentioned to all caregivers, allowing them to determine the final cosmetic appearance.

Scrotoplasty

In the last edition of this textbook "major" scrotoplasty using rotational skin flaps to correct penoscrotal transposition was illustrated. Today we no longer perform this maneuver, having found that we can correct transposition with ventral penoscrotal incisions leaving no visible scars. Instead, shaft skin adjoining the scrotum is incised ventrally to 3 and 9 o'clock, and then the scrotum is rotated down to create a new penoscrotal junction and sutured to the corpora on either side of the neourethra with 5-0 polydioxanone as shown in Figure 147-16.

POSTOPERATIVE MANAGEMENT

Urinary Diversion

Several studies reported that distal TIP urethroplasty in pre-toilet-trained boys can be done without diversion, expecting less than 5% to need catheterization early postoperatively and no increase in urethroplasty complications.

One trial of toilet-trained boys found greater dysuria, retention, and extravasation in those not catheterized, resulting in

catheter placement in 40% of those not randomized to diversion. Urethroplasty complications were not impacted by whether or not diversion was used.

There are no data indicating benefit of suprapubic diversion in addition to or as a substitute for urethral catheters.

Three studies reported results for midshaft to distal TIP urethroplasty without urinary diversion in non-toilet-trained patients:

- Almodhen and associates (2008) reported on 32 consecutive non-toilet-trained boys (mean age 18 months) who had TIP urethroplasty for distal to midshaft and proximal shaft ($n = 6$) hypospadias without a catheter. One (distal vs. proximal not stated) developed urinary extravasation on the second postoperative day that was treated with catheterization. One patient (3%) had a urethroplasty complication (meatal stenosis) during follow-up of 9 ± 6 months.
- Samuel and colleagues (2002) reported on 170 consecutive patients (mean age 19 months) who had distal TIP repair without diversion. None had urinary retention or needed catheterization. Urethroplasty complications occurred in 7% during follow-up to a mean of 3 years.
- Leclair and associates (2004) reported on 162 consecutive patients (mean age 16 months) with distal or midshaft ($n = 6$) TIP repair without diversion. Catheterization was needed for urinary retention in 4 patients (2.5%), 2 within hours of surgery and 2 at 1 week postoperatively, without subsequent complications. Urethroplasty complications occurred in 8%, both fistulas and meatal stenoses.

An RCT by El-Sherbiny (2003) compared outcomes in 64 toilet-trained boys (median age 6 years) to distal TIP urethroplasty with versus without catheterization, decided at the end of the operation. Urethroplasty complications were similar in both groups (3 of 35 stented vs. 6 of 29 not catheterized, $P = .3$). However, dysuria (14% vs. 45%), retention (0 vs. 24%), and extravasation (0 vs. 17%) occurred significantly more often in those not diverted. Of the 29 patients not catheterized, 12 (41%) were catheterized within 3 days of operation.

We have used urinary diversion to avoid need for postoperative catheterization in the minority of pre-toilet-trained patients who otherwise will develop retention or extravasation. A 6-Fr bladder stent is used for all repairs in prepubertal boys, versus a 12- to 14-Fr catheter after puberty. For patients who are operated before toilet training, the catheter drains into a single diaper. We never use suprapubic tubes in either primary or reoperative hypospadias repair.

Given that most infants undergoing distal repairs in these studies did not require diversion, we recently began performing distal TIP urethroplasty without a stent, which obviates need for postoperative antibiotics and facilitates early, normal bathing resumed at 48 hours after surgery.

Bandages

Two trials reported no differences in urethroplasty outcomes whether or not bandages were used.

To our knowledge only two studies consider the possible impact of postoperative bandages on urethroplasty outcomes:

- Van Savage and colleagues (2000) randomized 100 patients to a transparent waterproof adhesive bandage around the penis removed by parents 2 days after surgery versus no bandage. Two were excluded for bleeding at the end of the operation. There were no differences in urethroplasty complications at mean follow-up of 1 year, but telephone calls were significantly more frequent from parents of those without a bandage than from parents of those with a bandage (0.8 vs. 0.3 calls/patient). The authors did not state if these reported calls referred to wound questions versus other concerns.
- McLorie and associates (2001) allocated 120 patients at the end of repair to a transparent biomembrane adhesive film versus compressive wrap versus no bandage with polymyxin B and bacitracin zinc in white petrolatum applied at each diaper change for 7 days. Three patients were withdrawn for bleeding



Figure 147-24. Postoperative bandage.

requiring a compressive dressing. Bandages were removed at 3 or more days and white petrolatum was then applied for another 7 days. There were no differences among groups with regard to urethroplasty complications.

If bandages do not impact urethroplasty outcomes, then various wraps that may be painful to remove can be avoided. We use a Tegaderm (3M, St. Paul, MN) adhesive around the penis and a second holding a gauze over the wound, both of which fall off spontaneously at home (Fig. 147-24).

Medications

Antibiotics

One trial reported that postoperative oral cephalexin reduced the incidence of febrile UTI.

The only trial regarding postoperative antibiotics after hypospadias repair included 101 patients undergoing TIP urethroplasty who all received intraoperative intravenous cefonicid and then were randomized to postoperative oral cephalexin for 8 days during urinary diversion versus no antibiotic. Urethroplasty outcomes were the same but febrile UTI occurred in 3 of 52 antibiotic-treated versus 12 of 49 untreated patients ($P < .05$) (Meir and Livne, 2004).

We do not use intraoperative antibiotics during hypospadias repair except for those patients having oral mucosa harvest, to whom intravenous cefazolin is given. Postoperatively trimethoprim-sulfamethoxazole is given during urinary diversion.

Analgesics and Antispasmodics

We recommend oral ibuprofen 4 times daily alternating with acetaminophen for infants to children approximately 2 years of age. Older children are provided hydrocodone with acetaminophen to use between ibuprofen doses as needed.

Oxybutynin 0.2 g/kg per dose up to 5 mg is given twice daily, or as a single extended-release tablet, to patients 3 years of age or older.

OUTCOMES ASSESSMENT

Hypospadias repair is much more than simply urethroplasty, and outcome assessment includes genital appearance as well as penile functions of urination, erection, and ejaculation. In children most emphasis has been on urethroplasty complications, with less on cosmetic results. Available data regarding sexual functions in adults

are reviewed in the later section on [Adult Outcomes after Prepubertal Repair](#).

Duration of Follow-Up

Eighty percent of urethroplasty complications are diagnosed within 1 year after surgery, with indefinite follow-up needed in 14 patients for each complication subsequently encountered.

Snodgrass and colleagues (2014a) reported the time at which any urethroplasty complication was diagnosed after 887 primary and reoperative TIP repairs. There were a total of 125 complications—54 fistulas, 59 glans dehiscences, 9 meatal stenoses or neourethral strictures, and 3 diverticula—of which 64% were diagnosed at the first postoperative visit and 80% within the first postoperative year. Median time to encounter fistulas, meatal stenoses and strictures, and diverticula was 6 months, whereas glans dehiscence was diagnosed at a median of 2 months. After 1 year we calculated that 14 patients would require indefinite follow-up for each additional complication eventually diagnosed (Snodgrass et al, 2014a).

Continuous longitudinal follow-up to puberty has never been reported for patients undergoing prepubertal hypospadias repair. Several retrospective reviews evaluating the time to diagnosis of urethroplasty complications reported late complications (after 1 year) in those patients who returned because of their complication. Wood and associates (2008) studied fistulas and found that 70% were diagnosed by 1 year, but the tally did not reach 90% and 99% until follow-up at 8 and 20 years. Spinoit and colleagues (2013) reported 24% of reoperations for urethroplasty complications or unsatisfactory appearance were done at more than 2 years postoperatively, but that after 3 years 15 boys would need assessment for each additional complication found.

Clearly more complications are potentially found as duration of follow-up increases. However, many boys who will never have a complication have to be reviewed indefinitely for each additional one diagnosed after 1 year. We recommend office assessment at 6 weeks and then 6 months later (8 months postoperatively) after distal TIP urethroplasty and advise caregivers at the last visit that a complication may become apparent at a future date. After proximal repairs we request annual follow-up with the academic goal of determining functional outcomes pre- and postpuberty, given the greater degree of VC and the longer urethroplasty with proximal hypospadias.

Calibration

The minimum caliber of the normal urethra in boys varies in published reports. One study found that 14% of boys less than 3 years of age were less than 8 French.

Calibration of the neourethra is an objective means to establish that there is no anatomic obstruction after urethroplasty. We routinely calibrate pre-toilet-trained patients with a 10-Fr sound at the 8-month postoperative visit, but the very low prevalence of obstruction supports limiting calibration to infants with questionable obstructive voiding and/or a small-appearing meatus.

Normal meatal size was determined by Allen and colleagues (1972) in 100 consecutive full-term newborns using bougies à boule or olive-tipped catheters on day 2 of life. The mean and median was 8 French, with half the patients less than 8 French to as small as 4 French in 10%. Another study also used bougies à boule in 200 referred patients, reporting that 14% were less than 8 French to age 3 years (Litvak et al, 1976).

Uroflowmetry

No study provides flow rates in patients compared to age-matched controls, and outcomes based on nomograms may vary depending on the nomogram used.

Approximately 25% of patients after TIP repair or onlay or tubularized preputial flap repair have Qmax less than 2 standard deviations below normal based on varying nomograms, yet have

no symptoms. The significance of this finding in asymptomatic patients is unknown.

Following Tubularized Incised Plate Urethroplasty

Andersson and colleagues (2011) reported flow rates in 37 asymptomatic boys from a total of 126 distal and proximal TIP repairs. At 1 year the mean Qmax was 13.6 mL/sec (range 6 to 28), with half below the 5th percentile on the Miskolc nomogram. At an average of 6 years later the mean Qmax was 19 mL/sec and 32% were below the 5th percentile, a significant improvement. The authors stated that fewer patients would have been categorized as below the 5th percentile had the Toguri nomogram been used (Andersson et al, 2011).

Snodgrass (1999) reported uroflowmetry in 17 of the first 50 toilet-trained boys following TIP urethroplasty, determined at a mean of 45 months (range 6 months to 7 years) postoperatively. All peak flows were above the 5th percentile based on the nomogram used by Jayanthi and colleagues (1995) (which was not reported in the article).

Considering Qmax less than 2 standard deviations from normal a possible indication of obstruction, a review by Gonzalez and Ludwikowski (2011) of reported TIP uroflows found that 36 of 140 (26%) asymptomatic patients in three articles using different nomograms met that criterion.

We hypothesize that the Qmax changes little after initial healing but that at puberty the increased urethral diameter should increase the flow rate. Currently we have limited data in patients before and after pubertal development. In two the Qmax improved from 7 to 19 mL/sec and 13 to 20 mL/sec at Tanner stage 4. Three others have no change in Qmax at Tanner stage 2.

Following Preputial Flaps

Jayanthi and colleagues (1995), in a review of uroflows in 51 toilet-trained boys following either onlay or tubularized preputial flaps, reported that 27% had Qmax below the 5th percentile of an institutional nomogram.

Patel and coworkers (2004) obtained uroflowmetry a mean of 14 years after proximal repair in infancy (mean age 17 months) and reported a mean Qmax of 17 mL/sec without differences between onlay and tubularized flaps.

Cosmetic Results

Two studies used standardized photographs to compare TIP versus flap cosmetic outcomes, both reporting higher scores for TIP repairs. A questionnaire study compared TIP patients to controls after circumcision and found similar ratings by caregivers 6 weeks after surgery.

Objective assessment of genital appearance after hypospadias surgery is not commonly reported. Two studies used photography scored by blinded reviewers to compare TIP to Mathieu (appendix) or onlay flaps. Both reported TIP scores significantly higher (Ververidis et al, 2005; Scarpa et al, 2009).

Snodgrass and colleagues (2008) used a nonvalidated questionnaire answered by caregivers before physician examination 6 weeks after distal or proximal TIP urethroplasty versus controls following circumcision. There were no differences in Likert scale scores regarding overall appearance or the specific appearance of the meatus or penile skin.

Hayashi and associates (2007) compared photographs after standard onlay to photographs after a modified V-shaped incision ventrally to create a more vertical meatus shape. Overall improvement was reported, with 8 of 25 standard versus 12 of 18 modified repairs achieving a slit meatus ($P = .03$). A V-shaped incision was effective in all 4 patients with a deeply grooved and in 6 of 9 with a moderately grooved plate, but in only 2 of 5 with a flat configuration.

There are no other studies concerning aesthetic appearance of the penis after flap repairs. Although the V-shaped incision proposed by Hayashi and associates (2007) did result in more patients with a slit meatus, the patients most likely to have a rounded

appearance with flaps are those with a flat plate, and V-shaped incision was effective in fewer than 50% of those.

COMPLICATIONS

Risk Factors

Risk factors for urethroplasty complications include proximal meatus, reoperation, and glans width less than 14 mm. Studies in which patients did not routinely have barrier flaps over the neourethra have found that this is also a risk factor for complications (fistulas).

Bush and colleagues (2012) used multivariate analysis to evaluate potential risk factors for hypospadias urethroplasty complications among 669 consecutive prepubertal TIP repairs, using prospectively recorded data. These included patient age, meatal location, reoperation, glansplasty suture type (chromic vs. polyglactin), and surgeon learning curve (defined as the first 50 cases). Of these, the only independent factors were reoperation (odds ratio [OR] 3.07, 95% confidence interval [CI] 1.54 to 6.13) and proximal meatus (OR 1.79, 95% CI 1.33 to 2.40).

Bush and colleagues (2013) subsequently analyzed 391 patients with glans measurements for patient age, meatal location, reoperation, and glans width (in millimeters). Meatal location and reoperation remained independent factors, but so was glans width less than 14 mm (OR 3.7, 95% CI 1.6 to 8.5), with each 1-mm increase in glans size decreasing complications.

Two other reports used multivariate analysis of retrospectively collected data after TIP urethroplasty. Eassa and associates (2011) evaluated 391 patients operated by five surgeons, analyzing for age, meatal location, reoperation, surgeon, urethroplasty sutures (polyglactin vs. polydioxanone) and methods (interrupted vs. continuous), a flap over the neourethra, and urinary diversion. Only proximal meatus location (relative risk [RR] 2.81, 95% CI 1.42 to 5.52), age greater than 4 years (RR 3.25, 95% CI 1.44 to 7.35), and no barrier flap (RR 6.23, 95% CI 1.87 to 20.77) were risk factors. Sarhan and coworkers (2009) evaluated 500 patients operated by five surgeons, analyzing for age, meatal location, reoperation, urethroplasty suturing method (interrupted vs. continuous), neourethral coverage, urinary diversion, and learning curve (defined as the first 100 cases). Independent risk factors were proximal meatus, no barrier layer, and learning curve.

We cannot model for barrier layers or urinary diversion because both are used systematically. As discussed earlier, we did not find age at repair to be an independent risk factor for urethroplasty complications.

Modifying Risk Factors

Meatal Location

Only 10% of primary cases present with a meatus on the proximal shaft to the perineum. Case logs reported to the American Board of Urology by U.S. pediatric urologists requesting a certificate of added qualification indicated the average number of proximal repairs done annually was two (Kogan and Feustel, 2011). Given that proximal meatus location is a consistent risk factor for urethroplasty complications, we recommend that centers designate a single surgeon to perform these cases to increase his or her expertise.

Reoperation

Initial failure increases risk for additional failure. We recommend that surgeons review their personal outcomes and consider changes in procedure and/or technique to reduce complications, as we discussed earlier in the chapter. The Results section under Proximal Hypospadias Repair details technical modifications we have made that significantly reduced urethroplasty complications after proximal TIP urethroplasty.

Academic surgeons must ensure good outcomes for the patient when allowing trainees to actively participate in key steps of the surgery, especially urethroplasty and glansplasty.

A survey by [DeLair and coworkers \(2008\)](#) of mostly senior urology residents having completed more than 75% of their training found that few had performed glans wings dissection or urethroplasty. Fellows in our program also observe these key steps until faculty conclude that their skills are satisfactory, and they rarely perform more than 50% of any given repair. Bush compared distal TIP outcomes of our former fellows in consecutive cases done over a 2-year period beginning 3 or fewer years after training to those of Snodgrass during the same time frame. There were no significant differences in urethroplasty complications among the former fellows or between them and Snodgrass (Bush et al, unpublished).

We also recommend that reoperations in major centers be done by a single surgeon.

Glans Size

As discussed in the earlier section on [Preoperative Androgen Stimulation](#), preoperative androgens are known to increase glans width. We analyzed urethroplasty complications in patients who received adjuvant testosterone injections versus those with glans 14 mm or greater who did not. Mean glans width before stimulation was 12 mm, increasing to a mean of 16.5 mm with testosterone injections. Untreated patients had a mean glans width of 15.4 mm. Urethroplasty complications occurred in 34% with versus 11% without adjuvant androgens ($P < .0001$). Testosterone was found to be an independent risk factor for complications in this analysis (OR 3.1, 95% CI 1.2 to 8.1). Accordingly, we have stopped preoperative testosterone stimulation ([Bush et al, 2013](#)). Now we use the extended glans wings dissection described earlier for patients with glans width less than 14 mm. Although we do not yet have outcomes data, this technique has a reported glans dehiscence rate of 1 in 150 cases despite an average glans width of 12 mm (Tanakazi and Yoshino, personal communication).

Fistulas

Prevention. Subepithelial suturing and dartos flap coverage over the neourethra are thought to reduce fistulas. Two-layer subepithelial urethroplasty with tunica vaginalis flap coverage was reported to significantly reduce fistulas when compared to single-layer epithelial closure and dartos flap coverage in proximal TIP urethroplasty.

Subepithelial urethroplasty was superior in a retrospective analysis of [Mathieu operations by Ullman and associates \(1997\)](#). They compared single-layer continuous urethroplasty done in 36 initial patients with 6-0 polyglactin sutured through the epithelium to that done in 61 later boys using 7-0 polydioxanone subepithelial stitching. With follow-up of 6 to 12 months, fistulas occurred in 6 of the 36 patients with epithelial stitching (17%) versus 3 of the 60 patients with subepithelial stitching (5%) ($P < .01$).

Use of a barrier flap or not was the subject of a trial by [Savanelli and coworkers \(2007\)](#) that randomized 130 patients undergoing distal TIP repair. Three surgeons performed the operations using the same urethroplasty technique and suture. During median follow-up of 24 months, fistulas occurred more often in those without a dartos flap: 15 of 65 (23%) versus 5 of 65 (8%) ($P = .03$). Meatal stenosis and glans dehiscence were similar in both groups (4% and 5%, respectively).

[Bakan and Yildiz \(2007\)](#) compared a single-layer dartos flap to a two-layer flap. The single-layer dorsal dartos flap was used in 29 consecutive patients, followed by a two-layer flap in the next 45. More boys in the second group had midshaft to proximal hypospadias or reoperations, but fistulas only occurred in the single-layer patients (4 [14%] vs. 0, $P = .02$).

As mentioned, I (W.S.) made technical modifications to proximal TIP urethroplasty that reduced fistulas from an initial 5 of 15 (33%) to 2 of 20 (10%) to 0 of 24 consecutive patients (see [Results](#) section under [Proximal Hypospadias Repair](#)). The first 15 patients had single-layer epithelial suturing of the neourethra using 7-0 chromic catgut. The next 20 had two-layer subepithelial urethroplasty using interrupted 7-0 polyglactin and continuous 7-0 polydioxanone. Spongioplasty after urethral tubularization was added to the second group. In the last 24 cases a tunica vaginalis flap, rather than dartos, covered the repair ([Snodgrass and Bush, 2011](#)).

Surgical Repair. Repair includes assessment for distal obstruction, excision of the fistula tract with closure of the urethral opening, and flap coverage over the defect.

The neourethra is calibrated distally to determine if it is 8 French or greater. Then fluid is injected into the neourethra to confirm the fistula site(s). We make a median raphe incision that encircles the fistula and continues proximally ([Fig. 147-25](#)). The tract is excised and the urethral hole is closed in one layer using subepithelial

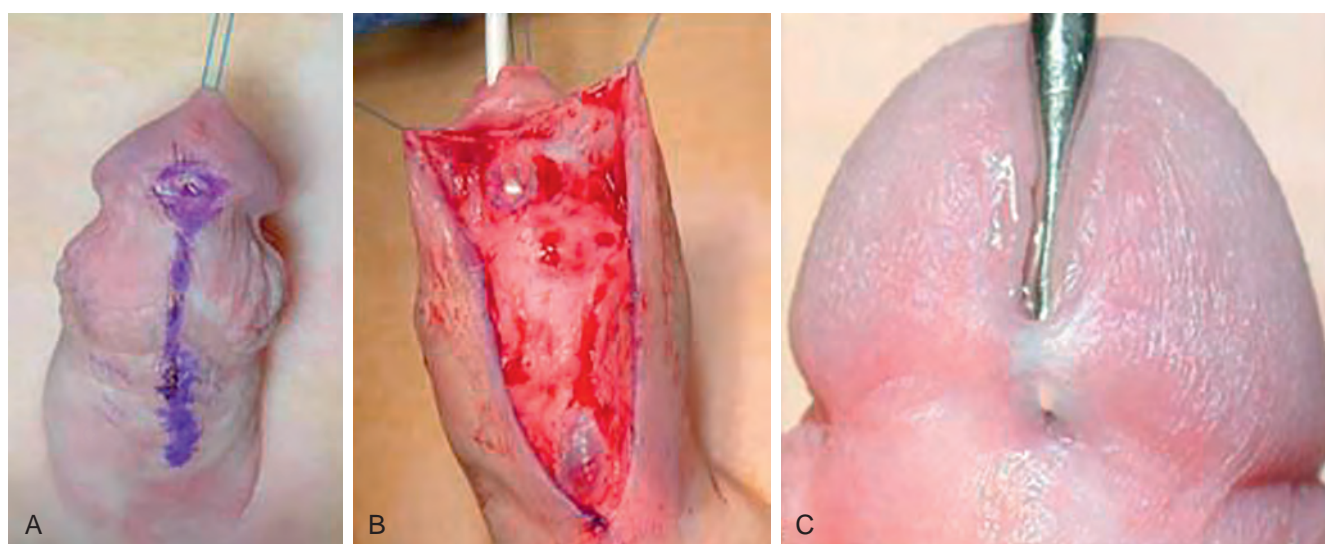


Figure 147-25. Fistula repair. A, Coronal fistula with good distal glans wings approximation. An incision is made around the fistula that continues in the median raphe distally to gain access to ventral dartos for a coverage flap and to revise the redundant shaft skin. B, Exposure showing the glans can be elevated away from the fistula to facilitate fistula closure and coverage with a ventral dartos flap without need for reoperative glansplasty. C, Coronal fistula with a band of skin holding the glans wings together. This requires tubularized incised plate reoperation rather than simple fistula closure.

interrupted 7-0 polyglactin. Repeat fluid injection confirms watertight closure. A ventral dartos flap is raised and used to cover the repair. We do not use urinary diversion.

Repair of coronal fistulas depends on the extent of glans fusion. When the glans is well formed the fistula can be closed by elevating the glans without reoperative hypospadias repair. When the glans wings are separated and held by only a band of skin (see Fig. 147-25C), reoperation is done as described in the later section on [Glans Dehiscence](#).

Results. Three series reported failure in from 6% to 29% of cases, with no differences whether or not urinary diversion was used.

A retrospective review by [Shankar and colleagues \(2002\)](#) had 113 cases of fistulas, of which 7% also had distal obstruction. Subepithelial closure and flap coverage were done, with urinary diversion for 1 week. A total of 29% of patients developed recurrent fistulas, more likely in those with initial fistulas greater than 2 mm versus those smaller. [Waterman and colleagues \(2002\)](#) used diversion in 54 of 100 fistula closures with “larger” defects but found no difference in recurrences, which also developed in 29% of patients, based on stenting. A third review by [Santangelo and associates \(2003\)](#) considered 69 “simple” and 25 “complex” fistulas (larger, and/or with distal obstruction or a diverticulum) that were corrected by closure and flap coverage generally without a stent or by reoperation/meatotomy plus fistula repair in which stents were used, respectively. Both groups had similar recurrences, which overall developed in 6%.

Our recurrence rate for fistula closure as described earlier, excluding those patients with hypospadias reoperation, is 8% (Snodgrass, unpublished data).

Glans Dehiscence

Glans dehiscence occurs more often following proximal and reoperative surgeries, and in patients with glans width less than 14 mm.

We define glans dehiscence as complete separation of the glans wings, with or without a band of skin bridging the gap between the wings (Fig. 147-26). In addition to abnormal appearance, glans dehiscence creates a functional impairment with a deviated and/or spraying stream. Partial dehiscence results in a larger meatus, but with glans wings fusion between the meatus and corona. We do not repair these unless there is a spraying stream, which is the same decision-making criterion we use in patients presenting with glanular hypospadias to determine who will have repair.

[Snodgrass and colleagues \(2011\)](#) used multivariate analysis in 641 consecutive patients following distal, proximal, and reoperative TIP urethroplasty (most of which was for prior dehiscence), and found glans dehiscence in 5%. Risk was nearly four times greater in proximal repairs and almost five times greater in reoperations.

This is our most frequent hypospadias complication, yet it is not often reported in other series. Our glansplasty technique may be inferior and/or this complication is underreported. Based on patients referred to us after failed surgery elsewhere, we believe the complication is more common than realized. However, after observing glansplasty in glans less than 14 mm in Japan, we also realized a potentially better glansplasty involving extended glans wings dissection could be done to reduce this occurrence, as described in this chapter.

Prevention

We first changed sutures from chromic to polyglactin after recognizing glans dehiscence, but the subsequent analysis mentioned earlier showed no difference based on these sutures. Next we used preoperative testosterone to increase glans size to 15 mm or greater, but similarly found no decrease in this complication in treated patients. Currently we dissect the glans wings from the corpora completely to 3 and 9 o'clock in all patients, which is a more systematic dissection than previously. Then in patients with glans width less than 14 mm, prior dehiscence, and/or subjective tight approximation after standard dissection, we further release the wings superiorly for about 4 mm as shown in [Figure 147-11](#).

Surgical Repair

Reoperative TIP or inlay grafting is used to repair glans dehiscence, as described in the later section on [Hypospadias Reoperations](#).

Results

[Villanueva and colleagues \(2012\)](#) reported outcomes for reoperations to correct glans dehiscence before adopting the extended glans wings dissection currently used. Instead, the glansplasty was basically repeated using dissection of the glans wings to approximately 3 and 9 o'clock and then approximation with three interrupted subepithelial 6-0 polyglactin sutures. Recurrent dehiscence developed in 18 of 111 patients (16%). Of these 18, 10 had a third similar glansplasty, but 5 of 8 (63%) with follow-up dehisced again. Today, if reoperative glansplasty with extended glans wings

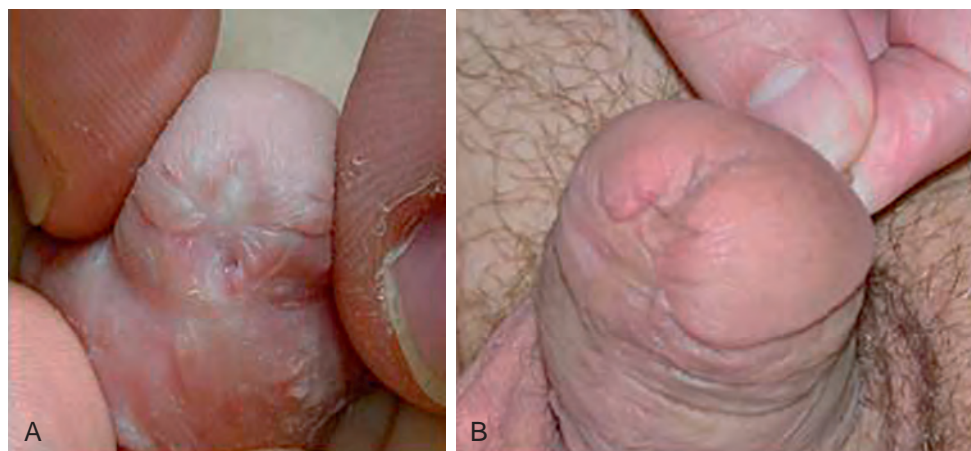


Figure 147-26. Glans dehiscence. A, Complete separation of the glans wings with a subcoronal meatus. B, The glans wings are separated, but a skin bridge between them gives the division of a glanular meatus. This patient had a spraying urinary stream corrected by reoperative glansplasty.

dissection fails, we advise no further surgery until the patient reaches late puberty.

Meatal Stenosis

There is no agreed-upon definition for meatal stenosis. We diagnose stenosis when the neomeatus is less than 8 French in a boy with voiding symptoms. Our results suggest that most meatal stenosis is iatrogenic. There is no report of outcomes for meatotomy after hypospadias repair.

We have evaluated for second opinions patients with a small-appearing meatus who are asymptomatic following hypospadias repair and have been recommended for meatotomy, yet a 10-Fr sound passes easily. These boys do not need intervention. There is no accepted definition of meatal stenosis, which we define as meatal size less than 8 French after repair in a symptomatic patient (i.e., one with dysuria, stranguria, retention, and/or febrile UTI). A standardized literature review by [Wilkinson and colleagues \(2012\)](#) included 15 case series describing distal TIP outcomes in 1872 patients. The authors noted that the diagnosis of meatal stenosis was not standardized, and so likely varied among these publications, but was reported in 3% of patients.

[Snodgrass and coworkers \(2010\)](#) reported outcomes in 426 consecutive patients with distal hypospadias, all of whom had TIP urethroplasty. Of these, 263 (62%) had calibration with none having meatal size less than 8 French. One patient developed secondary meatal stenosis from BXO 6 years following surgery.

Prevention

Given our outcomes, meatal stenosis after TIP urethroplasty appears to be avoidable. We have emphasized technical factors to reduce risk, including incision limited to the urethral plate, not extending into the glans distally, and continuing to near the underlying corpora; tubularization of the plate that begins at least 3 mm from its distal end, creating an oval opening; and independent glans wings approximation without suturing to the neourethra.

Surgical Repair

We incise the neomeatus dorsally to enlarge it without re-creating the hypospadias defect. Meatal stenosis that nearly obliterates the opening, or is the result of BXO, requires reoperative hypospadias repair as described in the later section on [Hypospadias Reoperations](#).

Results

We found no articles defining meatal stenosis or reporting outcomes from meatotomy after hypospadias repair.

Neourethral Stricture

Strictures of the neourethra are unusual following hypospadias repair using any of the techniques described in this chapter. A review of the outcomes tables that accompanied the hypospadias chapter in the prior edition of this textbook shows few mentions of stricture, the highest prevalence being 9% in both a report of tubularized preputial flaps ([Ghali, 1999](#)) and a report of Koyanagi flaps ([Koyanagi et al, 1994](#)).

We encountered no strictures in our series of 426 distal TIP repairs ([Snodgrass et al, 2010](#)). However, strictures did occur in 5 of 29 (17%) proximal TIP repairs in which the urethral plate and native urethra were dissected from the corpora to preserve the plate while straightening VC. All these patients presented 6 weeks to 1.5 years postoperatively with symptoms of retention and/or febrile UTI. Another 47 proximal TIP repairs without this maneuver had no strictures. Accordingly, we have discontinued this maneuver and not described it in this chapter.

However, a retrospective review by [Bhat \(2007\)](#) of 32 patients with urethral plate and native urethra elevation from the corpora

followed by tubularization done with ($n = 20$) or without TIP incision reported no strictures during an average 24 months of follow-up. We cannot explain the difference in these observations.

Treatment

Options include direct vision internal urethrotomy (DVIU), which is effective for strictures less than 1 cm following urethral plate tubularizations and onlay preputial flaps, but not tubularized flaps or grafts. Repeat DVIUs for recurrent strictures less than 1 cm all failed.

Mobilization of the urethra with stricture excision has not been reported for strictures after hypospadias repair, to our knowledge.

Inlay or two-stage oral mucosa grafting, described in the later section on [Hypospadias Reoperations](#), are both options depending on the etiology of the stricture (focal ischemia versus BXO, respectively), the extent to which the neourethra is obliterated, and the presence of secondary VC when there is neourethral contracture.

Results

A single DVIU was successful in approximately 66% of patients with strictures less than 1 cm after urethral plate tubularizations or onlay flaps. Repeat DVIUs all failed. Dorsal inlay grafting was used in one series with success in 94% at 2-year follow-up.

DVIU for strictures less than 1 cm achieved relief of voiding symptoms and Qmax greater than 12 mL/sec in 0 of 32 tubularized grafts and 2 of 18 (11%) tubularized flaps, versus 8 of 11 (72%) onlay flaps and 7 of 11 (63%) urethral plate tubularizations (each $P < .05$). Patients were randomized to post-DVIU dilations or not with no difference in outcomes. Repeat DVIU for 12 of 32 recurrent strictures still less than 1 cm were all failures. Follow-up was a minimum of 2 years ([Husmann and Rathbun, 2006](#)).

Dorsal inlay graft was used in 37 strictures after a mean of two hypospadias surgeries in a series of patients with mean age 12 years. During follow-up for a mean of 2 years, recurrent strictures were diagnosed in only 3 patients (6%) ([Ye et al, 2008](#)).

Diverticulum

Five of nine patients undergoing Byars flap repair for proximal hypospadias by me (W.S.) developed diverticula. None had distal obstruction and the strip that was tubularized was approximately the width of the open glans. I concluded that this ballooning resulted from the relatively fixed resistance of the glans and/or turbulent flow from poor fixation of the flap to the corpora, causing the preputial skin to stretch ([Fig. 147-27](#)).

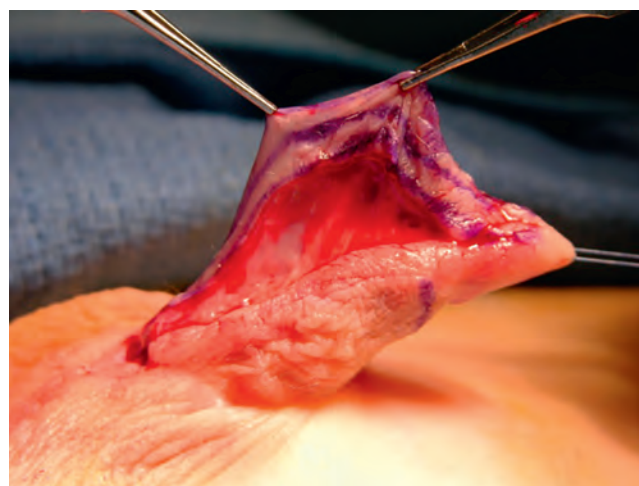


Figure 147-27. Byars flap.

Dartos under the flap prevents adherence of the epithelium to the underlying corpora, potentially increasing risk for turbulent flow and diverticulum formation.

A retrospective review of onlay versus tubularized preputial flap repairs by [Wiener and colleagues \(1997\)](#) found that 12% of those tubularized developed diverticulum during follow-up to a mean of 20 months, which might suggest that tubed flaps have greater risk than onlays for this complication. However, [Vallasciani and associates \(2013\)](#) reported 7% diverticula after both onlay and tubularized preputial flap repairs during mean follow-up of 7 years; none had distal obstruction. Therefore, diverticulum can develop after either single- or two-stage tubularized flaps or onlay preputial flaps despite absence of distal obstruction. Diverticula are much less often encountered after urethral plate or graft tubularizations.

Surgical Repair

Calibration is done to detect associated distal stenosis. Then the diverticulum is exposed by a ventral median raphe incision and opened. A dorsal strip of sufficient width is outlined and the excessive tissue to either side is de-epithelialized. The neourethra is sutured in two layers over a catheter to restore a normal caliber and the redundant and de-epithelialized flaps are closed with vest-over-pants suture to cover the repair.

Results

All 5 patients reported by [Vallasciani and associates \(2013\)](#) were successfully repaired without recurrent diverticulum during follow-up for an average of 9 years.

Balanitis Xerotica Obliterans

BXO can present both preoperatively and following hypospadias repair. It is clinically diagnosed by the characteristic white discoloration of the involved tissues ([Fig. 147-28](#)). BXO at the urethral meatus can both cause stenosis and extend into and along the urethra, inducing stricture.

Medical treatment using a topical steroid or tacrolimus has been reported. A double-blind RCT compared 0.05% mometasone furoate to placebo applied daily for 5 weeks for BXO phimosis. Although steroid therapy significantly improved foreskin retraction, histologic findings of BXO persisted ([Kiss et al, 2001](#)). Therefore best treatment is complete excision of all involved tissues with oral mucosa graft urethral replacement.

We have anecdotal experience with 2 patients with recurrent BXO after prior excision and oral mucosa grafting. In both the

condition recurred at the new junction of the glans to the neourethra, in one 9 years later. Both have been managed with periodic topical therapy to control symptoms, given concerns that BXO could recur again at the skin margin if further excision is done.

Surgical Repair

BXO is surgically excised. When it occurs at the meatus or within the urethra, all grossly involved tissues are removed and replaced with oral mucosa in a two-stage graft urethroplasty described in the later section on [Two-Stage Oral Mucosa Graft](#). Use of either genital or nongenital skin rather than oral mucosa is associated with BXO recurrence.

Results

[Bracka \(2011\)](#) changed from skin grafts to oral mucosa to treat BXO after observing initially good results with subsequent failure when BXO recurred. However, he did not present data indicating the percentage of recurrences or the time frame in which they occurred.

To our knowledge there are no credible reports of BXO recurrence within oral mucosa.

HYPOSPADIAS REOPERATIONS

Although fistulas are the most common complication following hypospadias repair, glans dehiscence is the most common indication for reoperative urethroplasty. Regardless of the problem requiring reoperation, decision making is systematic (see [Fig. 147-7](#)). If the urethral plate remains and is not grossly scarred, TIP urethroplasty is the first option. When the plate has been excised but a skin strip without gross scarring remains, then inlay grafting is the preferred repair. When the urethral plate or skin substitute is grossly scarred or there is VC greater than 30 degrees, neourethral hair, BXO, or stricture that nearly obliterates the lumen, two-stage oral mucosa grafting is done.

Although skin flap reoperations are an option when there is sufficient skin for urethroplasty without compromising penile shaft covering, we do not often encounter such patients and do not use flaps.

In addition, when a Mathieu or onlay flap has been done in a patient requiring reoperation, we remove the flap and perform TIP urethroplasty, both to securely approximate the glans wings and to avoid a potential diverticulum once the glans is well closed.

When there are indications for a two-stage graft repair, we completely excise the unhealthy neourethra to native urethra so that the

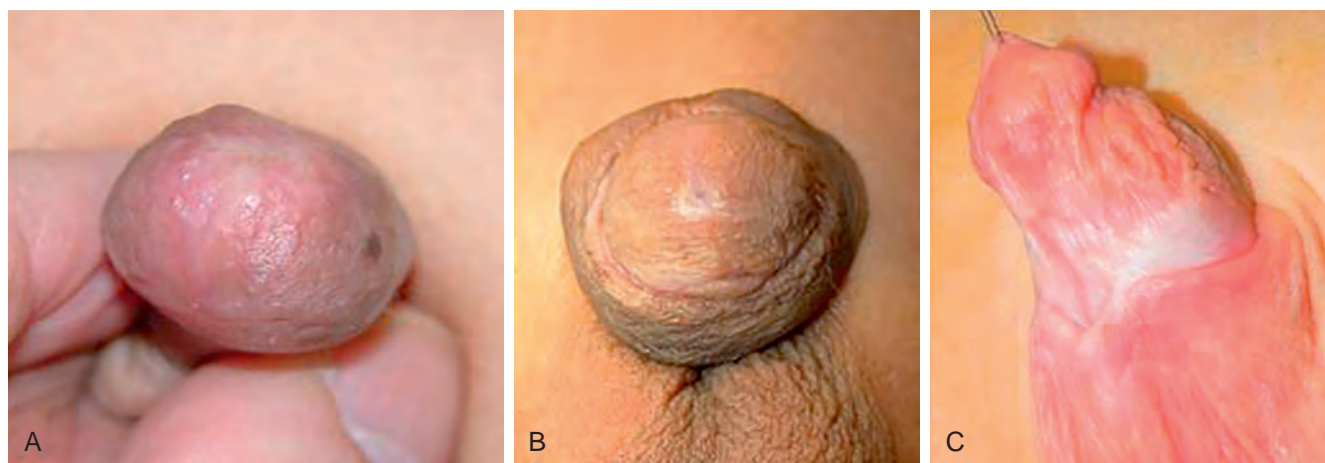


Figure 147-28. Balanitis xerotica obliterans (BXO). A, BXO causing secondary phimosis after prepuceplasty. B, Perimeatal BXO causing meatal stenosis. C, Wound dehiscence subsequently developed extensive BXO around the meatus and surrounding shaft skin.

final neourethra has uniform composition to reduce concern for contracture at tissue junctions or a diverticulum from tubularizing tissues of varying elasticity.

Tubularized Incised Plate Urethroplasty

Indications

Reoperative TIP urethroplasty is an option when the urethral plate remains after prior surgery and lacks gross scarring. In our series of 133 consecutive reoperations (Snodgrass et al, 2009), 69 patients (52%) with a mean of 1.1 failed repairs (range 1 to 3) met those criteria.

Surgical Technique

A ventral Y incision is made, re-creating glans wings along their visible junction to the urethral plate and continuing in the median raphe to near the penoscrotal junction (Fig. 147-29). The glans wings are first dissected laterally along the corpora to 3 and 9 o'clock, and then from superiorly another approximately 4 mm off the corpora as described in the earlier section on [Distal Hypospadias Repair](#) (see Fig. 147-11B).

Dissection along the ventral penile shaft is done immediately under the skin to preserve ventral dartos for a barrier flap. Degloving is not necessary unless there is excessive dorsal shaft skin or VC to revise.

If Mathieu or onlay flaps were previously done, this skin is now removed. Then the urethral plate is incised in the dorsal midline as with primary TIP repair and tubularized over a 6-Fr stent passed into the bladder. For distal reoperations, continuous subepithelial 7-0 polyglactin is used in two layers. More proximal reoperations have two-layer subepithelial urethroplasty using interrupted polyglactin followed by continuous polydioxanone. The neourethra is

next covered with either a ventral dartos flap or, if dartos is insufficient, a tunica vaginalis flap.

Glansplasty is done using subepithelial interrupted 6-0 polyglactin as described earlier for primary distal TIP urethroplasty. Excess ventral shaft skin is excised as needed and the skin edges are closed using subepithelial 7-0 polyglactin. The stent is maintained for 7 to 10 days.

Results

Urethroplasty complications were reported in 12% to 30% of patients after reoperative TIP repair. Prior urethral plate incision from either MAGPI or TIP repair does not impact outcomes. A dartos flap over the neourethra significantly reduced fistulas in one report.

Ninety percent of the patients in our series had distal hypospadias and failed an average of one prior repair (maximum of three) (Snodgrass et al, 2009). The indication for reoperation was glans dehiscence in 91%, with coronal fistulas, meatal stenoses, and diverticulum in the others. Initially I (W.S.) used a smaller incision and did not routinely cover the neourethra with a dartos flap, but after 5 of the first 10 cases developed fistulas a barrier layer was used systematically in all others, resulting in a significant reduction in fistulas (2 of 53 cases). Urethroplasty complications occurred in 12 of 63 patients (19%) with follow-up to a mean of 6 months (range 1 to 53), including seven fistulas and six recurrent glans dehiscences, before we implemented the extended glans wings dissection. Prior urethral plate incision from TIP urethroplasty or MAGPI (appendix) did not impact outcomes (Snodgrass et al, 2009).

A retrospective review by Ziada and colleagues (2006) had 30 TIP reoperations after a mean of 1.6 prior repairs (range 1 to 3) in which 63% were distal. Urethroplasty used subepithelial polyglactin covered by a dartos flap. During follow-up of more than 4 years there were nine complications (30%): eight meatal stenoses (five with fistulas) and one isolated fistula.

Another review included 40 patients for whom the meatal location and number of prior operations were not stated. During follow-up to a mean of 42 months, urethroplasty complications were diagnosed in 5 patients (12.5%) (Riccabona et al, 2003).

Dorsal Inlay Graft

Indications

This technique is used when the urethral plate has been removed but a strip of grossly healthy skin remains in its place. It is also used for neourethral strictures unless the lumen is nearly obliterated such that a dorsal incision and grafting are not practical.

Surgical Technique

The operation is done as described for TIP reoperations. The skin strip substituting for the urethral plate is incised dorsally as for TIP urethroplasty, but then the defect created is grafted using oral mucosa harvested from the upper lip for small grafts or the lower lip for longer grafts (Fig. 147-30). The visible margin of the lip is marked and two 5-0 polypropylene stays are placed to retract it open. The desired graft is outlined, injected with 1:100,000 epinephrine, and harvested. The graft is defatted. A small graft is easiest to handle by wetting a small area on the paper drapes, which holds it still. Then it is sewn to the perimeter of the incision using 7-0 polyglactin and quilted in the midline with 6-0 polyglactin on an RB-1 needle, which readily punctures the graft and secures it to the underlying tunica albuginea of the corpora. Urethroplasty, glansplasty, and skin closure then proceed as in TIP reoperations.

Results

Three reports all found urethroplasty complications in 15% of patients after inlay graft reoperation.



Figure 147-29. Ventral incision for hypospadias reoperations. Ventral incision for reoperative urethroplasty and glansplasty provides exposure to ventral dartos for barrier flap and facilitates cosmetic skin revision without need to deglove the penis.

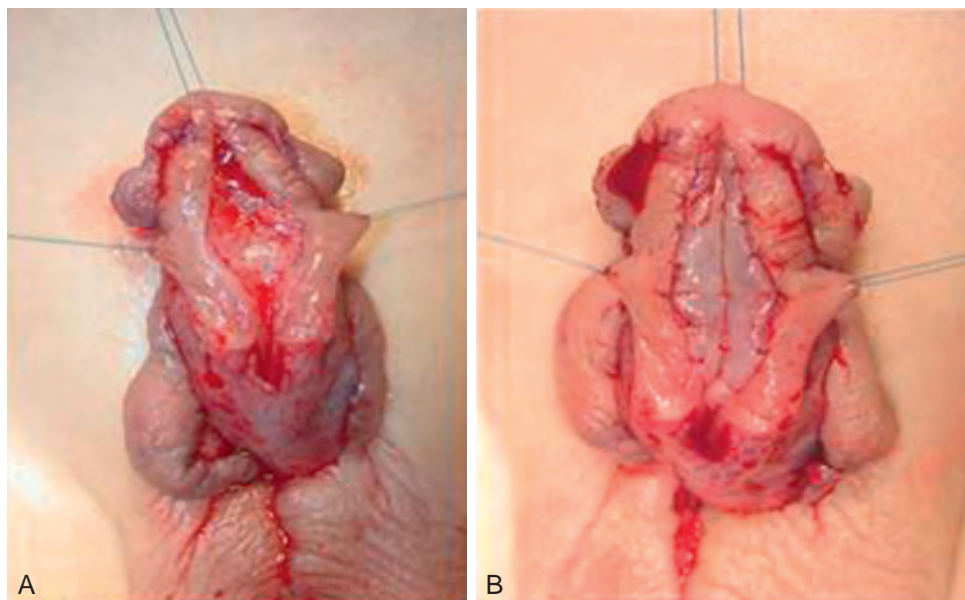


Figure 147-30. Inlay graft. A, Skin strip has been incised dorsally as for tubularized incised plate repair. B, Oral mucosa graft is sewn into the defect. Tubularization for single-stage repair is done next.

Our report with 133 reoperations included only 16 patients (12%) meeting criteria for inlay grafts (Snodgrass et al, 2009). The meatus was distal in 62% and the mean number of failed repairs was 1.9 (range 1 to 9). Indications were glans dehiscence in 15 patients and meatal stenosis with a diverticulum in 1 patient. Urethroplasty complications developed in 2 of 13 patients (15%) with follow-up: one recurrent glans dehiscence and one fistula (Snodgrass et al, 2009).

A retrospective report by Ye and colleagues (2008) included 53 patients with an average of 2 failed repairs (range 1 to 6). Seventy percent had strictures; the remainder had glans dehiscence. Mean graft length was 5 cm taken from the lower lip. Urethroplasty complications occurred in 8 patients (15%) during follow-up for a mean of 23 months: five fistulas and three recurrent strictures all at the proximal junction to the urethra.

Another review had 32 patients with an average of 4 failed repairs (range 1 to 18). Skin grafts harvested from prepuce, penile shaft, or groin were used with a mean length of 4 cm (range 1 to 15). Complications developed in 16% during follow-up to a mean of 30 months: one fistula and four strictures at the proximal urethral junction (Schwentner et al, 2006).

It is not clear from the reports by Ye and colleagues and Schwentner and coworkers why strictures occurred at the proximal junction to the urethra. We reduce likelihood for this complication by extending the midline dorsal incision approximately 5 mm into the normal urethra.

Two-Stage Oral Mucosa Graft

Indications

This reoperation is used when the urethral plate or skin substitute is grossly scarred, or there is VC greater than 30 degrees, BXO, strictures that nearly obliterate the lumen, or hair in the neourethra.

Surgical Technique (Fig. 147-31)

The same initial ventral Y incision is made as described earlier for other reoperations, re-creating glans wings and opening the median raphe. Then the entire neourethra is excised until normal urethra is

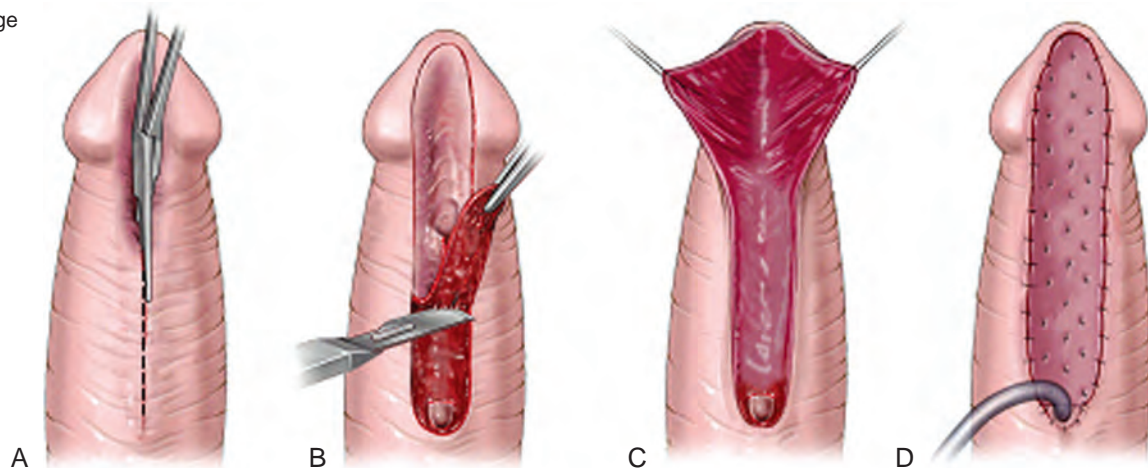
encountered. All scarred ventral tissues are excised from the corporal surface, which also reestablishes a groove between the glans wings. Polypropylene stays are placed into the glans wings at the corona on either side.

Most often VC is corrected by removal of the neourethra and scarred tissues, but when it persists ventral transverse corporotomies and/or dorsal plication are used for straightening as described in the section on [Ventral Curvature](#) earlier in this chapter. The native urethra is spatulated ventrally and proximal urethrostomy is done, suturing penile shaft skin or scrotum to the urethra at 4, 6, and 8 o'clock. Intravenous cefazolin is given before graft harvest. We do not prep the mouth or change gloves after harvest. The visible margin of the lower lip is marked and two 5-0 polypropylene stay stitches are placed to pull the lip down. A damp gauze is packed over the tongue to prevent blood from entering the throat. All available tissue should be harvested from near the gum line to near the vermilion border and laterally on either side where the lip joins the cheek (Fig. 147-32). This extent of graft will cover from the tip of the glans to deep within the scrotum. The graft is injected with 1:100,000 epinephrine and harvested. A gauze soaked in 1:1000 epinephrine is laid onto the harvest site to aid in hemostasis.

The graft is defatted and then laid into the defect. The distal end is secured first, suturing the graft to the glans near the stays using interrupted, epithelial 7-0 polyglactin. Then the graft is stitched along the distal edge of the glans with subepithelial sutures to prevent marks at the site of the future meatus. The graft is gently stretched proximally and secured to the shaft skin along its perimeter with 7-0 polyglactin. The proximal end is incised in the midline and each arm is extended to either side of the urethrostomy (Fig. 147-33). The graft is then quilted to the underlying tunica albuginea of the corpora using 6-0 polyglactin on an RB-1 needle. Sutures are placed at 1-cm intervals beginning in the midline and then on either side (see Fig. 147-33C).

Next, 5-0 polypropylene stitches are placed on either side near the urethrostomy and at intervals distally. A rolled Vaseline gauze gently compresses the graft, held into place by these stays tied over it. The tie-over bandage and a catheter in the urethrostomy are maintained for 1 week. The donor site is left untreated to re-epithelialize spontaneously.

1st stage



2nd stage

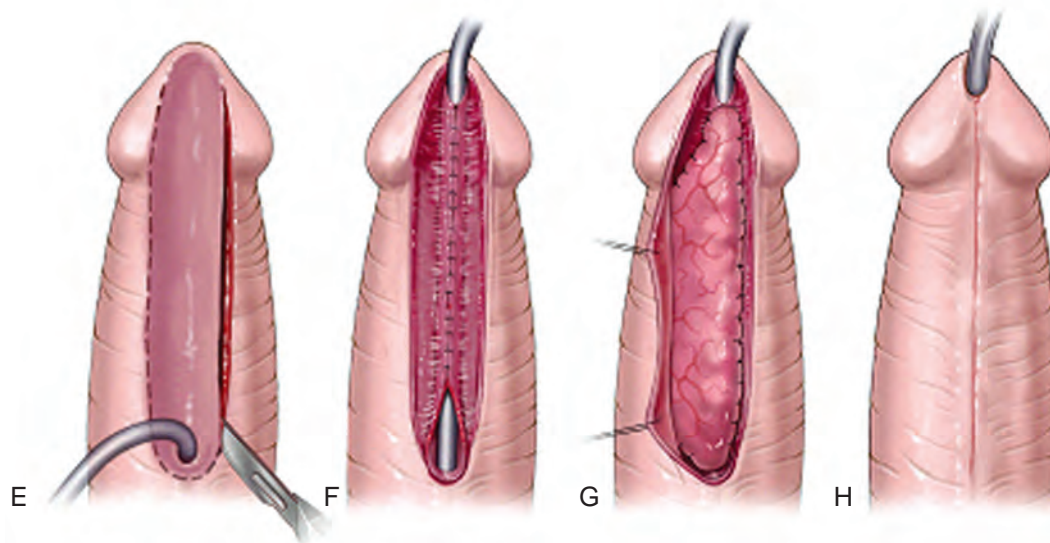


Figure 147-31. Two-stage buccal graft reoperation. A, Neourethra opened with ventral incision. B, All unhealthy tissues, usually entire neourethra, are excised. C, Deep glans groove reestablished and proximal urethrostomy completed. D, Buccal graft quilted into place from meatus to glans tip. Lip is used within the glans and subcoronal region, and cheek along the penile shaft. The junction of lip to cheek is made diagonally to minimize contraction. E, U-shaped incision along perimeter of neourethra 6 months later. F, Two-layer tubularization of the neourethra using interrupted subepithelial polyglactin followed by continuous polydioxanone. G, Barrier flap, usually tunica vaginalis, covers the entire neourethra. H, Glansplasty and skin closures completed with subepithelial sutures. (From Snodgrass W, Elmore J. Initial experience with staged buccal graft [Bracka] hypospadias reoperations. *J Urol* 2004;172(4 Pt. 2):1720-4.)

There is no need for any care of the revascularizing graft between stages. We always wait for 6 months before performing the second stage of the urethroplasty. In less than 10% of cases the graft will scar or contract such that partial or complete regrafting is required (Fig. 147-34). Focal narrowing can be corrected during the second stage either by inlay grafting or by incorporating shaft skin into the neourethra. At the second stage the oral mucosa is outlined with a marker and the glans wings are injected with 1:100,000 epinephrine. The wings and shaft skin are dissected from the neo-urethral plate. There is little need to dissect under the neoplate because usually its edges are sufficiently mobile for approximation. It is then tubularized using 6-0 polyglactin interrupted subepithelial stitches followed by continuous 6-0 polydioxanone for two-layer closure.

A testicle is exposed and tunica vaginalis harvested for a barrier flap as described earlier in the chapter. Then glansplasty is done with 6-0 polyglactin, and skin edges are closed with subepithelial stitches. The catheter remains for 2 weeks. Typical cosmetic results are shown in Figure 147-35.

Results

Graft Take. Graft contractures requiring regrafting occur in less than 10% of two-stage oral mucosa graft reoperations.

Snodgrass and colleagues (2009) reported the need for additional grafting in 5 of 48 cases (10%), requiring a patch in 4 and complete replacement in 1. Since that report we changed to the

lower lip as the donor site and harvested larger grafts. In the next 63 patients, 2 (3%) had regrafting for contractures. Because some extent of contracture can occur with grafts, we now harvest the largest piece available within the donor site, and then excise any excess during the second stage.

Two retrospective series also reported regrafting before tubularization. One noted partial graft loss needing regrafting in 2 of 34 (6%) buccal mucosa grafts (Gill and Hameed, 2011) and the other found 4 of 30 (13%) cheek and/or lip grafts requiring regrafting (Leslie et al, 2011).

Urethroplasty Complications. Urethroplasty complications were reported in up to 38% of patients after the second stage.

Snodgrass and colleagues (2009) reported urethroplasty complications after the second stage in 17 of 45 (38%) patients with follow-up. These included glans dehiscence ($n = 8$), fistulas ($n = 7$), and meatal stenosis ($n = 2$). All glans dehiscences in this series occurred when cheek, rather than lip, was used, possibly because

grafts from the cheek are visibly thicker, making glans closure more difficult and tenuous (Fig. 147-36). Dehiscence likely also related to glans width, because most of these reoperations were in patients born with proximal hypospadias, but we did not measure the glans at that time. We have subsequently observed glans dehiscence following two-stage graft repairs despite using lip mucosa. Therefore we continue to harvest lip but routinely additionally perform the more extended glansplasty we have described throughout this chapter at the second stage to reduce risk for this complication.

The series published by Gill and Hameed (2011) included a total of 100 patients, with most having two-stage grafting using other graft sources such as prepuce, postauricular skin, and medial upper arm skin. They did not report the total number of patients with complications but stated there were nine fistulas, six strictures, six patients with persistent hypospadias (most likely dehiscence), and four patients with persistent VC. Leslie and colleagues (2011) found complications in 11 of 30 (37%) cases: meatal stenosis in 5, fistulas in 3, and glans dehiscences in 3.

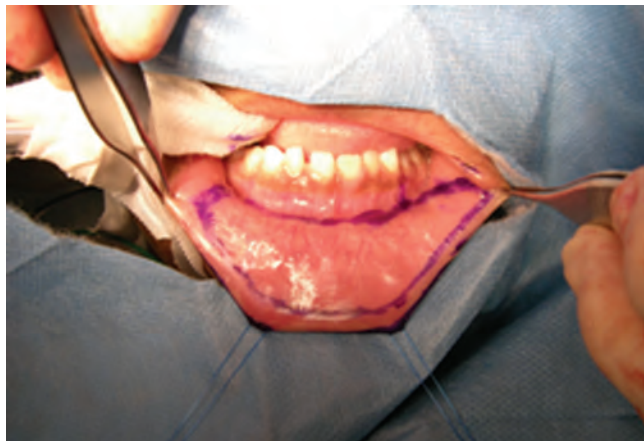


Figure 147-32. Labial graft harvest. Outline for graft harvest from lower lip, extending from the gum to within approximately 3 mm of the visible border of the lip. This graft will surface from the glans to the penoscrotal junction, or more proximally, in boys. The donor site is not sutured.

ADULT OUTCOMES AFTER PREPUBERTAL REPAIR

Despite the obvious need for information regarding urinary and sexual function in adults following hypospadias repair in childhood, few data are available. Rynja and colleagues (2011) conducted a systematic literature review through 2010 to determine outcomes in men of mean age 27 years operated for hypospadias at less than 6 years of age. Twenty studies with 1069 patients were included. The mean number of surgeries was 2.7, and proximal repair outcomes were available from 180 men. Procedures used included Ombredanne, Denis Browne, van der Meulen, and Cecil-Culp (no longer widely used), as well as MAGPI and Mathieu procedures, onlay and tubularized preputial flaps, and Byars flaps. There were 742 controls with mean age of 20 years. At this time there are no similar data for TIP outcomes in adults operated as children.

Urinary Function

Symptoms

Patients reported significantly more obstructive symptoms (77 of 217 [35.5%] vs. 30 of 196 [15%]), spraying (245 of 818 [30%] vs.



Figure 147-33. Oral mucosa graft. A, A single piece of lower lip graft has been used to fill the defect from the glans to within the scrotum. B, Note the extensions of graft to either side of the proximal urethrostomy. C, The graft is quilted and next a tie-over bandage will be placed.

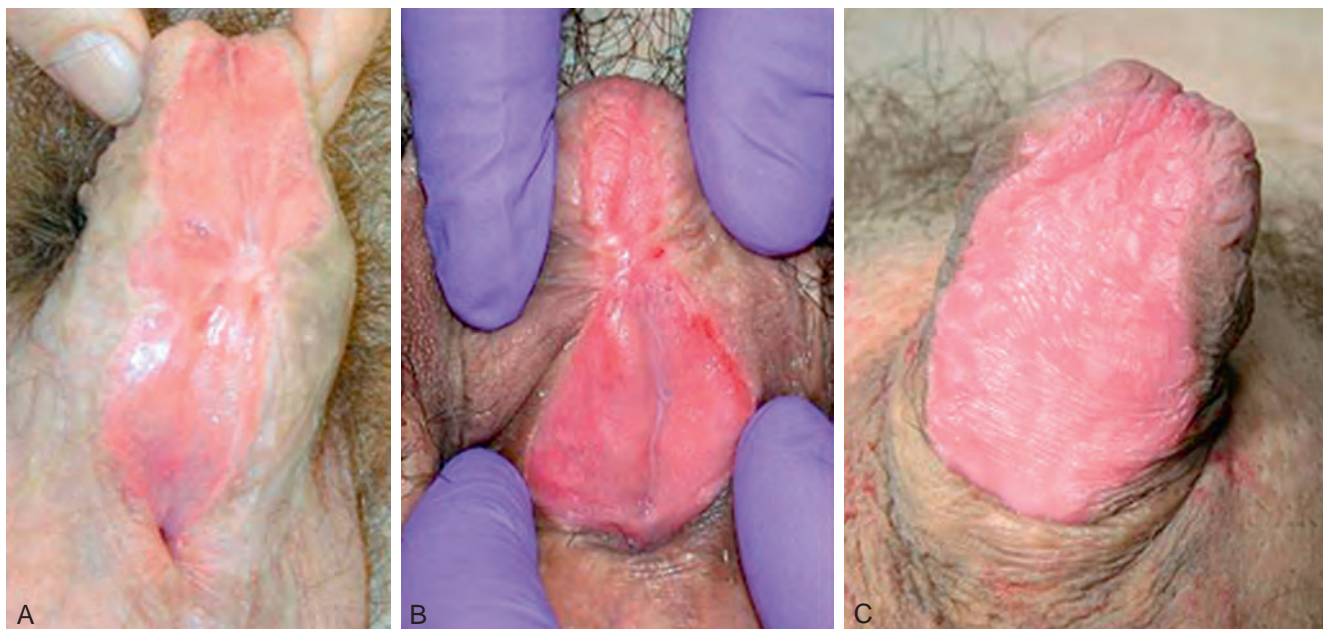


Figure 147-34. Graft scar and contracture. A, Stellate scar in midportion of graft. B, Distal graft contracture. C, Desired healthy appearance of well-vascularized graft. (From Snodgrass W, Elmore J. Initial experience with staged buccal graft [Bracka] hypospadias reoperations. *J Urol* 2004;172(4 Pt. 2):1720–4.)



Figure 147-35. Cosmetic outcomes after two-stage buccal graft reoperation. (From Snodgrass W, Elmore J. Initial experience with staged buccal graft [Bracka] hypospadias reoperations. *J Urol* 2004;172(4 Pt. 2):1720–4.)

17 of 231 [7%]), and deviated stream (69 of 267 [26%] vs. 9 of 81 [11%]) than did controls. Those with proximal hypospadias had more spraying (46 of 106 [43%]) than did patients with distal repairs (245 of 818 [30%]).

Uroflowmetry

Qmax was significantly less in patients than controls (mean 24 mL/sec vs. 30 mL/sec), as was Qmax less than two standard deviations (36 of 265 [13.5%] vs. 4 of 138 [3%]). Patients with proximal

hypospadias had significantly lower Qmax (mean 21 mL/sec) than did those with distal hypospadias.

Sexual Function

Ejaculation

Ejaculation problems, including milking semen and poor force, were significantly more common in patients than controls (99 of 385 [26%] vs. 0 of 48, $P < .01$).

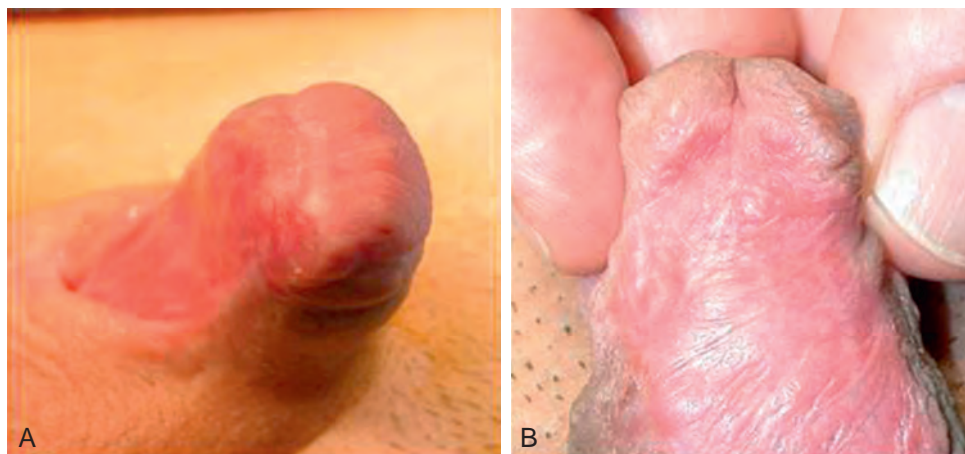


Figure 147-36. Cheek versus lip grafts. A, Cheek mucosa grafts are thicker and may complicate glansplasty. B, Labial grafts are thinner with significantly less likelihood for glans dehiscence.

Sexual Satisfaction

Patients were less satisfied with sexual function than controls (153 of 188 [81%] vs. 235 of 252 [93%], $P < .01$). Mean frequency of intercourse per month did not vary (5.8 vs. 6.4).

Cosmesis

Patients were more likely to be dissatisfied with penile appearance (143 of 493 [29%]) than were controls (24 of 581 [4%]). Those with proximal hypospadias were more dissatisfied with penile appearance than those with distal hypospadias (25 of 46 [54%] vs. 143 of 493 [29%]).

IMPROVING OUTCOMES

Upon relocating to Dallas in 1999, I (W.S.) began recording data prospectively into Excel spreadsheets. The articles referenced in this chapter since that date are all based on analysis of these databases, which today contain information on more than 1600 consecutive patients. Reviews of these data have improved our surgical techniques, outcomes, and understanding of the underlying factors that impact results in hypospadias repair.

Determining Results

At this time there is no computer software that connects preoperative, intraoperative, and postoperative data to create a surgeon scorecard, but with the growing reliance on electronic medical records it is only a matter of time before this occurs. Meanwhile, surgeons can enter pertinent data into an Excel spreadsheet to rapidly determine their personal outcomes. Recognizing the factors that best predict urethroplasty complications, a surgeon need only enter the patient name, date of operation, meatal location, glans width, primary versus reoperation, operative procedure, date of follow-up, and any complication noted. Depending on individual volume of repairs, that surgeon will learn his or her complication rate using reliable data within as little as 1 year at a cost of only a few minutes a week to enter the information after surgery or clinic.

Technical Changes

When surgeons decide to perform a quality assessment of their surgical outcomes, whether of hypospadias or other conditions, they most often learn there are opportunities for improvement. For example, I (W.S.) was surprised that my fistula rate after proximal

TIP urethroplasty was 25% despite using a dartos flap over the neourethra. However, these cases are relatively infrequent for most pediatric urologists, who according to the American Board of Urology perform an average of two per year, and so even this high a complication rate may go undetected because patients with complications present sporadically and recall bias limits our ability to tabulate them without spreadsheets or chart review. Having recognized this, I (W.S.) made a series of technical modifications described in this chapter that significantly reduced my fistula rate.

We similarly noted glans dehiscence at rates higher than reported, and initially thought it might be due to glans wings approximation using chromic catgut. I (W.S.) therefore changed to polyglactin, but subsequent multivariable analysis, made possible by ongoing data collection, showed that suture type did not impact this complication, which was seen to be more common in proximal than distal repairs despite the same surgeon using the same technique for glansplasty. That led to measurements of glans size, which confirmed suspicions that dehiscence and other urethroplasty complications were more prevalent when glans width was less than 14 mm. Knowing androgens will increase glans circumference, we embarked on a program of preoperative testosterone injections for the small glans. We learned that this objective patient selection resulted in double the number of boys receiving stimulation compared to our previous subjective use for a “small-appearing” glans. We also encountered unexpected androgen resistance in two thirds of those treated, requiring injections greater than 2 mg/kg to achieve targeted growth to 15 mm or greater. Most importantly, further outcomes review ultimately found that despite growing the glans to a size previously determined to have low complication rates, those patients who needed stimulation continued to have significantly more dehiscence than other boys whose glans was the desired size without stimulation. Because reduction in complications, not growth of the glans, was the aim of therapy, we then stopped androgen treatment.


This focus on glans size and dehiscence made me (W.S.) more aware of variations in glans wings dissection, and more receptive to change in my technique. When I observed two senior Japanese surgeons perform a more extended glans wings mobilization, I recognized its potential and incorporated it into our practice.

Improving Results

Prospective data collection, periodic outcomes review, and practice changes such as these make us better hypospadiologists and improve results for the young patients entrusted to our hands.

Of these, data collection is most important, because once a surgeon learns his or her actual results from data he or she knows

are reliable, changes in technique and improved outcomes inevitably follow. Conversely, if low complication rates are found, a surgeon benefits from knowing there is no need to change current practice, which is especially useful should a cluster of complications occur that otherwise might raise doubts. This is the core of evidence-based surgical practice.

 Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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 The complete reference list is available online at www.expertconsult.com.

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Definitions

Embryology of Testicular Development and Descent

Etiology

Diagnosis

Management

Prognosis

Cryptorchidism, or undescended testis, is a common genital anomaly that is extensively studied yet incompletely understood. Testicular descent is a complex and prolonged gestational event that is completed in the third trimester, or soon after birth. The fetal structure that orchestrates descent of the testis, the gubernaculum, is anatomically but not functionally well characterized. The genetic and/or environmental factors that contribute to failure of testicular descent remain largely unknown. Cryptorchidism was traditionally considered a congenital anomaly identifiable at birth, but more recent evidence confirms that an initial diagnosis well beyond the neonatal period is not uncommon. Clinically significant differences, if any, between the acquired and congenital presentations of cryptorchidism remain obscure. Present evidence supports surgery as the preferred treatment approach and provides improved understanding of the long-term risks, including impairment of fertility potential and testicular cancer.

DEFINITIONS

Because differing terminology is used to describe conditions related to normal and abnormal testicular descent and absence of a testis in the scrotum, we provide definitions for the following terms that are used throughout the chapter:

- **Normal scrotal position** has been defined as positioning of the midpoint of the testis at or below the midscrotum (Wohlfahrt-Weje et al, 2009). Although “high scrotal testes” are not routinely considered undescended by most clinicians, they have been included in the definition of undescended testis in some epidemiologic studies (Sijstermans et al, 2008). This is likely a heterogeneous group that includes stable descended testes that reside above the scrotal midpoint and retractile and undescended “gliding” testes (Hack et al, 2007), which are not stable.
- **Undescended testis** or **cryptorchidism** is the absence of one or both testes in normal scrotal position and during initial clinical evaluation may refer to palpable or nonpalpable testes, which are either cryptorchid or absent. Most absent testes are *vanishing* or *vanished*, being present initially in development but becoming lost as a result of vascular accident or torsion unilaterally (*monorchia*) or, very rarely, bilaterally (*anorchia*) (Abeyaratne et al, 1969).
- **Agenesis** refers to a testis that was never present and therefore is associated with ipsilateral müllerian duct persistence.
- **Congenital cryptorchidism** refers to testes that are extrascrotal at birth.

- **Acquired cryptorchidism** is defined as cryptorchid testes that were documented as scrotal at a previous examination without intervening inguinal surgery.
- **Recurrent cryptorchidism** is defined as cryptorchid testes that were undescended at birth, descended spontaneously, and are subsequently defined as extrascrotal.
- **Secondary cryptorchidism** and **testicular retraction** have been used to describe testes that are suprascrotal after inguinal hernia repair and as a complication of orchidopexy, respectively. Testicular malposition after hernia repair could be caused by either post-operative scarring or primary maldescent.
- **Retractile testes** are scrotal testes that retract easily out of the scrotum but can be manually replaced in a stable scrotal position and remain there at least temporarily until there is recurrent stimulation. Testes that are significantly retractile—that is, those that rarely remain in a stable scrotal position (spontaneously or with manipulation) and/or are located at rest in the high scrotum—may or may not be diagnosed as cases of acquired cryptorchidism on longitudinal examination.

EMBRYOLOGY OF TESTICULAR DEVELOPMENT AND DESCENT

Cryptorchidism represents a failure of testicular descent, which is in turn dependent on growth and hormonal function of the developing testis. Testicular descent is regulated by two Leydig cell hormones—insulin-like 3 (INSL3) via its receptor relaxin/insulin-like family peptide receptor 2 (RXFP2), and androgens via the androgen receptor (AR)—but downstream pathways are poorly defined. Altered expression or function of key molecules that participate in testicular and/or gubernacular development, as a result of genetic or environmental effects, could potentially contribute to an increased risk of cryptorchidism.

Differentiation of the Testis

Gonadal differentiation is more complicated than the original concept of ovarian development as the default pathway. Activation of specific genetic programs is required for both male and female sex determination in mice (Sekido and Lovell-Badge, 2013; Ungewitter and Yao, 2013). Although basic work has moved the field substantially forward in recent years, the mechanisms of cell-specific development in the testis remain incompletely understood (Svingen and Koopman, 2013). In the fetal mouse,

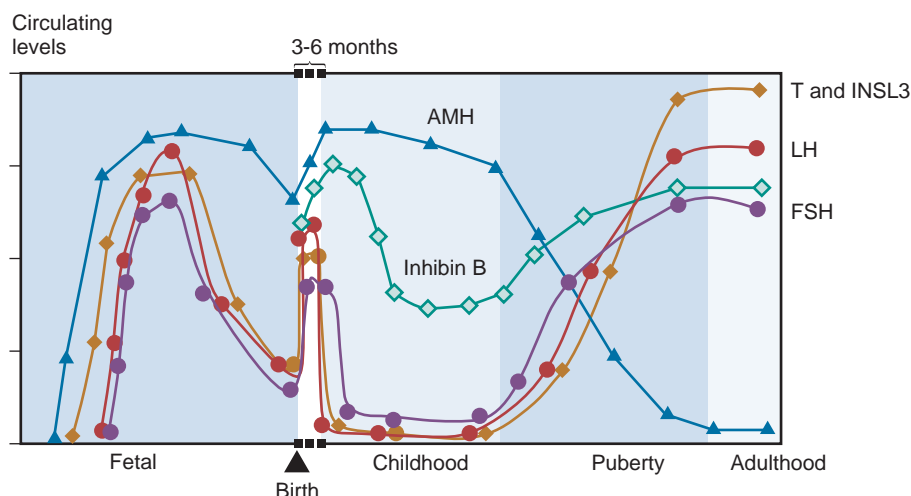


Figure 148-1. Circulating male hypothalamic-pituitary-gonadal axis hormones from conception to puberty. Schematic view shows the rise in testosterone (T), insulin-like 3 (INSL3), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and antimüllerian hormone (AMH) during early fetal life; secondary elevation of these hormones and of inhibin B soon after birth; and suppression of AMH at puberty. (Modified from Grinspon RP, Ropelato MG, Bedecarras P, et al. Gonadotrophin secretion pattern in anorchid boys from birth to pubertal age: pathophysiological aspects and diagnostic usefulness. *Clin Endocrinol [Oxf]* 2012;76:698–705.)

Sry (sex-determining region on the Y chromosome) expression in the indifferent gonad triggers testicular development and is activated in part by steroidogenic factor 1 (*Nr5a1/SF1*). In turn, SRY and SF1 proteins cooperate to promote prolonged expression of another transcription factor, SOX9 (SRY-box containing 9), in pre-Sertoli supporting cells. SRY is important for Sertoli cell specification, but downstream testis-determining genes including *Sox9*, *Fgf9* (fibroblast growth factor 9), *Amh* (antimüllerian hormone) and *Ptgds* (prostaglandin synthase) are required for Sertoli cell differentiation and proliferation (Kashimada and Koopman, 2010). Establishment of the Sertoli cell lineage is required for subsequent testicular cord formation. Studies in the fetal mouse indicate that patterning of the testis requires a temporal series of events that includes germ cell migration into the undifferentiated gonad and migration of interstitial cell precursors from the coelomic epithelium and the mesonephros (Combes et al, 2009; Cool and Capel, 2009; Wainwright and Wilhelm, 2010; McClelland et al, 2012).

In humans, gonads containing somatic and germ cells are first identified on the medial aspect of the urogenital ridge at 32 days postovulation (Hanley et al, 1999). At this sexually indifferent stage, the gonads and the internal and external genitalia are identical in males and females. Expression of SRY and SOX9 transcripts begins at 41 to 44 days (Hanley et al, 2000), followed by the histologic appearance of Sertoli cells (Ostrer et al, 2007). By 6 weeks' gestation, primordial germ cells migrate from the yolk sac and differentiate into gonocytes and by 8 weeks' gestation are localized within the testicular cords (Culty, 2009). Gonocytes become c-KIT+ at 7 weeks, and their numbers increase further during the remainder of the first trimester (Ostrer et al, 2007). During the second trimester, three subpopulations of germ cells, including gonocytes, intermediate spermatogonia, and prespermatogonia, can be distinguished by immunostaining for specific markers (Gaskell et al, 2004). POU5F1 (POU domain class 5 homeobox 1, also known as OCT4) and c-KIT are expressed in the earlier lineages and disappear with loss of gonocytes by 20 weeks, whereas gain of MAGE-A4 (melanoma antigen, family A, 4) immunopositivity occurs with emergence of prespermatogonia (Gaskell et al, 2004; Culty, 2009). Leydig cells become active at 6 to 7 weeks' gestation, proliferate until about 15 weeks, and involute after 24 weeks (Codesal et al, 1990; Habert et al, 2001; O'Shaughnessy et al, 2007). Before the end of the first trimester of gestation, the external genitalia are completely masculinized, the testis cords are established, and subpopulations of both proliferating and degenerating germ cells exist.

Sertoli and germ cell proliferation continues well into the second trimester (O'Shaughnessy et al, 2007).

Testicular Hormone Production

Hormonal function of the human fetal testis is critical for masculinization of the reproductive tract and testicular descent. Activation of testicular hormone production occurs at discrete intervals during fetal, postnatal, and pubertal life (Fig. 148-1). In the fetus, Leydig cell development is divided into three phases: a proliferation and differentiation phase at 7 to 14 weeks' gestation, a maturation phase until 18 weeks' gestation, and an involution phase that continues until term (Svechnikov and Soder, 2008). Synthesis of testosterone by fetal Leydig cells starts as early as 6 to 7 weeks' gestation and appears to be initially independent of gonadotropin stimulation. However, placental human chorionic gonadotropin (hCG) stimulates a peak in androgen production at 14 to 16 weeks, and the testis then becomes responsive to fetal luteinizing hormone (LH). INSL3 of Leydig cell origin is measurable in human amniotic fluid as early as 13 weeks' gestation (the earliest time point studied) and peaks at 15 to 17 weeks (Anand-Ivell et al, 2008; Bay et al, 2008). Fetal Sertoli cells produce AMH (also called müllerian inhibiting substance [MIS]) soon after they differentiate; the human fetal müllerian duct is responsive to AMH before week 8 of gestation, and the process of regression occurs at 9 to 10 weeks (Josso et al, 2006). Steroid hormones exert their effects via sex steroid receptors in the reproductive tract and testis. Androgen receptor (AR) and estrogen receptor β (ER- β) are expressed in the undifferentiated gonad at 7 weeks of age, although their role in testis development is unclear (Shapiro et al, 2005; Boukari et al, 2007). AR is present primarily in peritubular myoid cells and in some Leydig and interstitial cells, but absent in Sertoli cells during early development. Lack of AR expression in fetal and early postnatal Sertoli cells is physiologically important, because its presence would allow inappropriate androgen-induced inhibition of AMH production and precocious stimulation of spermatogenesis (Boukari et al, 2009; Rey et al, 2009). ER- β expression in fetal testis is observed in germ, peritubular myoid, Sertoli, and some Leydig cells, whereas expression of estrogen receptor α (ER- α) is limited (Shapiro et al, 2005) or absent (Boukari et al, 2007) in human fetal testis. Concomitant expression of aromatase during the same time frame suggests that locally produced estrogen may play a role in testis development.

Reactivation of the hypothalamic-pituitary-gonadal (HPG) axis occurs during the neonatal period, a phenomenon known as “mini-puberty” (see Fig. 148-1) with cross-sectional data suggesting that peak hormone levels occur at 1 to 3 months of age. Serum LH and FSH levels rise postnatally, followed by increases in testosterone, AMH, and inhibin B; INSL3 levels are high in both cord blood and at 3 months of age (Andersson et al, 1998; Bergada et al, 2006; Bay et al, 2007; Aksglaede et al, 2010). However, individual longitudinal data indicate that postnatal urinary LH, FSH, and testosterone levels peak earlier, at or before 1 month of age, and are more pronounced in preterm boys (Kuiiri-Hanninen et al, 2011). Studies of the androgen insensitivity syndrome provide evidence that the postnatal hormone surge is a response to maternal androgen withdrawal with secondary activation of hypothalamic and pituitary hormones (Quigley, 2002). Fetal Leydig cells regress after birth, followed by emergence of a neonatal Leydig cell population at 2 to 3 months of age (Prince, 2001). As postnatal hormonal levels wane, the fetal Leydig cells either degenerate or regress to immature, partially differentiated Leydig or interstitial cells that are less responsive to LH.

The postnatal hormone surge is accompanied by increased testicular volume, primarily as a result of Sertoli and germ cell proliferation (Grumbach, 2005). Several studies show significant growth of testes during the neonatal period (Berensztein et al, 2002; Main et al, 2006b; Kuijper et al, 2008), and increased testicular growth rate and HPG axis activation are correlated in preterm boys (Kuiiri-Hanninen et al, 2011), suggesting that growth is a direct response to hormonal stimulation. Sertoli cell proliferation continues in the first year of life and is a major determinant of ultimate testicular size (Sharpe et al, 2003). Undifferentiated germ cells, called *prespermatogonia*, *prospertmatogonia*, or *gonocytes* (Culty, 2013; McCarrey, 2013), migrate to the basement membrane after birth and become established as undifferentiated type A spermatogonia. In humans and primates, type Ad and Ap spermatogonia include a subpopulation of spermatogonial stem cells (Hermann et al, 2010; Griswold and Oatley, 2013). Because migration occurs in a similar time frame to HPG axis activation, a relationship is presumed (Hadziseimovic et al, 1986; Hutson et al, 2012), but regulation of this important event remains poorly understood. Some factors shown to regulate migration of *prespermatogonia* or *gonocytes* include platelet-derived growth factor, thyroid hormone, and cell adhesion molecules (Orth et al, 2000; Tres and Kierszenbaum, 2005; Basciani et al, 2008; Oatley et al, 2011). If migration fails to occur, *prespermatogonia* or *gonocytes* are at increased risk for apoptosis or future malignant transformation (Rajpert-de Meyts and Hoei-Hansen, 2007).

Gubernacular Development and Testicular Descent

The physiology of normal testicular descent and the cause of abnormal descent in humans remain poorly understood, although the morphologic events have been well studied in mammals. Knowledge of the regulation of testicular descent is inferred from studies of human diseases that include cryptorchidism and/or from animal models of the disease.

The human indifferent gonad develops adjacent to and becomes suspended from the mesonephros, which has replaced the pronephros by 5 weeks' gestational age (Lemeh, 1960). A rudimentary cranial mesonephric ligament connects to the diaphragm, disappearing by 13 weeks as the mesonephros regresses (Barteczko and Jacob, 2000) (Fig. 148-2). There is no direct connection between the gonad and this ligament; therefore no cranial gonadal ligament exists in humans as noted in other species. Using fixed sections, Barteczko and Jacob observed an “inner” or transabdominal descent of the human testis from a position at vertebral levels C7-T8 to T9-L3 at 5 to 7 weeks' gestation and to sacral level by 10 weeks; using dissections, others described the testis at the level of L4 by the 7th week (Lemeh, 1960) or always “close to the groin” (Wyndham, 1943). Caudal movement of the ovary is prevented by the ovarian ligament and development of the müllerian ducts.

Barteczko and Jacob (2000) described five major phases of testicular descent in the human fetus (Fig. 148-3). In **phase I** (5 weeks

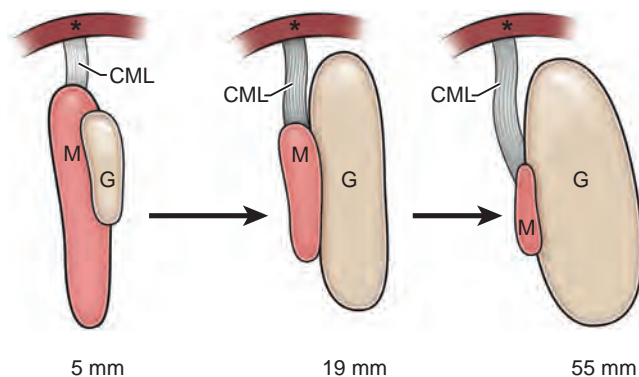


Figure 148-2. Development of the cranial mesonephric ligament (CML) and gonad (G) during embryonic regression of the mesonephros (M). Asterisks denote the anlage of the diaphragm. (From Barteczko KJ, Jacob MI. The testicular descent in human. Origin, development and fate of the gubernaculum Hunteri, processus vaginalis peritonei, and gonadal ligaments. *Adv Anat Embryol Cell Biol* 2000;156:iii-x, 1–98.)

of gestation), the caudal mesonephros contacts the future gubernaculum at the internal inguinal ring. In **phase II**, the genitofemoral nerve (GFN) is seen to accompany the newly formed gubernaculum (abdominal, interstitial, and subcutaneous portions) and processus vaginalis (7 weeks); subsequently, growth of the gubernaculum, deepening of the processus vaginalis, and extension of cremaster muscle fibers into the interstitial gubernaculum occur (8 to 10 weeks). In **phase III** (10 to 14 weeks), growth of the testis and regression of the müllerian ducts and mesonephros occur; the gubernaculum is visible as a thin cord in both sexes and begins its swelling phase in males after 12 weeks. In **phase IV** (14 to 20 weeks), swelling of the gubernaculum, further development of the cremaster muscle, and migration of the processus vaginalis produce widening of the inguinal canal. In **phase IV** (20 to 28 weeks), release of the distal subcutaneous attachment of the gubernaculum and transinguinal passage of the testis occur. Further caudal movement of the testis into the scrotum up until the time of birth is accompanied by regression of the gubernaculum.

The careful in situ anatomic observations by Barteczko and Jacob (2000) throughout gestation help clarify some aspects of human testicular descent. For example, transabdominal movement of the testis occurs before sexually dimorphic changes in the gubernaculum and thus is presumably not a male hormone-specific event. The subsequent male-specific swelling of the gubernaculum parallels the peak in Leydig cell secretion of testosterone (14 to 16 weeks) and INSL3 (15 to 17 weeks). The GFN precedes and accompanies the gubernaculum and developing processus vaginalis in both sexes beginning at an early stage (7 weeks), and both smooth muscle (in the abdominal portion) and skeletal muscle (in the interstitial and subcutaneous portion) fibers are present within these three segments of the gubernaculum. Both muscle types were also observed by other (Wyndham, 1943; Lemeh, 1960) but not all (Heyns, 1987; Costa et al, 2002; Niikura et al, 2008) researchers. However, studies of the in situ gubernaculum beginning at 20 weeks clearly show the presence of peripheral and centrally located striated muscle bundles (Barteczko and Jacob, 2000; Niikura et al, 2008) and infiltration of the gubernaculum by the GFN (Tayakkanonta, 1963). Controversy exists as to whether skeletal cremaster muscle fibers originate from abdominal wall musculature or from within the gubernaculum itself (van der Schoot, 1996; Barteczko and Jacob, 2000; Niikura et al, 2008), but their unique innervation and recent studies of transgenic mice (see later) suggest the latter.

Swelling of the gubernaculum is critically important to allow enlargement of the inguinal canal and testicular passage and is the result of both cellular proliferation and production of extracellular matrix (Heyns, 1987). Once the canal is created, unknown mechanical factors trigger a typically rapid transinguinal passage of

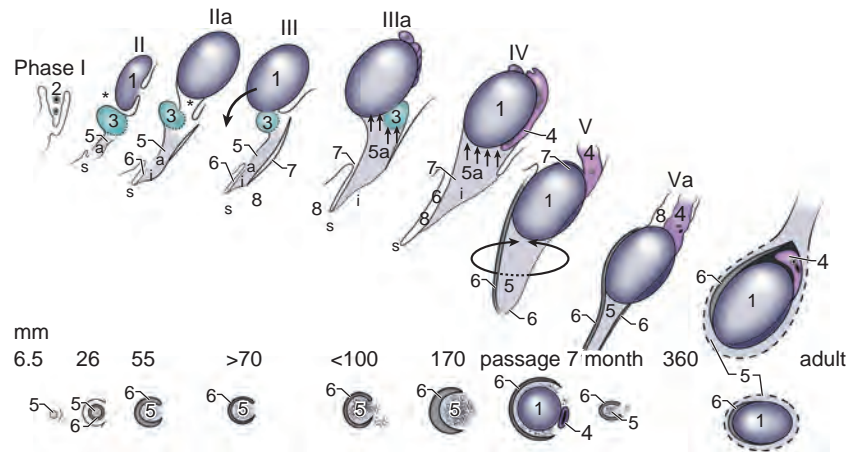


Figure 148-3. Overview of human testicular descent. Sagittal view (*top*) and transverse sections (*bottom*) at level of double line; 1, gonad; 2, mesonephros; 3, wolffian and müllerian duct; 4, vas deferens and epididymis; 5, gubernaculum—a, abdominal; i, interstitial; s, subcutaneous part; 6, processus vaginalis; 7, internal inguinal ring; 8, external inguinal ring. *Straight arrows* (phase I) show ventral side; *asterisks* (I to IIIa) show the link between the caudal pole of the testis and dorsal mesenchyme of genital ducts; *curved arrow* (III) shows direction of testicular migration; *short arrows* (IIIa to IV) indicate attachment between the testis or epididymis and gubernaculum; *oval arrowline* (V) indicates no connection between the boltlike gubernaculum and neighboring structures. (From Barteczko KJ, Jacob MI. The testicular descent in human. Origin, development and fate of the gubernaculum Hunteri, processus vaginalis peritonei, and gonadal ligaments. *Adv Anat Embryol Cell Biol* 2000;156:iii–x, 1–98.)

the testis. The gubernaculum is unattached distally during and after transinguinal passage (Fig. 148-4), and settling of the gubernaculum and testis into the preformed scrotum is gradual. The scrotum itself develops from genital swellings that are first visible at 7 weeks and fuse by 10 to 12 weeks in response to circulating dihydrotestosterone. Passage of the testis into the inguinal canal rarely occurs before 22 weeks in the human fetus, and the majority of testes are scrotal after 27 weeks; time spent in the inguinal canal seems to be limited for the majority of human fetal testes (Heyns, 1987; Sampaio and Favorito, 1998). The rapidity of transinguinal testicular transit, early innervation of the gubernaculum in human fetuses (Barteczko and Jacob, 2000), significance of the GFN in rodents (Hutson and Hasthorpe, 2005), and the complex anatomic distribution of cremaster muscle in and around the gubernaculum (Harnaen et al, 2007; Niikura et al, 2008) suggest that neuromuscular forces are required for testicular descent.

Regulation of Testicular Descent

Direct evidence for hormonal control of testicular descent is based on studies in animal models, primarily rodents. The relevance of rodent data to humans has been questioned because of anatomic differences, which in mice and rats include a less prominent interstitial gubernaculum, a cranial gonadal ligament, an elongated cord connecting the gubernaculum to the epididymis, a well-developed intrinsic cremaster muscle located in the periphery of the gubernaculum, an absent inguinal canal, and failure of closure of the processus vaginalis (Wensing, 1988). However, the developing processus vaginalis and cremaster muscle are sufficiently anatomically similar among species to warrant translational studies using rodent models (van der Schoot, 1996; Harnaen et al, 2007), and their normal development is essential for testicular descent.

Evidence from animal models and indirect clinical evidence suggest that *INSL3* and testosterone are the key hormones required for testicular descent. Transgenic or spontaneous rodent strains with inactivation of *Insl3*, *Rxfp2*, or *Ar* are cryptorchid (Zimmermann et al, 1999; Adham et al, 2000; Overbeek et al, 2001), as are boys with abnormalities of androgen synthesis or action (Barthold et al, 2000; Foresta et al, 2008; Gaspari et al, 2011). According to a paradigm developed by Hutson and



Figure 148-4. The distally unattached human gubernaculum just before transinguinal passage. Human fetus at 25 weeks of gestation (215-mm crown-rump length) just before transinguinal testicular descent. G, gubernaculum; P, penis; S, scrotum; T, testis. (From Heyns CF. The gubernaculum during testicular descent in the human fetus. *J Anat* 1987;153:93–112.)

colleagues, testicular descent occurs in two phases, transabdominal and transinguinal, regulated by INSL3 and by androgens via the GFN, respectively (Hutson and Hasthorpe, 2005). However, animal models show that INSL3 and androgen synergistically stimulate cellular proliferation and growth of the gubernaculum (Adham et al, 2000; Emmen et al, 2000; Kubota et al, 2002) and that both INSL3 binding and AR expression are present before and during the swelling phase of the fetal rat gubernaculum (Staub et al, 2005). Moreover, INSL3 and testosterone levels peak after 12 weeks in the human fetus, concomitant with gubernacular swelling, whereas transabdominal testicular descent occurs earlier, before 10 weeks' gestation (Barteczko and Jacob, 2000; Koskimies et al, 2003; McKinnell et al, 2005). In mice, INSL3 signaling also promotes development of the processus vaginalis, and androgen signaling causes regression of the cranial gonadal ligament (Adham et al, 2002; Koskimies et al, 2003; Adham and Agoulunik, 2004), a structure that does not exist in the human fetus.

More recent data suggest that both INSL3/RXFP2 and AR signaling are directly involved in development of the gubernaculum, specifically in myogenic differentiation of the cremaster. In transgenic mice with conditional deletion of *Rxfp2* or *Ar* in the gubernacular mesenchyme (but not differentiated muscle), testicular descent is disrupted (Kaftanovskaya et al, 2011, 2012). In the gubernaculum-specific *Rxfp2*^{-/-} transgenic mice, aberrant muscle cells exist within the developing mesenchymal core of the gubernaculum, and the cremaster muscle fails to develop normally, suggesting that proliferation, migration, and patterning of muscle precursors depend on INSL3/RXFP2 signaling. Moreover, migration and proliferation of AR-positive cells into the gubernaculum fail to occur normally in conditional *Rxfp2*^{-/-} fetuses, suggesting interaction between the RXFP2 and AR pathways. The defect in cremaster development is less severe with conditional deletion of *Ar* in gubernacular mesenchyme; however, muscle organization and growth are impaired, expression of muscle-specific markers is altered, and testicular descent fails to occur (Kaftanovskaya et al, 2012).

The definition of pathways and mechanisms of gubernacular development and testicular descent downstream of hormone signaling are provided by transgenic mouse models and human syndromes with phenotypes that include cryptorchidism (Barthold, 2008; Foresta et al, 2008). A theme that again emerges from these studies is the importance of myogenesis in gubernacular development. In mice, transgenic inactivation of genes including *Notch1* and several involved in Wnt pathway signaling, including *Ctnnb1*, *Sfrp1*, *Sfrp2*, *Wnt5a*, and *Ror2*, results in marked disruption of fetal muscle patterning (Warr et al, 2009; Kaftanovskaya et al, 2011; Chawengsaksophak et al, 2012). Gene expression in fetal rat gubernaculum after stimulation by dihydrotestosterone (Barthold et al, 2013) or INSL3 (Johnson et al, 2010) also supports activation of Wnt pathways by both hormones and strong overlap in their transcriptional response. Transgenic deletion of either of two homeobox genes, *Hoxa10* and *Hoxa11*, is associated with isolated cryptorchidism in mice (Satokata et al, 1995; Potter and Brannford, 1998) with evidence for delayed muscle development in the *Hoxa11* gubernaculum (Harisis et al, 2013). Also, the cremaster muscle is overdeveloped and associated with retractile testes in *Esr1* knockout mice (Donaldson et al, 1996). Other transgenic mouse models that include the cryptorchid phenotype provide insight into pathways required for testicular descent. These include targeted deletions of *Tgfb2* (Sanford et al, 1997), *Arid5b* (Lahoud et al, 2001), *Wt1* (Kaftanovskaya et al, 2013), *Ptgs* (Philibert et al, 2013), and *Loxl1* (Wood et al, 2009) and spontaneous mutations of *Ptch1* (Sweet et al, 1996) and *Bmp5* (Green, 1968).

Studies of rats with inherited cryptorchidism also suggest that innervation and/or muscle development within the gubernaculum is disrupted (Hrabovszky et al, 2001; Barthold et al, 2008), and recent three-dimensional images of the cryptorchid rat gubernaculum show muscle patterning defects (Barthold et al, 2014). Based on extensive rodent studies, Hutson and colleagues have shown that gubernacular innervation by the GFN is essential for its function, and they propose that release of calcitonin gene-related peptide (CGRP) from the GFN stimulates development and func-

tion of the gubernaculum (Yamanaka et al, 1993; Chan et al, 2009). Although a role for CGRP release from the GFN in human fetuses remains undefined, it is clear that the human gubernaculum contains and is surrounded by muscle and is innervated by the GFN beginning as early as 7 weeks' gestation (Lemeh, 1960; Tayakanonta, 1963; Barteczko and Jacob, 2000; Niikura et al, 2008).

In summary, the gubernaculum develops in both sexes beginning early in the second month of gestation, and the testicular hormones INSL3 and androgen stimulate development of the gubernaculum and testicular descent in the second and third trimesters. Enlargement and migration of the gubernaculum are key events that facilitate and direct caudal movement of the testis. INSL3 and androgens appear to synergistically target cellular proliferation, migration, and muscle patterning within the gubernaculum, in part via Wnt signaling. A consistent theme in experimental models of cryptorchidism is altered myogenesis of the cremaster, suggesting an important role in the process of testicular descent.

ETIOLOGY

The specific cause of isolated cryptorchidism is unknown in most cases, but indirect evidence suggests that the disease is heterogeneous and most likely the result of multiple genetic and environmental risk factors. Human data do not suggest strong genetic risk at a dominant locus but rather a multilocus, complex pattern of genetic susceptibility. Also, available human data have not identified any clear and consistent exposures associated with the disease, although animal models suggest that certain environmental chemicals have the potential to contribute to cryptorchidism risk. The most consistent perinatal factors correlating with risk of cryptorchidism are prematurity and/or low birth weight for gestational age (Damgaard et al, 2008; Bay et al, 2011; Brouwers et al, 2012; Jensen et al, 2012).

Epidemiology

Cryptorchidism is one of the most common congenital anomalies, occurring in 1% to 4% of full-term and 1% to 45% of preterm newborn boys (Sijstermans et al, 2008). It is a component of almost 500 syndromes causally linked, based on current information, to almost 200 genes according to the Winter-Baraitser Dysmorphology Database (www.lmddatabases.com); the most common associated syndromes are reviewed elsewhere (Foresta et al, 2008; Virtanen and Toppaari, 2008). The majority of cases are isolated, with the ratio of nonsyndromic to syndromic cryptorchidism reported as greater than 6:1 in a large cohort (Boyd et al, 2006). A subset of syndromic cases is associated with deficiency or insensitivity of HPG axis hormones.

Congenital Cryptorchidism

Studies of the prevalence of isolated cryptorchidism at birth are complicated by confounding factors that include subjectivity of the examination and differences in the definition of undescended testis (inclusion or exclusion of high scrotal testes), study populations, and experimental design (Sijstermans et al, 2008). Although most studies support a prevalence at birth of 2% to 4% and at 3 months of age of 1% to 2%, this varies geographically, with frequency as high as 9% in some studies (Boisen et al, 2004; Virtanen and Toppaari, 2008), supporting the possibility of an increase over time. However, other data suggest that country-specific trends are not increasing (Abdullah et al, 2007; Cortes et al, 2008; Bonney et al, 2009; Wagner-Mahler et al, 2011), and overall there do not appear to be reproducible trends in prevalence (Sijstermans et al, 2008). Perinatal risk factors most consistently associated with cryptorchidism include prematurity, low birth weight or small size for gestational age, breech presentation, and maternal diabetes (Damgaard et al, 2008; Virtanen and Toppaari, 2008; Jensen et al, 2012).

The reported frequency of spontaneous testicular descent after birth varies among series, likely because of similar confounding

factors, most notably variable inclusion of boys with high scrotal testes. In several population-based prospective studies, the frequency of spontaneous descent by 3 months of age in boys identified as cryptorchid at birth was reported as 50% to 87% (Berkowitz et al, 1993; Ghirri et al, 2002; Radpour et al, 2007; Wohlfahrt-Veje et al, 2009; Wagner-Mahler et al, 2011; van der Plas et al, 2013b). In smaller cohorts, spontaneous descent occurred in significantly more Danish (68%) than Finnish (45%) boys at 3 months of age, possibly attributable to increased severity of the disease in the latter group (Suomi et al, 2006). In another series, extrascrotal testes were less likely to descend by 1 year of age (50%) than high scrotal testes defined as cryptorchid at birth (87.5%) (Acerini et al, 2009). In contrast, of 95 cryptorchid infants referred to a urology practice, spontaneous descent occurred subsequently in 16% and 0% of those presented before and after 6 months of age, respectively (Wenzler et al, 2004). The lower rate of descent in this series could be related to ascertainment age and severity of cryptorchidism in this referral population, because spontaneous descent is common before 2 months of age (Kollin et al, 2013). The long-term risk of recurrent cryptorchidism is not well defined, but in two large longitudinal series, reascent occurred in 10% and 22% of boys, in most cases between 1 and 5 years of age (Wagner-Mahler et al, 2011; Kollin et al, 2013).

Acquired Cryptorchidism

In the past, cryptorchidism was considered a congenital anomaly identifiable at birth. However, since first reported 40 years ago (Myers and Officer, 1975), **acquired cryptorchidism, or testes that are diagnosed as cryptorchid after apparent full descent at birth or in the neonatal period, is now fully accepted as a clinical entity** (Barthold and Gonzalez, 2003; Taghizadeh and Thomas, 2008; Acerini et al, 2009; Wohlfahrt-Veje et al, 2009; Hack et al, 2012). Acquired undescended testes are diagnosed at an average age of 8 to 11 years and are more commonly in a lower position, associated with a closed processus vaginalis and normal epididymis, than in cases diagnosed as congenital. The reason for a later diagnosis remains unknown; theories include presence of a fibrous remnant of the processus vaginalis that tethers or foreshortens the cord over time or mobility of the testis within an open sac (Keys and Heloury, 2012). However, it is most likely that the testis is incompletely descended from birth, because many are located in a lateral (ectopic) position within the superficial inguinal pouch (SIP) (Barthold and Gonzalez, 2003; van Brakel et al, 2011). These testes may be highly mobile and initially appear descended until somatic growth results in relative widening of the distance between testis and scrotum (Redman, 2005; Agarwal et al, 2006). Acquired cryptorchidism is reportedly more common in boys with proximal hypospadias (Tasian et al, 2010; Itesako et al, 2011) and, like the congenital form, is associated with abnormal germ cell development (Rusnack et al, 2002).

A diagnosis of acquired cryptorchidism may be more likely in boys with retractile testes, although testis retractility is common in normal populations. In a hospital-based study of unselected boys, the testis was initially suprascrotal on examination (retractile) in up to 30% of boys at 4 years and 10% of boys 4 to 12 years of age but was intrascrotal in all boys over the age of 12 (Farrington, 1968). In population-based studies of healthy boys, retractile testes were present in 11% to 15% of boys up to 11 years of age (Wohlfahrt-Veje et al, 2009; Goede et al, 2011) and 4% of 7- to 12-year-old boys (Inan et al, 2008). Both prospective and retrospective studies of the natural history of retractile testes support the concept that a subset of these becomes undescended over time. However, a selection bias exists in studies of the risk of cryptorchidism in boys with retractile testes, because those referred for follow-up by specialists are likely those with the most severe retractility. For example, Wyllie prospectively studied a cohort of 100 boys with unilateral retractile testis and identified 64 cases in which testicular position, as documented by the distance between the pubic tubercle and midtestis and/or testicular size as estimated by orchidometer, was reduced after 5 years of follow-up (Wyllie, 1984). Orchidopexy was performed in

45 of these cases, although specific documentation of testicular position and size as indications for surgery were not reported. In retrospective case series it has been reported that cryptorchidism was diagnosed in up to 7% to 32% of boys with retractile testes followed a mean of 2.2 to 3.8 years by the same observer(s) (La Scala and Ein, 2004; Agarwal et al, 2006; Stec et al, 2007). However, in a prospective study of 1072 boys, 520 of whom were followed from birth to latest follow-up at 4.5 to 10 years of age, only 2.6% developed ipsilateral cryptorchidism, although an additional 13.5% with retractile testes had other forms of cryptorchidism (contralateral or prior ipsilateral) (Wohlfahrt-Veje et al, 2009). Although these data suggest an association between retractile testes and cryptorchidism, the nature of this association may reflect either difficulty in distinguishing the two entities or the fact that significant testicular retractility is a risk factor for acquired cryptorchidism. However, the smaller volume of retractile testes suggests a common pathogenesis (Goede et al, 2011). **Careful serial physical examination is recommended to accurately determine testicular position and identify cases of acquired cryptorchidism in boys with retractile testes.**

The true prevalence of acquired cryptorchidism is incompletely defined, because longitudinal data that provide documentation of prior scrotal position are limited and address only the first few years of life. In one study, 742 infants were followed with serial examinations for 2 years after birth, with complete follow-up in 326 (Acerini et al, 2009). The prevalence of extrascrotal testes was 2.7% at birth (27% nonpalpable, surgical findings not reported), and 0.2%, 1.8%, 0.3%, and 0% of testes in the studied population became extrascrotal at 3, 12, 18, and 24 months, respectively. The number of suprascrotal testes diagnosed at birth in this series (10) was the same as the number diagnosed subsequently (10), although almost half the boys were lost to follow-up during the study. Including high scrotal testes, a total of 5.7% were identified as cryptorchid at birth and 1% to 4% rose to a high scrotal position with each follow-up visit. In another study, 1072 boys were followed with serial examinations from birth to 4.5 to 10 years of age, with complete follow-up in 500 (Wohlfahrt-Veje et al, 2009). The prevalence of congenital cryptorchidism (including high scrotal testes) was 9% at birth but dropped to 1% at 18 months, whereas 8 (1.6%) acquired cases were observed during follow-up, suggesting that the prevalence of persistent congenital and acquired forms of cryptorchidism is similar. Retrospective series also suggest that acquired cryptorchidism is common, but they cannot reliably differentiate true acquired cases from delayed referral of congenital cases (Güven and Kogan, 2008; Jensen et al, 2011; Barthold et al, 2012; Hack et al, 2012; van der Plas et al, 2013b). **Acquired cryptorchidism most likely represents a milder presentation of congenital cryptorchidism that escapes detection in infancy.**

Genetic Susceptibility

Genetic studies of cryptorchidism suggest that the disease is heritable, but that susceptibility is likely polygenic and multifactorial. Clustering of cryptorchidism has been reported in a number of families affecting multiple individuals in the same generation and variable phenotype (Minehan and Touloukian, 1974; Pardo-Mindan et al, 1975; Czeizel et al, 1981; Savion et al, 1984). Extended pedigrees were not usually examined, but autosomal dominance with reduced penetrance was most often cited as the probable mode of inheritance. Population case-control studies also support genetic contribution to the disease. Familial aggregation suggesting moderate genetic risk was reported in a large cohort study of more than 1 million male births in the Netherlands based on extensive hospital registry data (Schnack et al, 2008). Recurrence risk ratio (RR) was 10.1 in twins, 3.5 in brothers, and 2.3 in offspring and was significantly higher in maternal than in paternal half-brothers. Another population-based study in Denmark, using different methodology, identified greater concordance rates of cryptorchidism diagnosis in maternal (6%) than in paternal (3.4%) half-brothers and in dizygotic (24%) and monozygotic (27%) twins relative to brothers (9%) (Jensen et al, 2010b). However, for

surgically treated orchidopexy, presumably limiting cases to only those involving persistent cryptorchidism, concordance rates were 7.5% in brothers, 17% in dizygotic twins, and 27% in monozygotic twins. These observations suggest that environmental effects and/or maternal genetic factors contribute to the risk of cryptorchidism in Denmark. Previous smaller studies reported a 5- and 7- to 10-fold increased prevalence in fathers and brothers, respectively, of affected as compared with unaffected individuals, and some also support the possibility that maternal factor(s), or X-linked risk alleles, influence expression of the disease (Czeizel et al, 1981; Jones and Young, 1982; Elert et al, 2003; Jensen et al, 2010b; Barthold et al, 2012).

The most promising gene candidates for nonsyndromic cryptorchidism based on animal studies include *INSL3*, *RXFP2*, *HOXA10*, and *HOXA11*. However, DNA coding variants of *INSL3* and *RXFP2* are reported in only 0.6% to 1.8% and 1.6% to 2.9% of persistently cryptorchid males, respectively (Foresta et al, 2008). Notably, apparent mutations in these genes are associated with a range of phenotypes that include unilateral or bilateral and persistent or spontaneously resolving presentations, and apparently deleterious mutations may exist in normal family members, as noted for an *INSL3* mutation showing reduced receptor activation (El Houate et al, 2007). Over 1500 cryptorchidism cases have been screened for mutations in *INSL3*, but of 10 exonic variants identified in cases but not controls, few are clearly functional (Ferlin et al, 2008; Foresta et al, 2008; Bay et al, 2011). A nonsynonymous polymorphism of the *RXFP2* gene, T222P, was considered a strong etiologic candidate for cryptorchidism based on absence in normal controls and in vitro studies showing curtailed cell membrane localization and activation of the abnormal receptor (Bogatcheva et al, 2007). However, cases and controls in other European populations show a similar frequency of the T222P allele (Nutti et al, 2008; Ars et al, 2011). Although these data suggest that mutations of *INSL3* and *RXFP2* are infrequent in cases of cryptorchidism, noncoding variants that alter expression levels of the protein may exist.

Analysis of other potential candidate genes for human cryptorchidism has failed to yield consistent results. *HOXA10* mutations reported by Kolon and colleagues (1999) were not confirmed in additional series, nor were mutations identified in *HOXA11* (Bertini et al, 2004; Wang et al, 2007). Studies of polymorphic trinucleotide (CAG and GGN) repeats of *AR* in cryptorchidism also show variable results, with some studies but not others showing altered repeat length in cases (Sasagawa et al, 2000; Ferlin et al, 2005; Silva-Ramos et al, 2006; Radpour et al, 2007; Davis-Dao et al, 2012). Differences among these series may relate to small sample size (most series involve fewer than 100 cases) and heterogeneity of populations. A specific haplotype of the gene encoding ER- α (*ESR1*) did not show a consistent association with cryptorchidism in three case-control series (Yoshida et al, 2005; Galan et al, 2007; Wang et al, 2008). In a larger series of patients from Spain and Italy (373 total cases), there was no association between an *ESR1* promoter polymorphism and cryptorchidism (Lo Giacco et al, 2011). Microdeletions of the Y chromosome have also been studied in cryptorchid children and previously cryptorchid men, with no consistent association observed (Gurbuz et al, 2008; Mamoulakis et al, 2013a). A specific polymorphism of the *SF1* gene that encodes a transcription factor that regulates expression of *INSL3*, *RXFP2*, and steroidogenesis genes was associated with cryptorchidism in a single report that included 72 cryptorchid Japanese males (Wada et al, 2006). An association between aryl hydrocarbon receptor-associated genes and cryptorchidism was also noted (Qin et al, 2012). No cryptorchidism-associated variants were identified in the sex hormone-binding globulin gene (*SHBG*) or in genes associated with hypogonadotropic hypogonadism (Laitinen et al, 2011; Mamoulakis et al, 2013b). Reliability of the results of many of these studies is limited because of insufficient sample size and/or lack of replication in other population groups.

Results of unbiased genome-wide studies of cryptorchidism are also limited. In a whole-genome analysis of copy number variation in boys with genital defects (Tannour-Louet et al, 2010), potential loci associated with cryptorchidism were identified in the 10p14 and Xq28 regions. A genome-wide association study (GWAS) of 488

men with at least one of the four phenotypes comprising the so-called testicular dysgenesis syndrome (TDS) (Sharpe and Skakkebaek, 2008) including infertility, cryptorchidism ($n = 138$), hypospadias, and/or testicular germ cell tumor (TGCT) (Dalgaard et al, 2012) was reported. Although the authors did not identify a locus associated with cryptorchidism that passed the stringent genome-wide significance threshold, they used a systems biology approach to identify less significant signals of potential importance. In doing so, they identified the transforming growth factor (TGF) receptor III (*TGFBR3*) gene, which is also associated with transient Leydig cell dysgenesis in knockout mice (Sarraj et al, 2010), as a potential locus associated with cryptorchidism and TGCT in both discovery and replication cohorts. *TGFBR3* protein is expressed in fetal Leydig cells (Dalgaard et al, 2012) and interacts with TGF- β 2 (Bilandzic and Stenvers, 2011). Incomplete testicular descent was reported in *Tgfb2*^{-/-} mice (Sanford et al, 1997) but not in *Tgfb3*^{-/-} mice, which rarely survive past birth.

In a larger GWAS of 844 boys with nonsyndromic cryptorchidism, signals showing suggestive association included those in *TGFBR3* and in cytoskeleton-related genes, but those reaching genome-wide significance were rare, occurred only in subphenotype analysis, and were not replicated in an independent population, suggesting significant genetic heterogeneity (Barthold et al, 2015a, 2015b).

In summary, studies to date are consistent with the assumption that cryptorchidism is a genetically complex disease, likely associated with multiple susceptibility loci. Failure to identify consistent loci associated with cryptorchidism is likely related to methodology, particularly insufficient sample size, phenotypic variability, and other confounding factors such as environmental influences. **Therefore, although multiple genetic variants likely contribute to the risk of nonsyndromic cryptorchidism, most remain unknown at this time.**

Environmental Risk Factors

Population-based studies suggest that the maternal environment may contribute to the risk of cryptorchidism, but it remains unclear if risk is related to maternal exposures, characteristics, or lifestyle. Maternal alcohol consumption or binge drinking was associated with cryptorchidism in some studies but not others (Thorup et al, 2006; Damgaard et al, 2007; Jensen et al, 2007; Mongraw-Chaffin et al, 2008; Strandberg-Larsen et al, 2009). A review of data for maternal smoking confirms inconsistent results but suggests that a small-to-moderate increased risk for cryptorchidism is present in offspring (Hakonsen et al, 2014). Several series have suggested increased risk with maternal use of acetaminophen or more than one analgesic in midpregnancy or earlier (Jensen et al, 2010a; Kristensen et al, 2011; Snijder et al, 2012). Parental occupation is not consistently associated with cryptorchidism in offspring, although some data suggest increased risk in horticulture-related professions (Weidner et al, 1998; Pierik et al, 2004; Andersen et al, 2008; Gabel et al, 2011; Morales-Suarez-Varela et al, 2011; Jørgensen et al, 2013, 2014). Although risk factors for acquired cryptorchidism have not been specifically addressed, a single study addressing this issue identified reduced breastfeeding and increased use of soy formula as variables associated with first diagnosis of cryptorchidism at an older age (Barthold et al, 2012).

Testicular dysgenesis syndrome is the term used to describe a potentially related constellation of reproductive abnormalities including cryptorchidism, hypospadias, infertility, and TGCT (Sharpe and Skakkebaek, 2008). The proposed cause is a deficiency in fetal androgen production resulting from exposure to endocrine-disrupting chemicals (EDCs). The concern for a link between EDCs and cryptorchidism arose because of a reported increased risk of cryptorchidism after maternal exposure to diethylstilbestrol (DES) (Gill et al, 1979). In a large cohort study of 1197 men previously exposed to DES and 1038 unexposed men, the RR of cryptorchidism was 1.9 (95% confidence interval [CI] 1.1 to 3.4) overall. When data were subdivided based on gestational age less than 11 weeks and exposure of 5 g or more, the RRs were 2.9 (95% CI

1.6 to 5.2) and 3.2 (95% CI 1.7 to 6.0), showing that early and significant exposure present the clearest risks (Palmer et al, 2009). Data supporting a link between EDCs other than DES and cryptorchidism are less clear (reviewed in Virtanen and Adamsson, 2012). Animal models suggest a relationship between prenatal exposure to antiandrogenic EDCs and risk of cryptorchidism and other reproductive end points, and suggest additive effects of chemical mixtures, although levels of exposure are much higher than applicable clinically (Rider et al, 2009) and concerns exist about the applicability of EDC animal models to humans (Habert et al, 2014). Notably, recent evidence suggests that species-specific, differential sensitivity to EDCs exists. Human testes appear insensitive to inhibition of steroidogenesis by phthalates or DES, but more sensitive to the inhibitory effects of bisphenol A (Lambrot et al, 2009; Heger et al, 2012; Mitchell et al, 2012; N'Tumba-Byn et al, 2012). In addition, measured levels of antiandrogenic and/or estrogenic EDCs in placenta, breast milk, or cord blood, including pesticides, polychlorinated biphenyls (PCBs), dioxins, perfluorinated compounds, flame retardants (polybrominated diphenyl ethers [PBDEs]), and organotin were not consistently higher in association with affected pregnancies (Damgaard et al, 2006; Main et al, 2007; Cook et al, 2011; Fenichel et al, 2012; Trabert et al, 2012; Virtanen et al, 2012; Rantakokko et al, 2013; Vesterholm Jensen et al, 2014). Consistent with data showing lack of inhibition of human fetal testicular steroidogenesis by phthalates, levels of individual phthalate metabolites did not show consistent correlation with occurrence of cryptorchidism or hormone levels in affected boys (Main et al, 2006a).

Because EDC exposure is difficult to measure at relevant fetal time points, an alternative approach that has been used to potentially link exposures that could inhibit virilization with reproductive outcomes is measurement of anogenital distance (AGD), or perineal length from the posterior margin of the scrotum to the anal verge. AGD is sexually dimorphic and correlated with newborn body weight (Sathyanarayana et al, 2010). Reduced AGD was correlated with phthalate exposure, AR CAG repeat length, cryptorchidism, hypospadias, and variants in genes linked to reproductive anomalies, including *ESR1* (Sathyanarayana et al, 2012; Dean and Sharpe, 2013; Eisenberg et al, 2013; Jain and Singal, 2013; Thankamony et al, 2014). These observations warrant further investigation into the association of fetal androgen action and cryptorchidism. However, the existence of TDS as an environmentally induced syndrome remains provisional, as the available evidence does not strongly support direct links between EDC exposure and their occurrence in humans (Akre and Richiardi, 2009; Thorup et al, 2010; Habert et al, 2014). A causal association between single chemicals or classes of EDCs and risk of cryptorchidism may be difficult to demonstrate in view of the presumed heterogeneity of susceptibility to the disease, but the wide variety of EDCs to which humans are exposed may allow for synergistic effects that are difficult to measure. **At present, epidemiologic data suggest potential associations in selected populations but do not strongly support environmental chemicals as a cause of increased susceptibility to cryptorchidism in the human population.**

Testicular hormones are required for testicular descent; therefore defective hormone production and/or action may contribute to the pathogenesis of cryptorchidism and may manifest during postnatal activation of the HPG axis (see Fig. 148-1). Prospective studies of varying size and quality are available that report postnatal hormone levels in cryptorchidism, and although some data suggest that the HPG axis is abnormal, results are conflicting and baseline levels do not directly reflect the status of germ cell development. In the first reported series of cryptorchid and control boys undergoing hormonal evaluation in the first few months of life, serum testosterone was lower in 7 of 17 (41%) persistently cryptorchid boys but comparable to control levels in 4 of 25 boys with spontaneous testicular descent (Gendrel et al, 1978). Subsequent studies have shown reduced hormone levels in some series (Facchinetti et al, 1983; Raivio et al, 2003; Pierik et al, 2009) but not others (De Muinck Keizer-Schrama et al, 1988; Barthold et al, 2004). In a larger series, Suomi and colleagues showed geographic differences in serum

inhibin B and follicle-stimulating hormone (FSH) levels but no differences in testosterone levels in cryptorchid infants from Finland (88 boys, 36% spontaneous descent) and Denmark (34 boys, 68% spontaneous descent) as compared with 300 and 399 control boys, respectively (Suomi et al, 2006). In a related cohort, INSL3 levels were reduced in cord blood but not in serum obtained at 3 months of age in persistently cryptorchid boys (Bay et al, 2007). These studies, however, do suggest that LH-to-testosterone and LH-to-INSL3 ratios are increased in boys with cryptorchidism, suggesting that reduced Leydig cell function may lead to upregulation of LH (Suomi et al, 2006; Bay et al, 2007). In the largest series to date of 225 boys with congenital cryptorchidism in whom LH, FSH, testosterone, and inhibin B were measured at 0 to 3 weeks, 2 months, and 6 months of age ($n \geq 57$ per time point), hormone levels were not significantly different among unilateral, bilateral, and spontaneously resolving cryptorchidism, and did not correlate with spermatogenesis (Kollin et al, 2012).

Other studies of Sertoli-germ cell function as determined by serum assays in boys with cryptorchidism suggest that abnormalities may exist, but data are inconsistent among studies. In a longitudinal study of 27 boys (mean age 4.8 years) undergoing orchidopexy, an increase in serum inhibin B was identified in a majority of patients 6 months postoperatively (Irkilata et al, 2004). In 69 older boys undergoing bilateral orchidopexy (median age 2 years), the majority (75%) with congenital cryptorchidism, FSH levels were increased in 17 (25%), inhibin B levels were decreased in 9 (13%), and germ cell counts were not closely correlated with hormone levels (Thorup et al, 2012). Elevated FSH levels normalized in 14 (82%) of patients postoperatively. In another series of 62 boys (mean age 7.7 years), no differences were identified in inhibin B levels or in LH, FSH, or testosterone levels before or after hCG stimulation (Christiansen et al, 2002). AMH levels were measured in three prospective studies of boys with cryptorchidism as compared with age-matched controls. Lower AMH levels were seen in a subset of patients younger than 8 years included in a study of 104 cryptorchid boys (mean age 4 to 5 years) (Yamanaka et al, 1991) and also in a case-control study of 12-month-old boys ($n = 20$ per group) in whom levels did not change after orchidopexy (Demircan et al, 2006). However, in another study, no differences in AMH levels were seen in 1- to 6-month-old cryptorchid ($n = 43$) versus control ($n = 113$) boys (Pierik et al, 2009).

These studies suggest that some cryptorchid boys have measurable abnormalities in pituitary and/or gonadal hormone secretion during infancy in the absence of generalized, persistent endocrine dysfunction. Inconsistent findings among studies are likely based on timing and type of assays, sample size, and heterogeneity based on age, severity, genetic background, and/or other interindividual differences. No hormonal studies to date have been shown to closely predict germ cell numbers or long-term testicular function in boys with cryptorchidism. Because multiple genetic and environmental factors likely contribute to cryptorchidism, identification of risk factors is difficult in case-control studies.

Syndromic Cryptorchidism

Undescended testes are frequently present in diseases associated with reduced androgen production and/or action, such as androgen biosynthetic defects, androgen insensitivity, Leydig cell agenesis, and gonadotropin deficiency disorders (Barthold et al, 2000; Foresta et al, 2008). These conditions are associated with generalized failure of masculinization, are considered disorders of sexual differentiation (DSD), and are not reviewed here. Persistent müllerian duct syndrome, a DSD resulting from defective AMH signaling, is also associated with cryptorchidism or transverse testicular ectopia (Josso et al, 2006). Gubernacular defects that are observed in these patients may be caused by hindrance of descent by retained müllerian ducts (Barteczko and Jacob, 2000) and/or via loss of direct proliferative effects of AMH on the gubernaculum (Kubota et al, 2002). The frequency of Klinefelter syndrome (47,XXY) is below 2% in large series of primarily nonsyndromic cryptorchidism but is higher when other anomalies, particularly hypospadias, are

present (Sasagawa et al, 1996; Moreno-Garcia and Miranda, 2002; Ferlin et al, 2008). Over half of prepubertal patients with Klinefelter syndrome have cryptorchidism (Pacenza et al, 2012). Other genomic rearrangements and trisomies, including Down syndrome (trisomy 21), are associated with cryptorchidism (Hadziselimovic, 1983).

Certain anomalies are associated with increased risk of cryptorchidism, many related to musculoskeletal, central nervous system (CNS), or abdominal wall or gastrointestinal defects. These include all cases of classic prune-belly (triad or Eagle-Barrett) syndrome, 80% of spigelian hernia (Durham and Ricketts, 2006; Bilici et al, 2012; Balsara et al, 2014), 41% to 54% of cerebral palsy (Rundle et al, 1982; Cortada and Kousseff, 1984), 38% of arthrogryposis (Fallat et al, 1991), 15% of myelomeningocele (Ferrara et al, 1998), 16% to 33% of omphalocele, 5% to 15% of gastroschisis (Kaplan et al, 1986; Koivusalo et al, 1998; Yardley et al, 2012), 19% of imperforate anus (Cortes et al, 1995b), 12% to 16% of posterior urethral valve (Krueger et al, 1980; Heikkila et al, 2008), and 6% of umbilical hernia (Kaplan et al, 1986) patients. Multisystem anomalies are often associated with omphalocele (80%) and prune-belly syndrome (45%), suggesting a syndromic cause (Loder et al, 1992; Koivusalo et al, 1998). Depue also reported a significant association of cryptorchidism with CNS dysfunction, particularly cerebral palsy (RR = 34), low IQ (RR = 2.7), and hypotonia (RR = 3.6) (Depue, 1988). Cortes and colleagues reported associations between renal and T10 to S5 spinal anomalies and cryptorchidism, with the affected testis on the same side as the renal anomaly in 90% of cases (Cortes et al, 1998). In addition, syndromic cryptorchidism, especially with CNS malformations, is more commonly bilateral (Cendron et al, 1993; Cortes et al, 1995b). These data support common origins of cryptorchidism and anomalies of urogenital ridge, abdominal wall, lumbosacral spine, and CNS development.

The occurrence of cryptorchidism with other nongenital anomalies may complicate and/or alter the timing of treatment. For example, spigelian hernia may be difficult to diagnose, and associated absence of the gubernaculum and inguinal canal may complicate orchidopexy (Bilici et al, 2012; Balsara et al, 2014). Spontaneous testicular descent is reported in 50% to 55% of gastroschisis patients (Hill and Durham, 2011; Yardley et al, 2012) suggesting that observation is warranted.

DIAGNOSIS

To best determine testicular position, boys should be examined in the supine and, if possible, upright cross-legged and standing positions. Abduction of the thighs contributes to inhibition of the cremasteric reflex, which is elevation of the testis that is elicited by scratching the inner thigh. The examination should include documentation of testicular palpability, position, mobility, size, and possible associated findings such as hernia, hydrocele, penile size, and urethral meatus position. Patient distraction, a warm room and hands, use of liquid soap on the examiner's hands, and repeated examinations also help to localize the testis and to limit cremaster muscle activity and resultant difficulty in determining testicular position. Sustained gentle traction on the cord can help to inhibit the cremaster reflex and allow a retractile testis to remain at least temporarily in stable scrotal position. Scrotal asymmetry can be a useful clinical sign because it is commonly present in boys with unilateral cryptorchidism (Fig. 148-5) (Snodgrass et al, 2011).

In large clinical series, the majority (75% to 80%) of undescended testes are palpable and 60% to 70% are unilateral; involvement of the right side is more common overall but less frequent in series of nonpalpable testes (Hadziselimovic, 1983; Cendron et al, 1993; Cortes et al, 2001; Giannopoulos et al, 2001). Position of undescended testes varies markedly with the population studied, which may in part be the result of different classification techniques. In a meta-analysis of surgical patients, testes were abdominal in 34%, near the internal ring ("peeping") in 12%, canalicular in 27%, and beyond the external ring in 27% (Docimo, 1995), whereas in large single-institution series testes were abdominal in 3% to 10%



Figure 148-5. Scrotal asymmetry in a boy with unilateral left cryptorchidism.

of total cases, canalicular in 16% to 27%, and distal to the external ring in the majority (Hadziselimovic, 1983; Moul and Belman, 1988; Cendron et al, 1993; Kraft et al, 2011). In a multi-institutional review of almost 40,000 European cryptorchid boys, 8% of testes were abdominal, 63% canalicular, 24% prescrotal, and 11% in the SIP or ectopic (Hadziselimovic, 1983). Moul and Belman classified all subinguinal testes with a lateral gubernacular attachment as ectopic (66% of their total cases).

Associated genital findings may warrant additional diagnostic studies that are best completed in the neonatal period. If neither testis is palpable, particularly if penile development is abnormal, karyotype and hormonal analyses are performed urgently to rule out congenital adrenal hyperplasia and obviate the potential adverse effects of undiagnosed salt wasting. Routine circumcision should be delayed until evaluation confirms a genetically normal male. Hypospadias is associated with cryptorchidism in 12% to 24% of cases (Cendron et al, 1993; Moreno-Garcia and Miranda, 2002; Cox et al, 2008). If proximal hypospadias is present, chromosomal analysis is warranted because the frequency of abnormalities is high (32% to 47%) (Cox et al, 2008; Sekaran et al, 2013). Micropenis was reported in 46% of boys with anorchia caused by bilateral vanishing testes (Zenaty et al, 2006) (also called *testicular regression syndrome*), and small penile size in association with cryptorchidism is also observed in cases of hypogonadotropic hypogonadism. In these patients, measurement of testosterone, LH, and FSH levels in the first few months of life during the window of opportunity afforded by the physiologic activation of the HPG axis can facilitate early identification of hormone deficiency or anorchia (Grumbach, 2005).

Palpable Testes

Undescended testes may be located along the line of normal descent between the abdomen and scrotum or in an ectopic position that is most commonly the SIP (anterior to the rectus abdominus muscle) or, more rarely, in a perirenal, prepubic, femoral, peripenile, perineal, or contralateral scrotal position (Fig. 148-6). Careful

examination of these areas is needed to correctly classify a testis as palpable or nonpalpable, a critical step that influences further diagnosis and treatment (Fig. 148-7). Every effort should be made by the examiner to determine the lowest position the testis may attain. Manual downward pressure with one hand along the ipsilateral inguinal canal from the anterior iliac spine to the scrotum and palpation with the opposite hand helps to identify the lowest position of a palpable testis.

Difficulty in the clinical classification of cryptorchidism when the testis is palpable is related to both documentation of testicular

position and differentiation of truly undescended from retractile testes, complicated by the fact that these entities may coexist. The gold standard for diagnosis remains careful examination of a child in several positions and confirmation of incomplete descent of the testis to a dependent scrotal position after induction of anesthesia. Prospective studies of intraobserver and interobserver variation show major differences in documentation of testicular position among examiners (Wit et al, 1987; Olsen, 1989). Olsen noted complete agreement between two examiners on scaled measures of testicular position and mobility in only 5 (13.5%, 95% CI 4.5% to 28.8%) of 37 boys. Cendron and colleagues reported that preoperative testicular position correlates poorly with intraoperative findings (Cendron et al, 1993). Variation in observed testicular position preoperatively and postoperatively may influence assessment of prognosis and outcome in boys with cryptorchidism.

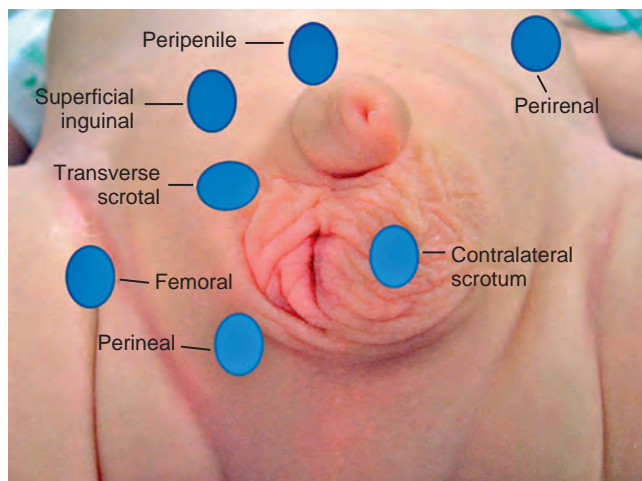


Figure 148-6. Positions of the ectopic testis. The ectopic testis can be identified in various positions, as shown. The most common location is the superficial inguinal pouch.

Nonpalpable Testes

When a testis is nonpalpable, possible clinical findings at surgery include (1) abdominal or transinguinal “peeping” location (25% to 50%) (Fig. 148-8; also see Fig. 148-6), (2) complete atrophy (vanishing testis, 15% to 40%) (Fig. 148-9), and (3) extra-abdominal location but nonpalpable testis because of body habitus, testicular size, and/or limited cooperation of the patient (10% to 30%) (Cendron et al, 1993; Cisek et al, 1998; Kirsch et al, 1998; Radmayr et al, 2003; Patil et al, 2005). If both testes are nonpalpable and not distal to the internal inguinal ring in a genetic male, at least 95% are abdominal, with cases of bilateral vanishing testis occurring rarely (Cendron et al, 1993; Moore et al, 1994). If neither vas nor spermatic artery is found at the time of laparoscopy, laparoscopic or surgical dissection of the perivesical area and retroperitoneum up to the level of the kidney is required for exclusion of the presence of a testis, because true agenesis is extremely rare. Perirenal or other abdominal testes may be associated with

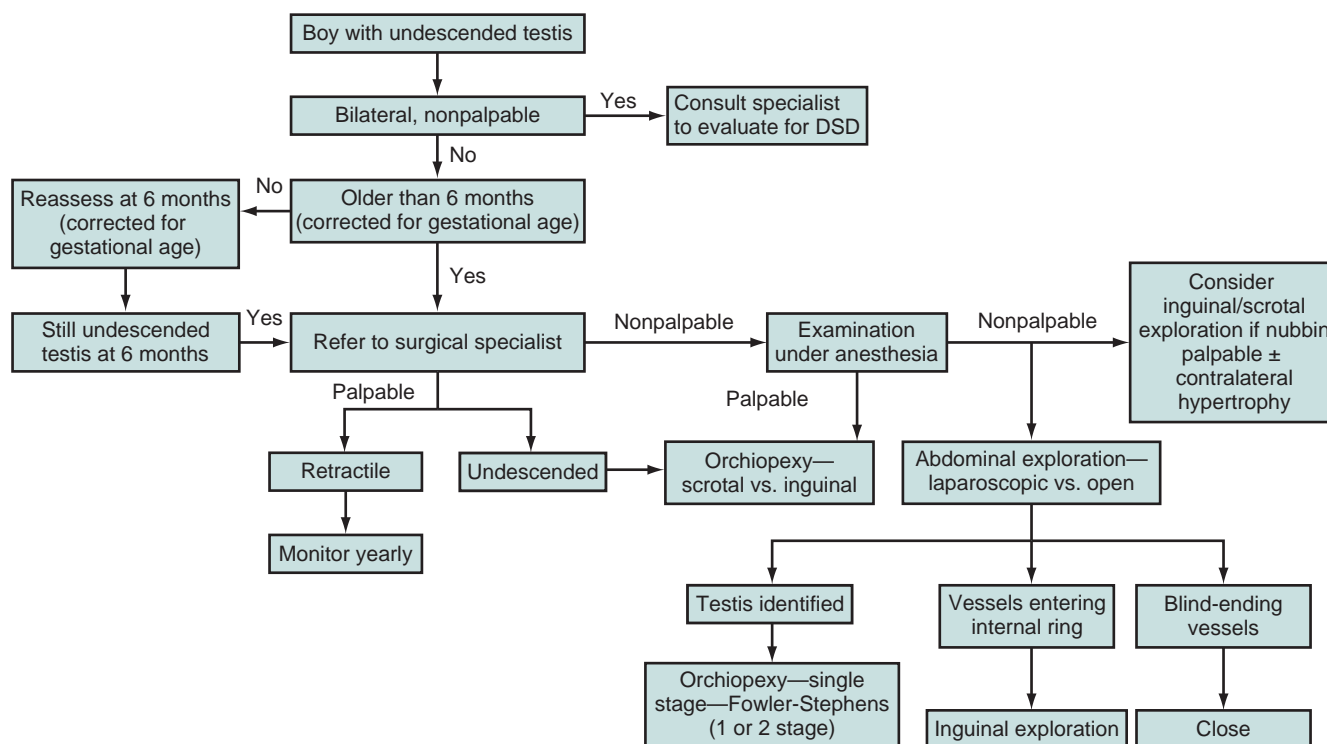


Figure 148-7. Algorithm for management of the undescended testis. The American Urological Association guideline algorithm for diagnosis and treatment of palpable and nonpalpable testes in patients confirmed to have undescended testis by an experienced examiner. DSD, disorder of sexual differentiation. (From Kolon TF, Herndon CDA, Baker LA, et al. Evaluation and treatment of cryptorchidism: AUA guideline. Figure 1, <<http://www.auanet.org/common/pdf/education/clinical-guidance/Cryptorchidism-Algorithm.pdf>>; 2014 [accessed 05.07.15].)

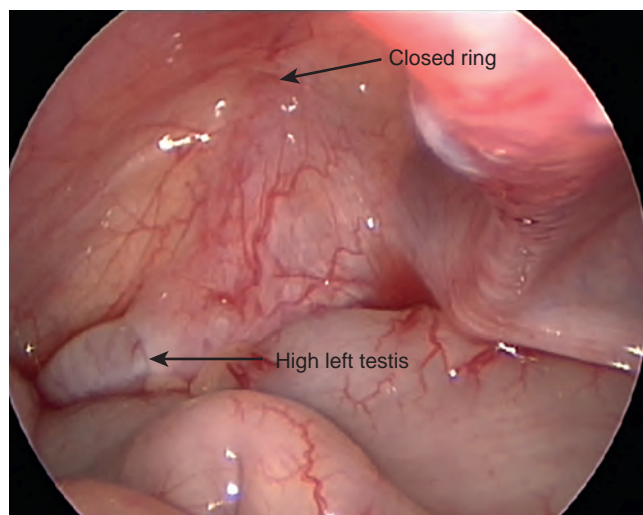


Figure 148-8. High intra-abdominal testis identified on laparoscopic evaluation. Left testis identified high in the abdomen is associated with a closed internal ring.

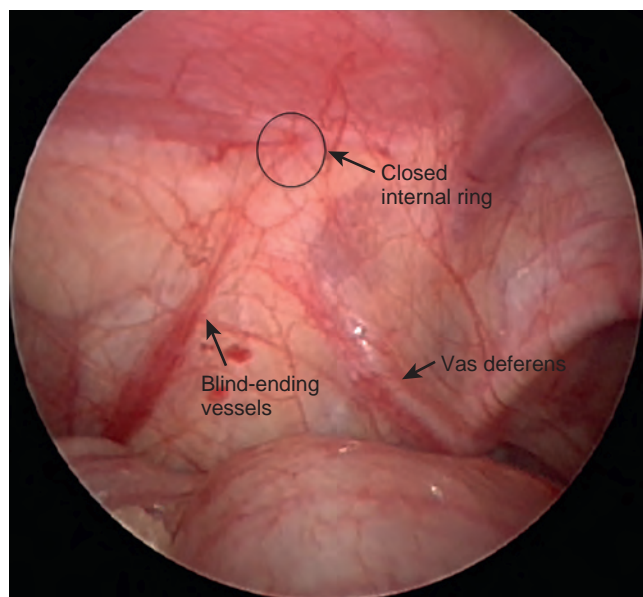


Figure 148-9. Vanishing testis noted on laparoscopic evaluation. Note the blind-ending spermatic vessels and vas deferens.

multicystic dysplastic or absent ipsilateral kidneys and/or nonunion of the testis and epididymis (Zaccara et al, 2004; Foley et al, 2005; Kim et al, 2005).

The cause of vanishing testis is not known but is thought to represent spermatic cord torsion or vascular accident occurring after completion of genital masculinization but before fixation of the testis in the scrotum. Evidence supporting this includes the presence of hemosiderin in remnant testicular nubbins excised at surgery (Turek et al, 1994) and reported cases of contralateral postnatal torsion (Gong et al, 1996). An enlarged contralateral testis (Huff et al, 1992) and absence of palpable intrascrotal appendage tissue (processus vaginalis, wolffian structures, or gubernaculum) are highly predictive of a vanishing testis (Mesrobian et al, 2002). Diagnosis of a vanishing testis requires documentation of blind-ending spermatic vessels in the abdomen, inguinal canal, or scrotum.

Endocrine evaluation in cases of suspected bilateral vanishing testes (anorchia) shows elevated basal serum gonadotropin levels and no response to hCG stimulation; however, gonadotropins may

be unexpectedly low in midchildhood in boys who are also unresponsive to hCG (Lustig et al, 1987; Lee, 2000). Because hCG stimulation testing is not well standardized and has the potential for side effects and inaccuracy, it is no longer the procedure of choice for documentation of anorchia (Kolon et al, 2014). In most cases, laparoscopic or surgical abdominal exploration is performed, although hormone testing can also be useful and may be sufficient for the diagnosis of anorchia. In the absence of testicular tissue, FSH and LH levels are higher than normal in early infancy and FSH level is reportedly always higher than 2 IU/L before age 6 (Grinspon et al, 2012). Very low or undetectable AMH and inhibin B levels are also reported as useful adjuncts in the diagnosis of anorchia (Grumbach, 2005; Brauner et al, 2011; Thorup et al, 2011b).

Inguinoscrotal ultrasonography and magnetic resonance imaging (MRI) are not usually helpful and are not recommended in the evaluation and management of a nonpalpable testis (Elder, 2002; Tasian et al, 2011) (Kolon et al, 2014). Overall, the sensitivity and specificity of ultrasound in localizing the nonpalpable testis are 45% and 78%, respectively (Tasian and Copp, 2011). In a recent meta-analysis, the sensitivity and specificity of MRI in identifying cryptorchid testes were 65% and 100%, respectively, and were higher for inguinal than for abdominal testes (Krishnaswami et al, 2013). No imaging modality is reliable for diagnosing vanishing testes. Some authors advocate very selective use of imaging if recommended by the managing surgical specialist after referral; in this situation the sensitivity of ultrasonography in identifying inguinal testes is reported to be as high as 95% to 97%, and abdominal testes are also seen in some cases (Cain et al, 1996; Nijs et al, 2007), but examination under anesthesia is likely to provide the same information (Tasian et al, 2011). Similarly, although MRI can be useful in some cases to identify nonpalpable abdominal testes, its accuracy is variable and the procedure requires sedation in younger children and is unlikely to change the management approach (Yeung et al, 1999; Siemer et al, 2000). The superior accuracy of magnetic resonance angiography (MRA) in localizing and differentiating viable from vanished testes (96% of 23 nonpalpable testes in 21 boys, mean age 2.5 years) was not replicated in a study of younger boys (57% of 29 testes in 26 boys, mean age 13 months) (Yeung et al, 1999; Desireddi et al, 2008). One indication for MRI may be identification of an ectopic abdominal testis not localized by laparoscopy. Imaging is not indicated for diagnosis of the nonpalpable testis, because it has limited accuracy and does not obviate the need for definitive surgical intervention.

Diagnostic laparoscopy, followed by laparoscopic orchidopexy if an abdominal testis is present, has become the preferred approach to the nonpalpable testis for many clinicians. Laparoscopy is preceded by an examination under anesthesia, which may be a useful adjunct that helps to define the appropriate course of action. Although laparoscopy does not always provide a direct diagnosis, in many cases it either provides visualization of the testis or guidance for the surgeon's next steps. Important laparoscopic observations include the size and position of the spermatic vessels and vas; testicular size, quality, and position if visible; and patency of the internal inguinal ring. The combination of a closed internal ring and a blind-ending spermatic artery and vas confirms an abdominal vanishing testis (see Fig. 148-9), whereas a hernia is frequently but not always associated with a viable abdominal or distal testis (Elder, 1994; Moore et al, 1994). An atretic spermatic cord coursing through a closed inguinal ring is suggestive of a distal vanishing testis, but this finding may be subjective and, conversely, normal-appearing vessels may be associated with both viable and vanishing testes (Zaccara et al, 2004). Moreover, the laparoscopic view may suggest abdominal blind-ending vessels despite a testis being present distally or in an ectopic abdominal position (Zaccara et al, 2004; Kim et al, 2005; Ellsworth and Cheuck, 2009). Therefore if laparoscopy does not unequivocally localize the testis or blind-ending spermatic artery, additional surgical exploration is needed for definitive diagnosis. This may be performed laparoscopically after the placement of additional working ports.

The need for excision and contralateral scrotal orchidopexy in vanishing testis cases remains controversial. Germ cells and/or

tubules are consistently present in 5% to 15% of excised testicular remnants (Moore et al, 1994; Tennenbaum et al, 1994; Turek et al, 1994; Cortes et al, 1995a; De Luna et al, 2003; Renzulli et al, 2005; Bader et al, 2011), but the risk of malignancy is unknown. A single case of carcinoma in situ (CIS) was reported by Rozanski and colleagues in a testicular remnant (Rozanski et al, 1996). Excision is appropriate when the spermatic vessels traverse the internal inguinal ring, to provide confirmation that no viable (or atrophic) testis is present, because the laparoscopic appearance of the spermatic vessels and processus vaginalis may be deceiving and may not reliably exclude the presence of an inguinal testis (Ellsworth and Cheuck, 2009). Vanishing testes are often in or near the scrotum; therefore, initial scrotal exploration should be considered when a palpable scrotal nubbin and contralateral testicular hypertrophy (testicular length ≥ 1.8 cm) are present (Belman and Rushton, 2003; Snodgrass et al, 2007). However, a trans-scrotal search will be time-consuming and unproductive when a vanishing testis is intra-abdominal. Moreover, in cases of testicular-epididymal dissociation, a scrotal nubbin may actually be the epididymis instead of a vanishing testis; a laparoscopic approach facilitates more accurate diagnosis and subsequent management of such cases (Wolffenbuttel et al, 2000; De Luna et al, 2003). Laparoscopy is the procedure of choice to confirm or exclude the presence of a viable or remnant abdominal testis, unless a prominent scrotal nubbin is palpable with other clinical signs of monorchism.

Contralateral fixation of a solitary testis in cases of monorchism is advocated by some but not universally supported. The possibility that prenatal torsion is the cause of vanishing testis (Gong et al, 1996) does not imply that the contralateral testis is likely to undergo a similar fate after the postnatal period. However, some surgeons empirically recommend contralateral fixation to eliminate the risk of such a devastating complication (Rozanski et al, 1996) and/or because a contralateral bell-clapper deformity (incomplete testicular fixation to the tunica vaginalis) may be present (Bellinger, 1985; Al-Zahem and Shun, 2006). However, review of the anatomy of the tunica vaginalis contralateral to vanishing testes suggests that the bell-clapper anomaly is rare and the risk of torsion of the solitary testis in these cases is minimal (Martin and Rushton, 2014).

Associated Pathology

Testicular Maldevelopment

Many observational studies of the histologic development of prepubertal cryptorchid testes have been published. Over 40 years ago, Mancini and colleagues systematically reported germ cell counts and related arrested development of spermatogonia with progressive loss in cryptorchid testes (Mancini et al, 1965). Subsequently, several large series, some with additional normal autopsy (Hedinger, 1982) or affected control (hernia, hydrocele) (Hadziselimovic et al, 1986) data and others that refer to these established age-dependent norms (Schindler et al, 1987; Gracia et al, 1995; McAleer et al, 1995; Cortes et al, 2001; Huff et al, 2001), have provided mainly consistent findings in cryptorchid boys. These data show that the number of spermatogonia (germ cells) per tubule is reduced after infancy and fails to increase normally with age in cryptorchid and to a lesser degree in contralateral scrotal testes. The frequency of abnormal histology in the contralateral testis varies among studies, ranging from 22% to 95%, and is likely reflective of differences in patient populations, use of control data, and methodology. Moreover, variability within and among biopsies from single testes has been reported (Hedinger, 1982; Schindler et al, 1987). However, these data provide strong evidence that abnormal germ cell development is often present after early infancy in cryptorchid testes. The degree of pathology was similar in true ectopic, SIP, and ascending testes (Herzog et al, 1992; Hutcheson et al, 2000b; Rusnack et al, 2002) and was more severe in limited samples from patients with myelomeningocele, posterior urethral valves, and prune-belly syndrome (Orvis et al, 1988; Patel et al, 2008). Findings are similar in boys with secondary cryptorchidism after hernia repair, suggesting that these may in fact be cases of primary

cryptorchidism (Fenig et al, 2001). In other studies, higher germ cell counts were correlated with reduced age-dependent interstitial fibrosis (Suskind et al, 2008), lower age at surgery, and increased likelihood of testicular palpability (Tasian et al, 2009; Kraft et al, 2011). In a series of 723 boys with cryptorchidism (14% bilateral), testicular volume did not predict germ cell count (Noh et al, 2000), but in a subsequent series of 1326 boys with unilateral cryptorchidism from the same institution, testis volume was positively correlated with germ cell counts in both undescended and contralateral descended testes (Kraft et al, 2011).

Detailed studies of peritubular myoid and Sertoli cells in cryptorchidism are limited, but their abnormal development or function may contribute to the observed germ cell abnormalities. The available data suggest disruption of prepubertal Sertoli cell morphology, failure of maturation at puberty, and evidence for reduced number after 4 months of age in cryptorchid testes (Lackgren and Ploen, 1984; Rune et al, 1992; Regadera et al, 2001; Zivkovic and Hadziselimovic, 2009). Reduced expression of type IV collagen, a product of both Sertoli and myoid cells that may function in cell-cell communication, was reduced in basement membranes of undescended and contralaterally descended testes (Santamaria et al, 1990).

Impaired transformation of gonocytes to spermatogonia is reported in cryptorchid testes and may help define fertility potential. Although the ratio of gonocytes to spermatogonia appears to be normal in cryptorchid testes at about 1.5 months of age, delays in the disappearance of gonocytes and in the appearance of adult dark (Ad) spermatogonia occur in the undescended as compared with the contralateral descended testis (Hadziselimovic et al, 1986; Huff et al, 2001). As noted for germ cell counts, the reported percentage of cryptorchid testes lacking Ad spermatogonia varies widely from 17% to 85% (Zivkovic et al, 2009; Thorup et al, 2013). Ad spermatogonial number may also be reduced in the contralateral testis of boys with unilateral cryptorchidism (Kraft et al, 2011). In addition, the appearance of primary spermatocytes at age 4 to 5 years is delayed in cryptorchid testes (Huff et al, 1989).

Kollin and colleagues studied testicular growth in undescended and scrotal testes and measured the effect in orchidopexy on testicular size using serial ultrasonography in prospective randomized studies of congenital cryptorchidism (Kollin et al, 2006, 2007, 2012, 2013). They showed that the undescended testis is smaller at birth and grows less well than the scrotal testis, even if spontaneous descent occurs. Postoperative testicular growth was superior in boys who underwent orchidopexy at age 9 months as compared with those randomized to surgery at age 3 years. Biopsies at the time of orchidopexy in these patients showed marked reductions in germ cell number and a less prominent reduction in Sertoli cells when orchidopexy was delayed until age 3. In these studies, inhibin B levels correlated with testicular volume, as reported previously for neonates with normal testes, where inhibin B levels were interpreted to primarily reflect differences in Sertoli cell number (Main et al, 2006b; Sharpe, 2006). These well-conducted prospective studies provide strong support for the concept that cryptorchidism is associated with both primary and secondary effects on testicular development, and that the extrascrotal position of the testis may have adverse effects even in infancy.

Anomalies of the Epididymis, Processus Vaginalis, and Gubernaculum

Attachment of the epididymis to the testis may be abnormal in cryptorchid boys (Marshall and Shermeta, 1979), but the reported frequency varies widely from 16% to 75% (Heath et al, 1984; Merksz and Toth, 1987; Gill et al, 1989; Mollaeian et al, 1994; Kraft et al, 2011), most likely because characterization of this anomaly may be subjective. Anatomic findings in decreasing order of frequency include partial or complete nonfusion between the caput and/or cauda epididymis and the testis, epididymal elongation and/or looping, and atresia (Fig. 148-10). The occurrence of epididymal anomalies correlates with both the severity of cryptorchidism and the degree of closure of the processus vaginalis (Elder,

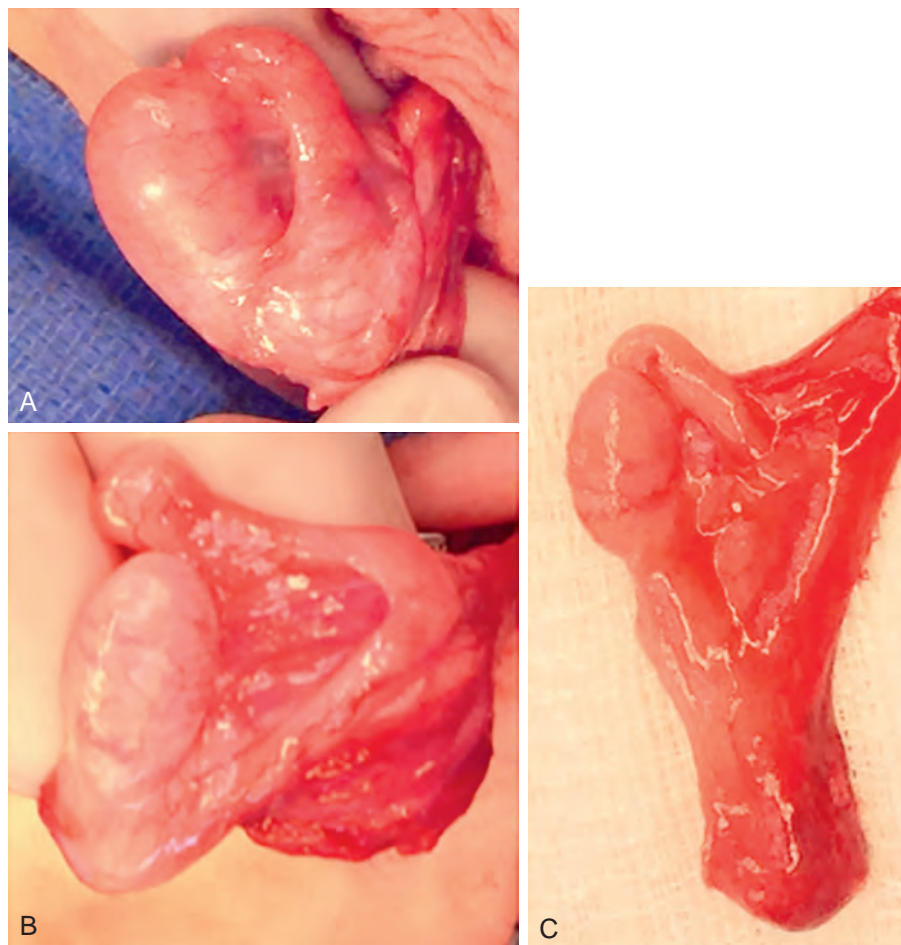


Figure 148-10. Epididymal anomalies. A, Normal epididymis. B, Looped epididymis. C, Malunion of the tail of the epididymis.

1992; Barthold and Redman, 1996). Epididymal anomalies were more common in congenital (37% to 60%) than acquired (11% to 31%) cryptorchidism (Barthold et al, 2012; van Brakel et al, 2012). Complete epididymal detachment or nonunion between the testis and epididymis and vas is rare and more likely to be associated with abdominal testes (Foley et al, 2005; Wakeman and Warner, 2010; Karaman et al, 2011; Sharma and Sen, 2013) but did not correlate with testicular histology (Kraft et al, 2011). However, the degree to which these anomalies alter sperm transport, if at all, and potentially contribute to subfertility in males with a history of cryptorchidism remains undefined.

Failure of closure of the processus vaginalis (inguinal hernia) and abnormal attachment of the gubernacular remnant are common in association with cryptorchidism. In their study of 759 patients, Cendron and colleagues identified a persistently patent processus vaginalis ipsilateral to 87% of unilateral and 71% of bilateral undescended testes. Specific notation of the gubernacular position available from this and another large study indicates aberrant attachment lateral to the scrotum in 66% to 75% of cases (Moul and Belman, 1988; Cendron et al, 1993). The processus is patent in 45% to 50% of boys with ascending testes, possibly related to older patient age and/or reduced severity of cryptorchidism in this group (Barthold and Gonzalez, 2003; Barthold et al, 2012; van Brakel et al, 2012). Inguinal hernia is also more common in family members of boys with cryptorchidism (Barthold et al, 2012). **Anomalies of the tunica and processus vaginalis in cryptorchidism predispose to development of testicular torsion or clinical hernia, respectively, in rare cases.** Torsion of an undescended testis can occur at any age (reviewed by Zilberman et al, 2006) and may be confused with an incarcerated inguinal hernia. The risk of torsion is higher in undescended than in scrotal testes and may be particularly high in

children with neuromuscular diseases such as cerebral palsy. Delay in diagnosis is common, and a high index of suspicion is needed to reduce the high risk of testicular loss. Of particular concern is the potential risk for delayed diagnosis with resultant testicular necrosis during the postnatal period when infants are observed for spontaneous testicular descent (Singal et al, 2013).

Other Testicular Anomalies Associated with Cryptorchidism

Several rare anomalies of testicular development associated with cryptorchidism, each with 100 to 150 reported cases in the literature, include polyorchidism, splenogonadal fusion, and transverse testicular ectopia. Because abdominal cryptorchidism commonly occurs in these cases, laparoscopy is useful in both diagnosis and treatment.

Polyorchidism is the presence of a supernumerary testis that is more commonly unilateral and on the left side, with rare cases of bilateral duplication or triplication reported in a comprehensive meta-analysis of the pediatric and adult literature (Bergholz and Wenke, 2009). The cause is unknown, but most authors speculate that this anomaly is related to duplication or division of the genital ridge with or without the wolffian duct as illustrated by Danrad and colleagues (2004). Testes are reported to be scrotal, inguinal, and abdominal in 75%, 20%, and 5% of cases, respectively (Kumar et al, 2008). Affected individuals are frequently asymptomatic, and the polyorchidism is identified at the time of orchidopexy or hernia repair, although a scrotal or inguinal mass and pain with or without torsion may occur and persistent müllerian remnants may coexist. Various classification schemes have been proposed, with a recent trend toward categorizing testes based on epididymal and vasal configuration (Bergholz et al, 2007; Khedis et al, 2008; Kumar et al,

2008). Kumar and colleagues suggest a classification that differentiates between testes that are drained by a vas deferens (type A1—separate epididymis and vas; type A2—separate epididymis; type A3—shared epididymis and vas) and those with no vasal drainage (type B1—epididymis present; type B2—no epididymis or vas). This classification can aid in management decisions that should be based not only on the anatomy of the accessory ducts but also the position, size, and attachments of the testis. Observation and periodic self-examination without surgery should be considered for sonographically normal scrotal testes and orchidopexy for testes that are undescended but with intact ductal drainage (Spranger et al, 2002; Bergholz et al, 2007; Khedis et al, 2008). Occasional cases of testicular tumor have been reported in supernumerary testes, but it is unclear if this is a risk related to polyorchidism per se or to associated cryptorchidism or persistent müllerian duct syndrome (Spranger et al, 2002; Ghose et al, 2007). Testicular torsion may also occur (Arlen et al, 2014).

Splenogonadal fusion is a defect characterized by continuous or discontinuous fibrous union between splenic tissue and the gonad, a condition much more commonly recognized in males (Khairat and Ismail, 2005) (Fig. 148-11). In the continuous form (55%) a cord connects the testis to the spleen, whereas in the discontinuous form the splenic tissue is attached to the gonad and not continuous with the main body of the spleen (Ferron and Arce, 2013). Approximately 30% of affected individuals have cryptorchidism, with the majority of cases abdominal and bilateral (59%), and 65% and 26% involving the left and right sides, respectively (Cortes et al, 1996). The continuous form of splenogonadal fusion is more commonly syndromic, associated with limb defects, micrognathia, microglossia, anal atresia, and pulmonary hypoplasia (McPherson et al, 2003) and less commonly with cardiac defects, cleft palate, imperforate anus, and myelomeningocele (Lin et al, 2010). The discontinuous form can manifest as a testicular mass, with distinctive ultrasound findings that include a somewhat hyper-echoic mass (relative to testis) that contains multiple hypoechoic

nodules and obvious vascularity (Ferron and Arce, 2013). The pathogenesis of splenogonadal fusion is unknown but, based on the constellation of defects observed, is hypothesized to represent a developmental field defect with aberrant migration of spleen cells occurring at 5 to 8 weeks' gestation. Most cases are found incidentally at the time of orchidopexy or inguinal hernia repair or with scrotal swelling related to illness-related reactive changes within the splenic tissue. Testicular malignancy is reported rarely in association with cryptorchidism and not likely related to the splenic anomaly. Treatment should focus on recognition of the defect at the time of orchidopexy and avoidance of unnecessary orchiectomy.

Transverse testicular ectopia may occur as an isolated anomaly in otherwise normal males with cryptorchidism or vanishing testes, or in association with persistent müllerian duct syndrome in 20% to 50% of cases (De Luna et al, 2003; Wuerstle et al, 2007; Thambidorai and Khaleed, 2008). The classic presentation is inguinal hernia with contralateral nonpalpable testis, although both testes may be palpable in the same hemiscrotum. The cause may be related to mechanical hindrance to descent by fusion of wolffian duct derivatives (Chacko et al, 2006) or persistent müllerian ducts, or to a primary gubernacular defect. It is interesting to note that in transgenic *Ins13*^{-/-} mice, complete loss of the gubernacular attachment, transverse ectopia, and/or torsion was observed (Nef and Parada, 1999; Zimmermann et al, 1999). Laparoscopy is a useful adjunct in diagnosis and treatment. Orchidopexy may be performed using open surgical or laparoscopic techniques, but in cases of vasal fusion the involved testis is mobilized ipsilaterally and a trans-septal approach used to place the testis in the contralateral scrotum (Chacko et al, 2006; Thambidorai and Khaleed, 2008).

MANAGEMENT

Surgical correction of cryptorchidism is indicated to optimize testicular function, potentially reduce and/or facilitate diagnosis of testicular malignancy, provide cosmetic benefits, and prevent complications such as clinical hernia or torsion. Except in certain cases of associated complex medical illness or in the post-natal period, treatment should proceed after confirmation of the diagnosis. An algorithm has been established and published as part of the American Urological Association (AUA) cryptorchidism guideline (Kolon et al, 2014) (see Fig. 148-7), which outlines the recommended approach to palpable and nonpalpable testes in patients confirmed to have an undescended testis by an experienced examiner.

In infants, observation is indicated for the first 6 postnatal months to allow spontaneous testicular descent. If spontaneous testicular descent does not occur, surgical treatment after 6 months of (corrected gestational) age is indicated. Support for this approach is based on the following rationale: (1) Spontaneous descent is unlikely in full-term males after age 6 months (Wenzler et al, 2004), (2) testicular growth is restored after early orchidopexy (Kollin et al, 2007), and (3) orchidopexy for abdominal testes may be facilitated in young infants, soon after the hormonal surge. In boys with a history of prematurity, spontaneous descent may be delayed, and therefore observation is continued for 6 months beyond the expected date of delivery or, especially if testicular position is marginal, until a year of age. After spontaneous testicular descent, continued observation is needed because of the risk for recurrent cryptorchidism or testicular reascent.

Investigators in the Netherlands (Sijstermans et al, 2006; Eijsbouts et al, 2007) adopted an observational approach to boys with acquired cryptorchidism and reported spontaneous descent in 75 of 132 (57%) and 98 of 129 (76%) testes, respectively, most by midpuberty. The mean volume of descended testes in the study by Eijsbouts and colleagues was closer to those of normal contralateral testes as compared with boys who underwent orchidopexy. However, in both of these series, high scrotal testes comprised the majority of those that descended, and low scrotal "unstable" testes (likely retractile) were also included. On the other hand, Eijsbouts and colleagues reported that in 19 of 82 unilateral cases the patients had

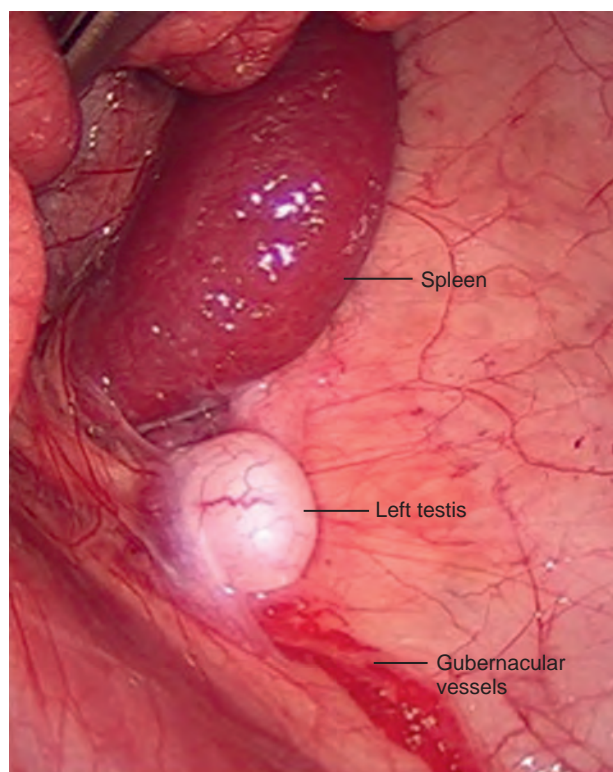


Figure 148-11. Splenogonadal fusion. A case of continuous splenogonadal fusion in a boy with a left nonpalpable testis, with fusion to the spleen as identified by laparoscopy.

undergone previous contralateral orchidopexy and that 10 boys required orchidopexy because of clinical hernia, pain, or torsion, suggesting a higher likelihood of true cryptorchidism in these patients. In follow-up studies of 391 boys with 464 acquired cryptorchid testes, 90% of high scrotal and 64.5% of inguinal or nonpalpable testes descended spontaneously at a mean age of 12.9 years (Hack et al, 2010). In contrast, a study from the same institution showed that testicular volumes were significantly smaller for age in 155 postpubertal patients who had undergone orchidopexy at diagnosis (the majority before puberty) after a mean of 6.6 ± 3.8 years' follow-up (van der Plas et al, 2013c). Because these individuals were selected for orchidopexy and the majority (92%) had suprascrotal testes, they are likely not comparable to the group of boys treated after puberty at the same institution (Hack et al, 2010). Furthermore, these studies were not randomized and provided no long-term data regarding functional outcome. Consequently, they fail to provide strong evidence in support of observation as the recommended approach for cases of acquired cryptorchidism.

Medical Therapy

Hormonal therapy has been used for a variety of indications in patients with cryptorchidism, including differentiation of retractile from true undescended testes, stimulation of testicular descent or germ cell maturation, and as an adjunct to abdominal orchidopexy. **Hormone therapy is not currently recommended, given the lack of rigorous data supporting its efficacy** (Thorsson et al, 2007; Kolon et al, 2014).

Several published reports address the usefulness of hormonal therapy in distinguishing retractile from true undescended testes. In prospective series reporting the response of putative retractile testes to hCG, success rates vary from 58% to 100% and may be dependent not only on age, degree of retractility, and accuracy of diagnosis, but also on the dosage regimen used (Rajfer et al, 1986; Miller et al, 2003; Metin et al, 2005). These data suggest that hCG fails to reliably distinguish retractile from cryptorchid testes and therefore does not eliminate the need for serial examinations in these patients.

Luteinizing hormone–releasing hormone (LHRH) and/or hCG has been used as hormonal therapy to induce descent of testes for over 70 years based on the premise that androgens promote testicular descent, but efficacy is questionable (Pyorala et al, 1995; Henna et al, 2004; Thorsson et al, 2007). Although the efficacy of either hormonal treatment is about 20% and superior to placebo in randomized trials, this effect is not clearly clinically significant. Overall, the evidence from rigorous studies indicates that LHRH therapy is marginally more effective than placebo, and although not studied in randomized placebo-controlled trials owing to its route of administration, hCG also shows limited efficacy. Other uses of hCG, including treatment of acquired cryptorchidism and facilitation of palpability and/or treatment of the abdominal testis (Polascik et al, 1996; Baker et al, 2001; Bukowski et al, 2001), also have limited efficacy.

The question of the effect of therapeutic doses of hCG or LHRH on germ cell development has been addressed in several conflicting studies that are limited by small sample size, absent or suboptimal randomization, and variable availability of biopsy data (Ong et al, 2005). In small, retrospective studies, hCG treatment was associated with increased germ cell apoptosis at biopsy and lower adult testis volume (Dunkel et al, 1997), and previous hCG or LHRH therapy was associated with reduced germ cell counts in 1- to 3-year-old boys as compared with surgery alone (Cortes et al, 2000). In contrast, Schwentner and colleagues randomized young boys (mean age 33 months, 21 per group) to LHRH or no hormonal therapy before surgery and reported that mean germ cell count was higher (1.05 ± 0.71) in LHRH-treated than in nontreated (0.52 ± 0.39) testes (Schwentner et al, 2005). In view of a lack of large prospective studies, it is unclear if hormone therapy for cryptorchidism is beneficial or harmful to germ cells in the short or long term.

Hadziselimovic and colleagues have advocated use of low-dose, long-term (every other day for 6 months) LHRH analogue (buserelin) therapy for stimulation of germ cell development in conjunc-

tion with orchidopexy. In a retrospective study of nonrandomized, non-age-matched patients receiving buserelin versus surgery only, germ cell counts were significantly higher in the treated group (Hadziselimovic et al, 1987b). A subset of patients from this same cohort with the most severe testicular histology underwent rebiopsy after completion of therapy and were compared with a group of boys (8) of unknown age who required reoperative orchidopexy (Hadziselimovic et al, 1987a). A significant improvement in testicular histology was seen in the buserelin-treated but not the surgical group. Similarly, in a smaller select group of boys treated with low doses of a related LHRH agonist, nafarelin, improved histology was observed in one or both testes at rebiopsy in 8 of 12 boys. In a randomized study of clinically matched boys receiving buserelin plus hCG, placebo plus hCG, or surgery alone (19 to 25 per group), germ cell counts were also significantly higher in those treated with buserelin (Bica and Hadziselimovic, 1992). In a nonrandomized retrospective study, buserelin-treated males (most also received hCG) with a history of unilateral cryptorchidism and poor pretreatment germ cell counts had much higher sperm counts than patients who underwent surgery only (15 patients per group) (Hadziselimovic, 2008). Unfortunately, these two groups were small and not clinically matched prospectively to limit other potential confounding factors such as testicular position, and sperm counts in the surgery-only group were lower than typical for unilateral cryptorchidism. Overall, these studies provide preliminary, suggestive evidence that buserelin may have both short- and long-term effects on testicular histology and/or fertility potential. However, the suboptimal design of the studies on which this evidence is based mandates that future well-designed prospective studies be conducted before buserelin treatment can be used routinely in cryptorchidism. In summary, little if any high-quality evidence exists showing benefit of hormonal therapy for cryptorchidism or for stimulation of germ cells.

Surgical Approach to the Palpable Testis

Timing of Surgery

The recommendation that surgical intervention proceed once failure of spontaneous descent is confirmed is now standard (Chan et al, 2014; Kolon et al, 2014) but is not new. Despite this, the average age at which orchidopexy is performed remains approximately 4 years in many series (Barthold and Gonzalez, 2003; Kokorowski et al, 2010; Bayne et al, 2011; Snodgrass et al, 2011; Barthold et al, 2012; Bradshaw et al, 2014; Nah et al, 2014). A review of the Pediatric Health Information System (PHIS) database by Kokorowski and colleagues demonstrated that only 18% of 28,204 boys who underwent surgery did so by 1 year of age. The reason for delayed intervention likely reflects a combination of factors, primarily including delayed referral of congenital cases and the occurrence of acquired cryptorchidism. Cases of congenital cryptorchidism may go undetected or untreated in infancy owing to prematurity or other morbidity, may undergo longer than necessary observation for spontaneous descent, or may represent cases of undetected reascent after spontaneous descent in infancy. Delay may also be exacerbated by difficulty in distinguishing undescended from retractile testes.

The traditional approach to surgical treatment of palpable testes is inguinal orchidopexy with repair of an associated hernia if present (Hutcheson et al, 2000a), although a primary scrotal approach as originally described and advocated by Bianchi and colleagues (Bianchi and Squire, 1989; Iyer et al, 1995) is an alternative approach. An option for pubertal and postpubertal boys is orchiectomy, especially if the testis is abdominal or difficult to mobilize because poor spermatogenesis and hypotrophy are usually present and the risk of CIS and torsion exist (Rogers et al, 1998).

Inguinal Orchidopexy

After induction of anesthesia, the patient is re-examined to confirm that the testis is palpable and to identify the lowest testicular

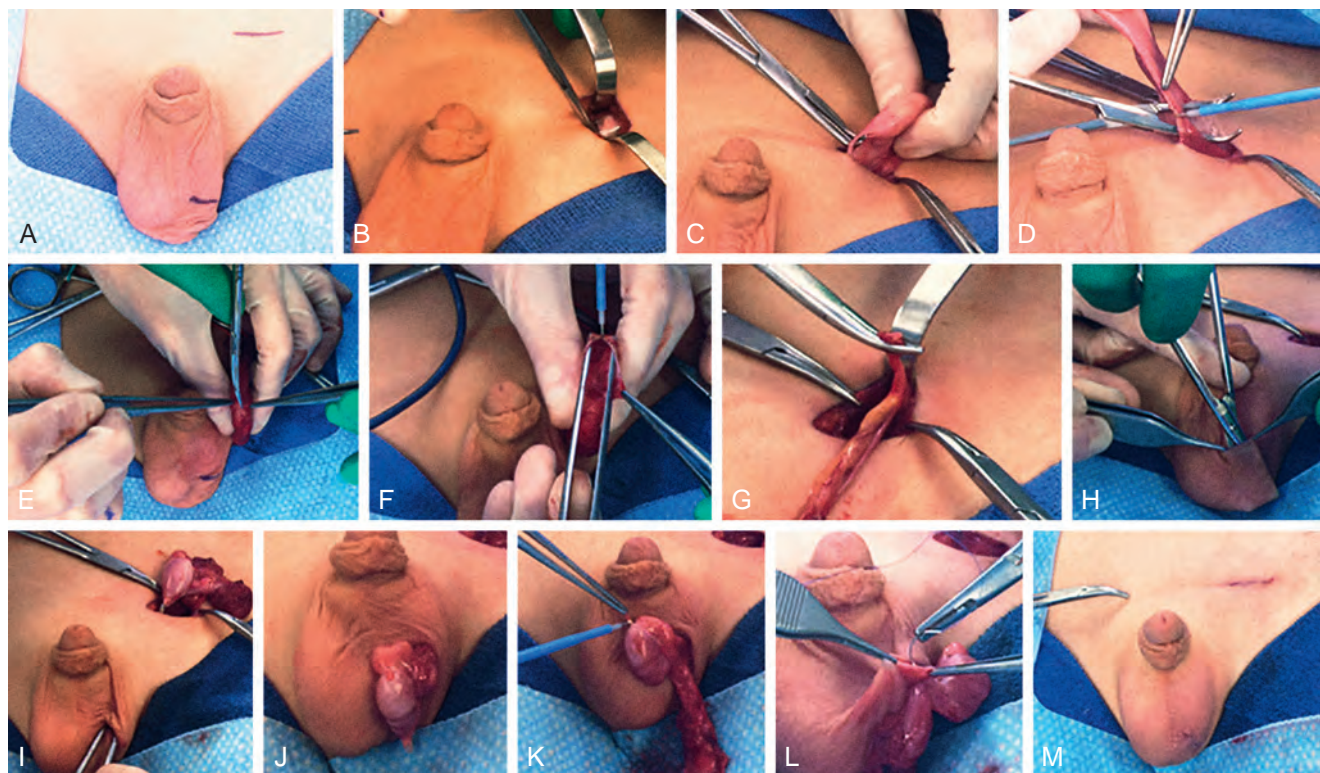


Figure 148-12. Inguinal orchiopexy. A, An incision is made at or below the inguinal crease superolateral to the pubic tubercle. B, The external oblique fascia is incised to expose the canal. C, The gubernaculum is transected distal to the sac. D, The internal spermatic fascia is incised. E, The tunica vaginalis is opened over the testis, and F, the incision is extended proximally along the length of the cord. G, The sac is mobilized to the level of the internal inguinal ring and suture-ligated. H, A transverse scrotal incision is made and a subdartos pouch created. I, A large clamp or a finger can be used to create a tunnel just anterior to the pubis. J, The testis is passed into the scrotum. K, Existing appendages are excised. L, The testis is secured within the pouch. M, Closure is completed with absorbable sutures.

position. In the standard inguinal approach (Fig. 148-12), a low transverse incision in Langer lines at or below the inguinal crease is made superolateral to the pubic tubercle. Dissection of the subcutaneous tissue should include a search for a testis within the SIP. After identification of the external ring, the external oblique fascia is incised to expose the canal, with care taken to avoid injury to the ilioinguinal nerve. Testis position is recorded relative to the inguinal canal. The spermatic cord is isolated and the remnant is dissected distally to its attachment to the gubernacular remnant. Dissection of the gubernaculum distal to the sac will avoid potential injury to a long-looping vas. Longitudinal incision of the internal spermatic fascia allows free mobilization of an intact hernia sac, if present, and minimizes skeletonization of the vas and spermatic vessels. Alternatively, the sac may be opened overlying the testis and the incision extended proximally along the length of the cord. Once isolated, the sac is mobilized to the level of the internal inguinal ring and suture-ligated. Incision of the internal spermatic and transversalis fascia at the level of the ring facilitates additional retroperitoneal mobilization of the vas and vessels, if needed. Further maneuvers to provide spermatic cord length include transection of lateral fascial bands along the cord, cranial retroperitoneal dissection, medial transposition of the testis beneath the epigastric vessels (Prentiss maneuver), and, if required, cranial extension of the incision. Very rarely, the testis cannot be brought to dependent scrotal position after these maneuvers and a two-stage procedure may be considered as an alternative to orchiectomy, which is preferentially reserved for visibly abnormal or atrophic testes, postpubertal patients, or cases associated with insufficient vasal length.

After mobilization of the spermatic cord, a transverse scrotal incision is made and a subdartos pouch created. A large clamp or

a finger can be used to create a tunnel just anterior to the pubis. The testis is passed through an opening in the dartos without twisting of the spermatic cord. Existing appendages should be excised and the epididymis inspected and any anomalies recorded. Recording of testicular volume by direct caliper measurement in three dimensions and similar (estimated) measurements of contralateral testicular volume can establish a baseline for postoperative assessment. Secure fixation of the testis within the pouch can be achieved by tension-free closure of the opening in the dartos around the cord, incorporating the cut edge of the tunica vaginalis. If needed, additional absorbable fixation sutures can be placed between the visceral tunica vaginalis and the dartos. Alternatively, suture fixation through the tunica albuginea to the scrotal wall may be performed. There is a theoretic risk of injury to the testis via inflammatory or vascular insult with suture placement through the tunica albuginea. Closure is completed with absorbable sutures. Supplemental local or regional techniques for perioperative pain control are advisable and may include local anesthetic infiltration, ilioinguinal nerve block, or caudal anesthesia; the latter is particularly useful in younger patients undergoing bilateral inguinal or concomitant penile surgery.

Testicular biopsy has been performed routinely in some centers and has been advocated by Hadziselimovic and colleagues as a method to determine prognosis for fertility (Hadziselimovic and Zivkovic, 2007). This approach is controversial and not recommended outside of research protocols because it does not change the current approach to treatment (Ritzen et al, 2007; Beckers and van der Horst, 2008). The risk to the cryptorchid testis from biopsy is theoretic; although long-term effects do not appear to include increased risk of microlithiasis or antisperm antibody formation

(Patel et al, 2005), other more subtle effects cannot be excluded from the available data. Biopsy is indicated in cases of sexual ambiguity or if clinical evidence of testicular dysgenesis is present.

Complications of inguinal orchidopexy are uncommon; those of greatest significance include testicular retraction and atrophy. Docimo reported a comprehensive review of the orchidopexy literature in 1995, before the routine use of laparoscopic orchidopexy, and including both palpable and nonpalpable testes (Docimo, 1995). He concluded that the overall risk of atrophy or nonscrotal position was approximately 15% overall in published reports, significantly higher in abdominal or peeping testes (24%) compared with those distal to the internal ring (10%) and higher in boys undergoing surgery after 6 years of age. More recently, analysis of boys with postoperative testis retraction over an 18-year period at a single institution consisted of less than 2% of 1886 primary open orchidopexies performed during that period, with a slightly higher risk of failure in older boys (McIntosh et al, 2013). However, these boys were not actively followed by the authors, so detailed clinical data were not available and the frequency of testicular atrophy could not be defined. In another series of 418 orchidopexies in 356 boys from a single institution with a median of 1-year follow-up, the risk of atrophy was 1.9% and of nonscrotal position was 10.3% (Thorup et al, 2011a). However, in this series the risk of complications was higher when surgery was performed at a younger age, and all boys with acquired cryptorchidism had a successful result. The authors concluded that earlier orchidopexy may be more technically demanding and supported the concept that expertise of the surgeon is relevant for more challenging cases.

A minimum of 6 months' follow-up is recommended to determine postoperative testis position and size. Long-term follow-up should be considered for counseling of the patient regarding fertility issues, risk of testicular malignancy, and self-examination. Torsion of a scrotal testis after orchidopexy has been reported but is very rare, and the risk may be minimized by routine extravaginal testicular fixation in a subdartos pouch. If complete intrascrotal testicular atrophy occurs postoperatively, further intervention is not needed, but the option of testicular prosthesis placement should be offered to the patient and family (Bodiwala et al, 2007). Implantation of a testicular prosthesis should occur at least 6 months after any scrotal procedure or after puberty and is best performed through an inguinal approach. Fixation of the prosthesis to the dartos and closure of the scrotal fascia above the implant using purse-string nonabsorbable suture are required. Complications including displacement, pain, or infection occur in less than 5% of cases. Clinical experience suggests that cryptorchid boys may request prosthesis implantation less frequently than males with acute testicular loss after puberty (Bodiwala et al, 2007).

Reoperation is indicated if a testis is nonscrotal after orchidopexy. If the testis is prescrotal, a primary scrotal approach can be considered and may allow adequate mobilization of the testis. If inguinal exploration is needed to provide sufficient cord length, several approaches are available. Redman described a primary or secondary orchidopexy that involves a lateral approach to the cord after mobilization of the external oblique and cremaster fasciae (Redman, 2000). This approach avoids traversal of the previously scarred layers anterior to the cord and affords a clearer view of the anatomy. Cartwright and colleagues described mobilization of the intracanalicular cord with an overlying patch of external spermatic fascia (Cartwright et al, 1993). The importance of correcting a persistently patent processus vaginalis and/or of adequate retroperitoneal mobilization of the cord in cases of high recurrent cryptorchidism has been stressed (Redman, 2000; Pesce et al, 2001; Ziylan et al, 2004). The results of secondary orchidopexy appear to be similar to the primary procedure, although the risk of vascular and vasal injury is theoretically higher (Pesce et al, 2001).

Trans-Scrotal Orchidopexy

A primary scrotal approach can be considered when the testis is palpable (Bianchi and Squire, 1989; Iyer et al, 1995; Cloutier et al, 2011) although some surgeons reserve this approach for testes that



Figure 148-13. Trans-scrotal orchidopexy. Various scrotal incisions that have been reported; A, Bianchi incision (Bianchi); B, transverse low scrotal approach (Misra); C, midline scrotal approach. (From Cloutier J, Moore K, Nadeau G, et al. Modified scrotal [Bianchi] mid raphe single incision orchiopexy for low palpable undescended testis: early outcomes. J Urol 2011;185:1088–92.)

are close to or can be drawn into the scrotum (Russinko et al, 2003; Rajimwale et al, 2004; Bassel et al, 2007; Takahashi et al, 2009). After induction of anesthesia, the patient is re-examined to confirm the position of the testis. An incision along the superior scrotal border is made as described by Bianchi and Squire for any palpable testicles. Alternatively, a transverse low scrotal approach (Misra et al, 1997) and midline scrotal approach (Cloutier et al, 2011) have been described for those testes that can be drawn into the scrotum (Fig. 148-13). After the testis has been delivered, the distal sac and overlying cremaster are mobilized proximally as far cranially as possible, "high above the inguinal canal" (Iyer et al, 1995). Some cases require conversion to an inguinal approach for ligation of the sac or to gain further length on the spermatic cord (Parsons et al, 2003; Dayanc et al, 2007). Rajimwale and colleagues confirmed in several cases that the hernia sac had been effectively ligated above the internal ring via the scrotal incision when a secondary inguinal incision was required for further mobilization of the testis (Rajimwale et al, 2004). Fixation sutures through the tunica albuginea have been used in many series of scrotal orchidopexy (Jawad, 1997; Russinko et al, 2003; Bassel et al, 2007; Dayanc et al, 2007; Takahashi et al, 2009), followed by placement of the testis in a subdartos pouch. In an extensive review of the literature by Gordon and colleagues, additional inguinal incisions were needed in 4.4% and there were early postoperative complications in 1.6% of cases (Gordon et al, 2010). The single institution long-term results reported by these authors included a reoperative rate of 4.9% and a 0.6% incidence of testicular atrophy. In a literature review of 1558 cases in 20 series reporting 3 months to 5 years of follow-up, a hernia was present in 30% and 3.5% of cases required an inguinal incision (Novaes et al, 2013). Complications included recurrence (0.6%), testicular atrophy or hypotrophy (0.3%), hematoma (1.4%), wound infection (0.8%), and vasal injury (1 case), with a low overall complication rate of 3%. Scrotal incision orchidopexy is used selectively in many series, but the available evidence suggests that efficacy and complication rates are similar to those of standard inguinal orchidopexy.

Surgical Approach to the Abdominal Testis

Once an abdominal testis has been identified, the surgeon must decide whether to proceed with an open or laparoscopic, one- or two-stage orchidopexy with possible spermatic vessel transection. Orchiectomy is appropriate for patients with testes that are poorly viable and/or at higher risk for tumor, which may include testes in postpubertal patients or very small or dysgenetic testes in postpubertal patients, and is in our opinion best performed laparoscopically.

Open Transabdominal Orchidopexy

Extensive dissection of the vas and vessels is facilitated by a longitudinal opening of the internal oblique and peritoneum through an extended inguinal incision (Kirsch et al, 1998) or via a higher incision medial to the pubic tubercle and a preperitoneal approach (Jones and Bagley, 1979; Gheiler et al, 1997). In the procedure described by Jones and Bagley, the internal ring is approached via a muscle-splitting incision, the peritoneum is opened, the testis delivered, and the vas and vessels freed from their peritoneal attachments. A tunnel is created to the scrotum and the testis is secured in place as for an inguinal orchidopexy. The reported success rate for this procedure for abdominal testes was 95% (Gheiler et al, 1997).

Laparoscopic Orchidopexy and Fowler-Stephens Orchidopexy

Operative laparoscopy emerged over 15 years ago as the procedure of choice for abdominal orchidopexy (Caldamone and Amaral, 1994; Jordan and Winslow, 1994), and the basic surgical approach and high success rates have stood the test of time (Table 148-1). The feasibility of primary versus Fowler-Stephens orchidopexy depends on the length of the vas and vessels, presence or absence of looping ductal structures, and age of the patient. Although laparoscopy allows the surgeon to assess some of these features before choosing a specific surgical procedure, the choice may be difficult (Yucel et al, 2007). Observed testicular position alone may correlate poorly with the ultimate length of the cord after mobilization.

After induction of anesthesia, a further attempt to palpate the testis is made, although a laparoscopic approach may be considered for mobilization of high canalicular testes as well. After decompression of the bladder and stomach, an infraumbilical 5-mm trocar is placed for passage of a 30-degree lens, and both internal rings are visualized. An open Hasson or Bailez technique is preferable for umbilical trocar placement in the pediatric age group to minimize risk of injury (Franc-Guimond et al, 2003). CO₂ pneumoperitoneum to a maximum pressure of 8 to 12 mm Hg is used. The size and position of the testis within the abdomen are determined before further decision making. For single-stage laparoscopic orchidopexy, additional 2- or 3-mm trocars are placed in the right and left lower quadrants to triangulate with the umbilicus and ipsilateral internal ring, or in the midclavicular line at the level of the umbilicus bilaterally for bilateral abdominal testes. The major steps are mobilization of any structures extending distal to the internal ring, including epididymis and vas and gubernacular remnant, transection of the peritoneum lateral to the vessels and distal to the vas, and proximal mobilization of the vessels while maintaining collateral blood supply between the vas and spermatic vessels. Samadi and colleagues advocate initial mobilization of the gubernaculum to be used as a handle for further mobilization of the testis, and minimal use of cautery during this maneuver (Samadi et al, 2003). Ability to mobilize the testis to the opposite internal ring has been used as a measure of adequate length for placement in the scrotum but was not predictable in some series. Once mobilized, the testis is brought through a new hiatus medial to the epigastrics and lateral to the medial umbilical ligament or through the existing internal inguinal ring. This maneuver can be completed using a trans-scrotal clamp or an additional port passed up from the scrotum. With tension on the extra-abdominal testis, peritoneal attachments overlying the cord can be more easily transected, thus providing addi-

tional length. In some cases the testis can only be brought into the upper scrotum; the long-term adequacy of this approach is not clear. Excessive tension on the vessels during placement of the testis should be avoided, because injury or avulsion of the spermatic vessels may occur (Esposito et al, 2002). A key strategy should be preservation of the blood supply between the vas and spermatic artery during dissection so that the Fowler-Stephens procedure can be performed if necessary.

Formal closure of the dissected internal ring is not necessary (Handa et al, 2005; Riquelme et al, 2007); indeed, previous experience with open hernia repair suggests that ligation is not needed if the internal ring is dissected (Mohta et al, 2003). No inguinal hernias were identified a mean of 41 to 50 months after laparoscopic orchidopexy in a retrospective series in which formal closure of the internal ring was performed in 54% of cases (Khairi et al, 2013). A contralateral patent processus vaginalis was identified in 9% of boys undergoing laparoscopic orchidopexy in one series, and laparoscopic repair was performed and recommended (Palmer and Rastinehad, 2008). However, the necessity for this approach in preventing clinical hernia formation is questionable based on studies of boys undergoing laparoscopic or open hernia repair (Schier, 2007).

For testes that are not near (variably defined as 2 to 4 cm above) the internal inguinal ring, transection of the spermatic vessels as originally described by Fowler and Stephens may be necessary (Fowler and Stephens, 1959); a long-looping vas facilitates but is not required for testicular mobilization to the scrotum. The Fowler-Stephens procedure is now typically performed laparoscopically with spermatic vessel clipping (Bloom, 1991) followed by laparoscopic or open testicular mobilization in the same setting, or in a staged approach 6 months later. The peritoneum should be left intact over the vasal vessels, and the gubernacular vessels should be left intact if possible. Although most surgeons transect the spermatic vessels at least 1.5 to 3 cm above the testis, Koff and Sethi proposed that ligation close to the testis is preferable (Koff and Sethi, 1996). This group subsequently studied the effect of low versus high transection of the vessels in prepubertal rats and showed a reduction in adult testicular sperm numbers that was similar in both groups (Srinivas et al, 2005). In human studies, testicular biopsies before and after spermatic vessel transection also showed a reduction in germ cell count, a finding that was significant in younger boys (Thorup et al, 1999; Rosito et al, 2004). In general, the preferred approach is avoidance of spermatic vessel transection whenever possible; the available data suggest this is possible in the majority of cases of abdominal orchidopexy. In rare cases, particularly if the testis is retrovesical, the vas is too short to allow scrotal placement of the testis, and orchiectomy is ultimately required (Perovic and Janic, 1997).

The success rates for laparoscopic procedures as shown in Table 148-1 appear to compare favorably with the corresponding 74%, 63%, and 77% overall success rates for open surgical and one-stage and two-stage Fowler-Stephens procedures, respectively (Docimo, 1995). The available data suggest that a primary procedure is more consistently successful (>90% in most series) than a Fowler-Stephens approach (variable success of 60% to 97%). In directly comparing the results of 156 abdominal orchidopexies at a single institution, Stec and colleagues observed significantly better results for a primary open (89% success) or laparoscopic (97%) approach than for one-stage (63%) or two-stage (68%) Fowler-Stephens procedures (Stec et al, 2009). Recent meta-analyses and/or systematic reviews of surgical treatment of abdominal testes (Elyas et al, 2010; Guo et al, 2011; Penson et al, 2013; Kolon et al, 2014) are primarily low-quality retrospective series with few, if any, adequately powered prospective controlled studies. Pooled success rates for primary one-stage Fowler-Stephens and two-stage Fowler-Stephens procedures are approximately 95%, 80%, and 85%, respectively. The available evidence suggests no clear difference in efficacy between open and laparoscopic procedures. Variation in reported results among series may reflect inherent selection bias resulting from differences in patient age, testicular position or quality, length of follow-up, and/or criteria used to define success, such as "intrascrotal" versus

TABLE 148-1 Results of Laparoscopic Orchidopexy*

PROCEDURE	SERIES	PATIENTS/ TESTES	AGE	FOLLOW-UP	HIGH POSITION	TOTAL ATROPHY	OVERALL SUCCESS
Laparoscopic orchidopexy	Baker et al, 2001	178/208	36 mo	7.7 mo (mean)	0.6%† (1/178)	2% (4/178)	97%
	Samadi et al, 2003	—‡/139	—	≥6 mo	3%† (4/139)	0	97%
	Handa et al, 2005	58/76	—	2.2 yr (median)	0†	3% (2/65)	97%
	Kim et al, 2010	—/69	2.4 yr	≥3 mo (mean, 22)	18% (9/49)	2% (1/49)	80%
	Castillo-Ortiz et al, 2014	—/48	4.4 yr	24 mo (mean)	6% (3/48)	0	94%
	El-Anany et al, 2007	—/46	5 yr	3 yr (mean)	9% (4/46)	0	90%
	Kaye and Palmer, 2008	19/38	9 mo (median)	12 mo	10% (4/38)	3% (1/38)	87%
	Alzahem, 2013	31/35	15.4 mo	12 mo (median)	9% (3/33)	3% (1/33)	88%
	Stec et al, 2009	—/32	12 mo (median)	16 mo (mean)	—	3% (1/32)	97%
	Powell et al, 2013	22/31	2.1 yr	11.3 mo (mean)	3% (1/31)	6.5% (2/31)	91%
Laparoscopic one-stage FS orchidopexy	Chang and Franco, 2008	38/38	2.9 yr	17.5 mo (mean)	0†	6% (2/35)	94%
	Esposito and Garipoli, 1997	33/33	3-10 yr (range)	30 mo (mean)	0	3% (1/33)	97%
	Baker et al, 2001	25/28	31 mo	8.6 mo (mean)	7%† (2/27)	22% (6/27)	71%
Laparoscopic two-stage FS orchidopexy	Alagaratnam et al, 2014	94/113	2.75 yr (median)	2.1 yr (median)	9% (9/102)	9% (9/102)	82%
	Stedman et al, 2014	78/83	1.9 mo (median)	12 mo (median)	7.5% (5/67)	10.4%§ (7/67)	82%
	Casanova et al, 2013	62/79	1.8 yr (median)	3.1 yr (median)	13% (10/77)	17%§ (14/82)	70%
	Baker et al, 2001	63/74	55 mo	20 mo (mean)	2%† (1/58)	10% (6/58)	88%
	Lotan et al, 2001	59/66	14 mo	3-12 mo (range)	—	—	84%
	Hvistendahl and Poulsen, 2009	65/—	5.7 yr (median)	3 mo	6%	14%	80%
	Dave et al, 2009	—/61	36.8 mo	13.5 mo (mean)	0	25% (15/61)	75%
	El-Anany et al, 2007	—/47	5 yr	3 yr (mean)	0	4% (2/47)	96%
	Abolyosr, 2006	—/41	5.3 yr	9-31 mo (range)	0	12% (5/41)	88%
	Moursy et al, 2011	—/36	16 mo (median)	34 mo (mean)	6% (2/36)	6% (2/36)	89%
	Alzahem, 2013	30/34	32.1 mo	15 mo (median)	7% (2/30)	30% (9/30)	63%
	Stec et al, 2009	—/32	12 mo (median)	16 mo (mean)	—	32% (12/32)	68%

*Reported results of abdominal, one-stage, and two-stage Fowler-Stephens (FS) orchidopexy in series with 30 or more treated testes (≥25 for one-stage FS). Age is expressed as the mean for the entire series unless otherwise noted. *High position* refers to testes not in dependent scrotal position.

†Position within scrotum not clearly documented.

‡Em dashes (—) indicate that information was insufficient.

§Series in which partial atrophy was also noted. *Overall success* refers to the frequency of nonatrophic testes in satisfactory scrotal position according to variably detailed criteria used by the authors.

"dependent scrotal" position. Despite their limitations, the available data seem to suggest that primary orchidopexy without transection of the spermatic vessels is preferable whenever possible. Some authors recommend that ultrasound be used to confirm testicular viability postoperatively (Esposito et al, 2002). Other complications of laparoscopic orchidopexy are rare and potentially include bladder or vascular injury, hypercapnia, and delayed small bowel obstruction (Esposito et al, 2003; Hsieh et al, 2009).

Laparoscopic techniques may be applicable in unusual cases, including bilateral orchidopexy, abdominal wall defects, polyorchidism, splenogonadal fusion, and transverse testicular ectopia with or without persistent müllerian ducts. Many authors recommend simultaneous bilateral abdominal orchidopexy (Kaye and Palmer, 2008), but the surgeon should consider a staged approach if both testes are very high or the viability of a testis is questioned during the course of orchidopexy as noted in Kaye and Palmer's algorithm. Depending on the outcome of the first procedure at 6 months' follow-up, the surgeon can choose an operative approach to the contralateral side that would appear to minimize the risk of bilateral testicular atrophy (Thorup et al, 2007). Some surgeons have considered microvascular orchidopexy to be a preferred approach to the solitary abdominal testis, particularly with historical success rates of 88% as compared with lower rates for open procedures (Docimo, 1995). At a center with substantial experience using the microvascular approach, long-term success rates of 96% for standard and 88% for laparoscopically assisted autotransplantation were reported (Bukowski et al, 1995; Tackett et al, 2002). The advantage of this approach is preservation of the spermatic vessels, at the cost of longer operative time and requirements for an experienced microvascular surgeon and hospital stay.

PROGNOSIS

Despite the common occurrence of cryptorchidism and voluminous literature on the subject, many gaps exist in our present understanding of the factors contributing to long-term outcome. This is likely because of the expectation that surgical correction will be successful in most cases, and prospective studies into adulthood are difficult and not routine in otherwise healthy males. These studies would need to (1) account for multiple confounding variables, many of which are incompletely defined, including severity of the disease (e.g., based on testicular position, laterality, epididymal anomalies), multifactorial cause, age at surgery, exposure to hormone therapy, and type of procedure performed, and (2) use standardized methodology based on adequate follow-up and complete documentation of complications to report results. Well-designed studies that provide higher-quality evidence are clearly needed.

Risk of Subfertility

Although there is strong evidence that a history of cryptorchidism is associated with subfertility in individual patients, the effects of age at diagnosis, type of treatment, and/or severity of disease on outcome remain incompletely defined. Major limitations in the interpretation of cryptorchidism outcome studies include selection bias resulting from incomplete follow-up of large patient cohorts and heterogeneity of diagnosis and timing/type of treatment. In a large review of retrospective studies published in the 50 previous years that did not take these concerns into consideration and did not include a statistical meta-analysis, Chilvers and colleagues reported overall rates of oligospermia and/or azoospermia of 75% for formerly bilaterally and 43% for formerly unilaterally cryptorchid men (Chilvers et al, 1986). The limited available data comparing earlier (age younger than 9) and later treatment did not show differences in the frequency of subfertility after unilateral (281 cases) or bilateral (123 cases) orchidopexy. Similarly, subset analysis failed to identify any effect of hCG treatment. Two subsequent large studies of semen parameters in men who underwent orchidopexy in childhood also found differences between bilateral and unilateral cryptorchidism but less consistent overall results. Okuyama and associates (Okuyama et al, 1989) reported normal

sperm density in 0%, 72%, 77%, and 42% of men after bilateral orchidopexy (61), unilateral orchidopexy (149), unilateral orchiectomy (26), and no treatment (38) for inguinal testes without hormone therapy. All of these patients underwent three semen analyses. In contrast, Gracia and colleagues reported normal semen samples in 10 of 55 (18%) men with a history of bilateral and 57 of 171 (33%) with previous unilateral cryptorchidism (Gracia et al, 2000). The majority of testes in this series were canalicular, and 80% of subjects received preoperative hCG therapy. These authors noted no differences based on testicular position, and semen quality was not correlated with age of surgery in either series. In 91 patients with unilateral cryptorchidism who underwent orchidopexy after the onset of puberty (age 14 to 29), the risk of azoospermia or oligospermia was 84% (Grasso et al, 1991) a trend in keeping with the data reported previously (Okuyama et al, 1989). In contrast, Puri and O'Donnell studied 142 men who underwent unilateral (119) or bilateral (23) orchidopexy at 7 years of age or older; these researchers reported normal sperm density in 84% and 50% of patients, respectively (Puri and O'Donnell, 1988).

Changes in the pattern of care over time, particularly earlier surgery without the confounding effects of hormonal therapy, may alter prognosis. However, potential benefits of early orchidopexy have not been shown because the mean age of operation for patients included even in more recent studies remains high, at over 7 years (Vinardi et al, 2001; Trsinar and Muravec, 2009; Kraft et al, 2012; van Brakel et al, 2013, 2014), and the number of participants in each series was fewer than 100. In these studies, the prevalence of normal sperm counts is similar to that reported previously, ranging from 60% to 84% and 18% to 53% in prior unilateral and bilateral cryptorchidism, respectively. Semen analysis data appear to be superior in a small series of 51 men who underwent orchidopexy before age 2, with normal sperm count in 96% of unilateral (27) and 75% of bilateral (24) cases (Feyles et al, 2014). The highest testis was abdominal in 6 (12%) and intracanalicular in 20 (39%) cases, and 29 boys (57%) received preoperative hormonal therapy. Although interesting, the reason for inconsistency with prior studies of bilateral cryptorchidism will require further studies.

Several studies suggest that mean germ cell counts obtained at biopsy correlate with long-term fertility potential as measured by mean semen analysis parameters (Engeler et al, 2000; Cortes et al, 2003a; Rusnack et al, 2003), although the usefulness of total germ cell counts as a predictor of fertility in individuals is limited, particularly in individual cases. More recent reports investigated the use of Ad spermatogonia number as a better predictor of semen quality in adulthood. Hadziselimovic and colleagues reported a strong correlation between the number of Ad spermatogonia in cryptorchid testes and sperm count in adulthood after previous unilateral or bilateral orchidopexy with or without prior hormonal therapy (Hadziselimovic et al, 2007; Hadziselimovic and Hoecht, 2008). In non-hormonally treated patients, total sperm count was normal (>40 million per ejaculate) in 84% of 25 men who had Ad spermatogonia present in biopsy specimens from both testes, whereas it was subnormal in all 18 men (10 of the 19 men in this series with a history of bilateral cryptorchidism) in whom biopsy results were negative for Ad spermatogonia. Total germ cell counts were reportedly not predictive of sperm concentration in this series (Hadziselimovic and Hoecht, 2008). In a larger series of men with prior unilateral (91) or bilateral (19) cryptorchidism, Kraft and colleagues observed lower mean sperm counts and higher FSH levels in adulthood when bilateral biopsy at surgery showed severe loss of germ cells or abnormal Ad spermatogonia counts, but, likely because of the variability of the data, group means remained within normal range and/or were not statistically significant, confirming that even analysis of Ad spermatogonia does not always predict fertility potential in individuals (Kraft et al, 2012). The reported hormone levels in adulthood also do not predict fertility status. In view of the heterogeneity of the disease and its treatment, most studies are likely underpowered to detect clear associations between histologic and phenotypic variables and fertility potential as estimated by semen analysis. Nevertheless, both Ad spermatogonia count and germ cell absence are potentially useful measures of fertility prognosis, but may be more useful in cases of bilateral

cryptorchidism. Additional, larger prospective studies of these parameters in boys who underwent surgery in infancy are needed.

The use of semen analysis alone to define outcome and predict fertility potential has limitations. For example, a large population study of fertile and infertile men with fertile partners suggests that there is extensive overlap between semen parameters in men with and without proven paternity (Guzick et al, 2001). In this study, the authors established lower infertile threshold levels for density ($13.5 \times 10^6/\text{mL}$), motility ($>35\%$), and normal morphology ($>9\%$) than had been established by World Health Association criteria. About 3% of fertile men in this series had a sperm density below $10 \times 10^6/\text{mL}$, and measurements between 13.4 and $48 \times 10^6/\text{mL}$ were considered indeterminate. Repeated semen analyses, rarely performed in studies of formerly cryptorchid men, were reportedly necessary to provide reliable data in normal men (Oshio et al, 2004). However, the reliability of semen analysis in adolescents is not fully known. Christman and associates recently addressed this question in Tanner stage V youths (age younger than 25) being evaluated for cryptorchidism (48) or varicocele (31) (Christman et al, 2013). In this study, semen parameters were not highly reproducible between samples in the same individual, yet the computed intraclass correlation coefficient was considered substantially reliable, particularly for total sperm counts, suggesting that a single sample, especially when normal, may suffice in estimating fertility potential. When semen analysis results are abnormal, repeat samples should be obtained whenever possible.

Determination of paternity status is an alternative measure of fertility that should be considered when determining prognosis. Limitations of this approach include paternal discrepancy and variability in the timing and degree of interest in attempts at paternity. Although of concern and not ethically retrievable, a recent review (Bellis et al, 2005) found that the median level of paternal discrepancy in 17 studies of unselected populations in Europe and the Americas was only 3.7% (interquartile range, 2% to 9.6%). Two retrospective cohort studies of men with previous cryptorchidism assessed paternity in 145 (Gilhooly et al, 1984) and 40 (Cendron et al, 1989) cases. Together, these studies identified successful paternity in 100 of 123 (81%) men with a history of unilateral and 19 of 54 (35%) men with a history of bilateral cryptorchidism. Lee and colleagues published a series of well-designed case-control studies of fertility in cryptorchidism (Lee et al, 1996, 1997; Coughlin et al, 1999; Lee et al, 2000; Lee and Coughlin, 2001, 2002b; Lee, 2005). Questionnaire, hormone, semen analysis, and paternity data were analyzed for a large cohort of men who underwent orchidopexy between 1955 and 1975 and a control group of similar age who were matched for timing of unrelated surgery. For all married or cohabitating men, 32 of 88 (36%) former bilateral, 322 of 609 (53%) former unilateral, and 413 of 708 (58%) controls had fathered children. **Of those attempting paternity, 32 of 49 (65%) former bilateral, 322 of 359 (90%) former unilateral, and 413 of 443 (93%) controls were successful.** There were no significant differences between the unilateral and control groups and no differences among groups in the frequency of attempted paternity or in other lifestyle factors that could adversely affect fertility. The frequency of successful paternity did not differ among men with previous unilateral cryptorchidism who had undergone orchiectomy and the control group. Risk for infertility was increased after hCG treatment (RR 4.7, $P = .002$) but not with higher testicular position or age at orchidopexy. Sperm density was $13 \times 10^6/\text{mL}$ or lower in all 8 patients with bilateral cryptorchidism who were studied; however, 3 of these men had fathered children (Lee and Coughlin, 2001). Sperm density and motility were normal in 83% of men in the unilateral group, and morphology did not differ from control values. Although hormone levels alone did not correlate directly with fertility, abnormal levels of serum inhibin B or FSH and/or sperm density provided cumulative risk of decreased fertility. However, the authors concluded that prediction of infertility is difficult in the absence of azoospermia or severe oligospermia. These investigators also found differences in basal and stimulated LH and in serum testosterone when comparing fertile and infertile or subfertile formerly cryptorchid men, and suggested that global

testicular dysfunction occurs in cryptorchid males. Moreover, there is some evidence from these studies of a relationship among improved testosterone, inhibin B, and FSH levels in males who underwent earlier orchidopexy (Coughlin et al, 1999; Lee and Coughlin, 2002a).

In limited series, investigators have addressed the possibility of defective spermatogenesis in adult patients with persistently retractile testes or with milder forms of acquired cryptorchidism, with or without apparent spontaneous descent of the testis at puberty. In small, retrospective outcome studies, Puri reported 74% paternity and normal testicular volume in a series of 43 adults with untreated retractile testes in childhood (Puri and Nixon, 1977). Conversely, Nistal and Paniagua and Caroppo and colleagues identified 23 and 34 males, respectively, from infertility clinic data and identified poor semen parameters in the majority of patients, but the duration and severity of retractility were poorly documented (Nistal and Paniagua, 1984; Caroppo et al, 2005). Two series reported varying degrees of abnormal germ or Sertoli cell development in retractile testes of boys who underwent elective orchidopexy as compared with boys with descended testes; differences were qualitatively similar to findings in cryptorchid testes (Hadziselimovic et al, 1987a; Caucci et al, 1997). Han and colleagues compared 61 retractile with 83 cryptorchid testis biopsy specimens and noted similar trends but did not include a control group (Han et al, 1999). Methodologic limitations prevent clear differentiation of retractile from acquired undescended testes in these studies. Prospective studies of well-characterized patients are needed, but there is insufficient evidence to support an increased risk of infertility in uncomplicated cases of retractile testis.

Similarly, the outcome data for acquired cryptorchidism are difficult to interpret, because to date they are based on retrospective, nonrandomized studies that analyzed cases of both spontaneous descent at puberty and prior orchidopexy. In a retrospective series of 45 men with spontaneous descent of bilaterally undescended testes after age 10 by history (without clear documentation of congenital vs. acquired classification), testicular volumes were below 15 mL in 62% and sperm counts below 20 million/mL in 44% of patients (Bremholm Rasmussen et al, 1988). Investigators from the Netherlands who have followed boys with either congenital or acquired cryptorchidism recently reported follow-up fertility data (van Brakel et al, 2013, 2014). In prior publications from these institutions, the majority of the acquired group, particularly those with spontaneous descent at puberty, included high scrotal and low scrotal "unstable" testes (likely retractile) (Sijstermans et al, 2006; Eijsbouts et al, 2007; Hack et al, 2010). Van Brakel and colleagues observed no differences in semen parameters or hormone levels in small subgroups of men with a history of acquired cryptorchidism after spontaneous testicular descent (24) or orchidopexy (26) at puberty. The fertility potential of men with acquired (65) and congenital (62) cryptorchidism was similar and reflected prior studies showing a worse prognosis in bilateral cases. Few of the men studied had attempted paternity. Unfortunately, these investigators and others (Trsinar and Muravec, 2009) have reported difficulty in recruiting subjects, with only 12% to 31% of eligible individuals participating. Consequently, the ability to draw conclusions from the majority of studies, particularly in subgroup analyses, is compromised by insufficient sample size and potential bias. However, **available data provide strong evidence that fertility potential is compromised in men with a history of bilateral cryptorchidism, but the frequency of abnormal semen parameters in unilateral cases is higher than the relative risk of infertility as measured by paternity data.** Unfortunately, the number of formerly bilaterally cryptorchid men who have been comprehensively studied is limited. Although data suggest the possibility of an association between age at surgery and risk of infertility, further studies are needed to elucidate the relationships between these factors.

Risk of Testicular Germ Cell Tumor

The increased risk of TGCT in males with a history of cryptorchidism has been known for many years. Both seminoma and

nonseminomatous germ cell tumors (NSGCTs) develop from CIS of the testis, also called *intratubular germ cell neoplasia, unclassified* (ITGCNU), and are believed to be developmental in origin (Rajpert-de Meyts and Høie-Hansen, 2007). The hypothesis that persistent gonocytes are the precursors of ITGCNU has existed for some time, and recent gene expression data indeed support a common origin for the two cell types (Sonne et al, 2009). The histologic data suggesting that gonocytes fail to transform normally in cryptorchid testes may coincide with eventual transformation of these persistent cells into ITGCNU and TGCT. Using placenta-like alkaline phosphatase (PLAP) as a marker of ITGCNU, Engeler and colleagues identified PLAP-positive cells in 5% of 440 patients, most (82%) younger than 3 years, who had undergone testicular biopsy and orchidopexy many years previously (Engeler et al, 2000). Although up to 50% of adults with ITGCNU are expected to develop TGCT over time, no tumor was detected in the 15 of 22 affected individuals that the authors were able to evaluate a median of 21 years later. It is now recognized that several markers of undifferentiated spermatogonia, including PLAP, OCT3/4, c-KIT, NANOG, and SCF (stem cell factor, or kit ligand), show decreasing expression in the fetus and normally disappear after birth, but are re-expressed in ITGCNU and TGCT (Honecker et al, 2004; Cools et al, 2005; Høie-Hansen et al, 2005; Stoop et al, 2008) and may be upregulated postnatally in individuals with dysgenetic gonads at higher risk of malignancy (Rajpert-De Meyts et al, 2004). The observation that PLAP-, c-KIT-, or OCT3/4-positive germ cells persist beyond the first few months of life in cryptorchid testes is consistent with known delayed maturation of germ cells (Thorup et al, 2013; Kvist et al, 2014). PLAP may have a role in defining the prognosis for spermatogenesis in cryptorchidism (Thorup et al, 2013), but to date no germ cell marker can differentiate between delayed germ cell maturation and ITGCNU in this population. In an isolated finding, Cortes and colleagues identified multinucleated spermatogonia in 13 (8%) of 163 consecutive patients undergoing biopsy at the time of orchidopexy (Cortes et al, 2003b). This occurred in younger boys and was associated with a germ cell count that was usually normal and higher than the mean for the majority of cases. Although this finding was not identified in normal boys, its relevance to tumor risk remains completely unknown.

Updated analyses have clarified the nature of increased TGCT risk in the previously cryptorchid and contralateral descended testis (Wood and Elder, 2009; Banks et al, 2012; Trabert et al, 2013). A history of cryptorchidism is associated with a twofold to fivefold increased risk of testicular cancer, lower than historical estimates. This incidence correlates with the reported risk of ITGCNU of 2% to 3% in previously cryptorchid men (Giwerzman et al, 1989); a much lower risk (0% to 0.4%) was reported in children with nonsyndromic cryptorchidism (Cortes et al, 2001; Husmann, 2005). Men with a history of cryptorchidism comprise about 10% of those with TGCT. Tumors may occur in the contralateral descended testis of men with a history of unilateral cryptorchidism, but Wood and Elder (2009) concluded that the relative risk of only

1 to 2 indicates a level comparable to the general population that is not related to cryptorchidism per se. However, two meta-analyses suggest that the risk of tumor is increased in the contralateral testis, with odds ratios (ORs) of 1.7 (95% CI 1.01 to 2.98) and 1.5 (05% CI 0.9 to 2.6), respectively (Akre et al, 2009; Banks et al, 2012). In another meta-analysis, Walsh and colleagues determined that the relative risk of TGCT was 5.8 (95% CI 1.8 to 19.3) in men who underwent orchidopexy after age 10 to 11 as compared with those undergoing earlier correction (Walsh et al, 2007). Population-based data are conflicting, showing twice the risk of TGCT in patients undergoing orchidopexy at or after age 13 in some series (Pettersson et al, 2007; Trabert et al, 2013) but no age-dependent differences in another series (Myrup et al, 2007), possibly related to ascertainment bias. Review of tumor pathology in treated versus untreated cryptorchidism shows that seminoma is associated with persistently cryptorchid testes (74%) and nonseminoma is present in the majority of scrotal testes (63%) (Wood and Elder, 2009).

In a population-based study in Sweden, hypospadias (OR 2.25, 95% CI 1.17 to 4.32); inguinal hernia (OR 1.30, 95% CI 1.06 to 1.60), and other genital malformations (OR 1.90, 95% CI 1.00 to 3.63) were independent risk factors for TGCT, in addition to cryptorchidism (OR 3.16, 95% CI 2.45 to 3.96) (Trabert et al, 2013). Consistent with the researchers' previous studies, ORs were lower when cryptorchidism was diagnosed before (OR 2.76, 95% CI 2.09 to 3.65) versus after (OR 4.96, 95% CI 3.06 to 8.04) puberty, whereas the reverse was true for hypospadias and hernia, wherein associations were stronger at a younger age at presentation. These data provide stronger support for a link between hypospadias and TGCT, but the authors cautioned that they did not confirm the existence of common risk factors in TDS conditions (Trabert et al, 2013).

The risk of TGCT is even greater in some types of syndromic cryptorchidism, as in conditions associated with chromosomal defects or DSD (Cortes et al, 2001; Husmann, 2005). Husmann has recommended that biopsy be performed in these individuals and in boys older than 12 undergoing orchidopexy, although the age cutoff and usefulness of biopsy during pubertal orchidopexy has not been clearly defined. Orchiectomy should be considered the preferred treatment of cryptorchid testes in postpubertal males up to the age of 50 (Wood and Elder, 2009). Swerdloff and colleagues reported in a retrospective cohort study that testicular biopsy at orchidopexy was associated with an increased risk of future TGCT compared with orchidopexy without biopsy (RR 6.7, 95% CI 2.7 to 13.5), but the indications for biopsy in this series were not clearly known (Swerdloff et al, 1997). A subsequent report from a large Scandinavian cohort showed that universal biopsy did not appear to increase the risk for TGCT beyond what is expected for previously cryptorchid men (Møller et al, 1998).

Testicular microlithiasis, characterized by multiple spectral calcifications within the testicular parenchyma (Fig. 148-14), is more frequently present in men with ITGCNU or TGCT, but is also present in 5% to 10% of the normal population and in a similar

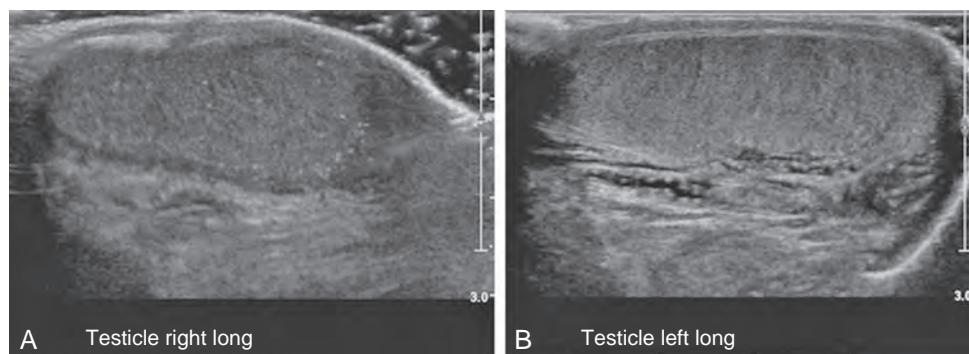



Figure 148-14. Associated sonographic abnormalities in boys with cryptorchidism. Ultrasound images from an 11-year-old boy with testicular asymmetry who underwent bilateral orchidopexies in infancy. A, Right microlithiasis. B, Ectasia of the left rete testis.

proportion of previously cryptorchid men (Patel et al, 2005; van Casteren et al, 2009). Although concern exists that the risk for TGCT may be higher when cryptorchidism coexists with microlithiasis in individual patients, no data exist to support this hypothesis and the appropriate follow-up strategy remains undefined. Even less well defined is the significance of microlithiasis in general, which is not clearly shown to be an independent risk factor for TGCT. A recent population-based analysis of the prevalence of microlithiasis in a series of primarily Caucasian boys shows that the prevalence is 4.2% and increases with age (Goede et al, 2009). In about half of these cases, the degree of microlithiasis was limited, defined as fewer than five lesions per testis, and not considered clinically significant. The general prevalence was 3.5% in boys with cryptorchidism and 6.4% in a series of 261 older boys (mean age 18.9) being followed after a diagnosis of acquired cryptorchidism

(Goede and Hack, 2012; van der Plas et al, 2013a). The occurrence of testicular tumors in boys with microlithiasis is rare and not yet reported in association with cryptorchidism (Goede and Hack, 2012). Other testicular abnormalities identified during ultrasound follow-up in males treated for cryptorchidism include ectasia of the rete testis (see Fig. 148-13) (Nistal et al, 1996) and intratesticular varicocele (Meij-de Vries et al, 2013). The significance of these entities in the context of cryptorchidism remains poorly defined. Although the U.S. Preventive Services Task Force does not recommend routine testicular self-examination in adolescents and adults because treatment for TGCT is highly effective, the recommendation does not include previously cryptorchid males (U.S. Preventive Services Task Force, 2011). Physicians should educate patients and their families about the risks of infertility and TGCT in cryptorchidism and should provide counsel about the potential benefits of testicular self-examination.

KEY POINTS

- Gonadal determination involves separate genetic pathways for development of testis and ovary. SRY is a master switch in males that regulates downstream testis-determining genes.
- Differentiation of gonocytes and Sertoli and Leydig cells occurs at 5 to 9 weeks' gestation, and the gubernaculum, the guide for testicular descent, appears at 7 weeks' gestation.
- Levels of the Leydig cell hormones testosterone and INSL3 peak at 14 to 17 weeks' gestation and are critical for testicular descent.
- Swelling of the gubernaculum, which starts in the second trimester, provides space for passage of the testis into the scrotum at 20 to 28 weeks' gestation.
- Cryptorchidism occurs in 1% to 4% of full-term male infants; both spontaneous descent (in the first few months of life, usually by 6 months) and reascent of testes may occur.
- The causes of cryptorchidism are largely unknown, but birth weight, gestational age, and genetic and environmental risk factors likely contribute to disease risk.
- The diagnosis of cryptorchidism may be acquired—that is, made in cases of apparent full descent at birth or after spontaneous descent of a cryptorchid testis—and may be more common in boys with retractile testes. Yearly testicular examinations are recommended.
- About 80% of undescended testes are palpable and 60% to 70% are unilateral.
- Many boys with nonsyndromic cryptorchidism have epididymal anomalies and a patent processus vaginalis, and some have reduced LH and/or testosterone levels during the postnatal surge.
- Orchidopexy is recommended for testes that remain undescended after 6 months of age; hormone therapy is not recommended.
- Laparoscopy is the procedure of choice, and imaging studies are rarely useful in the diagnosis and treatment of abdominal cryptorchidism.
- Sperm counts are reduced in at least 25% of formerly unilateral and the majority of formerly bilateral cryptorchid men, but paternity rates in the unilateral group are similar to those in control men.
- Ad spermatogonia counts may predict fertility potential in males with cryptorchidism.
- TGCT risk is two to five times higher in boys with cryptorchidism, especially after pubertal orchidopexy.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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Female Genital Embryology

Evaluation and Classification of Female Genital Anomalies

Congenital Disorders of Female External Genitalia

Acquired Disorders of the Female External Genitalia

As with the other organ systems, genital development in the female occurs in an orderly fashion through multiple complex steps that result in an anatomically and functionally normal child in the vast majority of cases. However, errors in development can occur, from minor, clinically insignificant disorders to severe abnormalities that are devastating to the child and parents. The abnormalities may affect the external genitalia alone or in combination with internal genital anomalies, and in some they may involve other organ systems. This chapter briefly describes normal female urogenital development and then discusses anomalies that arise when abnormal development occurs. Genital ambiguity may be the initial finding in these disorders.

FEMALE GENITAL EMBRYOLOGY

A comprehensive description of genitourinary embryology can be found in Chapters 122 and 150. To foster a deeper understanding of the complex combination of anomalies that can occur in patients with external genital/vaginal anomalies, a brief review of relevant embryologic events is presented.

The cloaca is an endoderm-lined primordial organ that is first apparent at the beginning of the second week of gestation (Grosfeld, 1996). This structure, which represents a confluence of the primitive hindgut (dorsally) and the allantois (ventrally) just before the fourth week of gestation, receives the mesonephric ductal system. The urorectal septum, which first appears during the fourth week of development, serves to separate the urogenital sinus (ventrally) from the anal canal (dorsally) (Moore and Persaud, 1995). The urorectal septum actually consists of two components. The first is the Tournoux fold, which develops along the coronal plane in the angle between the allantois and the hindgut and grows in a caudal fashion toward the cloacal membrane. As this septum nears the cloacal membrane, infoldings of the lateral walls of the cloaca form Rathke plicae, which coalesce in the coronal midline and form the urorectal septum caudally. By weeks 6 to 7 of development the urorectal septum has fused with the cloacal membrane and divided it into a ventral urogenital membrane and a dorsal anal membrane. The fibromuscular node of tissue that results from contact of the septum with the cloacal membrane serves as a critical insertion site for the perineal muscles and as the dividing point of the primitive cloacal sphincter complex into anterior (urogenital diaphragm) and posterior (external anal sphincter) components. **The common ontogeny of these two sphincter complexes explains why the pudendal nerve supplies all of these muscles.**

While the urorectal anlage is undergoing division, the developing mesonephric ducts, which have contacted the cloaca, enter the urogenital sinus near the müllerian tubercle (Churchill et al, 1978). An offshoot of the mesonephric duct, the ureteric bud, extends cranially to induce development of the metanephric blastema. The terminal branch point of the ureteral bud from the mesonephric duct is later absorbed into the wall of the urogenital sinus. Proper incorporation of this complex results in the ureters opening at the lateral aspect of the trigone.

During this critical phase of development, paired müllerian ducts, which form from the coelomic epithelium, develop lateral to the mesonephric ducts and cross medially to fuse in the midline. The close proximity of these two ductal systems helps explain the common association of paramesonephric abnormalities and ipsilateral renal anomalies. The paired müllerian ducts then proceed caudally to join the urogenital sinus, where they produce an elevation called the *müllerian tubercle*. The caudal fusion of portions of these ducts normally leads to dissolution of the shared midline partition and the formation of a common uterovaginal canal, which, as the name implies, gives rise to the uterus, cervix, and proximal two thirds of the vagina. Failure of septal regression can result in a number of possible müllerian duct abnormalities.

As first delineated by Koff in 1933 (Koff, 1933), contact of the uterovaginal primordium with the urogenital sinus forms the müllerian tubercle, which in turn induces the formation of paired caudal endodermal outgrowths called sinovaginal bulbs. Evidence suggests that these outpouchings may in fact represent the terminal segments of the wolffian ducts (Bok and Drews, 1983). Regardless of origin, the cells within these sinovaginal bulbs then proliferate to form a cord of tissue that develops into a distal vaginal plate, which is later canalized in a caudal-to-cranial direction to form the distal aspect of the vagina (Fig. 149-1). The portion of the urogenital sinus distal to the müllerian tubercle subsequently undergoes exstrophy and everts to become the vestibule. As a result of this process, the urethra and vagina acquire separate openings in the vulva. The lumen of the vagina is separated from the cavity of the urogenital sinus by the hymen, an invagination of the posterior wall of the urogenital sinus. Rupture of the hymen should occur during the perinatal period.

Various cystic structures may form along the luminal aspect of the vagina. Remnants of the prostatic ductal system and the wolffian duct give rise to the paraurethral glands of Skene and Gardner, respectively. Outgrowths from the urogenital sinus form the greater vestibular glands of Bartholin, which are homologs of the bulbourethral glands in the male.

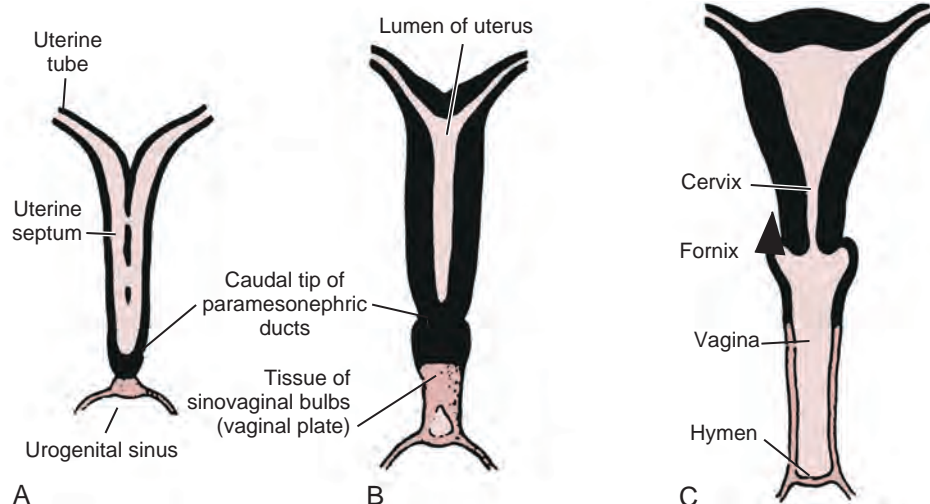


Figure 149-1. A to C, Formation of the vagina from the sinovaginal bulbs. (From Saler TW. Langman's medical embryology, 6th ed. Baltimore: Williams & Wilkins; 1990.)

Key events in skeletal formation occur concurrently with cloacal division and proper formation of the mesonephric and paramesonephric ductal systems (Churchill et al, 1978). The vertebrae develop in a craniocaudal direction, with the lower extremity limb buds developing from condensation of somites 25 through 29. These somites undergo critical differentiation from the fourth through the eighth weeks of development.

From the foregoing brief description of caudal embryology it should be evident that a disturbance in segmentation at the level of the caudal somites when the fetus is less than 10 mm (fourth to fifth weeks of human development) can affect many organ systems. In 1960, Duhamel (1961) described the association of these "coincidentally" occurring congenital malformations and introduced the term *caudal regression syndrome*. Laboratory data with teratogens support the concept that a key event occurs between the fourth and fifth weeks of gestation that results in an error in the simultaneous development of the terminal bowel, kidney, bladder, paramesonephric ductal system, and lumbosacral spine (Mesrobian et al, 1994). The actual inciting event remains unclear, although disordered mesodermal migration, reduced cellular proliferation, and premature apoptosis have been proposed as potential mechanisms (Kallen and Winberg, 1974; Alles and Sulik, 1993). Elements of the caudal regression syndrome are seen with increased frequency in infants of diabetic mothers, but the exact mechanism is still in question (Deuchar, 1978; Lynch et al, 1995). Specific gene deletions in the homeobox region of the mammalian genome (the region critical for proper mammalian spatial orientation and segmentation) have been shown to result in a constellation of anatomic findings, as predicted by Duhamel (Warot et al, 1997). Because differentiation of the somites progresses in a cranial-to-caudal direction, it would follow that the most complex anomalies (higher anorectal malformations) would occur as a result of aberrations at an earlier stage of development. This also helps explain the greater association of severe upper urinary tract malformations, internal genital duct abnormalities, and spinal anomalies in these patients than in those with less severe cases of imperforate anus.

Mesodermal disturbances are not limited to the caudal somites. As seen in the VATER (Vertebral defects, Anal atresia, Tracheoesophageal fistula with Esophageal atresia, and Radial and renal dysplasia) and MURCS (Müllerian duct aplasia, Renal aplasia, and Cervicothoracic Somite dysplasia) associations, mesodermally derived organs as cranial as the C1 vertebra and tracheoesophageal anlagen can be affected in association with congenital abnormalities of the mesonephric and paramesonephric ductal systems (Quan and Smith, 1973; Duncan et al, 1979).

KEY POINTS: FEMALE GENITAL EMBRYOLOGY

- The common ontogeny of the urogenital sphincter and the external anal sphincter explains why the pudendal nerve supplies both muscle complexes.
- The close proximity of the müllerian and wolffian ductal systems is responsible for the common association of paramesonephric abnormalities and ipsilateral renal anomalies.
- A disturbance in segmentation at the level of the caudal somites during the fourth or fifth weeks of development can result in a constellation of malformations involving the urogenital, skeletal, and gastrointestinal systems that are commonly referred to as the *caudal regression syndrome*.

EVALUATION AND CLASSIFICATION OF FEMALE GENITAL ANOMALIES

Structural anomalies of the vulva are numerous and varied. The differential diagnosis in the neonate and young child is broad and requires a thorough understanding of the diagnostic possibilities and a systematic evaluation. The age and racial background of the patient can help narrow the differential diagnosis, but physical examination remains the most useful tool for determining the specific pathology.

The physician must be sure to specifically reassure the girl that the examination will not be painful. With the child in the frog-leg position, the physician should note the size of the clitoris, the configuration of the hymen, the location of the urethra, and the character of the interlabial mass (e.g., smooth, lobulated, hemorrhagic). To aid in visualization, the labia majora can be gently grasped and pulled caudally and laterally to enable funneling of the introitus and vagina (the so-called pull-down maneuver) (Kaefer, 2010) (Fig. 149-2). Establishing the location of expected anatomic landmarks can facilitate determining the nature of a specific mass. In certain circumstances, the relationship of the mass to the vagina and urethra can be improved by gentle placement of a lubricated cotton applicator posteriorly or placement of a small feeding tube within the suspected urethral orifice, or both. Although an otoscope, nasal speculum, or pediatric vaginal speculum can be useful in evaluating the vagina while the patient is awake, complaints of vaginal origin (i.e., vaginal discharge or bleeding) are often best

investigated with a carefully performed examination and vaginoscopy under anesthesia. Renal-pelvic ultrasonography can be a useful adjunct in confirming or establishing the diagnosis in a few of these disorders.

Structural anomalies of the vagina can be grouped into three main categories: (1) those resulting from either hypoplasia or agenesis, (2) those caused by vertical fusion (canalization abnormalities resulting from abnormal contact of the müllerian

structures with the urogenital sinus), and (3) those resulting from lateral fusion (duplication). The clinical manifestations, physical findings, evaluation, and subsequent therapy vary considerably among these groups. Radiographic imaging is of central importance in determining the correct diagnosis. Ultrasonography is helpful not only in identifying the genital anatomy but also in screening for associated upper urinary tract abnormalities (Rosenberg et al, 1986; Fernandez et al, 1996). Magnetic resonance imaging (MRI) is considered by many to be the gold standard for defining müllerian anatomy (Fedeale et al, 1996; Russ et al, 1997; Lang et al, 1999). It is especially useful for determining the presence or absence of the cervix and the presence of functioning endometrium in complex anomalies. In complicated cases, additional information can be obtained by examination under anesthesia, vaginoscopy, hysteroscopy, and laparoscopy (Major et al, 1997). Obstructive anomalies typically require immediate intervention, but nonobstructive anomalies often do not require surgical intervention unless the patient has reached reproductive age and the condition affects intercourse or adversely affects fertility. Various systems have been proposed for the classification of these anomalies, with the system proposed by the American Society for Reproductive Medicine being the most inclusive (American Fertility Society, 1988).

CONGENITAL DISORDERS OF FEMALE EXTERNAL GENITALIA

Disorders of the Clitoris

Hypertrophied Clitoris

Clitoral hypertrophy is most commonly the result of excess androgenic metabolites arising secondary to an enzymatic defect in adrenal steroid synthesis (Fig. 149-3). The most commonly seen syndromes of congenital adrenal hyperplasia (CAH) result from a deficiency of either 21-hydroxylase or 11-hydroxylase. Some degree of clitoral enlargement can be appreciated in nearly every female patient with CAH. Although there is often concordance between the degree of clitoromegaly and the length of the common urogenital sinus, this does not always apply. Because the overwhelming majority of clitoral hypertrophy is secondary to CAH, any newborn noted to have this physical finding should undergo an evaluation of their serum electrolytes, 17-hydroxyprogesterone level, and karyotype. Replacement of glucocorticoids and mineralocorticoids will exert a negative feedback on the adrenal gland and thus eliminate further stimulation of the external genitalia from endogenously derived androgens. The role of surgery in this disorder is discussed elsewhere in this text.

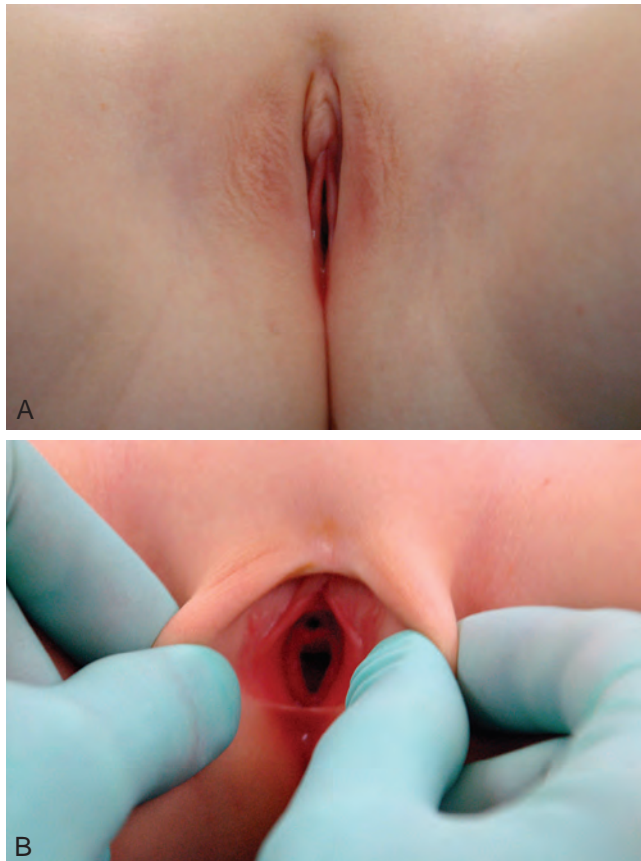


Figure 149-2. A and B, Photographs of the vaginal pull-down procedure. To aid in visualization of the female introitus, the labia majora are gently grasped and pulled caudally and laterally to enable funneling of the vagina.

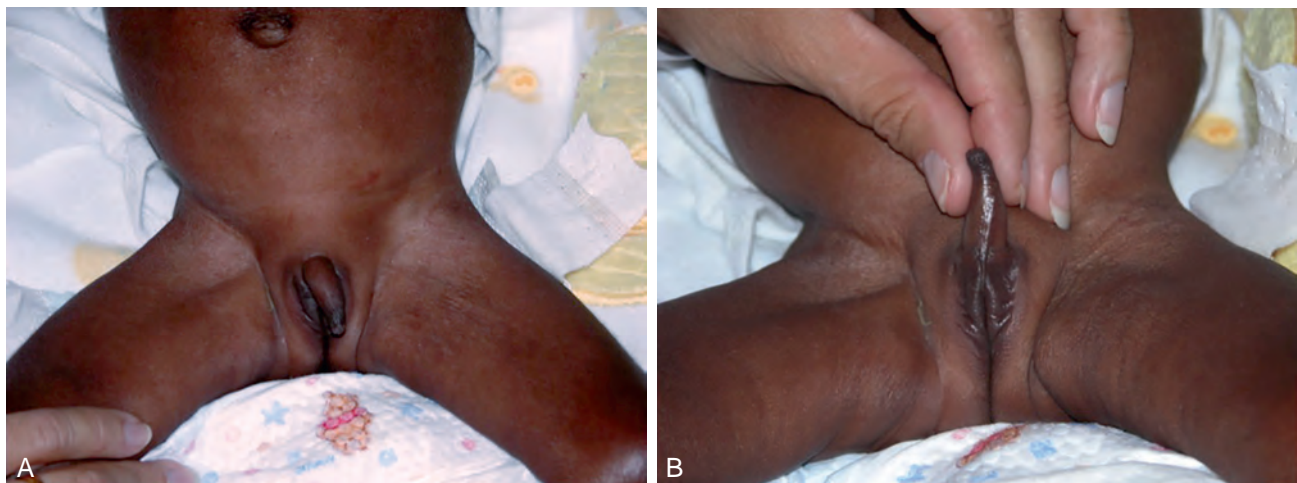


Figure 149-3. Clitoral hypertrophy in congenital adrenal hyperplasia.

Clitoral enlargement can result from other disorders. Endogenous androgen-producing tumors in the mother can result in stimulation of the fetal phallus. The presence of unilateral viable testicular tissue in a patient with Turner syndrome also has been reported (Haddad et al, 2003). Finally, local growth factor secretion from a neighboring plexiform neurofibroma in patients with neurofibromatosis has been reported on multiple occasions to result in clitoromegaly (Rink and Mitchell, 1983; Kearse and Ritchey, 1993; Kaefer et al, 1997; Yuksel et al, 2003; Cost et al, 2009).

Diminutive Clitoris

Small clitoral size is found in patients with complete androgen insensitivity syndrome (CAIS) (Fig. 149-4). One study evaluating 19 patients with known CAIS revealed a statistically significantly reduced mean clitoral length compared to that in controls (Crouch et al, 2011). In contrast, no difference was observed for the clitoral to urethral distance between the two groups.



Figure 149-4. Diminutive clitoris in complete androgen insensitivity syndrome.

Disorders of the Vestibule

Urethral Prolapse

Urethral prolapse generally involves complete circumferential eversion of the urethral mucosa at the level of the external urethral meatus (Fig. 149-5) (Lowe et al, 1986). This entity, which was first described by Solinger in 1732, occurs most often in prepubertal black girls and in postmenopausal white women (Epstein and Strauss, 1937; Richardson et al, 1982). Various causes that have been proposed for urethral prolapse include hypoestrogenism (Desai and Cohen, 1997), abnormal connections between the inner longitudinal and outer circular muscle layers of the distal urethra (Lowe et al, 1986), and episodic increases in intra-abdominal pressure (Lowe et al, 1986; Desai and Cohen, 1997; Valerie et al, 1999). The most common initial complaint is bleeding from the edematous and friable mucosa, which results in blood spotting on the underwear (Richardson et al, 1982; Chaouachi et al, 1989). Urethral prolapse is easily recognized as a doughnut-shaped mass with the urethral meatus at the center. If the diagnosis can be confirmed by passing a urethral catheter, radiographic evaluation is not indicated (Nussbaum and Lebowitz, 1983). Treatment options include observation, topical corticosteroids, and surgical excision (Redman, 1982; Fernandes et al, 1993). Sitz baths may be helpful. Nonoperative treatment may lead to spontaneous reduction of the prolapse, but a recurrence rate of up to 67% has been noted (Jerkins et al, 1984). Many methods of surgical repair have been described. Circumferential excision of the redundant mucosa with subsequent suturing of the normal urethra to the vestibule is the procedure of choice (Devine and Kessel, 1980). Other methods, including ligation over a transurethral catheter with subsequent sloughing and cryosurgery, should be discouraged (Owens and Morse, 1968; Klaus and Stein, 1973).

Urethral Polyp

The pediatric equivalent of a urethral caruncle, namely, a urethral polyp, is a rare lesion that can manifest as an interlabial mass (Fig. 149-6). The cause of these lesions has not been completely elucidated, but in a young child they probably represent either hamartomatous growth or a response to inflammation.

We described two young girls with an interlabial mass. Histologic examination of each excised mass revealed a benign urethral polyp covered with transitional and squamous epithelium (Klee et al, 1993). Urethral polyps should be included in the differential diagnosis of an interlabial mass in young female patients.

Vestibular Cysts

Introital cysts in the newborn can represent one of three entities: paraurethral cysts (i.e., Skene duct cyst), remnants of the mesonephric

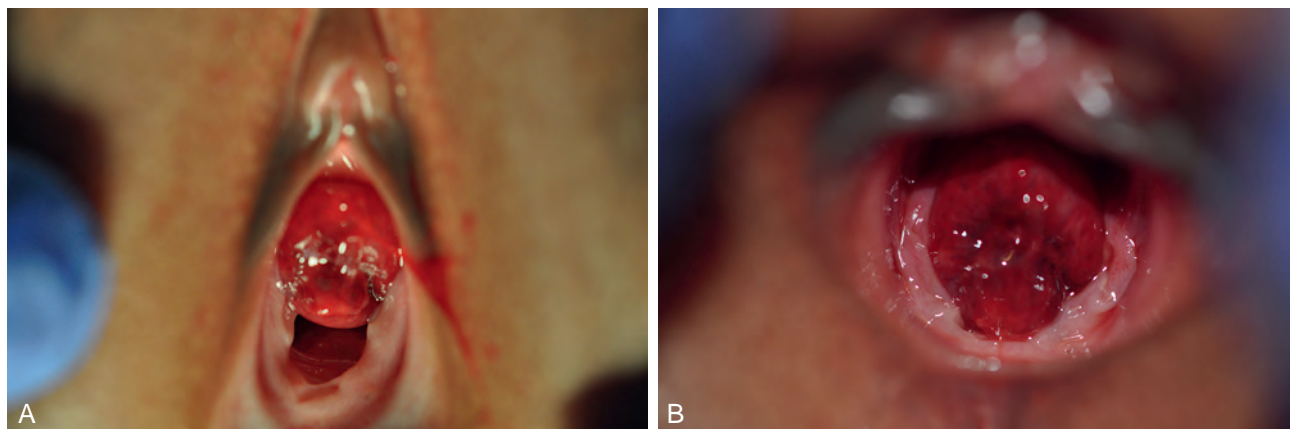


Figure 149-5. A and B, Urethral prolapse.



Figure 149-6. Urethral polyp. Probe in urethra and Babcock clamp on urethral polyp. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol* 2002;14:12.)



Figure 149-7. Paraurethral cyst. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol* 2002;14:12.)

ductal system (Gartner duct cyst), and a covered ectopic ureter. When the cyst is large and clearly emanating from the vaginal introitus, further investigation in the form of a renal-pelvic ultrasound evaluation is indicated to look for renal duplication.

Paraurethral cysts in a neonate represent a dilation of the periurethral glands, which are located just inside the urethral meatus (Fig. 149-7). These glands are homologs of the male prostatic



Figure 149-8. Retrograde injection of an ectopic ureter inserting into a Gartner duct cyst. After injection of a vaginal cyst, contrast agent ascends cranially into an atretic, dysplastic ureter.

glands and number between 6 and 30, with the two largest termed the *periurethral glands of Skene* (Skene, 1880; Gottesman and Sparkuhl, 1979). In a neonate the periurethral glands occasionally respond to maternal estrogen and secrete mucoid material, which can result in cyst formation. The main distinguishing feature of this condition is displacement of the urethral meatus by the mass and, consequently, an eccentric urinary stream. If the urethral meatus can be identified as being completely separate from the mass, radiographic evaluation is not needed to confirm the diagnosis (Nussbaum and Lebowitz, 1983). These cysts are frequently self-limited and often rupture spontaneously. If they are persistent, drainage by a small needle is easily achieved at the bedside.

Gartner duct cysts represent cystic remnants of the wolffian duct system and can be found along the anteromedial wall of the vagina (Pradhan and Tobon, 1986). A cystic structure related to a Gartner duct cyst is a covered ectopic ureter that enters into the vagina (Rosenfeld and Lis, 1993; Holmes et al, 1999). Embryologically, the ureter would not be expected to enter the vagina. However, an ectopically located ureter may end in a segment of the wolffian duct system, which in a female is represented by a Gartner duct cyst. In most instances this cystic structure spontaneously ruptures before delivery, thereby resulting in direct communication between the ectopic ureter and the vagina. However, if the surface epithelium fails to rupture, a covered, urine-filled cyst will exist within the vagina. Intraoperative injection of the cystic structure with radiographic contrast material may be beneficial in outlining the anatomy (Fig. 149-8). Incision of the cystic structure relieves the obstruction. As a general rule, the more ectopic the insertion of the ureter, the more dysplastic will be the segment that it drains. However, renal moieties that ectopically insert into the vagina may produce urine. Subsequent upper pole heminephrectomy may be indicated if the child has significant urine production from the segment (resulting in incontinence) or an infection develops after decompression.

Prolapsed Ureterocele

An ectopic ureterocele is a cystic dilation of the terminal portion of the ureter that occurs predominantly in white females (Mandell et al, 1980). Approximately 90% of ectopic ureteroceles are associated with the upper pole of a duplex collecting system. Although

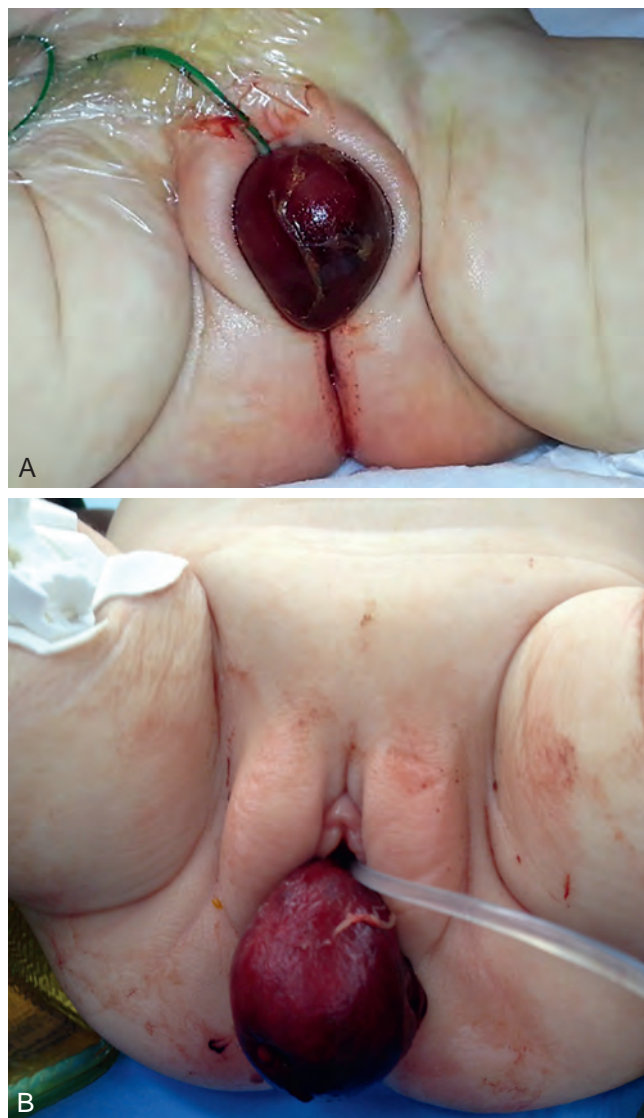


Figure 149-9. A, Prolapsed ureterocele. B, Prolapsed ureterocele with catheter inserted in the urethra.



Figure 149-10. A ureterocele evident on ultrasonography of the bladder. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol* 2002;14:12.)



Figure 149-11. Ectopic ureter to vestibule.

they normally remain positioned proximal to the bladder neck, some may prolapse through the urethra during micturition, almost always in infancy, and result in urinary retention and a relative urologic emergency (Gingell et al, 1971). Depending on the length of time that the ureterocele has been prolapsed, it may vary in color from pink to dusky purple (Fig. 149-9). If a prolapsed ureterocele is in the differential diagnosis, bladder-renal ultrasonography should be performed to look for upper pole hydronephrosis in a duplicated collecting system (Fig. 149-10).

Treatment of a prolapsed ureterocele consists of either needle decompression or incision and reduction and then placement of a urethral catheter. Although this occasionally can be achieved in the emergency department setting, abdominal straining by the infant may make this procedure difficult, and treatment under general anesthesia often is preferable. Injection of radiographic contrast material into the ureterocele can be helpful in identifying the relevant anatomy.

Ectopic Ureteral Insertion

In females an ectopic ureter may enter distal to the urethral sphincter. Ectopic ureters to the vestibule are typically associated with

diurnal incontinence in the presence of normal voiding habits (Fig. 149-11). Most commonly the ureter subtends an upper pole of a duplex system. However, single-system ectopic ureters also may manifest in this fashion and on occasion can be associated with apparent complete absence of the kidney. A thorough search for an ectopic kidney at times may prove fruitful in identifying the cause of the patient's wetting (Borer et al, 1998).

KEY POINTS: DISORDERS OF THE CLITORIS, VESTIBULE, AND URETHRA

- A diminutive clitoris is seen in patients with CAIS.
- Most children with labial adhesions do not require treatment unless they are symptomatic.
- Workup for a child with an introital (interlabial) mass that appears to be associated with the urethra always should include renal-pelvic ultrasonography.
- Urethral prolapse occurs most often in prepubertal black girls and in postmenopausal white women.

Disorders of the Vagina***Imperforate Hymen and Hymenal Skin Tags***

Hymenal skin tags are virtually a normal finding and are rarely symptomatic (Fig. 149-12). When symptomatic (i.e., bleeding), they should be excised to ensure that they do not represent a malignancy and to provide symptomatic relief. Congenital abnormalities of the hymen are not uncommon and range from an imperforate hymen to one with numerous small microperforations.

Imperforate hymen is probably the most common congenital obstructive anomaly of the female reproductive tract. The diagnosis is most frequently made at birth by noting the presence of a bulge along the posterior aspect of the introitus, which represents retained fluid within the vagina, or by palpation of a suprapubic mass from a distended vagina (Fig. 149-13). The buildup of retained vaginal secretions in the neonatal period, which imparts a whitish appearance to the bulging hymenal membrane, is caused by maternal estradiol stimulation. If the diagnosis is made after the neonatal period, the mucus often will have been reabsorbed and a bulge in the hymenal membrane may no longer be evident. On occasion, the diagnosis is not made until the adolescent period, when the patient experiences amenorrhea and possibly cyclic abdominal pain. In these circumstances, a bluish bulging hymen may be observed on genital inspection and a mass will be appreciated on rectoabdominal palpation. In newborns, repair by incision of the hymenal tissue at the bedside is performed in the transverse direc-

tion to avoid inadvertent extension of the incision anteriorly or posteriorly (which might injure the urethra or rectal structures). Simple aspiration of the vagina without a definite drainage procedure should be discouraged because incompletely evacuated material may be prone to ascending bacterial growth. In pubertal girls, general anesthesia with excision of excess hymenal tissue may be indicated (Fig. 149-14).

Acquired abnormalities of the hymenal ring usually result from sexual abuse. The associated finding of a hematoma, abrasion, or laceration in combination with hymenal transection should raise the possibility of this diagnosis. Proper examination under anesthesia and forensic swabbing of affected areas should be undertaken with the use of a standardized protocol.

Abnormalities of Vertical Fusion

Transverse Vaginal Septum. Transverse vaginal septa are believed to arise from a failure in fusion or canalization (or



Figure 149-13. Imperforate hymen. Note the significant distention from vaginal secretions.



Figure 149-12. Hymenal skin tag.



Figure 149-14. Intraoperative photograph showing incisional drainage of an imperforate hymen. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol* 2002;14:12.)

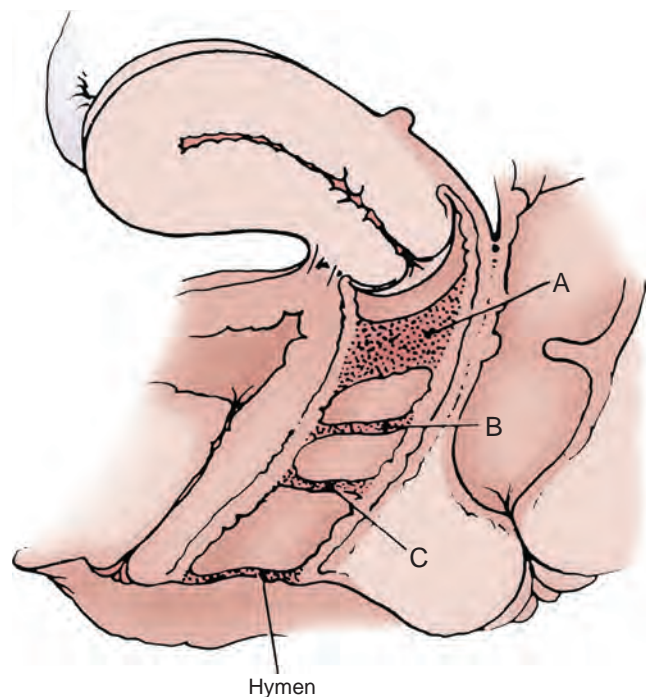


Figure 149-15. Transverse vaginal septum. A, High (upper vagina). B, Middle. C, Low.

both) of the urogenital sinus and müllerian ducts. The estimated incidence of transverse vaginal septum is 1 in 70,000 females (Banerjee and Laufer, 1998). Many of the patients have amenorrhea and a distended upper vagina. A complete transverse vaginal septum may be located at various levels in the vagina, but there is a higher frequency in the middle and upper third of the vagina. In one large series the distribution was 46% in the upper vagina, 40% in the middle vagina, and 14% in the lower vagina (Fig. 149-15) (Lodi, 1951). The septa are usually less than 1 cm thick and frequently have a small central or eccentric perforation (Suidan and Azoury, 1979). Even in cases in which a perforation is present, significant obstruction and ascending infection can occur. Transperineal, transrectal, and abdominal ultrasonography and MRI may be beneficial in establishing the diagnosis and determining the location and thickness of a transverse vaginal septum (Ammann et al, 1983; Doyle, 1992; Meyer et al, 1995; Caloia et al, 1998; Fedele et al, 1999; Lang et al, 1999). MRI can help determine whether a cervix is present so that a high septum can be differentiated from congenital absence of the cervix. Failure to differentiate between these diagnoses can result in significant patient morbidity (Casey and Laufer, 1997).

Several surgical treatment modalities have been developed to treat congenital transverse vaginal septa. If the patient's pain from hematocolpos is manageable, surgery may be delayed with suppression of endometrial activity by a gonadotropin-releasing hormone (GnRH) agonist or continuous oral contraceptives (Beyth et al, 2004). This may allow time for dilation of the lower vaginal segment, potentially improving the ease of surgical repair. Techniques include simple incision (Brenne et al, 1965; Buttram, 1983), surgical excision of the septum followed by approximation of the corresponding portions of the transversely cut edges of the upper and lower mucosal membranes of the septum (Rock et al, 1982) and the use of Z-plasties involving vaginal mucosa (Wierrani et al, 2003). Recently we described a method that improves the safety of entering the obstructed vaginal segment and subsequently excising the septum (Keenan and Kaefer, 2010). Under ultrasound guidance a 14-gauge angiocatheter is placed through the thick transverse septum. After aspiration reveals thick blood, a 0.35-mm Sensor wire (Boston Scientific, Marlborough, MA) is placed through the angiocatheter and the NephroMax (Boston Scientific) balloon dilating

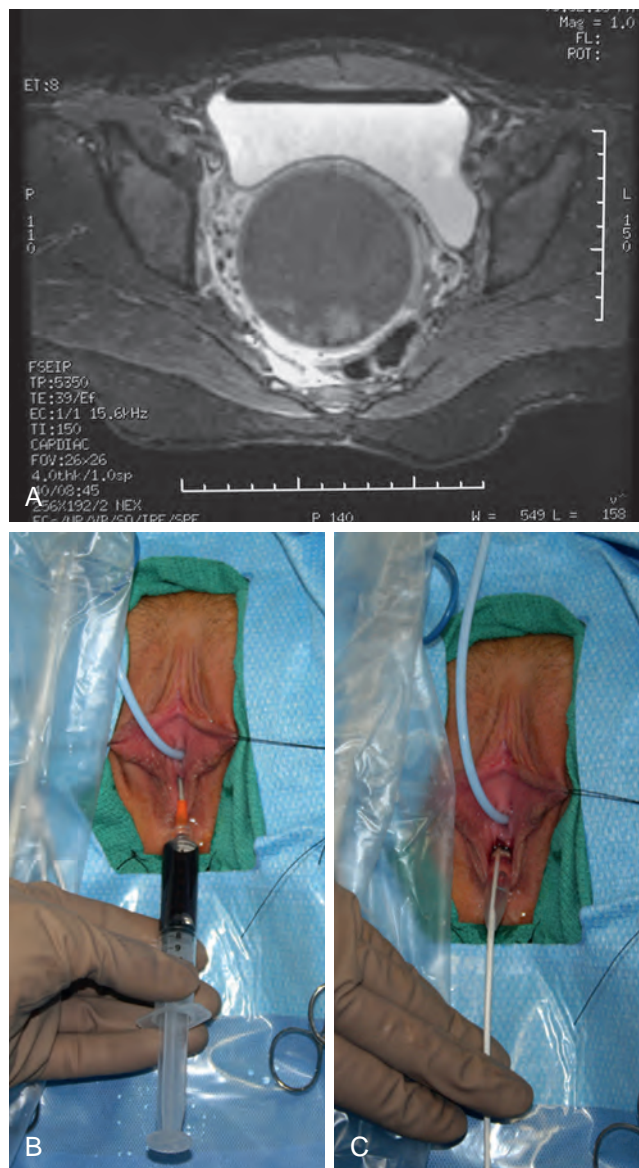


Figure 149-16. Balloon-assisted division of transverse vaginal septum. A, Hematocolpos on magnetic resonance imaging resulting from transverse vaginal septum. B, Angiocatheter placed into transverse vaginal septum (placed under ultrasound guidance). C, NephroMax balloon dilating the septum.

system is placed over the wire. The balloon is insufflated and subsequently removed, providing a generous aperture through which the remainder of the septum can be excised (Fig. 149-16).

Vaginal stenosis at the site of resection is the most common complication (Joki-Erkila and Heinonen, 2003). The primary advantage of a Z-plasty is that as the suture line contracts the incision is more likely to take on a longitudinal rather than a transverse orientation. Placement of a vaginal mold subsequent to surgery has been reported to further reduce the risk for postoperative stenosis (Bijsterveldt and Willemsen, 2009). Characteristics of molds for transverse septa are different from those used after a McIndoe vaginoplasty (see later). Whereas a solid mold may be used after a vaginoplasty skin graft (because there is no uterus), the mold used after resection of a transverse septum is ideally hollow, to allow egress of menstrual flow.

Vaginal Atresia (Distal Vagina). Vaginal atresia occurs when the urogenital sinus fails to contribute to formation of the lower (distal) portion of the vagina. This condition differs from vaginal

agenesis and testicular feminization in that the müllerian structures are not affected. As a result, the uterus, cervix, and upper portion of the vagina are normal. A very shallow dimple caudal to the urethral opening may be appreciated on physical examination. Palpation of a distended vagina on rectal examination may help distinguish this condition from testicular feminization or vaginal agenesis. Radiographic evaluation in the form of ultrasonography or MRI, or both, is mandatory to adequately define the müllerian anatomy before intervention.

Surgical correction consists of a transverse incision at the level of the hymenal ring. Dissection is carried out through the fibrous area of the absent lower vagina until the upper vagina is reached. As in treatment of a transverse vaginal septum, distention of the vagina with retained menstrual blood products can prove extremely beneficial in that it acts as a tissue expander. After the obstruction is drained and the vaginal mucosa is identified, a pull-through procedure can be performed to bring the distended vagina down to the introitus. The distance to bridge between the vagina and the perineal surface almost always can be successfully managed with perineal skin flaps or simple mobilization of the vagina (or both). [Ramenofsky and Raffensperger \(1971\)](#) described a combined abdominoperineal approach that can be of help in exposing and anastomosing the distal vagina to the perineal skin.

Vaginal Agenesis (Müllerian Aplasia). Vaginal agenesis, which occurs at an incidence of approximately 1 in 5000 live female births, is congenital absence of the proximal portion of the vagina in an otherwise phenotypically (i.e., normal secondary sexual characteristics), chromosomally (i.e., 46,XX), and hormonally (i.e., normal levels of luteinizing hormone and follicle-stimulating hormone) intact female ([Bryan et al, 1949](#); [Griffin et al, 1976](#)). Although Renaldus Columbus is credited by some authors as the first to describe a case of vaginal agenesis, [Mayer \(1829\)](#) was one of the first to report vaginal agenesis in stillborn children ([Lesavoy, 1985](#)).

In 1838, [Rokitansky \(1838\)](#) reported 19 adult autopsy cases of uterovaginal agenesis, including 3 with associated unilateral renal agenesis. In 1910, [Küster \(1910\)](#) recognized urologic associations, such as renal ectopy and agenesis, along with skeletal deformities. [Hauser and Schreiner \(1961\)](#) brought further attention to the frequent association of renal and skeletal anomalies in these patients and stressed the differences between patients with these findings and those with testicular feminization.

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, as the entity of müllerian aplasia has come to be known, results from failure of the sinovaginal bulbs to develop and form the vaginal plate ([Fig. 149-17](#)). This may be caused by improper induction of the sinovaginal bulbs from the neighboring uterovaginal primordium. Chronologically, the uterovaginal canal develops at a point in embryogenesis during which other critical mesodermally derived organ systems are also forming, which in part explains the many associated findings. Müllerian aplasia also has been associated with maternal deficiency of galactose-1-phosphate uridylyltransferase ([Cramer et al, 1996](#)). In contrast to vaginal atresia, the hymenal fringe is usually present, along with a small vaginal pouch, because they are both derived embryologically from the urogenital sinus. Most patients with MRKH syndrome are initially evaluated by the physician after the expected age of menarche because of primary amenorrhea. This syndrome is in fact second only to gonadal dysgenesis as a cause of primary amenorrhea. A minority of patients have cyclic abdominal pain caused by retention of menstrual blood in the uterus. Physical examination reveals absence of the vagina. Inguinal hernia is less common in this disorder than in the testicular feminization syndrome ([Schmid-Tannwald and Hauser, 1973](#)). The karyotype is that of a normal 46,XX woman. Radiographic evaluation is indicated to more fully delineate remnant müllerian structures and search for associated anomalies involving the renal and skeletal systems.

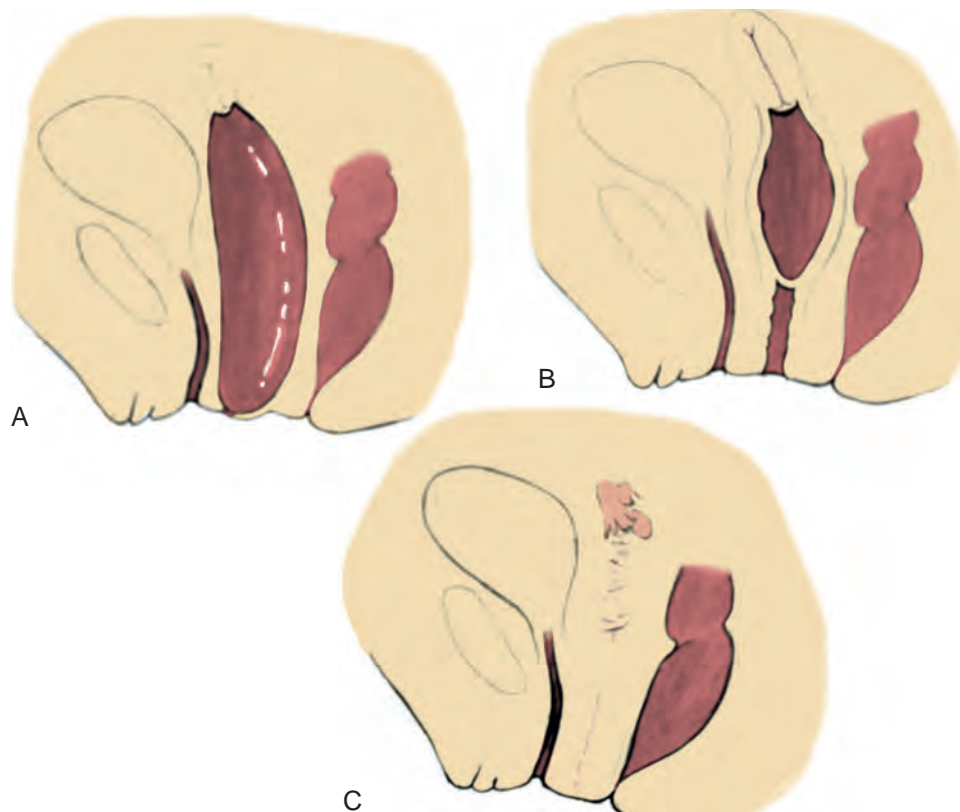


Figure 149-17. Forms of vaginal obstruction. A, imperforate hymen; B, transverse vaginal septum; C, vaginal agenesis. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol* 2002;14:12.)

Associated Findings. MRKH syndrome is associated with variable absence or hypoplasia of the cervix, uterus, and fallopian tubes. In approximately 10% of patients, a normal but obstructed uterus or a rudimentary uterus with functional endometrium is present (Murray and Gambrell, 1979; Singh and Devi, 1983; Bates and Wiser, 1985). In one of the largest single series to date, Salvatore and Lodovici (1978) reported that of 91 patients with vaginal agenesis, almost 25% lacked a uterus, 55% had a solid rudimentary uterus, and the remaining 30% had other abnormalities of this organ. In addition, they demonstrated that although the fallopian tubes were normal in 32% of cases, they were rudimentary in almost 50% and completely absent in 10%. Although occasionally cystic, the ovaries were almost always present and functional (Salvatore and Lodovici, 1978). It was subsequently recognized, based on the morphology of the retained müllerian structures, that MRKH syndrome could be divided into typical and atypical forms (Schmid-Tannwald and Hauser, 1977).

In the typical form of MRKH syndrome (type A), the patient has symmetrical uterine remnants and normal fallopian tubes. The atypical form (type B) is characterized by asymmetrical uterine buds or abnormally developed fallopian tubes. This distinction is important because the overwhelming majority of associated findings in other organ systems have been reported to be present with the atypical form, whereas in the typical form these findings are usually absent (Strubbe et al, 1992, 1993).

The association between vaginal agenesis and developmental abnormalities of the kidney was first recognized by Rokitansky (1838). Approximately a third of patients are found to have abnormal renal findings on intravenous pyelography or ultrasound examination (Strubbe et al, 1993). Renal anomalies are present almost exclusively in patients with the atypical subtype of vaginal agenesis (type B). In the series by Strubbe and colleagues (1993), 34 of 51 patients with type B anatomy had renal anomalies, but none of the 40 patients with type A (symmetrical) anatomy demonstrated such a deformity. A meta-analysis published by Griffin and associates (1976) demonstrated that the renal anomaly consists of either unilateral renal agenesis or ectopia of one or both kidneys in 74% of those affected. The close proximity of the mesonephric and paramesonephric structures during the early phase of fetal development is thought to be the reason for this frequent association of renal anomalies. Not surprisingly, the converse is also true: the incidence of associated genital abnormalities in female patients with renal anomalies ranges between 25% and 89% (Thompson and Lynn, 1966).

Associated congenital abnormalities of the skeletal system have been described in 10% to 20% of cases (Turunen, 1967; Willemssen, 1982; Strubbe et al, 1987). Congenital fusion (failure of segmentation) of the cervical vertebrae is known as the Klippel-Feil syndrome and occurs approximately once in 30,000 to 40,000 live births (Gunderson et al, 1967). An association between this abnormality of cervical somite development and vaginal agenesis was first recognized by Duncan (1977). He proposed the term *MURCS association* to describe the combination of müllerian duct aplasia, Renal aplasia, and Cervicothoracic Somite dysplasia, which many believe is caused by a generalized disordered development of mesodermal differentiation during the fourth week of fetal life (Duncan et al, 1979). Strubbe and colleagues (1992) demonstrated that the Klippel-Feil abnormality was found only in patients with the atypical form of MRKH syndrome (type B). Additional, albeit less common, skeletal abnormalities include scoliosis and abnormalities of the hands and face (Willemssen, 1982; Fisher et al, 2000). Unlike müllerian anomalies that are associated with abnormal cloacal septation, vaginal agenesis is not associated with an increased incidence of lumbosacral spinal disorders or occult spinal dysraphism (Gunderson et al, 1967).

Vaginal Replacement Surgery

Creation of a Skin Neovagina. Both nonoperative and operative treatment options exist for this anomaly. Regardless of the method used, it can be very helpful to have the patient speak with someone who has previously undergone treatment before treatment is initiated (Ingram, 1981). The nonoperative approach, initially popu-

KEY POINTS: DISORDERS OF THE VAGINA

- Anomalies of the female reproductive system can be grouped into three main categories, those resulting from (1) hypoplasia or agenesis, (2) vertical fusion, and (3) lateral fusion.
- Transverse vaginal septa are believed to arise from a failure in fusion or canalization (or both) of the urogenital sinus and müllerian ducts.
- Vaginal atresia occurs when the urogenital sinus fails to contribute to formation of the lower (distal) portion of the vagina.
- Vaginal agenesis is congenital absence of the proximal portion of the vagina in an otherwise phenotypically, chromosomally, and hormonally intact female.
- MRKH syndrome, as the entity of müllerian aplasia has come to be known, results from failure of the sinovaginal bulbs to develop from the vaginal plate.

larized by Frank (1938), involves gentle pressure of graduated hard dilators against the perineal surface to create a progressive invagination of the vaginal dimple. Ingram (1981) modified this technique by using a bicycle seat mounted on a stool. The nonoperative approach has greatest success when a vaginal dimple or pouch is already present (Williams et al, 1984, 1985). Gargollo and colleagues (2009) recently reported their experience with 69 females (mean 17.5 years) with vaginal agenesis treated with progressive perineal dilation. Success, defined as the ability to achieve sexual intercourse, vaginal acceptance of the largest dilator without discomfort, or a vaginal length of 7 cm, was achieved in 88% of patients. The authors concluded that progressive perineal dilation should be offered as first-line therapy in adolescents with congenitally absent vagina.

Modifications of the Frank technique of perineal pressure have been developed that incorporate the surgical placement of tension sutures to aid in directing pressure from a Plexiglas dilator against the vaginal dimple (Vecchietti, 1979). The mold, often referred to as an "olive," has sutures attached to it that are guided in a cranial direction through the vesicorectal space into the perineal cavity and brought out through the abdominal wall (Vecchietti technique). Tension is progressively increased via the abdominal wall sutures until sufficient vaginal length has been achieved. To avoid a formal laparotomy, laparoscopic techniques have been described to assist in dissection of the tissue plane for the Vecchietti technique (Borruto, 1992; Gauwerky et al, 1992; Fedele et al, 1996, 1999; Brucker et al, 2008). In the more recent series by Fedele and colleagues (2006), all patients were found to have healthy vaginal mucosa, with the average vaginal length being almost 8 cm at 3 months. This had limited use by urologists.

If the Frank method has been unsuccessful or is not accepted as a reasonable option by the patient or parents, creation of a functional vagina can be achieved by one of several techniques (Abbé, 1988; McIndoe and Banister, 1938; Hendren and Atala, 1994). The first landmark advance in vaginal reconstruction is attributed to Abbé in 1898. Abbé described dissecting a canal between the rectum and urethra and lining this area with split-thickness skin grafts. This method was later popularized by McIndoe, and the procedure that bears his name has gained wide acceptance in the United States (McIndoe and Banister, 1938). Preoperative preparation consists of full mechanical and antibiotic bowel preparation. A split-thickness skin graft is taken from the buttocks (0.018 to 0.022 inch) and tubularized over a stent (Fig. 149-18). A transverse incision is made at the level of the perineal dimple, and the potential space between the urethra and the rectum is carefully dissected up to the level of the peritoneal reflection. The graft and mold are then inserted into the potential space, and the labia minora are sutured around the stent to prevent extrusion during the initial healing phase (McIndoe, 1950). Many types of vaginal stents have been used for this purpose, including packed gauze, wood covered with a condom, silicone foam, acrylic, various metals, and an

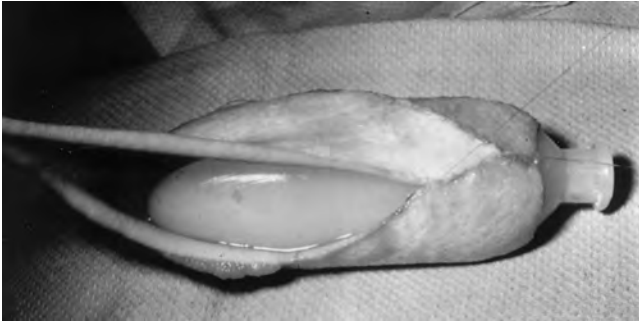


Figure 149-18. McIndoe skin vagina sewn over a vaginal stent.

inflatable vaginal stent (Concannon et al, 1993; Chen, 1994; Barutcu and Akguner, 1998). The Foley catheter is replaced by a suprapubic catheter, and postoperatively the patient is kept at strict bed rest for 1 full week. A high incidence of postoperative vaginal stenosis necessitates postoperative vaginal dilation (Ingram, 1981). Excellent patient satisfaction has been reported in most large series (Martinez-Mora et al, 1992; Strickland et al, 1993; Alessandrescu et al, 1996).

Other options for creation of a neovagina with local tissues include the use of full-thickness skin grafts from the buttocks or full-thickness skin flaps based on the labia majora. Those who champion the use of full-thickness skin grafts report a lower incidence of graft contracture than when split-thickness graft techniques are used (Sadove and Horton, 1988). The Williams (1964) vaginoplasty involves the creation of a vaginal pouch from the labia majora. The combination of this procedure and Frank-type dilation along the vaginal axis can provide a satisfactory result.

Many other surgical procedures have been developed for creation of a functional neovagina with various muscle flaps (e.g., pudendal thigh, rectus abdominis, buttock) (McCraw et al, 1976; Lilford et al, 1989; Dumanian and Donahoe, 1992; Wang and Hadley, 1993; Joseph, 1997). The pelvic peritoneum and human amnion are two other donor sites that have been used to create a neovagina (Davydov, 1977; Ashworth et al, 1986; Morton and Dewhurst, 1986; Tamaya and Imai, 1991; Marquis et al, 2008).

Creation of an Intestinal Neovagina. Baldwin first described the use of bowel for creation of the vagina in 1907. The procedure involved anastomosis of a U-shaped segment of sigmoid colon to the perineum with subsequent division of the intervening septum (Hensle and Dean, 1992). Additional experience with this technique was reported by Fall in 1940, but it did not gain widespread acceptance until the 1970s because of high patient morbidity and mortality (Fall, 1940; Pratt, 1972). Subsequent improvements in technique and postoperative care resulted in renewed enthusiasm for these techniques (Turner-Warwick and Kirby, 1990; Hendren and Atala, 1994; Hensle and Reiley, 1998; Tillem et al, 1998). Sigmoid, cecum, and small intestine have been used successfully for the creation of a functional neovagina.

The day before surgery, the patient undergoes full mechanical and antibiotic cleansing of the alimentary tract. The procedure is performed with the patient supine, the legs spread, and the knees bent (frog-leg position). In an older child, Allen stirrups can be used. For a sigmoid vaginoplasty, the intra-abdominal portion of the procedure begins by first identifying an appropriate length of distal sigmoid with a blood supply that will comfortably reach the perineum (Fig. 149-19). The distal end of the proposed segment is then divided and anastomosed to the perineum (Fig. 149-20). An intervening segment of sigmoid (~3 cm) is then excised to create a space between the oversewn proximal edge of the bowel vagina and the end of the sigmoid, which is anastomosed to the rectum. This maneuver prevents an overlap of suture lines and thereby has the potential advantage of limiting the incidence of fistula formation. The bowel vagina is thereafter fixed to the posterior peritoneum to prevent prolapse. Gosalbez (personal communication, 2009) described a modified Monti technique of bowel detubularization

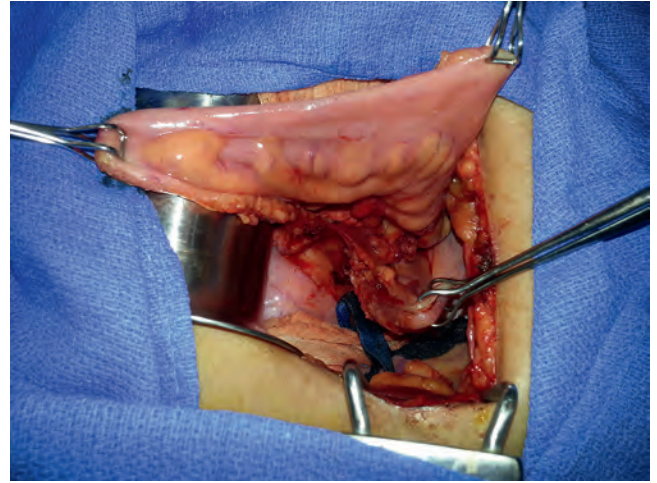


Figure 149-19. Sigmoid segment harvested for bowel vagina. Clamp on peritoneum.

for vaginal replacement that can aid in allowing the segment to reach the perineum. By opening the colonic segment close to its mesentery along one side of the bowel and then retubularizing in a Heineke-Mikulicz fashion, as described by Monti, the reconfigured segment allows for the mesentery to be located at the most cranial end of tube and allows the caudal end to extend more distally.

Although we have had the most success with the sigmoid, a small-bowel segment may be chosen with a vascular pedicle that is of adequate length to reach the perineum. After isolating an appropriate length of ileum and reestablishing bowel continuity, the segment is detubularized and reconfigured in a conical arrangement to provide increased internal diameter (Hendren and Atala, 1994). The segment is then brought down to the perineum and sewn in place, as for a sigmoid neovagina. To avoid a formal laparotomy, laparoscopically assisted techniques have been described for harvest and delivery of the bowel segment to the perineal location (Ota et al, 2000).

If there is a perineal dimple (i.e., the segment of vagina contributed by the urogenital sinus is present), the bowel segment should be anastomosed directly to it. When a direct perineal anastomosis is required, it is of critical importance to create a large enough space between the rectum and bladder to avoid compromise of the intestinal blood supply. Creation of such a space can be facilitated by the use of progressively larger Hegar dilators. Gentle passage of the intestinal segment into position is facilitated by placing the segment in a large lubricated Penrose drain before transfer to the perineum.

The functional results of bowel vaginoplasty have been excellent. Of the 65 patients reported by Hendren and Atala (1994), 16 experienced mild eversion of the bowel segment, which in every case was amenable to simple trimming. Eight patients experienced mild stenosis that was later corrected by appropriate Z-plasties to increase the circumference of the mucocutaneous junction. Patient satisfaction is high, and the majority of patients who are old enough to engage in sexual relations are able to achieve adequate coitus (Hensle and Reiley, 1998).

Stenosis has been reported more frequently after the use of ileum (Hensle and Dean, 1992). This higher stenosis rate may be due not only to the more narrow ileal lumen but also to the limited mobility of the small bowel mesentery. As a result, the authors and others believe that large intestine is the bowel segment of choice. Two specific indications for use of an ileal segment for bowel vaginoplasty are previous irradiation of the deep pelvis and the absence of large intestine (i.e., cloacal exstrophy). When ileum is used, various methods of reconfiguration can be used to increase the diameter (Hendren and Atala, 1994). Advantages of a bowel vagina over the McIndoe procedure include the lubricating properties of mucus (which may help facilitate

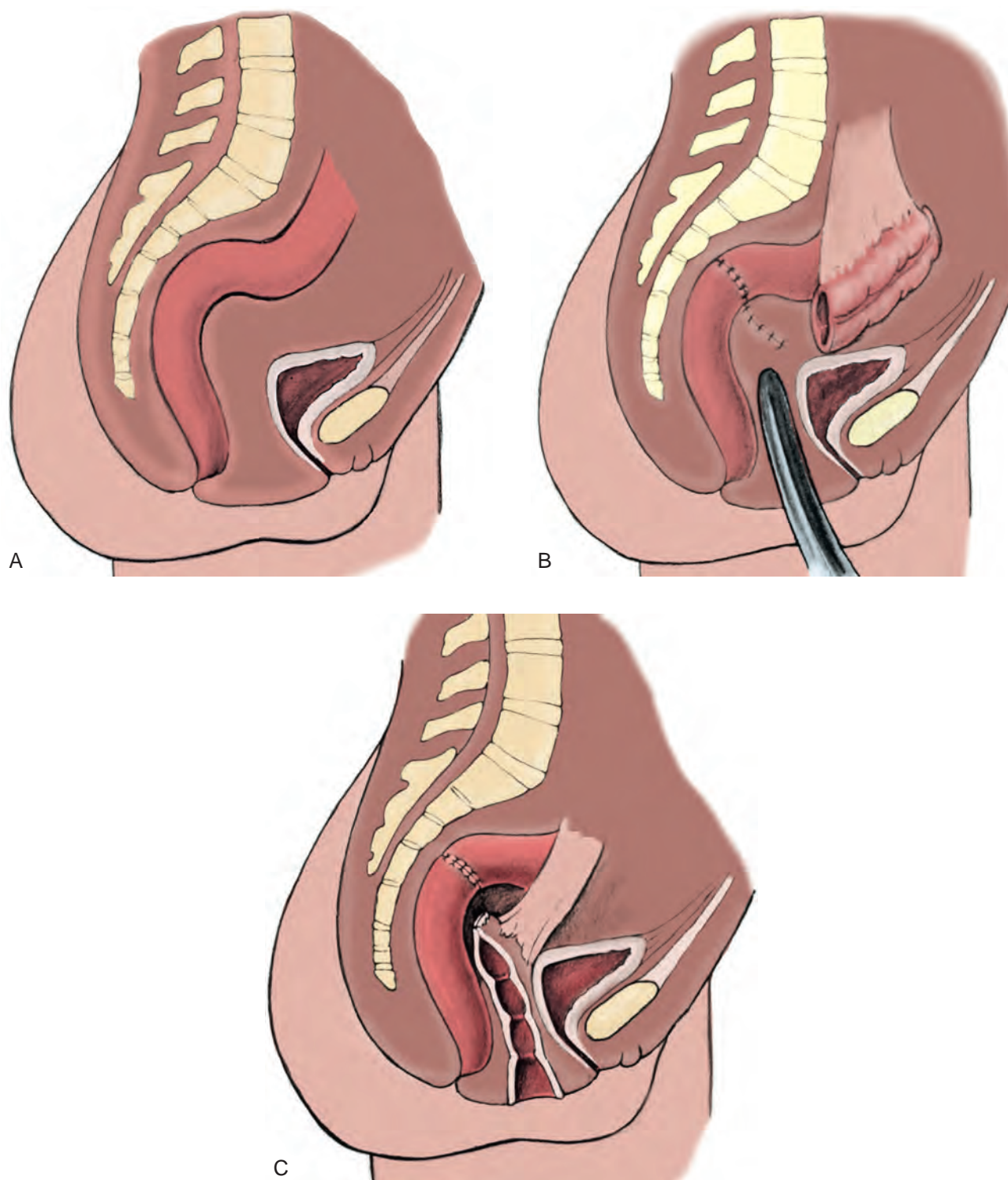


Figure 149-20. A, Vaginal agenesis. B, Harvest of colonic segment and creation of vaginal space. C, Colonic segment sewn in place.

intercourse) and the decreased incidence of postoperative contracture (and hence the reduced need for postoperative dilation). Disadvantages include the frequent need to wear pads because of the chronic vaginal discharge. Daily douching may be necessary to evacuate the mucus. Finally, the potential transmission of blood-borne pathogens such as hepatitis and human immunodeficiency virus may be increased (in comparison to a squamous epithelium-lined vagina) because of the poor barrier effect of the gastrointestinal tract.

All patients undergoing creation of a functional vagina with perineal skin require annual examination because there have been reports of condylomata acuminata and squamous cell carcinoma involving grafts (Duckler, 1972; Rotmensch et al, 1983; Buscema et al, 1987). Annual examination of the bowel vagina is also indicated because adenocarcinoma has been identified after this procedure (Andryjowicz et al, 1985).

The optimal timing of surgery remains a source of debate. The majority of surgeons who favor the McIndoe procedure for

construction of a neovagina think it is better to wait until adulthood to perform the procedure because a degree of maturity is required to consistently perform daily dilations. Many surgeons who favor the use of bowel for neovaginal reconstruction do not think vaginoplasty should be deferred until the patient reaches adulthood. [Hendren and Atala \(1994\)](#) think that delaying creation of a neovagina until adulthood may be psychologically traumatic to a young girl. The authors have based timing on the underlying diagnosis and need for a neovagina.

Special Considerations: Cervical Atresia. Cervical agenesis is an uncommon disorder that is associated with symptoms common to other obstructive entities of the female reproductive tract (i.e., primary amenorrhea, cyclic or chronic abdominal pain). Failure to establish the correct diagnosis and thereby choose the appropriate method of surgical intervention can be fraught with disaster and possible patient mortality. MRI is the most useful radiographic modality in establishing this diagnosis ([Fig. 149-21](#)). In many circumstances the patient is best served by hysterectomy with subsequent vaginal replacement by one of the previously described techniques ([Rock et al, 1982](#); [Cukier et al, 1986](#)). Successful direct anastomosis of the neovagina to the uterine remnant has been reported. [Deffarges and coworkers \(2001\)](#), in describing their experience with uterovaginal anastomosis, reported a 40% pregnancy rate in patients attempting to conceive. Cerclage was performed in only one case. All deliveries were by cesarean section. Although this procedure appears to be successful in the majority of cases, absence of the normal endocervical barrier can leave the patient predisposed to the development of life-threatening ascending infection ([Maciulla et al, 1978](#); [Niver et al, 1980](#); [Casey and Laufer, 1997](#)).

In cases in which it has not been possible to successfully achieve continuity between the uterus and vagina, in vitro fertilization plus transmyometrial embryo transfer has been performed, with subsequent delivery of a healthy fetus by cesarean section ([Anttila et al, 1999](#); [Lai et al, 2001](#)). If this option is considered, hormonal blockade of the endometrium until the time at which the patient desires to initiate a pregnancy is indicated to minimize discomfort and reduce the incidence of endometriosis from retrograde menstrual flow in the fallopian tubes.

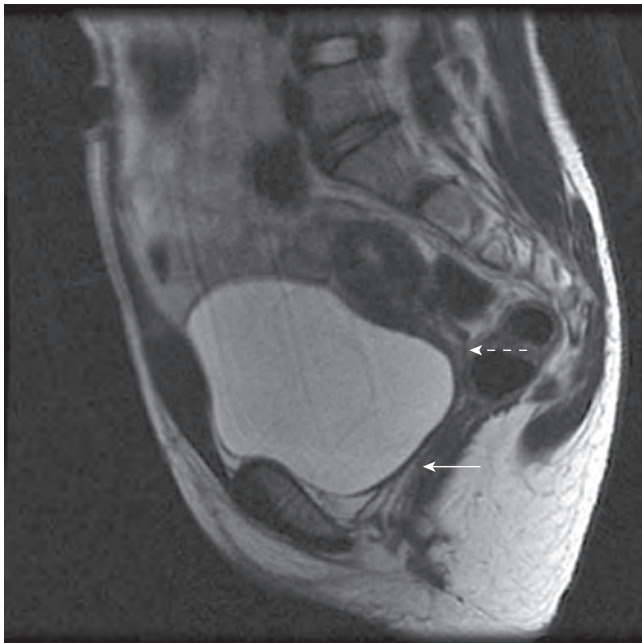


Figure 149-21. Magnetic resonance imaging scan of the pelvis in a 12-year-old girl with Klippel-Feil syndrome and associated proximal vaginal and cervical atresia. The *solid arrow* points to the most cranial portion of the perineal vaginal pit. The *dashed arrow* points to the most inferior aspect of the uterus, where no cervical impression can be appreciated.

KEY POINTS: VAGINAL REPLACEMENT SURGERY

- The McIndoe procedure (skin neovagina) is associated with a higher incidence of postoperative vaginal stenosis than a bowel neovagina.
- Vaginal stenosis after creation of an intestinal neovagina is more common with ileum than with large bowel.
- Vaginal reconstruction extending from the perineum to the uterus should be avoided in patients with cervical agenesis (because of the potential life-threatening complication of ascending bacterial infection).

Abnormalities of Lateral Fusion

Most abnormalities of lateral fusion have no functional significance. With the exception of those with uterus didelphys and unilateral vaginal obstruction, most patients are asymptomatic. Although an exhaustive description of the defects of lateral fusion is beyond the scope of this chapter, some general comments can be made ([Fig. 149-22](#)).

True duplication of the uterus is a rare event ([Fig. 149-23](#)). This anomaly results from duplication of the müllerian ducts and subsequent doubling of the reproductive structures on one or both sides. The much more frequently encountered anomaly of uterine didelphys consists of two separate uterine cavities and cervices as a result of failed resorption of the common medial wall of the paired müllerian duct structures during development. Although up to 75% of patients also have a septate vagina, most have adequate reproductive outcomes and do not require surgical intervention. If later in life the patient experiences difficulty with intercourse, vaginal delivery, or the need to use two tampons, surgical excision of the vaginal septum should be undertaken. If only the most cranial portion of the septum remains, a bicornuate uterus will result. The vagina is typically normal, and surgical incision of the uterine septum is rarely indicated except in cases of recurrent pregnancy loss ([DeCherney et al, 1986](#)).

Duplication of the Uterus and Cervix with a Unilaterally Imperforate Vagina. Although the majority of obstructive lesions are caused by abnormalities in vertical fusion, occasionally an obstructive process can be encountered in the context of

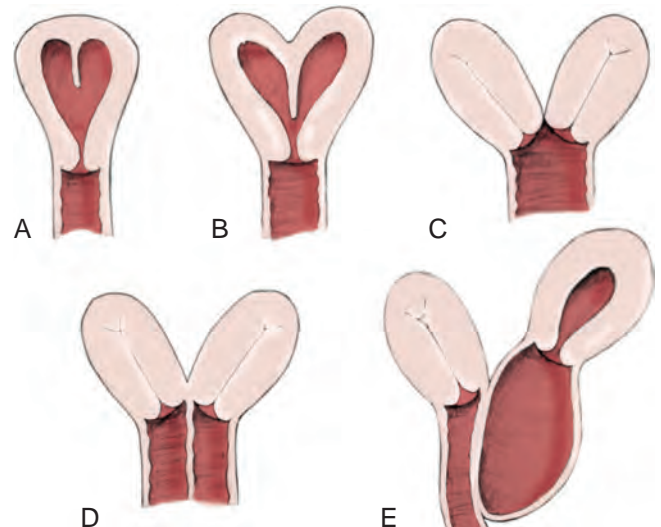


Figure 149-22. Fusion anomalies of the müllerian system. A, Bicornuate uterus (partial). B, Bicornuate uterus. C, Uterine duplication. D, Complete uterine and vaginal duplication. E, Duplication of the uterus and cervix with a unilateral imperforate vagina. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol* 2002;14:12.)



Figure 149-23. Genitogram of complete müllerian duplication (separated vagina and separate uteri).



Figure 149-24. Duplication of uterus and vagina with unilateral imperforate vagina. View through vagina with angiocatheter inserted into obstructed side.

an abnormality in lateral fusion (Fig. 149-24). More than 50 cases of uterus didelphys with a unilateral imperforate vagina have been reported in the world's literature (Allan and Cowan, 1963; Burbige and Hensle, 1984). As with other obstructive disorders, the patient may have cyclic or chronic abdominal pain. However, unlike other obstructive processes, duplication anomalies with unilateral obstruction do not result in primary amenorrhea. On physical examination, a unilateral abdominopelvic mass that termi-



Figure 149-25. Vaginal rhabdomyosarcoma. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol* 2002;14:12.)

nates in a bluish bulge in the lateral vaginal wall is often appreciated (Eisenberg et al, 1982). Abdominal ultrasonography and MRI are both excellent at defining the anatomy in a suspected case of unilateral noncommunicating uterine horn. Renal anomalies are frequently encountered on the side ipsilateral to the obstructed system, with renal agenesis being the most common (Eisenberg et al, 1982; Tridenti and Bruni, 1995). A prompt and accurate diagnosis is necessary to prevent injury to the genital organs as a result of chronic cryptomenorrhea and endometriosis. Treatment consists of wide incision of the vertical vaginal septum to release the entrapped menstrual blood.

Rhabdomyosarcoma

Vaginal rhabdomyosarcoma most often manifests as a grapelike cluster of tissue emanating from the posterior aspect of the vestibule (Fig. 149-25). The mean age of patients with primary vaginal tumors is younger than 2 years (Hays et al, 1988). Of all the female genital tract primary tumors, vaginal primary tumors appear to have the best prognosis. This excellent prognosis is thought to be a result of predominance of the embryonal cell type and relatively early detection because of symptoms of bleeding (Hays et al, 1988). Once a tissue diagnosis has been made by biopsy, proper staging with abdominal and pelvic computed tomography, chest radiography, and bone marrow biopsy is critical to optimal stratification of these patients into treatment protocols (Hays et al, 1985). Advances in chemotherapy have led to a reduction in the role of surgery for this disease with each subsequent Intergroup Rhabdomyosarcoma Study (IRS) trial: IRS-I, 100%; IRS-II, 70%; IRS-III, 30%; and IRS-IV, 13% (Andrassy et al, 1999). After chemotherapy, local resection may be required, but unlike other malignancies of the vagina, wide excision of the involved organ has no role except for persistent or recurrent disease (Hensley, 2000).

ACQUIRED DISORDERS OF THE FEMALE EXTERNAL GENITALIA

Labial Adhesions

Labial adhesions, also referred to as labial agglutination, and synechia vulvae are the most common interlabial abnormality identified in children, ranging in incidence from 0.6% to 1.8%



Figure 149-26. Labial adhesions.

(Leung et al, 1993; Norbeck et al, 1993). This condition occurs predominantly in the first 2 years of life, with a peak incidence between 13 and 23 months (Fig. 149-26). Fusion of the labia minora originates at the posterior fourchette and progresses for a variable distance toward the clitoris. It is important to differentiate this condition from the more serious entity of fusion of the labia majora, as is seen in certain disorders of sexual development. It has been hypothesized that hypoerogenism may play a role in adhesion of the labia minora. Labial adhesions have not been reported in newborn children, presumably because of the protective effect of maternal estrogen (Leung et al, 1993). However, the etiologic role of the hypoerogenic state has been brought into question by a number of authors (Caglar, 2007; Pulvino et al, 2008). Caglar (2007) measured circulating estradiol levels in 59 girls with labial adhesions and 60 control patients. He demonstrated no difference in the circulating level of estrogen in these two patient groups. It has been shown that estradiol may enhance wound re-epithelialization by promoting heparin-binding epidermal growth factor production in keratinocytes (Kanda and Watanabe, 2005). If there is a beneficial effect of topical estrogen it may be to promote healing after the adhesions have been separated. Nonhormonal factors may play an etiologic role in the formation of labial adhesions (Papagianni and Stanhope, 2003). Local irritation and tissue trauma appear to be important inciting events in many cases. Adhesions can rarely be associated with sexual abuse; in such cases, additional physical findings are often noted, including hematoma and lacerations (McCann et al, 1988). Although labial adhesions are usually asymptomatic, urine pooling within the vagina may lead to postvoid dribbling and perineal irritation and may make it difficult to obtain an accurate urinalysis sample or perform radiographic procedures.

Most children with labial adhesions do not require treatment unless they are symptomatic. With the rate of spontaneous resolution reported to be as high as 80% within 1 year, asymptomatic labial adhesions can comfortably be observed (Pokorny, 1992). When necessary, treatment ranges from the topical application of

various steroids to surgical division. The topical application of conjugated estrogens has been reported to be successful in separating adhesions in up to 90% of patients (Khanam et al, 1977; Leung et al, 2005). Concern over the possible side effects of breast budding and hyperpigmentation from prolonged use of conjugated estrogen led Myers and associates (2006) to treat a cohort of 19 prepubertal patients with topical betamethasone (0.05%). The authors reported success in 13 (68%) patients after administering one to three courses of twice-daily therapy for 4 to 6 weeks. It is important to have the family place the cream directly on the labia minora. In addition, it is helpful to have the family perform the pull-down procedure a few times a day to put light stress on the midline adhesions and hence facilitate their separation. If topical therapy is not successful, manual separation in the outpatient setting may be indicated. After the application of EMLA cream to the introitus, gentle pressure is applied to the thin connecting membrane with the use of a lubricated probe. Rarely, in cases in which the adhesions are extremely dense, surgical division is required. Although one group has recently advocated oversewing the separated edges with 7-0 chromic sutures (Nurzia et al, 2003), I have not found this to be necessary if the family is properly educated about keeping the labia separated (see Fig. 149-2) after the procedure. Recurrence rates appear to be similar when comparing children who have undergone manual separation (16.7%) versus surgical separation (15.4%), emphasizing the importance of having families continue to separate the labia after separation has been achieved (Muram, 1999).

Female Circumcision (Infibulation)

Acquired vaginal obstruction may be secondary to a number of ritual female genital mutilation procedures that are widespread in many countries in Africa (stretching in a band from the Horn of Africa through Central Africa to parts of Nigeria), the Middle East, and Muslim populations of Indonesia and Malaysia (Toubia, 1994; Dorkenoo, 1996). Although similar procedures were prescribed to U.S. and British women during the 19th century for the treatment of ailments ranging from epilepsy to lesbianism, all forms of genital mutilation are now illegal in these Western countries. Often referred to as “female circumcision,” the procedure continues to affect an estimated 80 to 110 million women worldwide (Toubia, 1994).

The age at which this procedure is performed ranges from birth to just before marriage. However, it is typically performed on preadolescent children between the ages of 4 and 10 years, most commonly at age 7 (American Medical Association, 1995). The procedure is usually performed without anesthesia in the context of a ceremony designating the rite of passage into adult society (American Medical Association, 1995). The extent of the mutilation varies according to ritual, but the practice predates Islam and is therefore not part of a religion (McCaffrey et al, 1995). In many countries the women have a deinfibulation procedure performed just before consummating the marriage.

The type of mutilation ranges from simple excision of the prepuce of the clitoris (termed *sunna*) to complete excision of all elements of the vulvar region (McCaffrey et al, 1995).

Toubia (1994) classified the more extensive female genital mutilation procedures according to the amount of tissue destruction:

Type I: Complete or partial removal of the clitoris.

Type II: Excision of the clitoris and a portion of the labia minora.

Type III: Excision of the entire clitoris and labia minora with incision of the labia majora along its medial aspect to create raw surfaces. The anterior two thirds of the labia majora are approximated to cover the urethra and introitus, with the lower third at the level of the posterior fourchette left for the passage of urine and menstrual fluid.

Type IV: Excision of the entire clitoris and labia minora with nearly complete approximation of the labia majora and only a pinhole opening left near the posterior fourchette for the passage of urine and menstrual fluid (Fig. 149-27).



Figure 149-27. Female infibulation. Note the scarred labia majora with only a pinhole opening for the passage of menstrual fluid and urine. (From Gonzales ET, Bauer SB, editors. *Pediatric urology practice*. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 599.)

Closing of the introitus, typically referred to as infibulation or pharaonic circumcision, is performed by a variety of means, including absorbable and nonabsorbable suture materials, thorns, and twigs. The child's legs are then bound for up to 40 days to ensure secondary healing in the ventral midline (McCaffrey et al, 1995).

The physical, psychological, and reproductive repercussions of these forms of genital mutilation are numerous and include immediate destruction and infection of local tissues (e.g., rectum, urethra). Long-term risks include chronic pain, recurrent urinary tract and vaginal infections, dysmenorrhea, dyspareunia, and apareunia. For individuals with the most narrowing, additional "surgeries" to revise the introital opening may be necessary for both intercourse and vaginal delivery (Aziz, 1980; Toubia, 1994).

Care of a patient who has undergone infibulation must be individualized, not only to provide functionality but also to respect the cultural and ritual desires of the woman. Educating the patient about the normal appearance of the external female genitalia is critical. Visual aids, including photographs or hand-drawn illustrations (or both) of the patient's anatomy and the planned revision, have been used as part of informed consent to avoid misunderstanding.

Condyloma Acuminatum

The incidence of genital warts in children has increased over the past 5 decades (Leclair et al, 2012). Although the majority will be found in the perianal region, involvement of the vestibule can at times occur. The treatment of condyloma acuminatum in pediatric patients is difficult, with a wide range of treatment options that yield variable success. The decision as to which treatment is most ideal will depend on patient age and location and severity of the

lesions. Although a very high suspicion for sexual abuse is warranted, it should be kept in mind that perinatal transmission is also a possible mechanism. De Jesus and associates (2001) reported that perinatal transmission occurred in 7 of their 17 patients.

Reports of spontaneous resolution have been reported (Leclair et al, 2012). Allen and Siegfried reported that spontaneous resolution of pediatric condyloma occurred in more than half of their subjects (Allen and Siegfried, 1998). Medical therapy can be effective. Imiquimod, an immune response modifier that works through the Toll-like receptor 7 pathway, has been used extensively in adults. Leclair and colleagues found this to be highly effective in a young child with rapidly progressing lesions that were not amenable to surgical resection. Although carbon dioxide laser ablation of anogenital lesions is straightforward, lesions directly involving the vestibule may be more challenging. In one series of 17 patients in whom 12 were female, nearly 70% responded favorably to CO₂ ablation therapy (Johnson et al, 1997). Because the cause of condyloma acuminatum is human papillomavirus, authors emphasize the primary prevention of HPV infection through vaccination as a key component in decreasing the incidence of this disease (Thornsberry and English, 2012).

Inguinal Hernias

Inguinal hernias occur far less frequently in girls than in boys, with a ratio between 1:5 and 1:10 reported in major series. Although usually an isolated event, this anatomic finding can be the manifesting symptom for a child with CAIS. Multiple authors have reported a 1% incidence of CAIS in patients presenting with an inguinal hernia (Sarpel et al, 2005; Hurme et al, 2009). It is therefore imperative that all phenotypic females who present with an inguinal hernia be evaluated to determine if they are a genetic male. Various methods of determining whether the patient has CAIS are available to the clinician. A karyotype, although definitive, is costly and therefore not obtained routinely by most practitioners. Recently, one group evaluated whether extraction of Y chromosome DNA from a buccal mucosal sample was feasible. They found that this test proved less expensive and provided quicker results than a standard karyotype (Rahman et al, 2012). A pelvic sonogram to evaluate for the presence (or absence) of a vaginal stripe also can be obtained, but has the similar drawback of added cost.

Simple evaluation by way of vaginoscopy at the time of hernia repair will reveal if a cervix is present. A patient with CAIS also may have a significantly shorter vagina. While the hernia is being repaired, inguinal laparoscopy can be performed to study the contralateral gonad and evaluate for the presence of uterus. The round ligament will be uniformly absent in genetic males.

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The complete reference list is available online at www.expertconsult.com.



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Normal Sexual Differentiation

Abnormal Sexual Differentiation

Evaluation and Management of the Newborn with Ambiguous Genitalia

Disorders of sexual differentiation are among the most fascinating and complex disease processes encountered by the urologist. This field has undergone a striking evolution over the past few decades. Remarkable advances in molecular biology and genetic research have provided new insight into the precise mechanisms responsible for sexual differentiation and for specific disorders of sexual development. In addition, there has been a major shift in nomenclature to promote precise communication among colleagues and respect for the sensitivity of patients by eliminating terms such as *pseudohermaphroditism*, which have been regarded as pejorative by patients. The term *intersex disorders* has been replaced by *disorders of sex development* (DSDs).

NORMAL SEXUAL DIFFERENTIATION

Under normal circumstances, sexual differentiation is a dynamic and sequential process. According to the Jost paradigm, three steps must occur: establishment of chromosomal sex at fertilization, which determines development of the undifferentiated gonads into testes or ovaries, and subsequent differentiation of the internal ducts and external genitalia as a result of endocrine functions associated with the type of gonad present (Jost et al, 1973). Therefore sexual development occurs as a result of different but complementary processes: genotypic effects, phenotypic events, and gender identity formation. Interference with this highly ordered process at any step can result in a disorder of sexual differentiation.

Normal Genotypic Development

Chromosomal Sex

In 1921, Painter demonstrated cytologically that humans have X and Y chromosomes. Based on chromosomal studies of *Drosophila*, it was assumed that sex was determined by the X chromosomes possessed by the individual (Bridges, 1921). The Y chromosome was thought to impart no genetic information until karyotyping of mammalian chromosomes, developed in the 1950s, demonstrated that the Y chromosome specified development of the testis. Specifically, reports in the late 1950s describing the karyotype 47,XXY as male with Klinefelter syndrome and 45,XO as female with Turner syndrome demonstrated that the presence of a Y chromosome, independent of the number of X chromosomes, resulted in the development of a male embryo, whereas in the absence of a Y chromosome the embryo developed as a female (Ford et al, 1959; Jacobs and Strong, 1959). Therefore the Y chromosome appeared to possess a gene or genes that determined the destiny of the bipotential gonad as a testis or ovary. In the human, the hypo-

thetical Y-chromosomal gene was termed the *testis-determining factor* (TDF).

During the following years the search for the TDF was the focus of intense research. The observation that antibodies raised in inbred female mice transplanted with male skin grafts resulted in graft rejection whereas female-to-male skin grafts were accepted in the same strain of mice led to the proposal that the histocompatibility-Y, or H-Y, antigen was the product of TDF (Eichwald and Silmser, 1955). Assays for quantifying H-Y antigen were developed. With the use of these assays it was discovered that the presence of a testis resulted in serologically detectable levels of H-Y antigen. This was confirmed in normal patients, patients with DSDs, and males of other species. Therefore it was believed that the H-Y gene was the TDF (Wachtel, 1977). This theory was considered valid for more than 10 years.

Problems with the H-Y antigen theory developed, however. A number of women with 45,X gonadal dysgenesis were found to be H-Y antigen positive. In addition, a mouse model for the male sex reversal syndrome (XX male) was studied in which mice have two X chromosomes and testes owing to a fragment of Y chromosome translocated onto one of the X chromosomes (McLaren et al, 1984). These mice were H-Y antigen negative and azoospermic. As a result of these findings, the hypothesis that the H-Y antigen was the product of TDF was excluded. Further study of the Y chromosome suggested that the genetic information responsible for maleness was on the short arm of the chromosome near the centromere. This theory was supported by data from animals with naturally occurring sex chromosome abnormalities. Gain or loss of DNA from the short arm of the Y chromosome on an XX genetic background resulted in either a male or female phenotype, respectively. Further progress was made by studying paradoxical 46,XX males who develop as phenotypic males in the presence of a presumably normal female 46,XX karyotype (Magenis et al, 1982). The simplest explanation for their sex reversal would be the presence of Y-chromosomal material (including TDF), as a result of mosaicism or submicroscopic cellular quantities. The application of molecular techniques to evaluate Y-chromosomal sequences present in XX males, as well as deletions of the Y chromosome in XY females, led to the cloning of TDF (Lukusa et al, 1992). Deletion maps based on the genomes of these individuals were constructed by a number of laboratories, and TDF was mapped to the most distal aspect of the Y-unique region of the short arm of the Y chromosome, adjacent to the pseudoautosomal boundary (Fig. 150-1).

ZFY and SRY

Page and coworkers (1987) constructed a more detailed genomic map and defined a 140-kilobase (kb) interval thought to contain

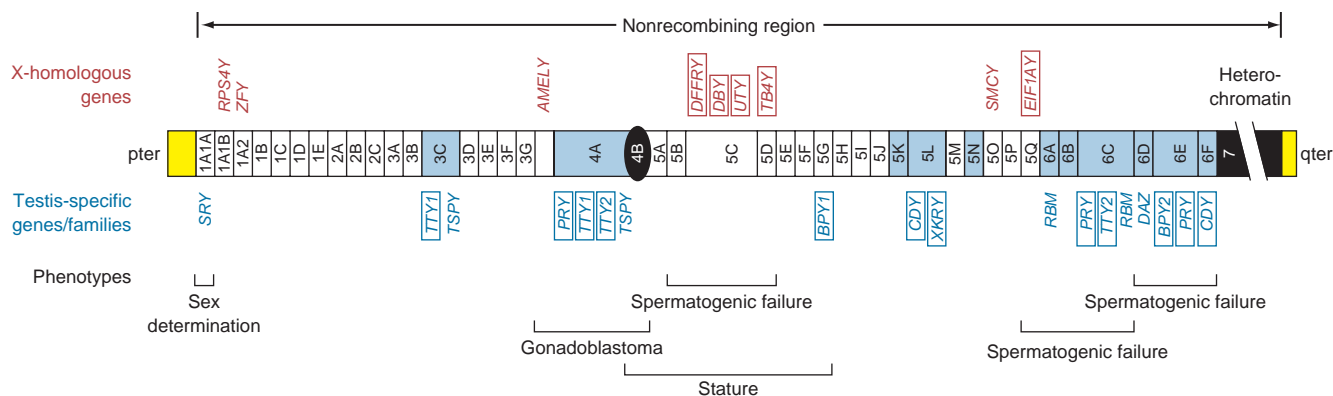


Figure 150-1. Genetic map of the short arm of the human Y chromosome. The pseudoautosomal region, where genetic crossing over may occur between sex chromosomes, is highlighted in yellow. The *SRY* and *ZFY* loci are located near the pseudoautosomal boundary on the short arm of the Y chromosome at the terminal end (pter). The *SRY* gene encodes the molecular switch that promotes gonadal sex determination. (Modified from Lahn BT, Page DC. Functional coherence of the human Y chromosome. *Science* 1997;278:675–80.)

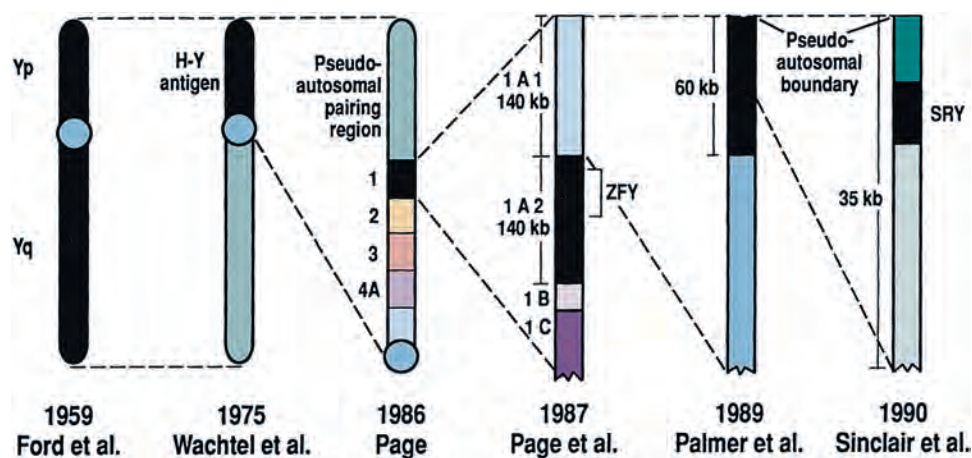


Figure 150-2. Diagrammatic representation of the historical search for the testis-determining factor (TDF). The area shaded in black on the Y chromosome is the region to which this factor has been localized. (From Grumbach MM, Conte FH. Disorders of sex differentiation. In: Wilson JD, Foster DW, editors. *Williams textbook of endocrinology*. Philadelphia: Saunders; 1998. p. 1315.)

the TDF by aligning the Y-specific DNA present in an XX male with a Y chromosome deletion of the same region in an XY female. These investigators identified a gene encoding a protein with multiple "zinc finger" domains, characteristic of a class of proteins that bind DNA in a sequence-specific manner and regulate transcription. In addition, these sequences demonstrated evolutionary conservation. Based on its position and structural similarity to other transcription factors, *ZFY* (zinc finger gene on Y chromosome) was proposed as a candidate for the TDF.

However, in subsequent years, data were accumulated that excluded *ZFY* as the TDF. This included the discovery that in marsupials *ZFY* was located not on the sex chromosomes but on autosomes (Sinclair et al, 1988). *ZFY* was excluded with certainty as a candidate for TDF when four individuals with testicular development were found to have inherited a fragment of the Y chromosome that did not include *ZFY* (Palmer et al, 1989).

The renewed search for TDF led to the discovery of Y-specific sequences in XX males lacking *ZFY* and the imposition of new limits on the location of TDF to a 35-kb region adjacent to the pseudoautosomal boundary (Fig. 150-2). Using probes from this region, Sinclair and colleagues (1990) discovered a single-copy male-specific sequence that was evolutionarily conserved. This

gene was termed *SRY* (sex-determining region Y gene) in humans and *Sry* in mice. Analysis of the *SRY* protein sequence demonstrated a highly conserved, 78-amino acid region with homology to a DNA-binding motif of the high-mobility group (HMG) family of proteins (Fig. 150-3). When DNA encoding the HMG box was used to probe a genomic library, a subfamily of closely related genes was identified. Members of this family, defined as those encoding a region with 60% or greater amino acid similarity to the *SRY* HMG box motif, are called SOX (SRY box-related) genes (Goodfellow and Lovell-Badge, 1993).

Considerable evidence has accumulated that *SRY* is the TDF. In the mouse, expression of *Sry* correlates with testicular determination in the gonadal ridge (Koopman et al, 1990). *SRY* is an evolutionarily conserved gene on the Y chromosome of mammals. Chromosomal fragments related to *SRY* (i.e., the SOX genes) are very much conserved evolutionarily, being demonstrated in various vertebrates and marsupials. *SRY* is localized to the smallest region of the Y chromosome capable of inducing testicular differentiation in humans and in mice (Gubbay et al, 1992). In fact, Koopman and coworkers (1991) introduced into XX mouse embryos a 14-kb mouse genomic DNA fragment containing *Sry* and no other Y-linked gene sequences and demonstrated that it was capable of giving rise

to normal testicular development in the transgenic mice. The *SRY* protein functions as a transcription factor that, by binding and producing bending of the DNA, promotes protein-protein interaction and is able to activate downstream gene expression. An expectation for TDF was that mutations in its protein sequence would result in sex reversal. Examination of the *SRY* sequence in XY females has identified more than 50 mutations in the protein-coding sequence, with the majority located within the DNA-binding domain. Another prediction for TDF is that its presence can cause XX male sex reversal. The majority of XX males to date have been found to have Y chromosome segments containing *SRY*. This suggests a causative role of *SRY* in most cases of XX sex reversal. Therefore, genetic and molecular data have established that *SRY* can be equated to the TDF.

Additional insights have been gained regarding *SRY* function as a molecular switch that promotes testis development. *SRY* is expressed and functions in the supporting cells of the developing male urogenital ridge. These cells participate in cord formation and ultimately develop into Sertoli cells.

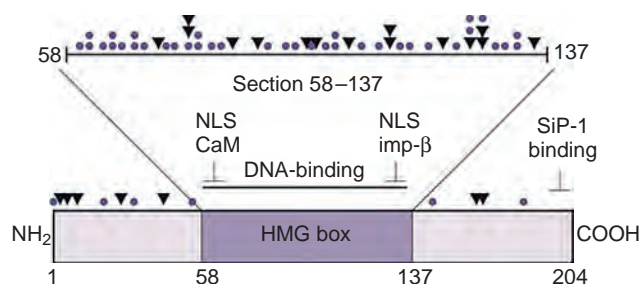


Figure 150-3. Diagram of the *SRY* (sex-determining region on the Y gene) locus, with the high-mobility group (HMG)-related box DNA-binding domain. Solid circles denote missense mutations that affect testicular development. Triangles indicate nonsense and frameshift mutations. (From Achermann JC, Hughes IA. Disorders of sex development. In: Melmed S, Polonsky KS, Larsen PR, et al, editors. Williams textbook of endocrinology. Philadelphia: Saunders; 2011.)

KEY POINTS: CHROMOSOMAL SEX

- Sinclair and colleagues (1990) discovered the TDF, a single-copy male-specific sequence that was evolutionarily conserved.
- This gene was termed *SRY* (sex-determining region Y gene) in humans and *Sry* in mice.

Additional Genes Involved in Gonadal Determination

Several additional genes involved in gonadal development have been identified and characterized. These include, but are not limited to, *WT1*, *NR5A1* (*SF1*), *SOX9*, *NR0B1* (*DAX1*), *WNT4*, *RSPO1*, and *FOXL2* (Fig. 150-4; Table 150-1). Newer data suggest that these factors function in defined but interrelated differentiation pathways during gonadal formation and determination.

WT1. The *WT1* gene was originally isolated in cloning experiments that identified an oncogene on human chromosome 11 as being involved in the development of Wilms tumor (Call et al, 1990). This gene, originally localized by examining chromosomal deletions in children with WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities, gonadoblastoma, and mental retardation), was found to be expressed primarily in the kidney and gonads of the developing human embryo (Kreidberg et al, 1993). The first reported mutations in the Denys-Drash syndrome, which includes Wilms tumor, renal failure, and gonadal and genital abnormalities, were found to involve the *WT1* protein (Pelletier et al, 1991a, 1991b). Indeed, mutations involving *WT1* have been found to be responsible for both the Frasier and Denys-Drash syndromes, which appear to represent a spectrum of genetically induced abnormalities involving the gonads and kidneys, owing to the earlier involvement of *WT1* in the differentiation of both structures. Frasier syndrome is characterized by both gonadal dysgenesis and renal abnormalities that result in streak gonads and a nephrotic syndrome (MacLaughlin and Donahoe, 2004). If it occurs in the XY genotype, sex reversal results. As a result of alternative splicing of the *WT1* gene, patients with Frasier syndrome are not susceptible to Wilms tumor, whereas those with Denys-Drash syndrome are (Koziell and Grundy, 1999).

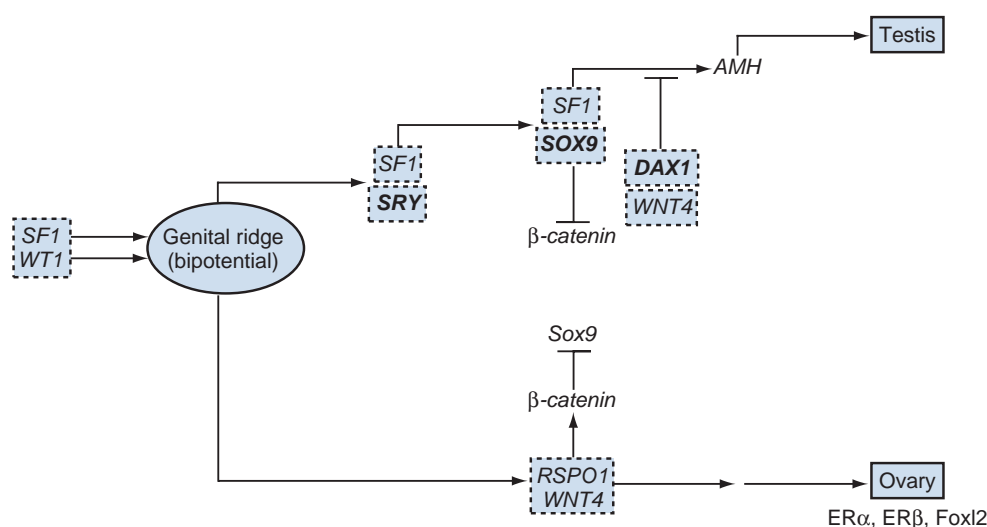


Figure 150-4. Genes determining testis or ovarian differentiation from bipotential gonad. *SF1* and *WT1* are essential for gonadal ridge formation and development. Gonadal determination is influenced by transient expression of the testis determination factor, *SRY*. *SOX9* upregulation by *SRY* leads to testis formation. Repression of *SOX9* by factors such as *DAX1* and *WNT4*/β-catenin results in inhibition of testis formation and promotion of ovarian development. (After Hughes IA. Intersex. *BJU Int* 2002;90:771; and Sekido R, Lovell-Badge R. Sex determination and *SRY*: down to a wink and a nudge? *Trends Genet* 2009;25[1]:19–29.)

TABLE 150-1 Loss of Function Phenotype (Human Data)

GENE	CHROMOSOME	46,XY	46,XX
<i>SRY</i>	Yp11.3	Female; gonadal dysgenesis (Swyer syndrome)	
<i>SOX9</i>	17q24.3-q25.1	Female; camptomelic dysplasia; ovaries to gonadal dysgenesis	Female; camptomelic dysplasia
<i>WT1</i>	11p13	Female; Wilms tumor; gonadal dysgenesis, mesangial sclerosis (Denys-Drash syndrome); streak gonads, glomerulosclerosis (Frasier syndrome)	Female; Wilms tumor; gonadal dysgenesis, mesangial sclerosis (Denys-Drash syndrome); streak gonads, glomerulosclerosis (Frasier syndrome)
<i>NR5A1 (SF1)</i>	9q33	Female; adrenal insufficiency; gonadal dysgenesis	
<i>NR0B1 (DAX1)</i>	Xp21.3-p21.2	Male; gonadal dysgenesis, hypogonadotropic hypogonadism; adrenal hypoplasia	
<i>WNT4</i>	1p36.23-p35.1		Male; aberrant müllerian structure development; wolffian development
<i>RSPO1</i>	1p34.3		Male; palmoplantar keratoderma; aberrant müllerian development; ovotestis
<i>FOXL2</i>	3q23		Female; blepharophimosis-ptosis-epicanthus inversus syndrome (BPES); premature ovarian failure (BPES type II)

In addition, with the Denys-Drash syndrome, gonads differentiate more completely than with Frasier syndrome. Research on *Wt1* in the mouse suggests that it exerts its effects upstream of *Sry* and is likely to be necessary for commitment and maintenance of gonadal tissue (Lim and Hawkins, 1998).

NR5A1 (SF1). Experiments in the mouse have demonstrated that nuclear receptor steroidogenic factor 1 (*SF1*) is expressed in all steroidogenic tissues, including adrenal cortex, testis (Leydig cells), ovarian theca, granulosa cells, and corpus luteum. *SF1* appears to be a key regulator of enzymes involved in steroid production, including the sex hormones, and may directly regulate pituitary gonadotropin expression (Parker et al, 2002). In addition, it appears to play a role in early gonadal development at multiple levels of the reproductive endocrine axis (Ingraham et al, 1994; Luo et al, 1994). *SF1* also appears to act synergistically with *WT1* in the regulation of müllerian-inhibiting substance expression (Shen et al, 1994; Imbeaud et al, 1995; Nachtigal et al, 1998) and may regulate *DAX1* (Yu et al, 1998) and *SOX9* expression (Sekido and Lovell-Badge, 2008).

SOX9. The *SOX9* gene was originally identified in patients with camptomelic dysplasia, a congenital disease of bone and cartilage formation that is often associated with XY sex reversal (Wagner et al, 1994). The *SOX9* gene is structurally quite similar to *SRY*, with a 71% sequence similarity of the HMG domain to that of *SRY*. Expression of the gene in adults is greatest in the testes. It is interesting to note that *SOX9* gene activity increases immediately after *SRY* expression, and cell lineage analyses show that *SOX9* protein is expressed in cells determined to become Sertoli cells (Sekido and Lovell-Badge, 2009). Therefore the *SOX9* gene may be a key downstream effector of *SRY* action. The activity of *SRY* on *SOX9* is synergistic with the activity of an additional transcription factor, *SF1*, which is essential for gonadal and adrenal development (Sekido and Lovell-Badge, 2008). A role for *SOX9* in male gonadal determination is further supported by data from genotypic males with *SOX9* mutations (46,XY) who exhibit ovarian development and male-to-female sex reversal (Foster et al, 1994; Wagner et al, 1994). *SOX9* also upregulates *AMH* gene expression (MacLaughlin and Donahoe, 2004).

NR0B1 (DAX1) and Dosage-Sensitive Sex Reversal (DSS). The first indication that an X-specific gene was involved in human sex

determination was provided in 1978 with the identification of a family with an X-linked mode of inheritance of 46,XY gonadal dysgenesis. Subsequent studies of a number of sex-reversed subjects confirmed the presence of additional X-chromosomal genetic material and a normal Y chromosome (Ogata et al, 1992). This finding suggested that duplication of an X-specific gene causes XY sex reversal by expressing a double dose of a region normally subject to X inactivation. Screening of XY females with a normal *SRY* gene detected such a submicroscopic duplication, involving a 160-kb region designated as the dosage-sensitive sex reversal (DSS) critical region (Bardoni et al, 1994). Parallel studies examining 46,XY males with gonadal dysgenesis, hypogonadotropic hypogonadism, and congenital adrenal hypoplasia resulted in the identification of a candidate gene, *NR0B1 (DAX1)*, within the DSS critical region (Muscatelli et al, 1994; Zanaria et al, 1994). It is interesting to note that *DAX1* can act to suppress or promote the testis determination pathway (Yu et al, 1998; Meeks et al, 2003). Although *DAX1* was initially believed to be the primary gene involved in DSS, several sex-reversed 46,XY patients have been identified with duplication of the DSS region in the absence of *DAX1* duplication, which suggests that the gene dosage effects of this region may be associated with an additional gene or genes (Zanaria et al, 1995).

WNT4. *WNT4* on chromosome 1p34 appears to be involved in müllerian duct regression and may also function by antagonizing *SRY* activity (Kim et al, 2006; Bernard and Harley, 2007). Early inactivation of *Wnt4* in mice causes failure of the formation of müllerian duct derivatives in both sexes. In addition, inactivation of *Wnt4* in female mice leads to wolffian duct development without testicular tissue formation and female external genitalia. Furthermore, a recent report supports the role of *WNT4* in development and maintenance of the female phenotype in women by regulating müllerian duct development and ovarian steroidogenesis (Biason-Laubier et al, 2004).

Rspo1. R-spondin-1 is encoded by the *Rspo1* gene. It belongs to a family of ligands that activate the Wnt and β -catenin signaling pathways. Expression of R-spondin-1 overlaps that of Wnt in many tissues and can synergize with Wnt by stabilizing cytoplasmic β -catenin. The *Rspo1* gene was identified as a candidate gene in ovarian determination by linkage analysis of a large consanguineous

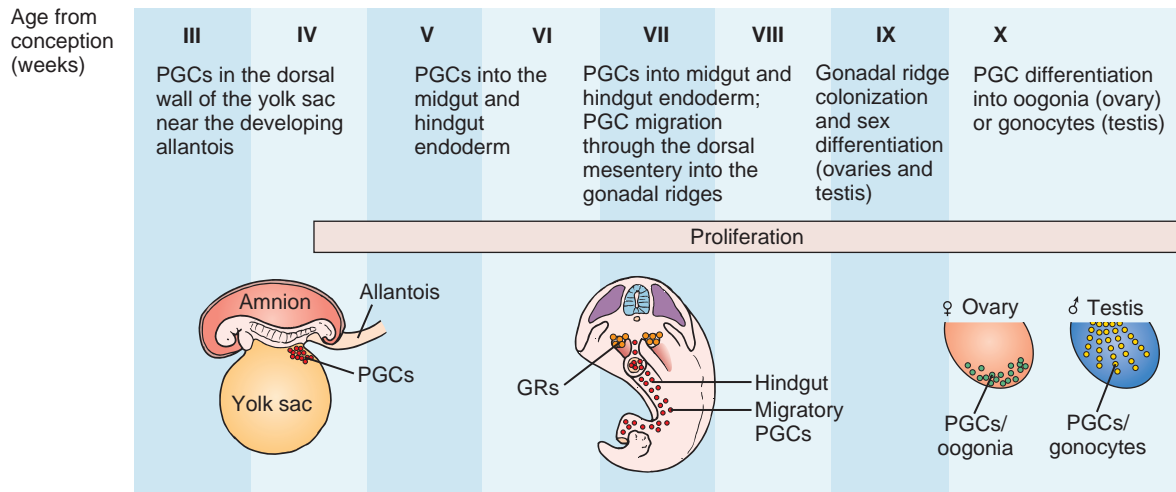


Figure 150-5. Migration of primordial germ cells. At 3 weeks, primordial germ cells (PGCs) are being formed and migrate along the wall of the yolk sac to reach the caudal part of the fetus. By 5 weeks, they have reached the level of the gonadal ridges (GRs). (Modified from DeFelici M. Origin, migration, and proliferation of human primordial germ cells. In: Coticchio G, Albertini DF, DeSantis L, editors. *Oogenesis*. London: Springer-Verlag; 2013. p. 21.)

Italian family with cosegregation of palmoplantar hyperkeratosis (PPK) trait and XX female-to-male sex reversal (Parma et al, 2006). A single nucleotide, frameshift mutation was found in affected individuals from the consanguineous family and deletion mutations in sporadic cases of PPK and XX sex reversal.

Normal Phenotypic Development

Gonadal Stage of Differentiation

During the first 6 weeks of embryonic development, the gonadal ridge, germ cells, internal ducts, and external genitalia are bipotential in both 46,XY and 46,XX embryos. Under the genetic influences of sex determination, the bipotential gonadal ridges differentiate into either ovaries or testes, and germ cells develop into either oocytes or spermatocytes. Primordial germ cells can be recognized in the third week of gestation on the posterior wall of the secondary yolk sac. Migration of the germ cells begins in the fifth week of gestation from the dorsal wall of the yolk sac through the mesentery to the medial ventral aspect of the urogenital ridge (DeFelici, 2013) (Fig. 150-5). This process is dependent on chemoattractants and cell adhesion molecules (Hughes, 2002). Overall, a population of 1000 to 2000 primordial germ cells reaches the gonadal blastema by the sixth week of gestation.

Transformation of the germ cells into spermatogonia and oogonia results from differentiation of the epithelial gonadal compartments referred to as testicular and ovarian "cords." *SRY* initiates the switch that induces a cascade of genes directing the indifferent gonad toward testicular organogenesis. The precise moment at which this occurs remains unknown. Initially, differentiation of Sertoli cells is noted as testicular cords form at 6 to 7 weeks' gestation, creating the basement membrane, or blood-testis barrier, of spermatogonia and Sertoli cells on one side and mesenchymal fibroblasts on the other. The differentiation of Sertoli cells is associated with the production of MIS, a glycoprotein encoded by a gene on the short arm of chromosome 19 (Haqq et al, 1994). In males, a second line of primordial cells of steroidogenic mesenchyme remain among the testicular cords and represent future Leydig cells, which differentiate at 8 to 9 weeks. In the absence of *SRY*, ovarian organogenesis results. Little is known about the genetic control of ovarian development. To date, no genes whose products direct development of the ovary have been identified. It does appear necessary that there be duplicate copies of at least one X-chromosomal locus (which presumably explains the dys-

genetic ovaries in the 45,XO Turner syndrome patients). A potential candidate may lie within the DSS critical region on Xp-21, which, when duplicated, promotes male-to-female "sex reversal" (Bardoni et al, 1994; Lopez et al, 1998).

Unlike the testis, which functions primarily as a fetal endocrine organ, the ovary has primarily exocrine activity. In embryonal ovaries, germ cells undergo intense mitotic proliferation (preceding the onset of meiotic prophase) and in the process exhaust their entire mitotic potential prenatally, reaching a maximum endowment of 20 million cells by 20 weeks' gestation. The presence of two X chromosomes appears to be responsible for differentiation of the granulosa cells into the protective mantle of the granulosa layer and "rescue" of 30% of germ cells (approximately 2 million) (Byсков and Westergaard, 1998).

KEY POINT: GONADAL STATE OF DIFFERENTIATION

- During the first 6 weeks of embryonic development the gonadal ridge, germ cells, internal ducts, and external genitalia are bipotential in both 46,XY and 46,XX embryos.

Gonadal Function

Testis

The initial endocrine function of the fetal testes is the secretion of MIS by the Sertoli cells at 7 to 8 weeks' gestation. MIS, one of the two hormones necessary for male sexual differentiation, acts locally to produce müllerian regression. It is a member of the transforming growth factor- β (TGF- β) family, and the human gene has been cloned and mapped to chromosome 19 (Cate et al, 1986). Little is known about the cellular mechanism of action of MIS. Because the hallmark of MIS-mediated müllerian duct regression is the formation of a ring of connective tissue around the epithelial cells, it is likely that the mesenchyme is the primary target of MIS. Testosterone secretion by the fetal testes is detectable shortly after the formation of Leydig cells in the interstitium at approximately 9 weeks' gestation (Siiteri and Wilson, 1974). There is a rise in serum and testicular testosterone to a peak concentration at 13 weeks and then a decline. The rate-limiting enzyme for fetal testosterone synthesis is 3 β -hydroxysteroid dehydrogenase, which is concentrated approximately 50 times more highly in the fetal testes

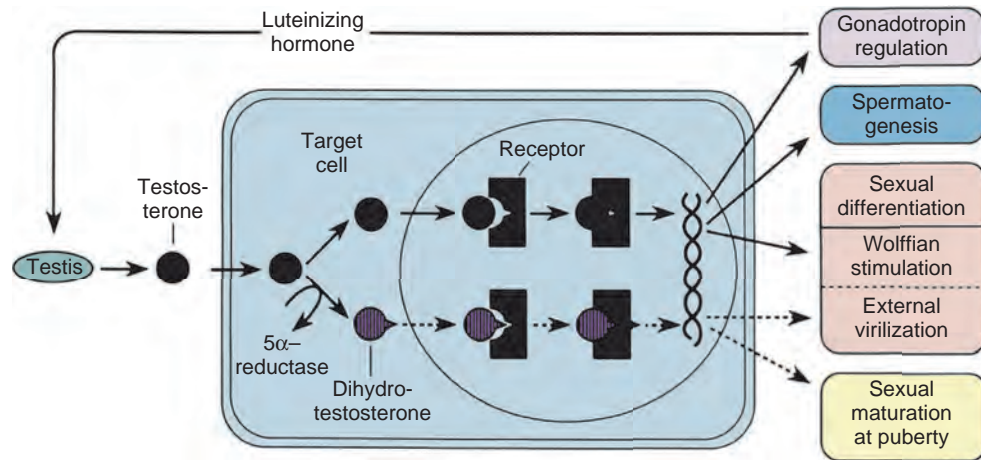


Figure 150-6. Schematic diagram of normal androgen physiology. The major actions of androgens are listed on the right. Testosterone enters androgen target tissues and either binds to the androgen receptor in cell nuclei or is converted by 5 α -reductase to dihydrotestosterone (DHT). DHT binds to the same receptor but with greater affinity. Androgen actions mediated by testosterone are indicated by solid arrows, and those mediated by DHT are indicated by dashed arrows. (From Griffin JE, Wilson JD. Syndromes of androgen resistance. *Hosp Pract* 1987;22:99–114.)

than in the ovary. Androgens are synthesized by the Leydig cells, initially autonomously, but then dependent on placental human chorionic gonadotropin (hCG) secretion. Later in gestation, with declining hCG concentrations, androgen synthesis is controlled by luteinizing hormone (LH) secretion by the fetal pituitary gland. [Jost and colleagues \(1973\)](#) clearly demonstrated that androgen is essential for virilization of wolffian duct structures, the urogenital sinus, and the genital tubercle. Testosterone, the major androgen secreted by the testes, enters target tissues by passive diffusion. Organs such as the wolffian duct, adjacent to the fetal testis, also take up testosterone by pinocytosis. The local source of androgen is important for wolffian duct development, which does not occur if testosterone is supplied only via the peripheral circulation. In some cells, such as those in the urogenital sinus, testosterone is converted to dihydrotestosterone (DHT) by intracellular 5 α -reductase. Testosterone or DHT then binds to a high-affinity intracellular receptor protein, and this complex enters the nucleus, where it binds to acceptor sites on DNA, resulting in new messenger RNA and protein synthesis ([Fig. 150-6](#)). The androgen receptor has been characterized as a high-affinity receptor that mediates the action of testosterone and DHT in all androgen-dependent tissues. In disorders of the androgen receptor, such as androgen insensitivity syndrome, testosterone production is normal but the hormone is unable to reach the nucleus and interact with DNA. Various defects in the androgen receptor result in a spectrum of phenotypic abnormalities in the genetic male. Because gonadal females have androgen receptor within their tissues, exogenous androgen produces virilization. DHT binds to the androgen receptor with greater affinity and stability than does testosterone. Therefore, in tissues equipped with 5 α -reductase at the time of sexual differentiation (e.g., prostate, urogenital sinus, external genitalia), DHT is the active androgen ([George and Peterson, 1988](#)). The 5 α -reductase activity has two optimal pH values in cultured genital skin fibroblasts—one at pH 5.5 and a second one near pH 8—that correspond to two distinct enzymes ([Jenkins et al, 1992](#)). The alkaline enzyme human steroid 5 α -reductase type 1 was cloned first; however, the primary enzyme in the prostate is 5 α -reductase type 2 ([Andersson and Russell, 1990](#)). A deletion in the gene coding for this enzyme has been discovered in intersex patients with 5 α -reductase deficiency ([Andersson et al, 1991](#)). The gene encoding the androgen receptor has been cloned and mapped to the X chromosome at Xq11-12 ([Lubahn et al, 1988](#)).

KEY POINT: GONADAL FUNCTION

- DHT binds to the androgen receptor with greater affinity and stability than does testosterone. Therefore in tissues equipped with 5 α -reductase at the time of sexual differentiation (e.g., prostate, urogenital sinus, external genitalia), DHT is the active androgen.

Ovary

Estrogen synthesis is detectable in the female embryo just after 8 weeks of gestation. The rate-limiting enzyme is aromatase, which is higher in the fetal ovary than in the fetal testis. Estrogens are not required for normal female differentiation of the reproductive tract, but they can interfere with male differentiation. Estrogen can block the effect of MIS on müllerian ducts, and prenatal estrogen treatment of mothers has been associated with male reproductive tract abnormalities ([Gill et al, 1979](#); [Vigier et al, 1989](#)).

Phenotypic Sexual Differentiation

Before the 8th week of gestation the urogenital tract is identical in the two sexes. Both the wolffian and the müllerian duct systems are present as anlagen of the internal accessory organs of reproduction ([Fig. 150-7](#)). In addition, at this stage the anlagen of the external genitalia of male and female embryos are indistinguishable ([Fig. 150-8](#)). In the male fetus, Sertoli cells produce MIS, which acts locally and unilaterally to suppress the müllerian ducts, and Leydig cells produce testosterone, which permits local development of the wolffian ducts. By 10 weeks of gestation, degeneration of the müllerian ducts is almost complete and the wolffian ducts have become more prominent (see [Fig. 150-7](#)). Adjacent to the testes, convolutions of the ducts organize to form the epididymis. The wolffian ducts of the epididymis join with the collecting portion of the testicular tubules (rete testis). Distally, the ducts join the urogenital sinus by about 30 days' gestation, where they develop into the seminal vesicles. In the female fetus, testosterone is not secreted by the ovaries and therefore the wolffian ducts regress. Because the ovary does not produce MIS, the müllerian ducts are

maintained and develop into the female internal reproductive tract. The cephalic ends are anlagen of the fallopian tubes, and the caudal ends fuse to form the uterus (see Fig. 150-7). Contact of the müllerian ducts with the urogenital sinus induces formation of the uterovaginal plate, which ultimately forms the lumen of the vagina. The relative contributions of the müllerian ducts and urogenital

sinus to the formation of the vagina remain somewhat controversial; however, there is some agreement that the proximal two thirds of the vagina is contributed by the müllerian ducts and the distal one third by the urogenital sinus. Masculinization of the male fetus starts at 7 to 8 weeks of gestation (Fig. 150-9). The first sign of male phenotypic differentiation is degeneration of the müllerian ducts adjacent to the testes as a result of MIS secretion by the Sertoli cells. Whereas the effects of androgen on the wolffian ducts are related to diffusion of testosterone from the adjacent gonad, masculinization of the external genitalia results from the systemic delivery of testosterone with local conversion to DHT. By 10 weeks, an increase in distance between genital tubercle and anal folds can be seen. The genital tubercle thickens and elongates to become the penis, and the urethral folds fuse from posterior to anterior over the urethral groove (Fig. 150-10). Near the bladder, the urethra is surrounded by the prostate. The urogenital swellings migrate posteriorly to the genital tubercle and fuse to form the scrotum. By 12 to 13 weeks' gestation, the genitalia of the male fetus are completed with closure of the elongated urogenital cleft. Under the influence of androgen secreted by the fetal testes, penile growth and testicular descent occur in the third trimester (see Fig. 150-9). In the female fetus the absence of circulating testosterone maintains the appearance of the external genitalia at the 6-week gestational stage. The genital tubercle develops only slightly to form the clitoris. The lateral genital swellings become the labia majora, and the adjacent urethral folds become the labia minora (Fig. 150-11). Between the labia minora will develop the vaginal introitus and urethral meatus.

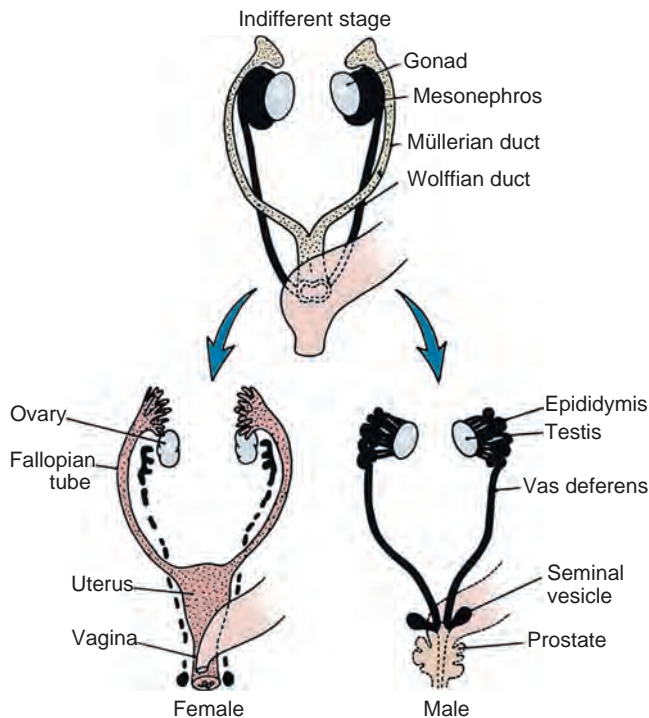


Figure 150-7. Differentiation of the wolffian and müllerian duct and urogenital sinus in the male and female. (From Wilson JD. *Embryology of the genital tract*. In: Harrison HH, Gittes RF, Perlmutter AD, et al, editors. *Campbell's urology*. 4th ed. Philadelphia: Saunders; 1979. p. 1473.)

Gender Identity, Gender Role, and Gender Orientation

Psychosexual Differentiation

Humans have been recognized as having sexually dimorphic behavior, which has several aspects: (1) *gender identity*, the identification of self as either male or female; (2) *gender role*, aspects of behavior in which males and females appear to differ; (3) *gender orientation*, or choice of sexual partner (heterosexual, homosexual, or bisexual); and (4) *cognitive differences* (Grumbach and Conte, 1998). Gender identity is a complex and poorly understood phenomenon in humans, and the mechanisms appear multifactorial. Experience in patients with congenital adrenal hyperplasia (CAH) who were exposed prenatally to androgen and in patients reared in a sex

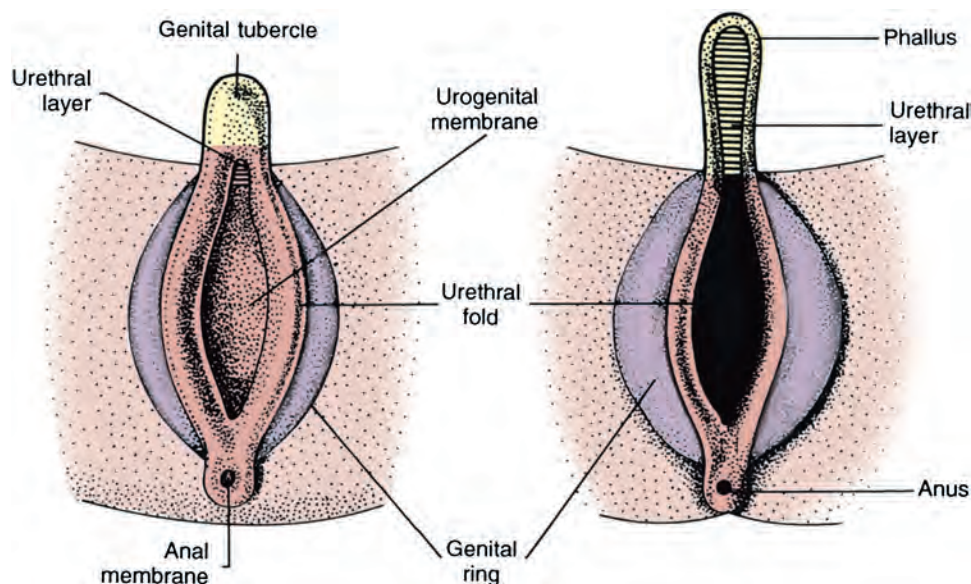


Figure 150-8. Schematic diagram of external genitalia in the undifferentiated period. (From Martinez-Mora J. *Development of the genital tract*. In: Martinez-Mora J, editor. *Intersexual states: disorders of sex differentiation*. Barcelona: Ediciones Doyma; 1994. p. 52.)

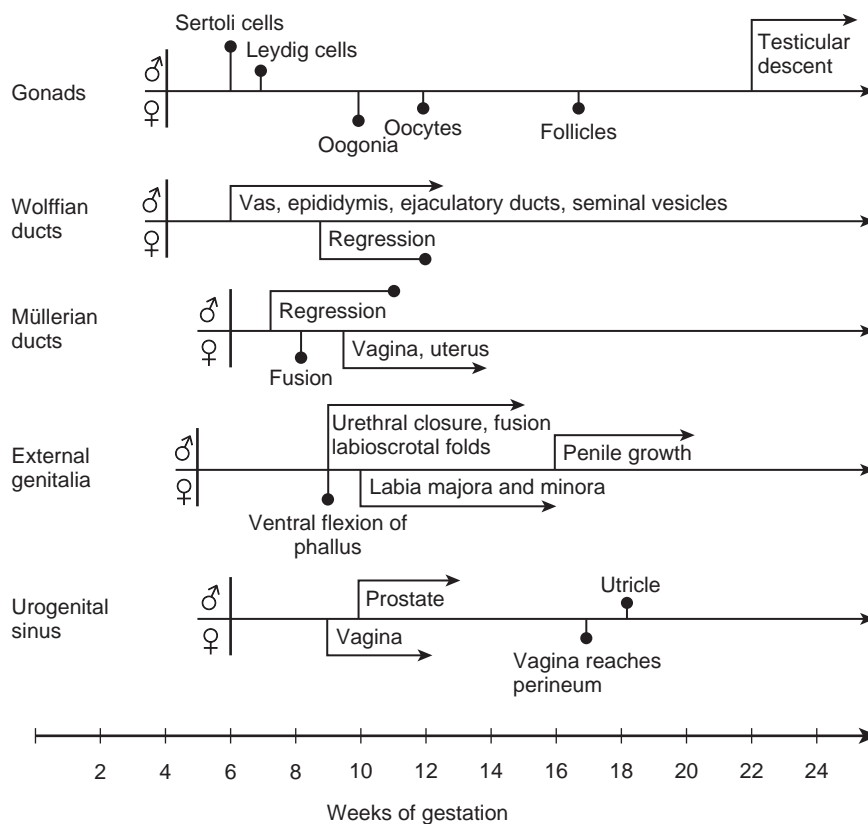


Figure 150-9. Timetable of normal sexual differentiation. (From White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev* 2000;21:245-91.)

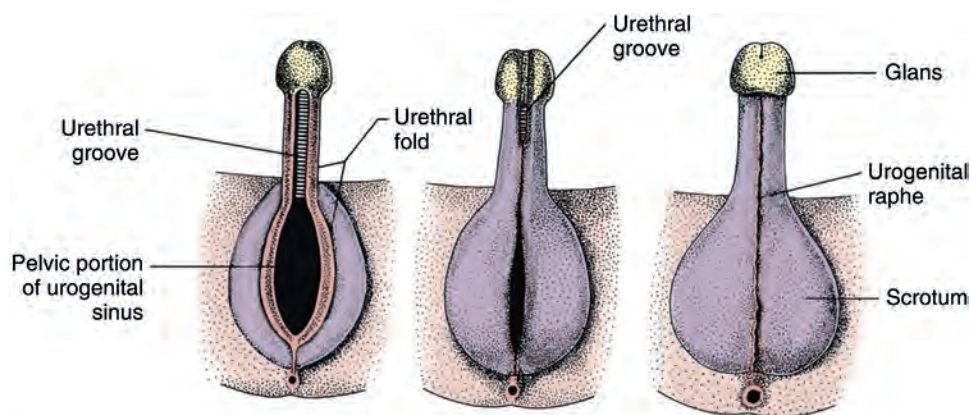


Figure 150-10. Schematic diagram of differentiation of the male external genitalia. (From Martinez-Mora J. Development of the genital tract. In: Martinez-Mora J, editor. *Intersexual states: disorders of sex differentiation*. Barcelona: Ediciones Doymer; 1994. p. 53.)

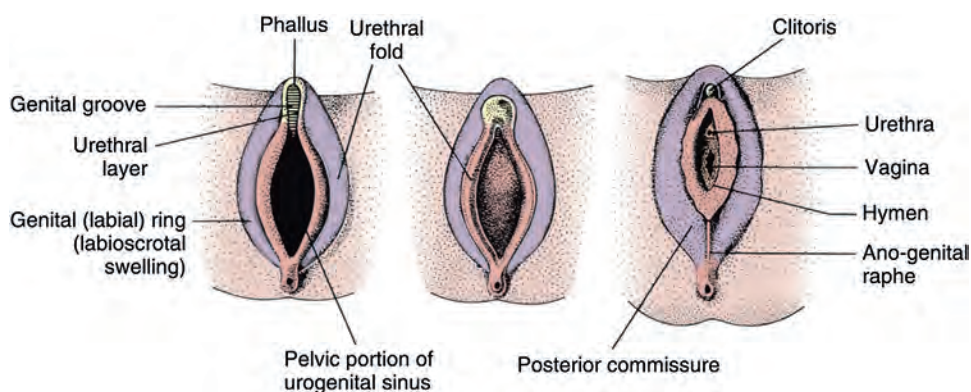


Figure 150-11. Schematic diagram of differentiation of the female external genitalia. (From Martinez-Mora J. Development of the genital tract. In: Martinez-Mora J, editor. *Intersexual states: disorders of sex differentiation*. Barcelona: Ediciones Doymer; 1994. p. 52.)

opposite to their chromosomal or gonadal sex have provided evidence to indicate that gender identity is not merely a function of chromosomal complement or prenatal endocrine milieu. Postnatal environmental factors and learning appear to have an important effect. However, strong evidence has accumulated for the impact of prenatal hormonal influences on sexually dimorphic behavior or gender role. For example, long-term follow-up with CAH patients has supported a greater interest in “tomboyish behavior” than in unaffected girls, although these patterns are not abnormal in relation to female behavior in Western society (Ehrhardt and Meyer-Bahlburg, 1981). Additional information regarding the influence of androgens on gender identity and gender role has arisen from one study of males with cloacal exstrophy who underwent gender reassignment within the first few months of life. A majority of these patients had behaviors and attitudes that reflected strong male-typical characteristics regardless of whether they were raised as males or females (Reiner and Gearhart, 2004). However, a subsequent British study of a similar 46,XY cloacal exstrophy cohort presented contradictory findings (Baker Towell and Towell, 2003). The previously accepted dogma that children are psychosexually neutral at birth and capable of being environmentally oriented (the blue room/pink room theory) has been seriously challenged by those who support the concept of prenatal psychosexual differentiation (Money and Ehrhardt, 1972; Diamond and Sigmundson, 1997). Support for either theory in humans is based on the assessment of a limited number of affected patients. An improved understanding of the “nature versus nurture” controversy will probably prove important in the optimal management of patients with DSDs. However, our increased awareness of physiologically normal patients with genuine “gender dysphoria” has illustrated the complexity of this process.

KEY POINT: PSYCHOSEXUAL DIFFERENTIATION

- The previously accepted dogma that children are psychosexually neutral at birth and capable of being environmentally oriented (the blue room/pink room theory) has been seriously challenged by those who support the concept of prenatal psychosexual differentiation.

ABNORMAL SEXUAL DIFFERENTIATION

The classification of DSDs (previously *intersex disorders*) has undergone evolutionary change as understanding of the etiologic mechanisms of normal and abnormal sexual differentiation has improved. As a result, classification systems vary. We have borrowed from the system used by Grumbach and Conte (1998), which incorporates the historical emphasis on classification by gonadal morphology, and introduced more contemporary terminology (Hughes et al, 2006). Descriptive terms for abnormal gonadal histology have been retained, with the exception of *true hermaphroditism*, which has been replaced by *ovotesticular DSD*. However, for masculinized 46,XX females with two ovaries, *female pseudohermaphroditism* has been replaced by 46,XX DSD; and for undermasculinized 46,XY males the term *male pseudohermaphroditism* has been replaced by 46,XY DSD. The first category consists of disorders of gonadal differentiation; the second includes ovotesticular DSD; the third includes 46,XX DSD (the masculinized female, that is, ovaries present but external genitalia exhibiting evidence of masculinization); the fourth includes 46,XY DSD (the undermasculinized male, that is, testes present but genital ducts and/or external genitalia incompletely masculinized); and the fifth category consists of unclassified forms. Within each category, remarkable advances in chromosomal and biochemical information have allowed subclassification of disorders based on etiologic mechanisms, contributing to a more rational classification system (Box 150-1).

BOX 150-1 Abnormal Sexual Differentiation

1. Disorders of gonadal differentiation
 - Seminiferous tubule dysgenesis
 - Klinefelter syndrome
 - 46,XX male
 - Syndromes of gonadal dysgenesis
 - Turner syndrome
 - Pure gonadal dysgenesis
 - Mixed gonadal dysgenesis
 - Partial gonadal dysgenesis (dysgenetic male pseudohermaphroditism)
 - Bilateral vanishing testis, testicular regression syndromes
2. Ovotesticular DSD (true hermaphroditism)
3. 46,XX DSD (masculinized female)
 - Congenital adrenal hyperplasia (21-hydroxylase, 11 β -hydroxylase, 3 β -hydroxysteroid dehydrogenase deficiencies)
 - Maternal androgens
4. 46,XY DSD (undermasculinized male)
 - Leydig cell agenesis, unresponsiveness
 - Disorders of testosterone biosynthesis
 - Variants of congenital adrenal hyperplasia affecting corticosteroid and testosterone synthesis
 - StAR deficiency (congenital lipoid adrenal hyperplasia)
 - Cytochrome P450 oxidoreductase (POR) deficiency
 - 3 β -Hydroxysteroid dehydrogenase deficiency
 - 17 β -Hydroxylase deficiency
 - Disorders of testosterone biosynthesis
 - 17,20-Lyase deficiency
 - 17 β -Hydroxysteroid oxidoreductase deficiency
 - Disorders of androgen-dependent target tissue
 - Androgen receptor and postreceptor defects
 - Syndrome of complete (severe) androgen insensitivity
 - Syndrome of partial androgen insensitivity
 - Mild androgen insensitivity syndrome (MAIS)
 - Disorders of testosterone metabolism by peripheral tissues
 - 5 α -Reductase deficiency
 - Disorders of synthesis, secretion, or response to müllerian-inhibiting substance
 - Persistent müllerian duct syndrome
5. Unclassified forms
 - In females: Mayer-Rokitansky-Küster-Hauser syndrome

DSD, disorder of sex development.

Disorders of Gonadal Differentiation and Development

Klinefelter Syndrome and Variants

In 1942, Klinefelter, Reifenstein, and Albright described a syndrome characterized by eunuchoidism, gynecomastia, azoospermia, increased gonadotropin levels, and small, firm testes. By 1959, these patients were noted to have a 47,XXY karyotype (Jacobs and Strong, 1959).

Klinefelter syndrome represents the most common major abnormality of sexual differentiation. By definition, males with at least one Y chromosome and at least two X chromosomes have Klinefelter syndrome. The classic 47,XXY complement arises as a result of nondisjunction during meiosis; it occurs in 1 of 600 live-born males (Morris et al, 2008). But the phenotype is also associated with 48,XXYY and 49,XXXYY, and an exaggerated form of the phenotype is associated with 48,XXXY and 49,XXXXY. The mosaic form

46,XY/47,XXY is associated with a milder version of the phenotypic features of classic 47,XXY Klinefelter syndrome. Perhaps as a result of phenotypic variability, Klinefelter syndrome is believed to be underdiagnosed, with a 25% diagnostic rate in one Danish study (Bojesen et al, 2004).

In 47,XXY adults, seminiferous tubules degenerate and are replaced with hyaline. As a result, testes are firm and small, less than 3.5 cm in length. Histologically, Leydig cells appear to be present in large numbers because they are seen in large clumps in certain areas of the testes, sometimes resembling Leydig cell tumors. However, the absolute volume of Leydig cells is not increased and is probably lower than normal. Serum levels of testosterone are low-normal and those of gonadotropins are elevated. Plasma estradiol levels tend to be high, with gynecomastia the result of an increased ratio of estradiol to testosterone. The vast majority of patients are azoospermic, and the presence of sperm suggests 46,XY/47,XXY mosaicism. There does appear to be a depletion of germ cells with the onset of puberty (Wikström et al, 2004). Fertility, with the benefit of testicular sperm extraction (TESE) and intracytoplasmic sperm injection, has been reported in patients with Klinefelter syndrome (Koga et al, 2007). Some infertility experts advocate coupling intracytoplasmic sperm injection with preimplantation diagnosis, given the lower rate of normal embryos from Klinefelter syndrome patients (54%) versus controls (77%) (Staessen et al, 2003).

The decreased androgen production may impair normal secondary sexual development. Muscle development may be poor, and the fat distribution is more female than male. Normal amounts of pubic and axillary hair may be present, but facial hair is sparse. Patients tend to be taller than average, mainly because of the disproportionate length of their legs, which is present even in childhood. Otherwise, few if any distinguishing features are present in the prepubertal child.

Gynecomastia, which can be quite marked, is a common pubertal development in patients with Klinefelter syndrome. As a result, these patients have eight times the risk for development of breast carcinoma compared with normal males (Hamden et al, 1971). In addition, they are predisposed to developing malignant neoplasms of extragonadal germ cell origin as well as Leydig and Sertoli cell tumors (Völkl et al, 2006). Therefore, routine surveillance scrotal ultrasonography has been advocated for postpubertal patients with Klinefelter syndrome.

An intriguing area of research has been in the neuropsychiatric function of Klinefelter syndrome patients. Studies have demonstrated depressed verbal ability and limitations in frontal executive functioning. Recent imaging studies have shown selective volume differences in corresponding areas of Klinefelter syndrome patients' brains versus those of normal subjects (Giedd et al, 2007). Other studies have demonstrated altered cerebral perfusion in Klinefelter syndrome, corresponding to impaired verbal skills (Itti et al, 2003).

Management of Klinefelter syndrome entails careful androgen supplementation in selected male patients to improve libido and reduction mammoplasty if necessary. Surveillance for testicular tumor and breast carcinoma is also appropriate. Assisted reproductive techniques now offer potential fertility to nonmosaic Klinefelter syndrome patients. Microdissection testicular sperm extraction (micro-TESE) results in sperm retrieval rates in the 40% to 50% range, with higher rates in younger men (Bryson et al, 2014). Research efforts to determine whether sperm retrieval rates are higher in adolescent males than in adult males are ongoing.

46,XX Males

The condition of 46,XX maleness, which occurs in 1 of every 20,000 males, may be closely related to that of Klinefelter syndrome. Historically, the genetic analysis of subjects with sex reversal who had a phenotypic sex different from that anticipated based on karyotype was crucial for identification of the SRY gene.

XX maleness, first recognized by de la Chappelle and coworkers in 1964, is characterized by testicular development in subjects

who have two X chromosomes and lack a normal Y chromosome. Most of these subjects have normal male external genitalia, but 10% have hypospadias and all are infertile. Among infertile adults, 2% have XX maleness (Van Dyke et al, 1991).

Two categories of patients with XX maleness have been identified: the 90% who are SRY positive and those who are SRY negative (Ergun-Longmire et al, 2005). The SRY-positive group rarely have genital abnormalities, but they have phenotypic features of Klinefelter syndrome, including hypogonadism, gynecomastia, azoospermia, and hyalinization of seminiferous tubules with altered hormonal levels at puberty (low testosterone, increased follicle-stimulating hormone [FSH] and LH) (Fechner et al, 1993). Often the diagnosis is made in a pubertal male who is seen for evaluation of gynecomastia. **These patients differ from those with Klinefelter syndrome in that they are shorter (mean height, 168 cm) and have normal skeletal proportions.** The 10% of XX males with no detectable SRY more commonly have genital ambiguity.

Three mechanisms have been proposed to explain XX sex reversal. **The most common is translocation of Y-chromosomal material, including SRY, to the X chromosome.** Clearly, this can be proven in the majority of patients. Alternatively, sex reversal could result either from the mutation of an autosomal or X-chromosomal gene, permitting testicular differentiation downstream from SRY, or from undetected mosaicism with a Y-bearing cell line. Clinical studies have demonstrated XX sex reversal to be a genetically and phenotypically heterogeneous condition (Fechner et al, 1993).

Treatment of XX maleness is similar to that for Klinefelter syndrome. Androgen replacement benefits selected patients, and reduction mammoplasty may be beneficial. It is likely that these patients will also be at increased risk for breast carcinoma and testis tumor. Because of their lack of germ cell elements, those classic patients with infertility would not benefit from testicular biopsy for potential intracytoplasmic sperm injection.

Syndromes of Gonadal Dysgenesis

Turner Syndrome. In 1938, Henry Turner described the combination of sexual infantilism, webbed neck, and cubitus valgus (increased carrying angle at the elbows) as a distinct entity. Subsequently, gonadal dysgenesis was recognized as part of this syndrome (Hall and Gilchrist, 1990). It was not until 1959 that Ford recognized that one missing X chromosome was the etiologic basis for the syndrome. Subsequent chromosomal studies showed that **Turner syndrome is characterized by the presence of only one normally functioning X chromosome.** The other sex chromosome may be absent or abnormal, or mosaicism may be present.

Turner syndrome, with a 45,X karyotype, is associated with four classic features: female phenotype, short stature, lack of secondary sexual characteristics, and a variety of somatic abnormalities. However, the clinical features of Turner syndrome are quite variable, and almost any combination of physical features may be seen with any X-chromosomal abnormality. The severity of phenotypic features does not necessarily correlate with karyotypic findings. The diagnosis of Turner syndrome should be considered in any infant with lymphedema or any young woman with short stature or primary amenorrhea. Deletions in the short stature homeobox gene (*SHOX*) located on the pseudoautosomal region of the X and Y chromosomes have been suggested as the basis for the short stature in this syndrome.

Turner syndrome has an incidence of 1 in 2500 live births. Half of the patients have a 45,X karyotype in all cells; this is believed to be secondary to loss of an X chromosome through nondisjunction in gametogenesis or an error in mitosis. From 12% to 20% of patients with Turner syndrome have an isochromosome X (duplication of one arm of the X chromosome with loss of the other arm). Mosaicism—the presence of two or more chromosomally different cell lines—occurs in 30% to 40% of these patients, the majority (10% to 15%) being 45,X/46,XX and 2% to 5% being 45,X/46,XY (Zinn et al, 1993). **The presence of Y-chromosomal material is of critical importance in patients with Turner**

syndrome because it predisposes them to potential masculinization and gonadoblastoma.

Turner syndrome may be diagnosed prenatally on the basis of a variety of ultrasound findings (increased nuchal translucency, lymphedema, cystic hygroma, coarctation of the aorta, renal anomalies) or by abnormal results of fetal karyotyping. Affected fetuses often abort spontaneously. Whereas a 45,X fetus identified prenatally has a prognosis similar to that of a child with Turner syndrome diagnosed postnatally, approximately 90% of fetuses in whom a 45,X/46,XX or 45,X/46,XY karyotype is incidentally diagnosed prenatally will have a normal female or male phenotype at birth. This so-called ascertainment bias in Turner syndrome has profound implications for prenatal counseling.

It is postulated that in Turner syndrome follicular cells that normally surround the germ cells and provide a protective mantle for the oocytes are inadequate (Stanhope et al, 1992). As a result, the rate of attrition of oocytes from apoptosis is so rapid that by birth few or no oocytes remain in the ovaries, which become streaks (Epstein, 1990). Typically, these streaks are white, fibrous structures, 2 to 3 cm long and approximately 0.5 cm wide, located in the broad ligament. Histologically, the streak possesses interlacing waves of dense fibrous stroma that is devoid of oocytes but is otherwise indistinguishable from normal ovarian stroma. Both estrogen and androgen are decreased, and levels of FSH and LH are increased. Secondary sexual development does not occur in the majority of patients. Pubic and axillary hair fails to develop in normal abundance, and the well-differentiated external genitalia, vagina and müllerian derivatives, and breasts remain small (Saenger, 1996). Turner syndrome is a common cause of primary amenorrhea, and the diagnosis is frequently made because pubertal development never occurs. Spontaneous pubertal development may occur in up to 30% of Turner syndrome patients, however.

The associated congenital anomalies that are thought typical in Turner syndrome include short stature, broad chest, widespread nipples, webbing of the neck, peripheral edema at birth, short fourth metacarpal, hypoplastic nails, multiple pigmented nevi, coarctation of the aorta, bicuspid aortic valve, and renal anomalies (Fig. 150-12). The majority of the associated congenital anomalies can be explained by the presence of lymphedema at critical points in development, leading to an imbalance in growth forces. This may be secondary to failed opening of embryonic lymphatic channels (Zinn et al, 1993).

Of paramount importance in the assessment of the patient with Turner syndrome is identification of Y-chromosomal material or

45,X/46,XY mosaicism, whose detection has been enhanced by use of the polymerase chain reaction (PCR) (Bianco et al, 2006). In patients with occult Y-chromosomal material, the risk of gonadoblastoma, an *in situ* germ cell cancer, is 12% and is being further defined (Schoemaker et al, 2008). Gonadoblastoma is associated with dysgerminoma or other germ cell neoplasms in 50% to 60% of patients, sometimes associated with virilization. Because the age of occurrence of gonadoblastoma is variable and has been reported as early as age 10 months (Palmer, personal communication, 2013), timely prophylactic excision of the streak gonads in the Y mosaic Turner syndrome patient is advised. This may be well performed laparoscopically. Streak gonads confirmed to be in 45,XO patients need not be removed. In the recent British national cohort study there was also an increased risk of bladder and urethral cancer in Turner syndrome patients followed into adulthood (Schoemaker et al, 2008).

From 33% to 60% of patients with Turner syndrome have structural or positional abnormalities of the kidney; this occurs most frequently in the classic 45,XO karyotype (Hall and Gilchrist, 1990). Horseshoe kidney accounts for 10%, duplication or renal agenesis for 20%, and malrotation for 15% of these abnormalities. Multiple renal arteries have been noted in 90% of patients with Turner syndrome as a result of their cardiovascular evaluation (Hall and Gilchrist, 1990).

The contemporary treatment of patients with Turner syndrome has undergone considerable advances. In the neonate, it entails a concerted search for occult Y-chromosomal material, including fluorescence *in situ* hybridization (FISH) or PCR and, subsequently, prophylactic gonadectomy if necessary, as well as ultrasound screening for renal and cardiac abnormalities. In the child, human growth hormone has successfully been used to achieve increased adult height (Pasquino, 2004). At an appropriate age, typically 12 to 15 years, exogenous hormonal therapy to induce puberty and then to maintain a normal female endocrine status is begun. An improved understanding of the long-term medical management of these patients, including cardiac surveillance and management of glucose intolerance and osteoporosis, has also resulted in considerable progress. Finally, with the remarkable advances in assisted reproductive technology, pregnancy is a realistic possibility for patients with Turner syndrome, although spontaneous fertility is rare (Sybert and McCauley, 2004). A spectrum of potential gonadal function has been noted in large series of patients with Turner syndrome (Kaneko et al, 1990). In one series, nonstreak gonads were reported in one third of such patients and were more commonly noted in girls with loss of only the short arm of the X chromosome. In 2% to 5% of Turner patients, spontaneous menses will occur with a potential to achieve pregnancy independently (Saenger et al, 2001). This appears most likely in women with mosaicism for a normal 46,XX cell line, a 47,XXX cell line, or distal Xp deletion. To date, more than 160 pregnancies have been reported among spontaneously menstruating Turner syndrome patients. For the vast majority with true streak gonads, for whom egg donor implantation is used, 40% to 50% pregnancy rates have been reported by centers specializing in *in vitro* fertilization (Saenger, 1993). However, among these rare pregnancies, the rates of miscarriage, stillbirth, and malformed infants are high (Abir et al, 2001). Because of a high likelihood of premature ovarian failure, early oocyte preservation may be useful for long-term fertility preservation. Techniques for mature oocyte cryopreservation have dramatically improved, resulting in a recent guideline stating that the technology should no longer be considered experimental (Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology, 2013). However, the risk of chromosomal abnormalities and unknown efficacy of oocyte preservation in this population require further investigation.

It is of great interest that neuroanatomic imaging studies of 45,XO Turner syndrome patients have demonstrated differences in parietal and temporal lobe anatomy and posterior fossa morphology that appear to correlate with certain established neurophysiologic and cognitive deficits (Brown et al, 2004; Rae et al, 2004).



Facial features

- Ptosis
- Hypertelorism
- Retrognathia
- Ear malformations

Body features

- Neck webbing
- Broad chest
- Widely spaced nipples
- Elbow deformity (cubitus valgus)

Reproductive tract

- Streak ovaries
- Amenorrhea
- Infertility

Figure 150-12. Patient with Turner syndrome as originally described by Ullrich in 1930. (From Ullrich O. Über typische Kombinationsbilder multipler Abartungen. *Z Kinderheilkd* 1930;49:271–76.)

KEY POINTS: TURNER SYNDROME

- In patients with Turner syndrome and occult Y-chromosomal material, the risk of gonadoblastoma, an in situ germ cell cancer, is 12% and is being further defined.
- Young women with Turner syndrome and spontaneous menses are at high risk for premature ovarian failure. Mature oocyte cryopreservation is now an option.

46,XX “Pure” Gonadal Dysgenesis. Patients with 46,XX “pure” gonadal dysgenesis are characterized by normal female external genitalia, normal müllerian ducts with absence of wolffian duct structures, a normal height, bilateral streak gonads, sexual infantilism, and a normal 46,XX karyotype. The streak gonads result in elevated serum gonadotropins. Because these subjects exhibit none of the somatic stigmata associated with Turner syndrome and their condition entails gonadal dysgenesis only, it has been regarded by some authors as “pure.”

A familial incidence of 46,XX gonadal dysgenesis has been reported as an autosomal recessive trait (Espinosa et al, 1970). This suggests the possibility that autosomal genes in addition to genes on the X chromosome may be involved in ovarian maintenance.

Management of patients with 46,XX pure gonadal dysgenesis entails proper cyclic hormone replacement with estrogen and progesterone. In contrast to Turner syndrome, growth is not abnormal with this condition, and therefore growth hormone should not be required. Because, by definition, these patients have no Y-chromosomal material, gonadectomy is not required.

Mixed Gonadal Dysgenesis. The term *mixed gonadal dysgenesis* was coined by Sohval in 1963. In 1975, Zah and associates reported on their series of more than 100 patients with 45,X/46,XY karyotypes, 72 of whom had mixed gonadal dysgenesis with a streak gonad on one side and a testis on the other.

Mixed gonadal dysgenesis is characterized by a unilateral testis, which is often intra-abdominal, a contralateral streak gonad, and persistent müllerian structures associated with varying degrees of inadequate masculinization. Most patients with mixed gonadal dysgenesis have a 45,XO/46,XY karyotype, which is probably the result of anaphase lag during mitosis. The 45,X/46,XY mosaicism is the most common form of mosaicism involving the Y chromosome.

The phenotypic spectrum of patients with XO/XY mosaicism ranges from phenotypic females with Turner syndrome, to those with ambiguous genitalia, to those with normal male genitalia (Johansen et al, 2012). In the neonatal period, mixed gonadal dysgenesis is the second most common cause of ambiguous genitalia (after CAH) and must be in the differential diagnosis. The majority of these patients have varying degrees of phallic development, a urogenital sinus with labioscrotal fusion, and an undescended testis. In virtually all of these patients, a uterus, vagina, and fallopian tube are present. Short stature and associated somatic stigmata are variable features.

KEY POINT: MIXED GONADAL DYSGENESIS

- In the newborn period, mixed gonadal dysgenesis is the second most common cause of ambiguous genitalia (after CAH) and must be in the differential diagnosis.

The phenotypic asymmetry of the internal ducts epitomizes the mechanism of local testosterone and MIS production on müllerian and wolffian duct regression and development. In the series of Mendez and colleagues (1993) consisting of 16 patients, all had a fallopian tube accompanied by a streak gonad, consistent with

absent MIS. Therefore, whereas a dysgenetic or streak gonad is associated with ipsilateral müllerian derivatives (uterus, fallopian tube) (Fig. 150-13), a well-differentiated testis with functional Sertoli and Leydig cells will have ipsilateral wolffian but no müllerian ducts (Davidoff and Federman, 1973). In addition, the presence of severe external genital ambiguity in many of these patients suggests that testosterone production in utero was inadequate to promote complete differentiation of the external genitalia. Paradoxically, the dysgenetic testis is capable of responding to gonadotropins and secreting testosterone in normal quantities at puberty. Yet, despite normal postpubertal endocrine function, it is postulated that fetal testicular endocrine function is either delayed or deficient. Histologically, the testes lack germinal elements, so infertility is the rule.

The risk of developing a gonadal tumor (gonadoblastoma, dysgerminoma) is increased in mixed gonadal dysgenesis, with an estimated incidence of 15% to 35% (Robboy et al, 1982; Wallace and Levin, 1990). Gonadoblastoma, a tumor of low malignant potential, is the most common. It was so named because it recapitulates gonadal development more completely than any other tumor (Scully, 1970). Although germ cell tumors occur both in the dysgenetic testes and in the streak gonads of individuals with 46,X/46,XY mosaicism, the risk of tumor is higher in the former (Verp and Simpson, 1987).

Patients with mixed gonadal dysgenesis are also at increased risk for Wilms tumor. Rajfer (1981) reported that 50% of 10 patients with an intersex disorder and Wilms tumor had mixed gonadal dysgenesis. He postulated that there was a genetic or teratogenic defect involving the urogenital ridge, the common embryonic anlage of both kidney and gonad. This concept was borne out by improved understanding of the Denys-Drash syndrome, now clearly associated with mutations in the Wilms tumor suppressor gene (*WT1*). In 1967, Denys and colleagues described a child with XX/XY mosaicism, nephropathy, genital abnormalities, and Wilms tumor. Drash and coworkers (1970) reported two further examples in 1970. The full triad of the syndrome includes nephropathy, characterized by the early onset of proteinuria and hypertension, and progressive renal failure in most of the patients. Renal histology demonstrates diffuse focal mesangial sclerosis. Because incomplete forms of the syndrome may occur, the nephropathy has become regarded as the common denominator of the syndrome (Habib et al, 1985). Wilms tumor may be diagnosed before, after, or simultaneously with presentation with nephropathy. The majority of the tumors are of favorable triphasic histology (Beckwith and Palmer, 1978). However, there is a high incidence of bilateral Wilms tumor in this syndrome. The genital abnormalities include frank ambiguity, hypospadias, and cryptorchidism. A large number of patients with Denys-Drash syndrome have been noted to have mixed gonadal dysgenesis. These have an increased risk of gonadal tumor of 40% (Table 150-2) (Lee et al, 2006). An interesting and relatively consistent finding with Denys-Drash syndrome is that of calyceal blunting without obstruction (Jadresic et al, 1990). The high mortality rate associated with this syndrome has prompted an aggressive treatment approach with prophylactic bilateral nephrectomy in an attempt to improve the prognosis for these children (Jadresic et al, 1990).

Frasier syndrome, a related disorder caused by mutations in the alternative splice donor site of exon 9 on *WT1*, manifests in similar fashion to Denys-Drash syndrome but with certain important distinctions (Klamt et al, 1998). The nephropathy caused by focal segmental glomerulosclerosis occurs later in life with a more gradual progression to renal failure (Koziell et al, 1999). There is no known predisposition to Wilms tumor. Gonadoblastomas in 46,XY individuals are far more common in Frasier syndrome than in Denys-Drash syndrome, with a gonadal tumor risk of 60% (see Table 150-2). Because 46,XX individuals with Frasier syndrome have normal gonadal development, they would have renal failure. However, it is presumed that many such 46,XX individuals go undiagnosed. Frasier syndrome should be considered in girls with steroid-resistant nephrotic syndrome, primary amenorrhea, and pubertal delay (Gwin et al, 2008).

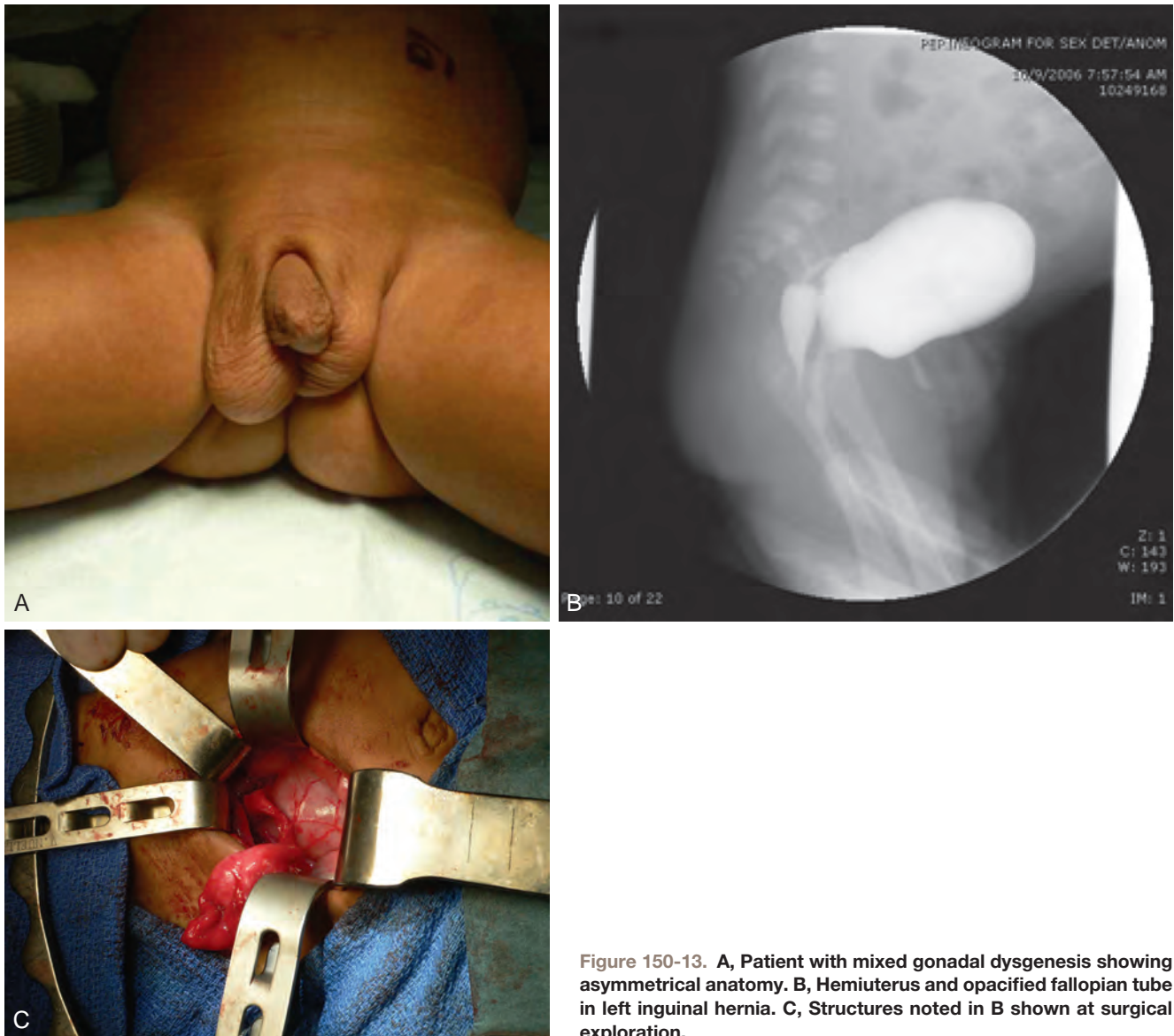


Figure 150-13. A, Patient with mixed gonadal dysgenesis showing asymmetrical anatomy. B, Hemiuterus and opacified fallopian tube in left inguinal hernia. C, Structures noted in B shown at surgical exploration.

The management of mixed gonadal dysgenesis entails gender assignment, appropriate gonadectomy, and proper screening for Wilms tumor. If the diagnosis is made in the neonatal period, the decision regarding sex of rearing should be based on the potential for normal function of the external genitalia and gonads. Historically, two thirds of patients with mixed gonadal dysgenesis have been raised as female. Potential fertility is not a significant issue in this disorder, and therefore the anatomy of the reproductive tract may direct the decision making. The likelihood of significant androgen imprinting is greater in association with a better-masculinized phenotype, and this may serve as the best clinical guide. For patients with Turner syndrome stigmata and growth below the fifth percentile, growth hormone therapy may be appropriate. If the male gender is elected and the testis can be brought to the scrotum, the decision between careful screening for gonadoblastoma (with physical examination and ultrasonography) versus prophylactic gonadectomy and androgen replacement must be made.

The expanded use of prenatal diagnosis has changed the understanding of 45,X/46,XY mosaicism. Studies have shown that 90% to 95% of all infants with 45,X/46,XY mosaicism have normal-appearing male genitalia (Hsu, 1989). Approximately 25% have abnormal gonadal histology (Chang et al, 1990). Because only a small proportion of those with dysgenetic gonads actually have

ambiguous genitalia, the possibility exists that some males with gonadal dysfunction have 45,X/46,XY mosaicism.

Partial Gonadal Dysgenesis. In 1967, Federman coined the term *dysgenetic male pseudohermaphroditism*, which is a condition closely related to mixed gonadal dysgenesis in that patients with abnormal sex differentiation have two dysgenetic testes rather than one dysgenetic testis and a streak gonad. Others have applied the term *partial gonadal dysgenesis* to this condition, to distinguish it from mixed and complete forms of gonadal dysgenesis. As with mixed gonadal dysgenesis, these individuals typically have a 45,X/46,XY or 46,XY karyotype. They may have a spectrum of external genital abnormalities, depending on the capability of the dysgenetic gonads to produce testosterone. Similarly, persistent müllerian structures are typically present, but to varying degrees depending on MIS secretion by the dysgenetic gonads.

On histology, the dysgenetic testis is found to be composed of immature hypoplastic seminiferous tubules and persistent stroma resembling that seen in the streak gonad.

Patients with partial gonadal dysgenesis are at increased risk for gonadal malignancy. Manuel and colleagues (1976) reported that the incidence of gonadoblastoma or dysgerminoma was 46% by age 40 years. These patients are also at risk for Denys-Drash syndrome (Borer et al, 1995).

The management of partial gonadal dysgenesis, in terms of gender assignment and surveillance for malignancy, is similar to that for patients with mixed gonadal dysgenesis.

46,XY Complete ("Pure") Gonadal Dysgenesis (Swyer Syndrome). Just as 46,XX males were of great importance in discovery

of the TDE, so too have been 46,XY females. **Patients with 46,XY complete gonadal dysgenesis are characterized by normal female genitalia, well-developed müllerian structures, bilateral streak gonads, and a nonmosaic karyotype.** Because there is complete absence of testicular determination in this condition, ambiguity of genitalia is not an issue, but sexual infantilism is the primary clinical problem.

The cause of 46,XY complete gonadal dysgenesis may well be an abnormality of the *SRY* gene that eliminates *SRY* function, or loss of another gene downstream from *SRY* that is necessary for *SRY* protein action. In either case, the absence of testicular determination would permit ovarian differentiation. To date, mutations in the *SRY* gene are the cause of 46,XY complete gonadal dysgenesis in 10% to 15% of cases. Mutation in the desert hedgehog (*DHH*) gene was noted in three of six patients with 46,XY complete gonadal dysgenesis, suggesting that the genetic origin of this entity is heterogeneous and that *DHH* is likely an important gene in gonadal differentiation (Canto et al, 2004). Investigation of a group of individuals with 46,XY complete gonadal dysgenesis has helped to identify a candidate chromosome interval containing the sex reversal gene to 9p24 (McDonald et al, 1997).

The majority of individuals with 46,XY complete gonadal dysgenesis are in their teens at presentation with delayed puberty and amenorrhea. Breast development is usually absent. The serum concentration of gonadotropins is abnormally elevated, which leads the clinician to the determination of karyotype and the subsequent diagnosis (Grumbach and Conte, 1998). The high concentration of serum LH in these patients is thought to be responsible for the increased androgen levels that lead to clitoromegaly in some individuals (Fig. 150-14).

The histology of the streak gonad is similar to that of Turner syndrome, with fibrous connective tissue resembling wavy ovarian stroma but without follicles. Some histologic variability has been noted, with more proliferative-appearing stroma in some and, rarely, preservation of intact primordial follicles. This variability in ovarian histology is thought to support the hypothesis that these

TABLE 150-2 Risk of Germ Cell Malignancy According to Diagnosis

RISK GROUP	DISORDER	MALIGNANCY RISK (%)
High	GD*(+Y)† intra-abdominal	15-35
	PAIS nonscrotal	50
	Frasier	60
	Denys-Drash (+Y)	40
Intermediate	Turner (+Y)	12
	17β-hydroxysteroid	28
	GD (+Y)† scrotal	Unknown
	PAIS scrotal gonad	Unknown
Low	CAIS	2
	Ovotesticular DSD	3
	Turner (–Y)	1

*Gonadal dysgenesis ([GD], including not further specified, 46,XY, 46,X/46,XY, mixed, partial, and complete).

†GBY region positive, including the *TSPY* (testis-specific protein Y encoded) gene.

CAIS, complete androgen insensitivity syndrome; DSD, disorder of sex development; PAIS, partial androgen insensitivity syndrome.

From Lee PA, Houk CP, Ahmed F, et al. Consensus statement on management of intersex disorders. *Pediatrics* 2006;118:e488–500.



Figure 150-14. A and B, External genitalia of a 15-year-old girl with amenorrhea and hirsutism who was diagnosed with 46,XY gonadal dysgenesis, demonstrating clitoromegaly and urogenital sinus. (Courtesy S. Bauer, MD.)

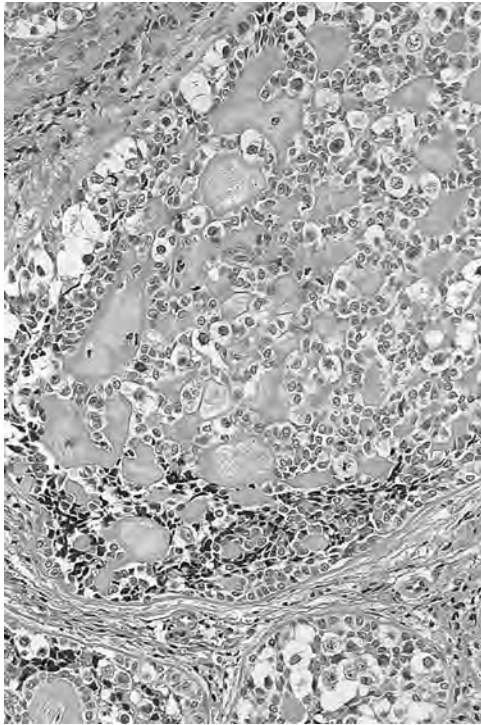


Figure 150-15. Pathology of gonadoblastoma discovered in the patient shown in Figure 150-14 with 46,XY gonadal dysgenesis. Encapsulated nests of gonadoblastoma consist of small sex cord-type cells arranged around rounded spaces of amorphous eosinophilic material and interspersed germ cells. (Courtesy S. Bauer, MD.)

gonads developed as ovaries in utero (German et al, 1978). This would resemble the process that occurs in the streak gonad of Turner syndrome.

Patients with 46,XY complete or pure gonadal dysgenesis are at significant risk for germ cell tumors. There appears to be up to a 35% risk of tumor development by age 30 years (Manuel et al, 1976; see Table 150-2). Gonadoblastoma is most common, and it is frequently bilateral (Fig. 150-15). Other tumors that may arise in this patient population include embryonal carcinoma, endodermal sinus tumor, choriocarcinoma, and immature teratoma. These more highly malignant tumors occur in fewer than 10% of patients with 46,XY complete gonadal dysgenesis (Scully, 1981).

Management of 46,XY complete gonadal dysgenesis entails removal of both streak gonads and proper cyclic hormone replacement with estrogen and progesterone.

Embryonic Testicular Regression and Bilateral Vanishing Testes Syndromes

The syndromes of embryonic testicular regression and bilateral vanishing testes are characterized by patients with a 46,XY karyotype and absent testes in whom there is clear evidence of testicular function at some point during embryogenesis. The syndrome entails the presence of testes that “vanish” during embryogenesis and is distinguished from pure gonadal dysgenesis, in which there is no evidence of testicular function in utero.

These syndromes have been regarded as synonymous by some authors. Other authors, including Migeon and colleagues (1994), have suggested a rational stratification whereby *embryonic testicular regression* refers to loss of testicular tissue within the first trimester and is associated with ambiguity of external genitalia, whereas

bilateral vanishing testes syndrome refers to individuals in whom male sexual differentiation of ducts and genitalia took place but loss of testicular tissue occurred subsequently in utero.

The cause of these disorders remains unclear. It is possible that regression of the testes in utero is caused by a genetic mutation, a teratogen, or bilateral torsion. A genetic cause is supported by the finding of familial instances of XY gonadism that might be consistent with the rare recessive trait. Marcantonio and associates (1994) suggested the possibility that embryonic testicular regression represents a variant of 46,XY gonadal dysgenesis. They noted a group of patients with absent testes but evidence of incongruity between the extent of Leydig cell and Sertoli cell function, suggesting that gonadal tissue in these patients was intrinsically abnormal before the testicular regression occurred. The occurrence of embryonic testicular regression in several subjects from one family in their series suggested a genetic basis for the condition, and the pattern of inheritance implicated the involvement of an X chromosome gene. In another group of patients, these authors noted multiple congenital anomalies, suggesting either a mutation in a single gene that functions in several developmental pathways or a defect of multiple genes that might be the result of a large chromosomal deletion. A heterozygous mutation in *SF1* has been noted in a series of patients with bilateral vanishing testes syndrome with micropenis (Philibert et al, 2007).

Clinically, these two syndromes represent a spectrum of phenotypes ranging in severity from complete female, to varying degrees of genital ambiguity in the embryonic testicular regression syndrome, to a normal male phenotype with microphallus and empty scrotum in the bilateral vanishing testes syndrome (Edman et al, 1977). The diagnosis can be made on the basis of a 46,XY karyotype, castrate levels of testosterone, elevated serum LH and FSH (Jarow et al, 1986), and undetectable MIS level (Lee et al, 2003). In the most severe form of embryonic testicular regression syndrome, agonadism is discovered in a 46,XY phenotypic female with no internal genital structures. This picture is presumed to result when the testis has elaborated MIS but vanishes at approximately day 60 to 70 of gestation, before the elaboration of androgen. Because of the absence of gonadal androgens later in fetal development and transient expression of MIS, the individual goes on to develop a sexually infantile female phenotype but lacks any internal ductal structures. At an intermediate point in the clinical spectrum is the 46,XY patient with absent gonads and internal ductal structures but with ambiguous genitalia resulting from incomplete elaboration of androgen by the vanishing testes. Finally, in bilateral vanishing testes syndrome, patients may appear as agonadal XY phenotypic males with fully developed wolffian structures but an empty scrotum, absent prostate, and microphallus. This represents testicular loss after complete anatomic development of the male external genitalia within the first trimester.

On surgical exploration of patients with bilateral vanishing testes syndrome, rudimentary cord structures are usually identified and biopsy of their distal ends demonstrates no recognizable testicular tissue histologically (Bergada et al, 1962). Atrophic epididymal remnants are occasionally seen.

The management of patients with embryonic testicular regression syndrome or bilateral vanishing testes syndrome is dictated by their position in the clinical spectrum of either disorder. Sexually infantile phenotypic females require estrogen supplementation at the time of expected puberty for development of secondary sexual characteristics and may require vaginal dilation or vaginoplasty. Similarly, phenotypic males require long-term androgen replacement beginning at the time of expected puberty. A study of 21 males so treated demonstrated that replacement therapy started at the correct time caused a normal pubertal growth spurt with normal secondary sex characteristics including penile growth, together with normal bone maturation (Aynsley-Green et al, 1976). In addition, these patients may benefit from placement of testicular prostheses. Patients with embryonic testicular regression syndrome and ambiguous genitalia require individualized assessment to determine the optimal gender assignment.



Figure 150-16. Infant with penile hypospadias, chordee, and bilaterally undescended testes who was found to have true hermaphroditism. (From Diamond D. *Intersex disorders: I and II. AUA Update Series*, vol. IX, lessons 9 and 10. Houston: American Urological Association Office of Education; 1990.)



Figure 150-17. Laparotomy findings from a true hermaphrodite noted in Figure 150-16; clamp is on uterus with bilateral, fimbriated fallopian tubes and bilateral ovotestes. (From Diamond D. *Intersex disorders: I and II. AUA Update Series*, vol. IX, lessons 9 and 10. Houston: American Urological Association Office of Education; 1990.)

Ovotesticular Disorder of Sex Development

Ovotesticular DSD describes individuals who have both testicular tissue with well-developed seminiferous tubules and ovarian tissue with primordial follicles, which may take the form of one ovary and one testis or, more commonly, one or two ovotestes.

Both the external genitalia and internal duct structures of ovotesticular DSD display gradations between male and female. In most patients the external genitalia are ambiguous but masculinized to variable degrees, and 75% are raised as male. Among those raised as male, hypospadias and chordee occur in approximately 80%. Among those patients raised as female, two thirds have clitoromegaly. Virtually all patients have a urogenital sinus, and in most patients a uterus is present (Figs. 150-16 and 150-17). The ovary is found in a normal location, more commonly on the left side. The testis or ovotestis may reside at any point along the path of testicular descent. Testes and ovotestes are more commonly located on the right side (Blyth and Duckett, 1991; Mittwoch, 2000). Sixty percent of gonads palpable in the inguinal canal or labioscrotal folds are ovotestes, which may be clinically suspected on the basis of a difference in firmness at either end of the gonad, consistent with polar segregation of ovarian and testicular tissue (Grumbach and Conte, 1998). Detailed evaluation of gonads from a large cohort of patients with ovotesticular DSD from South Africa suggests three distinct patterns of gonad development: admixed (central core containing stroma and a mixture of ovarian and testicular tissue), compartmentalized (ovarian tissue in upper pole with lower pole of testicular tissue encapsulated by mantle of ovarian tissue), and bipolar (strict polar distribution of testicular and ovarian tissue) (Wiersma and Ramdial, 2009).

Approximately 60% of patients with ovotesticular DSD have a 46,XX karyotype; 33% are mosaics with a second cell line containing a Y chromosome (46,XX/46,XY; 46,XX/46,XXY), and 7% are 46,XY. Chimerism (mosaicism) has been thought to result from fusion of a fertilized ovum with its polar body, fusion of two nuclei, or double fertilization. It has also been suggested that ovotesticular DSD may result from hidden mosaicism with a Y cell line. Ortenberg and colleagues (2002) demonstrated the SRY gene in ovotestes of all eight patients with ovotesticular DSD studied, supporting somatic mosaicism. Other studies have demonstrated heterogeneity of Y-specific DNA regions detected in patients with ovotesticular DSD (Hadjithanasiou et al, 1994). This supports a non-Y chromosome-related mechanism responsible for 46,XX ovotesticular DSD, such as mutation in an autosomal or X-linked gene involved in sex determination. Berkovitz and colleagues (1991)

suggested that 46,XY ovotesticular DSD may be a form of partial gonadal dysgenesis. According to this theory, a partial defect in testis determination results in both testicular and ovarian development. This is supported by the finding of ovarian stroma in some dysgenetic testes.

Just as the differentiation of external genitalia is variable in ovotesticular DSD, differentiation of the internal ducts is also quite variable and is related to the function of the ipsilateral gonad. Fallopian tubes are consistently present on the side of the ovary, and a vas deferens is always present adjacent to a testis (Berkovitz et al, 1991). The ovotestis, which comprises two thirds of gonads in ovotesticular DSD, is associated with a fallopian tube in two thirds of patients and with either a vas deferens only or both structures in one third of patients.

The ovarian portion of the ovotestis is frequently normal, whereas the testicular portion is typically dysgenetic. Therefore, although ovulation and pregnancy have been reported for female patients with 46,XX ovotesticular DSD, male fertility has not been clearly documented.

The incidence of gonadal tumors is approximately 3% in 46,XY ovotesticular DSD and rare in 46,XX ovotesticular DSD. Both gonadoblastoma and dysgerminoma have been described (Verp and Simpson, 1987).

The most important aspect of management in ovotesticular DSD is gender assignment. Sex assignment should be based on the functional potential of external genitalia, internal ducts, and gonads, according to the findings at laparoscopy or laparotomy. Unlike patients with most other forms of gonadal dysgenesis, individuals with ovotesticular DSD have the potential for fertility if raised as female with the appropriate ductal structures. Pregnancies have been reported in patients with ovotesticular DSD, the majority with the 46,XX karyotype (Starceski et al, 1988). If the patient is to be raised as female, all testicular and wolffian tissue should be removed. For those patients with an ovary, this is straightforward; if an ovotestis is present, surgical cleavage of the gonad with excision of the testicular portion has been performed successfully by Nihoul-Fekete and colleagues (1984). They recommend postoperative stimulation with hCG to confirm that all testicular tissue has been removed. In some settings the cleavage plane between testicular and ovarian tissues is unclear, as in admixed pathology as described earlier; gonadectomy is advisable. When ovarian tissue is preserved, normal ovarian function can occur at puberty, although hormonal replacement may be necessary. Careful surveillance for potential gonadal tumors in the patient raised as female is also advisable. If a male gender is assigned, as has been

most common historically, all ovarian and müllerian tissue should be removed. Consideration should be given to gonadectomy at puberty with appropriate androgen replacement in this setting, given the high risk of malignancy and unlikelihood of male fertility. At the very least, long-term gonadal surveillance ultrasound for tumor development would seem appropriate.

46,XX Disorder of Sex Development (Masculinized Female)

46,XX DSD (masculinized female) is a disorder of phenotypic sexual development in which 46,XX individuals with ovaries have a partially masculinized phenotype and ambiguous genitalia. By far the most common cause of the masculinized female is CAH, which is the most common cause of ambiguous genitalia in the newborn. Two very rare causes of 46,XX DSD (masculinized female) are maternal ingestion of androgens and virilizing tumors in the mother.

Congenital Adrenal Hyperplasia. The adrenogenital syndrome caused by CAH is a classic example of an inborn error of metabolism—in this case, an error involving cortisol synthesis. A defect in any one of the five enzymes involved in the cortisol biosynthetic pathway (cholesterol side chain cleavage enzyme, 3 β -hydroxysteroid dehydrogenase, 17-hydroxylase, 21-hydroxylase, and 11-hydroxylase) may result in CAH. The most commonly recognized syndromes result from a deficiency of one of the terminal two enzymes of glucocorticoid synthesis (21-hydroxylase or 11-hydroxylase) (New and Levine, 1984) (Fig. 150-18). As a result of deficiency of either terminal enzyme, formation of hydrocortisone is impaired, causing a compensatory increase in the secretion of adrenocorticotropic hormone (ACTH). This increase enhances formation of adrenal steroids proximal to the enzymatic defect and a secondary increase in the formation of testosterone, the active androgen in CAH.

KEY POINT: CONGENITAL ADRENAL HYPERPLASIA

- The most commonly recognized syndromes of CAH result from a deficiency of one of the terminal two enzymes of glucocorticoid synthesis (21-hydroxylase or 11-hydroxylase).

A deficiency of steroid 21-hydroxylase is responsible for 95% of cases of CAH; it occurs with an incidence ranging from 1 in 5000 to 1 in 15,000 in the United States and Europe. The highest incidence, 1 in 490, is reported in the Yupik Alaskan Eskimo population (New et al, 1994). Clinically, patients are divided into three categories: (1) salt wasters (patients with virilization and aldosterone deficiency), (2) simple virilizers (patients with virilization, but without salt wasting), and (3) nonclassic patients (those without evidence of virilization or salt wasting). Dramatic progress has been made in understanding the molecular basis of CAH, and 95% of the mutations that account for CAH have been identified. The wide clinical spectrum of the disease appears to represent different degrees of enzymatic compromise conferred by specific, identifiable genetic defects.

The 21-hydroxylase gene (*CYP21A2*) is located on chromosome 6p21.3 within the major human leukocyte antigen (HLA) complex and is transmitted in an autosomal recessive pattern (Wilson et al, 1995). Adjacent to the *CYP21A2* gene, separated by 30 kb, and adjacent to and alternating with *C4B* and *C4A* genes encoding the fourth component of serum complement is the *CYP21* pseudogene (*CYP21PA1*), so called because it encodes no proteins and is therefore inactive (Tusie-Luna and White, 1995). The inactive *CYP21PA1* is 98% homologous to the active gene *CYP21A2*. During meiosis, a gene conversion may occur that transfers segments from the *CYP21PA1* gene to the *CYP21A2* gene, rendering it inactive. Thus far, all mutations causing 21-hydroxylase deficiency appear to result from either a complete deletion of the genes *C4B* and *CYP21B* (a product of misalignment and unequal crossing-over between chromatids during meiosis). To date approximately 15 mutations constitute 90% to 95% of alleles and are derived from intergenic recombination of DNA sequences between the *CYP21A2* gene and the highly homologous *CYP21PA1*, whereas the remaining are spontaneous mutations (Forest, 2004). Approximately 100 different *CYP21* mutations have been reported.

The majority of patients with CAH secondary to 21-hydroxylase deficiency exhibit one of the two classic forms of the disease: 75% have salt wasting and 25% have simple virilization (Kohn et al, 1995). The higher proportion of patients with the salt-wasting form of the disease recognized in more recent series has been attributed to improved diagnostic capabilities and a high level of clinical suspicion as well as to increased survival as a result of prenatal screening and proper mineralocorticoid supplementation (Fife and Rappaport, 1983). Neonatal screening programs for CAH have been

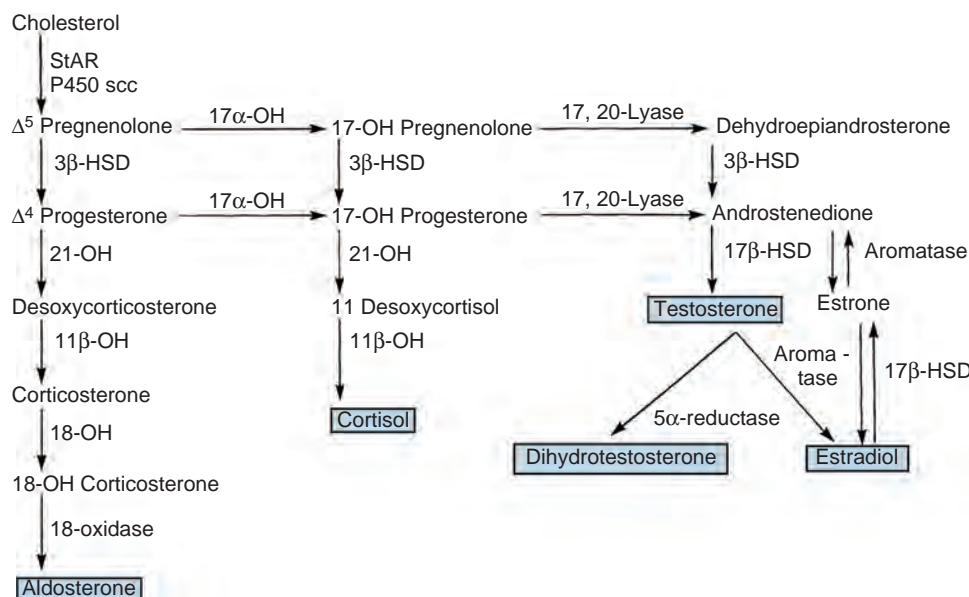


Figure 150-18. Steroid biosynthetic pathway for mineralocorticoid, glucocorticoid, and sex steroid hormone production.

credited with increasing the rate and shortening the time to diagnosis, particularly in males with the salt-wasting form of the disease. This has also proven to be an important means of diagnosing the simple virilizing form in the male and the nonclassic forms in some males and females (Brosnan et al, 1999).

In the female with the classic salt-wasting and simple virilizing forms of the disorder, a masculinized female results. Because impaired steroidogenesis begins early in life—at the time of formation of the external genitalia (beginning at 10 weeks' gestation)—there is virtually always evidence of some degree of masculinization at birth. This manifests as enlargement of the clitoris and varying degrees of labial fusion (Fig. 150-19). In addition, the vagina and urethra open into a common urogenital sinus. The enlargement of the clitoris may be so dramatic as to make it appear to be a hypospadiac penis with bilateral cryptorchidism or, rarely, a fully masculinized urethra to the tip of an apparent glans penis (Fig. 150-20). The severity of the virilization is usually greater in infants who experience salt wasting but not uniformly so. Prader (1958) classified the degrees of virilization of external genitalia in females with CAH (Fig. 150-21). The müllerian structures in these patients are typically normal. A recent study suggests an increased incidence (Nabhan and Eugster, 2007) of upper tract abnormalities (hydronephrosis, duplication) in CAH.

In both males and females with the salt-losing variant of CAH, symptoms begin within the first few weeks after birth, with failure to regain birth weight, progressive weight loss, and dehydration. In severely affected infants, adrenal crises occur within

the first 10 to 21 days of life (Grumbach and Conte, 1998). Vomiting is prominent and can be so extreme that a mistaken diagnosis of pyloric stenosis is made, particularly in the male. Without therapy, death may rapidly ensue from hyperkalemia, dehydration, and shock. In the male infant, in particular, the classic fluid and electrolyte abnormalities of CAH may be mimicked by urosepsis secondary to reflux or obstructive uropathy, which should be ruled out (Mastrandrea et al, 2005). After birth there is progression of masculinization of the untreated female; pubic and axillary hair develop prematurely, acne appears, and the voice deepens. There is rapid somatic maturation, resulting in premature epiphyseal closure and short adult stature. Although the internal genitalia are female, breast development and menstruation do not occur unless the excessive androgen production is suppressed by adequate steroid therapy.

In the male without salt wasting the chief clinical manifestations are those of isosexual precocity. The infant appears normal at birth, but signs of sexual and somatic precocity appear within the first 2 to 3 years of life. Although the testes remain normal in size, enlargement of the penis, scrotum, and prostate occur, accompanied by the appearance of pubic hair, acne, and deepening of the voice. The musculature is well developed (prompting the descriptive term "little Hercules"), and bone age is more advanced than appropriate for the chronologic age. The syndrome often goes unrecognized in the non-salt-wasting male until signs of androgen excess, such as accelerated height and precocious pubic hair, appear later in childhood.



Figure 150-19. External genitalia of a patient with congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency, showing labio-scrotal fusion and clitoromegaly.



Figure 150-20. Prader V patient with congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency demonstrating complete virilization of phallus.

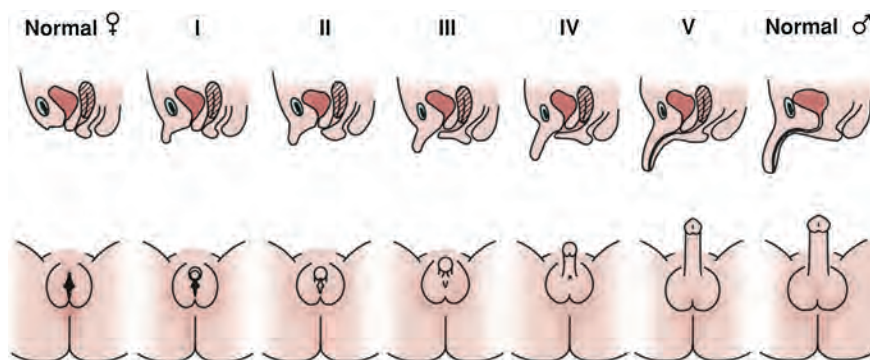


Figure 150-21. Classification by Prader of the various degrees of masculinization of the external genitalia in females with congenital adrenal hyperplasia, which has been applied by some authors to intersex states in general. (From Prader A. Die Häufigkeit der kongenitalen androgenitalen Syndroms. *Helv Paediatr Acta* 1958;13:426.)

In the non-salt-wasting male, two major long-term implications are short stature as well as infertility in 20% to 40%. Premature epiphyseal closure will result unless early medical control is instituted. This emphasizes the value of neonatal screening. Infertility has been noted in 30% of CAH males, often related to the finding of adrenal rest nodules most reliably diagnosed with scrotal ultrasonography. These nodules, present in 25% to 30% of males with CAH, represent hypertrophy of adrenal rests as a result of ACTH stimulation and when associated with impaired fertility warrant periodic scrotal ultrasonography, intensified glucocorticoid suppression, and possibly testis-sparing excision (Claahsen-van der Grinten et al, 2008). Some advocate sperm cryopreservation in postpubertal males with adrenal rest tumors. In addition, poor control of the disease in boys with classic CAH has been associated with small testes and infertility with reduced sperm counts (New and Wilson, 1999). This is a result of peripheral aromatization of excess androgen to estrogen that suppresses pituitary gonadotropins.

In classic 21-hydroxylase deficiency, plasma levels of progesterone and 17-hydroxyprogesterone are markedly elevated. Urinary levels of 17-ketosteroids and pregnanetriol are elevated. The diagnosis may be made biochemically with the use of radioimmunoassay of plasma 17-hydroxyprogesterone, which has replaced the more cumbersome 24-hour urine collection of metabolites (e.g., pregnanetriol). A pelvic ultrasound study demonstrating the presence of müllerian tissues is confirmatory. Some investigators have suggested that the finding of abnormally enlarged or "cerebriform"-appearing adrenal glands on neonatal ultrasonography, available before biochemical results, may represent the earliest diagnostic tool for CAH (Hernanz-Schulman et al, 2002).

More aggressive screening for 21-hydroxylase deficiency has provided considerable benefits. In one series, despite sexual ambiguity, one third to one half of the affected female newborns were not diagnosed as having 21-hydroxylase deficiency until they were identified by the screening test (Pang et al, 1985).

Nonclassic 21-hydroxylase deficiency represents an attenuated, late-onset form that is variable in its clinical severity because of partial deficiency of 21-hydroxylase and timing of onset. These patients do not have cortisol deficiency but do have hyperandrogenism. New and Wilson (1999) found the nonclassic 21-hydroxylase deficiency to be the most common autosomal recessive disorder in humans, with an incidence of 1 in 100. The presenting symptoms in females are commonly hirsutism and oligomenorrhea, male pattern baldness, and polycystic ovaries. In a recent study, 32% of women with nonclassic 21-hydroxylase deficiency were diagnosed only after delivering an offspring diagnosed with 21-hydroxylase deficiency CAH. In men with the nonclassic form of 21-hydroxylase deficiency, oligospermia and subfertility have been presenting features, and reversal of infertility with glucocorticoid therapy has been reported. Typically, lower doses of glucocorticoid are required for management of the nonclassic form of CAH.

A deficiency of 11 β -hydroxylase accounts for roughly 5% of cases of CAH. Both classic and mild forms have been recognized. Unlike 21-hydroxylase, 11 β -hydroxylase is not HLA linked. The defect results from mutations in the *CYP11B1* gene located on the long arm of chromosome 8 (Merke et al, 1998). To date, more than 50 mutations have been described that result in enzyme inactivation (Nimkarn and New, 2008). Like 21-hydroxylase deficiency, the nonclassic variant of 11 β -hydroxylase deficiency (late onset) is characterized by signs and symptoms of androgen excess in childhood or adolescence. Hypertension is a common finding in patients with this type of CAH, and it is believed to be secondary to increased serum levels of deoxycorticosterone (DOC). Although most of the patients are hypertensive, some are normotensive and others experience only intermittent hypertension. Marked virilization occurs in the severe form of the defect and may be as severe as in those patients with a 21-hydroxylase deficiency. In the late-onset form, mild virilization occurs in prepubertal and postpubertal patients.

The diagnosis of 11 β -hydroxylase deficiency can be confirmed by finding increased plasma levels of 11-deoxycortisol and 11-DOC. Urinary levels of 17-ketosteroids and 17-hydroxycorticoids

are increased. The treatment with glucocorticoids is identical to that of patients with 21-hydroxylase deficiency.

The least common enzyme deficiency responsible for a virilizing form of CAH is 3 β -hydroxysteroid dehydrogenase. This deficiency affects the early steps in steroid biosynthesis in both adrenals and gonads, resulting in inability to convert 3 β -hydroxysteroids to 3-ketosteroids. As a result, the severe form leads to impaired synthesis of aldosterone, cortisol, and sex steroids. Affected females exhibit mild clitoromegaly and labial fusion accompanied by symptoms of aldosterone and cortisol deficiency.

Two homologous genes have been identified for 3 β -hydroxysteroid dehydrogenase, both of which contain four exons (Merke et al, 1998). A number of mutations giving rise to the syndrome have been described. This defect has an autosomal recessive inheritance pattern and is heterogeneous in its biochemical and clinical appearance. A non-salt-losing form and mild- and late-onset forms have been described, although the nonclassic form appears to be exceedingly rare.

The diagnosis of 3 β -hydroxysteroid dehydrogenase is based on finding increased serum levels of 17-hydroxypregnenolone and dehydroepiandrosterone (DHEA). Pelvic ultrasound evaluation confirming the presence of müllerian tissue would be supportive. Treatment is similar to that of patients with 21-hydroxylase deficiency.

Currently, one of the most exciting aspects of CAH is the capability of diagnosing and treating the disorder prenatally. Prenatal diagnosis of CAH in the at-risk fetus was initially made by a measurement of amniotic fluid for 17-hydroxyprogesterone at 16 to 17 weeks' gestation (Laue and Rennert, 1995). Currently the diagnosis is made during the first trimester by HLA genotyping or by DNA analysis of genes within the HLA complex in cells obtained by chorionic villus sampling at 9 to 11 weeks' gestation (Hughes, 2002). Treatment of the mother with dexamethasone, which crosses the placenta, suppresses fetal secretion of ACTH, thereby preventing virilization of the genitalia. However, treatment should be instituted as soon as pregnancy is confirmed, and no later than 9 weeks after the last menstrual period, before initial development of the external genitalia (Nimkarn and New, 2007). There are certain complexities to this form of management. The diagnosis of CAH in the fetus may be determined on chorionic villous cells or on cells from amniotic fluid for families in which a prior member was affected. Therefore, it is not possible to confirm the diagnosis before therapy is initiated. Because virilization is not a concern with the male fetus and three of four female fetuses at risk are unaffected, given the autosomal recessive pattern of inheritance, seven of eight fetuses may be treated unnecessarily. Therefore, one goal in therapy has been earlier diagnosis to avoid unnecessary treatment. A promising approach that may enhance the prenatal diagnosis of CAH as early as 9 weeks' gestation is PCR analysis of free fetal DNA, from circulating trophoblastic cells, in the maternal circulation, which allows detection of Y chromosome, thus avoiding treatment of males (Rijnders et al, 2001).

A number of series have established the effectiveness of prenatal treatment for CAH with dexamethasone in 85% of cases (Migeon, 1990; Pang et al, 1990; Speiser et al, 1990). In some neonates there is no evidence of masculinization, suggesting totally successful therapy. In another group there is milder masculinization than that noted in an affected sibling. Although compliance and timing of initiation of treatment have been variable from series to series, this heterogeneity of response to therapy raises intriguing questions about the mechanisms involved in virilization of the CAH fetus. In addition, prenatal treatment with dexamethasone has raised ethical concerns. Although there is no arguing its ability to prevent androgen effects on the genitalia and potentially the brain of affected females, the long-term effects of dexamethasone on unaffected fetuses undergoing treatment prenatally remain largely unknown. A study by Meyer-Bahlburg and colleagues (2004a) demonstrated no cognitive or developmental motor impairment to have resulted from prenatal treatment of CAH fetuses, but others have suggested potential deleterious effects on verbal working memory (Hirvikoski et al, 2007). Miller (1999) and

others have advocated the use of prenatal treatment for CAH only as an experimental therapy in large centers and under institutional review board scrutiny. The importance of long-term follow-up of these neonates has been emphasized (Speiser, 1999).

Hughes (2002) and others have emphasized the close correlation in CAH of genotype and phenotype. New and colleagues (2013) noted a genotype-phenotype correlation in 21 of 45 cases. Certain genotypes were more frequent in specific ethnic groups. This has a number of practical implications. Molecular biologists can now predict not only the risk of a couple having an affected child but also the likely clinical form of the disease. Therefore, genotypes of severe mutations would motivate prenatal treatment, whereas genotypes of less severe mutations would not. In addition, less severe genotypes in the newborn would allow for modification of corticosteroid treatment to minimize side effects.

The treatment of affected children with hydrocortisone in childhood and adolescence achieves a number of goals, as noted by Bongiovanni and Root (1963): "to supply the deficient hormone; to suppress pituitary ACTH secretion and hence adrenal androgens and clinical virilization; to forestall abnormally rapid somatic growth and osseous advance; to permit normal gonadal development; and to correct salt-water loss or hypertension in the complicated forms." The required dose of glucocorticoid may be predicted by genotype, as noted by Hughes (2002), but should be adjusted for the individual patient based on bone age, linear growth, 24-hour excretion of ketosteroids, and clinical evidence of glucocorticoid deficiency or excess (Grumbach and Conte, 1998). The effectiveness of therapy may be assessed by measuring morning plasma 17-hydroxyprogesterone levels. Those children with the salt-losing form of the disease require increased salt intake and mineralocorticoid treatment in addition to hydrocortisone therapy. After control of electrolytes and blood pressure has been achieved in the acute setting, maintenance therapy with fludrocortisone should be instituted (Laue and Rennert, 1995; Grumbach and Conte, 1998). The preferred cortisol replacement is oral hydrocortisone (10 to 20 mg/m² per day in three divided doses). Doubling or tripling the oral dose of hydrocortisone is often recommended during physically stressful events such as surgery or infection. Infants with the salt-wasting form of CAH require replacement with fludrocortisone (0.1 to 0.2 mg/day) (Antal and Zhou, 2009).

In significantly virilized females (who will not have been diagnosed and treated prenatally), it is appropriate to perform feminizing genitoplasty at 3 to 6 months of age, when a well-established course of medical therapy has been instituted, the risks of anesthesia have become minimal, and the child has grown large enough to make the procedure technically feasible (Passerini-Glazel, 1990). **Long-term fertility in males and feminization, menstruation, and fertility in females can be anticipated in the well-treated patient.** Indeed, this potential in even the most masculinized female CAH patient has provided support for feminizing genitoplasty in virtually all 46,XX CAH patients. Although female gender rearing is supported by the 2006 consensus statement, it has been recently challenged by Lee and Husmann for those patients with 46,XX CAH who appear unambiguously male, for whom they recommend consideration of male gender assignment (Lee et al, 2010).

An important area of recent research has been the potential imprinting of the brain by elevated prenatal androgen levels. A number of recent studies confirm that prenatal hyperandrogenization is associated with masculinization of gender-related behavior but not masculinization of gender identity. Meyer-Bahlburg and associates (Meyer-Bahlburg et al, 2004b, 2008; Dessens et al, 2005) noted a close correlation between hormonal abnormalities as a function of severity of enzyme deficiency with sexual orientation (homosexuality, bisexuality rates). Furthermore, Berenbaum and colleagues (2003, 2004) noted that in females with CAH and virilized genitalia, psychological development is not compromised in those who are reared as females and receive good medical care. Meyer-Bahlburg and associates (2004a) noted in 46,XX CAH girls that marked masculinization of gender-related behavior in prenatally hyperandrogenized CAH girls was not associated with masculinization of gender identity. Therefore the psychosexual evidence

to date supports maintaining female gender in masculinized CAH patients diagnosed in infancy. Indeed, proper psychological support should be a component of long-term follow-up.

In an interesting new finding, both male and female patients with classic CAH have been noted on magnetic resonance imaging to have smaller amygdala volumes than controls, and altered amygdala function. The amygdala, regulated by glucocorticoids, is important in processing emotion (Ernst et al, 2007).

An intriguing area of surgical innovation in the management of CAH has been the experimental use of "prophylactic" adrenalectomy for selected patients. This approach is based on the premise that in certain patients it is more difficult to maintain adrenal suppression than to prevent adrenal crises. Clinically, these patients are the salt losers and extremely virilized females. For those with this most severe form of 21-hydroxylase deficiency, adequate suppression of adrenal production has required significant degrees of hypercortisolism, associated with poor growth, obesity, and infertility (in 40%). For the 25% of CAH patients who completely lack 21-hydroxylase enzyme activity and therefore produce neither cortisol nor aldosterone, adrenalectomy may be a practical approach (VanWyk et al, 1996). In general, these patients may be identified genotypically as homozygotes or compound heterozygotes for "null alleles" of the CYP21 gene (VanWyk et al, 1996). In a series of 18 patients with long-term follow-up, VanWyk and Ritzen (2003) noted bilateral adrenalectomy to be safe and effective in managing severe forms of CAH in which patients repeatedly escaped adrenal suppression. Most of these patients reported a better quality of life after bilateral adrenalectomy. In a recent series bilateral adrenalectomy proved more successful for those patients pursuing fertility rather than control of obesity and hyperandrogenism (Ogilvie et al, 2006).

Although these patients are rendered addisonian by this surgery, those with the most severe form of CAH would have a poor intrinsic adrenal response to metabolic stress (Gunther et al, 1997). One theoretic disadvantage of this approach is that if gene therapy were to one day allow functional CYP21 genes to be introduced into adrenal cortical tissue, adrenalectomized patients would not be candidates for such therapy (VanWyk et al, 1996).

Males with CAH must be followed for testicular adrenal rest tumors as a potential cause of infertility. This is ideally performed with annual screening testicular ultrasonography (Kang et al, 2011). **46,XX Disorder of Sex Development (Masculinized Female) Secondary to Maternal Androgens and Progestins and Maternal Tumors.** The masculinization of a female fetus as a result of maternal administration of synthetic progestational agents or androgens is a rare occurrence; lessons have been learned from prior unfortunate experiences. Historically, progestational agents were used to prevent threatened abortion. In one large series, masculinization occurred in 2% of female infants whose mothers were treated with progestins during pregnancy (Ishizura et al, 1962). In addition, danazol, a testosterone derivative used to treat endometriosis, has been associated with virilization of the female fetus. The degree to which any androgen or progestational agent affects female fetal development is a function of the strength of the agent, its maternal dosage, and timing and duration of administration (Bongiovanni and McFadden, 1960).

Very rarely, a maternal ovarian or adrenal tumor has virilizing effects on a female fetus. More typically, such a tumor has virilizing effects on the mother but no apparent effect on the fetus. Ovarian tumors that have resulted in masculinization of the female fetus include arrhenoblastoma, hilar cell tumor, lipoid cell tumor, ovarian stromal cell tumor, luteoma of pregnancy, and Krukenberg tumor (Calaf et al, 1994).

Rarer still are maternal adrenal tumors (adrenocortical carcinoma and adenoma), which have masculinizing effects on the female fetus.

Aromatase deficiency represents an even rarer cause of transplacental transport of excess androgens to the fetus. The cytochrome P450 aromatase enzyme catalyzes the conversion of androgens to estrogens. Normally, weak androgens produced by the fetal adrenal gland are converted to estrogens by placental aromatase and pass

to the maternal circulation. Mutations of the *CYP19* aromatase gene can result in profound virilization of the female fetus and mother during pregnancy. Although maternal virilization resolves postnatally, it recurs in subsequent pregnancies.

In any case of exogenous androgen effect on a female fetus, normal endocrine status is recognized postnatally and management is confined to external genital reconstruction, as required.

46,XY Disorder of Sex Development (Undermasculinized Male)

The term *46,XY DSD (undermasculinized male)* refers to 46,XY individuals with differentiated testes who exhibit varying degrees of feminization phenotypically. Impaired male differentiation in these patients is secondary to inadequate secretion of testosterone by the testes at the necessary period in development, inability of target tissue to respond to androgen appropriately, or impaired production or action of MIS.

Leydig Cell Aplasia (Luteinizing Hormone Receptor Abnormality). Leydig cell aplasia as a cause of undermasculinization of the male was first reported by Berthezene and colleagues in 1976. In its pure form, this rare disorder is characterized by a normal 46,XY male karyotype associated with a normal-appearing female phenotype. Typically, testes are palpable in the inguinal canals or labia majora. On investigation, there are no müllerian structures and the vagina is short. A low testosterone level is noted in conjunction with an elevated LH concentration. The absence of a rise in serum testosterone level after hCG stimulation is characteristic of this disorder (Brown et al, 1978). Physiologically, this disorder represents a spectrum between absent Leydig cells and Leydig cells with abnormal LH receptor (David et al, 1984). Because a number of inactivating mutations have been found in the LH receptor gene, a correlation can be made between the phenotype of patients with Leydig cell hypoplasia and the activity of their LH receptor alleles (Richter-Unruh et al, 2004). It is transmitted as an autosomal recessive trait expressed only in males. Incomplete forms of the syndrome occur, with the mildest form being expressed as primary hypogonadism with normal male external genitalia (Lee et al, 1982).

The clinical diagnosis of Leydig cell aplasia, or LH receptor abnormality, is typically made as a result of sexual infantilism and the absence of development of secondary sexual characteristics or the discovery of palpable gonads in the inguinal canal or labia on physical examination (Arnholt et al, 1985). The differential diagnosis includes androgen insensitivity syndrome or a terminal defect in androgen synthesis. The histology of the abnormal testes demonstrates absence of Leydig cells in intratubular spaces with normal Sertoli cells.

Disorders of Testosterone Biosynthesis

A defect in any of the five enzymes required for the conversion of cholesterol to testosterone can cause incomplete (or absent) virilization of the male fetus during embryogenesis. The first three enzymes (cholesterol side chain cleavage, 3 β -hydroxysteroid dehydrogenase, and 17 β -hydroxylase) are present in both adrenals and testes. Therefore, their deficiency results in impaired synthesis of glucocorticoids and mineralocorticoids in addition to testosterone. For all five enzyme deficiencies, the pattern of inheritance is autosomal recessive.

StAR (Cholesterol Side Chain Cleavage Enzyme) Deficiency. The first step in gonadal and adrenal steroidogenesis is conversion of cholesterol to pregnenolone, which is mediated by a single cholesterol side chain cleavage enzyme known as 450SCC (previously known as 20,22-desmolase). A defect in this enzyme, first described by Prader and Gurtner in 1955, was believed to result in the rare condition congenital lipoid adrenal hyperplasia, so named because the adrenal glands became large and lipid laden. However, more recent evidence suggests that a defect in cholesterol transport rather than a defective enzyme is etiologically responsible (Saenger, 1997). The steroidogenic acute regulatory protein (StAR)

stimulates cholesterol transport from the outer to the inner mitochondrial membrane (site of the cholesterol side chain cleavage complex). This appears to be the rate-limiting step in acute steroid synthesis.

StAR mutations are found in various ethnic groups but are most commonly reported in patients of Japanese, Korean, and Palestinian origin (Bhangoo et al, 2005). Affected 46,XY individuals have female or ambiguous external genitalia with a blind-ending vaginal pouch; intra-abdominal, inguinal, or labial testes; and absence of müllerian structures, consistent with functioning Sertoli cells (Hauffa et al, 1985). Wolffian ducts are present but rudimentary. Infants often are seen in the first few weeks of life with severe adrenal insufficiency and salt wasting, but delayed presentation has been reported (Lekarev et al, 2012).

A diagnosis of StAR (cholesterol side chain cleavage enzyme) deficiency should be entertained in any neonate with nonvirilized female external genitalia and evidence of cortisol and aldosterone deficiency with hyponatremia, hyperkalemia, and metabolic acidosis. Abdominal computed tomography demonstrates large, lipid-laden adrenal glands.

Management is similar to that for 21-hydroxylase deficiency. Classically, 46,XY patients with this disorder have been raised as females and have undergone gonadectomy (Laue and Rennart, 1995). Because testosterone production was never significant, brain imprinting is not a factor in gender assignment. However, phenotype can be quite variable, such that partial virilization or even normal male genitalia may result (Lekarev et al, 2012).

Cytochrome P450 Oxidoreductase Deficiency. Cytochrome P450 oxidoreductase (POR) deficiency has been recently added to the causes of both 46,XY and 46,XX DSDs. POR is a cofactor to all microsomal P450 enzymes, including 17-hydroxylase, 17,20-lyase, 21-hydroxylase, and aromatase. The condition emerged as a distinct entity through the realization that apparent combined deficiency of 17-hydroxylase and 21-hydroxylase enzymes is a single disorder resulting from lack of POR, a membrane-bound flavoprotein that plays a central role in electron transfer from nicotinamide adenine dinucleotide phosphate (NADPH) to P450 enzymes. It was originally characterized in patients with Antley-Bixler syndrome (a skeletal dysplasia syndrome), some of whom had ambiguous genitalia and abnormal steroidogenesis. Subsequently, it has become clear that POR deficiency can cause DSD unassociated with skeletal dysplasia and characteristics of Antley-Bixler syndrome (Hughes, 2008).

3 β -Hydroxysteroid Dehydrogenase Deficiency. 3 β -Hydroxysteroid dehydrogenase catalyzes the 3 β -hydroxysteroids (pregnenolone, 17-hydroxypregnenolone, and DHEA) to the three ketosteroids progesterone, 17-hydroxyprogesterone, and androstenedione. A congenital deficiency of 3 β -hydroxysteroid dehydrogenase was first described by Bongiovanni in 1962.

Affected individuals have various degrees of incomplete masculinization, resulting from a block in testosterone biosynthesis, and salt-wasting adrenal insufficiency resulting from impaired synthesis of aldosterone and cortisol. The lack of salt-retaining hormone and cortisol results in a salt-losing crisis soon after birth. However, partial deficiencies associated with severe salt wasting occur, consistent with genetic heterogeneity. Two isoenzymes, type I and type II 3 β -hydroxysteroid dehydrogenase, are involved in steroid biosynthesis. These enzymes are encoded by two genes, *HSD3B1* and *HSD3B2*, localized to chromosome 1 at locus p11-p13 (Chang et al, 1993). Classic 3 β -hydroxysteroid dehydrogenase deficiency results from inactivating mutations, 37 of which have been identified, in the *HSD3B2* gene (Welzel et al, 2008).

Males with this deficiency usually exhibit incomplete virilization of the external genitalia, with a small phallus, hypospadias with labioscrotal fusion, a urogenital sinus, and a blind-ending vaginal pouch. Testes are often scrotal, and wolffian ducts develop normally. As with other defects in testosterone biosynthesis, in which normal Sertoli cell function is preserved, müllerian structures are absent.

The diagnosis should be considered in 46,XY males with ambiguous genitalia and signs of adrenal insufficiency. Endocrine study

demonstrating increased levels of 3β -hydroxysteroids confirms the diagnosis.

Management of 3β -hydroxysteroid dehydrogenase is similar to that for patients with 21-hydroxylase deficiency.

17 α -Hydroxylase Deficiency. 17 α -Hydroxylase catalyzes the conversion of pregnenolone and progesterone to 17 α -hydroxypregnenolone and 17-hydroxyprogesterone, respectively, in adrenal and gonadal steroidogenesis. The first case of male pseudohermaphroditism caused by this enzyme deficiency was reported by New in 1970. The gene for this enzyme has been localized to chromosome 10 (Laue and Rennart, 1995).

Affected 46,XY individuals usually have female external genitalia with absent to slight masculinization. A deficiency in 17 α -hydroxylase activity impairs cortisol production, causing ACTH hypersecretion and resulting in increased levels of DOC, corticosterone, and 18-hydroxycorticosterone in the adrenals. These compounds with mineralocorticoid activity produce excess salt and water retention, hypertension, and hypokalemia.

The phenotype of affected individuals varies from female with external genitalia with a blind-ending vaginal pouch to male with perineal hypospadias and chordee. The diagnosis should be considered in a undervirilized male with hypertension. Endocrine laboratory evaluation demonstrates elevated serum progesterone, DOC, corticosterone, 18-hydroxycorticosterone, and ACTH.

Therapy with glucocorticoid replacement brings blood pressure and hypokalemia back to normal by suppressing ACTH and hence adrenal cortical stimulation. Some patients have been raised as females with gonadectomy and estrogen replacement at puberty. In partial forms, typically with reasonable phallic size, patients may be raised as male with testosterone replacement at puberty. Fertility has not been reported in patients with testosterone biosynthetic defects, and inadequate testosterone production makes androgen imprinting a less significant issue for these patients. Therefore, the phenotype may dictate gender assignment.

17,20-Lyase Deficiency. The enzyme 17,20-lyase has been demonstrated to be related to 17 α -hydroxylase in that the activities of both are linked to the same gene product on chromosome 10 (Laue and Rennart, 1995). However, in some patients with the genetic defect both biologic activities are absent, but in others only the 17,20-lyase function appears deficient. Zachmann and colleagues first described this clinical entity in 1972.

In cases in which the deficiency primarily involves 17,20-lyase, cortisol and ACTH secretion are normal. Aldosterone is secreted normally, and hypertension does not result. However, impaired biosynthesis of testosterone in the 46,XY individual results typically in ambiguous rather than totally female genitalia at birth. The deficient masculinization of the external genitalia can range from severe, resulting in a female gender assignment in the neonate, to mild, resulting only in hypospadias. At puberty, the secretion of testicular androgen remains low. Zachmann and colleagues (1982) have postulated that there are two types of 17,20-lyase deficiency—one that is partial and another that is a complete defect.

The diagnosis may be suspected in undervirilized males with absent müllerian derivatives and no defect in glucocorticoid or mineralocorticoid synthesis. At the time of expected pubertal development, the patients may have failure to develop secondary sexual characteristics and elevated gonadotropin levels. The diagnosis may be made prepubertally using hCG and ACTH stimulation.

Management entails plastic reconstruction of the external genitalia and appropriate sex steroid replacement at puberty.

17 β -Hydroxysteroid Oxidoreductase Deficiency. This last enzyme in the testosterone biosynthetic pathway catalyzes the conversion of androstenedione to testosterone, DHEA to androstanediol, and estrone to estradiol. Male undervirilization resulting from a deficiency in 17 β -hydroxysteroid oxidoreductase was first described by Saez and associates in 1971.

Clinically, this is the most interesting enzymatic defect in testosterone biosynthesis in its similarities to 5 α -reductase deficiency. At birth, affected individuals appear to have a normal female phenotype, without significant evidence of virilization.

Therefore a female gender assignment is usually made. However, these individuals have well-differentiated testes located intra-abdominally, inguinally, or in the labia and no müllerian structures. Surprisingly, wolffian ducts are normally developed, which may be secondary to the action of androstenedione or minimal amounts of testosterone produced during embryogenesis (Boehmer et al, 2001). At puberty, there is phallic growth and progressive development of male secondary sexual characteristics. These include increased muscle mass and development of pubic, axillary, and facial and body hair with male distribution. Gynecomastia may occur, and the testes may become palpable (Saez et al, 1972). In some cases, gender reassignment to male has been reported (Imperato-McGinley et al, 1979a; Rosler and Kohn, 1983).

The late onset of virilization is related to the pubertal increase in gonadotropin production, which may partially overcome the block in testosterone biosynthesis.

There is a characteristic hormonal profile in this disorder. In the prepubertal patient, plasma androstenedione and estrone levels may not be increased. At puberty, androstenedione, the immediate precursor of testosterone, is increased to 10 to 15 times the normal plasma concentration (Virdis and Saenger, 1984). Earlier precursors are within normal levels. Plasma testosterone is in the low-normal range. Serum levels of LH and FSH are markedly elevated, typically four to six times normal.

As a result of biochemical characterization and molecular cloning, five different 17 β -hydroxysteroid dehydrogenase isozymes have been identified to date. The type III 17 β -hydroxysteroid dehydrogenase isozyme, cloned by Andersson and Moghrabi (1997), catalyzes the biosynthesis of testosterone from androstenedione. A mutation involving the *HSD17B3* gene, mapped to chromosome 9q22, is responsible for male undervirilization. The type III isozyme is apparently expressed early in utero and is responsible for testosterone biosynthesis during the critical period of sexual differentiation, based on the observation that male adults homozygous for 17 β -hydroxysteroid dehydrogenase type III gene defects have ambiguous genitalia (Zhu et al, 1998).

The diagnosis is rarely made in the neonatal period. It may become apparent on discovery of a testis during a hernia repair in infancy or childhood. An hCG stimulation test resulting in an increased testosterone-to-androstenedione ratio would confirm the diagnosis and differentiate this condition from androgen insensitivity (Ahmed et al, 2000a). The primary management issue for patients with 17 β -hydroxysteroid oxidoreductase deficiency has been gender assignment. At this early stage, maintenance of the female sex of rearing with gonadectomy is usually elected. If the diagnosis is not made until puberty, when dramatic changes in virilization occur, certain families prefer a gender change to male. Cohen-Kettenis found gender role changes in 39% to 64% of 17 β -hydroxysteroid oxidoreductase deficiency patients raised as female (Cohen-Kettenis et al, 2005a). In an Arab cohort of 22 patients, Sobel and Imperato-McGinley (2004) noted 7 to undergo spontaneous gender role reversal to male without parental consent or psychiatric intervention. Traditionally, this decision has been strongly culturally influenced.

If a female sex of rearing is elected, gonadectomy, plastic reconstruction of the genitalia as necessary, and estrogen replacement therapy at puberty are indicated. For the patient maintained in the male gender, orchidopexy and reconstruction of the external genitalia are required. This entails hypospadias repair and chordee correction, which can be quite successful. However, phallic size remains small and infertility is the rule. Some have suggested that childhood treatment with intramuscular testosterone may result in a larger phallus (Sobel and Imperato-McGinley, 2004). Usually, endogenous androgen levels are adequate in the long term.

Two hypotheses have been proposed to explain the frequency of gender change from female to male with this enzyme deficiency, particularly among the cohort of Arab male pseudohermaphrodites with 17 β -hydroxysteroid dehydrogenase type III deficiency. One entails the potential male imprinting of the brain in utero as a result of the conversion of androstenedione to estrone; this theory is supported by studies in rats and rabbits demonstrating

that administration of estrogen or androstenedione is capable of inducing male sexual behavior (Reddy et al, 1974). The second is the possibility that 17 β -hydroxysteroid dehydrogenase activity is not deficient in the brain, its effect being mediated by the conversion of androstenedione to testosterone or estrogen (Imperato-McGinley et al, 1979a).

Androgen Receptor and Postreceptor Defects

Disorders of androgen receptor function represent the most common definable cause of 46,XY DSD or the undervirilized male. These patients characteristically have a 46,XY karyotype and testes and a spectrum of phenotypic abnormalities that vary from complete external feminization (syndrome of complete androgen insensitivity), to ambiguous genitalia (partial androgen insensitivity), to the phenotypically infertile male. Although the clinical presentations vary according to the severity of the disorder, the pathophysiology is similar (Wiener et al, 1997).

Syndrome of Complete (Severe) Androgen Insensitivity. The syndrome of complete androgen insensitivity is characterized clinically by a 46,XY karyotype, bilateral testes, female-appearing external genitalia, and absence of müllerian derivatives. Wilkins first suggested in 1950 that the clinical features of this syndrome were the result of androgen resistance. This condition has an incidence of 1 in 20,000 to 1 in 60,000 males, and it is transmitted as an X-linked trait.

The androgen receptor regulates the transcription of other specific genes, once activated by testosterone or DHT. This results in new mRNA synthesis from the downstream genes and protein production. The androgen receptor has been mapped to the X chromosome at Xq11-12, spanning 90 kb and comprising eight exons (Brown et al, 1989; Hiort and Holterhus, 2003). Males have only one copy of this gene. Point mutations of the gene account for more than 90% of cases of androgen insensitivity (Quigley et al, 1995). The identifiable molecular alterations of the androgen receptor gene cannot predict the resulting phenotype of the affected individual unless there is total loss of the receptor, which occurs in only 1% of all patients (Quigley et al, 1995).

Patients with complete androgen insensitivity have a normal female phenotype with the exception of diminished axillary and pubic hair. Their breast development and body habitus are feminine in character, and their external genitalia are unequivocally female, although the vagina is short and blind ending. It was previously believed that in utero resistance to testosterone action prevented stabilization of the wolffian ducts. Hannema and associates (2004), however, demonstrated wolffian duct derivatives in cases of complete androgen insensitivity. In 42% of patients, screening of the paratesticular area revealed well-developed epididymis and/or vasa deferentia. The mutations found in these patients entailed a single amino acid substitution in the androgen receptor ligand binding domain, rather than frameshift mutations, premature stop codons, or mutations in the DNA-binding domain, all of which were associated with absence of well-developed wolffian duct structures. These investigators suggest that mutant receptors with residual activity in vivo stimulate wolffian duct development. As a result, they should be classified as having *severe* rather than complete androgen insensitivity. Because the fetal testes secrete MIS, müllerian structures are absent. The testes may be found in the labia, inguinal canal, or abdomen.

These patients are rarely diagnosed in the neonatal period, unless a prenatal diagnosis is made on the basis of female phenotype and 46,XY karyotype on amniocentesis. With the increase in prenatal diagnostics, this is becoming a more common occurrence (Hughes and Patterson, 1994). More typically, however, the diagnosis is made as a result of primary amenorrhea or the finding of a testis at inguinal herniorrhaphy. Fifty percent of patients with complete (severe) androgen insensitivity syndrome have an inguinal hernia (Conte and Grumbach, 1989). Conversely, 1% to 2% of apparently female infants with inguinal hernia are found to have a 46,XY karyotype and complete androgen insensitivity syndrome (CAIS) (Wiener et al, 1997; Barthold et al, 2000). Therefore, routine

vaginostomy to confirm the presence of a cervix or endoscopy through a hernia sac to identify an intra-abdominal testis at the time of inguinal herniorrhaphy in female patients is a prudent maneuver. Histologically, the testes exhibit incomplete or absent spermatogenesis with normal or hyperplastic Leydig cells. They are comparable to immature, cryptorchid testes.

Endocrine evaluation in the neonatal period demonstrates normal male levels of testosterone, DHT, and gonadotropins. At puberty, gonadotropin levels rise, leading to increased levels of plasma estradiol, which results in feminization, including breast development.

Several types of mutant receptor abnormality that would account for this syndrome have been described, including (1) a decreased amount of apparently normal receptor; (2) absence of receptor binding; (3) a qualitatively abnormal receptor (thermolabile, or unstable); (4) other "receptor-positive" forms, including increased rate of dissociation of steroid receptor complex, defective upregulation of the androgen receptor, decreased affinity of ligand binding, and impaired nuclear retention of the ligand (Grumbach and Conte, 1998). In general, the severity of the defect in androgen receptor (quantity or quality) correlates with the phenotype. In addition, Hughes (2001) has noted the absence of coregulator proteins, without the absence of the androgen receptor, in cases of complete androgen insensitivity, suggesting that for androgen effects to be optimal an integrated array of transcriptional factors, coregulators, and ligands is required.

The diagnosis of complete (severe) androgen insensitivity may readily be made in the postpubertal patient on the basis of clinical and hormonal findings of amenorrhea, absence of pubic hair, or inguinal hernias containing testes. It is confirmed by a 46,XY karyotype and a normal male androgen and gonadotropin profile. Pelvic ultrasound examination confirms the absence of müllerian tissue, and a vaginal examination confirms a blind-ending vagina without a cervix.

In the prepubertal child, diagnosis is more difficult and requires an hCG stimulation test. Because of the time required for receptor binding quantification in genital skin, it is desirable to use PCR to characterize the androgen receptor gene in DNA obtained from a venous blood sample to detect a genetic marker for androgen insensitivity syndrome.

Management of complete (severe) androgen insensitivity relates primarily to the optimal timing of gonadectomy. Because the testes produce estradiol, which results in the appropriate changes for the female phenotype, it is considered by many preferable to leave the testes in situ until puberty is complete. Potential exceptions to the policy of delayed gonadectomy are palpable testes or testes associated with an inguinal hernia. One important caveat in deciding to leave the testes in situ is the need to confirm with absolute certainty that complete rather than partial androgen insensitivity exists by PCR characterization of the androgen receptor gene in venous blood DNA. If an incomplete form should exist, virilization at puberty could result (Batch et al, 1993). Another important consideration is the anticipated need to discuss with a postpubertal female the presence of testes that require removal, rather than doing so when the child is much younger and the psychosexual implications less charged. Because of the complexity of managing the CAIS patient, Hughes has advocated an individualized and holistic approach for each patient (Hughes et al, 2012).

A competing concern for retention of testicular tissue is the potential for malignant degeneration of the testes. In patients with complete androgen insensitivity who reach adulthood with a retained testis, the risk for development of a testis tumor—usually seminoma or gonadoblastoma—is thought to be 1% to 2%, only slightly higher than for a cryptorchid testis (Manuel et al, 1976; Müller and Skakkebaek, 1984). Before pubertal development the risk is extremely low, the youngest reported case of a germ cell tumor in an androgen insensitivity syndrome being in a 14-year-old (Ahmed et al, 2000b). Therefore, in general, delayed gonadectomy after puberty is believed to be safe (Cools et al, 2006).

After orchiectomy, cyclic estrogen-progestin therapy is begun. The majority of patients have successful treatment of their short

vagina with progressive dilation (Ismail-Pratt et al, 2007). Some patients may benefit from vaginoplasty (Boehmer et al, 2001). Currently, all studies of patients with complete androgen insensitivity support an unequivocal female gender identity, consistent with androgen resistance of brain tissue as well. In one study, no statistical differences were found between the complete androgen insensitivity group and normal controls in any quality-of-life or gender-related behavior criterion (Hines et al, 2003). To date, there has been no report of a patient with complete androgen insensitivity raised as a female who needed gender reassignment to male (Meyer-Bahlburg, 1999). In any event, age-appropriate psychological counseling is an important component of management in the androgen insensitivity syndromes.

Syndrome of Partial Androgen Resistance. The syndrome of partial androgen resistance includes syndromes that were once thought to represent separate entities: Reifenstein, Gilbert-Dreyfus, Rosewater, and Lubs syndromes (Griffin, 1992). These are X-linked disorders of incomplete masculinization that represent a spectrum of phenotypic abnormalities. The major finding is ambiguity of the external genitalia to varying degrees. The partial form of androgen insensitivity may be expressed variably even within the same family. The classic phenotype is that of a male with perineoscrotal hypospadias, cryptorchidism, rudimentary wolffian duct structures, gynecomastia, and infertility. However, the phenotypic spectrum can range from hypospadias and a pseudovagina to gynecomastia and azoospermia (Wilson et al, 1974). The differential diagnosis includes 5 α -reductase deficiency and 17 β -hydroxysteroid dehydrogenase. The endocrine profile of partial androgen insensitivity syndrome (PAIS) is similar to that of CAIS. At puberty, gynecomastia may develop. The phallus may enlarge slightly, but it remains small.

To date, over 800 mutations in the androgen receptor gene have been discovered (Hughes et al, 2012). It has been well recognized in PAIS that these mutations produce a diversity of phenotypes between and within affected families, consistent with additional factors that modulate responsiveness to androgen. This seems consistent with prior studies in the 1980s on genital skin fibroblasts, demonstrating two forms of receptor defect in PAIS: (1) a reduced number of normally functioning androgen receptors and (2) a normal receptor number but decreased binding affinity (Griffin and Durrant, 1982; Hughes, 2000).

The diagnosis of PAIS can be difficult. In the neonatal period, it may be made in the setting of a 46,XY karyotype, ambiguous external genitalia, and absent müllerian structures on pelvic ultrasound. Endocrine evaluation confirms normal male levels of testosterone and gonadotropins, and a normal testosterone/DHT ratio. An hCG stimulation test and characterization of the androgen receptor gene in serum DNA by PCR should confirm the diagnosis. A family history consistent with X-linked inheritance of ambiguous genitalia is of great assistance. A course of androgen injections in early infancy is often used to assess androgen responsiveness, which can aid in gender assignment.

Management must be individualized depending on the degree of genital ambiguity. In patients assigned a female gender, gonadectomy and surgical reconstruction of the external genitalia are indicated; at puberty, estrogen-progestin replacement is instituted. The majority of PAIS patients raised as males require treatment of cryptorchidism, reduction of gynecomastia, and genital reconstruction. Phallic size remains small, however, and the effects of supraphysiologic doses of testosterone have been disappointing (Migeon et al, 1994). A study by Szafran suggested a novel high content analysis (HCA) approach to study androgen receptor function at a single cell level in genital fibroblasts (Szafran et al, 2009). This could help individualize medical therapy. The risk of gonadal tumor is somewhat higher than in CAIS (up to 15%), and there is an increased risk of male breast cancer with PAIS (Cools et al, 2006; Hughes, 2006). Of importance in considering gender assignment in patients with partial androgen insensitivity is the recognition that the receptor defect affecting the external genitalia appears to affect brain receptors for testosterone similarly. Unfortunately, because of the distinct phenotypic variability, even within families, gender

assignment of patients with PAIS cannot be based on the specifically identified androgen receptor gene (Boehmer et al, 2001). The study by Melo and colleagues (2003) of 11 patients with PAIS (5 raised female, 6 raised male) demonstrated gender of rearing to be consistent with adult gender role. This suggests the possibility that in the setting of inadequate androgen imprinting of the fetal brain, sex of rearing may predominate in determination of gender identity. Unfortunately, this has not consistently proven to be the case.

Unfortunately, long-term outcome data in the management of patients with PAIS are limited. Migeon and colleagues' study (2002) of 14 patients with PAIS noted that 23% were dissatisfied with neonatal gender assignment irrespective of current status as male or female. Another study of 15 postpubertal males with PAIS documented major impairment in sexual function in all (Bouvattier et al, 2006). However, Mazur (2005) found that only 9% of patients with PAIS self-initiated a gender reassignment.

The current recommendation for PAIS is to allow virilization of the external genitalia to serve as a guide in gender assignment, in that this may be the best means of assessing androgen imprinting of the brain, for lack of a more precise marker (Sobel and Imperato-McGinley, 2004).

Mild Androgen Insensitivity Syndrome. A relatively new classification is that of mild androgen insensitivity syndrome discovered in the course of investigations for male factor infertility. Recent studies have demonstrated a variety of mutations, usually quite discrete within the androgen receptor gene, to account for the infertility (Hiort and Holterhus, 2003). Men with this syndrome may be normal phenotypically or have a history of mild hypospadias repair but are azoospermic or severely oligospermic. They have been found to have normal to elevated serum testosterone levels with normal to elevated LH levels. This suggests that infertility in otherwise normal males may be the clinical manifestation of partial androgen insensitivity, representing the far end of a variable phenotypic spectrum. To date, the pathophysiology of the abnormal spermatogenesis caused by androgen receptor mutations remains unknown (Hiort and Holterhus, 2003).

5 α -Reductase Deficiency

The disorder of 5 α -reductase deficiency is one of the most fascinating forms of male undervirilization. The clinical presentation of this enzyme disorder was actually predicted in 1972, before the description of such patients in 1974 by Walsh and Imperato-McGinley and their colleagues (Wilson, 1972; Imperato-McGinley et al, 1974; Walsh et al, 1974). Extensive characterization of the disease has been achieved since that time.

5 α -Reductase is a microsomal enzyme that catalyzes the conversion of testosterone to DHT. The condition is transmitted in an autosomal recessive pattern, and only homozygous males are affected. Two 5 α -reductase genes have been cloned; they encode different isoenzymes. The type 1 isoenzyme, encoded on chromosome 5, is expressed in low levels in the prostate and external genitalia. The type 2 isoenzyme is encoded on chromosome 2 and is expressed in high levels in the prostate and external genitalia (Thigpen et al, 1992b). Male undervirilization caused by 5 α -reductase deficiency is secondary to mutations in the type 2 gene. At least 68 mutations have been identified (Thigpen et al, 1992a; Imperato-McGinley, 2002; Berra et al, 2011). Identical mutations in individuals with widely different geographic and ethnic backgrounds support the concept of mutational "hot spots" on the gene.

On presentation individuals with this disorder are neonates with a 46,XY karyotype and a phenotype that may vary from normal female to markedly ambiguous genitalia (more common) to penoscrotal hypospadias to the rare, isolated microphallus (Maimoun et al, 2011). Typically the phallus is quite small, appearing as a normal or enlarged clitoris (Fig. 150-22). A urogenital sinus is present, with convergence of vaginal and urethral channels, and there is labioscrotal fusion (Fig. 150-23). The vaginal pouch is short and blind ending. Testes and epididymides are located in the labia, inguinal canals, or abdomen; and the vasa terminate in the



Figure 150-22. External genitalia of patient with 5 α -reductase deficiency. Note clitoromegaly with marked labioscrotal fusion and small vaginal introitus. (From Diamond D. *Intersex disorders: I and II*. AUA Update Series, vol. IX, lessons 9 and 10. Houston: American Urological Association Office of Education; 1990.)

blind-ending vaginal pouch. At puberty, partial masculinization occurs with an increase in muscle mass, development of male body habitus, increase in phallic size, and onset of erections (Peterson et al, 1977). Sperm production and fertility in affected individuals have been reported (Imperato-McGinley et al, 1982; Zhu et al, 1998). Other secondary sexual characteristics, including enlargement of the prostate and hairline recession, do not develop. Recently, the recognition of the rare 5 α -reductase patient with a female phenotype suggestive of CAIS has been made (Maimoun et al, 2011).

On endocrine evaluation these individuals have elevated mean plasma testosterone but low DHT levels. After hCG stimulation, the testosterone-to-DHT ratio increases to greater than 20:1. Genital skin fibroblast cultures demonstrate diminished to absent 5 α -reductase activity (Migeon et al, 1994). At puberty, virilization is presumed to occur because the androgen receptor binds markedly higher levels of testosterone at low affinity or because of the normal increase at puberty in the activity of the 5 α -reductase type 1 isoform, resulting in sufficient DHT for virilization (MacLaughlin and Donahoe, 2004). Indeed, the enzyme abnormalities in this disorder have been shown to be biochemically heterogeneous, ranging from reduced affinity of the enzyme for testosterone and reduced affinity for NADPH to altered pH activity profiles (Kupfer et al, 1992). The diagnosis is confirmed by sequencing the entire 5 α -reductase type 2 (*SRD5A2*) gene.

The phenotypic characteristics of this disorder have helped to clarify the roles of testosterone and DHT in normal development. Although DHT appears to be critical for the development of normal external genitalia in utero, testosterone alone appears sufficient for wolffian duct development.

Individuals in the pedigree studied by Imperato-McGinley and colleagues in the Dominican Republic underwent gender reversal at puberty and were known within the community as *guevedoces* ("penis at 12") (Imperato-McGinley et al, 1979b). This strong tendency toward reversal of gender identity in 5 α -reductase deficiency has been one of the most intriguing aspects of the disorder. It has



Figure 150-23. Unusual presentation of patient with 5 α -reductase deficiency with normal female external genitalia. A, Intraoperative examination of external genitalia; note enlarged clitoris, common urogenital sinus, and posterior labioscrotal fusion. B, Palpable testes exposed through labioscrotal incisions. C, Cystoscopic examination of vaginal channel revealing a blind-ending pouch and absent cervix.

lent support to the concept that testosterone exerts the primary male imprinting effect on the brain. However, the discovery that there are two isoenzymes for 5 α -reductase, only type 2 being deficient in this syndrome, allows for the possibility that 5 α -reductase type 1 has some impact on the brain (Thigpen et al, 1992b). As a

result, with early diagnosis of 5 α -reductase deficiency, a male gender assignment is generally favored, bearing in mind that the studies strongly supporting male gender identity in this disorder were performed in sociologically unique environments (Zhu et al, 1998). Cohen-Kettenis (2005a) noted 56% to 63% of 5 α -reductase deficiency patients to undergo gender reversal from female to male. The clinician must be open to familial cultural considerations regarding the value of male gender as well as the significance of penile size. In the setting of male gender assignment, cryptorchidism and hypospadias should be surgically corrected. Fertility is possible, particularly with the advent of intrauterine insemination (Katz et al, 1997). Exogenous DHT could be used at puberty in an attempt to promote phallic growth, but it would be likely to impair spermatogenesis. For some individuals with an unambiguously female phenotype (Fig. 150-24) or extremely small phallic size, female gender may be assigned. For these patients, gonadectomy should be performed as early as possible and certainly well before puberty to prevent virilization. Estrogen and progestin should be administered at the expected time of puberty. Vaginoplasty and clitoral reduction may be performed within the first year of life in those with a severe defect to provide for normal appearance of the external genitalia and to allay parental anxiety.

Persistent Müllerian Duct Syndrome

Persistent müllerian duct syndrome (PMDS), or *hernia uteri inguinalis*, the term originally used by Nilson (1939), characteristically describes a group of patients with a 46,XY karyotype and normal male external genitalia but internal müllerian duct structures. Typically, these phenotypic males have unilateral or bilateral undescended testes, bilateral fallopian tubes, a uterus, and an upper vagina draining into a prostatic utricle. The condition is commonly diagnosed after müllerian tissue is encountered during inguinal herniorrhaphy or orchidopexy.

Clarnette and coworkers (1997) suggested three categories for patients with PMDS: (1) the majority (60% to 70%) with bilateral intra-abdominal testes in a position analogous to ovaries; (2) a smaller group (20% to 30%) in which one testis is found in a hernia sac or scrotum in association with a contralateral inguinal hernia (the classic presentation of hernia uteri inguinalis); and (3) the smallest group (10%), in which both testes are located in the same hernia sac (as a result of transverse testicular ectopia) along with the fallopian tubes and uterus. Indeed, PMDS is believed to be etiologically important in transverse testicular ectopia, occurring in 30% to 50% of cases (Fujita, 1980).

The MIS gene was cloned in 1986 and localized on the short arm of chromosome 19 (Cates et al, 1986). It shows homology with the TGF- β superfamily of growth and differentiation factors (Imbeaud et al, 1995). PMDS is thought to be a heterogeneous disorder genetically in which some subjects have a defect in the gene for MIS located on chromosome 19p13 and others have a defect in the gene for its type II receptor located on chromosome 12q13 (MacLaughlin and Donahoe, 2004). The condition may occur sporadically or may be inherited as an X-linked (or autosomal dominant, sex-limited) trait (Migeon et al, 1994).

The treatment of PMDS is relatively straightforward, in that all patients are phenotypic males who require orchidopexy. The cases of adult patients with associated testis tumor (most commonly seminoma) probably reflect the increased risk of malignancy in intra-abdominal undescended testes. One treatment caveat relates to management of the rudimentary müllerian structures. The vasa deferentia are in close proximity to the uterus and proximal vagina, and historically preservation of the necessary müllerian structures to avoid injury to the vasa was recommended to preserve fertility (Sloan and Walsh, 1976). Eleven malignancies have now been reported in retained müllerian remnants, consistent with a risk of 3% to 8%, supporting careful surgical excision, which can be performed laparoscopically (Farikullah et al, 2012).

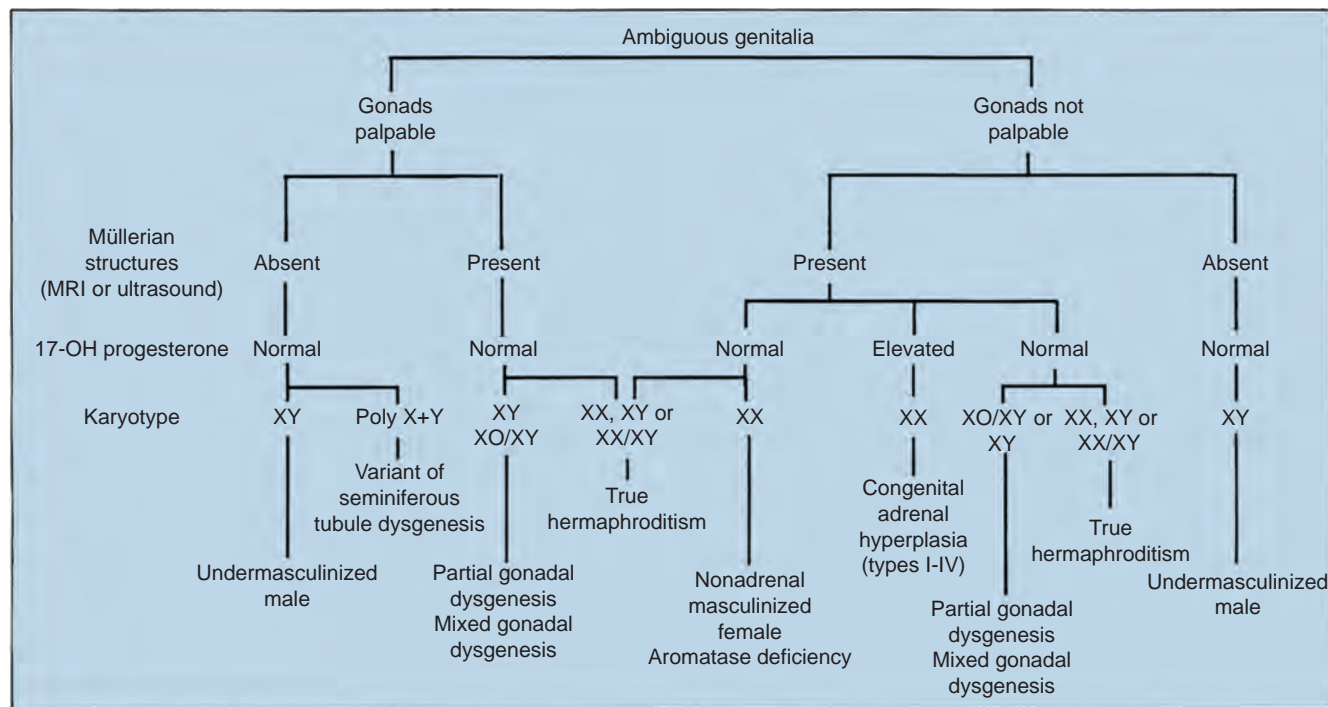


Figure 150-24. Diagnostic algorithm for a newborn with ambiguous genitalia based on gonadal palpability, presence or absence of müllerian structures, 17-hydroxyprogesterone concentration, and karyotype. MRI, magnetic resonance imaging (Modified from Grumbach MM, Conte FH. Disorders of sex differentiation. In: Wilson JD, Foster DW, editors. Williams textbook of endocrinology. Philadelphia: Saunders; 1998. p. 1401.)

Unclassified Forms: Mayer-Rokitansky-Küster-Hauser Syndrome

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare disorder entailing congenital absence of the uterus and vagina. It occurs in approximately 1 of every 4000 to 5000 female births. Patients with MRKH syndrome have a 46,XX karyotype and are normal-appearing females with normal secondary sex characteristics. The external genitalia appear normal, but only a shallow vaginal pouch is present. In the typical form of the syndrome there is symmetrical anatomy with absence of both vagina and uterus. Normal ovaries and fallopian tubes are present, and ovarian function is normal, but only symmetrical uterine remnants are found (Griffin et al, 1976). The report of a *WNT4* mutation in a woman with a phenotype resembling MRKH suggests the importance of this gene in müllerian duct formation (Biason-Lauber et al, 2004).

The most common clinical presentation for MRKH syndrome is primary amenorrhea, but patients may have infertility or dyspareunia. Upper urinary tract anomalies occur in approximately one third of patients and include renal agenesis, pelvic kidney, and horseshoe kidney.

Atypical forms of MRKH syndrome have been described in up to 10% of patients, in which asymmetrical uterine remnants and/or aplasia of one or both fallopian tubes is discovered. As a result, endometrial tissue or variable development of the uterus with hematometra may be present, resulting in a clinical presentation with cyclic abdominal pain. Urinary tract anomalies occur more commonly in patients with the atypical form of MRKH. In a study of 100 patients with MRKH syndrome, 38 of 56 patients (68%) with the atypical form of the condition had upper urinary tract abnormalities. None of the 44 patients with the typical form of MRKH syndrome had an upper urinary tract anomaly (Strubbe et al, 1994). In addition, associated cardiac anomalies have been noted in 16% of MRKH patients (Pitcock et al, 2005).

A radiologic evaluation with ultrasonography and magnetic resonance imaging may define müllerian anatomy accurately in MRKH and distinguish between typical and atypical forms of the disorder (Nussbaum-Blask et al, 1991; Reinhold et al, 1997).

Treatment entails creation of a neovagina, by means of dilation or surgically, to allow for sexual function (Ismail-Pratt et al, 2007). Given the frequent success of dilation and its comparable functional outcomes to surgery, it should be the first line of therapy as recommended by the American College of Obstetricians and Gynecologists (Gargollo et al, 2009; Morcel et al, 2013). If present, a hemiuterus should be removed, whereas a midline uterine structure should be hormonally suppressed rather than connecting this structure to a reconstructed vagina.

EVALUATION AND MANAGEMENT OF THE NEWBORN WITH AMBIGUOUS GENITALIA

The evaluation and initial management of the neonate with ambiguous genitalia must be regarded as a medical and psychosocial emergency and be handled with great sensitivity toward the family. Ideally, a medical team including a pediatric urologist, an endocrinologist, and a psychiatrist or psychologist experienced in managing intersex patients should work closely with the family. The team's goal should be to make a precise diagnosis of the disorder (which can be achieved in most cases) and, with the involvement of the parents, to assign a proper sex of rearing based on the diagnosis, the status of the child's anatomy, and the functional potential of the genitalia and reproductive tract.

In obtaining the history, certain pieces of information may be particularly valuable. A history of infant death within the family might suggest the possibility of CAH, and infertility, amenorrhea, or hirsutism might also suggest possible familial patterns of intersex states. Certainly, maternal use of medications, in particular steroids or contraceptives, during the pregnancy is of great importance.

The critical finding on physical examination is the presence of one or two gonads. This finding effectively rules out overmasculinization of the female. Because ovaries do not descend, a distinctly palpable gonad along the pathway of descent is highly suggestive of a testis. Rarely, an ovotestis undergoes descent to the inguinal canal and may be suspected on the basis of asymmetry of tissue texture of the poles of the gonad. This suspicion may be further supported by ultrasound findings. The patient with bilaterally impalpable testes or a unilaterally impalpable testis and hypospadias should be regarded as having a DSD until proven otherwise, whether or not the genitalia appear ambiguous. Kaefer and associates (1999) studied the incidence of DSDs in patients with cryptorchidism and hypospadias and without ambiguous genitalia. With a unilateral cryptorchid testis, the incidence of DSD was 30% overall—15% if the undescended testis was palpable and 50% if it was impalpable. In the setting of bilateral undescended testes and hypospadias, the incidence of DSD was quite similar—32% overall but only 16% if both gonads were palpable. If one of two undescended testes was impalpable, the incidence of DSD tripled to 47%, comparable to the rate in those with a unilateral, impalpable, cryptorchid testis. In addition, posterior urethral meatal position was noted to be a strong predictor of DSD in this group of patients—65%, versus 5% to 8% with a midshaft to anteriorly located hypospadiac meatus (Kaefer et al, 1999).

In addition to gonadal examination, penile size should be assessed and an accurate measure of stretched penile length recorded. The mean stretched penile length in full-term males born in the United States is 3.5 cm (± 0.04) (Lee et al, 2006).

An additional important finding on physical examination is the presence of a uterus, which is noted as an anterior midline cordlike structure on rectal examination. A more precise means of assessing müllerian anatomy is by pelvic ultrasonography, which may be performed immediately in the neonatal period. In addition to defining müllerian anatomy and confirming the presence or absence of a uterus, the gonads and adrenals should be studied. Normal anatomy of an undescended gonad should be confirmed, and a cyst within the gonad, consistent with ovotestis, should be ruled out.

Within the immediate neonatal period, a karyotype should be obtained. Typically this requires 2 days to perform. Therefore an attractive approach to obtain chromosomal data quickly is FISH, which rapidly identifies X and Y chromosomes. It is typically used to confirm the presence of a second X chromosome. The technique is much more rapid than karyotyping, producing results within a few hours.

Serum studies should be immediately sent to rule out a salt-wasting form of CAH. In addition to serum electrolytes, testosterone and DHT should be measured early. Migeon and colleagues (1994) emphasized that the androgen levels may drop quickly, necessitating early study. In addition, they suggested that serum 17-hydroxyprogesterone should not be measured until day 3 or 4 to rule out 21-hydroxylase deficiency, because the stress of delivery may result in physiologic elevation of this steroid precursor in the first 1 or 2 days of life.

In the absence of palpable testes, the presence or absence of testicular tissue should be determined by documentation of a markedly elevated LH level, consistent with anorchia, or by means of an hCG stimulation test, which can demonstrate normally functioning testicular tissue (Jarow et al, 1986). In addition to ruling out anorchia, the study can enable diagnosis of 5 α -reductase deficiency (by virtue of an increased ratio of testosterone to DHT) and can help distinguish between impaired testosterone synthesis (deficient response to hCG) and androgen insensitivity (normal response to hCG). Serum MIS measurement should be included as a marker of the presence of testicular tissue (Hughes et al, 2012).

Based on physical examination findings (largely, gonadal palpability), the presence or absence of müllerian structures on ultrasonography, 17-hydroxyprogesterone concentration, and the karyotype, a reasonable differential diagnosis may be formulated (Fig. 150-25). A precise diagnosis can virtually always be achieved for the 46,XX DSD (overvirilized female) but in only 50%

Karyotype

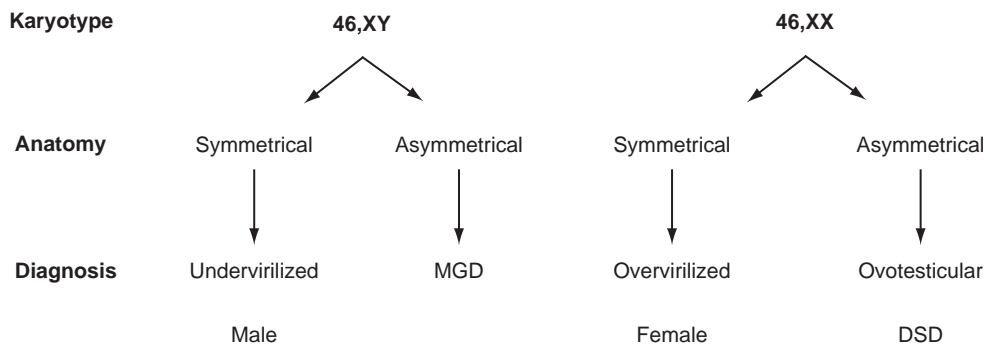


Figure 150-25. Likely diagnoses based on karyotype and anatomic symmetry. DSD, disorder of sex differentiation; MGD, mixed gonadal dysgenesis.

KEY POINTS: EVALUATION AND MANAGEMENT OF DISORDERS OF SEX DEVELOPMENT

- The team's goals should be to make a precise diagnosis of DSD (which can be achieved in most cases) and, with the involvement of the parents, to assign a proper sex of rearing based on the diagnosis, the status of the child's anatomy, and the functional potential of the genitalia and reproductive tract.
- The patient with bilaterally impalpable testes or a unilaterally impalpable testis and hypospadias should be regarded as having a DSD until proven otherwise, whether or not the genitalia appear ambiguous.

of 46,XY DSD undervirilized males (Lee et al, 2006). The presence of asymmetrical anatomy on examination and ultrasonography is an important observation and suggests mixed gonadal dysgenesis if the karyotype is 46,XY and ovotesticular DSD if it is 46,XX.

Performance of laparotomy or laparoscopy and gonadal biopsy is usually the next definitive clinical step required when a firm diagnosis based on the aforementioned data is impossible. **Laparotomy or laparoscopy in this setting remains a diagnostic maneuver; removal of gonads or reproductive organs should be deferred until the final pathology report is available and a gender has been assigned.** PCR characterization of the androgen receptor in venous blood DNA may define the precise genetic abnormality responsible for a given DSD, be it abnormal androgen receptor or an enzyme abnormality. These studies should be performed in specialized laboratories where normal values are well established.

Finally, anatomic definition of the urogenital sinus and ductal structures contributes to the correct diagnosis and is necessary before any surgical intervention. The urogenital sinus is well imaged by retrograde contrast injection, which also opacifies ductal structures, defines the entry of urethra and vagina into the sinus, and outlines the cervical impression within the vagina. Endoscopy can define these relationships further but is usually not necessary until surgical reconstruction becomes imminent.

Gender Assignment

After a definitive diagnosis has been reached, a thorough and candid discussion with the family regarding gender assignment should take place. **Issues related to the diagnosis-specific potential for normal sexual functioning and fertility and the risk of gonadal malignancy should be addressed.** Parents should understand that high-quality data regarding the long-term psychosocial outcomes of gender assignment for the majority of DSDs are lacking, although longitudinal studies are being pursued. Parental involvement in the decision-making process is essential. If the diagnosis of a DSD is made prenatally, it is important to present a plan

of management to the parents or risk termination of the pregnancy (Nihoul-Fekete, 2004).

In the setting of a 46,XX karyotype and masculinized female, gender assignment is usually appropriately female. In CAH, cortisol suppresses the undesired androgen; and if maternal androgen is responsible for virilization, its discontinued stimulation is corrective. In both cases there are normal ovaries and müllerian ducts, and a normal reproductive potential exists. **If the karyotype is 46,XY, the issue is a more complex one and includes factors such as penile length and evidence of androgen insensitivity.** For example, 46,XY patients with complete (severe) androgen insensitivity are appropriately assigned a female gender, whereas those with 5 α -reductase deficiency may be more appropriately assigned a male gender. The most frequent abnormal karyotype is 45,X/46,XY mosaicism, which has a variable phenotypic spectrum. The degree of masculinization of the external genitalia appears to vary with the amount of testicular tissue present, and gender assignment depends on the functional potential of the gonadal tissue, reproductive tracts, and genitalia. The best predictor of adult gender identity is initial gender assignment (Cohen-Kettenis, 2005b). Some investigators have suggested deferring the issue of gender assignment until patients reach an age at which they may declare their own gender identity. Such an approach, although rational, is difficult to implement given cultural norms and not recommended in the consensus statement (Lee et al, 2006). As Elliott (1998) states, "We treat these children the way we do (as male or female) because this is the way we see the world; most importantly it is the way that the children, themselves, are taught to see the world."

Overall, it is well to remember in the management of ambiguous genitalia the parameters of optimal gender policy outlined by Meyer-Bahlburg (1998):

- Reproductive potential (if attainable at all)
- Good sexual function
- Minimal medical procedures
- An overall gender-appropriate appearance
- A stable gender identity
- Psychosocial well-being

The importance of transparency with the family and patient in management of DSDs cannot be overemphasized. Uncertainties in outcomes with different gender assignment for different disorders mandate involvement of the parents in early decision making. In the long run, transparency is essential for a healthy physician-patient relationship as the child develops into adolescence and adulthood, affording them knowledgeable engagement in DSD management for the long term.

Ultimately, management of patients with disorders of sexual differentiation remains a challenging and humbling process. On the one hand, physicians have at their disposal sophisticated molecular biologic techniques that have enabled them to identify genetic disorders responsible for the majority of DSDs. On the other hand, the mysteries of brain dimorphism in the setting of sexual ambiguity remain to be solved to optimize the long-term psychosocial outcome of gender assignment for the individual patient.

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The complete reference list is available online at www.expertconsult.com.

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151 Surgical Management of Disorders of Sex Development and Cloacal and Anorectal Malformations

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Classification of Urogenital Sinus and Cloacal Anomalies

Surgical Reconstruction of Disorders of Sex Development and Urogenital Sinus

Surgical Reconstruction for Cloacal Malformations

Summary

The surgical management of disorders of sex development (DSD) and cloacal anomalies is one of the most complex problems a pediatric urologist/surgeon will ever encounter. The vast majority of children with DSD will be noted to have some genital ambiguity. Surgery in this group is perhaps the most controversial topic addressed in this entire textbook. The complexity of this topic has led to featured presentations by nearly every major television and print media outlet. Having a child born with DSD is very stressful for the parents and it is therefore imperative to create a supportive medical team that can not only help the family understand the diagnosis but also help them understand all controversies and options they have for medical and surgical management. Most families historically have opted for early surgery to “normalize” their child’s genitalia. The thought of “doing nothing” for their child with DSD has been noted to be stressful for families (Creighton et al, 2012). Most parents viewed surgery as obvious and necessary and something that did not involve decision making (Crissman et al, 2011). However, Lloyd and colleagues (2005) and Akbiyik and Kutlu (2010) have now shown there to be tremendous variability in genital proportions of “normal” adults and children who do not have a DSD. The family should also be informed of the possible long-term psychosocial experience of the child with DSD (Krishnan and Wisniewski, 2014). What is clear is that the parents must be made aware of all pros and cons of having surgery and also of not having surgery. **No parent or child should ever be talked into having surgery.** However, if surgery is elected the multidisciplinary medical team should be supportive of the family and should make sure the parents are aware of the options for timing of the surgery and the advantages and disadvantages for each surgical option. The parents should also be made aware of and have access to support groups such as the CARES Foundation (www.caresfoundation.org), Accord Alliance (accordalliance.org), and Magic Foundation (magicfoundation.org). This chapter addresses the surgical options and management of this complex spectrum of anomalies with the assumption that the parents and family agree that surgery is appropriate.

CLASSIFICATION OF UROGENITAL SINUS AND CLOACAL ANOMALIES

Because of the spectrum and complexity of urogenital sinus anomalies and the potential for other associated organ system abnormalities, evaluation and management must be meticulous. In urogenital sinus anomalies there is a persistent communication of the vagina with the urinary tract. Communication of the vagina with the urinary tract may occur at any point from the urethral meatus to the bladder, but the majority occur within the mid to distal portion of the urethra. The two structures join and exit on the perineum as a single common urogenital sinus channel.

A persistent urogenital sinus is seen in four entities. Most commonly it occurs in **genital ambiguity states**, most frequently with congenital adrenal hyperplasia (CAH) (Fig. 151-1). It can also occur as a **pure urogenital sinus** with normal external genitalia (Fig. 151-2). In **persistent cloacal anomalies** there is the added complexity of rectal involvement, with all three systems—genital, urinary, and intestinal—exiting as an isolated single perineal opening. More recently, **female exstrophy** has been thought to represent a form of persistent urogenital sinus (Adams, 2000).

Early descriptions of this confluence were based on previous medical training. Urologists described the vagina as entering the urethra, whereas gynecologists noted that the urethra entered the vaginal vestibule (Jones and Jones, 1954). Jaramillo and colleagues (1990) noted that on examination the external cloacal orifice appears vaginal in nature in some cases but in others appears more like a normal urogenital orifice (Figs. 151-3 and 151-4). **Regardless of how the confluence of the urinary and genital tracts is described, the confluence location in relation to the bladder neck is a more critical factor in surgical management than the length of the common channel** (Rink et al, 2005a).

Evaluation

Urogenital sinus abnormalities are most often seen in DSD states, most commonly in association with CAH, which has been

KEY POINT: UROGENITAL SINUS ANOMALIES—GENERAL

- Urogenital sinus anomalies are found in four entities: genital ambiguity states, pure urogenital sinus, persistent cloaca with rectal involvement, and female exstrophy.

noted to have an incidence as high as 1 in 500 in the nonclassic, mild form (Hughes, 1988). CAH is a group of inherited autosomal recessive genetic abnormalities of which the most common enzymatic defect resulting in genital ambiguity is 21-hydroxylase deficiency. This occurs in approximately 1 in 15,000 to 16,000 persons (Speiser and White, 2003; Merke and Bornstein, 2005). Mutations in the 21-hydroxylase gene (mutation in *CYP21A2* gene on the short arm of chromosome 6 in 90% to 95% of individuals) result in varying degrees of virilization corresponding to the type of mutation. CAH should be regarded as a spectrum disorder from mild

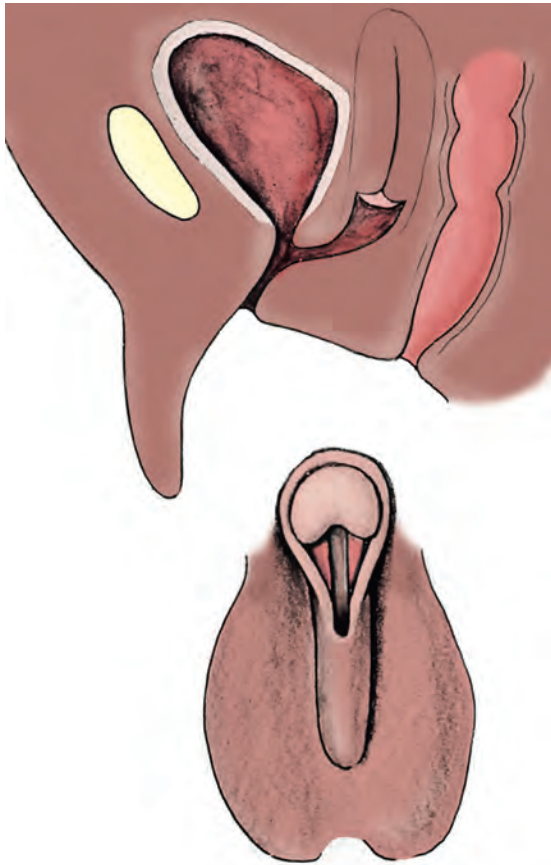


Figure 151-1. Urogenital sinus in a patient with intersex.



Figure 151-2. Pure urogenital sinus abnormality.



Figure 151-3. *Left*, Urethral-type urogenital sinus. *Right*, Urethral-type urogenital sinus with an anteriorly placed rectum.

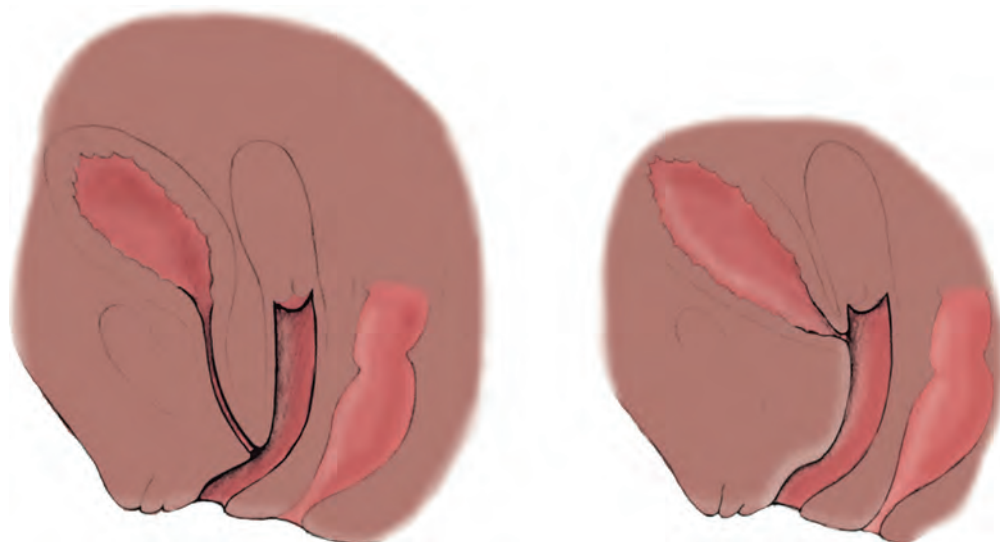


Figure 151-4. Vaginal-type urogenital sinus showing high (right) and low (left) confluence.

anomalies to those with deep impact on life (Nordenskjöld et al, 2008). Therefore initial management must focus on making an accurate diagnosis to allow proper gender identification. Every effort should be made to establish the genetic sex within 48 hours. Children with CAH require careful monitoring of fluid and electrolytes because 67% to 75% will have significant salt wasting owing to lack of aldosterone secretion (Speiser and White, 2003; Merke and Bornstein, 2005). The classic findings of salt wasting in 21-hydroxylase deficiency are hyponatremia, hyperkalemia, high urinary sodium, low serum and urinary aldosterone, and elevated plasma renin activity (New et al, 2014). This may lead to dehydration, poor feeding, hypotension, and even vascular collapse, shock, and death (adrenal crisis). Evaluation should include rapid karyotyping of cultured peripheral leukocytes, measurement of serum electrolyte levels, and determination of hormonal levels for CAH. All results are shared with the gender assignment team, which includes the parents, pediatric endocrinologist, pediatric urologist, neonatologist, geneticist, child psychiatrist/psychologist, and often clergy. The child should not be named until sex assignment is complete (Rink and Adams, 1998).

Cloacal anomalies are a much more complex problem involving multiple organ systems, but fortunately they occur in only 1 in every 40,000 to 50,000 patients (Karlin et al, 1989). They are the most challenging of the anorectal malformations and make up 13.6% of this group (Fleming et al, 1986). These children have a very broad spectrum of findings on examination of the external genitalia. Some may have a prominent phallic structure and also initially require evaluation for a DSD.

History and Physical Examination

Many children with urogenital sinus abnormalities are now identified by antenatal ultrasonography, with the findings of fluid-filled pelvic structures (vagina and bladder) with indeterminate genitalia. Furthermore, since 2009 newborn CAH screening programs have been carried out in all 50 states and in areas worldwide, which helps to identify some affected children (New et al, 2014). However, the history and the physical examination remain extremely helpful in cases of genital ambiguity and can often lead to the diagnosis itself. It is critical to determine whether the mother ingested any medications during pregnancy, especially androgenic substances. A family history of early infant death or fluid and electrolyte abnormalities suggests CAH. Have other children had genital ambiguity or gender dysphoria at puberty? Notation should be made of any family members with abnormal pubertal development.

The physical examination can at times be very useful in determining the appropriate gender and in helping to identify other organ systems involved. A general evaluation of the child's overall health should be completed before focusing on the genital examination. Abnormal facies suggesting a syndrome should be noted. Hypertension can occur in children with genital ambiguity secondary to CAH from 11 β -hydroxylase deficiency. Therefore blood pressure should be documented. Evidence of dehydration may also lead to a diagnosis of CAH. On abdominal examination a mass, particularly a suprapubic mass, may be present because of a distended bladder or hydrometrocolpos, or both. Hydrometrocolpos is frequently an initial sign and is often the only early finding in pure urogenital sinus abnormalities.

In cloacal anomalies, abdominal distention may be severe secondary to hydrometrocolpos and bladder and intestinal distention. Hydrometrocolpos was noted commonly in early series (Chappell and Bleloch, 1973; Klugo et al, 1974); its incidence ranged from 29% of Peña's patients (Peña, 1989) to 63% of those reported by Bartholomew and Gonzales (1978). It is caused most commonly by preferential flow of urine through the urogenital sinus into the vagina (or vaginas) with voiding and associated poor vaginal drainage. Maternal estrogen stimulation of the cervical glands results in mucus production, thereby further adding to the distention. Urine flow can occur into the rectum also. The distention of these pelvic structures has resulted in edematous, cyanotic legs and respiratory distress, as well as acidosis (Raffensperger, 1988).

The lower part of the back should be examined to identify any evidence of spinal cord abnormalities, which can be associated with urogenital sinus abnormalities and are very common with cloacal anomalies. Such abnormalities may take the form of a sacral dimple, hair patch, or area of abnormal pigmentation, but more commonly there is evidence of a bone abnormality, such as an abnormal buttock crease or flattened buttocks as a result of sacral agenesis.

Genital examination should note the size of the phallus and the consistency of the erectile bodies. Any degree of curvature should be documented. Huffman (1976) multiplied the width of the glans times the length of the phallus to determine the "clitoral index," which he noted should be less than 3.5 mm to be normal and was of concern when greater than 10 mm. The average clitoral length for a full-term girl in the United States was noted to be 4.0 ± 1.24 mm and the average width was 3.32 ± 0.78 mm (Hughes et al, 2006). Persistent isolated clitoral hypertrophy may be found in premature infants and is not associated with DSD or other signs of ambiguity (Williams et al, 2013). The location of the meatus of

the urogenital sinus should be noted and may occur in a spectrum from a near-normal introital location to the tip of a well-formed glans. The gonads should be sought and, when found, their number, location, and consistency should be noted. If both gonads are descended, it is extremely unlikely that a 46,XX chromosome makeup will be found. The labioscrotal folds should be examined for their relationship to the phallus and rectum, as well as for the degree of fusion. Increased pigmentation of the labioscrotal folds and areola may be seen in some cases of CAH as a result of increased levels of melanocyte-stimulating hormone.

In urogenital sinus anomalies the location of the anus should be noted. Although it is usually in the normal location, anterior displacement is not uncommon, and this bridges the gap to cloacal anomalies (see Fig. 151-3). A gentle rectal examination is helpful in identifying a cervix.

Examination of a child with a persistent cloaca deserves special mention. There is a single perineal orifice because the rectum also enters this common channel. The appearance of the external genitalia assumes a much wider spectrum, from a nearly normal female appearance to much more bizarre appearances such as complete genital transposition or a blank-appearing (doll-like) perineum (Fig. 151-5) (Hendren, 1989). In some instances there is an enlarged phallic structure that gives the genitalia an ambiguous appearance. The single perineal opening may exit what appears to be a normal vaginal introitus, or it may extend to the tip of a phallic structure. I as well as others have encountered children with a secondary accessory channel that exits the tip of the phallus (Hendren, 1989; Karlin et al, 1989; Krstic et al, 2001; Rink et al, 2005b).

Cloacal anomalies are associated with a high incidence of related anomalies in other organ systems. I found 14 of 23 patients with renal anomalies, including 6 with solitary kidneys, 4 with renal dysplasia, 2 with ureteropelvic junction obstruction, 1 with duplication, and 1 with crossed fused ectopia; there were also 2 with bladder duplications (Rink et al, 2005b). Sixty percent have some degree of septation of the vagina and uterus (Warne et al, 2003). Kay and Tank (1977) reported that 13% of patients with cloacal anomalies have cardiovascular abnormalities, 10% have central nervous system problems, and respiratory abnormalities are noted in 5%; vertebral, particularly sacral, anomalies are common. Many have the VACTERL association (Vertebral abnormalities, Anal atresia, Cardiac abnormalities, Tracheoesophageal fistula and/or Esophageal atresia, Renal agenesis and dysplasia, and Limb defects), so tracheoesophageal fistula is often present (Hendren, 1986, 1988). Other gastrointestinal anomalies have been noted, including duodenal atresia and rectal duplication in 2% (Karlin et al, 1989).

Radiographic and Endoscopic Evaluation

Urogenital Sinus Abnormalities

Certain critical details of the anatomy, including the length of the common urogenital sinus, the location of the vaginal confluence and its proximity to the bladder neck, the size of the vagina and the number of vaginas, the presence of a cervix, and bladder and urethral anatomy, must be defined. This can be done radiographically or endoscopically. I believe that the location of the vagina in

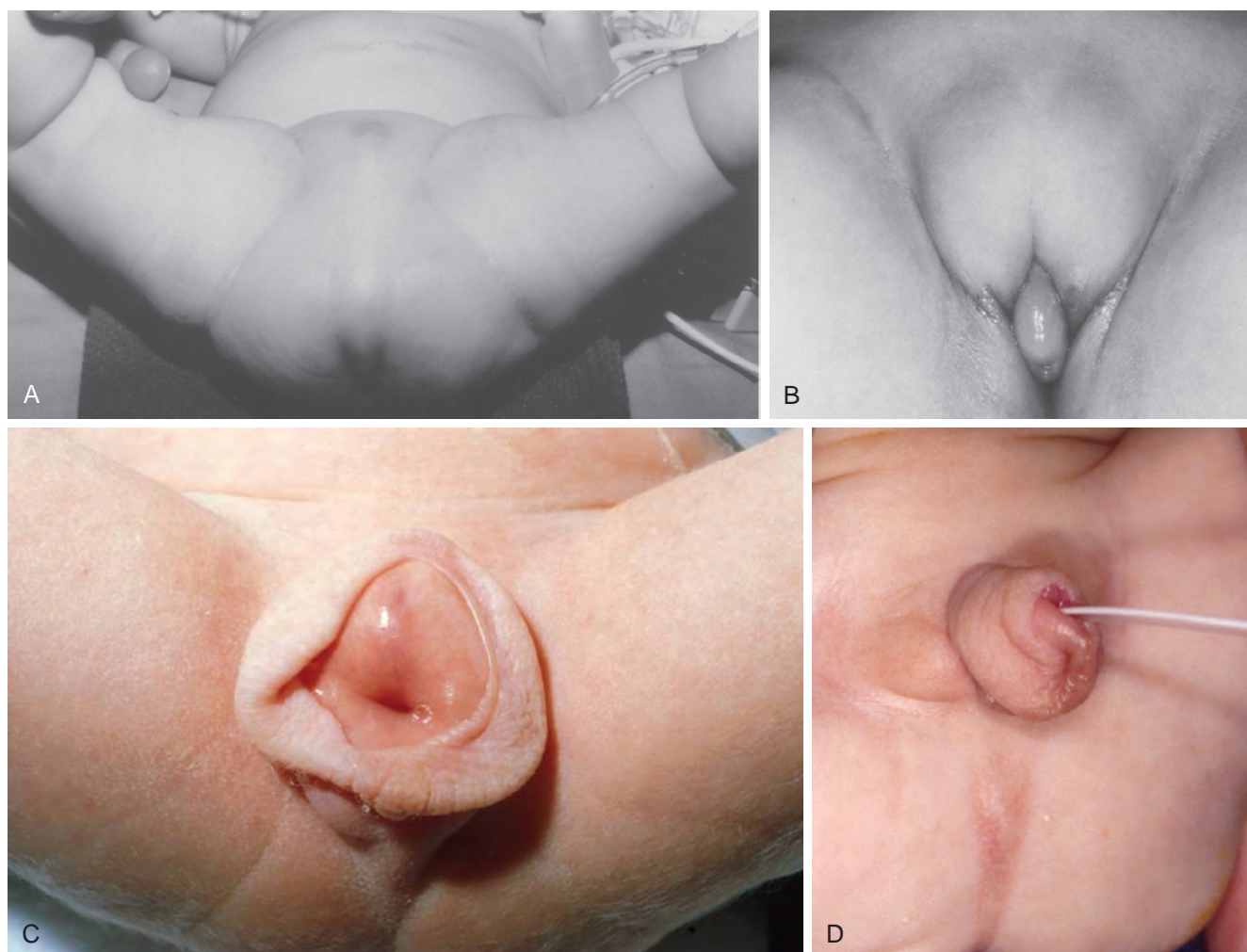


Figure 151-5. A, Cloaca with a blank perineal appearance. B, Cloaca with genital transposition. C, Cloaca, vaginal type, external appearance. D, Cloaca, urethral type, external appearance.

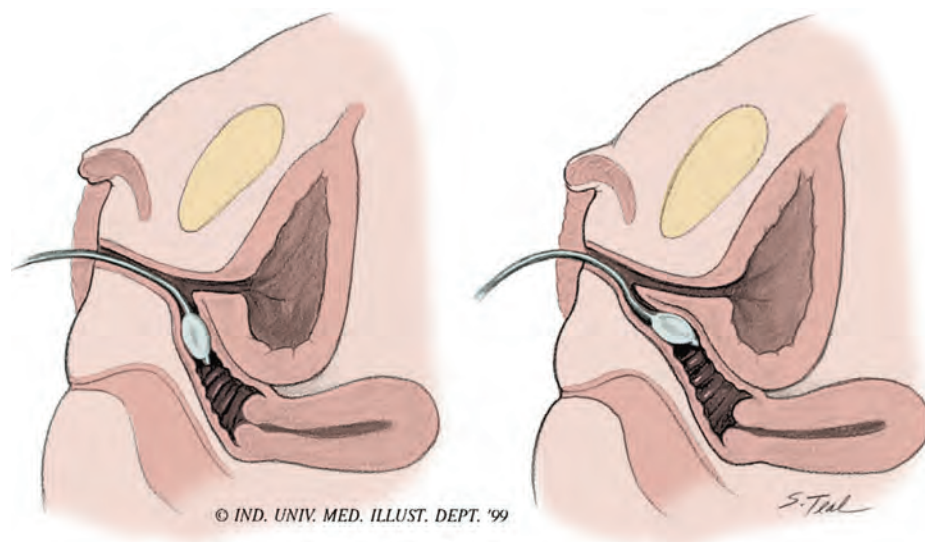


Figure 151-6. Fogarty catheter placed in the vagina in high confluence (*left*) and in low confluence (*right*). (© 1999, Indiana University Medical Illustration Department.)

KEY POINTS: UROGENITAL SINUS ANOMALIES—EVALUATION

- Key points of the history and physical examination are findings of a family history of sudden infant death, fluid and electrolyte abnormalities, hypertension, suprapubic mass, lower extremity cyanosis, palpable gonads, and hyperpigmentation, and number of perineal orifices.
- The level of the urethrovaginal confluence and the location of the rectum must be identified radiographically and endoscopically, with note made of their relationship to the bladder neck. Ultrasonography is mandatory to look for the uterus, ovaries, and kidneys.

relation to the bladder neck is the critical issue in determining the type of surgery, and this distance is far more important than the length of the common channel ([Rink et al, 2005a](#); [Ludwikowski and González, 2013](#)). Vaginal confluence with the urinary tract in pure urogenital sinus and cloacal anomalies occurs in a continuum from the bladder to a nearly normal location in the perineum. It is not simply “high” (proximal/suprasphincteric) or “low” (distal/infrasphincteric) ([Hendren and Crawford, 1969](#); [Powell et al, 1995](#); [Rink and Kaefer, 2002](#)) ([Fig. 151-6](#)). I am in agreement with [Ganesan and colleagues \(2002\)](#) that the confluence of the urethra and vagina in CAH is fairly constant with a normal proximal urethra. It is the distance from the vagina to the meatus that lengthens with increasing virilization, making some appear to be “very high.” Furthermore, this high confluence appearance is exacerbated in the more virilized urogenital sinus because there may be the appearance of a well-defined (male-like) external sphincter with a verumontanum appearance to the vaginal confluence just proximal to it and the bony pelvis is more masculinized.

A new urogenital sinus classification that measures the exact distance of the common channel and the distance of the bladder neck to the vagina has been devised to help delineate the exact level of the confluence, as well as clitoral size and appearance of the external genitalia ([Rink et al, 2005a](#)).

Ultrasonography of the urinary tract and pelvis is mandatory. The location and normalcy of the kidneys, ovaries, and uterus should be defined. Any bladder or vaginal distention should be



Figure 151-7. Genitography showing low confluence of the urethra and vagina.

noted. A cerebriiform appearance with enlargement of the adrenal glands is indicative of CAH ([Brock et al, 1998](#)).

Filling the entire bladder, urethra, vagina, and sinus with contrast (i.e., genitography) is critical in the anatomic evaluation of many children with a urogenital sinus ([Figs. 151-7 and 151-8](#)). Genitography is performed by placing a Foley catheter with the balloon occluding the perineal meatus and injecting a contrast agent. It is often helpful to pass a catheter into the bladder as for a voiding cystourethrogram. In some children, the vagina will only be demonstrated with voiding. A cervical impression at the vaginal dome denotes normal female internal organs. Magnetic resonance imaging (MRI) is of limited value in CAH but may be very helpful to define the anatomy in pure urogenital sinus anomalies or other DSD and cloacal conditions. In CAH patients, the internal anatomy can nearly always be defined by an endoscopy at the time



Figure 151-8. Genitography showing high confluence of the vagina entering near the bladder neck, with flow of contrast medium into the uterus.

of reconstruction, making genitography less useful in this group (VanderBrink et al, 2010). In our institution, the anatomy was accurately defined in CAH in only 72% of cases by genitography and it did not provide any information that could not be obtained by endoscopy, and genitography did not influence the type of timing of surgery (VanderBrink et al, 2010).

The most helpful diagnostic study in defining the anatomy for surgical reconstruction is endoscopy. In patients with CAH, endoscopy is usually performed at the time of reconstruction but may be necessary as a separate early procedure to help with gender identity in other DSD cases or in those with complex pure urogenital sinus anomalies or if the vagina is not identified on genitography (Rink and Kaefer, 2002). In the latter situation, multiple punctuate openings in the proximal portion of the urethra may be observed (Donahoe and Gustafson, 1994). I have found it helpful to pass a ureteral catheter into the opening and evaluate the vagina fluoroscopically in this situation (Rink and Kaefer, 2002). Again, the exact location, size, and number of the vaginas should be recorded (Fig. 151-9). Hendren has noted a male-like external sphincter in severely masculinized children, with the vagina entering proximal to it in a verumontanum-like structure (Hendren and Crawford, 1969; Hendren and Atala, 1995). In my initial experience, I thought this rarely if ever occurred (Adams and Rink, 1998), but as noted earlier, I have more recently seen several CAH children with a completely masculinized male-like urethra with an external sphincter and verumontanum-like structure.

Rarely, even with the evaluation described, some children with DSD require gonadal biopsy or evaluation of the internal genitalia, which has historically been done by laparotomy but in most cases can now be easily performed laparoscopically. Regardless of the means, it should be performed only when the findings would influence the gender of rearing (Rink and Adams, 1999). If a biopsy is



Figure 151-9. Endoscopic view of confluence. The urethra is superior; the vagina is inferior.

necessary, a deep incision should be made in the gonad because the ovarian component of ovotestes may completely surround the testicular component or be located at the poles (Hensle and Kennedy, 1998; Schnitzer and Donahoe, 2001). Finally, scrotal skin biopsy may at times be helpful in males with incomplete androgen insensitivity, decreased 5 α -reductase activity, or decreased dihydrotestosterone binding (Griffin and Wilson, 1989). Certainly all children with DSD should undergo chromosomal, endocrinologic, and genetic evaluation. This is well described in Chapter 150.

Cloacal Anomalies

Evaluation for cloacal anomalies begins with antenatal ultrasonography because several groups have now reported the prenatal diagnosis of persistent cloaca (Shalev et al, 1986; Petrikovsky et al, 1988; Cilento et al, 1994; Odibo et al, 1997; Adams and Rink, 1998; Cacciaguerra et al, 1998; Warne et al, 2002a). The diagnosis has been made as early as 19 weeks' gestation. The finding of transient fetal ascites with bilobed or trilobed pelvic cystic structures, bilateral hydronephrosis, and decreased amniotic fluid is diagnostic (Cacciaguerra et al, 1998; Warne et al, 2002b). The ascites is thought to develop via retrograde flow of urine into the uterus and out the fallopian tubes secondary to outlet obstruction from the distended vagina (Adams et al, 1998; Cacciaguerra et al, 1998).

Postnatal radiographic evaluation begins with a plain abdominal film (Jaramillo et al, 1990) and abdominal ultrasonography. A pelvic mass may be obvious on a kidneys, ureters, and bladder view. Retrograde flow of urine and meconium, as described earlier, may result in the classic linear calcifications or calcified meconium. More granular calcifications may be noted along the course of the rectum as a result of urine flow into the rectum that yields calcified meconium (Jaramillo et al, 1990). Abdominal ultrasonography is very important to visualize not only the pelvic anatomy but also the kidneys because hydronephrosis is common (Hendren, 1998). Hydronephrosis is usually related to hydrocolpos, with the distended vagina compressing the bladder neck and resulting in varying degrees of bladder outlet obstruction (Hendren, 1998). Ureteral compression may also occur; however, I have seen hydronephrosis caused by primary obstructive megaureter in patients with cloacal anomaly.

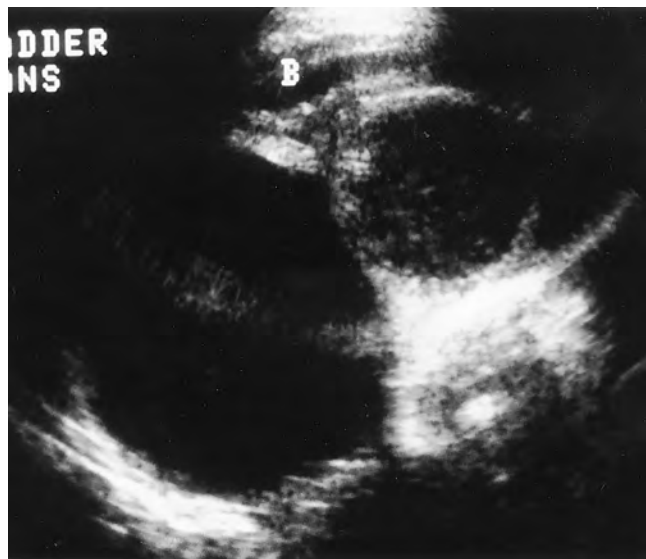


Figure 151-10. Pelvic ultrasonography in a patient with a cloaca. Duplicate fluid-filled vaginas are seen posterior to the decompressed bladder (B).

Ultrasonography may also detect other renal anomalies. Renal anomalies such as dysplasia, fusion anomalies, ectopia, uretero-pelvic junction obstruction, and duplication have been seen in 33% to 83% of children with a persistent cloaca (Kay and Tank, 1977; Warne et al, 2002a; Rink et al, 2005b).

As opposed to some urogenital sinus abnormalities in CAH in which genitography may be avoided, both genitography and endoscopy are mandatory to define the anatomy, which is even more complex with a cloacal anomaly.

The technique and goals of genitography and endoscopy are the same but must now include identification of the rectal as well as the vaginal confluence. The length of the urethra and its communication with the cloaca are important for reconstructive purposes. In Hendren's patients, the urinary communication to the cloaca was urethral in 77%, but in 23% there was virtually no urethra and the communication was noted at the bladder neck level (Jaramillo et al, 1990). The vaginal anatomy is also much more complex and variable. In Hendren's report of 154 patients, 66 had one vagina, 68 had two vaginas, and the vagina was absent in 20 (Hendren, 1998). Vaginal duplication has been seen in nearly all of my patient population (Rink and Yerkes, 2001) (Fig. 151-10). The duplication anatomy is also variable. Most authors have observed that the vaginas enter side by side with a single opening into the cloaca, but separate openings have been noted. The vaginas may be of different size, and one may enter the sidewall of the other. A cervix is usually seen at the top of each vagina. The vaginal entrance into the cloaca again lies along a spectrum from the bladder to a location near the perineum. Although the uterus is usually similar to the vagina (i.e., two vaginas with two uteri), the vagina may be absent with the uterus still present or the uterus may be hypoplastic. Hall and associates (1985) found a bicornuate uterus, hypoplastic uterus, or uterus didelphys in 35% of their patients with persistent cloaca.

The rectal confluence is equally complex, with the entrance in my experience most commonly located just at the level of the vaginal confluence. This rectal opening may be broad or it may have a long, narrow fistulous tract. It can even enter the vagina or bladder with no communication to the common cloaca itself. The most common entrance in my experience is within the septum of a duplicated vagina, with all three joining the cloaca together (Rink and Kaefer, 2002). The rectal communication has been found to be vaginal in 68% and cloacal in 11%, with the remainder in other locations (Jaramillo et al, 1990). The length and configuration of the common cloaca should also be noted because it has important surgical as well as anatomic implications. At times, the

common channel is narrow and appears very much like a urethra; in other instances, the channel is much larger and redundant and appears more like a vagina. The urethral appearance was found in 48% of patients and the vaginal appearance in 52% (Jaramillo et al, 1990). I and others have noted that the urethral types result in higher outlet resistance and are more likely to lead to hydrocolpos (Adams et al, 1998; Warne et al, 2002b).

The frequent presence of associated organ system abnormalities necessitates further radiographic evaluation. Echocardiography should always be performed. MRI is necessary for evaluating the lumbosacral spine and assessing the pelvic anatomy and musculature. Historically, it has been well recognized that sacral anomalies are common. Peña (1989) noted a normal sacrum in only 35% of his 54 patients, and Jaramillo and coworkers (1990) reported sacral agenesis in 40% of Hendren's 65 patients. De Filippo and associates (1999) found 10 of 21 patients with imperforate anus or cloaca to have an abnormality of the sacrum and spine. With the use of MRI, spinal cord abnormalities have been more commonly detected, with an incidence as high as 43% (Jaramillo et al, 1990). Hendren (1998) found that a third of his patients had a tethered spinal cord. Skin stigmata in the lumbosacral region were absent in 8 of 10 patients with spinal cord tethering in a report by Morimoto and colleagues (2003). MRI has also been very helpful in defining the level of the rectal atresia and in identifying the degree of sphincteric muscle development (Sato et al, 1988).

Because of the complexity of the anatomy and the frequency of hydrometrocolpos, a child with a cloacal anomaly often needs endoscopy early as a separate procedure to decompress the vagina and bladder and to define the anatomy. As a general rule, visualization of the vagina (or vaginas) is easily accomplished, but entry into the bladder can be very difficult and even impossible at times in a neonate because it is compressed very anteriorly by the distended vagina. The vagina should always first be emptied. Identification of the rectal fistula can also be difficult at times. Once it is located, mucus and fecal material should be irrigated from the colon, which can be done by irrigation through the scope in combination with irrigation through the mucous fistula of the divided colostomy. Passage of a small catheter through the mucous fistula when present can be very help in defining the location of the rectal confluence. The length of the urethra to the vaginal and rectal confluence as well as the length of the common cloacal channel should be documented. The length of the common channel is helpful in cloacal patients in predicting fecal continence outcomes (Peña et al, 2004).

SURGICAL RECONSTRUCTION OF DISORDERS OF SEX DEVELOPMENT AND UROGENITAL SINUS

Initial Management, Timing, and Principles

The majority of children born with a urogenital sinus have genital ambiguity, and this should be initially evaluated by the gender assignment team. It is extremely important that the family be made aware of all controversies surrounding genital surgery. Certainly, most families, physicians, and surgeons have historically made the decision to proceed with early feminizing procedures to "normalize" the child and allow a positive psychosocial adjustment (Schober, 1998). This has been thought to relieve the parents' distress and improve their outlook toward their child, although there is limited evidence for this. The thought has been that raising a child with genital ambiguity would be extremely difficult (Thomas, 2004). Creighton and colleagues (2012) have noted that the idea of "doing nothing" can be a stressful concept for the parents. Trakakis and associates (2009) stated that surgical treatment must be offered between 2 and 6 months because the tissues are maximally pliable and psychological trauma is minimized. Clearly, gender assignment when the individual's ultimate gender identity is unknown is a challenge and is at the core of this controversy (Mouriquand et al, 2014). A number of advocacy groups and physicians have begun to question the wisdom of early surgery. Informed

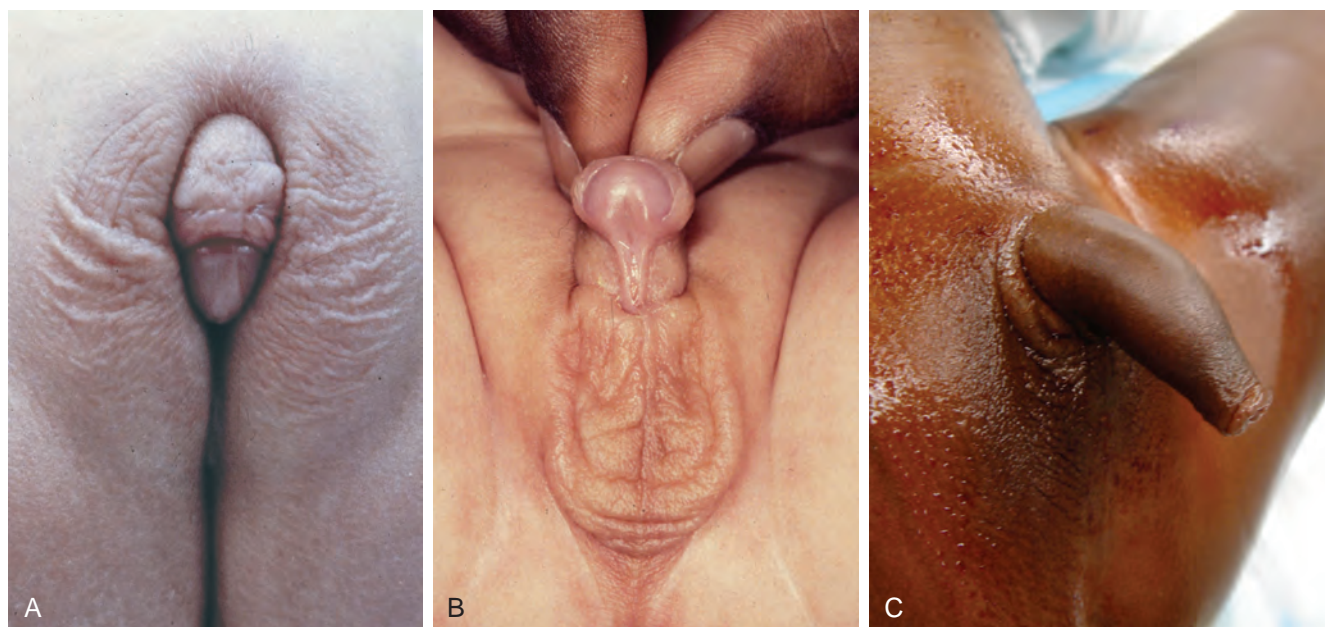


Figure 151-11. External appearance of genitalia in congenital adrenal hyperplasia. A, Moderately virilized with incomplete labioscrotal fusion. B, Moderately virilized with complete labioscrotal fusion. C, Severely virilized.

consent is impossible with an infant, and many believe that the decision for genital surgery is a right of the patient, not the parents. The ethical issues involving parents' rights and responsibilities to make decisions for their child remain unresolved (Lee and Witchel, 2002). Unfortunately, the infant is the passive center of the team but ultimately has the most important voice (Yerkes and Rink, 2010). In 2002, Rangecroft noted that data on the impact of raising a child with genital ambiguity are still lacking (Rangecroft, 2002). Regardless of one's personal beliefs, all pros and cons of both surgery and observation must be presented to the parents without bias, and certainly observation with psychological and peer support must be an option (Creighton and Liao, 2004). However, this same psychological and peer support should be given to the parents who do elect to proceed with early surgical management (Rink and Szymanski, 2015).

With current operative techniques, excellent cosmetic results can be achieved with feminizing genitoplasty for the virilized female. While anatomic appearance likely plays a role, it must be remembered that one's sexual identity is a result of many factors (Mouriquand et al, 2014). It is known that the brain is the dominant organ in sexual orientation (Woodhouse, 2004). Schober (1999) has pointed out that little is known about how adults adjust to genitoplasty, nor are there any data on what path infants undergoing genitoplasty might have chosen had the opportunity been given to them as adults. Feminizing genitoplasty is unique in that outcomes of early surgery are not known for perhaps 20 years and the results reported at this time may be based on techniques no longer used. However, it is clear that genital surgery does not "cure" a DSD. It is known that women with CAH are less satisfied with their genitalia than control subjects whether they had undergone an operation or not (Nordenskjöld et al, 2008).

Unfortunately, a dilemma remains for DSD surgery because there is no absolute correct answer at this time. Information should never be withheld from the parents. Secrecy from the family or patient has no place in the care of DSD. Counseling should be provided. Parents must be informed of all risks and options and be made aware of the current state of knowledge. They should also be given access to advocacy groups regardless of the group's stance on surgery. There is then a changing of attitudes toward early reconstructive procedures particularly with regard to clitoral surgery (Lee et al, 2006).

For the purposes of the remaining description of surgical techniques, it is assumed that all parties (parents and multidisciplinary team) agree that surgery is warranted.

Children born with a urogenital sinus associated with genital ambiguity usually have clitoral hypertrophy, some degree of fusion and anterior displacement of the labia majora with absence of the labia minora, and a common urogenital sinus (Fig. 151-11). Furthermore, it has been shown that there is significant variability in what is considered normal clitoral, vaginal, and labial size (Lloyd et al, 2005; Akbiyik and Kutlu, 2010). Genital reconstruction should address all of these issues and therefore generally involves three steps: (1) clitoroplasty, (2) labioplasty, and (3) vaginoplasty.

Historically, clitoroplasty has been performed early in life, but this has again been challenged by DSD advocacy groups and physicians. In the mid 1900s there was not thought to be an optimal timing for reconstruction (Jones and Jones, 1954; Lattimer, 1961), but more recently clitoral reconstruction has been carried out progressively earlier. Gross and colleagues (1966) and Spence and Allen (1973) noted that clitoral surgery can ideally be performed when the child is 1 year old. By the 1980s, clitoral surgery was recommended as early as the first few months of life (Snyder et al, 1983). More recently, de Jong and Boemers (1995) reported surgical correction at 1 to 3 weeks of age. Parents are now less likely to choose surgery for minimal clitoral hypertrophy (Lee and Witchel, 2002), and a consensus document recommends surgery for only the more severe degrees of hypertrophy (Prader III to IV) (Hughes et al, 2006). In a recent review on timing it was suggested that clitoral surgery be considered in infancy for Prader score of III or greater (Speiser et al, 2010). Most recent reports agree with early surgery for severe clitoral hypertrophy (Braga and Salle, 2009; Escala Aguirre et al, 2009; Speiser et al, 2010; Vidal et al, 2010; Acimi, 2013; Guarino et al, 2013; Willihnganz-Lawson et al, 2013). Johannsen and coworkers (2010) noted a higher satisfaction with clitoral function the younger the age at clitoral surgery.

The optimal timing for vaginoplasty continues to be debated. It is important to remember that the vagina serves no function in childhood. Some have based the timing partly on the level of the vaginal confluence. A consensus statement on CAH from the Lawson-Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) recommends

surgery in the 2- to 6-month-old range for those with a high vaginal confluence, and surgery between 12 months and adolescence is not recommended (Joint LWPES/ESPE CAH Working Group, 2002). "There is inadequate evidence currently in relation to establishment of functional anatomy, to abandon the practice of early separation of the vagina and urethra" (Hughes et al, 2006). In a poll of delegates at the IVth World Congress of the International Society of Hypospadias and Disorders of Sex Development, surgery before 2 years of age was preferred by 78% of surgeons and most suggested single-stage clitoroplasty, vaginoplasty, and labioplasty (Yankovic et al, 2013).

Simultaneous performance of clitoroplasty, vaginoplasty, and labioplasty has been the standard practice for a child with a low (distal) vaginal confluence. Two separate schools of thought have been put forth for a high vaginal confluence. Some believe that the high rate of vaginal stenosis warrants delay of vaginal surgery until after puberty, which also avoids any need for vaginal dilation (Sotiropoulos et al, 1976; Snyder et al, 1983; Alizai et al, 1999; Creighton et al, 2001; Rangecroft, 2002; Thomas, 2004; Escala Aguirre et al, 2009). Others have recommended that vaginoplasty for the small hypoplastic vagina (<3 cm) be delayed also (Salle et al, 2012). Others have found the incidence of vaginal stenosis to be higher in those who undergo surgery after puberty rather than during infancy (Eroglu et al, 2004). I along with others believe that vaginoplasty, regardless of the vaginal location, is best combined with clitoroplasty and labioplasty in a single-stage procedure. This allows the surgeon flexibility in using redundant phallic skin for the reconstruction, which is compromised when the skin has previously been mobilized (Mandell et al, 1988; Gonzalez and Fernandes, 1990; de Jong and Boemers, 1995; Hendren and Atala, 1995; Rink et al, 1997; Passerini-Glazel, 1998; Vidal et al, 2010). Lean and colleagues (2007) found any plans for one-stage repair to give better results. Furthermore, several authors have noted that maternal estrogen stimulation of the child's genitalia results in thicker vaginal tissue that is better vascularized, thus making it easier to perform early vaginal mobilization (Passerini-Glazel, 1989; Donahoe and Gustafson, 1994; de Jong and Boemers, 1995; Rink and Adams, 1999; Farkas et al, 2001; Hamza et al, 2001; Hensle and Bingham, 2002; Eroglu et al, 2004; Braga and Salle, 2009). Those in favor of pubertal surgery generally perform it for the high vagina and note the advantage of the patient being able to provide consent (Escala Aguirre et al, 2009; Guarino et al, 2013). Furthermore, Schober (2004) has noted that estrogen has a beneficial effect on tissue healing that along with vaginal growth and distention may result in improved outcomes, making puberty the best opportunity for reconstruction. Still others believe that a hybrid of these two—clitoroplasty and labioplasty in infancy with vaginoplasty at puberty—is most appropriate, particularly in the setting of a high vaginal confluence (Creighton and Farhat, 2005; Escala Aguirre et al, 2009; Guarino et al, 2013). The surgery is not easier and there is no evidence that actual healing is better at puberty (Braga and Salle, 2009). At this time there is no universal agreement among those caring for DSD children on optimal timing for vaginoplasty, nor are there adequate data comparing early versus late surgery.

The clitoris is a sexual organ; therefore when performing clitoroplasty, every effort is made to not only provide excellent cosmesis but also retain normal clitoral innervation for optimal sexual gratification. Clitoral surgery has undergone significant evolution since Hugh Hampton Young's work in 1934 (Young, 1937). Initial efforts were primarily directed at not just amputating the clitoris but also completely excising all clitoral tissue to avoid any later painful erection (Jones and Jones, 1954; Gross et al, 1966; Hendren and Crawford, 1969). Clitoral amputation was based on reports by Hampson (1955) and by Money (1955), who noted that the clitoris was not necessary for normal sexual response. As recognition of the importance of the clitoris evolved, several ingenious clitoral recession techniques that preserved the innervation and all clitoral tissue were reported. Lattimer (1961) recessed the clitoris in subcutaneous fat and buried it beneath the skin. He also denuded the glans epithelium, which would not be recommended today.

Kaplan (1967) reported an interesting technique of splitting the two corpora apart and performing closure in a transverse Heineke-Mikulicz fashion. Randolph and Hung (1970) and also Pellerin (1965) buried the corpora beneath the pubis. Efforts to preserve the glans based on a flap were attempted as early as the 1930s by Young, but the glans sloughed (Young, 1937). Schmid (1961) was the first to report excising corporeal tissue yet preserving the neurovascular bundle with the glans intact. Kumar and coworkers (1974) later noted a similar technique proposed by Kiefer the same year. Spence and Allen (1973) excised all of the clitoral shaft but left the glans intact to survive from the attached ventral urethral plate, but this technique excised all of the neurovascular bundle. Virtually all techniques since have been based on Schmid's preservation of the neurovascular bundle (Shaw, 1977; Barrett and Gonzales, 1980; Glassberg and Laungani, 1981; Mollard et al, 1981; Rajfer et al, 1982). Although the glans often did well with these techniques, shrinkage and devascularization occurred at times. Kogan and associates (1983) reported subtunical excision of the erectile tissue by incising laterally through the Buck fascia to resect the erectile corpus cavernosa tissue. Clitoroplasty techniques exhibited only minor technical advances until the recent demonstration of the neurovascular anatomy of the clitoris by Baskin and coworkers (1999). This work suggests that a ventral, rather than lateral, incision would preserve not only the main dorsal neurovascular bundle but also the neural branches that fan out laterally (Fig. 151-12). Currently, much research is under way to further evaluate clitoral neuroanatomy, as well as develop techniques to evaluate sexual sensitivity. I believe that the Buck fascia with its neurovascular bundle and glans should always be preserved. Pippi Salle reported a technique whereby the corporeal bodies are mobilized and disassembled and then placed in the labial fat. This allows the option of later use for reconstruction of the phallus should the patient choose a male gender identity (Pippi Salle et al, 2007).

Vaginoplasty techniques have similarly evolved, with all repairs based on a few landmark reports. Almost every vaginal repair today uses a posteriorly based perineal flap proposed by Lattimer and originally described by Fortunoff and coworkers in 1964. This wide-based "Fortunoff flap" has been modified to a more omega-shaped flap that has resulted in improved cosmesis (Jenak et al, 2001; Freitas-Filho et al, 2003). In 1969, Hendren and Crawford reported a "pull-through" vaginoplasty for a high vaginal confluence. Their efforts to establish the location of the vaginal confluence as the determining factor for the type of vaginoplasty remain the basis for all vaginoplasties today. Vaginal reconstruction techniques now generally take the form of one of four types:

1. The "cut-back" vaginoplasty is rarely used today. I and most authors believe it is only appropriate for simple labial fusion. However, Escala Aguirre and colleagues (2009) recently reported its use in Prader I and II children.
2. The "flap" vaginoplasty is applicable to a low (distal) vaginal confluence. In this procedure, the posterior walls of the sinus and vagina are opened, but the anterior wall of the vagina is left intact. The posterior perineal flap fits into the opened vagina. This procedure does not change the level of confluence; it simply widely opens the introitus and urogenital sinus (Rink and Adams, 1998). Mild degrees of female hypospadias are common with this technique. I and others believe that a flap vaginoplasty should never be used for patients with a very high vaginal confluence because it may result in a short hypospadiac urethra, vaginal voiding, infections, and even incontinence (Hendren and Atala, 1995; Rink and Adams, 1999).
3. The pull-through vaginoplasty may be used for any level of confluence but is generally reserved for a very high confluence. In this procedure, the vagina is separated from the urogenital sinus, and the sinus is used to create a urethra. The mobilized vagina may reach the perineum, but in most cases skin flaps have been required.
4. Complete vaginal replacement can be achieved by several techniques, but this is used only for a rudimentary or absent vagina.

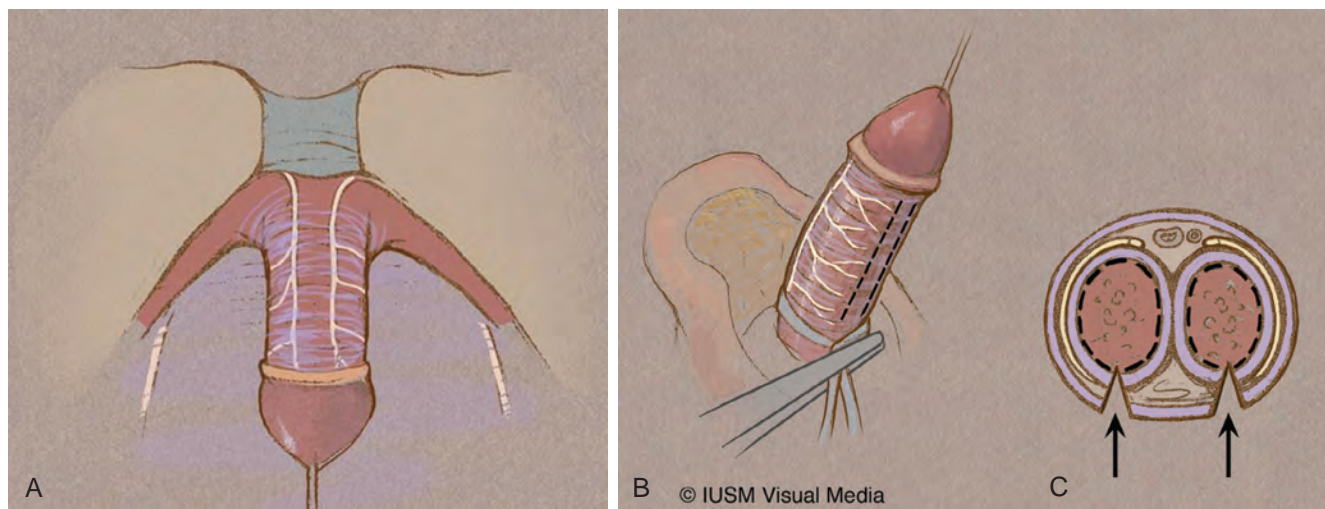


Figure 151-12. Hypertrophied clitoris with dorsal nerves and branches. A, Anteroposterior view. B, Side view. C, Cross-sectional view. (© Indiana University Medical Illustration Department.)

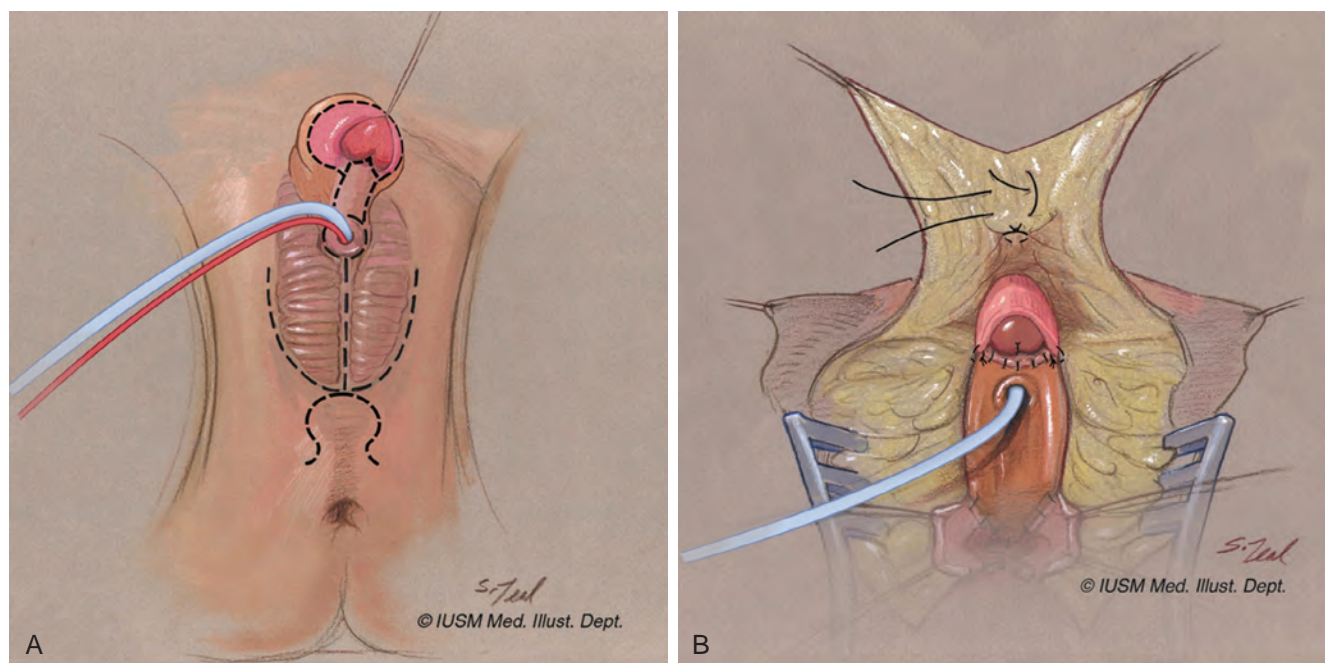


Figure 151-13. Labioplasty. A, Proposed incision lines for feminizing genitoplasty. Note preservation of skin cuff around glans clitoris that will be used to fashion clitoral hood. B, After recession of the glans clitoris the preputial skin is partially split to create the labia minora. The proximal preputial skin is plicated along its undersurface to create a "hooded" appearance to the segment of skin that will cover the glans. (© Indiana University Medical Illustration Department.)

Labioplasty techniques also continue to evolve. In CAH and other DSD states, the labia minora are absent and the labia majora are superior to the new vaginal introitus. Labia minora are created by using the split phallic skin as described by [Marberger \(1975\)](#). Both the labia majora and labia minora should be moved inferiorly by YV-plasty to create a normal cosmetic appearance of the vagina now located between the labia ([Hendren and Donahoe, 1980](#); [Rink and Adams, 1998](#)) ([Fig. 151-13](#)).

Regardless of the surgeon's personal bias toward reconstruction or its timing, a balanced presentation of all pros and cons of surgery versus no surgery is imperative. All current data should be made available to the parents and the risks associated with each

path clearly defined. The ultimate decision is the parents', but it should be made as a participant of a team. In the following sections, the techniques described are applicable to either infants or adolescents.

Current Operative Techniques for Female Disorders of Sex Development and Urogenital Sinus Repair

Preoperatively, it is important to ensure that the patient is metabolically stable, particularly a child with CAH. Most children with CAH only require an enema, but if there is an indication of a high

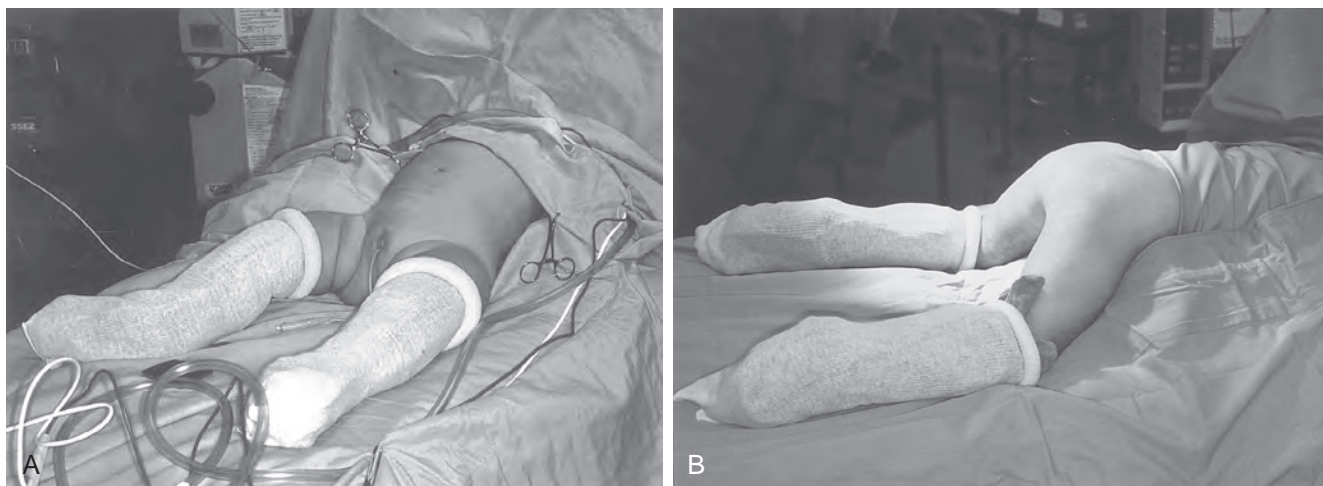


Figure 151-14. Total lower body preparation allows both supine (A) and prone (B) approaches.
(From Rink RC, Adams MC. Feminizing genitoplasty: state of the art. *World J Urol* 1998;16:212.)

confluence, complete bowel preparation with a polyethylene glycol-electrolyte solution (GoLYTELY) may be warranted. All children receive preoperative broad-spectrum antibiotics. Children with CAH must undergo “stress dose” steroid replacement at the time of surgery. After general anesthesia, endoscopy is performed as described previously. **After passing a Fogarty catheter into the vagina, the balloon is inflated and the catheter is clamped and left indwelling. A Foley catheter is then anchored in the bladder.** Both are kept sterile, and the child is prepared with povidone-iodine. Many surgeons prefer to place the child in lithotomy position, but I have found that this position limits vision to only the surgeon, hinders teaching, and does not allow manipulation of the child if a posterior or abdominal approach is unexpectedly needed. At the Riley Hospital for Children, all children undergo a complete lower body preparation from nipples to feet. The child’s legs are wrapped, and the lower part of the body is passed through the aperture in the drapes; this facilitates access to the entire perineum and abdomen and further allows the child to be rotated either supine or prone during the procedure (Fig. 151-14). In postpubertal patients such total body preparation may be difficult, necessitating the lithotomy position.

Low Vaginal Confluence: Clitoral Hypertrophy

The vast majority of children who undergo surgery for DSD or urogenital sinus conditions have a low vaginal confluence amenable to flap vaginoplasty. They usually have clitoral hypertrophy. Clitoroplasty and classic flap vaginoplasty are described. With the child in the supine position, a traction suture is placed through the glans and the proposed incisions are outlined with a skin scribe. Along these lines, 0.5% lidocaine with 1:200,000 epinephrine is injected subcutaneously for hemostasis. The proposed incision around the glans, leaving the inner surface of the prepuce intact, is drawn along with parallel longitudinal lines on either side of the ventral mucosal strip (urethral plate equivalent) extending around the meatus. A perineal omega-shaped flap with the apex near the meatus is outlined. A Y-shaped incision line is drawn around the inferior aspect of each labia majora. The incision begins on the dorsal aspect of the clitoris and all inner preputial skin is left intact for later construction of a clitoral hood. This skin has been shown to be second only to the glans in sensitivity (Schober and Ransley, 2002). The clitoris is degloved while keeping the ventral “urethral plate” intact with the meatus. Dissection is carried out to the level of the bifurcation of the corporeal bodies ventrally and the pubis dorsally, and care should be taken to not injure any neurovascular tissue (see Fig. 151-12). It is important to recognize that the clitoral arterial supply branches from the internal pudendal artery from the

KEY POINTS: UROGENITAL SINUS ANOMALIES—RECONSTRUCTION

- The three steps in surgical reconstruction are clitoroplasty, vaginoplasty, and labioplasty.
- Clitoroplasty is controversial. When performed, the glans and tunics with their neurovascular bundles must be preserved. Excision of erectile tissue, when performed, must be from the ventral aspect only.
- Vaginoplasties consist of four types: cut-back (generally no longer used), flap for a low to midlevel confluence, pull-through for a high confluence, and vaginal replacement for a rudimentary or absent vagina. The timing of vaginoplasties is controversial.
- Labia minora are absent in urogenital sinus patients with genital ambiguity. They are reconstructed from phallic skin. The anteriorly located labia majora should be moved inferiorly.
- It is helpful to place a Fogarty catheter with the balloon inflated in the vagina. For a low confluence, an omega-shaped perineal flap provides better cosmesis. The flap is sewn into the posteriorly opened sinus, and this flap must reach to the more proximal normal-caliber vagina.
- For a high confluence, the vagina may require separation from the urinary tract at its confluence and is “pulled through” toward the perineum. The sinus opening is closed to create a urethra. With a very small, very high confluence vagina the surgeon should strongly consider waiting until puberty for vaginoplasty.

Alcock canal near the ischial tuberosity. These arteries course ventrally and are on the medial aspect of the bifurcated corpora, where they then course dorsally along the phallic shaft (Schnitzer and Donahoe, 2001). The clitoral neural bundles ascend along the ischiopubic rami and meet as paired bundles that pass along the dorsal surface and then pass largely intact into the glans (Baskin et al, 1999; O’Connell et al, 2005). My current clitoroplasty technique is described but, regardless of technique, the just-described clitoral innervation must not be disturbed.

A tourniquet may be placed at the base of the clitoris or the bifurcated corpora may be compressed against the pubis with Kitner dissectors. Longitudinal incisions are then made through the Buck fascia on the ventralmost aspect of each corporeal body (Fig. 151-15); the incisions extend from the glans to the bifurcation to

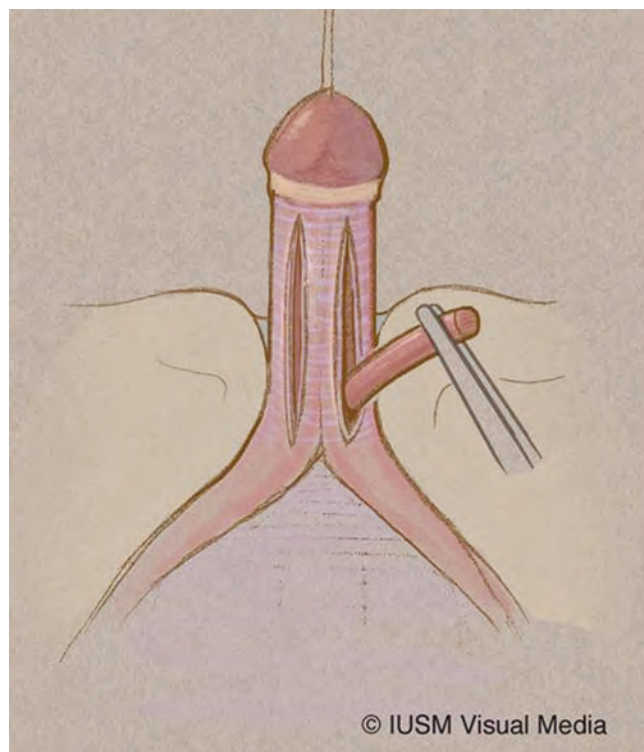


Figure 151-15. Proposed clitoral incisions. Note the ventral location.
(© Indiana University Medical Illustration Department.)

expose the corpora cavernosa tissue, which is dissected (often teased) from the tunics. The tunics are left undisturbed, except for the ventral incision. **No tunical tissue is excised. The dorsal neurovascular bundle should not be mobilized or disturbed in any way.** The proximal ends of the erectile tissue only are suture ligated. Other techniques involve mobilization of the neurovascular bundles from the corpora, but I believe this is more likely to injure clitoral sensitivity and vascularity. If mobilization is done, [Braga and Salle \(2009\)](#) pointed out the need to dissect in the exact plane (below the second layer of the Buck fascia just beneath the tunica albuginea) to avoid neurovascular injury. Efforts to decrease the size of the glans are controversial and, if attempted, should be done with great caution. Studies by [Juskiewinski and associates \(1982\)](#) and [Baskin and colleagues \(1999\)](#) would suggest that any glans excision should be performed ventrally near the midline (similar to hypospadias glans wings). The glans is innervated by perforating branches entering at the dorsal junction of the glans and corpora ([Baskin et al, 1999](#)). Excision of glanular epithelium to conceal the glans is to be avoided because the sensory neuropeptides are located just beneath this layer. **Remember there are no data to suggest that a large glans is detrimental to sexual function.** The glans is now secured to the coronal stumps. In my experience, a glans sewn to the pubis results in an abnormally high prominent position ([Rink and Yerkes, 2001](#)). [Pippi Salle and associates \(2007\)](#) described an alternative technique whereby the corpora are dissected from the neurovascular bundle, separated, and buried beneath the labia, which allows reversibility of the clitoroplasty in those patients with later gender dysphoria.

With clitoroplasty completed, the flap vaginoplasty is started. The previously outlined omega-shaped flap is incised, and the underlying fat is mobilized with the flap to expose the urogenital sinus. The flap must be made long enough to provide a tension-free anastomosis to the vagina and wide enough to provide a normal-caliber introitus without compromising the blood supply of the perineal body. It should not be redundant because this will create an obstructing mound of tissue at the introitus. The posterior wall of the sinus and vagina is now dissected free from the underlying

rectum. This initial posterior step in separating the vagina from the rectum is the most difficult. With stay sutures in the meatus, the posterior wall of the sinus is opened in the midline and extended proximally into the posterior wall of the vagina. **The distal third of the vagina is usually narrowed; therefore the posterior wall incision must be carried proximally until normal-caliber vagina is encountered.** Sutures are placed individually through the perineal flap and then through the split posterior wall of the vagina and tied.

The mobilized phallic skin is unfurled and divided longitudinally in the midline while stopping well short of the base to allow a clitoral hood. This tissue at its base is incorporated with the preputial skin to create a clitoral hood. Labia minora are now created with this split preputial skin, which is moved inferiorly and anastomosed to the preserved ventral plate and the lateral vaginal wall. I have found that the inferior placement of these flaps along the side of the vagina often results in an M-shaped clitoral hood, which can be overcome by plicating the dermis of the new hood to give it a more normal inverted U shape. The proposed Y-shaped incisions are now made around the inferior aspect of each labia majora. The labia are mobilized and secured inferiorly alongside the vagina as a YV-plasty. The vaginal introitus should now reside between the labia minora and majora rather than appear as an isolated hole on the perineum.

High Vaginal Confluence: with or without Clitoral Hypertrophy

Most believe that complete separation of the vagina from the urogenital sinus with a pull-through vaginoplasty, as proposed by [Hendren and Crawford \(1969\)](#), is the best solution to a high vaginal confluence. [Braga and Salle \(2009\)](#) recommend it only when the urogenital sinus is longer than 3 cm. Fortunately, this complex situation is found in only about 5% of patients with CAH ([Dumanian and Donahoe, 1992](#)). This high confluence is more commonly seen in pure urogenital sinus abnormalities. As noted earlier, I agree with [Ganesan and colleagues \(2002\)](#) that in the urogenital sinus associated with CAH, the severely virilized child may appear to have a high vaginal confluence but it is the shared common portion of the sinus that lengthens and there is relatively minimal shortening of the urethra. It is this lengthened common sinus in combination with the appearance of a more male-like external sphincter that gives it a high confluence appearance ([Ganesan et al, 2002](#)). Although the concept of vaginal separation and pull-through vaginoplasty was a major advance, the operation as originally described frequently resulted in an isolated vaginal opening that appeared to be separate from the remainder of the genitalia, and a mucosal lining was lacking ([Passerini-Glazel, 1989](#)). It was also technically difficult because of poor vision at the critical points ([Rink et al, 1997](#)). Several authors have addressed these issues. [Passerini-Glazel \(1989\)](#) used the mobilized sinus by dividing it dorsally; when tubularized with the phallic skin and folded back toward the vagina, it would create a more normal cosmetic result and provide excellent coverage in the area of the vaginal separation while helping to prevent a urethrovaginal fistula. He later used this as a flap to form the anterior vaginal wall rather than completely tubularizing it ([Passerini-Glazel, 1994](#)). [Gonzalez and Fernandes \(1990\)](#) used the preputial skin to construct the vaginal vestibule and anterior wall.

The critical and most technically demanding aspect of a pull-through vaginoplasty is the separation of the anterior wall of the vagina from the urethra and bladder neck. There is no obvious plane of dissection, and great care must be taken to avoid injury to the urinary tract and its sphincteric mechanism. This area is also the most difficult to visualize, and poor exposure naturally leads to poor results, with the potential for a stricture, fistula, diverticulum, or retained distal vagina ([Rink and Adams, 1998](#)). Furthermore this is an area of significant nerve supply for the vagina and urethra. Most surgeons have positioned the patient in the supine or lithotomy position. Several authors have reported means of improving exposure for this critical area. [Passerini-Glazel \(1989, 1994\)](#)

mobilized the vagina transtrigonally in difficult cases but later reported that this approach is seldom necessary. Similarly, the anterior sagittal transanorectal approach or ASTRA (division of the anterior rectal wall) has provided excellent exposure for separation of the vagina and certainly should be considered for those patients with a very high vaginal confluence (Di Benedetto et al, 1997; Dòmini et al, 1997; Rossi et al, 1998; Salle et al, 2012). A diverting colostomy has not been necessary with the ASTRA technique. Hendren and Atala (1995) reported lateral mobilization of the rectum but later stopped because of the difficulty of this maneuver. Rink and colleagues (1997) reported a midline posterior prone approach with retraction but not division of the rectum that provides excellent exposure for critical aspects of the pull-through vaginoplasty and is described here.

Endoscopy with Fogarty and Foley catheter placement and total-body preparation are as described for a flap vaginoplasty. If the child has associated clitoral hypertrophy, the clitoroplasty is performed with the child supine as described earlier for a low confluence. The child is then rotated to the prone position. In a patient with a pure urogenital sinus, the procedure is started with the patient in the prone position. Although I have found this to be very beneficial to provide improved exposure, others have not found it necessary (Ludwikowski and González, 2013).

The perineal omega-shaped flap incision is made as previously described, and then the flap is retracted posteriorly, with dissection now carried out in the midline between the posterior wall of the sinus/vagina and rectum. As dissection proceeds proximally, the rectum is easily retracted with a small Deaver retractor (Fig. 151-16) to expose the entire urogenital sinus without the need to divide the rectum. The entire length of the sinus may be divided in the midline posteriorly to the normal caliber of the vagina. The Deaver retractor is now placed in the vagina and with upward retraction easily exposes the anterior wall of the vagina at its confluence with the sinus. This allows dissection of the vagina from the urethra under direct vision (Fig. 151-17). The tissues are quite thin in this area, and one should always err on the side of the vagina. More proximally, the dissection becomes easier. Excellent vision is also

provided for tubularization of the sinus to create a urethra, which is closed in two or three layers over a Foley catheter. The anterior wall of the vagina is now mobilized inferiorly, closer to the perineum. "Pull-through" vaginoplasty is often a misnomer because frequently the separated vagina will not reach the perineum. In this situation, skin flaps have been used to reach up to the vagina (rather than the vagina "pulled through" to the perineum). Preputial skin may be sewn to the spatulated anterior vagina, as described by Gonzalez and Fernandes (1990) or as modified by Acimi (2013) (Fig. 151-18). When preputial skin is not available, a buttock flap or a laterally based skin flap can be used (Parrott and Woodard, 1991; Dumanian and Donahoe, 1992; Moriya et al, 2009) (Fig. 151-19). The child is returned to the supine position, and the posterior perineal flap is anastomosed to the vagina as described for the flap vaginoplasty. I believe that skin flaps are best avoided because they are more likely to stenose and may be hair bearing. The use of urogenital tissue to create the flaps is more reliable, as in the Passerini-Glazel flap.

Labioplasty is now completed as described earlier. If a laterally based flap is required for the anterior wall, posterior relocation of the labia majora may be performed at a later stage.

In patients with a high confluence, particularly if multiple flaps have been used, the legs are bound together loosely postoperatively to prevent tension on the flaps. Although rarely required for urogenital sinus associated with CAH, the high confluence in the pure urogenital sinus patient may benefit from the ASTRA procedure noted earlier. In this procedure, with the patient prone, the posterior wall of the rectum is divided in the midline allowing excellent exposure of the high vagina for its separation and mobilization. This does not affect rectal continence and does not require a temporary colostomy.

Total and Partial Urogenital Mobilization

In 1997, Alberto Peña proposed a maneuver called *total urogenital mobilization (TUM)* as a means to complete the urogenital sinus component of a cloacal repair. In this procedure the entire sinus

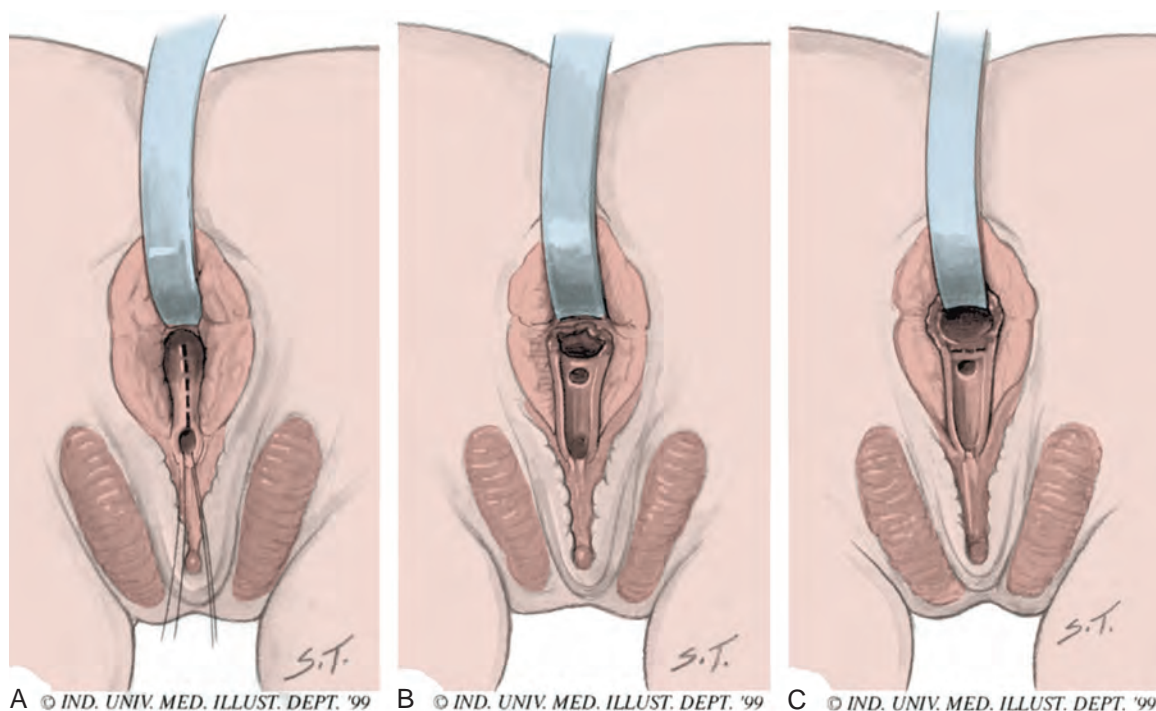


Figure 151-16. A, Posterior flap developed with the sinus exposed. B, Sinus opened in the posterior midline. C, Retractor in the vagina. (© 1999, Indiana University Medical Illustration Department.)

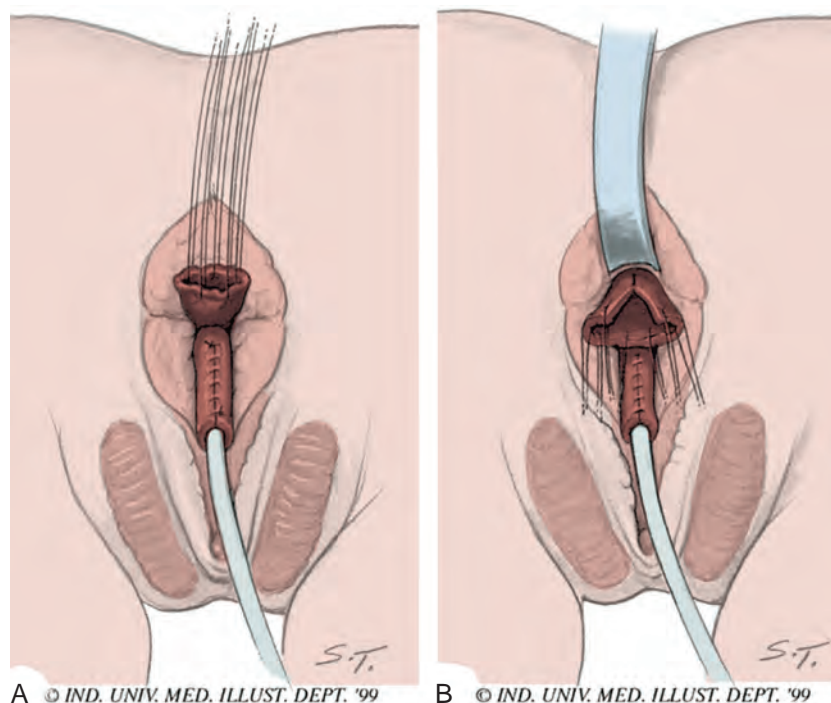


Figure 151-17. A, Vagina mobilized and the sinus tubularized to create a urethra. B, Posterior vagina spatulated. (© 1999, Indiana University Medical Illustration Department.)

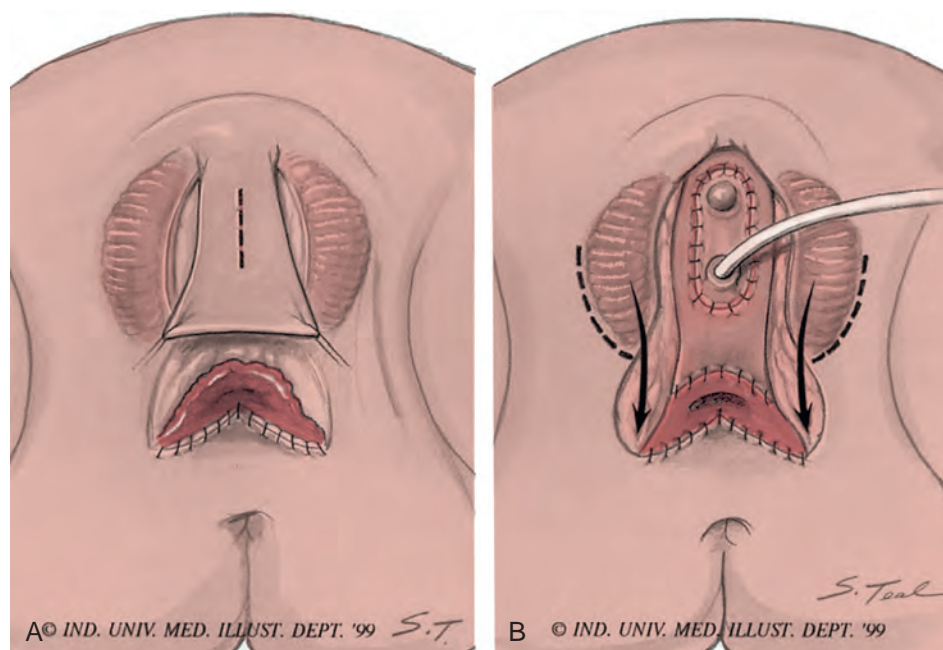


Figure 151-18. A and B, Modified Gonzalez preputial flap to create an anterior vaginal wall; the posterior flap has been anastomosed to the spatulated vagina. (© 1999, Indiana University Medical Illustration Department.)

is dissected circumferentially and mobilized toward the perineum. Peña noted a decrease in operative time by 70%, a superior cosmetic result, and less risk of fistula, vaginal stenosis, or acquired vaginal atresia with TUM because vaginal separation is not usually required (Peña, 1997). Since Peña's original description, TUM has been applied to several disorders, such as urogenital sinus, female exstrophy, and penile agenesis (Ludwikowski et al, 1999; Kropp and Cheng, 2000; Rink et al, 2006). Both Peña and Ludwikowski and

colleagues reported amputation of the mobilized sinus so that the vagina and urethra can be sewn flush to the perineum (Peña, 1997; Ludwikowski et al, 1999). I have reported using the mobilized sinus to provide a mucosa-lined vestibule or a Passerini flap to cover the anterior vaginal wall when a pull-through procedure is performed (Rink and Adams, 1999; Rink et al, 2006). Jenak and associates (2001) have since reported similar use of the mobilized sinus to create a mucosal vestibule, and Hamza and colleagues

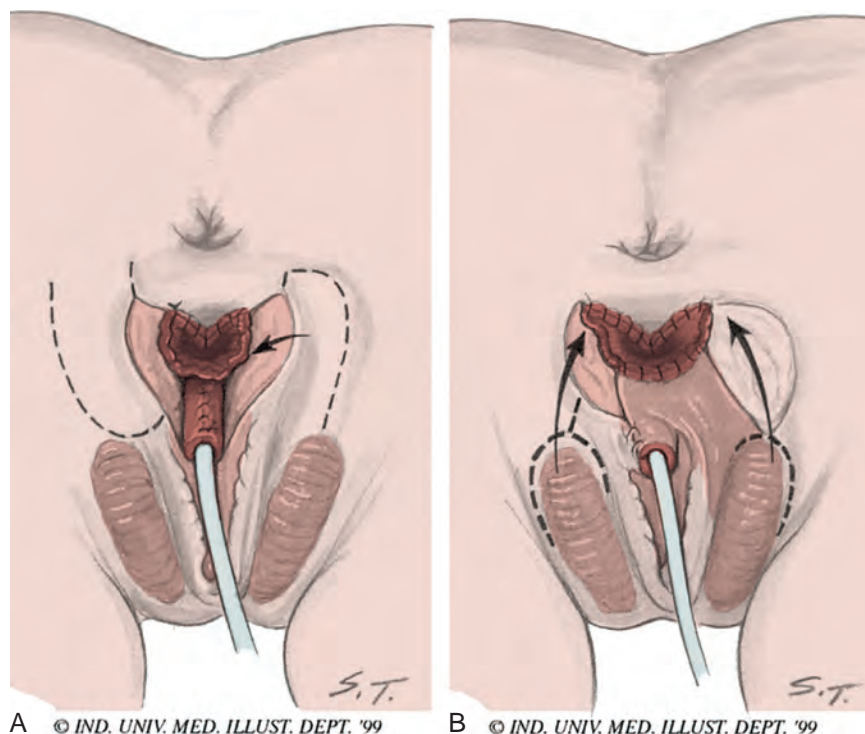


Figure 151-19. A and B, A buttocks- or labial-based flap may be used to create the anterior vaginal wall in a patient with a pure urogenital sinus. (© 1999, Indiana University Medical Illustration Department.)

(2001) have noted that the sinus may be used as a Passerini-like flap. There have been two recent descriptions of use of the mobilized sinus to replace the posterior perineal-based skin flap with a sinus flap. In one, the sinus is split laterally and rotated posteriorly (Rink and Cain, 2002; Rink et al, 2006). In the other, the sinus is split in half longitudinally and the two halves are rotated inferiorly (Gosalbez et al, 2005). At the Riley Hospital for Children, I have incorporated urogenital mobilization techniques into nearly all of our urogenital sinus repairs. This allows a midlevel confluence to reach the perineum without requiring vaginal separation. The highest level confluences may still need a pull-through procedure with separation of the vagina and urethra, but it is much more easily performed after the urogenital sinus has been mobilized.

TUM is often thought of as its own type of vaginoplasty but is, in fact, a technique to allow vaginoplasty that may result in the vagina being sewn flush to the perineum; however, a flap or pull-through vaginoplasty may still be required. Only rarely do I believe the vagina should be sewn flush to the perineum, owing to concerns of a circumferential anastomosis becoming stenotic. TUM is started, as previously described, with endoscopy to evaluate the anatomy, to note the level of the confluence, and to place a Fogarty catheter in the vagina and a Foley catheter in the bladder. A sponge is placed in the rectum, and the proposed incisions are outlined. Subcutaneous injection of 0.5% lidocaine with 1 : 200,000 epinephrine along the lines is carried out. Clitoroplasty is performed as previously described, with the meatus of the urogenital sinus and urethral plate being circumscribed with stay sutures to allow mobilization of the sinus from the corporeal bodies. This is initially carried out to just between the bifurcation of the corporeal bodies. The clitoroplasty is now completed as described earlier. The dissection is carried out in the midline posterior to the sinus until the peritoneal reflection is reached to allow access to the entire posterior wall of the vagina (Figs. 151-20 and 151-21). This circumferential mobilization is done directly on the urogenital sinus and continues proximally beneath the pubis. As the avascular ligaments from the pubis to the sinus are divided in this area, the entire

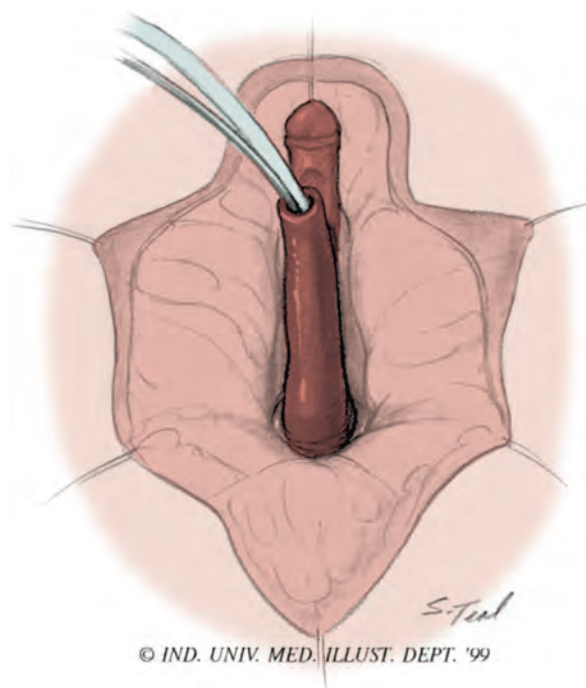


Figure 151-20. Skin mobilized with the sinus exposed. (© 1999, Indiana University Medical Illustration Department.)

urogenital sinus is felt to “give” and move toward the perineum (Fig. 151-22).

The Fogarty balloon is now easily palpable in the vagina. The posterior wall of the vagina is opened between stay sutures. If the vagina is now near the perineum, it may be sewn flush to the

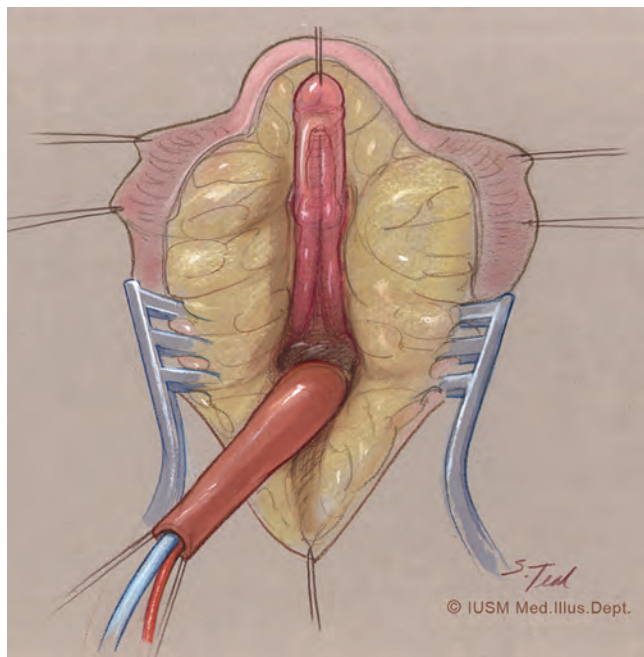


Figure 151-21. Total urogenital mobilization with the sinus mobilized. (© Indiana University Medical Illustration Department.)

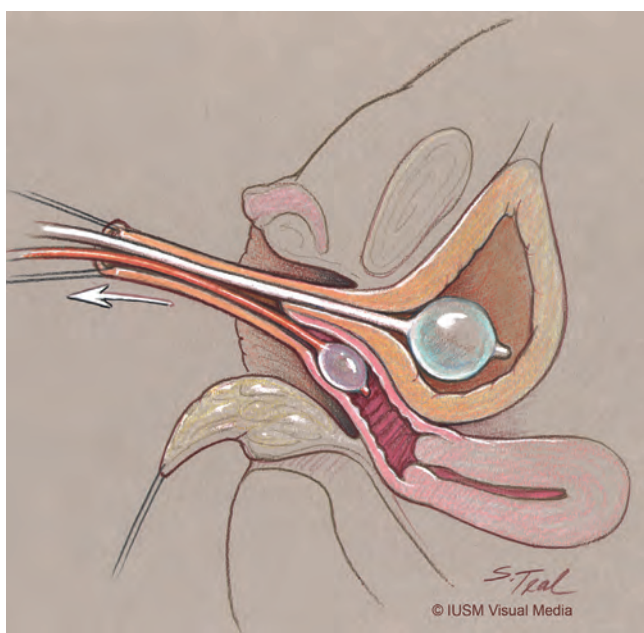


Figure 151-22. Total urogenital mobilization. The sinus is mobilized to a position beneath the pubis. (© Indiana University Medical Illustration Department.)

perineum, or an omega-shaped perineal flap may be placed into the spatulated posterior wall to augment the vaginal caliber; I prefer the latter. Rather than discard the mobilized sinus, as previously reported, it is helpful to split the sinus ventrally and use it to provide a mucosa-lined vestibule (Fig. 151-23). If the vagina is still quite high, the anterior wall of the vagina should be separated from the urethra and bladder neck as in the pull-through procedure (Peña, 1997; Rink and Kaefer, 2002; Rink et al, 2006). This is most easily performed with the child in the prone position to allow direct vision. The opening in the urethra is closed in two layers. The mobilized sinus in this situation is split anteriorly and then used

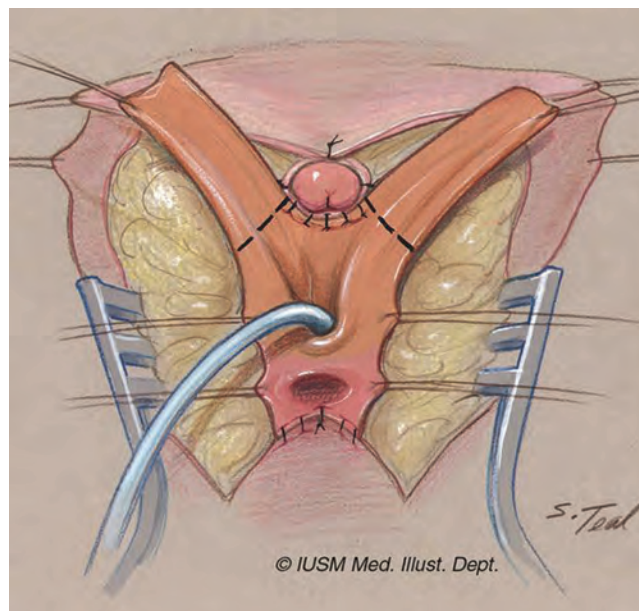


Figure 151-23. A ventral incision on the mobilized sinus allows the creation of a mucosa-lined vestibule. (© Indiana University Medical Illustration Department.)

as a Passerini-like flap to create the anterior vagina wall (Rink and Adams, 1999; Rink et al, 2006) (Fig. 151-24). The posterior perineal flap is approximated to the spatulated posterior vaginal wall. Labioplasty is performed as previously described. TUM has achieved great popularity, and reports to date reveal excellent cosmesis and no problems with continence (Palmer et al, 2012; Ludwikowski and González, 2013). No long-term results are available.

Some have expressed concern regarding the proximal circumferential dissection because of the potential risk for sphincteric musculature or nerve injury. There is concern for resultant stress incontinence or foreshortening of the vagina. To address these concerns, Rink and associates (2005c, 2006) proposed *partial urogenital mobilization (PUM)*, a technique that starts with the same circumferential dissection but stops at the level of the pubourethral ligament (Fig. 151-25). This still allows use of the mobilized sinus as described earlier to improve cosmesis, yet it avoids the aggressive retropubic and suprapubic dissection and is applicable to the majority of patients. If more mobilization is necessary for a very high vagina, TUM is easily carried out.

KEY POINTS: UROGENITAL MOBILIZATION

- TUM is a technique applicable to both urogenital sinus and cloacal anomalies. The entire sinus is dissected circumferentially to above the pubis to allow the confluence to move inferiorly to the perineum.
- With the TUM or PUM technique, the mobilized sinus tissue can be used to create a mucosa-lined vestibule or an anterior or posterior vaginal wall. This sinus tissue should not be discarded.
- PUM circumferentially mobilizes the sinus to the level of the pubourethral ligament but does not extend above this level.

Results of Urogenital Sinus and Disorders of Sex Development Surgery

There are a number of significant issues when reviewing the data on surgery for DSD. The data are limited and nearly always

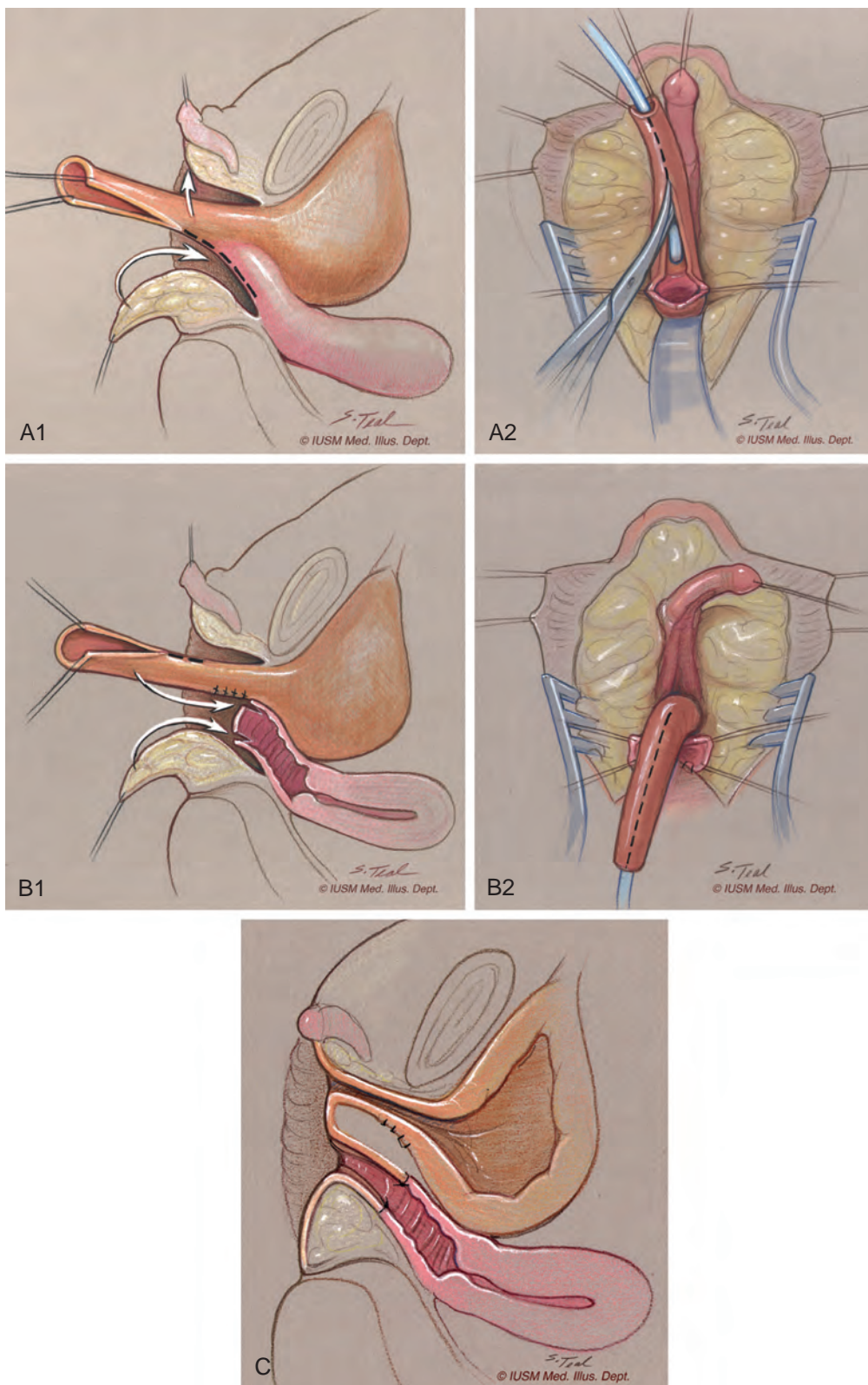


Figure 151-24. Total urogenital mobilization. A1 and A2, For flap vaginoplasty the sinus is split ventrally to create a mucosa-lined vestibule. B1 and B2, For pull-through vaginoplasty the sinus is split dorsally to create an anterior vaginal wall. C, The opened sinus now becomes the anterior vaginal wall. (© Indiana University Medical Illustration Department.)

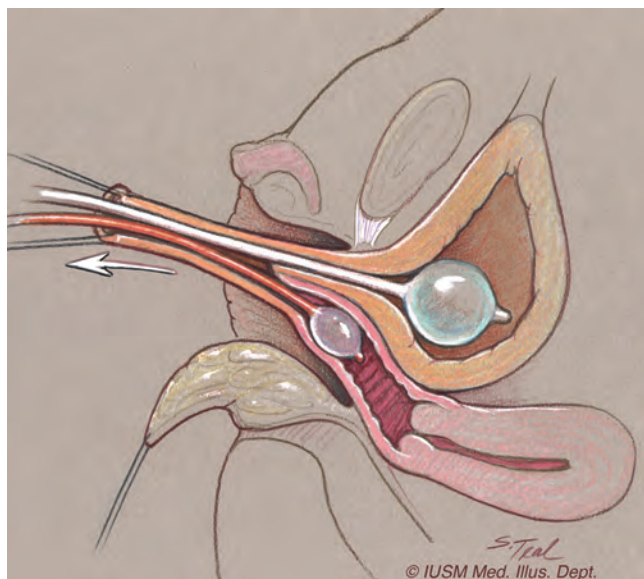


Figure 151-25. Partial urogenital mobilization. Dissection stops at the pubourethral ligament. (© Indiana University Medical Illustration Department.)

retrospective, reviewing only small numbers of patients, and the techniques reviewed are often outdated or not reported (Rink and Szymanski, 2015). Braga and Salle (2009) noted that available data were so poor that it was “scientifically pointless” to try to make sense of the current literature. Furthermore, most articles only look at success as an adequately open vagina with a feminized appearance. Success should include normal erotic sensation, lubrication, sexual satisfaction, orgasm, and intercourse without discomfort. These latter factors are just beginning to be studied. **Cosmetic and early functional results have uniformly been reported to be good. Long-term outcomes are of more concern.** Unfortunately in these studies it is often difficult to tell what procedures were done for what degree of severity of urogenital sinus, and none of the studies include data on the quality of endocrinologic control in these patients. Looking at what data are available, Jones and colleagues (1976) noted that 25 of 84 patients undergoing vaginoplasty required a secondary procedure to provide a vaginal outlet satisfactory for intercourse; 5 of these 25 also required a third procedure. **The poor results were caused by failure to exteriorize the vagina initially or by scar formation. The distal vagina is always narrow. The normal-caliber vagina must always be reached and exteriorized with current procedures.** Sotiropoulos and associates (1976) found that all patients undergoing prepubertal vaginoplasty required revision at puberty. Azziz and coworkers (1986) reported the results of attempted coitus in 42 women with CAH 23.6 years after vagina repair. Satisfactory coitus was noted in 62% (46% in salt wasters and 87% in those with the non-salt-losing form). There was a less favorable outcome when the initial procedure was performed before 1 year of age. Thirty secondary or tertiary procedures were needed to achieve the final results. These data are widely quoted, but almost all of these patients initially underwent a cut-back vaginoplasty (“incision of the urogenital sinus”), which is a procedure no longer used because it does not adequately open the vagina to the proximal normal caliber; specifically, the distal end of the vagina is narrowed and thus will be stenotic. Revisions for these patients involved the performance of a flap vaginoplasty, which currently would probably have been the initial procedure. In a series from Johns Hopkins Hospital, 28 patients (32% lost to follow-up) had adequate follow-up, 22 (78.6%) of whom needed further vaginal surgery (Bailez et al, 1992). Bailez and colleagues noted that if secondary surgery was needed for vaginal stenosis, success rates were high when the procedure was performed near puberty, with only 8 of 18 needing a secondary procedure requiring a flap. This

group also reported less favorable results in those younger than 1 year of age (Bailez et al, 1992). Nihoul-Fekete and colleagues (1982) noted that 30% of 43 CAH patients required secondary surgery. Hendren and Atala (1995), reporting on 16 patients with high vaginal confluence, noted that 6 of 9 adults had satisfactory coitus and 2 had vaginal stenosis.

Fourteen girls with CAH, 11 to 15 years old, who had undergone genitoplasty at a mean age of 2.5 years were assessed under anesthesia by Alizai and colleagues (1999), who noted that 13 of the 14 required additional vaginal surgery. Stenosis was seen in 43% and persistent urogenital sinus with or without fibrosis in 50%. Minto and coworkers (2003) found that 39% of 28 patients required secondary surgery and a third procedure was required in 11%. Al-Bassam and Gado (2004) noted vaginal stenosis in 16% of their patients who underwent various types of vaginoplasties (43 vaginoplasties: 26 flap, 11 pull-through, 2 cut-back, 3 sigmoid vaginal replacement). Nearly all underwent vaginal dilation. Vaginal stenosis was noted in 37% of Nordenskjöld and colleagues’ (2008) operated CAH patients, with 15 of 50 noting painful intercourse. However 24 of the 41 vaginoplasties were cut-backs, with 10 flaps and 7 combinations. In a cross-sectional study of Dutch women older than 15 years, 7 of 13 “single-stage” repairs required secondary surgery and of 20 women who had intercourse 8 complained of dyspareunia but only 2 had vaginal stenosis (van der Zwan et al, 2013). It is tempting to assume that postpubertal vaginal surgery may result in better outcomes, but there are no data to support this assumption. Furthermore Eroglu and associates (2004) actually noted less vaginal stenosis in those patients who underwent early single-stage repair (3.4%) than in those who underwent late vaginoplasty (42.8%). Lean and coworkers (2007) noted no difference whether the surgery was done before or after 2 years of age. In their series of 32 patients they noted good cosmesis in 72%, satisfactory in 22%, and poor in 6%. They believed that the planned one-stage operation gave better results than the planned multistage procedure, with only 2 of the 32 former patients requiring further major surgery and 3 needing minor revisions. Al-Bassam and Gado (2004) also recommended a single-stage repair at 3 to 6 months of age. It may be that the level of vaginal confluence and number of procedures is far more predictive of outcome than is the timing (van der Zwan et al, 2013).

It seems clear that a “single-stage” early vaginoplasty will probably require a secondary repair after puberty, but this should be expected because the orifice is likely to remain the size that was created given that there is no flow through the orifice in childhood. In my experience the secondary refinements are easily performed.

Surgical techniques to reduce clitoral size have dramatically improved and are now based on our current knowledge of clitoral neuroanatomy. Even though no long-term results are available for current techniques, some long-term results are now being reported for relatively modern techniques. Alizai and colleagues (1999) found clitoroplasty results to be unsatisfactory in 46% of the patients they assessed. Gearhart and coworkers (1995) looked at pudendal evoked potentials after clitoroplasty and noted that modern clitoroplasties preserve nerve conduction in the dorsal neurovascular bundle. Barrett and Gonzales (1980) found intact sensation in all of their patients after clitoroplasty. Chase (1996) reported that even with normal evoked potentials there may be an absence of sensation and orgasm. I have not noted vascularization defects after modern clitoroplasty. It is clear that further long-term studies are necessary. Minto and coworkers (2003) found the clitoris to be cosmetically normal in 59% of patients who had undergone clitoral surgery, but it was excessive in 20%, large in 7%, small in 7%, and absent in 7%. This group also reported that hot, cold, and vibratory sensation was markedly altered as recorded by a genitosensory analyzer. Sensation alone may be a poor indication of clitoral normality after surgery. Further studies to analyze the newest techniques are warranted. The erotic sensitivity and potential for orgasm should be studied. More recently, Nordenskjöld and colleagues (2008) compared 62 CAH patients with 62 controls. Of the 49 who underwent clitoroplasty, 16 had 1 operation, 14 had 2, 4 had 3, 4 had 4, and 11 had between 5 and 10 operative

procedures. Twenty percent were not satisfied with their surgery; they thought there was decreased sensitivity. However, 50% of the nonoperated patients thought their clitoris was too large. There was no difference in the ability to achieve orgasm between the two groups. The authors noted that women with CAH were less satisfied with their genitalia whether operated or not. [Nordenström and associates \(2010\)](#) noted that clitoral sensitivity was affected in nearly all patients who had undergone clitoroplasty. However, those with partial clitoral resection sparing more nerve function had a more favorable outcome and did not differ from those with no surgery. Initial degree of virilization also affected clitoral sensitivity.

The results of TUM and PUM are very early. These procedures are technically easier and the cosmetic results are superior, but whether the functional results are better is unknown. The potential for stress incontinence or denervation of the sphincteric mechanisms also is unknown. Most authors to date have not found continence to be altered by TUM ([Rink and Adams, 1999](#); [Hamza et al, 2001](#); [Kryger and Gonzales, 2004](#); [Rink et al, 2007](#); [Palmer et al, 2012](#); [Ludwikowski and González, 2013](#)). Until these results are available, these procedures should be used with caution.

Recently there has been effort to understand sexual function and mental health following feminizing genitoplasty. [Fagerholm and colleagues \(2012\)](#) noted that quality of life and health-related quality of life studies appeared normal in most patients and that mental health was similar to or better than published data from Finland. There were 5 of 24 patients who had some poorer scores because of distressful memories of too-late surgery, the operative treatment itself, or poor sexual function. This same group also noted that intercoital relationships started later in females who underwent genital reconstruction in childhood as compared to the normal population. In addition, the patients preferred surgery to be done early in life ([Fagerholm et al, 2012](#)). In a study of 62 Swedish women with CAH, [Nordenström and coworkers \(2010\)](#) reported several interesting results. Overall satisfaction with sexual function after feminizing genitoplasty was as good as controls except for the null genotype (salt-wasting CAH, most severely affected) CAH patients. The cosmetic score did not differ between those who were satisfied and those who were not, and cosmetic outcome did not contribute to sexual orientation. In this study, as in the study by [Wisniewski and colleagues \(2004\)](#), the physicians perceived the genital appearance as better than did the patients. [Callens and associates \(2012\)](#) noted that feminizing surgery did not seem to improve or hamper psychosexual outcome, especially in those patients with severe virilization.

There has been some concern that lower urinary tract symptoms are more likely in those patients with CAH ([Davies et al, 2005](#)) but in the recent study by [Fagerholm and colleagues \(2013\)](#) symptoms did not seem to differ in female DSD patients versus controls. Occasional lower urinary tract symptoms were common in both patients and controls ([Fagerholm et al, 2013](#)).

Timing of vaginoplasty remains quite controversial. Although the few reported long-term studies suggest that delayed vaginoplasty may be preferable, most surgeons continue to recommend early surgery, particularly for the CAH group ([Rink and Whittam, 2014](#); [Yankovic et al, 2013](#)). Most would recommend delaying vaginoplasty for the patient with a small, very high confluence vagina. They argue that the available long-term studies are based on outdated techniques and that there are tremendous surgical advantages to a single-stage repair. Supporters of early vaginoplasty well recognize that secondary introitoplasty may be necessary, but this is usually accomplished easily. The argument, which will not be settled soon, contrasts two approaches, both of which usually result in two procedures: (1) a simple procedure in an infant (i.e., clitorolabioplasty) with a postpubertal extensive procedure (i.e., vaginoplasty) or (2) an extensive single-stage clitorolabiovaginoplasty in an infant with a simple introitoplasty in the postpubertal period. There is also controversy on the correct timing to share information with the affected child. Unfortunately research on when to convey information is virtually nonexistent ([Sandberg et al, 2012](#)).

Several studies have noted that the most important factor affecting results is whether there was a surgeon or surgical team with a special interest in feminizing genitoplasty procedures ([Creighton et al, 2001](#); [Lean et al, 2007](#); [Nordenskjöld et al, 2008](#)). This suggests that support for Centers of Excellence may be appropriate for the care of children with DSD.

KEY POINTS: UROGENITAL SINUS ANOMALIES—OUTCOMES OF RECONSTRUCTION

- It is clear that neonatal vaginoplasties will usually require a secondary procedure for stenosis after puberty (25% to 100%).
- Successful coitus is often reported, but further studies should note sexual satisfaction, lubrication, and erotic sensitivity, as well as nonpainful coitus.
- Current techniques of clitoroplasty seem unlikely to injure sensation, but newer studies question whether sensitivity is an adequate indication of clitoral function. Some studies note decreased sensation with newer techniques.

SURGICAL RECONSTRUCTION FOR CLOACAL MALFORMATIONS

Initial Management, Timing, and Principles

The initial management of cloacal anomaly involves stabilization because the child is often quite ill with abdominal distention that at times results in respiratory compromise. As with all other anomalies, its management has evolved. Historically, after decompression of the distended organs it was common practice to perform a rectal pull-through procedure; genitourinary reconstruction followed at a later date, if at all ([Okonkwo and Crocker, 1977](#)). [Hall and coworkers \(1985\)](#) suggested that the vaginal surgery be done after puberty, when estrogen levels are higher. Although it is tempting to perform a pull-through procedure only, it is now clear that this piecemeal repair of the cloaca is a disservice to the child and is absolutely contraindicated. It is optimal to repair all abnormalities (i.e., rectal, vaginal, and urethral) in a single stage ([Kay and Tank, 1977](#); [Mollitt et al, 1981](#)). This allows the best exposure for the difficult rectal and vaginal separation. Furthermore, the tissues have not been previously violated, and the rectum does not require remobilization. [Hendren \(1982, 1986\)](#) pointed out that rectal pull-through should never be done as a separate procedure. Of his 154 patients with cloacal anomaly, 60 were secondary cases, many of whom had undergone a previous pull-through procedure. Definitive repair in this situation often requires repeat rectal mobilization. [Raffensperger \(1988\)](#) proposed neonatal complete repair but later noted that this may not be appropriate. [Levitt and Peña \(2005\)](#) have stated that there are three pitfalls in the management of neonates with cloacae: (1) failure to recognize and manage hydrocolpos, (2) colostomy or vesicostomy problems, and (3) clinical misdiagnosis.

Surgical management now involves four basic steps: (1) decompression of the gastrointestinal tract, (2) decompression of the genitourinary tract, (3) correction of nephron-destructive or potentially lethal urinary anomalies, and (4) definitive repair of the cloaca.

Decompression of the Gastrointestinal Tract

Decompression of the gastrointestinal tract is done by colostomy. Although nearly all surgeons agree on the need for colostomy initially, the best anatomic location of the colostomy is debated. Hendren initially recommended a low-loop colostomy but more recently has performed a right transverse colon divided colostomy ([Hendren, 1982, 1986, 1998](#)). This change was prompted by

difficulty in obtaining a bowel segment for vaginoplasty during the rectal pull-through procedure when a low colostomy has been performed. A divided transverse colostomy keeps the left colic blood supply intact (Hendren, 1992). Peña, as cited by Spitz and Coran (2006), preferred a descending colostomy because there was less surface area for resorption of urine. A divided colostomy in the descending colon just after the colon takes off from its retroperitoneal attachment is now recommended by Levitt and Peña (2005). This procedure maintains the availability of enough distal colon for future pull-through, and prolapse is less likely to occur. However, Peña did recommend leaving a long segment of sigmoid to prevent a difficult pull-through requiring abdominal exploration. Levitt and Peña (2005) noted that 24 of 361 patients had a colostomy too low that interfered with the rectal pull-through. I have favored a proximal colostomy but have at times found clinically challenging acidosis caused by urine absorption through the colonic mucosa. Masuko and associates (2005) reported successful decompression of the colon by balloon catheter drainage with irrigation of the bowel three times a day. This avoided temporary colostomy and allowed a single-stage repair.

At the time of colostomy, endoscopy may be performed to more clearly define the anatomy and to aid in decompression of the urinary tract. In my experience, as the cystoscope advances proximally through the cloacal channel, it tends to enter the vagina (or vaginas). In fact, entrance into the urethra/bladder can be extremely difficult in a neonate with a distended vagina because the vagina compressed the bladder to the anterior abdominal wall and obstructs the bladder neck. Drainage plus irrigation of the vagina (or vaginas) not only allows decompression and relief of abdominal distention but also may allow visualization of the bladder. Often, the rectal fistula is also difficult to locate; as noted previously, it is more often found within the septum of the duplicated vaginas but can enter at almost any location. With a combination of irrigation through the fistula and through the distal limb of the colostomy, the inspissated mucus and meconium can easily be cleared. It is often helpful to leave small feeding tubes in all channels and then obtain radiographic studies to further delineate the anatomy. In my experience this is best done in the radiology suite with fluoroscopy.

Decompression of the Genitourinary Tract

Even after decompression of all structures draining into the cloaca, at times voiding continues into the vagina (or vaginas) or the rectum (or both) and results in rapid distention of these structures with subsequent poor urinary drainage, persistent hydronephrosis, abdominal distention, urinary infection, and hyperchloremic acidosis. This can generally be managed by intermittent catheterization. The catheter often enters the vagina rather than the bladder, but it still functions to drain and decompress the genitourinary tract (Hendren, 1992). If the desired decompression is not achieved, further maneuvers are required. I agree with Hendren that, in a long urethra-like cloaca, catheterization can at times be difficult and a cut-back procedure (opening the cloaca) may be helpful to aid catheterization (Fig. 151-26). If this approach fails, further decompression can be achieved by either vesicostomy or vaginostomy (Kay and Tank, 1977). Levitt and Peña (2005, 2010) have found vaginostomy or tube vaginostomy to be helpful, but it is my belief that clean intermittent catheterization (CIC) should be the first-line treatment because it will usually keep the vagina adequately decompressed. Only when CIC fails should vesicostomy or vaginostomy be performed. The concern of tethering the vagina to the abdominal wall with later difficulty doing a pull-through or TUM has led some to recommend vesicostomy over vaginostomy but others have found this not to be a concern. It also necessitates an abdominal procedure. Levitt and Peña (2005) found that 25% of their cloaca patients had hydrocolpos but that in 59% of them it was either not identified or mismanaged. This resulted in significant morbidity from ureteral obstruction, urinary tract infection, acidosis, and failure to thrive. Adequate vaginal drainage resulted in resolution of these problems.



Figure 151-26. The urethra-like cloaca is opened, with a catheter in place; vesicostomy has also been performed.

Repair of Obstructive Urinary and Other Pathology

The third stage of care of a child with a cloacal anomaly is repair of any obstructive urinary tract pathologic process. Renal structural abnormalities, some of which were obstructive, have been identified in 60% to 83% of patients with persistent cloaca (Warne et al, 2003; Rink et al, 2005b). In those patients with a common channel longer than 3 cm, 91% had urologic defects (Peña et al, 2004). At times these anomalies are ignored early on while awaiting definitive cloacal repair, but this practice should be avoided. Obstructive lesions should be treated promptly. However, vesicoureteral reflux, which is quite common, can generally be managed medically if urinary infection is prevented. Other organ system anomalies (e.g., cardiac, spinal cord) should be fully evaluated. Some may require repair during this phase.

Definitive Repair of Cloacal Malformations

Definitive repair of a cloaca is usually carried out at 6 to 12 months of age, but obviously the child must be well nourished and thriving to proceed with repair. In healthy thriving children, Peña and colleagues (2004) operate at 1 month of age. Definitive repair should never occur until the urinary tract has been evaluated and hydrocolpos has been ruled out. If endoscopy has not been performed previously, it may be helpful as a separate procedure before the definitive repair. Defining the anatomy can be tedious, and it is helpful to thoroughly cleanse the distal colonic segment, which usually requires irrigation from the mucous fistula, as well as the distal limb of the colostomy. A standard Golytely bowel preparation should also be done.

Operative Technique: Cloaca

The definitive repair begins with endoscopy to reacquaint the surgeon with the anatomy. I have also found it is helpful to place

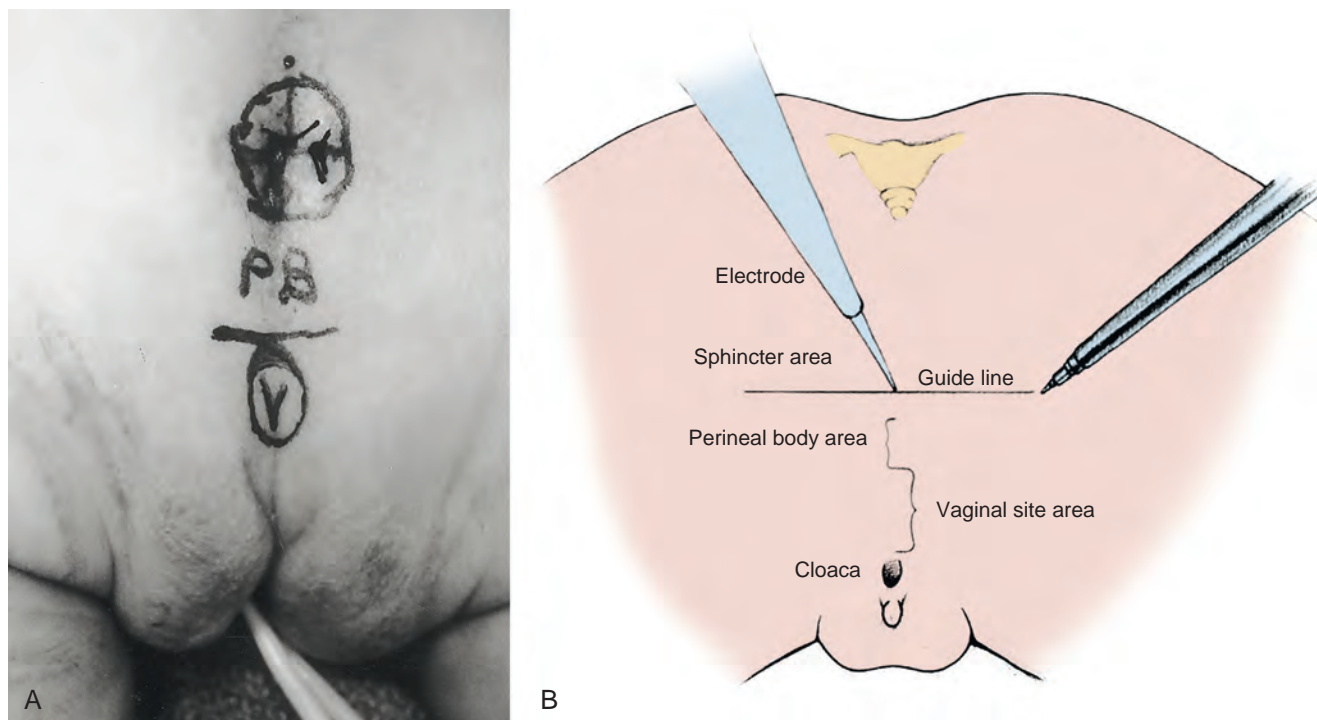


Figure 151-27. A, Cloaca: proposed location of the vagina (V) and perineal body (PB). B, Rectal location is identified by electrical stimulation.

a Foley catheter in the bladder and different-colored Fogarty catheters in the vagina (or vaginas) and rectum. The catheters are kept sterile during preparation. As described previously for urogenital sinus repair, a complete lower body preparation with povidone-iodine is done circumferentially from the level of the nipples to the toes, and the legs are wrapped sterily. Such preparation allows prone and supine positioning for perineal and abdominal surgery.

The definitive posterior sagittal anorectovaginourethroplasty (PSARVUP) is begun with the child in the prone position and the pelvis elevated on rolls to achieve a jackknife position. An electrical stimulator is used to determine the area of maximal contraction, which is marked with a skin scribe and with stay sutures for later rectal placement. The proposed locations of the perineal body and vagina are also marked (Fig. 151-27). I agree with Hendren (1992) that it is at times helpful to have a sound in the common cloacal channel, but the Foley and Fogarty catheters usually suffice. The entire dissection is done in the midline until mobilization of the rectum and vagina is begun. The most important advances of Peña's PSARVUP procedure are that it allows identification of the external sphincter and muscle complex of the rectum and provides excellent exposure for separation of the rectum and vagina (or vaginas) from the cloaca.

The initial incision extends from the tip of the coccyx in the midline to the posterior aspect of the cloacal orifice. Sutures mark the sphincteric muscular structures on either side as they are encountered. I have found it helpful in the past to open the common cloaca in the midline posteriorly to the level of the confluences to allow easy identification of the rectal and vaginal insertions. With TUM, this is less appropriate because it may limit the options for use of the sinus in the reconstruction as previously described for a urogenital sinus. When the rectal fistula is identified, it is opened posteriorly and multiple silk stay sutures are placed. These sutures are helpful in mobilizing the rectum away from the vagina (or vaginas). It is important to remember that the structures share a common wall initially and it is better to enter the vagina than either the rectum or urethra. Circumferential dissection of the rectum to well above the sacrum may be necessary. Separation of the peritoneum can be done from this position. Rarely, a child with a very

high rectal confluence needs to be turned to the supine position for abdominal exploration to free the rectum more proximally. Levitt and Peña (2010) have noted abdominal surgery to be more likely when the common channel is greater than 3 cm in length. Once adequate rectal mobilization to allow a tension-free anastomosis to the perineal skin has been achieved, the rectal stay sutures are used to retract the rectum from the genitourinary structures.

In the classic PSARVUP procedure, the vagina is now separated from the sinus. This dissection is even more tedious and difficult than the rectal separation. With TUM (described later), which has now achieved widespread acceptance for cloacal repair, the vagina may not require separation. In classic vaginal separation, as noted earlier, it is an error to enter the urinary tract during vaginal mobilization. Side-by-side vaginal duplication is most common, and the midline septum has been incised with electrocautery during the initial endoscopy. Hendren (1998) noted that 66 patients had a single vagina, 68 had two, and 20 had none. The Fogarty catheter (or catheters) within the vagina is easily palpable, and the posterior aspect of the vagina is opened at the level of the confluence. Again, circumferential stay sutures are very helpful in separating the vagina from the urethra and bladder. A malleable retractor inserted into the opened posterior vaginal wall exposes the anterior wall confluence for separation. Sharp dissection is less likely to injure the urinary tract than is cautery. Making dissection even more difficult is the realization that frequently the vagina almost encircles the urethra. Failure to recognize this situation can result in injury to these structures. Use of the stay suture for traction aids in further mobilization of the vagina (or vaginas). The outer wall of the vagina appears white, and identification of this color is helpful. Great care should be taken to avoid devascularization of the vagina during mobilization. Usually, vaginal mobilization allows the vagina to be "pulled through" to a position near the perineum. If after significant mobilization it still does not reach the perineum, skin flaps can be used to reach the spatulated vagina. With an extremely high vagina or the rare vaginal agenesis, it may be necessary to interpose a bowel segment to reach the perineum, which obviously requires abdominal surgery. With a very dilated vagina, a vaginal flap or vaginal "switch" can be created to reach the perineum, although care must

be taken to avoid devascularization and stenosis (Hendren, 1986; Peña, 1989; Peña et al, 2004).

Before the vagina is brought to the perineum, the openings in the common cloacal channel should be closed in two to three layers with absorbable suture to create a urethra. If the cloaca is large and resembles a vagina, it needs to be opened in its entirety and tailored over the Foley catheter. The vagina is then secured to the perineum. If there is any concern about vaginal injury, the vagina should be rotated to avoid overlapping suture lines (Hendren, 1992). The Foley catheter is left indwelling for 2 weeks.

Some surgeons have more recently noted that laparoscopic-assisted PSARVUP can help in achieving a low dissection of the fistula and accurate placements of the rectal pull-through, while allowing excellent visualization of the pelvic structures (Tei et al, 2003).

The perineal body is now reconstructed, and the rectum is pulled through to the perineum. Peña (1989) stressed the importance of tailoring the widened rectum. The amount of tailoring differs in each patient. The muscles must meet posterior to the rectum. The rectum is placed in the center of the sphincteric muscle mass and anastomosed to the skin. Rectal dilation is begun gradually at 2 to 3 weeks after surgery, and the colostomy is closed in 3 months if all has healed well.

Once the urethral catheter has been removed, it is imperative to monitor the urinary tract and voiding dynamics closely because poor emptying secondary to a neuropathic component is seen in almost a third of patients. If any concern arises about the child's ability to empty, CIC should be started and continued until normal bladder dynamics are ensured. Failure to do so can ultimately result in urinary tract infection, hydronephrosis, and even loss of renal function.

Peña's TUM technique is now widely accepted for cloacal anomalies. It is a technically easier procedure that requires less time with less blood loss. The basic technique involves 360-degree mobilization of the entire urogenital sinus after the rectum has been separated. The technique at this point is not different from that described earlier for TUM for urogenital sinus abnormalities. I have found this technique to be extremely helpful. It makes the most difficult part of cloacal surgery, vaginal separation, much more easily performed when necessary. If the confluence is only 2 to 3 cm from the perineum, separation may not be even necessary. In those patients with a high vaginal confluence, separation may still be necessary but it is much more easily accomplished (Rink et al, 1997). Concerns regarding continence have been raised, but to date the results have not been different than with standard repairs. Long-term results of the TUM procedure are needed.

KEY POINTS: CLOACAL RECONSTRUCTION

- Cloacal reconstruction involves four steps: (1) decompression of the gastrointestinal tract (colostomy); (2) decompression of the urinary tract (CIC, vesicostomy, vaginostomy); (3) correction of associated organ systems anomalies; and (4) cloacal repair (PSARVUP).
- TUM is now commonly used for cloacal anomalies after the rectum is separated.
- The results of cloacal repairs are often based on the presence or absence of a normal spinal cord. CIC is frequently required, as is a bowel program, to achieve urinary and fecal continence.

Results of Cloacal Surgery

Cloacal anomalies are exceedingly challenging to repair. The anatomy is complex and differs from patient to patient. The surgeon must be prepared for a long, tedious procedure, must be imaginative, and must be willing to handle the tissues with great care. One

might assume from this preface that the results would be dismal. On the contrary, most patients lead a productive life. We surgeons are indebted to Drs. W. Hardy Hendren and Alberto Peña for their pioneering work on children with cloacal anomalies, as well as their willingness to document their results.

Results have generally been reviewed in terms of urinary continence, fecal continence, and sexual capability; in the future, results should also focus on erotic sensitivity and fertility, pain-free intercourse, and orgasm as well as quality of life. Early results from a urinary standpoint were dismal: Chappell and Bleloch (1973) reported that all 5 of their patients had some degree of incontinence postoperatively, and Bartholomew and Gonzales (1978) had 5 of 7 patients wet after reconstruction. **It is now clear that a high percentage of patients have a neuropathic component to their incontinence.** De Filippo and colleagues (1999) reported urodynamic data on 26 patients with anorectal malformations (including 6 with cloacal anomalies). Twenty-one of the 26 had preoperative leak point pressures greater than 40 cm H₂O, and 15 had normal MRI of the spine. This means that even those not demonstrating a neurologic abnormality may have abnormally high outlet resistance, which adds to the risk for incontinence and upper tract changes. Muller and associates (2014) showed that the type of spinal abnormality may impact continence rates, with the short spinal cord having the greatest impact. Of Hendren's 141 patients, 83 (59%) voided spontaneously with control, 40 (28%) required CIC, 4 (3%) had undergone urinary diversion, and 1 (0.7%) was continent with urinary diversion; only 5 (3.5%) were wet, and in 8 the results were too early to assess (Hendren, 1998). Peña and coworkers (2004) reported a review of 339 patients operated on for cloacal anomalies, 193 of whom were evaluated for urinary continence. They found that spontaneous voiding was related to length of the common channel. Overall continence with spontaneous voiding occurred in 54%. Another 46% were dry with CIC (24% with a native urethra, 22% with a Mitrofanoff channel). However, when the common channel was less than 3 cm, 28% required CIC; if greater than 3 cm, 78% required CIC. Warne and associates (2002b) achieved 80% "social continence" but only 22% spontaneously voided, 12% performed CIC alone, and 46% required reconstructive urologic surgery to achieve continence (mean number of operations, 4.7). They likewise found that those patients with a common channel longer than 3 cm were less likely to void spontaneously (12% vs. 31%). In the series by Rink and coworkers (2005b), 86% were dry but only a third were continent with spontaneous voiding. The remainder required CIC with or without lower urinary reconstruction (Table 151-1). After TUM spontaneous voiding occurred in 43% to 66% of patients (Levitt and Peña, 2010). Warne and associates (2002b) also noted that a good bladder neck, short common channel, normal sacrum, and two normal kidneys were all good prognostic signs for continence and spontaneous voiding. I am in agreement with Peña and Levitt (2003) that voiding abnormalities are generally related to a noncontractile bladder and warrant CIC, but Warne and associates (2002b) found hyperreflexia to be the predominant pattern in those with abnormal dynamics. It is important to note that 75% of their patients had an abnormal sacrum.

Fecal continence is directly related to neurologic status (Peña, 1989). Hendren (1992) noted that certain factors bode well for continence: good perineal raphe, well-defined anal dimple, normal spine, normal MRI, and brisk muscle reflex. In 105 patients, Hendren (1992) noted that 47 had normal bowel function, 27 required enemas, 7 had a colostomy, 7 had fecal soiling, and 4 with an anterior anus had normal control. Peña and coworkers (2004) reported that 60% of 156 patients had voluntary bowel movements but only 28% of them never soiled. The 40% who are fecally incontinent remain "clean" with a bowel management program. The Malone antegrade continence enema (MACE) appendicovesicostomy has been very helpful in preventing constipation and achieving fecal continence in those refractory to bowel management programs.

Late vaginal stenosis and obstructed menstruation occurred in 36% to 41% of patients (Hall et al, 1985; Breech, 2010). Warne and

TABLE 151-1 Continence Rates after Cloacal Surgery

REFERENCE	VOIDING SPONTANEOUSLY	DRY WITH CIC ± CONTINENT RECTUM
Hendren (1998)	0.62	0.34
Peña et al (2004)	0.54	0.46
Warne et al (2002b)	0.22	0.58
Rink et al (2005b)	0.33	0.53

CIC, clean intermittent catheterization.

coworkers (2003) noted the vagina to be adequate for intercourse in 44%. Revision vaginoplasty is often needed.


Although not a direct result of reparative surgery, renal outcomes are worrisome. Renal insufficiency was found in 50% of the patients treated at Great Ormond Street Children's Hospital, and 17% of the patients progressed to end-stage renal failure (Warne et al, 2002a). In the series of Rink and colleagues (2005b), 18% had an abnormally elevated serum creatinine level and in another 26% it was borderline. Lifelong yearly urologic evaluation is warranted, and prompt recognition plus treatment of any obstructive pathologic process or urinary tract infection is imperative. Bladder dynamics must be evaluated and abnormalities addressed. Of 24 reported adult patients, 17 had coitus and 6 had borne children (five deliveries by cesarean section and one vaginal delivery) (Hendren, 1998).

Leclair and associates (2007) reported on cloacal repair using the TUM technique. Urethral stenosis occurred in 2 of 22 patients and both required a Mitrofanoff catheterizable channel. One child developed a urethrovaginal fistula, and 3 had vaginal stenosis. Continence was noted in 15 of 17 patients older than 4 years of age. Seven voided spontaneously and 8 emptied by CIC. Fecal continence was present in 12, with 9 having spontaneous bowel movements and 3 requiring MACE irrigations.

SUMMARY

Management of urogenital sinus and cloacal anomalies can be exceedingly complex. In children with DSD, prompt but very careful evaluation by an expert multidisciplinary team is mandatory. Family support and education with openness and respect for the child and family are required. Differing cultural practices must also be respected and accepted. Confidentiality must be maintained. Surgical reconstruction requires great care of tissues, meticulous attention to detail, and a lifelong commitment by the surgeon. These

complex anomalies require an entire team of physicians and nurses dedicated to the care of these problems. Urogenital sinus and cloacal anomalies are very challenging reconstructive problems. Those patients at the more severe end of the spectrum should be handled only in centers with great expertise and experience.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter. 

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The complete reference list is available online at www.expertconsult.com. 

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Definitions

The Process of Transition

Training Requirements

The Adolescent Clinic

Outcome Measures

DEFINITIONS

The special aspects of illness in children, as opposed to those in adults, have been recognized for centuries. In the 19th century, this was reflected in the foundation of specialist hospitals for children. A development at the end of the 20th century was the realization that many children, particularly those with major congenital anomalies, had holistic and medical needs that would continue for the rest of their lives. The problem then was to identify clinicians with the knowledge and interest to take on such care. The needs are the same everywhere, though at present the solutions are limited (Viner, 2013). Gradually, special units have appeared, particularly in Europe and Australia, to provide this service. Adolescent wards are being built, mainly in pediatric hospitals (Payne et al, 2012).

However, there is a further difficulty: children do not become adults overnight or on achieving an arbitrary birthday. **Adolescence is a phase of passing from childhood to adult life that is easily recognizable and creates unique problems in the management of chronic illness.** It has a variety of formal definitions. In the Oxford English Dictionary it is described as "between childhood and manhood (14 to 25 years old) or womanhood (12 to 21)." The Department of Health in the United Kingdom is imprecise about its beginning, but rules that its end is the 19th birthday, which means that all care must be transferred at once to standard adult clinics. Neither of these definitions is wholly satisfactory, if only because children mature into adulthood at variable rates. For example, when patients with congenital bladder disorders (mean age 20 years) were asked at what age they felt able to act independently from their parents, the mean answer was 17 years (median 16), but the range was 11 to 25 years (van der Toorn et al, 2013).

Although the need for a service to help the transition from pediatrics to adult medicine has been recognized in some specialties for 70 years or more, the main contribution of the 21st century has been the establishment of "transition clinics." Despite this, provision in the United States for long-term care remains limited (Wan, 2013). Most sub-specialties of pediatrics see the need for transition clinics, but the provision is sparse and for many chronically ill or disabled children, adult care is available only in the pediatric hospital or in a general adult clinic. The lack of facilities for long-term care is reflected in the paucity of literature on the subject. Figure 152-1 shows the number of publications in PubMed on transitional care.

The purpose of a transition clinic is to prepare children and their families for continuing medical and holistic care in the adult environment. It is predicated on the assumption that there is an adult unit to which such care may be transferred. In some chronic conditions of childhood, there is an obvious adult equivalent.

For example, a child with type 1 diabetes can eventually go to an adult diabetic specialist, but will have a need for adolescent care in the interim. Even so, good transition is frequently unavailable (Begley, 2013).

In urology there is no adult equivalent—there is no adult exstrophy, prune-belly syndrome, or disorder of sex development (DSD). Even the similarities that neural tube defects and posterior urethral valves (PUVs) have with acquired adult conditions are deceptive. **Children with major urologic conditions need care that continues for the rest of life.**

The prevalence of long-standing childhood illness in the United Kingdom is 17% to 19%. Data from other countries are limited. In the United States in 1992 it was estimated that 31% of children had a chronic condition; however, only 5% were considered to be severe and 29% moderately severe (Newacheck and Taylor, 1992). Even higher figures were recorded by Bethell and associates in 2011, but the increase was almost entirely accounted for by obesity. Excluding obesity, the prevalence of chronic disease in adolescents 12 to 17 years of age was 34.4%, of which 50% were deemed to be severe. Although no urologic condition appeared in the most common 20 conditions considered, it is clear that long-term care is a major numerical problem.

Definitions

- **Adolescence:** The period between childhood and adulthood. Specific ages are given by some authorities. In urology it is best considered as puberty to maturity as a young adult.
- **Transition:** The process of moving care from a pediatric to an adult environment. It is a difficult but essential period. Failure to manage it properly has serious consequences for the patient and for the health care system. Although it is recognized as essential, the logistics are still in the process of development.
- **Transition clinic:** A clinic staffed by pediatric and adolescent urology specialists that children attend on four or five occasions to facilitate the transfer to the adolescent clinic.

THE PROCESS OF TRANSITION

Barriers to Transition

Perhaps the most obvious barrier to movement of children with urologic anomalies into adult care is that there are very few clinics dedicated to receiving them! The conditions that will need attention in later life are of an adult nature and yet cannot be considered separately from the original congenital anomaly. This requires the services of an adult urologist who is also trained in pediatric

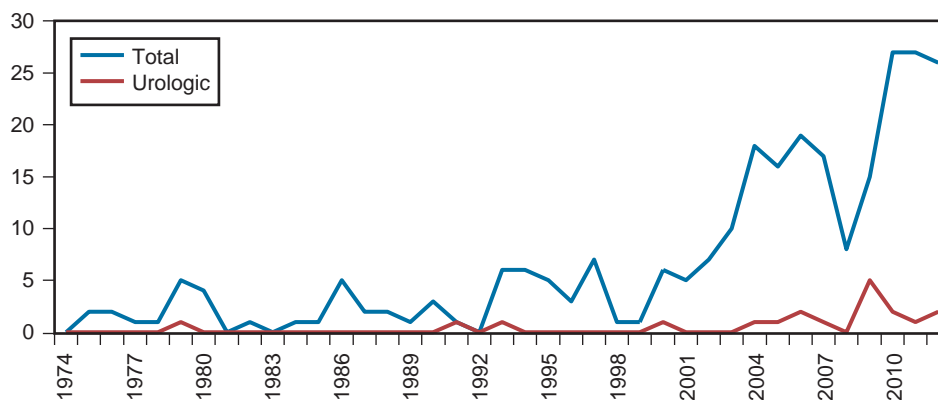


Figure 152-1. Papers listed in PubMed under “Transitional Care” (blue) and “Transitional Care, Urology” (red) from 1974, when the first paper appears, to 2012.

urology. At present there is no training program (see later) and few individuals are prepared to take on the financial burden of preparing themselves for a new specialty that is unlikely to attract a worthwhile reward unless there is public funding.

There are no figures available to show how many “adolescent urologists” are required. From the prevalence of the relevant conditions a total population of approximately 4 million would provide enough work for one urologist specializing in long-term care. This figure must be treated with great caution. The incidence of the given anomalies is not accurately recorded. The incidences are falling and will continue to do so as selective pregnancy terminations become more common. Nonetheless, the figure does illustrate that it is a small specialty. If there is an even distribution of age and a working life of 30 years (both doubtful suppositions), there would be a vacancy in the United Kingdom only in alternate years. In the United States there would be approximately 80 adolescent urologists.

The practical aspects of geography have to be considered. There will be far fewer adolescent urologists than there are pediatric urologists. If there is an adolescent urologist in the same city, a smooth transition should be possible. The more remotely the child lives, the more difficult will be the problem unless the family has the means and inclination to travel regularly.

In countries with some form of universal or socialized health system, it may be presumed that hospital funding would not be a problem. However, travel costs may not be refunded. In insurance-based systems, adolescents with long-term health problems are a poor commercial prospect. At least in the United States, it may be hoped that the *Patient Protection and Affordable Care Act* may help (Centers for Medicare and Medicaid Services, 2013).

The Transition Process

Children and their families are accustomed to the holistic care received in a pediatric setting. **Patients feel particularly vulnerable as they approach adulthood** (Crowley et al, 2011). Indeed, the strong attachment of the child to the pediatric staff has been shown to be a major barrier to transition (De Masi and Biermann, 2013; van der Toorn et al, 2013).

Pediatricians should start to prepare their patients at an early stage (Lemly et al, 2013). There can be no fixed time, but just the introduction of the idea that the doctor has a long-term plan is reassuring. General guidelines already exist, but remain to be validated (Colver et al, 2013; Lemly et al, 2013). Viner has identified three elements to ensure safe, effective transition. **First, a cultural shift in staff attitudes and training is required. In particular, medical practice must adapt to the needs of the adolescent and not vice versa. Second, systems must change to ensure that all pediatric chronic illness and disability services have effective transition programs in place. Third, young patients must become effective partners in their own transition** (Viner, 2008). Although he was writing about the National Health Service (NHS)

in the United Kingdom, the principles are universally applicable (Viner, 2013).

The first formal step, perhaps at 11 or 12 years of age, would be an assessment by the pediatric team of the long-term needs. At approximately 13 or 14 years of age, the child should start to attend a clinic with both the pediatric urologist and members of the team who will be taking over. This allows mutual introductions and the beginning of a medical record for adult care. It has been shown that a key factor in successful transition is continuity of care (Gleeson and Turner, 2012). At least four to five visits are required for the adolescent to build the same level of trust with the new physician that was experienced with the pediatrician (Klostermann et al, 2005). With this level of continuity of care it has been shown that, at least in diabetic adolescents, there were 23% fewer admissions compared to those with no transitional arrangements (Nakhla et al, 2009).

There then follows a transfer phase in which the consultations and decisions are made predominantly by the adolescent/adult clinicians. The pediatricians remain involved. Great care must be taken in the arrangement of joint clinics. Adolescents do not like the experience of facing a bank of clinicians together. There is also a danger that “management by committee” will lead to unsatisfactory decisions. A possible solution used in the transition of adolescents with DSD has worked well in the author’s experience. The patients are discussed by a large multidisciplinary team before the patient visit. Two or three clinicians well known to the patient (usually including a nurse specialist) then conduct the consultation. This allows a consideration of the surgical, endocrine, psychological, gynecologic, and sexual issues without a large cohort of people in the room. A critical element is to establish a dialogue on sexuality and fertility—a subject of paramount interest to the adolescent and that clinicians may be least willing to discuss.

Even this is subject to the difficulties of geography if the participants are all from different cities. To receive such specialist care, somebody has to travel. Different models are emerging. In the United Kingdom, most pediatric urology units have identified an “adult urologist” to continue the care. In the South Island of New Zealand, the relevant adult urologist travels to outlying pediatric units on a regular basis for transition and adult clinics; patients needing surgery or multidisciplinary care have to travel to the central hospital in Christchurch. In Sweden, a large country with a small population, the plan is to have two or three centers to which the patients must travel (Mark and Lackgren, personal communication, 2012).

Beyond childhood, clinicians should provide the same comprehensive care, but focused on adult life.

Consequences of Transition Failure

There are two very unsatisfactory possibilities—the child is “dumped” without any preparation or continues as a cuckoo in the pediatric nest.

Personal experience suggests that dumping has a poor outcome. In the well-structured transfer system in my practice, many patients were still lost. Those who returned in later life had sad accounts of their management in nonspecialist units. Intuitively it would be thought that a patient with a condition such as exstrophy, for example, would pose a challenge to a general urologist. However, there may well be patients who never returned and were happy with their management. In one series, 49% of potential transferees thought they could arrange their own urologic care (although only 24% knew what to expect) (van der Toorn et al, 2013).

If such patients continue their care in a pediatric hospital, it will soon cease to be pediatric—humans with a normal life span spend three quarters of their lives as adults. In a pediatric hospital in Rio de Janeiro with no transition arrangements, adolescents and adults made up 19.8% and 2.7% of outpatients, respectively (Jesus et al, 2014).

In a survey of academic pediatric units in the United States, 2% of admissions from 1999 to 2008 were of patients between 18 and 21 years of age and 0.8% were over 21 years. This gave 60,000 inappropriate admissions in the 10-year period, and there was a 6.9% annual increase (Goodman et al, 2011).

TRAINING REQUIREMENTS

There is no title, at present, for the specialist who looks after children from pediatric urology when they grow up. For want of anything better, the term *adolescent urologist* is used and understood by pediatricians and urologists. However, there is no point in having two transitions: childhood to adolescent care and then on to adult care. **Once the patient leaves childhood, it is adult physical and emotional problems that predominate and form the field of adolescent urology.**

There are three broad requirements: knowledge of the relevant anomalies in pediatric urology and their management, an understanding of the emotional and physical changes that occur in adolescence and a broad training in adult urology. The breeding ground of the adolescent urologist therefore will be in standard adult urology. Some training, perhaps a year, is needed in pediatric urology. The problem of training in adolescent medicine is unresolved. The specialty of adolescent medicine is new, and much of the training experience has been in family practice. Online training is available as a part of the NHS Health Education England program (<http://www.e-lfh.org.uk/projects/ah/index.html>).

KEY POINTS: THE PROCESS OF TRANSITION

- Children with chronic illness require life-long, holistic care, similar to the care they received as pediatric patients.
- Barriers to transition include fear of change on the part of the child and family, inadequacy of adolescent services, poor funding, and geographic problems for a small specialty, especially in large and sparsely populated countries.
- Discussion of sexuality and fertility is most important.

THE ADOLESCENT CLINIC

The huge majority of patients requiring long-term adolescent care will have one of the major congenital anomalies. Statistically, PUVs and spina bifida should account for 35% each, exstrophy approximately 5%, and others about 25%. However, the workload will be more a reflection of the complexity of the cases than the original diagnosis.

The age at which a patient transfers to the adolescent clinic must depend on the individual level of maturity. Because such clinics, at least in urology, are looking after people for the rest of their lives, the huge majority will definitely be adult. The clinical environment can be made appropriate for an adolescent, but the hospital or

clinic will be adult. In some countries, there is a legal age at which patients can be treated in an adult environment. In the United Kingdom it is 16 years of age. Patients with DSD should be seen in a separate clinic.

Most of the conditions are urologic in origin. The main exception is spina bifida. In the United States, most children with spina bifida are provided care in dedicated hospitals such as Shriners (<http://www.shrinershospitalsforchildren.org>). These are multidisciplinary units that provide an ideal environment for the management of a very difficult condition. Unfortunately, there are few replications of this for adolescents and adults. Because so many of the problems in children are with the bladder and kidneys, the long-term care is often based in urology.

As the urologic patients grow through adulthood, they have needs that go beyond the genitourinary system. It is necessary to have a group of clinicians who can share the care. Ideally, they should have an interest in the long-term care in their own fields, but this is not always possible. It is essential that they understand the idiosyncrasies of congenital urologic problems. All the conditions require the support of radiologists and nuclear medicine specialists. It is impractical to have multidisciplinary clinics with all the specialties, but so many have renal problems that a nephrologist is virtually essential for the running of an adolescent urology clinic. Table 152-1 shows the other specialists who may be needed.

There is a particular problem with psychology. Pediatric hospitals are usually well served with this specialty, but, even so, the

TABLE 152-1 Specialists Required to Support an Adolescent Urology Clinic*

CONDITION	SPECIALISTS REQUIRED
Renal anomalies	Nephrologist Physician in hypertension Transplant team
Spina bifida	Nephrologist Orthopedist Neurologist Neurosurgeon Podiatrist Gynecologist/obstetrician Geneticist Plastic surgeon
Intestinal reservoirs	Gynecologist/obstetrician Biochemist Stone surgeon Stoma therapist
Exstrophy	Gynecologist/obstetrician Orthopedist Psychologist Oncologist
Posterior urethral valves	Nephrologist Andrologist
Disorders of sex development	Endocrinologist Biochemist Gynecologist Geneticist Sex therapist Plastic surgeon Fertility specialist
Prune-belly syndrome	Nephrologist

*All patients are likely to need the help of specialist radiology and nuclear medicine services.

demand outstrips the supply. Many surgical papers point out the need for such support (Christie and Viner, 2009). Adolescent psychology is a well-defined sub-specialty but is absolutely confined to the management of adolescents up to the age of 19 or 20. The period of true adolescence is crucial to the long-term physical and mental health of the individual. There is a change in the perceived health and social priorities that require parental, medical, and psychological support (Viner et al, 2012).

Beyond this is a huge void in the provision of psychological expertise for the chronically ill. One of the difficulties is in understanding the relationship between the strictly physical problems of an uncorrectable congenital anomaly and its psychological effects.

Geographic factors are a particular problem when arranging psychological care. The management needs frequent visits, which may not be possible if the patient lives a long way from a major medical center.

Discharge without Long-Term Follow-Up

Dischargeable Patients

Children who have had inguino-scrotal surgery, successful pyeloplasty, surgery for undescended testis and a few other conditions may be considered cured and should be discharged. Late recurrence of renal obstruction after pelvic-ureteral junction (PUJ) repair is seen in less than 3% of children and is usually symptomatic (Psooy et al, 2003). Follow-up isotope scans have shown no deterioration at a mean of 5 years (van den Hoek et al, 2007). Similarly, later development of contralateral PUJ obstruction is seen in less than 2% of patients and most of them had some preexisting dilation to give a warning (Thomas et al, 1982). Parents should be warned about the risk for neoplasia in boys with undescended testes. However, there is no evidence that any of these conditions would be avoided by continuous follow-up.

Fetal ultrasound has identified large numbers of babies with hydronephrosis. The most common diagnosis is vesicoureteric reflux, over 80% of which is in males. There is a high rate of spontaneous resolution even in high grades, with up to 40% being normal by 2 years of age (Scott, 1993). Most will be discharged in childhood. Regardless of the age at diagnosis, long-term follow-up is required only if there is significant renal failure or for the development of hypertension, the latter probably in the community.

The second most common finding is an abnormality at the PUJ that may be obstructing. The management of this problem remains a matter of debate. Of the PUJ abnormalities, 90% of mild cases and 28% of severe cases resolve in childhood (Barbosa et al, 2012; Yang et al, 2010). Those who are left with normal kidneys can be discharged.

Unresolved Follow-Up Problems

Pelviureteric "Obstruction." It is difficult to know what to do with those who have been managed "conservatively" and whose abnormality is still present. There is an obvious attraction for parents in finding that surgery is not necessary. At what point, however, can they be told that their abnormality is really a variation of normal and not a disease? This is not only of medical importance but also is important for the mundane aspects of adulthood such as obtaining life or health insurance.

Perhaps the greatest dilemma is with the symptomless hydronephrotic kidney, especially those found on fetal ultrasound. After birth, most babies are managed conservatively. On Society of Fetal Urology grading, all with grade I are likely to remain stable. The more severe the hydronephrosis, the more likely it is that surgery will be performed, so that all of grade IV and about three quarters of grade III will have undergone surgery by the age of 10 years. Approximately half of all patients will have complete resolution of the hydronephrosis (Thomas, 2010; Yang et al, 2010), and in about 20% of children the hydronephrosis remains stable to the age of 16. Thomas (2010) quotes unpublished data from Chertin and

colleagues and from Dhillon's series from Great Ormond Hospital for Children that at least up to 22 years stability is maintained.

Limited evidence is available from adult practice. In asymptomatic or minimally symptomatic patients, 10 of 50 patients deteriorated within 2 years but none thereafter up to a mean of 4.5 years (Malki et al, 2012). Patients presenting with PUJ obstruction in adulthood are presumed to have had it since birth. The patients in this series presumably had stable hydronephrosis in adolescence, and 20% later deteriorated.

At present, however, inadequate evidence exists to decide whether silent deterioration will occur later.

Hypospadias. It is well documented that the results of hypospadias repair are not as good as surgeons often report (Garibay et al, 1995; Mureau et al, 1997; Holland et al, 2001). Some surgeons have advocated long-term follow-up of children to detect poor results and correct them (Bracka, 1989; Mouriquand et al, 2011). Garibay and associates (1995) pointed out that some children who had significant obstruction of flowmetry were symptomless but benefited from diagnosis and correction.

The psychological problems encountered in children and adults with hypospadias may have been underestimated. In infancy there is evidence that surgery between 6 and 15 months of age minimizes psychological damage (Dusková and Heldlová, 1987). This timing avoids five particularly sensitive phases of psychological development, the disruption of which is thought to predispose to psychological problems in later life (Freud, 1955). Unfortunately, this remains a theoretical concept. In a series of 40 patients who underwent surgery for hypospadias who were compared to more than 10,000 unaffected controls, the risk for psychological morbidity was unrelated to the age at surgery (Mondaini et al, 2002).

There is evidence that a good surgical result does produce a happier adult, even allowing for the disagreement between surgeons and patients over the definition of "good result." The worse the surgical result and the more severe the original hypospadias, the worse is the psychological outcome (Woodhouse and Christie, 2005).

The dilemma is whether long-term follow-up alters the physical or mental outcome for adults. There are no data to help, nor would it be easy to obtain it. It might be thought that an annual visit to the surgeon for the discussion and examination of a penis that the boy thought to be normal and about surgery of which he had no recollection, might generate a psychological problem that would not otherwise exist.

Acquisition of Patients in Adolescence

A few patients develop a urologic disease in adolescence, such as pelvic cancer or a late Wilms tumor. Occasionally, a congenital anomaly such as DSD (especially the androgen insensitivity syndromes) or a PUUV may be diagnosed late.

Drug abuse is an unfortunate fact of life in adolescence. Most of those that are commonly used have some genitourinary effects (Table 152-2) (Coull and O'Brien, 2008). The most serious is ketamine. This is an anesthetic agent widely used in veterinary practice and sometimes in humans. It is a legal medication and fairly cheap. Unfortunately it is the fastest growing drug of abuse, especially in the Far East and now in Europe (Chu et al, 2008). It has a destructive effect on many organs, including causing papillary necrosis, retroperitoneal fibrosis, and a shrunken, painful bladder. Relatively small doses will produce symptoms. Two grams per day gives painful frequency in 50% of individuals and 5 g/day in 100% (Cottrell et al, personal communication; European Association of Urology, poster, 2009). Discontinuation of drug use leads to improvement, but as many as 90% may continue to have some symptoms (Cheung et al, 2011). Prolonged use leads, among other things, to renal failure and a very small bladder that is painful when full. The first line of management is to treat the addiction. It is always difficult to reform addicts, but with ketamine the additional problem is that patients find that the best treatment for their bladder pain is more ketamine (Wood et al, 2011). A small bladder will require intestinal substitution, but resumption of

TABLE 152-2 Summary of the Effects of Drug Abuse on the Genitourinary System*

DRUG	PRICE/GRAM	ACUTE	LONG-TERM
Cocaine	£50/\$75	Priapism Placental insufficiency	Impotence Penile necrotizing vasculitis
Heroin	£45/\$67	Impotence	Penile vein thrombosis
Ecstasy (MDMA)	£3.50/\$4.75 per pill	Promiscuity Polydipsia	Unsafe sex Self-harming
Cannabis	Very cheap		Inhibited orgasm Increased sildenafil use Dyspareunia
Ketamine	£20/\$30	Painful frequency	Renal and bladder destruction

*Prices are approximate, researched in 2012.

ketamine use is likely to produce similar changes in the neobladder (Ng et al, 2013).

Patterns of Long-Term Follow-Up

- *Patients not requiring follow-up:* Inguino-scrotal surgery, successful pyeloplasty, resolved reflux, and renal pelvic dilation with normal kidneys
- *Patients requiring follow-up:* Damaged kidneys (especially with a glomerular filtration rate [GFR] < 60 mL/min/1.75 m²), exstrophy, PUV, spina bifida, intestinal urinary reservoirs, anorectal anomalies, cloacal exstrophy
- *Inadequate evidence to decide:* Hypospadias, unresolved reflux or PUJ “obstruction”

OUTCOME MEASURES

Renal Function

Patients with congenital abnormalities of the kidneys and urinary tract (CAKUT) have a significant risk for renal failure in adulthood. There is a close relationship between bladder dysfunction and renal damage, especially in utero and in early infancy. In babies born with exstrophy, for example, the kidneys are almost always normal (Turner et al, 1980). Subsequent renal damage is, therefore, a consequence of surgical management. In boys with PUVs, on the other hand, it is probable that irreversible damage is done to the kidneys in utero, by the bladder dysfunction (Woolf and Thiruchelvam, 2001). This is reflected in the observation that the incidence of end-stage renal failure (ESRF) at 30 years of age in 2005 was approximately 30%, unchanged in the previous 15 years (Parkhouse and Woodhouse, 1990; Holmdahl and Sillen, 2005).

The outcome is related to the final GFR after corrective surgery. Adolescents with a GFR above 60 mL/min/1.75 m² are likely to avoid renal failure providing there are no additional renal insults. Below this level, the incidence of ESRF increases (Table 152-3) (Neild et al, 2004). Renal function is usually stable until the onset of proteinuria. Once proteinuria exceeds 50 mg/mmol creatinine (0.5 g/day), deterioration is inevitable. However, the rate of functional loss in CAKUT is slower than for other progressive forms of renal disease and rarely exceeds 3 mL/min/yr. It can be slowed, but not prevented, by angiotensin-converting enzyme inhibitors (ACEIs) (Neild, 2009). Monitoring of proteinuria and renal function at least annually is essential.

Hypertension

Damaged kidneys are the most common cause of hypertension in childhood and adolescence. Although any renal damage can lead to hypertension, the asymmetric, shrunken kidneys called *renal dysplasia* are the most common culprit (Lewis, 2008).

TABLE 152-3 Incidence of ESRF after 16 Years According to the GFR in mL/min/1.75 m² at Age of Entry*

GFR AT ENTRY	INCIDENCE OF ESRF AT 16 YEARS OF FOLLOW-UP (%)
51-60	15
41-50	35
31-40	70
15-30	90

*Usually the end of puberty.

ESRF, end-stage renal failure; GFR, glomerular filtration rate.

Data from Neild GH, Thomson G, Nitsch D, et al. Renal outcome in adults with renal insufficiency and irregular asymmetric kidneys. BMC Nephrol 2004;5:12-22.

Once renal dysplasia (reflux nephropathy) was considered a disease of girls with recurrent urinary tract infection (UTI) (Hodson and Edwards, 1960), but when adults present with asymmetrical irregular kidneys, only 10% to 20% have a history of UTI or any concomitant diagnosis in childhood (Neild et al, 2004).

The incidence of hypertension is difficult to determine partly because of selection bias in different series and partly due to different definitions. Normal blood pressure increases with age during adolescence; if only an adult definition of hypertension is used, the incidence will be underestimated. The 50th percentile for diastolic blood pressure at 16 years of age is approximately 76 mm Hg (Blumenthal et al, 1977).

If long-term monitoring of blood pressure is the only adolescent requirement, it can be done in the community, providing the facility is available and the patient is adequately motivated.

Bladder Function

The close relationship between bladder and renal function is particularly seen in spina bifida. In a long-term follow-up of an unselected group of patients with spina bifida, 50% died by 35 years of age. Of the deaths, 25% in childhood and 32% in adulthood were due to ESRF as a result of bladder dysfunction and a leak point pressure above 40 cm H₂O (Wang et al, 1988; Hunt and Oakeshott 2003). This outcome can be largely prevented by aggressive early bladder management (Dik et al, 2006).

There is also a group of patients with chronically dilated urinary tracts in whom overfilling of the bladder causes upper tract deterioration but with low pressure. In this group it is often possible to define a critical bladder volume above which the kidneys do not drain and function deteriorates. If the volume is kept below this

level, renal function is, at least, stabilized and may be improved (Hale et al, 2009).

In patients with deteriorating renal function or increasing hydronephrosis (especially in the absence of proteinuria), investigation of bladder function is essential.

Continence of Urine

The problem with continence is not so much keeping the urine in, but keeping it in and getting it out in a socially acceptable and timely manner. Despite the fact that we intuitively know what is meant by *continence*, it has proved difficult to put a concise definition in writing. The expression “the dry interval” that is widely used in pediatric practice is not acceptable to the adolescent—what happens when the interval is exceeded? With this as the definition, the answer is that leakage begins. Adolescents want to go to the bathroom when it is convenient to them and not when it is convenient for the bladder.

Much effort has gone into constructing continent storage and emptying systems. Success requires a low-pressure reservoir with a capacity of approximately 500 mL, a conduit to the outside, a means to keep the urine in, and a means to empty it. The results of the various reconstructions are discussed elsewhere.

For emptying, many rely on clean intermittent self-catheterization (CIC) first described by Lapedes and colleagues (Lapedes et al, 1972). Fortunately, this is a system that has stood the test of time (Diokno et al, 1983). In most series of patients with continent reconstructions designed for CIC, more than 90% are continent.

The artificial urinary sphincter can be used in some conditions. However, there is a significant complication rate and need for replacement (or removal), especially when the urethra has undergone reconstruction. In one of the biggest series in children and young adults with a variety of diagnoses, the half-life of the AMS 800 sphincter (American Medical Systems, Minnetonka, MN) was 15 years on a Kaplan-Meier curve, but because the mean follow-up was only 7.5 years and the maximum 17 years, the result is likely to be overly optimistic. Of the patients in one group, 86% were continent but only 22% of them were able to void, with the rest performing CIC (Herndon et al, 2003).

None of the reconstructions is perfect. All have long-term problems for which monitoring is needed by imaging and biochemical screening at least once per year.

Sexuality, Fertility, and Pregnancy

These aspects are possibly the least well dealt with in pediatric practice. Therefore it is essential to raise them early after transition. Disability must not be a barrier to normal sexuality.

Within the spectrum of conditions in adolescence there are some that are incompatible with penetrative intercourse without some reconstruction, such as aphallia or Rokitansky syndrome. There are others in which intercourse is difficult, such as exstrophy, though men still manage intercourse in 75% to 100% of cases (Stein et al, 1996; Woodhouse 1998, 1999). Ultimately, the huge majority of patients will be able to have some form of sexual activity.

With the very severe abnormalities, special efforts must be made. In patients with spina bifida there is a woeful lack of sexual education. In a review in 1999, only 5% of young adults with spina bifida thought they had received adequate sexual education (Sawyer and Roberts, 1999). Intercourse is infrequent in those with spina bifida, but 90% of girls and all men without hydrocephalus have experienced intercourse, sometimes with sildenafil (Verhoef et al, 2005). Even men with micropenis (>2.5 standard deviations below mean stretched length) largely behave in a heterosexual manner, and 60% have satisfactory intercourse (Woodhouse, 1998).

In males, fertility may be impaired through testicular failure or obstructed sperm transport. However, at least in spina bifida, if the neurologic lesion is so high that natural erections do not occur (around T12 or L1), the testes do not have germ cells (Reilly and

Oates, 1992). In practice, therefore, men with exstrophy, PUV, hypospadias, spinal bifida below L1, and unilateral undescended testis are fertile. In some, however, reproductive technology may be needed (Woodhouse, 1998). There is early, but unconfirmed, evidence that men with PUV have abnormal semen that is thick and of very high pH and may reduce fertility (Woodhouse et al, 1989).

Females are fertile if they have normal internal genitalia that have not been damaged by surgery. Girls with DSD, especially congenital adrenal hyperplasia, may have reduced fertility even with normal genitalia because of deficient hormones (Mulaikal et al, 1987; Zacharin, 1999).

Pregnancy and delivery are primarily a problem in those with an inadequate pelvis, especially spina bifida and those in whom urine is stored in an intestinal reservoir. **Joint care of pregnancy between an adolescent urologist and an obstetrician is essential.**

In women with spina bifida (and the wives of men with spina bifida), it is essential to advise supplementation for at least 3 months before conception with folic acid 5 mg/day to limit the risk for a fetus with a neural tube defect (Medical Research Council Vitamin Study Research Group, 1991). During pregnancy, urologic problems, especially infections, are magnified (Visconti et al, 2012). Cesarean section (C-section) should be done only for obstetric reasons, because there is a high complication rate and slow recovery (Arata et al, 2000).

The urine of patients with intestinal reservoirs, male and female, is positive on human chorionic gonadotropin testing for pregnancy on 56% of occasions. It is most important that this high incidence of false-positive tests is impressed on all girls at the earliest opportunity. It is important not only for women who wish to be pregnant but to avoid disaster in those who do not (Nethercliffe et al, 2001; Nakhal et al, 2012).

In women with intestinal urinary reservoirs there is also an increased risk for infection. As the uterus enlarges, ureteric obstruction may occur in approximately 10% and requires nephrostomy and stenting. The reservoir may become compressed, reducing its functional volume. Self-catheterization may become difficult. Many women prefer to leave an indwelling catheter in the pouch during the last trimester (Greenwell et al, 2003). The main risk with delivery is the need for an emergency C-section. As the reservoir and its vascular pedicle lie in front of the uterus and particularly the lower segment, there is a substantial risk that it will be damaged in emergency surgery. It is safest to do an elective C-section in all such women.

Pregnancy in women with exstrophy remains difficult. In a series of 57 pregnancies in 19 women there were 34 live births. The rate of miscarriage was high, at 35%. There were 4 still births or neonatal deaths and 4 major delivery complications. They are clearly high-risk pregnancies and require specialist care (Deans et al, 2012).

Quality of Life

As an outcome, quality of life is not easy to measure, especially in the ever-changing environment of adolescence. Most attempts in urology have either focused on the views of caregivers, rather than the patients, or asked the wrong questions. In a comprehensive review of English language publications on quality of life, Gerharz and colleagues (2003) identified 30,000 from 1980 to 1998. Of these, 3600 were about children and adolescents and only 360 asked the opinion of the patients themselves. Only two asked adolescents their opinion on a specific urologic condition.

Instruments are available to measure the several domains of quality of life. Inevitably, they are concentrated on large groups so that normative values can be defined. They can be applied to adolescents, even with rare conditions, to examine aspects such as continence and emotional well-being. Even then, there may be questions that are of great importance to a specific group but not considered in a general instrument. For example, adolescents born with exstrophy dislike the absence of a normal umbilicus and wish to avoid being treated as “abnormal.” Such concerns emerge on detailed questioning but not with quality-of-life instruments with

TABLE 152-4 Occupation Audit Results by Diagnosis^a

	N	PROFESSIONAL ^b	ADMINISTRATIVE ^c	SKILLED ^d	UNSKILLED ^e	NOT EARNING ^f
Exstrophy	65	19	7	21	6	12
Spina bifida	20	10	1	2	1	6
Ano/rectal	11	2	1	2	2	4
Ureteric	8	3	0	2	1	2
PUV	6	2	2	0	1	1
Other	16	7	0	0	2	7
TOTALS (%)	126	43 (34)	11 (9)	27 (22)	13 (10)	32 (25)

PUV, posterior urethral valve.

^aThis table shows the results of a questionnaire undertaken in the adolescent clinic at University College London Hospital over an 8-week period in 2010. All patients were asked to name their current occupation, which was recorded against their principal diagnosis. No patient refused to answer.

^bProfessional examples: Doctor, intensive therapy unit nurse, teacher, bomb disposal, film director, pilot, information technology (IT) academic.

^cAdministrative examples: Social worker, practice manager, bookkeeper.

^dSkilled examples: Farmer, IT technician, footballer, comedian, electrician, shoemaker.

^eUnskilled examples: Telesales, decorator, receptionist, caretaker, disc jockey, chauffeur.

^fNot-earning examples: Student, housewife, unemployed, ill.

Modified from Woodhouse CRJ, Neild GH, Yu RN, et al. Adult care of children from pediatric urology. *J Urol* 2012;187:1164–71.

which patients with exstrophy are found to be “normal” (Wilson et al, 2007).

Investigations of urinary tract reconstruction and diversion have failed to identify dramatic differences in quality of life among the various systems or even between those that are continent and those that require a stoma bag. The exception is in the domains of body image and intimacy, which are of paramount concern to adolescents and young adults. Older patients, usually being operated for malignancy, are often more phlegmatic and may prefer the simplicity of a stoma over the perceived virtues of a continent reconstruction. In the very major congenital anomalies the same views also may be present; the urologic problems may be seen as only a small component of living with a cloaca or cloacal exstrophy. In unpublished work, Liao and associates (personal communication, 2013) have shown that women born with a cloaca prefer to have a urinary system in which they can have confidence rather than one that may be less visible but more troublesome (Liao et al, 2014).

Adult urologists should be aware that, in spite of many physical and emotional difficulties, adolescents with major congenital anomalies have an overwhelming desire to be normal, to be treated as normal, and to become normal adults. Their success may be measured from a survey of occupations they achieve (Table 152-4) (Woodhouse et al, 2012). Patients view their medical care not as an end in itself, but as a pathway to a normal life.

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The complete reference list is available online at www.expertconsult.com.



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KEY POINTS: OUTCOME MEASURES

- Urinary continence
- Preserved renal function
- Normal blood pressure
- Establishment of partnership
- Sexuality and fertility
- Education and employment
- Quality of life, especially the recognition that disability is compatible with normal life goals

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Pretransplant Assessment

Pretransplant Preparation

Transplantation

Complications

Summary

The child requiring renal replacement will more often than not be a boy with an obstructive uropathy. The challenge for the pediatric urologist is to ensure that the damage done to the native kidneys will not be repeated with the transplanted kidney. These patients are some of the most complex children to care for, mostly in developing a therapeutic plan to provide for several goals: (1) normal urinary drainage from the kidney into a reservoir, (2) a reservoir that permits low-pressure storage for a socially acceptable time, (3) volitional emptying of the reservoir, and (4) absence of infection, (5) all with the fewest surgical procedures and patient trauma. These goals are achievable, but it must be clear that until they are ensured, renal transplantation should be deferred, or a plan to achieve them with assurance of patient and family compliance must be in place.

Patient and family understanding and compliance are essential for successful urologic management of the child with an abnormal urinary tract and end-stage renal disease (ESRD). The integration of the entire care team in this preparation is also critical and demands a close working relationship among the urology team, the pediatric nephrology team, and the transplant team. The urologist must have a basic understanding of the needs and constraints of the nephrologists and transplant surgeons, if they are not performing the entire transplant. The ureteral implantation can be performed by the urologist or the transplant surgeons, but this should be dependent on the state of the bladder and the comfort level of the surgical teams with the particular aspects of the surgery and their postoperative management, including any complications.

PRETRANSPLANT ASSESSMENT

Screening

A large fraction of children in need of renal replacement will have some type of uropathy—congenital obstruction, vesicoureteral reflux, or neuropathic bladder dysfunction (North American Pediatric Renal Trials and Collaborative Studies [NAPRTCS], 2008; Van Arendonk et al, 2014). Younger boys will typically have obstructive uropathy, including posterior urethral valves, whereas the reflux and neuropathic bladder patients will be older, including young adults. Some children will have uncharacterized ESRD, and it is reasonable to have all children screened for urologic issues before transplant. A detailed history, renal ultrasonography, and postvoid residual urine volume by ultrasonography can effectively rule out most significant uropathies. Routine voiding cystourethrogram (VCUG) is not necessary unless there is a history of a specific urologic disease, febrile or recurrent urinary tract infection (UTI),

hydronephrosis, or clinically abnormal voiding (Ramirez et al, 2001; Singer et al, 2009) (Fig. 153-1).

Focused Assessment

The child with a known urologic abnormality will require a pretransplant assessment directed by the underlying condition and the status of the bladder and kidneys. In most, a VCUG will be useful to permit an assessment of voiding function, the state of the urethra, and the presence of reflux. When bladder dynamics are abnormal based on the VCUG or a renal sonogram, consideration for urodynamic evaluation is appropriate. The indications for urodynamic testing to assess bladder capacity, compliance, and emptying, as well as sphincter function, include a known neuropathic bladder abnormality, prior severe posterior urethral valves, and any ongoing voiding dysfunction, hydronephrosis, or recurrent UTI (Burns et al, 1992; Zermann et al, 2003; Riley et al, 2010). The principal goal of the urodynamic testing is to determine the need for further therapy for bladder function. This might include medical therapy with anticholinergics, the use of intermittent catheterization, and the potential need for bladder augmentation in severe cases.

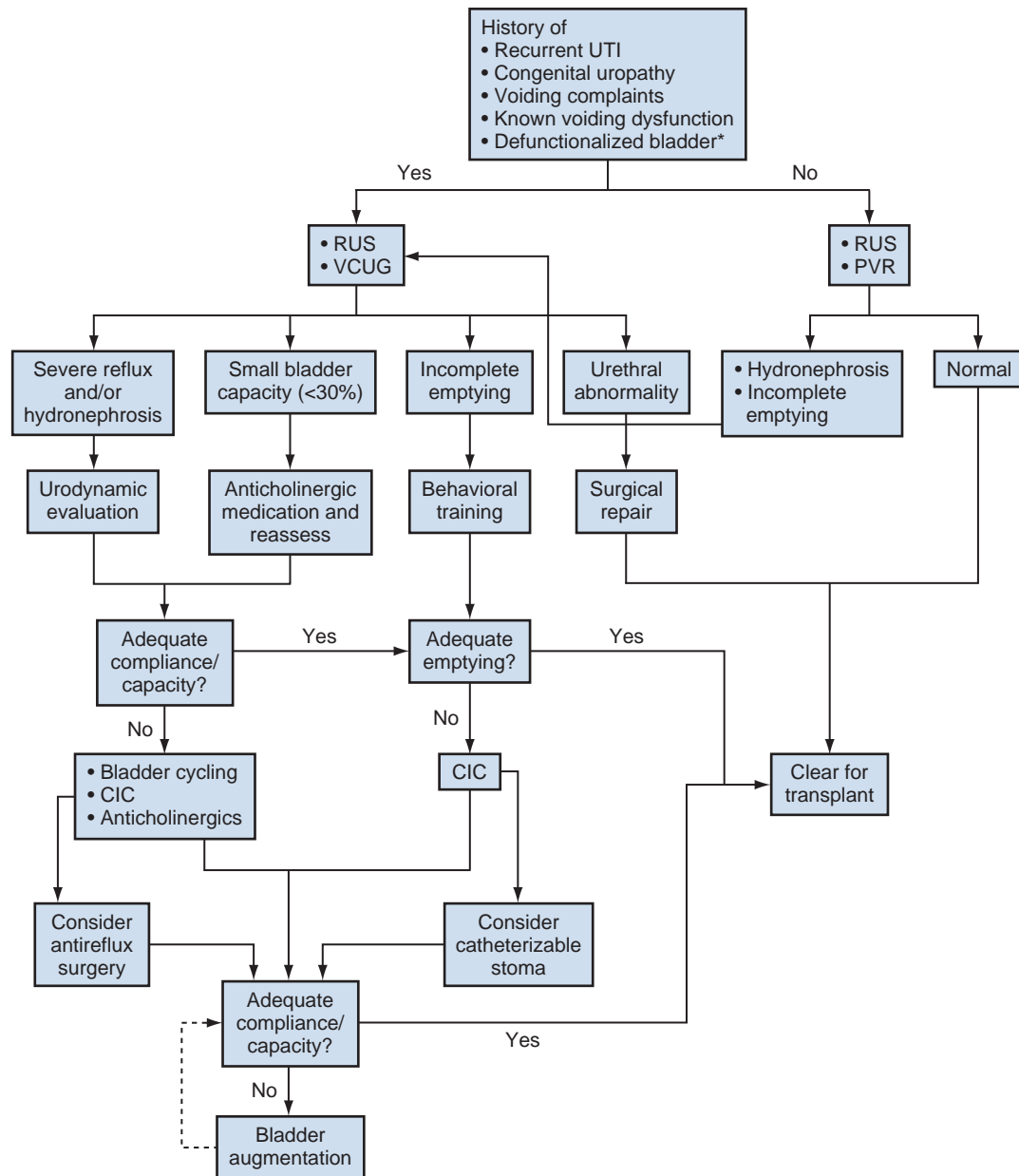
Urodynamics will also provide insight into bladder emptying function, which will be critical to prevent infection. Of course, if medical therapy for a noncompliant bladder is needed, this may impair bladder emptying and necessitate clean intermittent catheterization (CIC) to permit effective emptying. In the sensate child or in some with neuropathic bladders, the creation of a continent catheterizable stoma may be the ideal way to facilitate effective CIC. These decisions should be made and executed before transplant. Urodynamic evaluation will often be a regular monitoring evaluation in these children, and a critical element in ongoing optimization of bladder function. It will often be necessary to repeat the study to ensure that the therapeutic intervention has been effective and that the bladder is prepared for the transplant.

PRETRANSPLANT PREPARATION

Bladder Preparation

General Issues

The most common bladder abnormality associated with ESRD is the low-capacity, hypertonic bladder with poor compliance. This is the typical picture with posterior urethral valves, but it is important to recognize that these bladders continue to evolve and may



*If patient is anuric and has no urologic history, no further testing is essential; if there is a history of neurogenic bladder, posterior urethral valves, or complex urologic condition, consideration of bladder cycling and anticholinergics is appropriate.

Figure 153-1. Algorithm for evaluation and management of the bladder in patients in preparation for renal transplantation. The key element is the history of urologic conditions or symptoms. CIC, clean intermittent catheterization; PVR, postvoid residual; RUS, renal ultrasonography; VCUG, voiding cystourethrogram.

progress to a pattern of insufficient contractility to empty at all (Peters et al, 1990; Nguyen and Peters, 1999). They may still be hypertonic and pose ongoing renal risk and will require CIC in most cases. Hypertonicity is the most dangerous dynamic pattern because it will create an obstructive condition for the kidneys, even in the absence of reflux. Bladder dysfunction can increase graft loss (Herthelius and Oborn, 2007).

Hypertonicity

The hypertonic bladder is managed with medication as a first line, typically with anticholinergics, and with augmentation as the second line (Lopez Pereira et al, 2000). Medical management

requires diligence on the part of the family and follow-up that regularly assesses the response to therapy. It will usually require a combination of anticholinergics and CIC, although some children with posterior urethral valves can learn to void by Valsalva maneuver. It should never be assumed that they will be able to do so; they must demonstrate this by repeated low postvoid residual volumes on catheterization.

Anticholinergic therapy is best titrated with increasing doses, and watching for a change in catheterized volumes, wetting, and hydronephrosis. Urodynamic evaluation can more precisely define the efficacy. Often, medical therapy is introduced at the same time as CIC, although this is not essential. Compliance with CIC is often an excellent test of future patient and family compliance with the

KEY POINTS: UROLOGIC EVALUATION AND MANAGEMENT

- Goals:
 - Normal urinary drainage from the kidney into a reservoir
 - A urinary reservoir that permits low-pressure storage for a socially acceptable time
 - Volitional emptying of the reservoir, with continence
 - Absence of infection
 - The fewest surgical procedures and patient trauma
- A large fraction of children in need of renal replacement will have some type of uropathy—congenital obstruction, vesicoureteral reflux, or neuropathic bladder dysfunction.
- Pretransplant assessment is directed by the underlying condition and the status of the bladder and kidneys.
- Urodynamic testing aims to assess bladder capacity, compliance, and emptying, as well as sphincter function.
- Indications for urodynamics include a known neuropathic bladder, prior severe posterior urethral valves, and any child with ongoing voiding dysfunction, hydronephrosis, or recurrent UTI.

stringent requirements of renal transplant. If a family is unable to manage with CIC, their ability to manage medical care after a transplant should be questioned.

The goal of therapy is for the child to be able to hold up to capacity for age, at low pressure (<30 cm H₂O). I have had some success at teaching parents with children on CIC to measure the opening pressures at catheterization by estimating the height of the water column in the catheter. This may be a more natural measurement, although the strict correlation with outcomes has not been defined.

Capacity

Bladder capacity is another element of normal function and is the basis for both safe storage and social continence. Bladder capacity can be improved with anticholinergic medication but may ultimately require bladder augmentation. There is a clear shift away from augmentation in all patients, and there have been prior reports that augmentation is not needed in renal transplant (Alfrey et al, 1997; Salvatierra et al, 1999). Augmentation remains a necessary aspect of urologic management in children with complex uropathies with ESRD. Current indications would include nonsalvageable bladder (exstrophy, tumor, severe end-stage neuropathic bladder) or failure of medical and CIC therapy to achieve low-pressure storage for up to 3 hours. If pressures are safe for 1 hour only and the rest of the time they exceed 40 cm H₂O despite aggressive medical and catheterization therapy, consideration for augmentation is important.

There is no evidence, nor logic, that bladder augmentation in itself increases the risk of transplant, despite some reports (Alfrey et al, 1997), and indeed, it has permitted many effective transplants into very abnormal bladders (Sheldon et al, 1994; Koo et al, 1999; Luke et al, 2003; Taghizadeh et al, 2007; Djakovic et al, 2009; Broniszczak et al, 2010). There is no single approach that is ideal, although gastric augmentation gained popularity for ESRD children in the late 1980s and early 1990s. It offers the benefit of secreting acid in a patient who is typically acidotic, it can limit infection, and it has a lower rate of bladder stones (Traxel et al, 2011). Gastric augmentations, have, however, been linked with severe complications, particularly in the pretransplant anuric group, because of gastric juice injury of the native bladder segment and because of the fairly common hematuria-dysuria syndrome (Reinberg et al, 1992; Nguyen et al, 1993). Reports of malignancy, particularly in the transplant group, are worrisome, but are still too anecdotal for practice to be changed (Castellan et al, 2007; Husmann

and Rathbun, 2008). Caution and monitoring are essential. Composite gastric augmenting patches are useful and may have less morbidity. Ileum and sigmoid are all useful and may be more appropriate in some patients, depending on anatomy, prior surgery, and preferences for continent catheterizable stomas.

The augmented patch rarely will create an issue with the transplant, but the fact of the pedicle being present and its anatomic orientation must be recognized by the transplanting team. Similarly, continent stomas should be placed in such a location as to avoid conflicting with the anticipated transplant incision(s), and nearly always may be positioned medial to these. Again, recognition of the location and presence of the mesentery for the stoma is important.

The infant receiving a transplant may have an aortic anastomosis to the renal vessels, which will create a potential need to mobilize the mesentery of the augment or stoma. Coordination between the reconstructive and transplant teams is essential.

Infections

Many children with complex reconstruction of the urinary tract will have a history of recurrent UTI. This may be associated with intermittent catheterization. This is a potential hazard for the transplant, and pyelonephritis of the graft is certainly associated with graft loss (Dunn et al, 1987; Hanevold et al, 1987; Neuhaus et al, 1997; Howie et al, 2002; Herthelius and Oborn, 2007). The underlying cause of the infection is most likely inadequate emptying of the reservoir, either by catheterization or voiding, or urinary obstruction with hydronephrosis (Chu et al, 2013). This needs to be assessed and addressed in advance of the renal transplant. Strategies include double and triple voiding to avoid using CIC or, if CIC has already been instituted, ensuring adequate emptying or teaching proper methods to ensure emptying. In general, UTIs are not seen to present a major threat to the renal graft as long as they are managed appropriately (Fallahzadeh et al, 2011; Traxel et al, 2011).

Persistent UTI in the face of appropriate technique for CIC suggests either an anatomic abnormality that has not been detected or chronic colonization. The latter will sometimes respond to long-term antibiotic courses using agents including the fluoroquinolones and cephalosporins. The etiology and specific therapy for this situation are uncertain. Anatomic abnormalities such as diverticula may require more specific imaging studies but may be amenable to surgical cure, including a bladder diverticulum or nondraining ureteral stump; these are uncommon.

Clean Intermittent Catheterization

The use of CIC in managing the abnormal bladder has been a truly revolutionary lifesaver in the last four decades. Although it may be a challenge to initiate, once started it is nearly always well accepted. Careful preparation, teaching, support, and follow-up are critically important for long-term success.

The importance and principles of CIC must be well understood by the care providers and carefully communicated to the family, including all possible caregivers. The recognition that this is a means by which to reduce infection and attain both safe bladder storage and control over voiding is very important and yet may not be readily apparent on first pass.

The frequency of CIC must be determined by a measure of approximate urine outputs, as well as storage pressures based on urodynamic assessment or by home-catheterization opening pressure measurements. This permits an estimate of safe pressure-volume relationships for day-to-day life. Avoiding regular excesses of these volumes and therefore high pressures will facilitate healthy kidney function. The typical frequency is between 3 and 4 hours. Pressures should not exceed 40 cm H₂O for any prolonged period of time.

Initiating CIC in preparation for transplantation serves an assessment purpose as well. For families in which follow-through may be imperfect, CIC is a useful means of determining their commitment and ability to follow complex medical care plans. If CIC

cannot be instituted before transplant to manage an abnormal bladder, there is no reason to believe this ability will suddenly appear after transplant. **The response to CIC can predict the ability to manage the necessary transplant medication and care regimen as well.** The committed and understanding family will manage well, and this will serve to demonstrate their readiness for transplant.

The Defunctionalized Bladder

Neuropathic Bladder

The defunctionalized neurogenic bladder is becoming scarce because of better management but will occasionally manifest clinically in a transplant patient who has not had ongoing urologic care (Firlit, 1976; Serrano et al, 1996). **It is impossible to know without testing what the potential function of the bladder may be. It is also important to recognize that the bladder that has been defunctionalized will take some time to reach its maximal functional potential. This is often best accomplished by bladder cycling to increase capacity, determine bladder wall compliance, and assess the family's ability to perform CIC.**

Some have advocated simply implanting the transplant ureter into the bladder and anticipating normal function (Salvatierra et al, 1999). Although this may occur on rare occasions, it is a highly risky approach to the chronically defunctionalized bladder.

Cycling the defunctionalized bladder is best accomplished through a progressive program of catheterization with instillation of increasing volumes of saline, with a set dwell time and then catheter drainage (Alam and Sheldon, 2008). The amounts will be determined empirically based on initial tolerated volumes and should increase at regular intervals, usually 10 to 15 mL per day. The response to these instillations will give useful clues as to the utility of the bladder as a reservoir and any ability to empty spontaneously. Adjunctive anticholinergic medications are often necessary to increase bladder capacity and compliance.

The defunctionalized neurogenic bladder will almost certainly require intermittent catheterization for emptying. It is therefore reasonable to introduce this to the family. In the rare instance wherein the child can learn to empty satisfactorily, CIC may no longer be needed. This is a major step and requires a careful study of voiding diaries, postvoid testing, and assessment of the upper renal tracts.

The target volume is the anticipated capacity for age based on any of the available formulas (Koff, 1983; Kaefer et al, 1997). This may not be reached immediately, but if volumes increase steadily without significant leakage, further expansion is likely. Although storage capacity is important, compliance is equally critical, and this must be assessed formally with urodynamics. Only if capacity and compliance parameters near normal can be reached should the patient be cleared for transplant. Aggressive medical management is also important in this determination. If adequate storage and compliance cannot be attained, consideration for augmentation must be entertained. This should be performed before transplant unless there are pressing reasons.

Non-Neuropathic Bladder

The defunctionalized bladder associated with renal insufficiency is often attributable to posterior urethral valves or vesicoureteral reflux. These bladders may be more often salvaged to ultimately permit spontaneous voiding but should initially be approached as defunctionalized neurogenic bladders, with the assumption that CIC will be needed long term. The critical factor will be the storage capacity, and progressive cycling as described earlier can provide that assessment. At the same time, children can be asked to attempt to void after holding the instilled saline for a period of 15 or 20 minutes. Postvoid catheterization then is used to determine the postvoid residual volume.

The ability to empty spontaneously will also affect the decision regarding the need for a continent catheterizable stoma. This is more critical in boys with normal sensation, who may be

very resistant to urethral catheterization. The period of pretransplant CIC will permit assessment of both voiding ability and tolerance of urethral CIC. These decisions are best made concurrently with other reconstructive choices to permit an integrated strategy and a single surgical procedure if possible.

The Decision to Augment

Although the use of bladder augmentation is declining because of concerns regarding metabolic, infectious, and neoplastic complications, enterocystoplasty remains the most effective means to provide normal bladder storage function in both neurogenic and postobstructive bladder dysfunction (Barnett et al, 1987; Sheldon et al, 1994; Hatch et al, 2001; Nahas et al, 2002; DeFoor et al, 2003; Capizzi et al, 2004; Mendizabal et al, 2005; Rigamonti et al, 2005; Aki et al, 2006; Traxel et al, 2011). To lose a renal graft as a result of the same processes that contributed to native renal demise is unacceptable. The potential complications of augmentation must also be clearly recognized and anticipated, although some reports have presented extreme examples that are not my experience (Alfrey et al, 1997). A strategy of aggressive intermittent catheterization with medical management becomes the best approach to identify patients in whom augmentation is the only real option for successful renal transplantation. It is difficult to determine a meaningful incidence of the need for augmentation, because the effort expended by both family and health care team varies as much as the underlying pathology. With early aggressive bladder management, the need for augmentation in both neurogenic and obstructive bladder dysfunction has been declining.

Broad indications for augmentation before transplantation would be the inability to develop capacity greater than 75% of expected for age with pressures below 30 cm H₂O, using catheterization that is no more frequent than every 3 hours and using maximal anticholinergic medications. Tolerance to medication will obviously be an important element of these criteria. These thresholds are rules of thumb without strong clinical data to support them. Exceptions can be found wherein bladder capacity improves markedly after transplant, perhaps because of the effects of uremia, but they should serve as guidelines for determining when to augment before transplantation.

The availability of a dilated ureter to permit ureterocystoplasty (Kim et al, 1996; Landau et al, 1997; Kurzrock et al, 2002) should be explored, although results have been mixed. It is preferable to perform enterocystoplasty in this context, and efforts should be made to preserve the ureter when possible for this use, or for a continent catheterizable channel.

KEY POINTS: PRETRANSPLANT PREPARATION

- The most common bladder abnormality associated with ESRD is a low-capacity, hypertonic bladder with poor compliance.
- There is no evidence that bladder augmentation increases the risk of transplant.
- Recurrent pyelonephritis is a potential hazard for the transplant and is associated with graft loss.
- Initiating CIC in preparation for transplantation serves an assessment purpose as well as facilitating bladder emptying.
- Bladder refunctionalization is often best accomplished by bladder cycling to increase capacity, determine bladder wall compliance, and assess the family's ability to perform CIC.

Cutaneous Stomas

The defunctionalized bladder may be associated with a variety of urinary diversions, including ileal and colon conduits, as well as

ureterostomies. In the past, transplantation was performed with the ureters draining into the diversion. This is rarely appropriate today, although it remains an option, but UTIs are frequent (Broniszczak et al, 2010). A functioning ileal loop diversion in the setting wherein augmentation is determined to be necessary can be used as the augmenting patch with bladder refunctionalization, even if the patient is anuric. If augmentation is not needed, based on CIC cycling, and the patient continues to make urine and the native kidney will not be removed, it should be implanted to refunctionalize the bladder, and the loop discarded. If there is uncertainty regarding the need for augmentation, the loop may be preserved to be available for augmentation after transplant if essential.

Reconstruction Strategies

If bladder reconstruction will be needed, several factors must be considered in anticipation of the ultimate renal transplant. These considerations reflect the type of dialysis (either hemodialysis or peritoneal dialysis), likely placement of the graft, timing relative to both initiation of dialysis (if not already begun) and transplantation, the need for bowel surgery, and the native kidneys. Consideration of these factors will permit a more coordinated and efficient reconstruction.

Dialysis Issues

If a patient is already on peritoneal dialysis, any intraperitoneal surgery will likely require temporary transition to hemodialysis. Limiting this to one procedure is valuable. At times this can be linked with placement of a peritoneal dialysis catheter, but if bowel surgery is needed, this may increase the risk of infectious complications.

If the patient is not yet on dialysis but is approaching the need, there may be some consideration for initiating dialysis before reconstruction to improve the overall medical status of the child. This can promote more rapid wound healing and fewer complications. At the same time, this will affect the child on peritoneal dialysis as noted, and for those on hemodialysis, there is a risk of fistula injury during surgery because of low flow states, as well as direct pressure.

Graft Placement

Consideration should be given to the likely location of the graft. In the very small child in whom the graft will be placed intraperitoneally on the aorta, careful movement of any mesenteric pedicles away from the midline is advisable, as is trying to avoid a transuretero-ureterostomy. A psoas hitch for ureteral reimplantation of the native kidney, if it is to be salvaged, can make ipsilateral iliac graft placement difficult. There may be no feasible alternatives, and in such cases, careful documentation of the procedure is essential.

Timing

In general, any major urologic reconstruction should be undertaken well before anticipated transplantation (Taghizadeh et al, 2007). Minor ureteral surgery may be considered at the time of transplantation, but this is unusual. After enterocystoplasty or continent diversion, at least 6 weeks is needed for healing and 3 months would be preferable. Unilateral native nephrectomy is reasonable at the time of transplantation, but only in older children. Operative time in the infant may have more of a negative impact on graft function, and it seems imprudent to add this extra risk.

Enterocystoplasty

Enterocystoplasty in the setting of a dialysis patient or a child approaching ESRD is feasible and, when needed, can be successfully accomplished in a manner similar to that in any other child (Sheldon et al, 1994; DeFoor et al, 2003; Taghizadeh et al, 2007). The selection of bowel segments and reconstructive strategy

should be based on the functional anatomy and needs of the individual child. These include factors such as the need for a continent catheterizable stoma, the availability of native bladder tissue, the status of the bladder neck and continence mechanism, and bowel function. **If continent diversion is needed because of an unsalvageable bladder, there is no reason to defer this until after transplant.** The often-quoted contraindication to continent diversion in the setting of renal impairment is not applicable to these patients. They will need medical management of the metabolic effects of the diversion, but they require aggressive metabolic management at baseline. In some cases, by improving bladder dynamics and limiting infection, the progression to end-stage disease may be delayed.

The use of gastric segments was considered particularly appropriate for the child approaching end-stage failure and in selected patients can still be useful (Burns et al, 1992; DeFoor et al, 2003; Traxel et al, 2011). Because of the various complications of gastrocystoplasty, however, this approach has been used much less. The benefit of acid excretion for the child with chronic kidney disease can be helpful, but these children are also at risk for complex metabolic derangements with alkalosis. For the anuric child, the presence of gastric secretions in the empty bladder can lead to erosion and even perforation (Reinberg et al, 1992). Care must be taken in those children to use proton pump inhibitors and to irrigate with bicarbonate solutions until urine output is restored.

Native Nephrectomy

The decision regarding native nephrectomy must be made as a multidisciplinary team involving nephrology and urology providers as well as the family. There is controversy in this regard, and although in general it is preferable to leave the native kidneys (Fraser et al, 2013), **there are several situations where removal pretransplant is necessary. These include malignant hypertension, profound nephrotic syndrome with malnutrition from protein losses (Kim et al, 1992), recurrent upper tract infection, and massive reflux.** The last may be more relative, but with stasis and possible infection in an immunosuppressed child, removal is preferable and less risky. The usefulness of leaving a native kidney that produces some urine is in making dialysis more manageable with fewer fluid restrictions. This can facilitate nutritional support in the younger child. This must be balanced against the possible risks of infection and hypertension, as well as graft function.

In the infant undergoing renal transplantation, native nephrectomy is strongly recommended by some groups to enhance graft survival based on improving blood flow to the graft. Any shunting of blood from the graft in a small child, whose cardiac output may be a small fraction of that of the adult from whom the graft came, may potentially impair early graft function.

In a child in whom native nephrectomy is to be performed, the principal contributing factor is whether peritoneal dialysis is being performed. If so, laparoscopic transperitoneal removal will require temporary hemodialysis. Some have performed immediate peritoneal dialysis, but the risks of leakage with possible infection would argue against this practice. Retroperitoneoscopic nephrectomy can be performed with immediate peritoneal dialysis (Gundeti et al, 2007), but leaks may still be encountered. If the kidneys are small, then this is the optimal approach. For large kidneys in children on peritoneal dialysis, posterior open nephrectomy may be the overall optimal approach.

If peritoneal dialysis is not being performed, then any type of nephrectomy is acceptable. The incidence of postoperative adhesions is limited and is unlikely to affect the efficacy of peritoneal dialysis. There is the potential impact on the ultimate transplant procedure when the distal ureter is to be removed, because this will cause adhesions in the area of the iliac vessels. However, if there is significant reflux or obstruction and a dilated ureter, total removal may be best to limit the risk of infection. Renal embolization has been reported as an alternative to surgical nephrectomy (Capozza et al, 2007).

KEY POINTS: PRETRANSPLANT RECONSTRUCTION

- The ability to empty spontaneously will also affect the decision regarding the need for a continent catheterizable stoma.
- Indications for augmentation before transplantation include the following:
 - Capacity less than 75% of expected for age
 - Pressures below 30 cm H₂O
 - Catheterization every 3 hours
 - Maximal anticholinergic medications
- For patients on peritoneal dialysis, intraperitoneal surgery will likely require temporary transition to hemodialysis.
- In general, any major urologic reconstruction should be undertaken well before anticipated transplantation.
- Native nephrectomy is indicated for patients with the following:
 - Malignant hypertension
 - Profound nephrotic syndrome with malnutrition
 - Recurrent upper tract infection
 - Massive reflux

Managing Native Kidneys***Avoiding Removal***

In the absence of specific indications for nephrectomy, leaving the native kidneys offers the advantage of having a potential source of water excretion if the graft fails. Although this can be helpful in managing nutrition and lifestyle, it should not become a rigid goal if there are reasons to remove the kidneys. Their ultimate utility may be very limited, particularly after a period of graft function, because they often will regress in size and urine output.

Limiting Risk of Infection

Urinary infection in the setting of an immunosuppressed child with a renal graft is damaging to both child and graft. Preventing infection in the child with known urologic concerns is therefore a priority; interventions should be performed proactively, rather than purely in response to an infection. The damage from one infection may be critical to that child. Situations in which active prevention of infection may be useful include high-grade reflux, persisting hydronephrosis (Chu et al, 2013) with or without reflux, and, particularly, the need for intermittent catheterization. These patients are frequently colonized with bacteria and may be more susceptible to UTI. The nondilated, nonrefluxing native kidney is unlikely to be subject to infection and can usually be maintained in the absence of other indications for removal.

Ureteral Preservation

When nephrectomy is to be performed, ureteral preservation should be considered. If the ureter is normal, it should always be left to limit surgical dissection near the iliac vessels and to have an option for proximal transplant to native ureteroureterostomy for distal ureteral stenosis (Kockelbergh et al, 1993; Lapointe et al, 2001). If bladder function is abnormal and intermittent catheterization may be needed, preserving the ureter for use as a continent stoma is advisable. This is best performed pretransplant. Creation of the continent stoma at the time of transplant is an option.

Combining Nephrectomy and Transplant

Native kidneys may be removed at the time of the renal transplantation, but this is usually avoided to limit surgical complexity and time. It may be appropriate for a single native kidney, which may be swiftly removed through the transplant incision. In the absence of specific justification, however, this strategy in general is to be avoided.

TRANSPLANTATION

The technical elements of the vascular component of the transplantation are described in Chapter 47 and are appropriate to children. One exception may be transplantation into the infant wherein the vascular anastomoses are performed on the aorta. This usually is performed with anticoagulation, which may affect bladder surgery. More care with hemostasis is needed. For the pediatric urologist who is not performing the vascular anastomosis, the ureteral anastomosis becomes the focus of attention, as well as of complications.

Ureteral Anastomosis***Surgical Techniques and Options***

As with ureteroneocystostomy for vesicoureteral reflux, there are intravesical and extravesical techniques for the transplant ureteral anastomosis. I have attempted to perform an antirefluxing anastomosis in all cases, although it is clear that this is not essential. Although careful screening can identify patients who have bladder dysfunction and therefore are at risk for graft reflux, the method to prevent reflux is simple and effective and associated with minimal morbidity.

Extravesical ureteroneocystostomy is the preferred ureteral anastomosis. After the vascular anastomoses have been performed and hemostasis has been achieved, the bladder is partially filled with saline or a dilute antibiotic solution. The anterolateral aspect is cleared and traction sutures are placed to mobilize the lateral aspect upward and to provide tension on the vesical wall. The ureter is sized to ensure it will reach. The detrusor is incised to the level of the mucosa for a length of about 3 to 3.5 cm in a horizontal direction. Flaps of detrusor are elevated away from the mucosa and a small disc of mucosa is excised at the distal aspect of the trough. The bladder will drain and the traction sutures keep the trough in position. The ureter is trimmed loosely to length and spatulated for 4 to 5 mm. An interrupted, mucosa-to-mucosa anastomosis is performed using a fine absorbable suture. A monofilament is preferred. The detrusor flaps are then brought over the ureter. No advancement stitch is used, but two stitches are placed through the detrusor and the adventitia of the terminal ureter to prevent eversion of the ureter. The detrusor is closed with interrupted absorbable suture.

Alternatively, the widely used Barry technique (Barry, 1983; Barry and Hatch, 1985) may be used, whereby a 4-cm tunnel is created between parallel incisions through which the ureter is passed. A shorter tunnel has been used in some pediatric centers with reported success in small numbers (Vasdev et al, 2011).

If the bladder wall is particularly abnormal and thick, a longer tunnel is developed and the flaps are dissected back a bit further to provide a more robust antireflux tunnel and limit the risk of obstruction, as these are typically abnormally functioning bladders. Implanting the graft ureter into an augmented bladder poses further challenges, and it is preferable to perform the ureteroneocystostomy into the detrusor. On occasion this has necessitated an intravesical approach through the augment to reach the detrusor, which may be impossible to mobilize effectively otherwise. If there is no detrusor available, anastomosis into a colonic or gastric segment is preferable. It would always be advisable to perform a nonrefluxing ureteroneocystostomy in these settings, because these patients are inevitably on intermittent catheterization and often colonized with bacteria.

I no longer perform a routine open-bladder ureteroneocystostomy for transplant, but a modified Politano-Leadbetter procedure is an effective method. It does introduce a large cystotomy and bladder spasms. In the unusual setting in which this is considered appropriate, there is no specific need for stenting beyond the indications described later.

Transplant to native ureteroureterostomy is performed routinely in a few institutions for pediatric renal transplantation. Results have been reported as acceptable (Lapointe et al, 2001; Gurkan et al, 2006), but this does not seem to be a common

option, and of course its use depends on the availability of a normal, nonrefluxing native ureter. This option is available as a salvage procedure in the setting of distal ureteral stenosis.

Ureteral Stenting

The role of routine ureteral stenting in pediatric transplant is debated, but there are no data to demonstrate its routine usefulness (French et al, 2001; Simpson et al, 2006; Dharnidharka et al, 2008). It has not been the routine for me, but there are situations in which ureteral stenting is appropriate. These situations would include the difficult implant, particularly in an abnormal bladder or with a very damaged graft ureter. In adult series, stenting showed an advantage for cadaveric donors in terms of reducing the incidence of ureteral complications from 5.8% to 1.9% but had an increased risk of infection (Fayek et al, 2012). If a stent is to be used, a short double-J ureteral stent is placed and typically is removed in 4 weeks. This obviously requires a cystoscopy. I have not used extraction strings for children undergoing stented transplants.

KEY POINTS: TRANSPLANT URETERONEOCYSTOSTOMY

- Extravesical ureteroneocystostomy is the preferred ureteral anastomosis.
- Transplant to native ureteroureterostomy is an effective option.
- There are no data to support routine ureteral stenting at the time of transplantation.

COMPLICATIONS

The urologic complications of pediatric renal transplantation are discussed in this section. Those related to the graft directly, including vascular and rejection issues, are dealt with in Chapter 47. Table 153-1 presents a summary of reports of urologic complications in pediatric renal transplantation. The unique analysis of Khositseth and colleagues comparing the incidence of urologic complications in transplant recipients having a history of obstructive uropathy or

reflux with the incidence in those without that history shows the increased risk of all urologic complications in patients with preexisting uropathy (Khositseth et al, 2007). Posterior urethral valves are associated with an increased risk of graft dysfunction in some series (Luke et al, 2003; Adams et al, 2004), but not in others (Nuininga et al, 2001; Fine et al, 2011; Kamal et al, 2011). In nearly all series, however, obstructive uropathy is associated with a higher risk of urologic complications. Special vigilance and a lower threshold for intervention are appropriate in this population.

Urine Leaks

Urine leaks are typically identified in the early postoperative period with increasing fluid from the wound drains. The fluid creatinine level can reveal if this is a urine leak as opposed to lymphatic drainage. At first presentation, it is critical to assess all urinary drainage tubes, particularly the Foley catheter. If the catheter has been removed, it is often best to replace it. A transplant sonogram is performed to determine if there is hydronephrosis, although its absence does not rule out obstruction. If hydronephrosis is present, distal ureteral obstruction should be suspected and consideration for a percutaneous nephrostomy should be entertained. The level of the leak must then be determined, and either a mercaptoacetyl-triglycine (MAG3) scan (assuming adequate graft function) or a computed tomography (CT) scan can be effective. A cystogram may be useful to identify a bladder leak from the site of the anastomosis.

The indications for intervention are clinically based, and if the leak is limited, an observational approach is reasonable. I have seen leaks in the setting of very high post-transplant urine output in smaller children caused simply by a small bladder catheter. If a larger catheter may be placed, this may facilitate resolution. If there is significant urine leak despite adequate bladder drainage, exploration may be needed.

Exploration is to identify the cause and location of the leak and provide for repair. If the leak is bladder based, the use of simple repair and drainage is effective; but if the leak is a result of distal ureteral necrosis, some means of ureteral replacement is needed. For a short segment of necrosis, bladder mobilization and reimplantation is effective. If a long segment of ureter has been lost, native ureter, either ipsilateral or even contralateral, may be useful if available. A psoas hitch or bladder flap may be needed if the native ureter is not present. These strategies are similar to those used

TABLE 153-1 Urologic Complications in Pediatric Renal Transplantation

AUTHOR AND YEAR	PATIENTS	URETERAL STENOSIS	URINARY LEAK	VUR	STONE	COMMENT
Almeida et al, 2013	134	5	3			100% cadaveric
Routh et al, 2013	71		6	17		Underlying GU pathology
	140		10	6		No GU pathology
Irtan et al, 2010	193	10	6	25		Greater incidence with PUV
El Atat et al, 2010	50		2	5		70% LRD
Ruiz et al, 2006	23	0	0	0	0	Patients 1-10 yr old
El-Husseini et al, 2008	292	13	12			Younger than 20 years
Englesbe et al, 2008	147	5	4	7	0	
Khositseth et al, 2007	117	26	2	10	11	History of obstruction or VUR
	117	11	2	1	2	No obstruction or VUR
Lapointe et al, 2001	166	3	7	1	1	Ureteroureterostomy
Nuininga et al, 2001	183	7	8	0	5	183 transplants in 146 patients
Shokeir et al, 2005	250	11	10	0	1	All LRD
Tanabe et al, 1998	107	2	1	1	0	
TOTAL	1990	101 (5.1%)	65 (3.3%)	73 (3.7%)	20 (1.0%)	

GU, genitourinary; PUV, posterior urethral valves; LRD, living related donor; VUR, vesicoureteral reflux.

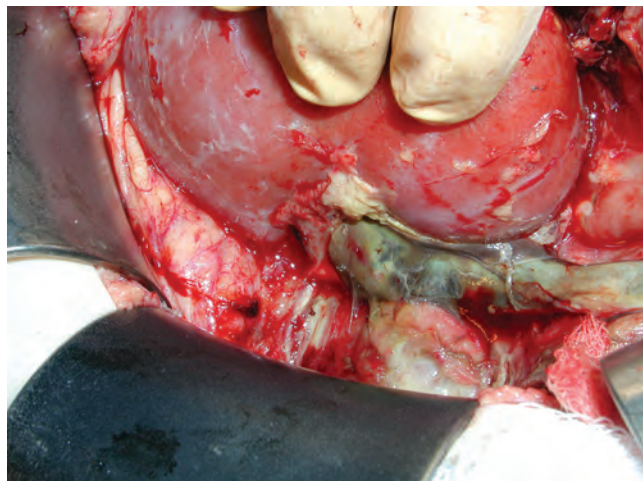


Figure 153-2. Ischemic loss of the entire renal pelvis and ureter in a cadaveric renal graft into a patient with a gastrocystoplasty. This manifested with urine leak after a period of acute tubular necrosis. The graft was salvaged with an augment bladder flap to the lower calyces of the graft.

for ureteral strictures. Careful stenting and drainage are essential (Fig. 153-2).

Infection

Urinary infection is a long-term and often delayed complication that largely reflects the status of bladder function and underlying urologic causes of renal failure (Herthelius and Oborn, 2007; Silva et al, 2010). The presence of hydronephrosis is often associated with pyelonephritis and worsening renal function (Chu et al, 2013). Routine assessment of bladder emptying, hydronephrosis, and occasionally use of a VCUG will usually identify the cause. If the patient is on CIC and no specific correctable cause is present, a strategy of prevention by way of prophylactic antibiotics and bladder irrigation may be effective. Aggressive management of bladder dysfunction, which should have been identified pretransplant, is essential to preserve graft function. If vesicoureteral reflux into the graft and infection with fever and altered renal function are present, correction of the reflux is warranted. Reflux in the absence of infection with normal bladder function may be observed with caution.

Reflux

Vesicoureteral reflux into the transplant is entirely distinct from routine reflux into an otherwise normal renal unit. Because this is a reimplanted ureter, the risk to renal function of an episode of pyelonephritis is greater in a transplanted kidney, and the patient is immunosuppressed (DeFoor et al, 2003; Coulthard and Keir, 2006). Routine evaluation for reflux after renal transplant has been my practice, even though not all patients were treated with surgery. Identification of this potential risk factor is useful for clinical decision making and ongoing risk assessment. If febrile UTIs occurred, the presence of transplant reflux justifies surgical correction with an open ureteral reimplantation (Hanevold et al, 1987). The risk of pyelonephritis in the graft is significant (Neuhaus et al, 1997; Ranchin et al, 2000; Barrero et al, 2007) and increases the potential for graft loss (Herthelius and Oborn, 2007) (Fig. 153-3). Identification of simultaneous bladder dysfunction is equally important (Casale et al, 2005), although this may not be correctable. In the setting of intermittent catheterization, any reflux should be corrected because these bladders will be chronically colonized. Reflux in the absence of infection and bladder dysfunction may be observed, and attempts made to improve any suggestion of bladder dysfunction. There are no data to suggest that low-grade sterile vesicoureteral reflux into a renal graft is harmful in children. Close

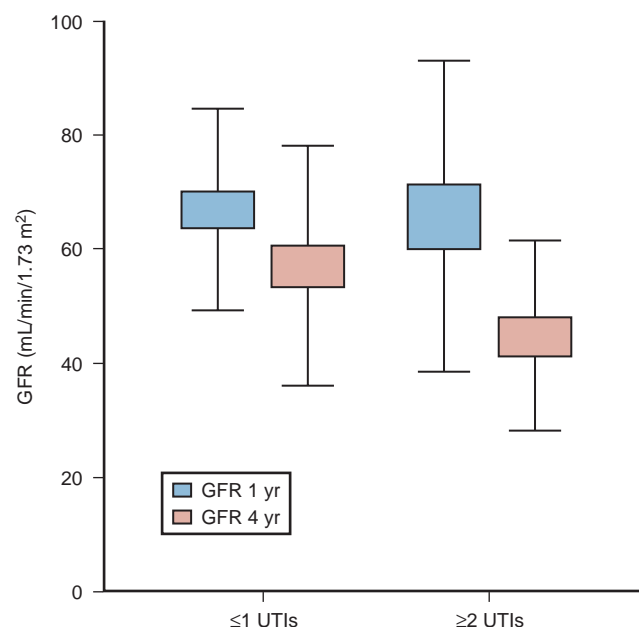


Figure 153-3. Graft function at 1 and 4 years in children with one or fewer and two or more urinary tract infections (UTIs). GFR, glomerular filtration rate. (From Herthelius M, Oborn H. Urinary tract infections and bladder dysfunction after renal transplantation in children. *J Urol* 2007;177:1883-6.)

observation for possible infection or deteriorating bladder function is warranted.

Surgical management of reflux into a transplanted ureter is never routine. The role of endoscopic therapy is limited and the few reports available suggest limited benefit, with resolution rates of 50% to 80% (Kitchens et al, 2006; Williams et al, 2008; Vemulakonda et al, 2010). This may be an option for asymptomatic reflux, but in the face of an episode of febrile UTI, the most certain definitive intervention is justified. There are few data as to relative efficacy of intravesical compared with extravascular methods (Krishnan et al, 2006), but my preference is intravesical, often with use of extravascular mobilization. A transtrigonal technique is effective if the contralateral native ureter can be avoided. Otherwise, an advancement or Politano-Leadbetter technique may be used. Ureteral stenting is advisable.

Hydronephrosis and Obstruction

A frequent urologic complication in pediatric renal transplant is hydronephrosis, and intervention for ureteral obstruction may be needed in as many as 8% of transplants (Shokeir et al, 2005; Smith et al, 2010; Chu et al, 2013). The presence of hydronephrosis necessitates careful evaluation and selective management to tailor appropriate treatment to the individual. The transplant kidney appears to be one of the rare situations in which obstruction may not be associated with hydronephrosis. This is uncommon and not well documented, but empirically it can occur. More commonly, obstruction is heralded by increasing renal dysfunction with a rising creatinine. Hydronephrosis is identified on ultrasonography or delayed drainage on MAG3 renal scan. More than half of obstructions in a recent series occurred within the first 100 days post-transplant (Smith et al, 2010). In the setting of normal prior bladder function, this pattern indicates ureteral obstruction until proven otherwise. If bladder dysfunction is known to be present, then both factors must be evaluated and managed because obstruction is more frequent in patients with bladder dysfunction, particularly posterior urethral valves (Smith et al, 2010) (Fig. 153-4).

In the setting of a rising creatinine level and hydronephrosis, obstruction and rejection may be intermingled. If the hydronephrosis is mild and there are other signs of rejection, the most

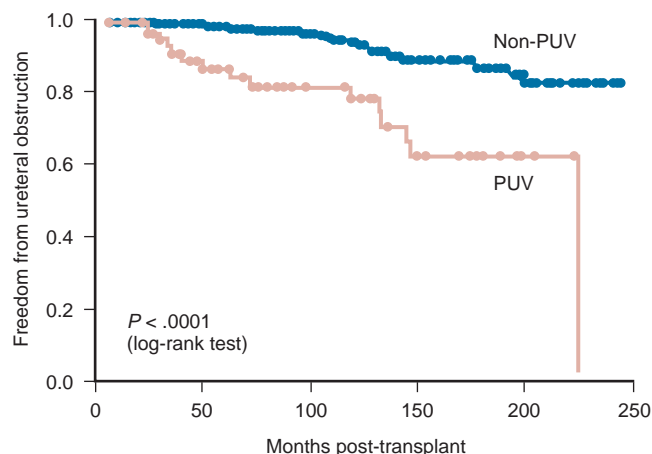


Figure 153-4. Obstruction-free survival in pediatric renal transplant patients with and without a history of posterior urethral valve (PUV). (From Smith KM, Windsperger A, Alanee S, et al. Risk factors and treatment success for ureteral obstruction after pediatric renal transplantation. *J Urol* 2010;183:317–22.)

efficient first step is biopsy (Khater and Khauli, 2012). If there is no clinical suggestion of rejection, ureteral stenting with or without a biopsy is the best first step. Diagnostic studies for obstruction in the transplant setting are not completely reliable; given the associated risks, I have adopted the approach of stenting to assess the impact on renal function. It has been in this setting, albeit rarely, that an acutely failing transplant with minimal or no hydronephrosis and no evidence of rejection has been stented with subsequent improvement in function. The more common situation is with moderate hydronephrosis and a rising creatinine level with some rejection on biopsy. If the graft is not failing rapidly, initial medical treatment of the rejection is justified, with stenting being reserved for lack of improvement. Whether obstruction increases the risk of rejection is unproven but empirically suggested. In that light, having a low threshold for stenting, which can provide a definitive diagnosis of functionally significant obstruction, is essential.

The source of ureteral obstruction is usually in the distal ureter, with stenosis at the reimplantation site (Martino et al, 2013), but may be anywhere along the ureter. In a recent analysis, neither ureteral implant method nor use of stents was a contributing factor to obstruction. However, the presence of bladder abnormalities, particularly resulting from posterior urethral valves, was a risk factor for post-transplant obstruction (Smith et al, 2010). Compression from a lymphocele or adenopathy from post-transplant lymphoproliferative disease (PTLD) are also possible causes (Dharmidharka et al, 2001; Buell et al, 2006). Definitive therapy is determined by the most likely cause. Focal ureteral narrowing on retrograde imaging may be effectively treated with balloon dilation and stenting for 4 to 6 weeks. Long-term stenting has been used in adult series with thermolabile nitinol stents, but whether this would be a satisfactory approach in children is uncertain (Bach et al, 2013). In recognition of the risk posed to the graft by obstruction, open definitive repair should not be delayed excessively (Smith et al, 2010). These procedures are never simple and may entail complex reconstruction using native ureter or bladder flaps (Kockelbergh et al, 1993). Avoiding use of nonurothelial segments, such as appendix (Corbetta et al, 2012), is advisable, although any of these methods may be needed. Pyeloureteral anastomosis can be an option if the native ureter remains and is healthy (Sandhu et al, 2012). All the principles of reoperative reconstruction must be adhered to for preservation of well-vascularized functional tissues.

Bladder Dysfunction

Bladder dysfunction may produce infection, but may also create an obstructive process that impairs renal graft function (Herthel

lius and Oborn, 2006; Van der Weide et al, 2006; Herthelius and Oborn, 2007; Nahas et al, 2008). Discriminating this from ureteral obstruction may not be simple, and on occasion has necessitated sequential diagnostic drainage steps. If a bladder catheter can be placed easily, then continued drainage for 1 to 2 weeks with reassessment of creatinine can usually enable identification of bladder dysfunction as the cause of graft dysfunction if the creatinine declines. If not, then combined stent and bladder drainage followed by a recheck of the creatinine is needed. It should be recognized that elements of bladder and ureteral dysfunction might contribute to graft failure. Both may need to be addressed. Treating bladder dysfunction involves measures to increase compliance using anticholinergics as well as instituting or enhancing an intermittent catheterization program. Bladder augmentation may also be needed, although only after aggressive medical management has been tried. When intermittent catheterization per urethra is difficult, creation of a continent stoma may be needed. Identification of these potential risks to graft function is best accomplished before the transplant whenever possible.

Stones

Nephrolithiasis in a pediatric renal transplant is uncommon, occurring in up to 5% of patients (Khositseth et al, 2004) but more likely to occur in less than 1% (Stravodimos et al, 2012); it is potentially dangerous for long-term graft survival. With appropriate management, stones were not seen to increase the risk of graft loss but were associated with more UTIs (Khositseth et al, 2004). There is a high incidence of bladder stones, approaching 50%, and several stones were caused by retained suture material in the bladder (Lipke et al, 2004). Detection of an asymptomatic stone on routine surveillance should prompt attempts at removal as well as a search for cause. Stone associated with renal graft dysfunction caused by obstruction or infection should be managed with urgent intervention to ensure drainage and prompt removal. All conventional means of stone management are appropriate in a renal graft but should be modulated by recognition of the potential balance of risk to the graft as well as relative efficacy of the various modalities. Selection of a modality that will have the highest likelihood of success with a single intervention is likely to be the best option in the long-term, even if this involves more complexity. A lower pole stone may be best managed with a percutaneous approach or ureteroscopic removal rather than extracorporeal shock wave lithotripsy, given the lower success of clearance of lower pole stones. These decisions should be individualized based on clinical presentation, location and size of the stone, and renal functional status.

KEY POINTS: COMPLICATIONS

- Common urologic complications for pediatric renal transplant include ureteral stenosis (6%), urinary leaks (3%), stones (2%), and clinically significant reflux (2%).
- Urine leaks are typically identified in the early postoperative period with increasing fluid from the wound drains.
- Urinary infection is a long-term and often delayed complication that largely reflects the status of bladder function.
- Vesicoureteral reflux into the transplant is entirely distinct from routine reflux; the risk to renal function of acute pyelonephritis is greater.
- In the setting of a rising creatinine level and hydronephrosis, obstruction and rejection may be intermingled.
- The source of ureteral obstruction is usually in the distal ureter, with stenosis at the reimplantation site.
- Bladder dysfunction may produce infection but may also create an obstructive process that impairs renal graft function.
- Nephrolithiasis is uncommon but may occur in up to 5% of patients.

SUMMARY

Preparation and management of the pediatric transplant patient, particularly with an underlying urologic condition, requires a thorough understanding of the patterns of bladder dysfunction and clear strategies for evaluation and treatment before transplant. Anticipating the needs and constraints of the transplant procedure and being involved in appropriate cases permits a smoother procedure and ongoing continuity of care by the pediatric urologist. Post-transplant monitoring should be aggressively expectant to identify pathologic processes before they have damaged renal graft function irreversibly. This takes a high index of suspicion and a clear sense of the patient's risk for these processes. A multidisciplinary collaboration among the pediatric nephrology, urology, and transplant surgical teams is critical to maximizing patient and graft survival.

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154 Pediatric Genitourinary Trauma

Douglas A. Husmann, MD

General Comments on Pediatric Renal Trauma

Radiographic and Endoscopic Assessment and Treatment of Upper Tract Genitourinary Injuries

Management of Renal Trauma

Management of Preexisting Hydronephrosis and Ureteropelvic Junction Disruption

Ureteral Trauma

Traumatic Bladder Injuries

Urethral Injuries

Penile Injuries

Scrotal, Vulvar, and Testicular Trauma

GENERAL COMMENTS ON PEDIATRIC RENAL TRAUMA

The Pediatric Kidney: Traumatic Renal Injuries and Congenital Renal Anomalies

The pediatric kidney is believed to be more susceptible to trauma owing to a decrease in the physical renal protective mechanisms found in childhood. Specifically, in contrast with the adult, the pediatric kidney is protected by an immature, more pliable thoracic cage, weaker abdominal musculature, and less perirenal fat and it sits in a lower abdominal position. Whether the incidence of renal injury following blunt abdominal trauma is truly increased in the pediatric versus the adult patient population is controversial, with statistical evaluations revealing mixed results, and the question remains in play (Brown et al, 1998; Chopra et al, 2002; McAleer et al, 2002a; Heyns, 2004).

What is known, however, is that preexisting renal abnormalities (i.e., ureteropelvic junction [UPJ] obstruction, hydronephrosis, horseshoe kidney) are three- to fivefold more common in pediatric patients undergoing a screening computed tomography (CT) scan for trauma than in the adult population (Brown et al, 1998; Chopra et al, 2002; McAleer et al, 2002a; Heyns, 2004).

Classically, patients with a preexisting congenital renal abnormality present with a history of hematuria disproportionate to the severity of trauma. Although it has been hypothesized that a preexisting congenital genitourinary (GU) anomaly would be associated with a higher stage of renal injury, this has not been documented to be true, with the majority of the patients still sustaining only renal contusions or minor renal fracture (Chopra et al, 2002; McAleer et al, 2002a; Al-Qudah and Santucci, 2006).

Screening for Genitourinary Injuries: the Difference between Adult and Pediatric Patients

Two major clinical findings suggest the need to work up the adult for a possible GU injury following trauma: the presence of gross hematuria or of microscopic hematuria (>50 red blood cells/high-power field) with shock (systolic pressure <90 mm Hg). In adults, if physicians use only these two criteria to screen for a traumatic GU injury, they will find 98% of the clinically significant GU injuries following blunt trauma and 90% of GU injuries associated with penetrating trauma (Mee et al, 1989; Heyns, 2004; Santucci et al, 2004a). Indeed, in the adult population 30% of the patients presenting with trauma-induced gross hematuria and 10% of the

patients with microscopic hematuria associated with shock are found to have a radiologically definable GU injury (Mee et al, 1989; Heyns, 2004; Santucci et al, 2004a). In contrast, in children there is poor correlation relating the degree of hematuria to the presence of renal injuries. In fact some studies have found that two thirds of children sustaining a grade 2 or higher renal injury will have a completely normal urinalysis (Morey et al, 1996; Buckley and McAninch, 2004, 2006; Santucci et al, 2004a). The correlation of hypotension to the extent of GU injury is also highly problematic; specifically, the sympathetic tone in children is able to sustain a normal blood pressure despite significant blood loss. In point of fact, in children serial hemoglobin/hematocrit values will invariably demonstrate significant decreases before orthostatic hypotension develops (Quinlan and Gearhart, 1990). In essence, in the pediatric patient presenting with a history of trauma the assessment of gross hematuria and microscopic hematuria with shock is not adequate to determine whom to screen for GU injuries. However, if two additional factors are added as screening criteria—the mechanism of injury and the presence of associated injuries—over 98% of clinically significant GU injuries can be identified. Notably, one of these two additional factors, the presence of coexisting injuries (i.e., injuries to the thoracic contents, intra-abdominal organs, and/or orthopedic fractures of the ribs, spine, pelvis, or femur), will on its own identify slightly less than 90% of the pediatric patients with a clinically significant traumatic renal injury (Levy et al, 1993; Morey et al, 1996; Buckley and McAninch, 2004, 2006; Heyns, 2004; Sahin et al, 2004; Santucci et al, 2004a, 2004b). These four crucial screening criteria have been found to be highly reliable and cost-effective in determining which pediatric patients should be screened for a possible GU injury and are outlined in Box 154-1 (Mee and McAninch, 1989; Mee et al, 1989; Herschorn et al, 1991; Heyns, 2004; Santucci et al, 2004a, 2004b; Wu and Gaines, 2007; Bernard 2009; Buckley and McAninch, 2011; Bartley and Santucci, 2012).

RADIOGRAPHIC AND ENDOSCOPIC ASSESSMENT AND TREATMENT OF UPPER TRACT GENITOURINARY INJURIES

FAST: Focused Assessment with Sonography for Trauma

Because of its low cost, wide availability, and freedom from ionizing radiation, ultrasonography has become a major screening tool in pediatric level 1 trauma centers. Use of the FAST examination to

BOX 154-1 Indications for Radiographic Assessment of Pediatric Patient for Possible Genitourinary Injury

All penetrating abdominal/pelvic traumas
or

A history of blunt abdominal trauma that meets one of the four following criteria:

1. A significant deceleration or high-velocity accident, fall from greater than 10 feet, or strike to the abdomen or flank with a foreign object (e.g., football helmet, baseball bat, hockey stick)
2. Significant trauma that has resulted in injuries to the thoracic contents and/or intra-abdominal organs, and/or orthopedic fractures of the ribs, spine, pelvis, or femur
3. Gross hematuria
4. Microscopic hematuria (>50 RBC/HPF) associated with shock (systolic blood pressure <90 mm Hg)

HPF, high-power field; RBC, red blood cells.

detect renal injuries has a reported specificity range of 95% to 100% (the ability to diagnose true negatives—kidneys without a clinically significant traumatic injury). However, the sensitivity (the ability to diagnose true positives—kidneys with a clinically significant traumatic injury) is highly variable and extremely operator dependent, with published sensitivity results ranging widely from 22% to 96% (McGahan et al, 1999; Jang et al, 2004; Sirlin et al, 2004; Suthers et al, 2004; Nural et al, 2005; Lee et al, 2007; Bent et al, 2008; Tsui et al, 2012). The clinical usefulness of a FAST scan is best when combined with serial physical examinations. If both the initial FAST examination and subsequent serial physical examinations performed for a 24-hour time period are within normal limits, the combination of these findings will virtually rule out the presence of clinically significant renal and/or intra-abdominal injuries (McGahan et al, 1999; Jang et al, 2004; Sirlin et al, 2004; Suthers et al, 2004; Nural et al, 2005; Lee et al, 2007; Bent et al, 2008; Tsui et al, 2012).

Because of the high specificity (true negative evaluation) of FAST, this examination has been proven to be extremely valuable in evaluating the hemodynamically unstable patient in whom emergent nephrectomy may become imperative. A rapid ultrasound assessment with Doppler verification of good blood flow to an uninjured kidney can be immensely helpful when faced with the possibility of an emergent nephrectomy resulting from a renal hilar injury (Riccabonna et al, 2011).

Abdominal and Pelvic Computed Tomography

The patient's hemodynamic stability determines whether, when, and occasionally what type of imaging studies can be done. The most sensitive and specific radiologic test to rule out a GU injury is a triphasic abdominal and pelvic CT study (precontrast scan, followed by a CT scan taken 1 to 3 minutes after injection of contrast [1.5 to 2 mL/kg] and then a 10-minute delayed scan). However, because of concerns for radiation exposure in children, a single-phase abdominal and pelvic CT study, with the scan taken within 5 minutes of injection of contrast, has clinically supplanted the triphasic CT study (Mee et al, 1989; Stein et al, 1994; Morey et al, 1996; Brown et al, 2001; Buckley and McAninch, 2004, 2006, 2011; Heyns, 2004; Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Lee et al, 2007; Hardee et al, 2013). Although the single-phase CT study is beneficial in determining renal perfusion and the presence of major renal fractures, it is frequently unable to accurately determine the presence of perinephric fluid extravasation and will miss the majority of the isolated ureteral injuries (Boone et al, 1993; Hardee et al, 2013). Because of this fact I personally recommend that a delayed CT image be obtained 10 to 15 minutes

TABLE 154-1 Grading of Renal Injuries

GRADE OF RENAL INJURY	DESCRIPTION
1	Renal contusion or subcapsular hematoma
2	Less than 1-cm parenchymal laceration, all renal fragments viable, no urinary extravasation
3	Greater than 1-cm parenchymal laceration, includes renal segmental injuries resulting in devitalized fragments, no urinary extravasation
4	Laceration extending into the collecting system, includes renal segmental injuries resulting in devitalized fragments, urinary extravasation is present. Grade 4 includes shattered kidney, renal pelvic lacerations, and complete ureteropelvic junction disruption.
5	Injury to the main renal vasculature: major renal vessel laceration or avulsion resulting in uncontrollable hemorrhage or renal thrombosis of the major renal vessels

From Buckley JC, McAninch JW. Revision of current American Association for the Surgery of Trauma renal injury grading system. *J Trauma* 2011; 70:35–7.

following injection of contrast on all patients with a grade 3 or higher renal injury.

Radiologic Assessment of the Clinically Unstable Patient

In the clinically unstable patient requiring emergent laparotomy, once the patient is stabilized in the operating room single-shot intravenous pyelography (IVP) (2 mL/kg intravenous bolus of contrast) is performed with the x-ray taken 10 to 15 minutes following injection. Alternatively, if readily available an intraoperative renal ultrasound may be beneficial if exploration for an expanding retroperitoneal hematoma is considered. I would caution the reader regarding the quality of the single-shot IVP; this study is frequently a suboptimal examination with poor excretion/visualization of contrast because of the patient's clinical status. The chief benefit of the single-shot IVP or intraoperative renal ultrasound is to detect a normally functioning contralateral kidney (ultrasound should show good renal blood flow) if unilateral nephrectomy is a consideration. As an alternative to the single-shot IVP or intraoperative renal ultrasound, the patient can be stabilized and a delayed abdominal and pelvic CT evaluation obtained. Definitive surgical repair of any GU injury is subsequently deferred for 12 to 24 hours (Azimuddin et al, 1997; Heyns, 2004; Riccabonna et al, 2011).

Renal Trauma Grading System (Revised 2011)

In 2011, Buckley and McAninch recommended revision of the classic 1989 renal organ injury scale. This revision was proposed to alleviate significant discrepancies that existed in the literature regarding the classification of high-grade (grades 4 and 5) renal injuries. Specifically of note is the moving of the "shattered kidney" into a grade 4 classification. The current classification of renal injuries based on these recommendations is outlined in Table 154-1, and Figures 154-1 through 154-5 provide examples (Dugi et al, 2010; Buckley and McAninch, 2011; Shenfeld and Gnessin, 2011).

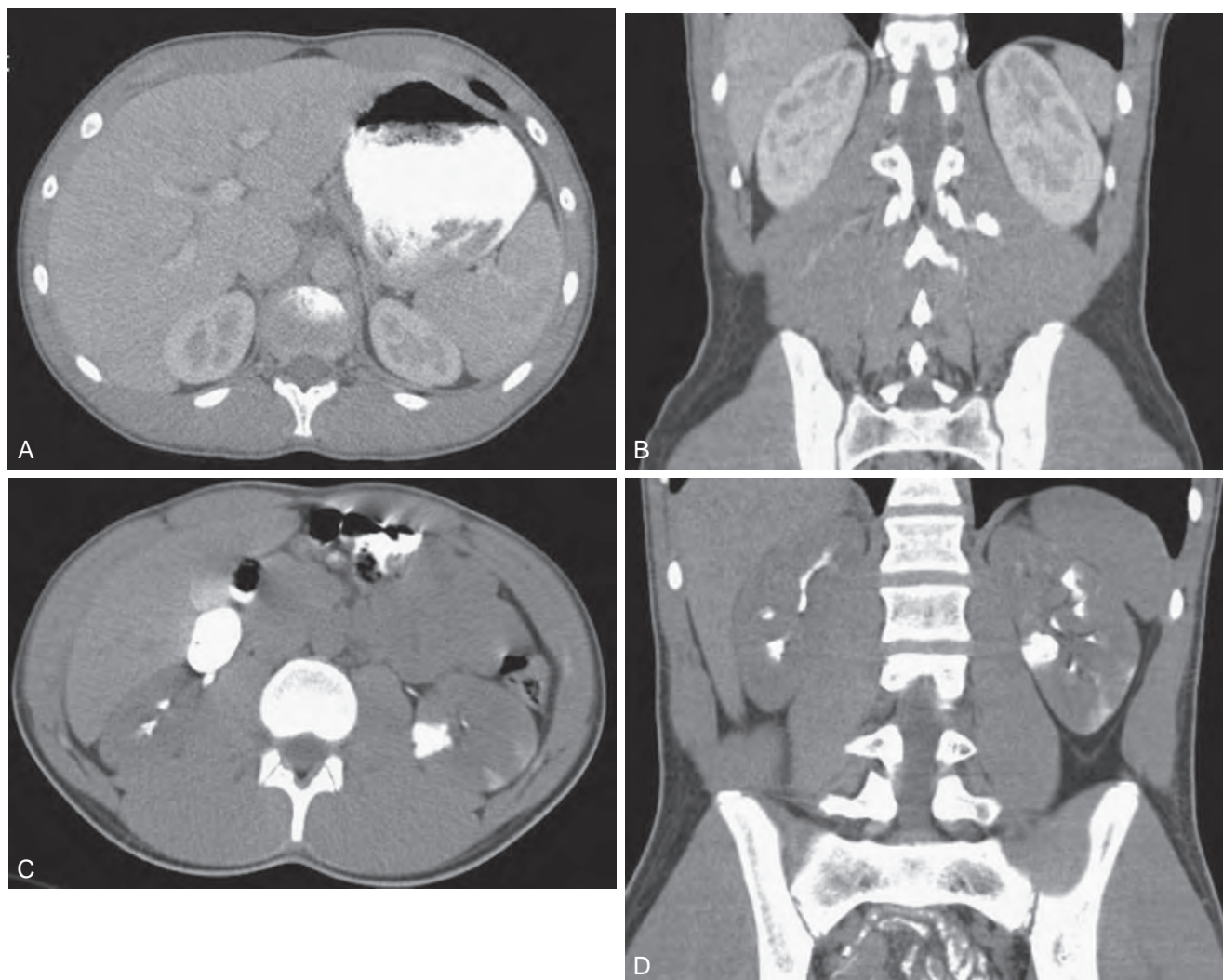


Figure 154-1. Computed tomography (CT) images, acute and delayed, with grade 1 renal trauma. **A**, Acute CT image of grade 1 renal trauma. Note normal-appearing parenchyma. **B**, Acute CT image coronal reconstruction of grade 1 renal trauma. **C**, Two-hour delayed CT image of grade 1 renal trauma revealing renal contusion with delayed excretion of contrast in cortex of contused renal parenchyma. **D**, Two-hour delayed coronal reconstruction of CT grade 1 renal trauma revealing delayed excretion of contrast in cortex of contused renal parenchyma.

Management of Complications from Traumatic Renal Injuries

The need for endoscopic, invasive radiologic, or open surgical intervention is dependent upon the patient's hemodynamic stability and the stage of renal injury, with few if any hemodynamically stable patients with grade 1 to 3 injuries (grade 3 with all renal fragments viable) requiring interventional management. In contrast, in hemodynamically stable patients with grade 3 to 5 renal injuries (grade 3 with devitalized fragments) intervention will be necessary for persistent or delayed bleeding in approximately 25% and intervention for symptomatic urinomas in approximately 15%. Surgical exploration to control complications not amenable to nonoperative techniques will occur in approximately 5% of patients. In essence, conservative management of hemodynamically stabilized patients with isolated grade 3 to 5 renal injuries will save approximately 95% of the patients an open surgical intervention (Husmann and Morris, 1990; Husmann et al, 1993b; El Khader et al, 1998; Bozeman et al, 2004; Buckley and McAninch, 2004, 2006; El-Sherbiny et al, 2004; Heyns, 2004; Santucci et al, 2004b; Broghammer et al, 2006, 2007; Henderson et al, 2007; Shariat et al,

2008; Cannon et al, 2008; Brewer et al, 2009; Umbreit et al, 2009; Eassa et al, 2010).

It is noteworthy that three classic CT findings are indicative that interventional therapy may become necessary (Cannon et al, 2008; Dugi et al, 2010; Bartley and Santucci, 2012). One is medial extravasation of contrast. This finding brings forth the concern for renal pedicle injury, UPJ disruption, or rupture of the renal pelvis. The latter two are considered in the differential diagnosis if there is medial extravasation of contrast associated with functioning renal parenchyma and no contrast is seen in the ipsilateral distal ureter. If there is medial extravasation of contrast, little to no functioning renal parenchyma, and a medial perinephric hematoma, and especially if there was intravascular contrast extravasation, concern for a renal pedicle injury arises. The finding of medial extravasation of contrast is no small matter, with approximately 75% of patients requiring either endoscopic, percutaneous, or open intervention. Second, a finding of lateral extravasation of contrast with no distal ureter visualized should generate a concern for ureteral injury and will either prompt the physician to obtain delayed radiographic images or prompt the need for cystoscopy and a retrograde pyelogram. Third, a perinephric hematoma of greater

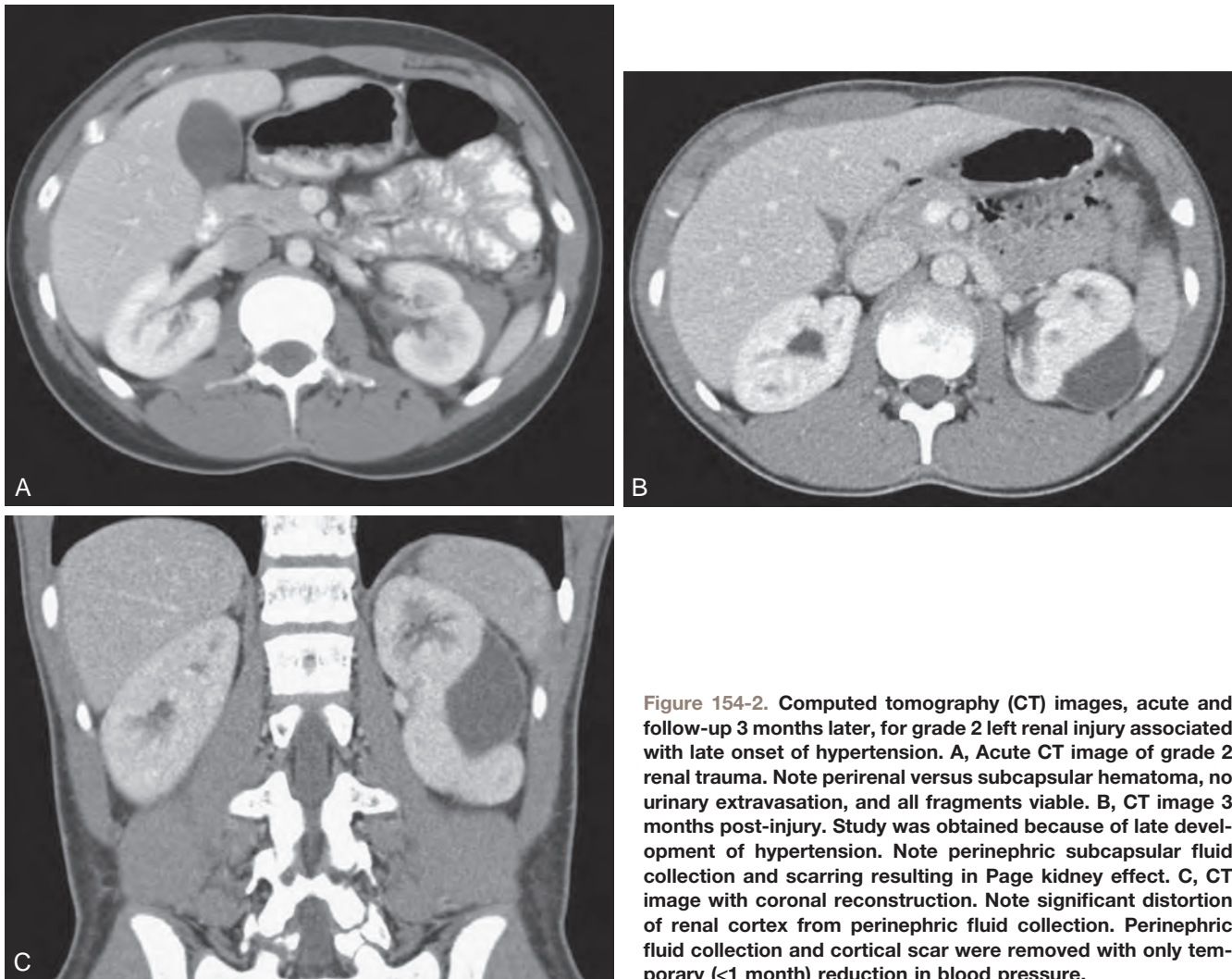


Figure 154-2. Computed tomography (CT) images, acute and follow-up 3 months later, for grade 2 left renal injury associated with late onset of hypertension. **A**, Acute CT image of grade 2 renal trauma. Note perirenal versus subcapsular hematoma, no urinary extravasation, and all fragments viable. **B**, CT image 3 months post-injury. Study was obtained because of late development of hypertension. Note perinephric subcapsular fluid collection and scarring resulting in Page kidney effect. **C**, CT image with coronal reconstruction. Note significant distortion of renal cortex from perinephric fluid collection. Perinephric fluid collection and cortical scar were removed with only temporary (<1 month) reduction in blood pressure.

than 2.5 cm, if in a lateral location, will usually be associated with persistent renal cortical bleeding that will require angiographic embolization. It is noteworthy that, if a hematoma of this size is medially located, concern for a major renal hilar injury that can result in sudden hemodynamic instability of the patient should be entertained (Nuss et al, 2009; Charbit et al, 2011).

Once the diagnosis of a traumatic renal injury is made, five possible complications can arise that may need to be addressed: (1) urinary extravasation, (2) an infected urinoma/perinephric abscess, (3) persistent or delayed renal hemorrhage, (4) hypertension, and (5) post-traumatic chronic pain syndrome.

Indications for and Use of Arteriography: Management of Persistent/Delayed Hemorrhage and Persistent Urinoma

Approximately 25% of patients with grade 3 to 5 renal trauma, managed in a nonoperative fashion, will develop persistent or secondary (delayed) hemorrhage (Wessells et al, 1997b; Dinkel et al, 2002; Goffette and Laterre, 2002; Kansas et al, 2004; Sofocleous et al, 2005; Al-Qudah and Santucci, 2006; Hotaling et al, 2011; Lin et al, 2013). Classically, delayed hemorrhage develops 5 to 14 days post-injury but may occur up to 1 month following the insult. Delayed hemorrhage usually arises from the development of arteriovenous fistulae or pseudoaneurysm malformations. In this scenario, the initial bleeding is tamponaded by the surrounding hematoma; as the hematoma resolves and liquefies, recurrent bleeding develops. Unlike the arteriovenous fistulae noted after

renal biopsy, for which a spontaneous resolution rate of greater than 70% is found, the vast majority of arteriovenous fistulae occurring after renal trauma will not spontaneously resolve, with almost all cases of delayed hemorrhage secondary to trauma requiring active intervention (Heyns and Van Vollenhoven, 1992; Dinkel et al, 2002; Goffette and Laterre, 2002; Heyns, 2004; Sofocleous et al, 2005; Al-Qudah and Santucci, 2006; Breyer et al, 2008; Umbreit et al, 2009; Eassa et al, 2010; Charbit et al, 2011; Hotaling et al, 2011). Angiographic embolization is currently the preferred treatment method for persistent or delayed bleeding with non-operative management protocols. Surgical exploration is reserved for embolization failure. Superselective angiographic embolization of isolated renal artery branches for persistent or secondary hemorrhage has a success rate approaching 80%. The percentage of salvaged renal function post-embolization varies depending upon the degree of the initial injury, but the median reported value is 30%. On occasion, angiographic embolization is used to treat persistent urinary fistulae. In this scenario, a functional transected fragment of a grade 4 renal injury is completely separated from the renal collecting system, and a persistent urinary fistula/urinoma has developed despite management by double-J stent and percutaneous nephrostomy tube placement. In these rare patients, selective angiographic embolization will resolve the urinary fistula by necrosing the isolated functional renal fragment (Pinto and Chimento, 1998; Heyns, 2004). Surgery if required following angiography is due to one of three problems: persistent or repetitive bleeding, postembolization abscess, or persistent urinary fistula from an isolated renal segment (Heyns and Van Vollenhoven, 1992;

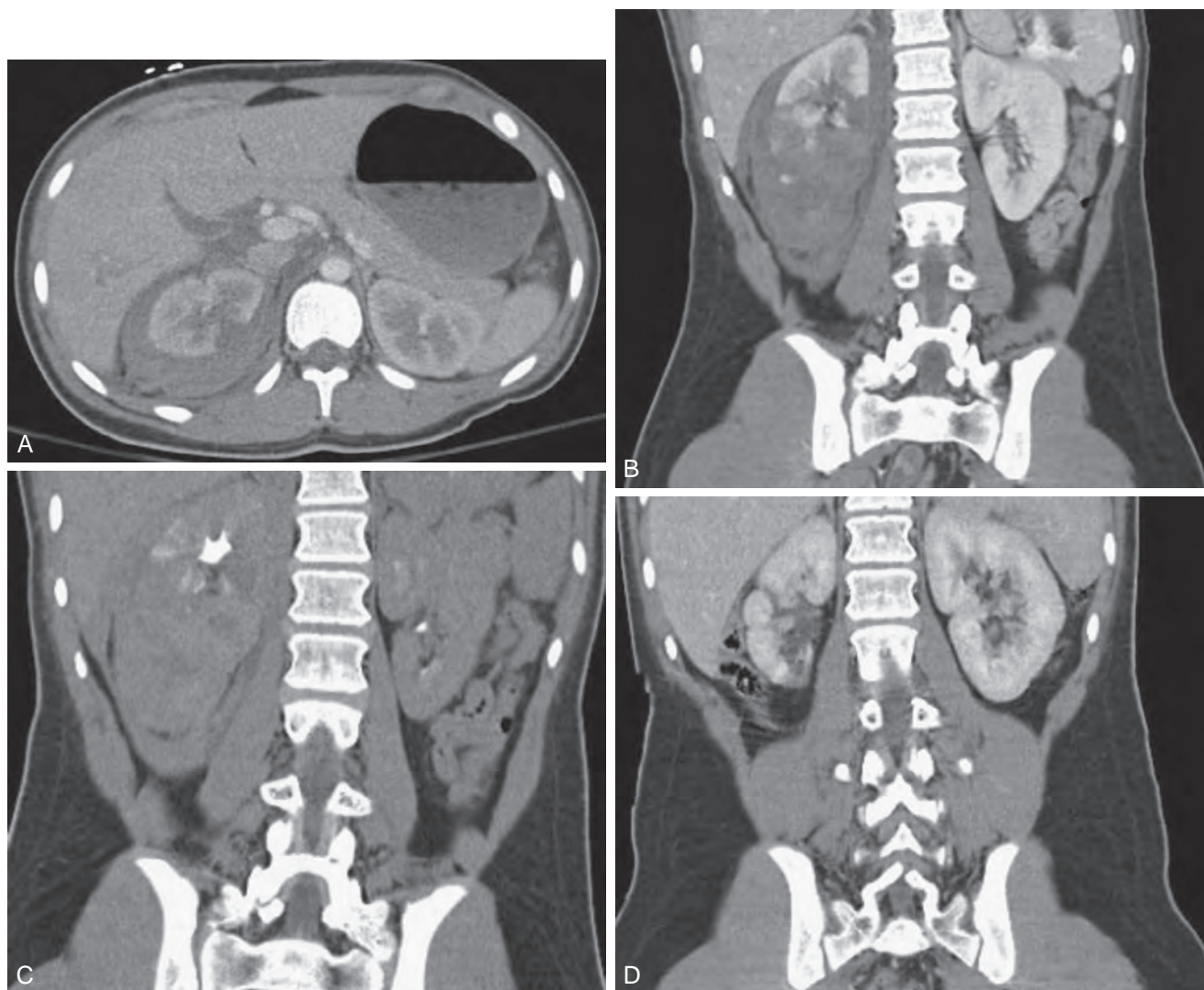


Figure 154-3. Computed tomography (CT) images of grade 3 right renal trauma—acute, delayed, and at 3-month follow-up. A, Acute CT image of grade 3 renal trauma showing greater than 1-cm laceration of midrenal pole with perinephric hematoma. B, Acute CT image coronal reconstruction of grade 3 renal trauma, with possible devitalization of the entire lower pole of the kidney. C, Two-hour delayed CT image coronal reconstruction of grade 3 renal trauma, with no urinary extravasation noted and lower pole with questionable devitalization versus contusion. D, CT image coronal reconstruction 3 months after traumatic injury revealing parenchymal scarring at site of laceration with scarred but functional lower pole consistent with healed parenchyma following severe renal contusion. Scarring of lower pole was believed to have occurred with impoverished blood supply owing to severe contusion.

Dinkel et al, 2002; Goffette and Laterre, 2002; Heyns, 2004; Sofocleous et al, 2005; Al-Qudah and Santucci, 2006; Breyer et al, 2008; Brewer et al, 2009; Umbreit et al, 2009).

Postembolization syndrome is a well-recognized and self-limiting condition manifested by pyrexia (up to 40° C), flank pain, and an adynamic ileus. Symptoms will usually resolve within 96 hours after the embolization. Unlike angioinfarction for renal tumors, after which up to 60% of patients may develop postembolization syndrome, approximately 10% of patients develop this complication following angioinfarction after a traumatic injury. The decrease in the frequency of this syndrome following trauma is believed to be secondary to fewer pyrogens being released from the already partially necrotic tissue (Oesterling et al, 1986; Kehagias et al, 1998; Kalman and Varenhorst, 1999; Heyns, 2004; Mitra et al, 2004; Sofocleous et al, 2005; Breyer et al, 2008). The problem faced with persistent pyrexia following embolization is the need to rule out bacterial seeding of the necrotic tissue. It is therefore

mandatory in the presence of a febrile response following embolization to obtain blood and urine cultures. Consideration for a repeat CT scan with possible aspiration, culture, and drainage of the hematoma/urinoma should be given if symptoms persist for greater than 96 hours (Sofocleous et al, 2005; Breyer et al, 2008).

Indications for and Use of Retrograde Pyelography, Percutaneous Nephrostomy, and Perinephric Drain Placement: Diagnosis of Ureteropelvic Junction Disruptions, Renal Pelvis Lacerations, and Management of Symptomatic Urinomas and Perinephric Abscesses

Two indications exist for the use of retrograde pyelography following renal trauma: (1) the need to diagnose a partial/total ureteral disruption or renal pelvic laceration and (2) the need to

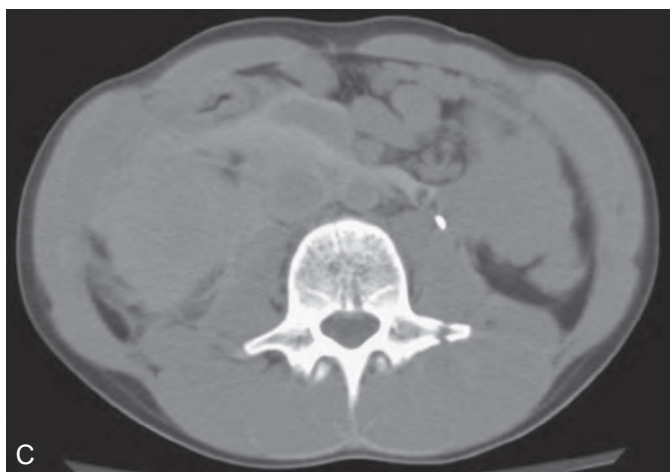
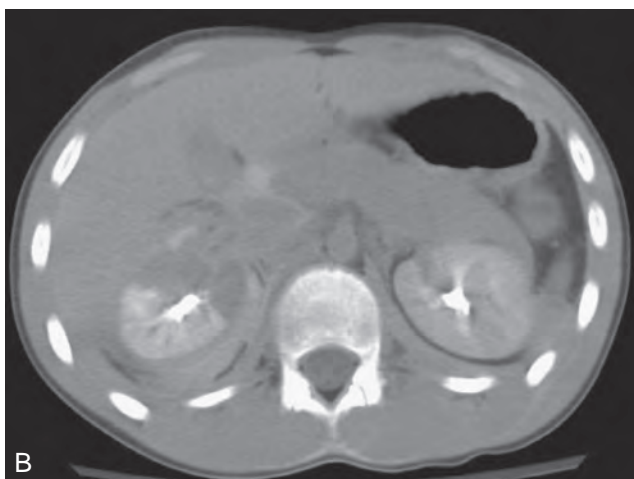
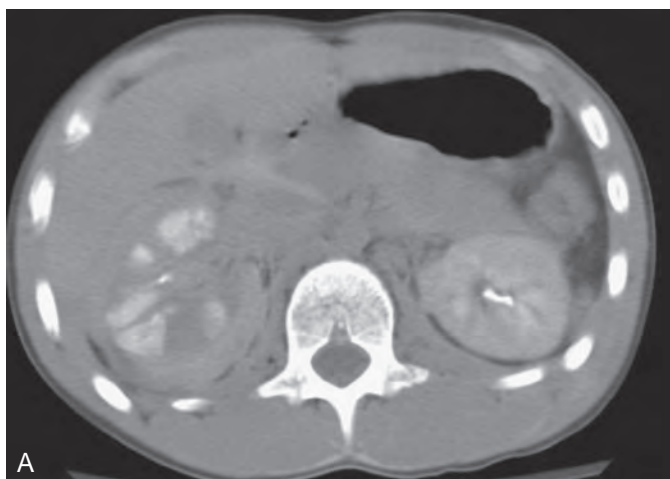


Figure 154-4. Computed tomography (CT) images of grade 3 renal trauma—patient unstable and no delayed images were performed. A and B, Acute CT images of grade 3 right renal trauma showing perinephric hematoma and multiple, less than 1-cm fractures, and association with either devitalized renal fragments, segmental renal artery occlusion, or severe renal contusion. C, Acute CT image showing no flow in distal right ureter. Patient required immediate surgical intervention as a result of acute respiratory difficulty secondary to multiple facial fractures with oral pharyngeal hematoma impairing airway. In addition, physical examination in emergency room revealed severe peritoneal irritation. Upon emergency surgery and after stabilization of patient, right retrograde pyelogram was obtained to rule out ureteral injury; no evidence of ureteral or collecting system injury was noted. Blood clot was seen to fill pelvis, and a ureteral stent was placed to aid drainage.

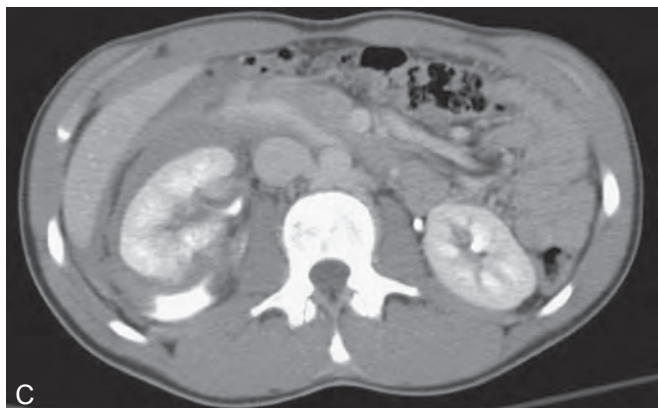
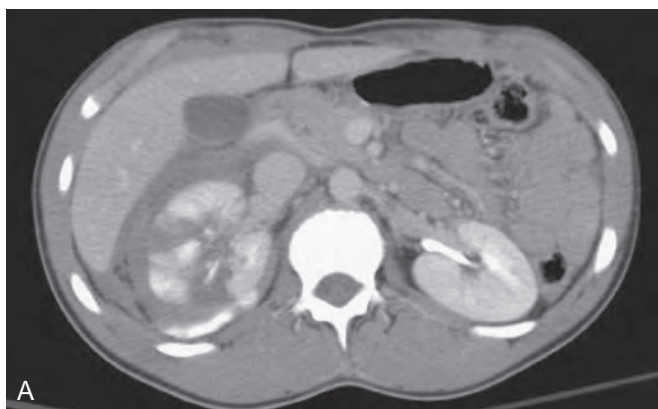


Figure 154-5. Acute and delayed images of grade 4 right renal injury. A and B, Acute computed tomography (CT) images of grade 4 renal trauma with perinephric hematoma, severe (>1 cm) fractures with devitalized renal segments, and urinary extravasation. C and D, Ten-minute delayed CT images revealing flow of contrast in ureter distal to injury, confirming patency of distal ureter. Patient was treated with observation only; no stent or drainage was necessary.

aid in the management of a symptomatic urinoma (Boone et al, 1993; Kawashima et al, 1997; Heyns, 2004; Santucci et al, 2004b). Concern for a ureteral injury usually arises when a CT scan reveals urinary extravasation and no ipsilateral distal ureter is seen. In the presence of these CT findings, a retrograde pyelogram is mandatory. This study is performed to either confirm or refute the diagnosis of a UPJ disruption or laceration of the renal pelvis, both of which require operative exploration and repair. If no evidence of these injuries is present I recommend that a ureteral stent be placed following the retrograde pyelogram. This recommendation is based on prior studies revealing that patients with trauma-induced urinary extravasation who have absence of contrast in the ipsilateral distal ureter are at a higher risk for developing a symptomatic urinoma if left unstented (Boone et al, 1993; Kawashima et al, 1997; Chopra et al, 2002; McAleer et al, 2002b; Smith et al, 2003; Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Broghammer et al, 2006; Cannon et al, 2008; Umbreit et al, 2009; Eassa et al, 2010; Bartley and Santucci, 2012).

The second consideration for intervention with cystoscopy and retrograde pyelography is the presence of a symptomatic urinoma. Although most post-traumatic urinomas are asymptomatic and have a spontaneous resolution rate approaching 85%, urinomas will occasionally persist. Symptomatic urinomas will develop a classic triad of findings: ipsilateral flank pain, adynamic ileus, and a low-grade temperature. Management of these patients is by endoscopic intervention, with cystoscopy, retrograde pyelography, placement of a ureteral stent, urethral catheter drainage, and intravenous antibiotics. When a ureteral stent is placed in conjunction with temporary placement of a urethral catheter, greater than 90% of the symptomatic urinomas will resolve (Al-Ali and Al-Hajaj, 2001; Alsikafi et al, 2006; Umbreit et al, 2009). Classically, the urethral catheter is removed 3 to 5 days after the patient's clinical symptoms have abated. Intravenous antibiotics are discontinued and prophylactic antibiotics initiated at the time of urethral catheter removal. I remove the ureteral stent 4 to 6 weeks post-injury and will maintain oral prophylactic antibiotic coverage for 48 hours after stent removal. It should be noted that percutaneous nephrostomy drainage and internal stenting are equally efficacious for the treatment of symptomatic urinomas (Husmann and Morris, 1990; Husmann et al, 1993b; Philpott et al, 2003; Bozeman et al, 2004; Heyns, 2004; Keller et al, 2004; Al-Qudah and Santucci, 2006; Umbreit et al, 2009). The advantage of an internal stent is that it prevents possible dislodgment of the drainage tube and the need for external drainage devices. The two major disadvantages of internal drainage are that both stent placement and removal, in the pediatric patient population, require general anesthesia. In addition, the small-size ureteral stents (4 to 5 French) placed in young children may become blocked with blood clots from the dissolving hematoma, resulting in persistence of the urinoma (Husmann and Morris, 1990; Husmann et al, 1993b; Umbreit et al, 2009).

The development of a perinephric abscess after renal injury is extremely rare, occurring in less than 1% of renal injuries following blunt trauma and in 5% of renal injuries caused by penetrating renal trauma. It is more commonly seen in patients when there is a confluence of injuries—specifically, a devitalizing grade 3 to 5 renal injury in conjunction with either duodenal, pancreatic, or colonic injuries. This complication will also arise on occasion as a result of bacterial seeding from an infected venous line, from an ascending infection following bacterial colonization of a urethral catheter in conjunction with an indwelling ureteral stent, or following wound debridement (Husmann and Morris, 1990; Husmann et al, 1993b; Umbreit et al, 2009).

Symptoms of a perinephric abscess are intermittent febrile spikes, flank pain, persistent ileus, and elevated white blood cell count. These symptoms may exactly mimic those associated with an undrained symptomatic urinoma. In the absence of gas within the soft tissues, the differential diagnosis between a symptomatic urinoma and a perinephric abscess may be very difficult. I choose to treat all patients with these findings for a symptomatic urinoma and will resort to additional percutaneous drainage of the perineph-

ric fluid collection only if there is gas in the soft tissue at the time of initial diagnosis, or if the patient's febrile course persists after 72 hours of drainage with a ureteral stent and urethral catheter or nephrostomy tube in situ (Husmann and Morris, 1990; Husmann et al, 1993b; Al-Qudah and Santucci, 2006).

Follow-up Radiographic Imaging after Renal Trauma: the ALARA Concept (As Low As Reasonably Achievable)

Recommendations for follow-up renal imaging in the pediatric patient sustaining renal trauma are a balance of the physician's need to assess the percentage of residual functional renal tissue remaining and/or the need to confirm the resolution of the perinephric urinoma versus the concern for the future risk of radiation-induced malignancy (Alsikafi et al, 2006; Brenner and Hall, 2007; Malcolm et al, 2008; Shah and Platt, 2008; Eeg et al, 2009; Davis et al, 2010; Shirazi et al, 2010; Bukur et al, 2011; Shenfeld and Gnessin, 2011). The principle that radiation exposure for diagnostic and follow-up purposes should be kept to a minimum is known as ALARA—as low as reasonably achievable. This concept currently permeates all of pediatric practice and has greatly impacted both the initial trauma workup and follow-up recommendations for the post-traumatic injury phase. Presently, a CT scan is repeated in the acute post-traumatic phase only for patients who have specific symptoms: persistent or new onset of fever, persistent ileus, worsening flank pain, or persistent gross hematuria greater than 72 hours after the traumatic insult (Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Buckley and McAninch, 2006; Bent et al, 2008; Malcolm et al, 2008; Davis et al, 2010; Shirazi et al, 2010; Bukur et al, 2011; Shenfeld and Gnessin, 2011). Although some authors have advocated performing a screening ultrasound in these circumstances, my experience in this situation is that the ultrasound is usually inconclusive, only serving to add to the financial cost of patient care and delay the inevitable CT scan. Based on my personal experience, I would preferentially recommend a CT scan for re-evaluation if the clinical circumstances suggest re-evaluation is necessary (Bent et al, 2008; Malcolm et al, 2008; Eeg et al, 2009; Tasian et al, 2010; Bukur et al, 2011).

Based on follow-up CT findings that renal scarring is essentially nonexistent after grade 1 to 2 renal injuries, no radiologic follow-up is recommended in this patient population. In contrast, approximately 50% to 60% of patients with grade 3 and 100% of patients with grades 4 and 5 renal injury will develop renal scars. For patients with grade 3 to 5 renal injuries, renal ultrasonography at 3 months is recommended for grade 3 lacerations where all fragments are viable. There is controversy regarding radiologic follow-up for grade 3 renal lacerations associated with devitalized fragments and for grade 4 and salvaged grade 5 renal injuries (Bent et al, 2008; Dunfee et al, 2008; Malcolm et al, 2008; Eeg et al, 2009; Umbreit et al, 2009; Davis et al, 2010; Shirazi et al, 2010; Bukur et al, 2011; Shenfeld and Gnessin, 2011). Although most authors recommend performing a repeat CT scan or magnetic resonance imaging (MRI) study at 3 months in this patient population, others advocate ultrasonography, with CT or MRI performed only in the presence of identifiable ultrasound abnormalities (Eeg et al, 2009). My personal experience is that a renal ultrasound will inevitably be abnormal following high-grade renal injuries, especially those associated with devitalized fragments, and the ultrasound will prompt additional evaluations. For cost-beneficial purposes, I will preferentially perform a CT evaluation, although consideration for an MRI study can be given in the older child when sedation/anesthesia would not be necessary. The delayed study (3 months post-injury) is done to document resolution of the urinary extravasation, assess the anatomy of the healed kidney, estimate percentage of renal function remaining, and rule out any occult complications (El-Sherbiny et al, 2004; Bent et al, 2008; Dunfee et al, 2008; Malcolm et al, 2008; Eeg et al, 2009; Umbreit et al, 2009; Davis et al, 2010; Shirazi et al, 2010; Tasian et al, 2010; Bukur et al, 2011; Shenfeld and Gnessin, 2011).

Serial dimercaptosuccinic acid (DMSA) scans obtained post-trauma have revealed that little, if any, renal parenchyma recovers function 1 week following injury. Therefore nuclear renography obtained any time within 1 week post-trauma results in a valid prognosis of renal function and can aid in the diagnosis of severe renal contusion versus a nonfunctional renal fragment following grade 3 kidneys with devitalized fragments or grade 4 and 5 injuries (see Fig. 154-3) (Wessells et al, 1997a; Moog et al, 2003). Currently, renal scans are obtained in two circumstances: when there is concern for long-term renal prognosis or in the presence of post-trauma-induced hypertension (Moog et al, 2003; Heyns, 2004). Classically, if the serum creatinine is normal, a differential renal function of greater than or equal to 30% demonstrates satisfactory ipsilateral renal function, which would prevent renal failure if the uninjured kidney is lost. In the presence of post-trauma-induced hypertension, captopril-enhanced mercaptoacetyl triglycine (MAG3) renography can be used to screen for trauma-induced renal vascular stenosis. Notably, the vast majority of patients with trauma-induced hypertension will have a kidney that has healed with a differential renal function of less than or equal to 20% and will be associated with poorly perfused renal parenchyma and not a major renal artery stenosis (Wessells et al, 1997a; Moog et al, 2003; Heyns, 2004; Keller et al, 2004; Santucci et al, 2004b; Chedid et al, 2006) (Fig. 154-6).

KEY POINTS: RADIOGRAPHIC AND ENDOSCOPIC ASSESSMENT AND TREATMENT OF PEDIATRIC UPPER TRACT GENITOURINARY INJURIES

- Radiographic assessment of the GU tract for a possible injury should occur following all penetrating abdominal trauma, as well as in blunt trauma victims who have one of four criteria: (1) a history of a significant deceleration or high-velocity injury; (2) significant trauma that has resulted in fractures of thoracic rib cage, spine, pelvis, or femur and bruising of the torso/perineum or signs of peritonitis; (3) gross hematuria; and (4) microscopic hematuria (>50 red blood cells/high-power field) associated with shock (systolic blood pressure <90 mm Hg).
- The two GU injuries most likely to be missed by a single-phase CT scan or single-shot IVP are perinephric fluid collections (urinomas) and isolated ureteral injuries. In patients with evidence of a grade 3 or higher renal injury, delayed excretory images are highly recommended.
- Three key findings noted on CT scan are suggestive that either endoscopic, interventional radiographic, or open surgical intervention will likely be necessary: medial extravasation of contrast, lateral extravasation of contrast with the ipsilateral distal ureter not visualized, and a perinephric hematoma of greater than 2.5 cm.
- Approximately 25% of patients with grade 3 to 4 renal trauma, managed in a nonoperative fashion, will develop persistent or secondary (delayed) hemorrhage. Superselective angioinfarction of the bleeding vessel is the preferred method to manage this complication.
- Most post-traumatic urinomas are asymptomatic and will spontaneously resolve. Approximately 15% of urinomas will be associated with continued flank pain, adynamic ileus, and/or low-grade temperature and require endoscopic or percutaneous management.
- Follow-up renal imaging is not recommended for grade 1 to 2 renal injuries and for grade 3 lacerations where all fragments are viable. Grade 3 renal lacerations associated with devitalized fragments and grade 4 and 5 renal injuries should have a repeat CT scan in the acute phase only if symptomatic; otherwise, a urinalysis and blood pressure check should be performed at 6 and 12 weeks post-injury and follow-up radiologic studies obtained at 12 weeks.

MANAGEMENT OF RENAL TRAUMA

Multiple studies have found that the nephrectomy rate in patients with traumatic renal injuries was higher with surgical exploration than with nonoperative management (Cass and Ireland, 1973; Cass et al, 1987; Kristjánsson and Pedersen, 1993; Hammer and Santucci, 2003; Keller et al, 2004; Broghammer et al, 2007). These papers suggested that hemorrhage from the severely injured kidney was held in check by a tamponade maintained by an intact Gerota fascia. Surgical exploration with disruption of the fascia resulted in uncontrollable renal bleeding and the need for emergent nephrectomy. Current studies reveal that this long-held hypothesis appears inaccurate. Specifically, with the enhanced ability of the CT scan to accurately stage renal injuries and with the development and application of trauma-related severity scores, multiple current studies reveal that the need for emergent nephrectomy during renal exploration is not due to intractable hemorrhage incited by the renal exploration; rather, emergent nephrectomy usually either is due to the severity of the initial renal injury or was performed in patients who had severe intraoperative hemodynamic instability as a result of multiple coexisting injuries. Nephrectomy in this latter situation was performed for expediency to save the hypothermic, coagulopathic, and clinically unstable patient (Husmann et al, 1993b; Wessells et al, 1997b; Gonzalez et al, 1999; Santucci and McAninch, 2001; Santucci et al, 2001, 2004b; Bozeman et al, 2004; Davis et al, 2006; Wright et al, 2006; Broghammer et al, 2007; Shariat et al, 2007, 2008; Umbreit et al, 2009).

Although all authorities agree that a clinically stable patient with an isolated renal injury should be managed in a nonoperative fashion, considerable controversy exists regarding the management of grade 3 or higher renal injuries when intra-abdominal injuries that mandate surgical exploration are found. There are three schools of thought in this controversy. One is that, provided no absolute indications for renal exploration are present, all renal trauma should be observed (Altman et al, 2000; Hammer and Santucci, 2003; Keller et al, 2004). A second is that renal exploration and renorrhaphy of a grade 3 or higher renal injury should be carried out if a laparotomy was to be performed for a coexisting intra-abdominal injury (especially if the stomach, duodenum, pancreas, or colon was injured) (Corriere et al, 1991; Husmann et al, 1993b; Heyns, 2004; Santucci et al, 2004b; Umbreit et al, 2009). A third is that renal exploration can be excluded in patients with concurrent intra-abdominal injuries provided the trauma surgeon separates the site of the enteric injury from the urinary tract by omentum or other alternative tissue and places perioperative drains. It is hypothesized that the separation of the two sites of injury and the placement of drains will prevent breakdown of enteric repairs caused by leaking urine and/or help prevent the development of urinary tract complications by removal of excess contaminating bacteria or pancreatic enzymes from the site of GU injury (Husmann et al, 1993b; Wessells and McAninch, 1996; Matthews et al, 1997; El Khader et al, 1998; Santucci et al, 2004b; Broghammer et al, 2007). Owing to the controversy, the major problem facing the urologist in the patient with traumatic renal injury is determining when to surgically intervene. The current recommendations on when to pursue operative intervention are based on three findings: the hemodynamic stability of the patient, an accurate radiographic staging of the renal trauma, and the presence of associated organ injury (Table 154-2) (Husmann and Morris, 1990; Husmann et al, 1993b; Wessells et al, 1997b; Heyns, 2004; Santucci et al, 2004b; Buckley and McAninch, 2006, 2011; Umbreit et al, 2009).

Nonoperative Therapy for Renal Trauma

The ideal candidate for nonoperative management is the hemodynamically stable patient sustaining either blunt or penetrating trauma, with or without associated intra-abdominal injuries, and having a grade 1 to 3 renal injury. Genitourinary complications in this subset of patients are minimal (Wessells et al, 1997b; Heyns, 2004; Santucci et al, 2004b; Charbit et al, 2011). Patients with grade 4 and 5 renal injuries who are hemodynamically stable, if

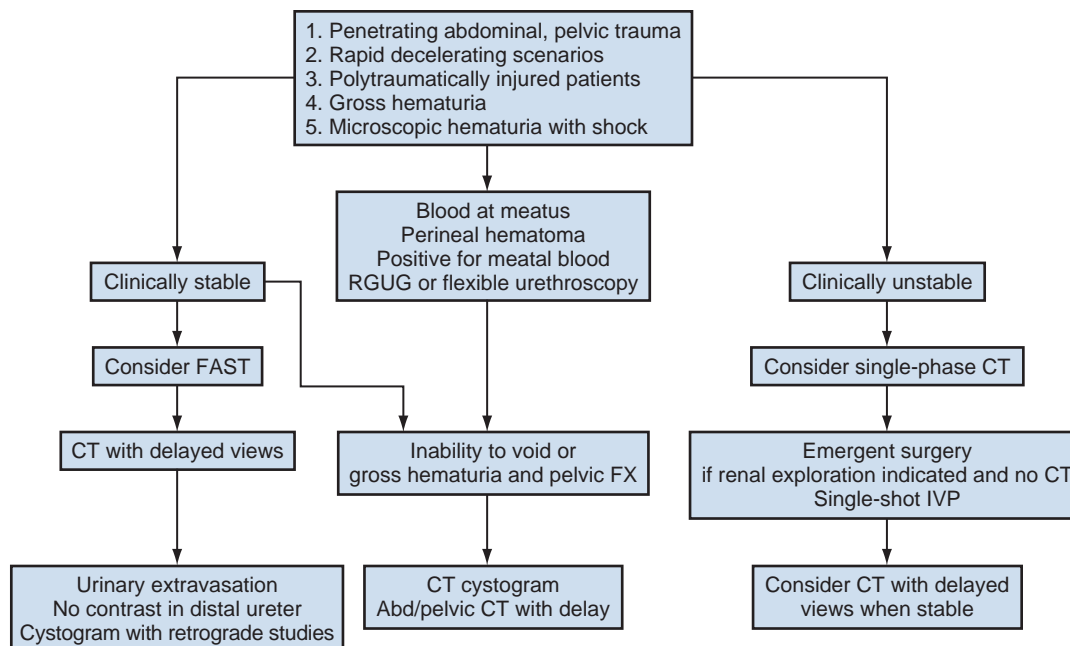


Figure 154-6. Recommended evaluation protocol for patients with a medical history or physical findings consistent with possible genitourinary injury. Abd, abdominal; CT, computed tomography; FAST, focused assessment with sonography for trauma; FX, fracture; IVP, intravenous pyelography; RGUG, retrograde urethrogram.

TABLE 154-2 Consensus Recommendations for Management of Renal Trauma

CLINICAL FINDINGS AND/OR GRADE OF RENAL INJURY	RECOMMENDED TREATMENT
Grade 1 or 2 renal injury irrespective of traumatic etiology*	Nonoperative
Isolated grade 3, grade 4, and hemodynamically stable grade 5 renal injuries	Nonoperative
Uncontrollable renal hemorrhage/vascular instability; occasionally grade 4 “shattered” kidneys and a high percentage of grade 5 injuries	Absolute requirement for surgical intervention
Persistent or delayed hemorrhage not responding to angiographic embolization	Absolute requirement for surgical intervention
Expanding pulsatile retroperitoneal mass found on surgical exploration for coexisting intra-abdominal injuries	Absolute requirement for surgical intervention (verify contralateral renal function prior to exploration)
Penetrating trauma, inadequate preoperative radiographic staging because of vascular instability of patient, retroperitoneal hemorrhage found on exploration	Retroperitoneal (renal) exploration recommended (verify contralateral renal function prior to exploration)
Blunt trauma; inadequate preoperative radiographic staging because of vascular instability of patient; no duodenal, pancreatic, or colonic injuries with retroperitoneal hemorrhage found on exploration	Observation—if FAST with bilateral blood flow. If no FAST obtained, consider intraoperative single-shot IVP/US with renal blood flow assessment or CT immediately following stabilization of patient
Blunt trauma; inadequate preoperative radiographic staging because of vascular instability of patient; duodenal, pancreatic, or colonic injuries with retroperitoneal hemorrhage found on exploration	Surgical interventions with renorrhaphy an option (verify contralateral renal function prior to exploration) or Drain intra-abdominal injuries. Observation—if FAST with bilateral blood flow. If no FAST obtained, consider intraoperative single-shot IVP/US with renal blood flow assessment or CT immediately following stabilization of patient
Blunt/penetrating trauma; radiographic screening studies reveal grade 3 renal injury with devitalized renal fragments, grade 4 or 5 renal injury, coexisting intra-abdominal injuries—especially duodenum, pancreas, and colon	Retroperitoneal (renal) exploration with renorrhaphy and repair recommended

CT, computed tomography; FAST, focused assessment with sonography for trauma; IVP, intravenous pyelography; US, ultrasound.

*Blunt or penetrating trauma.

they present with no other indications for surgical intervention, are also candidates for nonoperative treatment (Brewer et al, 2009). Even identification of a large segment of devitalized renal parenchyma, a perinephric hematoma greater than 2.5 cm in size, or a large medially or laterally placed urinoma is not an absolute contraindication for nonoperative management provided the patient is hemodynamically stable and the distal ureter is documented to be intact (see Fig. 154-5) (Umbreit et al, 2009; Buckley and McAninch, 2011; Charbit et al, 2011; Lin et al, 2013).

Nonoperative therapy consists of bed rest, close monitoring of vital signs and urine output, serial abdominal examinations, serial hemoglobin/hematocrit determinations, and transfusion as indicated (Heyns, 2004; Santucci et al, 2004b). In patients with a renal injury secondary to penetrating trauma who are on a nonoperative protocol, intravenous broad-spectrum antibiotics are recommended because of the risk of wound contamination. In renal injuries following blunt trauma, antibiotics may be considered if a large retroperitoneal hematoma, urinary extravasation, or extensive soft tissue injuries are present. The use of antibiotics following blunt renal trauma is advocated owing to the presence of indwelling urethral catheters and/or multiple intravascular catheters or superficial dermatologic abrasions, any of which could serve as a nidus for bacteremic colonization of the perinephric hematoma or urinoma (Husmann and Morris, 1990; Husmann et al, 1993b; Buckley and McAninch, 2004, 2006; Heyns, 2004; Kansas et al, 2004; Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Umbreit et al, 2009; Charbit et al, 2011).

If the child becomes hemodynamically unstable or continues to have a decreasing hemoglobin/hematocrit despite transfusions, options of management usually involve a repeat CT evaluation. In an attempt to reduce radiation exposure, I will frequently skip a repeat CT scan and proceed directly to renal angiography with selective angioinfarction of the bleeding site. Similarly, in the patient with a known urinoma who has persistent fever, ileus, or flank pain, the physician can consider proceeding directly to endoscopic management of the urinoma with confirmation of the persistent urine leak with a retrograde ureterogram at the time of stent placement (Umbreit et al, 2009; Bukur et al, 2011).

Ambulation is allowed as soon as gross hematuria has resolved. In patients with a grade 1 renal injury desiring to return to sporting activities, re-evaluation of the athlete and urinalysis 48 to 72 hours after the injury is recommended. Provided physical examination is normal and the hematuria has cleared, athletic activities can be resumed. In individuals with persistent symptoms and/or microhematuria follow-up can occur at weekly to biweekly intervals with clearance for participation in sports once the aforementioned criteria have been met. In patients with grades 2 to 5 renal injury, recommendations are for a 6-week hiatus from their athletic endeavors. At 6 weeks, a physical examination and urinalysis are obtained; if the physical examination is normal and hematuria has cleared, the patient is allowed to resume all activities. As noted previously, I do obtain a functional renal study—either a CT/MRI or nuclear renography—to assess for the extent of kidney function and resolution of the urinoma in all patients with grade 3 renal injury with devitalized fragments and those with grade 4 and 5 injuries at 3 months after the traumatic insult (Wessells et al, 1997b; Heyns, 2004; Kansas et al, 2004; Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Buckley and McAninch, 2006; Broghammer et al, 2007; Bukur et al, 2011).

Operative Intervention for Renal Trauma

Absolute indications for renal exploration are hemodynamic instability attributable to a renal source, an expanding or pulsatile retroperitoneal hematoma found at the time of surgical intervention for intra-abdominal injuries, and inability to stop persistent or delayed hemorrhage by selective vascular embolization. Relative indications for retroperitoneal renal exploration are a history of vascular instability resulting in an inability to obtain adequate preoperative radiographic evaluations, where surgical exploration for intra-abdominal injuries reveals duodenal, pancreatic, or colonic

injuries to coexist with a retroperitoneal hematoma. It is important to note that a single-shot IVP or renal ultrasound with assessment of renal blood flow to verify contralateral renal function is required before renal exploration (see Table 154-2) (Heyns, 2004; Santucci et al, 2004b). In this latter situation or in patients with a known grade 3 or higher renal injury undergoing exploratory laparotomy for multiorgan injury, options are either retroperitoneal renal exploration with renorrhaphy or placement of intraperitoneal and retroperitoneal drains with separation of the urinary tract injury from adjacent enteric injuries by interposing omentum. **Although the surgeon can choose between these two options, he or she should be aware that the consensus opinion is that renal exploration and renorrhaphy are preferred** (Husmann et al, 1993b; Wessells et al, 1997b; Santucci and McAninch, 2001; Buckley and McAninch, 2004, 2006; Heyns, 2004; Santucci et al, 2004b; Umbreit et al, 2009).

Renal salvage by renorrhaphy or partial nephrectomy requires complete exposure of the injured kidney, debridement of nonviable tissue, suture ligation of bleeding arterial vessels, and repair of the collecting system injury. Defects in the renal parenchyma may be closed primarily with renal capsule. For larger defects, I prefer the placement of Gelfoam (Pfizer, New York, NY) and Surgicel (Ethicon, Somerville, NJ) packing into the parenchymal defect, with coverage or closure of the renal capsule defect using woven polyglycolic acid mesh. Alternatively, perinephric fat, omentum, or thrombin-soaked gel foam may be used to pack the parenchymal defect. Watertight closure of the collecting system is not always possible and may be inadvisable. If the renal pelvis or ureter is closed with excessive stretch, further devascularization, tissue sloughing, and delayed urinary leakage may occur. If a major violation of the urinary drainage system is present, placement of intraoperative ureteral stents or a nephrostomy tube should be considered. Adequate drainage of the perinephric area following repair is vital. In the presence of concurrent duodenal, pancreatic, and colonic injuries, interposition of omentum or peritoneum between the site of the major renal injury and the site of the coexisting intra-abdominal injury is strongly advised. Nephrectomy should be considered in irreparable grade 4 or 5 renal injuries and in the hemodynamically unstable patient with multiorgan trauma. A nephrectomy may need to be performed in this latter situation to reduce operative time and help control bleeding in the hypothermic and coagulopathic patient (Heyns, 2004; Santucci et al, 2004b; Davis et al, 2006; Wright et al, 2006; Broghammer et al, 2007; Shariat et al, 2008; Umbreit et al, 2009).

Renal Vascular Injuries

In terms of arterial renal blood flow, the kidney is an end organ; only rarely is collateral blood flow outside of the main renal arterial supply sufficient to maintain renal function. **In a patient sustaining renal arterial trauma, the clinical triad of hemodynamic instability, inadequate collateral blood flow, and warm ischemic time almost invariably results in the inability to salvage renal function** (Turner et al, 1983; Knudson et al, 2000; Heyns, 2004; Santucci et al, 2004a; Dozier et al, 2013). In fact, attempted repair of the renal vascular injury in these crucially ill patients with grade 5 renal trauma has been associated with high failure rates and poorer patient outcomes than immediate nephrectomy (Turner et al, 1983; Knudson et al, 2000; Dozier et al, 2013). Because of these findings, no attempt to repair injuries to segmental renal vessels should be considered and repair of the traumatically injured main renal artery is seldom, if ever, indicated when a normal contralateral kidney is present. In essence, reconstruction of the main renal artery following trauma is only a primary consideration in patients who are hemodynamically stable with an injury to a solitary kidney or in patients with bilateral renal arterial injuries (Turner et al, 1983; Knudson et al, 2000; Heyns, 2004; Santucci et al, 2004a; Buckley and McAninch, 2011; Dozier et al, 2013). The infrequent exception to this rule is the presence of an incomplete arterial injury where perfusion to the kidney has been maintained by flow of blood either through the partially occluded main renal artery or through collateral vessels.

KEY POINTS: RENAL TRAUMA

- The ability of the CT scan to accurately stage renal injuries, combined with the application of trauma-related severity scores, suggests that emergent nephrectomy at the time of surgical exploration is usually due to either surgical expediency in the unstable patient or preexisting vascular damage, but it is not the consequence of intractable hemorrhage incited by the renal exploration.
- Nonoperative management is preferred in the hemodynamically stable patient with a grade 1 or 2 renal injury resulting from either blunt or penetrating trauma with or without associated intra-abdominal injuries. It is also the preferred treatment modality in isolated grade 3, 4, and 5 renal injuries when the patient is hemodynamically stable.
- Identification of a urinoma is not a contraindication for nonoperative management, provided that the distal ureter is documented to be intact.
- Absolute indications for renal exploration following trauma are (1) hemodynamic instability resulting from renal bleeding, (2) an expanding or pulsatile retroperitoneal hematoma, or (3) inability to stop persistent or delayed hemorrhage by selective vascular embolization.
- There are two relative indications for renal exploration. The first is finding a retroperitoneal hematoma at the time of surgical exploration for intra-abdominal injuries in a patient with inadequate preoperative radiographic staging. A single-shot IVP or intraoperative renal ultrasound with documentation of renal blood flow to verify contralateral renal function is required before renal exploration. The second is CT-documented presence of a grade 3 or higher renal injury coexisting with intra-abdominal injuries that require abdominal exploration.

native (Wessells et al, 1997b; Moog et al, 2003; Heyns, 2004; Keller et al, 2004; Santucci et al, 2004b; Chedid et al, 2006; Myrianthefs et al, 2007). Descriptions of treatment of hypertension caused by a subcapsular hematoma or fibrosis by decortication of the Page kidney have been published; however, the long-term results of this surgical treatment modality are extremely controversial (see Fig. 154-2) (Heyns, 2004; Santucci et al, 2004b; Myrianthefs et al, 2007).

KEY POINTS: RENAL VASCULAR INJURIES AND TRAUMA-INDUCED RENAL HYPERTENSION

- In renal arterial trauma, the clinical triad of hemodynamic instability, inadequate collateral blood flow, and warm ischemic time almost invariably results in inability to salvage renal function. Therefore repair of the traumatically injured main renal artery is seldom, if ever, indicated when a normal contralateral kidney is present.
- Hypertension secondary to renovascular trauma will usually develop within 36 months following the injury. If sustained hypertension does develop, evaluation with a DMSA scan to determine differential renal function and radiographic studies (MRI or CT angiography) to rule out development of an arteriovenous fistula as the source of the hypertension should be performed. Hypertension found to be related to an arteriovenous malformation may be treated with angiographic embolization.
- The most common clinical finding in post-trauma-induced hypertension is a small poorly functioning kidney (<20% function) associated with pan-nephric scarring, with nephrectomy being the best treatment alternative.

Trauma-Induced Renal Vascular Hypertension

The most common causes of post-traumatic renal hypertension are invariably renin mediated secondary to renal ischemia. Ischemia typically develops from one of four etiologies: (1) a partial arterial stenosis, (2) complete obstruction of a segmental or main renal artery with an intact peripheral blood supply, (3) trauma-induced alteration in blood flow resulting from an arteriovenous malformation or pseudoaneurysm, or (4) on extremely rare occasions, compression of the renal parenchyma by hematoma/fibrosis/urinoma (Page kidney model). **The presence of hypertension immediately following the traumatic insult may be secondary to pain and may resolve with observation. Persistent hypertension 30 days postinjury or hypertension developing within 3 months of the injury could be due to a trauma-induced renal source and the diagnosis should be considered.** The incidence of trauma-induced hypertension after a grade 3 or higher renal injury is approximately 5% (Heyns, 2004; Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Chedid et al, 2006; Henderson et al, 2007).

In patients with suspected traumatic hypertension, blood pressure is controlled with angiotensin-converting enzyme inhibitors. Also, evaluation with both nuclear renography to determine differential renal function and radiographic studies (MRI or CT angiography) to rule out an arteriovenous fistula or a pseudoaneurysm as the source of the hypertension should be performed. Hypertension resulting from a vascular malformation may be treated with angiographic embolization. If consideration for surgical intervention is entertained, renal vein renin sampling for split renin ratios should be considered. The latter is especially helpful in the presence of segmental renal scarring when partial nephrectomy is a consideration for surgical management. In this situation, hypertension proven to be related to segmental renal ischemia can be treated by partial nephrectomy. **The most common clinical finding in patients with post-traumatic hypertension is a small, poorly functioning kidney (<20% function) associated with pan-nephric scarring; nephrectomy is the best surgical alter-**

Trauma-Induced Chronic Flank Pain following Renal Injury

Chronic flank pain developing after traumatic renal injury is reported to occur in approximately 7% of patients following grade 3 or higher renal injuries. CT scans with delayed images and, occasionally, renograms using furosemide (Lasix) (Sanofi, Bridgewater, NJ) are warranted. Findings of renal lithiasis, UPJ obstruction, and persistent urinoma will occasionally be found. Unfortunately, the majority of patients will not have a clear etiology for their chronic pain syndrome. Treatment will usually involve pain management and, on rare occasions, nephrectomy. I would caution the surgeon that removal of the kidney does not necessarily correlate with resolution of the pain (Mogensen et al, 1980; Al-Qudah and Santucci, 2006).

Recommendations for Activities and Follow-up in Patients with a Solitary Kidney

The recommendations by the American Academy of Pediatrics are that all patients with a solitary kidney who desire to participate in contact sports should undergo individual physician assessment, with recommendations for participation based on the physician's findings. Most urologists are currently making their recommendations on the basis of the following facts. Contact sports are the third most common cause of renal injury in children (Table 154-3). However, the mean stage of traumatic renal injury occurring as a consequence of contact sports is lower than that of all other etiologic causes of traumatic renal injury in children. Specifically, the mean stage for renal injury following bicycle, motor cross, and dirt bike accidents is 2.7 ± 1.0 , that for all-terrain vehicle (ATV) accidents is 2.4 ± 1.3 , that for falls is 2.4 ± 1.2 , and that for motor vehicle collisions is 2.1 ± 1.0 compared with the severity of injuries caused by contact and miscellaneous sports, which is 1.7 ± 1.0 (Committee on Sports Medicine and Fitness, 2001; Gerstenbluth et al, 2002; McAleer et al, 2002a; Holmes et al, 2003; Johnson

TABLE 154-3 Incidence of Pediatric Renal Injury Related to Mechanism of Injury

MECHANISM OF RENAL INJURY	PERCENTAGE OF RENAL INJURIES CAUSED BY BLUNT TRAUMA IN A PEDIATRIC POPULATION
Motor vehicle collision (including motor vehicle vs. pedestrian)	45%
Bicycle accidents (including dirt bikes and motor cross)	17%
Contact sports	12%
All-terrain vehicle accident	10%
Sports—miscellaneous (sledding, skiing, snowboarding, horseback riding, rollerblading, etc.)	7%
Falls	6%
Abuse/assault	3%

Data from Emmanuel et al (1977), Amaral (1997), Gerstenbluth et al (2002), McAleer et al (2002b), Johnson et al (2005), Broghammer et al (2006), and Wu and Gaines (2007).

et al, 2005; Wu and Gaines, 2007; Brophy et al, 2008). The facts as noted have prompted most pediatric urologists to clear patients with one kidney for participation in organized contact sports, provided three baseline criteria are met: the remaining kidney has normal anatomy, it is in the normal anatomic position, and protective gear is worn. These facts have also resulted in the routine cautioning of parents and patients that the child with a solitary kidney should wear a seat belt or be restrained in a car seat at all times, and that ATV activities, motor cross, and dirt bike racing are associated with increased risk for renal injury and participation in these activities should be done with caution (Committee on Sports Medicine and Fitness, 2001; Gerstenbluth et al, 2002; McAleer et al, 2002a; Holmes et al, 2003; Johnson et al, 2005; Wu and Gaines, 2007; Brophy et al, 2008).

One of the major questions that arises in the families of patients undergoing an emergent nephrectomy for trauma is, "After this procedure, what is the risk that my child will need dialysis or a renal transplant because of the development of chronic renal failure?" This parental concern arises from the child's lifelong risk of other systemic illnesses (i.e., metabolic syndrome, hypertension, diabetes, nephrolithiasis, renal cell carcinoma, and hyperfiltration injury) and, as mentioned, of subsequent trauma to the remaining contralateral kidney. To answer this question, a recent review of data in the National Trauma Data Bank, the National Inpatient Sample database, and the U.S. Renal Data System as well as their university-based urban trauma center database was carried out by Dozier and associates (2013). Their findings revealed that loss of a kidney by trauma had played a role in 0.1% of patients with dialysis/transplant-dependent renal failure in the United States. Using these data, the estimated risk to an individual that a trauma nephrectomy would play a role in causing dialysis-dependent renal failure is 0.5% (Dozier et al, 2013). It is unknown if closer follow-up of patients to prevent the onset of metabolic syndrome and adequate treatment of hypertension or hyperfiltration injury would lessen this risk.

MANAGEMENT OF PREEXISTING HYDRONEPHROSIS AND URETEROPELVIC JUNCTION DISRUPTION

Disruption of the UPJ is most commonly caused by acceleration/deceleration injuries (falling from >10 feet) or by a sudden extreme

hyperextension of the trunk (pedestrian–motor vehicle accident, ejection injury associated with motor vehicle accident). The mechanism of injury is hypothesized to be a sudden displacement of the more mobile kidney associated with a relatively fixed ureter, with force vectors from the traumatic impact interacting at the UPJ (Boone et al, 1992; Chopra et al, 2002; McAleer et al, 2002a).

Although it has been reported that preexisting hydronephrosis or a congenital UPJ obstruction renders the patient more susceptible to a UPJ disruption, this is controversial. The vast majority of patients with a history of trauma and preexisting UPJ obstruction or hydronephrosis will be found to have a renal contusion or grade 1 renal injury on evaluation (Fig. 154-7). If the initial CT scan reveals poor renal function secondary to a thinned cortex from the preexisting obstruction, I will usually place a percutaneous nephrostomy tube for 4 weeks and reassess function with a renal scan. Repair is recommended for patients with a differential renal function of greater than 20%.

When urinary extravasation is seen, rupture of the renal pelvis or a major laceration extending through a thinned renal cortex into the collecting system (grade 3 renal injury) is the most common finding, not a UPJ disruption (Boone et al, 1993; Hall and Carpinito, 1994; Gschwend et al, 1995; Kattan, 2001; Chopra et al, 2002; McAleer et al, 2002a; Smith et al, 2003; Ashebu et al, 2004). The majority of patients sustaining a UPJ disruption will present with vascular instability, requiring emergent laparotomy with the patient unable to undergo preoperative imaging. Urinalysis on presentation will have some degree of hematuria in 70% of patients; however, 30% of patients with UPJ disruption will have a completely normal urinalysis. Emergent exploratory laparotomy for coexisting intra-abdominal injury is usually necessary, and exploration fails to reveal the presence of a retroperitoneal hematoma (Boone et al, 1993; Hall and Carpinito, 1994; Gschwend et al, 1995; Chopra et al, 2002; McAleer et al, 2002a; Smith et al, 2003; Ashebu et al, 2004; Al-Qudah and Santucci, 2006). Because of the frequent association of this injury with life-threatening trauma, the diagnosis of a UPJ disruption is delayed for greater than 36 hours in more than 50% of patients (Boone et al, 1993; Kattan, 2001; Chopra et al, 2002; McAleer et al, 2002a; Al-Qudah and Santucci, 2006). Patients will eventually come to attention because of CT abnormalities found during the workup of persistent postoperative fever, chronic flank pain, continued ileus, or sepsis (Boone et al, 1993; Kattan, 2001; Chopra et al, 2002; McAleer et al, 2002a; Al-Qudah and Santucci, 2006). Three classic findings on a triphasic CT scan are associated with UPJ disruption: (1) absence of parenchymal laceration, (2) medial extravasation of contrast in the perirenal and upper ureteral area, and (3) no visualization of the ipsilateral distal ureter (Boone et al, 1993; Kawashima et al, 1997; Kattan, 2001; Chopra et al, 2002; McAleer et al, 2002a; Al-Qudah and Santucci, 2006).

In children with preexisting hydronephrosis secondary to congenital hydronephrosis or a UPJ obstruction the site of the injury is almost invariably a major laceration through the thinned renal cortex (grade 3 renal injury) or laceration of the renal pelvis; rarely is disruption of the UPJ present. These patients should undergo a retrograde pyelogram to confirm continuity of the UPJ and then can be safely managed with either a percutaneous nephrostomy or double-J stent placement, with delayed pyeloplasty performed following stabilization of the patient (Husmann and Morris, 1990; Matthews et al, 1997; McAleer et al, 2002a; Smith et al, 2003; Dugi et al, 2010; Bartley and Santucci, 2012).

In patients with a disruption of the UPJ diagnosis can be delayed up to 12 weeks post-injury, which will significantly increase the risk of nephrectomy (Boone et al, 1993; Kattan, 2001; McAleer et al, 2002a; Smith et al, 2003; Kunkle et al, 2006; Pereira et al, 2010). In the clinically stable patient, when the diagnosis is made within 5 days after the traumatic insult, I prefer to proceed to immediate surgical repair with debridement of any devitalized tissue, spatulation and reanastomosis of the ureter over a stent, and placement of an intraoperative nephrostomy tube and retroperitoneal drain. Because the area of ureteral necrosis may extend for 2 to 3 cm,

mobilization and downward displacement of the kidney may be necessary to obtain a tension-free anastomosis (Boone et al, 1993; Kattan, 2001; McAleer et al, 2002a; Smith et al, 2003). In patients with a delayed diagnosis of 6 or more days, I prefer to place a nephrostomy tube and allow the patient and injury to stabilize for 12 weeks. Differential renal function is then obtained using a DMSA renal scan, and the length of the ureteral injury is ascertained by a combined antegrade and retrograde pyelogram. The combination of remaining renal function and the length of the surgical defect allow the surgeon to make the proper surgical plan. Surgical alternatives in this situation include primary ureteroureterostomy, ileal ureter, autotransplantation, and nephrectomy. Notably, at the time of delayed repair there is usually significant technical difficulty in mobilization of the kidney, renal pelvis, and blood vessels; thus the option of nephrectomy should always be discussed and may become necessary (Boone et al, 1993; Kattan, 2001; Heyns, 2004; Santucci et al, 2004b; Kunkle et al, 2006).

URETERAL TRAUMA

External Trauma Resulting in Ureteral Injury

In children, external trauma causing ureteral injuries is rare, occurring in less than 4% of penetrating traumas, and is reportable following blunt trauma (Velmahos and Degiannis, 1997; Velmahos and Demetriades, 2002; Hudolin and Hudolin, 2003; Kansas et al, 2004; Elliott and McAninch, 2006; Pereira et al, 2010). Ureteral injuries will be found in conjunction with other intraperitoneal organ injuries in 90% of the patients and coexisting with renal or bladder injuries in 10%. Because of the frequent presence of multiple organ injury, the mortality rate of a patient sustaining a ureteral injury from external trauma is in excess of 30% (Velmahos and Degiannis, 1997; Wessells et al, 1997b; Velmahos and Demetriades, 2002; Hudolin and Hudolin, 2003; Carver et al, 2004; Kansas et al, 2004; Elliott and McAninch, 2006).

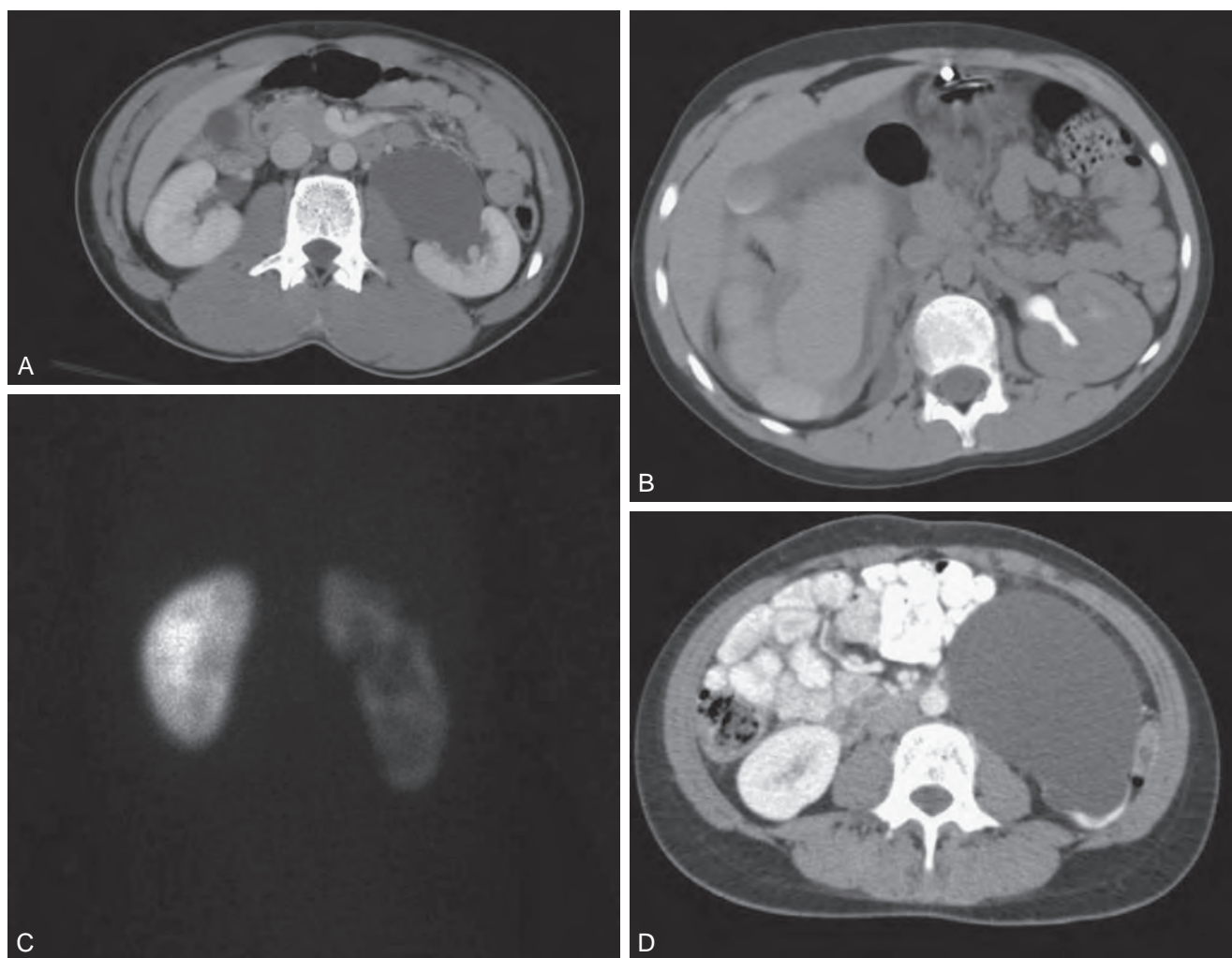


Figure 154-7. Spectrum of ureteropelvic junction (UPJ) obstructions presenting after renal trauma. **A,** A 16-year-old girl with gross hematuria and grade 1 left renal injury after a low-speed (<10 mph) motor vehicle collision. **B,** A 14-year-old boy with gross hematuria after being struck in the right flank with a soccer ball. Computed tomography (CT) scan revealed grade 1 injury. Percutaneous nephrostomy was placed for 4 weeks with follow-up mercaptoacetyl triglycine (MAG3) scan as noted in **C.** **C,** MAG3 renal scan revealing 25% function of right kidney 4 weeks following percutaneous nephrostomy tube placement. UPJ repair was subsequently performed. **D,** A 14-year-old girl presented with gross hematuria after a fall from a horse. Percutaneous nephrostomy was placed for 4 weeks, a DMSA renal scan showed less than 6% function at the end of 4 weeks, and a left nephrectomy was performed.

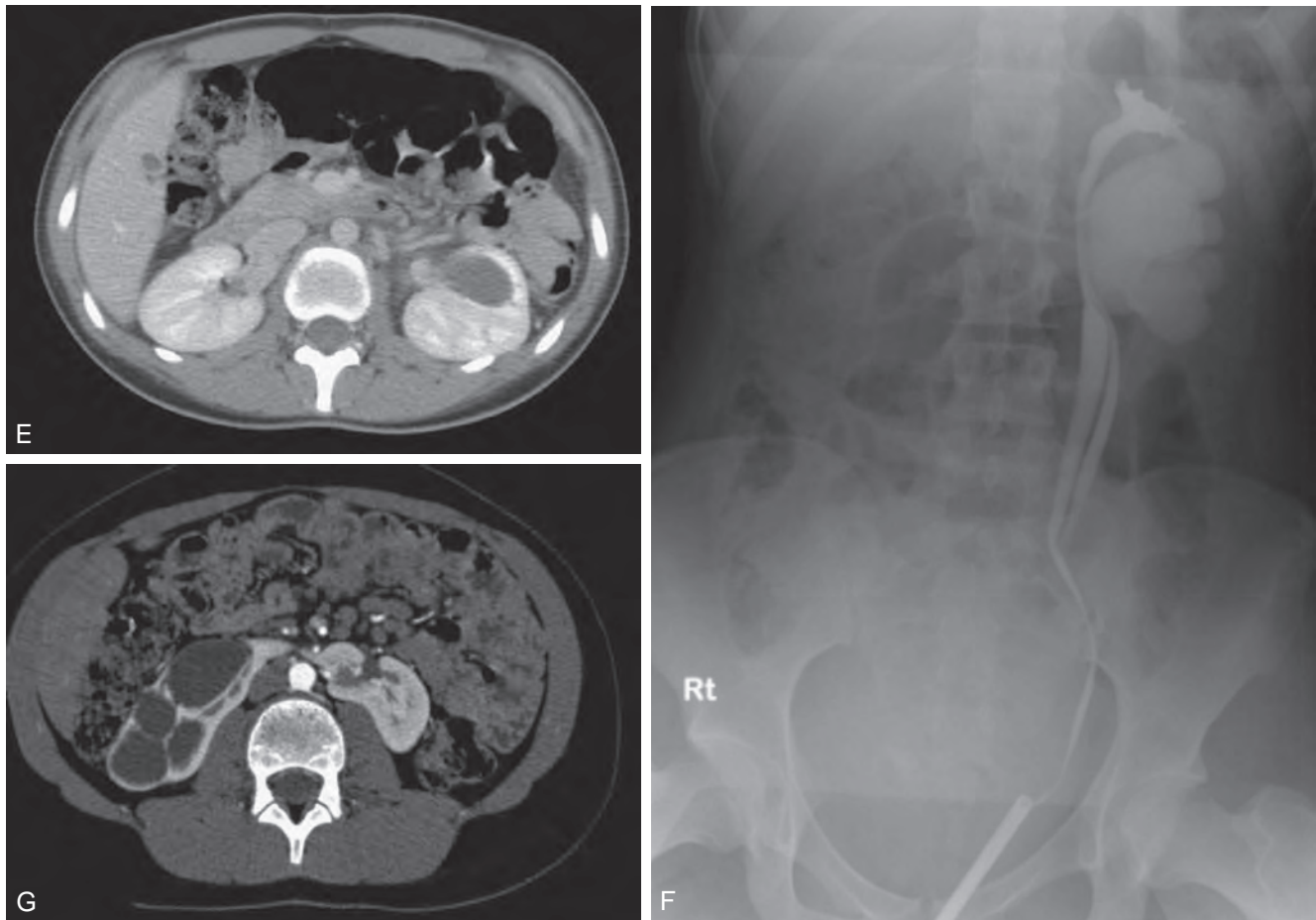


Figure 154-7, cont'd E, A 15-year-old boy presented with gross hematuria following a fall while running in a cross-country race; findings were suggestive of left lower pole UPJ obstruction. F, Left retrograde pyelogram confirmed incomplete left duplication with left lower pole UPJ obstruction. G, A 14-year-old male presented with gross hematuria following a collision while playing hockey. CT scan revealed horseshoe kidney with severe right UPJ obstruction.

Ureteral injuries associated with external trauma will lack the presence of hematuria in up to two thirds of the patients; the diagnosis is usually made by a triphasic CT study obtained to evaluate penetrating trauma and/or to rule out a GU injury following high-velocity deceleration or impact trauma (Velmahos and Degiannis, 1997; Wessells et al, 1997b; Medina et al, 1998; Velmahos and Demetriades, 2002; Hudolin and Hudolin, 2003; Carver et al, 2004; Kansas et al, 2004; Elliott and McAninch, 2006). Gunshot wounds caused by a high-velocity missile (>350 m/sec) deserve special mention. The kinetic energy of a high-velocity bullet creates a surrounding energy wave 30 to 40 times the missile diameter (Al-Ali and Haddad, 1996; Perez-Brayfield et al, 2001; Hudolin and Hudolin, 2003; Carver et al, 2004; Santucci et al, 2004b). In addition, the missile will frequently yaw or tumble during penetration, and the combination of blast injury and missile tumbling results in extensive damage to the surrounding tissues at a significant distance from its path. Of concern regarding high-velocity gunshot wounds to the torso is that radiographic and/or surgical evaluation at the time of the assault may not reveal the presence of a GU injury (Al-Ali and Haddad, 1996; Medina et al, 1998; Perez-Brayfield et al, 2001; Hudolin and Hudolin, 2003; Carver et al, 2004; Santucci et al, 2004b; Kunkle et al, 2006; Siram et al, 2010). In some patients with a high-velocity injury, the renal pelvis and/or ureter will appear intact or perhaps only slightly contused at the time of the radiographic examination and/or surgical exploration. As the high-velocity blast injury matures,

necrosis of the ureter or portions of the renal pelvis may develop. The extent of the GU injury finally comes to attention as urinary extravasation develops owing to delayed necrosis. Classically, blast injuries to the urinary drainage system present as an increase in urine output from surgically placed drains 3 to 5 days after the injury (Al-Ali and Haddad, 1996; Medina et al, 1998; Perez-Brayfield et al, 2001; Hudolin and Hudolin, 2003; Santucci et al, 2004b; Carver et al, 2004; Kunkle et al, 2006).

Iatrogenic Ureteral Injuries following Open, Laparoscopic, and Endoscopic Procedures

The most common iatrogenic ureteral injury in the pediatric population is injury following ureteroscopy; even these are rare events with ureteral perforations occurring in less than 2% of all prepubertal ureteroscopic procedures (Schuster et al, 2002; Wu and Docimo, 2004; Minevich et al, 2005). Ureteral perforation following ureteroscopy can almost invariably be managed with endoscopic intervention with ureteral stenting, with or without nephrostomy tube placement. Long-term results following endoscopic management are excellent (Schuster et al, 2002; Wu and Docimo, 2004; Minevich et al, 2005).

Traumatic ureteral injuries following laparoscopy or open surgical procedures are relatively common in adults following gynecologic and vascular surgery; however, literature reports of iatrogenic

ureteral injuries following laparoscopic and open procedures in pediatric patients are extremely rare (Elliott and McAninch, 2006; Routh et al, 2009). The management of traumatic ureteral injuries revolves around the timing of diagnosis, with a delay in the diagnosis of 6 days or greater found in 50% to 60% of both pediatric and adult patients sustaining these types of injury (Elliott and McAninch, 2006; Routh et al, 2009).

If recognized at the time of surgery, surgical division of the ureter and/or partial ureteral excision should be managed based on the location and length of the ureteral injury. Options are ipsilateral ureteroureterostomy, ureteral reimplantation with or without a psoas hitch, trans-ureteroureterostomy (beware of placing the contralateral normal kidney at risk), or, on rare occasions, ureteral ligation with placement of a nephrostomy tube and planned reconstruction in the next 48 to 72 hours. Ureteral contusions secondary to a high-velocity gunshot wound or inadvertent ligation of the ureter should be treated by removal of any offending clip or ligature and placement of a ureteral stent for 6 to 8 weeks. Long-term (1- to 2-year) radiologic follow-up after removal of the stent or ureteral repair is necessary because ureteral strictures or ureteral fistulae form over time (Al-Ali and Haddad, 1996; Ghali et al, 1999; Elliott and McAninch, 2006; Routh et al, 2009).

Patients diagnosed with a ureteral injury more than 5 days after traumatic insult are classically managed by placement of a temporary percutaneous nephrostomy tube with or without a concurrent ureteral stent and are offered delayed definitive repair 12 weeks postinjury. Acute repair is not recommended by some authors because of the intense inflammatory response noted at the site of the injury, making the repair more difficult and likely to be unsuccessful (Al-Ali and Haddad, 1996; Ghali et al, 1999). Other authors have challenged this recommendation, stating that a trial of acute endoscopic management is worth the effort. These authors recognize that management of delayed ureteral injuries with endoscopic methods is associated with a 40% complication rate, usually with the development of complex obliterative ureteral strictures, but is worth an initial attempt. In contrast, the classic delayed open repair has a complication rate of less than 10% and an attempt with endoscopic management risks infection in what could be an unstable patient recovering from major trauma, may significantly hinder the patient's hospital course, may worsen the extent of the ureteral stricture, and only defers the inevitable need for surgical repair (Campbell et al, 1992; Selzman and Spirnak, 1996; Elliott and McAninch, 2006; Kunkle et al, 2006; Routh et al, 2009; Pereira et al, 2010; Siram et al, 2010). I manage these patients using a combined approach, with an initial attempt to place a ureteral stent with or without a nephrostomy tube. If I successfully bridge the area of injury with a ureteral stent, I remove the stent 6 to 8 weeks following the traumatic insult and reassess the upper tract for developing hydronephrosis and renal function using ultrasonography and MAG3 diuretic renography 6 weeks later. If progressive hydronephrosis is noted, temporary drainage of the upper tract with a nephrostomy tube is performed. Diagnostic radiographic studies to assess renal function and to assess the location and extent of stricture are subsequently performed a total of 12 weeks following stent removal. If I was unsuccessful in bridging the area of ureteral injury, I assess the patient approximately 12 weeks following the traumatic injury. Radiographic assessment at this time may employ a variety of modalities: antegrade and retrograde pyelography, nuclear renography to assess differential renal function, CT urography, and cystography.

The type of delayed ureteral repair to be used is based on the location and the extent of ureteral damage. Options include direct ureteral anastomosis to the renal pelvis, ureterocalycostomy, primary ureteroureterostomy, trans-ureteroureterostomy, ureteral reimplantation with or without a psoas hitch, ileal ureter, autotransplantation, and, occasionally, nephrectomy. I would caution that the use of trans-ureteroureterostomy places the contralateral uninjured kidney and ureter at risk. Based on this concern, I dislike trans-ureteroureterostomy as a surgical alternative in managing the difficult problems that arise following traumatic ureteral injuries (Elliott and McAninch, 2006; Routh et al, 2009).

KEY POINTS: TRAUMATIC URETEROPELVIC JUNCTION DISRUPTION AND URETERAL INJURIES

- In patients sustaining a UPJ disruption, 30% will have a completely normal urinalysis.
- Because of the frequent association of traumatic UPJ disruption with life-threatening trauma, the diagnosis of this injury is delayed for greater than 36 hours in more than 50% of patients. Patients will eventually come to attention owing to CT abnormalities found during the workup of persistent postoperative fever, chronic flank pain, continued ileus, or sepsis.
- Three classic findings on a triphasic CT scan are associated with UPJ disruption: (1) medial extravasation of contrast in the perirenal and upper ureteral area, (2) contrast extravasation in the absence of parenchymal lacerations, and (3) no visualization of the ipsilateral distal ureter.
- In the clinically stable patient, when the diagnosis of UPJ or ureteral disruption is made within 5 days after the traumatic insult, immediate surgical repair is the preferred treatment modality.
- In patients with a delayed diagnosis of UPJ or ureteral disruption made 6 or more days after the traumatic insult, placement of a nephrostomy tube, with or without a ureteral stent, with delayed repair at 12 weeks is preferred.
- The type of ureteral repair used is based on the location and extent of the ureteral injury.

TRAUMATIC BLADDER INJURIES

General Comments

The urinary bladder is well protected from external trauma by the bony confines of the pelvis. Because of the extensive pelvic protective mechanisms, when bladder injuries do occur they are frequently associated with multiorgan trauma, with an average of three coexisting organ injuries and a mortality rate of 20% (Carroll and McAninch, 1984). It is noteworthy that 80% of bladder injuries are associated with pelvic fractures, conversely, only 5% to 10% of pelvic fractures are associated with a bladder injury. Several studies, however, have found that screening for a bladder injury in patients with a pelvic fracture alone, or in patients with a pelvic fracture and microhematuria, is neither cost beneficial nor of high yield for clinically significant bladder injuries (Mokoena and Naidu, 1995; Cunningham et al, 1998; Iverson and Morey, 2001; Zacharias et al, 2012). Currently, absolute indications for bladder imaging following blunt abdominal trauma are limited to only two: (1) the presence of gross hematuria coexisting with a pelvic fracture or (2) inability to void. Relative indications for bladder imaging following blunt abdominal trauma are urinary clot retention, perineal hematoma, and a history of a prior bladder augmentation. Bladder imaging following penetrating trauma should be performed any time concern exists that the missile could have injured the bladder and/or if free abdominal fluid is found on the initial CT scan (Cunningham et al, 1998).

Differences between Adults and Children in Traumatic Bladder Injuries: Lacerations through the Anterior Bladder Neck

Traumatic bladder lacerations in children are approximately two times more likely to extend through the bladder neck compared with the same injury in an adult (Husmann et al, 1990; Boone et al, 1992; Koraitim, 1997, 1999; Chapple, 2000; Ashley and Husmann, 2007; Routh and Husmann, 2007). The clinical importance of this fact is significant. Specifically, management of a bladder neck laceration with either a suprapubic tube alone and/or urethral

catheter alone without coexisting repair of the bladder neck may result in the persistent extravasation of urine with the possible development of a pelvic urinoma/abscess or pelvic osteomyelitis and an increased risk of permanent urinary incontinence (Husmann et al, 1990; Boone et al, 1992; Koraitim, 1997, 1999; Chapple, 2000; Ashley and Husmann, 2007; Routh and Husmann, 2007). The diagnosis of a bladder neck injury should be suspected any time extravasation of contrast is noted and a competent bladder neck cannot be documented with radiographic studies. If concern for a bladder neck injury is present, the patient should undergo surgical exploration with opening of the bladder at the dome. Repair of the bladder neck should be by an intravesical approach with a multilayered closure. Great care should be taken not to dislodge the pelvic hematoma to help prevent blood loss. The surgeon should be aware that anterior bladder neck lacerations are frequently associated with urethral injuries, and retrograde urethrography or cystoscopy to rule out this possibility should be considered. If a bladder neck laceration is repaired, a voiding cystourethrogram (VCUG) is necessary at the time of catheter removal to adequately visualize the bladder neck and confirm healing (Husmann et al, 1990; Boone et al, 1992; Koraitim, 1997, 1999; Chapple, 2000; Ashley and Husmann, 2007; Routh and Husmann, 2007).

Diagnosis of Bladder Injuries

The diagnosis of a traumatic bladder injury should be assessed by either standard or CT cystography. Either modality is accurate provided adequate bladder distention occurs. In a child, the amount of contrast instilled within the bladder should, at a minimum, be equal to one half of the estimated bladder capacity for age (60 mL at birth and 30 mL for each year thereafter). Instillation of contrast can stop at the maximum of bladder capacity for age, a total of 300 mL, or if a bladder contraction occurs. I would discourage performing a CT cystogram by plugging the catheter and evaluating the bladder at the time of the initial CT scan. Frequently, the injured patient has oliguria secondary to hypovolemia, resulting in diminished urine output with inadequate filling of the bladder. In my experience, performance of a CT cystogram by plugging the catheter alone has led to missing the diagnosis of a traumatic bladder injury on multiple occasions (Husmann, 1996; Haas et al, 1999; Peng et al, 1999; Deck et al, 2001; Iverson and Morey, 2001).

Classification and Treatment of Traumatic Bladder Injuries

All patients with traumatic bladder lacerations, either extra- or intraperitoneal, should initially be treated with intravenous antibiotics, with oral antibiotic therapy continued for 48 hours following removal of bladder catheters. Extraperitoneal injuries are twice as common as intraperitoneal injuries and are almost invariably associated with a pelvic fracture. Classically, extraperitoneal bladder ruptures will have a starburst appearance on radiographic studies. In the presence of an extraperitoneal bladder injury, consideration for open surgical intervention should be given if: (1) a bony spicule is found to protrude into the bladder on CT evaluation, (2) concern for a bladder neck laceration is present, (3) the patient is to undergo internal fixation of a pelvic fracture, or (4) the patient is to undergo an exploratory laparotomy for other injuries. In these select circumstances prompt repair of both intra- and extravesical bladder injuries has been associated with fewer complications and improved patient outcomes (Kotkin and Koch, 1995; Husmann, 1996; Gomez et al, 2004; Ashley and Husmann, 2007; Deibert and Spencer, 2011; Deibert et al, 2012). Uncomplicated extraperitoneal bladder injuries may be managed with catheter drainage; management by an indwelling urethral catheter can be considered. The age and size of the patient plays a major role in determining if the individual can be managed by an indwelling urethral catheter. In my experience, a small-caliber urinary catheter placed in young children will frequently be occluded by blood clots, resulting in persistent urinary extravasation and

possible bacterial colonization of a pelvic hematoma, leading to pelvic abscess or osteomyelitis. Placement of a large-bore urethral catheter to allow better drainage is a concern in young boys secondary to the possibility of urethral trauma resulting in a urethral stricture; therefore a large-caliber suprapubic tube should be placed (Kotkin and Koch, 1995). Urinary drainage through the bladder catheter is maintained for 7 to 10 days, and a cystogram should be obtained to verify healing of the injury prior to catheter removal.

Intraperitoneal bladder injuries will initially appear as free fluid in the abdomen on a CT scan. Instillation of contrast in the bladder will result in extravasation of the contrast into the peritoneal cavity. Almost all intraperitoneal bladder ruptures occur at the dome of the bladder, the site of least support by the perivesical surrounding structures. Because these lacerations are usually large in size, the integrity of the bladder neck frequently cannot be assessed by radiographic means (Husmann, 1996). In intraperitoneal bladder injuries, open surgical repair of the laceration is the recommended treatment modality, with multivariate analysis after controlling for overall body injury score revealing a reduction of in-hospital mortality by approximately 50% (4.3% with urethral catheter drainage vs. 2.1% with open repair) (Deibert and Spencer, 2011; Deibert et al, 2012). Open repair will allow the surgeon to reduce from the confines of the bladder any herniating omentum or small bowel that can result in persistent urinary extravasation and allows careful intravesical inspection of the bladder neck at the time of surgical exploration. In all patients, a perivesical drain is placed and a large-bore urinary catheter is used to provide urinary drainage. In younger females and/or boys, persistent gross hematuria with clots may occlude small-caliber urethral catheters, and placement of a larger-bore suprapubic tube is usually merited. Urinary drainage for 7 to 10 days after injury should be provided and a cystogram obtained prior to catheter removal.

KEY POINTS: TRAUMATIC BLADDER INJURIES

- Absolute indications for bladder imaging following blunt abdominal trauma are currently limited to two: (1) the presence of gross hematuria coexisting with a pelvic fracture or (2) complaints of inability to void.
- Bladder imaging following penetrating trauma should be performed any time concern exists that a missile could have injured the bladder and/or if free abdominal fluid is found on the initial CT scan.
- Traumatic bladder lacerations in children are approximately two times more likely to extend through the bladder neck compared with the same injury in the adult.
- Failure to repair a bladder neck injury may result in the persistent extravasation of urine, with the possible development of a pelvic urinoma/abscess or osteomyelitis and increased risk of permanent urinary incontinence.
- Traumatic bladder injuries can be accurately diagnosed by either standard or CT cystography, provided adequate bladder distention occurs. In a child, the amount instilled within the bladder should, at a minimum, be equal to one half of the estimated bladder capacity for age.
- In the presence of an extraperitoneal bladder injury, consideration for open surgical intervention should be given if a bony spicule is found to protrude into the bladder on CT evaluation or if concern for a bladder neck laceration is present. If these two complications are not present, management by an indwelling urethral catheter can be considered.
- In intraperitoneal bladder injuries, open surgical repair of the laceration is the recommended treatment modality. This allows the surgeon to reduce any herniating omentum or small bowel from the confines of the bladder and allows careful intravesical inspection of the bladder neck at the time of surgical exploration.

URETHRAL INJURIES

Differences between Pediatric and Adult Patients in Urethral Injuries

Because of the immature pelvis and the relatively intra-abdominal position of the child's bladder, children with a posterior urethral injury will differ from adults with this injury in four ways. First, a pelvic fracture is more likely to be unstable and associated with a severely and permanently displaced prostatic urethra. Second, the severe displacement of the prostate off the pelvic floor makes a complete posterior urethral disruption more common in boys than in men. Third, concurrent bladder and urethral injuries may occur in up to 20% of pediatric patients, with coexisting anterior longitudinal tears through the bladder neck and sphincteric complex being twofold more common in children compared with adults. Fourth, in prepubertal girls, pelvic fractures are four times more likely to be associated with a urethral injury than in adult women (Husmann et al, 1990; Boone et al, 1992; Perry and Husmann, 1992; Koraitim, 1997, 1999, 2004; Chapple, 2000; Hemal et al, 2000; Ashley and Husmann, 2007; Routh and Husmann, 2007).

The clinical impact of these differences is noteworthy. Permanent displacement of the prostate off the pelvic floor results in an increased need for either a transpubic, transsymphyseal, or combined transpubic and perineal dissection for urethral reconstruction compared with the adult patient population. Hypothetically, the severe displacement of the prostate off of the pelvic floor raises concern that erectile dysfunction will be more common in children sustaining a urethral injury than in adults (Boone et al, 1993; Koraitim, 1997; Chapple, 2000; Basiri et al, 2002). There is also apprehension that permanent urinary incontinence may be more likely in children following this injury as a result of the increased risk of combined injuries to the posterior urethra, bladder neck, and sphincteric complex (Husmann et al, 1990; Boone et al, 1992; Perry and Husmann, 1992; Hemal et al, 2000; Rosenstein and Alsikafi, 2006; Ashley and Husmann, 2007; Routh and Husmann, 2007).

Initial Presentation of Urethral Injury

Consideration for a urethral injury should arise any time a patient presents with a history of direct trauma to the penis, vagina, perineum, or pelvis. Radiographic or cystoscopic evaluations to rule out this injury are mandatory in the following circumstances: (1) when the patient presents with the classic triad of perineal/penile hematoma, blood at the meatus/vaginal introitus, and inability to void; (2) when there is a pelvic fracture with one or more fractured pubic rami or symphyseal diastases; or (3) when radiographic findings are suggestive of a bladder neck injury (Chapple, 2000; Rosenstein and Alsikafi, 2006).

Association of Pelvic Fractures to Posterior Urethral Distraction Injuries

Approximately 5% of patients sustaining a pelvic fracture will have a urethral injury. The risk of a urethral injury following a pelvic fracture is directly related to the number of pubic rami fractures present, the degree of separation of the pubic symphysis, and the presence of a concurrent diastasis of the sacroiliac joint. A Malgaigne fracture—that is, a pelvic fracture that has disruption of the ischiopubic rami coexisting with diastasis of the sacroiliac joint—has the highest risk of urethral injury (Colapinto, 1980; Kricun, 1990; Koraitim et al, 1996; Koraitim, 1999, 2004; Kommu et al, 2007). In turn, the likelihood of a urethral injury following isolated pelvic fractures of the acetabulum, ilium, and sacrum that do not involve a fracture of a ramus or the separation of the pubic symphysis is essentially zero.

Diagnosis of Urethral Injuries

In males, a retrograde urethrogram (RGUG) is the diagnostic modality of choice to rule out the presence of a urethral injury. In the pre- and postpubertal female, findings suggestive of a urethral injury are frequently noted on a CT evaluation; however, I prefer to confirm the diagnosis by cystoscopy and vaginoscopy performed under general anesthesia (Husmann et al, 1990; Boone et al, 1992; Perry and Husmann, 1992; Venn et al, 1999; Rosenstein and Alsikafi, 2006).

When a urethral injury is found to coexist with a pelvic fracture, a concurrent rectal injury will be present in 15% of children. It used to be mandatory that a digital rectal examination (DRE) be performed in these children to assess for the presence of the concurrent rectal injury. Current studies, however, have revealed the DRE to be highly inaccurate for diagnosing either a displaced prostate or a rectal injury. The ability of the DRE to correctly diagnose the presence of these findings was less than 15%, with radiographic studies and endoscopy being far more specific and sensitive for such a diagnosis. The emergency medicine community has subsequently recommended that the DRE be abandoned in the evaluation of the traumatically injured patient under these circumstances (Shlamovitz et al, 2007a, 2007b). When a rectal injury is identified to coexist with a urethral disruption, treatment with a temporary diverting colostomy is mandatory to prevent the disastrous consequences of pelvic abscess, pelvic osteomyelitis, and necrotizing fasciitis that can accompany an unrecognized rectal injury.

General Comments Regarding Repair of Urethral Injuries: Immediate, Delayed, and Late Urethroplasty

In the early phase of the injury, the most important potential urologic complication is infection induced by bacterial contamination of the pelvic/perineal hematoma and extravasated urine. Immediate treatment of urethral injuries should include the administration of broad-spectrum antibiotics, assessment of the competence of the bladder neck, and the establishment of urinary drainage. Repair of the urethral injury may be immediate (primary realignment or sutured primary end-to-end anastomosis, less than 2 days post-injury); delayed (primary realignment or sutured end-to-end anastomosis, occurring 2 to 14 days following injury); or late (any type of repair occurring 3 months or more after injury) (Boone et al, 1992; Perry and Husmann, 1992; Venn et al, 1999; Rosenstein and Alsikafi, 2006; Ashley and Husmann, 2007; Routh and Husmann, 2007).

Anterior Urethral Injuries

Anterior urethral (including bulbar) injuries in children are usually iatrogenic, resulting from urethral instrumentation, circumcision, or injury occurring during the repair of a congenital anorectal malformation. If the anterior urethra was injured as a result of urethral instrumentation, acute management should be with antibiotic therapy followed by establishment of urethral continuity with catheter drainage. Preferably, a urethral catheter is placed by either radiologic or endoscopic techniques and maintained for 5 to 21 days depending on the extent of the injury (Maheshwari and Shah, 2005; Kommu et al, 2007). If urethral continuity cannot be established, alternative treatments include temporary suprapubic tube placement or vesicostomy. If a urethral or suprapubic catheter is placed, a VCUG is obtained at the time of anticipated removal. If no persistent urethral injury is noted, in infants I obtain a follow-up RGUG after 3 months; alternatively, in a child who is toilet trained, a flow rate with ultrasound residual urine is adequate for follow-up. If a permanent urethral stricture develops, I will usually defer definitive surgical repair until the child is older than 1 year of age, or, if the child is older than 1 year of

age, wait at least 3 months from the time of the injury (i.e., a late urethroplasty). The delay in the repair allows the stricture to clearly delineate the extent of the injury, allowing the physician to plan for the urethral reconstruction (Voelzke et al, 2012).

Three types of urethral injuries can result following a circumcision: meatal injury, loss of the distal urethra secondary to partial or complete glanular amputation, or the development of a urethrocuteaneous fistula owing to ischemic necrosis of the urethra (Gluckman et al, 1995; Baskin et al, 1997). The latter injury usually occurs either when the urethra was crushed by a circumcision clamp or when a cautery or a suture ligature was used to stop bleeding from a vessel that was overlying the urethra (Baskin et al, 1997). Immediate repair of the acutely traumatized anterior urethra can be technically difficult. When the meatus is injured, a formal meatoplasty should be performed to prevent meatal stenosis from developing. When the glans with distal urethra has been amputated, it may be reattached successfully using a direct spatulated suture anastomosis of the urethra and glans with urethral stenting, perioperative antibiotics, and a compressive dressing for immobilization of the glans. When a partial distal urethral injury has occurred without substantial glans loss, suture reapproximation of the meatus (i.e., a meatoplasty) can be performed. After healing, a delayed repair using hypospadias techniques may be used if necessary. Urethrocuteaneous fistulae are repaired using techniques similar to those used to close fistulae following a hypospadias repair; this surgery is usually delayed until the child is 6 to 9 months of age for technical reasons (Gluckman et al, 1995; Baskin et al, 1997).

I have had a number of children referred to me for repair of urethral injuries that occurred at the time of surgical correction of their congenital anorectal malformation. In my experience, this injury is usually due to one of two causes: no urethral catheter was in situ at the time of the rectal repair or the urethral catheter had been placed into the rectum through the urethral-rectal fistula. In these circumstances, the proximal penile or bulbar urethra is usually excised or partially avulsed at the time of rectal dissection. The injury is frequently identified when the child is unable to void following surgery or voids through the perineal wound. The importance of an appropriately placed urethral catheter at the time of anorectal repair cannot be understated. Initial placement of the catheter prior to repair of the anorectal malformation may be difficult, because the catheter hangs up at the site of the rectourethral fistula or inadvertently passes into the rectum. Placement of the catheter over a cystoscopically placed guidewire prior to the surgical repair of this congenital anomaly is frequently helpful. This allows easy identification of the urethra, and if the urethral catheter becomes exposed during the case, the problem is recognized immediately and can usually be primarily repaired with rare long-term consequences (Spence, 1954; Williams and Grant, 1969; McLorie et al, 1998; Hong et al, 2002).

Assessment of Urethral Stricture prior to Delayed Repair

At the time surgical reconstruction is considered, usually 3 months post-injury, an RGUG followed by a simultaneous RGUG and VCUG are the first three studies done. If a suprapubic catheterization or vesicostomy has been performed, a static cystogram is also done. A correctly performed RGUG will allow the physician to identify the location of the urethral stricture but may not allow the appropriate determination of stricture length, especially if an extremely tight bulbar or posterior urethral distraction injury is present. Proper interpretation of these three radiographic studies is essential for true estimation of the defect between the disrupted urethral ends. Without correct interpretation of the studies, the urethral defect may be underestimated (contrast filling of a urinoma cavity associated with an incompetent bladder neck) or overestimated (nonfilling of the normal urethra as a result of failure of the bladder neck to open with voiding). When contrast from the static cystogram is found in the posterior urethra, it arouses suspicion for a bladder neck injury and mandates further evaluation as outlined later. If the bladder neck is competent, I obtain a simultaneous RGUG and VCUG. Great care should be taken in

interpreting these films. More often than not, the pediatric patient will be unable to void and will fail to open the bladder neck. This results in nonvisualization of the proximal urethral segment and may cause a spurious estimation of a long distraction defect. If the posterior urethra fills with contrast on the static cystogram, this could be due to either a poorly felt or described detrusor contraction or an incompetent bladder neck. Because of the significant impact the latter has on the surgical prognosis, if contrast is seen in the posterior urethra, a video-urodynamic study is necessary. If the video-urodynamic study documents an incompetent bladder neck, or if the patient was unable to open the bladder neck to allow visualization of the posterior urethra during VCUG, I perform a simultaneous flexible cystoscopy and urethroscopy. Occasionally, in children, the physician may need to use flexible ureteroscopes for this procedure. This examination allows the physician to confirm the anatomic detail of the bladder neck and allows determination of the extent of the urethral stricture. Specifically, I will obtain anteroposterior and oblique pelvic films with the flexible scopes placed at the distraction margins; this allows the physician to see the extent and orientation of the distraction injury. Alternatively, a pelvic MRI with three-dimensional reconstruction can be obtained to evaluate the prostatic urethral dislocation and distal bulbar urethral position. The latter radiographic study lacks the ability to evaluate bladder neck competence. If cystoscopy and video-urodynamics demonstrate an incompetent bladder neck, I discuss with the patient and his or her family the options of urethral reconstruction with the possible result of chronic incontinence or, alternatively, the performance of a continent abdominal stoma (appendicovesicostomy) as first-line therapy (Ashley and Husmann, 2007; Routh and Husmann, 2007) (Fig. 154-8) (also see the section Mitrofanoff Principle for Bladder Neck Incompetence following Posterior Urethral Injuries).

Endoscopic Repair of the Urethral Injury: Immediate Endoscopic Realignment, Delayed Urethroplasty with Direct Internal Visual Urethrotomy, and Delayed Urethroplasty with "Cut to Light" Procedure

Immediate endoscopic realignment using guidewires and urethral catheters for either partial or complete anterior or posterior urethral disruptions has been recommended by some authors (Husmann et al, 1990, 1993a; Koch, 1995; Elliott and Barrett, 1997; Freitas Filho et al, 2003; Maheshwari and Shah, 2005; Rosenstein and Alsikafi, 2006; Hadjizacharia et al, 2008). I believe this technique is extremely reasonable for partial urethral injuries secondary to iatrogenic catheter-induced or endoscopically induced urethral injuries; however, in my hands endoscopic realignment for noniatrogenic urethral trauma has produced abysmal long-term results. Indeed, in my patient population, with noniatrogenic urethral trauma managed by this technique, intermittent catheterization or repeated serial visual internal urethrotomies to maintain urethral patency were necessary in greater than 90% of children during long-term follow-up (Husmann et al, 1990, 1993a; Boone et al, 1992). Because of my poor experience with urethral realignment in children with noniatrogenic traumatic urethral injuries, I have elected not to pursue this treatment modality in prepubertal patients. In the postpubertal patient who is clinically stable with a posterior urethral distraction injury and a competent bladder neck, I will make a limited attempt at endoscopic realignment. If the alignment cannot be established within 10 minutes, I abandon the procedure for placement of a suprapubic tube and a delayed repair. The time limitation is used in an attempt to limit the risk of bacterial colonization of the pelvic hematoma and the possible consequence of osteomyelitis (Husmann et al, 1990, 1993a; Koch, 1995; Elliott and Barrett, 1997; Freitas Filho et al, 2003; Maheshwari and Shah, 2005; Rosenstein and Alsikafi, 2006; Hadjizacharia et al, 2008; Nerli et al, 2008).

The "cut to light" procedure, or antegrade and retrograde urethroscopy with either endoscopic incision or laser ablation of the obliterative urethral stricture, received publicity in the late 1980s as

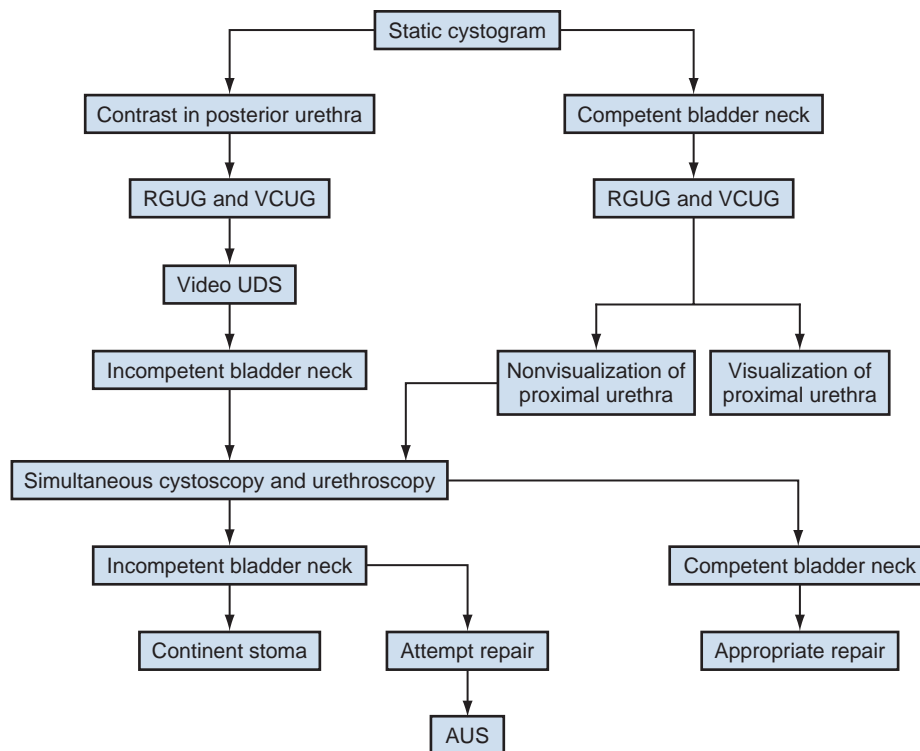


Figure 154-8. Workup of posterior urethral distraction injuries prior to delayed operative repair. AUS, artificial urethral sphincter; RGUG, retrograde urethrogram; UDS, urodynamic study; VCUG, voiding cystourethrogram.

a less invasive treatment for obliterative posterior urethral distraction injuries. Long-term follow-up has revealed a high recurrent stricture rate (>90%) with urethral patency being maintained only by daily use of intermittent catheterization. This finding has led most authorities in the field to abandon this treatment method (Tollefson et al, 2007).

Endoscopic urethrotomy for short (<1 cm) nonobliterative trauma-induced bulbar and penile urethral strictures is commonly performed for pediatric urethral stricture disease. Unfortunately, follow-up on these patients in adulthood is limited. Short-term follow-up of 1 year frequently reveals success rates as high as 75% to 100%; however, follow-up intervals of greater than 5 years reveal success decreasing into the 20% to 35% range, with some studies suggesting that long-term success can be doubled by repeating the urethrotomy at least one time. Repeating the urethrotomy more than one time does not appear to enhance its success and may, in fact, decrease the successful result of the eventual open urethral reconstruction (Roehrborn and McConnell, 1994; Albers et al, 1996; Duel et al, 1998; Hsiao et al, 2003; Hafez et al, 2005; Husmann and Rathbun, 2006).

Anastomotic Urethroplasty

The principles of anastomotic urethral reconstruction include complete excision of the scar tissue and a widely spatulated anastomosis with a tension-free epithelial-to-epithelial approximation associated with viable urethral margins. An anastomotic urethroplasty using either the perineal, transpubic, transsymphyseal, or combined approach has a reported success of greater than 90% in the pediatric patient population. The excellent outcome of this procedure verifies that the end-to-end anastomotic urethroplasty is the procedure of choice for distraction urethral injuries in both children and adults (Cooperberg et al, 2007; Tollefson et al, 2007; El-Sheikh et al, 2008). A direct end-to-end anastomosis of up to 2 cm may be performed in most children. Gaps of 3 cm or more

usually require partial or complete pubectomy or symphysiotomy with or without splitting the penile crura to accomplish the anastomosis (Boone et al, 1993; Chapple, 2000; Basiri et al, 2002; Koraitim, 2004; Park and McAninch, 2004; Cooperberg et al, 2007; El-Sheikh et al, 2008; Voelzke et al, 2012). As noted previously, because of the propensity of the child's prostatic urethra to be permanently displaced off the pelvic floor following a posterior urethral distraction injury, there will be a tendency for children to require either a partial pubectomy, symphysiotomy, or combined perineal and transpubic urethroplasty to complete the urethral reconstruction more often than would adults (Koraitim, 1997, 2004; Basiri et al, 2002; Park and McAninch, 2004; Ranjan et al, 2012; Voelzke et al, 2012).

Patch Urethroplasties: Flap versus Graft (One-, Two-, or Multistage Procedures)

Repair of traumatic urethral strictures of the bulbar, proximal, and penile urethra of greater than 3 to 4 cm in length in children is usually pursued using a one-stage flap procedure from the prepuce or penile shaft skin (Orandi procedure) or, if local skin is unavailable, a dorsal graft urethroplasty using a free-skin graft or buccal mucosa (Schreiter and Noll, 1989; Barbagli et al, 2004; Park and McAninch, 2004; Schulte-Baukloh et al, 2004; Dubey et al, 2005; Voelzke et al, 2012). I prefer to do a single-stage repair by approximating at least one side of the urethra and using the flap or graft on the opposing wall. If the defect is large enough that the flap or graft must be used in a circumferential manner (tube), I will opt for a two- or multistage approach. The use of a staged reconstruction is based on the realization that recurrent strictures are more likely to occur when any flap or graft is used in a circumferential manner (tube) as a single-stage procedure (Al-Ali and Al-Hajaj, 2001; Andrich and Mundy, 2001; El-Sherbiny et al, 2002; Dubey et al, 2003, 2005; Kessler et al, 2003; Manzoni et al, 2004;

Husmann and Rathbun, 2006; Voelzke et al, 2012). Staging the operation by performing a classic two-stage Johanson urethroplasty or, preferentially, a multistaged preputial flap or buccal graft urethroplasty allows the surgeon to verify flap/graft survival and provide time for neovascularity and the assessment of the urethral plate for possible hair-bearing skin prior to urethral closure. In general, the length of the urethral stricture, the availability of well-vascularized excess adjacent skin, and the health of the donor bed determine if I use a one-, two-, or multistage approach (Schreiter and Noll, 1989; Al-Ali and Al-Hajaj, 2001; Andrich and Mundy, 2001; El-Sherbiny et al, 2002; Dubey et al, 2003, 2005; Kessler et al, 2003; Manzoni et al, 2004; Schulte-Baukloh et al, 2004; Husmann and Rathbun, 2006; Ranjan et al, 2012; Voelzke et al, 2012).

Female Urethral Injuries

Urethral injuries in females are invariably associated with an unstable pelvic fracture and are usually caused by a disruption of the pubic symphysis with a longitudinal laceration extending through the bladder neck and into the urethra, or by dislocation of a bony fragment that lacerates the urethra, resulting in distraction of the two severed margins. Female urethral injuries may be quite insidious in nature and are associated with concurrent vaginal laceration in 75% and concurrent rectal injuries in 30% (Perry and Husmann, 1992; Venn et al, 1999; Chapple, 2000; Hemal et al, 2000). Blood at the vaginal introitus or the presence of a rectal injury in combination with a pelvic fracture should prompt the physician to consider a diagnosis of a female urethral injury. Urethroscopy and vaginoscopy should be considered mandatory in these individuals. If the patient is clinically stable, immediate end-to-end urethroplasty for avulsion distraction injuries, primary bladder neck repair, and repair of the longitudinal lacerated urethra over a urethral catheter should be performed. Concurrent repair of vaginal and rectal injuries (with a diverting colostomy) should be performed when indicated. Preliminary diversion with a suprapubic cystostomy without any treatment of the urethra will invariably result in either a urethral stricture, urinary fistula, or both. Delayed repairs of these injuries using a two-stage approach involving preliminary suprapubic cystostomy followed by a definitive reconstruction is less successful. Delayed urethral repair and establishment of urinary continence by bladder neck reconstruction, sling, or artificial urinary sphincter placement frequently results in incontinence, urethral erosion with fistula formation, or proximal urethral obliteration. Indeed, the need for urinary diversion or a continent abdominal stoma to manage complications of the female bladder neck and urethral injuries occurs in up to 30% of female pediatric patients (Perry and Husmann, 1992; Venn et al, 1999; Chapple, 2000; Hemal et al, 2000; Castera et al, 2001; Huang et al, 2003; Koraitim, 2004; Ashley and Husmann, 2007; Routh and Husmann, 2007).

Mitrofanoff Principle for Bladder Neck Incompetence following Posterior Urethral Injuries

In patients with bladder neck incompetence and concurrent urethral stricture disease, I have pursued two different treatment options. Initially, reconstruction of the bladder neck with reestablishment of urethral continuity is performed. If subsequent urinary incontinence persists, as it almost inevitably does, I proceed with placement of an artificial sphincter or bladder neck sling (Ashley and Husmann, 2007; Routh and Husmann, 2007). Alternatively, I may initially proceed with a continent catheterizable stoma using the Mitrofanoff principle, with no attempt to reestablish urethral continuity (Ashley and Husmann, 2007; Routh and Husmann, 2007). Indeed, personal experience with these two techniques has resulted in my preference for a continent stoma. Unfortunately, placement of an artificial urinary sphincter or sling around the bladder neck or urethra following bladder neck reconstruction and end-to-end urethroplasty is technically difficult and fraught with the risk of delayed urethral erosion (Ashley and Husmann, 2007).

Erectile Dysfunction and Urinary Incontinence following Urethral Injuries

For decades it was argued that immediate repair of posterior urethral disruption injuries by primary urethral anastomosis and/or primary urethral realignment was directly associated with an increased incidence of erectile dysfunction and urinary incontinence. Current studies have failed to reveal an association between the type of repair (immediate vs. late) and the incidence of erectile dysfunction and urinary incontinence. At this time, it is believed that the severity of the primary injury and not the initial treatment modality chosen is the cause of these complications (Husmann et al, 1990; Boone et al, 1992).

It should be noted that the incidence of erectile dysfunction is increased when total disruption of the urethra occurs and/or when the prostate is grossly dislocated, both of which are more common in children than in adults. The incidence of sexual dysfunction following this injury is correlated to the number of pubic rami fractured, the extent to which the pubic symphysis is distracted, and the length of the ensuing urethral stricture (Husmann et al, 1990; Boone et al, 1992; Koraitim, 1997, 1999; Chapple, 2000; Hemal et al, 2000). Long-term follow-up of children sustaining a posterior urethral disruption revealed that erectile dysfunction may occur in up to 70% when severe dislocation and injury to the apical prostatic urethra occurs, compared with a 30% incidence of erectile dysfunction when minimal dislocation of the pubic symphysis is present (Boone et al, 1992). Whether repair by an anastomotic urethroplasty increases the risk of erectile dysfunction is controversial (Das et al, 2004). Patients complaining about erectile dysfunction should undergo diagnostic testing to outline the etiology of the dysfunction. Although the etiology is usually neurogenic, vasculogenic, combined neurogenic and vasculogenic, and even psychogenic etiologies have all been found within this patient population, with therapy dictated by the diagnostic findings (Das et al, 2004; Feng et al, 2008; Tal et al, 2008).

Urinary incontinence following urethral injuries is almost invariably related to the presence of a concurrent bladder neck/urethral injury or is a consequence of pelvic or pudendal nerve damage resulting in denervation of the sphincteric complex (Husmann et al, 1990; Perry and Husmann, 1992; Koraitim, 1997; Chapple, 2000; Hemal et al, 2000; Ashley and Husmann, 2007; Kommu et al, 2007; Routh and Husmann, 2007).

PENILE INJURIES

Penile trauma in the pediatric patient population is most commonly iatrogenic and caused by circumcision. If excess penile skin is excised during circumcision, the majority of patients can be treated by wet-to-dry dressings and antibiotic ointment. Healing by secondary intention usually results in an excellent cosmetic appearance. If the penis is totally degloved, the penile shaft skin, if salvaged, can be defatted and replaced on the penis as a full-thickness skin graft (Gluckman et al, 1995; Baskin et al, 1997; El-Bahnasawy and El-Sherbiny, 2002).

Penile strangulation caused by a hair or thread is occasionally seen. In most cases it is hard to believe that this insult is purely accidental, and consideration should be given to a social services investigation for possible child abuse. The human hair-tie will result in the gradual onset of ischemia, with little or no discomfort to the child. If seen early, the glans or distal penis will be edematous, erythematous, and ulcerated. The constricting hair or thread may not be noticeable without careful inspection. Removal of the constricting agent at this stage usually results in no long-term complications. Unfortunately, if the child presents in a delayed fashion or if the original diagnosis is missed, the hair may continue to cut through the penis, causing damage to the neurovascular bundle, corporeal bodies, and urethra. Injuries range from loss of glanular sensation to the development of a urethrocutaneous fistula, and, in the extreme form, partial or complete penile amputation (El-Bahnasawy and El-Sherbiny, 2002; Radhakrishnan et al, 2002).

KEY POINTS: TRAUMATIC URETHRAL INJURIES

- A urethral injury should be ruled out in the following three circumstances: (1) if the classic triad of a perineal/penile hematoma, blood at the meatus/vaginal introitus, and inability to void is present; (2) if a pelvic fracture is associated with one or more fractured pubic rami and/or symphysis diastases; and (3) if radiographic findings are suggestive of a bladder neck injury.
- In a young girl with a pelvic fracture, if blood is noted at the vaginal introitus or if a concurrent rectal injury is present, urethral injury must be ruled out.
- Immediate treatment of urethral injuries should include the administration of broad-spectrum antibiotics, assessment of the competence of the bladder neck, and the establishment of urinary drainage.
- Short (<1 cm), nonobliterative bulbar and penile urethral strictures may be treated by a urethrotomy, with a success rate approaching 20% to 35%. Repeating the urethrotomy more than once does not appear to enhance its success and may, in fact, decrease the success of an open urethral reconstruction.
- Following a posterior urethral injury, the incidence of erectile dysfunction and urinary incontinence is directly related to the severity of the primary injury, that is, the severity of the prostatic dislocation, the concurrent presence of a bladder neck injury, or the presence of trauma-induced pelvic or pudendal nerve damage; it is not the result of the initial treatment modality chosen.

Domestic animal attack is the most severe form of penile trauma usually seen in childhood. These penile injuries are usually associated with significant tissue destruction and fraught with complications resulting from bacterial contamination. Treatment requires verification of a current tetanus vaccination and absence of rabies in the offending animal. The patient is treated with the liberal use of antibiotics, wound cleansing, and debridement and repair or reattachment of the penis as the injury would direct (El-Bahnasawy and El-Sherbiny, 2002; Radhakrishnan et al, 2002).

KEY POINTS: TRAUMATIC PENILE INJURIES

- During a circumcision, excision of excess penile skin in the vast majority of patients can be treated by wet- to-dry dressings and antibiotic ointment, with healing by secondary intention resulting in excellent cosmetic appearance.
- If during the circumcision the penis is totally degloved, the penile shaft skin, if salvaged, can be defatted and replaced back onto the penis as a full-thickness skin graft.
- Penile strangulation caused by a hair is occasionally seen, and consideration should be given to a social services investigation for possible child abuse.
- Domestic animal attack is the most severe form of penile trauma seen in childhood. Treatment requires verification of a current tetanus vaccination and absence of rabies in the offending pet. The patient is treated with the liberal use of antibiotics, wound cleansing, debridement, and repair or reattachment of the penis as the injury would direct.

SCROTAL, VULVAR, AND TESTICULAR TRAUMA

In the prepubertal and adolescent boy presenting with testicular/scrotal pain, the primary diagnosis should be testicular torsion until proven otherwise. Frequently, boys with testicular torsion will present with a trauma decoy, that is, a complaint of incidental scrotal trauma preceding the onset of testicular pain, with the patient's history masking the true diagnosis of torsion. **If clinical examination cannot clarify the diagnosis, scrotal ultrasonography is essential; any finding consistent with testicular torsion, hematocele, or irregular testicular outline mandates surgical exploration to rule out and/or repair a ruptured testis (Lee et al, 2008).**

In the pediatric patient, trauma to the scrotum or vulvar region is usually the result of athletic activities, an assault, or a fall. It is classically divided into the two categories of penetrating or blunt trauma. If the patient has sustained a penetrating scrotal or vulvar trauma, concern for associated injuries to the urethra and rectum exists (Husmann et al, 1993a; Lee et al, 2008). A history of vaginal or rectal penetrating injuries, hematuria or bloody rectal discharge, and the presence of blood staining/bruising in the scrotal, labial, or perineal area should prompt further evaluations for coexisting urethral and rectal injuries. In some situations, scrotal ultrasonography, pelvic CT, or MRI may be of significant benefit if the history is unclear, child abuse is suspected, and physical findings are worrisome. If sedation in the emergency room is inadequate in allowing the physician to perform a thorough physical examination of the genitalia, it may be necessary to bring the patient to the operative suite for general anesthesia. In all cases of penetrating trauma, a meticulous examination to determine the depth of penetration, along with cleansing and debridement of the wound, broad-spectrum antibiotics, and verification of an up-to-date tetanus immunization are employed.

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The complete reference list is available online at www.expertconsult.com.

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155 Pediatric Urologic Oncology: Renal and Adrenal

Michael L. Ritchey, MD, and Robert C. Shamberger, MD

Neuroblastoma

Wilms Tumor

Other Renal Tumors

NEUROBLASTOMA

Neuroblastoma is the most common extracranial solid tumor of childhood. Regrettably, over half of the children have metastatic disease on presentation. Neuroblastoma is known to arise from cells of the neural crest that form the adrenal medulla and sympathetic ganglia. Tumors may occur anywhere along the sympathetic chain within the neck, thorax, retroperitoneum, or pelvis, or in the adrenal gland. Seventy-five percent arise in the retroperitoneum, 50% in the adrenal, and 25% in the paravertebral ganglia. The variety of locations where these tumors arise and the spectrum of their differentiation results in a wide range of clinical presentations and behaviors (Brodeur, 1991). These tumors can undergo spontaneous regression (Brodeur, 1991), differentiate to benign neoplasms, or exhibit extremely malignant behavior. Biologic factors have been defined that predict and explain much of the variance in behavior from one tumor to the next.

Epidemiology and Genetics

Incidence

Neuroblastoma accounts for 8% to 10% of all childhood cancers. In the United States, the annual incidence is 10 cases per 1 million live births. It is the most common malignant tumor of infancy. A recent review of 3666 children enrolled in the cooperative group trials of the Pediatric Oncology Group and the Children's Cancer Group showed a median age at diagnosis of 19 months (Brodeur and Maris, 2006). Thirty-six percent were infants, 89% were younger than 5 years, and 98% were diagnosed by 10 years of age.

Genetics

A number of familial cases have been reported, which are postulated to represent an autosomal dominant pattern of inheritance (Knudson and Strong, 1972a; Robertson et al, 1991). Although the median age at diagnosis of neuroblastoma is 19 months, in familial cases it is 9 months (Kushner et al, 1986). At least 20% of patients with familial neuroblastoma have bilateral adrenal or multifocal primary tumors, which are quite unusual in spontaneous cases. The risk for development of neuroblastoma in a sibling or offspring of a patient with neuroblastoma is less than 6% (Kushner et al, 1986). Linkage analysis in seven families with two or more first-degree

relatives affected with neuroblastoma identified a single interval at chromosome 16p12-13 with consistent linkage (Maris et al, 2002). This suggested that a hereditary neuroblastoma predisposition gene may be located at this site and may explain the familial cases. Subsequent studies in these familial cases, which account for less than 1% of patients with neuroblastoma, have identified *PHOX2B* and *ALK* as hereditary predisposition genes (Mosse et al, 2004, 2008).

Constitutional Chromosome Abnormalities

Numerous karyotypic abnormalities have been found in neuroblastoma, and these are recognized to have prognostic significance. These changes occur in the form of chromosomal deletions, translocations, and cytogenetic evidence of gene amplification. Aneuploidy of the tumor DNA, an abnormal number of copies of the normal 23 chromosomes, occurs in a significant number of cases (55%) and is a favorable prognostic indicator when compared with tumors that have a normal or tetraploid number (Kaneko et al, 1987). Amplification of the *MYCN* oncogene defined as greater than 10 copies of this gene is seen in roughly 20% to 25% of primary tumors and is an adverse prognostic indicator (Look et al, 1991; Muraji et al, 1993). It is present in 40% of patients with advanced stage disease but in only 5% to 10% of children with low-stage disease (Brodeur et al, 1984). It is associated with rapid tumor progression and poor outcome from treatment. These findings have been so striking that neuroblastoma was the first tumor in which the intensity of chemotherapy for a patient was determined not only by the stage and histology of the tumor, but by its "biologic markers," which were primarily chromosomal (Matthay et al, 1998).

Deletion of the short arm of chromosome 1 (1p) is found in 25% to 35% of neuroblastomas and is an adverse prognostic marker (Brodeur et al, 1992; Caron et al, 1996). The deletions are of various lengths, but, in a series of eight cases, a consensus deletion included the segment 1p36.1-2, suggesting that a tumor suppressor may be present in this region. Although the involved genes have not been identified conclusively, *CHD5* is a strong candidate for this role (Weith et al, 1989; Maris et al, 2007; Fujita et al, 2008). This deletion is present in 70% of advanced-stage neuroblastomas, and it has been demonstrated to be an independent prognostic factor (Attiyeh et al, 2005). There have been reports of constitutional abnormalities involving the short arm of chromosome 1 (Laureys et al, 1990). Recently, it has been demonstrated that loss of

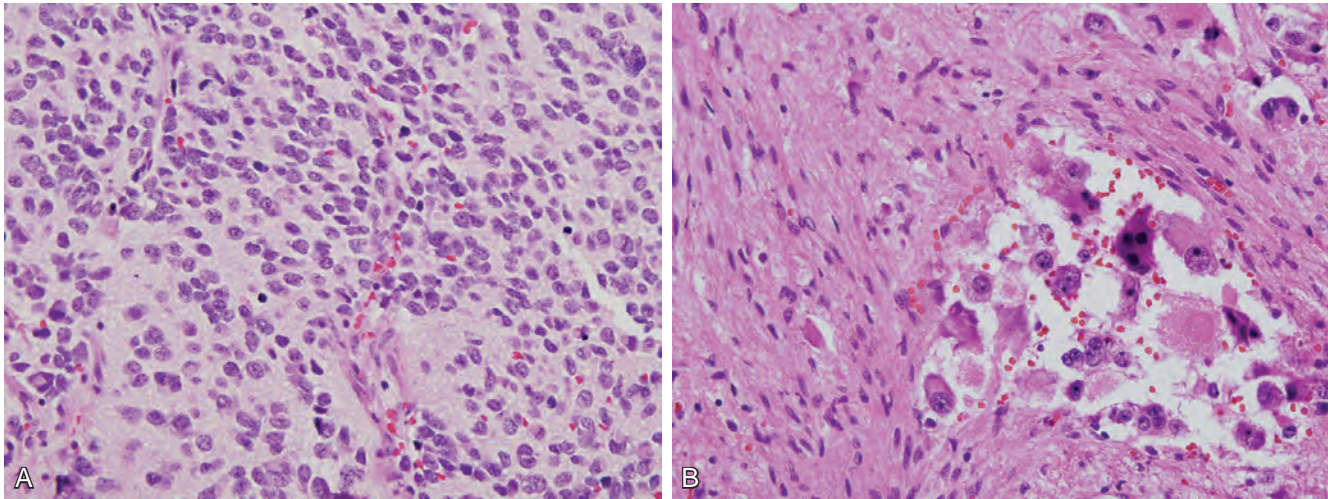


Figure 155-1. A, Poorly differentiated neuroblastoma with a minimal-to-moderate amount of neuropil. B, Ganglioneuroblastoma with more than 50% of surface area occupied by schwannian stroma on left. Lobule contains ganglion cells, immature ganglion cells, and poorly differentiated neuroblasts; only minimal neuropil is present within lobule. (Courtesy Dr. Harry Kozakewich.)

heterozygosity (LOH) at 1p36 and Unb11q is independently associated with a worse outcome in patients with neuroblastoma (Attiey et al, 2005). (Unbalanced LOH implies LOH at markers on 11q with retention of 11p material, in contrast with *whole-chromosome* 11 LOH, wherein there is LOH at every marker along the chromosome.) Of note, although the 1p deletions are seen in conjunction with advanced stage and *N-MYC* amplification, the 11q deletions are rarely seen in tumors with *N-MYC* amplification but are associated with other high-risk features (Spitz et al, 2006). An additional genetic abnormality, gain of one to three copies of 17q, often the result of translocation with chromosomes 1 or 11, has been demonstrated to correlate with more aggressive tumors (Bown et al, 1999). The breakpoints vary, but the addition of a region from 17q22-qter is common, suggesting that genes replicated in this region provide an advantage (Schleiermacher et al, 2004). In multivariate analysis, gain of 17q was the most powerful prognostic factor, followed by the presence of stage 4 disease and deletion of 1p.

Embryology and Spontaneous Regression

In 1963, Beckwith and Perrin coined the term *in situ neuroblastoma* for small nodules of neuroblasts found incidentally within the adrenal gland that are histologically indistinguishable from neuroblastoma (Beckwith and Perrin, 1963). *In situ* neuroblastoma was found during postmortem examination in 1 of 224 infants younger than 3 months. This represents an incidence of approximately 40 to 45 times greater than that of clinical tumors, suggesting that these small tumors regress spontaneously in most cases. Subsequent studies have shown that these neuroblastic nodules are found in all fetuses studied and typically regress (Ikeda et al, 1981). Neuroblastoma identified by prenatal ultrasonography has also been shown to have a clinically favorable course (Ho et al, 1993).

The concept of *in situ* neuroblastoma has been used to support the argument that many neuroblastomas arise and regress spontaneously. This concept has been further supported by population-based studies in Quebec province and in Japan, where prospective screening of infants for neuroblastoma has been performed based on urinary catecholamine excretion. An increased number of children were identified with low-stage neuroblastoma, a higher frequency than present clinically, but there was no decrease in the incidence of advanced-stage tumors seen at an older age (Hayashi et al, 1995; Woods et al, 1996). Evaluation of adrenal tumors resected in the neonatal period, whether cystic or solid, showed that

in most, the biologic markers were favorable (Kozakewich et al, 1998). The highly favorable outcome of infants diagnosed with neuroblastoma in the population screening studies led to attempts at expectant observation. These trials demonstrated a high rate of spontaneous resolution (Yamamoto et al, 1998; Yoneda et al, 2001). Spontaneous regression of these perinatally identified lesions also has been demonstrated radiographically (Holgersen et al, 1996). These findings led to a prospective study by the Children's Oncology Group (COG) evaluating treatment of infants with adrenal masses identified in the perinatal or neonatal period in which expectant observation for infants with small lesions with favorable catecholamine ratios was encouraged; this is discussed later.

Pathology

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma display a spectrum of histologic maturation and differentiation (Fig. 155-1). A grading classification of neuroblastoma, introduced in 1984 by Shimada and subsequently modified by him and others as the International Neuroblastoma Pathology Classification in 1999, has helped to define risk-based subtypes of ganglioneuroblastoma and neuroblastoma (Shimada et al, 1984, 1999a, 1999b). This revised system has been demonstrated to add independent prognostic information beyond the contribution of age that is contained in the system (Sano et al, 2006). Ganglioneuroma is a histologically benign, fully differentiated counterpart of neuroblastoma. It is unclear whether ganglioneuroma arises *de novo* or by maturation of a preexisting neuroblastoma or ganglioneuroblastoma. Metastatic lesions from neuroblastoma have been observed to develop the histology of mature ganglioneuroma, supporting the latter theory (Hayes et al, 1989).

The Shimada classification is an age-linked histopathologic classification. One of its important aspects is determining whether the tumor is stroma poor or stroma rich. Patients with stroma-poor tumors with unfavorable histopathologic features have a very poor prognosis (less than 10% survival) (Shimada et al, 1984). Stroma-rich tumors can be separated into three subgroups: nodular, intermixed, and well differentiated. Tumors in the last two categories more closely resemble ganglioneuroblastoma or immature ganglioneuroma and carry a higher rate of survival. The stroma-poor tumors can be divided into favorable and unfavorable subgroups based on the patient's age at diagnosis, the degree of histologic maturation, and the mitotic rate. When compared with other

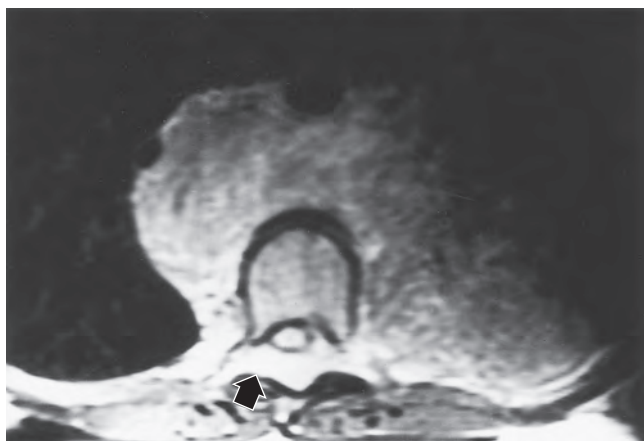


Figure 155-2. Magnetic resonance image of child with thoracic ganglioneuroma extending into the spinal canal (arrow).

clinical features, these histologic patterns were independently predictive of outcome (Shimada et al, 1984).

In contrast to neuroblastomas, ganglioneuromas are most often diagnosed in older children and are usually located in the posterior mediastinum and retroperitoneum, with only a small number arising in the adrenal glands (Enzinger and Weiss, 1988). Ganglioneuromas often grow to a very large size before they cause symptoms as a result of compression of adjacent structures or extension into the spinal canal (Benjamin et al, 1972) (Fig. 155-2). Because survival is not influenced by extent of resection, it should be used only in those in whom significant symptoms are present, and aggressive attempts at resection should be avoided (De Bernardi et al, 2008).

Clinical Presentation and Pattern of Spread

The clinical manifestations of neuroblastoma vary widely. Most children have abdominal pain or a palpable mass, but other neuroblastomas are identified because of manifestations of metastatic disease, including bone or joint pain and periorbital ecchymosis. Thoracic lesions may produce respiratory symptoms of cough or dyspnea. Direct extension of the tumor into the spinal canal may produce neurologic deficits as a result of cord compression.

Most primary tumors arise within the abdomen (65%); the frequency of adrenal tumors is slightly higher in children than in infants. Physical examination often reveals a fixed, hard abdominal mass. Pelvic neuroblastoma arising from the organ of Zuckerkandl accounts for 4% of tumors (Haase et al, 1995). Extrinsic compression of the bowel and bladder can produce symptoms of urinary retention and constipation (Fig. 155-3).

Metastases are present in 70% of patients with neuroblastoma at diagnosis and can be responsible for a variety of the clinical signs and symptoms at presentation. A number of unique paraneoplastic syndromes have been associated with both localized and disseminated neuroblastoma. Symptoms produced by catecholamine release may mimic those seen in pheochromocytoma: paroxysmal hypertension, palpitations, flushing, and headache. Secretion of vasoactive intestinal peptide (VIP) by the tumor can produce severe watery diarrhea and hypokalemia (Cooney et al, 1982). Another unusual presentation of neuroblastoma is acute myoclonic encephalopathy, in which patients develop myoclonus, rapid multidirectional eye movements (opsoclonus), and ataxia. It is thought to result from an interaction of antibodies produced against the neuroblastoma to normal neural tissues (Farrelly et al, 1984; Connolly et al, 1997). Although this syndrome is associated with a favorable outcome from an oncologic perspective (Altman and Baehner, 1976), prolonged neurologic impairment, including learning disabilities and developmental delay, is the rule in 70% to 80% of these children, and symptomatic therapy is often required (Russo et al, 1997; Rudnick et al 2001; Mitchell et al 2002). Adre-

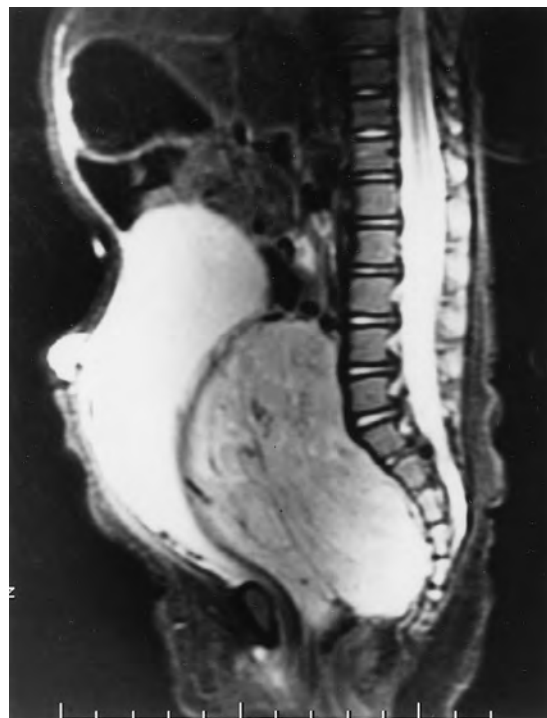


Figure 155-3. Magnetic resonance image demonstrating compression of bowel and bladder by a pelvic neuroblastoma.

nocorticotrophic hormone (ACTH) or steroids are the basis of most therapy, but other treatments include high-dose intravenous gamma globulin and cyclophosphamide. A recently completed protocol of the COG evaluated the efficacy of cyclophosphamide plus steroids in patients randomized to receive intravenous gamma globulin or not. Results have not yet been reported.

Diagnosis

Laboratory Evaluation

When sensitive techniques are used, increased levels of urinary metabolites of catecholamines, vanillylmandelic acid (VMA) and homovanillic acid (HVA), are found in 90% to 95% of patients (Williams and Greer, 1963). Therapy with various modalities produces a reduction in catecholamine metabolite excretion in most patients (Gerson and Koop, 1974). These metabolites can be monitored to detect tumor relapse and response to therapy.

Anemia is noted in children with widespread bone marrow involvement. Studies suggest that marrow biopsies add substantially to the detection of marrow involvement by tumor, compared with marrow aspirates alone (Franklin and Pritchard, 1983). It is recommended that two marrow aspirates and two biopsies be performed. In the future, neuroblastoma-specific immunocytology of marrow aspirates may obviate the need for marrow biopsies in most patients (Hsiao et al, 1990).

Imaging

Imaging studies play an important role in the evaluation of a child with neuroblastoma. Plain radiographs may demonstrate a calcified abdominal or posterior mediastinal mass. Computed tomography (CT) and magnetic resonance imaging (MRI) provide more information about the local extent of the primary tumors and vascular involvement. Invasion of the renal parenchyma is not common, but it can be detected radiographically with CT (Albregts et al, 1994). MRI has advantages over CT in evaluating intraspinal tumor extension, which is not uncommon in paravertebral lesions (see Fig. 155-2), and in demonstrating the relationship between the major vessels and the tumor (Azizkhan and Haase, 1993).

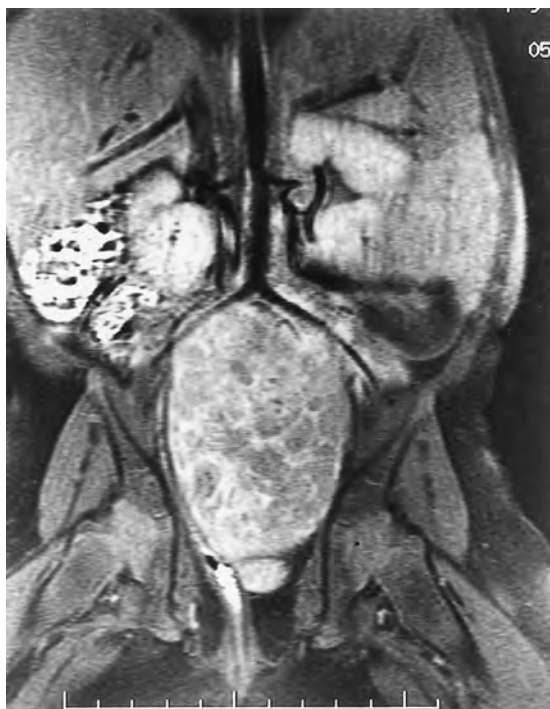


Figure 155-4. Magnetic resonance image of pelvic neuroblastoma. The bifurcation of the aorta and iliac vessels are well delineated, showing the relationship to the mass.

(Fig. 155-4). The finding of intratumoral calcifications, vascular encasement, or both on preoperative CT may help distinguish neuroblastoma from Wilms tumor (Dickson et al, 2008). Current COG protocols require both a radionuclide bone scan and metaiodobenzylguanidine (MIBG) scans for staging, but no longer require the classic skeletal survey. MIBG scans use iodine-131 (^{131}I) MIBG (Geatti et al, 1985), which is taken up by the adrenergic secretory vesicles of the tumor cells in both primary and metastatic sites. MIBG scintigraphy can determine the extent of disease and detect tumor recurrence after completion of therapy (Geatti et al, 1985). ^{123}I -MIBG has been shown to be more sensitive than either ^{131}I -MIBG or bone scans in detecting tumor relapse (Kushner et al, 2009). Osseous metastatic lesions occur most commonly in the long bones and skull.

Screening

Mass population screening for neuroblastoma has been widely used in Japan for more than 20 years (Nishi et al, 1987). The goal of screening programs is to detect disease at an earlier stage and to decrease the number of older children with advanced-stage disease, thereby improving survival. In fact, the children diagnosed as a result of screening studies have had almost uniformly favorable survival (>97%) (Suia, 2002). An increased number of infants younger than 1 year of age have been diagnosed through the mass screening program (Ishimoto et al, 1990), and most of these patients have lower-stage tumors (Sawada, 1992). Before mass screening, 20% of patients with neuroblastomas were diagnosed before 1 year of age, compared with 55% after its implementation. However, the number of children older than 1 year of age diagnosed with advanced-stage disease has not decreased. These results suggest that the aggressive advanced-stage tumors in older children did not arise from the low-risk tumors seen in the infants younger than 1 year.

There are biologic differences between tumors diagnosed by screening and those detected clinically (Hayashi et al, 1992). In one review of 48 cases discovered by screening, no tumors were observed to have amplified *MYCN* oncogene expression (Ishimoto et al, 1991), and in a second review of 20 infants, only one who did

poorly had amplification (Hase et al, 2002). Furthermore, 80% had a diploid chromosome pattern, which is also associated with a favorable prognosis. On follow-up, all 48 patients were still alive without tumor. In another series of 357 patients whose tumors were diagnosed by mass screening, the overall survival (OS) rate was 97% (Sawada, 1992). Given the favorable biologic characteristics of tumors discovered by screening, it is possible that many would spontaneously resolve without therapy, particularly given the increased incidence of neuroblastomas seen in the screened population.

Two large prospective population-based studies were conducted in the Province of Quebec and in Germany. These studies demonstrated that urine screening at various ages was successful in identification of neuroblastoma, but there was no decrease in the occurrence of neuroblastoma in older children and its subsequent mortality (Schilling et al, 2002; Woods et al, 2002).

Staging

Staging of neuroblastoma is an important aspect of management. The stage of the disease is a significant prognostic variable that determines adjuvant therapy. The International Neuroblastoma Staging System (INSS) is based on clinical, radiographic, and surgical evaluation of children with neuroblastoma (Brodeur et al, 1993) (Table 155-1). Earlier staging systems provided generally comparable results in terms of distinguishing low-stage, good-prognosis disease from high-stage, poor-prognosis disease. Use of a uniform international system, however, makes comparison of results from various studies much easier to compare. The biggest differences arise when the various systems are applied to those with intermediate-stage disease. It is in this cohort of children where use of the risk group classification, which combines pathologic findings, stage, and several of the biologic markers, best defines the child's risk for progressive disease (Table 155-2) (Katzenstein and Cohn, 1998). Although the classification appears complex, it provides the most accurate assessment of how intense the chemotherapy and radiotherapy must be to cure the child. The challenge with any staging system that uses extent of resection as a component, however, is that a more aggressive approach to a tumor at one institution may result in a different stage for the child than if he or she were treated at another.

A recent effort has been made to preoperatively identify tumors that are resectable without significant surgical risks. The Localised Neuroblastoma European Study Group (LNESEG) defined the radiographic criteria associated with higher surgical morbidity. This group validated that the presence of these criteria was associated with a lower rate of complete resection and a greater risk of surgical complications (Cecchetto et al, 2005). This finding has been confirmed by others (Simon et al, 2008). The International Neuroblastoma Risk Group (INRG) Task Force proposed a staging system based on tumor imaging rather than the extent of surgical resection to address this problem (Monclair et al, 2009). In this system, localized tumors are graded as L1 or L2 based on the absence or presence of one or more of 20 image-defined risk factors (IDRFs), which are primarily related to encasement of vessels or nerves. Metastatic tumors are termed stage M; MS refers to INSS stage 4S in children younger than 18 months, whereas in the INSS the age cutoff is 12 months. These factors were found to be prognostic; of 661 patients, those with L1 disease had a greater 5-year event-free survival (EFS) ($90\% \pm 3\%$) than those with L2 disease ($78\% \pm 4\%$, $P = .001$). A further description of these guidelines has been reported by this group (Brisse et al, 2011). Although a close correlation between presence of IDRFs and resectability of the tumor has been reported, other researchers have not supported this finding (Günther et al, 2011; Rich et al, 2011).

Prognostic Factors

Many variables affect the prognosis of neuroblastoma. In addition to the clinical features, there are now many biologic factors that can be used to stratify patients for treatment.

TABLE 155-1 International Neuroblastoma Staging System

STAGE	DEFINITION
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
3	Unresectable unilateral tumor infiltrating across the midline,* with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs.
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (less than 10% tumor) in infants younger than 1 year.

*The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

TABLE 155-2 Neuroblastoma Risk Group Classification

RISK GROUP	INSS STAGE	AGE (DAYS)	N-MYC STATUS	DNA INDEX	SHIMADA HISTOPATHOLOGY
Low	1	Any	Any	Any	Any
	2A, 2B	<365	Any	Any	Any
	2A, 2B	≥365	Nonamplified	Any	Any
	2A, 2B	≥365	Amplified	Any	Favorable
	4S	<365	Nonamplified	>1.0	Favorable
Intermediate	3	<365	Nonamplified	Any	Any
	3	≥365	Nonamplified	Any	Favorable
	4	<365	Nonamplified	Any	Any
	4S	<365	Nonamplified	1.0	Favorable
	4S	<365	Nonamplified	Any	Unfavorable
High	2A, 2B	≥365	Amplified	Any	Unfavorable
	3	<365	Amplified	Any	Any
	3	≥365	Nonamplified	Any	Unfavorable
	3	≥365	Amplified	Any	Any
	4	<365	Amplified	Any	Any
	4	≥365	Any	Any	Any
	4S	<365	Amplified	Any	Any

INSS, International Neuroblastoma Staging System.

Clinical Variables

Age remains an important indicator of outcome, as originally reported by Breslow (Breslow and McCann, 1971). Children age 1 year or younger have been recognized historically to have a better survival rate than older children (Nitschke et al, 1988). This may be attributed to more favorable biologic parameters in tumors diagnosed at this age. Recent retrospective reviews have suggested that age is a more “continuous” prognostic variable and that a cutoff of 460 days maximized the outcome difference between the younger and older patients (London et al, 2005), and more recent data from the INRG suggest that an age at diagnosis cutoff of older than 18 months is associated with a higher risk of disease recurrence (Moroz et al, 2011). Teenagers and adults with neuroblastoma have a particularly indolent and relentless disease (Gaspar et al, 2003; Kushner et al, 2003). The site of origin is of significance, with better survival noted for nonadrenal primary tumors (Haase et al, 1995).

Most children with thoracic neuroblastoma are younger at presentation, have localized disease, and have improved survival even when corrected for age and stage (Adams et al, 1993). Tumors at this site are less likely to have MYCN amplification and more likely to have a DNA index greater than 1.0, both favorable prognostic indicators (Morris et al, 1995).

Stage of the disease is a powerful independent prognostic indicator. Virtually all stage 1 patients with complete resection of the primary tumor survive. Stage 2 patients also have a favorable survival prospect, even though there may be incomplete excision (Matthay et al, 1989). Children with advanced regional disease, stage 3 or 4, fare less well and require more intensive treatment. The proportion of patients with localized, regional, or metastatic disease at presentation is age dependent (Nitschke et al, 1988). The OS for stage 1, 2, or 4S disease had a range of 75% to 90%, whereas children with stage 4 disease had a historical 2-year disease-free survival range of 19% to 30% despite intensive therapy, including

bone marrow transplantation. The outcome for infants younger than 1 year is substantially better than for older patients with the same stage of disease.

Stage 4S (S meaning special) is a distinct category referring to infants with small primary tumors and liver, skin, and bone marrow metastases without radiographic evidence of bone metastases. This group of patients has a good prognosis, with OS ranging from 80% to 88%. The INSS criteria later restricted this stage to children with less than 10% bone marrow involvement (Brodeur et al, 1993). This stage accounts for 7% to 10% of all cases of neuroblastoma. Many of these tumors undergo spontaneous regression (Evans et al 1987; Haas et al, 1990). In general, the tumors in infants with stage 4S neuroblastoma have favorable prognostic findings not typically seen in children with stage 4 disease (Hachitanda et al, 1991; Nickerson et al, 2000). Poor outcome in stage 4S patients is associated with elevated serum neuron-specific enolase (>100 nmol/mL), ferritin (>280 ng/mL), and urinary dopamine levels (>2500 nmol/mmol creatinine), as well as MYCN amplification and chromosome 1p deletion (Schleiermacher et al, 2003). Most deaths in this group are in infants younger than 2 months with extensive abdominal involvement and with respiratory compromise or disseminated intravascular coagulation (Nickerson et al, 2000).

Biologic Variables

The presence of homogeneously staining regions and double-minute chromosomes was noted in approximately one third of neuroblastoma tumors. These abnormalities are cytogenetic manifestations of gene amplification, and it was subsequently found that the MYCN oncogene was mapped to these regions. The association of MYCN amplification with the pathogenesis of neuroblastoma is unclear, but MYCN amplification is almost always present at the time of diagnosis (Brodeur, 1991). Seeger and colleagues (1985, 1988) showed that MYCN amplification is associated with rapid tumor progression and a poor prognosis. Amplification is found in 5% to 10% of patients with low-stage or stage 4S (Hachitanda et al, 1991) but in 30% to 40% of those with advanced-stage disease (Brodeur and Fong, 1989; Brodeur, 1990). The poor prognosis associated with MYCN amplification is independent of patient age or stage of disease at presentation (Iehara et al, 2006). However, not all patients with a poor outcome have MYCN amplification. Many advanced-stage tumors lack MYCN at diagnosis, and recurrence or progression of disease develops in most of these patients. A full INRG analytic cohort of 8800 patients from North America, Europe, and Japan provided an extensive analysis of the survival implications of multiple genetic characteristics shown in Table 155-2 (Cohn et al, 2009). Again, MYCN status was the most powerful predictor of EFS and OS along with ploidy, 11q, and 1p status and, to a lesser extent, 17q gain.

DNA content of tumor cells and ploidy number has been reported to have prognostic value in patients with neuroblastoma (Cohn et al, 1990). Studies of DNA content measured by flow cytometry showed that a "hyperdiploid" karyotype (or increased DNA content) was associated with a favorable outcome (Look et al, 1984; Kusafuka et al, 1994). DNA diploidy and tetraploidy were associated with decreased survival. A review of 2660 children with localized neuroblastoma registered with the INRG database evaluated tumor ploidy in children with MYCN-amplified tumors (Bagatell et al, 2009). They reported an improved prognosis in children with hyperdiploid tumors compared with diploid tumors. This could be used to identify children for reduction in therapy.

Deletions of the short arm of chromosome 1 have been found in 70% to 80% of the near-diploid tumors that have been karyotyped (Brodeur and Fong, 1989; Brodeur, 1990). Preliminary studies suggested a correlation between 1p deletion and poor survival (Brodeur and Fong, 1989; Hayashi et al, 1989). Children currently treated on protocols of the COG are assigned to a risk group that is determined by age, stage of disease, MYCN status, histologic grade, and DNA ploidy (Katzenstein et al, 1998) (see Table 155-2). Other factors that have been demonstrated to have prognostic significance, although they are often associated with these genetic

abnormalities, include expression of the gene encoding the high-affinity nerve growth factor receptor (termed *TRKA* proto-oncogene) and the low-affinity nerve growth factor receptor (Tanaka et al, 1995). Both are favorable prognostic predictors and are inversely related to amplification of the MYCN oncogene (Nakagawara et al, 1993). Lack of expression of CD44 glycoprotein on the tumor cell surface and increased levels of serum ferritin, serum neuron-specific enolase, and serum lactate dehydrogenase are all adverse prognostic factors (Chan et al, 1991; Silber et al, 1991). They have not, however, been shown by multivariate analysis to be independently predictive from age, stage, ploidy, and MYCN status. Telomere length has also been described as a significant prognostic parameter, and in a cohort of high-risk patients, it was the sole significant parameter that identified a group of patients with a favorable prognosis (Ohali et al, 2006).

Treatment

The treatment modalities primarily used in the management of neuroblastoma are surgery, chemotherapy, and radiation therapy. The role of each in individual patients varies depending on tumor stage, age, and biologic prognostic factors. These can be used to stratify patients into favorable and unfavorable categories by risk group (see Table 155-2).

Surgery

The goals of surgery are to establish the diagnosis, stage the tumor, excise the tumor (if localized), and provide tissue for biologic studies. Resectability of the primary tumor should take into consideration tumor location, mobility, relationship to major vessels (IDRFs), and overall prognosis of the patient. Neoadjuvant chemotherapy, given the efficacy of modern agents, is very successful in reducing the size of primary tumors. Sacrifice of vital structures to achieve resection at diagnosis should be avoided, particularly in young children in whom prognosis is excellent.

Low-Risk Disease (Stages 1, 2, and 4S). Children with stage 1 neuroblastoma have a disease-free survival rate of greater than 90% with surgical excision alone (O'Neill et al, 1985; Nitschke et al, 1988; De Bernardi et al, 1995). Chemotherapy is indicated only in the event of recurrence unless the child has MYCN amplification and unfavorable histology. The Pediatric Oncology Group reviewed 101 children with localized neuroblastoma who had complete gross excision of the primary tumor (Nitschke et al, 1988). Nine patients experienced relapse, but 6 were salvaged with chemotherapy. Radiation therapy has no role in this subset of patients. With current use of the risk factor grading, children with recurrence in the past may be identified now as the small number with adverse biologic markers. In a comparable study from the Children's Cancer Group, 374 stage 1 and 2 patients were treated primarily by resection (Perez et al, 2000). EFS and OS for stage 1 patients were $93\% \pm 3\%$ and $99\% \pm 1\%$, respectively, compared with $81\% \pm 4\%$ and $98\% \pm 2\%$ for stage 2 patients, respectively. Supplemental treatment was required in only 10% of stage 1 and 20% of stage 2 patients, and excellent OS was achieved in the stage 2 patients. MYCN amplification, unfavorable histology, age greater than 2 years, and positive lymph nodes predicted a lower OS. A recent COG trial of asymptomatic INSS stages 2A and 2B patients were treated with surgery alone (Strother et al, 2012). Chemotherapy in this study was reserved for patients with symptomatic disease or considered at risk for its development, or those with less than 50% resection with unresectable progressive disease after surgery. For all 915 enrolled patients, the 5-year EFS and OS were $89\% \pm 1\%$ and $97\% \pm 1\%$. In the cohort with stage 2B disease, the EFS and OS were significantly lower for those with unfavorable-histology or diploid tumors and OS was significantly lower for those 18 months or younger. The 5-year OS rates for patients with stage 1 and 4S were $99\% \pm 1\%$ and $91\% \pm 1\%$, respectively. Of patients observed after surgery, 11.1% experienced recurrence or progressive disease.

Radical resection resulting in removal of normal organs, particularly the kidney, is not justified in this group of patients. Radiation



Figure 155-5. Magnetic resonance image before and after chemotherapy showing marked reduction in size of right suprarenal neuroblastoma. A, Before chemotherapy. B, After chemotherapy.

of the local tumor bed has been advocated for treatment of residual disease in stage 2 cases. However, a review of 156 patients with stage 2 neuroblastoma found a 90%, 6-year, progression-free survival rate regardless of whether radiation therapy was used (Matthay et al, 1989). Therefore, radiation should be reserved for those relapsed patients who fail to respond to either primary or secondary chemotherapy. In stage 3 disease, or in stage 2 with extensive tumor around the kidney and renal vessels, preoperative treatment with chemotherapy significantly decreases the risk of nephrectomy as a result of resection of the tumor (Shamberger et al, 1998) (Fig. 155-5).

The generally favorable behavior of stage 4S disease has been explained by our current knowledge of the significance of biologic markers. The vast majority of these infants have tumors with entirely favorable markers, explaining their favorable behavior. However, a small fraction have adverse markers, and it is these children who have progressive disease that often is fatal. Resection of the primary is not mandatory (Nickerson et al, 1985; Evans et al, 1987). Although excellent survival has been reported after surgery (Martinez et al, 1992), information regarding histologic prognostic factors was not available for all of these patients. In a review of 110 infants with stage 4S disease, the entire cohort had an estimated 3-year survival rate of $85\% \pm 4\%$ (Katzenstein et al, 1998). This rate was significantly decreased to $6\% \pm 12\%$ for infants whose tumors were diploid; to $44\% \pm 33\%$ for those with *MYCN* amplification; and to $33\% \pm 19\%$ for those with unfavorable histology. Of note, there was no statistical difference in survival rate for infants who underwent complete resection of their primary tumor compared with those who had partial resection or only biopsy (Katzenstein et al, 1998; Nickerson et al, 2000; von Schweinitz et al, 2002). Patients with extensive metastatic disease and *MYCN* amplification represent a high-risk group (Martinez et al, 1992). These patients should be considered for a more aggressive treatment with multimodal therapy, according to the risk group classification (see Table 155-2) (Schleiermacher et al, 2003). Those with favorable biologic markers and no symptoms can be followed with supportive care and limited chemotherapy. Intensive chemotherapy is reserved for those with adverse markers, although these infants do poorly even with therapy.

Perinatal Neuroblastoma. Based on the favorable outcomes of infants identified with neuroblastoma from the screening studies discussed earlier and the favorable biology of these tumors, a prospective study was performed by the COG to assess the outcome of

expectant observation for neuroblastoma in young infants. Infants were enrolled who were younger than 6 months with small adrenal masses (≤ 16 mL in volume if solid or ≤ 65 mL if the mass was at least 25% cystic) and no evidence of spread beyond the primary tumor (Nuchtern et al, 2012). Serial abdominal sonograms and urinary catecholamine levels were obtained during a 90-week interval. Patients with a 50% increase in the volume of the mass or urine catecholamine values or an increase in the HVA-to-VMA ratio greater than 2 were referred for surgical resection. Eighty-seven infants were enrolled; in 83, observation was elected, and in 4, immediate surgery. Sixteen infants in the observation arm ultimately had surgery; 8 had INSS stage 1 neuroblastoma, 2 had higher-stage neuroblastoma (2B and 4S), 2 had a low-grade adrenocortical neoplasm, 2 had adrenal hemorrhage, and 2 had extralobar pulmonary sequestration. The 2 adrenal cortical tumors were resected because of a greater than 50% increase in tumor volume. The 3-year EFS for a neuroblastoma event was $97.7\% \pm 2.2\%$ within the entire cohort of infants. The 3-year OS was 100% with a median follow-up of 3.2 years. Following this protocol, 81% of the infants avoided resection, supporting the role of expectant observation in this selected population. A future study is planned to expand the size and location of these tumors.

Intermediate- and High-Risk Disease (Stages 3 and 4). There is debate regarding the extent of surgical resection that is required for stage 3 lesions. A report from the Children's Cancer Group of 58 patients with stage 3 disease found that 8 of 12 patients with initial complete excision, and 12 of 14 with subsequent resection of the primary tumor, were long-term survivors (Haase et al, 1989). This result contrasts with only 9 of 32 survivors among patients in whom complete tumor excision could not be accomplished. Significant morbidity was reported in association with the surgical procedures, including 21 major complications. The Italian Cooperative Group for Neuroblastoma found that complete resection after chemotherapy of extensive unresectable neuroblastoma was associated with improved survival, compared with partial resection only (Garaventa et al, 1993). Similar results have been noted by others (Le Tourneau et al, 1985; O'Neill et al, 1985; Powis et al, 1996). It has been suggested by some that even children with stage 3 disease do not need cytotoxic therapy if the biologic marker *MYCN* amplification is not present (Kushner et al, 1996). These results are not widely accepted, however, and confirmatory studies are required before this policy can be widely adopted.

In general, children with bulky pelvic tumors do quite well even with limited residual disease (Leclair et al, 2004). Extensive surgery at this site has been associated with long-term neurologic sequelae; thus the extent of resection must be balanced against this morbidity (Crucetti et al, 2000).

A recent study from the COG of intermediate-risk patients attempted to decrease the intensity of therapy while maintaining outcomes (Baker et al, 2010). Criteria included intermediate-risk neuroblastoma without *MYCN* including infants younger than 365 days with stage 3 or 4 disease, children older than 365 days who had stage 3 tumors with favorable histopathologic features, and infants who had stage 4S disease with a diploid DNA index or unfavorable histopathologic features. Children received four active agents in this disease: cyclophosphamide, doxorubicin (DOX), carboplatin, and etoposide. They received four cycles if they had favorable biology or eight cycles if they had unfavorable biology. Radiotherapy was used only for progressive disease or in patients with an unresectable primary tumor with unfavorable prognostic features. The 3-year estimate of OS for the entire group was $96\% \pm 1\%$; $98\% \pm 1\%$ for those with favorable biologic features and $93\% \pm 2\%$ for those with unfavorable biologic features. These findings supported the reduction in therapy for this cohort of patients. Complete data regarding surgical intervention were available for 235 patients. Gross total resection was achieved in 89 patients, near-total resection ($>90\%$ of the tumor) in 51, major resection ($>50\%$ of the tumor) in 26, and limited resection ($\leq 50\%$ of the tumor) in 54. No significant difference was demonstrated in OS according to the extent of resection (complete vs. incomplete $P = .37$). Of note, 28% of patients had one or more complications.

There is conflicting evidence regarding the benefit of extensive resection in children with stage 4 disease between studies that support (Le Tourneau et al, 1985; Haase et al, 1991; Tsuchida et al, 1992; La Quaglia et al, 1994; Chamberlain et al, 1995; DeCou et al, 1995; Yokoyama et al, 1995; Kuroda et al, 2003; Adkins et al, 2004; La Quaglia et al, 2004; Koh et al, 2005; McGregor et al, 2005) and those that refute that approach (Sitarz et al, 1983; Matsumura et al, 1988; Adams et al, 1993; Losty et al, 1993; Kiely, 1994; Kaneko et al, 1997; Castel et al, 2002; von Schweinitz et al, 2002; Simon et al, 2013). In a retrospective review, Kiely (1994) compared the results of radical tumor resection with those of more conventional surgery in patients with stage 3 or 4 disease. Kiely found no difference in survival between 46 patients treated with radical surgical procedures and 34 patients treated with more conventional surgery. Shorter and colleagues (1995) also did not find any evidence that the extent of surgical resection had an impact on the survival of stage 4 patients. In these nonrandomized studies, it has been difficult to determine whether improved survival in those with complete resection has been a result of the more favorable intrinsic biology of the tumor allowing resection or truly a result of the completeness of resection. La Quaglia assessed the results in 33 nonredundant studies that provided adequate surgical data for analysis of survival (La Quaglia, 2014). The analysis included 2599 patients for the survival analysis and 412 in the analysis of local progression. Meta-analysis revealed that the relative risk of mortality for stage 3 and 4 patients who had more than 90% resection was 0.67 (95% confidence interval [CI] 0.59 to 0.77) compared with those with a lesser resection. For stage 4 patients alone the relative risk was 0.75 (95% CI 0.62 to 0.92). The relative risk of local recurrence or progression in patients with stage 4 disease was 0.38 (95% CI 0.27 to 0.53) for those who underwent extensive primary resection compared with those who did not.

As the intensity of the therapy increases, including the use of autologous bone marrow transplantation and control of distant metastasis, the impact of maximal local control may become apparent. The combination of gross total resection and external beam irradiation has achieved local control in 84% to 90% of children (Wolden et al, 2000; Kushner et al, 2001). In another series of reports, intensive chemotherapy followed by double autologous bone marrow transplantation, aggressive surgical resection, and radiotherapy achieved an OS of 56% and a local recurrence rate of only 2.6% (Marcus et al, 2003; von Allmen et al, 2005).

Usually the safest approach for advanced tumors is to defer resection until after initial chemotherapy (Berthold et al, 1989; Shamberger et al, 1991; Shochat, 1992; La Quaglia et al, 1994; Black et al, 1996). The tumors are smaller and firmer, with less risk of rupture and hemorrhage after chemotherapy, resulting in a decreased rate of complications, particularly nephrectomy (Shamberger et al, 1998) (see Fig. 155-5). One specific complication that is encountered after resection of extensive tumor surrounding the celiac axis and the superior mesenteric artery is diarrhea (Kiely, 1994). It is thought to result from resection of the autonomic nerves to the gut found anterior to the aorta at the base of the superior mesenteric artery and the celiac axis (Rees et al, 1998). Preoperative chemotherapy does appear to increase the proportion of children able to achieve a complete resection (Adkins et al, 2004).

Surgery usually is performed 13 to 18 weeks after initiation of chemotherapy, allowing three to four courses of treatment (Azizkhan and Haase, 1993). Some tumors remain inoperable even after chemotherapy.

Infants younger than 1 year with extensive local disease or stage 4 disease comprise a special subset of patients. They have historically fared much better than children older than 1 year of age with comparable disease, but not as well as infants with stage 4S disease. It is now recognized that the biologic markers can be used to identify which infants have high-risk disease and require intensive therapy and which have intermediate-risk disease requiring less intensive therapy. The SIOPEX Infant Neuroblastoma European Study reported 120 infants with localized tumors and no *MYCN* amplification who were deemed unresectable based on IDRFs (Rubie et al, 2011). These infants were treated with low-dose cyclophosphamide and vincristine (VCR) repeated once to three times every 2 weeks until surgical excision could be safely performed. Infants with either one life-threatening symptom or an insufficient response were given carboplatin and etoposide (CaE), sometimes followed by VCR, cyclophosphamide, and DOX. Seventy-nine received the two-drug therapy with VCR, and 49 received CaE because of insufficient response. Thirty-two infants had life-threatening symptoms, and of these 30 received CaE. Anthracyclines were used in 46 infants. Surgery was performed in 102 infants, leading to gross surgical excision in 93. Relapse occurred in 12 patients (9 local and 3 distant). The 5-year OS and EFS were $9\% \pm 1\%$ and $90\% \pm 3\%$, respectively. The low-dose chemotherapy without an anthracycline was effective in 62% of these infants with an unresectable tumor and no *MYCN* amplification.

In a large cohort (134 infants), *MYCN* amplification, serum ferritin, Shimada histopathologic classification, and bone marrow involvement by immunocytology were analyzed. Although each factor had prognostic significance by univariate analysis, only *MYCN* amplification was significant by multivariate analysis; the EFS for infants without *MYCN* amplification was $93\% \pm 4\%$ versus $10\% \pm 7\%$ in those with amplification despite intensive therapy (Schmidt et al, 2000).

Recent trials in Europe evaluated these infants without *MYCN* amplification and achieved excellent survival (OS of 97.6% at 2 years) without chemotherapy in those with primaries extending across the midline or a positive skeletal survey (De Bernardi et al, 2009). Infants with overt metastases to the skeleton, lung, and central nervous system (CNS) were treated with a minimum of four chemotherapy courses and achieved a 2-year OS of 95.6%.

Chemotherapy

A variety of multiagent treatment regimens have been developed to treat high-risk patients with neuroblastoma. The goal of this treatment intensification is better disease control. Although initial response rates are improving, with a prolonged time to progression of disease, relapse continues to be a major problem.

The dose intensification of chemotherapy needed for local tumor control results in significant myelosuppression, limiting the amount of therapy that can be given. This has prompted the use of autologous bone marrow transplantation after sublethal chemotherapy or total-body irradiation. The use of marrow-ablative

chemoradiotherapy followed by autologous marrow reinfusion has resulted in complete remission in up to 50% of patients with recurrent stage 4 disease (Moss et al, 1987; Seeger et al, 1991; Dinndorf et al, 1992; Mugishima et al, 1994; Matthay et al, 1995; Grupp et al, 2000). However, a significant problem is the risk for late relapse. The randomized clinical trial of the German Society of Paediatric Oncology and Hematology of high-risk neuroblastoma showed improved EFS at 3 years with myeloablative therapy and autologous stem cell rescue compared with maintenance chemotherapy (Berthold et al, 2005). These results were similar to those of the COG study (Matthay et al, 1999). Regrettably, the OS rates were not statistically different in either study at initial report. A recent update of the latter study reveals that the 5-year OS of the patients receiving the autologous bone marrow transplant was improved (Matthay et al, 2009).

A subsequent study by the COG addressed the issue of the need for “purging” of the bone marrow before return to the patient to remove any potential remaining neuroblastoma cells. This study was terminated when interim analysis showed no difference in outcome between the two groups. A further study addressed the benefit between a single versus a paired autologous transplant to see if additional intensification would improve outcome. This study has completed enrollment, but results are not yet available.

The presence of bulky disease results in increased failure. Tumor debulking with surgery or radiation therapy is warranted before autologous bone marrow transplantation. There are many questions yet to be resolved about this modality of treatment. Toxicity of bone marrow transplantation can be lethal, and the long-term complications in patients with successful transplantation are unknown. However, these risks are acceptable given that long-term survival is difficult to achieve without such aggressive therapy.

New agents in phase I and II trials for relapsed neuroblastoma include temozolomide, irinotecan, and topotecan (Kushner et al, 2006; Rubie et al, 2006; Simon et al, 2007). As efficacy is established, they will be advanced into clinical trials for high-risk tumors with a goal of improving the overall outcome.

New Innovative Biologic Therapies

Because increasing the intensity of chemotherapy appears to have reached its limit with the use of double autologous bone marrow transplantation, other routes of treatment must be identified. The use of biologic modifiers is being investigated (Villablanca et al, 1995). 13-*cis*-Retinoic acid produces differentiation of neuroblastoma in cell cultures. It was given for a 6-month period after cytotoxic therapy in children with advanced-stage disease and significantly decreased the frequency of relapse (Matthay et al, 1999). Long-term follow up has shown that the 5-year OS is improved with the use of 13-*cis*-retinoic acid in these children after transplant or intensive chemotherapy (Matthay et al, 2009). Other avenues of treatment in current phase I and phase II trials include vaccine and antiangiogenic therapy. Antibody therapy against the GD2 cell surface marker occurring in neuroblastoma has been shown to be an effective adjuvant therapy in combination with granulocyte-macrophage colony-stimulating factor and interleukin-2 along with 13-*cis*-retinoic acid after autologous bone marrow transplant compared with 13-*cis*-retinoic acid alone (Yu et al, 2010).

A new synthetic retinoid, fenretinide, which has produced apoptosis rather than differentiation in neuroblastoma cell lines, is also in clinical trials for maintenance therapy. It has been shown to be effective against some neuroblastoma cell lines that are resistant to 13-*cis*-retinoic acid.

Inhibition of angiogenesis is another appealing avenue of therapy in this very vascular tumor, particularly once there is minimal residual disease. Another modality in the treatment of metastatic neuroblastoma is the use of ¹³¹I-MIBG (Hutchinson et al, 1992). The finding that both the primary tumor and metastatic areas take up this radiotracer suggested the possibility that therapeutic doses can be delivered to the tumor. Preliminary analysis indicates that objective responses do occur in terms of reduction of tumor volume, even in previously heavily treated patients (Howard

et al, 2005; Matthay et al, 2007). Significant myelosuppression is seen with dose escalation, however, and stem cell support is required.

Radiotherapy

Radiotherapy is effective for local control in neuroblastoma, and risk of local relapse can be correlated with the biologic markers. Although irradiation has not provided a benefit in low-stage tumors, it has increased local control in children with advanced stage 4 or bulky stage 3 tumors (Matthay et al, 1989; Castleberry et al, 1991; Evans et al, 1996). A randomized controlled trial to evaluate the efficacy of local control between radiotherapy alone and surgery has not been performed. Doses of external beam irradiation used have ranged from 15 to 30 Gy, depending on the patient's age, location of the tumor, and extent of residual disease.

Intraoperative radiation therapy has been used for patients with unresectable disease. This technique has the advantage of delivering a higher dose of radiation to the operative field while sparing normal adjacent tissues (Leavey et al, 1997). Although its use has been promoted, it has not been convincingly demonstrated to improve control when compared with external beam irradiation (Haas-Kogan et al, 2000).

Spinal Cord Compression

Extension of tumor into the spinal canal produces symptoms of spinal cord compression in up to 5% of patients with neuroblastoma (De Bernardi et al, 2001); up to 13% of patients have radiographic evidence of extension into the spinal canal (Plantaz et al, 1996). These children have been treated by decompressive laminectomy, radiotherapy, or chemotherapy. Neurologic outcome has been similar by all modalities and, regrettably, patients with severe motor deficits typically recover little function (De Bernardi et al, 2001; Katzenstein et al, 2001). Because of the delayed complications of scoliosis after laminectomy, current recommendations are to initiate treatment with chemotherapy and reserve laminectomy for children with progressive neurologic deterioration (Katzenstein et al, 2001). Radiotherapy is now avoided in general, because of its adverse effect on growth of the spine.

KEY POINTS: NEUROBLASTOMA

- Neuroblastoma is the most common extracranial solid neoplasm in children.
- Amplification of the *MYCN* oncogene is found in 20% to 25% of primary tumors and is an adverse prognostic factor. It is present in 40% of patients with advanced-stage disease but in only 5% to 10% of children with low-stage disease. It is associated with rapid tumor progression and poor outcome from treatment and is independent of age or stage of disease.
- Children 1 year old or younger have a better survival rate than older children. This may be attributed to more favorable biologic parameters in tumors diagnosed at this age.
- Children with stage 1 neuroblastoma have a disease-free survival rate of greater than 90% with surgical excision alone.
- Infants younger than 6 months with localized small adrenal masses can be managed with serial observation. Surgical resection can be avoided in 80% of such patients.

WILMS TUMOR

Wilms tumor, or nephroblastoma, is the most common primary malignant renal tumor of childhood. It is an embryonal tumor that develops from remnants of immature kidney. Treatment of patients with nephroblastoma has been extensively investigated in a number of large randomized clinical trials in North America and Europe.

TABLE 155-3 Gene Mutations in Wilms Tumors

GENE	TYPE OF MUTATION	FREQUENCY (%)	SOMATIC OR GERMLINE
11p15	H19 epimutation Paternal uniparental disomy	74	Both
<i>WTX</i>	Deletion or insertion Nonsense	33	Somatic only
<i>WT1</i>	Deletion or insertion Missense and nonsense	21	Both
<i>CTNNB1</i>	In-frame deletions Missense	20	Somatic only
<i>TP53</i>	Missense	4	Both

The focus of current trials is on reducing the morbidity of treatment for low-risk patients and reserving more intensive treatment for high-risk patients for whom survival remains poor. This section outlines current recommendations for treatment and reviews the latest developments in the biology of Wilms tumor.

Epidemiology

Wilms tumor accounts for 6% to 7% of all childhood cancers. It is the most common renal tumor of childhood, accounting for 95% of all kidney cancers in children under the age of 15 in the United States (Ali et al, 2012; Howlader et al, 2013). According to the Surveillance, Epidemiology, and End Results (SEER) registry, the average annual age-adjusted incidence rate of Wilms tumor is 8.0 per million (Breslow et al, 1993; Bernstein et al, 1999). More than 80% of patients are diagnosed before 5 years of age, with a median age of 3.5 years. Nevertheless, older children and occasionally even adults can be affected (Arrigo et al, 1990; Kalapurakal et al, 2004; Ali et al, 2012). The median age at diagnosis is lower in children with bilateral Wilms tumor (Breslow et al, 1993). Wilms tumor manifests at an earlier age among males with both unilateral and bilateral tumors.

In North America, Wilms tumor occurs slightly more frequently in females than in males. With regard to ethnicity, the incidence of Wilms tumor is lower in East Asian populations and higher in black populations compared with the incidence reported for North American and European Caucasians (Breslow et al, 1994; Fukuzawa et al, 2004; Axt et al, 2011). The fact that such variations are more closely associated with race than geography suggests that environmental risk factors likely play a minor etiologic role, certainly in comparison with adult epithelial cancers (Breslow et al, 1993). Black children often have a more advanced stage of disease at presentation, but it is not clear if this is related to tumor biology or reflects delays in diagnosis resulting from impaired access to health care (Axt et al, 2011). Several epidemiologic studies have investigated occupational, environmental, and lifestyle factors as risk factors for Wilms tumor. Although some studies have suggested that a number of parental exposures might be associated with an increased risk of Wilms tumor, very few have been established conclusively (Breslow et al, 1993).

Biology and Genetics

Children with Wilms tumor have been extensively studied to determine the role of genetic alterations in tumor development. We now recognize that the majority of Wilms tumors arise from somatic mutations restricted to tumor tissue and a much smaller percentage originate from germline mutations (Ruteshouser et al, 2008; Scott et al, 2012). It is apparent that several genetic events result in Wilms tumorigenesis and that the Knudson two-hit model of cancer formation does not explain most cases (Knudson and Strong, 1972b). Approximately 10% of children with Wilms tumor have congenital anomalies and syndromes; 5% to 10% of tumors are bilateral and

multicentric, and 1% to 2% are familial. These subsets of patients are the ones in whom the most thorough evaluation for genetic abnormalities have been conducted. A number of genes have been identified as playing a role in the development of Wilms tumor (Table 155-3).

WT1

The first gene mutation described in Wilms tumor was *WT1*, with both somatic and germline mutations noted. The identification and subsequent cloning of *WT1* resulted from cytogenetic observations of gross deletions at chromosome 11p13 in patients with the WAGR syndrome (Wilms tumor, aniridia, genital anomalies, mental retardation). These children were shown to have heterozygous germline deletions at 11p13 (Riccardi et al, 1978). Subsequent molecular analysis of the DNA mapping of this specific region led to the identification of *WT1* in 1990 (Bonetta et al, 1990; Call et al, 1990). *WT1* mutations are often associated with β -catenin (*CTNNB1*) mutations, defining a specific genetic subset of Wilms tumor (Li et al, 2004; Royer-Pokora et al, 2008). This subset has been called the ideal type 1 Wilms tumor (Breslow et al, 2006b). It is characterized by a stromal-predominant favorable histology, intralobar nephrogenic rests (ILNRs), early onset of Wilms tumor, and genitourinary abnormalities in males. Wilms tumors from patients with WAGR and Denys-Drash syndrome (DDS) belong to this subtype of tumors.

Aniridia, found in 1.1% of Wilms tumor patients, is caused by an abnormality of the *PAX6* gene located adjacent to the *WT1* gene. Aniridia patients with visible (microscopic) chromosomal deletions that include *WT1* were noted to be prone to the development of Wilms tumor (Muto et al, 2002). Fluorescence in situ hybridization analysis of aniridia patients has been used to identify submicroscopic deletions of *WT1* and is also a useful predictor of Wilms tumor development (van Heyningen et al, 2007). Wilms tumor will develop in approximately 40% to 70% of aniridia patients with deletions of *WT1*. Conversely, aniridia patients with normal *WT1* do not develop Wilms tumor (Grenskov et al, 2001; van Heyningen et al, 2007).

The *WT1* gene is important for normal kidney and gonadal development. *WT1* encodes a zinc finger transcription regulating mesenchymal to epithelial transition in kidney development (Pritchard-Jones 1990; Dressler, 1995). *WT1* is necessary for ureteric bud outgrowth and is also important in nephrogenesis. Targeted mutation of the *WT1* gene in mice results in failure of kidney and gonadal development (Kreidberg et al, 1997). DDS is the specific association of male pseudohermaphroditism, renal mesangial sclerosis, and nephroblastoma (Drash et al, 1970). The syndrome is caused by point mutations in the zinc finger DNA binding region of *WT1* (Coppes et al, 1993). More than 90% of DDS patients harbor germline point mutations in only one *WT1* allele (Pelletier et al, 1991; Coppes et al, 1992). Therefore the *WT1* mutation acts dominantly with respect to genitourinary abnormalities. The fact that the phenotype resulting from these heterozygous mutations is

far more severe than that resulting from constitutional deletion of one *WT1* allele (i.e., WAGR patients) suggests that the Denys-Drash mutations do not result in inactivation of the *WT1* protein, but rather in the production of a dysfunctional *WT1* protein. It is postulated that this abnormally expressed protein alters regulation of transcription and urogenital development. The majority of these patients progress to end-stage renal disease. Nephropathy usually manifests early in life, and renal biopsy demonstrates mesangial sclerosis. Some *WT1* mutations can lead to an incomplete DDS phenotype, with varying degrees of genitourinary anomalies, renal pathologies, and penetrance of Wilms tumor (McTaggart et al, 2001). Although XY individuals have been reported most often, DDS has been reported in genotypic or phenotypic females. WAGR and DDS patients are more likely to have bilateral tumors and are diagnosed at a younger age (Breslow et al, 2003, 2006b).

This risk for renal insufficiency in DDS is shared by children with WAGR and children with genitourinary abnormalities, all associated with a *WT1* mutation (Diller et al, 1998). **WAGR patients and those with genitourinary abnormalities have an increased risk of renal failure if they survive into puberty** (Breslow et al, 2000, 2005). Genitourinary anomalies (renal fusion anomalies, cryptorchidism, hypospadias) are present in 4.5% of patients with Wilms tumor (Breslow et al, 1993). The incidence of *WT1* mutations in patients with Wilms tumor not associated with any genitourinary abnormality is approximately 2% (Little et al, 2004). Recent studies of nontumoral renal tissue in children with WAGR and DDS have demonstrated smaller glomerular diameters than in controls (Dahan et al, 2007). This suggests a specific defect of *WT1* function during renal development that leads to subsequent deterioration in renal function with age.

WT1 was originally considered to be a classic tumor suppressor gene, and the loss of both copies or mutations of this gene would lead to Wilms tumor development (Rauscher, 1993). Although this may be the case for some tumors, only 20% of patients with Wilms tumor have a mutation in the germline or in tumor tissue (Diller et al 1998; Ruteshouser et al, 2008). It is well established that most constitutional cancer syndrome mutations, including *WT1*, are associated with younger age of onset. However, recent studies have also shown that the median age of onset in children with somatic *WT1* mutations was 14 months. It is postulated that *WT1* mutations are associated with a more rapid progression to Wilms tumor than other molecular abnormalities (Scott et al, 2012).

WTX

Another tumor suppressor gene, *WTX* is targeted by somatic mutations in up to 30% of cases of Wilms tumor, the most common type of pediatric kidney cancer (Rivera et al, 2007). Most tumors have deletions of the entire *WTX* gene, but one third of *WTX*-mutated Wilms tumors carry truncating mutations or missense mutations. The functional importance of the missense alterations is unclear, because the missense alteration can be present in normal tissue from the same patient, whereas the deletion and truncation mutations are always specific to the tumor. The location of *WTX* on the X chromosome is of particular interest because it is inactivated by a monoallelic or "single-hit" event rather than by the classical biallelic inactivation of autosomal tumor suppressor genes. It targets the single X chromosome in males and the active X chromosome in females with tumors and occurs at comparable frequencies in males and females. Initially it was reported that tumors caused by *WTX* mutations lack *WT1* mutations. Subsequently, it has been observed that *WTX* mutations occur with equivalent frequency in tumors with or without mutations in *WT1* and *CTNNB1* (Ruteshouser et al, 2008). *WTX*, like *WT1*, appears to play a role in the Wnt/ β -catenin signaling pathway. Mutations in *WT1*, *WTX*, and *CTNNB1* provide the genetic basis for about one third of Wilms tumors.

11p15

Additional molecular alterations are observed at the chromosome 11p15 locus, which contains a cluster of imprinted genes (Koufos

et al, 1989; Mannens et al, 1990). LOH or loss of imprinting (LOI) on 11p15 occurs in up to 70% of tumors (Scott et al, 2012). A *WT2* locus has been postulated for 11p15, but so far the respective gene has not been identified. **This region is known to harbor genes for the Beckwith-Wiedemann syndrome (BWS) and other syndromes with overgrowth features** (Koufos et al, 1989). These include **hemihypertrophy, which may occur alone or as part of BWS or Perlman, Soto, and Simpson-Golabi-Behmel syndromes** (Perlman et al, 1975; Neri et al, 1998). Most cases of BWS are sporadic, but up to 15% exhibit heritable characteristics with apparent autosomal dominant inheritance. The BWS critical region on 11p15 includes two domains of imprinted genes located in close proximity in band 11p15. Imprinting center region 1 (ICR1) regulates the expression of *IGF2* and *H19*, and center 2 (ICR2) regulates *CDKN1C*, *KCNQ10T1*, and *KCNQ1*. These imprinting centers are differentially methylated on the paternal and maternal allele, leading to expression of only one parent-specific allele (Choufani et al, 2013).

Wilms tumor associated with epigenetic alterations in the 11p15 region has been termed the ideal type 2 Wilms tumor (Breslow et al, 2006b). A type 2 Wilms tumor is characterized by limited nephrogenic differentiation and a mostly blastemal or epithelial-type histology; patients develop tumors at a later age and have a heavier birth weight. **The risk of nephroblastoma in children with BWS and hemihypertrophy is estimated to be 4% to 10%; 21% of children have bilateral disease at presentation** (Beckwith, 1996; DeBaun and Tucker, 1998; Porteus et al, 2000). The mean age at diagnosis of Wilms tumor in BWS and hemihypertrophy patients is similar to that of the general Wilms tumor population (Breslow et al, 1993). Adrenocortical neoplasms and hepatoblastoma also occur with increased frequency in BWS. Children with BWS found to have nephromegaly (kidneys greater than or equal to the 95th percentile of age-adjusted renal length) are at the greatest risk for the development of Wilms tumor (DeBaun et al, 1998). Investigators have been able to correlate genetic changes to identify which BWS patients are at risk for Wilms tumor development (DeBaun et al, 2002; Bliék et al, 2004; Brioude et al, 2013). An increased Wilms tumor risk is observed only in BWS patients with ICR1 gain of methylation and 11p15 uniparental disomy. In contrast, the tumor risk is lower in BWS with ICR2 loss of methylation and *CDKN1C* mutations.

Familial Wilms Tumor

As noted earlier, 1% to 2% of Wilms tumor patients have a family history of Wilms tumor (Breslow et al, 1996; Ruteshouser and Huff, 2004). Familial cases have an earlier age of onset and an increased frequency of bilateral disease. Two familial Wilms tumor genes have been localized (Ruteshouser and Huff, 2004). *FWT1* is located at 17q12-q21 and *FWT2* at 19q13.4 (Rahman et al, 1996; McDonald et al, 1998). Penetrance of these genes appears to be moderate, and these genes do not follow the typical tumor suppressor gene pattern of LOH (Strong, 2003).

Other Chromosomal Abnormalities

Mutations of the tumor suppressor gene *TP53* are frequently encountered genetic events in human cancer (Hollstein et al, 1991). *TP53* mutations are detected in up to 75% of Wilms tumor with anaplastic histology (AHWT) (Bardeesy et al, 1994). It has been suggested that a favorable-histology tumor may progress to an anaplastic tumor by acquiring a disruption of *TP53* function in a group of selected cells (Natrajan et al, 2007). The *TP53* mutations also have been correlated with advanced-stage disease (Malkin et al, 1990; Sredni et al, 2001), but indexing of p53 expression has not been shown to be an independent prognostic factor (Skotnicka-Klonowicz et al, 2001).

Loss of the long arm of chromosome 16 has been found in approximately 20% of Wilms tumors (Maw et al, 1992), suggesting the presence of a gene at 16q involved in the biology of Wilms tumor. Similarly, loss of the short arm of chromosome 1p has been found in approximately 10% of cases (Grundy et al, 1994). LOH at

1p and 16q is associated with an increased risk of tumor relapse and death (Grundy et al, 1994, 2005; Wittman et al, 2007). However, the prognostic significance of these features has been questioned (Bown et al, 2002). Confirming the usefulness of LOH of 16q and 1p to predict outcome was one of the major objectives of the fifth National Wilms Tumor Study (NWTs) (see later discussion). LOH of chromosome 11q is noted in approximately 20% of tumors. LOH of 11q is three to four times more frequent in anaplastic tumors (Wittman et al, 2007). There is a correlation with tumor recurrence and death, but only for tumors that have lost the entire long arm of chromosome 11.

Gain of 1q has also been identified to be another genetic change associated with outcome (Gratias et al, 2013; Segers et al, 2013). Gain of 1q has been noted in up to one fourth of favorable-histology Wilms tumors. It is important to note that 1q gain and LOH at 1p and 16q are not independent events. LOH at 1p and 16q often arises through chromosomal translocations that also result in 1q gain. After stratification for stage of disease, 1q gain was associated with a significantly increased risk of disease recurrence.

COG investigators have evaluated a large cohort of favorable-histology Wilms tumors for global gene expression patterns; *WT1*, *CTTNB1*, and *WTX* mutation; and 11p15 copy number and methylation patterns. They identified five subsets of tumors showing distinct differences in both their clinical and pathologic features. One unique subset was epithelial Wilms tumor in infants that lacked *WT1*, *CTTNB1*, and *WTX* mutations and nephrogenic rests (NRs), and none had recurrence of tumor. COG investigators hope to use this type of information to develop specific treatment strategies for different subsets of patients based on biology (Sredni et al, 2009; Gadd et al, 2012).

Screening

Screening with serial renal sonograms has been recommended in children at high risk for development of Wilms tumor. Review of most studies suggests that 3 to 4 months is the appropriate screening interval. Tumors detected by screening will usually be at a lower stage (Green et al, 1993; Choyke et al, 1999). No studies to date have demonstrated that early detection has improved patient survival. Early detection can provide an opportunity for nephron-sparing surgery, because these children are at an increased risk for bilateral disease. The smaller tumors found on screening studies are more amenable to renal-sparing surgery (Romao et al, 2012) (Fig. 155-6). It is recommended that screening be performed when a

condition has a Wilms tumor incidence of greater than 5% (Table 155-4) (Scott et al, 2006b). Screening of the contralateral kidney after nephrectomy for unilateral Wilms tumor is also recommended (D'Angio et al, 1993). Infants younger than 12 months found to have NRs in the resected kidney are at the greatest risk for metachronous tumors (Coppes et al, 1999). Ultrasound surveillance is performed from time of diagnosis until 5 years of age, with a frequency of every 3 to 4 months. Surveillance of patients who have BWS, Simpson-Golabi-Behmel syndrome, and familial Wilms histories should continue to 7 years (Scott et al, 2006b). CT or MRI should be performed if ultrasonography demonstrates a suspicious lesion. Nonmalignant renal lesions—for example, renal cysts—do occur at an increased rate in children with BWS, and recognition of these is important to avoid unnecessary nephrectomy when new lesions are identified on screening ultrasonography (Borer et al, 1999; Choyke et al, 1999).

An association between Wilms tumor and horseshoe kidney has been noted (Mesrobian et al, 1985). The diagnosis of horseshoe kidney can be missed on preoperative imaging because of the location of the tumor (Neville et al, 2002). Wilms tumor has been reported in patients with multicystic dysplastic kidney, but there is not sufficient evidence that this occurs at an incidence greater than for children with two normal kidneys (Narchi, 2005). There is an increased risk of müllerian duct anomalies in girls with Wilms tumor (Byrne and Nicholson, 2002). Approximately 10% of girls will have abnormalities such as duplication of the cervix or uterus or bicornuate uterus.

Pathology

Pathologists have made important contributions to the study of both the clinical behavior and the biology of Wilms tumor (Beckwith and Palmer, 1978; Weeks and Beckwith, 1987; Zuppan et al, 1991; Schmidt and Beckwith, 1995; Ravenel et al 2001; Vujanic and Sandstedt, 2002, 2010). Wilms tumor is characterized by tremendous histologic diversity, and classification of childhood tumors can be difficult. As noted in the earlier discussion, correlation of the pathologic findings with genetic events is improving our understanding of the development of Wilms tumor.

Favorable-Histology Wilms Tumor

Wilms tumor usually compresses the adjacent normal renal parenchyma, forming a pseudocapsule composed of compressed,

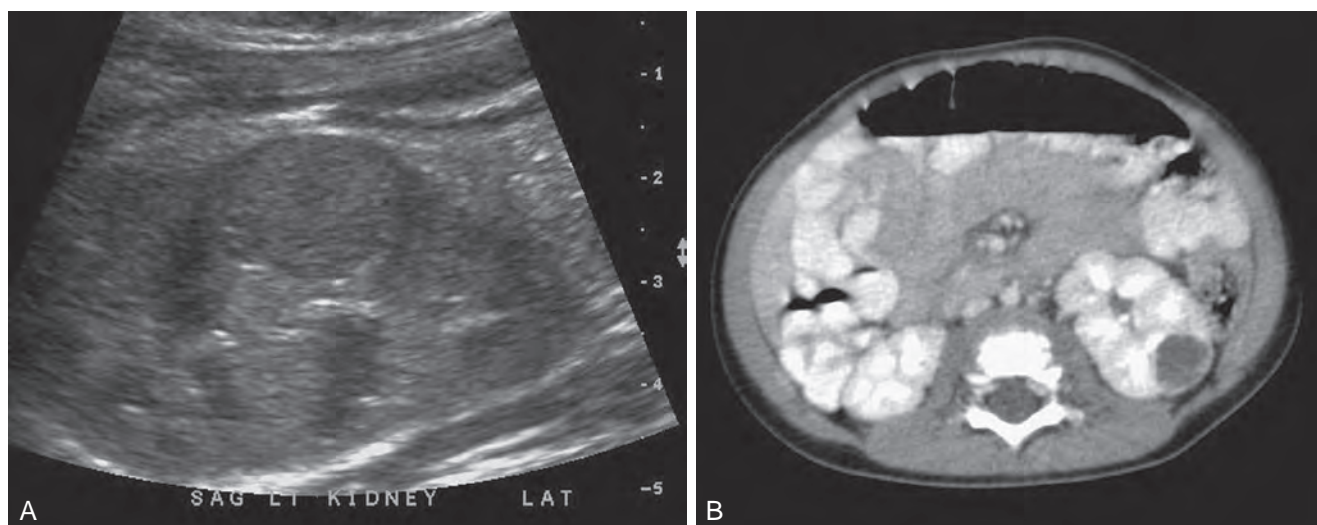


Figure 155-6. Small renal tumor found on serial screening. A, Ultrasound scan shows solid lesion just pushing out from the cortex. B, Computed tomography demonstrates that lesion is amenable to renal-sparing surgery.

TABLE 155-4 Syndromes Associated with Development of Wilms Tumor

SYNDROME	GENES	LOCUS	WILMS TUMOR RISK
WAGR	<i>WT1</i>	11p13	50%
Denys-Drash	<i>WT1</i>	11p13	50%
Frasier	<i>WT1</i>	11p13	5% to 10%
Beckwith-Wiedemann	<i>WT2</i>	IGF2, H19, p57, Klp2	5% to 10%
Familial Wilms tumor	<i>FWT1</i>	17q21	30%
	<i>FWT2</i>	19q13	
Perlman	Unknown		>20%
Mosaic variegated aneuploidy	<i>BUB1B</i>	15q15	>20%
Fanconi anemia D1	<i>BRCA2</i>	13q12.3	>20%
Simpson-Golabi-Behmel	<i>GPC3</i>	Xq26	10% (in males)
Li-Fraumeni	<i>P53</i>	17p13	Low
Neurofibromatosis	<i>NF1</i>	17q11	Low
Sotos	<i>NSD1</i>	5q35	Low
Trisomy 18	Unknown	18	Low
Bloom	<i>BLM</i>	15q26	Low

WAGR, Wilms tumor, aniridia, genital anomalies, mental retardation.

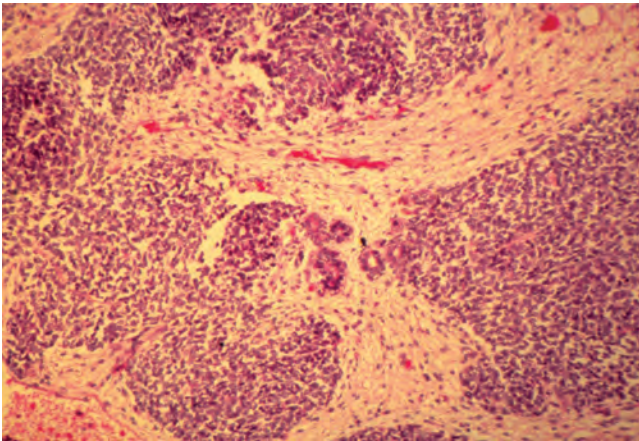


Figure 155-7. Typical Wilms tumor with blastemal, epithelial, and stromal components.

atrophic renal tissues. This intrarenal pseudocapsule can be helpful to distinguish Wilms tumor from NRs and other renal tumors. The texture of the tumors varies depending on the predominant histologic pattern. Many are soft and friable with necrotic or hemorrhagic areas frequently noted. This consistency increases the risk of intraoperative tumor rupture during primary nephrectomy. Most Wilms tumors are unicentric, but 12% are multicentric unilateral tumors (Breslow et al, 1988a). Extrarenal Wilms tumor arising in the retroperitoneum and elsewhere are rare and are thought to arise from displaced metanephric elements or mesonephric remnants. Derived from primitive metanephric blastema, Wilms tumor is characterized by tremendous histologic diversity (Beckwith and Palmer, 1978). In addition to expressing a variety of cell types found in a normal developing kidney, Wilms tumor often contains tissues such as skeletal muscle, cartilage, and squamous epithelium. These heterotopic cell types likely reflect the primitive developmental potential of metanephric blastema that is not expressed in normal nephrogenesis. "Classic" Wilms tumor is characterized by islands of compact undifferentiated blastema and the presence of variable epithelial differentiation in the form of embryonic tubules, rosettes, and glomeruloid structures separated by a significant stromal component (Fig. 155-7). The proportion of each of these

components varies from infrequent to abundant within and among individual tumors. Some Wilms tumors, however, are not triphasic, but demonstrate only biphasic or even monomorphous patterns, and the latter can present diagnostic difficulty (Schmidt and Beckwith, 1995). Wilms tumors with predominantly epithelial differentiation have a low degree of aggressiveness and the majority are stage I tumors (Beckwith et al, 1996; Vujanic and Sandstedt, 2010; Gadd et al, 2012). However, these tumors may be more resistant to therapy if they are at an advanced stage at presentation.

Anaplastic Wilms Tumor

Identification of tumors with unfavorable histologic features such as anaplasia was an important milestone accomplished by the inclusion of central pathologic review of the National Wilms Tumor Study Group (NWTSG) protocols (Beckwith and Palmer, 1978; Bonadio et al, 1985; Zuppan et al, 1988). It has allowed progressive use of adjuvant therapies in sequential studies based on the risk and response of the various pathologic tumor types. Anaplasia is characterized by the presence of three abnormalities: nuclear enlargement to three or more times the diameter of the adjacent cells, hyperchromasia of enlarged nuclei, and abnormal mitotic figures. Anaplasia is rarely seen in tumors of patients younger than 2 years at diagnosis (incidence about 2%), but its presence increases to a relatively stable incidence of about 13% in those older than 5 years (Bonadio et al, 1985; Green et al, 1994). Anaplasia is associated with resistance to chemotherapy. The presence of anaplasia has clearly been demonstrated to carry a poor prognosis even when the tumor is apparently confined to the kidney, stage I (Dome et al, 2006). Anaplasia has been further divided into focal and diffuse patterns to reflect further the different prognosis of anaplasia that is present throughout the kidney or in an extrarenal location (Faria et al, 1996). The later age at diagnosis and the general absence of anaplasia from NRs suggests that anaplasia develops from Wilms tumor cells that acquire additional genetic lesions (Williams et al, 2011).

Pathology after Preoperative Chemotherapy

The International Society of Paediatric Oncology (SIOP) studies have made some important observations on the histology of Wilms tumor after preoperative chemotherapy. Researchers performed an assessment of the tumor response after preoperative chemotherapy in terms of tumor volume and histology. The relative proportions

of histologic subtypes of Wilms tumor differ after preoperative chemotherapy when compared with those reported after primary surgical resection (Weirich et al, 2001). Stromal- and epithelial-predominant tumors are found more often after chemotherapy. These histologic subtypes may demonstrate a poor clinical response to therapy but have an excellent prognosis if the tumor is completely excised (Verschuur et al, 2010). The proportion of blastemal-predominant tumors is decreased after chemotherapy, indicating some response of this tumor type to the preoperative chemotherapy. However, patients with blastemal-predominant tumors after chemotherapy have a high rate of relapse (Reinhard et al, 2004b). Tumor progression during therapy occurred in 5% of patients enrolled in SIOP 93-01 (Ora et al, 2007). These patients were documented to have decreased OS.

SIOP classifies tumors with complete tumor necrosis after preoperative chemotherapy as “low-risk.” Children with stage I low-risk tumors after postchemotherapy nephrectomy receive no further chemotherapy (Boccon-Gibod et al, 2000). Tumors with diffuse anaplasia and blastemal predominance after chemotherapy are classified as “high-risk”; SIOP “intermediate-risk” tumors consist of all other histologies.

Nephrogenic Rests

More than one third of kidneys resected because of Wilms tumor contain precursor lesions known as *nephrogenic rests* (Beckwith et al, 1990; Beckwith, 1993). NRs have a varied natural history, and most do not form Wilms tumor. A rest can undergo maturation, sclerosis, involution, or complete disappearance. NRs have also been detected in 1% of kidneys in infants on postmortem examination—a much higher incidence than that of Wilms tumor. Hence, most apparently undergo involution (Beckwith, 1998).

NRs can be separated into two fundamentally distinct categories: *perilobar nephrogenic rests* (PLNRs) and *intralobar nephrogenic rests* (ILNRs) (Beckwith et al, 1990). These two types of NRs are distinguished by their location within the renal lobe. Relative position within the lobe is a direct reflection of the chronology of the embryologic development of the kidney. PLNRs are found only in the lobar periphery, which is elaborated late in embryogenesis, whereas ILNRs are found anywhere within the lobe, as well as the renal sinus and the wall of the pelvicaliceal system. Therefore, ILNRs are generally believed to be the result of earlier gestational aberrations (Beckwith, 1998). ILNRs are commonly stroma rich and intermingle with the adjacent renal parenchyma. PLNRs are usually subcortical, are sharply demarcated, and contain predominantly blastema and tubules. Of particular interest is the observation that PLNRs are usually found in children with BWS, linked to 11p15, whereas ILNRs are typically seen in children with aniridia, WAGR, and DDS or other features associated with *WT1*. The age at diagnosis is lower for Wilms tumor associated with *WT1* mutations and those tumors arising in association with ILNRs. These tumors have a stromal-predominant histology with varying degrees of rhabdomyogenesis (Fukuzawa et al, 2008).

Multiple rests in one kidney usually implies that NRs are present in the other kidney (Beckwith et al, 1990). Children younger than 12 months diagnosed with Wilms tumor who also have NRs, in particular PLNRs, have a markedly increased risk of developing contralateral disease and require frequent and regular surveillance for several years (Coppes et al, 1999). Surveillance is also recommended for those diagnosed after 12 months of age who have NRs (D'Angio et al, 1993). The occurrence of metachronous Wilms tumor in patients previously treated with conventional chemotherapeutic regimens suggests that NRs are not always eradicated.

NRs display a spectrum of appearances. Hyperplastic NRs can produce a renal mass that can be mistaken for a small Wilms tumor (Beckwith, 1998). Incisional biopsy of a hyperplastic rest is of little value in distinguishing this lesion from a Wilms tumor unless the interface between the rest and the normal kidney is included. Wilms tumor will have a pseudocapsule at the interface with the normal parenchyma, compressing the normal elements. The appearance of the lesion can provide some help in distinguishing between NR and

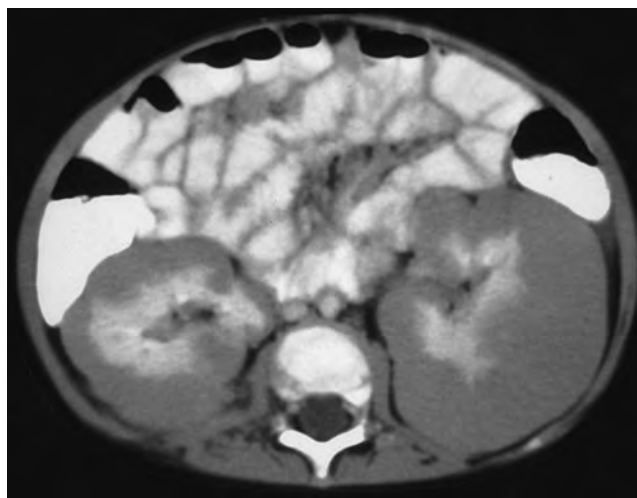


Figure 155-8. Typical appearance of diffuse hyperplastic perilobar nephrogenic rests with thick rind compressing the normal renal tissue centrally.

Wilms tumor. Wilms tumor will have a spheric shape, whereas hyperplastic rests will retain the appearance of the original rest and be more elliptical or lenticular in shape. MRI may be of some value in distinguishing between the two lesions, but this needs to be confirmed prospectively in large numbers of patients (Rohrschneider et al, 1998; Hoffer, 2005).

Nephroblastomatosis refers to the presence of multiple NRs. Diffuse overgrowth of PLNRs may produce a thick rind that enlarges the kidney but preserves its original shape (Fig. 155-8). Patients with nephroblastomatosis are prone to Wilms tumor development and bilateral lesions are common. Perlman and colleagues reviewed 52 cases of diffuse hyperplastic PLNRs reported to the NWTSG pathology center (Perlman et al, 2005). Wilms tumor developed in 23 patients at a median of 30 months. Of children receiving adjuvant therapy at diagnosis, 17 of 33 (52%) developed a Wilms tumor. There was an increased incidence of anaplasia noted in tumors that developed after chemotherapy in patients with nephroblastomatosis (Perlman et al, 2005).

Preoperative Evaluation and Staging

More than 90% of children with Wilms tumor have an asymptomatic abdominal mass discovered incidentally by a family member or physician. The mass may be extremely large relative to the size of the child and is not necessarily confined to one side. Approximately 20% of children with Wilms tumor have hematuria at diagnosis, and 25% will have hypertension at diagnosis. Gross hematuria warrants further evaluation to rule out tumor extension into the collecting system (Ritchey et al, 2008). Other symptoms include fever, anorexia, and weight loss in 10% of patients. Rarely, children may have acute abdominal pain from tumor rupture into the peritoneal cavity or bleeding within the tumor. Physical examination may reveal a firm, nontender mass that classically does not cross the midline.

Compression or invasion of adjacent structures may result in an atypical presentation. A persistent varicocele in the supine position or hepatomegaly may be reflective of inferior vena cava (IVC) obstruction from tumor thrombus. Atrial thrombus may manifest as hypertension or congestive heart failure. Such symptoms are found in less than 10% of patients with intracaval or atrial tumor extension (Ritchey et al, 1988; Shamberger et al, 2001). Occasionally, children with Wilms tumor have symptoms secondary to the production of bioactive substances by the tumor (Coppes, 1993). Hypertension can be caused by elevated plasma renin levels (Maas et al, 2007). This will usually resolve shortly after removal of the tumor. During the physical examination, it is important to assess

for signs of associated Wilms tumor syndromes such as aniridia, hemihypertrophy, and genitourinary anomalies.

Emergent operation is not necessary unless there is evidence of active bleeding or tumor rupture. The preoperative laboratory evaluation of a child with an abdominal mass should include a complete blood count, liver enzymes, and serum electrolytes, including blood urea nitrogen, creatinine, and calcium. Because as many as 8% of newly diagnosed patients with Wilms tumor will have acquired von Willebrand disease, coagulation studies should be considered (Coppes, 1993). This includes prothrombin time and partial thromboplastin time, which may be normal in the presence of von Willebrand disease. This defect can be corrected preoperatively with the administration of 1-desamino-8-D-arginine-vasopressin (DDAVP).

Imaging

A precise histologic diagnosis cannot be obtained on the preoperative imaging studies. All of the solid renal tumors of childhood have some common radiographic features including renal cell carcinoma (RCC) (Miniati et al, 2008; Smets, 2010). In the SIOP-9 study, 5.4% of patients in whom preoperative chemotherapy for Wilms tumor was commenced before diagnostic biopsy were found on nephrectomy to have renal malignancies other than Wilms tumor or benign renal conditions (Tournade et al, 2001). In the United Kingdom Children's Cancer Study Group (UKCCSG), 12% of renal tumors clinically and radiographically consistent with Wilms tumor were found to have some other diagnosis on biopsy (Vujanic et al, 2003). Other clinical parameters can provide some clues to the diagnosis. The development of a renal tumor in a child known to have aniridia, hemihypertrophy, or other syndromes associated with an increased incidence of nephroblastoma is most likely to be a Wilms tumor. Bilateral or multicentric tumors are more typical of Wilms tumor, but renal lymphoma can manifest in this fashion. Congenital mesoblastic nephroma (CMN) is the most likely diagnosis in a neonate with a renal mass. However, favorable-histology Wilms tumor and rhabdoid tumor of the kidney (RTK) can also manifest in the first few months of life (Ritchey et al, 1995; Leclair et al, 2005). The renal origin of the mass is usually apparent on CT, but it can be mistaken for neuroblastoma.

The clinical presentation—that is, as abdominal pain with tumor rupture—can create confusion regarding the preoperative diagnosis. In 2.5% of NWTSS-3 patients, there was an erroneous diagnosis before surgical exploration (Ritchey et al, 1992). Most of these children did not have any preoperative imaging studies performed, and this group of patients had an increased incidence of surgical complications. This emphasizes that defining the exact histology is not as important as establishing that the child has a solid renal tumor, allowing the surgeon to plan for a major cancer operation. Another important role of imaging is to confirm that the contralateral kidney is functioning before performing a nephrectomy.

Ultrasonography is often performed in children with an abdominal mass. This will demonstrate the solid nature of the lesion. Several studies have suggested that Doppler ultrasonography is particularly helpful to exclude intracaval tumor extension that occurs in 4% of Wilms tumor patients (Ritchey et al, 1988; Shamberger et al, 2001). MRI can reliably identify extension of tumor into the IVC (Schenk et al, 2008). A recent report from the COG demonstrated that CT was able to detect all clinically significant IVC tumor extension when compared with ultrasonography (Khanna et al, 2012).

All patients should undergo either CT of the abdomen and pelvis with oral and intravenous contrast or MRI of the abdomen and pelvis with gadolinium. MRI avoids radiation but typically requires anesthesia or sedation in young children. These imaging modalities can further define the extent of the lesion (Fig. 155-9) (Hoffer, 2005; Schenk et al, 2008). This allows improved preoperative planning by evaluating for extrarenal spread of disease, the relationship of the tumor to adjacent visceral structures, and the presence of synchronous tumors in the contralateral kidney. Routine exploration of the contralateral kidney at the time of nephrectomy is not necessary when preoperative imaging with thin slices on multi-

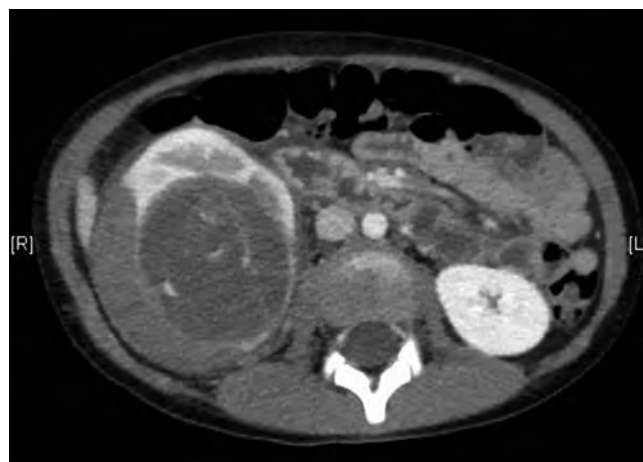


Figure 155-9. Computed tomography scan of a Wilms tumor that demonstrates preoperative rupture with perirenal hemorrhage.

tector helical CT scanners or MRI demonstrates a normal contralateral kidney (Ritchey et al, 2005).

However, the role of imaging studies in staging of the renal tumor continues to be defined. The COG found that CT has moderate specificity but poor sensitivity in the detection of preoperative tumor rupture (Khanna et al, 2013). Ascites beyond the cul-de-sac was most strongly associated with tumor rupture. If the preoperative imaging could accurately detect local extension of tumor beyond the renal capsule or into regional lymph nodes, it would obviate concerns regarding staging in patients treated with preoperative therapy. The local tumor burden (e.g., regional lymph node involvement) determines the intensity of the chemotherapy regimen and whether a child receives abdominal irradiation. Regional adenopathy can be identified on CT or MRI, but enlarged retroperitoneal benign lymph nodes are common in children, and correlation between pathologic findings and lymph node evaluation at surgical exploration in Wilms tumor patients has found significant false-positive and false-negative error rates (Othersen et al, 1990). It should not be expected that CT or MRI would have greater accuracy than visual inspection. Positron emission tomography (PET) has not been shown to have any advantages over conventional imaging modalities in preoperative assessment of Wilms tumor (Misch et al, 2008). Detection of extrarenal tumor extension into the perirenal fat and into adjacent structures is also problematic. Therefore determination of inoperability must be made at surgical exploration.

The lung is the most common site of distant metastasis in children with Wilms tumor. Preoperative chest CT with or without contrast is performed to rule out pulmonary metastases. The clinical significance of lung nodules detected on CT scan alone is controversial (Meisel et al, 1999; Owens et al, 2002; Grundy et al, 2012; Smets et al, 2012). CT will clearly detect more lesions than a standard chest radiograph, but not all of these lesions represent metastases (Ehrlich et al, 2006). Some reports have suggested that treatment of such patients with dactinomycin (AMD) and VCR is sufficient without the need for DOX or pulmonary radiation (Grundy et al, 2012; Smets et al, 2012). Others have found an increased risk of pulmonary relapse if more intensive treatment is not given (Owens et al, 2002).

Imaging surveillance after treatment of the primary tumor is recommended to detect tumor recurrence. COG studies advocate for periodic chest CT and either CT or MRI of the abdomen. However, some have begun to question the value of these studies and whether they will detect relapse early enough to improve survival (McHugh and Roebuck, 2014). Many patients will have clinical symptoms related to relapse before imaging detection. Omitting even the pelvic portion of the abdominal CT can significantly reduce the radiation exposure without compromising detection of relapse (Kaste et al, 2013).

TABLE 155-5 Staging System of the Children's Oncology Group

STAGE	
I	Tumor confined to the kidney and completely resected. The renal capsule is intact and the tumor was not ruptured before removal. No renal sinus extension. There is no residual tumor.
II	Extracapsular penetration, but tumor is completely resected. Renal sinus extension or extrarenal vessels may contain tumor thrombus or be infiltrated by tumor.
III	Residual nonhematogenous tumor confined to the abdomen: lymph node involvement, any tumor spillage, peritoneal implants, tumor beyond surgical margin either grossly or microscopically, or tumor not completely removed.
IV	Hematogenous metastases to lung, liver, bone, brain, and so on.
V	Bilateral renal involvement at diagnosis.

Clear cell sarcoma of the kidney (CCSK) and RCC have a propensity to metastasize to the skeleton (D'Angio et al, 1993; Indolfi et al, 2003). Skeletal surveys and bone scans are both recommended after the histologic diagnosis is confirmed (Feusner et al, 1990). Cranial CT or MRI is performed on all children with CCSK or with RTK, because both are associated with intracranial metastases (Weeks et al, 1989; Indolfi et al, 2003).

Staging

The most important determinants of outcome in children with Wilms tumor are the histopathology and tumor stage. Accurate staging of Wilms tumor allows treatment results to be evaluated and enables universal comparisons of outcomes. The current staging system used by the COG (Table 155-5) is based primarily on the surgical and histopathologic findings. Examination for extension through the capsule, residual disease, vascular involvement, and lymph node involvement are essential to properly assess the extent of the tumor at presentation.

Stage I tumors are limited to the kidney and are completely resected. However, evidence for tumor extension can be subtle. Tumor invasion of blood and lymphatic vessels in the renal sinus is the first sign of spread outside the kidney in stage II tumors (Weeks and Beckwith, 1987). Penetration through the renal capsule is the next most common finding of extrarenal spread. Clear demonstration of tumor cells in the perirenal fat is required to document capsular penetration. Any tumor spill leads to a stage III designation owing to the increased risk for local tumor recurrence (Shamberger et al, 1999; Ehrlich et al, 2013). For NWTS-5, the distribution by stage for patients with favorable-histology tumors was as follows: stage I, 24.9%; stage II, 29.9%; stage III, 30.6%; and stage IV, 14.5%. Patients with anaplastic tumors are more likely to have stage III or IV disease than those with favorable-histology tumors (Dome et al, 2006).

Prognostic Factors

As the treatment regimens for children with Wilms tumor have become more effective, the ability of retrospectively determined prognostic factors to predict outcomes has diminished. Traditional staging factors—for example, tumor size, histology, and lymph node metastases—relied on in the past to predict risk for tumor progression or relapse are now less able to stratify favorable-histology patients for treatment. Clinical cancer trials are now

incorporating biologic factors that predict tumor behavior to stratify patients for treatment.

Chromosomal Abnormalities. As noted earlier, LOH for a portion of chromosome 16q and/or 1p has been noted in 20% of Wilms tumors. This is associated with an increased risk for relapse (Grundy et al, 1994, 2005; Wittman et al, 2007; Messahel et al, 2009). This difference in outcome is independent of histology and stage. NWTS-5 patients with stage I or II favorable-histology tumors with LOH of either 1p or 16q had an increased risk of relapse and death in comparison with patients lacking LOH at either locus (Grundy et al, 2005). The risks of relapse and death for patients with stage III or IV favorable-histology tumors were increased only with LOH for both regions. Patients enrolled in the recently closed COG renal tumor protocols were selected for more intensive treatment if the tumor demonstrated LOH for 1p and 16q.

A number of other markers have been evaluated to predict tumor recurrence. High telomerase (a reverse transcriptase that maintains chromosome ends) activity has been found to be an unfavorable prognostic feature for several types of cancers. A case cohort study involving 291 patients with Wilms tumor confirmed the correlation between telomerase RNA expression and recurrence, and this was independent of tumor stage in multivariate analysis (Dome et al, 2005). A number of immunohistochemical markers have also been studied. It appears that most of the markers that are predictive of tumor progression are found in the blastemal component of the tumor (Routh et al, 2013; Ghanem et al, 2013). These markers will need to be evaluated in larger numbers of patients to determine their usefulness for risk stratification.

Cytokines. The growth of solid tumors is critically dependent on the induction of neovascularity by angiogenic cytokines. Vascular endothelial growth factor (VEGF) is an angiogenic cytokine detected with increased frequency and quantity in experimental and clinical specimens of Wilms tumor (Kayton et al, 1999; Karth et al, 2000). In experimental animals, lung metastases were far more likely to occur in animals with VEGF-positive tumors. Anti-VEGF therapy has been shown to suppress tumor growth in mice and can prevent development of metastases (Rowe et al, 2000; Frischer et al, 2004). Antiangiogenesis treatment would appear to be a promising adjunctive future treatment for patients with Wilms tumor.

Treatment

Surgical Considerations

The initial therapy for most children with Wilms tumor is radical nephrectomy. Nephrectomy should be performed via a transperitoneal approach. The surgeon is responsible for determining the extent of tumor. Accurate staging is essential for the subsequent determination of the need for radiation therapy and the appropriate chemotherapy regimen. Thorough exploration of the abdominal cavity is necessary to exclude local tumor extension, liver and nodal metastases, and peritoneal seeding. Exploration of the contralateral kidney is no longer mandated before nephrectomy if preoperative CT or MRI demonstrates a normal kidney (Ritchey et al, 2005). The renal vein and IVC are palpated to exclude intravascular tumor extension before vessel ligation. Wilms tumor extends into the IVC in approximately 6% of cases and may be clinically asymptomatic in more than 50% (Ritchey et al, 1988; Shamberger et al, 2001). The adrenal gland can be spared without increasing the risk for tumor spill or recurrence if it is not in close proximity to the tumor (Kieran et al, 2013a). Selective sampling of suspicious nodes is an essential component of local tumor staging. Formal retroperitoneal lymph node dissection is not recommended (Othersen et al, 1990; Shamberger et al, 1999). Extensive lymph node dissection, particularly above the renal hilum, can result in chylous ascites (Weiser et al, 2003). In a review of NWTS-4 and NWTS-5 patients, 12.5% of patients did not have lymph node sampling performed (Kieran et al, 2012). The likelihood of having a positive lymph node was greater if more than seven lymph nodes were sampled, but EFS was not improved with removal of more lymph nodes.

The other major responsibility when performing a nephrectomy for Wilms tumor is complete removal of the tumor without contamination of the operative field. Gentle handling of the tumor throughout the procedure is mandatory to avoid tumor spillage. A recent COG study reported intraoperative tumor spillage in 9.7% of patients undergoing primary nephrectomy (Gow et al, 2013). Multivariate analysis demonstrated that spillage was more common with right-sided tumors and larger tumors. Avoiding tumor spillage has a real impact on patient outcomes because these patients have an increase in local abdominal relapse (Shamberger et al, 1999). Shamberger and colleagues identified risk factors for local tumor recurrence as tumor spillage, unfavorable histology, incomplete tumor removal, and absence of any lymph node sampling (Shamberger et al, 1999). This study included both stage II and III disease. The risk of recurrence was highest in patients with stage II disease. More recent COG studies have treated all spill patients as having stage III disease. Review of these patients shows that the greatest risk of recurrence in stage III disease is associated with positive lymph nodes or residual disease (Ehrlich et al, 2013). Tumor spillage was not predictive of recurrence, likely because of the increased therapy currently given to these patients.

There have been several reports of laparoscopic nephrectomy for Wilms tumor. This is usually done in conjunction with preoperative chemotherapy and is likely more feasible after the tumor is reduced in size (Duarte et al, 2009). Experience with open nephrectomy after chemotherapy has shown that these tumors are less prone to tumor spillage (Powis et al, 2013). Although prechemotherapy laparoscopic nephrectomy has been reported, many more procedures will need to be performed to determine if there is an increased risk of tumor spillage, residual disease, or surgical complications (Barber et al, 2009).

Removing a large renal tumor in a small child is associated with some morbidity. NWT-4 patients undergoing primary nephrectomy had an 11% incidence of surgical complications (Ritchey et al, 1999). The most common complications encountered were hemorrhage and small bowel obstruction (Ritchey et al, 1992, 1993a, 1999). Factors that have been associated with an increased risk for surgical complications are higher tumor stage, tumor size greater than 10 cm, incorrect preoperative diagnosis, thoracoabdominal incision, intracaval tumor extension, and resection of other visceral organs.

Preoperative chemotherapy may influence surgical complication rates by producing tumor shrinkage. A recent report from the UKCCSG compared the complication rate for patients undergoing immediate nephrectomy versus delayed nephrectomy performed after 6 weeks of chemotherapy (Powis et al, 2013). They found significantly fewer complications in those undergoing delayed nephrectomy (1% vs. 5.8%). They also noted a much higher rate of tumor rupture or spill in those undergoing immediate nephrectomy (14.6% vs. 0%). This is similar to the rate of intraoperative tumor spill after immediate nephrectomy recently reported by the COG (Gow et al, 2013).

Cooperative Group Trials

Multiple randomized clinical trials have been conducted by the NWTSG, COG, SIOP, and UKCCSG to determine the appropriate role for each of the therapeutic modalities available. Patients are stratified into different treatment groups based on stage and pathology. The goals of these trials are to decrease the intensity of therapy for most patients in an effort to prevent late sequelae of treatment while maintaining excellent OS.

National Wilms Tumor Study Group and Children's Oncology Group. The NWTSG was formed in 1969 to study Wilms tumor. The early NWTSG studies, NWT-1 (1969 to 1973) and NWT-2 (1974 to 1978), showed that the combination of VCR and AMD was more effective than the use of either drug alone. The addition of DOX was found to improve survival for stage III and IV patients, and postoperative flank irradiation was unnecessary for stage I patients (D'Angio et al, 1976, 1981). A major achievement of the early trials was identification of prognostic factors that allowed

stratification of patients into high-risk and low-risk treatment groups. Patients with positive lymph nodes and diffuse tumor spill were found to be at increased risk of abdominal relapse and therefore considered stage III and given postoperative irradiation. One of the most important findings was the identification of the unfavorable histologic features that have a very adverse impact on survival.

NWT-3 (1979 to 1986) demonstrated that stage I and II patients could be treated with 18 weeks of AMD and VCR without irradiation (D'Angio et al, 1989). For stage III favorable-histology disease, 10.8 Gy of abdominal irradiation was shown to be as effective as 20 Gy in preventing abdominal relapse if DOX was added to VCR and AMD. NWT-4 (1987 to 1994) proved that treatment durations of 6 months produced comparable outcomes to 15 months of therapy for patients with stage II to IV favorable-histology tumors (Green et al, 1998). The NWTSG has assessed the impact of postoperative irradiation on flank recurrence and survival (Breslow et al, 2006a; Kalapurakal et al, 2010; Green et al, 2014). The investigators found that abdominal recurrence rates after tumor spillage were significantly higher among patients treated with two- or three-drug chemotherapy without radiation therapy. Irradiation with 10 Gy appeared to be successful in reducing tumor recurrence rates after tumor spillage, and 20 Gy even more so. Although radiation did decrease the incidence of flank recurrence, there was only an increase in OS for stage II patients with tumor spillage. This was attributed to a lower postrecurrence mortality rate in unirradiated patients. The overall risk for relapse is low in stage II favorable-histology disease with spillage, and one must weigh the risks of late effects of intensified treatment versus benefit of decreased relapse (Green et al, 2014).

NWT-5 (1995 to 2003) was a single-arm therapeutic trial. One of the major aims of the trial was to confirm the usefulness of LOH for chromosomes 16q and 1p to predict increased risk of tumor relapse and death (Grundy et al, 2005). Another objective was to evaluate the efficacy of treatment regimens for AHWT. Stage I patients with anaplastic tumors were treated with AMD and VCR, but this resulted in a low 4-year EFS of 69.5% (Dome et al, 2006). A new intensified chemotherapy regimen used for patients with stage II to IV diffuse anaplasia did not result in an improved survival.

In NWT-5, children younger than 2 years with stage I favorable-histology tumors weighing less than 550 g were defined as having very-low-risk Wilms tumor (VLRWT) and did not receive chemotherapy after nephrectomy. This portion of the study was closed early when the number of tumor relapses exceeded the limit allowed by the design of the study (Green et al, 2001a). A recent long-term review of this cohort was completed, comparing the outcomes with those of similar patients treated with postoperative AMD and VCR (Shamberger et al, 2010). The 5-year EFS for surgery alone was 84% compared with 97% for the treated group, but the 5-year OS was equivalent between the two groups at 98% and 99%, respectively ($P = .70$). There is a trade-off between more intensive therapy and the potential long-term sequelae for the 16% of children who relapse versus the avoidance of any postoperative chemotherapy in the majority. As noted earlier, COG investigators hope to use biologic prognostic factors to select patients who do not require adjuvant therapy. All VLRWT patients registered in NWT-5 who did not receive adjuvant chemotherapy were analyzed for LOH at 11p15 and for *WT1* mutation. LOH, as determined by 11p15 methylation analysis, was significantly associated with relapse in VLRWT, as were *WT1* abnormalities (Perlman et al, 2011). If these results are validated in an independent cohort of patients, it would be worthwhile to conduct a clinical trial that uses molecular genetic factors rather than the arbitrarily defined clinical factors of patient age and tumor weight to identify patients with stage I favorable-histology Wilms tumor who do not require adjuvant therapy. It is anticipated that such a trial would expand the number of patients who would be candidates to be treated with surgery only.

Relapse. A uniform approach for the treatment of tumor relapse was used in NWT-5. Patients with relapsed Wilms tumor may be divided into risk groups according to OS rates after salvage therapy (Spreafico et al, 2009). Children with nonanaplastic Wilms tumor

who relapse after therapy with only VCR and/or AMD are considered at standard risk and have survival rates in the 70% to 80% range (Green et al, 2007). Patients with nonanaplastic Wilms tumor who relapse after therapy with three or more agents are defined as having high risk and have survival rates in the 40% to 50% range (Malagolowkin et al, 2008). The very-high-risk group includes recurrent anaplastic or blastemal-type Wilms tumor; these patients have survival rates in the 10% range (Reinhard et al, 2008).

The first generation of COG studies (2006 to 2013) grouped patients by risk for recurrence (very low, low, standard, and high). The COG again examined the role of surgery-only treatment for patients with stage I favorable-histology Wilms tumor in which the tumor and kidney weighed less than 550 g and patient age was below 2 years. Children with stage I or II favorable-histology Wilms tumor and LOH of 1p and 16q were treated with VCR, AMD, and DOX without radiotherapy. Patients with stage III favorable-histology Wilms tumor disease without LOH of 1p and 16q were treated with VCR, AMD, and DOX and irradiation of the flank or abdomen. The COG evaluated a response-based approach for management of children with pulmonary metastases. Those with resolution of the pulmonary lesions on chest CT after 6 weeks of chemotherapy were continued on treatment with VCR, AMD, and DOX. Patients who did not have resolution of the pulmonary lesions by week 6 received more intensive chemotherapy and pulmonary irradiation. Children with stage I to III focal AHWI and stage I diffuse AHWI were treated with AMD, VCR, DOX, and abdominal irradiation. Patients with stage II, III, or IV (no measurable disease) diffuse AHWI, stage IV focal AHWI, stage IV clear cell sarcoma, or stage I to III malignant rhabdoid tumor were treated with a new chemotherapy regimen to try to improve OS. All of the COG studies are closed to patient accrual with the exception of the renal-sparing study (see later).

Wilms tumor occasionally occurs in adults. Earlier reports suggested that the outcome for adults with Wilms tumor was poor and that they require more intensive therapy (Arrigo et al, 1990). More recent reviews of adult patients with favorable-histology Wilms tumor have found improved survival compared with prior reports (Kalapurakal et al, 2004a; Reinhard et al, 2004a; Ali et al, 2012). The recommendation is that adult patients receive stage-appropriate combined-modality therapy.

International Society of Paediatric Oncology. In the randomized clinical trials conducted by SIOP, preoperative therapy is given before surgery. This approach usually results in tumor shrinkage (Fig. 155-10), reducing the risk of intraoperative rupture or spill (Lemerle et al, 1976). A greater number of patients have post-

chemotherapy stage I tumors as a result of disappearance of micro-metastases after neoadjuvant therapy. This was thought to be a significant advantage in terms of decreasing morbidity of treatment, particularly the late effects of radiotherapy.

Early SIOP studies evaluated prenephrectomy radiation therapy (Lemerle et al, 1976). SIOP-5 (1976 to 1980) showed that use of 4 weeks of AMD and VCR was as effective as prenephrectomy radiation therapy in avoiding surgical tumor rupture and increasing the proportion of patients with low-stage disease (Lemerle et al, 1983). SIOP-6 (1980 to 1987) demonstrated that patients with post-chemotherapy stage I disease can safely be treated with 18 weeks of AMD and VCR (Tournade et al, 1993). However, patients with post-chemotherapy stage II tumors and negative lymph nodes were found to have a higher rate of abdominal relapse if postoperative irradiation was omitted (Tournade et al, 1993). An anthracycline was subsequently added for treatment of these children. SIOP-6 confirmed the need for a three-drug chemotherapy regimen after nephrectomy for patients with postchemotherapy stage II lymph node positive and stage III tumors. SIOP-9 (1987 to 1993) demonstrated that the relapse rate for stage II patients with negative lymph nodes without radiation therapy was reduced with epirubicin (Tournade et al, 2001). This study also demonstrated that treatment with VCR and AMD for 4 weeks versus 8 weeks had comparable rates of stage distribution and tumor shrinkage in patients with stage I to III disease. The majority of tumor shrinkage was noted in the first 4 weeks of therapy. Radiotherapy was limited to patients with stage II node-positive and stage III disease, resulting in 18% of patients being irradiated (Graf et al, 2000). There were 59 children with stage I to -IV tumors who had complete tumor necrosis induced by chemotherapy, and 98% of these children had no evidence of disease at 5 years (Boccon-Gibod et al, 2000).

The SIOP 93-01 study (1993 to 2001) evaluated a reduction in postoperative therapy for patients with stage I intermediate risk and anaplastic Wilms tumor (de Kraker et al, 2004; Reinhard et al, 2004b; Graf et al, 2012). Patients were randomized to receive either 4 or 18 weeks of postoperative chemotherapy with AMD and VCR. Two-year EFS was 91.4% after 4 weeks and 88.8% after 18 weeks of therapy, demonstrating that survival can be maintained while shortening the duration of postnephrectomy therapy. Patients with stage II or III disease with low- or intermediate-risk histology received 4 weeks of AMD and VCR before surgery. Postoperative chemotherapy consisted of AMD, VCR, and epirubicin/DOX for 27 weeks. Flank or whole-abdomen irradiation was given for stage III disease. With a median follow-up of 8 years, 5-year EFS was 90% and OS was 95%. Patients with blastemal-type histology had a worse prognosis,

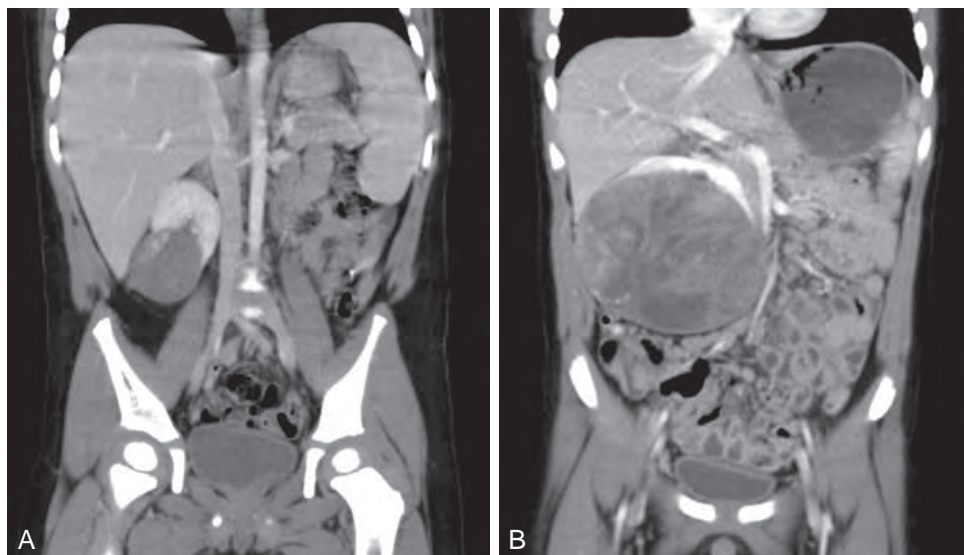


Figure 155-10. A, Computed tomography scan of a Wilms tumor that was pretreated with chemotherapy. B, After 6 weeks of chemotherapy, the tumor is much smaller.

with 62% EFS at 5 years. They comprised only 10% of patients but contributed to one third of the relapses and deaths. The other important prognostic factors were a large tumor volume at surgery and stage III disease.

The SIOP 2001 study asked whether patients with stage II or III intermediate-risk histology Wilms tumors could be safely treated without an anthracycline. Data from SIOP 93-01 had suggested that survival was not adversely affected when nonviable tumor was identified in the renal sinus and/or perirenal fat after preoperative chemotherapy (Vujanic et al, 2009). A total of 583 patients were randomized from 2001 to 2009 (Pritchard-Jones et al, 2011). For stage II or stage III intermediate-risk histology Wilms tumor, there was no significant disadvantage in removing DOX from postoperative chemotherapy. The SIOP group now recommends 6 months only of VCR and AMD rather than a three-drug regimen including DOX. This will significantly reduce the number of children receiving this cardiotoxic drug.

United Kingdom Children's Cancer Study Group. The UKCCSG has conducted several trials using prenephrectomy chemotherapy, but, unlike SIOP, this group performed biopsy before treatment (Pritchard et al, 1995; Mitchell et al, 2000; Pritchard-Jones et al, 2003). This is done to avoid giving chemotherapy to infants and children with benign tumors, which account for 1% of lesions thought to be Wilms tumor on imaging studies (Tournade et al, 2001). The other reason to perform biopsy is to avoid giving inappropriate chemotherapy to non-Wilms tumors, which often require more intensive therapy. The UKW3 trial noted a 12% incidence of non-Wilms tumors in patients with the typical features of Wilms tumor on imaging studies (Vujanic et al, 2003). The UKW1 and UKW2 studies evaluated the single agent VCR for treatment of stage I favorable-histology tumors (Pritchard et al, 1995; Mitchell et al, 2000). The OS of 96% compares well with two-drug chemotherapy, but age greater than 4 years was considered an adverse prognostic factor (Pritchard-Jones et al, 2003).

The UKW3 trial randomly assigned patients to either immediate surgery or to 6 weeks of preoperative chemotherapy and then delayed surgery (Mitchell et al, 2006). EFS and OS at 5 years were similar in the two groups. Around 20% of survivors avoided treatment with DOX or radiotherapy as a result of favorable stage distribution after preoperative therapy. The researchers concluded, like the SIOP group, that all children with nonmetastatic Wilms tumor should receive chemotherapy before tumor resection.

Preoperative Chemotherapy (Children's Oncology Group Recommendations)

On the COG renal tumor protocols, treatment is dependent on surgical and pathologic staging after immediate nephrectomy. There are, however, some situations wherein preoperative chemotherapy is recommended. These include children for whom renal-sparing surgery is planned (Blute et al, 1987), tumors inoperable at surgical exploration (Ritchey et al, 1994), and tumor extension into the IVC above the hepatic veins (Ritchey et al, 1993b; Shamberger et al, 2001; Szavay et al, 2004). The last two conditions are associated with an increased risk for surgical complications if primary nephrectomy is performed (Ritchey et al, 1992).

Inoperable Tumors. The surgeon, not the oncologist or radiotherapist, must make the determination that a tumor is inoperable. This decision should not be based on preoperative imaging studies, which can overestimate local tumor extension. As noted earlier, not all renal masses in children represent Wilms tumor (Vujanic et al, 2003; Reinhard et al, 2004b). If the tumor is found to be unresectable, pretreatment with chemotherapy almost always reduces the bulk of the tumor and renders it resectable (Ritchey et al, 1994; Grundy et al, 2004). Patients who are staged with imaging studies alone and receive preoperative chemotherapy before nephrectomy are also at risk for understaging (Tournade et al, 1993). A patient determined to have an inoperable tumor should be considered to have stage III disease and should be treated accordingly (Ritchey et al, 1994).

Repeat imaging is performed after 6 weeks of chemotherapy. Experience in SIOP has shown that the majority of reduction (48%) in tumor volume occurs in the first 4 weeks of therapy (Tournade et al, 2001) but that reduction extends out through 8 weeks (62%). After there has been adequate shrinkage of the tumor, definitive resection can usually be completed. A clinically good response (by imaging) is usually associated with a pathologically good response in terms of regressive histologic changes (Zuppan et al, 1991; Weirich et al, 2001). The converse is not always true. The distribution of histologic subtypes is different after preoperative chemotherapy compared with primary surgery, with differentiation of the tumor occurring after chemotherapy. Stromal- and epithelial-predominant tumors are found more often after treatment with preoperative chemotherapy. These histologic subtypes may demonstrate a poor clinical response to therapy but have an excellent prognosis if the tumor is completely excised. Patients with progressive disease have a poor prognosis, and these patients will require treatment with a more intensive chemotherapeutic regimen (Ritchey et al, 1994; Ora et al, 2007).

Bilateral Wilms Tumors. Synchronous bilateral Wilms tumors occur in 5% to 7% of children with Wilms tumor (Blute et al, 1987; Coppes et al, 1989; Montgomery et al, 1991). Children with bilateral tumors should not undergo initial radical nephrectomy. These children should receive preoperative chemotherapy with the goal of tumor shrinkage and renal-sparing surgery (Blute et al, 1987; Coppes et al, 1989; Kumar et al, 1998; Hamilton et al, 2011). Preservation of renal tissue is important to decrease the incidence of renal failure, which approaches 15%, at 15 years after treatment in patients with bilateral Wilms tumor (Ritchey et al, 1996; Breslow et al, 2005). The most common cause for renal failure was the need for bilateral nephrectomy for persistent or recurrent tumor in the remaining kidney after initial nephrectomy. Complete nephrectomy can be avoided in the majority of patients if a careful protocol is followed and the surgery is performed by surgeons experienced in renal-sparing techniques (Davidoff et al, 2008; Fuchs et al, 2011).

The current COG protocol for patients with bilateral Wilms tumor recommends 6 weeks of chemotherapy before surgery. Biopsy is not needed if the radiographic picture is consistent with Wilms tumor. Tumor response is assessed after 6 weeks with CT or MRI to determine the reduction in tumor volume and feasibility of partial resection. Patients with tumors amenable to renal-sparing procedures can proceed with surgery. Imaging cannot, however, predict the histology of the tumor based on changes in volume of the tumor after chemotherapy (Weirich et al, 2001; Olsen et al, 2004). Tumors not responding to therapy require bilateral open biopsy to determine histology. Open biopsies are recommended because they are more accurate than percutaneous needle biopsies when assessing for anaplasia, and bilateral biopsies are recommended because anaplasia is found to be discordant between the two kidneys in 83% of children (Hamilton et al, 2006). Failure to achieve a reduction in volume is likely a result of tumor differentiation (Fig. 155-11) (Weirich et al, 2001; Anderson et al, 2002; Shamberger et al, 2006). Differentiated tumors may show a poor clinical response to therapy, but they have an excellent prognosis if the tumor is completely excised. If renal-sparing surgery is not feasible, additional chemotherapy is then given based on the biopsy findings, but all patients should proceed to surgical resection within 12 weeks of starting therapy. Continuing treatment beyond 12 weeks will not likely provide any additional reduction in tumor burden.

At the time of second-look surgery, partial nephrectomy or wedge excision of the tumor is preferred with an attempt to achieve negative margins. The kidney with the lower tumor burden is addressed first. Tumor enucleation may be considered in lieu of a formal partial nephrectomy. This is often needed for large centrally located tumors when removal of a margin of renal tissue would compromise the vascular supply to the kidney (Cozzi et al, 1996; Horwitz et al, 1996). The concern is that enucleation will be more likely to result in positive surgical margins. For favorable-histology tumors, adjuvant therapy may still achieve a good outcome (Cozzi et al, 1996; Horwitz et al, 1996; Davidoff et al, 2008). However, if

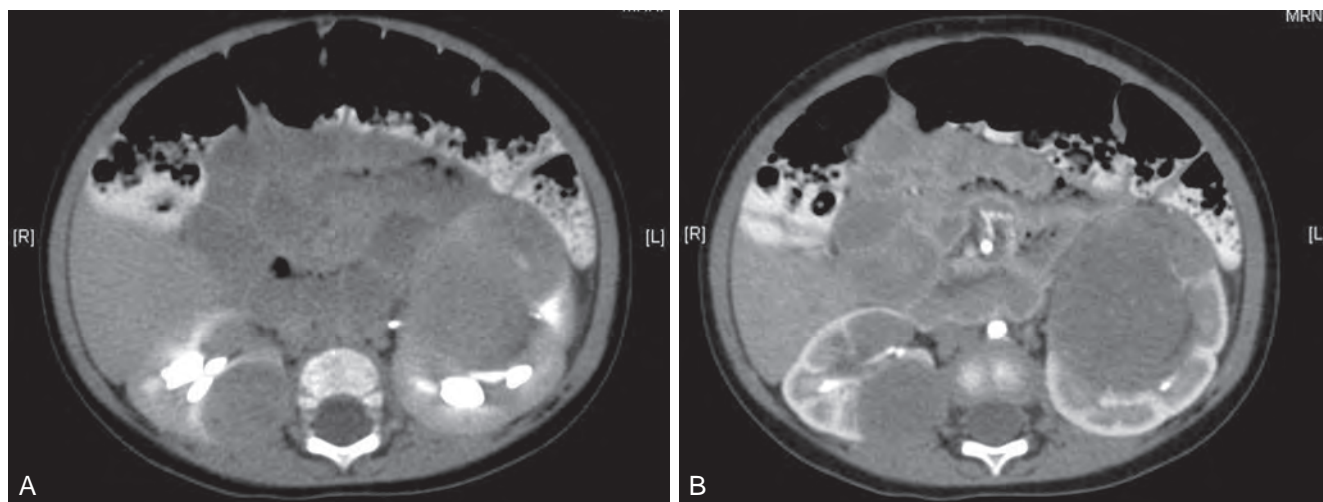


Figure 155-11. Patient with bilateral tumors who was treated with chemotherapy. **A**, Computed tomography (CT) before treatment. **B**, CT after 12 weeks of chemotherapy, revealing only minimal decrease in the size of the tumors. Bilateral partial nephrectomies were performed, revealing mature tumor elements with rhabdomyoblastic differentiation.



Figure 155-12. Postoperative image from patient shown in [Figure 155-11](#) demonstrates that the kidneys have near-normal volume after resection of the bilateral tumors.

there is anaplasia in the resected specimen, a positive margin will adversely affect survival and requires additional resection. Even when large bilateral masses remain after initial chemotherapy, a high percentage of children can be successfully managed with renal-sparing surgery ([Davidoff et al, 2008](#)). It is easy to underestimate the amount of renal parenchyma that can be salvaged as a result of compression by the tumor; therefore nephron-sparing surgery should be considered in all patients ([Fig. 155-12](#)). One concern regarding enucleation of large centrally located tumors is the potential for positive surgical margins. Kieran and colleagues reported a 23% incidence of positive surgical margins in a cohort of 21 patients with bilateral Wilms tumor undergoing renal-sparing surgery ([Kieran et al, 2013b](#)). They did not demonstrate an increased risk of local recurrence, but this was a small number of patients, with all receiving 10.5-Gy flank radiation.

Radical nephrectomy may be needed in a kidney with extensive tumor involvement. Bilateral nephrectomies and dialysis are rarely required when the tumors fail to respond to chemotherapy and radiation therapy. This is the most common cause of renal failure in patients with bilateral Wilms tumor ([Ritchey et al, 1996](#)). Fortunately, anephric patients can still be administered chemotherapy with some modifications ([Feusner et al, 2008](#)). The recommended interval between successful completion of treatment of the Wilms

tumor and renal transplantation varies ([Penn, 1979](#); [Kist-van Holthe et al, 2005](#)). Some advocate a waiting period of 2 years to ensure that the patient does not develop metastatic disease; others have found that a 1-year interval is sufficient ([Gregoriev et al, 2012](#)). Patients who develop renal failure after renal-sparing surgery should have removal of the remaining renal tissue before transplant to prevent tumor recurrence after starting immunosuppression ([Kubiak et al, 2004](#)).

All patients treated for bilateral Wilms tumor require close long-term follow-up. SIOP investigators noted that late relapses have occurred in patients with bilateral Wilms tumor more than 4 years after treatment and recommended long-term follow-up ([Coppes et al, 1989](#)). These patients should also have frequent assessment of renal function, urine protein, and blood pressure.

Partial Nephrectomy for Unilateral Tumors. Several centers have explored the role of parenchymal-sparing procedures in children with unilateral Wilms tumors ([McLorie et al, 1991](#); [Cozzi et al, 1996](#); [Moorman-Voestermans et al, 1998](#); [Haecker et al, 2003](#); [Linni et al, 2003](#); [Zani et al, 2005](#)). The primary motivation for this approach is concern about late occurrence of renal dysfunction after unilateral nephrectomy. However, the incidence of renal failure after nephrectomy for most children with unilateral Wilms tumor is low, 0.6% at 20 years after treatment ([Breslow et al, 2005](#); [Lange et al, 2011](#)). The risk of renal failure is higher for patients with genitourinary anomalies, DDS, and WAGR. As noted earlier, this is a result of mutation of *WT1*, which is necessary for normal renal development. Syndromic patients are more likely to have smaller tumors identified on screening studies that are more amenable to renal-sparing surgery ([Romao et al, 2012](#)).

Most Wilms tumors are too large at diagnosis to allow partial nephrectomy. After preoperative chemotherapy, partial nephrectomy can be performed in 10% to 15% of patients. Only the occasional child with Wilms tumor will have a lesion small enough to allow partial nephrectomy at diagnosis—for example, tumors detected on screening studies for Beckwith-Wiedemann syndrome and aniridia (see [Fig. 155-6](#)). As noted earlier, there are concerns regarding staging after chemotherapy, requiring some patients to receive added therapy to prevent local recurrence. Another concern is the increased risk for local recurrence after partial nephrectomy ([Horwitz et al, 1996](#); [Haecker et al, 2003](#)). Patients who develop intra-abdominal relapse have a markedly decreased survival ([Shamberger et al, 1999](#)).

The COG is conducting a renal-sparing protocol for select patients with unilateral Wilms tumors known to be at risk for bilateral disease or at increased risk for renal failure. These patients

are managed with a strict surgical protocol to minimize risk for residual disease (Cozzi et al, 2004). The lesion should be completely excised with a margin of normal renal parenchyma. These patients should not undergo partial nephrectomy if the tumor cannot be removed at stage I. Patients with high-risk histologic patterns such as anaplasia or persistent blastemal-predominant tumor after chemotherapy should be treated with complete nephrectomy because these tumors have resistance to chemotherapy (Reinhard et al, 2008).

Late Effects of Treatment

Numerous organ systems are subject to the late sequelae of anticancer therapy. Clinicians must be aware of the spectrum of problems that face children as they grow into adulthood. Our understanding of late effects in Wilms tumor survivors has been advanced through two large studies. The Childhood Cancer Survivor Study (CCSS) is a retrospectively ascertained cohort of 20,346 childhood cancer survivors diagnosed from 1970 to 1986. The CCSS reported a cumulative incidence of 65% for all chronic health conditions in Wilms tumor survivors at 25 years after completion of therapy (Termuhlen et al, 2011). The cumulative incidence of severe (grades 3 or 4) chronic health conditions was 24% (Termuhlen et al, 2011). The NWTSG Late Effects Study followed patients treated in NWTSG-1 to NWTSG-5. Despite the greatly improved therapy for Wilms tumor over time, the NWTSG Late Effects Study showed that survivors remain at elevated risk for death compared with the general population for many years after their original diagnosis (Cotton et al, 2009).

Fertility and Pregnancy

Gonadal radiation can produce hypogonadism and temporary azoospermia in boys (Kinsella et al, 1989). The severity of damage is radiation dose dependent. The Leydig cells are more radioresistant than the germ cells, but higher doses can produce damage resulting in inadequate production of testosterone. This can result in delayed sexual maturation. Chemotherapeutic agents can also adversely affect testicular function (Mustieles et al, 1995). Pelvic irradiation and exposure to alkylating agents are risk factors for ovarian failure and premature menopause in female Wilms tumor survivors (Green et al, 2009). Very few pregnancies have been reported in patients who received whole abdominal radiation therapy (Green et al, 2010). Pregnancy complications were evaluated extensively through the NWTSG. The offspring of irradiated female patients are at risk for low birth weights and premature birth. Radiation portals that include the pelvis and doses exceeding 20 Gy increase the risk of miscarriage (Kalapurakal et al, 2004b).

Second Malignancies

An increased incidence of second malignant neoplasms has been noted in children treated for Wilms tumor. There is a 1% cumulative incidence at 10 years post-diagnosis, and a rising incidence thereafter (Breslow et al, 1988b; Taylor et al, 2008; Breslow et al, 2010). One of the greatest risk factors is prior irradiation, and most tumors occur in the radiation field (Breslow et al, 1988b; Bassal et al, 2006; Taylor et al, 2008). The incidence of leukemia is highest during the first 5 years after Wilms tumor treatment. The incidence of solid tumors increases fivefold from age 15 years to age 40 years.

Cardiac Effects

The risk of cardiotoxicity in Wilms tumor survivors has been carefully studied. In a review of patients entered in NWTSG-1, NWTSG-2, NWTSG-3, and NWTSG-4, the frequency of congestive heart failure was 4.4% among DOX-treated patients who received this drug as part of their initial chemotherapy regimen (Green et al, 2001b). The risk was increased if the patient received whole-lung or left-flank irradiation. Of note, only one patient with congestive heart failure received a DOX cumulative dose below 150 mg/m², which is used in contemporary North American treatment regimens. However, subclini-

cal cardiotoxicity was not assessed, and it is possible that clinical effects with modern regimens will become apparent with longer follow-up.

OTHER RENAL TUMORS

Clear Cell Sarcoma of the Kidney

CCSK accounts for 3% of renal tumors reported to the NWTSG. The tumor derives its name from the clear cytoplasm of the predominant cell type (Schmidt and Beckwith, 1995). **Important predictors of improved survival are lower stage, younger age at diagnosis, treatment with DOX, and absence of tumor necrosis (Argani et al, 2000).** The addition of DOX improved both OS and relapse-free survival (D'Angio et al, 1989; Argani et al, 2000; Seibel et al, 2004). Patients with stage I tumors (using the current criteria of absence of renal sinus invasion) had a 98% survival rate. Unlike anaplastic Wilms tumor, even stage I CCSK lesions are associated with increased rates of relapse and require postoperative irradiation. Long-term follow-up of CCSK patients is needed because 30% of relapses occurred more than 3 years after diagnosis and some as late as 10 years. Unlike Wilms tumor, **CCSK is associated with bone and brain metastases.** Bilateral involvement has thus far not been reported, nor has the presence of Wilms tumor-associated congenital anomalies such as aniridia or hemihypertrophy. Patients with CCSK were treated in NWTSG-5 with a regimen combining VCR, DOX, cyclophosphamide, and etoposide in an attempt to further improve the survival of this high-risk group. However, outcomes for patients with CCSK treated in NWTSG-5 were similar to those seen in NWTSG-4 (5-year relapse-free survival and OS of 79% and 89%, respectively) (Seibel et al, 2006). Stage was found to be highly predictive of outcome; 5-year relapse-free survival rates for stages I, II, III, and IV in NWTSG-5 were 100%, 87%, 74%, and 36%, respectively. Similar outcomes have been reported by SIOP investigators (Furtwangler et al, 2013).

Rhabdoid Tumor of the Kidney

RTK is the most aggressive and lethal childhood renal tumor and accounts for 2% of renal tumors. RTK and CCSK both occur in renal and extrarenal locations, suggesting an origin from a non-organ-specific mesenchymal cell. These tumors are characterized by loss of function of the *SMARCB1/INI1/SNF5/BAF47* gene in chromosome band 22q11.2 (Biegel et al, 1999). Consistent with its role as a tumor suppressor gene, tumors arise after inactivation of both alleles of *SMARCB1*. Germline alterations of the *SMARCB1* gene are found in one third of the patients (Eaton et al, 2011). Germline mutations of *INI1* have been identified in renal rhabdoid tumors. Staining for the products of the *INI1* gene can be useful because RTK is consistently negative (Hoot et al, 2004).

Typical clinical features include early age of diagnosis (median age below 16 months), advanced stage, resistance to chemotherapy, and high mortality (Amar et al, 2001; Tomlinson et al, 2005). Younger age at diagnosis is an adverse prognostic factor. RTK is distinguished by its propensity to metastasize to the brain (D'Angio et al, 1993).

Congenital Mesoblastic Nephroma

CMN is the most common renal tumor in infants, with a mean age at diagnosis of 3.5 months (Howell et al, 1982; van den Heuvel-Eibrink et al, 2008). This is the most common renal tumor diagnosed on antenatal ultrasonography (Leclair et al, 2005). CMN is a very firm tumor on gross examination, and the cut surface has the yellowish gray trabeculated appearance of a leiomyoma. There are three histologic subtypes: classic, cellular, and mixed (showing areas of both classic and cellular). The classic subtype, characterized by interlacing sheets of bland spindle cells, resembles infantile fibromatosis. The cellular variant, with a solid sheetlike growth pattern and frequent mitoses, is virtually identical histologically to congenital fibrosarcoma (Beckwith, 1986; Joshi et al, 1986; Gormley

et al, 1989). Both tumors have a similar translocation that fuses the *ETV6 (TEL)* gene from 12p13 with the 15q25 neurotrophin-3 receptor gene, *NTRK3* (Argani et al 1998). In CMN, tumor induction is postulated to occur at a time when the multipotent blastema is predominately stromagenic (Snyder et al, 1981; Tomlinson et al, 1992). *WT1* is not expressed in CMN (Tomlinson et al, 1992).

The most important aspect of CMN is the usually excellent outcome with radical surgery only (Howell et al, 1982). The tumor can extend into the hilar or perirenal soft tissue; therefore complete surgical resection is important (Beckwith, 1986). Local recurrence and metastasis can occur, particularly with the cellular variant of CMN (Joshi et al, 1986; Gormley et al, 1989; Fitchey et al, 2003). The risk of recurrence is thought to be less in children younger than 3 months at diagnosis, but metastases have been reported in a few infants (Heidelberger et al, 1993). Neither chemotherapy nor radiation therapy is routinely recommended (Howell et al, 1982), but consideration for adjuvant treatment should be given to patients with cellular variants that are incompletely resected (Gormley et al, 1989). There are reports demonstrating response of both inoperable and recurrent tumors to chemotherapy (Loeb et al, 2002; McCahon et al, 2003).

Solitary Multilocular Cyst and Cystic Partially Differentiated Nephroblastoma

Solitary multilocular cyst, or multilocular cystic nephroma, is an uncommon, benign renal tumor. Fifty percent of multilocular cysts are found in young children, usually boys. The second peak incidence occurs in young adult women (Eble and Bonsib, 1998; Luthile et al, 2007). Although the majority of cases of multilocular cystic renal disease have been unilateral, there are rare reports of bilateral cases (Ferrer and McKenna, 1994). The gross appearance of the tumor is its most distinguishing feature. The cut surfaces reveal a well encapsulated multilocular tumor composed of varying sized cysts compressing the surrounding renal parenchyma. This tumor is distinguished by the finding of only mature cell types within the septa of the cyst wall. Multilocular cystic nephroma is cured by nephrectomy, but recurrence has occurred following incomplete excision by partial nephrectomy. If partial nephrectomy is considered, frozen section is indicated to exclude cystic, partially differentiated nephroblastoma or clear cell sarcoma, which can occasionally have a similar appearance.

Another entity reported in the literature with similar features is cystic partially differentiated nephroblastoma (CPDN). The majority of these lesions occur in the first 2 years of life (Joshi and Beckwith, 1989; Blakely et al, 2003; Luthile et al, 2007). Eble and Bonsib recommend that multilocular cystic nephroma and CPDN be considered the same entity (Eble and Bonsib, 1998). They are indistinguishable radiographically. Histologic examination reveals that blastemal cells or NRs may be found in the septa of both tumors. Surgery is curative in almost all patients, with recurrence the result of incomplete resection (Eble and Bonsib, 1998; Blakely et al, 2003). In a review of 21 children with CPDN reported to the NWTSG, there was 100% survival. Eight were treated with surgery alone (Blakely et al, 2003). Thirteen patients received postoperative chemotherapy, including 2 patients with stage II disease.

Metanephric Adenofibroma

Another tumor with prominent stromal features that can resemble CMN is metanephric adenofibroma (Arroyo et al, 2000). The epithelial component of these tumors can range from inactive metanephric adenoma to Wilms tumor. Other lesions contain areas morphologically identical to papillary RCC. This uncommon entity may be derived from ILNR (Arroyo et al, 2000). Metanephric adenofibromas with a composite Wilms tumor component occur at a young age (mean of 12 months), similar to other ILNR-related Wilms tumors that develop in patients with DDS and aniridia. None of these tumors have recurred after nephrectomy, but all have been treated with Wilms tumor chemotherapy.

Renal Cell Carcinoma

RCC is the most common renal malignancy in the second decade of life. Only 5% of RCCs occur in children (Hartman et al, 1982; Broecker, 1991). An abdominal mass is the most common presentation, but hematuria is more common than in Wilms tumor (Broecker, 1991). Imaging studies cannot differentiate RCC from other solid renal tumors. There is a higher incidence of papillary RCC in children (Renshaw et al, 1999; Selle et al, 2006). These tumors, typically seen in adolescence or young adults, are genetically unique in that they have chromosome translocations involving a common breakpoint in the *TFE* gene located at Xp11.2 (Bruder et al, 2004). These tumors differ from adult RCC in that immunoreactivity for epithelial markers is reduced or absent.

Another type of RCC more often seen in children is renal medullary carcinoma, found in patients with sickle cell hemoglobinopathy (Swartz et al, 2002). The median age at presentation is 13 years, but the tumor can be found in much younger children. It is a highly lethal tumor.

Complete tumor resection is the most important determinant of outcome in RCC. Raney and colleagues found that all children with stage I lesions survived, and others have reported 64% to 80% survival for patients with stage I and II tumors (Dehner et al, 1970; Castellanos et al, 1974; Raney et al, 1983; Aronson et al, 1996). Partial nephrectomy has been used in pediatric patients with RCC, but outcome data are limited (Cook et al, 2006). Younger age at diagnosis is a favorable prognostic factor (Raney et al, 1983). Regional lymph node involvement does not portend the same poor prognosis as adult RCC (Geller and Dome, 2004). Geller and colleagues reported that patients with TFE+ translocation and positive nodes were found to have 93% survival at a median follow-up of 4.3 years (Geller et al, 2008). However, others have noted higher rates of relapse (Perlman, 2010). Like RCC in adults, these tumors are typically not responsive to chemotherapy or radiation therapy, although case reports of successful adjuvant treatment have been published (Chowdhury et al, 2013).

Angiomyolipoma

Renal angiomyolipoma is a hamartomatous lesion that is only rarely seen in childhood. There is a clear association with the tuberous sclerosis complex (TSC), and presentation is more often bilateral in these patients (Blute et al, 1988; Ewalt et al, 1998). The renal lesions of the TSC include angiomyolipoma, simple cysts, polycystic kidney disease, and RCC. Angiomyolipoma develops in up to 80% of patients with TSC (Ewalt et al, 1998). Renal cysts occur in up to 30% of patients with TSC. Mutations of one of two genes on chromosome 9 (*TSC1*) and chromosome 16 (*TSC2*) are found in 85% of TSC patients (Crino et al, 2006). It has been postulated that these genes act as tumor suppressor genes and that the LOH of *TSC1* or *TSC2* may explain the progressive growth pattern of renal lesions seen in these patients (Henske, 2004).

The incidence of angiomyolipoma increases with age. Ewalt and colleagues reported on 60 patients with TSC who were followed with periodic ultrasonography. The average age at which a normal ultrasound scan became abnormal was 7.2 years (Ewalt et al, 1998). Angiomyolipomas were found in 45 children. Growth of the lesion was observed in 28 children. Girls were more likely to have an increase in the size of the lesion. All patients with lesions greater than 4 cm in diameter were postpubertal. Annual ultrasound examinations are recommended after puberty. Children with growing lesions (Fig. 155-13) can be managed with embolization or partial nephrectomy before they become symptomatic with bleeding (Lee et al, 1998; Williams et al, 2006). The risk of serious bleeding appears to correlate with a diameter greater than 4 cm (Blute et al, 1988; Dickinson et al, 1998; Steiner et al, 1993). Some lesions are fat poor, and differentiation from other renal tumors—for example, RCC—on imaging studies can be difficult (Hindman et al, 2012). In some cases, biopsy of the lesion may be needed to confirm diagnosis of angiomyolipoma before proceeding with treatment. Nephron-sparing approaches are recommended in children

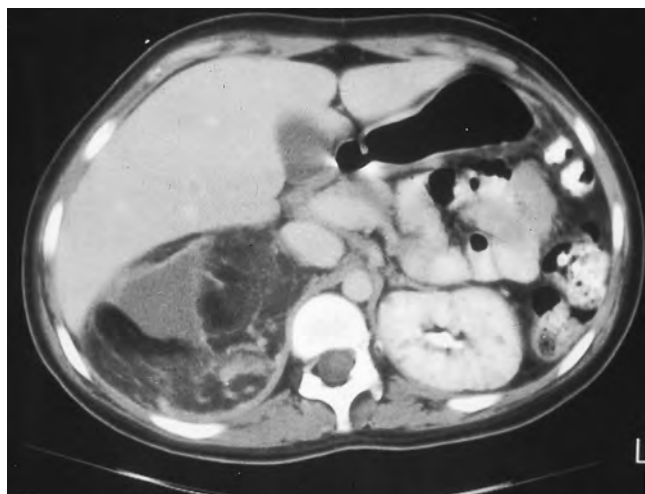


Figure 155-13. Angiomyolipoma of the right kidney in a patient with tuberous sclerosis.

with the TSC because of the presence of multiple, bilateral lesions and the risk of development of new lesions.

Mechanistic target of rapamycin (mTOR) inhibitors have shown promise as a new type of therapy for reducing the size of TSC-associated angiomyolipomas and represent the first systemic therapeutic approach to treat the underlying cause of TSC (i.e., targeting unregulated mTOR activation). *TSC1* or *TSC2* mutations in patients with TSC give rise to hyperactivation of the mTOR pathway. A randomized placebo-controlled trial reported that 42% of patients had at least a 50% reduction in total volume of angiomyolipoma after treatment with everolimus compared with 0% of placebo (Bissler et al, 2013). The patients were all age 18 years or older.

KEY POINTS: RENAL TUMORS

- Deletions of *WT1*, located on chromosome 11p, are found in patients with aniridia and Wilms' tumor. Mutations of *WT1* occur in DDS.
- All patients with Wilms tumor should undergo either CT or MRI of the abdomen. Routine exploration of the contralateral kidney at the time of nephrectomy is not necessary when preoperative imaging demonstrates a normal contralateral kidney.
- Screening with serial renal ultrasound examinations has been recommended in children at high risk for development of Wilms tumor. Review of most studies suggests that 3 to 4 months is the appropriate screening interval. It is recommended that screening be performed when a condition has a Wilms tumor incidence of greater than 5%.
- Local recurrence is increased in Wilms tumor patients with local tumor spillage, and this is now classified as stage III disease. The 2-year survival rate after local recurrence is 43%.
- Patients with bilateral Wilms tumor should be treated with preoperative chemotherapy. This will allow more patients to undergo renal-sparing surgery in an attempt to decrease the risk of renal failure.
- Congenital mesoblastic nephroma is the most common renal tumor in infants.
- There is a higher incidence of papillary RCC in adolescents. These tumors are genetically unique in that they have chromosome translocations involving a common breakpoint in the *TTF* gene located at Xp11.2.
- Angiomyolipoma develops in up to 80% of patients with TSC. mTOR inhibitors have shown promise as a new type of therapy for reducing the size of TSC-associated angiomyolipomas.

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The complete reference list is available online at www.expertconsult.com.

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Epidemiology and Syndromic Associations

Pathology and Molecular Biology

Presentation, Initial Evaluation, Management, and Staging

Treatment and Outcomes

Late Effects

Other Bladder Tumors

Female Genital Tract

Testicular Tumors

Paratesticular Rhabdomyosarcoma

Treatment strategies for patients with bladder/prostate rhabdomyosarcoma (RMS) have changed dramatically since the first Intergroup Rhabdomyosarcoma Study (IRS I; 1972-1978). Primary anterior exenteration ([Horn and Enterline, 1958](#); [Ferrer et al, 2006](#)) has been replaced by organ preservation strategies. In IRS IV (1993-1997), the bladder preservation rate among 88 analyzed patients was approximately 62%, which was significantly improved from IRS I (23%) ([Arndt et al, 2004](#)). However, a detailed evaluation of preserved bladder function is lacking, leaving the efficacy of this approach uncertain. The relative roles of surgery versus radiotherapy in local control also remain a subject of considerable debate. Simultaneously, continued advances in the molecular/genomic characterization of RMS promise improved risk stratification and new insights into molecular mechanistic drivers.

EPIDEMIOLOGY AND SYNDROMIC ASSOCIATIONS

Approximately 350 cases of RMS are diagnosed annually in the United States; of these, 15% to 20% arise from the genitourinary system ([Maurer et al, 1988](#); [Crist et al, 2001](#)). RMS is the most common soft-tissue sarcoma in children and is the third most common pediatric solid tumor, representing 5% to 15% of all childhood solid tumors. Bladder/prostate RMS demonstrates a bimodal age distribution with incidence peaking from ages 0 to 2 and again in adolescence. Boys are preferentially affected. The cause is unclear. Reports have suggested a higher risk of RMS in children with poor prenatal care or children conceived with assisted reproductive techniques, but overall, genetic factors are considered more important in pathogenesis than environmental factors ([Shrestha et al, 2013](#); [Williams et al, 2013](#)).

Most cases of RMS are considered to be sporadic; however, a genetic basis is inferred from the association of RMS with certain syndromic conditions. These include Li-Fraumeni syndrome, neurofibromatosis, basal cell nevus syndrome, Costello syndrome, Noonan syndrome, and multiple endocrine neoplasia type 2A.

Li-Fraumeni syndrome results from germline mutations of the p53 tumor suppressor gene. Patients are predisposed to sarcomas, breast cancer, brain tumors, adrenal carcinoma, and leukemia. The overall cancer risk in affected individuals may be 50% by age 30. Soft tissue sarcomas, typically seen by age 10, account for 15% to 20% of tumors in these patients ([Malkin et al, 1990](#); [Diller et al, 1995](#)). Neurofibromatosis is an autosomal dominant disorder.

Deregulation of Ras protein function predisposes patients to malignancy ([Oguzkan et al, 2006](#)). In IRS IV, the incidence of neurofibromatosis 1 among enrollees was noted to be 20 times greater than in the normal population. The lifetime risk of RMS has been estimated to be 10% among patients with neurofibromatosis 1 ([Sung et al, 2004](#)), who have a particular predilection for bladder/prostate RMS, prompting some authors to recommend surveillance ([Sung et al, 2004](#)). Basal cell nevus, or Gorlin syndrome, confers constitutive activation of the hedgehog signaling pathway as a result of defects in the *PTCH* gene ([Hahn et al, 1996](#); [Johnson et al, 1996](#)). These abnormalities cause tumor cell resistance to apoptosis ([Kappler et al, 2003](#)). This syndrome is characterized by overgrowth features, skeletal abnormalities, and benign and malignant tumors. Patients are at particular risk for basal cell carcinoma, medulloblastoma, and RMS. Noonan syndrome is distinguished by facial abnormalities, short stature, and cardiac abnormalities. Hematologic and solid tumors result from PTPN11 abnormalities affecting the Ras-mitogen-activated protein kinase signaling pathways ([Jongmans et al, 2011](#)). Costello syndrome is an autosomal dominant disorder that manifests clinically as mental retardation, unusual facial features, heart abnormalities, and short stature ([Quezada and Gripp, 2007](#)). In Costello syndrome, permanent activation of *HRAS* results in unchecked cell division ([Rauen, 2007](#)). Cancer eventually may occur in 15% of affected individuals. In one report of 200 patients, 13 (6.5%) eventually developed pelvic RMS prompting a recommendation for screening ultrasound scans every 3 to 6 months ([Gripp et al, 2002](#)). Multiple endocrine neoplasia type 2A is associated with medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. It is inherited in an autosomal dominant fashion and results in activating mutations of the *RET* proto-oncogene. Alveolar RMS has been reported in these patients, and some authors have recommended screening ([Jones et al, 2010](#)).

PATHOLOGY AND MOLECULAR BIOLOGY

The RMS histologic classification system was originally developed by [Horn and Enterline \(1958\)](#) and included four subtypes: embryonal, alveolar, pleomorphic, and undifferentiated. Recognition that pleomorphic tumors were anaplastic variants of embryonal RMS or alveolar RMS led to consolidation of the original system into the three histologic categories used today: embryonal, alveolar, and undifferentiated ([Kodet et al, 1993](#)). Histology alone serves as an independent prognostic indicator.

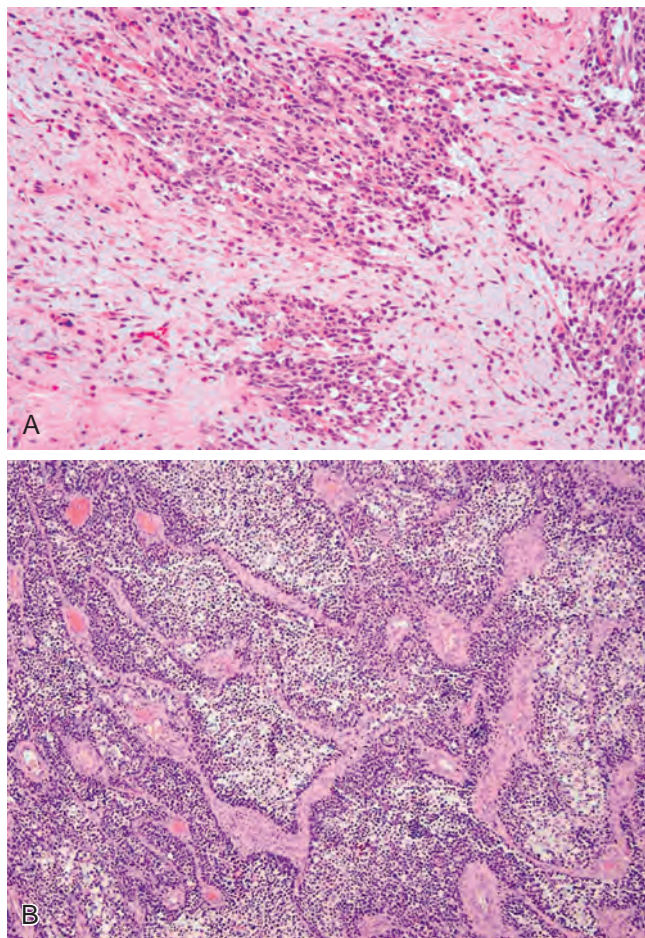


Figure 156-1. Histologic images of common rhabdomyosarcoma variants. A, Embryonal rhabdomyosarcoma (hematoxylin and eosin, $\times 200$). B, Alveolar rhabdomyosarcoma (hematoxylin and eosin, $\times 100$). (Courtesy Cheryl Coffin, Vanderbilt University Medical Center.)

Embryonal RMS is the most common form of RMS and the predominant bladder histology. Two variants of embryonal RMS account for two thirds of all genitourinary RMS: sarcoma botryoides and spindle cell. These tumors are most common in young children and have a survival rate of 85% to 90% (Ferrer and Ritchey, 2006). The botryoid variant includes polypoid tumors, often appearing as a “cluster of grapes.” They arise within a hollow viscus. Spindle cell tumors are commonly found in the paratesticular region.

Histologically, embryonal RMS resembles fetal striated muscle correlating to a gestational age of 7 to 10 weeks. Cells are spindle shaped with minimal cytoplasm, associated with larger cells harboring abundant eosinophilic cytoplasm or alternatively small, dark ovoid cells. Some cells may demonstrate characteristic cross striations (Fig. 156-1) (Horn and Enterline, 1958; Ferrer and Ritchey, 2006). Alveolar RMS is the second most common histologic type of RMS. It occurs most frequently in adolescents and young adults in the extremities and trunk. The histologic appearance correlates with striated muscle of 10 to 21 weeks’ gestational age. Small, round tumor cells form irregular nests that give the appearance of alveolar spaces (Horn and Enterline, 1958). Alveolar RMS expresses myogenin, a fetal myogenic regulatory gene, which serves as a useful immunohistochemical marker for alveolar RMS (Dias et al, 2000). Myogenin staining is absent or weak in embryonal RMS. Compared with embryonal RMS, alveolar RMS metastasizes more frequently and has a worse prognosis (Crist et al, 2001; Stevens et al, 2005). Undifferentiated tumors are the least common form of RMS and carry a poor prognosis. Histologically, they appear as primitive

round cells with scant cytoplasm and lack common antigenic markers (Dodd et al, 1989; Parham et al, 1991).

Histologic diagnosis is determined through standard immunohistochemistry and ultrastructural examination. Myogenic markers such as desmin, muscle-specific actin, myosin, and myoglobin are routinely used. As mentioned earlier, nuclear transcription factors that initiate myogenesis, MyoD and myogenin, are also being used (Cessna et al, 2001; Morotti et al, 2006; Parham and Barr, 2013).

The most significant development in more recent RMS research is the discovery of oncogenic fusion proteins produced by chromosomal translocations. Although histologic and clinical differences between embryonal RMS and alveolar RMS have long been recognized, molecular genetic analysis only more recently has been able to distinguish two distinct subtypes of alveolar RMS: fusion positive and fusion negative. Translocations between chromosomes 2;13 or 1;13 result in disruption of specific genes in 2q35 or 1p30 and 13q14. Rejoining these segments leads to the formation of fusion genes. The involved genes on chromosomes 2 and 1 are *Pax3* and *Pax7*. These genes are members of the paired box family of transcription factors (Barr et al, 1993; Davis et al, 1994). The chromosome 13 fusion partner is *FOXO1*, which encodes transcription factors from the forkhead family (Galili et al, 1993; Davis et al, 1994). The resulting fusion genes *Pax3-FOXO1* and *Pax7-FOXO1* are believed to encode proteins involved in alveolar RMS pathogenesis and confer a more aggressive phenotype (Parham and Barr, 2013). It appears that roughly 80% of alveolar RMS tumors are fusion positive.

The clinical relevance of these molecular features was highlighted in a report from the Children’s Oncology Group (COG) Soft Tissue Sarcoma Committee. In a survival analysis, patients with intermediate-risk RMS, *Pax3-FOXO1*⁺ alveolar RMS ($n = 85$), *Pax7-FOXO1*⁺ alveolar RMS ($n = 23$), and translocation-negative alveolar RMS ($n = 21$) and 305 patients with embryonal RMS were evaluated for event-free survival (EFS) and overall survival (OS). As expected, EFS and OS were worse at 5 years for patients with alveolar RMS compared with patients with embryonal RMS. *Pax3/Pax7-FOXO1* fusion-positive patients had inferior EFS compared with patients with fusion-negative alveolar RMS and embryonal RMS (Fig. 156-2). Additionally, OS was worse for patients with *Pax3* fusion compared with patients with *Pax7* fusion (Skapek et al, 2013). These findings provide insight into the 20% of patients with alveolar RMS who have outcomes more consistent with embryonal RMS, as 20% of patients with alveolar RMS are fusion negative. Future COG sarcoma studies will likely use fusion status to stratify patients into risk groups for treatment.

Studies are under way to understand the oncologic drivers downstream of these translocation proteins. Preliminary studies using genome-wide ChIP sequencing identified transcriptional targets of *Pax3-FOXO1* protein such as fibroblast growth factor receptor 4, which enhances proliferation and cell survival in alveolar RMS; insulin-like growth factor receptor 1, which is known to stimulate myoblast growth; and another growth-promoting gene, the c-Met receptor (Engert et al, 1996; Lagha et al, 2008; Cao et al, 2010; Crose et al, 2012; Keller and Guttridge, 2013; Epstein et al, 1996; Ginsberg et al, 1998). Finally, it appears that *Pax-FOXO1* fusion proteins also can disrupt the function of MyoD-regulated genes such as myogenin, p21, and muscle creatine kinase (Calhabeu et al, 2013).

KEY POINTS: PATHOLOGY AND MOLECULAR BIOLOGY

- Embryonal is the most common histology for bladder or prostate lesions.
- Alveolar histology is uncommon in the bladder or prostate; more recent studies indicated two distinct types, *PAX-FOXO1* fusion positive and negative, and fusion-positive tumors carry a worse prognosis.

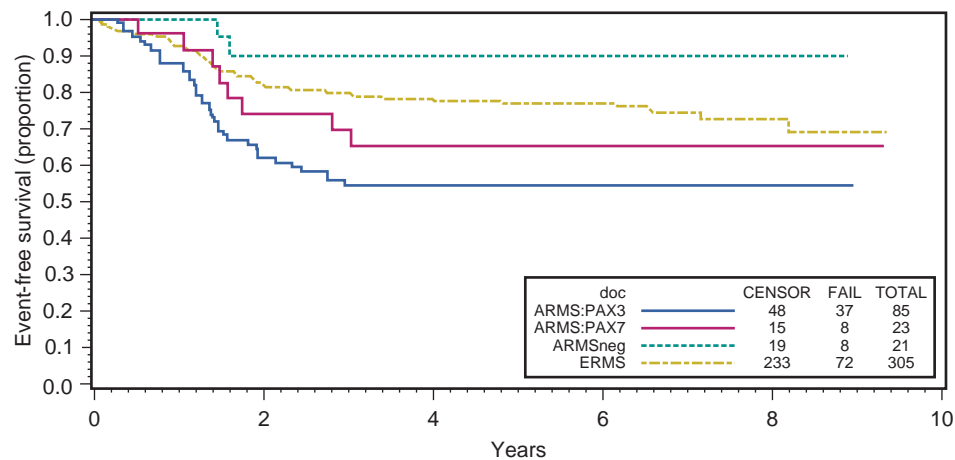


Figure 156-2. Event-free survival of patients with alveolar rhabdomyosarcoma (ARMS) based on *PAX-FOXO1* fusion status compared with an embryonal RMS (ERMS) cohort. (From Skapek SX, Anderson J, Barr FG, et al. *PAX-FOXO1* fusion status drives unfavorable outcome for children with rhabdomyosarcoma: a Children’s Oncology Group report. *Pediatr Blood Cancer* 2013;60:1411–7.)

TABLE 156-1 Nodal Drainage Patterns for Genitourinary Rhabdomyosarcoma

PRIMARY TUMOR SITE	NODAL DRAINAGE
Bladder/prostate	Pelvic and retroperitoneal nodes at or below renal arteries
Uterus/cervix	Pelvic and retroperitoneal nodes at or below level of renal arteries
Paratesticular	Pelvic and retroperitoneal nodes at or below level of renal arteries (inguinal nodes if scrotal skin is involved)
Vagina	Pelvic and retroperitoneal nodes at or below level of renal arteries
Vulva	Inguinal nodes
Retroperitoneum/pelvis	Pelvic and retroperitoneal nodes
Perianal/perineal	Inguinal and pelvic nodes; may cross midline

From Scarpato KR, Ferrer FA, Rodeberg DA, et al. Genitourinary rhabdomyosarcoma in children. AUA Update Series 2013;volume 32, lesson 9.

KEY POINT: PRESENTATION

- Bladder/prostate tumors typically manifest with symptoms of obstruction, retention, or hematuria.

Evaluation

An abdominal/pelvic ultrasound scan is commonly the first study obtained in children with hematuria or obstructive symptoms. When a mass lesion is suspected, definitive imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is indicated. The site of origin—prostate versus bladder—can be difficult to ascertain. The pelvic nodal basin of bladder/prostate tumors should be assessed using fine-cut CT or MRI. CT scan of the chest is required to exclude pulmonary metastasis (the most common site). Bone scan, bone marrow biopsy, and aspirates also are indicated. Any metastatic sites must be identified for appropriate treatment selection. Growing evidence suggests a role for positron emission tomography combined with CT (PET-CT) in staging and monitoring disease response. [Tateishi and colleagues \(2009\)](#) and [Federico and colleagues \(2013\)](#) suggested that TNM stage and restaging after treatment were more accurately described by PET-CT than by conventional imaging.

Biopsy Techniques and Management of Obstruction

Biopsy for definitive diagnosis can be challenging. The limited size of pediatric resectoscopes and narrow width of hot loupes makes adequate endoscopic biopsy difficult. Circumscribing a section of a polypoid tumor using cutting current and subsequently removing the section intact with biopsy forceps can aid in obtaining an adequate sample (Snyder, personal communication, 2005). Excessive use of cautery can lead to cautery artifact, which may mimic spindle cells. Coordination with an experienced on-site pathologist is essential to evaluate frozen sections. If adequate tissue for diagnoses cannot be obtained endoscopically, COG protocols recommend open transvesical biopsy with pelvic and para-aortic lymph node sampling.

Patients may require management of lower or upper urinary tract obstruction at presentation. Early and effective management of obstruction is essential in these patients to maximize renal function, which is taxed by systemic therapy. As a general rule, I prefer placement of a urethral catheter above a suprapubic tube for bladder

PRESENTATION, INITIAL EVALUATION, MANAGEMENT, AND STAGING

Presenting Symptoms and Examination

It is estimated that 5% to 10% of all RMS occur in the bladder or the prostate. Most of these tumors are localized at presentation. Presenting symptoms commonly include urinary obstruction, urinary retention, urgency, frequency, and incontinence. Gross or microscopic hematuria occurs when the tumor breaks through the mucosal layer ([Ferrer et al, 2006](#); [Ferrer, 2010](#)). On examination, a mass corresponding with a distended bladder or tumor may be palpated. Tumors within the bladder tend to grow intraluminally and are frequently botryoid in appearance. Rarely, tumor may prolapse into the urethra and be visible externally. Tumors of prostatic origin tend to be solid masses at presentation. Patients rarely present with evidence of systemic disease. Nodal drainage is to the pelvic nodes, and they are typically not palpable ([Table 156-1](#)).

BOX 156-1 Intergroup Rhabdomyosarcoma Study Group Pretreatment TNM Clinical Staging

Stage 1: Favorable site, nonmetastatic
 Stage 2: Unfavorable site, small tumor, negative nodes, nonmetastatic
 Stage 3: Unfavorable site, larger or positive nodes, nonmetastatic
 Stage 4: Any site, metastatic

TUMOR

T1: Confined to site of origin
 ≤5 cm
 >5 cm
 T2: Fixation to surrounding tissues
 ≤5 cm
 >5 cm

SITE

Favorable: orbit, nonparameningeal head and neck sites, male (paratesticular) or female (vagina, vulva, cervix, or uterus) genital tracts
Unfavorable: all other locations (e.g., bladder and prostate)

REGIONAL LYMPH NODES

N0: Regional lymph nodes not clinically involved
 N1: Regional lymph nodes clinically involved

METASTASES

M0: No distant metastases
 M1: Metastases present

outlet obstruction. Ureteral obstruction is best managed using indwelling ureteral catheters. If these cannot be placed in a retrograde fashion, percutaneous nephrostomy tube placement with conversion to internal catheters may be considered (Meir et al, 2004).

Staging and Children's Oncology Group Risk Group Assignment

Staging patients with RMS is complex and involves the use of a TNM staging system before treatment; a surgical-pathologic group system after biopsy or resection; and risk group stratification (low, intermediate, high), which is derived from the TNM and surgical-pathologic group systems (Box 156-1, Box 156-2, and Table 156-2). The pretreatment TNM system sorts patients into favorable and unfavorable sites. Favorable sites for genitourinary RMS include paratesticular, vulvar-vaginal, and uterine tumors. Bladder/prostate tumors arise from an unfavorable site (see Box 156-1). Local stage, tumor size, histology, nodal status, and metastasis also are considered in the pretreatment stage. The surgical-pathologic group score is affected by the presence of residual disease. With the advent of organ preservation strategies, more patients undergo initial biopsy in lieu of resection, which has shifted most patients with bladder/prostate RMS from group I to group III (see Box 156-2). Patients are then stratified into low-risk, intermediate-risk, and high-risk groups. Patients with bladder/prostate RMS are commonly in the intermediate-risk group (see Table 156-2). Patient age is another independent prognostic factor, with patients younger than 1 year old and older than 10 years having inferior survival (Joshi et al, 2004; Meza et al, 2006). PAX-FOXO1 fusion status will likely be used in future studies to segregate patients into risk groups.

BOX 156-2 Postoperative Clinical Group Assignments**GROUP I**

Localized disease, completely resected

GROUP II

Grossly resected tumor with microscopic residual disease
 Regional disease with involved nodes, completely resected with no microscopic residual
 Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node (from the primary site) in the dissection

GROUP III

Incomplete resection or biopsy with gross residual mass

GROUP IV

Distant metastasis

From Scarpato KR, Ferrer FA, Rodeberg DA, et al. Genitourinary rhabdomyosarcoma in children. AUA Update Series 2013;volume 32, lesson 9.

TABLE 156-2 Rhabdomyosarcoma Risk Stratification

HISTOLOGY	CLINICAL GROUP	STAGE	AGE	RISK GROUP
Embryonal, with variants	I, II, III	1	All	Low
Embryonal, with variants	I, II	2, 3	All	Low
Embryonal, with variants	III	2, 3	All	Intermediate
Embryonal, with variants	IV	4	<10 yr	Intermediate
Embryonal, with variants	IV	4	≥10 yr	High
Alveolar	I, II, III	1, 2, 3	All	Intermediate
Alveolar	IV	4	All	High

TREATMENT AND OUTCOMES**Evolution of Multimodal Treatment**

Advances in the treatment of RMS have been facilitated by collaborative groups including the COG (encompassing the IRS), the International Society for Pediatric Oncology (SIOP), the Italian Cooperative Group (ICG), and the German sarcoma study group, Cooperativen Weichteilsarkom Studie (CWS). At the initiation of IRS I (1972-1978), treatment of bladder/prostate RMS involved radical surgery (Horn and Enterline, 1958; Ferrer et al, 2006). The combination of up-front surgery with adjuvant chemotherapy resulted in OS of 78% with significant associated morbidity related to extirpative surgical procedures (Raney et al, 1993; Ferrer and Ritchey, 2006).

After IRS I, organ preservation became a primary focus for North American and European collaborative groups. IRS II (1979-1984) and SIOP RMS 75 were the first to use neoadjuvant chemotherapy and radiation. In 10% of patients, relapse-free survival was achieved with chemotherapy alone. OS was 80%, but the functional bladder preservation rate was only 25% (Crist et al, 1995; Raney et al, 2001). In IRS III (1985-1992), with the use of doxorubicin, cisplatin, and etoposide coupled with radiotherapy, OS for bladder/prostate RMS increased to 83%, and bladder preservation rates

increased to 60% (Crist et al, 1995; Hays et al, 1995; Lobe et al, 1996; Raney et al, 2001).

In IRS IV (1993-1997), pretreatment TNM staging and a regimen of vincristine, dactinomycin, and cyclophosphamide were used. Local recurrence rates increased because radiation was limited. Arndt and colleagues (2004) reported on the IRS IV outcomes for patients with bladder/prostate RMS. At 6.1 years, EFS was 77%, and OS was 82% (Arndt et al, 2004), but only 36 (40%) of the original 88 patients were failure-free with “normal” bladder function. This study prompted increased interest in true bladder function outcomes.

IRS V was the first protocol to use risk stratification. The 3-year failure-free survival rate was 88% for low-risk, 76% for intermediate-risk and less than 30% for high-risk patients (Ferrer et al, 2006; Ferrer and Ritchey, 2006; Alexander et al, 2012).

Current Multimodel Approaches: Children's Oncology Group

Most patients with bladder/prostate tumors have tumors that are unresectable at presentation and undergo diagnostic biopsy, as opposed to an up-front primary excision that could compromise organ function. If resection is attempted as a primary procedure (e.g., a bladder dome lesion) or later in the patient's course as a secondary procedure (rare), surgeons should mark any area outside the bladder lumen suspicious for residual disease with titanium clips because frozen-section margins may be unreliable. Patients undergo imaging of the appropriate nodal drainage pathways (see Table 156-1). Pathologic confirmation of any radiographically positive nodes should be performed to avoid unnecessary radiotherapy. If a patient presents with suspicious nodes, open bladder and concomitant pelvic and para-aortic nodal biopsy may be preferred.

COG protocols advise that complete response to nonoperative therapy (chemotherapy/radiation) may not be rapid and that radical surgery should be avoided. A residual mass does not always represent viable tumor. Tumor cells may involute leaving a mass that consists primarily of stroma. They also may differentiate into mature rhabdomyoblasts that do not require radical resection (Wu and Snyder, 2004, 2009). Furthermore, residual mass does not correlate with outcome. IRS III highlighted this fact, showing that 36% of patients without radiologic response to nonoperative treatment were in complete remission based on pathologic assessment of resection specimens (Hays et al, 1995; Raney et al, 2001). On the current protocol, indications for second-look or extirpative surgical procedures are rare, and the rationale should be carefully documented and potentially discussed with COG Soft Tissue Sarcoma Committee members to ensure that the child remains on study protocols.

After diagnostic biopsy, patients proceed to the appropriate risk-stratified treatment regimen, which in the current protocol involves chemotherapy and radiation therapy. The two principal objectives of the current COG intermediate-risk study ARST0531 were to (1) compare standard vincristine, dactinomycin, and cyclophosphamide with a regimen that alternated vincristine, dactinomycin, and cyclophosphamide with vincristine and irinotecan and (2) assess the efficacy of early radiotherapy at week 4 against historical control subjects that started radiation at 10 weeks. Patients may receive a total of 42 weeks of treatment. Radiation therapy for patients with gross residual disease (group III) is 45 to 50 Gy. Final results from ARST0531 were not available at the time of this writing. Study protocols are available through the principal investigator of each participating institution and have detailed surgical guidelines.

Current Multimodel Approaches—European Cooperative Groups

The philosophical approach of SIOP to bladder/prostate RMS has varied from that of IRS and later COG. Although the latter groups

KEY POINTS: STAGING AND TREATMENT

- Organ preservation is a principal goal of treatment, and most patients treated in COG protocols undergo endoscopic/open biopsy as the initial step.
- Pretreatment TNM staging and a surgical-pathologic group classification contribute to the patient's final risk group assignment, which determines therapy.
- Bladder/prostate tumors arise from an unfavorable site, and gross residual tumor usually remains after biopsy; therefore, most patients are assigned into the intermediate-risk group.
- A residual mass after chemotherapy/radiotherapy does not mean viable tumor remains.
- Rhabdomyoblasts are differentiated tumor cells that do not require further treatment.

focused on bladder preservation, SIOP Malignant Mesenchymal Tumor (MMT) 84, MMT 89, and MMT 95 (1984-2003) (Flamant et al, 1985; Stevens et al, 2005; Oberlin et al, 2012) took a fundamentally different view on local control, avoiding radiation. Similar to COG, biopsy is usually the first intervention. Patients are treated with chemotherapy and assessed for a response. In MMT 84, standard chemotherapy included ifosfamide, vincristine, and actinomycin. Patients enrolled in MMT 89 also received ifosfamide, vincristine, and actinomycin as primary therapy. In MMT 95, patients were randomly assigned to receive either ifosfamide, vincristine, and actinomycin or a six-drug regimen consisting of ifosfamide, vincristine, actinomycin D, carboplatin, epirubicin, and etoposide. Tumor response is evaluated radiographically and by endoscopy. Patients not exhibiting a complete response are considered for conservative surgery (tumorectomy, partial cystectomy, or prostatectomy). Radiotherapy is used only in cases in which a cure is not achieved by chemotherapy and surgery. If necessary, radical surgery is considered as opposed to external-beam radiotherapy to avoid the late consequences of external-beam radiotherapy (Flamant et al, 1985; Stevens et al, 2005; Oberlin et al, 2012).

Using this approach, SIOP reported the combined results for MMT 84, MMT 89, and MMT 95 (Jenney et al, 2014). There were 175 patients eligible for analysis. Botryoid and embryonal tumors were most common with alveolar tumors comprising only 6% of the total group. Key outcomes included EFS and OS, which were 63% and 77%, respectively. Although the 5-year OS was similar to other international groups, the EFS was lower than that reported by COG. It is assumed that the lower EFS is related to the diminished use of radiotherapy in these trials. The similar OS may reflect the ability to “recover” some of these patients with second-line therapy. The percentage of preserved bladders increased from 69% to 73% and, most recently in MMT 95, to 76% (Jenney et al, 2014). Similar to SIOP protocols, the most recently reported ICG studies, ICG-79 and ICG-88, focused on up-front three-drug chemotherapy and attempted to avoid radiotherapy. EFS and OS results were not significantly different from the results observed in SIOP studies (Rodeberg et al, 2011).

Results from the CWS study, CWS-96, were reported in 2011 (Seitz et al, 2011). Patients underwent biopsy and subsequently received neoadjuvant chemotherapy with three drugs. Radiologic response after 9 weeks determined local therapy. Patients with complete response did not receive radiotherapy, patients with better than two-thirds response received 32 Gy, and patients with less than two-thirds response received 45 Gy. Primary resection was discouraged unless it would not affect bladder function. Secondary surgery was performed only if residual disease remained after radiotherapy. There were 63 patients analyzed. Radiation was given to 60.3%, 51 underwent up-front biopsy, and only 12 had primary resection. Secondary resection was performed in 45 patients. The 5-year OS for the entire group (all stages) was 76.3%. Patients who had only chemotherapy/radiotherapy had an OS of 87.5%. Patients who had chemotherapy and surgery had an OS of 84%. Patients who had chemotherapy/radiotherapy followed by tumor resection

had an OS of 87.8%. Patients who had incomplete resection with follow-up radiotherapy/chemotherapy had an OS of only 39% (Seitz et al, 2011).

All of the cooperative groups have focused on bladder preservation. OS results between the two different approaches are similar. Protocols avoiding radiotherapy appear to have lower EFS but comparable OS suggesting that children who fail can be rescued with intensified chemotherapy. Survival for bladder/prostate RMS has not changed substantially in two decades. It is likely that novel therapies or an enhanced understanding of risk stratification, perhaps based on genomic analysis, will be required before further improvement is seen (Rodeberg et al, 2011).

Treatment of Very Young Children

Because of their increased susceptibility to treatment-related morbidity, management of infants with bladder/prostate RMS is a significant challenge, and age younger than 1 year is an adverse prognostic factor (Crist et al, 2001; Joshi et al, 2004; Malempati et al, 2011). Various collaborative groups have demonstrated significantly lower failure-free survival in infants (Ferrari et al, 2003; Joshi et al, 2004; Malempati et al, 2011). Because there is no clear evidence that the biology of RMS is different in young children, it is thought that reductions in prescribed radiotherapy are responsible. Specifically, studies by Ragab and associates (1986) and Malempati and colleagues (2011) demonstrated higher local failure rates for infants treated in IRS studies. These higher local failure rates have been associated with a reduction in recommended radiation therapy (Ferrari et al, 2003; Malempati et al, 2011). Puri and colleagues (2006) evaluated 20 infants and toddlers receiving external-beam radiotherapy; 7 of 20 experienced long-term morbidity, including altered ambulation, recurrent infections, and second malignant neoplasms. Current COG protocols allow the treating institution to deviate from protocol-prescribed radiation therapy for children younger than 24 months of age. Downward dose adjustments in chemotherapy in these young children also may be contributing to poorer outcomes. The issue of appropriate therapy for very young children remains a quandary.

Timing of Surgical Reconstruction

Although bladder preservation rates have increased, some cases still require extirpative surgery. In these instances, the appropriate timing for reconstruction is a central question. Several authors have suggested that it is feasible to perform reconstruction concomitantly with cystectomy or cystoprostatectomy. Lander and colleagues (1992) described performing immediate "le bag" neobladder reconstruction on three children undergoing cystectomy for RMS. The reconstructive procedures themselves were successful, and initial frozen sections of margins were negative. However, viable tumor was present on permanent sections, mandating further chemotherapy and radiotherapy to the reconstructed pelvis (Lander et al, 1992). Similarly, Megurian and associates (1998) noted that frozen section proved unreliable in predicting residual disease. Hensle and Cheng (2000) observed that although early reconstruction is feasible, it should be considered carefully and avoided if further local therapy is a possibility. A group from Padua, Italy, published their experience with continent orthotopic reconstruction using the "VIP" bladder (Castagnetti et al, 2014). Of nine patients undergoing urethral preservation, two experienced local recurrence despite negative intraoperative frozen-section and permanent-section evaluation. Contrasting this experience is that of the Mainz group (Stein et al, 2013). These investigators preferred to perform continent reconstruction at the time of cystectomy. Of 25 patients, 11 underwent continent cutaneous diversion, and two underwent a urethral ileocecal pouch. All of these patients are reported to be continent, and none appear to have had local recurrence (Stein et al, 2013).

The difficulty in predicting local recurrence and concerns related to irradiating the recently reconstructed genitourinary tract has prompted some authors to advocate for delayed recon-

struction. Duel and associates (1996) performed initial urinary diversion followed by delayed reconstruction in patients obtaining long-term cure. They used colonic segments to create a temporary conduit, avoiding the previously irradiated ileum. These segments were later reconfigured into the cutaneous continent reconstructions. Experience with delayed orthotopic reconstruction is limited. The group from Padua, Italy, described their disappointing continence results in two patients in which this approach was attempted (Castagnetti et al, 2014). Early reconstruction is feasible; however, the inaccuracy of intraoperative margin analysis increases the likelihood of positive margins, local tumor recurrence, and further local therapy in a reconstructed pelvis.

Outcomes

Rodeberg and colleagues (2011) looked at the outcomes of patients from IRS/COG, SIOP, ICG, and CWS collectively and comparatively; the outcomes of 379 patients were evaluated. Patients 0 to 5 years old constituted 74% of the cohort; 87% were younger than age 10. Of patients, 82% were boys. Analysis of pathology revealed that 322 of 379 (85%) had localized embryonal tumors. Metastases were observed in only 7% of patients with embryonal RMS. Non-embryonal pathology (alveolar or other) was present in 30 patients (8%). The site of origin was recorded as bladder in 59%, prostate in 29%, and bladder or prostate in 12% (Rodeberg et al, 2011). Prognostic features included local tumor invasion, tumor size, and histology. When evaluating the treatment of patients with localized bladder/prostate RMS, 48% of patients enrolled in SIOP/ICG received radiotherapy versus 85% of patients enrolled in IRS/CWS.

The collective outcomes demonstrated a 5-year failure-free survival of approximately 75% for patients with localized tumors. The 5-year OS was 84%. Most failures (88%) occurred within 3 years. The location of failures was local in 60%, regional nodes with or without local disease in 9%, and distant failure with or without local disease in 25% (Rodeberg et al, 2011). Comparative outcomes analysis of collaborative group protocols revealed no statistically significant difference between the groups in failure-free survival or OS when correcting for tumor invasion and tumor size between the groups (Rodeberg et al, 2011).

The last fully reported IRS/COG results come from IRS IV. The analysis included 88 patients. The OS at 6 years was 82%, and the EFS was 77%. The bladder was retained in 55 patients, but only 36 (40%) reported normal bladder function (Arndt et al, 2004). Functional bladder evaluation was limited in this study. In 2006, an international work group reported on continence of 62 patients age 6 years or older who did not undergo cystectomy; 43 (69%) were reported to be continent, 16 had nocturnal incontinence, and 9 had diurnal incontinence. Patients undergoing partial cystectomy had a continence rate of 73%. Of the entire group, only 11 underwent a formal urodynamics study (Raney et al, 2006). The often-cited series by Yeung and colleagues (1994) reported on 11 patients undergoing a complete urodynamics evaluation after cure for pelvic RMS; in this report, only children who did not receive radiation therapy had normal bladder function. Similarly, Hays and coworkers (1995) observed that patients receiving radiation therapy were more likely to have bladder functional sequelae and that a dose effect was present, with patients receiving doses of 40 Gy or greater having more complications.

OS has remained largely unchanged for two decades in patients with bladder/prostate RMS. The true success of bladder preservation strategies is unclear because gathered data have focused on bladder retention, not function.

LATE EFFECTS

The treatment of RMS at any pelvic site is associated with potential short-term and long-term morbidity. Relative to fertility and sexual function, Raney and coworkers (2006) analyzed the urologic complications of 164 patients treated for bladder/prostate RMS from an international cohort. Data were available on only 35 (21%)

of the patients. After treatment for bladder/prostate RMS, 25 men were potent, and 2 were impotent; 16 had preserved ejaculation, and 4 had anejaculation. Two of seven women with available data had abnormal menses (Raney et al, 2006). Mansky and colleagues (2007) used a questionnaire and serum analysis to evaluate survivors of pediatric sarcoma. Of 13 female participants, 7 (47%) became pregnant; 6 remained premenopausal, whereas 7 experienced premature menopause. With regard to male fertility, only 4 of 17 men (24%) fathered children. Among men who did not father children, nine consented to semen analysis for the study. Six of these men had azoospermia, two had oligospermia, and one had a normal semen analysis; only 29% were fertile based on history or semen evaluation. All three men who received pelvic x-ray therapy were infertile (Mansky et al, 2007). Spunt and colleagues (2005) reviewed the 20-year late effects of female survivors of pelvic RMS. Delayed morbidity was found in 24 of 26 patients. Of the whole group, 77% had endocrinologic/ovarian dysfunction, and 58% experienced gynecologic dysfunction, including absence of a uterus, ovaries, or vaginal stenosis. Although large detailed studies are lacking, it is clear that significant reproductive and sexual functional consequences occur with current treatments (Armstrong et al, 2014).

Bladder function may be impaired as a result of surgery, chemotherapy, or radiation. Arndt and colleagues' 2004 review of outcomes from patients in IRS IV suggests that despite bladder preservation strategies, more than 60% of patients have some degree of bladder dysfunction (Arndt et al, 2004). Only two studies have used urodynamics, the gold standard, to evaluate treatment. Yeung and colleagues (1994) evaluated 11 children treated for pelvic sarcoma. Seven patients received external-beam radiotherapy or brachytherapy, and all of them experienced decreased bladder capacity and irritative symptoms. Soler and colleagues (2005) evaluated eight children undergoing multimodal therapy; five experienced dysuria, urgency, frequency, and diminished capacity.

An increased risk of second malignant neoplasm is associated with radiotherapy and chemotherapy. Studies of survivors of pelvic RMS suggest that they develop secondary malignant disease at six times the normal rate (Cohen et al, 2005). Mansky and coworkers (2007) reported second malignancies including osteosarcoma, Ewing sarcoma, and T-cell lymphoma in 9% of patients treated for pelvic sarcoma. Osteosarcoma, colon adenocarcinoma, and cervical squamous cell carcinoma were among the second malignancies experienced in a series of 26 survivors (Spunt et al, 2005). International cooperative groups have validated these findings (Bisogno et al, 2012). Long-term monitoring of patients with bladder/prostate RMS in specialized survivorship clinics is recommended.

OTHER BLADDER TUMORS

Transitional Cell Carcinoma

Transitional cell carcinoma (TCC) of the bladder is an uncommon lesion in children and adolescents. In a review of 10,000 cases of bladder epithelial tumors by Javadpour and Mostofi (1969), only 38 cases of TCC occurred in patients younger than 20 years old. A more recent review indicated that about 125 cases have been reported in patients younger than age 20, only 20 of which were in patients younger than 10 years old (Lerena et al, 2010). A male-to-female preponderance of 3:1 to 9:1 exists (Hoenig et al, 1996; Lerena et al, 2010). In contrast to tumors in adults, which have been associated with environmental exposures and smoking, the etiology in children is unclear. Familial history or genetic conditions have not been associated with pediatric cases (Lerena et al, 2010). Cyclophosphamide treatment and more recently chronic exposure to dantrolene have been cited as possible etiologies (Hoenig et al, 1996; Dowling et al, 2007).

The most common presenting symptom is gross hematuria, although symptoms of bladder irritation and urinary tract infection have been noted. The diagnosis is frequently delayed in children and is often made when ultrasonography detects a lesion. It

has been postulated that ultrasonography approaches 100% sensitivity and is the preferred method for surveillance (Hoenig et al, 1996; Serrano-Durba et al, 1999). Voiding cystourethrogram is less sensitive because dye density may obscure the tumor (Lerena et al, 2010). The definitive diagnosis is made by cystoscopy and biopsy. Most lesions (75%) occur in the trigone and are unifocal, although multifocal lesions have been reported (Khasidy et al, 1990; Quillin and McAlister, 1991; Hoenig et al, 1996; Serrano-Durba et al, 1999). Most lesions (80%) are superficial, low-grade lesions. A small portion of lesions are high grade. A single case of invasive disease leading to death has been reported (Paduano and Chiella, 1988; Scott et al, 1989; Hoenig et al, 1996). Pediatric TCC is best treated with transurethral resection; intravesical therapy has had no defined role.

Typically, pediatric bladder TCC does not involve the upper tracts, and no recommendations for routine upper tract surveillance exist (Vikram et al, 2009). Recurrence appears to be rare, even when higher grade lesions have been reported (Lerena et al, 2010). Periodic surveillance with ultrasonography is recommended because it is quite sensitive in this scenario, obviating the need for serial cystoscopy. I obtain an ultrasound scan every 3 months for 1 year, every 6 months for the second year, and annually thereafter. No guidance exists regarding when to discontinue evaluation.

Cancer in the Augmented Bladder

Concern that patients undergoing urinary diversion were at risk for cancer began with extended observation of patients undergoing ureterosigmoidostomy (Husmann and Spence, 1990). It was assumed that by separating urinary and fecal streams, augmentation could avoid these complications; however, reports of cancer in patients with augmented bladders raised new concerns (Gittes, 1986; Golomb et al, 1989; Nurse and Mundy, 1989; Filmer and Spencer, 1990). Recommendations for annual endoscopic screening for patients beginning 5 to 10 years after reconstruction followed. These recommendations have been critically re-evaluated recently in light of the two following observations: (1) Most reported cases come from a patient pool biased toward infectious etiologies; few data on risk in patients with augmented bladders secondary to noninfectious etiologies are available (Golomb et al, 1989; Filmer and Spencer, 1990; Kamysan et al, 2000); (2) Patients with congenital bladder abnormalities related to exstrophy complex and spina bifida have a higher basal incidence of cancer than the normal population (Beare et al, 1956; Barrington et al, 1997; Austin et al, 2007). Husmann and Rathbun (2008) studied patients with augmented bladders who were compiled within a registry using the following criteria: (1) Patients had a minimum follow-up interval of 10 years; (2) no patient ever had a form of urinary diversion in which a mixture of feces and urine had occurred; (3) patients with a history of bladder exstrophy/epispadias complex could be included only if they had undergone bladder closure within the first 2 weeks of life; and (4) only patients with bladder augmentation secondary to neurogenic bladder, exstrophy/epispadias complex, or posterior urethral valve were included. Of the patients enrolled, 7 of 153 (4.5%) developed cancer; the median time to development of a tumor was 32 years. Bacteriuria did not correlate with the development of tumor. Incidence between ileal and colonic augments was not markedly different. Two patients who received bladder augmentation for neurogenic bladder developed multifocal TCC in their native bladder, but both had prolonged tobacco exposure. Of patients who received bladder augmentation for posterior urethral valve, 12% developed adenocarcinoma of the augmented bladder. All of these patients had end-stage renal disease, had undergone transplant, and were immunosuppressed. The authors commented that patients with a smoking history after augmentation or patients with end-stage renal disease, transplantation, and immunosuppression appear to be at greatest risk (Husmann and Rathbun, 2008).

Higuchi and colleagues (2010) compared 153 patients who had undergone ileal/colonic augmentation with age-matched and disease-matched control subjects without augmentation to

determine if an increased cancer risk was present. The authors documented no statistically significant increase in bladder cancers in patients with augmentation versus subjects without augmentation (4.6% vs. 2.6%). Their data suggested that patients with neurogenic bladder have a baseline increase in cancer rates. In addition, their data supported the concept that patients with exstrophy/epispadias are also at an increased risk. An increased risk of cancer was present in immunosuppressed patients with a history of opportunistic viral infection (Higuchi et al, 2010).

Regarding surveillance, Higuchi and colleagues (2011) evaluated the utility of annual cytology and endoscopy. The authors found cytology was not helpful because of a significant false-positive rate. The authors also noted that only 4 of 250 surveillance cystoscopies revealed suspicious lesions, none of which proved cancerous. Based on the current estimated rate of malignant transformation of 1.5% to 2.8%, the authors concluded that more than 980 cystoscopies would have to be performed over a decade to diagnose one tumor. Endoscopy of the augmented bladder was recommended only when the following criteria were met: (1) Four or more symptomatic urinary tract infections occur per year; (2) a history of gross hematuria and/or urinalysis with greater than 50 red blood cells per high-power field is present; (3) chronic perineal, pelvic, or bladder pain occurs; (4) abnormal radiographic screening studies are seen; or (5) patients with colon augmentations turn 50 years old, consistent with recommendations for colonoscopy (Higuchi et al, 2011). Similarly, using Markov model analysis, Kokorowski and associates (2011) concluded that annual cytology and endoscopy were not cost-effective and questioned their effectiveness overall.

It appears that the risk of cancer after augmentation may have been overstated. Patients with bladder augmentation who are immunosuppressed after transplantation or perhaps patients with a history of tobacco use may be in a higher risk group. The efficacy of annual cystoscopy and cytology appears questionable.

Urachal Carcinoma

Urachal adenocarcinomas in children are exceedingly rare (Rankin et al, 1993). A retrospective review of medical records from the Mayo Clinic from the period 1951-2005 identified no malignancies among urachal remnants in children (Ashley et al, 2007). A mucinous carcinoma of the urachus was reported more recently; the lesion was managed by complete surgical excision (Gupta et al, 2014).

Adenocarcinoma and Squamous Cell Carcinoma

Patients with bladder exstrophy are considered to be at increased risk for adenocarcinoma. In a review of patients with augmentation, 3 of 38 (8%) developed adenocarcinoma involving the bladder and an augmented bowel segment. The site of origin could not be determined, and all patients fared poorly. These findings are consistent with prior publications suggesting an increased risk of adenocarcinoma, squamous carcinoma, or tumors of mixed cell types in patients with bladder exstrophy (Beare et al, 1956; Smeulders and Woodhouse, 2001; Sahai et al, 2004; Woodhouse et al, 2006). The belief that early closure might diminish the rate of malignancy in patients with exstrophy does not appear to have held up because all three patients with exstrophy within the series by Husmann and Rathbun (2008) had early closure. Squamous cell carcinoma also has been reported in patients with exstrophy (Patil et al, 2012). The most common scenario appears to involve tumors occurring in patients with exposed bladders. In the absence of exstrophy or schistosomiasis, squamous cell carcinoma in pediatric patients is exceedingly rare; the youngest reported patient was 16 years old with a history of bladder calculus (Sung and Koyle, 2000).

Benign Bladder Tumors

Inflammatory myofibroblastic tumor (IMT) is a locally invasive lesion that can mimic RMS in children and young adults. The

diagnosis can be made endoscopically; however, in my experience, open biopsy is commonly needed to exclude RMS. The tumor consists of spindle cells with myofibroblastic differentiation in a collagen stroma with an inflammatory cell infiltrate. Abnormalities of the anaplastic lymphoma kinase gene (*ALK*) and the rain binding protein (*RANBP2*) have been reported. IMTs with these rearrangements are termed IMT-RA and have a higher risk of local recurrence and metastasis (Li et al, 2013). Tumors without rearrangement have been treated with celecoxib with or without surgery with some success (Berger et al, 2007; Chavez and Hoffman, 2013; Li et al, 2013).

Bladder hemangiomas or venous malformations of the bladder in children typically manifest with gross hematuria and can be difficult to distinguish from malignant lesions. An association between bladder hemangiomas and Proteus syndrome (a rare hamartomatous disorder) has been documented in two patients (Lopez-Gutierrez and Jaureguizar, 2010). These lesions can be treated by partial cystectomy or laser ablation (Ashley and Figueroa, 2010; Takemoto et al, 2011; March Villalba, 2012).

Nephrogenic adenoma is a benign papillary lesion of the bladder that is associated with recurrent infections, radiation, bladder surgery including bladder augmentation, and other forms of bladder injury. It has been rarely reported in children with congenital anomalies involving the bladder (Broecker et al, 2011). Nephrogenic adenoma also has been associated with renal transplantation (Mazal et al, 2002). Histologically, tumors have a polypoid or papillary pattern consisting of layers of cuboidal cells, which frequently organize themselves into tubular patterns (Heidenreich et al, 1999). Patients may present with symptoms including hematuria, dysuria, frequency, recurrent urinary tract infection, and bladder instability. Cystoscopy and biopsy are required for diagnosis. Treatment consists of minimizing or eliminating inflammatory stimuli (antibiotic prophylaxis or improvement in voiding function). Transurethral resection and fulguration have been used effectively. Recurrence is common, and long-term follow-up is warranted. Malignant transformation is rare (Hartmann et al, 2006).

FEMALE GENITAL TRACT

Vulvar Rhabdomyosarcoma

RMS of the vulva is extremely rare—the total number of patients with vulvar sarcoma enrolled in IRS I through IRS IV was 20. The age distribution was 12 patients younger than 10 years old and 8 patients between 10 and 20 years old (Arndt et al, 2001). Compared with other female genital sites, a larger percentage of these patients have alveolar/undifferentiated histology (9 of 20; 45%). However, because these tumors are typically localized at presentation, patients have a favorable prognosis (Andrassy et al, 1995; Martelli et al, 1999). The usual presenting symptom is a labial/vulvar mass. Clinicians should be aware that tumors also can manifest as clitoral or preclitoral masses (Bond et al, 1994; Ghushie and Drugas, 2007). Treatment may include up-front excision or biopsy followed by chemotherapy and local therapy per COG protocols; brachytherapy for treatment of vulvar lesions also has been reported (Magne and Haie-Meder, 2007; Magne et al, 2008).

Vaginal Rhabdomyosarcoma

The vagina is the most common location for RMS of the female genital tract. An analysis of IRS I through IRS IV identified 151 patients with female genital tract RMS (vulva, vagina, cervix, uterine), of which 84 (54%) originated from the vagina. Most (86%) were clinical group III, and 95% had botryoid/embryonal histology. Presenting complaints included vaginal bleeding, discharge, or a protruding mass (Fig. 156-3) (Andrassy et al, 1995, 1999; Arndt et al, 2001). The management of vaginal RMS has changed dramatically since IRS I. Each iteration of protocols has demonstrated a decreased need for surgical resection (IRS I, 100%; IRS II, 70%; IRS III, 30%; IRS IV, 13%) and excellent



Figure 156-3. Mass protruding from the vaginal introitus in a young girl with vaginal rhabdomyosarcoma.

disease-free survival (Andrassy et al, 1995, 1999; Arndt et al, 2001). OS in IRS III was approximately 83% (20 of 24). Most patients today undergo up-front biopsy followed by chemotherapy with or without local control measures (Andrassy et al, 1995, 1999; Arndt et al, 2001). Between 1997 and 2008, COG conducted two consecutive low-risk RMS studies (D9602, 1997-2004; ARST0331, 2004-2008); these studies initially limited or omitted radiotherapy for vaginal tumors. The higher than expected local failure rates prompted COG investigators to recommend that radiotherapy should not be omitted. Despite these local failures, OS was excellent in this series, suggesting good response to salvage therapy (Walterhouse et al, 2011). European studies have advocated brachytherapy documenting excellent results with survival rates of 91% (Magne and Haie-Meder, 2007; Magne et al, 2008).

Cervical/Uterine Rhabdomyosarcoma

Cervical or uterine RMS is the second most common site of female genital RMS. A more recent review using the Surveillance, Epidemiology, and End Results database described 26 cases from 1973-2006 (Kirsch et al, 2014). Of 151 patients with female genitourinary sarcoma in IRS I through IRS IV, 49 had tumors of the cervix or uterine body (Arndt et al, 2001). Patients typically present with vaginal bleeding or an abdominal mass (the latter is more common with uterine body tumors). As with vaginal RMS, radical surgery has given way to organ-sparing approaches. Corpron and colleagues (1995) published the IRS III and IRS IV pilot experience, which included 14 patients 4 months to 17 years old (mean age 5.5 years old). There were 13 patients with embryonal pathology and 1 patient with an alveolar tumor. Of eight patients with group III disease, five died; four of the deaths were due to sepsis and chemotherapy-related complications. All patients with group I disease and patients with metastatic disease at presentation survived (Corpron et al, 1995). A SIOP study using organ-sparing therapy reported survival of 10 of 11 patients with cervical/uterine RMS (Martelli et al, 1999). Organ-sparing procedures, such as cervicectomy, have been applied to select patients with cervical RMS (Kayton et al, 2009).

Ovarian Tumors

Ovarian tumors represent about 1% of childhood cancers. Similar to gonadal tumors in boys, these tumors are classified histologically as germ cell tumors (GCTs), sex cord-stromal tumors, or epithelial in origin. Tumors of epithelial origin are very rare before puberty (You et al, 2005). GCTs in girls arise from the primordial germ cells of the ovary and include teratoma (mature and immature), gonadoblastomas, and yolk sac (endodermal sinus) tumors. As in boys, gonadoblastomas occur in the setting of dysgenetic gonads and rarely metastasize. Mature teratomas (dermoid cysts) are typically benign and treated by resection alone. Immature teratomas and yolk sac tumors (YSTs) can exhibit aggressive behavior and are staged and treated according to COG protocols. YSTs along with rare embryonal carcinomas and choriocarcinomas produce serum markers, which play a role in treatment and follow-up. Prognosis for these tumors is generally very good. COG protocol 9048 treated these tumors with resection and platinum-based multiagent chemotherapy and demonstrated an overall 6-year survival of 95% for stage I tumors and 93% for stage II tumors (Rogers et al, 2004). Reports of excellent outcomes for children with stage III disease are also available. More recently, observation alone for patients with stage I tumors has been studied. Although EFS was decreased, most patients were salvaged by chemotherapy on recurrence (Billmire et al, 2014). Sex cord-stromal tumors in girls include thecafibromas, Sertoli cell tumors, Leydig cell tumors, and granulosa cell tumors. These tumors are hormonally active and may manifest with precocious puberty. Their course is typically benign (Schultz et al, 2006).

KEY POINTS: FEMALE GENITAL TRACT

- The vagina is the most common female genital site for RMS, most tumors are embryonal histology, and organ-preservation strategies have resulted in excellent OS.
- Ovarian tumors constitute 1% of all childhood cancers. Ovarian tumors are histologically classified as GCTs, sex cord tumors, or epithelial tumors.

TESTICULAR TUMORS

Prepubertal testicular tumors differ markedly from testicular tumors of postpubertal patients in that benign lesions are more common, and malignant tumors have a more favorable course. Estimates suggest that testicular tumors account for roughly 1% of pediatric solid tumors, with an incidence of 0.5 to 2 per 100,000 children. Much of the information regarding these tumors comes from the Pediatric Testis Tumor Registry (PTTR), established by the Urology Section of the American Academy of Pediatrics, or from large single-center or multi-institutional series. Conflicting data regarding the most frequent pathologic variant have raised questions about enrollment bias in the PTTR. These discrepancies do not affect clinical management, allowing for clear and simple algorithms.

Epidemiology

The PTTR suggests that the most common pathologic diagnosis in children with a testicular mass is a YST, followed by teratoma (Ross et al, 2002). A large single-center series from Turkey also found that YSTs were most common (Ciftci et al, 2001), but these findings are reversed in most single-center or multi-institutional series (Metcalf et al, 2003; Shukla et al, 2004; Agarwal and Palmer, 2006). A review from four large pediatric hospitals that included 98 patients younger than 12 years old found that teratoma was present in 48% of children; YSTs, in 15%; epidermoid cyst, in 14%; juvenile granulosa cell, in 5%; Leydig cell, in 4%; Sertoli cell, in 3%; and mixed gonadal stromal, in 1%. The remaining

9% included diagnoses such as gonadoblastoma, lymphoma, cystic dysplasia, and IMT (Pohl et al, 2004). Based on this analysis, more than 74% of prepubertal testis tumors are benign in nature. This topic was reviewed in detail by Agarwal and Palmer (2006), who acknowledged the discrepancy and concluded simply that teratoma and YSTs are the most common etiology of a testicular mass. Tumor incidence peaks near age 2, and a second increase in incidence is seen in the peripubertal period (Li and Fraumeni, 1972; Haas and Schmidt, 1995; Haas et al, 1995). Tumors are more frequent in whites than in nonwhites (Walsh et al, 2008). Incidence appears to vary with geographic location. When considering all males (prepubertal and postpubertal), some authors suggest that the incidence of testicular GCTs has been rising; however, it appears that postpubertal, not prepubertal, tumors account for this increase (Reuter, 2005).

Pathogenesis and Molecular Biology

GCTs comprise a heterogeneous group of neoplasms that derive primarily from the gonads but may arise from extragonadal sites along the migration route of the primordial germ cells to the genital ridge (midline mediastinum, peritoneum, and sacrum) (Looijenga and Oosterhuis, 1999; Oosterhuis and Looijenga, 2003; Slowikowska-Hilczar et al, 2003). Testicular GCTs comprise 98% of testicular tumors and are the most common cancer in males 15 to 35 years old (Bosl and Motzer, 1997). High levels of maternal estrogens, low and high birth weights, neonatal jaundice, and disorders of sex development (DSD) have been associated with the development of GCT. Many of these factors support the concept that initiating events occur in the prenatal or perinatal period (Depue et al, 1983; Ekblom and Akre, 1998; Richiardi et al, 2002; Reuter, 2005).

The most widely accepted association with GCT is cryptorchidism, with 10% of cases linked to a history of undescended testis (Schottenfeld et al, 1980; Halme et al, 1989a, 1989b). Patients with cryptorchidism have a fourfold higher lifetime risk of developing GCT. This risk does not appear to return to baseline after orchiopexy (Schottenfeld et al, 1980; Giwercman et al, 1987; Halme et al, 1989b; Wood and Elder, 2009). Finally, as is discussed in subsequent sections, patients with DSD are known to be at risk for the development of GCT (Rutgers and Scully, 1987, 1991; Collins et al, 1993; Skakkebaek et al, 2003). Patients with hypovirilization and gonadal dysgenesis are at highest risk.

Much remains unknown regarding the molecular pathogenesis of GCT. Intratubular germ cell neoplasia (IGCN) is considered by many authors to be a precursor lesion to GCT. Two theories predominate regarding the development of IGCN. The first suggests that aberrant chromatid exchange events lead to a chromosome 12p copy number increase; this allows zygote-pachytene spermatocytes to avoid the apoptotic effects of p53 and become cancerous (Chaganti and Houldsworth, 1998, 2000). The second theory maintains that fetal gonocytes undergo abnormal cell division owing to environmental factors and give rise to IGCN. Polyploidization precedes chromosome 12p abnormalities. These cells become vulnerable to postnatal or postpubertal development of invasive cancer (Chaganti and Houldsworth, 1998; Looijenga et al, 1999; Skotheim and Lothe, 2003). Pediatric cases are mostly diploid, with the exception of YSTs, which may be nondiploid. GCTs in children have been characterized by deletions of 1p, loss of chromosome 6q, and abnormalities of chromosome 2 and 3p (Silver et al, 1994; Jenderny et al, 1996; Stock et al, 1996; Schneider et al, 2001).

The COG conducted the largest study evaluating family history of cancer and subsequent development of malignant GCT (Poynter et al, 2010). The study enrolled 278 cases and 423 controls. No association was observed between a family history of cancer and GCT in the group as a whole. The study did observe an increased risk of GCT in males when a relative was diagnosed with cancer before age 40 years (OR 2.56, 95% confidence interval 1.02 to 6.44). Poynter and colleagues (2012) evaluated several susceptibility loci that had been identified in adult GCTs in a cohort of pediatric GCT. There were 52 cases from patients age 0 to 21 years

evaluated. Most patients were female, and the tumors were predominantly teratomas and YSTs. The single nucleotide polymorphism for *SPRY4* was significantly associated with an increased risk of GCT in young boys and adolescent boys. *BAK1* was associated with gonadal tumors in both sexes. Prior studies had identified similarities in chromosomal abnormalities present in adolescent boys and men with GCTs. These included losses on chromosomes 11, 13, and 18 and gains on 7, 8, and X (Bussey et al, 1999).

Presentation, Evaluation, and Staging

Testicular tumors most commonly manifest as a painless mass. Alternatively, the lesion may be incidentally discovered by an ultrasound scan of the scrotum to rule out torsion or investigate scrotal pain. A hydrocele is present in 15% to 20% of cases. The differential diagnosis includes other intrascrotal processes such as paratesticular tumors, epididymitis, benign epididymal lesions, hernias, and hydroceles. Patients with hormonally active tumors may be referred for precocious puberty. Patients with undescended testis may present when a testicular mass predisposes to intra-abdominal torsion (Agarwal and Palmer, 2006).

Ultrasonography

Although the sensitivity of ultrasonography approaches 100% for detection, an ultrasound scan cannot reliably distinguish benign from malignant testicular lesions. Common ultrasound features of benign and malignant testicular masses are summarized in Table 156-3 and discussed subsequently.

Teratomas appear as heterogeneous complex lesions on ultrasound scan, reflective of their composition, which typically includes three germ cell layers. They may contain cystic and solid components. Bony elements appear as calcifications with shadowing. Adipose tissue appears as echogenic areas without shadowing. Epidermoid cysts represent a monolayer teratoma and have a characteristic appearance described as "onion skin" comprised of concentric rings of alternating hypoechoic and hyperechoic lesions. YSTs are typically well circumscribed and heterogeneous in appearance. These tumors may be hypervascular in appearance and may have areas of hemorrhage and necrosis. Sertoli and Leydig cell tumors are similar in appearance and commonly manifest as a well-circumscribed hypoechoic mass. Granulosa cell tumors may contain cystic and solid components. Gonadoblastomas are solid, hypoechoic lesions and, in contrast to other testicular lesions, may occur bilaterally.

Interpretation of Biomarkers in Children

Serum biomarkers play an important role in the diagnosis and management of pediatric testicular lesions. Human chorionic gonadotropin- β is rarely elevated in prepubertal tumors. α -Fetoprotein (AFP) is normally produced by the fetal yolk sac, liver, and gastrointestinal tract. Serum AFP is elevated in YSTs, and measurement of AFP levels is valuable for diagnosis, staging, and management of patients with YST. As a result of the physiologically persistent elevation of AFP in infants younger than 1 year, interpretation of AFP levels in infants undergoing evaluation for a testis mass must be performed with caution. Although the accepted half-life of AFP is 5 days, levels may be particularly high after birth, and a normal half-life may not occur for 4 months. AFP levels frequently do not come down to basal levels until 6 to 8 months of age, and in some patients elevated levels may persist until 12 months. Several features of analysis of AFP level warrant mention. In YST, AFP is elevated (>10 ng/mL) in 92% of cases. If a child older than 1 year presents with a testicular mass and an elevated AFP, it is likely the patient harbors a YST, and an organ-sparing procedure should not be considered. Conversely, a normal AFP provides considerable assurance that the mass under evaluation is benign (Ross et al, 2002). Ross and colleagues (2002) made other nuanced observations that may help clinicians: (1) In children younger than 1 year with YST, median AFP levels

TABLE 156-3 Key Clinical and Radiologic Features of Common Testicular Tumors

NEOPLASM	AGE	KEY CLINICAL FEATURES	KEY IMAGING FEATURES
INTRATESTICULAR NEOPLASMS			
Germ Cell Tumors			
Seminomatous (seminoma)	30 yr	Rare in pediatric population	Uniformly hypoechoic, hypointense on T1, hyperintense on T2
Nonseminomatous			
Yolk sac tumor (endodermal sinus tumor)	2 yr	Common pediatric testicular neoplasm, AFP elevation	Well circumscribed, heterogeneous echogenicity Hypervascular
Teratoma	<4 yr	Postpubertal more likely to be malignant	Heterogeneous secondary to cystic/solid components, calcifications, adipose tissue
Embryonal	Late teens, adulthood	Elevated AFP and β -HCG	Heterogeneous and poorly marginated
Choriocarcinoma	Late teens, adulthood	Elevated β -HCG, gynecomastia	Heterogeneous, cystic/solid components
Sex Cord–Stromal			
Sertoli cell tumor	<1 yr	\pm Gynecomastia, Carney complex, Peutz-Jeghers syndrome	Nonspecific hypoechoic solid mass LCCSCT: heavy acoustic shadowing secondary to calcification
Leydig cell tumor	3-6 yr	Secrete androgens or estrogens, precocious puberty, African-American males	Well circumscribed, hypoechoic
Granulosa cell tumor	Juvenile: <1 yr	Mixed cystic and solid mass	Hypoechoic, solid and cystic components
	Adult: middle aged		
Mixed Germ Cell/Sex Cord			
Gonadoblastoma	5-10 yr	Phenotypic females with male karyotype	Solid and hypoechoic
SECONDARY TESTICULAR NEOPLASMS			
Leukemia/lymphoma	—	Bilateral testicular enlargement; treated leukemia/lymphoma	Decreased T2 signal intensity
EXTRATESTICULAR NEOPLASMS			
Adenomatoid tumor	20-50 yr	Nonspecific painless mass	Hyperechoic, homogeneous
Papillary cystadenoma	—	von Hippel-Lindau, bilateral ~40%	Echogenic
Extratesticular lipoma	—	Fatty lesion	Hyperechoic, homogeneous, T1 hyperintense
Paratesticular rhabdomyosarcoma	2 peaks: 5 yr and 16 yr	Solid extratesticular mass with variable heterogeneity	Hemorrhage and necrosis with increased flow on Doppler

AFP, α -fetoprotein; β -HCG, human chorionic gonadotropin- β ; LCCSCT, large-cell calcifying Sertoli cell tumor.

From Shah RU, Lawrence C, Fickenscher KA, et al. Imaging of pediatric pelvic neoplasms. Radiol Clin North Am 2011;49:729–48.

TABLE 156-4 Children's Oncology Group Staging System for Testicular Germ Cell Tumors

STAGE	EXTENT OF DISEASE
I	Tumor is limited to testis, completely resected by high inguinal orchiectomy. No clinical, radiographic, or histologic evidence of disease beyond the testes. If scrotal orchiectomy has been performed, all margins are negative after resection of proximal cord structures to the level of the internal inguinal ring. Tumor markers are negative after appropriate half-life decline. Patients with normal or unknown tumor markers at diagnosis must have a negative ipsilateral retroperitoneal node sampling to confirm stage I disease, if radiographic studies demonstrate lymph nodes >2 cm.
II	Microscopic residual disease is present in the scrotum or high in spermatic cord (<5 cm from proximal end). Tumor markers remain elevated after appropriate half-life interval. Tumor rupture or scrotal biopsy before complete orchiectomy.
III	Retroperitoneal lymph node involvement. Lymph nodes >4 cm by CT are considered metastases. Biopsy needed to document nodal metastases in lymph nodes >2 cm and <4 cm.
IV	Distant metastatic deposits.

CT, computed tomography.

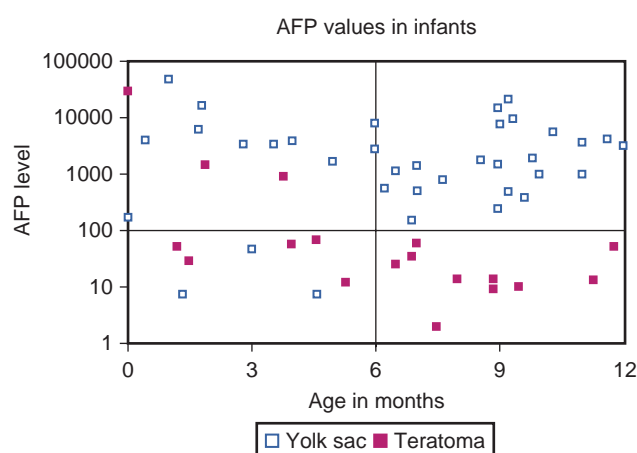


Figure 156-4. α -Fetoprotein (AFP) levels in infants with yolk sac tumor and teratoma (ng/mL). (From Ross JH. Prepubertal testicular tumors. *Urology* 2009;74:94–9.)

are higher than children with teratoma. (2) In children older than 6 months with teratoma, AFP levels rarely exceed 100 ng/mL (Fig. 156-4).

Staging

A careful physical examination is indicated with particular focus on any evidence of precocious puberty suggesting a hormonally active tumor. Disseminated disease is rare in children. After ultrasonography and serum tumor marker analysis, if concern exists that a lesion is malignant (elevated AFP), CT scan of the abdomen and retroperitoneum should be performed. The most common site of metastatic disease is the lung, which may be assessed by CT or radiography. The COG staging system is a post-surgical system based on assessment after primary orchiectomy and imaging (Table 156-4).

Tumors Associated with Disorders of Sex Development

Patients with dysgenetic testis or hypovirilization have an increased incidence of testicular tumors. Patients harboring Y chromosomal material in their karyotype are at highest risk. The noninvasive precursors of GCTs (primarily seminoma/nonseminoma and dysgerminoma/nondysgerminoma) in these patients are presumed to be carcinoma in situ and gonadoblastoma (Skakkebaek, 1972; Cools et al, 2006). Both arise from fetal germ cells. Immunohistochemistry, messenger RNA analysis, and the resem-

blance of subsequent tumors suggest a common origin for carcinoma in situ and gonadoblastoma (Gillis et al, 2007; Looijenga et al, 2007; Pleskacova et al, 2010). The pathogenesis of tumors in patients with DSD involves the transformation of immature germ cells. Several key factors in this transformation have been identified. OCT3/4, a transcription factor that has antiapoptotic functions in primordial germ cells and can be used to identify early fetal germ cells, is one such factor (Cheng et al, 2007). Another crucial element appears to be the expression of the testis-specific protein Y-encoded (TSPY) gene in the germ cells of DSD gonads (Oram et al, 2006). TSPY is the most likely candidate for the gonadoblastoma locus on the Y chromosome and defines the section of the Y chromosome that appears to confer risk for the development of GCT (Lau et al, 2009). It has been proposed that double staining for OCT3/4 and TSPY can help identify dysplastic cells early in patients with DSD (Kersemakers et al, 2005). Additionally, studies have identified that stem cell factor is a potentially useful carcinoma in situ and gonadoblastoma marker (Stoop et al, 2008). Combined analysis on biopsy specimens could help identify individuals at risk (Pleskacova et al, 2010). A consensus statement on the risk associated with various DSD diagnoses and recommended management was released in 2007 and provides guidance for counseling and management of these patients (Table 156-5) (Looijenga et al, 2007; Pleskacova et al, 2010).

Germ Cell Tumors

According to some series, teratomas are the most common testicular tumor in children and consist of variable combinations of the three primitive embryologic germ cell layers (Metcalfe et al, 2003; Pohl et al, 2004; Shukla et al, 2004). They have a characteristic ultrasound appearance that has been described earlier and do not express AFP. In contrast to lesions in men, most prepubertal lesions are benign, consisting of mature elements only (Gobel et al, 1998). The literature contains rare reports of teratomas harboring immature elements and metastasizing (Gobel et al 1998, 2006; De Backer et al, 2008). The combination of AFP measurements and characteristic ultrasound appearance can suggest to the surgeon the presence of teratoma. The preferred treatment for suspected teratomas is partial orchiectomy (see description of technique further on) (Ross and Kay, 2004; Shukla et al, 2004; Ross, 2009; Makari et al, 2010).

Epidermoid cysts are benign lesions in prepubertal boys and may account for more than 15% of prepubertal testis lesions (Pohl et al, 2004). They consist of cysts lined with keratin-producing epithelium. They demonstrate a mixed appearance (hypoechoic and hyperechoic) on ultrasound scan, and AFP levels are normal. They are managed by testis-sparing surgery. No surveillance is required after treatment (Walsh and Rushton, 2000; Ahmed et al, 2010).

TABLE 156-5 Testis Tumor Risk Associated with Specific Disorders of Sex Development and Recommended Management

RISK GROUP	DISORDER	MALIGNANCY RISK (%)	RECOMMENDED ACTION	STUDIES (N)	PATIENTS (N)
High	GD* (+Y)† intra-abdominal	15-35	Gonadectomy‡	12	>350
	PAIS nonscrotal	50	Gonadectomy‡	2	24
	Frasier	60	Gonadectomy‡	1	15
	Denys-Drash (+Y)	40	Gonadectomy‡	1	5
Intermediate	Turner (+Y)	12	Gonadectomy‡	11	43
	17β-HSD	28	Monitor	2	7
	GD (+Y)‡	Unknown	Biopsy§ and irradiation (?)	0	0
	PAIS scrotal gonad	Unknown	Biopsy§ and irradiation (?)	0	0
Low	CAIS	2	Biopsy§ and ???	2	55
	Ovotestis DSD	3	Testis tissue removal (?)	3	426
	Turner (–Y)	1	None	11	557
No (?)	5α-Reductase	0	Unresolved	1	3
	Leydig cell hypoplasia	0	Unresolved	2	

*Gonadal dysgenesis (including not further specified, 46XY, 46X/46XY, mixed, partial, complete).

†GBY region positive, including *TSPY* gene.

‡At time of diagnosis.

§At puberty, allowing investigation of at least 30 seminiferous tubules, with diagnosis preferably based on OCT3/4 immunohistochemistry.

||Question marks indicate that there was a lack of clear recommendation on how to proceed.

CAIS, complete androgen insensitivity syndrome; DSD, disorders of sex development; 17β-HSD, 17β-hydroxysteroid dehydrogenase deficiency; PAIS, partial androgen insensitivity syndrome.

From Looijenga LH, Hersmus R, Oosterhuis JW, et al. Tumor risk in disorders of sex development (DSD). *Best Pract Res Clin Endocrinol Metab* 2007;21:480–95.

YSTs have been variably reported to be the most common or second most common testicular tumor in prepubescent boys. It is the most common malignant prepubertal tumor. YSTs also have been referred to as endodermal sinus tumor or juvenile embryonal carcinoma. They are typically well-demarcated, heterogeneous masses, which may have hemorrhage or necrosis on ultrasound scan. Grossly, they are solid and gray-yellow in color. YSTs express positive stain for periodic acid–Schiff and AFP. Schiller-Duval bodies consist of a central blood vessel surrounded by two layers of tumor cells and are pathognomonic for YSTs (Fig. 156-5). AFP levels are elevated in about 90% of patients and represent a reliable marker for follow-up studies. Most prepubertal cases (>85%) are stage I at diagnosis (Grady et al, 1995; Grady, 2000). When metastases occur, YSTs often exhibit hematogenous spread to the lungs (approximately 20%), without retroperitoneal disease. For these reasons retroperitoneal lymph node dissection (RPLND) plays very little role in prepubertal YST. RPLND is used exclusively for patients with a residual retroperitoneal mass or persistently elevated AFP after chemotherapy and orchiectomy (Ahmed et al, 2010). About 20% of stage I patients experience recurrence after orchiectomy alone. After orchiectomy, stage I patients undergo a rigorous surveillance protocol that includes chest and retroperitoneal imaging and tumor marker assessment (Connolly and Gearhart, 1993). An inguinal incision should be used in all patients with a testicular mass. When a patient with a YST has undergone a trans-scrotal orchiectomy, if the pathologic margins are negative, the patient may be treated as stage I, so long as the cord is resected to the inguinal ring. If a prior trans-scrotal biopsy has been performed, the patient should undergo completion orchiectomy and is considered stage II (Rogers et al, 2004). Hemiscrotectomy is not required in these cases. If enlarged nodes are present on imaging, biopsy is

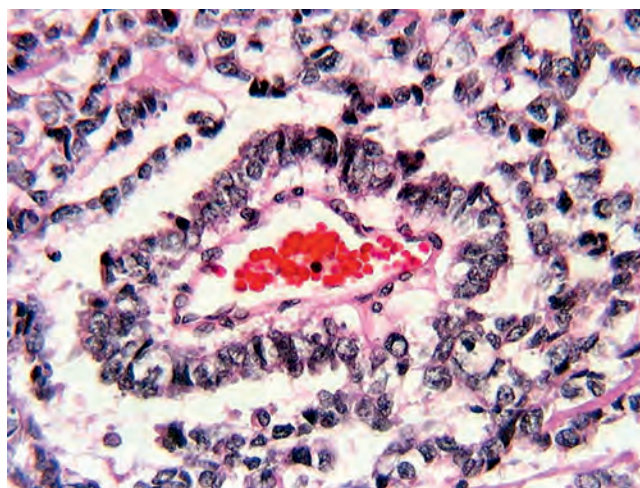


Figure 156-5. Schiller-Duval body. (From Department of Pathology, University of Pittsburgh, <<http://path.upmc.edu/cases/index.html>>.)

indicated. Patients with adenopathy and elevated AFP are treated as stage III. Treatment protocols that use multiagent chemotherapy are recommended by the North American, English, and European groups. Survival, including patients with metastasis, approaches 100% (Mann et al, 1989; Haas et al, 1999; Mann et al, 2000; Lo Curto et al, 2003; Schlatter et al, 2003).

Gonadal Stromal Tumors

Juvenile granulosa cell tumors are described to be the most common testicular tumors affecting neonates. They are easily differentiated from YSTs because they stain negatively for AFP and stain positively for markers such as inhibin α . They have been reported in patients with ambiguous genitalia (Cortez and Kaplan, 1993; Shukla et al, 2004). These lesions are benign and are treated with a testis-sparing approach.

Leydig cell tumors are hormonally active and are associated with precocious puberty. Leydig cell tumors are responsible for about 10% of all cases of precocious puberty. Other causes of precocious puberty include pituitary lesions, Leydig cell hyperplasia, large cell Sertoli cell tumors, and hyperplastic nodules in patients with congenital adrenal hyperplasia. If confusion exists, one can exclude pituitary lesions by demonstrating an increased testosterone level with age-appropriate luteinizing hormone and follicle-stimulating hormone levels. Patients with Leydig cell hyperplasia have normal urinary 17-ketosteroids. Patients with congenital adrenal hyperplasia usually present owing to poor control. Boys commonly present between the ages of 5 and 10 with virilization, although a small percentage present with gynecomastia (Cortez and Kaplan, 1993). The tumors may be small and appear as yellow-brown nodules; histologically, they contain diffuse layers of polygonal cells, and about 40% demonstrate Reinke crystals. Reinke crystals contain lipofuscin pigment and are rod-shaped, crystal-like structures 3 to 20 μm in diameter (Fig. 156-6). Their

purpose is unknown but they are unique to Leydig cell tumors. Elevated testosterone levels are commonly found; the testosterone levels may decline after resection, but the virilizing features may persist. Because of the small size of the lesions, intraoperative localization may be difficult. The lesions are managed with an organ-sparing approach; recurrence is rare (Wegner et al, 1997).

Sertoli cell tumors typically manifest at an earlier age than Leydig tumors (mean age 52 months) and have been reported in children ranging in age from 4 months to 10 years (Thomas et al, 2001). The usual presentation is a painless mass. They have been associated with endocrinologic and genetic syndromes such as Peutz-Jeghers and Carney syndromes. Of these tumors, 10% are hormonally active, and patients may present with virilization or feminization (Gabrilove et al, 1980; Thomas et al, 2001). The tumors are usually firm, well circumscribed, and tan-gray in gross appearance. They may contain areas of hemorrhage or cysts. For infants and children up to age 5, orchiectomy is usually sufficient treatment unless the tumor demonstrates the following features: large size ($>5\text{ cm}$), vascular invasion, necrosis, cellular atypia, or increased mitotic activity. Tumors possessing these features or tumors occurring in children older than age 5 warrant a full staging evaluation. Children with retroperitoneal metastasis may be candidates for RPLND, chemotherapy, and radiation. Large cell calcifying Sertoli cell tumors are a distinct entity seen in prepubertal children and adolescents; they can be managed by simple orchiectomy.

Leukemia and Lymphoma

The most common cancers with metastases to the testis are leukemia and lymphoma. Gonadal disease or relapse in the testis may occur in 20% of patients with bulky disease (Askin et al, 1981). Because of the high success rates of systemic chemotherapy and whole-body irradiation, routine biopsy of the testis is no longer required in these patients (Trigg et al, 2000). Burkitt lymphoma occasionally may manifest as a testicular lesion, and follicular lymphomas may occur primarily in the testis (Lamm and Kaplan, 1974; Finn et al, 1999).

Testicular Microlithiasis

The incidence of testicular microlithiasis in asymptomatic males age 0 to 19 years has been reported to be 2.4% (Goede et al, 2009). A concern that these lesions are harbingers of testicular cancer has prompted some authors to recommend surveillance with ultrasonography (Furness et al, 1998; Leenen and Riebel, 2002). However, more recent studies have determined that screening ultrasound scans are not required for patients without risk factors such as infertility associated with atrophic testis and microlithiasis or testis cancer and contralateral microlithiasis (Holm et al, 2003; Hoei-Hansen et al, 2005). Some more recent publications have questioned if an association between microlithiasis and GCTs exists at all in children (Volokhina et al, 2014). Routine self-examination is the current recommendation by many clinicians.

Management Algorithms

With the recognition that most of these tumors are benign, management of prepubertal testis tumors has evolved away from radical orchiectomy. This evolution began in the 1980s, facilitated by improvements in ultrasonography and the ability for frozen-section analysis to distinguish benign from malignant lesions accurately. At the present time, patients are preferentially treated with excisional biopsy and intraoperative frozen-section analysis followed by an organ-preserving procedure. The exception is when preoperative AFP or intraoperative biopsy suggests malignancy. Ross and colleagues (2002) published their recommended approach after reviewing the results from the Prepubertal Testis Tumor Registry of the Urology Section of the American Academy of Pediatrics (Fig. 156-7).

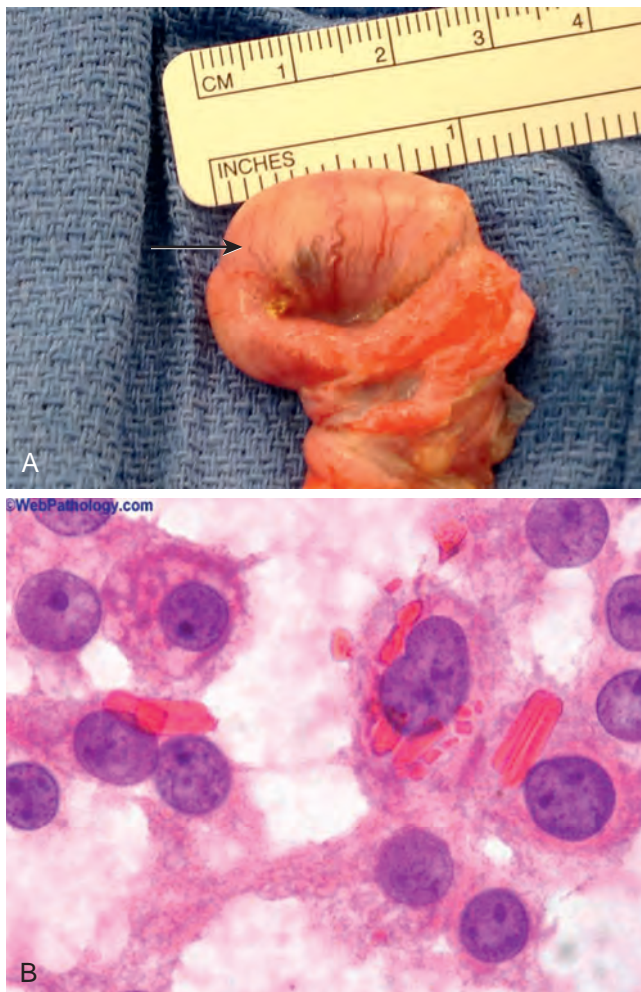


Figure 156-6. A, Leydig cell tumor demonstrating characteristic brown appearance related to abundant lipofuscin pigmentation. B, Reinke crystals. (A, Courtesy Fernando Ferrer, MD; B, from WebPathology.com, <<http://www.webpathology.com>>.)

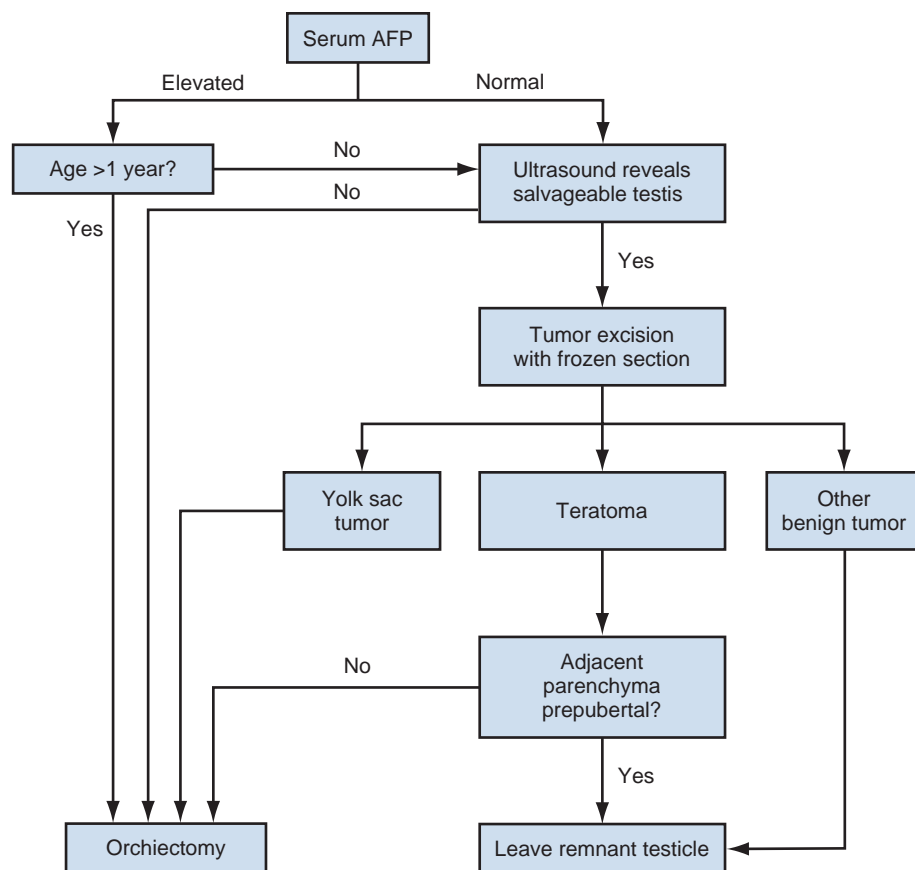


Figure 156-7. Algorithm for the management of prepubertal testis tumors. AFP, α -fetoprotein. (From Ross JH, Rybicki L, Kay R. Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: a summary of the Prepubertal Testis Tumor Registry. *J Urol* 2002;168[4 Pt. 2]:1675–8.)

Testis-Sparing Surgery Technique

Patients undergoing testis-sparing surgery should be counseled regarding the potential need for radical orchiectomy. Preoperative coordination of intraoperative frozen section is required. If the tumor is not palpable, intraoperative sonography should be available.

The testicle is approached through an inguinal incision, and early vascular control of the spermatic cord is achieved with a vessel loop or Penrose drain. The gonad is delivered through the inguinal incision, and the tunica vaginalis is incised to expose the testicle. With lesions involving or immediately adjacent to the tunica albuginea, an elliptical incision beyond the tumor margins should be made in the tunica albuginea. In patients with nonpalpable lesions, I have used intraoperative sonography for localization. Ice may be applied to reduce warm ischemia time. While awaiting intraoperative frozen pathology, the tunica albuginea may be reapproximated with 5-0 running interlocked polydioxanone suture. Intraoperative considerations for testis-sparing surgery include the presence of sufficient normal parenchyma to facilitate closure of the testis. If intraoperative frozen pathology reveals malignancy, a radical orchiectomy is completed. To my knowledge, no reports document a malignant diagnosis on final pathology when intraoperative frozen pathology revealed a benign diagnosis.

PARATESTICULAR RHABDOMYOSARCOMA

Paratesticular RMS arises from the testicular tunicae, epididymis, or spermatic cord. Up to 40% of paratesticular lesions are due to RMS (Shapiro and Strother, 1992). The tumor may invade

KEY POINTS: TESTIS TUMORS

- A large percentage of prepubertal testis tumors are benign, and testicular preservation approaches are often indicated.
- Ultrasonography cannot reliably distinguish benign from malignant lesions.
- AFP is the relevant biomarker in prepubertal testis tumors, and elevated AFP is associated with YSTs.
- AFP levels must be interpreted with caution because physiologic elevation above normal values is common in children younger than 1 year of age.

locally and/or involve the scrotal wall. These tumors represent 7% to 10% of all genitourinary RMS. Peak incidence occurs between ages 1 and 5 years, and a bimodal age distribution has been reported by some authors, with peaks at less than 1 year of age and at 16 years old (Ahmed et al, 2010). In general, patients with paratesticular RMS do better than patients with tumors arising at other sites because (1) most of these tumors are stage I at diagnosis (up to 80%), in contrast to RMS in general, in which only 13% of tumors are stage I; (2) more than 90% of patients have embryonal histology; and (3) patients with more aggressive alveolar histology appear to do better than patients presenting with alveolar histology at other locations (Wiener et al, 1994, 2001; Ferrari et al, 2002; Anderson et al, 2004; Ferrari et al, 2004).

Presentation and Staging

Patients present with a unilateral, firm, painless scrotal mass. The lesion may or may not be distinct from the gonad. Ultrasonography, typically the first interrogation, reveals a hyperechoic, heterogeneous, solid mass. Evaluation of these patients involves assessment of testicular tumor markers, liver function tests, and evaluation of the chest for metastasis using CT. Complete retroperitoneal imaging using double-contrast thin-cut CT (in patients <10 years old, 5 mm; in patients >10 years old, 7 mm) up to the level of the ipsilateral hilum is essential because this is the primary lymphatic landing site, and nodes are positive in 20% of patients.

Treatment

Patients with suspected paratesticular tumors should undergo inguinal exploration with resection of the spermatic cord up to the internal inguinal ring and marking of the stump site. Biopsy should be avoided because it may lead to contamination of the operative field. In cases where biopsy is believed to be essential, isolation of the gonad and the application of an atraumatic tourniquet is required. If frozen-section biopsy is consistent with tumor, the cord should be transected above the tourniquet, and the specimen should be kept in isolation. Any unprotected spill results in upstaging. For patients referred after trans-scrotal biopsy or resection, standard recommendations have included pretreatment re-excision of the surrounding scrotal skin, although more recent data from the German and Italian cooperative groups question the necessity for this (Dall'Igna et al, 2003; Stewart et al, 2003).

The appropriate management of regional lymph nodes is essential in patients with paratesticular RMS. Patients younger than 10 years old who are considered to be in clinical group 1 (total gross resection with negative margins) that have a negative retroperitoneal CT scan do not require further surgical treatment (Wiener et al, 2001). Patients younger than 10 years old who have evidence of positive nodes on CT scan should undergo staging ipsilateral RPLND; if all tumor is removed, the patients are classified as clinical stage II. A nerve-sparing ipsilateral technique is recommended by COG protocols, and in the hands of experienced surgeons, a laparoscopic approach is acceptable (Tomaszewski et al, 2010; Cost et al, 2012). Patients who have grossly positive lymph nodes on staging CT scan can be managed by confirmatory biopsy and are considered to be stage III. As opposed to children younger than age 10, children older than age 10 should always undergo staging ipsilateral RPLND regardless of negative CT findings. Paratesticular tumors rarely involve inguinal lymph nodes. However, when scrotal involvement occurs, inguinal node sampling should be performed. These are not considered "regional nodes," and patients with positive nodes are classified as clinical group IV.

Role of Retroperitoneal Lymph Node Dissection

Original protocols, which frequently used non-nerve-sparing bilateral RPLND for patients with paratesticular RMS, resulted in significant morbidity, such as intestinal obstruction (10%), ejaculatory dysfunction (8%), and lower extremity edema (5%). The IRS III analysis of 121 patients undergoing RPLND for paratesticular RMS compared CT evaluation of lymph nodes with the pathologic results of RPLND (mostly unilateral). Of the 121 patients, 81% had CT-negative lymph node status; of these, 14% had positive nodes on pathologic examination. Patients with negative nodes had a much higher 5-year EFS (96% vs. 69%) (Wiener et al, 1994). After IRS III, strategy shifted, and patients enrolled in IRS IV did not undergo RPLND if they had negative nodes on imaging (Crist et al, 2001). Further comparison between the two studies demonstrated a stage shift in patients categorized as group I, such that 68% of IRS III patients were group I versus 82% in IRS IV. This change was reflective of the reliance of CT only for staging in IRS IV. Comparative analysis between these studies demonstrated that adoles-

cents (>10 years old) were much more likely to have retroperitoneal disease and fared worse than children younger than age 10 (Wiener et al, 2001). As a result of these findings, COG recommendations shifted back such that all children older than 10 years should undergo RPLND.

The Italian and German groups compared the accuracy of CT versus pathologic assessment of the retroperitoneum and found that only 1 of 72 patients with a negative CT scan had positive RPLND. SIOP studies MMT 84 and MMT 89 treated patients with nonmetastatic, paratesticular RMS without RPLND (Stewart et al, 2003). Of 96 patients enrolled, 25 were age 10 or older. Only one patient underwent lymphadenectomy as initial therapy. The 5-year OS was 92%, and EFS was 82%. Relapse occurred in 16 patients, 14 in the retroperitoneum. Eight patients were salvaged with second-line chemotherapy, radiation, and in some cases lymphadenectomy. Although Stewart and colleagues (2003) recognized that these 16 patients may have been understaged, they pointed out that OS was comparable to IRS. Older age and primary tumors greater than 5 cm predisposed to poor outcome. A Surveillance, Epidemiology, and End Results–based study identified 225 cases of paratesticular RMS. Among 173 patients older than 10 years old, lymph node dissection was found to improve the 5-year OS rate from 64% to 86% ($P < .01$). Conversely, patients younger than 10 years fared well regardless of lymph node dissection status; the 5-year OS rate was 100% and 97%, respectively (Dang et al, 2013).

Although some European collaborative groups have avoided RPLND, the COG recommends RPLND for all children older than 10 years in the hope to avoid failure in the retroperitoneum and the burden of second-line therapy. The utility of PET-CT for detecting nodal involvement in RMS has been reported, and it may become a useful adjunct for retroperitoneal staging (Burnette et al, 2013).

Outcomes

Before the advent of multimodal therapy, surgery alone provided for a 2-year EFS of 50% (Sutow et al, 1970). In more recent studies from the SIOP and MMT 84 and MMT 89, the overall 5-year survival was 92%, and the EFS at 5 years was 82% (Stewart et al, 2003). These studies identified age older than 10 years and a primary tumor larger than 5 cm as adverse prognostic factors. The Italian and German cooperative groups jointly reported on 216 patients who had excellent 5-year OS and EFS of 94.6% and 90.7%, respectively (Ferrari et al, 2002). Patients with metastatic disease had a 5-year survival of only 22%. Similar to SIOP, this group has also transitioned away from RPLND. In IRS III, 3-year OS was 96%, and in IRS IV, it was 92% (Crist et al, 1995, 2001).

A unique feature of paratesticular RMS is the good outcome of patients with alveolar histology (Ferrari et al, 2004; Anderson et al, 2004). Why these patients do so well is an unanswered question. Some authors have speculated that the paratesticular location lends itself to earlier diagnosis; it is unclear if PAX fusion status of these tumors may have influenced outcome.

KEY POINTS: PARATESTICULAR RHABDOMYOSARCOMA

- Paratesticular RMS arises from the testicular tunicae, epididymis, or spermatic cord.
- In general, patients with paratesticular RMS have a favorable prognosis in part as a result of the following:
 - More than 80% are stage I at presentation.
 - Greater than 90% are embryonal histology.
 - Better than expected outcomes have been reported for patients with alveolar histology.
- Exploration through an inguinal incision should always be performed in patients suspected to have paratesticular tumors.
- Tumors in children older than age 10 require staging RPLND in COG protocols because of a higher retroperitoneal failure rate.

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The complete reference list is available online at www.expertconsult.com.

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INDEX

- A**
 AAP. See American Academy of Pediatrics
 AAST. See American Association for Surgery of Trauma
 Abdomen
 exiting of
 complications related to, 222
 after laparoscopic and robotic surgery, 210-211
 imaging studies of, for TGCTs, 793-794, 794f
 Abdominal aorta, in retroperitoneum, 775, 775f, 776.e1f, 775.e1f, 775.e2f
 Abdominal CT, 41, 42f-43f
 Abdominal hysterectomy, 1978
 Abdominal incisions, 115
 closure of, 115-117, 116t
 healing of, 115
 Abdominal leak point pressure (ALPP)
 measurement of, 1727, 1727f
 for sling procedure, 1989
 Abdominal masses
 neonatal, 2890
 prenatal imaging of, 2910
 Abdominal paravaginal repair, for pelvic organ prolapse, 1951t-1952t, 1959-1960, 1959f
 Abdominal plain film radiography
 for AKI, 1049
 indications for, 32
 limitations of, 33, 33f
 for pediatric patients, 2916
 technique for, 32
 Abdominal pressure, increased, urinary incontinence during, 1687
 Abdominal sacrocolpopexy, for apical pelvic organ prolapse repair, 1971-1974, 1971f-1973f
 Abdominal surgery, operative team placement for
 retroperitoneal procedures, 198, 199f
 transperitoneal procedures, 198, 198f, 198.e1f
 Abdominal wall
 anterior
 inguinal canal, 1613-1614, 1615f
 internal surface of, 1614, 1616f
 musculature of, 1611-1613, 1613f
 skin and subcutaneous fasciae, 1611, 1612f-1613f
 closure of, for classic bladder exstrophy, 3198-3201, 3199f-3200f
 defects in
 in bladder exstrophy, 3187
 prenatal imaging of, 2910-2911, 2912f
 posterior, flank musculature of, 765-769, 767f-769f, 769t
 in prune-belly syndrome, 3238, 3239f-3240f
 reconstruction of, for prune-belly syndrome, 3246
 Abdominopelvic processes, and sexual pain disorders, 762-763
- Page numbers followed by "f" indicate figures, "t" indicate tables, "b" indicate boxes, and "e" indicate online content.
- Abdominoperineal resection (APR), LIFT after, 1781-1782
 Abdominoscrotal hydrocele, 3387-3388
 Abiraterone, 2792-2793, 2792f-2793f, 2811-2812, 2811f
 Ablative technology, 2727-2737
 Ablative therapy
 adrenal surgery, 1594-1595
 cryoablation. See Cryoablation
 failure of, laparoscopic radical nephrectomy after, 1470
 focal. See Focal ablative therapy
 laparoscopic kidney, 1477-1479, 1494
 for renal tumors, 1484, 1499
 new modalities of, 1495-1499, 1499b
 RCC, 1347t, 1349-1351, 1350t
 RFA. See Radiofrequency ablation
 Abnormal adrenal function disorders, 1555-1556
 ABO blood groups, for renal transplantation, 1076
 ABP. See Androgen-binding protein
 Absorbable stapling techniques, for cutaneous continent urinary diversion, 2339
 comments on, 2342
 postoperative care for, 2342
 right colon pouch, 2339-2340, 2340f
 stapled sigmoid reservoir, 2340-2342, 2341f
 W-stapled reservoir, 2342, 2342f
 Absorbed dose, 26
 Absorbent products
 for bladder emptying/storage failure, 2082
 for urinary incontinence, in geriatric patients, 2099.e6
 Absorption, of ultrasound waves, 66-67, 67f
 Absorption effects, of anesthesia, 2966
 Absorptive hypercalciuria (AH), 1183-1184, 1209, 1210t
 agents for, 1224, 1225b
 orthophosphate for, 1225
 sodium cellulose phosphate for, 1224
 thiazides for, 1223-1224
 guidelines for, 1224
 type II, 1224-1225
 ACC. See Adrenal cortical carcinoma
 Access to care, 85
 Accreditation, for ultrasonography, 84
 ACE. See Angiotensin-converting enzyme
 Acetaminophen, for pediatric patients, 2957, 2957t
 Acetazolamide, in stone formation, 1197
 Acetohydroxamic acid, for infection stones, 1230-1231
 Acetylcholine (ACh)
 in bladder function, 1645
 botulinum toxins and, 1682-1683, 1874.e3
 for detrusor underactivity, 1817
 mechanism of action of, 1838
 in ureteral function, 990-991
 N-Acetylcysteine, 1175
 for ATN prevention, 1053
 for CKD prevention, 1061
 ACh. See Acetylcholine
- Acid-base balance
 pneumoperitoneum effects on, 214
 renal role in, 1023-1025, 1027b
 Acid-base disorders, renal pathophysiology involved in, 1025-1027, 1025b, 1026t, 1027b
 Acidemia, 1025
 Acidosis
 after augmentation cystoplasty, 3351
 metabolic, renal pathophysiology involved in, 1025-1026, 1025b
 respiratory, 1012
 RTA. See Renal tubular acidosis
 Acne inversa. See Hidradenitis suppurativa
 Acontractile detrusor, 1692-1693, 1729
 Acoustical shadowing, 67, 67f
 Acquired immunodeficiency syndrome (AIDS)
 Kaposi sarcoma in. See Kaposi sarcoma
 lower urinary tract dysfunction and, 1785-1786
 Acquired renal cystic diseases (ARCD), 3038-3040, 3040b
 clinical features of, 3038-3039
 etiology of, 3038
 evaluation of, 3039
 histopathology of, 3013, 3039
 treatment of, 3039-3040
 Acrosome, of spermatozoa, 535
 ACT. See Adjustable continence therapy
 ACTH-dependent Cushing syndrome, 1534-1535, 1534f
 Cushing disease, 1534
 ectopic ACTH syndrome, 1534, 1535t, 1539
 treatment, 1538-1539, 1538.e1f
 ACTH-independent bilateral macronodular adrenal hyperplasia (AIMAH), 1535
 ACTH-independent Cushing syndrome, 1535, 1539
 Actin, in thin filaments, 1641
 Actinomyosin cross-bridge cycling, 1642-1643, 1643b, 1643f
 Action potentials
 of smooth muscles, of bladder, 1644-1645, 1644f
 of ureteral muscle cells, 980-982, 981f-983f
 Active surveillance, for RCC, 1347t, 1351-1352, 1352t
 Active surveillance of prostate cancer
 biomarkers, 2635
 candidate identification for, 2633
 extended prostate biopsy for, 2634
 future research needs for, 2639-2640
 imaging for, 2634-2635
 localized, 2611-2613
 patient and disease factors in, 2635-2638
 patient and physician perceptions, 2635-2636
 psychosocial aspects, 2637-2638
 progression and triggers in, 2634-2635
 repeat prostate biopsy for, 2634
 selection criteria for, 2636, 2637t
 strategies for, 2636-2637
 treatment compared with, 2637t, 2638-2639, 2638f

- Activin, 516-518, 517f
- Activities of daily living (ADLs), of geriatric urology patient, 2086
- Activity product ratio, 1174
- Acupuncture
for CP/CPPS treatment, 325
for PE, 700.e1
- Acute adenolymphangitis (ADL), as filariasis clinical manifestation, 443
- Acute bacterial prostatitis, 310, 313
- Acute disseminated encephalomyelitis (ADEM), lower urinary tract dysfunction and, 1786
- Acute focal or multifocal bacterial nephritis, 278-279, 279f
- Acute glomerulonephritis (AGN), AKI caused by, 1043, 1044b
- Acute interstitial nephritis (AIN), AKI caused by, 1043-1044, 1044b
- Acute kidney injury (AKI), 1054b, 2866-2868
definition of, 1041, 1042t
differential diagnosis of, 1048-1049, 1048f-1049f, 1049t
imaging studies for, 1049
renal vein thrombosis, 1049
epidemiology and classification of, 1041-1042
intrinsic renal disease, 1043-1044, 1044b.
See also Acute tubular necrosis
postrenal, 1042
prerenal, 1042-1043, 1042b
etiology and evaluation of, 2867-2868, 2867b, 2868t
management of, 1049-1050, 1050b, 2868, 2868b
conservative, 1051-1052, 1051b
dialytic, 1052-1053
pharmacologic, 1050-1051
prevention of, 1053
prognosis of, 1053, 1053f
staging of, 1042t
- Acute physiology and chronic health evaluation (APACHE) score, 540
- Acute pyelonephritis, 275-278, 276f-277f, 278t, 285
- Acute rejection, of renal transplantation, 1084
- Acute renal abscess, and UTIs, 2936
- Acute renal injury, fractional excretion of sodium for, 1090
- Acute schistosomiasis, 436
- Acute scrotum, 3388-3393
epididymitis. *See* Epididymitis
pain sources, 3393
spermatic cord torsion. *See* Spermatic cord torsion
torsion of appendix testis and epididymis, 3392
- Acute transverse myelitis, lower urinary tract dysfunction with, 1778-1779
- Acute tubular necrosis (ATN)
incidence and etiology of, 1044, 1045b-1046b
intrinsic/extrinsic toxic-related, 1045-1046
management of, 1049-1050, 1050b
conservative, 1051-1052, 1051b
dialytic, 1052-1053
pharmacologic, 1050-1051
natural history of, 1046
pathophysiology of, 1046-1048, 1047f
pigment nephropathy/rhabdomyolysis in, 1044-1045
prevention of, 1053
prognosis of, 1053, 1053f
- Acute urinary retention (AUR)
age and, 2457, 2457f
with benign prostatic hyperplasia, 2455-2459, 2501-2502
epidemiology
of analytical, 2457-2459
of descriptive, 2456-2457, 2456t
- Acute urinary retention (AUR) (*Continued*)
lower urinary tract symptoms with, 2457, 2457t
management of, 2501-2502, 2501f
prevention with medical therapy, 2502
prostate volume in, 2458-2459, 2458f-2459f
serum PSA in, 2458-2459, 2458f-2459f
urodynamic parameters of, 2457-2458, 2458f
- AD. *See* Androgen deficiency; Atopic dermatitis
- Adalimumab, for BPS/IC oral therapy, 355
- ADAM questionnaire. *See* Androgen Deficiency in Aging Male questionnaire
- Adaptive immune system, 449-450, 449f
- Addison disease. *See* Decreased adrenal function disorders
- ADEM. *See* Acute disseminated encephalomyelitis
- Adenine, 459.e1-459.e3, 459.e2f
- Adenocarcinoma
of bladder, in pediatric patients, 3589
prostate. *See* Prostate adenocarcinoma
of rete testis, 812
of Skene gland, urethral diverticula differentiated from, 2162, 2162f
of upper urinary tract, 1371
- Adenohypophysis. *See* Anterior pituitary
- Adenomas
adrenal. *See* Adrenal adenomas
of kidneys
metanephric, 1303-1304, 1303f-1304f, 1304b
papillary, 1302-1303, 1303b
prostatic, enucleation of
retropubic simple prostatectomy for, 2538-2539, 2538f-2539f
in robot-assisted laparoscopic simple prostatectomy, 2541
suprapubic prostatectomy for, 2539-2540, 2539f-2540f
- Adenomatoid tumors, of testicular adnexa, 813
- Adenosine, in ED, 626
- Adenosine triphosphate (ATP)
in ATN, 1046
in ureteral function, 992-993
urothelium release of, 1639-1640
- Adenosquamous carcinoma, of penis, 875
- Adenylyl cyclase, in ED, 627
- ADH. *See* Antidiuretic hormone
- ADHD. *See* Attention-deficit/hyperactivity disorder
- Adhesion, in RCC, 1327b
- Adjustable balloons (ProAct), for male postprostatectomy SUI injection therapy, 2065-2066, 2067f, 2068t
- Adjustable continence therapy (ACT), for SUI injection therapy
female, 2060-2061, 2061f
male postprostatectomy, 2065-2066, 2067f, 2068t
- Adjuvant androgen deprivation
with radiation therapy, for locally advanced prostate cancer, 2763-2765
with radical prostatectomy, for locally advanced prostate cancer, 2762-2763
- Adjuvant chemotherapy, for muscle-invasive bladder cancer, 2231-2233
randomized trials of, 2231-2233, 2232t
- Adjuvant radiation therapy
for biochemical recurrence after radical prostatectomy, 2775-2777, 2775f-2776f
salvage radiation therapy *versus*, 2777
for localized prostate cancer, 2622
side effects of, 2623
after radical prostatectomy, for locally advanced prostate cancer, 2761-2762, 2761f
- ADL. *See* Acute adenolymphangitis
- ADLs. *See* Activities of daily living
- ADPKD. *See* Autosomal dominant polycystic kidney disease
- Adrenal adenomas
as benign lesions, 1535, 1562-1563, 1563b, 1563f
MRI of, 47
- Adrenal cortex, physiology of, 1529-1531, 1530f, 1531t
- Adrenal cortical carcinoma (ACC)
malignant lesions, 1531-1566, 1557f, 1557t-1558t, 1558b, 1559f, 1560b
MRI of, 47, 48f
pediatric, 1560
surgery, 1531-1566, 1581b
- Adrenal cyst, as benign lesion, 1565-1566, 1566b, 1566f
- Adrenal disorders, 1528, 1575-1576
of abnormal adrenal function, 1555-1556
anatomy and, 1528-1529, 1529b, 1528.e1f
benign lesions, 1558b
adenoma, 1535, 1562-1563, 1563b, 1563f
adrenal cyst, 1565-1566, 1566b, 1566f
ganglioneuromas, 1565, 1565b
myelolipoma, 1564-1565, 1564f, 1565b
oncocytoma, 1563-1564, 1564b
pheochromocytoma. *See* Pheochromocytoma
of decreased adrenal function, 1555, 1556b
clinical characteristics, 1553-1555, 1554t
diagnostic tests, 1555
overview and epidemiology, 1553
pathophysiology, 1553, 1554f
prognosis, 1555
treatment, 1555, 1556t
embryology and, 1528-1529
histology and, 1529, 1530t, 1528.e1f
historical background, 1528
of increased adrenal function
Cushing syndrome. *See* Cushing syndrome
pheochromocytoma. *See* Pheochromocytoma
primary aldosteronism. *See* Primary aldosteronism
malignant lesions, 1558b
adrenal cortical carcinoma, 1531-1566, 1557f, 1557t-1558t, 1558b, 1559f, 1560b
malignant pheochromocytomas, 1545-1547, 1552
metastases, 1560-1562, 1561f, 1562b
neuroblastoma. *See* Neuroblastoma
pheochromocytoma, 1545-1547, 1552
physiology and, 1529, 1532b
adrenal cortex, 1529-1531, 1530f, 1531t
adrenal medulla, 1531, 1532f, 1533t
- Adrenal glands, 1519, 1520f, 1526-1528, 1527b
anatomy, 1519, 1528-1529, 1529b, 1578, 1578f, 1528.e1f
embryology, 1522-1525, 1525f, 1528-1529
histology, 1525f, 1529, 1530t, 1528.e1f
nerves, 1522, 1524f, 1529
physiology, 1529, 1532b
adrenal cortex, 1529-1531, 1530f, 1531t
adrenal medulla, 1531, 1532f, 1533t
radiology, 1525-1526, 1526f
surgical landmarks, 1519, 1521f-1522f
vasculature, 1519-1522, 1522f-1523f, 1529, 1578, 1578f, 1528.e1f
- Adrenal hemorrhage, neonatal, 2891
- Adrenal incidentalomas
adrenal surgery for, 1581b
evaluation of, 1566, 1567t
- Adrenal insufficiency. *See* Decreased adrenal function disorders

- Adrenal medulla, physiology of, 1531, 1532f, 1533t
- Adrenal sex steroid hypersecretion, in evaluation of adrenal masses, 1574
- Adrenal surgery, 1577, 1595b
- ablative therapy, 1594-1595
 - complications, 1593-1594, 1593b-1594b
 - for Conn syndrome, 1581, 1581b
 - for Cushing syndrome, 1581, 1581b
 - evolution of, 1577-1578
 - future of, 1595
 - hand-assisted, 1590
 - indications, 1575, 1575f, 1576b, 1578-1580, 1578b-1579b
 - laparoendoscopic single-site, 1591
 - laparoscopic adrenalectomy, 1579-1580, 1579b
 - left, 1586-1587, 1586f-1589f, 1589-1590
 - outcomes, 1592-1593
 - retroperitoneal approach, 1589-1590, 1589f-1590f, 1592-1593
 - right, 1587-1588, 1588f, 1590, 1590f
 - transperitoneal approach, 1585-1590, 1586f-1588f, 1592-1593
 - natural orifice transluminal endoscopic surgery, 1591-1592
 - open adrenalectomy, 1581
 - anterior transabdominal approach, 1583-1584, 1583f-1584f
 - flank retroperitoneal approach, 1581-1582, 1581f-1582f
 - left, 1583-1584, 1583f-1584f
 - outcomes, 1592
 - posterior lumbodorsal approach, 1582-1583, 1583f
 - thoracoabdominal approach, 1584-1585, 1585f
 - outcomes, 1592-1593
 - partial adrenalectomy, 1592
 - for pheochromocytoma, 1580-1581, 1581b
 - preoperative and perioperative management for, 1580-1581, 1581b
 - robot-assisted adrenalectomy, 1590, 1590f-1591f, 1593
 - surgical anatomy, 1578, 1578f
- Adrenal tumors. *See also* Adrenal surgery
- ablative therapy for, 1594-1595
 - Cushing syndrome and, 1535
 - evaluation of, 1566
 - adrenal incidentalomas, 1566, 1567t
 - assessment of function, 1571-1575, 1572b, 1573f, 1574t, 1575b
 - biopsy, 1570-1571, 1571b, 1571f
 - imaging, 1567-1570, 1568f-1569f, 1569b
 - size and growth, 1569-1570, 1570b, 1570f, 1579
 - surgical indications, 1575, 1575f, 1576b
 - MRI of, 47-49, 48f-51f, 52t
 - pediatric, neuroblastoma. *See* Neuroblastoma
 - prenatal, 2885-2886
- Adrenalectomy. *See* Adrenal surgery
- Adrenergic agonists, for stress urinary incontinence, 1671
- α -Adrenergic agonists
- for stress urinary incontinence in women, 1867
 - ureteral response to, 987-988, 991-992
- β -Adrenergic agonists
- for overactive bladder, 1803-1804
 - for stress urinary incontinence in women, 1867-1868
 - ureteral response to, 987, 991-992, 1002
- α -Adrenergic antagonists, 664
- adverse events with, 2481
 - for benign prostatic hyperplasia, 2473-2482. *See also* Benign prostatic hyperplasia, α -adrenergic blockers for
 - for bladder and bowel dysfunction, 3308
 - bladder outlet obstruction effects of, 2480
 - classification of, 2474-2475, 2474t
 - comparison of, 2481
 - for CP/CPPS treatment, 322-323
 - for detrusor underactivity, 1818
 - in elderly, 2480
 - to facilitate bladder emptying, 1872-1874
 - to facilitate bladder filling and urine storage, 1839t, 1853-1854
 - with antimuscarinics, 1859-1860
 - with 5 α -Reductase inhibitors, 1861
 - intraoperative floppy iris syndrome, 2481
 - for PE, 700.e1
 - sexual side effects of, 2480
 - transurethral microwave therapy *versus*, 2520
 - ureteral response to, 991-992, 1001-1002
- β -Adrenergic antagonists
- to facilitate bladder filling and urine storage, 1839t, 1854-1855
 - with antimuscarinics, 1860
 - for stress urinary incontinence in women, 1868
 - ureteral response to, 991-992
- Adrenergic receptors
- pharmacology of
 - α -adrenergic receptors, 1670-1671, 1671f
 - β -adrenergic receptors, 1670
 - in ureteral function, 991-992
- Adrenocorticotrophic hormone. *See* ACTH-dependent Cushing syndrome
- Adriamycin. *See* Doxorubicin
- ADT. *See* Androgen deprivation therapy
- Adult stem cells (ASCs)
- for female SUI injection therapy, 2061-2062
 - for tissue engineering, 485, 485f
- AdvaSeal-S, 207.e2
- Adverse reactions, of TT, 546-547, 547b
- Aerobactin, 2928-2930
- Afferent neuropeptides, lower urinary tract and, 1671-1673
- endotherelins, 1672-1673
 - prostanoids, 1672
 - tachykinins, 1672, 1672t
- Afferent pathways
- in bladder emptying, 1901
 - in bladder storage, 1900-1901, 1901f
 - in detrusor underactivity, 1810-1812, 1812f
 - in lower urinary tract
 - cannabinoids, 1656
 - functional properties of, 1651-1654, 1653f
 - modulators of, 1654-1656
 - neuromodulation of, 1680
 - nitric oxide in, 1654, 1655f
 - pelvic organ interactions with, 1656-1657, 1657f
 - properties of, 1650
 - purinergic signaling, 1654, 1656f
 - spinal cord pathways of, 1650-1651, 1652f, 1652t
 - transient receptor potential cation channels, 1654-1656
 - in overactive bladder and detrusor overactivity, 1797-1798
- Affordable Care Act. *See* Patient Protection and Affordable Care Act of 2010
- Afinitor. *See* Everolimus
- AFP. *See* α -Fetoprotein
- African plum, for benign prostatic hyperplasia, 2500
- Age and aging
- acute urinary retention and, 2457, 2457f
 - biology and principles of, 2083-2085
 - demographics of, 2085, 2086f-2087f
 - detrusor muscle and, 1810, 1811f
 - HPG axis effects of, 519
 - lower urinary system and, 2084-2085
 - lower urinary tract dysfunction and, 1679-1680, 1680b, 1793, 3297-3298
 - orthoptic urinary diversion and, 2349
 - and PD, 723
 - physiologic, 2083-2084
 - prostate cancer diagnosis and, 2545
 - renal calculi and, 1171, 1255-1256
 - sperm chromosomal anomalies related to, 528
 - sperm genetic mutations related to, 528-529, 528b
 - ureter physiology effects of, 1002, 1002f-1003f
 - urinary incontinence and, 1747-1748
 - conservative interventions for, 1894-1895
 - UTUC prognosis and, 1374
 - UTUC variations and, 1365
 - vesicoureteral reflux and, 3135, 3135t
 - acquired scar and, 3148
 - resolution by, 3153, 3154f
- Aging Male Symptom (AMS) scale, 541, 541t
- AGN. *See* Acute glomerulonephritis
- AH. *See* Absorptive hypercalciuria
- AIDS. *See* Acquired immunodeficiency syndrome
- AIMAH. *See* ACTH-independent bilateral macronodular adrenal hyperplasia
- AIN. *See* Acute interstitial nephritis
- Air embolism. *See* Gas embolism
- Air-charged catheters, for urodynamic studies, 1723-1724
- AirSeal System, 203, 203.e2f
- AJCC and UICC staging systems. *See* American Joint Committee on Cancer and Union Internationale Contre le Cancer staging system
- AKI. *See* Acute kidney injury
- ALARA. *See* As Low As Reasonably Achievable
- Albumin, 565-566
- testosterone bound to, 539
- Albuminuria, in CKD, 1053-1054, 1054t, 1061
- Alcohol use
- benign prostatic hyperplasia and, 2441
 - and ED, 638, 638t
 - patient history of, 7-8
 - prostate cancer and, 2552
- Aldosterone hypersecretion, in evaluation of adrenal masses, 1573, 1573f
- Alfuzosin
- for benign prostatic hyperplasia, 2478-2479, 2479t
 - to facilitate bladder emptying, 1874.e1
- Aligning catheters, for PFUIs, 930-931
- Alkalemia, 1025
- Alkalosis
- after augmentation cystoplasty, 3352
 - metabolic, 1026, 1026t
 - respiratory, 1012-1013
- Allergic dermatitis
- atopic dermatitis, 389-390, 389f
 - contact dermatitis, 390, 391f
 - differential diagnosis, 389b
 - erythema multiforme and Stevens-Johnson syndrome, 390, 391f-392f
- Allergies, patient history of, 9
- Allium stents, 127

- Allocation, of kidneys for transplant candidates, 1074-1076
- Allogeneic hematopoietic stem cell transplantation, for RCC, 1506-1507, 1507t
- Allograft
processing of, 1947
for pubovaginal sling, 1991
outcomes of, 1999-2002, 2000t-2001t
renal, preparation of, 1080, 1080f
source of, 1946-1947
- Allograft nephrectomy, 1086-1087
- Allopurinol
for CP/CPPS treatment, 324
for hyperuricosuric calcium nephrolithiasis, 1225, 1227
- Alport syndrome, 2859
- ALPP. See Abdominal leak point pressure
- Alprostadil, 665
- Altered nuclear transfer, stem cells from, for tissue engineering, 483.e1
- Altered prostate host defense, in prostatitis etiology, 307
- Alternate-form reliability, 96, 96t
- Alternative hormone treatments, in ED, 660
- Alternative therapies
for ED, 667
for mesh complications in pelvic reconstructive surgery, 2047
- Alum, for hemorrhagic cystitis, 189-190
- Alveolar RMS, 3582-3583, 3583b, 3583f-3584f
- Alvimopan (Entereg), 108
- Alzheimer disease, and ED, 631
- AMACR gene. See α -Methylacyl coenzyme A racemase gene
- Amantadine, for delayed ejaculation, 707
- Ambiguous genitalia, 3495-3496, 3496f
- Ambulatory urodynamics, 1737
clinical utility of, 1737-1738
for detrusor underactivity, 1737
for overactive bladder evaluation, 1805
in pediatric patients, 3131-3133, 3132f
- Amebiasis, of genitourinary tract, 446
- American Academy of Pediatrics (AAP), vesicoureteral reflux guidelines of, 3144, 3144t
- American Association for Surgery of Trauma (AAST), Organ Injury Severity Scale for Kidney, 1149t
- American Joint Committee on Cancer and Union Internationale Contre le Cancer (AJCC and UICC) staging systems
for penile squamous cell carcinoma, 852-854, 853t, 854b, 854f
for RCC, 1336-1338, 1337t
prognosis and, 1339-1341, 1339t
for testicular tumors, 791t-792t, 793
for UTUC, 1372-1374, 1373t-1374t
- American Recovery and Reinvestment Act of 2009, 98
- American Society of Anesthesiologists (ASA) recommendations for prevention of perioperative peripheral neuropathies, 114-115, 114b
risk classification system of, 100-101, 101b
- American Urological Association (AUA)
best practice statement on antibiotic prophylaxis, 105-106, 106t-107t, 139-140, 158
best practice statement on use of VTE prophylaxis, 108-109, 109t, 223
injectable agent clinical practice guidelines from, 2054
MH guidelines of, 183, 185-187, 186f
RCC management guidelines of, 1352-1353, 1352t-1353t, 1354f-1355f
- American Urological Association Symptom Index, 551
- AMH. See Asymptomatic microhematuria; Müllerian-inhibiting substance
- Amiloride, for absorptive hypercalciuria, 1224
- Amino acids, PCT reabsorption of, 1015
- γ -Aminobutyric acid (GABA)
bladder dysfunction and, 1859
in efferent pathways to bladder, 1658
- Aminocaproic acid, for hemorrhagic cystitis, 190
- Aminoglutethimide, 2791
- Aminoglycosides
preoperative prophylaxis with, 106t-107t
prophylaxis with, for uncomplicated urologic procedures, 261t-262t
for UTIs, 255t-258t, 259-260, 259f
- Aminopenicillins, for UTIs, 256t-258t, 259
- Aminophylline, for ureteral relaxation, 1001
- Amitriptyline (Elavil)
for BPS/IC oral therapy, 352-353, 353t
urethral function effects of, 1005
- AML. See Angiomyolipoma
- Ammonium acid urate stones, 1195-1196
medical management of, 1231, 1231b
- Amniotic fluid, 2875
pulmonary development and, 2978-2979
- Amoxicillin, for UTIs, 256t-258t, 259, 267t, 296t
- Amoxicillin/clavulanate, preoperative prophylaxis with, 106t-107t
- Ampicillin
preoperative prophylaxis with, 106t-107t, 2959t
for UTIs, 256t-258t, 259, 278t, 296t
- Ampicillin/sulbactam, preoperative prophylaxis with, 106t-107t
- Amplatz dilators, for upper urinary tract collecting system, 168, 168f
- Amputation
penile, traumatic, 2381-2382, 916.e1, 916.e1f
of penis, for penile cancer, 856
- AMS scale. See Aging Male Symptom scale
- Amyloidosis
lower urinary tract dysfunction and, 1792
of urethra, reconstructive surgery for, 913
- Anaerobes, in urinary tract, 242
- Anaerobic bacteria, in prostatitis microbiology, 306
- Anal perineum, female, 1604
- Anal sphincter, 1604
- Anal triangle
female, 1603
male, 1617f-1619f, 1628-1629
- Analgesia
immediate postoperative, 112
for pediatric patients, 2958b
children of Jehovah's Witnesses, 2955
children with asthma, 2954-2955
children with CAH, 2955-2956
children with cancer, 2955
children with spina bifida, 2955, 2955f
children with URIs, 2954, 2954f
formerly premature infants, 2955
immunizations and, 2953-2954
for laparoscopic and robotic surgery, 2966, 2966f
neurotoxicity induced by, 2952-2953
NPO guidelines for, 2953
postoperative pain management with, 2956-2958, 2956t-2957t
preoperative preparation for, 2953
psychological and emotional preparation for, 2952
regional, 2956
regional anesthesia, 2956
risk factors for, 2952
- Analgesia (Continued)
for prostate biopsy, 2585
for urethroplasty, postoperative, 3417
urothelial cancer and, 2187
UTUC risk and, 1366
- Analgesics, for BPS/IC oral therapy, 355-356
- Anaplastic Wilms tumor, 3571
- Anastomosis instrumentation, for laparoscopic and robotic surgery, 207, 208f, 210, 207.e2f, 207.e3
- Anastomotic complications, with laparoscopic radical prostatectomy, 2680
- Anatomic abnormalities, and UTIs, 2931
- ANCA. See Antineutrophil cytoplasmic antibody
- Androgen axis
androgen sources in, 2788-2789, 2789t
ablation of, 2789
blockade mechanisms for, 2789-2793, 2789b
response to, 2793
molecular biology of, 2787-2788, 2787f-2788f
- Androgen deficiency (AD)
cerebral vascular disease association with, 548
CVD association with, 547-548
evidence-based integrated approach to definition of, 538
diagnosis of, 541-542, 541t, 542b, 543f
epidemiology of, 538-539, 539b-540b
etiology, 539-541
physiology of, 539-541, 540b, 540t
treatment of, 542-547, 543f, 544b-545b, 544t, 547b
- Androgen Deficiency in Aging Male (ADAM) questionnaire, 541, 541t
- Androgen deprivation therapy (ADT), 538, 547
adjuvant. See Adjuvant androgen deprivation
for biochemical recurrence after radiation therapy, 2782-2783
for biochemical recurrence after radical prostatectomy, 2777-2778
salvage radiation therapy with, 2774-2775
continuous, 2798-2801
with external beam radiation therapy
for localized prostate cancer, 2620
for locally advanced prostate cancer, 2619-2620, 2706
immediate versus delayed, 2801
intermittent versus continuous, 2801-2802, 2802f
for localized prostate cancer, 2624, 2624.e1b
immediate versus delayed, 2799, 2800f
for localized prostate cancer with radiation therapy, 2623
duration of, 2706
pelvic lymph node treatment and, 2706
for locally advanced prostate cancer, 2766-2767
immediate versus delayed, 2800-2801, 2801f
intermittent, 2766-2767
quality of life with, 2767
neoadjuvant. See Neoadjuvant androgen deprivation
radiation therapy with, 2705-2706, 2707t
before radical prostatectomy, 2618
watchful waiting with, 2746
- Androgen receptor-dependent chromatin remodeling, in prostate growth regulation, 2412-2413
- Androgen receptors (AR), 539, 2412b
in benign prostatic hyperplasia, 2427
chaperonin binding, 2408-2409
defects of, 3491-3492
dimerization of, 2410
DNA-binding domain, 2409-2410
function of, 2414b

- Androgen receptors (AR) (*Continued*)
 ligand-binding domain, 2410
 modulation of, for castration-resistant prostate cancer, 2812-2813, 2812f
 nuclear localization of, 2410
 post-translational modifications of, 2410
 in prostate cancer, 2556
 in prostate growth regulation, 2408-2412, 2408f-2409f
 structure of, 2414b
 transcriptional activation domains, 2397b, 2410-2412, 2411f
- Androgen-binding protein (ABP), 523
- Androgens, 516-517, 533-534. *See also specific hormones*
 and HSDD, 759, 760t, 759.e1-759.e2, 759.e1t
 lower urinary tract and, 1673
 manipulation of, for benign prostatic hyperplasia, 2482-2487. *See also* Benign prostatic hyperplasia, androgen manipulation for
 in nuclear matrix, 2413-2414
 plasma binding proteins of, 2401f, 2403
 in prostate cancer, 2549, 2553, 2554f
 in prostate growth, 2401-2402, 2402f
 metabolism of, 2405-2406, 2405f, 2406t
 regulation of, 2404-2405, 2404f
 role in benign prostatic hyperplasia, 2426-2428, 2427t
 sources of, 2788-2789, 2789t
 ablation of, 2789
 stromal-epithelial interaction regulation by, 2406
 synthesis inhibition, 2791-2793
- Andropause, 519
- Androstenedione, 2402, 2402f
- Anejaculation
 causes of, 702
 and neurologic disorders, 704
 treatment of, 705-707, 706f
- Anemia, hormonal therapy and, 2795
- Anesthesia
 in geriatric urology patient, 2090
 for laparoscopic and robotic surgery, complications related to, 220.e1
 for laparoscopic kidney surgery, 1447
 for laparoscopic radical prostatectomy, 2665-2666
 for pediatric patients, 2958b
 children of Jehovah's Witnesses, 2955
 children with asthma, 2954-2955
 children with CAH, 2955-2956
 children with cancer, 2955
 children with spina bifida, 2955, 2955f
 children with URIs, 2954, 2954f
 formerly premature infants, 2955
 immunizations and, 2953-2954
 for laparoscopic and robotic surgery, 2966, 2966f
 neurotoxicity induced by, 2952-2953
 NPO guidelines for, 2953
 postoperative pain management with, 2956-2958, 2956f-2957t
 preoperative preparation for, 2953
 psychological and emotional preparation for, 2952
 regional, 2956
 risks of, 2952
 for percutaneous access to upper urinary tract collecting system, 158
 for percutaneous nephrolithotomy, 1277-1278
 pregnancy precautions for, 104
- Anesthesia (*Continued*)
 preoperative considerations for, 110
 mode selection, 110-112
 pain management, 112
 pubovaginal sling procedure, 1993
 for retropubic radical prostatectomy, 2644-2645
 for scrotal surgery, 946
 for shock wave lithotripsy, 1267-1268
 for simple prostatectomy, 2537
 for vasectomy, 948
- Anesthetic lubricant, for urethral catheterization, 121-123
- Aneurysm, as laparoscopic and robotic surgery contraindication, 196
- Angioembolization, for renal injuries, 1151, 1152f
- Angiogenesis
 in castration-resistant prostate cancer, 2816-2817
 in RCC, 1325t, 1326-1327
 for regenerative medicine, 486, 486.e3
 in UTUC, 1375
- Angiography
 in adrenal radiology, 1526
 ATN prevention and, 1053
 CTA. *See* Computed tomography angiography
 MRA. *See* Magnetic resonance angiography
 for renovascular hypertension screening, 1032, 1032b
- Angiokeratomas of Fordyce, 415, 416f-417f
- Angiolymphatic system, urothelial cancer invasion of, 2192
- Angiomyolipoma (AML)
 in pediatric patients, 3580-3581, 3581f
 renal, 50, 55f, 1306-1309, 1307f, 1309b
- Angioplasty, renal artery, for renovascular hypertension, 1036-1039, 1037b, 1039b, 1040f
- Angiotensin, urethral function effects of, 1004
- Angiotensin II (AT2)
 in CKD, 1057
 renal vascular tone control by, 1009
 in tubulointerstitial fibrosis, 1100
- Angiotensin receptor blockers (ARBs)
 AKI caused by, 1042
 for CKD, 1062, 1063t
 for renovascular hypertension, 1090
- Angiotensin-converting enzyme (ACE), 1100
- Angiotensin-converting enzyme (ACE) inhibitors
 AKI caused by, 1042
 for CKD, 1062, 1063t
 for renovascular hypertension, 1090
- Anhydrous ethanol, for prostatic injections, 2534.e3
- Animal bites, of penis, 2381
- Animal models, laparoscopic training with, 224.e2-224.e3
- Annexin A3, as prostate cancer biomarker, 2575
- Anomalous kidneys, percutaneous access to, 168-170, 170f
- Anorectal defects
 in bladder exstrophy, 3187
 urinary fistula with, 3270, 3270f
- Anorectal malformation, 3289-3290
 pathogenesis of, 3290
 presentation of, 3289-3290, 3290b, 3291f
 specific recommendations for, 3290
- Anorectal triangle, 1940f, 1941
- ANP. *See* Atrial natriuretic peptide
- Antegrade approach, to upper urinary tract collecting system
 advanced guidance for, 165-166
 blind access, 166, 166f
- Antegrade approach, to upper urinary tract collecting system (*Continued*)
 fluoroscopic guidance for, 163-165, 163f-165f
 needles and guidewires for, 161-162, 162f
 ultrasonographic guidance for, 162-163, 163f
- Antegrade endopyelotomy, percutaneous. *See* Percutaneous antegrade endopyelotomy
- Antegrade endoscopy, for UTUC, 1372
- Antegrade pyelography
 for genitourinary tuberculosis diagnosis, 427
 of ureteral stricture disease, 1129
 for ureterovaginal fistula, 2120-2121, 2122f
 of urinary tract obstruction, 1093
- Antegrade ureterography, of ureteral injuries, 1161
- Anterior approaches, for open kidney surgery
 chevron incision, 1419-1420
 midline, 1419, 1419.e1f
 subcostal, 1419
- Anterior colporrhaphy, for pelvic organ prolapse, 1948-1953
 complications with, 1952-1953
 results with, 1949-1950, 1950t-1952t
 technique for, 1949, 1949f
- Anterior compartment prolapse, 1750
- Anterior extraperitoneal approach, to laparoscopic pyeloplasty, 1119
- Anterior pituitary
 anatomy of, 516-517, 517f
 in HPG axis, 516-517, 517f
- Anterior root stimulation, for lower urinary tract dysfunction, 1795
- Anterior transabdominal approach, to open adrenalectomy, 1583-1584, 1583f-1584f
- Anterior trunk, 1616-1617, 1618t
- Antidiuretics, 2789-2791
 and ED, 637, 638t
 nonsteroidal, 2789-2790
 withdrawal phenomenon, 2790-2791
- Antibiotics
 biofilm resistance to, 134-135
 for BPS/IC oral therapy, 355
 for Fournier gangrene of scrotal wall, 947-948
 for hypospadias, preoperative, 3402
 for infection stones, 1230
 for injection therapy for stress urinary incontinence, 2053
 mesh complications in pelvic reconstructive surgery, 2046
 pediatric stone disease and, 3104
 for percutaneous nephrolithotomy, 1277
 preoperative bowel preparation with, 106-108
- prophylaxis with
 for catheterization, 123-124
 for cystourethroscopy, 139-140, 141b
 for pediatric patients, 2958-2959, 2959t
 for percutaneous access to upper urinary tract collecting system, 157-158
 preoperative, 105-106, 105b, 106t-107t
 for renal transplantation, 1086, 1086f
 for scrotal surgery, 946-947
 for ureteral stents, 132
 for ureteroscopy, 150
 for prostate biopsy, 2584-2585, 2585t
 for renal calculi, pretreatment, 1237
 stent coatings with, 128
 urethral function effects of, 1006
 for urethroplasty, postoperative, 3417
 for UTIs, 2942
 for vesicoureteral reflux, 3156-3157
 for vesicovaginal fistula surgery, 2112

- Anticholinergic medication. *See also*
 Antimuscarinic agents
 for benign prostatic hyperplasia, 2491-2493, 2492t
 for bladder and bowel dysfunction, 3307-3308
 detrusor underactivity and, 1814
 for enuresis, 3315-3316
 for urinary incontinence, in geriatric patients, 2099.e3
- Anticholinesterases, ureteral response to, 991
- Anticoagulants
 holmium laser enucleation of prostate and, 2529
 management of
 for percutaneous access to upper urinary tract collecting system, 158
 preoperative, 109-110
 monopolar transurethral resection of prostate in, 2513-2514
 photoselective vaporization of prostate and, 2532
 for vena caval thrombectomy, 1433
 VTE prophylaxis with
 for laparoscopic and robotic surgery, 223
 in pediatric patients, 2959-2960
 preoperative, 108-109, 108t-109t, 109b, 197
- Anticoagulation, post-transplant, 1083
- Antidepressants, to facilitate bladder filling and urine storage, 1839t, 1856-1858
- Antidiuretic hormone (ADH), 1012. *See also*
 Arginine vasopressin; Desmopressin;
 Syndrome of inappropriate antidiuretic hormone secretion
 actions of, 1012, 1013f
 control of, 1012, 1013t
- Antiemetics, for PONV, 2961
- Antihistamines
 for BPS/IC oral therapy, 353-354
 premedication with, for preventing contrast media reactions, 29, 29b
- Antihypertensives, and ED, 635-636, 638t
- Anti-inflammatory agents, for CP/CPPS treatment, 323
- Antilymphocyte globulin, for post-transplant immunosuppression, 1084
- Antimicrobial prophylaxis, for UTIs, 255-260, 255t-258t, 259f
- Antimicrobial prophylaxis
 for uncomplicated urologic procedures, 260-265, 260b, 261t-262t, 264t-265t, 265b
 for lower tract endoscopy, 263
 for open and laparoscopic surgery, 264, 264t
 principles of, 260, 260b, 261t-262t
 for shockwave lithotripsy, 263
 special considerations, 264-265, 265t
 for transurethral resection of prostate and bladder, 263
 for TRUSP biopsy, 262-263
 for upper tract endoscopy, 263
 for urethral catheterization and removal, 260-262, 260b, 261t-262t
 for urodynamics, 262
 for UTIs, 238, 272-274, 272t
- Antimicrobial selection, for uncomplicated cystitis, 266-267, 267t
- Antimicrobial suppression, for UTIs, 238
- Antimicrobial therapy, for UTIs
 antimicrobial prophylaxis for, 255-260, 255t-258t, 259f
 bacterial resistance to, 254-255
 duration of, 260
 principles of, 253-260, 254t-258t, 259f, 260b
 prophylaxis, 238
- Antimicrobial therapy, for UTIs (*Continued*)
 selection of agents in, 260, 266-268, 267t
 suppression, 238
- Antimüllerian hormone (AMH). *See* Müllerian-inhibiting substance
- Antimuscarinic agents
 adverse effects of, 1840-1841
 clinical use of, 1840
 to facilitate bladder filling and urine storage, 1838-1841, 1839t, 1852b
 with α -adrenoreceptor antagonists, 1859-1860
 with β -adrenoreceptor antagonists, 1860
 atropine sulfate, 1841
 combinations of, 1860
 darifenacin hydrobromide, 1841-1842
 fesoterodine fumarate, 1842-1843
 flavoxate hydrochloride, 1851-1852
 imidafenacin, 1843-1844
 with mixed action, 1848-1852
 oxybutynin chloride, 1848-1850
 propantheline bromide, 1844
 propiverine hydrochloride, 1850-1851
 with 5 α -reductase inhibitors, 1860-1861
 solifenacin succinate, 1844-1845
 specific actions of, 1841-1848
 tolterodine tartrate, 1845-1847
 trospium chloride, 1847-1848
 mechanism of action of, 1838-1839
 for neuromuscular dysfunction of lower urinary tract, 3279-3281
 nocturnal polyuria and, 1827
 pharmacologic properties of, 1839-1840
 for urinary incontinence
 in geriatric patients, 2099.e4
 urgency, 1714-1715
- Antineutrophil cytoplasmic antibody (ANCA)-associated and ANCA-like vasculitis, 2860
- Antioxidants, stone disease and, 1175
- Antiplatelet agents, management of
 for percutaneous access to upper urinary tract collecting system, 158
 preoperative, 109-110
- Antiproliferative factor (APF), in BPS/IC etiology, 345.e8, 345.e8b, 345.e8t, 345.e9f
- Antireflux procedure
 for classic bladder exstrophy, 3205f-3206f, 3209-3210
 for urinary tract reconstruction, 3333-3334
 with intestinal segments, 3334
 psoas hitch for, 3334, 3335f
 transureteroureterostomy for, 3333-3334, 3334f
- Antiretroviral agents
 and ED, 638
 in stone formation, 1196-1197
 medical management of, 1231
- Antiseptics
 for cystourethroscopy, 140
 preoperative, 113-114
- Antisperm antibodies, 525
 after vasectomy, 953
- Antithrombotic therapy, preoperative
 management of, 109-110, 110t
- Antithymocyte globulin, for post-transplant immunosuppression, 1084, 1085t
- Antithyroid medications, preoperative, 103
- Antituberculosis drugs, 428-430, 429t-430t
- Anti-VEGF therapy, for RCC, 1326
- Aorta
 in radical nephrectomy, 1424-1426, 1425f, 1424.e1f
 resection and reconstruction of, RPLND with, 823
 in retroperitoneum, 775, 775f, 776.e1f,
- Aortic aneurysm, as laparoscopic and robotic surgery contraindication, 196
- APACHE score. *See* Acute physiology and chronic health evaluation score
- APF. *See* Antiproliferative factor
- Aphallia, 3373, 3373f
- Aphthous ulcers, 400-401, 401f
- Apoptosis
 cancer cell resistance to, 2717
 in CKD, 1056-1057
 as evolutionarily conserved process, 479
 in GU cancers, 479, 481b
 alternative regulators of, 480
 extrinsic pathway of, 479.e1-479.e2, 479.e1f-479.e2f
 global defects in, 479-480
 intrinsic pathway of, 479.e1, 479.e1f
 TP53 role in, 479
 regulation of, in benign prostatic hyperplasia, 2429
 after renal obstruction, 1100
- Apoptosis pathway, in castration-resistant prostate cancer, 2818
- Appendicovesicostomy, 3361-3363, 3362f
- Appendix
 for continent urinary diversions, 3361-3363
 in ileocecectomy, 3346
- APR. *See* Abdominoperineal resection
- Aprepitant, to facilitate bladder filling and urine storage, 1866.e4
- AQP. *See* Aquaporin
- AQP2. *See* Aquaporin 2
- Aquaporin (AQP), 1096
- Aquaporin 2 (AQP2), 1096
- AR. *See* Androgen receptor; Androgen receptors
- ARBs. *See* Angiotensin receptor blockers
- ARCD. *See* Acquired renal cystic diseases
- Arcus tendineus fascia pelvis (ATFP), 1598, 1599f, 1607
- Arcus tendineus levator ani (ATLA), 1598, 1599f
- L-Arginine, for BPS/IC oral therapy, 353t, 355
- Arginine vasopressin (AVP)
 actions and control of, 1012, 1013f, 1013t
 in water regulation, 1825-1826, 1826f
- Argon beam coagulator
 for laparoscopic and robotic surgery, 207.e1
 for monopolar electrosurgery, 225-226
- Aristolochic acid nephropathy, 1072
 in UTIC, 1366
- Arizona sexual experience scale (ASEX), 753.e2
- Aromatase inhibitors, for benign prostatic hyperplasia, 2487
- ARPKD. *See* Autosomal recessive polycystic kidney disease
- Arrhythmia, pneumoperitoneum causing, 212
- Arsenic, UTIC risk and, 1366
- ART. *See* Assisted reproductive technologies
- Arterial revascularization, in ED, 667
- Arterial supply, to male pelvis, 1615-1617, 1618t, 1620f
- Arterial system
 of retroperitoneum, 769t, 775-776, 775f, 775.e1f-775.e2f, 776.e1f
 surgical anatomy of, 2641, 2642f
- Arteriography
 of IVC tumor thrombus, 1356-1357, 1356f
 for pediatric genitourinary trauma, 3541-3542
 for renal tumor evaluation, 35
- Arteriovenous fistulas (AVFs), renal, 2999
- Arteriovenous malformations (AVMs), hematuria related to, 194
- Arthritis. *See* Reactive arthritis
- Artifacts, of ultrasonography images, 67-68, 67f-69f

- Artificial somatic-autonomic reflex pathway procedure, for neuromuscular dysfunction of lower urinary tract, 3283
- Artificial sweeteners, urothelial cancer and, 2187
- Artificial urinary sphincter (AUS)
for bladder neck reconstruction, 3338-3340
results with, 3338-3340
technique for, 3338, 3339f
complications with, 2181-2182, 2182b
infection, 2181
mechanical failure, 2182
urethral atrophy, 2181
urethral erosion, 2181
urinary retention, 2181
evaluation and diagnosis for, 2171-2173
history and development of, 2170, 2170f
implantation technique, 2175-2178, 2175f-2176f, 2178b
bladder neck, 2178
control pump placement, 2176, 2177f
making connections, 2176-2177, 2176f
outcomes of, 2178t
pressure-regulating balloon, 2176
tandem cuff, 2177-2178, 2177f
transcortical, 2177f, 2178, 2178t
transscrotal, 2177f, 2178
long-term results with, 2182, 2183b
mechanisms of action of, 2171
for neuromuscular dysfunction of lower urinary tract, 3282.e2
- As Low As Reasonably Achievable (ALARA), 73
- ASA. *See* American Society of Anesthesiologists
- ASB. *See* Asymptomatic bacteriuria
- Ascending route of infection, 241
- Ascites
laparoscopic and robotic surgery causing, 224.e1
as laparoscopic and robotic surgery contraindication, 196
after RPLND, 834
- ASCs. *See* Adult stem cells
- ASEX. *See* Arizona sexual experience scale
- Ask-Upmark kidney, 3009-3011, 3010f
- Aspiration, of gastric contents, during laparoscopic and robotic surgery, 220.e1
- Aspirin, management of
for percutaneous access to upper urinary tract collecting system, 158
preoperative, 110
- Assisted reproductive technologies (ART), 573.e5
- Asthma, perioperative care for pediatric patients with, 2954-2955
- Asymmetrical unit membrane (AUM), of urothelium of bladder, 1632-1633, 1633f
- Asymptomatic bacteriuria (ASB)
catheter-associated, 299-300
in elderly, 297-299, 299b
in geriatric patients, 2099.e10-2099.e11
in pregnancy, 293-295
uncomplicated cystitis and, 268, 268t-269t
and UTIs, 2935-2936
- Asymptomatic inflammatory prostatitis, clinical presentation, 311
- Asymptomatic microhematuria (AMH), 3
- AT2. *See* Angiotensin II
- ATFP. *See* Arcus tendineus fascia pelvis
- Atherosclerosis
renovascular hypertension caused by, 1032-1033, 1033t, 1034b
testosterone effects on, 548-549
- ATLA. *See* Arcus tendineus levator ani
- ATN. *See* Acute tubular necrosis
- Atopic dermatitis (AD), 389-390, 389f
- ATP. *See* Adenosine triphosphate
- Atrial natriuretic peptide (ANP)
for AKI, 1051
in bilateral ureteral obstruction, 1094-1095, 1095f
renal vascular tone control by, 1010, 1010f
- Atropine, ureteral response to, 991
- Atropine sulfate, to facilitate bladder filling and urine storage, 1839t, 1841
- Attention-deficit/hyperactivity disorder (ADHD)
lower urinary tract dysfunction and, 1793
and priapism, 673
- Attenuation mechanisms, in ultrasonography, 66-67, 66f-67f, 66t
- AUA. *See* American Urological Association
- AUA symptom index, 4-5
- AUASI. *See* American Urological Association Symptom Index
- Audiovisual and vibratory stimulation, in ED, 655
- Augmentation cystoplasty, 2070
alternatives to, 3356-3357
autoaugmentation, 3357-3359, 3358f
bladder regeneration, 3359, 3359f
seromuscular enterocystoplasty, 3358-3359, 3359f
ureterocystoplasty, 3356-3357, 3357f
approach to, 3355
bladder capacity after, 2071
bladder compliance after, 2070-2071, 3350-3351, 3351f
cecocystoplasty for, 3346
complications of, 3282.e1-3282.e2
complications with, 3350-3355
calculi, 3353
delayed spontaneous bladder perforation, 3353-3354, 3354f
metabolic, 3351-3352
mucus, 3352
tumor formation, 3353
urinary tract infection, 3352-3353
contraindications to, 2071-2072
detrusor overactivity and, 2071
gastrocystoplasty for, 3347-3348, 3349f
gastrointestinal effects of, 3350
historical perspective on, 2070
ileocecocystoplasty for, 3346, 3346f-3347f
ileocystoplasty for, 3344-3345, 3345f
indications for, 2070
intestinal segment management for, 3344
laparoscopic or robotic, 2263-2265
complications with, 2264-2265
evaluation for, 2263
indications for, 2263
outcomes with, 2264-2265
technique for, 2263-2264, 2264f
native bladder management for, 3344, 3344f
necessity of, 3355-3356
for neuromuscular dysfunction of lower urinary tract, 3282.e1-3282.e2
postoperative management of, 3348-3349
early, 3348
late, 3348-3349
pregnancy and, 3354-3355
quality of life and, 3356
in renal transplantation, 3532
results with, 3350-3355
segment choice for, 3355
sigmoid cystoplasty for, 3346-3347, 3348f
techniques for, 2071
for urinary tract reconstruction, in pediatric patients, 3342-3359
- Augmented bladders
renal transplantation and, 3531
tumors of, in pediatric patients, 3588-3589
- Augmented valved rectum, 2321
- AUM. *See* Asymmetrical unit membrane
- AUR. *See* Acute urinary retention
- AUS. *See* Artificial urinary sphincter
- Autoaugmentation
for augmentation cystoplasty, 3357-3359, 3358f
for neuromuscular dysfunction of lower urinary tract, 3282.e2
- Autoimmune responses, to prostate cancer biomarkers, 2573
- Autoimmunity, BPS/IC etiology and, 345.e2-345.e4, 345.e4b
- Autologous chondrocytes, for female SUI injection therapy, 2060
- Autologous fat, for female SUI injection therapy, 2062-2063, 2063t
- Autologous graft, for pubovaginal sling, 1990-1991
outcomes of, 1996-1999, 1997t-1998t
- Autonomic hyperreflexia
lower urinary tract dysfunction with, 1775-1776
symptoms of, 1776
treatment of, 1776, 1763.e1
- Autonomic nervous system
and ED, 657
in retroperitoneum, 778-780, 779f-780f
- Autoregulation, of GFR, 1007-1008
- Autosomal dominant polycystic kidney disease (ADPKD), 1058-1059, 1300-1302, 3017-3021, 3017t
clinical features of, 3018-3019
emerging therapeutics for, 3021
evaluation of, 3019-3020, 3020f
extrarenal manifestations of, 3019
genetics of, 3017-3018
histopathology of, 3019, 3019f
pathogenesis of, 3018
prenatal imaging of, 2909-2910
renal cell carcinoma association with, 3019
renal cell carcinoma in, 1336, 3019
treatment of, 3021
- Autosomal recessive polycystic kidney disease (ARPKD), 1300-1302, 3012-3017
clinical features of, 3013
evaluation of, 3013-3016, 3015f-3016f
genetics of, 3013
histopathology of, 3013, 3015f
prenatal imaging of, 2909-2910, 2910f
treatment of, 3016-3017
- Autotransplantation
renal, 1087-1088
for ureteral injuries, upper, 1162-1163
for ureteral stricture disease, 1141
- AVFs. *See* Arteriovenous fistulas
- Avitene Microfibrillar Collagen Hemostat, 207.e2
- AVMs. *See* Arteriovenous malformations
- AVP. *See* Arginine vasopressin
- Avulsion injury, ureteral, with ureteroscopy, 1167, 1284-1285
- Axial resolution, of ultrasonography images, 65, 66f
- Axitinib, for RCC, 1360t, 1513-1514
- Axoneme, 535-537, 536f
- Azathioprine, for post-transplant immunosuppression, 1084-1085, 1085t
- Azathioprine derivatives, for BPS/IC oral therapy, 353t, 354
- AZE. *See* Azoospermia factor
- Azoospermia, 573.e3
chromosomal abnormalities in, 526-528
- Azoospermia factor (AZF), 528
- Aztreonam, for UTIs, 256t-258t, 260

B

- Bacille Calmette-Guérin (BCG)**
 in bladder cancer, 447, 448f, 453-454, 453f
 for non-muscle-invasive bladder cancer, 2212-2214
 carcinoma treatment in situ with, 2212-2213
 contraindications to, 2214, 2214b
 mechanism of action of, 2212
 progression impact of, 2213
 recurrence prevention with, 2213
 residual tumor treatment with, 2213
 toxicity management of, 2215b
 treatment schedule determination, 2213-2214
 for UTUC, 1398-1399
- Backflow, in retrograde pyelography, 34, 35f**
- Baclofen**
 administration of, 1874.e2-3
 to facilitate bladder emptying, 1874.e2-1874.e3
 to facilitate bladder filling and urine storage, 1839t, 1859
 as treatment for priapism, 683
- Bacteremia, UTIs and, 291-293, 293b**
- Bacteria**
 anaerobic, in prostatitis microbiology, 306
 cell wall components, in septic shock, 292
 gram-positive, in prostatitis microbiology, 305-306
 mesh complication with, 2041
 urease production by, 1194, 1194f, 1195t, 1213, 1214t
 urea-splitting, 271
 in urinary sediment, 23, 24f
 urothelial cancer and, 2188
- Bacterial adherence, 242-243, 242f**
- Bacterial adhesins, 242, 242f**
- Bacterial fimbriae, 2928, 2929f, 2929t**
- Bacterial nephritis. See Renal infection**
- Bacterial persistence, in recurrent UTIs, 271**
- Bacterial "relapse," renal infection from, 286**
- Bacterial resistance, to UPI antimicrobial therapy, 254-255**
- Bacterial type 1 (mannose-sensitive) pili, 242-243**
- Bacterial vaginosis, 381, 381t**
- Bacteriology, sepsis and, 293**
- Bacteriuria**
 asymptomatic. *See* Asymptomatic bacteriuria
 after augmentation cystoplasty, 3352-3353
 catheter-associated, 299-300, 300b
 in elderly, 296
 asymptomatic, 297-299, 299b
 epidemiology, 297, 297f-298f, 297t
 laboratory diagnosis, 297-298, 297f
 management of, 299
 pathogenesis, 297, 298f
 screening for, 298-299
 in pregnancy, 293-294, 297b
 anatomic and physiologic changes and, 294-295, 294f, 295t
 complications of, 295-296
 management of, 295-296, 296t
 pathogenesis, 294
 renal insufficiency and, 296
 UTIs and, 237, 267-268, 268t-269t
- Balanitis**
 infection, 402
 pseudoepitheliomatous, keratotic, and micaceous, 414, 414f
 urethral reconstructive surgery for, 914
 Zoon, 416, 416f-417f
- Balanitis xerotica obliterans (BXO), 3422, 3422f. See also Lichen sclerosis**
- Balanoposthitis, 402, 403f**
- Ballistic lithotripsy, 1262-1263, 1263f**
 ultrasonic combined with, 1264-1265, 1265f
- Balloon catheters, as nephrostomy tubes, 170-171, 171f**
- Balloon dilation**
 for achieving extraperitoneal access and developing extraperitoneal space, 201-202
 for achieving retroperitoneal access and developing retroperitoneal space, 201-202, 202f, 201.e3
 for prostatitis, 326
 for ureteral stricture disease
 antegrade, 1130
 results with, 1130-1131
 retrograde, 1129-1130, 1130f-1131f
 for ureteroenteric strictures, 1142
- Balloon dilators, for upper urinary tract collecting system, 168, 168f-169f, 168.e1f**
- Balloon endopyelotomy, retrograde cautery wire. See Retrograde cautery wire balloon endopyelotomy**
- Balloon incision, cautery wire, for ureteroenteric strictures, 1142-1143**
- Bariatric surgery, nephrolithiasis and, 1220, 1220b**
- Barotrauma, during laparoscopic and robotic surgery, 217**
- Barrier function, of urothelium of bladder, 1638-1639, 1638f**
- Barrington nucleus, 1663**
- Bartter syndrome, 1184, 2862**
- Basal cell carcinoma (BCC)**
 as neoplastic condition, 413, 413f
 of penis, 873, 874f
- Basal cells**
 epididymis, 502-503, 530, 530f
 of prostate, 2397-2398, 2397f
- Base excision repair (BER), 465.e1, 465.e1f**
- Bashful bladder**
 detrusor underactivity and, 1816
 lower urinary tract dysfunction and, 1788-1789
- Basiliximab, for post-transplant immunosuppression, 1084-1085, 1085t**
- BBD. See Bladder and bowel dysfunction**
- BCC. See Basal cell carcinoma**
- BCG. See Bacille Calmette-Guérin**
- BCI. See Bladder contractility index**
- BCR. See Bulbocavernosus reflex**
- BD. See Behçet disease**
- Beckwith-Wiedemann syndrome (BWS), 2885**
 genomic alterations in, 468t, 3569
- Behavioral therapy (BT)**
 for enuresis, 3313-3314, 3314f
 levels of evidence and recommendations for, 1877t-1878t
 with urge suppression, 1886-1887, 1886f
 for urinary incontinence, in geriatric patient, 2099.e3
- Behavioral treatment programs**
 for bladder and bowel dysfunction, 3307
 for urinary incontinence
 adherence to, 1894
 assessment for, 1878-1879, 1880f
 bladder training, 1886f, 1889-1890
 common, 1875, 1876f
 conditions benefitting from, 1878b
 indications for, 1878
 levels of evidence and recommendations for, 1876t, 1879t
 lifestyle modifications as, 1892-1894
 patient education for, 1883
 for pelvic floor muscle dysfunction, 1894-1895, 1894f-1895f
- Behavioral treatment programs (Continued)**
 pelvic floor muscle electrical stimulation, 1888-1889
 pelvic floor muscle training. *See* Pelvic floor muscle training
 for prevention, 1894-1895
 urology practice model of, 1898
- Behçet disease (BD), 400-401, 401f**
- Benadryl. See Diphenhydramine**
- Benign bounce phenomenon, brachytherapy and, 2691**
- Benign cutaneous diseases, of external genitalia, of male genitalia**
 angiokeratomas of Fordyce, 415, 416f-417f
 ectopic sebaceous glands, 416, 416f-417f
 median raphe cysts, 416
 pearly penile papules, 415-416, 416f-417f
 sclerosing lymphangitis, 416
 Zoon balanitis, 416, 416f-417f
- Benign disease-targeted HRQOL instruments, 92t-95t, 95**
- Benign essential hematuria. See Lateralizing essential hematuria**
- Benign joint hypermobility syndrome, lower urinary tract dysfunction and, 1793**
- Benign lesions, adrenal, 1558b**
 adenoma, 1535, 1562-1563, 1563b, 1563f
 adrenal cyst, 1565-1566, 1566b, 1566f
 gangliogliomas, 1565, 1565b
 myelolipoma, 1564-1565, 1564f, 1565b
 oncocytoma, 1563-1564, 1564b
 pheochromocytoma. *See* Pheochromocytoma
- Benign multilocular cyst, 3031-3032, 3031f, 3033f**
- Benign prostatic enlargement (BPE)**
 α -adrenergic receptors in, 1671
 bladder outlet obstruction and, 1731
 as complication of TT, 546
 hematuria related to, 190-192
 HRQOL instruments for, 92t-94t
 lower urinary tract function and, 1700
 in MetS, 550-551
 terminology for, 2463
- Benign prostatic hyperplasia (BPH)**
 acute urinary retention with, 2501-2502
 as complication of, 2455-2459, 2456t-2457t, 2457f-2459f
 α -adrenergic blockers for, 2473-2482
 adverse events with, 2481
 alfuzosin, 2478-2479, 2479t
 anticholinergic receptor blockers with, 2491-2492, 2493f
 bladder outlet obstruction effects of, 2480
 classification of, 2474-2475, 2474t
 comparison of, 2481
 dose response of, 2475
 doxazosin, 2476-2477, 2477t
 in elderly, 2480
 hypertension with, 2480-2481
 intraoperative floppy iris syndrome, 2481
 literature interpretation for, 2475
 literature review for, 2475-2480
 naftopidil, 2480
 phosphodiesterase inhibitors with, 2497-2498
 rationale for, 2473-2474, 2474f
 sexual side effects of, 2480
 silodosin, 2479-2480
 study designs on, 2475
 summary for, 2481-2482
 tamsulosin, 2478, 2478t
 terazosin for, 2475-2476, 2476f, 2476t
 alcohol use and, 2441
 anatomic features of, 2433-2434, 2433f-2434f
 androgen manipulation for, 2482-2487
 aromatase inhibitors for, 2487
 cetorelix, 2486-2487

- Benign prostatic hyperplasia (BPH) (*Continued*)
 chlormadinone acetate, 2487
 dutasteride, 2486
 finasteride, 2483-2486, 2483f, 2484t, 2485f
 flutamide, 2486
 literature review for, 2483-2487
 pharmacologic classification for, 2482, 2482t
 rationale for, 2482
 studies interpretation for, 2482-2483
 summary for, 2487
 zanerone, 2486
 anticholinergic receptor blockers for, 2491-2493, 2492t
 α-adrenergic blockers with, 2491-2492, 2493f
 mirabegron, 2492-2493
 autopsy prevalence of, 2436-2437, 2437f
 bladder obstruction in
 measures of, 2440
 response to, 2435-2436
 body mass index and, 2442-2444, 2445t
 clinical prevalence of, 2437, 2438f
 combination therapy for, 2487-2491, 2488t
 Combination of Avodart and Tamsulosin Study, 2489-2491, 2491t
 Medical Therapy of Prostatic Symptoms trial, 2488-2489, 2489f-2490f, 2491t
 complications with, 2455-2459
 acute urinary retention, 2455-2459, 2456t-2457t, 2457f-2459f
 bladder decompression, 2455
 bladder stones, 2455
 hematuria, 2455
 mortality, 2455
 upper urinary tract deterioration, 2455
 urinary incontinence, 2455
 urinary tract infections, 2455
 cystometry for, 2470
 diagnosis of, 2464-2470, 2465f-2467f
 additional tests for, 2468
 initial evaluation, 2464-2468
 preoperative tests, 2468-2470
 diet and, 2442-2444, 2445t
 epidemiology of, 2436-2447
 analytical studies, 2440-2444
 definitions for, 2436
 descriptive studies for, 2436-2440
 parameter correlations, 2444-2447, 2446f-2447f, 2446t
 etiology of, 2425-2433
 androgen receptors in, 2427
 androgen role, 2426-2428, 2427t
 cytokines, 2431-2432, 2431f
 dihydrotestosterone in, 2427-2428, 2428f
 estrogen role in, 2428-2429
 familial factors in, 2432, 2432t
 genetic factors in, 2432, 2432t
 growth factors, 2429-2430, 2429f
 hyperplasia, 2425-2426
 inflammatory pathways in, 2431-2432, 2431f
 programmed cell death regulation, 2429
 prolactin, 2432-2433
 5α-reductase in, 2427-2428, 2428f
 signaling pathways in, 2430-2431
 stromal-epithelial interaction, 2429
 health-related quality of life and, 2438
 histologic features of, 2434, 2434f
 histologic prevalence of, 2436-2437
 hypertension and, 2442
 liver cirrhosis and, 2441
 in lower urinary tract symptoms, 2425, 2426f, 2463
- Benign prostatic hyperplasia (BPH) (*Continued*)
 management algorithm for, 2467f
 medical history for, 2464
 medical therapy for
 adverse events, 2472
 candidate selection for, 2473
 clinical end points of, 2470
 eliminating bias, 2471-2472
 future strategies for, 2503f
 impact of, 2473
 prevention with, 2473
 quantitative outcome measures for, 2470-2471
 safety and effectiveness of, 2470-2472
 sample size, 2472
 medications and, 2444
 effects of, 2505
 metabolic syndrome and, 2442-2444, 2445t
 minimally invasive and endoscopic
 management of. *See* Minimally invasive and endoscopic management of benign prostatic hyperplasia
 nonsurgical therapy for, 2442-2444, 2445t, 2472-2473
 components of, 2472-2473
 self-help, 2472-2473
 watchful waiting, 2472-2473
 obesity and, 2442-2444, 2445t
 pathology of, 2433-2434, 2433f-2434f
 pathophysiology of, 2433-2436, 2433f
 phosphodiesterase inhibitors for, 2493-2498, 2494t-2495t, 2496f-2497f
 α-adrenergic blockers with, 2497-2498
 conclusions for, 2498, 2498b
 physical activity and, 2442-2444, 2445t
 physical examination for, 2464
 phytotherapy for, 2498-2501
 extract composition for, 2498-2499, 2498b
Hypoxis rooperi (South African star grass), 2500
 lycopenes, 2500-2501
 mechanism of action, 2499-2501, 2499b
 origin of agents for, 2498, 2498t
Pygeum africanum (African plum), 2500
Serenoa repens (saw palmetto berry), 2499-2500
 summary for, 2501
 postvoid residual urine for, 2469
 pressure-flow studies for, 2469-2470
 prostate size and, 2438-2440, 2439f, 2505
 prostate-specific antigen in, 2465-2467
 religion and, 2440
 serum creatinine measurement for, 2464-2465
 sexual activity and, 2440-2441, 2443t
 smoking and, 2442
 smooth muscle in, 2434-2435, 2435f
 socioeconomic factors in, 2440, 2441t
 surgery for, 2440, 2459-2460, 2460f
 symptoms of
 assessment of, 2467-2468
 medical therapy for, 2470-2471
 severity and frequency of, 2437-2438
 terminology for, 2463
 untreated, natural history of, 2447-2459
 baseline symptom severity in, 2451
 clinical parameters for, 2447-2448, 2447t
 disease progression in, 2451-2452, 2452f, 2453t
 longitudinal population-based studies, 2453-2454, 2453t-2454t, 2454f
 outcomes of interest with, 2447-2448, 2447t
 perception of improvement, 2453
- Benign prostatic hyperplasia (BPH) (*Continued*)
 placebo control groups in, 2450, 2451t
 placebo/sham effect in, 2451
 sham control groups in, 2450-2451
 study methods for, 2448-2454, 2448t
 watchful waiting studies for, 2449-2450, 2449t-2450t, 2450f
 upper urinary tract in, deterioration of, 2455
 urethrocytostomy for, 2470
 urinalysis for, 2464
 uroflowmetry for, 2468-2469
 vasectomy and, 2440-2441
 Benign prostatic obstruction (BPO), bladder outlet obstruction and, 1731
 Benzodiazepines, to facilitate bladder emptying, 1874.e2
 BEP. *See* Bleomycin-etoposide-cisplatin
 BER. *See* Base excision repair
 Berger disease. *See* IgA nephropathy
 Bethanechol (Urecholine)
 administration of, 1871
 for detrusor underactivity, 1817
 efficacy of, 1871
 to facilitate bladder emptying, 1870-1872
 side effects of, 1871
 ureteral response to, 990-991
 Bethanechol supersensitivity test, 1730
 Bevacizumab, 472
 for RCC, 1326, 1508-1509, 1509f-1510f, 1509t, 1516, 1518
 Beverages
 carbonated, nephrolithiasis and, 1217, 1217b
 citrus juices, nephrolithiasis and, 1217, 1217b
 BE. *See* Biofeedback
 BHD. *See* Birt-Hogg-Dubé syndrome
 BHD gene, 1322t, 1325
 Bicalutamide, 2790
 Bicarbonate
 in collecting tubule, 1019
 loop of Henle reabsorption of, 1017
 PCT reabsorption of, 1014-1015, 1015f
 Bicarbonate buffer system, for acid-based balance, 1023-1025
 Bifid pelvis, 3001f, 3004
 Bifid scrotum, 3382, 3383f
 Bifid ureters, 3097-3098
 Biguanide lactic acidosis, contrast media causing, 30
 Bikunin, 1175
 Bilateral anterior subcostal approach, for open kidney surgery, 1419-1420
 Bilateral hydronephrosis, prenatal, 2889
 Bilateral renal agenesis (BRA), 2975-2985
 amniotic fluid production and, 2978-2979
 diagnosis of, 2979
 gross pathologic description of, 2978-2980
 phenotypic features of, 2978, 2979f
 postnatal evaluation of, 2979
 prognosis for, 2980
 syndromic associations with, 2975
 Bilateral ureteral obstruction (BUO)
 hemodynamic changes with, 1094-1095, 1095f
 postobstructive diuresis after, 1102
 renal recovery after, 1102
 tubular function with, 1095-1096
 Bilateral vanishing testes syndrome, 3483
 Bilirubin testing, urinary, 19-20
 Biochemical evaluation, in pheochromocytoma
 diagnostic tests, 1549-1550, 1549f, 1549t
 Biochemical recurrence
 after cryotherapy, 2783
 after high-intensity focused ultrasound ablation, 2783-2784

Biochemical recurrence (*Continued*)

- after radiation therapy, 2778-2783
 - androgen deprivation therapy after, 2782-2783
- biopsy for, 2778-2779
- imaging for, 2779
- natural history, 2778
- prostate-specific antigen bounce, 2778
- prostate-specific antigen recurrence, 2778
- salvage brachytherapy for, 2780-2782
- salvage cryotherapy for, 2780, 2781*t*
- salvage high-intensity focused ultrasound for, 2782
- salvage radical prostatectomy for, 2779-2780, 2780*t*
- after radical prostatectomy, 2770-2778
 - adjuvant radiation therapy, 2775-2777, 2775*f*-2776*f*
 - androgen deprivation therapy for, 2777-2778
 - androgen deprivation therapy with salvage radiation therapy for, 2774-2775
 - definition of, 2770
 - imaging of, 2772-2773, 2773*f*
 - management of, 2617-2618
 - natural history of, 2770-2771
 - prediction of, 2771, 2772*t*
 - salvage radiation therapy dose response, 2774
 - salvage radiation therapy for, 2773-2774
 - salvage *versus* adjuvant radiation therapy for, 2777
 - ultrasensitive prostate-specific antigen for, 2771-2772
 - whole-pelvis *versus* prostatic bed radiation therapy, 2775, 2775*f*-2776*f*

Biofeedback (BF)

- for bladder and bowel dysfunction, 3307
- for CP/CPPS treatment, 325
- levels of evidence and recommendations for, 1877*t*-1878*t*
- with PFMT, 1887-1888, 1887*f*-1888*f*

Biofilms

- on urinary tract biomaterials, 134-135
- and UTIs, 2934-2935, 2935*f*

BioGlue, 207*t*, 207*e2*

Biologic therapies, for neuroblastoma, 3567

- Biological grafts, for pelvic organ prolapse reconstructive surgery, 1946-1947

Biomarkers

- for active surveillance of prostate cancer, 2635
- for bladder cancer, 474
- for congenital obstructive uropathy, 3054-3055
- MH diagnostic evaluation with, 187
- for non-muscle-invasive bladder cancer, 2220, 2221*f*
- for penile cancer, 862-863
- for prostate cancer. *See* Prostate cancer, biomarkers for
- for RCC, 1325-1326, 1335-1336, 1340, 1341*b*
- telomerase activity as, 477-478
- for testicular tumors, 790-791, 794
- in pediatric patients, 3591-3593, 3593*f*
- urinary. *See* Urinary markers
- for UTUC, 1372, 1375-1376

Biopsy

- bladder, for RMS, 3584-3585
- penile, for squamous cell carcinoma, 850, 851*b*
- prostate. *See* Prostate biopsy
- renal
 - for CKD, 1062
 - laparoscopic, 1461-1462, 1462*f*
 - for tumor evaluation, 1317-1318
 - ultrasound guidance of, 74-75
- for renal tumor ablative therapy, 1489-1490

Biopsy (*Continued*)

- of retroperitoneal tumors, 1407-1408
- testis
 - complications of, 584
 - indications for, 582
 - open testis biopsy: microsurgical technique, 582, 583*f*
 - percutaneous, 582-583
 - percutaneous aspiration, 583
 - for TGCTs, 791
- in transurethral resection of bladder tumor, for non-muscle-invasive bladder cancer, 2210
- of upper urinary tract and ureters, for UTUC, 1371-1372, 1390, 1392-1394, 1395*f*-1396*f*
- Biotesometry, 656
- Bipolar electrosurgery, devices for, 227
- in laparoscopic and robotic surgery, 206, 206*e1f*
- Bipolar transurethral resection of prostate (B-TURP), 2516-2517
- complications with, 2516-2517
 - intraoperative, 2517
 - perioperative, 2517
 - postoperative, 2517
- concept for, 2516
- conclusion for, 2517
- outcomes with, 2516
 - comparative studies, 2516, 2516*e1f*
 - single-cohort studies, 2516
- technique for, 2516
- Birmingham Reflux Study, 3155
- Birt-Hogg-Dubé (BHD) syndrome, 1322*t*, 1324-1325
 - genomic alterations in, 468*t*, 472
- BISF-W. *See* Brief Index of Sexual Functioning for Women
- Bisphosphonates
 - for castration-resistant prostate cancer, 2819-2820
 - role in renal calculi management, 1221*t*, 1221*b*
- Bites, animal and human, penile, 2381
- Bladder
 - afferent pathways in
 - cannabinoids, 1656
 - in detrusor underactivity, 1810-1812, 1812*f*
 - functional properties of, 1651-1654, 1653*f*
 - modulators of, 1654-1656
 - nitric oxide in, 1654, 1655*f*
 - pelvic organ interactions with, 1656-1657, 1657*f*
 - properties of, 1650
 - purinergic signaling, 1654, 1656*f*
 - spinal cord pathways of, 1650-1651, 1652*f*, 1652*t*
 - transient receptor potential cation channels, 1654-1656
 - aging and, 1679-1680
 - anatomy of, 1631-1635, 1632*f*
 - lamina propria of, 1633-1634
 - in pediatric patients, 3121-3122
 - smooth muscle of, 1635, 1635*f*
 - stroma of, 1634
 - urothelium of, 1632-1633, 1633*f*. *See also* Urothelium, of bladder
 - vasculature of, 1633-1634, 1634*f*
 - antenatal sonographic findings of, 3173
 - capacity of, 1692
 - diminished. *See* Diminished bladder capacity
 - nocturnal, 3312
 - in pediatric patients, 3123, 3128
 - pharmacologic therapy to increase, 1836-1866
 - recognition of, 3122

Bladder (*Continued*)

- cells, receptivity in UTIs, 244-245, 246*f*
- changes, during pregnancy, 295
- closure of, for classic bladder exstrophy, 3198-3201, 3199*f*-3200*f*
- contractility of
 - bladder emptying and, 1870-1873
 - pharmacologic therapy to increase, 1836-1866
- contraction of
 - muscarinic receptors and, 1836-1837
 - normal, in voiding, 1686-1687
- decompensation, in benign prostatic hyperplasia, 2455
- defects in, in bladder exstrophy, 3189-3191, 3190*f*
- defunctionalized, lower urinary tract dysfunction and, 1792
- development of, 2836, 3173
- duplication of, 3179, 3179*f*, 3180*b*
- dynamics of, 3332
- dysfunction of, 3331
 - with posterior urethral valves, 3264-3266
- efferent pathways to, 1657-1663
 - adrenergic, 1659
 - in detrusor underactivity, 1810, 1812*f*
 - glutamate in, 1657-1658, 1659*f*
 - glycine and γ -aminobutyric acid in, 1658
 - purinergic, 1659-1660
 - reflex circuitry, 1660-1663, 1660*f*
 - serotonin in, 1658-1659
 - terminal nerve fibers, 1657
 - transmitters in, 1657-1660
- electrical stimulation of, 1914
- emptying failure of
 - absorbent products for, 2082
 - catheterization for, 1906-1907, 2077*f*
 - clean intermittent catheterization for, 1907
 - continent catheterizable channels for, 1906-1907, 2074*f*
 - continuous catheterization for, 1907
 - external collecting devices for, 2081-2082
 - intravesical pressure increases for, 2079-2081
- emptying of
 - benign prostatic hyperplasia and, 2471
 - electrical stimulation for disorders of, 1914-1916
 - failure of, 1689*b*, 1692
 - in pediatric patients, 3123
 - pharmacologic therapy to facilitate. *See* Pharmacologic therapy, to facilitate bladder emptying
 - reconstruction and, 3333
 - reflexes that promote, 1901
 - therapy to facilitate, 1691*b*
 - urodynamic studies of, 1729-1734
- estrogens and, 1673
- expansion of, at low pressures, 1755, 1755*b*
- exstrophy of, prenatal imaging of, 2910-2911, 2912*f*
- filling of. *See also* Continence
 - abnormalities of, 1688-1690, 1689*b*
 - bladder response to, 1686
 - low-pressure reservoir, 1755, 1755*b*
 - mechanics of, 1648-1649
 - outlet response to, 1686
 - pharmacologic therapy to facilitate. *See* Pharmacologic therapy, to facilitate bladder filling and urine storage
 - smooth muscles in, 1646-1648
 - therapy to facilitate, 1690*b*
 - urodynamic studies of, 1725-1729
- in genitourinary tuberculosis, 423
- glycosaminoglycan layer, 345*e6*-345*e7*, 345*e8b*

Bladder (*Continued*)

hernia of, 3180
 high-pressure, spinal cord injury with, host defense mechanisms in UTIs and, 249
 injuries of, 2385-2388
 clinical signs and symptoms of, 2386
 complications with, 2388
 diagnosis of, 2386
 etiology of, 2385-2388
 with holmium laser enucleation of prostate, 2529
 management of, 2387-2388, 2387b, 2387f-2388f, 2387.e1f
 outcomes with, 2388
 pediatric. *See* Pediatric genitourinary trauma, bladder
 radiographic imaging for, 2386-2387, 2386f-2387f
 innervation of, in pediatric patients, 3122, 3122f
 male
 circulation of, 1619f, 1621f, 1627-1628
 innervation of, 1628
 relationships with, 1616f, 1619f, 1624-1626, 1625f-1626f
 structure of, 1626, 1626f-1627f
 trigone of, 1626-1627, 1628f
 ureterovesical junction of, 1626-1627, 1628f
 mesh perforation of, in midurethral sling, 2029-2031, 2031f, 2032t, 2033b
 natural defenses of, 247-248, 248.e1
 necrosis of, with transurethral vaporization of prostate, 2517.e4
 neoplasia in, 474
 neural tube defects and, early intervention for, 3275, 3276f
 obstruction of
 prenatal imaging of, 2909-2910, 2910f, 2913
 in renal transplant candidates, 1073
 response to, 2435-2436
 RMS causing, 3584-3585
 overactive. *See* Overactive bladder
 paralytic, 1693-1694
 pediatric imaging of, ultrasonography, 2913, 2917f
 perforation of
 after augmentation cystoplasty, 3353-3354, 3354f
 in transurethral resection of bladder tumor, 2244, 2244f
 pharmacology of
 adrenergic mechanisms, 1670-1671, 1671f
 muscarinic receptors, 1667-1670, 1669t, 1670b
 sex steroids, 1673
 physical examination of, 10, 10f
 prenatal, 2874-2875, 2875f
 in prune-belly syndrome, 3236-3237, 3237f
 pudendal nerve stimulation and, 1681
 inhibitory and excitatory frequencies for, 1681
 reconstruction of. *See also* Urinary tract reconstruction
 after RMS treatment, 3587
 regeneration of, 488-489
 for augmentation cystoplasty, 3359, 3359f
 cell therapies in, 491-492
 matrices for, 489
 tissue formation for, 489-491, 490f-491f
 using cell transplantation, 489
 release of, in robotic-assisted radical cystectomy, 2271, 2273f

Bladder (*Continued*)

sensation of
 altered, filling/storage failure due to, 1688-1689
 detrusor underactivity and, 1816
 instruments for measurement of, 1800-1802, 1802t
 terminology for, 1745
 sensory input of, pharmacologic therapy to decrease, 1836-1866
 smooth muscles of, 294-295, 1640-1648. *See also* Detrusor muscle
 storage failure of, 1688-1690, 1689b, 1692
 absorbent products for, 2082
 augmentation cystoplasty for, 2070
 external collecting devices for, 2081-2082
 storage function of, 3330-3331
 electrical stimulation for disorders of, 1902-1914
 neural control of, 1754-1755
 pharmacologic therapy to facilitate, 1836-1870
 reflexes that promote, 1900-1901, 1901f
 after retropubic suspension surgery, 1933
 therapy to facilitate, 1690b
 urinary incontinence and, 1756
 urodynamic studies of, 1725-1729
 suburothelial interstitial cells of, 1640, 1640f
 transabdominal pelvic ultrasonography of, 75-77, 75f-76f
 transurethral resection of, 263
 trigone of, 1626-1627, 1628f
 tumors of. *See* Bladder tumors
 underactivity of
 emptying/voiding failure from, 1690-1691
 pediatric, 3310
 unstable, 1796
 UPEC persistence in, 246-247, 246f
 urothelium of, genetic alterations in, 474
 voiding of, 3331. *See also* Micturition
 bashful bladder, 1788-1789
 mechanics of, 1649
 Bladder advancement flap, laparoscopic or robotic, 2260, 2262f
 Bladder agenesis, 3175
 Bladder and bowel dysfunction (BBB)
 abdominal examination for, 3301-3303
 back examination for, 3301-3302, 3302f
 bladder and bowel diaries for, 3300, 3301f
 bladder wall thickness in, 3305
 Bristol Stool Scale for, 3305, 3305f
 conservative management of, 3306-3307
 evaluation of, 3300
 genital examination for, 3302-3303, 3303f
 history for, 3300
 investigative tools for, 3303-3305
 neurologic examination for, 3303
 neuromodulation for, 3308-3310, 3309t
 in pediatric patients, 3126, 3299
 pelvic ultrasound for, 3304, 3304f
 pharmacotherapy for, 3307-3308
 physical examination for, 3301
 postvoid residual in, 3304-3305
 psychological screening for, 3300-3301
 questionnaires for, 3300
 rectal distention in, 3305, 3305f
 spinal examination for, 3301-3302, 3302f
 treatment for, 3306
 urinalysis for, 3303
 urine culture and sensitivity for, 3303
 uroflowmetry for, 3303-3304
 urotherapy for, 3306
 and UTIs, 2931-2932, 2945-2946

Bladder anomalies in children

absent fetal bladder, 3175
 bladder agenesis, 3175
 bladder diverticulum, 3177-3178, 3178f, 3179b
 bladder duplication, 3179, 3179f, 3180b
 bladder hemangioma, 3180
 bladder hernia, 3180
 classification of, 3173-3180
 dilated fetal bladder, 3174
 congenital megacystis, 3174, 3174f
 in nonobstruction, 3174
 obstruction and, 3174
 eosinophilic cystitis, 3180, 3180f
 nephrogenic adenoma, 3180
 nondilated fetal bladder, 3174-3175
 bladder hypoplasia, 3175
 cloacal and bladder exstrophy, 3174-3175
 postnatally detected, 3175
 prenatally detected, 3173-3175, 3174f
 urachal, 3175-3177, 3176f, 3177b
 patent urachus, 3176-3177, 3177f
 umbilical-urachus sinus, 3177
 urachal cyst, 3177
 vesicourachal diverticulum, 3177
 Bladder augmentation
 calculi in, 1294
 treatment of, 1296
 pharmacologic therapy in, to facilitate bladder filling and urine storage, 1866
 in renal transplant candidates, 1073-1074
 Bladder calculi, 1291-1296
 in augmentation, 1294
 treatment of, 1296
 with benign prostatic hyperplasia, 2455
 bladder cancer and, 1296
 lithotripsy for, 1295
 EHL, 232.e2
 laser, 1295, 234.e2-234.e3
 pneumatic, 233.e1
 management of, 1295-1296, 1296b
 cystolitholapaxy in, 1295
 cystolithotomy in, 1295
 lithotripsy in, 1295
 nonoperative, 1295
 shock wave lithotripsy in, 1295-1296
 medical management of, 1232
 presentation of, 1295-1296, 1296b
 primary, 1292, 1292b
 secondary, 1292-1294, 1294b
 to bladder outlet obstruction, 1292-1293
 to intravesical foreign body, 1293
 to neurogenic bladder, 1293
 to organ transplantation, 1293-1294
 to spinal cord injury, 1293
 in urinary diversion, 1294
 treatment of, 1296
 Bladder cancer
 BCG in, 447, 448f, 453-454, 453f
 bladder calculi and, 1296
 bladder diverticula with, 2145-2146
 chronic inflammation role in, 451, 452f
 diminished bladder capacity and, 1829
 DNA methylation in, 463
 CDH1 and RASSF1A genes, 463-464
 hypomethylation, 464
 INK4A gene, 463
 genomic alterations in, 472-474
 alterations in normal and benign urothelium, 474
 detection and surveillance using, 474
 before neoplasia, 474
 in geriatric patients, 2099.e12-2099.e13
 global burden of, 2186

Bladder cancer (*Continued*)

- hematuria in, 3, 184, 184t, 185b
- HRQOL instruments for, 92t-94t
- immune checkpoint blockade in, 457
- immunotherapy for, 447
- long-term catheterization and, 1778
- metastatic. *See* Metastatic bladder cancer
- MetS and, 554
- muscle-invasive. *See* Muscle-invasive bladder cancer
- as non-AIDS-defining urologic malignancy, 386
- non-muscle-invasive. *See* Non-muscle-invasive bladder cancer
- pediatric
 - adenocarcinoma and squamous cell carcinoma, 3589
 - in augmented bladders, 3588-3589
 - RMS. *See* Bladder RMS
 - TCC, 3588
 - urachal carcinoma, 3589
- screening for, 185
 - molecular genetics-based assays for, 474
- superficial. *See* Non-muscle-invasive bladder cancer
- transurethral resection of. *See* Transurethral resection of bladder tumor
- urothelial. *See* Urothelial cancer
- after UTUC, 1368
- UTUC after, 1367

Bladder catheterization

- anatomic considerations for, 119
- biofilm formation during, 134-135
- catheters used for
 - design of, 121, 121f
 - materials and coatings for, 121
 - selection of, 120-121, 120t
- complications of, 123-124
- history of, 119
- indications for, 119-120, 120f
- suprapubic, 124-126, 125f
- technique for, 121-123, 123f

Bladder cell therapies, 491-492

Bladder compliance (C), 1649

- after augmentation cystoplasty, 3350-3351, 3351f
- impaired, urodynamic studies of, 1725-1727, 1725f-1726f

Bladder contractility index (BCI), 1732, 1732f, 1815

Bladder cooling reflex, 1656

- Bladder cuff, surgical management of, for UTUC, 1377-1379, 1378f-1380f, 1381-1382

Bladder diary

- for behavioral treatment programs, 1879, 1880f
- for bladder and bowel dysfunction, 3300, 3301f
- Questionnaire-Based Voiding Diary, 1879, 1881f-1882f
- for urinary incontinence, male, 1711-1712, 1712f

Bladder diverticula, 2140-2150, 2141f

- associated conditions, 2144-2146
 - bladder outlet obstruction, 2144
 - ipsilateral vesicoureteral reflux, 2146
 - malignancy, 2145-2146
- cause of, 2254
- classification of, 2140
- diagnosis of, 2141-2144, 2146b
 - endoscopic examination, 2144, 2145f
 - evaluation of, 2141
 - imaging of, 2141-2143, 2142f-2144f
 - presentation of, 2141
 - urodynamics of, 2143-2144

Bladder diverticula (*Continued*)

- diverticulectomy for. *See* Bladder diverticulectomy
- etiology of, 2140-2141
- evaluation of, 2140-2141
- management of, 2146-2150, 2147f, 2150b
 - endoscopic, 2146-2148
 - indications for intervention, 2146
 - observation and nonsurgical, 2146
- pathophysiology of, 2140-2141
- surgical indications for, 2140-2141
- surgical management of, 2148-2150
 - combined intravesical-extravesical approach to, 2148, 2151f
 - complication with, 2150
 - laparoscopic and robotic diverticulectomy, 2148-2150
 - transvesical bladder diverticulectomy, 2148, 2149f-2150f
 - vesicoureteral reflux and, 3151, 3151.e1f
- Bladder diverticulectomy, laparoscopic and robotic, 2148-2150, 2254-2257
 - approach to, 2254-2255
 - complications with, 2256, 2257f
 - evaluation for, 2254
 - indications for, 2254
 - outcomes with, 2256, 2257f
 - technique for, 2255-2256, 2255f-2257f
- Bladder dysfunction. *See also* Bladder and bowel dysfunction
 - after pediatric renal transplantation, 3536
 - Bladder exstrophy. *See* Classic bladder exstrophy
- Bladder filling, ureteral function effects of, 994-995
- Bladder functional assessment, for ureteral anomalies, 3082
- Bladder hemangioma, 3180
- Bladder hypoplasia, 3175
- Bladder infections, 274b
 - complicated cystitis, 268-269, 269b, 269t
 - recurrent UTIs, 270-271, 270f
 - bacterial persistence, 271
 - low-dose continuous prophylaxis for, 272-273, 272t
 - other strategies for, 274
 - postintercourse prophylaxis for, 274
 - reinfections, 271-274
 - self-start intermittent therapy for, 274
 - uncomplicated cystitis, 265-268
 - antimicrobial selection for, 266-267, 267t
 - asymptomatic bacteriuria and, 268, 268t-269t
 - clinical presentation, 265
 - differential diagnosis, 266
 - follow-up, 268
 - laboratory diagnosis, 265-266
 - management, 266-268, 266f, 267t
 - risk factors, 265b
 - unresolved UTIs, 269-270, 270b
- Bladder injury, during laparoscopic and robotic surgery, 222.e1
- Bladder lithiasis, 1292
- Bladder mucosa, in vesicovaginal fistula repair, 2117
- Bladder neck, 910.e2, 910.e2f
 - division of, 3342
 - lacerations through, 3552-3553
 - in laparoscopic radical prostatectomy
 - identification and transection of, 2669-2670, 2670f
 - reconstruction of, 2673
 - in neuromuscular dysfunction of lower urinary tract, 3282.e2-3282.e3
 - in retropubic radical prostatectomy
 - division of, 2654-2655, 2654f
 - preservation of, 2655-2656, 2655f

Bladder neck (*Continued*)

- reconstruction and anastomosis of, 2655-2656, 2655f-2656f
- Bladder neck closure
 - in classic bladder exstrophy
 - failure of, 3216
 - outcomes and results of, 3212-3213, 3212t
 - for vesicoureteral reflux, 1777
- Bladder neck contracture
 - with bipolar transurethral resection of prostate, 2517
 - with holmium laser enucleation of prostate, 2529-2530
 - with monopolar transurethral resection of prostate, 2515
 - after photoselective vaporization of prostate, 2532
 - after retropubic radical prostatectomy, 2657
- Bladder neck dysfunction
 - lower urinary tract dysfunction and, 1787-1788
 - video-urodynamics for, 1737
- Bladder neck reconstruction
 - artificial urinary sphincter for, 3338-3340
 - bladder neck division for, 3342
 - bulking agents for, 3337-3338
 - fascial sling for, 3336-3337
 - Pippi Salle procedure for, 3342, 3343f
 - urethral lengthening for, 3340-3342, 3341f
 - in urinary tract reconstruction, 3336-3342
 - Young-Dees-Leadbetter repair for, 3336
- Bladder neck slings, for neuromuscular dysfunction of lower urinary tract, 3282.e2-3282.e3
- Bladder neck stenosis, after transurethral microwave therapy, 2521
- Bladder outlet
 - closure of, 2074-2075, 2074f
 - in continence, 1755-1756
 - overactivity of, emptying/voiding failure from, 1691
 - response of, to filling, 1686
 - storage failure at, 2075b
 - bladder outlet closure, 2074-2075, 2074f
 - female intravaginal incontinence devices, 2073
 - female urethral occlusive devices, 2073
 - male urethral compression devices, 2072-2073, 2072f
 - myoplasty for, 2072
 - surgery of, for detrusor underactivity, 1819
 - underactivity of, filling/storage failure from, 1690-1691
 - ureterocele and, 3084-3085, 3085f
- Bladder outlet obstruction (BOO)
 - α -adrenergic blockers effects on, 2480
 - in benign prostatic hyperplasia, medical therapy and, 2470-2471
 - with bladder diverticula, 2144
 - detrusor underactivity and, 1812-1813, 1813b
 - dilated fetal bladder and, 3174
 - emptying/voiding failure from, 1691
 - in geriatric patients, 2099.e7
 - mechanisms of, 1676-1677, 1677b
 - nocturia and, 1829-1830
 - after pubovaginal sling procedure, 2004-2006
 - surgical management of, 2005-2006, 2006t
 - secondary bladder calculi and, 1292-1293
 - simple prostatectomy for, 2535
 - urodynamic studies of
 - in men, 1731-1732, 1732f
 - in women, 1732-1733
 - video-urodynamic studies of, in women, 1734f-1735f, 1735

- Bladder outlet obstruction (BOO) (*Continued*)
in women, lower urinary tract dysfunction and, 1788
- Bladder outlet relation (BOR), 1731, 1731f
- Bladder pain syndrome (BPS)
overactive bladder distinguished from, 1797f, 1803, 1803f
refractory, 370
terminology for, 364-368, 1796, 1797f
- Bladder pain syndrome and interstitial cystitis (BPS/IC), 334
classification, 351
definition of, 334-337, 335b, 337b, 339b, 339f, 364-365
diagnosis of, 336b, 346-351, 347b, 348f, 351b, 368f-369f
differential diagnosis, 350-351, 350t
markers in, 349
potassium chloride test, 349-350
epidemiology of
associated disorders, 342-344, 343f, 344b
characteristics and natural history, 341-342, 342b
prevalence, 339-341, 340f, 341b
etiology of, 344-345, 344f, 345.e12b
animal models, 345.e1, 345.e1f
antiproliferative factor, 345.e8, 345.e8b, 345.e8t, 345.e9f
autoimmunity and inflammation, 345.e2-345.e4, 345.e4b
bladder glycosaminoglycan layer and epithelial permeability, 345.e6-345.e7, 345.e8b
genetics, 345.e11-345.e12
infection, 345.e1-345.e2
mast cells and histamine, 345.e4-345.e6, 345.e4f, 345.e6b
neurobiology and inflammation, 345.e8-345.e10, 345.e10b
nitric oxide metabolism, 345.e11
other potential causes, 345.e12
pelvic organ cross-sensitization, 345.e10-345.e11, 345.e11b
urine abnormalities, 345.e11
historical perspective of, 335-339, 336b
management of, 364, 365t, 368f-369f
definition and, 364-365
history and initial assessment, 368
initial treatment, 368-370
philosophy, 370
refractory bladder pain syndrome, 370
secondary assessment, 370
mechanisms of, 1677-1679, 1679b
nomenclature, 365-368
pathology, 345-346, 346b
prostatitis, CPPS and, 309
surgical therapy for, 359-362, 361b
historical procedures, 360
for Hunner lesion, 360
hydrodistention, 359-360
major procedures, 360-362
surgical considerations, 360
taxonomy, 337-339, 338f, 338t
treatment of, 368-370, 368f-369f
assessment of results, 362-364, 362f, 363t-364t, 365b, 366f-367f
conservative therapies, 351
diet, 351-352, 352b
intravesical therapies, 353t, 356-358, 358b, 358.e1, 356.e1
neuromodulation, 358-359, 359b
oral therapies, 352-356, 353t, 356b
surgical therapy, 359-362, 361b
urgency in, 339, 339b, 339f
- Bladder psoas muscle hitch, distal ureterectomy and direct neocystostomy or ureteroneocystostomy with, 1385-1386, 1387f
- Bladder RMS, 3582
biopsy of, 3584-3585
epidemiology and syndromic associations of, 3582
imaging evaluation of, 3584
pathology and molecular biology of, 3582-3583, 3583b, 3583f-3584f
presenting symptoms and examination of, 3584, 3584b, 3584t
staging and COG risk group assignment of, 3585, 3585b
treatment of, 3586b
COG multimodal approaches to, 3586
European Cooperative Group approaches to, 3586-3587
evolution of multimodal, 3585-3586
late effects of, 3587-3588
outcomes of, 3587
surgical reconstruction, 3587
for very young children, 3587
- Bladder surgery, for genitourinary tuberculosis treatment, 431
- Bladder training
evidence for, 1890
for urinary incontinence, 1886f, 1889-1890
- Bladder tumors
benign, 2184-2185
cystitis cystica, 2185
cystitis glandularis, 2185, 2185f
epithelial metaplasia, 2184
inverted papilloma, 2184
leukoplakia, 2184
nephrogenic adenoma, 2184-2185
papilloma, 2184, 2185f
pediatric, 3589
malignant. *See* Bladder cancer
nonurothelial, 2201-2204, 2203b
prostatic urethral cancer, 2203-2204, 2203f
sarcomas, 2201-2203
- Bladder wall
collagen of, 1634-1635
elastin of, 1635
matrix of, 1635
stroma of, 1634
- Bland thrombus, IVC filtration and permanent interruption for, 1444
- Bleeding. *See also* Hemorrhage
with laparoscopic radical prostatectomy, 2680
after midurethral sling, 2036-2037, 2026.e1t-2026.e2t
in monopolar transurethral resection of prostate, 2512
post-transplant, 1083, 1083f
with prostate biopsy, 2588
renal. *See* Renal bleeding
urethral, 192-193, 193b-194b
in urine. *See* Hematuria
- Bleomycin, for penile cancer, 872-873
- Bleomycin-etoposide-cisplatin (BEP)
for NSGCTs, 799-802, 800t
for seminomas, 809
- Blind access, to upper urinary tract collecting system, 166, 166f
- Blind trocar placement, complications related to, 217-218
- α -Blockade, in pheochromocytoma treatment, 1550-1551, 1551f
- β -Blockade, in pheochromocytoma treatment, 1551f, 1552
- α -Blockers, for ureteral stent symptoms, 131-132
- β -Blockers, preoperative, 103
- Blood flow, renal. *See* Renal blood flow
- Blood pressure
anesthesia-related changes in, during laparoscopic and robotic surgery, 220.e1
increased. *See* Hypertension
- Blood product transfusions
for pediatric patients, 2960
children of Jehovah's Witnesses, 2955
preoperative considerations for, 112-113
for laparoscopic and robotic surgery, 196
- Blood tests, for male urinary incontinence, 1707-1708
- Blood-epididymis barrier, 530
- Blood-seminiferous tubule barrier. *See* blood-testis barrier
- Blood-testis barrier, 501, 523-525
- Blunt dissection instrumentation, for laparoscopic and robotic surgery, 205-206, 210
- Blunt trauma
renal, 1148
imaging of, 1149-1150
nonoperative management of, 1152
renal artery thrombosis with, 1155, 1156f
ureteral, 1157, 1157t
diagnosis of, 1160-1161
- BMI. *See* Body mass index
- BMP-7. *See* Bone morphogenetic protein-7
- BMSCs. *See* Bone marrow stem cells
- Boari flap
distal ureterectomy and direct neocystostomy or ureteroneocystostomy with, 1385-1386, 1387f
laparoscopic or robotic, 2260-2262
with bladder advancement flap, 2260, 2262f
complications with, 2261-2262
conclusions for, 2262
evaluation for, 2260
indications for, 2260
laparoendoscopic single-site, 2260-2261
with mega-Boari flap, 2260, 2263f
outcomes with, 2261-2262
technique for, 2260-2261, 2261f
for lower ureteral injuries, 1163, 1165f
with ureteroneocystostomy
laparoscopic, 1137-1139
open, 1136-1137, 1138f
- Body habitus, hormonal therapy and, 2795
- Body mass index (BMI), 542-543
benign prostatic hyperplasia and, 2442-2444, 2445t
male SUI and, 1711
orthoptic urinary diversion and, 2350
prostate cancer and, 2551-2552, 2552f
renal calculi and, 1172-1173
urinary incontinence and, 1748-1749
- Body weight, renal calculi and, 1172-1173
- Bone, PTH effects on, 1012
- Bone anchor bulbourethral sling
complications with, 2182, 2182b
history and development of, 2170, 2170f
implantation technique for, 2179-2180, 2180f
long-term results with, 2182, 2183b
mechanisms of action of, 2171, 2171f
- Bone marrow stem cells (BMSCs), for female SUI injection therapy, 2061-2062
- Bone metastases
radiation therapy for localized prostate cancer and, 2708
systemic radionuclide therapy for, 2708, 2708t

- Bone mineralization, renal regulation of, 1011-1012, 1011f
- Bone morphogenic protein-7 (BMP-7), in tubulointerstitial fibrosis, 1098-1099
- Bone scan
for metastatic disease detection, 2746
whole body, 39
- BoNT. *See* Botulinum toxin
- BoNT-A. *See* Botulinum toxin
- Bony pelvis
female, 1597, 1598f
male, 1598f, 1611
- Bony scaffolding, of pelvic floor, 1939, 1940f
- BOO. *See* Bladder outlet obstruction
- BOR. *See* Bladder outlet relation
- Bors-Comarr classification, of voiding dysfunction, 1694-1695, 1694b
- Bosniak classification for renal cystic lesions, 45, 1301-1302, 1301f-1302f, 1301t, 1318-1320, 1318f-1320f, 1319t, 1460t
- Botox. *See* OnabotulinumtoxinA
- Botulinum toxin (BoNT). *See also* OnabotulinumtoxinA
adverse effects of, 1862-1863
for bladder and bowel dysfunction, 3308
clinical use of, 1862
for detrusor underactivity, 1819
efficacy of, 1862
to facilitate bladder emptying, 1874.e3-1874.e4
to facilitate bladder filling and urine storage, 1839t, 1861-1863
mechanism of action of, 1861-1862
for neuromuscular dysfunction of lower urinary tract, 3282
for Parkinson disease, 1768
for prostatic injections, 2534.e3-2534.e4
- Bowel disorders
normal *versus*, 3318, 3318b
sacral nerve stimulation for, 1908
- Bowel entrapment, during laparoscopic and robotic surgery, 222
- Bowel function
abnormal *versus* normal, 3318, 3318b
urinary incontinence and, 1893-1894
- Bowel injury
during laparoscopic and robotic surgery, 220-221, 220f
in pediatric patients, 2971
laparoscopic kidney surgery causing, 1481, 1481f
- Bowel insufflation, during laparoscopic and robotic surgery, 216
- Bowel interposition, for ureteral injuries, upper, 1163
- Bowel mobilization, in transurethral resection of bladder tumor, 2246, 2246f
- Bowel obstruction, with intestinal anastomoses, 2290-2291, 2291t, 2292f
- Bowel preparation
preoperative, 106-108
for laparoscopic and robotic surgery, 196
for urinary tract reconstruction, 3333
- Bowel resection, orthotopic urinary diversion and, 2350-2351
- Bowen disease, 846-847, 847b, 846.e1f
of penis, 846.e1f
- Bowenoid papulosis
as neoplastic condition, 411, 411f
of penis, 846.e3
- BP. *See* Bullous pemphigoid
- BPE. *See* Benign prostatic enlargement
- BPH. *See* Benign prostatic enlargement; Benign prostatic hyperplasia
- BPO. *See* Benign prostatic obstruction
- BPS. *See* Bladder pain syndrome
- BPS/IC. *See* Bladder pain syndrome and interstitial cystitis
- BRA. *See* Bilateral renal agenesis
- Brachytherapy
benign bounce phenomenon and, 2691
for penile cancer, 868-869, 869t
for prostate cancer, 2621-2622, 2699-2702, 2699f-2700f
external irradiation with, 2701-2702
high-dose-rate, 2700-2701
implant outcome, 2701, 2701t
permanent implant quality assessment, 2700, 2700t
potency and, 2702
radiation dose and fields for, 2621
rectal toxicity with, 2702
results of, 2621
side effects of, 2621-2622
toxicity of, 2702
urinary toxicity with, 2702
salvage. *See* Salvage brachytherapy
for UUT, 1399
whole-gland salvage, for prostate cancer recurrence, 2747
- Bradley classification, of voiding dysfunction, 1695
- Brain circuits, in detrusor underactivity, 1810, 1812f
- Brain metastases, of TGCTs, 810, 811b
- Brain tumor
lower urinary tract dysfunction with, 1765
neurogenic bladder with, 3293
- Brainstem
bladder modulatory mechanisms of, 1663, 1666f
neurotransmitters and modulators within, 1664-1665
neuromuscular lower urinary tract dysfunction at and above, 1761b, 1763-1768
- Brainstem stroke, lower urinary tract dysfunction with, 1765
- Bremelanotide, and HSDD, 759.e2
- Bricker anastomosis, 2296t, 2298, 2298f
- Brief Index of Sexual Functioning for Women (BISF-W), 753.e2
- Brindley-Finetch system, for sacral root stimulation, 1914-1915, 1914f
- Bristol Stool Scale, 3305, 3305f, 3318, 3319f
- Broad ligament, 1600, 1601f
- Brushite calculi, surgical management of, 1242
stone fragility and, 1243.e1
- Brushite stone formers, 1177, 1178f
- Brushite stones, surgical management of, method selection for, 1243.e2
- BT. *See* Behavioral therapy
- B-TURP. *See* Bipolar transurethral resection of prostate
- Bulbocavernosus reflex (BCR), in pelvic floor disorders, 1701
- Bulbospongiosus, 1603
- Bulbourethral artery, 510
- Bulbourethral glands, 510
- Bulbous urethra, 510, 511f, 910.e1, 910.e2f
carcinoma of, 882-883, 882f-883f
- Bulkamid. *See* Polyacrylamide hydrogel
- Bullous pemphigoid (BP), 398, 399f
- Bumetanide, in stone formation, 1197
- BUO. *See* Bilateral ureteral obstruction
- Bupivacaine, for pediatric patients, 2956
- Burch colposuspension, 1920-1921, 1920f
Marshall-Marchetti-Krantz procedure comparison with, 1936
paravaginal defect repair comparison with, 1936
prophylactic, 1936
- Burch colposuspension (*Continued*)
pubovaginal sling comparison with, 1934-1935, 1935f
reoperative surgery, 1927-1928
results with, 1927
suspension configuration in, 1921
technique for, 1925-1927, 1926f
urethral elevation in, 1921
- Buried penis, 3374-3375, 3374f-3375f
- Burns, of penis, 2384-2385, 916.e2
- Buschke-Löwenstein tumor, 846.e1f, 846.e4, 846.e4b. *See also* Verrucous carcinoma
- N-Butylcyanoacrylate, vasectomy sterilization performed with, 951
- BWS. *See* Beckwith-Wiedemann syndrome
- BXO. *See* Balanitis xerotica obliterans
- Bypass techniques, for vena caval thrombectomy, 1441-1443, 1442f-1443f, 1442.e1f, 1443.e1f
- C**
- C. *See* Bladder compliance
- C3 complement, in prostatic secretions, 2417t, 2422
- CA. *See* Cryoablation
- Cabazitaxel, 2809-2810, 2810f
- Cabozantinib, for UUT, 1400-1401, 1401f
- CaD. *See* Caldesmon
- CAD. *See* Coronary artery disease
- Cadaveric fascia, for pelvic organ prolapse reconstructive surgery, 1956-1957, 1957f, 1957t
- Cadaveric models, laparoscopic training with, 224.e3
- Cadherins, in prostate growth regulation, 2406-2407
- Caffeine, stone formation and, 1217
- Caffeine reduction, for urinary incontinence, 1893
- CAH. *See* Congenital adrenal hyperplasia
- CaHA. *See* Calcium hydroxyapatite
- CA-IX. *See* Carbonic anhydrase IX
- Calcidiol. *See* 25-Hydroxycholecalciferol
- Calcifying nanoparticles (CNPs), 1176-1177
- Calciphylaxis, 1070
- Calcitonin gene-related peptide (CGRP)
in ED, 626-627
in ureteral function, 992
- Calcitriol. *See* 1,25-Dihydroxycholecalciferol
- Calcium
dietary, in renal calculi management, 1220-1221, 1221b
distal tubule reabsorption of, 1018
loop of Henle reabsorption of, 1016-1017
metabolism of, 1180
PCT reabsorption of, 1015, 1016f
in prostate cancer, 2550
PTH and, 1011f, 1012, 1180
sensitization to, 1643
in smooth muscle contraction, 1642-1643, 1643b, 1646, 1647f
in ureter physiology, 978-982, 981f, 984-985, 984f-985f
excitation-contraction coupling and, 985-986
as second messenger, 986-988, 987f-988f
vitamin D and, 1011f, 1012, 1183
- Calcium antagonists, urethral function effects of, 1005
- Calcium apatite, 1176
- Calcium channel blockers (CCBs)
for AKI, 1051
to facilitate bladder filling and urine storage, 1839t, 1852
in pheochromocytoma treatment, 1551f, 1552
ureteral function effects of, 1001-1002, 1005

- Calcium channels, in detrusor muscle, 1645-1646, 1647f
- Calcium citrate, for enteric hyperoxaluria, 1227
- Calcium hydroxyapatite (CaHA), for vesicoureteral reflux, 3169
- Calcium hydroxylapatite (Coaptite), for female SUI injection therapy, 2060
- Calcium oxalate stones
adherence of, 1175
of crystal formation, 1178-1179
formation of, 1174-1175
formers of, 1176-1177
homogeneous nucleation, 1175
Randall plaques and, 1175-1177, 1176f-1177f
surgical management of, 1242
stone fragility and, 1243.e1
- Calcium preparations, for enteric hyperoxaluria, 1227
- Calcium stones
hypercalciuria, 1182-1185, 1209-1210, 1210f
hyperoxaluria, 1185-1187, 1185f-1186f, 1210-1211, 1211b
hyperuricosuria, 1187, 1210
hypocitraturia, 1188, 1211-1212, 1211f, 1212b
hypomagnesiuria, 1190, 1212
- Calcium-induced calcium release (CICR), 1646
- Calculi
after augmentation cystoplasty, 3353
bladder. *See* Bladder calculi
HIV and, 384-385
pediatric. *See* Pediatric stone disease
pediatric imaging of
CT, 2918
ultrasonography, 2913, 2915f
after pediatric renal transplantation, 3536
preputial, 1299
prostatic, 1296-1297
renal. *See* Renal calculi
ureteral. *See* Ureteral calculi
urethral. *See* Urethral calculi
- Caldesmon (CaD), 1641-1642, 1643f
- Caliceal diverticula, renal calculi and, 1198
- Calicovesicostomy, for ureteropelvic junction obstruction, laparoscopic, 1122
- Calyceal diverticula, 2999-3001, 3000f, 3040, 3041f
renal calculi with, surgical management of, 1243-1244, 1278-1279, 1279f
- Calyceal diverticulectomy, laparoscopic, 1463-1464
- Calyces
hydrocalycosis, 3001-3002, 3001f
megacalycosis, 3002-3003, 3002f
renal, 155-156, 155f-156f, 968, 968.e1f. *See also* Pelviccalyceal system
normal urothelium of, 1369, 1369f-1370f
- Cameras, for laparoscopic and robotic surgery, 205, 205.e1f-205.e2f
- Casey II orthoptic substitute, 2355, 2356f
- cAMP. *See* Cyclic adenosine monophosphate
- Camper fascia, 1611, 1612f
- Cancer. *See also* Malignancy; Oncology; *specific cancers*
chronic inflammation in, 451, 453b
bladder cancer, 451, 452f
kidney cancer, 451-452
prostate cancer, 452-453
immunologic response to, 447, 451b
adaptive immune system, 449-450, 449f
immune editing hypothesis, 450-451, 450f
innate immune system, 447-448, 448f-449f, 448t-449t
- Cancer (Continued)
immunotherapy for, 447, 458b
BCG in bladder cancer, 447, 448f, 453-454, 453f
cancer vaccines, 454-456, 454f, 456f
immune checkpoint blockade, 456-458
molecular genetics of. *See* Molecular genetics of GU cancers
pediatric. *See* Pediatric oncology
perioperative care for children with, 2955
of testis, 568
with urinary intestinal diversion, 2314
vaccines for, 454, 454f, 456
for genitourinary tumors, 456
for kidney cancer, 454-455
for prostate cancer, 455-456, 456f
- Cancer patients, and female sexual function, 755, 755.e1
- Cancer-specific HRQOL instruments, 92t-94t, 95
- Candidal intertrigo, 407, 408f
- Candidiasis, 381, 381t
- Cannabinoids
in bladder afferent pathway, 1656
in ED, 623, 623t
to facilitate bladder filling and urine storage, 1866.e2-1866.e3
- Cantwell-Ransley procedure, for classic bladder exstrophy repair, 3204, 3207f-3208f
- Capacitive coupling, 220, 220f, 227
- Capillary hemangiomas, 419
- Capsaicin
to facilitate bladder filling and urine storage, 1839t, 1863
intravesical, 1863.e1
ureteral response to, 992
- Capsular perforation
with holmium laser enucleation of prostate, 2529
with transurethral incision of prostate, 2526
with transurethral vaporization of prostate, 2517.e4
- Capsular polysaccharide, 2930
- Captopril, for cystinuria, 1230
- Carbachol. *See* Carbamylcholine
- Carbamylcholine (Carbachol), ureteral response to, 990-991
- Carbon dioxide (CO₂)
acid-base balance and, 1023-1025
as insufflant choice, 211-212
- Carbon dioxide (CO₂) laser, 230
- Carbon monoxide (CO)
in ED, 626
renal vascular tone control by, 1010-1011
- Carbonated beverages, nephrolithiasis and, 1217, 1217b
- Carbon-coated zirconium beads (Durasphere), for female SUI injection therapy, 2057, 2057t
- Carbonic anhydrase inhibitors, in stone formation, 1197
medical management of, 1231
- Carbonic anhydrase IX (CA-IX, MN-9), 1325, 1341b
- Carboplatin
for NSGCTs, 801-802, 805
for penile cancer, 873
for seminomas, 806, 808-809, 808t
for UTUC, 1400
- Carcinoid tumors, of kidney, 1361t, 1363
- Carcinoma in situ (CIS)
of penis, 846-847, 847b, 846.e1f
UTUC association with, 1368
management guidelines for, 1396-1398, 1398f
- Cardiac arrest, anesthesia-related, during laparoscopic and robotic surgery, 220.e1
- Cardiac arrhythmia
anesthesia-related, during laparoscopic and robotic surgery, 220.e1
pneumoperitoneum causing, 212
- Cardiac disease, contrast media considerations in, 30
- Cardiac evaluation, preoperative, 101-102, 102f
- Cardiac glycosides, urethral function effects of, 1005
- Cardiac ischemia, during vena caval thrombectomy, 1444-1445
- Cardiac Risk Index, 101, 101t
- Cardinal ligament, 1600, 1602f
- Cardinal veins, retrocaval ureter and, 1125, 1128b
- Cardiopulmonary bypass (CPB), for vena caval thrombectomy, 1442-1443, 1442f-1443f, 1443.e1f
- Cardiovascular disease (CVD), 547-549
in CKD, 1064-1066
and ED, 632
in ESRD, 1070-1071
hormonal therapy and, 2795
MetS and, 551, 553
renal calculi and, 1173
testosterone and, 547-549, 549b
- Cardiovascular events, 539
- Cardiovascular system
abnormalities of, with cloacal exstrophy, 3228
pneumoperitoneum effects on, 212-213, 213t
postnatal considerations for, 2950
testosterone actions on, 548-549
coagulation, 549
endothelial dysfunction, 548-549
inflammation, 549
Wilms tumor treatment effects on, 3579
- Care. *See* Health care
- CARE trial. *See* Colpopexy and Urinary Reduction Efforts trial
- Carnitine, for PD, 734
- Carter-Thomason needle-point suture passer, 211, 211f
- Caruncle, urethral, urethral diverticula differentiated from, 2163, 2163f
- CASA. *See* Computer-assisted semen analysis
- Casale continent catheterizable stoma, 3364, 3365f
- Case mix, in outcomes research, 88
- Caspases, in GU cancers, 479
- Castration-resistant prostate cancer
anaplastic phenotype, 2820-2821, 2822f
androgen receptor-directed approaches to, 2811-2813
androgen receptor modulation, 2812-2813, 2812f
CYP17 inhibition, 2811-2812, 2811f
assessment of, 2805-2806
bisphosphonates for, 2819-2820
bone-targeted approaches to, 2818-2820
clinical considerations for, 2805-2807
cytotoxic chemotherapy for, 2807-2810
epidural cord compression in, 2818, 2819t
immunotherapy for, 2813-2815
immune checkpoint blockade, 2814-2815
ProstVac-VF, 2814, 2814f
sipuleucel-T, 2813-2814, 2814f
metastatic, 2806-2807
neuroendocrine phenotype, 2820-2821, 2822f
nonmetastatic, 2806
pain in, 2818, 2819t
palliative management of, 2818-2820

- Castration-resistant prostate cancer (*Continued*)
 prognostic considerations for, 2805-2806, 2805f
 radiopharmaceuticals for, 2820, 2821f
 RANKL inhibitors for, 2820
 targeted treatments for, 2815-2818
 angiogenesis, 2816-2817
 apoptosis pathway, 2818
 mesenchymal-epithelial transition signaling, 2817-2818
 PI3K/Akt/mTOR pathway in, 2815-2816
- Casts, in urinary sediment, 23, 23f
- Catch bonds, 243
- Catechins, of green tea, in prostate cancer prevention, 2564
- Catecholamine hypersecretion, in evaluation of adrenal masses, 1574-1575
- Catecholamine synthesis blockade, in pheochromocytoma treatment, 1551f, 1552
- Catecholamine testing, in pheochromocytoma diagnostic tests, 1549
- Catecholamines, adrenal medulla physiology and, 1531, 1533t
- Catheter placement, for urodynamics, 1706
- Catheter-associated bacteriuria, UTIs and, 299-300, 300b
- Catheterization
 bladder. *See* Bladder catheterization
 for bladder emptying failure, 1906-1907, 2077f
 continuous, 2078-2079
 suprapubic, 124-126, 125f
 ureteral. *See* Ureteral stents and catheters
 urethral, antimicrobial prophylaxis for urologic procedures and, 260-262
- Catheterized urine specimens, in urine collection, 250
- Catheters
 air-charged, for urodynamic studies, 1723-1724
 indwelling, in geriatric patients, 2099.e5
 long-term, bladder cancer and, 1778
 water-filled, for urodynamic studies, 1723-1724
- Cation transport, urinary tract obstruction and, 1096
- Cauda equina, 1781
- Cauda equina syndrome, 1781
- Caudal blocks, for pediatric patients, 2956
- Cauterization, energy modalities for
 electrosurgery, 225-227, 226f
 laser instrumentation, 228-230, 229f
 ultrasound instrumentation, 227-228
- Cautery wire balloon endopyelotomy, retrograde. *See* Retrograde cautery wire balloon endopyelotomy
- Cautery wire balloon incision, for ureteroenteric strictures, 1142-1143
- CAVD. *See* Congenital absence of vas deferens
- Cavernosal nerves, 506, 617f-618f, 910.e5
- Cavernosogram, of penis, 513, 514f
- Cavernous smooth muscle content test, 654
- Cavitation mechanism
 of stone comminution, 1269f, 1270
 in ultrasonography, 73
- Cavoplasty, for IVC, 1443-1444, 1443f
- CBAVD. *See* Congenital bilateral absence of vas deferens
- CBCL. *See* Child Behavior Checklist
- CBE. *See* Classic bladder exstrophy
- CC. *See* Corpora cavernosa
- CCBs. *See* Calcium channel blockers
- CCI. *See* Charlson Comorbidity Index
- CCSK. *See* Clear cell sarcoma of kidney
- CCT. *See* Cortical collecting tubule
- CDC. *See* Centers for Disease Control and Prevention
- CDH1 gene, in bladder cancer, 463-464
- CDKs. *See* Cyclin-dependent kinase inhibitors
- CDKN1B, in UTUC, 1375
- CEA. *See* Continuous epidural analgesia
- Cecocystoplasty, 3346
- Cefazolin, preoperative prophylaxis with, 2959t
- Cefotetan, preoperative prophylaxis with, 2959t
- Cefoxitin, preoperative prophylaxis with, 2959t
- Celecoxib, urethral function effects of, 1005
- Cell adhesion molecules, in prostate growth regulation, 2406-2407
- Cell cycle deregulation, in GU cancers, 460-461, 462b
- CDKs, 461-462, 461f
 cell cycle entry, 461.e1
 cell cycle progression through S phase, 461.e1
 cyclin-dependent kinases and cyclins, 461f, 461.e1
 G₁/S checkpoint, 461.e2
 G₂/M checkpoint, 461.e2
 mitosis, 461.e1-461.e2
 mitotic arrest and spindle assembly checkpoint, 461.e2
 RB1, 461, 461.e1
 S phase arrest, 461.e2
 TP53, 462, 462f, 461.e2
- Cell therapies
 bladder, 491-492
 penile, 492
- Cell transplantation, bladder regeneration using, 489
- Cell-based therapy, for female SUI injection therapy, 2061-2062
- CellCept. *See* Mycophenolate mofetil
- Cells, in urinary sediment, 21-23, 21f-22f
- Cellules, 2141-2142
- Cellulitis, 402, 403f
 genital skin loss and, 2384
- Centers for Disease Control and Prevention (CDC), 371
- Central perineal tendon, 910.e6f-910.e7f, 910.e8
- Central venous pressure, pneumoperitoneum effects on, 213
- Cephalad renal ectopia, 2986
- Cephalexin, for UTIs, 272t, 273, 278t
- Cephalosporins
 preoperative prophylaxis with, 106t-107t
 prophylaxis with, for uncomplicated urologic procedures, 261t-262t
 for UTIs, 256t-258t, 259, 296t
- Cerebellar ataxia, lower urinary tract dysfunction with, 1765-1766
- Cerebral palsy (CP)
 lower urinary tract dysfunction with, 1766
 pathogenesis of, 3292-3293
 presentation of, 3292
 specific recommendations of, 3293
- Cerebral vascular disease, AD and, 548
- Cerebrovascular accident (CVA), lower urinary tract dysfunction and, 1763-1765, 1764b
- Cerebrovascular disease, lower urinary tract dysfunction and, 1763-1765, 1764b
- Cerebrum, micturition control by, 1665-1666
- Cernilton, for diminished bladder, 1831, 1832t-1834t
- Cervical atresia, 3465
- Cervical myelopathy, lower urinary tract dysfunction with, 1778
- Cervical RMS, in pediatric patients, 3590
- Cervix, anatomy of, 1605, 750.e4
- Cesarean delivery, urinary incontinence and, 1748
- Cetorelix, for benign prostatic hyperplasia, 2077f
- CFTR. *See* Cystic fibrosis transmembrane conductance regulator
- CGA. *See* Comprehensive geriatric assessment
- cGMP. *See* Cyclic guanosine monophosphate
- CGRP. *See* Calcitonin gene-related peptide
- Chancroid, 373t, 377-378, 377f
- Chaperonin, androgen receptor binding of, 2408-2409
- Charges, for health care, 86
- Charlson Comorbidity Index (CCI), 2085
- Chemical examination of urine
 for AKI, 1048-1049, 1049f, 1049t
 dipstick testing, 14
 bilirubin and urobilinogen, 19-20
 glucose and ketones, 19
 hematuria, 14-16, 15t, 16f-18f
 leukocyte esterase and nitrite, 20, 20f
 proteinuria, 17-19, 19f
- Chemically induced inflammation, in prostatitis and CPPS etiology, 308
- Chemodervation, for urinary incontinence, in geriatric patients, 2099.e5
- Chemokines, 447-448, 449f, 449t
- Chemotherapy. *See also specific agents*
 adjuvant. *See* Adjuvant chemotherapy
 for castration-resistant prostate cancer, 2807-2810
 cabazitaxel, 2809-2810, 2810f
 clinical trials of, 2807-2810
 docetaxel, 2808-2809, 2808f-2809f
 mitoxantrone, 2807-2808
 hemorrhagic cystitis caused by, 188-190
 intravesical. *See* Intravesical chemotherapy
 for ITGCN, 797
 for metastatic bladder cancer, 2237-2238, 2237t
 randomized trials in, 2237t, 2238
 second-line, 2238, 2238t
 for metastatic RCC, 1516-1518, 1517f
 for muscle-invasive bladder cancer, 2234
 neoadjuvant. *See* Neoadjuvant chemotherapy
 for neuroblastoma, 3564-3567, 3565f
 at PC-RPLND, 830-831
 for penile cancer, 871, 873b
 adjuvant, 872
 combination, 871-872, 872t
 single-agent, 871
 surgical consolidation after, 872-873
 at primary RPLND, 827-829
 with radiation therapy, for locally advanced prostate cancer, 2765
 for RCC, resistance to, 1325, 1325t
 for retroperitoneal sarcomas, 1411-1412, 1411b
 for TGCTs, 786, 795-796
 with brain metastases, 810
 NSGCTs, 799-802, 800t, 804-806
 relapsed tumors, 804-806
 residual mass management after, 802-805, 803t, 809
 seminomas, 806, 808-810, 808t
 toxicity of, 811
 urothelial cancer and, 2188
 for UTUC
 instillation of, 1398-1399, 1398f, 1399t
 metastatic disease, 1400-1401, 1401f
 systemic, 1400
 UTUC risk and, 1366
 for Wilms tumor, 3571-3572, 3575, 3577-3579, 3578f
- Chest, imaging studies of, for TGCTs, 794
- Chevron incision, for open kidney surgery, 1419-1420
- Chief complaint, 1-7, 4t-5t
- Child Behavior Checklist (CBCL), 3301

- Childhood diseases, and male infertility, 560-561
- Children. *See* Pediatric patients
- Children's Oncology Group (COG)
staging systems and risk group assignments of
for bladder RMS, 3585, 3585b
for testicular tumors, 3593, 3593t
for Wilms tumor, 3574, 3574t
treatment recommendations of
bladder RMS approaches, 3586
Wilms tumor chemotherapy, 3577-3579, 3578f
Wilms tumor studies of, 3575-3576
- Chills, patient history of, 7
- Chlamydia*
as fastidious organism in UTIs, 242
as nongonococcal urethritis, 372
prostatitis microbiology and, 306
- Chloride
in collecting tubule, 1018-1019, 1018f
in distal tubule, 1018
in loop of Henle, 1016, 1017f
- Chloride absorption, after augmentation
cystoplasty, 3351
- Chlormadinone acetate, for benign prostatic
hyperplasia, 2487
- Chloroquine derivatives, for BPS/IC oral
therapy, 353t, 354
- Chlorthalidone, for absorptive hypercalciuria,
1224
- Cholecalciferol (vitamin D₃), 1011-1012
- Cholesterol
metabolic syndrome and, 551
testosterone synthesis from, 522
- Cholestyramine, for enteric hyperoxaluria, 1227
- Cholinergic agonists, ureteral response to,
990-991
- Chondrocytes, for vesicoureteral reflux, 3169.e1
- Chondroitin sulfate, in crystal formation,
1178-1179
- Chordee, in classic bladder exstrophy repair,
3203
- Chordee without hypospadias, 939-941, 939.e1,
940.e1
- Choriocarcinoma
histology of, 787f, 788
spread of, 793, 810
- Chromatin, of spermatozoa, 535
- Chromatin remodeling
androgen receptor-dependent, 2412-2413
in prostate cancer, 2555-2556
- Chromogranin A testing, in pheochromocytoma
diagnostic tests, 1550
- Chromophilic RCC. *See* Papillary RCC
- Chromophobe RCC, pathology of, 1329t-1330t,
1332-1333, 1332f
- Chromosomal abnormalities
in GU cancers, 465, 476b
bladder cancer, 472-474
bladder RMS, 3582-3583
CNAs, 467-468, 468t
gross abnormalities, 465-466, 465b
neuroblastoma, 3559-3560
prostate cancer, 466-471, 468t, 469f
renal cancer, 467, 468t, 471-472, 1321-
1325, 1322t-1323t, 1323f
testicular cancer, 467, 474-475, 3591
UTUC, 1375-1376
Wilms tumor, 468t, 3568-3570, 3568t,
3574
- male reproductive physiology and
age-related, 528
azoospermia and oligospermia resulting
from, 526-528
- Chromosomal instability
telomerase reversal of, 477
telomeres and, 476
- Chromosomal recombination, 526-527
- Chromosomal sex, 3469, 3470f
- Chromosomes, basics of, 459.e4
- Chronic bacterial prostatitis, clinical
presentation, 310-311
- Chronic inflammation, in cancer immune
response, 451, 453b
bladder cancer, 451, 452f
kidney cancer, 451-452
prostate cancer, 452-453
- Chronic kidney disease (CKD), 1068b,
2868-2869
clinical assessment of, 1060
function, 1060-1061
proteinuria, 1054t, 1061
radiographic, 1061-1062
UA and kidney biopsy, 1062
definition and classification of, 1053-1055,
1054t, 1055f-1056f
etiology of, 1058-1060, 1058b, 1058t, 1060b,
2869, 2869b, 2869t
genetic factors in, 1057-1058
hospitalization risk in, 1065-1067, 1067b,
1067t
management of
conservative, 1064
ESRD options, 1065, 1066b, 1066f, 1067t
RRT initiation, 1064-1065
mechanism of progression in, 1056-1057
medical complications of, 2869
after nephrectomy, 1344-1345, 1345b
preoperative evaluation for, 1063-1064
renal mass reduction and, 1055-1056
renal protective strategies in, 1062-1063, 1063t
- Chronic Kidney Disease Epidemiology
Collaboration (CKD-EPI) formula, 1009,
1090-1091
- Chronic pelvic pain syndrome (CPPS)
chronic prostatitis/chronic pelvic pain
syndrome. *See* Chronic prostatitis/chronic
pelvic pain syndrome
clinical presentation, 311
definition and classification, 310, 310b, 310t
epidemiology, 304, 305b
etiology, 309, 309b, 309f
altered prostate host defense in, 307
bladder pain syndrome and interstitial
cystitis associated with, 309
chemically induced inflammation in, 308
dysfunctional voiding in, 307
immunologic alterations in, 308
intraprostatic ductal reflux in, 307-308
microbiology, 305-307
neural sensitization, 308
pelvic floor muscle abnormalities in, 308
psychosocial associations, 308-309
histopathology, 305, 305f
historical perspective, 304
prostatic calculi and, 1297
- Chronic prostatitis (CP)
clinical presentation, 310-311
definition and classification, 310, 310t
etiology, 305-309
histopathology, 305
- Chronic prostatitis/chronic pelvic pain
syndrome (CP/CPPS)
clinical presentation, 311
evaluation
cytologic considerations, 314-315, 315f
diagnosis and classification approach, 317,
317f, 318b
- Chronic prostatitis/chronic pelvic pain
syndrome (CP/CPPS) (*Continued*)
endoscopy in, 315
lower urinary tract cytologic examination
and culture, 313-314, 313f-314f, 314b
microbiologic considerations, 314
other potential markers, 316
physical examination, 313-314, 313f-314f,
314b
prostate biopsy, 316
seminal vesiculitis and, 316
symptom assessment, 311-312, 312b, 312f
ultrasonography in, 315-316
urodynamics, 315
minimally invasive therapies for, 326-327
phenotype assessment in, 317-318, 318f, 319b
treatment, 319, 329, 329b
acupuncture, 325
 α -adrenergic blocker therapy, 322-323
allopurinol, 324
anti-inflammatory agents and immune
modulators, 323
antimicrobials, 319-322, 320t-321t
biofeedback, 325
conservative therapies, 326
hormone therapy, 323-324
muscle relaxants, 323
neuromodulator therapy, 324
pelvic floor physiotherapy, 325
phenotype-directed multimodal, 327-328,
328f
phytotherapeutic agents, 324
prostatic massage, 325
psychological support, 325-326
pudendal nerve entrapment therapy, 325
traditional surgery for, 327
- Chronic pyelonephritis, 285-286, 286f
- Chronic rejection, of renal transplantation,
1084
- Chronic renal failure, and ED, 641
- Chronic schistosomiasis, 437
- Chronic unilateral essential hematuria. *See*
Lateralizing essential hematuria
- CHXSRV-coated stents. *See* Sustained-release
varnish containing chlorhexidine-coated
stents
- Chylous ascites
laparoscopic and robotic surgery causing,
224.e1
after RPLND, 834
- Chyluria
as filariasis clinical manifestation, 444
nephrolysis for, 1464, 1464f
- Cialis. *See* Tadalafil
- CIC. *See* Clean intermittent catheterization
- CICR. *See* Calcium-induced calcium release
- Cidofovir, for condylomata acuminata, 846.e3
- Cigarette smoking. *See* Smoking
- Ciliary dyskinesia, of spermatozoa, 537
- Cimetidine, serum creatinine effects of,
1060-1061
- CIN. *See* Contrast-induced nephropathy
- Circle nephrostomy tubes, 172, 173f
- Circulating tumor cells (CTCs), as prostate
cancer biomarkers, 2573, 2573f
- Circulation. *See* Vascularity
- Circumcision, 2907, 2907f, 3370-3371
complications of, 3371-3373, 3371f-3372f
urethral reconstructive surgery and, 915
female, 3467-3468, 3468f
penile cancer management with, 855-856
penile carcinoma prevention with, 847-849
for posterior urethral valves, 3261-3262
and UTIs, 2930-2931

- Circumferential compression mechanism, of stone comminution, 1266f, 1269-1270
- CIS. *See* Carcinoma in situ
- Cisapride, to facilitate bladder emptying, 1871-1872
- Cisplatin. *See also* Bleomycin-etoposide-cisplatin for penile cancer, 871-873, 872t for TGCIs, 786, 799-801, 800t, 805 toxicity of, 811 for UTUC, 1400
- Cisplatin and gemcitabine (GC), for UTUC, 1400
- Citrate, in crystal formation, 1178, 1188
- Citric acid, in prostatic secretions, 2415
- Citrus juices, nephrolithiasis and, 1217, 1217b
- CKD. *See* Chronic kidney disease
- CKD-EPI formula. *See* Chronic Kidney Disease Epidemiology Collaboration formula
- Classic bladder exstrophy (CBE), 3174-3175 abdominal wall defects in, 3187 anatomic considerations in, 3185-3191 anorectal defects in, 3187 antireflux procedure for, 3205f-3206f, 3209-3210 chordee in, 3203 complete repair for, 3197, 3198f continence outcomes with, 3213-3214 technical aspects of, 3202, 3204f continence procedure for, 3205f-3206f, 3209-3210 continence with, 3218 continent urinary diversion for, 3217-3218 epispadias repair for, 3203 failure of, 3215f, 3216-3217 Erlangen approach to, 3198 continence outcomes with, 3213 evaluation of, at birth, 3193-3196, 3193f female genital defect in, 3189, 3189f immobilization techniques for, complications of, 3195f, 3196-3197 Kelly repair for, 3197 continence outcomes with, 3214 technical aspects of, 3202, 3203f long-term adjustment issues with, 3220-3221 male genital defect in, 3187-3188, 3187f-3188f management of, at birth, 3193-3196, 3193f Mitchell repair for, 3197, 3198f continence outcomes with, 3213-3214 technical aspects of, 3202, 3204f modern staged repair of exstrophy, 3198 bladder, posterior urethral, and abdominal wall closure for, 3198-3201, 3199f-3200f combined bladder closure and epispadias repair, 3201 management after, 3201-3202 osteotomy for, 3194-3196, 3195f-3196f complications of, 3195f, 3196-3197 outcomes and results of modern initial repair, 3210-3213 bladder neck repair, 3212-3213, 3212t epispadias repair, 3211-3212 initial closure, 3210-3211, 3212t pelvic floor defects in, 3186-3187, 3186f penile reconstruction for, 3203-3209 penile skin closure for, 3208 prenatal, 2880, 2881f prenatal imaging of, 2910-2911, 2912f reconstruction failures and complications, 3214-3218 epispadias repair, 3215f, 3216-3217 failed bladder neck repair, 3216 failed closure, 3214-3216, 3215f skeletal defects in, 3185-3186, 3185f surgical options in newborn with, 3197-3198 Mainz repair, 3197-3198
- Classic bladder exstrophy (CBE) (*Continued*) surgical reconstruction of, 3192-3210 alternative, 3217-3218 female exstrophy, 3209 patient selection for, 3193 postoperative care, 3210 postoperative problems, 3208-3209 small exstrophy bladder unsuitable for newborn closure, 3190f, 3193-3194 ureterosigmoidostomy for, 3217 urethral reconstruction for, 3203-3209, 3205f-3208f, 3215f urinary defects in, 3189-3191, 3190f Warsaw approach of, 3197 continence outcomes with, 3213
- Classic Wilms tumor, 3570-3571, 3571f
- Classical Cushing syndrome, 1535-1536, 1536f, 1537t
- Clean intermittent catheterization (CIC) for bladder and bowel dysfunction, 3307 for bladder emptying failure, 2078 for renal transplantation, 3530-3531 urinary tract infections and, 3275-3276
- Cleansing enema, for prostate biopsy, 2585
- Clear cell RCC chemotherapy for, 1516 familial form of, 468t, 471-472, 1321-1324, 1322t-1323t, 1323f hormonal therapy, 1516 immunologic approaches to, 1503-1504 allogeneic hematopoietic stem cell transplantation, 1506-1507, 1507t IL-2, 1505-1506, 1505t, 1506f immune checkpoint inhibitors, 1507 interferons, 1504t, 1505-1506, 1506f pathology of, 1329t-1330t, 1330-1331, 1330f targeted molecular therapies for basis of, 1507-1508, 1508f combination and sequential therapy with, 1516 mTOR pathway inhibitors, 1502-1503, 1514-1515, 1514t, 1515f others, 1514 VEGF inhibitors, 1502-1503, 1507-1514, 1508f-1512f, 1509t-1511t, 1513t
- Clear cell sarcoma of kidney (CCSK), in pediatric patients, 3579
- Clear cell variant of urothelial cancer, 2200-2201, 2201f
- Clearance. *See* Renal clearance
- Clenbuterol, for stress urinary incontinence in women, 1867-1868
- Climate, renal calculi and, 1171-1172
- Clindamycin preoperative prophylaxis with, 106t-107t, 2959t prophylaxis with, for uncomplicated urologic procedures, 261t-262t
- Clinical markers, of cardiac surgical risk, 101
- Clinical symptom scales, BPS/IC treatment assessment and, 363-364, 363t-364t, 365b, 366f-367f
- Clipping devices, for laparoscopic and robotic surgery, 208, 209b, 209f
- Clitoral bulbs, 750.e4
- Clitoris, 1604-1605, 1605f-1606f, 750.e2 disorders of, 3455-3456 diminutive clitoris, 3456, 3456f hypertrophied clitoris, 3455-3456, 3455f Clitoroplasty, initial management, timing, and principles for, 3504-3507, 3505f, 3507f
- Cloacal anomalies (*Continued*) radiographic and endoscopic evaluation of, 3503-3504, 3504f surgical reconstruction for. *See* Reconstructive surgery, for cloacal anomalies
- Cloacal exstrophy, 3174-3175, 3226-3229 anatomic considerations for, 3224f, 3226-3228 cardiovascular abnormalities with, 3228 evaluation of, at birth, 3229-3230 gender assignment for, 3230 genitourinary abnormalities with, 3228 intestinal tract abnormalities with, 3227-3228 long-term adjustment issues with, 3220-3221 long-term issues in, 3232 management of, at birth, 3229-3230, 3229b neurospinal abnormalities with, 3226-3227, 3227f prenatal, 2880-2881, 2882f prenatal diagnosis of, 3229 pulmonary abnormalities with, 3228 sexuality with, 3218-3219 male concerns, 3218 skeletal system abnormalities with, 3227-3228 surgical reconstruction of, 3229-3232 immediate, 3230 urinary continence creation in, 3232 urinary tract reconstruction of, 3230-3232 modern staged, 3228f-3230f, 3230-3231 osteotomy role in, 3231, 3231f single-stage, 3231-3232 variants of, 3228-3229
- Cloacal malformation, 2881, 2883f
- Clonidine to facilitate bladder emptying, 1873-1874 for pediatric patients, 2956
- Clonidine suppression testing, in pheochromocytoma diagnostic tests, 1550
- Cloning, for tissue engineering, 483-484, 484f
- Clopidogrel, preoperative, 110
- Clorapactin, for BPS/IC treatment, 356.e1
- Closed access techniques for achieving transperitoneal access and establishing pneumoperitoneum, 200 complications related to, 216
- Clostridial collagenase, for PD, 736
- Clots, hematuria with, 3
- CLPP. *See* Cough leak point pressure
- c-MET gene, 1322t, 1324, 1327b in UTUC, 1375
- CMG. *See* Cystometrography
- CMN. *See* Congenital mesoblastic nephroma
- CNAs. *See* Copy number alterations
- CNE. *See* Congenital nephrotic syndrome of Finnish type
- CNPs. *See* Calcifying nanoparticles
- CNT. *See* Connecting tubule
- CO. *See* Carbon monoxide
- CO₂. *See* Carbon dioxide
- Coagulation, testosterone effects on, 549
- Coaptite. *See* Calcium hydroxylapatite
- Coatings for catheters, 121 for urethral stents, 128
- Cocaine, urethral response to, 991-992
- Cockcroft-Gault formula, 1009
- Codeine, for pediatric patients, 2957-2958, 2957t
- Coffee, UTUC risk and, 1366
- COG. *See* Children's Oncology Group
- Cognition of geriatric urology patient, 2088-2089, 2089f hormonal therapy and, 2794-2795
- Cohen cross-trigonal technique, 3158-3163, 3162f
- Coital incontinence, 1711

- Colchicine, for PD, 734
- Collagen
- of bladder wall, 1634-1635
 - glutaraldehyde cross-linked bovine, for female SUI injection therapy, 2054-2057, 2055f, 2056t
 - porcine dermal, for female SUI injection therapy, 2060
 - of urethra, 1637
- Collagen disorders, and PD, 725
- Collecting duct RCC
- pathology of, 1329t-1330t, 1333
 - systemic therapy for, 1518
- Collecting system. *See also* Upper urinary tract collecting system
- anatomy of, 973, 974f
 - endoscopic, 976-977, 977b, 977.e1f
 - radiologic, 973-974
 - laparoscopic repair of, 1474-1475, 1475f
- Collecting tubule, functions of, 1018-1019, 1018f-1019f
- Colles fascia, 1611, 1612f, 910.e5-910.e7, 910.e6f-910.e7f
- Colon
- pseudo-obstruction of, 2292
 - reflection of, for simple nephrectomy, 1454, 1456f
 - for urinary diversion
 - preparation for, 2281-2284
 - selection of, 2281
 - surgical anatomy of, 2281.e1-2281.e2, 2281.e2f
- Colon conduit, 2306-2307, 2307f-2308f, 2309t
- Colon injury
- after percutaneous access to upper urinary tract collecting system, 179
 - in retroperitoneum, 773-775, 773f-774f, 773.e1f
- Colon pouches, right
- with intussuscepted terminal ileum, 2332-2333
 - operative technique variations for, 2339-2340, 2340f
 - for orthotopic urinary diversion, 2360
- Color, of urine, 13, 13t
- Color Doppler ultrasonography, 69
- transrectal, for prostate biopsy, 2588-2589, 2589f-2590f
 - for urinary tract obstruction, 1091
- Color flow with spectral display ultrasonography, 69
- Colorectal cancer, hereditary. *See* Hereditary nonpolyposis colorectal cancer
- Colpocleisis, for apical pelvic organ prolapse repair, 1974-1976
- in geriatric patients, 2099.e10
- partial
- results with, 1974-1976
 - technique for, 1974, 1975f-1976f
- total
- results with, 1974
 - technique for, 1974, 1977f
- Colpoperineorrhaphy, posterior, 1978-1979
- Colpopexy and Urinary Reduction Efforts (CARE) trial, 1707
- Colporrhaphy
- anterior
 - for pelvic organ prolapse, 1948-1953. *See also* Anterior colporrhaphy
 - retropubic suspension surgery comparison with, 1934 - posterior, for pelvic organ prolapse repair, 1979-1982. *See also* Posterior colporrhaphy
- Colposuspension
- Burch. *See* Burch colposuspension
 - definition of, 1920
 - laparoscopic, 1921, 1931
 - open retropubic, 1920
 - prophylactic, 1927
 - tension-free vaginal tape procedure compared with, 1936-1938
- CombAT Study. *See* Combination of Avodart and Tamsulosin Study
- Combination of Avodart and Tamsulosin (CombAT) Study, 2489-2491, 2491t
- Combination therapies, in ED, 667
- Combined intracavernosal injection and stimulation, in ED, 651
- Combined intravesical-extravesical diverticulectomy, for bladder diverticula, 2148, 2151f
- Comet tail artifact, 69f
- Common iliac arteries, 976, 976.e1f
- Common iliac veins, 976, 976.e1f
- Common penile artery, 910.e3-910.e5, 910.e5f
- Communicating hydrocele, epidemiology and pathogenesis of, 3384
- Community-partnered participatory research, 98
- Comorbid illness, preoperative optimization of, 103
- Comparative effectiveness research, 98
- Comparison groups, of HRQOL instruments, 97
- Compensatory renal growth, with urinary tract obstruction, 1100-1101
- Complete repair, for classic bladder exstrophy, 3197, 3198f
- continence outcomes with, 3213-3214
 - technical aspects of, 3202, 3204f
- Comprehensive geriatric assessment (CGA), 2090-2091
- Computed tomography (CT), 40-41, 41f-43f, 46b
- in adrenal mass evaluation, 1567-1569, 1568f-1569f
 - in adrenal radiology, 1526, 1526f
 - for biochemical recurrence after radical prostatectomy, 2773
 - of bladder diverticula, 2143, 2143f
 - of bladder injuries, 2386-2387, 2387f
 - of bladder RMS, 3584
 - for hematuria, 45-46, 48f
 - of IVC tumor thrombus, 1356-1357, 1356f
 - of kidney, 969, 971f
 - for kidney preoperative evaluation, 1414, 1415f
 - of matrix stones, 1242, 1243f
 - multidetector urography. *See* Multidetector computed tomography urography
 - of neuroblastoma, 3561-3562
 - noncontrast helical. *See* Noncontrast helical computed tomography
 - after orthotopic urinary diversion, 2346-2347, 2346f
 - pediatric
 - lower urinary tract and genitalia, 2921
 - upper urinary tract, 2918, 2920f - for pediatric genitourinary trauma, 3539
 - of pediatric stone disease, 3103
 - of penis, for squamous cell carcinoma, 852
 - radiation exposure with, 1092-1093
 - of RCC, 1338, 1338f
 - renal, 2906
 - of renal angiomyolipoma, 1307-1308, 1307f
 - of renal calculi, pretreatment assessment, 1237
 - for renal cyst evaluation, 43-45, 45f-46f, 1318-1320, 1318f-1320f, 1319t
- Computed tomography (CT) (Continued)
- of renal injuries, 1150, 1150f
 - of renal lymphoma, 1362-1363, 1362t
 - for renal masses, 43-45, 45f-46f
 - of renal tubular acidosis, 1211, 1211f
 - of renal tumor ablative therapy evaluation, 1489, 1489f
 - for renal tumor evaluation, 43-45, 45f-46f, 1316-1317, 1316f
 - for renovascular hypertension screening, 1032, 1032b
 - of retrocaval ureter, 1125, 1128f
 - of retroperitoneal fibrosis, 1144, 1144f
 - of retroperitoneal tumors, 1406-1408
 - of seminal vesicles, 959, 959f
 - of seminal vesicles and ejaculatory ducts, 505
 - of staghorn calculi, 1212, 1213f
 - for stone composition determination, 1208
 - TGCT staging with, 793-794, 794f
 - units used in, 41
 - of ureteral injuries, 1160-1161, 1161f
 - of ureteral stricture disease, 1129
 - of ureteropelvic junction obstruction, 1105-1106, 1106f-1107f
 - of ureterovaginal fistula, 2120-2121, 2122f
 - of urinary calculi, 1202, 1204f
 - of urinary tract obstruction, 1092-1093
 - upper, 1104
 - for urolithiasis, 41-43, 44f
 - for UTIs, 253, 276-277, 288, 288f, 2942
 - of UTUC, 1371
 - of Wilms tumor, 3573-3574, 3573f
- Computed tomography angiography (CTA), of kidneys, 972-973, 969.e2f
- Computer-assisted semen analysis, 568.e2
- Concentration product (CP), 1173
- Concentration product ratio (CPR), 1174
- Concurrent validity, 96-97, 97t
- Condom catheters, 2099.e6
- Conduction velocity, ureteral, 984
- Condyloma acuminatum, 3468
- Condylomata acuminata, malignant transformation of, 846.e2-846.e3
- Congenital absence of vas deferens (CAVD), 3397
- Congenital adrenal hyperplasia (CAH), 566, 1555-1556, 3485-3488, 3485f-3486f
- lower urinary tract dysfunction and, 1793
 - perioperative care for children with, 2955-2956
 - prenatal, 2882-2884
- Congenital bilateral absence of vas deferens (CBAVD), 577-578
- Congenital cryptorchidism, 3434-3435
- Congenital curvature of penis, 939-941, 939.e1, 940.e1
- Congenital disorders, and delayed ejaculation, 704
- Congenital diverticulum, urethral, reconstructive surgery for, 913-914
- Congenital heart defects, 2950
- Congenital megacystis, dilated fetal bladder and, 3174, 3174f
- Congenital mesoblastic nephroma (CMN), 2885
- in pediatric patients, 3579-3580
- Congenital nephrosis, 3023
- Congenital nephrotic syndrome of Finnish type (CNF), 3023
- Congenital obstructive uropathy (COU)
- clinical context of, 3043
 - clinical evaluation of, 3055
 - clinical presentation of, 3043

- Congenital obstructive uropathy (COU)
(Continued)
diagnosis of, 3054-3055
biomarkers for, 3054-3055
general issues in, 3054
general approach to, 3054-3055
general observations of, 3044-3045, 3046f
imaging for, 3055
management strategies for, 3055-3056
obstruction definition for, 3044
patterns of effect of, 3045-3053, 3049f
on differentiation, 3048-3049,
3049f-3050f
evidence and, 3050-3052, 3051f
fibrosis, 3049-3050, 3049f-3050f
functional integration, 3046t-3047t,
3052-3053
on growth, 3045-3048, 3046t-3047t
inflammatory mediators, 3053
presentation for, 3055
prognosis for, 3055-3056
progressive renal dysfunction with,
3043-3044, 3044f
reversal of, 3053-3054
Congenital penile nevi, 3379, 3379f
Congenital unilateral absence of vas deferens,
577
Congenital urethral fistula, 3379
Conn syndrome, adrenal surgery for, 1581, 1581b
Connecting tubule (CNT), functions of, 1018
Connective tissue supports, of pelvic floor, 1941,
1941f
Connexin 43, 1646, 1647f
Conservative therapies
for BPS/IC treatment, 351
for CP/CPPS treatment, 326
Constipation
management of, 1775-1776
sacral nerve stimulation for, 1908
Construct validity, 96-97, 97t
Contact dermatitis, 390, 391f
Content validity, 96-97, 97t
Contigen. *See* Glutaraldehyde cross-linked
bovine collagen
Continence
during abdominal pressure increases, 1687
bladder expansion in, 1755, 1755b
bladder outlet in, 1755-1756
in cloacal exstrophy, 3232
estrogens and, 1866
lower urinary tract neural control in,
1754-1755
in male epispadias, 3222, 3223t
mechanisms of, 1754
medical diagnoses and, 1699
after orthoptic urinary diversion, 2363-2366,
2364t-2365t, 2366b
after prepubertal repair, 3426-3427
promotion and advocacy for, 2099.e9
after radical prostatectomy for prostate cancer,
2617
reflex circuitry controlling, 1660-1663, 1660f
somatic to visceral reflexes, 1661
sphincter to bladder reflexes, 1661, 1661f,
1663f
storage phase, 1660-1661, 1661f-1662f,
1662t
sphincteric mechanisms in, 1755-1756
female, 1756, 1756b
male, 1755-1756, 1755f, 1756b
transitional urology and, 3526
Continence procedure, for classic bladder
exstrophy, 3205f-3206f, 3209-3210
Continent catheterizable channels, for bladder
emptying failure, 1906-1907, 2074f
Continent ileal reservoir, 2325, 2326f
Continent urinary diversions, 142
catheterizable stoma for, 3360-3366
for classic bladder exstrophy, 3217-3218
considerations for, 3360
continent vesicostomy, 3363-3366,
3365f
flap valves for, 3361-3363, 3362f
hydraulic valves for, 3363
ileocecal valve for, 3363
mechanisms for, 3360-3366
Mitrofanoff principle for, 3361-3363
nipple valves for, 3361, 3361f
for pediatric patients, 3360-3366, 3366b
results with, 3366
ureterosigmoidostomy for, 3360-3361
Continent vesicostomy, 3363-3366, 3365f
Continuous epidural analgesia (CEA), for
pediatric patients, 2956
Continuous incontinence, patient history of, 5
Continuous occlusion test, 1815-1816
Continuous positive airway pressure (CPAP)
for nocturnal polyuria, 1827
for obstructive sleep apnea, 2099.e8
Continuous renal replacement therapy (CRRT),
2870
Continuous urinary incontinence, 1710,
1744-1745, 1744f
Continuous wave lasers, 228
Contractile activity, of ureters, 984, 984f
calcium and excitation-contraction coupling,
985-986
proteins, 984-985, 985f
second messengers in, 986-988, 987f-988f
urothelial effects on, 986
Contractile proteins
of smooth muscles, 1641-1642, 1641f-1643f
of ureters, 984-985, 985f
Contractile tissue, epididymal, 530, 530f
Contralateral internal ring, 3387, 3387f
Contrast media, 27-28, 31b
ATN prevention and, 1053
CKD assessment and, 1061-1062
for CT, 41, 42f-43f
intravascular iodinated, 28
adverse reactions to, 28-30, 29b
delayed reactions to, 29-30
premedication strategies for, 29, 29b
specific considerations for, 30
for MRI, 30-31, 47, 56
for pediatric patients, 2909
in ultrasonography, 72
Contrast-induced nephropathy (CIN), 30, 1053,
1061-1062
Contusion, ureteral, 1161
Conventional radiography. *See* Radiography
Conventional RCC. *See* Clear cell RCC
Cooper ligament, 1611, 1612f
Cope catheters, as nephrostomy tubes, 171,
172f
Copy number alterations (CNAs), in GU
cancers, 467-468, 468t
Cordonnier and Nesbit techniques, in urinary
diversion, 2297
Coronary artery disease, 547
AD and, 548
Corpora amylacea, 305
Corpora cavernosa, 511-512, 614t, 669
anatomy of, 910.e1-910.e3, 910.e1f-910.e4f
reconstruction of, 492, 493f-494f
Corpus cavernosum electromyography and
single potential analysis of cavernous
electrical activity, 657
Corpus spongiosum, 511-512, 614t, 617t
anatomy of, 910.e1-910.e3, 910.e1f-910.e4f
Cortical collecting tubule (CCT), functions of,
1090-1091
Cortical microcystic disease, 3023
Corticobasal degeneration, lower urinary tract
dysfunction and, 1791
Corticosteroids
in genitourinary tuberculosis medical therapy,
430
for post-transplant immunosuppression,
1084-1085, 1085t
premedication with, for preventing contrast
media reactions, 29, 29b
preoperative, 103
Corticotropin-releasing factor (CRF),
1664-1665
Cortisol hypersecretion, testing for, 1571-1573
Corynebacterial infection
as cutaneous disease of external genitalia,
405, 407f
in prostatitis microbiology, 306
CoSeal, 207t, 207.e2
Cost-benefit analysis, 86-87
Cost-effectiveness analysis, 86
Costs of care, 85-86
for MIS, 2964-2965
patterns, 87-88
savings in urology, 88
terms and methods of analysis for, 86-87
value, 87, 98
COU. *See* Congenital obstructive uropathy
Cough leak point pressure (CLPP), 1727
Councill catheters, as nephrostomy tubes,
170-171, 171f
Countercurrent mechanism, of loop of Henle,
1017-1018, 1017f
Cowden syndrome, 1322t, 1325
COX inhibitors. *See* Cyclooxygenase inhibitors
COX-2. *See* Cyclooxygenase-2
COX-2 inhibitors
to facilitate bladder filling and urine storage,
1858
for postobstructive diuresis, 1102
urethral function effects of, 1005
for urinary tract obstruction, 1101
CP. *See* Cerebral palsy; Chronic prostatitis;
Concentration product
CPAP. *See* Continuous positive airway pressure
CPB. *See* Cardiopulmonary bypass
CP/CPPS. *See* Chronic prostatitis/chronic pelvic
pain syndrome
CPDN. *See* Cystic partially differentiated
nephroblastoma
CpG dinucleotide islands, in urothelial cancer,
2198-2199
CPPS. *See* Chronic pelvic pain syndrome
CPR. *See* Concentration product ratio
Crab lice. *See* Pediculosis pubis
CrCl. *See* Creatinine clearance
Creatinine
GFR and, 1008-1009, 1008f, 1090-1091
serum measurement
in AKI, 1041, 1042t
for benign prostatic hyperplasia,
2464-2465
in CKD, 1060-1061
Creatinine clearance (CrCl), GFR estimation
with, 1008
Crédé maneuver, 2079-2080
Creep, ureteral, 989, 996
Cremasteric artery, 498-500, 500f, 503, 519,
520f, 529
CRE. *See* Corticotropin-releasing factor
Criterion validity, 96-97, 97t
Crixivan. *See* Indinavir sulfate
Crockford-Gault formula, for GFR estimation,
1090-1091
Crossed renal ectopia, 2988-2993, 2990f-2991f,
2988.e1f

- Cross-linked bovine collagen
glutaraldehyde. *See* Glutaraldehyde cross-linked bovine collagen
for vesicoureteral reflux, 3169
- Crossmatch techniques, for renal transplantation, 1076
- Cross-organ sensitization, 1656-1657
- CrossSeal, 207t
- Cross-sectional imaging, in pheochromocytoma
diagnostic tests, 1547-1548
- CRRT. *See* Continuous renal replacement therapy
- Cryoablation (CA)
biochemical recurrence after, 2783
for localized prostate cancer, 2625-2626
focal, 2626.e1
whole-gland primary, 2625
whole-gland salvage, 2625-2626
for locally advanced prostate cancer, 2765
for prostate cancer, 2727, 2728f-2730f
outcomes with, 2736-2737
for RCC, 1347t, 1349-1351, 1350t
for renal tumors, 1485b
background and mode of action, 1484-1485
complications of, 1494-1495, 1496b, 1496f-1497f
duration, 1485
follow-up for, 1489-1490, 1490b
freeze-thaw cycles, 1485
laparoscopic, 1477
oncologic outcomes of, 1490-1494, 1491t-1492t, 1494b
percutaneous, 1487-1489, 1488f, 1494
RFA compared with, 1494
success of, 1489-1490, 1489f, 1490b
treatment temperature, 1485
salvage. *See* Salvage cryotherapy
- Cryptorchidism, 560-561, 568, 577
acquired, 3435
associated pathology, 3441-3443
epididymis anomalies with, 3441-3442, 3442f
gubernacular anomalies with, 3442
processus vaginalis anomalies with, 3442
testicular anomalies with, 3442-3443
testicular maldevelopment, 3441
cancer risk and, 784
congenital, 3434-3435
definitions for, 3430
diagnosis of, 3438-3443, 3438f
nonpalpable testes, 3439-3441, 3439f-3440f
palpable testes, 3438-3439, 3439f
environmental risk factors for, 3436-3437
epidemiology of, 3434-3438
genetic susceptibility to, 3435-3436
management of, 3439f, 3443-3449
medical therapy for, 3444
prognosis for, 3449-3452
subfertility with, 3449-3450
surgical approach to abdominal testis, 3447-3449
Fowler-Stephens orchidopexy, 3447-3449, 3448t
laparoscopic orchidopexy, 3447-3449, 3448t
open transabdominal orchidopexy, 3447
surgical approach to palpable testis, 3444-3446
inguinal orchiopexy, 3444-3446, 3445f
timing of, 3444
trans-scrotal orchidopexy, 3446, 3446f
syndromic, 3437-3438
- Cryptorchidism (*Continued*)
testicular embryology and, 3430-3434
testicular germ cell tumor with, 3450-3452, 3451f
- Crystallization
inhibitors and promoters of, 1178-1179
in urine, 1173-1174
- Crystals
aggregation of, 1175
homogeneous nucleation of, 1175
oxidative stress and, 1175
retention of, 1175
scanning electron micrographs of, 1202, 1203f
in urinary sediment, 23, 24f
- CT. *See* Computed tomography
- CT fluoroscopy, 40
- CT urogram (CTU), 40, 41f, 46b
for genitourinary tuberculosis diagnosis, 426, 427f
for hematuria, 45-46, 48f, 187
MH diagnostic evaluation with, 187
- CIA. *See* Computed tomography angiography
- CTCL. *See* Cutaneous T-cell lymphoma
- CICs. *See* Circulating tumor cells
- CTLA-4. *See* Cytotoxic T-lymphocyte antigen-4
- CTU. *See* CT urogram; Multidetector computed tomography urography
- Culp-DeWeerd spiral flap, for ureteropelvic junction obstruction, 1123, 1124f
- Cunningham clamp, 2072-2073, 2072f
- Curvatures of penis, 3377, 3377f
reconstructive surgery for, 939, 941b
acquired, 939, 941
congenital, 939-941, 939.e1, 940.e1
- Cushing disease, 1534
- Cushing syndrome
ACTH-dependent, 1534-1535, 1534f
Cushing disease, 1534
ectopic ACTH syndrome, 1534, 1535t, 1539
treatment, 1538-1539, 1538.e1f
ACTH-independent, 1535, 1539
ACTH-independent bilateral macronodular
adrenal hyperplasia, 1535
adrenal surgery for, 1538-1539, 1581, 1581b, 1538.e1f
adrenal tumors and, 1535
clinical characteristics
classical, 1535-1536, 1536f, 1537t
subclinical Cushing syndrome, 1536
diagnostic tests, 1536-1538, 1538b, 1538f, 1571-1573, 1572b
epidemiology of, 1531
exogenous, 1534
increased adrenal function in, 1531-1539, 1534f, 1535t, 1536f, 1537t, 1538b-1539b, 1538f, 1571-1573, 1572b, 1538.e1f
overview of, 1531, 1534
pathophysiology, 1532-1535, 1534f, 1535t
primary pigmented nodular adrenocortical disease, 1535
prognosis, 1539
treatment, 1538-1539, 1581, 1581b, 1538.e1f
- Cutaneous continent urinary diversion, 2319-2338
absorbable stapling techniques in, 2339
comments on, 2342
postoperative care for, 2342
right colon pouch, 2339-2340, 2340f
stapled sigmoid reservoir, 2340-2342, 2341f
W-stapled reservoir, 2342, 2342f
- Cutaneous continent urinary diversion (*Continued*)
comments on, 2318-2319
continent catheterizing pouches, 2322-2338, 2323f
continent ileal reservoir, 2325, 2326f
double T pouch, 2325-2328, 2327f-2328f
gastric pouch, 2336-2338, 2337f
general care for, 2324
general procedural methodology, 2323f, 2324
Indiana pouch, 2333-2335, 2334f-2335f
Mainz pouch I, 2328-2332, 2329f-2332f
Penn pouch, 2335-2336, 2335f-2336f
right colon pouches with intussuscepted terminal ileum, 2332-2333
cystectomy for, 2318, 2319f
general considerations for, 2317-2319
history of, 2344
operative technique variations for, 2338-2342
conduit conversion to continent reservoir, 2339
minimally invasive, 2338-2339
patient preparation for, 2317-2318
patient selection for, 2317
postoperative care for, 2318-2319
quality-of-life assessments, 2338
rectal bladder urinary diversion, 2320-2322
augmented valved rectum, 2321
folded rectosigmoid bladder, 2320
hemi-Kock pouch procedures with valved rectum, 2321-2322
Mainz II pouch, 2322
sigma-rectum pouch, 2322
T pouch procedures with valved rectum, 2321-2322, 2321f
- Cutaneous diseases, of external genitalia, 387, 419b
allergic dermatitis
atopic dermatitis, 389-390, 389f
contact dermatitis, 390, 391f
differential diagnosis, 389b
erythema multiforme and Stevens-Johnson syndrome, 390, 391f-392f
basic dermatology, 387, 388t
benign, of male genitalia
angiokeratomas of Fordyce, 415, 416f-417f
ectopic sebaceous glands, 416, 416f-417f
median raphe cysts, 416
pearly penile papules, 415-416, 416f-417f
sclerosing lymphangitis, 416
Zoon balanitis, 416, 416f-417f
common miscellaneous
capillary hemangiomas, 419
dermatofibroma, 418f, 419
epidermoid cyst, 416-419, 418f
lentigo simplex, 418f, 419
mole, 418f, 419
neurofibroma, 418f, 419
seborrheic keratosis, 418f, 419
skin tag, 416
vitiligo, 418f, 419-420
dermatologic therapy, 387-389, 389f
infections and infestations
balanitis, 402
balanoposthitis, 402, 403f
candidal intertrigo, 407, 408f
cellulitis, 402, 403f
corynebacterial infection (trichomycosis axillaris and erythrasma), 405, 407f
dermatophyte infection, 407-408, 409f
ecthyma gangrenosum, 405-406, 408f
erysipelas, 402
folliculitis, 404-405, 404f

Cutaneous diseases, of external genitalia

(Continued)

- Fournier gangrene, 402-404, 404f
- furunculosis, 405, 405f
- genital bite wounds, 406-407, 408f
- hidradenitis suppurativa, 405, 406f
- infestation, 408-410, 409f-410f
- STDs, 402, 403f
- neoplastic conditions
 - basal cell carcinoma, 413, 413f
 - bowenoid papulosis, 411, 411f
 - cutaneous T-cell lymphoma, 414-415, 416f
 - extramammary Paget disease, 414, 415f
 - Kaposi sarcoma, 413-414, 413f
 - melanoma, 414
 - pseudoepitheliomatous, keratotic, and micaceous balanitis, 414, 414f
 - squamous cell carcinoma, 411, 412f
 - squamous cell carcinoma in situ, 410-411, 411f
 - verrucous carcinoma (Buschke-Lowenstein tumor), 412, 412f
- noninfectious genital ulcers, 400, 400b
- aphthous ulcers and Behçet disease, 400-401, 401f
- pyoderma gangrenosum, 401, 402f
- traumatic causes, 401-402, 402f
- papulosquamous disorders, 392, 392b
- fixed drug eruption, 396, 397f
- lichen nitidus, 394
- lichen planus, 394, 395f
- lichen sclerosis, 395-396, 396f
- psoriasis, 392-393, 393f
- reactive arthritis, 393-394, 393f-394f
- seborrheic dermatitis, 396-397
- vesicobullous disorders, 397, 398b
- bullous pemphigoid, 398, 399f
- dermatitis herpetiformis, 398-399
- Hailey-Hailey disease, 399-400, 400f
- linear IgA bullous dermatosis, 398-399, 399f
- pemphigus vulgaris, 398, 398f
- Cutaneous fistula, 2137
- Cutaneous horn, of penis, 846.e1, 846.e1f
- Cutaneous lesions, penile premalignant, 846.e1
 - Buschke-Lowenstein tumor, 846.e1f, 846.e4, 846.e4b
 - non-human papillomavirus-related, 846.e1-846.e2, 846.e1f
 - virus-related, 846.e2-846.e4, 846.e4b
- Cutaneous T-cell lymphoma (CTCL), as neoplastic condition, 414-415, 416f
- Cut-to-the-light procedure, 2390-2391
- CV events. *See* Cardiovascular events
- CVA. *See* Cerebrovascular accident
- CVD. *See* Cardiovascular disease
- CyberKnife. *See* Stereotactic body radiotherapy
- CyberWand, 235, 235.e1
- Cyclamates, urothelial cancer and, 2187
- Cyclic adenosine monophosphate (cAMP), in ureteral contractions, 986-988, 987f
- Cyclic guanosine monophosphate (cGMP), in ureteral contractions, 986-988
- Cyclin-dependent kinase inhibitors (CDKIs), in GU cancers, 461-462, 461f
- Cyclin-dependent kinases, in GU cancers, 461f, 461.e1
- Cyclins, in GU cancers, 461f, 461.e1
- Cyclooxygenase (COX) inhibitors. *See also* COX-2 inhibitors
 - to facilitate bladder filling and urine storage, 1858
 - urethral function effects of, 1005
- Cyclooxygenase-2 (COX-2), in UTUC, 1376
- Cyclophosphamide, hemorrhagic cystitis caused by, 188-190

Cyclosporine

- for BPS/IC oral therapy, 353t, 354
- for post-transplant immunosuppression, 1084-1085, 1085b, 1085t
- CYP17 inhibition, 2811-2812, 2811f
- Cyproheptadine, for delayed ejaculation, 706-707
- Cyproterone acetate, 2789
- Cystadenomas, of testicular adnexa, 813
- Cystatin C, GFR estimation with, 1009
- Cystectomy
 - for cutaneous continent urinary diversion, 2318, 2319f
 - deep venous thromboses or pulmonary emboli after, 90
 - for non-muscle-invasive bladder cancer, 2218-2219, 2219b
 - partial. *See* Partial cystectomy
 - radical. *See* Radical cystectomy
 - simple/supratrigonal, 2277-2279. *See also* Simple/supratrigonal cystectomy
- Cystic dysplasia of rete testis, 3393
- Cystic fibrosis transmembrane conductance regulator (CFTR), 577-578
- Cystic kidneys. *See* Renal cysts
- Cystic nephroma, 1309, 1310b, 1310f, 3031-3032, 3031f, 3033f
- Cystic partially differentiated nephroblastoma (CPDN), in pediatric patients, 3580
- Cystine stones, 1193-1194, 1193f, 1213, 1213b, 1214f
 - medical management of, 1229-1230, 1230b
 - surgical management of, 1242
 - method selection for, 1243.e2
 - stone fragility and, 1243.e1
- Cystinuria, 1177, 1193
 - medical management of, 1229-1230, 1230b
- Cystitis. *See also* Uncomplicated cystitis
 - definition of, 237
 - diminished bladder capacity and, 1829
 - hemorrhagic. *See* Hemorrhagic cystitis
 - HRQOL instruments for, 92t-94t
 - mechanosensitive afferent sensitization with, 1677
 - spinal cord chemical changes with, 1677
 - with spinal cord injury, 1638
- Cystitis cystica, of bladder, 2185
- Cystitis glandularis, of bladder, 2185, 2185f
- Cystocele, 1750, 1759, 1943, 1943f
- Cystogram
 - of bladder injuries, 2386, 2386f
 - of vesicoureteral reflux, 3142-3143, 3143f
 - for vesicovaginal fistula, 2108-2109, 2108f-2109f
- Cystography
 - after modern staged repair of exstrophy, 3202
 - radionuclide, for pediatric patients, 2922-2923, 2925f
 - static. *See* Static cystography
- Cystolitholapaxy, for bladder calculi, 1295
- Cystolithotomy
 - for bladder calculi, 1295
 - historical overview of, 1291
 - transabdominal, 2279-2280, 2279f-2280f
- Cystolithotripsy
 - EHL for, 232.e2
 - laser lithotripsy for, 234.e2-234.e3
 - percutaneous, for pediatric stone disease, 3118, 3119f
 - pneumatic lithotripsy for, 233.e1
- Cystometrography (CMG)
 - for benign prostatic hyperplasia, 2470
 - in urodynamic studies, 1722, 1724f
- Cystometry
 - filling, for benign prostatic hyperplasia, 2470
 - sensate, 2470

Cystoplasty

- augmentation. *See* Augmentation cystoplasty
- reduction, for prune-belly syndrome, 3244
- sigmoid, 3346-3347, 3348f
- Cystoscopy, 1610
 - antimicrobial prophylaxis for, 263-264
 - for genitourinary tuberculosis diagnosis, 427, 428f
 - for injection therapy for stress urinary incontinence, 2051
 - MH diagnostic evaluation with, 186-187
 - after modern staged repair of exstrophy, 3202
 - for non-muscle-invasive bladder cancer, 2210-2211, 2211f
 - for non-muscle-invasive bladder cancer surveillance, 2219
 - for partial cystectomy, 2267
 - for pelvic floor disorder assessment, 1705-1706
 - in pubovaginal sling placement and fixation, 1995
 - in retropubic midurethral sling, 2013
 - for sphincteric urinary incontinence, 2173, 2173f
 - transurethral injection monitoring with, 2052-2053, 2053f
 - for transurethral resection of bladder tumor, 2243
 - for urothelial cancer, 2197
 - for UTUC, 1371
 - for vesicoureteral reflux, 3144-3145
 - in surgery, 3157
 - for vesicovaginal fistula, 2108, 2108f
- Cystotomy, in robotic repair of vesicovaginal fistula, 2116.e2-2116.e4, 2116.e2f-2116.e4f
- Cystourethrogram
 - of striated sphincter dyssynergia, 1772f
 - voiding. *See* Voiding cystourethrogram
- Cystourethroscopy, 142b
 - equipment for, 137-138, 139f-140f, 139t-140t
 - indications for, 139, 139b
 - patient preparation for, 139-141, 141b
 - special circumstances in
 - continent urinary diversions, 142
 - suprapubic cystostomy, 141-142
 - technique for, 141, 141f
 - for urethral diverticula, 2158, 2158f
- Cysts
 - of epididymis, 953
 - of Gartner duct, urethral diverticula
 - differentiated from, 2162, 2162f
 - pelvic, prenatal imaging of, 2910, 2911f
 - of prostate, on transrectal ultrasonography, 2582, 2582f
 - renal. *See* Renal cysts
 - of scrotal wall, excision of, 947
 - of seminal vesicles, 961-963
 - of Skene gland, urethral diverticula
 - differentiated from, 2162, 2162f
 - testicular, 812
 - urachal, 3176f, 3177
 - vestibular, 3456-3457, 3457f
- Cytochrome P450 oxidoreductase deficiency, 3489
- Cytokine therapy. *See* Interleukin-2
- Cytokines, 447-448, 449f, 449t
 - in benign prostatic hyperplasia, 2431-2432, 2431f
 - septic shock and, 292
 - in tubulointerstitial fibrosis, 1098-1100
 - in Wilms tumor, 3574
- Cytology. *See* Urine cytology
- Cytoreductive nephrectomy
 - laparoscopic, 1470
 - for metastatic RCC, 1501-1503, 1502f, 1503b, 1503t

- Cytosine, 459.e1-459.e3, 459.e2f
Cytotoxic T-lymphocyte antigen-4 (CTLA-4), 1325-1326
- D**
da Vinci Robotic System, 197-198, 200, 203, 205, 203.e4f, 197.e3f, 203.e4
instrumentation for, 209-210, 210f
virtual reality training for, 224.e3, 224.e3f
Dantrolene, to facilitate bladder emptying, 1874.e3
Dapoxetine, and PE, 698-699
Darifenacin hydrobromide, to facilitate bladder filling and urine storage, 1839t, 1841-1842
Darkfield examination, syphilis test, 375
DAs. *See* Dopamine agonists
Daytime urinary incontinence. *See* Bladder and bowel dysfunction
DBD. *See* Diabetes-induced bladder dysfunction
DCT. *See* Distal convoluted tubule
DDAVP. *See* Desmopressin
DDR. *See* DNA damage response
Death
 declaration of, for deceased organ donors, 1074-1075, 1074b
 kidney donation after. *See* Deceased donors after percutaneous access to upper urinary tract collecting system, 182
Debridement, of scrotal wall, for Fournier gangrene, 947-948, 948f
Debulking nephrectomy, for metastatic RCC, 1501-1503, 1502f, 1503b, 1503r
Deceased donors, of renal transplants, 1074
 ABO blood groups of, 1076
 allocation of, 1074-1076
 crossmatch techniques for, 1076
 declaration of death of, 1074-1075, 1074b
 histocompatibility of, 1076
 kidney preservation for, 1075, 1075t
Decreased adrenal function disorders, 1555, 1556b
 clinical characteristics, 1553-1555, 1554t
 diagnostic tests, 1555
 overview and epidemiology, 1553
 pathophysiology, 1553, 1554f
 prognosis, 1555
 treatment, 1555, 1556t
Decreased sexual desire screener (DSDS), 753.e2
DECT. *See* Dual-energy computed tomography
Deep brain stimulation, for Parkinson disease, 1767-1768
Deep perineal space, 910.e6f-910.e7f, 910.e8
Deep venous thrombosis (DVT)
 after cystectomy, nephrectomy, and prostatectomy, 90
 after laparoscopic and robotic surgery, 223
 prophylaxis for
 for laparoscopic and robotic surgery, 223
 in pediatric patients, 2959-2960
 preoperative, 108-109, 108t-109t, 109b
 after retropubic radical prostatectomy, 2657
Defecation disorders
 classification of, 3317, 3318b
 disimpaction for, 3322-3323
 epidemiology of, 3317, 3318b
 evaluation of, 3318-3319, 3319b, 3319f, 3319.e1f
 imaging studies of, 3319-3321, 3320f-3321f, 3320.e1f, 3321.e1f
 large bowel/rectum washout for, 3322-3323
 maintenance therapy for, 3323
 management of, 3321-3323, 3322f
Defecation disorders (*Continued*)
 nonpharmacologic interventions, 3321-3322
 overview of, 3317
 prognosis of, 3323-3324
 surgical management of, 3324-3329, 3324f, 3329b
 enema regimen for, 3327-3328, 3328f
 operative technique for, 3325-3327, 3325f-3327f
 outcomes with, 3328-3329, 3328t, 3329f
 patient selection and preparation for, 3324-3325
 urinary tract and, 3317, 3318f, 3317.e1f
Deferential artery, 498-500, 500f, 503, 519-520, 520f, 529
Deflazacort, for ureteral stone passage, 1001-1002
Deflux. *See* Dextranomer hyaluronic acid copolymer; Dextranomer/hyaluronic acid copolymer
Defunctionalized bladder, lower urinary tract dysfunction and, 1792
Degloving injuries, of penis, 916.e1-916.e2
Dehydroepiandrosterone (DHEA), 2400-2401, 2402f
 and female sexual response, 752
Delayed contrast reactions, 29-30
Delayed ejaculation
 causes of, 702, 702b
 and congenital disorders, 704
 and endocrinopathy, 703
 epidemiology of, 702
 evaluation of, 705, 705b
 iatrogenic causes of, 703
 and infective disorders, 704-705
 and neurologic disorders, 704
 psychological, 702-703
 terminology and definition of, 701-702
 treatment of, 705-707, 706f
 pharmacotherapy, 706-707, 706t
 psychological strategies, 706, 706.e1
 and treatment of pelvic cancers, 703-704
Delayed orchiectomy, 816
Delayed spontaneous bladder perforation, after augmentation cystoplasty, 3353-3354, 3354f
Delayed voiding, 1891
Delirium, 2095
Delivery
 sphincter function and, 1757
 urinary incontinence and, 1748
Dementia, lower urinary tract dysfunction with, 1765
Demerol. *See* Meperidine
Denervation, of spermatic cord, 956-957, 956f
Dent disease, 2861-2862
Depression, in geriatric urology patient, 2089
Dermatitis herpetiformis, 398-399
Dermatofibroma, 418f, 419
Dermatologic lesions. *See* Cutaneous lesions
Dermatophyte infection, 407-408, 409f
Dermoid cysts, testicular, 812
Desflurane, preoperative considerations for, 111
Desmopressin (DDAVP)
 in children, 1864-1865
 efficacy of, 1865
 for enuresis, 3315
 to facilitate bladder filling and urine storage, 1864-1866
 gender and, 1866
 for nocturia, 2099.e8
 for nocturnal enuresis, 1864-1865
 for nocturnal polyuria, 1827, 1829, 1830t
Desperation RPLND, 831-832, 831t
Desperation surgery, for NSGCTs, 805
Detrusor contraction assessment
 duration, 1814t, 1816
 speed, 1814t, 1816
 strength, 1814-1816, 1814t, 1815f
Detrusor hyperactivity with impaired contractility (DHIC), in geriatric patients, 2097, 2099.e7
Detrusor hyperreflexia, 1796
Detrusor leak point pressure (DLPP), urodynamic studies of, 1727-1728, 1728f
Detrusor muscle, 1640-1648
 acontractile, 1692-1693, 1729
 actinomyosin cross-bridge cycling, 1642-1643, 1643b, 1643f
 action potentials of, 1644-1645, 1644f
 aging and, 1679-1680, 1810, 1811f
 areflexia of, 1692-1693
 with cerebellar ataxia, 1765-1766
 after CVA, 1763-1764
 with lumbar disk protrusion, 1781
 with MS, 1769
 after traumatic brain injury, 1763
 urinary incontinence and, 1756
 urodynamic classification of, 1693, 1693b
 calcium signaling in, 1646, 1647f
 contractile proteins, 1641-1642, 1641f-1643f
 contraction of
 electrical stimulation and, 1888-1889
 muscarinic receptors and, 1836-1837
 electrical response propagation, 1646-1648, 1647f
 excitation-contraction coupling in, 1645-1646, 1645f
 interstitial cells of, 1648, 1648f
 involuntary contractions of, 1725
 membrane electrical properties of, 1644-1645, 1644f
 motor sensory network in, 1649, 1650f
 normal function of, 1729
 overactivity, neurogenic, 1692
 in pediatric patients, 3123, 3124f
Detrusor overactivity (DO)
 afferent mechanisms in, 1797-1798
 benign prostatic hyperplasia and, 2471
 with brain tumor, 1765
 after CVA, 1763
 herpesvirus infection and, 1783
 hypothesis of, 1797f, 1798-1799
 idiopathic. *See* Idiopathic detrusor overactivity
 interstitial cells and, 1648, 1648f
 with MS, 1769
 neurogenic, 1756
 neuromodulation for, rationale for, 1681, 1681f
 nocturnal, 1829
 with overactive bladder, 1804, 1805f
 pharmacologic therapy for, 1839t
 antimuscarinic agents, 1838
 phasic, 1805f
 spinal cord injury and, 1675-1676
 stress-induced, urodynamic studies of, 1728, 1728f
 with suprasacral spinal cord injury, 1772
 terminal, 1805f
 urodynamic studies of, 1725-1727, 1725f-1726f
 vasculature in, 1633-1634
Detrusor overactivity incontinence (DOI), 1714
 cough-induced, 1714
Detrusor pressure at voiding, 3123, 3124f
Detrusor sphincter dyssynergia (DSD), 1692-1693
 with autonomic hyperreflexia, 1776
 lower urinary tract dysfunction and, 1787

- Detrusor sphincter dyssynergia (DSD)
(*Continued*)
with Parkinson disease, 1767
urinary incontinence and, 1757
urodynamic classification of, 1693, 1693b
- Detrusor underactivity (DUA), 1692-1693,
1729-1730, 1807
definition of, 1807, 1808f, 1809b
diagnosis of, 1814-1816, 1814t, 1816b
ambulatory urodynamics, 1814t, 1816
bladder sensation, 1814t, 1816
detrusor contraction duration, 1814t, 1816
detrusor contraction speed, 1814t, 1816
detrusor contraction strength, 1814-1816,
1814t, 1815f
epidemiology of, 1807-1809, 1809b, 1809t,
1810f
etiopathogenesis of, 1810-1814, 1811f-1812f,
1815b
bladder outlet obstruction, 1812-1813,
1813b
diabetes mellitus, 1813-1814, 1813b
myogenic factors, 1810
neurogenic factors, 1810-1812
neurologic disease or injury, 1813b, 1814
specific factors, 1813, 1813b
in geriatric patients, 2099.e7
management of, 1816-1819, 1817f, 1820b
bladder outlet surgery for, 1819
botulinum toxin, 1819
conservative, 1816-1817
electrical stimulation, 1818-1819
initial assessment for, 1813b, 1816
pharmacotherapies for, 1817-1818, 1817f
reconstructive surgery for, 1819
urinary diversion for, 1819
prevalence of, 1809t
symptoms of, 1807, 1808f, 1809b
terminology for, 1807, 1809b
urinary incontinence and, 1756
- Development, of lungs and kidneys, clinical
implications of, 2949-2950
- Development of genitourinary tract, 2823,
2824f-2825f, 2847b
bladder and ureter development
bladder and continence mechanism, 2836
formation of trigone, 2833-2834, 2835f
formation of urogenital sinus, 2833,
2834f-2835f
ureter, 2834-2836
genital and reproductive tract
external genitalia, 2840-2844, 2841f-2843f
female structures, 2840, 2841f
formation of genital ridges and
paramesonephric ducts, 2836-2837,
2837f-2839f
gonadal descent, 2844-2845, 2844f
male structures, 2837-2838, 2839f
molecular mechanism of sex development,
2845-2847, 2846f
prostate and seminal vesicle, 2838-2840,
2840f
kidney development
collecting system, 2826-2829, 2829f
early events, 2823, 2826f
formation of nephric ducts, 2830
mesenchymal-epithelial conversion, 2833
metanephros, 2826, 2827f-2828f
molecular mechanism of, 2830, 2830f
pronephros and mesonephros, 2823-2826,
2827f
renal ascent, 2829-2830, 2829f
renal vascular, 2833
tubulogenesis, 2832-2833, 2832f
ureteric bud outgrowth toward metanephric
mesenchyme, 2830-2832, 2831f
- Developmental disorders, and male infertility,
577-578
- Dextranomer hyaluronic acid copolymer
(Deflux, Zuidex), for female SUI injection
therapy, 2063
- Dextranomer/hyaluronic copolymer
(DX/HA, Deflux), of vesicoureteral reflux,
3169
- Dextroamphetamine, for BPS/IC oral therapy,
355
- DG. *See* Diacylglycerol
- DHEA. *See* Dehydroepiandrosterone
- DHIC. *See* Detrusor hyperactivity with impaired
contractility
- DHT. *See* 5 α -Dihydrotestosterone
- Diabetes insipidus, 1023, 1835
- Diabetes mellitus, 549
CKD in, 1059
contrast media considerations in, 30
detrusor underactivity and, 1813-1814,
1813b
and ED, 639
hormonal therapy and, 2795
host defense mechanisms in UTIs and,
249
low urine pH and, 1190-1191
lower urinary tract dysfunction and,
1783-1784, 1783b
and PD, 723-724, 724f
renal calculi and, 1172-1173
ureteral function effects of, 1002
urologic disease and, 551-554
- Diabetes-induced bladder dysfunction (DBD),
1813
- Diabetic cystopathy, 1783b, 1784, 1813
- Diacylglycerol (DG), in ureteral contractions,
986, 988
- Diagnosis, of UTIs, 250-252, 251f, 252.e1t
- Diagnostic and Statistical Manual of Mental
Disorders (DSM-5), and premature
ejaculation, 695
- Diagnostic evaluation, in ED
laboratory tests, 650
physical exam, 648
questionnaires and sexual function symptom
scores, 648-650, 649f
sexual, medical, and psychosocial history,
647-648, 647f, 648t
- Dialysis
for AKI, 1052
prescription and modality for, 1052-1053
for CKD, 1064-1065, 1067b, 1067t
for ESRD, 1065, 1066b-1067b, 1066f, 1067t
incidence and prevalence of, 1069
long-term complications of, 1070
options for, 1069
results of, 1070
in renal development, 2870-2871, 2872b
in renal transplantation, 3532
- Diameter, of ureters, 989, 990f, 994
obstruction effects on, 995-999,
996f-999f
- Diaphragm, anatomy of, 1614, 1617f,
1939-1941, 1940f
- Diarrhea
with bowel preparation, 2283-2284
chronic, hypocitraturia in, 1212
medical management of, 1228
- Diathesis, gouty
medical management of, 1229
uric acid calculi in, 1212, 1212b, 1213f
- Dibenzylamine. *See* Phenoxybenzamine
- Diclofenac, urethral function effects of, 1005
- Diet
benign prostatic hyperplasia and, 2442-2444,
2442f
- Diet (*Continued*)
for BPS/IC treatment, 351-352, 352b
for CKD, 1062-1063
prostate cancer and, 2551
urinary incontinence and, 1749
weight-loss, nephrolithiasis and, 1220,
1220b
- Dietary hyperoxaluria, 1187, 1211, 1211b
- Dietary recommendations, for nephrolithiasis,
1218-1219, 1219b
- Difficult catheterization, 122-123, 123f
- Diffuse mesangial sclerosis (DMS), 3023
- Digital rectal examination (DRE), 11
for pelvic floor disorders, 1701
for prostate cancer, 2602
tumor extent prediction with, 2606
for simple prostatectomy, 2536
- Digital ureteroscopes, 144-146, 147f, 147t
care and sterilization of, 146
- Digoxin, and ED, 637
- 5 α -Dihydrotestosterone (DHT), 517-518, 518f,
539
in benign prostatic hyperplasia, 2427-2428,
2428f
epididymal function regulation by, 532
in prostate, 2400-2401, 2401t
in prostate cancer, 2553, 2554f
in vas deferens, 533-534
- Dihydroxyadenine stones, 1195
- 1,25-Dihydroxycholecalciferol (Calcitriol),
1011-1012
in calcium metabolism, 1180
- Dilation
of ureters, 995-999, 996f-999f
clinical assessment of, 998-999, 999f
urethral. *See* Urethral dilation
- Dilation devices
for upper urinary tract collecting system,
167-168, 167f-169f, 168.e1f
for ureteroscopy, 148
- Dimercaptosuccinic acid (DMSA), 38, 1102,
2921, 2921f
- Dimerization, of androgen receptors, 2410
- Dimethyl sulfoxide (DMSO), 356-357
to facilitate bladder filling and urine storage,
1858-1859
- Diminished bladder capacity
cause of, 1829
management of, 1829-1831, 1832t-1834t
nocturia and, 1824, 1824t, 1829-1831
nocturnal polyuria and, 1831-1834
- Diminutive clitoris, 3456, 3456f
- Diode lasers, 230
- Diphallia, 3373-3374
- Diphenhydramine (Benadryl), for contrast
media reactions, 28-29, 29b
- Dipsogenic polydipsia, 1835
- Dipstick testing, urine, 14
bilirubin and urobilinogen, 19-20
glucose and ketones, 19
hematuria, 14-16, 15t, 16f-18f
leukocyte esterase and nitrite, 20, 20f
proteinuria, 17-19, 19f
for RCC, 1335
- Direct access technique, for achieving
transperitoneal access in pediatric
patients, 2968, 2969b
- Direct neocystostomy, for UTUC, 1385-1386,
1387f
- Disabled women, and female sexual response,
754
- Disimpaction, 3322-3323
- Disk disease, lower urinary tract dysfunction
with, 1781
- Disk prolapse, lower urinary tract dysfunction
with, 1781

- Dismembered pyeloplasty
for ureteropelvic junction obstruction, 1108, 1116f-1117f
results of, 1120
for ureteropelvic junction obstruction in pediatric patients, 3059-3062, 3059f-3061f
- Disorders of sex development (DSD), 3400, 3477-3495
46,XX, 3485-3489
congenital adrenal hyperplasia, 3485-3488, 3485f-3486f
secondary to maternal androgens and progestins and maternal tumors, 3488-3489
46,XY, 3489
androgen receptor and postreceptor defects, 3491-3492
Leydig cell aplasia, 3489
Mayer-Rokitansky-Küster-Hauser syndrome, 3495
persistent müllerian duct syndrome, 3493f, 3494
5 α -reductase deficiency, 3492-3494, 3493f-3494f
testosterone biosynthesis disorders, 3489-3491
ambiguous genitalia, 3495-3496, 3496f
of gonadal differentiation and development, 3477-3495
46,XX males, 3478
bilateral vanishing testes syndrome, 3483
embryonic testicular regression, 3483
Klinefelter syndrome and variants, 3477-3478
syndromes of gonadal dysgenesis, 3478-3483
ovotesticular, 3484-3485, 3484f
surgical reconstruction of. *See* Reconstructive surgery, for disorders of sex development and urogenital sinus
- Dissection, energy modalities for
electrosurgery, 225-227, 226f
laser instrumentation, 228-230, 229f
ultrasound instrumentation, 227-228
- Dissectors, for laparoscopic and robotic surgery, 205-206, 210
- Distal convoluted tubule (DCT), functions of, 1018
- Distal renal tubular acidosis
type 1, 1188-1189, 1189f, 2862
type 4, 1189-1190, 2862
- Distal tubule, functions of, 1018
- Distal ureterectomy, for UTUC, 1381-1382
and direct neocystostomy or ureteroneocystostomy with bladder psoas muscle hitch or a Boari flap, 1385-1386, 1387f
laparoscopic, 1379, 1380f, 1381-1382, 1388
open, 1378, 1378f, 1381-1382
robotic, 1388
- Distal vagina, 3460-3461
- Distraction injuries, urethral
ED with, 937, 2391
PFULs causing. *See* Pelvic fracture urethral injuries
- Diuresis
postobstructive, 1102
ureteral function effects of, 994
- Diuretic renography
for UPJO and reflux differentiation, 1105
for ureteropelvic junction obstruction, 1106-1107, 1108f
for urinary tract obstruction, 1091-1092
- Diuretic scintigraphy, 38, 38f-39f
for pediatric patients, 2921-2922, 2922f-2925f
- Diuretic urography, for ureteropelvic junction obstruction, 1105, 1106f
- Diuretics, for AKI, 1050-1051
- Diverticula
bladder. *See* Bladder diverticula
calyceal. *See* Calyceal diverticula
urethral. *See* Urethral diverticula
- Diverticulectomy
bladder. *See* Bladder diverticulectomy
calyceal, 1463-1464
combined intravesical-extravesical, 2148, 2151f
laparoscopic, 2148-2150
transvesical bladder, 2148, 2149f-2150f
urethral, 2164f, 2165-2168, 2165b, 2166f, 2167t
- DLPP. *See* Detrusor leak point pressure
- DM. *See* Diabetes mellitus
- DMS. *See* Diffuse mesangial sclerosis
- DMSA. *See* Dimercaptosuccinic acid
- DMSO. *See* Dimethyl sulfoxide
- DNA
basics of, 459.e1-459.e3, 459.e2f
damage and repair of, 464-465, 465b
DSB repair, 465.e1-465.e2, 465.e1f-465.e2f
mechanisms of, 465.e1, 465.e1f
- DNA damage response (DDR), 464
- DNA hypermethylation, in prostate cancer, 2554-2555
- DNA methylation, 462-463, 464b
in bladder cancer, 463-464
in prostate cancer, 463
- DNA-binding domain, of androgen receptors, 2409-2410
- DO. *See* Detrusor overactivity
- Docetaxel
for castration-resistant prostate cancer, 2808-2809, 2808f-2809f
for non-muscle-invasive bladder cancer, 2216
for retroperitoneal sarcomas, 1411
- Docetaxel, cisplatin, and 5-fluorouracil (TPF), for penile cancer, 872, 872t
- Documentation, ultrasonography, 72-73, 72f
- DOI. *See* Detrusor overactivity incontinence
- Donors. *See* Deceased donors; Living donors
- Dopamine
for AKI, 1050-1051
in ED, 621-623, 623t
in ejaculatory response, 692
and female sexual response, 750
in PD, 1766-1767
- Dopamine agonists (DAs), for AKI, 1051
- Dopaminergic agonists, 664
- Doppler ultrasonography, 69
color. *See* Color Doppler ultrasonography
for renovascular hypertension screening, 1032, 1032b
for urinary tract obstruction, 1091
- Dorsal artery, of penis, 513f, 910.e3-910.e5, 910.e5f
- Dorsal genital nerve, electrical stimulation of, for bladder storage disorders, 1909-1910
- Dorsal lumbotomy approach, for open kidney surgery, 1417-1418, 1418f
- Dorsal nerve, of penis, 513, 514f, 619t
- Dorsal nerve conduction velocity, 656
- Dorsal plication, 3403, 3403f
- Dorsal vein
division of, in robotic-assisted radical cystectomy, 2271, 2273f
of penis, 508, 513, 1617, 1621f, 910.e3, 910.e5f
- Dorsal vein complex (DVC)
division of, in retropubic radical prostatectomy, 2647-2649, 2647f-2648f
ligation of
in laparoscopic radical prostatectomy, 2669, 2669f
in retropubic radical prostatectomy, 2646-2651, 2646f-2647f
- Dose, of radiation, 26, 28t
- Double dye test, for ureterovaginal fistula, 2120-2121
- Double T pouch, 2325-2328, 2327f-2328f
- Double-strand breaks (DSBs), repair of, 465.e1-465.e2, 465.e1f-465.e2f
- Dovitinib, for RCC, 1514
- Down training, 1892
- Doxazosin
for benign prostatic hyperplasia, 2476-2477, 2477t
for diminished bladder, 1831, 1832t-1834t
to facilitate bladder emptying, 1874.e1
to facilitate bladder filling and urine storage, 1853
ureteral response to, 992
- Doxepin, to facilitate bladder filling and urine storage, 1857
- Doxorubicin (Adriamycin), for non-muscle-invasive bladder cancer, 2216, 2216t
- Drainage
renal, for urinary tract obstruction, 1101
urinary tract. *See* Urinary tract drainage
- DRE. *See* Digital rectal examination
- Dribble-Stop, 1716
- Dromedary hump, 967
- Drug-induced erectile dysfunction, 635-639, 636t, 638t
- Drug-resistant tuberculosis, 432
- Drugs. *See also* Pharmacologic therapy; specific classes and agents
CKD effects on dosing of, 1064
lower urinary tract function and, 1699, 1699t
nephrotoxic, 1044-1046, 1044b-1045b
renal calculi induced by, 1196-1197
medical management of, 1231-1232, 1231b
surgical, for laparoscopic and robotic surgery, 207, 207t, 207.e2
transport of, prostatic secretions and, 2424, 2424b
- DSBs. *See* Double-strand breaks
- DSCT. *See* Dual-source CT
- DSD. *See* Detrusor sphincter dyssynergia; Disorders of sex development
- DSDS. *See* Decreased sexual desire screener
- DSM-5. *See* Diagnostic and Statistical Manual of Mental Disorders
- DSNB. *See* Dynamic sentinel node biopsy
- DUA. *See* Detrusor underactivity
- Dual modality lithotripters, 234, 235f, 236b
clinical use of, 235
CyberWand, 235, 235.e1
LithoClast Ultra, 234-235, 235.e1
tissue effects of, 235
- Dual-energy computed tomography (DECT), for stone composition determination, 1208
- Dual-source CT (DSCT), 40
- Ductuli efferentes, 519
- Ductus deferens. *See* Vas deferens
- Duke Activity Status Index, 101, 102t
- Duloxetine
to facilitate bladder filling and urine storage, 1839t, 1857

- Duloxetine (*Continued*)
 for stress urinary incontinence, 1675
 in men, 1870
 in women, 1868-1869
 for SUI, 1716
- Duodenum
 injury of, during radical nephrectomy, 1428
 in retroperitoneum, 773, 773f-774f, 773.e1f
- Duplex Doppler ultrasonography, for
 renovascular hypertension screening,
 1032, 1032b
- Duplex ultrasonography, in ED, 651-652,
 651f-652f
- Duplicated collecting system, ureteral calculi
 with, surgical management of, 1253
- Duplication anomalies, prenatal, 2879, 2879f
- Durasphere. *See* Carbon-coated zirconium beads
- Dutasteride, for benign prostatic hyperplasia,
 2486
- DVC. *See* Dorsal vein complex
- DVSS. *See* Dysfunctional voiding symptom score
- DVT. *See* Deep venous thrombosis
- DX/HA. *See* Dextranomer/hyaluronic copolymer
- Dye testing, for pelvic floor disorders, 1705
- Dynamic fracture process, in stone
 comminution, 1270, 1271f
- Dynamic infusion cavernosometry and
 cavernosography, in ED, 652-653, 653f
- Dynamic pressure perfusion studies, for
 ureteropelvic junction obstruction, 1107
- Dynamic sentinel node biopsy (DSNB), of
 inguinal nodes, for penile cancer, 864,
 893-894, 894f-895f, 895b
- Dysfunctional voiding, in prostatitis etiology,
 307
- Dysfunctional voiding symptom score (DVSS),
 3300, 3302f
- Dysplasia, of upper tract urothelium, 1369
- Dysreflexia. *See* Autonomic hyperreflexia
- Dysuria
 patient history of, 3
 after photoselective vaporization of prostate,
 2531-2533
 after transurethral needle ablation of prostate,
 2525
- E**
- E. coli*. *See* Uropathogenic *E. coli*
- EC. *See* Embryonal carcinoma
- Echinococcosis, of genitourinary tract,
 445-446
- ECM. *See* Extracellular matrix
- ECMO. *See* Extracorporeal membrane
 oxygenation
- Economics
 of laparoscopic radical prostatectomy, 2679
 of metabolic evaluation of renal calculi,
 1208-1209, 1209b
 of ureteral calculi surgical management,
 1254.e1
- ECRS. *See* Extracorporeal renal surgery
- Ecthyma gangrenosum, 405-406, 408f
- Ectopia, of kidney. *See* Renal ectopia
- Ectopic ACTH syndrome, 1534, 1535t, 1539
- Ectopic corticotropin-releasing hormone,
 1535
- Ectopic scrotum, 3382, 3384f
- Ectopic sebaceous glands, 416, 416f-417f
- Ectopic ureter. *See also* Ureteral anomalies
 anatomic description of, 3075, 3076f
 ureterostomy for, 3096
- ECV. *See* Effective circulating volume
- Eczema. *See* Atopic dermatitis
- ED. *See* Erectile dysfunction
- EDCs. *See* Endocrine-disrupting chemicals
- Edging artifact, in ultrasonography, 68, 68f
- EEC. *See* Exstrophy-epispadias complex
- Effective circulating volume (ECV), ADH control
 by, 1012
- Effective dose, 26, 28t
- Efferent pathways, to bladder, 1657-1663
 adrenergic, 1659
 in detrusor underactivity, 1810, 1812f
 glutamate in, 1657-1658, 1659f
 glycine and γ -aminobutyric acid in, 1658
 purinergic, 1659-1660
 reflex circuitry, 1660-1663, 1660f
 serotonin in, 1658-1659
 terminal nerve fibers, 1657
 transmitters in, 1657-1660
- EGFR. *See* Epidermal growth factor receptor
- EGFR therapy. *See* Epidermal growth factor
 receptor therapy
- Eggplant deformity, with penile fracture, 2379,
 2379.e1f
- EHL. *See* Electrohydraulic lithotripsy
- Ehlers-Danlos syndrome, lower urinary tract
 dysfunction and, 1791
- Ehrlich technique, 3247
- Ejaculation
 failure of, patient history of, 6
 premature. *See* Premature ejaculation
 after RPLND, 833
- Ejaculatory ducts. *See* Seminal vesicles and
 ejaculatory ducts
- Ejaculatory dysfunction
 in male infertility, 578-579
 after monopolar transurethral resection of
 prostate, 2515-2516
 after transurethral microwave therapy, 2521
 after transurethral needle ablation of prostate,
 2525
- Elastin, of bladder wall, 1635
- Elastography. *See* Sonoelastography
- Elavil. *See* Amitriptyline
- Elderly. *See also* Geriatric urology patient
 α -adrenergic blockers in, 2480
 bacteriuria in, 296
 asymptomatic, 297-299, 299b
 epidemiology of, 297, 297f-298f, 297t
 laboratory diagnosis, 297-298, 298f
 management of, 299
 pathogenesis, 297, 298f
 screening for, 298-299
 laparoscopic kidney surgery in, 1447
 midurethral sling outcomes in, 2023-2024,
 2024b
 mistreatment of, 2100-2101
 preoperative care for, 103-104
 sexual health in, 2099-2100
- Electrical activity, of ureters, 979
 action potentials, 980-982, 981f-983f
 pacemaker potentials and activity, 982-984,
 983f
 propagation, 984
 resting potential, 979-980, 980f, 982
- Electrical stimulation
 for detrusor underactivity, 1818-1819
 for emptying disorders, 1914-1916
 directly to bladder or spinal cord, 1914
 future research for, 1916-1917
 to nerve roots, 1914-1915, 1914f
 neurophysiology of, 1900-1902
 percutaneous tibial nerve stimulation,
 1916
 sacral neuromodulation for, 1916
 transurethral electrical bladder stimulation,
 1915-1916
 history of, 1899-1900
 levels of evidence and recommendations for,
 1877t-1878t
 of pelvic floor disorders, 1899-1900
- Electrical stimulation (*Continued*)
 for storage disorders, 1902-1914
 bilateral, 1908-1909
 future research for, 1916-1917
 neurophysiology of, 1900-1902
 sacral neuromodulation, 1903-1908
 sacral rhizotomy, 1903
 selection criteria for, 1902
 selective nerves, 1909-1910
 transcutaneous, 1910
 transurethral electrical bladder stimulation,
 1902-1903
 for voiding dysfunction, 1900t
- Electrohydraulic (spark gap) generator, for shock
 wave lithotripsy, 1265-1266, 1265f
- Electrohydraulic lithotripsy (EHL), 148, 230,
 231t, 232b, 1260-1261, 1261f
 for bladder stones, 232.e2
 chemical stone composition and, 232
 physics and mechanism of action of, 232
 tissue effects of, 232, 232f
 ureteroscopy with, 232.e1
- Electrolyte abnormalities, with urinary intestinal
 diversion, 2309-2311, 2310f, 2310t
- Electromagnetic generator, for shock wave
 lithotripsy, 1266, 1266f
- Electromotive drug administration (EMDA),
 737
- Electromyography (EMG)
 in urodynamic studies, 1722, 1724-1725
 in pediatric patients, 3130
 for urodynamics, 1706
- Electron micrograph
 of axoneme, 536f
 of epididymis, 530f
 of testis, 525f
- Electroporation. *See* Irreversible electroporation
- Electrostimulation, for neuromuscular
 dysfunction of lower urinary tract, 3282
- Electrosurgery
 bipolar. *See* Bipolar electrosurgery
 devices for, 227
 in laparoscopic and robotic surgery, 206,
 220-221, 220f, 206.e1f
 monopolar. *See* Monopolar electrosurgery
 safety of, 226-227
 tissue dissection and cauterization with,
 225-227, 226f
- Electrosurgical trauma
 during laparoscopic and robotic surgery,
 220-221, 220f
 safety considerations for, 226-227
- Electrotonic spread, in ureteral cells, 984
- Elephantiasis, as filariasis clinical manifestation,
 444, 444f
- 11p15 locus, in Wilms tumor, 3568t, 3569
- Elocalcitol, to facilitate bladder filling and urine
 storage, 1866.e1
- EM. *See* Erythema multiforme
- Embolism
 gas. *See* Gas embolism
 pulmonary. *See* Pulmonary embolism
 venous. *See* Venous thromboembolism
- Embolization
 before kidney surgery, 1414, 1414.e1f
 of prostate, 2534.e2-2534.e3
 for renal injuries, 1151, 1152f
 for renal tumors, targeted, 1499
- Embolotherapy, 3397
- Embryology
 of exstrophy-epispadias complex, 3184-3185,
 3184f
 of female genitalia, 3453-3454, 3454f
 of kidney, 2975
 neuroblastoma and, 3560
 of prune-belly syndrome, 3234

- Embryology (*Continued*)
 of testis, 3430-3434
 of unilateral renal agenesis, 2980, 2981f, 2980.e1f
 of ureteral anomalies, 3077, 3079b
 of ureterovesical junction, 3137
 of vagina, 3453-3454, 3454f
- Embryonal carcinoma (EC), histology of, 787f, 788
- Embryonal RMS, 3582-3583, 3583b, 3583f-3584f
- Embryonic stem cells (ESCs)
 for female SUI injection therapy, 2061-2062
 for tissue engineering, 483
 from altered nuclear transfer, 483.e1
 from arrested embryos, 483.e1
 from single-cell embryo biopsy, 483.e1
- Embryonic testicular regression, 3483
- EMDA. *See* Electromotive drug administration
- EMG. *See* Electromyography
- Emphysema, subcutaneous, during laparoscopic and robotic surgery, 217
- Emphysematous pyelonephritis, 279-280, 280f-281f
- Empirical treatment, in male infertility, 579, 579.e1
- EMT. *See* Epithelial-mesenchymal transition
- En bloc hilar vessel stapling, in laparoscopic radical nephrectomy, 1468-1469
- Encephalitis, and ED, 631
- Encrustation, of ureteral stents, 132
- Endo Close, 211
- Endo Stitch, 207, 207.e3
- EndoAvitene, 207t, 207.e2
- Endocarditis, antimicrobial prophylaxis for uncomplicated urologic procedures and, 264
- Endocrine evaluation, and male infertility, 564-566, 565b
- Endocrine-disrupting chemicals (EDCs), cryptorchidism and, 3436-3437
- Endocrinology
 basic concepts of, for HPG axis, 516, 517f
 hormones. *See* Hormones
 of prostate, 2399-2403, 2400f
 adrenal androgens, 2401-2402, 2402f
 androgen production by testes, 2400-2401, 2401f, 2401t
 androgen-binding proteins in plasma, 2401f, 2403
 estrogens in male, 2401t, 2402-2403
- End-of-life care, 2101-2102
- Endoglin, as prostate cancer biomarker, 2572-2573
- Endopelvic fascia, 1941, 1941f
 incision of, in retropubic radical prostatectomy, 2645, 2645f
- Endopyeloplasty, percutaneous, for ureteropelvic junction obstruction, 1111
- Endopyelotomy
 percutaneous antegrade. *See* Percutaneous antegrade endopyelotomy
 retrograde cautery wire balloon. *See* Retrograde cautery wire balloon endopyelotomy
 retrograde ureteroscopic. *See* Retrograde ureteroscopic endopyelotomy
 for ureteropelvic junction obstruction, 143
- Endoscopic correction, of vesicoureteral reflux, 3154, 3167-3169
- Endoscopy, 136, 152
 of bladder diverticula, 2144, 2145f
 management with, 2146-2148
 of cloacal anomalies, 3503-3504, 3504f
- Endoscopy (*Continued*)
 cystourethroscopy. *See* Cystourethroscopy
 equipment and video-endoscopic systems for, 136-137, 137f-138f
 female pelvis anatomy for, 1610
 in genitourinary tuberculosis treatment, 431
 history of, 136
 kidney anatomy for, 968.e2f
 for male urinary incontinence, 1708
 for non-muscle-invasive bladder cancer management. *See* Transurethral resection of bladder tumor
 in prostatitis evaluation, 315
 upper tract. *See* Upper tract endoscopy
 of ureteral anomalies, 3076f-3077f, 3085-3087, 3086f
 of ureters. *See* Ureteroscopy
 for urethral stricture disease, 919-920, 920f
 of urogenital sinus abnormalities, 3501-3503, 3502f-3503f
- Endothelial dysfunction, testosterone effects on, 548-549
- Endothelins (ETs)
 lower urinary tract and, 1672-1673
 renal vascular tone control by, 1009-1010
 urethral function effects of, 1005-1006
- EndoTIP trocar, for achieving transperitoneal access and establishing pneumoperitoneum, 200.e1, 200.e1f
- Endoureterotomy, for ureteral stricture disease, 1131
 antegrade approach to, 1133
 combined retrograde and antegrade approach, 1133
 results with, 1133
 retrograde ureteroscopic approach to, 1131-1133, 1132f
- Endourologic management
 for ureteral stricture disease, 1129-1133, 1133b
 for ureteroenteric anastomotic stricture, 1142-1143, 1143f
 for ureteropelvic junction obstruction, 1109, 1114b
- Endourology, rise of, 1235.e2-1235.e3
- Endovascular stents, for renovascular injuries, 1155
- EndoWrist instruments, 209-210, 210f
- End-stage renal disease (ESRD). *See also* Renal failure
 AD in, 539
 demographics of, 1065
 dialysis for, 1065, 1066b-1067b, 1066f, 1067t
 incidence and prevalence of, 1069
 long-term complications of, 1070
 options for, 1069
 results of, 1070
 etiologies of, 1058-1060, 1058t
 hospitalization risk in, 1065-1067, 1067b, 1067t
 neural tube defects and, early intervention for, 3277
 preoperative evaluation for, 1063-1064
 renal artery angioplasty and stenting for, 1038-1039, 1039b, 1040f
 renal transplantation for
 incidence and prevalence of, 1069
 other treatment options compared with, 1069-1070
- Enema
 cleansing, for prostate biopsy, 2585
 in surgical management of defecation disorders, 3327-3328, 3328f
- Energy modalities in urologic surgery
 intracorporeal lithotripsy. *See* Intracorporeal lithotripsy
 for laparoscopic surgery in pediatric patients, 2965
 for tissue dissection and cauterization
 electrosurgery, 225-227, 226f
 laser instrumentation, 228-230, 229f
 ultrasound instrumentation, 227-228
- Engineered tissues. *See* Tissue engineering
- Enoxaparin, preoperative VTE prophylaxis with, 109t
- Enteral nutrition, preoperative, 104
- Entereg. *See* Alvimopan
- Enteric hyperoxaluria, 1177, 1186-1187, 1186f, 1210
 medical management of, 1227, 1227b
- Enterobiasis, of genitourinary tract, 446
- Enterocoele, 1750, 1943-1944
- Enterocystoplasty. *See* Augmentation cystoplasty
- Enucleation, for small renal tumors, 1429-1431, 1430f
- Enuresis
 alarm for, 3314-3315
 alternative therapies for, 3316
 background on, 3311
 behavioral therapy for, 3313-3314, 3314f
 combination therapy for, 3316
 epidemiology of, 3311, 3311f
 evaluation of, 3313
 genetics of, 3311-3312
 natural history of, 3311, 3311f
 nocturnal, 1710, 1744-1745, 1744f
 pathophysiology of, 3312-3313, 3312f
 patient history of, 6
 pediatric, 3311-3316
 pharmacotherapy for, 3315-3316
 terminology for, 3311
 treatment of, 1716, 3313-3315
- Enuresis risoria. *See* Giggle incontinence
- Environment
 of preoperative patient
 positioning, 114-115, 114b
 safety considerations, 114
 skin preparation, 113-114
 temperature, 113
 urothelial cancer and, 2187
- Enzalutamide, 2790, 2790f, 2812-2813, 2812f
- Enzyme/prodrug gene therapy, for localized prostate cancer, radiation therapy with, 2710
- Eosinophilic cystitis, 3180, 3180f
- EP. *See* Etoposide-cisplatin
- EPD. *See* Extramammary Paget disease
- Ephedrine
 in stone formation, 1197
 medical management of, 1231-1232
 surgical management of, 1243.e3
 for stress urinary incontinence in women, 1867
- Epidemiology of Diabetes Interventions and Complications (UroEDIC) study, 551
- Epidermal growth factor receptor (EGFR), in RCC, 1327b
- Epidermal growth factor receptor (EGFR) therapy, for metastatic bladder cancer, 2240
- Epidermoid cysts, 416-419, 418f, 3593
- Testicular, 812
- Epididymal cancer, tumor excision for, 953-954
- Epididymectomy, 953, 954f
- Epididymis
 anatomy of, 503b, 533b
 arterial supply, 503
 gross structure, 501-502, 502f-503f

- Epididymis (*Continued*)
 lymphatic supply, 503
 microanatomic architecture, 502-503
 nerve supply, 503
 surgical, 946, 947b, 947f
 venous drainage, 503
 anomalies of, 3397
 with cryptorchidism, 3441-3442, 3442f
 appendix, torsion of, 3392
 cyst of, 953
 in genitourinary tuberculosis, 423
 HIV and, 383
 imaging of
 electron photograph, 530f
 ultrasound, 503, 504f
 physiology of, 533b
 cytoarchitecture, 530, 530f
 gross architecture, 529-530, 529f
 regulation of, 532-533
 sperm transport, storage, and maturation functions, 529-533, 531f-532f
 surgery of
 anatomical considerations for, 946, 947b, 947f
 complications of, 954
 indications for, 953
 partial and total epididymectomy, 953, 954f
 preoperative preparation for, 946-947
 spermatocectomy and cyst excisions, 953
 tumor excision, 953-954
- Epididymitis, 3392-3393
 as inflammatory and pain condition, 331-332, 331b-332b
 after photoselective vaporization of prostate, 2532
 as STD, 373
 surgical treatment of, 953
- Epididymo-orchitis, pediatric imaging of, ultrasonography, 2913, 2917f
- Epidural analgesia
 immediate postoperative, 112
 for pediatric patients, 2956
- Epidural anesthesia, preoperative considerations for, 111
- Epidural cord compression, in castration-resistant prostate cancer, 2818, 2819t
- Epigenetic anomalies, and male infertility, 574
- Epigenetic events, in prostate cancer, 2554
- Epigenetic modifications, as prostate cancer biomarkers, 2575-2576
- Epinephrine, for contrast media reactions, 29
- Espadias, 577, 3221-3226
 female, 3223-3226, 3223f-3224f
 associated anomalies, 3223
 operative techniques for, 3224-3226, 3225f
 surgical objectives for, 3224
 surgical results for, 3223t, 3226
 male, 3221-3223, 3221f
 associated anomalies, 3221
 genital reconstruction in, 3223
 surgical management of, 3221-3223
 urethral reconstruction in, 3222
 urinary continence in, 3222, 3223t
 repair of, 3203
 failure of, 3215f, 3216-3217
 outcomes and results with, 3211-3212
- Epitaxy, 1210
- Epithelial cell receptivity, in UTIs
 bladder cells, 244-245, 246f
 vaginal cells, 244-245, 245f
 variation in, 245
- Epithelial cells, in urinary sediment, 22-23, 22f
- Epithelial metaplasia, of bladder, 2184
- Epithelial permeability, bladder
 glycosaminoglycan layer and, 345.e6-345.e7, 345.e8b
- Epithelial spread, of UTUC, 1368
- Epithelial stem cells, of prostate, 2397f, 2398
- Epithelial-mesenchymal transition (EMT), in tubulointerstitial fibrosis, 1098
- Epithelium, epididymal, 530, 530f
- EPO. *See* Erythropoietin
- EQUIL 2, 1174
- Equivalent dose, 26
- Erbium:YAG (Er:YAG) laser lithotripsy, 231t, 234b, 233.e3, 234.e2, 234.e3, 234.e3f
 basic physics of, 233-234
 for bladder stones, 234.e2-234.e3
 for percutaneous nephrolithotomy, 234.e2
 popcorning technique for, 234
 ureteroscopy with, 234.e1
- Erectile bodies, of penis, 910.e1-910.e3, 910.e1f-910.e4f
- Erectile dysfunction (ED)
 AD in, 547
 causes of
 aging, systemic disease, and other, 630f, 639-641, 640t, 641b
 arteriogenic, 631b, 632-634, 634t
 cavernous (venogenic), 631b, 634-635
 drug-induced, 635-639, 636t, 638t
 endocrinologic, 631-632, 631b
 neurogenic, 631, 631b
 epidemiology, 643-644, 645b
 evaluation and management of
 diagnostic evaluation, 647-650, 647f, 648t, 658b
 historical perspective, 643, 644t
 management principles, 645-647, 645t, 646f
 public health significance, 643-644, 645b
 specialized evaluation and testing, 650-658, 650t, 651f-655f
 treatment considerations, 658-667, 659f, 661t-662t, 663b, 665t, 667b
 following pediatric urethral trauma, 3557
 HIV and, 384
 hormonal therapy and, 2794
 HRQOL instruments for, 92t-94t
 after laparoscopic radical prostatectomy, 2676, 2677t
 MetS and, 553
 pathophysiology of
 classification, 630-641, 630f, 631b, 634t, 636t, 638t, 640t, 641b
 incidence and epidemiology, 629-630, 641b
 and PD, 724
 penile cell therapies for, 492
 after photoselective vaporization of prostate, 2533
 primary, 641
 after retropubic radical prostatectomy, 2658
 risk factors for, 630
 surgery for
 complications of, 718-720, 718f, 719b
 conclusion of, 721
 patient satisfaction of, 720-721
 postoperative care, 717-718
 preoperative patient evaluation and preparation, 710-712, 711t, 712b
 special cases, 720
 surgical preparation and approach, 712-717, 713f-717f, 717b
 types of prostheses, 709-710, 710f-711f
 surgical complications of
 device malfunction, 719
 infection, 718-719, 718f, 719b
 other, 719-720
 surgical preparation for
 closure, 717
 cylindrical, 717
- Erectile dysfunction (ED) (*Continued*)
 pump placement, 716, 716f
 reservoir placement, 716-717, 716f-717f
 testosterone therapy for, 547, 547b
 with transurethral vaporization of prostate, 2517.e4
 with urethral distraction injury, 937, 2391
- Erectile function, after radical prostatectomy, 2617
- Erector spinae, 767f-769f, 769, 769t
- Ergot alkaloids, with RPE, 1144
- Erlangen approach, for classic bladder exstrophy, 3198
 continence outcomes with, 3213
- Erlotinib, for RCC, 1518
- Er:YAG laser lithotripsy. *See* Erbium:YAG laser lithotripsy
- Erysipelas, 402
- Erythema multiforme (EM), 390, 391f-392f
- Erythrasma. *See* Corynebacterial infection
- Erythrocytes
 production of, 1011
 in urinary sediment, 21, 21f-22f
- Erythrocytosis, as complication of TT, 546
- Erythroid progenitor cells, renal regulation of, 1011
- Erythromycin
 in pregnancy, 296t
 preoperative bowel preparation with, 107
- Erythroplasia of Queyrat, 846-847, 847b, 846.e1f
- Erythropoiesis, renal regulation of, 1011
- Erythropoietin (EPO), 1011
- ESCs. *See* Embryonic stem cells
- ESRD. *See* End-stage renal disease
- Essential hematuria. *See* Nonglomerular hematuria
- Established urinary incontinence, in geriatric patients, 2096-2098
- Estradiol, 517-518, 562, 565
- Estrogens, 516-518, 520-521
 benign prostatic hyperplasia role of, 2428-2429
 bladder and, 1673
 continence mechanism and, 1866
 and female sexual response, 751, 751.e1f
 and HSDD, 759
 in male, 2401t, 2402-2403
 for overactive bladder, 1863-1864
 in prostate cancer, 2549
 for stress urinary incontinence in women, 1866-1867
 supplementation of, for vesicovaginal fistula surgery, 2112
 urethra and, 1673
 for urgency urinary incontinence, 1863-1864
- ESWT. *See* Extracorporeal shock wave therapy
- Ethnicity
 renal calculi and, 1171
 prevalence of, 1201
 urinary incontinence and, 1748
- Etoposide. *See* Bleomycin-etoposide-cisplatin
- Etoposide-cisplatin (EP)
 for NSGCTs, 801
 for seminomas, 809
- Etoposide-ifosfamide-cisplatin (VIP), for NSGCTs, 802, 805
- ETs. *See* Endothelins
- European Cooperative Groups, bladder RMS
 treatment approaches of, 3586-3587
- Everolimus (Afinitor), 1327, 1360t
 for RCC, 1514t, 1515-1517, 1515f
- Evicel, 207.e2
- Evidence, levels of, 91
- Evidence-based health care policy, 98

- Excitation-contraction coupling
in detrusor muscle, 1645-1646, 1645f
in ureters, 985-986
- Excretory urography
ureter anatomy on, 975-976
of ureteral injuries, 1160, 1160f
of ureteropelvic junction obstruction, 1105, 1106f
of urinary tract obstruction, 1093
- Excurrent ducts, of testes, 581-582
- Exercise. *See also* Physical activity
for ED, 553
- Exogenous Cushing syndrome, 1534
- Exstrophy
prenatal imaging of, 2910-2911, 2912f
residual abnormality of, urethral
reconstructive surgery for, 915-916
- Exstrophy-epispadias complex (EEC),
3182-3185, 3183f
adolescents with, 3218
adults with, 3218
classic bladder exstrophy. *See* Classic bladder
exstrophy
cloacal exstrophy. *See* Cloacal exstrophy
embryology of, 3184-3185, 3184f
epispadias. *See* Epispadias
fertility with, 3219-3220
female patient, 3220
male patient, 3219-3220
historical aspects of, 3182
incidence of, 3182-3184
inheritance of, 3182-3184
long-term adjustment issues with, 3220-3221
prenatal diagnosis of, 3191-3192, 3192f
pseudoexstrophy, 3191
quality of life with, 3220
sexuality with, 3218-3219
female concerns, 3219
male concerns, 3218-3219
split symphysis variant of, 3191
variants of, 3191, 3191f-3192f
- Extended core prostate biopsy, 2586, 2586f
- Extended sentinel lymph node dissection, for
penile cancer, 863-864
- Extensively drug-resistant tuberculosis, 432
- External collecting devices, 2081-2082
- External genitalia
cutaneous diseases of. *See* Cutaneous diseases,
of external genitalia
female. *See* Female external genitalia
male. *See* Male external genitalia
prenatal, 2875
- External spermatic artery. *See* Cremasteric artery
- External-beam radiation therapy
for localized prostate cancer, 2692-2699
advances in radiation technology and,
2692-2694, 2693f-2694f, 2694t
brachytherapy with, 2701-2702
morbidity outcomes with, 2696-2697,
2696t
outcomes for, 2703-2705, 2704t-2705t
quality-of-life outcomes with, 2696-2697,
2696t
tumor control after, 2695, 2695t
for penile cancer, 868, 869t
- Extracellular matrix (ECM), of RCC, 1327b
- Extracorporeal membrane oxygenation (ECMO),
2870
- Extracorporeal renal surgery (ECRS), 1421, 1422f
preoperative considerations for, 1421-1423
surgical procedure for, 1423
- Extracorporeal shock wave therapy (ESWT)
and PD, 737
for prostatitis, 326
- Extramammary Paget disease (EPD)
as neoplastic condition, 414, 415f
of penis, 874f, 875
- Extraperitoneal approach
achieving access for, 201-202, 202.e1
anterior, to laparoscopic pyeloplasty,
1119
operative team placement for, 199,
199f
- Extraperitoneal space, development of, 201-202,
202.e1
- Extratesticular endocrine dysfunction, and male
infertility, 576-577
- Extravasation, of contrast media, 30
- Extrinsic apoptotic pathway, 479.e1-479.e2,
479.e1f-479.e2f
- Eye-ball UDS, 1706
- Eye-of-the-needle fluoroscopic guidance,
163-165, 164f
- F**
- F1. *See* Urinary prothrombin fragment 1
- FAAH. *See* Fatty acid amide hydrolase
- Fabry disease, 415, 416f-417f
- Face validity, 96-97
- Failed hypospadias repair, reconstructive surgery
for, 915-916
- Fallopian tubes
anatomy of, 1606-1607
for continent urinary diversions, 3363
- Falls, nocturia and, 1823
- Familial benign prostatic hyperplasia, 2432,
2432t
- Familial hypomagnesemia with hypercalciuria
and nephrocalcinosis (FHHNC), 1184
- Familial hypoplastic glomerulocystic kidney
disease, 3023
- Familial papillary RCC, molecular genetics of,
468t, 472, 1322t, 1324
- Familial RCC, 1321-1325, 1322t-1323t, 1323f
treatment of, 1353-1355, 1355f, 1429,
1429.e1f
- Familial Wilms tumor, 3569
- Family history, 7
- Fanconi syndrome, 2861
- Fasciae
of anterior abdominal wall, 1599f, 1611,
1612f
endopelvic, 1941, 1941f
pelvic
female, 1597-1599, 1599f
male, 1614-1615, 1618f
of perineum and perineal body, 1615,
1617f-1619f
- Fascial closure, after laparoscopic and robotic
surgery, 210-211
- Fascial sling
for bladder neck reconstruction,
3336-3337
results with, 3337
technique for, 3337
- FAST. *See* Focused assessment with sonography
for trauma
- Fast and calcium load test, for hypercalciuria,
1205
- Fast-twitch fibers, of urethral striated muscle,
1637
- Fatty acid amide hydrolase (FAAH), 1866.e2
- FDG-PET. *See* Fluorodeoxyglucose PET
- Fecal and perineal bacterial colonization, and
UTIs, 2931
- Fecal diversion, for radiation fistula, 2138
- Fecal impaction, transient urinary incontinence
and, 2096.e1
- Fecal incontinence (FI). *See also* Pelvic floor
disorders
in geriatric patients, 2099.e8-2099.e9
prevalence of, 1746f
sacral nerve stimulation for, 1908
ultrasound for, 1610, 1610f
- Female circumcision, 3467-3468, 3468f
- Female external genitalia, 1604-1605, 1605f-
1606f, 750.e2
acquired disorders of, 3466-3468
condyloma acuminatum, 3468
female circumcision, 3467-3468, 3468f
labial adhesions, 3466-3467, 3467f
defect of, in bladder exstrophy, 3189, 3189f
- Female genital cutting (FGC), 754.e2
- Female genitalia
abnormalities of
cervical atresia, 3465
clitoris. *See* Clitoris, disorders of
congenital, 3455-3466
lateral fusion. *See* Lateral fusion
abnormalities
structural, 3454-3455, 3455f
of vagina. *See* Vagina, disorders of
vestibule. *See* Vestibule, disorders of
anatomy of, 750.e4
embryology of, 3453-3454, 3454f
- Female orgasmic disorder (FOD), 761
etiology of, 761
evaluation of, 761
treatment of, 761, 761.e1
- Female patients
catheterization in, 122
urinary specimen collection in, 12-13
- Female pelvis
anatomy of
anal perineum of, 1604
bony pelvis of, 1597, 1598f
external genitalia of, 1604-1605,
1605f-1606f
fascia of, 1597-1599, 1599f
innervation of, 1601-1603
ligaments of, 1600, 1600f-1603f
lymphatic drainage of, 1601
muscles of pelvic floor, 1601, 1603f
organ support of, 1607, 1607f
organs of, 1605-1607, 1606f
perineum of, 1603-1604, 1605f
peritoneum of, 1597-1599, 1599f
urethra, 1607-1608, 1608f, 1636-1637, 1636f
vasculature of, 1601, 1604f
endoscopic anatomy of, 1610
examination of, 11
radiographic anatomy of, 1608-1610
fluoroscopy, 1608
magnetic resonance imaging, 1609, 1609f
ultrasound, 1609-1610, 1610f
- Female reproductive system. *See also specific
organs*
anatomy of, urethra, 119
pediatric tumors of, 3590b
cervical or uterine RMS, 3590
ovarian, 3590
vaginal RMS, 3589-3590, 3590f
vulvar RMS, 3589
regenerative medicine for, 493-494, 495f
- Female sexual arousal disorder (FSAD), 759-760
etiology of, 759
evaluation of, 759
treatment of
devices, 759-760
oral pharmacotherapy, 760, 760.e1
psychosocial, 759
- Female sexual concerns, 764b

- Female sexual distress scale (FSDS), 753.e2
- Female sexual dysfunction (FSD), 755-757, 757b
classification of, 757, 757t
epidemiology of, 755-757, 756t
semantics and controversy, 755, 755.e2
- Female sexual function index (FSFI), 753.e2
- Female sexual response
and central nervous system, 750.e7
hormonal aspects of, 751-752
menstrual cycle and sexuality, 752, 752.e1f
and neuroanatomy, 750.e7
and neurophysiology, 750-751, 750.e8
and pelvic floor musculature, 752
- Female-to-male transsexualism, reconstructive surgery for, 945, 945b
- Femoral nerve, 1619, 1621f, 1622t
- FemSoft insert, 1896, 1897f
- FE_{Na}. See Fractional excretion of sodium
- Fenoldopam, for AKI, 1051
- Fenretinide, for neuroblastoma, 3567
- Fentanyl, preoperative considerations for, 112
- FEPs. See Fibroepithelial polyps
- Fertility
with cryptorchidism, 3449-3450
with exstrophy-epispadias complex, 3219-3220
female patient, 3220
male patient, 3219-3220
RMS treatment effects on, 3587-3588
after RPLND, 833
sperm, 531-532, 532f
transitional urology and, 3526
Wilms tumor treatment effects on, 3579
- Fesoterodine
for diminished bladder, 1831, 1832t-1834t
to facilitate bladder filling and urine storage, 1839t, 1842-1843
for urinary incontinence, in geriatric patients, 2099.e4
- Fetal bladder
absent, 3175
dilated, 3174
nondilated, 3174-3175
- Fetal intervention, rationale and indications for, 2886-2887, 2886t
- Fetal uropathies, antenatal management of, 2888b
clinical experience, 2887-2888, 2887f
clinical outcomes, 2888
fetal intervention, 2886-2887
- α -fetoprotein (AFP)
in pediatric patients, 3591-3593, 3593f
in TGCTs, 790-791, 794
- Fever
patient history of, 7
after percutaneous access to upper urinary tract collecting system, 180-181
postoperative, 2961, 2961t
UTI diagnosis and, 252
- FFP. See Fresh frozen plasma
- FG. See Fournier gangrene
- FGC. See Female genital cutting
- FGF. See Fibroblast growth factors
- FGF-23. See Fibroblast growth factor-23
- FH gene, systemic therapy targeting, 1518
- FHHNC. See Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
- FI. See Fecal incontinence
- Fibrin glue, for laparoscopic and robotic surgery, 207t, 207.e2
- Fibroblast growth factor-23 (FGF-23), renal regulation of, 1011f, 1012
- Fibroblast growth factors (FGF), in prostate development, 2395
- Fibroblasts, in tubulointerstitial fibrosis, 1098, 1099f
- Fibroepithelial polyps (FEPs)
of ureter, 3098-3099, 3098f
of urethra, 879
- Fibrosis
with congenital obstructive uropathy, 3049-3050, 3049f-3050f
PC-RPLND findings of, survival outcomes associated with, 830, 830t
pelvic, as laparoscopic and robotic surgery contraindication, 196
retroperitoneal. See Retroperitoneal fibrosis
tubulointerstitial. See Tubulointerstitial fibrosis
- Fibrotic gene expression, and PD, 727f, 729
- Fibrous dysplasia, renovascular hypertension caused by, 1032-1033, 1033t, 1034b, 1034f-1035f
- Filariasis, of genitourinary tract, 442
diagnosis, 444
epidemiology, 442-443
organisms, 442, 442f
pathology and clinical manifestations, 443-444, 443f-444f
prevention and control, 445
treatment, 444-445
- Filling cystometry, for benign prostatic hyperplasia, 2470
- Finasteride
for benign prostatic hyperplasia, 2483-2486, 2483f, 2484t, 2485f
for BPH-related hematuria, 192
for diminished bladder, 1830-1831, 1832t-1834t
- Fine-needle aspiration cytology, for penile cancer, 863
- Fistulae
cutaneous, 2137
with intestinal anastomoses, 2290
radiation, 2137-2139
diversion procedures for, 2138
interpositional grafts for, 2138
management approaches for, 2138
recommendations for, 2138-2139
repair techniques for, 2138
- urethral, 3379
- urethrocutaneous, 2137
- of urinary tract
general considerations of, 2103, 2103b
management of, 2104b
after renal preservation surgery, 2137
after renal transplantation, 2137
surgical repair of, 2104b
- urocutaneous, 2137
- uroenteric, 2129-2135
pyeloenteric, 2132, 2132f
ureteroenteric, 2132
urethrorectal, 2132-2135. See also Urethrorectal fistula
vesicoenteric, 2129-2132. See also Vesicoenteric fistula
- urogynecologic, 2104-2129
ureterovaginal, 2119-2123. See also Ureterovaginal fistula
urethrovaginal, 2125-2129. See also Urethrovaginal fistula
vesicouterine, 2123-2124. See also Vesicouterine fistula
vesicovaginal, 2104-2119. See also Vesicovaginal fistula
- urovascular, 2135-2137
pyelovascular, 2135-2136
renovascular, 2135-2136
ureterovascular, 2136-2137, 2136.e1t
vesicorectal and vesicourethrorectal, 938-939, 939b
- Fixed drug eruption, as papulosquamous disorder, 396, 397f
- Fixed particle growth theory, 1175
- Flank approaches
for open kidney surgery, 1415-1416
subcostal, 1416-1417, 1416f-1417f, 1416.e1f
supracostal, 1417, 1417.e1f
to ureteropelvic junction obstruction in pediatric patients, 3062
- Flank musculature, of posterior abdominal wall, 765-769, 767f-769f, 769t
- Flank pain
trauma-induced, 3548
UTI diagnosis and, 252
- Flank retroperitoneal approach, in open adrenalectomy, 1581-1582, 1581f-1582f
- Flaps. See also specific flaps
for continent urinary diversions, 3361-3363, 3362f
for total penile reconstruction, 941-945, 943f, 945b
for ureteropelvic junction obstruction, 1122
Culp-DeWeerd spiral flap, 1123, 1124f
Foley Y-V plasty, 1122-1123, 1123f
intubated ureterotomy, 1123-1124, 1126f
salvage procedures, 1124-1125
Scardino-Prince vertical flap, 1123, 1125f
for urethral and penile reconstruction, 909-910, 909f-910f, 926-929, 927f-931f
- Flavoxate hydrochloride, to facilitate bladder filling and urine storage, 1851-1852
- Fleet Phospho-soda. See Sodium phosphate solution
- Flexible cystourethroscopes, 137-138, 140t
- Flexible lithotripters, 1260-1262
- Flexible ureteroscopes, 144, 146f-147f, 147t
care and sterilization of, 146, 148f
technique for, 152
- Flibanserin, and HSDD, 759.e1
- FloSeal, 207t, 207.e2
for renal trauma, 1154, 1155f
- Fluid prescriptions, for renal development, 2851-2852
- Fluids
for AKI, 1049, 1051
ATN prevention and, 1053
CKD prevention and, 1061
intake of
for cystinuria, 1229
for enteric hyperoxaluria, 1227, 1227b
for nephrolithiasis, 1216-1217, 1217b
renal calculi and, 1173
management of, 1892-1893
evidence for, 1893
excessive, 1892
inadequate, 1892
timing of, 1892-1893
perioperative, for pediatric patients, 2951-2952, 2951t, 2952b
- Fluorodeoxyglucose (FDG)-PET, in urologic oncology, 39-40
- Fluoroquinolones
prophylaxis with
for cystourethroscopy, 139-140
preoperative, 105-106, 106t-107t
for uncomplicated urologic procedures, 261t-262t
for UTIs, 256t-258t, 258-259, 267, 267t, 270, 272t, 273, 296t
- Fluoroscopy
CT, 40
of female pelvis, 1608
pediatric
genitalia, 2918, 2920f
upper and lower urinary tract, 2916-2918, 2919f

- Fluoroscopy (*Continued*)
 of pediatric stone disease, 3103
 percutaneous access guidance with, 163-165, 163f-165f
 in sacral nerve stimulation technique, 1904-1905, 1905f
 in shock wave lithotripsy, 1267
 ureteroscopy, 150
 for urodynamics, 1706
- 5-Fluorouracil
 for condylomata acuminata, 846.e3
 for penile cancer, 872-873, 872t
- Flurbiprofen, to facilitate bladder filling and urine storage, 1839t, 1858
- Flush stoma, 2293
- Flutamide
 for benign prostatic hyperplasia, 2486
 for prostate cancer, 2790
- Focal ablative therapy
 for localized prostate cancer, 2626
 cryoablation, 2626.e1
 high-intensity focused ultrasound ablation, 2626.e1
 laser ablation, 2626
 photodynamic therapy, 2626
 for locally advanced prostate cancer, 2765
 cryoablation, 2765
 high-intensity focused ultrasound, 2765
 for prostate cancer
 biochemical outcomes with, 2743-2744
 biopsy for, 2720-2722
 cancer control with, 2743
 complications with, 2743
 conceptual basis for, 2712-2714, 2713f-2714f
 cryotherapy, 2727, 2728f-2730f
 determination of failure, 2745-2746
 follow-up after, 2743-2745, 2744f
 high-intensity focused ultrasound, 2727-2732, 2731f-2735f
 histologic outcomes with, 2744-2745
 imaging outcomes with, 2745
 irreversible electroporation, 2733-2734, 2734f-2736f
 localization of disease for, 2720, 2720t
 multiparametric magnetic resonance imaging for, 2724-2727, 2725f-2727f
 nadir prostate-specific antigen, 2744
 outcomes with, 2736-2737
 overall data for, 2737-2743, 2739t-2742t
 overview of, 2711-2714
 patient population identification, 2719-2727, 2719f-2720f
 photodynamic therapy, 2732
 photothermal therapy, 2732-2733
 prostate-specific antigen density, 2744
 prostate-specific antigen kinetics, 2744
 quality of life with, 2743
 radiofrequency ablation, 2734-2736, 2736f-2737f
 salvage brachytherapy, 2749
 salvage cryotherapy, 2750
 salvage high-intensity focused ultrasound, 2750
 salvage therapy, 2748, 2748f-2749f
 side effects of, 2743
 technology for, 2727-2737
 ultrasound advances, 2722-2727
- Focal segmental glomerulosclerosis (FSGS), 1058, 2858
- Focused assessment with sonography for trauma (FAST), of upper urinary tract, 3538-3539
- Focused ultrasound
 for renal tumor ablation, 1495-1497
 for shock wave lithotripsy, 1267
- FOD. *See* Female orgasmic disorder
- Folded rectosigmoid bladder, 2320
- Foley Y-V plasty, for ureteropelvic junction obstruction, 1122-1123, 1123f
- Follicle-stimulating hormone (FSH), 516-519, 517f, 539-540, 565-566
- Folliculitis, 404-405, 404f
- Force-length relations, of ureters, 988-989, 989f
- Force-velocity relations, of ureters, 989, 990f
- Foreign body. *See* Intravesical foreign body
- Forgotten stents, 132
- Formalin, for hemorrhagic cystitis, 190
- Formation product (K_f), 1173-1174, 1174f
- 46,XX DSD, 3485-3489
- 46,XX males, 3478
- 46,XY complete, 3482-3483, 3482f-3483f, 3482t
- 46,XY DSD, 3489
- Fosfomycin, for UTIs, 255t-258t, 258
- Fosfomycin trometamol, for UTIs, 267, 267t
- Fossa navicularis, 510-511, 511f, 910.e1, 910.e2f
- Fournier gangrene (FG), 302-303, 303b, 402-404, 404f
 genital skin loss and, 2384-2385, 2385f
 of scrotal wall, debridement of, 947-948, 948f
- Fowler syndrome, 1789, 1874.e3
- Fowler-Stephens orchidopexy, 3447-3449, 3448t
- fPSA. *See* Free prostate-specific antigen
- Fractional excretion of sodium (FE_{Na}), urinary tract obstruction and, 1090
- Fracture
 pelvic. *See* Pelvic fracture
 of penis, 941, 2379-2381, 2380f-2381f, 2379.e1f, 2380.e1f
 of testis, 2383
- Frailty, 2091-2092, 2091f
- Frank hematuria. *See* Gross hematuria
- Frasier syndrome, 3480, 3482t
- Free crystal particle growth theory, 1175
- Free prostate-specific antigen (fPSA), 2569-2570, 2569t, 2604-2605
 isoforms of, 2570-2571, 2571f
- Frequency, urinary. *See* Urinary frequency
- Frequency-volume chart, 1823-1824
 nocturia classification with, 1824-1825, 1824t
- Fresh frozen plasma (FFP), preoperative considerations for, 112-113
- Fructose, in prostatic secretions, 2415
- FSAD. *See* Female sexual arousal disorder
- FSD. *See* Female sexual dysfunction
- FSDS. *See* Female sexual distress scale
- FSFI. *See* Female sexual function index
- FSGS. *See* Focal segmental glomerulosclerosis
- FSH. *See* Follicle-stimulating hormone
- Fuhrman's classification system for RCC, 1328, 1328t, 1340
- Functional capacity, preoperative evaluation of, 101, 102t
- Functional imaging
 in adrenal mass evaluation, 1569
 in pheochromocytoma diagnostic tests, 1548-1549, 1548f
- Funguria, and UTIs, 2947-2948
- Funiculopididymitis, as filariasis clinical manifestation, 443
- Furosemide
 for nocturnal polyuria, 1830t
 in stone formation, 1197
 in neonates, 1232
- Furunculosis, 405, 405f
- G**
- G₁/S checkpoint, deregulation of, in GU cancers, 461.e2
- G₂/M checkpoint, deregulation of, 461.e2
- GABA. *See* γ-Aminobutyric acid
- Gabapentin, to facilitate bladder filling and urine storage, 1866.e3
- Gadolinium
 CKD assessment and, 1061-1062
 MRI contrast media using, 30-31, 47, 56
- Ganglioneuroma, as benign lesion, 1565, 1565b
- Gangrene, of scrotal wall, debridement of, 947-948, 948f
- Gardasil, 379-380
- Gartner duct cysts, urethral diverticula differentiated from, 2162, 2162f
- Gas embolism
 during laparoscopic and robotic surgery, 216-217
 after percutaneous access to upper urinary tract collecting system, 180
 vena caval thrombectomy causing, 1444
- Gasless laparoscopic transperitoneal approach, 1588-1589, 1588f
- Gastric contents, aspiration of, during laparoscopic and robotic surgery, 220.e1
- Gastric pouch, for cutaneous continent urinary diversion, 2336-2338, 2337f
- Gastrocystoplasty, 3347-3348, 3349f
 using antrum, 3347
 using body, 3347-3348, 3349f
- Gastroenterologic changes, with aging, 2084
- Gastrointestinal injury
 during laparoscopic and robotic surgery, 216-218, 220-221, 220f
 laparoscopic kidney surgery causing, 1481, 1481f
 during radical nephrectomy, 1428
- Gastrointestinal tract
 abnormalities of, with cloacal exstrophy, 3227-3228
 after augmentation cystoplasty, 3350
 mesh complications in pelvic reconstructive surgery in, 2042-2043
 in prune-belly syndrome, 3239-3240
- Gastrointestinal viscera, in retroperitoneum, 773-775, 773f-774f, 773.e1f
- Gastroparesis, lower urinary tract dysfunction and, 1790
- GAX. *See* Glutaraldehyde cross-linked bovine collagen
- GBS. *See* Guillain-Barré syndrome
- GC. *See* Cisplatin and gemcitabine
- GCKD. *See* Glomerulocystic kidney disease
- GCTs. *See* Germ cell tumors
- GelPort, 203, 203.e3, 203.e3f
- Gemcitabine
 for non-muscle-invasive bladder cancer, 2216, 2216t
 for retroperitoneal sarcomas, 1411
 for UTUC, 1398, 1400
- Gender
 assignment of
 for cloacal exstrophy, 3230
 in newborn, 3496
 desmopressin and, 1866
 infection calculi and, 1213
 lower urinary tract dysfunction and, 3297-3298
 renal calculi and, 1170-1171, 1173b
 UTUC variations and, 1365
- Gender and age, and UTIs, 2930
- Gender identity, role, and orientation, 3475-3477
- Gene fusions, in prostate cancer, 2556-2557, 2557f-2558f
 as biomarkers for, 2574-2575

- Gene rearrangements
in prostate cancer, 466-467
in renal cancer, 467
in testicular cancer, 467
- Gene susceptibility loci, as prostate cancer biomarkers, 2576-2577
- General anesthesia
for laparoscopic and robotic surgery, complications related to, 220.e1
preoperative considerations for, 111-112
- General HRQOL instruments, 92-95, 92t-94t
- General observations, in physical examination, 9
- Genes
oncogenes, 460, 460b
structure of, 459.e4
tumor suppressor, 459-460, 460b, 460f
of vesicoureteral reflux, 3136-3137
- Genetic mutations, male reproductive physiology and, age-related, 528-529, 528b
- Genetic syndromes, and male infertility, 573-574
- Genetics. *See also* Molecular genetics
of autosomal dominant polycystic kidney disease, 3017-3018
of autosomal recessive polycystic kidney disease, 3013
in benign prostatic hyperplasia, 2432, 2432t
in BPS/IC etiology, 345.e11-345.e12
in CKD, 1057-1058
of enuresis, 3311-3312
of hernia and hydrocele, 3385
of juvenile nephronophthisis, 3014t, 3021-3022
lower urinary tract function and, 1700
of neuroblastoma, 3569
overview of, 3006
of prune-belly syndrome, 3234
of tuberous sclerosis complex, 3023-3024, 3025f
in urothelial cancer, 2186-2187
and UTIs, 2930
in UTUC, 1365-1366
- Genital bite wounds, 406-407, 408f
- Genital burns, 2384-2385, 916.e2
- Genital lymphedema, 3380-3381
- Genital nerve, dorsal, electrical stimulation of, for bladder storage disorders, 1909-1910
- Genital sexual response, in women, 750, 750.e6
- Genital ulcers
noninfectious, 400, 400b
aphthous ulcers and Behçet disease, 400-401, 401f
pyoderma gangrenosum, 401, 402f
traumatic causes, 401-402, 402f
- STDs, 373, 373t
chancroid, 373t, 377-378, 377f
granuloma inguinale, 378
herpes, 373t, 376-377, 376f, 377t
HPV, 378-380, 379f
lymphogranuloma, 373t, 378
molluscum contagiosum, 380-381, 380f
pediculosis pubis, 380
scabies, 380, 380f
syphilis, 373-376, 373t, 374f, 375t
vaginitis, 381-382, 381t
- Genital warts. *See* Condylomata acuminata
- Genitalia. *See also* External genitalia
ambiguous, 3495-3496, 3496f
pediatric imaging of
conventional radiography and fluoroscopy, 2918, 2920f
CT, 2921
MRI, 2915-2916
ultrasonography, 2913-2915, 2917f-2918f
- Genitalia (Continued)
reconstruction of
female, 493-494, 495f
male, 492-493, 493f-494f, 492.e2
- Genitocerebral evoked potential, 656
- Genitofemoral nerve, 500-501, 1613f, 1618-1619, 1622t
- Genitourinary (GU) cancer. *See* Cancer
- Genitourinary (GU) tract
abnormalities of, with cloacal exstrophy, 3228
mesh complications in pelvic reconstructive surgery in, 2041-2042, 2043f
pain arising in, 1-2
parasitic infections of. *See* Parasitic infections, of genitourinary tract
- Genitourinary trauma
in geriatric patients, 2099.e11
pediatric. *See* Pediatric genitourinary trauma
screening for, pediatric patient compared with adult, 3538, 3539b
- Genitourinary tuberculosis (GUTB), 421
clinical manifestations and pathologic features of, 422
bladder, 423
epididymis, vas deferens, testes, and scrotum, 423
kidney, 422-423
penis and urethra, 423
prostate and seminal vesicles, 423
ureter, 423
development of, 422
diagnosis of, 423-424
culture, 424
histopathology, 424
nucleic acid amplification tests, 424
radiography, 425-427, 425f-427f
screening tests, 424-425, 425b
management, in special situations, 432
relapse, 432
transmission and host immune response, 421-422
treatment of, 427-432
medical therapy, 428-430, 429t-430t
surgical therapy, 430-432
- Genome, GU cancer alterations in, 465, 476b
bladder cancer, 472-474
bladder RMS, 3582-3583
CNAs, 467-468, 468t
gross chromosomal abnormalities, 465-466, 465b
neuroblastoma, 3559-3560
prostate cancer, 466-471, 468t, 469f
renal cancer, 467, 468t, 471-472, 1321-1325, 1322t-1323t, 1323f
testicular cancer, 467, 474-475, 3591
UTUC, 1375-1376
Wilms tumor, 468t, 3568-3570, 3568t, 3574
- Genomic assessment, in male infertility, 570-571
- Genomic expression profiles, as prostate cancer biomarkers, 2576-2577
- Gentamicin, preoperative prophylaxis with, 2959t
- Geography, renal calculi and, 1171, 1171f
- Geriatric syndromes, 2091-2101
asymptomatic bacteriuria, 2099.e10-2099.e11
bladder outlet obstruction, 2099.e7
delirium, 2095
falls, 2092
fecal incontinence, 2099.e8-2099.e9
frailty, 2091-2092, 2091f
genitourinary malignancies, 2099
genitourinary trauma, 2099.e11
hematuria, 2099.e10-2099.e11
- Geriatric syndromes (Continued)
medication optimization, 2092-2095, 2093t-2094t
nocturia, 2099.e8
pelvic organ prolapse, 2099.e9-2099.e10
polypharmacy, 2092-2095
pressure ulcers, 2092
underactive bladder, 2099.e7
urinary incontinence, 2095-2099
urinary retention, 2099.e7
urinary tract infections, 2099.e10-2099.e11
- Geriatric urology patient
care coordination for, 2100
clinical evaluation of, 2085-2091, 2088f
activities of daily living, 2086
cognition of, 2088-2089, 2089f
comprehensive geriatric assessment, 2090-2091
depression in, 2089
functional assessment, 2085-2086
instrumental activities of daily living, 2086-2087
mobility of, 2087-2088
discharge planning for, 2100
end-of-life care, 2101-2102
surgical risk and medical optimization in, 2089-2090, 2090b
anesthesia in, 2090
prehabilitation, 2090
- Germ cell tumors (GCTs)
in female pediatric patients, 3590
testicular. *See* Testicular germ cell tumors
- Germ cells, of testis, 523, 525f
Sertoli cell interaction with, 524f, 528
in spermatogenesis, 523, 524f-525f, 526-528, 527f, 527t
- Gerota fascia, 968, 968.e1f
- GFR. *See* Glomerular filtration rate
- GH. *See* Gross hematuria
- Giant condyloma acuminatum, of penis, 846.e1f, 846.e4, 846.e4b
- Giggle incontinence, 1711, 3310
- Gil-Vernet procedure, 3170
- Gitelman syndrome, 2862
- Glans dehiscence, 3420-3421, 3420f
- Glans penis, 511-512, 614t, 617t
- Glanular adhesions, of penis, 3371, 3371f
- Gleason grading system, 2594-2596, 2595f, 2596b
- Glenn-Anderson technique, 3158, 3162f
- Glomerular disease, in renal development, 2857-2860, 2861b
diagnosis and management of, 2857-2860
evaluation of, 2857, 2857b
- Glomerular filtration rate (GFR), 1009b
aging and, 2083
in AKI, 1041, 1042t
in CKD, 1053-1055, 1054t, 1055f-1056f, 1060-1061
clinical assessment of, 1008-1009, 1008f
contrast media reaction risk based on, 31
determinants of, 1007
preoperative evaluation of, 1414
regulation of, 1007-1008
in renal development, 2849-2851
for renal transplant candidates, 1070
urinary tract obstruction and
in bilateral ureteral obstruction, 1094-1095, 1095f
estimation of, 1090-1091
renal blood flow and, 1093-1094
renal vascular resistance and, 1094
in unilateral ureteral obstruction, 1094, 1094f
- Glomerular hematuria, 15, 15t, 16f
- Glomerulocystic kidney disease (GCKD), 3038

- Glomerulonephritis, 2859
 AKI caused by, 1043, 1044b
 infection-related, 2859
- Glomerulosclerosis, with urinary tract obstruction, 1097, 1097f
- Glucocorticoids
 in adrenal cortex physiology, 1530-1531, 1531t
 hypercalcemia induced by, 1185
- Glucose, PCT reabsorption of, 1015, 1015f
- Glucose homeostasis. *See also* Diabetes mellitus
 slow-wave sleep and, 1822-1823
- Glucose testing, urinary, 19
- Glue, for laparoscopic and robotic surgery, 207t, 207.e2
- Glutamate, in efferent pathways to bladder, 1657-1658, 1659f
- Glutaraldehyde cross-linked bovine collagen (Contigen)
 for female SUI injection therapy, 2054-2057
 complications with, 2055-2057
 hypermobility and, 2055
 results with, 2055, 2055f, 2056t
 surgery *versus*, 2055
 for male postprostatectomy SUI injection therapy, 2065, 2066t
- Glycine, in efferent pathways to bladder, 1658
- Glycosaminoglycan layer, of bladder urothelium, 1639
- Glycosaminoglycans
 for BPS/IC treatment, 357-358
 in crystal formation, 1178-1179
 in crystal matrix, 1179
- GnRH. *See* Gonadotropin-releasing hormone
- Goldman's Cardiac Risk Index, 101, 101t
- Golombok Rust inventory of sexual satisfaction (GRISS), 753.e2
- GoLYTELY. *See* Polyethylene glycol solution
- Gonadal dysgenesis, 3478-3483
 46,XX "pure," 3480, 3482t
 46,XY complete, 3482-3483, 3482f-3483f, 3482t
 mixed, 3480-3481, 3481f, 3482t
 partial, 3481-3482
- Gonadal stage of differentiation, 3473, 3473f
 disorders of. *See* Disorders of sex development
- Gonadal stromal tumors, in male pediatric patients, 3595, 3595f
- Gonadal vein, dissection of, for RPLND, 820-821
- Gonadoblastomas, 812
- Gonadotropin-releasing hormone (GnRH), 516-519, 517f, 517t, 539-540
- Gonadotropin-releasing hormone (GnRH) antagonists, to facilitate bladder filling and urine storage, 1866.e3
- Gonocytes, 526
- Gouty diathesis
 medical management of, 1229
 uric acid calculi in, 1212, 1212b, 1213f
- Grafts
 for pelvic organ prolapse reconstructive surgery, 1945-1948
 anterior compartment, 1953-1958, 1955f
 biological, 1946-1947
 biological *versus* mesh, 1958
 cadaveric fascia, 1956-1957, 1957f, 1957t
 classification of, 1945, 1946f
 host interaction with, 1945-1946, 1946f
 polypropylene mesh, 1951t-1952t, 1955-1956, 1956f
- Grafts (Continued)
 porcine dermis, 1951t-1952t, 1958, 1958f
 posterior compartment, 1982
 synthetic, 1947-1948, 1948f
 for pubovaginal sling, 1990-1992
 harvest of, 1993-1994, 1993f
 in renal transplantation, 3532
 for urethral and penile reconstruction, 907-911, 908f, 923-929, 924f-926f, 916.e1-2
- Gram-negative uropathogens, in prostatitis microbiology, 305
- Gram-positive bacteria, in prostatitis microbiology, 305-306
- Granuloma inguinale, 378
- Granulomatous disease, hypercalcemia in, 1184
- Granulomatous prostatitis, histopathology, 305
- Granulosa cell tumors, of testis, 812
- Grasping instrumentation, for laparoscopic and robotic surgery, 205-206, 210
- Gray-scale ultrasonography, 68-69
- Greater omentum, in vesicovaginal fistula repair, 2116-2117, 2118f
- Green light laser. *See* Potassium titanyl phosphate laser
- Green tea catechin, in prostate cancer prevention, 2564
- GRISS. *See* Golombok Rust inventory of sexual satisfaction
- Gross hematuria (GH), 183, 188, 191b
 patient history of, 2-3
- Growth
 intrauterine
 lung development and, 2949-2950
 restriction of, 2949
 postnatal considerations for, 2950-2951
- Growth factors, in benign prostatic hyperplasia, 2429-2430, 2429f
- Grynfeltt lumbar triangle. *See* Lumbar notch
- GU tract. *See* Genitourinary tract
- Guaifenesin, in stone formation, 1197
 surgical management of, 1243.e3
- Guanine, 459.e1-459.e3, 459.e2f
- Guanylyl cyclase, in ED, 626
- Guarding reflex, 1900-1901, 1901f
 in bladder filling, 1686
- Gubernaculum
 anomalies of, cryptorchidism and, 3442
 development of, testis descent and, 3432-3433, 3432f-3433f
- Guidewires
 for percutaneous access to upper urinary tract collecting system, 161-162, 162f, 166-167, 167f
 for ureteroscopy, 146-148
- Guillain-Barré syndrome (GBS), lower urinary tract dysfunction with, 1784-1785
- Gunshot wounds
 penile, 2381
 renal, 1148
 nonoperative management of, 1152
 ureteral, 1157, 1157t
 diagnosis of, 1160-1161
- GUITB. *See* Genitourinary tuberculosis
- GVAX Prostate, 456
- Gynecologic laparoscopy, ureteral injuries after, 1158
- Gynecologic surgery patients, and female sexual function, 755
- Gynecomastia
 as complication of TT, 547
 hormonal therapy and, 2795
- H**
- Habit training, 1891
- Hailey-Hailey disease, 399-400, 400f
- Hair removal, for pediatric patients undergoing surgery, 2960
- Hald-Bradley classification, of voiding dysfunction, 1695, 1695b
- HALN. *See* Hand-assisted laparoscopic nephrectomy
- Haloperidol, for delirium, 2095
- Halothane, preoperative considerations for, 111
- Hammock anastomosis, in urinary diversion, 2300
- Hammock hypothesis, of urinary incontinence, 1636-1637, 1689-1690, 1757-1758, 1757f
- Hand port access, for transperitoneal access, 201
- Hand-assist devices, for laparoscopic and robotic surgery, 203-205, 203.e3, 203.e3f
- Hand-assisted adrenal surgery, 1590
- Hand-assisted laparoscopic kidney surgery, surgical approaches and access for, 1450-1452, 1451f-1452f
- Hand-assisted laparoscopic nephrectomy (HALN), 1467-1468, 1467f-1468f
- Harmonic scanning ultrasonography, 69, 70f
- Hasson technique
 for achieving extraperitoneal access and developing extraperitoneal space, 201-202
 for achieving retroperitoneal access and developing retroperitoneal space, 201, 202f, 201.e3
 for achieving transperitoneal access and establishing pneumoperitoneum, 200-201, 201f, 201.e1f
 complications related to, 216
- Hautmann pouch, for orthotopic urinary diversion, 2357-2358, 2357f
- hCG. *See* Human chorionic gonadotropin
- Hct. *See* Hematocrit
- HDCT. *See* High-dose chemotherapy
- HDL. *See* High-density lipoprotein
- HDR brachytherapy. *See* High-dose-rate brachytherapy
- Health care
 access to, 85
 costs of, 85-86
 for MIS, 2964-2965
 patterns, 87-88
 savings in urology, 88
 terms and methods of analysis for, 86-87
 value, 87, 98
 global implications for, 2085
 quality of, 88-89
 challenges in evaluation of, 91
 conceptual framework for, 89-90
 improvement frameworks, 91
 levels of evidence, 91
 metrics applied to urology, 90-91
 outcomes, 90
 process, 90
 structure, 89-90
- Health care policy, evidence-based, 98
- Health care providers, occupational exposure to HIV, 382.e6
- Health policy, in ED, 644, 645b
- Health services research. *See* Outcomes research
- Health-related quality of life (HRQOL), 90-91
 benign prostatic hyperplasia and, 2438
 caveats in data collection for, 97, 97b
 instruments measuring, 91-95
 benign disease-targeted, 92t-95t, 95
 cancer-specific, 92t-94t, 95

- Health-related quality of life (HRQOL)
(Continued)
general, 92-95, 92f-94t
psychometric validation of, 96-97,
96f-97t
selection of, 95
pelvic floor disorders and, 1703t-1704t
- Heart
postnatal considerations for, 2950
in prune-belly syndrome, 3239
- Heart and Estrogen/Progestin Replacement
Study (HERS), 1863
- Heart disease, renal calculi and, 1173
- Heart rate variability and sympathetic skin
response test, 657
- Heavy-particle radiotherapy, for prostate cancer,
262t, 2697-2699, 2697f, 2698t
- Hedgehog signaling pathway, in prostate
development, 2395
- Heineke-Mikulicz procedure, for lower ureteral
injuries, 1164
- Helium, as insufflant choice, 212
- Hemangiomas
bladder, in pediatric patients, 3180, 3589
congenital, 3383
renal, 1312
subcutaneous, 3383-3384
urethral, 879
reconstructive surgery for, 911
- Hematocrit (Hct), 546
- Hematogenous route of infection, 241
- Hematogenous spread, of UTUC, 1368
- Hematoma
adrenal, MRI of, 49
after midurethral sling, 2036-2037,
2026.e1t-2026.e2t
urinoma compared with, 1153
- Hematopoietic stem cell transplantation, for
RCC, 1506-1507, 1507t
- Hematospermia, patient history of, 7
- Hematuria, 183
with benign prostatic hyperplasia, 2455
chemical examination of, 14-16
differential diagnosis and evaluation, 15
glomerular, 15, 15t, 16f
nonglomerular, 15-16, 17f-18f
classification and timing of, 183
CT of, 45-46, 48f, 187
evaluation of, for urothelial cancer, 2197
in geriatric patients, 2099.e11
gross. *See* Gross hematuria
hemorrhagic cystitis causing, 188-189, 188b,
191b
management of, 189-190, 189f
HIV and, 384
malignancy causing, 2-3, 184, 184t, 185b,
192
microscopic. *See* Microhematuria
neonatal, 2891
patient history of, 2-3, 187
from prostatic origin, 190-192, 191f, 192b
in renal development, 2852-2854, 2852b,
2854b
evaluation of, 2852-2853, 2853f
management of, 2854
in renal injuries, 1148
observation of, 1150
after transurethral microwave therapy, 2521
from upper urinary tract, 193-194, 193b-194b
lateralizing essential hematuria and, 194
renal disease causing, 194
vascular conditions causing, 194
in ureteral injuries, 1160
urethral bleeding causing, 192-193,
193b-194b
UTUC causing, 1371
- Hematuria-dysuria syndrome, after
augmentation cystoplasty, 3352
- Hemiacidrin irrigation, for infection stones,
1230
- Hemi-Kock pouch
for orthotopic urinary diversion, 2355, 2356f
procedure for with valved rectum, 2321-2322
- Heminephrectomy, laparoscopic, 1471
- Hemodialysis, 2871
- Hemodynamics. *See also* Renal blood flow
changes in, with urinary tract obstruction,
1093-1095
during laparoscopic and robotic surgery,
approach and patient position effects on,
214
in renal development, 2851, 2859
- Hem-o-Lok clips, 208, 209b, 209f
- Hemolysis, 2930
- Hemorrhage
with holmium laser enucleation of prostate,
2529
with intestinal anastomoses, 2291-2292
during laparoscopic and robotic surgery, 216,
218-219, 218b, 219f, 221-222
in pediatric patients, 2971
laparoscopic kidney surgery causing,
1481-1482
with monopolar transurethral resection of
prostate, 2514-2515
nephrectomy and, 1153-1154
partial nephrectomy causing, 1433
after percutaneous access to upper urinary
tract collecting system
acute, 175-176, 176f-177f
delayed, 176-178, 177f-178f
with percutaneous antegrade endopyelotomy,
1111
with percutaneous nephrolithotomy, 1282
during vena caval thrombectomy, 1444
- Hemorrhagic cystitis, 188-189, 188b, 191b
management of, 189-190, 189f
- Hemostasis, for monopolar transurethral
resection of prostate, 2511-2512
- Hemostasis instrumentation, for laparoscopic
and robotic surgery, 206-207, 210,
206.e1f, 207.e1
for pediatric patients, 2965
- Hemostatic agents, for laparoscopic and robotic
surgery, 207, 207t, 207.e2
- Henoch-Schönlein purpura, 2859, 3393
- Heparin
for percutaneous access to upper urinary tract
collecting system, 158
for renal transplantation, 1083
for vena caval thrombectomy, 1433
VTE prophylaxis with
for laparoscopic and robotic surgery, 223
preoperative, 108-110, 108t-109t
- Heparin sulfate, in crystal formation, 1178-1179
- Heparin-coated stents, 128
- Hepatic dysfunction, during vena caval
thrombectomy, 1444
- Hepatic function, aging and, 2084
- Hepatic resections, RPLND with, 823
- Hepatobiliary evaluation, preoperative, 102
- Hepatorenal ligament, 967-968
- Hepatorenal syndrome (HRS), 1042-1043
- Hereditary hypophosphatemic rickets with
hypercalciuria (HHRH), 1183-1184
- Hereditary leiomyomatosis and RCC (HLRCC)
syndrome, 472, 1322t, 1324
pathology of, 1329t-1330t, 1331-1332, 1331f
systemic therapy for, 1518
- Hereditary nephritis, 2859
- Hereditary nonpolyposis colorectal cancer,
300
- Hereditary papillary RCC (HPRCC) syndrome
genomic alterations in, 468t, 472, 1322t,
1324
pathology of, 1329t-1330t, 1331-1332, 1331f
systemic therapy for, 1517-1518, 1517f
- Hereditary pheochromocytoma, 1545, 1546t,
1547, 1550, 1550f, 1552
- Hereditary prostate cancer (HPC), genomic
alterations in, 468-469, 468t, 469f
- Hereditary spastic paraplegia (HSP), lower
urinary tract dysfunction and, 1785
- Heredity, urothelial cancer and, 2187
- Hernia
of bladder, 3180
definitions for, 3384, 3385f
diagnosis of, 3385
embryology of, 3384
genetics of, 3385
inguinal. *See* Inguinal hernia
after laparoscopic and robotic surgery, 223
in pediatric patients, 2972
as laparoscopic and robotic surgery
contraindication, 196
radiologic imaging of, 3385, 3386f
- Herpes, genital ulcers, 373t, 376-377, 376f, 377t
- Herpesvirus infection, lower urinary tract
dysfunction with, 1783
- HERS. *See* Heart and Estrogen/Progestin
Replacement Study
- Hesitancy, urinary. *See* Urinary hesitancy
- HGPIN. *See* High-grade prostatic intraepithelial
neoplasia
- HHRH. *See* Hereditary hypophosphatemic
rickets with hypercalciuria
- Hidradenitis suppurativa (HS), 405, 406f
- HIFU. *See* High-intensity focused ultrasound
ablation
- High-density lipoprotein (HDL)
TT effects on, 546
urologic disease and, 551
- High-dose chemotherapy (HDCT)
for NSGCTs, 802, 805
RPLND after, 831, 831t
- High-dose-rate (HDR) brachytherapy, for
prostate cancer, 2700-2701
- High-frequency vibratory device. *See* Ultrasound
instrumentation
- High-grade prostatic intraepithelial neoplasia
(HGPIN), 2593-2594, 2594f
- High-intensity focused ultrasound ablation
(HIFU), 2626.e1
biochemical recurrence after, 2783-2784
for locally advanced prostate cancer, 2765
for prostate cancer, 2727-2732, 2731f-2735f
localized, 2626, 2626.e1
outcomes with, 2737
for renal tumor ablation, 1495-1497
salvage. *See* Salvage high-intensity focused
ultrasound ablation
whole-gland salvage, for prostate cancer
recurrence, 2748
- High-pressure bladder, spinal cord injury with,
host defense mechanisms in UTIs and,
249
- Hinge region, of urothelium of bladder,
1632-1633, 1633f
- Histamine
in BPS/IC etiology, 345.e4-345.e6, 345.e4f,
345.e6b
urethral function effects of, 1003-1004
- Histamine antagonists, urethral function effects
of, 1003-1004
- Histamine H2 receptor antagonists, and ED,
638
- Histocompatibility, for renal transplantation,
1076

- Histology, adrenal, 1525f, 1529, 1530t, 1528.e1f
- Histone post-translational modification, in prostate cancer, 2555-2556
- History. *See* Patient history
- HIV. *See* Human immunodeficiency virus
- hK2. *See* Human kallikrein 2
- hK3. *See* Prostate-specific antigen
- hK11. *See* Human kallikrein 11
- H-line measurement, 1609, 1609f
- HLRCC syndrome. *See* Hereditary leiomyomatosis and RCC syndrome
- HMG-CoA reductase inhibitors. *See* 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
- HOCM. *See* Hyperosmolar contrast media
- HoLEP. *See* Holmium laser enucleation of prostate
- Holmium laser enucleation of prostate (HoLEP), 2527-2530
- in anticoagulated patient, 2529
- complications with, 2529-2530
- intraoperative, 2529
- perioperative, 2529
- postoperative, 2529-2530
- conclusion for, 2530
- open prostatectomy *versus*, 2529
- outcomes with, 2528-2529
- comparative studies for, 2528-2529
- single-cohort studies for, 2528
- overview and concept for, 2527
- technique for, 2527-2528
- intraoperative, 2527-2528
- postoperative, 2528
- preoperative, 2527
- thulium laser *versus*, 2533-2534
- transurethral resection of prostate *versus*, 2528-2529
- Holmium:YAG (Ho:YAG) laser, 230
- Holmium:YAG (Ho:YAG) laser lithotripsy, 231t, 234b, 233.e3, 234.e2, 234.e3, 234.e3f
- basic physics of, 233-234
- for bladder stones, 234.e2-234.e3
- for percutaneous nephrolithotomy, 234.e2
- popcoming technique for, 234
- ureteroscopy with, 234.e1
- Homogeneous nucleation, 1175
- Hormonal evaluation, and ED, 657-658
- Hormonal therapy. *See also* Androgen deprivation therapy
- for CP/CPPS treatment, 323-324
- for ED, 659-660
- for metastatic RCC, 1516
- for priapism, 682-683
- for prostate cancer
- androgen axis blockade mechanisms, 2789-2793, 2789b
- androgen axis molecular biology and, 2787-2788, 2787f-2788f
- androgen blockade response in, 2793
- androgen synthesis inhibition, 2791-2793
- anemia, 2795
- antiandrogens for, 2789-2791
- body habitus changes with, 2795
- cardiovascular morbidity and mortality, 2795
- cognitive function and, 2794-2795
- combination therapy, 2795-2798
- combined androgen blockade, 2796-2798, 2798f
- complications of, 2793-2795
- diabetes and, 2795
- economic considerations for, 2802-2803
- gynecomastia, 2795
- historical overview of, 2786-2787
- Hormonal therapy (Continued)
- hot flashes, 2794
- metabolic syndrome and, 2795
- osteoporosis and, 2793-2794
- with radiation therapy, 2796, 2796f, 2797t
- with radical prostatectomy, 2795-2796, 2796t
- sexual dysfunction and, 2794
- timing of, 2798-2802
- urinary incontinence and, 1748
- Hormones
- and FSAD, 760.e1
- of HPG axis
- anterior pituitary, 516-517, 517f
- hypothalamus, 516, 517f, 517t
- testis, 517-518, 517f, 3431-3432, 3431f
- laparoscopic and robotic surgery effects on, 214
- renal
- ADH, 1012, 1013f, 1013t
- bone mineral regulation by, 1011-1012, 1011f
- erythropoiesis regulation by, 1011
- renal vascular tone control by, 1009-1011, 1009b, 1010f, 1011b
- Horseshoe kidneys, 969, 2993-2996, 2994f-2995f, 969.e2f
- percutaneous access to, 168-170, 170f
- renal calculi and, 1198
- surgical management of, 1244-1246, 1245f, 1279-1280
- Host defense mechanisms, alterations in, in UTI
- pathogenesis, 248-249
- diabetes mellitus, 249
- HIV, 249
- obstruction, 248
- pregnancy, 249, 249.e1
- RPN, 249, 249b
- spinal cord injury with high-pressure bladders, 249
- underlying disease, 249
- vesicoureteral reflux, 248
- Hot flashes, hormonal therapy and, 2794
- Hounsfield units (HU), 41
- Ho:YAG laser. *See* Holmium:YAG laser
- HPC. *See* Hereditary prostate cancer
- HPG axis. *See* Hypothalamic-pituitary-gonadal axis
- HPGCC syndrome. *See* Hereditary papillary RCC syndrome
- HPV. *See* Human papillomavirus
- HRQOL. *See* Health-related quality of life
- HRS. *See* Hepatorenal syndrome
- HS. *See* Hidradenitis suppurativa
- HSDD. *See* Hypoactive sexual desire disorder
- HSP. *See* Hereditary spastic paraplegia
- 5-HT. *See* Serotonin
- HTN. *See* Hypertension
- HU. *See* Hounsfield units
- HUCN. *See* Hyperuricosuric calcium nephrolithiasis
- Human bites, of penis, 2381
- Human chorionic gonadotropin (hCG), 540
- in TGCTs, 790-791, 794
- Human herpesvirus 8, penis tumors related to, 846.e3-846.e4
- Human immunodeficiency virus (HIV). *See also* Acquired immunodeficiency syndrome
- AD in, 539-540, 543
- AKI in, 1046
- circumcision protection against, 915
- genitourinary tuberculosis management and, 432
- host defense mechanisms in UTIs and, 249
- Human immunodeficiency virus (HIV) (Continued)
- occupational exposure to, 382.e6
- pathogenesis and natural history of, 382.e2-382.e4
- penis tumors related to, 846.e3-846.e4
- renal transplantation for patients with, 1071
- as STD, 382
- diagnosis, 382
- erectile dysfunction and, 384
- hematuria and, 384
- interactions with other STDs, 375, 382
- Kaposi sarcoma, 385
- management of sex partners and, 382.e6
- neoplasms and, 385-386
- non-AIDS-defining urologic malignancies, 385-386
- preexposure prophylaxis for, 382.e6
- prostatitis and, 383
- renal function and, 383-384
- renal infections, 383
- stones and, 384-385
- structure, 382.e1, 382.e1f-382.e2f
- testis, epididymis, seminal vesicles and, 383
- urologic manifestations of, 382, 382f
- UTI and, 383
- viral synapse and cell-to-cell transmission, 382.e2
- virology, 382.e1
- virus entry and replication, 382.e1, 382.e3f
- virus heterogeneity and mechanisms to escape therapy, 382.e2
- virus packaging and assembly, 382.e1-382.e2
- voiding dysfunction and, 384
- structure, 382.e1, 382.e1f-382.e2f
- treatment, 382.e5-382.e6, 382.e5f
- viral synapse and cell-to-cell transmission, 382.e2
- virology, 382.e1
- virus entry and replication, 382.e1, 382.e3f
- virus heterogeneity and mechanisms to escape therapy, 382.e2
- virus packaging and assembly, 382.e1-382.e2
- Human kallikrein 2 (hK2)
- as prostate cancer biomarkers, 2572
- in prostate cancer diagnosis, 2605
- in prostatic secretions, 2417t, 2418
- Human kallikrein 3 (hK3). *See* Prostate-specific antigen
- Human kallikrein 11 (hK11), in prostatic secretions, 2417t, 2419
- Human kallikrein 14 (KLK14), in prostatic secretions, 2417t, 2419
- Human kallikrein L1, in prostatic secretions, 2417t, 2418-2419
- Human papillomavirus (HPV)
- as genital ulcers, 378-380, 379f
- penis tumors related to carcinoma, 847-849
- preinvasive lesions, 846.e2-846.e3
- vaccine, 379-380
- Hunner lesion, surgery for, 360
- Hydraulic valves, for continent urinary diversions, 3363
- Hydrocalycosis, 3001-3002, 3001f
- Hydrocele, 520-521
- abdominoscrotal, 3387-3388
- communicating. *See* Communicating hydrocele
- definitions for, 3384, 3385f
- diagnosis of, 3385
- embryology of, 3384

- Hydrocele** (*Continued*)
 as filariasis clinical manifestation, 443-444, 444f
 genetics of, 3385
 noncommunicating. *See* Noncommunicating hydrocele
 radiologic imaging of, 3385, 3386f
 surgical repair of, 3386
- Hydrocelectomy**, 954
 complications of, 955-956, 955t
 inguinal surgical approach for, 954
 sclerotherapy and, 955-956
 scrotal surgical approaches for, 954-955, 955f
- Hydrocephalus**, normal-pressure
 lower urinary tract dysfunction with, 1766
 transient urinary incontinence and, 2096.e1
- Hydrocortisone**
 premedication with, for preventing contrast media reactions, 29
 preoperative, 103
- Hydrodistention**, for BPS/IC treatment, 359-360
- Hydrogen**, in collecting tubule, 1019
- Hydrogen ions**, transport of, urinary tract obstruction and, 1096
- Hydrogen sulfide**, in ED, 626
- Hydronephrosis**
 alternative measurements of, 2877
 categorizing, 2876-2877, 2877t
 Color Doppler ultrasonography for, 1091
 infected, 283
 neonatal diagnosis of, 1105
 pediatric imaging of
 diuretic scintigraphy, 2921-2922, 2922f-2925f
 ultrasonography, 2911, 2913, 2915f-2916f
 after pediatric renal transplantation, 3535-3536
 prenatal, 2875-2877, 2876f
 prenatal imaging of, 2909-2910, 2910f
 prevalence of, 1089
 retroperitoneal fibrosis with, 1144, 1144f
 with trauma, 3549-3550
 urinary tract obstruction and, 1091
 UTUC with, 1374
- Hydrothorax**, after percutaneous access to upper urinary tract collecting system, 179-180, 180f
- Hydroureter**
 pediatric imaging of
 diuretic scintigraphy, 2921-2922, 2922f-2925f
 ultrasonography, 2911, 2913, 2915f-2916f
 urinary tract obstruction and, 1089
- Hydroureteronephrosis** of pregnancy, 1002-1003
- 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors**, for CKD, 1062, 1064
- 25-Hydroxycholecalciferol (Calcidiol)**, 1011-1012
- 17 α -Hydroxylase deficiency**, 3490
- 3 β -Hydroxysteroid dehydrogenase deficiency**, 3489-3490
- 17 β -Hydroxysteroid oxidoreductase deficiency**, 3490-3491
- Hymen**, imperforate, 3459, 3459f
- Hymenal skin tags**, 3459, 3459f
- Hyperacute rejection**, of renal transplantation, 1083-1084
- Hyperbaric oxygen therapy**, for hemorrhagic cystitis, 190
- Hypercalcemia**
 glucocorticoid-induced, 1185
 in granulomatous disease, 1184
 malignancy-associated, 1185
 in RCC, 1334-1335
 in sarcoidosis, 1184
- Hypercalciuria**
 absorptive, 1183-1184, 1209, 1210t
 agents for, 1224, 1225b
 orthophosphate for, 1225
 sodium cellulose phosphate for, 1224
 thiazides for, 1223-1224
 type II, 1224-1225
 calcium stone formation associated with, 1182-1185, 1209-1212, 1210b
 differential diagnosis of, 1210t
 fast and calcium load test for, 1205
 renal, 1184, 1209, 1210t
 agents for, 1225, 1225b, 1226t
 resorptive, 1184-1185, 1209-1210, 1210t
- Hypercortisolism**. *See* Cushing syndrome
- Hyperfiltration injury**, in partial nephrectomy, 1428
- Hyperkalemia**, renal pathophysiology involved in, 1023, 1024b
- Hyperlipidemia**, and ED, 632-633
- Hypermobility**
 collagen and, 2055
 in stress urinary incontinence, 1919-1920, 1990
- Hypernatremia**, renal pathophysiology involved in, 1020f, 1021-1023, 1022f
- Hyperosmolality**, ADH control by, 1012
- Hyperosmolar contrast media (HOCM)**, 28
- Hyperoxaluria**
 calcium stone formation associated with, 1185-1187, 1210-1211, 1211b
 causes of, 1185
 dietary, 1187, 1211, 1211b
 enteric, 1186-1187, 1186f, 1210
 medical management of, 1227, 1227b
 idiopathic, 1187, 1210
 primary, 1185-1186, 1185f, 1210-1211
- Hyperparathyroidism**, primary
 medical management of, 1225, 1225b
 with resorptive hypercalciuria, 1184, 1209-1210
- Hyperprolactinemia** treatments, 660
- Hyperreflexia**. *See* Autonomic hyperreflexia
- Hypertension (HTN)**
 benign prostatic hyperplasia and, 2442
 with α -adrenergic blockers, 2480-2481
 and ED, 633
 neonatal, 2891
 in RCC, 1335
 renal calculi and, 1173
 in renal development, 2865-2866, 2866t, 2867b
 after renal injury, 1157
 renal protective strategies targeting, 1062, 1063t
 renovascular. *See* Renovascular hypertension
 with renovascular injuries, 1155
 transitional urology and, 3525
 with urinary tract obstruction, 1100
 urologic disease and, 551-553
 vesicoureteral reflux and, 3149
- Hyperthyroidism**, lower urinary tract dysfunction and, 1790
- Hypertrophied clitoris**, 3455-3456, 3455f
- Hyperuricosuria**
 in calcium stone formation, 1187
 in uric acid stone formation, 1192
- Hyperuricosuric calcium nephrolithiasis (HUCN)**
 in calcium oxalate calculi formation, 1210
 gouty diathesis differentiation from, 1212
 medical management of, 1225-1227, 1227b
- Hypoactive sexual desire disorder (HSDD)**
 and androgens, 759
 and cessation/modulation of medical therapy, 759
- Hypoactive sexual desire disorder (HSDD)** (*Continued*)
 and estrogens, 759
 etiology of, 757-759, 758b, 758t
 and psychosexual therapy, 758
 treatment of, 758
- Hypocitraturia**
 calcium stone formation associated with, 1188, 1211-1212, 1211f, 1212b
 in chronic diarrheal states, 1212
 medical management of, 1228
 in distal renal tubular acidosis, 1211-1212, 1211f, 1212b
 idiopathic, 1212
 medical management of, 1227-1228, 1228b
 thiazide-induced, 1212
 medical management of, 1228
- Hypofractionation**
 for localized prostate cancer, 2702-2703
 outcomes with, 2703-2705, 2704t-2705t
 radiobiology of, 2703
- Hypogastric artery**, 1601, 1604f, 1616, 1620f
- Hypogastric plexus**, 1603
- Hypoglycemic agents**, preoperative, 103
- Hypogonadism**, 558
 AD resulting from, 539-541, 540t
 biochemical definition of, 541, 541t
 and ED, 631-632
 and PD, 725
- Hypokalemia**
 in AKI, 1052
 renal pathophysiology involved in, 1023
- Hypomagnesuria**, in calcium stone formation, 1190, 1212
 medical management of, 1228-1229
- Hypomethylation**, in bladder cancer, 464
- Hyponatremia**, 1012
 with desmopressin, 1865-1866
 renal pathophysiology involved in, 1020-1021, 1020f-1022f, 1021b
- Hypophosphatemic rickets**, 2862
- Hypoplastic glomerulocystic disease**, 3023
- Hypospadias**, 577
 adult outcomes after, 3426-3428
 cosmesis, 3427-3428
 sexual function, 3427-3428
 urinary function, 3426-3427
 assessment and management for
 intraoperative, 3401-3416
 preoperative, 3399-3401
 complications with, 3418-3422
 diagnosis of, 3399, 3400f
 disorders of sex development, 3400
 imaging of, 3401
 improving outcomes for, 3428-3429
 inheritance of, 3399
 isolated *versus* syndromic, 3399
 nerve blocks for, 3402
 outcomes assessment for, cosmetic results, 3418
 postoperative management for, 3416-3417
 bandages, 3416-3417, 3417f
 medications, 3417
 urinary diversion, 3416
 preoperative androgen stimulation for, 3401
 prevalence of, 3399
 reoperations for, 3405f, 3422-3426
 dorsal inlay graft, 3423-3424, 3424f
 tubularized incised plate urethroplasty, 3407f, 3423, 3423f
 two-stage oral mucosa graft, 3424-3426, 3425f-3428f
 repair of, failure of, reconstructive surgery for, 915-916
 surgical repair for
 Byars flaps, 3414
 considerations for, 3401

- Hypospadias** (*Continued*)
 decision making for, 3408
 distal, 3404-3408
 flaps *versus* grafts, 3414, 3414f
 general aspects of, 3401-3402
 prepuceoplasty, 3414-3416, 3415f
 preputial flaps, 3413-3414, 3413f
 proximal, 3408-3416
 scrotoplasty, 3416
 two-stage graft, 3410-3413, 3412f
 thin urethra, 3404, 3405f
 urethral plate assessment for, 3402, 3402f
 urethroplasty for
 algorithm for, 3404, 3405f
 complications with, 3401
 distal tubularized incised plate, 3404-3408, 3406f-3408f
 proximal tubularized incised plate, 3408-3410, 3409f-3411f
 ventral curvature, 3402-3404
 artificial erection for, 3403
 correction of, 3403
 prevalence of, 3402-3403
 significance of, 3403
 surgical technique for, 3403-3404, 3403f-3404f
- Hypospermatogenesis**, 573.e3
- Hypothalamic-pituitary-adrenal axis** physiology, normal, 1532-1534, 1534f
- Hypothalamic-pituitary-gonadal (HPG) axis**, 519b
 AD and, 539-541
 aging of, 519
 basic endocrine concepts for, 516, 517f
 components of
 anterior pituitary, 516-517, 517f
 hypothalamus, 516, 517f, 517t
 testis, 517-518, 517f
 development of, 518-519, 518f
 and ED, 632
- Hypothalamus**
 anatomy of, 516
 in HPG axis, 516, 517f, 517t
 micturition control by, 1666
- Hypothermia**
 anesthesia-related, during laparoscopic and robotic surgery, 220.e1
 for laparoscopic partial nephrectomy, 1475
 for partial nephrectomy, 1429
 preoperative, 113
- Hypothermic arrest**, for vena caval thrombectomy, 1442-1443
- Hypoxis rooperi** (South African star grass), for benign prostatic hyperplasia, 2500
- Hysterectomy**
 laparoscopic, ureteral injuries after, 1158
 lower urinary tract dysfunction after, 1783
 transvaginal, for uterine prolapse, 1976
- Hysteresis**, ureteral, 988, 989f, 996, 996f
- Hysteropexy**
 abdominal, 1978
 vaginal, 1978
- I**
- IA reactions**. *See* Idiosyncratic anaphylactoid reactions
- IADLs**. *See* Instrumental activities of daily living
- Iatrogenic factors**
 and UTIs, 2932
 in UTUC etiology, 1366
- Iatrogenic priapism**
 ADHD and, 673
 intracavernous injections for, 672-673
- Iatrogenic trauma**, catheterization causing, 124
- IBS**. *See* Irritable bowel syndrome
- Ibuprofen**, for pediatric patients, 2957
- Ice-water test**, 1656, 1675
- ICI**. *See* International Consultation on Incontinence
- ICIQ-BD**. *See* International Consultation on Incontinence Questionnaire Bladder Diary
- ICIQ-MLUTS**. *See* International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms
- ICIQ-UI-SF**. *See* International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form
- ICS**. *See* International Continence Society
- IDC-P**. *See* Intraductal carcinoma of prostate
- IDCs**. *See* Involuntary detrusor contractions
- Idiopathic detrusor overactivity (IDO)**, 1673-1675, 1674f
 resiniferatoxin in, 1863.e1
- Idiopathic hypercalciuria**, 1183
- Idiopathic hyperoxaluria**, 1187, 1210
- Idiopathic hypocitraturia**, 1212
- Idiopathic scrotal edema**, 3393
- Idiosyncratic anaphylactoid (IA) reactions**, to intravascular iodinated contrast media, 28
- IDO**. *See* Idiopathic detrusor overactivity
- IELT**. *See* Intravaginal ejaculation latency time
- IFIS**. *See* Intraoperative floppy iris syndrome
- IFLND**. *See* Inguinofemoral lymph node dissection
- IFNs**. *See* Interferons
- Ifosfamide**
 hemorrhagic cystitis caused by, 188-189
 for NSGCI, 802, 805
- IgA nephropathy**, glomerular hematuria caused by, 15
- IGCCCG**. *See* International Germ Cell Cancer Collaborative Group
- IGFs**. *See* Insulin-like growth factors
- IGRAs**. *See* Interferon-gamma release assays
- IIIE**. *See* International Index of Erectile Function scale
- IILND**. *See* Ilioinguinal lymphadenectomy
- IL-2**. *See* Interleukin-2
- IL-18**. *See* Interleukin-18
- Ileal conduit**, 2304-2305, 2304f-2306f, 2306t
 in minimally invasive urinary diversion, 2370-2373, 2370t
- Ileal neobladder**, for orthoptic urinary diversion, 2357-2358, 2357f
- Ileal reservoirs**
 continent, 2325, 2326f
 for orthoptic urinary diversion, 2355
- Ileal ureteral replacement**, for UTUC, 1386-1387, 1387f
- Ileal ureteral substitution**
 for ureteral injury, upper, 1163
 for ureteral stricture disease
 laparoscopic, 1140-1141
 open, 1139-1140, 1140f
- Ileal vesicostomy**, 2307
- Ileocecal valve**
 for continent urinary diversions, 3363
 in ileocecostoplasty, 3346
- Ileocecostoplasty**, 3346, 3346f-3347f
- Ileocolonic pouch**, for orthoptic urinary diversion, 2358-2360, 2361f
- Ileocystoplasty**, 3344-3345, 3345f
- Ileum**. *See* Small bowel
- Ileus**, after RPLND, 833-834
- Iliac aneurysm**, as laparoscopic and robotic surgery contraindication, 196
- Iliac arteries**, 1615-1616, 1618t, 1620f
- Iliac crests**, 1598f
- Iliac lymph nodes**, 1601
- Iliac spines**, 1598f, 1612f
- Iliac veins**, 1617-1618, 1620f
- Iliacus**, 767f-769f, 769, 769t
- Iliococcygeus muscle**, 1601, 1603f
- Iliococcygeus suspension**, for apical pelvic organ prolapse repair, 1968-1971, 1970f
- Iliohypogastric nerve**, 1613f, 1618-1619, 1622t
- Ilioinguinal lymphadenectomy (IILND)**, for penile cancer, 859, 860f, 864-868
- Ilioinguinal nerve**, 1613f, 1618-1619, 1622t
- Illness**, patient history of
 present, 1-7, 4t-5t
 previous, 7
- IILND**. *See* Ilioinguinal lymphadenectomy
- IM**. *See* Intramuscular
- IMA**. *See* Inferior mesenteric artery
- Image storage**, ultrasonography, 72-73, 72f
- Imaging**. *See also specific imaging modalities*
 in adrenal mass evaluation, 1567-1570, 1568f-1569f, 1569b
 in pheochromocytoma diagnostic tests, 1547-1549, 1548f
 of urinary tract, 26. *See also specific imaging modalities*
 contrast media in. *See* Contrast media
 pediatric patient considerations for, 2909, 2923b
 radiation management in, 26-27, 27b, 27t-28t
- Imaging techniques**, for UTIs, 252-253, 253b
 CT and MRI, 253
 indications, 252-253, 253b
 radionuclide studies, 253
 ultrasonography, 253
 voiding cystourethrogram, 253
- Imidafenacin**, to facilitate bladder filling and urine storage, 1839t, 1843-1844
- Imipramine (Tofranil)**
 to facilitate bladder filling and urine storage, 1839t, 1857
 for nocturnal polyuria, 1827, 1830t
 for stress urinary incontinence in women, 1868
 ureteral response to, 991
- Imiquimod cream**, for condylomata acuminata, 846.e2-846.e3
- Immune checkpoint blockade**, 456-457
 in bladder cancer, 457
 in kidney cancer, 457
 in prostate cancer, 457-458
- Immune editing hypothesis**, 450-451, 450f
- Immune modulators**, for CP/CPPS treatment, 323
- Immune response**, pathogen recognition, 247-248, 248.e1
- Immune status**, and UTIs, 2932-2933
- Immunization**. *See* Vaccination
- Immunoglobulin A nephropathy**, 2859
- Immunoglobulins**, in prostatic secretions, 2417t, 2422
- Immunologic alterations**, in prostatitis and CPPS etiology, 308
- Immunologic effects**, of laparoscopic and robotic surgery, 214-215
- Immunologic function**, aging and, 2084
- Immunology**
 immune response in GU cancers, 447, 451b
 adaptive immune system, 449-450, 449f
 immune editing hypothesis, 450-451, 450f

- Immunology (*Continued*)
inflammation effects in, 451-453, 452f, 453b
innate immune system, 447-448, 448f-449f, 448t-449t
postnatal considerations for, 2950-2951
of RCC, 1325-1326, 1325t
Immunomodulator drugs, for BPS/IC oral therapy, 353t, 354-355
Immunosuppression protocols, for renal transplantation, 1084-1086, 1084f, 1085b, 1085t
Immunosuppressive agents, for retroperitoneal fibrosis, 1145
Immunotherapy
for GU cancers, 447, 458b
BCG in bladder cancer, 447, 448f, 453-454, 453f
cancer vaccines, 454-456, 454f, 456f
immune checkpoint blockade, 456-458
for localized prostate cancer, radiation therapy with, 2709
for non-muscle-invasive bladder cancer, 2212-2215
Bacille Calmette-Guérin, 2212-2214
interferon, 2214
investigational, 2214-2215
Impedance
sacral nerve stimulation and, 1911-1912
in ultrasonography, 66-67, 66f, 66t
Imperforate anus, neonatal, 2890
Imperforate hymen, 3459, 3459f
Implementation science, 98
Impotence, patient history of, 6
IMRT. *See* Intensity-modulated radiation therapy
IMT. *See* Inflammatory myofibroblastic tumor
IMV. *See* Inferior mesenteric vein
In vitro fertilization, 556, 573.e5
Incidentalomas, adrenal
adrenal surgery for, 1581b
evaluation of, 1566, 1567t
Incision instrumentation, for laparoscopic and robotic surgery, 206-207, 210, 206.e1f, 207.e1
Incisional hernia, after laparoscopic and robotic surgery, 223
Incomplete emptying, patient history of, 4t-5t
Inconspicuous penis, 3369t, 3374-3376
Incontinence. *See* Urinary incontinence
Incontinent urinary diversion, for neuromuscular dysfunction of lower urinary tract, 3282.e2
Increased adrenal function disorders
Cushing syndrome. *See* Cushing syndrome
pheochromocytoma. *See* Pheochromocytoma
primary aldosteronism. *See* Primary aldosteronism
Increased through-transmission, in ultrasonography, 68, 68f
Indapamide, for absorptive hypercalciuria, 1224
Inderal. *See* Propranolol
Indiana pouch, 2333-2335, 2334f-2335f
Indigo carmine, toxicity of, 1159
Indinavir sulfate (Crixivan), in stone formation, 1196-1197
medical management of, 1231
surgical management of, 1243.e3
Indium-111 capromab pendetide scanning, for biochemical recurrence after radical prostatectomy, 2772-2773
Indomethacin
to facilitate bladder filling and urine storage, 1839t, 1858
urethral function effects of, 1004-1005
Induced pluripotent stem cells, for tissue engineering, 484
Indwelling catheters, for urinary incontinence, in geriatric patients, 2099.e5
Indwelling orthopedic hardware, antimicrobial prophylaxis for uncomplicated urologic procedures and, 264-265
Infants, urinary specimen collection in, 12-13
Infected hydronephrosis and pyonephrosis, 283, 283f
Infection
with artificial urinary sphincter, 2181
in BPS/IC etiology, 345.e1-345.e2
from cutaneous diseases of external genitalia
balanitis, 402
balanoposthitis, 402, 403f
candidal intertrigo, 407, 408f
cellulitis, 402, 403f
corynebacterial infection (trichomycosis axillaris and erythrasma), 405, 407f
dermatophyte infection, 407-408, 409f
ecthyma gangrenosum, 405-406, 408f
erysipelas, 402
folliculitis, 404-405, 404f
Fournier gangrene, 402-404, 404f
furunculosis, 405, 405f
genital bite wounds, 406-407, 408f
hidradenitis suppurativa, 405, 406f
STDs, 402, 403f
host factors increasing risk of, 260b
with intestinal anastomoses, 2290
after laparoscopic and robotic surgery, in pediatric patients, 2971
after midurethral sling, 2031-2033
with percutaneous antegrade endopyelotomy, 1111
perioperative care for pediatric patients with, 2954, 2954f
postnatal considerations for, 2950-2951
after prostate biopsy, 2588
prostate cancer and, 2547-2548
renal transplantation and, 1086, 1086t, 3530, 3535
with sacral nerve stimulation, 1911
scrotal barriers to spread of, 946, 947f
of seminal vesicles, 958
surgical wound. *See* Surgical site infections
ureteral anomalies and, 3079-3080
ureteral function effects of, 1000-1001
with urinary intestinal diversion, 2313
urinary tract. *See* Urinary tract infection
urothelial cancer and, 2187-2188
UTUC risk and, 1366
Infection (struvite) stones, 1194-1195, 1213, 1213b, 1214t, 1215f
bacteriology of, 1194, 1195t
epidemiology of, 1195
medical management of, 1230-1231, 1231b
pathogenesis of, 1194, 1194f
urea-splitting bacteria causing, 271
urine culture for, 1202
Infections and inflammation, in male infertility, 560
Infectious granulomatous nephritis
malacoplakia, 289-290, 289f
renal echinococcosis, 290-291, 291f
XGP, 286-289, 287f-288f
Infective disorders, and delayed ejaculation, 704-705
Inferior mesenteric artery (IMA), in radical nephrectomy, 1427
Inferior mesenteric vein (IMV), in radical nephrectomy, 1427
Inferior vena cava (IVC)
filtration and permanent interruption of, 1444
patching, replacing, and interrupting of, 1444
Inferior vena cava (IVC) (*Continued*)
in radical nephrectomy, 1424-1426, 1425f, 1424.e1f
RCC involvement of, 1355-1358, 1356b, 1356f-1357f, 1470
surgery for. *See* Vena caval thrombectomy
reconstruction of, RPLND with, 822-823
in retroperitoneum, 775f, 776, 776.e1f, 777.e1f
Inferior vesical artery, 507, 507f
Infertility
male. *See* Male infertility
in TGCT patients, 795
Infestation, as cutaneous disease of external genitalia, 408-410, 409f-410f
Infibulation, 3467-3468, 3468f
Inflammation
in BPS/IC etiology, 345.e2-345.e4, 345.e4b, 345.e10b
in cancer immune response, 451, 453b
pain caused by, 1-2
pathways of, in benign prostatic hyperplasia, 2431-2432, 2431f
prostate cancer and, 2547-2548, 2548f
testosterone effects on, 549
triggers for, 2548
urothelial cancer and, 2187-2188
UTUC risk and, 1366
Inflammatory and pain conditions of male genitourinary tract
epididymitis, 331-332, 331b-332b
orchitis, 329-331, 330b, 330t, 332b
prostatitis. *See* Prostatitis
Inflammatory cell infiltration, in tubulointerstitial fibrosis, 1098
Inflammatory myofibroblastic tumor (IMT), in pediatric patients, 3589
Infundibulopelvic stenosis, 3003, 3004f
Inguinal canal, anatomy of, 1613-1614, 1615f
Inguinal hernia
epidemiology and pathogenesis of, 3384
female, 3468
surgical repair of, 3385-3386
complications with, 3386
laparoscopic, 3387
scrotal approach to, 3387
standard, 3386
Inguinal lymph nodes, 513
anatomy of, 890, 891f
penile cancer metastasis to
ILND for. *See* Inguinal lymphadenectomy
imaging studies for, 852
radiation therapy for, 870-871
risk-based management for, 865-868, 866f-867f
Inguinal lymphadenectomy (ILND), 856, 865b, 890, 906b
anatomic considerations for
inguinal anatomy, 890, 891f
penile lymphatics, 890
urethral lymphatics, 890
in clinically negative groins, 891
DSNB, 864, 893-894, 894f-895f, 895b
laparoscopic and robotic ILND, 864, 896-902, 897f-903f
modified complete ILND, 864, 895-896, 895f-896f
sentinel lymph node biopsy, 863-864, 891-892, 892f
superficial inguinal node dissection, 864, 894-895
in groins with palpable adenopathy or positive nodes, radical IFLND, 902-906, 903f-905f
immediate compared with delayed, 859

- Inguinal lymphadenectomy (ILND) (*Continued*)
 indications for modified procedures, 863-864
 indications for traditional procedures, 864-865
 indications for watchful waiting, 863, 863t
 laparoscopic and robotic. *See* Laparoscopic ILND; Robotic ILND
 modified complete. *See* Modified complete ILND
 molecular markers in selection for, 862-863
 morbidity compared with benefits of, 859-861, 860f, 860t
 palpable adenopathy in selection for, 857t-858t, 858-859
 for penile cancer, 856, 865b
 immediate compared with delayed, 859
 indications for modified procedures, 863-864
 indications for traditional procedures, 864-865
 indications for watchful waiting, 863, 863t
 molecular markers in selection for, 862-863
 morbidity compared with benefits of, 859-861, 860f, 860t
 palpable adenopathy in selection for, 857t-858t, 858-859
 prognostic significance of metastatic disease, 856-858, 857t-859t
 tumor histology in selection for, 861-862, 861t-862t
 prognostic significance of metastatic disease, 856-858, 857t-859t
 tumor histology in selection for, 861-862, 861t-862t
- Inguinal orchiopexy, 3444-3446, 3445f
- Inguinofemoral lymph node dissection (IFLND), 891
- radical. *See* Radical IFLND
- Inhalational general anesthesia, preoperative considerations for, 111
- Inhibin, 516-518, 517f
- Inhibitors, of crystal formation, 1178-1179
- Injectable preparations, testosterone, 544t, 545
- Injection therapy
 for bladder neck reconstruction, 3337-3338
 for incontinence after urinary diversion, 2068
 for prostate, 2534.e3-2534.e4
- Injection therapy for female stress urinary incontinence, 2049-2051
 additional testing for, 2050-2051
 agents for, 2050b
 adjustable continence therapy, 2060-2061, 2061f
 autologous chondrocytes, 2060
 autologous fat, 2062-2063, 2063t
 calcium hydroxylapatite, 2060
 carbon-coated zirconium beads, 2057, 2057t
 cell-based therapy, 2061-2062
 dextranomer hyaluronic acid copolymer, 2063
 glutaraldehyde cross-linked bovine collagen, 2054-2057, 2055f, 2056t
 polyacrylamide hydrogel, 2059-2060, 2059t
 porcine dermal collagen, 2060
 silicone microimplants, 2058-2059, 2058t
- cystoscopy for, 2051
 in geriatric patients, 2099.e5
 history of, 2049
 indications and contraindications for, 2049-2050
 outcome assessment for, 2054, 2054t
 outcomes of, 2063b
 pathophysiology of, 2049
- Injection therapy for male postprostatectomy SUI, 2067b
 agents for, 2065-2067
 adjustable balloons, 2065-2066, 2067f, 2068t
 glutaraldehyde cross-linked bovine collagen, 2065, 2066t
 silicone microimplants, 2065-2066
 pathophysiology for, 2064-2067
 periprocedure care for, 2065
 reinjections for, 2065
 techniques for, 2064-2065
 antegrade, 2064-2065, 2065f
 retrograde, 2064, 2065f
 workup for, 2064
- Injury. *See* Trauma
- INK4A gene (p16), in bladder cancer, 463
- Innate immune system, 447, 448f, 448t
 cytokines and chemokines, 447-448, 449f, 449t
- Innervation
 of bladder, 1628
 in pediatric patients, 3122, 3122f
 of labium majus, 1605
 motor nerve, of bladder smooth muscle, 1635, 1635f
 of pelvis
 female, 1601-1603
 male, 1613f, 1615f, 1618-1622, 1621f-1622f, 1622t
 of vagina, 1607
- Innominate bones, 1611
- Inositol 1,4,5-trisphosphate (IP₃), in ureteral contractions, 986, 988, 988f
- Insensible urinary incontinence, 1711
 pathophysiology of, 1758
- INSS. *See* International Neuroblastoma Staging System
- Instillation therapy, for UTUC, 1398-1399, 1398f, 1399t
- Instrumental activities of daily living (IADLs), of geriatric urology patient, 2086-2087
- Instruments, HRQOL, 91-95
 benign disease-targeted, 92t-95t, 95
 cancer-specific, 92t-94t, 95
 general, 92-95, 92t-94t
 psychometric validation of, 96-97, 96t-97t
 selection of, 95
- Insufflation, for laparoscopic and robotic surgery
 complications related to, 216-217
 gas selection for, 211-212
- Insulin resistance, low urine pH and, 1190-1191
- Insulin therapy, preoperative, 103
- Insulin-like growth factors (IGFs)
 in compensatory renal growth, 1100-1101
 in prostate cancer, 2549
- Insulin-like-3, 518
- Integral theory, 1758, 1988
- Integrated endoscopy systems, for laparoscopic surgery, 197, 197.e2f
- Integrative hypothesis, 1799
- Intensity-modulated radiation therapy (IMRT), 2693
- Interaortocaval lymph nodes, 500
- Intercalated cells, of CCT, 1019
- Interference, of ultrasound waves, 66-67, 67f
- Interferon-gamma release assays (IGRAs), for genitourinary tuberculosis, 424-425
- Interferons (IFNs)
 for condylomata acuminata, 846.e3
 for metastatic RCC, 1502, 1502f, 1503t
 for non-muscle-invasive bladder cancer, 2214
 for PD, 735-736
 for RCC, 1360, 1504t, 1505-1506, 1506f
- Interleukin-2 (IL-2)
 for metastatic RCC, 1501-1502
 for RCC, 1326, 1360
- Interleukin-18 (IL-18), in tubulointerstitial fibrosis, 1099
- Interleukins, 448, 449f, 449t
- Interlobular arteries, of kidney, 971, 972f-973f, 973b, 971.e1f-971.e2f
- Interlobular veins, of kidney, 971-972, 972f-973f, 973b, 971.e1f-971.e2f
- Intermediate cells, of prostate, 2397f, 2398
- Intermediate junctions, ureteral, 978, 984
- Intermediate outcomes. *See* Proxy measures
- Intermediate stratum, 1597, 1599f
- Intermittency, patient history of, 4, 4t-5t
- Internal consistency reliability, 96, 96t
- Internal genitalia
 female, 750.e2-750.e3
 male, development of, 518, 518f
- Internal iliac arteries, 976, 976.e1f
- Internal iliac lymph nodes, 508
- Internal iliac veins, 508, 976, 976.e1f
- Internal pudendal artery, 508-510, 910.e3, 910.e4f
- Internal spermatic artery, 519-520, 520f
- Internal urethrotomy, for urethral stricture disease, 921-922
- International Consultation on Incontinence (ICI)
 Oxford guidelines
 for behavior therapy, 1879t
 to facilitate bladder filling and urine storage, 1838, 1838t
 pelvic floor disorder questionnaires, 1702-1704, 1703t-1704t
- International Consultation on Incontinence Questionnaire Bladder Diary (ICIQ-BD), 1711
- International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms (ICIQ-MLUTS), 1712, 1712.e1f-1712.e2f
- International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form (ICIQ-UI-SF), 1712, 1713f
- International Continence Society (ICS)
 classification of voiding dysfunction, 1692, 1692b
 nocturia definition of, 1821
 transient incontinence causes, 1697, 1698t
- International Germ Cell Cancer Collaborative Group (IGCCCG), risk classification for advanced GCTs, 794-795, 795t
- International Index of Erectile Function (IIEF) scale, 542-543
- International Neuroblastoma Staging System (INSS), 3562, 3563t

- International Prostate Symptom Score (IPSS), 4-5, 4t-5t, 546
- for benign prostatic hyperplasia, 2467-2468
 - for male urinary incontinence, 1712
 - for nocturia, 1821
 - for pelvic floor disorders, 1702-1704
- International Reflux Study in Children, 3155
- International Society for Sexual Medicine, and Premature ejaculation, 693-695
- rationales for, 695.e1-695.e2
- International Society of Paediatric Oncology (SIOP) trials, 3576-3577, 3576f
- International Society of Urological Pathology, Gleason grading system, 2594-2596, 2595f, 2596b
- Interobserver reliability, 96, 96t
- Interpersonal process of care, 90
- InterStim procedure
- outcomes with, 1905-1906
 - technique for, 1903-1905, 1904f-1905f
- Interstitial cells
- bladder outlet obstruction and, 1676
 - of detrusor muscle, 1648, 1648f
- Interstitial cystitis
- bladder pain syndrome and. *See* Bladder pain syndrome and interstitial cystitis
 - HRQOL instruments for, 92t-94t
 - sacral nerve stimulation for, 1907
- Interstitium, of testis, 519
- Leydig cells in. *See* Leydig cells
 - in testosterone synthesis, 522-523, 522f
- Inter- α -trypsin, in crystal formation, 1179
- Intestinal anastomoses in urinary intestinal diversion, 2284-2294
- abdominal stomas with, 2292-2294
 - complications of, 2291t, 2294
 - flush, 2293
 - loop end ileostomy, 2293-2294, 2294f
 - nipple "rosebud," 2293, 2293f
 - with biofragmentable ring, 2289-2290
 - complications of, 2290-2292
 - bowel obstruction, 2290-2291, 2291t, 2292f
 - fistulas, 2290
 - hemorrhage, 2291-2292
 - infection, 2290
 - intestinal stenosis, 2292, 2292f
 - pseudo-obstruction, 2292
 - sepsis, 2290
 - complications of isolated intestinal segment, 2292
 - intestinal stricture, 2292
 - segment elongation, 2292, 2292f
 - compression, 2289-2290
 - laparoscopic and robotic, 2288-2289, 2289f
 - postoperative care for, 2290
 - stapled, 2286-2288
 - ileal-ileal end-to-end, 2288, 2288f
 - ileocolonic end-to-end, 2288, 2288f
 - ileocolonic with circular device, 2287-2288, 2287f
 - types of, 2284-2286
 - end-to-side ileocolic, 2286, 2286f
 - ileocolonic end-to-end, 2286, 2286f
 - single-layer suture, 2285-2286, 2285f
 - two-layer suture, 2285, 2285f
- Intestinal antireflux valves, in urinary intestinal diversion, 2300-2301
- intussuscepted ileal valve, 2300-2301, 2302f
 - intussuscepted ileocecal valve, 2300, 2302f
 - nipple valve, 2301, 2302f
- Intestinal motility, pneumoperitoneum effects on, 213-214
- Intestinal neobladders, pharmacologic therapy in, to facilitate bladder filling and urine storage, 1866
- Intestinal segments
- for antireflux procedure, 3334
 - in augmentation cystoplasty, 3344
 - effects of, 3350
 - used in urinary diversion. *See also* Urinary intestinal diversion
 - minimally invasive, 2370-2371
 - orthoptic, 2353, 2354b
- Intestinal stenosis, with intestinal anastomoses, 2292, 2292f
- Intestinal stricture, with intestinal anastomoses, 2292
- Intestinal tract abnormalities, with cloacal exstrophy, 3227-3228
- Intimal fibroplasia, renovascular hypertension caused by, 1033, 1033t, 1035f
- Intra-abdominal pressure, for laparoscopic and robotic surgery, 212, 213t
- Intra-abdominal vessels, injury of, during laparoscopic and robotic surgery, 218, 218b
- Intracavernosal injection, in ED, 664-665, 665t
- Intracellular bacterial colonies, and UTIs, 2934-2935, 2935f
- Intracorporeal lithotripsy, 1260-1265
- dual modality, 234, 235f, 236b, 235.e1
 - clinical use of, 235
 - CyberWand, 235, 235.e1
 - LithoClast Ultra, 234-235, 235.e1
 - tissue effects of, 235
- EHL. *See* Electrohydraulic lithotripsy
- laser. *See* Laser lithotripsy
- pneumatic, 231t, 232, 233b
- basic physics of, 232-233
 - for bladder stones, 233.e1
 - for percutaneous nephrolithotomy, 233.e1
 - tissue effects of, 233
 - ureteroscopy with, 233.e1
 - ultrasonic. *See* Ultrasonic lithotripsy
- Intracorporeal lithotripters, 1260-1265
- Intradetrusor therapies, for BPS/IC treatment, 358
- Intraductal carcinoma of prostate (IDC-P), 2593-2594
- Intraluminal lithotripsy
- ureteral access sheaths for, 149, 149f, 150t
 - ureteroscopic
 - devices for, 148
 - retropulsion prevention devices for, 149, 149f
 - stone retrieval devices for, 148-149
- Intramuscular (IM), 542-543
- Intramuscular preparations, testosterone, 544t, 545
- Intraobserver reliability, 96, 96t
- Intraoperative floppy iris syndrome (IFIS), α -adrenergic blockers and, 2481
- Intraprostatic ductal reflux, 307-308
- Intraprostatically injected drugs, to facilitate bladder filling and urine storage, 1866.e2
- Intrarenal calculi, ureteroscopic management of, 1285
- Intrarenal schwannoma, 1312
- Intratesticular varicocele, 3395
- Intratubular germ cell neoplasia (ITGCN), 784-785
- histology of, 786
 - treatment of, 797, 797b
- Intrauterine growth, lung development and, 2949-2950
- Intrauterine growth restriction (IUGR), clinical implications of, 2949
- Intrauterine insemination (IUI), 573.e5, 573.e5t
- Intravaginal ejaculation latency time (IELT), 697
- Intravaginal incontinence devices, for female
- Intravaginal slingplasty, 1988
- Intravascular radiologic contrast medium (IRCM), iodinated, 28
- adverse reactions to, 28-30, 29b
 - delayed reactions to, 29-30
 - premedication strategies for, 29, 29b
 - specific considerations for, 30
- Intravascular volume management, in pheochromocytoma treatment, 1551f, 1552
- Intravenous general anesthesia, preoperative considerations for, 111-112
- Intravenous urography (IVU), 31
- for genitourinary tuberculosis diagnosis, 425-426, 426f-427f
 - indications for, 32
 - technique for, 32, 32f
 - for ureterovaginal fistula, 2120-2121, 2121f
 - for vesicovaginal fistula, 2109, 2109f
- Intravesical chemotherapy, for non-muscle-invasive bladder cancer, 2215-2217, 2216t, 2217b
- combination therapy, 2216-2217
 - doxorubicin, 2216
 - mitomycin C, 2215-2216
 - novel agents, 2216
 - to prevent implantation, 2211-2212, 2212b
 - thiotepa, 2216
- Intravesical electrotherapy (IVE), for detrusor underactivity, 1807, 1818
- Intravesical foreign body
- laparoscopic, 2279-2280, 2279f-2280f
 - secondary bladder calculi with, 1293
- Intravesical pressure, increasing
- external compression for, 2079-2080
 - to facilitate bladder emptying, 1870-1873, 2079-2081
 - reflex contraction promotion or initiation, 2080
 - stimulated myoplasty, 2081
- Intravesical therapies, for BPS/IC treatment, 353t, 356-358, 358b, 358.e1, 356.e1
- Clorapactin, 356.e1
 - DMSO, 356-357
 - glycosaminoglycans, 357-358
 - intradetrusor therapies, 358
 - silver nitrate, 356.e1
- Intrinsic apoptotic pathway, 479.e1, 479.e1f
- Intrinsic renal disease, AKI due to, 1043-1044, 1044b. *See also* Acute tubular necrosis
- Intrinsic sphincter deficiency (ISD), 1689-1690
- causes of, 1757
 - midurethral sling for, outcomes of, 2020-2021
 - quantification of, 1727
 - sling procedure and, 1989
 - stress urinary incontinence and, 1758, 1919-1920, 1990
- Intrinsic sphincter dysfunction, 1689-1690
- Intubated ureterotomy
- for ureteral stricture disease, 1139
 - for ureteropelvic junction obstruction, 1123-1124, 1126f
- Intussuscepted ileal valve, 2300-2301, 2302f
- Intussuscepted ileocecal valve, 2300, 2302f
- Intussusception technique, for UTUC, 1378-1379, 1380f
- Inulin, GFR estimation with, 1008
- Inverted papilloma, of bladder, 2184
- Involuntary detrusor contractions (IDCs), 1725
- Iodinated contrast medium, 28
- adverse reactions to, 28-30, 29b
 - CKD assessment and, 1061-1062
 - delayed reactions to, 29-30
 - premedication strategies for, 29, 29b
 - specific considerations for, 30

- Ion channels
 in detrusor muscle, 1644-1646, 1644f
 in ED, 628
 Ion transport, across bladder urothelium, 1639
 IP₃. *See* Inositol 1,4,5-trisphosphate
 Ipilimumab, 1325-1326
 for RCC, 1507
 Ipsilateral vesicoureteral reflux, bladder diverticula with, 2146
 IPSS. *See* International Prostate Symptom Score
 IRCM. *See* Intravascular radiologic contrast medium
 IRE. *See* Irreversible electroporation
 Irinotecan, for penile cancer, 871-873, 872t
 Irreversible electroporation (IRE)
 for prostate cancer, 2733-2734, 2734f-2736f
 outcomes with, 2737
 for renal tumors, 1498-1499
 Irritable bowel syndrome (IBS), cross-organ sensitization in, 1656
 Irritative symptoms, of lower urinary tract, patient history of, 3-5, 4t-5t
 Isaacs syndrome, lower urinary tract dysfunction and, 1790
 Ischemic nephropathy, 1028
 pathophysiology of, 1029-1031, 1030f-1031f, 1031b
 renal artery angioplasty and stenting for, 1038-1039, 1039b, 1040f
 Ischial spine, 1597, 1598f
 Ischiococcygeus muscle, 1601, 1603f, 1939, 1940f
 Ischioanal fossa, 1604
 ISD. *See* Intrinsic sphincter deficiency
 Isoflurane, preoperative considerations for, 111
 Isoproterenol, ureteral response to, 987, 991-992, 1001-1002
 Isovolumetric pressure, 1815
 ITGCN. *See* Intratubular germ cell neoplasia
 IUGR. *See* Intrauterine growth restriction
 IUI. *See* Intrauterine insemination
 IV pyelography (IVP), 2906-2907
 for pediatric patients, 2916
 of renal injuries, 1150-1151
 for renal ptosis, 1462, 1463f
 for renal tumor evaluation, 1314-1316
 IVC. *See* Inferior vena cava
 IVC filters, for vena caval thrombectomy, 1433
 IVE. *See* Intravesical electrotherapy
 IVF. *See* In vitro fertilization
 IVP. *See* IV pyelography
 IVU. *See* Intravenous urography
- J**
 Jehovah's Witnesses, perioperative care for children of, 2955
 Jejunal conduit, 2305-2306, 2306t
 Jejunum. *See* Small bowel
 JESS, 1174
 Juices, citrus, nephrolithiasis and, 1217, 1217b
 Juvenile granulosa cell tumors, 3595
 Juvenile nephronophthisis, 3014t, 3021-3023
 clinical features of, 3022
 evaluation of, 3022-3023, 3022f
 genetics of, 3014t, 3021-3022
 treatment of, 3023
 Juvenile xanthogranuloma, 3379
 Juxtaglomerular cell tumors, renal, 1312
- K**
 Kalicinski plication technique, for megaureter in pediatric patients, 3072, 3072f
- Kaposi sarcoma (KS)
 HIV and, 385, 413-414, 413f
 as neoplastic condition, 413-414, 413f
 of penis, 846.e3-846.e4
 Kaposi sarcoma-associated herpesvirus. *See* Human herpesvirus 8
 Kaye Nephrostomy Tamponade Balloon, 176, 176f
 KDIGO. *See* Kidney Disease: Improving Global Outcomes
 Kelly repair, for classic bladder exstrophy, 3197
 technical aspects of, 3202, 3203f
 Ketamine, preoperative considerations for, 111-112
 Ketoconazole, 2791-2792
 Ketone testing, urinary, 19
 Ketorolac
 for pediatric patients, 2957
 for urinary tract obstruction, 1101
 Ketorolac-eluting (Lexington) stents, 128
 K_r. *See* Formation product
 Kidney cancer. *See* Renal cancer
 Kidney Disease: Improving Global Outcomes (KDIGO)
 AKI definition by, 1041, 1042t
 CKD classification by, 1053-1055, 1055f
 Kidney failure. *See* Renal failure
 Kidney infections, 291b
 infectious granulomatous nephritis
 malacoplakia, 289-290, 289f
 renal echinococcosis, 290-291, 291f
 XGP, 286-289, 287f-288f
 renal infection (bacterial nephritis), 274
 acute focal or multifocal bacterial nephritis, 278-279, 279f
 acute pyelonephritis, 275-278, 276f-277f, 278t, 285
 bacterial "relapse," 286
 chronic pyelonephritis, 285-286, 286f
 emphysematous pyelonephritis, 279-280, 280f-281f
 infected hydronephrosis and pyonephrosis, 283, 283f
 pathology, 274-275, 275f-276f
 perinephric abscess, 283-285, 284f
 renal abscess, 280-283, 281f-282f
 Kidney paired donation (KPD), 1078-1079, 1078f-1079f
 Kidney surgery, 1445b
 approaches used in, 1415
 anterior, 1419-1420, 1419.e1f
 dorsal lumbotomy, 1417-1418, 1418f
 flank, 1415-1417, 1416f-1417f, 1416.e1f, 1417.e1f
 thoracoabdominal, 1418-1419, 1418f-1419f, 1418.e1f, 1419.e1f
 for benign diseases
 ECRS, 1421-1423, 1422f
 open nephrectomy, 1420-1421, 1420.e2f
 partial nephrectomy, 1420, 1421f
 simple nephrectomy, 1420, 1420f, 1420.e1f
 historical perspective, 1414
 laparoscopic and robotic. *See* Laparoscopic kidney surgery
 for malignancies
 partial nephrectomy, 1428-1433, 1428f-1432f, 1431.e1f, 1432.e1f, 1429.e1f
 radical nephrectomy, 1423-1428, 1423f-1427f, 1424.e1f, 1427.e1f, 1425.e1f
 vena caval thrombectomy. *See* Vena caval thrombectomy
 preoperative evaluation and preparation for, 1414, 1415f, 1414.e1f
 prophylactic measures, 1414-1415
 surgical instruments, 1415
- Kidney tumors. *See* Renal tumors
 Kidneys
 AAST Organ Injury Severity Scale for, 1149t
 anatomy of, 967, 969b
 changes during pregnancy, 294
 congenital anomalies in, 969, 969.e2f
 gross and microscopic, 968-969, 970f, 968.e1f-968.e2f
 innervation, 973, 973.e2f
 intrarenal vasculature, 156-157, 157f
 lymphatic drainage, 973, 973.e1f
 parenchyma and collecting system, 155-156, 155f-156f
 perirenal, 154-155, 154f
 radiologic, 969, 969b, 971f, 969.e1f-969.e2f
 surface anatomy and relationships, 967-968, 968f, 968.e1f, 967.e1f-967.e3f
 vasculature, 971-973, 972f-973f, 973b, 971.e1f-971.e2f
 anomalous, 969, 969.e2f
 percutaneous access to, 168-170, 170f
 Ask-Upmark, 3009-3011, 3010f
 cake or lump, 2991-2992, 2992f
 calcium absorption in, 1180
 collecting system of. *See* Collecting system
 compensatory growth of, with urinary tract obstruction, 1100-1101
 cystic diseases of. *See* Renal cystic diseases
 deterioration of, in urinary intestinal diversion, 2296t, 2303
 development of, 2823-2833, 2826f
 clinical implications of, 2949-2950
 disc, 2992, 2992f
 drainage of, for urinary tract obstruction, 1101
 ectopic
 inferior, 2990
 superior, 2992
 embryology of, 2975
 in genitourinary tuberculosis, 422-423
 horseshoe. *See* Horseshoe kidneys
 impaired function of, after percutaneous access to upper urinary tract collecting system, 182
 localization, in UTI diagnosis, 252, 252.e1t
 L-shaped, 2992
 organoneogenesis of
 molecular mechanisms of, 2976
 new advances in, 2976-2978, 2977f
 pathologic changes of, with urinary tract obstruction, 1097
 pediatric, 3538
 physical examination of, 9, 9f
 physiology of. *See* Renal physiology
 pneumoperitoneum effects on, 213, 213t
 postnatal considerations for, 2951
 prenatal diagnostic findings of, 2873-2878, 2874f
 preservation of, for renal transplantation, 1075, 1075t
 in prune-belly syndrome, 3234-3235, 3235f
 pseudotumors of, 3003, 3003f
 PTH effects on, 1012
 regeneration of, 494-496, 496f, 495.e1
 sigmoid, 2990-2991
 size of, with spina bifida, 3277
 solitary, upper urinary tract calculi and, 1255
 supernumerary, 2984-2985, 2985f, 2985.e1f-2985.e2f
 thoracic, 2988, 2988f-2989f
 transplantation of. *See* Renal transplantation
 ultrasonography of. *See* Renal ultrasonography
 urine egress from, in urinary tract obstruction, 1095

- Kidney-ureter-bladder (KUB) radiograph
kidney anatomy on, 969, 969.e1f
for pediatric patients, 2916
- Kinins, urethral function effects of, 1004
- Kisspeptin protein, 518-519
- Klinefelter syndrome and variants, 3477-3478
- Klippel-Trénaunay-Weber syndrome, 3384
- KLK14. *See* Human kallikrein 14
- "The Knack," 1884, 1885b
- Kocher maneuver, for radical nephrectomy, 1424, 1424f
- Kock ileal reservoir, for orthoptic urinary diversion, 2355, 2356f
- Kock pouch, 2325, 2326f
- KPD. *See* Kidney paired donation
- KS. *See* Kaposi sarcoma
- K_{sp}. *See* Thermodynamic solubility product
- KTP laser. *See* Potassium titanyl phosphate laser
- KUB radiograph. *See* Kidney-ureter-bladder radiograph
- KUL-7211, ureteral response to, 991-992
- L**
- LABD. *See* Linear IgA bullous dermatosis
- Labia majora, 1604, 1605f-1606f, 750.e2
- Labia minora, 750.e2
- Labial adhesions, 3466-3467, 3467f
- Labioplasty, initial management, timing, and principles for, 3504-3507, 3505f, 3507f
- Labor
- sphincter function and, 1757
 - vesicovaginal fistulae with, 2105-2106
- Lactate dehydrogenase (LDH)
in prostatic secretions, 2417t, 2422
in TGCs, 790-791, 794
- Lamina propria, 1633-1634
- Laminectomy, LUT function and, 1781
- Langer lines of cleavage, 1611
- Lap Disc, 203, 203.e3, 203.e3f
- Laparoendoscopic single-site surgery (LESS), 1591
- access devices for, 203.e4, 203.e4f
 - for achieving transperitoneal access and establishing pneumoperitoneum, 201.e2
 - Boari flap, 2260-2261
 - instrumentation for, 210.e1, 210.e1f
 - for kidney surgery
 - clinical experience of, 1479-1480, 1479f
 - robotic, 1480
 - surgical approaches and access for, 1453-1454, 1453f-1454f, 1455t
 - in pediatric patients, 2969-2970
 - pyeloplasty, for ureteropelvic junction obstruction, 1119-1120, 1119f
- Laparoscopes, for laparoscopic and robotic surgery, 205, 205.e1f-205.e2f
- Laparoscopic adrenalectomy, 1579-1580, 1579b
- left, 1586-1587, 1586f-1589f, 1589-1590
 - outcomes, 1592-1593
 - retroperitoneal approach, 1589-1590, 1589f-1590f, 1592-1593
 - right, 1587-1588, 1588f, 1590, 1590f
 - transperitoneal approach, 1585-1590, 1586f-1588f, 1592-1593
- Laparoscopic approach
to orthoptic urinary diversion, 2360
to urinary diversion. *See* Minimally invasive urinary diversion
- Laparoscopic Boari flap. *See* Boari flap, laparoscopic or robotic
- Laparoscopic calicovesicostomy, for ureteropelvic junction obstruction, 1122
- Laparoscopic carts, 197, 197.e2f
- Laparoscopic colposuspension, 1921
- Laparoscopic dismembered tubularized flap pyeloplasty, for ureteropelvic junction obstruction, 1122
- Laparoscopic distal ureterectomy, for UTUC, 1379, 1380f, 1381-1382, 1388
- Laparoscopic donor nephrectomy (LDN), 1079, 1080f
- Laparoscopic foreign body excision, 2279-2280, 2279f-2280f
- Laparoscopic heminephrectomy, 1471
- Laparoscopic hysterectomy, ureteral injuries after, 1158
- Laparoscopic ileal ureteral substitution, for ureteral stricture disease, 1140-1141
- Laparoscopic ILND, for penile cancer, 864, 896-897
- surgical technique for, 897-902, 897f-903f
- Laparoscopic kidney surgery, 1446, 1482-1483, 1483b
- ablative techniques, 1477-1479, 1494
 - biopsy for medical renal disease, 1461-1462, 1462f
 - calyceal diverticulectomy, 1463-1464
 - complications of, 1480-1482, 1480b, 1481f
 - LESS
 - clinical experience of, 1479-1480, 1479f
 - robotic, 1480
 - surgical approaches and access for, 1453-1454, 1453f-1454f, 1455t
 - nephrolysis, 1464, 1464f
 - nephropexy, 1462, 1463f
 - procedure for, 1462, 1463f
 - results of, 1462-1463
- partial nephrectomy. *See* Laparoscopic partial nephrectomy
- patient evaluation and preparation for, 1446-1447
- penetrance of, among urologists, 1482
- radical nephrectomy. *See* Laparoscopic radical nephrectomy
- for renal cysts, 1457-1460, 1460f, 1460t
- procedure for, 1460-1461, 1461f
 - results of, 1461
- simple nephrectomy, 1454
- dissection of ureter, 1454, 1456f
 - identification of renal hilum, 1454-1455, 1457f
 - isolation of upper pole, 1456, 1457f
 - organ entrapment and extraction, 1456-1457, 1458f-1459f
 - postoperative management for, 1457
 - reflection of colon, 1454, 1456f
 - results of, 1457
 - securing of renal blood vessels, 1455, 1457f
- surgical approaches and access for, 1447
- hand-assisted modifications, 1450-1452, 1451f-1452f
 - LESS and NOTES, 1453-1454, 1453f-1454f, 1455t
 - retroperitoneal, 1448-1450, 1450f-1451f
 - robotic-assisted modifications, 1452-1453, 1453f
 - transperitoneal, 1447-1448, 1447f-1449f
- Laparoscopic orchidopexy, 3447-3449, 3448t
- Laparoscopic partial nephrectomy (LPN), 1470
- indications for, 1470-1472, 1471f
 - central and hilar tumors, 1471
 - clinical stage T1b and greater tumors, 1471
 - laparoscopic heminephrectomy, 1471
 - multiple tumor management, 1472
 - tumors in solitary kidneys, 1472
- outcomes of, 1476-1477
- long-term, 1477, 1478t
 - positive
- Laparoscopic partial nephrectomy (LPN)
(Continued)
procedure for
collecting system repair, 1474-1475, 1475f
hemostasis, 1473-1474, 1474f
renal hypothermia, 1475
retroperitoneal approach, 1472
robotic-assisted, 1472
technical issues, 1472
transperitoneal approach, 1472
tumor localization and excision, 1472-1473, 1473f
warm ischemia and hilar control, 1475-1476
- Laparoscopic prostatectomy, for localized prostate cancer, 2614
- Laparoscopic pyelolithotomy, for pediatric stone disease, 3118
- Laparoscopic pyeloplasty, for ureteropelvic junction obstruction, 1115-1120, 1122b
- anterior extraperitoneal approach to, 1119
 - with concomitant pyelolithotomy, 1122
 - dismembered tubularized flap for, 1122
 - indications and contraindications for, 1117
 - in pediatric patient, 3062-3066, 3066f-3067f
 - results of, 1120-1122, 1121t
 - retroperitoneal approach to, 1118
 - robotic-assisted, 1119-1120, 1121t
 - single-site surgery approach, 1119-1120, 1119f
 - techniques for, 1117-1120
 - transmesenteric modification of
 - transperitoneal approach to, 1118
 - transperitoneal approach to, 1117-1118, 1118f
 - vascular transposition for, 1118
- Laparoscopic pyelopyelostomy, for retrocaval ureter, 1125-1128
- Laparoscopic radical nephrectomy (LRN), 1465
- hand-assisted, 1467-1468, 1467f-1468f
 - retroperitoneal approach to, 1467
 - special considerations for
 - cytoreductive nephrectomy, 1470
 - en bloc hilar vessel stapling, 1468-1469
 - large tumors, 1468
 - local recurrence, 1469-1470, 1470f
 - lymphadenectomy, 1469
 - port-site recurrence, 1469
 - renal vein and caval tumor thrombus, 1470
 - specimen extraction, 1469
 - surgical salvage after failed ablative therapies, 1470
 - transperitoneal approach to, 1465-1467, 1465f, 1466t
- Laparoscopic radical nephroureterectomy, for UTUC, 1382-1384, 1382f-1384f
- Laparoscopic radical prostatectomy (LRP)
abdominal access in, 2667, 2667f
anastomotic complications with, 2680
anesthesia for, 2665-2666
apical dissection, 2672-2673, 2673f
bladder neck in, identification and transection of, 2669-2670, 2670f
bladder neck reconstruction, 2673
bleeding with, 2680
blood loss with, 2675
bowel preparation for, 2664
complications with, 2679-2680
contraindications for, 2664
deep dorsal venous complex ligation in, 2669, 2669f
economic considerations of, 2679
equipment malfunction in, 2680
evolution of, 2663
extraperitoneal approach to, 2667-2668, 2667f
transperitoneal approach versus, 2668

- Laparoscopic radical prostatectomy (LRP)
(Continued)
hospital stay with, 2675
indications for, 2664
informed consent for, 2665
instrumentation for, 2664, 2664b
insufflation in, 2667, 2667f
intraoperative inspection of prostate, 2673
neurovascular bundle preservation in, 2671-2672, 2671f-2672f
open conversion of, 2679
open *versus*, 2678-2679
operating room personnel for, 2665, 2665f
operative time for, 2675
outcomes with
functional, 2675-2676, 2677t
oncologic, 2676-2678, 2678t
perioperative, 2675-2679
patient positioning for, 2665, 2666f
complications with, 2679
patient selection for, 2664
pelvic lymphadenectomy in. *See* Pelvic lymphadenectomy, in laparoscopic radical prostatectomy
postoperative management for, 2674-2679
postoperative pain with, 2675
preoperative preparation for, 2664-2666
prostate and rectum plane development in, 2670, 2671f
prostatic pedicle control in, 2670-2671
rectal injury with, 2679-2680
robotic-assisted *versus*, 2666-2667
seminal vesicle dissection in, 2670, 2670f-2671f
space of Retzius development for, 2668-2669, 2668f
specimen
delivery in, 2674
entrapment in, 2673
summary for, 2683
thromboembolic complications with, 2680
transfusion for, 2680
transperitoneal approach to, 2667-2674
extraperitoneal approach *versus*, 2668
trocar placement in, 2667, 2667f
vasa deferentia dissection in, 2670, 2670f-2671f
vesicourethral anastomosis, 2673-2674, 2674f
posterior support of, 2673, 2674f
- Laparoscopic retropubic suspension surgery, 1930-1932, 1932b
- Laparoscopic RPLND (L-RPLND), 838
complications of, 843, 844t
controversy surrounding, 839
duplication of open RPLND with, 839
nerve-sparing techniques for, 843
outcomes and current status of, 843-845, 845t
postoperative care for, 843
preoperative patient preparation for, 839
rationale and evolution of, 838
staging with, 839
surgical technique for, 839
approach, 839
bilateral dissections, 842
left-sided dissection, 841f-842f, 842
patient positioning and port placement, 839-840, 840f
right-sided dissection, 840-841, 840f-842f
technical considerations, 839
- Laparoscopic simple/supratrigonal cystectomy.
See Simple/supratrigonal cystectomy, robotic or laparoscopic
- Laparoscopic stone removal, 1286-1287
- Laparoscopic surgery, 195. *See also specific surgeries*
access technology for
hand-assist devices, 203-205, 203.e3, 203.e3f
LESS devices, 203.e4, 203.e4f
trocars, 202-205, 203f, 203.e1f-203.e2f
complications and troubleshooting in, 215, 215t, 224b
anesthesia-related, 220.e1
early postoperative, 222-224
equipment-related, 215-216
exit-related, 222
late postoperative, 224, 224.e1
during learning curve, 215
pneumoperitoneum-related, 216
procedure-related, 220-222, 220f, 222.e1
trocar-related, 217-220, 219f
equipment placement for, 197, 197.e2f
instrumentation used in
for da Vinci Robotic System, 209-210, 210f
for grasping and blunt dissection, 205-206, 210
for incising and hemostasis, 206-207, 210, 206.e1f, 207.e1
for LESS, 210.e1, 210.e1f
for morcellation, 209, 209.e1
for NOTES, 210.e2
for port site closure, 211, 211f
for retraction, 209, 209.e2
for specimen entrapment, 208-209, 209f
for stapling and clipping, 207-208, 208f-209f, 209b
surgical pharmaceuticals, 207, 207t, 207.e2
for suturing and tissue anastomosis, 207, 208f, 210, 207.e2f, 207.e3
for visualization, 205, 205.e1f-205.e2f
for lower ureteral injuries, 1163-1164
operative team placement for
retroperitoneal upper abdominal procedures, 198, 199f
transperitoneal and extraperitoneal pelvic procedures, 199, 199f
transperitoneal upper abdominal procedures, 198, 198f
for partial nephrectomy, 1348, 3089-3090, 3091f
for pediatric patients, 2963, 2974, 2974b
advantages of, 2963
anesthesia for, 2966, 2966f
complications of, 2970-2972
contraindications to, 2965
disadvantages of, 2964-2965, 2964f
general applications of, 2964b, 2964t
hemostatic devices for, 2965
LESS, 2969-2970
outcomes of, 2972-2974, 2973t
retroperitoneal approach to, 2966-2969, 2967f, 2967t, 2969b-2970b
suturing for, 2965-2966
team development for, 2965
transperitoneal approach to, 2966-2969, 2967f, 2967t, 2968b-2969b
troubleshooting for, 2969, 2970b, 2970f-2972f, 2972b
physiologic considerations in, 211, 215b
hemodynamic effects related to approach and patient position, 214
hormonal and metabolic effects during surgery, 214
immunologic effects, 214-215
insufflation choice, 211-212
pneumoperitoneum effects on various systems, 212-214, 213t
- Laparoscopic surgery (Continued)
pneumoperitoneum pressure choice, 212, 213t
preoperative preparation for, 197b
blood products, 196
bowel preparation, 196
operating room setup, 196-197, 197b
patient positioning, 197, 197.e1f
patient selection and contraindications, 195-196
for pediatric patients, 2967
prophylaxis, 197
procedure for, 211b
abdomen exit, 210-211
achieving extraperitoneal access and developing extraperitoneal space, 201-202, 202.e1
achieving retroperitoneal access and developing retroperitoneal space, 201, 202f, 201.e3-201.e4, 202.e1
achieving transperitoneal access and establishing pneumoperitoneum, 200-201, 201f, 200.e1, 200.e1f, 201.e1f, 201.e2, 202.e1
hand-assist device placement, 203-205, 203.e3, 203.e3f
LESS device placement, 203.e4, 203.e4f
pediatric access techniques, 2967-2969, 2968b-2970b
port removal and fascial closure, 210-211
port site closure, 211, 211f
pre-incision checklist, 200
skin closure, 211
trocar placement, 202-205, 203f, 203.e1f-203.e2f
for radical nephrectomy, 1345, 1346f
for seminal vesicle procedures, 961, 964f
training and practicing for, 224.e2, 224.e4b
equipment for, 224.e2-224.e4, 224.e2f-224.e3f
formal programs for, 224.e4
uncomplicated urologic procedures, antimicrobial prophylaxis for, 264, 264t
ureteral injuries with, 1158
for vesicovaginal fistula. *See* Vesicovaginal fistula, laparoscopic approaches to
- Laparoscopic training boxes, 224.e2-224.e3, 224.e2f-224.e3f
- Laparoscopic transureteroureterostomy, for ureteral stricture disease, 1139
- Laparoscopic ureteral reimplantation. *See* Ureteral reimplantation, laparoscopic and robotic
- Laparoscopic ureterocalicostomy, for ureteropelvic junction obstruction, 1122
- Laparoscopic ureterolysis, for retroperitoneal fibrosis, 1146
- Laparoscopic ureteroneocystostomy, for ureteral stricture disease, 1135, 1135f
with Boari flap, 1137-1139
with psoas hitch, 1136
- Laparoscopic ureteroureterostomy, for ureteral stricture disease, 1134-1135
- Lapides classification, of voiding dysfunction, 1693-1695, 1693b
- Lapra-Ty clips, 207, 208f
- Laser ablation
for localized prostate cancer, 2626
for penile cancer, 855-856
- Laser instrumentation
for laparoscopic and robotic surgery, 206
for tissue dissection and cauterization
CO₂ laser, 230
delivery systems for, 228

- Laser instrumentation (*Continued*)
 diode laser, 230
 Ho:YAG laser, 230
 KTP laser, 229
 LBO laser, 229-230
 light-tissue interaction of, 228-229, 229f
 Nd:YAG laser, 229
 pulsed and continuous wave lasers for, 228
 soft tissue applications, 228-230
 Thulium laser, 230
- Laser interstitial thermal therapy (LITT), for renal tumors, 1498
- Laser lithotripsy, 1261-1262
 for bladder calculi, 1295, 234.e2-234.e3
 Ho:YAG and Er:YAG, 231t, 234b, 233.e3, 234.e2, 234.e3, 234.e3f
 basic physics of, 233-234
 for bladder stones, 234.e2-234.e3
 for percutaneous nephrolithotomy, 234.e2
 popcorning technique for, 234
 ureteroscopy with, 234.e1
- Laser treatments, for benign prostatic hyperplasia, 2526-2534, 2534b
 holmium laser enucleation of prostate. *See* Holmium laser enucleation of prostate
 photoselective vaporization of prostate. *See* Photoselective vaporization of prostate
 safety for, 2527
 thulium resection. *See* Thulium laser
- Laser urethrotomy, for urethral stricture disease, 922.e1
- Late relapse RPLND, 831t, 832
- Late-night salivary cortisol, in evaluation of adrenal masses, 1572
- Latent pacemakers, ureteral, 983-984
- Latent syphilis, 374
- Late-onset hypogonadism, 538, 547-548
- Lateral fusion abnormalities, 3465-3466, 3465f-3466f
 inguinal hernias, 3468
 rhabdomyosarcoma, 3466, 3466f
 uterus and cervix duplication, 3465-3466, 3466f
- Lateral plexuses, 1617
- Lateral resolution, of ultrasonography images, 65, 66f
- Lateralizing essential hematuria, 194
- Laxative abuse, ammonium acid urate stones from, 1195-1197, 1231, 1231b
- LBO laser. *See* Lithium triborate laser
- LDH. *See* Lactate dehydrogenase
- LDL. *See* Low-density lipoprotein
- LDN. *See* Laparoscopic donor nephrectomy
- Le Bag pouch, for orthotopic urinary diversion, 2358-2360, 2361f
- Le Duc technique, in urinary diversion, 2296t, 2299-2300, 2299f
- Leadbetter and Clarke technique, in urinary diversion, 2296, 2296f, 2296t
- Leak point pressures, urodynamic studies of, 1727-1728
 abdominal, 1727, 1727f
 detrusor, 1727-1728, 1728f
- Left adrenalectomy
 laparoscopic, 1586-1587, 1586f-1589f, 1589-1590
 open, 1583-1584, 1583f-1584f
- Leiomyomas
 renal, 1310-1312, 1311f, 1312b
 of urethra, 879
- Leiomyosarcomas
 of kidney, 1361-1362, 1362f
 retroperitoneal, 1405-1406
- Length of stay (LOS), 86
- Lentigo simplex, 418f, 419
- Leptin, 518-519
 in prostate cancer, 2550
- LESS. *See* Laparoendoscopic single-site surgery
- Leucine aminopeptidase, in prostatic secretions, 2417t, 2422
- Leukemia
 of kidney, 1361t, 1362-1363
 testicular metastases of, 812-813, 3595
- Leukocyte esterase testing, urinary, 20, 20f
- Leukocytes, in urinary sediment, 21-22, 22f
- Leukoplakia, of bladder, 2184
- Levator ani muscle, 1601, 1603f
 function of, 1942, 1942f
- Levator plate, 1601, 1603f
- Levels of evidence, 91
- Levitra. *See* Vardenafil
- Lexington stents. *See* Ketorolac-eluting stents
- Leydig cell aplasia, 3489
- Leydig cell tumors, 811-812, 3595, 3595f
- Leydig cells, 498, 528, 540
 testis physiology and, 521-523, 521f
 testosterone production by, 2400
 testosterone synthesis in, 522
 control of, 522
- LGPIN. *See* Low-grade prostatic intraepithelial neoplasia
- LGV. *See* Lymphogranuloma venereum
- LH. *See* Luteinizing hormone
- LHRH. *See* Gonadotropin-releasing hormone
- Libido, loss of
 hormonal therapy and, 2794
 patient history of, 6
- Lichen nitidus (LN), as papulosquamous disorder, 394
- Lichen planus (LP), as papulosquamous disorder, 394, 395f
- Lichen sclerosis (LS)
 male, 846.e1-846.e2
 circumcision and, 3372-3373, 3372f
 reconstructive surgery for, 912-913, 913f
 as papulosquamous disorder, 395-396, 396f
- Liddle syndrome, 2863
- Lidocaine
 for cystourethroscopy, 140
 for urethral catheterization, 122
- Life years (LYs), 86
- Lifestyle modifications
 for CP/CPPS treatment, 326
 for ED, 658
 for urinary incontinence, 1892-1894
 bowel function, 1893-1894
 caffeine reduction, 1893
 dietary irritants, 1893
 fluid management, 1892-1893
 levels of evidence and recommendations for, 1876t
 obesity and weight reduction, 1894
- Ligaments. *See also specific ligaments*
 of female pelvis, 1600, 1600f-1603f
- Ligand-binding domain, of androgen receptors, 2410
- LigaSure vessel-sealing system, 206, 206.e1f
- Ligation
 for laparoscopic surgery in pediatric patients, 2965
 of ureter, 1166, 1166f
 for UTUC, 1378, 1379f
- Linea alba, 1611-1613, 1613f
- Linear IgA bullous dermatosis (LABD), 398-399, 399f
- Lipid profile
 TT effects on, 546
 urologic disease and, 551
- Lipomas
 of kidney, 1361-1362, 1362f
 retroperitoneal, 1405-1406
- Lipomeningocele, 3284-3286
 pathogenesis of, 3284-3286, 3286f
 presentation of, 3284, 3284b, 3285f-3286f
 recommendations for, 3280t, 3286, 3287f
- Lipopolysaccharide (LPS), 248
- Liposarcoma
 of kidney, 1362
 retroperitoneal, 1404-1405, 1408
 of testicular adnexa, 813
- Lipotoxicity, 1192
- Lithium triborate (LBO) laser, 229-230
- LithoClast Ultra, 234-235, 235.e1
- Lithotomy, historical overview of, 1291
- Lithotripsy
 ballistic, 1262-1263, 1263f
 ultrasonic combined with, 1264-1265, 1265f
 for bladder calculi, 1295
 EHL. *See* Electrohydraulic lithotripsy
 intracorporeal. *See* Intracorporeal lithotripsy
 intraluminal. *See* Intraluminal lithotripsy
 laser. *See* Laser lithotripsy
 pneumatic, 231t, 232, 233b
 basic physics of, 232-233
 for bladder stones, 233.e1
 for percutaneous nephrolithotomy, 233.e1
 tissue effects of, 233
 ureteroscopy with, 233.e1
 shock wave. *See* Shock wave lithotripsy
 ultrasonic. *See* Ultrasonic lithotripsy
 for urethral calculi, 1299
- Lithotripters
 comparison of, 1268, 1268f-1269f
 dual modality. *See* Dual modality lithotripters
 flexible, 1260-1262
 intracorporeal, 1260-1265
 rigid, 1262-1264
- LITT. *See* Laser interstitial thermal therapy
- Live animal models, laparoscopic training with, 224.e2-224.e3
- Liver cirrhosis, benign prostatic hyperplasia and, 2441
- Liver injury, during radical nephrectomy, 1428
- Living donors, of renal transplants
 evaluation of, 1076-1078, 1077f
 matching incompatible recipients with, 1078-1079, 1078f-1079f
 operation on, 1079, 1080f
- LMN. *See* Lower motor neuron
- LN. *See* Lichen nitidus
- Local anesthesia
 for pediatric patients, 2956
 for percutaneous access to upper urinary tract collecting system, 158
- Localization, in UTI diagnosis, 252, 252.e1t
- Localized prostate cancer
 androgen deprivation therapy for, 2799, 2800f
 background on, 2609-2611
 patient evaluation, 2611
 primary tumor characterization, 2611
 conservative management of, 2611-2624, 2613b
 active surveillance for, 2611-2613
 watchful waiting for, 2611-2613
 cryoablation for. *See* Cryoablation, for
 localized prostate cancer
 focal therapy for, 2626
 laser ablation, 2626
 photodynamic therapy, 2626
 functional outcomes after treatment for, 2630-2631
 high-intensity focused ultrasound ablation, 2626
 focal, 2626.e1

- Localized prostate cancer (*Continued*)
 primary hormone therapy for, 2624, 2706, 2624.e1b
 quality of life after treatment for, 2630-2631
 radiation therapy for. *See* Radiation therapy for localized prostate cancer
 radical prostatectomy for. *See* Radical prostatectomy, for prostate cancer
 radiofrequency interstitial tumor ablation for, 2626.e1
 screening for, 2609-2611
 treatment recommendations for, 2626, 2627t
- Locally advanced prostate cancer
 androgen deprivation for, 2766-2767
 intermittent, 2766-2767
 quality of life with, 2767
 androgen deprivation therapy for continuous, 2800-2801, 2801f
 with external beam radiation therapy, 2619-2620
 clinical trials for, 2767, 2768t
 contemporary risk assessment for, 2752-2753, 2753b
 decision trees for, 2754-2755
 definition of, 2752-2754
 delayed sequelae with, 2767
 focal ablative therapy for, 2765
 cryoablation, 2765
 high-intensity focused ultrasound, 2765
 imaging modalities for, 2753, 2753f-2754f
 incidence trends of, 2754
 natural history of, 2755, 2756f, 2756t
 novel markers for, 2754, 2754t
 radiation therapy for, 2763-2765, 2764t
 adjuvant androgen deprivation with, 2763-2765
 chemotherapy with, 2765
 neoadjuvant androgen deprivation with, 2763
 radical prostatectomy for, 2755-2763
 adjuvant androgen deprivation with, 2762-2763
 adjuvant radiation therapy, 2761-2762, 2761t
 for clinical stage T3, 2756-2757, 2757t
 neoadjuvant androgen deprivation, 2758-2760, 2759t-2760t
 neoadjuvant chemotherapy and chemotherapy-hormonal therapy, 2760-2761, 2760t
 outcomes, 2757-2758, 2758f
 treatment trends of, 2754, 2755t
- LOH. *See* Late-onset hypogonadism
- Loop diuretics
 for AKI, 1050
 in stone formation, 1197
 surgical management of, 1243.e3
- Loop end ileostomy, 2293-2294, 2294f
- Loop of Henle, functions of, 1015-1018, 1016f-1017f
- Loopography, 34-35, 35f
- LOS. *See* Length of stay
- Low-density lipoprotein (LDL), TT effects on, 546
- Low-dose continuous prophylaxis, for recurrent UTIs, 272-273, 272t
- Low-dose unfractionated heparin, preoperative, 108-110, 108t-109t
- Lower motor neuron (LMN) lesion, voiding dysfunction after, 1694, 1694b
- Lower pole renal calculi, surgical management of, 1247-1250, 1247f, 1248t, 1249f
- Lower tract endoscopy
 antimicrobial prophylaxis for, 263
 cystoscopy, antimicrobial prophylaxis for, 263-264
- Lower urinary tract (LUT)
 afferent pathways in
 cannabinoids, 1656
 functional properties of, 1651-1654, 1653f
 modulators of, 1654-1656
 nitric oxide in, 1654, 1655f
 pelvic organ interactions with, 1656-1657, 1657f
 properties of, 1650
 purinergic signaling, 1654, 1656f
 spinal cord pathways of, 1650-1651, 1652f, 1652t
 transient receptor potential cation channels, 1654-1656
 aging and, 2084-2085
 anatomy of, 1631-1632, 1632f
 bladder. *See* Bladder, anatomy of urethra. *See* Urethra, anatomy of
- calculi of
 of bladder. *See* Bladder calculi
 preputial, 1299
 prostatic, 1296-1297
 urethral. *See* Urethral calculi
- cytologic examination and culture, for prostatitis, 313-314, 313f-314f, 314b
- drainage of
 anatomic considerations for, 119
 biofilm formation during, 134-135
 catheters used for, 120-121, 120t, 121f
 complications of, 123-124
 historic note on, 119
 indications for, 119-120, 120f
 suprapubic catheterization, 124-126, 125f
 urethral catheterization technique for, 121-123, 123f
- efferent pathways of, 1657-1663, 1658f-1665f, 1662t
- function of, 1836
 normal, 1685
 two-phase concept of, 1685-1687
- HRQOL instruments for, 92t-94t
- MRI of, 56, 57f
- neural control of, 1649-1667, 1754-1755
 parasympathetic pathways, 1649-1650, 1651f
 peripheral nervous system, 1649-1667, 1651f
 somatic pathways, 1650, 1651f-1652f
 supraspinal pathways, 1663-1667, 1666f-1668f
 sympathetic pathways, 1650, 1651f
- obstruction of, secondary bladder calculi with, 1292
- overview of, 1743
- pediatric imaging of
 conventional radiography and fluoroscopy, 2916-2918, 2919f
 CT, 2921
 MRI, 2915-2916
 ultrasonography, 2913-2915, 2917f-2918f
- in pediatric patients. *See* Pediatric patients, lower urinary tract in
- pharmacology of
 adrenergic mechanisms, 1670-1671, 1671f
 afferent neuropeptides, 1671-1673, 1672t
 muscarinic mechanisms, 1667-1670, 1669t
 sex steroids, 1673
 urethral tone in women, 1671
- posterior urethral valves and, 3253-3254, 3254t, 3255f-3256f
- Lower urinary tract (LUT) (*Continued*)
 supraspinal pathways in
 additional regions in, 1666-1667
 brain-bladder control model, 1667, 1668f
 brainstem modulatory mechanisms, 1663, 1666f
 central circuitry regulation of, 1663-1664
 cerebral control of voiding, 1665-1666
 human brain imaging studies in, 1665, 1667f
 modulators in, 1664-1665
 neurotransmitters in, 1664-1665
 pontine micturition center, 1663, 1666f
 symptoms in, patient history of, 3-6, 4t-5t
 transabdominal pelvic ultrasonography of, 75-77, 75f-77f
 trauma and, 1699
 urodynamic studies of, 1718
- Lower urinary tract dysfunction (LUTD), 1673-1683. *See also* Urinary incontinence; Voiding dysfunction
 aging and, 1679-1680, 1680b
 bladder outlet obstruction, 1676-1677, 1677b
 bladder pain syndrome and interstitial cystitis, 1677-1679, 1679b
 bowel dysfunction, 3299
 detrusor underactivity and, 1809
 future research for, 1683-1684
 idiopathic detrusor overactivity, 1673-1675, 1674f
 neurogenic. *See* Neurogenic lower urinary tract dysfunction
- neurologic diseases and
 acute disseminated encephalomyelitis, 1786
 AIDS, 1785-1786
 hereditary spastic paraplegia, 1785
 Lyme disease and, 1785
 reflex sympathetic dystrophy, 1786
 schistosomiasis, 1786
 syringomyelia, 1786
 systemic lupus erythematosus, 1786
 tropical spastic paraparesis, 1785
 tuberculosis, 1786-1787
- neuromodulation for
 to inhibit OAB, rationale for, 1681, 1681f
 inhibitory and excitatory stimulation frequencies, 1681
 onabotulinum toxin A, 1682-1683, 1682f-1683f
 pudendal nerve stimulation, 1681
 sacral, mechanism of action, 1680
 for voiding, rationale for, 1680-1681, 1680f
- neuromuscular. *See* Neuromuscular dysfunction of lower urinary tract
- nocturia, 1676
- overactive bladder, 1673-1675, 1674f
- pediatric. *See* Pediatric patients, lower urinary tract dysfunction in
- psychological associations with, 3299
- signs and symptoms of, 1743-1744, 1744t
- spinal cord injury and neurogenic detrusor overactivity, 1675-1676
- stress urinary incontinence, 1675
- terminology of, 1744-1745, 1744t
- urinary tract infections and, 3298
- vesicoureteral reflux and, 3298-3299
- Lower urinary tract symptoms (LUTS)
 with acute urinary retention, 2457, 2457t
 benign prostatic hyperplasia in, 2425, 2426f, 2463
 cause of, 1838
 as complication of TT, 546
 in detrusor underactivity, 1807, 1808f
 management algorithm for, 2465f-2466f

- Lower urinary tract symptoms (LUTS) (Continued)
 in MetS, 550-551
 with Parkinson disease, treatment of, 1767-1768
 pharmacologic therapy for, 1839t
 prevalence of, 1807, 1837-1838
 questionnaires for, 1703t-1704t
 terminology of, 1744-1745, 1744t
 urodynamic studies of, 1743-1744, 1744t
 evidence-based review of, 1740-1741
 video-urodynamics for, 1736
- Low-grade prostatic intraepithelial neoplasia (LGPIN), 2593
- Low-molecular-weight heparin
 preoperative, 108-110, 108t-109t
 for renal transplantation, 1083
- LP. See Lichen planus
- LPN. See Laparoscopic partial nephrectomy
- LPS. See Lipopolysaccharide
- LRN. See Laparoscopic radical nephrectomy
- LRP. See Laparoscopic radical prostatectomy
- L-RPLND. See Laparoscopic RPLND
- LS. See Lichen sclerosis
- Lubricant, for urethral catheterization, 121-123
- Lumbar notch, 166, 166f
- Lumbodorsal fascia, in retroperitoneum, 770, 770f-771f, 770.e1f
- Lumbosacral plexus, 780, 781f-782f, 781t, 1613f, 1615f, 1618-1619, 1620f, 1622f, 1622t, 780.e1f
- Lumbosacral trunk, 1619, 1620f, 1622t
- Luminal epithelial cells, 2397, 2397f
- Lungs
 development of
 amniotic fluid and, 2978-2979
 clinical implications of, 2949-2950
 in prune-belly syndrome, 3239
- Lupus nephritis, 2860
- LUT. See Lower urinary tract
- LUTD. See Lower urinary tract dysfunction
- Luteinizing hormone (LH), 516-517, 517f, 522, 539-540, 558, 565-566
- Luteinizing hormone receptor abnormality, 3489
- Luteinizing hormone-releasing hormone (LHRH). See Gonadotropin-releasing hormone
- LUTS. See Lower urinary tract symptoms
- LVI. See Lymphovascular invasion
- 17,20-Lyase deficiency, 3490
- Lycopenes
 for benign prostatic hyperplasia, 2500-2501
 in prostate cancer prevention, 2564
- Lyme disease, lower urinary tract dysfunction and, 1785
- Lymph node counts, RPLND outcomes and, 832
- Lymph nodes
 dissection of. See Lymphadenectomy
- iliac, 1601
- Lymphadenectomy. See also specific procedures
 laparoscopic radical nephrectomy with, 1469
 for RCC, 1358-1359, 1358t, 1359f, 1426-1427, 1426f-1427f, 1427.e1f
 in retroperitoneal radical prostatectomy, 2644-2645, 2645f
 for UTUC, 1379-1382, 1381f
- Lymphangiomas, renal, 1312
- Lymphatic drainage
 of bladder, 1621f, 1627-1628
 of kidneys, 973, 973.e1f
 of pelvis
 female, 1601
 male, 1618, 1621f
 of retroperitoneum, 777-778, 778f
 of ureters, 976, 976.e1f
- Lymphatic drainage (Continued)
 of uterus, 1606
 of vulva, 1605
- Lymphatic spread
 of infection, 241
 of UTUC, 1368, 1375
- Lymphedema
 as filariasis clinical manifestation, 443
 genital, 3380-3381
- Lymphocele
 laparoscopic and robotic surgery causing, 224.e1
 after RPLND, 834
- Lymphogranuloma venereum (LGV), 373t, 378
- Lymphoma
 of kidney, 1361t-1362t, 1362-1363
 prostatic, 2600
 retroperitoneal, 1404
 testicular metastases of, 812-813, 3595
- Lymphoreticular malignant neoplasm, of penis, 875
- Lymphovascular invasion (LVI), UTUC with, 1375
- LYs. See Life years
- M**
- M region, 1663
- Machado-Joseph (MJ) disease, lower urinary tract dysfunction and, 1792
- Macrohematuria. See Gross hematuria
- Macrophages, in urinary sediment, 25, 25f
- Macroplastique. See Silicone microimplants
- Magnesium
 in calcium stone formation, 1190
 in crystal formation, 1178
 distal tubule reabsorption of, 1018
 loop of Henle reabsorption of, 1016-1017
 metabolism of, 1181
 PCT reabsorption of, 1015
 supplemental, for enteric hyperoxaluria, 1227
 transport of, urinary tract obstruction and, 1096
- Magnesium preparation, for hypomagnesiuric calcium nephrolithiasis, 1229
- Magnesium salts, for hypomagnesiuric calcium nephrolithiasis, 1229
- Magnetic resonance angiography (MRA), for renovascular hypertension screening, 1031-1032, 1032b
- Magnetic resonance imaging (MRI), 46-47
 for active surveillance of prostate cancer, 2634-2635
 for adrenal masses, 47-49, 48f-51f, 52t
 evaluation of, 1567-1569, 1569f
 in adrenal radiology, 1526
 for biochemical recurrence after radical prostatectomy, 2773
 of bladder RMS, 3584
 contrast media for, 30-31, 47, 56
 cranial, 573, 573f
 and ED, 658
 of female pelvis, 1609, 1609f
 for genitourinary tuberculosis diagnosis, 427
 of IVC tumor thrombus, 1356-1357
 of kidneys, 969, 968.e2f
 for local recurrence diagnosis, 2747
 of locally advanced prostate cancer, 2753, 2754f
 of neuroblastoma, 3561-3562, 3561f-3562f
 pediatric
 lower urinary tract and genitalia, 2915-2916
 upper urinary tract, 2915
 for pelvic floor disorders, 1708
 of pelvic organ prolapse, 1751-1752, 1752f
 of penis, for squamous cell carcinoma, 80
- Magnetic resonance imaging (MRI) (Continued)
 of posterior urethral valves, 3257, 3258f
 for pretreatment prognostic factors for radiation therapy for localized prostate cancer, 2688
 of prostate, 56-57, 508, 508f
 T2-weighted, 58, 58f
 renal, 2906, 2906f
 of renal calculi, pretreatment assessment, 1237
 for renal masses, 50-61, 53f-55f, 56t
 for renal tumor ablative therapy evaluation, 1489, 1489f
 for renal tumor evaluation, 50-61, 53f-55f, 56t, 1316, 1317f
 of retroperitoneal fibrosis, 1144, 1144f
 of retroperitoneal tumors, 1406-1407
 of seminal vesicles, 959-960, 959f-960f
 of seminal vesicles and ejaculatory ducts, 505, 506f
 of ureteral anomalies, 3082, 3083f
 of urethral diverticula, 2159-2160, 2161f
 for urothelial carcinoma, 56, 57f
 for UTIs, 253, 2942
 whole-body, for metastatic disease, 2746-2747
 of Wilms tumor, 3573-3574
- Magnetic resonance urography (MRU)
 of urinary calculi, during pregnancy, 1288-1289, 1288f
 for urinary tract obstruction, 1093
- Magnetip stent, 129
- Mainz II pouch, 2322
- Mainz III, for orthotopic urinary diversion, 2358, 2360f
- Mainz pouch I, 2328-2332, 2329f-2332f
- Mainz repair, for classic bladder exstrophy, 3197-3198
- Major vascular reconstruction, RPLND with, 822-823
- Malacoplakia, 289-290, 289f
- Male climacteric, 519
- Male external genitalia
 anomalies of, 3368.e1t
 acute scrotum. See Acute scrotum
 epididymal and vasal, 3397
 hernia. See Hernia
 hydrocele. See Hydrocele
 penile. See Penile anomalies
 scrotal. See Scrotal anomalies
 varicocele. See Varicocele
 vascular lesions of, 3383-3384
 defect of, in bladder exstrophy, 3187-3188, 3187f-3188f
 development of, 518, 518f
 embryology of, 3368-3369
 skin loss from, 2384-2385, 2384f-2385f, 916.e1-916.e2
 trauma of, 941, 944-945, 2379-2385, 916.e1-2, 916.e1f, 916.e3b
 ultrasonography of, 3368, 3368.e1f
- Male genitalia, benign cutaneous diseases of
 angiokeratomas of Fordyce, 415, 416f-417f
 ectopic sebaceous glands, 416, 416f-417f
 median raphe cysts, 416
 pearly penile papules, 415-416, 416f-417f
 sclerosing lymphangitis, 416
 Zoon balanitis, 416, 416f-417f
- Male genitourinary tract, inflammatory and pain conditions of. See Epididymitis; Orchitis; Prostatitis
- Male infertility
 assisted reproduction, 573, 573.e5, 573.e5t
 causes of, 574-575, 575f
 and childhood diseases, 560-561
 testicular dysgenesis hypothesis, 561.e1

- Male infertility (*Continued*)
 chromosomal abnormalities in, 526-528
 and developmental disorders, 577-578
 diagnoses and therapies, 573-579, 575f, 579b,
 573.e3f-573.e4f, 573.e4b, 573.e5t
 and ejaculatory dysfunction, 578-579
 epidemiology, 556
 and epigenetic anomalies, 574
 and extratesticular dysfunction, 576-577
 and genetic syndromes, 573-574
 and genetics, 561
 and genomic assessment, 570-571
 history of, 556-562, 557t, 562b
 imaging of, 571-573, 572f-573f, 573b, 573.e3f
 abdominal, 573, 573.e2
 and infections and inflammation, 560
 laboratory evaluation of, 564-571, 565b, 566t,
 569f, 571b
 MetS and, 553-554, 554f
 and pediatric surgery, 560
 physical examination of, 562-564, 563f,
 564b
 and pituitary dysfunction, 575-576
 and structural chromosomal anomalies, 574
 and structural sperm abnormalities, 579
 surgical management of
 electroejaculation, 600
 orchiopexy in adults, 610-611, 611f
 sperm retrieval techniques, 600-604,
 601f-603f, 601t, 604t
 surgery of epididymis, 594-599, 595f-599f,
 595t
 surgical anatomy, 581-582, 581b
 testis biopsy, 582-584, 583f
 transurethral resection of ejaculatory ducts,
 599-600, 600f
 varicocele, 604-610, 604f, 604t,
 606f-609f, 606t
 vasography, 584-587, 584f-586f, 587b
 vasovasostomy, 587-594, 588f-589f, 590t,
 591f-594f
 testis histopathology, 573, 573.e3, 573.e3f-
 573.e4f, 573.e4b
- Male lichen sclerosus, 846.e1-846.e2
- Male menopause, 519
- Male orgasm and ejaculation, disorders of
 anatomy and physiology of ejaculatory
 response, 692, 693f
 delayed ejaculation, anejaculation, and
 anorgasmia, 700-707, 702b, 704t, 705b,
 706f, 706t, 707b
 painful ejaculation, 707
 postorgasmic illness syndrome, 707, 707.e1b
 premature ejaculation, 692-700, 694t, 696f,
 697b, 699f, 700b, 701t
 retrograde ejaculation, 707, 707b
- Male patients, catheterization in, 122
- Male pelvis, anatomy of
 anterior abdominal wall, 1611-1614,
 1612f-1615f
 arterial supply, 1615-1617, 1618t, 1620f
 bladder, 1616f, 1619f, 1624-1628,
 1625f-1628f
 bony pelvis of, 1598f, 1611
 innervation of, 1613f, 1615f, 1618-1622,
 1621f-1622f, 1622t
 lymphatics, 1618, 1621f
 musculature of, 1614, 1616f-1618f
 pelvic fascia of, 1614-1615, 1618f
 pelvic ureter, 1619f, 1623-1624
 perineum, 1617f-1619f, 1625f-1626f,
 1628-1630, 1629f
 perineum and perineal body fasciae, 1615,
 1617f-1619f
- Male pelvis, anatomy of (*Continued*)
 rectum, 1612f, 1617f, 1622-1623, 1623f,
 1625f
 soft tissues of, 1614-1615, 1616f-1619f
 urethra, 1635-1636, 1636f
 vasculature of, 1615-1618, 1618t, 1620f-1621f
 venous supply, 1617-1618, 1621f
 viscera, 1622-1628
- Male reproductive system. *See also specific organs*
 anatomy of
 epididymis, 501-503, 502f-504f, 503b, 946,
 947b, 947f
 penis, 511-513, 513b, 910.e1-3, 910.e1f-
 910.e7f, 910.e5, 910.e8b
 prostate, 506-508, 506f-508f, 509b
 scrotum, 513-514, 514b, 515f, 946, 947b,
 947f
 seminal vesicles and ejaculatory ducts, 505,
 505b, 506f, 957-958, 957f-958f
 spermatozoa, 535-537, 536f, 537b
 testis, 498-501, 499f-502f, 502b
 urethra, 119, 509f-511f, 511-512, 511b, 917,
 1635-1636, 1636f, 910.e1-910.e2,
 910.e2f-910.e3f
 vas deferens, 503-505, 504f, 505b, 946,
 947b, 947f
 pediatric tumors of
 paratesticular RMS, 3596-3597, 3597b
 testicular. *See* Testicular tumors
 physiology of, 516
 epididymis, 529-533, 529f-532f, 533b
 HPG axis. *See* Hypothalamic-pituitary-
 gonadal axis
 seminal vesicle and ejaculatory ducts,
 534-535, 534f-535f, 535b
 spermatozoa, 535-537, 536f, 537b
 testis, 519-529, 519f-522f, 524f-527f, 527t,
 528b-529b
 vas deferens, 533-534, 535b
 regenerative medicine for, 492-493, 493f-
 494f, 492.e2
- Male sterilization, for vasectomy, 950-951
- Malecot catheters, as nephrostomy tubes, 171,
 171f
- Males, urinary specimen collection in, 12
- Malignancy
 hematuria as sign of, 2-3, 184, 184t, 185b,
 192
 PC-RPLND findings of, survival outcomes
 associated with, 830, 830t
 in renal transplant candidates, 1072
 after renal transplantation, 1087
 Malignancy-associated hypercalcemia, 1185
 Malignant fibrous histiocytoma, retroperitoneal,
 1405
 Malignant lesions, adrenal, 1558b
 adrenal cortical carcinoma, 1531-1566, 1557f,
 1557t-1558t, 1558b, 1559f, 1560b
 malignant pheochromocytomas, 1545-1547,
 1552
 neuroblastoma. *See* Neuroblastoma
 Malignant pheochromocytoma, 1545-1547,
 1552
- Malrotation, of kidney, 969, 969.e2f
- Mammalian target of rapamycin (mTOR)
 inhibitors, for metastatic RCC, 1502-1503,
 1514-1515, 1514t, 1515f, 1517
 in RCC, 1325t, 1327
- Management principles, of ED
 cardiac risk assessment, 646, 646f
 early detection, 645, 645t
 follow-up care, 647
 goal-directed management, 645
 role of partner interview, 646
- Management principles, of ED (*Continued*)
 shared decision making and treatment
 planning, 646
 specialist referral, 646-647
 step-care approach, 646
 Mannitol, for AKI, 1050
 Manual dexterity, orthoptic urinary diversion
 and, 2350
 Manual dilation, for achieving retroperitoneal
 access and developing retroperitoneal
 space, 201.e4
 Marionette stitch, for minimally invasive urinary
 diversion, 2371, 2371f
 Markers. *See* Biomarkers
 Marshall-Marchetti-Krantz (MMK) procedure,
 1920-1921, 1920f
 Burch colposuspension comparison with,
 1936
 results with, 1925
 technique for, 1924-1925, 1924f
 Martius flap, in vesicovaginal fistula repair, 2116,
 2118f
 Masculinized female. *See* 46,XX DSD
 Mast cells, in BPS/IC etiology, 345.e4-345.e6,
 345.e4f, 345.e6b
 Maternal anemia, from bacteriuria in pregnancy,
 295
 Matrix
 of bladder wall, 1635
 of renal calculi, 1179
 Matrix stones, 1196
 composition of, 1242-1243, 1242f
 imaging of, 1242, 1243f
 Maturation arrest, 573.e3, 573.e4f
 Maximum urethral closure pressures (MUCPs),
 for sling procedure, 1987, 1989
 Maximum voided volume (MVV), 1824
 Mayer-Rokitansky-Küster-Hauser syndrome
 (MRKH), 2983, 3495
 MCDK. *See* Multicystic dysplastic kidney
 MCKD. *See* Medullary cystic kidney disease
 MCT. *See* Medullary collecting tubule
 MDCT. *See* Multidetector CT
 MDRD formula. *See* Modification of diet in
 renal disease formula
 MDSCs. *See* Muscle-derived stem cells
 Meatal stenosis, 3371-3372, 3372f, 3421
 urethral, reconstructive surgery for, 914-915
 MEC. *See* Methotrexate, etoposide, and cisplatin
 Mechanical assistants, for laparoscopic and
 robotic surgery, 209.e2
 Mechanical index (MI), in ultrasonography, 73
 Mechanical injury, during laparoscopic and
 robotic surgery, 221
 Mechanical properties, of ureters, 988
 force-length relations, 988-989, 989f
 force-velocity relations, 989, 990f
 pressure-length-diameter relations, 989, 990f
 Mecholyl. *See* Methacholine
 Medial fibroplasia, renovascular hypertension
 caused by, 1033, 1033t, 1034f
 Medial hyperplasia, 1033, 1033t
 Median raphe cysts, 416
 Medical conditions, urinary incontinence and,
 1749
 Medical devices, in ED, 666
 Medical expulsive therapy (MET), for ureteral
 calculi, 1251
 in megaureter, 1253
 stone localization and, 1251-1252
 Medical history, 7-9, 8t
 adrenal surgery and, 1579
 Medical management, in schistosomiasis
 treatment, 440-441

- Medical records, retrospective review of, 97
- Medical therapy
for adrenal cortical carcinoma, 1559-1560
for genitourinary tuberculosis treatment, 428-430, 429f-430f
- Medical Therapy of Prostatic Symptoms (MTOPS) trial, 2488-2489, 2489f-2490f, 2491f
- Medication change, for ED, 659
- Medication optimization, in geriatric patient, 2092-2095, 2093f-2094f
- Medication-related stones, 1196-1197
surgical management of, 1243.e3
- Medications. *See also* Drugs
benign prostatic hyperplasia and, 2444
patient history of, 7, 8t
transient urinary incontinence and, 2096.e1
- Medrol. *See* Methylprednisolone
- Medullary collecting tubule (MCT), functions of, 1019
- Medullary cystic kidney disease (MCKD), 3014t, 3021-3023
clinical features of, 3022
evaluation of, 3022-3023, 3022f
genetics of, 3014t, 3021-3022
treatment of, 3023
- Medullary sponge kidney (MSK), 3036-3038, 3037f
clinical features of, 3037
diagnosis of, 3037-3038
histopathology of, 3037
prognosis of, 3038
renal calculi and, 1198-1199
treatment of, 3038
- Megacalycoses, 3002-3003, 3002f
- Megacystis-megaureter association, 3152
- Megalourethra, prenatal, 2884, 2884f
- Megaureter
definition of, 3066-3067
pediatric. *See* Pediatric patients, megaureter in
ureteral calculi in, surgical management of, 1253
- Meiosis, testis germ cells, 526-527, 527t
- Melanocortin-receptor agonists, 664
- Melanocortins, in ED, 622, 623t
- Melanoma
as neoplastic condition, 414
of penis, 873-874, 874f
- Melatonin, 518-519
- Membrane potential, of smooth muscles, of
bladder, 1644-1645, 1644f
- Membranoproliferative glomerulonephritis (MPGN), 1058
- Membranous glomerulonephritis (MGN)
renal vein thrombosis with, 1049
with RPE, 1144
- Membranous urethra, 509-510, 510f-511f, 910.e1-910.e2, 910.e2f
carcinoma of, 882-883, 882f-883f
- Memokath 051 stents, 127
- MEN. *See* Multiple endocrine neoplasia
- Meningocele, lower urinary tract dysfunction with, 1779-1780
- Men's health, integrated
androgen deficiency. *See* Androgen deficiency
cardiovascular disease and testosterone, 547-549, 549b
metabolic syndrome and urologic diseases, 549-554, 550t, 554b, 554f
- Mental State Examination (MMSE), 2088
- Meperidine (Demerol), urethral function effects of, 1004
- 2-Mercaptoethane sulfonate, for hemorrhagic cystitis, 188-189
- α -Mercaptopyropionylglycine, for cystinuria, 1229-1230
- Mesenchymal condensation, 2394-2395
- Mesenchymal tumors, of prostate, 2599
- Mesenchymal-derived stem cells (MSCs),
for female SUI injection therapy, 2061-2062
- Mesenchymal-epithelial transition signaling, in
castration-resistant prostate cancer, 2817-2818
- Mesenteric blood flow, pneumoperitoneum effects on, 213-214
- Mesh complications, 2039, 2039b
in midurethral sling
exposure of, 2026-2028, 2026f, 2027t, 2028b
perforation of bladder, 2029-2031, 2031f, 2032t, 2033b
perforation of urethra, 2028-2029, 2028f, 2030t, 2033b
in pelvic reconstructive surgery, 2041-2043
anatomy of, 2041-2043
etiology of, 2041, 2042f-2043f
evaluation of, 2043-2045, 2044f-2045f, 2045t
excision of, 2046, 2047f
in gastrointestinal tract and surrounding structures, 2042-2043
in genitourinary tract and surrounding structures, 2041-2042, 2043f
in pelvic floor, 2042
terminology for, 2045, 2045t
treatment of, 2045-2047, 2047f
in vagina, 2042
- Mesh excision, laparoscopic or robotic, 2279-2280, 2279f-2280f
- Mesonephric duct, ureteral development from, 978-979
- Mesonephros, 2823-2826, 2827f
- Mesotheliomas, of testicular adnexa, 813
- Mesovarium, 1607
- MESTs. *See* Mixed epithelial and stromal tumors
- MET. *See* Medical expulsive therapy
- MET gene, systemic therapy targeting, 1517-1518, 1517f
- Meta-analyses, inherent weaknesses of, 2500, 2500b
- Metabolic acidosis, renal pathophysiology involved in, 1025-1026, 1025b
- Metabolic alkalosis, 1026, 1026t
- Metabolic changes, with aging, 2084
- Metabolic disorders, after percutaneous access to
upper urinary tract collecting system, 180
- Metabolic state
laparoscopic and robotic surgery effects on, 214
pneumoperitoneum effects on, 214
- Metabolic syndrome (MetS)
benign prostatic hyperplasia and, 2442-2444, 2445t
CVD and, 551, 553
ED, 639-641
hormonal therapy and, 2795
nephrolithiasis and, 1219-1220, 1220b
renal calculi and, 1172-1173
sleep duration and, 1822-1823
urologic diseases and, 549-550, 554b
BPE and LUTS, 550-551
cancer, 554
definition of, 549-550, 550t
ED, 553
epidemiology of, 549-550
male infertility, 553-554, 554f
prostatic diseases, 551
urinary incontinence, 551-552
urinary stones, 552-553
- Metabolomics, for prostate cancer biomarkers, 2039-2040
- Metanephric adenofibroma, in pediatric patients, 3580
- Metanephric adenoma, of kidney, 1303-1304, 1303f-1304f, 1304b
- Metanephric testing, in pheochromocytoma
diagnostic tests, 1549, 1549f, 1574t
- Metanephros, 2826, 2827f-2828f
- Metaplasia, of upper tract urothelium, 1369
- Metastasectomy, in advanced RCC, 1503, 1504b
- Metastasis
adrenal
disorder, 1560-1562, 1561f, 1562b
MRI of, 48-49, 50f-51f
brain. *See* Brain metastases
neuroblastoma with, 3561
penile, 875-876
of penile cancer, 852
ILND for. *See* Inguinal lymphadenectomy
primary tumor histology in prediction of, 861-862, 861t-862t
prognostic significance of, 856-858, 857t-859t
radiation therapy for, 870-871
risk-based management for, 865-868, 866f-867f
from prostate, castration-resistant, 2806-2807
of RCC. *See* Metastatic RCC
renal, 1361t, 1363
after renal tumor ablative therapy, 1493
of retroperitoneal sarcomas, 1406
testicular, 812-813, 3595
of UTUC, 1368, 1374
restaging for, 1402
treatment of, 1400-1401, 1401f
- Metastatic bladder cancer
chemotherapy for, 2237-2238, 2237t
randomized trials in, 2237t, 2238
second-line chemotherapy for, 2238, 2238t
multiagent, 2239-2240
single agent, 2238-2239, 2239t
targeted therapy for, 2240
- Metastatic RCC, 1338, 1340, 1359-1360
treatment of, 1500
chemotherapy, 1516
debulking or cytoreductive nephrectomy, 1501-1503, 1502f, 1503b, 1503t
hormonal therapy, 1516
palliative surgery, 1503, 1504b
prognostic factors and, 1500-1501, 1501f, 1501t
resection of metastases, 1503, 1504b
systemic therapy for non-clear cell variants, 1516-1518, 1517f
targeted molecular therapies, 1502-1503, 1507-1516, 1508f-1512f, 1509t-1511t, 1513t-1514t, 1515f
treatment of advanced, immunologic approaches, 1503-1507, 1504t-1505t, 1506f, 1507t
- Metformin
contrast media interactions with, 30
in prostate cancer prevention, 2562
- Methacholine (Methocholyl), ureteral response to, 990-991
- Methotrexate
for BPS/IC oral therapy, 353t, 355
for penile cancer, 872-873
- Methotrexate, etoposide, and cisplatin (MEC),
for UTUC, 1400
- Methotrexate, vinblastine, Adriamycin, and
cisplatin (MVAC), for UTUC, 1400
- Methotrexate, vinblastine, epirubicin, and
cisplatin (MVEC), for UTUC, 1400
- Methoxamine, for stress urinary incontinence in
women, 1867

- α -Methylacyl coenzyme A racemase (AMACR) gene, as prostate cancer biomarker, 2575
- Methylation. *See* DNA methylation
- Methylene blue
for pelvic floor disorder testing, 1705
toxicity of, 1159
ureteral response to, 988
- Methylprednisolone (Medrol), premedication with, for preventing contrast media reactions, 29, 29b
- Methysergide (Sansert), with RPE, 1144
- Metoclopramide, to facilitate bladder emptying, 1871-1872
- Metronidazole
preoperative prophylaxis with, 106t-107t
prophylaxis with, for uncomplicated urologic procedures, 261t-262t
- MetS. *See* Metabolic syndrome
- MGN. *See* Membranous glomerulonephritis
- MH. *See* Microhematuria
- MHCs. *See* Myosin heavy chains
- MI. *See* Mechanical index
- Microbiology
prostatitis and CPPS, 305-307
TB, 421
- Microdeletions, of AZF region, 528
- Microductal aplasia, 577-578
- Microexplosive generator, for shock wave lithotripsy, 1266-1267
- Microhematuria (MH), 183
diagnostic criteria for, 183
differential diagnosis of, 184, 184t, 188
evaluation of patients with, 184-186, 184t, 185b, 186f, 187b
cystoscopy in, 186-187
natural history in, 187
upper urinary tract imaging in, 187
urine cytology and urinary biomarkers in, 187
microscopic evaluation for, 183
patient selection for evaluation of, 184-185
screening for, 185
symptomatic, 188, 191b
- Microolithiasis, testicular, in pediatric patients, 3595
- Micropapillary urothelial carcinoma (MPUC), 1370, 2200, 2200f
- Micropenis, 3369t, 3376-3377, 3376f, 3368.e1t
- Microphotograph
of ejaculatory duct, 535f
of testis, 527f
- MicroRNA (miRNA), as prostate cancer biomarker, 2575
- Microsatellite instability, in UUTUC, 1376
- Microscopic analysis, of urinary sediment. *See* Sediment analysis
- Microscopic hematuria, 185b
patient history of, 2-3
- Microscopic reversal, of vasectomy, 951-952
- Microvascular replantation, of penis, 916.e1, 916.e1f
- Microwave ablation (MWA), for renal tumors, 1498
- Microwave hyperthermia and thermotherapy, for prostatitis, 326-327
- Micturition
brainstem modulatory mechanisms of, 1663, 1666f
cerebral control of, 1665-1666
mechanics of, 1649
neuromodulation for, rationale for, 1680-1681, 1680f
nitric oxide and, 1654
- Micturition (Continued)
in pediatric patients
control development of, 3123-3125
evolution of, 3123-3125, 3124f
physiology of, 1729, 1730f
pontine micturition center in, 1663
reflex circuitry controlling, 1660-1663, 1660f
emptying phase, 1661-1662, 1661f, 1662t
urethra to bladder reflexes, 1662-1663, 1663f-1665f
- Micturition cycle
bladder emptying/voiding in, 1685
failure of, pathophysiology of, 1689b, 1690-1691
urodynamic studies of, 1729-1734
bladder filling/storage in, 1685
failure of, pathophysiology of, 1688-1691, 1689b
urodynamic studies of, 1725-1729
dysfunction of, 1761, 1762t
phases of, 1685
mechanisms underlying, 1685-1687
- Micturitional urethral pressure profile (MUPP), 1732
- Midazolam, preoperative considerations for, 111-112
- Midodrine, for stress urinary incontinence in women, 1867
- Midurethral sling (MUS), 2008-2037
anatomy of, 2010b
complications of, 2026-2037, 2026.e1t-2026.e2t
bleeding after, 2036-2037, 2026.e1t-2026.e2t
infection and pain after, 2031-2033
mesh exposure in, 2026-2028, 2026f, 2027t, 2028b
mesh perforation of bladder, 2029-2031, 2031f, 2032t, 2033b
mesh perforation of urethra, 2028-2029, 2028f, 2030t, 2033b
regulatory and legal issues related to, 2037
serious, 2037
sexual dysfunction after, 2036
trocar injury to urinary tract, 2028
voiding dysfunction after, 2016t-2017t, 2019t, 2033-2036, 2034t-2035t, 2036b
evolution of, 1987-1988
materials for, 2010, 2010b
mechanics of, 2008-2009, 2010b
operative procedures for, 2010-2015
anesthesia for, 2010-2011
patient counseling for, 2010
positioning for, 2011-2012
preparation for, 2011-2012
outcomes of, 2015-2019
in elderly patients, 2023-2024, 2024b
for intrinsic sphincter deficiency, 2020-2021
for mixed urinary incontinence, 2019-2020
in obese patients, 2024, 2024b, 2025t
for pelvic organ prolapse, 2022-2023
for recurrent SUI, 2021-2022, 2022b
- retropubic
anatomy for, 2009
complications of, 2026-2037, 2028f
outcomes with, 2015-2017, 2016t
removal of, 2046
surgical approach to, 2012-2013, 2012f-2013f
- Midurethral sling (MUS) (Continued)
single-incision
anatomy for, 2010
complications of, 2026-2037, 2028f
outcomes with, 2018-2019, 2019t
surgical approach to, 2013-2015, 2014f
- transobturator
anatomy for, 2009-2010
complications of, 2026-2037, 2028f
in-to-out surgical approach, 2013, 2014f
outcomes with, 2017-2018, 2017t
out-to-in surgical approach, 2013
removal of, 2046
- Migration, of ureteral stents, 132
- Mild androgen insensitivity syndrome, 3492
- Mild nonidiosyncratic reactions, to intravascular iodinated contrast media, 28-29
- Milnacipran hydrochloride, to facilitate bladder filling and urine storage, 1857
- Mineral metabolism, 1182b
calcium, 1180
magnesium, 1181
oxalate, 1181
phosphorus, 1180-1181
- Mineralocorticoids, in adrenal histology, 1529, 1530t
- Mini-Cog, 2088, 2089f
- Minimally invasive and endoscopic management of benign prostatic hyperplasia
defining outcomes for, 2505-2509
comparing to other treatments, 2507-2509, 2508t
response rates, 2505-2506
secondary procedures, 2506-2507
epidemiology of, 2498b, 2504-2505
failed, failing, and future directions for, 2534
prostate embolization, 2534.e2-2534.e3
prostate stents, 2534.e1
prostate urethral lift, 2534.e1, 2534.e1f-2534.e2f
prostatic injections, 2534.e3-2534.e4
increasing age and, 2505
laser treatments, 2526-2534, 2534b
holmium laser enucleation of prostate. *See* Holmium laser enucleation of prostate
photoselective vaporization of prostate. *See* Photoselective vaporization of prostate
safety for, 2527
thulium resection. *See* Thulium laser
- marketshare, 2498b, 2504
- nonlaser options for, 2510-2526
bipolar transurethral resection of prostate. *See* Bipolar transurethral resection of prostate
monopolar transurethral resection of prostate. *See* Monopolar transurethral resection of prostate
transurethral incision of prostate. *See* Transurethral incision of prostate
transurethral microwave therapy. *See* Transurethral microwave therapy
transurethral needle ablation of prostate. *See* Transurethral needle ablation
transurethral vaporization of prostate. *See* Transurethral vaporization of prostate
presurgical factors for, 2509-2510, 2510b
antibiotic coverage for, 2509-2510
histologic specimen for, 2510
matching treatment with patient, 2510
treatment indications, 2509
workup for, 2505, 2506f-2507f

- Minimally invasive surgery (MIS). *See also specific surgeries*
 advantages of, 2963
 disadvantages of
 contraindications, 2965
 cost, 2964-2965
 learning curve, 2964, 2964f
 pediatric patient size, 2965
 laparoscopic. *See* Laparoscopic surgery
 penetrance of, among urologists, 1482
 robotic. *See* Robotic surgery
- Minimally invasive therapies, for CP/CPPS
 treatment, 326-327
- Minimally invasive urinary diversion
 complications with, 2376, 2377f
 functional outcomes with, 2376
 future direction for, 2378
 history of, 2369, 2369b
 hospital stay for, 2376
 ileal conduit creation, 2370-2373, 2370t
 bowel restoration, 2373, 2373f
 bowel segment isolation, 2371-2372, 2372f
 bowel selection for, 2370-2371
 conduit creation, 2371-2372, 2372f
 left ureter transfer for, 2370-2371
 marionette stitch, 2371, 2371f
 prestoma preparation, 2373
 ureteroileal anastomosis, 2372-2373, 2372f-2373f
 intracorporeal *versus* extracorporeal, 2376-2378
 learning curve for, 2376
 modified Studer neobladder creation, 2371t, 2374-2375, 2375b
 bowel detubularization, 2374
 bowel isolation, 2374
 closure of neobladder, 2375
 neobladder creation, 2374, 2374f
 neobladder-urethral anastomosis, 2374, 2374f
 uretero-neobladder anastomosis, 2374, 2374f-2375f
 operative technique for, 2375-2376, 2376t
 outcomes with, 2375, 2378b
 patient position for, 2370, 2371b
 patient selection for, 2369, 2370b
 port placement for, 2370, 2371b
 postoperative care for, 2375, 2375b
 preoperative care for, 2369, 2370b
- Minimally invasive vasectomy, 949-950, 950f-951f
- Mirabegron, 1670, 1714
 adverse effects of, 1855
 for benign prostatic hyperplasia, 2492-2493
 for diminished bladder, 1831, 1832t-1834t
 efficacy of, 1854-1855
 to facilitate bladder filling and urine storage, 1839t, 1854-1855
 with antimuscarinics, 1860
 pharmacokinetics of, 1854
 tolerability of, 1855
 for urinary incontinence, in geriatric patients, 2099.e4
- miRNA. *See* MicroRNA
- MIS. *See* Minimally invasive surgery; Müllerian-inhibiting substance
- Mismatch repair (MMR), 465.e1, 465.e1f
- Misoprostol, for BPS/IC oral therapy, 353t, 355
- Mitchell repair, for classic bladder exstrophy, 3197, 3198f
 continence outcomes with, 3213-3214
 technical aspects of, 3202, 3204f
- Mitomycin C (MMC)
 for non-muscle-invasive bladder cancer, 2215-2216, 2216t
 for UTUC, 1379, 1398-1399
- Mitosis, deregulation of, in GU cancers, 461.e1-461.e2
- Mitotic arrest, deregulation of, 461.e2
- Mitoxantrone, 2807-2808
- Mitrofanoff principle
 for continent urinary diversions, 3361-3363
 following pediatric urethral trauma, 3557
- Mixed epithelial and stromal tumors (MESTs), of kidney, 1309-1310, 1310b, 1311f
- Mixed gonadal dysgenesis, 3480-3481, 3481f, 3482t
- Mixed mesenchymal and epithelial tumors, renal, 1309, 1310b, 1310f-1311f
- Mixed urinary incontinence (MUI)
 definition of, 1710, 1744-1745, 1744f
 midurethral sling for, outcomes of, 2019-2020
 OAB and, 1802, 1803f
 pubovaginal sling for, outcomes of, 2003
 treatment of, 1716
- MJ disease. *See* Machado-Joseph disease
- MLCs. *See* Myosin light chains
- M-line measurement, 1609, 1609f
- MMC. *See* Mitomycin C
- MMK procedure. *See* Marshall-Marchetti-Krantz procedure
- MMR. *See* Mismatch repair
- MMSE. *See* Mental State Examination
- MN-9. *See* Carbonic anhydrase IX
- Moderate nonidiosyncratic reactions, to
 intravascular iodinated contrast media, 29
- Modern staged reconstruction, of cloacal exstrophy, 3228f-3230f, 3230-3231
- Modern staged repair of exstrophy (MRSE), 3198
 bladder, posterior urethral, and abdominal wall closure for, 3198-3201, 3199f-3200f
 combined bladder closure and epispadias repair, 3201
 management after, 3201-3202
- Modification of diet in renal disease (MDRD) formula, 1009
- Modified Cantwell-Ransley repair, for classic bladder exstrophy, 3204, 3205f-3206f
- Modified complete ILND, for penile cancer, 864, 895-896, 895f-896f
- Modified Young-Dees-Leadbetter bladder neck reconstruction, 3205f-3206f
- Modulators, within brainstem networks, 1664-1665
- Mohs micrographic surgery, for penile cancer, 855
- Mole, 418f, 419
- Molecular genetics of GU cancers, 459
 apoptosis, 479-480, 481b
 extrinsic pathway of, 479.e1-479.e2, 479.e1f-479.e2f
 intrinsic pathway of, 479.e1, 479.e1f
 basic concepts for
 chromosomes and gene structure, 459.e4
 DNA, 459.e1-459.e3, 459.e2f
 protein synthesis, 459.e3-459.e4, 459.e3f-459.e4f
 transcription, 459.e3, 459.e3f
 cell cycle deregulation, 460-461, 462b
 CDKs, 461-462, 461f
 cell cycle entry, 461.e1
 cell cycle progression through S phase, 461.e1
 cyclin-dependent kinases and cyclins, 461f, 461.e1
 G₁/S checkpoint, 461.e2
 G₂/M checkpoint, 461.e2
 mitosis, 461.e1-461.e2
 mitotic arrest and spindle assembly
- Molecular genetics of GU cancers (Continued)
 RB1, 461, 461.e1
 S phase arrest, 461.e2
 TP53, 462, 462f, 461.e2
 DNA damage and repair, 464-465, 465b
 DSB repair, 465.e1-465.e2, 465.e1f-465.e2f
 mechanisms of, 465.e1, 465.e1f
 DNA methylation, 462-463, 464b
 in bladder cancer, 463-464
 in prostate cancer, 463
 genomic alterations, 465, 476b
 in bladder cancer, 472-474
 in bladder RMS, 3582-3583
 CNAs, 467-468, 468t
 gross chromosomal abnormalities, 465-466, 465b
 neuroblastoma, 3559-3560
 in prostate cancer, 466-471, 468t, 469f
 in renal cancer, 467, 468t, 471-472, 1321-1325, 1322t-1323t, 1323f
 in testicular cancer, 467, 474-475, 3591
 in UTUC, 1375-1376
 in Wilms tumor, 468t, 3568-3570, 3568t, 3574
 oncogenes, 460, 460b
 stem cells, 480-481, 481b
 telomerase, 475-476, 477f, 478b
 chromosome stabilizing activity of, 477
 as potential diagnostic marker, 477-478
 therapies based on, 478
 telomeres, 475-476, 478b
 cancers and premalignant lesions with short, 476-477
 chromosomal instability and, 476
 prostate cancer prognosis using, 478
 as tumor suppressive mechanism, 476, 477f
 terminology for, 459.e1b-459.e2b
 tumor suppressor genes, 459-460, 460b, 460f
- Molecular mechanisms, in female sexual response, 750, 750.e7
- Molecular therapies, and radiation therapy for localized prostate cancer, 2709-2710
 enzyme/prodrug gene therapy, 2710
 immunotherapy, 2709
 oncolytics, 2710
 radio-gene therapy, 2709-2710
 targeted RNA-based therapy, 2709
- Molluscum contagiosum, 380-381, 380f
- Monfort technique, 3247-3249, 3247f-3249f
- Monitored anesthesia care, preoperative considerations for, 111
- Monopolar electrosurgery
 argon beam coagulator for, 225-226, 207.e1
 devices for, 227
 in laparoscopic and robotic surgery, 206
 generator settings for, 226
 physics of, 225, 226f
 safety of, 226-227
- Monopolar transurethral resection of prostate (M-TURP), 2510-2516
 in anticoagulated patient, 2513-2514
 complications with, 2514-2516
 intraoperative, 2514-2515
 perioperative, 2514-2515
 postoperative, 2515-2516
 conclusion for, 2516
 outcomes with, 2513
 technique for, 2510-2513
 intraoperative, 2511-2513, 2512f, 2511.e1f
 postoperative, 2513
 preoperative, 2510-2511
- Mons pubis, 1604, 1605f-1606f
- Montelukast, for BPS/IC oral therapy, 353t, 355
- Monti procedure, for ureteral injury, upper, 1163
- Morcellation instrumentation, for laparoscopic and robotic surgery, 209, 209.e1

- Morphine
for pediatric patients, 2957-2958, 2957t
urethral function effects of, 1004
- Mortality
with benign prostatic hyperplasia, 2455
early, nocturia and, 1821-1823
with locally advanced prostate cancer, 2755, 2756f
after RPLND, 835
- Mortality rates, of prostate cancer, 2543, 2544f
global, 2544-2545
screening effects of, 2545-2546
- Motility, sperm, 531, 531f-532f
- Motor nerve innervation, in detrusor muscle, 1635, 1635f, 1649, 1650f
- mPEG-DOPA₃ stents, 128
- MPGN. *See* Membranoproliferative glomerulonephritis
- mpMRI. *See* Multiparametric magnetic resonance imaging
- MPUC. *See* Micropapillary urothelial carcinoma
- MRA. *See* Magnetic resonance angiography
- MRI. *See* Magnetic resonance imaging
- MRKH. *See* Mayer-Rokitansky-Küster-Hauser syndrome
- MRSE. *See* Modern staged repair of exstrophy
- MRU. *See* Magnetic resonance urography
- MS. *See* Multiple sclerosis
- MSA. *See* Multiple system atrophy
- MSCs. *See* Mesenchymal-derived stem cells
- MSK. *See* Medullary sponge kidney
- MTOPS trial. *See* Medical Therapy of Prostatic Symptoms trial
- mTOR. *See* Mammalian target of rapamycin
- M-TURP. *See* Monopolar transurethral resection of prostate
- Mucosal plexus, 1633
- MUCPs. *See* Maximum urethral closure pressures
- Mucus, after augmentation cystoplasty, 3352
- MUI. *See* Mixed urinary incontinence
- Müllerian aplasia, 3461-3462, 3461f
- Müllerian duct, 2975-2976, 2976f
- Müllerian-inhibiting substance (MIS), 518, 518f
- Multichannel UDS, 1706, 1730f
- Multicystic dysplastic kidney (MCDK), 3028-3031, 3028f
clinical features of, 3029
etiology of, 3028
evaluation of, 3029-3030, 3029f-3030f
histopathology of, 3029, 3029f
prognosis of, 3030-3031
treatment of, 3030-3031
vesicoureteral reflux and, 3151-3152
- Multidetector computed tomography urography (CTU), for urinary tract obstruction, 1092
- Multidetector CT (MDCT), 40, 41f
- Multidrug-resistant tuberculosis, 432
- Multilocular cystic nephroma. *See* Solitary multilocular cyst nephroma
- Multiparametric magnetic resonance imaging (mpMRI), for prostate cancer localization, 2724-2727
biopsy guided with, 2724
cognitive targeted biopsies with, 2724
ultrasound fusion, 2724-2727, 2725f-2727f
- Multiple endocrine neoplasia (MEN), genomic alterations in, 468t
- Multiple malformation syndromes with renal cysts, 3014t, 3023-3028, 3028b
tuberosus sclerosis complex. *See* Tuberosus sclerosis complex
- von Hippel-Landau disease. *See* von Hippel-Landau disease
- Multiple sclerosis (MS)
cause of, 1769
lower urinary tract dysfunction and, 1768-1770, 1769b
overview of, 1768-1769
sacral nerve stimulation for, 1906-1907
treatment for, 1769-1770
- Multiple system atrophy (MSA), lower urinary tract dysfunction with, 1768
- MUPP. *See* Micturitional urethral pressure profile
- MUS. *See* Midurethral sling
- Muscarinic cholinergic agonists, ureteral response to, 987-988
- Muscarinic receptors
in bladder function, 1640
contraction, 1836-1837
distribution of, 1837-1839, 1838t
pharmacology of, 1667-1670, 1669t, 1670b
for detrusor underactivity, 1818
selectivity of, 1670
- Muscle relaxants, for CP/CPPS treatment, 323
- Muscle-derived stem cells (MDSCs), for female SUI injection therapy, 2061-2062
- Muscle-invasive bladder cancer
adjuvant chemotherapy for, 2231-2233
randomized trials of, 2231-2233, 2232t
bladder preservation with, 2233-2235
partial cystectomy, 2233-2234
primary chemotherapy, 2234
radiation monotherapy, 2234
radical transurethral resection, 2233
single modality treatment for, 2233-2234
trimodal therapy for, 2234-2235, 2235t
clinical presentation of, 2223-2225
clinical staging for, 2223-2224, 2224t
diagnosis of, 2223-2225
grossly positive nodes and, 2228-2229
histology of, 2223
natural history of, 2223
neoadjuvant chemotherapy for, 2230-2231, 2231t
pathologic staging for, 2225, 2225t
presentation of, 2223-2225
prognostic nomograms for, 2235-2237, 2236f
radical cystectomy and pelvic lymph node dissection for, 2225-2230. *See also* Radical cystectomy, with pelvic lymph node dissection
ureter involvement with, 2228-2229
- Muscles. *See also specific muscles*
of abdominal wall, anterior, 1611-1613, 1613f
of pelvic floor
female, 1601, 1603f
male, 1614, 1616f-1618f
in prune-belly syndrome, 3240
skeletal. *See* Skeletal muscle
smooth. *See* Smooth muscles
striated. *See* Striated muscles
- Muscular supports, of pelvic floor, 1939-1941, 1940f-1941f
- Musculoskeletal dysfunction, and sexual pain disorders, 763
- MVAC. *See* Methotrexate, vinblastine, Adriamycin, and cisplatin
- MVEC. *See* Methotrexate, vinblastine, epirubicin, and cisplatin
- MVV. *See* Maximum voided volume
- MWA. *See* Microwave ablation
- Myasthenia gravis, lower urinary tract dysfunction and, 1790
- Mycobacterium tuberculosis*, 242
- Mycophenolate, for post-transplant immunosuppression, 1084-1085, 1085t
- Mycophenolate mofetil (CellCept), for BPS/IC oral therapy, 354
- Mycoplasma genitalium*, 372
- Myelodysplasia
early intervention in, 3275-3277
renal dysfunction in, 3277
sexuality and, 3277-3279
- Myelolipoma
adrenal, MRI of, 47-48, 49f
as benign lesion, 1564-1565, 1564f, 1565b
- Myelomeningocele
lower urinary tract dysfunction with, 1779-1780
neurogenic bowel dysfunction in, 1775-1776
prenatal, 2884-2885
prenatal closure of, 3274
- Myocardial infarction, preoperative, 101
- Myofibroblasts, 1640, 1640f, 1648
and PD, 728-729
- Myoplasty
stimulated, 2081
for storage failure, 2072
- Myosin, in thick filaments, 1641, 1642f
- Myosin heavy chains (MHCs), 1641, 1642f
- Myosin light chains (MLCs), 1641
- Myotonic dystrophy, lower urinary tract dysfunction and, 1791
- N**
- N₂O. *See* Nitrous oxide
- NAATs. *See* Nucleic acid amplification tests
- NAD. *See* Neoadjuvant androgen deprivation
- Naftopidil
for benign prostatic hyperplasia, 2480
to facilitate bladder filling and urine storage, 1853-1854
for ureteral stone passage, 1001-1002
- Naloxone, to facilitate bladder emptying, 1873
- Narcotics. *See* Opioids
- Narrow band imaging (NBI), for non-muscle-invasive bladder cancer, 2211
- National Comprehensive Cancer Network (NCCN) Guidelines, for retroperitoneal sarcomas, 1409, 1409f-1410f
- National Institutes for Clinical Excellence, vesicoureteral reflux guidelines of, 3144
- National Wilms Tumor Study Group (NWTSG) trials, 3575-3576
- Native targeted progenitor cells, for tissue engineering, 485
- Natriuretic peptides, in ED, 626
- Natural orifice transluminal endoscopic surgery (NOTES), 1591-1592
instrumentation for, 210.e2
for kidney surgery, surgical approaches and access for, 1453-1454, 1453f-1454f
- Nausea and vomiting, postoperative, 2961
- NBCi. *See* Nocturnal bladder capacity index
- NBI. *See* Narrow band imaging
- NCCN Guidelines. *See* National Comprehensive Cancer Network Guidelines
- NCCT. *See* Noncontrast computed tomography
- NDI. *See* Nephrogenic diabetes insipidus
- NDO. *See* Neurogenic detrusor overactivity; Nocturnal detrusor overactivity
- Nd:YAG laser. *See* Neodymium:yttrium-aluminum-garnet laser
- Necrosis
PC-RPLND findings of, survival outcomes associated with, 830, 830t
UTUC with, 1375
- Necrotizing fasciitis of perineum. *See* Fournier gangrene

- Needle biopsy
for prostate adenocarcinoma, 2596-2597, 2597b
for prostate cancer, 2606-2607
- Needle drivers, for laparoscopic and robotic surgery, 207, 207.e2f
- Needle suspension repair, retropubic suspension surgery comparison with, 1934
- Needles
for achieving transperitoneal access and establishing pneumoperitoneum, 200
in pediatric patients, 2967-2968, 2968b
complications related to, 216
for percutaneous access to upper urinary tract collecting system, 161-162, 162f
- Negative feedback, in HPG axis, 516-518, 517f
- Neglected stents, 132
- Neoadjuvant androgen deprivation (NAD)
with radiation therapy, for locally advanced prostate cancer, 2763
with radical prostatectomy, for locally advanced prostate cancer, 2758-2760, 2759t-2760t
- Neoadjuvant chemotherapy
for muscle-invasive bladder cancer, 2230-2231, 2231t
with radical prostatectomy, for locally advanced prostate cancer, 2760-2761, 2760t
- Neoadjuvant chemotherapy-hormonal therapy, with radical prostatectomy, for locally advanced prostate cancer, 2760-2761, 2760t
- Neovascularization, 2717
- Neobladder-urethral anastomosis, for minimally invasive urinary diversion, 2374, 2374f
- Neocystostomy, for UTUC, 1385-1386, 1387f
- Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, 229
- Neomycin, preoperative bowel preparation with, 107
- Neonates
hydronephrosis diagnosis in, 1105
nephrolithiasis in, medical management of, 1232
with UPJO, 1106
urinary specimen collection in, 12-13
- Neoplasia, of bladder, 474
- Neoplasms, HIV and, 385-386
- Neoplastic conditions, of cutaneous diseases of external genitalia
basal cell carcinoma, 413, 413f
bowenoid papulosis, 411, 411f
cutaneous T-cell lymphoma, 414-415, 416f
extramammary Paget disease, 414, 415f
Kaposi sarcoma, 413-414, 413f
melanoma, 414
pseudoeplitheliomatous, keratotic, and micaceous balanitis, 414, 414f
squamous cell carcinoma, 411, 412f
squamous cell carcinoma in situ, 410-411, 411f
verrucous carcinoma, 412, 412f
- Neostigmine, ureteral response to, 991
- Neourethral stricture, 3421
- Nephrectomy
allograft, 1086-1087
deep venous thromboses or pulmonary emboli after, 90
for genitourinary tuberculosis treatment, 431
history of, 1314
LDN, 1079, 1080f
for metastatic RCC, 1501-1503, 1502f, 1503b, 1503t
open, technique of, 1420-1421, 1420.e2f
- Nephrectomy (*Continued*)
partial. *See* Partial nephrectomy
pretransplant, 1073, 1073b
radical. *See* Radical nephrectomy
for RCC
partial. *See* Partial nephrectomy
radical. *See* Radical nephrectomy
for von Hippel-Lindau disease and other familial RCCs, 1353-1355, 1355f
renal bleeding and, 1153-1154
for renal pelvis tumors, 1384-1385, 1385f
in renal transplantation, 3532-3533
for renal trauma
partial, 1154, 1154f
total, 1155
RPLND with, 822, 822t
segmental, for large renal tumors, 1431-1432, 1432f, 1432.e1f, 1431.e1f
simple. *See* Simple nephrectomy
for ureteral anomalies
laparoscopic partial, 3089-3090, 3091f
open partial, 3088-3089, 3089f-3090f
upper pole partial, 3088-3090
for ureteral injuries, upper, 1163
for ureteropelvic junction obstruction, 1109
- Nephric ducts, 2830
in ureteral development from, 978-979
- Nephroblastoma. *See* Wilms tumor
- Nephroblastomatosis, 3572, 3572f
- Nephrocalcin, 1175
in crystal formation, 1179
in crystal matrix, 1179
- Nephrogenesis and anatomic development, in renal development, 2849, 2850f
- Nephrogenic adenoma, of bladder, 2184-2185
in pediatric patients, 3180, 3589
- Nephrogenic diabetes insipidus (NDI), 2862-2863
- Nephrogenic rests, 3572, 3572f
- Nephrogenic systemic fibrosis (NSF), 31, 47, 1061
- Nephrolithiasis. *See* Renal calculi
- Nephrolithotomy
percutaneous. *See* Percutaneous nephrolithotomy
for ureteropelvic junction obstruction, percutaneous antegrade endopyelotomy simultaneous with, 1111
- Nephrolysis, laparoscopic, 1464, 1464f
- Nephroma. *See* Cystic nephroma
- Nephron, 969, 970f
hydrogen ion transport in, urinary tract obstruction and, 1096
sodium transport in, urinary tract obstruction and, 1096
- Nephron endowment, and renal development, 2850
- Nephronophthisis (NPH), juvenile. *See* Juvenile nephronophthisis
- Nephron-sparing surgery. *See* Partial nephrectomy
- Nephropathy
aristolochic acid, 1072, 1366
contrast-induced, 30, 1053, 1061-1062
IgA. *See* IgA nephropathy
ischemic. *See* Ischemic nephropathy
- Nephropexy, laparoscopic, 1462, 1463f
procedure for, 1462, 1463f
results of, 1462-1463
- Nephrostomy, percutaneous. *See* Percutaneous nephrostomy
- Nephrostomy tract, for percutaneous approach to UTUC, 1392, 1394f
- Nephrostomy tubes
biofilm formation on, 134-135
complications of, 135-136
historic note on, 133
indications for, 133-134
materials and design of, 133, 133f
after percutaneous surgery of upper urinary tract collecting system, 170, 174b
adjuncts to tubeless drainage, 174
balloon catheters, 170-171, 171f
circle nephrostomy tubes, 172, 173f
Cope catheters, 171, 172f
dislodgement of, 181
general considerations for, 172-173
Malecot catheters, 171, 171f
nephroureteral stents, 171-172, 172f, 171.e1f
totally tubeless drainage, 174
tubeless drainage with ureteral stents, 173-174, 174f
- Nephrotic syndrome
in infants, 2858
minimal change, 2858
in older children, 2858-2859
other etiologies of, 2858-2859
- Nephrotoxic agents
AKI caused by, 1044-1046, 1044b-1045b
ATN prevention and, 1053
- Nephroureteral stents, after percutaneous surgery of upper urinary tract collecting system, 171-172, 172f, 171.e1f
- Nephroureterectomy
for posterior urethral valves, 3262
radical. *See* Radical nephroureterectomy
- NER. *See* Nucleotide excision repair
- Nerve growth factor (NGF)
in bladder outlet obstruction, 1677
in bladder pain syndrome and interstitial cystitis, 1678
in detrusor overactivity, 1675
in overactive bladder, 1674
- Nerve injury, during laparoscopic and robotic surgery, 222
- Nerves, adrenal, 1522, 1524f, 1529
- Nervous system
of lower urinary tract, peripheral nervous system, 1649-1667, 1651f
of retroperitoneum, 778
autonomic nervous system, 778-780, 779f-780f
somatic nervous system, 780-782, 781f-782f, 781t, 780.e1f
in ureteral function, 989
parasympathetic, 990-991
purinergic, 992-993
sensory innervation and peptidergic agents, 992
sympathetic, 991-992
- Nested variant of urothelial cancer, 2200, 2201f
- Neural sensitization, in prostatitis and CPPS etiology, 308
- Neural tube defects (NTD), 3272-3279
early intervention for, 3275-3277
epidemiology of, 3272, 3273f
findings with, 3274-3275
pathogenesis of, 3273, 3273t
perinatal concerns with, 3273-3274
postnatal management of
initial, 3274
neurogenic bowel dysfunction, 3279
prenatal closure of, bladder function after, 3274
risk factors for, 3272-3273, 3273f
upper urinary tract deterioration with, 3274-3275, 3275f
- Neurobiology, in BPS/IC etiology, 345.e8-345.e10, 345.e10b

- Neuroblastoma, 1560, 3559, 3567b
clinical presentation and pattern of spread of, 3561, 3561f
diagnosis of
imaging, 3561-3562, 3561f-3562f
laboratory evaluation, 3561
screening, 3562
staging, 3562, 3563t
epidemiology and genetics of, 3559-3560
pathology of, 3560-3561, 3560f-3561f
prognosis of, 3562-3567
biologic variables affecting, 3564-3567
clinical variables affecting, 3563-3564
spontaneous regression of, 3560
treatment of
biologic therapies, 3567
chemotherapy, 3564-3567, 3565f
radiotherapy, 3567
spinal cord decompression, 3567
surgery, 3564-3566, 3565f
- Neuroendocrine cells, of prostate, 2397f, 2398
- Neurofibroma, 418f, 419
- Neurogenic bladder
autonomous, 1694
with CNS tumors, 3293
dilated fetal bladder and, 3174
diminished bladder capacity and, 1829
reflex, 1694
renal transplantation and, 3531
sacral nerve stimulation for, 1906
secondary bladder calculi with, 1293
sensory, 1693
uninhibited, 1694
ureteral function effects of, 994-995
urodynamic classification of, 1693, 1693b
and UUTs, 2932
- Neurogenic bowel dysfunction, in
myelomeningocele, 1775-1776
- Neurogenic detrusor overactivity (NDO), 1693, 1756
capsaicin for, 1863.e1
detrusor underactivity and, 1814
resiniferatoxin in, 1863.e1
- Neurogenic lower urinary tract dysfunction (NLUTD). *See also* Neuromuscular dysfunction of lower urinary tract
treatment of, 1793-1795, 1793b-1794b
urodynamic studies, evidence-based review of, 1741-1742
video-urodynamics for, 1736-1737, 1737f
- Neuroimaging, in ED, 655-656
- Neurologic complications, after RPLND, 835
- Neurologic evaluation, in ED, 656-657
- Neurologic examination, 12, 12f
for pelvic floor disorders, 1701
- Neuromodulation. *See also* Electrical stimulation
for bladder and bowel dysfunction, 3308-3310, 3309t
for BPS/IC treatment, 358-359, 359b
future research for, 1916-1917
for lower urinary tract dysfunction
anterior root stimulation, 1795
to inhibit OAB, rationale for, 1681, 1681f
inhibitory and excitatory stimulation frequencies, 1681
onabotulinum toxin A, 1682-1683, 1682f-1683f
pudendal nerve stimulation, 1681, 1794-1795
for voiding, rationale for, 1680-1681, 1680f
for neuromuscular dysfunction of lower urinary tract, 3282
for prostatitis, 326
sacral, mechanism of action, 1680
- Neuromodulation (*Continued*)
for urinary incontinence, in geriatric patients, 2099.e5
- Neuromodulator therapy, for CP/CPPS
treatment, 324
- Neuromuscular blockers, preoperative
considerations for, 112
- Neuromuscular dysfunction of lower urinary tract. *See also* Voiding dysfunction
aging and, 1793
amyloidosis, 1792
attention-deficit/hyperactivity disorder, 1793
bashful bladder, 1788-1789
benign joint hypermobility syndrome, 1793
bladder neck dysfunction, 1787-1788
bladder outlet obstruction in women, 1788
at or above brainstem, 1761b, 1763-1768
brain tumor, 1765
brainstem stroke, 1765
cerebellar ataxia, 1765-1766
cerebral palsy, 1766
cerebrovascular disease, 1763-1765, 1764b
dementia, 1765
multiple system atrophy, 1768
normal-pressure hydrocephalus, 1766
Parkinson disease, 1766-1768
traumatic brain injury, 1765
- in children
anorectal malformation, 3289-3290
causes of, 3272, 3273b
management principles for, 3279-3283, 3281t
medical management for, 3279-3281
neuromodulation for, 3282
renal function assessment with, 3277
surgical management of, 3282.e1-3282.e3
vesicoureteral reflux in, 3283-3284, 3283f
- congenital adrenal hyperplasia, 1793
corticobasal degeneration, 1791
dysfunctionalized bladder, 1792
detrusor sphincter dyssynergia and, 1787
detrusor underactivity and, 1813b, 1814
distal to spinal cord, 1763b, 1781-1785
diabetes mellitus, 1783-1784, 1783b
disk disease, 1781
Guillain-Barré syndrome, 1784-1785
herpesvirus infection, 1783
hysterectomy, 1783
radical pelvic surgery, 1781-1783
spinal stenosis, 1781
dysfunctional voiding, 1787
- Ehlers-Danlos syndrome, 1791
- Fowler syndrome, 1789
- gastroparesis, 1790
- general patterns of, 1761-1763
- hyperthyroidism, 1790
- Isaacs syndrome, 1790
- lipomeningocele. *See* Lipomeningocele
- Machado-Joseph disease, 1792
- myasthenia gravis, 1790
- myotonic dystrophy, 1791
- neural tube defects. *See* Neural tube defects
- organ dysfunction and, 1793
- peripheral reflex arc and, 1763b
- plasticity and, 1763
- radiation exposure, 1792
- sacral agenesis. *See* Sacral agenesis
- sacral coccygeal teratoma, 1791
- schizophrenia, 1790
- spinal cord involvement in, 1761b, 1768-1780
acute transverse myelitis, 1778-1779
autonomic hyperreflexia, 1775-1776
bladder cancer and, 1778
- Neuromuscular dysfunction of lower urinary tract (*Continued*)
cervical myelopathy, 1778
follow-up for, 1778
multiple sclerosis, 1768-1770, 1769b
neurologic and urodynamic correlation, 1773-1775
neuromuscular dysraphism, 1779-1780
pernicious anemia, 1780
poliomyelitis, 1780
sacral injury, 1773, 1775f
spinal cord injury, 1770-1778, 1771b
spinal shock, 1771
suprasacral injury, 1771-1773, 1772f, 1774f
tabes dorsalis, 1780
urinary tract infection, 1777
vesicoureteral reflux, 1776-1777
in women, 1777-1778
subacute combined degeneration, 1791
systemic sclerosis, 1791
urinary retention, 1789
postoperative, 1789-1790
Wernicke encephalopathy, 1790-1791
Williams-Beuren syndrome, 1792
- Neuromusculoskeletal injuries, after
percutaneous access to upper urinary tract collecting system, 181
- Neuropathy, perioperative, prevention of, 114-115, 114b
- Neurospinal abnormalities, with cloacal exstrophy, 3226-3227, 3227f
- Neurospinal dysraphism, lower urinary tract dysfunction with, 1779-1780
- Neurotoxicity, anesthesia-induced, in pediatric patients, 2952-2953
- Neurotransmitters, within brainstem networks, 1664-1665
- Neurovascular bundle (NVB)
preservation of, in laparoscopic radical prostatectomy, 2671-2672, 2671f-2672f
in retropubic radical prostatectomy, 2649-2651
high anterior release of, at apex, 2651, 2652f
identification of, 2649
interposition nerve grafting of, 2660-2661
preservation of, 2649-2651, 2650f-2651f
wide excision of, 2651, 2653f
- Nevus. *See* Mole
- NGF. *See* Nerve growth factor
- NHCT. *See* Noncontrast helical computed tomography
- NI reactions. *See* Nonidiosyncratic reactions
- Nicardipine, for PD, 735
- Nicotinic agonists, ureteral response to, 990-991
- Nifedipine
for BPS/IC oral therapy, 353t, 355
for ureteral relaxation, 1001-1002
- Nighttime, definition of, 1822t, 1823-1824
- Nilutamide, 2790
- Nintedanib, for RCC, 1514
- Nipple "rosebud" stoma, 2293, 2293f
- Nipple valve, 2301, 2302f
for continent urinary diversions, 3361, 3361f
- Nitric oxide (NO)
bladder afferent pathway and, 1654, 1655f
in ED, 621-623, 623t
to facilitate bladder emptying, 1874.e1
metabolism of, in BPS/IC etiology, 345.e11
and PD, 728
renal vascular tone control by, 1010
ureteral response to, 984-985, 987-988, 987f
urothelium release of, 1639
- Nitrite testing, urinary, 20, 20f

- NX-1207, to facilitate bladder filling and urine storage, 1866.e2
- O**
- OAB. *See* Overactive bladder
- Obesity
- bariatric surgery for, 1220
 - benign prostatic hyperplasia and, 2442-2444, 2445t
 - and ED, 633
 - as laparoscopic and robotic surgery contraindication, 195
 - laparoscopic kidney surgery and, 1447
 - in metabolic syndrome, 1219-1220
 - midurethral sling outcomes with, 2024, 2024b, 2025t
 - nephrolithiasis and, 1219-1220, 1220b
 - orthoptic urinary diversion and, 2350
 - preoperative care for, 104
 - prostate cancer and, 2551-2552, 2552f
 - renal calculi and, 1172-1173
 - upper urinary tract calculi and, 1255, 1281
 - urinary incontinence and, 1748-1749, 1894
 - urologic disease and, 551-553
 - weight-loss diets for, 1220
- Observations, in physical examination, 9
- Obstetric fistulae, 2106
- Obstructed labor injury complex, 2105-2106
- Obstruction
- bladder
 - in renal transplant candidates, 1073
 - response to, 2435-2436
 - RMS causing, 3584-3585
 - prenatal imaging of, 2909-2910, 2910f
 - of seminal vesicles and ejaculatory ducts, 534
 - of upper urinary tract collecting system, after percutaneous access to upper urinary tract collecting system, 181-182
 - ureteral function effects of, 995-999, 996f-999f
 - ureteropelvic junction. *See* Ureteropelvic junction obstruction
 - urinary tract. *See* Urinary tract obstruction
 - in UTI host defense mechanisms, 248
- Obstruction/maldevelopment, and renal development, 2850
- Obstructive sleep apnea (OSA)
- nocturnal polyuria with, 1826
 - treatment of, 2099.e8
- Obstructive symptoms, of lower urinary tract, patient history of, 3-5, 4f-5t
- Obturator internus, 1614, 1616f
- Obturator lymph node, 508
- Obturator nerve, 1619, 1622t
- OBIX. *See* OnabotulinumtoxinA
- Occupation
- renal calculi and, 1172
 - urothelial cancer and, 2187
- Occupational exposures, UTUC risk and, 1366
- ODS. *See* Output display standard
- Off-clamp LPN, 1475-1476
- Ogilvie syndrome, with intestinal anastomoses, 2292
- OKT3-antimurine CD3, for post-transplant immunosuppression, 1084-1085
- Oligohydramnios, neonatal, 2890
- Oligomeganephronia, 3009, 3010f
- Oligospermia, chromosomal abnormalities in, 528
- Omniport, 203, 203.e3, 203.e3f
- OnabotulinumtoxinA (OBIX)
- to facilitate bladder filling and urine storage, 1839t, 1861-1863
 - for MS, 1770
- OnabotulinumtoxinA (OBIX) (*Continued*)
- neuromodulation with, 1682-1683, 1682f-1683f
 - for overactive bladder, 1910-1911
 - for UUI, 1715
- Oncocytoma, 1563-1564, 1564b
- renal, 1304-1306, 1304f, 1306b, 1306f
- Oncogenes, 460, 460b
- Oncology
- chronic inflammation in GU cancers, 451, 453b
 - bladder cancer, 451, 452f
 - kidney cancer, 451-452
 - prostate cancer, 452-453
 - CT in, 43-46, 45f-46f
 - immunologic response in GU cancers, 447, 451b
 - adaptive immune system, 449-450, 449f
 - immune editing hypothesis, 450-451, 450f
 - innate immune system, 447-448, 448f-449f, 448t-449t
 - immunotherapy for GU cancers, 447, 458b
 - BCG in bladder cancer, 447, 448f, 453-454, 453f
 - cancer vaccines, 454-456, 454f, 456f
 - immune checkpoint blockade, 456-458
 - molecular genetics in. *See* Molecular genetics
 - MRI in, adrenal masses, 47-49, 48f-51f, 52t
 - nuclear medicine in, 39-40
 - pediatric. *See* Pediatric oncology
- Oncolytics, for localized prostate cancer, radiation therapy with, 2710
- Ondansetron (Zofran), for PONV, 2961
- One-kidney, one-clip model, of renovascular hypertension, 1029, 1030f
- Open access techniques
- for achieving extraperitoneal access and developing extraperitoneal space, 201-202
 - for achieving retroperitoneal access and developing retroperitoneal space, 201, 202f, 201.e3
 - for achieving transperitoneal access and establishing pneumoperitoneum, 200-201, 201f, 201.e1f
 - in pediatric patients, 2967-2968, 2968b
 - complications related to, 216
- Open adrenalectomy, 1581
- anterior transabdominal approach, 1583-1584, 1583f-1584f
 - flank retroperitoneal approach, 1581-1582, 1581f-1582f
 - left, 1583-1584, 1583f-1584f
 - outcomes, 1592
 - posterior lumbodorsal approach, 1582-1583, 1583f
 - thoracoabdominal approach, 1584-1585, 1585f-1586f
- Open cystolithotomy, for bladder calculi, 1295
- Open distal ureterectomy, for UTUC, 1378, 1378f, 1381-1382
- Open nephrectomy, technique of, for benign diseases, 1420-1421, 1420.e2f
- Open nephron-sparing surgery, for renal pelvis tumors, 1384-1385, 1385f
- Open radical nephroureterectomy, for UTUC, 1376-1377, 1377f, 1381-1382
- Open retropubic colposuspension, 1920
- Open segmental ureterectomy, for UTUC, 1385, 1386f
- Open simple prostatectomy, 2537
- incision for, 2537
 - patient positioning for, 2537
 - space of Retzius development for, 2537
- Open stone surgery, 1285-1286, 1286t
- for renal calculi, 1285-1286
 - for ureteral calculi, 1286
- Open surgery, uncomplicated urologic procedures, antimicrobial prophylaxis for, 264, 264t
- Open-Pass ureteral stent, 129
- Operating room setup, for laparoscopic and robotic surgery, 196-197, 197b
- Operative team placement, for laparoscopic and robotic surgery
- retroperitoneal upper abdominal procedures, 198, 199f
 - transperitoneal and extraperitoneal pelvic procedures, 199, 199f
 - transperitoneal upper abdominal procedures, 198, 198f, 198.e1f
- Opiates, and ED, 638
- Opioid-receptor antagonists, to facilitate bladder emptying, 1873
- Opioids
- AD resulting from, 539
 - for BPS/IC oral therapy, 356, 356b
 - and ED, 623, 623t
 - immediate postoperative, 112
 - for pediatric patients, 2956-2958, 2957t
 - preoperative considerations for, 112
 - urethral function effects of, 1004
 - for urinary tract obstruction, 1101
- OPTN. *See* Organ Procurement and Transplantation Network
- Oral preparations, testosterone, 544-545, 544t
- Oral therapies, for BPS/IC treatment, 352-356, 353t, 356b
- Orchialgia, surgical treatment of, 956-957, 956f
- Orchidopexy
- Fowler-Stephens, 3447-3449, 3448t
 - laparoscopic, 3447-3449, 3448t
 - for prune-belly syndrome, 3245-3246, 3246f
 - transabdominal, 3447
 - trans-scrotal, 3446, 3446f
- Orchiectomy, 956
- delayed, 816
 - evaluation after, 816
 - for ITGCN, 797, 797b
 - partial. *See* Partial orchiectomy
 - radical. *See* Radical orchiectomy
 - for TGCTs, 791, 791f-792t
- Orchiopexy
- inguinal, 3444-3446, 3445f
 - retractile or ectopic testes and, 611, 611f
- Orchitis, 329-331, 330b, 330t, 332b, 568
- pediatric imaging of, ultrasonography, 2913, 2917f
 - surgical treatment of, 956-957, 956f
- Orciprenaline, ureteral response to, 991-992
- Organ Injury Severity Scale for Kidney, of AAST, 1149t
- Organ ischemia, during vena caval thrombectomy, 1444-1445
- Organ preservation, in penile cancer management, 855
- Organ Procurement and Transplantation Network (OPTN), 1074
- Organ transplantation. *See* Transplantation
- Organomegaly, as laparoscopic and robotic surgery contraindication, 196
- Orgasm, absence of, patient history of, 6
- Orthophosphate, for absorptive hypercalciuria, 1225
- Orthoptic urinary diversion
- basic principles of, 2346-2347, 2346f, 2347b

Orthoptic urinary diversion (*Continued*)

- bladder substitution in
 - bowel segment selection for, 2353, 2354b
 - reflux prevention in, 2354, 2354b
 - complications of, 2361-2362
 - continence mechanism in, 2351, 2353b
 - continence preservation in
 - anterior apical dissection in male patient, 2351-2352, 2353b
 - urethra preservation in female patient, 2352-2353, 2352f
 - follow-up for, 2366-2367, 2367b
 - history of, 2344-2346, 2345f, 2346b
 - oncologic factors for, 2347-2349, 2349b
 - locally advanced tumor stage, 2348-2349
 - urethral recurrence risk in men, 2347-2348
 - urethral recurrence risk in women, 2348
 - patient selection for, 2347-2351
 - patient-related factors, 2349-2351, 2351b
 - perioperative management for, 2355
 - quality of life after, 2367-2368, 2368b
 - results with, 2361-2368
 - continence in, 2363-2366, 2364t-2365t, 2366b
 - urinary retention with, 2366, 2366b
 - surgical techniques for, 2355-2358
 - Camey II, 2355, 2356f
 - colon and ileocolic pouches, 2358-2360
 - ileal neobladder, 2357-2358, 2357f
 - ileal reservoirs, 2355
 - Kock ileal reservoir, 2355, 2356f
 - Le Bag pouch, 2358-2360, 2361f
 - minimally invasive, 2360
 - orthotopic Mainz pouch, 2358, 2360f
 - right colon pouch, 2360
 - serous-lined extramural tunnel, 2355-2357, 2357f
 - sigmoid pouch, 2360, 2362f
 - Studer pouch, 2358, 2359f
 - T pouch modification, 2358, 2359f
- Orthotopic Mainz pouch, for orthoptic urinary diversion, 2358, 2360f
- OSA. *See* Obstructive sleep apnea
- Osmolality, of urine, 13-14
- Osmotic diuretics, for AKI, 1050
- Osmotic effect, of urothelium of bladder, 1638
- Osteogenic sarcoma, of kidney, 1362
- Osteomalacia, with urinary intestinal diversion, 2312
- Osteopontin, in crystal formation, 1176, 1179
- Osteoporosis, hormonal therapy and, 2793-2794
- Osteotomy
 - for classic bladder exstrophy, 3194-3196, 3195f-3196f
 - complications of, 3195f, 3196-3197
 - in urinary tract reconstruction, of cloacal exstrophy, 3231, 3231f
- Ouabain, urethral function effects of, 1005
- Outcomes research, 85, 99b
 - access to care, 85
 - costs of care, 85-86
 - patterns, 87-88
 - savings in urology, 88
 - terms and methods of analysis for, 86-87
 - value, 87, 98
- future implications for, 98
- health-related quality of life. *See* Health-related quality of life
- methodologies for, 97-98
- quality of care, 88-89
 - challenges in evaluation of, 91
 - conceptual framework for, 89-90
 - improvement frameworks, 91

Outcomes research (*Continued*)

- levels of evidence, 91
 - metrics applied to urology, 90-91
 - outcomes, 90
 - process, 90
 - structure, 89-90
- Outflow resistance, 3332-3333
- Output display standard (ODS), in ultrasonography, 73
- Oval fat macrophages, in urinary sediment, 25, 25f
- Ovarian tumors, in pediatric patients, 3590
- Ovaries
 - anatomy of, 1607
 - function of, 3474
- Overactive bladder (OAB), 2097
 - afferent mechanisms in, 1797-1798
 - clinical assessment of, 1800-1803, 1801f, 1803b
 - bladder pain syndrome distinguished from, 1797f, 1803, 1803f
 - instruments for, 1800-1802, 1802t
 - mixed symptoms incorporating urinary urgency, 1802, 1803f
 - costs of, 1799-1800, 1800b
 - after CVA, 1765
 - detrusor overactivity with, 1804, 1805f
 - estrogens for, 1863-1864
 - etiology of, 1799, 1799b
 - evaluation of, 1804-1805
 - management of, 1804-1805
 - mechanisms of, 1673-1675, 1674f
 - neuromodulation for, 1680
 - rationale for, 1681, 1681f
 - nocturnal bladder capacity and, 3312
 - onabotulinumtoxinA for, 1910-1911
 - pathophysiology of, 1688, 1797-1799, 1797f-1798f, 1799b
 - pelvic organ prolapse and, 1753
 - pharmacologic therapy for, 1839t
 - antimuscarinic agents, 1838, 1840f
 - prevalence of, 1747f, 1799-1800, 1800b
 - questionnaires for, 1703t-1704t
 - after retropubic suspension surgery, 1933
 - sacral neuromodulation in, putative mechanism of, 1901, 1901f
 - terminology for, 1796, 1796b, 1797f
 - treatment of
 - initial, 1803-1804, 1804b
 - specialized, 1801f, 1805-1806, 1806b
 - urgency urinary incontinence with, 1710
 - urodynamic testing of, 1804-1805, 1805f
- Overflow urinary incontinence, patient history of, 6
- Overnight low-dose dexamethasone suppression test, in evaluation of adrenal masses, 1572
- Overnight water deprivation test (OWDT), 1835
- Ovotesticular disorder of sexual differentiation, 3484-3485, 3484f
- OWDT. *See* Overnight water deprivation test
- Oxalate
 - avoidance of, in nephrolithiasis, 1221-1222, 1222b
 - in calcium stone formation, 1185, 1187
 - foods containing, 1211b
 - metabolism of, 1181
- Oxazaphosphorines, hemorrhagic cystitis caused by, 188-190
- Oxford guidelines
 - for behavior therapy, 1879t
 - to facilitate bladder filling and urine storage, 1838, 1838t
- Oxidative stress, stone disease and, 1175
- Oxybutynin chloride
 - cognitive effects of, 1850
 - extended release, 1849
 - to facilitate bladder filling and urine storage, 1839t, 1848-1850
 - with α -adrenoreceptor antagonists, 1859-1860
 - with other antimuscarinics, 1860
 - immediate-release, 1849
 - intravesical administration of, 1850
 - rectal administration of, 1850
 - topical gel, 1850
 - transdermal, 1849-1850
- Oxycodone, for pediatric patients, 2957-2958, 2957t
- Oxygen free radicals and oxidative stress, and PD, 728
- Oxytocin
 - in ED, 621-623, 623t
 - and female sexual response, 750

P

- P (mannose-resistant) pili, 243
- p16. *See* INK4A gene
- Pacemaker cells, ureteral, 982-984, 983f
- Packed red blood cells (PRBCs), preoperative considerations for, 112-113
- Paclitaxel, cisplatin, and gemcitabine (PCG), for UTUC, 1400
- Paclitaxel, for non-muscle-invasive bladder cancer, 2216
- Paclitaxel, ifosfamide, and cisplatin (TIP) for NSGCTs, 805
- for penile cancer, 872-873, 872t
- Pad tests
 - for male urinary incontinence, 1712
 - for pelvic floor disorders, 1704-1705
- PADAM. *See* Partial androgen deficiency in aging male
- Pagano technique, in urinary diversion, 2296t, 2297, 2297f
- Paget disease, of penis, 874f, 875
- PAI-1. *See* Plasminogen activator inhibitor-1
- Pain
 - in castration-resistant prostate cancer, 2818, 2819t
 - hematuria associated with, 3
 - after laparoscopic and robotic surgery, 222-223
 - management of. *See also* Analgesia for pediatric patients, 2956-2958, 2956t-2957t
 - preoperative anesthetic considerations and, 112
 - in urinary tract obstruction, 1101
 - after midurethral sling, 2031-2033
 - patient history of, 1-2
 - scrotum
 - postvasectomy, 952
 - surgical treatment of, 956-957, 956f
 - ureteral anomalies and, 3080
- Painful bladder syndrome, sacral nerve stimulation for, 1907
- Palliative care, 2101-2102
- Palliative surgery, for metastatic RCC, 1503, 1504b
- Pampiniform plexus, 500, 501f, 519-520
- Pancreas, in retroperitoneum, 773, 773f-774f, 773.e1f
- Pancreatic injury
 - during laparoscopic and robotic surgery, 222.e1
 - during radical nephrectomy, 1428
- Panurothelial disease, UTUC, 1368-1369
- Papaverine, 665
- Papillary adenoma, of kidney, 1302-1303, 1303b

- Papillary carcinoma, 2188-2190, 2190t
- Papillary RCC
 molecular genetics of, 468t, 472, 1322t, 1324
 pathology of, 1329t-1330t, 1331-1332, 1331f
- Papillary urothelial neoplasia of low malignant potential (PUNLMP), 2188-2190, 2190t
- Papilloma
 of bladder, 2184, 2185f
 of upper urinary tract, 1369-1370
- Papulosquamous disorders, 392, 392b
 fixed drug eruption, 396, 397f
 lichen nitidus, 394
 lichen planus, 394, 395f
 lichen sclerosus, 395-396, 396f
 psoriasis, 392-393, 393f
 reactive arthritis, 393-394, 393f-394f
 seborrheic dermatitis, 396-397
- Paquin technique, 3158
- Paracolpium, 1607
- Paradoxical incontinence. *See* Overflow urinary incontinence
- Paralytic bladder, 1693-1694
- Paramental urethral cyst, 3378, 3378f
- Parametrium, 1607
- Paraneoplastic syndromes, in RCC, 1334-1335, 1334t
- Parapelvic cyst, 3040, 3041f
- Paraphimosis, 3369-3370, 3369f
 urethral reconstructive surgery for, 914
- Parasites, in urinary sediment, 24-25, 24f
- Parasitic infections, of genitourinary tract, 433
 filariasis, 442
 diagnosis, 444
 epidemiology, 442-443
 organisms, 442, 442f
 pathology and clinical manifestations, 443-444, 443f-444f
 prevention and control, 445
 treatment, 444-445
- nonfilarial
 amebiasis, 446
 echinococcosis, 445-446
 enterobiasis, 446
 trichomoniasis. *See* Trichomoniasis
- schistosomiasis, 433, 442b
 biology and life cycle, 433-434, 433f-434f
 clinical manifestations, 436-437
 diagnosis, 437-439, 439f-440f
 epidemiology, 434-435
 history, 433
 pathogenesis and pathology, 435-436, 435f, 438f-439f
 prevention and control, 441-442
 prognosis, 441
 treatment, 440-441
- Parasympathetic blocking agents, ureteral response to, 991
- Parasympathetic decentralization, LUTD and, 1782
- Parasympathetic nervous system
 in retroperitoneum, 778
 in ureteral function, 990-991
- Parasympathetic pathways, of lower urinary tract, 1649-1650, 1651f
- Parasympathomimetics
 for detrusor underactivity, 1817
 to facilitate bladder emptying, 1870-1872
- Paratesticular cancer
 RMS in pediatric patients, 3596, 3597b
 outcomes of, 3597
 presentation and staging of, 3597
 RPLND role in, 3597
 treatment of, 3597
 of testicular adnexa, 813
- Parathyroid hormone (PTH)
 in calcium metabolism, 1180
 in renal hypercalciuria, 1184
 renal regulation of, 1011f, 1012
 in resorptive hypercalciuria, 1184
- Paraureteral diverticula, 3178, 3178f
- Paravaginal repair procedures
 for female incontinence, 1920-1921, 1920f
 Burch colposuspension comparison with, 1936
 results with, 1929
 suspension configuration in, 1921
 technique for, 1928-1929, 1929f
 tissue approximation in, 1921
 urethral elevation in, 1921
 for pelvic organ prolapse
 abdominal for, 1951t-1952t, 1959-1960, 1959f
 vaginal, 1950t, 1953, 1954f-1955f
- Parenchyma, renal, 155-156, 155f-156f
- Parenchymal compression and clamping, for laparoscopic partial nephrectomy, 1476
- Parental age
 sperm chromosomal anomalies related to, 528
 sperm genetic mutations related to, 528-529, 528b
- Parenteral nutrition, preoperative, 104
- Parity, urinary incontinence and, 1748
- Parkinson disease (PD)
 detrusor underactivity and, 1814
 diagnosis of, 1767
 in ED, 631
 lower urinary tract dysfunction with, 1766-1768
 pathophysiology of, 1766-1767
 treatment for, 1767
- Paroxetine hydrochloride, to facilitate bladder filling and urine storage, 1857
- Partial adrenalectomy, 1592
- Partial androgen deficiency in aging male (PADAM), 519
- Partial colpocleisis, for apical pelvic organ prolapse repair
 results with, 1974-1976
 technique for, 1974, 1975f-1976f
- Partial cystectomy, 2267-2268
 complications with, 2268
 evaluation for, 2267
 indications for, 2267
 for muscle-invasive bladder cancer, 2233-2234
 outcomes with, 2268
 technique for, 2267, 2268f
 with transurethral resection of bladder tumor, 2252, 2253f
- Partial epididymectomy, 953, 954f
- Partial gonadal dysgenesis, 3481-3482
- Partial nephrectomy (PN)
 for benign diseases, 1420, 1421f
 laparoscopic. *See* Laparoscopic partial nephrectomy
 for malignancies, 1428-1433, 1428f
 complications of, 1432-1433
 enucleation for small cortical tumors, 1429-1431, 1430f
 preoperative considerations for, 1428-1429, 1429f, 1429.e1f
 segmental nephrectomy for large polar tumors, 1431-1432, 1432f, 1432.e1f, 1431.e1f
 wedge resection for large cortical tumors, 1431, 1431f
- Partial nephrectomy (PN) (*Continued*)
 for RCC, 1344-1349, 1345b, 1347t, 1348f-1349f
 local recurrence after, 1359, 1360b
 for renal pelvis tumors, 1384-1385, 1385f
 for renal trauma, 1154, 1154f-1155f
 for von Hippel-Lindau disease and other familial RCCs, 1353-1355, 1355f
 for Wilms tumor, 3578-3579
- Partial orchiectomy, 816
 technique for, 816
 for TGCT, 791
- Partial scrotoectomy, 947
- Partial transection, for lower ureteral injuries, 1164
- Partial ureteral obstruction (PUO),
 hemodynamic changes with, 1095
- Partial urogenital mobilization (PUM), 3510-3513, 3512f-3515f
- Passage stents, 127
- Patch cavoplasty, for IVC, 1443-1444, 1443f
- Patent urachus, 3176-3177, 3176f-3177f
- Pathogenesis
 of bacteriuria in elderly, 297, 298f
 of bacteriuria in pregnancy, 294
 UTI, 241-249, 250b, 300-301
 alterations in host defense mechanisms, 248-249, 249.e1
 bacterial virulence factors, 242
 early events in UPEC pathogenesis, 242-243, 242f
 epithelial cell receptivity, 244-247
 fastidious organisms, 242
 natural defenses of urinary tract against, 247-248, 248.e1
 phase variation of bacterial pili in vivo, 243-244, 244f
 routes of infection, 241
 urinary pathogens, 241-242
- Patient. *See also* Geriatric urology patient;
 Pediatric patient
 preoperative environment of
 positioning, 114-115, 114b
 safety considerations, 114
 skin preparation, 113-114
 temperature, 113
- Patient growth, after augmentation cystoplasty, 3351-3352
- Patient history
 chief complaint and present illness, 1-7, 4t-5t
 of hematuria, 2-3, 187
 medical, 7-9, 8t
 overview, 1
- Patient nonadherence, in renal transplant candidates, 1072
- Patient Perception of Intensity of Urgency Scale (PPIUS), 1802
- Patient positioning
 for laparoscopic and robotic surgery, 197, 2966, 197.e1f
 hemodynamic effects related to, 214
 in pediatric patients, 2966f, 2967, 2969
 for laparoscopic kidney surgery
 hand-assisted modifications, 1451-1452, 1451f-1452f
 LESS and NOTES, 1453-1454, 1453f-1454f, 1455t
 retroperitoneal approach, 1448-1450, 1450f-1451f
 robotic-assisted modifications, 1452-1453, 1453f
 transperitoneal approach, 1447-1448, 1447f-1449f

Patient positioning (*Continued*)

- for laparoscopic radical prostatectomy, 2665, 2666f
- complications with, 2679
- for laparoscopic RPLND, 839-840, 840f
- for open simple prostatectomy, 2537
- for percutaneous access to upper urinary tract collecting system, 158-159, 159f
- for perineal radical prostatectomy, 2662.e1, 2662.e1f
- preoperative, 114-115, 114b
- for prostate biopsy, 2585
- for robot-assisted laparoscopic simple prostatectomy, 2541
- for vesicoureteral reflux, 3157

Patient preparation

- for cystourethroscopy, 139-141, 141b
- for surgery. *See* Preoperative care
- for ureteroscopy, 150, 151b

Patient Protection and Affordable Care Act of 2010, 88, 98

Patient safety

- in pediatric imaging, 2909
- preoperative, 114
- in ultrasonography, 73

Patient Safety and Quality Improvement Act of 2005, 89

Patient satisfaction, 91

Patient-centered outcomes research, 98

- Patient-reported outcome measures, for male urinary incontinence, 1712, 1713f, 1712.e1f-1712.e2f

Patterns of care, 87-88

Pazopanib

- for RCC, 1360t, 1512-1513, 1513t
- for retroperitoneal sarcomas, 1412

PBR. *See* Peripheral benzodiazepine receptorPBS. *See* Prune-belly syndromePCA3. *See* Prostate cancer antigen 3PCG. *See* Paclitaxel, cisplatin, and gemcitabinePCI. *See* Protein C inhibitorPCN. *See* Percutaneous nephrostomyPCNL. *See* Percutaneous nephrolithotomyPCPT. *See* Prostate Cancer Prevention TrialPCr. *See* Plasma creatininePC-RPLND. *See* Postchemotherapy

retroperitoneal lymph node dissection

PCS. *See* Postchemotherapy surgeryPCI. *See* Proximal convoluted tubulePD. *See* Parkinson disease; Peyronie diseasePD-1. *See* Programmed death-1PDE5-I. *See* Phosphodiesterase type 5 inhibitorsPDEIs. *See* Phosphodiesterase inhibitorsPDS. *See* PolydimethylsiloxanePDT. *See* Photodynamic therapyPE. *See* Premature ejaculation; Pulmonary embolism

Peak flow rate, in pediatric patients, 3128, 3129f

Pearly penile papules, 415-416, 416f-417f

Pediatric ACC, 1560

Pediatric genitourinary trauma

- assessment of, 3538-3545
 - abdominal and pelvic computed tomography for, 3539
 - arteriography for, 3541-3542
 - focused assessment with sonography for trauma, 3538-3539
 - follow-up radiographic imaging, 3544-3545, 3546f
 - radiologic assessment, 3539
 - renal trauma grading system for, 3539, 3539t, 3540f-3543f
 - retrograde pyelography for, 3542-3544
- bladder, 3552-3553
 - children and adult differences in, 3552-3553
 - classification of, 3553

Pediatric genitourinary trauma (*Continued*)

- diagnosis of, 3553
 - general comments on, 3552
 - treatment of, 3553
- complication management for, 3540-3541
 - general comments on, 3538
- penile, 3557-3558
 - preexisting hydronephrosis and, 3549-3550
- renal trauma, 3545-3549, 3546t
 - activities and follow-up recommendations, 3548-3549, 3549t
 - chronic flank pain, 3548
 - hypertension with, 3548
 - nonoperative therapy for, 3545-3547
 - operative therapy for, 3547
 - vascular injuries, 3547
- screening for, pediatric patient compared with adult, 3538, 3539b
- scrotal, vulvar, and testicular, 3558
- treatment of
 - percutaneous nephrostomy, 3542-3544
 - perinephric drain placement for, 3542-3544
- ureteral, 3550-3552
 - external, 3550-3551
 - iatrogenic, 3551-3552
- ureteropelvic junction disruption with, 3549-3550, 3550f-3551f
- urethral, 3554-3557
 - anastomotic urethroplasty, 3556
 - anterior, 3554-3555
 - delayed repair assessment, 3555, 3556f
 - diagnosis of, 3554
 - endoscopic repair of, 3555-3556
 - erectile dysfunction following, 3557
 - female, 3557
 - Mitrofanoff principle following, 3557
 - patch urethroplasties, 3556-3557
 - pediatric and adult differences in, 3554
 - pelvic fractures and, 3554
 - presentation of, 3554
 - repair of, 3554
 - urinary incontinence, 3557

Pediatric oncology

- adrenal tumors, neuroblastoma. *See* Neuroblastoma

bladder tumors

- adenocarcinoma and squamous cell carcinoma, 3589
- in augmented bladders, 3588-3589
- benign, 3589
- RMS. *See* Bladder RMS
- TCC, 3588
- urachal carcinoma, 3589

female genital tract tumors, 3590b

- cervical or uterine RMS, 3590
- ovarian, 3590
- vaginal RMS, 3589-3590, 3590f
- vulvar RMS, 3589

male reproductive tumors

- paratesticular RMS, 3596-3597, 3597b
- testicular. *See* Testicular tumors
- renal tumors
 - angiomyolipoma, 3580-3581, 3581f
 - COSK, 3579
 - CMN, 3579-3580
 - CPDN, 3580
 - metanephric adenofibroma, 3580
 - RCC, 1320, 3580
 - RTK, 3579
 - solitary multilocular cyst nephroma, 3580
 - Wilms tumor. *See* Wilms tumor

Pediatric patients

- bladder and bowel dysfunction in, 3126
- bladder anomalies in. *See* Bladder anomalies

Pediatric patients (*Continued*)

- catheterization in, 122
- growth and maturation of postnatal, 2950-2951
- prematurity and IUGR, 2949
- proper intrauterine growth and lung development, 2949-2950
- imaging of, 2909, 2923b. *See also* specific imaging modalities
- safety in, 2909
- kidneys of, 3538
- laparoscopic and robotic surgery for, 2963, 2974, 2974b
 - advantages of, 2963
 - anesthesia for, 2966, 2966f
 - complications of, 2970-2972
 - contraindications to, 2965
 - disadvantages of, 2964-2965, 2964f
 - general applications of, 2964b, 2964t
 - hemostatic devices for, 2965
 - LESS, 2969-2970
 - outcomes of, 2972-2974, 2973t
 - retroperitoneal approach to, 2966-2969, 2967f, 2967t, 2969b-2970b
 - suturing for, 2965-2966
 - team development for, 2965
 - transperitoneal approach to, 2966-2969, 2967f, 2967t, 2968b-2969b
 - troubleshooting for, 2969, 2970b, 2970f-2972f, 2972b
- lower urinary tract dysfunction in, 3125-3126
 - bladder and bowel dysfunction. *See* Bladder and bowel dysfunction
 - clinical assessment of, 3126-3133, 3126b
 - clinical significance of, 3297
 - comorbidities with, 3298-3299
 - enuresis. *See* Enuresis
 - epidemiology of, 3125, 3297-3298
 - frequency volume chart for, 3127
 - giggle incontinence, 3310
 - history for, 3126-3127, 3127f
 - physical examination for, 3127
 - pollakiuria, 3310
 - prevalence of, 3125
 - quality-of-life and, 3298
 - self-esteem and, 3298
 - terminology of, 3125-3126, 3300
 - underactive bladder, 3310
 - urinalysis for, 3127
 - urodynamic studies for, 3128-3133
 - vaginal reflux, 3310
 - voiding diary and bowel diary for, 3127
- lower urinary tract in
 - bladder anatomy and innervation, 3121-3122
 - detrusor pressure at voiding, 3123, 3124f
 - functional parameter change in, 3123
 - micturition control development, 3123-3125
 - normal function development in, 3123-3125
 - normal function of, 3121-3125
 - normal micturition control evolution, 3123-3125
 - transitory detrusor-sphincter discoordination, 3125
- megaureter in, 3066-3073
 - cause, occurrence, and presentation of, 3067-3068
 - cutaneous ureterostomy for, 3069-3073, 3069f
 - definition of, 3066-3067
 - dilatation and stenting for, 3073
 - excisional tapering for, 3072-3073, 3072f
 - Kalicinski plication technique for, 3072, 3072f

- Pediatric patients (Continued)**
 outcomes with, 3073
 reconstruction for, 3070-3072, 3070f
 remodeling for, 3070-3072, 3071f
 Starr plication technique for, 3072, 3072f
 surgical indications for, 3068-3069
 ureteral polyps with, 3073
 ureteral strictures with, 3073
 neuromuscular dysfunction of lower urinary tract in. *See* Neuromuscular dysfunction of lower urinary tract, in children
 perioperative care for. *See* Perioperative care
 transitional urology for. *See* Transitional urology
 ureteral anomalies in. *See* Ureteral anomalies
 ureteropelvic junction obstruction in
 associated anomalies, 3057-3058
 clinical presentation of, 3057, 3058f
 complications with, 3066, 3068f
 definition of, 3057
 dismembered pyeloplasty for, 3059-3062, 3059f-3061f
 endoscopic approach to, 3062
 evidence for, 3057
 flank approach to, 3062
 laparoscopic pyeloplasty for, 3062-3066, 3066f-3067f
 minimally invasive techniques for, 3062-3066
 nondismembered pyeloplasty for, 3062, 3062f-3064f
 posterior lumbotomy for, 3062, 3065f
 surgical approach to, 3062
 surgical indications for, 3058
 surgical outcomes with, 3066
 surgical repair of, 3058-3062
 urinary calculi in, medical management of, 1232-1233
 urinary tract reconstruction in
 antireflux, 3333-3334, 3334f-3335f
 augmentation cystoplasty for, 3342-3359.
See also Augmentation cystoplasty
 continent urinary diversion, 3360-3366. *See also* Continent urinary diversion
 patient evaluation for, 3332-3333
 patient preparation for, 3333
 summary for, 3366
 urodynamic studies for, 3332
- UTIs in**
 classification of, 2933-2936, 2934f-2936f, 2936b
 definition of, 2927
 diagnosis of, 2936-2942, 2937t, 2939b, 2940t, 2942b
 evaluation and management of a child with a fever, 2926-2933, 2926b, 2927f-2929f, 2929t, 2930b, 2933b
 management of infection, 2942-2944, 2943t-2944t, 2947b
 pathogenesis of, 2927-2928
 sequelae of, 2946-2947, 2947b
 voiding dysfunction in, sacral nerve stimulation for, 1907-1908
- Pediatric renal transplantation (Continued)**
 bladder preparation for
 capacity, 3530
 clean intermittent catheterization, 3530-3531
 general issues, 3528-3531
 hypertonicity, 3529-3530
 infections, 3530
 complications with, 3534-3536, 3534t
 bladder dysfunction, 3536
 hydronephrosis, 3535-3536
- Pediatric renal transplantation (Continued)**
 infection, 3535
 obstruction, 3535-3536, 3536f
 reflux, 3535, 3535f
 stones, 3536
 urine leaks, 3534-3535, 3535f
 cutaneous stomas for, 3531-3532
 defunctionalized bladder, 3531
 augmentation decision, 3531
 neuropathic, 3531
 non-neuropathic, 3531
 native kidney management, 3533
 nephrectomy with, 3533
 pretransplant assessment for, 3528, 3529f
 pretransplant preparation for, 3528-3533
 reconstruction strategies for, 3532
 dialysis issues, 3532
 enterocystoplasty, 3532
 graft placement, 3532
 native nephrectomy, 3532
 timing of, 3532
 ureteral anastomosis, 3533-3534
 ureteral stenting, 3534
- Pediatric stone disease**
 conservative management of, 3103-3104
 endourologic management of, 3102-3103
 imaging of, 3103
 laparoscopic and robotic-assisted
 pyelolithotomy for, 3118
 percutaneous cystolithotripsy for, 3118, 3119f
 percutaneous nephrolithotomy for. *See* Percutaneous nephrolithotomy, pediatric
 shock wave lithotripsy for. *See* Shock wave lithotripsy, pediatric
 ureteroscopic management of, 3107-3112
 equipment for, 3107-3109, 3109f-3110f
 indications for, 3107, 3108t, 3109f
 limitations and complications of, 3110-3112
 technique for, 3109-3110, 3111f
- Pediatric Urinary Incontinence Quality of Life Score (PIN-Q), 3300**
- Pediatric urologic examination**
 abdominal and flank, 2900-2901
 extended physical, 2900t, 2902-2904, 2903f, 2898.e1t-2898.e2t
 general exam, 2900
 genital, 2901-2902, 2901f
 female perineal, 2902
 penile, 2902
 scrotal, 2901-2902, 2901f
- Pediatric urology, development of genitourinary tract. *See* Development of genitourinary tract**
- Pediculosis pubis**
 infestation, 408-409, 409f
 as STD, 380
- PEKMB. *See* Pseudoepitheliomatous, keratotic, and micaceous balanitis**
- Pelvic anatomy, in women, 750.e2-750.e4, 750.e3f, 750.e5f**
- Pelvic autonomic plexus, 1619-1622, 1623f**
- Pelvic CT, 41, 42f-43f**
- Pelvic cysts, prenatal imaging of, 2910, 2911f**
- Pelvic fascia**
 female, 1598, 1599f
 male, 1614-1615, 1618f
 surgical anatomy of, 2643, 2643f-2644f
- Pelvic fibrosis, as laparoscopic and robotic surgery contraindication, 196**
- Pelvic floor**
 defects in, in bladder exstrophy, 3186-3187, 3186f
- Pelvic floor (Continued)**
 female, 1597, 1598f
 muscles of, 1601, 1603f, 750.e4
 mesh complications in pelvic reconstructive surgery in, 2042
 muscle abnormalities, in prostatitis and CPPS
 etiology, 308
 supporting structures of, 1939-1941
 anterior, 1942
 apical (middle), 1942
 bony scaffolding, 1939, 1940f
 connective tissue supports, 1941, 1941f
 endopelvic fascia, 1941, 1941f
 muscular supports, 1939-1941, 1940f-1941f
 posterior, 1942
 surgical anatomy of, 1939-1942, 1944b
- Pelvic floor disorders (PFDs), 1697**
 diagnostic evaluation of
 general considerations for, 1697-1698, 1698b, 1698f, 1698t
 genetics and, 1700
 history for, 1698-1700, 1700b
 history of present illness, 1699
 male incontinence, 1700
 medications and, 1699, 1699t
 past medical and surgical history, 1699
 impact of, 1697
 management of, 1708-1709
 for incontinence, 1708-1709
 for pelvic prolapse, 1709
 physical examination for, 1700-1701, 1700b, 1701f, 1701t, 1702b
 prevalence of, 1746f
 supplemental evaluation of, 1702-1708, 1705b
 circumstances for, 1702, 1702b
 cystoscopy, 1705-1706
 dye testing, 1705
 pad tests, 1704-1705
 postvoid residual, 1705
 quality-of-life instruments for, 1702-1704, 1703t-1704t
 questionnaires for, 1702-1704, 1703t-1704t
 radiographic imaging, 1707-1708
 symptom quantification instruments for, 1702
 urinalysis, 1705
 urodynamics, 1706-1707, 1707b
 voiding diaries for, 1702
- Pelvic floor muscle (PFM)**
 assessment of, for PFMT, 1883
 contraction of, to prevent stress incontinence, 1716, 1884
 dysfunction of, behavioral training for, 1891-1892
 electrical stimulation of, 1888-1889
 female, 1601, 1603f
 teaching control of, 1883-1884
- Pelvic floor muscle exercise (PFME), for urinary incontinence, in geriatric patient, 2099.e3**
- Pelvic floor muscle training (PFMT)**
 biofeedback for, 1887-1888, 1887f-1888f
 evidence for, 1884-1885
 exercise regimens for, 1884, 1884b
 handout for, 1884, 1885b
 levels of evidence and recommendations for, 1877t-1878t
 overview of, 1883-1886
 PFM assessment for, 1883
 for SUI, 1716, 1884
 teaching of, 1883-1884
 vaginal cones for, 1885-1886, 1885f

- Pelvic floor physiotherapy
for CP/CPPS treatment, 325
for detrusor underactivity, 1816-1817
- Pelvic fracture, bladder trauma with, 2386
- Pelvic fracture urethral injuries (PFUIs), 929-931, 938b, 2388-2389, 2389f, 2388.e1f
evaluation of, 931-932
postoperative management for, 935-937, 937f
repair of, 932-935, 933f-936f, 937
- Pelvic inlet, female, 1597, 1598f
- Pelvic lymphadenectomy (PLND)
in laparoscopic radical prostatectomy, 2673, 2681-2683, 2683b
complications with, 2683
indications for, 2681-2682
surgical technique for, 2682-2683, 2682f
for penile cancer, 865
for prostate cancer staging, 2607-2608
radical cystectomy with
anatomic extent of, 2226-2227
bilateral, 2226
density of, 2228
intraoperative decision making, 2228-2229
intraoperative frozen sections of ureter, 2228-2229
managing female urethra in, 2229
for muscle-invasive bladder cancer, 2225-2230
number removed in, 2227-2228, 2227f
oncologic outcomes following, 2229-2230, 2229t
prostatic urothelial carcinoma and, 2229
in robotic-assisted radical cystectomy, 2271-2272, 2274f
with transurethral resection of bladder tumor, 2246-2247, 2247f-2248f
- Pelvic nerve afferents, 1651, 1652f, 1652t
- Pelvic organ cross-sensitization, in BPS/IC
etiology, 345.e10-345.e11, 345.e11b
- Pelvic organ prolapse (POP). *See also* Pelvic floor disorders
in anterior compartment, 1942, 1943f, 1943t
in apical compartment, 1943, 1943t
classification of, 1697, 1698f, 1750
systems for, 1700-1701, 1701f, 1701t
conditions associated with, 1753b
definition of, 1750
epidemiology of, 1752-1753, 1753b
in geriatric patients, 2099.e9-2099.e10
history of, 1699
imaging of, 1609, 1609f
incidence of, 1752
midurethral sling outcomes for, 2022-2023
pathophysiology of, 1758-1759, 1759f
surgical correlation of, 1942, 1942f
physical examination of, 1751-1752, 1751f-1752f
in posterior compartment, 1943-1944, 1943t, 1944f
prevalence of, 1746f, 1752
questionnaires for, 1703t-1704t
reconstructive surgery for. *See* Pelvic organ prolapse reconstructive surgery
risk factors for, 1752-1753
societal and personal costs of, 1754
SUI symptoms with, 1707
symptoms of, 1750-1751
treatment for, 1709
urinary incontinence and, 1753, 1753b
- Pelvic Organ Prolapse Quantification (POPQ), 1700-1701, 1701f, 1701t, 1751, 1751f
- Pelvic organ prolapse reconstructive surgery, 2039-2040
in anterior compartment
abdominal paravaginal repair, 1951t-1952t, 1959-1960, 1959f
anterior colporrhaphy, 1948-1953, 1949f, 1950t-1952t
with cadaveric fascia, 1956-1957, 1957f, 1957t
with grafts, 1953-1958, 1955f
with polypropylene mesh, 1951t-1952t, 1955-1956, 1956f
with porcine dermis, 1951t-1952t, 1958, 1958f
with sling, 1960-1961, 1960f
vaginal paravaginal repair, 1950t, 1953, 1954f-1955f
in apical vaginal compartment, 1961-1978
abdominal hysteropexy, 1978
abdominal sacrocolpopexy, 1971-1974, 1971f-1973f
colpocleisis, 1974-1976. *See also* Colpocleisis, for apical pelvic organ prolapse repair
iliococcygeus suspension, 1968-1971, 1970f
sacrospinous ligament fixation, 1965-1968. *See also* Sacrospinous ligament fixation
transvaginal hysterectomy, 1976
uterine preservation, 1977-1978
uterine prolapse, 1976
uterosacral ligament suspension, 1961-1965. *See also* Uterosacral vault suspension
vaginal hysteropexy, 1978
approach to, 1949t
epidemiology of, 2039-2040
graft materials for, 1945-1948
biological, 1946-1947
classification of, 1945, 1946f
host interaction with, 1945-1946, 1946f
synthetic, 1947-1948, 1948f
materials for, 2040
mesh complications in, 2041-2043
anatomy of, 2041-2043
etiology of, 2041, 2042f-2043f
evaluation of, 2043-2045, 2044f-2045f, 2045t
in gastrointestinal tract and surrounding structures, 2042-2043
in genitourinary tract and surrounding structures, 2041-2042, 2043f
in pelvic floor, 2042
terminology for, 2045, 2045t
treatment of, 2045-2047, 2047f
in vagina, 2042
in posterior compartment, 1978-1982
interposition graft repairs of, 1982
posterior colporrhaphy, 1979-1982
preoperative counseling for, 1945
preparation for, 1944-1945, 1945b
vaginal kits for, 1982-1984, 1983f
- Pelvic Organ Prolapse Urinary Incontinence Sexual Function Questionnaire (PISQ), 753.e2
- Pelvic organs, female, 1605-1607, 1606f
- Pelvic pain, chronic, sacral nerve stimulation for, 1907-1908
- Pelvic plexus, for retropubic radical prostatectomy, 2641-2642, 2642f
- Pelvic plexus injury, LUTD after, 1781-1782
- Pelvic reconstructive surgery. *See* Pelvic organ prolapse reconstructive surgery
- Pelvic resections, RPLND with, 823
- Pelvic side effects, 823
- Pelvic surgery
medical diagnoses and, 1699
operative team placement for, transperitoneal and extraperitoneal procedures, 199, 199f
pathogenesis for, 3292
presentation for, 3290-3292
specific recommendations for, 3292
- Pelvic ultrasonography, transabdominal. *See* Transabdominal pelvic ultrasonography
- Pelviculocystic system, anatomy of, 973, 974f
endoscopic, 976-977, 977b, 977.e1f
radiologic, 973-974
- Pelvis
female. *See* Female pelvis
imaging studies of
for penile squamous cell carcinoma, 852
for TGCTs, 793-794, 794f
male. *See* Male pelvis
physical examination of, 11
- Pemphigus vulgaris, 398, 398f
- Pendulous urethra. *See* Penile urethra
- Penectomy, for penile cancer, 856
- Penetrating trauma
of bladder, 2386
penile, 2381, 916.e1
renal, 1148
imaging of, 1150
nonoperative management of, 1152
scrotal, 2383
urethral, 1157-1158, 1157t
diagnosis of, 1160-1161
- D-Penicillamine, for cystinuria, 1229-1230
- Penile angiography, 653, 654f
- Penile anomalies, 3369-3382
abnormal number, 3373-3374
aphallia, 3373, 3373f
diphallia, 3373-3374
accessory urethral openings, 3379-3380
congenital urethral fistula, 3379
urethral duplication, 3379-3380, 3380f
curvature, 3377, 3377f
genital lymphedema, 3380-3381
inconspicuous penis, 3369t, 3374-3376
buried penis, 3374-3375, 3374f-3375f
webbed penis, 3375f, 3376
masses, 3378-3379, 3378f-3379f
congenital penile nevi, 3379, 3379f
inclusion cysts, 3378, 3379f
juvenile xanthogranuloma, 3379
median raphe cysts, 3378-3379, 3378f
parametatal urethral cyst, 3378, 3378f
micropenis, 3369t, 3376-3377, 3376f, 3368.e1t
penoscrotal transposition, 3381-3382, 3381f-3382f
prepuce, 3369-3373
circumcision, 3370-3371
phimosis and paraphimosis, 3369-3370, 3369f
priapism, 3381
torsion, 3377-3378, 3378f
- Penile brachial pressure index, 653
- Penile cancer, 846
chemotherapy for, 871, 873b
adjuvant, 872
combination, 871-872, 872t
single-agent, 871
surgical consolidation after, 872-873
inguinal lymph node dissection for. *See* Inguinal lymphadenectomy
as non-AIDS-defining urologic malignancy, 386
nonsquamous neoplasms, 873, 876b
adenosquamous carcinoma, 875
basal cell carcinoma, 873, 874f
EPD, 874f, 875

- Penile cancer (Continued)**
 lymphoreticular malignant neoplasm, 875
 melanoma, 873-874, 874f
 metastases, 875-876
 sarcomas, 874-875, 874f
 radiation therapy for, 871b
 adverse effects of, 870
 inguinal areas, 870-871
 primary lesion, 868-870, 869t
 risk-based management of inguinal region in, 865
 bulky adenopathy and fixed nodal metastasis, 866f-867f, 868
 high-risk patients, 866-868, 866f-867f
 low- to intermediate-risk patients, 866, 866f-867f
 very low-risk patients, 865-866, 866f-867f
- squamous cell carcinoma**
 biopsy of, 850, 851b
 delay in diagnosis of, 850
 differential diagnosis of, 854
 epidemiology of, 847, 849b
 etiology of, 847-848, 849b
 examination of, 850
 histologic features of, 850-851, 851b
 laboratory studies of, 851
 natural history of, 849, 850b
 presentation of, 849, 850b
 prevention of, 848-849, 849b
 radiologic studies of, 851-852, 852b
 staging of, 852-854, 853t, 854b, 854f
 Tis, 846-847, 847b, 846.e1f
 surgical management of, 856b, 856t
 amputation, 856
 circumcision and limited excision strategies, 855-856
 laser ablation, 855-856
 Mohs micrographic surgery, 855
 organ preservation, 855
- Penile cell therapies, 492**
- Penile elephantiasis, as filariasis clinical manifestation, 444**
- Penile erection. See also Erectile dysfunction**
 physiology of
 functional anatomy of, 612-616, 613f-615f, 613t-614t
 hemodynamics and mechanism of erection and detumescence, 616-617, 616f-617f, 617t
 historical aspects of, 612
 neuroanatomy and neurophysiology of, 617-623, 617f-618f, 619t-620t, 623t
 smooth muscle, 623-629, 624f-626f, 628f, 629b, 629t
- Penile magnetic resonance imaging, 654**
- Penile near infrared spectrophotometry, 654**
- Penile pain, patient history of, 2**
- Penile plethysmography, 653-654**
- Penile prostheses, 492, 492.e2**
- Penile prosthesis surgery, 667**
 indications for, 747
 outcomes of, 748t
 techniques for, 747
- Penile revascularization surgery, 667**
- Penile thermal sensory testing, 657**
- Penile traction, and PD, 737-738**
- Penile tumescence and rigidity monitoring, 654-655, 655f**
- Penile tumors, 846**
 malignant. *See* Penile cancer
 premalignant cutaneous lesions, 846.e1
 Buschke-Löwenstein tumor, 846.e1f, 846.e4, 846.e4b
- Penile tumors (Continued)**
 non-human papillomavirus-related, 846.e1-846.e2, 846.e1f
 virus-related, 846.e2-846.e4, 846.e4b
- Penile urethra, 510, 511f, 910.e1, 910.e2f**
 carcinoma of, 881-882, 881f-882f
- Penis**
 amputation of
 for penile cancer, 856
 traumatic, 2381-2382, 916.e1, 916.e1f
 anatomy of, 513b, 612-616, 613t
 arterial supply, 513f, 614-615, 614f, 910.e3-5, 910.e4f-910.e5f
 corpora cavernosa, corpus spongiosum, and glans penis, 614, 614t
 lymphatic supply, 513, 910.e5
 nerve supply, 513, 514f, 910.e5
 reconstructive surgery and, 910.e1-3, 910.e1f-910.e7f, 910.e5, 910.e8b
 structure, 511-512, 512f
 venous drainage, 513, 615-616, 615f, 910.e3, 910.e5f
- curvatures of. See Curvatures of penis**
 dorsal vein of, 1617, 1621f
 in genitourinary tuberculosis, 423
 imaging of, cavernosogram, 513, 514f
 injuries and trauma of, 2379-2385, 916.e3b
 amputation, 2381-2382, 916.e1, 916.e1f
 animal and human bites, 2381
 burns, 2384-2385, 916.e2
 with circumcision, 3372, 3372f
 curvatures caused by, 941
 degloving, 916.e1-916.e2
 fracture, 941, 2379-2381, 2380f-2381f, 2379.e1f, 2380.e1f
 gunshot wounds, 2381
 pediatric, 3557-3558
 penetrating, 2381, 916.e1
 radiation trauma, 916.e2
 strangulation, 2382
 total reconstruction after, 944-945
 zipper, 2382
- length of, 3368-3369, 3369t**
- lymphatics of, 890**
- neuroanatomy and neurophysiology of**
 neurotransmitters, 620-623, 623t
 spinal centers and peripheral pathways, 617-618, 617f-618f, 619t
 supraspinal pathways and centers, 618-620, 619t-620t
- physical examination of, 10**
- physiology of**
 corpora cavernosa, 616-617, 616f-617f
 corpus spongiosum and glans penis, 617, 617t
 smooth muscle, 623-629, 624f-626f, 628f, 629b, 629t
- preservation of, in penile cancer management, 855**
- reattachment of, 2381-2382, 2382b, 916.e1, 916.e1f**
- reconstructive surgery of, 492, 493f-494f, 907, 917b, 492.e2**
 for amyloidosis, 913
 anatomic considerations for, 910.e1-3, 910.e1f-910.e7f, 910.e5, 910.e8b
 for circumcision complications, 915
 in classic bladder exstrophy, 3203-3209
 corpora cavernosa, 492, 493f-494f
 for curvatures of penis, 939-941, 941b
 for failed hypospadias repair, 915-916
 for female-to-male transsexualism, 945, 945b
- Penis (Continued)**
 for fistulae of posterior urethra, 938-939, 939b
 for genital trauma, 916.e1-2, 916.e1f, 916.e3b
 for LS, 912-913, 913f
 in male epispadias, 3223
 for meatal stenosis, 914-915
 microvascular, 2382
 for paraphimosis, balanitis, and phimosis, 914
 for PFUs, 932-935, 933f-936f, 937
 posttraumatic, 2385
 principles of, 907-911, 908f-910f, 910b
 for reactive arthritis, 911-912
 for residual abnormality in patients with exstrophy, 915-916
 surgical technique generalities for, 910-911, 911b, 910.e1f
 total penile, 941-945, 943f, 945b
 for urethral diverticulum, 913-914
 for urethral hemangioma process, 911
 for urethral stricture disease, 920-929, 922f-931f, 931b
 for urethrocuteaneous fistula, 913
 for vesicourethral distraction defects, 937-938, 939b
 ultrasonography of, 80-82, 81f-82f
- Penn pouch, 2335-2336, 2335f-2336f**
- Penoscrotal transposition, 3381-3382, 3381f-3382f**
- Pentoxifylline, for PD, 734-735**
- Peptide hormones, of reproductive access, 516, 517f**
- Peptidergic agents, in ureteral function, 992**
- PERC Mentor, 175, 175f**
- Percutaneous ablative therapy, for renal tumors, 1487-1489, 1488f, 1494**
- Percutaneous access, to upper urinary tract**
 collecting system, 170b
 anatomic considerations for, 154-157, 154f-157f, 157b
 anesthesia for, 158
 antegrade approach to, 161-166, 162f-166f
 anticoagulant management for, 158
 complications of, 175-182, 176f-180f, 182b
 history of, 153
 indications for, 153-154
 modifications for special situations, 168-170, 170f
 patient positioning for, 158-159, 159f
 periprocedural antimicrobials for, 157-158
 postprocedural nephrostomy drainage for, 170-174, 171f-174f, 174b, 181, 171.e1f
 retrograde assistance for, 160-161, 161f, 160.e1f
 site selection for, 159-160, 160f
 training in, 175, 175f
 working access, 166-168, 167f-169f, 168.e1f
- Percutaneous antegrade endopyelotomy, for ureteropelvic junction obstruction, 1109-1111**
 complications with, 1111
 indications and contraindications for, 1109, 1109f
 nephrolithotomy simultaneous with, 1111
 patient preparation for, 1110
 postoperative care for, 1110-1111
 results with, 1111
 technique for, 1110, 1110f
- Percutaneous approach, to UTUC, 1392**
 results of, 1394-1396, 1397t
 technique and instrumentation for, 1392-1394, 1394f-1396f

- Percutaneous cystolithotomy, for bladder calculi, 1295
- Percutaneous cystolithotripsy
for pediatric stone disease, 3118, 3119f
stone-free status determination, 3119
- Percutaneous endopyeloplasty, for ureteropelvic junction obstruction, 1111
- Percutaneous nephrolithotomy (PCNL)
anesthesia for, 1277-1278
antibiotic prophylaxis for, 1277
bilateral simultaneous, 1281-1282
complications of, 1282
historical overview of, 1235.e2
laser lithotripsy for, 234.e2
morbid obesity and, 1255, 1281
old age and frailty and, 1255-1256
pediatric, 3112-3118, 3113t
outcomes with, 3113t, 3116-3118
planning for, 3112-3115, 3114f-3116f
technique for, 3115-3116, 3117f
pneumatic lithotripsy for, 233.e1
prior renal surgery and, 1256
for renal calculi, 1278
in calyceal diverticula, 1244, 1278-1281, 1279f
in horseshoe kidneys, 1246, 1279-1280
lower pole calculi, 1247-1250, 1247f, 1248t, 1249f
in renal ectopia, 1246-1247, 1247f
after renal transplantation, 1280, 1280f
stone composition and, 1242-1243, 1242f-1243f, 1243.e1
stone localization and, 1241-1242
renal function and, 1254-1255
renal transplants and, 1257
solitary kidney and, 1255
spinal deformity or limb contractures and, 1256
for staghorn calculi, 1240-1241, 1280-1281
stone burden and
between 1 and 2 cm, 1239-1240, 1239f
greater than 2 cm, 1239f, 1240
up to 1 cm, 1238-1239, 1238b
uncorrected coagulopathy and, 1256
for ureteral calculi
duplicated collecting system and, 1253
in megaureter, 1253
outcome of, 1257-1259
stone burden and, 1252-1253
stone composition and, 1253
stone localization and, 1251-1252, 1252t
urinary diversion and, 1256-1257
urinary tract infection and, 1254
- Percutaneous nephrostomy (PCN), 153-154
for pediatric genitourinary trauma, 3542-3544
tubes. *See* Nephrostomy tubes
- Percutaneous procedures, antimicrobial prophylaxis for, 264
- Percutaneous stone removal, historical overview of, 1235.e2
- Percutaneous suprapubic catheter placement, 125, 125f
- Percutaneous tibial nerve stimulation (PTNS)
for emptying disorders, 1916
for UIII, 1715
- Percutaneous transluminal renal angioplasty (PTR), for renovascular hypertension, 1036-1039, 1037b, 1039b, 1040f
- Perforation
of bladder, in transurethral resection of bladder tumor, 2244, 2244f
with monopolar transurethral resection of prostate, 2514
ureteral, ureteroscopic, 1167, 1283-1284
- Perfusion studies
for UPJO, 1107
for ureter obstruction, 998-999, 999f
- Perimedial fibroplasia, renovascular hypertension caused by, 1033, 1033t, 1034f
- Perinatal neuroblastoma, surgical treatment of, 3565
- Perinatal stem cells, for tissue engineering, 484-485
- Perinatal testicular torsion, 3391-3392, 3391f
- Perinatal urology
antenatal management of fetal uropathies, 2886-2888, 2886t, 2887f, 2888b
fetal diagnosis, 2873-2878, 2874f-2876f, 2874t, 2877t, 2878b
fetal imaging, 2873
neonatal urologic emergencies, 2889-2891, 2889t
postnatal management of antenatally detected urologic renal abnormalities, 2888-2889, 2889b
specific diagnoses, 2875f, 2878-2886, 2878f-2885f, 2886b
summary of, 2891
- Perineal body, 1603, 910.e6f-910.e7f, 910.e8
fasciae of, 1615, 1617f-1619f
- Perineal mass, in female, neonatal, 2889-2890
- Perineal membrane, 1603, 1939-1941
- Perineal pain, after transurethral needle ablation of prostate, 2525
- Perineal prostatectomy, for localized prostate cancer, 2614
- Perineal radical prostatectomy, 2662
closure for, 2662.e3
morbidity with, 2662.e4
nerve-sparing dissection, 2662.e2-2662.e3, 2662.e2f-2662.e3f
pathologic outcomes with, 2662.e4
patient positioning for, 2662.e1, 2662.e1f
patient selection for, 2662.e1
postoperative care for, 2662.e3-2662.e4
preoperative care for, 2662.e1
prostate exposure for, 2662.e1-2662.e2, 2662.e2f
summary for, 2662.e4, 2662.e4b
vesicourethral anastomosis, 2662.e3-2662.e4, 2662.e3f
- Perineal ultrasonography, of penis and male urethra, 80, 81f
- Perineorrhaphy, posterior colporrhaphy with, for pelvic organ prolapse repair, 1980
- Perinephric abscess
as renal infection, 283-285, 284f
after renal injury, 1157
- Perinephric drain placement, for pediatric genitourinary trauma, 3542-3544
- Perineum
fasciae of, 1615, 1617f-1619f
female, 1603-1604, 1605f
Fournier gangrene and, 402-404, 404f
male, 1617f-1619f, 1625f-1626f, 1628-1630, 1629f
anatomy of, 910.e5-910.e8, 910.e6f-910.e7f, 910.e8b
- Perioperative care, for pediatric patients, 2949
anesthesia and analgesia, 2952-2958, 2954f-2955f, 2956t-2957t, 2958b, 2966, 2966f
fluids, 2951-2952, 2951t, 2952b
growth and maturation considerations, 2949-2951, 2951b
intraoperative considerations, 2960, 2960b
postoperative complications, 2960-2961, 2961t-2962t, 2962b
surgical preparation, 2958-2960, 2959t, 2960b
- Perioperative chemotherapy, for retroperitoneal sarcoma, 1409-1411
- Perioperative management, for adrenal surgery, 1580-1581
- Perioperative radiotherapy, for retroperitoneal sarcomas, 1409-1411
- Peripheral benzodiazepine receptor (PBR), 522
- Peripheral nervous system, of lower urinary tract, 1649-1667, 1651f
afferent pathways, 1650-1657, 1652f-1653f, 1652t, 1655f-1657f
efferent pathways, 1657-1663, 1658f-1665f, 1662t
parasympathetic pathways, 1649-1650, 1651f
somatic pathways, 1650, 1651f-1652f
supraspinal pathways, 1663-1667, 1666f-1668f
sympathetic pathways, 1650, 1651f
- Peripheral neuropathy, perioperative, prevention of, 114-115, 114b
- Periprosthetic plexus, 508
- Perirenal anatomy, 154-155, 154f
- Peristalsis, of ureters, 978
age effects on, 1002, 1002f-1003f
cellular anatomy in, 978
contractile activity, 984-988, 984f-985f, 987f-988f
development pathways and, 978-979, 979f
drug effects on, 1003-1006
electrical activity, 979-984, 980f-983f
mechanical properties, 988-989, 989f-990f
nervous system function in, 989-993
pathologic processes affecting, 995-1002, 996f-1000f
pregnancy effects on, 1002-1003
urine transport by, 993-995, 994f-995f
- Peritoneal dialysis, 2870-2871
- Peritoneal flap, for vesicovaginal fistula repair, 2116, 2118f
- Peritoneum
female, 1597-1599, 1599f
male, 1614, 1616f
- Peritubular tissue, of testis, 523, 525f
- Periurethral abscess, 303, 303b
- Periurethral bulking agents
for neuromuscular dysfunction of lower urinary tract, 3282.e3
urethral diverticula differentiated from, 2163
- Periurethral glands, 1608
urethral diverticula and, 2153
- Periurethral injection technique, for stress urinary incontinence, 2051-2053, 2051f-2052f
- Periurethral nerve, external, electrical stimulation of, for bladder storage disorders, 1909
- Periurethral region, natural defenses of, 247
- Permeability, of urothelium of bladder, 1632, 1638-1639, 1638f
- Pernicious anemia, lower urinary tract dysfunction with, 1780
- Persistent genital arousal disorder (PGAD), 760-761
etiology of, 761
evaluation of, 761
treatment of, 761
- Persistent müllerian duct syndrome (PMDS), 3493f, 3494
- Persistent penile erection, with monopolar transurethral resection of prostate, 2514-2515
- Pessaries
incontinence, 1895, 1895f-1896f
for pelvic organ prolapse, 2099.e9
- PET. *See* Positron emission tomography
- Peyronie disease (PD)
and aging, 723
and collagen disorders, 725
and combination therapy, 738

- Peyronie disease (PD) (*Continued*)
 curvatures of penis associated with, 941
 and diabetes, 723-724, 724f
 diagnosis and management of
 conclusion, 748
 epidemiology, 723-725, 724f, 725b-726b
 etiology, 727f, 728-729, 729b
 evaluation of patient, 730-732, 730f-733f, 732b-733b
 general considerations, 722, 723b
 natural history of, 722-723
 nonsurgical treatment, 733-738, 739b, 739f-740t
 penile anatomy, 726-728, 726f-727f, 729b
 surgical, 738-747, 741b, 742t, 743f-744f, 744t, 748b, 748t
 symptoms, 730
 treatment protocols, 733, 739f
 and ED, 724
 and electromotive drug administration, 737
 and external force application, 740t
 and extracorporeal shock wave therapy, 737
 and fibrotic gene expression, 727f, 729
 and hypogonadism, 725
 and impact of wound healing, 727-728
 incidence of, 723
 intralesional injections for, 735-736, 740t
 oral medications for, 733-735, 739f
 and penile traction, 737-738
 and psychological aspects, 724-725
 and radiation therapy, 738
 and radical prostatectomy, 725
 and role of myofibroblasts, 728-729
 and role of nitric oxide, 728
 and role of oxygen free radicals and oxidative stress, 728
 and role of transforming growth factor- β 1, 729
 surgical management of
 indications, 738-741, 741b
 penile prosthesis, 747
 tunica lengthening procedures, 744-747
 tunical shortening procedures, 741-744, 743f-744f, 744t
 topical drug application for, 736
 and vacuum therapy, 738
 PFDs. *See* Pelvic floor disorders
 PFM. *See* Pelvic floor muscle
 PFME. *See* Pelvic floor muscle exercise
 PFMT. *See* Pelvic floor muscle training
 PFSE. *See* Profile of Female Sexual Function and Personal Distress scale
 PFUIs. *See* Pelvic fracture urethral injuries
 PG. *See* Pyoderma gangrenosum
 PGAD. *See* Persistent genital arousal disorder
 PGI-I. *See* Post-operative Patient Global Impression of Improvement
 PGs. *See* Prostaglandins
 pH
 renal maintenance of, 1023-1025
 urine, low
 in calcium stone formation, 1188
 in uric acid stone formation, 1190-1192, 1192f
 of urine, 14
 pH disturbances, renal pathophysiology
 involved in, 1025-1027, 1025b, 1026t, 1027b
 PHA-I. *See* Pseudohypoaldosteronism type I
 Pharmacologic therapy
 in ED
 intracavernosal injection, 664-665
 intraurethral suppositories, 665-666
 oral, 662-664
 transdermal/topical, 666
 Pharmacologic therapy (*Continued*)
 to facilitate bladder emptying, 1870-1874
 by bladder contractility, 1870-1873
 by decreasing outlet resistance, 1873-1874
 by increasing intravesical pressure, 1870-1873
 to facilitate bladder filling and urine storage, 1836-1870, 1839t
 α -adrenoreceptor antagonists, 1853-1854
 β -adrenoreceptor antagonists, 1854-1855
 antidepressants, 1839t, 1856-1858
 antimuscarinic agents, 1838-1841, 1839t, 1852b. *See also* Antimuscarinic agents, to facilitate bladder filling and urine storage in augmented or intestinal neobladders, 1866
 botulinum toxins, 1839t, 1861-1863
 cannabinoids, 1866.e2-1866.e3
 centrally acting drugs, 1866.e3-1866.e4
 combinations for, 1859-1861
 cyclooxygenase inhibitors, 1858
 desmopressin for, 1864-1866
 dimethyl sulfoxide, 1858-1859
 estrogens for, 1863-1864
 future possibilities of, 1866
 gabapentin, 1866.e3
 gonadotropin-releasing hormone antagonists, 1866.e3
 guidelines for, 1838, 1838f-1839t
 hormones for, 1864-1866
 by increasing outlet resistance, 1866-1870
 by inhibiting bladder contractility, 1836-1866
 intraprostatically injected drugs, 1866.e2
 membrane channel activity, 1839t, 1852-1853
 muscarinic receptors in, 1836-1837, 1838t
 NK $_1$ -receptor antagonists, 1866.e4
 phosphodiesterase inhibitors, 1855-1856
 prostanoid-receptor agonists and antagonists, 1866.e1-1866.e2
 toxins, 1861-1863
 tramadol, 1866.e3-1866.e4
 transient receptor potential channel antagonists, 1866.e1
 vanilloids for, 1863, 1863.e1
 vitamin D $_3$ -receptor analogues, 1866.e1
 for lower urinary tract
 adrenergic mechanisms, 1670-1671, 1671f
 afferent neuropeptides, 1671-1673, 1672t
 muscarinic mechanisms, 1667-1670, 1669t, 1670b
 sex steroids, 1673
 urethral tone in women, 1671
 Phenazopyridine, for pelvic floor disorder testing, 1705
 Phenergan. *See* Promethazine
 Phenol, vasectomy sterilization performed with, 951
 Phenotype-directed multimodal treatment strategy, for CP/CPPS, 327-328, 328f
 Phenotypic gender development, 516
 Phenotypic sexual differentiation, 3474-3475, 3475f-3476f
 Phenoxybenzamine (Dibenzylamine)
 to facilitate bladder emptying, 1874.e1
 ureteral response to, 992
 Phentolamine (Regitine), 665
 ureteral response to, 991-992
 Phenylephrine
 in priapism, 680-681
 ureteral response to, 991-992
 Phenylpropanolamine (PPA), for stress urinary incontinence in women, 1867
 Pheochromocytoma
 clinical characteristics, 1547, 1547t
 diagnostic tests, 1547-1550, 1548f-1549f, 1549t, 1574-1575, 1574t
 hereditary, 1545, 1546t, 1547, 1550, 1550f, 1552
 increased adrenal function in, 1545-1553, 1545f, 1546t-1547t, 1548f-1551f, 1549t, 1553b, 1574-1575, 1574t
 malignant, 1545-1547, 1552
 MRI of, 49, 51f
 overview and epidemiology, 1545, 1545f
 pathophysiology, 1545-1547
 prognosis, 1552-1553
 surgery, 1580-1581, 1581b
 treatment, 1550-1552, 1551f, 1580-1581, 1581b
 Phimosis, 3369-3370, 3369f
 urethral reconstructive surgery for, 914
 Phosphate
 in crystal formation, 1178
 FGF-23 and, 1011f, 1012
 PCT reabsorption of, 1015, 1015f
 transport of, urinary tract obstruction and, 1096
 Phosphatidylinositol 3-kinase (PI3K) pathway, in prostate cancer, 2557
 Phosphodiesterase
 in ED, 627-628
 for PE, 700
 Phosphodiesterase inhibitors (PDEIs)
 for benign prostatic hyperplasia, 2493-2498, 2494t-2495t, 2496f-2497f
 for BPS/IC oral therapy, 355
 to facilitate bladder filling and urine storage, 1839t, 1855-1856
 ureteral response to, 987, 1001
 Phosphodiesterase type 5 inhibitors (PDE5-I)
 for ED, 662-664, 662t, 663b
 TT combination therapy with, 547
 for PD, 735
 for priapism, 683
 for ureteral relaxation, 1001
 Phosphorus, metabolism of, 1180-1181
 Phosphorylcholine, in prostatic secretions, 2415-2416
 Photodynamic therapy (PDT)
 for prostate cancer
 localized, 2626, 2732
 outcomes with, 2737
 for refractory high-grade non-muscle-invasive bladder cancer, 2217
 Photoselective vaporization of prostate (PVP), 2530-2533
 in anticoagulated patients, 2532
 complications with, 2532-2533
 intraoperative, 2532
 perioperative, 2532
 postoperative, 2532-2533
 conclusion for, 2533
 outcomes with, 2531-2532
 comparative studies for, 2532
 single-cohort studies for, 2531
 overview and concept for, 2530
 technique for, 2530-2531
 intraoperative, 2530-2531
 postoperative, 2531
 preoperative, 2530
 Photothermal therapy, for prostate cancer, 2732-2733
 outcomes with, 2737
 PHs. *See* Primary hyperoxalurias
 Physical activity, benign prostatic hyperplasia and, 2442-2444, 2445t

- Physical examination, 9b
 bladder, 10, 10f
 female pelvis, 11
 general observations, 9
 kidneys, 9, 9f
 of male reproductive system, 562-564, 564b
 phallus exam, 564
 prostate and seminal vesicle exam, 564
 scrotal exam, 563
 spermatic cord, 563-564
 testis and epididymis exam, 563, 563f
 neurologic, 12, 12f
 penis, 10
 rectum and prostate, 11
 scrotum, 10-11, 11f
 in urinalysis, 13-14, 13t
- Physostigmine, ureteral response to, 991
- Phytotherapeutic agents, for CP/CPPS treatment, 324
- Phytotherapy
 for benign prostatic hyperplasia, 2498-2501
 extract composition of, 2498-2499, 2498b
 mechanism of action, 2499-2501, 2499b
 origin of agents for, 2498, 2498t
- PI3K pathway. *See* Phosphatidylinositol 3-kinase pathway
- PI3K/Akt/mTOR pathway, in castration-resistant prostate cancer, 2815-2816
- PIA. *See* Proliferative inflammatory atrophy
- Piezoelectric generator, for shock wave lithotripsy, 1266, 1267f
- Pigment nephropathy, ATN with, 1044-1045
- Pili
 bacterial type 1 (mannose-sensitive), 242-243
 P (mannose-resistant), 243
- PIN. *See* Prostatic intraepithelial neoplasia
- PIN-Q. *See* Pediatric Urinary Incontinence Quality of Life Score
- PIP. *See* Projected isovolumetric pressure
- Piperacillin/tazobactam, preoperative prophylaxis with, 106t-107t
- Pippi Salle procedure, for bladder neck reconstruction, 3342, 3343f
- Pirarubicin, for UUTUC, 1379
- PISQ. *See* Pelvic Organ Prolapse Urinary Incontinence Sexual Function Questionnaire
- Pituitary, anterior. *See* Anterior pituitary
- Pituitary dysfunction, and male infertility, 575-576
- Pivmecillinam, for UTIs, 256t-258t, 260, 267, 267t
- PKA. *See* Protein kinase A
- PKG. *See* Protein kinase G
- Placebo conundrum, BPS/IC treatment and, 362-363
- Plain film radiography, abdominal. *See* Abdominal plain film radiography
- Plaques, of urothelium of bladder, 1632-1633
- Plasma creatinine (PCR), GFR estimation with, 1008-1009, 1008f
- Plasma free metanephrines, in evaluation of adrenal masses, 1574-1575, 1574t
- Plasma markers, GFR estimation with, 1008-1009, 1008f
- Plasmacytoid tumor, 2201
- Plasminogen activator inhibitor-1 (PAI-1), 549
- Plasticity, in lower urinary tract dysfunction, 1763
- PLESS. *See* Proscar Long-Term Efficacy and Safety Study
- Pleural injury, after percutaneous access to upper urinary tract collecting system, 179-180, 180f
- PLND. *See* Pelvic lymphadenectomy
- Ploidy-flow cytometry, in UUTUC, 1376
- Pluripotent stem cells, induced, for tissue engineering, 484
- PMDs. *See* Persistent müllerian duct syndrome
- PN. *See* Partial nephrectomy
- PNET. *See* Primitive neuroectodermal tumor
- Pneumatic compression stockings, VTE prophylaxis with
 for laparoscopic and robotic surgery, 223
 preoperative, 108-109, 108t-109t
- Pneumatic lithotripsy, 231t, 232, 233b
 basic physics of, 232-233
 for bladder stones, 233.e1
 for percutaneous nephrolithotomy, 233.e1
 tissue effects of, 233
 ureteroscopy with, 233.e1
- Pneumaturia, patient history of, 7
- Pneumomediastinum, during laparoscopic and robotic surgery, 217
- Pneumopericardium, during laparoscopic and robotic surgery, 217
- Pneumoperitoneum, for laparoscopic and robotic surgery
 acid-base metabolic effects of, 214
 cardiovascular effects of, 212-213, 213t
 complications related to, 216
 establishment of, 200-201, 201f, 200.e1, 200.e1f, 201.e1f, 201.e2, 202.e1
 mesenteric blood flow and intestinal motility effects of, 213-214
 pressure of, 212, 213t
 renal effects of, 213, 213t
 respiratory effects of, 213, 213t
- Pneumothorax
 during laparoscopic and robotic surgery, 217
 after percutaneous access to upper urinary tract collecting system, 179-180
- Podophyllin, for condylomata acuminata, 846.e2-846.e3
- POIS. *See* Postorgasmic illness syndrome
- Polaris Loop stents, 127f
- Poliomyelitis, lower urinary tract dysfunction with, 1780
- Politano-Leadbetter technique, 3158
- Pollakiuria, 3310
- Polyacrylamide hydrogel (Bulkamid), for female SUI injection therapy, 2059-2060, 2059t
- Polyacrylate polyalcohol copolymer (PPC), for vesicoureteral reflux, 3169.e1
- Polyamines, in prostatic secretions, 2415
- Polyanion macromolecules, in crystal formation, 1178-1179
- Polycystic kidney disease
 autosomal dominant. *See* Autosomal dominant polycystic kidney disease
 autosomal recessive. *See* Autosomal recessive polycystic kidney disease
- Polycythemia, in RCC, 1335
- Polydimethylsiloxane (PDS), for vesicoureteral reflux, 3169
- Polyethylene glycol solution (GoLYTELY), 107
- Polyorchidism, 3442-3443
- Polypharmacy, 2092-2095
- Polypropylene mesh, for pelvic organ prolapse reconstructive surgery, 1951t-1952t, 1955-1956, 1956f
- Polytetrafluoroethylene paste (Teflon paste), in vesicoureteral reflux, 3169
- Polyuria
 etiology of, 1835
 management of, 1835, 1835b
 nocturia and, 1824, 1824t, 1835
 transient urinary incontinence and, 2096.e1
- Pontine micturition center, 1663, 1666f
- Pontine. *See* Copyrighted Material
- PONV. *See* Postoperative nausea and vomiting
- POP. *See* Pelvic organ prolapse
- Popcorn technique, 234
- POPQ. *See* Pelvic Organ Prolapse Quantification
- Population trends, aging and, 2083
- Porcine dermal collagen
 for female SUI injection therapy, 2060
 for pelvic organ prolapse reconstructive surgery, 1951t-1952t, 1958, 1958f
- Pore size, of grafts, 1946
- Port placement
 for laparoscopic RPLND, 839-840, 840f
 for robotic RPLND, 842-843, 843f
 for robotic surgery in pediatric patients, 2969, 2970b, 2970f-2972f
- Port removal, after laparoscopic and robotic surgery, 210-211
- Port site closure, after laparoscopic and robotic surgery, 211, 211f
- Portal vein, 777, 777.e2f
- Port-site recurrence, of renal malignancy, 1469
- Positioning. *See* Patient positioning
- Positron emission tomography (PET)
 for biochemical recurrence after radical prostatectomy, 2773, 2773f
 for penile squamous cell carcinoma, 852
 in urologic oncology, 39-40
- Postchemotherapy retroperitoneal lymph node dissection (PC-RPLND), 815, 817-818
 adjuvant chemotherapy at, 830-831
 auxiliary procedures for, 822, 824b
 hepatic resection, 823
 major vascular reconstruction, 822-823
 nephrectomy, 822, 822t
 pelvic resection, 823
 supradiaphragmatic disease management, 823-824, 824f
 in cases of clinical complete remission to induction chemotherapy, 825, 825t
 in high-risk populations, 832b
 desperation RPLND, 831-832, 831t
 after HDCT, 831, 831t
 late relapse RPLND, 831t, 832
 reoperative RPLND, 831t, 832
 salvage RPLND, 831, 831t
 histologic findings at, survival outcomes and, 829-831, 829f, 830t, 831b
 template use in PC-RPLND, 826-827, 828t
- Postchemotherapy surgery (PCS)
 for NSGCTs, 802-805, 803t
 for seminomas, 809
- Posterior colpoperineorrhaphy, 1978-1979
- Posterior colporrhaphy, for pelvic organ prolapse repair, 1979-1982
 results of, 1980-1982, 1981t
 technique for, 1979-1980, 1979f
 perineorrhaphy, 1980
 site-specific, 1979, 1980f
- Posterior compartment prolapse, 1750
- Posterior lumbodorsal approach, to open adrenalectomy, 1582-1583, 1583f
- Posterior lumbotomy, for ureteropelvic junction obstruction in pediatric patients, 3062, 3065f
- Posterior tibial nerve, electrical stimulation of, for bladder storage disorders, 1910
- Posterior urethral valves, prenatal, 2875f, 2880, 2880f
- Postexposure prophylaxis, for HIV treatment, 382.e6
- Posthysterectomy vesicovaginal fistulae, 2105
- Postmicturition leakage or dribble, 1711
 treatment of, 1717
- Postnatal growth and maturation, 2950-2951
- Postnatal sonography, 2911, 2913f-2914f
- Postobstructive diuresis, 1102

- Postoperative care
 for laparoscopic simple nephrectomy, 1457
 for pediatric patients, 2960
 complications, 2960-2961, 2961t-2962t, 2962b
 pain management, 2956-2958, 2956t-2957t
 for renal transplantation
 allograft nephrectomy, 1086-1087
 anticoagulation, 1083
 immunosuppression protocols, 1084-1086, 1084f, 1085b, 1085t
 infection, 1086, 1086t
 malignancy, 1087
 pregnancy and childbearing, 1087, 1087t
 rejection, 1083-1084
 surgical complications, 1083, 1083f
 for RPLND, 821-822
 laparoscopic, 843
 for vasectomy, 952
- Postoperative complications, adrenal surgery, 1594, 1594b
- Postoperative management, in
 pheochromocytoma treatment, 1552
- Postoperative nausea and vomiting (PONV), in
 pediatric patients, 2961
- Post-operative Patient Global Impression of
 Improvement (PGI-I), 1702-1704
- Postoperative urinary retention, lower urinary
 tract dysfunction and, 1789-1790
- Postorgasmic illness syndrome (POIS), 692, 707.e1, 707.e1b
- Postpartum, urinary incontinence and, 1748
 PFMT for, 1885
- Postprostatectomy incontinence (PPI), 1757
 injection therapy for. *See* Injection therapy for
 male postprostatectomy SUI
 pathophysiology of, 2064-2067
 PFMT for, 1885
 workup of, 2064
- Postrenal azotemia, 1042
- Post-stimulus voiding, 1915
- Poststreptococcal glomerulonephritis (PSGN), 2854, 2859
- Post-translational modifications, of androgen
 receptors, 2410
- Postvasectomy pain syndrome, 952
- Postvoid dribbling, patient history of, 4
- Postvoid residual (PVR)
 in benign prostatic hyperplasia, postoperative, 2469
 in bladder and bowel dysfunction, 3304-3305
 male urinary incontinence and, 1706-1707
 in pediatric patients, 3128, 3130, 3131f
 pelvic floor disorders and, 1705
 for sling procedure, 1989
 urinary flow rate with, 1730
 in urinary incontinence, in geriatric patients, 2099.e1
 in urodynamic studies, 1722
- Potaba, for PD, 733-734
- Potassium
 in collecting tubule, 1018-1019, 1018f
 in loop of Henle, 1016, 1017f
 PCT reabsorption of, 1014
 transport of, urinary tract obstruction and, 1096
- Potassium channel openers
 to facilitate bladder filling and urine storage, 1839t, 1852-1853
 urethral function effects of, 1005
- Potassium channels, in detrusor muscle, 1644-1645, 1644f
- Potassium chloride test, for BPS/IC diagnosis, 349-350
- Potassium citrate
 for cystinuria, 1229
 for enteric hyperoxaluria, 1227
 for gouty diathesis, 1229
 for hyperuricosuric calcium nephrolithiasis, 1227
 for hypocitraturia in chronic diarrhea, 1228
 for hypocitraturic calcium nephrolithiasis, 1228
 for hypomagnesiuric calcium nephrolithiasis, 1228-1229
- Potassium imbalances, renal pathophysiology
 involved in, 1023, 1023b-1024b
- Potassium titanyl phosphate (KTP) laser, 229
- Potassium-magnesium citrate, for
 hypomagnesiuric calcium nephrolithiasis, 1229
- Potency, brachytherapy and, 2702
- Potter syndrome, neonatal, 2890
- Pouch of Douglas, 1599, 1599f
- Power Doppler ultrasonography, 69
 transrectal, for prostate biopsy, 2588-2589, 2589f-2590f
- PPA. *See* Phenylpropanolamine
- PPC. *See* Polyacrylate polyalcohol copolymer
- PPI. *See* Postprostatectomy incontinence
- PPIUS. *See* Patient Perception of Intensity of
 Urgency Scale
- PPNAD. *See* Primary pigmented nodular
 adrenocortical disease
- Practice accreditation, for ultrasonography, 84
- Practice effect, 96
- Prazosin
 to facilitate bladder emptying, 1874.e1
 ureteral response to, 992
- PRBCs. *See* Packed red blood cells
- Precipitancy, 2097
- Precoital pseudoephedrine, for delayed
 ejaculation, 706-707
- Predictive validity, 96-97, 97t
- Prednisolone, for post-transplant
 immunosuppression, 1084-1085
- Prednisone
 for post-transplant immunosuppression, 1085t
 premedication with, for preventing contrast
 media reactions, 29, 29b
 preoperative, 103
- Preexposure prophylaxis, for HIV, 382.e6
- Pregnancy
 augmentation cystoplasty and, 3354-3355
 bacteriuria in, 293-294, 297b
 anatomic and physiologic changes and, 294-295, 294f, 295t
 complications of, 295-296
 management of, 295-296, 296t
 pathogenesis, 294
 renal insufficiency and, 296
 and female sexual function, 753-754
 genitourinary tuberculosis management
 during, 432
 host defense mechanisms in UTIs and, 249, 249.e1
 as laparoscopic and robotic surgery
 contraindication, 196
 PFMT during, 1885
 preoperative care for, 104
 renal calculi in, 1199
 medical management of, 1233
 after renal transplantation, 1087, 1087t
 RMS treatment effects on, 3587-3588
 transitional urology and, 3526
 ureter physiology effects of, 1002-1003
- Pregnancy (Continued)
 urinary calculi during
 etiology of, 1287
 evaluation of, 1288-1289, 1288f
 incidence of, 1287
 treatment of, 1289
 urinary incontinence and, 1748
 conservative interventions for, 1895
 vesicoureteral reflux and, 3152-3153
 Wilms tumor treatment effects on, 3579
- Pregnancy test, presurgical, 100
- Premature birth
 clinical implications of, 2949
 perioperative care for children with history of, 2955
- Premature ejaculation, 692, 700b
 and assessment of erectile function, 698
 causes of
 acquired premature ejaculation, 696
 comorbid erectile dysfunction, 696
 hyperthyroidism, 697
 lifelong premature ejaculation, 696
 prostate disease, 696-697
 sexual performance anxiety, psychological
 problems, and relationship problems, 696
 classification of, 692-693
 definition of, 693-695, 694t, 693.e1
 and determination of intravaginal ejaculation
 latency time, 697
 diagnosis of, 697
 evaluation of, medical history, 697, 697b
 patient history of, 6
 patient-reported outcome measures
 index of premature ejaculation, 698.e1
 premature ejaculation diagnostic tool, 698.e1
 premature ejaculation profile, 698.e1
 physical examination of, 698
 prevalence of, 695-696, 696f
 treatment of
 pharmacologic, 698-700, 699f, 701t
 psychosexual therapy, 698, 699f, 698.e2
- Prematurity, from bacteriuria in pregnancy, 295
- Premedication, for intravascular radiologic
 contrast medium, 29, 29b
- Prenatal imaging, ultrasonography, 2909-2911, 2910f-2912f
- Prenatal mortality, from bacteriuria in
 pregnancy, 295
- Prenatal urology, development of genitourinary
 tract. *See* Development of genitourinary
 tract
- Preoperative care, 100, 117b
 abdominal incisions and wound closure, 115-117, 116t
 for adrenal surgery, 1580-1581, 1581b
 anesthetic considerations, 110
 mode selection, 110-112
 pain management, 112
 blood product considerations, 112-113
 comorbid illness optimization, 103
 evaluation, 100
 cardiac, 101-102, 102t
 for CKD and ESRD, 1063-1064
 classification and risk stratification in, 100-101, 101b, 101t
 hepatobiliary, 102
 for kidney surgery, 1414-1415, 1415f, 1414.e1f
 for laparoscopic kidney surgery, 1446-1447
 pulmonary, 102

Preoperative care (*Continued*)

- for laparoscopic and robotic surgery, 197b
- blood products, 196
- bowel preparation, 196
- operating room setup, 196-197, 197b
- patient positioning, 197, 197.e1f
- patient selection and contraindications, 195-196
- for pediatric patients, 2967
- prophylaxis, 197
- for laparoscopic RPLND, 839
- for minimally invasive urinary diversion, 2369, 2370b
- patient environment
 - patient positioning, 114-115, 114b
 - patient temperature, 113
 - safety considerations, 114
 - skin preparation, 113-114
- preparation for surgery
 - antibiotic prophylaxis, 105-106, 105b, 106f-107f
 - antithrombotic therapy, 109-110, 110f
 - bowel preparation, 106-108
 - for kidney surgery, 1414-1415, 1415f, 1414.e1f
 - for laparoscopic kidney surgery, 1446-1447
 - for pediatric patients, 2958-2960, 2959f, 2960b
 - VTE prophylaxis, 108-109, 108f-109f, 109b
- presurgical testing, 100
- for RPLND, 818
- for scrotal surgery, 946-947
- in special populations
 - elderly, 103-104
 - morbid obesity, 104
 - poor nutritional status, 104
 - pregnancy, 104
- Preoperative evaluation, 100
- Preoperative management, in
 - pheochromocytoma treatment, 1550-1552
- Prepuceplasty, 3414-3416, 3415f
- Preputial calculi, 1299
- Prerenal azotemia, 1042-1043, 1042b
- Present illness, patient history of, 1-7, 4f-5f
- Pressure
 - transglomerular, 1007
 - of ureters, 989, 990f, 993-995, 995f
 - obstruction effects on, 995-999, 996f-999f
 - of UVJ, 999-1000, 1000f
- Pressure effects, of anesthesia, 2966
- Pressure ulcers, 2092
- Pressure-flow studies
 - for benign prostatic hyperplasia, 2469-2470
 - in urodynamic studies, 1722
 - for overactive bladder, 1805
- Presurgical testing, 100
- Preureteral iliac artery, 3100-3101
- Preureteral vena cava, 3099-3100, 3100f
- Prevesical space, 1598-1599, 1599f
- Previous illness, patient history of, 7
- Previous surgery, patient history of, 7
- Priapism, 338f
 - as complication of EDT, 673b
 - definition of
 - ischemic priapism (veno-occlusive, low-flow), 669, 670b, 670f
 - nonischemic priapism (arterial, high-flow), 669, 670b
 - stuttering priapism (intermittent), 669, 670b
- epidemiology and pathophysiology
 - in children, 674
 - etiology of ischemic priapism (veno-occlusive, low-flow), 670-673, 672b

Priapism (*Continued*)

- etiology of nonischemic (arterial, high-flow), 673-674, 674b, 675f
- etiology of stuttering (intermittent), 673
- evaluation and diagnosis of
 - history, 676, 676b
 - laboratory testing, 676-678, 678f, 678t
 - penile imaging, 678-679, 679f, 680b
 - physical exam, 676, 677f, 678t
- historical perspectives of, 669-670
- interventional angiography, 689-690, 689f
- medical treatments for
 - ischemic priapism, 679-682, 681f, 682b
 - stuttering, 682-683, 684b
- molecular basis of, 674-676
- and SCD, 671-672, 676b
- summary of, 690-691
- surgical management of arterial, 690, 690b, 690f
- surgical management of ischemic
 - immediate implantation of penile prosthesis, 670f, 684b, 687-689, 688b-689b, 688f
 - shunting, 684-687, 684b, 685f-687f, 686b, 688b
- Primary aldosteronism
 - clinical characteristics, 1540-1541
 - diagnostic tests, 1541-1544, 1541b-1542b, 1542f-1543f
 - increased adrenal function in, 1539, 1540f, 1541b-1542b, 1542f-1543f, 1545b
 - overview and epidemiology, 1539
 - pathophysiology, 1539-1540, 1540f
 - treatment and prognosis, 1544-1545, 1581b
- Primary cutaneous lesions, 387, 388t
- Primary erectile dysfunction, causes of
 - micropenis, 641
 - vascular abnormalities, 641
- Primary hormone therapy. *See* Androgen deprivation therapy
- Primary hyperoxalurias (PHs), 1185-1186, 1185f, 1210-1211
- Primary hypogonadism, AD resulting from, 539-541, 540t
- Primary paraureteral diverticula, 3178, 3178f
- Primary pigmented nodular adrenocortical disease (PPNAD), 1535
- Primary renal glucosuria, 2862
- Primary syphilis, 373-374, 373t, 374f
- Primitive neuroectodermal tumor (PNET), of
 - kidney, 1361t, 1364
- Principal cells
 - of CCT, 1018-1019, 1018f-1019f
 - epididymis, 502-503, 530, 530f
- Pringle maneuver, in vena caval thrombectomy, 1439, 1439.e1f
- Prior surgery, as laparoscopic and robotic surgery contraindication, 195-196
- ProAct. *See* Adjustable balloons
- Probiotics, for enteric hyperoxaluria, 1227
- Process of care, 90
- Processus vaginalis anomalies, cryptorchidism and, 3442
- Profile of Female Sexual Function and Personal Distress scale (PFSF), 753.e2
- Programmed cell death. *See* Apoptosis
- Programmed death-1 (PD-1), 1325-1326
- Projected isovolumetric pressure (PIP), 1815, 1815f
- Prolactin, 517, 517f
 - in benign prostatic hyperplasia, 2432-2433
 - in ED, 621-623, 623t
- Prolapsed ureterocele, 3457-3458, 3458f
- Proliferative inflammatory atrophy (PIA), prostate cancer and, 2547-2548
- Promethazine, 2547-2548

- Promoters, of crystal formation, 1178-1179
- Prompted voiding, 1891
- Pronephros, 2823-2826, 2827f
- Propagation, electrical, in ureteral cells, 984
- Propantheline bromide, to facilitate bladder filling and urine storage, 1839t, 1844
- Prophylactic antibiotics, for UTIs, 2945
- Prophylactic colposuspension, 1927
- Propiverine hydrochloride, to facilitate bladder filling and urine storage, 1850-1851
- with α -adrenoreceptor antagonists, 1859-1860
- Propofol, preoperative considerations for, 111-112
- Propranolol (Inderal), ureteral response to, 991-992
- Proscar Long-Term Efficacy and Safety Study (PLESS), 2451
- Prostaglandins (PGs)
 - in ED, 627
 - to facilitate bladder emptying, 1872
 - for hemorrhagic cystitis, 190
 - in prostatic secretions, 2416
 - urethral function effects of, 1004-1005
 - urothelium release of, 1640
- Prostanoid-receptor agonists and antagonists, to facilitate bladder filling and urine storage, 1866.e1-1866.e2
- Prostanoids
 - for detrusor underactivity, 1818
 - lower urinary tract and, 1672
- Prostate
 - altered host defense in, 307
 - anatomy of, 509b
 - arterial supply, 507, 507f
 - gross structure, 506, 506f-507f
 - lymphatic drainage, 508
 - microanatomic architecture, 507
 - nerve supply, 508
 - ultrasonographic, 2579, 2580f-2581f
 - venous drainage, 508
 - biopsy of, in prostatitis evaluation, 316. *See also* Prostate biopsy
 - cell types of, 2396t, 2397-2398, 2397f, 2398b
 - basal cells, 2397-2398, 2397f
 - epithelial stem cells, 2397f, 2398
 - intermediate cells, 2397f, 2398
 - luminal epithelial, 2397
 - neuroendocrine cells, 2397f, 2398
 - development of, 2393-2399, 2396t, 2397b, 2838-2840, 2840f
 - budding induction, 2394-2395
 - budding of, 2393, 2394f
 - cytodifferentiation, 2393
 - epithelial budding, 2395
 - fibroblast growth factors in, 2395
 - hedgehog signaling pathway, 2395
 - molecular features of, 2394-2396
 - Nkx3.1 and Sox9, 2395
 - regional differentiation, 2393
 - transforming growth factor- β superfamily, 2395-2396
 - zonal and lobar anatomy, 2396, 2396t
- diseases of, MetS correlation with, 551
- endocrine control of growth of, 2399-2403, 2400f, 2403b
- adrenal androgens, 2401-2402, 2402f
- androgen production by testes, 2400-2401, 2401f, 2401t
- androgen-binding proteins in plasma, 2401f, 2403
- estrogens in male, 2401t, 2402-2403
- expressed secretions of, in urinary sediment, 25, 25f
- in genitourinary tuberculosis, 423

Prostate (Continued)

- growth regulation of
 - androgen action at cellular level, 2404-2405, 2404f
 - androgen metabolism in, 2405-2406, 2405f, 2406t
 - androgen receptor-dependent chromatin remodeling, 2412-2413
 - androgen receptors in, 2408-2412, 2408f-2409f, 2412b
 - cell adhesion molecules, 2406-2407
 - at molecular level, 2407-2414
 - protein growth factors in, 2403-2407, 2403f
 - 5 α -reductase metabolism in, 2405-2406, 2405f, 2406t
 - steroid receptors, 2407-2414
 - steroids in, 2403-2407, 2403f
 - stromal-epithelial interactions, 2406
 - hematuria related to, 190-192, 191f, 192b
 - localization studies, 252
 - MRI of, 56-57
 - T2-weighted, 58, 58f, 508, 508f
 - physical examination of, 11
 - in prune-belly syndrome, 3237
 - secretions of. *See* Prostatic secretions
 - size of, benign prostatic hyperplasia and, 2438-2440, 2439f, 2505
 - stents for, 2534.e1
 - stroma of, 2398-2399
 - tissue matrix of, 2398-2399
 - transabdominal pelvic ultrasonography of, 75-77, 77f
 - transrectal ultrasound of, 83-84, 83f, 508, 508f, 2582, 2582f. *See also* Transrectal ultrasonography, of prostate
 - transurethral resection of, 263
 - TUNA of, 326
 - volume of
 - in acute urinary retention, 2458-2459, 2458f-2459f
 - transurethral microwave therapy and, 2518
- Prostate adenocarcinoma, 2594-2599
- Gleason grading of, 2594-2596, 2595f, 2596b
 - location of, 2594
 - needle biopsy of, 2596-2597, 2597b
 - radical prostatectomy specimens for, 2597-2599
 - spread of, 2594
 - staging classification for, 2594
 - subtypes of, 2599-2600
 - malignant tumors, 2600
 - mesenchymal, 2599
 - urothelial carcinoma, 2599-2600
 - transurethral resection specimens for, 2597
 - treatment effect and, 2599
 - volume of, 2594
- Prostate biopsy
- for adenocarcinoma, 2596-2597, 2597b
 - advanced techniques for, 2588-2592
 - analgesia for, 2585
 - antibiotic prophylaxis for, 2584-2585, 2585t
 - bleeding with, 2588
 - cleansing enema for, 2585
 - complications of, 2587-2588
 - contraindications for, 2584
 - extended, for active surveillance of prostate cancer, 2634
 - extended core techniques, 2586, 2586f
 - for focal therapy for prostate cancer, 2720-2722
 - saturation, 2721
 - systematic transrectal ultrasound-guided, 2720-2721
 - transperineal saturation, 2721

Prostate biopsy (Continued)

- transperineal template prostate mapping biopsy, 2721, 2722f-2723f
 - transrectal saturation, 2721
 - indications for, 2583-2584, 2584b
 - infections after, 2588
 - investigational techniques for, 2588-2592
 - multiparametric magnetic resonance imaging guidance for, 2724
 - cognitive targeted, 2724
 - ultrasound fusion, 2724-2727, 2725f-2727f
 - needle, 2606-2607
 - overdiagnosis with, 2711-2712, 2712f
 - patient positioning for, 2585
 - patient preparation for, 2584-2585
 - postradiation therapy, 2691-2692
 - imaging and sampling error, 2692
 - interpretation of, 2691-2692, 2691b
 - timing of, 2691
 - prostate cancer-specific mortality and, 2687, 2688f-2689f
 - PSA triggers for, 2603-2604
 - after radiation therapy, for biochemical recurrence, 2778-2779
 - repeat, 2586-2587
 - for active surveillance of prostate cancer, 2634
 - risks of, 2587-2588
 - saturation, 2586-2587
 - sextant, 2586, 2586f
 - transperineal, 2587
 - transrectal techniques, 2586-2587
 - transrectal ultrasound for. *See* Transrectal ultrasonography, of prostate
 - transurethral, 2587
 - ultrasound guidance of. *See* Transrectal ultrasonography, of prostate
- Prostate cancer
- abiraterone for, 2792-2793, 2792f-2793f
 - active surveillance of. *See* Active surveillance of prostate cancer
 - adenocarcinoma. *See* Prostate adenocarcinoma
 - aminoglutethimide for, 2791
 - androgen receptor in, 2556
 - androgens, influence of, 2549, 2553, 2554f
 - bicalutamide for, 2790
 - biology of, 2714-2719
 - clinically significant disease, 2714-2715
 - index lesion, 2715
 - low-grade low-volume lesion reclassification, 2715-2719, 2716f
 - tumor multifocality, 2714-2715
 - biomarkers for
 - for active surveillance, 2635
 - additional kallikrein tumor markers, 2572
 - annexin A3, 2575
 - autoimmune responses to, 2573
 - blood-based, 2567-2573
 - circulating tumor cells, 2573, 2573f
 - development of, 2566-2567
 - endoglin, 2572-2573
 - epigenetic modifications, 2575-2576
 - gene fusions, 2574-2575
 - gene susceptibility loci, 2576-2577
 - genomic expression profiles, 2576-2577
 - human kallikrein 2, 2572
 - metabolomics, 2575
 - α -methylacyl coenzyme A racemase gene, 2575
 - microRNA, 2575
 - performance assessment, 2567
 - prostate cancer antigen 3, 2573-2574, 2574f

Prostate cancer (Continued)

- prostate-specific antigen. *See* Prostate-specific antigen
- prostate-specific membrane antigen, 2571-2572
- tissue-based, 2575-2577
- urine-based, 2573-2575
- castration-resistant. *See* Castration-resistant prostate cancer
- chemoprevention of, 2559-2564
 - green tea catechin, 2564
 - lycopene, 2564
 - metformin, 2562
 - pharmacologic agents for, 2560-2562
 - Prostate Cancer Prevention Trial on, 2560-2562, 2561f
 - rationale for, 2559-2560, 2559f
 - 5 α -reductase inhibitors for, 2560-2562
 - Reduction by Dutasteride of Prostate Cancer Events, 2562
 - selenium, 2562-2563, 2563f
 - soy, 2563-2564
 - statins, 2562
 - toremifene citrate, 2562
 - vitamin E, 2562-2563, 2563f
- chronic inflammation role in, 452-453
- as complication of TT, 546
- and delayed ejaculation, 703
- diagnosis of, 2601-2605
 - age at, 2545
 - digital rectal examination for, 2602
 - errors in current pathway of, 2711-2712, 2712f
 - prostate cancer antigen 3, 2605
 - prostate-specific antigen for, 2602-2604
 - stage at, 2545
- distant disease detection, 2746-2747
 - biopsy of radiorecurrent cancer, 2747
 - bone scan for, 2746
 - choline PET/CT scan, 2746, 2746f
 - whole-body magnetic resonance imaging, 2746-2747
- DNA methylation in, 463
- enzalutamide for, 2790, 2790f
- epidemiology of, 2543-2546
 - molecular, 2548-2550, 2550b
 - epigenetic changes in, 2554-2556
 - etiology of, 2552-2559, 2559b
- flutamide for, 2790
- focal therapy for. *See* Focal ablative therapy, for prostate cancer
- gene fusions in, 2556-2557, 2557f-2558f
- genomic alterations in
 - gene rearrangements, 466-467
 - HPC, 468-469, 468t, 469f
 - sporadic prostate cancer, 469-471
- in geriatric patients, 2099.e12
- gonadotropin-releasing hormone inhibition for, 2791
- hematuria caused by, 192
- hereditary. *See* Hereditary prostate cancer
- hormonal therapy for. *See* Hormonal therapy, for prostate cancer
- HRQOL instruments for, 92t-94t
- immune checkpoint blockade in, 457-458
- incidence of, 2543, 2544f, 2544t, 2628, 2629f, 2629t
 - global, 2544-2545
 - screening effects of, 2545-2546
- ketoconazole for, 2791-2792
- localized. *See* Localized prostate cancer
- locally advanced. *See* Locally advanced prostate cancer
- MetS and, 554

Prostate cancer (*Continued*)

molecular genetics of, 2552-2559, 2559b
 mortality rates of, 2543, 2544f
 global, 2544-2545
 prostate-specific antigen-based screening and, 2630
 screening effects of, 2545-2546
 natural history of, 2628-2630
 nilutamide for, 2790
 NKX3-1 gene in, 2557
 as non-AIDS-defining urologic malignancy, 385-386
 noncurative management of
 overtreatment risks and, 2631
 rationale for, 2630-2631, 2631b
 observational strategies for, 2631-2635
 candidate identification for, 2632-2633, 2632t
 future research needs for, 2639-2640
 progression and triggers in, 2633-2635
 treatment compared with, 2637t, 2638-2639, 2638f
 overtreatment of, risks with, 2631
 phosphatidylinositol 3-kinase pathway, 2557
 prevalence of, 2628, 2629f, 2629t
 prognostic value of telomere length for, 478
 prostatic calculi and, 1297
 racial differences and, 2543-2544
 radiorecurrent
 biopsy of, 2747
 focal salvage brachytherapy for, 2749
 focal salvage cryotherapy, 2750
 location of, 2748-2749
 salvage radical prostatectomy for, 2747
 salvage therapy for, 2748, 2748f-2749f
 whole-gland salvage brachytherapy, 2747-2748
 whole-gland salvage high-intensity focused ultrasound, 2748
 whole-gland salvage therapy for, 2747-2748, 2748t
 RB1 in, 461
 in renal transplant candidates, 1072
 risk factors for, 2546-2552
 alcohol consumption, 2552
 androgens, 2549
 calcium, 2550
 diet, 2551
 estrogens, 2549
 familial, 2546-2547, 2546t, 2547b
 genetic, 2546-2547, 2547b, 2552f
 infection, 2547-2548
 inflammation, 2547-2548, 2548f
 insulin-like growth factor axis, 2549
 leptin, 2550
 obesity, 2551-2552, 2552f
 sexual activity, 2550-2551
 sexually transmitted infections, 2550-2551
 smoking, 2551
 vasectomy, 2551
 vitamin D, 2550
 vitamin D receptor, 2550
 screening for, 2601-2602
 general concepts of, 2601
 localized, 2609-2611
 randomized trials for, 2601
 specialty group recommendations for, 2601-2602
 SPOP mutations in, 2557
 sporadic, 469-471
 staging of, 2605-2608
 classifications for, 2605-2606, 2606t
 clinical *versus* pathologic, 2605
 combined pretreatment parameters in, 2607
 general concepts of, 2605-2606
 imaging for, 2607

Prostate cancer (*Continued*)

molecular, 2607
 needle biopsy, 2606-2607
 pelvic lymphadenectomy, 2607-2608
 prostate-specific antigen-based screening and, 2630
 tumor extent prediction, 2606
 stem cells in, 2553, 2555f
 TP53 gene in, 2557-2559
 tumor initiation and progression in, somatic mutations associated with, 2553-2559, 2556f
 tumorigenesis model for, 2559
 ultrasound advances and, 2722-2727
 untreated, 2628-2630
 observational studies of, 2628-2630
 randomized studies of, 2630
 vaccines for, 455-456, 456f
 vasectomy association with, 952-953
 watchful waiting of
 candidate identification for, 2632-2633
 progression and triggers in, 2634
 Prostate cancer antigen 3 (PCA3), as prostate cancer biomarker, 2573-2574, 2574f, 2605
 Prostate Cancer Prevention Trial (PCPT), 2560-2562, 2561f
 Prostate embolization, 2534.e2-2534.e3
 Prostate HistoScanning, 2590, 2722
 Prostate stem cell antigen (PSCA), in prostatic secretions, 2417t, 2420
 Prostate surgery
 lower urinary tract function and, 1700
 orthoptic urinary diversion and, 2350-2351
 Prostate urethral lift (PUL), 2534.e1, 2534.e1f-2534.e2f
 Prostatectomy
 applications of, 2535
 deep venous thromboses or pulmonary emboli after, 90
 history of, 2535
 holmium laser enucleation of prostate *versus*, 2529
 radical. *See* Radical prostatectomy
 retropubic, 2535
 simple, 2542b
 anesthesia for, 2537
 complications with, 2542
 contraindications for, 2536
 indications for, 2536
 open, 2537
 operating day preparation for, 2536
 postoperative management for, 2541-2542
 preoperative evaluation for, 2536
 retropubic, 2537-2539, 2537f-2538f
 robot-assisted laparoscopic, 2541
 summary for, 2542
 suprapubic, 2539-2541, 2539f-2540f
 surgical technique for, 2537-2541
 SUI following, 1716
 suprapubic, 2535-2536
 urinary incontinence and, conservative interventions for, 1895
 Prostate-specific antigen (PSA), 546
 in acute urinary retention, 2458-2459, 2458f-2459f
 in benign prostatic hyperplasia, 2465-2467
 in biochemical recurrence
 after radiation therapy, 2778
 after radical prostatectomy, 2771-2772
 after focal therapy
 density, 2744
 for failure determination, 2745-2746
 kinetics, 2744
 nadir

Prostate-specific antigen (PSA) (*Continued*)

free, 2569-2570, 2569t, 2570f
 isoforms of, 2570-2571, 2571f
 male urinary incontinence and, 1707-1708
 as post-treatment prognostic factor, 2689-2690
 doubling time, 2690-2691
 failure and, 2689-2690
 nadir value significance, 2690
 neoadjuvant hormones, 2691
 time to nadir of, 2690
 in prostate cancer, 2602-2604
 as biomarker, 2567-2571, 2567f-2568f
 biopsy triggers, 2603-2604
 clinical use for, 2603, 2603t
 complexed, 2605
 derivatives and molecular forms of, 2604-2605
 factors influencing, 2602-2603
 free, 2604-2605
 hexokinase 2, 2605
 isoforms, 2605
 mortality changes with, 2630
 multiplex tests, 2605
 stage migration with, 2630
 tumor extent prediction with, 2606
 velocity of, 2604
 volume-based parameters for, 2604
 in prostatic secretions, 2417-2418, 2417t
 derivatives of, 2417t, 2418
 velocity of, prostate cancer-specific mortality and, 2687
 Prostate-specific membrane antigen (PSMA)
 as prostate cancer biomarker, 2571-2572
 in prostatic secretions, 2417t, 2420
 Prostate-specific protein 94 (PSP-94), in prostatic secretions, 2417t, 2421
 Prostate-specific transglutaminases, in prostatic secretions, 2417t, 2419
 Prostatic acid phosphatase, in prostatic secretions, 2417t, 2420-2421
 Prostatic calculi, 1296-1297
 Prostatic injections, 2534.e3-2534.e4
 Prostatic intraepithelial neoplasia (PIN)
 high-grade, 2593-2594, 2594f
 low-grade, 2593
 Prostatic lymphoma, 2600
 Prostatic massage, for CP/CPPS treatment, 325
 Prostatic pain, patient history of, 2
 Prostatic secretions, 2414-2423
 drug transport and, 2424, 2424b
 nonpeptide components of, 2414-2416, 2418t
 citric acid, 2415
 fructose, 2415
 phosphorylcholine, 2415-2416
 polyamines, 2415
 prostaglandins, 2416
 zinc, 2416
 proteins in, 2416-2423, 2417t-2418t
 C3 complement, 2422
 human kallikrein 2, 2418
 human kallikrein 11, 2419
 human kallikrein 14, 2419
 human kallikrein L1, 2418-2419
 immunoglobulins, 2422
 lactate dehydrogenase, 2422
 leucine aminopeptidase, 2422
 prostate stem cell antigen, 2420
 prostate-specific antigen, 2417-2418
 prostate-specific antigen derivatives, 2418
 prostate-specific membrane antigen, 2420
 prostate-specific protein 94, 2421
 prostate-specific transglutaminases, 2419
 prostatic acid phosphatase, 2420-2421
 protein C inhibitor, 2422

- Prostatic secretions (*Continued*)
 semenogelins I and II, 2419-2420
 seminal vesicle secretory proteins, 2423
 transferrin, 2422
 zinc α_2 -glycoprotein, 2422-2423
- Prostatic urethra, 509, 510f-511f, 910.e2, 910.e2f
- Prostatic urethral cancer, 2203-2204, 2203f
- Prostatic utricle, 509
- Prostatitis
 acute bacterial, 310, 313
 chronic. *See* Chronic prostatitis
 chronic pelvic pain syndrome. *See* Chronic pelvic pain syndrome
 chronic prostatitis/chronic pelvic pain syndrome. *See* Chronic prostatitis/chronic pelvic pain syndrome
 clinical presentation
 acute bacterial, 310
 asymptomatic inflammatory prostatitis, 311
 chronic bacterial, 310-311
 CP/CPPS, 311
 definition and classification, 310, 310b, 310t
 epidemiology, 304, 305b
 etiology, 309, 309b, 309f
 altered prostate host defense in, 307
 bladder pain syndrome and interstitial cystitis associated with, 309
 chemically induced inflammation in, 308
 dysfunctional voiding in, 307
 immunologic alterations in, 308
 intraprostatic ductal reflux in, 307-308
 microbiology, 305-307
 neural sensitization in, 308
 pelvic floor muscle abnormalities in, 308
 psychosocial associations, 308-309
 evaluation, 317b
 cytologic considerations, 314-315, 315f
 diagnosis and classification approach, 317, 317f, 318b
 endoscopy in, 315
 lower urinary tract cytologic examination and culture, 313-314, 313f-314f, 314b
 microbiologic considerations, 314
 other potential markers, 316
 prostate biopsy, 316
 seminal vesiculitis and, 316
 ultrasonography in, 315-316
 urodynamics, 315
 granulomatous, 305
 histopathology, 305, 305f
 historical perspective, 304
 HIV and, 383
 HRQOL instruments for, 92t-94t
 prostatic calculi and, 1297
 treatment, 319, 329, 329b
 acupuncture, 325
 α -adrenergic blocker therapy, 322-323
 allopurinol, 324
 anti-inflammatory agents and immune modulators, 323
 antimicrobials, 319-322, 320t-321t
 biofeedback, 325
 conservative therapies, 326
 hormone therapy, 323-324
 muscle relaxants, 323
 neuromodulator therapy, 324
 pelvic floor physiotherapy, 325
 phenotype-directed multimodal, 327-328, 328f
 phytotherapeutic agents, 324
 prostatic massage, 325
 psychological support, 325-326
 pudendal nerve entrapment therapy, 325
 traditional surgery for, 327
- Prostheses, for ED
 inflatable, 709-710, 710f-711f
 semirigid rods, 709, 710f
- ProstVac-VE, 455-456, 456f, 2814, 2814f
- Proteases, RCC and, 1327b
- Protein, PCT reabsorption of, 1015
- Protein C inhibitor (PCI), in prostatic secretions, 2417t, 2422
- Protein kinase A (PKA), in ED, 627
- Protein kinase G (PKG), in ED, 626
- Protein synthesis, basics of, 459.e3-459.e4, 459.e3f-459.e4f
- Proteins
 androgen-binding, in plasma, 2401f, 2403
 of bladder urothelium
 tight junction, 1638, 1638f
 uroplakins, 1632-1633
 connexin 43, 1646, 1647f
 contractile, of smooth muscles, 1641-1642, 1641f-1643f
 restriction of, for nephrolithiasis, 1218, 1219b
 RhoA, 1643, 1643f
- Proteinuria
 chemical examination of, 17-19
 detection, 17-18
 evaluation, 18-19, 19f
 pathophysiology, 17
 in CKD assessment, 1054t, 1061
 in renal development, 2854-2856
 causes of, 2855, 2855b
 etiology of, 2854
 evaluation of, 2855-2856, 2856f
 measurement of, 2854-2855, 2854t
 "normal" urinary protein excretion, 2854, 2854t
 treatment of, 2856, 2857b
- Proximal convoluted tubule (PCT), functions of, 1013-1015, 1014f-1016f
- Proximal renal tubular acidosis, 1189, 2861
- Proxy measures, 90
- Prune-belly syndrome (PBS)
 adult presentation of, 3242
 clinical features of, 3234-3240
 abdominal wall defect, 3238, 3239f-3240f
 bladder in, 3236-3237, 3237f
 cardiac anomalies, 3239
 extragenitourinary abnormalities in, 3238-3240, 3238t
 gastrointestinal abnormalities, 3239-3240
 genitourinary anomalies in, 3234-3238
 kidneys in, 3234-3235, 3235f
 orthopedic abnormalities, 3240
 prostate in, 3237
 pulmonary anomalies, 3239
 sex organs, 3237
 testes, 3237-3238
 ureters in, 3235, 3236f-3237f
 urethra, anterior in, 3237, 3237f-3238f
 description of, 3234
 dilated fetal bladder and, 3174
 embryology of, 3234
 evaluation of, 3242-3249
 female syndrome, 3242
 genetics of, 3234
 incidence of, 3234
 incomplete, 3242
 long-term outlook with, 3249-3250
 management of, 3242-3249
 controversies in, 3243
 neonatal presentation of, 3239f, 3241
 prenatal, 2884
 diagnosis and management of, 3240-3241, 3240f-3241f
 presentation of, 3240-3242
- Prune-belly syndrome (PBS) (*Continued*)
 spectrum of, 3241-3242, 3241t
 surgical management of, 3243-3249
 abdominal wall reconstruction, 3246
 cutaneous vesicostomy, 3243, 3244f
 Ehrlich technique, 3247
 internal urethrotomy, 3243-3244
 modified approaches to, 3249, 3250f-3251f
 Monfort technique, 3247-3249, 3247f-3249f
 orchidopexy, 3245-3246, 3246f
 Randolph technique, 3247
 reduction cystoplasty, 3244
 supravescicular urinary diversion, 3243
 ureteral reconstruction, 3244-3245
 urethral reconstruction, 3244, 3244f-3245f
- PRX302, to facilitate bladder filling and urine storage, 1866.e2
- PSA. *See* Prostate-specific antigen
- PSCA. *See* Prostate stem cell antigen
- Pseudoepitheliomatous, keratotic, and micaceous balanitis (PEKMB), 846.e1
 as neoplastic condition, 414, 414f
- Pseudoexstrophy, 3191
- Pseudohypoadosteronism type I (PHA-I), 2863
- Pseudomembranous enterocolitis, with bowel preparation, 2283-2284
- Pseudo-obstruction of colon, with intestinal anastomoses, 2292
- Pseudotumors of kidney, 3003, 3003f
- PSGN. *See* Poststreptococcal glomerulonephritis
- PSMA. *See* Prostate-specific membrane antigen
- Psoas, 767f-769f, 769, 769t
- Psoas hitch
 femoral nerve in, 1619, 1621f
 for lower ureteral injuries, 1163, 1164f
 with ureteroneocystostomy
 laparoscopic, 1136
 open, 1135-1136, 1136f-1137f
 for urinary tract reconstruction, 3334, 3335f
- Psoriasis, as papulosquamous disorder, 392-393, 393f
- PSP-94. *See* Prostate-specific protein 94
- Psychological evaluation, in ED, 656
- Psychological support, for CP/CPPS treatment, 325-326
- Psychometric validation, of new HRQOL instruments, 96-97, 96t-97t
- Psychosexual differentiation, 3475-3477
- Psychosexual therapy, for ED, 659
- Psychotropic medications, and ED, 636-637, 638t
- PTEN gene, 1322t, 1325, 1327
- PTH. *See* Parathyroid hormone
- PINS. *See* Percutaneous tibial nerve stimulation
- PTRA. *See* Percutaneous transluminal renal angioplasty
- Puberty, 518-519
- Pubic lice. *See* Pediculosis pubis
- Pubic rami, 1597, 1598f
- Pubic tubercles, 1598f, 1612f
- Pubococcygeus muscle, 1601, 1603f
- Puboprostatic ligament, division of, in retropubic radical prostatectomy, 2645-2646, 2645f
- Pubourethralis, 1939, 1940f
- Pubovaginal sling (PVS), 1989-2008
 allograft
 materials for, 1991
 outcomes of, 1999-2002, 2000t-2001t
 anatomy for, 1990
 autologous graft
 materials for, 1990-1991
 outcomes of, 1996-1999, 1997t-1998t

- Pubovaginal sling (PVS) (*Continued*)
 complications of, 2006-2008, 2008b
 nonurologic, 2008
 perforation and exposure, 2006-2008, 2007t
 evolution of, 1987-1988
 materials for, 1990-1992
 mechanics of, 1990
 operative procedure for, 1992-1995
 anesthesia for, 1993
 counseling, 1992-1993
 graft harvest for, 1993-1994, 1993f
 patient positioning for, 1993
 preparation for, 1993
 outcomes of, 1996-2003, 2004b
 for mixed urinary incontinence, 2003
 for urethral reconstruction, 2003-2004
 postoperative care for, 1995
 removal of, 2046
 retropubic suspension surgery comparison with, 1934-1935, 1935f
 sling placement and fixation in, 1995, 1995f
 synthetic prosthetic
 materials for, 1991-1992, 1992t
 outcomes of, 2002
 vaginal approach to, 1994-1995, 1994f
 voiding dysfunction after, 2004-2006, 2007b
 surgical management of, 2005-2006, 2006t
 xenograft
 materials for, 1991
 outcomes of, 2002-2003, 2002t
 Pubovesical ligaments, 1600, 1607
 Pudendal artery, 614, 1604, 910.e3, 910.e4f
 preservation of, in retropubic radical prostatectomy, 2646, 2646f
 Pudendal nerve, 617f, 1602-1603, 910.e5
 electrical stimulation of, for bladder storage disorders, 1909
 stimulation of, 1681
 inhibitory and excitatory frequencies for, 1681
 for lower urinary tract dysfunction, 1794-1795
 Pudendal nerve entrapment therapy, for CP/ CPPS treatment, 325
 PUL. *See* Prostate urethral lift
 Pulmonary abnormalities, with cloacal exstrophy, 3228
 Pulmonary complications
 of radical nephrectomy, 1428
 after RPLND, 833
 Pulmonary embolism (PE)
 after cystectomy, nephrectomy, and prostatectomy, 90
 after laparoscopic and robotic surgery, 223
 after retropubic radical prostatectomy, 2657
 in vena caval thrombectomy, 1433
 vena caval thrombectomy causing, 1444
 Pulmonary evaluation, preoperative, 102
 Pulmonary hypoplasia, with posterior urethral valves, 3259, 3259f
 Pulsed wave lasers, 228
 PUM. *See* Partial urogenital mobilization
 PUNLMP. *See* Papillary urothelial neoplasia of low malignant potential
 PUO. *See* Partial ureteral obstruction
 Purinergic nervous system, in ureteral function, 992-993
 Purinergic signaling
 in bladder afferent pathway, 1654, 1656f
 in bladder pain syndrome and interstitial cystitis, 1678-1679
 PVP. *See* Photoselective vaporization of prostate
 PVR. *See* Postvoid residual
 PVS. *See* Pubovaginal sling
 Pyeloenteric fistula, 2132, 2132f
 Pyelogenic cyst. *See* Calyceal diverticula
 Pyelography
 antegrade. *See* Antegrade pyelography
 intravenous. *See* IV pyelography
 IV. *See* IV pyelography
 for pediatric patients, 2916
 retrograde. *See* Retrograde pyelography
 Pyelolithotomy, laparoscopic pyeloplasty with, for ureteropelvic junction obstruction with, 1122
 Pyelolymphatic backflow, in retrograde pyelography, 34, 35f
 Pyelonephritis, 238
 acute, 275-278, 276f-277f, 278t
 chronic, 285-286, 286f
 emphysematous, 279-280, 280f-281f
 with uroterointestinal anastomoses in urinary intestinal diversion, 2291t, 2296t, 2303
 XGP, 286-289, 287f-288f
 Pyeloplasty
 dismembered. *See* Dismembered pyeloplasty
 laparoscopic. *See* Laparoscopic pyeloplasty
 nondismembered. *See* Nondismembered pyeloplasty
 for ureteropelvic junction obstruction with concomitant pyelolithotomy, 1122
 laparoscopic dismembered tubularized flap, 1122
 open surgery, 1115
 results of, 1120-1122, 1121t
 salvage procedures for, 1124-1125
 Pyelopyelostomy, for retrocaval ureter
 laparoscopic, 1125-1128
 open, 1125, 1128f
 Pyelosinus backflow, in retrograde pyelography, 34, 35f
 Pyelotubular backflow, in retrograde pyelography, 34, 35f
 Pyeloureterostomy, for ureteral anomalies, 3094
 Pyelovascular fistula, 2135-2136
 Pyelovenous backflow, in retrograde pyelography, 34
Pygeum africanum (African plum), for benign prostatic hyperplasia, 2500
 Pyoderma gangrenosum (PG), 401, 402f
 Pyonephritis, and UTIs, 2936
 Pyonephrosis, infected, 283, 283f
 Pyridium, for pelvic floor disorder testing, 1705
 Pyridoxine, for enteric hyperoxaluria, 1227
 Pyrophosphate, in crystal formation, 1178
 Pyuria, 237

Q
 QALYs. *See* Quality-adjusted life years
 Q-tip test, for urethral mobility, 1700
 Quadratic sling
 implantation of, 2180
 mechanisms of action of, 2171, 2171f
 Quadratus lumborum, 767f-769f, 769, 769t
 Qualitative research, 98
 Quality improvement frameworks, 91
 Quality indicators, 90
 Quality metrics, for urology, 90-91
 Quality of care, 88-89
 challenges in evaluation of, 91
 conceptual framework for, 89-90
 improvement frameworks, 91
 levels of evidence, 91
 metrics applied to urology, 90-91
 outcomes, 90
 process, 90
 structure, 89-90
 Quality of life. *See also* Health-related quality of life
 with androgen deprivation therapy, 2767
 augmentation of, 2767
 Quality of life (*Continued*)
 with cutaneous continent urinary diversion, 2338
 with exstrophy-epispadias complex, 3220
 with focal therapy, 2743
 after localized prostate cancer treatment, 2630-2631
 with external-beam radiation therapy, 2696-2697, 2696t
 lower urinary tract dysfunction and, in pediatric patients, 3298
 after orthotopic urinary diversion, 2367-2368, 2368b
 with posterior urethral valves, 3267-3268
 transitional urology and, 3526-3527, 3527t
 Quality-of-life questionnaires
 for male urinary incontinence, 1712, 1713f, 1712.e1f-1712.e2f
 for pelvic floor disorders, 1702-1704, 1703t-1704t
 Quality-adjusted life years (QALYs), 86
 Quercetin, for BPS/IC oral therapy, 353t, 355
 Questionnaire-Based Voiding Diary (QVD), 1879, 1881f-1882f
 QVD. *See* Questionnaire-Based Voiding Diary

R
 RAA. *See* Renal artery aneurysm
 Race
 prostate cancer and, 2543-2544
 renal calculi and, 1171
 prevalence of, 1201
 urinary incontinence and, 1748
 and UTIs, 2930
 UTUC prognosis and, 1374-1375
 UTUC variations and, 1365
 vesicoureteral reflux and, 3135
 Racial/ethnic minorities, and female sexual function, 754
 Radiation
 for adrenal cortical carcinoma, 1559
 management of, in urology, 26-27, 27b, 27t-28t
 pregnancy precautions for, 104
 protection from, 27
 relative levels of, 27, 28t
 urothelial cancer and, 2188
 Radiation exposure, 26-27, 27t-28t
 with CT, 1092-1093
 lower urinary tract dysfunction and, 1792
 medical diagnoses and, 1699
 orthotopic urinary diversion and, 2350
 pediatric patient considerations for, 2909
 vesicovaginal fistulae with, 2106
 Radiation fistula, 2137-2139
 Radiation therapy (RT)
 adjuvant. *See* Adjuvant radiation therapy
 advances in, 2692-2694, 2693f-2694f, 2694t
 androgen suppression with, 2705-2706, 2707t
 biochemical recurrence after. *See* Biochemical recurrence, after radiation therapy
 brachytherapy. *See* Brachytherapy
 external-beam. *See* External-beam radiation therapy
 hemorrhagic cystitis caused by, 189-190
 for ITCN, 797, 797b
 for locally advanced prostate cancer, 2763-2765, 2764t
 adjuvant androgen deprivation with, 2763-2765
 chemotherapy with, 2765
 neoadjuvant androgen deprivation with, 2763
 for muscle-invasive bladder cancer, 2234
 for neuroblastoma, 3567
 after partial orchiectomy, 816

- Radiation therapy (RT) (*Continued*)
 for penile cancer, 871b
 adverse effects of, 870
 inguinal areas, 870-871
 primary lesion, 868-870, 869t
 for prostate cancer
 androgen deprivation therapy with, 2619-2620
 end points for, 2620
 field of treatment for, 2619
 heavy-particle, 2621
 hormonal therapy with, 2796, 2796f, 2797t
 localized. *See* Radiation therapy for localized prostate cancer
 radiation dose for, 2619
 salvage focal therapy for, 2745-2750
 side effects of, 2619
 treatment results of, 2620-2621
 for renal tumor ablation, 1497-1498
 for retroperitoneal sarcomas, 1409-1411
 salvage. *See* Salvage radiation therapy for seminomas, 806-807, 807t, 809
 side effects of, 2619
 stereotactic body. *See* Stereotactic body radiotherapy
 for TGCTs, 796
 sequelae of, 811
 for UTUC, 1399-1400
- Radiation therapy for localized prostate cancer
 adjuvant, 2622-2623
 androgen deprivation therapy with, 2623, 2705-2706, 2707t
 duration of, 2706
 pelvic lymph node treatment and, 2706
 brachytherapy. *See* Brachytherapy, for prostate cancer
 external-beam, 2692-2699
 advances in radiation technology and, 2692-2694, 2693f-2694f, 2694t
 morbidity outcomes with, 2696-2697, 2696t
 outcomes for, 2703-2705, 2704t-2705t
 quality-of-life outcomes with, 2696-2697, 2696t
 tumor control after, 2695, 2695t
 heavy-particle beam radiotherapy, 2621, 2697-2699, 2697f, 2698t
 historical perspective on, 2685
 hypofractionation, 2702-2703
 outcomes with, 2703-2705, 2704t-2705t
 intermediate risk, stratification of, 2686-2687, 2687f
 molecular therapies and, 2709-2710
 enzyme/prodrug gene therapy, 2710
 immunotherapy, 2709
 oncolytics, 2710
 radio-gene therapy, 2709-2710
 targeted RNA-based therapy, 2709
 for palliation, 2708-2709
 bone metastases, 2708
 radium-223 clinical experience, 2708-2709
 spinal cord compression, 2708
 systemic radionuclide therapy, 2708, 2708t
 postoperative, 2622-2623
 postirradiation therapy biopsy, 2691-2692
 imaging and sampling error, 2692
 interpretation of, 2691-2692, 2691b
 timing of, 2691
 post-treatment prognostic factors for, 2689-2692
 preoperative, 2623
- Radiation therapy for localized prostate cancer (*Continued*)
 pretreatment prognostic factors for, 2685-2688, 2686f
 multiparametric magnetic resonance imaging in, 2688
 prostate cancer-specific mortality
 positive prostate biopsy results and, 2687, 2688f-2689f
 prostate-specific antigen velocity and, 2687
 risk groups and, 2685-2686, 2686f
 prostate-specific antigen and, 2689-2690
 doubling time, 2690-2691
 failure and, 2689-2690
 nadir value significance, 2690
 neoadjuvant hormones, 2691
 time to nadir of, 2690
 radical prostatectomy comparison with, 2623-2624
 salvage, 2622-2623
 secondary radiation-induced malignancies, 2624
 stereotactic body radiotherapy, 2621, 2703, 2704f
- Radiation trauma, of penis, 916.e2
- Radical cystectomy
 continence preservation in
 anterior apical dissection in male patient, 2351-2352, 2353b
 urethra preservation in female patient, 2352-2353, 2352f
 history of, 2242
 oncologic outcomes of, 2242
 with pelvic lymph node dissection
 anatomic extent of, 2226-2227
 bilateral, 2226
 density of, 2228
 intraoperative decision making, 2228-2229
 intraoperative frozen sections of ureter, 2228-2229
 managing female urethra in, 2229
 for muscle-invasive bladder cancer, 2225-2230
 number removed in, 2227-2228, 2227f
 oncologic outcomes following, 2229-2230, 2229t
 prostatic urothelial carcinoma and, 2229
 robotic-assisted, 2268-2277. *See also* Robotic-assisted radical cystectomy
 with transurethral resection of bladder tumor
 female, 2250-2252, 2251f-2252f
 male, 2247-2250, 2249f-2250f
- Radical IFLND, for penile cancer, 902-906, 903f-905f
- Radical nephrectomy (RN)
 laparoscopic. *See* Laparoscopic radical nephrectomy
 for malignancies, 1423-1428, 1423f
 complications of, 1427-1428
 regional lymphadenectomy with, 1426-1427, 1426f-1427f, 1427.e1f
 surgical procedure for, 1424-1426, 1424f-1426f, 1424.e1f, 1425.e1f
 wound closure for, 1427
 for RCC, 1344-1345, 1345b, 1346f
 local recurrence after, 1359, 1360b
- Radical nephroureterectomy, for UTUC
 laparoscopic, 1382-1384, 1382f-1384f
 open, 1376-1377, 1377f, 1381-1382
- Radical orchiectomy, 815
 for ITGCN, 797, 797b
 technique for, 815-816
 for TGCTs, 791, 791t-792t
- Radical prostatectomy (RP)
 biochemical recurrence after. *See* Biochemical recurrence, after radical prostatectomy
 laparoscopic. *See also* Laparoscopic radical prostatectomy
 open conversion of, 2679
 open versus, 2678-2679
 for locally advanced prostate cancer, 2755-2763
 adjuvant androgen deprivation with, 2762-2763
 adjuvant radiation therapy, 2761-2762, 2761t
 for clinical stage T3, 2756-2757, 2757t
 neoadjuvant androgen deprivation, 2758-2760, 2759t-2760t
 neoadjuvant chemotherapy and chemotherapy-hormonal therapy, 2760-2761, 2760t
 outcomes, 2757-2758, 2758f
 pathologic findings with, 2754, 2755t and PD, 725
 perineal. *See* Perineal radical prostatectomy
 for prostate adenocarcinoma, 2597-2599
 for prostate cancer, 2614-2618
 cancer control with, 2616-2617
 complications with, 2617
 erectile function after, 2617
 hormonal therapy with, 2795-2796, 2796t
 patient selection for, 2615-2616
 postoperative biochemical recurrence management, 2617-2618
 postoperative care for, 2616
 preoperative androgen deprivation therapy for, 2618
 radiation therapy comparison with, 2623-2624
 salvage, 2618
 surgical approaches to, 2614-2615
 surgical technique for, 2616
 urinary continence after, 2617
 retropubic. *See* Retropubic radical prostatectomy
 robotic-assisted. *See* Robotic-assisted laparoscopic radical prostatectomy
 salvage. *See* Salvage radical prostatectomy
 urinary incontinence after
 prevalence of, 1750
 risk factors for, 1750
 sphincter function and, 1757
- Radiofrequency ablation (RFA)
 for prostate cancer, 2734-2736, 2736f-2737f
 for RCC, 1347t, 1349-1351, 1350t
 for renal tumors, 1487b
 background and mode of action, 1485-1487
 CA compared with, 1494
 complications of, 1494-1495, 1496b, 1496f-1497f
 equipment variations, 1486
 follow-up for, 1489-1490, 1490b
 intraoperative monitoring, 1487
 laparoscopic, 1477
 oncologic outcomes of, 1490-1494, 1491t-1492t, 1494b
 percutaneous, 1487-1489, 1488f
 treatment temperature, 1486-1487
- Radiofrequency interstitial tumor ablation (RITA), for localized prostate cancer, 2626.e1
- Radio-gene therapy, for localized prostate cancer, radiation therapy with, 2709-2710

- Radiography, 26
 abdominal plain film. *See* Abdominal plain film radiography
 of bladder injuries, 2386-2387, 2386f-2387f
 of cloacal anomalies, 3503-3504
 of defecation disorders, 3320f, 3327, 3320.e1f
 for genitourinary tuberculosis diagnosis, 425-427, 425f-427f
 intravenous urography. *See* Intravenous urography
 KUB, kidney anatomy on, 969, 969.e1f
 loopography. *See* Loopography
 for male urinary incontinence, 1708
 of neuroblastoma, 3561-3562
 pediatric
 genitalia, 2918, 2920f
 upper and lower urinary tract, 2916-2918
 of pediatric stone disease, 3103
 for pelvic floor disorders, 1707-1708
 physics of, 26, 27f
 radiation management in, 26-27, 27b, 27f-28f
 of renal calculi, 1202
 retrograde pyelography. *See* Retrograde pyelography
 retrograde urethrography. *See* Retrograde urethrography
 static cystography. *See* Static cystography
 for ureteropelvic junction obstruction, 1105, 1106f
 of urethral diverticula, 2159, 2159f-2160f
 of urogenital sinus abnormalities, 3501-3503
 voiding cystourethrogram. *See* Voiding cystourethrogram
- Radioisotopic penography, 654
 Radionuclide cystography, for pediatric patients, 2922-2923, 2925f
 Radionuclide imaging. *See* Nuclear scintigraphy
 Radionuclide renal scan, posterior urethral valves for, 3258
 Radionuclide studies, for UTIs, 253
 Radionuclide testicular scanning, for pediatric patients, 2923-2925
 Radionuclide therapy, systemic, for bone metastases, 2708, 2708t
 Radiopharmaceuticals, for castration-resistant prostate cancer, 2820
 RAE. *See* Renal artery embolization
 RALP. *See* Robotic-assisted laparoscopic radical prostatectomy
 RaLPN. *See* Robotic-assisted laparoscopic partial nephrectomy
 RALUR. *See* Robotic-assisted laparoscopic ureteral reimplantation
 Randall plaques, 1175-1177, 1176f-1178f
 Randolph technique, 3247
 RANKL inhibitors. *See* Receptor activator of nuclear factor- κ B ligand inhibitors
 Rapid eye movement (REM), 620, 1822
 Rapidly progressive glomerulonephritis (RPGN), 1043, 1044b
 RARC. *See* Robotic-assisted radical cystectomy
 RAS. *See* Renal artery stenosis
 RASSF1A gene, in bladder cancer, 463-464
 RB1. *See* Retinoblastoma susceptibility protein
 RBE. *See* Renal blood flow
 RCC. *See* Renal cell carcinoma
 RCCT. *See* Renal concentrating capacity test
 Reactive arthritis
 as papulosquamous disorder, 393-394, 393f-394f
 urethral involvement in, reconstructive surgery for, 911-912
 Real-time elastography (RTE), 70-71, 70f
 of scrotum, 70f, 79-80
- Reboxetine, for delayed ejaculation, 706-707
 Receptor activator of nuclear factor- κ B ligand (RANKL) inhibitors, for castration-resistant prostate cancer, 2820
 Reconstructive surgery
 after bladder RMS treatment, 3587
 for cloacal anomalies, 3516-3520
 definitive, 3517-3520, 3518f
 gastrointestinal tract decompression for, 3516-3517
 genitourinary tract decompression for, 3517, 3517f
 initial management, timing, and principles for, 3516
 obstructive urinary repair, 3517
 results of, 3519-3520, 3520t
 for detrusor underactivity, 1819
 for disorders of sex development and urogenital sinus
 high vaginal confluence; with or without clitoral hypertrophy, 3509-3510, 3510f-3512f
 initial management, timing, and principles, 3504-3507, 3505f, 3507f
 low vaginal confluence: clitoral hypertrophy, 3508-3509, 3509f
 results of, 3513-3516
 total and partial urogenital mobilization, 3510-3513, 3512f-3515f
 penile and urethral, 492, 493f-494f, 907, 917b, 492.e2
 for amyloidosis, 913
 anatomic considerations for, 910.e1-3, 910.e1f-910.e7f, 910.e5, 910.e8b
 for circumcision complications, 915
 in classic bladder exstrophy, 3203-3209
 corpora cavernosa, 492, 493f-494f
 for curvatures of penis, 939-941, 941b
 for failed hypospadias repair, 915-916
 for female-to-male transsexualism, 945, 945b
 for fistulae of posterior urethra, 938-939, 939b
 for genital trauma, 916.e1-2, 916.e1f, 916.e3b
 for LS, 912-913, 913f
 in male epispadias, 3223
 for meatal stenosis, 914-915
 microvascular, 2382
 for paraphimosis, balanitis, and phimosis, 914
 for PFUIs, 932-935, 933f-936f, 937
 posttraumatic, 2385
 principles of, 907-911, 908f-910f, 910b
 for reactive arthritis, 911-912
 for residual abnormality in patients with exstrophy, 915-916
 surgical technique generalities for, 910-911, 911b, 910.e1f
 total penile, 941-945, 943f, 945b
 for urethral diverticulum, 913-914
 for urethral hemangioma process, 911
 for urethral stricture disease, 920-929, 922f-931f, 931b
 for urethrocutaneous fistula, 913
 for vesicourethral distraction defects, 937-938, 939b
 regenerative medicine for. *See* Regenerative medicine
 RPLND with, 822-823
 for scrotum, posttraumatic, 2385
- Rectal carcinoma, and delayed ejaculation, 703
 Rectal distention, in bladder and bowel dysfunction, 3305, 3305f
 Rectal fac
- Rectal injury, with laparoscopic radical prostatectomy, 2679-2680
 Rectal toxicity, with brachytherapy, 2702
 Rectocele, 1750, 1943-1944, 1944f
 repair of, 1978-1982
 Rectourethral fistula (RUF), 2132. *See also* Urethrorectal fistula
 Rectouterine pouch, 1599, 1599f
 Rectovaginal fascia, defects in, 1598, 1944f
 Rectovaginal space, 1598-1599, 1599f
 Rectum
 anatomy of, 1612f, 1617f, 1622-1623, 1623f, 1625f
 physical examination of, 11
 Rectus abdominis, 1613, 1613f
 Rectus sheath, 1611-1613, 1613f-1614f
 Recurrent stenosis, after urethral injury, 2391
 Recurrent UTIs, 270-271, 270f
 bacterial persistence and, 271
 low-dose continuous prophylaxis for, 272-273, 272t
 other strategies for, 274
 postintercourse prophylaxis for, 274
 reinfections, 271-274
 self-start intermittent therapy for, 274
- Red blood cell casts, in urinary sediment, 23, 23f
 Red blood cells. *See* Erythrocytes
 REDUCE. *See* Reduction by Dutasteride of Prostate Cancer Events
 5 α -Reductase
 in benign prostatic hyperplasia, 2427-2428, 2428f
 deficiency of, 3492-3494, 3493f-3494f
 prostate metabolism of, 2405-2406, 2405f, 2406t
 5 α -Reductase inhibitors
 for chemoprevention of prostate cancer, 2560-2562
 to facilitate bladder filling and urine storage with α -adrenoreceptor antagonists, 1861
 with antimuscarinic agents, 1860-1861
 prostate-specific antigen and, 2602-2603
- Reduction by Dutasteride of Prostate Cancer Events (REDUCE), 2562
 Reflection, of ultrasound waves, 66-67, 66f
 Reflex circuitry
 controlling continence, 1660-1663, 1660f
 somatic to visceral reflexes, 1661
 sphincter to bladder reflexes, 1661, 1661f, 1663f
 storage phase, 1660-1661, 1661f-1662f, 1662t
 controlling micturition, 1660-1663, 1660f
 emptying phase, 1661-1662, 1661f, 1662t
 urethra to bladder reflexes, 1662-1663, 1663f-1665f
- Reflex contraction, promotion or initiation of, 2080
 Reflex sympathetic dystrophy (RSD), lower urinary tract dysfunction and, 1786
 Refractory bladder pain syndrome, 370
 Refractory storage symptoms, after urethrolisis, 2006
- Regenerative medicine, 482, 496-497, 497b
 biomaterials for, 486
 design and selection of, 486
 types of, 486.e1-486.e2, 486.e1f
 history of, 482
 stem cell sources for, 482-483, 483t
 adult, 485, 485f
 embryonic, 483, 483.e1
 induced pluripotent, 484
 native targeted progenitor cells, 485
 perinatal, 484-485
 SCNT, 483-484, 484f

Regenerative medicine (*Continued*)

- of urologic structures
 - bladder, 488-492, 490f-491f
 - genital and reproductive tissues, 492-493, 493f-495f, 492.e2
 - renal structures, 494-496, 496f, 495.e1
 - ureters, 492, 492.e1
 - urethra, 487-488, 487f-488f
 - vascularization for, 486, 486.e3
- Regional anesthesia
 - for pediatric patients, 2956
 - for percutaneous access to upper urinary tract collecting system, 158
 - preoperative considerations for, 111
- Regitine. *See* Phentolamine
- Reiter syndrome. *See* Reactive arthritis
- Rejection, of renal transplantation, 1083-1084
- Relapse, tumors
 - NSGCTs, 804-806
 - seminomas, 809-810
- Relative jet frequency (RJF), 1091
- Relative radiation level (RRL), 27, 28t
- Relative saturation ratio (RSR), 1174
- Reliability, of HRQOL instruments, 96, 96t
- Religion, benign prostatic hyperplasia and, 2440
- REM. *See* Rapid eye movement
- Renal abscess, 280-283, 281f-282f
- Renal agenesis, 3007
 - bilateral. *See* Bilateral renal agenesis
 - neonatal, 2890
 - prenatal, 2889
 - unilateral. *See* Unilateral renal agenesis
 - vesicoureteral reflux and, 3151-3152
- Renal arterial clamping, for laparoscopic partial nephrectomy, 1476
- Renal arteries, 776, 971-973, 972f-973f, 973b, 971.e2f, 776.e1f, 971.e1f
- occlusion of. *See* Ischemic nephropathy; Renovascular hypertension
- in radical nephrectomy, 1424-1426, 1425f, 1424.e1f
- in simple nephrectomy, 1455, 1457f
- Renal arteriovenous fistula, 2999
- Renal artery aneurysm (RAA), 2998-2999
- Renal artery embolization (RAE), before kidney surgery, 1414, 1414.e1f
- Renal artery stenosis (RAS)
 - in ischemic nephropathy, 1029-1031, 1030f-1031f, 1031b
 - management of, 1035
 - angioplasty and stenting for hypertension, 1036-1037, 1037b
 - angioplasty and stenting for renal function preservation, 1038-1039, 1039b, 1040f
 - medical therapy, 1035-1036, 1036b
 - surgical treatment, 1039-1040, 1040b
 - pathology of, 1032-1033, 1033t, 1034b, 1034f-1035f
 - physiologic significance of, 1033-1035, 1035b
 - in renovascular hypertension, 1028-1029, 1029f
- Renal artery thrombosis, neonatal, 2891
- Renal bleeding
 - nephrectomy and, 1153-1154
 - with renal injury, 1157
- Renal blood flow (RBF), 1007, 1009b
- aging and, 2083
- urinary tract obstruction and
 - in bilateral ureteral obstruction, 1094-1095, 1095f
 - GFR and, 1093-1094
 - in partial ureteral obstruction, 1095
 - renal vascular resistance, 1094
 - in unilateral ureteral obstruction, 1094, 1094f

Renal calculi, 1170

- ammonium acid urate stones in, 1195-1196
- anatomic predisposition to, 1197-1199
- caliceal diverticula, 1198
- horseshoe kidneys, 1198
- medullary sponge kidney, 1198-1199
- ureteropelvic junction obstruction, 1197-1198
- calcium stones in, 1182-1185, 1209-1212
 - hypercalciuria, 1182-1185, 1209-1210, 1210b, 1210t
 - hyperoxaluria, 1185-1187, 1185f-1186f, 1210-1211, 1211b
 - hyperuricosuria, 1187, 1210
 - hypocitraturia, 1188, 1211-1212, 1211f, 1212b
 - hypomagnesiuria, 1190, 1212
- classification of, 1182, 1182t, 1209-1216, 1210t
- clinical factors of, 1254-1257
 - duration, 1257
 - morbid obesity and, 1255, 1281
 - old age and frailty, 1255-1256
 - prior renal surgery, 1256
 - renal function, 1254-1255
 - renal transplants, 1257
 - solitary kidney, 1255
 - spinal deformity or limb contractures, 1256
 - uncorrected coagulopathy, 1256
 - urinary diversion, 1256-1257
 - urinary tract infection and, 1254
- composition of
 - imaging role in, 1208
 - relative occurrence and, 1182, 1182t
 - treatment decision based on, 1242-1243, 1242f-1243f
- cystine stones, 1193-1194, 1193f, 1213, 1213b, 1214f
- diagnostic criteria for, 1209-1216, 1210t, 1216t
- dihydroxyadenine stones in, 1195
- epidemiology of, 1170-1173, 1173b
 - age, 1171
 - cardiovascular disease, 1173
 - climate, 1171-1172
 - gender, 1170-1171, 1173b
 - geography, 1171, 1171f
 - obesity, diabetes, and metabolic syndrome, 1172-1173
 - occupation, 1172
 - race/ethnicity, 1171
 - water intake, 1173
- historical overview of, 1235.e1
- infection stones, 1194-1195, 1194f, 1195t, 1213, 1213b, 1214t, 1215f
- matrix stones in, 1196
- medical management of, 1216-1222, 1233b
 - dietary calcium in, 1220-1221, 1221b
 - dietary recommendations in, 1218-1219, 1219b
 - efficacy of, outside of academic center, 1222-1223
 - fluid recommendations in, 1216-1217, 1217b
 - obesity and, 1219-1220, 1220b
 - oxalate avoidance in, 1221-1222, 1222b
 - selective therapies for, 1222-1232, 1222t-1223t, 1224f
 - vitamin D and bisphosphonate role in, 1221, 1221b
- medication-related stones, 1196-1197
- metabolic abnormalities and analysis of, 1207-1208, 1207t, 1208b

Renal calculi (*Continued*)

- metabolic evaluation for, 1200-1206
 - economics of, 1208-1209, 1209b
 - extensive, 1204-1205, 1204t, 1205b
 - fast and calcium load test in, 1205
 - of first-time stone formers, 1200-1201, 1201b
 - in low-risk single-stone formers, 1201-1204, 1202b, 1203f-1204f, 1204b, 1204t
 - patient selection for, 1200, 1201b
 - simplified, 1205-1206, 1206f-1207f, 1207b
- mineral metabolism and, 1182b
 - calcium, 1180
 - magnesium, 1181
 - oxalate, 1181
 - phosphorus, 1180-1181
- mineralogical names of, 1207t
- natural history of, 1235-1237
- nonstaghorn. *See* Nonstaghorn renal calculi
- open stone surgery for, 1285-1286
- pediatric. *See* Pediatric stone disease
- physicochemistry of, 1173-1179, 1179b
 - inhibitors and promoters, 1178-1179
 - matrix of, 1179
 - nucleation and crystal growth, 1175-1178, 1176f
 - saturation state in, 1173-1175, 1174f
- in pregnancy, 1199
- medical management of, 1233
- in renal development
 - clinical presentation of, 2863
 - epidemiology of, 2863-2865
 - etiology of, 2863-2864
 - evaluation of, 2864
 - medical management of, 2864-2865, 2865b
- staghorn. *See* Staghorn calculi
- surgical management of
 - anatomic factors in, 1243-1250
 - in calyceal diverticula, 1243-1244, 1278-1281, 1279f
 - factors affecting, 1236b
 - historical overview of, 1235-1250, 1235.e1
 - in horseshoe kidneys, 1244-1246, 1245f, 1279-1280
 - imaging for, 1237
 - key points of, 1250b
 - laboratory tests for, 1237-1238
 - lower pole calculi, 1247-1250, 1247f, 1248t, 1249f
 - medical history for, 1237
 - pretreatment assessment for, 1237-1238
 - in renal ectopia, 1246-1247, 1247f
 - after renal transplantation, 1280, 1280f
 - stone burden and treatment decision, 1238-1241, 1238b, 1239f
 - stone composition and, 1242-1243, 1242f-1243f
 - stone factors in, 1238-1243
 - stone localization and, 1241-1242
 - treatment algorithm for, 1235, 1236f
 - in ureteropelvic junction obstruction, 1243
- uric acid stones in, 1190-1193, 1191f-1192f, 1212, 1212b, 1213f
 - hyperuricosuria, 1192
 - low urinary volume, 1193
 - low urine pH, 1190-1192, 1192f
 - with urinary intestinal diversion, 2313
 - in urinary tract obstruction, 1091
 - xanthine stones in, 1195
- Renal calyx, 155-156, 155f-156f, 968, 968.e1f
- normal urothelium of, 1369, 1369f-1370f
- Renal cancer, as non-AIDS-defining urologic malignancy, 386

Renal cell carcinoma (RCC)

autosomal dominant polycystic kidney disease association with, 1336, 3019
 clinical associations of, 1335-1336
 clinical presentation of, 1334-1335, 1334b, 1334t
 etiology of, 1320-1321
 familial, 1321-1325, 1322t-1323t, 1323f
 treatment of, 1353-1355, 1355f, 1429, 1429.e1f
 historical considerations for, 1314
 incidence of, 1320
 metastatic. *See* Metastatic RCC
 pathology of, 1328-1334
 chromophobe RCC, 1329t-1330t, 1332-1333, 1332f
 classification systems, 1328-1330, 1328t-1330t
 clear cell RCC, 1329t-1330t, 1330-1331, 1330f
 collecting duct RCC, 1329t-1330t, 1333
 papillary RCC, 1329t-1330t, 1331-1332, 1331f
 renal medullary RCC, 1329t-1330t, 1333
 sarcomatoid differentiation, 1333, 1333f
 unclassified, 1329t-1330t, 1334
 in pediatric patients, 1320, 3580
 prognosis of, 1338-1341, 1339b, 1339t, 1341b, 1342t, 1343f
 radiographic evaluation of, 1315b, 1316-1318, 1316f, 1338, 1338f
 cystic lesions, 1315b, 1318-1320, 1318f-1320f, 1319t
 screening for, 1335-1336, 1336b
 staging of, 1336-1338, 1337f-1338f, 1337t
 treatment of advanced, 1500
 chemotherapy, 1516
 debulking or cytoreductive nephrectomy, 1501-1503, 1502f, 1503b, 1503t
 hormonal therapy, 1516
 immunologic approaches, 1503-1507, 1504t-1505t, 1506f, 1507t
 palliative surgery, 1503, 1504b
 prognostic factors and, 1500-1501, 1501f, 1501t
 resection of metastases, 1503, 1504b
 systemic therapy for non-clear cell variants, 1516-1518, 1517f
 targeted molecular therapies, 1502-1503, 1507-1516, 1508f-1512f, 1509t-1511t, 1513t-1514t, 1515f
 treatment of localized, 1341-1344, 1343f
 active surveillance, 1347t, 1351-1352, 1352t
 management algorithms for, 1352-1353, 1352t-1353t, 1354f-1355f
 partial nephrectomy, 1344-1349, 1345b, 1347t, 1348f-1349f
 radical nephrectomy, 1344-1345, 1345b, 1346f
 renal function after, 1344-1345, 1345b, 1348-1349, 1348f
 thermal ablative therapies, 1347t, 1349-1351, 1350t
 in von Hippel-Lindau disease and other familial RCCs, 1353-1355, 1355f
 treatment of locally advanced, 1356b
 adjuvant therapy, 1359-1360, 1360b, 1360t
 IVC involvement, 1355-1358, 1356b, 1356f-1357f, 1470. *See also* Vena caval thrombectomy
 local recurrence, 1359, 1360b
 locally invasive, 1358
 lymph node dissection, 1358-1359, 1358t, 1359f, 1426-1427, 1426f-1427f, 1427.e1f
 with tuberosus sclerosis complex, 3025

Renal cell carcinoma (RCC) (Continued)

tumor biology clinical implications in
 angiogenesis and targeted pathways, 1325t, 1326-1327
 immunobiology and immune tolerance, 1325-1326, 1325t
 other signal transduction and cell cycle regulation pathways, 1325t, 1327, 1327b
 resistance to cytotoxic therapy, 1325, 1325t
 Renal clearance, 1008
 Renal concentrating capacity test (RCCT), 1835
 Renal cortex, 968-969, 968.e1f-968.e2f
 Renal cortical scintigraphy, for pediatric patients, 2921, 2921f
 Renal cystic diseases, 3011-3012, 3012f
 acquired. *See* Acquired renal cystic diseases
 benign multilocular cyst, 3031-3032, 3031f, 3033f
 classification of, 3011-3012, 3013b
 congenital nephrosis, 3023
 familial hypoplastic glomerulocystic kidney disease, 3023
 inheritable, 3013, 3014t
 medullary. *See* Medullary cystic kidney disease
 medullary sponge kidney. *See* Medullary sponge kidney
 multicystic dysplastic kidney. *See* Multicystic dysplastic kidney
 multiple malformation syndromes with. *See* Multiple malformation syndromes with renal cysts
 polycystic. *See* Autosomal dominant polycystic kidney disease; Autosomal recessive polycystic kidney disease
 Renal cysts, 1300-1302, 1301f-1302f, 1301t, 1302b, 3032-3036
 classification of, 3035-3036, 3035b, 3036f
 clinical features of, 3034
 evaluation of, 3034-3035, 3034f-3035f
 histopathology of, 3034
 laparoscopic surgery for, 1457-1460, 1460f, 1460t
 procedure for, 1460-1461, 1461f
 results of, 1461
 multiple malformation syndromes with. *See* Multiple malformation syndromes with renal cysts
 prenatal, 2878-2879, 2878f
 prognosis of, 3036, 3037f
 radiographic evaluation of, 1315b, 1318-1320, 1318f-1320f, 1319t
 CT, 43-45, 45f-46f, 1318-1320, 1318f-1320f, 1319t
 MRI, 50-56
 prenatal, 2909-2910, 2910f
 ultrasonography, 63, 64f
 treatment of, 3036, 3037f
 Renal descensus, for ureteral stricture disease, 1139
 Renal disease, hematuria related to, 194
 Renal drainage, for urinary tract obstruction, 1101
 Renal dysmorphism, with vesicoureteral reflux, 3147, 3147f, 3147t, 3147.e1f
 Renal dysplasia, 3007-3008, 3007f
 etiology of, 3007-3008, 3008f
 Renal echinococcosis, 290-291, 291f
 Renal ectopia, 969, 2889, 969.e2f
 cephalad, 2986
 crossed, 2988-2993, 2990f-2991f, 2988.e1f
 renal calculi in, surgical management of, 1246-1247, 1247f
 simple, 2985-2986, 2987f, 2985.e3f
 Renal exploration, of renal injuries, 1153-1154, 1153f

Renal failure, 1041

AKI causing. *See* Acute kidney injury
 CKD causing. *See* Chronic kidney disease
 vesicoureteral reflux and, 3149
 Renal function
 aging and, 2084
 HIV and, 383-384
 orthoptic urinary diversion and, 2349-2350
 in posterior urethral valves, 3267
 after RCC surgery, 1344-1345, 1345b, 1348-1349, 1348f
 shock wave lithotripsy and, 1274
 transitional urology and, 3525, 3525t
 upper urinary tract calculi and, 1254-1255
 urinary tract obstruction and, 1090-1091
 Renal function assessment
 for CKD, 1060-1061
 for ureteral anomalies, 3082, 3084f
 Renal functional development, disorders of
 clinical presentation of renal dysfunction, 2852-2869, 2852b, 2853f, 2854b-2855b, 2854t, 2856f, 2857b, 2861b, 2863b, 2865b, 2866t-2869t, 2867b-2869b
 development of renal function and transition to neonatal life, 2849-2850, 2850f, 2851b
 renal homeostasis, fluids, and electrolytes, 2851-2852, 2852b
 renal replacement therapy, 2870-2872, 2872b
 summary, 2872
 Renal growth, vesicoureteral reflux and, 3149
 Renal hilum, 968
 identification of, for simple nephrectomy, 1454-1455, 1457f
 Renal hypercalciuria, 1184, 1209, 1210t
 agents for, 1225, 1225b, 1226t
 Renal hypodysplasia, 3008f, 3011
 Renal hypoplasia, 3008-3009
 Renal immaturity, and renal development, 2851, 2852b
 Renal infection (bacterial nephritis), 274
 acute focal or multifocal bacterial nephritis, 278-279, 279f
 acute pyelonephritis, 275-278, 276f-277f, 278t, 285
 bacterial "relapse," 286
 chronic pyelonephritis, 285-286, 286f
 emphysematous pyelonephritis, 279-280, 280f-281f
 HIV and, 383
 infected hydronephrosis and pyonephrosis, 283, 283f
 pathology, 274-275, 275f-276f
 perinephric abscess, 283-285, 284f
 renal abscess, 280-283, 281f-282f
 UTIs and, 2936, 2936f
 Renal injuries, 1148-1157, 1157b
 angioembolization for, 1151, 1152f
 classification of, 1149-1151, 1149f, 1149t
 damage control for, 1155
 hematuria in, 1148
 observation of, 1150
 history for, 1148
 imaging of
 CT, 1150, 1150f
 indications for, 1149-1150, 1150f
 IVP, 1150-1151
 nonoperative management of, 1151-1153, 1153f
 operative management of
 complications with, 1155-1157
 indications for, 1153-1155
 partial nephrectomy, 1154, 1154f-1155f
 renal exploration for, 1153-1154, 1154f
 renal reconstruction, 1154-1155, 1154f
 renorrhaphy, 1154, 1155f
 for renovascular injuries, 1154-1155, 1156f
 total nephrectomy, 1155

- Renal injuries (*Continued*)
 pediatric, 3538
 presentation of, 1148
 renal trauma grading system for, 3539, 3539t, 3540f-3543f
 from shock wave lithotripsy
 acute, 1271-1273, 1272b-1273b, 1272f-1273f
 chronic, 1273-1274, 1274t
- Renal insufficiency
 bacteriuria in pregnancy and, 296
 benign prostatic hyperplasia and, 2471
 partial nephrectomy causing, 1433
- Renal ischemia. *See also* Ischemic nephropathy;
 Renovascular hypertension
 for laparoscopic partial nephrectomy, 1475-1476
 for partial nephrectomy, 1429, 1429f
- Renal malignancies
 chronic inflammation role in, 451-452
 classification of, 1314, 1315b
 genomic alterations in, 467, 468t, 471-472, 1321-1325, 1322t-1323t, 1323f
 in geriatric patients, 2099.e13
 hereditary. *See* Hereditary leiomyomatosis and RCC syndrome; Hereditary papillary RCC syndrome
 historical considerations for, 1314
 HRQOL instruments for, 92t-94t
 immune checkpoint blockade in, 457
 lymphoma and leukemia, 1361t-1362t, 1362-1363
 metastases, 1361t, 1363
 MetS and, 554
 others, 1361t, 1363-1364
 port-site recurrence of, 1469
 radiographic evaluation of, 1314-1318, 1315b, 1316f
 CT, 45, 46f, 1316-1317, 1316f
 MRI, 50-61, 53f-55f, 1316, 1317f
 prenatal, 2910, 2911f
 ultrasonography, 63, 64f, 1316
- RB1 in, 461
- RCC. *See* Renal cell carcinoma
- sarcomas, 1360-1362, 1361t, 1362f
- surgical techniques for. *See* Kidney surgery
- vaccines for, 454-455
- Renal mass reduction, CKD and, 1055-1056
- Renal masses, prenatal, 2885
- Renal medulla, 968, 968.e1f-968.e2f
- Renal medullary RCC, pathology of, 1329t-1330t, 1333
- Renal pain, patient history of, 2
- Renal papilla, 968, 968.e1f-968.e2f
- Renal papillary necrosis (RPN), host defense mechanisms in UTIs and, 249, 249b
- Renal parenchyma, 155-156, 155f-156f
 radiologic anatomy of, 969, 969b, 971f, 969.e1f-969.e2f
- Renal pelvis
 normal urothelium of, 1369, 1369f-1370f
 in urine transport, 993-994, 994f-995f
- Renal pelvis tumors, open nephron-sparing surgery for, 1384-1385, 1385f
- Renal physiology. *Continued*
 acid-base metabolism, 1023-1025, 1027b
 hormonal
 ADH, 1012, 1013f, 1013t
 bone mineral regulation, 1011-1012, 1011f
 control of renal vascular tone, 1009-1011, 1009b, 1010f, 1011b
 erythropoiesis regulation, 1011
- Renal physiology (*Continued*)
 pathophysiology
 acid-base disorders, 1025-1027, 1025b, 1026t, 1027b
 potassium imbalances, 1023, 1023b-1024b
 sodium and water imbalances, 1019-1023, 1020f-1022f, 1021b, 1023b
 renal tubular function, 1012-1013, 1013f-1014f, 1019b
 collecting tubule, 1018-1019, 1018f-1019f
 distal tubule, 1018
 loop of Henle, 1015-1018, 1016f-1017f
 PCT, 1013-1015, 1014f-1016f
 vascular
 blood flow. *See* Renal blood flow
 glomerular filtration. *See* Glomerular filtration rate
- Renal preservation surgery, urinary leak after, 2137
- Renal protective strategies, for CKD, 1062-1063, 1063t
- Renal replacement therapy (RRT)
 for AKI, 1052
 prescription and modality for, 1052-1053
 for CKD, 1064-1065, 1067b, 1067t
 for ESRD, 1065, 1066b-1067b, 1066f, 1067t
 incidence and prevalence of, 1069
 long-term complications of, 1070
 options for, 1069
 results of, 1070
 transplantation. *See* Renal transplantation
- Renal scarring, and UTIs, 2946
- Renal scintigraphy, 2906
 of vesicoureteral reflux, 3146, 3146f
- Renal sinus, 968
 cyst of, 3040, 3041f
- Renal stones, struvite, urea-splitting bacteria causing, 271
- Renal structures, regeneration of, 494-496, 496f, 495.e1
- Renal system, pneumoperitoneum effects on, 213, 213t
- Renal transplantation, 1088b, 2871-2872, 2872b
 AD and, 539
 autotransplantation, 1087-1088
 calculi removal after, percutaneous nephrolithotomy for, 1280, 1280f
 donor selection for, 1074
 deceased donors. *See* Deceased donors
 living donors. *See* Living donors
 for ESRD
 incidence and prevalence of, 1069
 other treatment options compared with, 1069-1070
 genitourinary tuberculosis management and, 432
 HRQOL instruments for, 92t-94t
 operation for
 allograft preparation, 1080, 1080f
 donor, 1079, 1080f
 recipient, 1080-1083, 1081f-1082f
 pediatric. *See* Pediatric renal transplantation
 in posterior urethral valves, 3267
 post-transplant care for
 allograft nephrectomy, 1086-1087
 anticoagulation, 1083
 immunosuppression protocols, 1084-1086, 1084f, 1085b, 1085t
 infection, 1086, 1086t
 malignancy, 1087
 pregnancy and childbearing, 1087, 1087t
 rejection, 1083-1084
 surgical complications, 1083, 1083f
- Renal transplantation (*Continued*)
 recipient selection for, 1070
 bladder outlet obstruction and, 1073
 disease cause considerations in, 1070
 malignancy considerations in, 1072
 native nephrectomy indications and timing in, 1073, 1073b
 nonadherence considerations in, 1072
 preliminary screening of, 1070, 1071f
 probability of perioperative morbidity or mortality in, 1071
 surgical evaluation for, 1072-1073
 urinary diversion and bladder augmentation and, 1073-1074
 urologic procedure considerations in, 1073, 1073t
 timing of nephrectomy for, 1073, 1073b
 urinary leak after, 2137
 urologist role in, 1069
- Renal trauma. *See* Renal injuries
- Renal tubular acidosis (RTA)
 acquired, causes of, 1211-1212, 1212b
 in calcium stone formation, 1188-1190, 1189f
 CT of, 1211, 1211f
 renal calcifications with, 1177
 renal pathophysiology involved in, 1026
 type 1 (distal), 1188-1189, 1189f
 hypocitratemia with, 1211-1212, 1211f
 medical management of, 1228
 type 2 (proximal), 1189
 type 4 (distal), 1189-1190
- Renal tubular cells, in urinary sediment, 22-23
- Renal tubules
 apoptosis in, 1100
 functions of, 1012-1013, 1013f-1014f, 1019b
 collecting tubule, 1018-1019, 1018f-1019f
 distal tubule, 1018
 loop of Henle, 1015-1018, 1016f-1017f
 PCT, 1013-1015, 1014f-1016f
 urinary tract obstruction and, 1095-1096
- Renal tumors
 benign, 1300
 angiomyolipoma, 1306-1309, 1307f, 1309b
 cystic nephroma, 1309, 1310b, 1310f
 cysts. *See* Renal cysts
 leiomyoma, 1310-1312, 1311f, 1312b
 MEST, 1309-1310, 1310b, 1311f
 metanephric adenoma, 1303-1304, 1303f-1304f, 1304b
 mixed mesenchymal and epithelial, 1309, 1310b, 1310f-1311f
 oncocytoma, 1304-1306, 1304f, 1306b, 1306f
 others, 1312, 1312b
 papillary adenoma, 1302-1303, 1303b
 classification of, 1314, 1315b
 malignant. *See* Renal malignancies
- pediatric
 angiomyolipoma, 3580-3581, 3581f
 CCSK, 3579
 CMN, 3579-3580
 CPDN, 3580
 metanephric adenofibroma, 3580
 neuroblastoma. *See* Neuroblastoma
 RCC, 1320, 3580
 RTK, 3579
 solitary multilocular cyst nephroma, 3580
 Wilms tumor. *See* Wilms tumor
- radiographic evaluation of, 1314-1318, 1315b, 1316f
 CT, 43-45, 45f-46f, 1316-1317, 1316f
 for cystic lesions, 1315b, 1318-1320, 1318f-1320f, 1319t

- Renal tumors (*Continued*)
 MRI, 50-61, 53f-55f, 56t, 1316, 1317f
 prenatal, 2910, 2911f
 ultrasonography, 63, 64f, 1316
 surgical techniques for. *See* Kidney surgery
- Renal ultrasonography
 for acute pyelonephritis, 276-277
 indications for, 73
 limitations of, 75
 normal findings in, 74, 74f
 procedural applications of, 74-75
 technique of, 73
 of vesicoureteral reflux, 3145-3146
- Renal vasculature
 anomalies of
 aberrant, accessory, or multiple vessels, 2997-2998, 2998f
 renal arteriovenous fistula, 2999
 renal artery aneurysm, 2998-2999
 injuries to, 3547
 tone of, hormonal control of, 1009-1011, 1009b, 1010f, 1011b
- Renal vein clamping, for laparoscopic partial nephrectomy, 1476
- Renal vein renin (RVR) ratio, 1033-1035
- Renal vein thrombosis (RVT)
 AKI caused by, 1049
 neonatal, 2891
 prenatal, 2885, 2885f
- Renal vein tumor thrombus, laparoscopic radical nephrectomy for, 1470
- Renal veins, 971-973, 972f-973f, 973b, 971.e1f-971.e2f
 in radical nephrectomy, 1424-1426, 1425f, 1424.e1f
 in simple nephrectomy, 1455, 1457f
- Reninomas. *See* Juxtaglomerular cell tumors
- Renography
 diuretic. *See* Diuretic renography
 normal curve of, 1092
 nuclear, for urinary tract obstruction, 1091-1092
- Renomedullary interstitial cell tumors, 1312
- Renorrhaphy, for renal trauma, 1154, 1155f
- Renovascular fistula, 2135-2136
- Renovascular hypertension, 1028
 incidence and etiology of, 1028, 1028b
 management of, 1035
 angioplasty and stenting for hypertension, 1036-1037, 1037b
 angioplasty and stenting for renal function preservation, 1038-1039, 1039b, 1040f
 medical therapy, 1035-1036, 1036b
 surgical treatment, 1039-1040, 1040b
 pathology of, 1032-1033, 1033t, 1034b, 1034f-1035f
 pathophysiology of, 1028-1029
 one-kidney, one-clip model of, 1029, 1030f
 two-kidney, one-clip model of, 1029, 1029f
 physiologic significance of renal artery lesions and, 1033-1035, 1035b
 screening tests for, 1031, 1031b
 angiography, 1032, 1032b
 CT, 1032, 1032b
 duplex Doppler ultrasonography, 1032, 1032b
 MRA, 1031-1032
 trauma-induced, 3548
- Renovascular injuries, operative management of, 1154-1155
- Reoperative RPLND, 831t, 832
- Replantation, of penis, 2381-2382, 2382b, 916.e1, 916.e1f
- Reports, ultrasonography, 72-73, 72f
- Reproductive system
 female. *See* Female reproductive system
 male. *See* Male reproductive system
- Reprogramming, stem cells from, for tissue engineering, 484
- Residual renal function (RRF), in CKD, 1059-1060, 1060b
- Residual tumor, after treatment
 NSGCTs with, 802-805, 803t
 seminomas with, 809
- Resiniferatoxin (RTX), 1654-1655
 to facilitate bladder filling and urine storage, 1839t, 1863
 in idiopathic detrusor overactivity, 1863.e1
 in neurogenic detrusor overactivity, 1863.e1
 urgency and, 1863.e1
- Resistance, to chemotherapy, RCC with, 1325, 1325t
- Resistive index (RI), urinary tract obstruction and, 1091
- Resolution, of ultrasonography images, 65-66, 66f
- Resonance metallic ureteral stents, 127, 127f
- Resorptive hypercalciuria, 1184-1185, 1209-1210, 1210t
- Resource utilization, in health care, 86
- Respiratory acidosis, 1012
- Respiratory alkalosis, 1012-1013
- Respiratory system
 aging and, 2084
 pneumoperitoneum effects on, 213, 213t
 RPLND complications of, 833
- Responsiveness, of HRQOL instruments, 97
- Resting membrane potential (RMP), of ureteral muscle cells, 979-980, 980f, 982
- Restriction point, RB1 and, 461.e1
- Rete testis, 519-521
 adenocarcinoma of, 812
 cystic dysplasia of, 3393
- Retinoblastoma susceptibility protein (RB1), in GU cancers, 461, 461.e1
- 13-*cis*-Retinoic acid, for neuroblastoma, 3567
- Retraction instrumentation, for laparoscopic and robotic surgery, 209, 209.e2
- Retrocaval ureter
 etiology and diagnosis of, 1125, 1128b, 1128f
 operative intervention for
 laparoscopic surgical intervention, 1125-1128
 open surgical intervention, 1125, 1128f
- Retrocaval tumors, resection of, 824, 824f
- Retrograde cautery wire balloon endopyelotomy, for ureteropelvic junction obstruction, 1113-1114
- Retrograde ejaculation
 with holmium laser enucleation of prostate, 2530
 with transurethral incision of prostate, 2526
 after transurethral needle ablation of prostate, 2525
 treatment of, 707, 707b
- Retrograde intrarenal surgery. *See* Ureterorenoscopy
- Retrograde pyelography
 complications of, 34, 35f
 for genitourinary tuberculosis diagnosis, 427
 indications for, 34
 limitations of, 34
 for pediatric genitourinary trauma, 3542-3544
 for pediatric patients, 2916
 technique for, 33-34, 34f
 of ureteral stricture disease, 1129
 of urinary tract obstruction, 1129
- Retrograde transurethral assistance, for percutaneous access to upper urinary tract collecting system, 160-161, 161f, 160.e1f
- Retrograde ureterography, of ureteral injuries, 1161
- Retrograde ureteroscopic endopyelotomy, for ureteropelvic junction obstruction, 1111-1113
 complications with, 1113
 indications and contraindications for, 1112
 results with, 1112
 technique for, 1112, 1113f-1114f
- Retrograde ureteroscopic endoureterotomy, for ureteral stricture disease, 1131-1133, 1132f
 antegrade approach combined with, 1133
- Retrograde urethrography, 36, 36f
- Retroperitoneal approach
 to laparoscopic adrenalectomy, 1589-1590, 1589f-1590f, 1592-1593
 for laparoscopic and robotic surgery
 achieving access for, 201, 202f, 201.e3-201.e4, 202.e1
 operative team placement for, 198, 199f
 for pediatric patients, 2966-2969, 2967f, 2967t, 2969b-2970b
 pyeloplasty, 1118
 to laparoscopic kidney surgery, 1448-1450, 1450f-1451f
 to laparoscopic partial nephrectomy, 1472
- Retroperitoneal fibrosis (RPF)
 evaluation of, 1144, 1144f-1145f
 management of
 initial, 1144-1145
 medical, 1144-1145
 presentation and etiology of, 1143-1146, 1147b
 ureterolysis for
 laparoscopic, 1146
 open, 1145-1146, 1146f
- Retroperitoneal incision, for renal exploration, 1153, 1154f
- Retroperitoneal lymph node dissection (RPLND), 817-818, 817f
 adjuvant chemotherapy at, 827-829
 auxiliary procedures for, 822, 824b
 hepatic resection, 823
 major vascular reconstruction, 822-823
 nephrectomy, 822, 822t
 pelvic resection, 823
 supradiaphragmatic disease management, 823-824, 824f
 complications of, 833, 834t, 835b
 chylous ascites, 834
 ileus, 833-834
 lymphocele, 834
 mortality, 835
 neurologic, 835
 pulmonary, 833
 VTE, 834-835
 high-risk, 832b
 desperation, 831-832, 831t
 after HDCT, 831, 831t
 late relapse, 831t, 832
 reoperative, 831t, 832
 salvage, 831, 831t
 laparoscopic. *See* Laparoscopic RPLND
 management of clinical complete remission to induction chemotherapy, 825, 825t
 for NSGCTs, 798-801, 799t, 804
 outcomes and functional considerations of, 835b
 fertility, 833
 lymph node counts, 832
 in paratesticular RMS, 3597

- Retroperitoneal lymph node dissection (RPLND) (*Continued*)
 postchemotherapy. *See* Postchemotherapy retroperitoneal lymph node dissection
 preoperative planning for, 818
 robotic. *See* Robotic RPLND
 surgical technique for, 818
 closure and postoperative care, 821-822
 gonadal vein dissection, 820-821
 interaortocaval packet dissection, 819-820, 820f
 left para-aortic packet dissection, 819
 nerve-sparing technique, 820f-821f, 821
 retroperitoneum exposure, 818, 818f
 right paracaval packet dissection, 820
 split and roll technique, 818, 819f
 template use in, 825-826, 826f, 827t
 TGCT staging with, 793-794
 in unique situations
 for SCSTs, 836, 836b
 for seminoma, 835-836, 836b
- Retroperitoneal space, development of, 201, 202f, 201.e3-201.e4, 202.e1
- Retroperitoneal tumors (RPTs), 1403, 1403b
 classification and pathology of
 benign lesions, 1404, 1406b
 malignant lesions, 1404-1406, 1405t, 1406b
 clinical presentation and workup of, 1406-1407, 1407b
 epidemiology, etiology, and pathogenesis of, 1403-1404, 1404b
 staging of, 1406, 1406b
 treatment of, 1413, 1413b
 evidence-based guidelines for, 1409, 1409f-1410f
 perioperative radiotherapy in, 1409-1411
 perioperative systemic therapy in, 1411-1412, 1411b
 principles of sarcoma surgery, 1407-1408, 1408t
 surveillance strategies after, 1412-1413, 1412f
- Retroperitoneum
 anatomy of, 765, 783b
 arterial system, 769t, 775-776, 775f, 775.e1f, 775.e2f, 776.e1f
 body surface landmarks, 765, 766f
 contents, 765, 765b, 766f, 765.e2f-765.e3f
 fasciae and spaces, 770-773, 772f, 773.e1f, 771.e1f-771.e2f
 gastrointestinal viscera, 773-775, 773f-774f, 773.e1f
 history of, 765.e1t
 lumbodorsal fascia, 770, 770f-771f, 770.e1f
 lymphatic system, 777-778, 778f
 nervous structures, 778-782, 779f-782f, 781t, 780.e1f
 posterior abdominal wall, 765-770, 767f-769f, 769t
 spine, 769, 769.e1f
 10th, 11th, and 12th ribs, 770, 770f, 770.e1f
 venous system, 775f, 776-777, 776.e1f, 777.e1f-777.e2f
 exposure of, for RPLND, 818, 818f
- Retropubic midurethral sling
 anatomy for, 2009
 complications of, 2026-2037, 2028f
 outcomes with, 2015-2017, 2016t
 removal of, 2046
 surgical approach to, 2012-2013, 2012f-2013f
- Retropubic prostatectomy, 2535
 for localized prostate cancer, 2614
 radical. *See* Retropubic radical prostatectomy
- Retropubic radical prostatectomy (RRP)
 accessory pudendal artery preservation in, 2646, 2646f
 anesthesia for, 2644-2645
 apical dissection in, 2646-2649
 dorsal vein complex division, 2647-2649, 2647f-2648f
 urethra division and suture placement, 2648-2649, 2648f
 bladder neck division, 2654-2655, 2654f
 bladder neck reconstruction and anastomosis, 2655-2656, 2655f-2656f
 complications with, 2656-2658
 bladder neck contracture, 2657
 erectile dysfunction, 2658
 intraoperative, 2656-2657
 postoperative, 2657-2658
 thromboembolic events, 2657
 urinary incontinence, 2657-2658
 dorsal vein complex ligation, 2646-2651, 2646f-2647f
 endopelvic fascia incision for, 2645, 2645f
 exposure for, 2645
 incision for, 2644-2645, 2645f
 instruments for, 2644
 lateral pedicle division in, 2651-2652, 2653f
 lymphadenectomy in, 2644-2645, 2645f
 neurovascular bundle in, 2649-2651
 high anterior release of, at apex, 2651, 2652f
 identification of, 2649
 preservation of, 2649-2651, 2650f-2651f
 wide excision of, 2651, 2653f
 posterior dissection in, 2651-2652, 2653f
 postoperative management for, 2656
 preoperative preparation for, 2644
 puboprostatic ligament division for, 2645-2646, 2645f
 salvage, 2661
 seminal vesicle excision in, 2654-2655, 2654f
 summary for, 2661-2662
 surgical anatomy for, 2641-2643
 pelvic fascia, 2643, 2643f-2644f
 pelvic plexus, 2641-2642, 2642f
 striated urethral sphincter, 2642-2643, 2642f-2643f
 venous and arterial, 2641, 2642f
 surgical modifications of, 2658-2661
 bladder neck preservation, 2659
 interposition nerve grafting, 2660-2661
 seminal vesicle sparing, 2659-2660
 surgical technique for, 2644-2656
- Retropubic simple prostatectomy, 2537-2539
 adenoma enucleation for, 2538-2539, 2538f-2539f
 hemostatic maneuvers in, 2537-2538, 2537f
 prostate exposure for, 2537, 2537f
- Retropubic suspension surgery for incontinence in women
 comparisons with, 1934-1938
 anterior colporrhaphies, 1934
 needle suspension, 1934
 pubovaginal sling, 1934-1935, 1935f
 between techniques, 1936
 tension-free vaginal tape procedure, 1936-1938
 complications of, 1932-1934, 1934b
 bladder overactivity, 1933
 postoperative voiding difficulty, 1932-1933
 vaginal prolapse, 1933-1934
 contraindications for, 1922-1923
 hypermobility in, 1919-1920
 indications for, 1922-1923, 1922f
- Retropubic suspension surgery for incontinence in women (*Continued*)
 intrinsic sphincter deficiency
 contribution, 1919-1920
 issues with, 1921
 key points for, 1937b
 laparoscopic, 1930-1932, 1932b
 outcome assessment for, 1921-1922
 cure definition for, 1921
 follow-up duration, 1921
 patient's *versus* physician's perspective, 1921-1922
 surgical procedures for, 1918, 1919b, 1920-1921
 Burch colposuspension, 1920-1921, 1920f.
 See also Burch colposuspension
 Marshall-Marchetti-Krantz procedure, 1920-1921, 1920f. *See also* Marshall-Marchetti-Krantz procedure
 paravaginal defect repair, 1920-1921, 1920f.
 See also Paravaginal repair procedures
 vagina-obturator shelf procedure, 1920-1921, 1920f. *See also* Vagina-obturator shelf procedure
 technical issues for, 1923-1924
 bladder drainage for, 1923-1924
 dissection for, 1923
 drains for, 1924
 suture material for, 1923
 technique selection for, 1919-1921
 therapeutic options for, 1918-1919, 1919b
 vaginal surgery *versus*, 1923
- Retropulsion prevention devices, for ureterscopic intraluminal lithotripsy, 149, 149f
- Retrorectal space, 1598-1599, 1599f
- Retrospective review, of medical records, 97
- Reverberation artifact, in ultrasonography, 68, 69f
- Reversal, of vasectomy, 951-952
- RFA. *See* Radiofrequency ablation
- Rhabdoid tumor of kidney (RTK), in pediatric patients, 3579
- Rhabdomyolysis
 ATN with, 1044-1045
 after laparoscopic and robotic surgery, 223-224
- Rhabdomyosarcoma (RMS), 3466, 3466f
 bladder. *See* Bladder RMS
 cervical or uterine, in pediatric patients, 3590
 paratesticular, in pediatric patients, 3596-3597, 3597b
 of prostate, 2599
 of testicular adnexa, 813
 vaginal, in pediatric patients, 3589-3590, 3590f
 vulvar, in pediatric patients, 3589
- Rhabdosphincter, 1637
- Rhizotomy, sacral, for storage disorders, 1903
- RhoA, 1643, 1643f
- Rhythmic suprapubic manual pressure, 2080
- RI. *See* Resistive index
- Ribs, in retroperitoneum, 770, 770f, 770.e1f
- Right adrenalectomy
 laparoscopic, 1587-1588, 1588f, 1590, 1590f
 open, 1584, 1584f
- Right colon pouches
 with intussuscepted terminal ileum, 2332-2333
 operative technique variations for, 2339-2340, 2340f
 for orthoptic urinary diversion, 2360
- Rigid cystourethroscopes, 137, 139f-140f, 139t
- Rigid lithotripters, 1262-1264

- RTTA. *See* Radiofrequency interstitial tumor ablation
- RJF. *See* Relative jet frequency
- R-LESS. *See* Robotic laparoscopic single-site surgery
- RMP. *See* Resting membrane potential
- RMS. *See* Rhabdomyosarcoma
- RN. *See* Radical nephrectomy
- RNA
in transcription, 459.e3, 459.e3f
in translation, 459.e3-459.e4, 459.e3f-459.e4f
- Robot-assisted adrenalectomy, 1590, 1590f-1591f, 1593
- Robot-assisted laparoscopic simple prostatectomy, 2541
abdominal access, insufflation, and trocar placement for, 2541
adenoma enucleation in, 2541
adenoma extraction and closure for, 2541
bladder neck incision for, 2541
hemostatic maneuvers for, 2541
patient positioning for, 2541
space of Retzius development for, 2541
- Robotic distal ureterectomy, for UTUC, 1388
- Robotic ILND, for penile cancer, 864, 896-897
surgical technique for, 897-902, 897f-903f
- Robotic laparoscopic single-site surgery (R-LESS), for kidney surgery, 1480
- Robotic RPLND, 838
development of technology for, 839
port placement and technique for, 842-843, 843f
- Robotic surgery, 195
access technology for
hand-assist devices, 203-205, 203.e3, 203.e3f
LESS devices, 203.e4, 203.e4f
trocars, 202-205, 203f, 203.e1f-203.e2f
complications and troubleshooting in, 215, 215t, 224b
anesthesia-related, 220.e1
early postoperative, 222-224
equipment-related, 215-216
exit-related, 222
late postoperative, 224, 224.e1
during learning curve, 215
pneumoperitoneum-related, 216
procedure-related, 220-222, 220f, 222.e1
trocar-related, 217-220, 219f
equipment placement for, 197-198, 197.e3f
instrumentation used in
for da Vinci Robotic System, 209-210, 210f
for grasping and blunt dissection, 205-206, 210
for incising and hemostasis, 206-207, 210, 206.e1f, 207.e1
for LESS, 210.e1, 210.e1f
for morcellation, 209, 209.e1
for NOTES, 210.e2
for port site closure, 211, 211f
for retraction, 209, 209.e2
for specimen entrapment, 208-209, 209f
for stapling and clipping, 207-208, 208f-209f, 209b
surgical pharmaceuticals, 207, 207t, 207.e2
for suturing and tissue anastomosis, 207, 208f, 210, 207.e2f, 207.e3
for visualization, 205, 205.e1f-205.e2f
operative team placement for
retroperitoneal upper abdominal procedures, 198, 199f
transperitoneal and extraperitoneal pelvic procedures, 199, 199f
transperitoneal upper abdominal procedures, 198, 198f, 198.e1f
- Robotic surgery (*Continued*)
for partial nephrectomy, 1348
for pediatric patients, 2963, 2974, 2974b
advantages of, 2963
anesthesia for, 2966, 2966f
complications of, 2970-2972
contraindications to, 2965
disadvantages of, 2964-2965, 2964f
general applications of, 2964b, 2964t
hemostatic devices for, 2965
LESS, 2969-2970
outcomes of, 2972-2974, 2973t
retroperitoneal approach to, 2966-2969, 2967f, 2967t, 2969b-2970b
suturing for, 2965-2966
team development for, 2965
transperitoneal approach to, 2966-2969, 2967f, 2967t, 2968b-2969b
troubleshooting for, 2969, 2970b, 2970f-2972f, 2972b
physiologic considerations in, 211, 215b
hemodynamic effects related to approach and patient position, 214
hormonal and metabolic effects during surgery, 214
immunologic effects, 214-215
insufflation choice, 211-212
pneumoperitoneum effects on various systems, 212-214, 213t
pneumoperitoneum pressure choice, 212, 213t
preoperative preparation for, 197b
blood products, 196
bowel preparation, 196
operating room setup, 196-197, 197b
patient positioning, 197, 197.e1f
patient selection and contraindications, 195-196
for pediatric patients, 2967
prophylaxis, 197
procedure for, 211b
abdomen exit, 210-211
achieving extraperitoneal access and developing extraperitoneal space, 201-202, 202.e1
achieving retroperitoneal access and developing retroperitoneal space, 201, 202f, 201.e3-201.e4, 202.e1
achieving transperitoneal access and establishing pneumoperitoneum, 200-201, 201f, 200.e1, 200.e1f, 201.e1f, 201.e2, 202.e1
hand-assist device placement, 203-205, 203.e3, 203.e3f
LESS device placement, 203.e4, 203.e4f
port removal and fascial closure, 210-211
port site closure, 211, 211f
pre-incision checklist, 200
skin closure, 211
trocar placement, 202-205, 203f, 203.e1f-203.e2f
for seminal vesicle procedures, 961, 964f
training and practicing for, 224.e2, 224.e4b
equipment for, 224.e2-224.e4, 224.e2f-224.e3f
formal programs for, 224.e4
- Robotic systems, 197-198, 197.e3f
- Robotic-assisted laparoscopic kidney surgery, surgical approaches and access for, 1452-1453, 1453f
- Robotic-assisted laparoscopic nephroureterectomy, for UTUC, 1383-1384, 1384f
- Robotic-assisted laparoscopic partial nephrectomy, 1348
- Robotic-assisted laparoscopic radical prostatectomy (RALP). *See also* Laparoscopic radical prostatectomy
evolution of, 2663
pure laparoscopic versus, 2666-2667
salvage, 2680-2681
complications with, 2681
postoperative care for, 2681
surgical technique for, 2681
- Robotic-assisted laparoscopic surgery
bladder diverticulectomy, for bladder diverticula. *See* Bladder diverticulectomy, laparoscopic and robotic
Boari flap. *See* Boari flap, laparoscopic or robotic
for lower ureteral injuries, 1163-1164
pyelolithotomy, for pediatric stone disease, 3118
pyeloplasty
laparoscopic versus, 1120, 1121t
for ureteropelvic junction obstruction, 1119
pyelopyelostomy, for retrocaval ureter, 1126
radical prostatectomy, for prostate cancer, 2614-2615
simple/supratrigonal cystectomy. *See* Simple/supratrigonal cystectomy, robotic or laparoscopic
stone removal, 1286-1287
ureteral injuries with, 1158
ureteral reimplantation. *See* Ureteral reimplantation, laparoscopic and robotic
ureterolysis, for retroperitoneal fibrosis, 1146
ureteroneocystostomy
with Boari flap, 1137-1139
with psoas hitch, 1136
for ureteral stricture disease, 1135, 1135f
ureteroureterostomy, for ureteral stricture disease, 1134-1135
urinary diversion. *See* Minimally invasive urinary diversion
for vesicovaginal fistula. *See* Vesicovaginal fistula, robotic repair of
- Robotic-assisted laparoscopic ureteral reimplantation (RALUR), 3170-3171
- Robotic-assisted radical cystectomy (RARC), 2268-2277
female, 2274-2277
complications with, 2277
conclusions for, 2277
outcomes with, 2277
technique for, 2275-2277, 2276f, 2278t
technique for, 2268-2277
anterior pedicle division in, 2270-2271, 2270f
bladder release in, 2271, 2273f
dorsal vein complex division in, 2271, 2273f
pelvic lymph node dissection in, 2271-2272, 2274f
port placement for, 2268-2269, 2269f
posterior bladder and prostatic pedicle division, 2271, 2272f
posterior plane development in, 2271, 2271f
surgical positioning for, 2268-2269, 2269f
ureter transposition in, 2273-2274, 2275f
ureteral identification and transection in, 2270, 2270f
urinary diversion, 2274, 2276f
- Rolipram, for ureteral relaxation, 1001
- RON, in UTUC, 1375
- Rosebud stoma, 2293, 2293f
- Round ligament, 1600, 1601f

- Roux-en-Y gastric bypass (RYGB),
nephrolithiasis and, 1220, 1220b
RP. See Radical prostatectomy
RPF. See Retroperitoneal fibrosis
RPGN. See Rapidly progressive
glomerulonephritis
RPLND. See Retroperitoneal lymph node
dissection
RPN. See Renal papillary necrosis
RPTs. See Retroperitoneal tumors
RRE. See Residual renal function
RRL. See Relative radiation level
RRP. See Retroperitoneal radical prostatectomy
RRT. See Renal replacement therapy
RSD. See Reflex sympathetic dystrophy
RSPO1 gene, 3470, 3471f, 3472t
RSR. See Relative saturation ratio
RT. See Radiation therapy
RTA. See Renal tubular acidosis
RTE. See Real-time elastography
RTK. See Rhabdoid tumor of kidney
RTX. See Resiniferatoxin
RUE. See Rectourethral fistula
RVR ratio. See Renal vein renin ratio
RVT. See Renal vein thrombosis
RYGB. See Roux-en-Y gastric bypass
- S**
S phase, deregulation of progression through, in
GU cancers, 461.e1
S phase arrest, deregulation of, in GU cancers,
461.e2
Saccharin, urothelial cancer and, 2187
Saccules, 2141-2142
SACD. See Subacute combined degeneration
Sacral agenesis, 3286-3289
pathogenesis of, 3289
presentation of, 3286-3289, 3287f-3289f
specific recommendations for, 3289
Sacral arteries, 1615-1616, 1618t, 1620f
Sacral coccygeal teratoma, lower urinary tract
dysfunction and, 1791
Sacral evoked response: bulbocavernosus reflex
latency, 656
Sacral nerve stimulation (SNS), 1680
in bladder storage disorders
bilateral, 1908-1909
outcomes with, 1905-1906
selective nerves, 1909-1910
special populations in, 1906-1908
technique for, 1903-1905, 1904f-1905f
complications of, 1911-1914
for emptying disorders, 1916
history of, 1899-1900, 1900t
for lower urinary tract dysfunction, 1795
for UIII, 1715
Sacral neuromodulation (SNM)
complications of, 1911-1914
decreased or absent response, 1911,
1912f
impedance testing, 1911, 1913f
for detrusor underactivity, 1818-1819
for emptying disorders, 1916
for neuromuscular dysfunction of lower
urinary tract, 3282
onabotulinumtoxinA compared with,
1910-1911
putative mechanism of, 1901
in overactive bladder, 1901, 1901f
in urinary retention, 1901-1902, 1902f
for storage disorders, 1903-1908
troubleshooting algorithm, 1912-1914
intermittent stimulation, 1913-1914
no stimulation, 1913
Sacral neuromodulation (SNM) (Continued)
for pocket discomfort, 1912-1913, 1913f
recurrent symptoms, 1913-1914
wrong location, 1913
Sacral plexus, 1601-1602
neuromodulation of, 1680
Sacral rhizotomy, for storage disorders, 1903
Sacral spinal cord injury
lower urinary tract dysfunction with, 1773,
1775f
management with, 1773b
Sacrocolpopexy, abdominal, for apical pelvic
organ prolapse repair, 1971-1974,
1971f-1973f
Sacroiliac ligaments, 1600
Sacrospinous ligament culdosuspension,
1602-1603
Sacrospinous ligament fixation (SSLF), for pelvic
organ prolapse repair, 1965-1968
complications with, 1968
results of, 1968, 1968t-1969t
surgical anatomy for, 1966-1968, 1967f
technique for, 1967-1968, 1967f
Sacrospinous ligaments, 1600
Sacrospinous ligaments, 1600
Sacrum, 1597, 1598f, 1611
Safety wires, for percutaneous access to upper
urinary tract collecting system, 166-167,
167f
Salvage brachytherapy
for biochemical recurrence after radiation
therapy, 2780-2782
for radiorecurrent cancer, 2749
Salvage cryotherapy
for biochemical recurrence after radiation
therapy, 2780, 2781t
for radiorecurrent cancer, 2750
Salvage high-intensity focused ultrasound
ablation
for biochemical recurrence after radiation
therapy, 2782
for radiorecurrent cancer, 2750
Salvage radiation therapy
for biochemical recurrence after radical
prostatectomy, 2773-2774
adjuvant radiation therapy *versus*, 2777
androgen deprivation therapy with,
2774-2775
dose response, 2774
whole-pelvis *versus* prostatic bed, 2775,
2775f-2776f
for localized prostate cancer, 2622-2623
Salvage radical prostatectomy
for biochemical recurrence after radiation
therapy, 2779-2780, 2780t
for localized prostate cancer, 2618
for recurrent prostate cancer, 2747
retroperitoneal, 2661
Salvage RPLND, 831, 831t
Sansert. See Methysergide
Sarcoidosis, hypercalcemia in, 1184
Sarcomas
of bladder, 2201-2203
signet ring cell carcinoma, 2202, 2202f
small cell carcinoma, 2202, 2202f
squamous cell cancer, 2203, 2203f
of kidney, 1360-1362, 1361t, 1362f
of penis, 874-875, 874f
of prostate, 2599
retroperitoneal
classification and pathology of, 1404-1406,
1405t, 1406b
clinical presentation and workup of,
1406-1407, 1407b
Sarcomas (Continued)
epidemiology, etiology, and pathogenesis
of, 1403-1404
staging of, 1406, 1406b
treatment of, 1407-1413, 1408t, 1409f-
1410f, 1411b, 1412f, 1413b
of testicular adnexa, 813
Sarcomatoid differentiation, in RCC, 1333,
1333f
Saturation biopsy, for focal therapy for prostate
cancer, 2721
transperineal, 2721
transrectal, 2721
Saw palmetto berry, for benign prostatic
hyperplasia, 2499-2500
SB. See Spina bifida
SBRT. See Stereotactic body radiotherapy
Scabies
infestation, 408-410, 410f
as STD, 380, 380f
Scales, HRQOL. See Instruments
Scalpel, for laparoscopic and robotic surgery,
206, 210
Scanning electron micrograph
of penis, 616f
of testis, 519f
Scanning electron microscope (SEM)
of bladder blood vessels, 1634f
of urothelium, 1632-1633, 1633f
Scardino-Prince vertical flap, for ureteropelvic
junction obstruction, 1123, 1125f
Scarpa fascia, 1611, 1612f
Scattering, of ultrasound waves, 66-67, 67f
SCC. See Squamous cell carcinoma
SCCs. See Squamous cell carcinoma in situ
SCD. See Sickle cell disease
Scheduled voiding regimens. See Toileting
programs
Schistosomal myelopathy, lower urinary tract
dysfunction and, 1786
Schistosomiasis, of genitourinary tract, 433, 442b
biology and life cycle, 433-434, 433f-434f
clinical manifestations, 436-437
diagnosis, 437-439, 439f-440f
epidemiology, 434-435
history, 433
pathogenesis and pathology, 435-436, 435f,
438f-439f
prevention and control, 441-442
prognosis, 441
treatment, 440-441
surgical management in, 441
Schizophrenia, lower urinary tract dysfunction
and, 1790
Schwannoma, intrarenal, 1312
SCI. See Spinal cord injury
Scintigraphy. See Nuclear scintigraphy; Renal
scintigraphy
Scissors, for laparoscopic and robotic surgery,
206, 210
Scleroderma, lower urinary tract dysfunction
and, 1791
Sclerosing lymphangitis, 416, 416f-417f
Sclerotherapy, 955-956, 3397
SCNT. See Somatic cell nuclear transfer
Screening tests, for genitourinary tuberculosis,
424-425, 425b
Scrotal agenesis, 3382, 3382.e1f
Scrotal anomalies, 3382
bifid scrotum, 3382, 3383f
ectopic scrotum, 3382, 3384f
scrotal agenesis, 3382, 3382.e1f
scrotal hypoplasia, 3382
scrotochisis, 3382, 3382.e1f

- Scrotal elephantiasis, as filariasis clinical manifestation, 444, 444f
- Scrotal engorgement, 3381-3382, 3381f-3382f
- Scrotal hypoplasia, 3382
- Scrotal pain, patient history of, 2
- Scrotoectomy, 947
- Scrotoplasty, 3416
- for benign scrotal conditions, 948, 949f
- Scrotochisis, 3382, 3382.e1f
- Scrotum
- acute. *See* Acute scrotum
 - anatomy of, 514b
 - arterial supply, 514, 946, 947b
 - gross structure, 513-514, 515f
 - lymphatic supply, 514
 - nerve supply, 514
 - surgical, 946, 947b, 947f
 - venous drainage, 514
- chronic pain of
- postvasectomy, 952
 - surgical treatment of, 956-957, 956f
- in genitourinary tuberculosis, 423
- pediatric imaging of, ultrasonography, 2913-2915, 2917f-2918f
- penetrating injuries to, 2383
- physical examination of, 10-11, 11f
- reconstructive surgery for, posttraumatic, 2385
- surgery of, 946, 957b
- anatomic considerations for, 946, 947b, 947f
 - hydrocelectomy, 954-956, 955f, 955t
 - for incidental testicular lesions, 965, 966f, 966t
 - for orchitis and chronic pain, 956-957, 956f
 - preoperative preparation for, 946-947
 - scrotal wall procedures, 947-948, 948f-949f
 - spermatocectomy and epididymis surgery, 953-954, 954f
 - vasectomy. *See* Vasectomy
- trauma of, pediatric, 3558
- ultrasonography of, 501
- for GCIs, 790, 790f
 - indications for, 78
 - limitations of, 80, 80f
 - normal findings in, 78, 78f-79f
 - procedural applications of, 78-79
 - sonoelastography, 70f-71f, 79-80
 - technique of, 77
- SCSTs. *See* Sex cord-stromal tumors
- SD. *See* Seborrhic dermatitis
- SDHRCC. *See* Succinate dehydrogenase RCC
- Sealants, for laparoscopic and robotic surgery, 207, 207t, 207.e2
- Seborrhic dermatitis (SD), as papulosquamous disorder, 396-397
- Seborrhic keratosis, 418f, 419
- Second malignancies
- after bladder RMS treatment, 3588
 - after Wilms tumor treatment, 3579
- Second messengers, in ureteral contractions, 986-988, 987f-988f
- Secondary cutaneous lesions, 387, 388t
- Secondary data analysis, 97-98
- Secondary hypogonadism, AD resulting from, 539-541
- Secondary paraureteral diverticula, 3178, 3178f
- Secondary syphilis, 374, 374f
- Second-look nephroscopy, for percutaneous approach to UTUC, 1394
- Sediment analysis
- for AKI, 1048, 1049t
 - bacteria, 23, 24f
 - casts, 23, 23f
- Sediment analysis (*Continued*)
- cells, 21-23, 21f-22f
 - crystals, 23, 24f
 - expressed prostatic secretions, 25, 25f
 - microscopic technique for, 21
 - parasites, 24-25, 24f
 - specimen collection and preparation for, 20-21
 - yeast, 22f, 23-24
- Segmental arteries, of kidney, 971-973, 972f-973f, 973b, 971.e1f-971.e2f
- Segmental hypoplasia, 3009-3011, 3010f
- Segmental nephrectomy, for large renal tumors, 1431-1432, 1432f, 1432.e1f, 1431.e1f
- Segmental ureterectomy, for UTUC, 1385, 1386f
- SELECT. *See* Selenium and Vitamin E Cancer Prevention Trial
- Selective serotonin reuptake inhibitors, 698 and PE, 698-700, 699f, 703
- Selenium, in prostate cancer prevention, 2562-2563, 2563f
- Selenium and Vitamin E Cancer Prevention Trial (SELECT), 2562-2563, 2563f
- Self-catheterization, orthoptic urinary diversion and, 2350
- Self-start intermittent therapy, for recurrent UTIs, 274
- Self-styled dilators
- for achieving extraperitoneal access and developing extraperitoneal space, 201-202
 - for achieving retroperitoneal access and developing retroperitoneal space, 201, 202f, 201.e3
- SEM. *See* Scanning electron microscope
- Semen, coagulation and liquefaction of, 2423-2424, 2424b
- Semen analysis, postvasectomy, 952
- Semen evaluation, in male infertility, 566-570
- acrosome reaction, 570.e1
 - bulk semen parameters, 566-568, 566t
 - comet assay, 570
 - computer-assisted semen analysis, 568.e2
 - denatured sperm DNA assays, 570
 - pyospermia assays, 569
 - reactive oxygen species, 570
 - secondary semen assays, 568-569
 - semen volume, 567
 - sperm density, 567
 - sperm DNA integrity assays, 569-570
 - sperm morphology, 568, 568.e1
 - sperm motility, 567-568
 - sperm mucous interaction, 570, 570.e2
 - sperm ovum interaction, 570, 570.e3
 - sperm ultrastructural assessment, 570
 - sperm vitality, 568, 568.e2
 - tertiary and investigational sperm assays, 569-570
 - tunel assay, 569
- Semenogelin I, 535
- Semenogelins I and II, in prostatic secretions, 2417t, 2419-2420
- Seminal vesicle secretory proteins, in prostatic secretions, 2417t, 2423
- Seminal vesicles
- dissection of, in laparoscopic radical prostatectomy, 2670, 2670f-2671f
 - in genitourinary tuberculosis, 423
 - HIV and, 383
 - in retropubic radical prostatectomy excision of, 2654-2655, 2654f
 - sparing of, 2659-2660
- Seminal vesicles and ejaculatory ducts, 535b
- anatomy of, 505b, 582
 - arterial supply, 505
 - gross anatomy of, 505b, 582
 - lymphatic supply, 505
 - microanatomic architecture, 505
 - nerve supply, 505
 - surgical, 957-958, 957f-958f
 - venous drainage, 505
- cancer of, 963-965
- congenital anomalies of, 958
- cysts of, 961-963
- development of, 2399, 2838-2840, 2840f
- imaging of
- CT, 505
 - MRI, 505, 506f
 - transrectal ultrasound, 505
- physiology of, 535b
- functions, 534-535
 - gross and cytoarchitecture, 534, 534f-535f
- surgery of, 957, 958b
- anatomic considerations for, 957-958, 957f-958f
 - anterior approaches to, 960, 961f-962f
 - approaches used for, 960
 - complications of, 965
 - for cysts, 961-963
 - evaluation for, 958-960, 958f-960f
 - for infectious processes, 958
 - laparoscopic and robotic-assisted, 961, 964f
 - posterior approaches to, 960-961, 963f
 - for tumors, 963-965
 - tumors of, 963-965
- Seminal vesiculitis, prostatitis evaluation and, 316
- Seminiferous epithelium, 573.e3, 573.e4f
- Seminiferous tubules, 498, 499f, 502, 518-519, 519f-521f, 523
- germ cells in. *See* Germ cells
 - Sertoli cells in. *See* Sertoli cells
- Seminomas, 784
- genomic alterations in, 467, 474-475
 - histology of, 787-788, 787f
 - treatment of, 796, 797b, 810b
 - clinical stage I tumors, 806-809, 807t-808t
 - clinical stage IIA and IIB tumors, 809
 - clinical stage IIC and III tumors, 809
 - relapsed tumors, 809-810
 - RPLND, 835-836, 836b
- Semirigid ureteroscopes, 143-144, 143f-144f, 145t
- care and sterilization of, 146
 - technique for, 150-152, 151f
- Sensation, bladder
- altered, filling/storage failure due to, 1688-1689
 - detrusor underactivity and, 1816
 - instruments for measurement of, 1800-1802, 1802t
 - terminology for, 1745
- Sensor-transducer function, of bladder urothelium, 1639-1640
- Sensory innervation, in ureteral function, 992
- Sentinel lymph node biopsy, of inguinal nodes, for penile cancer, 863-864, 891-892, 892f
- Sepsis
- with intestinal anastomoses, 2290
 - neonatal, 2890
 - after percutaneous access to upper urinary tract collecting system, 180-181
 - UTIs and, 291-293, 292b-293b
- Septic shock, UTIs and, 291-293, 293b
- Serenoa repens* (saw palmetto berry), for benign prostatic hyperplasia, 2499-2500
- Serlopitant, to facilitate bladder filling and urine storage, 1866.e4
- Serology, syphilis tests, 375
- Seromuscular enterocystoplasty, 3358-3359, 3359f

- Serotonin (5-HT)
 in ED, 621-623, 623t
 in efferent pathways to bladder, 1658-1659
 in ejaculatory response, 692
 and female sexual response, 750, 750.e8
 urethral function effects of, 1004
- Serotonin-noradrenaline uptake inhibitors, for stress urinary incontinence in women, 1868-1869
- Serotonin-receptor effectors, 664
- Serous-lined extramural tunnel, for orthoptic urinary diversion, 2355-2357, 2357f
- Sertoli cell tumors, 812, 3595
- Sertoli cells, 518, 524f, 528, 565, 573.e3, 573.e3f
 germ cell interaction with, 524f, 528
 testis physiology and, 523, 524f
- Serum creatinine, contrast media reaction risk based on, 30
- Serum gonadotropin measurements, 657-658
- Serum prolactin measurement, 658
- Serum testosterone measurements, 657
- Serum tests, for UTIs, 2939
- Serum thyroid function tests, 658
- Severe nonidiosyncratic reactions, to intravascular iodinated contrast media, 29
- Sevoflurane, preoperative considerations for, 111
- Sex cord-stromal tumors (SCSTs), 811-812
 treatment of, RPLND, 836, 836b
- Sex determination, 518
- Sex hormone binding globulin (SHBG), 562, 565-566, 565b
 testosterone bound to, 539-542, 542b
- Sex partners, HIV management and, 382.e6
- Sex steroids. *See also specific steroidal hormones*
 lower urinary tract and, 1673
 of male reproductive system, 516, 517f
- Sextant biopsy, of prostate, 2586, 2586f
- Sexual activity
 benign prostatic hyperplasia and, 2440-2441, 2443t
 prostate cancer and, 2550-2551
 and UTIs, 2931
- Sexual development disorders, testicular tumors associated with, 3593, 3594t
- Sexual differentiation, 3469-3477
 disorders of. *See Disorders of sex development*
 gender identity, role, and orientation, 3475-3477
 gonadal function, 3473-3474
 ovary, 3474
 testis, 3473-3474, 3474f
 gonadal stage of differentiation, 3473, 3473f
 normal genotypic development, 3469-3473
 additional genes in, 3471-3473, 3471f, 3472t
 chromosomal sex, 3469, 3470f
 ZFY and SRY, 3469-3471, 3470f-3471f
 normal phenotypic development, 3473
 phenotypic, 3474-3475, 3475f-3476f
 psychosexual differentiation, 3475-3477
- Sexual dysfunction. *See also Erectile dysfunction of female*, 755-757, 756t-757t, 757b, 755.e2
 conclusions of, 763, 764b
 hypoactive sexual desire disorder, 757-759, 758b, 758t, 760t, 759.e1-759.e2, 759.e1t
 orgasmic disorder, 761, 761.e1
 persistent genital arousal disorder, 760-761
 semantics and controversy, 755, 755.e2
 sexual arousal disorder, 759-760, 760.e1
- Sexual dysfunction (Continued)
 sexual pain disorders, 761-763, 762b, 762.e1f-762.e2f, 763.e1f
 hormonal therapy and, 2794
 after midurethral sling, 2036
 patient history of, 6
 after transurethral needle ablation of prostate, 2525
- Sexual function
 of female
 conclusions of, 763, 764b
 evaluation of sexual wellness, 752-753, 753b, 753.e1-753.e3, 753.e4f-753.e6f, 753.e5-753.e6
 female sexual response, 749-752, 750f, 752b, 751.e1f, 750.e1-750.e2, 750.e4, 750.e5f, 750.e6-750.e8, 752.e1f, 750.e3f
 mental aspects of sexual response, 752, 752.e2
 sexual wellness, 749, 749.e1
 special populations, 753-755, 755b, 754.e1-754.e2, 755.e1
 after prepubertal repair, 3427-3428
- Sexual Function Questionnaire (SFQ), 753.e2
- Sexual health
 α -adrenergic blockers and, 2480
 in elderly, 2099-2100
 transurethral microwave therapy and, 2521
- Sexual history, and male infertility, 562
- Sexual intercourse, penile fracture with, 2379
- Sexual maturation, 516
- Sexual pain disorders
 and empiric medical therapy, 763
 etiology of, 761-762, 762b
 evaluation of, 762, 762.e1f-762.e2f
 treatment of, 762-763
- Sexual response cycle, in women, 749-750, 750f, 750.e1
- Sexual wellness in women, evaluation of
 history, 752-753, 753.e1
 partner, 753, 753.e3
 physical examination, 753, 753.e4f-753.e6f, 753.e5-753.e6
 surveys, 753, 753.e2
- Sexuality
 with exstrophy-epispadias complex, 3218-3219
 female concerns, 3219
 male concerns, 3218-3219
 HRQOL instruments for, 92t-94t
 neural tube defects and, 3277-3279
 transitional urology and, 3526
- Sexually transmitted diseases (STDs), 386b
 CDC screening recommendations for, 371
 cutaneous infections and infestations from, 402, 403f
 epidemiology of, 371, 372t
 epididymitis, 373
 genital ulcers, 373, 373t
 chancroid, 373t, 377-378, 377f
 granuloma inguinale, 378
 herpes, 373t, 376-377, 376f, 377t
 HPV, 378-380, 379f
 lymphogranuloma, 373t, 378
 molluscum contagiosum, 380-381, 380f
 pediculosis pubis, 380
 scabies, 380, 380f
 syphilis, 373-376, 373t, 374f, 375t
 vaginitis, 381-382, 381t
 gonococcal infections, 371-372
 HIV, 382
 diagnosis, 382
 erectile dysfunction and, 384
 hematuria and, 384
- Sexually transmitted diseases (STDs) (Continued)
 interactions with other STDs, 375, 382
 Kaposi sarcoma, 385
 management of sex partners, 382.e6
 neoplasms and, 385-386
 non-AIDS-defining urologic malignancies, 385-386
 preexposure prophylaxis, 382.e6
 prostatitis and, 383
 renal function and, 383-384
 renal infections, 383
 stones and, 384-385
 structure, 382.e1, 382.e1f-382.e2f
 testis, epididymis, seminal vesicles and, 383
 treatment, 382.e5-382.e6, 382.e5f
 urologic manifestations of, 382, 382f
 UTI and, 383
 viral synapse and cell-to-cell transmission, 382.e2
 virology, 382.e1
 virus entry and replication, 382.e1, 382.e3f
 virus heterogeneity and mechanisms to escape therapy, 382.e2
 virus packaging and assembly, 382.e1-382.e2
 voiding dysfunction and, 384
 nongonococcal urethritis, 372-373
 chlamydia, 372
Mycoplasma genitalium and *Ureaplasma*, 372
 recurrent and persistent, 373
 treatment, 373
Trichomonas, 372-373
 reportable, 371
 urethritis, 371-373
- Sexually transmitted infections, prostate cancer and, 2550-2551
- SFQ. *See Sexual Function Questionnaire*
- Sharp dissection instrumentation, for laparoscopic and robotic surgery, 206
- SHBG. *See Sex hormone binding globulin*
- Shear stress mechanism, of stone comminution, 1269f, 1270
- Shear wave elastography (SWE), 70-71, 71f
- Shock wave lithotripsy (SWL), 1276b
 anesthesia for, 1267-1268
 antimicrobial prophylaxis for, 263
 attenuation values and, 1243.e2
 bioeffects of, 1271-1274
 acute renal injury as, 1271-1273, 1272b-1273b, 1272f-1273f
 chronic renal injury as, 1273-1274, 1274t
 extrarenal damage as, 1271, 1271f
 for bladder calculi, 1295-1296
 contraindications to, 1238b
 factors negatively affecting success of, 1238b
 generator types for, 1265-1267
 electrohydraulic (spark gap), 1265-1266, 1265f
 electromagnetic, 1266, 1266f
 focused ultrasound, 1267
 microexplosive, 1266-1267
 piezoelectric, 1266, 1267f
 historical overview of, 1235.e2-1235.e3
 imaging systems for, 1267
 methods of, 1265-1268
 morbid obesity and, 1255
 old age and frailty and, 1255-1256
 optimization of, 1275-1276, 1275b
 pediatric, 3104-3107, 3105t
 limitations and concerns with, 3106-3107
 stone size, location, and composition, 3106
 technique for, 3104-3106

- Shock wave lithotripsy (SWL) (*Continued*)
 prior renal surgery and, 1256
 for renal calculi
 in calyceal diverticula, 1244
 in horseshoe kidneys, 1245-1246
 lower pole calculi, 1247-1250, 1247f, 1248t, 1249f
 in renal ectopia, 1246
 stone composition and, 1242-1243, 1242f-1243f, 1243.e1
 stone localization and, 1241-1242
 renal function and, 1254-1255
 renal transplants and, 1257
 solitary kidney and, 1255
 spinal deformity or limb contractures and, 1256
 for staghorn calculi, 1240-1241
 stone burden and
 between 1 and 2 cm, 1239-1240, 1239f
 greater than 2 cm, 1239f, 1240
 up to 1 cm, 1238-1239, 1238b
 stone comminution in, 1268-1270, 1269f-1270f
 tissue injury from, 1275, 1275b
 uncorrected coagulopathy and, 1256
 for ureteral calculi
 duplicated collecting system and, 1253
 in megaureter, 1253
 outcome of, 1257-1259
 stone burden and, 1252-1253
 stone composition and, 1253
 stone localization and, 1251-1252, 1252t
 with ureteral stricture or stenosis, 1253-1254
 urinary diversion and, 1256-1257
 urinary tract infection and, 1254
- Short circuits, with sacral nerve stimulation, 1912
- Short Screening Instrument for Psychological Problems in Enuresis (SSIPPE), 3301
- Shy-Drager syndrome, lower urinary tract dysfunction with, 1768
- SI index, 47
- SIADH. *See* Syndrome of inappropriate antidiuretic hormone secretion
- Sickle cell disease (SCD), and priapism, 671-672, 676b
- Sigma-rectum pouch, 2322
- Sigmoid cystoplasty, 3346-3347, 3348f
- Sigmoid pouch, for orthotopic urinary diversion, 2360, 2362f
- Signal transmission, in urodynamic studies, 1723-1724
- Signet ring cell carcinoma, of bladder, 2202, 2202f
- Sildenafil (Viagra)
 to facilitate bladder filling and urine storage, 1839t, 1856
 for ureteral relaxation, 1001
- Silhouette stents, 127
- Silicate stones, 1197
- Silicone microimplants (Macroplastique), for SUI injection therapy
 female, 2058-2059, 2058t
 male postprostatectomy, 2065-2066
- Silodosin
 for benign prostatic hyperplasia, 2479-2480
 to facilitate bladder emptying, 1874.e1
 to facilitate bladder filling and urine storage, 1853
 ureteral response to, 992
- Silver nitrate
 for BPS/IC treatment, 356.e1
 for hemorrhagic cystitis, 190
- Silver stent coatings, 128
- Simple nephrectomy
 laparoscopic, 1454
 dissection of ureter, 1454, 1456f
 identification of renal hilum, 1454-1455, 1457f
 isolation of upper pole, 1456, 1457f
 organ entrapment and extraction, 1456-1457, 1458f-1459f
 postoperative management for, 1457
 reflection of colon, 1454, 1456f
 results of, 1457
 securing of renal blood vessels, 1455, 1457f
 open, 1420, 1420f, 1420.e1f
- Simple renal ectopia, 2985-2986, 2987f, 2985.e3f
- Simple/supratrigonal cystectomy, robotic or laparoscopic, 2277-2279
 complications of, 2279
 evaluation for, 2277
 indications for, 2277
 outcomes with, 2279
 technique for, 2277-2279
- Single umbilical artery, 2890
- Single-cell embryo biopsy, stem cells from, for tissue engineering, 483.e1
- Single-incision midurethral sling
 anatomy for, 2010
 outcomes with, 2018-2019, 2019t
 surgical approach to, 2013-2015, 2014f
- Single-photon emission computed tomography (SPECT), 2947
- Single-shot caudal blocks, for pediatric patients, 2956
- SIOP trials. *See* International Society of Paediatric Oncology trials
- Sipuleucel-T, 455-456, 2813-2814, 2814f
- Sirolimus, for post-transplant immunosuppression, 1085t
- Skeletal defects, in bladder exstrophy, 3185-3186, 3185f
- Skeletal muscle, smooth muscles compared with, 1641t
- Skeletal system abnormalities, with cloacal exstrophy, 3227-3228
- Skene gland, cysts of, urethral diverticula differentiated from, 2162, 2162f
- Skin, of external genitalia, loss of, 2384-2385, 2384f-2385f, 916.e1-916.e2
- Skin bridge, of penis, 3371, 3371f
- Skin closure, after laparoscopic and robotic surgery, 211
- Skin lesions. *See* Cutaneous lesions
- Skin preparation, preoperative, 113-114
- Skin tag, 416
 hymenal, 3459, 3459f
- SLE. *See* Systemic lupus erythematosus
- Sleep
 enuresis and, 3312-3313
 nocturia impact on, 1822
 states of, 1822
- Sleep apnea, as complication of TT, 547
- Slings
 alternative treatment options to, 1989
 bone anchor bulbourethral. *See* Bone anchor bulbourethral sling
 evolution of, 1987-1988
 midurethral. *See* Midurethral sling
 for pelvic organ prolapse, anterior compartment, 1960-1961, 1960f
 preoperative assessment for, 1988-1989
 pubovaginal. *See* Pubovaginal sling
 transobturator bulbourethral. *See* Transobturator bulbourethral slings
 urethral. *See* Urethral slings
 for urinary incontinence, in geriatric patients, 200
- Slow-twitch fibers, of urethral striated muscle, 1637
- Slow-wave sleep (SWS), glucose homeostasis and, 1822-1823
- SMA. *See* Superior mesenteric artery
- Small bowel
 in augmentation cystoplasty, 3344
 effects of, 3350
 for urinary diversion
 preparation for, 2281-2284
 selection of, 2281
 surgical anatomy of, 2281.e1, 2281.e1f
- Small bowel anastomoses, in urinary diversion, 2297-2300
 Bricker anastomosis, 2296t, 2298, 2298f
 Hammock anastomosis, 2300
 Le Duc technique, 2296t, 2299-2300, 2299f
 split-nipple technique, 2299f
 tunneled, 2298-2299, 2299f
 ureteral dipping technique, 2300
 ureteral-small bowel, 2300, 2301f
 Wallace technique, 2296t, 2298, 2298f
- Small cell carcinoma
 of bladder, 2202, 2202f
 of kidney, 1361t, 1363-1364
- Smoking
 benign prostatic hyperplasia and, 2442
 and ED, 638, 638t
 patient history of, 7-8
 penile cancer and, 848
 preoperative, 102-103
 prostate cancer and, 2551
 urinary incontinence and, 1749
 urothelial cancer and, 2187, 2199
 UTUC risk and, 1366
- Smooth muscles
 in benign prostatic hyperplasia, 2434-2435, 2435f
 of bladder, 1635, 1635f, 1640-1648
 actinomyosin cross-bridge cycling, 1642-1643, 1643b, 1643f
 action potentials of, 1644-1645, 1644f
 calcium signaling in, 1646, 1647f
 contractile proteins, 1641-1642, 1641f-1643f
 electrical response propagation, 1646-1648, 1647f
 excitation-contraction coupling in, 1645-1646, 1645f
 during filling, 1648-1649
 interstitial cells of, 1648, 1648f
 membrane electrical properties of, 1644-1645, 1644f
 motor sensory network in, 1649, 1650f
 during voiding, 1649
 skeletal muscle compared with, 1641t
 of urethral sphincter, 1637
 CVA and, 1764
- Smooth sphincter, decreasing outlet resistance at, to facilitate bladder emptying, 1873-1874
- Smooth sphincter dyssynergia, 1693
 with autonomic hyperreflexia, 1776
- SMV. *See* Superior mesenteric vein
- Snake stents, 127
- SNM. *See* Sacral neuromodulation
- SNS. *See* Sacral nerve stimulation
- Socioeconomic factors, in benign prostatic hyperplasia, 2440, 2441t
- Sodium
 collecting tubule reabsorption of, 1018-1019, 1018f
 distal tubule reabsorption of, 1018
 fractional excretion of, urinary tract obstruction and, 1090
 loop of Henle reabsorption of, 1016, 1017f

- Sodium (*Continued*)
 PCT reabsorption of, 1014, 1014f
 restriction of
 for cystinuria, 1229
 for nephrolithiasis, 1218, 1219b
 transport of, urinary tract obstruction and, 1096
- Sodium bicarbonate
 for ATN prevention, 1053
 in CIN prevention, 30
- Sodium cellulose phosphate, for absorptive hypercalciuria, 1224
- Sodium imbalances, renal pathophysiology involved in, 1019-1023, 1020f-1022f, 1021b, 1023b
- Sodium pentosan polysulfate, for BPS/IC oral therapy, 354
- Sodium phosphate solution (Fleet Phosphosoda), 107
- Solid masses, renal
 CT of, 43-45, 45f-46f
 ultrasonography of, 63, 64f
- Solifenacin
 for diminished bladder, 1830-1831, 1832t-1834t
 to facilitate bladder filling and urine storage, 1839t, 1844-1845
 with β -adrenoreceptor antagonists, 1860
 for ureteral stent symptoms, 131-132
- Solitary fibrous tumor, of kidney, 1312
- Solitary multilocular cyst nephroma, in pediatric patients, 3580
- Solubility product, 1173, 1174f
- Somatic cell nuclear transfer (SCNT), stem cells from, for tissue engineering, 483-484, 484f
- Somatic growth, vesicoureteral reflux and, 3149
- Somatic nervous system
 and ED, 656
 in retroperitoneum, 780-782, 781f-782f, 781t, 780.e1f
- Somatic pathways, of lower urinary tract, 1650, 1651f-1652f
- Sonoelastography
 mode of, 70-71, 70f-71f
 of prostate, 2589, 2590f
 of scrotum, 70f-71f, 79-80
- Sorafenib, 472
 for RCC, 1360t, 1509-1511, 1510t, 1511f, 1517
- South African star grass, for benign prostatic hyperplasia, 2500
- Sox9, 2395
- SOX9 gene, 3469, 3471f, 3472t
- Soy, in prostate cancer prevention, 2563-2564
- Space of Retzius, development of
 for laparoscopic radical prostatectomy, 2668-2669, 2668f
 of open simple prostatectomy, 2537
 of robot-assisted laparoscopic simple prostatectomy, 2541
- Spall fracture mechanism, of stone comminution, 1266f, 1269
- Spatial compounding ultrasonography, 69-70
- Specific gravity, of urine, 13-14
- Specimen collection, for urinalysis, 12-13, 20-21
- Specimen entrapment instrumentation, for laparoscopic and robotic surgery, 208-209, 209f
- Speckling, in ultrasonography, 67, 67f
- SPECT. *See* Single-photon emission computed tomography
- Sperm cryopreservation, for TGCT patients, 795
- Sperm retrieval, surgical techniques for, 600-604, 601t
 microsurgical epididymal sperm aspiration, 601-602, 601t, 602f
 percutaneous epididymal sperm aspiration, 601t, 602, 602f
 postmortem, 603-604
 testicular sperm aspiration, 601-602, 601t
 testicular sperm extraction, 601t, 602-603, 602f-603f, 604t
- Spermatic cord, 520-521
 dissection of, in laparoscopic RPLND, 840, 840f, 842
 microsurgical denervation of, 956-957, 956f
- Spermatic cord torsion, 3388-3391
 acute intravaginal, 3388-3390
 clinical presentation of, 3388-3389
 diagnostic studies of, 3389-3390, 3389f
 management and surgical treatment of, 3390
 predisposing factors for, 3388
 prognosis for, 3391
 extravaginal, 3391-3392, 3391f
 intermittent intravaginal, 3391
- Spermatids, 523, 524f, 527-528
- Spermatocectomy, 953
- Spermatocytes, 523, 524f-525f, 526
- Spermatocytic seminomas, histology of, 788
- Spermatogenesis
 cycle of, 525, 525f-526f
 duration of, 525, 526f
 genetics of, 528
 paternal age and, 528-529, 528b
 germ cells in, 523, 524f-525f, 526, 527f, 528
 imaging of, 573.e3f
 meiosis, 526-527, 527t
 Sertoli cells in, 523, 524f, 528
 spermiogenesis, 527-528
 testis stem cell migration, renewal, and proliferation, 526, 527f
- Spermatogonia, 523, 526, 527f
- Spermatotoxicity, 557-560
 medications affecting
 antibiotics, 558, 558.e2
 antihypertensives, 558, 558.e1
 anti-inflammatory agents, 559, 559.e1
 antipsychotics, 558
 cytotoxic chemotherapeutics, 558-559
 endocrine modulators, 557-558
 environmental toxicants, 559, 559.e3
 opioids, 558
 phosphodiesterase 5 inhibitors, 559, 559.e2
 radiation, 559-560
 recreational drugs, 558
 thermal toxicity, 559
- Spermatozoa
 abnormalities of, 537
 parental age and, 528-529, 528b
 age-related decline in, 519
 anatomy and physiology of, 535-537, 536f, 537b
 epididymis functions related to, 529
 maturation, 531-532, 531f-532f
 storage, 531
 transport, 531
 maturation of
 biochemical changes, 532
 fertility, 531-532, 532f
 motility, 531, 531f-532f
 neck of, 535
 production of. *See* Spermatogenesis
 structural abnormalities of, 537
 vas deferens functions related to, transport and storage, 533
- Spermiogenesis, 527-528
- Sphincter, urethral. *See* Urethral sphincter
- Sphincteric urinary incontinence
 cause of, 2169-2170, 2170t
 classification of, 2169-2170
 evaluation of, 2171-2173, 2172f, 2173b
 cystoscopy for, 2173, 2173f
 history for, 2171-2172
 laboratory studies for, 2172-2173
 physical examination for, 2172
 postsurgical, 2173
 urodynamics for, 2173
 implantation for, 2174-2180
 artificial urinary sphincter, 2175-2178, 2175f-2177f
 bone anchor bulbourethral sling, 2179-2180, 2180f
 preparation for, 2174
 quadratic sling, 2180
 transobturator bulbourethral slings, 2178-2179, 2179f
 indications for surgery, 2174, 2181b
 pathophysiology of, 2169-2170
- Spina bifida (SB)
 kidney size with, 3277
 lower urinary tract dysfunction with, 1779-1780
 perioperative care for children with history of, 2955, 2955f
- Spinal anesthesia, preoperative considerations for, 111
- Spinal cord
 abnormalities of, with cloacal exstrophy, 3226-3227, 3227f
 cystitis and, chemical changes with, 1677
 electrical stimulation of, 1914
 neuromuscular lower urinary tract dysfunction involvement of, 1761b, 1768-1780
 segment numbering for, 1770
- Spinal cord compression
 neuroblastoma causing, 3567
 radiation therapy for localized prostate cancer and, 2708
- Spinal cord injury (SCI)
 cystitis with, 1638
 and delayed ejaculation, 704, 704t
 epidemiology of, 1770-1771, 1771b
 general concepts of, 1770-1771, 1771b
 with high-pressure bladders, host defense mechanisms in UTIs and, 249
 lower urinary tract dysfunction with, 1770-1778, 1771b
 autonomic hyperreflexia, 1775-1776
 bladder cancer and, 1778
 follow-up for, 1778
 management of, 1794
 neurologic and urodynamic correlation, 1773-1775
 sacral, 1773, 1775f
 spinal shock, 1771
 suprasacral, 1771-1773, 1772f, 1774f
 urinary tract infection, 300-301, 302b, 1777
 vesicoureteral reflux, 1776-1777
 in women, 1777-1778
 morbidity of, 1770-1771, 1771b
 neurogenic detrusor overactivity and, 1675-1676
 sacral nerve stimulation with, 1906-1907
 secondary bladder calculi with, 1293
 traumatic, 3293-3295
 pathogenesis of, 3293-3294
 presentation of, 3293, 3293f
 specific recommendations for, 3294-3295
 urothelium and, 1638

- Spinal cord pathways, in lower urinary tract, 1650-1651, 1652f, 1652t
- Spinal dysraphism
lower urinary tract dysfunction with, 1779-1780
occult, 3301-3302, 3302f
- Spinal shock, lower urinary tract dysfunction with, 1771
- Spinal stenosis, lower urinary tract dysfunction with, 1781
- Spindle assembly checkpoint, deregulation of, 461.e2
- Spine, anatomy of, in retroperitoneum, 769, 769.e1f
- Splenic injury
during laparoscopic and robotic surgery, 222.e1
during radical nephrectomy, 1428
- Splenogonadal fusion, 3443, 3443f
- Splenorenal ligament, 967-968
- Split and roll technique, for RPLND, 818, 819f
- Split symphysis variant of exstrophy-epispadias complex, 3191
- Split-nipple technique, in urinary diversion, 2299f
- Spongy urethra. *See* Penile urethra
- SPOP mutations, in prostate cancer, 2557
- Sporadic prostate cancer, 469-471
- Squamous cell carcinoma (SCC)
of bladder, 2203, 2203f
in pediatric patients, 3589
as neoplastic condition, 411, 412f
of penis, 850, 851b
delay in diagnosis of, 850
differential diagnosis of, 854
epidemiology of, 847, 849b
etiology of, 847-848, 849b
examination of, 850
histologic features of, 850-851, 851b
laboratory studies of, 851
natural history of, 849, 850b
presentation of, 849, 850b
prevention of, 848-849, 849b
radiologic studies of, 851-852, 852b
staging of, 852-854, 853t, 854b, 854f
Tis, 846-847, 847b, 846.e1f
of upper urinary tract, 1371
- Squamous cell carcinoma in situ (SCCis), as neoplastic condition, 410-411, 411f
- Squeezing-splitting mechanism, of stone comminution, 1266f, 1269-1270
- SRY gene, 518, 3469-3471, 3470f-3471f
- SSIGN score. *See* Stage, Size, Grade and Necrosis score
- SSIPPE. *See* Short Screening Instrument for Psychological Problems in Enuresis
- SSIs. *See* Surgical site infections
- SSLE. *See* Sacrospinous ligament fixation
- SSRIs. *See* Selective serotonin reuptake inhibitors
- Stab wounds
renal, 1148
nonoperative management of, 1152
ureteral, 1157-1158, 1157t
diagnosis of, 1160-1161
- Stage, Size, Grade and Necrosis (SSIGN) score, for RCC, 1341
- Staghorn calculi
epidemiology of, 1195
historical overview of, 1236-1237, 1236f
imaging of, 1212, 1213f
surgical treatment selection for, 1240-1241, 1280-1281
- Stapled sigmoid reservoir, for cutaneous continent urinary diversion, 2340-2342, 2341f
- Stapling devices, for laparoscopic and robotic surgery, 207-208, 208f
- StAR. *See* Steroid acute regulatory protein
- Starr plication technique, for megaureter in pediatric patients, 3072, 3072f
- States of saturation, renal calculi and, 1173-1175, 1174f
- Static cystography, 36-37, 36f
- Statins
and ED, 637-638
in prostate cancer prevention, 2562
- Stauffer syndrome, 1335
- STDs. *See* Sexually transmitted diseases
- Stem cell transplantation, for RCC, 1506-1507, 1507t
- Stem cells
in GU cancers, 480-481, 481b
in prostate cancer, 2553, 2555f
testis, migration, renewal, and proliferation of, 526, 527f
for tissue engineering, 482-483, 483t
adult, 485, 485f
embryonic, 483, 483.e1
induced pluripotent, 484
native targeted progenitor cells, 485
perinatal, 484-485
SCNT, 483-484, 484f
- Stenosis, urethral, reconstructive surgery for, 914-915
- Stents
endovascular, for renovascular injuries, 1155
after percutaneous surgery of upper urinary tract collecting system, 171-172, 172f, 171.e1f
for prostate, 2534.e1
renal artery, for renovascular hypertension, 1036-1039, 1037b, 1039b, 1040f
ureteral. *See* Ureteral stents and catheters
for ureteroenteric strictures, 1142
for ureteropelvic junction obstruction, in percutaneous antegrade endopyelotomy, 1110
for urethral stricture disease, 922
- Stereotactic body radiotherapy (SBRT)
for localized prostate cancer, 2703, 2704f
for prostate cancer, 2621
- Sterilization, of ureteroscopes, 146
- Steroid acute regulatory protein (StAR), 522
deficiency of, 3489
- Steroid hormones, of male reproductive system, 516, 517f. *See also* specific steroidal hormones
- Steroids
preoperative, 103
for retroperitoneal fibrosis, 1145
sex, lower urinary tract and, 1673
for ureteral stone passage, 1001-1002
- Stevens-Johnson syndrome, 390, 391f-392f
- Stimulated myoplasty, 2081
- Stoma
for intestinal anastomoses in urinary intestinal diversion, 2292-2294
complications of, 2291t, 2294
flush, 2293
loop end ileostomy, 2293-2294, 2294f
nipple "rosebud," 2293, 2293f
in minimally invasive urinary diversion, preparation of, 2373
- Stomach, for urinary diversion
preparation for, 2281-2284
selection of, 2281
surgical anatomy of, 2281.e1, 2281.e1f
- Stone comminution, in shock wave lithotripsy, 1268-1270, 1269f-1270f
- Stone disease. *See* Calculi
- Stone fragility, 1243.e1, 1243.e1f
- Stone retrieval devices, for ureteroscopic
- Stones. *See* Calculi
- Stop test, 1815-1816
- Straddle fracture, urethral injuries with, 2388, 2388.e1f
- Straining, patient history of, 4, 4t-5t
- Strangulation injuries, of penis, 2382
- Stress incontinence, patient history of, 5-6
- Stress relaxation, ureteral, 988-989, 989f
- Stress strategies, 1884, 1885b
- Stress urinary incontinence (SUI), 551-552
adrenergic agonists for, 1671
with bipolar transurethral resection of prostate, 2517
BMI and, 1711
definition of, 1710, 1744, 1744f
female
algorithm for management of, 1922f
cause of, 1990
intravaginal incontinence devices for, 2073
pharmacologic treatment of, 1866-1869
pubovaginal sling. *See* Pubovaginal sling
urethral occlusive devices for, 2073
urodynamic studies, evidence-based review in, 1739-1740
genuine, 1689
hypermobility in, 1919-1920, 1990
male, pharmacologic treatment for, 1869-1870
mechanisms of, 1675
occult, urodynamic studies of, 1728
overactive bladder with, 1802, 1803f
pathophysiology of, 1689-1690, 1757-1758
injectable agents and, 2049
intrinsic sphincter deficiency in, 1990
intrinsic sphincteric dysfunction, 1758, 1919-1920
urethral support and, 1757-1758, 1757f
pelvic floor muscle training for, 1716, 1884
pelvic organ prolapse and, 1707
recurrent, midurethral sling outcomes for, 2021-2022, 2022b
treatment for, 1708-1709
male, 1716
midurethral sling. *See* Midurethral sling
options for, 1918
pharmacologic, 1840t, 1866-1870
pubovaginal sling. *See* Pubovaginal sling
urethral collagen and, 1637
urethral slings for, 1987
urodynamics and, 1706-1707
- Striated muscles, of urethral sphincter, 1637
fiber types of, 1637
- Striated sphincter, decreasing outlet resistance at, to facilitate bladder emptying, 1874
- Striated sphincter dyssynergia, 1693
botulinum toxin for, 1874.e3
with cerebellar ataxia, 1765-1766
after CVA, 1764
cystourethrography of, 1772f
with MS, 1769
with suprasacral spinal cord injury, 1772
- Striated urethral sphincter, surgical anatomy of, 2642-2643, 2642f-2643f
- Strickler technique, in urinary diversion, 2296t, 2297, 2297f
- Stricture
ureteral. *See* Ureteral stricture disease
ureteroenteric anastomotic. *See* Ureteroenteric anastomotic stricture
with ureterointestinal anastomoses in urinary intestinal diversion, 2302-2303
urethral. *See* Urethral stricture disease
- Stripping technique, for UTUC, 1378-1379, 1380f

- Stroke
and ED, 631
lower urinary tract dysfunction and, 1763-1765, 1764b
- Stroma
of bladder wall, 1634
of prostate, 2398-2399
urethral, 1637
- Stromal-epithelial interactions
in benign prostatic hyperplasia, 2429
in prostate growth, 2406
- Structural chromosomal anomalies, and male infertility, 574
- Structural sperm abnormalities, in male infertility, 579
- Structure of care, 89-90
- Struvite renal stones. *See* Infection stones
- Studer neobladder, modified, for minimally invasive urinary diversion, 2371t, 2374-2375
- Studer pouch, for orthoptic urinary diversion, 2358, 2359f
- Subacute combined degeneration (SACD), lower urinary tract dysfunction and, 1791
- Subclinical Cushing syndrome, 1536
- Subclinical filariasis, 443
- Subcostal flank approach, for open kidney surgery, 1416-1417, 1416f-1417f, 1416.e1f
- Subcutaneous emphysema, during laparoscopic and robotic surgery, 217
- Subcutaneous implant preparations, testosterone, 544t, 545-546
- Subepithelial plexus, 1633
- Substance A, 1179
- Substance P, in ureteral function, 992
- Suburothelial interstitial cells, 1640, 1640f
- Succinate dehydrogenase RCC (SDH/RCC), 1322t, 1324
- Succinylcholine, preoperative considerations for, 112
- Sudeck critical point, 2281.e2
- SUI. *See* Stress urinary incontinence
- Sulfonamides, and UTIs, 2945
- Sunitinib, 472
for RCC, 1360t, 1511, 1511t, 1512f, 1516-1517
- Superficial bladder cancer. *See* Non-muscle-invasive bladder cancer
- Superficial inguinal node dissection, for penile cancer, 864, 894-895
- Superficial perineal space, 910.e6f-910.e7f, 910.e7
- Superfocusing mechanism, of stone comminution, 1269f, 1270
- Superior lumbar triangle. *See* Lumbar notch
- Superior mesenteric artery (SMA), in radical nephrectomy, 1427
- Superior mesenteric vein (SMV), in radical nephrectomy, 1427-1428
- Superior vesical artery, 505
- Superior visceral artery, 504
- Supernumerary kidney, 2984-2985, 2985f, 2985.e1f-2985.e2f
- Suplatast tosilate, for BPS/IC oral therapy, 353t, 354
- Supracostal flank approach, for open kidney surgery, 1417, 1417.e1f
- Supradianthragmatic tumors, testicular tumors with, 823-824, 824f
- Suprapubic aspiration, in urine collection, 250
- Suprapubic catheter drainage, 124-126, 125f
for posterior urethral injury, 2389, 2389f
- Suprapubic cystostomy, 141-142
for posterior urethral injury, 2389, 2389.e1f
- Suprapubic pain, patient history of, 2
- Suprapubic prostatectomy, 2535-2536, 2539-2541
adenoma enucleation for, 2539-2540, 2539f-2540f
closure for, 2540-2541, 2540f
hemostatic maneuvers for, 2539f, 2540
prostate exposure for, 2539, 2539f
- Suprasacral spinal cord injury
lower urinary tract dysfunction with, 1771-1773, 1772f, 1774f
management with, 1773b
- Supraspinal pathways, in lower urinary tract additional regions in, 1666-1667
brain-bladder control model, 1667, 1668f
brainstem modulatory mechanisms, 1663, 1666f
central circuitry regulation of, 1663-1664
cerebral control of voiding, 1665-1666
human brain imaging studies in, 1665, 1667f
modulators in, 1664-1665
neurotransmitters in, 1664-1665
pontine micturition center, 1663, 1666f
- Supravesical urinary diversion, for prune-belly syndrome, 3243
- Surgery. *See also specific surgeries*
adrenal. *See* Adrenal surgery
in ED, 666-667
kidney. *See* Kidney surgery
patient history of, 7
percutaneous access for, 154
perioperative care for. *See* Perioperative care
postoperative care for. *See* Postoperative care
preoperative care for. *See* Preoperative care
Surgical history, adrenal surgery and, 1579
Surgical landmarks, of adrenal glands, 1519, 1521f-1522f
- Surgical neurectomy, cryoablation, and neuromodulation, of dorsal penile nerve, 700.e1
- Surgical pharmaceuticals, for laparoscopic and robotic surgery, 207, 207t, 207.e2
- Surgical risk evaluation, preoperative
cardiac, 101-102, 102t
classification and stratification in, 100-101, 101b, 101t
hepatobiliary, 102
pulmonary, 102
- Surgical site infections (SSIs)
antibiotic prophylaxis for, 105-106, 105b, 106t-107t
in pediatric patients, 2958-2959, 2959t
after laparoscopic and robotic surgery, 223
in pediatric patients, 2958-2961, 2959t, 2962t
wound closure and, 116-117
- Surgical wounds
abdominal incisions, 115
closure of, 115-117, 116t
healing of, 115
classification of, 105, 105b, 264t
in pediatric patients, 2958-2961, 2959t, 2962t
of radical nephrectomy, closure of, 1427
- Surrogate end points. *See* Proxy measures
- Surveillance
for NSGCTs, 798, 798t
for penile cancer, 863, 863t
for RCC, 1347t, 1351-1352, 1352t
for retroperitoneal sarcomas, 1412-1413, 1412f
for seminomas, 807-808, 808t
- Sustained-release varnish containing chlorhexidine (CHXSRV)-coated stents, 128
- Sutures, materials used in, 115-116, 116t
- Suturing instrumentation, for laparoscopic and robotic surgery, 207, 208f, 210, 207.e2f, 207.e3
for pediatric patients, 2965-2966
- SWE. *See* Shear wave elastography
- SWL. *See* Shock wave lithotripsy
- SWS. *See* Slow-wave sleep
- Swyer syndrome, 3482-3483, 3482f-3483f, 3482t
- Sympathetic nervous system
in retroperitoneum, 778, 779f-780f
in ureteral function, 991-992
- Sympathetic pathways, of lower urinary tract, 1650, 1651f
- Sympathomimetic agents, for neuromuscular dysfunction of lower urinary tract, 3281, 3282f
- Symptomatic MH, 188, 191b
- Syndrome of complete androgen insensitivity, 3491-3492
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH), 1020, 1021b
- Syndrome of partial androgen resistance, 3492
- Syndromic cryptorchidism, 3437-3438
- Synthetic grafts, for pelvic organ prolapse reconstructive surgery, 1947-1948, 1948f
- Synthetic prosthetic, for pubovaginal sling, 1991-1992, 1992t
outcomes of, 2002
- Syphilis
as genital ulcers, 373-376, 373t, 374f, 375t
HIV coinfection with, 375
treatment, 375-376, 375t
- Syringomyelia, lower urinary tract dysfunction and, 1786
- Systemic lupus erythematosus (SLE), lower urinary tract dysfunction and, 1786
- Systemic radionuclide therapy, for bone metastases, 2708, 2708t
- Systemic sclerosis, lower urinary tract dysfunction and, 1791
- T**
- T. *See* Testosterone
- T pouch
for orthoptic urinary diversion, 2358, 2359f
with valved rectum, 2321-2322, 2321f
- T1-weighted MR images, 47
- T2-weighted MR images, 47
- TA. *See* Thermal ablation
- Tabes dorsalis, lower urinary tract dysfunction with, 1780
- Tachykinins
lower urinary tract and, 1672, 1672t
in ureteral function, 992
- Tacrolimus, for post-transplant immunosuppression, 1084-1085, 1085b, 1085t
- Tadalafil (Cialis)
to facilitate bladder filling and urine storage, 1839t, 1856
for ureteral relaxation, 1001
- Tamm-Horsfall mucoprotein, 1018
in crystal formation, 1175, 1179
in crystal matrix, 1179
- Tamoxifen, for PD, 734
- Tamsulosin
for benign prostatic hyperplasia, 2478, 2478t
for detrusor underactivity, 1818
to facilitate bladder emptying, 1874.e1
to facilitate bladder filling and urine storage, 1853
with antimuscarinic agent, 1859-1860

- Tamsulosin (*Continued*)
 for nocturia, 1830
 ureteral response to, 992, 1001-1002
 for ureteral stent symptoms, 131-132
- Tanner classification, 3368-3369, 3369f
- Taqand, penile fracture with, 2379
- Targeted angioembolization, for renal tumors, 1499
- Targeted molecular therapies, for advanced RCC
 basis of, 1507-1508, 1508f
 combination and sequential therapy with, 1516
 mTOR pathway inhibitors, 1502-1503, 1514-1515, 1514t, 1515f, 1517
 VEGF inhibitors, 1502-1503, 1507-1514, 1508f-1512f, 1509t-1511t, 1513t, 1517
- Targeted RNA-based therapy, for localized prostate cancer, radiation therapy with, 2709
- TB. *See* Tuberculosis
- ^{99m}Tc pertechnetate. *See* Technetium 99m-pertechnetate
- TCAs. *See* Tricyclic antidepressants
- TCC. *See* Transitional cell carcinoma
- ^{99m}Tc-DMSA. *See* Technetium 99m-dimercaptosuccinic acid
- ^{99m}Tc-DTPA. *See* Technetium 99m-diethylene triamine pentaacetic acid
- ^{99m}Tc-MAG3. *See* Technetium 99m-mercaptoacetyl triglycine
- TCS. *See* Tethered cord syndrome
- TDS. *See* Testosterone deficiency syndrome
- TEBS. *See* Transurethral electrical bladder stimulation
- Technetium 99m-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA), 37-38, 2921
- Technetium 99m-dimercaptosuccinic acid (^{99m}Tc-DMSA), 38, 2921, 2921f, 2941-2942
- Technetium 99m-mercaptoacetyl triglycine (^{99m}Tc-MAG3), 38, 38f-39f, 2921, 2922f-2923f
- Technetium 99m-pertechnetate (^{99m}Tc pertechnetate), 2923-2925
- Technical process of care, 90
- Teflon paste. *See* Polytetrafluoroethylene paste
- Telomerase, in GU cancers, 475-476, 477f, 478b
 chromosome stabilizing activity of, 477
 as potential diagnostic marker, 477-478
 therapies based on, 478
- Telomeres, in GU cancers, 475-476, 478b
 cancers and premalignant lesions with short, 476-477
 chromosomal instability and, 476
 prostate cancer prognosis using, 478
 as tumor suppressive mechanism, 476, 477f
- Temperature
 epididymal function regulation by, 532-533
 of pediatric patients, 2960
 of preoperative patient, 113
- Temporal lobe epilepsy, and ED, 631
- Temsirolimus (Torisel), 1327
 for RCC, 1514-1517, 1514t, 1515f
- TENS. *See* Transcutaneous electrical stimulation
- Tension-free vaginal tape (TVT) procedure
 colposuspension compared with, 1936-1938
 evolution of, 1988
- TER. *See* Transepithelial resistance
- Teratomas, 796, 3593
 histology of, 787f, 788-789
 PC-RPLND findings of, survival outcomes associated with, 830, 830t
- Terazosin
 for autonomic hyperreflexia, 1776
 for benign prostatic hyperplasia, 2475-2476, 2476f, 2476t
 for diminished bladder, 1830, 1832t-1834t
 to facilitate bladder emptying, 1874.e1
- Tertiary or late syphilis, 374-375
- Testicular adnexa, tumors of, 813
- Testicular artery, 498-500, 500f, 503, 529
- Testicular cancer. *See also* Paratesticular cancer
 classification of, 784, 785b
 and delayed ejaculation, 703-704
 GCTs. *See* Testicular germ cell tumors
 genomic alterations in, 474-475
 gene rearrangements, 467
 non-germ cell
 adenocarcinoma of rete testis, 812
 dermoid and epidermoid cysts, 812
 secondary metastases, 812-813, 3595
 sex cord-stromal tumors, 811-812, 836, 836b
 pediatric, 3590, 3596b
 biomarkers for, 3591-3593, 3593f
 epidemiology of, 3590-3591
 GCTs. *See* Testicular germ cell tumors
 gonadal stromal tumors, 3595, 3595f
 leukemia and lymphoma metastases, 3595
 management algorithms for, 3595, 3596f
 microlithiasis, 3595
 pathogenesis and molecular biology of, 3591
 presentation of, 3591
 sexual development disorders associated with, 3593, 3594t
 staging of, 3593, 3593t
 testis-sparing surgery technique for, 3596
 ultrasonography of, 3591, 3592t
 staging of, 791t-792t, 793
 surgeries for, 815, 816b
 delayed orchiectomy, 816
 evaluation after, 816
 in high-risk populations, 831-832, 831t, 832b
 histologic findings and survival outcomes of, 829-831, 829f, 830t, 831b
 history, physical examination, imaging, and evaluation preceding, 815
 outcomes, functional considerations, and complications of, 832-835, 834t, 835b
 partial orchiectomy. *See* Partial orchiectomy
 radical orchiectomy. *See* Radical orchiectomy
 RPLND. *See* Retroperitoneal lymph node dissection
 for SCSIs, 836, 836b
 for seminoma, 835-836, 836b
 surgical decision making for, 825, 829b
 adjuvant chemotherapy at primary RPLND, 827-829
 in cases of clinical complete remission to induction chemotherapy, 825, 825t
 template use in PC-RPLND, 826-827, 828t
 template use in primary RLND, 825-826, 826f, 827t
- Testicular dysgenesis syndrome, 3436-3437
- Testicular germ cell tumors (TGCTs), 784, 789b
 clinical staging of, 791t-792t, 793, 796b
 chest imaging and, 794
 imaging studies, 793-794, 794f
 prognostic classification of advanced germ cell tumors, 794-795, 795t
 serum tumor markers in, 794
 sperm cryopreservation and, 795
 TNM system, 791t-792t
 with
- Testicular germ cell tumors (TGCTs) (*Continued*)
 diagnostic testing and initial management of, 793b
 contralateral testis biopsy, 791
 partial orchiectomy, 791
 radical inguinal orchiectomy, 791, 791t-792t
 scrotal ultrasonography, 790, 790f
 serum tumor markers, 790-791
 for suspected extragonadal GCTs, 793
 epidemiology of, 784-785
 genomic alterations in, 467, 474-475, 3591
 histologic classification of, 786, 786b
 choriocarcinoma, 787f, 788
 EC, 787f, 788
 ITGCN, 786
 seminoma, 787-788, 787f
 spermatocytic seminoma, 788
 teratoma, 787f, 788-789
 YSTs, 787f, 788
 initial presentation of, 789
 pathogenesis and biology of, 785-786
 pediatric, 3591, 3593-3594, 3594f
 risk factors for, 784-785
 treatment of
 brain metastases, 810, 811b
 ITGCN, 797, 797b
 NSGCTs, 796-806, 797b, 798t-800t, 803t, 806b
 relapse after, 804-806
 residual mass management after, 802-805, 803t, 809
 seminomas, 796, 797b, 806-810, 807t-808t, 810b
 sequelae of, 811, 811b
 therapeutic principles for, 795-796
 Testicular hypofunction, as complication of TT, 546-547
- Testicular hypotrophy, 3394
- Testicular injury
 complications with, 2383-2384
 diagnosis of, 2383, 2383f
 etiology of, 2382-2383
 management of, 2383, 2384f
 outcome of, 2383-2384
 pediatric, 3558
- Testicular microlithiasis, in pediatric patients, 3595
- Testicular pain, patient history of, 2
- Testicular rupture, 3393
- Testicular scintigraphy, for pediatric patients, 2923-2925
- Testicular torsion, 2894-2895
 pediatric imaging of, ultrasonography, 2913, 2917f
 perinatal, 3391-3392, 3391f
- Testicular tumors
 incidental nonpalpable, 965, 966f, 966t
 malignant. *See* Testicular cancer
 as non-AIDS-defining urologic malignancies, 385
 pediatric imaging of, ultrasonography, 2915, 2918f
- Testis
 anatomy of, 502b
 arterial supply, 498-500, 500f, 519
 blood supply, 581, 581b
 gross structure, 498, 499f, 502f
 lymphatic supply, 500
 microanatomic architecture, 498, 499f
 nerve supply, 500-501
 venous drainage, 500, 500f-501f
 androgen production by, 2400-2401, 2401f, 2401t
 anomalies of, cryptorchidism and, 3442-3443
 appendix, torsion of, 3392

- Testis (Continued)**
 descent of
 gubernacular development and, 3432-3433, 3432f-3433f
 regulation of, 3433-3434
 differentiation of, 3430-3431
 embryology of, 3430-3434
 function of, 3473-3474, 3474f
 in genitourinary tuberculosis, 423
 HIV and, 383
 hormones of, 517-518, 517f, 3431-3432, 3431f
 imaging of, 527f
 electron micrograph, 525f
 microphotograph, 527f
 scanning electron micrograph, 519f
 ultrasound, 501, 501f
 inflammation of. *See* Orchitis
 maldevelopment of, 3441
 pediatric imaging of, ultrasonography, 2913-2915, 2917f-2918f
 physiology of, 529b
 cytoarchitecture, 521-525, 521f-522f, 524f-525f
 gross architecture, 519-521, 519f-520f
 HPG axis functions, 517-518, 517f
 spermatogenesis. *See* Spermatogenesis
 in prune-belly syndrome, 3237-3238
 reconstruction of, 492-493
 trauma of, 2382-2384, 2383f
 ultrasonography of, 501, 501f
 indications for, 78
 limitations of, 80, 80f
 normal findings in, 78, 78f-79f
 procedural applications of, 78-79
 sonoelastography, 70f-71f, 79-80
 technique of, 77
 undescended. *See* Cryptorchidism
 vanishing, 3439-3441, 3440f
Testis cancer, in geriatric patients, 2099.e13
Testis stem cells, migration, renewal, and proliferation of, 526, 527f
Testis torsion, 560
Testis-sparing surgery
 for pediatric tumors, 3596
 for TGCT, 791
Testosterone (T), 751-752
 aging effects on, 519
 biosynthesis disorders of, 3489-3491
 cardiovascular system effects of, 548-549
 coagulation and, 549
 endothelial dysfunction and, 548-549
 inflammation and, 549
 CVD and, 547-549, 549b
 cycles of, 522-523, 522f
 deficiency of. *See* Androgen deficiency
 epididymal function regulation by, 532
 and female sexual response, 751-752
 in HPG axis, 517-518
 levels of, 538, 540-542, 541t
 lower urinary tract and, 1673
 in prostate cancer, 2553, 2554f
 sources of, 2788-2789
 structure of, 543f
 synthesis of, 522, 2401-2402, 2402f
 control of, 522
 transport and metabolism of, 539-541, 540t
 in vas deferens, 533-534
Testosterone deficiency syndrome (TDS), 580-581
Testosterone replacement, 659-660, 661t
 buccal, 660
 intramuscular, 660
 oral, 660
Testosterone replacement (Continued)
 subcutaneous, 660
 transdermal, 660
Testosterone therapy (TT)
 for AD, 542-544, 543f, 544b-545b, 548
 complications and controversies in, 546-547, 547b
 injectable preparations, 544t, 545
 oral preparations, 544-545, 544t
 subcutaneous implant preparations, 544t, 545-546
 transbuccal preparations, 544t, 545
 transdermal preparations, 544t, 545
 CVD and, 547-549
 for ED, 547, 547b
Testosterone undecanoate (TU), 544-545, 544t
Test-retest reliability, 96, 96t
Tethered cord syndrome (TCS), lower urinary tract dysfunction with, 1780
TGCTs. *See* Testicular germ cell tumors
TGF. *See* Tubuloglomerular feedback
TGF- β . *See* Transforming growth factor- β
TGP. *See* Transglomerular pressure
Theophylline, for ureteral relaxation, 1001
Therapeutic cloning, for tissue engineering, 483-484, 484f
Thermal ablation (TA), for RCC, 1347t, 1349-1351, 1350t
Thermal dose, 2517
Thermal index (TI), in ultrasonography, 73
Thermal injury, electrosurgical. *See* Electrosurgical trauma
Thermodynamic solubility product (K_{sp}), 1173, 1174f
Thermoregulation
 of pediatric patients, 2960
 of preoperative patient, 113
Thiazides
 for absorptive hypercalciuria, 1223-1224
 guidelines for, 1224
 hypocitraturia induced by, 1212
 medical management of, 1228
 for nephrolithiasis, 1226t
 for renal hypercalciuria, 1225, 1225b, 1226t
 in stone formation, 1197
Thick ascending limb, of loop of Henle, 1016-1018, 1016f
Thick filaments, 1641, 1642f
Thin descending limb, of loop of Henle, 1016, 1016f
Thin filaments, 1641
Thiopental, preoperative considerations for, 111-112
Thiotepa, for non-muscle-invasive bladder cancer, 2216, 2216t
Thoracic kidney, 2988, 2988f-2989f
Thoracoabdominal approach
 to open adrenalectomy, 1584-1585, 1585f-1586f
 for open kidney surgery, 1418-1419, 1418f-1419f, 1418.e1f, 1419.e1f
Thoracolumbar fascia. *See* Lumbodorsal fascia
Three-dimensional laparoscopic systems, 205, 205.e2f
Three-dimensional scanning, in ultrasonography, 71-72, 72f
Thromboembolic complications
 after laparoscopic radical prostatectomy, 2680
 after retropubic radical prostatectomy, 2657
Thrombosis. *See also* Venous thromboembolism
 renal vein, 1049
Thrombotic microangiopathies (TMA), 2860
Thulium laser, 2533-2534
 complications with, 2534
 intraoperative, 2534
 perioperative, 2534
 postoperative, 2534
 conclusions with, 2534
 holmium laser enucleation of prostate *versus*, 2533-2534
 outcomes with, 2533-2534
 comparative series for, 2533-2534
 single-cohort series for, 2533
 overview and concept for, 2533
 technique for, 2533
 transurethral resection of prostate *versus*, 2533
Thulium:YAG (Thu:YAG) laser, 230
Thu:YAG laser. *See* Thulium:YAG laser
Thymine, 459.e1-459.e3, 459.e2f
TI. *See* Thermal index
Tibial nerve, posterior, electrical stimulation of, for bladder storage disorders, 1910
Tibolone, and HSDD, 759.e1
Ticarcillin/clavulanate, preoperative prophylaxis with, 106t-107t
Tight junction (TJ) proteins, in bladder urothelium, 1638, 1638f
Timed voiding, 1890-1891
TIP. *See* Paclitaxel, ifosfamide, and cisplatin
Tisseel VH Fibrin Sealant, 207t, 207.e2
Tissue anastomosis instrumentation, for laparoscopic and robotic surgery, 207, 208f, 210, 207.e2f, 207.e3
Tissue engineering, 496-497, 497b
 biomaterials for, 486
 design and selection of, 486
 types of, 486.e1-486.e2, 486.e1f
 history of, 482
 stem cell sources for, 482-483, 483t
 adult, 485, 485f
 embryonic, 483, 483.e1
 induced pluripotent, 484
 native targeted progenitor cells, 485
 perinatal, 484-485
 SCNT, 483-484, 484f
 strategies for, 482
 of urologic structures
 bladder, 488-492, 490f-491f
 genital and reproductive tissues, 492-493, 493f-495f, 492.e2
 renal structures, 494-496, 496f, 495.e1
 ureters, 492, 492.e1
 urethra, 487-488, 487f-488f
 vascularization for, 486, 486.e3
Tissue matrix, of prostate, 2398-2399
Tissue sealants, for laparoscopic and robotic surgery, 207, 207t, 207.e2
Tissue transfer. *See also* Flaps
 principles of, 907-911, 908f
Tivozanib, for RCC, 1514
TJ proteins. *See* Tight junction proteins
TM. *See* Tropomyosin
TMA. *See* Thrombotic microangiopathies
TMP. *See* Trimethoprim
TMP-SMX. *See* Trimethoprim-sulfamethoxazole
TNF- α . *See* Tumor necrosis factor- α
TNM staging. *See* Tumor, nodes, and metastases staging
Tobacco. *See* Smoking
Tofranil. *See* Imipramine
Toileting programs
 bladder training, 1886f, 1889-1890
 caregiver-administered, challenges of, 1891
 delayed voiding, 1891
 habit training, 1891

- Toileting programs (*Continued*)
 prompted voiding, 1891
 timed voiding, 1890-1891
 understanding, 1889, 1889t
 for urinary incontinence, 1889-1891, 1889t
- Tolterodine, 1669-1670, 1669t
 for diminished bladder, 1831, 1832t-1834t
 to facilitate bladder filling and urine storage, 1839t, 1845-1847
 with α -adrenoreceptor antagonists, 1859-1860
 with other antimuscarinics, 1860
 for ureteral stent symptoms, 131-132
- Topical agents, and FSAD, 760.e1
- Topical local anesthetics, for PE, 700
- Topiramate, in stone formation, 1197
 medical management of, 1231
- Toremifene citrate, in prostate cancer prevention, 2562
- Torisel. *See* Temsirolimus
- Torsion of appendix testis and epididymis, 3392
- Total colpocleisis, for apical pelvic organ prolapse repair
 results with, 1974
 technique for, 1974, 1977f
- Total epididymectomy, 953, 954f
- Total nephrectomy, for renal trauma, 1155
- Total penile reconstruction, 941-945, 943f, 945b
 after trauma, 944-945
- Total scrotoectomy, 947
- Total urogenital mobilization (TUM), 3510-3513, 3512f-3515f
- Toxins
 AIN caused by, 1044-1046, 1045b
 to facilitate bladder filling and urine storage, 1839t, 1861-1863
 botulinum toxins, 1861-1863
 capsaicin, 1863
 resiniferatoxin, 1863
- TP53
 in apoptosis, 479
 in GU cancers, 462, 462f, 461.e2
 in Wilms tumor, 3569
- TP53 gene, in prostate cancer, 2557-2559
- TPE. *See* Tropical pulmonary eosinophilia
- TPE. *See* Docetaxel, cisplatin, and 5-fluorouracil
- Trabectedin, for retroperitoneal sarcomas, 1411
- Tramadol
 to facilitate bladder filling and urine storage, 1866.e3-1866.e4
 for PE, 700.e1
- Transabdominal cystolithotomy, laparoscopic or robotic, 2279-2280, 2279f-2280f
- Transabdominal orchidopexy, 3447
- Transabdominal pelvic ultrasonography
 indications for, 75
 limitations of, 76-77
 normal findings in, 75-76, 75f-77f
 procedural applications of, 76
 technique of, 75
- Transbuccal preparations, testosterone, 544t, 545
- Transcolonic technique of Goodwin, in urinary diversion, 2296-2297, 2297f
- Transcription, basics of, 459.e3, 459.e3f
- Transcriptional activation domains, of androgen receptors, 2397b, 2410-2412, 2411f
- Transcutaneous electrical stimulation (TENS), for storage disorders, 1910
- Transdermal agents, and FSAD, 760.e1
- Transdermal preparations, testosterone, 544t, 545
- Transducers, in urodynamic studies, 1723-1724
- Transfection, of ureter, delayed recognition, 1166-1167
- Transepithelial resistance (TER), 1638
- Transferrin, in prostatic secretions, 2417t, 2422
- Transforming growth factor- β (TGF- β)
 in prostate development, 2395-2396
 in tubulointerstitial fibrosis, 1098-1099
- Transforming growth factor- β 1, and PD, 729
- Transfusion
 blood products. *See* Blood product transfusions
 for laparoscopic radical prostatectomy, 2680
- Transgender persons, and female sexual function, 754, 754.e1
- Transglomerular pressure (TGP), 1007
- Transient receptor potential (TRP) channels
 antagonists of, to facilitate bladder filling and urine storage, 1866.e1
 in bladder afferent pathway, 1654-1656
- Transient urinary incontinence
 in geriatric patients, 2096
 with holmium laser enucleation of prostate, 2529
 after photoselective vaporization of prostate, 2533
- Transitional cell carcinoma (TCC). *See also* Urothelial cancer
 in pediatric bladder, 3588
 of upper urinary tract, ureteroscopy for, 142-143
- Transitional urology
 adolescent clinic in, 3523-3525, 3523t
 discharge without long-term follow-up, 3524
 dischargeable patients, 3524
 patient acquisition, 3524-3525, 3525t
 patterns of long-term follow-up, 3525
 unresolved follow-up problems, 3524
 barriers to, 3521-3523
 definitions for, 3521, 3522f
 failure consequences, 3522-3523
 outcome measures for, 3525-3527
 bladder function, 3525-3526
 continence, 3526
 hypertension, 3525
 quality of life, 3526-3527, 3527t
 renal function, 3525, 3525t
 sexuality, fertility, and pregnancy, 3526
 process for, 3521-3523
 training requirements for, 3523
- Transitory detrusor-sphincter discoordination, in infancy, 3125
- Translation, basics of, 459.e3-459.e4, 459.e3f-459.e4f
- Transneuronal tracing, 1663-1664
- Transobturator bulbourethral slings
 history and development of, 2170, 2170f
 implantation technique for, 2178-2179, 2179f
 mechanisms of action of, 2171, 2171f
 outcomes with, 2178t
- Transobturator midurethral sling
 anatomy for, 2009-2010
 complications with, 2182, 2182b
 long-term results with, 2182, 2183b
 outcomes with, 2017-2018, 2017t
 removal of, 2046
 surgical approach to
 in-to-out, 2013, 2014f
 out-to-in, 2013
- Transperineal prostate biopsy, 2587
 of radiorecurrent cancer, 2747
 saturation
 for focal therapy for prostate cancer, 2721
 transrectal ultrasound saturation *versus*, 2720-2721
- Transperineal template prostate mapping biopsy
 for focal therapy for prostate cancer, 2721, 2722f-2723f
 transrectal ultrasound biopsy *versus*, 2721-2722
- Transperitoneal approach
 to laparoscopic adrenalectomy, 1585-1590, 1586f-1588f, 1592-1593
 for laparoscopic and robotic surgery
 achieving access for, 200-201, 201f, 200.e1, 200.e1f, 201.e1f, 201.e2, 202.e1
 operative team placement for, 198-199, 198f-199f, 198.e1f
 for pediatric patients, 2966-2969, 2967f, 2967t, 2968b-2969b
 pyeloplasty, 1117-1118, 1118f
 to laparoscopic kidney surgery, 1447-1448, 1447f-1449f
 to laparoscopic partial nephrectomy, 1472
 to laparoscopic radical nephrectomy, 1465-1467, 1465f, 1466t
 robot-assisted, 1590, 1590f-1591f
- Transperitoneal laparoscopic
 nephroureterectomy, for UTUC
 dissection of distal ureter, 1383, 1383f
 laparoscopic removal of kidney down to mid-ureter, 1382-1383, 1382f
 open distal ureterectomy with excision of bladder cuff with, 1383
 proximal ureteronephrectomy, 1383, 1383f
- Transplantation
 hematopoietic stem cell, for RCC, 1506-1507, 1507t
 renal. *See* Renal transplantation
 secondary bladder calculi with, 1293-1294
- Transport, of sperm
 by epididymis, 531
 by vas deferens, 533
- Transrectal prostate biopsy, 2586-2587
- Transrectal ultrasonography (TRUS), 572-573
 of locally advanced prostate cancer, 2753, 2753f
 of prostate, 83-84, 83f, 508, 508f, 2579
 anatomy for, 2579, 2580f-2581f
 for biopsy, 83-84
 cancer, 2582, 2582f
 color Doppler, 2588-2589, 2589f-2590f
 cystic lesions, 2582, 2582f
 elastography, 2589, 2590f
 gray-scale, 2579-2583
 investigational techniques for, 2590-2592, 2591f
 machine settings for, 2580
 other malignancies and, 2583
 power Doppler, 2588-2589, 2589f-2590f
 probe manipulation in, 2580-2581, 2581f
 Prostate HistoScanning, 2590
 techniques for, 2580-2581
 after treatment, 2583
 volume calculations in, 2581-2582
 of seminal vesicles, 958-959, 958f
 of seminal vesicles and ejaculatory ducts, 505
 of vas deferens, 505
- Transrectal ultrasound biopsy
 of radiorecurrent cancer, 2747
 saturation
 for focal therapy for prostate cancer, 2721
 transperineal saturation *versus*, 2721
 systematic, for focal therapy for prostate cancer, 2720-2721
 transperineal template prostate mapping biopsy *versus*, 2721-2722

- Transrectal ultrasound-guided prostate (TRUSP) biopsy, antimicrobial prophylaxis for, 262-263
- Trans-scrotal orchidopexy, 3446, 3446f
- Transsexualism, female-to-male, reconstructive surgery for, 945, 945b
- Transureteroureterostomy (TUU)
for ureteral injuries, midureteral, 1163
for ureteral stricture disease
laparoscopic, 1139
open, 1139
for urinary tract reconstruction, 3333-3334, 3334f
for vesicoureteral reflux, 1777
- Transurethral cystolitholapaxy, for bladder calculi, 1295
- Transurethral electrical bladder stimulation (TEBS), 1902-1903
for emptying disorders, 1915-1916
- Transurethral incision (TUI), for ureterocele, 3094-3096, 3095f-3096f
reflux outcomes after, 3096
- Transurethral incision of prostate (TUIP), 2525-2526
complications with, 2526
intraoperative, 2526
perioperative, 2526
postoperative, 2526
outcomes with, 2526
comparative studies for, 2526
single-cohort studies for, 2526
overview and concept of, 2525
summary for, 2526
technique for, 2525, 2525f
transurethral resection of prostate *versus*, 2526
- Transurethral injection technique, for stress urinary incontinence
with cystoscopic monitoring, 2052-2053, 2053f
without cystoscopic monitoring, 2053
- Transurethral microwave therapy (TUMT), 2517-2522
 α -blocker *versus*, 2520
complications with, 2521
intraoperative, 2521
perioperative, 2519, 2521
postoperative, 2521
conclusions for, 2522
contraindications to, 2519
mechanism of action of, 2518
morphology changes, 2518
nerve degeneration and sensory changes, 2518
outcomes with, 2519-2521
comparative studies for, 2520-2521
prediction of, 2519
single-cohort studies for, 2519-2520
overview and concept of, 2517-2518, 2518f
sham *versus*, 2520
technique for, 2518-2519
intraoperative, 2519
perioperative, 2519, 2519f
postoperative, 2519
preoperative, 2518-2519
transurethral resection of prostate *versus*, 2520-2521
- Transurethral needle ablation (TUNA), 2522-2525
complications with, 2525
intraoperative, 2525
perioperative, 2525
postoperative, 2525
conclusion for, 2525
- Transurethral needle ablation (TUNA)
(*Continued*)
other minimally invasive surgical techniques *versus*, 2524
outcomes with, 2523-2524
comparative studies of, 2524
single-cohort studies of, 2523-2524
overview and concept of, 2522, 2522f
of prostate, 326
technique for, 2523
intraoperative, 2523, 2523f
postoperative, 2523
preoperative, 2523
transurethral resection of prostate *versus*, 2524
- Transurethral prostate biopsy, 2587
- Transurethral resection (TUR), 582
of ureteral orifice, for UTUC, 1378, 1380f
- Transurethral resection of bladder tumor (TURBT), 2242-2244, 2253b
bladder perforation with, 2244, 2244f
challenges with, 2243-2244
cystoscopy for, 2243
goal of, 2243, 2243f
history of, 2242
imaging for, 2242-2243
of muscle-invasive bladder cancer, radical, 2233
of non-muscle-invasive bladder cancer, 2208-2209
biopsy role in, 2210
complications of, 2209
repeat, 2209-2210
oncologic outcomes of, 2242
partial cystectomy with, 2252, 2253f
patient preparation for, 2244-2245, 2245f
pelvic lymphadenectomy with, 2246-2247, 2247f-2248f
physical examination for, 2242
postoperative care for, 2252-2253
radical cystectomy with
female, 2250-2252, 2251f-2252f
male, 2247-2250, 2249f-2250f
surgical technique for, 2245-2246, 2245f-2246f
- Transurethral resection of diverticular neck, for bladder diverticula, 2146-2148
- Transurethral resection of ejaculatory ducts (TURED), 582
complications of
epididymitis, 600
reflux, 600
retrograde ejaculation, 600
diagnosis for, 599
results for, 600
technique for, 599, 600f
- Transurethral resection of prostate (TURP)
for adenocarcinoma, 2597
bipolar. *See* Bipolar transurethral resection of prostate
holmium laser enucleation of prostate *versus*, 2528-2529
monopolar. *See* Monopolar transurethral resection of prostate
for nocturia, 1830
simple prostatectomy compared with, 2535
thulium laser *versus*, 2533
transurethral incision of prostate *versus*, 2526
transurethral microwave therapy *versus*, 2520-2521
transurethral needle ablation of prostate *versus*, 2524
urinary incontinence after
prevalence of, 1750
risk factors for, 1750
- Transurethral vaporization of prostate (TUVP), 2517
comparative studies for, 2517.e3-2517.e4
bipolar studies, 2517.e3-2517.e4
monopolar studies, 2517.e3
complications of, 2517.e4
intraoperative, 2517.e4
perioperative, 2517.e4
postoperative, 2517.e4
conclusion for, 2517.e4
electrodes for, 2517.e1, 2517.e1f-2517.e2f
outcomes with, 2517.e2-2517.e4
animal and in vitro studies for, 2517.e2
single-cohort studies for, 2517.e2-2517.e3
overview and concept of, 2517.e1
technique for, 2517.e1-2517.e2
intraoperative, 2517.e2
postoperative, 2517.e2
preoperative, 2517.e1-2517.e2
- Transvaginal hysterectomy, for uterine prolapse, 1976
- Transvaginal kits, for pelvic organ prolapse repair, 1982-1984
current controversy over, 1984-1986
- Transversalis fascia, 1597-1598, 1599f, 1613-1614, 1615f
- Transverse myelitis, 3295
pathogenesis of, 3295
presentation of, 3295, 3295f
specific recommendations for, 3295
- Transverse testicular ectopia, 3443
- Transverse vaginal septum, 3459-3460, 3460f
- Transvesical bladder diverticulectomy, for bladder diverticula, 2148, 2149f-2150f
- Transvesical ligation and detachment technique, for UTUC, 1378, 1379f
- Trauma
bladder, 2385-2388
of external genitalia, 2379-2385, 916.e3b
genital skin loss, 2384-2385, 2384f-2385f, 916.e1-916.e2
penis, 941, 944-945, 2379-2382, 3372, 3372f, 916.e1-2, 916.e1f
testis, 2382-2384, 2383f
genitourinary. *See* Genitourinary trauma
iatrogenic. *See* Iatrogenic trauma
LUT function and, 1699
noninfectious genital ulcers caused by, 401-402, 402f
renal. *See* Renal injuries
of spinal cord. *See* Spinal cord injury
ureteral. *See* Ureteral injuries
urethral, 2388-2392
- Traumatic brain injury, lower urinary tract dysfunction with, 1765
- Treatment of pelvic cancers, and delayed ejaculation, 703-704
- Treponemal syphilis tests, 375
- Triamterene, in stone formation, 1197
medical management of, 1231
surgical management of, 1243.e3
- Triangulation fluoroscopic guidance, 163-165, 165f
- Trichloroacetic acid, for condylomata acuminata, 846.e2-846.e3
- Trichomonas*, 372-373
- Trichomoniasis, 381, 381f
- Trichomycosis axillaris. *See* Corynebacterial infection
- Triclosan-eluting (Triumph) stents, 128
- Tricyclic antidepressants (TCAs)
for BPS/IC oral therapy, 353, 353f
for enuresis, 3315

- Tricyclic antidepressants (TCAs) (*Continued*)
to facilitate bladder filling and urine storage,
1839t, 1856-1858
and PE, 698-700, 699f
- Triglycerides, urologic disease and, 551
- Trigone of bladder, 1626-1627, 1628f
- Trimethoprim (TMP)
serum creatinine effects of, 1060-1061
for UTIs, 266, 267t, 296t
- Trimethoprim-sulfamethoxazole (TMP-SMX)
prophylaxis with
for cystourethroscopy, 139-140
preoperative, 106t-107t
for uncomplicated urologic procedures,
261t-262t
and UTIs, 2944-2945
for UTIs, 255t-258t, 258, 266, 267t, 272-273,
272t, 278t
- Triumph stents. *See* Triclosan-eluting stents
- Trocars
for laparoscopic and robotic access
complications related to placement of,
217-220, 219f
EndoTIP, 200.e1, 200.e1f
for laparoscopic and robotic access,
202-205, 203f, 203.e1f-203.e2f
in pediatric patients, 2966, 2967f, 2969,
2970b, 2970f-2972f
laparoscopic kidney surgery placements for
hand-assisted modifications, 1451-1452,
1451f-1452f
LESS and NOTES, 1453-1454, 1453f-1454f,
1455t
retroperitoneal approach, 1448-1450,
1450f-1451f
robotic-assisted modifications, 1452-1453,
1453f
transperitoneal approach, 1447-1448,
1447f-1449f
in midurethral sling, injury to urinary tract
with, 2028
- Tropical pulmonary eosinophilia (TPE),
as filariasis clinical manifestation,
444
- Tropical spastic paraparesis, lower urinary tract
dysfunction and, 1785
- Tropomyosin (TM), 1641-1642, 1643f
- Tropium chloride
for diminished bladder, 1831,
1832t-1834t
to facilitate bladder filling and urine storage,
1839t, 1847-1848
with other antimuscarinics, 1860
- TRP channels. *See* Transient receptor potential
channels
- TRPA1, 1655-1656
- TRPM8, 1656
- TRPV4, 1655
- TRUS. *See* Transrectal ultrasonography
- TRUSP biopsy. *See* Transrectal ultrasound-guided
prostate biopsy
- TSC. *See* Tuberous sclerosis complex
- TST. *See* Tuberculin skin test
- TT. *See* Testosterone therapy
- TU. *See* Testosterone undecanoate
- Tuberculin skin test (TST), 424, 425b
- Tuberculosis (TB), 421
drug-resistant, 432
epidemiology, 421
genitourinary. *See* Genitourinary
tuberculosis
history, 421
lower urinary tract dysfunction and,
1786-1787
microbiology, 421
relapse, 432
- Tuberous sclerosis complex (TSC), 1306,
3023-3025, 3024f
clinical features of, 3024-3025
genetics of, 3023-3024, 3025f
radiographic evaluation of, 3024f, 3025
renal cell carcinoma in, 1336, 3025
treatment of, 3025
- Tubular disorders, 2861-2863, 2863b
distal and collecting duct, 2862-2863
proximal, 2861-2862
- Tubular function, in renal development,
2849-2851
- Tubularized incised plate urethroplasty
distal, 3404-3408, 3406f-3408f
proximal, 3408-3410, 3409f-3411f
for reoperation, 3407f, 3423, 3423f
- Tubulogenesis, 2832-2833, 2832f
- Tubuloglomerular feedback (TGF), 1008
- Tubulointerstitial fibrosis, molecular
mechanisms of, 1098-1100, 1099f
- TUI. *See* Transurethral incision
- TUIP. *See* Transurethral incision of
prostate
- TUM. *See* Total urogenital mobilization
- Tumor, nodes, and metastases (TNM) staging,
2190-2191, 2191t
of penile squamous cell carcinoma, 852-854,
853t, 854b, 854f
for RCC, 1336-1338, 1337t
prognosis and, 1339-1341, 1339t
for retroperitoneal sarcomas, 1406
of testicular cancer, 791t-792t, 793
of urethral cancer, 880, 880t, 881f
for UTUC, 1372-1374, 1373t-1374t
- Tumor growth factor- α , in RCC, 1327b
- Tumor markers. *See* Biomarkers
- Tumor necrosis factor- α (TNF- α), in
tubulointerstitial fibrosis, 1099
- Tumor suppressor genes, 459-460, 460b, 460f
- Tumor syndromes, 467-468, 468t
in prostate cancer, 468-469, 468t, 469f
in renal cancer, 468t, 471-472, 1321-1325,
1322t-1323t, 1323f
- Tumor thrombus. *See* Venous tumor thrombus
- Tumorigenesis model, for prostate cancer, 2559
- Tumors. *See also* Malignancy; Oncology; *specific
tumors*
augmentation cystoplasty and formation of,
3353
pain caused by, 1-2
pediatric. *See* Pediatric oncology
- TUMT. *See* Transurethral microwave therapy
- TUNA. *See* Transurethral needle ablation
- Tunica albuginea, 498, 499f, 502f, 519, 612-614,
613f, 614t, 617t, 722
in penile fracture, 2379
- Tunica lengthening
graft materials for, 745-746
grafting surgical technique for, 746
postoperative management for, 746-747
Tunical shortening, procedures for, 741-744
- Tunneled small bowel anastomoses, in urinary
diversion, 2298-2299, 2299f
- TUR. *See* Transurethral resection
- Turbidity, of urine, 13
- TURBT. *See* Transurethral resection of bladder
tumor
- TURED. *See* Transurethral resection of
ejaculatory ducts
- Turner syndrome, 3478-3483, 3479f
- TURP. *See* Transurethral resection of prostate
- TUU. *See* Transureteroureterostomy
- TUVP. *See* Transurethral vaporization of
prostate
- TVT procedure. *See* Tension-free vaginal tape
- Two-kidney, one-clip model, of renovascular
hypertension, 1029, 1029f
- Tyramine, ureteral response to, 991-992
- Tyrosine kinase inhibitors
for RCC, 1346-1347
for retroperitoneal sarcomas, 1412
- U**
- UA. *See* Urinalysis
- UCBSCs. *See* Umbilical cord blood stem cells
- UCLA Integrated Staging System (UISS), for
RCC, 1341
- UID. *See* Urethral diverticula
- UDS. *See* Urodynamic studies
- UFC evaluation. *See* Urinary free cortisol
evaluation
- UI. *See* Urinary incontinence
- UISS. *See* UCLA Integrated Staging System
- UKCCSG trials. *See* United Kingdom Children's
Cancer Study Group trials
- Ulcers. *See* Genital ulcers
- Ultrasensitive prostate-specific antigen (uPSA)
testing, for biochemical recurrence after
radical prostatectomy, 2771-2772
- Ultrasonic lithotripsy, 231t, 233, 233b,
1263-1264, 1263f
ballistic combined with, 1264-1265, 1265f
basic physics of, 233
percutaneous surgery with, 233.e2
tissue effects of, 233
ureteroscopy with, 233.e2
- Ultrasonography, 63, 84b
in adrenal mass evaluation, 1567
in adrenal radiology, 1526
advances in, 2722-2727
for AKI, 1049
of antenatal bladder, 3173
for bladder and bowel dysfunction, 3304,
3304f
clinical urologic
penis and male urethra, 80-82, 81f-82f
renal, 73-75, 74f
scrotum, 70f-71f, 77-80, 78f-80f
transabdominal pelvic, 75-77, 75f-77f
TRUS of prostate, 83-84, 83f
contrast agents in, 72
of defecation disorders, 3320f, 3327,
3321.e1f
documentation and image storage in, 72-73,
72f
Doppler. *See* Doppler ultrasonography
of epididymis, 503, 504f
of exstrophy-epispadias complex, 3191-3192,
3192f
of female pelvis, 1609-1610, 1610f
history of, 63-64, 64f
of kidney, 969, 969.e1f
of male external genitalia, 3368, 3368.e1f
of mesh complications in pelvic
reconstructive surgery, 2045, 2045f
modes of
Doppler, 69
gray-scale, 68-69
harmonic scanning, 69, 70f
sonoelastography, 70-71, 70f-71f
spatial compounding, 69-70
three-dimensional scanning, 71-72, 72f
multiparametric magnetic resonance imaging
fusion with, for prostate biopsy,
2724-2727, 2725f-2727f
patient safety in, 73
pediatric
lower urinary tract, 2913-2915, 2917f-2918f
stone disease, 3103
testicular tumors, 3591, 3592t
upper urinary tract, 2911-2913, 2913f-2916f

- Ultrasonography (*Continued*)
 pediatric urology, 2904-2905, 2905f
 for pelvic floor disorders, 1708
 of penile fracture, 2380, 2380f
 of penis, for squamous cell carcinoma, 851
 percutaneous access guidance with, 162-163, 163f
 physical principles of, 64-65, 65f
 artifacts, 67-68, 67f-69f
 attenuation mechanisms, 66-67, 66f-67f, 66t
 image generation, 65, 65f
 resolution, 65-66, 66f
 of posterior urethral valves, 3257, 3257f
 postnatal, 2911, 2913f-2914f
 practice accreditation for, 84
 prenatal imaging with, 2909-2911, 2910f-2912f
 in prostatitis evaluation, 315-316
 of renal calculi, 1091
 pretreatment assessment, 1237
 for renal tumor evaluation, 63, 64f, 1316
 for renovascular hypertension screening, 1032, 1032b
 scrotal, 501, 571-572, 572f
 for GCIs, 790, 790f
 indications for, 78
 limitations of, 80, 80f
 normal findings in, 78, 78f-79f
 procedural applications of, 78-79
 sonoelastography, 70f-71f, 79-80
 technique of, 77
 in shock wave lithotripsy, 1267
 of testis, 501, 501f
 indications for, 78
 injury to, 2383, 2383f
 limitations of, 80, 80f
 normal findings in, 78, 78f-79f
 procedural applications of, 78-79
 sonoelastography, 70f-71f, 79-80
 technique of, 77
 transrectal. *See* Transrectal ultrasonography
 of ureteral anomalies, 3081, 3082f-3083f
 for ureteral calculi, 1091
 for ureteropelvic junction obstruction, 1105
 urethral, 511f
 of urethral diverticula, 2159
 for urinary tract obstruction, 1091
 for UTIs, 253, 276-277, 277f, 2940-2941
 Wilms tumor screening with, 3570, 3570f
- Ultrasound ablation, high-intensity focused. *See* High-intensity focused ultrasound ablation
- Ultrasound instrumentation
 for laparoscopic and robotic surgery, 206-207
 for tissue dissection and cauterization, 227-228
- Umbilical cord blood stem cells (UCBSCs), for female SUI injection therapy, 2061-2062
- Umbilical-urachus sinus, 3176f, 3177
- Umbrella cells, 1632, 1632f, 1638
- UMN. *See* Upper motor neuron
- Unclassified RCC, 1329t-1330t, 1334
- Uncomplicated cystitis
 antimicrobial selection for, 266-267, 267t
 asymptomatic bacteriuria and, 268, 268t-269t
 clinical presentation, 265
 differential diagnosis, 266
 follow-up, 268
 laboratory diagnosis, 265-266
 management, 266-268, 266f, 267t
 risk factors, 265b
- Underactive bladder. *See* Bladder, underactivity of
- Underactive detrusor. *See* Detrusor underactivity
- Undermasculinized male. *See* 46,XY DSD
- Undescended testis. *See* Cryptorchidism
- Unilateral hydronephrosis, prenatal, 2888-2889
- Unilateral multicystic dysplastic kidney, 2889
- Unilateral renal agenesis (URA), 2980-2984
 anomalies with, 2980-2981, 2982f
 in female, 2982-2983
 in male, 2981-2982, 2982f
 associations with, 2980
 diagnosis of, 2983
 embryology of, 2980, 2981f, 2980.e1f
 incidence of, 2980
 prognosis of, 2983-2984
- Unilateral ureteral obstruction (UJO)
 hemodynamic changes with, 1094, 1094f
 pathologic changes with, 1097, 1097f
 renal recovery after, 1101-1102
 tubular function with, 1095-1096
- United Kingdom Children's Cancer Study Group (UKCCSG) trials, 3577
- Unresolved UTIs, 269-270, 270b
- Unstable bladder, 1796
- Up training, 1892
- UPEC. *See* Uropathogenic *E. coli*
- UPJ. *See* Ureteropelvic junction
- UPJO. *See* Ureteropelvic junction obstruction
- UPP. *See* Urethral pressure profile
- Upper abdominal surgery, operative team
 placement for
 retroperitoneal procedures, 198, 199f
 transperitoneal procedures, 198, 198f, 198.e1f
- Upper motor neuron (UMN) lesion, voiding
 dysfunction after, 1694, 1694b
- Upper respiratory infections (URIs),
 perioperative care for pediatric patients with, 2954, 2954f
- Upper tract endoscopy, 152b
 antimicrobial prophylaxis for, 263-264
 equipment for, 143-150, 143f-144f, 145t, 146f-149f, 147t, 150t
 indications for, 142-143
 percutaneous procedures, antimicrobial prophylaxis for, 264
 technique, 150-152, 151b, 151f
 ureteroscopy, antimicrobial prophylaxis for, 263-264
 for UTUC, 1371-1372
- UTUC treatment with
 basics of, 1388, 1389f
 percutaneous approach, 1392-1396, 1394f-1396f, 1397t
 ureteroscopy and ureteropyeloscopy, 1388-1392, 1390f-1392f, 1393t
- Upper tract urothelial cancer (UTUC)
 adjuvant therapy for
 after complete excision, 1399-1400
 after organ-sparing therapy, 1398-1399, 1398f, 1399t
 basic and clinical biology of, 1365
 diagnosis of, 1371
 cystoscopy for, 1371
 cytology and other tumor markers in, 1372
 radiologic evaluation for, 1369
 ureteroscopic evaluation and biopsy for, 1371-1372
 endoscopic treatment of
 basics of, 1388, 1389f
 percutaneous approach, 1392-1396, 1394f-1396f, 1397t
 ureteroscopy and ureteropyeloscopy, 1388-1392, 1390f-1392f, 1393t
- Upper tract urothelial cancer (UTUC) (*Continued*)
 epidemiology of
 incidence and mortality rates, 1365
 variations by gender, race, and age, 1365
 etiology of
 external risk factors, 1366
 genetics, 1365-1366
 follow-up for
 assessing for recurrence, 1401, 1401f
 general procedures, 1401
 metastatic restaging, 1402
 specific procedures, 1401-1402
 histopathology of, 1369-1370
 abnormal upper tract urothelium, 1369-1371
 micropapillary variant, 1370
 normal upper tract urothelium, 1369, 1369f-1370f
 management guidelines for positive upper tract urinary cytology or CIS diagnosis, 1396-1398, 1398f
 metastatic disease treatment in, 1400-1401, 1401f
 natural history of
 chronology, 1367-1368
 CIS association, 1368
 dissemination, 1368
 panurothelial disease, 1368-1369
 recurrence origins and patterns, 1367
 ureter compared with collecting system malignancies, 1367
 prognostic factors of
 age, 1374
 grade, 1374
 hydronephrosis, 1374
 location, 1374
 lymph node involvement, 1375
 lymphovascular invasion, 1375
 molecular biology and markers, 1375-1376
 race, 1374-1375
 stage, 1374
 tumor architecture, 1374
 tumor multifocality, 1375
 tumor necrosis, 1375
 tumor size, 1374
 staging of, 1371
 clinical prediction tools for, 1376
 TNM, 1372-1374, 1373t-1374t
 surgical management of, 1376
 adjuvant therapy for, 1379
 distal ureter and bladder cuff management, 1377-1379, 1378f-1380f, 1381-1382
 distal ureterectomy and direct
 neocystostomy or ureteroneocystostomy with bladder psoas muscle hitch or a Boari flap, 1385-1386, 1387f
 ileal ureteral replacement, 1386-1387, 1387f
 laparoscopic or robotic distal ureterectomy and reimplantation, 1388
 laparoscopic radical nephroureterectomy, 1382-1384, 1382f-1384f
 lymphadenectomy, 1379-1382, 1381f
 open nephron-sparing surgery for renal pelvis tumors, 1384-1385, 1385f
 open radical nephroureterectomy, 1376-1377, 1377f, 1381-1382
 open segmental ureterectomy, 1385, 1386f
 results of, 1381-1382, 1384-1385, 1387-1388, 1388t

- Upper urinary tract
 anomalies of
 collecting system. *See* Upper urinary tract collecting system, anomalies of
 renal vasculature. *See* Renal vasculature, anomalies of
 rotation of, 2996-2997, 2996b, 2997f, 2996.e1f
 anomalies of ascent of
 cephalad renal ectopia, 2986
 simple renal ectopia, 2985-2986, 2987f, 2985.e3f
 thoracic kidney, 2988, 2988f-2989f
 anomalies of form and fusion of
 crossed renal ectopia, 2988-2993, 2990f-2991f, 2988.e1f
 horseshoe kidney, 2993-2996, 2994f-2995f
 anomalies of number of
 bilateral renal agenesis. *See* Bilateral renal agenesis
 supernumerary kidney, 2984-2985, 2985f, 2985.e1f-2985.e2f
 unilateral renal agenesis. *See* Unilateral renal agenesis
 calculi of
 renal. *See* Renal calculi
 ureteral. *See* Ureteral calculi
 defects in, in bladder exstrophy, 3189-3191, 3190f
 deterioration of
 with benign prostatic hyperplasia, 2455
 early intervention for, 3276
 with neural tube defects, 3274-3275, 3275f
 drainage of
 biofilm formation during, 134-135
 nephrostomy tube, 133-135, 133f
 percutaneous access for, 153-154
 after percutaneous surgery, 170-174, 171f-174f, 174b, 181, 171.e1f
 ureteral stents and catheters, 126-132, 126f-127f, 131f
 dysfunction of, 3331
 hematuria related to, 193-194, 193b-194b
 lateralizing essential hematuria and, 194
 renal disease causing, 194
 vascular conditions causing, 194
 imaging of, 56, 57f
 MH diagnostic evaluation with, 187
 pediatric imaging of
 conventional radiography and fluoroscopy, 2916-2918, 2919f
 CT, 2918, 2920f
 MRI, 2915
 ultrasonography, 2911-2913, 2913f-2916f
 posterior urethral valves and, 3254-3255, 3254i, 3256f
 transitional cell carcinoma of, ureteroscopy for, 142-143
 trauma of, renal. *See* Renal injuries
 urothelium of
 abnormal, 1369-1371
 normal, 1369, 1369f-1370f
- Upper urinary tract collecting system
 anatomy of, 155-156, 155f-156f
 anomalies of, 2999-3004
 bifid pelvis, 3001f, 3004
 calyceal diverticulum, 2999-3001, 3000f
 hydrocalycosis, 3001-3002, 3001f
 infundibulopelvic stenosis, 3003, 3004f
 megacalycosis, 3002-3003, 3002f
 pseudotumors of kidney, 3003, 3003f
 injury to, after percutaneous access, 178-179, 179f
 obstruction of, after percutaneous access to upper urinary tract collecting system, 181-182
- Upper urinary tract collecting system
 (Continued)
 percutaneous access to, 170b
 anatomic considerations for, 154-157, 154f-157f, 157b
 anesthesia for, 158
 antegrade approach to, 161-166, 162f-166f
 anticoagulant management for, 158
 complications of, 175-182, 176f-180f, 182b
 history of, 153
 indications for, 153-154
 modifications for special situations, 168-170, 170f
 patient positioning for, 158-159, 159f
 periprocedural antimicrobials for, 157-158
 postprocedural nephrostomy drainage for, 170-174, 171f-174f, 174b, 181, 171.e1f
 retrograde assistance for, 160-161, 161f, 160.e1f
 site selection for, 159-160, 160f
 training in, 175, 175f
 working access, 166-168, 167f-169f, 168.e1f
 urothelial cancer of. *See* Upper tract urothelial cancer
- Upper urinary tract malignancies
 adenocarcinomas, 1371
 others, 1371
 squamous cell cancers, 1371
 UTUC. *See* Upper tract urothelial cancer
- Upper urinary tract obstruction
 evaluation of, 1104
 retrocaval ureter. *See* Retrocaval ureter
 retroperitoneal fibrosis. *See* Retroperitoneal fibrosis
 ureteral stricture disease. *See* Ureteral stricture disease
 ureteroenteric anastomotic stricture. *See* Ureteroenteric anastomotic stricture
 ureteropelvic junction obstruction. *See* Ureteropelvic junction obstruction
- Upper urinary tract tumors
 benign
 others, 1371
 papilloma, 1369-1370
 von Brunn nests, 1369-1370
 malignant. *See* Upper urinary tract malignancies
- uPSA testing. *See* Ultrasensitive prostate-specific antigen testing
- URA. *See* Unilateral renal agenesis; Urethra Resistance Factor
- Urachal carcinoma, in pediatric patients, 3589
- Urachus, 1616f, 1624
 anatomy of, 3175, 3175f
 anomalies of, 3175-3177, 3176f, 3177b
 patent urachus, 3176-3177, 3177f
 umbilical-urachus sinus, 3177
 urachal cyst, 3177
 vesicourachal diverticulum, 3177
 development of, 3173
 surgery of, 2267-2268
 complications with, 2268
 evaluation for, 2267
 indications for, 2267
 outcomes with, 2268
 technique for, 2267, 2268f
- Uracil, 459.e1-459.e3, 459.e2f
- Urea
 in collecting tubule, 1019
 GFR estimation with, 1009
- Ureaplasma infection, 372
 in prostatic infection, 372
- Urease, bacteria production of, 1194, 1194f, 1195t, 1213, 1214t
- Urea-splitting bacteria, struvite renal stones caused by, 271
- Urecholine. *See* Bethanechol
- Ureter
 access of, for ureteroscopy, 150
 anatomy of, 968f, 974-975, 974f, 976b, 975.e1f, 968.e1f
 arteries, veins, and lymphatic drainage of, 976, 976.e1f
 cellular, 978
 endoscopic, 976-977, 977b, 977.e1f
 microscopic, 976, 976.e1f
 nerve supply, 976
 pelvic, 1619f, 1623-1624
 radiologic, 975-976, 976b
 aperistaltic segment of, 1104, 1105f
 development of, 2834-2836
 anomalies of. *See* Ureteral anomalies
 dissection of, for simple nephrectomy, 1454, 1456f
 duplication of, vesicoureteral reflux and, 3151, 3151.e1f
 in genitourinary tuberculosis, 423
 herniation of, 3101
 muscle-invasive bladder cancer involvement of, 2228-2229
 obstruction of, 995-999, 996f-999f
 clinical assessment of, 998-999, 999f
 physiology of, 978
 age effects on, 1002, 1002f-1003f
 cellular anatomy, 978
 contractile activity, 984-988, 984f-985f, 987f-988f
 development pathways, 978-979, 979f
 drug effects on, 1003-1006
 electrical activity, 979-984, 980f-983f
 mechanical properties, 988-989, 989f-990f
 nervous system function, 989-993
 pathologic processes affecting, 995-1002, 996f-1000f
 pregnancy effects on, 1002-1003
 urine transport, 993-995, 994f-995f
 prenatal, 2874-2875, 2875f
 in prune-belly syndrome, 3235, 3236f-3237f
 regeneration of, 492, 492.e1
 in renal transplantation, 3533
 retrocaval. *See* Retrocaval ureter
 surgical management of, for UTUC, 1377-1379, 1378f-1380f, 1381-1382
 transabdominal pelvic ultrasonography of, 75-77, 76f
 transection of, in robotic-assisted radical cystectomy, 2270, 2270f
 transposition of, in robotic-assisted radical cystectomy, 2273-2274, 2275f
 urothelium of
 abnormal, 1369-1371
 normal, 1369, 1370f
 vascular anomalies involving, 3099-3100
- Ureteral access sheaths, for ureteroscopy, 149, 149f, 150t
- Ureteral anomalies
 classification and anatomic description of, 3075-3079
 ectopic ureter, 3075, 3076f
 ureterocele, 3075-3077, 3076f-3077f
 clinical management of, 3087-3097
 goals for, 3087
 historical perspective on, 3087-3088
 observational, 3088
 relieve obstruction, prevent reflux, maintain continence, 3087
 summary for, 3096-3097, 3097f, 3097t
 clinical presentation of, 3079-3080

- Ureteral anomalies (*Continued*)
 clinical relevance of, 3077
 ectopic ureter. *See* Ectopic ureter
 embryology and etiology of, 3077, 3079b
 endoscopic evaluation of, 3076f-3077f,
 3085-3087, 3086f
 evaluation of, 3081-3087
 magnetic resonance imaging of, 3082,
 3083f
 physical examination, 3081, 3081f
 ultrasound of, 3081, 3082f-3083f
 excision of ureterocele and common-sheath
 reimplantation, 3091-3094, 3092f-3094f
 functional assessment of, 3082-3085
 bladder, 3082
 renal, 3082, 3084f
 voiding cystourethrogram for, 3083, 3084f
 imaging of, 3079
 incontinence and, 3080
 infection and, 3079-3080
 late presentation of, 3080
 lower tract reconstruction for, 3091-3094
 of number, 3097-3098
 pain and, 3080
 of position, 3099-3101
 prolapse of, 3080, 3080f
 pyeloureterostomy for, 3094
 reflux in, 3084
 total reconstruction for, 3088
 upper pole partial nephrectomy for,
 3088-3090
 complications with, 3090
 laparoscopic, 3089-3090, 3091f
 open, 3088-3089, 3089f-3090f
 outcomes with, 3090
 ureteral-trigonal-renal development and,
 3077-3079, 3078f
 ureteroceles. *See* Ureteroceles
 ureteroureterostomy for, 3094, 3095f
- Ureteral calculi
 clinical factors of, 1254-1257
 duration, 1257
 morbid obesity and, 1255
 old age and frailty, 1255-1256
 prior renal surgery, 1256
 renal function, 1254-1255
 renal transplants, 1257
 solitary kidney, 1255
 spinal deformity or limb contractures, 1256
 uncorrected coagulopathy, 1256
 urinary diversion, 1256-1257
 urinary tract infection and, 1254
 open stone surgery for, 1286
 spontaneous passage of, 1251, 1251t
 submucosal, 1284
 surgical management of, 1250-1259, 1250b
 anatomic factors, 1253-1254
 duplicated collecting system and, 1253
 economic factors of, 1254.e1
 historical overview of, 1235.e1-1235.e2
 megaureter and, 1253
 natural history for, 1250-1251, 1251t
 outcome of, 1257-1259
 pretreatment assessment for, 1251
 stone burden in, 1252-1253
 stone composition and, 1253
 stone factors for, 1251-1253
 stone location in, 1251-1252, 1252t
 ureteral stricture or stenosis, 1253-1254
 ureteral function effects of, 1001-1002
 ureteroscopic management of, 1282-1285
 complications of, 1283-1285
 ureteral access sheath for, 1283
 in urinary tract obstruction, 1091
- Ureteral catheterization, UTI diagnosis and, 252,
 252.e1t
- Ureteral dipping technique, in urinary diversion,
 2300
- Ureteral injuries
 cause of, 1157-1160
 diagnosis of
 hematuria, 1160
 intraoperative recognition, 1160
 external trauma, 1157-1158, 1157t
 contusion, 1161
 management for, 1161-1164
 pediatric, 3550-3551
 imaging of
 antegrade ureterography, 1161
 computed tomography, 1160-1161, 1161f
 excretory urography, 1160, 1160f
 retrograde ureterography, 1161
 key points of, 1167b, 1167f-1168f
 during laparoscopic and robotic surgery,
 222.e1
 lower
 Boari flap for, 1163, 1165f
 management of, 1163-1164
 minimally invasive repair for, 1163-1164
 partial transection for, 1164
 psoas bladder hitch for, 1163, 1164f
 ureteroneocystostomy for, 1163
 management of, 1161-1167, 1161f
 damage control, 1164
 general principles of, 1161, 1162f
 midureteral, 1163
 with monopolar transurethral resection of
 prostate, 2514
 pediatric, 3550-3552
 iatrogenic, 3551-3552
 surgical, 1158-1159
 avoidance and detection of, 1158-1159,
 1159f
 delayed recognition of, 1166-1167
 immediate recognition of, 1166
 ligation, 1166, 1166f
 robotic and laparoscopic, 1158
 tenuous ureteral blood supply, 1159
 timing of repair of, 1164-1166
 with vascular surgery, 1158
 upper, 1161-1163, 1162f
 autotransplantation for, 1162-1163
 bowel interposition for, 1163
 monitoring after repair, 1163
 nephrectomy for, 1163
 ureterocalicostomy for, 1162
 ureteroureterostomy for, 1161-1162,
 1162f
 ureteroscopic, 1159-1160
 avulsion, 1167, 1284-1285
 perforation, 1167, 1283-1284
 stricture, 1284
- Ureteral malignancies
 adenocarcinomas, 1371
 others, 1371
 squamous cell cancers, 1371
 UTUC. *See* Upper tract urothelial cancer
- Ureteral obstruction. *See also* Urinary tract
 obstruction
 bilateral. *See* Bilateral ureteral obstruction
 partial, hemodynamic changes with, 1095
 after pediatric renal transplantation, 3535-
 3536, 3536f
 unilateral. *See* Unilateral ureteral obstruction
 ureteral stenting for, 1101
- Ureteral orifice, transurethral resection of, for
 UTUC, 1378, 1380f
- Ureteral pain, patient history of, 2
- Ureteral polyps, with megaureter in pediatric
 patients, 3073
- Ureteral reconstruction, for prune-belly
 syndrome, 3244-3245
- Ureteral reimplantation, laparoscopic and
 robotic, 2257-2260
 complications with, 2259
 conclusions for, 2259-2260
 evaluation for, 2258
 indications for, 2258
 nonrefluxing, 2258, 2259f
 outcomes with, 2259
 refluxing, 2258-2259, 2259f
 technique for, 2258
- Ureteral replacement, for UTUC, 1386-1387,
 1387f
- Ureteral stenting
 for bladder diverticula, 2148
 for ureteral obstruction, 1101
 for ureteral stricture disease, 1129
 for ureterovaginal fistula, 2122
- Ureteral stents and catheters
 biofilm formation on, 134-135
 biomaterials used in, 126-128, 127f
 coatings for, 128
 complications of, 131-132
 design of, 128-129
 historic note on, 126
 indications for, 129-130
 after percutaneous surgery of upper
 urinary tract collecting system, 173-174,
 174f
 technique for, 130-131, 131f
 technology of, 126, 126f
 for ureteral obstruction, 1101
 for ureteral stricture disease, 1129
- Ureteral stricture
 with megaureter in pediatric patients,
 3073
 ureteroscopy for, 143
- Ureteral stricture disease
 autotransplantation for, 1141
 balloon dilation for
 antegrade, 1130
 results with, 1130-1131
 retrograde, 1129-1130, 1130f-1131f
 diagnostic studies of, 1129
 endoureterotomy for, 1131
 antegrade approach to, 1133
 combined retrograde and antegrade
 approach, 1133
 results with, 1133
 retrograde ureteroscopic approach to,
 1131-1133, 1132f
 etiology of, 1128-1129, 1129b
 ileal ureteral substitution
 laparoscopic, 1140-1141
 open, 1139-1140, 1140f
 intervention for
 endourologic, 1129-1133, 1133b
 indications for, 1129
 surgical, 1133-1141, 1133t, 1141b
 intubated ureterotomy for, 1139
 management algorithm for, 1132f
 renal descensus for, 1139
 transureteroureterostomy
 laparoscopic, 1139
 open, 1139
 ureteral stent placement for, 1129
 ureteroneocystostomy for, 1135
 laparoscopic Boari flap with, 1137-1139
 laparoscopic psoas hitch with, 1136
 minimally invasive, 1135, 1135f
 open Boari flap with, 1136-1137, 1138f

- Ureteral stricture disease (*Continued*)
 open psoas hitch with, 1135-1136, 1136f-1137f
 ureteroscopic, 1284
 ureteroureterostomy for, 1133-1135, 1133t
 laparoscopic or robotic approach, 1134-1135
 open approach, 1134, 1134f
 postoperative care, 1135
- Ureteral substitution, ileal. *See* Ileal ureteral substitution
- Ureteral surgery, for genitourinary tuberculosis treatment, 431
- Ureteral tapering, 999
- Ureteral trauma. *See* Ureteral injuries
- Ureteral tumors
 benign
 others, 1371
 papilloma, 1369-1370
 von Brunn nests, 1369-1370
 malignant. *See* Ureteral malignancies
- Ureteral-small bowel anastomoses, in urinary diversion, 2300, 2301f
- Ureterectomy, for UTUC, 1381-1382
 and direct neocystostomy or ureteroneocystostomy with bladder psoas muscle hitch or a Boari flap, 1385-1386, 1387f
 laparoscopic, 1379, 1380f, 1381-1382, 1388
 open, 1378, 1378f, 1381-1382
 open segmental, 1385, 1386f
 robotic, 1388
- Ureteroarterial fistulas, 1158
- Ureterocalicostomy
 for ureteral injury, upper, 1162
 for ureteropelvic junction obstruction
 laparoscopic and robotic-assisted, 1122
 for UPI reconstruction, 1124, 1126f
- Ureteroceles. *See also* Ureteral anomalies
 anatomic description of, 3075-3077, 3076f-3077f
 bladder outlet and, 3084-3085, 3085f
 excision of, and common-sheath reimplantation, 3091-3094, 3092f-3094f
 prenatal, 2879, 2879f
 prolapsed, 3080, 3080f, 3457-3458, 3458f
 transurethral incision for, 3094-3096, 3095f-3096f
 reflux outcomes after, 3096
 voiding dysfunction and, 3097
- Ureterocolonic anastomoses, in urinary diversion, 2296-2297
 Cordonnier and Nesbit techniques, 2297
 Leadbetter and Clarke technique, 2296, 2296f, 2296t
 Pagano technique, 2296t, 2297, 2297f
 Strickler technique, 2296t, 2297, 2297f
 transcolonic technique of Goodwin, 2296-2297, 2297f
- Ureterocystoplasty, 3356-3357, 3357f
- Ureteroenteric anastomotic stricture, 1143b
 evaluation of, 1142
 incidence and etiology of, 1141-1142
 intervention for
 endourologic, 1142-1143, 1143f
 indications for, 1142-1143
- Ureteroenteric fistula, 2132
- Ureterography
 antegrade. *See* Antegrade ureterography
 retrograde. *See* Retrograde ureterography
- Ureteroileal anastomosis, for minimally invasive urinary diversion, 2372-2373, 2372f-2373f
- Ureterointestinal anastomoses for urinary diversion, 2294-2303
 complications of, 2302-2303
 pyelonephritis, 2291t, 2296t, 2303
 stricture, 2302-2303
 urinary fistula, 2296t, 2302
 intestinal antireflux valves, 2300-2301
 intussuscepted ileal valve, 2300-2301, 2302f
 intussuscepted ileocecal valve, 2300, 2302f
 nipple valve, 2301, 2302f
 small bowel anastomoses, 2297-2300
 Bricker anastomosis, 2296t, 2298, 2298f
 Hammock anastomosis, 2300
 Le Duc technique, 2296t, 2299-2300, 2299f
 split-nipple technique, 2299f
 tunneled, 2298-2299, 2299f
 ureteral dipping technique, 2300
 ureteral-small bowel, 2300, 2301f
 Wallace technique, 2296t, 2298, 2298f
 ureterocolonic anastomoses, 2296-2297
 Cordonnier and Nesbit techniques, 2297
 Leadbetter and Clarke technique, 2296, 2296f, 2296t
 Pagano technique, 2296t, 2297, 2297f
 Strickler technique, 2296t, 2297, 2297f
 transcolonic technique of Goodwin, 2296-2297, 2297f
- Ureterolysis, for retroperitoneal fibrosis
 laparoscopic, 1146
 open, 1145-1146, 1146f
- Ureteroneocystostomy. *See also* Ureteral reimplantation
 for ureteral injuries, lower, 1163
 for ureteral stricture disease, 1135
 laparoscopic Boari flap with, 1137-1139
 laparoscopic psoas hitch with, 1136
 minimally invasive, 1135, 1135f
 open Boari flap with, 1136-1137, 1138f
 open psoas hitch with, 1135-1136, 1136f-1137f
 for UTUC, 1385-1386, 1387f
- Ureteropelvic junction (UPI)
 disruption of, with trauma, 3549-3550, 3550f-3551f
 flap reconstruction of, 1122
 Culp-DeWeerd spiral flap, 1123, 1124f
 Foley Y-V plasty, 1122-1123, 1123f
 intubated ureterotomy, 1123-1124, 1126f
 Scardino-Prince vertical flap, 1123, 1125f
 ureterocalicostomy for, 1124, 1126f
 injury of, 1157-1158
 surgical exposure to, 1115, 1116f-1117f
 urine transport and, 993, 994f
- Ureteropelvic junction obstruction (UPJO)
 acquired, 1105
 calicovesicostomy for, laparoscopic, 1122
 congenital, 1104-1105, 1105f
 diagnosis of, 1104
 flap reconstruction for, 1122
 Culp-DeWeerd spiral flap, 1123, 1124f
 Foley Y-V plasty, 1122-1123, 1123f
 intubated ureterotomy, 1123-1124, 1126f
 salvage procedures, 1124-1125
 Scardino-Prince vertical flap, 1123, 1125f
 ureterocalicostomy for, 1124, 1126f
 interventions for
 endourologic management of, 1109, 1114b
 historical notes on, 1114-1115
 indications for, 1107-1108
 management of complications for, 1125
 nephrectomy for, 1109
 operative, 1114-1115
 postoperative care for, 1125
 risk
- Ureteropelvic junction obstruction (UPJO)
 (*Continued*)
 selection of, 1108
 success with, 1108
 intrinsic, 1104-1105
 lower pole, 3057, 3058f
 nephrolithotomy for, percutaneous antegrade endopyelotomy simultaneous with, 1111
 pathogenesis of, 1104-1105, 1105f
 patient presentation and diagnostic studies for, 1105-1107, 1106f-1108f
 in pediatric patients. *See* Pediatric patients, ureteropelvic junction obstruction in
 percutaneous antegrade endopyelotomy for, 1109-1111, 1109f-1110f
 nephrolithotomy simultaneous with, 1111
 percutaneous endopyeloplasty for, 1111
 prenatal, 2878
 pyeloplasty for
 dismembered, 1108, 1116f-1117f
 laparoscopic and robotic intervention, 1115-1120, 1118f-1119f, 1122b
 laparoscopic dismembered tubularized flap, 1122
 open surgery, 1115
 postoperative care and complications, 1120
 with pyelolithotomy, 1122
 results of, 1120-1122, 1121t
 salvage procedures for, 1124-1125
 renal calculi with, 1197-1198
 surgical management of, 1243
 retrograde cautery wire balloon endopyelotomy for, 1113-1114
 retrograde ureteroscopic endopyelotomy for, 1111-1113, 1113f-1114f
 secondary, 3057
 surgical approaches to, 1115-1122
 ureterocalicostomy for, laparoscopic and robotic-assisted, 1122
 ureteroscopy for, 143
 urine transport and, 993, 994f
 vesicoureteral reflux and, 3149-3151, 3150f
- Ureteropelvic surgery, for genitourinary tuberculosis treatment, 431
- Ureteropyeloscopy, UTUC treatment with, 1388-1389
 results of, 1390-1392, 1393t
 technique and instrumentation for, 1389-1390, 1390f-1392f
- Ureterorenoscopy (URS)
 historical overview of, 1235.e2
 morbid obesity and, 1255
 old age and frailty and, 1255-1256
 prior renal surgery and, 1256
 for renal calculi
 in calyceal diverticula, 1244
 in horseshoe kidneys, 1246
 lower pole calculi, 1247-1250, 1247f, 1248t, 1249f
 in renal ectopia, 1246
 stone composition and, 1242-1243, 1242f-1243f, 1243.e1
 stone localization and, 1241-1242
 renal function and, 1254-1255
 solitary kidney and, 1255
 spinal deformity or limb contractures and, 1256
 for staghorn calculi, 1240-1241
 stone burden and
 between 1 and 2 cm, 1239-1240, 1239f
 greater than 2 cm, 1239f, 1240
 up to 1 cm, 1238-1239, 1238b
 uncorrected coagulopathy and, 1256
 for ureteral calculi
 duplicated collecting system and, 1253
 in megaureter, 1253
 outcome of, 1257-1259

- Ureterorenoscopy (URS) (Continued)**
 stone burden and, 1252-1253
 stone composition and, 1253
 stone localization and, 1251-1252, 1252t
 with ureteral stricture or stenosis, 1253-1254
 urinary diversion and, 1256-1257
 urinary tract infection and, 1254
- Ureteroscopic endopyelotomy, retrograde. See Retrograde ureteroscopic endopyelotomy**
- Ureteroscopic endoureterotomy, retrograde, for ureteral stricture disease, 1131-1133, 1132f**
- Ureteroscopy, 152b**
 antimicrobial prophylaxis for, 263-264
 EHL with, 232.e1
 equipment for, 143-150, 143f-144f, 145t, 146f-149f, 147t, 150t
 for genitourinary tuberculosis diagnosis, 427, 428f
 historical overview of, 1235.e2
 indications for, 142-143
 injuries with, 1159-1160
 avulsion, 1167, 1284-1285
 perforation, 1167, 1283-1284
 stricture, 1284
 for intrarenal calculi, 1285
 laser lithotripsy with, 234.e1
 for pediatric stone disease management. *See* Pediatric stone disease, ureteroscopic management of
 pneumatic lithotripsy with, 233.e1
 technique, 150-152, 151b, 151f
 ultrasonic lithotripsy with, 233.e2
 ureter anatomy for, 976-977, 977b, 977.e1f
 for ureteral calculi, 1282-1285
 complications of, 1283-1285
 ureteral access sheath for, 1283
 UTUC treatment with, 1371-1372, 1388-1389
 results of, 1390-1392, 1393t
 technique and instrumentation for, 1389-1390, 1390f-1392f
- Ureterosigmoidostomy**
 for classic bladder exstrophy, 3217
 for continent urinary diversions, 3360-3361
 history of, 2344
 tumor formation and, 3353
- Ureterostomy**
 cutaneous, for megaureter in pediatric patients, 3069-3073, 3069f
 for ectopic ureter, 3096
- Ureterotomy, intubated**
 for ureteral stricture disease, 1139
 for ureteropelvic junction obstruction, 1123-1124, 1126f
- Ureteroureterostomy**
 for ureteral anomalies, 3094, 3095f
 for ureteral injury, 1161, 1162f
 surgical ligation, 1166, 1166f
 upper, 1161-1162, 1162f
 for ureteral stricture disease, 1133-1135, 1133t
 laparoscopic or robotic approach, 1134-1135
 open approach, 1134, 1134f
 postoperative care, 1135
- Ureterovaginal fistula (UVF), 2119-2123, 2123b, 2265-2266**
 diagnosis of, 2120-2121, 2120f-2122f
 etiology of, 2119-2120, 2119b
 evaluation of, 2265
 laparoscopic approaches to
 complications with, 2266
 outcomes with, 2266
 technique for, 2265, 2266f
- Ureterovaginal fistula (UVF) (Continued)**
 management of, 2121-2123, 2123f
 presentation of, 2119-2120
 prevention of, 2120
 robotic repair of
 complications with, 2266
 outcomes with, 2266
 technique for, 2265, 2266f
 surgical indications with, 2265
- Ureterovascular fistula, 2136-2137, 2137b, 2136.e1t**
- Ureterovesical junction (UVJ), 978, 1626-1627, 1628f**
 antireflux mechanism of, 3137-3138, 3138f, 3137.e1t
 embryology of, 3137
 with epispadias, 3221, 3223
 physiology of, 995
 ureteral function relation with, 999-1000, 1000f
- Ureterovesical junction obstruction, prenatal, 2878**
- Ureters**
 bifid, 3097-3098
 quadruple, 3098
 triplication of, 3098
- Urethra**
 α-adrenergic receptors in, 1670-1671, 1671f
 anatomy of, 1632, 1632f
 common to both genders, 1637
 female, 119, 1607-1608, 1608f, 1636-1637, 1636f, 2151, 2152f
 male, 119, 509f-511f, 511-512, 511b, 917, 1635-1636, 1636f, 910.e1-910.e2, 910.e2f-910.e3f
 tone, 1637
 anomalies of, dilated fetal bladder and, 3174
 caruncle of, urethral diverticula differentiated from, 2163, 2163f
 closure of, for classic bladder exstrophy, 3198-3201, 3199f-3200f
 division of, in retropubic radical prostatectomy, 2648-2649, 2648f
 duplication of, 3269-3270, 3269f, 3379-3380, 3380f
 estrogens and, 1673
 female
 in orthotopic urinary diversion, 2352-2353, 2352f
 radical cystectomy and, 2229
 function of
 during filling/storage, 1692
 during voiding, 1692-1693
 in genitourinary tuberculosis, 423
 treatment, 431-432
 hypermobility of, filling/storage failure due to, 1689-1690
 instability of, filling/storage failure due to, 1690
 localization studies, 252
 lymphatics of, 890
 male
 anatomy of, 119, 509f-511f, 511-512, 511b, 917, 1635-1636, 1636f, 910.e1-910.e2, 910.e2f-910.e3f
 ultrasonography of, 80-82, 81f-82f, 511f
 mesh perforation of, in midurethral sling, 2028-2029, 2028f, 2030t, 2033b
 mobility of, Q-tip test for, 1700
 necrosis of, with transurethral vaporization of prostate, 2517.e4
 prolapse of, urethral diverticula differentiated from, 2162-2163
 in prune-belly syndrome, 3237, 3237f-3238f
- Urethra (Continued)**
 reconstructive surgery of, 492, 493f-494f, 907, 917b, 492.e2
 for amyloidosis, 913
 anatomic considerations for, 910.e1-3, 910.e1f-910.e7f, 910.e5, 910.e8b
 for circumcision complications, 915
 corpora cavernosa, 492, 493f-494f
 for curvatures of penis, 939-941, 941b
 for failed hypospadias repair, 915-916
 for female-to-male transsexualism, 945, 945b
 for fistulae of posterior urethra, 938-939, 939b
 for genital trauma, 916.e1-2, 916.e1f, 916.e3b
 for LS, 912-913, 913f
 for meatal stenosis, 914-915
 for paraphimosis, balanitis, and phimosis, 914
 for PFUIs, 932-935, 933f-936f, 937
 principles of, 907-911, 908f-910f, 910b
 for reactive arthritis, 911-912
 for residual abnormality in patients with exstrophy, 915-916
 surgical technique generalities for, 910-911, 911b, 910.e1f
 total penile, 941-945, 943f, 945b
 for urethral diverticulum, 913-914
 for urethral hemangioma process, 911
 for urethral stricture disease, 920-929, 922f-931f, 931b
 for urethrocuteaneous fistula, 913
 for vesicourethral distraction defects, 937-938, 939b
 regeneration of, 487-488, 487f-488f
 stroma of, 1637
 support mechanisms, stress urinary incontinence and, 1757-1758, 1757f
 tone of, in women, 1671
- Urethra catheterization**
 anatomic considerations for, 119
 biofilm formation during, 134-135
 catheters used for
 design of, 121, 121f
 materials and coatings for, 121
 selection of, 120-121, 120t
 complications of, 123-124
 history of, 119
 indications for, 119-120, 120f
 technique for, 121-123, 123f
- Urethra Resistance Factor (URA), 1731**
- Urethral atresia, 3268-3269, 3268f**
- Urethral atrophy, with artificial urinary sphincter, 2181**
- Urethral bleeding, 192-193, 193b-194b**
- Urethral calculi, 1297-1299**
 composition of, 1297-1298
 evaluation of, 1298
 migratory, 1297
 pathogenesis of, 1297-1298
 presentation of, 1298
 primary, 1297-1298
 treatment of, 1299
 within urethral diverticula, 1298, 2154, 2155f
- Urethral cancer**
 female, 889b
 anatomy and pathology of, 885-889, 886f
 diagnosis and staging of, 880t, 886
 distal carcinoma, 887
 epidemiology, etiology, and clinical presentation of, 885
 proximal carcinoma, 887-888
 recurrence after cystectomy, 888-889

Urethral cancer (*Continued*)

- treatment and prognosis of, 886-887, 887f-888t
 - male, 885b
 - carcinoma of bulbomembranous urethra, 882-883, 882f-883f
 - carcinoma of penile urethra, 881-882, 881f-882f
 - evaluation and staging of, 880, 880t, 881f
 - general considerations for, 879
 - pathology of, 880-883, 880f
 - treatment of, 881
 - urethra management after cystectomy, 883-885, 884f
- Urethral caruncle, 2099.e10
- Urethral catheterization and removal, antimicrobial prophylaxis for urologic procedures and, 260-262
- Urethral compression devices, for male urinary incontinence, 2072-2073, 2072f
- in geriatric patients, 2099.e6
- Urethral compressor, 1608
- Urethral devices, for urinary incontinence, 1896, 1897f
- Urethral dilation
- for neuromuscular dysfunction of lower urinary tract, 3282.e2
 - as surgical technique
 - for detrusor underactivity, 1819
 - for urethral stricture disease, 921
- Urethral discharge, patient history of, 7
- Urethral diverticula (UD)
- anatomy and histology of, 2154-2155, 2155f, 2156t
 - classification of, 2163-2164
 - differential diagnosis for, 2160-2163
 - Gartner duct abnormalities, 2162, 2162f
 - periurethral bulking agents, 2163
 - Skene gland abnormalities, 2162, 2162f
 - urethral caruncle, 2163, 2163f
 - urethral mucosal prolapse, 2162-2163
 - vaginal leiomyoma, 2160-2162, 2161f
 - vaginal wall cysts, 2162, 2163f
 - etiology of, 2151-2154, 2152f-2153f
 - evaluation and diagnosis of, 2157-2159
 - cystourethroscopy, 2158, 2158f
 - history and physical examination, 2157-2158, 2157f
 - urine studies, 2158
 - urodynamics, 2158-2159
- female, 2151-2168, 2152f
- imaging of, 2159-2160, 2159f-2161f
- management of, 2168b
- pathophysiology of, 2151-2154, 2152f-2153f
- presentation of, 2155-2157, 2157b
- prevalence of, 2154
- reconstructive surgery for, 913-914
- surgical repair of, 2164-2168
- alternative techniques for, 2165
- urethral calculi within, 1298, 2154, 2155f
- urethral diverticulectomy for
- complications of, 2167, 2167t
 - excision and reconstruction, 2165-2168, 2165b
 - indications for, 2164, 2164f
 - persistence of symptoms following, 2167-2168
 - postoperative care for, 2167
 - preoperative preparation for, 2165
 - procedure for, 2165-2167, 2166f
 - techniques for, 2165-2168, 2165b
- Urethral diverticulectomy, 2164f, 2165-2168, 2165b, 2166f, 2167t
- Urethral erosion, with artificial urinary sphincter, 2181

Urethral hemangioma, reconstructive surgery for, 911

- Urethral injury, 2388-2392
- anterior, 2391-2392, 2391.e1f
 - initial management of, 2391-2392, 2391.e1f
 - delayed reconstruction of
 - anterior, 2392
 - complications with, 2391
 - posterior, 2390-2391, 2390f, 2391.e1f
- distractor
- ED with, 937, 2391
 - PFUs causing. *See* Pelvic fracture urethral injuries
- gunshot wounds, 2381
- pediatric. *See* Pediatric genitourinary trauma, urethral
- pelvic fracture. *See* Pelvic fracture urethral injuries
- with penile fracture, 2379-2380
- posterior, 2388-2390
- complex injuries, 2390-2391
 - diagnosis of, 2388-2389, 2389f, 2388.e1f
 - etiology of, 2388, 2388.e1f
 - immediate open reconstruction for, 2389, 2389f
 - primary realignment for, 2390
 - suprapubic cystostomy, 2389, 2389.e1f
 - urethrography for, 2389, 2389f
- Urethral lengthening
- for bladder neck reconstruction, 3340-3342
 - results with, 3341-3342
 - technique for, 3340-3341, 3341f
- Urethral occlusive devices, for female stress urinary incontinence, 2073
- Urethral polyp, 3456, 3457f
- Urethral pressure, during bladder filling, 1686
- Urethral pressure profile (UPP)
- micturitional, 1732
 - in urodynamic studies, 1722
- Urethral pressure profilometry, urodynamic studies of, 1728-1729, 1729f
- Urethral prolapse, 3456, 3456f
- Urethral reconstruction
- in classic bladder exstrophy, 3203-3209, 3205f-3208f, 3215f
 - in male epispadias, 3222
 - for prune-belly syndrome, 3244, 3244f-3245f
 - pubovaginal sling for, outcomes of, 2003-2004
- Urethral region, natural defenses of, 247
- Urethral slings, stress urinary incontinence and, 1987
- Urethral sphincter
- coordination of, urodynamic studies of, 1733-1734, 1733f-1734f
 - CVA and, 1764
 - deficiency of, intrinsic, 1689-1690
 - quantification of, 1727
 - development of, 1637
 - dynamics of, 3332-3333
 - female, 1636, 1636f
 - male, 1636f
 - mechanisms of, 1755-1756
 - female, 1756, 1756b
 - male, 1755-1756, 1755f, 1756b
 - urinary incontinence and, 1757
 - micturition and, 1663
 - obstruction of, nonrelaxing, 1692-1693
 - orthoptic urinary diversion and, 2350
 - with Parkinson disease, 1767
 - tone of, 1637
- Urethral stricture
- with bipolar transurethral resection of prostate, 2517
 - with holmium laser enucleation of prostate,

Urethral stricture (*Continued*)

- with monopolar transurethral resection of prostate, 2515
 - orthoptic urinary diversion and, 2350
 - after photoselective vaporization of prostate, 2532
 - after transurethral microwave therapy, 2521
- Urethral stricture disease, 916-917, 918f, 920b
- anatomic considerations for, 917
 - diagnosis and evaluation of, 918-920, 919f-920f
 - etiology of, 917-918
 - treatment of, 920, 931b
 - dilation, 921
 - internal urethrotomy, 921-922
 - laser urethrotomy, 922.e1
 - open reconstruction with excision and reanastomosis, 922-929, 922f-931f
- Urethral tumors
- benign, 879
 - FEPs, 879
 - hemangiomas, 879
 - leiomyomas, 879
 - malignant. *See* Urethral cancer
- Urethral valves
- anterior, 3268
 - posterior
 - antenatal management of, 3266-3267
 - bladder dysfunction with, 3264-3266
 - circumcision for, 3261-3262
 - clinical presentation of, 3258-3260
 - delayed presentation of, 3259-3260
 - description of, 3252, 3253f
 - diagnosis of, 3257-3258
 - epidemiology of, 3252-3253
 - initial management of, 3258-3260
 - laboratory studies for, 3258
 - lower urinary tract and, 3253-3254, 3255f-3256f
 - nephroureterectomy, 3262
 - pathophysiology of, 3253-3256, 3254t, 3256b
 - pulmonary hypoplasia with, 3259, 3259f
 - quality of life with, 3267-3268
 - radionuclide renal scan for, 3258
 - renal function prognostic indicators in, 3267
 - surgical intervention for, 3260-3262
 - transplantation in, 3267
 - ultrasonography of, 3257, 3257f
 - upper tract diversion, 3260-3261, 3264f
 - upper urinary tract and, 3254-3255, 3256f
 - urinomas with, 3259, 3259f
 - valve ablation for, 3260, 3261f
 - valve bladder syndrome with, 3265-3266, 3265f
 - vesicostomy for, 3260, 3262f-3263f
 - vesicoureteral reflux and dysplasia, 3256, 3257f
 - vesicoureteral reflux in, 3258f, 3262-3264
 - voiding cystourethrography for, 3257-3258, 3258f
- Urethrectomy
- after cutaneous diversion, 884-885, 884f
 - after orthotopic diversion, 885
- Urethritis. *See also* Nongonococcal urethritis
- in differential diagnosis, 266
 - as STD, 371-373
- Urethrocuteaneous fistula, 2137
- reconstructive surgery for, 913
- Urethrocystoscopy, for benign prostatic hyperplasia, 2470
- Urethrography
- for posterior urethral injury, 2389, 2389f
 - retrograde. *See* Retrograde urethrography
 - for urethral stricture disease, 919-920, 919f-920f

- Urethrolisis**
for mesh complications in pelvic reconstructive surgery, 2046
for voiding dysfunction after pubovaginal sling, 2005-2006, 2006f
- Urethroplasty**
algorithm for, 3404, 3405f
anastomotic, for pediatric urethral trauma, 3556
complications with, 3401
balanitis xerotica obliterans, 3422, 3422f
diverticulum, 3421-3422, 3421f
fistulas, 3419-3420, 3419f
glans dehiscence, 3420-3421, 3420f
glans size, 3419
meatal location and, 3418
meatal stenosis, 3421
modifying risk factors, 3418-3420
neourethral stricture, 3421
reoperation, 3418-3419
risk factors with, 3418
outcomes assessment for, 3417-3418
patch, for pediatric urethral trauma, 3556-3557
for posterior urethral injury, 2391, 2391.e1f
tubularized incised plate
distal, 3404-3408, 3406f-3408f
proximal, 3408-3410, 3409f-3411f
for urethral stricture disease, 922-929, 922f-924f
uroflowmetry, 3417-3418
- Urethrorrectal fistula**, 2132-2135, 2135b
etiology of, 2132-2133, 2133f
management of, 2134-2135, 2135f
presentation of, 2133-2134, 2133f
- Urethrorrhagia**, 3270
- Urethrosocopy**
for posterior urethral injury, 2389
for urethral stricture disease, 919-920, 920f
- Urethrotomy**
internal, for prune-belly syndrome, 3243-3244
for urethral calculi, 1299
for urethral stricture disease, 921-922, 922.e1
- Urethrovaginal fistula**, 2125-2129, 2129b
diagnosis of, 2126-2127, 2126f-2127f
etiology of, 2125
presentation of, 2125, 2125f-2126f
repair of, 2127
adjuvant flaps and procedures in, 2128-2129
operative technique for, 2127-2128, 2128f
- Urge suppression, behavioral training with**, 1886-1887, 1886f
- Urgency, patient history of**, 4t-5t
- Urgency incontinence**, 1802
- Urgency incontinence, patient history of**, 6
- Urgency urinary incontinence (UUI)**
behavioral therapy with urge suppression for, 1886-1887, 1886f
definition of, 1710, 1744, 1744f, 1796, 1797f
estrogens for, 1863-1864
treatment of, 1714-1716
- Uric acid**
in calcium stone formation, 1187
in bladder, 1232
in uric acid stone formation, 1190, 1191f-1192f
- Uric acid stones**, 1190-1193, 1191f-1192f
in gouty diathesis, 1212, 1212b, 1213f
hyperuricosuria, 1192
low urinary volume, 1193
low urine pH, 1190-1192, 1192f
- Uricase**, 1190
- Urinalysis (UA)**
for AKI, 1048, 1049t
for behavioral treatment programs, 1879
for benign prostatic hyperplasia, 2464
for bladder and bowel dysfunction, 3303
chemical examination. *See* Chemical examination of urine
for CKD, 1062
MH diagnostic evaluation with, 187
in pediatric patients, for lower urinary tract dysfunction, 3127
for pelvic floor disorder assessment, 1705
physical examination, 13-14, 13t
rapid screen methods, 251
for RCC, 1335
for renal calculi, pretreatment assessment, 1237
sediment analysis. *See* Sediment analysis
specimen collection for, 12-13, 20-21
for sphincteric urinary incontinence, 2172-2173
for urethral diverticula, 2158
for urinary incontinence, male, 1711
for urinary tract obstruction, 1089-1090
for UTI diagnosis, 250-251
for UTIs, 2938
for vesicovaginal fistula, 2109
- Urinary acidification, urinary tract obstruction and**, 1096
- Urinary ascites, neonatal**, 2891
- Urinary calculi**
in children, medical management of, 1232-1233
microscopic appearance of, 1203f, 1204t
during pregnancy
etiology of, 1287
evaluation of, 1288-1289, 1288f
incidence of, 1287
treatment of, 1289
prevention of, 1222t
side effects of, 1223t
surgical management of, 1260-1287
lithotripters for. *See* Lithotripters
percutaneous nephrolithotomy for. *See* Percutaneous nephrolithotomy
- Urinary catheters, falls and**, 2092
- Urinary continence. *See* Continence**
- Urinary diversion. *See also* Continent urinary diversions**
bladder calculi in, 1294
treatment of, 1296
cutaneous continent. *See* Cutaneous continent
urinary diversion
for detrusor underactivity, 1819
for hypospadias postoperative management, 3416
for lower urinary tract dysfunction, 1795
minimally invasive. *See* Minimally invasive
urinary diversion
for neuromuscular dysfunction of lower urinary tract, 3282.e2
orthoptic. *See* Orthoptic urinary diversion
for posterior urethral valves, 3260-3261, 3264f
for radiation fistula, 2138
in renal transplant candidates, 1073-1074
in robotic-assisted radical cystectomy, 2274, 2276f
for urinary incontinence, in geriatric patients, 2099.e5
urinary incontinence after, injection therapy for, 2068
- Urinary extravasation, nonoperative management of**, 1153
- Urinary fistula**
with anorectal malformation, 3270, 3270f
partial nephrectomy causing, 1432-1433
with ureterointestinal anastomoses in urinary intestinal diversion, 2296t, 2302
- Urinary flow rate, with postvoid residual**, 1730
- Urinary fractionated metanephrines, in evaluation of adrenal masses**, 1574t, 1575
- Urinary free cortisol (UFC) evaluation, in evaluation of adrenal masses**, 1572-1573
- Urinary frequency, patient history of**, 3, 4t-5t
- Urinary hesitancy, patient history of**, 3-4
- Urinary incontinence (UI). *See also* Pelvic floor disorders**
anogenital herpes and, 1783
with benign prostatic hyperplasia, 2455
bladder cell therapies for, 491-492
with brain tumor, 1765
causes of, 1697, 1698b
classification of, 1743-1744
coital, 1711
conservative management of, 1875
adherence to, 1894
assessment for, 1878-1879
behavioral training with urge suppression, 1883, 1886-1887
biofeedback for, 1887-1888, 1887f-1888f
bladder training for, 1886f, 1889-1890
electrical stimulation for, 1888-1889
indications for, 1878
lifestyle modifications, 1892-1894
patient education for, 1883
for pelvic floor dysfunction, 1891-1892
pelvic floor muscle training, 1883-1886
for prevention, 1894-1895
toileting programs for, 1889-1891, 1889t
types of, 1875, 1876f
continuous, 1710, 1744-1745, 1744f
CVA and, 1764
daytime. *See* Bladder and bowel dysfunction
definition of, 1710, 1743-1744, 1744f
diagnosis of, 1698
epidemiology of, 1745-1747
female, 1745-1747
retropubic suspension surgery for. *See* Retropubic suspension surgery for incontinence in women
urethra and, 1636-1637
following pediatric urethral trauma, 3557
general comments on, 1745
in geriatric patients, 2095-2099
absorbent products for, 2099.e6
behavioral therapies for, 2099.e3
clinical evaluation of, 2099
costs of, 2096
established, 2096-2098
history for, 2099.e1
laboratory testing for, 2099.e2
negative impacts of, 2096
pharmacotherapies for, 2099.e3-2099.e4
physical examination for, 2099.e1
PVR assessment, 2099.e1
risk factors of, 2098-2099
surgical therapies for, 2099.e4-2099.e6
transient, 2096
treatment of, 2099
urine containment for, 2099.e6
urodynamic studies for, 2099.e2
voiding diaries, 2099.e1-2099.e2
giggle, 1711

Urinary incontinence (UI) (*Continued*)

- hammock hypothesis of, 1636-1637, 1689-1690, 1757-1758, 1757f
- herpesvirus infection and, 1783
- HRQOL instruments for, 92t-95t, 95
- incidence of, 1746-1747, 1747b
- insensible, 1711
- after laparoscopic radical prostatectomy, 2676, 2677t
- male, 1710, 1711b
 - cause of, 2169-2170, 2170t
 - classification of, 2169-2170
 - epidemiology of, 1750, 1750b
 - evaluation of, 1711-1714
 - first-line investigations for, 1711-1714
 - history for, 1711
 - incidence of, 1750
 - pathophysiology of, 2169-2170
 - physical examination for, 1711
 - prevalence of, 1750
 - remission rates of, 1750
 - risk factors for, 1750
 - sphincteric, 2169-2170, 2170t. *See also* Sphincteric urinary incontinence
 - treatment for, 1714-1717, 1715f-1716f
 - urethral compression devices for, 2072-2073, 2072f
- mechanical devices for, 1895-1896
 - urethral, 1896, 1897f
 - vaginal, 1895-1896, 1895f-1896f
- MetS and, 551-552
- mixed, 1710, 1744-1745, 1744f
 - treatment of, 1716
- nocturnal enuresis, 1710, 1744-1745, 1744f
 - treatment of, 1716
- in nursing home setting, 2098-2099
- pathophysiology of, 1756-1757
 - bladder storage and, 1756
 - sphincteric function, 1757
- patient history of, 5-6
- pelvic organ prolapse and, 1753, 1753b
- physiology of, 1754-1756
- postmicturition leakage or dribble, 1711
 - treatment of, 1717
- postpartum, 1748
 - PFMT for, 1885
- pregnancy and, 1748
- prevalence of
 - in adult women, 1745-1746, 1746b
 - factors influencing reported, 1745b
 - international estimates of, 1746, 1747f
 - population-based, 1746, 1746f
- questionnaires for, 1703t-1704t
- remission of, 1746-1747, 1747b
- after retropubic radical prostatectomy, 2657-2658
- risk factors for, 1747-1749, 1749b
- signs and symptoms of, 1743-1744, 1744t
- social impact of, 1754, 1754b
- societal costs of, 1753-1754, 1754b
- stress. *See* Stress urinary incontinence
- terminology of, 1744-1745, 1744t
- types of, 1710-1711
- ureteral anomalies and, 3080
- after urethral injury, 2391
- urgency, 1710, 1744, 1744f, 1796, 1797f
 - treatment of, 1714-1716
- after urinary diversion, injection therapy for, 2068
- urodynamic studies of, 1743-1744, 1744t

Urinary intestinal diversion

- bowel preparation for, 2281-2284
 - antibiotic, 2283, 2283t
 - diarrhea and pseudomembranous enterocolitis with, 2283-2284
 - mechanical, 2282-2283, 2282t

Urinary intestinal diversion (*Continued*)

- conduit urinary diversion types, 2303-2308
 - colon conduit for, 2306-2307, 2307f-2308f, 2309t
 - ileal conduit for, 2304-2305, 2304f-2306f, 2306t
 - ileal vesicostomy for, 2307
 - jejunal conduit for, 2305-2306, 2306t
 - management of, 2305f, 2307-2308
 - preparation for, 2304
 - intestinal anastomoses for. *See* Intestinal anastomoses in urinary intestinal diversion
 - metabolic complications with, 2309-2314
 - altered sensorium, 2311-2312
 - cancer, 2314
 - drug absorption abnormalities, 2312
 - electrolyte abnormalities, 2309-2311, 2310f, 2310t
 - growth and development, 2312
 - infection, 2313
 - nutritional problems, 2313-2314
 - osteomalacia, 2312
 - stones, 2313
 - neuromechanical aspects of intestinal segments in, 2314-2316
 - motor activity, 2315-2316, 2315f
 - volume-pressure considerations, 2314-2315, 2314f
 - renal deterioration in, 2296t, 2303
 - selection for, 2281
 - surgical anatomy for, 2281, 2281.e1f-2281.e2f
 - of colon for, 2281.e1-2281.e2, 2281.e2f
 - of small bowel for, 2281.e1, 2281.e1f
 - of stomach for, 2281.e1, 2281.e1f
 - ureterointestinal anastomoses for, 2294-2303. *See also* Ureterointestinal anastomoses for urinary diversion
- Urinary lithiasis. *See* Renal calculi
- Urinary markers, for urothelial cancer, 2197-2199, 2198t
- Urinary oxalate, 1174-1175
- Urinary percentage scale, 1800-1802
- Urinary prothrombin fragment 1 (F1), in crystal formation, 1179
- Urinary retention
 - with artificial urinary sphincter, 2181
 - with botulinum toxins, 1862
 - with brain tumor, 1765
 - after CVA, 1763
 - detrusor underactivity and, 1814
 - in geriatric patients, 2099.e7
 - lower urinary tract dysfunction and, 1789
 - after monopolar transurethral resection of prostate, 2515
 - neuromodulation for, 1680
 - after orthoptic urinary diversion, 2366, 2366b
 - postoperative, lower urinary tract dysfunction and, 1789-1790
 - sacral neuromodulation in, putative mechanism of, 1901-1902, 1902f
 - with spinal cord injury, 3294-3295
 - with transurethral incision of prostate, 2526
- Urinary sediment. *See* Sediment analysis
- Urinary sensation scale, 1800
- Urinary sheaths, 2099.e6
- Urinary specimens, collection of, 12-13
- Urinary stones, MetS and, 552-553
- Urinary storage symptoms
 - after monopolar transurethral resection of prostate, 2515
 - after photoselective vaporization of prostate, 2532
- Urinary

Urinary tract

- anaerobes in, 242
 - anatomic and physiologic changes during pregnancy, 294-295, 295t
 - defecation disorders and, 3317, 3318f
 - defects in, in bladder exstrophy, 3189-3191, 3190f
 - dysfunction of, 3331-3332
 - fistulae of. *See* Fistulae
 - functional, 3330-3332
 - active: voiding, 3331
 - passive: storage, 3330-3331
 - imaging of, 26. *See also* specific imaging modalities
 - contrast media in. *See* Contrast media
 - pediatric patient considerations for, 2909
 - radiation management in, 26-27, 27b, 27t-28t
 - lower. *See* Lower urinary tract
 - natural defenses against UTIs, 247-248
 - bladder, 247-248, 248.e1
 - periurethral and urethral region, 247
 - urine, 247
 - trocator injury to, in midurethral sling, 2028
 - upper. *See* Upper urinary tract
- Urinary tract drainage, 119, 134b
- lower
 - anatomic considerations for, 119
 - biofilm formation during, 134-135
 - catheters used for, 120-121, 120t, 121f
 - complications of, 123-124
 - historic note on, 119
 - indications for, 119-120, 120f
 - suprapubic catheterization, 124-126, 125f
 - urethral catheterization technique for, 121-123, 123f
- upper
 - biofilm formation during, 134-135
 - nephrostomy tube, 133-135, 133f
 - percutaneous access for, 153-154
 - after percutaneous surgery, 170-174, 171f-174f, 174b, 181, 171.e1f
 - ureteral stents and catheters, 126-132, 126f-127f, 131f
- Urinary tract infections (UTIs)
- antimicrobial prophylaxis for uncomplicated urologic procedures and, 260-265, 260b, 261t-262t, 264t-265t, 265b
- for lower tract endoscopy, 263
- for open and laparoscopic surgery, 264, 264t
- principles of, 260, 260b, 261t-262t
- for shock wave lithotripsy, 263
- special considerations, 264-265, 265t
- for transurethral resection of prostate and bladder, 263
- for TRUSP biopsy, 262-263
- for upper tract endoscopy, 263
- for urethral catheterization and removal, 260-262, 260b, 261t-262t
- for urodynamics, 262
- antimicrobial therapy for
 - agent selection in, 260, 266-268, 267t, 270, 295-296, 296t
 - antimicrobial formulary for, 255-260, 255t-258t, 259f
 - bacterial resistance to, 254-255
 - duration of, 260
 - principles of, 253-260, 254t-258t, 259f, 260b
 - prophylaxis, 238, 272-273, 272t
 - suppression, 238
- after augmentation cystoplasty, 3352-3353
- bacteremia and, 291-293, 293b
- bacteriuria in elderly, 296
- asymptomatic, 297-299, 299b
- epidemiology, 297, 297f-298f, 297t

Urinary tract infections (UTIs) (Continued)

- laboratory diagnosis, 297-298, 298f
- management of, 299
- pathogenesis, 297, 298f
- screening for, 298-299
- bacteriuria in pregnancy, 293-294, 297b
 - anatomic and physiologic changes and, 294-295, 294f, 295t
 - complications of, 295-296
 - management of, 295-296, 296t
 - pathogenesis, 294
 - renal insufficiency and, 296
- with benign prostatic hyperplasia, 2455, 2471
- bladder infections. *See* Bladder infections
- catheter-associated bacteriuria, 299-300, 300b
 - after catheterization, 123-126
 - clean intermittent catheterization and, 3275-3276
- clinical manifestations, 250-252, 252b
 - diagnosis, 250-252, 251f, 252.e1t
 - symptoms and signs, 250
- definitions, 237-238, 238f-239f, 239b
- Fournier gangrene, 302-303, 303b
- in geriatric patients, 2099.e10-2099.e11
- HIV and, 383
- HRQOL instruments for, 92t-94t
- imaging techniques, 252-253, 253b
 - CT, 253, 276-277
 - indications, 252-253, 253b
 - MRI, 253
 - radionuclide studies, 253
 - ultrasonography, 253, 276-277, 277f
 - voiding cystourethrogram, 253
- incidence and epidemiology, 239-241, 240f, 241b
- kidney infections. *See* Kidney infections
- pathogenesis, 241-249, 250b
 - alterations in host defense mechanisms, 248-249, 249.e1
 - bacterial virulence factors, 242
 - early events in UPEC pathogenesis, 242-243, 242f
 - epithelial cell receptivity, 244-247
 - fastidious organisms, 242
 - natural defenses of urinary tract against, 247-248, 248.e1
 - phase variation of bacterial pili in vivo, 243-244, 244f
 - routes of infection, 241
 - urinary pathogens, 241-242
- in pediatric patient, 3298
 - and acute renal abscess, 2936
 - and anatomic abnormalities, 2931
 - antibiotic treatment, 2942-2945, 2943t-2944t
 - and asymptomatic bacteriuria, 2935-2936
 - bacterial factors, 2928-2930, 2928f
 - and bacterial nephritis, 2936, 2936f
 - and biofilms, 2934-2935, 2935f
 - and bladder and bowel dysfunction, 2931-2932, 2945-2946
 - and circumcision, 2930-2931
 - classification of, 2933-2936, 2934f-2936f, 2936b
 - definition of, 2927
 - diagnosis of, 2936-2942, 2937t, 2939b, 2940t, 2942b
 - evaluation and management of a child with a fever, 2926-2933, 2926b, 2927f-2929f, 2929t, 2930b, 2933b
 - and fecal and perineal bacterial colonization, 2931
 - and funguria, 2947-2948
 - and gender and age, 2930

Urinary tract infections (UTIs) (Continued)

- and genetics, 2930
 - and iatrogenic factors, 2932
 - imaging of, 2939-2942, 2940t, 2942b
 - and immune status, 2932-2933
 - and intracellular bacterial colonies, 2934-2935, 2935f
 - laboratories, 2937-2939, 2939b
 - and long-term sequelae, 2947, 2947b
 - management of infection, 2942-2944, 2943t-2944t, 2947b
 - management of post infection, 2944-2946, 2947b
 - and neurogenic bladder, 2932
 - pathogenesis of, 2927-2928
 - physical examination, 2937
 - and pyonephritis, 2936
 - and race, 2930
 - sequelae of, 2946-2947, 2947b
 - and sexual activity, 2931
 - symptoms of, 2936-2937, 2937t, 2939b
 - ultrasonography of, 2911, 2916-2918
 - and viral cystitis, 2947
 - and VUR, 2931
 - periurethral abscess, 303, 303b
 - after photoselective vaporization of prostate, 2532
 - renal calculi and, 1254
 - in renal transplantation, 3533
 - risk factors, 265b
 - sepsis and, 291-293, 292b-293b
 - septic shock and, 291-293, 293b
 - with spinal cord injury, 1770, 1777
 - management of, 300-301, 302b
 - transient urinary incontinence and, 2096.e1
 - unresolved, 269-270, 270b
 - after ureteral stent placement, 132
 - vesicoureteral reflux and, 3139-3140
 - confirmation of, 3141
 - evaluation of, 3141-3142, 3142f
- Urinary tract injury, during laparoscopic and robotic surgery, 218, 222, 222.e1
- Urinary tract obstruction
- AKI caused by, 1043
 - cation transport and, 1096
 - causes of, 1090b
 - clinical impact of, 1100-1101
 - compensatory renal growth with, 1100-1101
 - congenital. *See* Congenital obstructive uropathy
 - diagnosis of
 - antegrade pyelography for, 1093
 - clinical presentation in, 1089
 - retrograde pyelography for, 1093
 - Whitaker test for, 1093
 - diagnostic imaging for, 1091
 - computed tomography, 1092-1093
 - excretory urography, 1093
 - magnetic resonance urography, 1093
 - nuclear renography, 1091-1092
 - ultrasonography, 1091
 - hemodynamic changes with, 1093-1095
 - bilateral ureteral obstruction, 1094-1095, 1095f
 - glomerular filtration and, 1093-1094
 - partial ureteral obstruction, 1095
 - renal vascular resistance, 1094
 - unilateral ureteral obstruction, 1094, 1094f
 - hydrogen ion transport and, 1096
 - hypertension with, 1100
 - laboratory studies for
 - fractional excretion of sodium, 1090
 - renal function assessment, 1090-1091
 - urinalysis, 1089-1090

Urinary tract obstruction (Continued)

- pain caused by, 1-2
 - pathologic changes with, 1097, 1097f
 - postobstructive diuresis after, 1102
 - prevalence of, 1089
 - renal recovery after, 1101-1102
 - sodium transport and, 1096
 - treatment of, 1101-1102
 - pain management, 1101
 - renal drainage, 1101
 - surgical intervention for, 1102
 - tubular function effects of, 1095-1096
 - tubulointerstitial fibrosis with, 1098-1100, 1099f
 - upper. *See* Upper urinary tract obstruction
 - urinary acidification and, 1096
 - urinary concentration ability with, 1096
 - urine egress from kidney in, 1095
- Urinary tract reconstruction
- in children. *See* Pediatric patients, urinary tract reconstruction in
 - for cloacal exstrophy, 3230-3232
 - modern staged, 3228f-3230f, 3230-3231
 - osteotomy role in, 3231, 3231f
 - single-stage, 3231-3232
- Urinary urgency, with holmium laser enucleation of prostate, 2529
- Urine
- abnormalities, in BPS/IC etiology, 345.e11
 - acidification of, urinary tract obstruction and, 1096
 - analysis of. *See* Urinalysis
 - blood in. *See* Hematuria
 - collection of
 - errors in, 1215-1216, 1215b
 - in UTI diagnosis, 250
 - concentration of, with urinary tract obstruction, 1096
 - crystallization in, 1173-1174
 - culture, for UTI diagnosis, 251-252, 251f
 - egress from kidney, in urinary tract obstruction, 1095
 - natural defenses of, 247
 - pH, low
 - in calcium stone formation, 1188
 - in uric acid stone formation, 1190-1192, 1192f
 - volume of, low, in uric acid stone formation, 1193, 1215
- Urine collection methods, for UTIs, 2937-2938
- Urine containment, for urinary incontinence, in geriatric patients, 2099.e6
- Urine culture
- for infection-related calculi, 1202
 - for UTIs, 2939
- Urine cytology
- endoscopic evaluation and collection of specimen for, 1389-1390
 - MH diagnostic evaluation with, 187
 - for non-muscle-invasive bladder cancer surveillance, 2219-2220
 - for UTUC diagnosis, 1372
 - management guidelines for positive result of, 1396-1398, 1398f
- Urine dipstick tests, for UTIs, 2938
- Urine flow rates, male urinary incontinence and, 1712-1713
- Urine leak, during laparoscopic and robotic surgery, in pediatric patients, 2971-2972
- Urine markers, for bladder cancer, 474
- Urine microscopic examination, for UTIs, 2938-2939
- Urine sediment, crystalluria in, 1202, 1203f

- Urine transport, by ureters
 bladder filling and neurogenic vesical dysfunction effects on, 994-995
 diuresis effects on, 994
 UPI physiology in, 993, 994f
 urinary bolus propulsion in, 993-994, 995f
 UVJ physiology and, 995
- Urinoma
 hematoma compared with, 1153
 with posterior urethral valves, 3259, 3259f
 prenatal, 2874-2875, 2875f
- Urethral stents, 128
- URIs. *See* Upper respiratory infections
- Urobilinogen testing, urinary, 19-20
- Urocutaneous fistula, 2137
- Urodynamic stress incontinence (USI), 1714
 detection of, 1804-1805
 diagnosis of, 1918
- Urodynamic studies (UDS)
 of acute urinary retention, 2457-2458, 2458f
 ambulatory, 1737
 clinical utility of, 1737-1738
 for detrusor underactivity, 1737
 for overactive bladder evaluation, 1805
 analysis and interpretation in, 1725
 antimicrobial prophylaxis for, 262
 of bladder diverticula, 2143-2144
 clinical applications of, evidence-based review, 1738-1739
 in lower urinary tract symptoms, 1740-1741
 in neurogenic lower urinary tract dysfunction, 1741-1742
 in stress incontinence in women, 1739-1740
 in clinical practice, 1718-1719, 1719b
 components of, 1720-1722
 conduction of, 1720
 cystometrography in, 1722, 1724f
 definition of, 1718
 of detrusor underactivity, 1807, 1808f
 electromyography in, 1722, 1724-1725
 equipment for, 1722-1725
 eyeball, 1706
 of filling/storage phase, 1725-1729
 detrusor overactivity and impaired compliance, 1725-1727, 1725f-1726f
 leak point pressures, 1727-1728, 1727f-1728f
 normal, 1725, 1725f
 occult stress incontinence, 1728
 stress-induced detrusor overactivity, 1728, 1728f
 urethral pressure profilometry, 1728-1729, 1729f
 guidelines for, 1718
 for injection therapy for stress urinary incontinence, 2050-2051
 key points of, 1707b
 for lower urinary tract dysfunction, 1794
 for male urinary incontinence, 1708
 of MS, 1769
 multichannel, 1706, 1730f
 neurologic injury and, 1773-1775
 of overactive bladder, 1804-1805, 1805f
 Parkinson disease and, 1767
 in pediatric patients
 ambulatory, 3131-3133, 3132f
 conventional fill, 3130-3131, 3132f
 for lower urinary tract dysfunction, 3128-3133
 natural fill, 3131, 3132f
 for pelvic floor disorders assessment, 1706-1707
 postvoid residual in, 1722
 preparation for, 1720, 1721b-1722b
 pressure-flow studies in, 1722
- Urodynamic studies (UDS) (Continued)
 in prostatitis evaluation, 315
 after radical pelvic surgery, 1782
 reproducibility of, 1707
 room for, 1720
 rules for, 1720
 signal transmission and transducers for, 1723-1724
 of sphincter urinary incontinence, 2173
 terminology for, 1721b-1722b
 of urethral diverticula, 2158-2159
 urethral pressure profile in, 1722
 of urinary incontinence, 1743-1744, 1744t
 in geriatric patients, 2099.e2
 for urinary tract reconstruction in pediatric patients, 3332
 uroflowmetry in, 1722, 1723f, 1724
 video. *See* Videourodynamics
 of voiding dysfunction, functional classification and, 1693, 1693b, 1719-1720, 1720b
 of voiding/emptying phase, 1729-1730
 bladder outlet obstruction in men, 1731-1732, 1732f
 bladder outlet obstruction in women, 1732-1733
 normal, 1729-1730, 1729f-1730f
 sphincter coordination, 1733-1734, 1733f-1734f
 voiding pressure-flow studies, 1730-1731, 1731f
- Urodynamic systems, 1722-1723
- UroEDIC study. *See* Epidemiology of Diabetes Interventions and Complications study
- Uroenteric fistulae, 2129-2135
 pyeloenteric, 2132, 2132f
 ureteroenteric, 2132
 urethrorectal, 2132-2135. *See also* Urethrorectal fistula
 vesicoenteric, 2129-2132. *See also* Vesicoenteric fistula
- Uroflow patterns, in pediatric patients, 3128-3130, 3129f-3130f
- Uroflowmetry
 for benign prostatic hyperplasia, 2468-2469
 for bladder and bowel dysfunction, 3303-3304
 for hypospadias, 3417-3418
 patterns for, 3303, 3304f
 in pediatric patients, 3128, 3128f
 electromyography during, 3130
 in urodynamic studies, 1722, 1723f, 1724
 for vesicoureteral reflux, 3143
- Urogenesis theory, 2199-2200
- Urogenital hiatus, 1603, 1615, 1617f, 1940f, 1941
- Urogenital sinus, 2833, 2834f-2835f
 abnormalities of
 classification of, 3498-3504, 3499f-3500f
 evaluation of, 3498-3500
 history and physical examination for, 3500-3501
 radiographic and endoscopic evaluation of, 3501-3503, 3502f-3503f
 surgical reconstruction of. *See* Reconstructive surgery, for disorders of sex development and urogenital sinus
- Urogenital tract. *See* Genitourinary tract
- Urogenital triangle, 1939-1941, 1940f
 female, 1603
 male, 1612f, 1619f, 1625f, 1629-1630, 1629f
- Urography
 CT. *See* CT urogram
 diuretic. *See* Diuretic urography
 excretory. *See* Excretory urography
 intravenous. *See* Intravenous urography
- Urography (Continued)
 IVUI. *See* Intravenous urography
 magnetic resonance. *See* Magnetic resonance urography
 multidetector, computed tomography. *See* Multidetector computed tomography urography
- Urogynecologic fistulae, 2104-2129
 ureterovaginal, 2119-2123. *See also* Ureterovaginal fistula
 urethrovaginal, 2125-2129. *See also* Urethrovaginal fistula
 vesicouterine, 2123-2124. *See also* Vesicouterine fistula
 vesicovaginal, 2104-2119. *See also* Vesicovaginal fistula
- Urolithiasis
 CT of, 41-43, 44f
 lithotripsy for. *See* Lithotripsy
 ureteroscopy for, 142
- Urologic evaluation of child
 chief complaint and history of present illness, 2893-2899, 2896f, 2899b, 2898.e1t-2898.e2t
 abdominal complaints, 2893-2894, 2894t
 ambiguous genitalia, 2898, 2898.e1t-2898.e2t
 antenatal hydronephrosis, 2898-2899
 congenital anomalies in neonates, 2899
 female genital symptoms, 2895, 2896f
 hematuria, 2897-2898
 male penile or urethral symptoms, 2895
 renal trauma, 2898
 scrotal symptoms, 2894-2895
 sexual abuse, 2895-2896
 urinary tract infection, 2897
 voiding symptoms, 2896-2897
 examination, 2900-2904, 2900t, 2901f, 2903f, 2904b, 2898.e1t-2898.e2t
 laboratory evaluation, 2904, 2907b
 medications and allergies, 2899-2900, 2900b
 office surgical procedures, 2907-2908, 2907f, 2908b
 past medical and surgical history, 2899, 2900b, 2900t, 2898.e1t-2898.e2t
 radiographic evaluation, 2904-2907, 2905f-2906f, 2907b
 summary of, 2908
 urodynamic evaluation and biofeedback training, 2907, 2908b
- Urological concerns of women, and female sexual function, 755
- UroLume stent, for urethral stricture disease, 922
- Uromodulin. *See* Tamm-Horsfall mucoprotein
- Uropathogenic *E. coli* (UPEC), 241
 pathogenesis, early events in, 242-243, 242f
 persistence, in bladder, 246-247, 246f
- Uroplakins, of bladder urothelium, 1632-1633
- Uropontin, in crystal formation, 1179
- Uroselectivity, 1837
- Urothelial cancer, 2185-2201
 angiolymphatic invasion of, 2192
 complementary medicine treatments for, 2199-2200
 CT of, 46
 detection of, 2197, 2199b
 direct extension of, 2193
 dissemination of, 2192-2193
 epidemiology of, 2185, 2186b, 2186f
 demographic differences of, 2185-2186
 global burden of, 2186
 mortality with, 2186
 etiology of, 2186-2188
 external risk factors in, 2187-2188, 2188b
 genetic factors, 2186-2187

- Urothelial cancer (Continued)**
 histologic variants of, 2200-2201
 clear cell, 2200-2201, 2201f
 glandular or adenocarcinoma
 differentiation, 2201, 2201f
 micropapillary, 2200, 2200f
 nested variant, 2200, 2201f
 plasmacytoid tumor, 2201
 histology of, 2188-2190, 2189t-2190t, 2190f
 molecular biology of, 2193-2199, 2194f,
 2194t-2195t
 MRI for, 56, 57f
 origin of, 2192-2193
 pagetoid spread of, 2192, 2193f
 pathology of, 2188-2190, 2189b, 2189t
 precursor lesions to, 2188
 prevention of, 2199-2200, 2200b
 primary, 2192
 prognostic factors for, 2193
 of prostate, 2599-2600
 recurrence of, 2192-2193, 2229
 staging of, 2190-2192, 2191t, 2192b
 upper tract. *See* Upper tract urothelial cancer
 urine markers for, 2197-2199, 2198t
- Urothelial cell carcinoma, genomic alterations**
 in, 473-474
- Urothelium**
 of bladder, 1632-1633, 1633f
 asymmetrical unit membrane, 1632-1633,
 1633f
 barrier function of, 1638-1639, 1638f
 genetic alterations in, 472-474
 glycosaminoglycan layer of, 1639
 hinge region of, 1632-1633, 1633f
 ion transport of, 1639
 permeability of, 1632, 1638-1639, 1638f
 physiology of, 1637-1640
 plaques of, 1632-1633
 sensor-transducer function of, 1639-1640
 suburothelial interstitial cells, 1640, 1640f
 umbrella cells of, 1632, 1632f, 1638
 idiopathic OAB and, 1674
 of upper urinary tract
 abnormal, 1369-1371
 normal, 1369, 1369f-1370f
 of ureters, contractile activity and, 986
- Urothelium-derived inhibitory factors, 1640**
- Urotherapy, for bladder and bowel dysfunction,**
 3306
- Urovascular fistulae, 2135-2137**
 pyelovascular, 2135-2136
 renovascular, 2135-2136
 ureterovascular, 2136-2137, 2136.e1t
- URS. *See* Ureterorenoscopy**
- USI. *See* Urodynamic stress incontinence**
- Uterine artery, 1601, 1604f, 1605**
- Uterine body, anatomy of, 1605**
- Uterine prolapse, 1943, 1976**
 exstrophy-epispadias complex and, 3219
 hysteropexy
 for abdominal, 1978
 for vaginal, 1978
 transvaginal hysterectomy for, 1976
 uterine preservation and, 1977-1978
- Uterine RMS, in pediatric patients, 3590**
- Uterosacral fold, 1599, 1599f**
- Uterosacral ligament, 1600, 1602f**
 defects with, 1943
 surgical anatomy of, 1962-1965, 1962f
- Uterosacral vault suspension, for apical vaginal
 prolapse repair, 1961-1965**
 abdominal approach to, 1964, 1966f
 high suspension, 1962-1964, 1963f-1965f
 results of, 1957t, 1964-1965
- Uterus, 750.e4**
 anatomy of, 1605-1607
 imaging of, 1609, 1609f
- UTIs. *See* Urinary tract infections**
- UTUC. *See* Upper tract urothelial cancer**
- UII. *See* Urgency urinary incontinence**
- UUO. *See* Unilateral ureteral obstruction**
- Uventa stents, 127**
- UIVF. *See* Ureterovaginal fistula**
- UVJ. *See* Ureterovesical junction**
- V**
- Vaccination**
 for GU cancers, 454, 454f
 genitourinary tumors, 456
 kidney cancer, 454-455
 prostate cancer, 455-456, 456f
 for pediatric patients undergoing surgery,
 2953-2954
- Vacuum therapy, and PD, 738**
- Vagina**
 anatomy of, 1607, 750.e3-750.e4
 disorders of, 3459-3466
 associated findings, 3462
 hymenal skin tags, 3459, 3459f
 imperforate hymen, 3459, 3459f
 transverse vaginal septum, 3459-3460,
 3460f
 vaginal agenesis, 3461-3462, 3461f
 vaginal atresia, 3460-3461
 vertical fusion, 3459-3465
 embryology of, 3453-3454, 3454f
 leiomyoma of, urethral diverticula
 differentiated from, 2160-2162, 2161f
 mesh complications in pelvic reconstructive
 surgery in, 2042
 reconstruction of, 494, 495f
- Vaginal agenesis, 3461-3462, 3461f**
- Vaginal atresia, 3460-3461**
- Vaginal cells, receptivity of, in UTIs, 244-245, 245f**
- Vaginal cones**
 for pelvic floor muscle training, 1885-1886,
 1885f
 for urinary incontinence, in geriatric patient,
 2099.e3
- Vaginal devices, for urinary incontinence,**
 1895-1896, 1895f-1896f
- Vaginal hysteropexy, 1978**
- Vaginal kits, for pelvic organ prolapse repair,**
 1982-1984, 1983f
 current controversy over, 1984-1986
- Vaginal paravaginal repair, for pelvic organ
 prolapse, 1950t, 1953, 1954f-1955f**
- Vaginal prolapse**
 repair of, vaginal kits for, 1982-1984, 1983f
 after retropubic suspension surgery,
 1933-1934
- Vaginal pull-down maneuver, 3454-3455, 3455f**
- Vaginal reflux, pediatric, 3310**
- Vaginal replacement surgery, 3462-3465**
 intestinal neovagina creation for, 3463-3465,
 3463f-3464f
 skin neovagina creation for, 3462-3463, 3463f
- Vaginal RMS, in pediatric patients, 3589-3590,
 3590f**
- Vaginal vault prolapse, 1943**
- Vaginal wall cysts, urethral diverticula
 differentiated from, 2162, 2163f**
- Vaginitis, 381-382, 381t**
 in differential diagnosis, 266
- Vagino-obturator shelf (VOS) procedure,**
 1920-1921, 1920f
 results with, 1929
 suspension configuration in, 1921
- Vagino-obturator shelf (VOS) procedure
 (Continued)**
 technique for, 1929, 1930f
 tissue approximation in, 1921
 urethral elevation in, 1921
- Vaginoplasty, initial management, timing, and
 principles for, 3504-3507, 3505f, 3507f**
- Validity, of HRQOL instruments, 96-97, 97t**
- Valsalva leak point pressure (VLPP), 1727,
 1758**
- Valsalva maneuver, 2079-2080**
- Value of care, 87**
 maximization of, 98
- Valve bladder syndrome, 3265-3266, 3265f**
- Vancomycin**
 preoperative prophylaxis with, 106t-107t,
 2959t
 prophylaxis with, for uncomplicated urologic
 procedures, 261t-262t
 for UTIs, 255t-258t
- Vanilloids, to facilitate bladder filling and urine
 storage, 1863, 1863.e1**
- Vanillylmandelic acid (VMA) testing, in
 pheochromocytoma diagnostic tests,
 1549, 1549f**
- Vanishing testis, 3439-3441, 3440f**
- Vardenafil (Levitra)
 to facilitate bladder filling and urine storage,
 1839t, 1856**
 for ureteral relaxation, 1001
- Varicocele, 568, 578, 3393-3397**
 associated pathologic processes, 3394
 diagnosis and classification of, 3393-3394,
 3394t
 epidemiology of, 3393
 hormonal function, 3395
 intratesticular, 3395
 pathogenesis of, 3393
 sclerotherapy or embolotherapy for, 3397
 semen quality in, 3395
 surgical repair of, 3395, 3396t
 testicular histology, 3394-3395
 treatment for, 3395-3397
 varicolectomy for
 retroperitoneal or laparoscopic, 3396,
 3396f
 subinguinal or inguinal microsurgical,
 3395-3396
- Varicolectomy, 956**
 complications of
 hydrocele, 609-610
 testicular artery injury, 610
 varicocele recurrence, 610
 laparoscopic, 605, 3396, 3396f
 microsurgical inguinal and subinguinal
 operations for, 605-609, 3395-3396
 anesthesia for, 606
 approaches for, 606-607, 606f-607f, 606t
 delivery of testis, 608-609, 609f
 dissection of cord, 607-608, 607f-608f
 radiographic occlusion techniques for, 609
 results for, 610
 retroperitoneal operations for, 604-605, 604f,
 3396, 3396f
 scrotal operations for, 604
 techniques of, 604t
- Vas deferens**
 anatomy of, 505b
 arterial supply, 504
 blood supply, 581, 581b
 gross structure, 503-504, 504f
 lymphatic supply, 504
 microanatomic architecture, 504
 nerve supply, 504

Vena caval thrombectomy (Continued)

- surgical, 946, 947b, 947f
 venous drainage, 504
 anomalies of, 3397
 dissection of, in laparoscopic radical
 prostatectomy, 2670, 2670f-2671f
 in genitourinary tuberculosis, 423
 imaging of
 transrectal ultrasound, 505, 573.e1
 vasogram, 504f, 505
 physiology of, 535b
 absorption and secretion functions,
 533-534
 cytoarchitecture, 533
 gross architecture, 533
 sperm transport and storage functions,
 533
 surgery of
 anatomical considerations for, 946, 947b,
 947f
 preoperative preparation for, 946-947
 vasectomy. *See* Vasectomy
 Vasal artery. *See* Deferential artery
 Vascular changes, with aging, 2084
 Vascular conditions, hematuria related to, 194
 Vascular endothelial growth factor (VEGF)
 inhibitors of
 for metastatic bladder cancer, 2240
 for metastatic RCC, 1502-1503, 1507-1514,
 1508f-1512f, 1509t-1511t, 1513t, 1517
 in RCC, 1325t, 1326-1327
 Vascular evaluation, in ED, 650-653, 650t
 Vascular injury
 during laparoscopic and robotic surgery, 216,
 218, 218b, 221-222
 in pediatric patients, 2971
 laparoscopic kidney surgery causing, 1481
 during radical nephrectomy, 1427-1428
 Vascular malformations, 3384
 Vascular reconstruction, RPLND with, 822-823
 Vascular surgery, ureteral injuries with, 1158
 Vascular transposition, for laparoscopic
 pyeloplasty, 1118
 Vascularization, for regenerative medicine, 486,
 486.e3
 Vasculature
 adrenal, 1519-1522, 1522f-1523f, 1529, 1578,
 1578f, 1528.e1f
 of bladder, 1619f, 1621f, 1627-1628,
 1633-1634, 1634f
 of epididymis, 503
 of pelvis
 female, 1601, 1604f
 male, 1615-1618, 1618t, 1620f-1621f
 of penis, 513f, 910.e3-5, 910.e4f-910.e5f
 of prostate, 507-508, 507f
 renal, 971-973, 972f-973f, 973b,
 971.e1f-971.e2f
 hormonal control of, 1009-1011, 1009b,
 1010f, 1011b
 of scrotum, 514, 946, 947b
 of seminal vesicles and ejaculatory ducts,
 505
 of testis, 498-500, 500f-501f, 519
 of ureters, 976, 976.e1f
 of urethra, 1608, 1608f
 of uterus, 1605
 of vagina, 1607
 of vas deferens, 504
 Vasectomy, 568, 948, 953b
 anesthetic techniques for, 948
 antisperm antibodies after, 953
 complications of, 952
 conventional technique for, 948-949
 microscopic reversal of, 951-952
 minimally invasive, 949-950, 950f-951f
 no-scalpel technique for, 949, 950f
 postoperative care and follow-up semen
 analysis for, 952
 prostate cancer and, 2551
 systemic disease associated with, 952-953
 vasal obstruction and male sterilization
 methods used in, 950-951
 Vasoactive drugs, for PE, 700.e1
 Vasoactive intestinal peptide (VIP), in ED, 627
 Vasoactive intestinal polypeptide, 665
 Vasoconstrictor hypertensive model, 1029, 1029f
 Vasoconstrictors, renal vascular tone control by,
 1009-1010, 1009b, 1010f
 Vasodilators, renal vascular tone control by,
 1009b, 1010-1011
 Vasoepididymostomy
 indications for, 595
 long term follow up for, 599
 techniques for
 classic end-to-side technique, 596-597,
 597f
 compromised vasal length, 598, 599f
 and microsurgical end-to-side, 585f,
 595-596, 595f-596f, 595t
 two-stitch longitudinal intussusception
 technique, 597-598, 598f
 Vasogram, of vas deferens, 504f, 505
 Vasography
 complications of
 hematoma, 587
 injury to vasal blood supply, 587
 sperm granuloma, 587
 stricture, 587
 fine-needle, 586-587
 indications for, 584-587, 587b
 of male, 572
 technique of and interpretation of findings,
 584-586, 584f-586f
 transrectal and seminal vesiculography, 587
 Vasopressin, renal vascular tone control by, 1010
 Vasovasostomy, 587-594
 and anastomosis in convoluted vas, 588f-
 589f, 591-593, 593f
 anastomotic techniques for, 590-591
 anesthesia for, 588
 crossed, 593
 technique for, 593, 593f
 long-term follow-up evaluation for, 594
 and microsurgical multilayer microdot
 method, 591, 591f-593f
 and multiple vasal obstructions, 590
 postoperative complications of, 594
 postoperative management for, 594
 preoperative evaluation for, 587-588
 laboratory tests, 587-588
 physical examination, 587
 preparation of vasa, 588-589, 588f-589f
 set-up for, 591
 surgical approaches for, 588
 inguinal incision, 588
 scrotal incision, 588, 588f
 and transposition of testis, 593-594, 594f
 and varicocele, 590
 and vasoepididymostomy, 589-590, 590t
 wound closure, 594
 VCUG. *See* Voiding cystourethrogram
 VDR. *See* Vitamin D receptor
 VEGF. *See* Vascular endothelial growth factor
 Velp. *See* Vinblastine-ifosfamide-cisplatin
 Vena caval replacement, 1444, 1444f
 Vena caval thrombectomy, 1433-1445, 1445b
 bypass techniques for, 1441-1443, 1442f-
 1443f, 1442.e1f, 1443.e1f
 IVC filtration and permanent interruption for
 budding thrombus, 1444, 1444f
 level I, right-sided tumor technique,
 1433-1435, 1437f, 1433.e1f
 level II, left-sided tumor technique,
 1435-1436, 1438f, 1435.e1f
 level III-IV
 combined intra-abdominal and
 intrathoracic approach, 1441, 1441f,
 1441.e1f
 intra-abdominal approach technique,
 1436-1440, 1438f-1441f, 1439.e1f
 patching, replacing, and interrupting of IVC
 in, 1443-1444, 1443f-1444f
 perioperative complications of, 1444-1445
 preoperative considerations for, 1433, 1434f,
 1435t, 1436f
 Venereal warts. *See* Condylomata acuminata
 Venography, 572, 572.e1
 Venous flow, pneumoperitoneum effects on, 212
 Venous reconstruction, in ED, 667
 Venous supply, to male pelvis, 1617-1618, 1621f
 Venous system
 of retroperitoneum, 775f, 776-777, 776.e1f,
 777.e1f-777.e2f
 surgical anatomy of, 2641, 2642f
 Venous thromboembolism (VTE)
 after percutaneous access to upper urinary
 tract collecting system, 181
 prophylaxis for
 for laparoscopic and robotic surgery, 223
 in pediatric patients, 2959-2960
 preoperative, 108-109, 108t-109t, 109b, 197
 after RPLND, 834-835
 Venous tumor thrombus
 laparoscopic radical nephrectomy for, 1470
 in RCC, 1328, 1330-1331, 1334, 1336-1340,
 1355-1358, 1356b, 1356f-1357f, 1470
 surgery for. *See* Vena caval thrombectomy
 Venovenous bypass (VVB), for vena caval
 thrombectomy, 1441-1442, 1442f,
 1442.e1f
 Ventral corporal lengthening, 3404, 3404f
 Verapamil, for PD, 735
 Veress needle
 for achieving transperitoneal access and
 establishing pneumoperitoneum, 200
 in pediatric patients, 2967-2968, 2968b
 complications related to, 216
 Verrucous carcinoma (Buschke-Lowenstein tumor)
 as neoplastic condition, 412, 412f
 of penis, 846.e1f, 846.e4, 846.e4b
 Vertebrae, in retroperitoneum, 769, 769.e1f
 Vertebral column abnormalities, with cloacal
 exstrophy, 3226-3227, 3227f
 Vertical fusion disorders, 3459-3465
 Verumontanum, 509, 510f-511f
 Vesical pain, patient history of, 2
 Vesicobullous disorders, 397, 398b
 bullous pemphigoid, 398, 399f
 dermatitis herpetiformis, 398-399
 Hailey-Hailey disease, 399-400, 400f
 linear IgA bullous dermatosis, 398-

- Vesicourachal diverticulum, 3177
- Vesicoureteral reflux (VUR), 248
- acquired scar
 - age and, 3148
 - bacterial virulence in, 3149
 - congenital defects *versus*, 3146-3147
 - host susceptibility and response, 3149
 - hypertension and, 3149
 - papillary anatomy in, 3148, 3148f-3149f
 - pathophysiology of, 3148-3149
 - renal failure and, 3149
 - renal growth and, 3149
 - somatic growth and, 3149
 - age and, 3135, 3135t
 - antibiotics for, 3156-3157
 - associated anomalies and conditions, 3149-3153
 - bladder diverticula, 3151, 3151.e1f
 - megacystis-megaureter association, 3152
 - renal anomalies and, 3151-3152
 - ureteral duplication, 3151, 3151.e1f
 - ureteropelvic junction obstruction with, 3149-3151, 3150f
 - bladder cell therapies for, 491-492
 - cause of, 3138-3139
 - CKD in, 1059
 - clinical correlates of, 3139, 3140f
 - complications of ureteral reimplantation for, 3165-3166
 - contralateral reflux, 3165-3166
 - obstruction, 3165-3166
 - persistent reflux, 3165-3166
 - cortical defects in, 3146-3149
 - microorganisms in, 3147-3148
 - renal dysmorphism, 3147, 3147f, 3147t, 3147.e1f
 - defecation disorders and, 3317, 3317.e1f
 - demographics of, 3135, 3135b
 - diagnosis of, 3141-3142
 - endoscopic correction of, 3154, 3167-3169
 - autologous materials for, 3169-3170
 - calcium hydroxyapatite, 3169
 - chondrocytes, 3169.e1
 - cross-linked bovine collagen, 3169
 - cross-trigonal reimplant, 3171
 - dextranomer/hyaluronic copolymer, 3169
 - follow-up for, 3168
 - injection technique, 3167-3168, 3167f-3168f
 - materials used for, 3168-3169, 3168b
 - nonautologous materials, 3169
 - polyacrylate polyalcohol copolymer, 3169.e1
 - polydimethylsiloxane, 3169
 - polytetrafluoroethylene paste for, 3169
 - recurrence after, 3169-3170
 - with epispadias, 3221, 3223
 - evaluation of, 3141-3142
 - extravesical procedures for, 3163-3165, 3164f
 - extravesical tunnel creation, 3163-3165
 - ureteral approach, 3163
 - fetal reflux and, 3135
 - gender of, 3135
 - genetics of, 3136-3137
 - grading of, 3140-3141, 3140f-3141f, 3140t
 - historical perspective on, 3134-3135
 - infrahiatal tunnels for, 3158-3163
 - Cohen cross-trigonal technique, 3158-3163, 3162f
 - Glenn-Anderson technique, 3158, 3162f
 - inheritance and, 3135-3137
 - intravesical procedures for, 3158
 - ureter approach, 3158
 - ureter mobilization, 3158
- Vesicoureteral reflux (VUR) (*Continued*)
- landmark studies of, 3155-3156
 - Birmingham Reflux Study, 3155
 - International Reflux Study in Children, 3155
 - prospective studies, 3155
 - laparoscopic surgery for, 3170-3171
 - detrusorraphy, 3170
 - extravesical reimplant, 3170
 - Gil-Vernet procedure for, 3170
 - robotic approach to, 3170-3171
 - trocarr placement, 3170
 - tunnel creation, 3170
 - ureteral dissection, 3170
 - lower urinary tract assessment for, 3142-3145
 - American Academy of Pediatrics guidelines for, 3144, 3144t
 - controversies with, 3143
 - cystographic imaging, 3142-3143, 3143f
 - cystoscopy for, 3144-3145
 - National Institutes for Clinical Excellence guidelines for, 3144
 - top-down approach to, 3143-3144
 - uroflowmetry for, 3143
 - lower urinary tract infection and, 3139-3140
 - confirmation of, 3141
 - evaluation of, 3141-3142, 3142f
 - management of, 2946
 - principles of, 3153-3154, 3153.e1t
 - randomized intervention for, 3155-3156
 - watchful waiting for, 3154-3155
 - natural history of, 3153-3157
 - neural tube defects and, early intervention for, 3276
 - in neuromuscular dysfunction of lower urinary tract, 3283-3284, 3283f
 - pediatric imaging of
 - cystourethrography, 2916-2918
 - radionuclide cystography, 2922-2923, 2925f
 - ultrasonography, 2911-2913
 - in pediatric patients, 3298-3299
 - with posterior urethral valves, 3258f, 3262-3264
 - pregnancy and, 3152-3153
 - prevalence of, 3135
 - primary, 3138
 - race and, 3135
 - redo reimplantation for, 3166-3167, 3167f
 - after renal transplantation, 3535, 3535f
 - resolution of
 - by age, 3153, 3154f
 - by grade, 3153
 - spontaneous, 3153
 - secondary, 3138-3139
 - sibling reflux and, 3135-3136
 - suprahiatal tunnels for, 3158
 - Paquin technique, 3158
 - Politano-Leadbetter technique, 3158
 - technique for, 3158, 3159f-3161f
 - ureteral anastomosis in, 3158
 - surgical management of, 3157
 - cystoscopy for, 3157
 - incision for, 3157
 - positioning for, 3157
 - postoperative evaluation for, 3165
 - principles of, 3157
 - upper urinary tract assessment for, 3145-3146
 - rationale for, 3145
 - renal scintigraphy, 3146, 3146f
 - renal sonography, 3145-3146
 - ureteral function relation with, 999-1000, 1000f
 - ureteropelvic junction obstruction with, 1105
- Vesicoureteral reflux (VUR) (*Continued*)
- urinary tract dysfunction with, 1776-1777 and UTIs, 2931
 - Valsalva maneuver and, 2080
 - Vesicoureteral reflux and dysplasia (VURD), posterior urethral valves and, 3254t, 3256, 3257f
 - Vesicourethral distraction defects, 937-938, 939b
 - Vesicourethrectomy fistula, 938-939, 939b
 - Vesicouterine fistula, 2123-2124, 2124b
 - diagnosis of, 2123, 2124f
 - etiology of, 2123-2124
 - management of, 2123-2124
 - presentation of, 2123-2124
 - Vesicouterine pouch, 1599, 1599f
 - Vesicovaginal fistula (VVF), 2104-2119, 2104f, 2119b, 2265-2266
 - abdominal techniques for, 2113-2114
 - suprapubic intraperitoneal or extraperitoneal, 2113-2114, 2116f-2117f
 - transvesical, 2114
 - vaginal *versus*, 2111-2112, 2111t, 2112.e1b
 - adjuvant procedures in repair of, 2116-2117
 - greater omentum, 2116-2117, 2118f
 - Martius flap, 2116, 2118f
 - other flap and graft techniques, 2117
 - peritoneal flap, 2116, 2118f
 - clinical features of, 2107-2109
 - cystoscopy for, 2108, 2108f
 - diagnosis of, 2107
 - evaluation of, 2107
 - imaging for, 2108-2109, 2108f-2109f
 - physical examination of, 2107-2108, 2107f
 - presentation of, 2107
 - urine studies for, 2109
 - conservative and minimally invasive therapy for, 2109-2110, 2110f
 - etiology of, 2104-2106, 2104f, 2106b
 - evaluation of, 2265
 - history of, 2104.e1
 - intraoperative risk factors for, 2106-2107
 - laparoscopic approaches to, 2114-2116, 2116.e7, 2116.e8t
 - complications with, 2266
 - outcomes with, 2266
 - robot-assisted *versus*, 2116.e7
 - special considerations for, 2116
 - technique for, 2265, 2266f
 - transabdominal transvesical, 2116
 - posthysterectomy, 2105
 - prevalence of, 2104-2105
 - robotic repair of, 2116, 2116.e1b, 2116.e1t, 2116.e7, 2116.e9t
 - complications of, 2266, 2116.e7
 - cystotomy in, 2116.e2-2116.e4, 2116.e2f-2116.e4f
 - laparoscopic *versus*, 2116.e7
 - outcomes with, 2266
 - port placement for, 2116.e2, 2116.e2f
 - position for, 2116.e2
 - postoperative care and follow-up for, 2116, 2116.e6
 - preparation for, 2116.e2
 - special considerations for, 2116
 - surgical steps of, 2116.e2-2116.e5, 2116.e4f-2116.e5f
 - technique for, 2265, 2266f
 - surgery for
 - conclusions on, 2116
 - indications for, 2113
 - outcomes of, 2117-2119, 2117.e1t
 - preoperative counseling for, 2113

- Vesicovaginal fistula (VVF) (*Continued*)
 surgical considerations for, 2110-2113
 abdominal *versus* vaginal approach, 2111-2112, 2111t, 2112.e1b
 adjuvant flaps or grafts, 2112
 antibiotics, 2112
 estrogen supplementation, 2112
 excision *versus* no excision, 2112
 immediate *versus* delayed, 2110-2111
 postoperative drainage, 2113
 sexual activity documentation, 2112
 surgical indications with, 2265
 treatment for, 2109-2119
 urinary diversion and, 2119
 vaginal techniques for, 2113
 abdominal *versus*, 2111-2112, 2111t, 2112.e1b
 complications with, 2113
 other techniques, 2113
 vaginal flap or flap-splitting technique, 2113, 2114f-2115f
- Vesicovaginal space, 1598-1599, 1599f
- Vesiculodeferential artery, 505
- Vestibular cysts, 3456-3457, 3457f
- Vestibule, disorders of, 3456-3458
 ectopic ureteral insertion, 3458, 3458f
 prolapsed ureterocele, 3457-3458, 3458f
 urethral polyp, 3456, 3457f
 urethral prolapse, 3456, 3456f
 vestibular cysts, 3456-3457, 3457f
- Vestibulodynia, and sexual pain disorders, 763, 763.e1f
- VHL. *See* von Hippel-Landau disease
- VHL gene, 1321-1324, 1322t-1323t, 1323f, 1327b, 1507-1508, 1508f
- Viagra. *See* Sildenafil
- Victims of sexual violence, and female sexual function, 750, 754, 750.e1, 754.e2
- Video-endoscopic systems, 136-137, 137f-138f
- Video-urodynamics (VURDS), 1706, 1734-1737
 for bladder neck dysfunction, 1737
 for BOO diagnosis in women, 1734f-1735f, 1735
 for LUTS in men, 1735, 1735f
 methods of, 1734
 for neuropathic voiding dysfunction, 1736-1737, 1737f
 in pediatric patients, 3131, 3132f
 with upper urinary tract effects, 1735-1736
 for voiding phase dysfunction, 1735
- Vinblastine, for UTUC, 1400
- Vinblastine-ifosfamide-cisplatin (VeiP)
 for NSGCTs, 802, 805
 for seminomas, 810
- Vincet's curtsey sign, 3126, 3127f
- Vincristine, for penile cancer, 872-873
- VIP. *See* Etoposide-ifosfamide-cisplatin; Vasoactive intestinal peptide
- Viral cystitis, and UTIs, 2947
- Virtual reality trainers, for laparoscopic and robotic surgery, 224.e3, 224.e3f
- Virus-related tumors, of penis, 846.e2, 846.e4b
 Bowenoid papulosis, 846.e3
 HPV, 847-849, 846.e2-846.e3
 Kaposi sarcoma, 846.e3-846.e4
- Visceral injury
 during laparoscopic and robotic surgery, 216-218
 in pediatric patients, 2971
 laparoscopic kidney surgery causing, 1481, 1481f
 after percutaneous access to upper urinary tract collecting system, 179
 during radical nephrectomy, 1428
- Visible hematuria. *See* Gross hematuria
- Vitamin D
 in absorptive hypercalciuria, 1183
 in calcium metabolism, 1180
 in prostate cancer, 2550
 renal regulation of, 1011-1012, 1011f
 role in renal calculi management, 1221, 1221b
- Vitamin D receptor (VDR), 1183
 in prostate cancer, 2550
- Vitamin D₃. *See* Cholecalciferol
- Vitamin D₃-receptor analogues, to facilitate bladder filling and urine storage, 1866.e1
- Vitamin E
 for PD, 734
 in prostate cancer prevention, 2562-2563, 2563f
- Vitiligo, 418f, 419-420
- VLP. *See* Valsalva leak point pressure
- VMA testing. *See* Vanillylmandelic acid testing
- Voided urine specimens, in urine collection, 250
- Voiding. *See also* Micturition
 absence of, neonatal, 2890
 bashful bladder, 1788-1789
 detrusor pressure at, 3123, 3124f
 with normal bladder contraction, 1686-1687
 therapy to facilitate, 1691b
- Voiding cystourethrogram (VCUG), 37, 37f, 2888-2889, 2905-2906, 2905f
 of bladder diverticula, 2142-2143, 2142f
 of mesh complications in pelvic reconstructive surgery, 2044-2045, 2044f
 for pediatric patients, 2916-2918, 2919f
 for pelvic floor disorders, 1707-1708
 of posterior urethral valves, 3257-3258, 3258f
 for ureteral anomalies, 3083, 3084f
 for UTIs, 253, 2941
 for vesicovaginal fistula, 2108-2109, 2108f-2109f
- Voiding diaries
 for benign prostatic hyperplasia, 2468
 for pediatric patients, 3127
 for PFDs evaluation, 1702
 for urinary incontinence, in geriatric patients, 2099.e1-2099.e2
- Voiding dysfunction, 1692-1693
 behavioral treatment for, 1891-1892
 benign prostatic hyperplasia in, 2425, 2426f
 classification of, 1691-1695
 Bors-Comarr, 1694-1695, 1694b
 Bradley, 1695
 functional, 1688t, 1689b, 1691-1693, 1692b, 1719-1720, 1720b
 Hald-Bradley, 1695, 1695b
 International Continence Society, 1692, 1692b
 Lapedes, 1693-1695
 urodynamic, 1693, 1693b
 electrical stimulation for, 1900t
 HIV and, 384
 lower urinary tract dysfunction and, 1787
 after midurethral sling, 2016t-2017t, 2019t, 2033-2036, 2034t-2035t, 2036b
 management of, 2035-2036
 neuropathic
 general patterns of, 1761-1763, 1761b, 1763b
 video-urodynamics for, 1736-1737, 1737f
 pediatric, sacral nerve stimulation for, 1907-1908
 in pediatric patients, 3126-3133, 3126b
 postoperative
 after retropubic suspension surgery, 1932-1933
 sacral nerve stimulation for, 1907
 after pubovaginal sling procedure, 2004-2006, 2007b
 surgical management of, 2006t
- Voiding dysfunction (*Continued*)
 treatment of, 1690b-1691b, 1691-1692
 ureterocele and, 3097
 urodynamic studies of, functional classification, 1719-1720, 1720b
 video-urodynamics for, 1735
- Voiding frequency, in pediatric patients, 3123, 3123f
- Volume hypertensive model, 1029, 1030f
- von Brunn nests, of upper urinary tract, 1369-1370
- von Hippel-Landau disease (VHL), 3026-3028
 classification of, 3026
 clinical features of, 3026
 etiology of, 3026
 evaluation of, 3027
 histopathology of, 3026-3027, 3027t
 screening for, 3027, 3027t
 treatment of, 3027-3028
- von Hippel-Lindau syndrome
 genomic alterations in, 468t, 471-472, 1321-1324, 1322t-1323t, 1323f
 RCC screening for, 1336
 targeted molecular therapies for
 basis of, 1507-1508, 1508f
 combination and sequential therapy with, 1516
 mTOR pathway inhibitors, 1502-1503, 1514-1515, 1514t, 1515f
 VEGF inhibitors, 1502-1503, 1507-1514, 1508f-1512f, 1509t-1511t, 1513t
 treatment of RCC in, 1353-1355, 1355f
- VOS procedure. *See* Vagino-obturator shelf procedure
- VTE. *See* Venous thromboembolism
- Vulva, 1605, 1605f-1606f
 trauma of, pediatric, 3558
- Vulvar dermatoses, and sexual pain disorders, 763
- Vulvar RMS, in pediatric patients, 3589
- Vulvovaginal atrophy, and sexual pain disorders, 763
- VUR. *See* Vesicoureteral reflux
- VURD. *See* Vesicoureteral reflux and dysplasia
- VURDS. *See* Video-urodynamics
- VVB. *See* Venovenous bypass
- VVE. *See* Vesicovaginal fistula
- W**
- Wallace technique, in urinary diversion, 2296t, 2298, 2298f
- Wallstents, 127
- Warfarin, management of
 for percutaneous access to upper urinary tract collecting system, 158
 preoperative, 109-110
- Warsaw approach, for classic bladder exstrophy, 3197
 continence outcomes with, 3213
- WAS. *See* Water avoidance stress
- Watchful waiting. *See also* Surveillance
 with androgen deprivation therapy, 2746
 for benign prostatic hyperplasia, 2472-2473
 studies on, 2449-2450, 2449t-2450t, 2450f
 of prostate cancer
 candidate identification for, 2632-2633
 localized, 2611-2613
 progression and triggers in, 2634
 for vesicoureteral reflux, 3154-3155
- Water
 in collecting tubule, 1019, 1019f
 hardness of, nephrolithiasis and, 1216-1217
 intake of, renal calculi and, 1173
 loop of Henle reabsorption of, 1017-1018, 1017f
 PCT reabsorption of, 1015
 urothelium permeability to, 1638

- Water avoidance stress (WAS), bladder pain syndrome and interstitial cystitis and, 1679
- Water imbalance
diabetes insipidus, 1023, 1835
renal pathophysiology involved in, 1019-1023, 1020f-1022f, 1021b, 1023b
- Water-filled catheters, for urodynamic studies, 1723-1724
- Watts factor (WF), 1815
- WB-MRI. *See* Whole-body magnetic resonance imaging
- WBS. *See* Williams-Beuren syndrome
- Weak stream, patient history of, 4t-5t
- Webbed penis, 3375f, 3376
- Wedge resection, for large renal tumors, 1431, 1431f
- Weight, renal calculi and, 1172-1173
- Weight loss
for ED, 553
for urinary incontinence, 552
- Weight reduction, for urinary incontinence, 1894
- Wernicke encephalopathy, lower urinary tract dysfunction and, 1790-1791
- WE. *See* Watts factor
- WHI. *See* Women's Health Initiative
- Whitaker test, for urinary tract obstruction, 1093
- Whole-body bone scan, 39
- Whole-body magnetic resonance imaging (WB-MRI), for metastatic disease detection, 2746-2747
- Whole-gland salvage therapy, for prostate cancer recurrence, 2747-2748, 2748t
brachytherapy, 2747
high-intensity focused ultrasound, 2748
salvage radical prostatectomy, 2747
- Williams-Beuren syndrome (WBS), lower urinary tract dysfunction and, 1792
- Wilms tumor, 1361t, 1364, 3567-3568, 3581b
biology and genetics of, 468t, 3568-3570, 3568t, 3574
epidemiology of, 3568
pathology of, 3570
anaplasia, 3571
favorable histology, 3570-3571, 3571f
- Wilms tumor (*Continued*)
nephrogenic rests, 3572, 3572f
after preoperative chemotherapy, 3571-3572
preoperative evaluation of, 3572-3573
imaging, 3573-3574, 3573f
prognostic factors, 3574
staging, 3574, 3574t
screening for, 3570, 3570f, 3571t
treatment of
chemotherapy, 3571-3572, 3575, 3577-3579, 3578f
cooperative group trials evaluating, 3575-3577, 3576f
late effects of, 3579
partial nephrectomy, 3578-3579
relapse after, 3575-3576
surgery, 3574-3575
- WNT4 gene, 3470, 3471f, 3472t
- Wolffian duct, 2975-2976
- Women's Health Initiative (WHI), 1863
- World Health Organization
GCT classification of, 786b
RCC classification system of, 1328-1330, 1329t-1330t
testicular tumors classification of, 785b
- Wound. *See also* Surgical wounds
genital bite, 406-407, 408f
- Wound healing, and PD, 727-728
- Wound infection, of surgical site. *See* Surgical site infections
- W-stapled reservoir, for cutaneous continent urinary diversion, 2342, 2342f
- WT1 gene, 3469, 3471f, 3472t, 3568-3569, 3568t
- WTX gene, 3568t, 3569
- X**
- X chromosome, in spermatogenesis, 528
- Xanthine stones, 1195
surgical management of, 1243.e3
- Xanthogranulomatous pyelonephritis (XGP), 286-289, 287f-288f
and UTIs, 2946-2947
- Xenograft
processing of, 1947
for pubovaginal sling, 1991
outcomes of, 2002-2003, 2002t
source of, 1946-1947
- XGP. *See* Xanthogranulomatous pyelonephritis
- Y**
- Y chromosome, in spermatogenesis, 528
- Yang-Monti technique, 3363, 3364f
- Yeast, in urinary sediment, 22f, 23-24
- Yolk sac tumors (YSTs)
in female pediatric patients, 3590
testicular
histology of, 787f, 788
in pediatric patients, 3594, 3594f
- Young-Dees-Leadbetter bladder neck reconstruction, 3336
modified, 3205f-3206f
results with, 3336
technique for, 3336
- Yq microdeletions, 528
- YSTs. *See* Yolk sac tumors
- Z**
- ZAG. *See* Zinc α_2 -glycoprotein
- Zanotone, for benign prostatic hyperplasia, 2486
- ZFY gene, 3469-3471, 3470f-3471f
- Zinc, in prostatic secretions, 2416
- Zinc α_2 -glycoprotein (ZAG), in prostatic secretions, 2417t, 2422-2423
- Zipper injuries, to penis, 2382
- Zofran. *See* Ondansetron
- Zona fasciculata, in adrenal cortex physiology, 1530-1531, 1530f, 1531t
- Zona glomerulosa, in adrenal cortex physiology, 1530
- Zona reticularis, in adrenal cortex physiology, 1531
- Zonal anatomy, prostate, 506, 507f-508f, 508
- Zonisamide, in stone formation, 1197
- Zoon balanitis, 416, 416f-417f
- Zuidex. *See* Dextranomer hyaluronic acid copolymer

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